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Influence of Ag(I) and Li(I) Catalysts for 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides. Reversal of the Stereochemistry

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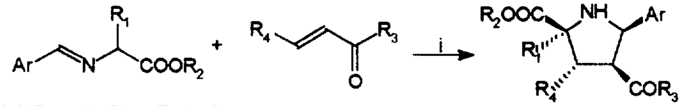
Abstract: The 1,3-dipolar cycloadditions of ester stabilised azomethin ylides to aryl-nitro olefines catalysed by Li(I) gave products of different stereoselectivity than those arising from processes catalysed by Ag (I). The cycloadditions involve the stereospecific generation of dipoles. The formation of products with reverse stereochemistry when using different metal salt catalysts is caused by the differences in endo and exo approaches of nitro-ethylene compounds.

INTRODUCTION

The 1,3 dipolar cycloaddition of azomethine ylides with an olefin offers a convenient one-step route for the construction of a variety of complex pyrrolidine derivatives[1] with stereogenic centers because the reactions usually proceed in a concerted process.[2] Although many examples of regio- and/or stereoselective 1,3 dipolar cycloadditions have been reported their selectivity usually depends upon the nature of the dipoles and dipolarophiles used. It means the substrate control is so far the only useful way for the stereo- and/or regiocontrol of dipolar cycloadditions. There are only a few reports when the regioselection can be controlled by influencing the ylide precursors[3] while the only known way to affect the stereochemistry of cycloadducts is the different route for the azomethine ylide generation thereby influencing the geometry of dipole.

As a part of our ongoing program[4] concerning the synthesis of novel analogues of *Cephalotaxus* alkaloids we required a short and efficient procedure for the preparation of pyrrolidines bearing an aromatic substituent at C-3 and a nitro-group at C-4 in *trans*-position.[5] Pursuant to our synthetic objective we chose to investigate the synthesis of pyrrolidines by cycloaddition of azomethine ylides derived from acceptor-substituted imines, to 1-aryl-2-nitroethylenes. This type of reaction has been intensively investigated by the groups of *Grigg,*[6] *Kanemasa,*[7] and others.[8] They have found that the stereospecific NH-azomethine ylide formation by 1,2-prototopy in aryl imines activated by electron withdrawing groups offer simple routes to a wide range of novel polyfunctionalised pyrrolidines. The dipoles thermally generated from the imines of glycine ester undergo stereoselective cycloadditions with highly activated cyclic dipolarophiles such as maleinimides, leading the exclusive formation of *endo* adducts of E,E-ylides.[9] However, their cycloadditions to less reactive olefin dipolarophiles such as maleates and fumarates are no longer stereoselective.[10] The application of a wide range of metal salt/tertiary amine combinations has proved to be effective for increasing the rate of the cycloaddition of aryl imines to less reactive dipolarophiles at room temperature with excellent regio- and stereocontrol as well.[6-9] The chiral versions of these processes have been developed succesfully.[6d,6e,8] In these cycloadditions the remarkable rate acceleration indicates that either the presumably formed metallo-azomethine ylides are more reactive than the NH-azomethine ylides or the dipolarophiles are also activated by coordination with the metal salt or both. The most efficient and most often employed catalysts are the silver (I) and lithium(I) salts with triethylamine as a base. Although the alkenes can react in an *endo* or in an *exo* mode (*endo* and *exo* being referred to the electron-withdrawing group on the alkene) to best of our knowledge, in all cases the *endo*-adduct was the major or exclusive product (Scheme 1).



