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1,3-Dipolar Cycloaddition Approach towards the Stereoselective Preparation of Aza-Cephalotaxine Skeleton

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Abstract An aza-analogue of cephalotaxine **1** has been prepared stereoselectivly using 1,3-dipolar cycloaddition of azomethine ylide as a key step.

INTRODUCTION

Conifers of the genus *Cephalotaxine* (Cephalotaxaceae) which are indigenous to south east Asia contain a group of alkaloids.[1] These compounds have been the target of much synthetic interest not only due to their potential anticancer chemotherapeutic properties[2] but also because of their unique structure. The most abundant member of this group is cephalotaxine **1**, which is accompanied in nature by small quantities of related alkaloids, such as cephalotaxinone **2** as well as by several cephalotaxine esters (for instance harringtonine **3**, homoharringtonine **4**, and deoxyharringtonine **5**) that posess significant antitumor activity. Various approaches have been devised for the construction of the skeleton of **1**, including eleven total syntheses.[3] Most recently Isomo and Mori gave the first example of the synthesis of (-)-cephalotaxine.[3p] In addition considerable effort has been made to synthesize a variety of structural analogues of cephalotaxine **1**.[4]

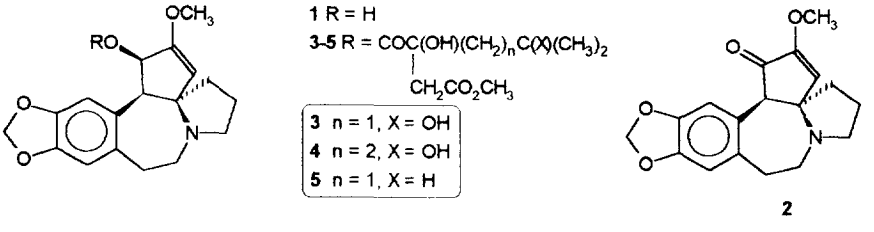

Fig.1

We reported[5] earlier our attempts towards the synthesis of aza-analogues **6** of the cephalotaxine skeleton containing the requisted stereochemistry at the spiro centre and suitable functionalities for the introduction of aliphatic ester side chains. In this account we wish to give full details of this work.

RESULTS AND DISCUSSION

Our synthetic plan was based on the stereoselective formation of the substituted pyrrolidine **7** by 1,3-dipolar cycloaddition. We assumed that **7** could be converted by a short sequence of steps to the new aza-cephalotaxin skeleton (Fig.2).

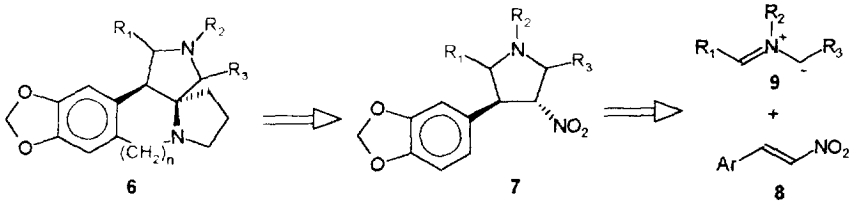

Fig.2

First we investigated the 1,3-dipolar cycloaddition of nonstabilized azomethine ylide[6] generated from sarcosine **10** and paraformaldehyde. The ylide was trapped with a substituted nitrostyrene **8** under reflux in toluene to furnish cycloadduct **11**. Michael addition of methyl acrylate to the anion derived from **11** yielded nitro-ester **12** as a single isomer. The structure of **12** was confirmed by ^{1}H-n.m.r. When irradiating the H-3 proton of **12** n.O.e. enhancements of the side chain protons were observed (a: 1.5 % at 2.77 ppm and b: 4.0 % at 2.30 ppm) indicating the *cis* configuration of the 3-aryl and 4-nitro groups. Its exclusive formation may be due to the presence of the bulky phenyl group on the adjacent carbon atom. The reductive spirocyclisation of nitro-ester **12** using zinc in ethanolic HCl surprisingly gave the diastereomeric mixture (1:1 ratio) of lactams **14a** and **14b** from which only **14a** possesses the correct stereochemistry for our synthetic goal. Since epimerisation of **12** did not occur in ethanolic hydrochloric acid, (only transesterification to give **13**) (Fig.3), partial inversion at C-4 should take place during the reduction.

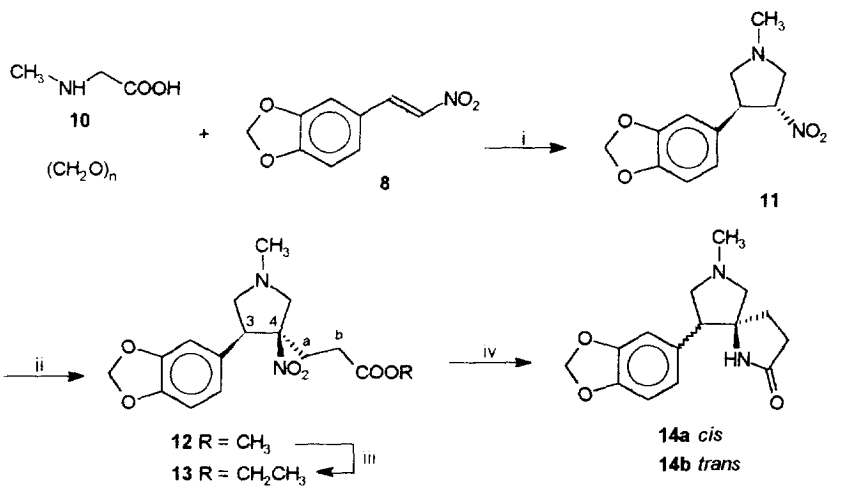

Fig.3 i. toluene, reflux; ii. CH_2=$CHCO_2CH_3$, CH_3CN, Triton B; iii. HCl, EtOH, reflux; iv. Zn, HCl, EtOH;

This epimerisation probably could be the result of radical processes: one can suppose that during the reduction of the NO_2 group radical or radical anion may be formed as an intermediates which abstracts the hydrogen from the position 3 of the pyrrolidine ring. As a consequence this stereocentre can epimerizes partially giving a mixture of **14a** and **14b**. The use of different metal (Fe) or alternative method ($NaBH_4$ with catalytic quantities of $NiCl_2$[10]) did not give any product to allow us to explore the role of the reduction process for the epimerisation.

In order to overcome the difficulties encountered in the separartion of the two isomers by chromatography we examined this reaction sequence with other cycloadducts. First we attempted reactions with adducts **16** and **19** derived from two different ester-stabilised azomethine ylides. To obtain **16** the corresponding dipole component was generated by the modified deprotonation route for 1,3-dipolar cycloaddition of azomethine ylides.[7] Ethyl sarcosinate **15** was condensed with benzaldehyde under reflux in toluene and the product was smoothly trapped by nitrostyrene **8** (Fig.4).

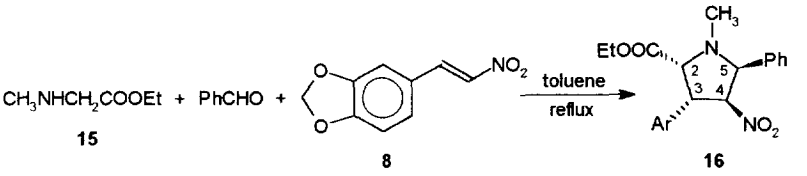

Fig.4

The analogous cycloadduct **19** was prepared from **17** and **8** by the *N*-metallation route. Imine **17** was deprotonated with triethylamine at room temperature in the presence of lithium bromide in acetonitrile to generate the 1,3-dipole, existing in an *N*-lithiated azomethine ylide structure or in a chelated form.[8] The cycloaddition was carried out without any trouble, followed by benzylation of the highly substituted pyrrolidine **18** (Fig. 5).

