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Synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised Baylis–Hillman adducts of isatin

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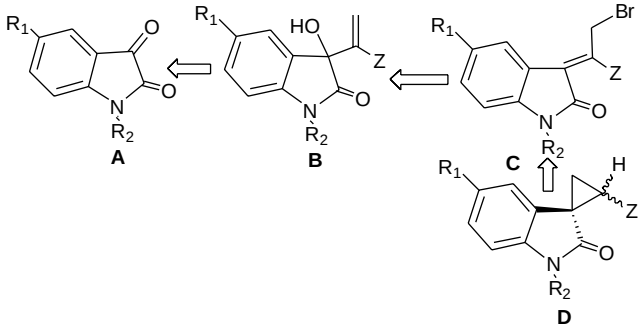
Abstract—A facile, high yield stereoselective synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones (**10–17a**,**b**) from the isomerised bromo derivatives of Baylis–Hillman adducts of isatin(**2–9a**,**b**) by reductive cyclization with sodium borohydride is reported.

1. Introduction

Construction of cyclopropane ring systems is of great interest of organic chemists due to its existence as a basic unit in a number of natural products.[1] Cyclopropane ring systems are versatile building blocks in complex molecular construction. In view of their importance as synthons, numerous synthetic methods have been reported for their synthesis.[2] The synthesis of spirocycloindolones are of great interest because they display a variety of biological activities and many of them used as starting materials for alkaloid synthesis.[3] Different synthetic strategies are known for the construction of 3-spirocycloalkylindolones[4] but the synthesis of 3-spirocyclopropane-2-indolones by reductive cyclization of isomerised bromo derivative of Baylis–Hillman adducts of isatin is unexplored to date. Amongst various carbon–carbon bond forming reactions, the Baylis–Hillman reaction is an important reaction giving rise to densely functionalized molecules and is considered atom economic. Highly functionalized Baylis–Hillman adducts have been used as starting materials for various stereoselective preparations of functionalized intermediates and in natural product synthesis.[5] We have been working on novel synthetic applications of the Baylis–Hillman adducts.[6] Thus, in this paper, we wish to outline the synthesis of 3-spirocyclopropane-2-indolones by reductive cyclization of isomerised Baylis–Hillman adducts of isatin for the first time.

2. Results and discussion

The synthetic strategy of present study is depicted in Scheme 1. Reductive cyclization of isomerised bromo derivative of Baylis–Hillman adduct of isatin **C** would provide functionalized 3-spirocyclopropane-2-indolones **D**. The isomerised bromo derivative of Baylis–Hillman adduct of isatin **C** could be synthesized from the Baylis–Hillman adduct of isatin **B** by isomerisation reaction with 46% aqueous HBr under microwave irradiation. In turn, adducts **B** could be prepared from the corresponding substituted isatins **A**.



Scheme 1. Retrosynthetic analysis.

The details of the study are shown in Scheme 2. Some of the Baylis–Hillman adducts of isatin used in the present study were prepared according to literature procedure.[7] Thus, as shown, the model substrate **1** was prepared by the treatment of *N*-methyl isatin with ethyl acrylate using 10% mole percent of DABCO in methanol at rt in good yield.

The pure adduct **1** with aqueous HBr (4 equiv) embedded on silica gel (0.2 gm) was irradiated in a microwave oven for

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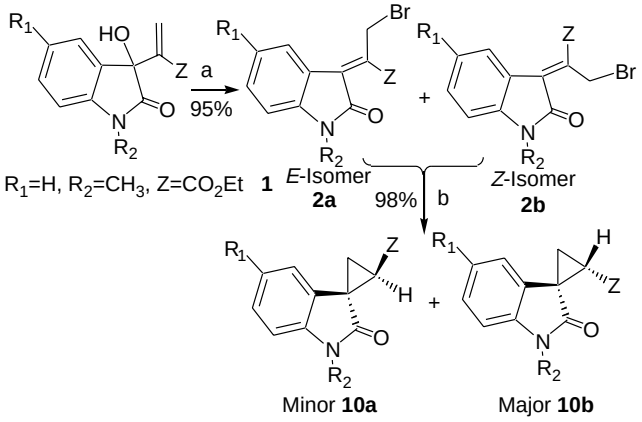


Scheme 2. Cyclopropanation of isomerised BH adducts. Reagents and condition: (a) 4 equiv 46% HBr, silica gel, μw, 750 W, 3 min; (b) 2 equiv, $NaBH_4$, THF, 0.5 h.

