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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 ($\text{BH}_3 \cdot \text{Me}_2\text{S}$, 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 [$\text{BH}_3 \cdot \text{THF}$ (4.0 eq),^[2] $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (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), $\text{Me}_4\text{NBH}(\text{OAc})_3$ (6.0–10.0 eq)],^[6] or to both function reductions [$\text{BH}_3 \cdot \text{THF}$ (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** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{H}$; 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: $\text{BH}_3 \cdot \text{Me}_2\text{S}$ [borane dimethyl sulfide (BMS)], $i\text{Bu}_2\text{AlH}$ [diisobutyl aluminium hydride (DIBAH)], $\text{NaAlH}_2(\text{OC}_2\text{H}_4\text{OCH}_3)_2$ [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) hydroxy-aminoether **3**, resulting from the reduction of both amide and ketal functions,

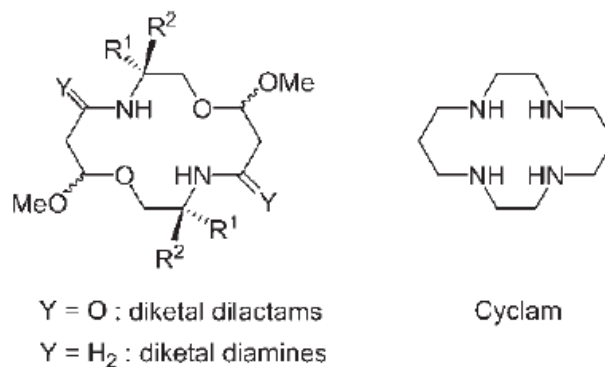
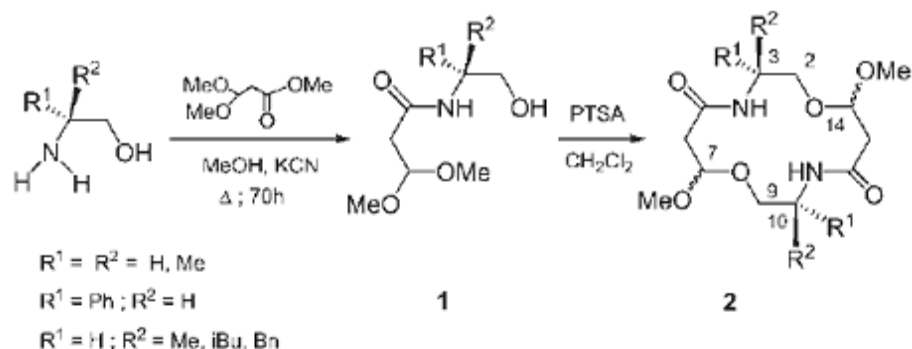


Figure 1. Structure of diketal dilactams, diketal diamines, and cyclam.

Amide Link of Acyclic and Macrocyclic Amidoketals



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).

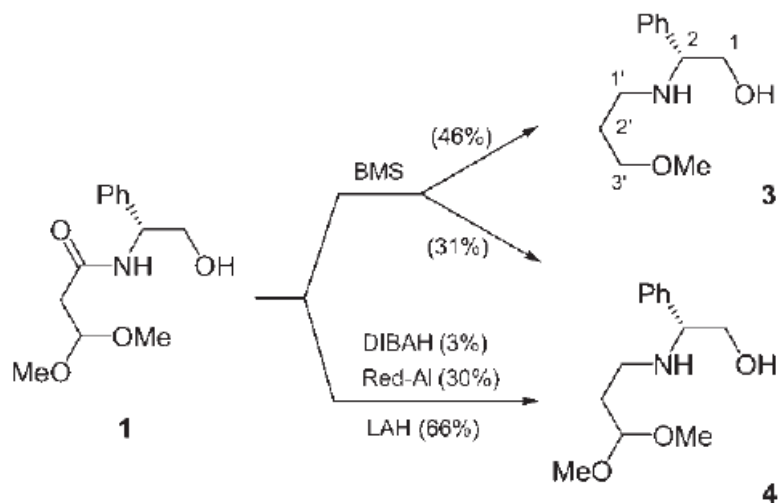
Reduction with LAH was performed in THF at reflux with 10 eq. of reagent (5 for each carbonyl as established previously). The most significant experimental results are reported in Table 2.

