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Guanidinium Receptors as Enantioselective Amino Acid Membrane Carriers

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Abstract: A number of artificial carriers for the transport of zwitterionic aromatic amino acids across bulk model membranes (U-tube type) have been prepared and evaluated. 1,2-Dichloroethane and dichloromethane were employed in the organic phase. All compounds are based on a bicyclic chiral guanidinium scaffold that ideally complements the carboxylate function. The guanidinium central moiety was attached to crown ethers or lasalocid A as specific subunits for ammonium recognition as well as to aromatic or hydrophobic residues to evaluate their potential interaction with the side chains of the guest amino acids. The subunits were linked to the guanidinium through ester or amide connectors. Amides were found to be better carriers than esters, though less enantioselective. On the other hand, crown ethers were superior to lasalocid derivatives. As expected, transport rates were dependent on the carrier concentration in the liquid membrane. Reciprocally, enantioselectivities were much higher at lower carrier concentrations. The results show that our previously proposed three-point binding model (*J. Am. Chem. Soc.* **1992**, *114*, 1511−1512), involving the participation of the aromatic or hydrophobic residue to interact with the side chains of the amino acid guest, is unnecessary to explain the high enantioselectivities observed. Molecular dynamics fully support a two-point model involving only the guanidinium and crown ether moieties. These molecules constitute the first examples of chiral selectors for underivatized amino acids acting as carriers under neutral conditions.

Introduction

The design and study of artificial membrane carriers constitutes an active current goal of supramolecular chemistry, since model systems are much simpler than natural ionophores, and they can thus be developed into practical molecular devices. Among the potential applications of facilitated transport technology we could mention separations, such as purification or resolution of racemates,[1] the development of ion-selective electrodes, or the possibility of using carriers for drug delivery.[2]

In sharp contrast to the well-developed coordination chemistry of cations,[3] molecular recognition of neutral or negatively charged molecules has received attention only recently.[4] Much interest in the field has been focused on biorelevant oxoanions, such as nucleic acids or amino acids. The main recognition sites for zwitterionic amino acids under neutral conditions are both the ammonium and the carboxylate functions. In addition, common amino acids provide a rich variety of side chains as other potential fixation sites for chemo- and enantioselective recognition. To achieve chiral discrimination, a simultaneous binding of the positively charged ammonium group and the anionic carboxylate should be performed. In the resulting complex, the side chain should be located in a more favorable orientation in one particular enantiomer. However, the zwitterion is a challenging structure to recognize, because the electronic densities of the carboxylate and the ammonium functions are greatly affected by their mutual vicinity, causing the binding forces of complementary groups of the receptor to be less effective for the complexation.[5] On the other hand, most receptors based on positively and negatively charged binding sites are of little interest because they collapse internally or aggregate into dimers or oligomers. Therefore, the design of model receptors for amino acids has been mainly performed using single charged substrates, under acidic (amino acid or amino ester salts)[6] or basic (carboxylate salts or *N*-protected

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amino acids)[7] conditions. Recognition of the side chain, which is decisive for selectivity, is also a difficult task. For nonfunctionalized side chains, where weak hydrophobic interactions or steric repulsions are the only tools available, strategies must be based on the use of stacking interactions or on the encapsulation of nonpolar side chains inside lipophilic cavities. In the best example so far described, chiral recognition was only moderate.[8]

For dynamic processes, such as extraction or transport, the strongly solvated zwitterion must be taken away from the water solution to a medium of much lower dielectric constant, and this acts often as a formidable and unsurpassable barrier to cross. Again, many efforts have been directed to transport the basic or the acidic forms of the amino acids, instead of the neutral zwitterions, across bulk and supported liquid membranes.[9] Transport of aromatic amino acids (Phe, Trp, Tyr) in a U-tube system was described by Sessler using compounds where sapphyrin has been attached to the acyclic natural polyether lasalocid A.[10] In this case the sapphyrin subunit is responsible for carboxylate binding,[11] whereas the lasalocid subunit recognizes the ammonium group.[12] Another strategy consists of binding the amino acid's primary ammonium group by means of crown ethers and related chelators. However, besides the pioneering work of Cram,[13] only a few examples of carriers for amino acids, based on these subunits, are available.[14]

A remarkable example of an abiotic organic receptor for zwitterionic aromatic amino acids was described one decade ago in our group by means of the bicyclic guanidinium host **1a** (Chart 1).[15] This compound featured (i) non self-complementary binding sites for carboxylate (guanidinium function) and ammonium (crown ether unit), preventing the receptor from internal collapse; (ii) a naphthalene ring for an additional interaction with the side chain of aromatic amino acids; and (iii) a chiral structure for enantioselective recognition. The affinity of **1a** toward amino acids was determined by liquid−liquid single extraction experiments. The extraction efficiencies in the organic phase for Trp, Phe, and Val were ca. 40% for Trp and Phe, but Val, lacking the aromatic side chain, was seldom extracted. Competition experiments with the three amino acids resulted in 100:97:6 Phe/Trp/Val ratios, while chiral recognition was confirmed by ^{1}H NMR. The corresponding D-enantiomers were not observed by HPLC analysis of diastereomeric dipeptides prepared from extracts of racemic samples of Phe or Trp and an optically pure L-Leu derivative.[16] However, an enantiomeric excess of ca. 80% in favor of the L-enantiomers was found when the extracts were directly poured into the HPLC column and a chiral amino acid complex was added as a cosolvent. Molecular dynamics in vacuo showed that guanidinium ion-pairing contributes about one-half of the total enthalpic interaction, whereas the remaining binding energy is provided by the aza-crown ether (one-third) and the naphthalene subunit (one-sixth).[17] Subsequently, Schmidtchen prepared a related host, having a triaza-crown ether attached to the bicyclic guanidinium through a chemically more robust thioether bridge.[18] As the aromatic surface for stacking interaction was not incorporated, this receptor exhibited a weaker enantioselectivity (40% for Phe).

The main objective of the present work is to evaluate compound **1a** and other related guanidinium receptors as enantioselective carriers for aromatic amino acids across liquid membranes (Chart 1). These include amide **1b**, more stable to hydrolysis and presenting two additional potential hydrogen donors for carboxylate binding, as well as derivatives **2a**−**d**, aimed at analyzing the contribution of different subunits to the interaction with the aromatic side chains of Trp or Phe. Thus, silyl ether groups (either with or without aromatic substituents) were incorporated in **2a**, **2b**, and **2d**, whereas **2c** bears a free OH substituent. As before, amide **2b** was prepared to be compared to ester **2a**. Compounds **3** and **4** contain the more rigid benzo-crown ether subunit, whereas in compound **5** the crown ether was linked to the guanidinium through a thioether. Finally, compound **6** was designed, featuring an additional well-oriented hydrogen donor for the carboxylate. A five-atom chain connecting the two hydrogen donors seems adequate to ideally poise the new binding site, and attempts using pyrrole-based chains (with extra hydrogen donors)[19] or pyridine-containing spacers (preorganized by chelation)[20] have been reported. However, the advantages of such a preorganized, chelated structure are not evident.[21] The binding pocket present in **6** contains a thioether whose lone pairs contribute to preorganization without interacting repulsively with the carboxylate guest.[22]

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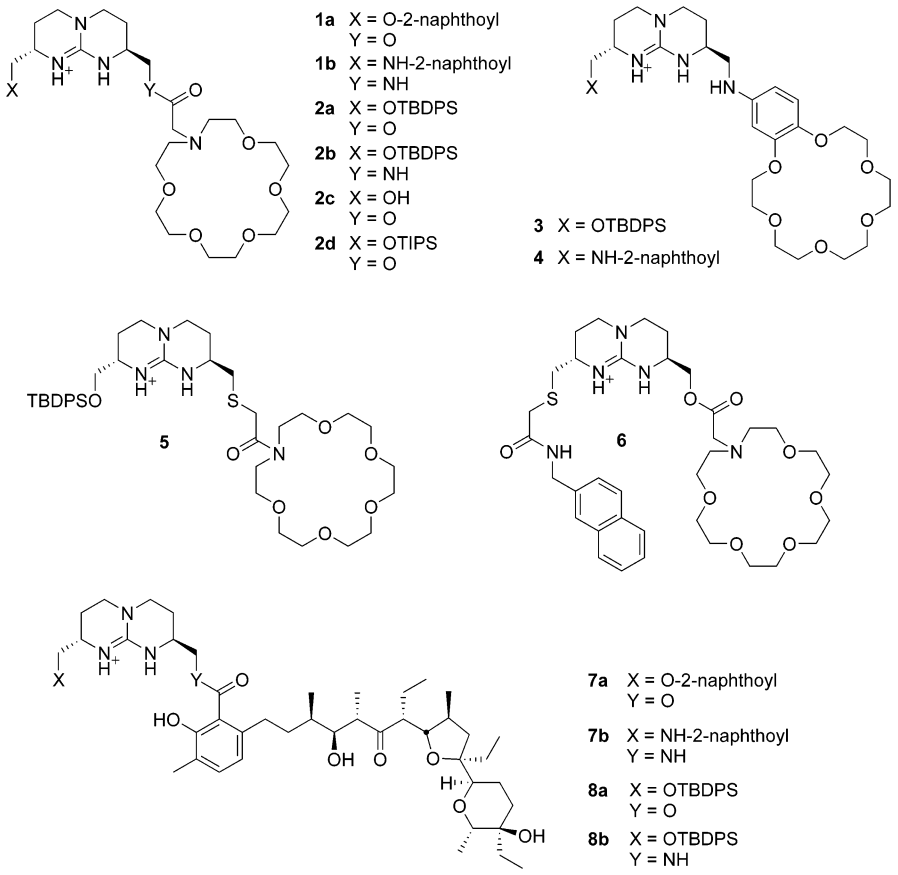
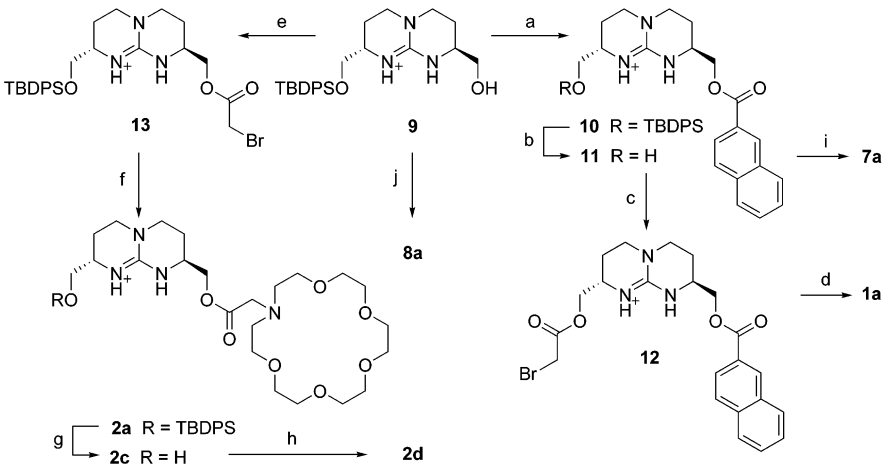
Chart 1. Guanidinium Amino Acid Carriers Synthesized



Scheme 1 [a]



[a] Conditions: (a) 2-naphthoyl chloride, Et_3N, THF (87%); (b) 70% HF/Py, THF (95%); (c) bromoacetic acid, DCC, CH_2Cl_2 (82%); (d) 1-aza-18-crown-6, DMF (58%); (e) bromoacetic acid, DCC, CH_2Cl_2 (70%); (f) 1-aza-18-crown-6, DMF (73%); (g) 70% HF/Py, THF (38%); (h) TIPSOTf, 2,6-lutidine, DMF (45%); (i) lasalocid A, EDCI, HOBt, Py, DMF (38%); (j) lasalocid A, EDCI, HOBt, Py, DMF (20%).

As already pointed out, lasalocid A has been recently used for the recognition of ammonium by synthetic receptors. Thus, carriers **7a**,**b** and **8a**,**b**, endowed with the natural acyclic polyether instead of the macrocyclic crown, were prepared for comparison.

The (*S*,*S*) compounds were usually prepared, although for compounds **1a**,**b** and **2b** the (*R*,*R*) enantiomers were also synthesized (Chart 1). Only the (*R*,*R*) form was prepared for benzo-crown derivatives **3** and **4** and aza-crown **6**.

Results and Discussion

Synthesis. For the synthesis of **1a** some variations with respect to the previously described procedure were introduced.[15] Thus, **11** was obtained in two steps from **9** (Scheme 1).[23] For the synthesis of aza-crown derivatives **2a**−**d** as well as for **8a**, the hydroxymethyl derivative **9** was again employed as the starting material. Esterification with bromoacetic acid in the

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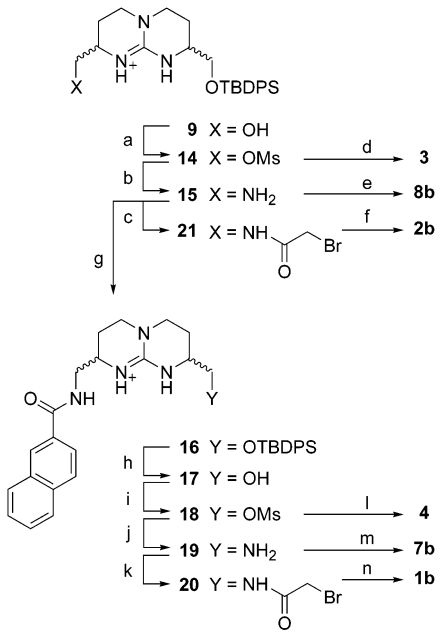
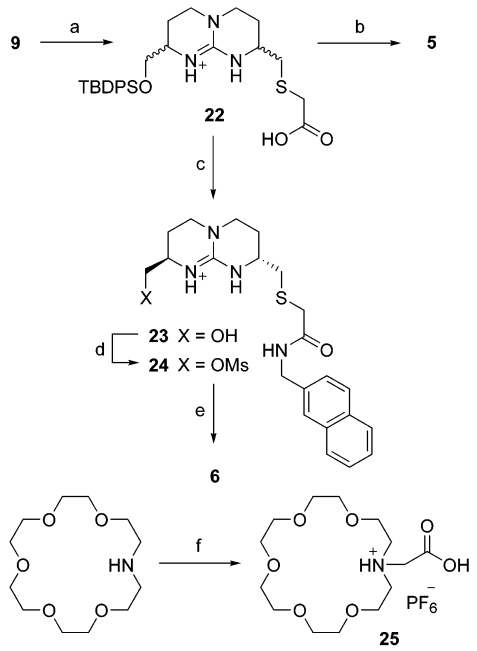
Scheme 2 [a]



[a] Conditions: (a) Ms_2O, Et_3N, THF (98%); (b) aqueous NH_3, MeOH (96%); (c) bromoacetic acid, PyBOP, HOBt, NMM, CH_2Cl_2 (74%); (d) 4-aminobenzo-18-crown-6, NMM, DMF (77%); (e) lasalocid A, PyBOP, HOBt, NMM, DMF (71%); (f) 1-aza-18-crown-6, DMF (73%); (g) 2-naphthoyl chloride, Py, THF (73%); (h) 70% HF/Py, THF (88%); (i) Ms_2O, NMM, THF (71%); (j) aqueous NH_3, MeOH (94%); (k) bromoacetic acid, PyBOP, HOBt, NMM, DMF (60%); (l) 4-aminobenzo-18-crown-6, NMM, DMF (42%); (m) lasalocid A, PyBOP, HOBt, NMM, DMF (81%); (n) 1-aza-18-crown-6, DMF (46%).

