Intramolecular organolithium addition to indol-2(3*H*)-ones; an approach to the synthesis of pyrrolo[1,2-*a*]indoles and pyrido[1,2-*a*]indoles

Keith Jones *† and John M. D. Storey †

Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS

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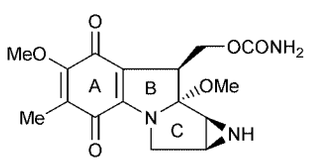
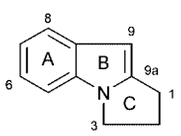
Cyclisation of **3** and **10** by lithium–halogen exchange followed by reduction with lithium aluminium hydride gives pyrrolo[1,2-*a*]indoles **11** and **13** respectively. Similar treatment of bromides **4a** and **4b** gives pyrido[1,2-*a*]indoles **12a** and **12b**.

Introduction

The tricyclic pyrrolo[1,2-*a*]indole skeleton has been the target



Mitomycin A



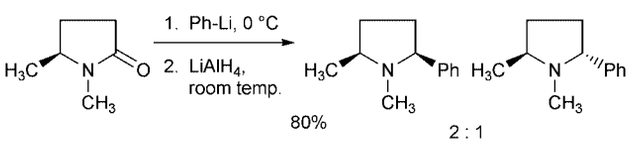
2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole

of considerable activity among synthetic chemists since the elucidation of the structure of the clinically useful mitomycins nearly 40 years ago.[1] The many different syntheses of this tricyclic system can be divided into 3 basic routes. The approach which led to the first successful synthesis of the mitomycins by Kishi and co-workers in 1977 involves formation of the B- and C-rings simultaneously using a transannular cyclisation from an eight-membered ring precursor.[2a] This strategy has also been used by Ban and co-workers[2b,c] and Kosikowski and Mugrage.[2d] A variation on this theme has been used by Danishefsky and co-workers to create the B- and C-rings in a one-pot procedure using the sequential formation of these two rings under the same reaction conditions.[3] An alternative method for the simultaneous creation of these two rings was published by Streith and co-workers and involved the Diels–Alder reaction of nitrosobenzene with pentadienal and *in situ* rearrangment of the initial cycloaddition products.[4]

Formation of the B-ring as the key step has been investigated by a number of groups. Takada *et al.* used carbene chemistry to create the indole-2,3 bond.[5a] Kametani *et al.* used the intramolecular capture of a benzyne intermediate to create the *N*-aryl bond.[5b] Reinhoudt's group[5c] prepared a number of pyrrolo[1,2-*a*]indoles by thermal cyclisation to create the 9, 9a bond while Rapoport and co-workers reported a photochemical cyclisation to create ring B.[5d] Finally in this area, Knolker *et al.* reported the synthesis of pyrrolo[1,2-*a*]indoles using the electrophilic nature of iron tricarbonyl cyclohexadienyl complexes to prepare the *N*-aryl bond.[5e]

Probably the most popular route for the synthesis of the pyrrolo[1,2-*a*]indole skeleton is the addition of the C-ring onto an indole or indole-related system. Examples of this approach include the cyclisation of a 2-lithioindole by displacement of a tosylate from an *N*-alkyl-substituent,[6a] cyclisation by *N*-alkylation using a suitable 2-substituted indole,[6b] dipolar cycloaddition chemistry[6c] and a variety of cyclisations onto the 2-position of indole using radical chemistry from the groups of Ziegler,[6d] Moody[6e] and Caddick.[6f]

Our own contributions to this area have focussed on the use of oxindoles as key intermediates as first suggested by Raphael and Ravenscroft.[7] Using the electrophilic nature of the carbonyl group both the intra-[8a] and intermolecular[8b] addition of organolithiums has been developed as a method for the synthesis of pyrrolo[1,2-*a*]indoles. This approach is based firmly on the pioneering observation by Fowler and co-workers that the intermolecular addition of organolithiums to lactams followed by a reductive work-up leads to α-substituted cyclic amines in good yields (Scheme 1).[9] We now wish to report on our intramolecular approach in detail.



Scheme 1

Results

In order to explore the generation and cyclisation of organolithiums onto the oxoindole carbonyl, we chose to use 3,3-dimethyloxoindole carrying a suitable bromoalkyl chain on the nitrogen from which the organolithium could be derived by lithium–halogen exchange. The presence of the *gem*-dimethyl group adjacent to the carbonyl ensured that deprotonation to give the enolate was not possible, although the intermolecular additions reported by Fowler and co-workers contained equally acidic protons which caused no problems.[9] The first requirement was a convenient preparation of 3,3-dimethyloxoindole **2**. This was achieved by removal of the *N*-benzyl group from oxoindole **1**, the synthesis of which has been reported[8b] *via* radical cyclisation. Exposure of **1** to lithium in liquid ammonia for 8 minutes led to clean debenzylation in 85% yield with no problems arising from Birch reduction of the aromatic ring (Scheme 2). *N*-Alkylation of **2** was first undertaken with 1,3-dibromopropane using sodium hydride in THF. The *N*-(3-bromopropyl)oxoindole **3** was isolated in 97% yield. A similar reaction using 1,4-dibromobutane as the alkylating agent gave

