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Preparation of glycoluril monomers for expanded cucurbit[*n*]uril synthesis

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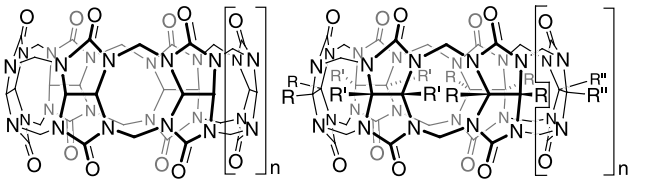
Abstract—Glycoluril derivatives bearing free ureidyl groups (**1**) and bis(cyclic ethers) (**2**) are the fundamental building blocks for the synthesis of cucurbituril, its derivatives, and its congeners. The known derivatives of **1** and **2** fall into two main classes—those bearing alkyl or aryl functional groups on their convex face. In this paper we present a third class of glycolurils, namely those bearing substituents that are electron withdrawing in character. This class of compounds carries carboxylic acid derived functional groups on their convex face and are derived from diesters **1e** and **2e**. An improved synthesis of **1e** and **2e** is reported and their modification described. For example, **1e** and **2e** are converted into secondary amides (**10**–**15**) by heating in solutions of the neat primary amines. The secondary amides can be transformed into imides (**19**–**22**, **24**, **25**) by heating with PTSA in $ClCH_2CH_2Cl$. The isolation of these compounds in pure form in high yields is accomplished by simple and scalable washing or recrystallization procedures. We also present the X-ray crystallographic characterization of bis(cyclic ethers) **2e**, **8**, and **22**. We anticipate that the ready availability of ester, carboxylate, acid, secondary amide, imide, and tertiary amide derivatives of **1** and **2** will expand the scope of the synthesis of cucurbituril derivatives by providing a new class of building blocks with electron withdrawing substituents. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

In 1905, Behrend reported that the condensation of glycoluril and formaldehyde in dilute HCl yielded an insoluble polymeric material now known as Behrend's polymer. By heating Behrend's polymer in H_2SO_4, a substance was obtained that formed crystalline complexes with a variety of salts.[1] The molecular structure of this substance was disclosed by Mock and co-workers in 1981 who named it cucurbituril.[1b] Cucurbituril, Q[6],[2] is composed of six glycoluril rings and 12 methylene bridges. Q[6] has two carbonyl lined portals that allow access to its hydrophobic cavity. The diameter of these portals is 3.9 Å, the cavity is 5.8 Å in diameter with a volume of 164 Å^3, and the overall depth of Q[6] is 9.1 Å.[3] The geometry of Q[6] and its structural rigidity leads to outstanding molecular recognition properties. In particular, Q[6] binds tightly to alkylammonium species by a combination of ion–dipole interactions and the hydrophobic effect.[4–6] Q[6] has also been demonstrated to perform well in a variety of applications including the preparation of molecular necklaces,[7,8] bowls,[9] DNA complexes,[10] molecular switches,[11,12] non-covalent modification of dendrimers,[13] ion and molecular complexation studies,[4–6,14] and the catalysis of dipolar cycloadditions.[15–17]



Q[5]	(n = 0)	$Me_{10}Q[5]$	(R = Me, n = 0)
Q[6]	(n = 1)	$Cy_5Q[5]$	(R = R' = R'' = $(CH_2)_4$, n = 0)
Q[7]	(n = 2)	$Cy_6Q[6]$	(R = R' = R'' = $(CH_2)_4$, n = 1)
Q[8]	(n = 3)	$Ph_2Q[1,5]$	(R = R' = H, R'' = Ph, n = 1)
Q[10]	(n = 5)	$Me_6Q[3,3]$	(R = H, R' = R'' = Me, n = 1)

Despite the range of useful properties of Q[6], several drawbacks prevent its more widespread use. These drawbacks include: (1) the small cavity volume of Q[6] which limits the range of molecular guests that can be bound, (2) the poor solubility of Q[6] in water and common organic solvents, and (3) a lack of easily manipulated functional groups that would allow derivatization. Several groups have been involved in efforts to alleviate each of these problems. For example, the groups of Day and co-workers and Kim and co-workers have reported the synthesis and isolation of Q[5], Q[7], and Q[8].[2,3,18,19] More recently, Day and co-workers reported the isolation and crystallographic

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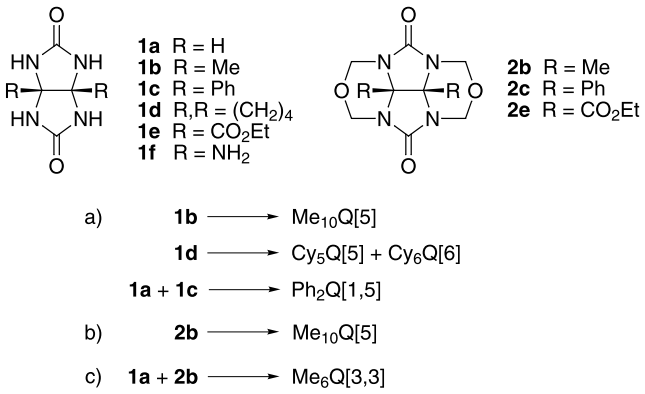
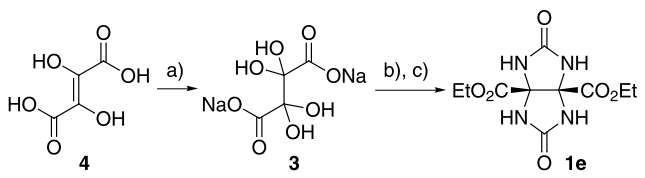


Scheme 1. Chemical structures of **1** and **2** and synthesis of known Q[*n*] derivatives. (a) Homomeric Q[*n*] and Q[*s*,*u*] forming reactions of **1**. (b) Homomeric Q[*n*] forming reactions of **2b**. (c) Heteromeric Q[*s*,*u*] forming reaction of **1a** with **2b**.

characterization of Q[5]@Q[10].[20] These studies partially address the first two drawbacks by increasing the volume of the cavity and by improving the solubility in salt-free water. These advances have already resulted in the preparation of molecular Russian dolls,[21] gyroscopes,[20] ball bearings,[22] molecular sieves,[23,24] ionophores with pronounced Pb^{2+} selectivity,[25] the recognition of charge transfer complexes[26] and viologens,[27,28] the catalysis of a 2+2 photoreaction,[29] and studies of molecular polarizability.[30]

Efforts to improve the solubility of the cucurbiturils in organic media have focused on the use of glycoluril derivatives bearing functional groups on their convex face (e.g. **1** and **2**) in Q[*n*] and Q[*s*,*u*] forming reactions.[18] To date, the synthesis, purification, and full characterization of $Me_{10}Q[5]$,[2,31] $Cy_5Q[5]$ and $Cy_6Q[6]$,[32] $Ph_2Q[1,5]$,[33] and $Me_6Q[3,3]$[34] have been reported in the literature.[35] The synthesis of these substituted Q[*n*] have taken place by three distinct routes involving the reaction of glycoluril and its derivatives (**1**) and bis(cyclic ethers) **2** (Scheme 1). For example, the synthesis of $Me_{10}Q[5]$ is accomplished either by the reaction of **1b** with formaldehyde or by the reaction of bis(cyclic ether) **2b** under acidic conditions (Scheme 1a and b). Both reactions are examples of homomeric cyclization reactions. Day recently demonstrated that heteromeric cyclization reactions are also possible (Scheme 1c). For example, the reaction of **1a** and **2b** yields D_{3h} symmetrical $Me_6Q[3,3]$ whose substituents alternate.[34,36] These fully substituted Q[*n*] ($Me_{10}Q[5]$, $Cy_5Q[5]$, and $Cy_6Q[6]$) and partially substituted Q[*s*,*u*] ($Ph_2Q[1,5]$ and $Me_6Q[3,3]$) impart solubility in organic solvents and have already begun to expand the range of applications to include the preparation of ion-selective electrodes.[32]

Our group has been engaged in the synthesis and recognition properties of methylene bridged glycoluril dimers.[36–41] The methylene bridged glycoluril dimer substructure (bold in Q[6]) constitutes the fundamental substructure of the cucurbit[*n*]uril family. We have found that glycoluril derivatives bearing electron withdrawing functional groups (ex: ester, carboxylate, amide, and imide) on their convex face are more efficient substrates for the formation of the methylene bridged glycoluril dimer substructure than are those bearing substituents capable of stabilizing an adjacent carbocation (ex: cyclohexyl and phenyl).[39] The implication is that glycoluril derivatives **1** and **2** bearing electron withdrawing functional groups should participate in Q[*n*] forming reactions. Glycoluril derivatives bearing ester, amide, and imide functional groups have a high degree of organic solubility unlike most other known glycolurils. This paper presents practical syntheses of glycoluril derivatives bearing free ureidyl groups and cyclic ethers carrying a range of electron withdrawing functional groups (ester, carboxylate, amide, and imide). These compounds are novel monomers which have the potential for the synthesis of substituted Q[*n*].



