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Note

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A General Method for High-Pressure Promoted Postfunctionalization of Unclosed Cryptands – Potential Phase-Transfer Catalysts

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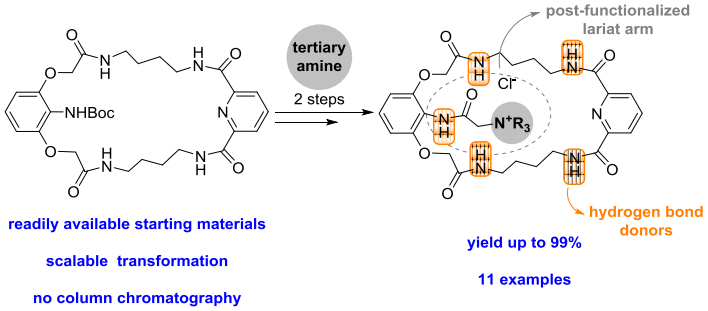
Supporting Information Placeholder



ABSTRACT: We report a high-pressure approach to facile late-stage functionalization of unclosed cryptands (UCs) (11 examples, yield up to 99%). Direct comparison of classic and high-pressure conditions of the quaternization reaction in sterically crowded intraannular position is investigated, and differences in the reactivity of tertiary amine substrates are discussed. Finally, we demonstrated the application of UCs as catalysts for synthetically important alkylation reactions under phase-transfer conditions.

Among many efficient and versatile onium catalysts developed so far, neutral macrocyclic compounds with an accurate define pocket, represent promising phase-transfer catalysts.[1] Although utilization of this type of compounds in phase-transfer catalysis (PTC) was introduce by Cram in 1981.[2] The majority of work in this field, however, has pertained exclusively to coronands,[3] calixarenes,[4] and cyclic peptoids,[5] which are hosts for cations. Recently cation-dependent macrocyclic ion-pair receptor was applied to catalyze Ritter reaction.[6] Therefore, the design of novel macrocyclic architectures showing affinity for anions could hold still undiscovered potential in PTC, since most reactions involve organic anions generated *in situ* (Figure 1).[7]

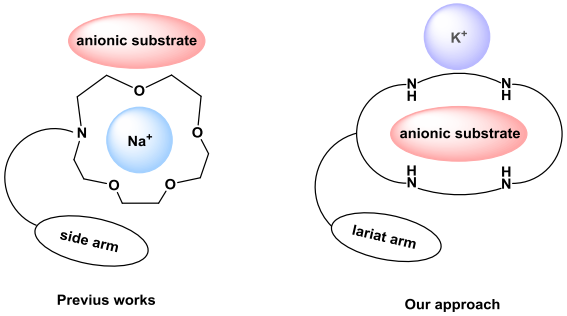


Figure 1. Schematic presentation of methodologies used

Within the last few years we have extensively studied tailor-made macrocyclic anion hosts, which we have called unclosed cryptands (UCs).[8] Such system's ability to form stable complexes with carboxylates and phosphates turned our attention to applying this type of macrocyclic hosts as supramolecular catalysts. The well-defined location of the amide groups that are incorporated in the macrocyclic scaffold of UCs and a flexible intraannular substituent (lariat arm) permits for unprecedented interaction with anionic substrates *via* hydrogen bonds formation. Similar strategy of introducing the proton donating groups cooperating with the phase-transfer catalysts, achieved wide applications over the past few years.[9] Recently, we have presented a class of bifunctional catalysts, based on *Cinchona* alkaloids and decorated with amide function in enantioselective alkylation of glycine derivative.[10] These outcomes open up an opportunity for macrocyclic amide type phase-transfer catalysts to become a valuable alternative to classic onium salts, bifunctional catalysts and macrocyclic compounds possessing cation recognition ability.

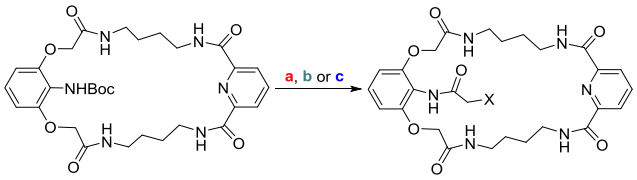
Even though modern organic synthesis strives to prepare increasingly complex compounds, particularly ones based on a macrocyclic scaffold, this is often inefficient due to the entropy unfavorable macrocyclization step.[11] In this context postfunctionalization of the macrocyclic skeleton, after the yield-limiting step, is a beneficial strategy. However, only few synthetic procedures addressing this problem have so far been reported, especially in postfunctionalization of sterically demanding intraannular substituents.[12] Along these lines we have recently developed a general method for the late-stage installation of an intraannular substituent in 20-membered UCs[13] and chiral BINOL-based azacoronands.[14] Some difficulties associated with late-stage functionalization can be solved through the utilization of the high-pressure technique. [15] Notably reac-

tions characterized by a negative activation volume, including quaternization reactions, have been found to accelerate under high-pressure conditions.[16] Consequently, this strategy has proved to be particularly useful for reactions that are inefficient for steric and stereoelectronic reasons. This impact of high pressure was previously utilized by in the synthesis of macrocyclic compounds, and was found that it prevents negative entropy effects and gave access to the products without using unfavorable high-dilution conditions.[17] To date, the remarkable input of the high-pressure technique has also been observed in organocatalysis,[18] as well as in organometallic and transition metal catalysis.[19]

Taking into account above considerations, herein we present a high-pressure approach to the postfunctionalization of 26-membered UCs in sterically demanding intraannular position, which enables the facile synthesis of prospective phase-transfer catalysts. For the best of our knowledge the macrocyclic anionic hosts were not applied before as phase-transfer catalysts.

