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Guanidinium-catalyzed addition of pyrrolidine to 2-(5*H*)-furanone

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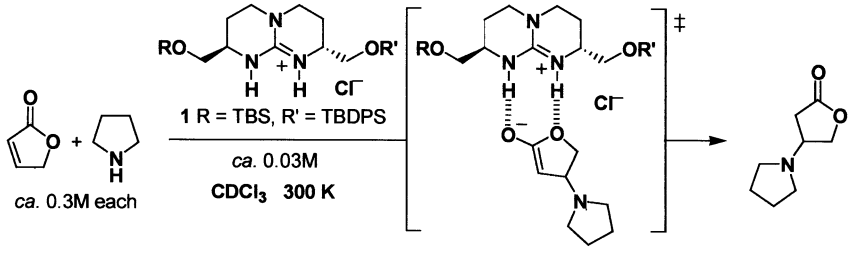
Abstract—Bicyclic guanidinium derivatives with different side arms efficiently catalyze the conjugate addition of pyrrolidine to 2-(5*H*)-furanone, the best results being obtained when the two chains are an aromatic residue and an amine or imidazole, respectively. The catalysis is likely due to the development of strong ion-pairing and hydrogen-bonding in the transition state.

1. Introduction

Enzymatic catalysis has focused the interest of many researchers in the field of Supramolecular Chemistry, due to its high efficiency, regio- and stereoselectivity. It is generally accepted that the origin of the rate acceleration is the transition-state stabilization by the enzyme.[1] Virtually, all types of enzymes operate conjugating several factors in order to reduce the transition-state energy.[2] For example, the catalytic activity of many hydrolases has been attributed to the presence of the guanidinium moiety of the arginine residue, able to set hydrogen bonds stronger with the transition state than with the substrate as well as neutralizing the negative charge that develops as the reaction proceeds.[3]

Ideally, a designed catalyst should be more complementary to the transition-state than to either the products or the reactants. However, the design of these molecules suffers from several limitations,[4] including product inhibition and the unknown structural details of most transition-states.[5] Thus, stabilization of negative charges developing in transition states, in processes where the charge is cancelled in a subsequent fast reaction step, should result in neat rate accelerations and high turnovers.

Michael-type additions of amines to α,β-unsaturated lactones provides a simple example of such a reaction, since protonation of the enolate-like intermediate results in a non-charged saturated compound. The enolate could be stabilized in apolar solvents by means of a guanidinium group present in the catalyst, since two strong, well oriented hydrogen bonds could be formed in the transition state, in addition to ion-pairing. An example was provided by the conjugate addition of nitronates to lactones (Henry reaction).[6] Also, we have previously shown that addition of pyrrolidine to unsaturated lactones can be efficiently catalyzed by the bicyclic, chiral guanidinium salt **1**.[7] Later, another example has been provided using a chromenone cleft-type receptor.[8] In the case of **1**, up to 8-fold half-life reduction was observed for the reaction with 2-(5*H*)-furanone in the presence of a catalytic amount (0.1 equiv.) of **1** (Scheme 1). Although some hydrogen bonding stabilization is present in either the initial components and the final



Scheme 1.

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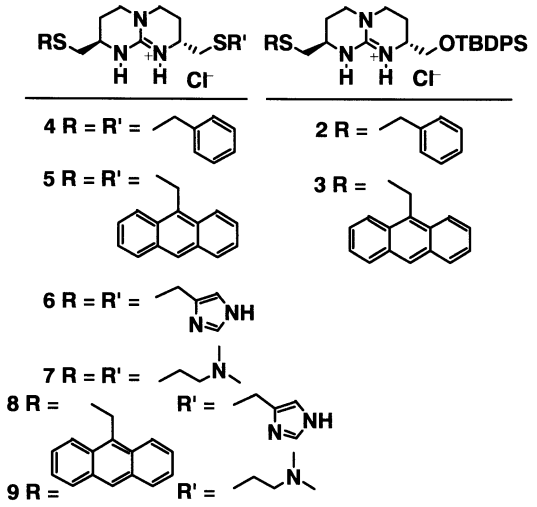


