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A convenient preparation of furo[2,3-*b*]indoles by conjugated addition of organomagnesium reagents to 2-hydroxyindolylidenemalonates

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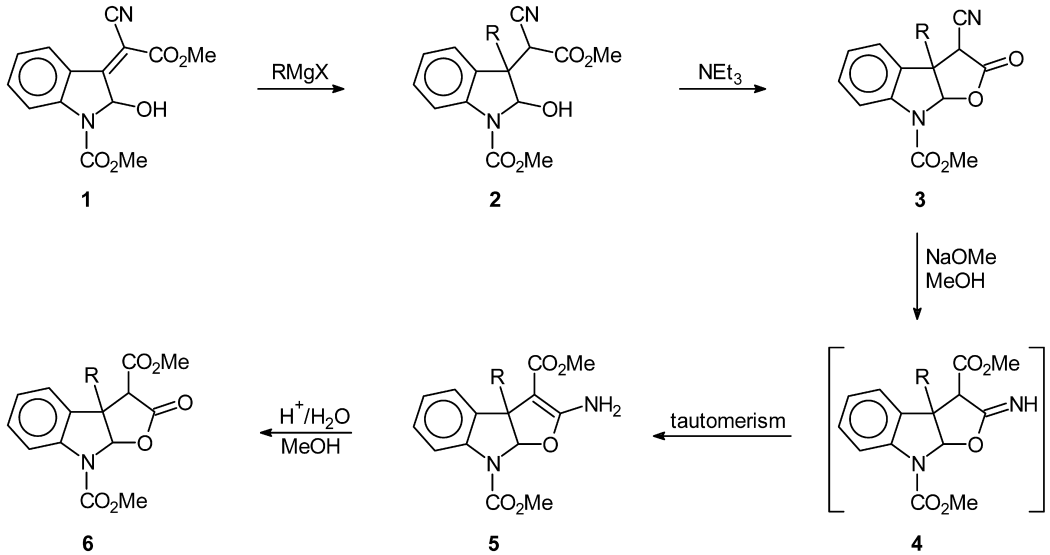
Abstract—The chelate-controlled conjugated addition of Grignard reagents to 2-hydroxyindolylidenemalonates was studied as a means of preparing 3a-alkyl-3-methoxycarbonyl-2-oxofuro[2,3-*b*]indoles in one or two steps. In addition to the alkylorganometallic group variation, the effects of substitution at the aromatic ring on the reaction outcome were established. The indolylidenemalonates were found to be less reactive than the analogous indolylidenecyanoacetates. © 2003 Published by Elsevier Science Ltd.

1. Introduction

The furo[2,3-*b*]indole ring system is a structural unit in natural products.[1] Due to its inherent biological activity and the use as synthetic target of numerous natural compounds, there is a demand for general synthetic methods for this ring system.[2] We have previously reported that the reaction of 2-hydroxyindolylidenecyanoacetate **1** with alkylorganometallic reagents resulted in the syntheses of 3-cyano-2-oxofuro[2,3-*b*]indoles **3**.[3,4] This process started by the chelate-controlled conjugated Grignard addition to **1**, leading to structures **2** that cyclize to give **3**. Further rearrangement of the 3-cyano-2-oxofuro[2,3-*b*]indoles **3** via the γ-lactone imines **4** gave the 2-amino-3-carbomethoxyfuro[2,3-*b*]indoles



1 **2** **3** **4** **5** **6**

Scheme 1.

Keywords: indolylidenemalonates; indolylidenecyanoacetates; furo[2,3-*b*]indoles; chelate-controlled conjugated Grignard addition; X-ray analysis.

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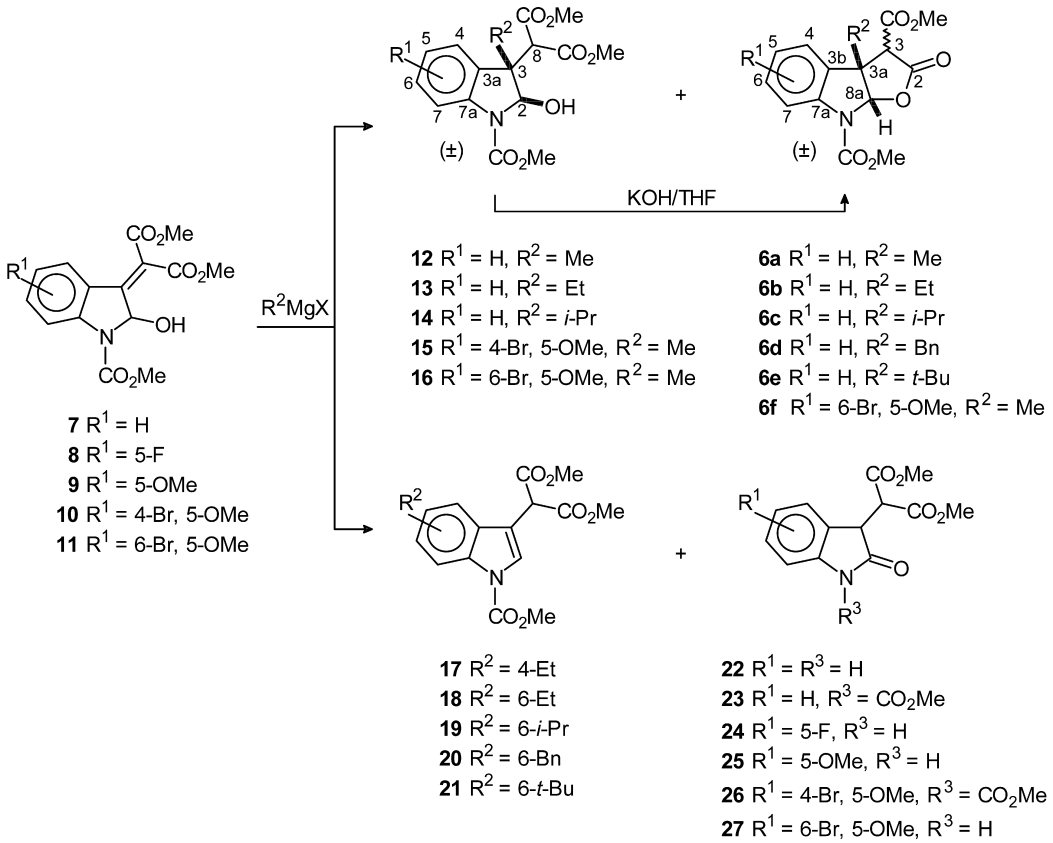


Scheme 2.

5. The acid-catalyzed hydrolysis of **5** finally afforded the 3-methoxycarbonyl-2-oxofuro[2,3-*b*]indoles **6** (Scheme 1).[4]

While the conjugated addition reaction of an organometallic to α,β-unsaturated carbonyl compounds is a versatile carbon–carbon bond forming reaction,[5] application of this method to α,β-unsaturated nitriles[6] and esters[7] is difficult and requires chelate-controlled addition. This highly ordered transition state influences the stereochemical outcome of the process, which occurs with excellent chemo- and stereoselectivity.[3] In connection with our work on the total syntheses of indole alkaloids and related compounds,[8] we required a short and practical procedure for an efficient preparation of

Table 1. Products and yields (%) in the reaction of **7**–**11**, **1a** and **1b** with R^2MgX according to general procedure

Entry	Substrate	Reagent		Conditions		Alkylation at C-3		Alkylation at Ar	
		R^2	X	Temperature (°C)	Time (h)	Indolines	Furoindoles	Indoles	Oxindoles
1	**7**	Me	I	25	5	**12** (49)	–	–	**22** (15)
2	**7**[a]	Me	I	0	5	**12** (38)	–	–	**22** (16)
3	**7**	Et	Br	25	5	**13** (48)	**6b** (16)	**17**+**18** (<2)[b]	–
4	**7**	*i*-Pr	Br	25	5	**14** (22)	**6c** (41)	**19** (9)	–
5	**7**[c]	*i*-Pr	Br	0	5	**14** (19)	**6c** (40)	**19** (9)	–
6	**7**[c]	Bn	Br	25	5	–	**6d** (49)	**20** (8)	–
7	**7**[d]	*t*-Bu	Br	25	5	–	**6e** (<5)	**21** (9)	**22** (18)+**23** (18)
8	**8**	Me	I	25	4	–	–	–	**24** (55)
9	**9**	Me	I	25	2	–	–	–	**25** (48)
10	**10**	Me	I	0	2	**15** (58)	–	–	**26** (12)
11	**11**	Me	I	25	3	**16** (18)	–	–	**27** (6)
12	**1a**	Et	Br	0	3	–	**3a** (60)	–	–
13	**1a**[d]	Et	Br	−78	3		**3a** (30)	–	–
14	**1a**	Bn	Br	0	3	–	**3b** (64)	–	–
15	**1a**[e]	Bn	Br	−78	3	–	**3b** (50)	–	–
16	**1b**	Et	Br	−78	2	–	**3c** (58)	–	–
17	**1b**	Bn	Br	−78	2	–	**3d** (62)	–	–

[a] Unreacted starting material was recovered in 20% yield.
[b] Yield of the isomeric mixture.
[c] Unreacted starting material was recovered in 7% yield.
[d] Unreacted starting material was recovered in 40% yield.
[e] Unreacted starting material was recovered in 12% yield.

3a-alkyl-3-methoxycarbonyl-2-oxofuro[2,3-*b*]indoles **6**. In this paper we analyze the scope and limitations of the conjugated addition of alkylorganometallic reagents to indolylidenemalonates **7**–**11**, to give in one or two steps, the desired furoindoles **6**. In addition, we compare the reactivity of indolylidenemalonates **7**–**11** with that of indolylidenecyanoacetates **1a** and **1b** towards the Grignard addition reaction.

