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Stereocontrolled Synthesis of 3-Alkylindolines from (*Z*)-2-Hydroxyindolenines

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Summary. A convenient process for the synthesis of 3-alkylindolines **2** and their transformation into *cis*-fused tricyclic γ-lactones **3** from allylic alcohols **1**, mediated by a *Grignard* reagent, is described. This process proceeds with high stereocontrol at the two newly formed contiguous stereogenic centres. By oxidation with chromium oxide, 2-oxindole derivatives **4** are obtained from 3-alkylindolines **2**.

Keywords. 2-Hydroxyindolenines; Stereocontrolled *Grignard* alkylation; 3-Alkylindolines; Furo[2,3-*b*]indol-2-ones.

Stereokontrollierte Synthese von 3-Alkylindolinen aus (*Z*)-2-Hydroxyindoleninen

Zusammenfassung. Eine einfache Methode zur Herstellung der 3-Alkylindoline **2** und deren Umsetzung zu den *cis*-kondensierten tricyclischen γ-Lactonen **3** aus den Allylalkoholen **1** mittels einer *Grignard*-Verbindung wird beschrieben. Die Reaktion verläuft unter hoher Stereoselektivität bezüglich der zwei neu gebildeten Asymmetriezentren. Durch Oxidation mit Chromtrioxid erhält man aus den 3-Alkylindolinen **2** die 2-Oxindolderivate **4**.

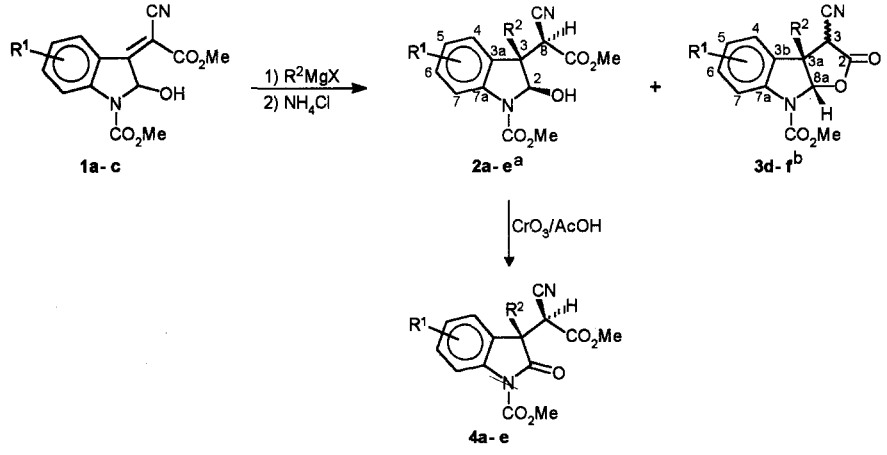
Introduction

In the course of our research on 2-hydroxyindolenines, we recently investigated the conjugated addition of methylmagnesium iodide to 2-hydroxyindolenine **1a** and to its 5-methoxyl derivative as a new route towards the synthesis of physostigmine [1], the main component of *Physostigma venenosum* Balf. In the present work, we describe a general approach to the synthesis of 3-alkylindolines **2** *via* the stereocontrolled formation of a carbon–carbon bond and of *cis*-fused γ-lactones **3** which are of potential interest for the synthesis of alkaloids with a hexahydropyrrolo[2, 3-*b*]indole framework [2].

Results and Discussion

In this study we have found that treatment of (*Z*)-2-hydroxyindolenines **1a–c**, possessing a tetrasubstituted double bond, with 4 molar equivalents of *Grignard* reagent (R^2MgX; R^2 = methyl, ethyl, *iso*-propyl and *tert*-butyl) in a solvent mixture

