Preparation of a Variety of Macrocyclic Di- and Tetraamides and Their Peraza-Crown Analogs Using the Crab-Like Cyclization Reaction

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Twelve new macrocyclic di- and tetraamides have been synthesized from the reaction of a bis(α-chloroamide) with a primary amine or with a diamine. Some of these cyclic di- and tetraamides contained pendant aminoalkyl groups attached on one or more ring nitrogen atoms. Two macrocyclic dithiadiamides were prepared from the reaction of a bis(α-chloroamide) and a dimercaptan. In every case, 12-, 14- and 15-membered cyclic di- and tetraamides were isolated in good yields. The 9-, 17- and 18-membered macrocycles were prepared in lower yields. Four of the amide-containing macrocycles were reduced by diborane to the peraza-crown compounds.

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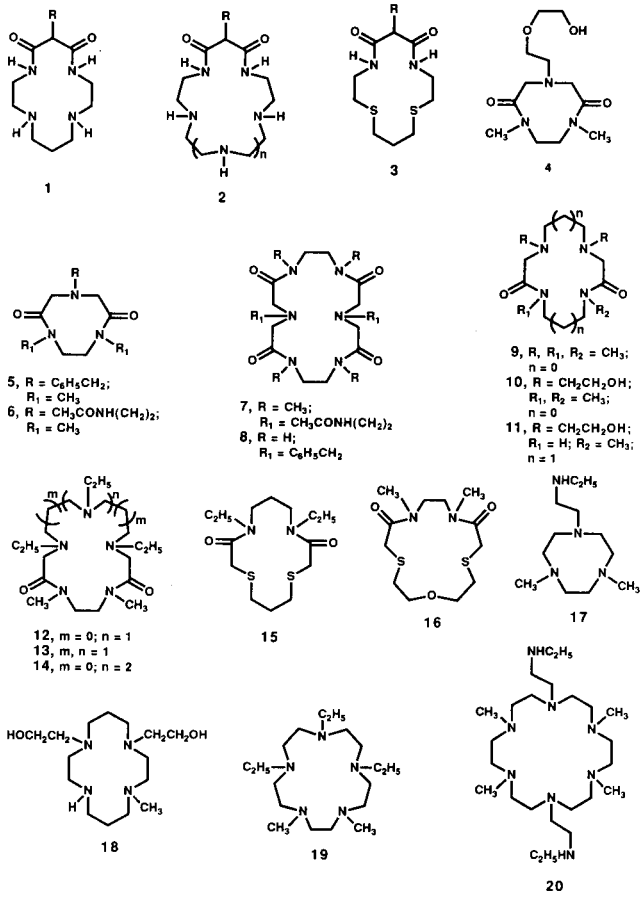
Introduction.

We have published several papers on the use of a crab-like cyclization reaction for the synthesis of polyaza macrocycles. The reaction sequence uses the reaction of a diamine with chloroacetyl chloride to form the starting crab-like bis(α-chloroamide) intermediate. These materials resemble a crab with two reactive alkyl chloride groups poised and ready to react with a primary amine or a diamine to form a macrocyclic diamide. The diamide can be reduced to form the polyaza-crown ligands. The reaction is useful for the preparation of polyaza-crowns [1-4], peraza-crowns [2,3,5], *N*-pivot lariat polyaza-crowns [2,4-6], functionalized aza- and peraza-crowns [2-6] and peraza-cage ("belt") compounds [7].

The advantages of this cyclization procedure are: 1) the process is a straight forward one-step procedure from simple and inexpensive starting materials; 2) the amide nitrogen is unreactive under the reaction conditions which alleviates the need for nitrogen-protecting groups, such as *N*-tosyl, which often are difficult to remove; 3) the process is shorter and the overall yields are higher than when protecting groups are used.

The intermediate macrocyclic ligands with two amide moieties are useful in their own right for the complexation of metal ions. Similar amide-containing macrocycles such as **1-3** (see Figure 1) have shown chelating properties with various metal ions [8-11]. Macrocycle **1** selectively complexed with Cu(II), Ni(II), Pd(II), Pt(II) and Co(II) ions over other metal cations [8-10]. Ligand **3** was selective for Pt(II) and Pd(II) ions while the reduced macrocycle was less selective and complexed with those ions and also with Cu(II) and Ni(II) ions [11]. Macrocycles **1** and **2** were prepared from substituted diethyl malonates in 15-30% yields. Our crab-like synthesis of similar macrocyclic diamides usually gave yields of 30-75% and an extended reaction period, which is often required for the malonate ester-amine reaction, is not needed [1-6].

