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Alkaloid inspired spirocyclic oxindoles from 1,3-dipolar cycloaddition of pyridinium ylides†

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Cycloaddition reactions between pyridinium ylides and 3-alkenyl oxindoles that proceed in high yield and with very good regio- and diastereoselectivity are reported. The resulting cycloadducts have the same stereochemistry of biologically active oxindole alkaloids, such as strychnofoline.

Introduction

Natural products and their signature fragments are an enduring resource for identifying biological modulators.[1] A number of biologically active alkaloids, such as strychnofoline and isorhynchophylline (Fig. 1), feature spiroindolizidine oxindoles.[2,3] This fragment is considered 'privileged' for potential therapeutic investigation and there is much interest in developing expedient synthesis of such structures.[4]

Target spiroindolizidineoxindole structures may be efficiently accessed by 1,3-dipolar cycloaddition of 3-alkylideneindoline-2-ones.[5] Serov *et al.* described reactions between *N*-phenylacylquinolinium ylides with 3-alkylidene oxindoles,[6] while extended studies of this type of reaction have recently been reported.[7] The latter cycloadducts have a relatively high molecular weight due to additional aromatic rings and it is not easy to envisage strategies for their transformation into natural products or drug-like scaffolds.

There are no literature descriptions of corresponding 1,3-dipolar cycloadditions of pyridinium ylides to 3-alkylidene oxindoles, yet such cycloadducts would be attractive for access to spirooxindole alkaloids and possible therapeutics. Cycloaddition reactions of pyridinium ylides have previously been reported but *in situ* oxidation is commonly used, leading to valuable unsaturated indolizines.[8] Of course, such oxidations destroy the rich stereochemical information accumulated during the cycloaddition. Early investigation of general pyridinium ylide cycloadditions noted limited stability of the tetrahydroindolizine cycloadducts and this may have discouraged further investigation of these products.[9] The 1,2-dihydropyridine motif embedded within tetrahydroindolizine cycloadducts is generally regarded as unstable with few exceptions,[10] although there have been exciting developments in unlocking their synthetic potential.[11]

This report demonstrates that cycloaddition reactions between pyridinium ylides **2** (Table 1) and 3-alkylidene oxindoles

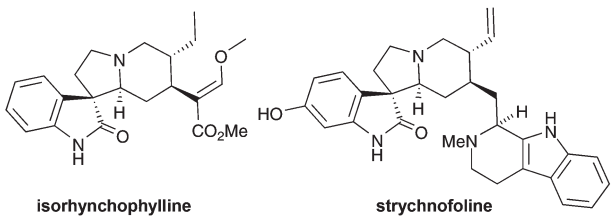
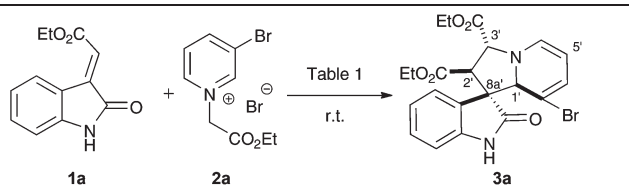


Fig. 1 Example spirooxindole alkaloids.

Table 1 Optimisation of conditions



Solvent	Base	Time (h)	Yield[a] (%)
Toluene	Et_3N	3	65
EtOAc	Et_3N	4	64
CH_2Cl_2	Et_3N	2	88
DMF	Et_3N	1	61
EtOH	Et_3N	4	40
CH_2Cl_2	DBU	3	73
CH_2Cl_2	^tBuOK	3	71
THF	NaH	2	82

[a] Yield after chromatography.

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1 proceed with good selectivity to produce generally isolable spirotetrahydroindolizineoxindole cycloadducts **3** in good yield.

Results and discussion

Starting materials for this route are readily accessible by olefination of isatin to give 3-alkylidene-2-oxindoles;[12]† pyridinium salts were obtained by alkylation.[13]† Pyridinium salts featuring *N*-methylene groups attached to an electron withdrawing group can be readily deprotonated using mild base to give the ylide.[14,15]

Initially, we set out to briefly investigate the role of solvent and base on yield. An excess of pyridinium salt **2a** relative to dipolarophiles **1a** was used to suppress further cycloaddition onto the initial tetrahydroindolizine product.[9]

Generally, high yields of cycloadduct were obtained using a variety of solvents and base at room temperature, although suspending the reagents in dichloromethane, then initiating the reaction by addition of triethylamine is convenient (Table 1). The cycloadduct **3a** is stable to chromatography and could be stored under argon in the freezer for no more than a week.

Cycloaddition between the ylide derived from 3-bromopyridinium salt **2a** and oxindole **1a** appears to be highly regio- and diastereoselective, giving a single product **3a** (Table 1). ^{1}H-NMR spectroscopy of the cycloadduct revealed an apparent triplet for the 5′ proton (J = 7.0 Hz) indicative of reaction at the C-2 position of the pyridinium salt. Initial NOESY analysis revealed enhancements between protons corresponding to 1′ ring junction and 2′ position adjacent to the spirocentre, but not between the 1′ and 3′ positions adjacent to nitrogen.

Ultimately, single crystal X-ray diffraction of this material gave unequivocal evidence of the diastereoselectivity of the reaction (Fig. 2).‡ The relative stereochemistry of the spirocentre (position 8a′) and the 1′ position is diagnostic of *exo* or *endo* selectivity; co-location of the oxindole carbonyl and 1′ proton on the same face of the cycloadduct is suggestive of an attractive interaction between the electron rich oxindole aromatic ring and the electron deficient pyridinium in the transition state. The *trans* arrangement of the 1′ and 3′ protons is also confirmed, indicating that the ylide is *S*-shaped in the transition state (Scheme 1). This relative stereochemistry is the same as that required for alkaloids related to strychnofoline and isorhynchophylline.

We next carried out investigation into the generality of the reaction using various 3-alkylideneoxindoles **1b–f** (Table 2).[11]† Cycloaddition with the ylide derived from 3-bromopyridinium

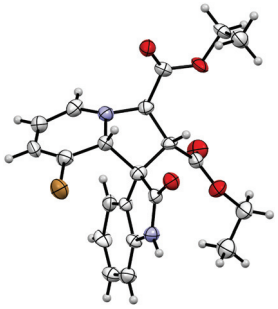
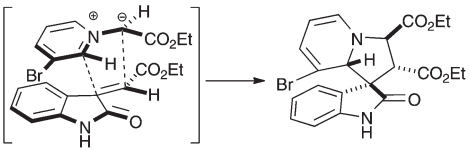


Fig. 2 Crystal structure of cycloadduct **3a** (CCDC 927103). Ellipsoids are drawn at the 50% probability level.



Scheme 1 Proposed origin of observed diastereoselectivity.

salt **2a** generally proceeded to give good yields (80–90%) of cycloadducts **3b–f** as single diastereoisomers with relative stereochemistry similar to cycloadduct **3a** as judged by ^{1}H NMR spectroscopy. 3-Methylene oxindole **1f** is a stable solid that readily undergoes cycloaddition reactions in good yield (entry 5). Unfortunately, *N*-substituted 3-methylene oxindoles are highly reactive and generally met with polymerisation before cycloaddition could be attempted.[16] On the other hand, *N*-propargyl and *N*-acetyl substituted oxindoles (entries 3 and 4, **1d** and **1e** respectively) bearing an ethyl ester gave good yields of cycloadducts (**3d** and **3e** respectively).

