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A New and Rapid Access to a 14-Membered Diketal Dilactam Ring

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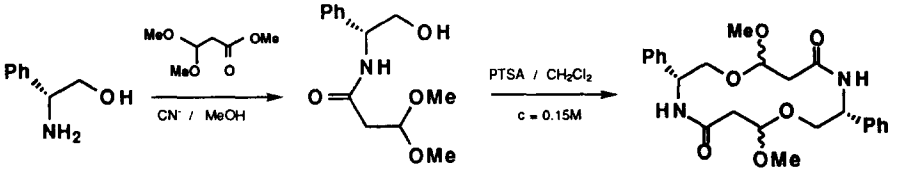
Abstract: Macrocyclic dioxadilactam **2** was obtained in two steps from *R*-(-)-phenylglycinol *via* the chiral amido-ketal **1**. Cyclization of **1** in acidic conditions (PTSA) and concentrated solution (c = 0.15 M) afforded **2** as three diasteromers **2a+2b+2c**, two of which show a C-2 symmetry.

Natural macrocyclic molecules are well known for their biological importanc as antibiotics, hormones and as ions carriers.[1-3] Their activities, in relation with their binding abilities, are believed to be largely determined by their three dimensional arrangement in space.[1,2] Among these macrocyclic structures, polyether-lactams.[2,4,5] which are synthetic intermediates of azacrowns[6] exhibit specific properties[7] and can act as hosts for biological molecules,[8] or be strongly donating *N*-ligands for transition metal complexes[9] or neutral ionophores for alkaline earth ions.[3,10]

In most cases, the elaboration of the lactam ring involves the reaction of activated diacids with diamines.[2, 5a,6b,11] In a more specific case, macrocyclic diazadilactams can be obtained by dimerization of azapenams.[12] For our part, we envisaged building a macrocycle from substrates already containing the amide function and a transacetalation seemed to be an attractive process.

Herein we report the rapid synthesis of a new 14-membered ring: the dioxadilactam **2**. Our scheme is based on the acid catalyzed cyclization of a chiral hydroxy-amido ketal **1**. The latter was obtained in 69% yield by condensation of 3,3-dimethoxy methylpropionate on a chiral amino-alcohol *i.e.* *R*-(-)-phenylglycinol, in the presence of catalytic amount of potassium cyanide (MeOH, 60°C, 5 days).[13] Compound **1** exhibits three reactive centers: ketal, amide and primary alcohol functions, and its cyclization to a 4, 7 or 14 membered rings might be expected.



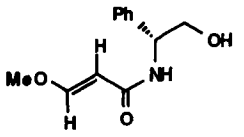
R-(-)-phenylglycinol **1** **2**

The cyclization of **1** was studied in various acidic conditions. The most significant experimental results are reported in Table. In the presence of $TiCl_4$ or $SnCl_4$ (exp 1 and 2), the reaction partially gave rise to an elimination derivative **3** and essentially tended towards polymer formation. With $BF_3.OEt_2$, two products were generated; the difluoroboroenolate **4**[14] was obtained in 72% yield at high dilution (exp 3) while a more concentrated solution afforded dilactam **2** in appreciable yield (exp 4). Using camphorsulfonic acid (CSA), the reaction led to unsaturated ether **3** and dilactam **2**; however the reaction was incomplete at 40°C (exp 5) while at higher temperature the yield of polymers increased (exp 6). The best result in dilactam formation (51% yield) was obtained with *p*-toluenesulfonic acid (PTSA) at 40°C under relatively concentrated solution (exp 8). The choice of the concentration was essential in the course of the reaction and the range allowing the formation of the 14-membered ring was quite small since the formation of dimer **2** resulted in both inter- and intramolecular

processes. Higher concentrations indeed led to further polymerisation.

