Pergamon

Tetrahedron 57 (2001) 1129–1137

TETRAHEDRON

2-Oxoindolin-3-ylidene derivatives as 2π components in 1,3-dipolar cycloadditions of azomethine ylides

Imre Fejes,[a] Miklós Nyerges,[a,*] Áron Szöllõsy,[b] Gábor Blaskó[c] and László Tõke[a]

[a]*Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P.O.B. 91, Hungary*
[b]*Institute for General and Analytical Chemistry, Technical University of Budapest, H-1111 Budapest Gellért tér 4, Hungary*
[c]*EGIS Pharmaceuticals Ltd, H-1475 Budapest, P.O.B. 100, Hungary*

Received 14 September 2000; revised 26 October 2000; accepted 9 November 2000

Abstract—The 1,3-dipolar cycloadditions of various azomethine ylides to 2-oxoindolin-3-ylidene derivatives have been investigated. The structure and stereochemistry of cycloadducts were studied in detail by NMR spectroscopic methods.

1. Introduction

1,3-Dipolar cycloaddition is one of the simplest approaches for the construction of five-membered heterocyclic rings.[1] The ease of generation of 1,3-dipoles, coupled with the often observed highly regio-, and stereoselective nature of their cycloaddition reaction, has led to a number of syntheses which utilize such a reaction as the key step.[2]

As a part of our study on naturally occurring spiro-2-oxindole derivatives[3] we started to examine some of the 1,3-dipolar cycloadditions of 2-oxoindolin-3-ylidene derivatives **4a** and **4b** to different azomethine ylides.[4] In spite of the obvious possibility to construct a spiro-indolenine framework in one stereoselective step, only a few experiments[5] and only one application of the 1,3-dipolar cycloadditions for the synthesis of the simplest oxindole alkaloid, horsfilline (**1**), have been described in the literature.[6] Our initial studies were further inspired by the recent results published by Danishefsky and co-workers[7] on the synthesis of Spirotryprostatine A **3a** and analogues (e.g. **3b**). They found that some of the synthesis intermediates (e.g. **2**) were three to four orders of magnitude more potent than the natural product at inhibiting cancer cell growth (Scheme 1).

2. Results and discussion

2.1. Reactions with non-stabilized azomethine ylides

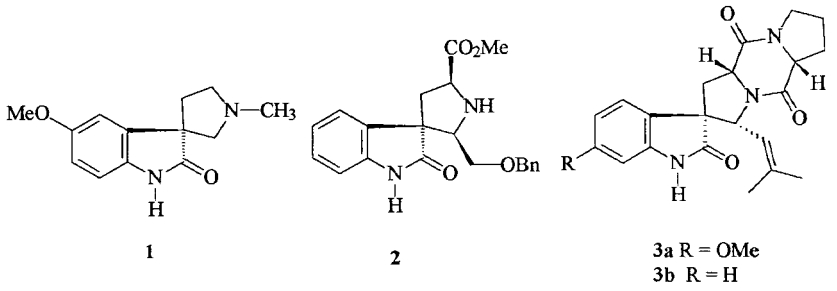
The 2-oxoindolin-3-ylidene derivatives **4a**[8] and **4b**[9] (synthesized conveniently from isatin) reacted smoothly with the non-stabilized azomethine ylide **5** (generated by the desilylation method[10]) at room temperature giving rise to the formation of cycloadducts **6a** and **6b** in good yield (Scheme 2). This is the only applicable 1,3-dipolar cycloaddition directly to the compound **4b** in which the $4\pi+2\pi$ process is dominant over the easy polymerization in the presence of any base. Earlier we have demonstrated the use a precursor of **4b** in base catalysed cycloadditions, where the azomethine ylide and the base sensitive dipolarophile have been generated at the same time in situ.[11]

On the other hand, the isatylidene acetates **4a** and **4c**[12] reacted smoothly with non-stabilized azomethine ylides generated in the reaction of sarcosine with an aldehyde, forming a variety of cycloadducts (Schemes 3 and 4). Most of the reactions provided stereoisomeric mixtures due to the two possible approaches of the substituted azomethine ylide to the double bond. In all cases the main cycloadduct was isolated, and proved to be *endo* (*endo* and *exo* referring to the position of the two aromatic rings) by the observed ^{1}H n.O.e. effect between the H-2 and H-4 protons.

Usually the yields were good, but the stereoselectivity varied depending on the substituent on the aromatic ring of the azomethine ylides. The substituent on the indole part has no noticeable effect (Table 1). With this method, substituents with an olefinic bond were easily introduced to these spiro-oxindole derivatives (e.g. **9** and **10**) providing a short access to this type of compound.

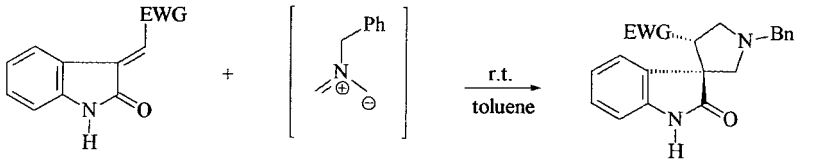
Keywords: cycloadditions; pyrrolidines; azomethine ylides; oxindole alkaloids.
* Corresponding author. Tel.: +361-463-22-13; fax: +361-463-36-48; e-mail: nyerges.oct@chem.bme.hu

0040–4020/01/$ - see front matter
PII: S0040-4020(00)01085-1



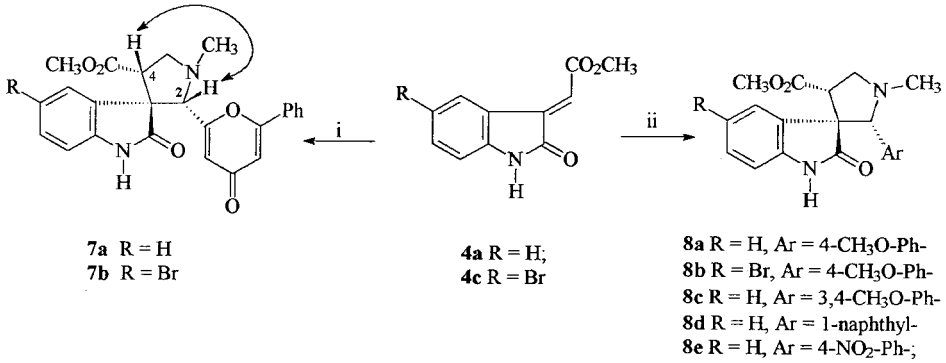
1 **2** **3a** R = OMe **3b** R = H

Scheme 1.



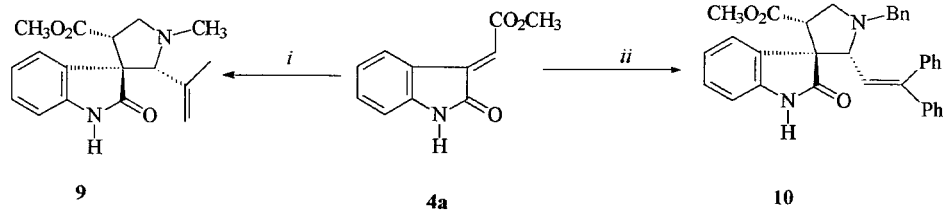
4a EWG = COOMe; **4b** EWG = NO_2; **5** **6a** EWG = COOMe (92 %) **6b** EWG = NO_2 (78 %)

Scheme 2.



7a R = H **7b** R = Br **4a** R = H; **4c** R = Br **8a** R = H, Ar = 4-CH_3O-Ph- **8b** R = Br, Ar = 4-CH_3O-Ph- **8c** R = H, Ar = 3,4-CH_3O-Ph- **8d** R = H, Ar = 1-naphthyl- **8e** R = H, Ar = 4-NO_2-Ph-;

Scheme 3. *Reagents and conditions*: (i) 6-phenyl-4*H*-pyran-4-one-2-carbaldehyde,[13] sarcosine, toluene, reflux; (ii) sarcosine, ArCHO, toluene, reflux.



9 **4a** **10**

Scheme 4. *Reagents and conditions*: (i) sarcosine, CH_2=CH(CH_3)CHO, toluene, reflux (44%); (ii) *N*-benzylglycine, Ph_2C=CHCHO, toluene, reflux (59%).

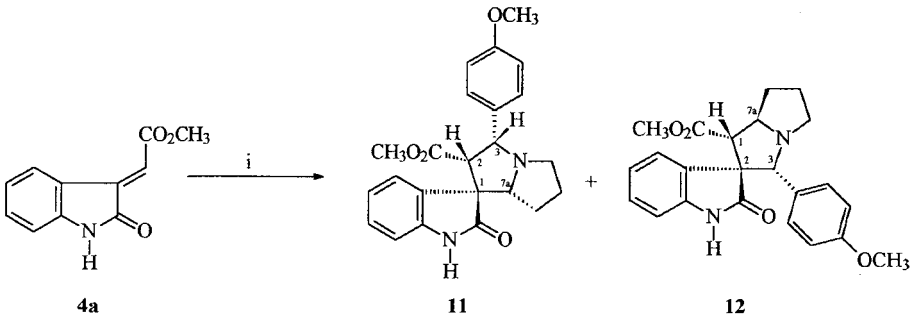
Table 1.

