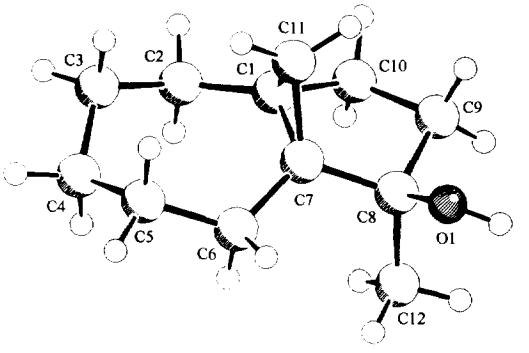
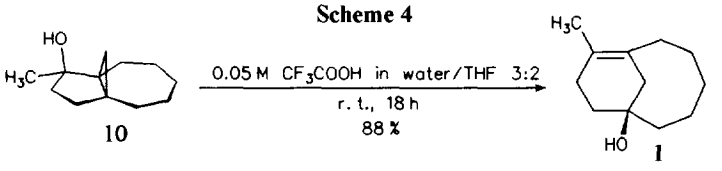
Figure 1: Crystal structure of **10**



Compound **10** was rearranged in 0.05 M trifluoracetic acid in water / THF (3:2) at room temperature to **1** with high selectivity (Table).

Scheme 4



The disappearance of **10** was followed by gc. It reacts to **1** and **11**, the latter is also converted to **1** (Scheme 5, Table). The tricyclic carbocation is probably an intermediate which rearranges by an endocyclic opening of the cyclopropane ring to the bicyclic carbocation which then solvolyzes to **1**. The diastereomer **12** could not be detected. The energy difference of at least 18 kcal/mole between **1** and the other compounds, which for the most part can be attributed to the energy gain resulting from opening of the cyclopropane ring, explains the unusually high product selectivity. A concerted reaction from **10** to **1** cannot be excluded, whilst this of **11** must lead to an exocyclic opening of the cyclopropane ring.

Scheme 5

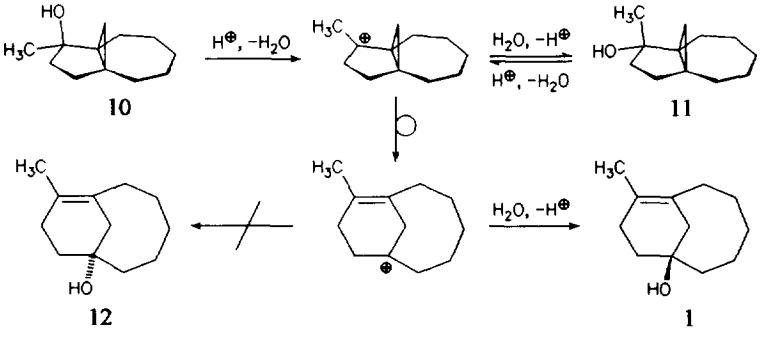


Table : Time dependence of the rearrangement of **10** and calculated heats of formation of **1,10-12**

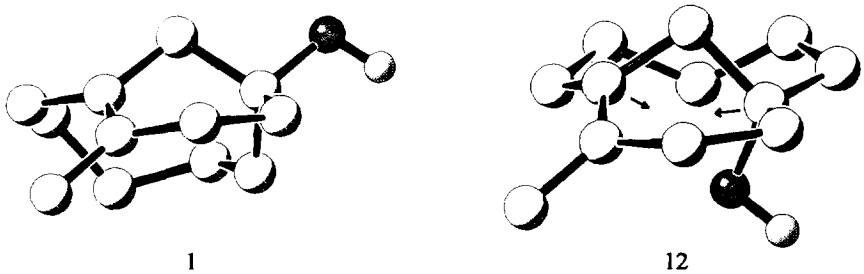
Compound	Conversion of **10** and formation of **1**[a] 20 min	140 min	18 h	Calculated heat of formation[b]
10	12 %	5 %	<1%	- 56 kcal/mol
11	58 %	22 %	<1%	- 55 kcal/mol
12	0 %	0 %	0 %	- 35 kcal/mol
1	7 %	57 %	97 %	- 74 kcal/mol

a: Conditions: 0.05 M trifluoracetic acid in water / THF (3:2), room temperature, 18 h; product analysis by gc: column: HP-1, 25m × 0.32mm × 0.52μm.

b: Semiempirical AM1 calculation[12].