† Current Address: School of Applied Chemistry, Kingston University, Penrhyn Road, Kingston-upon-Thames, Surrey, UK KT1 2EE

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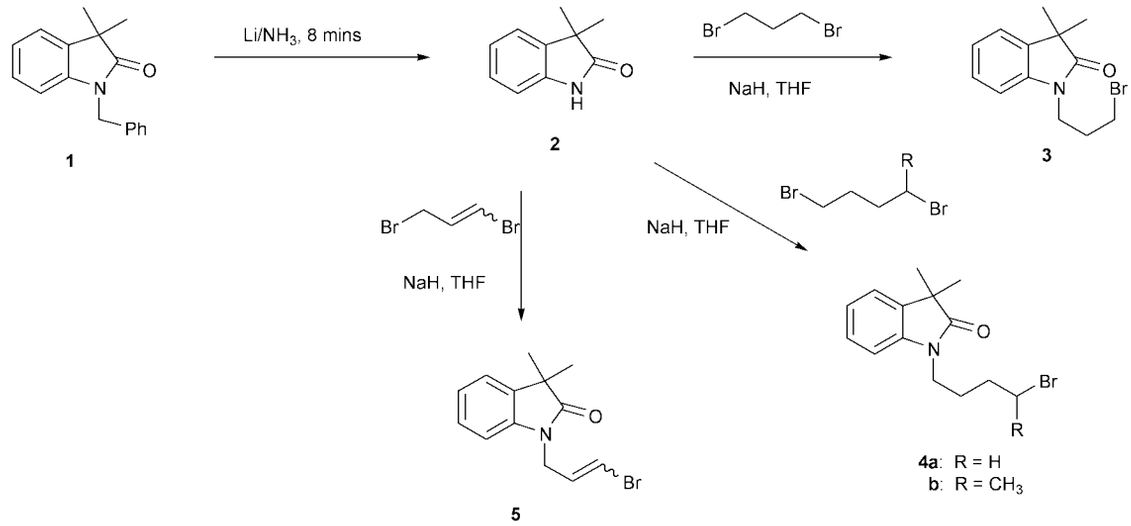
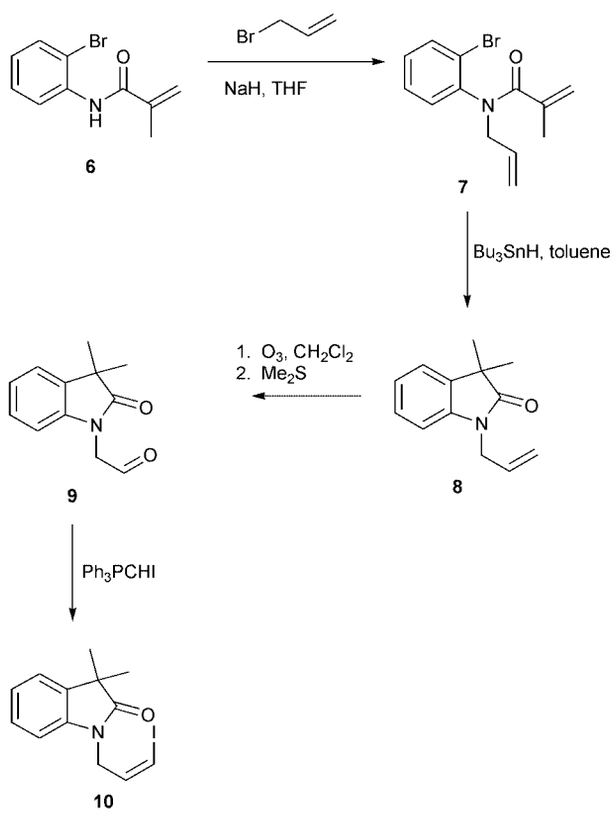


Scheme 2

the *N*-(4-bromobutyl)oxoindole **4a** in 66% yield. We wished to explore the formation and cyclisation of a secondary organolithium species and to this end, reaction of **1** with sodium hydride in THF and 1,4-dibromopentane was carried out leading to the *N*-(4-bromopentyl)oxoindole **4b** in 54% yield. Our previous use of this reaction to prepare tetrahydrocarbazoles[10] by organolithium cyclisation from C-3 of the oxoindole had shown that vinyllithium species were excellent nucleophiles and moreover gave products with functionality (an alkene) which could be further exploited. In this case, cyclisation of a suitable vinyllithium would give rise to a pyrrolo[1,2-*a*]indole containing an alkene in the correct position for elaboration into the aziridine found in the mitomycins.

Reaction of 3,3-dimethyloxoindole **1** with sodium hydride and commercially available 1,3-dibromopropene gave the vinyl bromide **5** as approximately a 1 : 1 mixture of geometric isomers as determined by NMR spectroscopy. This was confirmed by separation of the isomers on silica gel, although this turned out to be difficult to achieve. The starting 1,3-dibromopropene was an unassigned 55 : 45 mixture of isomers.

