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Chelidamic acid derivatives: Precursors to functionalized pyridyl cryptands & functionalized metal ligands

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ABSTRACT

Pyridyl cryptands, such as **12**–**16** formed from pyridine-2,6-dicarbonyl chloride (**4**) and crown ether diols **7**–**11**, have been demonstrated to be excellent hosts for viologens (*N,N′*-dialkyl-4,4′-bipyridinium salts, **2**) with K_a values of ~10^4 to 10^6 M^{-1} and thus are considered to be ideal building blocks for supramolecular systems. However, in order to incorporate these host motifs into useful starting materials, functionalization is required; in this article we describe syntheses of 23 new chelidamic acid (2,6-dicarboxy-4-hydroxypyridine, **5**) derivatives that can be used to prepare functional pyridyl cryptands and functional metal ligands. The preparation and characterization of three new functionalized pyridyl cryptands are also included.

1. Introduction

The application of host-guest chemistry to supramolecular chemistry requires powerful and specific interactions between the two components to ensure efficient self-assembly processes [1–11]. A well-used host-guest motif is the interaction of crown ethers, such as bis(*m*-phenylene)-32-crown-10 (**1**), with viologens (*N,N′*-dialkyl-4,4′-bipyridinium salts) **2**, which afford association constants (K_a) in the range 20–3333 M^{-1} [12,13]. Conversion of bis(*m*-phenylene)-32-crown-10 (**1**) to cryptand **3** by incorporation of a third ethyleneoxy arm increased K_a 100-fold to 6.1 x 10^4 M^{-1}, totally due to its preorganization, which reduced the entropic penalty [14]. Further, conversion of the crown ether diol **8** to pyridyl cryptand **13** (Scheme 1), thus introducing a nitrogen for interaction with the viologen, by reaction with diacid chloride (**4**) increased the association constant by two more orders of magnitude to 5× 10^6 M^{-1} (Table 1) [15]. Therefore, other crown ethers have been converted to their pyridyl cryptands, thus providing a family of more efficient building blocks for supramolecular chemistry (Scheme 1, Table 1). Recently a template method was reported to increase the cyclization yields of the pyridyl cryptands dramatically [24]; this method coupled with templation of the formation of dibenzo crown ethers via the Wang-Pederson-Wessels protocol (using KPF_6) [18,25,26] allows efficient preparation of these powerful hosts at scale. However, to be useful these cryptands need to possess functional groups that allow them to be incorporated into well-designed, larger building blocks. The present article describes approaches to functional precursors to such cryptands, i. e., derivatives of chelidamic acid (**5**). Conveniently, there is a high-yielding (81%) literature procedure for the synthesis of chelidamic acid from acetone and diethyl oxalate via aldol condensation to form chelidonic acid (**6**), which is converted to **5** by reaction with ammonia [27]. The hydroxyl group at the 4-position of chelidamic acid is ideal for functionalization, given the wide range of reactions available for hydroxyl moieties.

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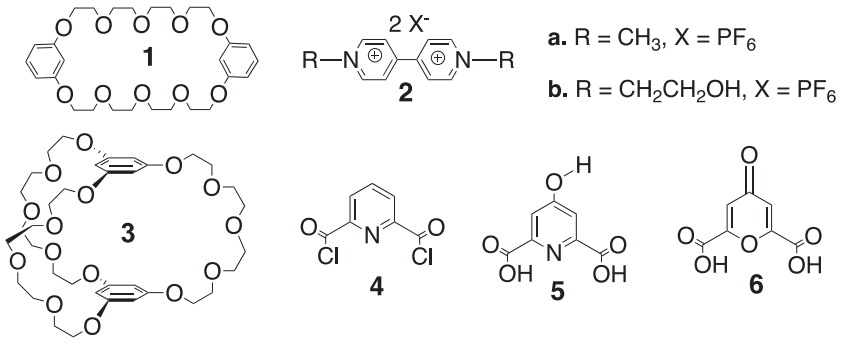


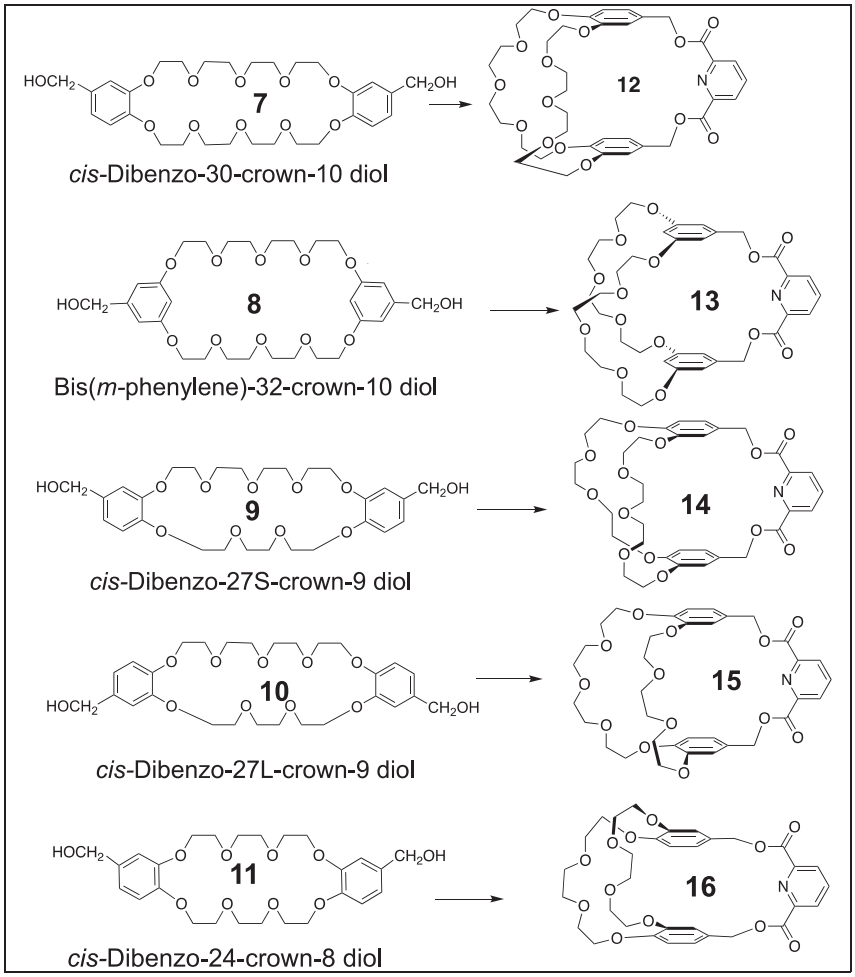
2. Results & discussion

2.1. Heck cross coupling

Initial efforts focused on Heck coupling reactions [28]. Chelidamic acid was converted to the 4-bromo diesters **17a** and **17b** in good yields (Scheme 2). **17a** was subjected to Heck coupling first with *p*-chloromethylstyrene to afford reactive monomer **18**, entirely in the *E* isomeric form of the stilbene-like double bond; basic hydrolysis of the ester moieties and the chloromethyl group yielded **19**. Heck conditions with **17b** and ethyl vinyl ether afforded **20**, in which the *E* isomer slightly predominated over the *Z* by 52:48%. The disappointing yields of these couplings, presumably due to complexation of the Pd catalyst by the pyridine nitrogen, led us to abandon this approach.

2.2. Williamson ether synthesis

The venerable, classic Williamson ether synthesis is an obvious approach for general functionalization of chelidamic esters. Therefore, dimethyl and diethyl chelidamates (**21a** and **21b**) were prepared [29].



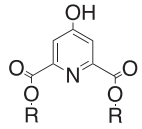
Scheme 1. Syntheses of pyridyl cryptands from crown ether diols using pyridine-2,6-diarboxylic acid chloride.

Table 1
Association constants for crown ether and cryptand hosts with viologens **2a** and **2b** in acetone at 22–25 °C.

Host	Guest	K_a (mol/L)	Ref.
1	**2a**	760	[16]
3	**2a**	6.1 x 10^4	[14]
8	**2a**	5.7 x 10^2	[14]
13	**2a**	5.0 x 10^6	[15]
7	**2a**	1.1 x 10^3	[17]
12	**2a**	2.0 x 10^5	[18]
12	**2b**	1.0 x 10^5	[18]
9	**2a**	NA[a]	
14	**2a**	2.49 x 10^5	[19]
14	**2b**	6.70 x 10^4	[19]
10		NA[a]	
15	**2a**	5.11 x 10^4	[19]
15	**2b**	8.08 x 10^3	[19]
11		NA[b]	
16	**2b**	1.0 x 10^4	[20]

[a] NA = not available in the literature.
[b] NA = probably complicated by ion pairing effects [21–23].

Initially using the dimethyl ester **21a** we successfully introduced the aldehyde (formyl) group into the chelidamic acid residue as shown in Scheme 3. Using cesium carbonate as the base and DMF as the solvent, preparation of the desired ether **22** proceeded in high yield. Basic hydrolysis afforded the corresponding diacid **23**; interestingly the good yield indicated that the possible Cannizzaro side reaction [30] induced by the strongly basic conditions did not interfere.