Scheme 3 [a]



[a] Conditions: (a) (1) Ms_2O, NMM, THF; (2) sodium thioacetate, *t*-BuOK, MeOH, THF (95%); (b) 1-aza-18-crown-6, BOP, HOBt, NMM, DMF (90%); (c) (1) 2-aminomethylnaphthalene, NMM, BOP, HOBt, DMF; (2) CsF, CH_3CN (84%); (d) Ms_2O, NMM, THF (83%); (e) **25**, Cs_2CO_3, CH_3CN (94%); (f) (1) methyl bromoacetate, Cs_2CO_3, CH_3CN; (2) LiOH, H_2O, THF; (3) HPF_6 (77%).

presence of dicyclohexylcarbodiimide (DCC) resulted in **13** (Scheme 1). For the substitution of **13** an excess aza-crown (acting as both nucleophile and base) was used to give **2a**. Finally, deprotection of **2a** afforded **2c**, from which the triisopropyl silyl ether derivative **2d** was easily obtained (Scheme 1).[24]

The syntheses of compounds **7a** and **8a** were readily performed from the corresponding naphthoyl or hydroxyguanidinium derivatives **11** and **9**, respectively.

The preparation of the amide **1b** started through mesylate **14**, obtained quantitatively from **9** with methanesulfonic anhydride under smooth reaction conditions. Addition of MeOH and 30% aqueous NH_3 to **14** gave amine **15**, which was transformed into alcohol **17** by acylation with 2-naphthoyl chloride and deprotection. Again, transformation of alcohol **17** into amine **19** was easily achieved via the corresponding mesylate **18**. Reaction of **19** with bromoacetic acid to give amide **20** was performed with 1*H*-benzotriazol-1-yloxy tris(pyrrolidino) phosphonium hexafluorophosphate (PyBOP). Finally, compound **1b** was obtained by reaction of **20** with an excess of aza-crown ether (Scheme 2).

Amide **2b** was prepared in two steps from amine **15**. As for **1a**, compound **2b** was synthesized in both enantiomeric forms (*R*,*R* and *S*,*S*). Benzo-crown derivatives **3** and **4** were easily synthesized from mesylates **14** and **18**, respectively, using 4-aminobenzo-18-crown-6. For the amide compounds **7b** and **8b** the synthesis started from amines **19** and **15**, respectively (Scheme 2).

Thioether derivatives **5** and **6** (Scheme 3) were prepared from compound **22**, readily obtained from compound **9**. Compound **5** was prepared via coupling to the aza-crown using BOP, whereas **6** was obtained in several steps: condensation to 2-aminomethylnaphthalene, followed by protecting group removal, gave amide **23**, which was subsequently activated as a mesylate and reacted with aza-crown acid **25** under basic conditions to give **6** (Scheme 3).

Transport Rates. Transport studies were performed in a U-tube cell, consisting of a 1,2-dichloroethane or dichloromethane phase separating two neutral aqueous source and receiving phases. As fluxes obtained from U-tube systems are hard to reproduce due to the many factors influencing transport rates, experiments were performed in all cases at least twice under strict similar conditions. Errors could be estimated as ±5%.

Preliminary studies were performed with L-Trp and the (*S*,*S*) receptors, as these had been found to be the best partners in our previous studies with **1a**. Changes in Trp concentrations at both source and receiving phases were measured spectrophotometrically.

Constant initial concentrations in source and membrane phases were employed in all cases to allow comparison of transport rate constants. Values for **1a**, **1b**, **2b**, **7a**, and **8a** (PF_6 salts) were $k_{1a} = 6.8 \times 10^{-6}$, $k_{1b} = 8.3 \times 10^{-6}$, $k_{2b} = 2.0 \times 10^{-6}$, $k_{7a} = 1.7 \times 10^{-6}$, and $k_{8a} = 0.8 \times 10^{-6}$ m cm^{-2} h^{-1}, respectively. These values were calculated from the slopes of plots of amino acid concentration in the receiving phase versus time at the early stages of the transport process.

(24) To ensure complete deprotonation of tertiary amine in the crown ether subunits, the following general procedure was adopted for all compounds to be tested as carriers in transport experiments: the final product was dissolved in dichloromethane, washed with 0.1 N HPF_6, and then purified by column chromatography, and finally washed with a solution of TRIS buffer at pH 9.1.

Table 1. Enantioselective Transport Results for Guanidinium Carriers

receptor	time (h)	% Trp	% ee	time (h)	% Phe	% ee
	2	1	28	3	3	20
1a	3	2.5	34	4	4.5	24
	6	10	22	5	5.2	24
	2	1	0	2	8	2
1b	3.5	8	0	6	10	0
	20	44	0	21	50	0
	1	0.5	32	2	4	20
2a	2.5	6	26	3	5	18
	4	12	26	6	12	14
	2	1	12	2	1.5	6
2b	4	1.5	12	4	3	8
	9	7.4	10	5	4	6
	2.5	4	0			
2c	4.3	11	0	n.d.	n.d.	n.d.
	6	20	0			
	2.5	2	22			
2d	3.5	4	22	n.d.	n.d.	n.d.
	5	8	16			
	2	6	3			
3	4	12	4	n.d.	n.d.	n.d.
	7	14	2			
	2	6	2			
4	3	10	2	n.d.	n.d.	n.d.
	8	18	0			
	2.5	8	2			
5	4	12	2	n.d.	n.d.	n.d.
	6	15	2			
	2	8	4			
6	4.5	16	6	n.d.	n.d.	n.d.
	6	18	6			
	13	1	14	3	1.5	14
7a	15	2	14	4	2	12
	20	3.5	10	6	4	16
7b	25	13	0	5	1	8
	28	18	0	25	5	3
				4	1.5	8
8a	15	0.5	2	5	3.5	4
	17	1	0	7	5	4
	6	3	20	5	3	8
8b	7	3.5	18	6	4.5	6
	9	5	18	8	6	6

In these preliminary experiments aza-crown ethers were found to be superior to lasalocid derivatives (Table 1, compare **1a** to **7a**), probably due to their better preorganization for the ammonium recognition. All receptors were able to transport tryptophan efficiently, while guanidinium **10**, lacking the ammonium recognition site, was unable to act as a Trp carrier even after 4 days. Diamide **1b** turned out to be the most efficient carrier for Trp under the conditions described in Table 1. Since amide NH's contribute favorably to carboxylate binding, the increased uptake from the source phase could explain its superior carrier ability with respect to diester **1a**.

Enantioselective Amino Acid Transport of Underivatized Amino Acids. The same U-tube liquid membrane employed in the previous section was used for chiral separations, although a few modifications were introduced in the experiments.[25] Thus, saturated solutions of racemic Trp or Phe were used in the source phase, instead of measuring transport rates independently for each enantiomer,[14a−c] to have a more realistic insight into the enantioselective abilities of our carriers. The enantiomeric excesses in the receiving phase were measured by chiral HPLC (UV detection) until ca. 10% of the initial substrate had been transported, since enantioselectivity vanishes as the amount of the least well transported enantiomer continuously increases at the source phase. Thus, the largest enantioselectivities are expected at the early stages of the process. These results are also collected in Table 1.

Ester **1a**, despite being a slower carrier than amide **1b** (see preceding section), showed a higher enantioselectivity. Likely, the simultaneous contribution of the two amide NH's in carboxylate binding forces both guanidinium sidearms to lie almost in the same plane, thus preventing an efficient transmission of the chiral information from the bicyclic framework to the bound substrate. A similar effect was observed for receptors **2a** and **2b**. Differences between diamide **1b** and monoamide **2b** agree with these observations: while the first compound was not selective, a slight enantioselectivity was observed for **2b**, bearing only one amide group. In experiments involving **2b** and Phe, a small amount of the complex **2b**−Phe was detected in the receiving phase, as an additional peak in the chromatogram, along with the two peaks corresponding to amino acid enantiomers. On the other hand, neither pure **2b** nor its complex with Trp was soluble in water and remained in the organic phase.

Ester **2a**, containing a TBDPS group, surprisingly showed an enantioselectivity for Trp similar to that for **1a**, endowed with a naphthoyl aromatic chain. The same trend was observed for phenylalanine. Since TBDPS contains aromatic rings that could participate in the side chain recognition by means of stacking interactions, a control with the nonaromatic triisopropylsilyl protecting group TIPS (**2d**) was performed. Since a similar selectivity was found, it must be concluded that the effect was not caused by aromatic stacking interactions and should arise from hydrophobic or steric effects.

Neither benzo-crown derivatives **3** and **4** nor thioethers **5** and **6** were enantioselective for Trp. Nevertheless, all these compounds turned out to be excellent carriers in terms of transport rates. In particular, compound **6**, endowed with an improved binding pocket for carboxylate, was among the best carriers for Trp but seldom selective (18% Trp transported after 6 h but only 6% enantioselective).

Finally, lasalocid-containing derivatives were slower and poorer enantioselective carriers than the crown ether based compounds. The trend for the superior selectivities but weaker rates of esters was generally followed, with the curious exception of monoamide **8b**, which showed a remarkable selectivity for L-Trp, but not for L-Phe.

For receptor **1a** a more detailed study was performed in order to improve the moderate enantioselectivities observed, which were in sharp contrast to the high values reported earlier for extractions.[15] Most remarkably, when transport experiments were performed reducing the receptor concentration in the membrane phase, the enantiomeric excess of the amino acid in the receiving phase increased considerably, becoming close to the values observed in the former extraction experiments. (Table 2). Also, as a consequence of the lower receptor concentration, the transport was slower.

Typically, the enantioselectivity decreased as more amino acid was transported. This is mainly due to the enrichment of the "wrong" enantiomer in the source phase. In fact, when the source phase was carefully analyzed after >10% of the amino acid was transported, a racemic Trp mixture was observed in the upper part, whereas an aliquot close to the interface revealed

(25) A bigger stirring bar at 1000 rpm and a digital magnetic stirrer were used in the experiments. Temperature (25 °C) and volumes of the three phases were kept constant.

Table 2. Influence of the Concentration of Receptor **1a** on the Transport Results

[**1a**] (mM)	time (h)	% Trp	% ee
0.125	1.5	1.2	79
	2.0	2.2	73
	3.0	4.0	66
	5.0	7.1	62
	6.5	9.8	60
0.25	1.0	1.4	76
	1.5	2.4	69
	2.0	3.7	66
	3.0	6.7	60
	4.5	9.7	56
0.5	0.5	1.2	59
	1.0	4.3	50
	2.0	9.6	41
	3.0	14.1	38
1.0	0.5	1.7	35
	1.0	5.3	28
	2.0	11.8	20
	3.0	16.8	16

Table 3. Influence of Stirring the Source Phase (concentration receptor **1a** = 0.25 mM)

	no stirring		stirring	
time (h)	% Trp	% ee	% Trp	% ee
2.0	3.7	66	4.3	66
3.0	6.7	60	6.2	66
4.0	8.1	57	8.6	65
5.0	10.3	56	12.0	64

Table 4. Naphthoyl vs Alcohol Subunits and the Effect of the Counterion (concentration receptor = 0.125 mM)

receptor	time (h)	% Trp	% ee
2c	1.5	1.2	58
	2.0	2.1	52
	3.0	5.6	48
1a	1.5	1.2	79
	2.0	2.2	73
	3.0	4.0	66
	4.0	5.0	64
	22	30	46
1a (Cl^-)	1.5	0.3	82
	4.0	0.6	77
	22	3.3	73

both a lower concentration of amino acid and an enrichment of the "wrong" enantiomer (65/35). This indicates that a concentration gradient was generated in the source phase during the transport experiment, so only the initial measurements were considered to quote the enantiomeric excess. In fact, the enantiomeric excess could be maintained high during most of the transport experiment by gently stirring mechanically the source phase. Results are summarized in Table 3.

To account for the effect of the substituent in the receptor, **1a** was compared again with **2c**, but at a lower concentration (0.125 mM instead of 1.5 mM). Table 4 shows that transport rates were comparable in both experiments and, most remarkably, that **2c** was indeed moderately enantioselective, despite its lack of the large substituent. Therefore, the substituent in the crowned guanidinium is not essential for chiral recognition.

Finally, when the counterion in the receptor was changed from hexafluorophosphate to chloride, the transport was found to be much slower (Table 4). However, enantioselectivities were somewhat higher after the same transport time. Given the small amount of amino acid transported, no significant improvement can be obtained by counterion exchange.

Table 5. Enantioselectivities in Extraction Experiments

receptor	% ee
1a	75
2a	77
2c	51
2d	79

Single Extraction Experiments. Besides the transport experiments, some single extraction experiments were performed to have a quick insight into the best candidates for chiral recognition. For guanidinium compounds with chloride as counterion, little or no extraction was achieved into the organic phase. The best results never surpassed 25−30%.[15] However, when the anion was hexafluorophosphate, almost 1 equiv could be extracted into the organic phase. To determine the enantioselectivity of a receptor toward a racemic amino acid, HPLC analysis of the evaporated organic phase was performed after the extraction experiment. Retention times of the detected peaks were equal to those of the free amino acid, meaning that in the solvent employed in the analysis (MeOH−H_2O) the complex was destroyed. The enantiomeric excesses depend on the size of the attached substituent (Table 5). For receptor **2c** only a moderate selectivity was observed, whereas for receptors **1a**, **2a**, and **2d** a very good discrimination of both enantiomers of Trp was found. The observed enantiomeric excesses are close to the transport results at low concentration described above.

Structural and Molecular Dynamics Studies on Complexes of 1a with Trp. Both complexes of **1a** with L-Trp and D-Trp showed ill-defined, broad NMR spectra, especially in the case of the least stable D-Trp. No NOE signals could be detected between the naphthalene ring and the indole side chain, although for the complex with L-Trp a few contacts could be attributed to proximity between the side chain and the guanidinium crown ether, accounting for a more compact structure.

In view of the scarce data obtained from the NMR spectra, extensive molecular mechanics and dynamics calculations (1 ns) were performed in a box of chloroform. Suitable fragments were selected from related X-ray structures to build up the initial geometries that were fully optimized by ab initio quantum mechanics (see Experimental Section), and the amino acid was manually docked into the binding pocket by facing each of its zwitterion functionalities (carboxylate and ammonium groups) to the two anchoring groups provided by the receptor (guanidinium and aza-crown, respectively). The naphthoyl moiety was placed perpendicular to the plane delimited by the aza-crown, as no NOE was observed between the aromatic hydrogens and the aza-crown hydrogens. The overall conformation of L-Trp was determined by the information provided by the NMR spectra (NOE). This conformation reduced the number of alternative docking orientations and placed the indole ring oriented toward the ester group linking the aza-crown subunit to the guanidinium.

The hexafluorophosphate anion ended up close to the edge of the bicyclic guanidinium on the opposite side of that facing the indole ring, regardless of its initial location (Figure 1a).