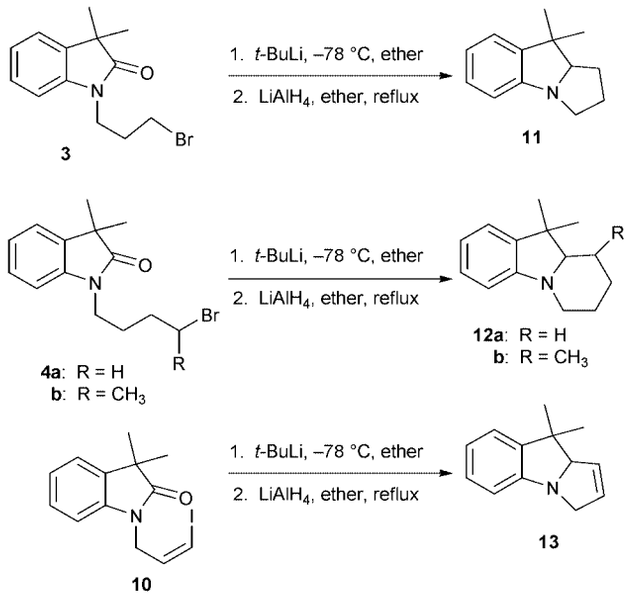
The fact that cyclisation precursor **5** was a mixture of isomers gave us some cause for concern. The lithium–halogen exchange reaction is known to occur with retention of configuration at the alkene[11] and the stereochemical interconversion of vinyllithium species is a slow process under the conditions we planned to use (relatively non-polar solvent and low temperature).[12] It was clear that the derived *trans*-vinyllithium would be unable to cyclise whilst at the same time, the *cis*-vinyl bromide is ideally arranged for elimination to an alkyne. To address both these worries, we decided to synthesise the *cis*-vinyl iodide **10** according to the procedure of Stork and Zhao (Scheme 3).[13] *N*-Allylation of methacryloylanilide **6** using sodium hydride in THF gave the tertiary anilide **7** in 80% yield. As seen in other examples of this system that we have prepared, the methylene group adjacent to the nitrogen is diastereotopic with a chemical shift difference between the two protons of 1 ppm. This effect is caused by the asymmetry around the aryl carbon–nitrogen bond. This form of atropisomerism has been discussed previously[14] and has been utilised in asymmetric synthesis.[15] Cyclisation of **7** under standard tin hydride radical conditions, gave a 3 : 1 mixture of the desired *N*-allyloxoindole **8** and the corresponding *N*-allyl-3-methyldihydroquinolone from which **8** could be isolated in 73% yield by column chromatography. This remarkable selectivity for cyclisation onto the acryloyl double bond and not the allyl double bond has been commented upon[14] and is under further investigation in our laboratory. Ozonolysis of the double bond of **8** followed by decomposition of the ozonide using dimethyl sulfide gave the somewhat



Scheme 3

unstable aldehyde **9** in 89% yield. This was swiftly reacted with the ylide prepared by reaction of iodomethyltriphenylphosphonium bromide with sodium hexamethyldisilazide to give vinyl iodide **10** as a 4 : 1 mixture of *cis*- and *trans*-isomers from which the *cis*-isomer was isolated in 54% yield.

With five cyclisation precursors in hand, attention now focussed on the generation and cyclisation of the organolithium species. Initially, we doubted that formation of the pyrrolo[1,2-*a*]indole ring system would be possible using such a cyclisation, as the organolithiums derived from **3**, **5** and *cis*-**10** appear to lack the conformational flexibility to achieve a suitable angle of approach to the oxoindole carbonyl group. Indeed, an explorative reaction using the chloro analogue of **3** had given only minor amounts of cyclised product.[8a] Treatment of **3** with *tert*-butyllithium in ether at −78 °C followed by warming to 0 °C and addition of $LiAlH_4$, gave the pyrrolo[1,2-*a*]indole **11**

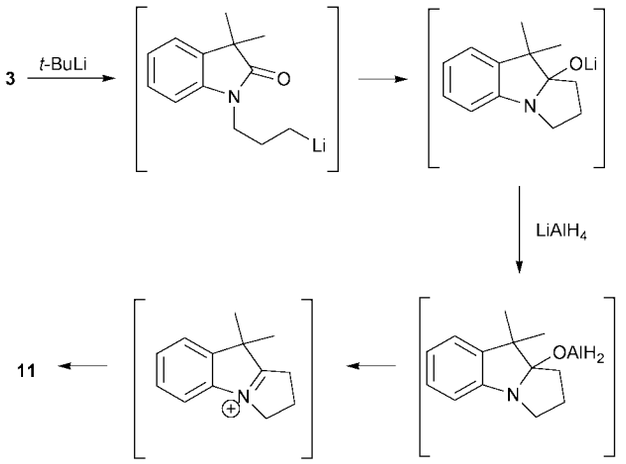


Scheme 4

in 47% yield after column chromatography (Scheme 4). This illustrates the advantages of the alkyl bromides over the alkyl chlorides for the generation of organolithiums by lithium–halogen exchange.[16] The pyrido[1,2-*a*]indole system is little studied[17] and we believed that the cyclisation of the organolithiums derived from **4a** and **4b** should be easier than that derived from **3** owing to the greater flexibility available in the chain. Treatment of **4a** under the same conditions (*t*-BuLi, then $LiAlH_4$) gave the tricycle **12a** in 95% yield seemingly indicating that this analysis is correct (Scheme 4). Similar reaction of **4b** was less successful giving pyrido[1,2-*a*]indole **12b** in 64% yield as a 3:1 mixture of diastereoisomers (Scheme 4). There was some evidence in the NMR spectrum of the crude product that alkene formation occurred by elimination of HBr from the secondary bromide **4b**. The major diastereoisomer of **12b** was assigned the *cis*-methyl–10a-H stereochemistry on account of a $J_{1\text{-H/10a-H}}$ value of 10.3 Hz.