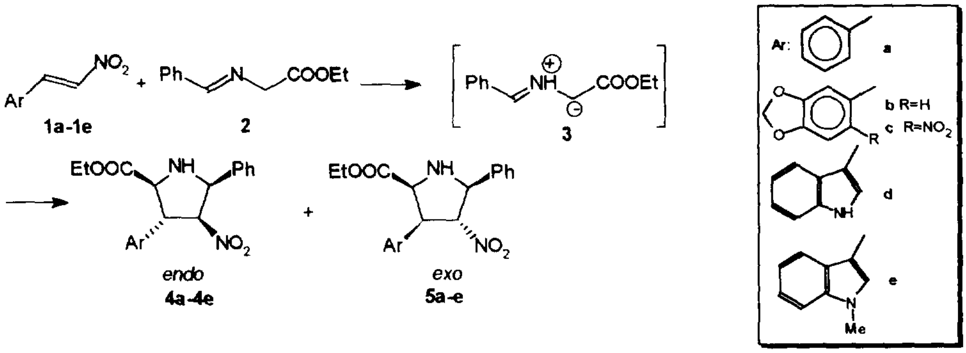
i. LiBr or AgOAc, Et_3N, CH_3CN, r.t.

Scheme 1

RESULTS AND DISCUSSIONS

In our laboratories we have found these processes catalysed by Li (I) gave major products with different stereoselectivity than those arising from the reactions catalysed by Ag(I) using various aryl-nitro olefines as dipolarophile.

Starting from the corresponding aromatic aldehydes the nitro-olefines **1a-e** were prepared.[11] These were then allowed to react with the glycine-derived azomethine ylide **3** generated in acetonitrile solution from the corresponding imine **2** with triethylamine in the presence LiBr or AgOAc. In each case single regioisomers were obtained from the reaction mixture (Scheme 2).



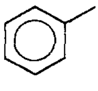
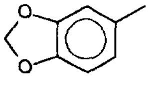
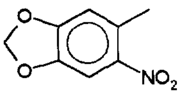
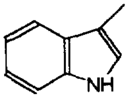
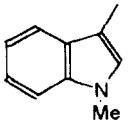
Scheme 2

Except for the cycloadducts derived from β-nitro-styrene **1a** the yields were determined after the usual work-up when the major product was crystallized from the reaction mixture. In the case of **4a** and **5a** the yields were based on column chromatographic separation. The exact product ratios were determined by HPLC using the purified cycloadducts as standard (Table 1).

In all cases the dipolarophiles **1a-e** were allowed to react with the thermally generated azomethine ylide (110 °C, toluene)[10] and because of their sluggish reactivity the formation of two additional isomers presumably derived from the (E,Z)-azomethine ylide as minor products **6** and **7** and the loss of diastereoselectivity were observable. This reaction has no preparative value because the isomer mixture obtained proved to be unseparable.

Scheme 3

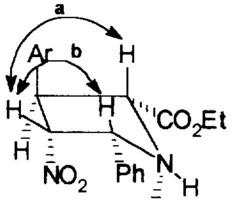
With the exception the reaction of dipolarophile **1a**, in all cases reversal of diastereoselectivity was detected when metal salt/triethylamine system was changed by from the LiBr to AgOAc. From preparative point of view it is very favourable as all major cycloadducts were easily obtained from the reaction mixture in pure form and in a moderate yield. When Ar=Ph the LiBr catalysed reaction showed poor, but usual diastereoselectivity while with AgOAc no significant change were noticed. In the light of the previous theoretical considerations based on the experimental results it seems to be very likely to us that the secondary orbital interactions of the aryl-groups play a major role in this changing of the stereoselectivity. The interaction might work in the case of AgOAc catalyst between the "second ring" of the Ar substituent while the "monocyclic" phenyl ring not a well disposed for this interaction. The diastereomers **4a-e** obtained from the LiBr catalysed cycloadducts can arise from the transition state suggested by *Tsuge et al*[7c] in which both dipole and dipolarophile are considered to be coordinated to the same Li (I) cation.

