Concave Pyridines with Extended π-Systems[‡]

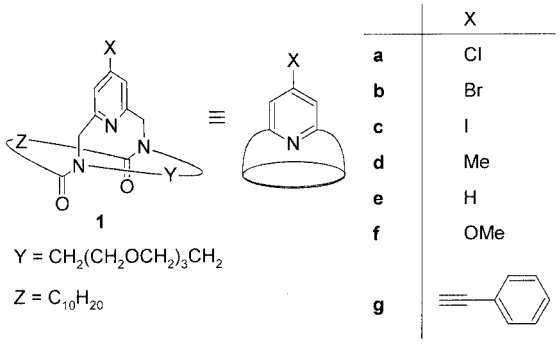
Ole Storm,[a] Ulrich Lüning*[a]

Keywords: Acetylenes / Concave reagents / Macrocycles / Sonogashira coupling / UV spectra

New 4-substituted concave pyridines **1b–d** have been synthesised as precursors to allow extension of the pyridine π-system. With the Sonogashira coupling as the key synthetic step, the 4-iodo pyridine **1c** was coupled with phenylacetylene (**11**) to give **1g** in 77% yield. Because of its conjugated π system, the new concave pyridine **1g** has UV absorption maxima at λ_{max1} = 286 nm and λ_{max2} = 303 nm with ε_{max1} = 43300 $Lmol^{-1}cm^{-1}$ and ε_{max2} = 39300 $Lmol^{-1}cm^{-1}$, respectively, allowing its potential application as a sensor.

Introduction

The concept of concave reagents mimics the nature of enzymes, through the incorporation of a functional group in a concave environment.[1–3] One such class of reagents is that of concave pyridines such as **1** (Scheme 1).[4–6] The pyridine nitrogen atom is the most basic centre, and can thus be used either as a concave base or, in protonated form, as a concave acid.[7] Furthermore, this pyridine nitrogen atom can form hydrogen bonds, a fact that has been exploited in the activation of hydroxyl groups. When alcohols are mixed with ketenes, and pyridines are added, the rate of addition of the alcohol to the ketene is enhanced.[8] If a concave pyridine is used as the catalyst, the special geometry of the concave pyridine **1** is responsible for an enhanced selectivity. This not only makes it possible to differentiate between different alcohols (primary, secondary and tertiary[9]), but also allows selective acylation of one OH group in a polyol, in a sugar derivative for instance.[10]



Scheme 1

The selectivity-determining step is still unknown. On one hand, the concave shielding of the pyridine nitrogen atom in a concave reagent may influence the stability of the hydrogen-bonded complexes between the alcohol and the ketene. Additionally, though, the accessibility of the oxygen atom of the alcohol in such a complex will be different for complexes composed of various alcohols and various ketenes.

The formation of a hydrogen bond can be investigated by various means, such as by studying alterations of spectroscopic properties upon complexation.[11] As well as study of hydrogen bond formation between an alcohol and a concave pyridine **1** in homogeneous solution, the possibility of investigating the formation of hydrogen bonds between hydroxyl groups of a surface and hydrogen bond acceptors is also extremely interesting, since this would allow the characterisation of surfaces of − for example − silica gels or celluloses, to name just a few.

The use of concave pyridines **1** in such an investigation could allow the accessibility of different hydroxyl groups on such surfaces to be studied. Differentiation between hydroxyl groups at edges or faces of crystals might be conceivable. In order to "see" these differences − by microscope, for example − the concave pyridine **1** would have to be attached to a reporter group, which would allow the formation of the hydrogen bond to be recognized.

Such a target molecule would therefore have to contain the following domains: (i) the recognition site for the hydroxyl group, which is the concave pyridine, and (ii) a chromophore that would allow analysis by UV/Vis spectroscopy or by fluorescence techniques. In order to provide the maximum change in the spectroscopy, the reporter group and the pyridine should be conjugated, preferentially through the 4-position of the pyridine ring.

[‡] Concave Reagents, 38. Part 37: U. Lüning, M. Abbas, F. Fahrenkrug, *Eur. J. Org. Chem.* **2002**, 3294–3303.

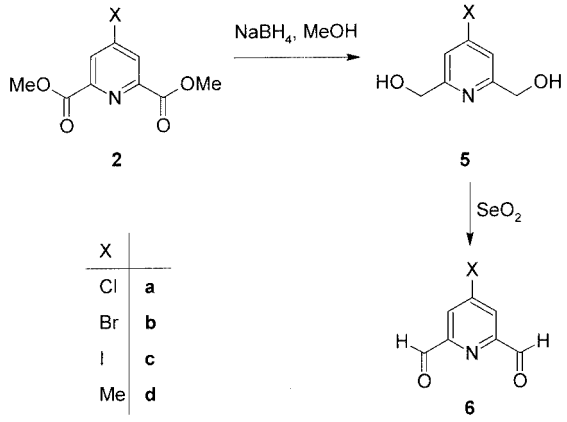
[a] Institut für Organische Chemie, Universität Kiel, Olshausenstr. 40, 24098 Kiel, Germany
Fax: (internat.) +49−(0)431/880 1558
E-mail: luening@oc.uni-kiel.de

Concave pyridines **1** have already been attached to a polymeric resin[12,13] and to dendrimers.[14,15] In both cases the connecting functional group was a benzyl ether. For the synthesis of a large delocalised π-system incorporating the pyridine nitrogen, several different synthetic approaches are conceivable. To allow broad variation of both chromophore and pyridine [e.g., different side chains Y and Z (see Scheme 1)], a functionality should be incorporated into the 4-position of the pyridine early in the synthesis. After the synthesis of the 4-substituted concave pyridine **1**, easy connection to various chromophores should be possible.