2. Results and discussion

Our interest in indolylidenemalonates **7**–**11** for use in the synthesis of 3a-alkyl-3-methoxycarbonyl-2-oxofuro[2,3-*b*]-indoles **6** led us to explore the regio- and stereoselectivity of the addition of organomagnesium reagents to these compounds (Scheme 2). The reaction could lead to addition of the organomagnesium reagents to either the carbonyl ester groups or to the vinylic C-3 carbon of **7**–**11**. The required indolylidenemalonates **7**–**11** were prepared by reaction of 3-indolylmalonates[9] with bromine in CCl_4 followed by hydrolysis during the aqueous workup procedure,[10] except compound **9** which was obtained in low yield by oxidation with NBS. Indolylidenecyano-acetates **1a** and **1b** were prepared by oxidation of 3-indolylcyanoacetates with CrO_3 in AcOH according to our previous reported procedure.[3]

2.1. Effect of alkylorganometallic group

All reactions of indolylidenemalonate **7** were carried out under an argon atmosphere, in anhydrous THF/ether with 4 equiv. of the organomagnesium reagents (Table 1). When the reaction mixtures were stirred at 25°C for 5 h, moderated yield of conjugated additions of methyl, ethyl, *i*-propyl and benzyl groups to indolylidenemalonate **7** were obtained. Under these conditions, the initially formed 2-hydroxy-indolines cyclize to the corresponding γ-lactones **6** in variable yields, excepting **12**, and in no case 1,2 addition products were produced (entries 1, 3, 4, 6). The spontaneous partial cyclization is driven by the size of the angular alkyl substituent, which in the case of the methyl group is meaningless. The resulting product distribution demonstrated a significant dependence of the ratio of indolines vs furoindoles as a function of the bulkiness of the alkyl group of the Grignard reagent. In fact, increasing the effective size of the alkyl group resulted in enhancement of annulation product formation, except for the *t*-Bu group, for which no 2-hydroxyindolenine is obtained. Thus, when **7** was reacted with MeMgI only indoline **12** was isolated in 49% yield, together with a by product identified as oxindole **22** (entry 1). Repetition of this reaction at lower temperature produced smaller amounts of **12** and unreacted starting material was recovered in 20% (entry 2).

The use of more sterically hindered Grignard reagents, such as EtMgBr and *i*-PrMgBr, led to a mixture of the corresponding indolines **13** and **14** along with the furoindoles **6b** and **6c**, respectively (**13/6b**=3:1, 64% and **14/6c**=1:2, 63%) (Table 1, entries 3, 4). Reaction with *i*-PrMgBr showed little variation on the annulation product ratio when conducted at 0°C (entry 5). Also formed in small amounts are the corresponding benzene ring alkylated

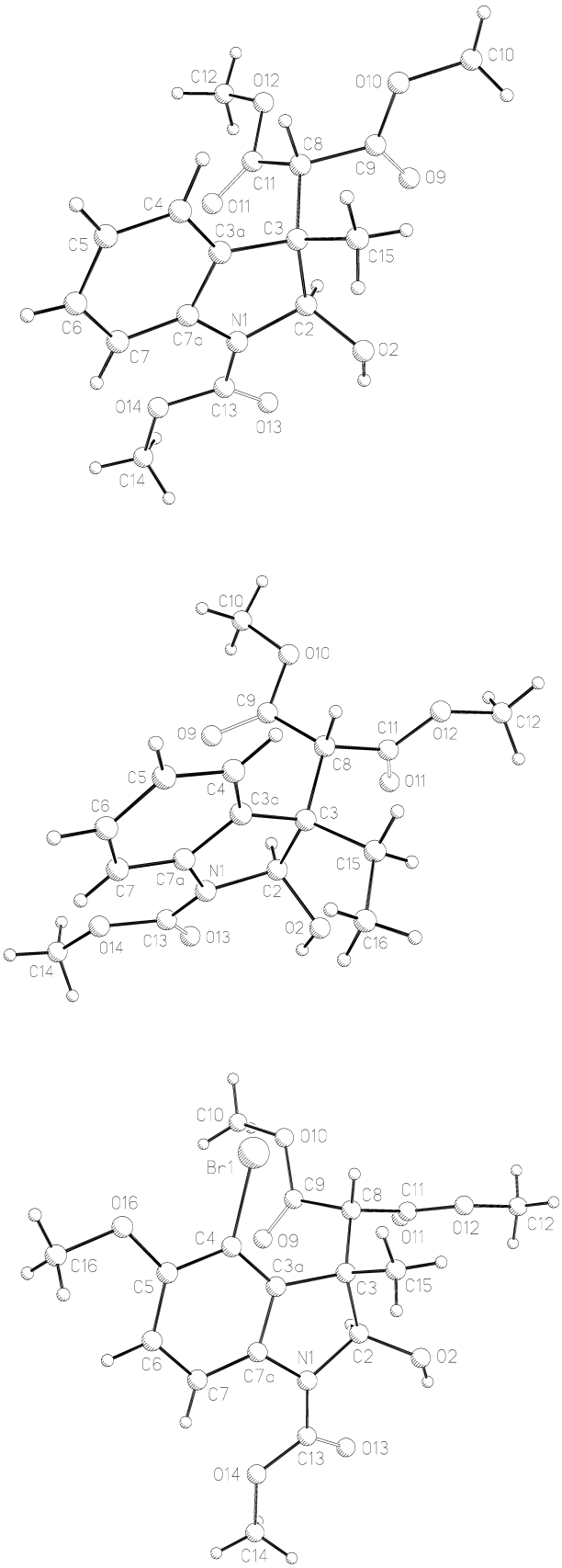


Figure 1. X-Ray structures of **12** (top), **13** (center), and **15** (bottom).

Table 2. X-Ray data collection and processing parameters for furoindoles **3b** and **3d**, and indolines **12**, **13** and **15**

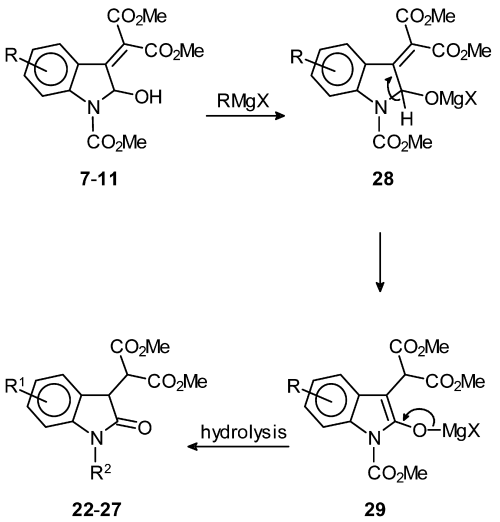
Compound	**3b**	**3d**	**12**	**13**	**15**
Formula	$C_{20}H_{15}N_2O_4F$	$C_{22}H_{20}N_2O_5$	$C_{16}H_{19}NO_7$	$C_{17}H_{21}NO_7$	$C_{17}H_{20}NO_8Br$
Size (mm)	0.16×0.42×0.60	0.20×0.30×0.45	0.45×0.32×0.20	0.31×0.39×0.85	0.29×0.23×0.29
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	$P2_1/n$	$P1$(bar)	$P1$(bar)	$P1$(bar)	$P2/c$
a (Å)	9.292(1)	10.390(4)	8.643(3)	8.617(1)	14.5763(6)
b (Å)	11.267(5)	11.184(3)	8.861(3)	8.756(1)	10.2888(4)
c (Å)	16.926(2)	18.927(2)	11.474(4)	13.106(2)	13.3425(6)
α (°)	90.0	104.72(2)	84.191(15)	75.081(4)	90.0
β (°)	91.043(9)	92.02(2)	96.525(13)	76.278(4)	112.318(1)
γ (°)	90.0	107.52(2)	111.339(12)	66.606(4)	90.0
V (Å^3)	1771.7	2013.5	811.5	866.7	1851.1
D_{calcd} (g/cm^3)	1.373	1.29	1.38	1.35	1.60
Z-value	4	4	2	2	4
μ (mm^{-1})	0.87 (Mo Kα)	0.77 (Mo Kα)	0.93 (Cu Kα)	0.11 (Mo Kα)	2.27 (Mo Kα)
T (K)	295	293	293	294	293
$2\theta_{range}$ (°)	4.72–54.95	2.43–54.96	3.89–55.00	1.63–26.06	1.51–26.01
Total reflections	4269	5155	2001	5487	10022
Unique reflections	2214	4787	1856	3252	3626
R_{int} (%)	3.9	2.4	7.2	2.5	3.5
$I \geq 3\sigma(I)$	2214	4548	1644	2463	2325
Parameters	293	620	246	263	324
R (%), R_w (%)	3.9, 10.1	4.9, 13.3	5.2, 14.4	4.8, 12.7	3.3, 6.2
ρ_{max} (e Å^{-3})	0.81	0.22	0.23	0.21	0.40
CCDC deposition	204984	204985	204986	204987	204988

indoles **17**–**19**. Furoindoles **6b** and **6c** were formed by intramolecular cyclization of **13** and **14**, respectively. Alternatively, conversions of **12**–**14** to **6a**–**c** were conducted in quantitative yields by treatment with KOH in THF at room temperature for 20 min (Scheme 2). When a more bulky organomagnesium reagents was used such as BnMgBr, furoindole **6d** was obtained in 49% yield, unaccompanied by detectable amounts of the corresponding C-3 alkylated indoline (entry 6). The reaction also yielded the alkylated indole **20** (8%) and dibenzyl (11%), which resulted from benzyl bromide Wurtz-type coupling. Finally, the use of highly hindered *tert*-butyl magnesium bromide was ineffective for the formation of **6e**, the reaction yielded alkylated indole **21** and a mixture of oxindoles **22** and **23** (entry 7). The C-4 and C-6 orientation of the ring-alkylated products is consistent with the vinylogous conjugate addition reaction.