Dipolarophiles (Ar =)	**Catalyst**	**Temperature**	**Yields**	**Product ratio**
	- LiBr AgOAc	110 °C r.t. r.t.	- **4a*** : 22 % **5a*** : 17 %	**4a:5a** - 1: 1 **4a:5a** - 1.4: 1 **4a:5a** - 1.25: 1
	- LiBr AgOAc	110 °C r.t. r.t.	- **4b** : 61 % **5b** : 42 %	**4b:5b** - 1: 1.25 **4b:5b** - 2.5: 1 **4b:5b** - 1: 1.7
	- LiBr AgOAc	110 °C r.t. r.t.	- **4c** : 39 % **5c** : 44 %	decomp. **4c:5c** - 2.6:1 **4c:5c** - 1:1.9
	- LiBr AgOAc	110 °C r.t. r.t.	- **4d** : 47 % **5d** : 36 %	appr. 1:1$^{\#}$ **4d:5d** - 3.5:1 **4d:5d** - 1:2.3
	- LiBr AgOAc	110 °C r.t. r.t.	- **4e** : 59 % **5e** : 51 %	appr. 1:1$^{\#}$ **4e:5e** - 3.0:1 **4e:5e** - 1: 2.3

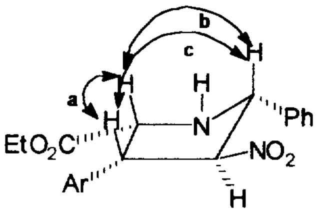
* After column chromatography
$^{\#}$ determined by ^{1}H-NMR

Table 1

The relative stereochemistries of the cycloadducts were established by n.O.e. studies. The predominating conformers are depicted in Scheme 3 (arrows show the steric proximity obtained from n.O.e. (NOESY) experiments) established with the help of dihedral angles calculated from modified Karplus equation. We have found the predominating conformation of *endo*-products is an envelope with N-1 as an out of plane atom, while the *exo*-products exist as an envelope with C-5 as the out of plane atom.



4a-e



5a-e

Selected n.O.e. dates:		
4b a = 1.6 %, b = 6.5 %	**5b** a = 4.7 %, b = 5.2 %, c = 5.0 %	
4e a = 4.3 %, b = 6.7 %	**5c** a = 5.1 %, b = 4.3 %	
	5d a+b = 18 %	
	5e a = 6.7 %, b = 3.5 %, c = 1.2 %	

In conclusion we have shown that the 1,3-dipolar cycloaddition of an azomethine ylide to aryl-nitro ethylenes occur with reverse stereoselectivity depending on the catalysts used. This exploration allow us to obtain the *exo-* or *endo*-cycloadduct according to the current synthetic goal.

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 cc. sulphuric acid and 1 ml anisaldehyde) and heated at ca. 150°C. IR spectra were measured on a SPECORD75 and NICOLET FT-IR instrument. Low resolution electron impact mass 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, in all cases TMS served us the internal standard. Melting points are uncorrected.

General procedure: 10 mM ethyl (benzylideneamino)acetate and 9 mM aryl-nitroethylene were dissolved in 50 mL acetonitrile then 1.7 mL (1.21 g, 12 mM) triethylamine and 2.5 g (15 mM) AgOAc or 1.26 g LiBr (15 mM) were added to the well stirred reaction mixture. After 1-3 h when the reaction was completed (judged by TLC) 25 mL saturated aqueous ammonium chloride was added, the precipitate was filtered off and the residue was extracted with ether. The combined organic fractions were dried over magnesium sulfate, evaporated and the residue was trituated with ether. The crystallised product was collected to yield white powders.

