Dendronized Molecular Knots: Selective Synthesis of Various Generations, Enantiomer Separation, Circular Dichroism

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Abstract: For the first time, knot molecules (of the amide type) are synthesized, which bear one to three dendritic units of various generations at their periphery. They were obtained through two different routes: i) attachment of dendritic wedges to new mono-, di- and trihydroxy functionalized dodecaamide knots that have been obtained by selective debenzylation of oligobenzyloxy substituted knots, or ii) cyclization of already dendron substituted pyridine-2,6-dicarbonyl dichlorides with an "extended diamine" to directly yield the "tri-dendroknots". The derivatization of knot molecules by functional substituents and even large dendritic units is an important advance in the synthesis and property variation of molecular knots. This holds true in particular for substitution of the pyridine units of the knots, whereas the isophthalic acid units seem not to tolerate larger substitutents, as reflected in lower knot yields. These syntheses also demonstrate knots to be accessible indirectly by substitution of the corresponding mono-, di- and trifunctionalized knot skeleton. An advantage of dendritic "decoration" is the control of solubility and chromatographic behaviour of the molecular knots (knotanes). Suggestions are made about the threading mechanism by supramolecular template effects leading to the formation of amide-based molecular knots. The topological chirality of the new "dendroknots" is shown by efficient enantioseparations (separation factor α between 1.22 and 1.48). For this purpose (commercially unavailable) chiral column material of the Chiralpak type was used, in which the chiral component is covalently bonded to the silica gel support. The racemate splittings provide additional evidence for the knotted structure, as all other conceivable isomers such as macromonocyclic or catenated dodecaamides would not be chiral. The pure enantiomers obtained exhibit pronounced Cotton effects in their circular dichroism spectra. By comparison with the unsubstituted knot, the absolute configuration (Λ, Δ) of all new knots is derived.

Keywords: chirality · dendrimers · knotanes · supramolecular chemistry · template synthesis

Introduction

The synthesis of molecular knots[1, 2] ("Knotanes"[3]) is among the most challenging in today's chemistry. The topological chirality of the trefoil knots makes their synthesis particularly interesting. Also template effects play an important role in the knot synthesis. Historically, the first synthetic knots were of the phenanthrolin type,[4] but nucleic acid type,[5] crown-quat type[6] and open-knot metal complex knots[7] could also be synthesized. Simultaneously peptide-based knots were discovered in nature.[8]

While molecular knots were initially synthesized for their characteristic intertwined structure, their functionalization seemed to be difficult.[2] Recently, we have been able to show that molecular knots of the amide type can be equipped with various small substituents such as chloro and methoxy.[3] In order to improve and control the (sparing) solubility of these knots and to improve chromatographic enantiomer separations, we aimed at the introduction of larger substituents such as dendritic wedges[9] at the periphery of amide knots, creating decorated "dendroknots".[10] This contribution therefore describes the syntheses of a series of new molecular knots of the amide type, bearing protected and free functional groups such as O-benzyl and OH that allow us to further derivatize and in particular dendrylate the naked scaffold.[3b] The knot syntheses were carried out successfully by supramolecular

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template reactions that are—like corresponding amide catenane and rotaxane syntheses[11–14]—assisted mainly by hydrogen bonds between host and guest amide groups.

The complete separation of the knot racemates was achieved using special chiral column materials. The measurement of the circular dichroisms allowed the assignment of the absolute molecular chirality to the knot enantiomers.

Results

Synthesis of mono-, di-, and tribenzyl- and hydroxy-functionalized amide knots

General remarks: Our early efforts in amide-based knots revealed the difficulties related to their synthesis in general and functionalization in particular.[2] When we had tried to attach substituents on the isophthalic acid benzene ring the yields of the synthesized hexaamide trefoil knots dropped with increasing size of the substituents.[3a] However, we have now achieved an important advance in the synthesis of these amide knot compounds by attaching functional groups to the pyridine rings of **5**. Further insights came from preliminary experiments: Large groups in the 5-position (R′ in **4** and **5**) of the isophthalic acid unit **A** were not acceptable; in this case, the synthesis is directed towards the formation of macrocyles and catenanes, as can be already seen when replacing R′ = H by a methyl or a *tert*-butyl group as substituent. The yields for the resulting trisubstituted knotanes are very low (< 1 %)[3a, 3c] in these cases. In contrast, the 4-position on the pyridine unit **B** tolerates much larger substituents up to dendritic wedges, as shown below. This surprising result, may be explained by the location of the pyridine units at the periphery of the knot. In contrast, a previous X-ray crystal structure[15] shows the isophthalic units to be "hidden" inside the knot. Based on these findings, we could increase step by step the size of the substituents at the pyridine rings **B**, going from smaller to higher generation dendritic wedges, as described below.

