Published in Monatshefte für Chemie / Chemical Monthly 140, issue 3, 349-354, 2009
which should be used for any reference to this work

Macrocyclisation of 2-(5-(2-hydroxyethyl)furan-2-yl)acetic acid model compounds of nonactic acid

Carine Eng · Jean-Mary Simone · Akane Hartenbach · François Loiseau · Reinhard Neier

Abstract The macrocyclisation of hydroxyethylfuranyl acetic acid and of dehydrogenated model compounds of nonactic acid was investigated to develop a facile synthesis of nonactin analogues. By applying the Yamagushi macrocyclisation to our ω-hydroxyacids, we were able to isolate a mixture of di-, tri-, tetra- and pentameric macrocycles.

Keywords Heterocycles · Macrocycles · Natural product analogues · Nonactin · Protecting groups

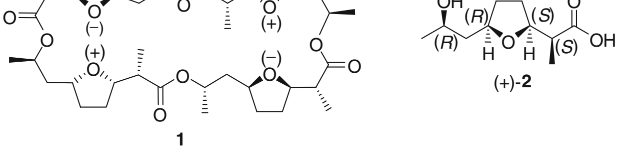
Introduction

Nonactin (**1**), a macrotetralide antibiotic, is used as an ionophore in ammonium ion selective electrodes. First reported in 1955 [1], **1** is isolated from *Streptomyces* cultures and is the lowest homologue of the nactin family. Nonactin (**1**) consists of four nonactic acids (**2**) (Scheme 1) condensed in a (+)(−)(+)(−) atypical fashion, which confers S_4 symmetry (*meso* compound) to this macrocycle. To the best of our knowledge, six total syntheses of nonactin have been reported in the literature [2–7]. Two methodologies have been used to assemble the four nonactic acid units to obtain **1**. The first methodology consists in a step-by-step assembly of the four units of nonactic acids to obtain a linear tetramer. To achieve this stepwise condensation, selective O-deprotections of both the alcohol and carboxylic acid ends have to be achieved. The final step is the macrocyclisation of the linear tetramer. The second method consists in the cyclodimerisation of a linear dimer composed of two nonactic acids. The reported syntheses of **1** do not compete successfully with fermentation [8]. Nonactin (**1**) is therefore expensive. The major difficulties encountered to date are the making of (+) and (−)—nonactic acids (**2**) in enantiopure form and the controlled assembly of the enantiomers to the macrotetralide.

As part of our ongoing studies on macrocycle **1**, we have developed a method for synthesising 2,5-disubstituted furans and tetrahydrofurans as nonactic acid precursors and analogues [9–11]. The key steps used to introduce the alkyl chains to the furan ring are radical couplings. We report here the O-deprotection of the 2,5-disubstituted furans **3**–**5**, and the cyclopolymerisation of ω-hydroxyacids **9** and **10** under Yamagushi's conditions (Scheme 2).

Results and discussion

We studied first the selective O-debenzylation of the 2,5-disubstituted furans **3**–**5**. Deprotecting the furans **3**–**5** was not a trivial undertaking. Neither hydrogenations using catalysts, such as rhodium over alumina, Pd/C or *Raney*-Ni catalysts, nor debenzylation using MeI/TMSCl in MeCN, $Pd(OH)_2/Et_3SiH/Et_3N$ in CH_2Cl_2 or $SnCl_4$ in CH_2Cl_2 gave



1

(+)-**2**

Scheme 1

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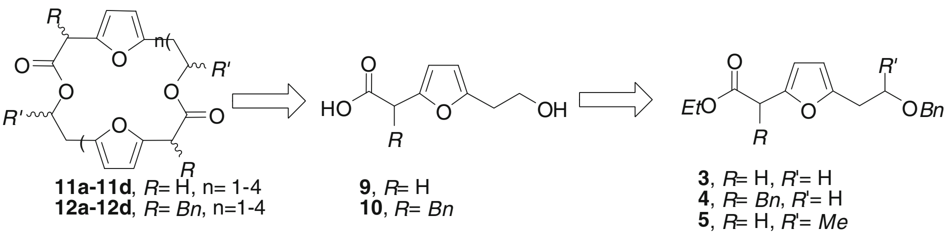
Scheme 2