3,5-Diphenyl-2-ethoxycarbonyl-4-nitro-pyrrolidine

Isomer **4a**: white powder; m.p. 118-20 °C; ^{1}H-NMR (250 MHz) δ: 7.2-7.5 (m,10H, Ph), 5.29 (dd, 1H, J=3.7 Hz and 6.6 Hz, H-4), 4.89 (d, 1H, J= 6.6 Hz, H-5), 4.20 (q, 2H, CH_2), 4.17 (dd, 1H, J= 7.6 Hz and J= 3.7 Hz, H-3), 4.08 (d, 1H, J=7.6 Hz, H-2), 1.2 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 171.2 (C=O), 138.4 (3-Ar-1'C), 134.5 (5-Ar-1'C), 129.1 (3-Ar-3' and 5'C), 128.5 (5-Ar-3' and 4' and 5'C), 127.9 (3-Ar-4'C), 127.4 (3-Ar-2' and 6'C), 126.4 (5-Ar-2' and 6'C), 96.8 (C-4), 67.5 (C-5), 67.3 (C-2), 61.5 (CH_2), 55.3 (C-3), 14.0 (CH_3); IR (KBr, cm^{-1}): 3340, 2982, 1731, 1604, 1551, 1496, 1455, 1370, 1203, 1130, 1097, 1029, 945, 906, 757, 699; MS *m/z* (rel. intensity %): 340 (M^+, 9), 294 (4), 267 (15), 220 (57), 193 (46), 191 (35), 178 (12), 165 (10), 117 (78), 115 (98), 103 (34), 91 (65), 77 (base peak), 65 (13), 51 (45); Anal. calcd. for $C_{19}H_{20}N_2O_4$: C 67.05, H 5.92, N 8.23; found C 67.01, H 5.98, N 8.25

Isomer **5a**: white powder; m.p.110-1 °C; ^{1}H-NMR (250 MHz) δ: 7.2-7.6 (m, 10H, ArH), 5.21 (t, 1H, J= 8.3 Hz, H-4), 4.75 (d, 1H, J=8.3 Hz, H-5), 4.48 (d, 1H, J=9.0 Hz, H-2), 4.40 (t, 1H, J= 9.0 Hz, H-3), 3.7-3.8 (m, 2H, CH_2), 2.75 (broad s, 1H, NH), 0.8 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 171.4 (C=O), 137.7 (3-Ar-1'C), 136.1 (5-Ar-1'C), 129.0 (3-Ar-3' and 5'C), 128.9 (5-Ar-4'C), 128.7 (5-Ar-3' and 5'C), 128.1 (3-Ar-4'C), 128.0 (3-Ar-2' and 6'C), 126.9 (5-Ar-2' and 6'C), 95.2 (C-4), 67.5 (C-5), 64.1 (C-2), 61.2 (CH_2), 53.7 (C-3), 13.5 (CH_3); IR (KBr, cm^{-1}): 3360, 3058, 3032, 2982, 2901, 1732, 1602, 1548, 1490, 1452, 1381, 1367, 1301, 1256, 1203, 1184, 1094, 1053, 1033; MS *m/z* (rel. intensity %): 340 (M^+, 14), 267 (22), 220 (22), 193 (44), 178 (20), 165 (9), 117 (85), 115 (base peak), 103 (39), 91 (61), 77 (96), 65 (10), 51 (51); Anal. calcd. for $C_{19}H_{20}N_2O_4$: C 67.05, H 5.92, N 8.23; found C 67.00, H 5.94, N 8.23.

3-(1,3-Benzodioxole-5-yl)-2-ethoxycarbonyl-4-nitro-5-phenyl-pyrrolidine

Isomer **4b**: 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-3'C), 147.2 (Ar-4'C), 137.7 (Ph-1'C), 129.6 (Ar-1'C), 128.8 (Ph-3'C and Ph-5'C), 128.7 (Ph-4'C), 126.7 (Ph-2'C and Ph-6'C), 121.0 (Ar-6'C), 108.1 (Ar-2'C and Ar-5'C), 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.

Isomer **5b**: 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, J= 6.7 Hz,1H, 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-1'C), 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.

2-Ethoxycarbonyl-4-nitro-3-(6-nitro-1,3-benzodioxole-5-yl)-5-phenyl-pyrrolidine

Isomer **4c**: yellow powder; m.p. 108 °C; ^{1}H-NMR (80 MHz) δ: 7.6-7.15 (m, 6H, Ph-H and Ar-6'H), 6.9 (s, 1H, Ar-3'H), 6.10 (s, 2H, OCH_2O), 5.0 (dd, 1H, H-4), 4.65 (d, 1H, H-5), 4.55 (t, 1H, H-3), 4.2 (q, 2H, CH_2), 4.0 (d, 1H, H-2), 3.2 (bs, 1H, NH), 1.3 (t, 3H, CH_3); IR (KBr, cm^{-1}): 3400, 3294, 1735, 1619, 1549, 1511, 1475, 1324, 1263, 1205, 1036, 931, 874; MS *m/z* (rel. intensity %): 429 (M^+, 7), 382 (26), 356 (22), 310 (75), 292 (86), 282 (base peak), 235 (55), 206 (79), 177 (25), 163 (44), 148 (67), 117 (96), 103 (30), 77 (21); Anal. calcd. for $C_{20}H_{19}N_3O_8$: C 55.94, H 4.46, N 9.79; found C 55.98, H 4.51, N 9.81.