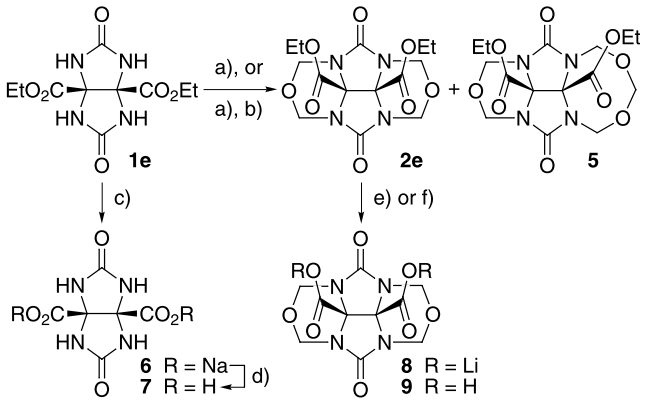
Scheme 2. Synthesis of glycoluril ethyl ester **1e**.[45] *Conditions*: (a) CH_3CO_2H, Br_2, H_2O; (b) EtOH, HCl; (c) PhH, H_2NCONH_2, TFA, reflux.

2. Results and discussion

For the synthesis of glycoluril derivatives bearing a range of electron withdrawing functional groups on their convex face, we viewed the ethoxycarbonyl groups of **1e** as an ideal common intermediate (Scheme 2). The synthesis of **1e** from disodium dihydroxytartrate **3** has been known for over 100 years.[42–45] Until recent years, compound **3** was an inexpensive commercial precursor to the manufacture of the commonly known dye tartrazine. With the phasing out of the use of tartrazine, however, **3** has become prohibitively expensive for use in the synthesis of **1e**. We prepare **3** by the oxidation of **4** with Br_2 in glacial acetic acid.[46,47] This reaction is scalable and delivers **3** in high yield and purity. The conversion of **3** into **1e** using the procedure reported by Rebek[45] reliably delivers **1e** in the reported yield (47%). We have discovered a modification of this procedure that leads to more straightforward product isolation and higher yields (58–64%). With large quantities of **1e** in hand, we turned our attention to functional group modification including transformations to corresponding cyclic ethers.

For the transformation of **1e** into **2e**,[48] we considered the two step procedure developed by Nolte and co-workers for the synthesis **2c**.[49] To avoid the aqueous conditions used by Nolte we developed a one step procedure that proceeds under anhydrous acidic conditions where the CO_2Et groups are stable (Scheme 3). We used anhydrous TFA in this reaction as it is sufficiently acidic, easy to remove, and an excellent solvent for **1e**. This reaction delivers **2e** in modest yield (46%) along with acetal **5** (20%). We hypothesized that **5** was a kinetic product that might be converted to **2e** under more highly acidic conditions. Accordingly, treatment of the crude reaction mixture with anhydrous PTSA in $ClCH_2CH_2Cl$ at reflux for 2 h allows the isolation of **2e** in 92% yield from **1e**.

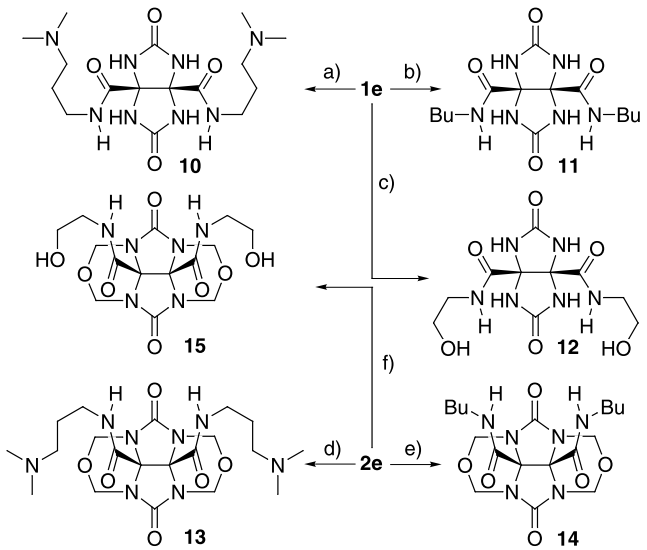
With good methods in hand for the synthesis of **1e** and **2e**—the two building blocks for potential use in the synthesis of substituted Q[*n*]—we explored the transformations of their



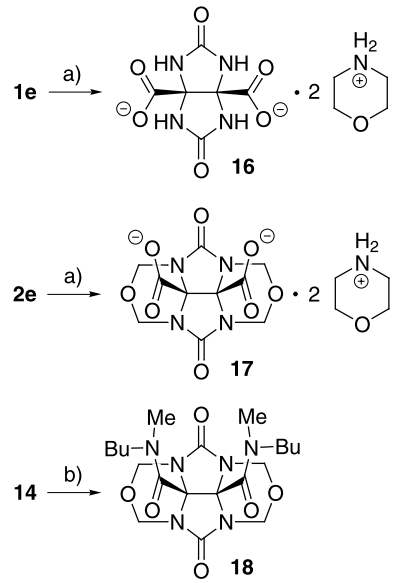
Scheme 3. Transformations of **1e** and **2e**. *Conditions*: (a) TFA, $(CH_2O)_n$, reflux; (b) PTSA, $ClCH_2CH_2Cl$; (c) H_2O, NaOH, 80°C, 90%; (d) PTSA, 46%; (e) CH_3OH, H_2O, LiOH, 70°C, 80%; (f) CH_3OH, H_2O, LiOH, then TFA, 76%.

CO_2Et groups. We first investigated the formation of carboxylate salts and the corresponding carboxylic acids (Scheme 3). Compound **6** was first reported by Anschutz in 1891, but the experimental details and spectroscopic data are scant.[44] We repeated this reaction and isolated **6** in 90% yield as an insoluble powder. Conversion of **6** into the carboxylic acid **7**[42,43] was possible by treatment with an excess of PTSA. Hydrolysis of **2e** occurs in 80% yield by treatment with excess LiOH. Diacid **9** was isolated after acidification with TFA. The good solubility of **6**–**9** suggests that these compounds as water soluble monomers have the potential for improved aqueous solubility of a similarly substituted Q[*n*].

In previous work we have found that 3-dimethylaminopropyl amide derivatives of glycoluril impart outstanding solubility characteristics in both organic and aqueous media.[48] Direct amidation reactions of **1e** and **2e** in neat primary amines (75–90°C) converts the esters into amide functional groups (Scheme 4). For example, **1e** was converted into **10**–**12** by treatment with *N*,*N*-dimethylaminopropylamine, *n*-butylamine, and ethanolamine, respectively. Similar reactions were used to transform **2e** into **13**–**15**. Purification can be achieved by simply removing the excess amine by distillation followed by washing of the resulting solid with solvents in which **10**–**15** are insoluble.