of diethyl ether and tetrahydrofuran leads with high regio- and stereoselectivity to the corresponding conjugated addition products (Scheme 1). The generality of the present reaction is indicated in Table 1; it can be seen that both the nature and the ratio of the obtained products **2** and **3** are influenced by the bulkiness of the alkyl group of the *Grignard* reagent as well as by the experimental conditions. Thus, reaction of compounds **1a–c** with methylmagnesium iodide leads to equilibrated C-2 epimeric mixtures of (2*R**,3*S**,8*S**)- and (2*S**,3*S**,8*S**)-3-methylindolines (*ca.* 1:1), resulting from a ring–chain tautomerization [3]. Diastereomerically pure (2*R**,3*S**,8*S**)-3-methylindolines **2a–c** (entries 1–4) could be isolated from this mixture by fractionated crystallization (mother liquour contains always a C-2 epimeric mixture in the ratio of *ca.* 1:1). The success of the stereocontrolled alkylation can be ascribed to the directing effect of the hydroxyl group [4]. The relative stereochemistry of 3-alkylindolines **2** was fully supported by X-ray analysis of **2a** [1c] and ^{1}H NMR spectra. Pure samples of (2*R**,3*S**,8*S**) isomers of **2** gave ^{1}H NMR spectra in which the signal due to H-2 was always present as a doublet ($^3J_{H,H}$ with the hydroxyl hydrogen), whereas the H-2 proton of the (2*S**,3*S**,8*S**) isomers appears as a broad singlet, as was observed in the crude epimeric mixtures.



1–4	R^1	R^2	2–4	R^1	R^2
a	H	Me	**d**	H	Et
b	5-Br	Me	**e**	H	*i*-Pr
c	6-Br	Me	**f**	H	*t*-Bu

[a] Isolated by crystallization from the epimetric mixture; [b] epimeric mixtures (except **3f**)

Scheme 1

The alkylation of 2-hydroxyindolenine **1a** with ethyl or *iso*-propyl *Grignard* reagents also proceeds with high regioselectivity to afford, after crystallization, the corresponding diastereomerically pure 3-alkylindolines **2d** (R^2 = Et) or **2e** (R^2 = *i*-Pr), in addition to the predominantly lactonized products **3d** or **3e** as shown in entries 5–9 of Table 1. The predominance of the lactonized products can be explained by the steric hindrance of the alkyl group at C-3 which favors intramolecu-

Table 1. Reaction of **1a–c** with R^2MgX according to the general procedure

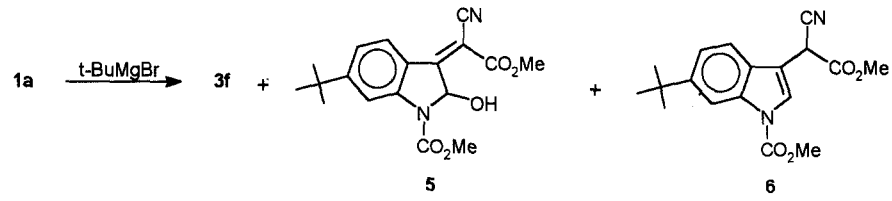
Entry	Substrate	Reagent		Conditions		Overall yield[a] (%)	Products	Ratio **2**/**3**[b]
		R^2	X	Temp. (°C)	Time (min)			
1[c]	**1a**	Me	I	25	15	40	**2a**	1:0
2	**1b**	Me	I	25	20	33	**2b**	1:0
3	**1b**	Me	I	0	20	47	**2b**	1:0
4	**1c**	Me	I	25	20	29	**2c**	1:0
5	**1a**	Et	Br	25	5	30	**2d**, **3d**	3:7
6	**1a**	Et	Br	0	15	46	**2d**, **3d**	4:6
7	**1a**	Et	Br	−78	60	61	**2d**, **3d**	4:6
8	**1a**	*i*-Pr	Br	0	15	58	**2e**, **3e**	4:6
9	**1a**	*i*-Pr	Br	−78	60	74	**2e**, **3e**	3:7
10[c]	**1a**	*t*-Bu	Br	0	30	21	**3f**	0:1

[a] Estimated from the isolated pure products **2** and **3**; [b] obtained as equilibrated mixtures of *anti*/*syn* diastereomers (2:1, except **3f**) according to NMR; [c] attempts to perform the reaction at −78 °C failed

lar cyclization of the initially formed 3-alkylindoline. This conclusion is based on the observation that compounds **2d** and **2e** were smoothly converted into the corresponding lactones **3d** and **3e** by standing at room temperature in tetrahydrofuran containing traces of triethylamine. As expected, the less hindered 3-methylindoline **2a** is recovered as a mixture of two diastereomers (*ca.* 1:1) under the conditions described above. It is worth noting that the thermodynamically controlled ring closure of 3-alkylindolines **2** affords *cis*-fused γ-lactones **3**, as was inferred from NOE experiments, implying that an epimerization occurs at the C-2 hemiaminalic stereogenic center [3] before cyclization.

