Electronic Supplementary Material (ESI) for ChemComm.

Electronic Supplementary Information for:

Total Synthesis of Dehaloperophoramidine using a highly diastereoselective Hosomi-Sakurai reaction

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General Information

Chemicals were obtained from Sigma-Aldrich, Fischer Scientific, Alfa Aesar, Fluka or Fluorochem and were used as received unless otherwise stated. Air/moisture sensitive reactions were carried out in oven-dried (140 °C) or flame-dried glassware and assembled while hot under a positive pressure of nitrogen. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated.

Thin-layer chromatography (TLC) was performed using glass plates coated with silica gel (with fluorescent indicator UV_{254}). Developed plates were air-dried and analysed under a UV lamp (254/365 nm) unless otherwise stated. Flash chromatography was performed using silica gel (40-63 μm). Melting points were recorded in open capillaries using an Electrothermal 9100 melting point apparatus. Values are quoted to the nearest 1 °C and are uncorrected. Infrared spectra were recorded on either a Perkin Elmer Paragon 1000 FT spectrometer or a Shimadzu IRAffinity-1S FT spectrometer equipped with an ATR attachment. Absorption maxima are reported in wavenumbers (cm^{-1}). Mass spectrometry data were acquired through the University of St Andrews School of Chemistry mass spectrometry service or through the EPSRC national mass spectrometry service centre (Swansea, UK)

Nuclear magnetic resonance (NMR) spectra were recorded on a Brüker Advance 500 (^{1}H, 500; ^{13}C 126 MHz), a Brüker Advance 400 (^{1}H, 400; ^{13}C, 100 MHz) or a Brüker Advance 300 (^{1}H 300; ^{13}C, 75 MHz) spectrometer. ^{13}C NMR spectra were recorded using the PENDANT pulse sequence. All NMR spectra were acquired using deuterated solvents and the lock and the residual solvent as the internal standard. Chemical shifts are reported as δ values in units parts per million (ppm). Proton-proton coupling constants (*J*) are quoted in Hz to the nearest 0.1 Hz. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), broad (br) or some combination of these i.e. doublet of triplets (dt). NM-R data was analysed using *TopSpin* or *MestReNova* NMR processor software.

Optical rotations were measured using a PerkinElmer Model 341 polarimeter using the sodium D line at 20 °C. Units for [α] are $degcm^3g^{-1}dm^{-1}$ and c is g cm^{-3}.

General experimental procedures

General Procedure A

To a stirred solution of methyl indole-3-carboxylate (1 eq.) in CH_2Cl_2 at 0 °C was added *N*-chlorosuccinimide (1.1 eq.) and *N*,*N*′-dimethylpiperazine (0.55 eq.). After 2 hours, a mixture of trichloroacetic acid (0.25 eq.) and the appropriate amine (2 eq.) in CH_2Cl_2 was added. After a further 2 hours, the reaction mixture was warmed to room temperature and washed with 10% aq. $NaHCO_3$ aq. HCl (1.0 M), water and brine. The organic layer was dried using $MgSO_4$, concentrated *in vacuo* and purified by recrystallization from CH_2Cl_2/hexane.

General Procedure B

A stirred suspension of the appropriate indole-3-carboxylate in Ph_2O was heated at reflux for 2.5 hours whilst removing the methanol that was formed during the reaction by distillation. After cooling, the resulting precipitate was collected by filtration and washed with Et_2O and dried *in vacuo* to afford the appropriate indoloquinoline.

General Procedure C

A stirred suspension of the appropriate indoloquinoline (1 eq.) in $POCl_3$ (35 eq.) was refluxed for 2 hours. After cooling to room temperature, the reaction was concentrated *in vacuo*. The residue was added to an ice-water mixture and basified (to ~ pH 9) by careful addition of sat. aq. $NaHCO_3$ solution. The initially yellow residue turned orange and then the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried using $MgSO_4$ and concentrated *in vacuo* to afford the appropriate crude chloro compound.

General procedure D

To a stirred suspension of sodium (3 eq.) in THF was added allyl alcohol (5.7 eq.) over the course of 0.5 hours. The mixture was left to stir for 3 hours before being added *via* cannula addition to a stirred suspension of the appropriate chloro compound (1 eq.) in THF. After 18

hours the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with water, brine, dried using $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallisation of the resulting solid from EtOAc afforded allyl ether compound.

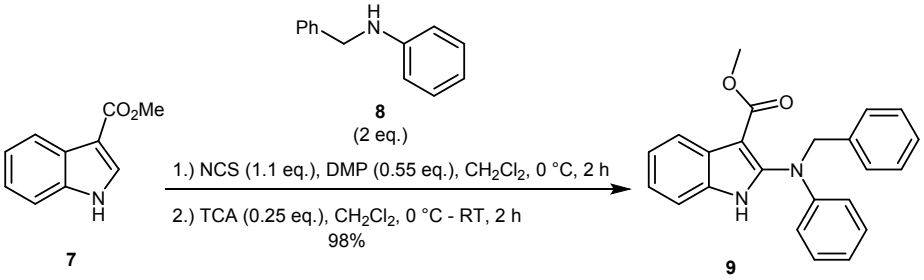
General Procedure E

A stirred solution of the appropriate allyl ether (1 eq.) in PhMe was refluxed for 1 hour. The reaction mixture was concentrated *in vacuo* and the resulting solid purified by recrystallisation from EtOAc to give the appropriate allyl ketone.

Experimental Procedures for the Synthesis of the tetracyclic core of S1 from 7 and 8

The route used to prepare **S1** followed our previously reported synthesis of the *N*-Me analogue of **S1**.[1]

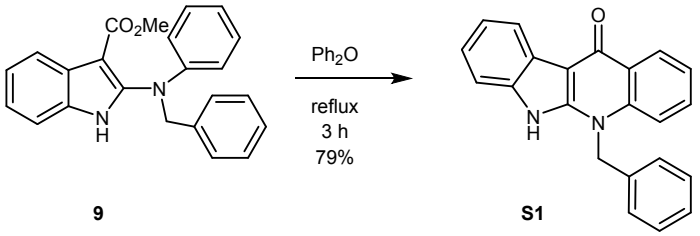
Methyl 2-(benzyl(phenyl)amino)-1*H*-indole-3-carboxylate (9)



Following general procedure **A**. To a stirred solution of methyl indole-3-carboxylate (**7**) (15.0 g, 85.7 mmol) in CH_2Cl_2 (170 mL) at 0 °C was added *N*-chlorosuccinimide (12.6 g, 94.3 mmol, 1.1 eq.) and *N*,*N*′-dimethylpiperazine (5.37 g, 6.4 mL, 47.1 mmol, 0.55 eq.). After 2 hours, a mixture of trichloroacetic acid (3.42 g, 21.4 mmol 0.25 eq.) and *N*-benzylaniline (**8**) (31.4 g, 29.7 mL, 171.4 mmol, 2 eq.) in CH_2Cl_2 (170 mL) was added. After a further 2 hours, the reaction mixture was warmed to room temperature and washed with 10% aq. $NaHCO_3$ (1 x 150 mL), aq. HCl (1 x 150 mL, 1.0 M), water (1 x 150 mL) and brine (1 x 150 mL). The organic layer was dried using $MgSO_4$, concentrated *in vacuo* and purified by recrystallisation from CH_2Cl_2/hexane to afford **9** (29.9 g, 84.0 mmol, 98%) as an off-white solid.

m.p. 162-164 °C; **IR** (KBr) ν_{max}: 3270, 1669, 1599, 1543, cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{23}H_{20}N_2O_2$ 379.1422 $[M+Na]^+$, found 379.1427; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.14 (d, *J*=7.1 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.26 – 7.16 (m, 6H), 6.94 – 6.82 (m, 3H), 5.14 (s, 2H), 3.81 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.7, 147.2, 147.1, 138.9, 132.0, 129.3 (2C), 128.8 (2C), 127.3, 127.0 (2C), 126.8, 123.0, 122.1, 121.8, 120.9, 116.9 (2C), 110.7, 98.8, 56.7, 51.0.

5-Benzyl-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (S1)



9 **S1**

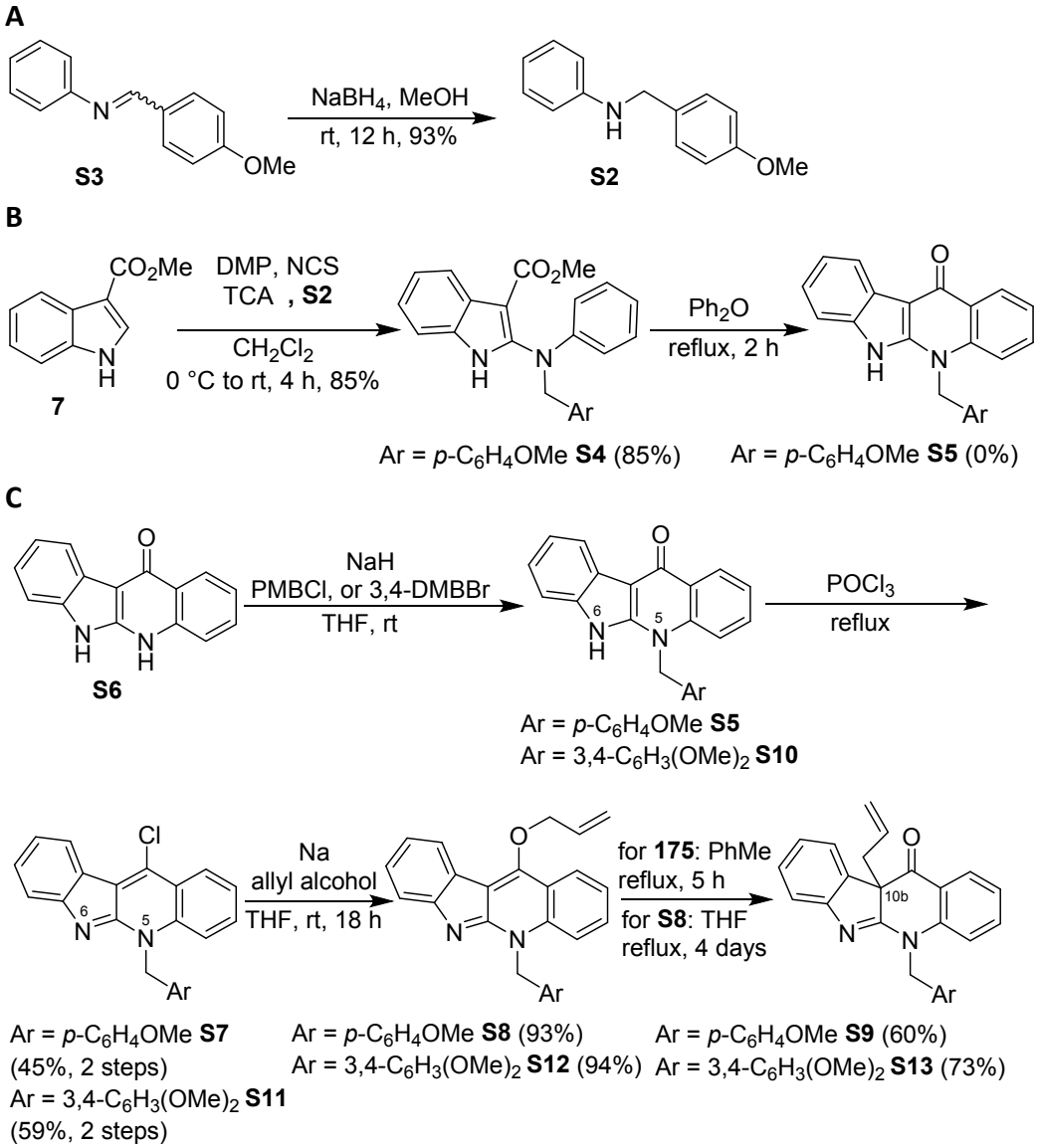
Following general procedure **B**. A stirred suspension of **9** (25.0 g, 70.2 mmol) in Ph_2O (140 mL) was heated at reflux for 2.5 hours whilst removing the methanol that was formed during the reaction by distillation. After cooling, the resulting precipitate was collected by filtration and washed with Et_2O (3 x 50 ml) and dried *in vacuo* to afford **S1** (18.0 g, 55.4 mmol, 79%) as a beige solid.

m.p. *ca*. 300 °C (dec.); **IR** (KBr) ν_{max}: 3061, 1609, 1576, 1514 cm^{-1}; **HRMS** (CI) *m/z* calcd. for $C_{22}H_{17}N_2O^+$ 325.1341 $[M+H]^+$, found 325.1348; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.41 (d, *J*=7.5 Hz, 1H), 8.27 – 8.21 (m, 1H), 7.68 – 7.59 (m, 2H), 7.52 – 7.43 (m, 1H), 7.40 – 7.22 (m, 6H), 7.25 – 7.14 (m, 2H), 5.86 (s, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 171.7, 147.0, 138.4, 135.8, 134.8, 131.3, 128.9 (2C), 127.5, 126.0 (2C), 126.0, 124.9, 124.1, 122.9, 121.9, 121.3, 120.2, 115.6, 110.9, 102.3, 48.6.

Synthesis of Analogues of S1 and 6 with alternative *N*-protecting groups

Initial studies also focused on the attempted preparation of a derivative of **S1** that was *N*-protected by a *p*-methoxybenzyl (PMB) group rather a benzyl group. *N*-(*p*-methoxybenzyl)aniline (**S2**) was synthesised in good yield by the sodium borohydride reduction of the corresponding, commercially available, imine **S3** (**Scheme S1A**).[2] Subsequent conversion of **S2** to **S4** was achieved in an analogous manner to the preparation of **9** in 85% yield (**Scheme S1B**). However, a clean transformation of **S4** to **S5** could not be achieved with mixtures of compounds resulting. The ^{1}H NMR spectrum associated with the crude reaction mixture showed features consistent with loss of the PMB group: two *N*H signals were present at 12.30 ppm and 11.65 ppm and only traces of the signals associated with the benzyl protons of the PMB group were present. It was therefore concluded that the PMB protecting group was incompatible with the high temperatures involved in this synthetic route.

An alternative route to **S5** was therefore attempted using the approach shown in **Scheme S1C**. After preparation of **S6** (see experimental below), alkylation of **S6** led to the formation of **S5** although purification was not carried out and the crude **S5** was converted directly to the chloride **S7** which was purified by flash column chromatography. Subsequent conversion of **S7** to **S8** (**Scheme S1C**), the precursor to the [3,3]-Claisen rearrangement in the PMB series was followed by conversion to the *N*-PMB protected analogue **S9** of *N*-benzyl protected ketone **6** that was used here. This protocol was also applied to the preparation of *N*-3,4-dimethoxybenzyl protected ketone **S13** (*via* the analogous **S10**, **S11** and **S12**). Whilst ketones **S9** and **S13** were not used in the reported synthesis of (±)-dehaloperophoramidine (**2**), it seems likely that much of the chemistry in subsequent steps is applicable to these potentially easier to deprotect substrates.



Scheme S1. **A.** Reduction of *N*-(*p*-methoxybenzylidine)aniline (**S3**) to *N*-(*p*-methoxybenzyl)aniline (**S2**); **B.** Attempted conversion of **S2** to **S5**. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid; **C.** Preparation of PMB and 3,4-DMB protected substrates **S9** and **S13**. PMBCl = *p*-methoxybenzyl chloride, 3,4-DMBBr = 3,4-dimethoxybenzyl bromide.

Preparation of *N*-(*p*-methoxybenzyl)aniline (S2)[2]

$NaBH_4$ (3.78 g, 100 mmol) was added to a stirred solution of (*E*)-*N*-[(4-methoxyphenyl)methylene]benzenamine (**S3**) and MeOH (80 ml). After 12 hours, water (20 ml) was added and the MeOH was evaporated at reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 20 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and the CH_2Cl_2 was evaporated *in vacuo*. The residue was crystallised from hexane to afford

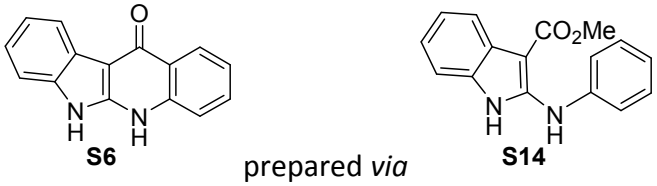
the title compound **S2** as colourless crystals (5.00 g, 23.5 mmol, 93%). Spectroscopic data was in accordance with that published in the literature.[2] **m.p**. 58-60 °C (lit.[2] 61-62 °C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27-7.32 (m, 2H), 7.14-7.21 (m, 2H), 6.86-6.91 (m, 2H), 6.72 (tt, *J* = 7.2, 1.0 Hz, 1H), 6.62 (m, 2H), 4.25 (s, 2H), 3.94 (br s, 1H), 3.80 (s, 3H).

Preparation of 2-[(4-methoxybenzyl)phenylamino]-1*H*-indole-3-carboxylic acid methyl ester (S4)

Prepared from indole-3-carboxilic acid methyl ester (**7**) (1.88 g, 10.8 mmol) in CH_2Cl_2 (50 ml) and *N*-(*p*-methoxybenzyl)aniline (**S2**) (4.59 g, 21.5 mmol) using general procedure **A**.

The crude product was purified by flash chromatography (5% to 10% EtOAc/hexane) to afford the title compound **S4** as colourless crystalline solid (3.54 g, 9.16 mmol, 85%). **m.p**. 158-159 °C; **IR** (KBr) ν_{max}: 3284, 2949, 1668, 1560, 1542 cm^{-1}; **HRMS** (CI) *m/z* calcd. for $C_{24}H_{23}N_2O_3^+$ 387.1709 $[M+H]^+$, found 387.1705; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.11-8.15 (m, 1H), 7.15-7.25 (m, 7H), 6.77-6.90 (m, 5H), 5.04 (s, 2H), 3.78 (s, 3H), 3.73 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.8, 158.8, 147.3, 132.1, 130.8, 129.4 (2C), 128.3 (2C), 126.8, 122.9, 122.1, 121.7, 120.9, 117.1 (2C), 114.2 (2C), 110.7, 98.7, 56.0, 55.4, 51.1.

Preparation of 5,6-dihydroindolo[2,3-*b*]quinolin-11-one (S6)[3]



2-phenylamino-1*H*-indole-3-carboxylic acid methyl ester (**S14**) was prepared from commercially available indole-3-carboxilic acid methyl ester (25.9 g, 148 mmol) in CH_2Cl_2 (600 ml) and aniline (26.9 ml, 295 mmol) using general procedure **A** (see above). The crude product was crystallised twice from CH_2Cl_2/hexane to afford the title compound **S14** as pale yellow crystals (19.8 g, 74.4 mmol, 50%). Spectroscopic data was in accordance with that published in the literature.[3]

m.p. 121-122 °C (lit.[3] 121-122 °C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.22 (s, 1H), 7.46-7.38 (m, 2H), 7.80 (d, *J* = 7.7, 1H), 7.30-7.24 (m, 2H), 7.22-7.10 (m, 3H), 7.08-7.03 (m, 1H), 3.93 (s, 3H).

S6 was then prepared from **S14** (17.5 g, 65.7 mmol) in Ph_2O (90 ml) with a reaction time of 3.5 hours using general procedure **B**.

The title compound **S6** was obtained as a light brown solid (14.6 g, 62.3 mmol, 95%). Spectroscopic data was in accordance with that published in the literature.[3] **m.p** > 400 °C (lit.[3] > 360 °C); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.95 (br s, 2H), 8.29 (d, *J* = 7.7 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.63-7.58 (m, 1H), 7.48-7.42 (m, 1H), 7.15-7.31 (m, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 172.7, 145.7, 138.7, 135.4, 131.1, 125.7, 124.2, 123.9, 123.0, 121.8, 121.2, 120.4, 117.8, 111.3, 102.2.

Preparation of 11-chloro-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (S7) – prepared from S6 *via* S5 (Scheme S1C)

Sodium hydride (80 mg of a 60% dispersion in oil, 2.00 mmol) was added to a stirred suspension of 5,6-dihydroindolo[2,3-*b*]quinolin-11-one (**S6**) (469 mg, 2.00 mmol) in THF (30 ml), maintained under an argon atmosphere. When effervescence ceased, *p*-methoxybenzyl chloride (0.4 ml, 3.00 mmol) and tetrabutyl ammonium iodide (222 mg, 0.601 mmol) were added and the reaction mixture was stirred at room temperature for 4 days. $NH_4Cl_{(aq)}$ (20 ml) was added and the THF was evaporated at reduced pressure. The residue was collected by filtration and washed with water (50 ml) and CH_2Cl_2 (100 ml) to afford crude 5,6-dihydro-5-(*p*-methoxybenzyl)indolo[2,3-*b*]quinolin-11-one (**S5**) as a colourless solid (420 mg). A portion of crude **S5** (150 mg) and $POCl_3$ (4 ml) were heated at reflux for 1.5 hours, under an argon atmosphere according to general procedure **C**. After cooling the reaction mixture to room temperature, the excess $POCl_3$ was evaporated at reduced pressure and $NaHCO_{3(aq)}$ (150 ml) was added to the residue. The aqueous suspension was then extracted with CH_2Cl_2 (3 x 70 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatography (60% to 100% EtOAc/hexane) to afford the title compound **S7** as a bright orange solid (120 mg, 0.322 mmol, 76%).

m.p. 207-208 °C; **IR** (KBr) ν_{max}: 2925, 1631, 1610, 1561, 1515 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{23}H_{18}N_2O^{35}Cl^+$ 373.1108 $[M+H]^+$, found 373.1108; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.6 Hz, 1H), 8.41 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.56-7.66 (m, 3H), 7.41-7.47 (m, 1H), 7.30 (t, *J* = 7.5 Hz), 7.14-7.19 (m, 2H), 6.75-6.81 (m, 2H), 6.09 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 155.9, 155.5, 136.5, 131.2, 129.9, 128.2 (2C), 127.7, 126.3, 125.3, 124.3, 124.1, 122.4, 120.5, 119.6, 118.1, 115.4, 114.5 (2C), 55.4, 49.2.

Preparation of 11-allyloxy-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (S8)

Prepared from 11-chloro-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (**S7**) (110 mg, 0.300 mmol) in THF (5 ml), with the alkoxide generated from allyl alcohol (0.70 ml, 10.5 mmol) and sodium (35 mg, 1.50 mmol) in THF (5 ml), using general procedure **D**.

In this case, the crude product was purified by flash chromatograph (60% → 80% EtOAc/hexane) to afford the title compound **S8** as a dark yellow solid (110 g, 0.279 mmol, 93%).

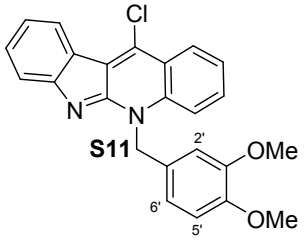
m.p. 133-134 °C; **IR** (KBr) ν_{max} 1643, 1561, 1513; **HRMS** (CI) *m/z* calcd. for $C_{26}H_{23}N_2O_2$ 395.1760$^+$ $[M+H]^+$, found 395.1761; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4, Hz, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.50-7.62 (m, 3H), 7.13-7.39 (m, 4H), 6.74-6.78 (m, 2H), 6.26 (ddt, *J* = 17.0, 10.5, 1.5, 1H), 6.09 (s, 2H), 5.56 (dq, *J* = 17.0, 1.3 Hz, 1H), 5.38 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.98 (dt, *J* = 5.7, 1.3 Hz, 2H), 3.69 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.1, 158.9, 156.9, 154.3, 137.7, 133.0, 130.9, 128.5, 128.2 (2C), 128.1, 124.5, 123.3, 122.9, 121.7, 120.2, 118.9, 118.4, 117.9, 116.7, 115.3, 114.3 (2C), 75.3, 55.3, 48.9.

Preparation of 5,10b-dihydro-10b-allyl-5-(*p*-methoxybenzyl)-10b*H*-indolo[2,3-*b*]quinolin-11-one (S9)

A mixture of 11-allyloxy-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (**S8**) (110 mg, 0.279 mmol) and THF (10 ml) was heated at reflux for 4 days, under an argon atmosphere, and was then cooled to room temperature. The THF was evaporated at reduced pressure and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford the title compound **S9** as a bright yellow crystalline solid (66 mg, 0.167 mmol, 60%)

m.p. 121-122 °C; **IR** (KBr) ν_{max}: 2959, 1691; **HRMS** (CI) *m/z* calcd. for $C_{26}H_{23}N_2O_2$ 395.1760$^+$ $[M+H]^+$, found 395.1752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.6 Hz), 7.70-7.73 (m, 1H), 7.28-7.51 (m, 5H), 7.06-7.19 (m, 3H), 6.84-6.89 (m, 2H), 5.80 (d, *J* = 16.2 Hz, 2H), 5.33-5.47 (m, 1H), 5.10 (d, *J* = 16.2 Hz, 2H), 4.99-5.03 (m, 1H), 4.81-4.88 (m, 1H), 3.78 (s, 3H), 2.90 (dd, *J* = 13.1, 6.7 Hz, 1H), 2.53 (dd, *J* = 13.1, 7.8 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.0, 172.3, 159.2, 153.7, 144.8, 135.8, 133.4, 130.3, 129.0, 128.5, 128.3, 128.2 (2C), 124.8, 123.3, 122.6, 120.5, 119.3, 118.9, 115.6, 114.5 (2C), 66.2, 55.5, 49.2, 45.1.

Preparation of 11-chloro-5-(3,4-dimethoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (S11) using S15 and *via* S10



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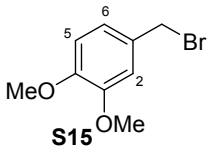


The required 3,4-dimethoxybenzyl bromide (**S15**)[4] was prepared as follows: A solution of PBr_3 (6.29 ml, 66.6 mmol) and Et_2O (20 ml) was slowly added to a stirred solution of commercially available 3,4-dimethoxybenzyl alcohol (5.63 g, 33.5 mmol) in Et_2O (50 ml) at 0 °C, maintained under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and, after 12 hours, water (100 ml) was cautiously added. When the vigorous reaction had subsided, the Et_2O was separated and the aqueous phase was further extracted with Et_2O (3 x 50 ml). The Et_2O extracts were combined, dried ($MgSO_4$) and the Et_2O was evaporated at reduced pressure. The residue was crystallised from EtOAc/hexane to afford the title compound **S15** as colourless crystals (4.72 g, 20.4 mmol, 61%) Spectroscopic data was in accordance with that published in the literature.[5]

m.p. 47-49 °C (lit.[5] 50-51 °C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz), 6.81 (d, *J* = 8.2 Hz), 4.51 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H).