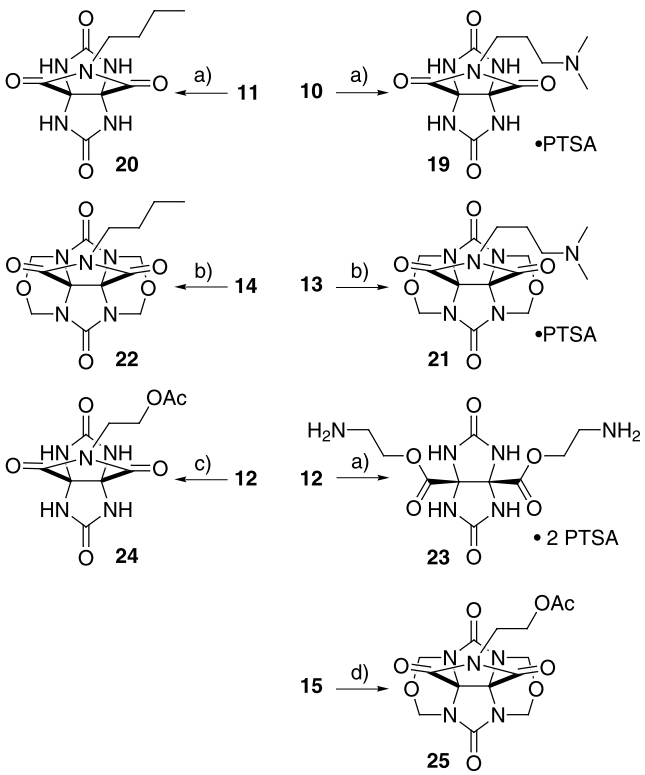
Scheme 4. Amidation reactions of **1e** and **2e**. *Conditions*: (a) $H_2N(CH_2)_3NMe_2$, 90°C, 86%; (b) $CH_3(CH_2)_3NH_2$, 75°C, 87%; (c) $H_2NCH_2CH_2OH$, 80°C, 85%; (d) $H_2N(CH_2)_3NMe_2$, 78°C, 88%; (e) $CH_3(CH_2)_3NH_2$, 78°C, 90%; (f) $H_2NCH_2CH_2OH$, 85°C, 93%.



Scheme 5. Synthesis of tertiary amide **18**. *Conditions*: (a) $HN(CH_2CH_2)_2O$, 128°C; (b) THF, NaH, MeI, reflux, 75%.

Potential limitations of secondary amides **10**–**15** in Q[*n*] synthesis include their ability to react with formaldehyde and their propensity to form the corresponding imides which, if incomplete, could lead to complex reaction mixtures. Tertiary amides would not suffer from these limitations and should be stable to the strongly acidic aqueous conditions (ex: 9 M HCl, 75°C) used in Q[*n*] synthesis. We attempted the direct amidation of **1e** and **2e** by heating in neat morpholine at 128°C (Scheme 5). The products of these reactions were ammonium salts **16** and **17** rather than the desired tertiary amides. Alkylation of **14** with MeI in THF delivered tertiary amide **18** in 75% yield.

We next considered the conversion of diamides **10**–**15** into the corresponding imides by treatment with PTSA in $ClCH_2CH_2Cl$ (Scheme 6). The conversion of **10** and **11** into imides **19** and **20** occurred smoothly in high yield (>85%). The conversion of **13** and **14** into imides **21** and **22** occurred without incident in comparatively lower yield (>66%). In these cases it was necessary to work at low concentration (≈10 mM) to minimize polymerization reactions analogous to the formation of Behrend's polymer. Heating **12** under similar conditions did not result in the formation of the expected imide; an N- to O-acyl transfer reaction[50] occurred instead delivering **23** as its PTSA salt. To prevent the N- to O-acyl transfer reaction, we acetylated diol **14** and induced ring closure to the imide in a single step delivering **24** in 73% yield. Similarly, **15** was converted into **25** in 73% yield. We believe that these imide substituted glycoluril derivatives hold excellent promise in the synthesis of Q[*n*] derivatives. For example, the ester (**1e** and **2e**) and amide (**10**–**15**) derived glycolurils might be expected to undergo hydrolysis and imide forming reactions



Scheme 6. Synthesis of glycoluril imides. *Conditions*: (a) $ClCH_2CH_2Cl$, PTSA, 25–32 mM, reflux; (b) $ClCH_2CH_2Cl$, PTSA, ≈10 mM, reflux; (c) Ac_2O, AcOH, then PTSA, (d) $ClCH_2CH_2Cl$, Ac_2O, then PTSA.

under the aqueous acidic reaction conditions typically used for Q[*n*] synthesis. In contrast, imides **19**–**22** are expected to be stable to these reaction conditions.

2.1. X-Ray crystallographic characterization

We were able to obtain crystals of **2e**, **5**, **8**, **17**, and **22** that were suitable for X-ray structural determination. Figure 1 shows ORTEP plots of the structures of **2e**, **8**, and **22** in the crystal. The structural details of these molecules are similar to those determined previously for glycoluril derivatives and Q[*n*] (Table 1). We briefly discuss here the structural details that are most relevant to their potential use as monomers for Q[*n*] synthesis. All five compounds have *cis*-fused five-membered rings with both functional groups displayed on one face of the molecule. The dihedral angles between the substituents at C3a and C6a are small. The angles between the mean planes defined by the two five-membered rings are between 103.9° and 112.1°. These values are similar to that measured for **2b** which has been successfully converted into $Me_{10}Q[5]$, but as expected is smaller than those observed for glycolurils bearing free ureidyl groups (**1a**,**b**, and **f**) and cucurbiturils (Q[6] and $Me_{10}Q[5]$). The distance between the two carbonyl oxygen atoms (O7–O8) defines the cavity depth of the hypothetical Q[*n*]. For the five cyclic ethers given in Table 1, this distance increases from 4.979 to 5.271 Å in the following order (**2b**<**17**<**2e**<**8**<**22**). This suggests that lithium carboxylate **8** and imide **22** are the sterically least demanding in this series and might be expected to best form the larger Q[*n*] homologs most efficiently. As expected these O–O distances are considerably smaller than those observed for **1a**,**b**, and **f** (5.754–5.997 Å) and $Me_{10}Q[5]$ and Q[6] (5.98–6.06 Å) since they increase as the ring size of the laterally fused *n*-membered rings increases.[51,52] These structural details suggest the potential utility of ester, carboxylate, and imide based glycolurils in Q[*n*] forming reactions.

3. Conclusions

In previous work, we have determined that glycoluril derivatives bearing electron withdrawing ethyl ester groups on their convex face are highly proficient at forming the protected methylene bridged glycoluril dimers. Substructures of this type in the unprotected form are basic building blocks of Q[*n*] and its derivatives.[36,37,39] This observation implies that the synthesis of Q[*n*] derivatives might be best performed using glycoluril building blocks **1** and **2** bearing carboxylic acid derived functional groups on their convex face. We have presented an improved synthesis of **1e** which serves as a common synthetic intermediate for the preparation of glycoluril derivatives with unfunctionalized ureidyl N-atoms. Compound **1e** can also be converted to bis(cyclic ether) **2e** which serves as a similar common intermediate. Compounds **1e** and **2e** can be converted into carboxylate salts (**6** and **8**) by basic hydrolysis reactions and

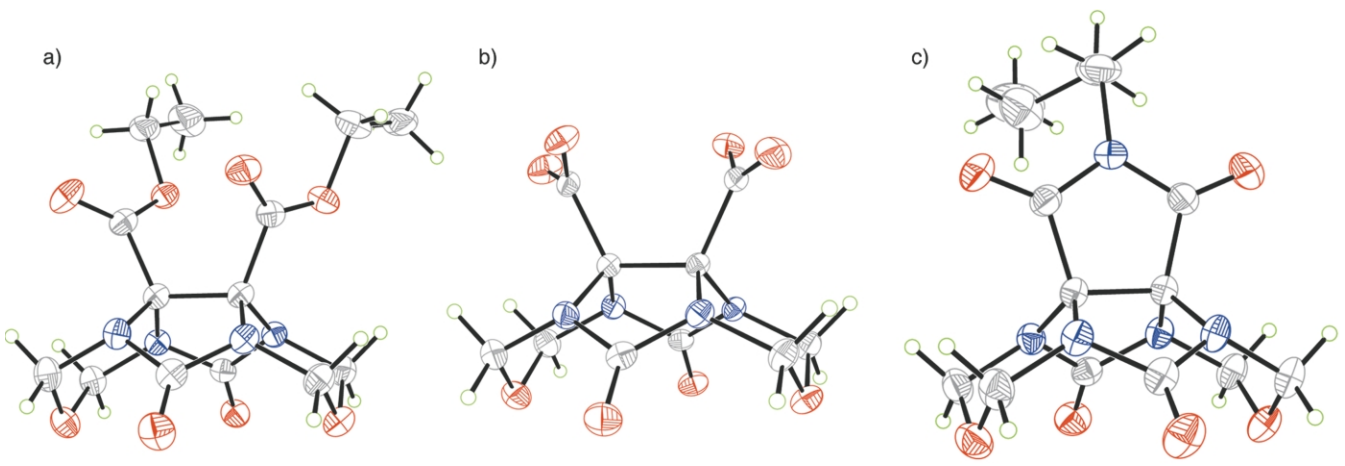
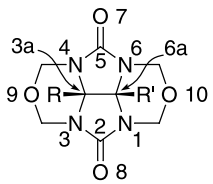


Figure 1. ORTEP plots of the molecular structures of: (a) **2e**, (b) **8**, and (c) **22** in the crystal. The lithium counterions have been removed from the structure of **8**. Thermal ellipsoids are drawn at the 50% probability level.