Reaction of the vinyl bromide **5** (as a mixture of stereoisomers) under the cyclisation conditions gave a mixture of products in which the desired tricycle **13** could be tentatively identified along with alkyne arising from HBr elimination. Turning to the vinyl iodide **10** instead, cyclisation gave the pyrrolo[1,2-*a*]indole **13** in 60% yield (Scheme 4). This improvement in the reaction of the iodide almost certainly arises from the two factors discussed above, namely the improved lithium–halogen exchange for the iodide and the generation of the *cis*-organolithium exclusively.

Finally, we carried out a series of experiments to trap the intermediate hydroxymethylamine using methylating and silylating agents. The course of the reaction is outlined in Scheme 5 based mainly on the observation that the intermediate hydroxymethylamine can be isolated in the hexahydrocarbazole synthesis if the $LiAlH_4$ step is omitted.[10] The first step involves the addition of the organolithium to the lactam carbonyl to give the *O*-lithiated hydroxymethylamine. On addition of $LiAlH_4$, we believe that transmetallation occurs to give the aluminate complex which readily eliminates the oxygen to give an iminium ion. The iminium ion is then rapidly reduced by the $LiAlH_4$. Addition of a methylating agent after the initial cyclisation and omission of the reductive step should allow introduction of the C-9a methoxy group characteristic of the mitomycins. The cyclisation of **3** was carried out as before by treatment with *t*-BuLi followed by warming to 0 °C and addition of an appropriate electrophile. The addition of methyl iodide, methyl triflate, water, trimethylsilyl chloride and trimethylsilyl iodide were all investigated but in no case were any identifiable products isolated.



Scheme 5

In summary, we have shown that both the pyrrolo[1,2-*a*]-indole and the pyrido[1,2-*a*]indole ring systems can be synthesised in reasonable to excellent yields using *in situ* lithium–halogen exchange and subsequent reductive cyclisation of the organolithium on to the carbonyl group of oxoindoles. The exploration of this reaction in systems containing enolisable protons represents the next step in this project.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM360 or AM250 spectrometer at 360 and 250 MHz respectively using $CDCl_3$ as solvent with $SiMe_4$ as an internal standard, unless otherwise stated. *J*-values are given in Hz. IR spectra were recorded on a Perkin–Elmer 983G infrared spectrometer, using Nujol mulls or carbon tetrachloride solutions unless otherwise stated. All values in cm^{-1}. Mass spectral data were recorded on a JEOL AX505W with complement data system. Samples were ionised electronically at 70 eV with typical accelerating voltage of 6 kV. Melting points were determined using a Kofler hot plate apparatus and are uncorrected. All column chromatography was carried out using the flash chromatography technique, using Merck 60 (230–400 mesh) silica gel. Analytical TLC was carried out on Merck plastic backed TLC plates, coated with silica gel 60 F-254. Plates were visualised using ultraviolet light, unless otherwise stated. Eluting solvent systems are stated where appropriate. All dry reactions were performed in an inert argon atmosphere using a vacuum–argon manifold for the exclusion of water. Stirring was by internal magnetic bead. All syringes, needles and glassware were pre-dried at 110 °C and cooled in an anhydrous atmosphere before use. Diethyl ether, THF, and toluene were pre-dried over Na wire and refluxed over Na under Ar with benzophenone as an indicator in the reaction vessel. Dichloromethane was refluxed under Ar, over CaH_2 and distilled directly into the reaction vessel.

3,3-Dimethylindol-2(3*H*)-one 2

A solution of lithium metal (0.138 g, 19.7 mmol) in dry ammonia (100 ml) at −78 °C was treated with *N*-phenylmethyl-3,3-dimethylindol-2(3*H*)-one **1** (3.24 g, 12.9 mmol) in THF (50 ml). The mixture was stirred for 8 minutes then rapidly quenched with methanol (40 ml) and warmed to room temperature whilst blowing off ammonia with a stream of nitrogen. Solvent was removed at reduced pressure and the resultant residue was dissolved in diethyl ether (100 ml). The ether solution was washed with water (3 × 50 ml), dried with magnesium sulfate and the solvent was removed at reduced pressure to give a yellow oil. The crude product was purified by column chromatography on

silica using petroleum (40–60 °C)–ethyl acetate (4:1) as eluent to give the *3,3-dimethyloxoindole* **2** (1.76 g, 85%) as a white crystalline solid, mp 161 °C (Found: C, 74.48; H, 6.97; N, 8.47. $C_{10}H_{11}NO$ requires C, 74.50; H, 6.87; N, 8.68%); ν_{max} (CCl_4)/cm^{-1} 3445, 3185, 1705, 1617; δ_H (360 MHz), 1.41 (6H, s, C(3)Me), 6.97 (1H, dd, *J* 8, 1.1, H-7), 7.05 (1H, dt, *J* 8, 1.1, H-5), 7.18 (1H, dd, *J* 8, 1.1, H-4), 7.19 (1H, dt, *J* 8, 1.1, H-6), 9.34 (1H, br s, N-H); *m/z* (EI) 161 (70%), 146 (100).

