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Studies on the Selective Reduction of the Amide Link of Acyclic and Macrocyclic Amidoketals: Unexpected Cleavage and *trans*-Acetalization with Red-Al®

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Abstract: Selective reduction of the amide moiety of acyclic and macrocyclic amidoketals was studied in presence of various reagents ($BH_3 \cdot Me_2S$, $iBuAlH_2$, Red-Al®, $LiAlH_4$). The best results were obtained with lithium aluminium hydride in the presence of triethylamine traces, whereas borane dimethyl sulfide gave rise to a partial ketal reduction of the acyclic compound and Red-Al® to a cleavage of the macrocyclic molecule accompanied by an unexpected *trans*-acetalization.

Keywords: acyclic and macrocyclic amido and aminoketals, selective reduction, *trans*-acetalization

INTRODUCTION

Over the past few decades, selective reduction of an amide or lactam function in the presence of other reducible groups has been thoroughly investigated.[1] Concerning the reduction of amidoketals, several examples can be found in the literature. Depending on the substrate, on the hydride nature, and on the reaction conditions, they give rise to compounds corresponding either to the amide reduction [$BH_3 \cdot THF$ (4.0 eq),[2] $BH_3 \cdot Me_2.S$ (4.6 eq),[3] $NaAlH_4$ (2.0 eq),[4] $LiAlH_4$ (2.0–6.35 eq)[5]], to the ketal reduction [KBH_4 (2.0 eq), $Me_4NBH(OAc)_3$ (6.0–10.0 eq)],[6] or to both function reductions [$BH_3 \cdot THF$ (10.0 eq),[7] $LiAlH_4$ (9.5 eq)[8]].

We are presently interested in the reduction of new diversely substituted 14-membered ring compounds bearing diketal and dilactam functions (Fig. 1), of which synthesis, conformation and cationic recognition properties were previously reported.[9] Selective reduction of the lactam link of these molecules leads to diketal diamines, analogs of cyclams whose metal complexes find important applications in chemistry and medicine, such as (1) polluted water-decontaminating agents,[10] (2) oxygen binding systems,[11] (3) imaging contrast agents for radioactive diagnosis and treatment,[12] and (4) anti-HIV agents.[12]

Macrocyclic diketal dilactams were prepared from β-aminoalcohols in two steps via hydroxyamidoketal intermediates (Scheme 1) and obtained under two or three diastereoisomeric forms depending on the achiral or chiral character of the molecules.[9a]

The present article reports the first results of our investigations on the reduction of these compounds and on the choice of the reducing agent able to affect the amide moiety without touching the ketal group. The study was led on the $3\alpha,10\alpha$-phenyl-$7\alpha,14\alpha$-OMe macrocycle **2** ($R^1 = Ph$; $R^2 = H$; major isomer) and on its hydroxyamidoketal precursor **1**, used as acyclic model.

RESULTS AND DISCUSSION

Reduction of hydroxyamidoketal **1** was successively attempted with four reagents: $BH_3 \cdot Me_2S$ [borane dimethyl sulfide (BMS)], $i\text{Bu}_2AlH$ [di-isobutyl aluminium hydride (DIBAH)], $NaAlH_2(OC_2H_4OCH_3)_2$ [Red-Al®], and $LiAlH_4$ [lithium aluminium hydride (LAH)]. The results are summarized in Table 1.

Reduction with BMS[1c,3] led to a mixture of two compounds: *(i)* hydroxyaminoether **3**, resulting from the reduction of both amide and ketal functions,