Table 1. Selected details from X-ray structures



Compound	Mean plane angle (°)[a]	Dihedral R–C3a–C6a–R′ (°)	O7–O8 (Å)	O9–O10 (Å)
2e	106.9	11.2	5.120	5.004
5	112.1	1.3	5.505	
8	106.5	8.2	5.174	5.100
17	103.9	7.5	4.995	5.152
22	110.7	0.9	5.271	4.925
$Me_{10}Q[5]$[31]	116.7–120.0	1.2–3.5	6.02–6.06	
Q[6][1b]	118.1–121.5	1.0–7.5	5.98–6.04	
1a[53]	120.3	0	5.997	
1b[54]	115.1	0	5.754	
1f[55]	118.4	9.5	5.935	
2b[56]	103.9	2.6	4.979	5.062

[a] Defined as the angle between the best mean planes through N1, C2, N3, C3a, and C6a and N4, C5, N6, C6a, and C3a.

into secondary amides (**10**–**15**) by heating in solutions of neat primary amines. The workup and purification is simple and the yields are high. The amide derived glycolurils can be converted into the imides (**19**–**22**) by heating with PTSA in $ClCH_2CH_2Cl$. We have obtained structural information for the ester, carboxylate, and imide derived bis(cyclic ethers) **2e**, **8**, **17**, and **22** by single crystal X-ray diffraction studies. The efficient production of these fundamental monomeric building blocks will allow an investigation of their incorporation in Q[*n*] derivatives and may expand the scope of Q[*n*] synthesis.

4. Experimental

4.1. General

Starting materials and were purchased from commercial suppliers and were used without further purification. THF and toluene were distilled from sodium benzophenone ketyl and methylene chloride was distilled from CaH_2 immediately before use. TLC analysis was performed using precoated glass plates. Column chromatography was performed using silica gel (230–400 mesh, 0.040–0.063 μm) from E. Merck using eluents in the indicated v:v ratio. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were recorded as KBr pellets or thin films on NaCl plates and are reported in cm^{-1}. NMR spectra were measured on instruments operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Mass spectrometry was performed using a magnetic sector instrument by electron impact (EI) or by fast atom bombardment (FAB) using the indicated matrix. The matrix 'magic bullet' is a 5:1 (w:w) mixture of dithiothreitol: dithioerythritol. Elemental analyses were performed by Midwest MicroLab (Indianapolis, IN).

4.2. Synthetic procedures

4.2.1. Compound 1e. This modification of the known procedures[42–45] delivers **1e** in the highest yield to date. A slurry of **3** (35.0 g, 133.5 mmol) in absolute EtOH (350 mL) is cooled to 0°C in an ice-water bath. The reaction mixture is slowly saturated with HCl over a period of 45 min at 0°C and then stirred at rt for 24 h. The reaction mixture is again cooled to 0°C, saturated with HCl over 30 min at 0°C and stirred for an additional 24 h. The reaction mixture is filtered through a medium porosity frit to remove NaCl, and the NaCl washed with EtOH (50 mL). To this clear solution was added urea (20.0 g, 337.6 mmol). The resulting solution was concentrated by rotary evaporation ($T \approx 40$–45°C). Benzene (50 mL) was added and then removed by rotary evaporation. To the resulting oil was added benzene (200 mL) and TFA (24 mL). The flask was equipped with a Dean-Stark trap and immersed in an oil bath that had been preheated to 140°C. The initial EtOH containing distillate (50 mL) was siphoned off and the reaction mixture was maintained at reflux for 6 h. The reaction mixture was cooled to rt and the solvent thoroughly decanted. EtOH (100 mL) was added to the solid product and the mixture was stirred overnight at rt. The white solid was collected by filtration, washed with CH_3COCH_3, and dried on the frit at atmospheric pressure giving **1e** (22.0–24.5 g, 58–64%).

4.2.2. Compound 2e and 5. *Method* 1. Compound **1e** (1.00 g, 3.50 mmol) was dissolved in TFA (4 mL) and paraformaldehyde (1.05 g, 35.0 mmol of CH_2O) was added in one portion. The reaction mixture was stirred and heated at 72°C for 6 h. After removal of TFA by rotary evaporation, the residue was dissolved in EtOAc (250 mL), washed with sat. Na_2CO_3, dried over anh. $MgSO_4$, and concentrated. Flash chromatography (SiO_2, $CHCl_3$/hexanes/EtOAc 2:1:1) gave **2e** (0.592 g, 1.62 mmol, 46%) and **5** as white solids. Compound **5** was recrystallized from EtOAc (0.270 g, 0.682 mmol, 20%).

Method 2. Compound **1e** (1.00 g, 3.50 mmol) was dissolved in TFA (4 mL) and paraformaldehyde (1.05 g, 35.0 mmol) was added in one portion. The mixture was heated at reflux for 16 h, concentrated, and dried under high vacuum. A mixture of the crude material, PTSA (3.90 g, 20.5 mmol) and $ClCH_2CH_2Cl$ (100 mL) was heated under N_2 at reflux

under an addition funnel filled with molecular sieves (4 Å) for 2 h. The reaction mixture was diluted with EtOAc (250 mL), washed with sat. Na_2CO_3 and brine, dried over anh. $MgSO_4$, concentrated and dried under high vacuum to yield **1** as a white solid (1.17 g, 3.19 mmol, 92%).

Compound **2e**. Mp 189–190°C. TLC ($CHCl_3$/hexanes/EtOAc 2:1:1) R_f 0.38. IR ($CHCl_3$, cm^{-1}): 2940w, 2911w, 2873w, 1755s, 1735s, 1474s, 1403s, 1380s, 1294s, 1170, 1027s. ^1H NMR (400 MHz, $CDCl_3$): δ 5.53 (d, J=11.3 Hz, 4H), 4.82 (d, J=11.3 Hz, 4H), 4.31 (q, J=7.2 Hz, 4H), 1.32 (t, J=7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 156.7, 74.4, 72.2, 63.6, 13.7. MS (FAB, Magic Bullet): m/z 371 (27, $[M+H]^+$); 341 (100, $[M+H-CH_2O]^+$). HR-MS (FAB, Magic Bullet): m/z 371.1197 ($[M+H]^+$, $C_{14}H_{19}O_8N_4$, calcd 371.1203). X-Ray crystal structure.

Compound **5**. Mp 204–206°C. TLC ($CHCl_3$/hexanes/EtOAc 2:1:1) R_f 0.14. IR (KBr, cm^{-1}): 2979w, 2940w, 2909w, 1744s, 1754s, 1724s, 1474s, 1443s, 1425m, 1403m, 1393m, 1369m, 1323m, 1286s, 1237s, 1216s, 1188m, 1125s, 1095s, 1072m, 1044m, 1022m, 1006m. ^1H NMR (400 MHz, $CDCl_3$): 5.51 (d, J=11.2 Hz, 2H), 5.45–5.35 (br. s, 3H), 4.90–4.80 (br. s, 3H), 4.72 (d, J=11.2 Hz, 2H), 4.35–4.20 (m, 4H), 1.30 (t, J=7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.8, 164.4, 155.4, 78.5, 74.2, 73.7, 72.4, 63.7, 63.6, 13.9, 13.8. (only 11 of the 12 expected resonances were observed). MS (EI): m/z 400 (10, $[M]^+$), 370 (40, $[M-CH_2O]^+$), 327 (100, $[M-C_3H_5O_2]^+$). HR-MS (EI): m/z 400.1239 ($[M]^+$, $C_{15}H_{20}N_4O_9$, calcd 400.1230). X-Ray crystal structure (from EtOAc).

