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Concave Reagents. 12 [1]

Polymerfixation of Concave Pyridines

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Abstract. Via a metal ion template directed synthesis and a high dilution cyclization, a bimacrocyclic 4-benzyloxyethoxy-substituted concave pyridine **8** was synthesized from dialdehyde **3**, diamine **4** and diacyl dichloride **7** in 54 % overall yield. Pd-catalyzed hydrogenolysis of **8** afforded the OH-substituted concave pyridine **9** which could be attached to a Merrifield resin **10** after deprotonation with NaH. The modified polymer **11** contained 10 % (w/w) of **8**.

Convave bases have been investigated in model reactions [2] and selectivity increases by the use of these reagents have been found in several cases [2a – c]. But for a larger scale application of the concave pyridines or the concave 1,10-phenanthrolines [3], the problem of recovery of these reagents has not yet been solved satisfactorily (recycling via chromatography).

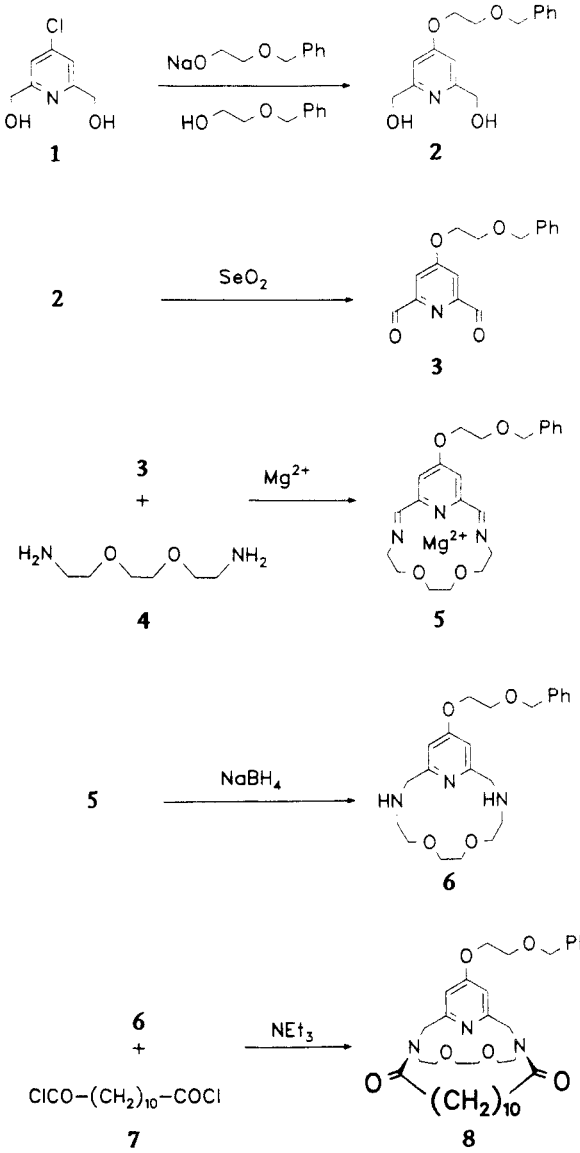
In this paper we describe the fixation of a concave pyridine to a Merrifield resin. In order to avoid any blocking of the concave reaction site of the concave pyridine by the polymer network, we connected the concave pyridine to the polymer via its convex back side by a spacer[1]. Therefore a substituent had to be introduced into the 4-position of the pyridine ring.

In theory, two pathways towards a polymer bound concave pyridine are conceivable: (i) the concave pyridine is synthesized first and is **then** covalently bound to the polymeric resin, or (ii) the concave pyridine is built up stepwise **on** the polymer. The latter method however has the draw-back that by-products will remain on the polymer. Because the selectivity of the resulting mixture of polymer bound molecules in model reactions would not be predictable, we have chosen the first approach. The Scheme shows the synthesis of a concave pyridine which contains a glycol unit as a spacer in 4-position. Via the ω-hydroxyl function of the glycol, the concave pyridine was then connected to the Merrifield resin. During the synthesis of the concave pyridine, however, it was necessary to protect this hydroxyl group.