The calculations reveal that the configuration of the hydroxyl group in the diastereomers **1** and **12** has a great influence on the heat of formation. Its *exo*-configuration in **1**, which is also present in the AB ring of taxol **(2)**, is strongly favoured by 39 kcal/mol compared with the *endo*-configuration. These results can be explained by the calculated molecular structure of **1** and **12** (Figure 2). The *endo*-configuration leads to a ring contraction (arrows) and so more than compensates the effect of cyclopropyl ring opening.

Figure 2: Calculated molecular structure of **1** and **12**



1 **12**

The results demonstrate that the bicyclo[5.3.1]undecenol ring system, that constitutes the AB ring of taxane can be prepared in three steps and 50% overall yield starting from hydroazulenones, for which a great number of syntheses is known. The application of the cyclopropyl-carbinyl rearrangement to the synthesis of higher substituted taxane intermediates is currently investigated.

EXPERIMENTAL

General. All melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on the FT IR spectrometers Nicolet 5 DXC and Bruker IFS 28. NMR spectra were measured with a Bruker WM 300 (^{1}H: 300 MHz, ^{13}C: 75.4 MHz). The chemical shifts are

expressed in parts per million (ppm) downfield from tetramethylsilane, using tetramethylsilane (δ = 0) and/or residual chloroform (δ = 7.24) as internal standard. Signal characteristics are described using standard abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad signal. Gas chromatography/mass spectrometry (GC/MS) were conducted with a MS Finnigan MAT 8230 (70 eV) coupled with a Varian GC 3400 and combined with the data system Finnigan SS 300, and a Varian GC 3400 coupled with a Varian Saturn II (ion trap). GC analyses were performed on a Hewlett Packard HP 5890 II gas chromatograph using a capillary column (HP-1, 0.2 mm × 25 m). Thin-layer chromatography (TLC) was conducted on Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm, Art. 5715). HPLC was done with a Knauer HPLC system, using a preparative column (Nucleosil 100-7, 32 mm × 250 mm). The following abbreviations were used for solvents: THF (tetrahydrofuran), PE (petroleum ether).

Tricyclo[5.3.1.$0^{1,7}$]undecan-8-one (6)[7]. To a mixture of sodium hydride (612 mg, 25.5 mmol) and trimethyl sulfoxonium iodide (5.61 g, 25.5 mmol) was slowly added dimethyl sulfoxide (30 ml). A vigorous evolution of hydrogen ensued, which ceased after 15-20 min. The milky-white suspension was stirred and a solution of **5** (3.0 g, 20 mmol) in dimethyl sulfoxide (5 ml) was added with slight external cooling of the reaction flask. After stirring at room temperature for 2 h and at 50 °C for 1 h the mixture was cooled to room temperature, poured into 80 ml cold water and extracted with Et_2O (3 × 80 ml). The combined extracts were washed with water (3 × 50 ml), dried ($MgSO_4$) and evaporated. The resulting yellow oil was purified by chromatography (PE/Et_2O, 1:1) to yield **6** as a colourless oil (1.90 g, 11.6 mmol, 58%). IR (neat): 3059 (w, CH_2 of cyclopropane), 2921 (s, CH_2), 2849 (s, CH_2), 1719 (s, C=O), 1455 (s), 1372 (m), 1301 (m), 1078 (m), 1057 (m), 968 (m), 835 (w), 794 (m), 769 (w). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (s, 2H, CH_2 of cyclopropane), 1.10-1.25 (m, 3H, CH_2), 1.35-1.62 (m, 5H, CH_2), 1.78-1.97 (m, 2H, CH_2), 2.00-2.15 (m, 3H, 9-H, 2× 10-H), 2.38-2.50 (m, 1H, 9-H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 26.05, 26.62, 27.13, 28.21, 32.28, 33.19 (7t, C-2, C-3, C-4, C-5, C-6, C-10, C-11), 35.05 (t, C-9), 37.91 (s, C-1), 42.43 (s, C-7), 215.57 (s, C=O). MS m/z (%) : 164 (60) [M^+], 136 (20) [M^+ - CO], 122 (70) [M^+ - CH_2CO], 107 (70), 93 (92), 79 (100), 67 (30), 53 (22), 39 (86).