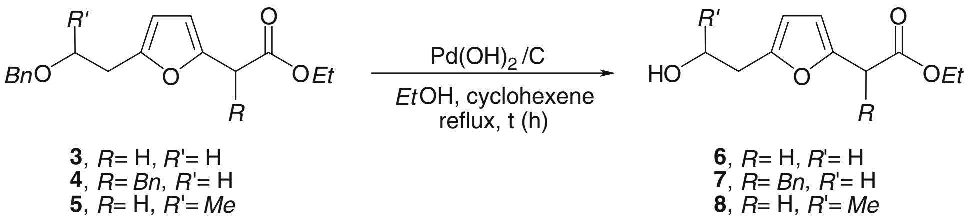


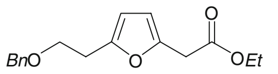
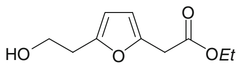
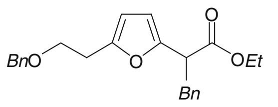
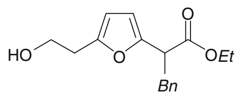
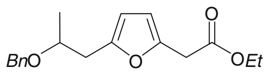
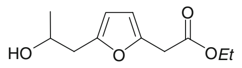
the deprotected products in good selectivity and high yields. Applying Hanessian's transfer hydrogenation conditions [12]—Pd(OH)$_2$ and cyclohexene in refluxing EtOH—to our substrates resulted in a high selectivity of the expected O-debenzylated products **6–8** in 71–90% yields (Table 1).

Using the conditions reported by Schmidt et al. [13], we were able to saponify the ethylesters of alcohols **6** and **7** using KOH in EtOH at room temperature. To avoid polymerisation of the ω-hydroxyacids **9** and **10** that formed, substrates **6** and **7** had to be submitted only for a short time to the reaction conditions (Table 2).

With the unstable ω-hydroxyacids **9** and **10** in hand, we studied the Yamagushi macrocyclisation conditions [14], which are known to give good yields of macrocycles, minimizing the amount of linear polymers formed [15]. Treating monomer **9** under these macrocyclisation conditions, we obtained a mixture of di-, tri-, tetra- and pentamer **11a**– in almost a 77% overall yield. As **1** is known to effectively complex potassium cations, we hoped that the tetramer of our furan analogue would also be stabilized by complexation to potassium cations. We attempted to take advantage of a template effect using K$_2$CO$_3$ [16] in order to increase the proportion of the tetramer. The application of Yamagushi conditions to monomer **10** in the presence of added K$_2$CO$_3$ did not favour the amount of tetramer formed. Under these modified conditions, the overall yield of macrocycles **12a–d** decreased drastically. The use of the potassium cation has been reported to increase the yield of calix [9–11] furan formation [16], while chelation can be used for the assembly of furan rings into a macrocycle. In our case, the rigid furan rings reduce the flexibility needed for the assembly into macrocycles. This may explain why chelation with potassium decreased the yield of macrocycle formation.

Table 1 O-debenzylation under Hanessian's conditions



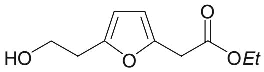
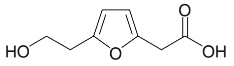
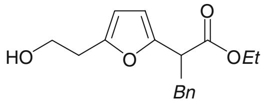
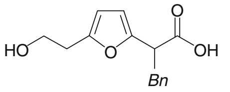
Reagent	t/h	Product and yield
 **3**	4[a]	 **6**, 90%
 **4**	4	 **7**, 71%
 **5**	2.5	 **8**, 90%