The synthetic route towards concave pyridines has already been worked out [3, 4, 5]. A benzyl group seemed to be a promising OH-protective group because during the synthesis a variety of different reaction conditions exist (oxidation, reduction, acidic and basic milieu). Analogous to the introduction of a methoxy group, we introduced a benzyloxyethoxy unit into the 4-position of a pyridine-2,6-dimethanol **1** (see scheme). The following steps were straightforward: The oxidation of the resulting bisalcohol **2** with SeO_2 to the dialdehyde **3** (87 %) was followed by the Mg^{2+}-templated condensation with 3,6-dioxaoctane-1,8-diamine (**4**). The resulting bis(Schiff base) **5** was not isolated but was reduced by $NaBH_4$ to the macrocyclic diamine **6** (crude yield 88 %, based on **3**). This macrocycle **6** was bridged with the diacyl dichloride **7** under high dilution conditions to give the bimacrocyclic concave pyridine **8** in 61 % yield.

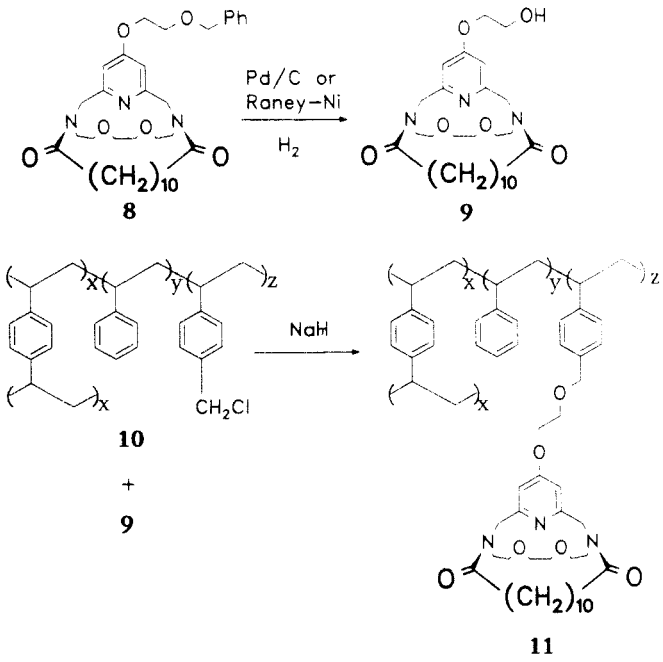
This concave pyridine **8** showed the same behaviour as the parent compounds with a hydrogen atom or a methoxy-substituent in the 4-position [4, 5a]. In the ^{1}H-NMR spectrum, three amide conformers (*ZZ*, *ZE* and *EE*) could be observed in a 53 : 27 : 20 ratio.

[1] A spacer reduces the influence of the polymeric backbone on the reactive site of the concave pyridine. However if the spacer were too long, there would be a chance that the concave pyridine folds back onto the polymer. Therefore a limited length of the spacer (5 atoms between the aromatic rings of the polymer and the concave pyridine) was used.



To deprotect this benzyloxy-substituted concave pyridine **8** a variety of catalysts were checked in catalytic hydrogenolyses. The difficulty in this reductive cleavage is the fact that a benzyl ether shall be cleaved in the presence of heterobenzylic amide groups in the 2- and 6-positions of the pyridine. The best method was a low conversion hydrogenolysis of **8** with Pd/C (10 %) in ethyl acetate with recovery and recycling of still protected **8** . After two cycles, the yield of the deprotected bimacrocyclic pyridine **9** was 43 % (at a conversion of 88 %). 25 % yield could be obtained when the hydrogenolysis was carried out with Raney-Ni in ethanol.

Before the concave base **9** could be connected to the polymer **10**, the reaction conditions had to be worked out in model reactions. The first investigation determined NaH (in excess) as a base which could deprotonate the OH-group of **9** without side-reactions.