Table

Exp	Acid nature	eq	Solvent	Concent.	T (t) °C (h)	1 %	2 %	3 %	4 %
1	$TiCl_4$	1.1	CH_2Cl_2	2.0×10^{-1}	0° (0.5)	4	4	10	-
2	$SnCl_4$	1.1	CH_2Cl_2	1.0×10^{-1}	-10° → +10° (0.5)	-	-	11	-
3	BF_3.OEt	1.25	CH_2Cl_2	5.0×10^{-3}	0° (2) → 20° (2)	5	7	-	72
4	BF_3.OEt	1.5	CH_2Cl_2	1.25×10^{-1}	0° (3) → 20° (2)	19	28	-	24
5	CSA	0.4	CH_2Cl_2 + 4Å m.s.	5.0×10^{-2}	40° (16)	50	25	10	-
6	CSA	0.15	Benzene + 4Å m.s.	1.8×10^{-2}	80° (15)	7	21	5	-
7	PTSA	0.1	CH_2Cl_2 + 4Å m.s.	5.0×10^{-2}	40° (4)	6	20	15	-
8	PTSA	0.1	CH_2Cl_2 + 4Å m.s.	1.5×10^{-1}	40° (10)	8	51	4	-



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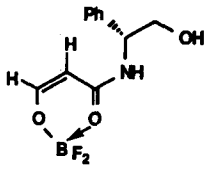

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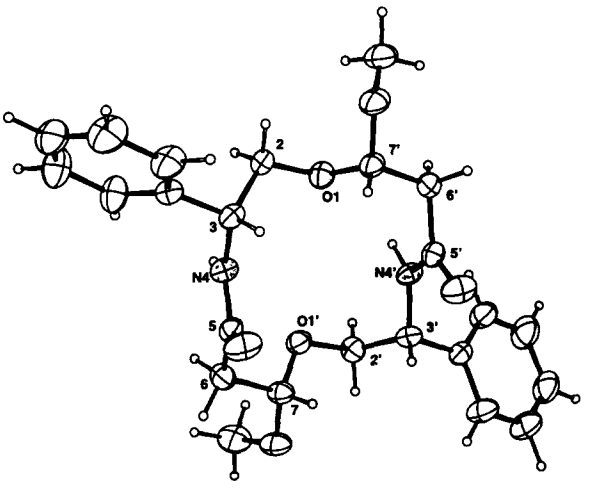
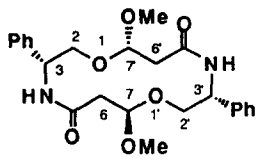
For exp. 8 (Table 1) the dilactam **2** was formed as three diastereomers **2a+2b+2c**[15] in a 37/8/55 ratio respectively. Isomers **2a** and **2b** were obtained as an inseparable mixture **2a+2b** (83/17). In contrast, the major isomer **2c** could be isolated pure. The structure and relative stereochemistry of each compound were inferred from NMR data (^1H , ^{13}C and 2D experiments). In ^1H and ^{13}C NMR spectra, isomer **2a** exhibited double signals for each pair of identical groups of the macrocycle *e.g.* the two OCH_3 signals appeared as two singlets at 3.14 and 3.16 ppm by ^1H NMR, and as two peaks at 52.4 and 53.8 ppm by ^{13}C NMR. In contrast isomers **2b** and **2c** showed one signal for each pair of identical groups *e.g.* the two OCH_3 signals appeared as one singlet at 3.25 ppm in **2b** and at 3.15 ppm in **2c** by ^1H NMR, and as one peak at 54.5 ppm in **2b** and at 53.2 ppm in **2c** by ^{13}C NMR. These data revealed an asymmetry of the two chains in compound **2a** and a total symmetry in compounds **2b** and **2c**. Moreover, an X-Ray diffraction analysis performed on **2c**[16] (Figure) allowed determination of absolute configurations 7*S* and 7'*S* and confirmed the C-2 symmetry of the macrocycle.