4.2.3. Compound 3. The procedure described by Fenton for oxidation of dihydroxymaleic acid was adapted for use with dihydroxyfumaric acid.[46,47] To a suspension of **4** (25.0 g, 150 mmol) in AcOH (70 mL) was added dropwise a solution of Br_2 (8.8 mL, 27.3 g, 171 mmol) in AcOH (10 mL). Occasionally during the addition, small quantities of H_2O (1 mL) were added to aid in decolorization. After the addition was complete and the solution was homogenous, the solvent was removed by rotary evaporation. The resulting oil was dissolved in water (500 mL) and transferred to a 2 L beaker equipped with an efficient stir bar. The solution was treated with solid Na_2CO_3 until bubbling ceased and the solution was basic. The heavy white precipitate was collected by filtration, resuspended in water, filtered, suspended in CH_3COCH_3, and filtered. The resulting white solid was dried at atmospheric pressure on the frit yielding **3** (33.8–35.3 g, 86–90%).

4.2.4. Compound 6.[44] A mixture of **1e** (1.010 g, 3.53 mmol), NaOH (0.286 g, 7.15 mmol), and deionized H_2O (7 mL), was heated at 80°C for 3 h. After cooling to room temperature, the reaction mixture was filtered, and the residue was dried under high vacuum to give **6** (0.872 g, 3.18 mmol, 90%) as a white powder. Mp>340°C (dec.). IR (KBr, cm^{-1}): 3473w, 3282s, 2819m, 1709s, 1638s, 1396w, 1382w, 1168m, 1029m. ^1H NMR (400 MHz, D_2O/H_2O (1:1) selective excitation): 7.34 (br., 4H). ^{13}C NMR (100 MHz, D_2O): 171.4, 162.6, 80.6. MS (FAB, glycerol): m/z 275 (10, $[M+H]^+$), 115 (100, $[C_3H_3N_2O_3]^+$). HR-MS (FAB^-, glycerol): m/z 229.0210 ($[M+H-2Na]^-$) $C_6H_5N_4O_6$, calcd 229.0209.

4.2.5. Compound 7.[42,43] A solution of PTSA·H_2O (0.914 g, 4.80 mmol) in H_2O (10 mL) was added to **6**. The excess H_2O was removed by rotary evaporation and the resulting residue was dried under high vacuum. The residue was washed with MeOH (5×5 mL) and dried under high vacuum to give **7** (0.256 g, 1.11 mmol, 46%) as a white solid. Mp 195–198°C. IR (KBr, cm^{-1}): 3418s, 3322s, 2920w, 1747m, 1685w, 1653s, 1506m, 1275m, 1167s. ^1H NMR (400 MHz, DMSO-d_6): 7.76 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): 169.0, 159.8, 77.9. MS (FAB, Magic Bullet): m/z 231 (100, $[M+H]^+$). HR-MS (FAB, Magic Bullet): m/z 231.0360 ($[M+H]^+$, $C_6H_7N_4O_6$, calcd 231.0366). Anal. calcd for $C_6H_6N_4O_6·H_2O$ (248.15): C, 29.04; H, 3.25. Found: C, 29.06; H, 3.07.

4.2.6. Compound 8. A mixture of **2e** (0.205 g, 0.554 mmol), LiOH (0.173 g, 7.24 mmol), deionized H_2O (150 mL), and MeOH (150 mL) was heated at 70°C for 1 week. The reaction mixture was filtered, excess H_2O/MeOH was removed by rotary evaporation, and the residue was dried under high vacuum. The solid was crystallized from MeOH (120 mL), filtered, and dried under high vacuum to give **8** (0.144 g, 0.443 mmol, 80%) as a white crystalline solid. Mp>300°C (dec.). IR (KBr, cm^{-1}): 3542s, 2965w, 1719s, 1674s, 1476s, 1382m, 1305m, 1247m, 1178m, 1010s. ^1H NMR (400 MHz, buffered D_2O, pD=7.41): 5.29 (d, J=11.6 Hz, 4H), 4.71 (d, J=11.6 Hz, 4H). ^{13}C NMR (100 MHz, buffered D_2O, pD=7.41): 168.9, 159.5, 77.4, 72.3. ES-MS: m/z 645 (100, $[2M-Li]^-$), 319 (8, $[M-Li]^-$). X-Ray crystal structure.

4.2.7. Compound 9. A mixture of **2e** (0.503 g, 1.35 mmol), LiOH (0.324 g, 13.51 mmol), H_2O (125 mL), and MeOH (125 mL) was heated at 70°C for 24 h. The reaction mixture was concentrated and dried under high vacuum. The residue was dissolved in H_2O (20 mL) and neutralized with TFA (1.56 g, 13.65 mmol). The solution was concentrated and dried under high vacuum. The resulting solid was washed with CH_3CN (4×5 mL), dried under high vacuum, and redissolved in H_2O (2.5 mL). Addition of conc. HCl (2 mL) provided a precipitate that was filtered then dried under high vacuum to give **9** (0.322 g, 1.03 mmol, 76%) as a white solid. Mp>300°C (dec.). IR (KBr, cm^{-1}): 3532s, 2960m, 1757s, 1700s, 1478m, 1379m, 1228w, 1174m, 1012s, 930s. ^1H NMR (400 MHz, DMSO-d_6): 5.32 (d, J=11.1 Hz, 4H), 4.87 (d, J=11.1 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): 165.8, 157.2, 74.5, 72.1. MS (FAB, glycerol): m/z 313 (100, $[M-H]^-$). HR-MS (FAB, glycerol): m/z 313.0413 ($[M-H]^-$, $C_{10}H_9N_4O_8$, calcd 313.0420).

4.2.8. Compound 10. A mixture of **1e** (1.035 g, 3.62 mmol) and 3-(dimethylamino)propylamine (25 mL) was heated at 90°C for 24 h. The excess amine was removed by rotary evaporation and the residue was dried under high vacuum. The solid was crystallized from MeOH (50 mL), filtered, and dried under high vacuum to give **10** (1.243 g, 3.12 mmol, 86%) as an off-white crystalline solid. Mp 231–233°C. IR (KBr, cm^{-1}): 3324m, 3246m, 2947m, 2862m, 2780m, 1734m, 1685s, 1533s, 1466s. ^1H NMR (400 MHz, DMSO-d_6): 7.88 (t, J=5.5 Hz, 2H), 7.48 (s, 4H), 3.03 (m, 4H), 2.19 (t, J=6.8 Hz, 4H), 2.10 (s, 12H), 1.50 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): 166.5, 160.9, 79.1, 57.0, 45.1, 38.3, 26.3. MS (FAB, PEG): m/z 399 (30,

$[M+H]^+$), 45 (100, $[C_2H_7N]^+$). HR-MS (FAB, PEG): *m/z* 399.2482 ($[M+H]^+$, $C_{16}H_{31}N_8O_4$, calcd 399.2468).

4.2.9. Compound 11. A mixture of **1e** (1.084 g, 3.79 mmol) and *n*-butylamine (50 mL) was heated at 75°C for 20 h. The excess amine was removed by rotary evaporation and the resulting residue was dried under high vacuum. The resulting solid was crystallized from MeOH (50 mL), filtered, and dried under high vacuum to give **11** (1.122 g, 3.30 mmol, 87%) as a white crystalline solid. Mp>283°C (dec.). IR (KBr, cm^{-1}): 3303s, 2960s, 2874s, 1714s, 1541s, 1465s, 1378m, 1312w, 1277w, 1163s. ^1H NMR (400 MHz, DMSO-d_6): 7.61 (t, *J*=5.7 Hz, 2H), 7.48 (s, 4H), 2.98 (m, 4H), 1.36 (m, 4H), 1.25 (m, 4H), 0.85 (t, *J*=7.2 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): 166.5, 160.8, 79.1, 39.2, 30.8, 19.5, 13.7. MS (FAB, Magic Bullet): *m/z* 341 (38, $[M+H]^+$), 225 (100, $[C_9H_{13}N_4O_3]^+$). HR-MS (FAB, Magic Bullet): *m/z* 341.1944 ($[M+H]^+$, $C_{14}H_{25}N_6O_4$, calcd 341.1937). Anal. calcd for $C_{14}H_{24}N_6O_4$ (340.38): C, 49.40; H, 7.11. Found: C, 49.12; H, 7.14.

