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Synthesis of Aza-1,2-thiophenophanes by Double Ring Enlargement

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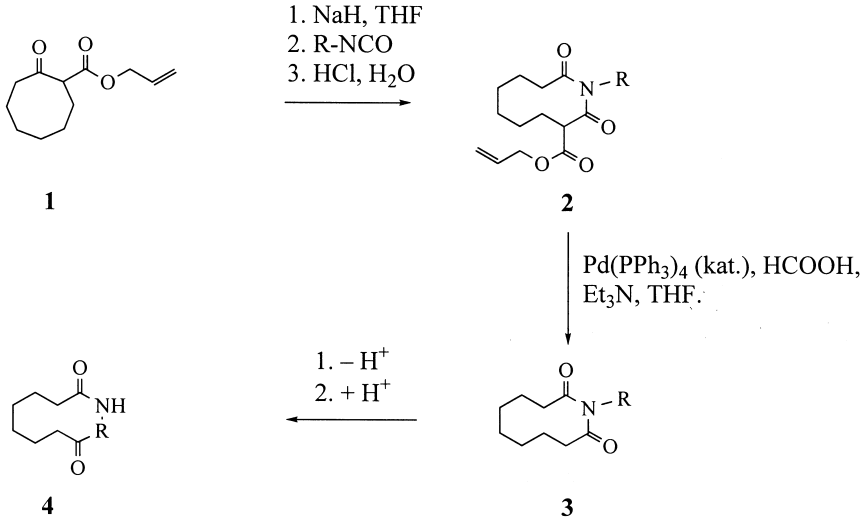
Abstract—Two ring enlargement reactions are used to transform the alicyclic 8-membered allyl 2-oxocyclooctane-1-carboxylate (**11**) to the 13-membered 10-aza-[11]-(2,3)-thiophenophane-1,9-dione (**17**). The first step yielded the macrocyclic imide allyl *N*-(3-thienylmethyl)-2,10-dioxo-1-azacyclodecane-3-carboxylate (**15**) and, after deprotection, *N*-(3-thienylmethyl)-1-azacyclodecane-2,10-dione (**16**). In the second step the *N*-thienyl substituent is incorporated in the large ring by the use of LDA. The overall yield was 45%. This method was also used to convert the 12-membered allyl 2-oxocyclododecane-1-carboxylate (**20**) to the 17-membered 14-aza-[15]-(2,3)-thiophenophane-1,13-dione (**23**).

Introduction

A well-established method for the synthesis of substituted medium and large ring compounds is the ring enlargement reaction.[1] In quite a number of cases, the syntheses of the corresponding *aza*, *oxa* and *thia* compounds succeed with high yields.

Some years ago, a very powerful reaction was reported where the CH-acidic ketone **1** was treated with base to



Scheme 1.

Keywords: 1,2-thiophenophanes; ring enlargement; isocyanates.

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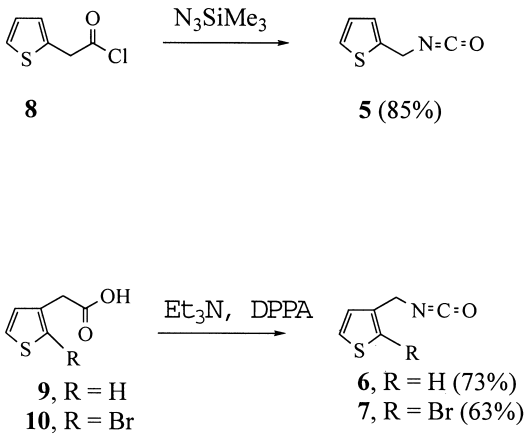
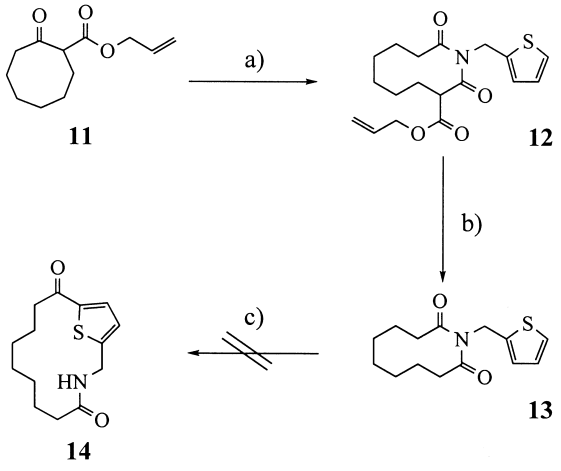


Scheme 2.



Scheme 3. (a) NaH, THF, 2-thienylmethyl isocyanate (**5**), 72%; (b) $Pd(PPh_3)_4$(kat.), HCOOH, Et_3N, THF, 88%; (c) $^nBuLi/^tBuLi$/LDA.

give the corresponding anion which reacts smoothly with isocyanate to form the large-ring imide **2**. For this step, yields between 50 and 95% have been reported, depending on both the ring size of the activated ketone and the nature of the isocyanate substituent R.[2,3] If, after deprotection, the residue R can stabilize the negative charge, a second enlargement reaction is possible and R becomes a member of the new ring. During this process, the imide is changed to amide **4** (see Scheme 1).