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. ($^{\circ}\text{C}$) | 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) |

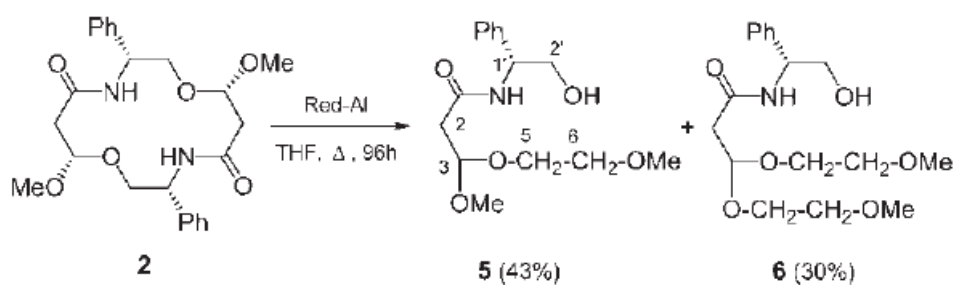
^aIsolated yield by column chromatography.



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 AlCl₃ traces in LAH, by adding small amounts of triethylamine (entries 2–5). Traces of AlCl₃, incompletely removed from the hydride preparation, may be present in LiAlH₄ 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 NEt₃ (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.

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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 | — |

^aIsolated yield by column chromatography.

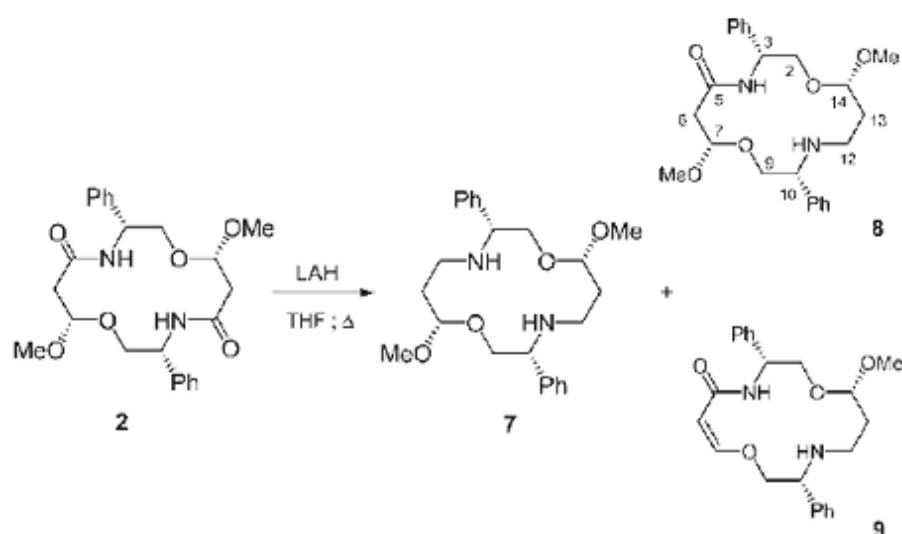
^bLAH in THF solution.

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 AlCl₃ 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.

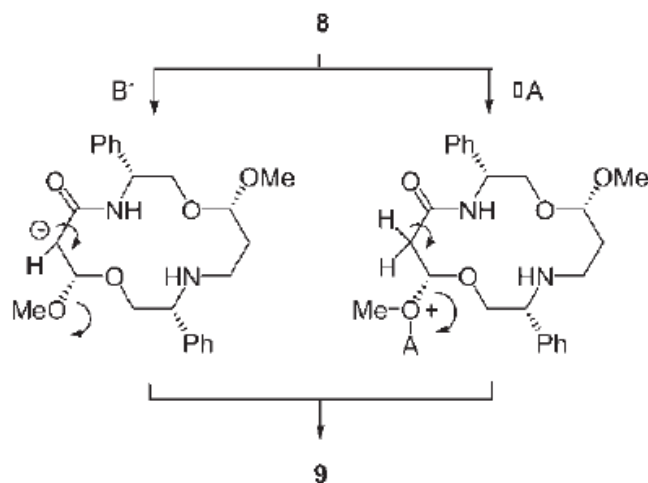
EXPERIMENTAL

General

Organic layers were dried on Mg₂SO₄. Silica gel was used for analytical and flash chromatography. IR were recorded on a Perkin-Elmer 881 spectrophotometer



Scheme 4.