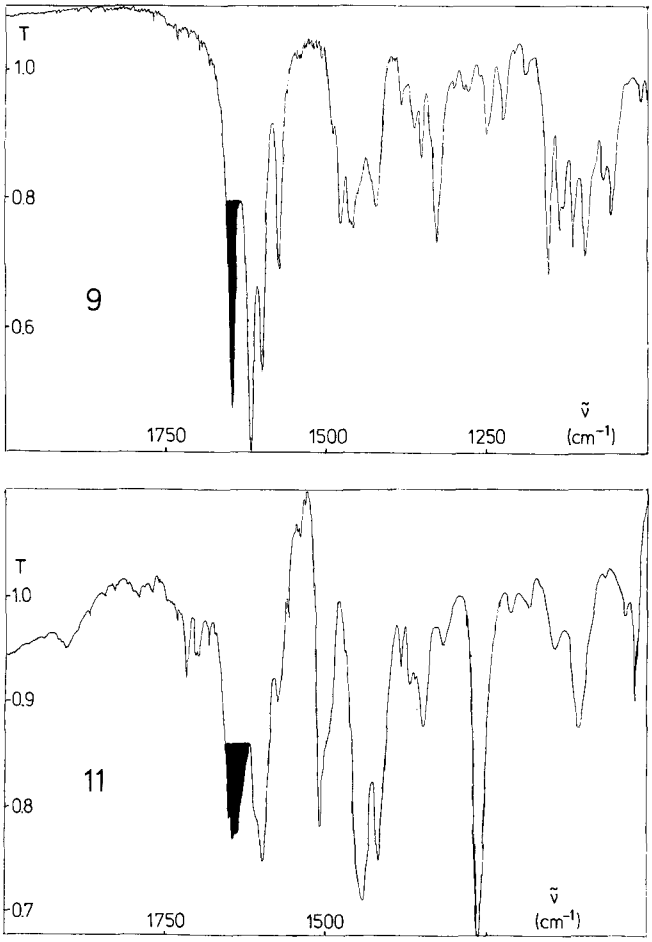


The resulting anion was alkylated with the monomer analog of the Merrifield resin **10**, benzyl chloride. Quantitative alkylation gave the benzyl protected concave pyridine **8** which was proven by TLC and ^{1}H-NMR.

The second investigation examined the nucleophilic displacement of the chlorine atoms of the polymer **10**. Methoxy and benzyloxyethoxy anions were reacted with the resin **10** in a variety of solvents. In all cases substitution could be observed (elemental analyses). Higher reaction temperatures (refluxing N,N-dimethylacetamide or diglyme) gave higher degrees of substitution, but because at these temperatures the concave pyridine **9** is not infinitively stable in the presence of NaH, refluxing THF was used as the solvent during the coupling of **9** to the polymer **10** (for details see Experimental). After the coupling of the concave base **9** to the Merrifield resin **10**, excess NaH was hydrolyzed, and the polymer **11** was washed extensively and was dried in vacuo. FT-IR spectra of resin **10**, the concave base **9** and the modified polymer **11** proved[2] the fixation of the concave pyridine (see Figure 1). Via elemental analysis and via titration, the amount of bound concave pyridine per g of resin could be measured: 0.15 – 0.17 mmol (92 – 104 mg) of **8** / g resin.

Thus, it could be shown that concave pyridines may be attached to polymers which will facilitate their recovery (filtration). But it is also conceivable to fill a column with a polymeric concave reagent and to pass substrates through such a column continuously.

[2] The concave base is covalently bound to the polymer and not absorbed because in an experiment where the deprotonation of **9** failed it could be shown that **9** could be removed from the Merrifield resin completely by extraction.