In previous work, we demonstrated the practical four-step synthesis of 26-membered N-Boc-protected macrocycle **1**,[8a] starting from commercially available and inexpensive materials (Scheme 1). Owing to favorable templatation effects caused by intramolecular hydrogen bonds, which helped to achieve a bended conformation of the linear intermediate, the crucial macrocyclization step was complete already after 8h with relatively high yield (61%). The easily cleavable N-Boc-protecting group allows us to readily install an amide function in the intraannular position of compound **1**. For the above reasons, we became more interested in employing this molecule as a potential phase-transfer catalyst.

Scheme 1. One-pot deprotection and postfunctionalization of the macrocycle **1**



1, 61% ref. 8a

2, 92% (X = Cl), route a and route b
3, 90% (X = Br), route c

route a: i. 4M HCl in dioxane (5 eq.), DCM, 0 ^{0}C - rt, 1.5 h
ii. Et_3N (6.3 eq.), chloroacetyl chloride (1.2 eq.)
route b: i. 4M HCl in dioxane (5 eq.), DCM, 0 ^{0}C - rt, 1.5 h
ii. Et_3N (6.3 eq.), bromoacetyl bromide (1.2 eq.)
route c: i. TFA (5 eq.), DCM, rt, 24 h
ii. Et_3N (6.3 eq.), bromoacetyl bromide (1.2 eq.)

Taking advantage of widely exploited one-pot approach, we carried out deprotection of the amine group under acidic conditions with subsequent addition of corresponding chloroacetyl chloride, leading directly to derivative **2** with near quantitative yields (Scheme 1, route a). Owing to halide substitution, a reaction with bromoacetyl bromide under the same conditions (Scheme 1, route b) resulted in exclusive formation of chloride **2** instead of the expected bromide derivative **3**. To circumvent this issue, we decided to deprotect the N-Boc group using trifluoroacetic acid instead of hydrogen chloride, to avoid the presence of chloride ions in the reaction environment. Under these conditions we ensured access to macrocyclic bromide **3** (Scheme 1, route c).

Having the required precursors **2** and **3** in hand, we attempted to synthesize the UC-based quaternary ammonium salts. For further investigation we selected compound **2**, with better solubility in DMF. Firstly, we employed the thermal methodology and quaternization reactions were performed in refluxing DMF under Argon atmosphere with excess of tertiary amine (Table 1, route a). Selected collection of various tertiary amines **4-14** differentiated in sterically and electronic terms is shown in Figure 2.

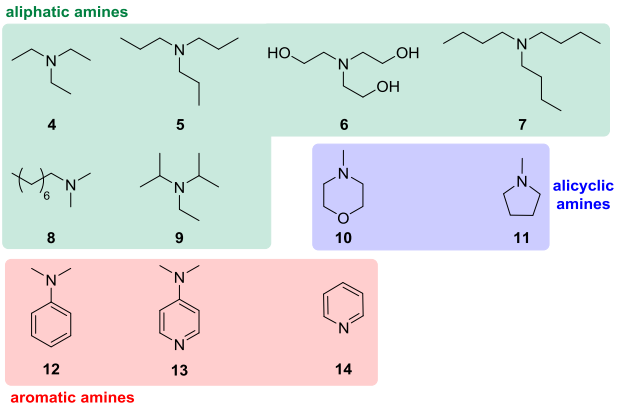
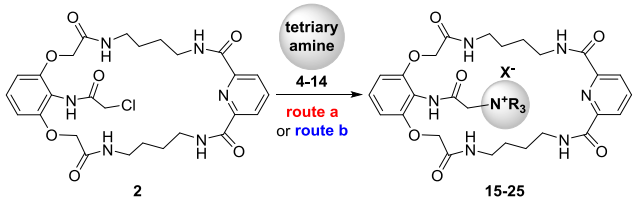


Figure 2. Tertiary amines used as substrates in the synthesis of macrocyclic catalysts **15-25**

Table 1. Influence of high pressure on quaternization reaction yield



route a: 4 eq. of amine **4-14**, DMF, reflux, ambient pressure, 48 h
route b: 1.1 eq. of amine **4-14**, DMF, room temperature, 10 kbar, 48 h

entry	tertiary amine	corresponding product	yield [%] route a	yield [%] route b
1	**4**	**15**	76	85
2	**5**	**16**	28	85
3	**6**	**17**	52	85
4	**7**	**18**	65	85
5	**8**	**19**	65	93
6	**9**	**20**	0	38 (52)*
7	**10**	**21**	76	90
8	**11**	**22**	79	99
9	**12**	**23**	0	30 (69)*
10	**13**	**24**	69	91
11	**14**	**25**	80	90

* after 6 days reaction under 10 kbar at 40 ˚C

The reaction was the most efficient for the relatively less crowded amine **14** (yield 80%), but in most cases products were obtained in moderate yields. However, in the case of amine **9** (sterically demanding) or amine **12** (electronically unfavored) this method completely failed, even after extension of reaction time we observed degradation of precursor **2** instead of the desired product formation (Table 1, entries 6 and 9, respectively). What is more, in all cases traces of unreacted substrate **2** or its decomposition products considerably ham-

pered the purification of the final compounds (see ESI for details). Therefore, this method was too cumbersome and also not scalable, and so cannot be used for synthesis of more advanced structures.