Retrosynthetic analysis offers two possibilities: the 4-position of the pyridine should either carry a leaving group, to be substituted by a carbon fragment [by palladium-catalysed cross coupling reactions[16] with an alkyne (Sonogashira),[17] an alkene (Heck) or a stannyl compound (Stille), for instance], or a carbon atom should already be bound in the 4-position, with subsequent C-C bond formation reactions such as the long known aldol condensation being used to extend the substituted pyridine.[18]

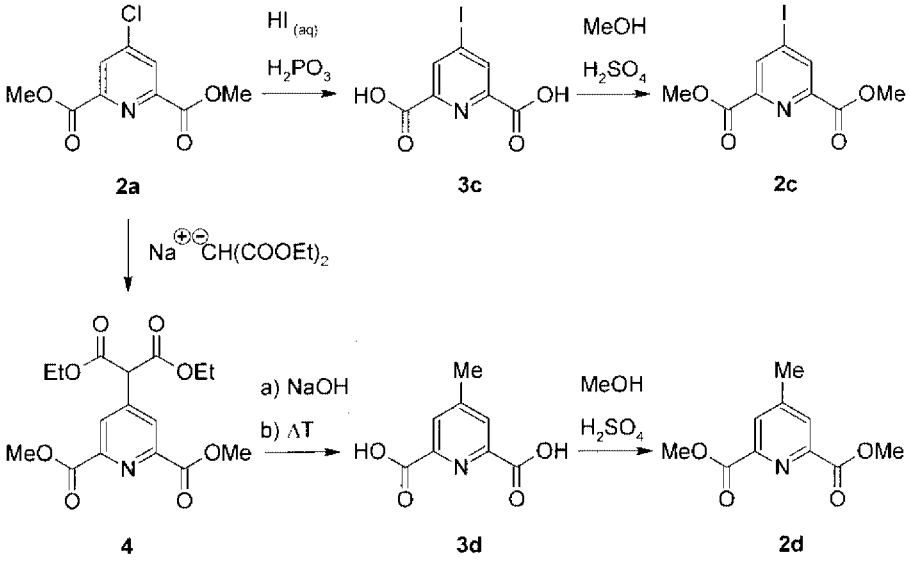
2,4,6-Substituted pyridine precursors are needed for both approaches. Such a substitution pattern is easily accessible from chelidamic acid (4-hydroxypyridine-2,6-dicarboxylic acid[19,20]). Treatment with PCl_5 produces 4-chloropyridine-2,6-dicarboxylic acid dichloride, which reacts with methanol to give dimethyl 4-chloropyridine-2,6-dicarboxylate (**2a**).[21]

The analogous bromo compound **2b** has been synthesised by use of PBr_5 in place of PCl_5.[22] Iodine can be introduced by treatment of **2a** with aqueous HI, although the diester is hydrolysed during the workup process to give the diacid **3c** (Scheme 2). The ester functionality is therefore reestablished in a second reaction step, by esterification with methanol in the presence of concentrated sulfuric acid. The 4-iododiester **2c** can thus be synthesised in 63% yield based on **2a**. Starting from the 4-chlorodiester **2a**, a methyl group can also be introduced into the 4-position by using malonate as the nucleophile as described previously.[23,24] Hydrolysis of the resulting product **4** and decarboxylation gives 4-methylpyridine-2,6-dicarboxylic acid (**3d**). Subsequent esterification with methanol in the presence of concentrated sulfuric acid gives the 4-methyl-substituted diester **2d** in 37% yield (over three steps). From the diesters **2a–d,** the dialdehydes **6a–d** can be obtained in two steps, firstly by reduction to the dialcohols **5a–d** with sodium borohydride and then by oxidation with selenium dioxide (Scheme 3). This transformation gives the dialdehydes **6** in overall yields of 45–63% (two steps).[25]



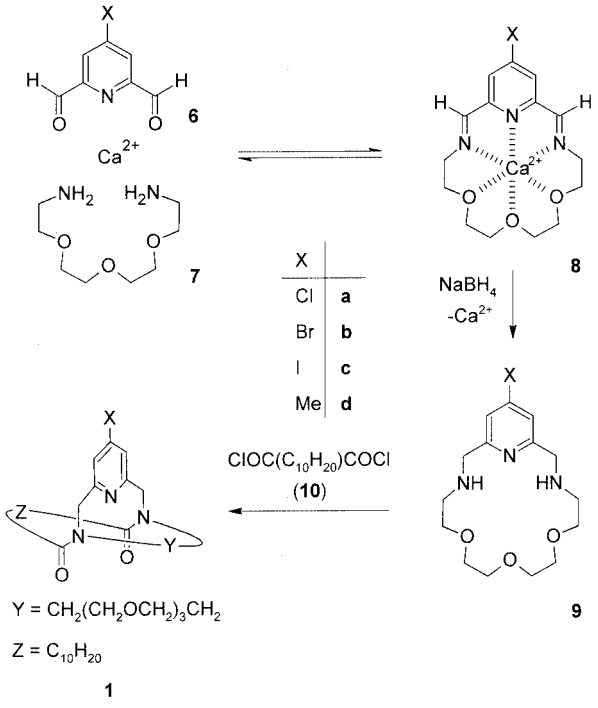
Scheme 3

The dialdehydes **6** are the starting materials for the synthesis of the bimacrocyclic concave pyridines **1a–d**, as already described for a number of concave pyridines.[4–6,10] Since the best selectivities in acylation reactions between polyols and ketenes, especially diphenylketene, have been observed[10] with concave pyridines (**1e** and **1f**, for example) containing one chain derived from tetraethylene glycol and one decamethylene chain, this size of bimacrocycle was also chosen for the 4-substituted derivatives studied in this work. The first step of the synthesis of the concave pyridines **1a–d**