Once the geometry of the complex with L-Trp was further characterized, as described below, the refined structure was used to model the initial complex of the receptor with D-Trp by

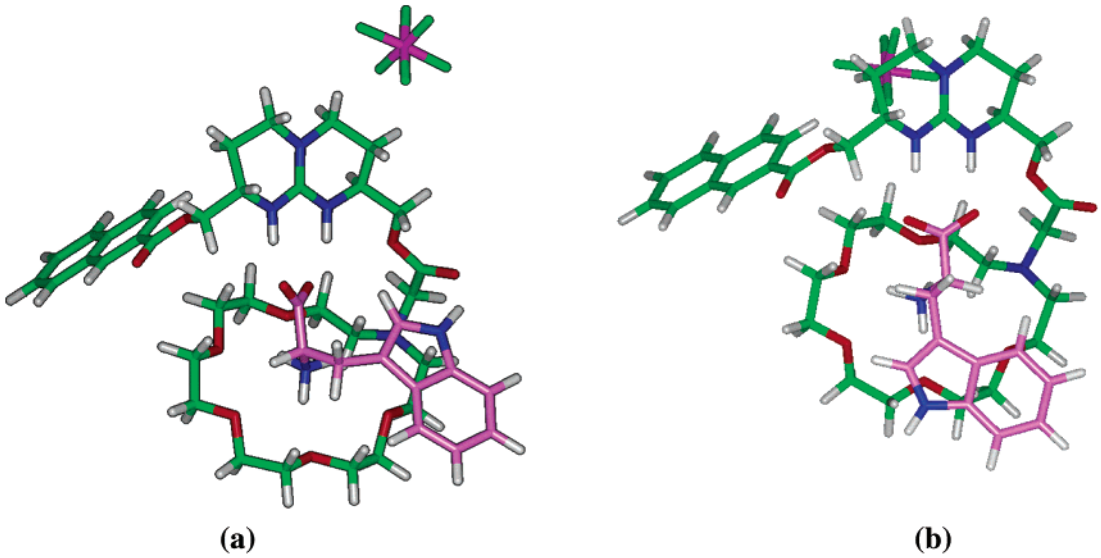


Figure 1. Optimized structures of complexes between **1a** and (a) L-tryptophan, or (b) D-tryptophan.

simply replacing the standard amino acid by its enantiomer. No important deviations from the starting conformations were observed during the unrestrained molecular dynamics simulations of both complexes. The ammonium group of the amino acid is facing the midpoint center of the aza-crown ether and is fixed onto the macrocycle by an alternating pattern of hydrogen bonds involving the ether oxygens but not the ring nitrogen. The plane of the carboxylate group is slightly tilted with respect to the plane of the guanidinium nitrogens, like in related acetate complexes,[26] yet two good hydrogen bonds can be formed and a strong electrostatic interaction can be expected. The arm with the naphthalene ring fluctuated slightly from its original position without losing its orientation relative to the aza-crown. This result agrees with the NMR experiments that show a broad signal for the aromatic hydrogens, suggesting that this arm could be oscillating in solution at room temperature. This finding suggests that this arm is not involved in the recognition of the amino acid, in agreement with findings using **2c**, which also succeeded in the enantioselective recognition of L-amino acids.

Rather surprisingly, in the simulation of the complex between the receptor and D-Trp (Figure 1b), the relative distances and disposition of the two anchored pairs are quite similar to those observed in the complex with L-Trp. This finding suggests that establishing the two complementary pairs with a D-amino acid is indeed feasible, even though the resulting complex must be much less stable as judged from the results of the extraction and transport experiments. In fact, we do find differences in the disposition of the amino acid side chain and also in the calculated intermolecular energy terms. In the complex with L-Trp the indole ring is folded over the aza-crown, thereby excluding some additional polar surface from interactions with the apolar solvent, whereas in the complex with D-Trp the aromatic ring is dangling into the solvent. When representative interaction energies were calculated for each complex during the last 300 ps of the simulations (Figure 2), both the van der Waals and the electrostatic contributions to the binding energy were systematically more favorable and less fluctuating for L-Trp than for D-Trp. These results provide a rationale for the pronounced enantioselectivity of the receptor in favor of L-amino acids and also strengthen the view that hydrophobic interactions are comparatively of much less importance in an apolar solvent than electrostatic interactions are. This principle must be borne

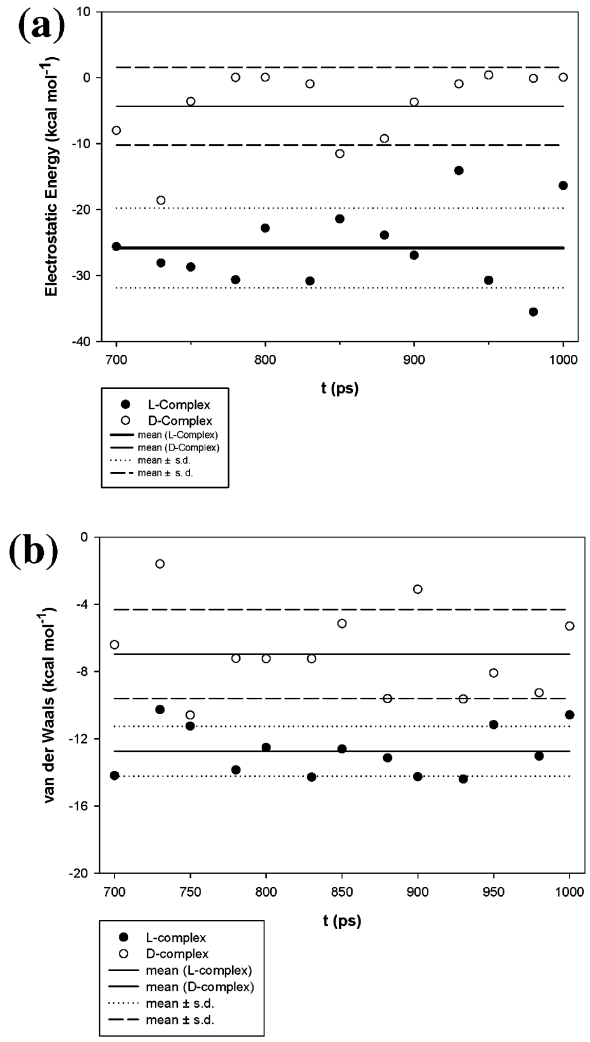


Figure 2. Time course of the (a) electrostatic and (b) van der Waals contributions to the binding energy.

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in mind when designing supramolecular systems for specific recognition of amphipathic ligands. Balancing both types of interactions represents a difficult compromise and a real challenge.

Conclusions

Although modest as compared with the enantiomeric ratios achieved through asymmetric synthesis or molecular recognition, we have shown that enantioselectivity can indeed be achieved with our crown-guanidinium carriers up to ca. 80% ee even in the rather complex process of transporting zwitterionic amino acids across a model membrane.

Overall, receptor **1a** turned out to be our best "chiral selector", followed by ester **2a**. In view of the results, it is likely that binding to the side chain of either Trp or Phe is mostly hydrophobic in origin. The guanidinium−carboxylate ion pair in combination with the crown ether−ammonium complex are the major contributors to achieve enantioselective transport, although the nature of the remaining substituent at the guanidinium moiety is essential to increase transport rates and, to some extent, to optimize the selectivity. Since an ideal chiral selection is to be expected for three interactions of comparable strength, future work will be aimed at designing new receptors with improved contacts (enthalpically or entropically driven) to the lateral chains of the target amino acids.

One advantage of the guanidinium receptors described here is their availability in a multigram scale in both enantiomeric forms from rather cheap starting materials. This opens the way to use "resolving machines" based on W-tubes containing opposite enantiomers at both sidearms to keep enantioselectivities constant along the transport process.[27] Such experiments are currently underway, and the results will be reported in due time.

Experimental Part

General Procedures. Synthesis. All commercially available (Aldrich, Fluka, Acros, NovaBiochem, Panreac) reagents were used without any further purification unless specified. The solvents were dried and distilled following standard procedures. All reactions were performed under argon unless specified. Compounds **1a**, **1b**, and **2b** were synthesized also in the (*R*,*R*) enantiomeric form according to the method described for the (*S*,*S*) enantiomer.

Chromatography. Silica gel (40−60 mm) was employed for column chromatography. HPLC chromatograms were recorded on a Perkin-Elmer Integral 4000 (UV detector) and on a Waters 600 controller (detector UV−vis Waters 2487, software: Millennium). The columns used in HPLC were a reversed-phase LC18 (Scharlau) and a Chirobiotic T chiral column (ASTEC). The solvents used in HPLC analyses were provided by Scharlau and Merck (HPLC gradient grade).

Analysis. Melting points were measured with a Gallenkamp apparatus. The optical rotations $[\alpha]_D^{20}$ were determined on a Perkin-Elmer 241 MC polarimeter using a cell (1 dm) at 20 °C (Na_D 589 nm). ^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz), AC-300 (300 MHz), AMX-300 (300 MHz), and DRX-500 (500 MHz) spectrometers, and the ^{13}C NMR spectra were performed with the same apparatus using magnetic fields at 50, 75, and 125 MHz, respectively. Mass spectra were recorded on VG AutoSpec (FAB) or Reflex-3 (MALDI-TOF) spectrometers. Elemental analyses were performed on a Perkin-Elmer 2400 CHN or a 2400 CHNS apparatus. The UV spectra were recorded on a Hewlett-Packard 8453 UV−vis (Kayak XA) spectrophotometer.

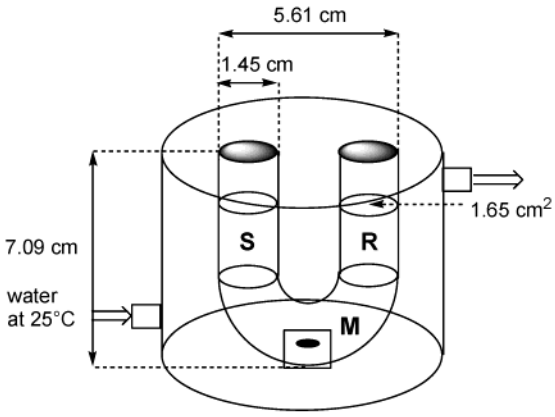

Figure 3. Transport cell.

Transport Experiments. All transport experiments were performed using the U-tube cell represented in Figure 3.

The cell was thermostated by means of a continuous flow of water at 25 °C coming from a circulator that kept the temperature constant in a range of ±0.1 °C. In preliminary experiments the source phase (S) was formed by 3 mL of a saturated solution of the amino acid (50 mM of Trp) at neutral pH; the membrane phase (M) consisted of 10 mL of a receptor solution (1.5 mM) in dichloroethane; and the receiving phase (R) was composed of 3 mL of deionized water. Stirring in these experiments was kept constant at 2600 rpm (measured by a tachometer), using a stave-shaped stirring bar of 3 × 6 mm dimensions. Samples from the receiving phase (0.5 mL) were collected by a 1 mL Hamilton syringe and added back to the solution after UV measurement.

For the enantioselective transport experiments the source phase was 3 mL of a saturated solution of the racemic solution of amino acid (12 mM DL-Trp, 36 mM DL-Phe) in water. The membrane phase (M) consisted of 10 mL of a receptor (PF_6) solution (1.5 mM) in dichloromethane, and the receiving phase (R) was 3 mL of deionized water (Milli Q, 18 MΩ). A different stirring bar was used in this case (oval, 3/8 in. × 3/16 in.), and the stirring speed was kept constant at 1000 rpm (measured directly from the digital magnetic stirrer). Dichloroethane and dichloromethane were synthesis grade. The samples of receptors and amino acids were weighed in a microbalance for <10 mg amounts and in an analytical balance for >10 mg amounts. Samples from the receiving phase (10 or 5 μL) were taken with a Hamilton syringe and directly injected into the chiral HPLC column. Reversed-phase conditions (H_2O−MeOH, 40:60, for Trp or 50:50 for Phe, flow 1 mL/min) were employed, and $\lambda = 280$ or $\lambda = 254$ nm were used for UV monitoring of Trp and Phe.

Single Extraction Procedure. The receptor was dissolved in dichloromethane (1 mg/mL), and an equal volume amount of a saturated aqueous solution (Milli Q, 18 MΩ deionized water) of the appropriate amino acid (DL-Trp, DL-Phe) was added. The mixture was shaken for 3−5 min and left unstirred for at least 5 min to separate the layers. A small amount of the organic layer (e.g., 0.5 mL) was collected by means of a 1 mL Hamilton syringe and filtered over cotton. After evaporating the solvent, a mixture of MeOH−H_2O (1 mL, HPLC grade) was added to clarify the solution. The ratio MeOH−H_2O had no influence on the subsequent HPLC analyses. Receptors samples were weighed in a microbalance. HPLC analysis was performed as for the transport experiments.

Calculations. (a) Model Building of the Complexes. X-ray crystal structures of the chiral bicyclic guanidinium,[28] the aza-crown moieties,[29]

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and the hexafluorophosphate counterion[30] were used as references. The geometries of the fragments were fully optimized with the ab initio quantum mechanical program Gaussian 94[31] at the Hartree−Fock level using the 3-21G(d) basis set. Partial atomic charges were then obtained using the RESP methodology[32] with the 6-31G(d) basis set. The same set of charges was used in the programs AMBER[33] and DelPhi,[34] described below. The receptor structure was assembled from its component fragments as previously reported.[17]

(b) Molecular Mechanics and Dynamics Calculations. The updated (parm99) second-generation[33] AMBER force field[35] was used. Each complex was immersed in a periodic box of ∼200 chloroform molecules that extended up to 10 Å away from any solute atom. Parameters for chloride, carbon, and hydrogen atoms in the solvent molecules were taken from the AMBER 7 database.[36] Periodic boundary conditions were applied, and electrostatic interactions were represented using the smooth particle mesh Ewald method[37] with a grid spacing of 1 Å. A dielectric constant of 1 was used, and the cutoff distance for the nonbonded interactions was 10 Å. Molecular dynamics simulations were carried out at 300 K and 1 atm using the SANDER module in AMBER 6.[35] SHAKE[38] was applied to all bonds involving hydrogens, and the integration time step was 2 fs. A compressibility value of 108.6 $\times$ 10^{-6} bar^{-1} was used for chloroform; under these conditions the experimental density of this solvent (1.47 g cm^{-3}) was well reproduced (1.44 $\pm$ 0.005 g cm^{-3}). The simulation protocol consisted of a series of progressive energy minimizations followed by a 20 ps heating phase and a 250 ps equilibration period during which distance restraints (10 kcal mol^{-1} $Å^{-2}$) were applied to maintain the hydrogen bonds (2.8 $\pm$ 0.1 Å) between the carboxylate of the amino acid and the guanidinium group of the receptor, and also between the ammonium group of the amino acid and the oxygens of the aza-crown, as these electrostatic interactions were thought to be of prime importance for complex stabilization in an aprotic solvent. These restraints were removed thereafter, and system coordinates were then collected every picosecond for 1 ns, which yielded an ensemble of 1000 structures of each complex for further analysis.