Entry		R	Ar	Yield (%)[a]	Isomer ratio[b]
1	**7a**	H	–	76	1:0
2	**7b**	Br	–	42	5:1
3	**8a**	H	4-CH_3O-Ph-	52	3:1
4	**8b**	Br	4-CH_3O-Ph-	62	3:1
5	**8c**	H	3,4-CH_3O-Ph-	56	2:1
6	**8d**	H	1-naphthyl	53	3:1
7	**8e**	H	4-NO_2-Ph-	80	1:0
8	**9**	–	–	44	2:1
9	**10**	–	–	59	4:1

[a] Isolated yield of the main isomer.
[b] Determined by ^{1}H NMR from the crude reaction mixture.

The reaction of cyclic, non-stabilized azomethine ylides generated by the decarboxylative condensation of an aromatic aldehyde and cyclic amino acids gave a different result: (a) in the case of pipecolinic acid an unseparable mixture of regio- and stereoisomers was obtained (b) with proline after careful chromatographic separation it was possible to isolate and characterize the two main regioisomeric products **11** and **12** (ratio ca. 1:1) (Scheme 5).

The structure and stereochemistry of both cycloadducts were confirmed by NMR methods. The relative stereochemistry of the cycloadducts **11** and **12** were established by ^{1}H{^{1}H} n.O.e. studies (Tables 2 and 3). In the case of **12**,

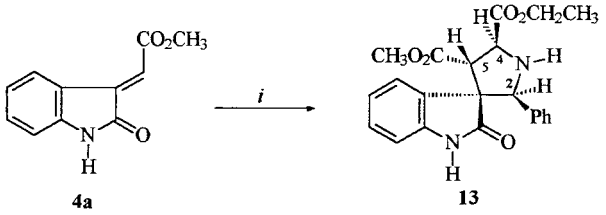


Scheme 5. *Reagents and conditions*: (i) *p*MeOC$_6$H$_4$CHO, *dl*-proline, toluene, reflux.

Table 2. Selected NMR data for compound **11**

	δH	^{1}H{^{1}H} n.O.e. data[a]	δC
Ind-4′	7.34 d	H-7a, Ind-5′H	125.4
Ar-2 and 6	7.42 d	H-5$_\alpha$, H-2, H-3, CO_2CH_3	128.5
2	3.61 d	Ar-2′6′H, H-3	62.9
3	5.16 d	H-5$_\beta$, H-2, Ar-2′6′H	70.2
7a	4.66 t	Ind-4′H, H$_2$-7	73.3

[a] Obtained by 2D-NOESY spectroscopy.



Scheme 6. *Reagents and conditions*: (i) PhCH=NCH$_2$CO$_2$Et; LiBr, CH_3CN; Et_3N, r.t. (68%).

where there is no difference in the chemical shift of the protons H-3 and H-7a only indirect evidence of stereochemistry was obtained for the suggested structure.

2.2. Reactions with metallo-dipoles

The dipoles, thermally generated from the imines of glycine esters undergo stereoselective cycloadditions with highly activated cyclic dipolarophiles such as maleinimides, leading to the exclusive formation of *endo* adducts of *E*,*E*-ylides.[14] However, their cycloadditions to less reactive olefin dipolarophiles such as maleates and fumarates are no longer stereoselective.[15] The application of a wide range of metal salt/tertiary amine combinations 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.[16] The cycloaddition of **4a** with an azomethine ylide, derived from ethyl (benzylideneamino)acetate, in the presence of LiBr at room temperature took place giving the pure spiro-indolo derivative **13** in 68% yield (Scheme 6). The nitro compound **4b** polymerized fast in the presence of Et_3N preventing the cycloaddition. The relative stereochemistry of the cycloadduct **13** was established mostly by ^{1}H{^{1}H} n.O.e. studies. Selected NMR data are collected in Table 4.

In the case when the azomethine ylide was generated from the conjugated imine[17] **14**, the reaction provided a mixture of *endo*- and *exo*-isomers (in 3:2 ratio) of cycloadducts **15**, originating from the *E*,*E*-ylide (Scheme 7). The relative stereochemistry of **15a** was easily proved by the comparison of the results of 1D-difference spectroscopy and $J_{4,5}$ to the data of compound **13**. The '*all-cis*' configuration of the pyrrolidine-ring protons in **15b** was established from the observed n.O.e. enhancements between all these protons.

2.3. Reactions with other ester-stabilized azomethine ylides

The condensation of various aldehydes with *N*-alkyl or *N*-aryl α-amino esters leads to *N*-substituted azomethine ylides. These ylides can be trapped smoothly by the added dipolarophiles since there are no other reactive reagents (e.g. base, Lewis acids) in the reaction mixture.[18]

The isatylidene compound **4a** reacted easily in this way with the dipole formed from *N*-methyl **16a** (R=Me), and *N*-benzyl glycine ester **16b** (R=Bn) and benzaldehyde to yield the corresponding cycloadducts **17a** and **17b** (Scheme 8). Selected NMR data for cycloadduct **17b** are collected in Table 5.

The 1,3-dipolar cycloadditions of azomethine ylides derived from isoqinolinium salts **18** by deprotonation was previously studied in detail by us.[19] Its reaction with the reactive dipolarophile **4a** afforded cycloadducts **19** practically in

Table 3. Selected NMR data for compound **12**

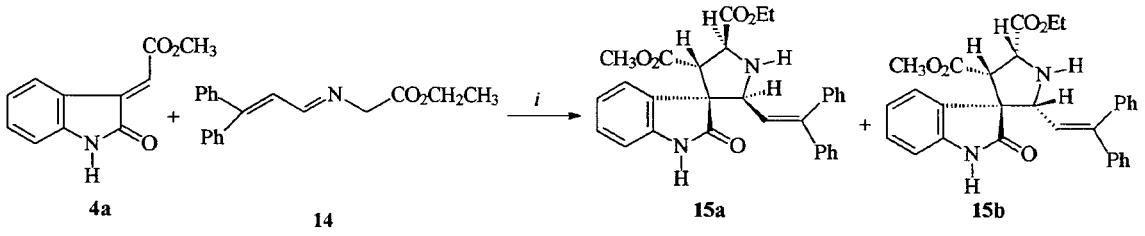
	δH	^{1}H{^{1}H} n.O.e. data[a]	δC
Ind-4′	7.53 d	Ar-2′6′H, Ind-5′H, H-7(+3?)	126.4
Ar-2 and 6	7.12 d	Ind-4′H, H-5$_\alpha$, H-3(+7?)	128.7
1	3.56 d	H-6$_\beta$, H-7(+3?)	157.5
3+7a	4.44 m (dd+s)	Ar-2′6′H, Ind-4′H, H-1, H-5$_\alpha$, H-7$_\alpha$, H$_2$-6	76.2 and 64.4

[a] Obtained by 2D-NOESY spectroscopy.

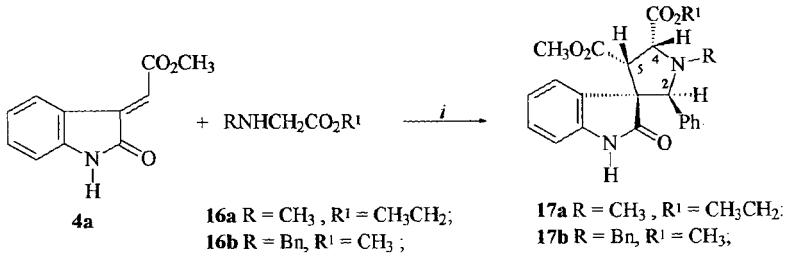
Table 4. Selected NMR data for compound **13**

	δH	^{1}H{^{1}H} n.O.e. data[a]	δC	HMBC connections
2	4.58 s	H-4 (5.6), Ph-2′,6′ (8.3)	73.1	H-5, Ph-2′,6′
4	4.72 d[b]	H-5 (2.2)	63.5	H-5
5	3.67 d[b]	H-4 (1.6), Ph-2′,6′ (7.4)	56.9	H-4
Ind-4	7.27 d	H-2 (2.9)	123.8	Ind-6
Ph-2″,6″	6.89 d	H-4 (7.6), Ph-3′,5′ (12.5)	126.1	H-2, Ph-3′,5′, Ph-4′

[a] Obtained by 1D-difference spectroscopy, n.O.e. enhancements are in parentheses.
[b] ^3J=8.0 Hz.



Scheme 7. *Reagents and conditions*: (i) AgOAc, toluene, r.t.



Scheme 8. *Reagents and conditions*: (i) **16a** or **16b**, PhCHO, toluene, reflux.