Scheme 2

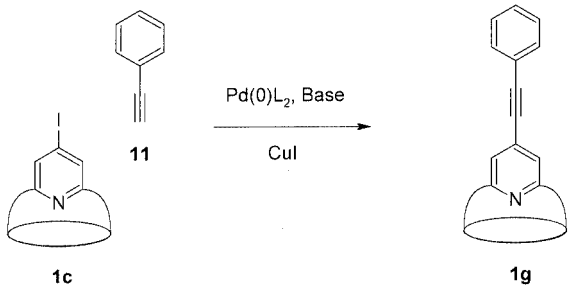
was therefore the Ca^{2+} template-directed macrocyclization of the dialdehydes **6** with the α,ω-diamine **7**, followed by reduction of the resulting diimine complexes **8** to give the macrocyclic diamines **9** (Scheme 4). The oily diamines **9b−d** have not been completely characterised. However, their reactions to give the bimacrocyclic concave pyridines **1b−d** constitute additional structural corroboration. This subsequent macrocyclization reaction of **9** with dodecanedioyl dichloride (**10**) was performed under high-dilution conditions, the 4-substituted concave pyridines **1a−d** being isolated in 23−37% yield (based on the dialdehydes **6**). The new bimacrocyclic concave pyridines **1b−d** have been fully characterised. Like all other concave pyridines **1** with amide bridgeheads, they exist as mixtures of *E* and *Z* conformers, and the substitution in the 4-position does not notably change the ratio.[10]



Scheme 4

These halo- and methyl-substituted concave pyridines **1a−d** now had to be connected with the chromophores. For 2,6-di-*tert*-butyl-4-methylpyridine it was known that condensation with benzaldehydes using 2-butyllithium as base gave conjugated styryl-substituted pyridines.[26,27] This also works well with other lithium bases such as *tert*-butyllithium and LDA. Aldol condensations between the methyl-substituted concave pyridine **1d** and benzaldehyde were therefore attempted with various lithium bases, but, in contrast to the di-*tert*-butyl-substituted analogue, only decomposition of the starting material or no deprotonation at all could be observed.

Palladium cross-couplings of the halo-substituted concave pyridines **10a−c** were therefore tried next, Sonogashira coupling with an acetylene having been reported for the diester **2c**.[28] The Sonogashira coupling of the iodo compound **1c** with phenylacetylene **11** was also successful and gave the concave pyridine **1g** in good yield (77%, Scheme 5).



Scheme 5

In **1g**, the desired extended π-system is established, and the compound's UV absorption is enhanced and shifted towards longer wavelengths relative to non-extended systems (**1b−e**, see Table 1). Figure 1 compares the UV spectrum of **1e** with that of **1g**. The introduction of a phenylethynyl group shifts the maximum long-wavelength absorbances and increases the extinction coefficients. In dichloromethane, λ_{max1} = 286 nm (ε_{max1} = 43300 $Lmol^{-1}cm^{-1}$) and λ_{max2} = 303 nm (ε_{max2} = 39300 $Lmol^{-1}cm^{-1}$), while in methanol λ_{max1} = 285 (ε_{max1} = 44200 $Lmol^{-1}cm^{-1}$) and λ_{max2} = 302 nm (ε_{max2} = 39600 $Lmol^{-1}cm^{-1}$). Use of phenylacetylenes with further substituents at the phenyl ring should make it possible to fine-tune the absorbance characteristics as desired. Even the alteration of the basicity of the pyridine nitrogen should be possible.

Table 1. UV Absorption maxima λ_{max} and extinction coefficients ε in dichloromethane for concave pyridines **1**.

	λ_{max1} [nm]	ε_{max1} [$Lmol^{-1}cm^{-1}$]	λ_{max2} [nm]	ε_{max1} [$Lmol^{-1}cm^{-1}$]
1b	267	4370	274	3900
1c	270	5150	277	4320
1d	263	4370		
1e	266	5020		
1g	286	43300	303	39300

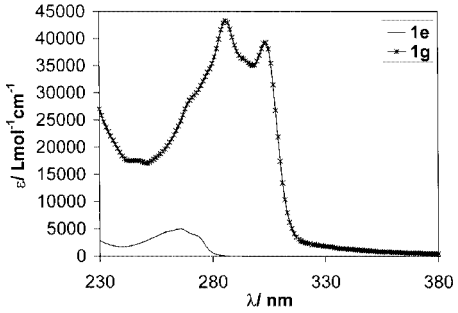


Figure 1. UV spectrum of **1e** and **1g**

Experimental Section

General: The following chemicals were obtained commercially and were used without further purification: bis(triphenylphosphanyl)-palladium(II) dichloride (Fluka), calcium chloride (Fluka), copper(I) iodide (Fluka), dodecanedioyl dichloride (**10**, Aldrich), hydrogen iodide (57%, Merck), phenylacetylene (**11**, Janssen), phosphorous acid (Riedel-de Haën), selenium dioxide (Fluka), and sodium borohydride (Fluka).

The following chemicals were prepared by literature procedures: dimethyl 4-bromo-2,6-pyridinedicarboxylate (**2b**),[24] dimethyl 4-chloro-2,6-pyridinedicarboxylate (**2a**),[21] dimethyl 4-methylpyridine-2,6-dicarboxylate (**2d**),[23] and 3,6,9-trioxa-1,11-undecanediamine (**7**).[5] Dichloromethane was dried by distillation from calcium hydride, dry methanol was distilled from magnesium, and dry triethylamine was prepared by azeotropic distillation (only the dry middle fraction was used). Dioxane was distilled from potassium hydroxide before use. Column chromatography was carried out on silica gel (0.04−0.063 mm, Machery−Nagel). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 200, Bruker AM 300 or Bruker DRX 500 machines (200−500 MHz or 50−125 MHz, resp.). IR spectra were recorded on a Perkin−Elmer 1600 Series spectrometer. MS spectra were recorded on a Finnegan MAT 8230 instrument. Elemental analyses were carried out on a VarioEl (Elementaranalysensysteme GmbH). For some intermediates, elemental analyses did not give satisfactory data; HR-MS spectra have been measured whenever possible. In all cases, the transformations into the fully characterised final products constitute additional evidence of the structure of these intermediates. UV/Vis spectra were recorded on a Perkin−Elmer Lambda 14 machine.

