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# Efficient, one-pot transformation of indoles into functionalized oxindole and spirooxindole systems under Swern conditions

Pilar López-Alvarado, Judith Steinhoff, Sonia Miranda, Carmen Avendaño, J. Carlos Menéndez *

*Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain*

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ABSTRACT

The reaction of indole derivatives bearing a 3- or 4-hydroxyalkyl chain with dimethylsulfoxide and oxalyl chloride under Swern conditions led to a one-pot, three-component process involving three different synthetic transformations, namely oxidation of indole to oxindole, introduction of a chlorine substituent at the oxindole C-3 position and substitution of the hydroxyl group in the side chain by chlorine, in good to excellent overall yields. The same conditions, applied to a 2-methylindole, afforded a 2-formylindole derivative oxidized at its side chain. The reaction starting from one indole with a 2-hydroxyalkyl chain furnished 3-(2-hydroxyalkyl)oxindoles. Finally, application of the Swern conditions to derivatives of indole-3-propionic or -butyric acid afforded 3-spirooxindole lactones.



## 1. Introduction

Dimethylsulfoxide is widely employed as an oxidant, most notably in the transformation of primary alcohols into aldehydes.[1] In indole substrates where nucleophilic groups are tethered to the C-3 position, activated dimethylsulfoxide induces synthetically interesting transformations. Thus, indole derivatives bearing a C-3 side chain with a nucleophilic group (**1**) may give tricyclic derivatives **2**, in a transformation that involves overall oxidation at the C-2 position of indole. This behaviour has been found in the case of tryptamine derivatives; for instance, the Swern reaction of *N*-acetyltryptophan methyl ester gave 35% of compound **3**, and this reaction was rationalized as shown in Scheme 1A.[2] When the same reaction was performed on *cyclo*-(L-Trp-L-Pro), a similar cyclization occurred but a methylthiomethyl group was introduced at C-4 of indole; this side process could be prevented by using oxalyl chloride instead of the initially employed TFAA, and by carrying out the reaction at −78 °C, but the cyclized product was obtained in only 12% yield.

In this context, we report here in full[3] our findings on the Swern oxidation of compounds related to structures **1** where the side chain nucleophile is an oxygen nucleophile, including β, γ- or δ-hydroxy and β- or γ-carboxy groups. We show that a reaction pathway alternative to that in Scheme 1A is possible, involving the formation of highly functionalized 3-chlorooxindole (**4**) or 3-spirooxindole (**5**) systems, together with other synthetically valuable compounds (Scheme 1B). The transformation of indoles into oxindoles by dimethylsulfoxide under acidic conditions is well known,[4] although this reaction is not general due to the low stability of indole derivatives in acidic media and is not accompanied by additional functionalization.

The transformation of indoles into highly functionalized oxindoles is of considerable interest, since oxindole is a key structural element in several bioactive natural products,[5] including the antifungal ascidian metabolite cynthichlorine,[6] the cell cycle inhibitor spirotryprostatin B,[7] the antibiotic speradine[8] and the MDR inhibitor and antimicrotubule agent *N*-methylwelwitindolinone C isothiocyanate (welwistatin)[9,10] (Fig. 1). The oxindole moiety is also present in large number of unnatural compounds with pharmaceutical interest, including growth hormone secretagogues,[11] analgesic[12] and antiinflammatory[13] compounds, and SNC active agents such as serotonergics[14] and the anti-Parkinson drug ropirinole.[15] Most of these compounds bear a variety of substituents at the oxindole C-3 position, and many of them are 3-spirooxindoles.

## 2. Results and discussion

The starting materials for our study were prepared according to Scheme 2. Primary alcohol **7a** was obtained from 1-methylindole-3-carbaldehyde through a Wittig olefination–reduction sequence, while compound **7b** was prepared by the same strategy from **6b**, which was known in the literature.[16] The secondary alcohols **7c**–**h**[17] came from an ytterbium triflate-catalyzed Michael reaction[18] of

* Corresponding author. Tel.: +34 91 3941840; fax: +34 91 3941822.
*E-mail address:* josecm@farm.ucm.es (J. Carlos Menéndez).

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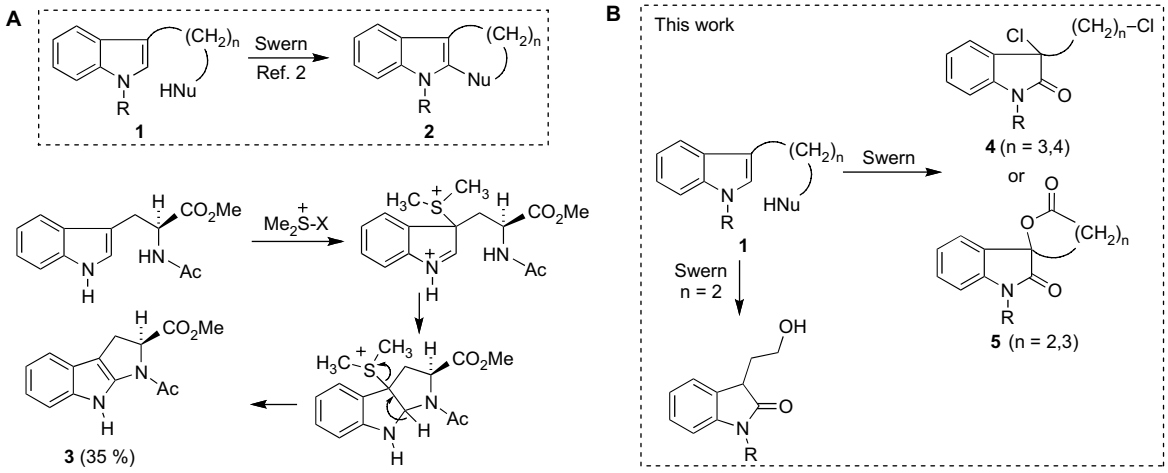



**Scheme 1.** Swern reactions of indoles bearing side-chain nucleophilic groups: comparison between the reactivity found for tryptamine derivatives (Ref. 2) and the results described in this paper.

indoles **6c**–**f** with the corresponding α,β-unsaturated ketones to give compounds **8c**–**h**,[19] followed by sodium borohydride reduction. Compound **7i** was obtained by lithium aluminium hydride reduction of commercially available 4-(3-indolyl)butyric acid, using a slightly modified literature method.[20]

As shown in Scheme 3 and Table 1, the reaction between 3-(3-hydroxyalkyl)indole derivatives **7a**–**g** and **7i** and dimethylsulfoxide under Swern conditions gave good to excellent yields of oxindole derivatives **9**, bearing chloro substituents at the C-3 position of both the oxindole and the side chain. In two cases (**c** and **d**), these products were accompanied by small amounts of the corresponding 3-chlorooxindole oxidized in the γ position of the side chain (compounds **10c**,**d**).[21] Although we routinely employed the standard Swern conditions, we found that addition of triethylamine is unnecessary (for instance, compound **10f** was obtained in 88% yield in the absence of added base). In the cases where R was different from hydrogen (**c**–**g** and **i**), compounds **9** were obtained as 2:1 to 3:1 diastereomeric mixtures that could not be separated because column chromatography must be very fast in order to avoid the hydrolysis of compounds **9**. The one-pot process leading to compounds **9** can be considered as a three-component reaction[22] because the final product incorporates substantial structural elements from the indole substrate, oxalyl chloride and dimethylsulfoxide (see the mechanistic discussion below).

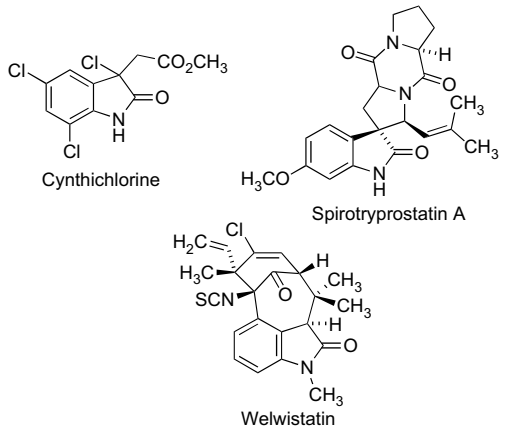
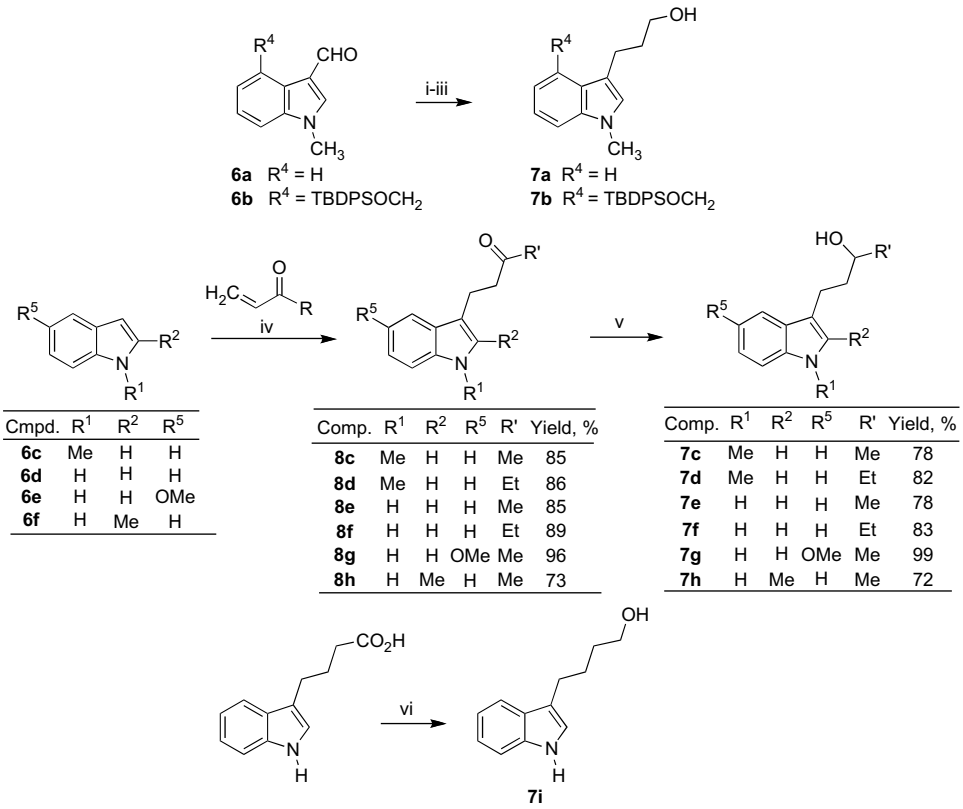



**Figure 1.** Structures of some biologically relevant 3-substituted oxindoles.

It is noteworthy that this unexpected transformation seems to require the presence of the hydroxypropyl side chain since it was not observed when simple indole derivatives (e.g., 3-methylindole) were employed as starting materials. On this basis, a rationalization for the formation of the observed products has been proposed (Scheme 4). The initial reaction between the nucleophilic C-3 position of indoles **7** and one of the sulfonium species present in the reaction medium leads to the iminium derivative **11**, where the C-2 position is highly electrophilic and is trapped by a second molecule of dimethylsulfoxide to give intermediates **12**. The latter compounds would yield **13** by spirocyclization, thus protecting the side chain hydroxyl group from oxidation, and then **13** would be transformed into oxindole **14** by reaction with a molecule of oxalyl chloride. Intermediate **14** would then undergo ring opening by attack of chloride anion to the position adjacent to the oxonium group, giving **15**,[23] followed by decarbonylation and decarboxylation of the oxalyl moiety. The formation of minor products **10** can be explained by the possibility that **12** may undergo oxidation of the secondary hydroxyl rather than spirocyclization. This step would be followed by displacement of a molecule of dimethyl sulfide from the C-3 position by a chloride anion and generation of the oxindole carbonyl after elimination of HCl and $SMe_2$.

An alternative pathway can be proposed (Scheme 5), involving cyclization of the side-chain oxygen onto the iminium cation function in **11** to give **16**, followed by elimination of dimethyl sulfide furnishing the fused pyrano[2,3-*b*]indole or oxepino[2,3-*b*]indole systems **17**. Further reaction of the indole C-3 position with the Swern reagent to give **18** followed by two final steps involving nucleophilic attack by chloride with opening of the oxygenated ring to give **19** and displacement of a second molecule of dimethyl sulfide, would lead to the observed products **9**.

In order to discriminate between these two mechanistic possibilities, we submitted 2-(1-methyl-3-indolyl)ethanol (*N*-methyl tryptophol, **20**) to the Swern conditions because in this case the intermediate corresponding to **13** would have a highly strained spirooxetane structure, while that corresponding to **17** should be much more easily formed and in fact it would be an analogue of the species generated from *N*-acetyltryptamine, as previously mentioned.[1] In the event, as shown in Scheme 6, this reaction did not give a dichlorooxindole derivative, as would be expected if the second mechanism was in operation, but instead afforded the known[24] oxindole **21** in 67% yield. This experiment leads us to

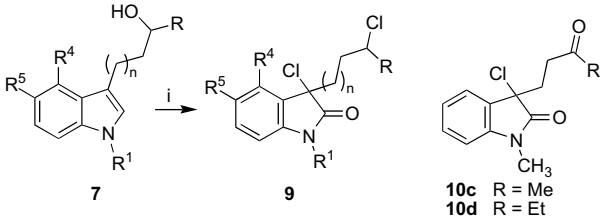



| Cmpd. | $R^1$ | $R^2$ | $R^5$ |
|---|---|---|---|
| **6c** | Me | H | H |
| **6d** | H | H | H |
| **6e** | H | H | OMe |
| **6f** | H | Me | H |

| Comp. | $R^1$ | $R^2$ | $R^5$ | R' | Yield, % |
|---|---|---|---|---|---|
| **8c** | Me | H | H | Me | 85 |
| **8d** | Me | H | H | Et | 86 |
| **8e** | H | H | H | Me | 85 |
| **8f** | H | H | H | Et | 89 |
| **8g** | H | H | OMe | Me | 96 |
| **8h** | H | Me | H | Me | 73 |

| Comp. | $R^1$ | $R^2$ | $R^5$ | R' | Yield, % |
|---|---|---|---|---|---|
| **7c** | Me | H | H | Me | 78 |
| **7d** | Me | H | H | Et | 82 |
| **7e** | H | H | H | Me | 78 |
| **7f** | H | H | H | Et | 83 |
| **7g** | H | H | OMe | Me | 99 |
| **7h** | H | Me | H | Me | 72 |

**Scheme 2.** Synthesis of starting materials. *Reagents and conditions*: (i) for **a**: $Ph_3P{=}CHCO_2Et$, EtOH, rt, 90 min (98%, *E*/*Z*=4:1); for **b**: same reagents, 110 °C, 48 h (87%, *E*/*Z*=6:1); (ii) for **a**: $H_2$, Pd/C, rt, 4 h (90%); for **b**: same reagents, 8.5 h (100%); (iii) for **a**: $LiAlH_4$, THF, rt, 16 h (85%); for **b**: same conditions (88%); (iv) $Yb(OTf)_3$, MeCN, rt, 16 h; (v) $NaBH_4$, EtOH, rt, 45 min; (vi) $LiAlH_4$, THF, rt, 14 h.