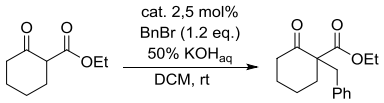
Taking into account that quaternization reaction occurs in the sterically hindered lariat arm of UCs we decided to use the high-pressure technique for substrate activation. To probe the feasibility of this concept for late-stage funtionalization of **2** with tertiary amines **4-14** reactions were carried out under 10 kbar pressure in DMF for 48 h in ambient temperature (Table 1, route b). Consequently, we achieved a significant enhancement of yields (up to 93% for amine **8**). Owing to low reactivity of amine **12** (quaternization reaction yield 30%) as compared with amine **14** (quaternization reaction yield 90%) in case of DMAP (**13**) possessing two reactive sites we observed selective formation of product as a pyridinium salt. Contrary to the thermal approach, we were able to isolate the anticipated macrocyclic products in very high yields, *via* simple precipitation of products, directly after completion of the reaction (Figure 3).

Figure 3. The equipment for conducting high-pressure promoted reactions

The presented path overcomes previous limitations concerning preparation of UC derivatives **20** and **23** (52% and 69%, respectively), unavailable under thermal conditions. However, for these compounds we were constrained to adopt a purification procedure similar to that used in synthesis under thermal conditions, first separating out the unreacted intermediate **2** (see ESI for details).

With macrocyclic compounds **15**–**25** in hand we tested their catalytic properties using alkylation of *β*-ketoester **26** with benzyl bromide as a model reaction under classic PTC conditions (Table 2). Under these conditions, the non-catalyzed benzylation reaction was sluggish and significant formation of side-product was observed (50% yield after 24 h; Table 2, entry 1). Subsequently, we examined commonly used phase-transfer catalysts: ammonium salts and coronands (Table 2, entries 2-6), to compare the efficiency of the UC-based catalysts developed here. In the case of the classic catalysts examined, we noted short reaction time (1-4 h) but side-products were formed and reaction yields were found to be around 80%. Under the same conditions, the UC-based catalysts **15-25** were tested and improvement of reaction efficiency was observed, since desired product **27** was formed in 2-15 h with yield up to 95%. Major steric hindrance in the lariat arm of UC, caused a significant decrease in its catalytic efficiency which was reflected in longer time of reaction catalyzed by **17** and **20**. Similar results were observed for catalysts **23** and **25** with aromatic substituents, however, the only exception was catalyst **24** with DMAP core in the lariat arm. On the other hand, catalysts characterized by relatively low bulkiness and flexible tertiary amine in the structure show improved catalytic activity. Therefore, the best result was noted for catalyst **15,** when the reaction was completed after 2 h with 90% yield (Table 2, entry 7). The higher loading of this catalyst, however, did not cause higher yields, but the reaction time was slightly shorter **(**Table 2, entry 18). We assumed that properly orienting the amide groups in the macroring plays an essential role the in activity of UC-based phase-transfer catalyst. Complexation and preorganization of an anionic substrate result in a more selective reaction course. Nevertheless, the base transport from water to organic solvent is not efficient enough, so the reaction course is slower as compared with classic phase-transfer catalysts. To allow even better catalytic activity we conducted the reaction with 2.5% mol of catalyst **15** in the presence of 2.5% mol of 18-crown-6 (Table 2, entry 20) to provide cooperative catalysis conditions, [20] and we observed product formation with almost quantitative yield after 15 minutes. The interaction of 18-crown-6 with the K^+ promoted transport of the base from the aqueous to organic phase, which further accelerated the course of the reaction, and macrocyclic scaffold of catalyst **15** ensured adequate orientation of substrate and exclusive formation of the desired product **27**. Similar efficient in *β*-ketoesters alkylation reaction was observed by Nguyen and co-workers, however, they used NHO-based phase-transfer catalysts required anhydrous conditions.[21]

Table 2. Screening of various catalysts



26 **27**

entry	catalysts	time [h]	yield [%]
1	no catalyst	24	50
2	TBACl	4	79
3	TBAI	2	83
4	TBABr	1.5	82
5	18-crown-6	1	80
6	cryptofix	2	70
7	**15**	2	90
8	**16**	3	90
9	**17**	15	95
10	**18**	3,5	89
11	**19**	5	93
12	**20**	14	88
13	**21**	4	83
14	**22**	3,5	90
15	**23**	12	85
16	**24**	3	80
17	**25**	12	95
18	**15** (5 mol%)	1.5	92
19	**15** (1 mol%)	4	90
20	**15** + 18-crown-6	0.25	98

Deeper insight into the properties of catalyst **15** was sought from crystallographic structure analysis (Figure 4). Importantly, all amide groups were found to point convergently to the center of the binding pocket, which suggest, together with the absence of intramolecular hydrogen-bonding interactions, that

convergent geometry supports host interaction with a centrally positioned chloride anion. In the structure one can observe two NH···Cl hydrogen bonds, originating from groups located in both the macrocyclic scaffold and the lariat arm. These outcomes reveal the significant contribution of amide groups in special arrangement of the anionic species, but also clarify the effects of substituents located in the lariat arm on catalytic activity.