N-(3-Bromopropyl)-3,3-dimethylindol-2(3*H*)-one 3 (general method 1)

Sodium hydride (80 %w/w, 19.6 mg, 0.68 mmol) was prewashed with petroleum ether (3 × 5 ml) and the washings discarded. A solution of 3,3-dimethylindol-2(3*H*)-one **2** (100 mg, 0.62 mmol) in THF (5 ml) was added and when hydrogen evolution ceased 1,3-dibromopropane (150 mg, 0.74 mmol) was added as a solution in THF (5 ml). The reaction was stirred at room temperature for 12 hours, whereupon the solvent was removed at reduced pressure. The residue was diluted with ether (20 ml), the ethereal solution was washed with water (3 × 10 ml), dried and concentrated at reduced pressure. The crude product was purified by column chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (10:1) as eluent to give *N-(3-bromopropyl)oxoindole* **3** (0.17 g, 97%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 3045, 2966–2925, 1712, 1610; δ_H (360 MHz), 1.35 (6H, s, C(3)Me), 2.24 (2H, quintet, *J* 6.5, H-2′), 3.42 (2H, t, *J* 6.5, H-1′), 3.85 (2H, t, *J* 6.5, H-3′), 6.93 (1H, dd, *J* 7.8, 0.9, H-7), 7.05 (1H, td, *J* 7.8, 0.9, H-5), 7.20 (1H, dd, *J* 7.8, 0.9, H-4), 7.25 (1H, dt, *J* 7.8, 0.9, H-6); *m/z* (EI) (Found: M^+, 281.0422/283.0403. $C_{13}H_{16}NOBr$ requires: M^+, 281.0415/283.0396) 281/283 (10%), 202 (40), 163 (30), 83 (100).

N-(4-Bromobutyl)-3,3-dimethylindol-2(3*H*)-one 4a

According to general method 1, a suspension of NaH (80 % w/w) (19.6 mg, 0.68 mmol) in THF (10 ml) at 0 °C was treated with 3,3-dimethylindol-2(3*H*)-one **2** (100 mg, 0.62 mmol) in THF (3 ml), followed by 1,4-dibromobutane (161 mg, 0.74 mmol). The reaction was heated at 40 °C for 12 hours, cooled, and diluted with ether (30 ml). The crude product was purified by chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (6:1) as eluent to give *N-(4-bromobutyl)oxoindole* **4a** (122 mg, 66%) as a clear viscous oil. ν_{max} (CCl_4)/cm^{-1} 3000–2800, 1711, 1610; δ_H (360 MHz), 1.37 (6H, s, C(3)Me), 1.78 (2H, quintet, *J* 6.8, H-2′), 2.24 (2H, quintet, *J* 6.8, H-3′), 3.39 (2H, t, *J* 6.8, H-1′), 3.90 (2H, t, *J* 6.8, H-4′), 7.00 (1H, td, *J* 7.0, 0.8, H-5), 7.18 (1H, dd, *J* 7.0, 0.8, H-7), 7.23 (2H, m, H-6, H-4); *m/z* (EI) (Found: M^+, 295.0563. $C_{14}H_{18}NOBr$ requires: M^+, 295.0572) 296 (20%), 216 (40).

N-(4-Bromopentyl)-3,3-dimethylindol-2(3*H*)-one 4b

According to general method 1 a suspension of NaH (80 %w/w) (19.6 mg, 0.68 mmol) in THF (5 ml) at 0 °C was treated with 3,3-dimethylindol-2(3*H*)-one **2** (100 mg, 0.68 mmol) in THF (5 ml) followed by 1,4-dibromopentane. The reaction was heated at reflux overnight and the crude product was purified by chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (5:1) as eluent to give *N-(4-bromopentyl)-oxoindole* **4b** (114 mg, 54%) as a colourless oil. ν_{max} (CCl_4)/cm^{-1} 3045, 2966–2925, 1710; δ_H (360 MHz), 1.37 (6H, s, C(3)Me), 1.69 (3H, d, *J* 6.6, H-5′), 1.83 (3H, m, H-2′,H-3′), 1.94 (1H, m, H-3′), 3.74 (2H, m, H-1′), 4.19 (1H, m, H-4′), 6.88 (1H, dd, *J* 7.7, 0.8, H-7), 7.06 (1H, dt, *J* 7.7, 0.8, H-5), 7.25 (2H, m, H-4, H-6); *m/z* (EI) (Found: M^+, 309.0731/311.0711. $C_{15}H_{20}NOBr$ requires: M^+, 309.0729/311.0709) 311/309 (M^+, 81%), 230 (70), 146 (100).