29-Bromo-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (1b): A solution of the bromo compound **9b** (1.17 g, ca. 3.1 mmol) in dry dichloromethane (150 mL) and a solution of dodecanedioyl dichloride (**10**, 0.83 g, 2.8 mmol) in dry dichloromethane (150 mL) were added in parallel and dropwise (duration 3 h) to a vigorously stirred solution of dry triethylamine (4 mL) in dry dichloromethane (300 mL). After this addition, 1 h of additional stirring and 72 h of standing at room temp., the reaction mixture was concentrated to 150 mL in vacuo. The organic layer was extracted with sodium hydroxide solution (2 N, 50 mL), and the organic layer was separated and dried with magnesium sulfate. The solvents were removed in vacuo to yield 1.97 g of a brown oil. The oil was purified chromatographically (dichloromethane/ethanol, 10:1; $R_f = 0.69$). The product crystallised over several days to give a colourless solid. Yield: 400 mg (23% over two steps, based on **6b**). M.p. 94 °C. IR (film): $\tilde{\nu}$ = 2923 cm^{-1} (s, CH_2), 2852 (s, CH), 1651 (s, C=O), 1568 (m, arom. C=C), 1470 (m), 1099 (s, C−O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.55 (m, ca. 20 H, CH_2), 3.00−4.20 (m, ca. 16 H, OCH_2), 4.60−5.40 (m, 4 H, Ar-CH_2), 7.11 (d, ^4J = ca. 1 Hz, 0.26 H, *ZE*, Py-*H*), 7.20 (s, 1.39 H, *ZZ*, Py-*H*), 7.35 (d, ^4J = ca. 1 Hz, 0.27 H, *ZE*, Py-*H*), 7.59 (s, 0.08 H, *EE*, Py-*H*) ppm. Ratio of conformers *ZZ*/*ZE*/*EE* = 70:26:4. ^{13}C NMR (75 MHz, $CDCl_3$)[29]: δ = 24.30 (t, *C*H$_2$CH$_2$C=O), 26.84, 27.80, 28.32 [3 t, C$_2$H$_4$(*C*H$_2$)$_6$C$_2$H$_4$], 31.82 (t, *C*H$_2$C=O), 48.37 (t, NCH$_2$CH$_2$), 55.52 (t, NCH$_2$Py), 70.87 (t, OCH$_2$), 70.92 (t, OCH$_2$), 71.17 (t, OCH$_2$), 121.57 (d, Py-*C*3, Py-*C*5), 134.10 (s, Py-*C*4), 159.92 (s, Py-*C*2, Py-*C*6), 174.49 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 569 (96) [M(^{81}Br)$^+$], 567 (100) [M(^{79}Br)$^+$], 488 (43), 458 (62), 212 (48), 185 (49). CI-MS (isobutane): *m*/*z* (%) = 570 (100) [M(^{81}Br)$^+$ + 1], 568 (94) [M(^{79}Br)$^+$ + 1], 524 (22). HRMS: ($C_{27}H_{42}{}^{81}BrN_3O_5$) calcd. 569.22876; found 569.22870; ($C_{27}H_{42}{}^{79}BrN_3O_5$) calcd. 567.23077; found 567.23070. $C_{27}H_{42}BrN_3O_5$: (568.544): calcd. C 57.04, H 7.45, N 7.39; found C 57.33, H 7.32, N 6.98.

29-Iodo-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (1c): The same procedure as for the synthesis of **1b** was used: **9c** (3.99 g, ca. 9.4 mmol) in dry dichloromethane (250 mL) and **10** (2.45 g, 9.18 mmol) in dry dichloromethane (250 mL) were added simultaneously over 7 h to dry triethylamine (6.6 mL) in dry dichloromethane (500 mL). Purification by chromatography (dichloromethane/ethanol, 10:1; R_f = 0.06, gradient to 1:1). The crystallisation took a week.

Yield: 2.13 g (37% two steps, based on **6c**). M.p. 139 °C. IR (KBr): $\tilde{\nu}$ = 2925 cm^{-1} (s, CH_2), 2854 (s, CH), 1646 (s, C=O), 1561 (m, arom. C=C), 1461 (m), 1125 (s, C−O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.55 (m, ca. 20 H, CH_2), 3.00−4.20 (m, ca. 16 H, OCH_2), 4.60−5.40 (m, 4 H, Ar-CH_2), 7.31 (d, ^4J = 1.2 Hz, 0.23 H, *ZE*, Py-*H*), 7.41 (s, 1.43 H, *ZZ*, Py-*H*), 7.57 (d, ^4J = 1.2 Hz, 0.26 H, *ZE*, Py-*H*), 7.80 (s, 0.08 H, *EE*, Py-*H*) ppm. Ratio of conformers *ZZ*/*ZE*/*EE* = 71:25:4. ^{13}C NMR (75 MHz, $CDCl_3$)[29]: δ = 24.29 (t, *C*H$_2$CH$_2$C=O), 26.87, 27.78, 28.36 [3 t, C$_2$H$_4$(*C*H$_2$)$_6$C$_2$H$_4$], 31.71 (t, *C*H$_2$C=O), 48.37 (t, NCH$_2$CH$_2$), 55.39 (t, NCH$_2$Py), 70.90 (t, OCH$_2$), 70.93 (t, OCH$_2$), 71.21 (t, OCH$_2$), 106.89 (s, Py-*C*4), 127.42 (d, Py-*C*3, Py-*C*5), 159.22 (s, Py-*C*2, Py-*C*6), 174.74 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 615 (100) [M$^+$], 458 (31), 233 (21). CI-MS (isobutane): *m*/*z* (%) = 616 (100) [M$^+$ + 1]. HRMS ($C_{27}H_{42}IN_3O_5$): calcd. 615.21692; found 615.21670; ($C_{26}{}^{13}CH_{42}IN_3O_5$) calcd. 616.22028; found 616.22030. $C_{27}H_{42}IN_3O_5$: (615.544): calcd. C 52.68, H 6.88, N 6.83; found C 53.06, H 6.85, N 6.63.