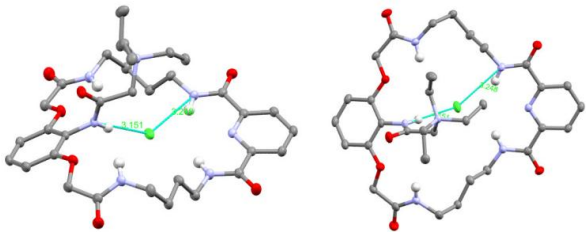


Figure 4. Crystal structure of catalyst **15**, side view (left) and top view (right); nonacidic protons and disorder acetonitrile were omitted for clarity, thermal ellipsoids are drawn at the 50% probability level, for more views see ESI

In conclusion, using the high-pressure approach for post-macrocyclization quaternization, we have successfully designed and synthesized a library of UC-based phase-transfer catalysts. Their catalytic activity was demonstrated in model alkylation reactions under PTC regime and, for the first time, macrocyclic hosts with anion recognition ability have been successfully applied as phase-transfer catalysts. The catalytic activity firmly depends on the substituent on the lariat arm and the interaction of substrate with amide groups incorporated into the catalyst structure. The best result was obtained for a cooperative catalytic system, generated by the addition of 18-crow-6, when alkylation product was obtained with almost quantitative yield after 15 minutes. Further studies in the development of this concept in asymmetric transformation and other types of chemical reactions are in progress and will be reported in due course.

EXPERIMENTAL SECTION

Materials and Methods

All the reagents were used as received. All solvents were obtained from common suppliers and used as received (including anhydrous DCM and DMF). All reactions were performed avoiding moisture by standard procedures and under a argon atmosphere. Flash column chromatography was performed on silica gel (230−400 mesh), thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on Varian 600 at 600 and 125 MHz, respectively, and on Bruker Mercury 400 instrument at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm and are set to solvent residue peak. The splitting pattern of multiplets is described by abbreviations (s – singlet, d – doublet, t – triplet, q – quartet, dd – doublet of doublets, m –multiplet, c – covered signal, b – broad peak). *J* coupling constants values are reported in Hz. Melting points are uncorrected. High resolution mass spectra (HRMS) were recorded using ESI-TOF technique.

High-pressure experiments

All high-pressure experiments were performed in Teflon® ampoules using piston-cylinder-type apparatus U101, which can operate at up to 15 kbars. Scheme and photography of a typical piston-cylinder apparatus and ampoules is presented in Supporting Information Figure S1. A typical experiment under high pressure was run in the following manner: the reaction mixture was placed in a tightly closed Teflon® ampoule, and the ampoules (several at a time) were put in the high-pressure chamber filled with a petroleum ether as a transmission liquid, which is compressed by a mobile piston moved by hydraulic press.

General Procedure A for obtaining macrocyclic precursor 2

To the suspension of macrocyclic compound **1** (3.50 g, 5.71 mmol) in anhydrous DCM (50 mL) at 0 ˚C, ca. 4M HCl in dioxane (7.25 mL, 28.75 mmol, 5 equiv) was added and mixture was then stirred at room temperature for 1.5 h. After this time, the mixture was cooled to 0 ˚C and triethylamine (5.00 mL, 36.00 mmol, 6.3 equiv) was added and after 10 minutes, chloroacetyl chloride (0.55 mL, 6.88 mmol, 1.2 equiv) or bromoacetyl bromide (0.60 mL, 6.88 mmol, 1.2 equiv) was added. The mixture was stirred for a further 15 minutes and solvent was evaporated yielding solid residue. This residue was dissolve in small amount of 5% MeOH in DCM and the same amount of cold acetone was added. After 18 hours in the fridge needles of triethylamine hydrochloride was formed. After filtration of the precipitate, the filtrate was evaporated to give the desire product **2** as a white powder with 92% yield (3.10 g, 5.27 mmol).

General Procedure B for obtaining macrocyclic precursor 3

To the suspension of macrocyclic compound **1** (0.3 g, 0.49 mmol) in anhydrous DCM (10 mL) trifluoroacaetic acid (0.19 mL, 2.45 mmol, 5 equiv) was added and mixture was then stirred at room temperature for 24 h. After this time, the mixture was cooled to 0^{o}C and triethylamine (0.4 mL, 3.1 mmol, 6.3 equiv) was added and after 10 minutes, bromoacetyl bromide (51 µL, 0.59 mmol, 1.2 equiv) was added. The mixture was stirred for a further 15 minutes and solvent was evaporated yielding solid residue which was purified by column chromatography using 5% MeOH in DCM as the eluent. It gives desired product **3** as a white powder with 90% yield (0.28 g, 0.44 mmol).