4.2.10. Compound 12. A mixture of **1e** (0.521 g, 1.82 mmol) and ethanolamine (25 mL) was heated at 80°C for 24 h. The excess amine was removed by vacuum distillation and the resulting residue was washed with H_2O (3×10 mL), and then dried under high vacuum to give **12** (0.491 g, 1.55 mmol, 85%) as a white powder. Mp 278°C. IR (KBr, cm^{-1}): 3483s, 3403m, 2950w, 2932m, 2889m, 1742s, 1706s, 1545s, 1420m, 1253m, 1170m. ^1H NMR (400 MHz, DMSO-d_6): 7.72 (t, *J*=5.5 Hz, 2H), 7.56 (s, 4H), 4.60 (t, *J*=5.6 Hz, 2H), 3.37 (m, 4H), 3.08 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): 166.9, 160.6, 79.0, 59.2, 42.1. MS (FAB, glycerol): *m/z* 317 (100, $[M+H]^+$). HR-MS (FAB, glycerol): *m/z* 317.1212 ($[M+H]^+$, $C_{10}H_{17}N_6O_6$, calcd 317.1210). Anal. calcd for $C_{10}H_{16}N_6O_6$ (316.27): C, 37.98; H, 5.10. Found: C, 37.55; H, 5.10.

4.2.11. Compound 13. A mixture of **2e** (0.539 g, 1.46 mmol) and 3-(dimethylamino)propylamine (12 mL) was heated at 78°C for 20 h. The amine was removed by rotary evaporation and the residue was dried under high vacuum. The residue was suspended in Et_2O, filtered, and dried under high vacuum to give **13** (0.618 g, 1.28 mmol, 88%) as a yellow powder. Mp 168–170°C. TLC ($CHCl_3$/MeOH, 9:1, 2% NH_4OH) R_f 0.12. IR (KBr, cm^{-1}): 3295s, 2942m, 2872m, 2766s, 1767s, 1738s, 1690s, 1538s, 1469s, 1242s, 1180s. ^1H NMR (400 MHz, $CDCl_3$): 9.62 (br., 2H), 5.52 (d, *J*=11.2 Hz, 4H), 4.63 (d, *J*=11.2 Hz, 4H), 3.36 (m, 4H), 2.45 (t, *J*=5.6 Hz, 4H), 2.19 (s, 12H) 1.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 162.6, 157.6, 75.7, 72.3, 59.0, 44.8, 41.7, 23.9. MS (FAB, Magic Bullet): *m/z* 483 (100, $[M+H]^+$). HR-MS (FAB, Magic Bullet): *m/z* 483.2693 ($[M+H]^+$, $C_{20}H_{35}N_8O_6$, calcd 483.2680). Anal. calcd for $C_{20}H_{34}N_8O_6$ (482.53): C, 49.78; H, 7.10. Found: C, 49.96; H, 6.97.

4.2.12. Compound 14. A mixture of **2e** (0.205 g, 0.554 mmol) and *n*-butylamine (10 mL) was heated at 78°C for 20 h. The amine was removed by rotary evaporation and the residue was dried under high vacuum. The residue was suspended in Et_2O, filtered, and dried under high vacuum to give **14** (0.211 g, 0.499 mmol, 90%) as a white powder. Mp 238–242°C. TLC ($CHCl_3$/MeOH, 25:1) R_f 0.19. IR (KBr, cm^{-1}): 3286s, 2954m, 2932m, 2874m, 1766s, 1743s, 1688s, 1469m, 1410s, 1303m, 1243m, 1180m. ^1H NMR (400 MHz, $CDCl_3$): 6.64 (t, *J*=5.3 Hz, 2H), 5.53 (d, *J*=11.3 Hz, 4H), 4.59 (d, *J*=11.3 Hz, 4H), 3.28 (m, 4H), 1.50 (m, 4H), 1.33 (m, 4H), 0.92 (t, *J*=7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 162.5, 157.2, 75.5, 72.5, 40.4, 31.1, 20.0, 13.6. MS (FAB, Magic Bullet): *m/z* 425 (100, $[M+H]^+$). HR-MS (FAB, Magic Bullet): *m/z* 425.2166 ($[M+H]^+$, $C_{18}H_{29}N_6O_6$, calcd 425.2149). Anal. calcd for $C_{18}H_{28}N_6O_6$ (424.45): C, 50.93; H, 6.65. Found: C, 50.85; H, 6.71.

4.2.13. Compound 15. A mixture of **2e** (0.236 g, 0.637 mmol) and ethanolamine (20 mL) was heated at 85°C for 20 h. The excess amine was removed by vacuum distillation and the resulting residue was washed with EtOH (3×10 mL), and then dried under high vacuum to give **15** (0.238 g, 0.595 mmol, 93%) as a white powder. Mp 276–279°C. IR (KBr, cm^{-1}): 3422s, 3335s, 2948m, 1758m, 1736s, 1692s, 1486m, 1419m, 1040m, 1028m. ^1H NMR (400 MHz, DMSO-d_6): 8.53 (t, *J*=5.8 Hz, 2H), 5.29 (d, *J*=11.3 Hz, 4H), 4.69 (d, *J*=11.3 Hz, 4H), 4.59 (t, *J*=5.9 Hz, 2H), 3.41 (m, 4H), 3.16 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): 162.6, 157.5, 75.4, 72.0, 59.0, 42.5. MS (FAB, Magic Bullet): *m/z* 401 (100, $[M+H]^+$). HR-MS (FAB, Magic Bullet): *m/z* 401.1418 ($[M+H]^+$, $C_{14}H_{21}N_6O_8$, calcd 401.1421). Anal. calcd for $C_{14}H_{20}N_6O_8$ (400.34): C, 42.00; H, 5.04. Found: C, 41.99; H, 5.05.

4.2.14. Compound 16. A mixture of **1e** (2.010 g, 7.02 mmol) and morpholine (150 mL) was heated at 128°C for 96 h. The excess amine was removed by rotary evaporation and the residue was dried under high vacuum. The solid was washed with hot MeOH (50 mL), filtered, and dried under high vacuum to give **16** (1.599 g, 3.95 mmol, 56%) as a white solid. Mp 211–214°C. IR (KBr, cm^{-1}): 3417m, 3256s, 2867m, 1675s, 1638s, 1382m, 1364w, 1162m, 1104m, 1044m, 1025m. ^1H NMR (400 MHz, DMSO-d_6): 6.92 (s, 4H), 3.72 (t, *J*=4.6 Hz, 8H), 3.00 (t, *J*=4.6 Hz, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.9, 161.2, 79.6, 63.9, 43.2. ES-MS: *m/z* 483 (100, $[2M+4H+Na-2C_4H_{10}NO]^+$), 405 (2, $[M+H]^+$). ES-MS: *m/z* 229 (100, $[M+H-2C_4H_{10}NO]^-$).

4.2.15. Compound 17. A mixture of **2e** (0.506 g, 1.37 mmol) and morpholine (50 mL) was heated at 128°C for 72 h. The amine was removed by rotary evaporation and the residue was dried under high vacuum. The residue was suspended in MeOH (2×5 mL), decanted, and dried under high vacuum to give **17** (0.550 g, 1.13 mmol, 82%) as an off-white powder. Mp 214–218°C. IR (KBr, cm^{-1}): 3036m, 2874m, 1715s, 1654s, 1473m, 1435m, 1379s, 1308m, 1105m, 1015s. ^1H NMR (400 MHz, DMSO-d_6): 5.21 (d, *J*=10.7 Hz, 4H), 4.79 (d, *J*=10.7 Hz, 4H), 3.72 (t, *J*=4.8 Hz, 8H), 3.00 (t, *J*=4.8 Hz, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): 167.7, 158.2, 76.1, 71.7, 63.4, 42.8. MS (FAB, Magic Bullet): *m/z* 489 (4, $[M+H]^+$), 88 (100, $[C_4H_{10}NO]^+$). X-Ray crystal stucture (from MeOH).