Tricyclo[5.3.1.$0^{1,7}$]undecan-8-ol (7). To a stirred suspension of lithium aluminium hydride (231 mg, 6.09 mmol) in Et_2O (20 ml) was added a solution of **6** (1.00 g, 6.09 mmol) in Et_2O (10 ml) dropwise at 0 °C. The suspension was stirred for 60 min at 0 °C and then water (the first 10 ml dropwise, then 60 ml) and Et_2O (40 ml) was added. The mixture was separated and the aqueous layer was extracted with Et_2O (2 × 70 ml). The combined extracts were washed with sat. aq. NH_4Cl (30 ml, 15 ml) and water (15 ml), dried ($MgSO_4$) and concentrated to give **7** (985 mg, 5.92 mmol, 97 %) as a colourless oil. GC/MS analyses and the ^{1}H NMR spectrum show, that **7** consists of a pair of two diastereomers (1:20, the minor diastereomer has the lower retention time in gc). **Minor diastereomer:** MS m/z (%) : 166 (38) [M^+], 148 (50) [M^+ - H_2O], 137 (40), 123 (64), 109 (54), 105 (64), 91 (100), 79 (96), 67 (70), 55 (64), 41 (74). **Major diastereomer:** IR (neat): 3582 (br., OH), 3055 (w, CH_2 of cyclopropane), 2916 (s, CH_2), 2849 (s, CH_2), 1456 (s), 1328 (w), 1059 (s), 1023 (m), 995 (m), 927 (w), 878 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.28 (d, ^2J = 4.8 Hz, 1H, 11-H), 0.73 (d, ^2J = 4.8 Hz, 1H, 11-H), 1.03 (m_c, 1H, CH_2), 1.20 - 1.72 (m, 12H, CH_2), 1.82-1.93 (m, 2H, CH_2), 2.10 (dt, J = 4.5 Hz, J = 14.0 Hz, 1H, 9-H), 4.26 (t, J = 8.1 Hz, 1H, CHOH). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 16.71 (t, C-11), 26.72, 29.86, 30.13, 31.58 (5t, C-2, C-3, C-4, C-5, C-6), 32.25 (s, C-1), 32.72 (t, C-10), 34.81 (t, C-10), 37.07 (s, C-7), 77.20 (d, CHOH). MS

m/z (%) : 166 (40) [M^+], 151 (22) [M^+ - CH_3], 148 (44) [M^+ - H_2O], 137 (46) [M^+ - C_2H_5], 133 (40) [148 - CH_3], 123 (90) [M^+ - C_3H_7], 119 (34) [137 - H_2O], 109 (54) [M^+ - C_4H_9], 105 (64) [123 - H_2O], 91 (100), 79 (86), 67 (66), 55 (65), 41 (73). Anal. calc. for $C_{11}H_{18}O$: C, 79.46%; H, 10.91. Found: C, 79.42%; H, 10.99%.

Tricyclo[5.3.1.0$^{1',7'}$]undec-8'-yl-*p*-nitrobenzoate (8). Compound **7** (310 mg, 1.86 mmol) was added to a suspension of *p*-nitrobenzoyl chloride (349 mg, 1.88 mmol) in pyridine (5 ml) at room temperature. After 2 min the mixture was cooled to 0 °C, stirred for 3 h and then poured on an ice/water-mixture (30 ml). After filtration the insoluble material was washed with water (10 ml), sat. aq. $NaHCO_3$ (2 × 10 ml) and water again (3 × 10 ml). The residue was dried *in vacuo* over P_2O_5 for 72 h to yield **8** (556 mg, 1.76 mmol, 95 %) as a yellow solid: mp: 56-58 °C. IR (KBr): 2919 (s, CH_2), 2850 (m, CH_2), 1712 (s, C=O), 1608 (m, C=C), 1527 (s, NO_2), 1456 (m), 1349 (s, C-NO_2), 1296 (m), 1286 (m), 1124 (m), 1104 (m), 715 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.51 (d, ^2J = 5.0 Hz, 1H, 11'-H), 0.97 (d, ^2J = 5.0 Hz, 1H, 11'-H), 1.15 - 2.25 (m, 14H, 2× 2'- H, 3'-H, 4'-H, 5'-H, 6'-H, 9'-H, 10'-H), 5.54 (t, J = 8.1 Hz, 1H, COOCH), 8.17 (d, ^3J = 8.6 Hz, 2H, 2-H, 6-H), 8.24 (d, ^3J = 8.6 Hz, 2H, 3-H, 5-H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 18.53 (t, C-11'), 26.69, 26.96, 30.00, 31.81 (5t, C-2', C-3', C-4', C-5', C-6'), 32.11 (s, C-1'), 32.57 (t, C-10'), 34.50 (s, C-7'), 34.78 (s, C-9'), 81.82 (d, COO<u>C</u>H), 123.37 (d, C-3, C-5), 130.65 (d, C-2, C-6), 136.17 (s, <u>C</u>-COO), 150.39 (s, C-NO_2), 165.09 (s, <u>C</u>OOCH). MS m/z (%) : 148 (90) [M^+ - $HOOCC_6H_4NO_2$], 133 (65), 119 (68), 105 (90), 91 (100), 79 (55), 67 (30), 39 (47). Anal. calc. for $C_{18}H_{21}NO_4$: C, 68.55%; H, 6.71%; N, 4.44%. Found: C, 68.46%; H, 6.90%; N, 4.63%.