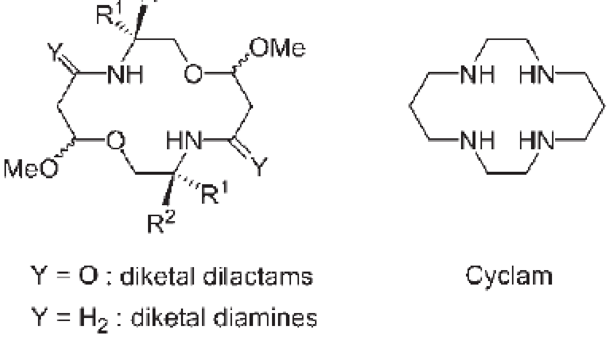
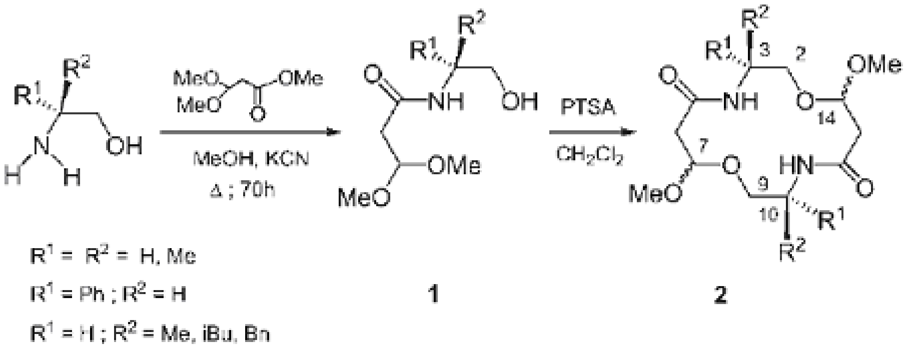


Figure 1. Structure of diketal dilactams, diketal diamines, and cyclam.



Scheme 1.

and *(ii)* hydroxyaminoketal **4**, corresponding to the selective reduction of the amide link (ratio **3**/**4** = 60/40, total yield 77%) (Scheme 2). Use of DIBAH[1d,13] as hydride provided **4** in very poor yield (3%) at a weak conversion rate (32%), even after 72 h of heating in toluene. In contrast, reduction with Red-Al[14] and LAH[5] afforded **4** in medium (30%) and good (66%) yields, respectively. Using LAH, the reagent/substrate ratio providing the best yield was 5 eq. as shown by the following results: 3 eq.: 59%, 5 eq.: 66%, 10 eq.: 57%.

Based on these results, the reduction of the macrocyclic diketal dilactam **2** was studied exclusively with Red-Al® and LAH. Reaction with Red-Al (7 eq.) in THF gave rise to compounds **5** (43%) and **6** (30%), in which the carbonyl group was unreduced (Scheme 3). Both derivatives come from a double-ring cleavage and an unexpected *trans*-acetalization of one or two methoxy groups by the hydride ether chain. Hydroxyamidoketal **5**, which possesses two asymmetric carbons, was obtained under two diastereoisomeric forms (ratio: 55/45).

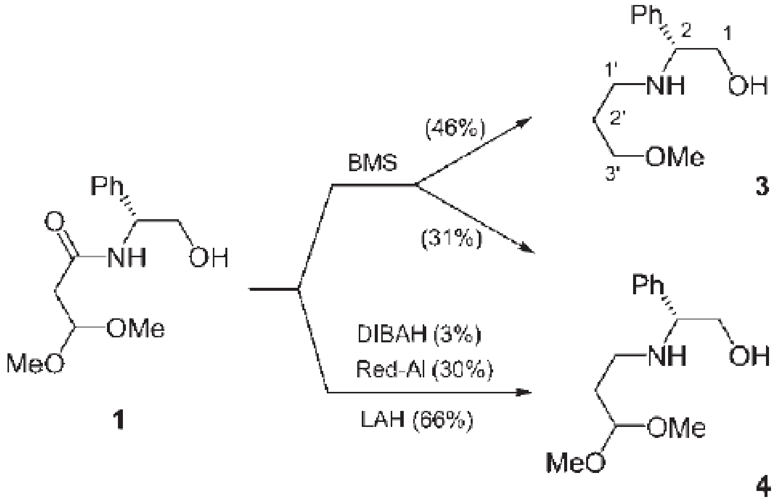
Reduction with LAH was performed in THF at reflux with 10 eq. of reagent (5 for each carbonyl as established previously). The most significant experimental results are reported in Table 2.

A first attempt, realized in exploratory conditions (entry 1), led to the expected diketal diamine **7**, accompanied by two other compounds: diketal aminolactam **8** and unsaturated ketal aminolactam **9** (Scheme 4).