A selection of pyridinium salts (**2g–l**) were also evaluated (Table 3). Cycloadducts arising from reaction with unsubstituted pyridinium salt (**2l**) could be detected by mass spectrometry of the reaction mixture but were not stable to purification by chromatography, however the saturated indolizidine **3l** could be obtained by *in situ* reduction using RANEY® nickel in good yield.

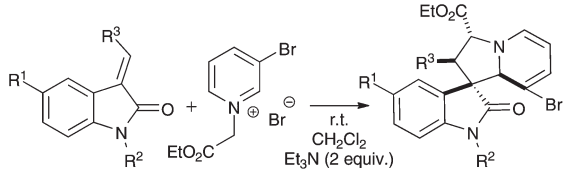
Pyridinium salts featuring methyl, or phenyl substituents at the 3- or 4-pyridinium position (not shown) did not give observable products in their respective cycloaddition reactions using these condition, which we presume to be due to their instability.

Pleasingly, less acidic pyridinium salts featuring either nitrile (**2m**) or phenyl (**2n**) ylide stabilising groups could be deprotonated with sodium hydride, leading to good yields of the corresponding cycloadducts **3m** and **3n** respectively as single diastereoisomers (Scheme 2).

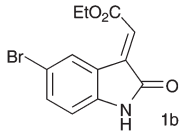
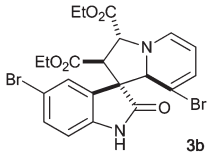
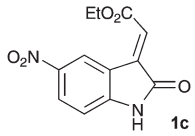
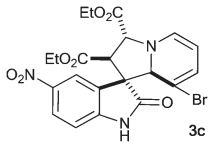
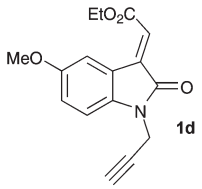
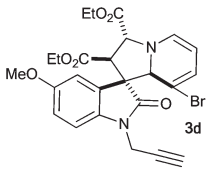
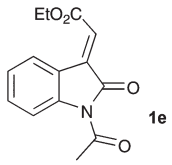
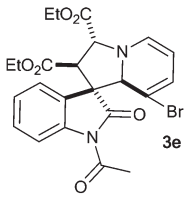
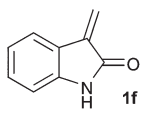
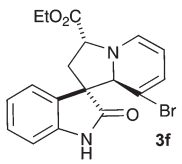
Pyridinium salts featuring resonance stabilising groups (**2g–i**) in the 3-position gave good overall yields of spiroindolizidine oxindoles arising from reaction at the C-6 position of the pyridinium ring, *i.e.* opposite to the electron withdrawing substituent. These products (**3g–i**) were obtained as a mixture of two diastereoisomers in varying ratios.

‡Crystal data for **3a**. $C_{21}H_{21}BrN_2O_5$, M = 507.38, triclinic, a = 8.5537(12), b = 9.0560(14), c = 16.2097(17) Å, U = 1147.4(3) Å^3. T = 120(2)K, space group $P\bar{1}$, Z = 2, 8522 reflections measured, 4490 unique with R = 0.0804, wR_2 = 0.2241. CCDC 927103. Crystal data for **3g′**. $C_{19}H_{17}N_3O_3$, M = 335.35, triclinic, a = 8.8865(5), b = 9.3125(3), c = 10.9460(5) Å, U = 826.26(7) Å^3. T = 120(2) K, space group $P\bar{1}$, Z = 2, 15 441 reflections measured, 3480 unique with R = 0.0346, wR_2 = 0.0903. CCDC 927102.

Table 2 Cycloaddition with varied oxindoles

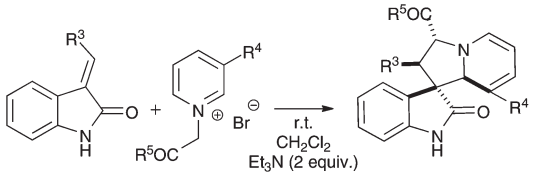


1 - 1 equiv. **2a** - 2 equiv. **3**

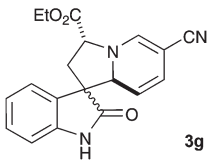
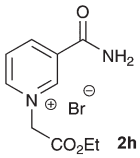
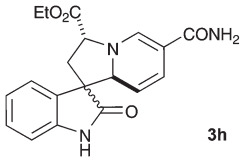
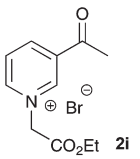
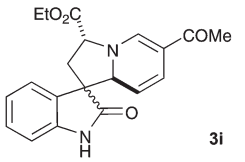
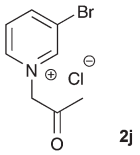
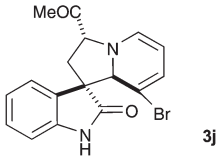
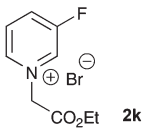
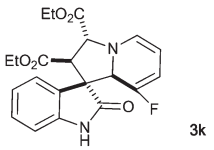
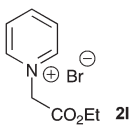
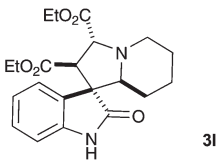
Entry	Oxindole	Cycloadduct	Yield[a] (%)
1	 **1b**	 **3b**	93
2	 **1c**	 **3c**	91
3	 **1d**	 **3d**	82
4	 **1e**	 **3e**	83
5	 **1f**	 **3f**	81

[a] Yield after chromatography.

Table 3 Cycloaddition with various pyridinium salts



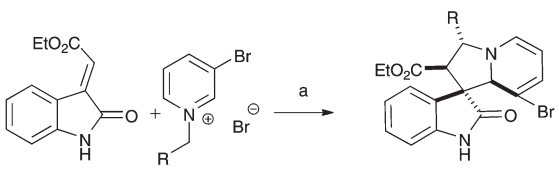
1a/1f - 1 equiv. **2** - 2 equiv. **3**

Entry	Pyridinium salt	Cycloadduct	Yield[a] (%) [ratio]
1	 **2g**	 **3g**	77 [2 : 1][b]
2	 **2h**	 **3h**	95 [7 : 3][b]
3	 **2i**	 **3i**	81 [1 : 1][b]
4	 **2j**	 **3j**	76
5	 **2k**	 **3k**	87
6	 **2l**	 **3l**	63[c]

[a] Yield after chromatography. [b] Inseparable mixture of two diastereoisomers, ratio in parenthesis from relative integration of ^{1}H NMR spectrum. [c] Crude cycloadduct subject to H_2/RANEY® nickel (~10 mol%) in EtOAc.

Crystals were obtained from the 3-cyanopyridine derived cycloadduct **3g** that X-ray diffraction revealed to feature the 1′ proton on the opposite face to the oxindole carbonyl (Fig. 3).‡ This product was later confirmed as the minor diastereoisomer **3g′** by ^{1}H NMR spectroscopy.