Figure 1. New Macrocyclic Di- and Tetraamides and Amines



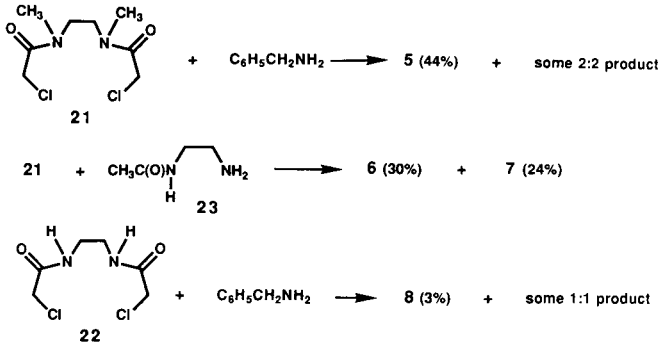
We now report the synthesis of a variety of macrocyclic di- and tetraamide ligands containing 9, 12, 14, 15, 17 and 18 ring members (**5-14**, see Figure 1) and two macrocyclic diamides each containing two sulfur atoms in the macroring (**15-16**). Some of these macrocyclic polyamides were reduced to form peraza-crowns **17-20**. Two of the polyamides have hydrogen atoms on the amide nitrogens

(**8** and **11**) which make them reactive towards metal ions and thus they could be stronger complexing ligands. The complexation properties of these new macrocycles have not been determined. This paper covers the synthesis and physical properties of these interesting new ligands.

Results and Discussion.

The crab-like cyclization reactions shown in Schemes 1-4 do not need high-dilution techniques. The reactions were carried out generally at reflux temperatures and the yields were all 40-50% or higher for the 12-, 14- and 15-membered cyclic polyamides. The reactions can be carried out by two procedures: 1) mixing both starting materials and the anhydrous sodium carbonate in refluxing acetonitrile (10^{-2} *M* substrates in 250 ml of acetonitrile) for 24 to 48 hours; or 2) slowly and simultaneously adding the two reactants to the refluxing acetonitrile using syringe pumps. This latter process often gave higher yields by about 15% [5]. The dosing of starting materials by syringe pumps has been used extensively for high dilution techniques to prepare cyclic diamides from the reaction of diacid chlorides and diamines giving 50% or higher yields as compared to a few percent when the reaction mixture was not dilute [12,13].

Scheme 1. Preparation of Macrocycles 5-8

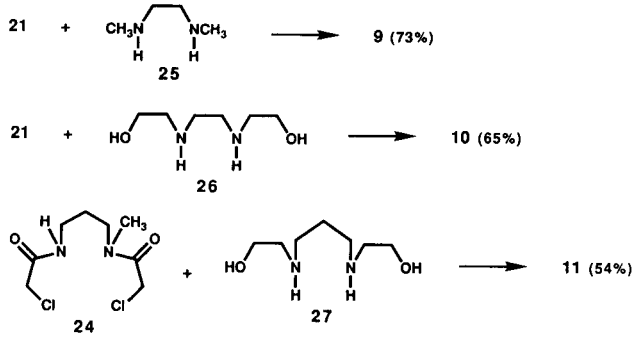


The preparation of 9-membered ring macrocycles is often difficult. The reaction can be a 1:1 cyclization to form the 9-membered ring or a 2:2 cyclization to the 18-membered ring [14-16]. Macrocycle **4** was prepared previously in a good yield with no detectable amount of the 2:2 cyclization product (18 membered ring) by reacting **21** with 2-(2-hydroxyethoxy)ethylamine [6]. Presumably, the oxygen in the side chain and one carboxy oxygen from the bis(α-chloroamide) formed a complex with sodium cation so that only the 1:1 cyclization product formed. Crab-like dichlorides **21** and **22** were reacted with a primary amine in hopes of forming derivatives of 1,4,7-triazacyclononane compounds (Scheme 1). When benzylamine or *N*-acetylethylenediamine was reacted with dichlorides **21** or **22**, both 1:1 and 2:2 cyclizations took place (see Scheme 1). The reaction of crab-like **21** and benzylamine gave mainly 1:1 product **5** with only a little of the 2:2 product which was not isolated but was observed by a gcms analysis. The reaction of crab-like **21** with *N*-acetylethylenediamine **23** gave both **6** (1:1 adduct) and **7** (2:2 adduct) both of which could be isolated in reasonable yields.