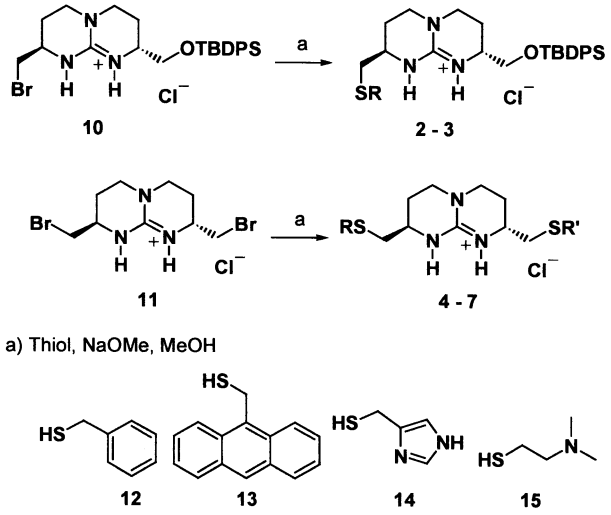
Figure 1. Designed receptors **2**–**9**.

adduct (K_s ca. 30 M^{-1}), substantial charge separation only develops in the transition state. Unfortunately, the stereogenic centers in the catalyst are too distant from the new stereocenter generated in the adduct to allow enantioselectivity to be observed. In a more recent example a different chiral bicyclic guanidinium salt has been shown to accelerate the same reaction under the conditions previously reported by us,[7] although neither in this case was asymmetrical induction observed.[9]

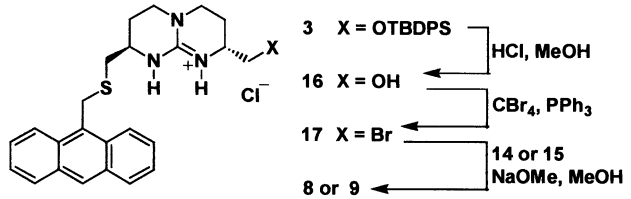
In this paper we have developed further guanidinium-based catalysts, somewhat more complex, in which the side arms could also contribute to the binding and stabilization of the transition state. Eventually, more rigid complexes could lead to chiral induction.

2. Receptors design and synthesis

Receptors **2**–**5** were designed to provide aromatic surfaces that could interact by π–π stacking to the planar, electron-poor 2-(5*H*)-furanone ring in the transition state. Inspection of CPK models of the reaction complex suggested a



Scheme 2.



Scheme 3.

CH_2SCH_2 spacer as the most suitable to attach the side chains to the central guanidinium moiety in order to maximize surface contacts. Models clearly reveal that the aromatic residue could effectively block one face of the furanone forcing the pyrrolidine attack from the opposite side. Receptors endowed with two aromatic substituents (**4** and **5**) might allow to estimate cooperativity effects.

It is known that proton transfer leading to the final adduct in a Michael addition can be assisted by a base.[10] Receptors **6** and **7** were thus designed. These receptors should accelerate the reaction rate by providing a basic nitrogen residue, as it was previously shown for reactions carried out in the presence of a large excess of simpler guanidinium-based receptors.[11] Finally, combination of both strategies led to molecules **8** and **9** that fulfil all the above requirements (Fig. 1).

Receptors **2** and **3** were prepared by reaction of bromoguanidinium salt **10**[12] with thiols **12** and **13**,[13] respectively, under basic conditions (NaOMe/MeOH). Similarly, compounds **4**–**7** were obtained from dibromoguanidinium salt **11** and thiols **12**–**15** (Scheme 2).

Catalysts **8** and **9** were readily obtained from **3** by deprotection and bromination to give **17**, which was subsequently reacted with thiols **14**[14] and **15** as described above (Scheme 3).

3. Results and discussion

The reaction of 2-(5*H*)-furanone with pyrrolidine in $CDCl_3$ at room temperature (300 K) in the presence of a catalytic amount of catalysts **1**–**5** and **7**–**9** (0.1 equiv.) was monitored by ^1H NMR.[15] Half-lives ($t_{1/2}$) were deduced from the ^1H NMR spectra, monitoring the intensity of the lactone methylene protons α to the oxygen atom, since these signals are well differentiated in both the starting and final products. (δ at ca. 4.8–4.9 ppm for the unsaturated lactone and at 4.0–4.4 ppm for the adduct).

Concentration of both pyrrolidine and 2-(5*H*)-furanone was kept constant at 0.3 M and only 10% catalyst (0.03 M) was added in each case. Half-lives for the reactions are collected in Table 1.

In good agreement with our design principles, the presence of aromatic residues (entries 3–6) significantly increased the efficiency of the catalysts. The effect was even higher with two aromatic side arms (entries 5 and 6).

