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A Route to the Pyrrolo[1,2-a]Indolenine Ring System via Intermolecular Organolithium Addition to an Oxindole

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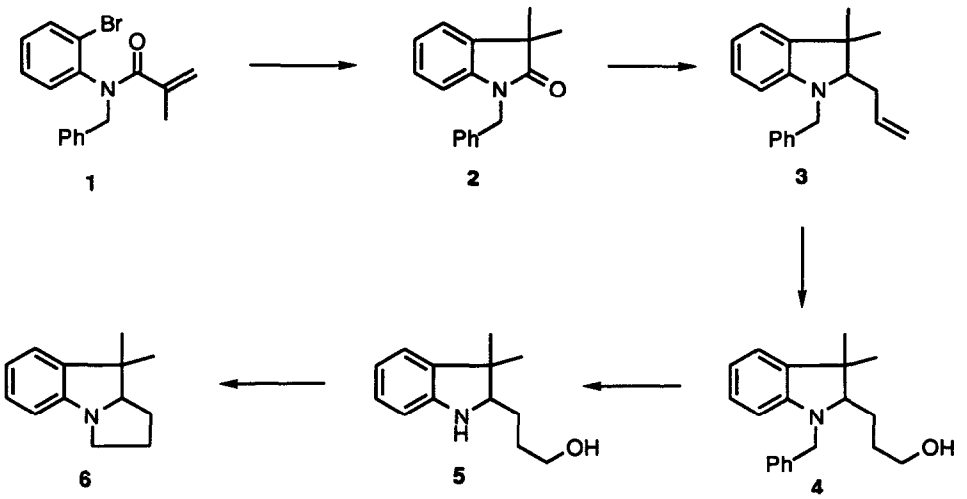
Abstract A synthesis of the pyrrolo[1,2 a]indolenine **6** in four steps from *N*-benzyl-3,3-dimethyloxindole **2** is presented involving an organolithium addition to the oxindole carbonyl group. Additions of vinyllithiums to the oxindole **2** are presented

We have recently developed an approach to oxindoles based on the cyclisation via the derived aryl radical of *ortho*-bromoacryloylanilides[1]. The oxindoles thus formed are ideally suited for elaboration into a range of indole-based natural products by utilising the electrophilic nature of the carbonyl group at the 2-position[2]. In this paper, we wish to report a synthesis of the pyrrolo[1,2 a]indolenine ring system, which is closely related to the basic ring system found in the medicinally-important mitomycins[3].

There have been many synthetic approaches to the pyrrolo[1,2 a]indole[4] and pyrrolo[1,2 a]indolenine[5] rings systems. In 1988, Raphael and Ravenscroft[6] reported an attempted synthesis of the pyrrolo[1,2 a]indolenine ring system via an oxindole. Unfortunately, their plan to achieve the carbon/carbon bond formation to the oxindole carbonyl using acetylene anion chemistry did not succeed and they were unable to complete the third ring. In 1991, we reported a route to this ring system involving an intramolecular addition of an organolithium species generated *in situ* from an alkyl/vinyl bromide/iodide followed by a reductive work up[7]. This chemistry was based firmly on the work of Fowler[8] in which he studied the intermolecular addition of organolithium species to lactams followed by a reductive treatment to give α-substituted cyclic amines. Our initial studies on the reaction of oxindoles with organolithium reagents appeared to indicate that whilst alkyl- and alkenyllithiums reacted as expected to give 2-substituted dihydroindoles, allyllithium reactions failed to show any signs of carbon/carbon bond formation[9].

This problem was overcome by preparing solid allyllithium in a glove box by treatment of a pentane

solution of tetra-allyltin with n-butyllithium. Filtration and drying gave a white powder which could be stored for several months under an inert atmosphere at -30°C. Reaction of *N*-benzyl-3,3-dimethyloxindole **2** (prepared by radical cyclisation[1] of acryloylanilide **1**) with a suspension of this allyllithium reagent in diethyl ether followed by addition of an ethereal solution of $LiAlH_4$ and refluxing overnight gave the 2-allylated dihydroindole **3** in 82% yield. With this problem surmounted, we planned to functionalise the double bond and remove the benzyl group to provide a 1,4-aminoalcohol which precedent suggested should be readily cyclised to the pyrrolidine by treatment under Mitsunobu conditions[10].