The reaction of crab-like **22** with benzylamine was most difficult. Crab-like **22** was not soluble in acetonitrile so that a mixture of acetonitrile and dimethylformamide (DMF) was needed. Even when syringe pumps were used to add the reactants, the isolated yield of **8** was poor. The tlc analyses suggested only one product. Only product **8** was detected by gcms with a yield of 3%. We suspect that the 1:1 cyclization product was also present as an impurity but under mass spectrometry conditions of high vacuum and high temperature, it may have converted to the 2:2 product. Such conversions from smaller to the larger compounds have been observed [17,18]. It is also possible that **8** and its 1:1 cyclization analog were insoluble in acetonitrile as was starting **22** and they separated during the synthesis and were lost with the inorganic salts. Because of the poor yields, the reactions of crab **22** and benzylamine were not studied further.

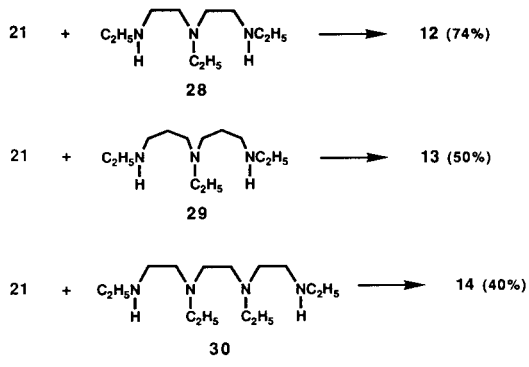
Cyclizations to form the 12- and 14-membered rings (Scheme 2) were much more successful. The yield for **9** was 73% without using high dilution. Even when the syringe pumps were used, the yield of **9** was about the same. Macrocycle **10** was also prepared in a good yield from the reaction of **21** and **26**. In this case, separation of the product was more difficult than for **9** because of some other impurities. Cyclam **11** was likewise isolated in a good yield from the reaction of **24** and **27** in mixed acetonitrile-DMF solvent in the presence of sodium carbonate and using the syringe pumps to add the reactants. DMF was used because diol **27** was not soluble in acetonitrile. Notice that under these reaction conditions with sodium carbonate as the base, crab-like reactants **21** and **24** reacted with the secondary amine groups of **26** and **27** rather than with the non-deprotonated alcohol groups.

Scheme 2. Preparation of Macrocycles 9-11



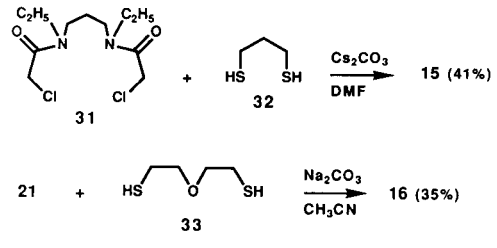
Formation of the 15-, 17- and 18-membered rings (Scheme 3) was carried out in acetonitrile in the presence of sodium carbonate base as above. Compound **12** was formed in a high yield as was reported for other peraza-15-crown-5 compounds [2,3,6]. Compounds **13** and **14** were formed in lower yields and purification was more difficult due to by-product impurities. The starting polyamines **29** and **30** were not purified prior to use which could account for the impurities in the products. The tlc for the products showed two spots very close together but the gcms analyses showed only one sharp peak indicating that each product could have two isomeric forms.

Scheme 3. Preparation of Macrocycles 12-14



Macrocyclic diamides containing two macroring sulfur atoms, **15** and **16** (Scheme 4), were prepared in 41% and 35% yields, respectively. The lower yield for **16** could be a result of the sodium carbonate being not basic enough to deprotonate the dimercaptan in acetonitrile. The reaction probably would give better yields using the more basic cesium carbonate (the cesium effect [19,20]). Our method for the preparation of **15** ad **16** cannot be compared to the method for the preparation of **3** because the yield for **3** was not reported [11]. Our results show that the crab-like intermediates can react with mercaptan groups as well as primary and secondary amines. These thiaaza-crowns could have interesting complexation properties [11].