Isomer **5c**: yellow powder; m.p. 115 °C; ^{1}H-NMR (250 MHz) δ: 7.47 (s, 1H, Ar-6'H), 7.23 (s, 5H, Ph), 6.95 (s, 1H, Ar-3'H), 6.13 (s, 2H, OCH_2O), 5.25 (dd, 1H, J= 6.6 Hz and 3.4 Hz, H-4), 4.91 (d, 1H, J=6.6 Hz, H-5), 4.83 (dd, 1H, J=3.4 Hz and J=6.8 Hz, H-3), 4.24 (q, 2H, CH_2), 4.07 (d, 1H, J=6.8 Hz, H-2), 3.37 (bs, 1H, NH), 1.22 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 171.0 (CO), 152.4 (Ar-3'C), 147.7 (Ar-4'C), 143.3 (Ar-6'C), 134.1 (Ph-1'C), 129.5 (Ar-1'C), 128.7 (Ph-3'C, 4'C and 5'C), 126.4 (Ph-2'C and 6'C), 107.8 (Ar-2'C), 106.0 (Ar-5'C), 103.4 (OCH_2O), 96.2 (C-4), 67.4 (C-5), 66.5 (C-2), 61.9 (CH_2-ester), 51.0 (C-3), 13.9 (CH_3); IR

(KBr, cm^{-1}):3450, 3291, 1737, 1616, 1546, 1506, 1473, 1395, 1327, 1263, 1200, 1038, 931, 873; MS *m/z* (rel. intensity %): 429 (M^+, 3), 382 (24), 356 (18), 310 (80), 292 (78), 282 (base peak), 263 (28), 235 (50), 206 (70), 177 (42), 163 (42), 148 (71), 117 (82), 103 (44), 77 (17); Anal. calcd. for $C_{20}H_{19}N_3O_8$: C 55.94, H 4.46, N 9.79; found C 55.97, H 4.50, N 9.78.

2-Ethoxycarbonyl-3-(indol-3-yl)-4-nitro-5-phenyl-pyrrolidine

Isomer **4d**: white powder; m.p. 138 °C; ^{1}H-NMR (500 MHz) δ: 8.52 (s, 1H, Ind-NH), 7.58 (d, 1H, Ind-4'H), 7.35 (d, 1H, Ind-7'H), 7.30-7.25 (m, 5H, Ph), 7.22 (t, 1H, Ind-6'H), 7.16 (t, 1H, Ind-5'H), 7.11 (d, 1H, Ind-2'H), 5.34 (dd, 1H, J= 2.9 and 6.1 Hz, H-4), 4.88 (d, 1H, J= 6.1 Hz, H-5), 4.52 (dd, 1H, J=2.8 and 6.8 Hz, H-3), 4.32 (d, 1H, J=6.8 Hz, H-2), 4.26 (q, 2H, CH_2), 3.5 (broad s, 1H, NH), 1.21 (t, 3H, CH_3); ^{13}C-NMR (125 MHz) δ: 170.9 (C=O), 135.8 (Ph- 1'C), 133.5 (Ind-7a'C), 122.7 (Ph-3'C and Ph-5'C), 127.6 (Ph-4'C), 125.4 (Ph-2'C and Ph-6'C), 125.0 (Ind-3a'C), 121.9 (Ind-2'C), 121.0 (Ind-6'C), 119.2 (Ind-5'C), 117.4 (Ind-4'C), 112.4 (Ind-7'C), 110.8 (Ind-3'C), 95.2 (C-4), 66.2 (C-5), 64.8 (C-2), 66.8 (ester-CH_2), 47.2 (C-3), 13.1 (CH_3); IR (KBr, cm^{-1}): 3408, 3272, 3178, 3109, 3047, 2978, 2926, 3873, 2678, 2492, 1735, 1647, 1618, 1543, 1497, 1458, 1374, 1342, 1297, 1254, 1199, 1144, 1096, 1027, 924; MS *m/z* (rel. intensity %): 379 (M^+, 18), 332 (8), 259 (43), 232 (98), 217 (7), 202 (10), 191 (52), 154 (32), 143 (17), 130 (50), 115 (base peak), 102 (17), 91 (21), 77 (28), 65 (12), 51 (19), 43 (23); Anal. calcd. for $C_{21}H_{21}N_3O_4$: C 66.48, H 5.58, N 11.07; found C 66.47, H 5.61, N 11.07.