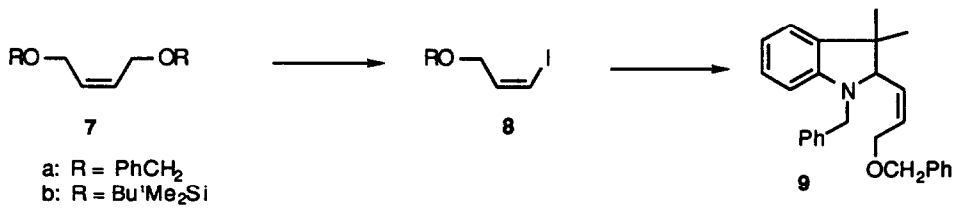


Scheme 1

Hydroboration/oxidation of dihydroindole **3** to alcohol **4** was accomplished in 92% yield by reaction with borane-dimethyl sulphide followed by treatment with basic hydrogen peroxide. Removal of the benzyl group of **4** was achieved by catalytic hydrogenation over a palladium catalyst to give aminoalcohol **5** in 89% yield. Reaction of **5** with triphenylphosphine and diethyl azodicarboxylate[11] at 40°C for 4 hours led to complete disappearance of starting material and the pyrrolo[1,2 a]indolenine **6** was isolated in 64% yield after chromatography. This material proved to be identical to a sample prepared by our intramolecular cyclisation route[7].

We decided to further explore this approach towards mitomycins by incorporating a 1,2-double bond suitable for functionalisation to the aziridine found in the mitomycins. This required the addition of a C_3-vinyllithium species, carrying a protected alcohol group on the C-3, to our oxindole. This was achieved as shown in Scheme 2. Formation of the bisbenzyl ether of 2-butene-1,4-diol using benzyl bromide and KH in THF at reflux gave the desired ether **7a** in 99% yield. Ozonolysis of the double bond in **7a** under the usual conditions gave α-benzyloxyacetaldehyde which was too reactive to isolate[12]. Treatment of a dichloromethane solution of this aldehyde with the iodomethylenetriphenylphosphorane developed by Stork[13] gave the *cis*-vinyliodide **8a** in 57% yield after chromatography. It is important to have the *cis*-double bond in order to close the pyrroline ring and it is known that the lithium/iodine exchange occurs with retention[14] and that vinyllithiums are configurationally stable under the usual conditions[15]. Formation of the corresponding

vinyllithium proceeded smoothly on treatment with t-butyllithium at low temperature and addition of the oxindole **2** followed by $LiAlH_4$ gave the 2-substituted dihydroindole **9** in 58% yield. Removal of the benzyl groups by catalytic hydrogenation was precluded by the presence of the double bond but, based on previous experience[7], it was expected that brief treatment with sodium in liquid ammonia would be successful. However, although these conditions led to complete debenzylation, it was always accompanied by Birch reduction of the aromatic ring. The obvious solution was to change the protecting groups on both the vinyllithium and the oxindole nitrogen. To this end, 2-butene-1,4 -diol was treated with t-butyldimethylsilyl chloride (TBDMSCl) to form the bis-silyl ether **7b** in 97% yield. Ozonolysis and *in situ* Wittig reaction as described above gave the *cis*-vinyliodide **8b** in 39 % yield. Unfortunately, treatment with t-BuLi followed by a variety of electrophiles gave no identifiable products. It appears that either lithium/iodine exchange fails in this case or the viyllithium produced is unstable.



Scheme 2

In summary, we have shown that the intermolecular addition of an allyllithium to a suitable oxindole followed by a Mitsunobu ring closure is a good route to simple pyrrolo[1,2 a]indolenines. Attempts to incorporate a double bond into this strategy have demonstrated that the addition of the vinyllithium is successful but considerable work may be required to find appropriate protecting groups.

