# Synthesis and Oxidative Cleavage of Oxazinocarbazoles: Atropselective Access to Medium-Sized Rings

Gu Liu,[1] Christopher S. Lancefield,[1] Magali M. Lorion, Alexandra M. Z. Slawin, Nicholas J. Westwood*

School of Chemistry and Biomedical Sciences Research Complex, University of St Andrews and EaStCHEM, North Haugh, St Andrews, Fife, UK

Fax +44(1334)462595; E-mail: njw3@st-andrews.ac.uk

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Dedicated to Professor Philip D. Magnus on the occasion of his 70th birthday

**Abstract:** Polycyclic systems can be converted into medium-sized-ring-containing compounds through the controlled oxidative cleavage of internal double bonds. This approach is particularly accessible in systems that contain a suitably substituted indole ring. Here, a robust approach to the synthesis of the understudied oxazinocarbazole system is reported. After regioselective incorporation of a carbonyl functional group, *m*-chloroperoxybenzoic acid (MCPBA) is used to cleave the indole 2,3-double bond that this system contains. This results in a competition between two processes, oxidative cleavage of the double bond and a pinacol-type rearrangement, both of which occur with very high diastereoselectivity. The balance between the two processes is studied as a function of the substrate structure. Extensive use of X-ray crystallographic analysis of the products enables detailed mechanistic conclusions to be drawn.

**Key words:** atropisomerism, diastereoselectivity, macrocycles, epoxidation, heterocycles

Pyrazinocarbazoles of general structure **1** (Figure 1) are of interest because of their reported biological activity, in particular as monoamine oxidase A inhibitors.[2] Given the interest shown in this type of compound, it is perhaps surprising that there are relatively few reports on the synthesis and biological characterisation of the related oxazinocarbazole systems with general structure **2**.[3] Here, we address this issue and show that, as well as being interesting molecules in their own right, oxazinocarbazoles can be converted into substrates of a highly diastereoselective oxidative cleavage reaction.

Oxidative cleavage of the indole 2,3-double bond has been achieved by using a wide range of reagents including ozone, metal-based and electrocatalytic methods, hypervalent iodine reagents, peroxidases, molecular oxygen and peracids such as *m*-chloroperoxybenzoic acid (MCPBA).[4–6] In our case, MCPBA was used. Whilst exploring the scope of this reaction, we observed a competing rearrangement reaction for some substrates.[7] This work extends our previous studies on the oxidative cleavage of compounds of general structure **3**, providing additional information on the mechanism of this type of reaction.[8]

Commercially available cyclic ketones **4** ($n$ = 1–3, Scheme 1) were treated with ethyl formate under basic conditions to afford α-functionalised ketones **5** ($n$ = 1–3). Japp–Klingemann modified Fisher indole synthesis[9] using a range of anilines gave carbazol-1-ones **6b–j**[10a,11] via the corresponding hydrazones **7b–j**[10] in reasonable yields, with the exception of **6f**[12] (see Table 1 for substituent and ring size). Selective N-alkylation of **6a–j** under biphasic reaction conditions gave **8a–j** in good yields.[10,11] Subsequent reduction of **8a–j** with $NaBH_4$ led to the formation of the morpholine ring in one pot to give oxazinocarbazoles **2a–j**.

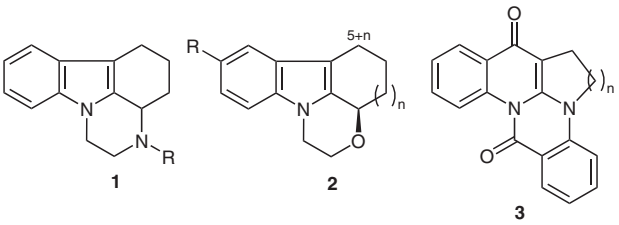


**Figure 1** Structures of the pyrazino- and oxazino-carbazole systems **1** and **2**, respectively, and the polycyclic system **3**, which was the focus of our recent asymmetric oxidative cleavage studies[8]

Use of the Corey–Bakshi–Shibata (CBS) catalyst enabled asymmetric reduction of **8c** to **9c** in high yield and 98% ee as judged by chiral HPLC analysis (Scheme 1 and Figure S1).[13] Subsequent cyclisation of **9c** using potassium *tert*-butoxide gave highly optically enriched (*R*)-**2c**. The absolute configuration of **2c** (and hence **9c**) prepared by this route was assigned based on the X-ray crystallographic analysis of **11c** derived from (*R*)-**2c** as discussed in more detail below. Oxazinocarbazole analogues containing a five-membered ring ($n$ = 0 in general structure **2**, Figure 1) could not be prepared by this route, with formation of the morpholine ring in the final step proving unsuccessful (Scheme S1).

Having established a robust route to **2**, we next explored oxidation of the C(5+$n$) position in **2** (Figure 1). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidation[14] of **2a–j** resulted in the formation of **10a–j** (see Table 1 for structures and yields) with X-ray crystallographic studies confirming the structures of a racemic sample of **10c** and its homologue **10h**.[15]

Conversion of **10a** into the corresponding nine-membered-ring-containing compound **11a** was achieved in low yield on reaction with 2.5 equivalents of MCPBA

