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Syntheses of spiro[cyclopropane-1,3′-oxindole]-2-carboxylic acid and cyclopropa[*c*]quinoline-7b-carboxylic acid and their derivatives

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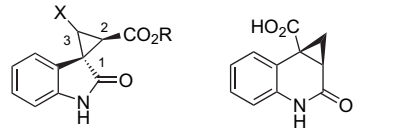
Abstract—The synthesis of spiro[cyclopropane-1,3′-oxindole]-2-carboxylic acid, including novel 3-(2- and 3-pyridyl)-substituted analogues and the novel cyclopropa[*c*]quinoline-7b-carboxylic acid and their ester and amide derivatives is described. These syntheses involve diastereoselective cyclopropanation reactions of methyl 2-(2-nitrophenyl)acrylate and (3*E*)-(pyridin-2-ylmethylene)- and (3*E*)-(pyridin-3-ylmethylene)-1,3-dihydro-2*H*-indol-2-one with ethyl (dimethyl sulfuranylidene) acetate (EDSA). The synthesis of methyl cyclopropa[*c*]-quinoline-7b-carboxylate involves a regioselective reductive cyclization of a nitro-diester precursor. The relative stereochemistry of key compounds has been determined by single-crystal X-ray structural analysis.

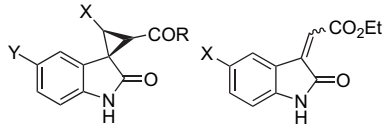
1. Introduction

3′-Spirocyclo-oxindoles, of synthetic or natural origin, have a range of biological activities.[1–3] As part of a medicinal chemistry project, we have been focusing on the synthesis of novel 3′-spirocyclo-oxindoles as scaffolds for new drug discovery. We recently reported the preparation of 3′-spiro-pentacyclo-oxindole derivatives using phosphine-catalyzed [3+2]-cycloaddition reactions.[4] As an extension of this project, we required the synthesis of 3′-spirocyclopropyl-oxindole-2-carboxylic acid **1**, and its 3-(2-pyridyl)- and 3-(3-pyridyl)-substituted analogues **2**, and the novel cyclopropa[*c*]quinoline-7b-carboxylic acid **3**.



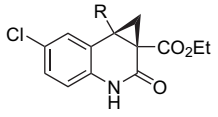
1, X = H, R = H
2, X = 2- or 3-pyridyl, R = Et

3



4; R = OH, O-alkyl or NHR;
X = H, Y = H or Br
5; R = OEt; X = Ph, Y = H
6; R = Ph; X = Ar; Y = H
7; R = Ph; X = H; Y = H

8



9; R = alkyl

During the course of this project He et al.[2a] reported that some ester and amide derivatives of 5′-bromo-3′-spirocyclopropyl-oxindole-2-carboxylic acid **4** (R=OH, Y=Br) were potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) on both wild-type and drug resistant mutant viruses. The ethyl ester of compound **4** (R=OEt, X=H, Y=Br) was prepared from 3-carboethoxymethylene derivative of 5-bromoisatin (**8**, X=Br) by treatment with diazomethane to generate the cyclopropanated product, via its diazo intermediate. Similar reactions have been utilized earlier to prepare the ethyl ester of **1** (R=Et),[5,6] and 2-substituted-3′-spirocyclopropyloxindole-2-carboxylic esters.[5] 3-Phenyl-3′-spirocyclopropyloxindole-2-carboxylic ester (**5**) and 3,3-diphenyl-3′-spirocyclopropyloxindole-2-carboxylic ester have also been prepared from **8** (X=H) using phenyldiazomethane[5] and diphenyldiazomethane,[6] respectively.[7] Indeed prior to the work disclosed here, no methods were available to prepare 3-aryl-3′-spirocyclopropyloxindole-2-carboxylic esters, including the desired 3-(2- and 3-pyridyl)-substituted

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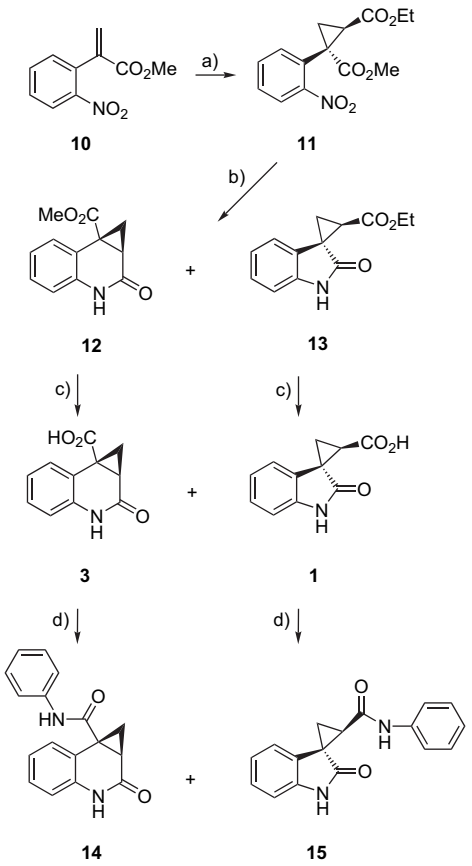
analogues **2** that did not employ potentially hazardous diazo compounds.[8] Earlier work by Croce et al.,[9] however, showed that the related phenyl ketone derivatives, **6** and **7**, could be prepared by the reaction of dimethylsulfonium phenacylide (Me_2S=CHC(O)Ph) with **8** (X=H) or 3-methylene-indoline-2-one, respectively. The former products were formed as a mixture (1.5–3.5:1) of diastereomers.

In 2006 He et al.,[10] disclosed that derivatives of ethyl cyclopropa[*c*]quinoline-1c-carboxylate **9**, closely related structures to our target molecule **3**, also had potent HIV antiviral activities as NNRTIs. We report here our own efforts for preparing 3′-spirocyclopropyloxindole derivatives related to **1** and a method for preparing, for the first time, 3-pyridyl-substituted analogues **2** using stabilized sulfur ylides. Furthermore, we report an efficient and highly diastereoselective synthesis of cyclopropa[*c*]quinoline-7b-carboxylic acid **3**, a new isomer of He's compound **9**, and its ester and benzamide derivatives.

2. Results and discussion

The synthesis of the corresponding esters of **1** and **3**, i.e., **13** and **12**, respectively (Scheme 1) could in principle be achieved by regioselective reductive cyclization reactions



Scheme 1. Reagents and conditions: (a) $Me_2SCH_2CO_2Et\cdot Br$ (2 equiv), DBU (1.5 equiv), anhydrous toluene, 20 h, 80%; (b) Zn dust (40 equiv), EtOH, H_2O, HCl, reflux, 3 h (12:1 of **12**/**13**), 70% (**12**), 5% (**13**) or H_2, Pd/C, 2 days (4:1 of **12**/**13**), 61% (**12**), 18% (**13**); (c) K_2CO_3, (2 equiv), MeOH/H_2O, sealed tube, 60 °C, 18 h, 50% (**3**), 80% (**1**); (d) aniline (1.6 equiv), HOBT (1 equiv), EDCI (1 equiv), anhydrous MeCN, rt, 3 days, 77% (**14**), 18% (**15**) (Compounds **1**, **2** and **11**–**15** are racemic).

of the nitro-diester **11**. Based on literature precedent of related but non-cyclopropanated nitro-diesters, cyclization should favour the formation of a quinoline ring system over an oxindole ring structure.[11] However, at the onset of this study, the effect of the cyclopropane moiety in **11** on the regioselectivity of such a reductive cyclization reaction was not certain. Nitro-diester **11** was prepared in 80% yield in a completely diastereoselective fashion by treatment of the acrylate **10**[4,12] with ethyl (dimethyl sulfuranylidene) acetate (EDSA, 1.5 equiv) in anhydrous toluene for 20 h at rt. Single X-ray crystallographic analysis of **11** showed that the two polar ester groups had a trans-stereochemical relationship (Fig. 1). This stereochemical outcome was expected based on literature precedent of related reactions.[14]

