

# One-step transformation of 2-oxa-3-azabicyclo[2.2.1]hept-5-ene and methyl 2,3-diazabicyclo[2.2.1]heptane-2-carboxylate to ion uptake systems

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Dedicated to Professor P. T. Narasimhan on of his 75<sup>th</sup> birthday

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## Abstract

Linker generated duplexes of the title compounds- prepared from cyclopentadiene- with possibility for positioning of four oxygen in the cavity, are shown to be excellent ion uptake systems. Mass spectrometric doping studies with lithium, sodium, potassium and silver ions, show a clear preference for lithium complexation. The lithium salts of the best examples have been prepared and characterized.

**Keywords:** Flexible open cavities, ion uptake

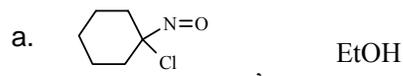
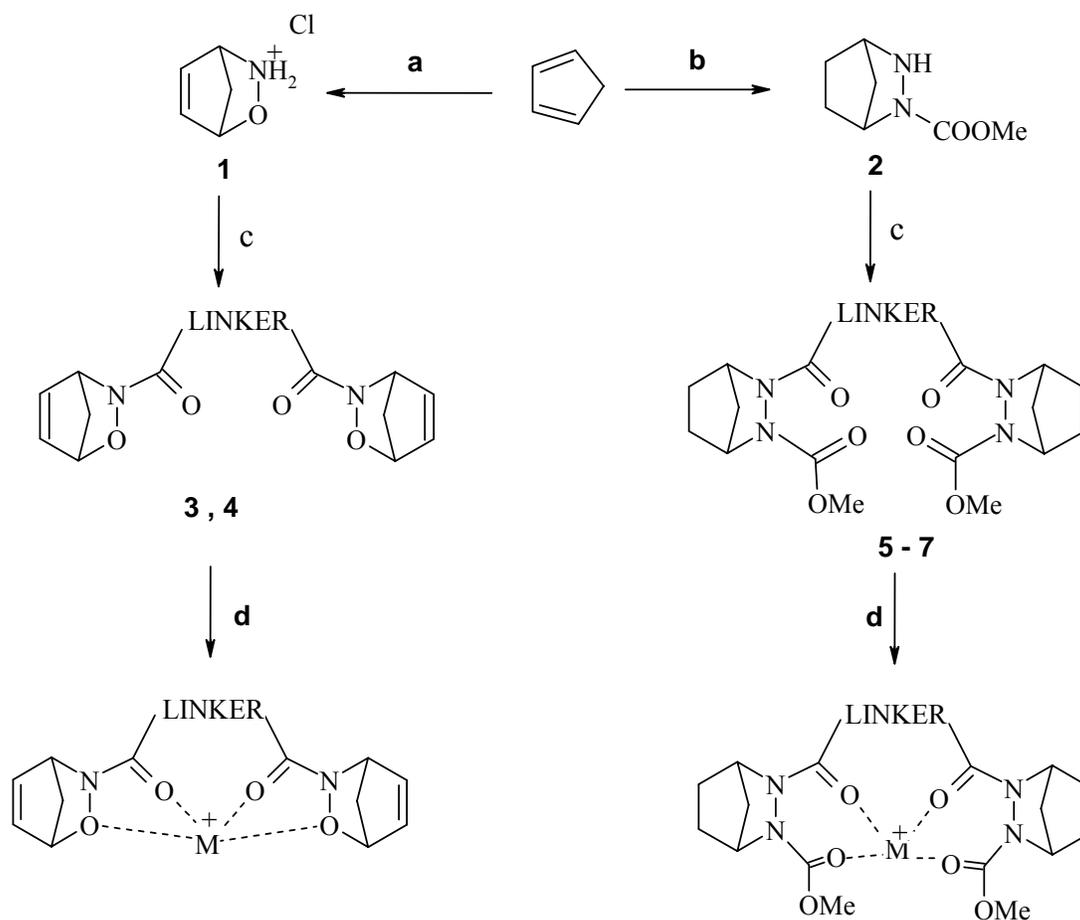
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## Introduction