3 min to afford a 1:2 mixture of *E*:*Z* isomers of bromo derivative **2a** and **2b** in 95% combined yield after purification by silica gel column chromatography. Stereoselective cyclopropane formation from the mixture **2a** and **2b** in dry THF with 2 equiv of sodium borohydride at rt for 0.5 h afforded functionalized 3-cylopropyl-2-indolones as diastereomeric mixture of **10a** and **10b** in 98% combined yield. The ratio of the products (**10a/10b**) was found as 1:2 as estimated by ^{1}H NMR. The new compounds were characterized by spectral (IR, ^{1}H and ^{13}C NMR) and HRMS data.

In order to study the selectivity in diastereomeric mixture (**10a** and **10b**) formation, we separated the *E* and *Z* isomers of Baylis–Hillman bromo derivatives (**2a** and **2b**) by column chromatography and reduced them under optimized reduction condition separately. To our surprise, the separated geometrical isomers **2a** and **2b** provided the same mixture and same ratio of cyclopropanes **10a** and **10b** on exposure to sodium borohydride. Hence, it is understood that both the isomers are undergoing reductive cyclopropanation through a common stable intermediate. The formation of diastereomeric mixture through a common intermediate could be explained based on the plausible mechanism proposed in Scheme 3. Thus, the hydride ion attack on double bond of the isomerised Baylis–Hillman adducts leads to a common enolate intermediate A, which undergoes cyclopropanation as shown in Scheme 3.

Characterization of the minor and major products (**10a** and **10b**) was achieved based on the analysis of ^{1}H NMR spectra and coupling constant studies. In order to confirm the projection of ester group (α or β) in isomers **13a** and **13b**, the chemical shift variation of aromatic protons H_d and $H_{d'}$ was used as a tool. These are visualised in Figures 1 and 2. For example, the H_d proton appeared at δ 7.51 due to anisotropic influence of ester carbonyl in **13a** while the $H_{d'}$ proton appeared at δ 6.94 due to no influence of ester group

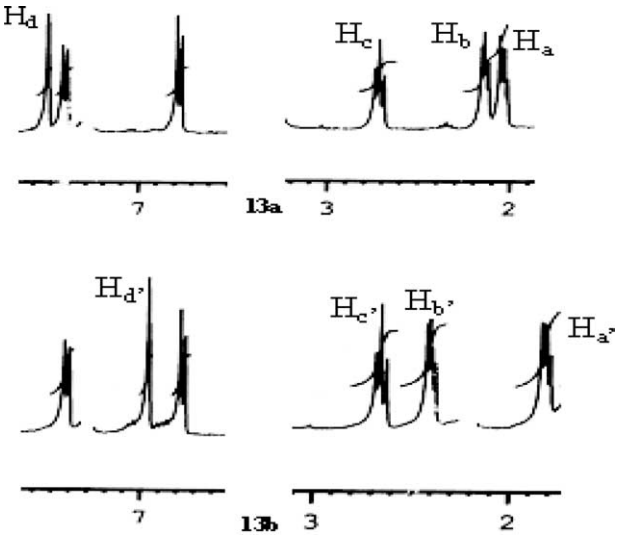


Figure 1.

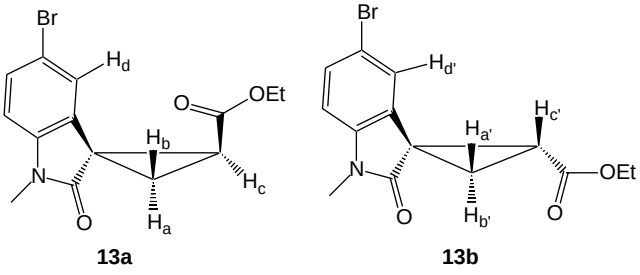
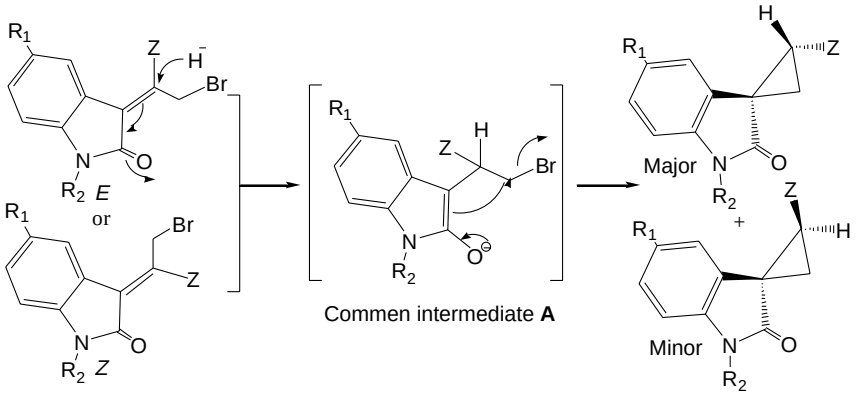
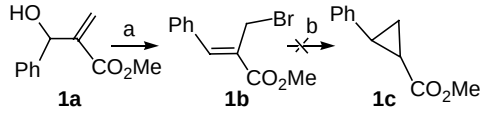