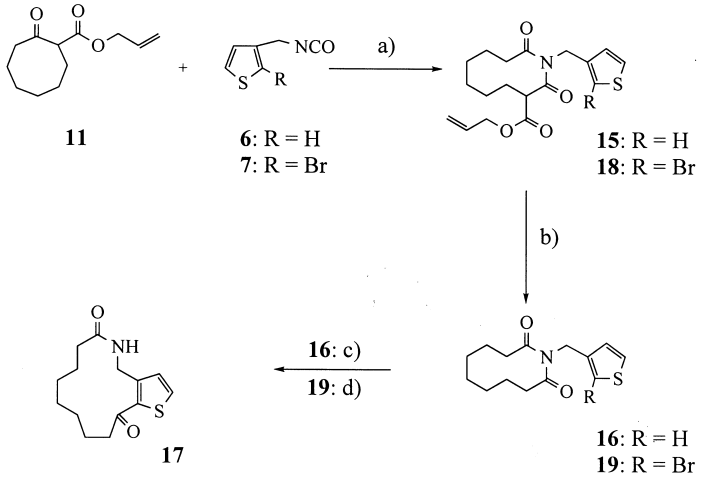
It was of interest to study the possibility of incorporating a thiophene ring into the enlarged ring by this method. Therefore, three thiophene isocyanates were prepared, 2-thienylmethyl isocyanate (**5**), 3-thienylmethyl isocyanate (**6**), and 2-bromo-3-(thienylmethyl) isocyanate (**7**). Compound **5** was synthesized from 2-thienylacetic acid chloride (**8**) by treatment with trimethylsilylazide.[4]

Results and Discussion

Starting from 3-thienylacetic acid (**9**) in the presence of triethylamine and diphenylphosphorylazide (DPPA), 3-thienylmethyl isocyanate (**6**) was formed in 73% yield[5] (see Scheme 2). The corresponding 2-bromo-3-(thienylmethyl) isocyanate (**7**) was prepared in an analogous way to **6** from the 2-bromoacid **10** but in lower yield (63%).

The ring enlargement reaction of the anion of allyl 2-oxocyclooctane-1-carboxylate (**11**) with 2-thienylmethyl isocyanate (**5**) gave in good yield the enlarged product **12** which was decarboxyallylated to give the imide **13**. It was not possible to obtain the 14-membered oxolactam **14** by treatment of the 10-membered imide **13** with *n*-BuLi, *t*-BuLi or lithiumdiisopropylamide (LDA). Decomposition was observed when LDA was used in excess or at higher temperature (see Scheme 3). It is very likely that steric properties are responsible for the negative result in this case.

Therefore, in order to avoid steric hindrance, we tried using the isocyanate **6** in which a hydrogen atom was incorporated at the 2-position and the methyl isocyanate substituent was at the 3-position of the thiophene. The resulting reaction is depicted in Scheme 4. The formation of the 10-membered imide **15** from the 8-membered **11** and the isocyanate **6** proceeded under normal conditions with 72% yield. Decarboxyallylation of **15** formed the imide **16**. Strong IR absorptions at approx. 1690 cm^{-1} are typical of an imide ring. The structure of **16** was confirmed by an X-ray crystallographic analysis (Fig. 1).



Scheme 4. (a) NaH, THF, 72%; (b) $Pd(PPh_3)_4$(kat.), HCOOH, Et_3N, THF, 91%; (c) 4 eq. LDA, THF, −80°C, 4 h, 68%; (d) 1.1 eq. ^nBuLi, Et_2O, hexane, −80°C, 3 h, 72%.

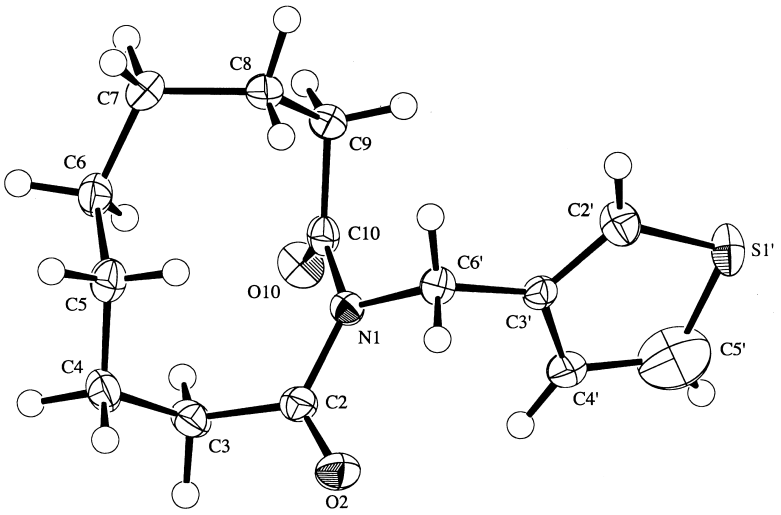


Figure 1. The molecular structure of **16** showing the major conformation of the 5-membered ring (50% probability ellipsoids).