Innovations in the design of ionophores with preferential transport profile continue unabated. <sup>1</sup> Our interest in 2-oxa-3-aza-bicyclo[2.2.1]hept-5-ene hydrochloride (**1**), which can be prepared in quantities from cyclopentadiene and chloronitroso cyclohexane in EtOH, <sup>2</sup>, made it logical to take advantage of the proximate and restrained positioning of the nitrogen and the oxygen units present to design ion uptake systems. A natural extension of this concept would be related studies on the cyclopentadiene-azodicarboxylate adduct derived **2**. Simple bis amidation of **1** and **2** would lead to cavities capable of ion uptake (Chart 1). It could be seen from Chart 1 that composites from **1** would have pairs of amide oxygens and ether oxygens for complexation and that from **2**, pairs of carbamate oxygens and ester oxygens.

## Results and Discussion

The reaction of **1** and **2** with bis acid chlorides derived from succinic, glutaric, and octane dioic acid afforded compounds **3-7** in good yields (Chart 1).



COMPOUND	LINKER	M <sup>+</sup>
<b>3, 5</b>	(CH <sub>2</sub> ) <sub>2</sub>	Li, Na, K, Ag.
<b>4, 7</b>	(CH <sub>2</sub> ) <sub>8</sub>	Li, Na, K, Ag.
<b>6</b>	(CH <sub>2</sub> ) <sub>3</sub>	Li, Na, K

Chart 1

FAB mass spectra studies<sup>3</sup> have established the ion uptake profile of these systems. The FAB mass spectrum of **3** shows the presence of the parent ion ( $m/z$  277 ( $M+H$ )<sup>+</sup>; 34%) and a base peak at  $m/z$  180, which represents the loss of one of the bicycloheptene units. The Li complex exhibits clean complexation ( $m/z$  283 ( $M+Li$ )<sup>+</sup>; 100%); neither the uncomplexed **3** nor the fragmented intermediate was seen, clearly suggesting the stability of the Li complex. A comparison of the mass spectral behavior of salts of Li, Na, and K is interesting. Whereas the mass spectrum of the Li salt showed no leakage of the ion, that of Na and K showed increasing fragility. Thus, in the case of the Na salt, peaks corresponding to the complexation ( $m/z$  299 ( $M+Na$ )<sup>+</sup>) and that arising from the loss of one of the bicycloheptene units were equally prominent, and constituted the base peaks. In addition, the uncomplexed **3** was also seen ( $m/z$  277 ( $M+H$ )<sup>+</sup>; 29 %). Even worse was the profile of the K salt where the base peak was that arising from the loss of one of the units with the complexed and uncomplexed showing equal importance. Of interest is the formation of the silver complex from **3**. Such complexes have potential in <sup>111</sup>Ag-based radio immuno therapy.<sup>4</sup> The mass spectrum of the Ag complex shows the presence of the Ag complex exhibiting the typical, nearly equal isotope doublet ( $m/z$  383,385 ( $M+Ag$ )<sup>+</sup>; 16%). However considerable leakage was observed as could be seen from the presence of peaks corresponding to the starting materials and fragmented intermediates. Similar studies on the bis amide system represented by **5** are shown in Figure 1. The FAB mass spectrum of **5** (Figure 1a) showed the presence of the parent ion ( $m/z$  395 ( $M+H$ )<sup>+</sup>; 28 %) and the base peak corresponding to loss of one of the bicycloheptene unit ( $m/z$  239). The profile of the Li complex from **5** (Figure 1b) is truly exceptional. The spectrum was clean and essentially consisted of the Li complex ( $m/z$  401 ( $M+Li$ )<sup>+</sup>). In the whole series, compound **5**, showed maximum promise for Li uptake. This is supported by the energy minimized representation of the Li complex derived from **5**, which suggests a near tetrahedral arrangement of the oxygen atoms in the ionophore cavity (Figure 2). The trend with Na and K complex (Figure 1c, 1d) was quite similar to that seen from **3**. Compound **7** of the series afforded a Ag complex ( $m/z$  585,587 ( $M+Ag$ )<sup>+</sup>; 13 %). The mass spectral ion uptake profiles of **3-7** are presented in Table 1. Efforts to demonstrate ion transport across layers with **3** and **5** gave poor results.<sup>5</sup> The lack of transport may either be due to the nonavailability of the reagents to the metal salts or due to the insolubility of the metal complex in chloroform.

