SYNTHESIS OF 5,7,8,9,10,11-HEXAHYDRO-7-OXO-8,11-IMINOAZEPINO[1,2-*b*]ISOQUINOLINES

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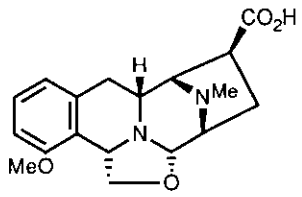
Abstract – Methyl 4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylates have been converted into methyl 5,7,8,9,10,11-hexahydro-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylates.

There has been considerable interest in the development of synthetic routes[1] to the antitumour[2] metabolite quinocarcin (**1**);[3] we and Garner[4] have utilised strategies in which the key 3,8-diazabicyclo[3.2.1]octane nucleus is constructed *via* a dipolar cycloaddition to a 3-oxidopyrazinium, though the methods employed for the generation of this 1,3-dipole are quite different. Garner generates a 5-oxo-3-oxidopyrazinium by photolysis of an aziridino-succinimide, previously formed by addition of methyl azide to the double bond in a maleimide, then photochemical extrusion of nitrogen; this route has been developed into an elegant total synthesis of quinocarcin itself, in homochiral form.[5] Another elegant synthesis of the natural substance utilises a quite different synthetic strategy.[6]



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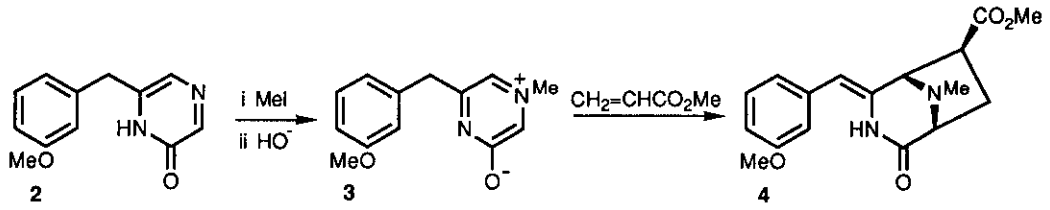
BACKGROUND

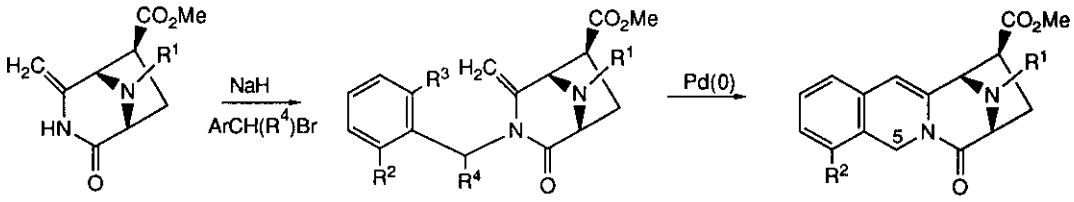
We have shown that 1,5-dimethyl-3-oxidopyrazinium can be produced straightforwardly from 6-methylpyrazin-2-one *via* quaternisation then deprotonation, that the zwitterion is quite stable and easy to handle and store with few precautions, and that it readily undergoes dipolar cycloadditions, with the regiochemistry required for the construction of quinocarcin.[7]

We have described a route to a 6-benzylpyrazin-2-one (**2**) such as might be required for a synthesis of the natural product, and described its further development, *via* the corresponding



oxidopyrazinium (**3**) into **4**,[8] which had been previously synthesised by Weinreb[9] by a completely different route.

In this paper we describe the elaboration of methyl 4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylates (**5a** and **b**) (the methyl acrylate adducts derived originally from 6-methylpyrazin-2-one) into tetracyclic, 5,7,8,9,10,11-hexahydro-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinolines (**7a-c**) having four of the five rings of quinocarcin, and with ester and amide carbonyl functions appropriately placed for further elaboration.