(c) Computation of the Electrostatic and van der Waals Contributions to the Binding Energy. The van der Waals contributions to complex stabilization were obtained by using the ANAL module in AMBER and including all atom pairs in the calculation. To estimate the electrostatic contribution to the binding free energy, finite difference solutions to the linearized Poisson equation,[34] as implemented in the DelPhi module of Insight II,[39] were used to calculate electrostatic potentials and energies at zero ionic strength. Cubic grids with a resolution of 0.25 Å were centered on the molecular systems considered, and the charges were distributed onto the grid points.[40] Solvent-accessible surfaces, calculated with a spherical probe of 2.2 Å radius, defined the solute boundaries, and a minimum separation of 8 Å was left between any solute atom and the borders of the box. The potentials at the grid points delimiting the box were calculated analytically by treating each charge atom as a Debye−Hückel sphere. Since the Poisson equation was solved, this amounts to calculating the electrostatic potential generated by the rest of the charges at these points.

Following the classical approach,[41] the overall electrostatic free energy change upon binding (ΔG_{ele}) was calculated from the total electrostatic energy of the system by running three consecutive calculations on the same grid: one for all the atoms in the complex (G^{AR}_{ele}), a second one for the amino acid atoms alone (G^{A}_{ele}), and a third one for the receptor atoms alone (G^{R}_{ele}). Since the grid definition is the same in the three calculations, the artifactual grid energy cancels out and the electrostatic contribution to the binding free energy can be expressed as the difference in energy between the complex and the unbound molecules:

$$\Delta G_{ele} = G^{AR}_{ele} - (G^{A}_{ele} + G^{R}_{ele})$$

The atomic coordinates employed were those obtained from the molecular dynamics trajectories once the explicit solvent molecules were removed. A dielectric of 1 was considered for the interior of the receptor, the amino acids, and the complexes, whereas the surrounding solvent was assigned a dielectric of 4.9, which is the experimental dielectric constant for chloroform.

Synthesis of (2*S*,8*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-(naphthalene-2-carbonyloxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (10). To a solution of guanidinium salt **9** (Cl)[23] (204 mg, 0.431 mmol) and Et_3N (1 mL) in dry THF (8 mL) was added dropwise 2-naphthoyl chloride (174 mg, 0.916 mmol) in dry THF (2 mL), and the reaction was stirred for 24 h at room temperature. After removing the solvent and addition of CH_2Cl_2 the solution was washed subsequently with 1 N HCl, H_2O, saturated $NaHCO_3$, H_2O, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated to give an oil that was purified by column chromatography (2%, 3%, 5% MeOH−CH_2Cl_2), resulting in **10** (Cl) (234 mg, 87%) as a white solid. Mp (Cl): 196−198 °C; $[\alpha]_D^{20}$ (Cl) +49 (*c* 1.0, $CHCl_3$). ^{1}H NMR (Cl) (200 MHz, $CDCl_3$): δ 9.40 (s, 1H, NH), 9.12 (s, 1H, NH), 8.90 (s, 1H, H_1 naph), 8.08 (d, J = 8.7 Hz, 2H, H_3−H_5 naph), 7.81 (d, J = 8.2 Hz, 1H, H_4 naph), 7.78 (d, J = 8.2 Hz, 1H, H_8 naph), 7.58−7.42 (m, 6H, H_6−H_7 naph, PhSi), 7.35 (m, 6H, PhSi), 4.55 (dd, J = 11.2, J = 5.3 Hz, 1H, CH_2OCO), 4.16 (dd, J = 11.2, J = 7.6 Hz, 1H, CH_2OCO), 3.82 (m, 2H, CHα, CH_2OSi), 3.46 (m, 2H, CHα′, CH_2OSi), 3.23 (m, 4H, $CH_2\gamma$), 2.07−1.75 (m, 4H, $CH_2\beta$), 0.99 (s, 9H, *tert*-Bu). ^{13}C NMR (Cl) (50 MHz, $CDCl_3$): δ 166.3 (COOR), 151.1 (C guan) 135.5, 135.2, 132.6, 132.2, 129.9, 128.3, 128.1, 127.8, 127.5, 126.6, 126.2, 125.1 (C, CH arom), 65.5 (CH_2OCO), 65.0 (CH_2O), 49.1, 47.3 (CHα), 44.8, 44.7 ($CH_2\gamma$), 26.7 (CH_3 *tert*-Bu), 22.6 ($CH_2\beta$), 19.1 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 592.2 [$(M - Cl)^+$, 100%]. Anal. Calcd for $C_{36}H_{42}ClN_3O_3Si$: C 68.8, H 6.7, N 6.7. Found: C 68.9, H 6.6, N 6.6.

Synthesis of (2*S*,8*S*)-2-Hydroxymethyl-8-(naphthalene-2-carbonyloxymethyl)-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (11). To compound **10** (Cl) (255 mg, 0.407 mmol) in dry THF

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(10 mL) was added 70% HF−Py (1 mL) at 0 °C, and the mixture was stirred for 4 h at room temperature. Then H_2O (10 mL) and solid Na_2CO_3 were added until neutral pH. The THF was evaporated, and the water solution was washed three times with diethyl ether. The product was extracted from the aqueous solution with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concentrated to afford **11** (Cl) (151 mg, 95%) as a white solid pure enough to be used in the next reaction. The counterion can be exchanged for PF_6,[42] Mp (Cl): 158−160 °C; $[\alpha]_D^{20}$ (Cl) +84 (*c* 1.5, $CHCl_3$). ^{1}H NMR (Cl) (200 MHz, $CDCl_3$): δ 8.88 (s, 1H, H_1 naph), 8.71 (s, 1H, NH), 8.46 (s, 1H, NH), 8.12 (d, J = 8.4 Hz, 2H, H_3−H_4 naph), 7.88 (d, J = 8.5 Hz, 1H, H_5 naph), 7.84 (d, J = 8.3 Hz, 1H, H_8 naph), 7.55 (m, 2H, H_6−H_7 naph), 4.96 (s, 1H, OH), 4.56 (dd, J = 11.2, J = 5.0 Hz, 1H, CH_2OCO), 4.21 (dd, J = 11.2, J = 7.7 Hz, 1H, CH_2OCO), 3.95−3.49 (m, 4H, CHα, CH_2O), 3.31 (m, 4H, $CH_2\gamma$), 2.07−1.91 (m, 4H, CH_2). ^{1}H NMR (PF_6) (300 MHz, $CDCl_3$): δ 8.71 (s, 1H, H_1 naph), 8.08 (m, 4H, H_3−H_4−H_5−H_8 naph), 7.69 (m, 2H, H_6−H_7 naph), 4.64 (dd, J = 12.0, J = 4.0 Hz, 1H, CH_2OCO), 4.44 (dd, J = 12.0, J = 8.0 Hz, 1H, CH_2OCO), 4.12 (s, 1H, OH), 3.99−3.78 (m, 2H, CH_2O), 3.66−3.48 (m, 6H, CHα, $CH_2\gamma$), 2.39−1.83 (m, 4H, CH_2). ^{13}C NMR (Cl) (50 MHz, $CDCl_3$): δ 166.2 (COOR), 151.4 (C guan) 135.7, 132.6, 131.9, 129.8, 128.4, 128.2, 127.5, 126.6, 126.3, 125.3 (C, CH arom), 65.9 (CH_2OCO), 64.1 (CH_2-OH), 50.9, 47.6 (CHα), 45.8, 45.0 ($CH_2\gamma$), 23.0, 22.8 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 354.5 [(M − Cl)$^+$, 100%]. Anal. Calcd for $C_{20}H_{24}ClN_3O_3$: C 61.6, H 6.2, N 10.8. Found: C 61.3, H 6.2, N 10.8.

Synthesis of (2*S*,8*S*)-2-(2-Bromoacetoxymethyl)-8-(naphthalene-2-carbonyloxymethyl)-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (12). A mixture of bromoacetic acid (87 mg, 0.626 mmol) and DCC (130 mg, 0.626 mmol) in CH_2Cl_2 (3 mL) was stirred for 30 min at 0 °C. Then a solution of guanidinium **11** (Cl) (156 mg, 0.313 mmol) in CH_2Cl_2 (3 mL) was added, and the reaction was stirred overnight at room temperature. The mixture was diluted with CH_2Cl_2, washed with 1 N NH_4Cl, dried (Na_2SO_4), filtered, and concentrated to give a solid, which was triturated several times with a mixture of Et_2O−CH_2Cl_2 (10:1). The solid was purified by column chromatography (3% *i*PrOH−CH_2Cl_2), resulting in **12** (Cl) (158 mg, 82%) as a white solid.[42] Mp (Cl): 158−159 °C; $[\alpha]_D^{25}$ (Cl) +44 (*c* 0.5, $CHCl_3$). ^{1}H NMR (Cl) (200 MHz, $CDCl_3$): δ 9.05 (s, 1H, NH), 8.96 (s, 1H, H_1 naph), 8.90 (s, 1H, NH), 8.16 (d, J = 9.0 Hz, 1H, H_3 naph), 8.13 (dd, J = 8.4, J = 1.8 Hz, 1H, H_5 naph), 7.87 (d, J = 8.4 Hz, 1H, H_4 naph), 7.84 (d, J = 9.0 Hz, 1H, H_8 naph), 7.55 (m, 2H, H_6−H_7 naph), 4.60 (dd, J = 11.3, J = 4.8 Hz, 1H, CH_2OCO), 4.49−4.31 (d, J = 15.5 Hz, 2H, CH_2Br), 4.05−4.22 (m, 2H, CH_2O), 3.92 (m, 1H, CHα), 3.83 (m, 1H, CHα), 3.35 (m, 4H, $CH_2\gamma$), 2.07−1.91 (m, 4H, $CH_2\beta$). ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.73 (s, 1H, H_1 naph), 8.08 (m, 4H, H_3−H_5−H_4−H_8 naph), 7.69 (m, 2H, H_6−H_7 naph), 7.42 (s, 1H, NH), 7.26 (s, 1H, NH), 4.62 (dd, J = 11.4, J = 4.0 Hz, 1H, CH_2OCO naph), 4.49−4.18 (m, 3H, CH_2OCO naph, CH_2OCO), 4.11(s, 2H, CH_2Br), 3.93 (m, 1H, CHα), 3.72−3.62 (m, 5H, CHα, $CH_2\gamma$), 2.46−1.81 (m, 4H, $CH_2\beta$). ^{13}C NMR (Cl) (50 MHz, $CDCl_3$): δ 167.4, 166.4 (COOR), 151.4 (C guan), 135.7, 132.6, 132.1, 129.9, 128.4, 128.1, 127.5, 126.6, 126.1, 125.3 (C, CH arom), 66.7, 65.7 (CH_2OCO), 47.6, 47.0 (CHα), 44.9 ($CH_2\gamma$), 41.4 (CH_2Br), 22.8 ($CH_2\beta$). FAB/LSIMS *m*/*z* 474.1 [(M − Cl)$^+$, 100%].

Synthesis of (2*S*,8*S*)-8-(Naphthalene-2-carbonyloxymethyl)-2-(2−1,4,7,10,13-pentaoxa-16-azacyclooctadec-16-yl-acetoxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (1a). A solution of guanidinium **12** (Cl) (58 mg, 0.039 mmol) and 1-aza-18-crown-6 (61 mg, 0.232 mmol) in DMF (10 mL) was stirred at 100 °C during 12 h. After evaporation of the solvent, the resulting solid was purified by washing with CH_2Cl_2−diethyl ether (1:4), resulting in **1a** (Cl), which was dissolved in CH_2Cl_2 and washed with 0.01 N HPF_6 and TRIS buffer solution (pH 9), filtered over cotton, and concentrated to give **1a** (PF_6) (40 mg, 58%). Mp (Cl): 59−61 °C; $[\alpha]_D^{25}$ (Cl) +50 (*c* 0.8, $CHCl_3$). ^{1}H NMR (Cl) (300 MHz, $CDCl_3$): δ 8.72 (s, 1H, H_1 naph), 8.41 (s, 1H, NH), 8.23 (s, 1H, NH), 8.04 (m, 2H, H_3−H_5 naph), 7.84 (m, 2H, H_4−H_8 naph), 7.52 (m, 2H, H_6−H_7 naph), 4.51 (dd, J = 11.0, J = 5.0 Hz, 1H, CH_2OCO), 4.26 (m, 2H, CH_2OCO), 4.12 (m, 1H, CH_2OCO), 3.94−3.38 (m, 28H, CHα, CH_2O crown, CHγ, CH_2N), 3.01 (m, 2H, CH_2N), 2.15−1.88 (m, 4H, $CH_2\beta$). ^{13}C NMR (Cl) (75 MHz, $CDCl_3$): δ 167.4, 166.4 (COOR), 151.4 (C guan), 135.7, 132.6, 132.1, 129.9, 128.4, 128.1, 127.5, 126.6, 126.1, 125.3 (C, CH arom), 70.4, 70.1, 69.9, 69.8 (CH_2O), 66.6, 65.8 (CH_2OCO), 54.5 ($COCH_2N$), 48.9, 47.6, 47.2, 45.2, 44.9 (CH_2N, CHα, $CH_2\gamma$), 22.8, 22.5 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 657.6 [(M − Cl)$^+$, 100%]; 679.6 [(M − HCl + Na)$^+$, 7%]; 715.6 [(M + NaCl)$^+$, 6%]. HRMS calcd for $C_{34}H_{49}N_4O_9$: 657.3500; found 657.3520.

Synthesis of (2*S*,8*S*)-8-(2-Bromoacetoxymethyl)-2-(*tert*-butyldiphenylsilanyloxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (13). A mixture of bromoacetic acid (174 mg, 1.26 mmol) and DCC (260 mg, 1.26 mmol) in CH_2Cl_2 (10 mL) was stirred for 30 min at 0 °C. Then a solution of guanidinium **9** (PF_6) (200 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction was stirred overnight at room temperature. The mixture was diluted with CH_2Cl_2, washed with 0.1 N NH_4PF_6 and H_2O, dried by filtering over cotton, and concentrated to give a white solid that was purified by column chromatography (1% *i*PrOH−CH_2Cl_2), affording compound **13** (PF_6) (201 mg, 70%). ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 7.74−7.72 (m, 4H, PhSi), 7.51−7.48 (m, 6H, PhSi), 7.26 (s, 1H, NH), 7.11 (s, 1H, NH), 4.41 (dd, J = 11.4, J = 4.7 Hz, 1H, CH_2OCO), 4.36 (s, 2H, $COCH_2Br$), 4.26 (dd, J = 11.5, J = 4.7 Hz, 1H, CH_2OCO), 3.94 (m, 1H, CH_2OSi), 3.83 (m, 3H, CH_2OSi, CHα), 3.62−3.56 (m, 4H, $CH_2\gamma$), 2.29−2.20 (m, 2H, $CH_2\beta$), 2.19−2.01 (m, 2H, $CH_2\beta$), 1.09 (s, 9H, *tert*-Bu). ^{13}C NMR (PF_6) (75 MHz, $CDCl_3$): δ 167.5 (CO), 150.7 (C guan), 135.6, 132.5, 130.0, 127.9 (CH, C arom), 66.7 (CH_2OCO), 65.3 (CH_2OSi), 49.9, 47.4, 45.2, 44.9 (CHα, $CH_2\gamma$), 33.8 (CH_2Br), 26.8 (CH_3 *tert*-Bu), 22.6 ($CH_2\beta$), 19.2 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 558.0 [(M − PF_6)$^+$, 34%].