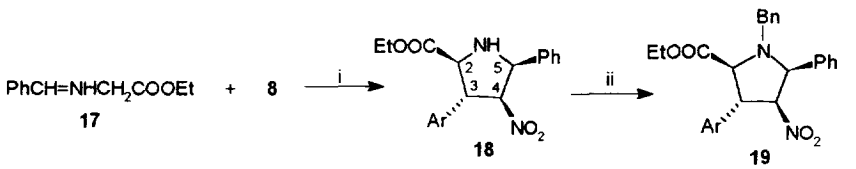

Fig.5 i.LiBr, Et_3N, CH_3CN, r.t.; ii. BnBr, K_2CO_3, DMF;

The stereochemistry for both cycloadducts was assigned on the basis of n.O.e. measurements. For **16** a n.O.e. enhancement of H-5 (11.0 %) is observed upon irradiation of H-4, and irradiation of H-3 resulted in 7.4 % enhancement of H-2. Whereas no n.O.e. was observed between H-3 and H-4 . However in the case of **18** the irradiation of the H-4 proton resulted in enhancements of H-2 (1.6 %) and H-5 (6.2 %). Upon irradiation of H-3 apart from the enhancement of Ar-2'H and 6'H protons no n.O.e. was observed.

Michael addition of **16** and **19** to methyl acrylate furnished the corresponding adducts **20,** and **21,** respectively. It is noteworthy that **20** is an unstable compound. It is transformed rapidly into the corresponding

pyrrole derivative **23** at room temperature in the presence of air. Under the conditions of reductive spirocyclisation **20** gave an unseparable mixture of two lactams, presumably **22a** and **22b** (approx. 2:1) similarly to the reaction of **12** to **14a** and **14b** (Fig.6). Unfortunately the strongly overlapped multiplett signals did not allow us to prove the stereochemistry of these products which would be important to understand this epimerisation process. It seems to us there is a key role of the nature of the N-substituent during this epimerisation which could be affect the predominating conformation of the pyrrolidine ring during the epimerisation process. The reduction of **21** gave the *trans*-lactam **24** as a single product (Fig.7). In the case of **24** n.O.e. was not observed between H-4 and H-9.

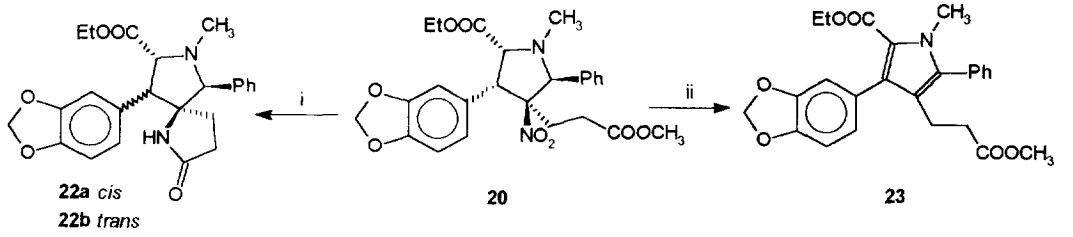

Fig.6 i. Zn, HCl, EtOH, reflux; ii. air, r.t.

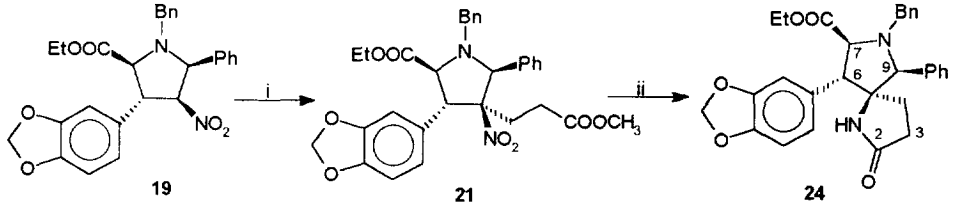

Fig. 7 i.CH_2=CHCOOCH_3, CH_3CN, Triton B, r.t.; ii. Zn, HCl, EtOH, reflux;

However the third attempt was successful. When 1,3-dipolar cycloaddition of imine **17** was performed in the presence of AgOAc the cycloadduct **25** was obtained. Protection of the amine by acylation with acetic anhydride gave **26**. Michael-addition of **26** to methyl acrylate resulted in **27**. Reductive spirocyclisation of **27** followed by reduction with $LiAlH_4$ led to **29**. This compound possesses the required stereochemistry at the spiro centre, as shown by ^{1}H-n.m.r.

Irradiated	enhancement *(%)*			
H-6	Ar-6'H *(11.3)*	H-4[b] *(4.9)*	H-7 *(9.1)*	H-9 *(10.3)*
H-7	CH_2OH *(2.9)*	H-4[a] *(1.7)*	H-4[b] *(3.6)*	H-6 *(6.8)*
H-9	H-2[c] *(1.5)*	H-2[d] *(1.8)*	H-4[a] *(1.7)*	H-6 *(7.8)*

[a] δ 1.79 [b] δ 1.77 [c] δ 2.75 [d] δ 2.62

Table 1. Selected n.O.e data of **29**

Amine **29** was cyclized under Pictet-Spengler conditions with formaldehyde to the corresponding isoquinoline analogue **30** (Fig.8). The attempted use of Eschenmoser's salt instead of formaldehyde to obtain **30** resulted in a complex mixture of products.

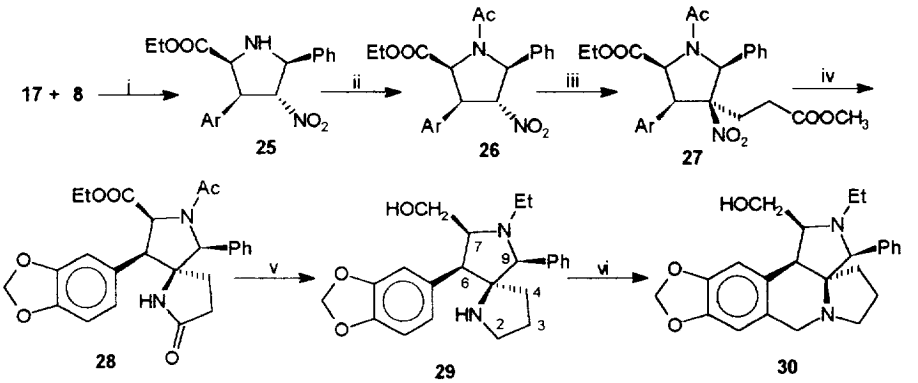

Fig.8 i.AgOAc, Et_3N, CH_3CN, r.t.; ii. Ac_2O, pyridine; iii. $CH_2=CHCO_2CH_3$, CH_3CN, Triton B; iv. Zn HCl, EtOH, reflux; v. $LiAlH_4$, THF, reflux; vi. $(CH_2O)n$, HCl, benzene, reflux;

Our attention was then focused on the synthesis of the benzazepine analogue (**6**, n=2). Although we have not achieved the goal yet we describe here some results obtained during this study. Initial approaches at ring closure of **29** involved primarily the preparation of the aldehyde **32**. Treatment of **29** with a variety of alkylating agents ($BrCH_2CO_2Et$, $BrCH_2(OEt)_2$, $CH_3ON(CH_3)COCH_2Br$[9]) in the presence of various bases (Na_2CO_3, K_2CO_3, $KOBu^t$) did not give **31**.

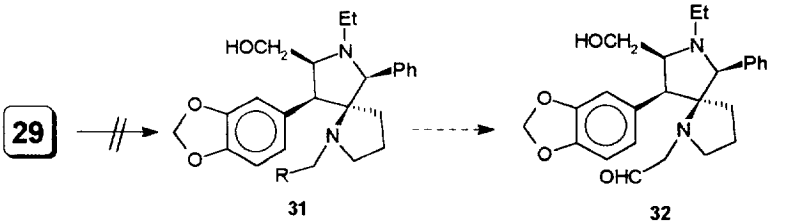

Fig.9

We attempted to use of the Pummerer reaction[31-n] for the construction of the seven membered B-ring. Thus amine **29** was successfully converted into amide **33** followed by $NaIO_4$ oxidation to yield sulfoxide **34**. Unfortunately our efforts failed to result in the desired ring closure using trifluoroacetic anhydride (1 equiv.) in CH_2Cl_2 at room temperature or anhydrous toluene-*p*-sulphonic acid (PTSA 5 equiv.) in boiling 1.2-dichloroethane.