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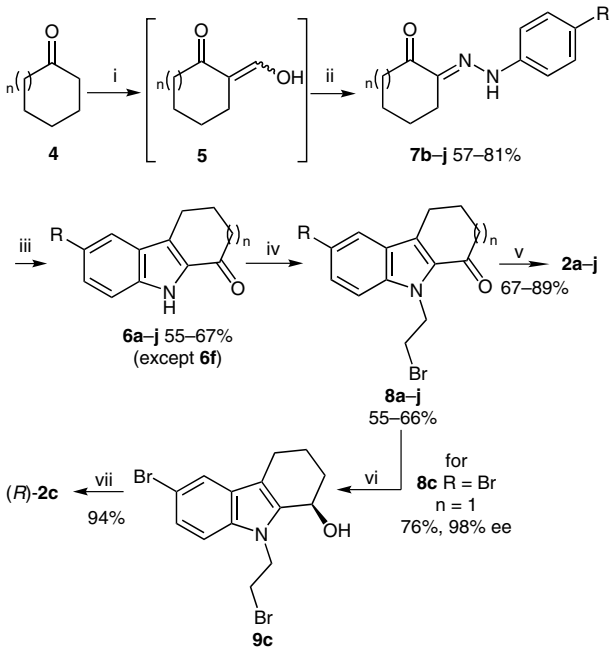
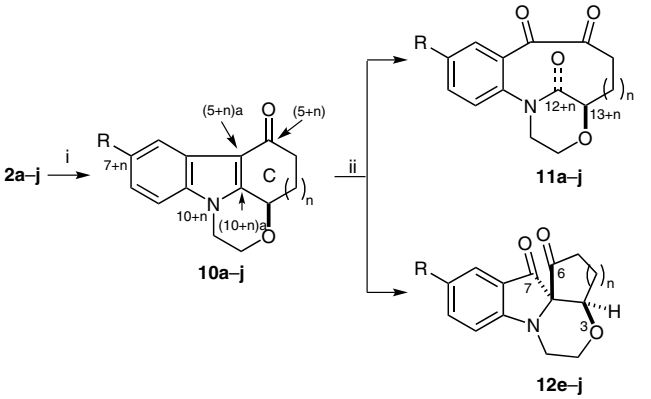



**Scheme 1** Synthesis of **2**. *Reaction conditions*: (i) NaH, ethyl formate, EtOH, THF, 0 °C to r.t., overnight; (ii) aniline, $NaNO_2$, concd HCl, $H_2O$, 20 min, then **5** in MeOH–$H_2O$–NaOAc, 15 min; yield (%): **7b** (81), **7c** (75), **7d** (76), **7e** (69), **7f** (57), **7g** (83), **7h** (73), **7i** (79), **7j** (67); (iii) HCl, AcOH, 120 °C, 25 min; yield (%): **6b** (67), **6c** (64), **6d** (61), **6e** (55), **6f** (12), **6g** (66), **6h** (66), **6i** (55), **6j** (67), **6a** (prepared according to Li and Vince[11b] in 65% yield); (iv) dibromoethane, TBAB, 9 M NaOH (aq), r.t., overnight; yield (%): **8a** (64), **8b** (65), **8c** (55), **8d** (61), **8e** (62), **8f** (65), **8g** (65), **8h** (66), **8i** (64), **8j** (64); (v) $NaBH_4$, EtOH, 60 °C, 6 h; yield (%): **2a** (67), **2b** (68), **2c** (68), **2d** (68), **2e** (77), **2f** (69), **2g** (81), **2h** (89), **2i** (86), **2j** (89); (vi) (*S*)-oxazaborolidine, $BH_3$·DMS, $CH_2Cl_2$, –20 °C, 3.5 h, 76%, 98% ee; (vii) *t*-BuOH, *t*-BuOK, r.t., overnight, 94%.

(Table 1, entry 1). However, increasing the number of equivalents of MCPBA used in this reaction from 2.5 to 4, resulted in increased conversion and hence significantly improved isolated yield of **11a** (entry 2). In-house purified MCPBA was used throughout this study. Interestingly, incorporation of an 8-chloro substituent in **10b** led to a significant improvement in the efficiency of the cleavage reaction, with **11b** being formed from **10b** in 83% isolated yield even in the presence of 2.5 equivalents of MCPBA (entry 3). Ketones **10c**–**e**, **10i** and **10j** all gave the corresponding oxidatively cleaved products **11c**–**e**, **11i** and **11j**, respectively (entries 4–8, 12 and 13). We[5g,8] and others[16] have reported that compounds containing medium-sized rings of this general type can exhibit atropisomerism due to the inability of the carbonyl group [C13 in the case of **11a**–**e** (*n* = 1), C15 for **11i** and **11j** (*n* =3), Table 1] to pass through the medium-sized ring. In this system, the results of low-level computational studies were consistent with this view, suggesting that compounds of type **11** contain one stereogenic centre at the C13+*n* position and one axis of chirality due to restricted rotation about the N-aryl bond and could therefore exist as two diastereoisomers. Interestingly, $^1$H NMR analysis of the crude reaction mixtures obtained on treatment of **10** with MCPBA showed that, in all cases where **11** was produced, only one isomer of **11** was formed and subsequently isolated. This oxidative cleavage reaction is therefore highly diastereoselective. X-ray crystallographic analysis of **11c**[15] confirmed that the relative configuration at C13 (*n* = 1) and C14 (*n* = 1) was as shown in Table 1 (Figure 2, A).