There are two possible explanations for these observed results. One is that pyridinium resonance stabilising groups influence the orientation of the transition state. Alternatively, interconversion of cycloadducts *via* ring opening to restore the pyridinium ring, then rotation about the former 2′–8′a bond and rejoining of the enolate with the pyridinium may proceed.[17] An analogous reversible Mannich reaction mechanism is well known to occur in either acidic or basic media, leading to interchange between related spirocyclic oxindole alkaloid diastereoisomers, such as isorhynchophylline and



1a - 1 equiv. **2m** R = CN, **2n** R = Ph - 2 equiv. **3m** R = CN, 72% **3n** R = Ph, 70%

Scheme 2 *Reagents and conditions*: a, NaH (2 equiv.), THF, rt.

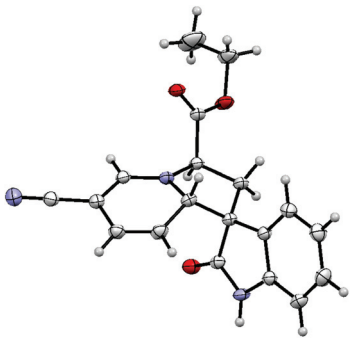
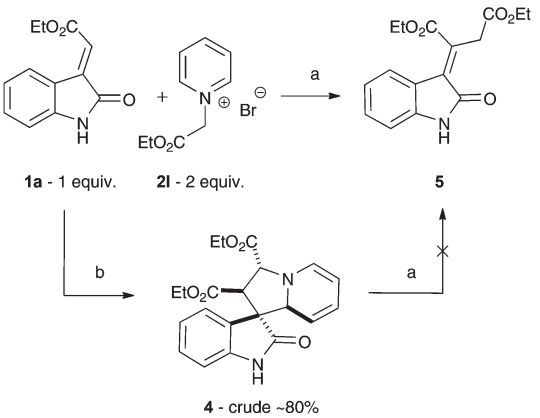


Fig. 3 Crystal structure of the minor diastereoisomer of cycloadduct **3g′** (CCDC 927102). Ellipsoids are drawn at the 50% probability level.

rhynchophylline.[18] Diastereoisomer **3g′** remained unchanged when exposed to the same cycloaddition conditions for 14 hours, however.[19]

A recent paper described reactions of very closely related pyridinium ylides and 3-alkylideneoxindoles in ethanol with 20 mol% triethylamine at 50 °C, but alkene products arising from elimination of pyridine were the exclusive reported products.[20] A similar reaction product was obtained when the cycloaddition reaction between pyridinium ylide **2l** with 3-alkylideneoxindole **1a** was performed in ethanol at room temperature, resulting in clean conversion to the elimination product **5** in 60% yield (Scheme 3). Presumably, the reaction proceeds *via* 1,4-conjugate addition and not cycloaddition, with subsequent elimination of pyridine.[21,22]

Significantly, crude cycloadduct **4** obtained from cycloaddition in dichloromethane at room temperature did not undergo elimination when stirred in ethanol with triethylamine. This result, when considered alongside the observation for cycloadduct **3g′** above, suggests that the reversible mechanism is not occurring in these cases. Overall, these studies underline that, for these reagents, cycloaddition and 1,4-conjugate addition reaction outcomes are under the subtle influence of solvent.



Scheme 3 *Reagents and conditions*: a, Et_3N (2 equiv.), ethanol, rt, 60%; b, Et_3N (2 equiv.), CH_2Cl_2, rt.

Conclusions

In summary, 1,3-dipolar cycloadditions between pyridinium ylides and 3-alkenyloxindoles that give spiroindolizidine oxindole products in high yield and with excellent regioselectivity and diastereoselectivity are reported for the first time. These cycloadducts are highly reminiscent of biologically active alkaloids, especially isorhynchophylline and strychnofoline. Specific modification of this general cycloaddition route to facilitate highly convergent access to such alkaloids and related targets is underway.

Experimental

General information

Experimental describing precursor preparation is included within the ESI.†

General procedure for preparation of cycloadducts (3). Base (2 equiv.) was added to pyridinium salt (2 equiv.) in dry solvent, under argon and the mixture stirred at room temperature for 5 minutes. Oxindole (1 equiv.) was added and the mixture stirred at room temperature for 2–4 hours. Water was added and the organic layer separated, washed with water (2×), brine, dried over Na_2SO_4, filtered and evaporated. The crude products were purified by column chromatography on silica gel (using either MeOH–CH_2Cl_2; 1/10 or EtOAc–petrol; 1/1 as eluent) or recrystallised with ethanol.

(1′*R,2′*S**,3′*S**,8a′*S**)-Diethyl 8′-bromo-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3a).** Brown solid; 121 mg (88%); m.p. 76–78 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3442, 3136, 2984, 2482, 1734, 1639, 1622, 1563, 1471, 1372, 1340, 1249, 1191; NMR δ_H (400 MHz, d^6-DMSO) 10.68 (1H, br s, N*H*), 7.26–7.22 (1H, m, Ar*H*), 7.17 (1H, d, J = 7.4 Hz, Ar*H*), 6.91 (1H, m, Ar*H*), 6.86 (1H, d, J = 7.4 Hz, Ar*H*), 6.61 (1H, d, J = 7.0 Hz, N–C*H*=CH), 6.10 (1H, d, J = 7.0 Hz, CH–C*H*=CBr), 5.06 (1H, d, J = 7.0 Hz, NC*H*(CO_2Et), 5.00 (1H, s, NC*H*C–Br), 4.45 (1H, app t, J = 7.0 Hz, NCH=C*H*), 4.21 (2H, q, J = 7.1 Hz, NCHCO_2C*H*$_2$CH$_3$), 3.65 (2H, q, J = 7.1 Hz, CCH(CO_2C*H*$_2$CH$_3$)), 3.45 (1H, d, J = 7.0 Hz, CC*H*(CO_2Et), 1.23 (3H, t, J = 7.1 Hz, NCHCOCH$_2$C*H*$_3$), 0.62 (3H, t, J = 7.1 Hz, CCO_2CH$_2$C*H*$_3$); NMR δ_C (100 MHz, d^6-DMSO) 176.2 (C), 171.4 (C), 168.4 (C), 144.0 (C), 134.9 (CH), 129.5 (CH), 128.9 (CH), 126.5 (C), 124.7 (CH), 121.5 (CH), 109.9 (CH), 106.9 (C), 93.2 (CH), 72.6 (CH), 64.8 (CH), 64.2 (C), 62.0 (CH_2), 61.4 (CH_2), 52.8 (CH), 14.5 (CH_3), 13.5 (CH_3); m/z (HRMS-ESI+) 461.0697 (M + H $C_{21}H_{22}{}^{79}BrN_2O_5$ requires 461.0712), 463.0700 (M + H $C_{21}H_{22}{}^{81}BrN_2O_5$ requires 463.0692).