Compounds **3** and **5** afforded the lithium complexes on treatment with lithium nitrate in THF-DMSO followed by evaporation and trituration with water, as very fine needles that decomposed without melting. The structural assignments for these are supported by mass spectra.

The present work has shown that FAB mass spectrometric doping experiments can be a useful tool in the initial recognition of ion uptake systems as well as to give a notion of uptake preferences.

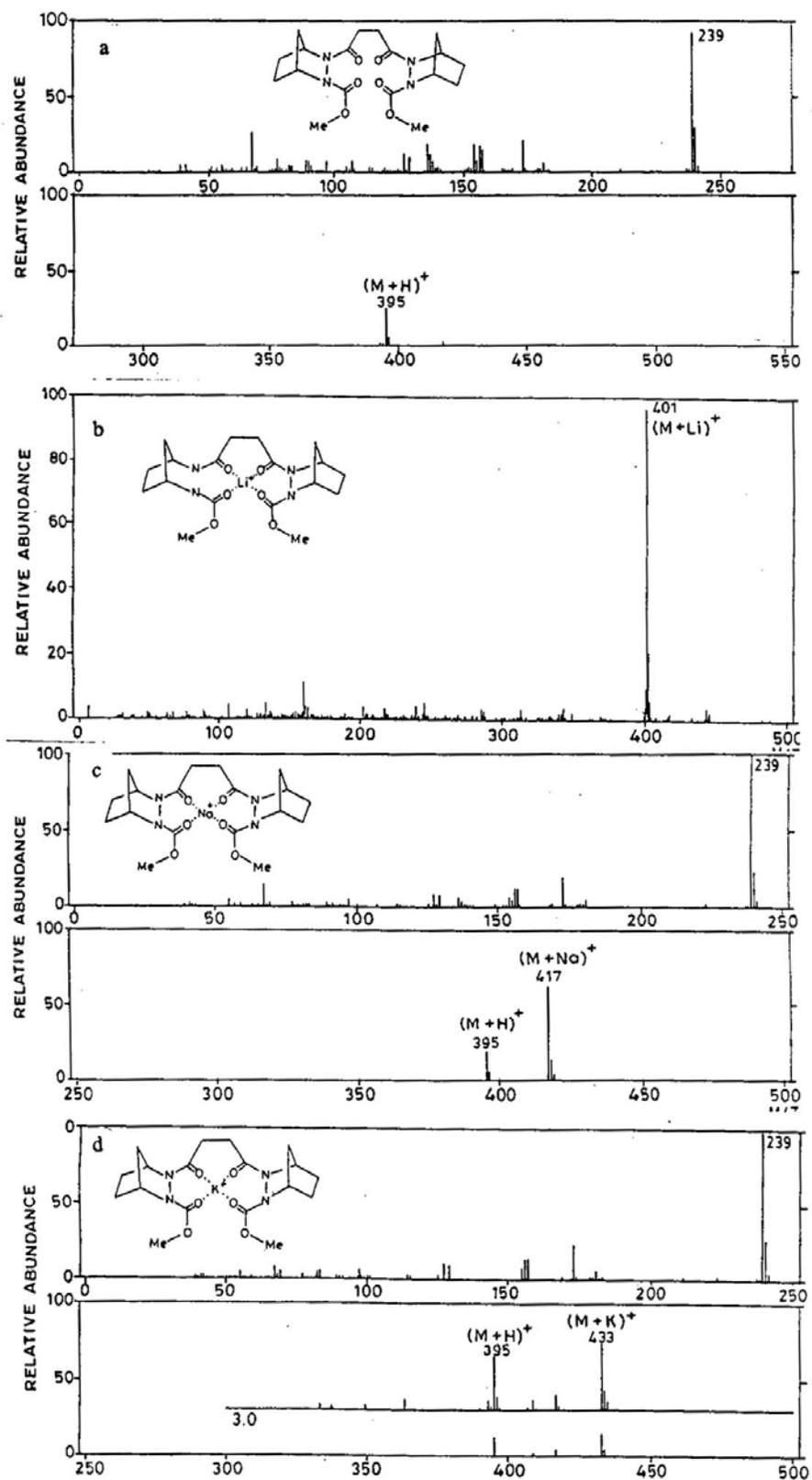
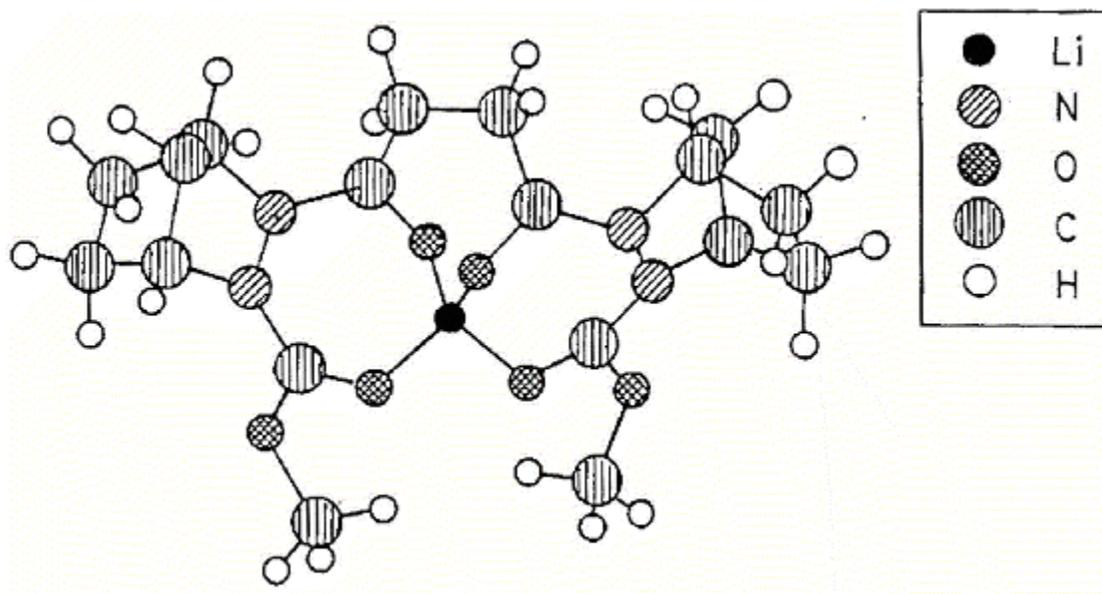