Isomer **5d**: white powder; m.p. 173 °C; ^{1}H-NMR (250 MHz) δ: 11.03 (broad s, 1H, Ind-NH), 7.69 (d, 1H, Ind-H'4), 7.61 (d, 2H, Ph-2'H, Ph-6'H), 7.50-7.35 (m, 4H, Ph-3'H, Ph-4'H, Ph-5'H and Ind-H'7), 7.28 (d, 1H, Ind-H'2), 7.11 (t, 1H, Ind-6'H), 7.04 (t, 1H, Ind-H'5), 5.42 (dd, 1H, J=8.8 Hz and 9.8 Hz, H-4), 4.81 (d, 1H, J=8.8, H-5), 4.75 (dd, 1H, J=9 Hz and J=9.5 Hz, H-3), 4.54 (d, 1H, J=9.0 Hz, H-2), 3.87 (broad s, 1H, NH), 3.60 (m, 2H, CH_2), 0.54 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 172.2 (C=O), 140.2 (Ind-C'7a), 136.2 (Ph-C'1), 128.7 (Ph-C'3 and Ph-C'5), 128.4 (Ph-C'4), 127.2 (Ph-C'2 and Ph-C'6), 126.9 (Ind-C'3a), 123.0 (Ind-C'2), 121.5 (Ind-C'6), 118.9 (Ind-C'5), 118.8 (Ind-C'4), 111.6 (Ind-C'7), 108.6 (Ind-C'3), 95.0 (C-4), 66.5 (C-5), 62.9 (C-2), 59.8 (CH_2), 45.6 (C-3), 13.1 (CH_3); IR (KBr, cm^{-1}): 3405, 3343, 3063, 3028, 2981, 2938, 2903, 1713, 1622, 1553, 1493, 1459, 1434, 1374, 1358, 1339, 1327, 1266, 1234, 1217, 1122, 1110, 1078, 1047, 1022; MS *m/z* (rel. intensity %): 379 (M^+, 22), 332 (10), 259 (23), 232 (base peak), 217 (6), 202 (8), 191 (18), 154 (31), 143 (20), 130 (38), 117 (93), 115 (73), 102 (18), 90 (22), 77 (45), 65 (10), 51 (17); Anal. calcd. for $C_{21}H_{21}N_3O_4$: C 66.48, H 5.58, N 11.07; found C 66.48, H 5.59, N 11.09.