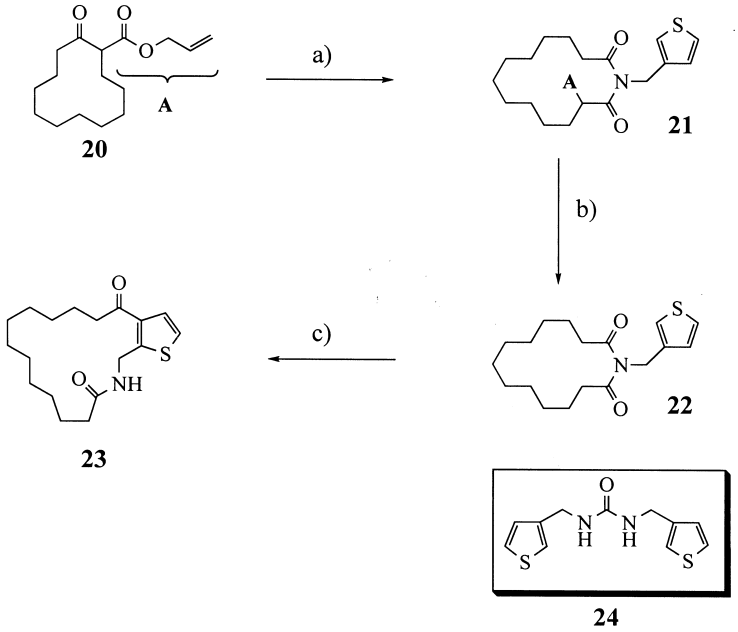
If the anion of compound **16** was formed by treatment of LDA at −80°C in THF, the ring enlargement to the expected 13-membered 10-aza-[11]-(2,3)-thiophenophane-1,9-dione (**17**) took place with a good yield of 68%. The same product was observed when *N*-(2-bromo-3-(thienylmethyl)-1-aza-cyclodecane-2,10-dione (**19**), prepared in an analogous manner via **18** from compound **11** and the bromothienyl isocyanate **7**, was treated at −80°C in diethyl ether with *n*-BuLi (see Scheme 4). Even the yield was similar to that of the non-brominated material.

In a further ring enlargement reaction, 3-thienylmethyl isocyanate (**6**) was used to synthesize the 17-membered **23** in an overall yield of 37% starting from the 12-membered allyl 2-oxocyclododecane-1-carboxylate (**20**, see Scheme 5).

It should be mentioned that when the isocyanate **6** is treated with base, it is converted in variable yield to 3,3′-ureylene-di-(3-methylene-thiophene) (**24**). This is a side reaction observed quite frequently when compound **6** is used as a reactant.

Conclusion

If the substituent R in compound **3** (see Scheme 1) is able to carry a negative charge and if there is no steric hindrance, the ring in these types of imide compounds can easily be enlarged by several atoms depending on the nature of the substituent.



Scheme 5. (a) NaH, THF, 3-thienylmethyl isocyanate (**6**), 68%; (b) $Pd(PPh_3)_4$(kat.), HCOOH, Et_3N, THF, 87%; (c) 4 eq. LDA, THF, −80°C, 4 h, 62%.

Experimental

General

All solvents were distilled prior to their use. Purification of the solvents was performed according to standard methods. Melting points were determined on a Mettler FP-5 instrument. IR spectra ($CHCl_3$) were obtained using a Perkin–Elmer 297 or Perkin–Elmer 781 spectrophotometer; bands are given in cm^{-1}. ^1H NMR spectra were recorded on a Bruker ARX 300 (300 MHz) or Bruker AMX 600 (600 MHz) spectrometer; chemical shifts in δ (ppm) relative to TMS using the appropriate solvent as an internal standard. ^{13}C NMR spectra at 75.47 MHz using a Bruker ARX 300 spectrometer. Chemical shifts are reported as for ^1H and the multiplicities of the signals determined by DEPT experiments with s=singlet, d=doublet, t=triplet, q=quadruplet. EI- and CI-MS: Finnigan SSQ 700 or Finnigan-MAT 90; *m/z* (rel. intensity in %); Electrospray-Ionization (ESI): Finnigan TSQ 700.

2-Thienylmethyl isocyanate (5). A solution of 4.0 g (25.0 mmol) of 2-thienylacetic acid chloride (**8**, Fluka) in 40 ml water free toluene and 3.95 ml (30.0 mmol) of N_3SiMe_3 were refluxed for 2 h. It was evaporated under vacuum and the residue distilled at 80–110°C/15 Torr. The product was not purified further. IR of the raw material: 2260s.

