Pergamon

Tetrahedron 54 (1998) 12379–12388

TETRAHEDRON

Synthesis of Azaspiro[4.5]decane Systems by Oxidative Cyclization of Olefinic Precursors

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Received 4 June 1998; revised 22 July 1998; accepted 30 July 1998

Abstract: The synthesis of 6-benzyloxycarbonyl-1-oxa-6-azaspiro[4.5]decan-2-one (**17**) and 6-benzyloxycarbonyl-1,6-diazaspiro[4.5]decan-2-one (**18**) from the D,L-pipecolic acid derivative **10**, is described. The synthesis of (±)-6-benzyl-3-methyl-1,6-diazaspiro[4.5]dec-3-ene-2,7-dione (**29**), the spiro structural unit of (±)-pandamarine (**8**) has been achieved by oxidative cylization of the (*Z*) and (*E*) isomers of 5-(N-benzyl-4-carboxamidobutylidene)-3-methyl-3-pyrrolin-2-one (**25**) and (**26**). The stereoselectivity obtained in the intramolecular cyclization process has also been discussed.

Keywords: alkaloids; amino acids and derivatives; spiro compounds; lactones; lactams.

Introduction

The spiropiperidine structural unit is found in a variety of natural alkaloids which display interesting biological properties[1-3]. Among them, some representatives containing the azaspiro[5.5]undecane system are well known in the literature; histrionicotoxin (HTX) (**1**) (Fig.1) and its fully hydrogenated analog perhydronicotoxin (H_{12}-HTX) (**2**) inhibit the ion transport mechanism of the cholinergic receptor. It has been shown that they block postsynaptic membrane depolarization while not interfering with acetylcholine binding. [4-7]

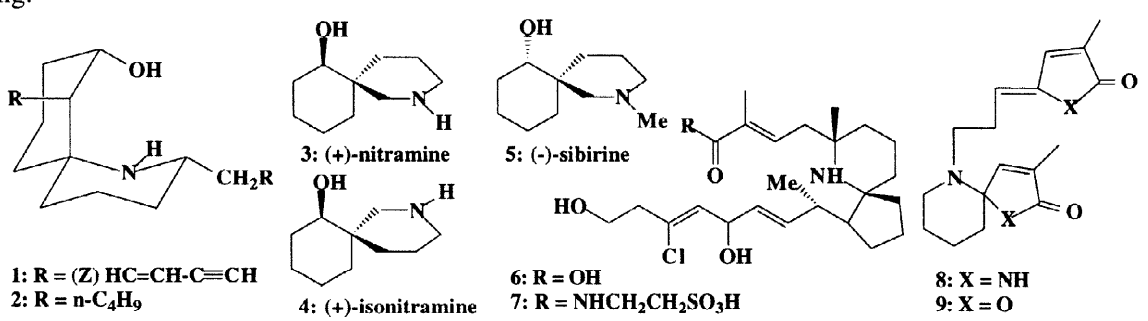


Fig. 1

The piperidine *Nitraria* alkaloids, (+)-nitramine (**3**), (+)-isonitramine (**4**) and (-)-sibirine (**5**) have received considerable synthetic attention because of their structural resemblance to the above mentioned neurotoxins. [8-10]

Two novel polyketides containing the 6-azaspiro[4.5]decane unit, pinnaic acid (**6**) and tauropinnaic acid (**7**) have shown phospholipase A2 (PLA_2) inhibitory activity; therefore, (**6**) and (**7**) have been

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00746-7

considered to be potential drugs for treatment of inflammation and other disease states, since PLA_2 is linked to the initial step in the cascade of enzymatic reactions which lead to the generation of inflammatory mediators.[11] On the other hand, interesting biological activities have been linked to the azaspiro[4.5]decane structural unit present in the piperidine alkaloids, (±)-pandamarine (**8**) and (-)-pandamarilactone (**9**), isolated from some *Pandanus* species.[12-14]

As a part of a synthetic project aimed at the synthesis of (**8**) and (**9**), we have recently described two different methods to prepare 1,6-diazaspiro[4.5]decane and 1-oxa-6-azaspiro[4.5]decane systems via oxidative intramolecular cyclization of olefinic precursors.[15,16] Our intention now is to provide full experimental details on the above mentioned synthetic processes.

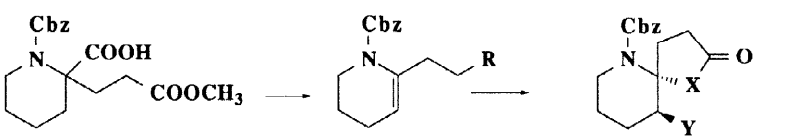
Results and discussion

*Synthesis of 6-benzyloxycarbonyl-1-oxo-6-azaspiro[4.5]decan-2-one **17** and 6-benzyloxycarbonyl-1,6-diazaspiro[4.4]decan-2-one **18** from D,L-pipecolic by iodocyclization processes.*

Our first approach to the synthesis of the 1,6-diazaspiro[4.5]decane and 6-aza-1-oxaspiro[4.5]decane systems is outlined in Scheme 1 and is based on the oxidative cyclization of the N-substituted tetrahydropyridine derivatives **12** and **14**.