While the NMR spectra of furoindoles **6a**–**c** were in accordance with published data,[4b] furoindoles **6d**–**f** and indolines **12**–**14** were fully characterized by spectroscopic and X-ray analyses. As in the case of furoindoles **6a**–**c**, $CDCl_3$ solutions of **6d** and **6f** also proved to be mixtures of C-3 *endo*/*exo* epimers, at the equilibrium, the *exo* isomer is favored in a 3:2 ratio, whereas **6e**, carrying a highly hindered *tert*-butyl group, appears as a single C-3 *endo* epimer. The relative stereochemistry was determined by NOESY experiments. The ^{13}C NMR spectrum of indoline **12**, used as model compound, showed the methyl-substituted C-3 carbon at 48.9 ppm and the C-8 carbon at 58.9 ppm, with a ^1J(C–H) coupling of 133.4 Hz confirming the presence of a C3–C8 single bond. A single exclusive relative configuration in **12**–**14** was evidenced by ^1H NMR. The relative configuration between C(2) and C(3) of **12** and **13**, established by X-ray crystal structure analysis, indicated that the hydroxyl group at C-2 and the corresponding alkyl group at C-3 are on the same side of the pyrrole ring with O2–C2–C3–C15 torsion angle values of +2.2° and −3.7°, respectively (Fig. 1). Crystal data are reported in Table 2. In agreement, MMX calculations[11] for **12**–**14** predict the stereoisomer having the C-2 hydroxyl and the C-3 alkyl groups in a *syn* relationship to be 0.7, 1.4 and 0.3 kcal/mol lower in energy than the corresponding *anti* isomer, respectively. The stereoselective formation of **12**–**14** would be explained by a chelate-controlled addition involving the hemiaminal hydroxyl oxygen atom. This means that the *cis* fused furoindoles **6a**–**f** arose via intramolecular annulation of the γ-hydroxyester after inversion of the hemiaminal C-2 carbon, via a hemiaminal/aldehyde ring-chain tautomerism.[12]

2.2. Effect of substituents on the benzene ring

Substitution at the aromatic ring produced results that differed significantly from those of the unsubstituted indolylidenemalonate **7** (Table 1). Treatment of the 5-F indolylidenemalonate **8** with MeMgI at 25°C for 5 h, surprisingly, gave only simple N-decarbomethoxylated tautomeric product **24** in 55% yield, without any addition product formation (entry 8). A similar substrate scope was observed for reaction of 5-MeO indolylidenemalonate **9** with MeMgI affording oxindole **25** in 48% yield (entry 9). The oxindole **25** was characterized in the ^1H NMR spectrum by the presence of a broad singlet at δ 8.56 owing to the N–H group, while the aliphatic C–H signals occurred at δ 4.21 and 4.05 ppm as doublets, with a ^3J(H–H) coupling of 4.1 Hz. An intense stretching vibration at 1732 cm^{-1} in the IR spectrum indicates that a carbonyl group is now part of the heterocyclic ring. Since the corresponding C-3 alkylated indoles could not be detected in the reaction products, it suggests that the rate of the conjugated addition to **8** and **9** would be very slow, and/or the rate of the isomerization would be increased, resulting in complete tautomerization under the basic reaction conditions. These products must arise by abstraction of the hemiaminal proton from 2-alkoxyindolylidene **28**, followed by tautomerization



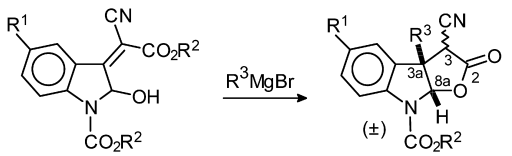
Scheme 3.

to **29**, driving the reaction toward oxindoles **22**–**27**, Scheme 3.

A similar treatment of 6-bromo-5-methoxyindolylidenemalonate **11** with MeMgI gave the corresponding conjugated addition product **16**, along with the N-decarbomethoxylated oxindole **27** in low yields (18 and 6% yields, respectively, entry 11). When the same reaction was conducted at 0°C, only unreacted starting material was recovered. In contrast, reaction of the 4-bromo-5-methoxyl congener **10**, under similar reaction conditions, gave the conjugated addition product **15** in a substantially increased yield (58%, entry 10). Thus, the 4-bromine substituent plays a pivotal role in the addition reaction, the effect being believed to be due to a transition state in which a cyclic chelate involves the hemiaminal hydroxyl group and the bromine atom. X-Ray diffraction analysis of **15** (Fig. 1) indicated that this compound exhibits the C-2 hydroxyl group and the C-3 alkyl groups in a *syn* relationship, with a O2–C2–C3–C-15 torsion angle value of −19.2°. Attempted cyclization reactions of indolines **15** and **16**, using KOH in THF at room temperature for 20 min, yielded recovered starting material **15** and the corresponding furoindole **6f**, in quantitative yield, respectively. These results suggest that the failure of indolylmalonate **15** to undergo annulation is due to the steric inhibition of the hemiaminal/aldehyde ring-chain tautomerism posed by the bromine atom at C-4, thereby preventing the inversion of the hemiaminal C-2 carbon.

2.3. Reactions of indolylidenecyanoacetates with organomagnesium reagents

At this point, of particular interest was to compare the reactivity of indolylidenemalonates with that of indolylidenecyanoacetates towards the Grignard addition reaction. Indolylidenecyanoacetates **1a** and **1b** (Scheme 4) were expected to be better substrates than the corresponding indolylidenemalonates **8** and **9** for the nucleophilic addition, because the ethylenic β carbon atom in the former compounds is more electron-deficient, due to a more extensive delocalization of the π-electrons, than in the latter compounds.[13] In fact, inspection of Table 3 reveals



1a R^1 = F, R^2 = Me
1b R^1 = 5-OMe, R^2 = Et

3a R^1 = F, R^2 = Me, R^3 = Et
3b R^1 = F, R^2 = Me, R^3 = Bn
3c R^1 = 5-OMe, R^2 = R^3 = Et
3d R^1 = 5-OMe, R^2 = Et, R^3 = Bn

Scheme 4.

that C-3 in indolylidenemalonates **8** and **9** resonates ca. 12 ppm highfield relative to C-3 of the corresponding indolylidenecyanoacetates **1a** and **1b**. In accord with this assertion, we found that the reaction of 5-methoxyindolylidenecyanoacetate **1b** with 4 equiv. of RMgX (R=Et and Bn) was completed after only 2 h at −78°C, even for the somewhat hindered benzyl group. These reactions occurred with high regioselectivity to give only the corresponding furo[2,3-*b*]indoles **3c** and **3d** in 58 and 62% yield, respectively (entries 16 and 17). When the 5-fluoro derivative **1a** was reacted with 4 equiv. of RMgBr (R=Et, Bn) at −78°C for 3 h the corresponding furo[2,3-*b*]indoles **3a** and **3b** were formed as the only products in 30 and 50% yield, respectively (Table 1, entries 13 and 15). In both cases the presence of the fluorine atom retards the addition reaction, and unreacted 5-fluoroindolylidene **1a** was recovered in 40 and 12%, respectively. However, with increased reaction temperature the yields of **3a** and **3b** increased to 60 and 64%, respectively (entries 12 and 14).

The furo[2,3-*b*]indoles **3a**–**d** were obtained as mixtures of two equilibrated epimers at the C-3 chiral center. The relative stereochemistry at the three chiral centers C-3, C-3a and C-8a was elucidated mainly on the basis of NOESY correlations. Thus, NOESY cross-peaks for H-3/(C3a)R (R=Et, Bn) indicated a 1,2-*anti* relationship of (C3a)R/(C3)CN, while for H-8a/(C3a)R the corresponding NOESY peaks indicated a *cis* B/C ring fusion. The epimeric C-3 *endo*/*exo* ratio (at 25°C) was determined by comparing the respective H-3 signals in the ^{1}H NMR spectra ($CDCl_3$) whose chemical shift values are larger for the *endo* isomers than for the *exo* isomers. At equilibrium, the *endo* isomer is favored in a 7:3 ratio for **3a** and **3c**, and 9:2 for **3b** and **3d**, in

Table 3. ^{13}C NMR chemical shifts of the exocyclic double bond of indolenines **1a**, **1b**, **7**–**11**

Compound	^{13}C (δ)	
	C-3	C-8
1a[a]	162.4	97.3
1b[a,b]	163.6	96.0
7[c,d]	149.2	118.8
8[a,d]	150.0	119.6
9[a]	151.4	118.4
10[c,d]	148.6	123.4
11[c,d]	148.6	118.9

[a] In $CDCl_3$.
[b] From Ref. 3.
[c] In DMSO-d_6.
[d] From Ref. 10.