Sodium hydride (205 mg of a 60% dispersion in oil, 5.12 mmol) was added to a stirred suspension of 5,6-dihydroindolo[2,3-*b*]quinolin-11-one (**S6**) (1.00 g, 4.27 mmol) in THF (30 ml), maintained under an argon atmosphere. When effervescence ceased, a solution of 3,4-dimethoxybenzyl bromide (**S15**) (1.48 g, 6.40 mmol) and THF (5 ml) was added and the reaction mixture was stirred at room temperature for 24 hours. $NH_4Cl_{(aq)}$ (5 ml) was added and the THF was evaporated at reduced pressure. The residue was washed with water and was then, after decanting the water, pulverised under Et_2O until a fine powder resulted. The product was collected by filtration and washed with Et_2O to afford crude 5,6-dihydro-5-(3,4-dimethoxybenzyl)indolo[2,3-*b*]quinolin-11-one (**S10**) as a light brown solid (1.50 g). A portion of crude **S10** (500 mg) and $POCl_3$ (5 ml) were heated at reflux for 1.5 hours, under an argon atmosphere. After allowing the reaction mixture to cool to room temperature, the

excess $POCl_3$ was evaporated at reduced pressure and $NaHCO_{3(aq)}$ (30 ml) was added to the residue. The aqueous suspension was extracted with CH_2Cl_2 (3 x 30 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatography (80% to 100% EtOAc) to afford the title compound **S11** as a bright orange solid (340 mg, 0.844 mmol, 59%).

m.p. 217-218 °C; **IR** (KBr) ν_{max}: 1637, 1608, 1561, 1519 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{25}H_{20}N_2O_2{}^{35}Cl^+$ 403.1213 $[M+H]^+$, found 403.1201; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.6 Hz), 8.43 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.65-7.70 (m, 2H), 7.59 (td, *J* = 7.6, 1.2 Hz, 1H), 7.46 (ddd, *J* = 8.0, 6.0, 2.3 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 6.90 (d, *J* = 1.3 Hz, 1H), 6.68-6.75 (m, 2H), 6.10 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.9, 155.5, 149.6, 148.7, 136.6, 136.5, 131.2, 129.9, 128.2, 126.3, 125.3, 124.3, 124.1, 122.5, 120.6, 119.6, 119.1, 118.1, 115.4, 111.5, 110.3, 56.1, 56.0, 49.6.

Preparation of 11-allyloxy-5-(3,4-dimethoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (S12)

Prepared from 11-chloro-5-(3,4-dimethoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (**S11**) (320 mg, 0.794 mmol) in THF (15 ml), with the alkoxide generated from allyl alcohol (1.90 ml, 27.9 mmol) and sodium (91 mg, 3.79 mmol) in THF (5 ml), using general procedure **D** as described above. The crude product was purified by flash chromatograph (60% to 80% EtOAc/hexane) to afford the title compound **S12** as a dark yellow solid (316 g, 0.744 mmol, 94%).

m.p. 146-148 °C; **IR** (KBr) ν_{max}: 2935, 1639, 1613, 1565, 1516 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{27}H_{25}N_2O_3{}^+$ 425.1865 $[M+H]^+$, found 425.1876; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.61-7.71 (m, 2H), 7.56 (td, *J* = 7.5, 1.2 Hz, 1H), 7.40 (ddd, *J* = 8.2, 6.5, 1.6 Hz, 1H), 7.30 (td, *J* = 7.5, 1.0, 1H), 6.90 (s, 1H), 6.72-6.74 (m, 2H), 6.28 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 6.11 (s, 2H), 5.57 (dq, *J* = 17.2, 1.3, 1.3 Hz, 1H), 5.40 (dq, *J* = 10.5, 1.3, 1.3 Hz, 1H), 5.01 (dt, *J* = 5.6, 1.3 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9, 157.0, 154.4, 149.5, 148.6, 137.8, 133.0, 131.0, 128.6, 128.5, 124.6, 123.3, 123.0, 121.8, 120.2, 119.1, 119.0, 118.4, 118.0, 116.8, 115.4, 111.4, 110.4, 75.3, 56.1, 56.0, 49.3.

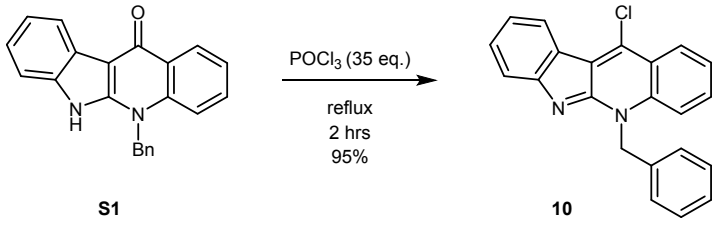
Preparation of 5,10b-dihydro-10b-allyl-5-(3,4-dimethoxybenzyl)-10b*H*-indolo[2,3-*b*]quinolin-11-one (S13)

Followed general procedure **D**. A solution of 11-allyloxy-5-(3,4-dimethoxybenzyl)-6*H*-indolo[2,3-*b*]quinoline (**S12**) (290 mg, 0.683 mmol) and PhMe (20 ml) was refluxed under an argon atmosphere for 5 hours. After cooling to room temperature, the PhMe was evaporated at reduced pressure and the residue was purified by flash chromatography (10% to 20% EtOAc/hexane) to afford the title compound **S13** as a bright yellow crystalline solid (211 mg, 0.497 mmol, 73%).

m.p. 132-135 °C; **IR** (KBr) ν_{max}: 2936, 1693, 1594, 1557, 1516 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{27}H_{25}N_2O_3^+$ 425.1865 $[M+H]^+$, found 425.1862; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.49 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.35 (td, *J* = 7.5, 1.3 Hz, 1H), 7.07-7.20 (m, 3H), 6.89-6.96 (m, 2H), 6.82 (d, *J* = 8.2, 1H), 5.83 (d, *J* = 16.5, 1H), 5.36-5.51 (m, 1H), 5.07 (d, *J* = 16.5 Hz, 1H), 4.98-5.03 (m, 1H), 4.80-4.88 (m, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.91 (dd, *J* = 13.0, 7.1 Hz, 1H), 2.53 (dd, *J* = 13.0, 7.4, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.9, 172.2, 153.6, 149.6, 148.6, 144.8, 135.9, 133.3, 130.2, 129.0, 128.8, 128.5, 124.9, 123.4, 122.7, 120.5, 119.2, 119.0, 118.9, 115.6, 111.5, 110.2, 66.2, 56.1 (2C), 49.5, 45.0.

Experimental Procedures for the Synthesis of 6 from S1

5-Benzyl-11-chloro-5*H*-indolo[2,3-*b*]quinoline (10)



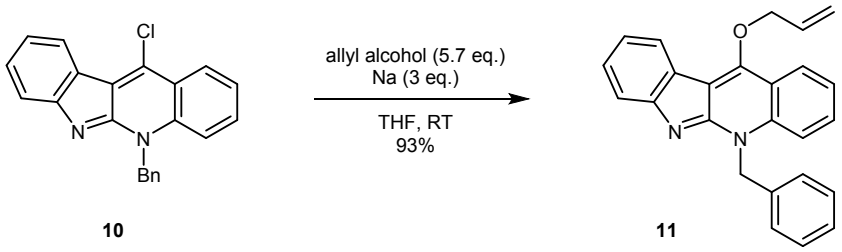
S1 **10**

Following general procedure **C**. A stirred suspension of **S1** (15.0 g, 46.3 mmol) in $POCl_3$ (247.5 g, 150 mL, 1609 mmol, 35 eq.) and was refluxed for 2 hours. After cooling to room temperature, the reaction was concentrated *in vacuo*. The residue was added to an ice-

water mixture and basified (to ~ pH 9) by careful addition of sat. aq. $NaHCO_3$ solution. The initially yellow residue turned orange and then the aqueous phase was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were dried using $MgSO_4$ and concentrated *in vacuo* to afford crude **10** (15.1 g, 44.0 mmol, 95%) as a red solid. Chloride **10** was used without further purification.

m.p. 220-222 °C; **IR** (KBr) ν_{max}: 2920, 1632, 1611, 1560, 1523 cm^{-1}; **HRMS** (CI) *m/z* calcd. for $C_{22}H_{16}N_2{}^{35}Cl^+$ 343.1002 $[M+H]^+$, found 343.0998; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (ddd, *J*=7.8, 1.3, 0.7 Hz, 1H), 8.49 – 8.45 (m, 1H), 7.78 – 7.75 (m, 1H), 7.69 – 7.66 (m, 2H), 7.61 (ddd, *J*=8.0, 7.3, 1.3 Hz, 1H), 7.49 (ddd, *J*=8.2, 5.2, 2.9 Hz, 1H), 7.33 (ddd, *J*=7.7, 1.0 Hz, 1H), 7.30 – 7.19 (m, 5H), 6.22 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.4, 154.7, 136.6, 136.4, 135.4, 131.2, 129.9, 129.0 (2C), 127.8, 126.7 (2C), 126.2, 124.9, 124.0, 124.0, 122.6, 120.6, 119.5, 117.9, 115.4, 49.8.

11-(Allyloxy)-5-benzyl-5*H*-indolo[2,3-*b*]quinoline (11)

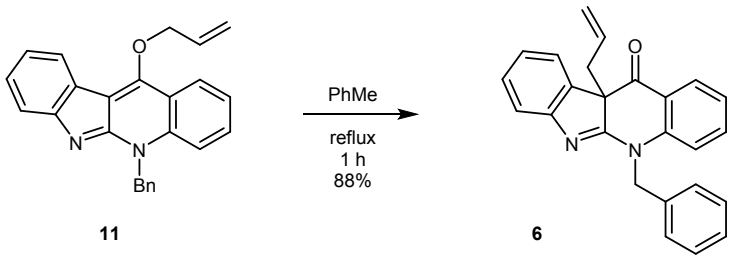


10 **11**

Followed general procedure **D**. To a stirred suspension of sodium (2.6 g, 113 mmol, 3 eq.) in THF (15 mL) was added allyl alcohol (12.6 g, 14.8 mL, 217 mmol, 5.7 eq.) over the course of 0.5 hours. The mixture was left to stir for 3 hours before being added *via* cannula addition to a stirred suspension of **10** (13.0 g, 38.0 mmol, 1 eq.) in THF (190 mL). After 18 hours the reaction was quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with water (1 x 50 mL), brine (1 x 50 mL), dried using $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallisation of the resulting solid from EtOAc afforded **11** as a yellow/orange solid (12.8 g, 35.2 mmol, 93%).

m.p. 146-148 °C; **IR** (FTIR-ATR) ν_{max}: 1642, 1560, 1520 cm^{-1}; **HRMS** (CI) *m/z* calcd. for $C_{25}H_{21}N_2O^+$ 365.1654 $[M+H]^+$, found 365.1650; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.34 (d, *J*=8.1 Hz, 1H), 8.16 (d, *J*=7.5 Hz, 1H), 7.77 (d, *J*=8.0 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.55 (dd, *J*=7.7, 1.3 Hz, 1H), 7.46 – 7.34 (m, 1H), 7.34 – 7.18 (m, 6H), 6.29 (ddd, *J*=17.1, 10.5, 5.6 Hz, 1H), 6.18 (s, 2H), 5.59 (dd, *J*=17.1, 1.5 Hz, 1H), 5.41 (dd, *J*=10.4, 1.2 Hz, 1H), 5.02 (dd, *J*=5.6, 1.4 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9, 157.0, 154.2, 137.7, 136.0, 132.9, 131.0, 129.0 (2C), 128.5, 127.6, 126.7 (2C), 124.6, 123.3, 122.9, 121.8, 120.3, 119.0, 118.5, 117.9, 116.7, 115.3, 77.2, 75.3, 49.5.

(±)-10b-Allyl-5-benzyl-5,10b-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (6)



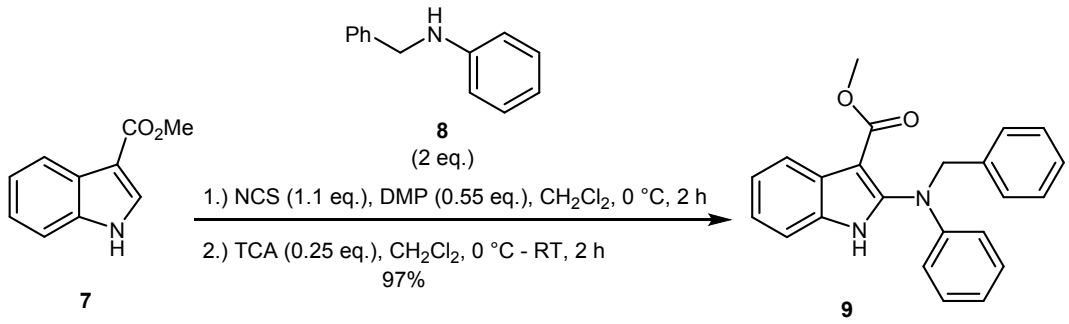
11 6

Followed general procedure **E**. A stirred solution of **11** (12.4 g, 34.1 mmol) in PhMe (110 mL) was refluxed for 1 hour. The reaction mixture was concentrated *in vacuo* and the resulting solid purified by recrystallisation from EtOAc to give **6** (10.9 g, 29.9 mmol, 88%) as a yellow crystalline solid.

m.p. 136-138 °C; **IR** (FTIR-ATR) ν_{max}: 3263, 1657, 1586, 1539 cm^{-1}; **HRMS** (EI) *m/z* calcd. for $C_{25}H_{20}N_2O^+$ 364.1576 $[M+H]^+$, found 364.1570; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (dd, *J*=7.8, 1.6 Hz, 1H), 7.62 (ddd, *J*=7.3, 1.1, 0.6 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.16 (m, 7H), 7.06 (ddd, *J*=7.3, 1.3 Hz, 1H), 7.02 – 6.96 (m, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 5.81 (d, *J*=16.6 Hz, 1H), 5.31 (dddd, *J*=16.9, 10.1, 7.7, 6.8 Hz, 1H), 5.02 (d, *J*=16.5 Hz, 1H), 4.94 – 4.88 (m, 1H), 4.80 – 4.71 (m, 1H), 2.82 (dd, *J*=13.3, 6.7 Hz, 1H), 2.45 (dd, *J*=13.3, 7.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.9, 172.2, 153.6, 144.8, 136.3, 135.8, 133.3, 130.3, 129.1 (2C), 128.9, 128.5, 127.7, 126.7 (2C), 124.8, 123.3, 122.6, 120.5, 119.2, 118.9, 115.6, 66.2, 49.7, 45.0.

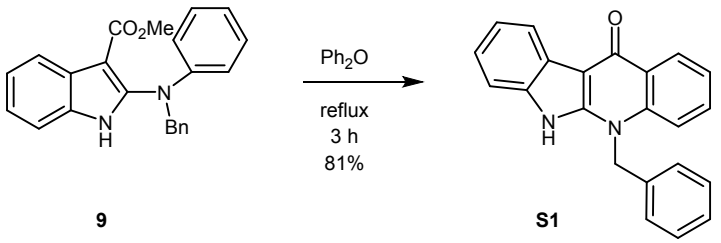
Experimental Procedures for the large scale preparation of 6

Methyl 2-(benzyl(phenyl)amino)-1*H*-indole-3-carboxylate (9)



To a stirred solution of methyl indole-3-carboxylate (**7**) (99.8 g, 570 mmol, 1 eq.) in CH_2Cl_2 (950 mL) at 0 °C was added *N*-chlorosuccinimide (83.7 g, 627 mmol, 1.1 eq.) and *N*,*N*′-dimethylpiperazine (35.76 g, 42.4 mL, 313 mmol, 0.55 eq.). After 2 hrs, a mixture of trichloroacetic acid (24.51 g, 150 mmol 0.25 eq.) and *N*-benzylaniline (**8**) (191 g, 178.7 mL, 1042 mmol, 2 eq.) in CH_2Cl_2 (950 mL) was added. After 2 hrs, the reaction mixture was warmed to RT and sequentially washed with 10% aq. $NaHCO_3$ (950 mL), aq. HCl (950 mL, 1.0 M), water (950 mL) and brine (950 mL). The organic layer was dried using $MgSO_4$, concentrated *in vacuo* and purified by recrystallization from CH_2Cl_2/ hexane to afford **9** (197 g, 553 mmol, 97%) as an off-white solid. ^1H NMR spectroscopic data was consistent with previously reported data for **9**.

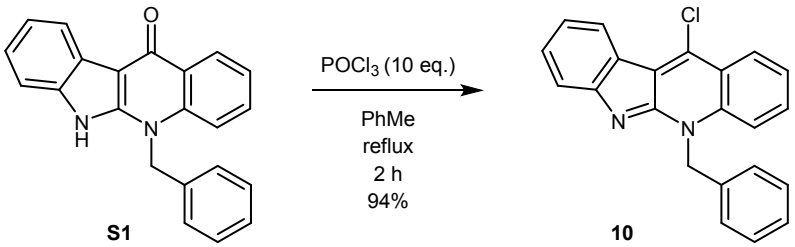
5-Benzyl-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (S1)



9 **S1**

A stirred suspension of **9** (99.8 g, 280 mmol) in Ph_2O (560 mL) was heated at reflux for 3 hrs while removing the methanol that is formed during the reaction by distillation. The precipitate was collected by filtration and washed with Et_2O and dried *in vacuo* to afford **S1** (74 g, 228 mmol, 81%) as a beige solid. ^{1}H NMR spectroscopic data was consistent with previously reported data for **S1**.

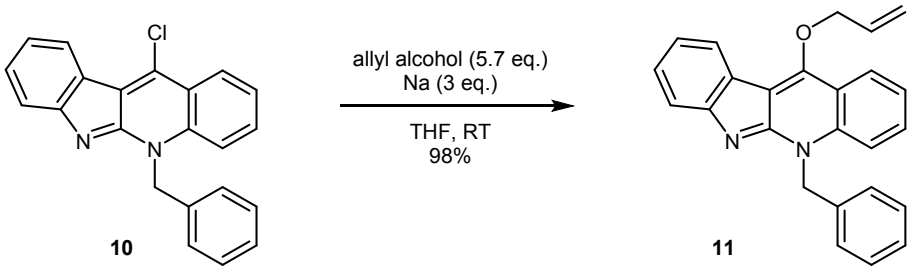
5-Benzyl-11-chloro-5*H*-indolo[2,3-*b*]quinoline (10)



S1 **10**

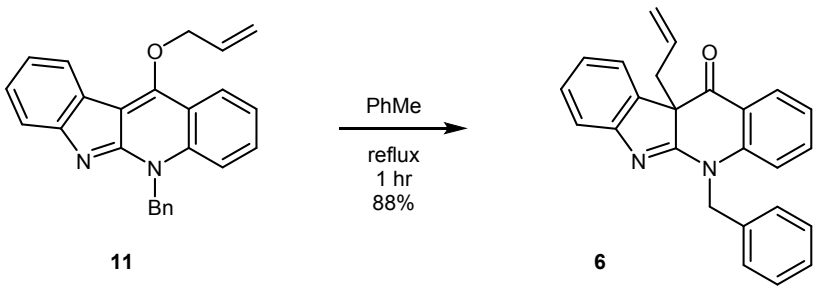
A stirred suspension of **S1** (70.0 g, 216 mmol, 1 eq.) in $POCl_3$ (329.6 g, 200 mL, 2150 mmol, 10 eq.) and toluene (230 mL) was refluxed for 2 hrs. After cooling to RT, the reaction was concentrated *in vacuo*. The residue was added to an ice-water mixture and basified (~ pH 9) by careful addition of sat. aq. $NaHCO_3$ solution. The yellow residue turned orange and then the aqueous phase was extracted with CH_2Cl_2 (5 × 250 mL). The combined organic phases were dried using $MgSO_4$ and concentrated *in vacuo* to afford crude **10** (69.5 g, 202 mmol, 94%) as an orange solid. Chloride **10** was used without further purification. ^{1}H NMR spectroscopic data was consistent with previously reported data for **10**.

11-(Allyloxy)-5-benzyl-5*H*-indolo[2,3-*b*]quinoline (11)



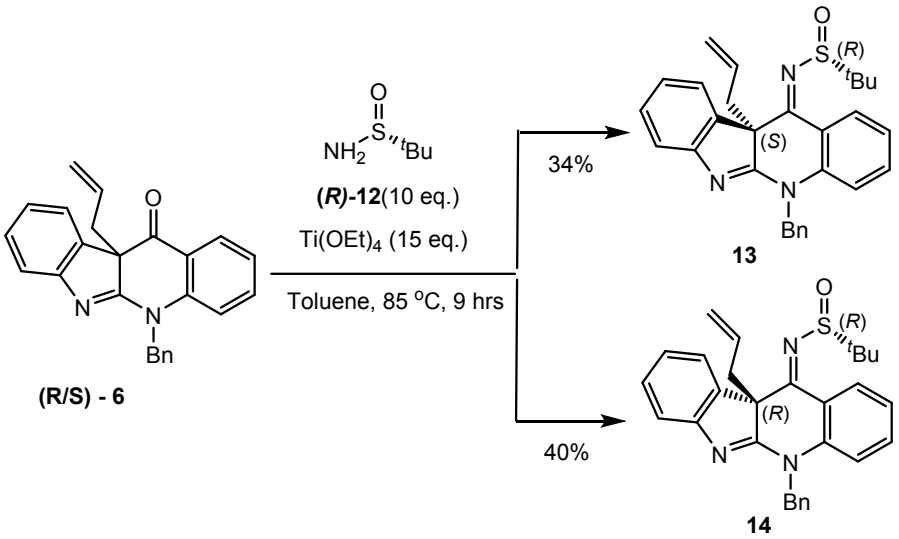
To a stirred suspension of sodium (13.7 g, 597 mmol, 3 eq.) in THF (50 mL) was added allyl alcohol (65.8 g, 77 mL, 1133 mmol, 5.7 eq.) over the course of 0.5 hrs. The mixture was left to stir for 3 hr before adding to stirred suspension of **10** (68.5 g, 199 mmol, 1 eq.) in THF (1000 mL) *via* cannula addition. After 24 hrs, the reaction was quenched with sat. aq. NH_4Cl (200 mL) and concentrated (~500 mL) *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (3 x 300 mL) and the combined organic extracts were washed with water (200 mL), brine (200 mL), dried using $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallisation from EtOAc afforded **11** as a yellow/orange solid (71.1 g, 195 mmol, 98%). ^{1}H NMR spectroscopic data was consistent with previously reported data for **11**.

(±)-10b-Allyl-5-benzyl-5,10b-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (6)



A stirred solution of **11** (71.1 g, 195.3 mmol) in PhMe (400 mL) was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*. Purification by recrystallisation from EtOAc afforded **6** (62.6 g, 171.9 mmol, 88%) as a yellow crystalline solid. ^{1}H NMR spectroscopic data was consistent with previously reported data for **6**.

Experimental procedures for the resolution of ketone 6



To a stirred solution of **6** (3.50 g, 9.61 mmol, 1 eq.) and $Ti(OEt)_4$ (30.2 mL, 32.9 g, 144.2 mmol, 15 eq.) in toluene (32 mL) was added (*R*)-*tert*-butanesulfinamide (**12**) (11.7 g, 96.1 mmol, 10 eq.). The mixture was heated to 85 ˚C for 9 hours before cooling to room temperature. The reaction mixture was diluted with EtOAc (200 mL) and quenched with brine (100 mL). The thick yellow/ orange gel was filtered through a Celite® pad and washed thoroughly with EtOAc until no yellow/orange colour remained on the filter cake. The filtrate was washed with brine (3 x 250 mL) before extracting from the aqueous liquid with EtOAc (3 x 250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a crude mixture. Purification on silica (5 to 50% EtOAc: Hexane) afforded **13** (1.52 g, 3.27 mmol, 34%) and **14** (1.81 g, 3.88 mmol, 40%) as yellow amorphous solids. Starting material **6** (385 mg, 1.06 mmol, 11%) was also recovered from the reaction.

(*R*)-*N*-((*S*,*E*)-10b-allyl-5-benzyl-5,10b-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-ylidene)-2-methylpropane-2-sulfinamide (13)

$[\alpha]_D^{20}$ +1359.4 (*c* = 0.806 in $CHCl_3$); **r.f.** 0.3 (30:70 EtOAc: Hexane); **IR** (FTIR-ATR) ν_{max} 3040, 1560; **HRMS** (ESI) *m/z* clacd. for $C_{29}H_{30}O_1N_3S_1^+$ 468.2104 $[M+H]^+$, found 468.2095; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.48 (ddd, *J* = 7.4, 1.3, 0.7 Hz, 1H), 7.42 – 7.27 (m, 8H), 7.15 – 7.10 (m, 1H), 7.08 (td, *J* = 7.4, 1.3 Hz, 1H), 6.99 (dd, *J* = 8.4, 1.0 Hz, 1H), 5.97 (dd, *J* = 16.6, 0.9 Hz, 1H), 5.55 (dddd, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.08 – 5.03 (m, 1H),

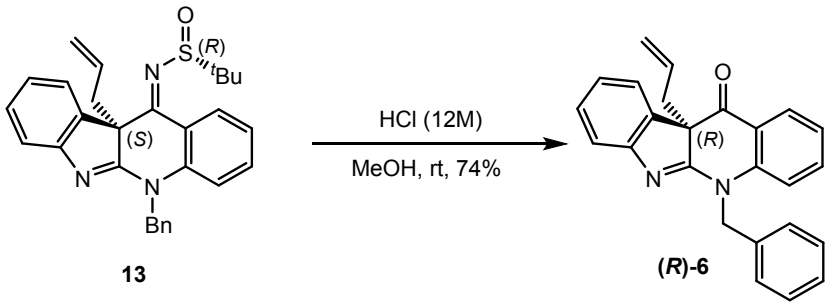
4.89 – 4.79 (m, 2H), 2.90 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.47 – 2.39 (m, 1H), 1.12 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2, 170.9, 154.6, 143.2, 136.7, 134.4, 133.5, 131.5, 131.0, 129.0, 128.8, 127.6, 126.4, 126.3, 122.3, 121.8, 120.1, 118.5, 117.6, 115.8, 64.0, 59.3, 50.2, 42.6, 22.6.