4.2.16. Compound 18. A solution of **14** (0.502 g, 1.23 mmol) in anh. THF (20 mL) was treated with NaH (0.123 g, 5.13 mmol) and heated at 40°C for 5 min. Methyl iodide (1.739 g, 12.26 mmol) was added and the reaction

mixture was heated at reflux for 5 h. An additional portion of CH_3I (1.140 g, 8.03 mmol) was added and reflux continued for 2 h. The reaction mixture was concentrated and dried under high vacuum. The residue was suspended in H_2O (500 mL) and extracted with EtOAc (3×100 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, $CHCl_3$/MeOH, 50:1) to give **18** (0.415 g, 0.918 mmol, 75%) as a foam. TLC ($CHCl_3$/MeOH, 25:1) R_f 0.47. IR (KBr, cm^{-1}): 2959s, 2874m, 1756s, 1736s, 1664s, 1470m, 1410s, 1301m, 1179s, 1030s, 1008s. ^1H NMR (400 MHz, $CDCl_3$): 5.57 (d, J=7.8 Hz, 2H), 5.52 (d, J=11.1 Hz, 2H), 4.9 (m, 2H) 4.56 (m, 2H), 3.57 (m, 0.5H), 3.43 (m, 1.5H), 3.27 (m, 1H), 3.13 (m, 0.5H), 2.96 (s, 2H), 2.82 (s, 2.5H), 2.80 (s, 1.5H), 2.60 (m, 0.5H), 1.47 (m, 3H), 1.30 (m, 3H), 1.17 (m, 2H), 0.94 (t, J=7.3 Hz, 4H), 0.83 (t, J=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 162.0, 161.9, 161.6, 161.5, 155.9, 155.8, 138.0, 75.7, 75.5, 73.0, 71.8, 71.6, 51.0, 50.9, 50.8, 36.6, 36.0, 30.6, 30.5, 29.0, 28.8, 20.0, 19.7, 14.2, 13.8, 13.6, 10.9. MS (FAB, Magic Bullet): m/z 453 (46, $[M+H]^+$), 100 (100, $[C_5H_{10}NO]^+$). HR-MS (FAB, Magic Bullet): m/z 453.2469 ($[M+H]^+$, $C_{20}H_{33}N_6O_6$, calcd 453.2462.

4.2.17. Compound 19. A mixture of **10** (0.254 g, 0.637 mmol), $ClCH_2CH_2Cl$ (25 mL), and PTSA·H_2O (0.607 g, 3.19 mmol) was heated at reflux for 20 h. After rotary evaporation, the residue was dried under high vacuum. The residue was washed with EtOH, filtered, and dried under high vacuum to give **19** (0.270 g, 0.576 mmol, 91%) as a white solid. Mp 132–138°C. IR (KBr, cm^{-1}): 3443s, 2946w, 2919w, 1718s, 1700s, 1653w, 1635w, 1457m, 1191s, 1125m. ^1H NMR (400 MHz, DMSO-d_6): 9.25 (br., 1H), 8.70 (s, 4H), 7.46 (d, J=7.9 Hz, 2H), 7.10 (d, J=7.9 Hz, 2H), 3.48 (t, J=7.4 Hz, 2H), 3.05 (m, 2H), 2.75 (d, J=4.6 Hz, 6H), 2.28 (s, 3H), 1.84 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.5, 158.9, 145.5, 137.8, 128.2, 125.5, 73.8, 54.1, 52.3, 35.8, 22.4, 20.8. MS (FAB, Magic Bullet): m/z 297 (100, $[M+H-CH_3C_6H_4SO_3]^+$). HR-MS (FAB, Magic Bullet): m/z 297.1313 ($[C_{11}H_{17}N_6O_4]^+$, $C_{11}H_{17}N_6O_4$, calcd 297.1311).

4.2.18. Compound 20. A mixture of **11** (0.508 g, 1.49 mmol), $ClCH_2CH_2Cl$ (50 mL), and PTSA·H_2O (1.40 g, 7.35 mmol) was heated at reflux for 20 h. The solvent was removed by rotary evaporation and the resulting residue was dried under high vacuum. The residue was suspended in H_2O, filtered, and dried under high vacuum to give **20** (0.336 g, 1.26 mmol, 85%) as a white solid. Mp>345°C (dec.). IR (KBr, cm^{-1}): 3297m, 3229m, 2934w, 2858w, 1723s, 1468m, 1446m, 1386m, 1158m. ^1H NMR (400 MHz, DMSO-d_6): 8.69 (s, 4H), 3.45 (t, J=7.0 Hz, 2H), 1.47 (m, 2H), 1.19 (m, 2H), 0.85 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.8, 159.0, 73.8, 38.0, 28.8, 19.3, 13.5. MS (FAB, Magic Bullet): m/z 268 (100, $[M+H]^+$). HR-MS (FAB, Magic Bullet): m/z 268.1040 ($[M+H]^+$, $C_{10}H_{14}N_5O_4$, calcd 268.1046). Anal. calcd for $C_{10}H_{13}N_5O_4$ (267.24): C, 44.94; H, 4.90. Found: C, 44.75; H, 4.91.

4.2.19. Compound 21. A mixture of **13** (0.515 g, 1.07 mmol), $ClCH_2CH_2Cl$ (100 mL), and PTSA·H_2O (1.05 g, 5.52 mmol) was heated at reflux for 20 h. The solvent was removed by rotary evaporation and the residue was dried under high vacuum. The residue was washed with EtOH, filtered, and dried under high vacuum to give **21** (0.389 g, 0.704 mmol, 66%) as a white solid. Mp 210–215°C. IR (KBr, cm^{-1}): 3443s, 2960w, 2727w, 1725s, 1653w, 1647w, 1436m, 1375m, 1218s, 1182s, 1011m. ^1H NMR (400 MHz, DMSO-d_6): 9.23 (br., 1H), 7.47 (d, J=7.9 Hz, 2H), 7.10 (d, J=7.9 Hz, 2H), 5.43 (d, J=11.3 Hz, 4H), 5.09 (d, J=11.3 Hz, 4H), 3.54 (t, J=7.1 Hz, 2H), 3.07 (m, 2H), 2.75 (d, J=4.8 Hz, 6H), 2.28 (s, 3H), 1.91 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 167.0, 157.8, 145.4, 137.8, 128.1, 125.5, 72.3, 70.2, 54.1, 42.3, 36.5, 22.0, 20.7. MS (FAB, Magic Bullet): m/z 381 (29, $[M+H-CH_3C_6H_4SO_3]^+$) 58 (100, $[C_3H_8N]^+$). HR-MS (FAB, Magic Bullet): m/z 381.1530 ($[C_{15}H_{21}N_6O_6]^+$, $C_{15}H_{21}N_6O_6$, calcd 381.1523).

4.2.20. Compound 22. *Method* 1. A mixture of **14** (0.050 g, 0.118 mmol), $ClCH_2CH_2Cl$ (20 mL), and PTSA·H_2O (0.114 g, 0.589 mmol) was heated at reflux for 20 h. The solvent was removed by rotary evaporation and the residue was dried under high vacuum. The residue was washed with H_2O (3×8 mL) and dried under high vacuum to give **22** (0.034 g, 0.096 mmol, 82%) as an off-white solid.