21
a. R = CH_3
b. R = CH_2CH_3
c. R = $CH(CH_3)_2$

Then diethyl ester **21b** was subjected to Williamson reaction conditions with *p*-chloromethylstyrene (Scheme 4). The substituted styrene product, obtained in modest yield, consisted of two isomers in 80:20 ratio, the desired *O*-alkylated isomer (**24**) and the *N*-alkylated product (**25**), respectively, as a result of the tautomerism between the quinoidal and the aromatic forms of the starting diester.

We reasoned that bulky esters would restrict the Williamson reaction to the desired *O*-alkylated product. Therefore, diisopropyl chelidamate (**21c**) was prepared [29] and subjected to the same reaction conditions (Scheme 5). The sole product was the desired *O*-alkylated product **26**, which afforded the substituted diacid **27** upon basic hydrolysis. To demonstrate the usefulness of this reaction, product **26** was elaborated to the secondary benzylic bromide **28**, which was isolated as a mixture with an unknown minor component. Nonetheless, when subjected to treatment as shown in Scheme 6, the tetramethylpiperidine-*N*-oxide (TEMPO) derivative **29** was isolated.

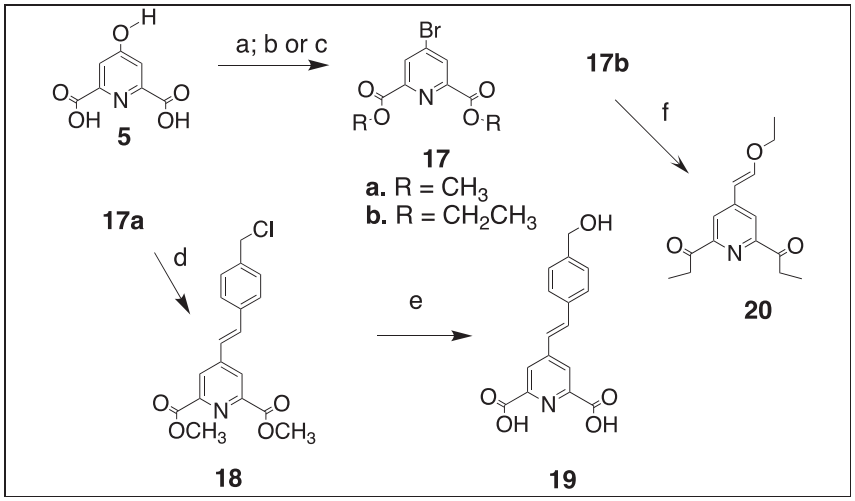
With the alkylation reaction under control we moved forward with other Williamson ether derivatizations of diisopropyl chelidamate **21c**.

Scheme 7 displays reactions of diisopropyl chelidamate (**21c**) with other electrophiles with chloride leaving groups. Similarly, Scheme 8 summarizes reactions of **21c** with alkyl bromides and hydrolysis of the diesters to the diacids. Bromo compounds **33** and **34** (Scheme 8) were reported earlier [31]. The C_{10} dimer ester **43** and derived diacid **44** (Scheme 8) were also reported earlier as building blocks for supramolecular polymers [32].

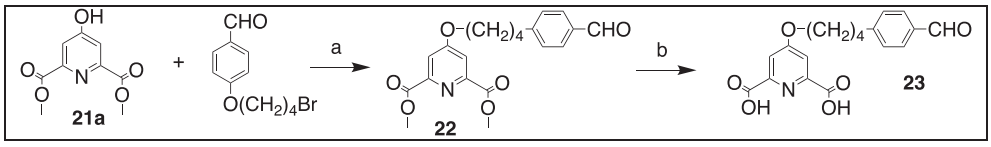
Scheme 9 summarizes reactions of **21c** with electrophiles with tosylate leaving groups; the dimeric chelidamate **47** and the corresponding diacid **48** were reported earlier as building blocks for supramolecular polymers [32]. The target molecule of the reaction between **21c** and *p*-bis(tosyloxyethoxy)benzene at 2:1 stoichiometry, respectively, was **47**, but **45** was isolated as the main product. The reaction of **21c** (2 eq.) with the ditosylate (1 eq.) in the presence of potassium carbonate was executed using acetonitrile as the solvent and also using acetone. Acetone gave a 4:1 ratio of **45**:**47** as described in the Experimental section, but with acetonitrile the product ratio was 1:>99 **45**:**47** [32]. Acetone retarded the reaction speed vs. acetonitrile, allowing temporal control over mono- or di-additions. Note that the yields of these reactions are not optimized; indeed, some of the low yields can be attributed to small reaction scales and some to solubility issues.

2.3. Potential applications

The aldehyde derivatives **22**, **23**, **32**, **41** and **42** were prepared as



Scheme 2. Heck coupling reactions starting with chelidamic acid: a) PBr_3, b) CH_3OH (91%); c) CH_3CH_2OH (95%); d) *p*-chloromethylstyrene/$Pd(OAc)_2$/$P(C_6H_5)_3$/Na_2CO_3/DMF (14%); e) KOH/THF-H_2O (71%); f) ethyl vinyl ether/$Pd(OAc)_2$/$P(C_6H_5)_3$/K_2CO_3/DMF (35%).



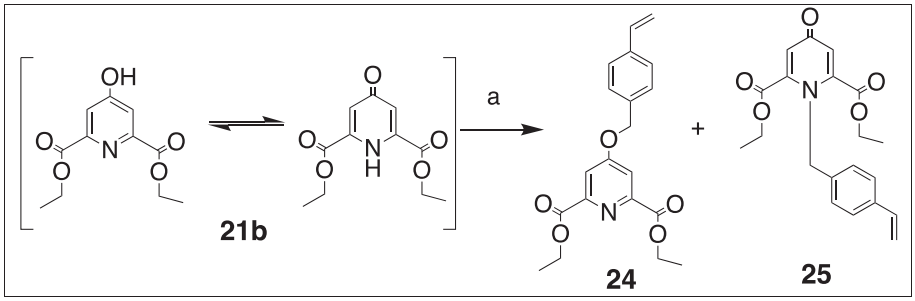
Scheme 3. Synthesis of dimethyl chelidamate formyl derivatives: a) Cs_2CO_3/DMF/90 °C (88%); b) KOH/H_2O/reflux (80%).

chain reaction terminators in ring opening metathesis polymerizations (ROMP) [33–35]; they will react with the growing polymers' metal carbene end groups to produce macromolecules with chelidamate functions at the ends for further supramolecular construction, either via conversion to active metal complexes [29,36–38] (including chirality [38–40]) or to cryptands tailored for specific supramolecular interactions.

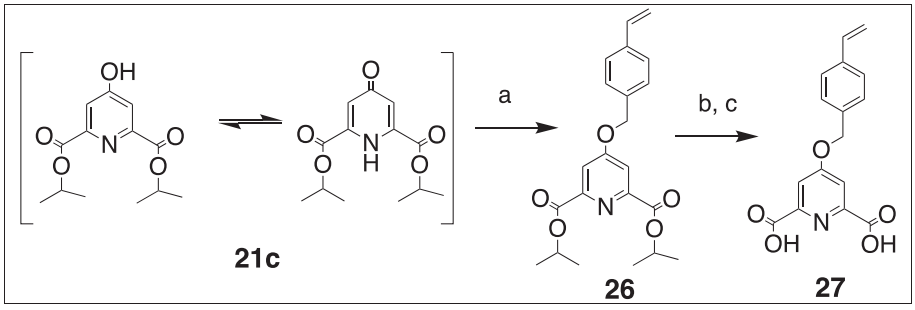
The secondary bromo derivative **28** is an initiator for atom transfer radical polymerization (ATRP) [41] of vinyl monomers. The corresponding TEMPO compound **29** is an initiator for nitroxide mediated radical polymerization (NMP) [42] of vinyl monomers. The products of these two types of polymerizations will bear chelidamate end groups that could be used to form active metal ligands [29,36–40], as noted above, or cryptands tailored for specific supramolecular interactions.

The halide functionalized compounds **18**, **30**, **33**–**38** were designed as substrates for Heck [28], Sonogshira [43] and related Suzuki couplings [44]. **18** could also be a substrate for further Williamson ether syntheses.