(*R*)-*N*-((*S*,*E*)-10b-allyl-5-benzyl-5,10b-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-ylidene)-2-methylpropane-2-sulfinamide (14)

$[\alpha]_D^{20}$ -1059.2 (*c* = 0.806 in $CHCl_3$); **r.f.** 0.6 (30:70 EtOAc: Hexane); **IR** (FTIR-ATR) ν_{max} 2924, 1560; **HRMS** (ESI) *m/z* clacd. for $C_{29}H_{30}O_1N_3S_1^+$ 468.2104 $[M+H]^+$, found 468.2099; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.57 (ddd, *J* = 7.4, 1.3, 0.7 Hz, 1H), 7.43 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.39 – 7.26 (m, 7H), 7.17 – 7.08 (m, 2H), 7.05 (dd, *J* = 8.4, 1.0 Hz, 1H), 5.83 (d, *J* = 16.5 Hz, 1H), 5.49 (dddd, *J* = 16.8, 10.1, 7.7, 6.7 Hz, 1H), 5.07 – 4.99 (m, 2H), 4.85 (dd, *J* = 16.9, 1.5 Hz, 1H), 2.98 – 2.89 (m, 1H), 2.50 (ddt, *J* = 13.5, 7.8, 1.0 Hz, 1H), 1.11 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.7, 170.7, 154.2, 142.5, 136.3, 134.2, 134.1, 132.6, 130.7, 129.0, 128.8, 127.7, 126.6, 126.5, 122.7, 122.7, 120.3, 118.5, 118.3, 115.9, 64.3, 49.8, 42.8, 22.1.

Experimental Procedures for the Hydrolysis of Imines 13 and 14

Experimental Procedure for the Hydrolysis of 13 to *(R)*-6

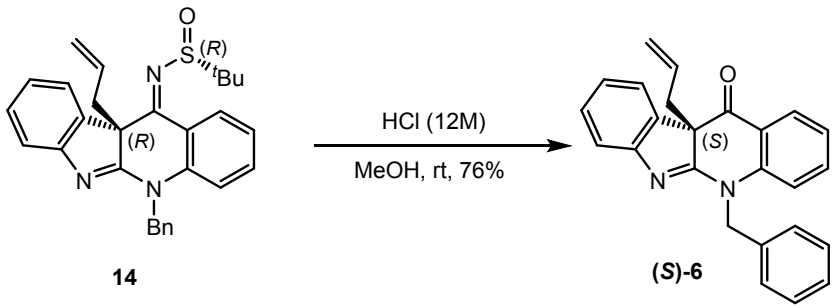


13 **(*R*)-6**

A stirred solution of **13** (1.20 g, 2.56 mmol) in MeOH (128 mL) was treated with HCl (12M) dropwise until TLC analysis indicated no starting material remained. The reaction was diluted with water (130 mL) and treated with $NaHCO_{3\ (aq)}$ until the solution was neutral by pH paper. The reaction mixture was extracted with EtOAc and washed with brine. The aqueous phase was re-extracted with EtOAc before combining the organic fragments and concentrating *in vacuo*. Purification on silica gel (5 to 15% EtOAc: hexane) afforded (*R*)-**6** (690 mg, 1.89 mmoles, 74%, >99% *ee*) after recrystallisation from EtOAc: Pet Ether (40:60). ^{1}H NMR spectroscopic data was consistent with previously reported data for **6**.

$[\alpha]_D^{20}$ +130.6 (*c* = 1 in $CHCl_3$); **HPLC** Retention time of 23.561 minutes - Chiracel OD-H column with 5% 2-propanol in hexane as the eluent.

Experimental Procedure for the Hydrolysis of 14 to (*S*)-6



14 **(*S*)-6**

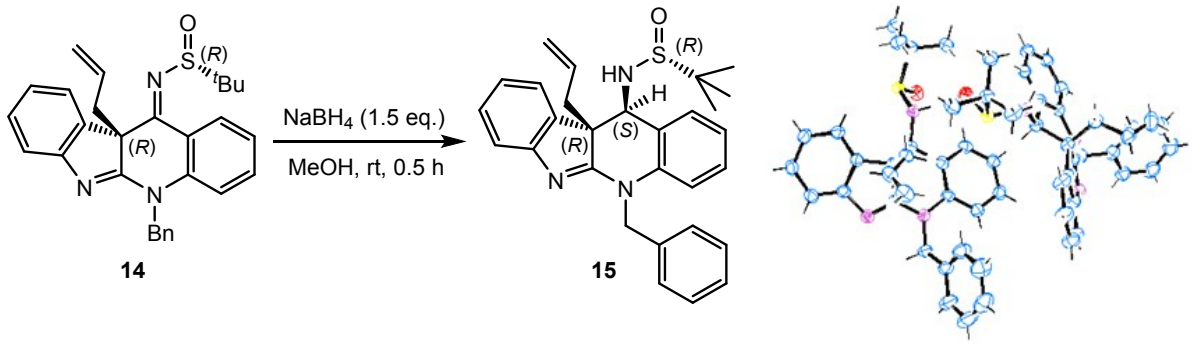
A stirred solution of **14** (1.41 g, 3.02 mmol) in MeOH (150 mL) was treated with HCl (12M) dropwise until TLC analysis indicated no starting material remained. The reaction was diluted with water (150 mL) and treated with $NaHCO_{3\ (aq)}$ until the solution was neutral by pH paper. The reaction mixture was extracted with EtOAc and washed with brine. The aqueous phase was re-extracted with EtOAc before combining the organic fragments and

concentrating *in vacuo*. Purification on silica gel (5 to 15% EtOAc: hexane) afforded (*S*)-**6** (835 mg 2.29 mmoles, 76%, >99% *ee*) after recrystallisation from EtOAc: Pet Ether (40:60). ^{1}H NMR spectroscopic data was consistent with previously reported data for **6**.

$[\alpha]_D^{20}$ -134.1 (*c* = 1); **HPLC** Retention time of 12.217 minutes - Chiracel OD-H column with 5% 2-propanol in hexane as the eluent.

Experimental procedure for the reduction of imine 14 to 15

(*R*)-*N*-((10b*R*,11*S*)-10b-allyl-5-benzyl-10b,11-dihydro-5*H*-indolo[2,3-*b*]quinolin-11-yl)-2-methylpropane-2-sulfinamide



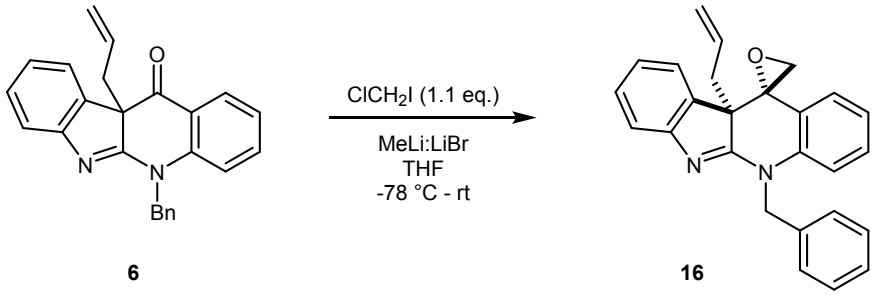
To a stirred solution of **14** (25 mg, 53.5 µmol, 1 eq.) in MeOH (1 mL) was added $NaBH_4$ (5 mg, 132 µmol, 2.5 eq.) and the mixture was left to stir at room temperature for 0.5 h. The reaction was quenched with brine (1 mL) and diluted with EtOAc (5 mL). The organic layer was concentrated *in vacuo* to afford beige solid. Recrystallisation from $CDCl_3$:Pet. ether afforded long, needle like, crystals of **15** which were of sufficient quality for X-ray crystallographic analysis (CCDC 1486344)[6] (23 mg, 49.0 µmol, 92%).

$[\alpha]_D^{20}$ -45.6 (*c* = 0.86 in $CHCl_3$); **m.p.** 186 – 188 °C; **IR** (FTIR-ATR) ν_{max} 3185, 2955, 1555 cm^{-1} **HRMS** (ESI) *m/z* clacd. for $C_{29}H_{32}O_1N_3S_1^+$ 470.2261 $(M+H)^+$, found 470.2261; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.37 – 7.27 (m, 6H), 7.25 – 7.19 (m, 2H), 7.10 (td, *J* = 7.6, 1.1 Hz, 1H), 7.03 (td, *J* = 7.3, 1.3 Hz, 1H), 6.93 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.77 (d, *J* = 16.5 Hz, 1H), 5.35 – 5.23 (m, 1H), 4.99 (d, *J* = 16.5 Hz, 1H), 4.91 – 4.82 (m, 3H), 4.12 (d, *J* = 9.9 Hz, 1H), 2.60 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.48 – 2.40 (m, 1H), 1.48 (s,

9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.8, 155.9, 140.3, 136.9, 136.7, 132.6, 129.3, 129.0, 128.9, 127.9, 127.4, 126.7, 125.8, 124.0, 123.6, 122.3, 118.9, 117.9, 115.4, 60.6, 57.4, 56.4, 50.0, 35.0.

Experimental procedure for the synthesis of 16

(±)-10b-allyl-5-benzyl-5,10b-dihydrospiro[indolo[2,3-*b*]quinoline-11,2'-oxirane] (16)

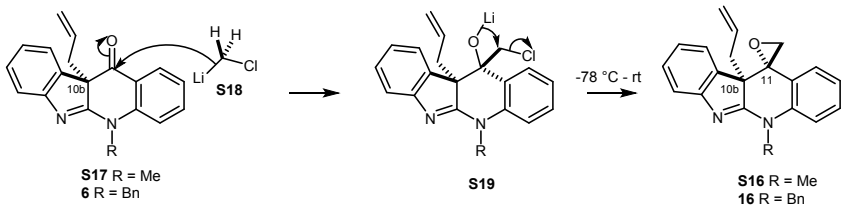


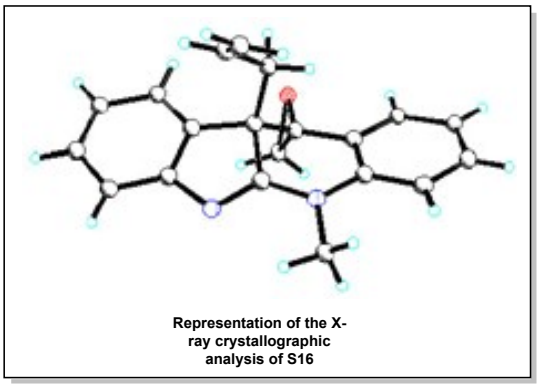
6 **16**

To a stirred solution of **6** (42.1 g, 115.6 mmol, 1 eq.) and chloroiodomethane (22.4 g, 9.3 mL, 127.2 mmol, 1.1 eq.) in THF (570 mL) at -78 °C was added methyllithium lithium bromide complex solution (78.8 mL, 173.4 mmol, 2.2 M in Et_2O, 1.5 eq.) dropwise. After 1 hr, the reaction was warmed to rt. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL) and the combined organic extracts were washed with water (300 mL), brine (300 mL), dried using $MgSO_4$ and concentrated *in vacuo* to afford crude **16** as a yellow amorphous solid – as a single diastereoisomer. Epoxide **16** was used without further purification.

IR (FTIR-ATR) ν_{max}: 2925, 1560 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{26}H_{23}N_2O^+$ 379.1805 $[M+H]^+$, found 379.1799; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.35 – 7.31 (m, 3H), 7.30 – 7.24 (m, 4H), 7.23 – 7.19 (m, 1H), 7.07 – 7.00 (m, 2H), 6.94 (dd, *J*=8.2, 1.0 Hz, 1H), 5.88 (d, *J*=16.5 Hz, 1H), 5.31 (dddd, *J*=16.7, 10.1, 7.9, 6.3 Hz, 1H), 4.94 (d, *J*=16.5 Hz, 1H), 4.90 – 4.83 (m, 2H), 3.10 (d, *J*=5.6 Hz, 1H), 2.89 (dd, *J*=13.9, 6.4 Hz, 1H), 2.70 (dd, *J*=13.9, 7.9 Hz, 1H), 2.55 (d, *J*=5.6 Hz, 1H); **^{13}C NMR** 172.4, 155.5, 141.4, 136.9, 134.3, 132.0, 129.5, 129.0 (2C), 128.9, 127.4, 126.7 (2C), 123.9, 123.3, 123.3, 122.9, 119.0, 118.1, 115.2, 60.3, 55.1, 53.7, 49.8, 38.4.

Assignment of the relative stereochemistry of 16





Scheme S2: Diastereoselective synthesis of epoxide **16** from **6**. The relative stereochemistry of **16** was inferred from that assigned to the related compound **S16** whose structure was assigned by small molecule X-ray crystallographic analysis (representation of analysis of **S16** is shown).

Epoxide **16** was synthesised *via* a modified Corey-Chaykovsky reaction[7] and isolated as a single diastereoisomer. The relative stereochemistry of **16** was determined by comparison of the analytical data associated with **16** with that of a compound **S16** previously synthesised from **S17**[1] in our laboratory (see Scheme S2 and experimental protocol below). The relative stereochemistry of **S16** was confirmed by small molecule X-ray crystallographic analysis (CCDC 1478153).[6] One explanation for the observed relative stereochemistry of **S16** is that the lithiated species **S18**, formed *in-situ via* Li-halogen exchange, attacks the carbonyl group in **S17** (or **6** in the case of the formation of **16**) from the opposite face to the allyl group at C10b (more accessible face) to give intermediate **S19** en route to **S16**. Figure S1 and Table S1 show a comparison of the key signals in the ^{1}H NMR spectra of **S16** and **16**.

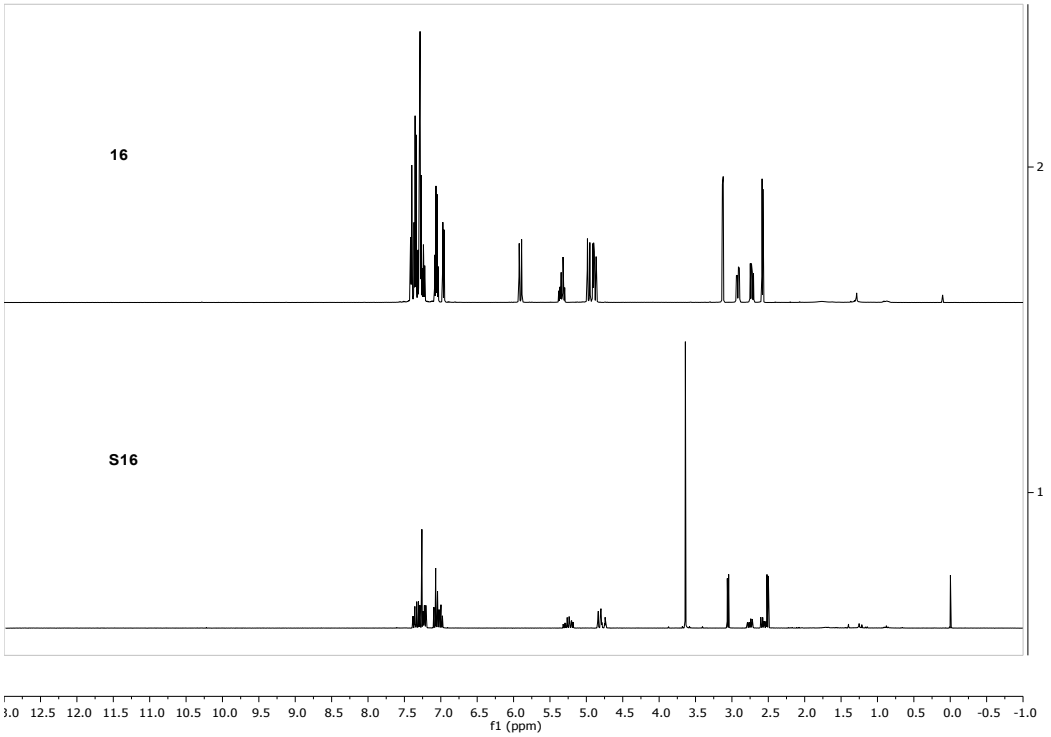
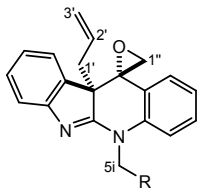


Figure S1: ^{1}H NMR analysis of epoxides **S16** and **16** emphasising the strong similarity between the spectra and hence presumably the structures.

Table S1: Comparison of the chemical shifts of the signals in the aliphatic regions of the ^{1}H NMR spectra of epoxides **16** and **S16**



S16 where R = H
16 where R = Ph

Assignment	*N*-Methyl Protected (S16, R = H)	*N*-Benzyl Protected (16, R=Ph)
1'	2.81 – 2.71 (m) and 2.62 – 2.52 (m)	2.89 (dd, *J*=13.9, 6.4) and 2.70 (dd, *J*=13.9, 7.9)
2'	5.25 (dddd, *J* = 16.7, 10.1, 8.0, 6.5)	5.31 (dddd, *J*= 16.7, 10.1, 7.9, 6.3)
3'	4.86 – 4.72 (m)	4.90 – 4.83 (m)
1''	3.05 (d, *J* = 5.6) and 2.51 (d, *J* = 5.6)	3.10 (d, *J*=5.6) and 2.55 (d, *J*=5.6)
5i	3.64 (s)	5.88 (d, *J*=16.5) and 4.94 (d, *J*=16.5)

Preparation of (±)-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinolin-11-spiro-2'-oxirane (S16)

MeLi-LiBr (15.0 ml of a 1.5 M solution, 22.5 mmol) was slowly added, over a period of 20 minutes, to a mixture of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**S17**)[1] (5.40 g, 18.7 mmol), chloroiodomethane (1.70 ml, 23.9 mmol) and THF (75 ml) at -78 °C, maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm the room temperature and stirring was continued for 12 hours. $NH_4Cl_{(aq)}$ was added and the solvent was evaporated at reduced pressure. Water (40 ml) and Et_2O (40 ml) were added to the residue. The Et_2O was separated and the aqueous phase was further extracted with Et_2O (3 x 40 ml). The combined Et_2O extracts were dried ($MgSO_4$) and filtered through a plug of silica. The Et_2O solution of the crude product was then placed in an open flask and allowed to slowly evaporate at ambient temperature and pressure until nearly dry (*ca*. 10 ml Et_2O remaining). There was thus obtained the title compound **S16** as large colourless crystals (4.98 g, 16.5 mmol, 88%). Crystals from Et_2O were suitable for X-ray analysis (CCDC 1478153).[6]

m.p. 119-120 °C; **IR** (KBr) ν_{max}: 3062, 2988, 1558 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{20}H_{19}N_2O^+$ 303.1497 $[M+H]^+$, found 303.1492; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18-7.40 (m, 5H), 6.97-7.11 (m, 3H), 5.18-5.32 (m, 1H), 4.73-4.85 (m, 2H), 3.64 (s, 3H), 3.06 (d, *J* = 5.5 Hz, 1H), 2.75 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.57 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.51 (d, *J* = 5.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4, 155.6, 141.7, 134.2, 132.0, 129.6, 129.0, 124.0, 123.3, 123.2, 122.9 (2C), 118.8, 118.0, 114.2, 60.3, 55.0, 53.8, 38.4, 32.9.

Experimental Procedures for the Conversion of 16 to 5

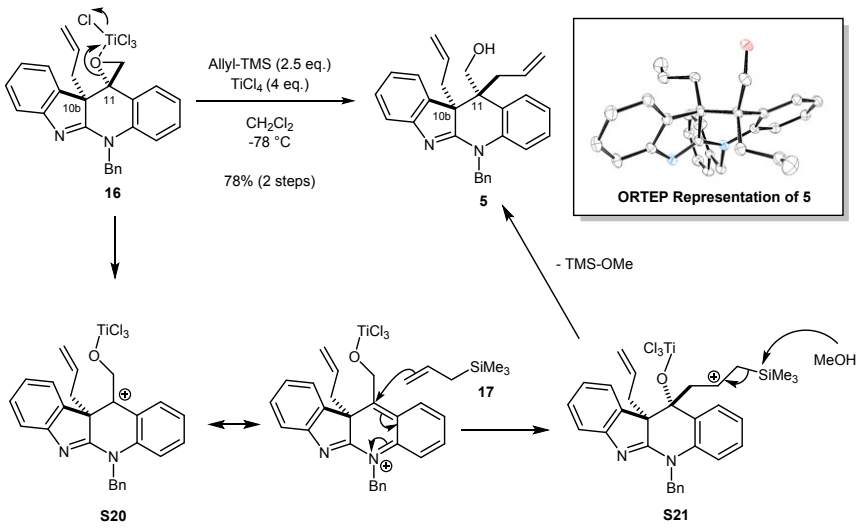
((±)-10b,11-diallyl-5-benzyl-10b,11-dihydro-5*H*-indolo[2,3-*b*]quinolin-11-yl)methanol (5)

To a stirred solution of crude **16** (115.6 mmol, 1 eq.) and allyltrimethylsilane (32.9 g, 45.8 mL, 289 mmol, 2.5 eq.) in CH_2Cl_2 (570 mL) at -78 °C was added $TiCl_4$ (87.8 g, 50.9 mL, 462.4 mmol, 4 eq.) dropwise. After 0.5 h, the reaction was quenched with MeOH (100 mL) before warming to rt. The reaction mixture was sequentially washed with brine (200 mL), sat. aq. $NaHCO_3$ (2 x 250 mL), brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by recrystallisation from EtOAc afforded **5** as a yellow solid (38.1 g, 90.7 mmol, 78%, over 2 steps) as a single diastereoisomer. The crystals were suitable for X-ray crystallographic analysis (CCDC 1478152).

m.p. 171 – 173 °C **IR** (FTIR-ATR) ν_{max}: 3206, 1550, cm^{-1}; **HRMS** (ESI-ion trap) *m/z* $[M+H]^+$ calcd. for $C_{29}H_{29}N_2O^+$ 421.2274 $[M+H]^+$, found 421.2274; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.1 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.33 – 7.21 (m, 5H), 7.20 – 7.14 (m, 1H), 7.07 – 7.00 (m, 2H), 6.98 (d, *J*=8.1 Hz, 1H), 5.68 (d, *J*=16.3 Hz, 1H), 5.32 – 5.16 (m, 1H), 5.12 – 4.97 (m, 2H), 4.83 (d, *J*=10.0 Hz, 1H), 4.80 – 4.69 (m, 3H), 4.52 – 4.37 (m, 2H), 2.90 (dd, *J*=13.6, 6.4 Hz, 1H), 2.64 (dd, *J*=13.9, 7.8 Hz, 1H), 2.20 (dd, *J*=14.4, 6.3 Hz, 1H), 1.99 (dd, *J*=14.4, 8.6 Hz, 1H), 1.88 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.2, 156.4, 140.5, 137.1, 136.1, 134.4, 133.0, 128.7 (2C), 128.7, 128.2, 127.5, 127.3, 127.1 (2C), 126.9, 124.1, 123.0, 122.6, 118.3, 118.1, 117.6, 116.1, 64.8, 59.9, 50.1, 47.0, 38.1, 37.4.

Rationalisation of the observed stereochemical outcome in the conversion of 16 to 5

Coordination of $TiCl_4$ to the oxygen of the epoxide **16** likely gives rise to the iminium intermediate **S20**, which was susceptible to allylsilylation at C11. The approach of the electrophile was from the opposite face to the C10b allyl substituent as previously observed in the conversion of **6** to **16** (Scheme S2). The cationic intermediate **S21** was stabilised by the ß-silicon atom and gave rise to the desired alcohol **5** upon quenching the reaction with methanol.

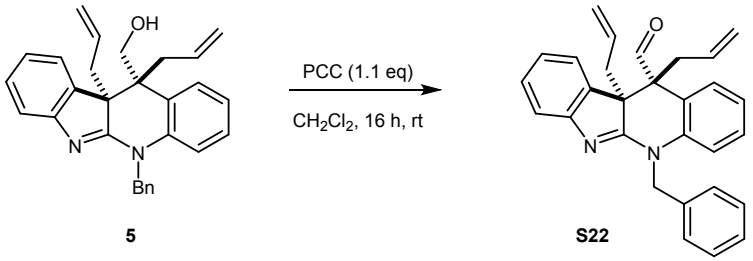


Scheme S3: Proposed mechanism for the allylsilylation of epoxide **16** to alcohol **5**. The stereochemistry at C11 was lost upon opening of the epoxide group to give **S20**. Allylsilylation of the intermediate **S20** reinstated the C11 stereocentre in intermediate **S21**.

Oxidation of 5 to the corresponding aldehyde S22 and carboxylic acid S23

The required oxidation of **5** to **S23** proved more challenging than expected. Whilst it was possible to convert **5** to the aldehyde **S22** using either the Dess-Martin periodinane[8] (yields of **S22** >80% were obtained on <0.1 mmol scale) or catalytic TPAP[9](yield of **S22** 91% was obtained on a 0.5 mmol scale) on a small scale, these reagents were less appropriate for use on larger scales (see below for protocols). Larger scale oxidations of **5** to **S22** were achieved using PCC (up to >25 mmol scale), although attempts to carry out this reaction catalytically[10] proved unsuccessful. Subsequent conversion of **S22** to the corresponding acid **S23** was achieved using either Jones[11] or Pinnick[12] oxidation conditions (see below for protocols). Attempted one pot oxidation of alcohol **5** delivered the required acid **S23** in an isolated yield of 39% along with an unidentified second product making this protocol unusable.