Figure 2.

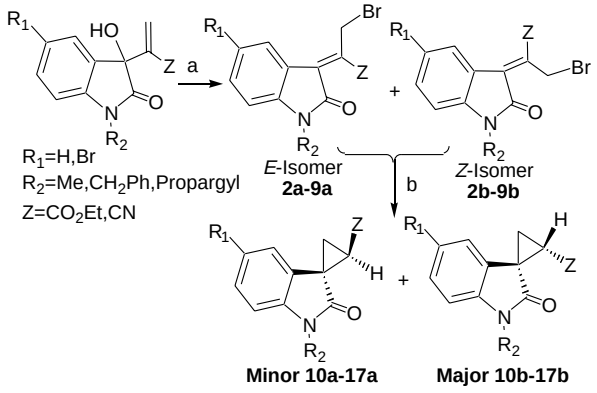


Scheme 3. Plausible mechanism for cyclopropanation.

in **13b**. To fix the nature of protons of the cyclopropane rings, the coupling constant and chemical shift correlation studies were used as a tool. Thus, in compound **13a**, the H_a proton appeared at δ 2.03 (dd, $J_{gem}=4.5$ Hz, $J_{cis}=8.7$ Hz), H_b proton appeared at δ 2.13 (dd, $J_{gem}=4.5$ Hz, $J_{trans}=7.2$ Hz) and H_c proton appeared at δ 2.71 (dd, $J_{cis}=8.7$ Hz, $J_{trans}=7.2$ Hz). In contrary, in compound **13b**, the $H_{a'}$ proton appeared at δ 1.80 (dd, $J_{gem}=5.1$ Hz, $J_{cis}=8.7$ Hz), $H_{b'}$ proton appeared at δ 2.38 (dd, $J_{gem}=5.1$ Hz, $J_{trans}=8.1$ Hz) and $H_{c'}$ proton appeared at δ 2.64 (dd, $J_{cis}=8.7$ Hz, $J_{trans}=8.1$ Hz). Hence, the structure with relative stereochemistry of minor and major compounds **13a** and **13b** was assigned as shown in Figure 2.



Scheme 4. Cyclopropanation of simple isomerised BH adduct. (a) 4 equiv 46% HBr, CH_2Cl_2, rt, 0.5 h; (b) 2 equiv $NaBH_4$, THF, 0.5 h.



Scheme 5. Generality of the cyclopropanation. (a) 4 equiv 46% HBr, silica gel, μw, 750 W, 3 min; (b) 2 equiv $NaBH_4$, THF, 0.5 h.

To investigate the limitation and applicability of cyclopropanation reaction to the simple Baylis–Hillman adducts, the adduct **1a** derived from benzaldehyde with methyl acrylate on isomerisation with aqueous HBr at rt to afford corresponding isomerised product **1b** as a single isomer. The isomerised bromo derivative **1b** in dry THF upon reduction with 2 equiv of $NaBH_4$ (optimised conditions) did not yield the expected cyclopropane derivative **1c**. Careful repeatation and altering the reaction conditions provided only the unreacted starting material. Thus, it is clear that only isomerised bromo derivative of isatins are suitable substrates for the cyclopropanation under reductive cyclization condition. The reaction is shown in Scheme 4.

Encouraged by the preliminary results and to show the generality of the reaction, the reaction of isomerised bromo adducts of isatin **2ab–9ab** under optimized conditions afforded the corresponding functionalized 3-cylopropyl-2-indolones **10a/10b–17a/17b** in excellent yield. The reaction is showed in Scheme 5 and the results are summarized in Table 1. All the new compounds were thoroughly characterized by spectral (IR, ^{1}H and ^{13}C NMR, DEPT-135) and HRMS data.