As for γ-lactones **3d** and **3e**, they were obtained as unseparable mixtures of two diastereomers in *ca.* 2:1 ratios as determined by ^1H NMR in $CDCl_3$ solution. In these two cases, the partial epimerization occurs at the acidic stereogenic center C-3 as evidenced by the markedly fast deuterium exchange at C-3 when diastereomeric mixtures of **3d** and of **3e** were treated with D_2O. A steric hindrance between ethyl or *iso*-propyl groups and the nitrile group should favor *anti* compounds. We have also observed that the conjugated addition is slower at lower temperature, but in general it gave the best results in terms of overall yield. The reaction between **1a** and ethylmagnesium bromide was performed at different temperatures (entries 5–7, Table 1). In the range 25 to 0 °C, the relative yield of **2d** changed from 30 to 40%. A further decrease of temperature (−78 °C) did not change the ratio between **2d** and **3d**, but the maximum overall yield (61%) was reached. The structures of compounds **2b–e** were confirmed by reaction with chromium oxide in acetic acid to provide oxindoles **4b–e** as diastereomerically pure compounds (Scheme 1) in 59, 47, 72, and 51% of isolated yield, respectively.

In agreement with the preceding results, the reaction of **1a** with the bulkier *tert*-butylmagnesium bromide (Table 1, entry 10) results in the formation of lactone



Scheme 2

3f (R^2 = *t*-Bu) as a single diastereomer in which the nitrile and the *tert*-butyl group at C-3/C-3a are *anti* oriented. The stereochemical assignment was confirmed by a NOE experiment in which irradiation of the *tert*-butyl group (δ = 1.06 ppm) resulted in an enhancement of the H-3 (δ = 4.32 ppm) and H-8a (δ = 6.37 ppm) signals. In this case, the conjugated addition occurred with a comparatively low yield of 21%, and the initially formed 3-*t*-butylindoline could not be detected. However, two 6-alkylated products were obtained (Scheme 2). These byproducts were isolated by chromatography in 21 and 13% yield and identified by their IR, ^{1}H, and ^{13}C NMR data as methyl (*Z*)-3-(1-cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-2-hydroxy-6-*t*-butyl-1*H*-indole-1-carboxylate (**5**) and methyl 3-(1-cyano-2-methoxy-2-oxoethyl)-6-*t*-butyl-1*H*-indole-1-carboxylate (**6**) (cf. Tables 2 and 3).

The results described above show that the conjugated addition depends strongly on the reaction conditions. These include not only the type of *Grignard* reagent, but also reaction time and temperature. The structures of all 3-alkylindolines, their corresponding lactonized products, and oxindole derivatives are confirmed by their HRMS, IR, ^{1}H NMR (Table 2), and ^{13}C spectroscopic data (Tables 3 and 4). Selective proton decoupling and ^{13}C-^{1}H correlation experiments helped to assign the signals. In conclusion, we have developed a useful and reliable method for the regiospecific introduction of virtually any alkyl group derived from a *Grignard* reagent into 2-hydroxyindolenines to give 3-alkylindolines with stereocontrol at the C-3 and C-8 stereogenic centers, as well as their lactonized derivatives, which may be interesting intermediates in indole alkaloid synthesis [5, 6].

Experimental

All organic solvents were dried according to standard procedures. Starting 2-hydroxyindolenines **1a–c** were prepared from the corresponding methyl 3-(1-cyano-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylates according to a previously published procedure [7]. Compounds **2a** and **4a** are known [1a]. The preparation of 3-alkylindolines and their corresponding lactones were carried out in an Ar atmosphere. *Grignard* reagents were synthesized according to known procedures [8]. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were obtained using a Perkin Elmer 16F PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL300 spectrometer working at 300 MHz and 75.4 MHz, respectively, and chemical shifts reported in ppm downfield from *TMS*. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh). Analytical TLC was performed on silica gel $60F_{254}$ coated aluminium sheets. HRMS were measured on a Jeol JMS-SX 102A spectrometer with polyethylene glycol 400 as internal standard. The physical and spectroscopic properties of the new products are given in Tables 2–4.