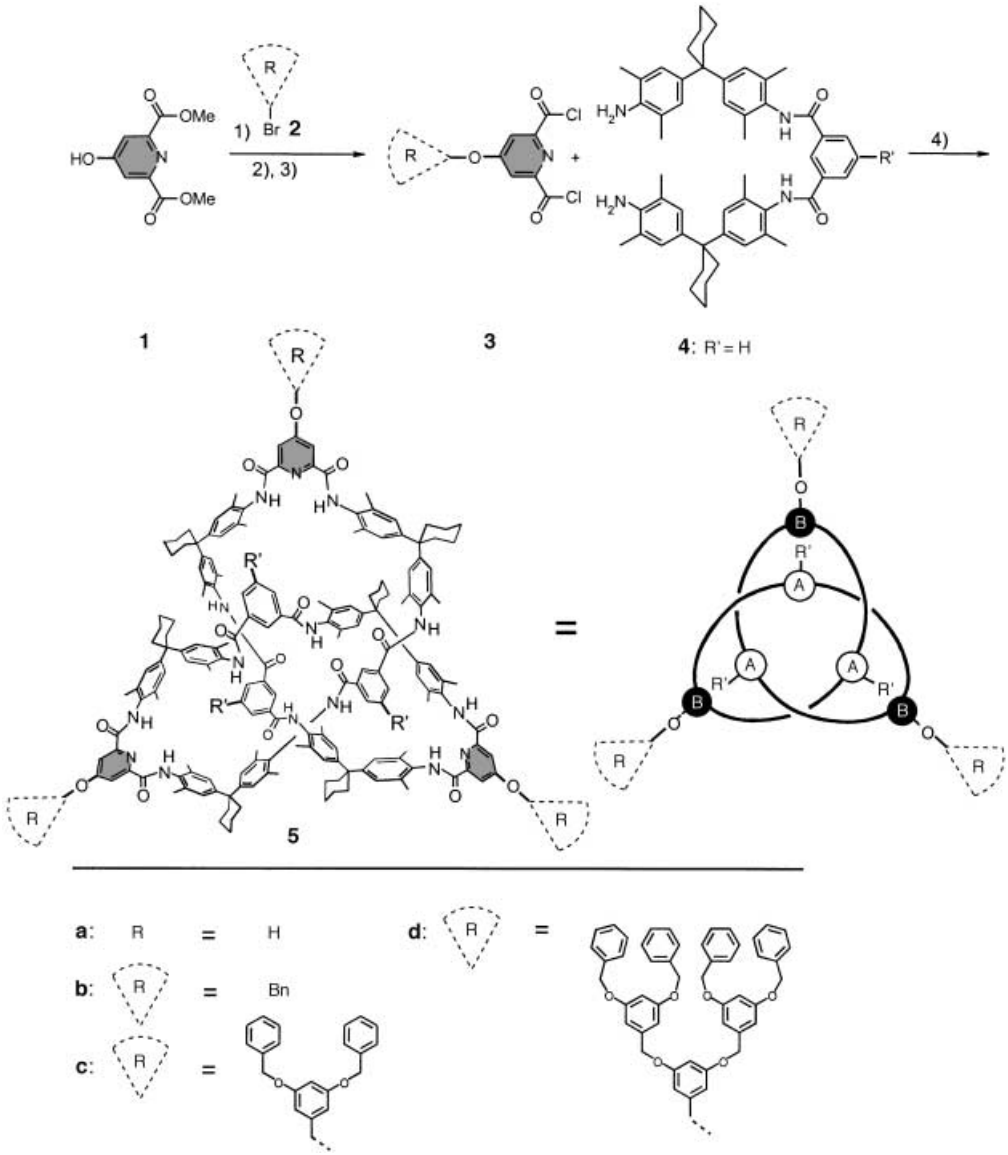

Figure 1. "Direct" synthesis of the knotanes **5b** and **5c** bearing three dendritic groups at the pyridine units. 1) K_2CO_3, acetone; 2) KOH, ethanol; 3) $(COCl)_2$, benzene; 4) NEt_3, CH_2Cl_2.

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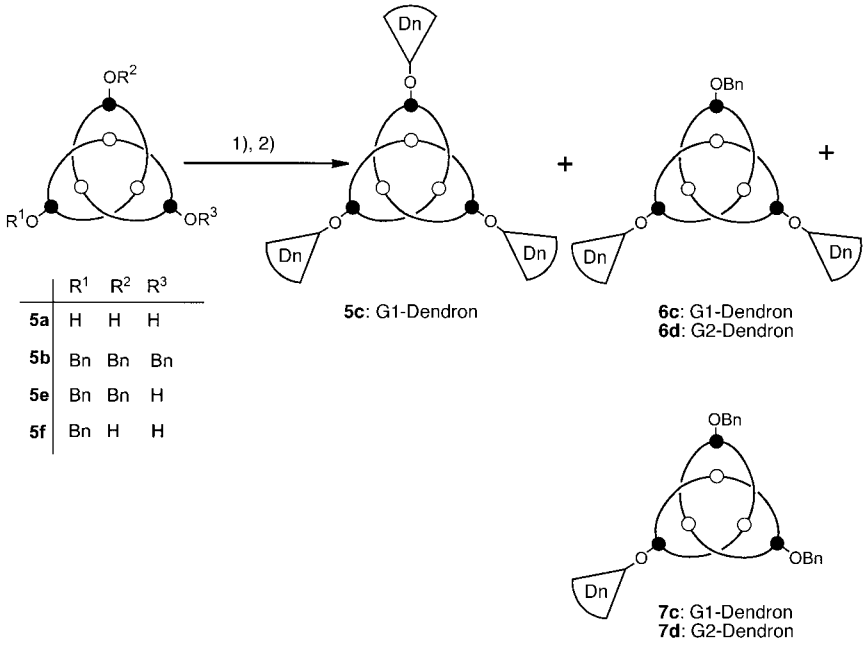
"Direct synthesis" of dendryl functionalized amide knots: For the synthesis of dendritically substituted molecular knots we started from the "extended" diamine **4**[11, 13a] and the benzyl- and dendrylated 4-hydroxypyridine dicarboxylic dichloride **3b–d** prepared by nucleophilic substitution of the di-ester **1** with the corresponding Fréchet-type dendryl chlorides **2c,d**.[16] The reactions were carried out under moderate dilution conditions (approx. 1.4 mM) in dichloromethane. This reaction yields 5% of pure knot **5b** and 2% of **5c**, respectively, after purification by column chromatography on silica gel. The dendroknot **5d** could not be isolated by this direct route, likely due to steric repulsion increasing with dendron size (Figure 1).

"Indirect" synthesis of mono-, di-, and tribenzyl- and hydroxy-functionalized amide knots: The complete deprotection by hydrogenation (H_2, Pd/C) of all three benzyl groups from the tris(benzyloxy) knot **5b** was only partially successful and a mixture of mono-, di-, and trihydroxy knotanes **5a,e** and **f** was formed. We exploited this fact to synthesize mono-, di- and tridendrylated knots simultaneously, reacting dendritic wedges **2** directly with the hydroxyknot mixture (Figure 2). The reactions of the hydroxy knot mixture **5a,e** and **f** with first- and second-generation dendryl bromides led to the expected mixtures of dendroknots **5c**, **6c**, **7c**, and **6d**, **7d**. Their HPLC separation is described below along with the HPLC separation of the enantiomers on a chiral stationary phase.

In summary we conclude: In comparison to Sauvage's[2, 4] Cu^I based template synthesis (Figure 3a), no additional templating agent (external template) is necessary. In our case, all six reactand molecules of **3** and **4** react in an "internal templating" reaction to generate the molecular knot: Taking into consideration the crystal X-ray structure of the amide



	R^1	R^2	R^3
5a	H	H	H
5b	Bn	Bn	Bn
5e	Bn	Bn	H
5f	Bn	H	H

Figure 2. Deprotection of **5b** leading to mono, di-, and tridendryl substituted knots **5c–7c**, **6d** and **7d**. 1) Pd/C, H_2, $CHCl_3$/MeOH; 2) R-Br, K_2CO_3, acetone.

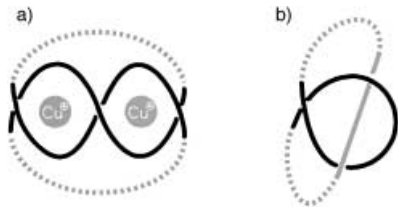


Figure 3. a) Cu^+ assisted knot formation of the Sauvage-type; b) proposal for a hydrogen bond template driven formation of dodecaamide trefoil knotanes. Helical host loop (black); amide guest (grey). For hydrogen bonding assistance see text. Dotted lines indicate open ends that need to be connected for knot formation.

knotane,[15] the progression of the assembly is proposed to begin with the formation of a helical loop (Figure 3b) followed by threading of the guest amide through this loop. The hydrogen bonding pattern in this weakly bonded complex likely resembles that found in the X-ray structure. The two remaining acid chloride molecules **3** react in the subsequent reaction step with the remaining terminal amino groups of the loop to close the knot (dotted lines in Figure 3b). The synthesis of the dodecaamide knotane therefore represents a new pre-organisation mechanism.

This type of synthesis can be varied only in a narrow range as far as substituents at the isophthalic acid rings are concerned. A much greater variety in substitution is possible at the pyridine rings, so that further derivatisations can lead to hitherto unknown molecular knots[17] with a variety of re-functionalisable substituents.