Table 1. Reduction of hydroxyamidoketal **1**

Reagent (eq.)	Solvent	$c_{\text{substrate}}$ (10^{-2} M)	Temp. (°C)	Time (h)	Conversion (%)	Results cpd (%)[a]
BMS (5)	THF	4.0	65	9	100	**3** (46) + **4** (31)
DIBAH (3)	Toluene	20.0	110	72	32	**4** (3)
Red-Al (3)	THF	20.0	65	24	100	**4** (30)
LAH (5)	THF	6.7	65	2	100	**4** (66)

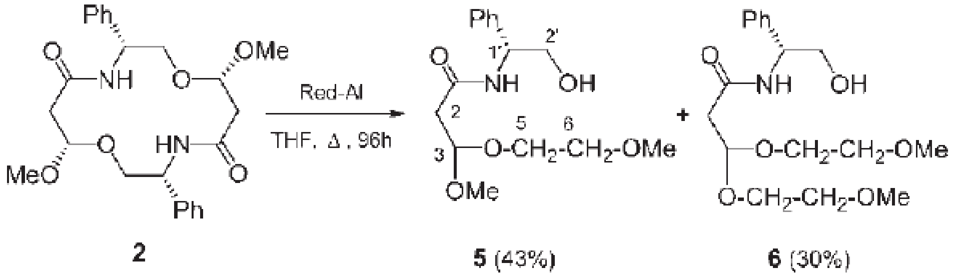
[a] Isolated yield by column chromatography.



Scheme 2.

Derivatives **7** and **8** correspond to the di- and mono-reduction products, respectively, whereas **9** probably arises from **8** by methanol elimination, which can theoretically occur either in basic or acid conditions (Scheme 5).

It appeared difficult to avoid a basic medium, probably because of the liberation of LiOH during the workup. In contrast, we did attempt to neutralize a potential acidity, imputable to the presence of $AlCl_3$ traces in LAH, by adding small amounts of triethylamine (entries 2–5). Traces of $AlCl_3$, incompletely removed from the hydride preparation, may be present in $LiAlH_4$ as previously suggested in Corey's paper.[15] The best results were obtained with a 25×10^{-3} M concentration in the substrate, which led to an increase of the **7**/**8** ratio, and in the presence of NEt_3 (0.04 eq. referring to LAH, i.e, 0.4 eq. referring to the substrate), which led to a decrease in the amount of the undesired compound **9** (entry 3). In all cases, the reduction occurred with a moderate total yield ($\approx$50%), which was not improved by use of a more important excess of reagent (entry 4) or a more concentrated substrate solution (entry 5). This result may be explained by a complexation between the generated diketal diamine **7** and the Li^+ cation, which could therefore no longer catalyze the reaction,[16] as previously reported in the reduction of various compounds with LAH in the presence of a macrocyclic ligand.[16a,c]



Scheme 3.

Table 2. Reduction of macrocyclic diketal dilactam **2** by LAH

Entry	$c_{\text{substrate}}$ (10^{-3} M)	LAH (eq.)	NEt_3 (eq.)	Time (h)	Conversion (%)	**7** (%)[a]	**8** (%)[a]	**9** (%)[a]
1	17	10	—	9	90	21	16	14
2	21	10	0.2	11	92	26	13	11
3	25	10	0.4	11	95	30	8	8
4	25	15	0.6	11	90	28	9	8
5	30	10[b]	0.4	11	80	20	2	—

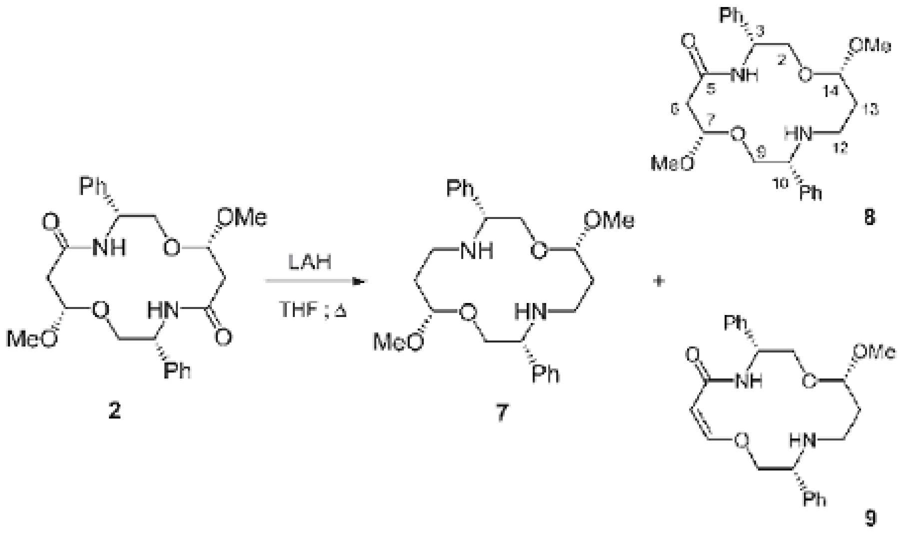
[a] Isolated yield by column chromatography.
[b] LAH in THF solution.

