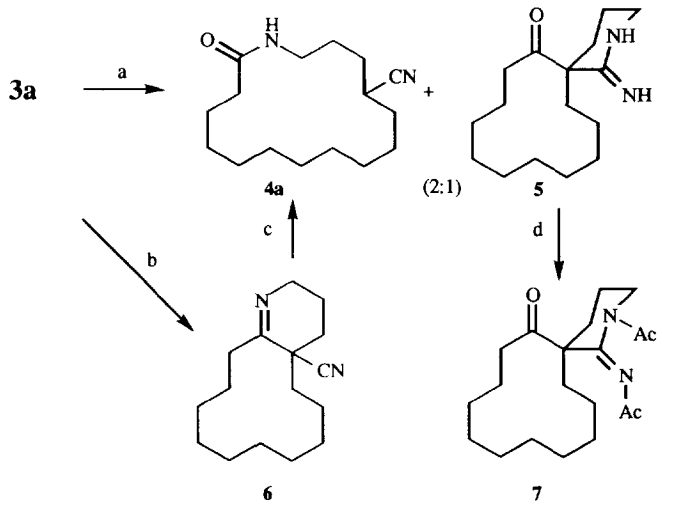
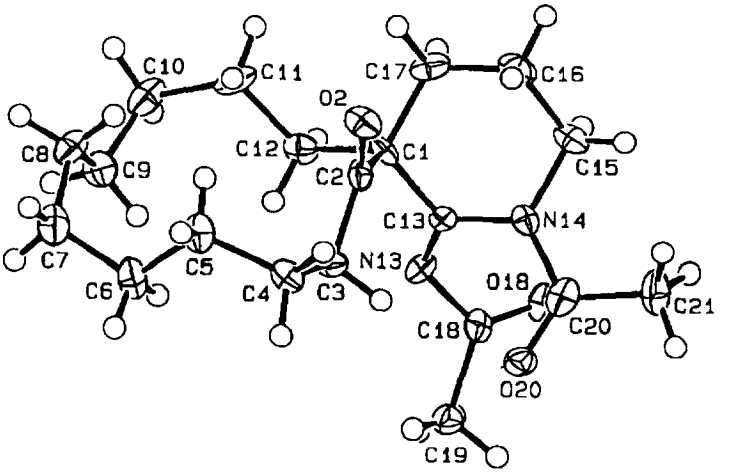
without modifying the ratio **4a/5**. The stable conformation of the 6-membered ring in compound **7** could explain the formation of **5**, as a competitive process, in spite of the driving force of the ring expansion.



a) SmI_2 (3.3 eq.), THF, rt, 2 h, 92%; b) H_2 / Lindlar catalyst, EtOH, rt, 85% or PPh_3,THF, rt, 18 h, 98%; c) 2 N KOH, MeOH, rt, 4 d, 89%; d) $(MeCO)_2O$, pyridine, rt, 12 h, 65%.

Scheme 3



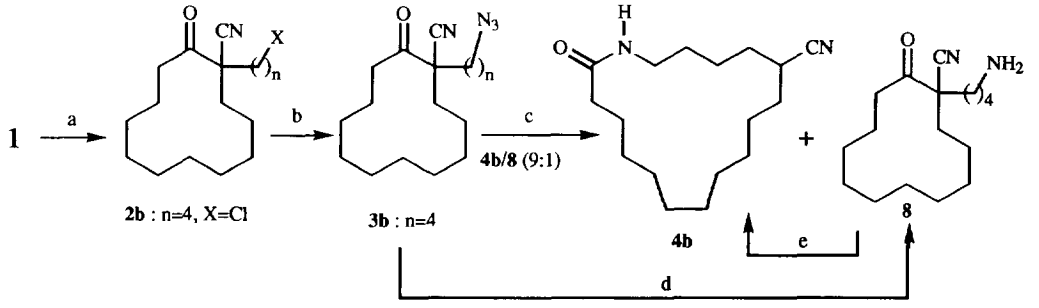
Scheme 4: X-Ray structure of *N*-(2-acetyl-7-oxo-2-azaspiro[5,11]heptadec-1-ylidene)-acetamide (7)

The 16-membered lactam **4a** was prepared from **3a** in two steps by another route for direct comparison. Catalytic hydrogenation of azide **3a** with Lindlar catalyst[16] afforded the bicyclic imine **6** which was hydrolyzed

to the lactam **4a** (Scheme 3). The stability of **6** and the drastic conditions required to obtain **4a** illustrate that the nitrile group is in protic solvent not withdrawing enough to activate the carbonyl group and to induce the direct ring expansion.[2] These results emphasize the advantage of SmI_2 induced ring enlargement of **3a** where no trace of the imine **6** was detected.