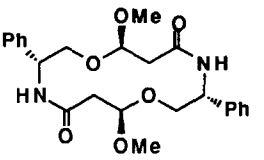


Figure

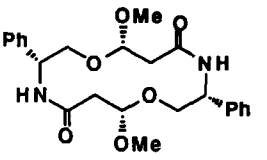
Consequently the following configurations could be inferred to the three isomers: **2a** (3*R*, 3'*R*, 7*R*, 7'*S*), **2b** (3R, 3'*R*, 7*R*, 7'*R*), **2c** (3*R*, 3'*R*, 7*S*, 7'*S*).



2a



2b



2c

As shown in Figure, the two amide nitrogens of the major compound **2c** point in the same direction, perpendicular to the macrocycle. The measured torsion angles confirmed the sp^2 character of the nitrogens, while the measured distances betweeen identical atoms of the dimeric macrocycle *e.g.* $d(N_4\text{-}N_4') = 4.14$ Å, $d(O_1\text{-}O_1') = 4.096$ Å gave the precise dimensions of the cage. Moreover in the crystal, the molecules are stacked along the binary axis and are linked by two hydrogen bonds NH--O [2.949(4) Å].
In conclusion, the reported synthesis constitues a new and rapid access (2 steps) to novel macrocyclic dioxadilactams substituted by two possible binding methoxy groups.[17] Generalization of this macrocyclization reaction to a large variety of non-racemic β-amino alcohols and study of their complexation with metal ions are under investigation.

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14. Selected spectra data for compound **4**: IR (neat) υ 3356, 1636 cm^{-1}; ^1H NMR (acetone D_6, 200 MHz) δ ppm: 3.75 (br. s, 1H, OH), 3.85 (dd, 1H, CH_B-O, J = 11.4, 7.0 Hz), 3.95 (dd, 1H, CH_A-O, J = 11.4, 4.7 Hz), 5.20 (ddd, 1H, CHPh, J = 8.4, 7.0, 4.7 Hz), 5.67 (d, 1H, =CH, J = 5.2 Hz), 7.30-7.50 (m, 6H, =CH-O + 5 Ar-H), 9.2 (br. s, 1H, NH); ^{13}C NMR (acetone D_6, 50 MHz) δ ppm: 57.9 (CHPh), 65.4 (CH_2O), 91.3 (=CH), 127.9-129.6 (5 Ar-CH), 139.3 (Ar-C), 167.3 (=CH-O), 169.7 (CO); MS (IE) *m/z* 224 [12, $M^{+\cdot}$-(^{11}B)-CH_2OH], 223 [3, $M^{+\cdot}$-(^{10}B)-CH_2OH], 205 (24, 224-F), 204 (4, 223-F), 154 (32), 153 (8), 149 (20), 106 (60), 91 (32), 28 (100).
15. Selected spectra data for isomers **2a**, **2b**, **2c**.

    2a : ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 2.58 (m, 3H, H-6B, H-6'B, H-6'A), 2.86 (dd, 1H, H-6A, J = 16.1, 8.4 Hz), 3.14 (s, 3H, OMe-8), 3.16 (s, 3H, OMe-8'), 3.71 (dd, 1H, H-2B, J = 9.5, 5.5 Hz), 3.74 (dd, 1H, H-2'B, J = 9.0, 3.3 Hz), 4.08 (dd, 1H, H-2A, J = 9.5, 3.2 Hz), 4.13 (dd, 1H, H-2'A, J = 9.5, 3.1 Hz), 4.77 (t, 1H, H-7, J = 8.4 Hz), 4.82 (dd, 1H, H-7', J = 6.9, 3.4 Hz), 5.29 (m, 1H, H-3'), 5.40 (ddd, 1H, H-3, J = 8.7, 5.5, 3.2 Hz), 6.77 (d, 1H, NH, J = 8.7 Hz), 7.25-7.39 (m, 10H, 10 Ar-H), 7.62 (d, 1H, NH', J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 39.8 and 41.3 (C-6, C-6'), 51.9 and 52.7 (C-3, C-3'), 52.4 and 53.8 (2 OCH_3), 67.1 and 70.1 (C-2, C-2'), 99.8 and 101.0 (C-7, C-7'), 126.6-128.7 (10 Ar-CH), 138.9 and 139.9 (2 Ar-C), 168.0 and 168.4 (2 CO).