Catalyst **7** with two appended amino groups showed a

Table 1. Half-lives for the guanidinium-catalyzed Michael additions of pyrrolidine to 2-(5*H*)-furanone

Entry	Guanidium salt	$t_{1/2}$ (min)[a]
1	–	180
2	**1**	40
3	**2**	34
4	**3**	33
5	**4**	28
6	**5**	21
7	**6**	–[b]
8	**7**	26
9	**8**	18[c]
10	**9**	28

[a] Obtained by non-linear regression analysis, $r^2>0.99$.
[b] Insoluble, not measured.
[c] Only 6% of receptor was employed due to solubility problems.

similar rate enhancement as **5** or **6** endowed with aromatic residues. Combination of both effects (aromatic surfaces and basic residues) in compounds **8** and **9** proved again to be successful. The higher catalytic activity of the imidazole-containing derivative **8** compared to the dimethylamino analogue **9**, even at 6% concentration, could be attributed to the presence of the two nitrogen atoms working cooperatively in the proton transfer, as well as to its increased preorganization.

Chirality transfer in the above reaction would result in splitting of the ^{1}H NMR signals in the diastereomeric product complexes. Such splitting was observed only in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's reagent)[16] as chiral shift reagent, but no significant chiral induction was obtained by signal integration.

4. Conclusions

A proper choice of the substituents attached to the bicyclic guanidinium subunit leads to higher efficiency in the catalysis of the Michael addition of amines to α,β-unsaturated lactones. Both stacking interactions provided by planar aromatic surfaces and general base catalytical groups independently decrease the half-life of the reaction, and combination of these two key catalytic features into the same synthetic receptor results in even better catalysts. Unfortunately, no chiral discrimination was observed, probably due to the flexibility of the systems and the long distance between the stereogenic centers of substrate and receptor.

5. Experimental

5.1. General procedures

Optical rotations were determined in a Perkin-Elmer polarimeter 241 MC. Low and high resolution mass spectra were obtained on a VG AutoSpec mass spectrometer, using either the LSIMS$^+$ or EI techniques. ^{1}H and ^{13}C NMR spectra were recorded on Brucker AC-200 (200 MHz) or AMX-300 (300 MHz) spectrometers. Solvent residual peak was used as the internal reference.

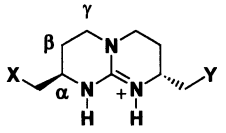


Figure 2. Convention for the numbering of the guanidinium subunit.

The following convention was used for the numbering of the guanidinium subunit in the NMR spectra (Fig. 2).

5.2. General synthetic procedures and data

5.2.1. General procedure A for the formation of a single thioether linkage with the guanidinium subunit. To a rt stirred solution of a thiol (2.2 mmol) in 0.24 M NaOMe/MeOH bromoguanidines **10** or **17** (1.1 mmol) in methanol (9 mL) were added. After stirring for 12 h, aqueous HCl 5% was added and the mixture was concentrated by rotary evaporation. The residue was dissolved in dichloromethane (50 mL) and washed with water and brine. The combined organic phases were dried (Na_2SO_4) and the solvent was eliminated. Silica gel column chromatography (CH_2Cl_2→CH_2Cl_2/3% MeOH) afforded the required products in the yields specified.

5.2.2. General procedure B for the formation of two thioether linkages with the guanidinium subunit. To a rt stirred solution of a thiol (1.2 mmol) in 0.14 M NaOMe/MeOH bromoguanidine **11** (0.4 mmol) in methanol (9 mL) was added. Work up and purification of the corresponding crude mixture proceeded as above unless otherwise stated.