Method 2. A mixture of **20** (0.199 g, 0.749 mmol), TFA (0.5 mL), and paraformaldehyde (0.091 g, 3.00 mmol) was heated at 75°C for 12 h. TFA was removed by rotary evaporation, the residue dissolved in EtOAc (50 mL), washed with sat. aq. Na_2CO_3 (3×50 mL), and dried over anh. $MgSO_4$. After filtration and rotary evaporation, the residue was purified by flash chromatography (SiO_2, $CHCl_3$/EtOAc/hexanes, 2:1:1) to give **22** (0.079 g, 0.225 mmol, 30%) as a white crystalline solid. Mp 182–184°C. TLC ($CHCl_3$/EtOAc/hexanes, 2:1:1) R_f 0.43. IR (KBr, cm^{-1}): 2959w, 1778s, 1732s, 1478m, 1465m, 1371m, 1307m, 1230m, 1200m, 1035m, 1013m. ^1H NMR (400 MHz, $CDCl_3$): 5.51 (d, J=11.1 Hz, 4H), 5.09 (d, J=11.1 Hz, 4H), 3.59 (t, J=7.3 Hz, 2H), 1.59 (m, 2H), 1.30 (m, 2H), 0.92 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.3, 157.6, 72.4, 70.4, 39.1, 29.1, 19.7, 13.4. MS (FAB, Magic Bullet): m/z 352 (89, $[M+H]^+$), 322 (100). HR-MS (FAB, Magic Bullet): m/z 352.1268 ($[M+H]^+$, $C_{14}H_{18}N_5O_6$, calcd 352.1257). X-Ray crystal structure. Anal. calcd for $C_{14}H_{17}N_5O_6$ (351.32): C, 47.86; H, 4.88. Found: C, 48.01; H, 5.07.

4.2.21. Compound 23. A mixture of **12** (0.505 g, 1.60 mmol), $ClCH_2CH_2Cl$ (50 mL), and PTSA·H_2O (3.09 g, 16.24 mmol) was heated at reflux for 24 h. The solvent was removed by rotary evaporation and the resulting residue was dried under high vacuum. The residue was washed with EtOH (3×8 mL), then with EtOAc (1×5 mL), and dried under high vacuum to give **23** (0.114 g, 0.173 mmol, 11%) as an off-white solid. Mp 240–244°C. IR (KBr, cm^{-1}): 3438s, 3186s, 2929w, 1752s, 1724m, 1694s, 1496s, 1279s, 1186m, 1126s. ^1H NMR (400 MHz, DMSO-d_6): 8.11 (s, 4H), 7.79 (br., 6H), 7.46 (d, J=7.8 Hz, 4H), 7.11 (d, J=7.8 Hz, 4H), 4.25 (t, J=4.8 Hz, 4H), 3.12 (m, 4H), 2.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): 166.7, 159.1, 145.2, 138.0, 128.2, 125.5, 77.8, 62.4, 37.9, 20.8. MS (FAB, Magic Bullet): m/z 317 (15, $[M+H-2C_7H_8O_3S]^+$), 44 (100, $[C_2H_6N]^+$). HR-MS (FAB, Magic

Bullet): *m/z* 317.1223 ($[M+H-2C_7H_8O_3S]^+$, $C_{10}H_{17}N_6O_6$, calcd 317.1210).

4.2.22. Compound 24. A mixture of **12** (0.502 g, 1.59 mmol), acetic anhydride (0.490 g, 4.76 mmol), and acetic acid (50 mL) was heated at reflux for 24 h. To this solution, PTSA·H_2O (1.51 g, 7.94 mmol) was added and reflux continued for 24 h. The reaction mixture was concentrated and dried under high vacuum. The residue was washed with EtOH (4×4 mL) and dried under high vacuum to give **24** (0.338 g, 1.14 mmol, 72%) as a white solid. Mp 329–332°C. IR (KBr, cm^{-1}): 3245s, 2961m, 1762m, 1735s, 1698s, 1399m, 1374m, 1334m, 1229s, 1165m. ^1H NMR (400 MHz, DMSO-d_6): 8.68 (s, 4H), 4.16 (t, J=5.2 Hz, 2H), 3.71 (t, J=5.2 Hz, 2H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.5, 170.2, 158.9, 73.7, 59.6, 37.7, 20.3. MS (EI): *m/z* 297 (45, $[M]^+$), 254 (100, $[C_8H_8N_5O_5]^+$). HR-MS (EI): *m/z* 297.0717 ($[M]^+$, $C_{10}H_{11}N_5O_6$, calcd 297.0709). Anal. calcd for $C_{10}H_{11}N_5O_6$ (297.22): C, 40.41; H, 3.73. Found: C, 40.29; H, 3.66.

4.2.23. Compound 25. A mixture of **15** (0.435 g, 1.09 mmol), acetic anhydride (0.336 g, 3.26 mmol), and $ClCH_2CH_2Cl$ (160 mL) was heated at reflux for 1 h. To this solution, PTSA·H_2O (1.034 g, 5.44 mmol) was added and reflux continued for 24 h. The excess $ClCH_2CH_2Cl$ was removed by rotary evaporation and the resulting residue was dried under high vacuum. The residue was washed with H_2O (4×10 mL) and dried under high vacuum to give **25** (0.301 g, 0.790 mmol, 73%) as a white solid. Mp 251–254°C. TLC ($CHCl_3$/EtOAc, 2:1) R_f 0.35. IR (KBr, cm^{-1}): 2935w, 2885w, 1780m, 1757s, 1730m, 1385s, 1235s, 1205m, 1027m, 1009s. ^1H NMR (400 MHz, $CDCl_3$): 5.52 (d, J=11.1 Hz, 4H), 5.09 (d, J=11.1 Hz, 4H), 4.27 (t, J=5.2 Hz, 2H), 3.86 (t, J=5.2 Hz, 2H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 167.2, 157.6, 72.4, 70.5, 59.8, 38.6, 20.5. MS (EI): *m/z* 381 (89, $[M]^+$), 351 (100, $[C_{13}H_{13}N_5O_7]^+$). HR-MS (EI): *m/z* 381.0928 ($[M]^+$, $C_{14}H_{15}N_5O_8$, calcd 381.0921). Anal. calcd for $C_{14}H_{15}N_5O_8$ (381.30): C, 44.10; H, 3.97. Found: C, 43.82; H, 3.91.

4.3. X-Ray crystallographic analyses

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-199739 (**2e**), CCDC-199740 (**5**), CCDC-199741 (**8**), CCDC-199742 (**17**), and CCDC-199743 (**22**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

4.3.1. Crystal data for 2e, 5, 8, 17, and 22. Crystal data for **2e**: $[C_{14}H_{18}N_4O_8]$ (370.32); monoclinic, space group $P2(1)/c$; colorless block, a=10.5694(6) Å, b=8.6990(4) Å, c=17.9484(10) Å; α=90°, β=100.815(5)°, γ=90°, V=1620.92(15) Å^3; Z=4; T=153(2) K; $R(F)$=0.0402; GOF on F^2=1.057. Crystal data for **5**: $[C_{15}H_{20}N_4O_9]$ (400.35); monoclinic, space group $P2(1)/n$; colorless block, a=12.1504(7) Å, b=11.3265(6) Å, c=12.8924(7) Å; α=90°, β=103.3320(10)°, γ=90°, V=1726.45(16) Å^3; Z=4; T=193(2) K; $R(F)$=0.0352; GOF on F^2=1.084. Crystal data for **8**: $[C_{10}H_{12}Li_2N_4O_{10}]$ (362.12); monoclinic, space group $P2(1)/n$; colorless rod, a=7.8069(3) Å, b=12.1012(5) Å, c=15.2717(6) Å; α=90°, β=94.6540(10)°, γ=90°, V=1438.00(10) Å^3; Z=4; T=293(2) K; $R(F)$=0.0344; GOF on F^2=1.077. Crystal data for **17**: $[C_{19}H_{32}N_6O_{11}]$ (520.51); triclinic, space group P-1; colorless block, a=10.5703(4) Å, b=10.9034(4) Å, c=10.9550(4) Å; α=75.6780(10)°, β=80.0040(10)°, γ=74.3000(10)°, V=1169.99(8) Å^3; Z=2; T=193(2) K; $R(F)$=0.0337; GOF on F^2=1.044. Crystal data for **22**: $[C_{14}H_{17}N_5O_6]$ (351.33); monoclinic, space group $P2(1)/n$; colorless plate, a=8.2888(7) Å, b=12.5119(11) Å, c=15.6990(14) Å; α=90°, β=91.706(2)°, γ=90°, V=1627.4(2) Å^3; Z=4; T=193(2) K; $R(F)$=0.0380; GOF on F^2=1.087.

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