Table 5. Selected NMR data for compound **17b**

	δH	^{1}H{^{1}H} n.O.e. connections[a]	δC	HMBC correlations
2	5.09 s	H-4, Ph-2″,6″, $BzCH_2(x)$, $BzCH_2(y)$	76.8	H-5, $BzCH_2(y)$
4	4.20 d[b]	H-5	53.1	H-5
5	4.27 d[b]	H-4, BzPh-2‴,6‴	62.9	H-4, $BzCH_2(y)$, $BzCH_2(x)$
$BzCH_2(x)$	3.29 d[c]	$BzCH_2(y)$, BzPh-2‴,6‴, H-2	51.4	H-2, BzPh-2‴,6‴
$BzCH_2(y)$	3.84 d[c]	$BzCH_2(y)$, BzPh-2‴,6‴, H-2		
Ind-4	7.85 d	H-5, H-2′	125.6	H-6

[a] Obtained by 2D-NOESY spectroscopy.
[b] ^3J=8.2 Hz.
[c] ^2J=14.4 Hz.

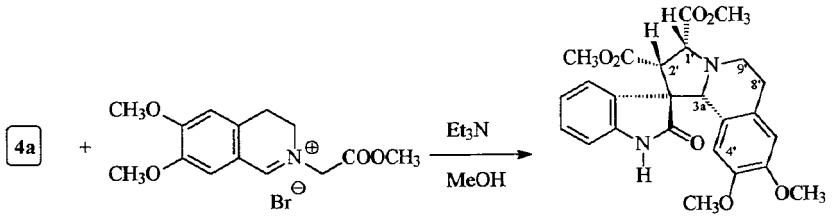
quantitative yield as a single diastereoisomer (Scheme 9). The intensive NOESY cross-peaks in **19** proved the *cis* configuration of 1′ and 2′ protons, the coupling constants in some five-membered ring systems are less informative. A further proof of the structure was the drastically shielded aromatic H-4′ proton with a chemical shift of 5.59 ppm, as a consequence of the anisotropy of the amide carbonyl group (Table 6).

In summary, we have studied the reactivity of three highly reactive oxindole dipolarophiles **4a–c** towards different azomethine ylides. These studies showed the azomethine ylide cycloadditions in most cases are highly regio-, and stereoselective in contrast with the Diels–Alder reactions[20] or other 1,3-dipolar cycloadditions[21] described earlier for **4a,b**. This method provides an easy access to the spiro-indolenine framework which frequently occurs in alkaloids such as horsfilline,[22] or the more complex alkaloids of the *Strychnos*, *Aspidosperma* and *Mitragyna* species.[23]

3. Experimental

3.1. General

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 NICOLET FT-IR



18 19

Scheme 9.

Table 6. Selected NMR data for compound **19**

	δH	$^1H\{^1H\}$ n.O.e. connections[a]	δC	HMBC correlations
Ind-4	7.57 d	Ind-5, H-3a	124.3	H-6
1	4.55 d[b]	H-2, H_{ax}-9, H_{eq}-9	68.2	H-2
2	3.97 d[b]	H-1, H_{ax}-9	54.3	H-1
3a	5.25 s	H-4, H-4	70.3	H-4, H-1
4	5.59 s	H-3a	107.1	H-3a
ax-8	2.71 m	H_{eq}-8, H_{eq}-9, H-7	27.8	H-7
eq-8	2.84 m	H_{ax}-8, H_{eq}-9, H-7		
ax-9	3.51 m	H_{eq}-9, H_{eq}-8, H-1	46.9	H-1, H-3a
eq-9	3.05 m	H_{ax}-9, H_{eq}-8, H_{ax}-8, H-1		

[a] Obtained by 2D-NOESY spectroscopy.
[b] ^3J=7.6 Hz.

instrument. Low-resolution electron impact mass spectra were obtained on a Varian CH5-D spectrometer. NMR measurements were carried out on Varian UNITY plus 500 and Brucker 250 instruments. Chemical shifts are given relative to δ_{TMS}=0.00 ppm.

3.1.1. 1′-Benzyl-4′-methoxycarbonyl-spiro-[3*H*-indol-3,3′-pyrrolidin]-2(1*H*)-one (6a). 3-(Methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one **4b** (0.18 g, 0.88 mmol) and *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]-amine (0.50 g, 2.1 mmol) were dissolved in dry toluene (7 ml) and one drop of trifluoroacetic acid was added. After 24 h stirring at room temperature the precipitated product was filtered off as a white powder (0.27 g, 92%); mp 112°C; Found: C, 71.5; H, 6.0; N, 8.4. $C_{20}H_{20}N_2O_3$ requires C, 71.40; H, 6.00; N, 8.33%; δ_H (250 MHz, $CDCl_3$+DMSO-d_6): 10.27 (1H, s, N*H*), 7.54 (2H, m, Ph-2′ and 6′*H*), 7.40 (3H, m, Ph-3′,4′ and 5′*H*), 7.27 (1H, d, *J*=7.5 Hz, Ind-4′*H*), 7.20 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 6.97 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.92 (1H, d, *J*=7.5 Hz, Ind-7′*H*), 4.47 (2H, s, CH_2—Ph), 4.05 (1H, t, *J*=9.0 Hz, *H*-4), 3.82 (1H, t, *J*=9.0 Hz, H_2-5), 3.52–3.70 (3H, m, H_2-5 and H_2-2), 3.25 (3H, s, OCH_3); δ_C (63 MHz, $CDCl_3$+DMSO-d_6): 178.3 (q), 168.7 (q), 141.8 (q), 132.3 (q), 130.2 (2×CH), 129.3 (CH), 129.1 (2×CH), 129.0 (CH), 128.5 (q), 123.9 (CH), 122.5 (CH), 110.2 (CH), 60.4 (CH_2), 58.8 (CH_2), 55.1 (q), 53.4 (CH_2), 51.9 (CH_3), 51.0 (CH); IR (KBr, cm^{-1}): 3193, 3017, 2956, 1734, 1670, 1471, 1436, 1343, 1267, 1202, 1179, 1124; CIMS *m/z* (rel. intensity, %): 337 (MH^+, 100), 305 (5), 259 (7), 146 (18), 115 (49).

3.1.2. 1′-Benzyl-4-nitro-spiro-[3*H*-indol-3,3-pyrrolidin]-2(1*H*)-one (6b). 3-(Nitro-methylene)-1,3-dihydro-2*H*-indol-2-one **4b** (0.15 g, 0.78 mmol) and *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]amine (0.50 g, 2.1 mmol) were dissolved in dry toluene (7 ml) and one drop of trifluoroacetic acid was added. After 1 h stirring at room temperature the precipitated product was filtered off as a white powder (0.20 g, 78%); mp 101°C; Found: C, 66.7; H, 5.4; N, 12.9. $C_{18}H_{17}N_3O_3$ requires C, 66.85; H, 5.30; N, 13.00%; δ_H (250 MHz, $CDCl_3$) δ: 10.52 (1H, s, N*H*), 7.40 (1H, d, *J*=7.4 Hz, Ind-4′*H*), 7.24 (6H, m, Ar-*H*), 6.95 (1H, t, *J*=7.4 Hz, Ind-6′*H*), 6.80 (1H, t, *J*=7.4 Hz, Ind-5′*H*), 5.35 (1H, dd, *J*=5.1 and 9.2 Hz, *H*-4), 3.86 (1H, dd, *J*=5.1 and 12.4 Hz, H_2-5), 3.70 (2H, s, CH_2), 3.30–3.78 (4H, m, H_2-2 and H_2-5); δ_C (63 MHz, $CDCl_3$+DMSO-d_6): 169.8 (q), 141.4 (q), 132.7 (q), 129.9 (2×CH), 129.8 (CH), 129.2 (CH), 128.8 (2×CH), 128.1(q), 124.6 (CH), 122.9 (CH), 111.1 (CH), 92.0 (CH), 61.4 (CH_2), 59.7 (CH_2), 55.3 (q), 54.2 (CH_2); IR (nujol, cm^{-1}): 1757, 1732, 1618, 1556, 1544, 1461, 1452, 1402, 1367, 1339, 1257, 1207; CIMS *m/z* (rel. intensity, %): 324 (MH^+, 100).

3.1.3. 1,3-Dipolar cycloaddition of isatilydene acetates 4a and 4c, with non-stabilized dipoles generated from aromatic aldehydes and sarcosine. General procedure. The corresponding aldehyde (1 mmol), sarcosine (2 mmol) and the 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one (**4a** or **4c**, 1 mmol) were refluxed in toluene (10 ml) under Dean–Stark conditions for 1–3 h. After the completion of the reaction (judged by TLC) all the solvents were removed and the residue was purified by flash chromatography, followed by recrystallization from ether–hexanes solvent mixtures to yield the main isomer.