(1′*R,2′*S**,3′*S**,8a′*S**)-Diethyl 5,8′-dibromo-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3b).** Brown solid; 85 mg (93%); m.p. 68–70 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3437, 2982, 1732, 1639, 1618, 1564, 1465, 1373, 1309, 1130; NMR δ_H (400 MHz, d^6-acetone) 9.84 (1H, br s, N*H*), 7.45–7.41 (2H, m, Ar*H*), 6.95 (1H, dd, J = 8.2, 0.4 Hz, Ar*H*), 6.61 (1H, d, J = 7.1 Hz, N–C*H*=CH), 6.14 (1H, app dt, J = 6.4, 1.0 Hz, CH–C*H*=CBr), 5.20 (1H, d, J = 1.0 Hz, NC*H*CBr), 5.05 (1H, d, J = 6.6 Hz, NC*H*(CO_2Et), 4.58 (1H, dd, J = 7.1, 6.4 Hz, NCH=C*H*), 4.27

(2H, q, J = 7.1 Hz, NCHCO$_2$CH_2CH$_3$), 3.76 (2H, q, J = 7.1 Hz, CCHCO$_2$CH_2CH$_3$), 3.69 (1H, d, J = 6.6 Hz, CCHCO$_2$Et), 1.29 (3H, t, J = 7.1 Hz, NCHCOCH$_2$CH_3), 0.78 (3H, t, J = 7.1 Hz, CCHCO$_2$CH$_2$CH_3); NMR δ_C (100 MHz, d^6-acetone) 175.3 (C), 170.6 (C), 168.0 (C), 143.0 (C), 134.0 (CH), 131.9 (CH), 129.0 (C), 128.8 (CH), 127.5 (CH), 113.3 (C), 111.3 (CH), 106.8 (C), 93.3 (CH), 72.8 (CH), 64.8 (CH), 64.4 (C), 61.6 (CH$_2$), 61.1 (CH$_2$), 52.8 (CH), 13.6 (CH$_3$), 12.9 (CH$_3$); m/z (HRMS-ESI+) 538.9808 (M + H $C_{21}H_{21}{}^{79}Br_2N_2O_5$ requires 538.9812), 540.9806 (M + H $C_{21}H_{21}{}^{81}Br_2N_2O_5$ requires 540.9792).

(1′*R,2′*S**,3′*S**,8a′*S**)-Diethyl 8′-bromo-5-nitro-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3c).** Yellow solid; 88 mg (91%); m.p. 83–85 °C; IR (ν_{max}/cm^{-1}, CHCl$_3$) 3249, 2981, 1745, 1626, 1603, 1455, 1343, 1125; NMR δ_H (400 MHz, d^6-acetone) 10.30 (1H, br s, NH), 8.28 (1H, dd, J = 8.7, 2.3 Hz, ArH), 8.17 (1H, d, J = 2.3 Hz, ArH), 7.22 (1H, d, J = 8.7 Hz, ArH), 6.70 (1H, d, J = 7.1 Hz, N–CH=CH), 6.15 (1H, d, J = 6.4 Hz, CH–CH=CBr), 5.27 (1H, s, NCHC–Br), 5.15 (1H, d, J = 6.5 Hz, NCH(CO$_2$Et)), 4.62 (1H, dd, J = 7.1, 6.4 Hz, NCH=CH), 4.28 (2H, q, J = 7.1 Hz, NCHCO$_2$CH_2CH$_3$), 3.77 (1H, d, J = 6.5 Hz, CCH(CO$_2$Et)), 3.76 (2H, q, J = 7.1 Hz, CCH(CO$_2$CH_2CH$_3$)), 1.30 (3H, t, J = 7.1 Hz, NCHCOCH$_2$CH_3), 0.77 (3H, t, J = 7.1 Hz, CCH(CO$_2$CH$_2$CH_3)); NMR δ_C (100 MHz, d^6-acetone) 176.0 (C), 170.4 (C), 167.9 (C), 149.9 (C), 142.4 (C), 134.0 (CH), 129.1 (CH), 127.5 (C), 126.3 (CH), 120.2 (CH), 109.7 (CH), 106.4 (C), 93.6 (CH), 73.2 (CH), 65.0 (CH), 64.2 (C), 61.7 (CH$_2$), 61.4 (CH$_2$), 52.8 (CH), 13.6 (CH$_3$), 12.9 (CH$_3$); m/z (HRMS-ESI+) 506.0569 (M + H $C_{21}H_{21}{}^{79}BrN_3O_7$ requires 506.0558), 508.0552 (M + H $C_{21}H_{21}{}^{81}BrN_3O_7$ requires 508.0537).

(1′*R,2′*S**,3′*S**,8a′*S**)-Diethyl 8′-bromo-5-methoxy-2-oxo-1-(prop-2-yn-1-yl)-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3d).** Grey solid; 74 mg (82%); m.p. 125–127 °C (ethanol); IR (ν_{max}/cm^{-1}, CHCl$_3$) 3309, 3011, 1738, 1718, 1639, 1605, 1495, 1370, 1339, 1192; NMR δ_H (400 MHz, d^6-acetone) 7.07 (1H, d, J = 8.5 Hz, ArH), 6.99 (1H, d, J = 2.4 Hz, ArH), 6.94 (1H, dd, J = 8.5, 2.4 Hz, ArH), 6.61 (1H, d, J = 7.1 Hz, N–CH=CH), 6.08 (1H, dt, J = 6.4, 0.9 Hz, CH–CH=CBr), 5.21 (1H, d, J = 0.9 Hz, NCHC–Br), 5.06 (1H, d, J = 6.9 Hz, NCH(CO$_2$Et)), 4.63 (1H, d, J = 17.8, 2.6 Hz, NCH_aH$_b$), 4.57 (1H, dd, J = 7.1, 6.4 Hz, NCH=CH), 4.50 (1H, d, J = 17.8, 2.5 Hz, NCH$_a$$H_b$), 4.27 (2H, q, J = 7.1 Hz, NCHCO$_2$CH_2CH$_3$), 3.74 (3H, s, OCH$_3$), 3.73 (1H, d, J = 6.9 Hz, CCH(CO$_2$Et), 3.72 (2H, q, J = 7.1 Hz, CCH(CO$_2$CH_2CH$_3$)), 2.80 (1H, dd, J = 2.6, 2.5 Hz, C≡CH), 1.30 (3H, t, J = 7.1 Hz, NCHCOCH$_2$CH_3), 0.73 (3H, t, J = 7.1 Hz, CCH(CO$_2$CH$_2$CH_3)); NMR δ_C (100 MHz, d^6-acetone) 172.8 (C), 170.7 (C), 167.9 (C), 155.6 (C), 137.0 (C), 133.9 (CH), 128.5 (CH), 126.9 (C), 113.3 (CH), 111.8 (CH), 109.3 (CH), 106.4 (C), 93.3 (CH), 76.9 (C), 72.8 (CH), 72.7 (C), 64.8 (CH), 61.5 (CH$_2$), 61.0 (CH$_2$), 52.3 (CH), 55.1 (CH), 52.3 (CH$_3$), 29.2 (CH$_2$), 13.6 (CH$_3$), 12.9 (CH$_3$); m/z (HRMS-ESI+) 529.0957 (M + H $C_{25}H_{26}{}^{79}BrN_2O_6$ requires 529.0969), 531.0951 (M + H $C_{25}H_{26}{}^{81}BrN_2O_6$ requires 531.0949).