Synthesis of (2*S*,8*S*)-8-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(2−1,4,7,10,13-pentaoxa-16-aza-cyclooctadec-16-yl-acetoxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (2a). A solution of guanidinium **13** (PF_6) (199 mg, 0.283 mmol) and 1-aza-18-crown-6 (200 mg, 0.760 mmol) in DMF (8 mL) was stirred overnight at 100 °C. After removing the solvent, the crude was treated several times with a mixture of diethyl ether−CH_2Cl_2 (4:1). The resulting solid was dissolved in CH_2Cl_2 and washed with 0.1 N HPF_6. After filtering over cotton, the compound was obtained as dication **2a** ($2PF_6$) (184 mg, 73%). Before being used in transport experiments it was washed with a solution of TRIS buffer (pH 9.1). Mp ($2PF_6$): 76−78 °C; $[\alpha]_D^{20}$ ($2PF_6$) +82 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($2PF_6$) (300 MHz, $CDCl_3$): δ 7.65−7.61 (m, 4H, PhSi), 7.43−7.40 (m, 6H, PhSi), 6.19 (s, 1H, NH guan), 6.07 (s, 1H, NH guan), 4.30 (dd, J = 11.5, J = 3.5 Hz, 1H, CH_2OCO), 4.14 (dd, J = 11.5, J = 7.6 Hz, 1H CH_2OCO), 3.75−3.28 (m, 30H, CH_2OSi, CH_2O crown, CHα, $CH_2\gamma$, $COCH_2N$), 2.71 (m, 4H, CH_2N), 2.17−1.71 (m, 4H, $CH_2\beta$), 1.06 (s, 9H, *tert*-Bu). ^{13}C NMR ($2PF_6$) (75 MHz, $CDCl_3$): δ 174.6 (CO), 150.5 (C guan), 135.6, 132.5, 130.0, 127.9 (CH, C arom), 69.0, 68.5, 68.2, 66.9 (CH_2O), 65.3 (CH_2-OSi), 56.4 (CH_2N) 54.6 ($COCH_2N$), 50.1, 47.8, 45.6, 45.1 (CHα, $CH_2\gamma$), 26.8 (CH_3 *tert*-Bu), 22.6, 22.4 ($CH_2\beta$), 19.1 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 909.4 [(M + $NaPF_6$)$^+$, 88%], 763.4 [(M − HPF_6 + Na)$^+$, 54%], 741.4 [(M − PF_6)$^+$, 69%]. HRMS calcd for $C_{39}H_{60}N_4NaO_8Si$: 763.4078 (M − HPF_6 + Na)$^+$; found 763.4088.

Synthesis of (2*S*,8*S*)-8-Hydroxymethyl-2-(2−1,4,7,10,13-pentaoxa-16-aza-cyclooctadec-16-yl-acetoxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (2c). To compound **2a** (PF_6) (284 mg 0.32 mmol) in dry THF (10 mL) was added a solution of 70% HF−Py (1.5 mL) at 0 °C. The reaction was stirred at room temperature

(42) Anion exchange was performed as follows: the chloride salt was dissolved in dichloromethane and washed with a solution of 0.1 N NH_4PF_6, filtered over cotton, evaporated, and dried. Reciprocally, a dichloromethane solution of the PF_6 salt can be exchanged to chloride by washing successively with a solution of 2 N KOH and 1 N ammonium chloride, filtering, and drying as above.

for 5 h. The mixture was then neutralized by adding solid Li_2CO_3 and H_2O. After removing the THF, the solution was washed with diethyl ether and the product was extracted from water with CH_2Cl_2. Trituration with diethyl ether−CH_2Cl_2 (4:1) resulted in **2c** (PF_6) (80 mg, 38%) as a white solid. Mp (PF_6): 73 °C; $[\alpha]_D^{20}$ (PF_6) +45 (*c* 0.5, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 7.25 (s, 1H, NH), 7.11 (s, 1H, NH), 4.56 (s, 2H, $COCH_2N$), 4.47 (d, J = 11.5 Hz, 1H, CH_2OCO), 4.32 (d, J = 11.5 Hz, 1H, CH_2OCO), 3.98−3.53 (m, 36H, CH_2OH, CH_2O crown, CHα, $CH_2\gamma$, CH_2N), 2.28−1.85 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, acetone-d_6): δ 166.2 (CO), 151.5 (C guan), 70.8, 70.5, 70.3, 69.9, 67.5 (CH_2O), 64.6, 64.5 (CH_2OH, CH_2COO), 55.2 ($COCH_2N$), 51.4, 51.1, 47.9, 45.9, 45.3 (CHα, $CH_2\gamma$, CH_2N), 23.0, 22.7 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 503.3 [(M − PF_6)$^+$, 100%].

Synthesis of (2*S*,8*S*)-8-(Triisopropylsilanyloxymethyl)-2-(2−1,4,7,-10,13-pentaoxa-16-aza-cyclooctadec-16-yl-acetoxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (2d). To compound **2c** (PF_6) (42 mg, 0.053 mmol) in DMF (1.5 mL) were added TIPSOTf (43 μL, 0.159 mmol) and 2,6-lutidine (37 μL). The reaction was stirred overnight at room temperature. The solvent was removed, and the crude was dissolved in CH_2Cl_2 and washed subsequently with 0.1 N HPF_6 and water. After concentration and purification by column chromatography (3% *i*PrOH−CH_2Cl_2) compound **2d** ($2PF_6$) (19 mg, 45%) was obtained as a colorless oil:[24] $[\alpha]_D^{20}$ (PF_6) +27 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($2PF_6$) (300 MHz, acetone-d_6): δ 7.28 (s, 1H, NH), 6.94 (s, 1H, NH), 4.47 (dd, J = 11.5, J = 7.7 Hz, 1H, CH_2OCO), 4.31 (dd, J = 11.5, J = 10.7 Hz, 1H, CH_2OCO), 3.96−3.59 (m, 28H, CH_2OSi, CH_2O crown, CHα, $CH_2\gamma$), 2.91−2.82 (m, 9H, CH_2N, CHSi), 2.32−2.01 (m, 4H, $CH_2\beta$), 1.08−1.16 (m, 18H, CH_3*i*Pr). ^{13}C NMR ($2PF_6$) (75 MHz, acetone-d_6): δ 172.0 (CO), 151.1 (C guan), 69.0, 68.9, 68.8, 68.7, 66.9, 66.3 (CH_2O), 65.6 (CH_2OSi), 55.4 (CH_2COO), 54.1, 52.1, 50.7, 47.6, 45.3, 44.9 (CHα, $CH_2\gamma$, CH_2N), 22.4, 22.3 ($CH_2\beta$), 17.4, 11.7 (CH, CH_3, *i*Pr). FAB/LSIMS: *m*/*z* 659.4 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{32}H_{63}N_4O_8Si$: 659.4415; found 659.4427.

Synthesis of (2*S*,8*S*)-2-(6-{7-[5-Ethyl-5-(5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl)-3-methyl-tetrahydrofuran-2-yl]-4-hydroxy-3,5-dimethyl-6-oxo-nonyl}-2-hydroxy-3-methylbenzoyloxymethyl)-8-(naphthalene-2-carbonyloxymethyl)-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (7a). Guanidinium salt **11** (Cl) (98 mg, 0.263 mmol) and lasalocid A sodium salt (125 mg, 0.204 mmol) were dissolved in anhydrous DMF (5 mL) and dry pyridine (0.1 mL). Then a solution of EDCI (69 mg, 0.36 mmol) and a catalytic amount of HOBt in anhydrous DMF (2 mL) were added, and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the crude was purified by column chromatography (1%, 2% *i*PrOH−CH_2Cl_2). The resulting product was dissolved in CH_2Cl_2 and washed with H_2O to remove the sodium ion. The organic phase was filtered over cotton and the solvent evaporated to give **7a** (Cl) (105 mg, 38%) as a white solid. To transform the chloride into the hexafluorophosphate, the product was washed with 0.1 N HPF_6 and TRIS buffer solution (pH 9.1). Mp (PF_6): 120−121 °C; $[\alpha]_D^{20}$ (PF_6) +22 (*c* 0.5, $CHCl_3$). ^{1}H NMR (Cl) (500 MHz, $CDCl_3$): δ 11.4 (br s, 1H, OH), 8.78 (s, 1H, H_1 naph), 8.09−8.04 (m, 3H, H_3−H_5 naph, NH guan), 7.90−7.84 (m, 2H, H_8−H_4 naph), 7.55 (m, 3H, H_6−H_7 naph, NH guan), 7.12 (d, J = 7.2 Hz, 1H, H_4 las), 6.63 (d, J = 7.2 Hz, 1H, CH las), 4.76−4.70 (m, 1H, CH_2OCO), 4.52−4.42 (m, 3H, CH_2OCO), 4.05−3.31 (m, 16H, CHα, $CH_2\gamma$, CH, CH_2O las), 3.01−2.77 (m, 1H, CH_2 las), 2.97−2.45 (m, 3H, CH_2 las), 2.20 (s, 3H, CH_3Ph), 2.31−0.76 (m, 40H, $2CH_2\beta$, CH_3 las, CH_2 las). ^{13}C NMR (Cl) (125 MHz, $CDCl_3$): δ 171.5 (CO las), 166.2 (COO naph), 161.0 (COO las), 151.1 (C guan), 143.6, (C las), 135.6 (C naph), 135.4 (CH las), 132.5 (C naph), 131.6 (CH naph), 129.6 (CH naph), 128.4 (CH naph), 128.2 (CH naph), 128.1 (C las), 127.6 (CH naph), 126.6 (CH naph), 126.5 (C naph), 125.2 (CH naph), 124.3 (C las), 121.8 (CH las), 110.7 (C las), 86.9 (C las), 84.6 (CH−O las), 72.8, 70.7 (CH−O las), 70.3 (C−OH las), 65.3, 65.2 (CH_2OCO), 54.5 (CH las), 48.2 (CH, CH_3 las), 47.9, 47.7 (CHα), 45.7, 45.0 ($CH_2\gamma$), 38.3 (CH_2 las), 36.1, 35.3 (CH_2 las), 34.6, 34.5 (CH, CH_3 las), 30.5, 29.7, 29.4, (CH_2 las) 23.0, 22.6 ($CH_2\beta$), 20.2 (CH_2 las), 16.6 (CH_2 las), 15.8, 15.4, 14.1, 13.7, 12.7 (CH, CH_3 las). FAB/LSIMS: *m*/*z* 926.6 [(M − Cl)$^+$, 68%]. HRMS calcd for $C_{54}H_{76}N_3O_{10}$: 926.5531; found 926.5564.

Synthesis of (2*S*,8*S*)-8-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(6-{7-[5-ethyl-5-(5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl)-3-methyltetrahydrofuran-2-yl]-4-hydroxy-3,5-dimethyl-6-oxo-nonyl}-2-hydroxy-3-methylbenzoyloxymethyl)-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (8a). Guanidinium salt **9** (Cl) (106 mg, 0.224 mmol) and lasalocid A sodium salt (97 mg, 0.158 mmol) were dissolved in anhydrous DMF (3 mL) and dry pyridine (0.1 mL). Then a solution of EDCI (59 mg, 0.308 mmol) and a catalytic amount of HOBt in anhydrous DMF (0.5 mL) was added, and the mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the crude was purified by column chromatography (3% *i*PrOH−CH_2Cl_2). The resulting product was dissolved in CH_2Cl_2 and washed with H_2O to remove the sodium salt. The organic phase was filtered over cotton and concentrated to dryness, affording compound **8a** (Cl) (41 mg, 20%) as a white solid. To transform the chloride into the hexafluorophosphate, the product was dissolved in CH_2Cl_2 and washed with 0.1 N HPF_6 and a TRIS buffer solution (pH 9.1). Mp (PF_6): 100−110 °C; $[\alpha]_D^{20}$ (PF_6) +19 (*c* 0.3, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, $CDCl_3$): δ 11.3 (br s, 1H, OH−Ph), 7.63 (m, 4H, PhSi), 7.41 (m, 6H PhSi), 7.29 (s, 1H, NH guan), 7.17 (d, J = 7.6 Hz, 1H, CH las), 6.76 (s, 1H, NH guan), 6.62 (d, J = 7.6 Hz, 1H, CH las), 4.81 (dd, J = 12.0, J = 3.0 Hz, 1H, CH_2OCO), 4.38 (dd, J = 12.0, J = 3.0 Hz, 1H, CH_2OCO), 4.09−2.34 (m, 18H, CH_2OSi, CHα, $CH_2\gamma$, CH, CH_2O las, CH_2 las), 2.20 (s, 3H, CH_3−Ph), 2.23−0.63 (m, 42H, $CH_2\beta$, CH_3 las, CH_2 las, CH_3 *tert*-Bu).^{13}C NMR (Cl) (125 MHz, $CDCl_3$): δ 170.9 (CO las), 161.3 (COO las), 150.8 (C guan), 143.1 (C las), 135.4 (C PhSi), 133.9 (CH las), 132.7, 129.9, 129.8, 127.8 (C, CH PhSi), 124.3 (C las), 121.9 (CH las), 111.8 (C las), 87.2 (C las), 84.7 (CH las), 73.5, 71.5 (CH las), 69.9 (C las), 65.3 (CH_2OSi), 65.0 (CH_2OCO), 54.9 (CH las), 49.5 (CH, CH_3 las), 48.2, 47.3 (CHα), 45.5, 44.0 ($CH_2\gamma$), 38.2 (CH_2 las), 36.0 (CH_2 las), 34.6, 34.3 (CH, CH_3 las), 31.2, 29.6, 29.3 (CH_2 las), 26.8 (CH_3 *tert*-Bu), 23.0, 22.6 ($CH_2\beta$), 20.1 (CH_2 las), 19.2 (C *tert*-Bu), 16.1 (CH_2 las), 15.9, 15.1, 14.0, 13.8, 12.6, 8.8, 6.3 (CH, CH_3 las). FAB/LSIMS: *m*/*z* 1010.8 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{59}H_{88}N_3O_9Si$: 1010.6290; found 1010.6283.

Synthesis of (2*S*,8*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-methanesulfonyloxymethyl-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (14). To a solution of guanidinium salt **9** (PF_6) (1.15 g, 1.98 mmol) and Et_3N (1.5 mL, 10.8 mmol) in dry THF (40 mL) was added a solution of methanesulfonic anhydride (774 mg, 4.31 mmol) in dry THF (10 mL) at 0 °C. The reaction was stirred at this temperature for 1 h. The solvent was removed, and after addition of CH_2Cl_2, the organic phase was washed with 0.1 N NH_4PF_6, filtered over cotton, and concentrated and the crude was purified by column chromatography (2% MeOH−CH_2Cl_2) affording **14** (PF_6) (1.32 g, 98%) as a white solid.[43] Mp (PF_6): 60−62 °C; $[\alpha]_D^{20}$ (PF_6) +43 (*c* 0.5, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, $CDCl_3$): δ 7.63 (m, 4H, PhSi), 7.62 (m, 6H, PhSi), 6.24 (s, 1H, NH), 6.08 (s, 1H, NH), 4.30 (m, 1H, CH_2OMs), 4.17 (m, 1H, CH_2OMs), 3.80 (m, 1H, CHα), 3.65 (m, 2H, CH_2OSi), 3.57 (m, 1H, CHα), 3.33 (m, 4H, $CH_2\gamma$), 3.08 (s, 3H, CH_3SO_3), 2.05−1.89 (m, 4H, $CH_2\beta$), 1.06 (s, 9H, *tert*-Bu). ^{13}C NMR (PF_6) (75 MHz, $CDCl_3$): δ 150.6 (C guan), 135.5, 132.5, 130.0, 128.9 (CH, C arom), 69.5 (CH_2OMs), 66.2 (CH_2OSi), 50.1, 47.7 (CHα), 45.3, 44.9 ($CH_2\gamma$), 37.1 (CH_3SO_3), 26.7 (CH_3, *tert*-Bu), 22.4, 21.9 ($CH_2\beta$), 19.1 (C, *tert*-Bu). FAB/LSIMS *m*/*z* 516.2 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{26}H_{38}N_3O_4SSi$: 516.2352; found 516.2354.