EXPERIMENTAL PART

Methods. Column chromatography was performed using *Merck Kieselgel 60* (70-230 mesh), TLC on aluminium sheets coated with *Kieselgel 60* F_{254}. Plates were stained with anisaldehyde solution (100 mL glacial acetic acid, 2 mL concd. sulfuric acid and 1 mL anisaldehyde) and heated at ca. 150°C. IR spectra were measured on a SPECORD75 IR or a NICOLET FT-IR instrument. Low resolution electron impact mass

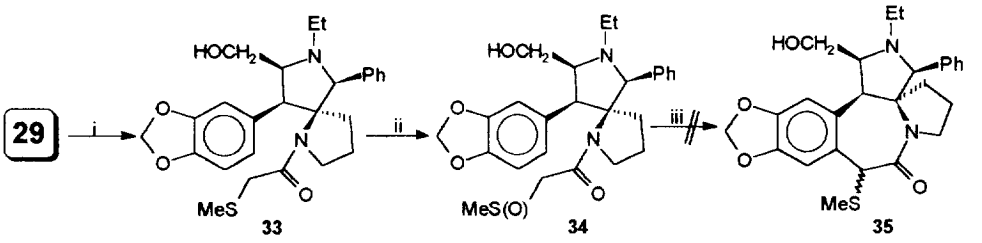

Fig.10 i. $MeSCH_2CO_2H$, ClCOOEt, Et_3N, CH_2Cl_2; ii. $NaIO_4$, CH_2Cl_2, H_2O, MeOH; iii. TFAA or PTSA

spectra were obtained on a Varian CH5-5 spectrometer. ^{1}H-and ^{13}C-NMR spectra were recorded in $CDCl_3$, chemical shifts are given on the δ scale (δ_{TMS}=0 ppm). Melting points are uncorrected.

3-(1,3-Benzodioxol-5-yl)-4-(2-methoxycarbonyl-ethyl)-N-methyl-4-nitro-pyrrolidine (12). 3.5 g (14 mM) **11**[6] was dissolved in 60 mL acetonitrile, and 3.8 mL (3.61 g, 42 mM) methyl acrylate and 0.2 mL Triton B (N-benzyltrimethylammonium-hidroxide) was added. The mixture was stirred at room temperature under nitrogen for 6-8 hours, and then poured into dilute HCl (30 mL), and $CHCl_3$ (50 mL). The aqueous layer was separated and further extracted with $CHCl_3$ (3x50 mL). The combined organic exracts were washed sequentially with 50 mL portions of saturated Na_2CO_3, and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo to yield a gum. The residue was purified by column chromatography over Kieselgel eluting with acetone to produce **12** as a pale yellow oil, 3.55 g (75 %). ^{1}H-NMR (250 MHz) δ: 6.63-6.72 (m, 3H, Ar-H), 6.91 (s, 2H, OCH_2O), 3.68 (s, 3H, OMe), 3.55 and 3.06 (d, 1H, and d, 1H, 5-H_2), 3.42 (dd, 1H, H-3), 3.04 (m, 2H, 2-H_2), 2.77 (m, 1H) and 2.32 (m, 2H) and 2.30 (m, 1H) (CH_2CH_2), 2.45 (s, 3H, N-Me); ^{13}C-NMR (62.5 MHz) δ: 172.2 (C=O), 147.6 (Ar-4'C), 147.4 (Ar-3'C), 129.0 (Ar-1'C), 121.7 (Ar-6'C), 108.1 (Ar-5'C), 108.1 (Ar-2'C), 101.1 (OCH_2O), 99.5 (C-4), 62.5 (C-5), 59.9 (C-2), 56.2 (OMe), 51.7 (C-3), 41.6 (N-Me), 33.0 ($\underline{C}H_2CH_2CO_2Me$), 29.4 ($CH_2$-$\underline{C}H_2CO_2Me$); IR (film, cm^{-1}): 2960, 2920, 2860, 2800, 1850, 1720, 1540, 1500, 1450, 1360, 1310, 1260, 1040, 940, 860, 820, 630; MS *m/z* (rel.intensity %): 336 (M^+, 41), 305 (23), 290 (75), 247 (74), 216 (83), 202 (72), 185 (42), 173 (47), 157 (54), 147 (47), 135 (65), 129 (48), 115 (94), 108 (83), 94 (base peak), 89 (70), 77 (58), 65 (57), 57 (70), 42 (80);

3-(1,3-Benzodioxol-5-yl)-4-(2-ethoxycarbonyl-ethyl)-N-methyl-4-nitro-pyrrolidine (13). 0.6 g (1.78 mM) nitro-ester **12** was dissolved in 10 mL ethanol, and 0.5 mL conc. HCl was added. The reaction mixture was refluxed for 12 hours. It was concentrated, dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated *in vacuo* to yield **13**; 0.5 g (80 %) colorless oil; ^{1}H-NMR (250 MHz) δ: 6.73 (s, 1H, Ar-5'H), 6.70 (s, 1H, Ar-2'H), 6.65 (s, 1H, Ar-6'H), 5.92 (s, 2H, OCH_2O), 4.14 (q, 2H, $COOCH_2$), 3.57 (d, 1H, H-5), 3.44 (dd, 1H, J=9.0 Hz and 6.8 Hz, H-3), 3.07 (m, 3H, H-2 and H-5), 2.77 (m, 2H, $C\underline{H}_2CH_2CO_2Et$), 2.53 (s, 3H, NMe), 2.30 (m, 2H, $CH_2C\underline{H}_2CO_2Et$), 1.25 (t, 3H, Me); ^{13}C-NMR (62.5 MHz) δ: 171.8 (C=O), 147.4 (Ar-3'C), 147.7 (Ar-4'C), 128.9 (Ar-1'C), 121.8 (Ar-6'C), 108.2 (Ar-2'C), 108.1 (Ar-5'C), 101.1 (OCH_2O), 99.6 (C-4), 62.5 (C-5), 60.7 ($O\underline{C}H_2$-CH_3), 56.2 (C-3), 41.6 (N-Me), 32.9 ($\underline{C}H_2CH_2CO_2Et$),

29.7 ($CH_2\underline{C}H_2CO_2Et$), 14.0 ($OCH_2$-$\underline{C}H_3$); IR (film, cm^{-1}): 2940, 2847, 2786, 1732, 1541, 1488, 1444, 1379, 1347, 1305, 1252, 1190, 1120, 1102, 1038, 932;

6-(1,3-Benzodioxol-5-yl)-8-methyl-2-oxo-1,8-diazaspiro-[4.4]-nonane (14). To a stirred solution of nitro-ester **12** (1.20 g, 3.55 mM) in ethanol (200 mL) zinc dust (4.0 g, 60 mM) was added with stirring. This mixture was heated to 40-45 °C then was added conc. HCl (5 mL) in portions, the temperature was kept between 45-50 °C. The reaction mixture was then refluxed for 12 h, filtered, evaporated *in vacuo* nearly to dryness. The residue was dissolved in saturated $NaHCO_3$ solutiun (20 mL), and CH_2Cl_2 (40 mL), filtered and extracted in CH_2Cl_2 (3x50 mL). The combined organic extracts was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to yield a brownish solid 0.67 g (68 %) m.p. 99-108 °C. The isomers can be separated by column chromatography (eluent: chloroform:methanol:ammonium hydroxide, 8:3:1 vol/vol). **14a** R_f= 0.6; yield: 0.29 g (25%); m.p.118-9 °C; ^{1}H-NMR (250 MHz) δ: 6.77 (1H, Ar-2'H), 6.72 (1H, Ar-5'H), 6.66 (1H, Ar-6'H), 5.91 (s, 2H, OCH_2O), 6.80 (s, 1H, NH), 3.24 (1H, H-6), 2.94 (o, 2H, H-7), 2.77 (s, 2H, H-9), 2.0-2.3 (m, 4H, H-3, and H-4), 2.41 (s, 3H, N-Me); ^{13}C-NMR (62.5 MHz) δ: 167.8 (C-2), 147.7 (Ar-3'C), 146.5 (Ar-4'C), 131.6 (Ar-1'C), 121.8 (Ar-6'C), 108.7 (Ar-2'C), 108.1 (Ar-5'C), 100.8 (OCH_2O), 68.3 (C-9), 62.3 (C-5), 61.1 (C-7), 54.7 (C-6), 42.2 (NMe), 32.5 (C-4), 30.1 (C-3); IR (KBr, cm^{-1}): 3450, 3140, 2900, 2790, 1680, 1480, 1220, 1020, 930, 800, 750, 610; Anal calcd. for $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61, N 10.21; found C 65.62, H 6.67, N 10.22; **14b** R_f= 0.3; yield: 0.23 g (20 %); m.p.138-40 °C; ^{1}H-NMR (250 MHz) δ: 7.01 (1H, Ar-2'H), 6.73 (1H, Ar-6'H), 6.42 (1H, Ar-5'H), 5.92 (s, 2H, OCH_2O), 3.70 and 3.45 (m, 4H, H-2, and H-5), 3.33 (m, 1H, H-3), 2.79 (s, 3H, N-Me), 2.0-2.2 and 1.77 (m, 1H, and m, 3H, H_2-3, and H_2-4); ^{13}C-NMR (62.5 MHz) δ: 168.3 (C-2), 147.9 (Ar-3'C), 147.4 (Ar-4'C), 127.4 (Ar-1'C), 122.9 (Ar-6'C), 108.3 (Ar-5'C), 101.1 (OCH_2O), 72.4 (C-5), 63.7 (C-9), 60.4 (C-7), 54.5 (C-6), 42.5 (N-Me), 26.9 (C-4), 26.1 (C-3); IR (KBr, cm^{-1}): 3450, 3140, 2900, 2790, 1680, 1480, 1220, 1020, 930, 800, 750, 610; Anal calcd. for $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61, N 10.21; found C 65.60, H 6.65, N 10.17;