In conclusion, lithium aluminium hydride appears to be the best reagent for the selective reduction of the amide moiety of the studied acyclic and cyclic amidoketals. The addition of small amounts of triethylamine to neutralize the $AlCl_3$ traces present in LAH appreciably reduced the effects of a side elimination reaction in the reduction of the cyclic compound. Extension of this procedure to other macrocyclic diketal dilactams is in progress in our laboratory to evaluate their binding abilities toward the radiometal ^{99m}Tc. Furthermore, the surprising and interesting *trans*-acetalization accompanying the reaction of Red-Al® with ketal **2** is of potential value for easy methoxy-ethoxy group introduction.

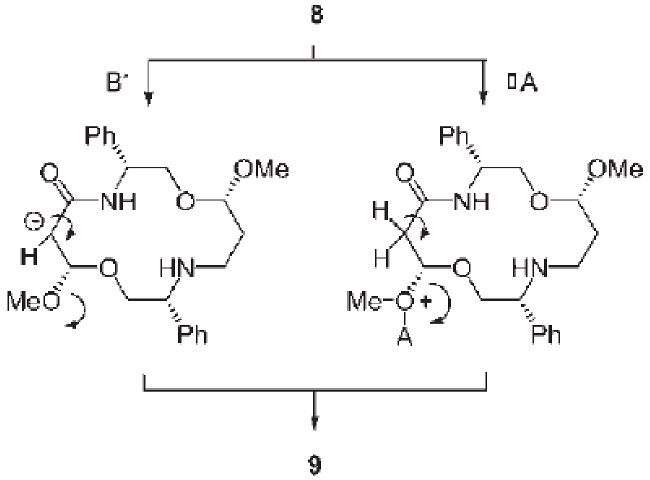
EXPERIMENTAL

General

Organic layers were dried on Mg_2SO_4. Silica gel was used for analytical and flash chromatography. IR were recorded on a Perkin-Elmer 881 spectrophotometer



Scheme 4.



Scheme 5.

[ν in centimeters^{-1}]. Mass spectra were measured on HP 5989B (CI), micro Q-TOF Waters (ESI), or ZabSpec TOF Micromass (ESI) apparatus. NMR spectra [1D (^{1}H and ^{13}C) and 2D (correlation spectroscopy (COSY) ^{1}H-^{1}H and heteronuclear single quantum correlation (HSQC) ^{1}H-^{13}C)] were performed on a Bruker AC 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz), equipped with a ^{1}H/^{13}C probe. Values of δ are given in parts per million (ppm) and J in hertz (Hz). The solvent ($CDCl_3$) was taken as internal reference.

(2*R*)-2-(3-Methoxypropylamino)-2-phenyl-ethanol 3

A 2 M solution of $BH_3 \cdot SMe_2$ in THF (1 mL, 2 mmol) was added dropwise to a solution of hydroxyamidoketal **1** (101 mg, 0.4 mmol) in dry THF (9 mL, $c_{\text{substrate}} = 4 \times 10^{-2}$ M). The mixture was stirred at reflux for 9 h under argon. After slow addition of MeOH (2 mL) to destroy BH_3 in excess, the organic solvents were removed, and the residue was dissolved in THF (2 mL). Then, a solution of TMEDA[1c] (30 µL, 23 mg, 0.2 mmol) in THF (1 mL) was added by syringe, and the mixture was refluxed for 1 h. After filtration and concentration under vacuum, the crude material was purified by flash chromatography on silica gel with Et_2O/MeOH (gradient: 100/0–90/10) to afford compounds **3** (38.3 mg, 183 µmol, 46%) and **4** (29.7 mg, 124 µmol, 31%, spectroscopic data: vide infra).