Table 2. Melting points, IR and ^{1}H NMR data of compounds **1**–**6**

Compound	Molecular formula[a,b]	mp. (°C)[c]	IR (KBr, cm^{-1})			^{1}H NMR ($CDCl_3$/*TMS*) *δ*, *J*(Hz)
			ν_{OH}	ν_{CN}	$\nu_{C=O}$	
1b	$C_{14}H_{11}BrN_2O_5$ (367.2)	194–196	3516	2224	1722	3.83 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, NCO_2CH_3), 6.69 (dd, J = 8.0, 1.2, 1 H, H-2), 7.52 (d, J = 8.1, 1 H, OH), 7.81 (d, J = 8.7, 1 H, H-6), 7.84 (br s, 1 H, H-7), 8.33 (dd, J = 2.4, 1.2, 1 H, H-4)[d]
2b	$C_{15}H_{15}BrN_2O_5$ (383.2)	153–155	3434	2260	1738, 1702	1.62 (s, 3 H, CH_3), 3.53 (s, 1 H, H-8), 3.69 (br s, 3 H, CO_2CH_3), 3.92 (br s, 3 H, NCO_2CH_3), 6.08 (d, J = 4.4, 1 H, H-2), 7.42 (d, J = 1.9, 1 H, H-4), 7.43 (d, J = 5.5, 1 H, H-6), 7.70 (very br, 1 H, H-7)
2c	$C_{15}H_{15}BrN_2O_5$ (383.2)	135–138	3466	2246	1726, 1686	1.60 (s, 3 H, CH_3), 3.51 (s, 1 H, H-8), 3.73 (s, 3 H, CO_2CH_3), 3.94 (br s, 3 H, NCO_2CH_3), 6.10 (d, J = 4.4, 1 H, H-2), 7.19 (d, J = 8.0, 1 H, H-4), 7.24 (dd, J = 8.1, 1.7, 1 H, H-5), 7.65 (very br, 1 H, H-7)
2d	$C_{16}H_{18}N_2O_5$ (318.3)	141–143	3442	2254	1744, 1702	0.99 (t, J = 7.3, 1 H, CH_3CH_2), 1.96 and 2.34 (2dq, J = 14.4, 7.3, 2 H, CH_3CH_2), 3.62 (br s, 3 H, CO_2CH_3), 3.73 (s, 1 H, H-8), 3.93 (s, 3 H, NCO_2CH_3), 6.20 (d, J = 4.1, 1 H, H-2), 7.06 (td, J = 7.6, 1.0, 1 H, H-5), 7.23 (d, J = 7.7, 1 H, H-4), 7.30 (td, J = 7.8, 1.3, 1 H, H-6), 7.60 (very br, 1 H, H-7)
2e	$C_{17}H_{20}N_2O_5$ (332.4)	147–149	3434	2254	1752, 1700	0.99 and 1.09 (br s and d, J = 6.9, 6 H, $CH(CH_3)_2$), 2.58 (sept, J = 6.8, 1 H, $CH(CH_3)_2$), 3.69 (br s, 3 H, CO_2CH_3), 3.93 (s, 3 H, NCO_2CH_3), 4.16 (s, 1 H, H-8), 6.18 (d, J = 3.6, 1 H, H-2), 7.09 (td, J = 7.5, 1.0, 1 H, H-5), 7.24 (d, J = 7.6, 1 H, H-4), 7.31 (td, J = 7.8, 1.3, 1 H, H-6), 7.60 (very br, 1 H, H-7)
3d	$C_{15}H_{14}N_2O_4$ (286.3)	135–137	–	2258	1792, 1724	mixture of diastereomers (*anti* and *syn*): 0.92 and 0.88 (2t, J = 7.5, 3 H, CH_3CH_2), 2.06 and 1.94 (2dq, J = 14.3, 7.3, 2 H, CH_3CH_2), 3.95 (br s, 3 H, CO_2CH_3), 4.14 and 4.05 (2s, 1 H, H-3)[e], 6.28 and 6.33 (2br s, 1 H, H-8a), 7.21 and 7.17 (2td, J = 7.6, 1.1, 1 H, H-5), 7.42 and 7.39 (2t, J = 7.7, 1 H, H-6), 7.64 (d, J = 7.6, 1 H, H-4), 7.86 (very br, 1 H, H-7)
3e	$C_{16}H_{16}N_2O_4$ (300.3)	203–204	–	2252	1782, 1724	mixture of diastereomers (*anti* and *syn*): 0.80, 1.15 and 0.74, 1.13 (4d, J = 6.8, 6 H, $CH(CH_3)_2$), 2.21 and 2.62 (2sept, J = 6.8, 1 H, $CH(CH_3)_2$), 3.95 (br s, 3 H, CO_2CH_3), 4.15 and 4.02 (2s, 1 H, H-3)[e], 6.26 and 6.37 (2br s, 1 H, H-8a), 7.21 and 7.17 (2td, J = 7.7, 1.1, 1 H, H-5), 7.44 and 7.40 (2td, J = 7.9, 1.3, 1 H, H-6), 7.68 (d, J = 7.6, H-4), 7.93 (very br, 1 H, H-7)