29-Methyl-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (1d): The same procedure as for the synthesis of **1b** was used: **9d** (1.76 g, 6.0 mmol) in dry dichloromethane (250 mL) and **10** (1.60 g, 6.0 mmol) in dry dichloromethane (250 mL) were added simultaneously over 7 h to dry triethylamine (4.4 mL) in dry dichloromethane (500 mL). Purification by chromatography (dichloromethane/ethanol, 10:1; R_f = 0.4). Yield: 1.05 g (35% last two steps referred to **6c**). M.p. 118−119 °C. IR (KBr): $\tilde{\nu}$ = 1664 cm^{-1} 1650 (s, C=O), 1565 (arom. C=C), 1115 (m, C−O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.9−2.35 (m, ca. 24 H, CH_2, NCH_2), 2.35 (s, 3 H, CH_3), 3.2−4.0 (m, ca. 12 H, OCH_2), 4.5−5.5 (m, 4 H, Py-CH_2), 6.75 (d, ^4J = 1.2 Hz, 0.33 H, *ZE*, Py-*H*), 6.84 (s, 1.20 H, *ZZ*, Py-*H*), 6.99 (d, ^4J = 1.2 Hz, 0.34 H, *ZE*, Py-*H*), 7.23 (s, 0.13 H, *EE*, Py-*H*) ppm. Ratio of conformers *ZZ*/*ZE*/*EE* = 60:34:6. ^{13}C NMR (75 MHz, $CDCl_3$):[29] δ = 21.41 (t, *C*H$_3$), 24.35 (t, *C*H$_2$CH$_2$C=O), 26.95, 27.78, 28.17 [3 t, C$_2$H$_4$(*C*H$_2$)$_6$C$_2$H$_4$], 32.13 (t, *C*H$_2$C=O), 47.91 (t, NCH$_2$CH$_2$), 55.46 (t, NCH$_2$Py), 70.70, 70.84, 71.08 (t, OCH$_2$), 118.92 (s, Py-*C*3, Py-*C*5), 148.25 (s, Py-*C*4), 158.06 (s, Py-*C*2, Py-*C*6), 174.61 (s, C=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 503 (100) [M$^+$], 473 (22), 161 (28), 121 (61). CI-MS (isobutane): *m*/*z* (%) = 504 (100) [M$^+$ + 1], 282 (14). HRMS ($C_{28}H_{45}N_3O_5$): calcd. 503.33591; found 503.33570; ($C_{27}{}^{13}CH_{45}N_3O_5$) calcd. 504.33926; found 504.33890. $C_{28}H_{45}N_3O_5$: (503.674): calcd. C 66.77, H 9.00, N 8.34; found C 66.09, H 8.96, N 8.03.

29-Phenylethynyl-1,14,33-triaza-17,20,23-trioxatricyclo-[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (1g): Compound **1c** (864 mg, 1.40 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (23 mg, 0.033 mmol) and copper(I) iodide (34 mg, 0.18 mmol) were dissolved in dry tetrahydrofuran (7.5 mL) and dry triethylamine (7.5 mL), and were then subjected to ultrasound for 5 min under argon. Phenylacetylene (**11**, 190 mg, 1.86 mmol), dissolved in tetrahydrofuran (5 mL), was added by syringe. The reaction mixture was

stirred for 4 h at 50 °C and the solvents were removed in vacuo. The residue was dissolved in chloroform (30 mL) and extracted four times with water (10 mL each). The organic layer was separated and dried, and the solvent was removed in vacuo. The residue was purified by chromatography (dichloromethane/ethanol, 10:1; R_f = 0.35). Yield: 638 mg (77%). IR (KBr): $\tilde{\nu}$ = 2925 cm^{-1} (s, CH_2), 2854 (m), 2214 (w, C≡C), 1645 (s, C=O), 1601 (m, arom. C=C), 1462 (m), 1123 (m, C−O), 759 (w, Ar-C−H), 692 (w, Ar-C−H). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.60 (m, ca. 20 H, CH_2), 3.20−4.30 (m, ca. 16 H, OCH_2), 4.60−5.30 (m, 4 H, PyCH_2), 7.04 (d, ^4J = 1.5 Hz, 0.36 H, *ZE,* Py-*H*), 7.14 (s, 1.28 H, *ZZ,* Py-*H*), 7.29 (d, ^4J = 1.5 Hz, 0.36 H, *ZE*, Py-*H*), 7.41 (m, 2 H, Ar-3,5-*H*), 7.56 (m, 3 H, Ar-2,6-*H*, Ar-4-*H*) ppm. Ratio of conformers *ZZ*/*ZE*/*EE* <64:<36:not assignable. ^{13}C NMR (75 MHz, $CDCl_3$):[29,30] δ = 24.32 (t, *C*H_2CH$_2$C=O), 26.88−29.44 (several t, CH$_2$*C*H$_2$CH$_2$), 32.10 (t, *C*H$_2$C=O), 47.99 (t, N*C*H$_2$CH$_2$), 55.38 (t, N*C*H$_2$Py), 70.54−71.01 (several t, O*C*H$_2$), 86.72 (s, Ar-*C*≡C), 94.00 (s, Py-*C*≡C), 119.89 (d, Py-*C*3, Py-*C*5), 121.85 (s, Ar-*C*1), 128.41 (d, Ar-*C*3, Ar-*C*5), 129 (d, Ar-*C*4), 132.52 (d, Ar-*C*2, Ar-*C*6), 158.43 (s, Py-*C*2, Py-*C*6), 174.57 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 589 (100) [M^+], 233 (39), 207 (72). CI-MS (isobutane): *m*/*z* (%) = 590 (53) [M^+ + 1], 429 (25), 279 (100), 99 (42). HRMS ($C_{35}H_{47}N_3O_5$): calcd. 589.35156; found 589.35110; ($C_{34}{}^{13}CH_{47}N_3O_5$): calcd. 590.35492; found 590.35440. $C_{35}H_{47}N_3O_5$ (589.79): calcd. 71.28, H 8.03, N 7.12. $C_{35}H_{47}N_3O_5{\cdot}H_2O$, 0.2 CH_2Cl_2: calcd. C 67.67, H 7.97, N 6.73; found C 67.50, H 8.36, N 6.42.