3: $[\alpha]_D^{20} = -43.9$ (*c* 0.54, $CHCl_3$). IR ($CHCl_3$): $\nu = 3684$ (OH), 3028 (NH) cm^{-1}. ^{1}H NMR, COSY ^{1}H-^{1}H ($CDCl_3$): $\delta = 1.70$ (br. s, 2H, NH, OH), 1.75 (qui, 2H, 2 H-2′, $J = 6.6$), 2.58 (dt, 1H, H-1′B, $J = 12.0, 6.6$), 2.67 (dt, 1H, H-1′A, $J = 12.0, 6.6$), 3.32 (s, 3H, OCH_3), 3.44 (t, 2H, 2 H-3′, $J = 6.2$), 3.51 (dd, 1H, H-1B, $J = 10.3, 8.5$), 3.71 (dd, 1H, H-1A, $J = 10.3, 4.4$), 3.76 (dd, 1H, H-2, $J = 8.5, 4.4$), 7.30–7.40 (m, 5H, 5 Ar-H). ^{13}C NMR, HSQC ($CDCl_3$): $\delta = 30.2$, 45.0, 58.7, 64.7, 66.7, 71.5, 127.2 (2C), 127.6, 128.7 (2C), 141.0. MS (CI): m/z (%) = 210 (100) [MH^+], 192 (20) [$MH^+ - H_2O$], 178 (19) [$MH^+ - CH_3OH$], 150 (10), 121 (6) [$MH^+ - H_2N\text{-}(CH_2)_3\text{-}OCH_3$]. HRMS (ESI): m/z calculated for [$C_{12}H_{19}NO_2 + H^+$]: 210.1494; found: 210.1498.

(2*R*)-2-(3,3-Dimethoxypropylamino)-2-phenyl-ethanol 4

To a suspension of $LiAlH_4$ (152 mg, 4.0 mmol) in dry THF (2 mL), a solution of hydroxyamidoketal **1** (202 mg, 0.80 mmol) in dry THF (10 mL, $c_{\text{substrate}} = 67 \times 10^{-3}$ M) was added dropwise. The reaction mixture was refluxed under stirring for 2 h. The excess of hydride was destroyed by addition of H_2O (720μL, 40 mmol). The precipitates were filtrated and washed with THF (2 mL) and CH_2Cl_2 (2 mL). The organic layers were dried on $MgSO_4$ and evaporated under vacum. A purification by flash chromatography (silica gel) with Et_2O/MeOH (gradient: 100/0–90/10) led to hydroxyaminoketal **4** (127 mg, 0.53 mmol, 66%).

$[\alpha]_D^{25} = -56.6$ (c 0.94, $CHCl_3$). IR ($CHCl_3$): $\nu = 3620$ (OH), 3440, 3320 (NH) cm^{-1}. ^1H NMR, COSY ^1H-^1H ($CDCl_3$): $\delta = 1.77$ (q, 2H, 2 H-2′, $J = 6.0$), 2.52 (dt, 1H, H-1′B, $J = 12.0, 6.0$), 2.60 (dt, 1H, H-1′A, $J = 12.0, 6.0$), 3.24 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.36 (br. s, 2H, NH, OH), 3.54 (t, 1H, H-1B, $J = 9.8$), 3.67 (dd, 1H, H-1A, $J = 9.8, 4.2$), 3.74 (dd, 1H, H-2, $J = 9.8, 4.2$), 4.39 (t, 1H, H-3′, $J = 6.0$), 7.30–7.40 (m, 5H, 5 Ar-H). ^{13}C NMR, HSQC ($CDCl_3$): $\delta = 32.6$, 43.0, 53.0, 53.1, 64.8, 66.4, 103.6, 127.3 (2C), 127.7, 128.7 (2C), 140.1. MS (CI): m/z (%) = 240 (100) [MH^+], 208 (7) [$MH^+ - CH_3OH$]. HRMS (ESI): m/z calculated for [$C_{13}H_{21}NO_3 + H^+$]: 240.1600; found: 240.1606.