Reductive cyclization of **11** using zinc and HCl under refluxing conditions, led to the formation of the expected products, **12** and **13**. This reaction was highly regioselective (**12**/**13**=12:1) in favour of the formation of the quinoline **12** (70% isolated yield) over the indolone **13** (5% isolated yield). In contrast, catalytic hydrogenation of **11** using Pd/C and H_2 led to a less regioselective reaction providing a 4:1 mixture of **12** and **13**, in favour of the quinoline product **12** (61% isolated yield). The higher regioselectivity found in the former method may be due to Zn^{2+} activation of the less hindered ester carbonyl by coordination, leading to more of the quinoline product **12**. Compounds **12** and **13** were readily separated by column chromatography and their structures were established by single-crystal X-ray crystallographic analysis (Fig. 2).[13] The ^{1}H NMR spectral data of **13** at 300 MHz were similar to that reported in 1978 by Bennett et al.[5] for the same compound at 60 MHz. We thus assume that the same diastereomeric compound was produced from these two different synthetic routes. Furthermore, the ^{1}H NMR spectral data for the cyclopropane resonances of **13** matched very closely to that of the analogous *N*-methyl analogue of **13** that were recently reported.[7] Saponification of **12** and **13** gave the carboxylic acids, **3** (structure confirmed by X-ray structural analysis)[13] and **1**, respectively, which were converted to their respective amide derivatives **14** and **15**, under EDCI/HOBT coupling conditions with aniline.

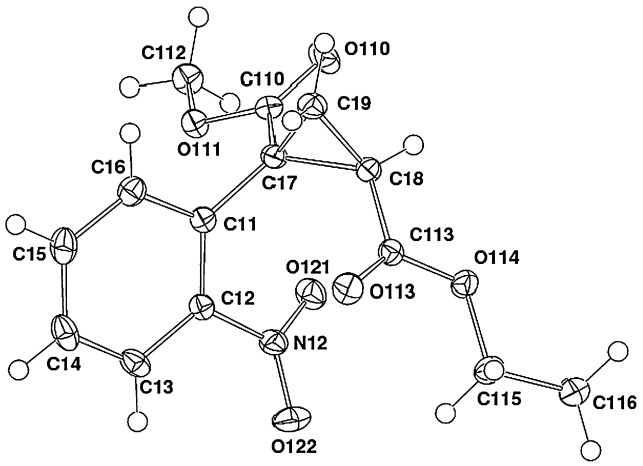


Figure 1. Molecular projection of **11**. This and subsequent figures depict 50% probability amplitude displacement envelopes for the non-hydrogen atoms and hydrogen atoms having arbitrary radii of 0.1 Å; crystallographic numbering is also shown.

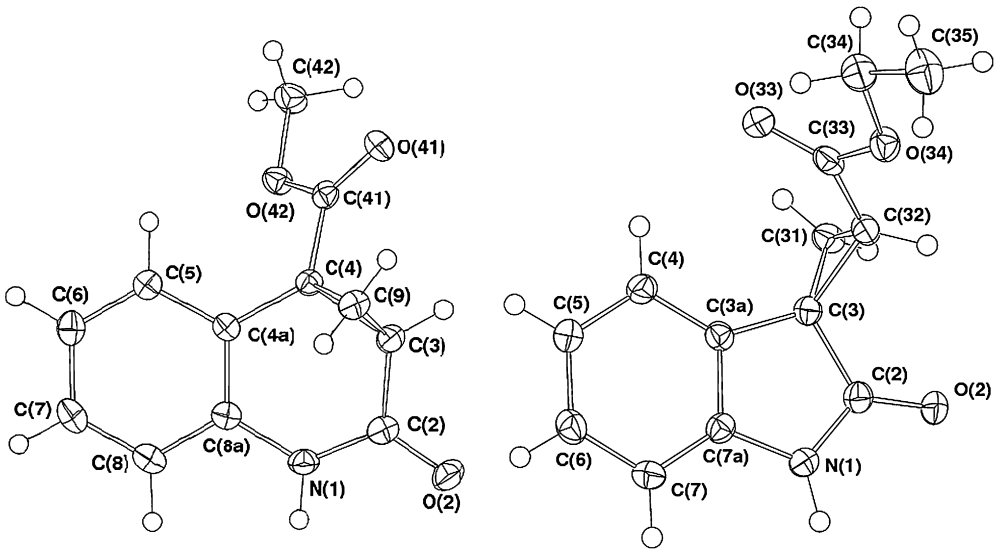
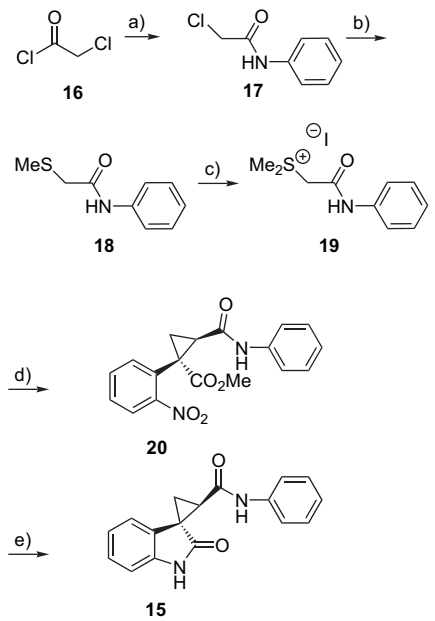


Figure 2. Molecular projection of **12** (left) and **13** (right).

A more direct method to synthesize the indolone amide **15**, involved cyclopropanation of the acrylate **10** with the amide-stabilized ylide derived from the sulfonium salt **19**, which was readily prepared in three synthetic steps from chloroacetyl chloride **16**, as outlined in Scheme 2. Although far less common than their ester-sulfonium analogues, amide-sulfonium salts like **19** have been previously used for the cyclopropanation reactions of electron deficient alkenes, however, normally as their tertiary amide derivatives.[15]



Scheme 2. Reagents and conditions: (a) aniline (1.1 equiv), pyridine (1.5 equiv), anhydrous CH_2Cl_2, 0 °C→rt, 1 h, 74%; (b) MeSNa (1.1 equiv), anhydrous MeOH, rt, 15 min, 98%; (c) MeI (10 equiv), anhydrous CH_2Cl_2, rt, 2 days, 52%; (d) **10**, **19** (1.5 equiv), DBU (1.1 equiv), anhydrous CH_2Cl_2, rt, 2 days, 39%; (e) Fe (8 equiv), AcOH, EtOH, sonication, 2 h, 60% (Compounds **15** and **20** are racemic).

The cyclopropanation reaction of the acrylate **10** and the amide-stabilized ylide generated in situ from the sulfonium salt **19** (1.5 equiv) with DBU (1.1 equiv) in anhydrous CH_2Cl_2 for 2 days at rt yielded solely the trans product **20** in 39% yield. The structure of **20** was unequivocally established by single-crystal X-ray structural analysis (Fig. 3).[13] The reductive cyclization of **20**, using the methods described in Scheme 1, however, was not productive. Previously, it was found that reduction of aromatic nitro compounds can proceed using iron with acetic acid under sonication.[16] This method successfully yielded the desired product **15** in a yield of 60%.