Bicyclo[5.3.1]undec-7-enol (9). To a suspension of $CaCO_3$ in acetone/water (70:30, v/v, 20 ml) was added the ester **8** (400 mg, 1.27 mmol). The mixture was stirred and heated at reflux for 40 h. After cooling the mixture to room temperature, water (60 ml) and Et_2O (80 ml) were added. The layers were separated and the water layer extracted with Et_2O (50 ml). The combined organic layers were washed with water (2 × 40 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by HPLC (Et_2O/PE, 2:1) to give **7** (6.3 mg, 38 mmol, 3 %), **9** (52.8 mg, 0.32 mmol, 25 %) as a colourless oil and recovered **8** (219 mg, 0.69 mmol, 55 %). **9**: IR (neat): 3349 (s, br., OH), 3039 (w, CH_{olefin}), 2922 (s, CH_2), 2840 (s, CH_2), 1670 (w, C=C), 1612 (w, C=C), 1441 (s), 1347 (m), 1332 (m), 1090 (s), 1014 (s), 921 (m), 857 (m), 776 (m), 752 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.90-1.05 (m, 1H, CH_2), 1.20-1.98 (m, 13H, CH_2, OH), 2.08-2.38 (m, 5H, CH_2), 5.29-5.34 (m, 1H, C=CH). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 24.50, 24.70, 28.81, 35.48, 36.19, 36.87 (7t, C-2, C-3, C-4, C-5, C-6, C-9, C-10), 41.38 (t, C-11), 74.17 (s, C-OH), 122.37 (d, C=<u>C</u>H), 137.96 (s, <u>C</u>=CH). MS m/z (%) : 166 (26) [M^+], 148 (36) [M^+ - H_2O], 123 (38), 110 (75), 91 (63), 79 (60), 67 (70), 55 (40), 39 (100). Anal. calc. for $C_{11}H_{18}O$: C, 79.46%; H, 10.91%. Found: C, 79.27%; H, 10.98%.

***exo*- (10) and *endo*-8-Methyltricyclo[5.3.1.0^{1,7}]undecan-8-ol (11).** To a solution of **6** (240 mg, 1.5 mmol) in dry Et_2O (100 ml) methylmagnesium bromide (4.0 ml, 3.0 M solution in Et_2O, 12 mmol) was added at 0 °C. After stirring for 3 h at 0 °C a sat. aq. NH_4Cl solution (100 ml) was added and the aqueous layer was extracted with Et_2O (2 × 100 ml). The organic phase was dried ($MgSO_4$) and evaporated to afford a mixture of **10** and **11** as a colourless, viscous oil (**10**:**11** = 11:1, 260 mg, 97%).