**Scheme 3.** *Reagents and conditions*: (i) DMSO, $(COCl)_2$, −78 °C, 10 min, then $Et_3N$, −78 °C to rt, 1 h (method A); (ii) same conditions, without $Et_3N$ (method B).

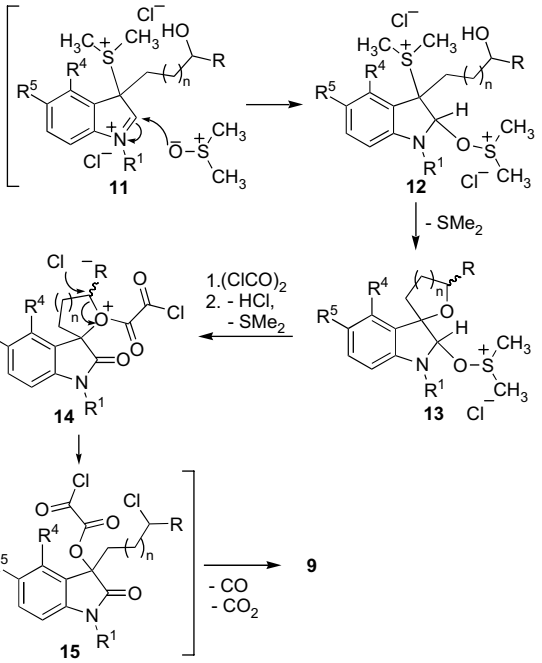
favour the first mechanism, although the second one cannot be completely discarded since it can be argued that, due to their different ring sizes, intermediates **18** and **24** are not completely equivalent in terms of their ability to react with activated DMSO.

The formation of **21** can be explained (Scheme 7) by the initial generation of **22**, analogous to **17**. Elimination of dimethyl sulfide from this intermediate to give **23**, with assistance from the indoline nitrogen, followed by elimination of HCl, would give a fused dihydrofuran **24**, which would be opened under the acidic workup conditions (a similar acid-catalyzed ring opening has been described for a 3a-hydroxy analogue of **22**, presumably also through an intermediate fused dihydrofuran,[25] and also for the pyrane analogue of this intermediate[21b]).

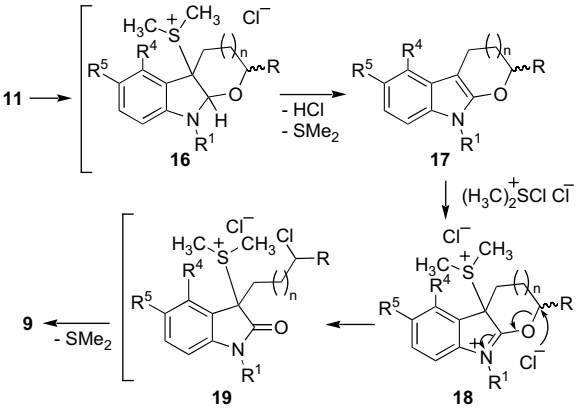
**Table 1**
Yields obtained in the synthesis of chlorooxindoles **9**

| Compd | $R^1$ | $R^4$ | $R^5$ | R | *n* | Method | Yield (%) | dr |
|---|---|---|---|---|---|---|---|---|
| **a** | Me | H | H | H | 1 | A | 82 | — |
| **b** | Me | $TBDPSOCH_2$ | H | H | 1 | A | 90 | — |
| **c** | Me | H | H | Me | 1 | A | 71[a] | 2:1 |
| **d** | Me | H | H | Et | 1 | A | 73[b] | 2:1 |
| **e** | H | H | H | Me | 1 | A | 80 | 2:1 |
| **f** | H | H | H | Et | 1 | A | 87 | 2:1 |
| **f** | H | H | H | Et | 1 | B | 88 | 2:1 |
| **g** | H | H | OMe | Me | 1 | A | 81 | 3:1 |
| **i** | H | H | H | H | 2 | A | 85 | — |

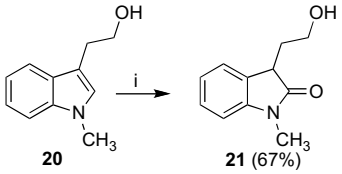
[a] Together with 15% of **10c**.
[b] Together with 12% of **10d**.



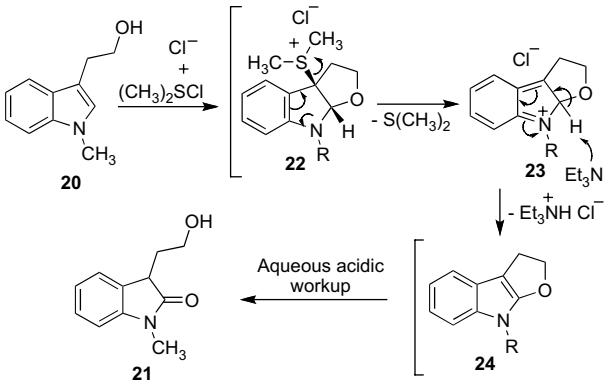

**Scheme 4.** First mechanistic proposal for the isolation of compounds **9**.




**Scheme 5.** Alternative mechanistic rationale for the isolation of **9**.

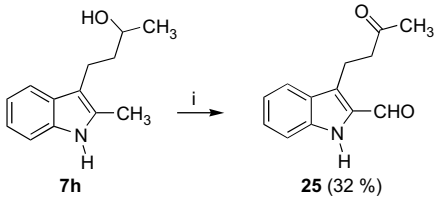



**Scheme 6.** Transformation of *N*-methyltryptophol into **21** under Swern conditions. *Reagents and conditions*: (i) DMSO, $(COCl)_2$, −78 °C, 10 min, then $Et_3N$, −78 °C to rt, 1 h.

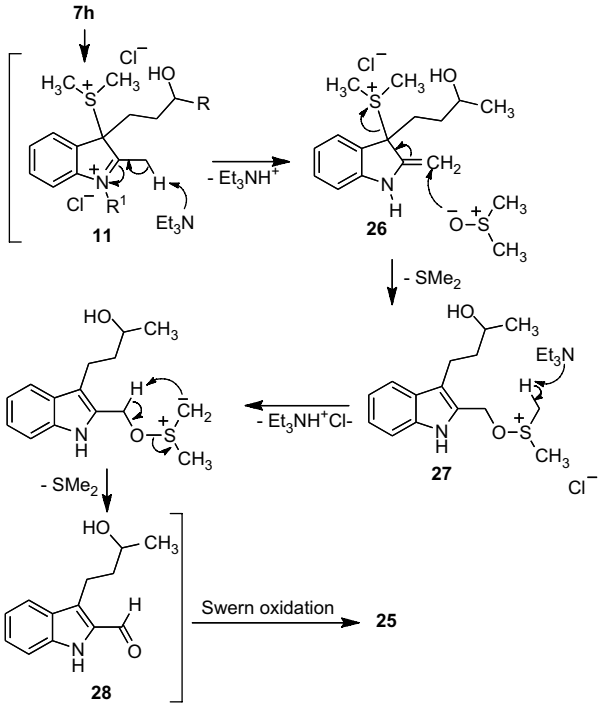



**Scheme 7.** Proposed mechanism for the isolation of compound **21**.

For comparison purposes, and also in order to contribute to the mechanistic study, we considered it relevant to examine the reaction of compound **7h**, bearing a C-2 methyl substituent and therefore uncapable of generating an oxindole system. Exposure of **7h** to standard Swern conditions gave a rather complex mixture of products, from which only aldehyde **25** could be isolated in a moderate 32% yield (Scheme 8).



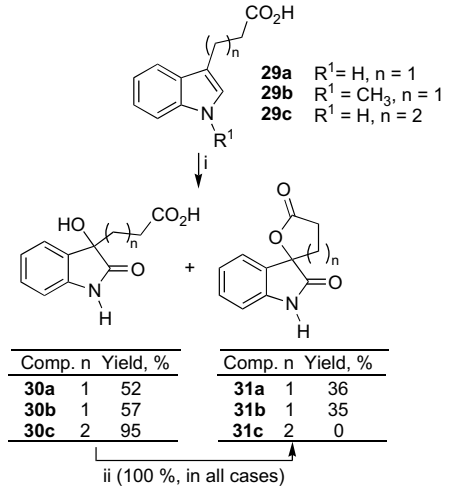

**Scheme 8.** Oxidation of 2-methylindole **7h** to 2-formylindole **25**. *Reagents and conditions*: (i) DMSO, $(COCl)_2$, −78 °C, 10 min, then $Et_3N$, −78 °C to rt, 1 h.




**Scheme 9.** Rationale for the oxidation of a $C_2$-methyl substituent under Swern conditions.

In order to account for the formation of **25**, we propose the mechanism outlined in Scheme 9, where the initially generated species **11** cannot evolve by addition of a DMSO molecule to the occupied C-2 position and hence it is deprotonated by triethylamine to yield **26**, which then undergoes an allylic nucleophilic displacement of dimethyl sulfide by a molecule of DMSO to give sulfonium salt **27**. This species has the same structure as the intermediate of the Swern oxidation and thus it is transformed into aldehyde **28** following the usual mechanism involving a retro hetero-ene type process. A final oxidation of the secondary hydroxyl by the Swern reagent affords the observed product **25**.

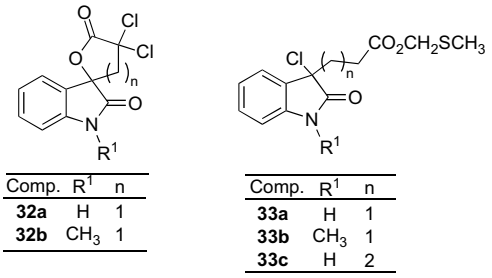
At this stage, we became interested in studying the application of our conditions to indole-3-propionic and indole-3-butyric acid derivatives. Some examples of oxidative cyclization of indole-3-propionic acids are known in the literature, often initiated by the addition of a halogenating reagent (e.g., *N*-bromosuccinimide) to




| Comp. | n | Yield, % |
|---|---|---|
| **30a** | 1 | 52 |
| **30b** | 1 | 57 |
| **30c** | 2 | 95 |

| Comp. | n | Yield, % |
|---|---|---|
| **31a** | 1 | 36 |
| **31b** | 1 | 35 |
| **31c** | 2 | 0 |

**Scheme 10.** Transformation of ω-(3-indolyl)alkanoic acids **29** in the presence of DMSO–oxalyl chloride. *Reagents and conditions*: (i) DMSO, $(COCl)_2$, −78 °C, 20 min; (ii) $H_2SO_4$ (trace), $CHCl_3$, rt, 8 h.



| Comp. | $R^1$ | n |
|---|---|---|
| **32a** | H | 1 |
| **32b** | $CH_3$ | 1 |

| Comp. | $R^1$ | n |
|---|---|---|
| **33a** | H | 1 |
| **33b** | $CH_3$ | 1 |
| **33c** | H | 2 |

**Figure 2.** Side products isolated when the reaction of compounds **29** with DMSO–oxalyl chloride was performed in the presence of triethylamine.

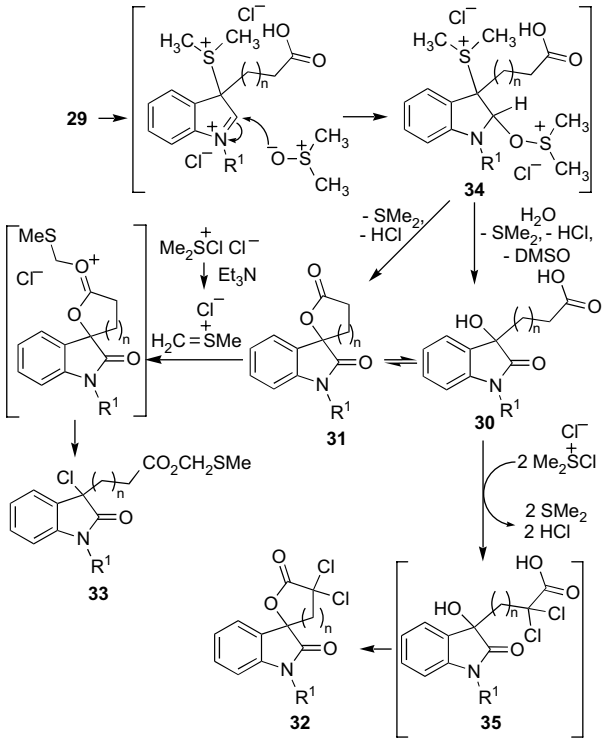
the indole C-3, a clear disadvantage of the method being the often observed concomitant halogenation of the C-5 position.[26] Alternative methods include the use of very strong oxidants like $Fe^{2+}$-*tert*-butyl hydroperoxide[27] and the very toxic thallium trinitrate.[28] To our knowledge, only a few precedents of the use of dimethylsulfoxide for this transformation are known. The first one was reported by Büchi during his total synthesis of tryptoquivaline G, where exposure of two *N*-acyltryptophan derivatives to DMSO–trichloromethanesulfonyl anhydride at −20 °C for 5 h gave the corresponding five-membered spirolactones in ca. 65% yields, as mixtures of diastereomers.[29] Alternatively, both Casnati and Labroo have employed a DMSO–*tert*-butyl bromide mixture (40 °C, 1.5–4.5 h) to obtain 3-spirolactones from tryptophan derivatives in moderate to good yields.[30]

As shown in Scheme 10, when indole-3-propionic acids **29a**,**b** were submitted to the Swern conditions in the absence of triethylamine, the reactions cleanly afforded mixtures of compound hydroxy acids **30a**,**b** and spirolactones **31a**,**b**.[31] Indole-3-butyric acid **29c** gave hydroxy acid **30c** as the only product, in an excellent 95% yield. The three hydroxy acids **30** were transformed into the corresponding lactones **31**[32] in quantitative yield by exposure to a trace of sulfuric acid in chloroform solution. This method for the synthesis of indole-3-spirolactones compares very favourably with previously existing ones in terms of yield, experimental convenience and use of simple, inexpensive and non-toxic starting materials and catalysts.