3.1.4. 4-Methoxycarbonyl-*N*-methyl-2-(6-phenyl-pyran-4-one-2-yl)-spiro-[3*H*-indole-3,3′-pyrrolidin]-2(1*H*)-one (7a). White powder (0.33 g, 76%); mp 234–236°C; Found: C, 70.0; H, 5.1; N, 6.6. $C_{25}H_{22}N_2O_5$ requires C, 69.76; H, 5.15; N, 6.51%; δ_H (250 MHz, $CDCl_3$): 8.93 (1H, s, N*H*), 7.64–7.58 (2H, m, Ph-2′ and 6′*H*), 7.44–7.39 (3H, m, Ph-3′,4′ and 5′*H*), 7.32 (1H, d, *J*=7.6 Hz, Ind-4′*H*), 7.05 (1H, dt, *J*=1.0 and 7.6 Hz, Ind-6′*H*), 6.88 (1H, t, *J*=7.6 Hz, Ind-5′*H*), 6.68 (1H, d, *J*=7.6 Hz, Ind-7′*H*), 6.49 (1H, d, *J*=2.2 Hz, *H*-2″), 6.36 (1H, d, *J*=2.2 Hz, *H*-4″), 4.08 (1H, dd, *J*=10.3 and 6.6 Hz, *H*-5), 4.06 (1H, s, *H*-2), 3.91 (1H, dd, *J*=10.3 and 6.6 Hz, *H*-4), 3.18 (3H, s, OCH_3), 3.05 (1H, t, *J*=10.3 Hz, *H*-5), 2.53 (3H, s, NCH_3); δ_C (125 MHz, $CDCl_3$+DMSO-d_6): 179.8 (q), 177.5 (q), 170.0 (q), 164.2 (q), 163.0 (q), 140.7 (q), 131.4 (CH), 130.5 (q), 129.0 (2×CH), 128.2 (CH), 126.3 (q), 126.1 (CH), 125.5 (2×CH), 122.5 (CH), 114.2 (CH), 110.5 (CH), 109.5 (CH), 74.6 (CH), 61.0 (q), 55.2 (CH_2), 51.7 (CH_3), 49.9 (CH), 41.1 (CH_3); IR (KBr, cm^{-1}): 3450, 3060, 3024, 2949, 2879, 1730, 1655, 1617, 1591, 1470, 1450, 1412, 1367, 1239, 1197, 1182, 1155; CIMS *m/z* (rel. intensity, %): 431 (MH^+, 100), 228 (25), 214 (27), 187 (22).

3.1.5. 5′-Bromo-4-methoxycarbonyl-*N*-methyl-2-(6-phenyl-pyran-4-one-2-yl)-spiro-[3*H*-indole-3,3′-pyrrolidin]-2(1*H*)-one (7b). White powder (0.21 g, 42%); mp 255–257°C; Found: C, 59.5; H, 4.2; N, 5.4. $C_{25}H_{21}N_2O_5Br$ requires C, 59.32; H, 4.16; N, 5.5%; δ_H (250 MHz, $CDCl_3$): 10.43 (1H, s, N*H*), 7.65 (2H, br s, Ph-2′ and 6′*H*), 7.50 (3H, s, Ph-H), 7.36 (1H, s, Ind-4′*H*), 7.15 (1H, d, *J*=8.2 Hz, Ind-6′*H*), 6.60 (1H, d, *J*=8.2 Hz, Ind-7′*H*), 6.51 (1H, s, *H*-2″), 6.21 (1H, s, *H*-4″), 4.03 (1H, dd, *J*=7.3 and 10.0 Hz, *H*-5), 3.89 (1H, s, *H*-2), 3.85 (1H, dd, *J*=7.3 and 10.0 Hz, *H*-4), 3.26 (3H, s, OCH_3), 3.01 (1H, t, *J*=10.0 Hz, *H*-5), 2.51 (3H, s, NCH_3); δ_C (125 MHz, $CDCl_3$+DMSO-d_6): 180.9 (q), 178.1 (q), 175.2 (q), 163.3 (q), 162.9 (q), 140.5 (q), 131.6 (CH), 131.3 (CH), 130.4 (q), 129.1 (2×CH), 128.5 (CH), 126.1 (q), 125.6 (2×CH), 114.2 (CH), 111.1 (CH), 110.6 (CH), 101.6 (q), 74.5 (CH), 60.8 (q), 54.8 (CH_2), 51.7 (CH_3), 49.5 (CH), 40.8 (CH_3); IR (KBr, cm^{-1}): 3417, 3090, 2841, 1749, 1728, 1654, 1593, 1469, 1449, 1411, 1369, 1207, 1182; CIMS *m/z* (rel. intensity, %): 511 (M^{+2}, 81), 509 (M^+, 79), 431 (21), 284 (23), 228 (100), 214 (40), 187 (30).

3.1.6. 4-Methoxycarbonyl-2-(4-methoxyphenyl)-*N*-methyl-spiro-[3*H*-indole-3,3′-pyrrolidin]-2(1*H*)-one (8a). White powder (0.19 g, 52%); mp 170–172°C; Found: C, 69.0; H, 5.9; N, 7.6. $C_{21}H_{22}N_2O_4$ C, 68.84; H, 6.05; N, 7.65%; δ_H (250 MHz, $CDCl_3$): 8.21 (1H, s, N*H*), 7.46 (1H, d, *J*=7.2 Hz, Ind-4′*H*), 7.07–6.87 (4H, m, Ar-*H*), 6.60–6.48 (3H, m, Ind-7′*H* and Ar-*H*), 4.06 (1H, dd, *J*=9.8 and 6.0 Hz, *H*-5), 3.90 (1H, s, *H*-2), 3.86 (1H, dd, *J*=11.3 and 6.0 Hz, *H*-4), 3.64 (3H, s, CH_3O), 3.13 (3H, s, CH_3OOC), 2.90 (1H, t, *J*=10.3 Hz, *H*-5), 2.27 (3H, s, CH_3N); δ_C (63 MHz, $CDCl_3$): 179.1 (ester), 171.1 (Ind-2′*C*), 158.8 (Ar-4′*C*), 140.5 (Ind-7a′*C*), 129.1 (Ar-2′ and 6′*C*), 128.0 (Ind-6′*C*), 127.9 and 127.1 (Ind-3a′*C* and Ar-1′*C*), 126.4 (Ind-4′*C*), 121.7 (Ind-5′*C*), 112.8 (Ar-3′ and 5′*C*), 109.2 (Ind-7′*C*), 78.0 (*C*-2), 62.6 (*C*-3), 54.9 (*C*H_3O), 54.6 (*C*H_2), 51.5 (*C*H_3O), 49.0 (*C*-4), 40.1 (*C*H_3N); IR (KBr, cm^{-1}): 3402, 3177, 3068, 2949, 2846, 2390, 1741, 1709, 1615, 1510, 1470, 1244, 1208, 1037; CIMS *m/z* (rel. intensity, %): 367 (MH^+, 100).

3.1.7. 5′-Bromo-4-methoxycarbonyl-2-(4-methoxyphenyl)-*N*-methyl-spiro-[3*H*-indole-3,3′-pyrrolidine]-2(1*H*)-one (8b). White powder (0.28 g, 62%); mp 195–197°C; δ_H (250 MHz, $CDCl_3$+DMSO-d_6): 9.82 (1H, s, N*H*), 7.53 (1H, s, Ind-4′*H*), 7.37 (1H, d, *J*=8.3 Hz, Ind-6′*H*), 7.11 (1H, d, *J*=8.3 Hz, Ind-7′*H*), 6.95 (2H, d, *J*=8.3 Hz, Ar-2′ and 6′*H*), 6.57 (2H, d, *J*=8.3 Hz, Ar-3′ and 5′*H*), 4.00 (1H, dd, *J*=5.2 and 9.1 Hz, *H*-5), 3.82 (1H, s, *H*-2), 3.80 (1H, dd, *J*=11.0 and 5.2 Hz, *H*-4), 3.80 (3H, s, CH_3O), 3.22 (3H, s, CH_3OOC), 2.89 (1H, t, *J*=10.5 Hz, *H*-5), 2.27 (3H, s, CH_3N); δ_C (125 MHz, $CDCl_3$+DMSO-d_6): 179.3 (q), 171.7 (q), 158.6 (q), 140.5 (q), 131.9 (CH), 131.5 (CH), 129.3 (2×CH), 128.7 (CH), 127.9 (CH), 127.5 (q), 112.9 (2×CH), 102.0 (q), 77.7 (CH), 62.4 (q), 54.9 (CH_3), 54.3 (CH_2), 51.6 (CH_3), 49.2 (CH), 40.3 (CH_3); IR (KBr, cm^{-1}): 3359, 3192, 2950, 2839, 1733, 1710, 1615, 1513, 1473, 1301, 1251, 1207, 1174, 1038; CIMS *m/z* (rel. intensity, %): 447 (M^{+2}, 51), 445 (M^+, 56), 367 (100), 352 (49), 259 (25), 87 (65); HRMS (EI): Found: 444.0691. $C_{21}H_{21}N_2O_4Br$ requires 444.0684.