(*Contd.*)

Table 2. (*Continued*)

Compound	Molecular formula[a,b]	mp. (°C)[c]	IR (KBr, cm^{-1})			^1H NMR ($CDCl_3/TMS$) δ, J(Hz)
			ν_{OH}	ν_{CN}	$\nu_{C=O}$	
3f	$C_{17}H_{18}N_2O_4$ (314.3)	187–188	–	2252	1798, 1730	1.06 (s, 9 H, $C(CH_3)_3$), 3.95 (br s, 3 H, CO_2CH_3), 4.32 (s, 1 H, H-3)[e], 6.37 (br s, 1 H, H-8a), 7.21 (td, J = 7.7, 1.1, 1 H, H-5), 7.44 (t, J = 7.4, 1 H, H-6), 7.78 (d, J = 7.8, H-4), 7.95 (very br, 1 H, H-7)
4b	$C_{15}H_{13}BrN_2O_5$ (381.2)	88–89	–	2246	1778, 1744	1.63 (s, 3 H, CH_3), 3.65 (s, 3 H, CO_2CH_3), 4.05 (s, 3 H, NCO_2CH_3), 4.30 (s, 1 H, H-8), 7.53 (dd, J = 8.7, 2.1, 1 H, H-6), 7.71 (d, J = 1.8, 1 H, H-4), 7.90 (d, J = 8.8, 1 H, H-7)
4c	$C_{15}H_{13}BrN_2O_5$ (381.2)	131–132	–	2250	1778, 1736	1.64 (s, 3 H, CH_3), 3.63 (s, 3 H, CO_2CH_3), 4.06 (s, 3 H, NCO_2CH_3), 4.29 (s, 1 H, H-8), 7.38 (dd, J = 8.1, 1.8, 1 H, H-5), 7.47 (d, J = 8.1, 1 H, H-4), 8.20 (d, J = 1.7, 1 H, H-7)
4d	$C_{16}H_{16}N_2O_5$ (316.3)	oil	–	2254	1754[f]	0.70 (t, J = 7.4, 3 H, CH_3CH_2), 2.12 and 2.18 (2dq, J = 14.8, 7.4, 2 H, CH_3CH_2), 3.56 (s, 3 H, CO_2CH_3), 4.05 (s, 3 H, NCO_2CH_3), 4.31 (s, 1 H, H-8), 7.25 (td, J = 7.6, 1.0, 1 H, H-5), 7.41 (td, J = 7.9, 1.4, 1 H, H-6), 7.57 (ddd, J = 7.5, 1.4, 0.5, 1 H, H-4), 7.97 (d, J = 7.9, 1 H, H-7)
4e	$C_{17}H_{18}N_2O_5$ (330.3)	114–116	–	2249	1767, 1740	0.67 and 1.31 (2d, J = 6.9, 6 H, $CH(CH_3)_2$), 2.51 (sept, J = 6.8, 1 H, $CH(CH_3)_2$), 3.54 (s, 3 H, CO_2Me), 4.04 (s, 3 H, CO_2CH_3), 4.04 (s, 3 H, NCO_2CH_3), 4.45 (s, 1 H, H-8), 7.24 (td, J = 7.6, 1.1, 1 H, H-5), 7.39 (ddd, J = 8.2, 7.6, 1.4, 1 H, H-6), 7.55 (dd, J = 7.5, 1.4, 1 H, H-4), 7.93 (d, J = 8.5, 1 H, H-7)
5	$C_{18}H_{20}N_2O_5$ (344.4)	oil	3566	2220	1728[f]	1.36 (s, 9 H, $C(CH_3)_3$), 3.94 (s, 6 H, $2CO_2CH_3$), 4.48 (br s, 1 H, OH), 6.78 (br s, 1 H, H-2), 7.23 (dd, J = 8.6, 1.8, 1 H, H-5), 8.07 (very br, 1 H, H-7), 8.38 (d, J = 8.6, 1 H, H-4)
6	$C_{18}H_{20}N_2O_4$ (328.4)	117–120°	–	2248	1744	1.40 (s, 9 H, $C(CH_3)_3$), 3.82 (s, 3 H, CO_2CH_3), 4.06 (s, 3 H, NCO_2CH_3), 4.93 (d, J = 0.9, 1 H, H-8), 7.41 (dd, J = 8.4, 1.7, 1 H, H-5), 7.58 (d, J = 8.4, 1 H, H-4), 7.76 (d, J = 0.9, 1 H, H-2), 8.29 (br s, 1 H, H-7)