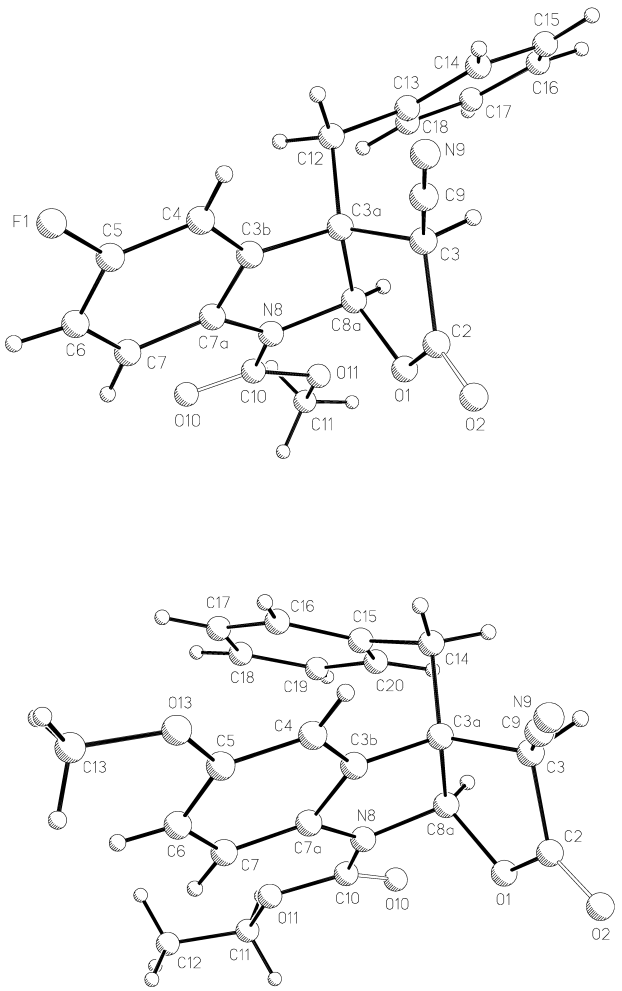


Figure 2. X-Ray structures of **3b** (top), and **3d** (bottom).

contrast to that observed for furoindoles **6a–d** and **6f** in which the *exo* epimer is the preferred one.

Very slow crystallization of furoindoles **3b** and **3d** from methyl sulfoxide provided the *endo* isomers shown in Figure 2. Several features of the structures deserve comment. First, the crystal structures of **3b** and **3d** are characterized by a folded shape along the C3a–C8a bond, with a *cis*-like fusion of the two five-membered rings. The *s-trans* to H4 conformation of the benzyl group of **3b** may be readily observed from the C3b–C3a–C12–C13 torsion angle of −1739° whereas for **3d** the C3b–C3a–C14–C15 torsion angle of −58.8° indicates a *s-cis* conformation for the same group. In addition, in **3d** the 5-*O*-methyl group is oriented *s-trans* to H4, and the carbamate N8–C10 bond shows an *s-cis* geometry, which in **3b** is *s-trans* oriented.

3. Conclusions

The synthesis of 3a-alkyl-3-methoxycarbonyl-2-oxofuro[2,3-*b*]indoles has been accomplished in moderated yield with complete regio- and stereoselectivity. The yield of the initial conjugated addition of the organomagnesium reagents to the indolylidenemalonate derivative is strongly dependent not only on electronic effects but also on the chelation of the Grignard reagent to the neighboring hydroxyl and bromine atoms. A study of substituent effects has provided information as to the scope as well the utility of the reaction. Less reactive or highly hindered Grignard reagents showed greater propensity for oxindole formation.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran and ethyl ether were distilled from sodium using benzophenone as indicator. Yields refer to chromatographically and spectroscopically (^{1}H) homogeneous materials. All reagents were purchased at highest commercial quality and used without further purification.

Melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 16F PC FT spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on Varian XL-300GS and Mercury spectrometers working at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. EIMS were obtained on Hewlett–Packard 5989A or Varian Saturn 2000 mass spectrometers. HRMS were measured on a Jeol JMS-SX 102A spectrometer. Analytical thin-layer chromatography was performed on silica gel F_{254} coated aluminum sheets. Flash chromatography was performed using silica gel 60 (230–400 mesh) from Aldrich. X-Ray data for **3a**, **3d**, **13** and **15** were collected on a Bruker Smart 6000 CCD diffractometer using crystals grown from DMSO. The structures were solved and refined by using SHELX97. X-Ray data for **12** were collected on a Nicolet R3m diffractometer. The structure was solved by direct methods using SHELX86. Crystal data, collection and refinement parameters are given in Table 2.

4.1.1. Methyl 2-(*Z*-1-carbomethoxy-5-fluoro-2-hydroxy-1,2-dihydroindol-3-ylidene)cyanoacetate (1a). The title compound was prepared from methyl 2-(1-carbomethoxy-5-fluoro-1*H*-indol-3-yl)cyanoacetate[14,15] by a method analogous to the previously described synthesis of **1b**[3] in 67% yield. Yellow crystals, mp 173–175°C ($CHCl_3$); R_f 0.24 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3566, 3022, 2224, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, dd, J=8.6, 2.7 Hz, H4), 8.00 (1H, br s, H7), 7.32 (1H, ddd, J=9.0, 8.4, 2.7 Hz, H6), 6.81 (1H, br s, H2), 4.46 (1H, br s, OH), 3.96 (3H, s, CO_2*Me*), 3.94 (3H, s, NCO_2*Me*); ^{13}C ($CDCl_3$) δ 162.9 (*C*O_2Me), 162.4 (C3), 158.8 (d, J=244.8 Hz, C5), 151.6 (N*C*O_2Me), 144.1 (C7a), 124.4 (d, J=23.8 Hz, C6), 122.2 (C3a), 116.8 (d, J=7.7 Hz, C7), 114.8 (CN), 112.5 (d, J=25.5 Hz, C4), 97.3 (C8), 83.4 (C2) 53.7 (CO_2*Me*), 53.5 (NCO_2*Me*); EIMS m/z 306 (M^+, 43), 247 (100), 215 (44); HRMS m/z 306.0656 (M^+, $C_{14}H_{11}N_2O_5F$ requires 306.0652).

4.1.2. Dimethyl 2-(1-carbomethoxy-2-hydroxy-5-methoxy-1,2-dihydroindol-3-ylidene)malonate (9). To a solution of dimethyl 2-(1-carbomethoxy-5-methoxy-1*H*-indol-3-yl)malonate[10] (70 mg, 0.21 mmol) in CCl_4 (12 mL) was added *N*-nitroso-*N*-methylurea (5 mg, 0.05 mmol) and NBS (80 mg, 0.45 mmol) at room temperature. The mixture was

stirred at this temperature for 2 h, diluted with CH_2Cl_2 (100 mL), washed with brine (3×20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel to give dimethyl 2-(4-bromo-1-carbomethoxy-5-methoxy-1*H*-indol-3-yl)malonate[10] (15 mg, 17%) and the oxidized product **9** (10 mg, 13%). Starting material was also recovered from the chromatography (45 mg, 64%). Compound **9**, a yellow solid, showed mp 146–148°C (EtOAc); R_f 0.19 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3572, 3012, 1720, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (1H, br s, H7), 7.05 (1H, dd, J=9.0, 2.6 Hz, H6), 6.85 (1H, br s, H4), 6.68 (1H, br s, H2), 4.34 (1H, br s, OH), 3.91 (3H, br s, NCO_2Me), 3.96 and 3.87 (6H, 2s, $2CO_2Me$), 3.77 (3H, s, OMe); ^{13}C ($CDCl_3$) δ 166.1 and 164.6 ($2CO_2$Me), 155.8 (C5), 152.3 (NCO_2Me), 151.4 (C3), 140.6 (C7a), 122.8 (C3a), 121.3 (C6), 118.4 (C8), 116.5 (C7), 108.8 (C4), 83.0 (C2), 55.6 (OMe), 53.1 (NCO_2Me), 52.9 ($2CO_2Me$); EIMS m/z 351 (M^+, 12), 292 (30), 232 (100); HRMS m/z 351.0958 (M^+, $C_{16}H_{17}NO_8$ requires 351.0954).

4.2. General procedure using Grignard reagents

To a stirred suspension (at the temperature indicated in Table 1) of the Grignard reagent, prepared from the corresponding alkyl halide (14.0 mmol) and Mg turnings (0.34 g, 14 mmol) in dry ether (50 mL) under argon, was added dropwise a solution of the appropriate indolylidene-malonate **7**–**11** (3.5 mmol) or indolylidenecyanoacetate **1a** and **1b** (3.5 mmol) in THF (50 mL) over a 0.5 h period. After the reaction mixture was left for the reaction time and temperature indicated in Table 1, the resulting suspension was quenched with saturated NH_4Cl solution (10 mL), and diluted with EtOAc (150 mL). The organic layer was separated, washed with brine (2×15 mL), dried over Na_2SO_4 and evaporated. The reaction products were then purified by flash column chromatography on silica gel (EtOAc–hexane 1:4). Products and yields are reported in Table 1. Compounds **6b** and **6c** were identical in all respects to the products previously obtained.[4b]