Scheme 5.

$[\nu$ 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 (¹H and ¹³C) and 2D (correlation spectroscopy (COSY) ¹H-¹H and heteronuclear single quantum correlation (HSQC) ¹H-¹³C)] were performed on a Bruker AC 400 spectrometer (¹H: 400 MHz, ¹³C: 100 MHz), equipped with a ¹H/¹³C probe. Values of δ are given in parts per million (ppm) and J in hertz (Hz). The solvent (CDCl₃) was taken as internal reference.

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

A 2 M solution of BH₃ · SMe₂ 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 BH₃ in excess, the organic solvents were removed, and the residue was dissolved in THF (2 mL). Then, a solution of TMEDA^[1c] (30 μ L, 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 Et₂O/MeOH (gradient: 100/0–90/10) to afford compounds **3** (38.3 mg, 183 μ mol, 46%) and **4** (29.7 mg, 124 μ mol, 31%, spectroscopic data: vide infra).

3: $[\alpha]_{\text{D}}^{20} = -43.9$ (c 0.54, CHCl₃). IR (CHCl₃): $\nu = 3684$ (OH), 3028 (NH) cm⁻¹. ¹H NMR, COSY ¹H-¹H (CDCl₃): $\delta = 1.70$ (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, OCH₃), 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). ¹³C NMR, HSQC (CDCl₃): $\delta = 30.2, 45.0, 58.7, 64.7, 66.7, 71.5, 127.2$ (2C), 127.6,

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128.7 (2C), 141.0. MS (CI): m/z (%) = 210 (100) [MH⁺], 192 (20) [MH⁺ - H₂O], 178 (19) [MH⁺ - CH₃OH], 150 (10), 121 (6) [MH⁺ - H₂N-(CH₂)₃-OCH₃]. HRMS (ESI): m/z calculated for [C₁₂H₁₉NO₂ + H⁺]: 210.1494; found: 210.1498.

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

To a suspension of LiAlH₄ (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 H₂O (720 μL, 40 mmol). The precipitates were filtrated and washed with THF (2 mL) and CH₂Cl₂ (2 mL). The organic layers were dried on MgSO₄ and evaporated under vacuum. A purification by flash chromatography (silica gel) with Et₂O/MeOH (gradient: 100/0–90/10) led to hydroxyaminoketal **4** (127 mg, 0.53 mmol, 66%).

$[\alpha]_{\text{D}}^{25} = -56.6$ (c 0.94, CHCl₃). IR (CHCl₃): $\nu = 3620$ (OH), 3440, 3320 (NH) cm⁻¹. ¹H NMR, COSY ¹H-¹H (CDCl₃): $\delta = 1.77$ (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, OCH₃), 3.25 (s, 3H, OCH₃), 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). ¹³C NMR, HSQC (CDCl₃): $\delta = 32.6, 43.0, 53.0, 53.1, 64.8, 66.4, 103.6, 127.3$ (2C), 127.7, 128.7 (2C), 140.1. MS (CI): m/z (%) = 240 (100) [MH⁺], 208 (7) [MH⁺ - CH₃OH]. HRMS (ESI): m/z calculated for [C₁₃H₂₁NO₃ + H⁺]: 240.1600; found: 240.1606.

(1R)-N-(2-Hydroxy-1-phenylethyl)-3-methoxy-3-(2-methoxyethoxy)-propanamide **5** and (1R)-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 H₂O (360 μL, 20 mmol). After evaporation of THF, the aqueous phase was extracted by ether (2 × 1 mL) and dichloromethane (2 × 1 mL). The organic layers were dried on MgSO₄ and evaporated under vacuum. Purification by flash chromatography on silica gel with CH₂Cl₂/MeOH (gradient: 100/0–95/5) afforded amidoketals **5** (14.7 mg, 49.5 μmol, 43%) and **6** (11.8 mg, 34.6 μmol, 30%), conversion = 96%.

Data

5: two inseparable diastereoisomers (maj/min = 55/45). IR (CHCl₃): $\nu = 3615$ and 3590 (OH), 3440 and 3370 (NH), 1667 (CO) cm⁻¹. MS (CI): m/z (%) = 298 (100) [MH⁺], 266 (23) [MH⁺ - CH₃OH], 222 (17). HRMS (ESI): m/z calculated for [C₁₅H₂₃NO₅ + Na⁺]: 320.1474 ; found: 320.1485 .