(±)-10b,11-diallyl-5-benzyl-10b,11-dihydro-5*H*-indolo[2,3-*b*]quinoline-11-carbaldehyde (S22)



5 **S22**

To a stirred suspension of crude **5** (28.30 mmol) and Celite® (6.71 g) in CH_2Cl_2 (280 mL) was added pyridinium chlorochromate (6.71 g, 31.13 mmol, 1.1 eq.) and the reaction was left to stir at rt. After 16 hrs, the reaction was filtered through a pad of Celite® and concentrated *in vacuo* to afford crude **S22** as a yellow/brown amorphous solid. Aldehyde **S22** was used without further purification.

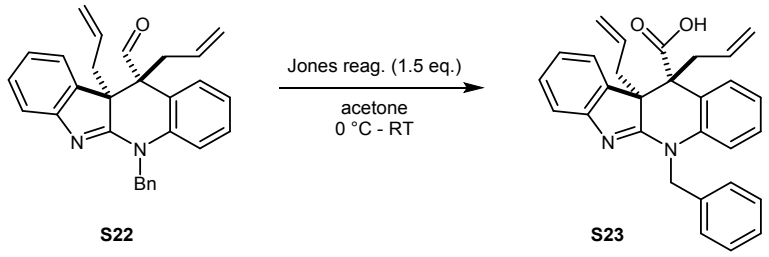
Alternatively a **TPAP Oxidation** was used: alcohol **5** (200 mg, 0.48 mmol, 1 eq.) was dissolved in DCM (5 mL) before NMO (168 mg, 1.43 mmol, 3 eq.) and TPAP (10 mg, 0.028 mmol, 0.06 eq.) were added and the mixture was left to stir for 8 hours. Further NMO (112 mg, 0.95 mmol, 2 eq.) was added and the reaction was left to stir overnight. The reaction mixture was quenched with a saturated solution of aq. Na_2SO_3 (5 mL) before extracting with EtOAc (5 mL) and washing the organic layer with water (5 mL) and brine (5 mL) The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to afford **S22** (181 mg, 0.43 mmol, 91%) as a brown solid. No further purification was performed.

Alternatively a **Dess-Martin oxidation** was used: alcohol **5** (20 mg, 0.048 mmol, 1 eq.) was dissolved in DCM (0.6 mL) at room temperature before adding Dess-Martin periodinane (30 mg, 0.071 mmol, 1.5 eq.). The reaction was left to stir for 1 hour before quenching with a saturated solution of aq. $NaHCO_3$ (1 mL). The mixture was diluted with DCM (5 mL) and washed with water (2.5 mL), brine (2.5 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to afford a brown oil. Purification by column chromatography on silica gel (5% to 10% EtOAc/hexane) afforded **S22** as a brown oil (16 mg, 0.038 mmol, 80%).

IR (FTIR-ATR) ν_{max}: 2925, 1715, 1560 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{29}H_{27}N_2O^+$ 419.2118 $[M+H]^+$, found 419.2113; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.40 (d, *J*=7.5 Hz, 2H),

7.34 – 7.20 (m, 6H), 7.10 – 7.00 (m, 4H), 6.90 – 6.84 (m, 1H), 5.63 (d, *J*=16.3 Hz, 1H), 5.24 (ddd, *J*=17.3, 10.0, 7.4 Hz, 1H), 5.16 (d, *J*=16.3 Hz, 1H), 5.08 (ddd, *J*=13.9, 10.3, 7.2 Hz, 1H), 4.84 – 4.75 (m, 3H), 4.65 – 4.57 (m, 1H), 2.90 (dd, *J*=13.5, 7.6 Hz, 1H), 2.64 – 2.54 (m, 2H), 2.04 (dd, *J*=14.1, 7.3 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.3, 171.1, 156.0, 140.2, 136.8, 134.5, 132.6, 131.6, 130.2, 129.1, 129.1, 128.8 (2C), 127.5, 127.2 (2C), 123.0, 122.8, 122.8, 122.7, 119.3, 119.3, 118.0, 116.1, 58.5, 56.8, 49.8, 37.3, 35.9.

(±)-10b,11-diallyl-5-benzyl-10b,11-dihydro-5*H*-indolo[2,3-*b*]quinoline-11-carboxylic acid (S23)



S22 **S23**

To a stirred solution of crude **S22** (28.3 mmol, 1 eq.) in acetone (280 mL) at 0 °C was added Jones reagent (31.7 mL, 42.5 mmol, 1.34 M, 1.5 eq.) dropwise. After 1 h, the reaction was warmed to rt. After 16 h, the reaction was quenched with isopropyl alcohol (20 mL) before concentrating (~140 mL) *in vacuo*. The reaction was extracted with Et_2O (2 x 150 mL) and the combined organic extracts were washed with water (2 x 100 mL), brine (100 mL), dried using $MgSO_4$ and concentrated *in vacuo* to afford crude **S23** as a yellow/brown solid. Carboxylic acid **S23** was used without additional purification.

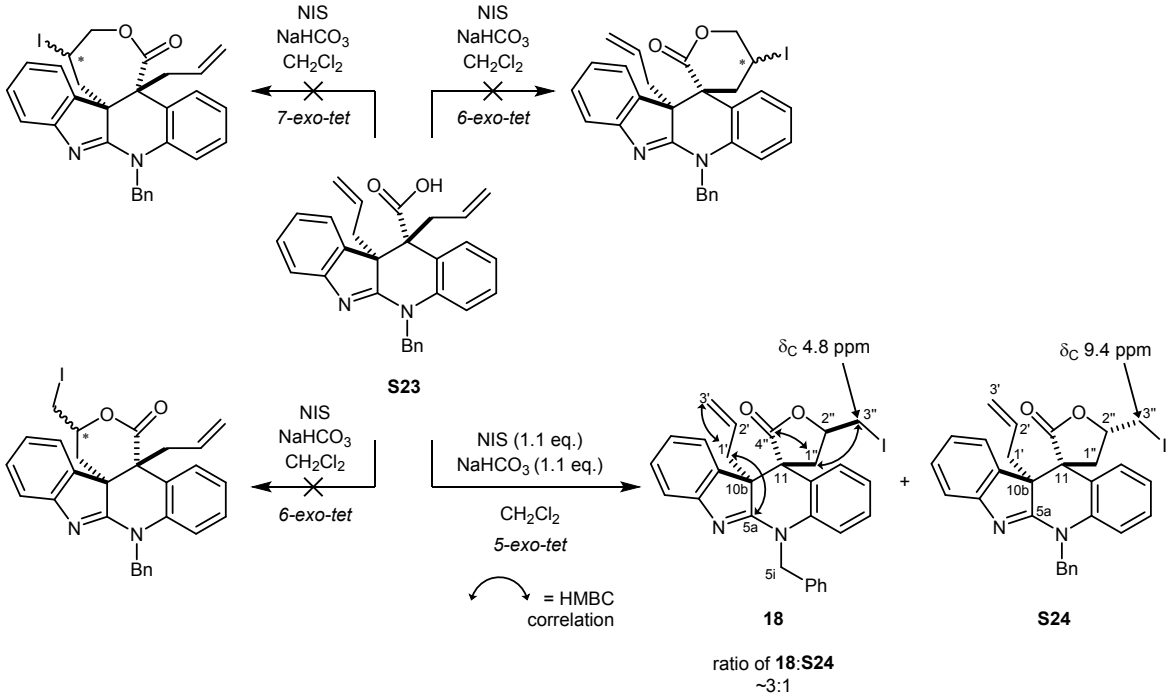
Alternatively, A 10 mL round bottomed flask was charged with **S22** (151 mg, 0.361 mmol) and 2-methyl-bute-2-ene (0.4 mL, 265 mg, 3.78 mmol) before dissolving in tetrahydrofuran (2 mL). A solution consisting of NaH_2PO_4 (248 mg, 1.80 mmol) and sodium chlorite (80 %, 203 mg, 18.0 mmol) in water (2 mL) was prepared and added to the reaction flask and left to stir for 18 hours. The reaction mixture was extracted with ethyl acetate (5 mL) before transferring to a separating funnel and washing the organic layer with water (2 x 5 mL) and brine (2 x 5 mL). The aqueous layer was extracted with ethyl acetate (5 mL) and the combined organic fragments were dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **S23** as a beige solid (141 mg, 0.325 mmol, 90%).

Finally, a one-pot procedure was also achieved from direct Jones oxidation of alcohol **5** to **S23**. To a stirred solution of **5** (20 mg, 47.6 µmol) in acetone (0.5 mL) at 0 °C was added Jones reagent (0.12 mL, 160.8 µmol, 1.34 M) dropwise. After 1 h, the reaction was warmed to rt. After 1 h, the reaction was quenched with isopropyl alcohol (0.5 mL). The reaction was extracted with Et_2O (2 x 5 mL) and the combined organic extracts were washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (1% to 5% MeOH/CH_2Cl_2) **S23** (8 mg, 18.4 µmol, 39%).

IR (FTIR-ATR) ν_{max}: 2955, 1717, 1697, 1684, 1558, 1541, 1456; **HRMS** (ESI) *m/z* calcd. for $C_{29}H_{27}N_2O_2^+$ 435.2067 $[M+H]^+$, found 435.2062; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J*=7.5 Hz, 2H), 7.35 (d, *J*=7.7 Hz, 1H), 7.32 – 7.21 (m, 4H), 7.20 – 7.14 (m, 2H), 7.05 – 6.92 (m, 4H), 5.67 (d, *J*=16.6 Hz, 1H), 5.45 (ddd, *J*=14.6, 9.9, 7.5 Hz, 1H), 5.25 (d, *J*=16.6 Hz, 1H), 5.11 – 4.99 (m, 1H), 4.84 – 4.76 (m, 3H), 4.56 (d, *J*=17.2 Hz, 1H), 2.90 (dd, *J*=14.1, 8.0 Hz, 1H), 2.74 – 2.63 (m, 2H), 2.12 (dd, *J*=13.8, 7.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3, 172.0, 155.1, 139.1, 136.7, 134.3, 133.3, 132.2, 131.6, 129.0, 128.8 (2C), 128.6, 127.6, 127.2 (2C), 124.0, 123.4, 123.1, 122.5, 119.2, 119.0, 117.3, 115.8, 58.2, 56.8, 50.5, 38.5, 38.1.

Iodolactonisation protocol and evidence for structure of the major diastereomer 18

It was envisaged that four possible core structures could be formed when **S23** was treated with an electrophilic source of iodine with variation resulting from the size of the lactone ring formed and which allyl group was involved in the reaction (Scheme S4). However only the five-membered ring in **18** (major isomer) and **S24** (minor) were formed. The structure of **18** was assigned based on detailed NMR analysis of the mixture of diastereoisomers (Figures S2-S4).



Scheme S4 Four possible outcomes of an iodolactonisation reaction of **S23**. However, only **18** and its C2''epimer **S24** were isolated as an inseparable 3:1 mixture. * = inconsequential mixture of epimers.

The regioselectivity of the reaction was confirmed by HBMC analysis (Figure S2); a correlation between H-1'' and C3'' was observed as well as a correlation between H-1'' and C4''. Furthermore, a correlation between H-1' and C3' was observed as well as a correlation between H-1' and C5a which proved that the C10b allyl substituent was not involved in the iodolactonisation. Presumably, the formation of the intermediate iodonium ion was reversible, but because the *5-exo-tet* cyclisation was kinetically favoured only **18**/**S24** were formed in the reaction.

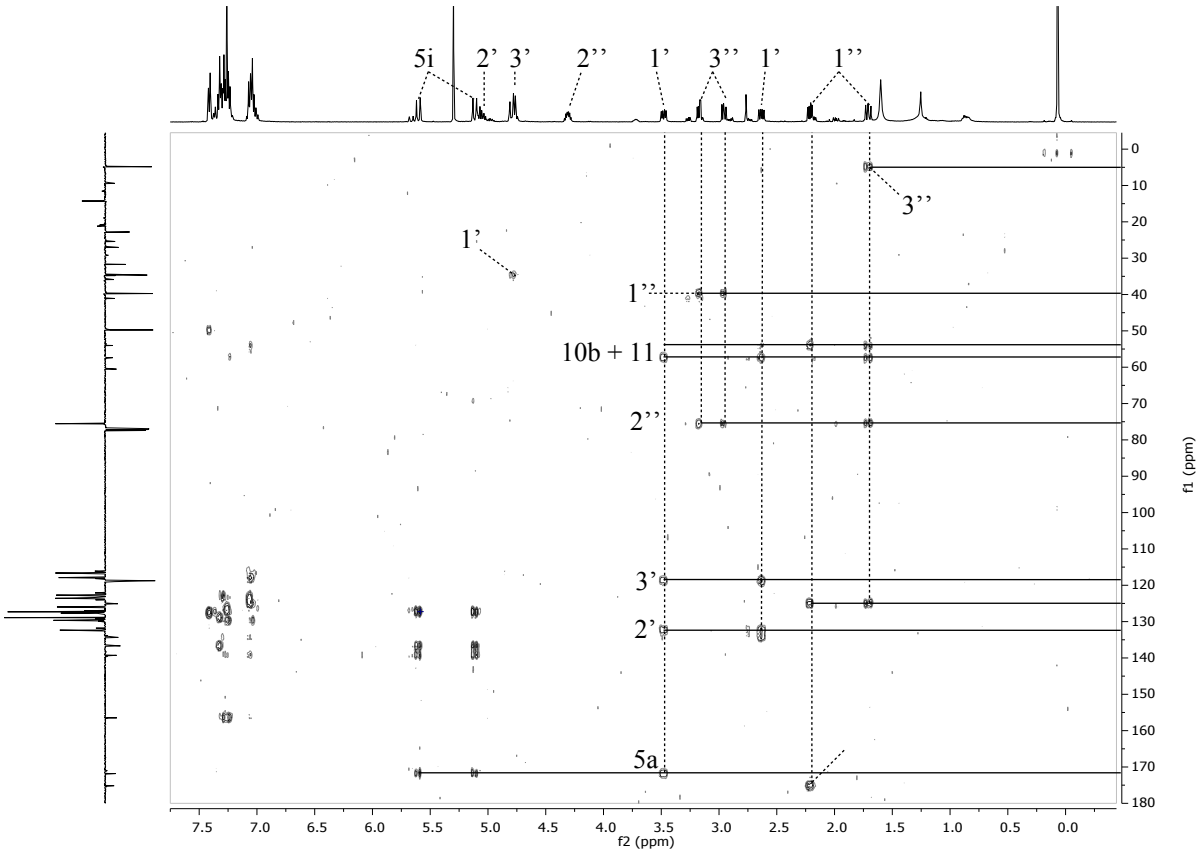


Figure S2 The HMBC spectrum of iodolactones **18/S24**. The key non-aromatic proton signals are highlighted.

Computational models of the epimers **18/S24** were calculated and their structures were minimised using the AM1 level of theory (Figure S3). The models were then examined to establish if any of the expected nOe enhancements would confirm the identity of the major epimer. It was proposed, if the relative stereochemistry was as drawn in **18**, the distance between the protons H-1 and H-2'' would be ~3.5 Å and an enhancement should be observed. Conversely, if the stereocentre at C2'' had the *S* configuration (as drawn in **S24**), the distance between the protons at H-10 and H-2'' would be ~3.6 Å and an enhancement should be observed. The signal associated with the H-2'' proton (**18**, δ_H 4.34 ppm) was selectively irradiated and several enhancements were observed (Figure S4) An enhancement of the signals corresponding to the protons H-3'' (**18**, δ_H 3.20, 2.98 ppm) and one of the protons of H-1'' (**18**, δ_H 2.24 ppm) was observed. This was expected as these protons are situated on the adjacent carbon atoms. An enhancement was observed in the multiplet at δ_H 7.12 – 7.01 ppm which integrated to 4 protons and 2D-NMR analysis confirmed that the signal for the H-1 proton resides within that multiplet (the protons H-2, H-7 and H-4 are the other signals present in the multiplet). The multiplet at δ_H 7.37 – 7.24 ppm integrated to 7

protons and the signal for the H-10 proton was found within that multiplet. A nOe enhancement was not observed to the multiplet (δ_H 7.37 – 7.24 ppm) and therefore the stereochemistry of the major epimer **18**.

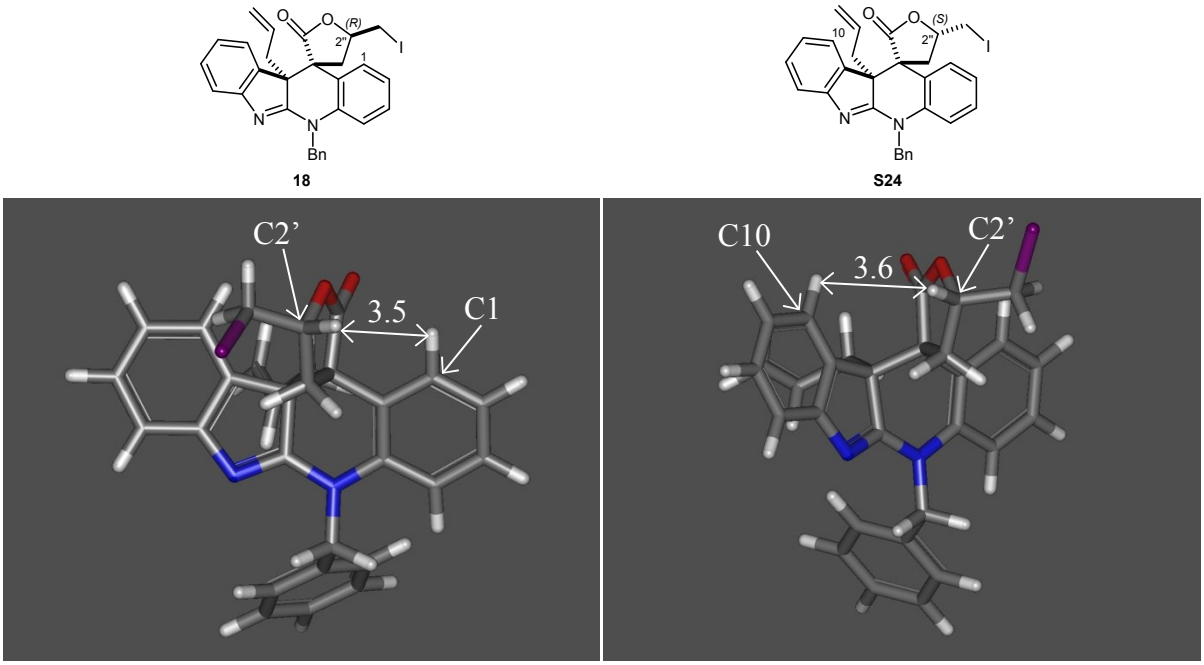


Figure S3 Computational models of **18** and **S24** were minimised (AM1 level of theory). The distance between the protons H-2'' and H-1 (in **18**) and protons H-2'' and H-10 (in **S24**) are shown.

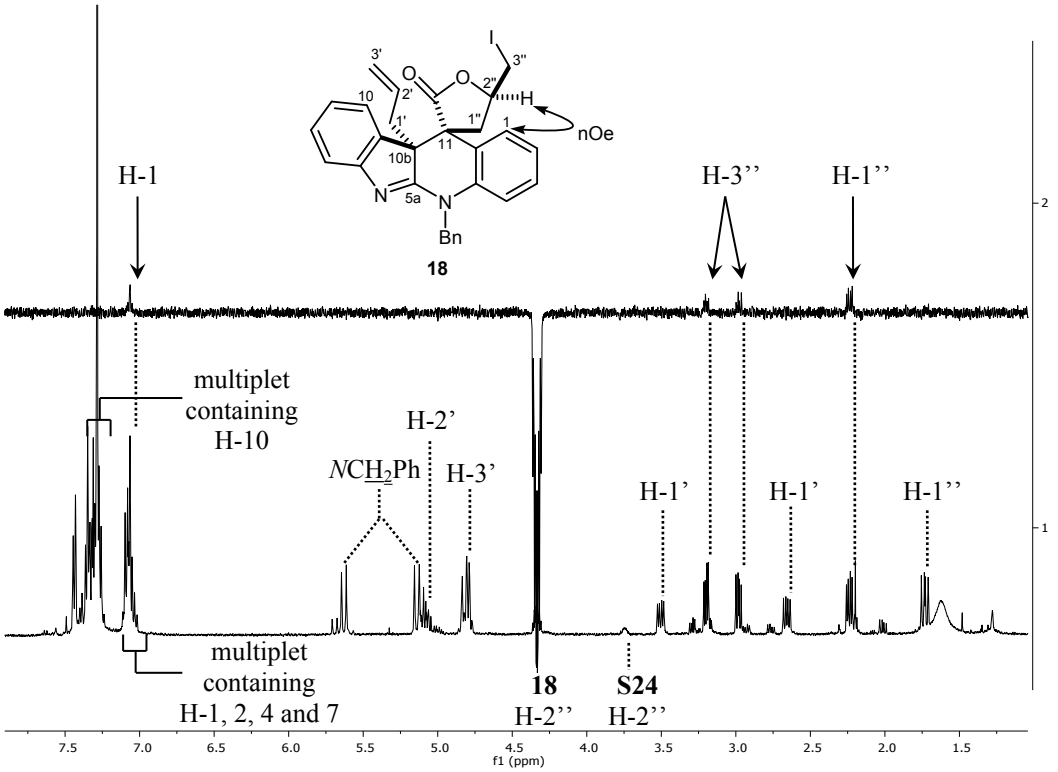
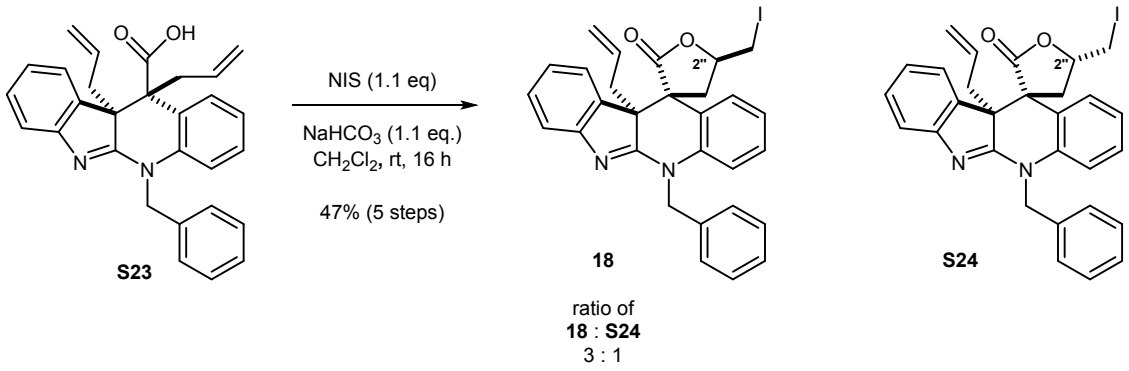


Figure S4 A nOe experiment of iodolactone **14/S24**. A selective pulse irradiated the H-2'' proton in **14** and an enhancement was observed to the H-1 proton. The major epimer **14** was assigned as the *R* configuration (as drawn) at C2''.

(±)-10b'-allyl-5'-benzyl-5-(iodomethyl)-4,5,5',10b'-tetrahydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinolin]-2-one (18) and (±)-C2''-epi-10b'-allyl-5'-benzyl-5-(iodomethyl)-4,5,5',10b'-tetrahydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinolin]-2-one (S24)



To a stirred suspension of crude **S23** (28.3 mmol, 1 eq.) in CH_2Cl_2 (280 mL) was added *N*-iodosuccinimide (7.00 g, 31.1 mmol, 1.1 eq.) and $NaHCO_3$ (2.61 g, 31.1 mmol, 1.1 eq.). After 16 hours, the reaction was quenched with sat. aq. sodium thiosulfate (100 mL) and stirred for 15 mins. The reaction mixture was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (10% → 30% EtOAc/hexane) afforded an inseparable mixture of **18** and its diastereomer **S24** (**18**:**S24** ~3:1, 7.25 g, 12.9 mmol, 46%, 5 steps from 6) as an orange/brown solid.

HRMS (ESI) *m/z* calcd. for $C_{29}H_{26}N_2O_2I$ 561.1033 $[M+H]^+$, found 561.1035.

Major Epimer 18

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J*=7.5 Hz, 2H), 7.35 – 7.21 (m, 8H), 7.10 – 6.98 (m, 4H), 5.60 (d, *J*=16.2 Hz, 1H), 5.11 (d, *J*=16.0 Hz, 1H), 5.11 – 5.00 (m, 1H), 4.83 – 4.73 (m, 2H), 4.35 – 4.27 (m, 1H), 3.48 (dd, *J*=14.2, 6.5 Hz, 1H), 3.17 (dd, *J*=10.4, 5.0 Hz, 1H), 2.96 (dd, *J*=10.4, 7.1 Hz, 1H), 2.63 (dd, *J*=14.3, 7.8 Hz, 1H), 2.21 (dd, *J*=12.9, 5.7 Hz, 1H), 1.71 (dd, *J*=12.8, 10.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 171.8, 156.5, 139.3, 136.7, 134.4, 132.3, 129.7, 129.6, 128.9 (2C), 127.7, 127.3 (2C), 126.0, 125.1, 123.6, 123.5, 122.7, 118.7, 117.9, 116.6, 75.5, 57.4, 54.0, 49.7, 39.7, 34.7, 4.8.