On the other hand, as shown in Figure 2 and Table 2, the use of our standard conditions (i.e., DMSO–oxalyl chloride in the presence of triethylamine) led to more complex mixtures that contained hydroxy acids **30**, the corresponding lactones **31**, dichlorolactones **32** and compounds **33**, bearing a methylthiomethyl ester chain. Compounds **31** must arise by spirocyclization from an intermediate **34**, related to **12** (Scheme 11). This allows the formation of hydroxy acids **30** from **34** and traces of water in the reaction medium or during acidic workup. In both cases this reaction is accompanied by elimination of HCl and dimethyl sulfide with concomitant generation of the oxindole carbonyl. The hydroxy acid/lactone ratio was altered during silica gel chromatography, which, as expected, favoured the lactonization reaction. In the reaction starting from indole-3-butyric acid **29c** ($n$=2), because the equilibrium between hydroxy acids and lactones is more favourable for the five-membered rings than for the six-membered ones, the only product isolated was hydroxy acid **30c**. In the presence of base, the cyclization of **34** to **31** is probably favoured and a base-catalyzed chlorination by the Swern reagent explains the isolation of dihalo-

**Table 2**
Results obtained in the reaction of compounds **29** with DMSO–oxalyl chloride in the presence of triethylamine

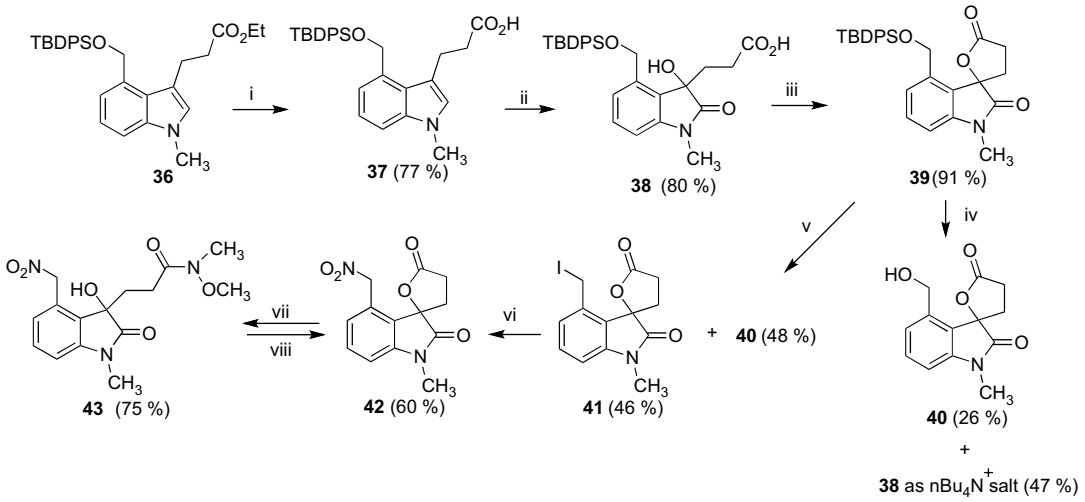
| Compd | $R^1$ | $n$ | % **30** | % **31** | % **32** | % **33** |
|---|---|---|---|---|---|---|
| **a** | H | 1 | 40 | 11 | 22 | 10 |
| **b** | $CH_3$ | 1 | 0 | 11 | 25 | 17 |
| **c** | $CH_3$ | 2 | 43 | 0 | 0 | 22 |



**Scheme 11.** Mechanistic explanation of the results of the Swern reaction of ω-(3-indolyl)alkanoic acids **29**.

lactones **32**. This halogenation does not take place on lactones **31**, since a separate experiment showed that neither γ-butyrolactone nor δ-valerolactone reacted under our conditions, while aliphatic acids (e.g., phenylacetic acid) gave the corresponding α,α-dichloro derivatives. Hence, we propose that compounds **32** come from the lactonization of the α,α-dichlorohydroxy acids **35**. Finally, the isolation of methylthiomethyl esters **33** in the presence of base can be explained by a Pummerer-type reaction of the lactone carbonyl oxygen with *S*-methyl methylenesulfonium chloride, generated by deprotonation of chlorodimethylsulfonium chloride by triethylamine, followed by ring opening after attack of the chloride anion.

Finally, we started a study on the application of the chemistry previously described in this paper to more complex starting materials in an effort to achieve the synthesis of compounds containing the welwistatin ABC core (Scheme 12). To this end, the known[16] compound **36** was hydrolyzed to **37** under basic conditions. Application of the Swern oxidation protocol described here afforded an 80% yield of hydroxy acid **38**, which could not be cyclized to the corresponding lactone under acid catalysis, as previously described for compounds **30**, because these conditions led only to a low yield of the unprotected derivative of the starting material. After some unsuccessful attempts using other methods found in the literature,[30b,33] we discovered that the desired lactonization to **39** could be effected in excellent yield by heating the hydroxy acid in vacuo. We next planned to deprotect the hydroxyl group in compound **39** in order to prepare a suitable precursor for the preparation of a iodide using the excellent method described by Olah from primary alcohols, trimethylsilyl chloride and sodium iodide,[34] but in this case the conventional conditions (tetrabutylammonium fluoride in THF) afforded only a low yield of the expected product **40**, together with hydroxy acid **38**, which was isolated as a tetrabutylammonium salt and comes from hydrolysis of the lactone ring in **39**. Since the intermediate of the Olah protocol is a trimethylsilyl ether, we attempted, albeit unsuccessfully, the direct reaction of **39** with sodium iodide. However, treatment of **39** with trimethylsilyl chloride and sodium iodide under the




**Scheme 12.** *Reagents and conditions*: (i) KOH, $CH_3OH$, rt, 12 h; (ii) DMSO, $(COCl)_2$, −78 °C, 20 min; (iii) 110 °C, 0.1 Torr, 8 h; (iv) TBAF, THF, rt, 16 h; (v) TMSCl, NaI, $CH_3CN$, −78 °C to rt, 7 h; (vi) $NaNO_2$, urea, DMF, −38 °C to −20 °C, 2 h; (vii) MeONHMe·HCl, $Me_2AlCl$, $CH_2Cl_2$, rt, 4 h; (viii) DBU, THF, t.a., 3 h (80%).

conditions normally employed for alcohols afforded equimolecular amounts of the desired iodide **41** and alcohol **40**, which was generated from the iodide during the purification process as verified by examination of the NMR spectra of the crude reaction product.

Although the yield of **41** was only moderate and it could not be further improved, the reaction did provide a sufficient amount of the iodide to continue with our study. Treatment of this iodide **41** with sodium nitrite in DMF in the presence of urea to increase the solubility of the nitrite[35] afforded nitro derivative **42** in 60% yield, accompanied again by a small amount of alcohol **40**. Unfortunately, all attempts to cyclize **42** to a compound related to the welwistatin ABC fragment were unsuccessful. As an alternative, compound **42** was transformed into the Weinreb amide **43** by treatment with *O*,*N*-dimethylhydroxylamine hydrochloride in the presence of chlorodimethyl-aluminium,[36] but again all attempts at the cyclization of this material were unsuccessful. These failures at the cyclization stage notwithstanding the results summarized in Scheme 12 prove that the chemistry described in this paper is suitable for the preparation of C-4 functionalized 3-spirooxindole systems.

## 3. Conclusions

In conclusion, we have shown that Swern conditions, involving the use of very simple and inexpensive reagents, allow the one-pot transformation of indole derivatives with a C-3 alkyl chain bearing γ- or δ-hydroxy and β- or γ-carboxy groups into synthetically valuable, highly functionalized oxindole and spirooxindole systems. These findings constitute a significant addition to the growing list[37] of non-conventional synthetic applications of activated dimethylsulfoxide.

## 4. Experimental

### 4.1. General

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (from SDS) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 40–230 mesh). Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as films on a NaCl disk. NMR spectra were obtained on a Bruker Avance instrument (250 MHz for $^1H$, 62.9 MHz for $^{13}C$), maintained by the Servicio de RMN, Universidad Complutense, with $CDCl_3$ as solvent. Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

### 4.2. 3-(1-Methyl-3-indolyl)propanol (7a)

To a solution of 1-methylindole-3-carbaldehyde (1.333 g, 8.37 mmol) in ethanol (20 ml) was added carbethoxymethylenetriphenylphosphorane (5.83 g, 16.7 mmol). The solution was heated for 90 min in an oil bath at 90 °C, under an argon atmosphere. The ethanol was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (40 ml), which was washed with water (3×20 ml). The organic phase was dried ($Na_2SO_4$) and evaporated, and the residue was chromatographed on silica gel, eluting with petroleum ether–ethyl acetate (gradient from 8:1 to 4:1), yielding 1.521 g (79%) of (*E*)-ethyl 3-(1-methyl-3-indolyl)prop-2-enoate and 0.369 g (19%) of the corresponding *Z* isomer. *Data for the (E) isomer*: mp 96 °C. IR (NaCl): 1698.3 (C=O), 1617.3 (C=C), 1284.0 (C–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 8.05–8.20 (m, 2H, H-4, H-1′); 7.65–7.40 (m, 3H, H-5,6,7); 7.44 (s, 1H, H-2); 6.62 (d, 1H, $J$=15.9 Hz, H-2′); 4.48 (q, 2H, $J$=7.1 Hz, $CO_2CH_2CH_3$); 4.02 (s, 3H, $NCH_3$); 1.56 (t, 3H, $J$=7.1 Hz, $CO_2CH_2CH_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 168.8 ($CO_2CH_2CH_3$); 138.4 (C-7a); 134.3 (C-1′); 133.5 (C-2′); 126.4 (C-3a); 123.3 (C-5); 121.6 (C-4); 121.0 (C-6); 112.9 (C-2); 112.5 (C-3); 110.3 (C-7); 60.4 ($CO_2CH_2CH_3$); 33.6 ($NCH_3$); 14.9 ($CO_2CH_2CH_3$) ppm. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 73.02; H, 6.57; N, 5.96. *Data for the (Z) isomer*: mp 94–96 °C. IR (NaCl): 1699.7 (C=O), 1623.9 (C=C), 1280.2 (C–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 8.89 (s, 1H, H-2); 7.76 (d, 1H, $J$=7.6 Hz, H-4); 7.45–7.20 (m, 4H, H-5,6,7,1′); 5.85 (d, 1H, $J$=12.5 Hz, H-2′); 4.32 (q, 2H, $J$=7.1 Hz, $CO_2CH_2CH_3$); 3.80 (s, 3H, $NCH_3$); 1.42 (t, 3H, $J$=7.1 Hz, $CO_2CH_2CH_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 168.0 ($CO_2CH_2CH_3$); 136.8 (C-7a); 135.8 (C-C-1′); 135.3 (C-2′); 129.6 (C-3a); 122.8 (C-5); 121.2 (C-4); 118.3 (C-6); 111.1 (C-2); 110.7 (C-3); 110.1 (C-7); 60.1 ($CO_2CH_2CH_3$); 33.6 ($NCH_3$); 14.9 ($CO_2CH_2CH_3$). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 73.63; H, 6.85; N, 5.91.

To a solution of the *E* isomer described above (1.521 g, 6.64 mmol) in methanol (20 ml) was added 10% Pd–C (152 mg). The suspension was stirred at room temperature for 4 h under a balloon filled with hydrogen. Filtration through Celite and evaporation gave

1.525 g (100%) of ethyl 3-(1-methyl-3-indolyl)propanoate. The reaction starting from the Z isomer or from an *E–Z* mixture gave an identical result. $^1$H NMR ($CDCl_3$) $\delta$ 7.65 (d, 1H, $J$=7.8 Hz, H-4); 7.35–7.15 (m, 2H, H-6,7); 7.14 (t, 1H, $J$=7.8 Hz, H-5); 6.89 (s, 1H, H-2); 4.16 (q, 2H, $J$=7.1 Hz, $CO_2CH_2CH_3$); 3.75 (s, 3H, $NCH_3$); 3.12 (t, 2H, $J$=7.4 Hz, H-1′); 2.72 (t, 2H, $J$=7.5 Hz, H-2′); 1.27 (t, 3H, $J$=7.1 Hz, $CO_2CH_2CH_3$) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 173.9 ($CO_2CH_2CH_3$); 137.4 (C-7a); 128.0 (C-3a); 126.7 (C-2); 121.9 (C-5); 119.1 (C-6); 113.9 (C-3); 109.6 (C-7); 60.7 ($CO_2CH_2CH_3$); 35.7 (C-2′); 32.9 ($NCH_3$); 20.9 (C-1′); 14.6 ($CO_2CH_2CH_3$) ppm. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.13; H, 7.36; N, 6.66. Found: C, 72.81; H, 7.52; N, 6.30.