Interestingly, the X-ray crystallographic analysis of **11c** also showed that the amide bond was twisted away from the expected planar orientation, with a C11a-N12-C13-O13 torsion angle of 17.9°. When (*R*)-**2c** was carried through the two-step ketone incorporation/oxidative cleavage sequence, highly optically enriched (*R*)-**11c** (96% ee, Figure S2) was formed in 50% yield when 2.5 equivalents of MCPBA was used. Incorporation of a bro-

**Table 1** DDQ-Mediated Oxidation of **2a**–**j** and Oxidative Cleavage of the Oxazinocarbazole System[a]




| Entry | 10–12 | R | *n* | MCPBA (equiv) | Yield (%) 10[b] | 11[c] | 12[c] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | H | 1 | 2.5 | 74 | 19 | 0 |
| 2 | **a** | H | 1 | 4.0 | 0 | 87 | 0 |
| 3 | **b** | Cl | 1 | 2.5 | 15 | 83 | 0 |
| 4 | **c** | Br | 1 | 2.5 | 43 | 50 | 0 |
| 5 | **c** | Br | 1 | 4.0 | 0 | 87 | 0 |
| 6 | **d** | I | 1 | 2.5 | 66 | 32 | 0 |
| 7 | **d** | I | 1 | 4.0 | 0 | 83 | 0 |
| 8 | **e** | OMe | 1 | 2.5 | 63 | 15 | 15 |
| 9 | **f** | $NO_2$ | 1 | 2.5 | 67 | 0 | 27 |
| 10 | **g** | H | 2 | 2.5 | 37 | 0 | 53 |
| 11 | **h** | Br | 2 | 2.5 | 35 | 0 | 61 |
| 12 | **i** | H | 3 | 2.5 | 53 | 17 | 17 |
| 13 | **j** | Br | 3 | 2.5 | 47 | 23 | 21 |

[a] Reaction conditions: (i) DDQ, THF–$H_2O$, 0 °C to r.t. 2 h; yield (%): **10a** (65%), **10b** (68), **10c** (65), **10d** (61), **10e** (66), **10f** (57), **10g** (64); **10h** (67), **10i** (65), **10j** (61); (ii) MCPBA (2.5 or 4.0 equiv), $CH_2Cl_2$, r.t. 18 h.

[b] Isolated yield of recovered starting material **10**.

[c] Isolated yield of products **11** and/or **12**.

mo- or an iodo-substituent at the C8-position in **10** ($n$ = 1) had little observable effect on the outcome of the reaction when four equivalents of MCPBA was used, with **11c** and **11d** being formed in a similar yield to that of **11a** (cf. Table 1, entries 2, 5 and 7). However, when 2.5 equivalents of MCPBA was used, the reaction conversion followed a clear trend with Cl > Br > I > H (cf. entries 3, 4, 6, 1). Because these four reactions were carried out under analogous conditions, it is clear that the incorporation of a C8-halogen substituent in **10** ($n$ = 1) increased the rate of formation of **11**.

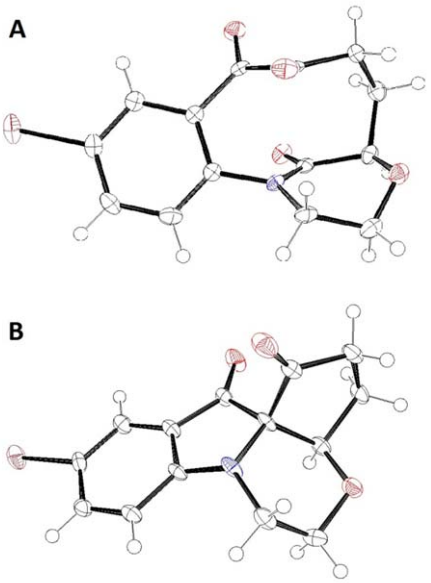
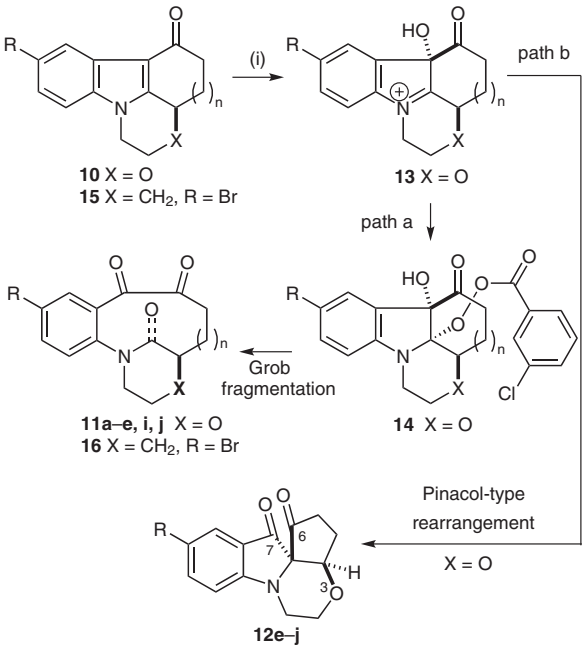



**Figure 2** Representations of the X-ray crystallographic analysis of (A) (*R*)-**11c** and (B) **12c**. For molecular formulae, crystal data, collection and analysis methods and selected bond lengths and angles see the Supporting Information Tables S1–S6

One possible explanation for the role of the C8-halogen is that mesomeric electron-donation leads to localisation of additional electron density at N-11 in **10** ($n$ = 1), rendering the indole C6a–C11 double bond in **10** ($n$ = 1) more electron-rich and prone to react with MCPBA (see Table 1 for numbering). Within the halogen series, the observed trend may reflect the relative ability of the various halogens to donate electron density in this system.

Interestingly when a strong mesomerically electron-donating C8-methoxy-substituent was introduced in **10e**, no increase in yield of **11e** was observed compared with the reaction of **10a** to give **11a** (cf. entries 8 and 1). However, a second product **12e** (Scheme 2) with an unusual structure[17] was also isolated from this reaction. When a strong electron-withdrawing C8-nitro-substituent was incorporated, none of the expected cleavage product **11f** was obtained, with the rearranged product **12f** being the only isolated product (entry 9). X-ray crystallographic studies confirmed the structure of **12f**.[15] Detailed analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated that the formation of **12f** was a highly diastereoselective process (Scheme 2). High diastereoselectivity was also achieved in the formation of **12e** and **12g–j** on reaction of **12e** and **12g–j**, respectively.