Figure 1. Ion complexation with 5.



**Figure 2.** DTMM Profile of the lithium complex with 5.

The actual isolation of the lithium complexes from **3** and **5** seem to support this view.

## Experimental Section

**General Procedures.** Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 580/1600 FT instrument either as neat liquids or as KBr pellets. Only prominent IR peaks are reported.  $^1\text{H}$  NMR spectra were obtained on WM 400 Bruker, WP 80 Bruker and Hitachi R 600 at 60 MHz, in  $\text{CDCl}_3$  unless otherwise stated. The chemical shifts are recorded in ppm with TMS at 0.00 as the internal standard. FAB mass spectra were recorded on a JEOL SX-120/DA-6000 double focusing mass spectrometer with reverse geometry using 6kv argon beam (10mA). The accelerating voltage was 10 Kev and the spectra were recorded at room temperature with *m*-nitro benzyl alcohol as the matrix. Elemental analysis was carried out in automatic C, H, N analyzers. Silica gel G (Merck) was used for TLC and column chromatography was done on silica gel (acme, 100-200 mesh) columns, which were made from slurry in hexane or benzene. Reactions were monitored whenever possible by TLC. The organic extracts were dried over anhydrous  $\text{MgSO}_4$  and the solvents evaporated *in vacuo*. Ether and benzene were dried using Na-benzophenone ketyl method. Dry alcohol was prepared by Na-diethyl phthalate method.