3-(1,3-Benzodioxol-5-yl)-2-ethoxycarbonyl-N-methyl-4-nitro-5-phenyl-pyrrolidine (16). Ethyl sarcosinate hydrochloride **15** (1.54 g, 10 mM), nitrostyrene **8** (0.97 g, 5 mM), benzaldehyde (1.06 g, 1.02 mL, 10 mM). and triethylamine (1,01 g, 1.40 mL, 10 mM) were heated under reflux in dry toluene (80 mL) for 48 hours. The water formed was continuously removed by the aid of a Dean-Stark trap. After the completion of reaction the mixture was poured into saturated NH_4Cl solution (40 mL), and was extracted with ether (3x 75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was trituated with hexane-ethyl acetate 3:1 (vol/vol), and crystalline product was formed, which was filtered. Yield.: 0.9 g (45 %); **16** white powder; m.p. 156-7 °C; ^{1}H-NMR (250 MHz) δ: 7.3-7.5 (m, 5H, Ph), 6.70-6.73 (m, 3H, Ar-H), 5.95 (s, 2H, OCH_2O), 5.82 (dd, 1H, J= 7.3 and 10.0 Hz, H-4), 4.87 (d, 1H, J=10.0 Hz, H-5), 4.62 (dd, 1H, J= 7.3 and 10.2 Hz, H-3), 4.28 (d, 1H, J=10.2 Hz, H-2), 4.02 (q, 2H, $CH_3\underline{C}H_2O$), 2.30 (s, 3H, NMe), 1.07 (t, 3H, $\underline{C}H_3CH_2O$); ^{13}C-NMR (62.5 MHz) δ: 171.3 (C=O), 148.0 (Ar-3'C), 147.3 (Ar-4'C), 136.3 (Ph-1'C), 128.7 (Ph-4'C), 128.4 (Ph-2' and 6'C), 128.2 (Ph-3' and 5'C), 127.7 (Ar-1'C), 120.9 (Ar-6'C), 108.4 (Ar-5'C), 108.1 (Ar-2'C), 101.2 (OCH_2O), 92.2 (C-4), 70.9 (C-2), 69.7 (C-5), 60.6 ($CH_3\underline{C}H_2O$), 49.3 (C-3), 35.8 (NMe), 14.1 ($\underline{C}H_3CH_2O$); IR (KBr, cm^{-1}): 3410, 3062, 2988, 2863, 2802, 1717, 1608, 1557, 1508, 1492, 1472, 1443, 1378, 1351, 1304, 1265, 1250, 1202, 1174, 1123, 1100, 1057, 1038, 934; MS *m/z* (rel. intensity %): 398 (M^+, 10),

352 (49), 325 (63), 278 (80), 263 (7), 248 (15), 237 (64), 220 (17), 207 (29), 178 (31), 139 (39), 115 (51), 103 (24), 91 (34), 77 (50), 65 (21), 51 (28), 42 (base peak); Anal calcd. for $C_{21}H_{22}N_2O_6$: C 63.31, H 5.57, N 7.03; found C 63.34, H 5.60, N 7.00;

3-(1,3-Benzodioxol-5-yl)-2-ethoxycarbonyl-4-nitro-5-phenyl-pyrrolidine (18). To a mixture of imine **17** (1.9 g, 10 mM) and nitrostyrene **8** (1.9 g, 10 mM) in acetonitrile (50 mL) was added lithium bromide (1.26 g, 15 mM) and the triethylamine (1.21 g, 1.7 mL, 12 mM). The mixture was stirred at room temperature under nitrogen for 1-2 hours (judged by TLC) and poured into concentrated aqueous NH_4Cl (25 mL). The product was extracted with ether (3x50 mL) and the combined organic extracts were dried over $MgSO_4$, and evaporated *in vacuo*. The residue was trituated with a few amount of ether, the formed solid was filtered, to yield 2.33 g (61 %) **18** as a white powder; m.p. 138 °C; ^{1}H-NMR (250 MHz): 7.54 (m, 2H, Ph-2'H and Ph-6'H), 7.37 (m, 3H, Ph-3'H, 4'H and 5'H), 6.78 (m, 1H, Ar-6'H), 6.73 (m, 2H, Ar-2'H and Ar-5'H), 5.91 (s, 2H, OCH_2O), 5.11 (dd, 1H, J= 7.8 Hz and 8.3 Hz, H-4), 4.72 (d, 1H, J=8.3 Hz, H-5), 4.42 (d, 1H, J=8.8 Hz, H-2), 4.28 (dd, 1H, J=8.8 Hz, and 7.8 Hz, H-3), 3.87 (q, 2H, CH_2), 2.78 (s, 1H, NH), 0.93 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz): 171.1 (CO), 147.7 (Ar-C'3), 147.2 (Ar-C'4), 137.7 (Ph-C'1), 129.6 (Ar-C'1), 128.8 (Ph-3'H and Ph-5'H), 128.7 (Ph-4'H), 126.7 (Ph-2'H and Ph-6'H), 121.0 (Ar-C'6), 108.1 (Ar-C'2 and Ar-C'5), 101.2 (OCH_2O), 95.3 (C-4), 67.1 (C-5), 63.8 (C-2), 60.9 (CH_2-ester), 53.1 (C-3), 13.5 (CH_3); IR (KBr, cm^{-1}): 3300, 2979, 2840, 2896, 2675, 2604, 2497, 1735, 1550, 1505, 1490, 1444, 1381, 1368, 1297, 1253, 1239, 1220, 1196, 1094, 1037, 931; MS *m/z* (rel. intensity %): 384 (M^+, 5), 337 (8), 311 (3), 308 (6), 264 (20), 237 (base peak), 207 (32), 191 (9), 178 (56), 160 (13), 152 (21), 146 (31), 130 (21), 117 (96), 102 (54), 89 (85), 77 (98), 65 (53), 63 (63), 51 (65); Anal. calcd. for $C_{20}H_{20}N_2O_6$: C 62.48, H 5.25, N 7.29; found C 62.44, H 5.30, N 7.29.