**Scheme 2** Proposed mechanism for the formation of **11** and **12** (**a–f**, $n$ = 1; **g–h**, $n$ = 2; **i–j**, $n$ = 3). *Reaction conditions*: (i) MCPBA (2.5 or 4.0 equiv), $CH_2Cl_2$, r.t. 18 h; see Table 1 for results with **10a–j**; **15** was converted exclusively into **16** using MCPBA (2.5 equiv) in 67% yield

In contrast to other related systems we have studied,[8] this system enables a much clearer picture of the mechanism of the conversion of **10** into **11** and/or **12** to be deduced. The formation of **11a–e** can be rationalised by initial epoxidation of **10a–e**, leading to the formation of iminium ion **13**. Subsequent trapping of **13** with a second equivalent of MCPBA then occurs to give **14**, in line with previous reports of the directed addition of a nucleophile to an iminium ion (Scheme 2, path a).[18] Grob fragmentation can still occur in **14**, with the C6a–C11a bond being able to adopt an antiperiplanar arrangement with the O–O bond. This mechanism would predict that the C13 carbonyl group in, for example **11c**, should be *anti* to the C8-alkoxy-substituent, which is consistent with the experimental observation (Scheme 2 and Figure 2). The same high diastereoselectivity was also observed when this reaction was carried out on **15**, an analogue of **10c** in which the oxygen was replaced by a methylene group. The oxidative cleavage reaction of **15** gave exclusively **16** (Scheme 2 and Schemes S2 and S3 for further details of the preparation of **15** and its conversion into **16**). This observation supports the view that initial attack of MCPBA on **10** is controlled by the sterically preferred approach of the reagent from the opposite side to the C3-substituent.

For substrates **10e–j**, the corresponding rearranged product **12e–j** was observed either in almost equal quantities to **11** (**12e**, **12i**, and **12j**) or as the only product (**12f**, **12g**, and **12h**). The stereochemistry at the newly formed quaternary

centre in **12** was assigned based on X-ray crystallographic analysis of not only **12f**, as discussed above, but also **12c** (Figure 2, B), and **12h**.[15] The formation of **12** can be rationalised by iminium ion **13** undergoing a pinacol-type rearrangement with acyl group migration (Scheme 2, path b). This mechanism is consistent with the highly diastereoselective formation of isomer **12**. Whilst it is difficult to rationalise fully the subtle impact of remote substituents on the formation of **12** (cf. entries 1 with 8 and 9), a dramatic difference in behaviour was observed on changing the size of the C-ring in **10** (Table 1). When $n = 2$ in **10** (entries 10 and 11) then the only products observed result from path b, giving **12g** and **12h** in reasonable yield. This contrasts with the situation in which $n = 1$ for **10** (only cleavage to give **11**, entries 1 and 4) and $n = 3$ for **10** (both processes, entries 12 and 13). One possible explanation is that as the size of the C-ring changes subtle steric constraints may hinder attack of the second equivalent of MCPBA and hence block the conversion of **13** into **14**. This, in turn, would be expected to promote the pinacol-type rearrangement to give **12**. The fact that **10c** was converted into **12c** in 95% yield on reaction with dimethyldioxirane (DMDO), which is an epoxidising agent that is capable of generating **13** but not converting it into **14**, implies that in the absence of a nucleophile (or when nucleophilic attack is slowed for steric reasons) rearrangement to **12** occurs.

Whilst oxidative cleavage of the indole 2,3-double bond has been extensively studied, it remains rare for complex substrates that raise interesting stereochemical questions to be used in this reaction. Here, we address this issue by using the understudied oxazinocarbazole class of indole-containing structures. A robust five-step approach to the synthesis of the required substrates **10a–j** is described. These substrates differ in both the nature of the C-8 substituent and the size of the C-ring. Reaction of **10** with MCPBA results in almost all cases in the highly diastereoselective oxidative cleavage to deliver medium-sized-ring-containing compounds **11**. The relative stereochemistry of these cleaved products enables a detailed mechanistic insight to be gained. In addition, a competing pinacol-type rearrangement occurs for some substrates, leading to complex spirocycles of type **12** with high diastereocontrol. Further investigations into the biological activity of the reported oxazinocarbazoles, medium-sized-ring-containing derivatives and spirocycles will be reported in the near future.

Chemicals and reagents were obtained from either Aldrich or Alfa-Aesar and were used as received unless otherwise stated. All reactions involving moisture-sensitive reagents were performed in oven-dried glassware under a positive pressure of argon. Tetrahydrofuran (THF), dichloromethane ($CH_2Cl_2$) and toluene were obtained anhydrous from a solvent purification system (MBraun, SPS-800). Dimethyldioxirane (DMDO) was prepared by using a reported procedure.[19] Thin-layer chromatography was performed by using glass plates coated with silica gel (with fluorescent indicator $UV_{254}$) (Aldrich). Developed plates were air-dried and analysed under a UV lamp. Flash column chromatography was performed using silica gel (40–63 μm) (Fluorochem). Melting points were recorded in open capillaries with an Electrothermal 9100 melting point apparatus. Values are quoted to the nearest 1 °C and are uncorrected. Elemental microanalyses were performed with a Carlo Erba CHNS analyser within the School of Chemistry at the University of St Andrews. Infrared spectra were recorded with a Perkin Elmer Spectrum GX FT-IR spectrophotometer using either thin films on NaCl plates (NaCl) or KBr discs (KBr) as stated. Absorption maxima are reported as wavenumbers ($cm^{-1}$) and intensities are quoted as strong (s), medium (m), weak (w) and broad (br). Low-resolution (LR) and high-resolution (HR) electrospray mass spectral (ES-MS) analyses were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI) within the School of Chemistry, University of St Andrews. Low- and high-resolution ESI MS were carried out with a Micromass LCT spectrometer and low- and high-resolution CI MS were carried out with a Micromass GCT spectrometer recorded with a high-performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a Waters 2975 HPLC. Only the major peaks are reported and intensities are quoted as percentages of the base peak. NMR spectra were acquired with either a Bruker Avance 300 ($^1$H, 300 MHz; $^{13}$C, 75 MHz), Bruker Avance 400 ($^1$H, 400 MHz; $^{13}$C, 100 MHz) or a Bruker Avance 500 ($^1$H, 500 MHz; $^{13}$C, 125 MHz) spectrometer, in the deuterated solvent stated. $^{13}$C NMR spectra were acquired by using the PENDANT or DEPTQ pulse sequences. All NMR spectra were acquired by using the deuterated solvent as the lock. Coupling constants (*J*) are quoted in Hz, and are recorded to the nearest 0.1 Hz. The following abbreviations are used; s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dt, doublet of triplets; t, triplet; m, multiplet; q, quartet; quint, quintet; and br, broad.