(1′*R,2′*S**,3′*S**,8a′*S**)-Diethyl 1-acetyl-8′-bromo-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3e).** Yellow solid; 80 mg (83%); m.p. 108–110 °C; IR (ν_{max}/cm^{-1}, CHCl$_3$) 2981, 1744, 1710, 1636, 1561, 1466, 1370, 1308, 1272, 1191, 1023; NMR δ_H (400 MHz, d^6-acetone) 8.22 (1H, d, J = 8.2 Hz, ArH), 7.45–7.39 (2H, m, ArH), 7.21 (1H, td, J = 8.2, 1.4 Hz, ArH), 6.63 (1H, d, J = 7.1 Hz, N–CH=CH), 6.11 (1H, d, J = 6.5 Hz, CH–CH=CBr), 5.37 (1H, s, NCHC–Br), 5.05 (1H, d, J = 7.3 Hz, NCH(CO$_2$Et)), 4.58 (1H, dd, J = 7.1, 6.5 Hz, NCH=CH), 4.29 (2H, q, J = 7.1 Hz, NCHCO$_2$CH_2CH$_3$), 3.86 (1H, d, J = 7.3 Hz, CCH(CO$_2$Et), 3.69 (2H, q, J = 7.1 Hz, CCH(CO$_2$CH_2CH$_3$)), 2.66 (3H, s, NCOCH_3), 1.31 (3H, t, J = 7.1 Hz, NCHCOCH$_2$CH_3), 0.69 (3H, t, J = 7.1 Hz, CCH(CO$_2$CH$_2$CH_3)); NMR δ_C (100 MHz, d^6-acetone) 175.3 (C), 170.4 (C), 170.3 (C), 167.4 (C), 141.5 (C), 133.8 (CH), 129.4 (CH). 129.1 (CH), 125.4 (C), 124.7 (CH), 123.9 (CH), 115.9 (CH), 106.3 (C), 93.5 (CH), 74.3 (CH), 64.5 (CH), 63.8 (C), 61.7 (CH$_2$), 61.2 (CH$_2$), 53.6 (CH), 25.8 (CH$_3$), 13.5 (CH$_3$), 12.7 (CH$_3$); m/z (HRMS-ESI+) 503.0800 (M + H $C_{23}H_{24}{}^{79}BrN_2O_6$ requires 503.0813), 505.0788 (M + H $C_{23}H_{24}{}^{81}BrN_2O_6$ requires 505.0792).

(1′*S,3′*R**,8a′*S**)-Ethyl 8′-bromo-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-3′-carboxylate (3f).** Brown solid; 107 mg (81%); m.p. 144–146 °C; IR (ν_{max}/cm^{-1}, CHCl$_3$) 3434, 2962, 2361, 1732, 1621, 1472, 1374, 1261, 1106; NMR δ_H (400 MHz, CDCl$_3$) 8.55 (1H, s, NH), 7.33–7.28 (2H, m, ArH), 7.09–7.04 (1H, m, ArH), 6.97 (1H, d, J = 7.3 Hz, ArH), 6.25 (1H, d, J = 7.2 Hz, NCH=CH), 6.07 (1H, d, J = 7.2 Hz, CH=CBr), 5.38 (1H, s, CH), 4.62 (1H, app.t, J = 7.2 Hz, NCH=CH), 4.44 (1H, dd, J = 8.4, 7.9 Hz, CHCO$_2$Et), 4.29 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 2.52 (1H, dd, J = 13.4, 7.9 Hz, CH_aH$_b$), 2.22 (1H, dd, J = 13.4, 8.4 Hz, CH$_a$$H_b$), 1.35 (3H, t, J = 7.1 Hz, CH$_2$CH_3); NMR δ_C (100 MHz, CDCl$_3$) 178.0 (C), 171.7 (C), 141.1 (C), 132.8 (CH), 130.6 (C), 128.6 (CH), 127.4 (CH), 123.6 (CH), 122.5 (CH), 110.0 (CH), 109.3 (C), 94.9 (CH), 71.5 (CH), 64.1 (CH), 61.8 (CH$_2$), 60.9 (C), 37.7 (CH$_2$), 14.2 (CH$_3$); m/z (HRMS-ESI+) 389.0494 (M + H $C_{18}H_{18}{}^{79}BrN_2O_3$ requires 389.0501), 391.0476 (M + H $C_{18}H_{18}{}^{81}BrN_2O_3$ requires 391.0480).

(1′*S,3′*R**,8a′*S**)-Ethyl 6′-cyano-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-3′-carboxylate (3g) and (1′*R**,3′*R**,8a′*S**)-ethyl 6′-cyano-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-3′-carboxylate (3g′).** Yellow solid; 90 mg (77%); m.p. 188–190 °C; IR (ν_{max}/cm^{-1}, CHCl$_3$) 3203. 2981, 2938, 2203, 1731, 1643, 1621, 1574, 1485, 1469, 1391, 1133; NMR δ_H (400 MHz, d^6-acetone, 2 : 1 mixture of diastereoisomers, *indicates minor where different from major) 9.65 (1H, br s, NH), 9.50 (1H, br s, NH*), 7.35–7.20 (3H, m, ArH, NCC=CH), 7.07–6.95 (2H, m, ArH), 5.80 (1H, app dt, J = 10.0, 1.5 Hz, CNC–CH*=CH), 5.67 (1H, app dt, J = 10.1, 1.5 Hz, CNC–CH=CH), 5.06 (1H, t, J = 2.1 Hz, NCH*), 4.98–4.93 (2H, m, CHCO$_2$Et, NCH), 4.86 (1H, app t, J = 7.7 Hz, CH*CO$_2$Et), 4.60 (1H, ddd, J = 10.0, 2.1, 1.0 Hz, CH=CH*–CH), 4.52 (1H, ddd, J = 10.1, 2.1, 0.8 Hz, CH=CH–CH), 4.35–4.24 (2H, m, CH_2CH_3), 2.57 (1H, dd, J = 13.4, 8.6 Hz, CH_a*), 2.48–2.43 (2H, m, CH_2CHCO$_2$Et), 2.37 (1H, dd, J = 13.4, 7.7 Hz, CH_b*), 1.30 (3H, t, J = 7.1 Hz, CH$_2$CH_3); NMR δ_C (100 MHz, d^6-acetone) 179.3 (C), 176.5 (C), 171.8 (C), 171.6 (C), 147.8 (CH), 146.6 (CH), 143.5 (C), 142.3 (C), 132.1 (C), 129.8 (CH), 129.4 (CH), 127.9 (C), 126.4 (C), 124.7 (CH), 124.0 (CH), 123.7 (CH), 123.2 (CH), 123.0 (CH), 120.9 (C), 120.7 (C) 111.9 (CH), 111.5 (CH), 110.7 (CH), 110.2 (CH), 78.6 (C), 78.4 (C), 67.8 (CH), 67.4 (CH), 63.9

(CH), 63.2 (CH), 62.4 (CH_2), 62.3 (CH_2), 37.2 (CH_2), 34.9 (CH_2), 14.5 (CH_3); *m/z* (HRMS-ESI+) 358.1162 (M + Na $C_{19}H_{17}N_3NaO_3$ requires 358.1162).