For the preparation of target molecules **2**, the α-methylene indolinones **21a** and **21b** were prepared according to the literature.[17] Their *E*-geometries were unequivocally established by single-crystal X-ray structural analysis (structures not shown).[13] The cyclopropanation reactions of either **21a** or **21b** with EDSA in anhydrous acetonitrile (compounds **21a**,**b** were not soluble in toluene) for 24 h at rt yielded a mixture of three diastereomeric cyclopropane products (Scheme 3). For the reaction using **21a**, ^{1}H NMR analysis of the crude reaction mixture revealed a 5.6:1.8:1 mixture of the diastereomeric products, **22a**, **23a** and **24a**, respectively. In contrast, the cyclopropanation reaction using **21b** proved to be a much more diastereoselective reaction giving a 43:7:1 mixture of the diastereomeric products, **22b**, **23b** and **24b**, respectively. Separation of these diastereomeric

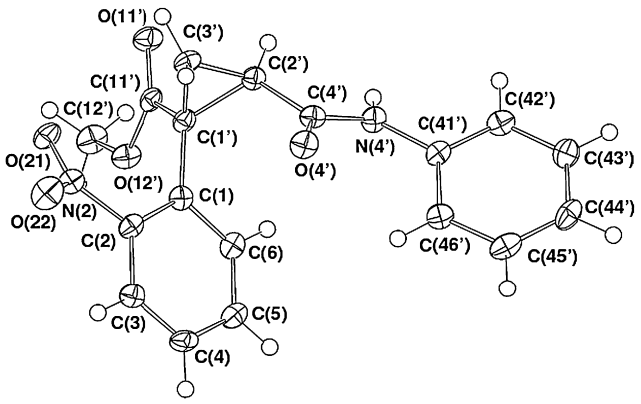
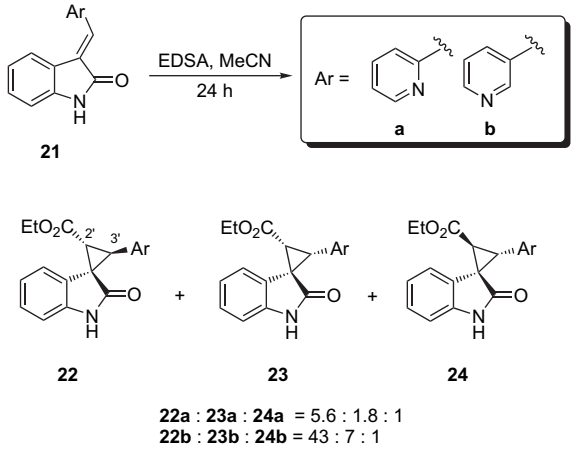


Figure 3. Molecular projection of **20**.

products by column chromatography proved to be difficult and only compounds **22a** and **24a** could be isolated as diastereomerically pure in yields of 27 and 12%, respectively. The remaining chromatographic fractions consisted of mixtures of all three isomers. In contrast, the major trans-isomer **22b** was readily isolated in diastereomerically pure form in 61% yield from **21b**. Diastereomerically pure samples of the other isomers, **23b** and **24b**, however, could not be obtained from the inseparable mixtures.



Scheme 3. All compounds are racemic.

The structure of **22b** was unequivocally established by single-crystal X-ray structural analysis (Fig. 4).[13] The assignment of the relative stereochemistries of the diastereomeric products produced in Scheme 3 is based on the coupling constants observed for the cyclopropane methines, CH-3′ and CH-2′. The chemical shifts and coupling constants for the major isomers of both reactions (**22a** and **22b**) and corresponding minor isomers according to prevalence ((**23a** and **23b**) and (**24a** and **24b**)) were almost identical, indicative of their same relative configurations. For the isomeric set **22a**–**24a**, the methine cyclopropane ^{1}H NMR resonances appeared as doublets for all diastereomers, with one methine of the major isomer **22a** having the most downfield signal (δ 3.93) and one at δ 3.46. For the isomer **23a** both cyclopropane methines had very similar chemical shifts and appeared almost like an ABq (δ 3.86 and 3.82). While one methine for the isomer **24a** had the most upfield signal (δ 3.08) and one at δ 3.57. The cyclopropane vicinal coupling constants for two of the products, **22a** and **24a**, were found to be the same, $^3J\sim$8 Hz. This was in contrast to isomer **23a**, which had a vicinal coupling constant of $^3J\sim$10 Hz. Since in cyclopropanes, cis-vicinal coupling constants ($^3J_{cis}$ 6–10 Hz) are usually larger than trans-vicinal coupling constants ($^3J_{trans}$ 3–6 Hz),[18] the diastereomers **22a** and **24a** were assigned as the trans-isomers and **23a** as the cis-isomer. While the synthesis of **5** was reported in 1978,[5] the relative stereochemistry of the 3-phenyl substituent was not defined. A comparison of the ^{1}H NMR data of **5** (δ 3.73, d, J 8 Hz; δ 3.20, d, J 8 Hz) with that of **22a** suggests that they have the same relative stereochemistries.

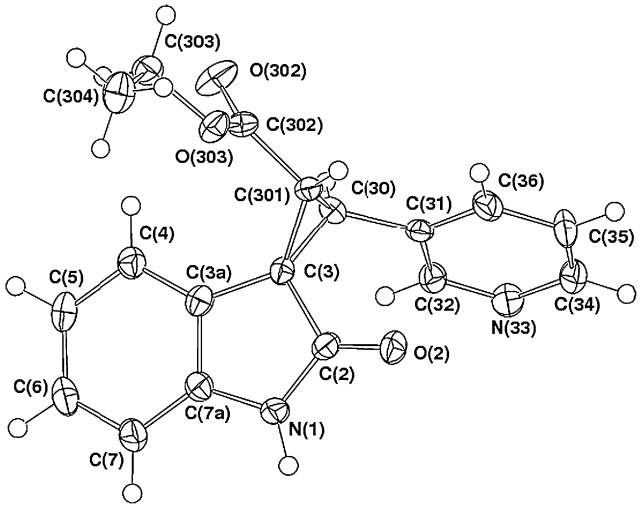
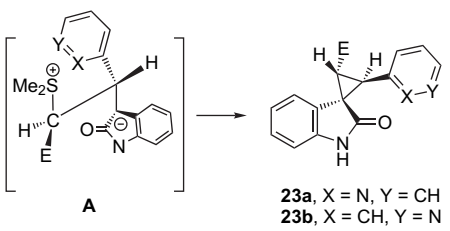


Figure 4. Molecular projection of **22b**.

Pedregal and Monn[14c] reported that the reaction of EDSA with acyclic enones in toluene gave the *trans*-cyclopropane isomers (ester and ketone groups are trans) as the exclusive products. The *cis*-cyclopropanated products were formed as minor isomers in more polar chloroform solution. In some cases a small amount (10%) of another trans-isomer was formed from epimerization of the minor cis-isomer under the basic reaction conditions. Based upon this report, we speculate that our minor trans-isomers **24a**,**b** may arise from epimerization of their respective cis-isomers **23a**,**b**. In this case, we assign the stereochemistry of **23a**,**b** as shown in Scheme 3. Unfortunately pure samples of **23a**,**b** could not be obtained to examine this possibility or to perform meaningful NOESY NMR experiments.

For cyclopropanation reactions of electron deficient alkenes (RCH=CHW) using EDSA, DeLuca and Curley[14b] have proposed a mechanism that involves equilibration of the initially formed *syn*-betaines ($Me_2S(+)$ and CH(−)W are *syn* due to electrostatic attraction) and then subsequent collapse of these betaines, via their corresponding *anti*-conformations, to the cyclopropanated products. Of the four possible racemic *anti*-betaine intermediates that could be involved in the cyclopropanation reactions of **21a/b**, conformation **A** (Scheme 4) would be expected to be favoured in terms of minimizing unfavourable steric and repulsive dipole–dipole interactions (between the ester group (E) and the oxindole carbonyl dipole).[14b,19] Indeed, this betaine would give rise to the major diastereomeric products **22a** and **22b**. The lower diastereoselectivity found in the cyclopropanation of **21a** compared to **22b**, may be a result of a more unfavourable dipole–dipole interaction in betaine **A** between the oxindole carbonyl group and the pyridine nitrogen atom, in the 2-pyridyl series (**A**, X=N, Y=CH) compared to the 3-pyridyl series (**A**, X=CH, Y=N). Such an interaction would destabilize **A** relative to other reactive *trans*-betaine conformations



Scheme 4.