Separation of the enantiomers, chiroptical and other properties

The racemates of the tribenzyl knot **5b** and tridendryl knot **5c** were successfully separated into their enantiomers using the "Chiralpak AD" column material.[18] This non-commercial column material contains tris(3,5-dimethylphenylcarbamate)amylose covalently linked to the silica gel support, therefore making it unlikely for the chiral stationary phase to be washed out when using lipophilic solvents. Figure 4 shows the successful close-to-baseline separation of the tribenzyl knot **5b**. Further enantiomeric separations were carried out successfully for the molecular knots **6c,d** and **7c,d**.

After the preparative separation of the enantiomers the circular dichroisms were recorded. As an representative example, Figure 5 shows the CD spectrum of **5b**. It is similar to that of the unsubstituted knot **5** (R = R′ = H).[15] The pronounced, mirror symmetri-

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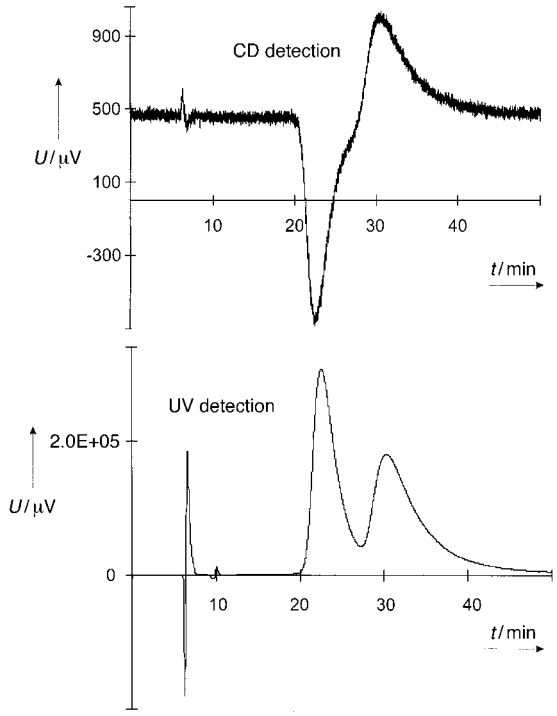

Figure 4. Separation of the enantiomers of **5b** (column: Chiralpak AD, eluent: hexane/chloroform/isopropanol 60:40:2, CD detection at 254 nm).

cal circular dichroisms of the enantiomers (Figures 5 and 8b) confirm the purity of the compounds and of the enantiomers.

In Figure 6, a part of the mass spectrum of the racemic benzyloxy knot **5b** is shown. MALDI-TOF mass spectra and ^{1}H NMR prove the high purity of these and other racemic and enantiomeric knot samples.

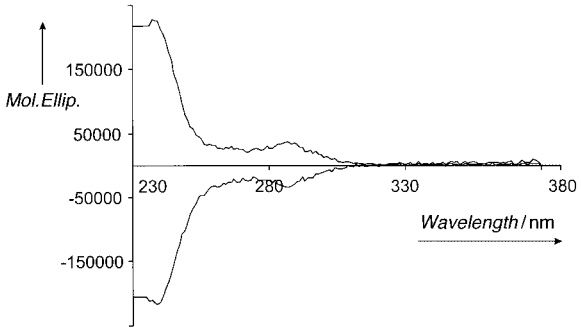

Figure 5. CD spectra of tribenzyl knotane **5b** (in chloroform: (+)-enantiomer $c = 6.5 \times 10^{-4}$ M, (−)-enantiomer $c = 8.9 \times 10^{-4}$ M).

The absolute configuration of the two enantiomers of a trefoil knot with their Δ- and *Λ*- stereochemistry[2] is shown schematically in Figure 7. We are assigning to the enantiomer **5b** with the positive Cotton effects around 240 and 290 nm the configuration *Λ*,[17] as its CD spectrum strongly resembles that of the unsubstituted knot.[3a]

The mixtures of tri, di-, and monodendryl substituted knotanes **5c**, **6c** and **7c** described above (with benzyl groups remaining at the positions still protected, compare Figure 2) were also completely separated on a chiral HPLC column.[18]

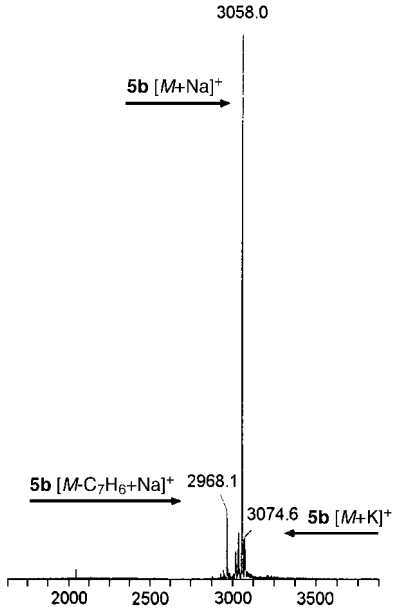

Figure 6. Detail of the Maldi-TOF mass spectrum of knot **5b** (matrix: 2,5-dihydroxybezoic acid).

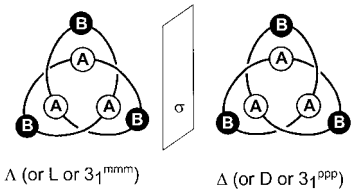

Figure 7. Absolute configuration of trefoil amide knots.

Simultaneously the enantiomers were resolved (Figure 8a). From the partially benzyl deprotected hydroxy compounds, the monobenzyl-didendryl derivatives **6c** and **d** of Frechét-type generation one and two were obtained. In the case of the second-generation dendrons, only the mono and disubstituted dendroknots **6d** and **7d** were obtained, most probably due to increasing steric effects with increasing generations and substitution (see above).

All dendrylated knots of generation zero (**5b**) and one (**5c**, **6c** and **7c**) could be isolated in enantiomerically pure form so that we could compare the CD spectra. Figure 8b shows CD spectra of the mono-, di- and tridendryl knots of generation one. The comparison of the first-generation derivatives shows the intensity of the Cotton effect of tridendryl knot **5c** to be substantially higher than that of the mono- and di-substituted analogues (**6c**, **7c**).

Discussion

Hydrogen-bonding patterns and propeller orientation: The knot **5a** described here presents three hydroxy functional groups that can be used as anchor groups to affix large substituents at the periphery. This architectural feature may be compared to that at a tetravalent carbon atom, a trigonal carbon atom, an adamantane moiety (with four substituents), a benzene ring (with six substituents) and to dendrimers, which have already been used as polyfunctional core building blocks