Dimethyl 4-Iodopyridine-2,6-dicarboxylate (2c): Concd. sulfuric acid (1.5 mL) was added dropwise to 4-iodopyridine-2,6-dicarboxylic acid (**3c**, 34.3 g, 117 mmol) in dry methanol (100 mL). The reaction mixture was heated under reflux for 4 h. The larger part of the solvent was removed in vacuo, and the remaining solution was neutralised with saturated sodium hydrogen carbonate solution. The residue was filtered off and recrystallised from methanol. Yield: 25 g (70%). M.p. 173 °C (168 °C[31]). IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1} (w), 3066 (w), 2948 (w, CH_2), 1725 (s, C=O), 1711 (s), 1566 (s, arom. C=C), 1443 (m), 1326 (s), 1263 (s, C−O), 1144 (m), 717 (m, Ar-C−H). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.03 (s, 6 H, OCH_3), 8.67 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.37 (q, *C*H$_3$), 106.88 (s, Py-*C*4), 137.07 (d, Py-*C*3, Py-*C*5), 148.28 (s, Py-*C*2, Py-*C*6), 163.81 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 321 (8) [M^+], 291 (23), 263 (100), 231 (31). CI-MS (isobutane): *m*/*z* (%) = 322 (100) [M^+ + 1], 196 (41).

4-Iodopyridine-2,6-dicarboxylic Acid (3c): Hydrogen iodide solution (57%, 128 mL) was added at 0 °C to dimethyl 4-chloropyridine-2,6-dicarboxylate (**2a**, 28.4 g, 136 mmol) and phosphorous acid (3.4 g, 41 mmol). The mixture was heated and methyl iodide distilled off (ca. 42 °C). The mixture was heated under reflux for further 5 h. After cooling to 90 °C, the mixture was neutralised with sodium hydroxide (10 M). After addition of water (75 mL), the mixture was allowed to cool to room temp. The product crystallised in light brown needles, and was filtered off and washed with cold water. Yield: 34.3 g (90%). M.p. 206 °C (208 °C[31]). IR (KBr): $\tilde{\nu}$ = 3466 cm^{-1} (m, COOH), 1734 (s, C=O), 1560 (s, arom. C=C), 1311 (m, C−O), 1207 (m), 1172 (m), 896 (w), 784 (w), 681 (m, Ar-C−H). ^{1}H NMR (200 MHz, CD_3OD): δ = 8.68 (s, 2 H, Py-*H*) ppm. EI-MS (70 eV): *m*/*z* (%) = 293 (1.6) [M^+], 249 (100), 231 (55), 76 (30). CI-MS (isobutane): *m*/*z* (%) = 308 (98) [M^+ + CH_3], 294 (100) [M^+ + 1], 250 (26), 168 (12).

2,6-Bis(hydroxymethyl)-4-iodopyridine (5c): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**2c**, 25.0 g, 77.9 mmol) was dissolved in dry methanol (200 mL).The reaction mixture was cooled with ice, and sodium borohydride (13.5 g, 245 mmol) was added in small portions over 45 min. The mixture was then heated under reflux for 17 h. After addition of acetone (30 mL) to destroy the excess hydride, the solution was stirred for 1 h. The solvents were removed in vacuo. The residue was heated to reflux in sat. potassium carbonate solution (30 mL) for 1 h. After addition of distilled water (45 mL), the aqueous layer was continuously extracted with chloroform for 3 days. The solvents were removed in vacuo. Yield: 14.3 g (70%). M.p. 153 °C (153 °C[28]). IR (KBr): $\tilde{\nu}$ = 3310 cm^{-1} (s, OH), 3060 (s, Ar-H), 1560 (s, arom. C=C), 1350 (m, C−O), 855 (m), 800 (m, Ar-C−H). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.43 (br. s, 4 H, CH_2), 7.78 (s, 2 H, Py-*H*)[32] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.40 (t, *C*H$_2$), 107.20 (s, Py-*C*4), 128.00 (d, Py-*C*3, Py-*C*5), 160.45 (s, Py-*C*2, Py-*C*6) ppm. EI-MS (70 eV): *m*/*z* (%) = 265 (19) [M^+], 264 (25), 247 (18), 83 (100). CI-MS (isobutane): *m*/*z* (%) = 266 (100) [M^+ + 1], 140 (84).

2,6-Bis(hydroxymethyl)-4-methylpyridine (5d): Compound **5d** was synthesised analogously to **5c**, from **2d** (11.3 g, 54.0 mmol) in dry methanol (135 mL) by addition of sodium borohydride (9.25 g, 245 mmol). Yield: 6.95 g (82%); m.p. 85−86 °C. IR (KBr): $\tilde{\nu}$ = 3364 cm^{-1} (s, OH), 1613 (s, arom. C=C), 1086 (s, C−O). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.33 (s, 3 H, CH_3), 4.48 (d, *J* = 5.7 Hz, 4 H, CH_2), 5.33 (t, *J* = 5.7 Hz, 2 H, O*H*), 7.14 (s, 2 H, Py-*H*) ppm. EI-MS (70 eV): *m*/*z* (%) = 153 (45) [M^+], 152 (100), 143 (51). CI-MS (isobutane): *m*/*z* (%) = 154 (100) [M^+ + 1]. HRMS ($C_8H_{11}NO_2$): calcd. 153.07898; found 153.07890; ($C_7{}^{13}CH_{11}NO_2$): calcd. 154.08234; found 154.08230.