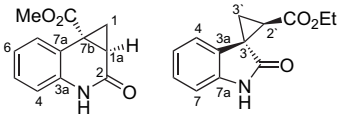
(for example, one in which oxindole carbonyl group is *anti* to the pyridine ring) leading to an erosion of product diastereoselectivity by increased formation of the cis-isomer **23a**.

In conclusion, the synthesis of spiro[cyclopropane-1,3′-oxindole]-2-carboxylic acid **1**, including novel 3-(2- and 3-pyridyl)-substituted analogues **22**–**24** and the novel cyclopropa[*c*]quinoline-7b-carboxylic acid **3** and the ester and amide derivatives of these acids has been achieved. These syntheses involve diastereoselective cyclopropanation reactions of methyl 2-(2-nitrophenyl)acrylate and (3*E*)-(pyridin-2-ylmethylene)- and (3*E*)-(pyridin-3-ylmethylene)-1,3-dihydro-2*H*-indol-2-one with ethyl (dimethyl sulfuranylidene) acetate (EDSA). The synthesis of methyl cyclopropa[*c*]quinoline-7b-carboxylate **12** involves the regioselective reductive cyclization of a nitro-diester precursor **11**. The relative stereochemistry of key compounds has been unequivocally determined by single-crystal X-ray structural analysis.

3. Experimental

3.1. General

Petrol refers to the fraction of petroleum spirit with a boiling point of 40–60 °C. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted. All spectra were referenced to $CDCl_3$ (^{1}H δ 7.26 ppm and ^{13}C NMR δ 77.00 ppm). ^{1}H NMR assignments were achieved with the aid of gCOSY, and in some cases with NOESY and TOCSY experiments. ^{13}C NMR assignments were based upon DEPT, gHSQC and gHMBC experiments. All solvents were dried over anhydrous magnesium sulfate, unless stated otherwise. The atom numbering for compounds **12** and **13** and their derivatives is as indicated below.



3.2. (1*R**,2*R**)-2-Ethyl-1-methyl-1-(2-nitrophenyl)-cyclopropane-1′,2′-dicarboxylate (11)

A solution of ethyl dimethylsulfonium acetate bromide (1.56 g, 6.8 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (0.76 mL, 5.1 mmol) in anhydrous toluene (30 mL) was stirred under an N_2 atmosphere at rt for 30 min. A solution of **10** (709.7 mg, 3.4 mmol) in anhydrous toluene (10 mL) was added and stirring was continued for 20 h. The reaction mixture was washed with 10% HCl solution (2×40 mL) and the aqueous washings were extracted with EtOAc (3×100 mL). The combined extracts were dried, filtered and evaporated under reduced pressure. The crude mixture was purified by column chromatography, elution with 10–25% EtOAc/petrol yielded **11** as a light-yellow semicrystalline oil, which crystallized upon standing (799.7 mg, 2.7 mmol, 80%, R_f=0.5 in 20% EtOAc/petrol), and recovered **10** (41.8 mg, 2×10^{-4} mol, 6%). MS (ESI+ve) *m*/*z* 294 (100%) [MH$^+$], 248 (43%) [M$^+$−OEt]. HRMS (ESI+ve) Calcd for $C_{14}H_{16}NO_6$ [MH$^+$]: 294.0978; found: 294.0981. ^{1}H NMR δ 8.06 (br d, *J* 6.6 Hz, 1H, ArC*H*-3), 7.62 (br d, *J* 7.5 Hz, 1H, ArC*H*), 7.51–7.46 (m, 2H, ArC*H* and ArC*H*-4), 3.92 (q, *J* 7.0 Hz, 2H, CH_2CH$_3$), 3.64 (s, 3H, OCH_3), 3.02 (br s, 1H, CH-2), 2.02–1.99 (m, 2H, CH_2-3), 1.08 (t, *J* 7.0 Hz, 3H, CH_3CH$_2$). ^{13}C NMR δ 171.3 (*C*O$_2$Me), 169.5 (*C*O$_2$Et), 149.2 (Ar*C*-1), 133.5 (Ar*C*H-5 and Ar*C*H-6), 131.0 (Ar*C*-2), 128.9 (Ar*C*H-4), 124.8 (Ar*C*H-3), 61.2 (*C*H$_2$CH$_3$), 53.0 (O*C*H$_3$), 36.1 (C-1′), 29.7 (*C*H-2), 22.1 (*C*H$_2$-3), 13.8 (CH$_2$*C*H$_3$). The structure of **11** was confirmed by X-ray crystallography (Fig. 1).

3.3. Methyl (1a*R**,7b*R**)-2-oxo-1,1a,2,3-tetrahydro-7b*H*-cyclopropa[*c*]quinoline-7b-carboxylate (12) and ethyl (1′*R**,2′*R**)-2-oxo-1,2-dihydrospiro-[cyclopropane-1′,3-indole]-2′-carboxylate (13)

The title compounds were prepared using two methods. *Method 1*: to a solution of **11** (493.8 mg, 1.68 mmol) in EtOH/H_2O (12.8 mL:3.2 mL) were added activated Zn dust (2.627 g, 40 mmol) and 8.9 M HCl (2.54 mL). The mixture was stirred and heated at reflux for 3 h. The mixture was filtered through a bed of Celite and washed with EtOH. ^{1}H NMR analysis of the crude reaction mixture revealed a 12:1 mixture of **12** and **13**, respectively. The crude product was purified by column chromatography using 20–50% EtOAc/petrol as eluent and then further purified using CH_2Cl_2/petrol/EtOAc (2:2:1) as eluent to yield **12**, as white needles (253.6 mg, 1.17 mmol, 70%), and **13**, as white needles (19.3 mg, 8.3×10^{-5} mol, 5%). *Method 2*: to a solution of **11** (167.6 mg, 5.7×10^{-4} mol) in EtOAc (8.6 mL) was added 10% Pd/C (33 mg). The system was flushed with H_2 gas and left to stir under a H_2 atmosphere (balloon) for 2 days. ^{1}H NMR analysis of the crude reaction mixture revealed a 4:1 mixture of **12** and **13**, respectively. The crude product was purified by column chromatography and then by PTLC using 30% EtOAc/petrol as eluent to yield **12** as white needles (76.1 mg, 3.5×10^{-4} mol, 61%, R_f=0.15 in 30% EtOAc/petrol, mp166–170 °C) and **13** as white needles (23.9 mg, 0.1 mmol, 18%, R_f=0.3 in 30% EtOAc/petrol, mp 136–138 °C (lit.[5] mp 154–156 °C).

Compound **12**: MS (EI) *m*/*z* 217 (55%) [M$^{\bullet+}$], 202 (58%) [M$^+$−Me], 158 (53%) [M$^+$−CO$_2$Me]. HRMS (EI) Calcd for $C_{12}H_{11}NO_3$ [M$^{\bullet+}$]: 217.0739; found: 217.0735. ^{1}H NMR δ 8.75 (br s, 1H, N*H*), 7.72 (dd, *J* 8.1, 1.2 Hz, 1H, ArC*H*-4), 7.20 (dt, *J* 7.8, 1.5 Hz, 1H, ArC*H*-6), 7.07 (dt, *J* 7.5, 1.5 Hz, 1H, ArC*H*-5), 6.81 (dd, *J* 8.1, 1.0 Hz, 1H, ArC*H*-7), 3.80 (s, 3H, CH_3), 2.58 (ddd, *J* 10.5, 5.1, 1.3 Hz, 1H, C*H*-1a), 2.43 (dd, *J* 4.2, 10.5 Hz, 1H, CH_AH$_B$-1), 1.03 (dd, *J* 5.7, 4.8 Hz, 1H, CH_BH$_A$-1). ^{13}C NMR δ 170.4 (*C*O$_2$Me), 167.2 (*C*-2), 134.3 (Ar*C*-7a), 129.8 (Ar*C*H-4), 127.8 (Ar*C*H-6), 123.0 (Ar*C*H-5), 119.2 (Ar*C*-3a), 115.7 (Ar*C*H-7), 52.7 (*C*H$_3$), 29.9 (*C*-7b), 28.6 (*C*H-1a), 17.9 (*C*H$_2$-1). The structure of **12** was confirmed by X-ray crystallography (see Fig. 2).