The protocols used for the synthesis of **6** from **4** are known,[10,11] with modifications, and analytical data to support the assigned structures are provided in the Supporting Information.

**General Alkylation Procedure**

Compound **6** (10.0 mmol) was suspended in 1,2-dibromoethane (10 mL) or 1,3-dibromopropane (10 mL), and 9 M aq NaOH (10 mL) and tetra-*n*-butyl ammonium bromide (TBAB; 0.086 g, 3.00 mmol, 0.03 equiv) were added. The mixture was stirred at r.t. for 18 h, then diluted with $CH_2Cl_2$ (30 mL) and $H_2O$ (30 mL), the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography by silica gel (EtOAc–hexanes, 1:19) to afford product **8**. The preparation of **8a–f** has been reported previously.[10a,11b] Compounds **8g–j** are novel, with full characterisation being provided here for **8j** as an example. Analytical data to support the structural assignment of **8g–i** are provided in the Supporting Information.

**2-Bromo-5-(2-bromoethyl)-8,9,10,11-tetrahydro-5*H*-cycloocta[*b*]indol-6(7*H*)-one (8j)**

Yield: 2.04 g (6.40 mmol, 64%); light-brown solid; mp 119–120 °C.

IR (KBr): 2967 (m), 2855 (m, Ar-H), 1629 (s, C=O), 819 (m, C-Br), 730 (Ar-H) $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, $^4J$ = 2.0 Hz, 1 H, H-1), 7.25 (dd, $^3J$ = 9.0 Hz, $^4J$ = 2.0 Hz, 1 H, H-3), 7.13 (d, $^3J$ = 9.0 Hz, 1 H, H-4), 4.82 (t, $^3J$ = 7.0 Hz, 2 H, H-1′), 3.61 (t, $^3J$ = 7.0 Hz, 2 H, H-2′), 3.27 (t, $^3J$ = 7.0 Hz, 2 H, H-11), 2.97 (t, $^3J$ = 7.5 Hz, 2 H, H-7), 1.66–1.83 (m, 4 H, H-10, H-8), 1.33–1.41 (m, 2 H, H-9).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 195.6 (C6), 137.4 (C4a), 134.8 (C5a), 129.4 (C3), 128.3 (C11b), 123.6 (C1), 123.4 (C11a), 113.6 (C2), 112.0 (C4), 47.0 (C1′), 42.2 (C7), 30.8 (C2′), 25.5 (C9), 24.02 (C10), 23.99 (C8), 22.6 (C11).

MS ($ES^+$): *m*/*z* (%) = 397.97 (100) $[M + H]^+$, 399.97 (100) $[M + H]^+$.

HRMS ($ES^+$): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}NO^{79}Br_2$: 397.9677; found: 397.9677.

**Sodium Borohydride-Mediated Reduction of 8; General Procedure**

Ketone **8** (5.0 mmol, 1.0 equiv) was dissolved in EtOH (100 mL) and $NaBH_4$ (0.57 g, 15.0 mmol, 3.0 equiv) was added. The reaction mixture was heated at 60 °C for 6 h, then the solvent was removed in vacuo and the residue was partitioned between $CH_2Cl_2$ (50 mL) and $H_2O$ (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was purified by using flash column chromatography over silica gel (EtOAc–hexanes, 3:7) to afford **2**. Compounds **2a**–**j** are novel, with full characterisation being provided here for **2j** as a representative example. Analytical data to support the structural assignment of **2a**–**i** are provided in the Supporting Information.

**10-Bromo-1,2,3a,4,5,6,7,8-octahydro-3-oxa-12b-azacyclooct a[*jk*]fluorene (2j)**

Yield: 1.42 g (4.45 mmol, 89%); pale-yellow solid; mp 107–108 °C.

IR (KBr): 2926 (m, Ar-H), 1103 (s, C-O), 1606 (m, C=C Ar), 790 (m, C-Br), 739 (m, C-H Ar) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, $^4J$ = 2.0 Hz, 1 H, H-9), 7.25 (dd, $^3J$ = 9.0 Hz, $^4J$ = 2.0 Hz, 1 H, H-11), 7.13 (d, $^3J$ = 9.0 Hz, 1 H, H-12), 5.12 (dd, $^3J$ = 9.5, 5.0 Hz, 1 H, H-3a), 4.21–4.39 (m, 1 H, H-2a), 3.91–4.10 (m, 3 H, H-2b, H-1), 2.68–2.95 (m, 2 H, H-8), 2.00–2.22 (m, 2 H, H-4), 1.52–1.86 (m, 6 H, H-7, H-6, H-5).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 134.9 (C13a), 133.8 (C12a), 129.5 (C8a), 123.6 (C11), 120.8 (C9), 112.7 (C10), 110.0 (C12), 109.0 (C8a), 73.7 (C3a), 61.1 (C2), 42.2 (C1), 35.2 (C4), 27.7 (C7), 26.1 (C6), 22.0 (C5), 21.2 (C8).