4.2.1. Dimethyl 3a-benzyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-3,8-dicarboxylate (6d). Prepared from **7** as a C-3 diastereomeric mixture (2:3 *endo*–*exo* ratio by ^1H NMR analysis), colorless solid; mp 127–129°C (Et_2O–hexane); R_f 0.28 (EtOAc–hexane 1:3); IR ($CHCl_3$) ν_{max} 3020, 1792, 1732, 1444 cm^{-1}; (major *exo*-isomer) ^1H NMR ($CDCl_3$) δ 7.58 (1H, br s, H7), 7.35–7.00 (7H, m, Ar), 6.62 (1H, d, J=6.9 Hz, H4), 6.47 (1H, br s, H8a), 4.00 (1H, s, H3), 3.95 (3H, s, CO_2Me), 3.77 (3H, s, NCO_2Me), 3.14 and 2.94 (2H, dd, J=13.0 Hz, CH_2Ph); ^{13}C ($CDCl_3$) δ 169.0 (C2), 167.0 (CO_2Me), 151.4 (NCO_2Me), 140.5 (C7a), 133.4 (C*i*), 130.3 (C6), 130.2 (C3b), 129.3 (C4, C*o*), 128.9 (C*m*), 127.9 (C*p*), 124.3 (C5), 115.7 (C7), 95.4 (C8a), 57.1 (C3), 56.0 (C3a), 53.3 (CO_2Me), 53.2 (NCO_2Me), 39.8 (CH_2Ph); (minor *endo*-isomer) ^1H NMR ($CDCl_3$) δ 7.88 (1H, br s, H7), 7.35–7.00 (7H, m, Ar), 6.62 (1H, d, J=6.9 Hz, H4), 6.34 (1H, br s, H8a), 4.04 (1H, s, H3), 3.88 (3H, s, NCO_2Me), 3.77 (3H, s, CO_2Me), 3.26 and 3.11 (2H, dd, J=14.0 Hz, CH_2Ph); ^{13}C ($CDCl_3$) δ 168.5 (C2), 166.2 (CO_2Me), 151.4 (NCO_2Me), 140.5 (C7a), 134.0 (C*i*), 130.5 (C6), 130.2 (C3b), 129.3 (C4, C*o*), 128.9 (C*m*), 127.9 (C*p*), 123.9 (C5), 115.7 (C7), 92.3 (C8a), 56.2 (C3a), 53.4 (NCO_2Me), 52.6 (C3, CO_2Me), 43.3 (CH_2Ph); EIMS m/z 381 (M^+, 88), 264 (33), 246 (100); HRMS m/z 381.1214 (M^+, $C_{21}H_{19}NO_6$ requires 381.1212).

4.2.2. Dimethyl 3a-*tert*-butyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-3,8-dicarboxylate (6e). Prepared from **7** as colorless oil; R_f 0.59 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3020, 1788, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (1H, br, H7), 7.33 (1H, td, J=7.8, 1.4 Hz, H6), 7.11 (1H, dd, J=7.8, 1.4 Hz, H4), 7.02 (1H, td, J=7.8, 1.1 Hz, H5), 6.29 (1H, br s, H8a), 4.06 (1H, s, H3), 3.94 (3H, br s, NCO_2Me), 3.37 (3H, s, CO_2Me), 1.07 (9H, s, 3 Me); ^{13}C ($CDCl_3$) δ 170.5 (C2), 167.1 (CO_2Me), 152.4 (NCO_2Me), 141.8 (C7a), 129.8 (C6), 128.2 (C3b), 125.7 (C4), 123.1 (C5), 115.3 (C7), 93.7 (C8a), 62.0 (C3a), 53.7 (C3), 53.5 (NCO_2Me), 52.5 (CO_2Me), 36.8 (CMe_3), 25.4 (CMe_3); EIMS m/z 347 (M^+, 10), 305 (65), 246 (100), 188 (89); HRMS m/z 347.1369 (M^+, $C_{18}H_{21}NO_6$ requires 347.1361).

4.2.3. Dimethyl 2-(1-carbomethoxy-2-hydroxy-3-methyl-2,3-dihydro-1*H*-indol-3-yl)malonate (12). Prepared from **7** as colorless crystals, mp 142–144°C (Et_2O); R_f 0.38 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3594, 3020, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (1H, br s, H7), 7.49 (1H, br s, OH), 7.23 (1H, td, J=7.6, 0.9 Hz, H6), 7.12 (1H, dd, J=7.6, 0.9 Hz, H4), 7.01 (1H, td, J=7.6, 0.9 Hz, H5), 6.32 (1H, d, J=4.3 Hz, H2), 3.90 (3H, br s, NCO_2Me), 3.68 and 3.49 (6H, 2s, $2CO_2Me$), 3.61 (1H, s, H8), 1.56 (3H, s C3–*Me*); ^{13}C ($CDCl_3$) δ 167.6 and 167.3 ($2CO_2$Me), 153.0 (NCO_2Me), 139.7 (C7a), 133.8 (C3a), 128.8 (C6), 123.4 (C4), 123.1 (C5), 114.6 (C7), 86.9 (C2), 58.9 (C8), 52.9 (NCO_2Me), 52.4 ($2CO_2Me$), 48.9 (C3), 18.0 (Me); EIMS m/z 337 (M^+, 8), 305 (34), 287 (41), 260 (97), 202 (100); HRMS m/z 337.1160 (M^+, $C_{16}H_{19}NO_7$ requires 337.1162).

4.2.4. Dimethyl 2-(1-carbomethoxy-3-ethyl-2-hydroxy-2,3-dihydro-1*H*-indol-3-yl)malonate (13). Prepared from **7** as colorless crystals, mp 117–118°C (Et_2O–hexane); R_f 0.22 (EtOAc–hexane 1:3); IR ($CHCl_3$) ν_{max} 3594, 3012, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (1H, br s, H7), 7.22 (1H, td, J=7.6, 1.2 Hz, H6), 7.10 (1H, br d, J=7.6 Hz, H4), 7.00 (1H, td, J=7.6, 1.1 Hz, H5), 6.49 (1H, d, J=3.8 Hz, H2), 3.90 (3H, s, NCO_2Me), 3.85 (1H, s, H8), 3.73 and 3.47 (6H, 2s, $2CO_2Me$), 2.24 and 1.76 (2H, 2 dq, J=14.5, 7.2 Hz, CH_2), 0.83 (3H, t, J=7.2 Hz); ^{13}C ($CDCl_3$) δ 167.6 and 167.3 ($2CO_2$Me), 153.7 (NCO_2Me), 140.6 (C7a), 131.7 (C3a), 128.5 (C6), 123.5 (C4), 122.7 (C5), 114.2 (C7), 87.3 (C2), 58.0 (C8), 52.8 (NCO_2Me), 52.5 and 52.2 ($2CO_2Me$), 51.9 (C3), 26.5 (CH_2), 9.7 (Me); EIMS m/z 351 (M^+, 9), 319 (6), 219 (100), 187 (53), 160 (34); HRMS m/z 351.1320 (M^+, $C_{17}H_{21}NO_7$ requires 351.1318).

4.2.5. Dimethyl 2-(1-carbomethoxy-2-hydroxy-3-*iso*-propyl-2,3-dihydro-1*H*-indol-3-yl)malonate (14). Prepared from **7** as colorless crystals, mp 121–122°C (Et_2O–hexane); R_f 0.20 (EtOAc–hexane 1:3); IR ($CHCl_3$) ν_{max} 3594, 3010, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (1H, br s, H7), 7.21 (1H, td, J=7.4, 1.2 Hz, H6), 7.06 (1H, dd, J=7.4, 1.2 Hz, H4), 6.95 (1H, td, J=7.4, 1.1 Hz, H5), 6.64 (1H, d, J=3.6 Hz, H2), 4.0 (1H, s, OH), 3.91 (3H, s, NCO_2Me), 4.20 (1H, s, H8), 3.80 and 3.44 (6H, 2s, $2CO_2Me$), 2.58 (1H, sept, J=6.7 Hz, CH), 1.08 and 0.71 (6H, 2 d, J=6.7 Hz, 2 Me); ^{13}C ($CDCl_3$) δ 167.9 and 167.6 ($2CO_2$Me), 154.2

(N*C*O$_2$Me), 141.0 (C7a), 130.1 (C3a), 128.5 (C6), 123.4 (C4), 122.2 (C5), 113.9 (C7), 87.7 (C2), 55.2 (C8), 52.8 (NCO$_2$*Me*), 52.7 and 52.3 (2CO$_2$*Me*), 54.0 (C3), 29.5 (CH), 19.7 and 17.7 (2 Me); EIMS *m/z* 365 (M$^+$, 6), 233 (100), 218 (33); HRMS *m/z* 365.1492 (M$^+$, $C_{18}H_{23}NO_7$ requires 365.1475).

4.2.6. Dimethyl 2-(4-bromo-1-carbomethoxy-2-hydroxy-5-methoxy-3-methyl-2,3-dihydro-1*H*-indol-3-yl)malonate (15). Prepared from **10** as colorless crystals, mp 145–146°C (EtOAc–hexane); R_f 0.20 (EtOAc–hexane 2:3); IR (CHCl$_3$) ν_{max} 3596, 3026, 1734, 1058 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.69 (1H, br s, H7), 6.77 (1H, d, *J*=8.8 Hz, H6), 6.41 (1H, d, *J*=3.9 Hz, H2), 4.63 (1H, br s, H8), 3.88 (3H, br s, NCO$_2$*Me*), 3.84 (3H, s, OMe), 3.43 (6H, 2s, 2CO$_2$*Me*), 1.67 (3H, s C3–*Me*); ^{13}C (CDCl$_3$) δ 167.0 and 166.6 (2*C*O$_2$Me), 152.0 (N*C*O$_2$Me), 151.2 (C5), 135.0 (C7a), 132.9 (C3a), 113.5 (C7), 111.3 (C6), 108.4 (C4), 85.9 (C2), 56.9 (OMe), 56.0 (C8), 53.2 (NCO$_2$*Me*), 52.9 and 52.6 (2CO$_2$*Me*), 51.2 (C3), 18.1 (Me); EIMS *m/z* 445/447 (M$^+$, 20/20), 313/315 (100/98), 281/283 (49/48); HRMS *m/z* 445.0369 (M$^+$, $C_{17}H_{20}NO_8Br$ requires 445.0372).