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Experimental

Solutions were dried over anhydrous magnesium sulphate and THF was distilled from potassium benzophenone ketyl immediately before use. Purification was carried out by column chromatography using the flash chromatography technique. The solvent used is given in terms of the ratio of petroleum ether to ethyl acetate used. Nmr were obtained on a Bruker AM360 operating at 360 MHz for ^1H and all spectra were recorded as solutions in $CDCl_3$ unless otherwise stated. Mass spectra were run at the SERC Mass Spectrometry Centre, University College Swansea. Melting points are uncorrected.

***N*-(Phenylmethyl)-3,3-dimethylindol-2(3H)-one (2)**

Tributyltin hydride (1.01 g, 3.47 mmol) was added to a solution was added to a solution of acryloylanilide **1** (1.00 g, 3.02 mmol) and AIBN (catalytic, 0.05 g) in toluene (80 ml) at room temperature under an argon atmosphere. The reaction was refluxed for 1 hour and then allowed to cool to room temperature. The toluene was removed *in vacuo* and the residue dissolved in diethyl ether (200 ml). The ethereal solution was washed with aqueous ammonia solution (20%, 5 x 50 ml). The organic solution was dried and concentrated *in vacuo* to give an oil This was purified by flash chromatography (4:1) to give the product **2** as a white crystalline solid (0.531 g, 70%), m.p. 76-77°C (Found: C, 81.02; H, 6.71; N, 5.44; M^+, 251.1318. $C_{17}H_{17}NO$

requires C, 81.24; H, 6.81; N, 5.57; M^+ 251.1306.); δ_H 1.43 (6H, s, 2xCH_3), 4.29 (2H, s, CH_2Ph), 6.72 (1H, d, *J*7.7 Hz, H-7), 7.06 (1H, t, *J*7.7 Hz, H-5), 7.13 (1H, t, *J*7.7 Hz, H-6), 7.21 (1H, d, *J*7.7 Hz, H-4), 7.24-7.31 (5H, m, C_6H_5); ν_{max} 1712 (s, C=O), 1611 (s, C=C aromatic); **m/z** 251 (M^+, 90%), 236 (45%), 160 (30%), 91 (100%).

***N*-(Phenylmethyl)-3,3-dimethyl-2-(prop-2'-ene)-2,3-dihydroindole (3)**

To a stirred suspension of freshly prepared solid allyllithium (286 mg, 5.91 mmol) in diethyl ether (20 ml) at 0°C under argon, was added slowly a solution of **2** (1.0 g, 3.9 mmol) in diethyl ether (10 ml) The reaction was allowed to warm to room temperature and followed by tlc until all the oxindole had been consumed whereupon lithium aluminium hydride (1M, 3 ml, 3.0 mmol) was added and the reaction refluxed overnight. After cooling to room temperature, the reaction was carefully quenched with aqueous NaOH (2M, 20 ml, 40 mmol) followed by addition of a saturated solution of Rochelle's salt and stirring for 1 hr. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3x50 ml). The organic extracts were combined, dried and concentrated *in vacuo* to yield an oil whivh was purified by flash chromatography (10:1) furnishing **3** as an oil (900 mg, 82%), (Found: M^+, 277.1812. $C_{20}H_{23}N$ requires M^+ 277.1830.); δ_H 1.27 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.58 (2H, m, CH_2CH), 3.37 (1H, t, *J*5.3 Hz, H-2) 4.40 (2H, ABq, *J*16.5 Hz, CH_2Ph), 5.10 (1H, dq, *J*8.6, 1.7 Hz, H-3'trans), 5.18 (1H, dq, *J*17.1, 1.6 Hz, H-3'cis), 5.91 (1H, m, H-2'), 6.41 (1H, dd, *J*7.7, 0.9 Hz, H-7), 6.76 (1H, td, *J*7.7, 0.9 Hz, H-5), 7.07 (2H, m, H-4, H-6), 7.40 (5H, m, C_6H_5); ν_{max} 3200-2800 (m, C-H), 1600 (s, C=C); **m/z** 277 (M^+, 100%), 235 (40%), 145 (20%), 91 (21%).