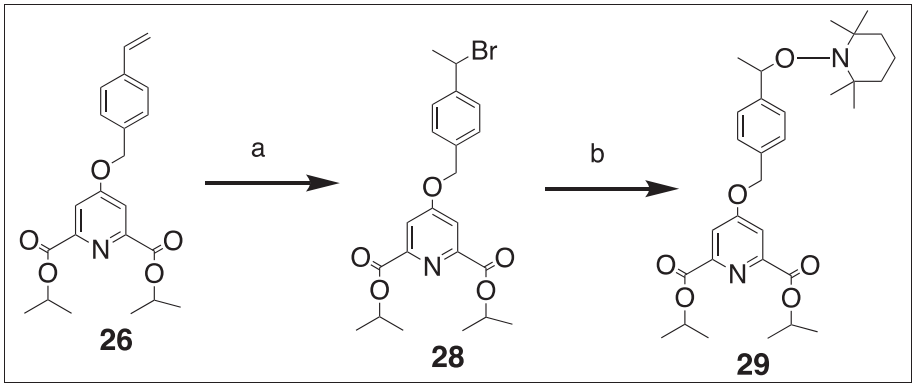
The styryl monomers **24**, **26** and **27** are obvious targets for vinyl



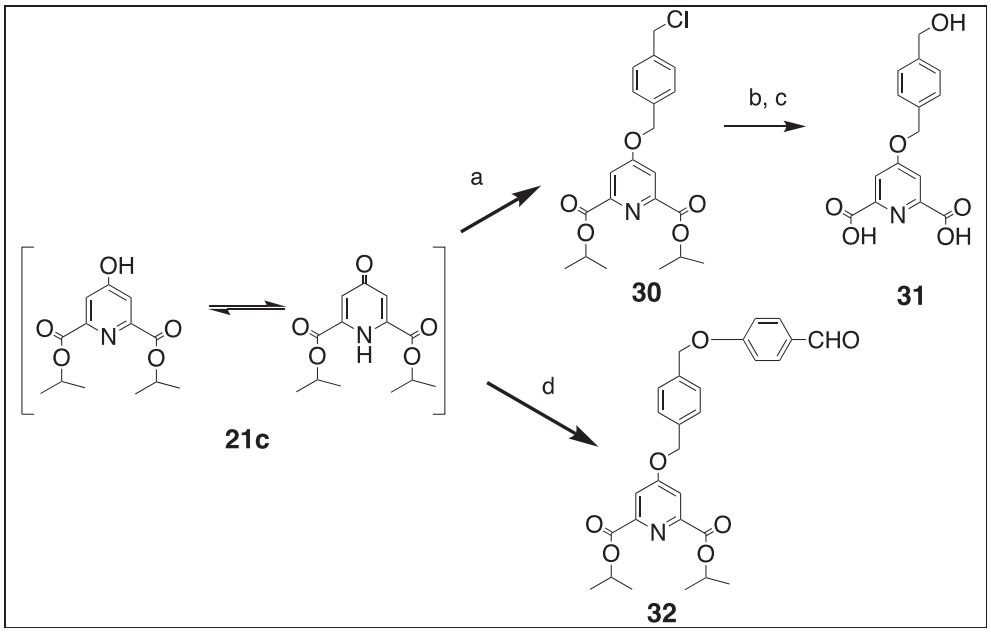
Scheme 4. Williamson ether synthesis with diethyl chelidamate: a) *p*-chloromethylstyrene/K_2CO_3/acetone, reflux (57%).



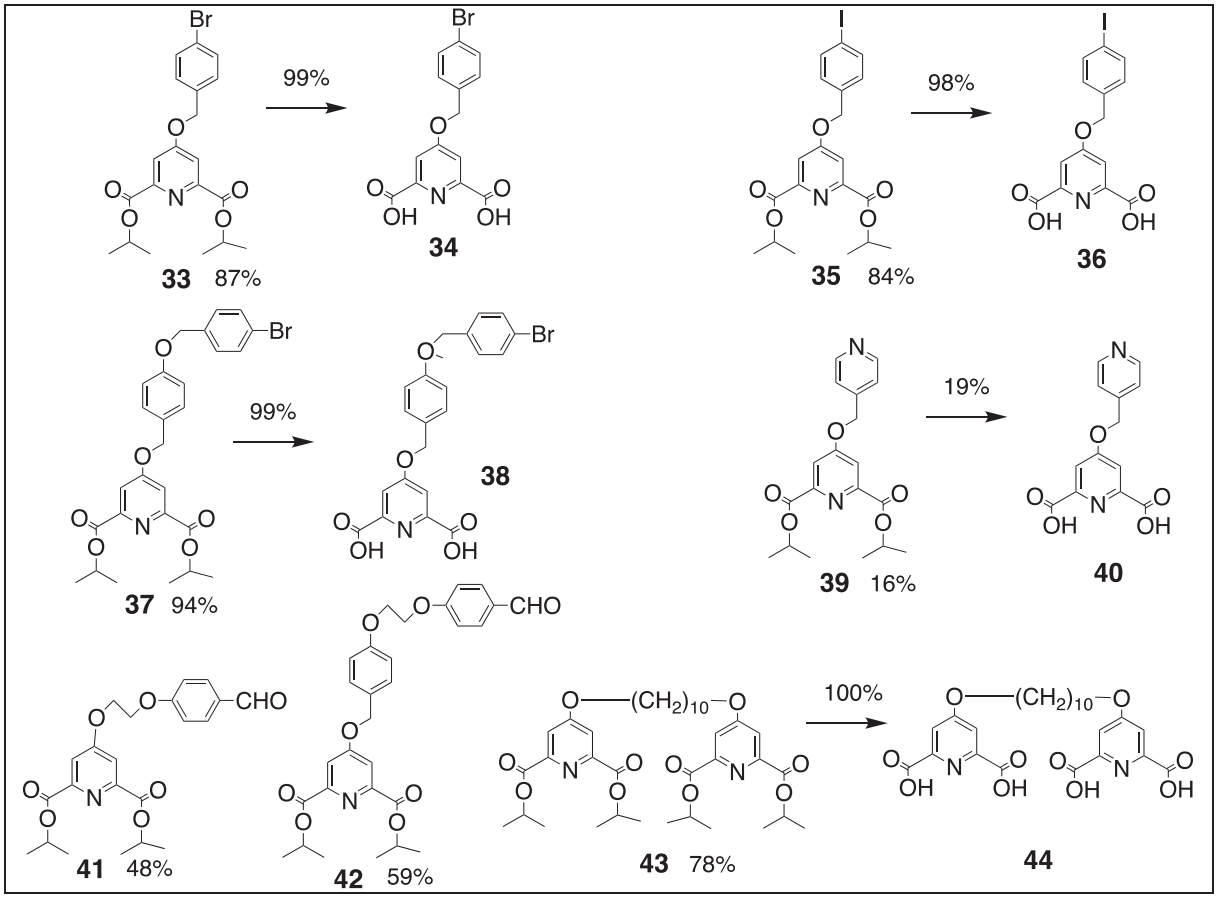
Scheme 5. Williamson ether synthesis with diisopropyl chelidamate: a) *p*-chloromethylstyrene/K_2CO_3/acetone, reflux (64%); b) KOH/THF-H_2O/rt; c) HCl (97%).



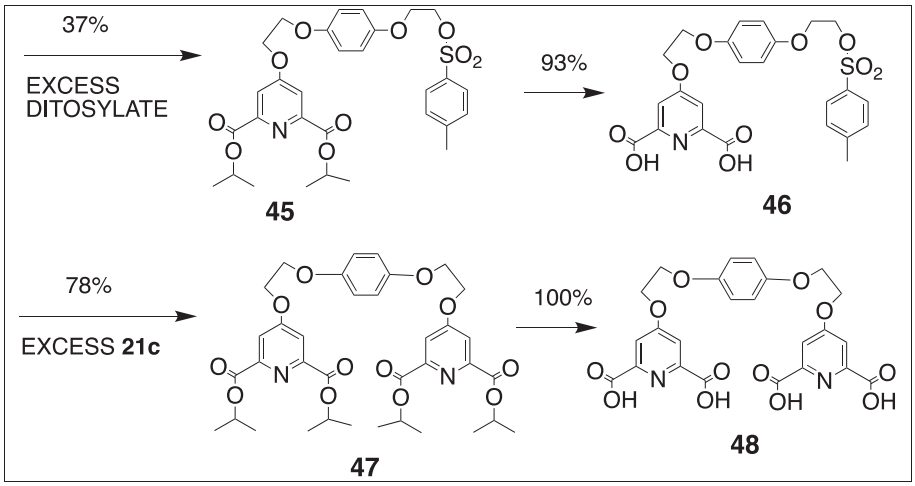
Scheme 6. Conversion of styrene **26** to bromide **28** and thence to TEMPO derivative **29**: a) PBr_3 @ SiO_2/CH_2Cl_2, rt, 2h (86%, a mixture); b) TEMPO/Cu powder/Cu(OTf)$_2$/PMDETA/benzene/reflux (57%).



Scheme 7. Williamson ether synthesis with diisopropyl chelidamate (**21c**) and electrophiles with benzylic chloride leaving groups: a) *p*-bis(chloromethyl)benzene/K_2CO_3/acetone, reflux (15%); b) KOH/THF-H_2O/rt; c) HCl (97%); d) *p*-(*p*'-chloromethylbenzyloxy)benzaldehyde/K_2CO_3/acetone/reflux (59%).



Scheme 8. Chelidamic acid derivatives prepared by Williamson ether synthesis from diisopropyl chelidamate (**21c**) and electrophiles with bromide leaving groups: alkyl bromide/K_2CO_3/acetone/reflux. Hydrolyses: KOH/THF-H_2O/rt.



Scheme 9. Chelidamic acid derivatives prepared by Williamson ether syntheses from diisopropyl chelidamate (**21c**) and electrophiles with tosylate leaving groups: tosylate/K_2CO_3/acetone/reflux. Hydrolyses: KOH/THF-H_2O/rt.

polymerization via free radical and cationic techniques.

The pyridyl functionalized systems **39** and **40** were envisioned to be useful because of the additional ligand binding site [29,36–40] they provide as well as their ability to be protonated.