General Procedure C for obtaining macrocyclic compounds 15-25 under thermal conditions

To the solution of macrocyclic compound **2** (0.1 g, 0.170 mmol) in DMF (4 mL) corresponding tertiary amine (4 eq.) was added and the reaction mixture was stirred at reflux for 24-48 hours under Ar atmosphere. After this time DMF was evaporated, residue was dissolved in small amount of MeOH and 10 mL of cold acetone was added. After filtration of the precipitate, the filtrate was evaporated, and residue was dissolved in 5% MeOH in DCM and dropped into cold diethyl ether. The white precipitate of final product was filtrate and dried under vacuum.

General Procedure D for obtaining macrocyclic compounds 15-25 under high-pressure conditions

To the 5 mL Teflon® ampoule solution of macrocyclic compound **2** (0.1 g, 0.170 mmol) in hot DMF (4 mL) and corresponding tertiary amine (0.187 mmol, 1.1 eq.) was added. The reaction ampoule with reaction mixture was place in high pressure apparatus for next 48 hours. After this time, the mixture was dropped into cold diethyl ether. The white precipitate of final product was filtrate and dried under vacuum.

General Procedure E for obtaining macrocyclic compounds 20 and 23 under high-pressure conditions at 40 ˚C

To the 5 mL Teflon® ampoule solution of macrocyclic compound **2** (0.1 g, 0.170 mmol) in hot DMF (4 mL) and corre-

sponding tertiary amine (0.85 mmol, 5 eq.) was added. The reaction ampoule with reaction mixture was place in high pressure apparatus for next 6 days at 40 ℃. After this time, the mixture was dropped into MTBE. The white precipitate was dissolved in 2 mL of MeOH and dropped into diethyl ether. The white precipitate of final product was filtrate and dried under vacuum.

General Procedure F for catalytic benzylation of ethyl 2-oxocyclohexane carboxylate (26)

To the solution of catalyst (0.0094 mmol) and 2-oxocyclohexane carboxylate **26** (60 μL, 0.375 mmol) in DCM (3 mL) the benzyl bromide (53 μL, 0.45 mmol, 1.2 eq) was added. Then 50% aqueous solution of KOH (150 μL) was added. The heterogeneous mixture was intensively stirred (1500 rpm) at room temperature. The reaction was controlled using TLC. After reaction completion the solvent was evaporated under vacuum and the residue was purified employing column chromatography.

Characterization Data

2-chloro-N-{4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}acetamide ***(2)***. Following Procedure A using chloroacetyl chloride (0.55 mL, 6.88 mmol) the target product was obtained as white powder (3.10 g, 92%). mp 275 ℃ (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.31 (s, 2H), 8.27–7.88 (m, 5H), 7.17 (t, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 2H), 4.51 (s, 4H), 4.14 (s, 2H), 3.64–2.84 (c with H_2O, m, 8H), 1.89–1.25 (m, 8H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.6, 165.8, 163.5, 152.9, 149.4, 139.6, 128.3, 124.5, 114.2, 105.9, 67.5, 42.7, 39.5, 38.6, 27.5, 26.8; Anal (%) Calc. for $C_{37}H_{56}N_7O_7Br \cdot 0.5$ MeOH: C 50.85, H 5.43, N 12.94, Br 12.30, found: C 50.97, H 5.69, N 12.61, Br 12.49; HRMS (m/z) Calc. for $C_{27}H_{33}ClN_6O_7Na^+$ $[M+Na]^+$: 611.1997, found: 611.1988.

2-bromo-N-{4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29- hexaen-31-yl}acetamide ***(3)***. Following Procedure B the target product was obtained as white powder (0.28 g, 90%). mp 283 ℃ (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.35 (s, 2H), 8.33 – 7.88 (m, 5H), 7.18 (s, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 4.50 (s, 4H), 3.94 (s, 2H), 3.58 – 3.01 (c with H_2O,m, 8H), 1.74-1.38 (m, 8H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 167.5, 166.2, 163.5, 152.8, 149.4, 139.7, 128.2, 124.5, 114.1, 105.90, 67.5, 38.6, 28.7, 27.6, 26.8; HRMS (m/z) Calc. for $C_{27}H_{33}BrN_6O_7Na^+$ $[M+Na]^+$: 655.1492, found: 655.1470.

triethyl[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]azanium chloride ***(15)***. Following Procedure C using triethylamine (95 μL, 0.68 mmol) the target product was obtained as white powder (89 mg, 76%); following Procedure D using triethylamine (26 μL, 0.187 mmol) the target product was obtained as white powder (98 mg, 85%). mp 277-280 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 9.48 (s, 2H), 8.35 (d, *J* = 7.8 Hz, 2H), 7.99 (c with DMF, t, *J* = 7.8 Hz, 1H), 7.31 (s, 2H), 7.26 (c with $CHCl_3$, t, *J* = 11.2Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 4.63 (s, 2H), 4.52 (s, 4H), 3.75–3.15 (m, 14H), 2.02–1.53 (c with H_2O, m, 8H), 1.24 (t, *J* = 7.2 Hz, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4 , 163.9 , 162.2, 153.5, 149.4, 138.6, 129.5, 124.78 , 113.4, 106.3, 67.8, 56.7, 54.7, 39.3, 38.2, 27.0, 26.1, 7.9; HRMS (m/z) Calc. for $C_{33}H_{48}N_7O_7^+$ $[M]^+$: 654.3615, found: 654.3630. These data correspond to product obtained according to the Procedure D.