5.2.3. (4*R*,8*R*)-8-Benzylthiomethyl-4-(*tert*-butyldiphenylsilyloxymethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene hydrochloride (2). General procedure A with **10** (60 mg, 0.11 mmol), thiol **12** (26 μL, 0.22 mmol) and 1.9×10^{-2} M NaOMe. Yield: 36 mg, 56%. Mp 47°C; $[\alpha]_D^{20}=-65.0°$ (c=0.5, MeOH); ^{1}H RMN ($CDCl_3$, 300 MHz) δ 9.17 (s, 1H, NH_{gua}), 8.75 (s, 1H, NH_{gua}), 7.56 (m, 5H, CH_{arom}), 7.30 (m, 10H, CH_{arom}), 3.76 (m, 1H, CH_2O), 3.71 (s, 2H, SCH_2Ph), 3.47 (m, 1H, CH_2O), 3.38 (m, 2H, CH_α), 3.10 (m, 4H, $CH_{2\gamma}$), 2.79 (dd, J=4.2, 13.5 Hz, 1H, CH_2S), 2.44 (dd, J=9.4, 13.5 Hz, 1H, CH_2S), 2.05–1.65 (m, 4H, $CH_{2\beta}$), 1.00 (s, 9H, *t*-butyl); ^{13}C RMN ($CDCl_3$, 50 MHz, DEPT) δ 151.2 (C_{gua}), 135.6, 135.5, 132.7, 130.0, 128.9, 128.7, 127.9, 127.2, 65.2 (CH_2O), 49.0, 48.1 (CH_α), 45.1, 44.6, 37.2, 36.0 (CH_2), 26.9 [$C(CH_3)$], 24.8, 22.8 (CH_2), 19.2 [$C(CH_3)$]. MS (FAB$^+$) m/z 544 (M^+-Cl, 100.00). Exact mass: calcd for $C_{32}H_{42}N_3OSiS$, 544.2819; found, 544.2810.

5.2.4. (4*R*,8*R*)-8-(9-Anthracenemethylthiomethyl)-4-(*tert*-butyldiphenylsilyloxymethyl)-1,5,7-triazabicyclo-[4.4.0]dec-5-ene hydrochloride (3). General procedure A with **10** (600 mg, 1.11 mmol), thiol **13** (500 mg, 2.23 mmol) and 0.24 M NaOMe. Yield: 520 mg, 69%. Mp 86°C; $[\alpha]_D^{20}=-47.2°$ (c=0.5, MeOH). ^{1}H RMN ($CDCl_3$, 300 MHz) δ 9.41 (s, 1H, NH_{gua}), 8.76 (s, 1H, NH_{gua}), 8.38 (s, 1H, CH-10$_{anth}$), 8.29 (d, J=8.8 Hz, 2H, CH-1 and CH-8$_{anth}$), 7.98 (d, J=8.6 Hz, 2H, CH-4$_{anth}$ and CH-5$_{anth}$), 7.70–7.36 (m, 14H, CH_{arom} and CH_{anth}), 4.82 (AB system, J=12.5 Hz, 2H, SCH_2-anth), 3.82 (m, 1H, CH_2O), 3.51 (m, 3H, CH_2O, CH_α), 3.20–2.95 (m, 5H, CH_2S, $CH_{2\gamma}$), 2.72 (dd, J=9.2, 13.4 Hz, 1H, CH_2S), 2.05–1.65 (m, 4H, $CH_{2\beta}$), 1.06

(s, 9H, *t*-butyl). ^{13}C RMN ($CDCl_3$, 50 MHz, DEPT) δ 150.3 (C_{gua}), 134.9, 132.0, 130.6, 129.3, 129.1, 128.4, 127.9, 127.3, 126.8, 125.7, 124.5, 123.5, 64.7 (CH_2O), 48.6, 47.8 (CH_α), 44.2, 43.8, 37.1, 29.4 (CH_2), 26.3 [$C(CH_3)$], 24.1, 22.0 (CH_2), 18.5 [$C(CH_3)$]. MS (FAB$^+$) *m/z* 644 (M^+-Cl, 100.00). Exact mass: calcd for $C_{40}H_{46}N_3OSiS$, 644.3131; found, 644.3137.

5.2.5. (4*R*,8*R*)-4,8-Bis-(benzylthiomethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene hydrochloride (4). General procedure B with **11** (200 mg, 0.55 mmol), thiol **12** (195 μL, 1.66 mmol) and 0.12 M NaOMe. Yield: 36 mg, 55%. Mp 47°C. $[\alpha]_D^{20}=-11.4°$ (*c*=1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.04 (s, 2H, NH_{gua}), 7.31 (m, 10H, CH_{arom}), 3.77 (s, 4H, SCH_2Ph), 3.37 (m, 2H, CH_α), 3.16 (t, *J*=6.6 Hz, 4H, $CH_{2\gamma}$), 2.83 (dd, *J*=4.6, 13.5 Hz, 2H, CH_2S), 2.50 (dd, *J*=9.0, 13.5 Hz, 2H, CH_2S), 2.10–2.01 (m, 2H, $CH_{2\beta}$), 1.78–1.69 (m, 2H, $CH_{2\beta}$). ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT) δ 150.3 (C_{gua}), 137.4, 128.5, 128.1, 126.7, 47.7 (CH_α), 44.6, 36.6, 35.6, 24.6 (CH_2). MS (FAB$^+$) *m/z* 412 (M^+-Cl, 100.00) Exact mass: calcd for $C_{23}H_{30}N_3S_2$, 412.1881; found, 412.1879.