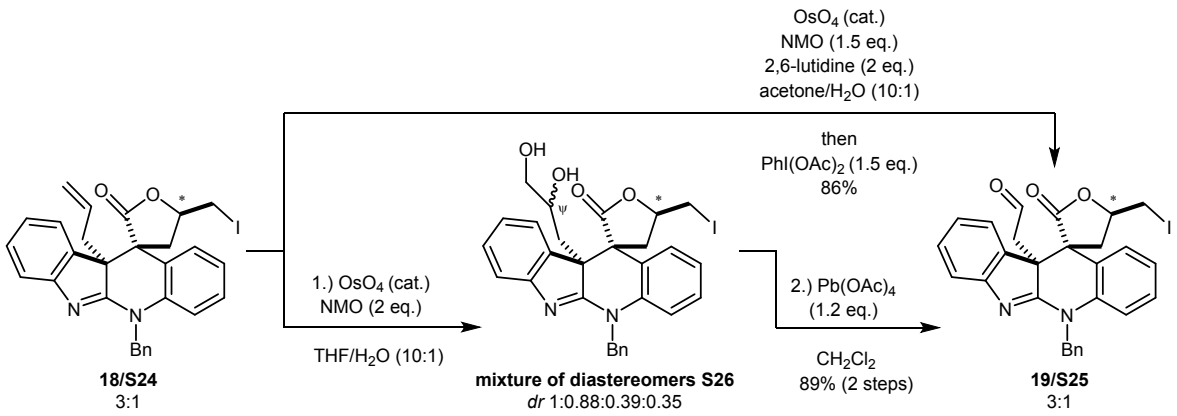
Minor Epimer S24

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J*=7.6 Hz, 1H), 7.35 – 7.20 (m, 8H), 7.10 – 6.98 (m, 4H), 5.66 (d, *J*=16.4 Hz, 1H), 5.11 (d, *J*=16.0 Hz, 1H), 4.97 (dd, *J*=9.5, 7.0 Hz, 1H), 4.83 – 4.73 (m,

2H), 3.72 (ddd, *J*=11.8, 7.4, 3.7 Hz, 1H), 3.27 (dd, *J*=10.8, 5.9 Hz, 1H), 3.14 (dd, *J*=3.7 Hz, 1H), 2.90 (dd, *J*=14.2, 6.3 Hz, 1H), 2.73 (dd, *J*=14.2, 7.4 Hz, 1), 2.17 (dd, *J*=7.4, 4.9 Hz, 1H), 1.99 (dd, *J*=13.7, 8.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.4, 171.0, 156.5, 139.5, 136.7, 133.8, 131.8, 129.9, 129.3, 128.9 (2C), 127.6, 127.5, 127.0 (2C), 125.1, 124.0, 123.4, 122.1, 119.0, 118.2, 116.1, 75.7, 57.7, 53.6, 49.9, 41.1, 35.9, 9.4.

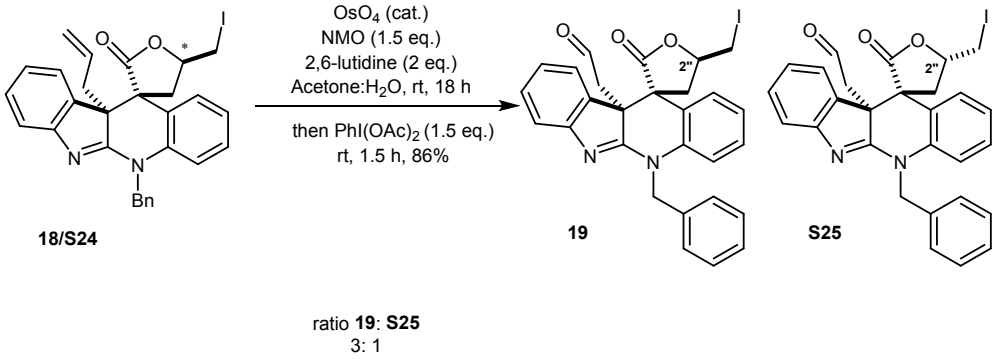
Oxidative cleavage of 18/S24

A two-step dihydroxylation, diol cleavage protocol using literature conditions[13] for the dihydroxylation and subsequent lead tetracetate cleavage was achieved (see below for protocols). However, a one pot protocol involving dihydroxylation and then in situ cleavage of the diol with iodobenzene diacetate was preferred (Scheme S5). Use of 2,6-lutidine in the dihydroxylation step was carried out in line with literature precedent initially.[14]



Scheme S5 The two step, one-pot oxidative cleavage[15] **18/S24** *versus* the two step protocol.[13] ? = inconsequential mixture of epimers; * = mixture of epimers 3:1.

One step protocol: (±)-2-(5'-benzyl-5-(iodomethyl)-2-oxo-4,5-dihydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinoline]-10b'(5'*H*)-yl)acetaldehyde (19) and (±)-C2''-epi-2-(5'-benzyl-5-(iodomethyl)-2-oxo-4,5-dihydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinoline]-10b'(5'H)-yl)acetaldehyde (S25)



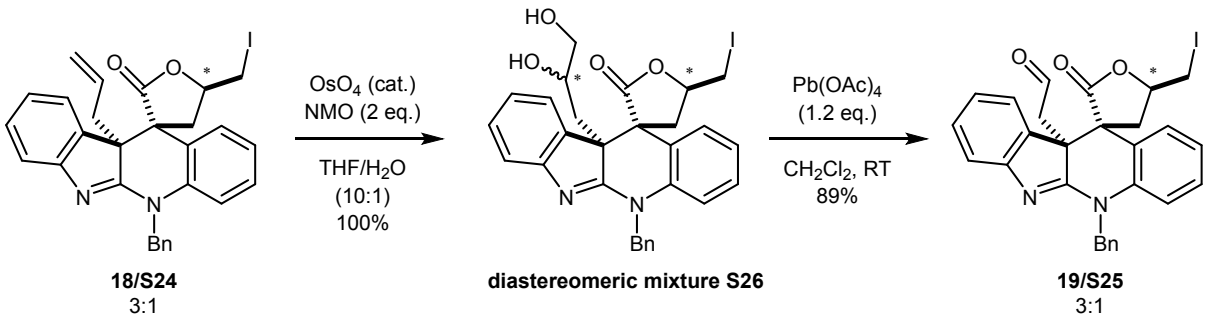
ratio **19**: **S25**
3: 1

To a stirred suspension of **18/S24** (8.57 g, 15.3 mmol, 1 eq.) in acetone/H_2O (176 mL, 10:1) was added *N*-methylmorpholine-*N*-oxide (2.69 g, 23.0 mmol, 1.5 eq.), 2,6-lutidine (3.27 g, 3.56 mL, 30.6 mmol, 2 eq.) and OsO_4 (0.2 mL of a 2.5% by wt. solution in ^{t}BuOH, 0.13 mol%). After 18 hours, $PhI(OAc)_2$ (7.39 g, 22.95 mmol, 1.5 eq.) was added and the reaction stirred for a further 1.5 h. The reaction was then quenched with sat. aq. sodium sulfite (80 mL) and sat. aq. $NaHCO_3$ (80 mL) and stirred vigorously for 0.5 h. The aqueous was extracted with EtOAc (2 x 100 mL) and combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (20% → 40% EtOAc/hexane) afforded **19/S25** (7.38 g, 13.1 mmol, 86%) – as an inseparable mixture of epimers at C2'' (~3:1).

Major Epimer 19

HRMS (ESI) *m/z* calcd. for $C_{28}H_{24}N_2O_3I^+$ 563.0826 $[M+H]^+$, found 563.0818; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.95 (t, *J*=2.6 Hz, 1H), 7.40 – 7.24 (m, 8H), 7.14 – 7.00 (m, 4H), 5.66 (d, *J*=16.1 Hz, 1H), 5.12 (d, *J*=16.1 Hz, 1H), 4.30 (ddd, *J*=10.4, 7.0, 5.5 Hz, 1H), 3.88 (dd, *J*=16.2, 2.4 Hz, 1H), 3.19 (dd, *J*=10.5, 4.9 Hz, 1H), 2.99 (dd, *J*=10.5, 7.1 Hz, 1H), 2.76 (dd, *J*=16.2, 2.9 Hz, 1H), 2.20 (dd, *J*=12.8, 5.7 Hz, 1H), 1.71 (dd, *J*=12.8, 10.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.6, 174.9, 171.0, 156.1, 138.9, 136.3, 132.8, 130.6, 130.1, 129.1 (2C), 127.9, 127.0 (2C), 126.0, 124.3, 124.1, 124.0, 123.0, 118.7, 117.1, 75.5, 53.8, 53.8, 49.9, 42.7, 38.6, 4.7.

Two step protocol:

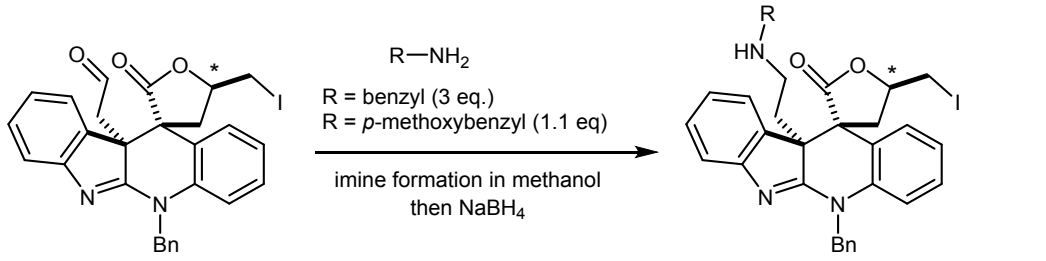


To a stirred suspension of **18/S24** (1.09 g, 1.95 mmol) in THF/H_2O (22 mL, 10:1) was added *N*-methylmorpholine-*N*-oxide (0.457 g, 3.90 mmol) and OsO_4 (0.5 mL, of a 2.5% by wt. solution in ^{t}BuOH). After 18 h, the reaction was quenched with sat. aq. sodium sulfite (20 mL) then stirred vigorously for 0.5 h. The aqueous was extracted with EtOAc (2 x 50 mL) and washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* to afford **S26** (1.16 g, 1.95 mmol, 100%) – as an inconsequential mixture of diastereoisomers. Diols **S26** were used in the next step without additional purification. **LRMS** (ESI) *m/z* 595 ([M+H]$^+$, 100), 617 ([M+Na]$^+$, 38); **HRMS** (ESI) *m/z* calcd. for $C_{29}H_{28}N_2O_4I^+$ 595.1088 [M+H]$^+$, found 595.1092.

To a stirred solution of **S26** (4.87 g, 8.20 mmol) in CH_2Cl_2 (85 mL) was added lead(IV) acetate (4.36 g, 9.85 mmol). After 1 h, the reaction was filtered through a pad of Celite®, washed with CH_2Cl_2 then concentrated *in vacuo*. Purification by column chromatography on silica gel (20% → 40% EtOAc/hexane) afforded **19/S25** (4.12 g, 7.33 mmol, 89%) as a light brown solid. NMR data was in agreement with the above one pot procedure.

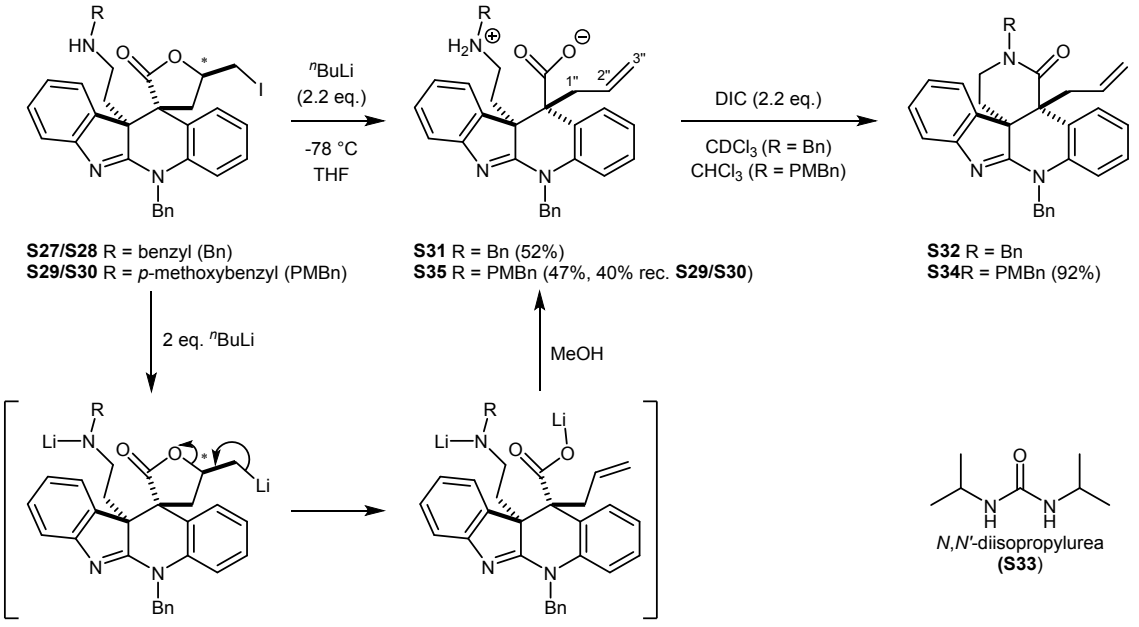
Reductive Amination of 19/S25

Initial studies focused on the use of benzylamine or *p*-methoxybenzylamine (Scheme S6). The diastereomeric mixture of aldehydes **19**/**S25** was converted to the corresponding mixtures of secondary amines **S27**/**S28** or **S29**/**S30** in variable yields. Attempts to use aqueous ammonia[16] or various ammonia surrogates[17] proved unsuccessful.



Scheme S6 The reductive amination of **19/S25** with aliphatic amines benzylamine and *p*-methoxybenzylamine. *Reaction conditions*: benzylamine or *p*-methoxybenzylamine, MeOH; then $NaBH_4$ (1.1 eq.); * = mixture of epimers 3:1.

Subsequent conversion of **S27**/**S28** to the corresponding amino acid **S31** (Scheme S7) by opening of the lactone ring enabled the synthesis of the *N*-protected lactam **S32** although it proved very difficult to remove all of the *N*,*N*-diisopropyl urea (**S33**) side product from the sample of **S32** (see experimental protocols below and Figure S5). The ^{1}H NMR spectrum of **S31** showed as series of broad peaks.



Scheme S7 The synthesis of pentacyclic lactams **S32** and **S34** *via* amino acids **S31** and S**35** respectively. The structure of the urea by-product (**S33**) that was found to contaminate **S32** is shown. * = mixture of epimers 3:1.

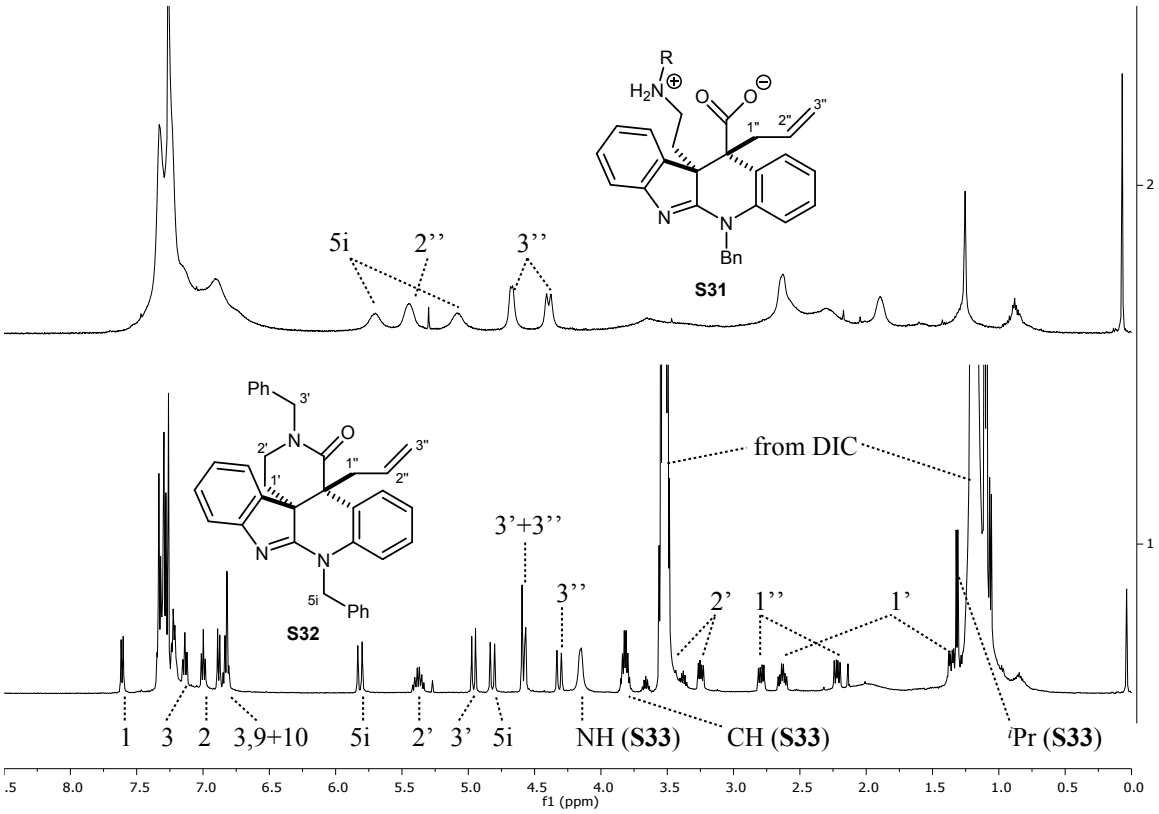
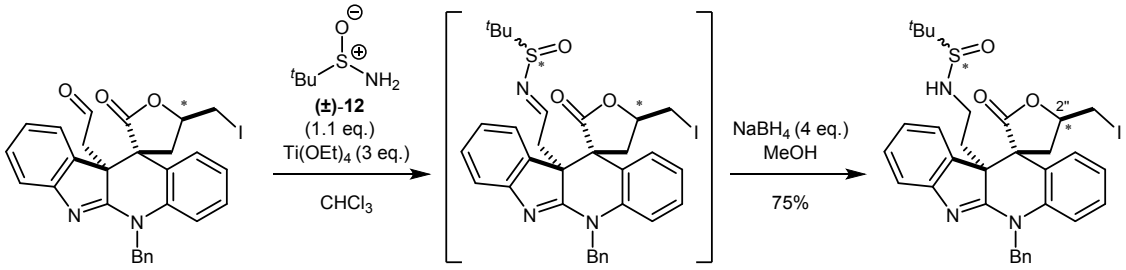


Figure S5 The ^{1}H NMR spectrum of **S31** (top spectrum) and the ^{1}H NMR spectrum of the crude reaction mixture on formation of **S32**.

The analogous conversion of aldehydes **19**/**S25** to **S34** *via* **S29**/**S30** and **S35** was also achieved (Scheme S5) and in this case a pure sample of **S34** was obtained (see below for analytical data). Finally, it was decided that the lactam *N*-protecting groups may prove very challenging to remove later in the synthesis and so another alternative was explored.

In an attempt to balance nucleophilicity with ease of protecting group removal it was decide to use a sulfinamide for the reductive amination.[18,19] In this case (*R*/*S*)-*tert*-butanesulfinamide (**12**) was used. Reaction of the diastereomeric mixture **19**/**S25** with (*R*/*S*)-**12** gave **S36** as a mixture of diastereomers (3:1 at C2'', not separated) via the corresponding imines **S37** (Scheme S8).



19/S25
3:1 at C2"

S37
3:1 at C2"

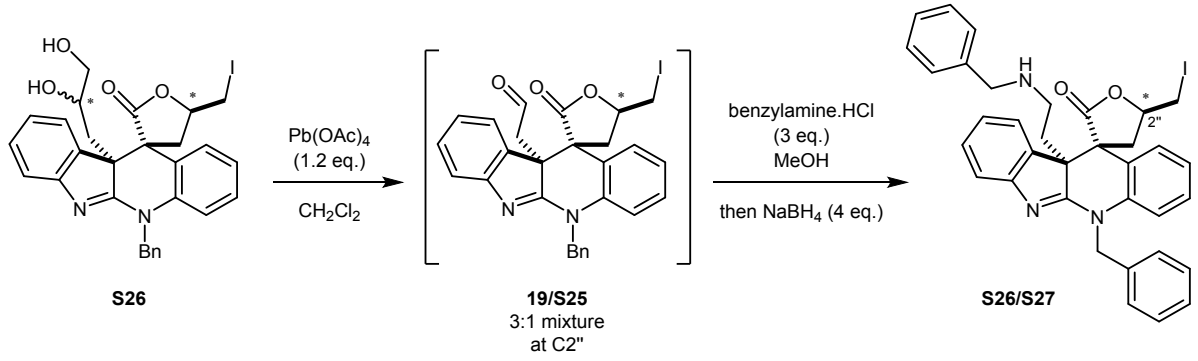
S36
3:1 at C2"

Scheme S8 Reductive amination of **19/S25** with the (*R*/*S*)-sulfinamide (**12**). * = mixture of epimers (3:1 at C2'' and 1:1 at S4').

In addition alternative protocols for the retro-iodolactonisation were also considered resulting in the use of excess zinc in place of the ^{n}BuLi (see below).

Experimental procedure for the conversion of 20 to 4

(±)-5'-benzyl-10b'-(2-(benzylamino)ethyl)-5-(iodomethyl)-4,5,5',10b'-tetrahydro-2*H*-5^{l}3-spiro[furan-3,11'-indolo[2,3-*b*]quinolin]-2-one (S26) and (±)-C2''-epi-5'-benzyl-10b'-(2-(benzylamino)ethyl)-5-(iodomethyl)-4,5,5',10b'-tetrahydro-2*H*-5^{l}3-spiro[furan-3,11'-indolo[2,3-*b*]quinolin]-2-one (S27)



S26 | **19/S25** 3:1 mixture at C2" | **S26/S27**

To a stirred solution of the diastereomeric mix **S26** (100 mg, 168 µmol) in CH_2Cl_2 (4 mL) was added lead(IV) acetate (89 mg, 202 µmol). After 0.5 hours, the reaction was filtered through a pad of Celite®, washed with CH_2Cl_2 and concentrated *in vacuo* to afford **19/S25** which was used in the next step without further purification.

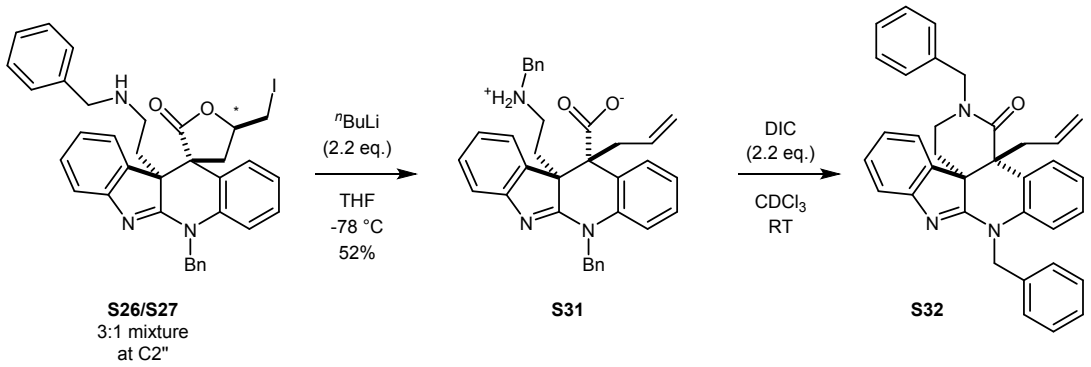
To a stirred solution of **19/S25** in MeOH (2 mL) was added benzylamine.HCl (72 mg, 504 µmol). After 3 hours, $NaBH_4$ (26 mg, 672 µmol) was added. After 1 hour, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and sat. aq. $NaHCO_3$ (3 mL) then extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (5% MeOH/CH_2Cl_2) afforded **S26/S27** (53 mg, 81 µmol, 48%, 2 steps) as a colourless oil.

IR (FTIR) ν_{max}: 3431, 1775, 1555 cm^{-1}; **LRMS** (ESI) *m/z* 564 ([M+H]$^+$, 100);

Major Epimer S26

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.36 – 7.15 (m), 7.12 – 6.96 (m, 7H), 5.51 (d, *J*=16.2 Hz, 1H), 5.16 (d, *J*=16.2 Hz, 1H), 4.27 (ddd, *J*=12.6, 10.6, 5.9 Hz, 1H), 3.51 – 3.40 (m, 1H), 3.15 (dd, *J*=10.3, 5.1 Hz, 1H), 3.03 – 2.90 (m, 2H), 2.31 – 2.10 (m, 3H), 2.01 (dd, *J*=10.0, 4.0 Hz, 1H), 1.66 (dd, *J*=12.8, 10.1 Hz, 1H).

(±)-14b-allyl-2,10-dibenzyl-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (S32) *via* S31

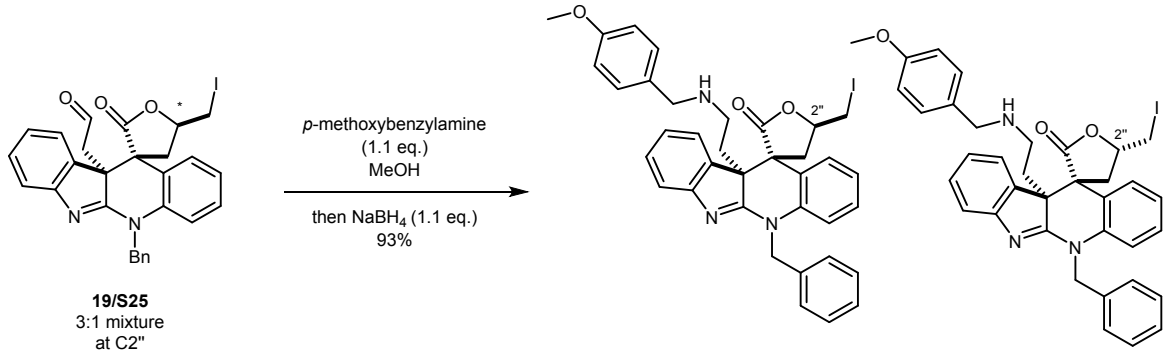


To a stirred solution of **S26/S27** (19 mg, 29.1 µmol) in THF (1 mL) at -78 °C was added *n*-butyllithium (30 µL, 64 µmol, 2.5 M solution in hexanes). After 10 minutes, the reaction was quenched with MeOH (1 mL) before the reaction was warmed to RT. The reaction was extracted with CH_2Cl_2 (2 x 5 mL) and washed with brine (5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (5% → 15% MeOH/CH_2Cl_2) afforded **S31** (8 mg, 15 µmol, 52%). **LRMS** (ESI) *m/z* 528 ($[M+H]^+$, 100); for ^{1}H NMR spectrum see Figure S5.