    2b : ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 2.58 (m, 2H, H-6B, H-6B'), 2.80 (dd, 2H, H-6A, H-6'A, J = 16.0, 7.2 Hz), 3.25 (s, 6H, 2 OMe), 3.80 (dd, 2H, H-2B, H-2'B, J = 9.5, 4.4 Hz), 4.08 (dd, 2H, H-2A, H-2'A, J = 9.5, 3.2 Hz), 4.77 (m, 2H, H-7, H-7'), 5.29 (m, 2H, H-3, H-3'), 7.38 (d, 2H, 2NH), 7.25-7.39 (m, 10H, 10 Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 40.0 (C-6, C-6'), 52.5 (C-3, C-3'), 54.5 (2 OCH_3), 67.6 (C-2, C-2'), 101.1 (C-7, C-7'), 127.3-127.8 (10 Ar-CH), 139.5 (2 Ar-C), 167.9 (2 CO).

    2c : white solid; mp 235-240°C (MeOH); $[\alpha]_D^{25}$ -84.0 (c 3.2, $CHCl_3$); IR ($CHCl_3$) υ 3390, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 2.60 (dd, 2H, H-6B, H-6B', J = 14.5, 3.3 Hz), 2.64 (dd, 2H, H-6A, H-6'A, J = 14.5, 6.2 Hz), 3.15 (s, 6H, 2 OMe), 3.82 (dd, 2H, H-2B, H-2'B, J = 9.6, 3.3 Hz), 4.05 (dd, 2H, H-2A, H-2'A, J = 9.6, 4.9 Hz), 4.78 (dd, 2H, H-7, H-7', J = 6.2, 3.2 Hz), 5.28 (ddd, 2H, H-3, H-3', J = 8.0, 4.9, 3.3 Hz), 7.09 (d, 2H, 2NH, J = 8.0 Hz), 7.28-7.40 (m, 10H, 10 Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 41.2 (C-6, C-6'), 52.5 (C-3, C-3'), 53.2 (2 OCH_3), 70.5 (C-2, C-2'), 101.2 (C-7, C-7'), 126.7-128.6 (10 Ar-CH), 139.3 (2 Ar-C), 168.4 (2 CO); MS (FAB$^+$) *m/z* 443 (98, MH^+), 411 (73), 222 (94), 190 (39), 149 (30), 126 (66), 121 (100), 103 (73). Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.37; H, 6.89; N, 6.32.
16. Crystal structure of compound **2c**. Crystal data: C_{24} H_{30} N_2 O_6, M_w = 442.51, monoclinic, space group C 2, Z = 2, a = 17.975 (12), b = 4.987 (5), c = 14.888 (8) Å, β = 120.86 (3)°, V= 1145 (1) $Å^3$, d_{calc} = 1.28 g cm^{-3}, F(000) = 472, λ (Cu Kα) = 1.5418 Å, μ = 0.72 mm^{-1}. Enraf-Nonius CAD-4 diffractometer. (θ-2θ) scan technique up to θ = 66°. Of the 3871 collected reflexions ($-20 \le h \le 20$, $-5 \le k \le 5$, $-17 \le l \le 17$), 1997 were unique (R_{int} = 0.095) of which 1758 were considered as observed having $I \ge 3.0\ \sigma(I)$. R = 0.048 and R_w = 0.067 (with $R_w = [\sum w(Fo-|Fc|)^2 / \sum wFo^2]^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.0013\ Fo^2]$. The residual electron density in the final difference map was located between -0.30 and 0.63 e $Å^3$. The structure was solved by direct methods using *SHELXS86* and refined by full-matrix least-squares with *SHELX76*, minimizing the function $\sum w(Fo-|Fc|)^2$. The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions (d(C-H) 1.00 Å). Atomic coordinates, bond lenghts, bond ans torsion angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. UK.
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