5.2.6. (4*R*,8*R*)-4,8-Bis-(9-anthracenemethylthiomethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene, hydrochloride (5). General procedure B with **11** (150 mg, 0.41 mmol), thiol **13** (279 mg, 1.25 mmol) and 0.14 M NaOMe. Yellow solid, yield 172 mg, 64%. Mp 112–114°C. $[\alpha]_D^{20}=-66.0°$ (*c*=0.30, MeOH) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.17 (s, 2H, NH_{gua}), 8.39 (s, 2H, CH-10_{anth}), 8.32 (d, *J*=8.8 Hz, 4H, CH-1_{anth} and CH-8_{anth}), 7.99 (d, *J*=8.4 Hz, 4H, CH-4_{anth} and CH-5_{anth}), 7.62–7.56 (m, 8H, CH-2, CH-3, CH-6_{anth} and CH-7_{anth}), 4.85 (AB system, *J*=12.6 Hz, 4H, SCH_2-anth), 3.60 (m, 2H, CH_α), 3.18–2.99 (m, 6H, $CH_{2\gamma}$, CH_2S), 2.75 (dd, *J*=8.9, 13.4 Hz, 2H, CH_2S), 2.04–1.96 (m, 2H, $CH_{2\beta}$), 1.78–1.69 (m, 2H, $CH_{2\beta}$). ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT) δ 150.8 (C_{gua}), 131.3, 129.0, 128.5, 127.9, 127.4, 126.3, 125.0, 124.1, 48.3 (CH_α), 44.7, 37.6, 29.9, 24.7 (CH_2). MS (FAB$^+$) *m/z* 612 (M^+-Cl, 55.17). Exact mass: calcd for $C_{39}H_{38}N_3S_2$, 612.2507; found, 612.2503.

5.2.7. (4*R*,8*R*)-4,8-Bis-(4-imidazolemethylthiomethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene, hydrochloride (6). General procedure B with **11** (150 mg, 0.41 mmol), thiol **14** (188 mg, 1.25 mmol) and 0.28 M NaOMe. In this case the crude reaction mixture was washed with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (15 mL). The aqueous phase was basified with Na_2CO_3 and then evaporated. The product was extracted from the inorganic salts with EtOH, yield 106 mg, 60%. ^{1}H NMR (MeOH-d_4, 200 MHz) δ 7.68 (s, 2H, C-2_{im}), 7.17 (s, 2H, C-4_{im}), 3.77 (s, 4H, SCH_2-im), 3.60–3.28 (m, 6H, CH_2S, CH_α), 2.81–2.52 (m, 4H, $CH_{2\gamma}$), 2.15–1.80 (m, 4H, $CH_{2\beta}$). ^{13}C NMR (MeOH-d_4, 50 MHz, DEPT) δ 152.6 (C_{gua}), 137.2, 136.4, 118.8, 49.0 (CH_α), 46.8, 37.4, 29.1, 27.0 (CH_2).

5.2.8. (4*R*,8*R*)-4,8-Bis-(2-dimethylaminoethylthiomethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene, hydrochloride (7). General procedure B with **11** (200 mg, 0.55 mmol), thiol **15** (262 mg, 1.66 mmol) and 0.28 M NaOMe. In the work up a saturated NH_4Cl solution was used. The product was extracted from the inorganic salts with CH_3CN. Colorless oil, yield 171 mg, 75%. $[\alpha]_D^{20}=-73.6°$ (*c*=0.36, MeOH). ^{1}H RMN ($CDCl_3$, 300 MHz) δ 8.89 (s, 2H, NH_{gua}), 3.65–3.54 (m, 2H, CH_α), 3.38–3.31 (m, 4H, $CH_{2\gamma}$), 2.97–2.57 (m, 12H, $CH_2SCH_2CH_2N$), 2.30 (s, 12H, NCH_3), 2.28–2.17 (m, 2H, $CH_{2\beta}$), 2.00–1.85 (m, 2H, $CH_{2\beta}$). ^{13}C RMN ($CDCl_3$, 50 MHz, DEPT) δ 150.5 (C_{gua}), 58.8 (CH_2), 48.3 (CH_α), 45.0 (CH_3), 36.6, 30.8, 25.0 (CH_2). MS (FAB$^+$) *m/z* 374.3 (M^+-Cl, 97.64). Exact mass: calcd for $C_{17}H_{36}N_5S_2$, 374.2412; found, 374.2416.