4-Iodopyridine-2,6-dicarbaldehyde (6c): 2,6-Bis(hydroxymethyl)-4-iodopyridine (**5c**, 14.3 g, 54.2 mmol) and selenium dioxide (6.00 g, 54.2 mmol) were suspended in dioxane (300 mL, including 4 mL of water). The suspension was heated under reflux until conversion to **6c** was complete (5.5 h, monitored by TLC). The mixture was filtered through Celite while still hot, and the solvent was removed in vacuo. The remaining solid was purified by chromatography (ethyl acetate/dichloromethane, 3:1; R_f = 0.64). Yield: 12.6 g (90%). M.p. 151−155 °C. IR (KBr): $\tilde{\nu}$ = 3056 cm^{-1} (w, aliph. CH), 2842 (w, H-CO), 1702 (s, C=O), 1558 (m, arom. C=C), 1348 (m), 1261 (m), 936 (m, Ar-C−H), 696 (m, Ar-C−H), 652 (m, Ar-C−H). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.50 (s, 2 H, Py-*H*), 10.09 (s, 2 H, C*H*O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.5 (s, Py-*C*4), 134.4 (d, Py-*C*3, Py-*C*5), 152.8 (s, Py-*C*2, Py-*C*6), 191.1 (d, *C*HO) ppm. EI-MS (70 eV): *m*/*z* (%) = 261 (98) [M^+], 233 (100), 205 (20), 78 (49). CI-MS (isobutane): *m*/*z* (%) = 262 (100) [M^+ + 1]. HRMS ($C_7H_4INO_2$): calcd. 260.92868; found 260.92850; ($C_6{}^{13}CH_4INO_2$): calcd. 261.93204; found 261.93190.

4-Methylpyridine-2,6-dicarbaldehyde (6d): Compound **6d** was synthesised analogously to **6c**, from **5d** (3.37 g, 21.6 mmol) and selenium dioxide (3.51 g, 31.7 mmol) in dioxane/water (50 mL). Purification by chromatography (cyclohexane/ethyl acetate, 2:1; R_f = 0.38). Yield: 1.76 g (55%). M.p. 158 °C (158.5 °C [33]). IR (KBr): $\tilde{\nu}$ = 2857 cm^{-1} (w, aliph. CH), 1708, 1698 (C=O), 1597 (arom. C=C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 7.99 (s, 2 H, Py-*H*), 10.15 (s, 2 H, C*H*O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.12 (q, *C*H$_3$), 126.04 (d, Py-*C*3, Py-*C*5), 150.29 (s, Py-*C*4), 153.00 (s, Py-*C*2, Py-*C*6), 192.61 (d, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 149 (46) [M^+], 121 (100), 93 (60), 65 (55). CI-MS (isobutane): *m*/*z* (%) = 150 (100) [M^+ + 1]. HRMS ($C_8H_7NO_2$): calcd. 149.04768; found 149.04750; ($C_7{}^{13}CH_7NO_2$): calcd. 150.05104; found 150.05150.

19-Bromo-3,15,21-triaza-6,9,12-trioxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9b): 4-Bromopyridine-2,6-dicarbaldehyde[34] (**6b**,

650 mg, 3.03 mmol) and calcium chloride (333 mg, 3.00 mmol) were dissolved in dry methanol (100 mL). Over 30 min, diamine **7** (580 mg, 3.02 mmol) in dry methanol (30 mL) was added dropwise to this solution. After the addition, the mixture was stirred for 1 h at room temp. and was then heated under reflux for 3 h. Sodium borohydride (820 mg, 21.6 mmol) was slowly added with stirring at 0 °C. The reaction mixture was stirred for 20 h at room temp. After addition of water (20 mL), the mixture was stirred for another 2 h. Concentration in vacuo gave a white suspension. The residue were filtered and extracted with dichloromethane (30 mL). The aqueous layer was extracted four times with dichloromethane (100 mL each) and the combined organic layers were dried with magnesium sulfate. The solvents were removed in vacuo, giving 1.17 g of a brown oil. Crude yield: 1.17 g (quant.). IR (film): $\tilde{\nu}$ = 2878 cm^{-1} (m, CH_2), 1568 (s, ring), 1109 (s, C−O). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.84 (m, 4 H, NCH_2CH_2), 2.90−3.10 (br. s, 2 H, N*H*), 3.60−3.70 (m, 12 H, OCH_2), 3.82 (s, 4 H, Py-CH_2), 7.25 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 47.93 (t, N*C*H_2CH_2), 53.30 (t, N*C*H_2Py), 69.27, 69.41 (2 t, O*C*H_2), 122.95 (d, Py-*C*3, Py-*C*5), 132.11 (s, Py-*C*4), 159.17 (s, Py-*C*2, Py-*C*6) ppm. EI-MS (70 eV): *m*/*z* (%) = 375 (4.3) [M(^{81}Br)$^+$], 373 (6.2) [M(^{79}Br)$^+$], 228 (93), 226 (100), 212 (79), 185 (69). CI-MS (isobutane): *m*/*z* (%) = 376 (97) [M(^{81}Br)$^+$+1], 374 (100) [M(^{79}Br)$^+$+1].

19-Iodo-3,15,21-triaza-6,9,12-trioxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9c): Compound **9c** was synthesised analogously to **9b**, from 4-iodopyridine-2,6-dicarbaldehyde (**6c**, 2.425 g, 9.220 mmol) and calcium chloride (1.017 g, 9.162 mmol) in dry methanol (225 mL), and diamine **7** (1.742 g, 9.073 mmol) in dry methanol (75 mL). Later on, sodium borohydride (2.08 g, 54.7 mmol) was added according to the above procedure. Crude yield: 3.99 g (quant.). IR (film): $\tilde{\nu}$ = 2869 cm^{-1} (m, CH_2), 1565 (s, arom. C=C), 1116 (s, C−O). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.84 (s, 4 H, NCH_2CH_2), 3.10−3.30 (br. s, 2 H, N*H*), 3.60−3.70 (m, 12 H, OCH_2), 3.82 (s, 4 H, Py-CH_2), 7.46 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.00 (t, N*C*H_2CH_2), 54.17 (t, N*C*H_2Py), 70.31, 70.40, 70.50 (3 t, O*C*H_2), 106.40 (s, Py-*C*4), 129.81 (d, Py-*C*3, Py-*C*5), 159.74 (s, Py-*C*2, Py-*C*6) ppm. EI-MS (70 eV): *m*/*z* (%) = 421 (6) [M$^+$], 315 (38), 274 (100), 233 (49). CI-MS (isobutane): *m*/*z* (%) = 422 (100) [M$^+$ + 1], 296 (20), 193 (29).