Allyl *N*-(2-thienylmethyl)-2,10-dioxo-1-azacyclodecane-3-carboxylate (12). A solution of 1.0 g (4.8 mmol) of allyl 2-oxocyclooctane-1-carboxylate (**11**),[3] 70 ml water free THF and 250 mg NaH (5.7 mmol, 55% NaH in oil) was stirred for 30 min at room temperature until an orange-yellow color appeared. A solution of 0.79 g (5.7 mmol) **5** in 2 ml THF was slowly added under vigorous stirring. After 1 h it was neutralized with 1N aq. HCl at 0°C, extracted with $CHCl_3$, the extract was dried ($MgSO_4$) and evaporated. The residue gave after chromatography (hexane/EtOAc 4:1) 1.19 g (3.4 mmol, 72%) **12** as a yellowish oil. ^1H NMR: 7.15–7.13 (m, H-C(5′)); 6.91–6.81 (m, H-C(3′), H-C(4′), 2H); 5.87–5.76 (m, C*H*=CH_2); 5.27–4.36 (m, CH=C*H*$_2$, OCH_2, NCH_2, H-C(3), 5H); 2.95–2.86 (m, 1H); 2.45–2.35 (m, 1H); 2.04–1.94 (m, 1H); 1.83–1.74 (m, 2H); 1.63–1.13 (m, 7H). ^{13}C NMR: 180.31 (s, C(2)); 171.91 (s, C(10)); 169.43 (s, COOR); 138.47 (s, C(2′)); 131.64 (d, *C*H=CH_2); 126.67, 126.48, 124.88 (3d, C(3′), C(4′), C(5′)); 117.90 (t, CH=*C*H$_2$); 65.57 (t, OCH_2); 51.52 (d, C(3)); 42.41 (t, NCH_2); 36.99, 28.63, 26.90, 22.82, 22.32, 22.03 (6t, $6CH_2$). CI-MS (NH_3): 367 (10, $[M+NH_4]^+$), 351 (20), 350 (100, $[M+H]^+$).

***N*-(2-Thienylmethyl)-1-azacyclodecane-2,10-dione (13).** To a solution of 600 mg (1.7 mmol) of **12** in 20 ml dry THF was added a mixture of 129 μl of HCOOH, 600 μl of Et_3N and 80 mg Pd $(PPh_3)_4$ in 2.5 ml dry THF. After the formation of carbon dioxide had ceased, the solution was stirred for 1 h and the solvent evaporated. Purification of the residue was done by flash chromatography (hexane/EtOAc 4:1): 400 mg (1.5 mmol, 88%) **13** as a yellow lacquer. IR: 2930s, 2850m, 1710s, 1675s, 1440m, 1360w, 1345m, 1330m, 1265w, 1200br, 1160w, 1140m, 1065w, 1040w, 915m. ^1H NMR: 7.18–7.16 (m, H-C(5′)); 6.94–6.92 (m, H-C(3′)); 6.89–6.86 (m, H-C(4′)); 4.94 (s, NCH_2); 2.76–2.72 (m, (4H); 1.79–1.71 (m, 4H); 1.46–1.35 (m, 6H). ^{13}C NMR: 178.31 (s, 2CO); 139.21 (s, C(2′)); 126.48, 126.38 (2d, C(3′),C(4′)); 125.64 (d, C(5′)); 42.21 (t, NCH_2); 34.32, 24.87, 23.74, 22.20 (4t, $7CH_2$). EI-MS: 266 (23, $[M+H]^+$), 265 (50, $[M]^{+\cdot}$), 238 (16), 237 (100), 208 (12), 194 (28), 180 (19), 166 (31), 152 (26), 112 (38), 111 (17), 110 (12), 97 (78), 55 (17).

3-Thienylmethyl isocyanate (6). To a mixture of 2.0 g (14.1 mmol) of 3-thienylacetic acid (**9**, Fluka) and 15 ml of dry MeCN were added slowly, first 2.1 ml (15.0 mml) of Et_3N and afterwards 3.24 ml (15.0 mml) of DPPA. The deep green colored reaction mixture was heated for 2 h at 55°C and evaporated. The residue was solved in CH_2Cl_2 and two times washed with hexane, dried in vacuo at 35°C: 1.43 g (10.3 mmol, 73%) **6**. It was further purified by distillation (0.04 Torr, 67–88.5°C). IR (measurement in situ): 2265s. ^1H NMR: 7.36–7.34 (m, H-C(2)); 7.23–7.22 (m, H-C(5)); 7.06–7.05 (m, H-C(4)); 4.49 (s, CH_2). ^{13}C NMR: 139.76, 137.84 (2s, C(3), N*C*O); 126.93, 126.23, 122.01 (3d, C(2), C(4), C(5)).

Allyl *N*-(3-thienylmethyl)-2,10-dioxo-1-azacyclodecane-3-carboxylate (15). In accordance with experiment 3, 0.735 g (3.5 mmol) of **7**, 172 mg NaH (3.6 mmol, 55% in oil) and 0.5 g (3.6 mmol) of **6** dissolved in 20 ml of dry THF were treated in a similar way. Purification was done by flash chromatography (hexane/EtOAc 4:1): 1.01 g (2.9 mmol, 72%) **15** as a yellowish oil. IR: 3000w, 2940s, 2860m, 1730s, 1670s, 1510m, 1450m, 1415w, 1370w, 1330w, 1270m, 1165w, 1045w, 990w, 940m, 860w, 830w. ^1H NMR: 7.29–7.26 (m, H-C(3′)); 7.13–7.12 (s, H-C(2′); 7.00–6.98 (m, H-C(4′)); 5.96–5.82 (m, C*H*=CH_2); 5.34–5.19 (m, CH=C*H*$_2$); 4.65–4.47 (m, OC*H*$_2$, NC*H*$_2$, *H*-C(3); 5H); 2.96–2.84 (m, 1H); 2.48–2.39 (m, 1H); 2.15–2.05 (m, 1H); 1.94–1.73 (m, 2H); 1.72–1.16 (m, 7H). ^{13}C NMR: 178.66 (s, C(2)); 171.79 (s, C(10)); 169.33 (s, COOR); 137.76 (s, C(3′)); 131.53 (d, *C*H=CH_2); 127.32, 126.37, 122.37 (3d, C(2′), C(5), C(5′)); 118.60 (t, CH=*C*H$_2$); 65.95 (t, OCH_2); 52.78 (d, C(3)); 42.63 (t, NCH_2); 36.47, 28.71, 26.94, 25.46, 24.23, 22.35 (6t, $6CH_2$). EI-MS: 350 (26, $[M+H]^+$), 349(9, $M^{+\cdot}$), 321 (11), 250 (12), 152 (11), 138 (13), 113 (14), 112 (100), 97 (76), 55 (32).