A suspension of $LiAlH_4$ (402 mg, 6.93 mmol) in dry THF (10 ml), under an argon atmosphere, was externally cooled in an ice bath. A solution of ethyl 3-(1-methyl-3-indolyl)propanoate (400 mg, 1.73 mmol) in dry THF (6 ml) was added via cannula, and the suspension thus obtained was stirred at room temperature overnight. Excess $LiAlH_4$ was destroyed by successive addition of ethyl acetate, water and solid $NaHCO_3$. The suspension obtained was filtered and the solid was washed with ethyl acetate. The combined filtrates were dried ($Na_2SO_4$) and evaporated, yielding 279 mg (85%) of compound **7a**. IR (NaCl): 3364.2 (OH), 1613.8 (C=C), 1471.9 (C=C), 1247.9 (C–O) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (d, 1H, $J$=7.8 Hz, H-4); 7.45–7.20 (m, 2H, H-6,7); 7.10 (t, 1H, $J$=7.8 Hz, H-5); 6.87 (s, 1H, H-2); 3.75 (m, 2H, H-3′); 3.73 (s, 3H, $NCH_3$); 2.89 (t, 2H, $J$=7.3 Hz, H-1′); 1.98 (quint, 2H, $J$=7.5 Hz, H-2′); 1.58 (br s, 1H, OH) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 137.4 (C-7a); 128.1 (C-3a); 126.6 (C-2); 121.9 (C-5); 119.4 (C-4); 119.0 (C-6); 114.8 (C-3); 109.5 (C-7); 63.1 (C-3′); 33.5 (C-2′); 33.0 ($NCH_3$); 21.6 (C-1′) ppm. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.89; H, 7.64; N, 7.14.

Compound **7b** was prepared by a very similar route, which has been described in Ref. 16.

### 4.3. Michael additions to indole derivatives. General procedure

To a solution of the starting indole derivative and the suitable enone (2.2 equiv) in $CH_3CN$ (1 ml per mmol of indole), under an argon atmosphere, was added ytterbium(III) triflate (0.02 equiv). The solution was stirred at room temperature for 14 h and filtered through silica gel, eluting with a 10:1 petroleum ether–ethyl acetate mixture or with $CH_2Cl_2$. Data for compounds **8c**,[19a] **8e**,[19a] **8f**[19c] and **8h**[19d] were known in the literature. Characterization data for previously unknown compounds are given below.

#### 4.3.1. 4-(1-Methyl-3-indolyl)-2-butanone (*8c*)

Starting from 590 mg (4.5 mmol) of 1-methylindole, a yield of 762 mg (85%) of compound **8c** was obtained. Spectral data were identical to those published in Ref. 19a.

#### 4.3.2. 1-(1-Methyl-3-indolyl)-3-pentanone (*8d*)

Starting from 500 mg (3.81 mmol) of 1-methylindole, a yield of 705 mg (86%) of compound **8b** was obtained. IR (NaCl): 1713 (C=O) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.39 (d, 1H, $J$=7.0 Hz, H-4′); 7.15–7.00 (m, 2H, H-6′,7′); 6.91 (t, 1H, $J$=6.6 Hz, H-5′); 6.65 (s, 1H, H-2′); 3.52 (s, 3H, $NCH_3$); 2.85 (t, 2H, $J$=7.6 Hz, H-1); 2.62 (t, 2H, $J$=7.6 Hz, H-2); 2.22 (q, 2H, $J$=7.3 Hz, H-4); 0.86 (t, 3H, $J$=7.2 Hz, H-5) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 211.9 (C-3); 137.4 (C-7a′); 127.9 (C-3a′); 126.8 (C-2′); 121.9 (C-5′); 119.2 (C-4′); 119.1 (C-6′); 114.2 (C-3′); 109.6 (C-7′); 43.4 (C-2); 36.5 (C-4); 32.9 ($NCH_3$); 19.7 (C-1); 8.2 (C-5) ppm. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.91; H, 8.12; N, 6.20.

#### 4.3.3. 4-(3-Indolyl)-2-butanone (*8e*)

Starting from 500 mg (4.27 mmol) of indole, a yield of 686 mg (85%) of compound **8c** was obtained. Spectral data were identical to those published in Ref. 19a.

#### 4.3.4. 5-(3-Indolyl)-3-pentanone (*8f*)

Starting from 500 mg (4.27 mmol) of indole, a yield of 764 mg (89%) of **8d** was obtained. Spectral data were identical to those published in Ref. 19c.

#### 4.3.5. 4-(5-Methoxy-3-indolyl)-2-butanone (*8g*)

Starting from 500 mg (3.39 mmol) of 5-methoxyindole, a yield of 707 mg (96%) of compound **8g** was obtained. Mp 110–112 °C. IR (NaCl): 3365.9 (NH), 1703.5 (C=O) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.88 (br s, 1H, NH); 7.23 (d, 1H, $J$=7.8 Hz, H-4′); 7.03 (d, 1H, $J$=2.0 Hz, H-7′); 6.97 (s, 1H, H-2′); 6.85 (dd, 1H, $J$=7.7 and 1.9 Hz H-6′); 3.87 (s, 3H, $OCH_3$); 3.02 (t, 2H, $J$=7.1 Hz, H-1); 2.84 (t, 2H, $J$=7.1 Hz, H-2); 2.16 (s, 3H, H-4) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 209.6 (C-3); 154.2 (C-5′); 131.8 (C-7a′); 127.9 (C-3a′); 122.7 (C-2′); 115.0 (C-4′); 112.5 (C-6′); 112.4 (C-3′); 100.9 (C-7′); 56.3 ($OCH_3$); 44.3 (C-2); 30.5 ($NCH_3$); 19.7 (C-1′) ppm. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.66; H, 6.79; N, 6.40.

#### 4.3.6. 4-(2-Methyl-3-indolyl)-2-butanone (*8h*)

Starting from 500 mg (3.81 mmol) of 2-methylindole, a yield of 559 mg (73%) of compound **8h** was obtained. Spectral data were identical to those published in Ref. 19d.

### 4.4. Reduction of Michael adducts (8). General procedure

To a solution or suspension of the suitable compound **8** in ethanol (1 ml per 100 mg of substrate) was added an equimolecular amount of sodium borohydride, in small portions, over 15 min. The reaction mixture was stirred at room temperature for 30 min. It was then poured on a mixture of water (10 ml) and 1 M aqueous HCl (2 ml) and stirring was continued for another 10 min. The aqueous phase was extracted with ethyl acetate (3×50 ml), which was dried ($Na_2SO_4$) and evaporated, yielding the pure secondary alcohols **7c–h**. Compounds **7e**[17a] and **7g**[17b] were known in the literature. Data for other compounds and previously unpublished characterization data are given below.

#### 4.4.1. 4-(1-Methyl-3-indolyl)-2-butanol (*7c*)

Starting from 762 mg (3.8 mmol) of **8c**, a yield of 874 mg (78%) of compound **7c** was obtained. IR (NaCl): 3379.3 (OH) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.62 (d, 1H, $J$=7.8 Hz, H-4′); 7.35–7.20 (m, 2H, H-6′,7′); 7.11 (t, 1H, $J$=6.9 Hz, H-5′); 6.87 (s, 1H, H-2′); 3.90 (q, 1H, $J$=6.1 Hz, H-3); 3.75 (s, 3H, $NCH_3$); 2.98–2.72 (m, 2H, H-4); 1.87 (q, 2H, $J$=6.6 Hz, H-2); 1.41 (br s, 1H, OH); 1.25 (d, 3H, $J$=6.2 Hz, H-1) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 137.4 (C-7a′); 128.2 (C-3a′); 126.5 (C-2′); 121.9 (C-5′); 119.4 (C-6′); 119.0 (C-6′); 115.0 (C-3′); 109.6 (C-7′); 68.2 (C-2); 40.0 (C-3); 33.0 ($NCH_3$); 24.0 (C-4); 21.8 (C-1) ppm. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.50; H, 8.42; N, 6.75.

#### 4.4.2. 5-(1-Methyl-3-indolyl)-3-pentanol (*7d*)

Starting from 300 mg (1.40 mmol) of **8d**, a yield of 247 mg (82%) of compound **7d** was obtained. IR (NaCl): 3382.2 (OH) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.56 (d, 1H, $J$=7.0 Hz, H-5′); 7.35–7.20 (m, 2H, H-6′,7′); 7.06 (t, 1H, $J$=6.6 Hz, H-5′); 6.82 (s, 1H, H-2′); 3.70 (s, 3H, $NCH_3$); 3.60–3.52 (m, 1H, H-3); 2.95–2.70 (m, 2H, H-1); 1.85–1.55 (m, 2H, H-2); 1.60–1.30 (m, 2H, H-4); 0.90 (t, 3H, $J$=7.5 Hz, H-5) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 137.4 (C-7a′); 128.2 (C-3a′); 126.5 (C-2′); 121.9 (C-5′); 119.4 (C-6′); 119.0 (C-6′); 115.1 (C-3′); 109.6 (C-7′); 73.4 (C-3); 37.8 (C-2); 33.0 ($NCH_3$); 30.7 (C-4); 21.7 (C-1); 10.3 (C-5) ppm. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.01; H, 8.72; N, 6.20.

#### 4.4.3. 4-(3-Indolyl)-2-butanol (*7e*)

Starting from 606 mg (3.24 mmol) of **8e**, a yield of 479 mg (78%) of compound **7e** was obtained. IR (NaCl): 3541.0, 3414.4, 3200 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.96 (br s, 1H, NH); 7.63 (d, 1H, $J$=7.7 Hz, H-4′);

7.37 (d, 1H, *J*=7.9 Hz, H-7′); 7.21 (t, 1H, *J*=7.6 Hz, H-6′); 7.12 (t, 1H, *J*=7.0 Hz, H-5′); 7.02 (s, 1H, H-2′); 3.91 (sext, 1H, *J*=6.2 Hz, H-3); 3.00–2.78 (m, 2H, H-1); 1.89 (q, 2H, *J*=7.6 Hz, H-2); 1.26 (t, 3H, *J*=6.2 Hz, H-1) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 136.7 (C-7a′); 127.8 (C-3a′); 122.3 (C-2′); 121.5 (C-5′); 119.6 (C-4′); 119.3 (C-6′); 116.5 (C-3′); 111.5 (C-7′); 68.3 (C-2); 39.8 (C-3); 24.0 (C-1); 21.8 (C-4) ppm. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.91; H, 7.82; N, 7.20.

#### 4.4.4. 1-(3-Indolyl)-3-pentanol (**7f**)

Starting from 660 mg (3.28 mmol) of **8f**, a yield of 552 mg (83%) of compound **7f** was obtained. IR (NaCl): 3568.2, 3412.0, 3340.9 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 8.20 (br s, 1H, NH); 7.85 (d, 1H, *J*=7.7 Hz, H-4′); 7.46 (d, 1H, *J*=7.6 Hz, H-7′); 7.37 (t, 1H, *J*=7.8 Hz, H-6′); 7.32 (t, 1H, *J*=7.4 Hz, H-5′); 7.22 (s, 1H, H-2′); 3.92–3.80 (m, 1H, H-3); 3.20–2.95 (m, 2H, H-1); 2.20–2.00 (m, 2H, H-2); 1.85–1.60 (m, 2H, H-4); 1.18 (t, 3H, *J*=7.4 Hz, H-5) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 136.7 (C-7a′); 127.8 (C-3a′); 122.3 (C-2′); 121.5 (C-5′); 119.6 (C-4′); 119.3 (C-6′); 116.7 (C-3′); 111.5 (C-7′); 73.4 (C-3); 37.5 (C-2); 30.7 (C-4); 21.8 (C-1); 10.3 (C-5) ppm. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.21; N, 6.71.

#### 4.4.5. 4-(5-Methoxy-3-indolyl)-2-butanol (**7g**)

Starting from 500 mg (2.30 mmol) of **8g**, a yield of 504 mg (99%) of compound **7g** was obtained. IR (NaCl): 3541.2, 3409.3, 3335.6 (OH, NH) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 8.21 (br s, 1H, NH); 7.22 (d, 1H, *J*=7.9 Hz, H-4′); 7.07 (d, 1H, *J*=2.1 Hz, H-7′); 6.94 (s, 1H, H-2′); 6.86 (dd, 1H, *J*=7.8 and 2.1 Hz, H-6′); 4.48–4.32 (m, 1H, H-2); 3.86 (s, 3H, $OCH_3$); 2.90–2.62 (m, 2H, H-4); 1.95–1.70 (m, 2H, H-3); 1.25 (d, 3H, *J*=6.5 Hz, H-1) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 154.1 (C-5′); 132.0 (C-3a′); 128.2 (C-7a′); 122.6 (C-2′); 112.3 (C-3′); 112.1 (C-7′); 101.1 (C-4′,6′); 69.8 (C-2); 56.3 ($OCH_3$); 38.2 (C-3); 23.6 (C-1); 21.8 (C-4) ppm. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.06; H, 7.79; N, 6.40.

#### 4.4.6. 4-(2-Methyl-3-indolyl)-2-butanol (**7h**)

Starting from 559 mg (2.78 mmol) of **8h**, a yield of 405 mg (72%) of compound **7h** was obtained. IR (NaCl): 3568.2, 3399.8, 3224.8 (NH and OH) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.74 (br s, 1H, NH); 7.53 (d, 1H, *J*=7.1 Hz, H-4′); 7.28 (d, 1H, *J*=6.4 Hz, H-7′); 7.17–7.02 (m, 2H, H-5′,6′); 3.84 (sext, 1H, *J*=6.2 Hz, H-3); 2.81 (t, 1H, *J*=7.6 Hz, H-1); 1.78 (q, 2H, *J*=7.1 Hz, H-2); 2.40 (s, 3H, $CH_3$); 1.23 (d, 3H, *J*=6.2 Hz, H-4) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 135.6 (C-7a′); 131.2 (C-2′); 128.9 (C-3a′); 121.3 (C-5′); 119.5 (C-4′); 118.4 (C-6′); 111.8 (C-3′); 110.6 (C-7′); 68.2 (C-3); 40.2 (C-2); 24.1 (C-4); 20.8 (C-1); 12.0 ($C_2$-$CH_3$) ppm. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.51; H, 8.16; N, 6.71.