The pair of diastereomers was separated by HPLC (PE/Et_2O, 1:2) to give **10** as colourless crystals and **11** as a colourless oil. **10**: mp: 68-70 °C. IR (KBr): 3300 (s, OH), 2917 (s, CH_2), 2853 (m), 1454 (s), 1400 (s), 1361 (m), 1198 (m), 1157 (m), 1123 (s) cm^{-1}.^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.46 (d, 1H, ^2J = 5.3 Hz, 11-H), 0.49 (d, 1H, ^2J = 5.3 Hz, 11-H), 0.98-1.83 (m, 14H, CH_2), 1.24 (d, 3H, J = 1.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 11.09 (t), 25.52 (q, CH_3), 26.35 (t), 26.69 (t), 27.30 (t), 31.78 (t), 32.25 (t), 33.29 (s), 33.66 (t), 37.47 (t), 39.12 (s), 82.09 (s, COH). MS m/z (%): 180 (8) [M^+], 165 (60) [M^+-CH_3], 163 (100) [M+H^+-H_2O], 147 (38), 137 (20), 119 (37), 105 (65), 91 (76), 79 (65), 67 (52), 55 (31). Anal. calc for $C_{12}H_{20}O$: C, 79.94%; H, 11.18%. Found: C, 79.97%; H, 11.45%. **11**: IR (neat): 3456 (s, OH), 2922 (s, CH_2), 1454 (s), 1373 (m), 1197 (m), 1160 (s), 1085 (s), 918 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.08 (d, ^2J = 5.3 Hz, 1H, 11-H_a), 0.52 (d, ^2J = 5.3 Hz, 1H, 11-H_b), 1.10-1.97 (m, 14H, CH_2), 1.19 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 14.29 (t), 23.22 (q, CH_3), 26.55 (t), 26.79 (t), 27.09 (t), 31.88 (t), 32.08 (t), 33.56 (t), 34.57 (s), 37.27 (t), 39.36(s), 83.81 (s, COH). MS m/z (%): 180 (10) [M^+], 165 (36) [M^+-CH_3], 163 (83) [M+H^+-H_2O], 147 (49), 133 (23), 122 (53), 105 (82), 91 (90), 79 (84), 67 (61), 55 (33). Anal. calc for $C_{12}H_{20}O$: C, 79.94%; H, 11.18%. Found: C, 80.21%; H, 10.90%.

8-Methylbicyclo[5.3.1]undec-7-enol (1). To a solution of **11** (122 mg, 0.675 mmol) in THF (10 ml) a 0.05 M solution of trifluoracetic acid in water (15 ml, 0.75 mmol) was added. The resulting mixture was stirred at room temperature for 18 h and then sat. aq. Na_2CO_3 was added until the pH was weakly alkaline. The aqueous layer was extracted with Et_2O (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and concentrated. The resulting product was purified by chromatography (PE/Et_2O, 1:4) to provide **1** as a colourless oil (107 mg, 0.594 mmol, 88%). IR (neat): 3335 (s, OH), 2920 (s, CH_2), 1439 (s), 1343 (m), 1123 (m), 1094 (m), 1012 (m), 934 (w). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02-1.25 (m, 1H), 1.3-2.0 (m, 17H), 2.1-2.4 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 17.79 (q, CH_3), 24.63 (t), 28.88 (t), 29.05 (t), 30.97 (t), 36.73 (t), 39.39 (t), 42.97 (t), 74.64 (s, COH), 127.82 (s, C=C), 129.92 (s, C=C). MS : m/z (%) 180 (100) [M^+], 162 (82) [M^+-H_2O], 147 (80), 107 (98), 91 (99). HRMS calc. for $C_{12}H_{20}O$: 180.1514, found 180.1511.

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11. X-ray diffraction analysis of **10**: A colourless irregular crystal of $C_{12}H_{20}O$ (size 0.4 x 0.3 x 0.1 mm) was measured at 223 K on an Enraf-Nonius CAD4-diffractometer using Cu Kα radiation (λ = 1.54178 Å) and graphite monochromator. 2426 reflections were collected in the 2Θ-range $6.8 \leq 2\Theta \leq 100.0°$. Crystal system: Monoclinic, space group C2/c (No. 15), $Z = 16$, a = 31.212(10) Å, b = 14.278(3) Å, c = 9.962(3) Å, β = 98.18(3)°, V = 4394(2) Å^3, D_x = 1.090 Mg/m^3, μ = 0.508 mm^{-1}, empirical absorption correction using ψ-scan data ($0.926 \leq T \leq 0.999$). Structure was solved with direct methods (SHELXS-86) and refined with riding hydrogen atoms in calculated position. Anisotropic refinement on F^2 for all non-hydrogen atoms using 2253 independent reflections led to R = 0.064 and wR^2 = 0.145 (SHELXL-93). The asymmetric unit contains two almost identical molecules (one shown in Figure 1). In crystal structure four molecules form a tetramer by hydrogen bonding. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the deposition number CSD-404074, the names of the authors, and the journal citation.
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Samarium Diiodide Induced Ring Enlargement of Azidocyclododecanones to Various Macrocyclic Lactams

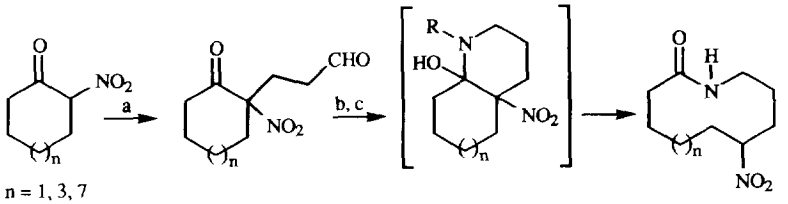
Catherine Goulaouic-Dubois, Armin Guggisberg and Manfred Hesse*