MS ($ES^+$): *m*/*z* (%) = 342.06 (100) $[M + Na]^+$, 344.05 (95) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{18}NOBrNa$: 342.0572; found: 342.0577.

**Synthesis of (*R*)-6-Bromo-9-(2-bromoethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol [(*R*)-9c]**

To a solution of **2c** (0.37 g, 1 mmol, 1.0 equiv) in $CH_2Cl_2$ (20 mL) at –20 °C was added (*S*)-oxazaborolidine (0.277 g, 1 mmol, 1.0 equiv). The solution was stirred for 20 min, then $BH_3$·DMS (95 μL, 1.0 equiv) was added dropwise over 10 min. The mixture was then stirred for 3.5 h at –20 °C, then the reaction was quenched by addition of isopropyl alcohol (2 mL) and warmed to r.t. The solvent was removed in vacuo and the crude material was passed through a plug of silica eluting with dichloromethane. The organic washings were concentrated in vacuo and the resulting solid was recrystalised from EtOAc–hexane to give the desired product. The optical purity of (*R*)-**9c** prepared by this method was determined to be 98% ee by chiral HPLC analysis (see Figure S1 in the Supporting Information). The assignment of the absolute configuration of (*R*)-**9c** was based on the absolute stereochemistry of the stereogenic centre present in **11c**, which was determined by small-molecule X-ray crystallographic analysis of **11c**.

Yield: 0.28 g (0.76 mmol, 76%); white solid; mp 167–168 °C; $[\alpha]_D^{20}$ 77.0 (*c* = 0.004, $CH_2Cl_2$).

IR (KBr): 3325 (br, O-H), 2927 (m), 2868 (m), 1478 (m), 1405 (m), 815 (m, C-Br) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, $^4J$ = 2.0 Hz, 1 H, H-5), 7.34 (dd, $^3J$ = 9.0 Hz, $^4J$ = 2.0 Hz, 1 H, H-7), 7.22 (d, $^3J$ = 9.0 Hz, 1 H, H-8), 4.98–5.05 (m, 1 H, H-1), 4.48–4.70 (m, 2 H, H-1′), 3.59–3.78 (m, 2 H, H-2′), 2.76–2.86 (m, 1 H, H-2a), 2.53–2.65 (m, 1 H, H-2b), 2.00–2.18 (m, 2 H, H-4), 1.90–1.99 (m, 2 H, H-5).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 121.9 (C5), 125.3 (C7), 110.5 (C8), 62.0 (C1), 44.9 (C1′), 29.4 (C2′), 21.0 (C2), 33.4 (C4), 18.4 (C3), 112.7 (C6), 106.2 (C4a), 134.7 (C9a), 131.2 (C8a), 128.3 (C4b).

MS ($ES^+$): *m*/*z* (%) = 373.95 (100) $[M + H]^+$, 371.83 (60) $[M + H]^+$.

HRMS ($ES^+$): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}NO^{79}Br$: 373.9506; found 373.9511.

**DDQ-Mediated Oxidation; General Procedure**

To a solution of **2** (1.0 mmol, 1.0 equiv) in THF–$H_2O$ (11 mL, 9:1) at 0 °C, was added a solution of DDQ (0.454 g, 2.00 mmol, 2.0 equiv) in THF (4 mL) dropwise with stirring under a nitrogen atmosphere. The reaction mixture was stirred for 1 h and then concentrated in vacuo. The resulting solid was partitioned between $H_2O$ (50 mL) and EtOAc (50 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a red solid, which was purified by flash column chromatography over aluminium oxide eluting with EtOAc to yield the title compound. Compounds **10a**–**j** are novel, with full characterisation being provided here for **10j** as a representative example. Analytical data to support the structural assignment of **10a**–**i** are provided in the Supporting Information.

**10-Bromo-1,2,4,5,6,7-hexahydro-3-oxa-12b-azacyclooct a[*jk*]fluoren-8(3a*H*)-one (10j)**

Yield: 0.20 g (0.61 mmol, 61%); white solid; mp 200–201 °C.

IR (KBr): 2940 (m), 2851 (m, Ar-H), 1625 (s, C=O), 1106 (s, C-O), 1433 (m), 1444 (m, $CH_2$), 796 (m, C-Br) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, $^4J$ = 2.0 Hz, 1 H, H-9), 7.37 (dd, $^3J$ = 8.5 Hz, $^4J$ = 2.4 Hz, 1 H, H-11), 7.17 (d, $^3J$ = 8.5 Hz, 1 H, H12), 5.83 (dd, $^3J$ = 10.5, 7.5 Hz, 1 H, H3a), 4.22–4.32 (m, 1 H, H-2a), 4.06–4.16 (m, 3 H, H-2b, H-1), 2.65–2.84 (m, 2 H, H-7), 1.90–2.19 (m, 3 H, H-4, H-5a), 1.50–1.83 (m, 3 H, H-5b, H-6).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 195.6 (C8), 141.5 (C13a), 134.6 (C11a), 127.6 (C8b), 125.9 (C11), 125.2 (C9), 116.8 (C10), 115.2 (C8a), 109.9 (C12), 73.0 (C3a), 58.8 (C2), 42.1 (C7), 41.9 (C2), 31.6 (C4), 23.8 (C5), 22.5 (C6).

MS ($ES^+$): *m*/*z* (%) = 355.93 (100) $[M + Na]^+$, 357.94 (80) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{16}NO_2Na^{79}Br$: 356.0258; found: 356.0262; *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{16}NO_2Na^{81}Br$: 358.0239; found: 358.0242.