***N*-(3-Thienylmethyl)-1-azacyclodecane-2,10-dione (16).** The hydrolysis and decarboxylation of 400 mg (1.2 mmol) of **15** was realized in a similar way as given in experiment 4: 87 μl HCOOH, 400 μl Et_3N and 54 mg Pd $(PPh_3)_4$ in 2.5 ml dry THF: 277 mg (1.1 mmol, 91%) **16** as colorless crystals. Mp 84.3–84.5°C. IR: 2920s, 2835m, 1710s, 1675s, 1440m, 1360w, 1345w, 1330m, 1265w, 1200*br*, 1170w, 1145m, 1070w, 1015w, 995w, 965w, 920w, 830w. ^1H NMR: 7.27–7.23 (m, H-C(5′)); 7.12–7.11 (s, H-C(2′)); 6.99–6.97 (m, H-C(4′)); 4.89 (s, NCH_2); 2.75–2.71 (t, *J*=6.3 Hz, 4H); 1.82–1.74 (m, 4H); 1.47–1.30 (m, 6H). ^{13}C NMR: 178.65 (s, C(2), C(10)); 137.77 (s, C(3′)); 126.88, 126.34, 122.23, (3d, C(2′), C(4′), C(5′)); 42.60 (t, NCH_2); 34.38, 24.48, 23.76, 22.26 (4t, $7CH_2$). CI-MS (NH_3): 531 (11), 267 (16), 266 (100, $[M+H]^+$), 265 (27), 237 (38), 166 (11), 112 (25), 97 (27). EI-MS: 265 (15, $[M]^{+\cdot}$), 237 (15), 194 (13), 180 (15), 166 (18), 152 (20), 127 (25), 125 (12), 113 (25), 112 (99), 111 (31), 110 (19),

98 (23), 97 (100), 55 (40). ESI-MS (MeOH): 288 ([M+Na]$^+$), 266 ([M+H]$^+$). ESI-MS/MS (DAU 288, −30 eV, MeOH): 288 (50, [M+Na]$^+$), 97 (100). ESI-MS/MS (DAU 266, −30 eV, MeOH): 266 (17, [M+H]$^+$), 248 (20), 135 (40), 97 (100). Anal. Calcd for $C_{14}H_{19}NO_2S$ (265.37): C 63.37, H 7.22, N 5.28; found: C 63.10, H 7.10, N 5.26.

For the X-ray crystallographic analysis, the sample was crystallized from hexane/diethyl ether.

10-Aza-[11]-(2,3)-thiophenophane-1,9-dione (17). From **16**: To a solution of 130 mg (0.5 mmol) of **16** in 20 ml of dry THF at −80°C, 4.0 equiv. of LDA (350 μl of a 1.4 M solution in hexane) was dropwise with stirring. After 5 h, the yellowish colored solution was quenched by dropwise addition of 1N aq. HCl. It was warmed to room temperature and the mixture extracted with CH_2Cl_2. The solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/MeOH 19:1): 88 mg (0.3 mmol, 68%) of **17** as a colorless lacquer.

From **19**: All additions were performed through the rubber septum using nitrogen-flushed syringes which were rinsed with abs. THF before use. The assembly was flame dried (at 0.02 mbar) and flushed with dry N_2 while cooling. The flask was charged with a solution of **19** (112 mg, 0.325 mmol) in 25 ml THF using a syringe and the solution was cooled to −80°C. A ca. 1.6 M solution of *n*-BuLi in hexane (0.25 ml, 0.4 mmol) was added dropwise through the septum and stirred for 2 h at −80°C. The mixture slowly reached room temperature overnight. The flask was cooled in an ice bath while satd. aq. NH_4Cl solution was added dropwise and the mixture was stirred for 30 min at 0–4°C (still under N_2). Small amounts of H_2O were added to dissolve any precipitates and the mixture was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, evaporated and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 19:1) resulting in 62 mg (72%) of **17**. IR: 3450m, 2995w, 2915s, 2860m, 1660s, 1505s, 1410m, 1380m, 1275m, 1135w, 1020w, 840w. ^{1}H NMR: 7.44 (d, *J*=4.9 Hz, H-C(5′)); 7.20 (d, *J*=4.9 Hz, H-C(4′)); 6.95 (s, NH); 4.53 (d, *J*=6.6 Hz, NCH_2); 2.81–2.77 (m, C*H*$_2$CO); 2.16–2.12 (m, C*H*$_2$NHCO); 1.91–1.83 (m, 2H); 1.60–1.46 (m, 4H); 1.24–1.15 (m, 2H); 1.03–0.96 (m, 2H). ^{13}C NMR: 197.19 (s, CO); 173.13 (s, NHCO); 146.78 (s, C(2′)); 134.93 (s, C(3′)), 132.70 (d, C(5′)); 129.92 (d, C(4′)); 43.59 (t, *C*H$_2$CO); 38.84 (t, NH*C*H$_2$); 35.53 (t, *C*H$_2$NHCO); 28.34, 26.62, 26.41, 25.39, 24.78 (5t, 5CH$_2$). EI-MS: 266 (15), 265 (100, M$^{+\cdot}$), 237 (35), 209 (29), 192 (14), 166 (18), 154 (12), 153 (11), 152 (39), 140 (14), 139 (12), 138 (16), 125 (19), 112 (16), 111 (13), 55 (13), 41 (11). ESI-MS (MeOH): 288 ([M+Na]$^+$), 266 ([M+H]$^+$). ESI-MS/MS (DAU 288, −30 eV, MeOH): 288 (100, [M+Na]$^+$). ESI-MS/MS (DAU 266, −30 eV, MeOH): 266 (40, [M+H]$^+$), 249 (20), 151 (22), 135 (50), 97 (100).