Table 1. Synthesis of 3-spirocyclopropane-2-indolones

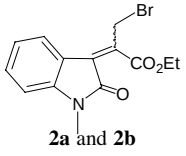
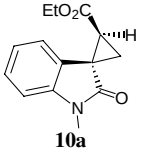
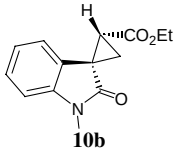
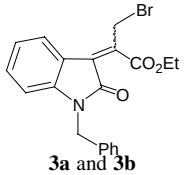
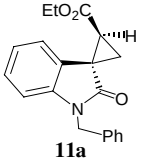
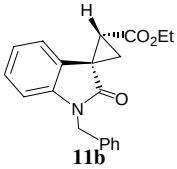
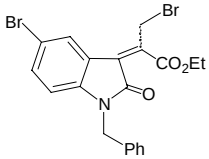
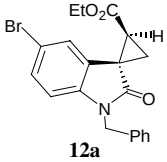
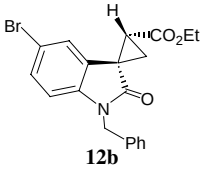
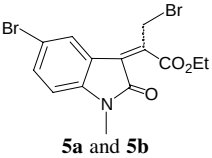
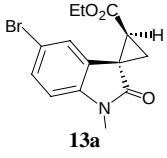
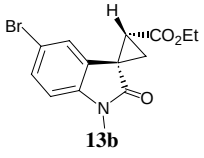
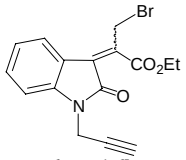
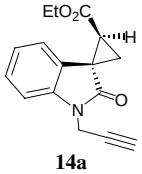
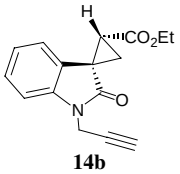
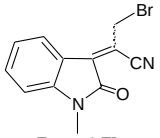
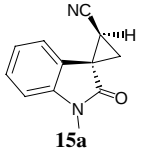
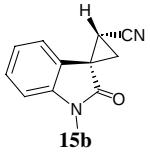
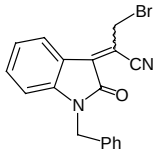
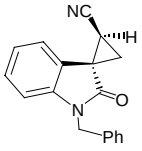
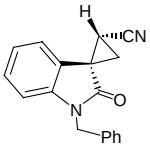
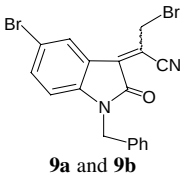
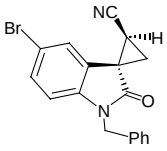
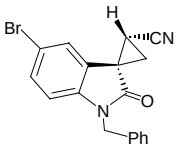
Entry	Reactant (*E* and *Z*)[a]	Condition[b]	Products[c]		Ratio	Combined yield (%)[d]
			Minor	Major		
1	 **2a** and **2b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **10a**	 **10b**	1:2	98
2	 **3a** and **3b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **11a**	 **11b**	1:2	93
3	 **4a** and **4b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **12a**	 **12b**	1:2	95
4	 **5a** and **5b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **13a**	 **13b**	1:1.5	96

Table 1 (*continued*)

Entry	Reactant (*E* and *Z*)[a]	Condition[b]	Products[c]		Ratio	Combined yield (%)[d]
			Minor	Major		
5	 **6a** and **6b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **14a**	 **14b**	1:2	88
6	 **7a** and **7b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **15a**	 **15b**	1:2	94
7	 **8a** and **8b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **16a**	 **16b**	1:2.5	98
8	 **9a** and **9b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **17a**	 **17b**	1:1.5	86

[a] *E*/*Z* mixture was used as starting material.
[b] See typical procedure.
[c] The isomers were separated by column chromatography.
[d] Estimated after column purification of the products.

3. Conclusion

In conclusion, we have demonstrated a short, novel and facile method for the synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones from isomerised bromo derivatives of Baylis–Hillman adducts of isatin by reductive cyclopropanation methodology as a key step for the first time. Further studies to apply this strategy for the synthesis of natural products are underway in our laboratory.