#### 4.4.7. 4-(3-Indolyl)butanol (**7i**)

A suspension of $LiAlH_4$ (1.143 g, 30 mmol, 6.1 equiv) in dry THF (20 ml), under an argon atmosphere, was externally cooled in an ice bath. A solution of 4-(3-indolyl)butanoic acid (1 g, 4.92 mmol) in dry THF (5 ml) was added via cannula, and the suspension thus obtained was stirred at room temperature overnight. Excess $LiAlH_4$ was destroyed by successive addition of ethyl acetate, water and solid $NaHCO_3$. The suspension obtained was filtered and the solid was washed with ethyl acetate. The combined filtrates were dried ($Na_2SO_4$) and evaporated, yielding 790 mg (85%) of compound **7i**.[20]

### 4.5. Reaction of 3-(3-indolyl)propanol and 4-(3-indolyl)-butanol derivatives with the Swern reagent. General procedure for the synthesis of compounds (9)

To a solution of oxalyl chloride (5 equiv) in dry $CH_2Cl_2$ (10 ml), at −78 °C under an argon atmosphere, was added DMSO (7 equiv). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of the suitable alcohol **7** (0.77 mmol) in dry $CH_2Cl_2$ (3 ml) was added dropwise via cannula, and the red solution was stirred for 10 min at −78 °C. Triethylamine (10 equiv) was then added and the solution was left to warm to room temperature for 20 min, while stirred. The reaction mixture was diluted with $CH_2Cl_2$ (20 ml) and washed with saturated aqueous $NH_4Cl$ (3×20 ml). The organic layer was dried ($Na_2SO_4$) and evaporated, and the residue was purified by rapid chromatography on silica gel, eluting with petroleum ether–ethyl acetate mixtures. Slower chromatographic separation may lead to considerable amounts of decomposition products, specially from hydrolysis of the terminal chloromethylene moiety.

#### 4.5.1. 3-Chloro-3-(3′-chloropropyl)-1-methylindolin-2-one (**9a**)

Starting from 143 mg (0.76 mmol) of alcohol **7a**, a yield of 160 mg (82%) of compound **9a** was obtained. IR (NaCl): 1728.5 (C=O), 1613.6 (C=C) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.40–7.25 (m, 2H, H-4,6); 7.08 (t, 1H, *J*=7.4 Hz, H-5); 6.80 (d, 1H, *J*=6.8 Hz, H-7); 3.42 (t, 2H, *J*=6.5 Hz, H-3′); 3.18 (s, 3H, $NCH_3$); 2.33 (t, 2H, *J*=8.3 Hz, H-1′); 1.75–1.55 (m, 2H, H-2′) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 173.9 (CO); 142.9 (C-7a); 130.7 (C-4); 129.5 (C-3a); 124.6 (C-6); 123.9 (C-5); 109.2 (C-7); 64.6 (C-3); 44.5 (C-3′); 37.0 (C-1′); 27.8 (C-2′); 27.1 ($NCH_3$) ppm. Anal. Calcd for $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43. Found: C, 55.53; H, 5.34; N, 5.46.

#### 4.5.2. 4-tert-Butyldiphenylsilyloxy-3-chloro-3-(3′-chloropropyl)-1-methylindolin-2-one (**9b**)

Starting from 100 mg (0.22 mmol) of alcohol **7b**, a yield of 120 mg (90%) of compound **9b** was obtained. IR (NaCl): 1731.6 (C=O), 1112.9 (C–O) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.73–7.67 (m, 4H, H-2″,6″); 7.50–7.35 (m, 8H, H-5,6,3″,4″,5″); 6.77 (d, 1H, *J*=7.6 Hz, H-7); 5.07 (d, 1H, *J*=14.2 Hz, $CH_2O$); 4.90 (d, 1H, *J*=14.2 Hz, $CH_2O$); 3.31–3.13 (m, 2H, H-3′); 3.21 (s, 3H, $NCH_3$); 2.40–2.17 (m, 2H, H-1′); 1.43–1.28 (m, 2H, H-2′); 1.12 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 173.2 (C-2); 142.4 (C-7a); 139.1 (C-4); 135.5 (C-2″,6″); 133.0 (C-1″); 130.5 (C-6); 129.9 (C-4″); 127.8 (C-3″,5″); 123.2 (C-3a); 121.6 (C-5); 107.4 (C-7); 64.4 (C-3); 60.9 ($CH_2O$); 43.6 (C-3′); 35.6 (C-1′); 27.7 (C-2′); 26.85 ($NCH_3$); 26.75 ($C(CH_3)_3$); 19.3 ($C(CH_3)_3$) ppm. Anal. Calcd for $C_{29}H_{33}Cl_2NO_2Si$: C, 66.15; H, 6.32; N, 2.66. Found: C, 65.97; H, 6.02; N, 2.36.

#### 4.5.3. 3-Chloro-3-(3′-chlorobutyl)-1-methylindolin-2-one (**9c**)

Starting from 193 mg (0.95 mmol) of alcohol **7c**, a yield of 184 mg (71%) of compound **9c** was obtained, as a 2:1 mixture of diastereomers (major diastereomer, **9ca**; minor diastereomer, **9cb**), together with 35 mg (15%) of 3-chloro-3-(3′-oxobutyl)-1-methylindolin-2-one (**10c**).

*Data for* ***9c***: IR (NaCl): 1729.4 (C=O) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.45–7.32 (m, 2H, H-4,6); 7.20 (t, 1H, *J*=6.7 Hz, H-5); 6.88 (d, 1H, *J*=7.8 Hz, H-7); 4.05–3.85 (m, 1H, H-3′); 3.26 (m, 3H, $NCH_3$); 2.55–2.21 (m, 2H, H-1′); 1.80–1.70 (m, 2H, H-2′); 1.49 (d, 3H, *J*=6.6 Hz, $CH_3$, **9ca**); 1.47 (d, 3H, *J*=6.6 Hz, $CH_3$, **9cb**) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 174.0 (*C*O); 142.9 (C-7a); 130.7 (C-4); 129.7 (C-3a, **9ca**); 129.4 (C-3a, **9cb**); 124.6 (C-6); 124.0 (C-5, **9cb**); 123.9 (C-5, **9ca**); 109.2 (C-7); 64.6 (C-3); 58.2 (C-3′, **9cb**); 58.0 (C-3′, **9ca**); 36.9 (C-1′, **9cb**); 36.5 (C-1′, **9ca**); 35.1 (C-2′, **9cb**); 34.8 (C-2′, **9ca**); 27.1 ($NCH_3$); 25.7 ($CH_3$, **9cb**); 25.5 ($CH_3$, **9ca**) ppm. Anal. Calcd for $C_{13}H_{15}Cl_2NO$: C, 57.37; H, 5.56; N, 5.15. Found: C, 57.68; H, 5.88; N, 5.17.

*Data for* ***10c***: IR (NaCl): 3422.0 (OH), 1728.2 and 1717.0 (2C=O) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.39 (d, 1H, *J*=7.6 Hz, H-4); 7.37 (t, 1H, *J*=7.6 Hz, H-6); 7.15 (t, 1H, *J*=6.9 Hz, H-5); 6.87 (d, 1H, *J*=7.6 Hz, H-2); 3.25 (s, 3H, $NCH_3$); 2.65–2.40 (m, 4H, H-1′,2′); 2.11 (s, 3H, $COCH_3$) ppm. $^{13}$C NMR ($CDCl_3$) $\delta$ 206.9 (C-3′); 173.9 (C-2); 142.7 (C-7a); 130.8 (C-4); 129.8 (C-3a); 124.5 (C-6); 123.9 (C-5); 109.2 (C-7);

64.4 (C-3); 38.4 (C-2′); 33.2 (C-1′); 30.4 ($CH_3$); 27.0 ($NCH_3$) ppm. MS (*m*/*z*, %): 251 ($M^+$). Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.35; H, 5.81; N, 5.62.

*4.5.4. 3-Chloro-3-(3′-chloropentyl)-1-methylindolin-2-one (**9d**)*

Starting from 160 mg (0.74 mmol) of alcohol **7d**, a yield of 155 mg (73%) of compound **9d** was obtained, as a 2:1 mixture of diastereomers (major diastereomer, **9da**; minor diastereomer, **9db**), together with 22 mg (12%) of 3-chloro-3-(3′-oxopentyl)-1-methylindolin-2-one (**10c**).

*Data for **9d***: IR (NaCl): 1729.0 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.35–7.25 (m, 2H, H-4,6); 7.07 (t, 1H, *J*=7.6 Hz, H-5); 6.80 (d, 1H, *J*=7.8 Hz, H-7); 3.75–3.60 (m, 1H, H-3′); 3.18 (m, 3H, $NCH_3$); 2.70–2.10 (m, 2H, H-1′); 1.80–1.35 (m, 2H, H-2′); 0.95–0.80 (m, 3H, H-4′) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.1 (C-2); 143.0 (C-7a, **9da**); 142.9 (C-7a, **9db**); 130.7 (C-4); 129.7 (C-3a, **9da**); 129.5 (C-3a, **9db**); 124.6 (C-6); 124.0 (C-5, **9db**); 123.9 (C-5, **9da**); 109.1 (C-7); 65.1 (C-3′, **9db**); 64.9 (C-3′, **9da**); 64.7 (C-3); 36.8 (C-1′, **9db**); 36.3 (C-1′, **9da**); 33.1 (C-2′, **9db**); 32.7 (C-2′, **9da**); 31.8 (C-4′, **9da**); 31.5 (C-4′, **9db**); 27.1 ($NCH_3$); 11.3 (C-5′) ppm. Anal. Calcd for $C_{14}H_{17}Cl_2NO$: C, 58.75; H, 5.99; N, 4.89. Found: C, 58.80; H, 5.91; N, 4.99.

*Data for **10d***: IR (NaCl): 3420.1 (OH), 1727.8 and 1718.1 (2C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.35–7.15 (m, 2H, H-4,6); 7.09 (t, 1H, *J*=6.6 Hz, H-5); 6.79 (d, 1H, *J*=8.0 Hz, H-2); 3.17 (s, 3H, $NCH_3$); 2.50–2.05 (m, 4H, H-1′,2′); 1.40–1.10 (m, 2H, C-4′); 0.80 (t, 3H, *J*=7.5 Hz, C-5′) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 210.4 (C-3′); 173.1 (C-2); 142.9 (C-7a); 131.8 (C-3a); 130.7 (C-4); 124.6 (C-6); 123.9 (C-5); 109.1 (C-7); 59.2 (C-3); 37.1 (C-2′); 36.4 (C-4′); 33.3 (C-1′); 27.0 ($NCH_3$); 8.1 (C-5′) ppm. MS (*m*/*z*, %): 265 ($M^+$). Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27. Found: C, 62.98; H, 5.79; N, 4.95.

*4.5.5. 3-Chloro-3-(3′-chlorobutyl)indolin-2-one (**9e**)*

Starting from 275 mg (1.46 mmol) of alcohol **7e**, a yield of 310 mg (80%) of compound **9e** was obtained, as a 2:1 mixture of diastereomers (major diastereomer, **9ea**; minor diastereomer, **9eb**). IR (NaCl): 3257.8 (NH), 1731.5 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.72 (br s, 1H, NH); 7.32 (d, 1H, *J*=7.5 Hz, H-4); 7.21 (t, 1H, *J*=6.6 Hz, H-6); 7.07 (t, 1H, *J*=7.6 Hz, H-5); 6.84 (d, 1H, *J*=7.8 Hz, H-7); 3.95–3.78 (m, 1H, H-3′); 2.60–2.10 (m, 2H, H-1′); 1.75–1.55 (m, 2H, H-2′); 1.42 (d, 3H, *J*=6.5 Hz, H-4′, **9ea**); 1.38 (d, 3H, *J*=6.5 Hz, H-4′, **9eb**) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.8 (CO); 140.2 (C-7a); 130.8 (C-4); 130.0 (C-3a, **9ea**); 129.8 (C-3a, **9eb**); 124.9 (C-6); 124.0 (C-5, **9ea**); 123.9 (C-5, **9eb**); 111.4 (C-7); 65.4 (C-3, **9ea**); 65.2 (C-3, **9eb**); 58.2 (C-3′, **9eb**); 58.0 (C-3′, **9ea**); 36.9 (C-1′, **9eb**); 36.5 (C-1′, **9ea**); 35.1 (C-2′, **9eb**); 34.9 (C-2′, **9ea**); 25.7 (H-4′, **9eb**); 25.5 (H-4′, **9ea**) ppm. Anal. Calcd for $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43. Found: C, 55.55; H. 4.82; N, 5.12.

*4.5.6. 3-Cloro-3-(3′-chloropentyl)indolin-2-one (**9f**)*

Starting from 200 mg (0.98 mmol) of alcohol **7f**, a yield of 230 mg (87%) of compound **9f** was obtained, as a 2:1 mixture of diastereomers (major diastereomer, **9fa**; minor diastereomer, **9fb**). IR (NaCl): 3261.3 (NH), 1727.9 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 8.92 (s, 1H, NH, **9fa**); 8.85 (s, 1H, NH, **9fb**); 7.38 (d, 1H, *J*=7.4 Hz, H-4); 7.29 (t, 1H, *J*=7.7 Hz, H-6); 7.11 (t, 1H, *J*=7.5 Hz, H-5); 6.95 (d, 1H, *J*=7.7 Hz, H-7); 3.61–3.39 (m, 1H, H-3′); 2.58–2.40 (m, 2H, H-1′); 2.38–2.15 (m, 2H, H-2′); 1.55–1.15 (m, 4H, H-4′); 0.88 and 0.86 (2 t, 6H, *J*=7.4 Hz, H-5′) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 175.6 (CO, **9fa**); 175.0 (CO, **9fb**); 139.4 (C-7a, **9fb**); 139.2 (C-7a, **9fa**); 129.3 (C-4, **9fa**); 129.1 (C-4, **9fb**); 128.7 (C-3a, **9fa**); 128.5 (C-3a, **9fb**); 123.5 (C-6, **9fb**); 123.3 (C-6, **9fa**); 122.4 (C-5, **9fa**); 122.3 (C-5, **9fb**); 110.0 (C-7, **9fa**); 109.8 (C-7, **9fb**); 71.6 (C-3, **9fa**); 71.4 (C-3, **9fb**); 64.6 (C-3′, **9fa**); 64.5 (C-3′, **9fb**); 34.4 (C-1′, **9fa**); 34.2 (C-1′, **9fb**); 30.2 (C-2′, **9fa**); 30.0 (C-2′, **9fb**); 28.8 (C-4′, **9fa**); 28.7 (C-4′, **9fb**); 9.2 (C-5′, **9fb**); 8.9 (C-5′, **9fa**) ppm. Anal. Calcd for $C_{13}H_{15}Cl_2NO$: C, 57.37; H, 5.56; N, 5.15. Found: C, 57.13; H, 5.32; N, 4.97.