$\alpha$ -Chloro- $\alpha$ -nitrosocyclohexane<sup>6</sup> and 2,3-dimethyl-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate<sup>7</sup> were prepared according to literature procedures and adequately characterized.

**Table 1.** The FAB Mass spectra of metal complexes <sup>a</sup>

No	Parent	Li	Na	K	Ag
3	277(M+H) <sup>+</sup> (34)	283(M+Li) <sup>+</sup> (100) 277(M+H) <sup>+</sup> (9)	299(M+Na) <sup>+</sup> (100) 277(M+H) <sup>+</sup> (29)	315(M+K) <sup>+</sup> (17) 277(M+H) <sup>+</sup> (26)	383, 385(M+Ag) <sup>+</sup> (16) 277(M+H) <sup>+</sup> (49)
5	395(M+H) <sup>+</sup> (28)	401(M+Li) <sup>+</sup> (100) 395(M+H) <sup>+</sup> (~0)	417(M+Na) <sup>+</sup> (63) 395(M+H) <sup>+</sup> (26)	433(M+K) <sup>+</sup> (43) 395(M+H) <sup>+</sup> (34)	
4	361(M+H) <sup>+</sup> (100)	367(M+Li) <sup>+</sup> (100) 361(M+H) <sup>+</sup> (16)	383(M+Na) <sup>+</sup> (59) 361(M+H) <sup>+</sup> (84)	399(M+K) <sup>+</sup> (62) 361(M+H) <sup>+</sup> (100)	
7	479(M+H) <sup>+</sup> (36)	485(M+Li) <sup>+</sup> (100) 479(M+H) <sup>+</sup> (1)	501(M+Na) <sup>+</sup> (37) 479(M+H) <sup>+</sup> (14)	517(M+K) <sup>+</sup> (54) 479(M+H) <sup>+</sup> (29)	585, 587(M+Ag) <sup>+</sup> (13) 479(M+H) <sup>+</sup> (51)
6	409(M+H) <sup>+</sup> (40)	415(M+Li) <sup>+</sup> (100) 409(M+H) <sup>+</sup> (1)	431(M+Na) <sup>+</sup> (100) 409(M+H) <sup>+</sup> (14)	447(M+K) <sup>+</sup> (100) 409(M+H) <sup>+</sup> (40)	

<sup>a</sup>  $m/z$  values with percentage abundance.

**2-Oxa-3-azabicyclo[2.2.1]hept-5-ene hydrochloride (1).** Freshly cracked and dry cyclopentadiene (22.4 g, 340 mmol) was added at once to a stirred and ice cooled solution of chloronitroso cyclohexane (5.5 g, 37mmol) in ether: EtOH = 80: 15 mL. The reaction mixture was left stirred for 3 h during which the blue color of the reaction mixture completely disappeared. The separated white crystalline hydrochloride was filtered under dry nitrogen atmosphere, washed with ether and dried *in vacuo*. Yield: 30 mmoles, 4.0 g (82%). mp: 82-83 °C. Anal.Calcd.for C<sub>5</sub>H<sub>8</sub>ClNO (M.W.133.5): C, 44.94; H, 5.99%. Found: C, 45.19; H, 5.70%. ir:  $\nu_{max}$  (KBr) cm<sup>-1</sup>: 3300 (br, NH). <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>): 6.95, 6.75 (m, m, 2H, -CH=CH-), 5.75 (s, 1H, 1-H), 5.35 (s, 1H, 4-H), 2.35 (m, 2H, -CH-CH<sub>2</sub>-CH-).