We have already reported the DPPA-promoted thermal fragmentation of the α–substituted pipecolic acid derivative **10**. This clean decarbonylation process has proved to be of general application to the synthesis of indolizidines starting from D,L-pipecolic acid. The synthesis of the carboxylic acid **10** from D,L-pipecolic acid has been achieved by application of a seven-step synthetic sequence with 24 % overall yield.[17,18]

The alkaline hydrolysis of the methyl ester **11** followed by acid addition to the aqueous solution afforded the carboxylic acid **12** in quantitative yield. Transformation of the carboxylic acid **12** into the amide **13** was achieved by treatment with DCC and N-hydroxysuccinimide followed by addition of aqueous ammonia solution in 52% yield.



10

11: R = $COOCH_3$
12: R = COOH
13: R = $CONH_2$
14: R = $C(OSiMe_3)=NSiMe_3$

15: X = O; Y = I
16: X = NH; Y = I
17: X = O; Y = H
18: X = NH; Y = H

Scheme 1

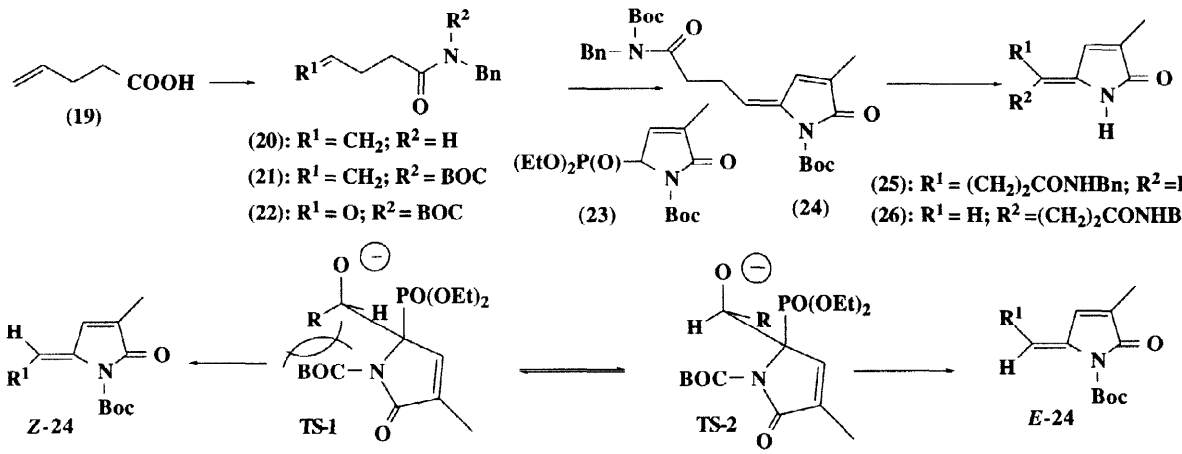
Intramolecular oxidative cyclization of the γ,δ-unsaturated acid **12** was achieved by treatment with N-iodosuccinimide (NIS) ans sodium bicarbonate in dichloromethane at 0 °C. The iodolactone **15** was obtained with 75% yield and proved to be rather unstable under chromatographic conditions. The crude spiro iodolactone was immediately reduced by treatment with tri-n-butyltin hydride and AIBN in tetrahydrofuran at 40 °C to afford 6-benzyloxycarbonyl-1-oxo-6-azaspiro[4.5]decan-2-one **17** in 72% yield. Structural assignment was confirmed by full spectroscopic analysis.

The oxydative cyclization of amide **13** first required the transformation into the N,O-bis(trimethylsilyl)imidate **14**.[19] Reaction of the unsaturated amide **13** with trimethylsilyl triflate followed by

addition of iodosuccinimide (NIS) led to the spiro iodolactam **16** which was further reduced with tri-n-butyltin hydride to give 6-benzyloxycarbonyl-1,6-diazaspiro[4.4]decan-2-one **18** in 54% yield.

*Synthesis of (±)-6-benzyl-3-methyl-1,6-diazaspiro[4.5]decan-3-ene-2,7-dione **29** from 4-pentenoic acid by iodocyclization of (Z)- and (E)- 5-(N-benzyl-4-carboxamidobutylidenyl)-3-methyl-3-pyrrolin-2-ones.*

Our second approach to access to the 1,6-diazaspiro[4.5]decane structural unit is depicted in Scheme 2. The amidobutylidene derivatives **25** and **26** (Scheme 2), substrates for the oxidative cyclization process, have been easily prepared from aldehyde **22**. Reaction of 4-pentenoic acid **19** with benzylamine by using N,N-dicyclohexylcarbodiimide (DCC) in the presence of N-hydroxysuccinimide afforded the unsaturated benzamide **20** in excellent yield. The amide was further transformed into the t-butyloxycarbonyl derivative **21** by treatment of the crude amination product with di-*tert*-butyl dicarbonate in refluxing THF. Ozonolysis of **21** followed by reductive work up afforded the carboxaldehyde **22** quantitatively.