5.2.9. (4*R*,8*R*)-4-(9-Anthracenemethylthiomethyl)-8-(4-imidazolemethylthiomethyl)-1,5,7-triazabicyclo[4.4.0]-dec-5-ene, hydrochloride (8). General procedure A with **17** (50 mg, 0.1 mmol), thiol **14** (41 mg, 0.2 mmol) and 0.39 M NaOMe. Pale yellow solid, yield 31 mg, 58%. Mp 122–123°C. $[\alpha]_D^{20}=-62.9°$ (*c*=0.27, MeOH). ^{1}H NMR ($CDCl_3$+MeOH-d_4, 300 MHz) δ 8.28 (s, 1H, CH-10_{anth}), 8.17 (d, *J*=8.8 Hz, 2H, CH-1_{anth} and CH-8_{anth}), 7.88 (d, *J*=8.4 Hz, 2H, CH-4_{anth} and CH-5_{anth}), 7.56 (s, 1H, C-2_{im}), 7.45–7.33 (m, 4H, CH-2_{anth}, CH-3_{anth}, CH-6_{anth}, and CH-7_{anth}), 6.91 (s, 1H, C-4_{im}), 4.70 (s, 2H, SCH_2-anth), 3.63 (s, 2H, SCH_2-im), 3.30–2.96 (m, 6H, $CH_{2\gamma}$, CH_α), 2.87–2.38 (m, 4H, CH_2S), 2.02–1.82 (m, 2H, $CH_{2\beta}$), 1.75–1.50 (m, 2H, $CH_{2\beta}$). ^{13}C NMR ($CDCl_3$+MeOH-d_4, 75 MHz, DEPT) δ 150.4 (C_{gua}), 135.1, 132.8, 131.3, 129.7, 129.1, 128.2, 127.5, 126.2, 125.0, 123.8, 118.2, 48.2, 47.7 (CH_α), 45.0, 44.9, 37.1, 35.8, 29.2, 27.5, 25.2, 24.9 (CH_2). MS (FAB$^+$) *m/z* 502.3 (M^+-Cl, 27.69) Exact mass: calcd for $C_{28}H_{32}N_5S_2$, 502.2099; found, 502.2088.

5.2.10. (4*R*,8*R*)-4-(9-Anthracenemethylthiomethyl)-8-(2-dimethylaminoethylthiomethyl)-1,5,7-triazabicyclo[4.4.0]-dec-5-ene, hydrochloride (9). General procedure A with **17** (50 mg, 0.1 mmol), thiol **15** (30 mg, 0.2 mmol) and 0.37 M NaOMe. In the work up the crude reaction mixture was washed with a saturated NH_4Cl solution and chromatography was performed on neutral alumina (CH_2Cl_2→CH_2Cl_2/5% AcOEt). Pale yellow solid, yield 29 mg, 55%. Mp 38–40°C. $[\alpha]_D^{20}=-47.6°$ (*c*=0.38, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.32 (s, 1H, NH_{gua}), 9.18 (s, 1H, NH_{gua}), 8.37 (s, 1H, CH-10_{anth}), 8.29 (d, *J*=8.9 Hz, 2H, CH-1_{anth}, CH-8_{anth}), 7.97 (d, *J*=8.4 Hz, 2H, CH-4_{anth}, CH-5_{anth}), 7.60–7.43 (m, 4H, CH-2_{anth}, CH-3_{anth}, CH-6_{anth}, and CH-7_{anth}), 4.81 (s, 2H, SCH_2-anth), 3.67–3.45 (m, 2H, CH_α), 3.33–2.50 (m, 12H, CH_2), 2.28 (s, 6H, NCH_3), 2.15–1.62 (m, 4H, $CH_{2\beta}$). ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT) δ 151.0 (C_{gua}), 131.4, 129.8, 129.1, 128.5, 127.5, 126.4, 125.1, 124.1, 58.8 (CH_2), 48.45, 48.42 (CH_α), 45.1 (CH_3), 45.0, 44.9, 37.5, 36.7, 30.7, 30.0, 25.0, 24.8 (CH_2). MS (FAB$^+$) *m/z* 493.3 (M^+-Cl, 100.00). Exact mass: calcd for $C_{28}H_{37}N_4S_2$, 493.2460; found, 493.2457.