**10-Bromo-2,3,3a,4,5,6-hexahydro-1*H*-pyrido[3,2,1-*jk*]carbazol-1-one (15)**

Yield: 0.20 g (0.65 mmol, 65%); white solid; mp 235 °C (dec.).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, $^4J$ = 2.0 Hz, 1 H, H-11), 7.35 (dd, $^3J$ = 8.5 Hz, $^4J$ = 2.0 Hz, 1 H, H-9), 7.14 (d, $^3J$ = 8.5 Hz, 1 H, H-8), 4.24 (q, $^3J$ = 6.5 Hz, 1 H, H-6a), 3.80 (dt, $^2J$ = 13.0 Hz, $^3J$ = 6.0 Hz, 1 H, H-6b), 2.97–3.01 (m, 1 H, H-3a), 2.59–2.65 (m, 2 H, H-2), 2.10–2.41 (m, 4 H, H-5, H-4a, H-3a), 1.76–1.90 (m, 1 H, H-3b), 1.35–1.50 (m, 1 H, H-4b).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 193.1 (C1), 139.0 (C3b), 136.6 (C7a), 128.7 (C11a), 125.6 (C9), 124.2 (C11), 116.4 (C10), 110.6 (C8), 109.9 (C11b), 41.9 (C6), 38.8 (C2), 33.6 (C3a), 31.4 (C3), 26.9 (C4), 22.6 (C5).

MS ($ES^+$): *m*/*z* (%) = 326.08 (100) $[M + Na]^+$, 328.08 (100) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}NONa^{79}Br$: 326.0156; found: 326.0154; *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}NONa^{81}Br$: 328.0136; found: 328.0139.

**MCPBA-Mediated Oxidative Fragmentation; General Procedure**

Compound **10** (0.5 mmol, 1.0 equiv) was dissolved in anhydrous $CH_2Cl_2$ (50 mL) and purified MCPBA (0.344 g, 2.0 mmol, 4.0 equiv) was added to the solution. The reaction mixture was stirred at r.t. under $N_2$ for 16 h, then sat. $Na_2S_2O_3$ solution (10 mL) followed by sat. $NaHCO_3$ solution (20 mL) were added and the reaction mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined



organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give a brown solid, which was purified by flash column chromatography (EtOAc–$CH_2Cl_2$, 3:7) to give the product.

Compounds **11a–e**, **11i**, **11j** and **12e–j** are novel, with full characterization being provided here for **11c** and **12f** as representative examples. Analytical data to support the structural assignment of **11a**, **11b**, **11d**, **11e**, **11i**, **11j** and **12e–j** are provided in the Supporting Information.

**11-Bromo-6,7-dihydro-2*H*-1,5-methanobenzo[*e*][1,4]oxaazacycloundecine-8,9,14(3*H*,5*H*)-trione (11c)**

Compound **11c** was afforded when MCPBA (2.5 equiv) was used. Recrystallisation from acetone afforded analytically pure **11c** suitable for small-molecule X-ray crystallographic analysis.

Yield: 0.084 g (0.25 mmol, 50%); pale-yellow solid; mp 205–206 °C.

IR (KBr): 2861 (m), 2920 (m), 1682 (s, C=O), 1648 (s, C=O), 1710 (s, C=O), 1466 (s), 1429 (s), 1102 (s, C-O), 836 (m, C-Br) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, $^4J$ = 2.5 Hz, 1 H, H-10), 7.71 (dd, $^3J$ = 8.5 Hz, $^4J$ = 2.5 Hz, 1 H, H-12), 7.11 (d, $^3J$ = 8.5 Hz, 1 H, H-9), 4.50 (d, $^3J$ = 6.0 Hz, 1 H, H-5), 4.02–4.08 (m, 1 H, H-3a), 3.77–3.86 (m, 1 H, H-3b), 3.67–3.72 (m, 1 H, H-2a), 3.28–3.38 (m, 1 H, H-2b), 3.12–3.20 (m, 1 H, H-7a), 2.63–2.73 (m, 1 H, H-7b), 2.48–2.60 (m, 1 H, H-6a), 2.26–2.36 (m, 1 H, H-6b).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 202.3 (C9), 190.3 (C8), 173.3 (C14), 139.7 (C11), 136.9 (C12), 135.7 (C9a), 133.3 (C10), 126.1 (C13), 122.0 (C13a), 77.3 (C5), 62.2 (C3), 49.4 (C2), 34.2 (C7), 29.7 (C6).

MS ($ES^+$): *m*/*z* (%) = 359.89 (100) $[M + Na]^+$, 361.89 (90) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}NO_4Na^{79}Br$: 359.9847; found: 359.9845; *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}NO_2Na^{81}Br$: 361.9827; found: 361.9831.

Anal. Calcd for $C_{14}H_{12}NO_4Br$: C, 49.73; H, 3.58; N, 4.14. Found: C, 49.64; H, 3.41; N, 4.19.

Compound (*M*,*R*)-**11c** was prepared in an analogous manner. Chiral HPLC analysis (Figure S2) indicated that the prepared sample of (*M*,*R*)-**11c** had 96% ee.

**10-Nitro-3,3a,5,6-tetrahydro-1*H*-cyclopenta[2,3][1,4]oxazino[4,3-*a*]indole-1,12(2*H*)-dione (12f)**

Compound **12f** was afforded when MCPBA (2.5 equiv) was used. Recrystallisation from acetone afforded analytically pure **12f**, which was suitable for small-molecule X-ray crystallographic analysis.

Yield: 0.04 g (0.14 mmol, 27%); yellow solid; mp 115–116 °C.