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

Abstract: The synthesis of 2-cyanocyclododecanones **3 a-c** α-substituted by an azidoalkyl chain is described. Compounds **3a** (n=3) and **3b** (n=4) were treated with SmI_2 to afford in one step, the macrocyclic lactams **4a** and **4b** *via* five- and six- membered rings, respectively. For comparison, these lactams were also synthesized from **3a-b** by a standard procedure. The synthesis of the 23-membered ring lactam **4c** from **3c** (n=10) was then attempted by both methods.

INTRODUCTION

The development of new efficient routes to macrocyclic lactams represents a synthetic challenge because ring closure is sometimes difficult to achieve. The lactam ring formation can be done by several methods.[1] Our group[2] reported the retro aldol type ring enlargement of 2-nitrocycloalkanones in basic medium (Scheme 1).[2] The aldehyde side chain was incorporated by Michael addition to acrylaldehyde. Reductive amination of the aldehyde then allows the nitrogen atom to react with the carbonyl group to give a bicyclic intermediate. This method generally afforded macrocyclic lactams in moderate yield and required the presence of a nitro group to activate the ketone. The Bu_3SnH induced ring expansion reaction of α-(alkylazido)-β-ketoesters to lactams was recently reported under conditions known for radical reactions.[3] The discovery that alkylazides could be reduced by SmI_2[4] led us to investigate the ring enlargement of readily available azidocyclododecanones **3** to large-sized lactams **4** using this reagent.



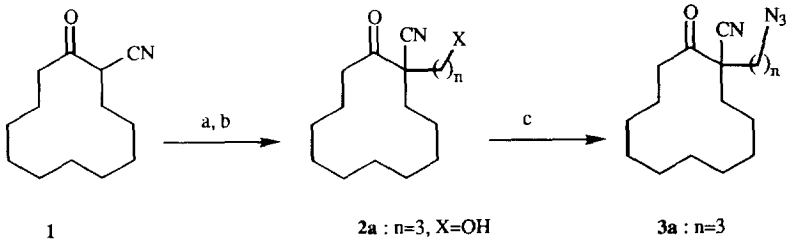
n = 1, 3, 7

a) CH_2=CHCHO; b) RNH_2, $NaBH_3CN$; c) $NaHCO_3$, H_2O, MeOH

Scheme 1

RESULTS AND DISCUSSION

The alcohol **2a** was obtained in two steps by Michael addition of cyclododecanone **1**[5] to acrylaldehyde followed by selective reduction of the aldehyde by $NaBH_4$ in methanol.[6,7] Alcohol **2a** was converted to the azide **3a** *via* reaction of the corresponding mesylate with NaN_3 by phase-transfer catalysis (Scheme 2).[8]



1 **2a** : n=3, X=OH **3a** : n=3

a) CH_2=CHC(O)H, Bu_4NF, THF, 2 h, 72%; b) $NaBH_4$, MeOH, 0°C, 40 min, 90%;
c) $MeSO_2Cl$, Et_3N, toluene, 0°C, 40 min then NaN_3, Bu_4NBr, H_2O, 60°C, 89%.

Scheme 2

Treatment of the 12-membered azide **3a** with SmI_2[9] (3.3 equiv.) in THF at room temperature for 2 hours gave a smooth transformation to the 16-membered lactam **4a** and the unexpected amidine **5** (Scheme 3).

Elucidation of the structure **5** was not obvious because some of the IR and ^{13}C NMR data (ν 1660 cm^{-1} δ 168 ppm;) did not correlate well with an amidine structure.[10] Spiro adduct **5** was acetylated in presence of a mixture (2:1) of acetic anhydride and pyridine at room temperature to give the crystalline product **7**. Structure assignment of **7** was unambiguously supported by spectral data as well as by X-ray structure determination (Scheme 4).[11] The ORTEP representation, revealed that the 6-membered ring is chair shaped with the carbonyl (C-2 and O-2) pointed opposite to the imine of the amidine function (C-13 and N-13).

Attempts to decrease the formation of **5** by conducting the reaction with different amounts of SmI_2 (2-5 equiv.) or under high dilution conditions were unsuccessful. These modifications tend to decrease the yields