3-(1,3-Benzodioxol-5-yl)-N-benzyl-2-ethoxycarbonyl-4-nitro-5-phenyl-pyrrolidine (19). 0.23 g (0.16 mL, 1.34 mM) benzyl bromide was added to a solution of **18** (0.50 g, 1.30 mM) and 0.2 g K_2CO_3 in dry DMF (10 mL). The mixture was stirred and refluxed for 2 hours, and poured into water (4 mL), the product was extracted with diethyl ether (3x20 mL) the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The product **19** 0.6 g (100 %) white powder; m.p. 158-9 °C; ^{1}H-NMR (250 MHz) δ: 7.63 (d, 2H, Ph-2'H and Ph-6'H), 7.44-7.13 (m, 8H, Ph-H and Bz-H), 6.65 (m, 1H, Ar-2'H), 6.58 (m, 2H, Ar-5'H and Ar-6'H), 5.90 (s, 2H, OCH_2O), 4.96 (dd, 1H, J=3.2 and 9.5 Hz, H-4), 4.66 (d, 1H, J=3.2 Hz, H-5), 4.66 (d, 1H, J= 9.7 Hz, H-2), 4.03 (t, 1H, J= 9.7 Hz, H-3), 4.00 (d, 1H, NCH_2), 3.94-3.68 (m, 3H, NCH_2 and OCH_2), 1.05 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz): 172.1 (C=O), 147.5 (Ar-3'C), 147.2 (Ar-4'C), 140.0 (Bz-1'C), 136.3 (Ph-1'C), 129.6 (Ar-1'C), 128.8 (Ph-2'C és Ph-6'C), 128.3 (Ph-4'C), 128.0 (Bz-2'C és Bz-6'C), 127.4 (Ph-3'C, 5'C, Bz-3'C, 5'C), 126.0 (Bz-4'C), 121.7 (Ar-6'C), 108.3 (Ar-2'C and Ar-5'C), 101.3 (OCH_2O), 96.2 (C-4), 71.0 (C-5), 68.2 (C-2), 61.0 (OCH_2), 57.2 (NCH_2), 51.4 (C-3), 13.8 (CH_3); (IR (KBr, cm^{-1}): 3061, 3030, 2901, 2816, 1736, 1552, 1505, 1491, 1446, 1369, 1354, 1260, 1246, 1191, 1155, 1119, 1039, 1027, 930, 754; Anal. calcd. for $C_{27}H_{26}N_2O_6$: C 68.34, H 5.52, N 5.90; found: C 68.33, H 5.46, N 5.91.

3-(1,3-Benzodioxol-5-yl)-4-(2-methoxycarbonyl-ethyl)-2-ethoxycarbonyl-N-methyl-4-nitro-5-phenyl-pyrrolidine (20) was prepared analogously to **12** from compound **16** and methyl acrylate, and isolated after 48

hours in 85 % yield as a yellow oil, which is very unstable in the presence of air, always contaminated by **23**. ^{1}H-NMR (250 MHz) δ:7.30 (m, 5H, Ph), 6.75 (m, 2H, Ar-2'H and Ar-5'H), 6.60 (m, 1H, Ar-6'H), 5.94 (s, 2H, OCH_2O) 5.20 (d, 1H, H-3), 4.59 (s, 1H, H-5), 4.40 (d, 1H, H-2), 4.12 (q, 2H, CH_2-ester), 3.55 (s, 3H, OMe), 2.25 (s, 3H, NMe), 1.82 (m, 2H) and 1.63 (m, 1H) and 1.45 (m, 1H CH_2CH_2), 1.15 (t, 3H, $\underline{CH_3}$-CH_2); IR (film, cm^{-1}): 2983, 2952, 2896, 1739, 1543, 1505, 1491, 1446, 1352, 1255, 1237, 1198, 1120, 1074, 1039, 930;

3-(1,3-Benzodioxol-5-yl)-N-benzyl-4-(2-methoxycarbonyl-ethyl)-2-ethoxycarbonyl-4-nitro-5-phenyl-pyrrolidine (21) was prepared analogously to **12** from compound **19**. After a week the product was crystallized from the reaction mixture in 62 % yield. White solid, m.p. 159-60 °C; ^{1}H-NMR (250 MHz) δ: 7.40 (bs, 5H, Bz), 7.17 (s, 5H, Ph), 6.58 (m, 2H, Ar-2'H and Ar-6'H), 6.70 (d, 1H, Ar-5'H), 5.96 (s, 2H, OCH_2O), 4.85 (s, 1H, H-5), 4.03 (d, 1H, J= 13.7 Hz, N-$C\underline{H_2}$-Ph), 4.02 (d, 1H, J= 10.7 Hz, H-2), 3.98 (d, 1H, J= 13.7 Hz, N-$C\underline{H_2}$-Ph), 3.80 (d, J= 10.7 Hz, H-3), 3.78 (dq, 1H) and 3.68 (dq, 1H, OCH_2CH_3), 3.46 (s, 3H, MeO), 2.36 (m, 1H), and 1.98 (m, 1H), and 1.78 (m, 2H, CH_2CH_2), 0.97 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 172.1 ($\underline{C}O_2Et$, and $\underline{C}O_2Me$), 148.2 (Ar-3'C), 147.6 (Ar-4'C), 138.2 (Ph-1'C), 136.7 (Bz-1'C), 129.5 (Ph-2'C, Ph-6'C, Bz-2'C, Bz-6'C), 128.4 (Ph-4'C), 127.8 (Ph-3'C, Ph-5'C, Bz-3'C, Bz-5'C), 127.2 (Bz-4'C), 125.5 (Ar-1'C), 122.6 (Ar-6'C), 108.4 (Ar-2'C, Ar-5'C), 102.0 (C-4), 101.2 (OCH_2O), 73.7 (C-5), 68.1 (C-2), 60.9 (O-CH_2), 57.4 (N-CH_2), 57.4 (O-CH_3), 51.5 (C-3), 28.3 (CH_2-CH_2), 13.8 (CH_3); IR (KBr, cm^{-1}): 3063, 2954, 2902, 1730, 1536, 1502, 1491, 1443, 1384, 1331, 1287, 1243, 1195, 1139, 1069, 1036; Anal. calcd. for $C_{31}H_{32}N_2O_8$: C 66.42, H 5.75, N 5.00; found: C 66.44, H 5.76, N 5.01;

6-(1,3-Benzodioxol-5-yl)-7-ethoxycarbonyl-8-methyl-9-phenyl-2-oxo-1,8-diaza-spiro-[4.4]-nonane (22) was prepared analogously to **14** from compound **20**, and isolated in 88 % yield as a diastereomeric mixture. White foam, m.p. 87-93 °C; ^{1}H-NMR (250 MHz) δ: strongly overlapped multiplett signals; ^{13}C-NMR (62.5 MHz) δ:(signals of major isomer) 177.1 ($\underline{C}OOEt$), 172.5 (C-2), 148.1 (Ar-3'C), 147.5 (Ar-4'C), 137.7 (Ph-1'C), 129.2 (Ar-1'C), 129.1 (Ph-2'C and Ph-6'C), 128.6 (Ph-3'C and Ph-5'C), 127.0 (Ph-4'C), 124.1 (Ar-6'C), 110.1 (Ar-2'C), 108.6 (Ar-5'C), 101.6 (OCH_2O), 71.9 (C-9), 69.3 (C-2), 60.8 (C-6), 60.7 (C-5), 58.7 (CH_2-ester), 35.6 (NMe), 30.2 (C-4), 21.4 (C-3), 14.5 (CH_3-ester); IR (KBr, cm^{-1}): 3422, 3060, 2966, 2935, 1727, 1686, 1624, 1503, 1490, 1445, 1373, 1252, 1236, 1191, 1081, 1038, 929; MS *m/z* (rel. intensity %): 422 (M^+,4), 349 (27), 306 (8), 205 (base peak), 190 (9), 175 (21), 160 (42), 132 (28), 91 (7), 43 (20);