(1′*R,3′*S**,8a′*R**)-Ethyl 6′-carbamoyl-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-3′-carboxylate (3h) and (1′*R**,3′*S**,8a′*S**)-ethyl 6′-carbamoyl-2-oxo-3′,8a′-dihydro-2′*H*-spiro-[indoline-3,1′-indolizine]-3′-carboxylate (3h′).** Yellow solid; 109 mg (95%); m.p. 138–140 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3352. 2926, 2359, 2340, 1710, 1648, 1620, 1585, 1471, 1382, 1290, 1196, 1104; NMR δ_H (400 MHz, d^6-DMSO, 7 : 3 mixture of diastereoisomers, *indicates minor where different from major) 10.63 (1H, s, N*H*), 10.40 (1H, s, N*H**), 7.38 (2H, s, C*H*=CCONH$_2$), 7.27–7.16 (4H, m, Ar*H*), 7.02–6.84 (4H, m, Ar*H*), 6.54 (4H, br s, NH_2), 6.28 (1H, dt, *J* = 10.2, 2.1 Hz, NH_2COC–C*H**=CH), 6.14 (1H, dt, *J* = 10.2, 2.1 Hz, NH_2COC–C*H*=CH), 4.95 (1H, dd, *J* = 8.8, 7.4 Hz, C*H*CO_2Et), 4.92 (1H, dd, *J* = 8.8, 7.4 Hz, C*H**CO_2Et), 4.78 (2H, app dd, *J* = 2.1, 0.6 Hz, NC*H*), 4.38 (1H, ddd, *J* = 10.2, 2.1, 0.6 Hz, CH=C*H**–CH), 4.35 (1H, ddd, *J* = 10.2, 2.1, 0.6 Hz, CH=C*H*–CH), 4.24 (4H, m, C$H_2$$CH_3$), 2.47 (1H, dd, *J* = 13.3, 8.8 Hz, CH_a*H_b), 2.35–2.17 (2H, m, CH_b*, C$H_a$$H_b$), 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3*), 1.27 (3H, t, *J* = 7.1 Hz, CH_2CH_3); NMR δ_C (100 MHz, d^6-DMSO) 179.3 (C), 176.6 (C), 172.2 (C), 172.1 (C), 167.4 (C), 167.3 (C), 143.0 (C), 142.6 (CH), 141.9 (C), 141.5 (CH), 132.0 (C) 129.0 (CH), 128.7 (CH), 128.0 (C) 124.8 (CH), 124.2 (CH), 124.1 (CH), 123.2 (CH), 122.1 (CH), 122.0 (CH) 110.0 (CH), 109.9 (CH), 109.1 (CH), 107.5 (CH), 101.1 (C), 101.0 (C), 68.1 (CH), 67.5 (CH), 63.5 (CH), 62.6 (CH), 61.8 (CH_2), 61.7 (CH_2), 55.6 (C), 55.4 (C), 36.5 (CH_2), 34.3 (CH_2), 14.6 (CH_3), 14.5 (CH_3); *m/z* (HRMS-ESI+) 354.1442 (M + H $C_{19}H_{20}N_3O_4$ requires 354.1454).

(1′*R,3′*S**,8a′*R**)-Ethyl 6′-acetyl-2-oxo-3′,8a′-dihydro-2′*H*-spiro-[indoline-3,1′-indolizine]-3′-carboxylate (3i) and (1′*R**,3′*S**,8a′*S**)-ethyl 6′-acetyl-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-3′-carboxylate (3i′).** Brown solid, 97 mg (81%); m.p. 118–120 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3434, 3010, 2447, 1731, 1621, 1573, 1472, 1373, 1251, 1180; NMR δ_H (400 MHz, $CDCl_3$, 1 : 1.3 mixture of diastereoisomers, *indicates minor where different from major) 8.35 (1H, s, N*H**), 8.21 (1 H, s, N*H*), 7.47 (1H, s, NC*H**=CCOCH_3), 7.42 (1H, s, NC*H*=CCOCH_3), 7.27–6.94 (8H, m, Ar*H*), 6.53 (1H, d, *J* = 10.3 Hz, (COCH_3) C*H*=CH–CH), 6.36 (1H, d, *J* = 10.3 Hz, (COCH_3)C*H**=CH–CH), 5.18 (1H, t, *J* = 1.8 Hz, (COCH_3)CH=CH–C*H**), 5.05 (1H, t, *J* = 1.8 Hz, (COCH_3)CH=CH–C*H*), 4.81 (1H, t, *J* = 7.8 Hz, C*H*CO_2Et), 4.67 (1H, dd, *J* = 10.3, 1.8 Hz, (COCH_3)CH=C*H*–CH) 4.61 (1H, t, *J* = 7.8 Hz, C*H**CO_2Et) 4.53 (1H, dd, *J* = 10.3, 1.8 Hz, (COCH_3)CH=C*H**–CH), 4.38–4.30 (4H, m, C$H_2$$CH_3$), 2.70–2.58 (2H, m, CH–C$H_a$$CH_b$), 2.45–2.33 (2H, m, CH–$CH_aCH_b$), 2.18 (3H, s, CO$CH_3$*), 2.13 (3H, s, CO$CH_3$), 1.41–1.34 (3H, m, CH_2CH_3); NMR δ_C (100 MHz, $CDCl_3$) 191.8 (C), 179.6 (C), 176.8 (C), 171.2 (C), 170.6 (C), 146.2 (CH), 144.3 (CH), 141.6 (C), 140.3 (C), 130.7 (C), 129.2 (CH), 128.9 (CH), 126.8 (C), 123.9 (CH), 123.7 (CH), 123.5 (CH), 123.2 (CH), 122.9 (CH), 122.8 (CH), 122.6 (CH), 110.4 (CH), 110.3 (CH), 108.7 (CH), 68.1 (CH), 67.1 (CH), 63.3 (CH), 62.8 (CH), 62.4 (CH_2), 62.2 (CH_2), 58.8 (C), 58.4 (C), 36.9 (CH_2), 34.4 (CH_2), 14.2 (CH_3); *m/z* (HRMS-ESI+) 353.1498 (M + H $C_{20}H_{21}N_2O_4$ requires 353.1501).

(1′*R,3′*S**,8a′*S**)-3′-Acetyl-8′-bromo-3′,8a′-dihydro-2′*H*-spiro [indoline-3,1′-indolizin]-2-one (3j).** Brown solid; 63 mg (76%); m.p. 126–128 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3438, 3011, 2928, 2437, 1780, 1721, 1622, 1471, 1426, 1390, 1240, 1170; NMR δ_H (400 MHz, d^6-DMSO) 10.53 (1H, s, N*H*), 7.27–7.19 (2H, m, 2× Ar*H*), 6.96 (1H, td, *J* = 7.6, 1.0 Hz, Ar*H*), 6.86 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.43 (1H, d, *J* = 7.0 Hz, CH–C*H*=CBr), 6.09 (1H, d, *J* = 7.0 Hz, N–C*H*=CH), 4.88 (1H, s, NC*H*), 4.70 (1H, t, *J* = 7.0 Hz, NCH=C*H*), 4.49 (1H, t, *J* = 6.8 Hz, C*H*$COCH_3$), 2.19 (3H, s, COCH_3), 2.11–2.06 (2H, m, C$H_a$$H_b$); NMR δ_C (100 MHz, d^6-DMSO) 207.3 (C), 177.7 (C), 142.8 (C), 135.2 (CH), 131.3 (C), 128.7 (CH), 128.2 (CH), 123.8 (CH), 121.8 (CH), 109.9 (CH), 108.0 (C), 93.3 (CH), 71.7 (CH), 70.5 (CH), 61.3 (C), 36.4 (CH_2), 26.7 (CH_3); *m/z* (HRMS-ESI+) 359.0370 (M + H $C_{17}H_{16}{}^{79}BrN_2O_2$ requires 359.0395), 361.0359 (M + H $C_{17}H_{16}{}^{81}BrN_2O_2$ requires 361.0375).