Compound **13**: MS (EI) *m*/*z* 231 (68%) [M$^{\bullet+}$], 186 (32%) [M$^+$−OEt]. HRMS (EI+ve) Calcd for $C_{13}H_{13}NO_3$ [M$^{\bullet+}$]: 231.0895; found: 231.0896. ^{1}H NMR (500 MHz) δ 9.26 (br s, 1H, N*H*), 7.34 (d, *J* 7.5 Hz, 1H, ArC*H*-4), 7.22 (dt,

J 7.5, 1.5 Hz, 1H, ArC*H*-6), 7.00 (dt, *J* 8.0, 1.0 Hz, 1H, ArC*H*-5), 6.98 (d, *J* 7.5 Hz, 1H, ArC*H*-7), 4.08–4.21 (m, 2H, CH_2CH$_3$), 2.72 (dd, *J* 8.5, 7.5 Hz, 1H, C*H*-2′), 2.17 (dd, *J* 7.5, 4.5 Hz, 1H, CH_ACH$_B$-3′), 2.03 (dd, *J* 8.5, 4.5 Hz, 1H, CH_BCH$_A$-3′), 1.21 (t, *J* 7.3 Hz, 3H, CH_3). ^{13}C NMR (125 MHz) δ 177.2 (*C*-2), 168.6 (*C*O$_2$Et), 141.5 (Ar*C*-7a), 127.7 (Ar*C*H-6), 126.2 (Ar*C*-3a), 122.9 (Ar*C*H-4), 122.2 (Ar*C*H-5), 110.0 (Ar*C*H-7), 61.3 (*C*H$_2$CH$_3$), 34.0 (*C*-3), 32.9 (*C*H-2′), 20.8 (*C*H$_2$-3′), 14.1 (*C*H$_3$). The structure of **13** was confirmed by X-ray crystallography (Fig. 2).

3.4. (1a*R**,7b*R**)-2-Oxo-1,1a,2,3-tetrahydro-7b*H*-cyclopropa[*c*]quinoline-7b-carboxylic acid (3)

To a solution of **12** (91.5 mg, 0.4 mmol) in MeOH (1.5 mL) contained within a sealed tube was added a solution of K_2CO_3 (109 mg, 0.8 mmol) in H_2O (1 mL). The tube was sealed and the mixture was left stirring at 60 °C for 18 h. The solvent was removed by evaporation in vacuo, and the residue was dissolved in H_2O (15 mL) and washed with Et_2O (15 mL). The aqueous solution was then acidified to ~pH 1 with 10% HCl and extracted with Et_2O (3×20 mL). The combined extracts were dried to yield **3** as a white powder (40.3 mg, 2.0×10^{-4} mol, 50%, R_f=0 in 30% EtOAc/petrol, mp 152–156 °C). MS (EI) *m*/*z* 203 (35%) [M$^{\bullet+}$], 159 (24%), 130 (30%), 111 (32%), 97 (45%), 71 (60%), 57 (97%), 43 (87%). HRMS (EI) Calcd for $C_{11}H_9NO_3$ [M$^{\bullet+}$]: 203.0582; found: 203.0580. ^{1}H NMR (CD_3OD) δ 7.77 (dd, *J* 7.8, 1.5 Hz, 1H, ArC*H*-4), 7.17 (dt, *J* 7.5, 1.2 Hz, 1H, ArC*H*-6), 7.03 (dt, *J* 7.5, 1.2 Hz, 1H, ArC*H*-5), 6.87 (dd, *J* 8.1, 0.9 Hz, 1H, ArC*H*-7), 2.46 (dd, *J* 10.5, 5.4 Hz, 1H, C*H*-1a), 2.36 (dd, *J* 10.5, 3.9 Hz, 1H, CH_ACH$_B$-1), 0.92 (dd, *J* 5.8, 4.0 Hz, 1H, CH_BCH$_A$-1). ^{13}C NMR (CD_3OD, 125 MHz) δ 173.3 (*C*O$_2$H), 169.6 (*C*-2), 136.2 (Ar*C*-7a), 131.0 (Ar*C*H-4), 128.6 (Ar*C*H-6), 123.7 (Ar*C*H-5), 121.1 (Ar*C*-3a), 116.8 (Ar*C*H-7), 30.8 (*C*-7b), 29.3 (*C*H-1a), 18.3 (*C*H$_2$-1). The structure of **3** was confirmed by X-ray crystallography.[13]

3.5. (1′*R**,2′*R**)-2-Oxo-1,2-dihydrospiro[cyclopropane-1′,3-indole]-2′-carboxylic acid (1)

The title compound was prepared using a similar method to that described above for the synthesis of **3** starting with **13** (38.2 mg, 0.16 mmol) to yield **1** as white needles (25.4 mg, 0.13 mmol, 80%, R_f=0 in 30% EtOAc/petrol, mp 142–145 °C). MS (EI) *m*/*z* 203 (29%) [M$^{\bullet+}$]. HRMS (EI) Calcd for $C_{11}H_9NO_3$ [M$^{\bullet+}$]: 203.0582; found: 203.0579. ^{1}H NMR (CD_3OD) δ 7.27 (dd, *J* 7.5, 1.0 Hz, 1H, ArC*H*-4), 7.21 (dt, *J* 7.5, 1.3 Hz, 1H, ArC*H*-6), 6.96 (d, *J* 7.5 Hz, 1H, ArC*H*-7), 6.95 (dt, *J* 7.5, 1.2 Hz, 1H, Ar*C*H-5), 2.48 (dd, *J* 8.5, 7.3 Hz, 1H, C*H*-2′), 2.00 (dd, *J* 7.2, 4.3 Hz, 1H, CH_ACH$_B$-3′), 1.82 (dd, *J* 8.4, 4.5 Hz, 1H, CH_BCH$_A$-3′). ^{13}C NMR (CD_3OD, 125 MHz) δ 178.7 (*C*O$_2$H), 171.2 (*C*-2), 143.5 (Ar*C*-7a), 128.8 (Ar*C*H-6), 127.6 (Ar*C*-3a), 123.6 (Ar*C*H-4), 123.0 (Ar*C*H-5), 111.0 (Ar*C*H-7), 34.7 (*C*-3), 33.9 (*C*H-2′), 21.0 (*C*H$_2$-3′).