Scheme 2

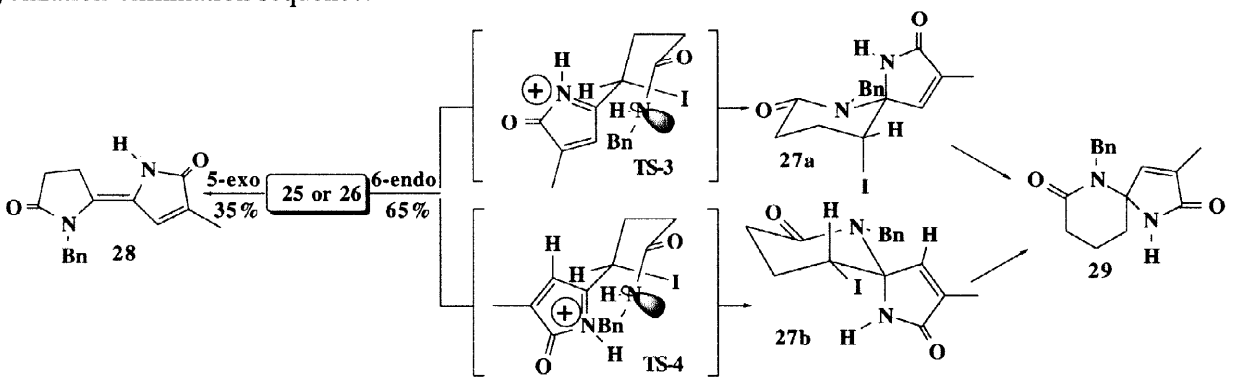
Treatment of carboxaldehyde **22** with the anion generated from phosphonate **23**[20-24] with sodium hydride in THF led stereoselectively to (E)-N-Boc-5-alkylidene-3-methyl-3-pyrrolin-2-one ***E*-24**, which was isolated by flash chromatography in 75% yield. No trace of the geometrical isomer ***Z*-24** was detected by ^{1}H NMR analysis of the crude reaction mixture. The stereoselectivity of the olefination process may be easily explained by the steric interactions which influence the diastereomeric transition states of the Horner-Emmons reaction; the strong steric interactions developed in TS-1 between the side chain and the N-Boc protecting group will lead to the exclusive formation of ***E*-24** via the TS-2 transition state. This new approach represents a remarkable improvement in the synthesis of **24** in comparison with other previously reported procedures.[16] However, deprotection of **24** by treatment with excess of trifluoroacetic acid in dichloromethane at 0°C led to the thermodynamic mixture of deprotected pyrrolinones **25** and **26** (**25**: **26** = 2:3) which was fractionated by flash chromatography on silica gel. Structural assignments of both diastereomers were made based on spectroscopic analysis and comparison with those obtained in similar systems.[25]

Iodolactamization of amines **25** or **26** with N-iodosuccinimide in dichloromethane (conditions suitable for ring closure)[26] yielded the same mixture of iodolactams **27a** and **27b** (65%) and the 5-alkylidene pyrrolinone **28** (35%). The ^{1}H NMR analysis of the crude cyclization mixture exhibited the presence of two

multiplets at δ: 4.42 ($W_{1/2}$ = 8Hz) and δ: 4.18 ($W_{1/2}$ = 15Hz) easily assignable to H-10 of both diastereomers, which by integration gave a ratio of **27a**: **27b** = 3:1.

The 6-*endo* cyclization mode accounts for the formation of the iodolactams **27a** and **27b** via the chair-like transition states with the acyliminium ion with equatorial (TS-3) or axial (TS-4) orientation. Our assumption to rationalize the formation of **27a** as the major isomer in the mixture of iodolactams is that the attack through TS-3 is preferred because of the *antiperiplanar* orientation between the nitrogen electron lone pair and the acyliminium functionality. In Ts-4 however, the nitrogen lone pair and the acyliminium functionality are *synclinal* each other.[27-29]

The 5-*exo* cyclization mode would lead to the formation of the 5-alkylidene-3-pyrrolin-2-one **28** by a cyclization-elimination sequence.



Scheme 3

Treatment of both iodolactams **27a** and **27b** with tri-n-butyltin hydride and azobisisobutyronitrile in tetrahydrofuran at 45 °C led to (±)-6-benzyl-3-methyl-1,6-diazaspiro[4.5]dec-3-en-2,7-dione (**29**) in excellent yield.