As in the case of the samarium Barbier reaction,[9d] the mechanism of our reaction is unclear too. The reduction of the azido group in **3a** by SmI_2[4] can generate an aminyl radical[12] (by loss of N_2) or a transient amido samarium species after reduction of the aminyl radical. These intermediates could cyclize on a samarium(III) activated carbonyl[13,14] to afford **4a** or on a nitrile group[15] to yield **5**. The enhanced reactivity observed in the SmI_2 mediated ring enlargement might be ascribed to the ability of the ketone to chelate samarium ion, thereby facilitating the addition of the nitrogen species to the carbonyl group. We have excluded the hypothesis of the formation of a ketyl radical involved in the ring enlargement reaction because it would lead to the formation of **6**.[14e] Nevertheless, further mechanistic studies are needed to establish whether these two reactions mediated by SmI_2 proceeded by a radical or an anionic mechanism.

We then investigated the enlargement of **1** *via* a 7-membered ring in order to extend this method to larger increments. 2-Oxo-cyclododecane-1-carbonitrile was alkylated with 1-bromo-4-chlorobutane by phase-transfer catalysis[5] to afford compound **2b** in quantitative yield (Scheme 5). The azide **3b** was obtained by nucleophilic substitution of the chloroderivative **2b** with sodium azide.



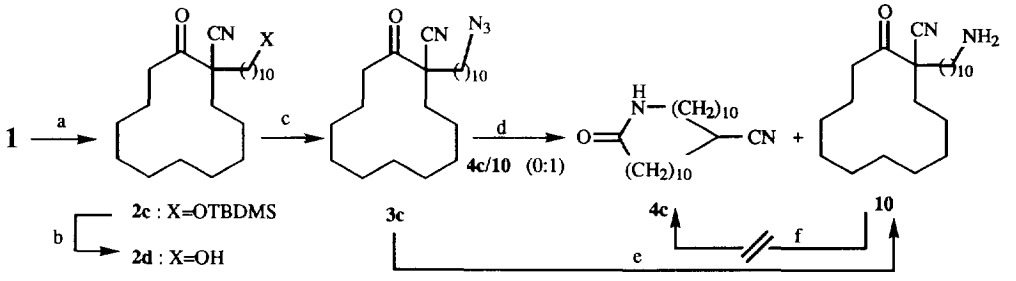
a) Cl-$(CH_2)_4$-Br, Bu_4NHSO_4, 2 N NaOH, CH_2Cl_2, rt, 48 h, quant.; b) NaN_3, DMF, 55°C, 30 h, 88%; c) SmI_2 (3.3 eq.), THF, rt, 2 h, 77%; d) H_2 / Lindlar catalyst, EtOH, rt, 12 h, 75%; e) 2 N KOH, MeOH, rt, 9 d, 63%.

Scheme 5

Treatment of the azide **3b** with SmI_2 (3.3 equiv.) in THF afforded the desired 17-membered lactam **4b** and the reduction product, the amine **8**. It is noteworthy that in this case, ring enlargement reaction is competitive with simple reduction of the azide and not with the cyclization on the nitrile group (7-exo Dig). Attempts to minimize the formation of directly reduced product **8** by performing the reaction in high dilution conditions, with a slow addition of SmI_2 or by catalyzing the reaction with tris-(dibenzoylmethido)iron (III) ($Fe(DMM)_3$)[14a] were unsuccessful. For the sake of comparison, the lactam **4b** was prepared by a non-radical process. The azide **3b** was hydrogenated with Lindlar catalyst to afford the primary amine **8**. Treatment of **8** with 2 N KOH/methanol

at room temperature for 9 days afforded the ring-expanded product **4b**. These drastic conditions and the low ring expansion rate demonstrated the efficiency of the SmI_2 methodology.

A final study was conducted to investigate whether SmI_2 could promote ring-expansion of azide **3** with a longer chain (n=10) (Scheme 6). The commercial 10-bromo-1-decanol was protected as its *tert*-butyldimethylsilyl ether **9** and the latter was used to alkylate 2-cyanocyclododecanone **1** under phase transfer conditions. The silyl group of **2c** was removed with fluoride ion and the resulting alcohol **2d** was converted to the azide **3c** by reaction with mesyl chloride and sodium azide.



a) Br-$(CH_2)_{10}$-OTBDMS **9**, Bu_4NHSO_4, 2 N NaOH, rt, 5 d, 81%; b) TBAF, THF, rt, 6 h, 84%; c) $MeSO_2Cl$, Et_3N, toluene, 0°C, 40 min then Bu_4NBr, NaN_3, 60°C, 24 h, 88%; d) SmI_2 (3.3 eq.), THF, rt, 2 h, 80%; e) H_2/Lindlar catalyst, rt, 12 h, 60%; f) 2N KOH, MeOH or KH/[18]crown-6/DME or $NaHCO_3$/ H_2O/MeOH.

Scheme 6

Azide **3c** was treated with SmI_2 (3.3 equiv.) in THF but did not yield the desired 23-membered lactam **4c**. The amine **10** was the sole compound obtained in 80% under these conditions. Attempts to promote the ring enlargement reaction by heating the reaction mixture in THF under reflux, by slow addition of SmI_2 or by performing the reaction in the presence of hexamethylphosphoric triamide (HMPA)[14e,17] did not allow us to detect the desired product **4c**. No reaction occurred when the primary amine **10** was treated by different bases[2] (KOH/methanol, $NaHCO_3$/methanol or KH/[18]crown-6/DME). The use of sodium hydride led to a partial decomposition of the starting material. These failures demonstrate that the SmI_2 promoted ring enlargement process is limited by entropic factors. Therefore, the 13-membered bicyclic intermediate of this reaction cannot be formed. Nevertheless, this case underlines the efficient selectivity reduction of **3c** by SmI_2 compared to hydrogenation/ *Lindlar* catalyst method.