3.1.8. 2-(3,4-Dimethoxyphenyl)-4-methoxycarbonyl-*N*-methyl-spiro-[3*H*-indole-3,3′-pyrrolidin]-2(1*H*)-one (8c). White powder (0.22 g, 56%); mp 188–190°C; Found: C, 66.9; H, 5.9; N, 7.1. $C_{22}H_{24}N_2O_5$ requires C, 66.65; H, 6.10; N, 7.07%; δ_H (250 MHz, $CDCl_3$): 8.56 (1H, br s, N*H*), 7.51 (1H, d, *J*=7.5 Hz, Ind-4′*H*), 7.04 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 6.94 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.69–6.49 (4H, m, Ar-*H*), 4.07 (1H, dd, *J*=9.7 and 5.8 Hz, *H*-5), 3.93–3.82 (2H, m, *H*-2 and *H*-4), 3.71 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.14 (3H, s, OCH_3), 2.92 (1H, t, *J*=10.4 Hz, *H*-5), 2.28 (3H, s, NCH_3); δ_C (125 MHz, $CDCl_3$): 178.8 (q), 171.0 (q), 148.3 (q), 148.0 (q), 140.6 (q), 128.2 (CH), 128.1 (q), 127.6 (q), 126.4 (CH), 121.5 (CH), 120.7 (CH), 110.8 (CH), 109.9 (CH), 109.3 (CH), 78.4 (CH), 62.6 (q), 55.6 (2×CH_3), 54.6 (CH_2), 51.5 (CH_3), 49.0 (CH), 40.1 (CH_3); IR (KBr, cm^{-1}): 3412, 2948, 2817, 1721, 1617, 1513, 1467, 1266, 1230, 1203, 1158, 1025; CIMS *m/z* (rel. intensity, %): 397 (MH^+, 100), 259 (8), 180 (19), 151 (18), 134 (10).

3.1.9. 4-Methoxycarbonyl-*N*-methyl-2-(naphth-1-yl)-spiro-[3*H*-indole-3,3′-pyrrolidin]-2(1*H*)-one (8d). White powder (0.22 g, 53%); mp 199–201°C; Found: C, 74.4; H, 5.9; N, 7.2. $C_{24}H_{22}N_2O_3$ requires C, 74.59; H, 5.74; N, 7.25%; δ_H (250 MHz, $CDCl_3$): 8.23 (1H, d, *J*=6.5 Hz, Ar-*H*), 8.11 (1H, s, N*H*), 7.65 (1H, d, *J*=7.1 Hz, Ar-*H*), 7.58–7.42 (3H, m, Ar-*H*), 7.39–7.22 (2H, m, Ar-H), 7.12 (1H, t, *J*=7.5 Hz, Ar-*H*), 6.98–6.83 (2H, m, Ar-*H*), 6.36 (1H, br s, Ar-H), 4.84 (1H, s, *H*-2), 4.13 (1H, dd, *J*=10.0 and 4.5 Hz, *H*-5), 3.99 (1H, dd, *J*=10.0 and 4.5 Hz, *H*-4), 3.09 (3H, s, OCH_3), 3.00 (1H, t, *J*=10.0 Hz, *H*-5), 2.25 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) δ: 179.1 (q), 171.2 (q), 140.5 (q), 133.2 (q), 132.1 (q), 130.7 (q), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.6 (CH), 125.7 (CH), 125.0 (CH), 124.4 (CH), 122.9 (CH), 121.5 (CH), 109.0 (CH), 72.4 (CH), 62.1 (q), 55.0 (CH_2), 51.4 (CH_3), 49.9 (CH), 40.2 (CH_3); IR (KBr, cm^{-1}): 3440, 3185, 2842, 1741, 1708, 1618, 1469, 1344, 1203; EIMS *m/z* (rel. intensity, %): 386 (M^+, 20), 182 (100), 167 (7), 130 (10).

3.1.10. 4-Methoxycarbonyl-*N*-methyl-2-(4-nitrophenyl)-spiro-[3*H*-indole-3,3′-pyrrolidine]-2(1*H*)-one (8e). White powder (0.30 g, 80%); mp 182–184°C; Found: C, 63.0; H, 4.9; N, 11.0. $C_{20}H_{19}N_3O_5$ requires C, 62.99; H, 5.02; N, 11.02%; δ_H (250 MHz, $CDCl_3$): 8.93 (1H, br s, N*H*), 7.87 (2H, d, *J*=8.6 Hz, Ar-2′ and 6′*H*), 7.44 (1H, d, *J*=7.4 Hz, Ind-4′*H*), 7.27 (2H, d, *J*=8.6 Hz, Ar-3′ and 5′*H*), 7.02 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.93 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 6.59 (1H, d, *J*=7.6 Hz, Ind-7′*H*), 4.16–4.09 (2H, m, *H*-2 and *H*-5), 3.94 (1H, dd, *J*=5.6 and 10.6 Hz, *H*-4), 3.17 (3H, s, OCH_3), 3.02 (1H, t, *J*=10.6 Hz, *H*-5), 2.33 (3H, s, NCH_3); δ_C (125 MHz, $CDCl_3$): 178.1 (q), 170.5 (q), 147.3 (q), 143.2 (q), 140.3 (q), 128.7 (2×CH), 128.5 (CH), 126.9 (q), 126.2 (CH), 122.7 (2×CH), 122.0 (CH), 109.4 (CH), 77.4 (CH), 62.6 (q), 54.8 (CH_2), 51.7 (CH_3), 49.3 (CH), 40.2 (CH_3); IR (KBr, cm^{-1}): 3414, 3190, 2950, 2848, 2783, 1722, 1708, 1610, 1607, 1524, 1471, 1437, 1345, 1230, 1208, 1178, 1111; CIMS *m/z* (rel. intensity, %): 382 (MH^+, 100), 352 (69), 307 (8), 279 (59), 259 (13), 179 (13).

3.1.11. 4′-Methoxycarbonyl-2′-(1-methyl-ethenyl)-1′-methyl-spiro-[3*H*-indolo-3,3′-pyrrolidin]-2(1*H*)-one (9). Prepared from sarcosine (0.50 g, 2.46 mmol), 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one (0.25 g, 1.23 mmol), methacrolein (0.13 g, 1.85 mmol) by the same procedure as **7** or **8**. The product is a pale yellow oil, which crystallized slowly

upon standing (0.16 g, 44%); mp 131–133°C; Found: C, 67.8; H, 6.5; N, 9.4. $C_{17}H_{20}N_2O_3$ requires C, 67.98; H, 6.71; N, 9.33%; δ_H (250 MHz, $CDCl_3$): 9.07 (1H, s, N*H*), 7.34 (1H, d, *J*=7.5 Hz, Ind-4′*H*), 7.17 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 6.95 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.87 (1H, d, *J*=7.5 Hz, Ind-7′*H*), 4.89 (1H, s, C=CH_2), 4.71 (1H, s, C=CH_2), 3.97 (1H, dd, *J*=5.9 and 10.3 Hz, *H*-4), 3.77 (1H, dd, *J*=5.9 and 10.3 Hz, *H*-5), 3.36 (1H, s, *H*-2), 3.15 (3H, s, OCH_3), 2.82 (1H, t, *J*=10.3 Hz, *H*-5), 2.31 (3H, s, NCH_3), 1.26 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) δ: 179.6 (ester *C*=O), 170.9 (Ind-2′*C*), 140.8 (Ind-7a′*C*), 139.7 (Ind-3a′*C*), 128.4 (CH_2=*C*—), 128.2 (Ind-6′*C*), 126.8 (Ind-4′*C*), 121.9 (Ind-5′*C*), 115.4 (*C*H_2=C—), 109.3 (Ind-7′*C*), 79.5 (*C*-2), 61.1 (*C*-3), 54.9 (*C*-5), 51.5 (*C*H_3O), 49.7 (*C*-4), 40.6 (N*C*H_3), 19.9 (*C*H_3); IR (nujol, cm^{-1}): 1740, 1709, 1618, 1459, 1192, 1040; CIMS *m/z* (rel. intensity, %): 301 (MH^+, 100), 97 (5).

3.1.12. 1′-Benzyl-2-(2,2-diphenyl-ethenyl)-4′-methoxycarbonyl-spiro-[3*H*-indol-3,3′-pyrrolidine]-2(1*H*)-one (10). Prepared from 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one (0.146 g, 0.72 mmol), β-phenyl-cinnamaldehyde (0.15 g, 0.72 mmol) and *N*-benzyl-glycine (0.19 g, 1.15 mmol) as for **7** or **8**. Yield: 0.20 g (59%); white powder; mp 189–191°C; δ_H (250 MHz, DMSO-d_6): 10.46 (1H, s, N*H*), 7.49 (1H, d, *J*=7.2 Hz, Ind-4′*H*), 7.42–7.26 (7H m, Ar-*H*), 7.23 (1H, t, *J*=6.6 Hz, Ar-*H*), 7.17–7.10 (4H, m, Ar-H), 7.08 (1H, t, *J*=7.3 Hz, Ind-5′*H*), 6.91–6.87 (2H, m, Ar-H), 6.85 (1H, d, *J*=7.5 Hz, Ind-7′*H*), 6.70–6.67 (2H, m, Ar-*H*), 5.64 (1H, d, *J*=10.0 Hz, C*H*=), 3.95 (1H, d, *J*=12.0 Hz, NCH_2), 3.50 (1H, dd, *J*=5.6 and 10.1 Hz, *H*-4), 3.40 (3H, m, *H*-5, NCH_2 and *H*-2), 3.37 (3H, s, OCH_3), 2.62 (1H, t, *J*=10.3 Hz, *H*-5); δ_C (125 MHz, DMSO-d_6): 178.3 (q), 170.6 (q), 145.1 (q), 142.2 (q), 141.3 (q), 139.2 (q), 138.5 (q), 131.8 (q), 129.2 (2×CH), 128.5 (2×CH), 128.2 (3×CH), 128.1 (4×CH), 128.0 (q), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.9 (2×CH), 126.6 (CH), 124.6 (CH), 121.3 (CH), 109.2 (CH), 71.0 (CH), 59.3 (q), 57.2 (CH_2), 54.3 (CH_2), 51.3 (OCH_3), 51.0 (CH); IR (KBr, cm^{-1}): 3446, 3183, 3027, 2821, 1743, 1712, 1617, 1472, 1339, 1213, 1164, 1028; CIMS *m/z* (rel. intensity, %): 515 (MH^+, 12), 312 (20), 218 (15), 160 (20), 134 (50), 85 (100); HRMS (EI): Found: 514.2242. $C_{34}H_{30}N_2O_3$ requires 514.2256.