Synthesis of (2*S*,8*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-(aminomethyl)-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (15). The mesylate derivative **14** (PF_6) (301 mg, 0.456 mmol)

(43) Compound **14** could be used directly for amine formation (one-pot), with a similar yield.

was dissolved in a mixture of MeOH (10 mL) and 30% aqueous NH_3 (4 mL). The resulting solution was stirred for 30 min at room temperature. Then the solvent was removed and the crude dissolved in CH_2Cl_2 and washed with 0.1 N NH_4PF_6. After filtration over cotton and evaporation of the solvent, the product was precipitated with CH_3CN, resulting in **15** ($2PF_6$) (308 mg, 96%) as a white solid. Mp: 81 °C; $[\alpha]_D^{25}$ +31 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($2PF_6$) (300 MHz, acetone-d_6): δ 7.73−7.71 (m, 4H, PhSi), 7.51−7.48 (m, 6H, PhSi), 7.18 (s, 1H, NH), 7.13 (s, 1H, NH), 4.13−4.07 (m, 2H, CH_2OSi), 3.84 (m, 2H, CHα), 3.69−3.59 (m, 4H, $CH_2\gamma$), 2.61−2.52 (m, 2H, CH_2NH_2), 2.37−2.15 (m, 4H, $CH_2\beta$), 1.09 (s, 9H, *tert*-Bu). ^{13}C NMR ($2PF_6$) (75 MHz, acetone-d_6): δ 151.3 (C guan), 135.9, 133.3, 130.5, 128.4 (CH, C arom), 66.2 (CH_2OSi), 51.7 (CH_2NH_2), 50.6, 47.6 (CHα), 45.5, 44.6 ($CH_2\gamma$), 26.7 (CH_3 *tert*-Bu), 23.3, 22.6 ($CH_2\beta$), 19.1 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 437.3 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{25}H_{37}N_4OSi$: 437.2736; found 437.2734.

Synthesis of (2*S*,8*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-{[(naphthalene-2-carbonyl)-amino]methyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (16). To a solution of **15** (PF_6) (225 mg, 0.475 mmol) and dry pyridine (0.116 mL) in dry THF (4 mL) was added a solution of 2-naphthoyl chloride (110 mg, 0.577 mmol) in THF (4 mL), and the mixture was stirred at room temperature overnight. After removing the solvent, the crude was dissolved in CH_2Cl_2 and washed with H_2O, 2 N KOH, 1 N NH_4PF_6, and 0.1 N HPF_6. After filtering over cotton, evaporation of the solvent, and purification by column chromatography (3% *i*PrOH−CH_2Cl_2), product **16** (PF_6) (254 mg, 73%) was obtained as a white solid. Mp (PF_6): 78−80 °C; $[\alpha]_D^{20}$ (PF_6) +25 (*c* 0.5, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, acetone d_6): δ 8.32 (s, 1H, H_1 naph), 7.90 (d, J = 7.7 Hz, 1H, H_3 naph), 7.82 (t, J = 6.0 Hz, 1H, NH am), 7.79−7.69 (m, 3H, H_4−H_5−H_8 naph), 7.59−7.56 (m, 4H, PhSi), 7.49−7.32 (m, 8H, PhSi, H_6−H_7 naph), 6.85 (s, 1H, NH guan), 6.41 (s, 1H, NH guan), 3.71−3.44 (m, 6H, CH_2-NHCO, CHα, CH_2OSi), 3.32−3.20 (m, 4H, $CH_2\gamma$), 2.02−1.81 (m, 4H, $CH_2\beta$), 1.00 (s, 9H, *tert*-Bu). ^{13}C NMR (PF_6) (75 MHz, $CDCl_3$): δ 169.1 (CO), 150.6 (C guan) 135.4, 134.8, 132.5, 130.1, 129.4, 128.4, 127.9, 127.4, 126.6, 123.4 (C, CH arom), 65.6 (CH_2O), 50.1, 49.5, 45.6, 45.2, 43.5 (CHα, $CH_2\gamma$, CH_2N), 26.7 (CH_3 *tert*-Bu), 23.6, 22.6 ($CH_2\beta$), 19.1 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 591.3 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{36}H_{43}N_4O_2Si$: 591.3155; found 591.3179.

Synthesis of (2*S*,8*S*)-2-Hydroxymethyl-8-{[(naphthalene-2-carbonyl)amino]methyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (17). To a solution of amide **16** (PF_6) (620 mg, 0.84 mmol) in dry THF (40 mL) was added 70% HF−Py (3 mL) at 0 °C, and the reaction was stirred at room temperature for 4 h. The mixture was neutralized by adding water (10 mL) and solid Na_2CO_3. Then it was washed with diethyl ether and the product was extracted from the aqueous phase with CH_2Cl_2. The organic phase was washed with 2 N KOH and 0.1 N NH_4PF_6, filtered over cotton, and concentrated to afford **17** (PF_6) (368 mg, 88%) as a white solid. Mp (PF_6): 89 °C; $[\alpha]_D^{20}$ (PF_6) +28 (*c* 0.6, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.61 (s, 1H, H_1 naph), 8.52 (s, 1H, NH am), 8.11−8.10 (m, 4H, H_3−H_4−H_5−H_8 naph), 7.80−7.68 (m, 2H, H_6−H_7 naph), 7.62 (s, 1H, NH guan), 7.53 (s, 1H, NH guan), 4.56 (br s, 1H, OH), 3.96−3.63 (m, 10H, CHα, $CH_2\gamma$, CH_2O, CH_2N), 2.32−1.98 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, acetone-d_6): δ 168.8 (CO), 151.8 (C guan) 135.7, 133.4, 132.2, 129.7, 129.0, 128.6, 128.5, 128.4, 127.6, 124.8 (C, CH arom), 64.8 (CH_2OH), 51.6, 50.4 (CHα), 46.3, 46.0 ($CH_2\gamma$), 44.4 (CH_2NH), 24.6, 23.5 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 353.2 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{20}H_{25}N_4O_2$: 353.1977; found 353.1965.

Synthesis of (2*S*,8*S*)-2-Methanesulfonyloxymethyl-8-{[(naphthalene-2-carbonyl)-amino]-methyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidin-1-ium (18). To a solution of **17** (PF_6) (628 mg, 1.22 mmol) and NMM (0.55 mL, 4.88 mmol) in dry THF (25 mL) was added methanesulfonic anhydride (437.8 mg, 2.44 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. After removing the solvent, the crude was dissolved in CH_2Cl_2 and washed with 0.1 N NH_4PF_6, filtered over cotton, concentrated, and purified by column chromatography (4% MeOH−CH_2Cl_2) to afford **18** (PF_6) (489 mg, 71%) as a white solid. ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.39 (s, 1H, H_1 naph), 8.22 (s, 1H, NH am), 7.91−7.84 (m, 4H, H_3−H_4−H_5−H_8 naph), 7. 58−7.49 (m, 2H, H_6−H_7 naph), 7.38 (s, 1H, NH guan), 7.31 (s, 1H, NH guan), 4.36 (dd, J = 15.0, J = 3.5 Hz, 1H, CH_2OMs), 4.18 (dd, J = 15.0, J = 3.5 Hz, 1H, CH_2OMs), 3.80−3.73 (m, 2H, CHα), 3.71−3.46 (m, 6H, $CH_2\gamma$, CH_2N), 3.08 (s, 3H, CH_3), 2.21−1.89 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, acetone-d_6): δ 168.9 (CONH), 151.6 (C guan) 135.6, 133.4, 132.2, 129.7, 128.9, 128.6, 128.5, 128.4, 127.6, 124.7 (C, CH arom), 71.5 (CH_2OMs), 50.6, 48.7 (CHα), 46.1, 45.5 ($CH_2\gamma$), 44.2 (CH_2NH), 37.0 (OCH_3), 24.3, 22.7 ($CH_2\beta$).

Synthesis (2*S*,8*S*)-2-Aminomethyl-8-{[(naphthalene-2-carbonyl)-amino]methyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (19). Compound **18** (PF_6) (428 mg, 0.74 mmol) in MeOH (20 mL) and 30% aqueous NH_3 (10 mL) were stirred at room temperature for 1 h. After removing the solvent, the crude was dissolved in CH_2Cl_2 and washed with 0.1 N NH_4PF_6, filtered over cotton, concentrated, and purified by column chromatography (3% MeOH−CH_2Cl_2) to afford **19** (450 mg, 94%) as a white solid. Mp (PF_6): 80 °C; $[\alpha]_D^{20}$ (PF_6) +31 (*c* 1, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.46 (s, 1H, H_1 naph), 8.32 (s, 1H, NH am), 7.97 (m, 4H, H_3−H_4−H_5−H_8 naph), 7.59 (m, 3H, H_6−H_7 naph, NH guan), 7.24 (s, 1H, NH guan), 3.96−3.37 (m, 10H, CHα, $CH_2\gamma$, CH_2O, CH_2N), 3.13−3.07 (m, 2H, CH_2-NH_2), 2.32−1.87 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, $CDCl_3$): δ 167.8 (CONH), 150.8 (C guan), 136.1, 133.2, 132.6, 128.0, 127.8, 127.5, 127.1, 126.8, 125.8, 125.6 (C, CH arom), 53.2, 52.1, 49.3, 47.9, 45.3 (CHα, $CH_2\gamma$, CH_2NHCO, CH_2NH), 24.2 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 352.2 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{20}H_{26}N_5O$: 352.1977; found 352.1965.

Synthesis of (2*S*,8*S*)-2-Bromoacetylaminomethyl-8-{[(naphthalene-2-carbonyl)amino]methyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (20). To a mixture of compound **19** (PF_6) (106 mg, 0.18 mmol), bromoacetic acid (28 mg, 0.19 mmol), PyBOP (103.5 mg, 0.19 mmol), and HOBt (catalytic) in DMF (4 mL) was added NMM (43 μL, 0.41 mmol), and the reaction was stirred for 2 h at room temperature. The solvent was removed, and the crude was dissolved in CH_2Cl_2, washed with 0.1 N NH_4PF_6 and H_2O, dried by filtering over cotton, concentrated, and purified by column chromatography (6−8% MeOH−CH_2Cl_2) to afford **20** (PF_6) (67 mg, 60%) as a white solid. ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.55 (s, 1H, H_1 naph), 8.39 (s, 1H, NH am), 8.04 (s, 4H, H_3−H_4−H_8−H_5 naph), 7.91 (s, 1H, NH am), 7.65−7.61 (m, 3H, H_6−H_7 naph, NH guan), 7.41 (s, 1H, NH guan), 3.97(s, 2H, CH_2Br), 3.94−3.37 (m, 10H, CHα, $CH_2\gamma$, CH_2O, CH_2N), 3.13−3.07 (m, 2H, CH_2NH) 2.34−1.82 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, $CDCl_3$): δ 173.0 ($CONHCH_2$), 167.8 (CONH naph), 150.7 (C guan), 134.0, 131.9, 130.6, 128.2, 127.6, 126.9, 126.8, 126.1, 124.2, 123.2 (C, CH naph), 52.1, 51.3, 48.9, 48.8 (CH_2NH), 45.0, 44.7 (CHα), 44.5, 44.3 ($CH_2\gamma$), 33.8 (CH_2Br), 23.4, 22.9 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 472.1 [(M − PF_6)$^+$, 100%].

Synthesis of (2*S*,8*S*)-8-{[(Naphthalene-2-carbonyl)amino]methyl}2-[(2−1,4,7,10,13-pentaoxa-16-aza-cyclooctadec-16-yl-acetylamino)-methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (1b). A solution of guanidinium **20** (PF_6) (130 mg, 0.21 mmol) and 1-aza-18-crown-6 (245 mg, 0.93 mmol) in DMF (8 mL) was stirred at 100 °C for 12 h. The solvent was removed, and CH_2Cl_2 was added. The organic phase was washed with 0.1 N HPF_6, dried by filtering over cotton, and concentrated. The product was purified by column chromatography (10% MeOH−CH_2Cl_2), dissolved in CH_2Cl_2, and washed with a TRIS buffer solution (pH 9.1) to obtain compound **1b** (PF_6) (78 mg, 46%) as a white solid. Mp (PF_6): 65−67 °C; $[\alpha]_D^{20}$ (PF_6) +19 (*c* 0.5, $CHCl_3$). ^{1}H NMR (PF_6) (300 MHz, $CDCl_3$): δ 8.43 (s, 1H, H_1 naph), 8.41 (t, J = 6.0 Hz, 1H, NH am), 8.30 (s, 1H, NH guan), 7.98−7.59 (m, 5H, H_3−H_4−H_5−H_8 naph), 7.52−7.34 (m, 2H H_6−H_7 naph), 7.15 (t, J = 5.0 Hz, 1H, NH am), 6.96 (s, 1H, NH guan),

3.60−3.03 (m, 30H, CH_2NHCO, CH_2O crown, CHα, $CH_2\gamma$), 2,67 (m, 2H, CH_2N), 2.06−1.71 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, acetone-d_6): δ 172.2 (CONH), 167.2 (CONH naph), 150.0 (C guan), 134.0, 131.9, 130.6, 128.2, 127.6, 126.9, 126.8, 126.1, 124.2, 123.2 (C, CH naph), 69.7, 69.2, 69.1, 68.7 (CH_2O), 57.6 ($COCH_2N$), 55.2, 48.9, 48.8 (CH_2NH), 45.0, 44.7 (CHα), 44.5, 44.3 ($CH_2\gamma$), 23.0, 22.7 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 655.2 [(M − PF_6)$^+$, 84%]. HRMS calcd for $C_{34}H_{51}N_6O_7$: 655.3819, found 655.3813.