In conclusion, we have described the first ring expansion of azidoketones promoted by SmI_2. This method is efficient and mild in the synthesis of 16- and 17-membered ring lactams. Further generalization of these observations are the object of ongoing investigations.

EXPERIMENTAL

Reagents were purchased from Fluka. THF was freshly distilled over sodium and benzophenone. HMPA was distilled from calcium hydride and stored under argon. Samarium diiodide was prepared according to the method of Kagan.[18]

TLC was performed on Merck aluminium sheets coated with silica gel 60 F_{254}. Column chromatographies were performed with silica gel 60 (230-400 mesh, Merck).

^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker AC 300 n.m.r. spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin Elmer IR-297 spectrometer. Mass spectra (MS) were obtained using a Finnigan SSQ 700 or Finnigan MAT 90; Chemical ionization (CI) utilizing NH_3 as reactant gas and electronic impact (EI) operated with 70 eV.

Melting points were determined on a Mettler FP-5 instrument.

Starting materials available by literature methods: ***2-Oxo-cyclododecane-1-carbonitrile (1)***[5]***; 1-(3-Hydroxypropyl)-2-oxo-cyclododecane-carbonitrile (2a)***[6,7]**.**

1-(3-Azidopropyl)-2-oxo-cyclododecanecarbonitrile **(3a):** To a stirred solution of the alcohol **2a** (3.45 g, 13 mmol) and NEt_3 (1.81 mL, 13 mmol) in toluene (56 mL) was added methanesulfonyl chloride (1 mL, 13 mmol), under nitrogen, at 0°C. After stirring for 40 min, Bu_4NBr (792 mg, 2.6 mmol) and a solution of NaN_3 (7 g, 109 mmol) in water (28 mL) were added. The reaction was heated to 60°C for 24 h. After cooling at room temperature, the reaction mixture was diluted with ether (300 mL) and washed with brine. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. Purification by chromatography (silica gel, CH_2Cl_2 gave **3a** as a white solid (3.36 g, 89%) mp 67.0-67.9 °C (ether/hexane). IR ($CHCl_3$) 2235 (CN), 2100 (N_3), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.15-2.12 (*m*, 22 H), 2.64-2.92 (*m*, 2 H, CH_2CO), 3.37 (*t*, J = 6.0 Hz, 2 H, CH_2N_3) ppm; δ_C (75 MHz, $CDCl_3$) 20.67, 21.37, 22.26, 22.43, 22.72, 23.51, 25.13, 26.23, 26.27, 31.06, 35.07, 35.25, 50.99 (CH_2N_3), 54.82 (*C*CN), 120.09 (CN), 203.55 (C=O) ppm; Cl-MS m/z 291 $[M+H]^+$; Anal. calc. for $C_{16}H_{26}N_4O$: C 66.17, H 9.02, N 19.29; found C 66.35, H 9.16, N 19.38.

12-Cyano-15-pentadecanelactam **(4a)** ***and 1-Imino-2-aza-spiro[5,11]heptadecan-7-one*** **(5):** To a 0.1 M solution of SmI_2 in THF (18.5 mL, 1.85 mmol) was added dropwise a well-degassed solution of **3a** (163 mg, 0.561 mmol) in THF (1 mL), under argon, at room temperature. After stirring for 2 h, the reaction mixture was quenched with a 4 M solution of K_2CO_3. The aqueous layer was extracted with $CHCl_3$ (3X) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (silica gel, ethyl acetate/hexane 4:1 to $CHCl_3$/MeOH/ammonia water 25% 90:10:0.5) gave first the ring enlargement product **4a** (92 mg, 62%) and then the amidine **5** (44 mg, 30%).

4a: mp 50-50.5°C (ethyl acetate/hexane); IR ($CHCl_3$) 3620 (NH), 3450 (NH), 2240 (CN), 1665 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.12-1.71 (*m*, 22 H), 2.05-2.22 (*m*, 2 H, CH_2CO), 2.61 (*p*, J = 6.0 Hz, 1 H, *C*HCN), 3.11-3.22 (*m*, 1 H, CH_2NHCO), 3.44-3.61 (*m*, 1H, CH_2NHCO) ppm; δ_C (75 MHz, $CDCl_3$) 22.72, 23.51, 25.03, 25.50, 25.71, 25.78, 26.92, 27.27, 27.41, 27.80, 28.11, 29.72, 30.59, 31.96, 36.56, 37.81, 122.42

(CN), 173.51 (NHC=O) ppm; EI-MS m/z 264 $[M]^{+\bullet}$; Anal. calc. for $C_{16}H_{28}N_2O$: C 72.68, H 10.67, N 10.59; found C 72.49, H 10.51, N 10.34.