3-(1,3-Benzodioxol-5-yl)-2-ethoxycarbonyl-4-(2-methoxycarbonyl-ethyl)-N-methyl-5-phenyl-pyrrole (23). 1.0 g (2 mM) nitro-ester **20** in ethanolic solution was stirred at room temperature for 72 hours, during which time the mixture turned into red, and some solid precipitated. It was filtered, dried to result **23** as a white powder, 0.3 g (38 %); m.p. 90-2 °C. ^{1}H-NMR (250 MHz) δ: 7.65 (m, 2H, Ph-2' and 6'H), 7.30 (m, 3H, Ph-3'H, Ph-4'H, Ph-5'H), 6.82 (d, 1H, Ar-5'H), 6.78 (d, 1H, Ar-2'H), 6.75 (d, 1H, Ar-6'H), 5.98 (s, 2H, OCH_2O), 4.06 (q, 2H, $CH_3\underline{CH_2}O$-), 3.69 (s, 3H, CO_2Me), 3.48 (s, 3H, NMe), 2.61 (t, 2H, $CH_2\underline{CH_2}CO_2Me$), 2.06 (t, 2H, $\underline{CH_2}$-CH_2CO_2Me), 1.00 (t, 3H, $\underline{CH_3}CH_2O$); ^{13}C-NMR (62.5 MHz) δ: 173.1 ($\underline{C}O_2Me$), 161.9 ($\underline{C}O_2Et$), 146.9 (Ar), 146.2 (Ar), 137.7 (Ar), 131.8 (Ar), 131.4 (Ar), 130.5 (Ph-C'2 and C'6), 129.9 (Ar), 128.6 (Ph-C-3 and C-5), 128.4 (Ph-C'4), 120.0 (Ar), 118.9 (Ar), 110.7 (Ar), 107.6 (Ar), 100.8 (OCH_2O), 59.5 ($CH_3\underline{CH_2}O$), 51.3 ($\underline{Me}O_2C$), 34.4 (NMe), 34.8 and 19.8 (CH_2-CH_2), 13.8 ($\underline{C}H_3CH_2O$); IR (KBr, cm^{-1}): 3440, 2976, 1734, 1688,

1523, 1491, 1475, 1450, 1400, 1366, 1334, 1284, 1248, 1232, 1189, 1128, 1103, 1062, 1037, 935; MS *m/z* (rel. intensity %): 435 (M^+, base peak), 362 (51), 332 (22), 316 (68), 288 (30), 260 (12), 244 (8), 202 (16), 189 (12), 167 (19), 115 (27), 77 (15), 59 (39), 42 (22); Anal. calcd. for $C_{25}H_{25}NO_6$: C 68.95, H 5.79, N 3.22; found: C 69.01, H 5.76, N 3.25;

6-(1,3-Benzodioxol-5-yl)-8-benzyl-7-ethoxycarbonyl-9-phenyl-2-oxo-1,8-diaza-spiro-[4.4]-nonane (24). was prepared analogously to **14** from compound **21**, and isolated as a white powder in 93 % yield; m.p. 122 °C; ^{1}H-NMR (250 MHz) δ: 7.65 (broad s, 1H, NH), 7.40-6.70 (m, 13H, Ar), 5.90 (s, 2H, OCH_2O), 4.55 (s, 1H, H-9), 4.38 (d, J= 9.2 Hz, 1H, H-7), 4.10 (s, 2H, $NC\underline{H}_2$-Ph), 3.58 (d, 1H, J= 9.2 Hz, H-6), 3.50 (q, 2H, $CO_2C\underline{H}_2CH_3$), 1.95 (m, 1H), and 1.60 (m, 2H), and 1.45 (m, 1H, H_2-3 and H_2-4), 0.85 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 173.4 ($\underline{C}O_2Et$), 168.4 (C-2), 147.8 (Ar-3'C), 147.4 (Ar-4'C), 141.4 (Ph-1'C), 138.1 (Bz-1'C), 129.5 (Ph-2'C, Ph-6'C, Bz-2'C, Bz-6'C), 128.7 (Ph-3'C, Ph-5'C), 128.3 (Bz-3'C, Bz-5'C), 127.5 (Ph-4'C), 126.8 (Bz-4'C) 127.0 (Ar-1'C), 123.6 (Ar-6'C), 109.8 (Ar-2'C), 108.2 (Ar-5'C), 100.9 ($O\underline{C}H_2O$), 74.2 (C-9), 69.8 (C-7), 60.8 (C-6), 60.4 (O-$\underline{C}H_2$-CH_3), 59.0 (N-$\underline{C}H_2$-Ph), 58.8 (C-5), 26.5 (C-4), 25.4 (C-3), 10.5 (CH_3); IR (KBr, cm^{-1}): 3447, 3063, 2887, 1734, 1684, 1617, 1491, 1446, 1200, 1050; Anal. calcd. for $C_{30}H_{30}N_2O_5$: C 72.27, H 6.06, N 5.62; found C 72.34, H 6.02, N 5.60.

3-(1,3-Benzodioxol-5-yl)-2-ethoxycarbonyl-4-nitro-5-phenyl-pyrrolidine (25). was prepared analoguosly to **18**, but instead of LiBr 2.5 g (15 mM) silver acetate catalyst was used. Yield: 1.61 g (42 %); white powder m.p. 118 °C; ^{1}H-NMR (250 MHz) δ: 7.44 (s, 5H, Ph-H), 6.80 (d, 1H, Ar-H), 6.77 (d 1H, Ar-H), 6.74 (dd, 1H, Ar-H), 5,97 (s, 2H, OCH_2O), 5.24 (dd, 1H, J= 6.7 Hz and 3.9 Hz, H-4) 4.87 (d, 1H, J= 6.7 Hz, H-5), 4.20 (q, 2H, CH_2), 4.10 (dd, 1H, J= 3.9 Hz and 7.6 Hz, H-3) 4.02 (d, 1H, J= 7,6 Hz, H-2) 3,28 (broad s, 1H, NH), 1.26 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 171.1 (CO), 148.2 (Ar-3'C), 147.2 (Ar-4'C), 134.5 (Ph-H'1), 132.0 (Ar-1'C), 128.5 (Ph-3'C and 5'C), 126.4 (Ph-2'C and 6'C), 120.9 (Ar-6'C), 120.5 (Ph-4'C), 108.6 (Ar-5'C), 107.5 (Ar-2'C), 101.1 (OCH_2O), 96.9 (C-4), 67.4 (C-2), 67.4 (C-5), 61.5 (CH_2-ester), 55.2 (C-3), 14.0 (CH_3); IR (KBr, cm^{-1}): 3300, 2990, 2904, 1729, 1542, 1505, 1491, 1447, 1377, 1246, 1202, 1140, 1033, 931; MS *m/z* (rel. intensity %): 384 (M^+,20), 337 (30), 311 (36), 264 (63), 237 (base peak), 207 (59), 191 (47), 175 (55), 159 (38), 145 (42), 132 (90), 117 (88), 103 (78), 91 (52), 77 (63), 63 (51), 51 (53); Anal. calcd. for $C_{20}H_{20}N_2O_6$: C 62.48, H 5.25, N 7.29; found C 62.42, H 5.26, N 7.31.

N-Acetyl-3-(1,3-benzodioxol-5-yl)-2-ethoxycarbonyl-4-nitro-5-phenyl-pyrrolidine (26). Acetic anhydride (2.4 mL, 2.60 g, 29 mM) was added at 0 °C to a solution of adduct **25** (1 g, 2.6 mM) in pyridine (2 mL). The mixture was stirred at room temperature for 3 hours, then was poured into ice-water. The products were extracted with CH_2Cl_2 (3x15 mL), then the organic layer was washed sequentially with 3 % HCl (3x10 mL), saturated aqueous $NaHCO_3$, and brine. Then was dried over $MgSO_4$, and concentrated *in vacuo*.The residue was trituated with acetone and afforded crystalline **26** 1.10 g (96 %) as a white powder; m.p. 197 °C; ^{1}H-NMR (250 MHz) δ: 7.19 (d, 1H, Ar-H), 7.44 (d, 2H, Ar-H), 6.69 (s, 5H, Ph), 5.94 (s, 2H, OCH_2O), 5.60 (dd, 1H, J= 8.3 and 12.1 Hz, H-4), 5.32 (d, 1H, J= 8.3 Hz, H-5), 5.06 (d, 1H, J= 9.4 Hz, H-2), 4.29 (dd, 1H, J= 9.4 and 12.1 Hz, H-3), 3.95 (q, 2H, CH_2), 1.66 (s, 3H, CH_3CO), 0.96 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 170.7 ($\underline{C}O_2Et$), 170.4 ($\underline{C}OCH_3$), 148.2 (Ar-C'3), 148.0 (Ar-C'4), 137.9 (Ph-1'C), 129.6 (Ph-2'C, Ph-6'C), 129.4 (Ph-