Allyl *N*-(3-thienylmethyl)-2,14-dioxo-1-azacyclotetradecane-3-carboxylate (21). The conversion of 0.68 g (2.6 mmol) of allyl 2-oxocyclododecane-1-carboxylate (**20**)[3] and 0.375 g (2.7 mmol) of **6** to 716 mg (2.9 mmol, 68%) of the yellowish oil of **21** was done in a similar manner to experiment 3 in the presence of 125 mg NaH (2.6 mmol, 55% NaH in oil); IR: 2970s, 2930m, 1740s, 1700s, 1520w, 1460m, 1440m, 1415w, 1370m, 1235w, 1160m, 1140m, 1105w, 1080w, 990m, 940m, 860w, 840w, 690w. ^{1}H NMR: 7.23–7.20 (m, H-C(5′)); 7.07–7.05 (s, H-C(2′)); 6.93–6.91 (m, H-C(4′)); 5.90–5.77 (m, C*H*=CH$_2$); 5.28–5.17 (m, CH=C*H*$_2$); 4.59–4.56 (m, OCH$_2$); 4.54–4.42 (m, NCH$_2$); 4.32–4.27 (m, H-C(3); 2.86–2.76 (m, 1H); 2.43–2.35 (m, 1H); 2.05–1.93 (m, 1H); 1.86–1.74 (m, 2H); 1.55–1.10 (m, 17H). ^{13}C NMR: 176.82 (s, C(2)); 172.71 (s, C(14)); 169.63 (s, COOR); 137.76 (s, C(3′)); 131.86 (d, *C*H=CH$_2$); 126.89, 126.51, 122.31 (3d, C(2′), C(4′), C5′); 118.38 (t, CH=*C*H$_2$); 65.81 (t, OCH$_2$); 52.61 (d, C(3)); 43.15 (t, NCH$_2$); 35.94, 28.92, 26.27, 26.06, 25.97, 25.85, 25.73, 25.17, 24.99, 24.08 (10t, 10CH$_2$). CI-MS (NH_3): 423 (38, [M+NH$_4$]$^+$), 407 (21), 406 (100, [M+H]$^+$), 337 (13).

***N*-(3-Thienylmethyl)-1-azacyclotetradecane-2,14-dione (22).** Analogously to experiment 4, 359 mg (0.9 mmol) of **21**, 67 μl HCOOH, 186 μl Et_3N and 41 mg of Pd (PPh_3)$_4$) in 2 ml dry THF were converted to 248 mg (0.8 mmol, 87%) of **22** as colorless crystals. For flash chromatography hexane/EtOAc 4:1 was used. Mp. 70.5–72.0°C. IR: 2930s, 2860m, 1690s, 1455m, 1370m, 1320w, 1160m, 1135m, 980w, 830w. ^{1}H NMR: 7.29–7.26 (m, H-C(5′)); 7.10–7.08 (m, H-C(2′)); 6.99–6.97 (m, H-C(4′)); 4.90 (s, 2H); 2.78–2.73 (t, *J*=6.6 Hz, 4H); 1.68–1.61 (m, 4H); 1.37–1.27 (m, 14H). ^{13}C NMR: 177.32 (s, C(2), C(10)); 138.34 (s, C(3′)); 126.94, 125.43, 122.04 (3d, C(2′), C(4′), C(5′)); 43.16 (t, NCH$_2$); 36.37, 29.14, 26.13, 25.90, 25.65, 24.64 (6t, 11CH$_2$). CI-MS (NH_3): 322 ([M+H]$^+$). EI-MS: 322 (16, [M+H]$^+$), 321 (83, M$^{+\cdot}$), 294 (16), 293 (90), 196 (30), 183 (11), 166 (18), 138 (13), 137 (13), 113 (29), 112 (83), 111 (28), 110 (14), 98 (13), 97 (100), 81 (11), 69 (13), 57 (21), 55 (29), 54 (11), 43 (14), 41 (30). ESI-MS (MeOH+NaI): 344 ([M+Na]$^+$). ESI-MS/MS (DAU 344, −26 eV, MeOH+NaI): 344 (50, [M+Na]$^+$), 97 (100).