(1*R*)-*N*-(2-Hydroxy-1-phenylethyl)-3-methoxy-3-(2-methoxyethoxy)-propanamide 5 and (1*R*)-*N*-(2-Hydroxy-1-phenylethyl)-3,3-bis-(2-methoxyethoxy)-propanamide 6

A solution of Red-Al® in toluene (252 μL, 0.84 mmol, 65% in weight, $d_{\text{solution}} = 1.036$) was added dropwise to a solution of diketal diamine **2** (53 mg, 0.12 mmol) in dry THF (5 mL, $c_{\text{substrate}} = 24 \times 10^{-3}$ M). The mixture was stirred at room temperature for 4 days under argon. The excess of hydride was destroyed by addition of H_2O (360 μL, 20 mmol). After evaporation of THF, the aqueous phase was extracted by ether (2 × 1 mL) and dichlorometane (2 × 1 mL). The organic layers were dried on $MgSO_4$ and evaporated under vacum. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (gradient: 100/0–95/5) afforded amidoketals **5** (14.7 mg, 49.5 mmol, 43%) and **6** (11.8 mg, 34.6 mmol, 30%), conversion = 96%.

Data

5: two inseparable diastereoisomers (maj/min = 55/45). IR ($CHCl_3$): $\nu = 3615$ and 3590 (OH), 3440 and 3370 (NH), 1667 (CO) cm^{-1}. MS (CI): m/z (%) = 298 (100) [MH^+], 266 (23) [$MH^+ - CH_3OH$], 222 (17). HRMS (ESI): m/z calculated for [$C_{15}H_{23}NO_5 + Na^+$]: 320.1474; found: 320.1485.

Major isomer: ^1H NMR ($CDCl_3$): $\delta = 2.60$ (dd, 1H, H-2B, $J = 13.7, 4.4$), 2.68 (dd, 1H, H-2A, $J = 13.7, 7.1$), 3.10 (br. s, 1H, OH), 3.35 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.53–3.70 (m, 3H, H-5B, 2 H-6), 3.75–3.88 (m, 3H, 2 H-2′, H-5A), 4.83 (dd, 1H, H-3, $J = 7.1, 4.4$), 5.09 (ddd, 1H, H-1′, $J = 7.5, 6.5, 3.5$), 7.08 (d, 1H, NH, $J = 7.5$), 7.28–7.38 (m, 5H, 5 Ar-H). ^{13}C NMR ($CDCl_3$): $\delta = 41.4$, 54.1, 55.9, 59.0, 66.3, 66.6, 71.7, 101.3, 126.8 (2C), 127.8, 128.8 (2C), 139.2, 169.5.

Minor isomer: ^1H NMR ($CDCl_3$): $\delta = 2.59$ (dd, 1H, H-2B, $J = 13.8, 4.3$), 2.72 (dd, 1H, H-2A, $J = 13.8, 6.3$), 3.10 (br. s, 1H, OH), 3.32 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.53–3.70 (m, 3H, H-5B, 2 H-6), 3.75–3.88 (m, 3H, 2 H-2′, H-5A), 4.82 (dd, 1H, H-3, $J = 6.3, 4.3$), 5.08 (ddd, 1H, H-1′, $J = 6.8, 6.5, 3.5$), 7.19 (d, 1H, NH, $J = 6.8$ Hz), 7.28–7.38 (m, 5H, 5 Ar-H). ^{13}C NMR ($CDCl_3$): $\delta = 40.9$, 53.7, 55.7, 59.0, 65.3, 66.1, 71.7, 101.1, 126.8 (2C), 127.7, 128.8 (2C), 139.2, 169.5.

6: $[\alpha]_D^{25} = -23.5$ (c 0.71, $CHCl_3$). IR ($CHCl_3$): $\nu = 3615$ and 3590 (OH), 3440 and 3370 (NH), 1667 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 2.68$ (d, 2H, 2 H-2, $J = 5.2$), 3.25 (br. s, 1H, OH), 3.34 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.54 (m, 2H, OCH_2), 3.57 (m, 2H, OCH_2), 3.68 (m, 2H, OCH_2), 3.78 (m, 2H, OCH_2), 3.86 (m, 2H, 2 H-2′), 4.94 (t, 1H, H-3, $J = 5.1$), 5.09 (ddd, 1H, H-1′, $J = 7.3, 6.6, 3.7$), 7.19 (d, 1H, NH, $J = 7.3$), 7.31–7.36 (m, 5H, 5 Ar-H). ^{13}C NMR ($CDCl_3$): $\delta = 41.5$, 55.7, 59.0 (2C), 65.0, 65.9, 66.2, 71.7 (2C), 100.3, 126.8 (2C), 127.6, 128.7 (2C), 139.3, 169.4. MS (CI): m/z (%) = 342 (100) [MH^+], 298 (59), 266 (91), 222 (24), 190 (97). HRMS (ESI): m/z calculated for [$C_{17}H_{27}NO_6 + Na^+$]: 364.1736; found: 364.1724.