Scheme 4. Preparation of Macrocycles 15 and 16



The crab-like cyclization reaction is an important improvement for the synthesis of aza-, peraza- and thioaza-crown compounds. The best results are obtained for the preparation of the 14-membered cyclams and 12- and 15-membered aza-, peraza- and thiaaza-crowns. Larger and smaller rings were prepared with difficulty. This method is also important for the formation of aza macrocycles with various functional groups at the end of pendant arms as in the case of macrocycles **6**, **7**, **10** and **11**.

Cyclic polyamides **6**, **11**, **12** and **7** were reduced using borane-THF or borane-dimethyl sulfide to give **17-20**, respectively. This reaction is straight forward but some precautions are necessary. The reduction must be done under argon on cyclic polyamides which are free of impurities. Cyclic polyamides that have been chromatographed are generally pure enough, but care must be taken in removing the solvents after column chromatography. The borane must be fresh and used in excess. The complexed macrocycle-BH_3 was decomposed overnight at room temperature using aqueous 18% hydrochloric acid and then refluxing the mixture for about 15 minutes. An extended reflux period in aqueous hydrochloric acid could decompose some of the product polyaza-crowns [13] which would decrease the yield. The borane-complex could also be decomposed with iodine in the presence of magnesium acetate [13,21]. The decomposed complex solution was made strongly basic and was extracted using chloroform from which hydrochloric acid and phosgene had been removed. There have been many reports of successful reductions of the cyclic diamides [1-6, 22-26]. Reduction of the cyclic diamides using lithium aluminum hydride generally gave poor yields especially for the preparation of **17**.

The purification of the product peraza-crowns also needs to be done carefully. Silica gel chromatography is a problem because the cyclic polyamines have affinity for silica gel and it is difficult to remove them from the column (especially the macrocycles with tertiary amine moieties). Purification is possible on a short silica gel column using a mixed methanol-ammonium hydroxide solution as eluant or by reverse phase chromatography [22].

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer FT 1600 spectrometer. The proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on a Varian Gemini 200 spectrometer using deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. Starting diamines, polyamines and hydroxyamines were purchased when available (Aldrich, Alfa, Phaltz and Bauer Chemical Companies).

Starting bis(α-chloroamides) **21**, **22**, **24** and **31** were prepared as reported [3] to give **21**, mp 134° (recrystallized from ethanol and methanol) (lit value 135° [27]; **22**, mp 174° (recrystallized from ethanol) (lit value 176° [27], 175° [28], 171-172° [29]); **24**, an oil purified on silica gel (toluene/ethanol:5/1); **31**, an oil purified on silica gel (toluene/ethanol; 20/1). Starting **27** [30, 31] was

prepared as follows. 1,3-Dibromopropane (10.5 g, 0.05 mole) in 50 ml of ethanol was slowly added to 60 g (1 mole) of 95% 2-aminoethanol and 20 g of sodium carbonate at reflux temperature. The mixture was stirred under reflux for 16 hours, filtered, evaporated and the excess 2-aminoethanol was removed under reduced pressure. About 100 ml of methylene chloride was added to the residue and the mixture was filtered. The filtrate was evaporated and the residue was distilled at about 150°/0.25 mm. This distillate fraction was chromatographed on silica gel (methanol/ammonia: 30/1 then methanol/ammonia: 7/1) to give 3 g (36%) of **27**; ^{1}H nmr: δ 1.6 (m, 2H), 2.5 (b, 2H), 2.7 (m, 8H), 2.9 (b, 2H), 3.6 (t, 4H). The ^{1}H nmr peaks at 2.5 and 2.9 δ disappeared in deuterium oxide.

General Procedure for the Preparation of Macrocyclic Di- and Tetraamides **5**, **8-10**, **13** and **14** (Schemes 1-3).