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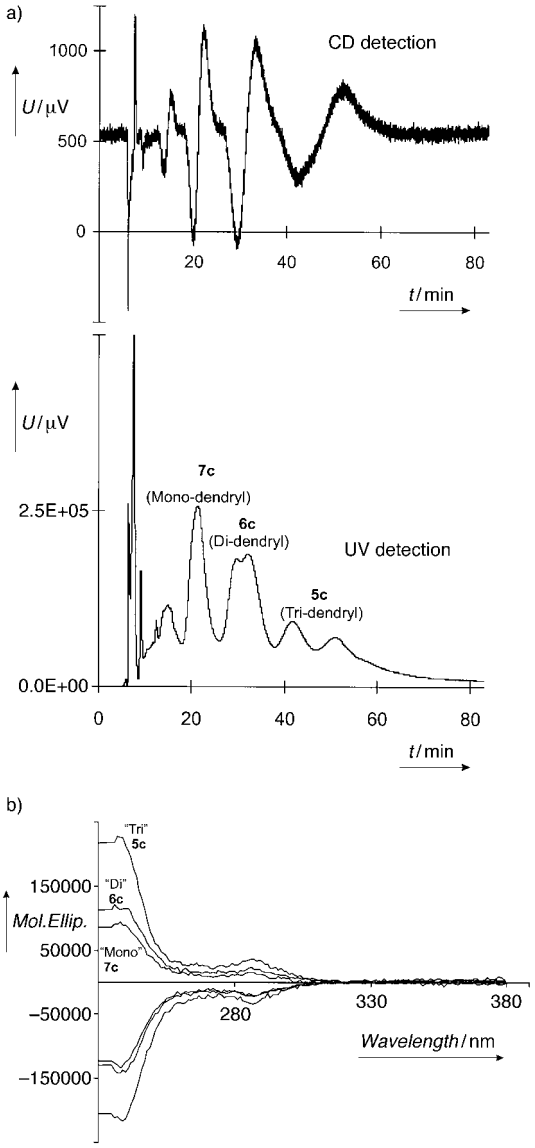

Figure 8. a) Analytical separation of first generation mono-, di-, and tridendryl knots **5c**–**7c** by HPLC on Chiralpak AD, detected by UV and CD spectra at wavelength 254 nm (eluent hexane/chloroform/isopropylalcohol 60:40:2); and b) their CD spectra (**5c**, **6c** and **7c** from top to bottom).

for dendrimer synthesis.[20] Our tri-functionalized knots, however, represent large core units (chiral tectons)[21]: A nano-sized chiral core that allows for the orientation of three substituents in space.

Besides the hydrogen bonding pattern (including solvent participation, see Figure 9), the X-ray analysis reveals a propeller-type orientation of the three pyridine and the three isophthalic units. It also shows the peripheral arrangement of the former and the inner, more hidden placement of the latter.

In the crystal, all pyridine rings (shaded in Figures 1, 9–11) are localized peripherically and the knotanes look somewhat like a flattened hat. Due to the hydrogen-bond pattern, the three pyridine dicarbamide units (P1–P3 in Figure 10) form a near to right angled triangle with two cathetes of equivalent length. All three pyridine dicarbamide units are propeller-like oriented towards the plane **P** (N56, N112, N168, see Table 1).

Due to the fact that all three isophthalic diamide units are involved in the intramolecular hydrogen bond pattern the distances between the I1–I3 units are shorter. They also form a propeller-like arrangement to the plane **I** (C28, C84, C140). While the orientation of I1 and I2 is similar to those found for the pyridine dicarbamide system, the orientation of I3, due to the hydrogen-bonded amide unit N133/O134, is different. I3 lies above the C28-C84-C140 triangle. Again, all isophthaloyl diamine units are at the same side of the plane **I** and twisted in the same direction (Table 2, Figure 11).

The two planes **P** and **I** are twisted by 37° and the six-membered aromatic rings show in opposite direction towards the surface of the knot (Figure 11).

The knot consists of a regular alternated sequence of building blocks P1-I1-P2-I2-P3-I3 (P = pyridine dicarbamide, I = isophthaloyl diamide) linked by diphenylmethane units. All the pyridine dicarbamide units show cisoid orientation of the N-H groups,[22] while in I1 and I3 the orientation is transoid (in I2 cisoid). Cisoid orientation of the N-H groups leads to bifurcate hydrogen bonds between the two NH donors and an acceptor (here C=O or O(MeOH)). Only four (five) of the twelve amide groups participate in intramolecular hydrogen bonds, only one pyridine dicarbamide unit (P1) but all three isophthaloyl diamide units. The sequence for the intramolecular hydrogen bond pattern is P1-I3-I1-I2. This pattern resembles that recently found in [2]rotaxanes.[23] Both amino groups of P1 are involved in a bifurcate hydrogen bond to I3 (O134) while the connected NH group (N133) forms a hydrogen bond to I1 (O29). The transoid carbonyl group of I1 (O22) forms an asymmetric bifurcate hydrogen bond to the cisoid amino groups of I2 (N77, N86). The remaining amino groups of the transoid isophthalic diamides I1 (N21, N30) and I3 (N142) form hydrogen bonds to solvent molecules (meth-

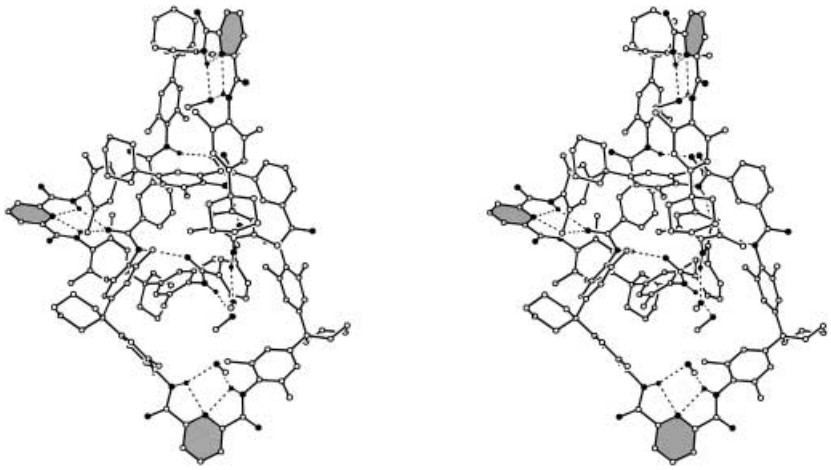

Figure 9. Stereopicture of knotane **5** (R′ = R = H)[15] crystal structure. Hydrogen atoms other than amide protons are left out. Hydrogen bonds are indicated as dotted lines. Solvent molecules are methanol. Pyridine rings are shaded.

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Table 1. Plane **P** formed by the nitrogen atoms of the three pyridine rings and orientation of pyridine dicarbamide units in the amide knotane **5** (distances Å, angles in °).

distances in plane **P**					
N56–N112	15.8	N112-N56-N168	83	Z(P)–N56	8.1
N56–N168	16.6	N56-N112-N168	50	Z(P)–N112	11.3
N112–N168	21.5	N56-N168-N112	47	Z(p)–N168	11.7
angle of the pyridine dicarbamide units to the plane **P**		distance of the *para*-C-atom from plane **P**			
P1	31°	1.4 (C53)			
P2	21°	0.8 (C109)			
P3	10°	0.3 (C165)			
twist of the pyridine dicarbamide and plane **P**					
P1	+44°				
P2	+32°				
P3	+25°				
inter-plane angles					
	P	P1	P2		
P1	125				
P2	58	109			
P3	26	108	80		

Table 2. Plane **I** and orientation of isophthaloyl diamide units (distances Å, angles in °).

distances in plane **I**					
C28–C84	4.5	C84-C28-C140	83	Z(I)–C28	3.1
C28–C140	7.1	C28-C84-C140	63	Z(I)–C84	5.1
C84–C140	7.9	C28-C140-C84	34	Z(I)–C140	4.6
angle of the isophthaloyl diamide units to the plane **I**		distance of the *para*-C-atom from plane **I**			
I1	25°	1.1 (C25)			
I2	15°	0.7 (C81)			
I3	123°	2.3 (C137)			
twist of the isophthaloyl diamide and plane **I**					
I1	+53°				
I2	+48°				
I3	+7°				
inter-plane angles					
	I	I1	I2		
I1	63				
I2	133	87			
I3	122	84	13		

anol) outside the knot, while the two other pyridine dicarbamide units P2 and P3 form bifurcate hydrogen bonds to methanol solvent molecules inside the knot. The remaining C=O groups are involved in hydrogen bonding with peripheral solvent molecules. Additionally the NH groups of the pyridine dicarbamide units form bifurcate hydrogen bonds with the pyridine N atom. In Table 3, the distances and angles of hydrogen bonds are listed.