**3-[4-(2-Oxa-3-azabicyclo[2.2.1]hept-5-en-3yl)-4-oxobutanoyl]-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (3).** To an ice cooled and stirred solution of **1** (3 g, 22.56 mmol) and triethylamine (2.95 g, 29.2 mmol) in benzene (20 mL) was added, in drops, succinoyl chloride (2.8 g, 18.06 mmol) in benzene (15 mL) followed by another lot of triethylamine (2.95 g, 29.2 mmol) in benzene (15 mL). The reaction mixture was left stirred for 5 h, the organic layer washed with water (2 x 10 mL), dried and solvents evaporated *in vacuo*, leaving a dark colored material which was purified by Soxhlet extraction with EtOAc to give **3** as a white powder. Yield: 6.7 mmol, 1.85 g, 60%. mp: 110° C. Anal.Calcd.for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (M.W.276): C, 60.87; H, 5.79; N, 10.14%. Found:

C, 60.59; H, 6.05; N, 9.74%. ir:  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 2963, 1700, 1688, 1661, 1381, 1330, 1240.  $^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ): 6.53, 6.38 (m, m, 4H,  $-\text{CH}=\text{CH}-$  x 2), 5.31 (m, 1H, 4H x 2), 2.56 (m, 4H,  $-\text{OC}-\text{CH}_2-\text{CH}_2-\text{CO}-$ ), 2.00 (m, 4H,  $-\text{CH}-\text{CH}_2-\text{CH}-$  x 2). ms: (FAB)  $m/z$  277 ( $\text{M}+\text{H}$ ) $^+$  (34%).

**3-[4-(2 Oxa-3-azabicyclo[2.2.1]hept-5-en-3-yl)-4-oxobutanoyl]-2 oxa-3-azabicyclo[2.2.1]hept-5-ene (3) – lithium nitrate complex.** A solution of **3** (0.014 g, 0.05 mmol) in dry THF-DMSO, was admixed with lithium nitrate (0.05 g, 0.075 mmol), left stirred at rt for 3 h, solvents evaporated and the residue triturated with water to afford the complex as fine needles in quantitative yields. Mp. (dec.) FAB-MS: 283 ( $\text{M}+\text{Li}$ ) $^+$  (100 %); 277 ( $\text{M}+\text{H}$ ) $^+$  (< 1%).

**3-[10-(2Oxa-3-azabicyclo[2.2.1]hept-5-en-3-yl)-10-oxodecanoyl]-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (4).** To an ice cooled and stirred suspension of **1** (2 g, 14.93 mmol) in dry benzene (15 mL) was added triethylamine (4.2 g, 41.58 mmol). After 5 min a solution of sebacyl chloride (1.78 g, 7.47 mmol) in dry benzene (15 mL), was introduced in drops, over 0.5 h, admixed with another batch of triethylamine (2.1 g, 20.79 mmol) and left stirred at  $\sim 0-5^\circ\text{C}$  for 4 h. Solvents were evaporated *in vacuo* and the crude product after column chromatography using PhH: EtOAc (10:1) afforded **4** as a semisolid. Yield: 3.9 mmol, 1.4 g, 52%. Anal. Calcd. for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4$  (M.W.360): C, 66.67; H, 7.78; N, 7.78 %. Found: C, 66.59; H, 7.38; N, 8.01 %. ir:  $\nu_{\max}$  (neat)  $\text{cm}^{-1}$ : 2929, 1729, 1652, 1443, 1327, 1245.  $^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ): 6.53, 6.38 (m, m, 4H,  $-\text{CH}=\text{CH}-$  x 2), 5.25 (m, 1H, 4H x 2), 2.22 (m, 4H,  $-\text{CO}-\text{CH}_2-$  x 2), 1.88 (m, 4H,  $-\text{CH}-\text{CH}_2-$  x 2), 1.28 (m, 12H,  $-\text{CO}-\text{CH}_2-$  ( $\text{CH}_2$ ) $_6$ - $\text{CH}_2-\text{CO}-$ ). ms: (FAB)  $m/z$ : 361 ( $\text{M}+\text{H}$ ) $^+$  (100%).