(2′*S,3′*S**,8a′*S**)-Diethyl 8′-fluoro-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3k).** Yellow oil; 80 mg (87%); IR (ν_{max}/cm^{-1}, $CHCl_3$) 3691, 3440, 3010, 1736, 1620, 1597, 1472, 1391, 1314, 1192, 1025; NMR δ_H (400 MHz, d^6-acetone) 9.66 (1H, br s, N*H*), 7.26–7.22 (2H, m, Ar*H*), 6.97–6.91 (2H, m, Ar*H*), 6.35–6.32 (1H, m, N–C*H*=CH), 5.39–5.34 (1H, m, CH–C*H*=CF), 5.17 (1H, s, NC*H*C–F), 5.03 (1H, dd, *J* = 7.4, 1.2 Hz, NC*H*(CO_2Et)), 4.54–4.49 (1H, m, NCH=C*H*), 4.27 (2H, q, *J* = 7.1 Hz, NCHCO_2C$H_2$$CH_3$), 3.81–3.66 (3H, m, NCH(CO_2Et)C*H*(CO_2Et), NCH(CO_2Et)CH-(CO_2C$H_2$$CH_3$)), 1.29 (3H, t, *J* = 7.1 Hz, NCHCOCH_2CH_3), 0.70 (3H, t, *J* = 7.1 Hz, NCH(CO_2Et)CH(CO_2CH_2CH_3)); NMR δ_C (100 MHz, d^6-acetone) 174.9 (C), 170.9 (C), 168.1 (C), 149.3 (d, J^{C-F} = 252 Hz, C), 143.0 (C), 130.5 (d, J^{C-F} = 4 Hz, CH), 129.0 (CH), 126.6 (C), 124.6 (CH), 121.3 (CH), 109.6 (CH), 103.1 (d, J^{C-F} = 14 Hz, CH), 91.1 (d, J^{C-F} = 5 Hz, CH), 68.0 (d, J^{C-F} = 33 Hz, CH), 65.3 (d, J^{C-F} = 1 Hz, CH), 62.6 (d, J^{C-F} = 3 Hz, C), 61.5 (CH_2), 60.9 (CH_2), 52.9 (CH), 13.6 (CH_3), 12.8 (CH_3); *m/z* (HRMS-ESI+) 401.1507 (M + H $C_{21}H_{22}FN_2O_5$ requires 401.1507).

(1′*R,2′*S**,3′*S**,8a′*R**)-Diethyl 2-oxo-3′,5′,6′,7′,8′,8a′- hexahydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′,3′-dicarboxylate (3l).** Following the general procedure described above but the product was not stable to chromatography on silica gel, so the crude cycloadduct **4** was reduced without purification using the following procedure.

Crude cycloadduct **4** (75 mg) and RANEY® nickel (10 mol%) were dissolved in anhydrous ethyl acetate (4 mL), under argon. The atmosphere was replaced with H_2 and the mixture stirred until reduction was complete by TLC analysis and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and purified *via* column chromatography (EtOAc–petrol; 1/4) to give spiroindolizidine **3l** as a yellow oil; 48 mg (63%); IR (ν_{max}/cm^{-1}, $CHCl_3$) 3440, 3198, 2942, 1732, 1621, 1471, 1373, 1339, 1319, 1184, 1097; NMR δ_H (400 MHz, $CDCl_3$) 8.66 (1H, br s, N*H*), 7.31 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.22 (1H, td, *J* = 7.6, 1.0 Hz, Ar*H*), 7.00 (1H, t, *J* = 7.6 Hz, Ar*H*), 6.92 (1H, d, *J* = 7.6 Hz, Ar*H*), 4.59 (1H, d, *J* = 5.6 Hz, NC*H*CO_2Et), 4.35–4.20 (2H, m, NCH(COCH_2CH_3)), 4.00 (1H, d, *J* = 5.6 Hz, NCH(CO_2Et)C*H*), 3.81–3.61 (2H, m, CH(COCH_2CH_3)), 3.41 (1H, dd, *J* = 10.9, 2.4

Hz, NC*H*C)), 3.09 (1H, d, J = 9.5 Hz, CH_aH$_b$), 2.45 (1H, t, J = 9.5 Hz, CH$_a$$H_b$), 1.64–1.53 (2H, m, C$H_aH_b$, CH$_a$$H_b$), 1.42–1.12 (6H, m, C$H_aH_b$, CH$_a$$H_b$, CH$_aCH_b$, CH$_2CH_3$), 0.74–0.64 (4H, m, CH$_2CH_3$, C$H_aCH_b$); NMR δ_C (100 MHz, CDCl$_3$) 178.4 (C), 172.4 (C), 143.1 (C), 131.7 (C), 128.2 (CH), 126.5 (C), 125.8 (CH), 122.2 (CH), 109.4 (CH), 67.7 (CH), 64.1 (CH), 60.9 (CH$_2$), 60.6 (CH$_2$), 60.0 (C), 54.2 (CH), 47.5 (CH$_2$), 25.9 (CH$_2$), 25.3 (CH$_2$), 22.6 (CH$_2$), 14.4 (CH$_3$), 13.3 (CH$_3$); m/z (HRMS-ESI+) 387.1908 (M + H $C_{21}H_{27}N_2O_5$ requires 387.1920).

(1′*S,2′*R**,3′*R**,8a′*R**)-Ethyl 8′-bromo-3′-cyano-2-oxo-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′-carboxylate (3m).** White solid; 145 mg (72%); m.p. 159–161 °C (acetone); IR (ν_{max}/cm^{-1}, CHCl$_3$) 3691, 3439, 3009, 2482, 2245, 1735, 1640, 1621, 1569, 1485, 1378, 1191; NMR δ_H (400 MHz, d^6-acetone) 9.74 (1H, br s, N*H*), 7.28 (1H, app t, J = 7.6 Hz, Ar*H*), 7.22 (1H, d, J = 7.3 Hz, Ar*H*), 7.01–6.91 (2H, m, Ar*H*), 6.67 (1H, d, J = 7.2, N–C*H*=CH), 6.12 (1H, d, J = 6.4 Hz, CH–C*H*=CBr), 5.48 (1H, d, J = 6.4 Hz, NC*H*CN, 5.25 (1H, s, NC*H*C–Br), 4.72 (1H, app t, J = 6.4 Hz, NCH=C*H*), 3.77 (1H, d, J = 6.4 Hz, C*H*CO$_2$CH$_2$CH$_3$), 3.72 (2H, q, J = 7.1 Hz, CCH(CO$_2$CH_2CH$_3$)), 0.74 (3H, t, J = 7.1 Hz, NCHCOCH$_2$CH_3); NMR δ_C (100 MHz, d^6-DMSO) 176.1 (C), 167.9 (C), 144.6 (C), 132.8 (CH), 130.3 (CH), 129.1 (CH), 126.7 (C), 125.5 (CH), 122.3 (CH), 119.1 (C), 110.6 (CH), 109.1 (C), 96.7 (CH), 72.9 (CH), 63.8 (C), 62.3 (CH$_2$), 55.6 (CH), 54.9 (CH), 13.7 (CH$_3$); m/z (HRMS-ESI+) 436.0273 (M + Na $C_{19}H_{16}{}^{79}BrN_3NaO_3$ requires 436.0273), 438.0256 (M + Na $C_{19}H_{16}{}^{81}BrN_3NaO_3$ requires 438.0256).