2.4. Formation of new pyridyl cryptands

The conversion of these chelidamic acid derivatives to cryptands is illustrated by the following examples, which involve pseudo-high dilution syntheses, inasmuch as the present work was done prior to the development of the template synthetic approach to cryptands [24]. Known [45] 4-benzyloxypyridine-2,6-dicarbonyl chloride (**49**) underwent cyclization with *cis*-dibenzo30-crown-10 diol (**7**) [18], yielding cryptand **50** (Scheme 10); attempts to deprotect the phenolic functionality by hydrogenolysis led to an unknown mixture of the desired phenol as a minor component, apparently the result of cleavage of the ester moieties. Formyl functionalized cryptand **51** resulted from *cis*-dibenzo-30-crown-10 diol (**7**) [18] and chelidamate **23** (Scheme 11). These cyclization yields could no doubt be improved by using the template method reported in the meantime [24].

And finally the new diamide cryptand **54** resulted from reaction of known diamine **52** [prepared from chelidamic acid (**5**)] [46] and known dibenzo-30-crown-10 diacid chloride **53** [47] (Scheme 12).

The complexation properties of new cryptands **50**, **51** and **54** were not examined in this work.

Attempts to remove the benzyl protecting group from **50** by hydrogenolysis to form the phenolic cryptand were futile; it appeared that the ester moieties were cleaved under these conditions.

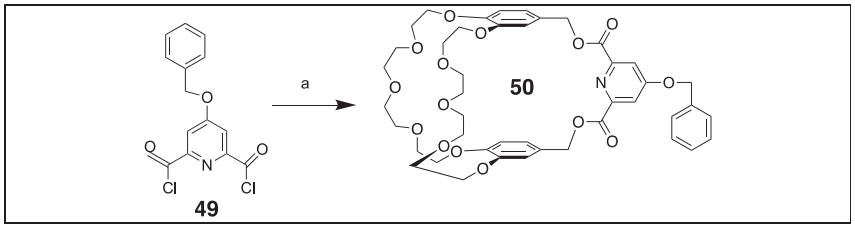
3. Conclusions

We reported several derivatizations of chelidamic acid to produce useful precursors to pyridyl cryptands and/or metal ligands [29,36–40]. Heck cross coupling under unoptimized conditions afforded only low yields of products. Williamson ether conditions with variety of electrophiles efficiently provide a wide range of functionalized derivatives. In all, here we reported 23 new derivatives of chelidamic acid and three new pyridyl cryptands.

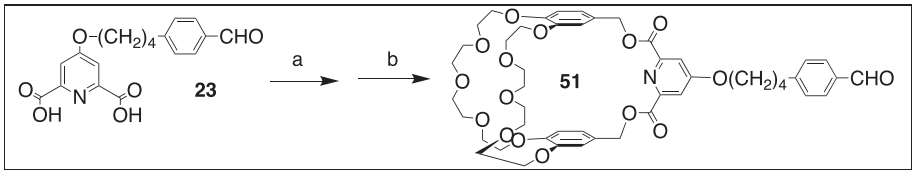
4. Experimental section

4.1. General

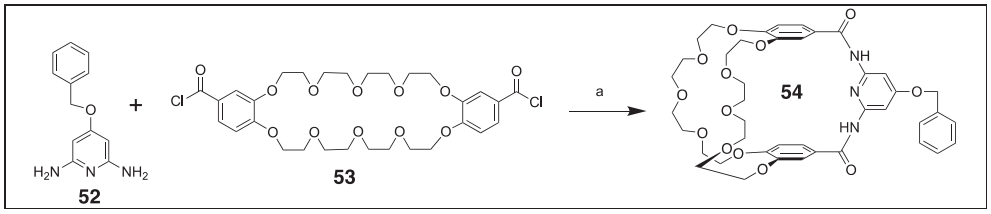
^{1}H NMR spectra were obtained on JEOL Eclipse-500, Bruker-500 and Agilent-NMR-vnmrs400 spectrometers; signal assignments were made using COSY. ^{13}C NMR spectra were collected at 126, 126 and 101 MHz on these instruments, respectively. High resolution electrospray mass spectra (HR ESI MS) were obtained using an Agilent HP121 or HP921 LC-ESI-TOF system with acetonitrile as solvent; fast atom bombardment (FAB) spectra were obtained in both low and high resolution modes (LR and HR, respectively) using a JEOL Model HX 110 Dual Focusing Mass Spectrometer with xenon gas for ionization; the samples were mixed in nitrobenzoic acid/poly(ethylene glycol) (NBA/PEG). Unless noted starting materials were obtained from commercial sources and used as received. The following compounds were made in accordance with literature procedures; yields similar to those reported were achieved: **5** [27], di(4-hydroxymethylbenzo)-30-crown-10 (**7**) [18], 4-bromoesters **17a** and **17b** [48], dialkyl chlidamates (**21a**–**21c**) [29], *p*-iodobenzyl bromide [49], *p*-bis(2′-tosyloxyethoxy)benzene [50], *p*-(2′-



Scheme 10. Synthesis of new benzyloxy cryptand **50** from 4-benzyloxypyridine-2,6-dicarbonyl chloride (**49**) a) *cis*-dibenzo-30-crown-10 diol (**7**)/pyridine/dichloromethane/syringe pump addition/pseudo-high dilution (42%).



Scheme 11. Synthesis of new formyl functionalized cryptand **51** from diacid **23**: a) $SOCl_2$/reflux; b) *cis*-dibenzo-30-crown-10 diol (**7**)/pyridine/dichloromethane/syringe pump addition/pseudo-high dilution (23%).



Scheme 12. Synthesis of new diamide cryptand **54** from 4-benzyloxypyridine-2,6-diamine (**52**) and *cis*-dibenzo-30-crown-10 dicarbonyl chloride (**53**): a) pyridine/dichloromethane/pyridinium trifluoromethylsulfonylimide template [24] (21%).

bromoethoxy)benzaldehyde [51], *p*-(*p'*-chloromethylbenzyloxy) benzaldehyde [52], 4-benzyloxypyridine-2,6-dicarbonyl chloride (**52**) [45] and di(4-chlorocarbonylbenzo)-30-crown-10 (**53**) [47].

(*E*-) Dimethyl 4-(*p'*-chloromethylstyryl)pyridine-2,6-dicarboxylate (18). Dimethyl 4-bromopyridine-2,6-dicarboxylate (**17a**) (0.83g, 3.0 mmol), $Pd(OAc)_2$ (22.2 mg, 0.0989 mmol), PPh_3 (63.5 mg, 0.242 mmol), and Na_2CO_3 (0.45 g, 4.2 mmol) were added to a flask containing a magnetic stir bar. The solvent, DMF (80 mL), and *p*-vinylbenzyl chloride (0.60 mL, 4.3 mmol) were added to the flask once an oil bath had been preheated to 90 °C. The reaction mixture was allowed to stir at 90 °C under nitrogen for 60 h. A portion of solvent was removed by rotary evaporation and the remaining mixture was dissolved in chloroform; the mixture was washed with 1 M HCl (x2), water (x3), and dried over Na_2SO_4. After filtration and evaporation of the solvent, a minimal amount of chloroform was used to dissolve the product and it was precipitated into ether (~100 times the volume of chloroform): a yellow tinted solid, 146.5 mg (14%), mp 175.0–177.0 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 7.62–7.41 (m, 5H), 7.14 (d, J = 16 Hz, 1H), 4.62 (s, 2H), 4.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.38, 148.85, 147.59, 138.78, 135.68, 135.11, 129.34, 128.98, 127.77, 125.05, 53.38, 45.83 (12 peaks expected and 12 peaks found). HR ESI MS: calc. for $C_{18}H_{17}NO_4Cl$ $[M+H]^+$: *m/z* 346.0841; found: *m/z* 346.0860 (error 5.7 ppm).

General procedure 1: (*E*- & *Z*-) 4-(*p'*-hydroxymethylstyryl) pyridine-2,6-dicarboxylic acid (19). **18** (187.8 mg, 0.5431 mmol) was dissolved in THF (50 mL) and a solution of 10 wt % aq. KOH (30 mL) was added to the stirred solution. The solution was stirred for 12 h and THF was removed by rotary evaporation. The remaining aqueous solution was acidified to pH 1 and the white precipitate was collected by filtration: 115.6 mg (71%), mp 85.6–91.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (s, 2H), 7.78 (d, J = 16 Hz, 1H), 7.69 (d, J = 8 Hz, 2H), 7.46 (d, J = 16 Hz, 1H), 7.37 (d, J = 8 Hz, 2H), 4.53 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, major signals) δ 166.15, 149.28, 148.33, 144.35, 135.64, 134.93, 127.84, 127.37, 124.60 (two closely spaced peaks), 63.18 (11 peaks expected and 11 peaks found). HR ESI MS: calc. for $C_{16}H_{14}O_5N$ $[M+H]^+$: *m/z* 300.0867; found: *m/z* 300.0872 (error −2 ppm).