The question of intramolecular chiral induction: Due to the (topological) chirality of trefoil knots, it was expected that further insight into the question of "intramolecular chiral induction"[10b] could be gained. In particular, we were interested in seeing if the chirality of the knotane core would result in a preferred clockwise/counterclockwise propeller twist of the arene units in the peripheral dendrons. This question is of interest with respect to the frequently observed phenomenon of "crypto optical activity"[19] in chiral dendrimers: How does the chirality of "dendroknots" depend on the dendrimer generation and the propeller angles formed by the three hydroxy pyridine units (shaded in Figure 9–11) of knotanes of type **5**? Comparison of the CD spectra of the first-generation dendroknots (Figure 8b) shows that the tridendrylated knot **5c** gives a much more pronounced Cotton effect at around 240 nm than the mono- and didendrylated species **6c** and **7c**. This increase in the molar ellipticity clearly shows the emergence of some effect which will need to be investigated further. CD spectra of the second-generation dendroknots with their molar ellipticity could not be recorded, because of the small amounts isolated so far.

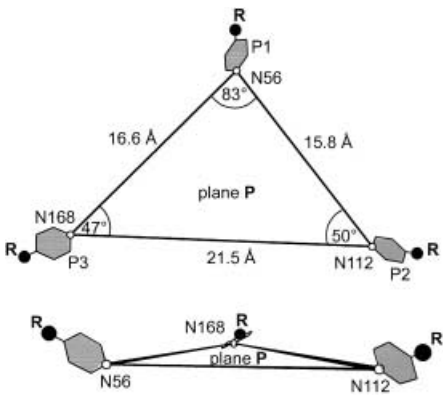

Figure 10. Plane **P** formed by the nitrogen atoms of the three pyridine rings (shaded).

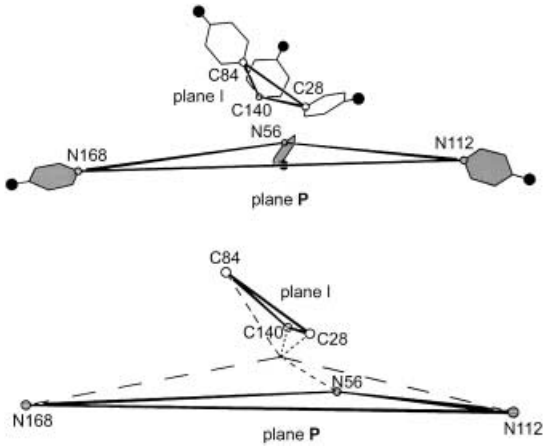

Figure 11. Mutual orientation of planes **P** and **I** (see Figure 10) in the knot **5** (R′ = R = H). Pyridine rings are shaded.

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Table 3. Hydrogen bonds in **5** (distances Å, angles in °).

	N-H	H···O	N···O	N-H···O
P1-I3:				
N49-H49···O134	0.88	2.57	3.36	149
N58-H58···O134	0.88	2.29	3.04	143
I3–I1:				
N133-H133···O29	0.88	2.14	3.00	165
I1–I2:				
N77-H77···O22	0.88	1.96	2.79	157
N86-H86···O22	0.88	3.49	4.17	136
P2:				
N105-H105···O3M	0.88	2.10	2.91	154
N114-H114···O3M	0.88	2.15	2.97	156
P3:				
N2-H2···O2M	0.88	2.17	3.01	158
N161-H161···O2M	0.88	2.14	2.97	158
I1:				
N21-H21···O4M	0.88	2.13	2.99	165
N30-H30···O1M	0.88	2.04	2.85	153
I3:				
N142-H142···O5M	0.88	2.04	2.84	149

Property tuning by dendryl[3b] substituents: Dendritic substituents were chosen, because we did hope to control the lipophilic/hydrophilic balance of the nanometer-sized molecular knots within a wide range, increasing their otherwise limited solubility in different solvents. In addition, this type of amide knot, once evaporated to dryness, is often difficult to solubilize again. With the introduction of dendritic wedges we were able to improve the solubility of the knots to some extent which facilitated column chromatography. Their overall solubility still needs some improvement before the amide knots can be handled in less lipophilic solvents.

Another reason for derivatization of molecular knots is to use the knotted scaffold as a core not only for dendritic peripheral groups but in a more general scheme.[24]

Conclusion

The results show that it was possible to partially derivatise molecular knots using simple protecting group chemistry; this would allow further chemical reactions[25] to introduce sterically demanding substituents as well as improving the general solubility of the knotanes. This should then in turn allow to study the interactions of the chiral knot core with the peripheral chromophoric groups[23] in more detail. The methodology applied here also opens the possibility to produce nano-sized arrays[29] and to use chiral substituents that will lead to the formation of diastereomers. These diastereomers should be easier to separate than enantiomers and allow for further variations of solubility, steric effects and chiral induction. We believe that our studies also contribute to the understanding of the threading mechanism in hydrogen-bond assisted supramolecular template syntheses and we hope that in the future other knot types beyond the trefoil knot can be synthesized. It probably is just a matter of time and skill until further structural and chiral variations of molecular knots will appear.

At an early stage, molecular knots have been regarded as a rather exotic class of substances due to the difficulties in their synthesis and their topological chirality.[2] In the near future, they may become a more generally usable very stable chiral platform. They could be used as an anchoring group accommodating additional functionalities that increase solubility or facilitate crystallization, carrying chromophoric or light harvesting groups, similar to the modifications that have been made with the (non-chiral) fullerene tecton.[21]

Experimental Section

General remarks: All starting materials were purchased from commercial sources or prepared using known literature procedures. The solvents were dried using standard techniques. Whenever possible, reactions were monitored by thin-layer chromatography using TLC silica gel coated aluminium plates $60F_{254}$ (Merck). Compounds were detected by UV light (254 nm). MPLC was done using a Büchi pump. Melting points were determined in a Reichert Thermovar microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using 250, 300 and 400 MHz Bruker instruments; the solvent signal was used for internal calibration. Mass spectra were recorded using a MS-50 from A.E.I., Manchster, GB (EI), a Concept 1H from Kratos Analytical Ltd., Manchester, GB (FAB), MALDI-TofSpec-E from MICROMASS, GB (MALDI) and Voyager-DE from PE Biosystems (MALDI). Elemental analysis were provided by Mikroanalytische Abteilung, Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn.