*4.5.7. 3-Chloro-3-(3′-chlorobutyl)-5-methoxyindolin-2-one (**9g**)*

Starting from 200 mg (0.91 mmol) of alcohol **7g**, a yield of 212 mg (81%) of compound **9g** was obtained, as a 3:1 diastereomer mixture (major diastereomer, **9ga**; minor diastereomer, **9gb**). IR (NaCl): 3296.0 (N–H), 1718.7 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 8.96 (s, 1H, NH, **9ga**); 8.90 (s, 1H, NH, **9gb**); 6.96 (d, 1H, *J*=2.4 Hz, H-4); 6.88 (d, 1H, *J*=8.5 Hz, H-6); 6.82 (dd, 1H, *J*=8.5 and 2.4 Hz, H-7); 4.05–3.85 (m, 1H, H-3′); 3.81 (s, 3H, $OCH_3$); 2.60–2.40 (m, 2H, H-1′); 2.40–2.20 (m, 2H, H-2′); 1.48 (d, 3H, *J*=6.5 Hz, $CH_3$ **9ga**); 1.46 (d, 3H, *J*=6.3 Hz, $CH_3$ **9gb**) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 177.1 (CO); 156.3 (C-5); 141.1 (C-7a); 134.1 (C-3a, **9gb**); 133.8 (C-3a, **9ga**); 115.7 (C-7, **9gb**); 115.5 (C-7, **9ga**); 111.8 (C-4, **9ga**); 111.5 (C-4, **9gb**); 111.3 (C-6); 68.0 (C-3); 58.2 (C-3′, **9gb**); 58.0 (C-3′, **9ga**); 56.2 ($OCH_3$); 36.9 (C-1′, **9gb**); 36.5 (C-1′, **9ga**); 35.1 (C-2′, **9gb**); 34.8 (C-2′, **9ga**); 25.7 ($CH_3$, **9gb**); 25.5 ($CH_3$, **9ga**) ppm. Anal. Calcd for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.25; N, 4.86. Found: C, 53.95; H, 5.12; N, 4.75.

*4.5.8. 3-Chloro-3-(4′-chlorobutyl)indolin-2-one (**9i**)*

Starting from 500 mg (2.65 mmol) of alcohol **7i**, a yield of 580 mg (85%) of compound **9i**, which is very sensitive to chromatography, was obtained. IR (NaCl): 3257.4 (NH), 1731.8 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 9.54 (s, 1H, NH); 7.37 (d, 1H, *J*=7.5 Hz, H-4); 7.29 (t, 1H, *J*=7.6 Hz, H-6); 7.14 (t, 1H, *J*=7.6 Hz, H-5); 6.99 (d, 1H, *J*=7.6 Hz, H-7); 3.45 (t, 2H, *J*=6.6 Hz, H-4′); 2.29 (t, 2H, *J*=6.6 Hz, H-1′); 1.85–1.55 (m, 2H, H-3′); 1.50–1.25 (m, 2H, H-2′) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 177.1 (CO); 140.4 (C-7a); 130.7 (C-4); 129.9 (C-3a); 124.8 (C-6); 123.9 (C-5); 111.4 (C-7); 65.6 (C-3); 44.7 (C-4′); 38.7 (C-1′); 32.5 (C-3′); 22.2 (C-2′) ppm. Anal. Calcd for $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43. Found: C, 55.45; H, 4.86; N, 5.34.

*4.5.9. 3-(2′-Hydroxyethyl)-1-methylindolin-2-one (**21**)*

To a solution of tryptophol (1.2 g, 7.4 mmol) in $CH_2Cl_2$ (20 ml) was added tetrabutylammonium bisulfate (223 mg, 0.67 mmol, 0.09 equiv). A 50% aqueous solution of KOH (1 ml) was added and the biphasic system was vigorously stirred for 5 min. Methyl iodide (0.55 ml, 1.26 g, 8.88 mmol) was added and vigorous stirring was maintained for 14 h. The reaction mixture was poured onto a saturated aqueous $NH_4Cl$ solution and the resulting mixture was extracted with $CH_2Cl_2$ (3×25 ml). The combined organic layers were dried ($Na_2SO_4$) and evaporated and the residue was chromatographed on silica gel, eluting with $CH_2Cl_2$, to yield 1.21 g (93%) of 1-methyltryptophol **20**, whose spectral data were identical to those found in the literature.[38]

To a solution of oxalyl chloride (0.38 ml, 4.28 mmol) in dry $CH_2Cl_2$ (10 ml), at −78 °C under an argon atmosphere, was added DMSO (0.42 ml, 6.0 mmol). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of 1-methyltryptophol (150 mg, 0.857 mmol) in dry $CH_2Cl_2$ (3 ml) was added dropwise via cannula, and the red solution was stirred for 10 min at −78 °C. Triethylamine (1.22 ml, 8.57 mmol) was then added and the solution was left to warm to room temperature for 20 min, while stirred. The reaction mixture was diluted with $CH_2Cl_2$ (20 ml) and washed with saturated aqueous $NH_4Cl$ (3×20 ml). The organic layer was dried ($Na_2SO_4$) and evaporated, and the residue was purified by chromatography on silica gel, eluting with $CH_2Cl_2$, to yield 109 mg (67%) of compound **21**, whose spectral data were identical to those found in the literature.[24]

*4.5.10. 3-(3′-Oxobutyl)indole-2-carbaldehyde (**25**)*

To a solution of oxalyl chloride (0.56 ml, 6.45 mmol) in dry $CH_2Cl_2$ (15 ml), at −78 °C under an argon atmosphere, was added DMSO (0.64 ml, 9.03 mmol). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of alcohol **7h** (262 mg, 1.29 mmol) in dry $CH_2Cl_2$ (3 ml) was added dropwise via cannula, and the red solution was stirred for 10 min at −78 °C.

Triethylamine (1.31 ml, 13 mmol) was then added and the solution was left to warm to room temperature for 20 min, while stirred. The reaction mixture was diluted with $CH_2Cl_2$ (20 ml) and washed with saturated aqueous $NH_4Cl$ (3×20 ml). The organic layer was dried ($Na_2SO_4$) and evaporated, and the residue was purified by chromatography on silica gel, eluting with a 10:1 petroleum ether–ethyl acetate to yield 88 mg (32%) of compound **25**. IR (NaCl): 3316.1 (NH), 1715.3 (C=O), 1651.5 (CHO) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 10.04 (s, 1H, CHO); 8.19 (br s, 1H, NH); 7.60 (d, 1H, $J$=7.2 Hz, H-4); 7.35–7.21 (m, 2H, H-6,7); 7.12–7.00 (m, 1H, H-5); 3.31 (t, 2H, $J$=7.3 Hz, H-1′); 2.85 (t, 2H, $J$=7.3 Hz, H-2′); 2.06 (s, 3H, H-4′) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 207.6 (C-3); 181.4 (CHO); 132.3 (C-7a); 127.9 (C-6); 127.7 (C-3a); 127.6 (C-2); 126.9 (C-3); 121.6 (C-5); 121.1 (C-4); 112.8 (C-7); 45.0 (C-2′); 30.6 (C-4′); 17.8 (C-1′) ppm. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.15; H, 5.72; N, 6.17.

### 4.6. Reaction of 3-(3-indolyl)propanoic acid and 4-(3-indolyl)butanoic acid derivatives with the Swern reagent. General procedures

*Method A*. To a solution of oxalyl chloride (5 equiv) in dry $CH_2Cl_2$ (10 ml), at −78 °C under an argon atmosphere, was added DMSO (7 equiv). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of the suitable acid in dry $CH_2Cl_2$ (3 ml) was added dropwise via cannula, and the red solution was stirred for 10 min at −78 °C. Triethylamine (10 equiv) was then added and the solution was left to warm to room temperature for 20 min, while stirred. The reaction mixture was diluted with $CH_2Cl_2$ (20 ml) and washed with saturated aqueous $NH_4Cl$ (3×20 ml). The organic layer was dried ($Na_2SO_4$) and evaporated, and the residue was purified by rapid chromatography on silica gel, eluting with petroleum ether–ethyl acetate mixtures.

*Method B*. Same procedure as in Method A, without the addition of triethylamine.

#### 4.6.1. Swern reaction of ***29a***

Starting from carboxylic acid **29a** (150 mg, 0.79 mmol), triethylamine (1.13 ml, 7.93 mmol, 10 equiv) and dimethylsulfoxide (0.1 ml) (method A), the following products were obtained: 70 mg (40%) of **30a**, 17 mg (11%) of **31a**, 47 mg (22%) of **32a** and 23 mg (10%) of **33a**.

When the reaction was performed in the absence of triethylamine (method B), starting from 150 mg (0.79 mmol) of **29a**, the products obtained were hydroxy acid **30a** (91 mg, 52%) and lactone **31a** (55 mg, 36%).

*4.6.1.1. 3-[3′-Hydroxy-2′-oxoindolin-3′-yl]propanoic acid (**30a**).* Spectral data were identical to those published in the literature.[30b]

*4.6.1.2. 3-[3′-Hydroxy-2′-oxoindolin-3′-yl]propanoic acid lactone (**31a**).* Spectral data were identical to those published in the literature.[30b]

*4.6.1.3. 2,2-Dichloro-3-[3′-hydroxy-2′-oxoindolin-3-yl]propanoic acid lactone (**32a**).* IR (NaCl): 1806.9, 1745.9 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 8.11 (s, 1H, NH); 7.55 (d, 1H, $J$=7.6 Hz, H-4); 7.31 (t, 1H, $J$=7.7 Hz, H-6); 7.06 (t, 1H, $J$=7.6 Hz, H-5); 6.88 (d, 1H, $J$=7.8 Hz, H-7); 3.60 (d, 1H, $J$=15.5 Hz, H-1′); 3.36 (d, 1H, $J$=15.6 Hz, H-1′) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 172.0 and 168.1 (2C=O); 141.7 (C-7a); 132.5 (C-4); 126.4 (C-3a); 125.5 (C-6); 124.4 (C-5); 111.5 (C-7); 80.4 (C-3); 75.8 (C-2′); 51.3 (C-1′) ppm. Anal. Calcd for $C_{11}H_7NO_3Cl_2$: C, 48.56; H, 2.59; N, 5.15. Found: C, 48.23; H, 2.23; N, 4.89.

*4.6.1.4. Methylthiomethyl 3-[3′-chloro-2′-oxoindolin-3′-yl]propionate (**33a**).* $^1H$ NMR ($CDCl_3$) $\delta$ 8.90 (s, 1H, NH); 7.35 (d, 1H, $J$=7.5 Hz, H-4′); 7.30 (t, 1H, $J$=7.6 Hz, H-6′); 7.12 (t, 1H, $J$=7.4 Hz, H-5′); 6.95 (d, 1H, $J$=7.4 Hz, H-7′); 5.07 (d, 1H, $J$=11.7 Hz, $CH_2S$); 5.03 (d, 1H, $J$=11.7 Hz, $CH_2S$); 2.70–2.35 (m, 4H, H-1,2); 2.19 (s, 3H, $SCH_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.6 and 176.0 (2C=O); 140.1 (C-7a′); 130.9 (C-4′); 129.5 (C-3a′); 124.9 (C-6′); 124.0 (C-5′); 111.2 (C-7′); 69.0 ($CH_2S$); 64.6 (C-3′); 34.2 (C-2); 29.6 (C-1); 15.8 ($SCH_3$) ppm. Anal. Calcd for $C_{13}H_{14}NO_3SCl$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.45; H, 4.45; N, 4.97.

#### 4.6.2. Swern reaction of ***29b***

Starting from carboxylic acid **29b** (200 mg, 0.98 mmol) and using Method A, the following products were isolated after chromatography eluting with petroleum ether–ethyl acetate (gradient from 10:1 to 4:1): 24 mg (11%) of **31b**, 70 mg (25%) of **32b** and 51 mg (17%) of **33b**.

*4.6.2.1. 3-[3′-Hydroxy-1′-methyl-2′-oxoindolin-3′-yl]propanoic acid lactone (**31b**).* Spectral data were identical to those published in the literature.[31b]

*4.6.2.2. 2,2-Dichloro-3-[3′-hydroxy-1′-methyl-2′-oxoindolin-3-yl]-propanoic acid lactone (**32b**).* IR (NaCl): 1794.8, 1734.7 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.57 (d, 1H, $J$=7.6 Hz, H-4′); 7.41 (t, 1H, $J$=7.8 Hz, H-6′); 7.09 (t, 1H, $J$=7.8 Hz, H-5′); 6.86 (d, 1H, $J$=7.8 Hz, H-7′); 3.56 (d, 1H, $J$=15.4 Hz, H-1); 3.34 (d, 1H, $J$=15.4 Hz, H-1); 3.17 (s, 3H, $NCH_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 172.0 (C=O); 168.0 (C=O); 144.4 (C-7a′); 132.5 (C-4′); 125.9 (C-3a′); 125.3 (C-6′); 124.3 (C-5′); 109.7 (C-7′); 80.3 (C-3′); 75.9 (C-2); 51.3 (C-1); 27.2 ($NCH_3$) ppm. Anal. Calcd for $C_{12}H_9Cl_2NO_3$: C, 50.38; H, 3.17; N, 4.90. Found: C, 50.63; H, 3.49; N, 4.64. MS ($m/z$): 285, 287 and 289 ($M^+$); 251 and 253 ($M^+$−Cl); 222 and 224; 206 and 208.