***N*-(Phenylmethyl)-3,3-dimethyl-2-(propan-3'-ol)-2,3-dihydroindole (4)**

To a stirred solution of **3** (100 mg, 0.36 mmol) in THF (10 ml) at room temperature under argon was added borane-dimethyl sulphide complex (10M, 0.1 ml, 1 mmol). The reaction was heated under reflux overnight, cooled to room temperature and quenched with water (2 ml). A mixture of hydrogen peroxide (100 vol, 2 ml) and NaOH solution (2M, 2 ml, 4 mmol) was added and the mixture stirred for 30 mins. The solution was poured into saturated aqueous sodium hydrogen carbonate solution (3 ml) and the solvents removed *in vacuo*. The resultant residue was dissolved in a small volume of methanol and passed through a silica gel plug (1 g, 20 mm diameter sinter). Removal of the solvent gave **4** which was sufficiently pure for the next step (98.1 mg, 92%), (Found M^+, 295.1944. $C_{20}H_{25}NO$ requires M^+, 295.1936); δ_H 1.21 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.61 (2H, m, H-2'), 1.75 (2H, m, H-1'), 3.25 (1H, t, *J*5.5 Hz, H-2), 3.63 (2H, t, *J*6.0 Hz, H-3'), 4.40 (2H, ABq, J16.4 Hz, CH_2Ph), 6.44 (1H, d, *J*7.6 Hz, H-7), 6.72 (1H, t, *J*7.6 Hz, H-5), 7.01 (2H, m, H-4, H-6), 7.25 (5H, m, C_6H_5); ν_{max} 3500-3000 (m, O-H) 1596 (m, C=C); **m/z** 295 (M^+, 35%), 236 (100%).

3,3-Dimethyl-2-(propan-3'-ol)-2,3-dihydroindole (5)

To a stirred solution of **4** (89 mg, 0.30 mmol) in ethyl acetate (10 ml) was added palladium on carbon (5%, 20 mg) and the reaction mixture stirred under an atmosphere of hydrogen overnight at room temperature. After filtration through celite, the solvents were removed *in vacuo* to give an oil (54.6 mg, 89%) which was used without further purification; (Found: M^+, 205.1465. $C_{13}H_{19}NO$ requires M^+, 205.1466); δ_H 1.04 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.50-1.75 (4H, m, H-1', H-2'), 3.36 (1H, t, *J*6.8 Hz, H-2), 3.72 (2H, t, *J*6.0 Hz, H-3'), 6.62 (1H, dd, *J*8, 1 Hz, H-7), 6.74 (1H, td, *J*8.4, 1 Hz, H-5), 7.00 (2H, m, H-4, H-6); ν_{max} 3400-2800 (s, O-H, N-H, C-H), 1597 (w, C=C); **m/z** 205 (M^+, 20%), 146 (100%).

9,9-Dimethyl-2,3,9,9a-tetrahydro(1H)pyrrolo-[1,2a]-indole (6)

To a stirred solution of **5** (25 mg, 0.12 mmol) in THF (10 ml) under an argon atmosphere was added dry triphenylphosphine (34.7 mg, 0.13 mmol) and diethyl azodicarboxylate (20µl, 0.13 mmol). The reaction was

heated to 40°C after which time no starting material could be detected by tlc. The solvent was removed and the crude product purified by flash chromatography (15:1) to give **6** as a clear oil (14.3 mg, 64%), (Found: M^+, 187.1360. $C_{13}H_{17}N$ requires M^+ 187.1361); $\delta_H(C_6D_6)$ 0.85-0.98 (2H, m, H-2), 1.13 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.35-1.56 (2H, m, H-1), 2.95 (1H, dt, *J*10.5 and 8.4 Hz, H-3), 3.15-3.30 (2H, m, H-3, H-9a), 6.53 (1H, dd, *J*7..6 and 0.9 Hz, H-5), 6.84 (1H, td, *J*7.6 and 0.9 Hz, H-7) 6.94 (1H, dd, *J*7.6 and 0.9 Hz, H-8), 7.13 (1H, td, *J*7.6 and 0.9 Hz, H-6); ν_{max} 3229 (s, C-H), 2957-2870 (m, C-H); **m/z** 187 (M^+, 65%), 172 (100%), 144 (70%).