In a NMR tube (6 mm), **S31** was dissolved in $CDCl_3$ (0.6 mL) and diisopropylcarbodiimide (8 mg, 10 µL, 63 µmol) was added. The reaction was sonicated for 0.5 h then quenched by addition of sat. aq. Na_2CO_3 (2 mL). The reaction was extracted with CH_2Cl_2 (2 x 3 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford **S32** as a yellow oil.

HRMS (ESI) *m/z* calcd. for $C_{35}H_{32}N_3O^+$ 510.2540 $[M+H]^+$, found 510.2532; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J*=7.7 Hz, 1H), 7.39 – 7.23 (m, 12H), 7.19 – 7.14 (m, 1H), 7.06 – 7.01 (m, 1H), 6.91 (d, *J*=8.2 Hz, 1H), 6.90 – 6.82 (m, 2H), 5.85 (d, *J*=16.5 Hz, 1H), 5.49 – 5.35 (m, 1H), 5.00 (d, *J*=14.2 Hz, 1H), 4.85 (d, *J*=16.5 Hz, 1H), 4.61 (dd, *J*=12.3, 8.4 Hz, 2H), 4.35 (d, *J*=16.9 Hz, 1H), 3.59 – 3.49 (m, 1H), 3.27 (dd, *J*=12.6, 6.5 Hz, 1H), 2.83 (dd, *J*=14.2, 6.9 Hz, 1H), 2.66 (td, *J*=12.8, 6.6 Hz, 1H), 2.25 (dd, *J*=14.1, 8.1 Hz, 1H), 1.39 (dd, *J*=13.5, 5.5 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.8, 169.9, 155.6, 138.9, 137.0, 136.8, 135.0, 133.7, 129.1, 129.0 (2C), 128.9 (2C), 128.7, 128.7 (2C), 128.2, 127.9, 127.5, 126.5 (2C), 125.0, 123.5, 122.9, 122.1, 118.5, 118.1, 115.4, 53.9, 51.2, 50.3, 49.4, 43.9, 40.6, 27.7.

(±)-5'-benzyl-5-(iodomethyl)-10b'-(2-((4-methoxybenzyl)amino)ethyl)-4,5,5',10b'-tetrahydro-2*H*-5^{l}3-spiro[furan-3,11'-indolo[2,3-*b*]quinolin]-2-one (S29) and C2''-epi-(±)-5'-benzyl-5-(iodomethyl)-10b'-(2-((4-methoxybenzyl)amino)ethyl)-4,5,5',10b'-tetrahydro-2*H*-5^{l}3-spiro[furan-3,11'-indolo[2,3-*b*]quinolin]-2-one (S30)



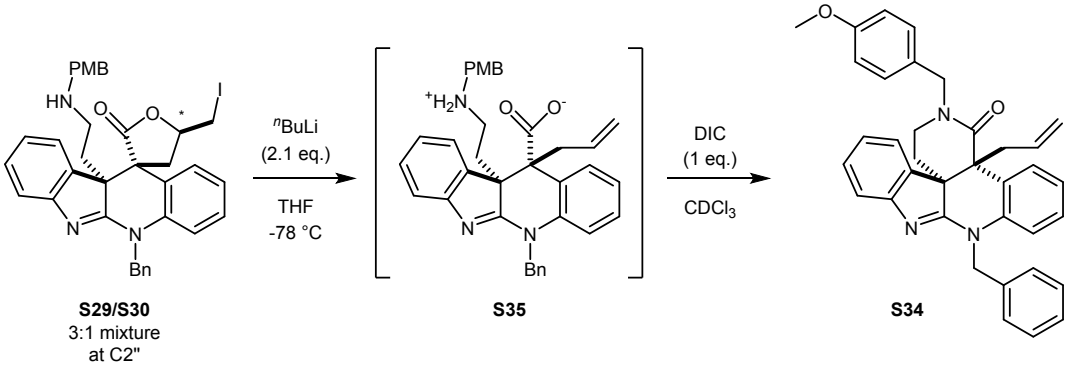
To a stirred solution of *p*-methoxybenzylamine in $CHCl_3$ (3.5 mL, 0.05 M) was added **19/S25** (90 mg, 0.168 mmol). After 1.5 h, a suspension of $NaBH_4$ (7 mg, 0.185 mmol) in MeOH (1 mL) was added. The reaction was quenched with sat. aq. NH_4Cl (4 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* Purification by column chromatography on silica gel (1% → 5% MeOH/CH_2Cl_2) afforded **S29/S30** (102 mg, 0.149 mmol, 93%) as a yellow oil as a mixture of epimers (3:1).

IR (FTIR-ATR) ν_{max}: 2961, 2922, 1771, 1553 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{36}H_{35}IN_3O_3^+$ 684.1718 $[M+H]^+$, found 684.1710;

Major Epimer S29

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.34 – 7.28 (m, 5H), 7.27 – 7.21 (m, 3H), 7.09 – 6.96 (m, 5H), 6.78 – 6.72 (m, 2H), 5.53 (d, *J*=16.2 Hz, 1H), 5.15 (d, *J*=16.1 Hz, 1H), 4.28 (dddd, *J*=10.7, 7.1, 5.4 Hz, 1H), 3.76 (s, 3H), 3.39 (dd, *J*=12.7 Hz, 2H), 3.16 (dd, *J*=10.4, 5.1 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.28 – 2.08 (m, 3H), 2.00 (dd, *J*=10.7, 5.3 Hz, 1H), 1.65 (dd, *J*=12.8, 10.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.0, 172.2, 158.6, 156.5, 139.1, 136.7, 134.4, 132.3, 129.7, 129.6, 129.3 (2C), 129.0 (2C), 127.7, 127.2 (2C), 126.0, 125.1, 123.7, 123.6, 122.7, 118.0, 116.7, 113.8 (2C), 75.4, 56.2, 55.4, 54.3, 53.3, 49.6, 45.0, 39.5, 29.9, 4.9.

(±)-14b-allyl-10-benzyl-2-(4-methoxybenzyl)-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (S34) via amino acid S35



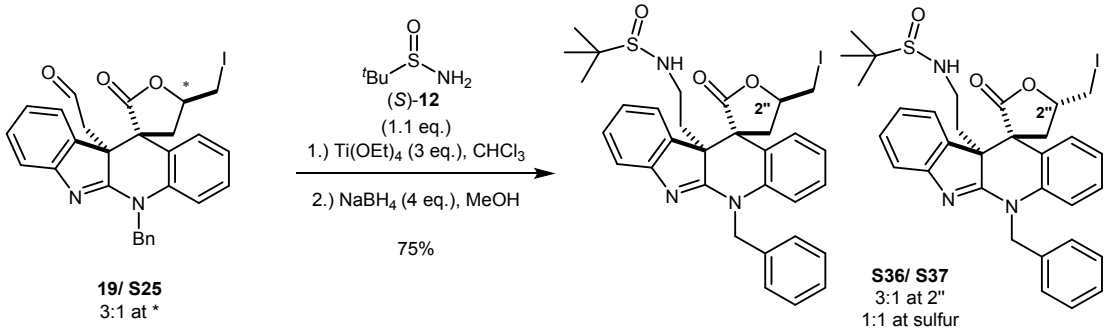
To a stirred solution of **S29/S30** (102 mg, 149 µmol) in THF (2.5 mL) at -78 °C was added ^{n}BuLi (0.13 mL, 313 µmol, 2.3 M solution in hexanes) dropwise. After 0.5 h, the reaction was quenched with MeOH (1 mL) then warmed to RT. The reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (1 → 5% MeOH/CH_2Cl_2) afforded **S35** (39 mg, 70 µmol, 47%) and recovered starting material **S29/ S30** (41 mg, 60 µmol, 40%).

To a stirred solution of diisopropylcarbodiimide in $CHCl_3$ (3 mL, 0.05 M) was added **S35** (28 mg, 50 µmol). The reaction was sonicated for 0.5 h then quenched by addition of sat. aq. Na_2CO_3 (2 mL). The reaction was extracted with CH_2Cl_2 (2 x 3 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (15% → 25% EtOAc/hexane) afforded **S34** (25 mg, 46 µmol, 92%) as a yellow oil.

IR (FTIR-ATR); ν_{max}: 2967, 1616, 1558, 1508 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{36}H_{34}N_3O_2^+$ 540.2646 $[M+H]^+$, found 540.2641; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (dd, *J*=7.8, 1.4 Hz, 1H), 7.34 – 7.29 (m, 7H), 7.28 – 7.23 (m, 2H), 7.16 (ddd, *J*=8.3, 1.5 Hz, 1H), 7.03 (1H, ddd, *J*=7.7, 1.0 Hz, 1H), 6.92 – 6.84 (m, 4H), 6.83 – 6.80 (m, 1H), 5.85 (d, *J*=16.5 Hz, 1H), 5.46 – 5.36 (m, 1H), 4.87 – 4.82 (m, 2H), 4.64 – 4.59 (m, 2H), 4.37 – 4.32 (m, 1H), 3.82 (s, 3H), 3.53 (ddd, *J*=12.4, 5.7 Hz, 1H), 3.26 (dd, *J*=12.3, 6.3 Hz, 1H), 2.82 (dd, *J*=14.1, 6.8 Hz, 1H), 2.64 (ddd, *J*=12.7, 6.6 Hz, 1H), 2.24 (dd, *J*=14.1, 8.0 Hz, 1H), 1.38 (dd, *J*=13.3, 4.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.9, 169.8, 159.4, 155.6, 138.9, 137.0, 135.1, 133.8, 130.2 (2C), 129.1, 129.0

(2C), 129.0, 128.7, 128.2, 127.5, 126.5 (2C), 125.1, 123.5, 122.9, 122.1, 118.5, 118.0, 115.4, 114.2 (2C), 55.5, 53.9, 50.6, 50.3, 49.4, 43.7, 40.6, 27.7.

(±)-*N*-(2-(5'-benzyl-5-(iodomethyl)-2-oxo-4,5-dihydro-2*H*-5l3-spiro[furan-3,11'-indolo[2,3-*b*]quinoline]-10b'(5'*H*)-yl)ethyl)-2-methylpropane-2-sulfinamide (S36) and (±)-C2''-epi-*N*-(2-(5'-benzyl-5-(iodomethyl)-2-oxo-4,5-dihydro-2*H*-5l3-spiro[furan-3,11'-indolo[2,3-*b*]quinoline]-10b'(5'*H*)-yl)ethyl)-2-methylpropane-2-sulfinamide (S37)



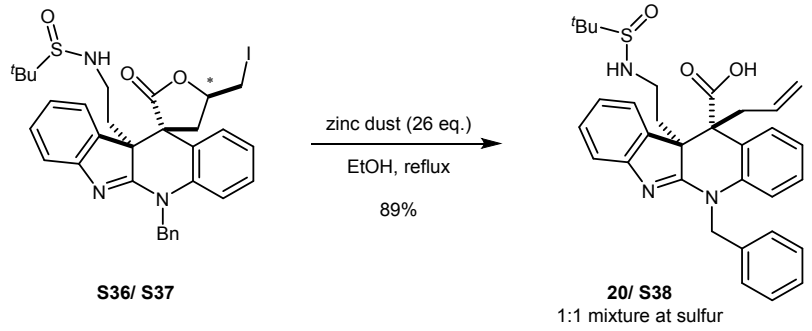
To a stirred solution of **19/S25** (7.37 g, 13.1 mmol, 1.1 eq.) and $Ti(OEt)_4$ (8.98 g, 8.25 mL, 39.4 mmol, 3 eq.) in $CHCl_3$ (130 mL) was added (±)-**12** (1.75 g, 14.44 mmol, 1.1 eq.). After 16 h, a suspension of $NaBH_4$ (2.0 g, 52.56 mmol, 4 eq.) in MeOH (30 mL) was prepared at 0 °C and added dropwise immediately. After 0.5 h, the reaction mixture was poured into a mixture of sat. aq. NH_4Cl (30 mL) and brine (130 mL) and vigorously stirred for 0.5 h then filtered through a pad of Celite® and washed with CH_2Cl_2. The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (100 mL). Combined organic extracts were washed with brine (50 mL), dried using $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography on silica gel (40% → 60% EtOAc/hexane) afforded **S36**/ **S37** (6.54 g, 9.81 mmol, 75%) as a yellow solid – as a complex mixture of epimers and rotamers.

IR (FTIR-ATR) ν_{max}: 2953, 2924, 2361, 1773, 1554 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{31}H_{34}N_3O_3IS^+$ 668.1438 $[M+H]^+$, found 668.1432; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 10H), 7.30 – 7.21 (m, 6H), 7.15 – 7.10 (m, 2H), 7.09 – 6.99 (m, 8H), 5.67 – 5.40 (m, 2H), 5.35 – 5.13 (m, 2H), 4.32 – 4.20 (m, 2H), 3.18 – 3.12 (m, 2H), 3.09 – 2.90 (m, 4H), 2.87 – 2.61 (m, 4H), 2.23 – 2.06 (m, 4H), 7.42 – 7.31 (m, 18H), 1.71 – 1.58 (m, 1H), 1.10 – 0.99 (m, 15H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 175.0, 171.8, 171.7, 156.4, 156.3, 138.9, 138.8, 136.6,

136.5, 133.8, 133.7, 130.1, 130.0, 129.8 (2C), 129.1 (2C), 129.1 (2C), 127.9, 127.9, 127.5 (2C), 127.3 (2C), 126.0, 125.9, 124.9, 124.8, 123.9, 123.9, 123.7, 123.7, 122.9, 122.8, 118.5, 118.4, 116.9, 116.8, 75.4 (2C), 56.0, 55.8, 55.7, 55.6, 54.2, 54.2, 49.5, 49.4, 42.3, 42.2, 39.4, 31.4 (2C), 22.6 (2C), 4.8 (2C).

Note double the number of peaks in ^{1}H and ^{13}C spectrum due to inseparable mixtures of epimers at sulfur.

(10b*S*,11*R*)-11-allyl-5-benzyl-10b-(2-(((*R*/*S*)-*tert*-butylsulfinyl)amino)ethyl)-10b,11-dihydro-5*H*-indolo[2,3-*b*]quinoline-11-carboxylic acid (20) and (10b*R*,11*S*)-11-allyl-5-benzyl-10b-(2-(((*R*/*S*)-tert-butylsulfinyl)amino)ethyl)-10b,11-dihydro-5*H*-indolo[2,3-*b*]quinoline-11-carboxylic acid (S38)



S36/ S37 → **20/ S38**
1:1 mixture at sulfur

A stirred suspension of **S36/S37** (1.99 g, 2.99 mmol, 1 eq.) and activated zinc (5.10 g, 78.5 mmol, 26 eq.) in EtOH (30 mL) was refluxed for 5 h. The reaction was filtered through a pad of Celite®, washed with CH_2Cl_2 then concentrated *in vacuo*. Purification by column chromatography on silica gel (5% → 10% MeOH/CH_2Cl_2) afforded the diastereomeric mix **20**/ **S38** (1.43 g, 2.65 mmol, 89%) as an off-white solid.

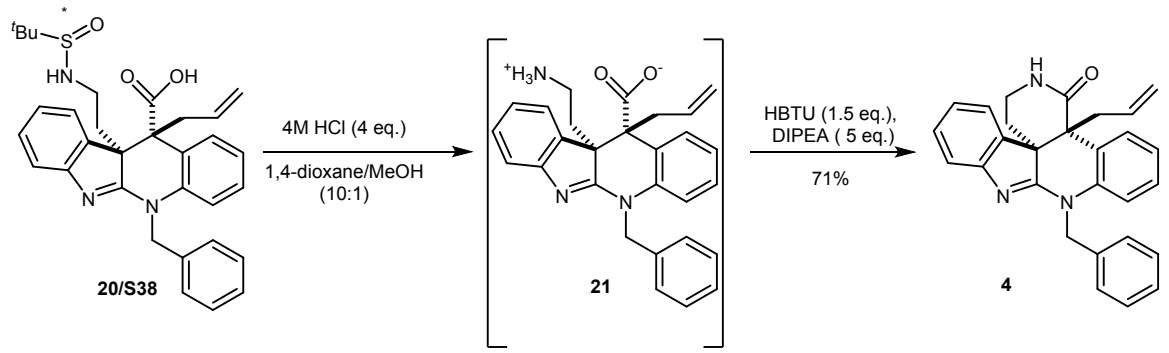
IR (FTIR-ATR) ν_{max}: 3400, 2926, 2362, 1770, 1558 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{32}H_{36}N_3O_3S^+$ 542.2472, found 542.2469 $[M+H]^+$, **^{1}H NMR** (300 MHz, CD_3OD) δ 7.48 – 7.40 (m, 4H), 7.40 – 7.32 (m, 6H), 7.32 – 7.22 (m, 8H), 7.22 – 7.14 (m, 4H), 7.12 – 7.05 (m, 2H), 7.05 – 6.97 (m, 2H), 5.61 – 5.41 (m, 4H), 5.37 – 5.21 (m, 2H), 4.74 – 4.68 (m, 2H), 4.48 – 4.34 (m, 2H), 2.85 – 2.62 (m, 2H), 2.64 – 2.51 (m, 2H), 2.54 – 2.12 (m, 2H), 2.06 – 1.92 (m, 2H), 1.08 – 1.02 (m, 18H). **^{13}C NMR** (101 MHz, CD_3OD) δ 173.9 (2C), 173.4 (2C), 154.4 (2C), 140.1, 140.0, 138.1, 138.0, 135.7, 135.6, 130.0, 129.8 (4C), 129.1 (2C), 128.5, 128.3 (2C), 128.2,

126.6 (2C), 125.2 (2C), 123.6 (2C), 118.6 (2C), 117.6, 117.6, 116.9, 116.8, 58.3, 58.3, 57.8 (2C), 56.8 (2C), 50.6, 50.6, 43.0, 43.0, 39.3 (2C), 36.4, 36.3, 23.0 (6C)

Note double the number of peaks in ^{1}H and ^{13}C spectrum due to inseparable mixtures of epimers at the sulfur.

Experimental protocol for the conversion of 20/S38 to 4

(±)-14b-allyl-10-benzyl-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (4) *via* 21



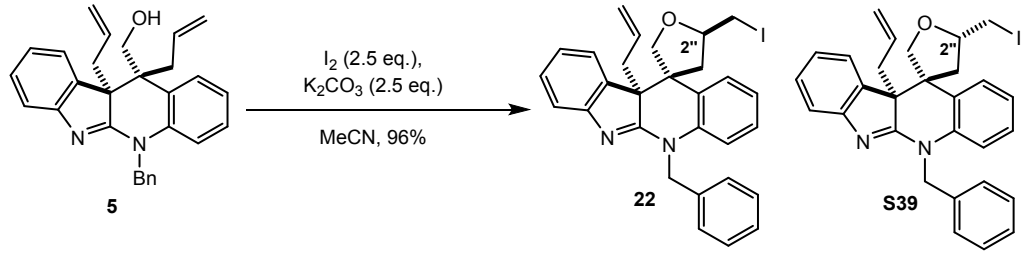
To a stirred solution of **20**/**S38** (0.58 g, 1.08 mmol) in 1,4-dioxane (10 mL) and MeOH (1 mL) was added HCl (0.8 mL, 3.24 mmol, 4 M, 3 eq.). After 1 h, HBTU (0.61 g, 1.62 mmol, 1.2 eq.) was added to the suspension. After 15 min., DIPEA (0.68 g, 0.92 mL, 5.39 mmol, 5 eq.) was added. After 16 hrs, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The reaction was extracted with CH_2Cl_2 (2 x 20 mL) and washed with aq. HCl (10 mL, 0.5 M), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (0% → 2% MeOH/CH_2Cl_2) afforded **4** (0.32 g, 0.77 mmol, 71%) as a yellow amorphous solid.

IR (FTIR-ATR) ν_{max}: 3335, 2968, 1607, 1558, 1541 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{28}H_{26}N_3O^+$ 420.2070 $[M+H]^+$, found 420.2063; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (dd, *J*=7.8, 1.6 Hz, 1H), 7.39 – 7.29 (m, 7H), 7.29 – 7.24 (m, 1H), 7.18 (ddd, *J*=8.5, 7.4, 1.6 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.93 (dd, *J*=8.2, 1.2 Hz, 1H), 6.28 (s, 1H), 5.87 (d, *J*=16.5 Hz, 1H), 5.37 (dddd, *J*=16.9, 10.1, 8.1, 6.8 Hz, 1H), 4.87 (d, *J*=16.5 Hz, 1H), 4.66 – 4.60 (m, 1H), 4.38 – 4.31 (m, 1H), 3.68 (ddd, *J*=12.4, 5.5 Hz, 1H), 3.39 (dddd, *J*=12.0, 6.4, 3.0, 1.2 Hz, 1H), 2.77 (dd, *J*=14.1, 6.8 Hz, 1H), 2.67 (ddd, *J*=12.7, 6.5 Hz, 1H), 2.26 (dd, *J*=14.0, 8.1 Hz, 1H), 1.43 (dd, *J*=13.4, 5.3 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 172.3, 155.7, 139.0, 137.0, 134.9, 133.3, 129.3, 129.0 (2C), 128.8, 128.0, 127.5, 126.5 (2C), 124.6, 123.6, 123.1, 122.3, 118.6, 118.4, 115.4, 53.5, 49.8, 49.5, 40.0, 39.1, 27.8.

Experimental procedures for the conversion of 5 to 4 *via* imine 25

(±)-10b'-allyl-5'-benzyl-5-(iodomethyl)-4,5,5',10b'-tetrahydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinoline] (22) and (±)-C2''-epi-10b'-allyl-5'-benzyl-5-(iodomethyl)-4,5,5',10b'-tetrahydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinoline] (S39)



A stirred suspension of **5** (5.01 g, 11.9 mmol, 1 eq.) and K_2CO_3 (4.11 g, 29.8 mmol, 2.5 eq.) in acetonitrile (120 mL) was treated with I_2 (7.56 g, 29.8 mmol, 2.5 eq.). The reaction mixture was left to stir for 3 hours before being quenched with $Na_2S_2O_{3(aq)}$ (25 mL) and then diluted with EtOAc (150 mL). The organic layer was washed with water (2 x 50 mL) and brine (2 x 25 mL). The aqueous liquids were combined and extracted with EtOAc (2 x 50 mL). The combined organic extracted were dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford **22/ S39** (11:1) as an amorphous brown solid (6.24 g, 11.4 mmol, 96%).

IR (FTIR) ν_{max} 3025, 2925, 1560 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{29}H_{28}N_2OI$ 547.1246

$[M+H]^+$, found 547.1229;

Major Epimer (22)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.35 – 7.29 (m, 5H,), 7.28 – 7.23 (m, 1H), 7.22 – 7.17 (m, 1H), 7.09 – 7.02 (m, 2H), 6.98 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.76 (d, *J* = 16.3 Hz, 1H), 5.18 – 5.07 (m, 1H), 5.03 (d, *J* = 16.3 Hz, 1H), 4.85 – 4.74 (m,

2H), 4.70 – 4.57 (m, 2H), 3.97 (dq, *J* = 9.6, 5.7 Hz, 1H), 3.11 – 3.02 (m, 2H), 2.61 (ddt, *J* = 13.8, 7.5, 1.2 Hz, 1H, 2.40 – 2.32 (m, 1H,), 1.94 – 1.87 (m, 1H), 1.52 (dd, *J* = 12.4, 9.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.8, 156.6, 139.3, 137.1, 134.6, 132.2, 129.6, 129.3, 128.8 (2C), 128.6, 127.5, 127.0 (2C), 126.5, 123.5, 123.5, 122.8, 119.0, 117.9, 115.7, 77.4, 57.2, 52.3, 49.9, 40.9, 37.5, 9.9.

Determining the Absolute Configuration at the C2'' stereocentre in the major epimer 22

The direct iodoetherification of **6** proceeded in an analogous fashion to the iodolactonisation of **S23** described above *via* a 5-*exo*-*tet* reaction to afford the products **22/S39** (11:1 ratio of epimers at C2''). Again, nOe analysis confirmed the confirguration at the C2'' stereocentre in the major epimer of **22** (Figure S6).

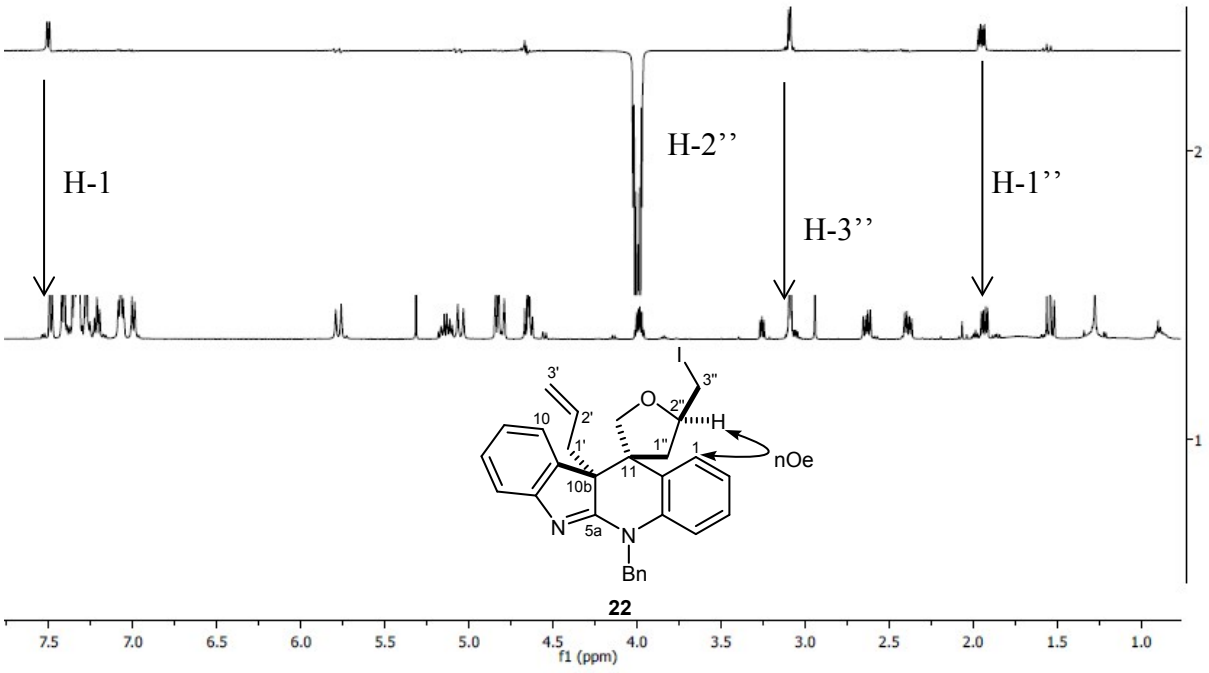
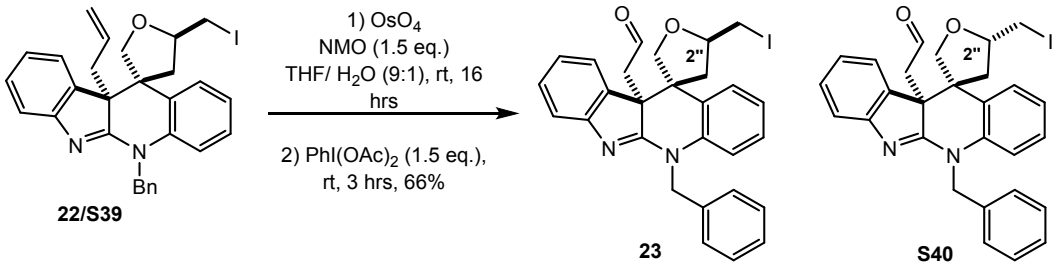


Figure S6: Selective pulse irradiation at the H2'' proton. Again, nOe enhancements inferred the configuration at the C2'' stereocentre (*R*) in the major epimer **22**. The result was consistent with the nOe data obtained for iodolactone **18** in which the configuration at the C2'' stereocentre in the major epimer was also found to be (*R*). Further nOe enhancements were also observed at H3'' and H1''.