**2,3-Dimethyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate.** A solution of 2,3-dimethyl-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (3.5g, 16.36 mmol) in dry methanol (20 mL) containing a few drops of acetic acid was hydrogenated over catalytic amount of Pd (0) /C (5%) under a positive pressure of hydrogen till the absorption of hydrogen ceased ( $\sim 10$ h). It was filtered to remove catalyst and solvents evaporated to give 2,3-dimethyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate, as a thick liquid. Yield: 16 mmoles, 3.40g, (96%). ir:  $\nu_{\max}$  (neat)  $\text{cm}^{-1}$ : 2946, 1746, 1443, 1338 1279, 1169, 1115.  $^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ): 4.55 (m, 2H, 1H, 4H), 3.84 (s, 6H, ester), 1.75 (m, 6H,  $-\text{CH}-$ ( $\text{CH}_2$ ) $_2$ - $\text{CH}-$  and  $-\text{CH}-\text{CH}_2-\text{CH}-$ ).

**Methyl -2,3-diazabicyclo[2.2.1]heptane-2-carboxylate (2).** A solution of the hydrogenated compound from above (1 g, 4.67 mmol) in methanolic KOH (0.23 g, 4.13 mmol KOH in 0.9 mL dry MeOH) was refluxed under nitrogen atmosphere for 5h. It was cooled to rt, the precipitated  $\text{K}_2\text{CO}_3$  filtered, the filtrate evaporated nearly to dryness, extracted with ether, solvents dried and evaporated *in vacuo* to give **2** as a viscous liquid. Yield: 3.8 mmoles, 0.6g (82%). ir:  $\nu_{\max}$  (neat)  $\text{cm}^{-1}$ : 3208, 2954, 1696, 1595.  $^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ): 4.56 (m, 1H, 4H), 3.75 (s, 3H, ester), 1.72 (m, 6H,  $-\text{CH}-$ ( $\text{CH}_2$ ) $_2$ - $\text{CH}-$  and  $-\text{CH}-\text{CH}_2-\text{CH}-$ ).

**Methyl 3-[4-(2-methoxycarbonyl-2,3-diazabicyclo[2.2.1]hept-3-yl)-4-oxobutanoyl] -2,3-diazabicyclo[2.2.1]heptane-2-carboxylate (5).** To an ice cooled and stirred solution of **2** (1.0 g, 6.4 mmol) and triethylamine (1.3 g, 12.8 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) was added, in drops, succinoyl chloride (0.50 g, 3.3 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) over a period of 10 min, left stirred for 10 h, at  $\sim 0-5^\circ\text{C}$ , diluted with ethyl acetate (25 mL), washed with water, dried and solvents evaporated *in vacuo* leaving a dark colored material which was purified by Soxhlet extraction

using EtOAc to give **5** as white crystals. Yield: 1.6 mmol, 0.63 g, 50%. mp: 168<sup>o</sup>C. Anal.Calcd.for C<sub>18</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub> (M.W.394): C, 54.82; H, 6.60; N, 14.21%. Found: C, 55.20; H, 6.45; N, 14.12%. ir:  $\nu_{max}$  (KBr) cm<sup>-1</sup>: 2954, 1732, 1667, 1651, 1284. <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>): 4.69 (m, 1H, 4H x 2), 3.81 (s, 6H, ester), 2.69 (m, 4H, -OC-CH<sub>2</sub>-CH<sub>2</sub>-CO-), 1.84 (m, 12H, -CH- (CH<sub>2</sub>)<sub>2</sub>-CH- x 2 and -CH-CH<sub>2</sub>-CH- x 2). ms: (FAB) *m/z*: 395 (M+H)<sup>+</sup> (28%).