*4.6.2.3. Methylthiomethyl 3-[3′-chloro-1′-methyl-2′-oxoindolin-3′-yl]propionate (**33b**).* IR (NaCl): 3445.9 (OH), 1730.4 (C=O), 1613.3 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.33 (d, 1H, $J$=6.8 Hz, H-4′); 7.31 (t, 1H, $J$=6.8 Hz, H-6′); 7.07 (t, 1H, $J$=6.8 Hz, H-5′); 6.80 (d, 1H, $J$=7.7 Hz, H-7′); 5.03 (d, 1H, $J$=11.8 Hz, $CH_2S$); 4.95 (d, 1H, $J$=11.8 Hz, $CH_2S$); 3.18 (s, 3H, $NCH_3$); 2.58–2.32 (m, 4H, H-1,2); 2.14 (s, 3H, S–$CH_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.4 (C=O); 172.0 (C=O); 142.9 (C-7a′); 130.9 (C-4′); 129.2 (C-3a′); 124.6 (C-6′); 123.9 (C-5′); 109.2 (C-7′); 68.9 ($CH_2S$); 64.2 (C-3′); 34.3 (C-2); 27.1 (C-1); 27.1 ($NCH_3$); 15.8 ($SCH_3$) ppm. Anal. Calcd for $C_{14}H_{16}ClNO_3S$: C, 53.59; H, 5.14; N, 4.46; S, 11.48. Found: C, 53.25; H, 5.53; N, 4.79; S, 11.19.

#### 4.6.3. Swern reaction of ***29c***

Starting from 500 mg (2.46 mmol) of carboxylic acid **29c**, the following compounds were obtained: **30c** (250 mg, 43%) and **33c** (150 mg, 20%). When the reaction was performed in the absence of triethylamine (Method B), a yield of 50 mg (95%) of compound **30c** was obtained.

*4.6.3.1. 4-[3′-Hydroxy-2′-oxoindolin-3′-yl]butanoic acid (**30c**).* IR (NaCl): 3208.7 (NH, OH), 1731.6, 1713.9 (2C=O), 1694.0 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 9.63 (s, 1H, $CO_2H$); 8.24 (s, 1H, NH); 7.35 (d, 1H, $J$=7.9 Hz, H-4′); 7.25 (t, 1H, $J$=7.8 Hz, H-6′); 7.08 (t, 1H, $J$=7.8 Hz, H-5′); 6.95 (d, 1H, $J$=7.8 Hz, H-7′); 2.42–2.18 (m, 4H, H-1,3); 1.67–1.45 (m, 2H, H-2) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 178.2 (C=O); 177.4 (C=O); 140.3 (C-7a′); 129.8 (C-4′); 129.0 (C-3a′); 124.8 (C-6′); 124.0 (C-5′); 111.5 (C-7′); 65.5 (C-3′); 38.6 (C-1); 33.8 (C-3); 20.0 (C-2) ppm. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.98; H, 5.31; N, 5.58.

*4.6.3.2. Methylthiomethyl 4-[3′-chloro-1′-methyl-2′-oxoindolin-3′-yl]butanoate (**33c**).* IR (NaCl): 3215.1 (NH), 1731.8, 1715.0 (C=O), 1694.1, 1682.1 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 9.46 (s, 1H, NH); 7.34 (d, 1H, $J$=7.7 Hz, H-4′); 7.28 (t, 1H, $J$=7.7 Hz, H-6′); 7.08 (t, 1H, $J$=7.7 Hz,

H-5′); 6.93 (d, 1H, *J*=7.7 Hz, H-7′); 5.05 (s, 2H, $CH_2S$); 2.42–2.18 (m, 4H, H-1,3); 2.19 (s, 3H, $SCH_3$); 1.68–1.45 (m, 2H, H-2) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.9 (C=O); 172.8 (C=O); 140.4 (C-7a′); 130.7 (C-4′); 129.8 (C-3a′); 124.9 (C-6′); 123.9 (C-5′); 111.4 (C-7′); 68.7 (C-3′); 65.4 ($CH_2S$); 38.6 (C-3); 33.9 (C-1); 20.1 (C-2); 15.8 ($SCH_3$) ppm. Anal. Calcd for $C_{14}H_{16}NO_3ClS$: C, 53.59; H, 5.14; N, 4.46. Found: C, 53.32; H, 4.92; N, 4.22.

### 4.7. Lactonization on hydroxy acids 30

#### 4.7.1. Lactonization of ***30a***

To a solution of the hydroxy acid **30a** (70 mg, 0.32 mmol) in $CHCl_3$ (1 ml) was added 96% $H_2SO_4$ (one drop). The solution was stirred at room temperature for 8 h. After addition of solid $NaHCO_3$ (200 mg), the solution was filtered and evaporated, yielding 64 mg (100%) of lactone **31a**.

#### 4.7.2. Lactonization of ***30c***

To a solution of the hydroxy acid **30c** (275 mg, 1.1 mmol) in $CHCl_3$ (1 ml) was added 96% $H_2SO_4$ (one drop). The solution was stirred at room temperature for 24 h and the precipitated solid was filtered, giving 240 mg (100%) of 4-[3′-hydroxy-2′-oxoindolin-3′-yl]butanoic acid lactone (**31c**). Mp 132–133 °C ($CHCl_3$); lit.[31a] 134–135 °C (ethyl acetate–hexane). IR (NaCl): 3255.9 (NH), 1723.5 (C=O), 1619.0 $cm^{-1}$. $^1H$ NMR (acetone-$d_6$, 250 MHz) $\delta$ 9.81 (s, 1H, NH); 7.50 (d, 1H, *J*=7.6 Hz, H-4′); 7.30 (t, 1H, *J*=7.7 Hz, H-6′); 7.05 (t, 1H, *J*=7.7 Hz, H-5′); 6.95 (t, 1H, *J*=7.7 Hz, H-7′); 2.50–2.25 (m, 4H, H-1,3); 1.60–1.30 (m, 2H, H-2) ppm. $^{13}C$ NMR (acetone-$d_6$) $\delta$ 174.7 (C=O); 173.7 (C=O); 141.6 (C-7a′); 130.7 (C-4′); 129.9 (C-3a′); 124.9 (C-6′); 123.1 (C-5′); 110.8 (C-7′); 65.7 (C-3′); 38.4 (C-3); 33.1 (C-1); 20.3 (C-2) ppm. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.02; H, 4.82; N, 6.21.

### 4.8. Subsequent transformations of 3,4-difunctionalized oxindoles

#### 4.8.1. 3-[4′-(tert-Butyldimethylsilyloxymethyl)-1′-methylindol-3′-yl]propanoic acid (***37***)

To a solution of compound **36** (400 mg, 0.80 mmol) in 5% methanolic KOH (7 ml) was added water (three drops) and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and the residue was dissolved in water (10 ml), which was acidified with 1 M aqueous HCl to pH 1–2 and extracted with ethyl acetate (3×20 ml). The combined organic layers were dried ($Na_2SO_4$) and evaporated, affording compound **37** as a white solid (292 mg, 77%). IR (NaCl): 3500–2700 ($CO_2H$), 1708.5 ($CO_2H$), 1111.9 (Si–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.83–7.72 (m, 4H, H-2″,6″); 7.44–7.31 (m, 6H, H-3″,4″,5″); 7.25–7.12 (m, 3H, H-5′,6′,7′); 6.85 (s, 1H, H-2′); 5.15 (s, 2H, $TBDPSOCH_2$); 3.73 (s, 3H, $NCH_3$); 3.20 (t, 2H, *J*=7.5 Hz, H-3); 2.64 (t, 2H, *J*=7.5 Hz, H-2); 1.11 (s, 9H, $C(CH_3)_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 179.7 ($CO_2H$); 137.9 (C-7a′); 136.1 (C-2″,6″); 135.2 (C-4′); 134.0 (C-1″); 130.1 (C-4″); 128.1 (C-3″,5″); 127.0 (C-2′); 125.0 (C-3a′); 121.8 (C-5′); 118.5 (C-6′); 113.9 (C-3′); 109.1 (C-7′); 65.0 ($TBDPSOCH_2$); 35.8 (C-2); 33.18 ($NCH_3$); 27.3 ($C(CH_3)_3$); 22.2 (C-3); 19.7 ($C(CH_3)_3$) ppm. Anal. Calcd for $C_{29}H_{33}NO_3Si$: C, 73.85; H, 7.05; N, 2.97. Found: C, 73.68; H, 7.21; N, 3.08.

#### 4.8.2. 3-[4′-(tert-Butyldimethylsilyloxymethyl)-3′-hydroxy-1′-methyl-2′-oxoindolin-3′-yl]propanoic acid (***38***)

To a solution of oxalyl chloride (0.51 ml, 5.85 mmol) in dry $CH_2Cl_2$ (4 ml), at −78 °C under an argon atmosphere was added DMSO (0.58 ml, 8.19 mmol). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of acid **37** (500 mg, 1.17 mmol) in dry $CH_2Cl_2$ (3 ml) was added dropwise via cannula, and the red solution was stirred for 20 min at −78 °C and left to warm to room temperature for 45 min, while stirred. The reaction mixture was diluted with $CH_2Cl_2$ (20 ml) and washed with saturated aqueous $NH_4Cl$ (3×20 ml). The organic layer was dried ($Na_2SO_4$) and evaporated, and the reddish oily residue (682 mg, 80%) was identified as hydroxy acid **38**. IR (NaCl): 3500 (broad signal, OH), 1731.6 (C=O), 1112.6 (Si–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.82–7.66 (m, 4H, H-2″,6″); 7.48–7.33 (m, 8H, H-5′,6′,3″,4″,5″); 6.83–6.76 (m, 1H, H-7′); 4.95 (m, 2H, *J*=12.5 Hz, $TBDPSOCH_2$); 3.22 (s, 3H, $NCH_3$); 2.58 (t, 2H, *J*=7.5 Hz, H-3); 2.44 (t, 2H, *J*=7.5 Hz, H-2); 1.25 (s, 1H, OH); 1.09 (s, 9H, $C(CH_3)_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.7 (C-2′); 172.0 ($CO_2H$); 141.4 (C-7a′); 138.0 (C-4′); 134.6 and 134.5 (C-2″,6″); 133.8 (C-1″); 129.6 (C-6′); 128.9 (C-4″); 126.8 (C-3″,5″); 122.4 (C-3a′); 121.3 (C-5′); 106.6 (C-7′); 63.1 (C-3′); 59.9 ($TBDPSOCH_2$); 32.0 (C-2); 27.9 (C-3); 25.5 ($C(CH_3)_3$); 25.4 ($NCH_3$); 14.1 ($C(CH_3)_3$) ppm. Anal. Calcd for $C_{29}H_{33}NO_5Si$: C, 69.16; H, 6.60; N, 2.78. Found: C, 68.81; H, 6.46; N, 2.59.

#### 4.8.3. 3-[4′-(tert-Butyldimethylsilyloxymethyl)-3′-hydroxy-1′-methyl-2′-oxoindolin-3′-yl]propanoic acid lactone (***39***)

The neat hydroxy acid **38** (50 mg, 0.1 mmol) was heated at 110 °C and 0.1 Torr for 8 h, affording lactone **39** as a pale brown syrup (44 mg, 91%). IR (NaCl): 1790.0 (C=O), 1731.7 (C=O), 1690.4 (C=O), 1160.4 (C–O), 1111.9 (Si–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.77–7.58 (m, 4H, H-2″,6″); 7.47–7.37 (m, 7H, H-6′,3″,4″,5″); 7.23 (d, 1H, *J*=7.5 Hz, H-5′); 6.79 (d, 1H, *J*=7.5 Hz, H-7′); 4.89–4.56 (m, 2H, $TBDPSOCH_2$); 3.18 (s, 3H, $NCH_3$); 3.12–2.96 (m, 1H); 2.81–2.71 (m, 1H); 2.56–2.31 (m, 2H) (H-2,3); 1.08 (s, 9H, $C(CH_3)_3$) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.3 (C=O); 175.0 (C=O); 144.0 (C-7a′); 139.1 (C-4′); 136.0 and 135.9 (C-2″,6″); 133.3 and 133.0 (C-1″); 131.5 (C-6′); 130.4 (C-4″); 128.4 and 128.3 (C-3″,5″); 123.6 (C-5′); 123.0 (C-3a′); 108.3 (C-7′); 83.2 (C-3′); 61.9 ($TBDPSOCH_2$); 30.0 (C-2); 27.9 (C-3); 27.2 ($C(CH_3)_3$); 26.9 ($NCH_3$); 19.7 ($C(CH_3)_3$) ppm. Anal. Calcd for $C_{29}H_{31}NO_4Si$: C, 71.72; H, 6.43; N, 2.88. Found: C, 71.36; H, 6.28; N, 2.78.

#### 4.8.4. Removal of silicon protection from spirolactone (***39***)

To a solution of spirolactone **39** (1.628 g, 3.35 mmol) in dry $CH_2Cl_2$ (20 ml) was added a 1 M solution of tetrabutylammonium fluoride in THF (12 ml, 12 mmol). The solution was stirred at room temperature for 16 h, poured onto pH 7 aqueous buffer (65 ml) and extracted with $CH_2Cl_2$ (3×30 ml). The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated, and the residue was chromatographed on silica gel, eluting with 1:2 ethyl acetate–petroleum ether (1:2), followed by ethyl acetate–methanol (9:1) and methanol, affording 215 mg (26%) of 3-[3′-hydroxy-4′-hydroxymethyl-1′-methyl-2′-oxoindolin-3′-yl]propanoic acid lactone (**40**) as a white solid. The aqueous layer from the first extraction was acidified with 2 M aqueous HCl and submitted to continuous extraction with ethyl acetate over 24 h. The ethyl acetate was dried over anhydrous $Na_2SO_4$ and evaporated, affording 778 mg (47%) of the tetrabutylammonium salt of compound **38**. Characterization data for **40**: mp 60 °C. IR (NaCl): 3415.2 (OH), 1788.1 ($C_1$=O), 1726.9 ($C_{2'}$=O), 1163.5 (C–O), 1051.6 (Si–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.40 (t, 1H, *J*=7.5 Hz, H-6′); 7.15 (d, 1H, *J*=7.5 Hz, H-5′); 6.82 (d, 1H, *J*=7.5 Hz, H-7′); 4.78–4.66 (m, 2H, $CH_2OH$); 3.20 (s, 3H, $NCH_3$); 3.22–3.14 (m, 1H); 2.82–2.70 (m, 2H); 2.69–2.48 (m, 1H) (H-2,3); 1.26 (t, 1H, *J*=7.5 Hz, OH) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.5 (C-2′); 144.6 (C-7a′); 139.1 (C-4′); 131.7 (C-6′); 124.3 (C-3a′); 123.7 (C-5′); 108.8 (C-7′); 83.4 (C-3′); 62.1 ($CH_2OH$); 30.6 (C-2); 28.3 (C-3); 26.9 ($NCH_3$) ppm. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.94; H, 5.45; N, 5.38.