4.2.7. Dimethyl 2-(6-bromo-1-carbomethoxy-2-hydroxy-5-methoxy-3-methyl-2,3-dihydro-1*H*-indol-3-yl)malonate (16). Prepared from **11** as colorless crystals, mp 138–140°C (EtOAc–hexane); R_f 0.21 (EtOAc–hexane 2:3); IR (CHCl$_3$) ν_{max} 3588, 3020, 1734, 1056 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.05 (1H, br s, H7), 7.61 (1H, br s, OH), 6.73 (1H, s, H4), 6.27 (1H, d, *J*=3.7 Hz, H2), 3.91 (3H, br s, NCO$_2$*Me*), 3.86 (3H, s, OMe), 3.70 and 3.57 (6H, 2s, 2CO$_2$*Me*) 3.60 (1H, br s, H8), 1.55 (3H, s, C3–*Me*); ^{13}C (CDCl$_3$) δ 167.5 and 167.2 (2*C*O$_2$Me), 152.9 (N*C*O$_2$Me), 152.3 (C5), 134.4 (C7a), 133.4 (C3a), 119.4 (C7), 111.7 (C6), 107.9 (C4), 87.4 (C2), 58.6 (C8), 56.8 (OMe), 53.1 (NCO$_2$*Me*), 52.6 and 52.5 (2CO$_2$*Me*), 49.2 (C3), 17.9 (Me); EIMS *m/z* 445/447 (M$^+$, 84/90), 313/315 (56/58), 254/256 (100/96); HRMS *m/z* 445.0367 (M$^+$, $C_{17}H_{20}NO_8Br$ requires 445.0372).

4.2.8. Dimethyl 2-(1-carbomethoxy-4-ethyl-1*H*-indol-3-yl)malonate (17) and dimethyl 2-(1-carbomethoxy-6-ethyl-1*H*-indol-3-yl)malonate (18). Prepared from **7** as an inseparable (2:3, ^{1}H NMR analysis) isomeric mixture; colorless oil; R_f 0.40 (EtOAc–hexane 1:3); IR (CHCl$_3$) ν_{max} 3018, 1738, 1444 cm^{-1}; ^{1}H NMR (DMSO-d_6) **17** (minor 4-ethyl-isomer) δ 8.05 (1H, d, *J*=7.9 Hz, H7), 7.64 (1H, s, H2), 7.32 (1H, t, *J*=7.9 Hz, H6), 7.11 (1H, d, *J*=7.9 Hz, H5), 5.30 (1H, s, H8), 3.99 (3H, br s, NCO$_2$*Me*), 3.74 (6H, s, 2CO$_2$*Me*), 2.87 (2H, q, CH$_2$), 1.21 (3H, t, Me); ^{13}C (DMSO-d_6) δ 168.2 (*C*O$_2$Me), 150.4 (N*C*OMe), 136.5 (C7a), 135.1 (C4), 126.3 (C3a), 125.0 (C2), 124.6 (C6), 123.2 (C5), 112.9 (C7), 112.6 (C3), 54.3 (NCO*Me*), 53.1 (CO$_2$*Me*), 49.6 (C8), 25.0 (CH$_2$), 15.4 (Me); **18** (major 6-ethyl-isomer) ^{1}H NMR (DMSO-d_6) δ 7.96 (1H, br s, H7), 7.71 (1H, s, H2), 7.52 (1H, t, *J*=8.1 Hz, H4), 7.15 (1H, dd, *J*=8.1, 1.5 Hz, H5), 5.32 (1H, s, H8), 3.99 (3H, br s, NCO$_2$*Me*), 3.69 (6H, s, 2CO$_2$*Me*), 2.73 (2H, q, CH$_2$), 1.22 (3H, t, Me); ^{13}C (DMSO-d_6) δ 168.1 (*C*O$_2$Me), 150.7 (N*C*OMe), 140.9 (C6), 136.5 (C7a), 126.8 (C3a), 125.0 (C2), 123.3 (C5), 120.0 (C4), 113.6 (C7), 113.1 (C3), 54.2 (NCO*Me*), 52.8 (CO$_2$*Me*), 48.4 (C8), 28.7 (CH$_2$), 16.2 (Me); EIMS *m/z* 333 (M$^+$, 77), 274 (100), 214 (34); HRMS *m/z* 333.1212 (M$^+$, $C_{17}H_{19}NO_6$ requires 333.1212).

4.2.9. Dimethyl 2-(1-carbomethoxy-6-*iso*-propyl-1*H*-indol-3-yl)malonate (19). Prepared from **7** as colorless oil; R_f 0.40 (EtOAc–hexane 1:3); IR (CHCl$_3$) ν_{max} 3010, 1738, cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.08 (1H, br s, H7), 7.74 (1H, s, H2), 7.48 (1H, d, *J*=8.0 Hz, H4), 7.17 (1H, dd, *J*=8.0, 1.5 Hz, H5), 4.87 (1H, s, H8), 4.02 (3H, br s, NCO$_2$*Me*), 3.77 (6H, s, 2CO$_2$*Me*), 3.04 (1H, m, *CH*Me$_2$), 1.31 (6H, d, CH*Me*$_2$); ^{13}C (CDCl$_3$) δ 167.9 (*C*O$_2$Me), 151.1 (N*C*OMe), 146.4 (C6), 135.6 (C7a), 127.0 (C3a), 124.5 (C2), 122.1 (C5), 118.9 (C4), 112.8 (C7), 112.7 (C3), 53.8 (NCO*Me*), 53.0 (CO$_2$*Me*), 49.1 (C8), 34.7 (*CH*Me$_2$), 24.4 (CH*Me*$_2$); EIMS *m/z* 347 (M$^+$, 100), 333 (20), 289 (80); HRMS *m/z* 347.1364 (M$^+$, $C_{18}H_{21}NO_6$ requires 347.1369).

4.2.10. Dimethyl 2-(1-carbomethoxy-6-benzyl-1*H*-indol-3-yl)malonate (20). Prepared from **7** as colorless oil; R_f 0.35 (EtOAc–hexane 1:3); IR (CHCl$_3$) ν_{max} 3014, 1738, 1446, cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.09 (1H, br s, H7), 7.75 (1H, d, *J*=0.8 Hz, H2), 7.47 (1H, d, *J*=8.0 Hz, H4), 7.30–7.16 (5H, m, Ar), 7.12 (1H, dd, *J*=8.0, 1.5 Hz, H5), 4.86 (1H, d, *J*=0.8 Hz, H8), 4.11 (2H, s, *CH*$_2$Ph), 4.01 (3H, br s, NCO$_2$*Me*), 3.77 (6H, s, 2CO$_2$*Me*); ^{13}C (CDCl$_3$) δ 168.0 (*C*O$_2$Me), 151.2 (N*C*OMe), 141.4 (C*i*), 138.5 (C6), 135.7 (C7a), 128.8 (C*o*), 128.4 (C*m*), 127.3 (C3a), 126.0 (C*p*), 124.8 (C2), 124.5 (C5), 119.2 (C4), 115.6 (C7), 112.8 (C3), 53.8 (NCO*Me*), 53.0 (CO$_2$*Me*), 49.1 (C8), 42.3 (*CH*$_2$Ph); EIMS *m/z* 395 (M$^+$, 100), 336 (91), 200 (17); HRMS *m/z* 395.1366 (M$^+$, $C_{22}H_{21}NO_6$ requires 395.1369).

4.2.11. Dimethyl 2-(1-carbomethoxy-6-*tert*-butyl-1*H*-indol-3-yl)malonate (21). Prepared from **7** as colorless oil; R_f 0.66 (EtOAc–hexane 2:3); IR (CHCl$_3$) ν_{max} 3012, 1738 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.27 (1H, br s, H7), 7.75 (1H, s, H2), 7.50 (1H, d, *J*=8.4 Hz, H4), 7.36 (1H, dd, *J*=8.4, 1.8 Hz, H5), 4.87 (1H, s, H8), 4.03 (3H, br s, NCO$_2$*Me*), 3.78 (6H, s, 2CO$_2$*Me*), 1.39 (9H, s, CMe$_3$); ^{13}C (CDCl$_3$) δ 168.1 (*C*O$_2$Me), 151.3 (N*C*OMe), 148.7 (C6), 135.7 (C7a), 126.7 (C3a), 124.8 (C2), 121.2 (C5), 118.7 (C4), 112.6 (C3), 111.9 (C7), 53.8 (NCO*Me*), 53.0 (CO$_2$*Me*), 49.1 (C8), 35.1 (*C*Me$_3$), 31.7 (C*Me*$_3$); EIMS *m/z* 361 (M$^+$, 20), 346 (100); HRMS *m/z* 361.1522 (M$^+$, $C_{19}H_{23}NO_6$ requires 361.1525).

4.2.12. Dimethyl 2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-malonate (22). Prepared from **7** as colorless crystals, mp 109–110°C (EtOAc–hexane); R_f 0.19 (EtOAc–hexane 2:3); IR (CHCl$_3$) ν_{max} 3440, 1734 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.69 (1H, br s, NH), 7.29 (1H, br d, *J*=7.8 Hz, H4), 7.20 (1H, td, *J*=7.8, 1.0 Hz, H6), 6.98 (1H, td, *J*=7.8, 1.0 Hz, H5), 6.86 (1H, br d, *J*=7.8 Hz, H7), 4.21 (1H, d, *J*=4.2 Hz, H8), 4.06 (1H, d, *J*=4.2 Hz, H3), 3.80 and 3.58 (6H, 2s, 2CO$_2$*Me*); ^{13}C NMR (CDCl$_3$) δ 177.2 (C2), 168.1 and 167.2 (2*C*O$_2$Me), 141.7 (C7a), 128.6 (C6), 125.9 (C3a), 124.7 (C4), 122.4 (C5), 109.8 (C7), 52.9 and 52.7 (2CO$_2$*Me*), 52.0 (C8), 45.1 (C3); EIMS *m/z* 263 (M$^+$, 66), 231 (48), 204 (85), 172 (100); HRMS *m/z* 263.0799 (M$^+$, $C_{13}H_{13}NO_5$ requires 263.0794).