N-(3-Bromoprop-2-enyl)-3,3-dimethylindol-2(3*H*)-one 5

According to general method 1 a suspension of NaH (80 %w/w) (29.5 mg, 1.02 mmol) in THF (15 ml) at 0 °C was treated with 3,3-dimethylindol-2(3*H*)-one **2** (0.15 g, 0.93 mmol) in THF (5 ml) followed by 1,3-dibromoprop-1-ene (205 mg, 1.02 mmol). The reaction was warmed to room temperature and stirred for 6 hours. Water (2 ml) was then added and the solvent removed at reduced pressure. The organic residue was dissolved in ether (100 ml), washed with water (3 × 25 ml) and dried with magnesium sulfate. The crude product was purified by chromatography on silica using petroleum (40–60 °C)–ethyl acetate (5:1) as eluent to give *vinyl bromide* **5** (191 mg, 73%) as a clear oil. After iterative chromatography it was possible to separate *cis*- and *trans*-isomers. ν_{max} (neat)/cm^{-1} 3193, 2969, 2927, 1722; δ_H (360 MHz), (*cis*-isomer) 1.39 (6H, s, C-(3)Me), 4.53 (2H, dd, *J* 6.2, 1.7, H-1′), 6.10 (1H, m, H-2′), 6.43 (1H, dt, *J* 7.1, 1.7, H-3′), 6.89 (1H, dd, *J* 7.7, 1.2, H-7), 7.07 (1H, td, *J* 7.7, 1.2, H-5), 7.24 (2H, m, H-6, H-4); (*trans*-isomer) 1.38 (6H, s, C-(3)Me), 4.30 (2H, dd, *J* 5.4, 0.8, H-1′), 6.25 (1H, m, H-2′), 6.31 (1H, dt, *J* 13.7, 0.8, H-3′), 6.82 (1H, dd, *J* 7.7, 0.9, H-7), 7.07 (1H, td, *J* 7.7, 0.9, H-5), 7.25 (2H, m, H-6, H-4); *m/z* (EI) (Found: M^+, 281.0231/279.0261. $C_{13}H_{14}NOBr$ requires: M^+, 281.0235/279.0255) 281/279 (M^+, 30%), 202 (10), 163 (20), 56 (100).

N-(2-Bromophenyl)-*N*-(prop-2-enyl)-2-methylpropenamide 7

According to the general method 1, a suspension of NaH (80 % w/w) (14 mg, 0.48 mmol) in THF (5 ml) was treated with *N*-(2-bromophenyl)-2-methylpropenamide **6** (100 mg, 0.44 mmol) in THF (5 ml) followed by allyl bromide (80.2 mg, 0.66 mmol). The reaction was stirred at room temperature for 12 hours, diluted with ether, washed with water (3 × 10 ml) and dried with magnesium sulfate. The crude product was purified by column chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (5:1) as eluent to give the *tertiary anilide* **7** (82 mg, 80%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 3078, 1670, 1640; δ_H (360 MHz), 1.83 (3H, s, C(3)Me), 3.82 (1H, dd, *J* 14.6, 7.4, H1″), 4.80 (1H, dd, *J* 14.6, 4.7, H1″), 4.98 (1H, s, H-4), 5.00 (1H, s, H-4), 5.07 (1H, dd, *J* 17.0, 1.3, H3″-*cis*), 5.11 (1H, dd, *J* 8.0, 1.3, H3″-*trans*), 5.91 (1H, m, H2″), 7.16 (1H, td, *J* 7.6, 1.6, H-4′), 7.18 (1H, dd, *J* 7.6, 1.6, H-6′), 7.30 (1H, td, *J* 7.6, 1.0, H5′), 7.67 (1H, dd, *J* 7.6, 1.0, H-3′); *m/z* (EI) (Found: M^+, 279.0252/281.0248. $C_{13}H_{14}NOBr$ requires: M^+, 279.0259/281.0238) 279/281 (M^+, 20%), 210 (60), 49 (100).

N-(Prop-2-enyl)-3,3-dimethylindol-2(3*H*)-one 8

N-(2-Bromophenyl)-*N*-(prop-2-enyl)-2-methylpropenamide **7** (92.1 mg, 0.32 mmol) was added to tributyltin hydride (105 mg, 0.36 mmol) and a catalytic amount of AIBN in de-gassed toluene (50 ml). The reaction was heated to 110 °C for 1 hour, cooled, diluted with ether and washed with ammonia solution (20%) (5 × 20 ml). After drying and removal of solvents at reduced pressure the crude product was purified by chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (5:1) as eluent to give the *N-allyloxoindole* **8** and *N-allyl-3-methylquinol-4(2H)-one* as a 3:1 mixture (64.8 mg, 98%) as a clear oil. Iterative chromatography resulted in the isolation of pure *N-(prop-2-enyl)-3,3-dimethylindol-2(3H)*-one **8**. ν_{max} (neat)/cm^{-1} 3056, 1713, 1610; δ_H (360 MHz), 1.38 (6H, s, C(3)Me), 4.34 (2H, dt, *J* 5.2, 1.6, H-1′), 5.21 (2H, m, H-3′), 5.84 (1H, m, H-2′), 6.82 (1H, d, *J* 7.4, H-7), 7.04 (1H, t, *J* 7.4, H-5), 7.21 (2H, m, H-4, H-6); *m/z* (EI) (Found: M^+, 201.1155. $C_{13}H_{15}NO$ requires: M^+, 201.1153) 201 (M^+, 100%), 186 (90), 171 (60), 130 (90).