(*E*- & *Z*-) Diethyl 4-(2′-ethoxyvinyl)pyridine-2,6-dicarboxylate (20). To a flask containing DMF (100 mL) were added $Pd(OAc)_2$ (57.5 mg, 0.256 mmol), diethyl 4-bromopyridine-2,6-dicarboxylate (**17b**, 2.16 g, 7.88 mmol), K_2CO_3 (1.30 g, 9.41 mmol), PPh_3 (156 mg, 0.595 mmol), and ethyl vinyl ether (1.0 mL, 10 mmol). The reaction mixture was stirred under nitrogen at 90 °C for 19 h. Solvent was removed by rotary evaporation and the crude material was dissolved in chloroform. The solution was washed with 1 M HCl (x3) and water (x3), followed by drying over Na_2SO_4. Filtration and removal of the solvent provided a material which was purified by passing through a silica column, eluting with hexanes:ethyl acetate (EA) 1:1, to give a mixture of *E*- and *Z*-isomers, the latter slightly predominating 52:48%; 0.74 g (35%), mp 48.2–55.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 2.0H), 8.04 (s, 1.8H), 7.39 (d, J = 13 Hz, 0.94H), 6.54 (d, J = 7 Hz, 1.0H), 5.82 (d, J = 13 Hz, 0.88H), 5.31 (d, J = 7 Hz, 1.0H), 4.46 (m, 8H), 4.11 (q, J = 7 Hz, 2.0H), 3.99 (q, J = 7 Hz, 1.7H), 1.35–1.50 (m, 18.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.37, 165.22, 153.56, 152.85, 148.83, 148.66, 147.75, 146.18, 126.36, 123.29, 102.87, 102.16, 70.52, 66.79, 62.37, 62.22, 15.46, 14.80, 14.31 (20 peaks expected, 19 peaks observed). HR ESI MS: calc. $C_{15}H_{20}NO_5$ [M+H]: 294.1366, found *m/z* 294.1301 (error −2.2 ppm); calc. for $C_{30}H_{38}N_2O_{10}Na$ $[2\,M+Na]^+$: *m/z* 609.2419, found: *m/z* 609.2364 (error −8.9 ppm).

***p*-(4′-bromobutoxy)benzaldehyde**. K_2CO_3 (5.75g, 38.0 mmol), *p*-hydroxybenzaldehyde (4.93 g, 38.0 mmol), and 1,4-dibromobutane (41.00 g, 190 mmol, distilled) were added to acetone (240 mL) and the mixture was refluxed for 6 h under N_2. The reaction mixture was cooled to rt and solvent was removed. H_2O (100 mL), 2 M HCl (100 mL), and CH_2Cl_2 (400 mL) were added and mixed. The organic phase was collected and washed with 10% Na_2CO_3 (x2). The organic phase was dried with Na_2SO_4, filtered, and concentrated to an oil, which was subjected to silica gel chromatography. The excess dibromobutane was eluted with hexanes and the product was eluted with diethyl ether as a pale-yellow oil (5.16 g, 68%), reported [53] mp 32–34 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.89 (s, 1H), 7.84 (m, 2 H), 6.99 (m, 2H), 4.09 (t, J = 6 Hz, 2H), 3.50 (t, J = 10 Hz, 2H), 1.95–2.13 (m, 4H). LR FAB MS (NBA): *m/z* 257, 100% $[M(^{79}Br)+H]^+$; 258, 28% $[M+H+1]^+$; 259, 87% $[M(^{81}Br)+H$ and $M(^{79}Br)+H+2]^+$; 260, 15% $[M(^{81}Br)+H$ and $M(^{79}Br)+H+3]^+$.

Dimethyl 4-[4'-(*p''*-formylphenoxy)butoxy]pyridine-2,6-dicarboxylate (22). Dimethyl chelidamate (**21a**) (1.48 g, 7.1 mmol), *p*-(4′-bromobutoxy)benzaldehyde (2.97 g, 11.0 mmol), and Cs_2CO_3 (2.88 g, 9.0 mmol) were stirred in DMF (20 mL) at 85 °C under nitrogen for 4 h. The solvent was removed and the reaction mixture was partitioned in H_2O/ethyl acetate. The aqueous phase was extracted with EA (x3). The combined organic phase was

washed with 10% Na_2CO_3, H_2O (x2) and sat. NaCl and then dried with Na_2SO_4; the solution was filtered, and the solvent was evaporated. The product was isolated via column chromatography (silica, 3:2 EA:hexanes): 2.42 g (88%), mp 89.9–91.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.95 (s, 1H), 7.85 (d, J = 8 Hz, 2H), 7.81 (s, 2H), 7.00 (d, J = 8 Hz, 2H), 4.25 (t, J = 4 Hz, 2H), 4.16 (t, J = 4 Hz, 2H), 4.02 (s, 6H), 2.07 (m, 4H). LR FAB MS (NBA): m/z 388.14, 100% [**22** + H]$^+$; 389.14, 20% [**22** + H + 1]$^+$. HR FAB MS (PEG): m/z 388.1376 [**22**+H]$^+$, calcd. for $C_{20}H_{22}O_7$ 388.1396, error 5.2 ppm.

4-[4'-(*p*''-Formylphenoxy)butoxy]pyridine-2,6-dicarboxylate (23). Diester **22** (3.67 g, 9.47 mmol) was suspended in stirring EtOH at 0 °C. Aqueous KOH (3.20 g, 57.0 mmol) was added dropwise and the mixture was stirred for 2 h and warmed to rt. The pH was adjusted to <2 and **23** precipitated as a white solid (2.72 g, 80%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.85 (s, 1H), 7.84 (d, J = 8 Hz, 2H), 7.69 (s, 2H), 7.11 (d, J = 8 Hz, 2H), 4.29 (m, 2H), 4.16 (m, 2H), 1.91 (m, 4H). LR FABMS (NBA): m/z 238.8, 100% [**23**–OC_6H_4CHO]$^+$; 239.8, 15% [**23**–OC_6H_4CHO+1]$^+$; 273, 10% [**23**–2 CO_2]$^+$; 273, <5% [**23**–2 CO_2+1]$^+$; 360.9, 50% [**23**+H]$^+$; 361.9, 10% [**23**+H+1]$^+$. HR FAB MS: m/z 360.1077 [**23** + H]$^+$, calcd. for $C_{18}H_{18}NO_7$: 360.1039, error 1.8 ppm.

Diethyl 4-(*p*'-vinylbenzyloxy)pyridine-2,6-dicarboxylate (24) and minor product diethyl 4-oxo-N-(*p*'-vinylbenzyl)-1,4-dihydropyridine-2,6-dicarboxylate (25). To a flask containing acetone (100 mL) with a magnetic stir bar were added diethyl chelidamate (**21b**, 1.64 g, 6.86 mmol), *p*-vinylbenzyl chloride (1.5 mL, 11 mmol) and K_2CO_3 (1.44 g, 10.4 mmol). The mixture was held at reflux under nitrogen for 16 h, after which solvent was removed by rotary evaporation and the crude material was dissolved in chloroform and washed with 1 M HCl (x3), saturated aq. NaCl (x3) and dried over $MgSO_4$. The solution was filtered and the solvent was removed by rotary evaporation to give the product; 2.18 g, (57%), white solid, mp 64.2–70.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$, major signals only) δ 7.85 (s, 2H), 7.45 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 6.72 (dd, J = 18, 11 Hz, 1H), 5.78 (d, J = 18 Hz, 1H), 5.29 (d, J = 11 Hz, 1H), 5.20 (s, 2H), 4.46 (q, J = 7 Hz, 4H), 1.44 (t, J = 7 Hz, 6H). Integrations of major and minor signals demonstrated that the product consisted of 80% *O*-alkylated isomer and 20% *N*-alkylated isomer. ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.59 (s), 164.71, 150.29, 138.10, 136.18, 134.14, 128.00, 126.66, 114.63, 114.33, 70.53, 62.43, 14.20 [26 peaks expected and 26 peaks found, 13 for *O*-alkylation (80%) and 13 for *N*-alkylation (20%)]. HR ESI MS: calc. for $C_{20}H_{21}NO_5$ [M+H]$^+$: m/z 356.1492; found: m/z 356.1463 (error 8.1 ppm).

Diisopropyl 4-(*p*'-vinylbenzyloxy)pyridine-2,6-dicarboxylate (26). To a flask containing acetone (200 mL) were added *p*-vinylbenzyl chloride (7.0 mL, 50 mmol), diisopropyl chelidamate (**21c**, 8.65 g, 32.4 mmol) and K_2CO_3 (7.4 g, 54 mmol). The mixture was held at reflux under nitrogen for 22 h with magnetic stirring and filtered through Celite p545®. The solvent was removed by rotary evaporation. The crude material was triturated with hexanes and the remaining solid was collected: 7.98 g (64%), mp 96.2–98.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.45 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 6.72 (dd, J = 18, 11 Hz, 1H), 5.78 (d, J = 18 Hz, 1H), 5.36–5.22 (m, 3H), 5.19 (s, 2H), 1.41 (d, J = 6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.53, 164.20, 150.72, 138.18, 136.27, 134.30, 128.15, 126.73, 114.81, 114.46, 70.58, 70.26, 21.89 (13 peaks expected and 13 peaks found). HR ESI MS: calc. for $C_{22}H_{26}NO_5$ [M+H]$^+$: m/z 384.1806; found: m/z 384.1798 (error 2 ppm).