2-Ethoxycarbonyl-3-(N-methyl-indol-3-yl)-4-nitro-5-phenyl-pyrrolidine

Isomer **4e**: white powder; m.p. 116 °C; ^{1}H-NMR (250 MHz) δ: 7.59 (d, 1H, Ind-4'H), 7.34 (s, 5H, Ph), 7.30-7.15 (m, 3H, Ind-H), 7.07 (s, 1H, Ind-2'H), 5.34 (dd, 1H, J=6.1 and 2.9 Hz, H-4), 4.91 (d, 1H, J=6.1 Hz, H-5), 4.51 (dd, 1H, J= 2.7 and 6.6 Hz, H-3), 4.34 (d, 1 H, J= 6.6 Hz, H-2), 4.28 (q, 2H, CH_2), 3.78 (s, 3H, NMe), 1.26 (t, 3H, CH_3); ^{13}C-NMR (62.5 MHz) δ: 171.7 (C=O), 137.4 (Ind-C'7a), 134.4 (Ph-1'C), 128.7 (Ph-3'C, Ph-5'C), 128.5 (Ph-4'C), 126.5 (Ind-2'C), 126.3 (Ph-2'C, Ph-6'C, Ind-C'3a), 122.5 (Ind-6'C), 119.8 (Ind-4'C), 118.6 (Ind-5'C), 112.0 (Ind-3'C), 109.8 (Ind-7'C), 96.2 (C-4), 67.3 (C-5), 65.8 (C-2), 61.7 (CH_2), 48.2 (C-3), 32.8 (N-Me), 14.1 (CH_3); IR (KBr, cm^{-1}): 3446, 3303, 3048, 2981, 2896, 1731, 1616, 1548, 1458, 1365, 1303, 1249, 1186, 1133, 1029, 866; MS *m/z* (rel. intensity %): 393 (M^+, 22), 346 (17), 320 (5), 273 (30), 246 (base peak), 230 (8), 203 (10), 191 (35), 168 (20), 155 (15), 144 (36), 131 (36), 117 (88), 103 (10), 91 (21), 77 (36), 65 (8), 51 (12), 42 (37); Anal. calcd. for $C_{22}H_{23}N_3O_4$: C 67.16, H 5.89, N 10.68; found C 67.12, H 5.94, N 10.66.

Isomer **5e**: white powder; m.p.164-166 °C; ^{1}H-NMR (300 MHz) δ: 7.62 (d, 1H, Ind-4'H), 7.57 (d, 2H, Ph-2'H and Ph-6'H), 7.42-7.32 (m, 3H, Ph-3'H, 4'H and 5'H), 7.23-7.20 (m, 2H, Ind-6'H and 7'H) 7.12 (m, 1H, Ind-5'H), 6.97 (s, 1H, Ind-2'H), 5.28 (t, 1H, J= 8.2 Hz, H-4), 4.79 (d, 1H, J=8.2 Hz, H-5), 4.75 (t, 1H J=8.3 Hz, H-3) 4.58 (d, 1H, J=8.2 Hz, H-2), 3.64 (s, 3H, NMe), 3.69-3.51 (m, 2H, CH_2), 2.76 (s, 1H, NH), 0.54 (t, 3H, ester CH_3); ^{13}C-NMR (75 MHz) δ: 172.1 (C=O), 138.1 (Ind-7a'C), 136.8 (Ph-1'C), 128.9 (Ph-3'C and Ph-5'C), 128.7 (Ph-4'C), 127.1 (Ind-3a'C), 126.8 (Ph-2'C and Ph-6'C), 126.3 (Ind-2'C), 122.1 (Ind-6'C), 119.3 (Ind-4'C), 119.0 (Ind-5'C), 109.2 (Ind-7'C), 109.0 (Ind-3'C), 95.1 (C-4), 67.3 (C-2), 63.5 (C-5), 60.7 (CH_2), 45.8 (C-3), 32.6 (NCH_3), 13.0 (CH_3); IR (KBr, cm^{-1}): 3320, 3054, 2990, 2937, 2891, 1897, 1817, 1724, 1684, 1618, 1543, 1464, 1393, 1377, 1336, 1268, 1244, 1210, 1155, 1129, 1111, 1084, 1038, 1013; MS *m/z* (rel. intensity %): 393 (M^+, 53), 346 (11), 320 (4), 273 (49), 246 (base peak), 230 (12), 203 (21), 191 (73), 168 (30), 154 (18), 144 (38), 131 (62), 117 (91), 115 (93), 103 (13), 91 (32), 77 (40), 65 (11), 51 (13), 43 (13); Anal. calcd. for $C_{22}H_{23}N_3O_4$: C 67.16, H 5.89, N 10.68; found C 67.14, H 5.92, N 10.68.

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