4. Experimental

4.1. General consideration

All the experiments were carried out in oven-dried glassware. Analytical thin-layer chromatography was performed on silica gel TLC plates. Purification by gravity column chromatography was carried out using silica gel (100–200 mesh). Mixture of ethyl acetate and hexane and pure ethyl acetate were used as eluent as required. IR spectra were run on a Nicolet (impact 400D FT-IR) spectrophotometer. NMR spectra were obtained using chloroform-*d* as solvent on Bruker DPX 300 MHz NMR spectrometer. Chemical shifts are given in δ scale with TMS as internal reference. HRMS were measured at the JMS 600 JEOL Mass Spectrometer. Yields refer to quantities obtained after chromatography. Solvents used are reagents grade and were purified before use according to the literature procedure.[8]

4.2. Typical experimental procedure for isomerisation of Baylis–Hillman adducts

A mixture of Baylis–Hillman adduct **1** derived from isatin (100 mg, 0.382 mmol) was added 4 equiv of 46% HBr and silica gel (0.2 g) to make a slurry. The slurry was subjected to microwave irradiation (750 W, 5 s pulse) over a period of 3 min. The crude mixture was cooled to rt and then extracted with CH_2Cl_2 and the organic phase was washed with water. The organic layer was separated and dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure isomerised bromo derivatives **2a** and **2b** in 95% combined yield (118 mg).

4.3. Typical experimental procedure for the synthesis of 3-spirocyclopropane-2-indolones

A mixture of isomerised bromo derivatives of Baylis–Hillman adducts **2a** and **2b** (40 mg, 0.123 mmol) in dry tetrahydrofuran (3 mL) was added 2 equiv of sodium borohydride (9.3 mg, 0.245 mmol). The mixture was stirred

at rt until complete disappearance of starting material (TLC, ca. 0.5 h). Then, the THF was removed under reduced pressure. The crude material was extracted with ethyl acetate (2×30 mL) and the combined organic layer was washed with water followed by brine. The organic layer was separated and dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure cyclopropane derivatives **10a** and **10b** in 98% combined yield (29 mg).

4.4. Spectral data of new compounds

4.4.1. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-methyl-2′-oxo-, ethyl ester, 10a. IR (CH_2Cl_2) 2968, 2925, 2863, 1746, 1722, 1617, 1468 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.20 (t, J=6.9 Hz, 3H), 2.01 (dd, J=4.5, 8.7 Hz, 1H), 2.13 (dd, J=4.5, 7.5 Hz, 1H), 2.70 (dd, J=7.5, 8.7 Hz, 1H), 3.28 (s, 3H), 4.13 (q, J=6.9 Hz, 2H), 6.90 (d, J=7.8 Hz, 1H, Ar), 7.02 (t, J=7.8 Hz, 1H, Ar), 7.29 (t, J=7.8 Hz, 1H, Ar), 7.36 (d, J=7.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.33, 20.89, 26.87, 29.54, 32.94, 61.43, 108.21, 122.40, 122.80, 126.06, 127.86, 144.45, 169.03, 175.29; HRMS: Calcd for $C_{14}H_{15}NO_3$: 245.1052; Found: 245.1045.

4.4.2. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-methyl-2′-oxo-, ethyl ester, 10b. IR (CH_2Cl_2): 3057, 2963, 2937, 2852, 1739, 1709, 1611, 1466 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, J=6.9 Hz, 3H), 1.72 (dd, J=4.8, 8.4 Hz, 1H), 2.31 (dd, J=4.8, 8.1 Hz, 1H), 2.57 (dd, J=8.1, 8.4 Hz, 1H), 3.19 (s, 3H), 4.14 (q, J=6.9 Hz, 2H), 6.77 (d, J=7.2 Hz, 1H, Ar), 6.82 (d, J=7.8 Hz, 1H, Ar), 6.98 (t, J=7.5 Hz, 1H, Ar), 7.22 (t, J=7.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.36, 20.73, 27.07, 29.42, 32.87, 61.84, 108.82, 122.67, 122.48, 126.53, 127.76, 143.56, 168.68, 174.29; HRMS: Calcd for $C_{14}H_{15}NO_3$: 245.1052; Found: 245.1043.