(±)-2-(5'-benzyl-5-(iodomethyl)-4,5-dihydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinoline]-10b'(5'H)-yl)acetaldehyde (23) and (±)-C2''-epi-2-(5'-benzyl-5-(iodomethyl)-4,5-dihydro-2*H*-spiro[furan-3,11'-indolo[2,3-*b*]quinoline]-10b'(5'*H*)-yl)acetaldehyde (S40)



11:1 mixture **23**/**S40** at 2"

To a stirred solution of **22**/ **S39** (5.81 g, 10.6 mmol, 1 eq.) in THF (103 mL) and water (12 mL), was added NMO (1.87 g, 16.0 mmol, 1.5 eq.). To this mixture, OsO_4 (0.2 mL, 2.5 % w/w solution in *n*-butanol, 0.19 mol%) was added and the reaction was left to stir for 16 hours. After this time, iodosobenzene diacetate (5.57 g, 16.0 mmol) was added and the reaction was left to stir for 3 hours. The reaction was quenched with a saturated solution of $Na_2SO_{3\,(aq)}$ (10 mL) and saturated $NaHCO_{3\,(aq)}$ (10 mL). The reaction mixture was extracted with ethyl acetate (120 mL) and the organic layer was washing with water (2 x 50 mL) and brine (2 x 50 mL). The aqueous liquids were further extracted with EtOAc (2 x 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel (20 → 40 % EtOAc: Hexane) to afford **23/S40** as an off white amorphous solid (3.83 g, 7.00 mmol, 66%).

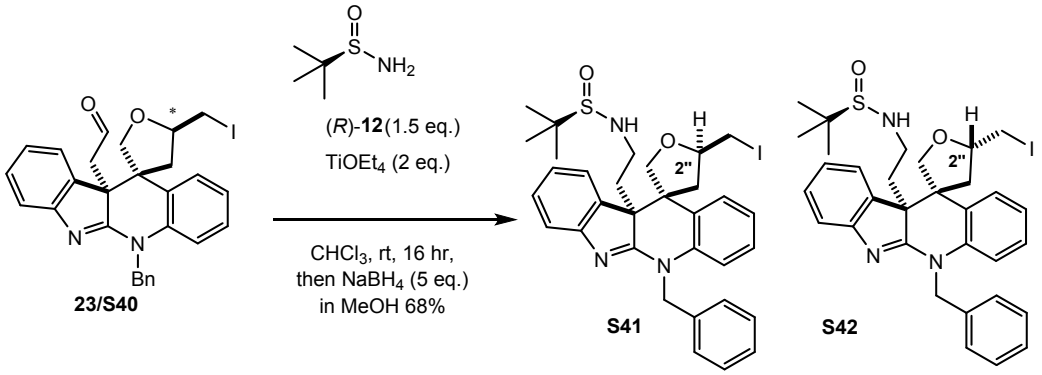
IR (FTIR) ν_{max}: 2925, 1695, 1560 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{28}H_{26}N_2O_2I$ 549.1039 $[M+H]^+$, found 549.1027.

Major Epimer (23)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 3.2, 2.1 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.39 – 7.32 (m, 7H), 7.28 – 7.25 (m, 2H), 7.24 – 7.20 (m, 1H), 7.08 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.04 – 7.01 (m, 1H), 5.77 (d, *J* = 16.2 Hz, 1H), 5.09 (d, *J* = 16.3 Hz, 1H), 4.64 (d, *J* = 8.9 Hz, 1H), 4.58 –

4.53 (m, 1H), 3.97 (dt, *J* = 9.6, 5.6 Hz, 1H), 3.07 (d, *J* = 5.5 Hz, 2H), 2.81 (dd, *J* = 15.8, 2.1 Hz, 1H), 2.59 (dd, *J* = 15.7, 3.3 Hz, 1H), 1.95 – 1.89 (m, 1H), 1.52 (dd, *J* = 12.4, 9.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.0, 171.8, 156.2, 139.0, 136.8, 133.1, 130.2, 129.1, 129.1 (2C), 128.6, 127.7, 126.9 (2C), 126.6, 124.1, 123.8, 123.6, 118.6, 116.1, 77.6, 72.8,, 52.1, 50.1, 45.0, 40.0, 9.7.

(±)-(*R*)-N-(2-(5'-benzyl-5-(iodomethyl)-4,5-dihydro-2H-spiro[furan-3,11'-indolo[2,3-b]quinoline]-10b'(5'H)-yl)ethyl)-2-methylpropane-2-sulfinamide (S41) and (±)- C2''-epi-(*R*)-N-(2-((±)-5'-benzyl-5-(iodomethyl)-4,5-dihydro-2H-spiro[furan-3,11'-indolo[2,3-b]quinoline]-10b'(5'H)-yl)ethyl)-2-methylpropane-2-sulfinamide (S42)



To a stirred solution of **23/S40** (3.71 g, 6.77 mmol) in $CHCl_3$ (75 mL) and $Ti(OEt)_4$ (3.0 mL 14. 1 mmol, 2 eq.) in $CHCl_3$ was added (*R*)-**12** (1.20 g, 9.92 mmol, 1 eq.). The mixture was left to stir at room temperature overnight before the addition of a slurry of $NaBH_4$ (1.07 g, 28.2 mmol) in MeOH (15 mL). The reaction was left to stir vigorously for 1 hour before quenching with brine (20 mL) and $Na_2SO_{4\,(aq)}$ (20 mL). The mixture was filtered through a celite pad and rinsed thoroughly with DCM (30 mL). The organic liquid was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude solid was purified by column chromatography on silica gel (20 → 80 % EtOAc: Hexane) to afford **S41/ S42** (3.00 g, 4.59 mmol, 68%) as an off white powder – as an inseparable complex mixture of epimers.

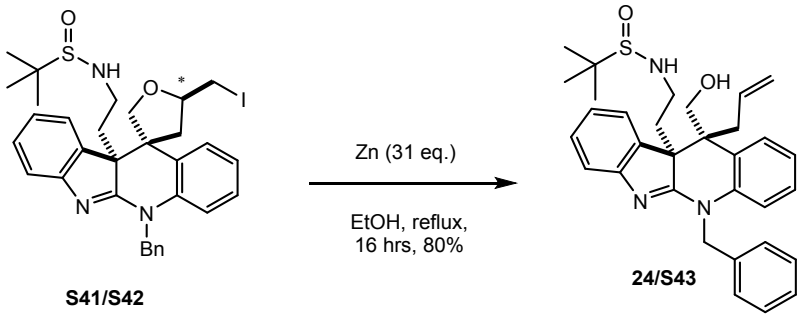
m.p. 81 – 83 °C; **IR** (FTIR) ν_{max}: 2930, 1555 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{32}H_{37}IN_3O_2S$ 654.1651 $[M+H]^+$, found 654.1639;

Major Diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.41 – 7.29 (m, 14H), 7.28 – 7.24 (m, 2H), 7.21 (tt, *J* = 7.7, 1.4 Hz, 2H), 7.10 – 6.98 (m, 6H), 5.63 (dd, *J* = 16.2, 13.9 Hz, 2H), 5.18 (dd, *J* = 16.2, 12.8 Hz, 2H), 4.68 – 4.55 (m, 4H), 3.95 (ddd, *J* = 9.5, 5.6, 1.6 Hz, 2H), 3.05 (d, *J* = 5.6 Hz, 4H), 2.89 – 2.63 (m, 2H), 2.61 – 2.37 (m, 2H), 2.28 – 2.13 (m, 2H), 1.95 – 1.81 (m, 4H), 1.47 (ddd, *J* = 12.4, 9.5, 1.1 Hz, 2H), 1.03 – 1.02 (m, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.4, 156.4, 156.3, 138.9, 138.8, 137.0, 136.9, 134.1, 134.0, 129.7, 129.4, 129.4, 129.0 (6C), 128.7, 128.7, 127.7, 127.2, 127.1 (4C), 126.6, 123.8, 123.8, 123.6, 123.5, 123.3, 123.2, 118.3, 115.8, 77.5, 73.0, 55.9, 55.8, 55.8, 52.5, 49.8, 49.7, 42.6, 42.6, 40.5, 34.8, 34.6, 22.6 (6C), 9.8.

Note double the number of peaks in ^{1}H and ^{13}C spectrum due to inseparable mixtures of epimers at the sulfur.

(*R*)-*N*-(2-((10b*S*,11*R*)-11-allyl-5-benzyl-11-(hydroxymethyl)-5,11-dihydro-10b*H*-indolo[2,3-*b*]quinolin-10b-yl)ethyl)-2-methylpropane-2-sulfinamide (24) and (*R*)-*N*-(2-((10b*R*,11*S*)-11-allyl-5-benzyl-11-(hydroxymethyl)-5,11-dihydro-10b*H*-indolo[2,3-*b*]quinolin-10b-yl)ethyl)-2-methylpropane-2-sulfinamide (S43)



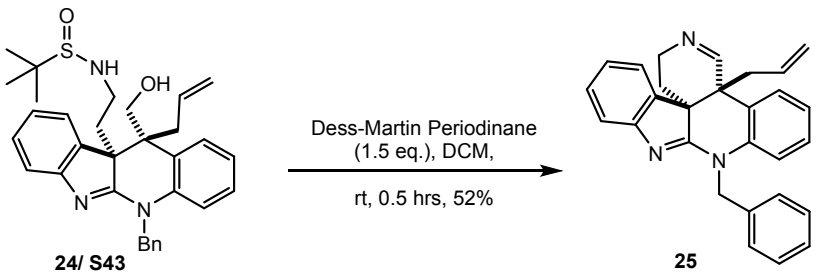
S41/S42 **24/S43**

A stirred solution of **S41/S42** (2.77 g, 4.24 mmol) and zinc dust (8.07 g, 130 mmol, 31 eq.) in ethanol (43 mL) was refluxed for 16 hours. Having cooled to room temperature, the reaction mixture was filtered through a Celite® pad and the filtrate was washed with EtOAc (50 mL) before concentrating under reduced pressure. The crude solid was purified by column chromatography on silica gel (40 → 90 % EtOAc: Hexane) to afford **24/S43** as an inseparable mixture of diastereoisomers (1.1:1), as an off white powder (1.79 g, 3.39 mmol, 80%).

m.p. 90 – 93°C; **IR** (FTIR) ν_{max}: 2935, 1560 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{32}H_{38}N_3O_2S^+$ 528.2685 $[M+H]^+$, found 528.2671; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.54 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.42 – 7.25 (m, 16H), 7.23 – 7.18 (m, 2H), 7.10 – 7.01 (m, 6H), 5.74 – 5.67 (m, 2H), 5.27 – 5.11 (m, 4H), 4.85 – 4.79 (m, 2H), 4.75 – 4.66 (m, 2H), 4.42 (d, *J* = 2.1 Hz, 4H), 2.90 – 2.39 (m, 6H), 2.26 – 2.09 (m, 4H), 1.97 – 1.91 (m, 2H), 1.06 – 1.01 (m, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.1, 172.9, 156.4, 156.2, 140.3, 140.1, 137.2, 137.1, 135.8, 135.8, 134.1, 134.1, 129.0 (2C), 128.9 (4C), 128.3, 128.2, 127.9, 127.9, 127.5 (4C), 127.0, 126.5, 124.7 (2C), 124.3 (2C), 123.1, 123.0, 122.9, 122.9, 118.2 (2C), 118.0, 118.0, 116.1, 116.0, 64.4, 64.4, 58.7, 58.5, 55.8, 55.7, 49.8, 49.7, 47.1, 47.1, 43.0, 42.7, 37.7, 37.7, 34.6, 34.4, 22.6 (6C)

Note double the number of peaks in ^{1}H and ^{13}C spectrum due to inseparable mixtures of epimers at the sulfur.

(±)-(4a*S*,14b*R*)-14b-allyl-10-benzyl-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6] – naphthyridine (25)



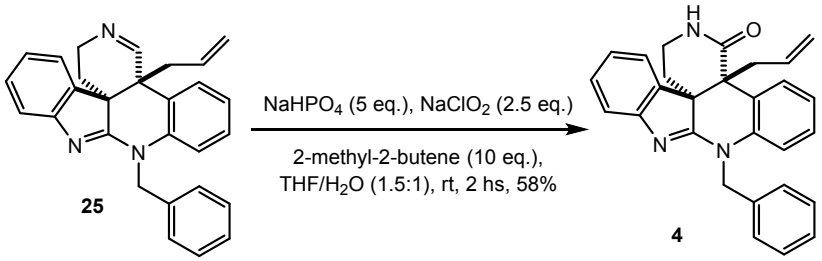
24/ S43 **25**

To a stirred solution of **24/S43** (320 mg; 0.61 mmol) in DCM (24 cm^3) was added Dess-Martin periodinane (DMP, 386 mg; 91 mmol) and left to stir for 30 minutes. The solution was quenched with $Na_2S_2O_{3\,(aq)}$ (5 mL) and $NaHCO_{3\,(aq)}$ (5 mL). The solution was diluted with DCM (18 mL) and the organic layer washed with brine (10 mL); dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was columned on alumina (10 → 20% EtOAc: Hexane) to afford **25** (127 mg; 0.32 mol, 52%) as a yellow amorphous solid.

IR (FTIR) ν_{max} 2930, 1560 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{28}H_{26}N_3^+$ 404.2127 $[M+H]^+$, found 404.2109; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (t, *J* = 2.8 Hz, 1H), 7.38 – 7.27 (m, 7H), 7.19 (dd, *J*

= 7.6, 1.5 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.04 – 7.01 (m, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 6.91 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.86 (d, *J* = 16.5 Hz, 1H), 5.40 – 5.23 (m, 1H), 4.93 (d, *J* = 16.5 Hz, 1H), 4.89 (d, *J* = 1.9 Hz, 1H), 4.63 (dd, *J* = 16.9, 1.7 Hz, 1H), 3.90 (dt, *J* = 7.7, 2.7 Hz, 2H), 2.43 – 2.35 (m, 1H), 2.32 – 2.24 (m, 2H), 1.31 (dd, *J* = 4.5, 2.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.5, 165.3, 155.2, 138.5, 136.8, 135.6, 131.4, 129.0 (2C), 129.0, 128.6, 128.3, 127.5, 127.4, 126.5 (2C), 123.2, 123.2, 122.4, 120.1, 118.4, 115.7, 51.1, 49.3, 46.1, 42.2, 40.5, 29.9.

(±)-(4a*S*,14b*R*)-14b-allyl-10-benzyl-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (4)

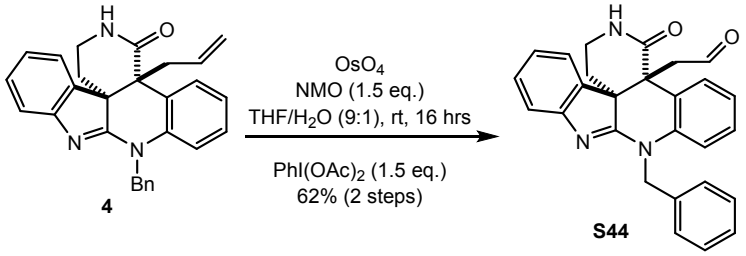


To a stirred solution of **25** (123 mg, 0.31 mmol, 1 eq.), $NaClO_2$ (134 mg, 1.49 mmol, 5 eq.) and 2-methylbuten-2-ene (0.3 mL, 0.20 g 2.86 mmol, 10 eq.) in THF (2.9 mL) was added a solution of $NaH_2PO_4.H_2O$ (105 mg, 0.76 mmol, 2.5 eq.) in water (2 mL) dropwise over 1 minute. The reaction was left to stir for 3 hours before diluting with EtOAc (20 mL) and washing with brine (2 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford **4** as an off white amorphous solid. The crude material was used without any further purification.

Alternatively, following the same procedure, 102 mg (0.25 mmol) of **25** gave 58 mg (0.14 mmol, 58%) of **4** after purification on silica gel (20 → 50% EtOAc:Hexane). Spectroscopic data was consistent with previously reported data for **4** above.

Experimental procedures for the synthesis of (±)-dehaloperophoramidine (2)

(±)-2-(10-benzyl-1-oxo-1,2,3,4-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6] -naphthyridin-14b(10*H*)-yl)acetaldehyde

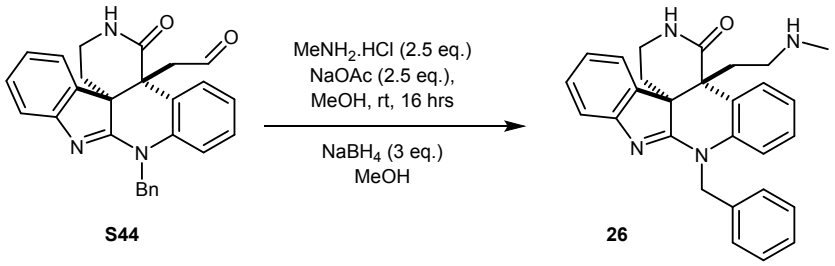


To a stirred solution of crude **4** (128 mg, 0.305 mmol, 1 eq.*) in THF (2.7 mL) and H_2O (0.3 mL), was added and NMO (54 mg, 0.458 mmol, 1.5 eq.). To this mixture, OsO_4 (0.1 mL, 2.5 % w/w solution in *n*-butanol, 3.2 mol%) was added and the reaction was left to stir for 16 hours. After this time, iodosobenzene diacetate (147 mg, 0.456 mmol, 1.5 eq.) was added and the reaction was left to stir for a further 3 hours. The reaction was quenched with saturated $Na_2SO_{3\ (aq)}$ (5 mL) and saturated $NaHCO_{3\ (aq)}$ (5 mL). The reaction mixture was extracted with ethyl acetate (25 mL) and the organic layer was washing with water (2 x 5 mL) and brine (2 x 5 mL). The aqueous liquids were extracted with EtOAc (2 x 10 mL). The combined organic liquid was dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel (25 → 70 % EtOAc: Hexane) to afford **S44** as an off white powder (80 mg, 0.190 mmol, 62% over 2 steps from **25**).

*Crude material from synthesis of lactam **4**, assumed theoretical 100% yield for mass and no. of moles calculation.

IR (FTIR) ν_{max} (cm^{-1}) 2960, 1715, 1555 cm^{-1}; **HRMS** calcd. for $C_{27}H_{24}N_3O_2^+$ 422.1869 $[M+H]^+$, found 422.1862; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.58 (dd, *J* = 4.1, 1.2 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 – 7.30 (m, 6H), 7.29 – 7.19 (m, 3H), 7.07 – 7.02 (m, 2H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.39 (s, 1H), 5.85 (d, *J* = 16.4 Hz, 1H), 5.04 (d, *J* = 16.4 Hz, 1H), 3.74 (td, *J* = 12.2, 5.9 Hz, 1H), 3.51 – 3.43 (m, 1H), 2.70 (ddd, *J* = 13.6, 11.9, 7.0 Hz, 1H), 2.52 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.15 (dd, *J* = 16.0, 1.3 Hz, 1H), 1.56 (dd, *J* = 13.4, 5.9 Hz, 1H; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.4, 171.4, 171.3, 155.6, 138.3, 136.5, 134.0, 129.9, 129.8, 129.1 (2C), 128.4, 127.6, 126.4 (2C), 123.7, 123.6, 123.0, 122.8, 118.9, 116.4, 53.9, 49.4, 48.9, 44.5, 39.1, 25.2.

(±)-10-benzyl-14b-(2-(methylamino)ethyl)-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (26)

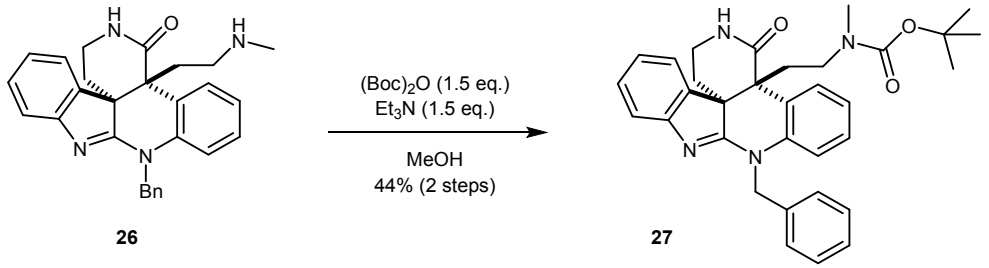


S44 **26**

To a stirred solution of **S44** (0.393 g, 0.93 mmol) in MeOH (10 mL) was added $MeNH_2$.HCl (0.126 g, 1.87 mmol) followed by NaOAc (0.153 g, 1.87 mmol). After 18 h, $NaBH_4$ (0.106 g, 2.78 mmol) was added in portions. After 1 hr, the reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Amine **26** was used without additional purification

HRMS (ESI) *m/z* calcd. for $C_{28}H_{29}N_4O^+$ 437.2336 $[M+H]^+$, found 437.2335; **IR** (FTIR-ATR) ν_{max}: 3369, 2926, 1645, 1550; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J*=7.7 Hz, 1H), 7.37 – 7.23 (m, 8H), 7.21 – 7.16 (m, 1H), 7.04 – 6.98 (m, 2H), 6.95 (d, *J*=8.2 Hz, 1H), 6.21 (s, 1H), 5.83 (d, *J*=16.4 Hz, 1H), 5.02 (d, *J*=16.5 Hz, 1H), 3.67 (ddd, *J*=12.1, 5.6 Hz, 1H), 3.38 (dd, *J*=11.1, 7.0 Hz, 1H), 2.64 (ddd, *J*=12.7, 6.7 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.12 (s, 1H), 2.05 – 1.94 (m, 2H), 1.48 (ddd, *J*=22.2, 11.0, 6.3 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.7, 172.5, 155.6, 138.5, 136.8, 134.9, 129.3, 129.0 (2C), 128.9, 128.2, 127.6, 126.5 (2C), 124.7, 123.5, 123.0, 122.5, 118.7, 115.6, 54.3, 49.3, 48.9, 48.8, 39.1, 36.1, 34.2, 26.8.

(±)-*tert*-butyl-(2-(10-benzyl-1-oxo-1,2,3,4-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-14b(10*H*)-yl)ethyl)(methyl)carbamate (27)

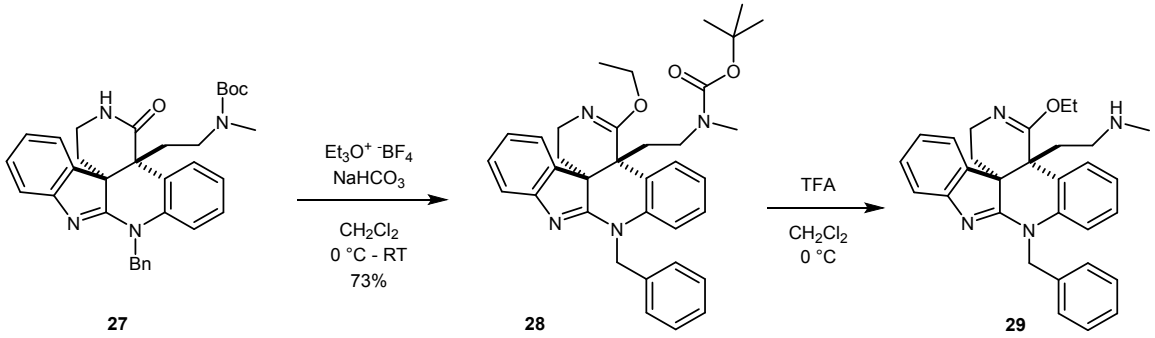


26 **27**

To a crude stirred solution of **26** in MeOH (10 mL) was added di-*tert*-butyl dicarbonate (0.235 g, 1.08 mmol) and Et_3N (0.109 g, 0.15 mL, 1.08 mmol). After 1 h, the reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with aq. HCl (10 mL, 0.5 M), sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (1% → 5% MeOH/CH_2Cl_2) afforded **27** (0.221 g, 0.412 mmol, 44%, 2 steps from **S44**) as a white amorphous solid.