4-(*p*'-Vinylbenzyloxy)pyridine-2,6-dicarboxylic acid (27). General procedure 1 (above) was used with styrene chelidamic ester **26** (0.24 g, 0.63 mmol), THF (15 mL) and 10% wt. aqueous KOH (50 mL) to produce 0.16 g (86%) of colorless solid, mp 140.2–144.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 2H), 7.50 (d, J = 8 Hz, 2H), 7.44 (d, J = 8 Hz, 2H), 6.73 (dd, J = 18, 11 Hz, 1H), 5.84 (d, J = 18 Hz, 1H), 5.34 (s, 2H), 5.26 (d, J = 11 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.07, 165.97, 150.45, 137.76, 136.88, 135.85, 128.83, 127.00, 115.40, 114.68, 70.54 (11 peaks expected, 11 peaks found). HR ESI MS: calc. for $C_{16}H_{14}O_5N$ [M+H]$^+$: m/z 300.0866; found: m/z 300.0864 (error 0.7 ppm).

Diisopropyl 4-[*p*'-(1''-bromoethyl)benzyloxy]pyridine-2,6-dicarboxylate (28). This procedure follows that applied to styrene itself [54]. To a flask containing silica (2.20 g) were added diisopropyl 4-(*p*-vinylbenzyloxy)pyridine-2,6-dicarboxylate (**29**, 0.383 g, 0.998 mmol) and dicloromethane (DCM) (10 mL) with magnetic stirring under nitrogen. PBr_3 (0.08 mL, 0.85 mmol) was dissolved in DCM (1 mL) and added dropwise to the flask. After the addition was complete, the flask was allowed to stir for 2 h. The mixture was filtered and the filtrate was washed with aq. $NaHCO_3$ (x3), saturated aq. NaCl (x2) and dried over Na_2SO_4. Filtration and rotary evaporation provided the product: 400 mg (86%), white solid, mp 244.1–246.0 °C (dec). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.49 (d, J = 8 Hz, 2H), 7.41 (m, 4H), 7.36 (d, J = 8 Hz, 2H, 7.09 (s, 3H), 5.32–5.24 (m, 6H), 5.19 (s, 2H), 5.18 (q, J = 7 Hz, 2H), 4.47 (s, 1H), 2.04 (dd, J = 5, 5 Hz, 3H), 1.41 (d, J = 7 Hz, 6H), 1.39 (d, J = 5, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.38, 164.09, 150.67, 143.85, 143.85, 134.94, 129.38, 128.13, 127.35, 127.30, 114.34, 70.22, 48.67, 32.84, 26.74, 21.81 (13 peaks expected and 16 peaks found; 3 extra aromatic peaks found). On the basis of the ^{1}H and ^{13}C NMR spectra, the product was believed to be a mixture of the desired compound and another compound or compounds).

Diisopropyl 4-{*p*'-[1''-(2''',2''',6''',6'''-tetramethylpiperidin-N-oxy)ethyl]benzyloxy}-pyridine-2,6-dicarboxylate (29). To a round bottom flask containing benzene (10 mL) were added copper (II) trifluoromethanesulfonate (8.9 mg, 0.025 mmol), copper powder (48.2 mg, 0.758 mmol), TEMPO (0.149 g, 0.952 mmol), the impure diisopropyl 4-[*p*-(1′-bromoethyl)benzyloxy]pyridine-2,6-dicarboxylate (**28**, 0.287 g, 0.618 mmol), and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) (0.02 mL, 0.1 mmol) with magnetic stirring under nitrogen. The mixture was held at reflux for 30 h, diluted with DCM, filtered through Celite p545®, and the solvent was removed by rotary evaporation. The residue was purified using column chromatography (neutral alumina, eluting with DCM:MeOH 99:1); the product eluted as the first fraction: 0.1893 g (57%), white solid, mp 113.1–116.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.40–7.35 (m, 4H), 5.34–5.24 (m, 2H), 5.20 (s, 2H), 4.80 (q, J = 6 Hz, 1H), 1.52–1.23 (m, 23H), 1.16 (s, 4H), 1.02 (s, 3H), 0.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.53, 164.12, 150.62, 146.55, 133.20, 127.66, 127.09, 114.41, 82.78, 70.75, 70.11, 59.69, 40.35, 34.45, 34.17, 23.52, 21.82, 20.34, 17.21 (19 peaks expected and 19 peaks found). HR ESI MS: calc. for $C_{31}H_{45}O_6N_2$ [M+H]$^+$: m/z 541.3272; found: m/z 541.3283 (error −2.0 ppm).

Diisopropyl 4-(*p*'-chloromethylbenzyloxy)pyridine-2,6-dicarboxylate (30). To a round bottom flask containing acetone (300 mL) were added *p*-bis(chloromethyl)benzene (3.57 g, 20.4 mmol) and K_2CO_3 (3.08 g, 22.3 mmol) with magnetic stirring. Diisopropyl chelidamate (**21c**, 0.91 g, 3.4 mmol) was dissolved in acetone and placed in an addition funnel attached to the reaction flask under nitrogen. The reaction flask was held at reflux and the solution of **21c** was added dropwise. After the addition was complete, the mixture was kept at reflux for 36 h, filtered through Celite p545® and the solvent was removed by rotary evaporation. The crude material was triturated with hexanes and the solid was collected via filtration and purified on a silica column, eluting with DCM: 0.21 g (15%), mp 141.1–143.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.43 (s, 4H), 5.33–5.22 (m, 2H), 5.20 (s, 2H), 4.59 (s, 2H), 1.41 (d, J = 6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.56, 164.27, 150.85, 138.25, 135.28, 129.38, 128.42, 114.67, 70.54, 70.31, 45.91, 22.04 (12 peaks expected and 12 peaks found). HR ESI MS: calc. for $C_{21}H_{25}NO_5Cl$ [M+H]$^+$: m/z 406.1416; found: m/z 406.1405

(error 2.7 ppm).

4-(*p'*-Hydroxymethylbenzyloxy)pyridine-2,6-dicarboxylic acid (31). General procedure 1 was used with diisopropyl 4-(*p'*-chloromethylbenzyloxy)pyridine-2,6-dicarboxylate (**33**, 214.1 mg, 0.5275 mmol), 10% wt. aq. KOH (30 mL) and THF (30 mL) to produce 23.7 mg (15%) of colorless solid, mp 127.0–134.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (s, 2H), 7.50 (bs, 4H), 5.39 (s, 2H), 4.78 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.36, 165.24, 149.78, 137.66, 135.73, 129.05, 128.05, 113.91, 69.70, 45.77 (10 peaks expected and 10 peaks found). HR ESI MS: calc. for $C_{15}H_{13}O_6N$ $[MH]^-$: *m/z* 302.0670; found: *m/z* 302.0681 (error 3.6 ppm).

Diisopropyl 4-[*p'*-(*p''*-formylphenoxymethyl)benzyloxy]pyridine-2,6-dicarboxylate (32). To a flask containing acetone (60 mL) were added *p*-(*p'*-chloromethylbenzyloxy)benzaldehyde (0.88 g, 3.4 mmol), diisopropyl chelidamate (**21c**, 0.87 g, 3.3 mmol) and K_2CO_3 (0.90 g, 6.5 mmol) with magnetic stirring under nitrogen. The reaction mixture was held at reflux for 31 h, cooled to room temperature, passed through Celite p545® and evaporated. The product was obtained by triturating the crude material with hexanes: a yellow solid, 0.94 g (59%), mp 124.4–127.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.85 (d, J = 9 Hz, 2H), 7.82 (s, 2H), 7.49 (s, 4H), 7.08 (d, J = 9 Hz, 2H), 5.29 (hept, J = 6 Hz, 2H), 5.23 (s, 2H), 5.18 (s, 2H), 1.42 (d, J = 6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.74, 166.38, 164.10, 163.54, 150.68, 136.62, 135.00, 132.02, 130.28, 128.15, 127.89, 115.14, 114.34, 70.32, 70.22, 69.81, 21.81 (17 peaks expected and 17 peaks found). HR ESI MS: calc. for $C_{28}H_{30}NO_7$ $[M+H]^+$: *m/z* 492.2017; found: *m/z* 492.2029 (error 2.4 ppm).

Diisopropyl 4-(*p'*-iodobenzyloxy)pyridine-2,6-dicarboxylate (35). To a round bottom flask containing acetone (75 mL) were added *p*-iodobenzyl bromide (0.55 g, 1.9 mmol), diisopropyl chelidamate (**21c**, 0.59 g, 2.2 mmol), and K_2CO_3 (0.52 g, 3.8 mmol). The mixture was placed under nitrogen and held at reflux for 1 day, after which it was allowed to cool and filtered through Celite p545®. The solvent was removed by rotary evaporation and the crude material was purified via flash column chromatography (silica, eluting with 100% DCM to 100% EA; product eluted in 10% EA): 0.75 g (84%), white solid, mp 187.3–189.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.76 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 5.29 (hept, J = 6 Hz, 2H), 5.15 (s, 2H), 1.43 (d, J = 6 Hz, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.23, 164.06, 150.75, 138.00, 134.52, 129.50, 114.26, 94.42, 70.21, 69.99, 21.81 (11peaks expected and 11 peaks found). HR ESI MS: calc. for $C_{20}H_{23}O_5NI$ $[M+H]^+$: *m/z* 484.0615; found: *m/z* 484.0586 (error 6.0 ppm).