[a] The purity of the isolated compounds were determined by TLC in different solvents; [b] satisfactory HRMS values were obtained ($m/z \pm 0.003$ amu); [c] recrystallization solvent: AcOEt for **1b**, Et_2O for **2b–e**, **3d–f**, **4e**, and **6** acetone/hexane for **4b** and **4c**; [d] solvent for **1b**: *DMSO*-d_6; [e] interchangeable by deuterium; [f] in $CHCl_3$

Table 3. ^{13}C NMR data of compounds **1**, **2**, and **4–6** ($CDCl_3/TMS$, δ)

Compound	C2	C3	C3a	C4	C5	C6	C7	C7a	C8	Substituents
1b	82.8	161.0	123.6	127.2	114.8	138.7	116.9	145.9	97.0	160.8 CO_{ester}, 151.3 $CO_{carbamate}$, 115.5 CN, 53.2[a] $OCH_{3\,ester}$, 53.1[a] $OCH_{3\,carbamate}$
2b	86.9	49.7	133.7	127.3	116.0	132.8	116.4	138.6	46.6	164.3 CO_{ester}, 153.0 $CO_{carbamate}$, 114.3 CN, 53.7[a] $OCH_{3\,ester}$, 53.4[a] $OCH_{3\,carbamate}$, 16.9 CH_3
2c	87.0	49.5	130.7	125.5	126.7	123.7	118.2	140.6	46.4	164.4 CO_{ester}, 153.3 $CO_{carbamate}$, 114.4 CN, 53.7[a] $OCH_{3\,ester}$, 53.5[a] $OCH_{3\,carbamate}$, 16.6 CH_3
2d	87.5	53.0	129.8	124.6	123.2	129.7	114.8	140.9	45.6	164.6 CO_{ester}, 154.0 $CO_{carbamate}$, 114.7 CN, 53.4[a] $OCH_{3\,ester}$, 53.2[a] $OCH_{3\,carbamate}$, 25.6 and 24.9 CH_3CH_2, 10.0 and 9.8 CH_3CH_2
2e	88.6	55.8	128.2	124.3	123.3	129.7	114.5	140.4	44.7	164.5 CO_{ester}, 154.0 $CO_{carbamate}$, 115.1 CN, 53.5[a] $OCH_{3\,ester}$, 53.1[a] $OCH_{3\,carbamate}$, 30.6 $CH(CH_3)_2$, 18.6 and 18.0 $CH(CH_3)_2$
4b	174.8	47.7	130.4	125.8	118.4	132.8	117.2	138.2	44.5	163.4 CO_{ester}, 151.0 $CO_{carbamate}$, 113.9 CN, 54.3[a] $OCH_{3\,ester}$, 54.1[a] $OCH_{3\,carbamate}$, 24.4 CH_3
4c	175.0	47.6	127.2	123.8	128.4	123.6	119.1	140.1	44.6	163.4 CO_{ester}, 150.9 $CO_{carbamate}$, 114.0 CN, 54.4[a] $OCH_{3\,ester}$, 54.0[a] $CO_{carbamate}$, 24.3 CH_3
4d	175.0	52.3	126.5	122.8	125.4	129.8	115.3	140.1	44.7	163.6 CO_{ester}, 151.1 $CO_{carbamate}$, 114.3 CN, 54.1[a] $OCH_{3\,ester}$, 53.8[a] $OCH_{3\,carbamate}$, 31.4 and 29.8 CH_3CH_2, 8.1 and 7.7 CH_3CH_2
4e	173.7	54.2	127.7	122.2	125.4	129.6	115.0	140.0	43.2	164.0 CO_{ester}, 151.1 $CO_{carbamate}$, 114.4 CN, 54.1[a] $OCH_{3\,ester}$, 53.8[a] $OCH_{3\,carbamate}$, 36.5 $CH(CH_3)_2$, 16.8 and 15.9 $CH(CH_3)_2$
5	83.5	162.7	119.4	126.4	121.9	163.5	112.7	148.3	94.4	163.7 CO_{ester}, 151.9, $CO_{carbamate}$, 115.6 CN, 53.4 $2OCH_3$, 36.1, $C(CH_3)$, 30.9 $C(CH_3)_3$)
6	124.7	110.3	125.0	118.4	121.7	151.0	112.1	136.0	35.4	164.7 CO_{ester}, 149.6, $CO_{carbamate}$, 114.7 CN, 54.0 $2OCH_3$, 35.2, $C(CH_3)_3$, 31.7 $(CCH_3)_3$