[a] Decreasing the reaction time to 1 h 40 afforded 87% yield

Table 2 Saponification of the ethyl ester function

6, *R*= H
7, *R*= *Bn*

9, *R*= H
10, *R*= *Bn*

Reagent	t/min	Product and yield
 **6**	30	 **9**, 95%
 **7**	30	 **10**, 98%

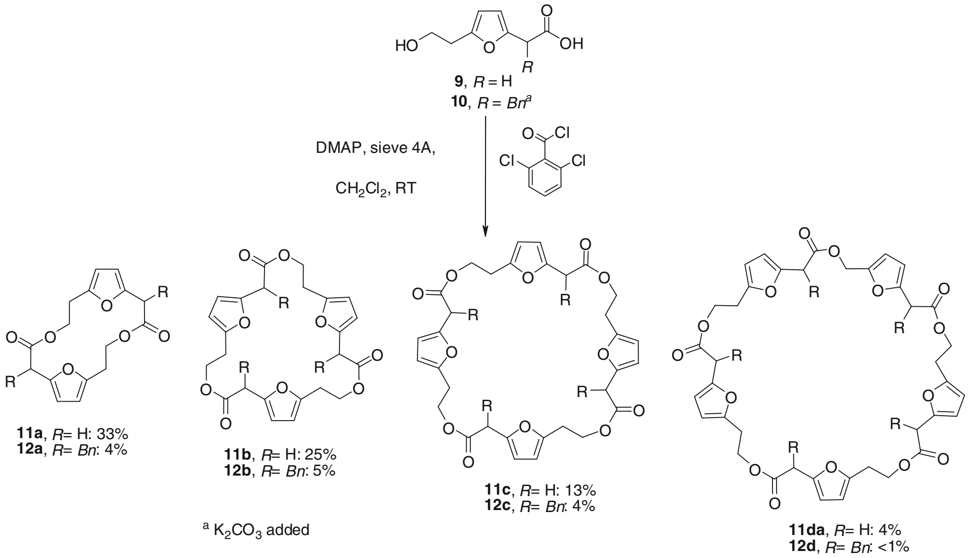
To reduce the amount of the di- and trimer formed, we worked at higher dilutions—unfortunately, also without success (Scheme 3).

In conclusion, we have achieved the macrocyclisation of ω-hydroxyacids **9** and **10**. This direct macrocyclisation represents a very short method to producing furan-containing macrotetralides. These furan-containing macrotetralides represent interesting precursors for the synthesis of nonactin and analogues of nonactin. To study the ionophore properties of these macrocycles, which can be obtained by reduction from our products, we are currently investigating methods for the catalytic hydrogenation of the furan rings.

Experimental

All moisture-sensitive reactions were carried out under Ar and N_2 using oven-dried glassware. All reagents were of commercial quality if not specifically mentioned. Solvents were freshly distilled prior to use. Flash chromatography (FC): Brunschwig silica gel 60, 0.032–0.063 mm; positive pressure. Thin-lay chromatography (TLC): Merck precoated silica gel thin-layer sheets 60 F 254; detection by UV and treatment with basic $KMnO_4$ solvent. Mp: Gallenkamp MFB–595. IR spectra: Perkin Elmer Spectrum One FT-IR, in cm^{-1}. NMR spectra: Bruker Avance-400 [400 MHz

Scheme 3



9, *R* = H
10, *R* = *Bn*[a]

11a, *R*= H: 33%
12a, *R*= *Bn*: 4%

11b, *R*= H: 25%
12b, *R*= *Bn*: 5%

11c, *R*= H: 13%
12c, *R*= *Bn*: 4%

11da, *R*= H: 4%
12d, *R*= *Bn*: <1%

[a] K_2CO_3 added

(^{1}H) and 100 MHz (^{13}C)], at room temperature (rt), chemical shifts δ in ppm relative to $CDCl_3$ ($^{1}H = 7.264$ ppm, $^{13}C = 77.0$ ppm) as internal reference, coupling constants J in Hz. ESI-MS Finnigan LCQ. HR-ESI-MS analyses of novel compounds agreed favourably with calculated values (Fig. 1).

General procedure for O-debenzylation under Hanessian's conditions

Palladium hydroxide over charcoal (10%) was added to the benzylether and freshly distilled cyclohexene in EtOH, and the mixture was refluxed. After several hours, the mixture was filtered on celite and the volatiles removed by evaporation in vacuo. The residue was purified by chromatography on a silica gel column using *n*-hexane/AcOEt as an eluent.

*Ethyl [5-(2-hydroxyethyl)-furan-2-yl]acetate (**6**, $C_{10}H_{14}O_4$)*
General procedure with 1.22 g of **3** (4.24 mmol), 24 cm^3 of cyclohexene and 0.23 g of palladium hydroxide over charcoal in 48 cm^3 of EtOH over a 4-h period. Thus, 0.75 g of product **6** (3.80 mmol, 90%) was obtained. Oil; $R_f = 0.06$ (*n*-hexane/AcOEt 75/25 + 1% MeOH); IR (film): $\bar{\nu} = 3{,}440$, 2,982, 1,740, 1,644, 1,614, 1,566, 1,467, 1,446, 1,397, 1,371, 1,338, 1,266, 1,228, 1,186, 1,097, 1,031, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.14$ (d, J = 3.1, H-4), 6.06 (dd, J = 3.1, H-5), 4.19 (q, J = 7.1, H-1^1), 3.86 (t, J = 6.2, H-8), 3.65 (s, H-2), 2.88 (t, J = 6.2, H-7), 1.93 (br, OH), 1.29 (t, J = 7.1, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.1$ (C-1), 152.8 (C-3), 147.1 (C-6), 109.1 (C-4), 107.9 (C-5), 61.6 (C-1^1), 61.5 (C-8), 34.6 (C-2), 32.0 (C-7), 14.5 (C-1^2) ppm; ESI-MS: $m/z = 221$ (100, $[M + Na]^+$).