Experimental

All the reactions were carried out using dry solvents under nitrogen or argon atmosphere. All the solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. Tetrahydrofuran, diethyl ether and toluene were dried over sodium benzophenone ketyl. Methylene chloride was dried over CaH_2 under argon and kept over molecular sieves. ^{1}H-NMR and ^{13}C-NMR spectra were measured in a Bruker WP-200-SY spectrometer operating at 200 MHz and 50.3 MHz respectively; chemical shifts were reported in ppm (δ), and the coupling constants were indicated in Hz. ^{1}H-NMR spectra were referenced to either the residual proton in the deuterated solvent or TMS. ^{13}C-NMR spectra were referenced to the chemical shifts of the deuterated solvent. The IR spectra were determined on a Bomen MB-100 IR-FT spectrophotometer as indicated in each case; the frequencies in the IR spectra were indicated in cm^{-1}. Microanalysis were realized by Dr. Benigno Macías-Sánchez (Inorganic Chemistry Dept. University of Salamanca) in a Perkin-Elmer 240-B analyzer. Unless otherwise indicated, preparative chromatography was performed with silica gel (40-63 mm) using the technique of flash chromatography.[30]

Methyl 3-(1'-benzyloxycarbonyl-1',4',5',6'-tetrahydropyridin-2'-yl)-propanoate (11). To a solution of **10** (0.94 g, 2.9 mmol) in toluene (8 ml) was added TEA (0.48 ml, 3.48 mmol) and DPPA (0.62 ml, 2.9 mmol) under nitrogen and at room temperature. The mixture was heated at 90°C for 1 h. The reaction was

then cooled to room temperature and poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine and dried on Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude product which was purified by flash chromatography on silica gel (hexane-AcOEt 8:2) to give a colorless oil **11** (0.738 g, 84%). IR ν_{max} (film) 3395, 3055, 2949, 2172, 1738, 1709, 1659, 1441, 1402, 1344, 1265, 1190, 1051, 964, 737, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.73 (m, 2H), 2.05 (m, 2H), 2.42 (t, 2H, J = 7.6), 2.81 (t, 2H, J = 7.6), 3.57 (t, 2H, J = 5.4), 3.63 (s, 3H), 5.04 (t, 1H, J =3.5), 5.15 (s, 2H), 7.35 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 22.86 (t), 23.20 (t), 30.67 (t), 32.89 (t), 45.17 (t), 51.33 (q), 67.35 (t), 113.60 (d), 128.1 (d), 128.5 (d), 136.40 (s), 138.27 (s), 154.05 (s), 173.40 (s). Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; N, 4.62. Found: C, 67.28; H, 7.02; N, 4.57.

3-(1'-Benzyloxycarbonyl-1',4',5',6'-tetrahydropyridin-2'-yl)-propanoic acid (12). 10M Sodium hydroxide (0.5 ml) was added to a solution of **11** (0.715 g, 2.36 mmol) in methanol (2.5 ml). The reaction mixture was stirred for 1.5 h at room temperature under nitrogen atmosphere. Evaporation of the solvent was followed by addition of water (5 ml) and acidification to pH 2 with 1M HCl. The aqueous solution was extracted with chloroform and the combined layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave **12** (0.53 g, 78%). IR ν_{max} (film) 3343, 2947, 1709, 1659, 1452, 1402, 1344, 1252, 1194, 1053, 754, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.75 (m, 2H), 2.04 (m, 2H), 2.41 (t, 2H, J = 7.7), 2.81 (t, 2H, J = 7.7), 3.58 (t, 2H, J = 5.5), 5.08 (m, 1H), 5.14 (s, 2H), 7.34 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 22.58 (t), 22.92 (t), 30.14 (t), 32.6 (t), 44.98 (t), 67.35 (t), 113.8 (d), 127.9 (d), 129.21 (d), 135.98 (s), 137.20 (s), 154.05 (s). Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.38; H, 6.49; N, 4.78.

6-Benzyloxycarbonyl-10-iodo-1-oxa-6-azaspiro[4.5]decan-2-one (15). To a solution of **12** (0.208 g, 0.72 mmol) in chloroform (2.5 ml) was added NIS (0.21 g, 0.93 mmol) at 0°C and under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 3 h in the dark. Evaporation of the solvent gave a crude product which was diluted with AcOEt. The organic layer was washed with 10% $NaHSO_3$ and brine and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude product which was purified by flash chromatography on silica gel (hexane-AcOEt 8:2) to give **15** (0.22 g, 78%). IR ν_{max} (film) 2950, 1790, 1713, 1395, 1217, 1190, 880 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65-2.61 (m, 6H), 2.80-2.97 (m, 1H), 3.17-3.41 (m, 2H), 4.05 (dt, 1H, J = 4.2, J = 13.4), 4.29 (t, 1H, J = 4.9), 5.11 (AB syst., 2H), 7.35 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 20.09 (t), 28.43 (t), 29.65 (t), 33.28 (t), 42.07 (t), 56.10 (d), 67.68 (t), 95.82 (s), 127.95 (d), 128.18 (d), 128.46 (d), 135.65 (s), 154.86 (s), 175.36 (s). Anal. Calcd. for $C_{16}H_{18}NO_4I$: C, 52.17; H, 4.89; N, 3.8. Found: C, 52.09; H, 4.80; N, 3.72.