4.4.3. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-benzyl -2′-oxo-, ethyl ester, 11a. IR (CH_2Cl_2): 2927, 2849 (cyclopropane), 1721 (ester, amide), 1608 (Ar), 1464 (cyclopropane) cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.25 (t, J=6.9 Hz, 3H), 2.08 (dd, J=4.2, 8.4 Hz, 1H), 2.18 (dd, J=4.2, 7.5 Hz, 1H), 2.77 (dd, J=7.5, 8.4 Hz, 1H), 4.15 (q, J=6.9 Hz, 2H), 5.10 (s, 2H), 6.84–7.45 (m, 9H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.35, 21.27, 32.12, 33.15, 44.52, 61.51, 109.24, 118.80, 122.73, 122.95, 124.93, 127.55, 127.79, 127.85, 128.40, 128.99, 136.03, 143.60, 168.99, 175.11; HRMS: Calcd for $C_{20}H_{19}NO_3$: 321.1363; Found: 321.1359.

4.4.4. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′ -benzyl -2′-oxo-, ethyl ester, 11b. IR (CH_2Cl_2): 2983, 2927, 1735, 1705, 1613, 1466 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.25 (t, J=7.1 Hz, 3H), 1.85 (dd, J=4.8, 8.4 Hz, 1H), 2.43 (dd, J=4.8, 7.8 Hz, 1H), 2.68 (dd, J=7.8, 8.4 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 4.89 (d, J=15.6 Hz, 1H), 5.04 (d, J=15.6 Hz, 1H), 6.76–7.26 (m, 9H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.38, 21.16, 32.44, 33.79, 44.25, 61.63, 109.33, 118.39, 122.46, 127.38, 127.51, 127.77, 127.82, 128.93 (2C), 129.14, 136.14, 142.95, 167.23, 173.67; HRMS: Calcd for $C_{20}H_{19}NO_3$: 321.1365; Found: 321.1363.

4.4.5. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-benzyl-5′-bromo-2′-oxo-, ethyl ester, 12a. IR (CH_2Cl_2): 2931, 2854, 1727, 1713, 1603, 1473 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.23 (t, J=6.9 Hz, 3H), 2.10 (dd, J=4.5, 8.7 Hz, 1H), 2.17 (dd, J=4.5, 7.5 Hz, 1H), 2.78 (dd, J=7.5, 8.7 Hz, 1H), 4.18 (q, J=6.9 Hz, 2H), 4.99 (2d, J=15.6 Hz, 2H), 6.65 (d, J=8.4 Hz, 1H, Ar), 7.26–7.32 (m, 6H, Ar, Ph), 7.52 (d, J=2.1 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.15, 21.48, 31.91, 33.24, 44.35, 61.57, 110.36, 115.14, 116.63, 125.98, 127.24 (2C), 127.82, 128.87 (2C), 130.41, 135.29, 142.36, 167.98, 175.01; HRMS: Calcd for $C_{20}H_{18}BrNO_3$: 399.0470; Found: 399.0466.

4.4.6. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-benzyl-5′-bromo-2′-oxo-, ethyl ester, 12b. IR (CH_2Cl_2): 3060, 2988, 2925, 1741, 1713, 1617, 1483 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.26 (t, J=7.2 Hz, 3H), 1.86 (dd, J=5.1, 8.7 Hz, 1H), 2.25 (dd, J=5.1, 8.1 Hz, 1H), 2.69 (dd, J=8.1, 8.7 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 4.87 (d, J=15.6 Hz, 1H), 5.02 (d, J=15.6 Hz, 1H), 6.62 (d, J=8.1 Hz, 1H, Ar), 6.95 (d, J=2.1 Hz, 1H), 7.24–7.33 (m, 6H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.13, 19.81, 32.01, 33.85, 44.09, 61.56, 110.51, 114.96, 121.93, 127.19 (2C), 127.73, 128.80 (3C), 130.36, 131.01, 135.39, 166.58, 172.87; HRMS: Calcd for $C_{20}H_{18}BrNO_3$: 399.0470; Found: 399.0464.

4.4.7. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′ -methyl-5′-bromo-2′-oxo-, ethyl ester, 13a. IR (CH_2Cl_2): 2984, 2921 (cyclopropane), 1717 (ester, amide), 1606 (Ar), 1464 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.23 (t, J=6.9 Hz, 3H), 2.03 (dd, J=4.5, 8.7 Hz, 1H), 2.13 (dd, J=4.5, 7.2 Hz, 1H), 2.71 (dd, J=7.2, 8.7 Hz, 1H), 3.26 (s, 3H), 4.17 (q, J=6.9 Hz, 2H), 6.76 (d, J=8.1 Hz, 1H, Ar), 7.42 (d, J=8.1 Hz, 1H, Ar), 7.51 (d, J=1.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.15, 21.11, 26.76, 29.67, 33.06, 61.50, 108.04, 115.03, 125.86, 127.94, 130.49, 143.30, 168.46, 174.17; HRMS: Calcd for $C_{14}H_{14}BrNO_3$: 323.0157; Found: 323.0149.