tripropyl[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]azanium chloride ***(16)***. Following Procedure C using tripropylamine (129 μL, 0.68 mmol) the target product was obtained as white powder (35 mg, 28%); following Procedure D using tripropylamine (36 μL, 0.187 mmol) the target product was obtained as white powder (106 mg, 85%). mp 148-150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.36 (s, 2H), 8.31 (d, *J* = 7.8 Hz, 2H), 7.96 (c with DMF t, *J* = 7.8 Hz, 1H), 7.34 (s, 2H), 7.24 (c with $CHCl_3$, t, *J* = 8.8 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 4.68 (s, 2H), 4.51 (s, 4H), 3.87–3.07 (m, 14H), 1.91–1.49 (m, 14H), 0.84 (t, *J* = 7.0 Hz, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 164.0, 162.2, 153.5, 149.4, 138.6, 129.6, 124.9, 113.1, 106.2, 67.7, 62.0, 58.0, 39.2, 38.2, 27.1, 26.1, 15.9, 10.5; HRMS (m/z) Calc. for $C_{36}H_{54}N_7O_7^+$ $[M]^+$: 696.4085, found: 696.4070. These data correspond to product obtained according to the Procedure D.

tris(2-hydroxyethyl)[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18 23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]azanium chloride ***(17)***. Following Procedure C using triethanolamine (90 μL, 0.68 mmol) the target product was obtained as white powder (65 mg, 52%); following Procedure D using triethanolamine (25 μL, 0.187 mmol) the target product was obtained as white powder (107 mg, 85%). mp 160-161 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.33 (t, *J* = 5.9 Hz, 2H), 8.24 – 8.06 (m, 3H), 7.86 (t, *J* = 5.7 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 2H), 5.28 (t, *J* = 4.8 Hz, 2H), 4.50 (s, 4H), 3.93-3.58 (m, 8H), 3.43 – 3.03 (c with H_2O, m, 12H), 1.53 (m, 8H); ^{13}C{^{1}H} NMR (101 MHz, DMF-d_7) δ 167.4, 163.4, 162.3, 153.9, 149.6, 139.2, 128.6, 124.3, 113.9, 105.9, 67.8, 65.3, 63.6, 55.7, 39.1, 38.0, 27.0, 26.5; HRMS (m/z) Calc. for $C_{33}H_{48}N_7O_{10}^+$ $[M]^+$: 702.3463, found: 702.3452. These data correspond to product obtained according to the Procedure D.

tributyl[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]azanium chloride ***(18)***. Following Procedure C using tributylamine (162 μL, 0.68 mmol) the target product was obtained as white powder (86 mg, 65%); following Procedure D using tributylamine (44.5 μL, 0.187 mmol the target product was obtained as white powder (112 mg, 85%). mp 103-105 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 9.48 (s, 2H), 8.35 (d, *J* = 9.2 Hz, 2H), 7.98 (c with DMF, t, *J* = 7.8 Hz, 1H), 7.36 (s, 2H), 7.27 (c with $CHCl_3$, t, *J* = 8.8 Hz 1H), 6.63 (d, *J* = 10.2 Hz, 2H), 4.66 (s, 2H), 4.55 (s, 4H), 3.78–3.08 (m, 12H), 1.96–1.43 (c with H_2O, m, 12H), 1.35–1.10 (m, *J* = 14.4, 7.2 Hz, 6H), 0.90 (t, *J* = 7.3 Hz, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 164.0, 162.2, 153.4, 149.4, 138.5, 129.4, 124.9 106.2, 67.7, 60.2, 39.3, 38.3, 27.2, 26.0, 24.0, 19.5, 13.4. HRMS (m/z) Calc. for $C_{39}H_{60}N_7O_7^+$ $[M]^+$: 738.4554, found: 738.4533. These data correspond to product obtained according to the Procedure D.

dimethyl(octyl)[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]azanium chloride ***(19)***. Following Procedure C using *N*,*N*-dimethyloctylamine (140 μL, 0.68 mmol) the target product was obtained as white

powder (82.5 mg, 65%); following Procedure D using *N*,*N*-dimethyloctylamine (32 μL, 0.187 mmol) the target product was obtained as white powder (118 mg, 93%). mp 251-253 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 9.36 (t, 2H), 8.34 (d, *J* = 7.8 Hz, 2H), 7.98 (c with DMF, t, *J* = 7.7 Hz, 1H), 7.38 (t, 2H), 7.27 (c with $CHCl_3$, t, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 4.79 (s, 2H), 4.51 (s, 4H), 3.48 (qd, *J* = 13.5, 7.3 Hz, 10H), 3.17 (s, 6H), 1.91–1.54 (c with H_2O, m, 10H), 1.38–1.06 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3, 163.9, 161.8, 153.3, 149.4, 138.7, 129.6, 124.9, 113.3, 106.1, 67.7, 66.9, 63.3, 51.8, 39.3, 38.2, 31.5, 28.9, 28.9, 27.0, 26.0, 25.9, 22.8, 22.5, 14.0; HRMS (m/z) Calc. for $C_{37}H_{56}N_7O_7^+$ $[M]^+$: 710.4241, found: 710.4222. These data correspond to product obtained according to the Procedure D.