6-Benzyloxycarbonyl-1-oxa-6-azaspiro[4.5]decan-2-one (17). Tri-n-butyltin hydride (0.02 ml, 0.075 mmol) and AIBN (20 mg) were added to a stirred solution of **15** (0.02 g, 0.05 mmol) in THF (1 ml) under nitrogen at 40°C. After 10 min stirring at the same temperature the reaction mixture was allowed to cool to room temperature and an aqueous solution of NaF was added. After 5 min stirring the reaction was extracted with ether, washed with brine and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude product which was purified by flash chromatography on silica gel (hexane-AcOEt 1:1) to give **17** (10

mg, 72%); m.p. 84-86°C (hexane). IR ν_{max} (film) 3021, 2957, 1765, 1707, 1408, 1267, 1217, 1171 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.62-2.18 (m, 6H), 2.49 (m, 2H), 2.88 (m, 2H), 3.49 (m, 1H), 3.67 (m, 1H), 5.04-5.10 (d, 1H, J = 12.1), 5.11-5.17 (d, 1H, J = 12.1), 7.31 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.29 (t), 22.53 (t), 29.50 (t), 34.84 (t), 37.84 (t), 67.66 (t), 95.75 (s), 128.25 (d), 128.60 (d), 135.94 (s), 155.58 (s), 176.34 (s). MS (EI) (m/z, %): 289 (1.94), 234 (3.06), 216 (9.48), 190 (5.10), 155 (15.51), 110 (12.82), 91 (100), 65 (7.88). Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.37; H, 6.49; N, 4.80.

3-(1'-Benzyloxycarbonyl-1',4',5',6'-tetrahydropyridin-2'-yl)-propanamide (13). To a mixture of **12** (0.696 g, 2.41 mmol) and N-hydroxysuccinimide (0.416 g, 3.61 mmol) in CH_2Cl_2 (7 ml) at 0°C and under nitrogen atmosphere was added *N,N'*-dicyclohexylcarbodiimide (0.75 g, 3.61 mmol). After 1.5 h stirring at the same temperature, a 30% ammonia (0.4 ml, 7.23 mmol) was added to the reaction mixture. The solution was allowed to warm to room temperature and stirred for 1 h. Filtration was followed by evaporation of the organic solvent to give a crude product which, after purification by flash chromatography (diisopropyl ether-AcOEt = 7:3), afforded 0.36 g (52%) of a white solid **13**; m.p. 64°C (hexane). IR ν_{max} (film) 3430, 3190, 2929, 2860, 1714, 1684, 1457, 1388, 1332, 1257 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.77 (m, 2H), 2.03 (m, 2H), 2.23 (t, 2H, J = 7.7), 2.78 (t, 2H, J = 7.7), 3.58 (m, 2H), 5.06 (t, 1H, J = 3.8), 5.12 (s, 2H), 5.82 (m, 2H), 7.33 (m, 5H), 7.60 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 22.52 (t), 22.92 (t), 30.82 (t), 34.28 (t), 44.98 (t), 67.11 (t), 113.29 (d), 127.80 (d), 128.28 (d), 136.12 (s), 138.04 (s), 156.85 (s), 175.10 (s). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.67; H, 6.94; N, 9.72. Found: C, 66.59; H, 6.89; N, 9.67.

6-Benzyloxycarbonyl-10-iodo-1,6-diazaspiro[4.5]decan-2-one (16). To a solution of **13** (0.1 g, 0.35 mmol) and triethylamine (0.1 ml, 0.77 mmol) in dry pentane was added, at 0°C, trimethylsilyl trifluoromethanesulfonate (0.15 ml, 0.77 mmol). The reaction mixture was stirred under nitrogen atmosphere at room temperature for 30 min. The supernatant liquid was transferred to a second flask under nitrogen. The residue was washed with additional pentane which was transferred to the second flask. The rest of organic solvent was carefully removed by using an aspirator equipped with a calcium chloride drying tube; then the residue (**14**) was dissolved in dry tetrahydrofuran (5 ml) and sodium bicarbonate ($NaHCO_3$) (0.06 g, 0.7 mmol) and N-iodosuccinimide (NIS) (0.164 mg, 0.7 mmol) were successively added. The reaction mixture was stirred for 1h in the dark. The reaction was quenched with water and extracted with ether, washed with 10 % $Na_2S_2O_3$ and brine, dried over Na_2SO_4 and evaporated to afford a crude product which was purified by flash chromatography on silica gel (hexane-AcOEt 3:7) to give **16** (77 mg, 54%). IR ν_{max} (film) 3401, 2959, 1717, 1690, 1395, 1260, 1171, 1096, 1024 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (m, 2H), 2.37 (m, 6H), 3.17 (td, 1H, J =7.5, J = 14.5), 3.88 (dt, 1H, J = 3.5, 14.5), 4.52 (dd, 1H, J = 4.6, 6), 5.03 (s, 2H), 7.26 (m, 5H), 7.95 (1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 26.45 (t), 30.3 (t), 35.29 (t), 36.88 (d), 44.48 (t), 67.63 (t), 78.40 (d), 128.08 (d), 128.29 (d), 128.56 (d), 135.84 (s), 156.58 (s), 176.05 (s). Anal. Calcd. for $C_{16}H_{19}N_2O_3I$: C, 46.38; H, 4.59; N, 6.76. Found: C, 46.29; H, 4.50; N, 6.68.