3'C, Ph-5'C), 126.9 (Ph-4'C), 124.4 (Ar-1'C), 121.5 (Ar-6'C), 108.6 (Ar-2'C), 108.1 (Ar-5'C), 101.4 (OCH_2O), 93.6 (C-4), 66.8 (C-5), 63.8 (C-2), 61.4 ($O\underline{C}H_2$-), 49.6 (C-3), 22.7 ($\underline{C}H_3$-CO), 13.7 ($\underline{C}H_3CH_2$); IR (KBr, cm^{-1}): 2950, 2880, 1730, 1640, 1540, 1480, 1440, 1380, 1300, 1240, 1210, 1020; MS *m/z* (rel. intensity %): 426 (M^+, 79), 380 (19), 338 (61), 306 (60), 264 (75), 237 (30), 207 (31), 178 (51), 131 (20), 115 (50), 103 (34), 77 (45), 71 (35), 57 (20), 43 (base peak); Anal. calcd. for $C_{22}H_{22}N_2O_7$: C 61.97, H 5.20, N 6.57; found: C 62.01, H 5.19, N 6.61;

N-Acetyl-3-(1,3-benzodioxol-5-yl)-2-ethoxycarbonyl-4-(2-methoxycarbonyl-ethyl)-4-nitro-5-phenyl-pyrrolidine (27) was prepared analogously to **12** from **26**. The reaction was completed after 3 days. The product was purified by column chromatography (eluent: ethyl acetate-hexane 3:1 vol/vol) to afford crystalline **27** 0.86 g (65 %); m.p. 95-96 °C; ^{1}H-NMR (250 MHz) δ: 7.57 (m, 2H, Ph-2'H and Ph-6'H), 7.34 (m, 3H, Ph-3'H, Ph-4'H, Ph-5'H), 6.72 (d, 1H, Ar-5'H), 6.60 (m, 2H, Ar-2'H and Ar-6'H), 5.93 (s, 2H, OCH_2O), 5.17 (s, 1H, H-5), 5.07 (m, 1H, H-3), 4.20 (q, 2H, CH_2CH_3), 3.99 (d, 1H, J=4.0 Hz, H-2), 3.62 (s, 3H, CH_3O), 2.72 (m, 1H) and 2.52 (m, 1H) and 2.28 (m, 2H CH_2CH_2), 1.86 (CH_3CO); ^{13}C-NMR (62.5 MHz) δ: 172.2 ($\underline{C}O_2Me$), 170.5 ($\underline{C}O_2Et$), 168.4 ($\underline{C}OMe$), 148.1 (Ar-3'C), 148.0 (Ar-4'C), 135.2 (Ph-1'C), 129.1 (Ph-2'C, Ph-6'C), 128.8 (Ph-3'C, Ph-5'C), 127.3 (Ph-4'C), 125.2 (Ar-1'C), 124.4 (Ar-6'C), 110.5 (Ar-2'C), 108.3 (Ar-5'C), 101.4 (OCH_2O), 99.4 (C-4), 71.9 (C-5), 64.1 (C-2), 61.1 (CH_3-$\underline{C}H_2$), 54.6 (OMe), 51.9 (C-3), 30.3 ($\underline{C}H_2$-CH_2CO_2Me), 29.5 (CH_2-$\underline{C}H_2CO_2Me$), 22.7 ($CO\underline{C}H_3$), 13.8 ($CH_2\underline{C}H_3$); IR (KBr, cm^{-1}): 2983, 2953, 1739, 1654, 1551, 1506, 1492, 1448, 1393, 1050; MS *m/z* (rel.intensity %): 512 (M^+,22), 466 (35), 424 (52), 392 (38), 350 (41), 318 (12), 276 (44), 264 (9), 246 (18), 191 (15), 115 (25), 91 (37), 77 (30), 59 (19), 43 (base peak); Anal. calcd. for $C_{26}H_{28}N_2O_9$: C 60.93, H 5.51, N 5.47; found: 60.93, H 5.54, N 5.44;

8-Acetyl-6-(1,3-benzodioxol-5-yl)-7-ethoxycarbonyl-9-phenyl-2-oxo-1,8-diaza-spiro-[4.4]-nonane (28) was prepared analogously to **14** from compound **27**, and isolated as a white powder in 92 % yield; m.p. 118-20 °C; ^{1}H-NMR (250 MHz) δ: 7.6-7.2 (m, 5H, Ph), 7.1-6.6 (m, 3H, Ar), 5.95 (s, 2H, OCH_2O), 4.91 (s, 1H, H-9), 4.81 (d, 1H, J= 9.4 Hz, H-7), 4.20 (q, 2H, $C\underline{H}_2$-CH_3), 3.49 (d, 1H, J= 9.4 Hz, H-6), 2.20 (m, 2H, H_2-3), 2.05 (m, 2H, H_2-4), 1.61 (s, 3H, CH_3-CO), 1.16 (t, 3H, $C\underline{H}_3$-CH_2); ^{13}C-NMR (62.5 MHz) δ: 176.0 (CH_3-$\underline{C}O$), 173.5 ($\underline{C}OOEt$), 171.1 (C-2), 148.1 (Ar-3'C), 148.0 (Ar-4'C), 136.6 (Ph-1'C), 129.0 (Ph-2'C, Ph-6'C), 128.8 (Ph-3'C, Ph-5'C), 127.9 (Ph-4'C), 125.4 (Ar-1'C), 123.9 (Ar-6'C), 110.2 (Ar-2'C), 108.4 (Ar-5'C), 101.3 (OCH_2O), 73.3 (C-9), 71.6 (C-5), 64.6 (C-7), 61.9 ($\underline{C}H_2$-CH_3), 54.6 (C-6), 28.7 (C-4), 28.6 (C-3), 23.2 ($CO\underline{C}H_3$), 13.7 ($\underline{C}H_3CH_2$); IR (KBr, cm^{-1}): 3450, 2940, 1690, 1640, 1480, 1430, 1390, 1330, 1300, 1245, 1220, 1200, 1090, 1020, 910, 790, 700; MS *m/z* (rel. intensity %): 450 (M^+, 15), 377 (17), 302 (49), 257 (22), 230 (32), 220 (40), 191 (17), 148 (18), 130 (12), 117 (60), 106 (32), 89 (30), 77 (20), 65 (11), 56 (19), 43 (base peak); Anal. calcd. for $C_{25}H_{26}N_2O_6$: C 66.66, H 5.82, N 6.22; found: C 66.69, H 5.78, N 6.22;

6-(1,3-Benzodioxol-5-yl)-8-ethyl-7-(hydroxy-methyl)-9-phenyl-1,8-diaza-spiro-[4.4]-nonane (29). To a stirred suspension of lithium aluminium hydride (1.4 g, 36.7 mM) in rigorously dried THF (20 mL, distilled from potassium) under nitrogen was added the lactam **28** (1.1 g, 2.4 mM) dissolved in 15 ml THF. The reaction mixture was then heated, and stirred at reflux for 3 days, then cooled, and treated with water (2 mL) and 20% NaOH solution (4 mL). The mixture was warmed to room temperature, 80 mL ether was added, then was