Macrocyclic Diketal Diamine 7, Diketal Aminolactam 8, and Unsaturated Ketal Aminolactam 9

To a suspension of $LiAlH_4$ (57 mg, 1.5 mmol) in THF (1 mL), NEt_3 (60 μL of a 1 M solution in THF, 60 μmol, 0.04 eq/LAH) and a solution of diketal dilactam **2** (66.4 mg, 0.15 mmol) in dry THF (5 mL, $c_{\text{substrate}} = 25 \times 10^{-3}$ M) were added. The reaction mixture was refluxed under stirring for 11 h. The excess of hydride was destroyed by addition of H_2O (270 μL, 15 mmol). The precipitates were filtrated and washed with THF (1 mL) and CH_2Cl_2 (1 mL). The organic layers were dried on $MgSO_4$ and evaporated under vacum. Purification by flash chromatography (silica gel) with $Et_2O/MeOH$ (gradient: 100/0–60/40) led to three compounds: diketal diamine **7** (17.7 mg, 42.8 μmol, 30%), diketal aminolactam **8** (4.9 mg, 11.4 μmol, 8%), and unsaturated ketal aminolactam **9** (4.5 mg, 11.4 μmol, 8%); conversion: 95%.

Data

7: $[\alpha]_D^{25} = -73.9$ (c 0.42, $CHCl_3$). IR ($CHCl_3$) $\nu = 3368$ and 3342 (NH) cm^{-1}. ^1H NMR, COSY ^1H-^1H ($CDCl_3$), $\delta = 1.79$ (dddd, 2H, H-6B, H-13B, $J = 14.4, 7.9, 2.1, 1.0$), 1.96 (dddd, 2H, H-6A, H-13-A, $J = 14.4, 9.5, 8.0, 1.5$), 2.46 (ddd, 2H, H-5B, H-12B, $J = 11.3, 9.5, 1.0$), 2.50 (br. s, 2H, 2 NH), 2.72 (ddd, 2H, H-5A, H-12A, $J = 11.3, 7.9, 1.5$), 3.20 (s, 6H, 2 OCH_3), 3.59 (dd, 2H, H-2B, H-9B, $J = 10.2, 2.8$), 3.78 (dd, 2H, H-2-A, H-9A, $J = 10.2, 9.1$), 3.93 (dd, 2H, H-3, H-10, $J = 9.1, 2.8$), 4.69 (dd, 2H, H-7, H-14, $J = 8.0, 2.1$), 7.25–7.44 (m, 10H, 10 Ar-H). ^{13}C NMR, HSQC ($CDCl_3$): $\delta = 31.6$ (2C), 43.5 (2C), 51.5 (2C), 63.0 (2C), 72.1 (2C), 104.4 (2C), 127.5 (2C), 127.9 (4C), 128.4 (4C), 140.3 (2C). MS (CI): m/z (%) = 415 (100) [MH^+], 383 (76) [$MH^+ - CH_3OH$], 218 (22), 192 (26) [$M/2 + H^+$], 176 (40), 162 (17), 150 (26), 132 (12), 118 (34), 104 (21). HRMS (FAB^+): m/z calculated for [$C_{24}H_{34}N_2O_4 + H^+$]: 415.2596; found: 415.2584.