*Ethyl [5-(2-hydroxyethyl)-furan-2-yl]-3-phenyl propionate (**7**, $C_{17}H_{20}O_4$)*
General procedure with 842 mg of **4** (2.23 mmol), 12 cm^3 of cyclohexene and 0.13 g of palladium hydroxide over charcoal in 24 cm^3 of EtOH over a 4-h period. Thus, 458 mg of product **7** (1.59 mmol, 71%) was obtained. Oil; $R_f = 0.07$ (*n*-hexane/AcOEt 75/25 + 1% MeOH); IR (film): $\bar{\nu} = 3{,}446$, 3,087, 3,063, 3,030, 2,980, 2,959, 2,935, 1,736, 1,605, 1,560, 1,496, 1,455, 1,370, 1,334, 1,277, 1,217, 1,153, 1,096, 1,078, 1,034, 790, 749, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$–7.14 (m, *Ph*), 6.14 (d, J = 3.2, H-4), 6.04 (d, J = 3.2, H-5), 4.10-4.16 (m, J = 7.2, Ha-1^1), 4.105 (dq, J = 10.9, J = 7.2, Hb-1^1), 3.96 (t, J = 7.9, H-2), 3.85 (t, J = 6.2, H-8), 3.31 (dd, J = 13.7, J = 8.3, Ha-2^1), 3.19 (dd, J = 13.7, J = 7.6, Hb-2^1), 2.88 (t, $J \approx 6.0$, H-7), 1.78 (br, OH), 1.18 (t, J = 7.1, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.8$ (C-1), 152.5 (C-3), 150.9 (C-6), 138.9, 129.3, 128.7, 127.0, 108.2 (C-4), 107.9 (C-5), 61.6 (C-8, C-1^1), 37.6 (C-2^1), 32.0 (C-7), 14.5 (C-1^2) ppm; ESI-MS: $m/z = 312$ (30), 311 (100, $[M + Na]^+$).

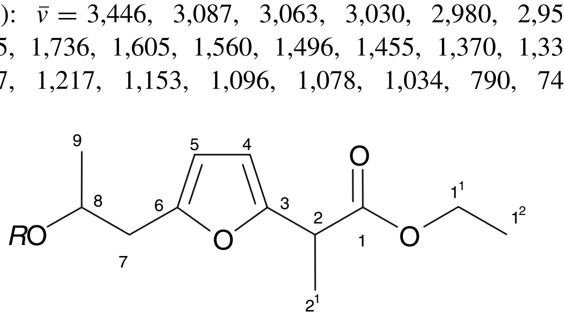


Fig. 1 Labeling used for nuclear magnetic resonance assignment

*Ethyl [5-(2-hydroxypropyl)-furan-2-yl]acetate (**8**, $C_{11}H_{16}O_4$)*
General procedure with 705 mg of **5** (2.33 mmol), 12 cm^3 of cyclohexene and 0.14 g of palladium hydroxide over charcoal in 25 cm^3 of EtOH over a 2.5-h period. Thus, 445 mg of product **8** (2.10 mmol, 90%) was obtained. Oil; $R_f = 0.09$ (*n*-hexane/AcOEt 75/25 + 1% MeOH); IR (film): $\bar{\nu} = 3{,}432$, 2,975, 2,932, 1,740, 1,614, 1,565, 1,447, 1,402, 1,370, 1,338, 1,268, 1,233, 1,182, 1,082, 1,031, 1,015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.14$ (d, J = 3.1, H-4), 6.06 (d, J = 3.1, H-5), 4.19 (q, J = 7.1, H-1^1), 4.12–4.04 (m, H-8), 3.65 (s, H-2), 2.79 (dd, J = 14.9, J = 4.6, Ha-7), 2.71 (dd, J = 14.9, J = 7.6, Hb-7), 1.96 (br, OH), 1.28 (t, J = 7.1, H-1^2), 1.24 (d, J = 6.2, H-9) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$ (C-1), 152.8 (C-3), 147.2 (C-6), 109.1 (C-4), 108.4 (C-5), 67.1 (C-8), 61.6 (C-1^1), 38.3 (C-7), 34.6 (C-2), 23.0 (C-9), 14.5 (C-1^2) ppm; ESI-MS: $m/z = 236$ (12), 235 (100, $[M + Na]^+$).