(1′*S,2′*R**,3′*R**,8a′*R**)-Ethyl 8′-bromo-2-oxo-3′-phenyl-3′,8a′-dihydro-2′*H*-spiro[indoline-3,1′-indolizine]-2′-carboxylate (3n).** White solid; 149 mg (70%); m.p. 176–178 °C (acetone); IR (ν_{max}/cm^{-1}, CHCl$_3$) 3692, 3441, 3009, 1731, 1601, 1562, 1484, 1379, 1247, 1117, 1027; NMR δ_H (400 MHz, d^6-acetone) 9.71 (1H, br s, N*H*), 7.51–7.41 (5H, m, Ar*H*), 7.36–7.25 (2H, m, Ar*H*), 7.01 (1H, td, J = 7.7, 0.8 Hz, Ar*H*), 6.97 (1H, d, J = 7.7 Hz, Ar*H*), 6.32 (1H, d, J = 6.7 Hz, N–C*H*=CH), 6.07 (1H, d, J = 6.7 Hz, CH–C*H*=CBr), 5.43 (1H, d, J = 8.5 Hz, NC*H*Ph, 4.51 (1H, app t, J = 6.7 Hz, C*H*=CHN), 3.78 (1H, dq, J = 10.8, 7.1 Hz, CH_aH$_b$), 3.67 (1H, dq, J = 10.8, 7.1 Hz, CH$_a$$H_b$), 3.4 (1H, d, J = 8.5 Hz, C*H*CO$_2$Et), 0.77 (3H, t, J = 7.1 Hz, *CH*$_3$); NMR δ_C (100 MHz, d^6-acetone) 176.6 (C), 169.3 (C), 144.5 (C), 143.2 (C), 134.6 (CH), 130.0 (CH), 129.9 (CH), 129.4 (CH), 128.7 (CH), 127.5 (C), 127.2 (CH), 125.6 (CH), 122.2 (CH), 110.4 (CH), 108.3 (C), 94.1 (CH), 73.7 (CH), 68.1 (CH), 64.8 (C), 61.6 (CH$_2$), 59.4 (CH), 13.8 (CH$_3$); m/z (HRMS-ESI+) 465.0800 (M + H $C_{24}H_{22}{}^{79}BrN_2O_3$ requires 465.0808), 467.0786 (M + H $C_{24}H_{22}{}^{81}BrN_2O_3$ requires 465.0793).

Diethyl 2-(2-oxoindolin-3-ylidene)succinate 5. Method as cycloaddition, but ethanol was used as solvent and reaction performed at 50 °C. Yellow oil (60%); NMR δ_H (400 MHz, CDCl$_3$, 5 : 1 mixture of diastereoisomers, only major diastereoisomer peaks are quoted) (ν_{max}/cm^{-1}, CHCl$_3$) 3446, 3011, 2986, 1726, 1617, 1470, 1370, 1334, 1295, 1192; NMR δ_H (400 MHz, CDCl$_3$) 8.38 (1H, s, N*H*), 7.66 (1H, d, J = 8.0 Hz, Ar*H*), 7.29 (1H, td, J = 8.0, 1.2 Hz, Ar*H*), 6.98 (1H, td, J = 8.0, 1.2 Hz, Ar*H*), 6.85 (1H, d, J = 8.0 Hz, Ar*H*), 4.43 (2H, q, J = 7.2 Hz, CH_2CH$_3$), 4.41 (2H, s, CH_2CO$_2$Et), 4.22 (2H, q, J = 7.2 Hz, CH_2CH$_3$), 1.40 (3H, t, J = 7.2 Hz, CH$_2$CH_3), 1.29 (3H, t, J = 7.2 Hz, CH$_2$CH_3); NMR δ_C (100 MHz, CDCl$_3$) 169.7 (C), 169.2 (C), 167.4 (C), 141.0 (C), 135.0 (C), 130.9 (CH), 129.4 (C), 125.1 (CH), 122.3 (CH), 120.8 (C), 109.9 (CH), 61.9 (CH$_2$), 61.2 (CH$_2$), 34.7 (CH$_2$), 14.2 (CH$_3$), 14.0 (CH$_3$); m/z (HRMS-ESI+) 326.0982 ([M + Na] 100%) requires $C_{16}H_{17}NO_5Na^+$ 326.0999.

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Notes and references

1 B. Over, S. Wetzel, C. Grutter, Y. Nakai, S. Renner, D. Rauh and H. Waldmann, *Nat. Chem.*, 2013, **5**, 21–28.
2 C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758.
3 C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209–2219.
4 G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104–6155.
5 For recent examples and references: (*a*) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735–740; (*b*) T.-L. Liu, Z.-Y. Xue, H.-Y. Tao and C.-J. Wang, *Org. Biomol. Chem.*, 2011, **9**, 1980–1986.
6 A. B. Serov, V. G. Kartsev, Y. A. Aleksandrov and F. M. Dolgushin, *Russ. Chem. Bull.*, 2005, **54**, 2432–2436.
7 L. Wu, J. Sun and C.-G. Yan, *Org. Biomol. Chem.*, 2012, **10**, 9452–9463.
8 B. X. Wang, X. C. Zhang, J. Li, X. Jiang, Y. F. Hu and H. W. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1571–1575. See ref. 22 also.
9 S. Kanemasa, S. Takenaka, H. Watanabe and O. Tsuge, *J. Org. Chem.*, 1989, **54**, 420–424.
10 S. J. Taylor, A. M. Taylor and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2004, **43**, 1681–1685.
11 For recent developments: M. A. Ischay, M. K. Takase, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2013, **135**, 2478–2481 and references therein.
12 (*a*) For Wittig olefination for **1a–e**: S. W. Duan, Y. Li, Y. Y. Liu, Y. Q. Zou, D. Q. Shi and W. J. Xiao, *Chem. Commun.*, 2012, **48**, 5160–5162; (*b*) For Peterson route to **1f**: T. Watanabe, M. Arisawa, K. Narusuye, M. S. Alam, K. Yamamoto, M. Mitomi, Y. Ozoe and A. Nishida, *Bioorg. Med. Chem.*, 2009, **17**, 94–110.
13 A. R. Katritzky, N. E. Grzeskowiak and J. Alvarezbuilla, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1180–1185.
14 W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, 1970, **35**, 3144–3147.
15 X.-M. Zhang, F. G. Bordwell, M. Van Der Puy and H. E. Fried, *J. Org. Chem.*, 1993, **58**, 3060–3066.

16 R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, 1964, **29**, 2431–2437.
17 For a related synthetic process: B. Viswambharan, K. Selvakumar, S. Madhavan and P. Shanmugam, *Org. Lett.*, 2010, **12**, 2108–2111.
18 G. Laus, *J. Chem. Soc., Perkin Trans. 2*, 1998, 315–317.
19 Diastereoisomers, such as **3g : 3g′** could not be separated by column chromatography on silica gel. No change was observed to the diastereomeric ratio in the crude product obtained from cycloaddition reactions performed in various solvents at a range of temperatures.
20 Q. Fu and C.-G. Yan, *Tetrahedron*, 2013, **69**, 5841–5849.
21 For related solvent effects: N. E. Dontsova, V. N. Nesterov and A. M. Shestopalov, *Tetrahedron*, 2013, **69**, 5016–5021.
22 A very recent paper describing stepwise reaction of pyridinium ylides with Michael acceptors: D. S. Allgäuer and H. Mayr, *Eur. J. Org. Chem.*, 2013, DOI: 10.1002/ejoc.201300784.