1,4-Dibenzyloxybut-2-ene (7a)

Potassium hydride (5.98 g, 35% w/v, 49.9 mmol) was prewashed with petroleum ether and the washings discarded. THF (100 ml) was added and to this stirred suspension was added at room temperature a solution of 2-butene-1,4-diol (2.00 g, 22.7 mmol). When hydrogen evolution had ceased (30 mins) benzyl bromide (15.5 g, 90.4 mmol) was added and the reaction heated under reflux for 12 hrs. After cooling, the THF was removed *in vacuo* and the crude mixture was diluted with diethyl ether (100 ml). This was washed with water (3 x 30 ml), dried and stirred under high vacuum overnight to remove the excess benzyl bromide. The crude mixture was purified by flash chromatography (10:1) to furnish **7a** as a clear oil (6.01 g, 99%), (Found: M^+, 268.1454. $C_{18}H_{20}O_2$ requires M^+ 268.1463); δ_H 4.03 (4H, d, *J*4.4 Hz, 2xCH_2), 4.46 (4H, s, 2x$PhCH_2$), 5.76 (2H, d, *J*4.4 Hz, olefinic-H), 7.3 (10H, m, 2xPh); ν_{max} 3000-2800 (m, C-H); **m/z** 268 (M^+, 100%).

***O*-Benzyl-3-iodoprop-2-enol (8a)**

A stirred solution of bisether **7a** (1.00 g, 3.7 mmol) in dichloromethane (40 ml) was cooled to -78°C and ozone was bubbled through the solution until a permanent blue colouration was observed. Nitrogen was bubbled through the solution for 5 mins and then triphenylphosphine (1.07 g, 4.1 mmol) was added to the solution over 1 hr whilst the temperature was maintained at 0°C. The dichloromethane solution was then transfered by cannula using argon into a cooled (-78°C) solution of iodomethylenetriphenylphosphorane prepared from iodomethyltriphenylphosphonium iodide (1.53 g, 3.07 mmol), sodium hexamethyldisilazide (3.07 ml, 1M solution) and HMPA (1 ml, excess) in THF. After completion of addition of the dichloromethane solution, the mixture was stirred for 1 hr at -78°C and then warmed to room temperature over 1 hr. The solution was washed with water (3 x 20 ml), dried and the solvent removed *in vacuo*. The crude material was purified by flash chromatography (10:1) to give 8a as a clear oil (0.48 g, 57%), (Found: M^+, 273.9884. $C_{10}H_{11}OI$ requires M^+ 273.9856); δ_H 4.10 (2H, dd, *J*5.5 and 1.6 Hz, CH_2), 4.50 (2H, s, $PhCH_2$), 6.34 (1H, dt, *J*7.5 and 1.6 Hz, H-3), 6.45 (1H, dt, *J*7.5 and 5.5 Hz, H-2), 7.25 (5H, m, Ph); ν_{max} 3200-3000 (w, C-H), 1600 (m, C=C); **m/z** 274 (M^+, 5%), 167 (30%), 147 (20%), 91 (100%).