6-Benzyloxycarbonyl-1,6-diazaspiro[4.5]decan-2-one (18). n-Bu_3SnH (0.06 ml, 0.23 mmol) and AIBN were added to a solution of **16** (0.065 g, 0.16 mmol) in THF (2 ml) under nitrogen atmosphere at 40°C. After 1 h of stirring at the same temperature the reaction was allowed to room temperature and an aqueous solution of NaF was added. After 10 min stirring, the reaction was extracted with chloroform, washed with

brine and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude product which was purified by flash chromatography on silica gel (Cl_3CH-MeOH 94:6) to give a white solid **18** (0.024 g, 54%); m.p. 146-148°C (hexane). IR ν_{max} (film) 3401, 2959, 1717, 1690, 1395, 1260, 1171, 1096, 1024 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.13-1.90 (m, 6H), 2.22 (m, 2H), 2.50 (m, 2H), 3.50 (m, 1H), 3.62 (m, 1H), 5.09 (s, 2H), 7.33 (m, 5H), 7.60 (1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 19.12 (t), 23.2 (t), 26.61 (t), 30.16 (t), 37.51 (t), 44.16 (t), 67.19 (t), 75.64 (d), 128.08 (d), 128.44 (d), 136.25 (s), 156.08 (s), 177.12 (s). MS (EI) (m/z, %): 288 (10.45), 200 (0.12), 181 (8.33), 153 (9.57), 136 (21.36), 91 (100), 65 (9.12). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.67; H, 6.94; N, 9.72. Found: C, 66.61; H, 6.85; N, 9.68.

N-Benzyl-4-pentenamide (20). To a mixture of 4-pentenoic acid (**19**) (0.5 g, 5 mmol) and N-hydroxysuccinimide (0.69 g, 6 mmol) in dichloromethane (15 ml), N, N'-dicyclohexylcarbodiimide (1.2 g, 6 mmol) was added at 0°C and under nitrogen atmosphere. After 1.5 h stirring at the same temperature, benzylamine (1.6 g, 15 mmol) was added to the reaction mixture. The solution was allowed to warm to room temperature and stirred for 1 h. Filtration of the solids was followed by evaporation of the organic solvent to give a crude pproduct which, after purification by flash chromatography (hexane-AcOEt 1:1), afforded **20** (0.95 g, 100%). IR ν_{max} (film) ($CHCl_3$) 3295, 3081, 3005, 2928, 2855, 1643, 1553, 1497, 1454, 1433, 1356, 1267, 1219, 1115, 1082, 1030, 995, 914, 754, 698, 665 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$) δ 2.33 (m, 4H); 4.42 (d, 2H); 4.98-5.10 (m, 2H); 5.8 (m, 1H); 7.29 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 29.3 (t); 35.3 (t); 43.07 (t); 115.0 (t); 126.66-128.19 (d); 136.62 (d); 138.37 (s); 172.22 (s). Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.98; N, 7.40. Found: C, 76.08; H, 7.89; N 7.36.

N-Benzyl-N-*tert*-butoxycarbonyl-4-pentenamide (21). To a solution of **20** (0.7 g, 3.7 mmol) in 20 ml of THF at room temperature and under nitrogen atmosphere, triethylamine (0.62 ml, 4.5 mmol), di-t-butyl dicarbonate BOC_2O (1.0 ml, 4.5 mmol) and DMAP (20 mg) were succesively added. The reaction mixture was stirred for 3 h and then diluted with AcOEt. The mixture was washed with citric acid (5%), brine and dried over Na_2SO_4. Evaporation of the solvent afforded a crude product which was purified on silica gel (hexane: AcOEt 8:2) to give **21** (1.0 g, 95%). IR ν_{max} (film) 3077, 3038, 2980, 2934, 1738, 1697, 1642, 1605, 1497, 1455, 1439, 1370, 1314, 1244, 1215, 1150, 1078, 997, 914, 855, 781, 745, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9H); 2.44 (c, 2H); 3.02 (t, 2H, J = 7); 4.89 (s, 2H); 5.03 (m, 1H); 7.27 (m, 5H) ^{13}C NMR ($CDCl_3$) δ= 27.63 (c); 29.16 (t); 47.30 (t); 88.49 (s); 115.04 (t); 126.96 (d); 127.42 (d); 128.18 (d); 137.32 (d); 138.36 (s); 153.05 (s); 175.20 (s). Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.48; H, 7.96; N 4.79.

N-Benzyl-N-*tert*-butoxycarbonyl-4-oxo-butanamide (22). A stream of ozone was bubbled through a solution of **21** (0.5 g , 1.73 mmol) in dichloromethane (5 ml) at -78°C until a pale blue color developed. Oxygen was allowed to bubble through the solution for 30 min to remove the excess of ozone. Dimethyl sulfide (1.4 ml, 17.3 mmol) was added and the solution was allowed to warm to room temperature over 15 h under stirring. The solvents were removed *in vacuo* to give a crude which was fractioned on silica gel (hexane: AcOEt 9:1) to yield **22** (0.43 g, 85%). IR ν_{max} (film) 3034, 2980, 2828, 2728, 1728, 1694, 1497, 1479, 1456, 1437, 1371, 1348, 1316, 1217, 1152, 1082, 1020, 1003, 853, 777, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.79 (t, 2H); 3.29 (t, 2H); 4.88 (s, 2H); 7.24 (m, 5H); 9.81 (s, 1H) ; ^{13}C NMR ($CDCl_3$)

δ 27.62 (q); 31.11 (t); 38.51 (t); 47.25 (t); 83.17 (s); 126.63 (d); 127.16 (d); 128.03 (d); 137.97 (s); 152.73 (s); 174.19 (s); 200.19 (s). Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.89; H, 7.20; N 4.78.