IR (KBr): 3041 (m), 2955 (m), 2876 (m, Ar-H), 1650 (s, C=O), 1640 (s, C=O), 1557 (s), 1340 (s) ($NO_2$), 1102 (s, C-O) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, $^4J$ = 2.0 Hz, 1 H, H-2), 8.38 (dd, $^3J$ = 9.5 Hz, $^4J$ = 2.0 Hz, 1 H, H-4), 6.90 (d, $^3J$ = 9.5 Hz, 1 H, H-5), 4.13 (d, $^3J$ = 4.0 Hz, 1 H, H-9a), 3.97–4.02 (m, 1 H, H-8a), 3.70–3.76 (m, 1 H, H-7a), 3.38–3.54 (m, 2 H, H-8b, H-7b), 2.80–2.92 (m, 1 H, H-10a), 2.54–2.79 (m, 2 H, H-11), 2.22–2.32 (m, 1 H, H-10b).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 206.7 (C12), 190.5 (C1), 161.8 (C5a), 139.4 (C3), 132.7 (C4), 122.7 (C2), 119.0 (C1a), 108.5 (C5), 81.5 (C12a), 78.3 (C9a), 65.4 (C8), 41.7 (C7), 32.9 (C11), 24.5 (C10).

MS ($ES^+$): *m*/*z* (%) = 311.26 (100) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}N_2O_5Na$: 311.0699; found: 311.0695.

**10-Bromo-2,3,4,5,6,7-hexahydro-1,5-methanobenzo[*b*][1]azacycloundecine-7,8,14-trione (16)**

Yield: 0.11 g (0.34 mmol, 67%); yellow solid; mp 139–140 °C.

IR (KBr): 2861 (m), 2920 (m, Ar-H), 1682 (s), 1648 (s, C=O), 1466 (s), 1419 (s, $CH_2$), 836 (s, C-Br) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, $^4J$ = 2.5 Hz, 1 H, H-9), 7.76 (dd, $^3J$ = 8.5 Hz, $^4J$ = 2.5 Hz, 1 H, H-11), 7.12 (d, $^3J$ = 8.5 Hz, 1 H, H-12), 3.82–3.90 (m, 1 H, H-1a), 3.27–3.36 (m, 2 H, H-1b, H6a), 2.84–2.97 (m, 1 H, H-4), 2.54–2.63 (m, 1 H, H-6b), 2.39–2.50 (m, 1 H, H-3a), 2.05–2.22 (m, 3 H, H-3b, H-5a, H-2a), 1.77–1.94 (m, 2 H, H-5b, H-2b).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 204.7 (C7), 191.2 (C8), 174.7 (C14), 142.0 (C12a), 137.2 (C11), 136.6 (C8a), 132.9 (C9), 124.8 (C12), 120.7 (C10), 50.0 (C1), 40.7 (C4), 35.3 (C6), 28.9 (C3), 25.4 (C5), 18.7 (C2).

MS ($ES^+$): *m*/*z* (%) = 357.85 (100) $[M + Na]^+$, 359.85 (95) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}NO_3Na^{79}Br$: 358.0057; found: 358.0055; *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}NO_3Na^{81}Br$: 360.0041; found: 360.0034.

Anal. Calcd for $C_{14}H_{12}NO_4Br$: C, 53.59; H, 4.20; N, 4.17. Found: C, 53.73; H, 3.99; N, 4.19.

**9-Bromo-3,3a,5,6-tetrahydro-1*H*-cyclopenta[2,3][1,4]oxazino[4,3-*a*]indole-1,12(2*H*)-dione (12c)**

Compound **10c** (0.500 g, 1.63 mmol, 1 equiv) was dissolved in anhydrous $CH_2Cl_2$ (10 mL) and dimethyl dioxirane acetone solution (0.01 M, 81.5 mL, 5 equiv) was added dropwise. The mixture was stirred at r.t. for 30 min, then concentrated in vacuo and purified by flash column chromatography (EtOAc–hexane, 3:7).

Yield: 0.500 g (1.56 mmol, 95%); yellow solid; mp 196–197 °C.

IR (KBr): 2861 (m), 2920 (m), 1682 (s, C=O), 1648 (s, C=O), 1466 (s), 1429 (s), 1132 (s, C-O), 813 (C-Br) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, $^4J$ = 2.0 Hz, 1 H, H-8), 7.56 (dd, $^3J$ = 9.0 Hz, $^4J$ = 2.0 Hz, 1 H, H-10), 6.79 (d, $^3J$ = 9.0 Hz, 1 H, H-11), 4.03 (d, $^3J$ = 4.5 Hz, 1 H, H-3a), 3.86–3.92 (m, 1 H, H-2a), 3.60–3.66 (m, 1 H, H-1a), 3.30–3.45 (m, 2 H, H-1b, H-2b), 2.75–2.89 (m, 1 H, H-4a), 2.64–2.75 (m, 1 H, H-5a), 2.52–2.64 (m, 1 H, H-5b), 2.16–2.26 (m, 1 H, H-4b).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 208.6 (C6), 191.4 (C7), 159.1 (C11a), 140.1 (C10), 127.8 (C8), 121.1 (C7a), 111.0 (C11), 110.4 (C9), 80.5 (C6a), 78.2 (C3a), 65.2 (C2), 41.7 (C1), 33.3 (C5), 24.4 (C4).

MS ($ES^+$): *m*/*z* (%) = 343.84 (100) $[M + Na]^+$, 345.84 (90) $[M + Na]^+$.

HRMS ($ES^+$): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}NO_3Na^{79}Br$: 343.9885; found: 343.9898; *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}NO_3Na^{81}Br$: 345.9892; found: 345.9878.

Anal. Calcd for $C_{14}H_{12}NO_3Br$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.39; H, 3.56; N, 4.38.

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