5: IR ($CHCl_3$) 3320 (NH), 3240 (NH), 1710 (CO), 1660 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.12-2.02 (*m*, 20 H), 2.32-2.61 (*m*, 3 H), 3.03-3.17 (*m*, 1H), 3.28-3.52 (*m*, 2 H), 8.30, 8.98 and 9.43 (3*s*, 2H, NH) ppm; δ_C (75 MHz, $CDCl_3$) 17.77, 19.87, 21.36, 22.21, 22.74, 23.26, 25.56, 26.15, 26.23, 34.55, 35.24, 40.84 (CH_2CO), 54.93 (*C*CN), 168.39 (C=N), 204.90 (C=O) ppm; CI-MS m/z 265 $[M+H]^+$; Anal. calc. for $C_{16}H_{28}N_2O$: C 72.68, H 10.67, N 10.59; found C 72.91, H 10.88, N 10.72.

1-Cyano-13-azabicyclo[10.4.0]hexadec-12-ene (6):

Method A: A solution of **3a** (300 mg, 1.03 mmol) in ethanol (40 mL) was stirred with Lindlar catalyst (100 mg, 5% $Pd/CaCO_3$) under 1 atm of hydrogen for 2 h. The catalyst was filtered off, and the filtrate was concentrated under vacuum. Purification by flash chromatography (silica gel, ethyl acetate/hexane 2:3) gave **6** as a colorless oil.

Method B: A solution of **3a** (171 mg, 0.589 mmol), PPh_3 (193 mg, 0.736 mmol) in THF (2 mL) was stirred for 18 h at room temperature under nitrogen. After removal of the solvent the residue was taken up in ether, washed successively with water, brine and then dried (Na_2SO_4). After evaporation under vacuum, the crude product was purified by flash chromatography (silica gel, ethyl acetate/hexane 2:3) to provide **6** (142 mg, 98%) as a colorless oil. IR ($CHCl_3$) 2235 (CN), 1660 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.21-2.72 (*m*, 24 H), 3.42-3.86 (*m*, 2 H) ppm; δ_C (75 MHz, $CDCl_3$) 19.54, 21.03, 22.80, 22.98, 23.49, 23.76, 24.13, 25.11, 26.38, 26.70, 28.93, 30.37, 30.61, 30.92, 34.74, 36.02, 38.74, 39.99, 49.16 (CH_2N), 122.39 (CN), 163.02 (C=N) ppm; CI-MS m/z 247 $[M+H]^+$.

4a: A solution of **6** (157 mg, 0.637 mmol), 2 N KOH (3.18 mL, 6.37 mmol) in methanol (3 mL) was stirred at room temperature for 4 days. The reaction mixture was neutralized by addition of 1 N HCl. The methanol was evaporated under reduced pressure and the aqueous phase extracted with chloroform. Flash chromatography (silica gel, ethyl acetate/hexane 4:1) gave **4a** (150 mg, 89%) as a white solid. For characterization, see above.

***N-(2-Acetyl-7-oxo-2-azaspiro[5,11]heptadec-1-ylidene)-acetamide* (7):** A solution of **5** (35 mg, 0.133 mmol) in a (1:1) mixture of acetic anhydride (0.200 mL) and pyridine (0.200 mL) was stirred for 12 h at room temperature. After removal of the solvent, the crude product was purified by flash chromatography (silica gel, ethyl acetate/hexane 3:2) to provide 31 mg of **7**. IR ($CHCl_3$) 1705 (CO), 1685 (NCO), 1675 (NCO)), 1635 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13-2.05 (*m*, 21 H), 2.09 (s, 3 H, CH_3CO), 2.10-2.27 (*m*, 1 H), 2.30 (s, 3 H, CH_3CONC), 2.74 (*dt*, *J* = 4.5 and 12 Hz, 1 H, CH_2N), 3.15-3.48 (*m*, 2H), 3.78 (*dt*, *J* = 4.5 and 12 Hz, 1H, CH_2N) ppm; δ_C (75 MHz, $CDCl_3$) 18.73, 21.43, 21.72, 21.90, 22.44 (CH_3), 22.67, 23.30, 24.54 (CH_3), 26.23, 26.35, 30.19, 33.20, 35.05, 49.16 (CH_2CO), 60.41 (*C*C=N), 169.34 ($NCOCH_3$), 183.23 (C=N*C*OCH_3), 206.96 (C=O) ppm; CI-MS m/z 349 $[M+H]^+$; Anal. calc. for $C_{20}H_{32}N_2O_3$: C 68.93, H 9.26, N 8.04; found C 68.62, H 9.21, N 7.71.