**Methyl 3-[4-(2-methoxycarbonyl-2,3-diazabicyclo[2.2.1]hept-3-yl)-4-oxobutanoyl]-2,3-diazabicyclo[2.2.1]heptane-2-carboxylate (5) – lithium nitrate complex.** A solution of **5** (0.020 g; 0.05 mmol) in dry THF-DMSO was admixed with lithium nitrate (0.05 g; 0.075 mmol), left stirred at rt for 3 h, solvents evaporated and the residue triturated with water to afford the complex as fine needles in quantitative yields. Mp. (dec.) FAB-MS: 401(M+Li) (100 %); 395(M+H)<sup>+</sup> (< 1 %).

**Methyl 3-[5-(2-methoxycarbonyl-2,3-diazabicyclo[2.2.1]hept-3-yl)-5-oxopentanoyl]-2,3-diazabicyclo[2.2.1]heptane-2-carboxylate (6).** To an ice cooled and stirred solution of **2** (0.20 g, 1.33 mmol) and triethylamine (0.29 g, 2.88 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added, in drops, glutaroyl chloride (0.112 g, 0.67 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) over a period of 10 min. The mixture was left stirred at ~-5 °C for 24h, solvents evaporated *in vacuo*, and the crude product chromatographed over silica gel. Elution with PhH: EtOAc (85:15) gave **6**, as a white solid. Yield: 0.34 mmol, 0.14 g, 52%. mp: 143-145<sup>o</sup>C. Anal.Calcd.for C<sub>19</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub> (M.W.408): C, 55.88; H, 6.86; N, 13.73%. Found: C, 55.60; H, 6.48; N, 13.98 %. ir:  $\nu_{max}$  (KBr) cm<sup>-1</sup>: 2956, 1734, 1665, 1428, 1263, 1154. <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>): 4.81, 4.63 (m, 1H, 4H x 2), 3.88 (s, 6H, -ester), 2.50 (t, 4H, -OC-CH<sub>2</sub>- x 2), 2.09-1.47 (m, 14H, -OC-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CO-, -CH-CH<sub>2</sub>-CH<sub>2</sub>-CH- x 2 and CH-CH<sub>2</sub>-CH- x 2). ms: (FAB) *m/z*: 409 (M+H)<sup>+</sup> (40%).

**Methyl 3-[10-(2-methoxycarbonyl-2,3-diazabicyclo[2.2.1]hept-3-yl)-10-oxodecanoyl]-2,3-diazabicyclo[2.2.1]heptane-2-carboxylate (7).** To an ice cooled and stirred solution of **2** (1.0 g, 6.4 mmol) and triethylamine (1.3 g, 12.8 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added, in drops, sebacoyl chloride (0.77 g, 3.28 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL), over a period of 15min, followed by another lot of triethylamine (0.65 g, 6.4 mmol). The mixture was left stirred at ~-5 °C for 24 h, solvents evaporated *in vacuo*, and the crude product chromatographed over silica gel. Elution with PhH: EtOAc (85:15) afforded **7**, as a gummy material. Yield: 1.26 mmol, 0.6 g, 39%. Anal.Calcd.for C<sub>24</sub>H<sub>38</sub>N<sub>4</sub>O<sub>6</sub> (M.W.478): C, 60.25; H, 7.95; N, 11.72%. Found: C, 60.51; H, 7.45; N, 11.52 %. ir:  $\nu_{max}$  (KBr) cm<sup>-1</sup>: 2930, 1738, 1668, 1441, 1277, 1168. <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>): 4.78, 4.66 (m, 1H, 4H x 2), 3.81 (s, 6H, ester), 2.34 (t, 4H, -CO-CH<sub>2</sub>- x 2), 2.00-1.00 (m, 24H, -OC-CH<sub>2</sub>- (CH<sub>2</sub>)<sub>6</sub>-CH<sub>2</sub>-CO-, -CH- (CH<sub>2</sub>)<sub>2</sub>-CH- x 2 and -CH-CH<sub>2</sub>-CH- x 2). ms: (FAB) *m/z*: 479 (M+H)<sup>+</sup> (36%).

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