4-(*p'*-Iodobenzyloxy)pyridine-2,6-dicarboxylic acid (36). General procedure 1 was used with diisopropyl 4-(*p'*-iodobenzyloxy)pyridine-2,6-dicarboxylate (**35**, 0.75 g, 1.6 mmol), THF (50 mL), and 10% wt. aq. KOH (50 mL) to produce 0.61 g (98%) of white solid, mp 187.3–189.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (m, 4H), 7.30 (d, J = 8 Hz, 2H), 5.34 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.27, 165.23, 149.78, 137.34, 135.41, 129.96, 113.91, 94.44, 69.40 (9 peaks expected and 9 peaks found). HR ESI MS: calc. for $C_{14}H_{11}O_5NI$ $[M+H]^+$: *m/z* 399.9676; found: *m/z* 399.9709 (error 8.3 ppm).

***p*-[*p'*-Bromobenzyloxy]benzyl bromide.** To a flask containing DCM (200 mL) were added *p*-(*p'*-bromobenzyloxy)benzyl alcohol (6.88 g, 23.5 mmol) and PBr_3 (1.4 mL, 15 mmol) with magnetic stirring under nitrogen. The solution was held at reflux for 39 h, after which it was poured into water, followed by washing the organic phase with water (x2), saturated aq. NaCl (x2) and drying over sodium sulfate. Filtration and removal of the solvent provided the product as a light brown solid, 8.21 g (98%), mp 76.4–78.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 6.91 (d, J = 8 Hz, 2H), 5.01 (s, 2H), 4.49 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.77, 135.96, 131.96, 130.74, 130.69, 129.27, 122.20, 115.27, 69.51, 34.00 (10 peaks expected and 10 large peaks found; also very small impurity signals possibly due to product instability. Since the product was an intermediate, it was used without further purification). HR ESI MS: calc. for $C_{14}H_{12}OBr$ $[MBr]^+$: *m/z* 275.0067; found: *m/z* 275.0065 (error −0.7 ppm).

Diisopropyl 4-[*p'*-(*p''*-bromobenzyloxy)benzyloxy]pyridine-2,6-dicarboxylate (37). To a round bottom flask containing acetone (200 mL) were added diisopropyl chelidamate (**21c**, 5.50 g, 20.6 mmol), K_2CO_3 (4.00 g, 28.9 mmol), and *p*-(*p'*- bromomethylphenoxymethyl)bromobenzene (7.91 g, 22 mmol) with magnetic stirring under nitrogen. The reaction mixture was held at reflux for 19 h, followed by filtration through Celite p545® and removal of the solvent via rotary evaporation. The solid was triturated with boiling hexanes and filtered: a white solid, 10.51 g (94%), mp 90.4–92.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.51 (d, J = 8 Hz, 2H), 7.36 (d, J = 9 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 6.98 (d, J = 9 Hz, 2H), 5.28 (hept, J = 6 Hz, 2H), 5.13 (s, 2H), 5.04 (s, 2H), 1.42 (d, J = 6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) 166.68, 164.35, 159.09, 150.82, 135.95, 132.02, 129.94, 129.25, 127.58, 122.20, 115.37, 114.63, 70.71, 70.42, 69.52, 22.04 (16 peaks expected and 16 peaks found). HR ESI MS: calc. for $C_{27}H_{28}O_6NBrNa$ $[M+Na]^+$: *m/z* 564.0992; found: *m/z* 564.0983 (error −2 ppm).

4-[*p'*-(*p''*-Bromobenzyloxy)benzyloxy]pyridine-2,6-dicarboxylic acid (38). General procedure 1 was used with diisopropyl 4-[*p'*-(*p''*-bromobenzyloxy)benzyloxy]pyridine-2,6-dicarboxylate (**37**, 1.21 g, 2.23 mmol), 10% wt. aq. KOH (20 mL) and THF (30 mL) to produce a white solid, 1.01 g (99%), mp 189.1–192.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77 (s, 2H), 7.58 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 5.27 (s, 2H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.05, 165.87, 158.74, 150.30, 137.03, 131.93, 130.38 (two closely spaced peaks), 128.37, 121.51, 115.44, 114.49, 70.51, 68.95 (14 peaks expected and 14 peaks found). HR ESI MS: calc. for $C_{21}H_{17}O_6NBr$ $[M+H]^+$: *m/z* 458.0234; found: *m/z* 458.0238 (error 0.9 ppm).

Diisopropyl 4-(4′-pyridylmethoxy)pyridine-2,6-dicarboxylate (39). Diisopropyl chelidamate (**21c**, 1.80 g, 6.73 mmol), 4-bromomethylpyridine hydrobromide (2.00 g, 7.91 mmol), and K_2CO_3 (2.50 g, 18.1 mmol) were combined in a round bottom flask with acetone (60 mL) under nitrogen and held at reflux for 4 days. After cooling, the mixture was filtered through Celite p545® and the solvent was removed by rotary evaporation. The product was isolated by flash column chromatography on silica, eluting with DCM to EA: 0.39 g (16%) of colorless solid, mp 102.8–104.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 6 Hz, 2H), 7.82 (s, 2H), 7.38 (d, J = 6 Hz, 2H), 5.30 (m, 2H), 5.25 (s, 2H), 1.43 (d, J = 6.3 Hz, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.96, 163.98, 150.88, 150.36, 143.85, 121.51, 114.17, 70.31, 68.66, 21.81 (10 peaks expected and 10 peaks found). HR ESI MS: calc. for $C_{19}H_{23}N_2O_5$ $[M+H]^+$: *m/z* 359.1601; found: *m/z* 359.1616 (error 4.2 ppm).

4-(4′-Pyridylmethoxy)pyridine-2,6-dicarboxylic acid (40). General procedure 1 was used with diisopropyl 4-(pyridin-4′-ylmethoxy)pyridine-2,6-dicarboxylate (**39**, 0.39 g, 1.1 mmol), 10% wt. aq. KOH (20 mL) and THF (20 mL) to produce a white solid, 56.6 mg (19%), mp 205.1–207.3 °C (dec.). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (br s, 2H), 8.09 (br s, 2H), 7.90 (br s, 2H), 5.74 (br s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.68, 165.19, 149.99, 143.07, 142.77, 123.85, 113.99, 67.77 (8 signals expected and 8 signals found). HR ESI MS: calc. for $C_{13}H_{11}N_2O_5$ $[M+H]^+$: *m/z* 275.0662; found: *m/z* 275.0674 (error 4.4 ppm).

Diisopropyl 4-(*p'*-formylphenoxyethoxy)pyridine-2,6-dicarboxylate (41). To a round bottom flask containing acetone (125 mL) were added *p*-(2′-bromoethoxy)benzaldehyde (4.77 g, 18.5 mmol), diisopropyl chelidamate (**21c**, 4.14 g, 15.5 mmol), and K_2CO_3 (3.82 g, 27.6 mmol) with magnetic stirring. The mixture was held at reflux under nitrogen for 31 h, filtered through Celite p545® and evaporated to provide a material which was purified by flash

column chromatography (silica gel, eluting with DCM/EA). The product was found in the third fraction as a yellow tinted solid: 3.10 g (48%), mp 111.8–112.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.87 (d, J = 9 Hz, 2H), 7.81 (s, 2H), 7.06 (d, J = 9 Hz, 2H), 5.30 (hept, J = 6 Hz, 2H), 4.55 (dd, J = 6, 3 Hz, 2H), 4.48 (dd, J = 6, 3 Hz, 2H), 1.43 (d, J = 6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.69, 166.31, 164.04, 163.16, 150.74, 132.03, 130.54, 114.83, 114.07, 70.23, 66.88, 66.25, 21.80 (13 peaks expected and 13 peaks found). HR ESI MS: calc. for $C_{22}H_{25}NO_7$ $[M+H]^+$: m/z 416.1704; found: m/z 416.1700 (error −1 ppm).

Diisopropyl 4-[(*p*'-formylphenoxyethoxy)-*p*''-benzyloxy]pyridine-2,6-dicarboxylate (42). To a flask containing 60 mL of acetone was added *p*-[(p'-chloromethyl)benzyloxy]benzaldehyde (0.88 g, 3.4 mmol), diisopropyl chelidamate (**21c**) and K_2CO_3 (0.90 g, 6.5 mmol) with magnetic stirring under nitrogen. The reaction mixture was held at reflux for 31 h. After cooling to room temperature the mixture was passed through Celite® p545 and solvent was removed by rotary evaporation. The desired product was obtained by triturating the crude material with hexanes: 0.94 g (59%) of colorless solid, mp 124.4–127.4 °C· ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.82 (s, 2H), 7.49 (s, 4H), 7.08 (d, J = 8.8 Hz, 2H), 5.29 (hept, J = 6.3 Hz, 2H), 5.23 (s, 2H), 5.18 (s, 2H), 1.42 (d, J = 6.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.74, 166.38, 164.10, 163.54, 150.68, 136.62, 135.00, 132.02, 130.28, 128.15, 127.89, 115.14, 114.34, 70.32, 70.22, 69.81, 21.81 (17 peaks expected and 17 peaks found). HR ESI MS: m/z 491.1956 $[M]^+$; calc. for $C_{28}H_{29}NO_7$ 491.1944, error −2.4 ppm.