3.6. (1a*R**,7b*R**)-2-Oxo-*N*-phenyl-1,1a,2,3-tetrahydro-7b*H*-cyclopropa[*c*]quinoline-7b-carboxamide (14)

To a solution of **3** (52.4 mg, 2.6×10^{-4} mol) and HOBT (34.9 mg, 2.6×10^{-4} mol) in anhydrous MeCN (3 mL) at 0 °C (ice-bath) was added aniline (0.04 mL, 4.1×10^{-4} mol). The solution was stirred for 10 min at 0 °C before the addition of EDCI (49.5 mg, 2.6×10^{-4} mol) and left to stir at rt for 2 h, then at 50 °C for 18 h and then again at rt for 3 days. The solvent was then removed, and the residue was diluted with CH_2Cl_2 (15 mL) and washed successively with 10 mL of 10% HCl, H_2O and brine. The organic extracts were then combined, dried and evaporated in vacuo. Purification of the crude product by column chromatography using 10% MeOH/$CHCl_3$ as the eluent yielded **14** as an amber coloured oil (56 mg, 2.0×10^{-4} mol, 77%, R_f=0.28 in 50% EtOAc/petrol). MS (EI) *m*/*z* 278 (63%) [M$^{\bullet+}$], 263 (26%), 206 (12%), 186 (27%), 158 (47%), 130 (94%). HRMS (EI) Calcd for $C_{17}H_{14}N_2O_2$ [M$^{\bullet+}$]: 278.1055; found: 278.1051. ^{1}H NMR (500 MHz) δ 9.57 (br s, 1H, N*H*-3), 8.23 (br s, 1H, N*H*Ph), 7.56–7.54 (m, 3H, Ar*C*H-7 and Ar*C*H-*o*), 7.33 (t, *J* 8.0 Hz, 2H, ArC*H*-*m*), 7.16 (t, *J* 7.0 Hz, 1H, ArC*H*-5), 7.13 (t, *J* 7.3 Hz, 1H, ArC*H*-*p*), 7.06 (t, *J* 7.7 Hz, 1H, ArC*H*-6), 6.90 (d, *J* 8.0 Hz, 1H, ArC*H*-4), 2.58 (dd, *J* 10.7, 4.7 Hz, 1H, CH_ACH$_B$-1), 2.18 (dd, *J* 10.5, 5.7 Hz, 1H, C*H*-1a), 0.89 (t, *J* 5.7 Hz, 1H, CH_BCH$_A$-1). ^{13}C NMR (125 MHz) δ 168.8 (*C*-2), 166.7 (*C*ONHPh), 137.7 (Ar*C*-*i*), 135.3 (Ar*C*-3a), 129.1 (Ar*C*H-*m*), 128.4 (Ar*C*H-7), 128.3 (Ar*C*H-5), 124.6 (Ar*C*H-*p*), 123.7 (Ar*C*H-6), 120.0 (Ar*C*-7a), 119.6 (Ar*C*H-*o*), 116.6 (Ar*C*H-4), 33.3 (*C*-7b), 27.6 (*C*H-1a), 15.1 (*C*H$_2$-1).

3.7. (1′*R**,2′*R**)-2′-Oxo-*N*-phenyl-1′,2′-dihydrospiro-[cyclopropane-1,3′-indole]-2-carboxamide (15)

The title compound was prepared using two methods. *Method 1*: the title compound was prepared using a similar method to that described above for the synthesis of **14** starting from **1** (25.9 mg, 1.3×10^{-4} mol). The crude product after acidic workup was purified initially by column chromatography using 10% MeOH/$CHCl_3$ as eluent and then further purified on a Chromatotron (0–1% MeOH/$CHCl_3$) to yield **15** as a beige powder (6.4 mg, 2.3×10^{-5} mol, 18%, R_f=0.23 in 50% EtOAc/petrol). MS (EI) *m*/*z* 278 (94%) [M$^{\bullet+}$], 263 (31%), 206 (13%), 186 (34%), 158 (64%). HRMS (EI) Calcd for $C_{17}H_{14}N_2O_2$ [M$^{\bullet+}$]: 278.1055; found: 278.1051. *Method 2*: to a solution of **20** (15.7 mg, 4.6×10^{-5} mol) in a mixture of H_2O (1 mL), AcOH (2 mL) and EtOH (2 mL), contained within a sealed tube, was added Fe (20 mg, 3.6×10^{-4} mol). The mixture was subjected to sonication for 2 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed successively with satd K_2CO_3 solution (20 mL) and H_2O (100 mL). The solution was dried, filtered and the solvent was removed in vacuo. The crude product was purified on a Chromatotron using 40–100% EtOAc/petrol and then MeOH to yield **15**, as light brown solid (7.8 mg, 2.8×10^{-5} mol, 60 %), and recovered **20** (0.4 mg, 1.2×10^{-6} mol, 2%). MS (EI) *m*/*z* 278 (34%) [M$^{\bullet+}$], 235 (15%), 223 (10%), 185 (47%) [M$^+$−NHPh], 157 (30%) [M$^+$−CONHPh], 146 (42%), 130 (96%), 103 (30%). HRMS (EI) Calcd for $C_{17}H_{14}N_2O_2$ [M$^{\bullet+}$]: 278.1055; found: 278.1049. ^{1}H NMR (500 MHz, CH_3OD) δ 7.47 (d, *J* 7.5 Hz, 2H, ArC*H*-*o*), 7.30 (d, *J* 8.0 Hz, 1H, ArC*H*-4), 7.25 (t, *J* 8.3 Hz, 2H, ArC*H*-*m*), 7.18 (dt, *J* 7.0, 1.0 Hz, 1H, ArC*H*-6), 7.04 (t, *J* 7.8 Hz, 1H, ArC*H*-*p*), 6.95 (d, *J* 8.0 Hz, 1H, ArC*H*-7), 6.92 (t, *J* 8.0 Hz, 1H, ArC*H*-5), 2.81 (dd, *J* 8.5, 7.5 Hz, 1H, C*H*-2′), 2.25 (dd, *J* 7.3, 4.3 Hz, 1H, CH_ACH$_B$-3′), 1.91 (dd, *J* 8.7,

4.3 Hz, 1H, CH_BCH$_A$-3′). ^{13}C NMR (125 MHz, CH_3OD) δ 179.0 (*C*-2), 167.1 (*C*ONH), 143.5 (Ar*C*-7a), 139.7 (Ar*C*-*i*), 129.7 (Ar*C*H-*m*), 128.6 (Ar*C*H-6), 128.0 (Ar*C*-3a), 125.2 (Ar*C*H-*p*), 123.5 (Ar*C*H-5), 123.0 (Ar*C*H-4), 121.2 (Ar*C*H-*o*), 110.9 (Ar*C*H-7), 36.2 (C*H*-2′), 35.0 (*C*-3), 20.1 (CH_2-3′).

3.8. 2-Chloro-*N*-phenylacetamide (17)

To a solution of pyridine (0.46 mL, 5.6 mmol) and aniline (0.38 mL, 4.1 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added chloroacetyl chloride (0.3 mL, 3.8 mmol). The mixture was allowed to warm to rt and left for stirring at rt for 1 h. The crude mixture was washed with 50 mL of citric acid and then with satd K_2CO_3 solution, dried and the solvent was removed in vacuo to yield a white solid (796.5 mg, 4.7 mmol), which was recrystallized from EtOAc/petrol to yield off-white crystalline plates (465.5 mg, 2.8 mmol, 74%, R_f=0.61 in 30% EtOAc/PS, mp 122–125 °C, lit.[20] mp 132–134 °C (from MeOH)). The NMR data for **17** were not reported. MS (EI) *m*/*z* 169 (70%), 171 (36%) [M$^{\bullet+}$], 120 (54%) [M$^+$−CH_2Cl]. HRMS (EI) Calcd for $C_8H_8NO^{35}Cl$ [M$^{\bullet+}$]: 169.0294; found: 169.0295. ^{1}H NMR δ 8.30 (br s, 1H, N*H*), 7.54 (dd, *J* 7.5, 1.2 Hz, 2H, ArC*H*-*o*), 7.35 (dt, *J* 7.8, 1.9 Hz, 2H, ArC*H*-*m*), 7.16 (tt, *J* 7.2, 1.2 Hz, 1H, ArC*H*-*p*), 4.17 (s, 2H, CH_2). ^{13}C NMR δ 163.9 (*C*O), 136.6 (Ar*C*-*i*), 129.0 (Ar*C*H-*m*), 125.2 (Ar*C*H-*p*), 120.1 (Ar*C*H-*o*), 42.8 (CH_2).