4.2.13. Dimethyl 2-(2-carbomethoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)malonate (23). Prepared from **7** as colorless oil, R_f 0.4 (EtOAc–hexane 2:3); IR (CHCl$_3$) ν_{max} 3020, 1734, cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.94 (1H, d, *J*=7.7 Hz, H7), 7.35 (1H, td, *J*=7.7, 1.0 Hz, H6), 7.34 (1H, d, *J*=7.7 Hz, H4), 7.16 (1H, td, *J*=7.7, 1.0 Hz, H5), 4.26 (1H, d,

J=3.9, Hz, H8), 4.23 (1H, d, *J*=3.9 Hz, H3), 4.03 (3H, s, NCO_2*Me*), 3.77 and 3.64 (6H, 2s, $2CO_2$*Me*); ^{13}C NMR ($CDCl_3$) δ 173.4 (C2), 167.7 and 167.1 ($2CO_2$Me), 151.3 (NCO_2Me), 140.2 (C7a), 129.1 (C6), 124.8 (C5), 124.3 (C3a), 123.9 (C4), 115.2 (C7), 54.0 (NCO_2*Me*), 53.0 and 52.9 ($2CO_2$*Me*), 52.6 (C3), 45.3 (C8); EIMS *m*/*z* 321 (M^+, 23), 289 (54), 257 (100), 230 (60); HRMS *m*/*z* 321.0834 (M^+, $C_{15}H_{15}NO_7$ requires 321.0849).

4.2.14. Dimethyl 2-(5-fluoro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)malonate (24). Prepared from **8** as yellow crystals, mp 108–109°C (EtOAc–hexane); R_f 0.12 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3024, 1734, 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, br s, NH), 7.12 (1H, br dd, *J*=8.3, 2.9 Hz, H4), 6.93 (1H, td, *J*=8.8, 2.9 Hz, H6), 6.80 (1H, dd, *J*=8.8, 4.2 Hz, H7), 4.22 (1H, d, *J*=3.9 Hz, H8), 4.04 (1H, br d, *J*=3.9 Hz, H3), 3.83 and 3.60 (6H, 2s, $2CO_2$*Me*); ^{13}C NMR ($CDCl_3$) δ 176.7 (C2), 168.0 and 167.0 ($2CO_2$Me), 158.8 (C5), 137.5 (C7a), 127.5 (C3a), 115.0 (C4), 113.2 (C6), 110.2 (C7), 53.1 and 52.9 ($2CO_2$*Me*), 51.9 (C8), 45.5 (C3); EIMS *m*/*z* 281 (M^+, 23), 249 (24), 222 (47), 190 (100); HRMS *m*/*z* 281.0692 (M^+, $C_{13}H_{12}NO_5F$ requires 281.0699).

4.2.15. Dimethyl 2-(5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)malonate (25). Prepared from **9** as brown crystals, mp 161–163°C (EtOAc–hexane); R_f 0.11 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3032, 1732, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.56 (1H, br s, NH), 6.96–6.70 (3H, m, Ar), 4.21 (1H, d, *J*=4.1 Hz, H8), 4.05 (1H, d, *J*=4.1 Hz, H3), 3.83 and 3.76 (6H, 2s, $2CO_2$*Me*), 3.61 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) δ 177.1 (C2), 168.3 and 167.3 ($2CO_2$Me), 155.7 (C5), 135.2 (C7a), 127.3 (C3a), 113.3 (C7), 112.1 (C6), 110.1 (C4), 55.7 (OMe), 52.9 and 52.7 ($2CO_2$*Me*), 52.0 (C8), 45.5 (C3); EIMS *m*/*z* 293 (M^+, 42), 233 (83), 202 (100), 174 (22); HRMS *m*/*z* 293.0884 (M^+, $C_{14}H_{15}NO_6$ requires 293.0899).

4.2.16. Dimethyl 2-(4-bromo-1-carbomethoxy-5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)malonate (26). Prepared from **10** as colorless crystals, mp 174–175°C (EtOAc–hexane); R_f 0.27 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3018, 1734, 1216, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, d, *J*=9.0 Hz, H7), 7.07 (1H, d, *J*=9.0 Hz, H6), 5.04 (1H, d, *J*=3.9 Hz, H8), 4.29 (1H, br d, *J*=3.9 Hz, H3), 4.00 (3H, s NCO_2*Me*), 3.89 and 3.61 (6H, 2s, $2CO_2$*Me*), 3.89 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) δ 172.1 (C2), 167.5 and 167.1 ($2CO_2$Me), 153.0 (C5), 151.3 (NCO_2Me), 135.0 (C7a), 125.7 (C3a), 114.9 (C7), 111.6 (C6), 108.5 (C4), 56.6 (OMe), 54.1 (2 NCO_2*Me*), 53.3 and 52.9 ($2CO_2$*Me*), 50.6 (C8), 47.2 (C3); EIMS *m*/*z* 429/431 (M^+, 30/31), 365/367 (97/100), 352/354 (52/53); HRMS *m*/*z* 429.0058 (M^+, $C_{16}H_{16}NO_8Br$ requires 429.0059).

4.2.17. Dimethyl 2-(6-bromo-5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)malonate (27). Prepared from **11** as colorless crystals, mp 166–167°C (EtOAc–hexane); R_f 0.15 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3030, 1736, 1232, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, br s, NH), 7.09 (1H, s, H7), 7.08 (1H, s, H4), 4.26 (1H, d, *J*=3.5 Hz, H8), 3.98 (1H, dd, *J*=3.5, 1.0 Hz, H3), 3.86 (3H, s, OMe), 3.85 and 3.59 (6H, 2s, $2CO_2$*Me*); ^{13}C NMR ($CDCl_3$) δ 176.5 (C2), 168.5 and 167.1 ($2CO_2$Me), 152.0 (C5), 135.7 (C7a), 126.2 (C3a), 114.4 (C7), 111.5 (C6), 110.7 (C4), 56.9 (OMe), 53.1 and 52.8 ($2CO_2$*Me*), 51.8 (C8), 45.4 (C3); EIMS *m*/*z* 371/373 (M^+, 60/61), 339/341 (35/36), 280/282 (90/90); HRMS *m*/*z* 370.9997 (M^+, $C_{14}H_{14}NO_6Br$ requires 371.0004).

4.2.18. Methyl 3-cyano-3a-ethyl-5-fluoro-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (3a). Prepared from **1a** as a C-3 diastereomeric mixture (7:3 *endo*–*exo* ratio by ^{1}H NMR analysis), colorless crystals, mp 155–156°C (EtOAc–hexane); R_f 0.39 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3018, 2360, 1732, 1206 cm^{-1}; (major *endo*-isomer) ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, br s, H7), 7.37 (1H, dd, *J*=7.9, 2.6 Hz, H4), 7.14 (1H, td, *J*=8.8, 2.6 Hz, H6), 6.27 (1H, br s, H8a), 4.08 (1H, s, H3), 3.94 (3H, br s, NCO_2Me), 2.06 and 1.95 (2H, dq, *J*=15.8, 7.5 Hz, CH_2), 0.94 (3H, t, *J*=7.5 Hz, Me); ^{13}C NMR ($CDCl_3$) δ 164.6 (C2), 159.6 (C5), 151.9 (NCO_2Me), 136.6 (C7a), 128.6 (C3b), 117.6 (C6), 116.8 (C7), 113.2 (C4), 112.3 (CN), 95.4 (C8a), 54.2 (NCO_2*Me*), 53.8 (C3a), 42.1 (C3), 31.1 (CH_2), 8.5 (Me); (minor *exo*-isomer) ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, br s, H7), 7.14 (1H, td, *J*=8.8, 2.6 Hz, H6), 6.92 (1H, dd, *J*=7.9, 2.6 Hz, H4), 6.33 (1H, br s, H8a), 3.99 (1H, s, H3), 3.94 (3H, br s, NCO_2*Me*), 2.06 and 1.95 (2H, dq, *J*=15.8, 7.5 Hz, CH_2), 0.91 (3H, t, *J*=7.5 Hz, Me); ^{13}C NMR ($CDCl_3$) δ 164.6 (C2), 159.6 (C5), 151.9 (NCO_2Me), 136.6 (C7a), 132.2 (C3b), 117.5 (C6), 117.1 (C7), 111.8 (CN), 111.1 (C4), 96.4 (C8a), 54.2 (NCO_2*Me*), 53.8 (C3a), 42.4 (C3), 28.6 (CH_2), 8.2 (Me); EIMS *m*/*z* 304 (M^+, 100), 231 (45), 187 (41), 162 (32); HRMS *m*/*z* 304.0853 (M^+, $C_{15}H_{13}N_2O_4F$ requires 304.0859).