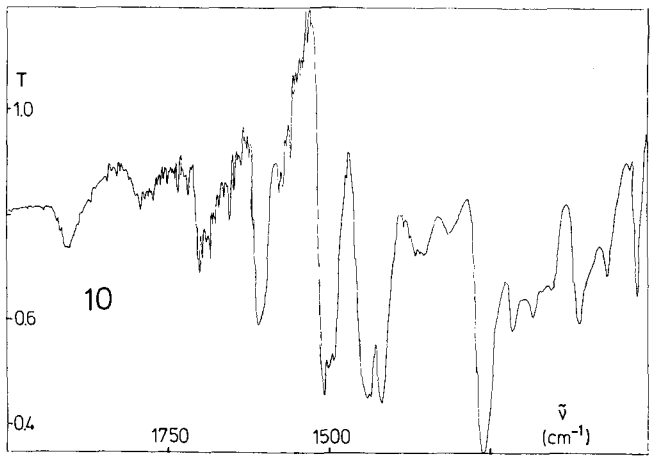


Fig. 1 Comparison of the FT-IR spectra (wave number vs. transmission) of the concave base **9**, the Merrifield resin **10** and the functionalized polymer **11**. The amide absorptions at 1645 cm^{-1} of the concave pyridines are blackened.

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Experimental

General remarks: see [5].
FT-IR: Perkin-Elmer IFS 25.

4-(2-Benzyloxyethoxy)-pyridine-2,6-dimethanol (**2**)

During 5 min, 6.90 g (288 mmol) of NaH which had been washed with dry petroleum ether (b. p. 30 – 50 °C) was added to 200 g (1.32 mol) of 2-benzyloxyethanol [6] which was stirred and cooled by ice. Then slowly 5.0 g (29 mmol) of 4-chloropyridine-2,6-dimethanol (**1**) [3] was added to the orange reaction mixture. After 15 min of stirring, the mixture was heated to 150 °C (bath temperature) for 4 h. Already after 3 h, TLC (silica gel, ethyl acetate/conc. methanolic ammonia 10 : 1, $R_f = 0.23$) showed complete conversion of the educt **1**. To isolate the product, ca. 150 g of the solvent was distilled off at 15 Torr, the mixture was cooled to room temp., diluted with 100 ml of water, cooled and neutralized with 2 N HCl until pH 4 was reached. After separation of the layers, the organic layer was extracted five times with 100 ml of 2 N HCl. The aqueous layers were poured into ca. 350 ml of 4 N NaOH immediately. A white solid precipitated, water was distilled off until the mixture was concentrated to 200 ml, and then this alkaline mixture (pH 13) was extracted five times with 100 ml of diethyl ether. After the organic layer was dried with $MgSO_4$, evaporation of the solvent yielded 21.8 g of a mixture of **2** and benzylglycol ether [7]. Chromatography (silica gel, ethyl acetate/conc. methanolic ammonia 10 : 1) gave 1.84 g (21 %) of **2**, m.p. 66 – 67 °C. – IR (KBr): $\nu = 3500 - 3100\ cm^{-1}$ (O-H), 1590, 1560 (arom.), 1140, 1070 (C-O). – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.79$ (m_c, 2H), 3.9 (br.s, >2H), 4.15 (m_c, 2H), 4.58 (s, 2H), 4.63 (s, 4H), 6.71 (s, 2H), 7.25 – 7.38 (m, 5H). – MS (EI, 70 eV): *m/z* (%) = 289 (100), 288 (55), 155 (90), 91 (36).

$C_{16}H_{19}NO_4 \cdot 0.5\ H_2O$	Calcd.	C 64.42	H 6.76	N 4.70
(298.33)	Found	C 64.50	H 6.47	N 4.84

4-(2-Benzyloxyethoxy)pyridine-2,6-dicarbaldehyde (**3**)

To 500 mg (1.7 mmol) of 4-(2-benzyloxyethoxy)pyridine-2,6-dimethanol (**2**) in 50 ml of peroxide-free dioxane containing 5 % of water, 200 mg (1.7 mmol) of SeO_2 was added. The mixture was heated to reflux and turned first