5.2.11. (4*R*,8*R*)-4-(9-Anthracenemethylthiomethyl)-8-(hydroxymethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene, hydrochloride (16). A solution of **3** (515 mg, 0.76 mmol) in a 1:2 12 M HCl/MeOH mixture (100 mL) was stirred at rt for 12 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with water and brine. The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography (CH_2Cl_2→CH_2Cl_2/5% MeOH) to obtain **16** as a yellow solid (286 mg, 86%). Mp 88–90°C;

$[\alpha]_D^{20}=-24.6°$ (c=1.00, $CHCl_3$). ^1H RMN ($CDCl_3$, 300 MHz) δ 8.81 (s, 1H, NH_{gua}), 8.39 (s, 1H, CH-10_{anth}), 8.30 (d, J=8.8 Hz, 2H, CH-1_{anth} and CH-8_{anth}), 8.22 (s, 1H, NH_{gua}), 7.61–7.44 (m, 4H, CH-2_{anth}, CH-3_{anth}, CH-6_{anth}, and CH-7_{anth}), 4.81 (s, 2H, SCH_2-anth), 3.90–3.47 (m, 4H, CH_α, CH_2O), 3.36–3.10 (m, 4H, $CH_{2\gamma}$), 3.00 (m, 1H, CH_2S), 2.71 (m, 1H, CH_2S), 2.07–1.75 (m, 4H, $CH_{2\beta}$). ^{13}C RMN ($CDCl_3$, 50 MHz, DEPT) δ 150.8 (C_{gua}), 131.1, 129.6, 128.8, 128.4, 127.2, 126.2, 124.9, 124.0, 63.7 (CH_2O), 50.2, 48.2 (CH_α), 45.1, 44.8, 37.6, 29.8, 24.9, 22.5 (CH_2). MS (FAB^+) m/z 406.2 (M^+-Cl, 48.30). Exact mass: calcd for $C_{24}H_{28}N_3OS$, 406.1953; found, 406.1954.

5.2.12. (4*R*,8*R*)-4-(9-Anthracenemethylthiomethyl)-8-(bromomethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene, hydrochloride (17). Alcohol **16** (230 mg, 0.51 mmol) in dichloromethane (5 mL) was stirred for 12 h at rt in the presence of triphenylphosphine (341 mg, 1.3 mmol) and carbon tetrabromide (432 mg, 1.3 mmol). The crude mixture was washed with water and brine, dried and evaporated. Silica column chromatography (AcOEt→CH_2Cl_2/3% MeOH) afforded **17** as a pale yellow solid (210 mg, 80%). Mp 6870°C. $[\alpha]_D^{20}=-49.4°$ (c=0.5, MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.33 (s, 1H, NH_{gua}), 9.13 (s, 1H, NH_{gua}), 8.40 (s, 1H, CH-10_{anth}), 8.30 (d, J=8.2 Hz, 2H, CH-1_{anth} and CH-8_{anth}), 7.99 (d, J=8.3 Hz, 2H, CH-4_{anth} and CH-5_{anth}), 7.62–7.45 (m, 4H, CH-2_{anth}, CH-3_{anth}, CH-6_{anth}, and CH-7_{anth}), 4.84 (AB system, J=12.6 Hz, 2H, SCH_2-anth), 3.78–3.66 (m, 1H, CH_α), 3.61–3.55 (m, 2H, CH_α, CHBr), 3.37–3.05 (m, 6H, CHBr, $CH_{2\gamma}$, CHS), 2.73 (dd, J=8.7, 13.4 Hz, 1H, CHS), 2.05–1.67 (m, 4H, $CH_{2\beta}$). ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT) δ 150.4 (C_{gua}), 131.0, 129.4, 128.7, 128.2, 127.1, 126.1, 124.8, 123.8, 48.6, 48.1 (CH_α), 44.6, 44.1, 37.4, 33.5, 29.7, 24.6, 24.0 (CH_2). MS (FAB^+) m/z 468.1 (M^+-Cl, 97), 470.1 ($[M+2]^+$-Cl, 100). Exact mass: calcd for $C_{24}H_{27}N_3SBr$, 468.1109; found, 468.1106.

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