4.4.8. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′ -methyl-5′-bromo-2′-oxo-, ethyl ester, 13b. IR (CH_2Cl_2): 2982, 1741, 1712, 1610, 1465 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.27 (t, J=7.2 Hz, 3H), 1.80 (dd, J=5.1, 8.7 Hz, 1H), 2.38 (dd, J=5.1, 8.1 Hz, 1H), 2.64 (dd, J=8.1, 8.7 Hz, 1H), 3.24 (s, 3H), 4.20 (q, J=7.2 Hz, 2H), 6.75 (d, J=8.1 Hz, 1H, Ar), 6.94 (d, J=1.8 Hz, 1H, Ar), 7.40 (dd, J=8.1, 1.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.13, 21.32, 26.67, 32.15, 33.39, 61.53, 109.52, 114.85, 121.85, 130.02, 131.02, 142.68, 166.67, 172.75; HRMS: Calcd for $C_{14}H_{14}BrNO_3$: 323.0157; Found: 323.0142.

4.4.9. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-propargyl-2′-oxo-, ethyl ester, 14a. IR (CH_2Cl_2): 3063, 2959, 2927, 2846, 1728, 1706, 1611, 1462 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, J=7.1 Hz, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 2.26 (t, J=2.4 Hz, 1H), 2.74 (m, 1H), 4.11 (q, J=7.1 Hz, 2H), 4.57–4.62

(d, J=2.4 Hz, 2H), 6.75–7.48 (m, 4H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.83, 21.72, 29.79, 32.76, 33.29, 47.92, 61.65, 72.54, 109.83, 119.20, 122.85, 127.94, 128.44, 142.21, 167.50, 173.13; HRMS: Calcd for $C_{16}H_{15}NO_3$: 269.1052; Found: 269.1050.

4.4.10. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-propargyl-2′-oxo-, ethyl ester, 14b. IR (CH_2Cl_2): 3054, 2986, 2930, 1740, 1719, 1612, 1467 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.26 (t, J= 7.2 Hz, 3H), 1.82 (dd, J=5.1, 8.7 Hz, 1H), 2.24 (t, J=2.4 Hz, 1H), 2.39 (dd, J=5.1, 8.1 Hz, 1H), 2.66 (dd, J=8.1, 8.7 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 4.48–4.68 (d, J=2.4 Hz, 2H), 6.86 (d, J=7.2 Hz, 1H, Ar), 7.05–7.34 (m, 3H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.32, 21.52, 29.70, 32.42, 33.68, 47.97, 61.62, 72.48, 109.37, 118.79, 122.83, 127.91, 128.95, 141.91, 167.04, 172.55; HRMS: Calcd for $C_{16}H_{15}NO_3$: 269.1052; Found: 269.1047.

4.4.11. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′-methyl -2′-oxo-2-nitrile, 15a. IR (CH_2Cl_2): 3086, 3027, 2236, 1701, 1614, 1469 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.89 (dd, J=4.8, 6.9 Hz, 1H), 2.13 (dd, J=4.8, 9.3 Hz, 1H), 2.44 (dd, J=6.9, 9.3 Hz, 1H), 3.30 (s, 3H), 6.97 (d, J=7.8 Hz, 1H, Ar), 7.12–7.42 (m, 3H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.78, 21.31, 26.85, 31.70, 108.66, 116.85, 120.91, 122.89, 124.07, 128.83, 144.10, 172.97; HRMS: Calcd for $C_{12}H_{10}N_2O$: 198.0793; Found: 198.0790.