brown then black. After 2 h, TLCs (silica gel, ethyl acetate/dichlorormethane 3 : 1; $R_f = 0.79$) showed that the mixture did not change its composition anymore. The hot mixture was filtered through layers of celite and $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography (silica gel treated with 5 % water, ethyl acetate/dichloromethane 3 : 1). Besides the bisaldehyde **3**, also the 40 mg (9 %) of 4-(2-benzyloxyethoxy)-6-(hydroxymethyl)-2-pyridinecarbaldehyde was obtained. The still redish product **3** was sublimed at 0.02 Torr and a bath temp. of 75 °C to give 430 mg (87 %) of **3**, m.p. 61 °C. – IR (KBr): $\nu = 1700\,cm^{-1}$ (C=O), 1570, 1550 (arom.), 1105, 1040 (C-O). – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.85$ (m_c, 2H), 4.31 (m_c, 2H), 4.59 (s, 2H), 7.24 – 7.38 (m, 5H), 7.65 (s, 2H), 10.08 (s, 2H). – MS (EI, 70 eV): *m/z* (%) = 286 (7), 285 (35), 180 (48), 179 (63), 152 (74), 105 (100).

$C_{16}H_{15}NO_4$	Calcd.	C 67.36	H 5.30	N 4.91
(285.3)	Found	C 67.25	H 5.39	N 4.87

16-(2-Benzyloxyethoxy)-6,9-dioxa-3,12,18-triazabicyclo [12.3.1]octadeca-1(18),14,16-trien (**6**)

Under nitrogen 420 mg (2.8 mmol) of 3,6-dioxaoctan-1,8-diamine (**4**) was added to a stirred solution of 800 mg (2.8 mmol) of 4-(2-benzyloxyethoxy)-pyridine-2,6-dicarbaldehyde (**3**) and 570 mg (2.8 mmol) of $MgCl_2 \cdot 6H_2O$ in 50 ml of dry methanol. After 15 min at room temp. and 15 min at reflux temp. TLC (silica gel, ethyl acetate/methanol 3 : 1) showed complete conversion. Then at 0 °C, 530 mg (14 mmol) of $NaBH_4$ was added to the yellow mixture. Hydrogen evolved and the solution turned lighter, then redish brown. After 2 h, TLC (silica gel, ethanol/conc. NH_4OH 5 : 1) showed complete reduction. After hydrolysis with 20 ml of water, the redish milky suspension was stirred for 30 min and extracted three times with 50 ml of dichloromethane. After drying with $MgSO_4$ and evaporation of the solvent, 1.46 g of crude **6** remained. 25 ml of toluene and 25 ml of chloroform was added and the mixture was sonicated in an ultrasonic bath for 2 min. After filtration and evaporation of the solvents, 1.0 g (88 %) of **6** remained. Further purification by chromatography [silica gel, (1) dichloromethane/ethanol 10 : 1 (to eluate impurities), (2) ethanol/conc. NH_4OH 5 : 1 (to eluate **6**)] was possible and gave **6** as a colorless oil. – IR (KBr): $\nu = 3300\,cm^{-1}$ (N-H), 1590, 1560 (arom.) 1150 – 1070 (C-O). – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 2.81$ (t, $J = 5.25$ Hz, 4H), 3.50 (br. s, 4H, H_2O, NH), 3.60 (s, 4H), 3.66 (t, $J = 5.25$ Hz, 4H), 3.77 (m_c, 2H), 3.80 (s, 4H), 4.13 (m_c, 2H), 4,59 (s, 2H), 6.54 (s, 2H), 7.24 – 7.38 (m, 5H). – MS (EI, 70 eV): *m/z* (%) = 402 (6), 401 (24), 298 (28), 284 (27), 91 (100).

$C_{22}H_{31}N_3O_4 \cdot H_2O$	Calcd.	C 62.99	H 7.93	N 10.02
(419.51)	Found	C 63.27	H 7.60	N 10.01

26-(2-Benzyloxyethoxy)-17,20-dioxa-1,14,30-triazatricyclo[12.8.7.1^{24,28}]triaconta-24,26,28(30)-trien-2,13-dione (**8**)