*ethylbis(propan-2-yl)[({4,11,17,24-tetraoxo-2,26-dioxa-5,10, 18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12 (32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]azanium chloride (**20**).* Following Procedure E using DIPEA (148 μL, 0.85 mmol) the target product was obtained as white powder (63.8 mg, 52%), following Procedure D using DIPEA (30 μL, 0.187 mmol) the target product was obtained as white powder (46.4 mg, 38%). mp 205-207 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 9.46 (s, 2H), 8.33 (d, *J* = 7.6 Hz, 2H), 7.98 (s, 1H), 7.34 (t, 2H), 7.27 (c with $CHCl_3$, 1H), 6.63 (d, *J* = 9.2 Hz, 2H), 4.57 (m, 6H), 4.13 (q, 2H), 3.76 – 3.23 (m, 10H), 2.01 – 1.21 (m, 23H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.60, 164.0, 163.2, 153.5, 149.33, 138.5, 129.4, 124.7, 113.7, 106.2, 67.6, 65.1, 55.4, 54.3, 49.4, 39.3, 38.3, 26.9, 26.1, 19.0, 18.9, 10.4; HRMS (m/z) Calc. for $C_{35}H_{52}N_7O_7^+$ $[M]^+$: 682.3928, found: 682.3912. These data correspond to product obtained according to the Procedure E.

*4-methyl-4-[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15, 27,29-hexaen-31-yl}carbamoyl)methyl]morpholin-4-ium chloride (**21**).* Following Procedure C using *N*-methylmorpholine (75 μL, 0.68 mmol) the target product was obtained as white powder (89 mg, 76%); following Procedure D using *N*-methylmorpholine (21 μL, 0.187 mmol) the target product was obtained as white powder (206 mg, 90%). mp 247 ˚C (decomposition); ^{1}H NMR (500 MHz, CD_2Cl_2:DMSO-d_6 3:1) δ 10.83 (s, 1H), 9.50 (t, *J* = 6.1 Hz, 2H), 8.22 (d, *J* = 1.8 Hz, 1H), 8.20 (s, 1H), 8.16 (dd, *J* = 8.9, 6.3 Hz, 1H), 7.97 (t, *J* = 5.6 Hz, 2H), 7.24 (t, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 4.70 (s, 2H), 4.55 (s, 4H), 3.89–3.64 (m, *J* = 26.4 Hz, 4H), 3.56 – 3.40 (m, 4H), 3.30 (c with multiplet 3.38–3.15, s, 3H) 3.38–3.15 (c with H_2O, m, 8H), 1.72–1.40 (m, 8H); ^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2:DMSO-d_6 3:1) δ 167.0 , 162.8, 148.9, 124.2, 105.6, 67.4, 60.2, 59.6, 39.9, 39.8, 39.6, 39.4, 37.6, 26.7, 26.3; HRMS (m/z) Calc. for $C_{32}H_{44}N_7O_8^+$ $[M]^+$: 654.3251, found: 654.3271. These data correspond to product obtained according to the Procedure D.

*1-methyl-1-[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15, 27,29-hexaen-31-yl}carbamoyl)methyl]pyrrolidin-1-ium chloride (**22**).* Following Procedure C using *N*-methylpyrrolidine (71 μL, 0.68 mmol) the target product was obtained as white powder (90.5 mg, 79%); following Procedure D using *N*-methylpyrrolidine (19 μL, 0.187 mmol) the target product was obtained as white powder (113 mg, 99%). mp 278 ˚C (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 9.40 (t, *J* = 5.6 Hz, 2H), 8.33 (d, *J* = 7.8 Hz, 2H), 7.99 (c with DMF, t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 4.8 Hz, 2H), 7.25 (c with $CHCl_3$, t, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 4.84 (s, 2H), 4.50 (s, 4H), 3.76 – 3.28 (m, 12H), 3.24 (s, 3H), 2.29 – 1.93 (m, 4H), 1.93 – 1.44 (c with H_2O, m, 8H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 163.9, 162.4, 153.3, 149.3, 138.8, 129.5, 124.9, 113.3, 106.2, 67.7, 65.8, 65.7, 63.4, 50.1, 39.3, 38.2, 26.9, 26.1, 21.5, 15.2; HRMS (m/z) Calc. for $C_{32}H_{44}N_7O_7^+$ $[M]^+$: 638.3301, found: 638.3302. These data correspond to product obtained according to the Procedure D.