General procedure for ethyl ester deprotection

A 2 *M* solution of KOH in EtOH was added to the ethyl ester at room temperature. After 30 min, the mixture was acidified with 32% HCl and the product extracted twice with AcOEt. The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation in vacuo of the volatiles resulted in the product, which contained traces of AcOH.

*2-(5-(2-hydroxyethyl)furan-2-yl)acetic acid (**9**, $C_8H_{10}O_4$)*
General procedure with 683 mg of ester **6** (3.44 mmol) in 10 cm^3 of 2 *M* solution of KOH in EtOH. Two extractions with 80 cm^3 of AcOEt each time afforded 559 mg **9** (3.28 mmol, 95%) with approximately 63 mg of AcOH. Oil; IR (film): $\bar{\nu} = 3{,}600$–3,300, 2,962, 2,338, 1,718, 1,644, 1,617, 1,567, 1,400, 1,376, 1,236, 1,046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.38$–6.20 (br, OH, CO_2H), 6.16 (d, J = 3.1, H-4), 6.06 (d, J = 3.1, H-5), 3.87 (t, J = 6.2, H-8), 3.69 (s, H-2), 2.87 (t, J = 6.2, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.0$ (C-1), 153.0 (C-3), 146.4 (C-6), 109.6 (C-4), 108.0 (C-5), 61.4 (C-8), 34.2

(C-2), 31.8 (C-7) ppm; ESI-MS: *m*/*z* = 194 (10), 193 (100, $[M + Na]^+$), 143 (11).

*2-(5-(2-hydroxyethyl)furan-2-yl)-3-phenylpropanoic acid (**10**, $C_{15}H_{16}O_4$)*

General procedure with 253 mg of ester **7** (0.88 mmol) in 5 cm^3 of 2 *M* solution of KOH in EtOH. Two extractions with 25 cm^3 of AcOEt each time afforded 224 mg **10** (0.86 mmol, 98%) with approximately 10 mg of *Ac*OH. Oil; IR (film): $\bar{\nu}$ = 3,600–3,000, 3,063, 3,030, 2,959, 2,632, 1,713, 1,605, 1,584, 1,560, 1,496, 1,455, 1,393, 1,235, 1,180, 1,078, 1,033, 789, 738, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.13 (m, *Ph*), 7.13–6.12 (br, OH, CO_2H), 6.12 (d, *J* = 3.2, H-4), 6.04 (d, *J* = 3.2, H-5), 4.00 (t, *J* = 7.8, H-2), 3.85 (t, *J* = 6.2, H-8), 3.34 (dd, *J* = 13.8, *J* = 7.6, Ha-2^1), 3.20 (dd, *J* = 13.8, *J* = 8.0, Hb-2^1), 2.88 (t, *J* = 6.2, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9 (C-1), 152.8 (C-3), 149.9 (C-6), 138.5 (C-2^2), 129.2, 128.8, 127.1, 108.9 (C-4), 108.0 (C-5), 61.4 (C-8), 47.4 (C-2), 37.2 (C-2^1), 31.9 (C-7) ppm; APCI-MS: *m*/*z* = 279 (20), 278 (28, $[M + H_2O]^+$), 277 (24),.262 (19), 261 (100, $[M + H]^+$), 257 (15), 143 (32), 216 (15), 215 (91), 197 (33).