#### 4.8.5. 3-[3′-Hydroxy-4′-iodomethyl-1′-methyl-2′-oxoindolin-3′-yl]propanoic acid lactone (***41***)

To a solution of spirolactone **39** (34 mg, 0.07 mmol) and sodium iodide (74 mg, 0.49 mmol) in dry acetonitrile (1 ml),

at −78 °C and under an argon atmosphere, was added trimethylsilyl chloride (24 μl, 0.19 mmol). The reaction was left to warm to room temperature and the reaction mixture was stirred for 7 h at this temperature. The reaction was then poured 10% aqueous sodium thiosulfate and extracted with diethyl ether (3×10 ml), and then with $CH_2Cl_2$ (3×10 ml). The combined ether layers were dried over anhydrous $Na_2SO_4$ and evaporated, affording 8 mg (48%) of alcohol **40**. Similarly, evaporation of the $CH_2Cl_2$ extracts afforded 11 mg (46%) of iodide **41**, as a yellow solid with the following characterization data: mp 143 °C. IR (NaCl): 1790.3 ($C_1$=O), 1727.2 ($C_{2'}$=O), 1159.8 (C–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.27 (t, 1H, $J$=7.9 Hz, H-6′); 7.02 (d, 1H, $J$=7.9 Hz, H-5′); 6.67 (d, 1H, $J$=7.8 Hz, H-7′); 4.47 (d, 1H, $J$=10.2 Hz, $CH_2I$); 4.30 (d, 1H, $J$=10.2 Hz, $CH_2I$); 3.20–3.13 (m, 1H); 3.08 (s, 3H, $NCH_3$); 2.99–2.86 (m, 1H); 2.80–2.73 (m, 1H); 2.49–2.40 (m, 1H) (H-2,3) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 177.2 (C-1); 175.6 (C-2′); 143.4 (C-7a′); 139.0 (C-4′); 132.9 (C-6′); 127.3 (C-5′); 124.2 (C-3a′); 109.7 (C-7′); 84.1 (C-3′); 29.6 (C-2); 28.9 (C-3); 27.8 ($NCH_3$); 0.00 ($CH_2I$) ppm. Anal. Calcd for $C_{13}H_{12}INO_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 43.40; H, 3.73; N, 3.61.

#### 4.8.6. 3-[3′-Hydroxy-1′-methyl-4′-nitromethyl-2′-oxoindolin-3′-yl]propanoic acid lactone (**42**)

A mixture of sodium nitrite (48 mg, 0.69 mmol) and urea (53 mg, 0.88 mmol), pre-dried in an oven at 90 °C for 24 h, was dissolved in dry dimethylformamide (4 ml), which required a slight heating. To this solution, cooled to −38 °C, was dropwise added a solution of iodide **41** (142 mg, 0.40 mmol) in dry dimethylformamide (3 ml). The reaction mixture was stirred at −20 °C for 2 h, poured on water (10 ml) and with ethyl acetate (3×10 ml). The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated. The residue was chromatographed on silica gel, eluting with a 8:1 petroleum ether–ethyl acetate mixture, affording 56 mg (60%) of nitro compound **42** and 19 mg (18%) of alcohol **40**, both as pale yellow oils. Characterization data for **42**: IR (NaCl): 1791.3 ($C_1$=O), 1726.8 ($C_{2'}$=O), 1557.5 and 1373.1 ($NO_2$), 1159.8 (C–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.50 (t, 1H, $J$=7.5 Hz, H-6′); 7.23 (d, 1H, $J$=7.5 Hz, H-5′); 6.95 (d, 1H, $J$=7.5 Hz, H-7′); 5.57 (d, 1H, $J$=12.5 Hz, $CH_2NO_2$); 5.45 (d, 1H, $J$=12.5 Hz, $CH_2NO_2$); 3.30–3.22 (m, 1H); 3.22 (s, 3H, $NCH_3$); 2.86–2.58 (m, 3H) (H-2,3) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.0 (C-1); 174.6 (C-2′); 144.9 (C-7a′); 132.3 (C-6′); 127.7 (C-4′); 126.3 (C-5′); 125.7 (C-3a′); 110.9 (C-7′); 82.8 (C-3′); 75.5 ($CH_2NO_2$); 31.7 (C-2); 27.7 (C-3); 27.0 ($NCH_3$) ppm. Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.23; H, 4.02; N, 9.87.

#### 4.8.7. 3-(3′-Hydroxy-1′-methyl-4′-nitromethyl-2′-oxoindolin-3′-yl)-N-methyl-N-methoxypropanamide (**43**)

To a stirred suspension of *N*-methoxy-*N*-methylamine hydrochloride (25 mg, 0.26 mmol) in dry $CH_2Cl_2$ (8 ml), at 0 °C and under an argon atmosphere, was added a 1 M dimethylaluminium chloride solution in hexanes (260 μl, 0.26 mmol). The reaction mixture left to warm to room temperature over 1 h, while stirred. A solution of nitro lactone **42** (24 mg, 0.087 mmol) in dry $CH_2Cl_2$ (4 ml) was added and stirring at 0 °C was maintained for 4 h. The reaction mixture was then poured onto pH 8 aqueous buffer (0.78 ml, 0.26 mmol) and was filtered through Celite, which was washed with $CHCl_3$. The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated, yielding 21 mg (75%) of Weinreb amide **43**, as a pale yellow oil. IR (NaCl): 1731.6 (C=O), 1557.2 and 1373.5 ($NO_2$), 1260.3 (C–O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.37 (t, 1H, $J$=7.5 Hz, H-6′); 7.12 (d, 1H, $J$=7.5 Hz, H-5′); 6.87 (d, 1H, $J$=7.5 Hz, H-7′); 6.01 (d, 1H, $J$=12.5 Hz, $CH_2NO_2$); 5.61 (d, 1H, $J$=12.5 Hz, $CH_2NO_2$); 3.69 (s, 3H, $NOCH_3$); 3.21 (s, 3H, $NCH_3$); 3.19 (s, 3H, $NCH_3$); 3.10–2.95 (m, 1H); 2.50–2.40 (m, 1H); 2.10–1.95 (m, 2H) (H-2,3) ppm. $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.5 (C-1); 173.6 (C-2′); 134.7 (C-7a′); 129.0 (C-6′); 126.0 (C-4′); 124.5 (C-5′); 124.5 (C-3a′); 108.6 (C-7′); 74.9 ($CH_2NO_2$); 60.2 (C-3′); 33.2 (C-3); 28.9 (C-2); 29.3 ($NOCH_3$); 25.3 ($2NCH_3$) ppm.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.12.029.

## References and notes

1. For a review of the Swern oxidation, see: Tidwell, T. T. *Synthesis* **1990**, 857.
2. Bailey, P. D.; Cochrane, P. J.; Irvine, F.; Morgan, K. M.; Pearson, D. P. J.; Veal, K. T. *Tetrahedron Lett.* **1999**, *40*, 4593.
3. For a preliminary communication dealing with the synthesis of compounds **9a**–**h**, see: López-Alvarado, P.; Steinhoff, J.; Miranda, S.; Avendaño, C.; Menéndez, J. C. *Synlett* **2007**, 2792.
4. For representative examples, see: (a) Szabo-Pusztay, K.; Szabo, L. *Synthesis* **1979**, 276; (b) Underwood, R.; Prasad, K.; Repic, O.; Hardtmann, G. *Synth. Commun.* **1992**, *22*, 343; (c) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323. For a review of the synthesis of 2-oxindoles, see: (d) Karp, G. M. *Org. Prep. Proced. Int.* **1993**, *25*, 481.
5. For early surveys of oxindole alkaloids, see: (a) Cordell, G. A. *An Introduction to Alkaloids: A Biogenetic Approach*; Wiley-Interscience: New York, NY, 1981; (b) Bindra, J. S. In *Oxindole Alkaloids*; Manske, R. H. F., Ed.; The Alkaloids-Chemistry and Physiology; Academic: New York, NY, 1973; Vol. 14, p 83.
6. Abourriche, A.; Abboud, Y.; Maoufoud, S.; Mohou, H.; Seffaj, T.; Charrouf, M.; Chaib, N.; Benamara, A.; Bontemps, N.; Francisco, C. *Farmaco* **2003**, *58*, 1351.
7. (a) Isolation: Cui, C. B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527; (b) Structure: Cui, C.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651; (c) Cytotoxic activity: Edmondson, S. E.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147.
8. Tsuda, M.; Mugishima, T.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Shiro, M.; Hirai, M.; Ohizumie, Y.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 3227.
9. (a) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241; (b) Zhang, X.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288.
10. For reviews of the chemistry of the welwitindolinones, see: (a) Avendaño, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65; (b) Menéndez, J. C. In *Bioactive Heterocycles V*; Khan, M. T. H., Ed.; Topics in Heterocyclic Chemistry; Springer: Berlin, Heidelberg, 2007; Vol. 11, p 63.
11. Tokunaga, T.; Hume, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789.
12. Zaveri, N. T.; Jiang, F.; Olsen, C. M.; Deschamps, J. R.; Parrish, D.; Polgar, W.; Toll, L. *J. Med. Chem.* **2004**, *47*, 2973.
13. Alcaraz, M.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowa, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.* **2005**, *9*, 555.
14. Kikuchi, C.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2549.
15. Gallagher, G.; Lavanchi, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533.
16. Miranda, S.; Avendaño, C.; Menéndez, J. C. *Open Org. Chem. J.* **2007**, *1*, 1.
17. Some compounds **7** have been described in the literature: (a) Compound **7e**: Novikov, A. V.; Sabahi, A.; Nyong, A. M.; Rainier, J. D. *Tetrahedron: Asymmetry* **2003**, *14*, 911; (b) Compound **7g**: Francis, P.; Smith, I.; Finnie, M. D. A. *Biomed. Mass Spectrom.* **1980**, *7*, 294.
18. Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047.
19. Some compounds **8** have been described in the literature: (a) Compound **8c**: Harrington, P. E.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256; (b) Compound **8e**: Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A. *J. Org. Chem.* **2003**, *68*, 4594; (c) Compound **8f**: Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484; (d) Compound **8h**: Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165.
20. Wuest, F. R.; Kniess, T. *J. Labelled Compd. Radiopharm.* **2005**, *48*, 31.
21. The *N*-demethyl analogue of compound **9a** has been previously obtained in 7% yield by treatment of the corresponding alcohol with NCS in $CH_2Cl_2$ followed by addition of aqueous $NH_4Cl$. See: (a) Hino, T.; Miura, H.; Nakagawa, T.; Murata, R.; Nakagawa, M. *Heterocycles* **1975**, *3*, 805; (b) Hino, T.; Miura, H.; Murata, R.; Nakagawa, M. *Chem. Pharm. Bull.* **1978**, *26*, 3695.
22. For selected reviews and monographs on multicomponent reactions, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Bienaymé, H.;

Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321; (c) Ugi, A. *Pure Appl. Chem.* **2001**, *73*, 187; (d) Ugi, A. *Molecules* **2003**, *8*, 53; (e) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (f) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133; (g) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (h) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; (i) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (j) For a symposium in print on this topic, see: Marek, I., Ed. *Tetrahedron* **2005**, *67*, 11299.

23. For a mechanistic proposal involving an intermediate related to **15**, see: Raina, S.; Singh, V. K. *Tetrahedron* **1995**, *51*, 2467.
24. Nozoye, T.; Shibanuma, Y.; Nakai, T.; Hatori, H. *Chem. Pharm. Bull.* **1988**, *36*, 4980.
25. McComas, C. C.; Perales, J. B.; Van Vranken, D. L. *Org. Lett.* **2002**, *3*, 2337.
26. See, for instance: (a) Lawson, W. B.; Patchornik, A.; Witkop, B. *J. Am. Chem. Soc.* **1960**, *82*, 5918; (b) Kornet, M. J.; Thio, A. P.; Thornstenson, J. H. *J. Pharm. Sci.* **1977**, *66*, 1022.
27. Stöhrer, G. *J. Heterocycl. Chem.* **1976**, *13*, 157.
28. (a) Ohnuma, T.; Kasuya, H.; Kimura, Y.; Ban, Y. *Heterocycles* **1982**, *17*, 377; (b) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969. However data for **31a** are not reported in these references.
29. Büchi, G.; DeShong, P. R.; Katsumura, S.; Sagimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084.
30. (a) Palla, G.; Marchelli, R.; Casnati, G.; Dossena, A. *Gazz. Chim. Ital.* **1982**, *112*, 535; (b) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637.
31. (a) For a synthesis of **31a** from the corresponding 3-bromooxindole-3-propionic acid, see: Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431. Compound **31a** has also been obtained in 54% yield by oxidative lactonization of **29a** in the presence of thallium trinitrate in the course of work aimed at the synthesis of tryptoquivaline G[30]; (b) For an alternative, experimentally more complex synthesis of **31b** involving a $Ru_3(CO)_{12}$-catalyzed intermolecular cyclocoupling of isatin, ethylene and carbon monoxide, see: Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663.
32. Compound **31c** has been previously obtained in two steps (31% overall yield) by oxidation of non-commercially available 1-hydroxy-1,2,3,4-tetrahydrocarbazole with iodine pentoxide ($I_2O_5$) to a lactol, followed by PCC oxidation. See: Yoshida, K.; Goto, J.; Ban, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4700.
33. Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, *55*, 4901.
34. (a) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247; (b) Olah, G. A.; Balaram Gupta, B. G.; Malhotra, R.; Narang, S. C. *J. Org. Chem.* **1980**, *45*, 1638.
35. Kornblum, N. *Org. React.* **1962**, *12*, 101.
36. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.
37. For some recent examples, see: (a) Brewer, M. *Tetrahedron Lett.* **2006**, *47*, 7731; (b) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789.
38. Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399.