3.1.13. Reaction of 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one, prolin and 4-methoxy-benzaldehyde. With the same procedure as **7** or **8**. The product was a mixture of isomers as a pale yellow oil, which was separated by column chromatography.

3.1.14. 2′-Methoxycarbonyl-3′-(4-methoxyphenyl)-1′,2′,3′,5′,6′,7′-hexahydro-spiro-[3*H*-indol-3,1′-pyrrolizin]-2(1*H*)-one (11). 37% as a colourless oil; δ_H (500 MHz, $CDCl_3$): 8.44 (1H, s, N*H*), 7.42 (2H, d, *J*=8.6 Hz, Ar-2′ and 6′*H*), 7.34 (1H, d, *J*=7.6 Hz, Ind-4′*H*), 7.21 (1H, t, *J*=7.6 Hz, Ind-6′*H*), 6.99 (1H, t, *J*=7.6 Hz, Ind-5′*H*), 6.87 (1H, d, *J*=7.6 Hz, Ind-7′*H*), 6.86 (2H, d, *J*=8.6 Hz, Ar-3′ and 5′*H*), 5.16 (1H, d, *J*=6.3 Hz, *H*-3), 4.66 (1H, t, *J*=7.5 Hz, *H*-7a), 3.80 (3H, s, Ar—OCH_3), 3.61 (1H, d, *J*=6.3 Hz, *H*-2), 3.24 (3H, s, CO_2CH_3), 3.11 (1H, m, H_2-5$_\alpha$), 2.81 (1H, m, H_2-5$_\beta$), 2.14 (1H, m, H_2-6$_\alpha$), 2.03 (1H, m, H_2-6$_\beta$), 1.76–1.62 (2H, m, H_2-7); δ_C (125 MHz, $CDCl_3$): δ 180.0 (ester *C*=O), 170.0 (Ind-2′*C*), 158.8 (Ar-4′*C*), 141.1 (Ind-7a′*C*), 132.4 (Ar-1′*C*), 128.8 (Ind-6′*C*), 128.5 (Ar-2′ and 6′*C*), 128.1 (Ind-3a′*C*), 125.4 (Ind-4′*C*), 122.9 (Ind-5′*C*), 113.6 (Ar-3′ and 5′*C*), 109.7 (Ind-7′*C*), 73.3 (*C*-7a), 70.2 (*C*-3), 62.9 (*C*-2), 59.2 (*C*-1), 55.4 (Ar—O*C*H_3), 54.1 (*C*-5), 51.3 (CO_2CH_3), 29.0 (*C*-6), 27.6 (*C*-7); IR (film, cm^{-1}): 3183, 3027, 2821, 1737, 1713, 1622, 1424, 1318, 1260, 1169, 1090, 1031; HRMS (EI): Found: 392.1740. $C_{23}H_{24}N_2O_4$ requires 392.1736.

3.1.15. 1′-Methoxycarbonyl-3′-(4-methoxyphenyl)-1′,2′,3′,5′,6′,7′-hexahydro-spiro-[3*H*-indol-3,2′-pyrrolizin]-2(1*H*)-one (12). 33% as a colourless oil; δ_H (500 MHz, $CDCl_3$): 8.36 (1H, s, N*H*), 7.53 (1H, d, *J*=7.4 Hz, Ind-4′*H*), 7.12 (2H, d, *J*=8.6 Hz, Ar-2′ and 6′*H*), 7.04 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.94 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 6.61 (1H, d, *J*=7.6 Hz, Ind-7′*H*), 6.55 (2H, d, *J*=8.6 Hz, Ar-3′ and 5′*H*), 4.44 (2H, m, *H*-3 and *H*-7a), 3.64 (3H, s, Ar—OCH_3), 3.56 (1H, d, *J*=8.9 Hz, *H*-1), 3.27 (3H, s, CO_2CH_3), 2.92 (1H, m, H_2-5$_\alpha$), 2.60 (1H, m, H_2-5$_\beta$), 2.23 (1H, m, H_2-7$_\alpha$), 2.11 (1H, m, H_2-6$_\alpha$), 1.95 (1H, m, H_2-6$_\beta$), 1.83 (1H, m, H_2-7$_\beta$); δ_C (125 MHz, $CDCl_3$): 178.2 (ester *C*=O), 170.6 (Ind-2′*C*), 159.0 (Ar-4′*C*), 140.6 (Ind-7a′*C*), 129.6 (Ar-1′*C*), 127.4 (Ind-3a′*C*), 128.7 (Ar-2′ and 6′*C*), 128.3 (Ind-6′*C*), 126.4 (Ind-4′*C*), 122.2 (Ind-5′*C*), 113.1 (Ar-3′ and 5′*C*), 109.4 (Ind-7′*C*), 76.1 (*C*-3), 64.7 (*C*-2), 64.4 (*C*-7a), 57.5 (*C*-1), 55.2 (Ar—O*C*H_3), 53.5 (*C*-5), 51.8 (CO_2CH_3), 33.3 (*C*-7), 26.6 (*C*-6); IR (film, cm^{-1}): 3173, 3025, 2825, 1736, 1711, 1628, 1425, 1322, 1173, 1093, 1022; HRMS (EI): Found: 392.1737. $C_{23}H_{24}N_2O_4$ requires 392.1736.

3.1.16. 5-Ethoxycarbonyl-4-methoxycarbonyl-2-phenyl-spiro-[3*H*-indol-3,3′-pyrrolidin]-2(1*H*)-one (13). 3-(Methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one **4a** (0.19g, 0.94 mmol) and ethyl-(benzylideneamino)acetate (0.197 g, 1 mmol) were dissolved in toluene (5 ml). Lithium bromide (0.13 g, 1.5 mmol) and triethylamine (0.12 g, 0.17 ml, 1.2 mmol) was added. The reaction mixture was stirred at room temperature. After 1–3 h when the reaction was completed (judged by TLC) 5 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 sulphate and evaporated. The residue was purified by column chromatography (hexanes:ethyl acetate 1:1 vol/vol) to yield the product as a white powder (0.25 g, 68%); mp 102°C; Found: C, 67.3; H, 5.5; N, 7.1. $C_{22}H_{22}N_2O_5$ requires C, 66.99; H, 5.62; N, 7.10%; δ_H (500 MHz, $CDCl_3$): 8.09 (1H, br s, N*H*), 7.27 (1H, d, *J*=7.5 Hz, Ind-4′*H*), 7.22 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 7.13 (1H, t, *J*=7.9 Hz, Ph-4′*H*), 7.08 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 7.06 (2H, d, *J*=7.9 Hz, Ph-2′ and 6′*H*), 6.71 (1H, d, *J*=7.5 Hz, Ind-7′*H*), 6.89 (2H, d, *J*=7.9 Hz, Ph-2′ and 6′*H*), 4.72 (1H, d, *J*=8.0 Hz, *H*-4), 4.58 (1H, s, *H*-2), 4.31 (2H, q, *J*=7.3 Hz, CH_2CH$_3$), 3.67 (1H, d, *J*=8.0 Hz, *H*-5), 3.44 (3H, s, OCH_3), 1.32 (3H, t, *J*=7.3 Hz, CH$_2$CH_3); δ_C (125 MHz, $CDCl_3$+DMSO-d_6) δ: 179.0 (ester *C*=O), 171.3 (ester *C*=O), 170.9 (Ind-2′*C*), 141.3 (Ind-7a′*C*), 134.5 (Ph-1′*C*), 128.9 (Ind-6′*C*), 128.0 (Ph-4′*C*), 127.9 (Ph-2′ and 6′*C*), 127.6 (Ind-3a′*C*), 126.1 (Ph-3′ and 5′*C*), 123.8 (Ind-4′*C*), 122.6 (Ind-5′*C*), 109.9 (Ind-7′*C*), 73.1 (*C*-2), 63.8 (*C*-3), 63.5 (*C*-4), 61.6 (*C*H_2), 56.9 (*C*-5), 52.0 (O*C*H_3), 14.2 (*C*H_3); IR (KBr, cm^{-1}): 3389, 3063, 2985, 2952, 2818,

1738, 1704, 1617, 1473, 1452, 1362, 1270, 1245, 1212; CIMS *m/z* (rel. intensity, %): 395 (MH^+, 100).