*Synthesis of macrocycles **11a–11d** from acid **9***

Acid **9** (73 mg, 85% purity, 362 μmol) and 168 mg DMAP (1.38 mmol) were dissolved in 30 cm^3 of CH_2Cl_2 under an argon atmosphere in the presence of 2 g molecular sieve (4 Å). At RT, 2, 0.08 cm^3, 113 mg 6-dichlorobenzoyl chloride (539 μmol) was added. After 23 h, the molecular sieve was filtered off, and the organic layer was washed with three times with 0.3 *M* HCl. The combined aqueous layers were extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$). The volatiles were removed by evaporation in vacuo. The residue was purified by chromatography on a silica gel column using *n*-hexane/AcOEt as an eluent, and four macrocycles were isolated. These are, in order of decreasing polarity: 184 mg dimer **11a** (60.5 μmol, 33.4 %), 137 mg trimer **11b** (30.0 μmol, 24.9%), 1.2 mg tetramer **11c** (2.0 μmol, 2.2%), 7.0 mg of a second isomer of the tetramer **11c** (11.5 μmol, 12.7%) and 1.9 mg pentamer **11d** (2.5 μmol, 3.5%). The overall yield is 76.7%.

*4,13,19,20-Tetraoxatricyclo[14.2.1.$1^{7,10}$]icosa-1(18)7,9,16-tetraene-3,12-dione **11a***

Oil; R_f = 0.5 (after three elutions in *n*-hexane/AcOEt 75/25 + 1% *Me*OH); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.00 (d, *J* = 3.1, H-4), 5.92 (d, *J* = 3.1, H-5), 4.37 (t, *J* = 5.6, H-8), 3.60 (s, H-2), 2.90 (t, *J* = 5.6, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (C-1), 151.8 (C-3), 146.7 (C-6), 109.0 (C-4), 108.0 (C-5), 63.3 (C-8), 35.1 (C-2), 27.9 (C-7) ppm; ESI-MS: *m*/*z* = 625 (11), 327 (100, $[M + Na]^+$).

*4,13,22,28,28,30-Hexaaoxatetracyclo [23.2.1.$1^{7,10}$.$1^{16,19}$]triaconta-1(27)7,9,16,18,25-hexaene-3,12,21-trione **11b***

Oil; R_f = 0.34 (after three elutions in *n*-hexane/AcOEt 75/25 + 1% MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.06 (d, *J* = 3.1, H-4), 5.94 (d, *J* = 3.1, H-5), 4.35 (t, *J* = 6.1, H-8), 3.63 (s, H-2), 2.92 (t, *J* = 6.1, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (C-1), 151.8 (C-3), 146.8 (C-6), 109.1 (C-4), 107.8 (C-5), 63.4 (C-8), 34.8 (C-2), 28.0 (C-7) ppm; ESI-MS: *m*/*z* = 480 (24), 479 (100, $[M + Na]^+$).

*4,13,22,31,37,39,40-Octaaoxapentacyclo [32.2.1.$1^{7,10}$.$1^{16,19}$.$1^{25,28}$]tetraconta-1(36)7,9,16,18,25,27,34-octaene-3,12,21,30-tetrone **11c***

Oil; R_f = 0.11 (after three elutions in *n*-hexane/AcOEt 75/25 + 1% MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.08 (d, *J* = 3.1, H-4), 5.96 (d, *J* = 3.1, H-5), 4.34 (t, *J* = 6.5, H-8), 3.63 (s, H-2), 2.93 (t, *J* = 6.5, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (C-1), 151.7 (C-3), 146.8 (C-6), 109.1 (C-4), 107.8 (C-5), 63.4 (C-8), 34.6 (C-2), 28.0 (C-7) ppm; ESI-MS: *m*/*z* = 632 (28), 631 (100, $[M + Na]^+$).

*4,13,22,31,40,46,47,48,49,50-Decaaoxahexacyclo [41.2.1.$1^{7,10}$.$1^{16,19}$.$1^{25,28}$.$1^{34,37}$]pentaconta-1(45)7,9,16,18,25,27,34,36,43-decaene-3,12,21,30,39-pentone **11d***

Oil; R_f = 0.04 (after three elutions in *n*-hexane/AcOEt 75/25 + 1% MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.09 (d, *J* = 3.1, H-4), 5.97 (d, *J* = 3.1, H-5), 4.34 (t, *J* = 6.6, H-8), 3.63 (s, H-2), 2.94 (t, *J* = 6.6, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (C-1), 151.7 (C-3), 146.8 (C-6), 109.1 (C-4), 107.8 (C-5), 63.4 (C-8), 34.6 (C-2), 28.0 (C-7) ppm; ESI-MS: *m*/*z* = 785 (11), 784 (36), 783 (100, $[M + Na]^+$), 632 (23), 631 (100).