19-Methyl-3,15,21-triaza-6,9,12-trioxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9d): Compound **9d** was synthesised analogously to **9b**, from dialdehyde **6d** (1.11 g, 7.50 mmol) and calcium chloride (831 mg, 7.50 mmol) in dry methanol (200 mL), and diamine **7** (1.44 g, 7.50 mmol) in dry methanol (40 mL). Later on, sodium borohydride (1.70 g, 45 mmol) was added according to the procedure. A light yellow solid remained. Crude yield: 1.76 g (82%). M.p. 42−45 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 2.85 (m, 4 H, NCH_2CH_2), 3.5−3.7 (m, ca. 14 H, CH_2, N*H*), 3.83 (s, 4 H, Py-CH_2), 6.88 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.88 (q, *C*H_3), 49.11 (t, N*C*H_2CH_2), 54.78 (t, N*C*H_2Py), 70.33, 70.37, 70.56 (3 t, O*C*H_2), 121.78 (d, Py-*C*3, Py-*C*5), 147.76 (s, Py-*C*4), 158.40 (s, Py-*C*2, Py-*C*6) ppm.

[1] See biochemistry textbooks (e.g., L. Stryer, *Biochemistry*, 4th ed., W. H. Freeman and Company, New York, **1995**).
[2] *Comprehensive Supramolecular Chemistry*, executive editor J. L. Atwood, chairman of the editorial board J.-M. Lehn, Oxford, Pergamon, **1996**ff.
[3] J.-M. Lehn, *Supramolecular Chemistry*, VCH Verlagsgesellschaft, Weinheim, **1995**.
[4] U. Lüning, *Liebigs Ann. Chem.* **1987**, 949−955.
[5] U. Lüning, R. Baumstark, K. Peters, H. G. von Schnering, *Liebigs Ann. Chem.* **1990**, 129−143.
[6] U. Lüning, R. Baumstark, M. Müller, *Liebigs Ann. Chem.* **1991**, 987−998.
[7] U. Lüning, *J. Mater. Chem.* **1997**, *7*, 175−182.
[8] U. Lüning, R. Baumstark, W. Schyja, *Liebigs Ann. Chem.* **1991**, 999−1002.
[9] U. Lüning, S. Petersen, W. Schyja, W. Hacker, T. Marquardt, K. Wagner, M. Bolte, *Eur. J. Org. Chem.* **1998**, 1077−1084.
[10] S. Petersen, U. Lüning, *Eur. J. Org. Chem.* **1999**, 847−854.
[11] H.-J. Schneider, A. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*, J. Wiley & Sons Ltd., Chichester, **2000**.
[12] U. Lüning, M. Gerst, *J. Prakt. Chem./Chem.-Ztg.* **1992**, *334*, 656−660.
[13] U. Lüning, W. Hacker, *J. Prakt. Chem.* **1999**, *341*, 662−667.
[14] T. Marquardt, U. Lüning, *Chem. Commun.* **1997**, 1681−1682.
[15] U. Lüning, T. Marquardt, *J. Prakt. Chem.* **1999**, *341*, 222−227.
[16] F. Diederich, P. J. Stang (Ed.), *Metal-catalysed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.
[17] H. Takalo, I. Hemmilä, T. Suvela, M. Latva, *Helv. Chim. Acta* **1996**, *79*, 789−802.
[18] E. Jacobson, C. L. Reimer, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2602−2608.
[19] R. Riegel, D. Zwilgmeyer, *Org. Synth.* **1950**, *Coll. Vol. 2*, 126−128.
[20] L. R. Fibel, P. E. Spoerri, *J. Am. Chem. Soc.* **1948**, *70*, 3908−3911.
[21] D. G. Markees, G. W. Kidder, *J. Am. Chem. Soc.* **1956**, *78*, 4130−4135.
[22] B. Schmidt, D. H. Ehlert, *Tetrahedron Lett.* **1998**, *39*, 3999−4002.
[23] E. Koenigs, W. Jaeschke, *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 1351−1357.
[24] C. Lewis, *J. Biol. Chem.* **1972**, *247*, 1861−1868.
[25] For a comparison of various synthetic routes to pyridine-2,6-dialdehydes see ref.[5].
[26] M. E. Wright, S. R. Pulley, *J. Org. Chem.* **1987**, *52*, 1623−1624.
[27] M. E. Wright, S. R. Pulley, *J. Org. Chem.* **1987**, *52*, 5036−5037.
[28] H. Takalo, P. Pasanen, J. Kankare, *Acta Chem. Scand., Ser. B* **1988**, *42*, 373−377.
[29] Three sets of signals can be distinguished, only the signals of the most intensive set (*ZZ*) are given.
[30] The assignment of the signals between δ = 20 and δ = 70 ppm may be incorrect, due to intense signal density.
[31] R. Graf, *J. Prakt. Chem.* **1937**, *148*, 13−23.
[32] Because of the addition of a small amount of CD_3OD in order to dissolve the sample completely, O*H* could not be detected.
[33] W. Mathes, W. Sauermilch, *Chem. Ber.* **1955**, *88*, 1276−1283.
[34] Compound **6b** has already been synthesised and characterised: H. Takalo, J. Kankare, *J. Heterocycl. Chem.* **1990**, *29*, 167−169. It can also be obtained by oxidation of **5b** with SeO_2.

Received May 3, 2002
[O02235]