Via two simultaniously driven 100 ml syringes, 400 mg (1.0 mmol) of crude 16-(2-benzyloxyethoxy)-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene (**6**) in 200 ml of dry THF (5 mM) and 267 mg (1.0 mmol) of dodecan-1,10-dioyl dichloride (**7**) in 200 ml of dry THF (5 mM) were synchronously added to 0.6 g (6 mmol) of dry triethylamine in 200 ml of dry THF with a rate of ca. 20 ml/h. After the solutions were added the mixture was stirred for additional 30 min, the precipitate (triethylamine hydrochloride) was filtered off and the solvent was evaporated in vacuo and the residue was dissolved in 50 ml of dichloromethane. This solution was washed with 2 ml of 2N NaOH, dried with $MgSO_4$ and concentrated to dryness. 1.2 g of crude material remained which was purified by chromatography (silica gel, dichloromethane/ethanol 10 : 1) giving 360 mg (61 %) of **8**. – IR (KBr): $\nu = 1645\,cm^{-1}$ (C=O), 1590, 1560 (arom.), 1150 – 1030 (C-O). – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 1.1 - 1.8$ (m, 10H), 2.1 – 2.6 (2m, 4H), 2.91 – 4.08 (m, 8H), 3.80 (m, 2H), 4.14 (m_c, 2H), 4.33 (d, $J = 15.7$ Hz, 0.16H), 4.42 (d, $J = 17.2$ Hz, 0.5H), 4.59, 4.61 (2s, 2H), 4.76 (d, $J = 15.7$ Hz, 0.16H), 4.79 (d, $J = 17.2$ Hz, 0.5H), 5.24 (d, $J = 15$ Hz, 0.16H), 5.34 (d, $J = 15$ Hz, 0.16H), 6.54 (s, 1.09H), 6.59, 6.72 (2d, $J = 3$ Hz, 0.55H), 6.83 (s, 0.36H), 7.25 – 7.37 (m, 5H). – MS (EI, 70 eV): *m/z* (%) = 598 (5), 597 (20), 595 (55), 91 (100). – MS (high resolution/$C_{34}H_{49}N_3O_6$): calcd./found = 595.7796/595.3607

$C_{34}H_{49}N_3O_6 \cdot H_2O$	Calcd.	C 66.53	H 8.38	N 6.86
(613.81)	Found	C 66.70	H 8.64	N 6.87

26-(2-Hydroxyethoxy)-17,20-dioxa-1,14,30-triazatricyclo-[12.8.7.1^{24,28}]triaconta-24,26,28(30)-trien-2,13-dione (**9**)

By Stepwise Hydrogenolysis with Pd/C (10 %) in Ethyl Acetate: To 700 mg (1.2 mmol) of **8** which was dissolved in ca. 100 ml of dry ethyl acetate, 200 mg of Pd/C (10 %) was added and hydrogen was added at 50 °C. After the consumption of ca. 26 ml of hydrogen (calculated amount), TLC (silica gel, dichlorethane/ethanol 10 : 1) showed educt **8** ($R_f = 0.53$), product **9** ($R_f = 0.3$) and by-products ($R_f = 0.08$ and 0). Chromatography (silica gel, dichloromethane/ethanol 10 : 1) gave 180 mg (31 %) of the desired product **9** and 380 mg (54 %) of the educt **8** which was subjected to hydrogenolysis again giving additional 70 mg **9** and 110 mg of the starting material **8**. Conversion in two cycles: 84 %, yield of **9**: 43 %, still remaining educt **8**: 16 %. – IR (KBr): $\nu = 3340\,cm^{-1}$ (OH), 1630 (C=O), 1605, 1590, 1560, (arom.), 1150 – 1090 (C-O). – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 0.88 - 1.84$ (m, 20H), 2.06 – 2.60 (2m, 4H), 2.72 – 4.22 (m, 8H), 3.92 (m_c, 2H), 4.06 (m_c, 2H), 4.31 (d, $J = 16.5$ Hz, 0.16H), 4.39 (d, $J = 17.3$ Hz, 0.5H), 4.74 (d, $J = 16.5$ Hz, 0.16H), 4.77 (d, $J = 17.3$ Hz, 0.5H), 5.18 (d, $J = 15$ Hz, 0.16H), 5.29 (d, $J = 15$ Hz, 0.16H), 6.54 (s, 1.05H), 6.57, 6.71 (2d, $J = 2$ Hz, 0.55), 6.80 (s, 0.4H). – MS (EI, 70 eV): *m/z*(%) = 506 (21), 505 (69), 167 (100). – MS (high resolution, $C_{27}H_{43}N_3O_6$): calcd./found = 505.6549/505.3146.