14-Aza-[15]-(2,3)-thiophenophane-1,13-dione (23). A solution of 200 mg (0.6 mmol) of **22** and 10 ml dry THF was treated at −80°C with 4.0 equiv. of LDA (443 μl of a 1.4 M solution in hexane) as described for experiment 8. Yield after flash chromatography (CH_2Cl_2/MeOH 19:1) 123 mg (0.4 mmol, 62%) of **23** as a colorless lacquer. IR: 3440m, 2930s, 2860m, 1655s, 1505m, 1455w, 1410m, 1380w, 1350w, 1270w, 1110w, 905w, 840w. ^{1}H NMR: 7.45 (d, *J*=4.9 Hz, H-C(5′)); 7.23 (d, *J*=4.9 Hz, H-C(4′)); 6.93 (s, NH); 4.52 (d, *J*=6.5 Hz, 2H); 2.93–2.90 (m, 2H); 2.15 (t, *J*=7.3 Hz, 2H); 1.53–1.09 (m, 18H); ^{13}C NMR: 194.73 (s, CO); 173.02 (s, CONHR); 146.24 (s, C(2′)). 136.71 (s, C(3′)); 132.80, 130.00 (2d, C(5′), C(4′)); 40.76, 37.97, 36.82, 29.32, 27.81, 27.46, 27.10, 26.85, 26.43, 26.05, 25.07, 24.21 (12t, 12CH$_2$). CI-MS (NH_3): 323 (19), 322 (100, [M+H]$^+$), 643 (10 [2M+H]$^+$). EI-MS: 322(19, [M+H]$^+$), 321 (100, [M]$^{+\cdot}$), 294 (16), 293 (92), 265 (28), 153 (16), 152 (19), 140 (13), 138 (12), 125 (12), 112 (17), 57 (63), 56 (14), 45 (36), 41 (28). ESI-MS (MeOH/$CHCl_3$ 3:1+NaI): 344 ([M+Na]$^+$), 322 ([M+H]$^+$). ESI-MS/MS (DAU 344, −30 eV, MeOH/$CHCl_3$ 3:1+NaI): 344 (100, [M+Na]$^+$).

3,3′-Ureylene-di-(3-methylenethiophene) (24). This compound was always observed when the isocyanate **6** was treated with base under the conditions given in experiments

6 and 9. The yields are irreproducible. ^{1}H NMR (300 MHz, DMSO-d_6): 7.47–7.44 (m, *H*-C(5)); 7.22 (s, H-C(2)); 7.02 (d, *J*=4.9 Hz, *H*-C(4)); 6.31 (t, *J*=5.8 Hz, N*H*); 4,21 (d, *J*=5.8 Hz, CH_2). ^{13}C NMR (300 MHz, DMSO-d_6): 158,03 (s, CO); 142.00 (s, C(3)); 127.58, 126.32, 121.20 (3d, 3 arom. *C*-H), 38.80 (t, *C*H_2). CI-MS (NH_3): 254 (13), 253 (100, $[M+H]^+$).

2-Bromo-(3-thienyl)-acetic acid (10). A solution of 3.0 g (21.1 mmol) of 3-thienyl acetic acid (**9**) in 40 ml acetic acid and 1.1 ml (21.4 mmol) of Br_2 in 10 ml acetic acid was refluxed for 2 h. After addition of a small amount of $NaHSO_3$, the reaction mixture was poured into 100 ml ice-water at 0°C. It was filtered and the filtrate extracted with $CHCl_3$. After evaporation, the residue was dried in HV: 3.01 g (13.6 mmol, 64.5%) of **10** as a yellowish oil. ^{1}H NMR: 11.66 (s, COO*H*); 7.20 (d, *J*=5.6 Hz, *H*–C(5)); 6.89 (d, *J*=6.1 Hz, *H*–C(4)); 3.64 (s, CH_2). EI-MS: 222, 220 (34, 32, $M^{+\cdot}$), 177, 175 (82, 76, $[M-HCO_2]^{+\cdot}$).

2-Bromo-(3-thienylmethyl) isocyanate (7). According to experiment 5, 2.25 g (10.2 mmol) of **10** in 20 ml MeCN were treated first with 1.6 ml (11.2 mmol) Et_3N, afterwards with 2.3 ml (11.2 mmol) of DPPA and worked up: 1.39 g (6.4 mmol, 63%) of **7**. IR: 2270s.

Allyl *N*-(2-bromo-3-thienyl)-2,10-dioxo-1-azacyclodecane-3-carboxylate (18). The reaction between 0.5 g (2.4 mmol) of **11**, 131 mg NaH (2.8 mmol, 55% NaH in oil) and 0.52 g (2.4 mmol) of **7** in 15 ml dry THF was carried out as described for experiment 6 and gave 0.64 g (1.5 mmol, 63%) of **18** as a yellowish oil. ^{1}H NMR: 7.22 (d, *J*=5.7 Hz, H-C(5′)); 6.88 (d, *J*=5.5 Hz, H-C(4′)); 5.97–5.85 (m, C*H*=CH$_2$); 5.35–5.19 (m, CH=CH_2); 4.67–4.47 (m, OCH$_2$, NCH$_2$, H-C(3), 5H); 3.04–2.93 (m, 1H); 2.47–2.37 (m, 1H); 2.15–1.21 (m, 10H). CI-MS (NH_3): 447, 445 (45, 51, $[M+NH_4]^+$), 446 (12), 431 (17), 430, 428 (87, 100, $[M+H]^+$), 429 (25), 387 (10), 350 (20), 349 (21), 348 (77, $[M-Br]^+$), 313 (13), 309 (14), 236 (11), 228 (14).