Diisopropyl 4-(*p*'-(2''-tosyloxyethoxy)phenoxyethoxy)pyridine-2,6-dicarboxylate (**45**). To a flask containing acetone (300 mL) were added *p*-bis(2′-tosyloxyethoxy)benzene (3.33 g, 6.57 mmol), diisopropyl chelidamate (**21c**, 3.59 g, 13.4 mmol) and K_2CO_3 (3.18 g, 23.0 mmol) with magnetic stirring under a stream of nitrogen. The reaction mixture was held at reflux for 24 h, cooled to room temperature, filtered through Celite p545® and the solvent was removed by rotary evaporation. The crude material was dissolved in DCM and washed with aq. Na_2CO_3 (x2), saturated aq. NaCl (x3) and dried over sodium sulfate. After filtration and removal of solvent, the material was purified by silica flash column chromatography, eluting with DCM to acetonitrile, 1.47 g (37%), a white solid **48**:**50** = 4:1, mp 102.4–109.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$, major signals only) δ 7.84 (d, J = 8 Hz, 2H), 7.82 (s, 2H), 7.37 (d, J = 8 Hz, 2H), 6.86 (d, J = 9 Hz, 2H), 6.77 (d, J = 9 Hz, 2H), 5.32 (hept, J = 6 Hz, 2H), 4.53–4.46 (m, 2H), 4.39–4.35 (m, 2H), 4.35–4.32 (m, 2H), 4.16–4.10 (m, 2H), 2.48 (s, 3H), 1.45 (d, J = 6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$, major signals only) δ 166.50, 164.11, 152.97, 152.76, 150.68, 144.92, 132.96, 129.85, 128.03, 115.84, 115.69, 114.14, 70.17, 68.17, 67.29, 66.70, 66.25, 21.81, 21.66 (19 peaks expected and 19 peaks found). HR MS: calc. for $C_{30}H_{36}NO_{10}S$ $[M+H]^+$: m/z 602.2054; found: m/z 602.2064 (error 1.7 ppm).

4-[*p*'-(2''-Tosyloxyethoxy)phenoxyethoxy]pyridine-2,6-dicarboxylic acid (46). General procedure 1 was used with diisopropyl 4-[*p*'-(2''-tosyloxyethoxy)phenoxyethoxy]pyridine-2,6-dicarboxylate (**45**, 0.2570 mg, 0.4271 mmol), 10% wt. aq. KOH (20 mL) and THF (40 mL) to produce 0.2051 g (93%) of colorless solid, mp 103.8–107.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, J = 8 Hz, 2H), 7.76 (s, 2H), 7.47 (d, J = 8 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 6.77 (d, J = 9 Hz, 2H), 4.58–4.53 (m, 2H), 4.31–4.26 (m, 4H), 4.10–4.07 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.60, 165.34, 152.55, 152.05, 149.82, 145.06, 132.27, 130.20, 127.70, 115.59, 115.47, 113.76, 69.27, 67.67, 66.48, 65.85, 21.13 (17 peaks expected and 17 peaks found). HR ESI MS: calc. for $C_{24}H_{24}NO_{10}S$ $[M + H]^+$: m/z 518.1115; found: m/z 518.1077 (error −7.3 ppm).

Dibenzo-30-crown-10-based 4-benzyloxypyridyl cryptand (50). *cis*-DB30C10 diol (**7**, 0.34 g, 0.57 mmol, dried in a pistol) in DCM (20 mL) and 4-benzyloxy-2,6-pyridinedicarboxylic acid dichloride (**52**, 0.18 g, 0.57 mmol) in DCM (20 mL) were added separately by syringe pump at 0.75 mL/h to a mixture of pyridine (0.1 mL, 1 mmol, dried) and dichloromethane (1.5 L, distilled from P_2O_5). The mixture was stirred for an additional 5 d after addition. The solvent was evaporated, yielding about 2 g of crude yellow oil. The crude product was dissolved in chloroform and washed with 2 M H_2SO_4 and then H_2O. The organic phase was dried with Na_2SO_4, filtered, and the solvent was evaporated. The product was then subjected to alumina chromatography (elution with $CHCl_3$) to afford a colorless solid (0.20 g, 42%), mp 150.8–154.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.91 (s, 2H), 7.47–7.35 (m, 5H), 6.94 (m, 4H), 6.77 (m, 2H), 5.31 (s, 4H), 5.25 (s, 2H), 4.16 (m, 4H), 4.00 (m, 4H), 3.93 (m, 4H), 3.83 (m, 4H), 3.75 (m, 4H), 3.70 (m, 8H), 3.65 (m, 4H). LR FAB MS (NBA): m/z 833.5, 10% $[M]^+$; 834.5, 100% $[M+H]^+$; 835.5, 50% $[M+H+1]^+$; 836.5, 13% $[M+H+2]^+$; 837.5, 3% $[M+H+3]^+$; HR FAB MS (NBA/PEG): m/z 834.3356 $[M+H]^+$, calcd. for $C_{44}H_{52}NO_{15}$: 834.3337, error 2.2 ppm.

Dibnzo-30-crown-10-based formyl functionalized cryptand 51. Diacid **23** (0.21 g, 0.58 mmol) was stirred in refluxing $SOCl_2$ (25 mL) under N_2 for 12 h. The mixture was cooled and solvent was evaporated, yielding a brown oily material, which was used in the next reaction without further purification. The diacid chloride (assumed to be 0.58 mmol) was dissolved in toluene (40 mL) and *cis*-DB30C10 diol (**7**, 0.344 g, 0.58 mmol) was dissolved in chloroform (40 mL). The reactants were separately added at 0.2 mL/h via syringe pump to a solution of 1 mL pyridine in 2.0 L of DCM (distilled from P_2O_5). The mixture was stirred for 5 d after the addition of the reactants. The solvent was evaporated, producing a yellow oily solid. This material was dissolved in $CHCl_3$ and washed with 5% HCl (x2), water and NaCl (sat.). The organic phase was dried with Na_2SO_4 and the solid was filtered and the solvent was evaporated to a yellow solid, which was purified using alumina chromatography (2.5% CH_3OH in EA): 0.12 g (23% yield), which decomposed prior to obtaining a mp. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.90 (s, 1H), 7.85 (d, J = 8Hz, 2H), 7.83 (s, 2H), 7.01 (d, J = 8 Hz, 2H), 6.95 (m, 4H), 6.77 (m, 2H), 5.31 (s, 4H), 4.25 (m, 2H), 4.17 (m, 6H), 4.01 (m, 4H), 3.94 (m, 4H), 3.82 (m, 4H), 3.75 (m, 5H), 3.71 (m, 9H), 3.66 (m, 5H), 2.07 (m, 4H). LR FAB MS (NBA): m/z 392.1, 50% $[M-CH_2OC_6H_4CHO]^{2+}$; 393, 11% $[M-CH_2OC_6H_4CHO + 1]^{2+}$; 418, 25% $[M-C_6H_5CHO + Na]^{2+}$; 419, 5% $[M-C_6H_5CHO+Na+1]^{2+}$; 461.0, 100% $[M]^{2+}$; 462, 27% $[M+1]^{2+}$; 473, 45% $[M+Na]^{2+}$; 474, 13% $[M+Na]^{2+}$; 920.7, 7% $[M+H]^+$; 921.8, 28% $[M+H+1]^+$; 922.8, 14% $[M+H+2]^+$; 923.8, 4% $[M+H+3]^+$. HR FAB MS (PEG): m/z 920.3666 $[M+H]^+$, calc'd for $C_{48}H_{58}NO_{17}$: 920.3705, error −4.2 ppm.

Dibenzo-30-crown-10-based Diamide Cryptand 54. 4-(Benzyloxy)pyridine-2,6-diamine (**52**, 0.17 g, 0.78 mmol) was dissolved in 700 mL of dry DCM (distilled from CaH_2). To this, PyTFSI (1.4 g, 3.9 mmol), and pyridine (1.2 mL, 15.6 mmol) were added and stirred for 30 min. Then, the *cis*-diacid chloride of dibenzo-30-crown-10 (**53**, 0.52 g, 0.78 mmol) was added and the mixture was stirred for 48 h at room temperature. The solvent was removed by rotary evaporation and the crude material was subjected to column chromatography on basic alumina eluting with EA/hexane (1:1 v:v), affording a colorless solid, 0.133 g (21%). ^{1}H NMR (400 MHz, CDCl3) δ: 7.69 (dd, J = 2, 2 Hz, 2H), 7.56 (d, J = 4 Hz, 2H), 7.44–7.33 (m, 8H), 6.85 (d, J = 8 Hz, 2H), 5.32 (s, 2H), 4.18–4.16 (m, 8H), 3.90–3.87 (m, 8H), 3.78–3.75 (m, 8H), 3.69–3.66 (m, 8H). ^{13}C NMR (101 MHz, CDCl3) δ 166.11, 153.02, 148.26, 136.21, 128.56, 128.15, 128.12, 124.09, 122.81, 114.74, 112.24, 70.98, 70.92, 70.71, 70.68, 69.59, 69.45, 69.15, 68.88, 66.50 (23 peaks expected, 20 peaks observed). HR ESI MS: m/z 822.3705, $(M+NH_4)^+$; calculated for $C_{42}H_{54}N_4O_{13}$: 822.3687, error 2.2 ppm.

Declaration of competing interest

There are no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132333.

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