5*E*-5-[3-(N-Benzyl-N-*tert*-butoxycarbamoyl)-1-propylidenyl]-1-tert-butoxycarbonyl-3-methyl-3-pyrrolin-2-one (24). Sodium hydride (72 mg, 1.8 mmol) as a dispersion in mineral oil (60%) was placed in a two-neck round-bottom flask under argon atmosphere. Freshly distilled dry pentane (2.5 ml) was added and the resulting suspension was stirred for 15 min; stirring was suppressed and after decantation the organic solvent was removed via syringe. Then dry tetrahydrofuran (15 ml) was added and the reaction was kept at 0°C. A solution of phosphonate **23**[26] (0.54 g, 1.8 mmol) in tetrahydrofuran (5 ml) was added dropwise and the reaction mixture was stirred for 30 min at that temperature. A solution of carboxaldehyde **22** (0.45g, 1.5 mmol) in tetrahydrofuran (5 ml) was added dropwise and the reaction was stirred overnight at room temperature. The reaction was quenched by addition of an aqueous sat. NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to afford a crude product which was purified by flash chromatography on silica gel (hexane-AcOEt 7:3) to give **24** (0.66 g, 95%). IR ν_{max} (film) 3076, 2980, 2932, 1767, 1732, 1703, 1479, 1454, 1368, 1298, 1256, 1150, 1078, 1028, 853, 774, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9H); 1.6 (s, 9H); 1.94 (s, 3H); 2.70 (q, 2H); 3.12 (t, 2H); 4.89 (s, 2H); 6.60 (t, 1H); 7.24 (m, 5H); 7.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 10.66 (q); 23.83 (t); 27.90 (q); 28.16 (q); 38.26 (t); 47.49 (t); 83.38 (s); 117.98 (d); 127.15 (d); 127.42 (d); 128.32 (d); 131.02 (d); 131.87 (s); 135.87 (s); 137.98 (s); 149.50 (s); 152.85 (s); 168.45 (s), 174.5 (s). Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.27; H, 7.22; N, 5.87.

5*E*-5-[3-(N-Benzylcarbamoyl)-1-propylidenyl]-3-methyl-3-pyrrolin-2-one (25) and 5*Z*-5-[3-(N-benzylcarbamoyl)-1-propylidenyl]-3-methyl-3-pyrrolin-2-one (26). To a solution of **24** (1 g, 2.1 mmol) in dichloromethane (5 ml) was added trifluoroacetic acid (5 ml) at 0 °C. The mixture was stirred for 4 h at room temperature. Evaporation of the solvent at reduced pressure afforded a crude product wich was purified by flash chromatography on silica gel (Cl_3CH-MeOH= 94: 6) to give **25** (0.26 g, 40%): IR ν_{max} (film) 3439, 3318, 3069, 3017, 2926, 1688, 1547, 1497, 1454, 1433, 1379, 1358, 1217, 1150, 1080, 1030, 993, 847, 700, 667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.76 (d, 3H); 2.26 (t, 2H); 2.50 (q, 2H); 4.21 (s, 2H); 5.35 (t, 1H); 6.95 (m, 1H); 7.08 (m, 5H) ; ^{13}C NMR ($CDCl_3$) δ 10.73 (q); 24.87 (t); 37.20 (t); 44.09 (t); 114.44 (d); 128.07 (d); 128.40 (d); 129.44 (d); 129.18 (d); 135.67 (s); 139.60 (s); 139.86 (s); 174.14 (s); 174.42 (s). Anal. Calcd. for $C_{16}H_{17}N_2O_2$: C, 71.37; H, 6.32; N, 10.41. Found: C, 71.40; H, 6.27; N, 10.38.
26 (0.38 g, 60%): IR ν_{max} (film) 3439, 3318, 3069, 3017, 2926, 1688, 1547, 1497, 1454, 1433, 1379, 1358, 1217, 1150, 1080, 1030, 993, 847, 700, 667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.82 (d, 3H); 2.3 (t, 2H); 2.49 (q, 2H); 4.29 (s, 2H); 5.14 (t, 1H); 6.34 (m, 1H); 7.19 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.3 (q); 24.67 (t); 36.36 (t); 44.09 (t); 114.44 (d); 128.06 (d); 128.45 (d); 129.26 (d); 134.36 (d); 139.28 (s); 139.86 (s); 145.84 (s); 173.59 (s); 174.59 (s). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.65; N, 10.29.