A mixture of 0.01 mole each of the appropriate bis(α-chloroamide) (**21** or **22**) amine or diamine (benzylamine, **25**, **26**, **29** or **30**) and 20 g of anhydrous sodium carbonate was stirred in 200-300 ml of refluxing acetonitrile for 12-36 hours. In the formation of **8**, the solvent system was 30% DMF in acetonitrile. In an alternate method for the preparation of **5**, **13** and **14**, the two reactants each in 50 ml of acetonitrile were added to the stirred, refluxing acetonitrile using syringe pumps over a 48 hour period. The reaction mixture was then filtered, the filtrate was evaporated under reduced pressure and the resulting crude cyclic diamide was chromatographed on a short silica gel column using methanol, ethanol or methanol/ammonium hydroxide as eluant. The solvent was evaporated under reduced pressure for a few hours. Often benzene was added to completely remove any water in the product. The residue was checked by ir for traces of solvent and water. The products were all viscous oils. The product yields and spectral properties are as follows:

Compound **5** was obtained in 44% yield; ^{1}H nmr: δ 2.95 (s, 6H), 3.4 (s, 4H), 3.7 (s, 2H), 3.8 (s, 4H), 7.25 (m, 5H); M$^+$/e 275.

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.68. Found: C, 65.26; H, 7.75.

Compound **8** was obtained in 3% yield; ^{1}H nmr: δ 3.2 (d, 8H), 3.4 (d, 8H), 3.7 (s, 4H), 7.3 (s, 10H), 7.75 (b, 4H); M$^+$/e 494.

Anal. Calcd. for $C_{26}H_{34}N_6O_4$: C, 63.14; H, 6.92. Found: C, 63.25; H, 6.77.

Compound **9** was obtained in 73% yield; ^{1}H nmr: δ 2.2 (s, 6H), 2.3 (m, 4H), 2.5 (s, 4H), 2.9 (s, 6H), 3.15 (m, 4H); M$^+$/e 256.

Anal. Calcd. for $C_{12}H_{24}N_4O_2$: C, 56.22; H, 9.43. Found: C, 55.96; H, 9.52.

Compound **10** was obtained in 65% yield; ^{1}H nmr: δ 2.6 (m, 8H), 3.0 (m, 10H), 3.6 (m, 10H); M$^+$/e 316.

Anal. Calcd. for $C_{14}H_{28}N_4O_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 52.93; H, 8.99; N, 17.56.

Compound **13** was obtained in 50% yield; ^{1}H nmr: δ 1.0 (m, 9H), 1.55 (m, 4H), 2.5 (m, 14H), 2.95-3.7 (m, 14H); M$^+$/e 383.

Anal. Calcd. for $C_{20}H_{41}N_5O_2$: C, 62.63; H, 10.77. Found: C, 62.68; H, 10.69.

Compound **14** was obtained in 40% yield; ^{1}H nmr: δ 1.0 (m, 12H), 2.6 (m, 20H), 2.9-3.6 (m, 14H); M$^+$/e 426.

Anal. Calcd. for $C_{22}H_{46}N_6O_2$: C, 61.94; H, 10.87. Found: C, 61.76; H, 10.72.

Preparation of Macrocyclic Dithiadiamide **15**.

Bis(α-chloroamide) **31** (1.4 g, 0.005 mole) and 0.54 g (0.005 mole) of dimercaptan **32** were stirred in 200 ml of DMF in the presence of 10 g of anhydrous cesium carbonate at 60-100°. The mixture was cooled, filtered, evaporated and the residue was chromatographed on silica gel using toluene/ethanol: 20/1 as eluant to give 0.65 g (41%) of **15**, mp 70°; ^{1}H nmr: δ 1.1 (t, 3H), 1.15 (t, 3H), 1.85 (m, 4H), 2.7 (t, 2H), 3.0 (t, 2H), 3.3 (s, 2H), 3.4 (m, 10 H); M$^+$/e 318.

Anal. Calcd. for $C_{14}H_{26}N_2S_2O_2$: C, 52.80; H, 8.23. Found: C, 52.88; H, 7.91.

Preparation of Macrocyclic Dithiadiamide **16**.