***1-(4-Chlorobutyl)-2-oxo-cyclododecanecarbonitrile* (2b):** To a solution of **1** (3.01 g, 14.5 mmol), 1-bromo-4-chloropropane (1.83 mL, 15.9 mmol) and Bu_4NHSO_4 (0.535 g, 1.59 mmol) in dichloromethane (30 mL), was added 2 N aq. NaOH (8.8 mL, 17.7 mmol). After 48 h at room temperature, the two phases were

separated and the aqueous layer was extracted with dichloromethane (3 x). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (silica gel, chloroform) gave **2b** as a white solid (4.31 g, quant.), mp 84.3-84.7°C (ether/hexane); IR ($CHCl_3$) 2235 (CN), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.21-2.12 (*m*, 22 H), 2.69-2.94 (*m*, 2H, CH_2CO), 3.59 (*t*, *J* = 6 Hz, 2 H, CH_2Cl) ppm; δ_C (75 MHz, $CDCl_3$) 20.71, 21.25, 22.17, 22.43, 22.64, 23.42, 26.11, 26.23, 32.12, 33.11, 34.93, 35.17, 44.07 (CH_2Cl), 55.34 (*C*CN), 120.39 (CN), 203.95 (C=O) ppm; CI-MS m/z 298 $[M+H]^+$; Anal. calc. for $C_{17}H_{28}ClNO$: C 68.55, H 9.47, N 4.70; found C 68.22, H 9.33, N 4.63.

***1-(4-Azidobutyl)-2-oxo-cyclododecanecarbonitrile* (3b):** To a stirred solution of **2b** (2.80 g, 9.40 mmol) in dry DMF (20 mL) was added solid sodium azide (1.22 g, 18.8 mmol), under argon, at room temperature. The reaction mixture was then treated for 30 h at 55°C. After removal of the solvent, the residue was taken up in dichloromethane and the dichloromethane solution was washed successsively with water, and brine, and dried (Na_2SO_4). After evaporation, the residual oil was purified by chromatography (silica gel, dichloromethane) to afford 2.53 g of **3b** as a white solid. mp 43.5-45.3°C (ether/hexane); IR ($CHCl_3$) 2235 (CN), 2100 (N_3), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13-2.12 (*m*, 24 H), 2.63-2.86 (*m*, 2 H, CH_2CO), 3.38 (*t*, *J* = 6 Hz, 2 H, CH_2N_3) ppm; δ_C (75 MHz, $CDCl_3$) 20.72, 21.24, 22.45, 22.60, 22.64, 24.06, 26.11, 26.23, 28.60, 33.39, 34.96, 35.22, 50.84 (CH_2N_3), 55.09 (C quart), 120.15 (CN), 203.69 (C=O) ppm; CI-MS m/z 322 $[M + NH_4]^+$; Anal. calc. for $C_{17}H_{28}N_4O$: C 67.07, H 9.27, N 18.40; found C 67.03, H 9.24, N 18.34.

***12-Cyano-16-hexadecanelactam* (4b) *and 1-(4-Aminobutyl)-2-oxo-cyclododecanecarbonitrile* (8):** To a 0.1 M solution of SmI_2 in THF (21.7 mL, 2.17 mmol) was added dropwise a well-degassed solution of **3b** (200 mg, 0.657 mmol) in THF (1 mL) under argon at room temperature. After stirring for 2 h, the reaction mixture was quenched with a 4 M solution of K_2CO_3. The aqueous layer was extracted with chloroform (3 x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (silica gel, ethyl acetate/hexane 9:1 to chloroform/methanol/ammonia water 25% 85:14:1) gave first the ring enlargement product **4b** (126 mg, 69%) and then the amine **8** (15 mg, 8%).

4b (pale yellow oil): IR ($CHCl_3$) 3420 (NH), 2220 (CN), 1665 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.12-1.73 (*m*, 24 H), 2.10-2.22 (*m*, 2 H, CH_2CO), 2.55 (*p*, *J* = 6.60 Hz, 1 H, *CH*CN), 3.18-3.47 (*m*, 2 H, CH_2NH), 5.75 (*s*, 1 H, NH) ppm; δ_C (75 MHz, $CDCl_3$) 23.55, 24.44, 25.65, 26.64, 26.71, 27.91, 28.14, 29.24, 29.54, 30.20, 30.58, 36.76, 38.80, 122.60 (CN), 173.37 (C=O) ppm; CI-MS m/z 279 $[M+H]^+$; Anal. calc. for $C_{17}H_{30}N_2O$: C 73.33, H 10.86, N 10.06; found C 73.20, H 11.07, N 9.80.

8-Hydrochloride: mp 169.2-169.7 °C (ether/ethanol); IR (KBr) 2240 (CN), 1705 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.14-2.05 (*m*, 24 H), 2.75-2.88 (*m*, 2 H, CH_2CO), 3.02-3.15 (*m*, 2 H, $CH_2NH_3^+$), 8.13 (*br s*, 3 H, NH_3^+) ppm; δ_C (75 MHz, $CDCl_3$) 21.04, 21.41, 22.32, 22.52, 22.68, 22.75, 23.58, 26.21, 26.34, 27.25, 33.72, 34.92, 34.98, 39.55 (CH_2CO), 55.79 ($CH_2NH_3^+$), 58.34 (*C*CN), 120.20 (CN), 204.28 (C=O) ppm; CI-MS m/z 279 $[M+H]^+$; Anal. calc. for $C_{17}H_{30}N_2O{\cdot}HCl$: C 64.84, H 9.92, N 8.90; found C 65.12, H 10.07, N 8.97.