8: $[\alpha]_D^{25} = -59.0$ (c 0.28, $CHCl_3$). IR ($CHCl_3$): $\nu = 3420$ (NH), 1660 (CO) cm^{-1}. ^1H NMR, COSY ^1H-^1H ($CDCl_3$): $\delta = 1.70$ (dddd, 1H, H-13B, $J = 14.0, 6.0, 1.7, 0.8$), 1.86 (br. s, NH), 1.98 (dddd, 1H, H-13A, $J = 14.0, 10.7, 9.2, 0.5$), 2.47 (ddd, 1H, H-12B, $J = 11.2, 10.7, 0.8$), 2.64 (dd, 1H, H-6B, $J = 15.1, 2.0$), 2.65 (ddd, 1H, H-12A, $J = 11.2, 6.0, 0.5$), 2.77 (dd, 1H, H-6A, $J = 15.1, 5.5$), 2.99 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.60 (dd, 1H, H-9B, $J = 9.5, 2.7$), 3.82 (dd, 1H, H-9A, $J = 10.1, 9.5$), 3.84 (dd, 1H, H-2B, $J = 10.2, 2.8$), 3.92 (dd, 1H, H-10, $J = 10.1, 2.7$), 3.97 (dd, 1H, H-2A, $J = 10.2, 5.0$), 4.66 (dd, 1H, H-14, $J = 9.2, 1.7$), 4.83 (dd, 1H, H-7, $J = 5.5, 2.0$), 5.30 (ddd, 1H, H-3, $J = 8.0, 5.0, 2.8$), 7.25–7.39 (m, 10H, 10 Ar-H), 7.47 (d, 1H, NH, $J = 8.0$). ^{13}C NMR, HSQC ($CDCl_3$): $\delta = 31.6$, 40.9, 44.4, 50.4, 52.5, 54.7, 63.0, 69.3, 71.7, 100.7, 104.2, 126.9–128.6 (10C), 139.6 (2C), 168.4. MS (CI): m/z (%) = 429 (100) [MH^+], 397 (36) [$MH^+ - CH_3OH$], 371 (8), 339 (5). HRMS (ESI): m/z calculated for [$C_{24}H_{32}N_2O_5 + H^+$]: 429.2390; found: 429.2390.

9: $[\alpha]_D^{25} = 37.8$ (c 0.34, $CHCl_3$). IR ($CHCl_3$): $\nu = 3440$ (NH), 1670 (CO), 1610 (C=C) cm^{-1}. ^1H NMR, COSY ^1H-^1H ($CDCl_3$): $\delta = 1.78$ (br. s, NH), 1.72 (dddd, 1H, H-13B, $J = 14.1, 6.8, 1.7, 0.5$), 1.98 (dddd, 1H, H-13A, $J = 14.1, 11.0, 9.5, 0.5$), 2.42 (ddd, 1H, H-12B, $J = 11.4, 11.0, 0.5$), 2.68

(ddd, 1H, H-12A, $J = 11.4, 6.8, 0.5$), 2.88 (s, 3H, OCH_3), 3.82 (dd, 1H, H-2B, $J = 9.4, 3.2$), 3.93 (dd, 1H, H-10, $J = 10.0, 3.3$), 4.01 (dd, 1H, H-9B, $J = 10.3, 3.3$), 4.14 (dd, 1H, H-2A, $J = 9.4, 2.0$), 4.17 (dd, 1H, H-9A, $J = 10.3, 10.0$), 4.63 (dd, 1H, H-14, $J = 9.5, 1.7$), 5.05 (d, 1H, H-6, $J = 6.9$), 5.36 (ddd, 1H, H-3, $J = 8.4, 3.2, 2.0$), 6.55 (d, 1H, H-7, $J = 6.9$), 7.25–7.42 (m, 10H, 10 Ar-H), 8.08 (d, 1H, NH, $J = 8.4$). ^{13}C NMR, HSQC ($CDCl_3$): $\delta = 31.6$, 44.6, 49.5, 51.9, 63.8, 70.3, 79.1, 104.1, 104.6, 127.0–128.9 (10C), 140.2 (2C), 152.6, 164.7. MS (CI): m/z (%) = 397 (100) [MH^+], 365 (45) [$MH^+ - CH_3OH$], 339 (27). HRMS (ESI) m/z calculated for [$C_{23}H_{28}N_2O_4 + H^+$]: 397.2127; found: 397.2128.

ACKNOWLEDGMENT

The authors thank B. Légeret and F. Pélissier for performing the mass spectra, R. Egrot for recording the 2D NMR spectra, and Professor A. Alexakis for valuable discussions.

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