Oxidative cyclization of 5*E*-5-[3-(N-Benzylcarbamoyl)-1-propylidenyl]-3-methyl-3-pyrrolin-2-one (25): To a solution of **25** (0.21 g, 0.78 mmol) in dichloromethane (10 ml) were successively added $HNaCO_3$ (0.08 g, 0.9 mmol) and N-iodosuccinimide (0.21 g, 0.9 mmol) at 0°C under nitrogen atmosphere. The

reaction mixture was stirred at 0°C for 1 h in the dark. The reaction was then diluted with CH_2Cl_2, washed with $Na_2S_2O_3$ (10%) and brine, dried over Na_2SO_4 and evaporated to afford a crude product which was purified by flash chromatography on silica gel (Cl_3CH-MeOH 94:6) to yield **27a** (203 mg, 49%), **27b** (68 mg, 16%) and **28** (76 mg, 35%).

(5R*, 10S*)-6-Benzyl-10-iodo-3-methyl-1,6-diaza-spiro[4.5]dec-3-ene-2,7-dione (27a): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80 (d, 3H); 2.19-2.46 (m, 2H); 2.65-2.96 (m, 2H); 3.92 (d, 1H); 4.42 (m, 1H, $W_{1/2}$= 8 Hz); 4.90 (d, 1H); 6.42 (quintet, 1H); 7.24 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.05 (q); 29.18 (t); 39.02 (t); 31.20 (d); 45.23 (t); 78.89 (d); 126.91 (d); 127.35 (d); 128.26 (d); 136.96 (s); 138.40 (s); 145.74 (d); 169.66 (s); 172.13 (s). Anal. Calcd. for $C_{16}H_{19}N_2O_2I$: C, 50.28; H, 5.00; N, 7.33. Found: C, 50.21; H, 4.90; N, 7.30.

(5S*, 10R*)-6-Benzyl-10-iodo-3-methyl-1,6-diaza-spiro[4.5]dec-3-ene-2,7-dione (27b): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.77 (s, 3H); 2.19-2.46 (m, 2H); 2.65-2.96 (m, 2H); 3.92 (d, 1H); 4.18 (m, 1H, $W_{1/2}$= 15 Hz); 4.61, 4.70 (d, 1H); 6.23 (quintet, 1H); 7.13-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.12 (q); 29.30 (t); 31.26 (d); 32.26 (t); 44.59 (t); 78.96 (s); 126.90 (d); 127.49 (d); 128.69 (d); 135.45 (s); 137.01 (s); 144.23 (d); 170.65 (s); 172.30 (s). Anal. Calcd. for $C_{16}H_{19}N_2O_2I$: C, 50.28; H, 5.00; N, 7.33. Found: C, 50.18; H, 4.92; N, 7.23.

5-(1-Benzyl-5-oxo-pyrrolidin-2-enyl)-3-methyl-3-pyrrolin-2-one (28): IR ν_{max} (film) 3287, 3021, 2926, 1712, 1634, 1553, 1441, 1215, 1155, 1030 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.88 (d, 3H); 2.45 (t, 2H); 3.04 (t, 2H); 4.36 (d, 2H); 7.01 (m, 1H); 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.81 (q); 34.94 (t); 35.33 (t); 42.75 (t); 126.34 (d); 127.15 (d); 127.85 (d); 134.98 (s); 136.62 (d); 139.06 (s); 140.41 (s); 170.45 (s); 172.24 (s). Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.43. Found: C, 71.57; H, 6.10; N 10.36.

The oxidative cyclization of **26** under the above mentioned conditions afforded a mixture of **27a** (48%), **27b** (17%) and **28** (35%).

(±)-6-Benzyl-3-methyl-1,6-diazaspiro[4.5]dec-3-ene-2,7-dione (29). To a solution of **27a** (68 mg, 0.17 mmol) in tetrahydrofuran (5 ml) was dropwise added a solution of tri-n-butyltin hydride (0.05 ml, 0.19 mmol) and AIBN (20 mg) in 5 ml of tetrahydrofuran at 45 °C under argon atmosphere and the reaction mixture was stirred overnight at that temperature. Then, the reaction was allowed to cool to room temperature and an aqueous solution of NaF was added. After 1 h stirring, the mixture was extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude product which was purified by flash chromatography on silica gel (Cl_3CH-MeOH 95:5) to give an oil **29** (40 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 (d, 3H); 1.64-2.09 (m, 4H); 2.64 (m, 2H); 3.97, 4.05 (d, 1H); 4.70, 4.78 (d, 1H); 6.24 (quintet, 1H); 7.25 (m, 5H); 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.14 (q); 18.30 (t); 32.37 (t); 34.75 (t); 44.55 (t); 77.65 (s); 126.88 (d); 127.52 (d); 128.34 (d); 135.43 (s); 144.2 (d); 145.8 (s); 170.73 (s); 172.15 (s). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.02; H, 6.65; N, 10.40.

Acknowledgements

Financial support of this work by the Junta de Castilla y León (SA22/97) and Ministerio de Educación y Ciencia of Spain (DGICYT PB95-0943) is gratefully acknowledged.

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