A solution of **3b** (320 mg, 1.05 mmol) in ethanol (20 mL) was stirred with Lindlar catalyst (100 mg, 5% $Pd/CaCO_3$) under 1 atm of hydrogen for 12 h. The catalyst was filtered off and the filtrate was concentrated

under vacuum. The crude product was taken up in ethanol (5 mL) and converted to its hydrochloride by addition of 4 N HCl until the pH was < 2 reached. The white solid was collected by filtration to yield 248 mg of **8** as its hydrochloride (75%).

4b: A solution of **8** (93.5 mg, 0.297 mmol), 2 N KOH (1.48 mL, 2.97 mmol) in methanol (3 mL) was stirred at room temperature for 9 days. The reaction mixture was neutralized by addition of 1 N HCl. The methanol was evaporated under reduced pressure. The aqueous phase was then extracted with chloroform. Flash chromatography (silica gel, ethyl acetate/hexane 9:1) gave **4b** (52 mg, 63%) as a pale yellow oil.

***10-Bromo-1-(*tert*-butyldimethylsilyloxy)-decane*(9):** A solution of 10-bromo-1-decanol (2.00 g, 8.43 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl) (1.90 g, 12.65 mmol), imidazole (0.860 g, 12.65 mmol) in dichloromethane was stirred for 48 h at room temperature. After removal of the solvent, the residual oil was distilled under reduced pressure (140°C/2 mmHg) to give 2.90 g of the desired compound **9** (98%). [1]; δ_H (300 MHz, $CDCl_3$) 0.01 (s, 6 H, CH_3Si), 0.85 (*s*, 9 H, CH_3C), 1.25-1.53 (*m*, 14 H), 1.81 (quin, *J* = 6.93 Hz, 2 H, CH_2CH_2O), 3.36 (*t*, *J* = 6.93 Hz, 2 H, CH_2Br), 3.55 (*t*, *J* = 6.93 Hz, 2 H, CH_2O) ppm; δ_C (75 MHz, $CDCl_3$) 18.26, 25.67, 25.87 (CH_3Si), 28.06, 28.63, 29.25, 29.38, 32.75, 33.87, 63.18 (CH_2OTBDMS) ppm; CI-MS m/z 351 $[M+H]^+$.

***1-[(10-*tert*-Butyldimethylsilyloxy)-decyl]-2-oxo-cyclododecanecarbonitrile* (2c):** To a solution of **1** (1.56 g, 7.50 mmol), **9** (2.90 g, 8.25 mmol) and Bu_4NHSO_4 (0.278 g, 0.825 mmol) in dichloromethane (16 mL), was added 2 N aq. NaOH (4.56 mL, 9.15 mmol). After 5 days at room temperature, the two phases were separated and the aqueous layer was extracted with dichloromethane (3 x). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (silica gel, dichloromethane) gave **2c** as a colorless oil (2.90 g, 81%). IR (CH_2Cl_2) 2240 (CN), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 (*s*, 6 H, CH_3Si), 0.85 (*s*, 9 H, CH_3C), 1.12-1.96 (*m*, 36 H), 2.62-2.71 (*m*, 2 H, CH_2CO), 3.56 (*t*, *J* = 5.90 Hz, 2 H, CH_2OTBDMS) ppm; δ_C (75 MHz, $CDCl_3$) 18.25 (CH_3Si), 20.99, 21.26, 22.24, 22.57, 22.71, 23.48, 25.29, 25.67, 25.87, 26.13, 26.33, 29.05, 29.11, 29.26, 29.31, 29.42, 32.76, 34.40, 34.95, 35.06, 55.69 (*C*CN), 63.18 (CH_2OTBDMS), 120.31 (CN), 204.09 (C=O) ppm; EI-MS m/z 477 $[M]^{+\bullet}$; Anal. calc. for $C_{29}H_{55}NO_2Si$: C 72.89, H 11.66, N 2.93; found C 72.61, H 11.63, N 2.80.

***1-(10-Hydroxydecyl)-2-oxo-cyclododecanecarbonitrile* (2d):** A solution of TBAF 1 M in THF (6.3 mL, 6.3 mmol) was added at room temperature to a solution of **2c** (2.02 g, 4.19 mmol) in THF. After stirring at this temperature for 6 h, the solvent was evaporated under vacuum. The residue was taken up in chloroform and quenched with water. The aqueous layer was extracted with chloroform (3 x). The combined organic layers were washed with brine and dried (Na_2SO_4) and concentrated under vacuum. Purification by chromatography (silica gel, chloroform/methanol 99:1) gave **2d** as a white solid (1.28 g, 84%). mp 75.9-78.1°C (ether/hexane); IR ($CHCl_3$) 3620 (OH), 3420 (OH), 2235 (CN), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13 (m, 36 H), 2.57-2.75 (*m*, 2 H, CH_2CO), 3.51 (*t*, *J* = 6.0 Hz, 2 H, CH_2OH), 3.80 (br *s*, 1H, OH) ppm; δ_C (75 MHz, $CDCl_3$) 21.01, 21.27, 22.25, 22.57, 22.72, 23.49, 24.56, 24.84, 25.26, 25.59, 26.13, 26.33, 29.06, 29.22, 29.35, 29.58, 32.66, 34.41, 34.94, 35.07, 55.76 (*C*CN), 62.91 (CH_2OH), 120.31 (CN), 204.18 (C=O) ppm; CI-MS m/z 364 $[M+H]^+$; Anal. calc. for $C_{23}H_{41}NO_2$: C 75.98, H 11.37, N 3.85; found C 75.70, H 11.57, N 3.79.