[a] Assignment of the peaks may be reversed

Table 4. ^{13}C spectroscopic data of compounds **3** ($CDCl_3/TMS$, δ)

Compound	C2	C3	C3a	C3b	C4	C5	C6	C7	C7a	C8	Substituents
3d	165.2	42.3	54.6	127.2	125.8	124.6	130.8	115.7	140.4	95.3	152.1 $CO_{carbamate}$, 112.7 CN, 53.7 OCH_3, 31.3 CH_3CH_2, 8.6 CH_3CH_2
3e	165.3	42.1	57.7	124.9	126.8	124.3	130.9	115.7	141.0	95.3	151.8 $CO_{carbamate}$, 113.2 CN, 53.7 OCH_3, 36.6 $CH(CH_3)_2$, 17.9 $(CH(CH_3)_2$
3f	165.5	38.8	60.6	125.8	127.5	124.1	130.9	115.7	140.8	93.6	151.2 $CO_{carbamate}$, 113.7 CN, 53.7 OCH_3, 36.2 $C(CH_3)_3$, 25.7 $C(CH_3)_3$

[a] Two diastereomers (except **3f**), data of main diastereomer

(2R,3S*,8S*)-Methyl-3-ethyl-3-(1-cyano-2-methoxy-2-oxoethyl)-2,3-dihydro-2-hydroxy-1H-indole-1-carboxylate* (**2d**) and *3a,8a-cis-8-Carbomethoxy-3-cyano-3a-ethyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole-2-one* (**3d**); *general procedure*

To a cooled (−78 °C) solution of EtMgBr (463 mg, 3.47 mmol) in a solvent mixture of Et_2O (13 ml) and *THF* (20 ml), a cold solution of **1a** (250 mg, 0.868 mmol) in *THF* (10 ml) was added over a period of 25 min with stirring. The temperature was maintained at −78 °C for 1 h during which time the mixture turned orange. The reaction was quenched with sat. NH_4Cl solution (5 ml), allowed to warm to r.t. and diluted with AcOEt (30 ml). The organic layer was decanted, washed with sat. NH_4Cl solution (2 × 10 ml), and dried (Na_2SO_4). After evaporation of the solvent *in vacuo*, the residue was separated by flash column chromatography (silica gel, CH_2Cl_2/AcOEt 24:1) to give 95 mg **3d** (38%) and then 110 mg **2d** (39%). Two recrystallizations from Et_2O gave slightly greenish crystals of **3d** (yield: 87 mg (35%); mp.: 135–137 °C) and white needles of **2d** (yield: 73 mg (26%); mp.: 141–143 °C. For further details see Table 1.

(3S,8S*)-Methyl 3-alkyl-3-(1-cyano-2-methoxy-2-oxoethyl)-2,3-dihydro-2 oxo-1H-indole-1-carboxylates* (**4b–e**); *general procedure*

To a stirred solution of 3-alkylindolines **2b–e** (0.34 mmol) in AcOH (5 ml), a solution of CrO_3 (1.0 mmol) in H_2O (0.4 ml) was added at 15 °C and stirring was continued at r.t. for 1 h. The mixture was poured over cracked ice (20 g) and extracted with AcOEt (2 × 50 ml). The organic layer was dried (Na_2SO_4) and concentred under reduced pressure. The crude product was purified by silica gel chromatography (CH_2Cl_2/Et_2O 24:1) giving pure (TLC) oxindoles **4b–e**. For physical and spectroscopic data see Tables 2 and 3.

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