3.1.17. 4-Ethoxycarbonyl-5-methoxycarbonyl-2-(2,2-diphenyl-ethenyl)-spiro-[3*H*-indol-3,3′-pyrrolidin]-2(1*H*)-one (15a and b). 3-(Methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one **4a** (94 mg, 0.46 mmol) and imine **14** (0.136 g, 0.46 mmol) were dissolved in toluene (5 ml). Silver acetate (0.11 g, 0.69 mmol) and triethylamine (46 mg, 0.46 mmol) were added. The reaction mixture was stirred at room temperature. After 1–3 h when the reaction was completed (judged by TLC) 5 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 sulphate and evaporated. The residue was separated by column chromatography (hexanes:ethyl acetate 1:1 vol/vol) to yield the products.

(15a). White powder (70 mg, 30%); mp 128–130°C; δ_H (250 MHz, $CDCl_3$) δ: 8.96 (1H, br s, N*H*), 7.25–7.00 (10H, m, Ar-*H*), 6.88 (1H, d, *J*=7.8 Hz, Ar-*H*), 6.82 (1H, d, *J*=7.6 Hz, Ar-*H*), 6.61 (1H, d, *J*=7.6 Hz, Ar-*H*), 6.54 (1H, d, *J*=7.2 Hz, Ar-*H*), 6.05 (1H, d, *J*=9.8 Hz, C*H*=CPh$_2$), 4.52 (1H, d, *J*=8.3 Hz, *H*-4), 4.26 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 4.06 (1H, d, *J*=9.8 Hz, *H*-2), 3.66 (1H, d, *J*=8.3 Hz, *H*-5), 3.30 (3H, s, CH_3O), 1.28 (3H, t, CH_3CH$_2$); δ_C (63 MHz, $CDCl_3$) δ: 179.9 (q), 170.9 (q), 170.7 (q), 147.5 (q), 141.1 (q), 141.0 (q), 138.5 (q), 129.2 (2×CH), 128.5 (CH), 128.1 (2×CH), 128.0 (2×CH), 127.8 (CH), 127.4 (2×CH), 127.3 (q), 127.1 (CH), 124.3 (CH), 122.7 (CH), 122.2 (CH), 109.7 (CH), 68.7 (CH), 63.9 (CH), 61.6 (CH_2), 57.3 (CH), 51.9 (CH_3O), 14.2 (*C*H_3CH$_2$); IR (nujol, cm^{-1}): 1737, 1721, 1616, 1463, 1375, 1220, 1202, 1185, 1025; EIMS *m/z* (rel. intensity, %): 497 (MH^+, 7), 322 (12), 294 (100), 204 (47), 172 (33), 146 (9), 85 (7), 57 (7); HRMS (EI): Found: 496.1989. $C_{30}H_{28}N_2O_5$ requires 496.1998.

(15b). White powder (50 mg, 21%); mp 136–138°C; Found: C, 72.3; H, 5.5; N, 5.5. $C_{30}H_{28}N_2O_5$ requires C, 72.56; H, 5.68; N, 5.64%; δ_H (250 MHz, $CDCl_3$): 8.85 (1H, s, N*H*), 7.28–6.97 (7H, m, Ar-*H*), 7.05–6.99 (2H, m, Ar-*H*), 6.96–6.84 (2H, m, Ar-*H*), 6.76 (1H, d, *J*=7.1 Hz, Ar-*H*), 6.55 (2H, d, *J*=7.5 Hz, Ar-*H*), 5.85 (1H, dd, *J*=9.8 and 1.7 Hz, C*H*=CPh$_2$), 4.68 (1H, d, *J*=6.6 Hz, *H*-4), 4.24 (2H, q, *J*=6.6 Hz, CH_2CH$_3$), 4.16 (1H, d, *J*=9.8 Hz, *H*-2), 3.99 (1H, d, *J*=6.6 Hz, *H*-5), 3.46 (3H, s, CH_3O), 1.29 (3H, t, CH_3CH$_2$); δ_C (63 MHz, $CDCl_3$): 179.6 (q), 173.3 (q), 170.4 (q), 148.2 (q), 141.3 (q), 141.1 (q), 138.5 (q), 129.6 (2×CH), 128.3 (CH+q), 128.0 (2×CH), 127.9 (2×CH), 127.8 (CH), 127.4 (2×CH), 127.2 (CH), 122.8 (CH), 122.7 (CH), 121.6 (CH), 109.8 (CH), 67.8 (CH), 62.3 (q), 61.8 (CH), 61.6 (CH_2), 56.4 (CH), 52.3 (CH_3O), 14.1 (*C*H_3CH$_2$); IR (nujol, cm^{-1}): 1734, 1706, 1628, 1463, 1372, 1214, 1104, 1023; EIMS *m/z* (rel. intensity, %): 497 (17, M^+), 322 (12), 294 (100), 204 (47), 172 (32), 159 (12), 146 (10), 85 (9), 57 (9).

3.1.18. 5-Ethoxycarbonyl-4-methoxycarbonyl-2-phenyl-1-methyl-spiro-[3*H*-indolo-3,3′-pyrrolidin]-2(1*H*)-one (17a). Ethyl sarcosinate hydrochloride (0.23 g, 2 mmol), 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one (0.2 g, 0.9 mmol), benzaldehyde (0.15 g, 1.4 mmol) and triethylamine (0.15 g, 0.21 ml, 1.5 mmol) were heated under reflux in dry benzene (20 ml) for 48 h. The water formed was continuously removed by the aid of a Dean–Stark trap. After completion of the reaction the mixture was poured into saturated NH_4Cl solution (10 ml), and was extracted with ether (3×15 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (hexanes–ethyl acetate 1:1 vol/vol) to yield the product as a white powder (0.21 g, 62%); mp 129°C; δ_H (500 MHz, $CDCl_3$) δ: 7.81 (1H, d, Ind-4′*H*), 7.14 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 7.10 (3H, m, Ph-*H*), 7.03 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.95 (2H, m, Ph-H), 6.60 (1H, d, *J*=7.5 Hz, Ind-7′*H*), 4.75 (1H, s, *H*-4), 4.35 (1H, d, *J*=7.9 Hz, *H*-2), 4.29 (2H, q, *J*=7.4 Hz, CH_2CH$_3$), 4.15 (1H, d, *J*=7.9 Hz, *H*-5), 3.12 (3H, s, CO_2CH_3), 2.21 (3H, s, NCH_3), 1.34 (3H, t, *J*=7.4 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) δ: 179.2 (*C*=O), 169.5 (*C*=O), 167.5 (*C*=O), 140.5 (Ind-7a′*C*), 135.2 (Ph-1′*C*), 128.4 (Ind-4a′*C*), 128.0 (Ph-2′ and 6′*C*), 127.9 (Ph-3′ and 5′*C*), 125.7 (Ind-6′*C*), 123.0 (Ind-5′*C*), 121.8 (Ind-4′*C*), 108.9 (Ind-7′*C*), 67.2 (*C*-4), 60.7 (CH_2), 53.0 (*C*-2), 52.0 (*C*-3), 51.4 (CO_2—CH_3), 34.7 (NCH_3), 34.2 (*C*-1), 14.4 (CH_3), IR (nujol, cm^{-1}): 1737, 1711, 1624, 1467, 1415, 1372, 1219, 1033; HRMS (EI): Found: 408.1678. $C_{23}H_{24}N_2O_5$ requires 408.1685.

3.1.19. 4,5-Bis(methoxycarbonyl)-2-phenyl-1-benzyl-spiro-[3*H*-indolo-3,3′-pyrrolidin]-2(1*H*)-one (17b). Methyl *N*-benzylglycinate (0.24 g, 1.4 mmol), 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one (0.25 g, 1.2 mmol), benzaldehyde (0.16 g, 1.5 mmol) were heated under reflux in dry toluene (10 mmol) for 24 h. The water formed was continuously removed by the aid of a Dean–Stark trap. After completion of the reaction the mixture was poured into saturated NH_4Cl solution (10 ml), and was extracted with ether (3×15 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (hexanes: ethyl acetate 1:1 vol/vol) to yield the product as a white powder (0.40 g, 76%); mp 139°C; δ_H (500 MHz, $CDCl_3$): 7.85 (1H, d, *J*=7.5 Hz, Ind-4′*H*), 7.78 (1H, s, N*H*), 7.39 (2H, d, Ar-*H*), 7.33 (2H, d, Ar-*H*), 7.26 (1H, t, Ar-*H*), 7.20 (1H, t, *J*=7.6 Hz, Ind-6′*H*), 7.14 (5H, br s, Ar-*H*), 7.09 (1H, t, *J*=7.6 Hz, Ind-5′*H*), 6.71 (1H, d, *J*=7.6 Hz, Ind-7′*H*), 5.09 (1H, s, *H*-2), 4.27 (1H, d, *J*=8.1 Hz, *H*-5), 4.2 (1H, d, *J*=8.1 Hz, *H*-4), 3.84 (1H, d, *J*=14.4 Hz, NCH_2), 3.81 (3H, s, OCH_3), 3.29 (1H, d, *J*=14.4 Hz, NCH_2), 3.11 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$): 179.2 (*C*=O), 172.2 (*C*=O), 169.4 (*C*=O), 140.8 (Ind-7a′*C*), 138 (Bn-1′*C*), 135.6 (Ph-1′*C*), 130.3 (Ind-3a′*C*), 128.4 (Ind-6′*C*), 128.3 (4×CH), 128.1 (3×CH), 127.9 (2×CH), 127.3 (Bn-4′*C*), 125.6 (Ind-4′*C*), 122.9 (Ind-5′*C*), 109 (Ind-7′*C*), 76.8 (*C*-2), 62.9 (*C*-5), 61.6 (*C*-3), 53.1 (*C*-4), 51.5 (NCH_2), 51.4 (OCH_3), 51.3 (OCH_3); IR (KBr, cm^{-1}): 3380, 3050, 2985, 1736, 1713, 1627, 1466, 1410, 1377, 1041; HRMS (EI): Found: 470.1852. $C_{28}H_{26}N_2O_5$ requires 470.1841.