***1-(10-Azidodecyl)-2-oxo-cyclododecanecarbonitrile* (3c):** According to the procedure for **3a**, starting from **2c** (0.99 g, 2.75 mmol), triethylamine (383 µL, 2.75 mmol), methane sulfonyl chloride (212 µL, 2.75 mmol) in toluene (12 mL) and then Bu_4NBr (167 mg, 0.55 mmol), sodium azide (1.5 g, 23 mmol) and water (6 mL), there was obtained 0.940 g of **3c** after chromatography (silica gel, dichloromethane) as a white solid (88%), mp 36.2-36.5°C (ether/hexane); IR ($CHCl_3$) 2235 (CN), 2100 (N_3), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.10-2.13 (*m*, 36 H), 2.66-2.81 (*m*, 2 H, CH_2CO), 3.25 (*t*, J = 6.30 Hz, 2H, CH_2N_3) ppm; δ_C (75 MHz, $CDCl_3$) 21.07, 21.36, 22.32, 22.64, 22.79, 23.56, 23.88, 24.16, 24.21, 24.41, 24.54, 24.64, 25.25, 25.81, 25.89, 26.23, 26.41, 26.67, 28.81, 29.06, 29.16, 29.23, 29.30, 34.46, 35.06, 35.13, 51.46 (CH_2N_3), 55.79 (*C* quart), 120.37 (CN), 204.13 (C=O) ppm; CI-MS m/z 389 $[M+H]^+$; Anal. calc. for $C_{23}H_{40}N_4O$: C 71.09, H 10.37, N 14.42; found C 71.29, H 10.58, N 14.25.

***1-(10-Aminodecyl)-2-oxo-cyclododecanecarbonitrile Hydrochloride* (10):**

Method A: To a 0.1 M solution of SmI_2 in THF (18.7 mL, 1.87 mmol) was added dropwise a well-degassed solution of **3c** (220 mg, 0.566 mmol) in THF (1 mL) under argon at room temperature. After stirring for 2 h the reaction mixture was quenched with a 4 M solution of K_2CO_3. The aqueous layer was extracted with chloroform (3 x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness. Purification by flash chromatography (silica gel, chloroform/methanol/ammonia water 25% 90:10:0.5) gave **10** as a colorless oil (164 mg, 80%). Compound **10** was taken up in ethanol and converted to its hydrochloride by addition of 4 N HCl.

Method B: A solution of **3c** (340 mg, 0.875 mmol) in ethanol (30 mL) was stirred with Lindlar catalyst (100 mg, 5% $Pd/CaCO_3$) under 1 atm of hydrogen for 12 h. The catalyst was filtered off, the filtrate was concentrated under vacuum and the resulting compound was purified as above mentioned (190 mg, 60%).

IR ($CHCl_3$) 3400 (NH), 2220 (CN), 1720 (CO) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.18-2.05 (*m*, 36 H), 2.65-2.80 (*m*, 2 H, CH_2CO), 3.01 (br *s*, 2H, $CH_2NH_3^+$), 8.25 (br *s*, 3H, NH_3^+) ppm; δ_C (75 MHz, $CDCl_3$) 21.11, 21.38, 22.21, 22.33, 22.63, 22.80, 23.58, 25.40, 26.34, 26.41, 26.85, 27.17, 29.20, 29.38, 29.49, 32.30, 33.10, 34.55, 34.87, 35.12, 39.49, 41.92, 47.99 ($CH_2NH_3^+$), 55.98 (*C*CN), 120.38 (CN), 204.27 (C=O) ppm; CI-MS m/z 363 $[M+H]^+$; Anal. calc. for $C_{23}H_{42}N_2O$•HCl +2/5 H_2O: C 68.00, H 10.87, N 6.89; found C 68.39, H 10.53, N 6.50.

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Efficient Kg-Scale Synthesis of Thrombin Inhibitor CRC 220

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Abstract: Potent thrombin inhibitor **2** is prepared in 10 steps with 20% overall yield from commercial **4** on a kg-scale by the convergent approach depicted in Schemes 1 and 2. The (*R*)-configuration of the 4-amidinophenylalanine piperidide moiety is controlled by asymmetric hydrogenation. A novel method, the hydrogenolysis of amidoximes **11** and **21**, is employed to attain a particularly clean transformation of the cyano into the amidinium functionality. Despite of the amorphous nature of target compound **2**, the approach is devoid of any chromatographic purification.