Major isomer: ¹H NMR (CDCl₃): $\delta = 2.60$ (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, OCH₃), 3.37 (s, 3H, OCH₃), 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). ¹³C NMR (CDCl₃): $\delta = 41.4, 54.1, 55.9, 59.0, 66.3, 66.6, 71.7, 101.3, 126.8$ (2C), $127.8, 128.8$ (2C), $139.2, 169.5$.

Minor isomer: ¹H NMR (CDCl₃): $\delta = 2.59$ (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, OCH₃), 3.40 (s, 3H, OCH₃), 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). ¹³C NMR (CDCl₃): $\delta = 40.9, 53.7, 55.7, 59.0, 65.3, 66.1, 71.7, 101.1, 126.8$ (2C), $127.7, 128.8$ (2C), $139.2, 169.5$.

6: $[\alpha]_D^{25} = -23.5$ (c 0.71, CHCl₃). IR (CHCl₃): $\nu = 3615$ and 3590 (OH), 3440 and 3370 (NH), 1667 (CO) cm⁻¹. ¹H NMR (CDCl₃): $\delta = 2.68$ (d, 2H, 2 H-2, $J = 5.2$), 3.25 (br. s, 1H, OH), 3.34 (s, 3H, OCH₃), 3.35 (s, 3H, OCH₃), 3.54 (m, 2H, OCH₂), 3.57 (m, 2H, OCH₂), 3.68 (m, 2H, OCH₂), 3.78 (m, 2H, OCH₂), 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). ¹³C NMR (CDCl₃): $\delta = 41.5, 55.7, 59.0$ (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 [C₁₇H₂₇NO₆ + Na⁺]: 364.1736 ; found: 364.1724 .

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

To a suspension of LiAlH₄ (57 mg, 1.5 mmol) in THF (1 mL), NEt₃ (60 μ L of a 1 M solution in THF, 60 μ mol, 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 H₂O (270 μ L, 15 mmol). The precipitates were filtrated and washed with THF (1 mL)

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and CH₂Cl₂ (1 mL). The organic layers were dried on MgSO₄ and evaporated under vacuum. Purification by flash chromatography (silica gel) with Et₂O/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: $[\alpha]_{\text{D}}^{25} = -73.9$ (*c* 0.42, CHCl₃). IR (CHCl₃) $\nu = 3368$ and 3342 (NH) cm⁻¹. ¹H NMR, COSY ¹H-¹H (CDCl₃): $\delta = 1.79$ (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 OCH₃), 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). ¹³C NMR, HSQC (CDCl₃): $\delta = 31.6$ (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⁺ – CH₃OH], 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 [C₂₄H₃₄N₂O₄ + H⁺]: 415.2596; found: 415.2584.

8: $[\alpha]_{\text{D}}^{25} = -59.0$ (*c* 0.28, CHCl₃). IR (CHCl₃): $\nu = 3420$ (NH), 1660 (CO) cm⁻¹. ¹H NMR, COSY ¹H-¹H (CDCl₃): $\delta = 1.70$ (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, OCH₃), 3.38 (s, 3H, OCH₃), 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). ¹³C NMR, HSQC (CDCl₃): $\delta = 31.6$, 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⁺ – CH₃OH], 371 (8), 339 (5). HRMS (ESI): *m/z* calculated for [C₂₄H₃₂N₂O₅ + H⁺]: 429.2390; found: 429.2390.

9: $[\alpha]_{\text{D}}^{25} = 37.8$ (*c* 0.34, CHCl₃). IR (CHCl₃): $\nu = 3440$ (NH), 1670 (CO), 1610 (C=C) cm⁻¹. ¹H NMR, COSY ¹H-¹H (CDCl₃): $\delta = 1.78$ (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, OCH₃), 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, $J = 8.4$). ¹³C NMR, HSQC (CDCl₃): $\delta = 31.6, 44.6, 49.5, 51.9, 63.8, 70.3, 79.1, 104.1, 104.6, 127.0$ – 128.9 (10C), 140.2 (2C), 152.6, 164.7. MS (CI): m/z (%) = 397 (100) [MH⁺], 365 (45) [MH⁺ – CH₃OH], 339 (27). HRMS (ESI) m/z calculated for [C₂₃H₂₈N₂O₄ + H⁺]: 397.2127; found: 397.2128.

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