*N,N-dimethyl-N-[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23, 32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32), 13,15,27,29-hexaen-31-yl}carbamoyl)methyl]anilinium chloride (**23**).* Following Procedure D using *N*,*N*-dimethylaniline (22 μL, 0.187 mmol) the target product was obtained as white powder (36 mg, 30%); following Procedure E *N*,*N*-dimethylaniline (148 μL, 0.85 mmol) the target product was obtained as white powder (82.8 mg, 69%). mp 126-128 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 9.30 (s, 2H), 8.29 (d, *J* = 7.5 Hz, 2H), 7.95 (t, *J* = 7.5 Hz, 1H), 7.72 (d, 2H), 7.55 (s, 2H), 7.44 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 5.36 (s, 2H), 4.41 (s, 4H), 3.70 (s, 6H), 3.60 – 3.25 (c with Et_2O, m, 8H), 1.91 – 1.50 (c with Et_2O, m, 8H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 164.0, 161.5, 153.1, 149.4, 145.6, 138.6, 131.1, 130.8, 129.3, 124.9, 119.6, 113.3, 105.9, 67.6, 65.8, 56.1, 39.4, 38.3, 26.9, 26.0; HRMS (m/z) Calc. for $C_{35}H_{44}N_7O_7^+$ $[M]^+$: 674.3302, found: 674.3321. These data correspond to product obtained according to the Procedure E.

*4-(dimethylamino)-1-[({4,11,17,24-tetraoxo-2,26-dioxa-5,10, 18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12 (32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]pyridin-1-ium chloride (**24**).* Following Procedure C using DMAP (83 mg, 0.68 mmol) the target product was obtained as white powder (83 mg, 69%); following Procedure D using DMAP (22.8 mg, 0.187 mmol) the target product was obtained as white powder (110 mg, 91%). mp 163-165 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.54 (s, 2H), 8.25 (d, *J* = 7.8 Hz, 2H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.42 (s, 2H), 7.20 (t, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 8.4, 2H), 6.53 (d, *J* = 6.8, 2H), 5.49 (s, 2H), 4.46 (s, 4H), 3.71 – 3.33 (m, 8H), 3.20 (s, 6H), 2.11 – 1.43 (m, 8H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 164.6, 164.0, 153.5, 149.4, 142.4, 138.4, 129.1, 124.6, 114.1, 107.2, 106.5, 100.0 , 67.9, 58.5, 40.4, 39.3, 38.1, 27.0, 26.1; HRMS (m/z) Calc. for $C_{34}H_{43}N_8O_7^+$ $[M]^+$: 675.3255, found: 675.3242. These data correspond to product obtained according to the Procedure D.

*1-[({4,11,17,24-tetraoxo-2,26-dioxa-5,10,18,23,32-pentaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12(32),13,15,27,29-hexaen-31-yl}carbamoyl)methyl]pyridin-1-ium chloride (**25**).* Following Procedure C using pyridine (55 μL, 0.68 mmol) the target product was obtained as white powder (91 mg, 80 %); following Procedure D using pyridine (15 μmL, 0.187 mmol) the target product was obtained as white powder (102 mg, 90%). mp 265-268 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 9.52 (s, 2H), 9.04 (s, 2H), 8.42 (s, 1H), 8.26 (d, *J* = 7.1 Hz, 2H), 7.90 (d, *J* = 5.4 Hz, 3H), 7.47 (s, 2H), 7.21 (c with $CHCl_3$, s, 1H), 6.59 (d, *J* = 7.9 Hz, 2H), 6.12 (s, 2H), 4.48 (s, 4H), 3.54 (m, 8H), 1.83 (m, 8H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.2, 163.4, 162.8, 153.1, 148.8, 146.1, 145.7, 139.3, 128.1, 127.4, 124.2, 113.7, 105.8, 67.5, 61.7, 38.8, 37.6, 26.5, 26.3; HRMS (m/z) Calc. for $C_{32}H_{38}N_7O_7^+$ $[M]^+$:632.2833, found: 632.2834. These data correspond to product obtained according to the Procedure D.

*ethyl 1-benzyl-2-oxocyclohexane-1-carboxylate (**27**)*. Following Procedure F, using 2-oxocyclohexane carboxylate **26** (60 µL, 0.375 mmol) and 2.5mol% of **15** and 2.5mol% of 18-crown-6 as a catalysts, compound **27** was obtained as colorless oil (98%, 96 mg). Reported data are identical with literature.[21] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 18.0, 6.7 Hz, 3H), 7.09 (d, *J* = 6.8 Hz, 2H), 4.06 (dd, *J* = 13.4, 6.9 Hz, 2H), 3.28 (d, *J* = 13.7 Hz, 1H), 2.85 (d, *J* = 13.7 Hz, 1H), 2.51 – 2.31 (m, 3H), 1.97 (d, *J* = 6.8 Hz, 1H), 1.76 – 1.51 (m, 3H), 1.43 (dd, *J* = 17.2, 7.5 Hz, 1H), 1.14 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 207.3, 171.0, 136.7, 130.4, 128.0, 126.7, 62.3, 61.3, 41.4, 40.5, 36.0, 27.7, 22.6, 14.1.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Description of high-pressure apparatus, copies of NMR spectra (PDF), and X-ray crystallographic information for **15**·MeCN and **21**·0.13 H_2O (CIF).

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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