Dimercaptan **33** (0.7 g, 0.005 mole) was stirred in 200 ml of acetonitrile in the presence of 15 g of anhydrous sodium carbonate at reflux temperature for a few minutes. After cooling, 1.2 g (0.005 mole) of bis(α-chloroamide) **21** was added and the mixture was stirred under reflux for 24 hours. The mixture was cooled, filtered, evaporated and the residue was purified on silica gel (isopropyl alcohol, ethanol) to give 0.55 g (35%) of **16**, mp 107-108°; ^{1}H nmr: δ 2.7 (m, 2H), 2.8 (m, 2H), 2.95 (m, 6H), 3.75 (m, 12H); M$^+$/e 306.

Anal. Calcd. for $C_{12}H_{22}N_2S_2O_3$: C, 47.03; H, 7.23. Found: C, 47.15; H, 7.13.

General Procedure for the Preparation of Cyclic Polyamides **6**, **7**, **11** and **12** and Their Reduction to Form **17-20**.

A mixture of 0.01 mole each of the appropriate bis(α-chloramide) (**21** or **24**), polyamine **23**, **27** or **28** and 20 g of anhydrous sodium carbonate was stirred in 200-300 ml of refluxing acetonitrile for 24-36 hours. In the formation of **11**, the solvent system was 20% DMF in acetonitrile. The reaction mixture was then filtered, the filtrate was evaporated under reduced pressure and the resulting crude cyclic di- or tetramide was chromatographed on a short silica gel column using methanol, ethanol or methanol/ammonium hydroxide as eluent. The solvent was completely evaporated under reduced pressure for a few hours to give 46% of **6**, 25% of **7**, 40% of **11** or 45% of **12**. These crude materials were not analyzed but were reduced by adding 0.01 mole of **7**, **11** or **12** to 100-120 ml of 1 *M* diborane in THF at room temperature. Lactam **6** was added to a diborane-dimethyl sulfide complex. The resulting mixtures were refluxed for 12-36 hours. After cooling, 10-20 ml of water was carefully dripped into the solution to decompose the excess diborane. The solvent was evaporated under reduced pressure to dryness and 80-100 ml of 18% aqueous hydrochloric acid was added. The mixture was stirred overnight at room temperature and then at 80-100° for 15 minutes. In the case of the borane-methyl sulfide complex, the aqueous hydrochloric acid solution was refluxed for 3 hours. The mixture was then evaporated under reduced pressure and 30 ml of water was added to the residue. This mixture was filtered and ammonium hydroxide was added to the filtrate to make the solution basic (*p*H about 12). The solution was extracted several times with 100 ml portions of purified chloroform (contains no hydrochloric acid or phosgene). The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give **17-20**. The crude product was chromatographed on 200-400 mesh silica gel on a short (3-5 cm) column using methanol/ammonium hydroxide as eluant. After evaporation of the solvents, the purified product was dissolved in toluene, filtered to remove any silica gel from the product and evaporated. The products were all viscous oils. Products yields and spectral properties are as follows:

Compound **17** was obtained in 30% yield; ^{1}H nmr: δ 1.25 (t, 3H), 2.35 (s, 6H), 2.6 (m, 18H), 3.5 (b, 1H); M$^+$/e 228.

Anal. Calcd. for $C_{12}H_{28}N_4$: C, 63.11; H, 12.35. Found: C, 63.03; H, 12.44.

Compound **18** was obtained in 54% yield; ^{1}H nmr: δ 1.65 (m, 4H), 2.5 (m, 24H), 3.6 (m, 4H), 5.0 (b, 2H); M$^+$/e 302.

Anal. Calcd. for $C_{15}H_{34}N_4O_2$: C, 59.57; H, 11.32. Found: C, 59.69; H, 11.49.

Compound **19** was obtained in 76% yield; ^{1}H nmr: δ 1.0 (t, 9H), 2.2 (s, 6H), 2.55 (m, 26H); M$^+$/e 327.

Anal. Calcd. for $C_{18}H_{41}N_5$: C, 66.00; H, 12.62. Found: C, 65.83; H, 12.67.

Compound **20** was obtained in 23% yield; ^{1}H nmr: δ 1.1 (t, 6H), 1.4 (b, 2H), 2.25 (s, 12H), 3.5 (m, 36H); M$^+$/e 456.

Anal. Calcd. for $C_{24}H_{56}N_8 \cdot {}^3/_4H_2O$: C, 61.29; H, 12.32. Found: C, 61.49; H, 11.91.

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