N-(2-Formylmethyl)-3,3-dimethylindol-2(3*H*)-one 9

N-(Prop-2-enyl)-3,3-dimethylindol-2(3*H*)-one **8** (40 mg, 0.19 mmol) in dichloromethane (50 ml) at −78 °C was treated with a steady stream of ozone until a blue colouration persisted. Dimethyl sulfide (14.8 mg, 0.24 mmol) was then added to the

solution which was warmed to room temperature while stirring over 1.5 hours. The reaction was stirred at room temperature for 1 hour then solvent was removed at reduced pressure. Purification by chromatography on silica using petroleum spirit (40–60 °C)–EtOAc (6:1) as eluent gave the *aldehyde* **9** as a white crystalline solid which proved to be unstable (34 mg, 89%), mp 75 °C. ν_{max} (neat)/cm^{-1} 3100–2900, 1725, 1700; δ_H (360 MHz), 1.43 (6H, s, C(3)Me), 4.52 (2H, s, H-1′), 6.65 (1H, dd, *J* 8.0, 0.9, H-7), 7.09 (1H, td, *J* 8.0, 0.9, H-5), 7.25 (2H, m, H-6, H-4), 9.67 (1H, s, H-2′); *m*/*z* (EA) (Found: M$^+$, 203.0945. $C_{12}H_{13}NO_2$ requires: M$^+$, 203.0946) 203 (30%), 174 (65), 161 (15), 146 (100).

N-(3-Iodoprop-2-enyl)-3,3-dimethylindol-2(3*H*)-one 10

Sodium hexamethyldisilazide (1 M solution in THF) (0.25 ml, 0.25 mmol) was added to a stirred suspension of iodomethyltriphenylphosphonium iodide (134 mg, 0.25 mmol) in THF (10 ml) at room temperature. After 1 minute the solution was cooled to −60 °C and HMPA (0.073 ml, 0.4 mmol) was added, followed by cooling the mixture to −78 °C. The reaction was stirred at this temperature for 5 minutes whereupon a solution of *N*-(formylmethyl)-3,3-dimethylindol-2(3*H*)-one **9** (43 mg, 0.21 mmol) in THF (5 ml) was slowly added. The reaction was allowed to slowly warm to room temperature over 1 hour and diluted with ether (100 ml). The ethereal solution was washed with water (3 × 10 ml), dried with magnesium sulfate and the solvents removed at reduced pressure. The crude product was purified by column chromatography using petroleum spirit (40–60 °C)–ethyl acetate (6:1) as eluent to give the *cis-vinyl iodide* **10** (36.7 mg, 54%) as a clear oil. ν_{max} (neat)/cm^{-1} 3200–3000, 1654, 556; δ_H (360 MHz), 1.38 (6H, s, C(3)Me), 4.43 (2H, dd, *J* 6.0, 1.9, H-1′), 6.24 (1H, m, H-2′), 6.53 (1H, dt, *J* 10.7, 1.9, H-3′), 6.86 (1H, dd, *J* 7.8, 0.9, H-7), 7.07 (1H, td, *J* 7.8, 0.9, H-5), 7.25 (2H, m, H-6, H-4); *m*/*z* (EI) (Found: M$^+$, 327.0137. $C_{13}H_{14}NOI$ requires: M$^+$, 327.0120) 327 (20%), 200 (100).

9,9-Dimethyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole 11 (general method 2)

A solution of *N*-(3-bromopropyl)-3,3-dimethylindol-2(3*H*)-one **3** (67 mg, 0.24 mmol) in ether (10 ml) at −78 °C was treated with *tert*-butyllithium (1.7 M, 0.31 ml, 0.53 mmol). The reaction was maintained at −78 °C for 1 hour then slowly warmed to 0 °C and stirred for a further hour. $LiAlH_4$ (1 M solution in ether, 0.32 ml, 0.32 mmol) was then added and the reaction heated at reflux overnight. After cooling to room temperature the reaction was cautiously quenched with NaOH (2 M, 2 ml), followed by rapid stirring with a saturated solution of Rochelle's salt (10 ml) for one hour. The organic phase was separated and the aqueous phase extracted with ether (3 × 10 ml). The combined organic extracts were dried with magnesium sulfate, the solvent was removed at reduced pressure, and the crude product was purified by chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (20:1) as eluent to give the *tricycle* **11** (21 mg, 47%) as a pale yellow oil. ν_{max} (CCl_4)/cm^{-1} 3229, 2957–2870; δ_H (360 MHz; C_6D_6; Me_4Si) 0.85–0.98 (2H, m, H-2), 1.13 (3H, s, C(3)Me), 1.24 (3H, s, C(3)Me), 1.35–1.56 (2H, m, H-1), 2.95 (1H, dt, *J* 10.5, 8.4, H-3), 3.15–3.30 (2H, m, H-3, H-9a), 6.53 (1H, dd, *J* 7.6, 0.9, H-5), 6.84 (1H, td, *J* 7.6, 0.9, H-7), 6.94 (1H, dd, *J* 7.6, 0.9, H-8), 7.13 (1H, td, *J* 7.6, 0.9, H-6); *m*/*z* (EI) (Found: M$^+$, 187.1360. $C_{13}H_{17}N$ requires M$^+$, 187.1361) 187 (65%), 172 (100), 144 (70).