Synthesis of (2*S*,8*S*)-8-[(2-Bromoacetylamino)methyl]-2-(*tert*-butyldiphenylsilanyloxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidin-1-ium (21). To a mixture of compound **15** (PF_6) (305 mg, 0.45 mmol), PyBOP (260 mg, 0.50 mmol), bromoacetic acid (70 mg, 0.50 mmol), and a catalytic amount of HOBt in CH_2Cl_2 (7 mL) was added NMM (0.11 mL, 1.1 mmol), and the reaction was stirred at room temperature for 5 h. Then more CH_2Cl_2 (10 mL) was added, and the solution was washed with 0.1 N NH_4PF_6 and filtered over cotton. After removing the solvent, the crude was purified by column chromatography (2% MeOH−CH_2Cl_2) to obtain **21** (PF_6) (236 mg, 74%) as a white solid. Mp (PF_6): 58−60 °C; $[\alpha]_D^{20}$ (PF_6) +68 (*c* 0.7, $CHCl_3$). ^1H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.01 (s, 1H, NH am), 7.72−7.51 (m, 4H, PhSi), 7.46−7.32 (m, 6H, PhSi), 7.03 (s, 1H, NH guan), 6.71 (s, 1H, NH guan), 4.03−3,22 (m, 12H, CH_2NHCO, $COCH_2Br$, CH_2OSi, CHα, $CH_2\gamma$), 2.30−1.78 (m, 4H, $CH_2\beta$), 1.02 (s, 9H, *tert*-Bu).^{13}C NMR (PF_6) (75 MHz, acetone-d_6): δ 167.1 (CONH), 151.1 (C guan), 135.6, 132.7, 130.0, 127.9 (CH, C arom), 65.6 (CH_2-OSi), 53.4, 49.8, 49.1, 45.2, 42.5 (CHα, $CH_2\gamma$, CH_2N, CH_2Br), 26.8 (CH_3 *tert*-Bu), 22.9 ($CH_2\beta$), 19.2 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 558.1 [(M − PF_6)$^+$, 74%].

Synthesis of (2*S*,8*S*)-8-(*tert*-Butyldiphenylsilanyloxymethyl)-2-[(2−1,4,7,10,13-pentaoxa-16-azacyclooctadec-16-yl-acetylamino)-methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (2b). A solution of compound **21** (PF_6) (234 mg, 0.33 mmol) and 1-aza-18-crown-6 (224 mg, 0.85 mmol) in DMF (12 mL) was stirred at 100 °C for 12 h. The solvent was removed, and the crude was dissolved in CH_2Cl_2 and washed with 0.1 N HPF_6. The organic phase was filtered over cotton and concentrated. The crude was purified by column chromatography (6% MeOH−CH_2Cl_2), affording compound **2b** ($2PF_6$) (250 mg, 73%). The product was dissolved again in CH_2Cl_2 and washed with a solution of TRIS buffer (pH 9.1). Mp (PF_6): 72−74 °C; $[\alpha]_D^{20}$ (PF_6) +27 (*c* 0.6, $CHCl_3$). ^1H NMR (PF_6) (300 MHz, $CDCl_3$): δ 7.73−7.62 (m, 5H, PhSi, NH am), 7.43−7.40 (m, 6H, PhSi), 6.91 (s, 1H, NH guan), 6.83 (s, 1H, NH guan), 3.76−3.21 (m, 32H, CH_2OSi, CH_2O crown, CHα, $CH_2\gamma$, $COCH_2N$), 2.34 (m, 4H, CH_2N), 2.17−1.76 (m, 4H, $CH_2\beta$), 1.06 (s, 9H, *tert*-Bu). ^{13}C NMR (PF_6) (75 MHz, $CDCl_3$): δ 173.2 (CONH), 150.9 (C guan), 135.5, 132.6, 130.0, 127.9 (CH, C arom), 70.5 69.9, 69.7, 68.3, 66.0, (CH_2O), 65.3 (CH_2-OSi), 58.3, 54.2 ($COCH_2N$), 50.1, 49.2, 46.1, 45.3 (CHα, $CH_2\gamma$, CH_2N), 26.8 (CH_3 *tert*-Bu), 24.1, 22.8 ($CH_2\beta$), 19.2 (C *tert*-Bu). FAB/LSIMS *m*/*z* 740.2 [(M − PF_6)$^+$, 73%]. HRMS calcd for $C_{39}H_{62}N_5O_7Si$: 740.4418; found 740.4408.

Synthesis of (2*R*,8*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-[(6,7,9,10,12,13,15,16,18,19-decahydro-5,8,11,14,17,20-hexaoxabenzocyclooctadecen-2-ylamino)methyl]-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (3). To a solution of mesylate **14** (*R*,*R*, PF_6) (268 mg, 0.405 mmol) and 4-aminobenzo-18-crown-6 (229 mg, 0.526 mmol) in DMF (9 mL) was added NMM (0.22 mL, 2.11 mmol), and the reaction was stirred at 120 °C for 5 h. Then the solvent was removed and CH_2Cl_2 was added. The organic phase was washed with an aqueous solution of $LiPF_6$, filtered over cotton, and concentrated. The crude was purified by column chromatography (4% MeOH−CH_2-Cl_2), affording product **3** (PF_6) (280 mg, 77%) as a brown solid. Mp (PF_6): 98 °C; $[\alpha]_D^{20}$ (PF_6) −16 (*c* 0.30, MeOH). ^1H NMR (PF_6) (500 MHz, acetone-d_6): δ 7.72−7.69 (m, 4H, PhSi), 7.52−7.44 (m, 6H, PhSi), 7.04 (s, 1H, NH), 7.03 (s, 1H, NH), 6.84 (d, *J* = 8.7 Hz, 1H, H_a), 6.50 (d, *J* = 2.5 Hz, 1H, H_c), 6.29 (dd, *J* = 2.5, *J* = 2.5 Hz, 1H, H_b), 4.19−4.12 (m, 4H, CH_2O), 3.91−3.79 (m, 8H, CHα, CH_2O, CH_2-OSi), 3.73−3.68 (m, 12H, CH_2O), 3.58−3.55 (m, 4H, $CH_2\gamma$), 3.38−3.27 (m, 2H, CH_2NH) 2.28−1.96 (m, 4H, $CH_2\beta$), 1.07 (s, 9H, *tert*-Bu). ^{13}C NMR (PF_6) (125 MHz, acetone-d_6): δ 151.3 (C guan), 143.7, 140.2 (C Ph), 135.7, 133.2, 130.3, 128.2 (C, CH PhSi), 112.7, 104.1, 99.4 (C, CH, Ph), 70.0, 69.7, 69.5, 69.2, 69.0, 67.0, 66.7, 66.4 (CH_2O), 50.7 (CH_2N), 48.9, 48.7 (CHα), 45.8, 45.4 ($CH_2\gamma$), 26.6 (CH_3 *tert*-Bu), 24.2, 22.7 ($CH_2\beta$), 19.2 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 915.4 [(M + $NaPF_6$)$^+$, 100%]; 769.4 [(M − HPF_6 + Na)$^+$, 57%]; 747.4 [(M − PF_6)$^+$, 46%]. HRMS calcd for $C_{41}H_{59}N_4O_7Si$: 747.4153; found 747.4162.

Synthesis of (2*R*,8*R*)-8-[(6,7,9,10,12,13,15,16,18,19-Decahydro-5,8,11,14,17,20-hexaoxabenzocyclooctadecen-2-yl amino)methyl]-2-{[(naphthalene-2-carbonyl)amino]methyl}-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (4). To a solution of mesylate **18** (*R*,*R*, PF_6) (51 mg, 0.088 mmol) and 4-aminobenzo-18-crown-6 (43 mg, 0.132 mmol) in DMF (3 mL) was added NMM (15 μL, 0.144 mmol), and the reaction was stirred at 110 °C overnight. The solvent was removed, and the crude was purified by column chromatography (5% MeOH−CH_2Cl_2) to obtain compound **4** (PF_6) (30 mg, 42%) as an oil: $[\alpha]_D^{20}$ (PF_6) −15 (*c* 1, MeOH). ^1H NMR (PF_6) (500 MHz, acetone-d_6): δ 8.49 (s, 1H, H_1 naph), 8.33 (t, 1H, *J* = 6.0 Hz NH am), 8.03−7.97 (m, 4H, H_3−H_4−H_5−H_8 naph), 7.67−7.61 (m, 2H, H_6−H_7), 7.31 (s, 1H, NH guan), 7.23 (s, 1H, NH guan), 6.81 (d, *J* = 8.6 Hz, 1H, H_a), 6.48 (s, 1H, H_c), 6.26 (dd, *J* = 8.0, *J* = 2.5 Hz, 1H, H_b), 4.17−4.10 (m, 4H, CH_2O), 3.96−3.54 (m, 28H, CHα, CH_2O, CH_2NHCO, $CH_2\gamma$), 3.44−3.28 (m, 2H, CH_2NH−Ph) 2.29−1.94 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (125 MHz, acetone-d_6): δ 168.5 (CONH), 151.3 (C guan), 148.6, 140.2 (C Ph), 135.3, 133.0, 131.8, 129.2, 128.6, 128.2, 128.1, 128.0, 127.3, 124.3 (C, CH naph), 112.9, 104.1, 99.5 (C, CH, Ph), 69.8, 69.7, 69.6, 69.3, 69.1, 67.1, 66.7 (CH_2O), 50.4 (CH_2N), 48.8, 48.7 (CHα), 45.9, 45.8 ($CH_2\gamma$), 43.8 (CH_2N), 24.4, 24.2 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 830.2 [(M + $NaPF_6$)$^+$, 72%]; 684.2 [(M − HPF_6 + Na)$^+$, 38%]; 662.4 [(M − PF_6)$^+$, 40%]. HRMS calcd for $C_{36}H_{48}N_5O_7$: 662.3554; found 662.3570.

Synthesis of (2*S*,8*S*)-2-(6-{7-[5-Ethyl-5-(5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl)-3-methyltetrahydrofuran-2-yl]-4-hydroxy-3,5-dimethyl-6-oxo-nonyl}-2-hydroxy-3-methyl[(benzoylamino)-methyl]-8-[naphthalene-2-(carbonylamino)methyl]-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (7b). To guanidinium **19** (PF_6) (40 mg, 0.08 mmol) in anhydrous DMF (10 mL) were added lasalocid A sodium salt (59 mg, 0.096 mmol), PyBOP (50 mg, 0.096 mmol), a catalytic amount of HOBt, and NMM (30 μL, 0.31 mmol), and the reaction was stirred overnight at room temperature. The solvent was removed, and the resulting product was dissolved in CH_2Cl_2, washed with H_2O, filtered over cotton, and purified by column chromatography (3% MeOH−CH_2Cl_2), resulting in **7b** (PF_6) (72 mg, 81%) as a white solid. Mp (PF_6): 96−98 °C; $[\alpha]_D^{20}$ (PF_6) +15 (*c* 0.6, $CHCl_3$). ^1H NMR (PF_6) (300 MHz, $CDCl_3$): δ 9.15 (br s, 1H, OH−Ph), 8.43 (s, 1H, H_1 naph), 7.99−7.75 (m, 4H, H_3−H_4−H_5−H_8 naph), 7.58−7.44 (m, 3H, H_6−H_7 naph, NH guan), 7.39 (t, *J* = 6.0 Hz, 1H, NH am), 7.10 (t, *J* = 6.0 Hz, 1H, NH am), 7.04 (d, *J* = 7.2 Hz, 1H, CH las), 6.65 (d, *J* = 7.2 Hz, 1H, CH las), 4.05−3.31 (m, 16H, CHα, $CH_2\gamma$, CH, CH_2O las), 3.01−2.77 (m, 2H, CH_2 las), 2.90−2.69 (m, 2H, CH_2 las), 2.66−2.53 (m, 2H, CH_2 las) 2.49−2.38 (m, 2H, CH_2), 2.20 (s, 3H, CH_3−Ph), 2.31−0.76 (m, 40H, $CH_2\beta$, CH_3 las, CH_2 las). ^{13}C NMR (PF_6) (125 MHz, $CDCl_3$): δ 171.6 (CO las), 169.9 (CONH), 151.0 (C guan), 138.7 (C las), 135.3 (C naph), 133.0 (CH las), 132.9 (C naph), 130.7 (CH naph), 129.8 (CH naph), 128.7 (CH naph), 128.6 (CH naph), 128.2 (C las), 127.9 (CH naph), 127.0 (CH naph), 124.2 (C naph), 123.4 (CH naph), 121.4 (CH las), 87.2 (C las), 73.2, 71.6 (CH las), 70.4 (C las), 53.8 (CH las), 50.7 (CH, CH_3 las), 46.3, 46.1 (CHα), 45.9, 44.1 ($CH_2\gamma$), 43.7 (CH_2 las), 34.9, 34.0 (CH_2 las), 31.3, 31.2, 30.1 (CH_2 las) 24.5, 24.3 ($CH_2\beta$), 20.2 (CH_2 las), 16.8 (CH_2 las), 16.2, 15.7, 14.3, 13.1, 12.9, 9.4, 6.5 (CH, CH_3 las). FAB/LSIMS: *m*/*z* 924.6 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{54}H_{78}N_5O_8$: 924.5976; found 924.5969.

Synthesis of (2*S*,8*S*)-8-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(6-{7-[5-ethyl-5-(5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl)-3-methyltetrahydrofuran-2-yl]-4-hydroxy-3,5-dimethyl-6-oxo-nonyl}-2-hydroxy-3-methyl[(benzoylamino)methyl]-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (8b). To guanidinium **15** (PF_6) (104 mg, 0.14 mmol) in anhydrous DMF (10 mL) were added lasalocid A sodium salt (96 mg, 0.16 mmol), PyBOP (89 mg, 0.19 mmol), a catalytic amount of HOBt, and NMM (35 μL, 0.34 mmol). The reaction was stirred overnight at room temperature. The solvent was removed, and the resulting product was dissolved in CH_2Cl_2, washed with H_2O, filtered over cotton, and purified by column chromatography (2% MeOH−CH_2Cl_2) resulting in **8b** (PF_6) (115 mg, 71%) as a white solid. Mp (PF_6): 116−118 °C; $[\alpha]_D^{20}$ (PF_6) +20 (*c* 0.2, $CHCl_3$).^{1}H NMR (PF_6) (300 MHz, $CDCl_3$): δ 7.98 (s, 1H, OH−Ph), 7.63−7.61 (m, 4H, PhSi), 7.43−7.37 (m, 6H, PhSi), 7.06 (d, J = 7.2 Hz, 1H, CH las), 6.98 (t, J = 6.0 Hz, 1H, NH am), 6.71 (s, 1H, NH guan), 6.67 (d, J = 7.2 Hz, 1H, CH las), 6.52 (s, 1H, NH guan), 3.78−3.26 (m, 16H, CHα, $CH_2\gamma$, CH, CH_2O las), 3.01−2.77 (m, 1H, CH_2 las), 2.97−2.45 (m, 3H, CH_2 las), 2.20 (s, 3H, CH_3−Ph), 2.31−0.76 (m, 52H, $CH_2\beta$, CH_3 las, CH_3 *tert*-Bu, CH_2 las). ^{13}C NMR (PF_6) (125 MHz, $CDCl_3$): δ 172.0 (CO las), 162.7 (CONH), 151.0 (C guan), 138.8 (C las), 136.0 (C PhSi), 135.9 (CH las), 133.2 (C PhSi), 130.5 (C PhSi), 128.3 (C PhSi), 123.9 (C las), 121.8 (CH las), 87.3 (C las), 72.8, 71.7 (CH las), 65.7 (CH_2-OSi), 55.1 (CH las), 53.8 (CH_2NHCO), 50.3 (CH, CH_3 las), 49.6, 48.8 (CHα), 45.8, 45.4 ($CH_2\gamma$), 43.5 (CH_2NH), 36.7 (CH_2 las), 35.1, 34.0 (CH, CH_3 las), 31.3, 30.0 (CH_2 las), 27.2 (CH_3 *tert*-Bu), 23.9, 22.9 ($CH_2\beta$), 20.2 (CH_2 las), 19.6 (C *tert*-Bu), 16.1 (CH_2 las), 15.8, 14.3, 13.1, 9.4, 6.6 (CH, CH_3 las). FAB/LSIMS: *m*/*z* 1009.6 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{59}H_{89}N_4O_8Si$: 1009.6575; found 1009.6543.