4.2.19. Methyl 3a-benzyl-3-cyano-5-fluoro-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (3b). Prepared from **1a** as a C-3 diastereomeric mixture (9:1 *endo*–*exo* ratio by ^{1}H NMR analysis), colorless crystals, mp 173–174°C (EtOAc–hexane); R_f 0.46 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3020, 2360, 1734, 1206 cm^{-1}; (major *endo*-isomer) ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, br s, H7), 7.41–6.79 (7H, m, Ar), 6.72 (1H, s, H8a), 6.36 (1H, br s, H8a), 4.12 (1H, s, H3), 3.90 (3H, br s, NCO_2*Me*), 3.10 (2H, s, CH_2Ph); ^{13}C NMR ($CDCl_3$) δ 164.2 (C2), 159.6 (C5), 150.3 (NCO_2Me), 136.3 (C7a,), 132.8 (C*i*), 129.9 (C*m*), 129.5 (C*o*), 128.6 (C*p*), 128.0 (C3b), 117.8 (C6), 117.1 (C7), 113.2 (C4), 112.1 (CN), 93.9 (C8a), 55.1 (C3a), 53.8 (NCO_2*Me*), 42.2 (CH_2Ph), 40.3 (C3); EIMS *m*/*z* 366 (M^+, 82), 231 (58), 187 (35), 91 (100); HRMS *m*/*z* 366.1009 (M^+, $C_{20}H_{15}N_2O_4F$ requires 366.1016).

4.2.20. Ethyl 3-cyano-3a-ethyl-5-methoxy-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (3c). Prepared from **1b** as a C-3 diastereomeric mixture (7:3 *endo*–*exo* ratio by ^{1}H NMR analysis), colorless crystals, mp 135–136°C (EtOAc–hexane); R_f 0.43 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3036, 2358, 1800, 1724 cm^{-1}; (major *endo*-isomer) ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, br s, H7), 7.19 (1H, d, *J*=2.6 Hz, H4), 6.94 (1H, dd, *J*=8.8, 2.6 Hz, H6), 6.28 (1H, br s, H8a), 4.36 (2H, br s, OCH_2), 4.15 (1H, s, H3), 3.82 (3H, s, OMe), 2.06 and 1.95 (2H, dq, *J*=14.1, 7.4 Hz, C3a–CH_2), 1.41 (3H, br t, *J*=7.0 Hz, OCH_2*Me*), 0.91 (3H, t, *J*=7.4 Hz, C3a–CH_2*Me*); ^{13}C NMR ($CDCl_3$) δ 165.2 (C2), 156.8 (C5), 151.3 (NCO_2Et), 134.0 (C7a), 128.0 (C3b), 116.4 (C7), 116.1 (C6), 112.7 (CN),

111.2 (C4), 95.6 (C8a), 62.9 (O*CH*$_2$Me), 55.8 (OMe), 54.3 (C3a), 42.3 (C3), 31.1 (C3a–*CH*$_2$Me), 14.4 (O*CH*$_2$Me) 8.6 (C3a–CH$_2$*Me*); (minor *exo*-isomer) ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, br s, H7), 6.89 (1H, dd, J=8.8, 2.6 Hz, H6), 6.74 (1H, d, J=2.6 Hz, H4), 6.34 (1H, br s, H8a), 4.36 (2H, br s OCH$_2$), 4.06 (1H, s, H3), 3.80 (3H, s, OMe), 2.06 and 1.95 (2H, dq, J=14.1, 7.4 Hz, C3a–CH$_2$), 1.41 (3H, br t, J=7.0 Hz, OCH$_2$*Me*), 0.91 (3H, t, J=7.4 Hz, C3a–CH$_2$*Me*); ^{13}C NMR ($CDCl_3$) δ 165.2 (C2), 157.1 (C5), 151.3 (N*C*O$_2$Et), 134.0 (C7a), 128.0 (C3b), 116.7 (C7), 115.2 (C6), 112.3 (CN), 109.7 (C4), 96.6 (C8a), 62.9 (O*CH*$_2$Me), 55.8 (OMe), 54.7 (C3a), 42.6 (C3), 28.6 (C3a–*CH*$_2$Me), 14.4 (O*CH*$_2$Me) 8.2 (C3a–CH$_2$*Me*); EIMS m/z 330 (M$^+$, 100), 258 (13), 213 (45), 174 (70); HRMS m/z 330.1201 (M$^+$, $C_{17}H_{18}N_2O_5$ requires 330.1216).

4.2.21. Ethyl 3a-benzyl-3-cyano-5-methoxy-2-oxo-2,3,3a, 8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (3d). Prepared from **1b** as a C-3 diastereomeric mixture (9:1 *endo*–*exo* ratio by ^{1}H NMR analysis), colorless crystals, mp 161–163°C (EtOAc–hexane); R_f 0.51 (EtOAc–hexane 2:3); IR (CH_2Cl_2) ν_{max} 3006, 2360, 1798, 1724 cm^{-1}; (major *endo*-isomer) ^{1}H NMR ($CDCl_3$) δ 7.75 (1H, br s, H7), 7.35–6.79 (7H, m, Ar), 6.36 (1H, br s, H8a), 4.32 (2H, br q, J=6.8 Hz, OCH$_2$), 4.16 (1H, s, H3), 3.82 (3H, s, OMe), 3.12 (2H, s, *CH*$_2$Ph), 1.37 (3H, t, J=6.8 Hz, OCH$_2$*Me*); ^{13}C NMR ($CDCl_3$) δ 164.7 (C2), 156.8 (C5), 150.8 (N*C*O$_2$Me), 133.2 (C*i*), 132.9 (C7a), 129.9 (C*o*), 129.5 (C3b), 129.3 (C*m*), 128.3 (C*p*), 116.6 (C7), 116.0 (C6), 112.5 (CN), 111.0 (C4), 94.1 (C8a), 62.9 (OCH$_2$), 55.8 (OMe), 55.2 (C3a), 42.3 (*CH*$_2$Ph), 40.7 (C3), 14.4 (OCH$_2$*Me*); EIMS m/z 392 (M$^+$, 100), 275 (30), 185 (24), 91 (39); HRMS m/z 392.1364 (M$^+$, $C_{22}H_{20}N_2O_5$ requires 392.1372).

4.3. General lactonization procedure

To a precooled (0°C) stirred solution of the appropriate 2-hydroxyindoline **12**–**14**, and **16**, (0.19 mmol) in THF (5 mL) was added 6% aqueous KOH (0.2 mL) at once. The resulting mixture was stirred at room temperature for 20 min, then treated with 10% aqueous HCl to reach pH 4–5, and extracted with EtOAc (2×20 mL). The organic layer was washed with brine (2×15 mL) and dried over Na_2SO_4. The resultant crude product was purified by flash chromatography on silica gel eluting with CH_2Cl_2 to give the corresponding furoindoles **6a**–**c** and **6f**, respectively, in quantitative yields. Compound **6a** was identical in all respects to the product previously obtained.[4b]

4.3.1. Dimethyl 6-bromo-5-methoxy-3a-methyl-2-oxo-2, 3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-3,8-dicarboxylate (6f). Prepared from **16** as a C-3 diastereomeric mixture (2:3 *endo*–*exo* ratio by ^{1}H NMR analysis), colorless oil; R_f 0.24 (EtOAc–hexane 2:3); IR ($CHCl_3$) ν_{max} 3030, 1742, 1206, 1096 cm^{-1}; (minor *endo*-isomer) ^{1}H NMR (DMSO-d_6) δ 7.82 (1H, br s, H7), 6.68 (1H, s, H4), 6.23 (1H, s, H8a), 4.32 (1H, s, H3), 3.82 (3H, br s, NCO$_2$Me), 3.77 (3H, s, OMe), 3.67 (3H, s, CO$_2$Me), 1.61 (3H, s, Me); ^{13}C NMR (DMSO-d_6) δ 169.1 (C2), 166.2 (*C*O$_2$Me), 152.0 (N*C*O$_2$Me), 151.8 (C5), 134.3 (C7a), 131.9 (C3b), 118.3 (C7), 110.9 (C6), 108.7 (C4), 95.6 (C8a), 56.5 (OMe), 55.5 (C3), 53.5 (NCO$_2$*Me*), 52.6 (CO$_2$*Me*), 51.8 (C3a), 24.5 (Me); (major *exo*-isomer) ^{1}H NMR (DMSO-d_6) δ 7.82 (1H, br s, H7), 7.37 (1H, s, H4), 6.33 (1H, s, H8a), 4.38 (1H, s, H3), 3.85 (3H, s, OMe), 3.84 (3H, br s, NCO$_2$Me), 3.81 (3H, s, CO$_2$Me), 1.31 (3H, s, Me); ^{13}C NMR (DMSO-d_6) δ 169.3 (C2), 166.5 (*C*O$_2$Me), 152.4 (C5), 152.0 (N*C*O$_2$Me), 134.3 (C7a), 131.9 (C3b), 118.3 (C7), 110.7 (C6), 109.4 (C4), 96.3 (C8a), 56.6 (OMe), 55.5 (C3), 53.5 (NCO$_2$*Me*), 53.2 (CO$_2$*Me*), 51.8 (C3a), 19.8 (Me); EIMS m/z 413/415 (M$^+$, 94/100), 310/312 (64/62), 187 (20); HRMS m/z 413.0110 (M$^+$, $C_{16}H_{16}NO_7Br$ requires 413.0100).

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15. Pale green crystals of methyl 2-(1-carbomethoxy-5-fluoro-1*H*-indol-3-yl)cyanoacetate ($C_{14}H_{11}N_2O_4F$) were grown from EtOAc–hexane. Data collection was conducted at 293 K on a monoclinic crystal $P2_1/n$; a=10.661(1) Å, b=8.098(1) Å, c=16.281(2) Å, β=107. 292(3)° V=1342.1(3) Å^3, Z=4; R_1=4.2%, wR_2=10.3%, GOF=0.954. CCDC deposition number 204989.