*Synthesis of macrocycles **12a–12d** from acid **10***

Acid **10** (220 mg, 761 μmol) and 300 mg DMAP (2.46 mmol) were dissolved in 45 cm^3 of CH_2Cl_2 under an argon atmosphere in the presence of 2.3 g molecular sieve (4 Å) and 0.65 g K_2CO_3 (4.70 mmol). After 45 min, 0.14 cm^3 2,6-dichlorobenzoyl chloride (977 μmol) was added. After 23 h, the molecular sieve was filtered off, and the organic layer was washed three times with 0.3 *M* HCl. The combined aqueous layers were extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$). The volatiles were removed by evaporation in vacuo. The residue was purified by chromatography on a silica gel column using *n*-hexane/AcOEt as an eluent, and three macrocycles were isolated. The products were, in order of decreasing polarity: 6.5 mg dimer **12a** (13.4 μmol, 3.5 %), 9.6 mg trimer **12b** (13.2 μmol, 5.2%), 7.3 mg tetramer **12c** (7.5 μmol, 4.0%); traces of the probable pentamer **12d** may be identified on the TLC. The overall yield is 12.7%.

2,11-Bis(phenylmethyl)-4,13,19,20-tetraoxatricyclo[14.2.1.1^{7,10}]icosa-1(18)7,9,16-tetraene-3,12-dione ***12a***

Oil; $R_f = 0.29$ (*n*-hexane/AcOEt 75/25 + 1% MeOH); ESI-MS: *m*/*z* = 1,170 (13), 1,169 (16), 992 (13), 991 (19), 508 (34), 507 (100, $[M + Na]^+$).

2,11,20-Tris(phenylmethyl)-4,13,22,28,28,30-hexaaoxatetracyclo[23.2.1.1^{7,10}.1^{16,19}]triaconta-1(27)7,9,16,18,25-hexaene-3,12,21-trione ***12b***

Oil; $R_f = 0.19$ (*n*-hexane/AcOEt 75/25 + 1% MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.11 (m, *Ph*), 5.98–5.96 (m, H-4), 5.82–5.80 (m, H–5), 4.40–4.10 (m, H-8), 3.96–3.91 (m, H-2), 3.33–3.20 (m, Ha-2^1), 3.15 (dd, *J* = 13.7, *J* = 7.1, Hb-2^1), 2.84 (t, *J* = 5.8, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.5$ (C-1), 151.62, 151.59, 151.55, 151.52 (C-4), 150.5, 150.4 (C-6), 138.9 (C-2^2), 129.3, 128.8, 126.9 (*Ph*), 108.3, 108.2 (C-4), 107.7 (C-5), 63.23, 63.18 (C-8), 47.8 (C-2), 37.3, 37.2 (C-2^1), 28.0 (C-7) ppm; ESI-MS: *m*/*z* = 751 (14), 750 (52), 749 (100, $[M + Na]^+$).

2,11,20,29-Tetrakis(phenylmethyl)-4,13,22,31,37,39,40-octaaoxapentacyclo[32.2.1.1^{7,10}.1^{16,19}.1^{25,28}]tetraconta-1(36)7,9,16,18,25,27,34-octaene-3,12,21,30-tetrone ***12c***

Oil; $R_f = 0.14$ (*n*-hexane/AcOEt 75/25 + 1% MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.11 (m, *Ph*), 6.00–5.97 (m, H-4), 5.81–5.77 (m, H-5), 4.30–4.11 (m, H-8), 3.92 (t, *J* = 7.8, H-2), 3.31–3.25 (m, Ha-2^1), 3.14 (dd, *J* = 13.8, *J* = 7.2, Hb-2^1), 2.80 (t, *J* = 6.7, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.5$ (C-1), 151.4 (C-4), 150.5, 150.4 (C-6), 138.8 (C-2^2), 129.3, 128.8, 126.9 (*Ph*), 108.4, 108.3 (C-4), 107.7 (C-5), 63.2 (C-8), 47.7 (C-2), 37.2 (C-2^1), 28.0, 27.3 (C-7) ppm; ESI-MS: *m*/*z* = 993 (22), 992 (65, $[M + Na]^+$), 991 (100), 837 (11), 749 (12).

Acknowledgments The NMR spectra (400 MHz) were measured by Heinz Bursian and Dr. Claude Saturnin, the mass spectra by Dr. Manuel Tharin and Dr. Bernard Jean-Denis. We thank the University of Neuchâtel and the Swiss National Science Foundation for financial support.

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