10,10-Dimethyl-1,2,3,4,10,10a-hexahydropyrido[1,2-*a*]indole 12a

According to general method 2, *N*-(4-bromobutyl)-3,3-dimethylindol-2(3*H*)-one **4a** (56 mg, 0.19 mmol) in ether (10 ml) was treated with *tert*-butyllithium (1.7 M, 0.23 ml, 0.39 mmol) followed by $LiAlH_4$ (1 M solution in ether, 0.2 ml, 0.20 mmol). The crude product was purified by chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (20:1) as eluent to give the *tricycle* **12a** (36.2 mg, 95%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 2937, 2865 1606, 1481; δ_H (360 MHz; C_6D_6; Me_4Si) 1.01 (6H, s, C(3)Me), 1.00–1.75 (6H, m, H-1, H-2, H-3), 2.26 (1H, m, H-4), 2.46 (1H, dd, *J* 10.3, 2.0, H-4), 3.38 (1H, dd, *J* 10.3, 1.2, H-10a), 6.44 (1H, dd, *J* 7.7, 1.0, H-6), 6.82 (1H, td, *J* 7.7, 1.0, H-8), 7.06 (1H, dd, *J* 7.7, 1.0, H-9), 7.13 (1H, td, *J* 7.7, 1.0, H-7); *m*/*z* (EI) (Found: M$^+$, 201.1523. $C_{14}H_{19}N$ requires: M$^+$, 201.1517) 201 (M$^+$, 40%), 186 (100), 171 (15).

1,2,3,4,10,10a-Hexahydro-1,10,10-trimethylpyrido[1,2-*a*]indole 12b

According to general method 2, a stirred solution of *N*-(5-bromopentyl)-3,3-dimethylindol-2(3*H*)-one **4b** (100 mg, 0.323 mmol) in ether (10 ml) at −78 °C was treated with *tert*-butyllithium (1.7 M, 0.39 ml, 0.663 mmol), followed by $LiAlH_4$ (1 M solution in ether, 0.32 ml, 0.323 mmol). The crude product was purified by chromatography on silica using petroleum spirit (40–60 °C)–ethyl acetate (40:1) as eluent to give the *tricycle* **12b** (44.4 mg, 64%) as a pale yellow oil which rapidly darkened on standing in air. ν_{max} (neat)/cm^{-1} 3045, 2950; δ_H (360 MHz; C_6D_6; Me_4Si) 0.81 (3H, d, *J* 6.4, C(1)Me), 1.08 (3H, s, C(10)Me), 1.10–1.60 (4H, m, H-2, H-3), 1.31 (3H, s, C(10)Me), 2.21 (2H, m, H-4), 3.30–3.50 (1H, m, H-10a), 6.42 (1H, d, *J* 7.7, H-9), 6.83 (1H, t, *J* 7.7, H-7), 6.87 (1H, d, *J* 7.7, H-6), 6.99 (1H, t, *J* 7.7, H-8); *m*/*z* (EI) (Found: M$^+$, 215.1684. $C_{15}H_{21}N$ requires: M$^+$, 215.1674) 215 (60%), 200 (100), 144 (50).

9,9a-Dihydro-9,9-dimethyl-3*H*-pyrrolo[1,2-*a*]indole 13

According to general method 2 a solution of *N*-(3-iodoprop-2-enyl)-3,3-dimethylindol-2(3*H*)-one **10** (33.6 mg, 0.10 mmol) in ether (10 ml) was treated with *tert*-butyllithium (1.7 M, 0.14 ml, 0.22 mmol) followed by $LiAlH_4$ (1 M solution in ether, 0.15 ml, 0.15 mmol). The crude product was purified by chromatography using petroleum spirit (40–60 °C)–ethyl acetate (10:1) as eluent to give the *tricycle* **13** (11 mg, 59%) as a clear oil. ν_{max} (neat)/cm^{-1} 3200–3000, 1650; δ_H (360 MHz; C_6D_6; Me_4Si) 1.35 (3H, s, C(3)Me), 1.51 (3H, s, C(3)Me), 3.71 (1H, dd, *J* 7.0, 1.2, H-9a), 5.10 (2H, m, H-3), 6.02 (1H, m, H-2), 6.35 (1H, m, H-1), 6.95 (1H, d, *J* 8.1, H-5), 7.10 (1H, m, H-7), 7.25 (1H, m, H-6), 7.30 (1H, m, H-8); *m*/*z* (EI) (Found: M$^+$, 185.1208. $C_{13}H_{15}N$ requires: M$^+$, 185.1204) 185 (M$^+$, 100%).

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