By Catalytic Hydrogenolysis with Raney-Ni in Ethanol: 210 mg (0.35 mmol) of **8** was dissolved in ca. 100 ml of dry ethanol containing 100 mg of Raney-Ni. During 24 h the mixture consumed ca. 50 ml of hydrogen at 50 °C. After addition of 100 mg of catalyst, again 50 ml of hydrogen was consumed. The mixture was then filtered through celite and the solvent was evaporated in vacuo. The yellow residue (65 mg) was analyzed by TLC (silica gel, dichloromethane/ethanol 10 : 1) and purified by chromatography (TLC-conditions) to give 16 mg (25 %) of **9**.

Model reaction: 26-(2-Benzyloxyethoxy)-17,20-dioxa-1,14,30-triazatricyclo[12.8.7.1^{24,28}]triaconta-24,26,28(30)-trien-2,13-dione (**8**) *by Benzylation of 26-(2-Hydroxyethoxy)-17,20-dioxa-1,14,30-triazatricyclo-[12.8.7.1^{24,28}]triaconta-24,26,28(30)-trien-2,13-dione* (**9**)

58 mg (0.12 mmol) of the deprotected bimacrocycle **9** was dissolved in 10 ml of dry THF and treated with 5 mg (0.2 mmol) of NaH which had been washed twice with 5 ml of dry petroleum ether (b.p. 30 – 50 °C) and had then been dried in vacuo. After refluxing for 10 min, 100 mg (0.8 mmol) of benzyl chloride was added. TLC (silica gel, ethyl acetate/conc. methanolic ammonia 10:1) and ^{1}H-NMR analysis showed quantitative alkylation to **8**.

Coupling of **9** *with Merrifield resin* (**10**)

680 mg of Merrifield resin **10** (Lancaster Synthesis Ltd, crosslinked with 2% divinylbenzene, ca. 5.5 mmol Cl/g; elemental analysis: 5.8 mmol Cl/g) were soaked in 50 ml of dry THF for 24 h. Then 130 mg (5.4 mmol) of NaH [previously washed twice with 5 ml of petroleum ether (b.p. 30 – 50 °C) and dried in vacuo] and 180 mg (0.36 mmol) of **9** was added and the mixture was heated to reflux for 24 h. At 0 °C, excess NaH was hydrolyzed, the polymer was filtered off and washed twice with 10 ml of water and twice with 10 ml of dichloromethane. The filtrate was extracted twice with 20 ml of dichloromethane, the extract was dried with $MgSO_4$ and evaporated to dryness. 90 mg remained which could be identified as **9** (^{1}H-NMR). The polymer **11** was washed with DMF (2 × 10 ml), dioxane (2 × 10 ml), dichloromethane (2 × 10 ml), and methanol (2 × 10 ml) and dried in vacuo. *Caution*: loss of polymer **11** may occur due to its dustiness. Yield: 640 mg. FT-IR: see Figure 1.

Elemental analysis (two experiments):
Found: C 75.04 Cl 7.87 H 6.34 N 0.61

Titration: 300 mg of functionalized polymer **11** were stirred with 2.00 ml (0.200 mmol) of a 0.1 N ethanolic *p*-TosOH·H_2O solution for 5 min. After filtration, the polymer **11** was washed five times with 1 ml of dry ethanol (the last batch was neutral). The combined ethanolic layers were titrated with 0.084 N ethanolic KOH (indicator: thymol blue, color change from red to yellow). 1.78 ml (0.150 mmol) were needed, therefore 300 mg of the polymer **11** had bound 0.050 mmol of acid.

Contents of bound concave pyridine in the polymer **11**:
By elemental analysis (calculated via the N contents): 0.15 mmol (92 mg) of **8**/g resin. By titration: 0.17 mmol (104 mg) of **8**/g resin.

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