Synthesis of (2*S*,8*S*)-8-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(carboxymethylsulfanylmethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidin-1-ium (22). To a solution of **9** (PF_6) (410 mg, 0.768 mmol) and NMM (0.253 mL, 2.304 mmol) in THF (35 mL) was added a solution of methanesulfonic anhydride (276 mg, 1.536 mmol) in THF (5 mL), and the reaction was stirred for 1 h. Then the solvent was evaporated and CH_2Cl_2 (40 mL) and 0.1 N NH_4PF_6 (20 mL) were added. The organic layer was filtered over cotton and evaporated, and the resulting product (**14**) was dissolved in THF (10 mL). To this solution a mixture of sodium thioacetate (271 mg, 2.304 mmol) and potassium *tert*-butoxide (previously stirred for 20 min in 20 mL MeOH) was added, and the reaction was stirred for 90 min. Then the solvent was evaporated, and CH_2Cl_2 (70 mL) and saturated $NaHCO_3$ (40 mL) were added. The aqueous phase was extracted two times more with CH_2Cl_2 (15 mL). The combined organic phases were washed with water (40 mL) and 1 N HCl (20 mL), dried (Na_2SO_4), and evaporated. The product was precipitated by dissolving in CH_2Cl_2, adding EtOAc, and evaporating the CH_2Cl_2. After cooling, product **22** (Cl) (401 mg, 95%) was obtained as a white solid. Mp (Cl): 166−168 °C; $[\alpha]_D^{20}$ (Cl) +50 (*c* 0.50, MeOH).^{1}H NMR (Cl) (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, NH), 8.16 (s, 1H, NH), 7.65−7.60 (m, 4H, PhSi), 7.41−7.39 (m, 6H, PhSi), 3.78−3.76 (dd, J = 11.0, J = 4.0 Hz, 1 H, CH_2OSi), 3.59 (m, 3H, CH_2OSi, CHα), 3.43 (d, J = 15.0 Hz, 1H, SCH_2CO), 3.36 (d, J = 15.0 Hz, 1H, SCH_2CO), 3.28−3.23 (m 4H $CH_2\gamma$), 2.95−2.71 (m, 2H, CH_2S) 2.12−1.85 (m, 4H, $CH_2\beta$), 1.07 (s, 9H, *tert*-Bu). ^{13}C NMR (Cl) (75 MHz, $CDCl_3$): δ 171.9 (CO), 150.9 (C gua), 135.5, 135.4, 132.6, 129.8, 127.8 (C PhSi), 65.3 (CH_2O), 49.3, 48.0 (CHα), 45.1, 44.7 ($CH_2\gamma$), 36.7 (CH_2S), 34.5 (SCH_2CO), 26.7 (CH_3 *tert*-Bu), 24.8, 22.5 ($CH_2\beta$), 19.1 (C *tert*-Bu). FAB/LSIMS *m*/*z* 512.4 [(M − Cl)$^+$, 100%]. Anal. Calcd for $C_{27}H_{38}N_3O_3SSiCl\cdot H_2O$: C 57.1, H 7.1, N 7.4, S 5.6. Found: C 57.5, H 6.8, N 7.3, S 5.5.

Synthesis of (2*S*,8*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-[2-oxo-2-(1,4,7,10,13-pentaoxa-16-aza-cyclooctadec-16-yl)ethylsulfanyl-methyl]-3,4,6,7,8,9,-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (5). Guanidinium **22** (Cl) (40 mg, 0.073 mmol), 1-aza-18-crown-6 (40 mg, 0.15 mmol), BOP (42 mg, 0.08 mmol), and HOBt (catalytic) were dissolved in DMF (3 mL). After addition of NMM (11 μL, 0.08 mmol), the reaction was stirred for 24 h at room temperature. The solvent was removed, and the crude was dissolved in CH_2Cl_2 and washed with H_2O. After evaporation the product was purified by column chromatography (8% MeOH−CH_2Cl_2) to afford **5** (Cl) (52 mg, 90%) as a yellow oil. The product was again dissolved in CH_2Cl_2 and washed with 0.1 N HPF_6 and a TRIS buffer solution at pH 9.1 to afford **5** (PF_6) as a yellow oil: $[\alpha]_D^{20}$ +15 (*c* 0.3, $CHCl_3$). ^{1}H NMR (Cl) (300 MHz, $CDCl_3$): δ 8.97 (s, 1H, NH), 8.71 (s, 1H, NH), 7.80−7.62 (m, 4H, PhSi), 7.41−7.38 (m, 6H, PhSi), 3.83−3.52 (m, 32H, CH_2OSi, CH_2O crown, CHα, SCH_2CO), 3.26−3.17 (m 4H $CH_2\gamma$), 2.93−2.70 (m, 2H, CH_2S) 2.09−1.86 (m, 4H, $CH_2\beta$), 1.05 (s, 9H, *tert*-Bu). ^{13}C NMR (Cl) (75 MHz, $CDCl_3$): δ 169.2 (CO), 151.2 (C guan), 135.6, 135.5, 132.7, 129.9, 127.9, 127.8 (C, CH arom), 70.9, 70.7, 70.6, 70.3, 69.7, 69.4 (CH_2O), 65.1 (CH_2OSi), 49.7, 49.0 (CHα), 47.2, 44.6 ($CH_2\gamma$), 36.3 (CH_2S), 34.6 (SCH_2CO), 26.8 (CH_3 *tert*-Bu), 24.9, 22.7 ($CH_2\beta$), 19.2 (C *tert*-Bu). FAB/LSIMS: *m*/*z* 757.4 [(M − Cl)$^+$, 100%].

Synthesis of (2*R*,8*R*)-8-Hydroxymethyl-2-{[(naphthalen-2-ylmethyl)carbamoyl]methylsulfanylmethyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (23). Compound **22** (*R*,*R*, PF_6) (180 mg, 0.352 mmol), BOP (171 mg, 0.387 mmol), 2-aminomethylnaphthalene hydrochloride (75 mg, 0.387 mmol), HOBt (catalytic), and NMM (40 μL, 0.387 mmol) in DMF (15 mL) were stirred at room temperature for 1.5 h. The solvent was evaporated, CH_2Cl_2 was added, and the organic phase was washed with 0.1 N NH_4PF_6, dried filtering over cotton, evaporated, and used directly in the next step. The crude was dissolved in CH_3CN, and CsF (150 mg, 1.06 mmol) was added. The reaction was stirred overnight at room temperature. After filtering and evaporating the solvent, the crude was dissolved in CH_2Cl_2, washed with 2 N KOH and 0.1 N NH_4PF_6, filtered over cotton, and evaporated. After purification by column chromatography (5% MeOH−CH_2Cl_2) product **23** (PF_6) (165 mg, 84%) was obtained as a white solid. Mp (PF_6): 68 °C; $[\alpha]_D^{20}$ (PF_6) −73 (*c* 0.6, MeOH). ^{1}H NMR (PF_6) (300 MHz, acetone-d_6): δ 8.08 (t, J = 6.0 Hz, 1H, NHCO), 7.94−7.75 (m, 4H, H_3−H_4−H_5−H_8 naph), 7.68 (s, 1H, NH guan), 7.56−7.23 (m, 2H, H_6−H_7), 7.00 (s, 1H, NH), 4.60 (d, J = 6.0 Hz, 2H, CH_2NH), 4.33 (br s, 1H, OH), 3.79−3.69 (m, 1H, CH_2O), 3.67−3.58 (m, 1H, CH_2O), 3.53−3.38 (m, 8H, CHα, SCH_2CO, $CH_2\gamma$), 3.06 (dd, J = 14.0, J = 5.0 Hz, 1H CH_2S), 2.73 (dd, J = 14.0, J = 9.0 Hz, 1H, CH_2S), 2.17−1.99 (m, 2H, $CH_2\beta$), 1.88−1.58 (m, 2H, $CH_2\beta$). ^{13}C NMR (PF_6) (75 MHz, acetone-d_6): δ 170.9 (CONH), 151.7 (C guan), 137.5, 134.3, 133.6, 129.0, 128.5, 127.1, 126.8, 126.7, 126.6 (C, CH naph), 64.9 (CH_2O), 51.5 (CH_2N), 49.4, 46.2 (CHα), 46.0, 44.1 ($CH_2\gamma$), 38.8, 36.4 (CH_2S), 26.5, 23.4 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 413.2 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{22}H_{29}N_4O_2S$: 413.2011; found 413.2027.

Synthesis of (2*R*,8*R*)-8-Methanesulfonyloxymethyl-2-{[(naphthalen-2-ylmethyl)carbamoyl]-methylsulfanylmethyl}-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (24). To a solution of compound **23** (PF_6) (78 mg, 0.140 mmol) and NMM (62 μL, 0.560 mmol) in THF (6 mL) was added methanesulfonic anhydride (61 mg, 0.35 mmol) in THF (2 mL), and the reaction was stirred at room temperature for 2 h. After evaporation of the solvent, the crude was dissolved in CH_2Cl_2 and washed with 0.1 N NH_4PF_6. The organic phase was filtered over cotton and evaporated, and the crude was purified by column chromatography (5% MeOH−CH_2Cl_2) to afford compound **24** (PF_6) (74 mg, 83%). Mp (PF_6): 77 °C; $[\alpha]_D^{20}$ (PF_6) −62 (*c* 0.5, MeOH). ^{1}H NMR (PF_6) (500 MHz, acetone-d_6): δ 9.12 (s, 1H, NH guan), 8.69 (s, 1H, NH guan), 8.03 (t, J = 6.0 Hz, 1H, NHCO), 7.63 (m, 4H, PhSi), 7.43 (m, 6H, PhSi), 3.83−3.54 (m, 6H, CHα, CH_2O, CH_2NHCO) 3.30−3.19 (m, 4H, $CH_2\gamma$), 2.87 (d, J = 15.0 Hz, 1H, CH_2S), 2.66 (d, J = 15.0 Hz, 1H, CH_2S), 2.19−1.44 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (125 MHz, acetone-d_6): δ 168.5 (CONH), 151.3 (C guan), 148.6, 140.2 (C naph), 135.3, 133.0, 131.8, 129.2, 128.6, 128.2, 128.1, 128.0, 127.3, 124.3 (C, CH naph), 112.9, 104.1, 99.5 (C, CH arom), 69.8, 69.7, 69.6, 69.3, 69.1, 67.1, 66.7 (CH_2O), 50.4 (CH_2N), 48.8, 48.7 (CHα), 45.9, 45.8 ($CH_2\gamma$), 43.8 (CH_2N), 24.4, 24.2 ($CH_2\beta$). Anal. Calcd for

$C_{23}H_{31}F_6N_4O_4PS_2$: C 43.39, H 4.91, N 8.80, S 10.07. Found: C 42.93, H 4.97, N 8.70, S 10.82.

Synthesis of 1,4,7,10,13-Pentaoxa-16-aza-cyclooctadec-16-yl-acetic Acid (25). A solution of 1-aza-18-crown-6 (475 mg, 1.804 mmol), Cs_2CO_3 (882 mg, 2.71 mmol), and methyl bromoacetate (270 μL, 2.71 mmol) in CH_3CN (25 mL) was stirred at 80 °C for 30 min. After cooling to room temperature and filtering over cotton, the solvent was evaporated and the crude was dissolved in a mixture of THF (30 mL) and LiOH (10 mL, 0.5 M in H_2O). The mixture was stirred for 1.5 h, and subsequently a solution of 0.1 N HPF_6 (40 mL) was added. After evaporation of the THF, the product was extracted from the aqueous phase with CH_2Cl_2, resulting in **25** (PF_6) as a solid (650 mg, 77%). Mp (PF_6): 102−104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.95 (br s, COOH), 3.56−3.53 (br s, 22H, NCH_2CO, CH_2O crown), 3.03 (m, 2H, CH_2N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2 (COOH), 70.5, 70.3, 70.2, 69.8, 67.5 (CH_2O), 54.0 (CH_2N). FAB/LSIMS *m*/*z* 322.2 [(M − PF_6)$^+$, 100%]. HRMS calcd for $C_{14}H_{28}NO_7$: 322.1866; found 322.1856.

Synthesis of (2*R*,8*R*)-2-{[(Naphthalen-2-ylmethyl)carbamoyl]-methylsulfanylmethyl}-8-(2−1,4,7,10,13-pentaoxa-16-aza-cyclooctadec-16-yl-acetoxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium (6). A solution of compound **24** (*R*,*R*, PF_6) (42.5 mg, 0.067 mmol), crown ether derivative **25** (PF_6) (31.2 mg, 0.067 mmol), and Cs_2CO_3 (21.8 mg, 0.067 mmol) in CH_3CN (4 mL) was stirred for 1 h at 80 °C. Then the solid was filtered and the solvent evaporated. The crude was dissolved in CH_2Cl_2 and washed with 0.1 N HPF_6 and H_2O. Compound **6** ($2PF_6$) (63.2 mg, 94%) was obtained after trituration with diethyl ether.[24] Mp (PF_6): 78 °C; $[\alpha]_D^{20}$ (PF_6) −33 (*c* 0.50, MeOH). ^{1}H NMR (PF_6) (500 MHz, acetone-d_6): δ 8.18 (t, 1H, NHCO) H_1 naph), 7.95−7.86 (m, 5H, H_1−H_3−H_4−H_5−H_8 naph), 7.71 (s, 1H, NH), 7.57−7.51 (m, 2H, H_6−H_7), 7.13 (s, 1H, NH), 4.66 (d, J = 6.0 Hz, 2H, $NHCH_2$ naph), 4.50 (dd, J = 11.2, J = 5.0 Hz, 1H, CH_2OCO), 4.28 (dd, J = 11.5, J = 7.1 Hz, 1H, CH_2OCO), 4.17−3.41 (m, 34H, CHα, CH_2O, CH_2N, $CH_2\gamma$, SCH_2CO), 3.08 (dd, 1H, J = 14.0, J = 4.7 Hz, 1H, CH_2S), 2.77 (dd, 1H, J = 14.0, J = 8.8 Hz, 1H, CH_2S), 2.26−1.85 (m, 4H, $CH_2\beta$). ^{13}C NMR (PF_6) (125 MHz, acetone-d_6): δ 183.2 (CONH), 170.6 (COO), 151.1 (C guan), 136.9, 128.5, 127.9, 126.6, 126.1, 125.9, 109.6, 108.6 (C naph), 70.5, 70.4, 69.8, 69.7, 66.8 (CH_2O crown), 64.6 (CH_2O) 54.4 (CH_2NH), 48.8, 47.9 (CHα), 45.4, 45.0, ($CH_2\gamma$), 43.5 (CH_2N), 38.2, 35.8 (CH_2S), 25.6, 22.4 ($CH_2\beta$). FAB/LSIMS: *m*/*z* 716.4 [(M − PF_6)$^+$, 6%]. HRMS calcd for $C_{36}H_{55}N_5O_8S$: 716.3693; found 716.3704.

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Supporting Information Available: NMR spectra for receptors **1**−**8**. Selected HPLC chromatograms for transport experiments. This material is available free of charge via the Internet at http://pubs.acs.org

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