***N*-(Phenylmethyl)-3,3-dimethyl-2-(prop-3'-benzyloxy-1'-ene)-2,3-dihydroindole (9)**

To a stirred solution of vinyliodide **8a** (100 mg, 0.36 mmol) in ether (10 ml) at -78°C under argon was added Bu^tLi (0.45 ml, 1.7M in pentane, 0.76 mmol). The reaction was stirred for 30 mins and then allowed to warm slowly to 0°C, stirred at this temperature for 30 mins and then oxindole **2** (91 mg, 0.36 mmol) in ether (5 ml) was added dropwise. The reaction was maintained at 0°C and monitored by tlc until all the oxindole was consumed (3 hr) at which point $LiAlH_4$ (1 ml, 1M solution) was added and the mixture heated under reflux for 12 hrs. The reaction was cooled, quenched with dilute NaOH (2 ml) and the stirred vigorously with a saturated solution of Rochelle's salt (50 ml). The organic layer was separated and the aqueous layer extracted with ether (3 x 20 ml). The combined ethereal extracts were dried, concentrated and purified by flash chromatography (15:1) to give **9** as a clear oil (79.9 mg, 58%), (Found: M^+, 383.2252. $C_{27}H_{29}NO$ requires M^+ 383.2249.); δ_H 1.06 (3H, s, $C\underline{H}_3$), 1.13 (3H, s, $C\underline{H}_3$), 3.75 (1H, m, H-2), 3.80 (4H, m, $\underline{H}_2$-3, $PhC\underline{H}_2$) 4.25 (2H, ABq, *J*16.5 Hz, $C\underline{H}_2Ph$), 5.52 (1H, m, H-2'), 5.85 (1H, m, H-1'), 6.40 (1H, dd, *J*7.2, 1 Hz,

H-7), 6.77 (1H, td, *J*7.3, 1 Hz, H-5), 7.00-7.50 (12H, m, H-4, H-6, 2 x Ph); ν_{max} 3050-2800 (m, C-H), 1602 (s, C=C); **m/z** 383 (M^+, 25%), 292 (30%), 91 (21%).

1,4-Di-(t-butyldimethylsiloxy)-but-2-ene (7b)

To a stirred soltion of 2-butene-1,4-diol (0.15 g, 1.70 mmol) and imidazole (0.51 g, 7.5 mmol) in THF (30 ml) was added a solution of TBDMSCl (0.56 g, 3.74 mmol) in THF (10 ml). The solution was stirred at room temperature for 4 hrs after which the solvent was removed *in vacuo* and the resulting residue dissolved in ether (100 ml). The ethereal solution was washed with ice-cold HCl (3 x 20 ml, 1M) then with saturated sodium bicarbonate solution (2 x 20 ml) and finally with water (2 x 20 ml). The soltuion was dried and the ether was removed *in vacuo*. The crude product was purified by flash chromatography (4:1) to give **7b** as a clear oil (0.526 g, 97%), (Found: M^+, 316.2250. $C_{16}H_{36}O_2Si_2$ requires M^+ 316.2253); δ_H 0.06 (12H, s, $4xSiCH_3$), 0.89 (18H, s, Bu^t), 4.23 (4H, d, *J*4 Hz, $2xCH_2$), 5.54 (2H, d, *J*4 Hz, =CH); ν_{max} 3000-2800 (m, C-H), 1260 (s, Si-C), 1100 (s, Si-O), 850 (s, Si-C); **m/z** (CI) 316 (M^+, 60%), 302 (70%), 149 (100%).

1-(t-Butyldimethylsiloxy)-3-iodoprop-2-ene (8b)

This was carried out as for **8a** above. Alkene **7b** (0.5 g, 1.58 mmol) and the phosphorane derived from iodomethyltriphenylphoshonium iodide (0.5 g, 1.91 mmol) gave, after flash chromatography (12:1), **8b** as a viscous oil (0.207 g, 39%), δ_H 0.09 (6H, s, $2xSiCH_3$), 0.90 (9H, s, Bu^t), 4.00 (2H, dd, *J*5.4 and 1.8 Hz, CH_2), 6.22 (1H, dt, *J*7.6 and 1.8 Hz, H-3), 6.40 (1H, m, H-2); ν_{max} 2970 (m, C-H), 1607 (m, C=C), 1100 (s, Si-O), 840 (s, Si-C); **m/z** no molecular ion nor identifiable fragments could be obtained.

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