3.1.20. 10′,11′-Bis(methoxycarbonyl)-5′,6′-dimethoxy-(2′,3′,8′,9′,10′,11′-hexahydro)-spiro-[3*H*-indol-2,9′-pyrrolo[1′,2′-*j*′]isoquinolin]-2(1*H*)-one (19). 3-(Methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one (0.162 g, 0.8 mmol) and 6,7-dimethoxy-(2-methoxycarbonylmethyl)-

3,4-dihydroiso-quinolinium bromide **18** (0.29 g, 0.85 mmol) were dissolved in dry methanol (7 ml) and triethylamine (0.14 ml, 0.10 g, 1 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo, the residue was suspended in ether (20 ml). The ethereal solution was washed with water (10 ml) and brine (5 ml), dried over $MgSO_4$ and evaporated in vacuo to yield a white solid which was recrystallized from ethanol (0.366 g, 98%); mp 137°C; Found: C, 64.5; H, 5.5; N, 6.0. $C_{25}H_{26}N_2O_7$ requires C, 64.37; H, 5.62; N, 6.01%; δ_H (500 MHz, $CDCl_3$): 10.33 (1H, br d, N*H*), 7.57 (1H, d, *J*=7.5 Hz, Ind-4′*H*), 7.27 (1H, t, *J*=7.5 Hz, Ind-6′*H*), 7.08 (1H, t, *J*=7.5 Hz, Ind-5′*H*), 6.84 (1H, d, *J*=7.5 Hz, Ind-7′*H*), 6.65 (1H, s, *H*-7′), 5.59 (1H, s, *H*-4′), 5.25 (1H, s, *H*-3a), 4.55 (1H, d, *J*=7.6 Hz, *H*-1), 3.97 (1H, d, *J*=7.6 Hz, *H*-2), 3.72 (3H, s, CO_2CH_3), 3.67 (3H, s, 6′-OCH_3), 3.51 (1H, m, *H*-9_{ax}), 3.25 (3H, s, CO_2CH_3), 3.20 (3H, s, 5′-OCH_3), 3.05 (1H, m, *H*-9_{eq}), 2.84 (1H, m, *H*-8_{eq}), 2.71 (1H, m, *H*-8_{ax}); δ_C (125 MHz, $CDCl_3$): 178.5 (*C*-2), 172.0 (*C*=O), 169.4 (*C*=O), 147.3 (*C*-6′), 146.2 (*C*-5′), 142.3 (*C*-7a′), 129.9 (*C*-3a′), 128.4 (*C*-6), 126.9 (*C*-7a′), 124.3 (*C*-4), 124.1 (*C*-3b′), 121.9 (*C*-5), 111.2 (*C*-7′), 109 (*C*-7), 107.1 (*C*-4′), 70.3 (*C*-3a′), 68.2 (*C*-1′), 62.4 (*C*-3), 55.1 (6′-OCH_3), 54.3 (*C*-2′), 54.2 (5′-OCH_2), 51.5 (CO_2CH_3), 51.2 (CO_2CH_3), 46.9 (*C*-9′), 27.8 (*C*-8′); IR (KBr, cm^{-1}): 3515, 1750, 1719, 1618, 1522, 1470, 1450, 1441, 1348, 1271, 1227, 1203, 78, 1111, 1011, 820, 764, 605. CIMS *m/z* (rel. intensity, %): 467 (MH^+, 100).

Acknowledgements

This work was financially supported by the National Fund for Science and Research, Hungary (OTKA Project No. F 029198 and T 032221). N. M. thanks the Hungarian Academy of Sciences for a Bolyai J. fellowship.

References

1. Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, Vols. 1 and 2; Wiley: New York, 1984.
2. (a) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893. (b) Garner, P.; Ho, W. B.; Shin, C. *J. Am. Chem. Soc.* **1993**, *115*, 10742. (c) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773. (d) Pham, V. C.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 8051. (e) Fiswick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1996**, *37*, 3915. (f) Daubié, C.; Mutti, S. *Tetrahedron Lett.* **1996**, *37*, 3915.
3. Part of this work has been published in preliminary form: Nyerges, M.; Gajdics, L.; Szöllõsy, Á.; Tõke, L. *Synlett* **1999**, 111..
4. (a) Tsuge, O.; Kanemasa, S. In *Adv. in Heterocyclic Chemistry*, Katritzky, A., Ed.; Academic Press: New York, 1989; Vol. 45, pp 232–349. (b) Grigg, R.; Sridharan, V. In *Adv. in Cycloaddition*, Curran, D. P., Ed.; JAI Press: Greenwich, London, 1993; Vol. 3, pp 161.
5. (a) Grigg, R.; Basanagoudar, L. D.; Kennedy, D. A.; Malone, J. F.; Thianpatanagui, S. *Tetrahedron Lett.* **1982**, *23*, 2903. (b) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagui, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182.
6. Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron Asymmetry* **1996**, *7*, 1.
7. (a) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1138. (b) Edmondson, S. D.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147.
8. Brandman, H. *J. Heterocycl. Chem.* **1973**, *10*, 383.
9. Long, D. R.; Richards, C. G.; Ross, M. S. F. *J. Heterocycl. Chem.* **1978**, *15*, 633.
10. Padwa, A.; Chen, Y.-Y.; Dent, W.; Nimmesgern, H. *J. Org. Chem.* **1985**, *50*, 4006.
11. Fejes, I.; Nyerges, M.; Tõke, L.; Pak, C. S. *Tetrahedron* **2000**, *56*, 623.
12. Kozminykh, E. N.; Berezina, E. S.; Kozminykh, V. O. *Russ. J. Gen. Chem.* **1996**, *66*, 1100.
13. Rudas, M.; Fejes, I.; Nyerges, M.; Szöllõssy, Á.; Tõke, L.; Groundwater, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1167.
14. Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.
15. Grigg, R.; Kemp, J. *Tetrahedron Lett.* **1980**, *21*, 2461.
16. Nyerges, M.; Rudas, M.; Tóth, G.; Herényi, B.; Bitter, I.; Tõke, L. *Tetrahedron* **1995**, *51*, 13321.
17. Groundwater, P. W.; Sharif, T.; Arany, A.; Hibbs, D. E.; Hurthouse, M. B.; Garnett, I.; Nyerges, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2837.
18. Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.
19. (a) Bende, Z.; Simon, K.; Tóth, G.; Tõke, L.; Weber, L. *Liebigs Ann. Chem.* **1982**, 924. (b) Bende, Z.; Bitter, I.; Tõke, L.; Weber, L.; Tóth, G.; Janke, F. *Liebigs Ann. Chem.* **1982**, 2146. (c) Bende, Z.; Tõke, L.; Weber, L.; Tóth, G.; Janke, F.; Csonka, G. *Tetrahedron* **1983**, *40*, 369. (d) Tóth, G.; Tischer, T.; Bende, Z.; Szejtli, G.; Tõke, L. *Monatsh. Chem.* **1990**, *121*, 529. (e) Janke, F.; Himmelreich, U.; Tóth, G.; Tischer, T.; Bende, Z.; Tõke, L. *J. Heterocycl. Chem.* **1991**, *28*, 867.
20. (a) Richards, C. G.; Ross, M. S. F. *Tetrahedron Lett.* **1968**, *9*, 4391. (b) Okada, K.; Sakuma, H.; Inoue, S. *Chem. Lett.* **1979**, 131. (c) Okada, K.; Sakuma, H.; Kondo, M.; Inoue, S. *Chem. Lett.* **1979**, 213. (d) Richards, C. G.; Thurston, D. E. *Tetrahedron* **1983**, *39*, 1817.
21. Franke, A. *Liebigs Ann. Chem.* **1978**, 717.
22. (a) Jossang, P.; Jossang, A.; Hadi, H. A.; Sévenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527. (b) Bascop, S.-I.; Sápi, J.; Laronza, J.-Y.; Lévy, J. *Heterocycles* **1994**, *38*, 725.
23. Southon, I. W.; Buckingham, J. *Dictionary of Alkaloids*, Chapman & Hall: New York, 1989.