IR (FTIR-ATR) ν_{max}: 2963, 2380, 1684 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{33}H_{36}N_4O_3Na^+$ 559.2680 $[M+Na]^+$; found 559.2667; **^{1}H NMR** (500 MHz, Tol-d_8, 363.5 K) δ 7.65 (d, *J*=7.7 Hz, 1H), 7.36 (d, *J*=7.8 Hz, 1H), 7.27 (d, *J*=7.6 Hz, 2H), 7.18 – 7.09 (m, 2H), 7.05 – 7.00 (m, 1H), 6.90 – 6.80 (m, 3H), 6.79 – 6.75 (m, 1H), 5.71 (d, *J*=16.1 Hz, 1H), 5.48 (s, 1H), 4.89 (d, *J*=16.1 Hz, 1H), 3.31 (ddd, *J*=13.0, 4.7 Hz, 1H), 2.99 (ddd, *J*=11.9, 5.8 Hz, 1H), 2.88 – 2.75 (m, 1H), 2.51 – 2.45 (m, 1H), 2.43 (s, 3H), 2.30 – 2.17 (m, 2H), 1.73 (ddd, *J*=13.5, 11.7, 4.6 Hz, 1H), 1.27 (s, 9H), 0.86 (dd, *J*=13.2, 5.2 Hz, 1H).

(±)-*tert*-butyl-(2-(10-benzyl-1-ethoxy-3,4-dihydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-14b(10*H*)-yl)ethyl)(methyl)carbamate (28) and (±)-2-(10-benzyl-1-ethoxy-3,4-dihydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-14b(10*H*)-yl)-*N*-methylethan-1-amine (29)



27 **28** **29**

To a stirred suspension of **27** (177 mg, 0.33 mmol) and $NaHCO_3$ (150 mg, 1.79 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added a solution of Et_3O^+ BF_4^- (0.9 mL, 0.895 mmol, 1 M in CH_2Cl_2). After 1 hr, the reaction was allowed to warm to RT then quenched with sat. aq. $NaHCO_3$ (20 mL) after 1 hr. The reaction was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (0% → 5% MeOH/CH_2Cl_2) afforded **28** (0.148 mg, 0.262 mmol, 73%) as a colourless oil and recovered **27** (10 mg, 0.018 mmol, 5%).

28

HRMS (ESI-ion trap) *m/z* calcd. for $C_{35}H_{41}N_4O_3^+$ 565.3173 $[M+H]^+$, found 565.3165.

To a stirred solution of **28** (0.146 g, 0.26 mmol) in anhydrous CH_2Cl_2 (24 mL) at 0 °C was added TFA (1.3 mL) dropwise. After 30 minutes, the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 25 mL), the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **29** which was used in the next step without additional purification.

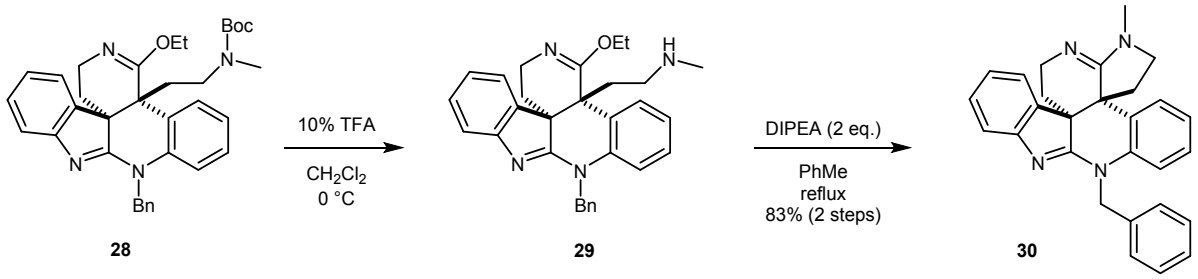
Alternatively, purification by column chromatography on silica gel (5% MeOH/CH_2Cl_2/0.1% NH_4OH) afforded **29** (19 mg, 40.9 µmol, 96%) as a colourless oil; starting with **28** (24 mg, 42.5 µmol).

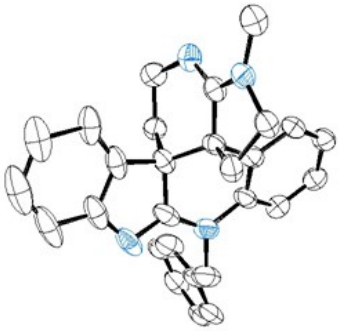
29

HRMS (ESI) *m/z* calcd. for $C_{30}H_{33}N_4O^+$ 465.2649 $[M+H]^+$, found 465.2653; **IR** (FTIR-ATR) ν_{max}: 2932, 2855, 2378, 2309. 1559; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (dd, *J*=7.8, 1.5 Hz, 1H), 7.34 – 7.29 (m, 5H), 7.28 – 7.22 (m, 2H), 7.15 (ddd, *J*=8.4, 7.4, 1.5 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.00 – 6.95 (m, 2H), 6.91 (dd, *J*=8.2, 1.2 Hz, 1H), 5.84 (d, *J*=16.5 Hz, 1H), 4.96 (d, *J*=16.3 Hz, 1H), 4.39 – 4.28 (m, 2H), 3.81 – 3.64 (m, 2H), 2.55 (td, *J*=11.4, 4.7 Hz, 1H), 2.41 (ddd, *J*=13.0, 11.3, 6.8 Hz, 1H), 2.10 (s, 3H), 2.06 (td, *J*=11.5, 4.8 Hz, 1H), 1.93 (ddd, *J*=13.8, 11.2, 4.8 Hz, 1H), 1.51 (ddd, *J*=13.9, 11.3, 4.7 Hz, 1H), 1.44 (t, *J*=7.1 Hz, 3H), 1.26 – 1.24 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.1, 161.8, 155.4, 138.3, 136.9, 135.5, 129.0 (2C), 129.0, 128.8, 128.1,

127.5, 126.5, 126.5 (2C), 123.3, 123.3, 122.5, 118.4, 115.7, 61.6, 54.2, 49.2, 48.7, 45.1, 43.0, 35.1, 32.8, 27.5, 14.6.

(±)-12-benzyl-3-methyl-2,3,5,6-tetrahydro-1*H*,12*H*-benzo[*c*]indolo[3,2-*j*]pyrrolo[3,2-*e*][2,6]naphthyridine (30)





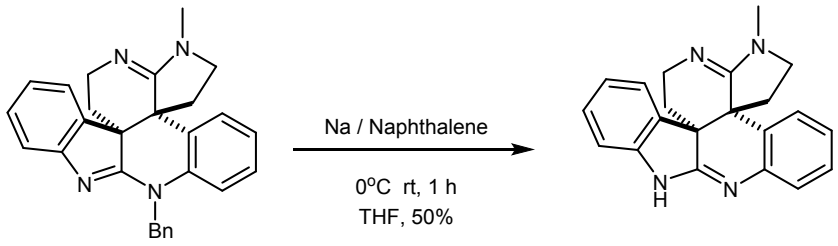
To a stirred solution of **28** (0.146 g, 0.259 mmol) in dry CH_2Cl_2 (23.7 mL) at 0 °C was added TFA (1.3 mL) dropwise. After 30 minutes, the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 25 mL), the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **29** which was used in the next step without additional purification.

A stirred solution of **29** (0.259 mmol) and DIPEA (66 mg, 90 µL, 0.518 mmol) in dry PhMe (25 mL) was refluxed for 18 hrs. The reaction was concentrated *in vacuo* and purification by column chromatography on silica gel (5% MeOH/CH_2Cl_2/0.1% NH_4OH) afforded **30** (90 mg, 0.215 mmol, 83%, 2 steps) as an off-white amorphous solid. Recrystallisation of a small sample of **30** in DCM/ Hexane afforded crystals was suitable for X-ray analysis (CCDC 1478154).[6]

IR (FTIR-ATR) ν_{max}: 2932, 2855, 2378, 2309, 1559, 1541, 1506 cm^{-1}; **HRMS** (ESI) *m/z* calcd. for $C_{28}H_{27}N_4^+$ 419.2230 $[M+H]^+$, found 419.2228; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 5H), 7.30 – 7.23 (m, 2H), 7.16 (ddd, *J*=7.9, 1.5 Hz, 1H), 7.13 – 7.11 (m, 1H), 7.00 (ddd, *J*=7.4, 1.2 Hz, 1H), 6.98 – 6.93 (m, 2H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1H), 5.74 (d, *J*=16.4 Hz, 1H), 5.14 (d,

J=16.4 Hz, 1H), 3.83 – 3.67 (m, 2H), 3.35 (ddd, *J*=9.9, 6.0 Hz, 1H), 3.22 (s, 3H), 3.11 (t, *J*=9.1 Hz, 1H), 2.33 (ddd, *J*=13.4, 10.1, 7.8 Hz, 1H), 1.83 (ddd, *J*=12.2, 10.1, 8.7 Hz, 1H), 1.71 (dd, *J*=12.2, 5.9 Hz, 1H), 1.45 (ddd, *J*=13.4, 6.6, 1.5 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.9, 161.8, 155.6, 137.8, 136.7, 135.2, 129.1, 129.0 (2C), 128.8, 127.6, 127.1, 126.5 (2C), 126.2, 123.4, 123.1, 122.9, 118.1, 116.0, 52.2, 49.0, 47.6, 46.8, 42.8, 31.6, 29.9, 25.6.

(±)-Dehalo-perophoramidine (2)



30 **(±) 2**

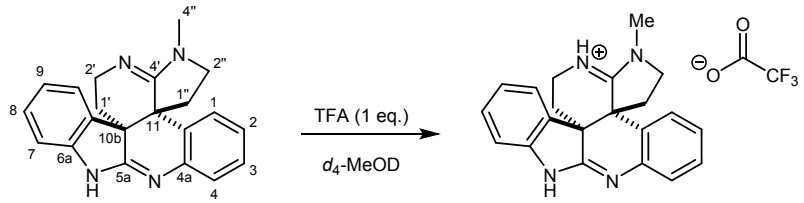
To a stirred solution of **30** (10 mg, 0.024 mmol) in THF (2 mL) at 0 °C, was added a freshly prepared solution of sodium naphthalide (1 M in THF) until the reaction mixture remained green in colour. The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with brine (2 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatograph on silica gel (10% MeOH/CH_2Cl_2/1% NH_4OH) afforded **2** (4 mg, 0.012 mmol, 50%) as a yellow oil.

HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}N_4^+$ 329.1761 $[M+H]^+$, found 329.1764; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.15 (d, *J*=7.7 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.02 – 6.95 (m, 2H), 6.90 (dd, *J*=7.6, 1.4 Hz, 1H), 3.70 (dt, *J*=9.9, 3.8 Hz, 2H), 3.34 (td, *J*=9.7, 5.9 Hz, 1H), 3.19 (s, 3H), 3.08 (t, *J*=9.1 Hz, 1H), 2.29 – 2.21 (m, 1H), 1.90 – 1.81 (m, 1H), 1.73 (dd, *J*=12.1, 5.8 Hz, 1H), 1.39 – 1.34 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.9, 161.3, 150.5, 139.0, 132.3, 128.9, 128.7, 127.0, 126.0, 124.1, 123.9, 122.2, 120.3, 114.1, 50.0, 47.1, 46.5, 43.0, 31.4, 30.1, 25.3.

Comparison of synthetic (±)-2 to other reported spectra in the literature

Comparison of Synthetic Dehaloperophoramidine TFA salt (±)-2.TFA with Material Provided by Prof. Chris Ireland

Synthetic (±)-**2** was converted to the corresponding TFA salt (**(±)-2.TFA**) by treatment with TFA in deuterated MeOH (Scheme S9). The ^{1}H NMR spectrum obtained was found to be in agreement with an authentic sample of **2.TFA** provided by C. Ireland (Figure S7).



(±)-Dehalo-perophoramidine **(2)**

(±)-Dehalo-perophoramidine . TFA salt **(2.TFA)**

Scheme S9: Preparation of the TFA salt **(2.TFA)**. This compound was prepared in order to compare it with an authentic sample of authentic **2.TFA**, provided by Prof Chris Ireland.

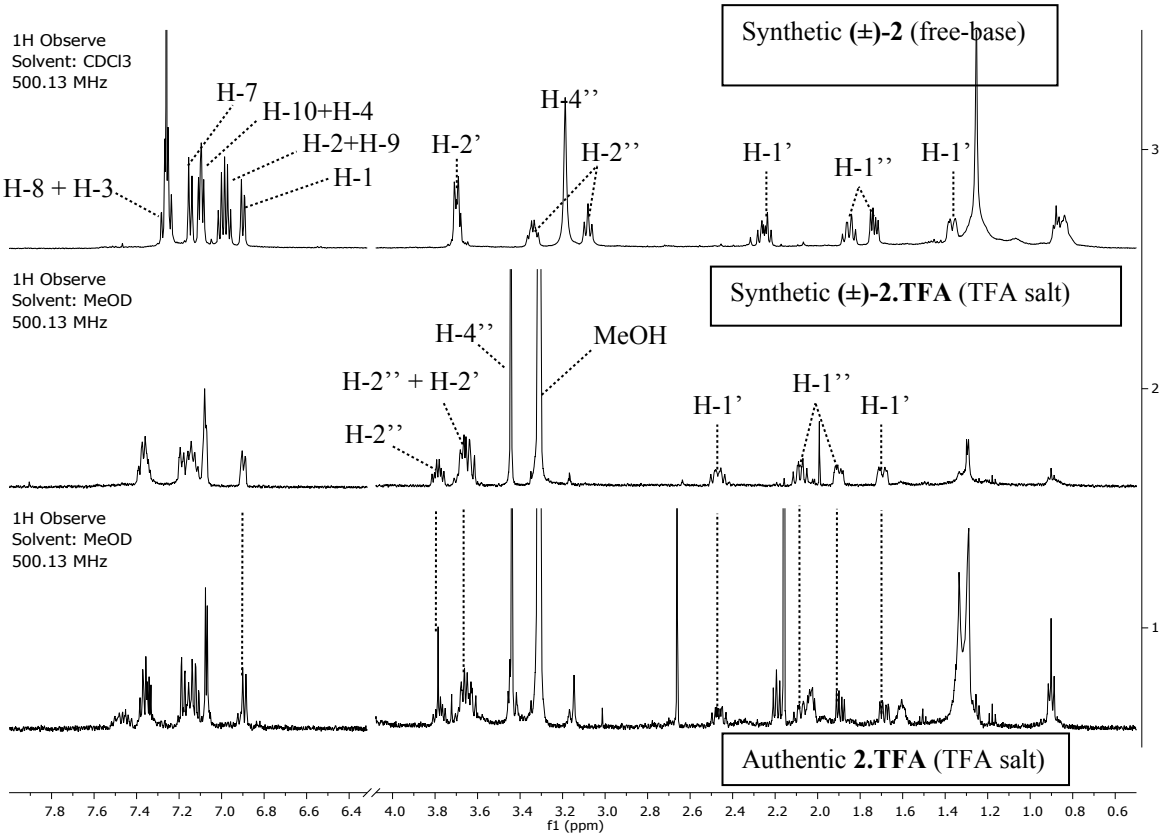


Figure S7. The ^{1}H NMR spectra of synthetic (±)-**2** (free-base in $CDCl_3$, spectrum 3); synthetic (±)-**2.TFA** (TFA salt in d_4-MeOD, spectrum 2) and an authentic sample of **2.TFA** (TFA salt in d_4-MeOD, spectrum 1). The region 6.35 – 4.50 ppm contained a broad water signal in spectra 1 and 2 and has therefore been left out for clarity.

Doping Experiment of Authentic 2.TFA with synthetic (±)-2.TFA for Structure Confirmation

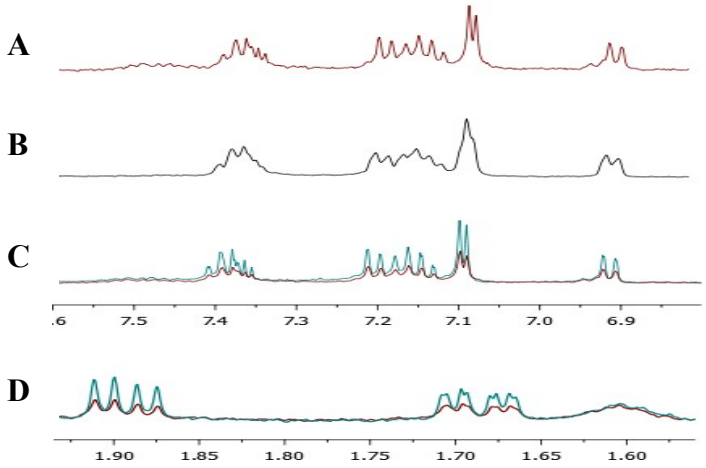


Figure S8. ^{1}H NMR (d_4-MeOD) comparison of the aromatic region (7.60-6.80 ppm) of authentic **2.TFA** (spectrum **A**) and synthetic **2.TFA** (spectrum **B**). A sample of authentic **2.TFA** was doped with synthetic **2.TFA** and the resulting ^{1}H NMR has been superimposed on that of authentic **2.TFA** (spectrum **C**). A selected region in the aliphatic region (spectrum **D**; 1.97-1.55 ppm) showed that whilst the signals associated with H-1'' and H1' increased, a signal associated with a decomposition product from authentic **2.TFA** remained unchanged.

A ^{1}H NMR spectrum (d_4-MeOD) of authentic **2.TFA** was acquired (Figure S9; red spectrum) before doping the sample with synthetic (±)-**2.TFA** and submitting for further ^{1}H NMR analysis (Figure S9; blue spectrum). The two spectra were overlaid (Figure S9).

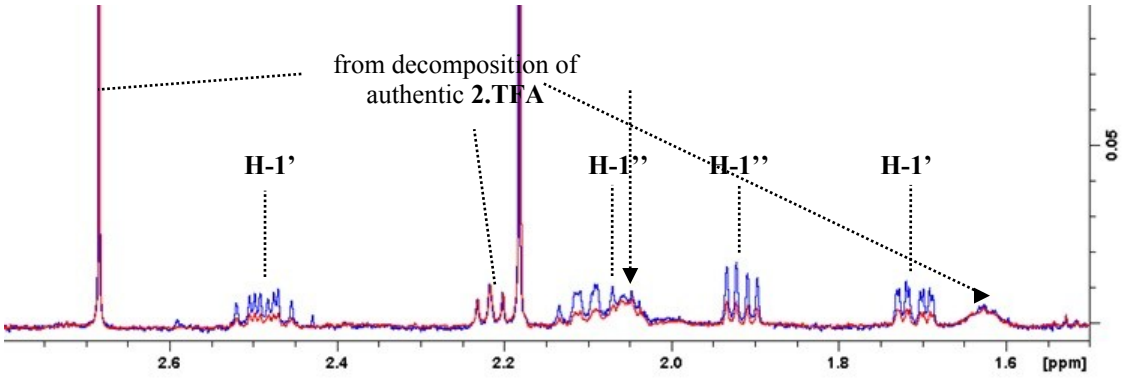
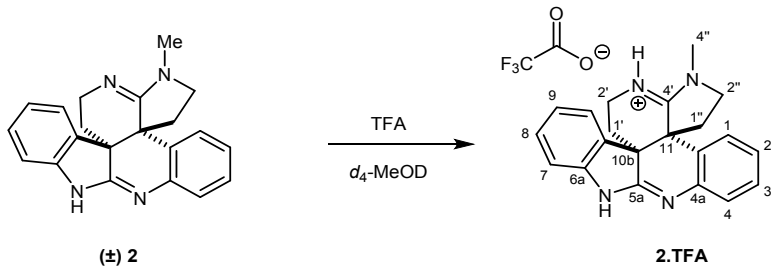


Figure S9 The ^{1}H NMR spectrum (d_4-MeOD) from δ_H 2.80 – 1.50 ppm of an authentic sample of **2.TFA** (red spectrum) and the ^{1}H NMR spectrum of authentic **2.TFA** doped with synthetic (±)-**2.TFA** (blue spectrum). An increase in the signals associated with protons H-1' and H-1'' were observed and the signal associated with a decomposition product in authentic **2.TFA** (δ_H 2.22 ppm and 1.63 ppm) were unchanged.

The unknown impurity peaks from authentic **2.TFA** were used as an internal reference. Whilst the peaks corresponding to **2.TFA** increased, the impurity did not increase in intensity.

(±)-Dehalo-perophoramidine.TFA salt (2.TFA)



(±) 2 **2.TFA**

A solution of TFA in d_4-CD_3OD was added to (±)-**2** to afford the TFA salt of (±)-dehalo-perophoramidine (**2.TFA**).

^{1}H NMR (500 MHz, CD_3OD) δ 7.40 – 7.32 (m, 2H), 7.22 – 7.10 (m, 3H), 7.10 – 7.05 (m, 2H), 6.92 – 6.88 (m, 1H), 3.79 (td, *J*=10.9, 5.9 Hz, 1H), 3.71 – 3.60 (m, 3H), 3.44 (s, 3H), 2.47 (ddd, *J*=13.1, 11.1, 8.5 Hz, 1H), 2.08 (ddd, *J*=12.5, 10.5, 8.9 Hz, 1H), 1.90 (dd, *J*=13.1, 5.7 Hz, 1H), 1.69 (dd, *J*=15.0, 6.0 Hz, 1H).

Tabulated Comparison of (±)-2.TFA vs Isolation Paper

Assignment	Ireland[20]	Westwood	Takemoto[21]
8	7.34 (ddd, *J* = 7.9, 7.9, 1.2)	7.38 – 7.30 (m)	Chemical shifts not written up in paper but a comparison of the published ^{1}H NMR spectrum of authentic **2.TFA** with the material prepared by this group was provided.
3	7.31 (dd, *J* = 7.8, 7.8)		
7	7.19 (d, *J* = 7.9)	7.20 (dd, *J* = 7.9, 1.3 Hz)	
4	7.12 (d, *J* = 7.8)	7.15 – 7.07 (m)	
1	7.09 (d, *J* = 7.8)		
9	7.07 (7.9, *J* = 7.8)		
2	7.04 (dd, *J* = 7.8, 7.8)		
10	6.73 (dd, *J* = 7.8, 1.2)	6.72 (dd, *J* = 7.7, 1.4 Hz)	
2''	3.75 (m)	3.74 – 3.62 (m)	
2''	3.71 (m)		
2'	3.67 (m)		
4''	3.61 (s)	3.59 (s, 3H)	
2'	3.46 (dd, *J* = 10.5, 8.9)	3.42 (dd, *J* = 10.9, 8.7 Hz,)	
1''	2.41 (ddd, *J* = 14.1, 10.6, 8.3)	2.40 (ddd, *J* = 14.0, 10.5, 8.3 Hz)	
1'	2.10 (ddd, *J* = 12.5, 8.9, 8.7)	2.08 (ddd, *J* = 12.4, 10.4, 8.7 Hz)	
1'	1.91 (dd, *J* = 12.5, 5.8)	1.91 (dd, *J* = 12.5, 5.8 Hz)	
1''	1.68 (ddd, *J* = 14.1, 5.1, 1.2)	1.65 (ddd, *J* = 14.0, 5.3, 2.3 Hz).	

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Table S2 Full comparison of the chemical shifts of our synthetic **(±)-2.TFA** *vs* authentic **2.TFA** reported by Ireland *et al*. Spectra run at 500 MHz in $CDCl_3$ and referenced to 7.24 ppm. [a]During our attempts to prepare a sample of our synthetic **(±)-2.TFA** for comparison it was found that the chemical shifts of peaks in the 1H NMR analysis were very sensitive to the amount of TFA used. This led to significant challenges in preparing a sample that was analogous to previous reports.[20,21]

Tabulated Comparison of Reported Syntheses of (±)-2 (free base) in $CDCl_3$

	Takemoto[21]	Somfai[22]	Westwood
Aromatic Region	7.29-7.23 (m, 2H)	7.30 – 7.26 (m, 1H) 7.25 – 7.22 (m, 1H)	7.29 – 7.23 (m, 2H)
	7.18 (d, *J* =7.7 Hz, 1H)	7.17 (d, J = 7.7 Hz, 1H)	7.15 (d, *J*=7.7 Hz, 1H)
	7.14-7.10 (m, 2H)	7.13 – 7.09 (m, 2H)	7.12 – 7.07 (m, 2H)
	7.00 (dd, *J* = 7.0, 7.0 Hz, 1H)	7.02 – 6.89 (m, 3H)	7.02 – 6.95 (m, 2H)
	6.97 (dd, *J* = 7.0, 7.0 Hz, 1H)		
	6.93 (d, *J* = 7.4 Hz, 1H)		6.90 (dd, *J*=7.6, 1.4 Hz, 1H, 1H)
Aliphatic Region	3.72-3.69 (m, 2H)	3.75 – 3.65 (m, 2H)	3.70 (dt, *J*=9.9, 3.8 Hz, 2H)
	3.32 (ddd, *J* = 9.6, 9.6, 5.7 Hz, 1H)	3.32 (td, *J* = 9.7, 5.9 Hz, 1H)	3.34 (td, *J*=9.7, 5.9 Hz, 1H)
	3.15 (s, 3H)	3.15 (s, 3H)	3.19 (s, 3H)
	3.06 (dd, *J* = 9.0, 9.0 Hz, 1H)	3.06 (t, *J* = 8.9 Hz, 1H)	3.08 (t, *J*=9.1 Hz, 1H)
	2.26 (ddd, *J* = 13.2, 8.9, 8.9 Hz, 1H)	2.31 – 2.20 (m, 1H)	2.29 – 2.21 (m, 1H)
	1.88-1.82 (m, 1H)	1.91 – 1.79 (m, 1H)	1.90 – 1.81 (m, 1H)
	1.74 (dd, *J* = 12.0, 6.0 Hz, 1H)	1.74 (dd, *J* = 12.0, 5.7 Hz, 1H)	1.73 (dd, *J*=12.1, 5.8 Hz, 1H)
	1.35 (ddd, *J* = 13.2, 5.0, 2.4 Hz, 1H)	1.40 – 1.31 (m, 1H)	1.39 – 1.34 (m, 1H)

Table S3 Full comparison of the chemical shifts in $CDCl_3$ of synthetic **(±)-2.TFA** reported by Takemoto[21] (relative to TMS 0.00 ppm), Somfai[22] (*appears to be relative to $CDCl_3$) and Westwood[c] (relative to $CDCl_3$ 7.26 ppm)

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6. CCDC 1486344 (**15**) CCDC 1478153 (**S16**), CCDC 1478152 (**5**) and CCDC 1478154 (**30**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
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