4-Benzyloxypyridine-2,6-dicarboxylic dimethyl ester: K_2CO_3 (11.0 g, 79.6 mmol) was added to a stirred solution of 4-hydroxy-pyridine-2,6-dicarboxylic dimethyl ester[30] (8.00 g, 37.9 mmol) and benzyl bromide (13.5 g, 78.9 mmol) in acetone (250 mL), and the solution was heated under reflux overnight. After allowing the reaction mixture to cool down to room temperature, the unsoluble residue was removed by filtration and the solvent evaporated at reduced pressure. The crude product was dissolved in chloroform (300 mL), washed three times with water, dried over Na_2SO_4; after filtration the solvent removed under reduced pressure. Re-crystalisation from ethyl acetate (30 mL) yielded the desired product (8.80 g, 77 %). M.p. 102–103 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 3.98$ (s, 6H; COOCH_3), 5.20 (s, 4H; OCH_2), 7.39 (s, 5H; Ph*H*), 7.87 (s, 2H; Pyr*H*); ^{13}C NMR (75.6 MHz, $CDCl_3$): $\delta = 53.2$ (COO*C*H$_3$), 70.8 (O*C*H$_2$), 114.8 (Pyr*C*H), 127.7, 128.7, 128.8 (Ph*C*H), 134.6 (Pyr*C*), 149.8 (Ph*C*), 165.1 (Pyr*C*), 166.7 (*C*OOR); EI-MS(+): *m/z*: calcd for $C_{16}H_{15}NO_5$: 301.1; found: 301.2; elemental analysis calcd (%) for $C_{16}H_{15}NO_5$: C 63.7, H 5.02, N 4.65; found: C 63.81, H 5.03, N 4.53.

4-Benzyloxypyridine-2,6-dicarboxylic dipotassium salt: A solution of KOH (4.00 g, 71.8 mmol) in ethanol (50 mL) was added to a hot solution of 4-benzyloxypyridine-2,6-dicarboxylic dimethyl ester (6.10 g, 20.3 mmol) in ethanol (150 mL), leading to the formation of a voluminous precipitate. After heating for 30 min the reaction mixture was cooled to room temperature and the white precipitate was filtered off and dried, yielding the desired product (6.93 g, 98 %). Elemental analysis calcd (%) for $C_{14}H_9NO_5K_2$: C 48.12, H 2.60, N 4.01; found: C 47.84, H 2.87, N 3.82.

4-Benzyloxypyridine-2,6-dicarbonyl dichloride (3b): 4-Benzyloxypyridine-2,6-dicarboxylic dipotassium salt (5.94 g, 17.0 mmol) was added in small portions over the course of 2 h to a warm solution (oilbath at 30 °C) of oxaloyl chloride (12.0 mL, 142 mmol) in dry benzene (30 mL). The reaction mixture was then heated under reflux. After 4 h the solvent was removed at reduced pressure. The crude product was taken up in dry dichloromethane, filtered and the solvent evaporated. After re-crystallisation from *n*-hexane the desired product was obtained (4.80 g, 91 %). M.p. 113–114 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.26$ (s, 2H; OCH_2), 7.42 (s, 5H; Ph*H*), 7.87 (s, 2H; Pyr*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 71.5$ (O*C*H$_2$), 115.6 (Pyr*C*H), 127.7, 129.0, 129.1 (Ph*C*H), 133.8 (Pyr*C*), 150.6 (Ph*C*), 167.1 (Pyr*C*), 169.5 (*C*OCl); EI-MS(M+) calcd for $C_{14}H_9Cl_2NO_3$: 309.0; found: 309.1; elemental analysis calcd (%) for $C_{14}H_9Cl_2NO_3$: C 54.22, H 2.93, N 4.52; found: C 54.48, H 3.02, N 4.44.

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"O-Benzyl knot": [3_1]Cyclopropane[29′,65′,101′-benzyloxy-5′,17′,23′,35′,41′,53′,59′,71′,77′,89′,95′,107′,110′,112′,115′,117′,120′,122′,125′,127′,130′,132′,135′,137′-tetracosamethyl-8′,14′,26′,32′,44′,50′,62′,68′,80′,86′,98′,104′-dodecaoxohexaspiro{tricyclohexane-1-2″,20′-1″,38′-1‴-[7′,15′,25′,33′,43′,51′,61′,69′,79′,87′,97′,105′,116′,126′,136′]penta-decaazanonadecacyclo[104.2.2.$2^{3',6'}$.$2^{16',19'}$.$2^{21',24'}$.$2^{34',37'}$.$2^{39',42'}$.$2^{52',55'}$.$2^{57',60'}$.$2^{70',73'}$.$2^{75',78'}$.$2^{88',91'}$.$2^{93',96'}$.$1^{9',13'}$.$1^{27',31'}$.$1^{45',49'}$.$1^{63,67,67'}$.$1^{81',85'}$.$1^{99',103'}$]octatriacontahectane[3′,5′,9′,11′,13′(111′),16′,18′,21′,23′,27′,29′,31′(116′),34′,36′,39′,41′,45′,47′,49′(121′),52′,54′,57′,59′,63′,65′,67′(126′),70′,72′,75′,77′,81′,83′,85′(131′),88′,90′,93′,95′,99′,101′,103′(136′),106′,108′,109′,112′,114′,117′,119′,122′,124′,127′,129′,132′,134′, 137′]tetrapentacontaene-56′-1′′′′,74′-1′′′′′,92′-1′′′′′-tricyclohexane}]knotane[3b] **(5b)**: A solution of *N*,*N*′-bis{4′-[1′-(4‴,5‴-dimethylphenyl)cyclohexyl]-2′,6′-dimethylphenyl}isophthalic diamide[11] (1.20 g, 1.55 mmol) and Et_3N (0.4 mL) in dry dichloromethane (250 mL) and a solution of **3b** (0.48 g, 1.55 mmol) in dry dichloromethane (250 mL) were added simultaneously into a flask containing a stirred solution of dry dichloromethane (700 mL). After 6 h the addition was complete and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the crude product was purified via column chromatography ($CHCl_3$/acetone 20:1), yielding the desired product (70 mg, 5%). M.p. >300 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.86, 0.94, 1.06, 1.14, 1.23, 1.29, 1.36, 1.48,1.56, 1.60, 1.81, 1.98, 2.04,2.08, 2.12, 2.18, 2.25, 2.27, 2.31, 2.47, 2.67, 4.26, 4.37, 4.54, 4.98, 5.31, 5.42, 5.77, 6.45, 6.58,6.82, 6.89, 6.96, 6.99, 7.11, 7.16, 7.26–7.58, 7.76, 7.84–7.95, 8.02, 8.26, 8.64, 8.66, 9.06, 9.12, 9.17, 9.40, 9.58, 9.84, 10.26, 10.37, 10.50, 10.54, 11.02, 11.05; MALDI-MS(M+): *m*/*z*: calcd for $C_{198}H_{207}N_{15}O_{15}$: 3036.9; found: 3037.1.