3.9. 2-(Methylsulfanyl)-*N*-phenylacetamide (18)

To a solution of **17** (257 mg, 1.52 mmol) in anhydrous MeOH (35 mL) was added sodium thiomethoxide (95%, 123.7 mg, 1.68 mmol). The reaction was stirred at rt for 15 min. The solvent was removed in vacuo in a fume cupboard. The residue was diluted with CH_2Cl_2 (25 mL) and washed with satd K_2CO_3 solution (15 mL) and dried to yield a cream solid (270.1 mg, 1.5 mmol, 98%, R_f=0.52 in 30% EtOAc/petrol). ^{1}H NMR data were in close agreement with the literature values.[21] MS (EI) *m*/*z* 181 (49%) [M$^{\bullet+}$], 135 (45%) [MH$^+$−SMe]. HRMS (EI) Calcd for $C_9H_{11}NOS$ [M$^{\bullet+}$]: 181.0561; found: 181.0562. ^{1}H NMR δ 8.85 (br s, 1H, N*H*), 7.54 (d, *J* 7.5 Hz, 2H, ArC*H*-*o*), 7.29 (t, *J* 7.9 Hz, 2H, ArC*H*-*m*), 7.09 (t, *J* 7.4 Hz, 1H, ArC*H*-*p*), 3.28 (s, 2H, CH_2), 2.14 (s, 3H, CH_3). ^{13}C NMR δ 167.0 (*C*O), 137.4 (Ar*C*-*i*), 128.7 (Ar*C*H-*m*), 124.3 (Ar*C*H-*p*), 119.7 (Ar*C*H-*o*), 38.7 (CH_2), 16.0 (CH_3).

3.10. 2-Anilino-2-oxoethyl-(dimethyl)sulfonium iodide (19)

To a solution of **18** (270.1 mg, 1.5 mmol) in anhydrous DCM (2 mL) was added MeI (0.94 mL, 15 mmol). The flask was sealed and the Superseal was tightly wrapped with Parafilm and left for stirring at rt for 2 days. The reaction was found to be incomplete by TLC analysis and further MeI (0.94 mL, 15 mmol) was added and the mixture was left for further 2 days at rt. The mixture was diluted with CH_2Cl_2 (5 mL) and **19** was filtered off as an off-white solid (253.3 mg, 7.84×10^{-4} mol, 52%, R_f=0 in 30% EtOAc/petrol) and the starting material **18** was recovered from the filtrate (105.1 mg, 5.8×10^{-4} mol, 39%). MS (ESI+ve) *m*/*z* 196 (100%) [M$^+$−I], (ESI−ve) *m*/*z* 127 (100%) [I$^-$]. The NMR data for this salt proved impossible to assign due to peak broadening.

3.11. Methyl (1′*R**,2′*R**)-2′-(anilinocarbonyl)-1′-(2-nitrophenyl)cyclopropanecarboxylate (20)

To a solution of **19** (214.3 mg, 6.6×10^{-5} mol) in anhydrous CH_2Cl_2 (3 mL) was added DBU (0.07 mL, 4.7×10^{-4} mol) and the solution was stirred under an N_2 atmosphere at rt for 30 min. A solution of **10** (91.5 mg, 4.4×10^{-4} mol) in CH_2Cl_2 (2 mL) was added and stirring was continued for 2 days. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the solution was washed with 1 M HCl solution (2×40 mL). The aqueous layers were back-extracted with CH_2Cl_2 (2×50 mL). The combined extracts were then dried and evaporated under reduced pressure to yield a brown yellow solid. The crude product was purified by column chromatography using 20–50% EtOAc/petrol as eluent to yield **20** as a white solid (59 mg, 1.7×10^{-4} mol, 39%, R_f=0.4 in 30% EtOAc/petrol, mp 226–228 °C) and recovered **10** (51.5 mg) and **19** (60 mg). MS (EI) *m*/*z* 340 (40%) [M$^{\bullet+}$], 294 (90%) [M$^+$−NO_2]. HRMS (EI) Calcd for $C_{18}H_{16}N_2O_5$ [M$^{\bullet+}$]: 340.1058; found: 340.1055. ^{1}H NMR δ 8.04 (dd, *J* 8.1, 1.3 Hz, 1H, ArC*H*-3), 7.65–7.54 (m, 2H, ArC*H*-5 and ArC*H*-6), 7.45 (dt, *J* 7.5, 1.6 Hz, 1H, ArC*H*-4), 7.24–7.19 (m, 4H, ArC*H*-*o* and ArC*H*-*m*), 7.07–7.02 (m, 1H, ArC*H*-*p*), 3.65 (s, 3H, CH_3), 3.01 (br s, 1H, C*H*-2′), 2.28 (br s, 1H, CH_ACH$_B$-3′), 1.98 (dd, *J* 8.4, 4.8 Hz, 1H, CH_BCH$_A$-3′). ^{13}C NMR δ 171.9 (CO_2Me), 165.3 (*C*ONH), 149.0 (Ar*C*-1), 137.4 (Ar*C*-*i*), 133.4 (Ar*C*H-5 and Ar*C*H-6), 130.8 (Ar*C*-2), 129.0 (Ar*C*H-4), 128.8 (Ar*C*H-*o*), 125.2 (Ar*C*H-3), 124.5 (Ar*C*H-*p*), 120.0 (Ar*C*H-*m*), 53.0 (OCH_3), 35.9 (C-1′), 32.8 (*C*H-2′), 21.0 (CH_2-3′). The structure of **20** was confirmed by X-ray crystallography (Fig. 3).

3.12. Ethyl (1′*R**,2′*R**,3′*R**)-2-oxo-3′-pyridin-2-yl-1,2-dihydrospiro[cyclopropane-1′,3-indole]-2′-carboxylate (22a), ethyl (1′*R**,2′*R**,3′*S**)-2-oxo-3′-pyridin-2-yl-1,2-dihydrospiro[cyclopropane-1′,3-indole]-2′-carboxylate (23a) and ethyl (1′*R**,2′*S**,3′*S**)-2-oxo-3′-pyridin-2-yl-1,2-dihydrospiro[cyclopropane-1′,3-indole]-2′-carboxylate (24a)

To a solution of ethyl dimethylsulfonium acetate bromide (173.6 mg, 7.6×10^{-4} mol) in anhydrous MeCN (3.7 mL) was added DBU (0.07 mL, 4.7×10^{-4} mol) and the solution was stirred under an N_2 atmosphere at rt for 30 min. A solution of **21a**[17] (108.8 mg, 4.7×10^{-4} mol) was added and stirring was maintained for 24 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% HCl solution (2×40 mL). The organic extracts were dried and evaporated under reduced pressure to yield a crude product as a peach coloured solid (155.6 mg, 5.0×10^{-4} mol). ^{1}H NMR analysis of the crude reaction mixture revealed a 5.6:1.8:1 mixture of **22a**, **23a** and **24a**, respectively. The crude mixture was purified by column chromatography using 30–50% EtOAc/petrol as eluent to yield **22a** as clear needle-like crystals (41.3 mg, 1.3×10^{-4} mol, 27%, R_f= 0.24 in 50% EtOAc/petrol, mp 178–180 °C) and **24a** as a cream oil (17.4 mg, 5.6×10^{-5} mol, 12%, R_f=0.31 in 50% EtOAc/petrol). Compound **23a** was unable to be isolated as a pure sample but was identified as the cis-isomer and

had: ^{1}H NMR δ 3.57 (d, *J* 9.9 Hz, 1H, C*H*-2′) and 3.08 (d, *J* 10.2 Hz, 1H, C*H*-3′).