Introduction

Thrombin is crucially involved in the formation of fibrin and platelet aggregates. Under pathophysiological conditions where the capacity of the natural thrombin inhibitor antithrombin III is depleted, the action of thrombin needs to be controlled in order to prevent or moderate severe diseases such as unstable angina pectoris, myocardial infarction, venous thrombosis, and stroke.[1] Therefore, many research groups have focussed their attention on the elaboration of synthetic thrombin inhibitors (STI).[1-3] The synthetic access to this class of compounds is not well developed as indicated by the low global yields published by the researchers.[2,3] For Ro 46-6240 **1** , a STI in clinical evaluation,[1d] a convergent synthesis has been reported, which consists of 10 steps (4.7 % overall yield) based on **1a** and 5 steps (10.7 % overall yield) based on commercial **1b**.[1d, 2a] The preparation of **1** thus requires 15 synthetic steps, at least 5 silica gel chromatographies and one final RP18 chromatography.[1d, 2a] In this paper we report the kg-scale preparation of CRC 220 **2**, a potent, highly selective inhibitor of thrombin (K_i = 2.5 nM).[3] This process is convergent and exempt of any chromatography, all purifications being achieved by recrystallizations and salt precipitations.

Conception of the Synthesis

STI **2** can be regarded as a dipeptide analogue. It contains the proteinogenic amino acid (*L*)-aspartic acid

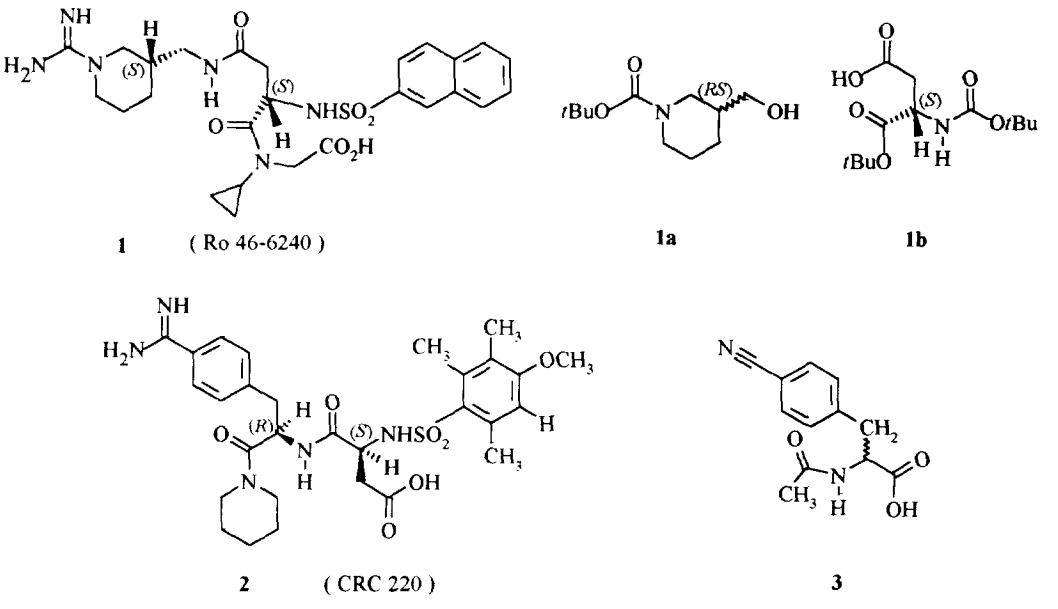

Figure 1. Thrombin inhibitors Ro 46-6240 **1** and CRC 220 **2**

(Asp) as the central unit. Its *C*-terminal phenylalanine (Phe) unit exists in the unnatural (*R*)-configuration, carries a *p*-amidino functionality and is derivatized to a piperidide: 4-amidinophenylalanine piperidide (Adf-pip). As a substitute for a *N*-terminal amino acid, **2** contains the 4-methoxy-2,3,5-trimethyl-phenylsulfonyl (Mtr) group, better known as a side-chain amino protecting group in peptide synthesis.[4] An efficient preparation of **2** has to obey certain key requirements. Adf-pip must form an amide bond regioselectively with the α-carboxyl of Asp . As regards the Asp-unit this can in principle be achieved by a highly regioselective derivatization or a regiospecific protection. We have investigated both approaches and results are reported here. Since Adf-pip has the (*R*)-configuration, it cannot be prepared by any functionalization of proteinogenic Phe. In the published research synthesis of **2**, the (*R*)-configuration was controlled by kinetic enantioselective deacylation of racemic **3**, catalyzed by kidney acylase.[5] However, since the enzymatic reaction is subject to severe product inhibition, it could not be scaled up. Based on ample precedent for the preparation of homochiral amino acids by asymmetric hydrogenation of *N*-acyl-dehydroamino acids [6] and on our good experience with this technique on other types of substrates,[7] we envisioned a rhodium(I)-(2*S*,4*S*)-1-*tert.*-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine (BPPM) [8] catalyzed enantioselective hydrogenation as the key step. Very careful consideration was warranted, how and when to introduce the amidino group and how to purify target compound **2**. X-ray powder diffraction patterns of hydrochloride **2a**, of salts with alternative counter ions such as acetate, of the free base **2**, and of derivatives with a protected Asp-β-carboxyl group, indicated that they are uniformly non-crystalline amorphous solids. This means that they cannot be purified by recrystallization. The simultaneous presence of a highly polar, basic and sensitive amidino group, polar and acidic carboxy and