4-[3,5-Bis(benzyloxy)benzyloxy]-pyridine-2,6-dicarboxylic dimethyl ester: A stirred mixture of chelidamic acid dimethylester[30] (1.06 g, 5.00 mmol), 3,5-bis(benzyloxy)benzyloxybromide[16] (3.83 g, 10.0 mmol), K_2CO_3 (1.50 g, 10.9 mmol) and [18]crown-6 (0.80 g, 3.00 mmol) in dry acetone (60 mL) was refluxed for 2 days. After cooling to room temperature the reaction mixture was filtered and the solvent removed under reduced pressure. The crude product was purified by MPLC on silica gel (Lichroprep Si 60 (15–25 μm)) using a 98:2 mixture of dichloromethane/methanol, yielding a white solid (1.9 g, 74%). R_f = 0.52 (dichloromethane/methanol 97:3); m.p. 125.9 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$)δ = 3.92 (s, 6H; COOCH_3), 4.96 (s, 4H; ArOCH_2), 5.07 (s, 2H; ArOCH_2), 6.53 (t, 1H, *J* = 2 Hz; Ar*H*), 6.57 (d, 2H, *J* = 2 Hz; Ar*H*), 7.22–7.35 (br m, 10H; Ph*H*), 7.78 (s, 2H; Pyr*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.2 (OCH_3), 70.2, 70.6 (CH_2O), 102.2, 106.5 (Ar*C*H), 114.8 (Pyr*C*), 127.5, 128.1, 128.6 (Ar*C*H), 136.6, 137.0 (Ar*C*), 149.9 (Pyr*C*), 160.4 (Ph*C*), 165.1 (Pyr*C*), 166.6 (*C*OOR); FAB-MS(+): *m*/*z*: calcd for $C_{30}H_{27}NO_7$: 513.55; found: 514.1; elemental analysis calcd (%) for $C_{30}H_{27}NO_7$: C 70.17, H 5.30, N 2.73; found: C 70.25, H 5.22, N 2.57.

4-[3,5-Bis(benzyloxy)benzyloxy]-pyridine-2,6-dicarbonyl dichloride (3c): A solution of NaOH (0.50 g, 12.5 mmol) in ethanol (20 mL) was added to a stirred solution of 4-[3,5-bis(benzyloxy)benzyloxy]-pyridine-2,6-dicarboxylic dimethyl ester (1.80 g, 3.50 mmol) in ethanol (400 mL). After stirring and heating for 15 min, the voluminous precipitate was filtered and dried. The disodium salt was added in small portions to a warm solution of oxalylchloride (4 mL) in benzene (10 mL). The reaction mixture was then heated to 85 °C and stirred for 2 h. The solvent was distilled off at 14 mbar and the yellowish residue was taken up in dry dichloromethane and filtered through a celite plug under a nitrogen atmosphere. Removal of the solvent under reduced pressure yielded the title compound (0.97 g, 53%) with sufficient purity for the knot synthesis. M.p. 98.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.04 (s, 4H; OCH_2), 5.18 (s, 2H; OCH_2), 6.60 (s, 3H; Ar*H*), 7.24–7.42 (br m, 10H; Ph*H*), 7.81 (s, 2H; Pyr*H*); EI-MS(M+): *m*/*z*: calcd for $C_{28}H_{21}O_5Cl_2$: 521.1; found: 521.1; for analytical purposes a small amount of the acid chloride was hydrolyzed to the corresponding free acid and analyzed: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.78 (br s, 2H; COO*H*), 5.08(s, 4H; OCH_2), 5.28 (s, 2H; OCH_2), 6.63 (t, 1H, *J* = 3 Hz; Ar*H*), 6.73 (d, 2H, *J* = 3 Hz; Ar*H*), 7.27–7.45 (br m, 10H; Ph*H*), 7.77 (s, 2H; Pyr*H*); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 69.8, 70.3(OCH_2), 102.0, 107.0 (Ar*C*H), 114.4 (Pyr*C*H), 128.1, 128.3, 128.8 (Ph*C*H), 137.3 (Ph*C*), 138.3 (Ar*C*), 150.1 (Pyr*C*), 160.1 (Ar*C*), 165.7 (*C*OOH), 166.8 (Pyr*C*H).

"G1 *Tridendryl knot*": [3_1]Cyclopropane[29′,65′,101′-(3,5-bis(benzyloxy)-benzyloxy)-5′,17′,23′,35′,41′,53′,59′,71′,77′,89′,95′,107′,110′,112′,115′,117′,120′,122′,125′,127′,130′,132′,135′,137′-tetracosamethyl-8′,14′,26′,32′,44′,50′,62′,68′,80′,86′,98′,104′-dodecaoxohexaspiro{tricyclohexane-1–2″,20′-1″,38′-1‴-[7′,15′,25′,33′,43′,51′,61′,69′,79′,87′,97′,105′,116′,126′,136′]penta-decaazanonadecacyclo[104.2.2.$2^{3',6'}$.$2^{16',19'}$.$2^{21',24'}$.$2^{34',37'}$.$2^{39',42'}$.$2^{52',55'}$.$2^{57',60'}$.$2^{70',73'}$.$2^{75',78'}$.$2^{88',91'}$.$2^{93',96'}$.$1^{9',13'}$.$1^{27',31'}$.$1^{45',49'}$.$1^{63',67'}$.$1^{81',85'}$.$1^{99',103'}$]octatriacontahectane[3′,5′,9′,11′,13′(111′),16′,18′,21′,23′,27′,29′,31′(116′),34′,36′,39′,41′,45′,47′,49′(121′),52′,54′,57′,59′,63′,65′,67′(126′),70′,72′,75′,77′,81′,83′,85′(131′),88′,90′,93′,95′,99′,101′,103′(136′),106′,108′,109′,112′,114′,117′,119′,122′,124′,127′,129′,132′,134′, 137′]tetrapentacontaene-56′-1′′′′,74′-1′′′′′,92′-1′′′′′-tricyclohexane}]-knotane[3b] **(5c)**: A solution of *N*,*N*′-bis{4′-[1″-(4‴,5‴-dimethylphenyl)cyclohexyl]-2′,6′-dimethyl-phenyl}isophthalic diamide[11] (1.20 g, 1.55 mmol) and Et_3N (0.40 mL) in dry dichloromethane (250 mL) and a solution of **3c** (0.78 g, 1.55 mmol) in dry dichloromethane (250 mL) were added simultaneously into a flask with a stirred solution of dry dichloromethane (700 mL). After 7 h the addition was complete and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography ($CHCl_3$/acetone 25:1), yielding the desired product (52 mg, 3%). M.p. >300 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 0.86, 0.94, 0.95, 1.14, 1.23, 1.38, 1.48, 1.58, 1.99, 2.08, 2.12, 2.18, 2.25, 2.28, 2.33, 2.50, 2.55, 2.67, 3.29, 3.34, 3.40, 3.42, 4.59, 5.12, 5.34, 5.38, 5.40, 5.77, 5.81, 6.41, 6.46, 6.52, 6.64, 6.71, 6.75, 6.76,6.83, 6.90, 6.99, 7.18, 7.26–7.48,7.55, 7.87, 7.90, 8.26, 8.61, 9.06, 9.17, 9.40, 9.60, 9.83, 10.23, 10.49, 10.55, 11.22, 11.35; FAB-MS: *m*/*z*: calcd for $C_{240}H_{243}N_{15}O_{21}$: 3670.8; found: 3672.9 [*M*]$^+$.