***N*-(2-Bromo-3-thienylmethyl)-1-azacyclodecane-2,10-dione (19).** The decarboxyallylation of 0.4 g (1.0 mmol) of **18** was performed according to experiment 4 with 75 μl HCOOH, 350 μl Et_3N and 47 mg Pd $(PPh_3)_4$ in 2 ml dry THF. Chromatography was done with hexane/EtOAc 20:1, colorless crystals. Mp 73.2–75.4°C. IR: 2940s, 2870m, 1710s, 1675s, 1440m, 1410m, 1360m, 1345m, 1330m, 1270w, 1220w, 1165m, 1150m, 1070w, 1020w, 995w, 965w, 915, 820w. ^{1}H NMR: 7.13 (d, *J*=5.7 Hz, H–C(5′)); 6.76 (d, *J*=5.7 Hz, H–C(4′)); 4.70 (s, NCH$_2$); 2.65–2.61 (m, 4H); 1.71–1.54 (m, 4H); 1.35–1.29 (m, 8H). ^{13}C NMR: 178.72 (s, 2CO); 138.86 (s, C(2′)); 127.96 (d, C(5′)); 126.46 (d, C(4′)); 110.01 (s, C(3′)); 41.86 (t, NCH$_2$); 34.37, 24.82, 23.75, 22.24 (4t, 7CH$_2$). CI-MS (NH_3): 363, 361 (52, 60, $[M+NH_4]^+$), 346, 344 (98, 89, $[M+H]^+$), 264 (100, $[M-Br]^+$).

X-Ray crystallographic details for compound 16.[6] $C_{14}H_{19}NO_2S$, M_r=265.37, orthorhombic, space group *Pbca*, *a*=22.111(1), *b*=11.175(1), *c*=11.050(1) Å, *V*=2730.2(4) Å^3, *Z*=8, D_c=1.291 Mg m^{-3}, *F*(000)=1136, *T*=173(1) K, (MoKα)=0.231 mm^{-1}, colorless crystals, dimensions: 0.20×0.32×0.40 mm^3, Rigaku AFC5R diffractometer, graphite-monochromated Mo K_α radiation, λ=0.71073 Å, cell constants from 25 centered reflections, ω–2θ scans, intensities of three standards checked after every 150 reflections, no decay, 2θ range 5–60°, 4749 measured reflections of which 3984 were unique (R_{int}=0.048). The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Structure solution by direct methods using SHELXS-86.[7] The five-membered ring is disordered in that it is mirrored about the line from C(3′) to the mid-point of the S(1′)–C(5′) bond. Two positions were defined for S(1′) and C(5′), so that the site of S(1′) is partially occupied by the alternate position of C(5′) and vice versa. The two orientations are occupied unequally with the major orientation, shown in Fig. 1, contributing to approximately 70% of the total structure. The structure was refined on *F* by full-matrix least-squares methods using TEXSAN.[8] The non-H atoms were refined anisotropically. The position of the H-atom attached to C(5a′) was calculated, all other H-atoms were refined isotropically. The refinement of 258 parameters using 2563 observed reflections with $I>2\sigma(I)$ gave *R*=0.0427, *wR*=0.0357, *S*=1.437, weights: $[\sigma^2(F_o)+(0.005F_o)^2]^{-1}$, max. and min. Δρ=0.23; −0.26 e Å^{-3}.

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References

1. Hesse, M. *Ring Enlargement in Organic Chemistry*, Verlag Chemie: Weinheim, 1991.
2. (a) Ognyanov, V. I.; Hesse, M. *Helv. Chim. Acta* **1989**, *72*, 1522–1526. (b) Ognyanov, V. I.; Hesse, M. *Helv. Chim. Acta* **1990**, *73*, 272–276. (c) Koch, T.; Ognyanov, V. I.; Hesse, M. *Helv. Chim. Acta* **1992**, *75*, 62–68.
3. Koch, T.; Hesse, M. *Helv. Chim. Acta* **1994**, *77*, 819–828.
4. Kricheldorf, H. R. *Synthesis* **1972**, 551–553.
5. (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205. (b) Gilman, J. W.; Otonari, Y. A. *Synth. Commun.* **1993**, *23*, 335–341. (c) Danieli, B.; Lesma, G.; Palmisano, G.; Tollari, S. *Synthesis* **1984**, 353–356. (d) Choshi, T.; Tonari, A.; Yoshioka, H.; Harada, K.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1993**, *58*, 7952–7954. (e) Lyga, J. W. *Synth. Commun.* **1986**, *16*, 163–167. (f) Mironov, V. F. *J. Organomet. Chem.* **1984**, *271*, 207–224.
6. Crystallographic data (excluding structure factors) for the structure of **16** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-145511. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
7. Sheldrick, G. M. *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473.
8. TEXSAN; Single Crystal Structure Analysis Software, Version 5.0. Molecular Structure Corporation, The Woodlands, TX, USA, 1989.