4.4.12. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′-methyl -2′-oxo-2-nitrile, 15b. IR (CH_2Cl_2): 3031, 2963, 2916, 2848, 2247, 1705, 1611, 1466 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.99 (dd, J=5.1, 9.3 Hz, 1H), 2.19 (dd, J=5.1, 7.2 Hz, 1H), 2.35 (dd, J=7.2, 9.3 Hz, 1H), 3.34 (s, 3H), 6.79 (d, J=7.1 Hz, 1H, Ar), 6.96 (d, J= 7.1 Hz, 1H, Ar), 7.07 (t, J=7.8 Hz, 1H), 7.35 (t, J=7.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 15.09, 21.14, 26.90, 31.83, 108.41, 115.89, 118.84, 122.56, 126.02, 128.87, 144.17, 171.49; HRMS: Calcd for $C_{12}H_{10}N_2O$: 198.0793; Found: 198.0795.

4.4.13. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′ -benzyl -2′-oxo-2-nitrile, 16a. IR (CH_2Cl_2): 3030, 2925, 2855 (cyclopropane), 2240 (CN), 1717 (amide), 1612 (Ar), 1465 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.94 (dd, J=5.1, 6.9 Hz, 1H), 2.20 (dd, J=5.1, 9.3 Hz, 1H), 2.52 (dd, J=6.9, 9.3 Hz, 1H), 4.95 (s, 2H), 6.87 (d, J= 7.8 Hz, 1H, Ar), 6.96 (d, J=7.1 Hz, 1H, Ar), 7.07 (t, J= 7.8 Hz, 1H), 7.05–7.34 (m, 8H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): 15.00, 21.58, 30.91, 44.50, 109.67, 116.84, 121.00, 122.92, 124.08, 127.34 (2C), 127.88, 128.76, 128.89 (2C), 135.32, 143.27, 173.16; HRMS: Calcd for $C_{18}H_{14}N_2O$: 274.1106; Found: 274.1103.

4.4.14. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′ -benzyl -2′-oxo-2-nitrile, 16b. IR (CH_2Cl_2): 3032, 2928, 2252, 1719, 1618, 1467 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 2.03 (dd, J=4.8, 9.0 Hz, 1H), 2.25 (dd, J=4.8, 7.5 Hz, 1H), 2.35 (dd, J=7.5, 9.0 Hz, 1H), 4.95–5.08 (2d, J=15.6 Hz, 2H), 6.81–7.33 (m, 9H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): 15.35, 21.35, 31.84, 44.48, 109.74, 115.82, 118.93, 122.58, 126.02, 127.55, 127.83 (2C), 128.73, 128.86 (2C), 135.58, 143.18, 171.62; HRMS: Calcd for $C_{18}H_{14}N_2O$: 274.1106; Found: 274.1098.

4.4.15. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′ -benzyl-5′-bromo -2′-oxo-2-nitrile, 17a. IR (CH_2Cl_2): 2975, 2852 (cyclopropane), 2249 (CN), 1721 (CO), 1613 (Ar), 1479 (cyclopropane) cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.94 (dd, J=5.1, 7.2 Hz, 1H), 2.21 (dd, J=5.1, 9.3 Hz, 1H), 2.55 (dd, J=7.2, 9.3 Hz, 1H), 4.98 (s, 2H), 6.72 (d, J=8.1 Hz, 1H, Ar), 7.27–7.40 (m, 7H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.18, 21.01, 44.59, 31.56, 109.67, 122.92, 124.23, 127.26, 127.48, 127.87, 128.75, 128.89, 128.99, 131.68, 134.85, 135.44, 142.3, 172.60; HRMS: Calcd for $C_{18}H_{13}BrN_2O$: 352.0211; Found: 352.0203.

4.4.16. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′-benzyl-5′-bromo-2′-oxo-2-nitrile, 17b. IR (CH_2Cl_2): 2926, 2853, 2246, 1714, 1614, 1480 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 2.03 (dd, J=5.1, 9.3 Hz, 1H), 2.29 (dd, J=5.1, 7.5 Hz, 1H), 2.37 (dd, J=7.5, 9.3 Hz, 1H), 4.93–5.07 (2d, J=15.6 Hz, 2H), 6.70 (d, J=8.4 Hz, 1H, Ar), 6.94 (s, 1H, Ar), 7.26–7.34 (m, 6H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 15.34, 21.54, 31.63, 44.58, 111.05, 11.23, 121.63, 125.22, 127.26, 127.47, 128.01, 128.11, 128.95, 131.52, 131.67, 135.83, 142.16, 172.03; HRMS: Calcd for $C_{18}H_{13}BrN_2O$: 352.0211; Found: 352.0193.

5. Supplementary data

Scanned copies of the ^{1}H and ^{13}C NMR spectra of all the diastereomeric mixtures available as supporting data.

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