Compound **22a**: MS (EI) *m*/*z* 308 (26%) [M$^{\bullet+}$], 262 (46%), 235 (94%), 217 (31%), 205 (44%). HRMS (EI+ve) Calcd for $C_{18}H_{16}N_2O_3$ [M$^+$]: 308.1161; found: 308.1165. ^{1}H NMR (500 MHz) δ 8.88 (br s, 1H, N*H*), 8.52 (d, *J* 4.0 Hz, 1H, ArC*H*-3″), 7.62 (dt, *J* 7.5, 1.5 Hz, 1H, ArC*H*-5″), 7.45 (d, *J* 7.5 Hz, 1H, ArC*H*-4), 7.33 (d, *J* 7.5 Hz, 1H, ArC*H*-6″), 7.18–7.14 (m, 2H, ArC*H*-4″ and ArC*H*-6), 6.99 (t, *J* 7.7 Hz, 1H, ArC*H*-5), 6.74 (d, *J* 7.5 Hz, 1H, ArC*H*-7), 4.26–4.14 (m, 2H, CH_2), 3.93 (d, *J* 8.0 Hz, 1H, C*H*-2′), 3.46 (d, *J* 8.0 Hz, 1H, C*H*-3′), 1.25 (t, *J* 7.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz) δ 173.8 (*C*-2), 168.1 (*C*O$_2$Et), 153.1 (Ar*C*-1″), 149.1 (Ar*C*H-3″), 141.4 (Ar*C*-7a), 136.1 (Ar*C*H-5″), 127.7 (Ar*C*H-6), 126.1 (Ar*C*-3a), 123.9 (Ar*C*H-6″), 122.8 (Ar*C*H-4), 122.4 (Ar*C*H-4″), 122.1 (Ar*C*H-5), 109.8 (Ar*C*H-7), 61.5 (*C*H$_2$), 40.7 (*C*H-2′), 39.5 (*C*-3), 36.8 (C*H*-3′), 14.1 (*C*H$_3$).

Compound **24a**: ^{1}H NMR δ 8.60 (br s, 1H, N*H*), 8.55 (dm, *J* 4.8 Hz, 1H, ArC*H*-3″), 7.51 (dt, *J* 7.5, 1.9 Hz, 1H, ArC*H*-5″), 7.19 (t, *J* 4.0 Hz, 1H, ArC*H*-6″), 7.11 (ddd, *J* 7.5, 4.8, 1.2 Hz, 1H, ArC*H*-4″), 7.03 (dt, *J* 7.5, 1.5 Hz, 1H, ArC*H*-6), 6.80 (d, *J* 7.8 Hz, 1H, ArC*H*-7), 6.75 (d, *J* 7.5 Hz, 1H, ArC*H*-4), 6.68 (dt, *J* 7.2, 1.0 Hz, 1H, ArC*H*-5), 4.21–4.13 (m, 2H, CH_2), 3.86 (d, *J* 8.1 Hz, 1H, C*H*-2′), 3.82 (d, *J* 8.1 Hz, 1H, C*H*-3′), 1.21 (t, *J* 7.0 Hz, 3H, CH_3). ^{13}C NMR δ 174.7 (*C*-2), 167.2 (*C*O$_2$Et), 152.9 (Ar*C*-1″), 148.8 (Ar*C*H-3″), 141.3 (Ar*C*-7a), 136.5 (Ar*C*H-5″), 127.5 (Ar*C*H-6), 126.1 (Ar*C*-3a), 125.6 (Ar*C*H-6″), 122.6 (Ar*C*H-4″), 122.5 (Ar*C*H-4), 121.8 (Ar*C*H-5), 109.7 (Ar*C*H-7), 61.4 (*C*H$_2$), 40.2 (*C*H-2′), 40.1 (*C*-3), 35.7 (*C*H-3′), 14.2 (*C*H$_3$).

3.13. Ethyl (1′*R**,2′*R**,3′*R**)-2′-oxo-3-pyridin-3-yl-1′,2′-dihydrospiro[cyclopropane-1,3′-indole]-2-carboxylate (22b), ethyl (1′*R**,2′*R**,3′*S**)-2′-oxo-3-pyridin-3-yl-1′,2′-dihydrospiro[cyclopropane-1,3′-indole]-2-carboxylate (23b) and ethyl (1′*R**,2′*S**,3′*S**)-2′-oxo-3-pyridin-3-yl-1′,2′-dihydrospiro[cyclopropane-1,3′-indole]-2-carboxylate (24b)

The title compounds were prepared using a method similar to that described above for the synthesis of **22a**–**24a** except using **21b**[17] (104.4 mg, 4.7×10^{-4} mol). After extraction the crude product was a peach coloured powder (101.7 mg, 3.3×10^{-4} mol, 70%). ^{1}H NMR analysis of the crude reaction mixture revealed a 43:7:1 mixture of **22b**, **23b** and **24b**, respectively. The crude product was purified by column chromatography using 40–60% EtOAc/petrol as eluent to yield **22b** as cream needles (88.2 mg, 2.9×10^{-4} mol, 61%, R_f=0.38 in 10% MeOH/CHCl$_3$, mp 208–210 °C). Compounds **23b** and **24b** could not be isolated as pure samples but were identified as the cis and trans-isomers, respectively. Compound **23b**: ^{1}H NMR δ 3.45 (dd, *J* 9.6, 0.6 Hz, 1H, C*H*-2′) and 3.05 (d, *J* 9.6 Hz, 1H, C*H*-3′). Compound **24b**: ^{1}H NMR δ 3.65 (d, *J* 5.7 Hz, 1H, C*H*-2′) and 3.63 (d, *J* 5.1 Hz, 1H, C*H*-3′).

Compound **22b**: MS (EI) *m*/*z* 308 (46%) [M$^{\bullet+}$], 262 (57%) [M$^+$−OEt], 235 (96%) [M$^+$−CO$_2$Et]. HRMS (EI) Calcd for $C_{18}H_{16}N_2O_3$ [M$^{\bullet+}$]: 308.1161; found: 308.1158. ^{1}H NMR (500 MHz) δ 9.40 (br s, 1H, N*H*), 8.57 (br s, 1H, ArC*H*-2″), 8.49 (br s, 1H, ArC*H*-4″), 7.66 (d, *J* 8.5 Hz, 1H, ArC*H*-6″), 7.46 (d, *J* 7.5 Hz, 1H, ArC*H*-4), 7.22 (t, *J* 7.7 Hz, 2H, ArC*H*-6 and ArC*H*-5″), 7.03 (t, *J* 7.5 Hz, 1H, ArC*H*-5), 6.82 (d, *J* 7.7 Hz, 1H, ArC*H*-7), 4.27–4.15 (m, 2H, CH_2), 3.73 (d, *J* 8.0 Hz, 1H, C*H*-2′), 3.34 (d, *J* 8.0 Hz, 1H, C*H*-3′), 1.26 (t, *J* 7.7 Hz, 3H, CH_3). ^{13}C NMR (125 MHz) δ 173.7 (*C*-2), 167.9 (*C*O$_2$Et), 150.4 (Ar*C*H-2″), 148.4 (Ar*C*H-4″), 141.5 (Ar*C*-7a), 136.6 (Ar*C*H-6″), 128.8 (Ar*C*-1″), 127.9 (Ar*C*H-6), 125.9 (Ar*C*-3a), 122.8 (Ar*C*H-5″), 122.6 (Ar*C*H-4), 122.1 (Ar*C*H-5), 110.0 (Ar*C*H-7), 61.7 (*C*H$_2$CH$_3$), 39.5 (*C*-3), 37.0 (*C*H-2′), 36.6 (*C*H-3′), 14.1 (*C*H$_3$CH$_2$). The structure of **22b** was confirmed by X-ray crystallography (Fig. 4).

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Supplementary data

Details of the X-ray crystal/refinement data (2 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.051.

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