filtered and the filtrate washed sequentially with 20% NaOH solution (15 mL), brine, then dried over $MgSO_4$, and concentrated to yield compound **29** as a viscous oil 0.9 g (98 %); ^{1}H-NMR (250 MHz) δ: 7.4-7.3 (m, 5H, Ph), 7.27 (s, 1H, Ar-2'H), 6.98 (d, 1H, Ar-6'H), 6.76 (d, 1H, Ar-5'H), 5.94 (s, 2H, OCH_2O), 4.12 (s, 1H, H-9), 3.70 (dd, 1H, J=3.5 and 11.6 Hz, HO-C$\underline{H}_2$), 3.56 (dd, 1H, J=1.3, and 11.6 Hz, HO-C$\underline{H}_2$), 3.36 (d, 1H, J=9.5 Hz, H-6), 3.20 (ddd, 1H, J= 1.3 and 3.4 and 9.5 Hz, H-7), 2.75 (m, 1H, H-2) 2.62 (m, 1H, H-2), 2.40 (q, 2H, -C$\underline{H}_2$CH$_3$), 1.79 (m, 1H, H-4), 1.77 (m, 1H, H-4), 1.04 (m, 1H, H-3), 1.02 (t, 3H, -CH$_2$C$\underline{H}_3$), 0.93 (m, 1H, H-3); ^{13}C-NMR (62.5 MHz) δ: 147.7 (Ar-3'C), 146.6 (Ar-4'C), 138.5 (Ph-1'C), 130.4 (Ar-1'C), 128.5 (Ph-2'C, Ph-6'C), 128.2 (Ph-3'C, Ph-5'C), 127.9 (Ph-4'C), 124.5 (Ar-6'C), 110.9 (Ar-2'C), 107.9 (Ar-5'C), 100.8 (OCH_2O), 75.4 (C-9), 72.1 (C-5), 65.2 (C-7), 62.3 ($\underline{C}H_2OH$), 59.9 (C-6), 47.5 (N-CH_2), 46.6 (C-2), 32.3 (C-4), 25.8 (C-3), 11.7 (CH_3); IR (film, cm^{-1}): 3400, 3000, 2910, 1480, 1440, 1220, 1150, 1020, 910, 790, 680; MS *m/z* (rel. intensity %): 380 (M^+, 8), 350 (62), 304 (13), 292 (10), 246 (17), 228 (14), 216 (58), 203 (71), 191 (50), 176 (81), 159 (80), 148 (90), 134 (56), 118 (58), 104 (39), 91 (base peak), 86 (56), 77 (55), 65 (33), 56 (55); Anal. calcd. for $C_{23}H_{28}N_2O_3$: C 72.61, H 7.42, N 7.36; found: C 72.69, H 7.49, N 7.33;

2-Ethyl-1-(hydroxymethyl)-3-phenyl-1,3,4,5,8,12a-hexahydro-[1.3]dioxolo[4,5-g]pyrrolo[3,4-c]pyrrolo [1,2-b]isoquinoline (30). Amine **29** (0.5 g, 1.36 mM) and paraformaldehyde (0.40 g 13.6 mM) were dissolved in benzene, and one drop conc. HCl was added. After 3 h reflux the cooled mixture was poured into saturated $NaHCO_3$ solution, extracted into $CHCl_3$, and the $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to yield a white solid 0.4 g (81 %); m.p. 136 °C; ^{1}H-NMR (500 MHz) δ: 7.32-7.25 (m, 5H, Ph), 6.70 (s, 1H, H-12), 6.67 (s, 1H, H-8), 5.94 (d, 2H, H-10), 4.32 (d, 1H, J=15.2 Hz, H-12b), 3.72 (s, 1H, H-3), 3.45 (dd, 1H, J=15.2 Hz and 2.5 Hz), 3.44 (m, 1H), 3.35-3.28 (m, 2H), 3.20 (m, 1H), 2.65 (m, 1H, H-6), 2.53 (m, 1H, H-6), 2.47 (q, 2H, NCH_2CH_3), 1.98 (m, 1H, H-4), 1.60 (m, 1H, H-4), 1.09 (m, 1H, H-5), 0.80 (t, 3H, CH_3), 0.72 (m, 1H, H-5); ^{13}C-NMR (62.5 MHz) δ: 146.6 (C-11a), 146.5 (C-8a), 139.6 (Ph-1'C), 133.2 (C-7a), 130.5 (C-12a), 128.5 (Ph-4'C), 127.4 (Ph-2'C and Ph-6'C), 127.3 (Ph-3'C and Ph-5'C), 110.9 (C-12), 108.8 (C-8), 101.1 (C-10), 79.5 (C-3), 71.3 (C-3a), 66.0 (C-1), 61.9 (CH_2OH), 55.0 (C-7), 53.2 (N$\underline{C}H_2CH_3$), 50.4 (C-12b), 44.4 (C-6), 39.3 (C-4), 24.1 (C-5), 9.2 (CH_3); IR (KBr, cm^{-1}): 3427, 2961, 2919, 2860, 2790, 1501, 1487, 1452, 1373, 1326, 1253, 1238, 1173, 1125, 1093, 1039, 936, 700; Anal. calcd. for $C_{24}H_{28}N_2O_3$: C 73.44, H 7.19, N 7.14; found C 73.42, H 7.16, N 7.14.

6-(1,3-Benzodioxol-5-yl)-8-ethyl-7-(hydroxymethyl)-1-[(methylthio)acetyl]-9-phenyl-1,8-diaza-spiro-[4.4]-nonane (33). 0.09 g (0.87 mM) (methylthio)acetic acid and 0.12 mL (0.087 g, 0.87 mM) triethylamine was dissolved in 2 mL CH_2Cl_2 and at 0°C 0.082 mL (0.094 g, 0.87 mM) and ethyl chloroformate in 2 mL CH_2Cl_2 was added. After one hour stirring at 0°C 0.3 g (0.79 mM) **29** amine in 5 mL CH_2Cl_2 was added and the reaction mixture was stirred at room temperature for 24 hours. After the evaporation of solvent the crude product was purified by column chromatography (eluent: hexane - ethyl acetate 1:1 vol/vol) to yield **33** as a pale yellow oil 0.28 g (78 %). ^{1}H-NMR (250 MHz) δ: 7.4-7.3 (m, 5H, Ph), 7.31 (s, 1H, Ar-2'H), 7.02 (d, 1H, Ar-6'H), 6.70 (d, 1H, Ar-5'H), 5.98 (s, 2H, OCH_2O), 4.41 (dd, 1H, J=10.7 Hz and 6.6 Hz, H-7), 4.25 (dd, 1H, J=10.7 Hz and 5.6 Hz, C$\underline{H}_2$OH), 4.18-4.10 (m, 2H, H-6 and C$\underline{H}_2$OH), 3.99 (s, 1H, H-9), 3.17 (s, 2H, SCH_2), 2.77 (q, 2H, NC$\underline{H}_2$CH$_3$), 2.61 (m, 1H, H-2), 2.49 (m, 1H, H-2), 2.20 (s, 3H, SMe), 2.03 (m, 1H, H-4), 1.85 (m, 1H, H-4), 1.09 (m, 1H, H-3), 1.00 (m, 1H, H-3), 0.94 (t, 3H, $NCH_2C\underline{H}_3$); ^{13}C-NMR (62.5 MHz) δ: 170.1

(C=O), 146.9 (Ar-3'C), 146.1 (Ar-4'C), 139.0 (Ph-1'C), 131.3 (Ar-1'C), 128.3 (Ph-2'C and Ph-6'C), 128.1 (Ph-3'C and Ph-5'C), 127.4 (Ph-4'C), 124.2 (Ar-6'C), 111.0 (Ar-2'C), 107.3 (Ar-5'C), 69.8 (C-7), 63.4 (SCH_2), 62.3 ($HO\underline{C}H_2$), 55.5 (C-6), 47.0 ($N\underline{C}H_2CH_3$), 35.5 (C-2), 33.9 (C-4), 24.7 (C-3), 14.1 (MeS), 10.5 ($NCH_2\underline{C}H_3$); IR (film, cm^{-1}) 3300, 2905, 2820, 1725, 1641, 1479, 1433, 1250, 1145, 1113, 1019, 910, 799;

6-(1,3-Benzodioxol-5-yl)-8-ethyl-7-(hydroxymethyl)-1-[(methylsulfinyl)acetyl]-9-phenyl-1,8-diaza-spiro-[4.4]-nonane (34). 0.22 g (0.48 mM) **33** was dissolved in 2 mL methanol and 2 mL CH_2Cl_2 at 0°C than 0.15 g $NaIO_4$ in 3 mL water was added. The reaction mixture was stirred at room temperature overnight and filtered. 15 mL CH_2Cl_2 was added, washed with brine, dried over $MgSO_4$, and evaporated to yield 0.28 g (81.3 %) **34** as pale red oil. ^{1}H-NMR (80 MHz) δ: 7,5- 7,3 (bs, 5H, Ph), 7.0-6.6 (m, 3H, Ar-H), 5,9 (s, 2H, OCH_2O), 4,4-1,1 (m, 15H), 2,7 (s, 3H, S(O)Me), 0,9 (t, 3H, N-CH_2-$C\underline{H}_3$); IR (film, cm^{-1}): 3400, 2950, 1720, 1470, 1430, 1360, 1240, 1100, 1020, 920, 820;

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