4-[3,5-Bis[3′,5′-bis(benzyloxy)benzyloxy]benzyl]-pyridine-2,6-dicarboxylic dimethyl ester: A mixture of chelidamic dimethylester (0.30 g, 1.4 mmol), 3,5-bis[3′,5′-bis(benzyloxy)benzyloxy]benzylbromide[16] (2.75 g, 3.40 mmol) and K_2CO_3 (0.39 g, 2.8 mmol) in dry DMF (20 mL) was stirred at 80 °C for 16 h. After cooling to room temperature the reaction mixture was filtered and the solvent removed under reduced pressure. The residue was washed with water, filtered and dried. The crude product was purified by MPLC on silica gel (Lichroprep Si 60 (15–25 μm)) using a 98:2 mixture of dichloromethane/methanol, yielding a viscous oil (1.3 g, 41%). R_f = 0.48 (dichloromethane/methanol 97:3); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.88 (s, 3H; COOCH_3)4.86 (s, 4H; ArOCH_2), 4.91 (s, 8H; ArOCH_2), 5.01 (s, 2H; ArOCH_2), 6.47 (m, 2H; Ar*H*), 6.53 (d, 2H, *J* = 3 Hz; Ar*H*), 6.57 (d, 5H, *J* = 2 Hz; Ar*H*), 7.17–7.32 (br m, 20H, Ph*H*), 7.76 (s, 2H, Pyr*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.2 (COOCH_3), 70.16, 70.18, 70.6 (OCH_2), 101.7, 105.8, 106.4, 106.6 (Ar*C*H), 114.8 (Pyr*C*), 127.6, 128.0, 128.6 (Ph*C*H), 136.9 (Ph*C*), 137.1, 139.1, 139.4 (Ar*C*), 150.0 (Pyr*C*), 160.2 (Ar*C*), 165.1(*C*OOR), 166.7 (Pyr*C*).

4-[3,5-Bis[3′,5′-bis(benzyloxy)benzyloxy]benzyl]-pyridine-2,6-dicarbonyl dichloride (3d): Acid chloride **3d** was prepared analogous to **3c** with 3,5-bis[3′,5′-bis(benzyloxy)benzyloxy]benzylbromide,[16] yielding a viscous oil (0.86 g, 44%). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 4.86 (s, 4H; ArOCH_2), 4.91 (s, 8H; OCH_2), 5.02 (s, 2H; OCH_2), 6.46 (t, *J* = 2 Hz, 2H,; Ar*H*), 6.49 (s, 2H; Ar*H*), 6.55 (d, 5H, *J* = 2 Hz; Ar*H*), 7.16–7.33 (br m, 20H, Ph*H*), 7.70 (s, 2H, Pyr*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 68.2, 68.3, 69.4 (CH_2O), 99.7, 100.6, 104.5, 104.7 (Ar*C*H), 113.8 (Pyr*C*), 125.7, 126.2, 126.7 (Ph*C*H), 134.3, 134.9, 137.1 (Ar*C*), 148.7 (Pyr*C*), 158.4, 158.5 (Ph*C*), 165.1 (Pyr*C*), 167.6 (*C*OCl).

Mono-, di-, and trihydroxy knot: Pd/C(10%) (5 mg) was added to a stirred solution of **5b** (22.0 mg, 0.007 mmol) in chloroform (4 mL) and methanol (1 mL), and the mixture was hydrogenated at 4 atm H_2 pressure for 8 h. The crude product was taken up in of a 1:1 mixture of acetone/chloroform (30 mL) and filtered through a celite plug. The solvent was removed at reduced pressure, yielding a mixture of mono-, di-, and trihydroxy knot, as well as some unreacted starting material as a white powder (18 mg). This product was used for the following reactions (below): MALDI-MS for monohydroxy knot: calcd for $C_{191}H_{201}N_{15}O_{15}Na$: 2967.5; found: 2969.0 [*M*+Na]$^+$; MALDI-MS for dihydroxy knot: calcd for $C_{184}H_{195}N_{15}O_{15}Na$: 2877.5; found: 2879.0 [*M*+Na]$^+$; MALDI-MS for trihydroxy knot calcd for $C_{198}H_{207}N_{15}O_{15}Na$: 2787.4; found: 2789.0 [*M*+Na]$^+$.

"G1 Mono-, di-, and tridendryl knot" (5c, 6c, 7c): 3,5-Bis(benzyloxy)benzylbromide[16] (7.00 mg, 0.018 mmol) was added under an argon atmosphere to a stirred mixture of mono-, di-, trihydroxy knot (18 mg, 0.006 mmol) and K_2CO_3 (20.0 mg) in dry acetone (25 mL). After 8 h the crude product was filtered through a silica gel plug and washed with chloroform (2 × 10 mL). The solvent was removed at reduced pressure, yielding a mixture **5c**, **6c** and **7c** as a white powder (24 mg). The crude mixture was purified and simultaneously separated into its enantiomers using semipreparative HPLC (column: Chiralpak AD, eluent: hexane/chloroform/isopropanol 60:40;2, CD detection at 254 nm). The separated products were identified by MALDI-TOF mass spectrometry: MS: *m*/*z*: calcd for **7c** $C_{226}H_{231}N_{15}O_{17}$-Na: 3269.7; found: 3272.1 [*M*+Na]$^+$; MS: *m*/*z*: calcd for **6c** $C_{226}H_{231}N_{15}O_{19}$-

Na: 3482.5; found: 3487.3 $[M+Na]^+$; MS: calcd for **5c** $C_{240}H_{243}N_{15}O_{21}Na$: 3693.8; found: 3696.3 $[M+Na]^+$.

"G2 Mono- and didendryl knot" (6d and 7d): 3,5-Bis[3′,5′-bis(benzyloxy)benzyloxy]benzylbromide[16] (16.0 mg, 0.02 mmol) was added under an argon atmosphere to a stirred mixture of mono-, di-, trihydroxy knot (10.0 mg, 0.003 mmol) and K_2CO_3 (20 mg) in dry acetone (15 mL). After 5 d the crude product was filtered through a silica gel plug and washed with chloroform (2×10 mL). The solvent was removed at reduced pressure, yielding a mixture of **6d** and **7d** as a white powder (22 mg). The crude mixture was purified and simultaneously separated into its enantiomers using semipreparative HPLC (column: Chiralpak AD, eluent: hexane/chloroform/isopropanol 60:40:4, CD detection at 254 nm). The separated products were identified by MALDI-TOF mass spectrometry: MS: *m/z*: calcd for **7d** $C_{282}H_{279}N_{15}O_{27}Na$: 4330.1; found: 4335.2 $[M+Na]^+$; MS: *m/z*: calcd for **6d** $C_{240}H_{243}N_{15}O_{21}Na$: 3693.8; found: 3699.6 $[M+Na]^+$.

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