5	R^1
a	Bn
b	Me

6	R^1	R^2	R^3	R^4
a	Me	H	H	H
b	Me	H	H	Me
c	Bn	H	Br	H
d	Me	H	Br	H
e	Me	MeO	Br	H

7	R^1	R^2
a	Bn	H
b	Me	H
c	Me	MeO

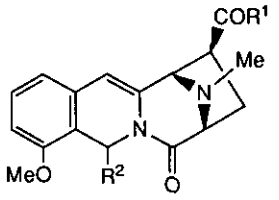
RESULTS

The development of the bicyclic compounds (**5**) into tetracycles (**7**) requires the fusion of a benzyl unit, the benzylic carbon to become attached to nitrogen and the *ortho* aromatic carbon to the exocyclic methylene carbon of **5**. It seemed that the first of these objectives might be achievable *via* an *N*-alkylation, using a benzylic halide and the trimethylsilyl derivative of enamides (**5**), however in a trial experiment, only a poor yield of the *N*-benzyl derivative (**6a**) could be achieved by this method.

Formation of the sodium salts of enamides (**5**) by reaction with sodium hydride, did, however, allow *N*-benzylation to proceed well, even with the more hindered 1-bromoethylbenzene, generating substituted derivatives (**6b-e**) the site of alkylation being confirmed as nitrogen (not

oxygen) by the continued presence of amide carbonyl stretching absorption in the IR spectra of these products.

Formation of the second bond, to fashion the reduced isoquinoline nucleus, required functionality at the *ortho* position, and this was provided by utilising 2-bromobenzyl bromide, and 2-bromo-6-methoxybenzyl bromide,[10] giving **6c-e**. Our original intention was to utilise these halides to generate aryl radicals for cyclisation,[11] however exploratory work along these lines led to no clear results, so we turned to the use of palladium methodology. Treatment of the halides (**6c-e**) with (catalytic) palladium acetate together with triphenylphosphine and silver carbonate in refluxing THF gave the desired products (**7a-c**) in yields between 62 and 76%.[12]

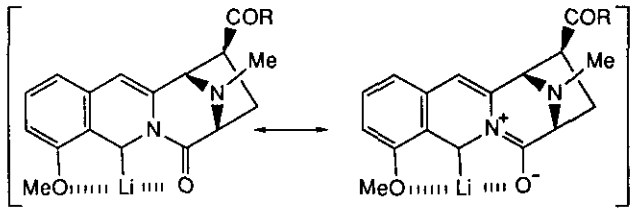


8 R^1 R^2

a *n*-Bu H

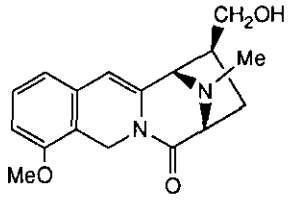
b *t*-Bu H

c *n*-Bu D



9 R = OMe or *n*-Bu

Tetracycle (**7c**) requires an additional carbon located at C-5, for a continuation of the synthesis; we believed that this carbon could be introduced *via* lithiation at the benzylic position, facilitated by coordination from both the aromatic methoxyl group and from the amide carbonyl oxygen[13] (*cf.* **9**). Attempts to achieve this were thwarted by side reaction at the ester, for example treatment with either *n*-butyllithium or *t*-butyllithium led after quenching to ketones, (**8a** and **b**) respectively. However, that lithiation does indeed take place, and in the desired fashion, was clearly demonstrated by the isolation, from the blue solution produced by lithiation, quenched with D_2O, of the deuteriated ketone (**8c**) it being uncertain whether the benzylic lithiation had taken place before, or after nucleophilic displacement at the ester. Attempts to C-lithiate the alcohol (**10**) derived from **7c** by lithium aluminium hydride reduction, were unsuccessful.



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EXPERIMENTAL

General. All reaction were conducted under an atmosphere of argon or nitrogen. Solutions in organic solvents were dried over anhydrous Na_2SO_4. Chromatography was conducted using silica gel.

Methyl 3-benzyl-8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-exo-6-carboxylate, (6a).– A mixture of methyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylate[6] (**5b**) (50 mg, 0.24 mmol) and chlorotrimethylsilane (cat.) was refluxed in 1,1,1,3,3,3-hexamethyldisilazane (5 ml) for 5 h, then the solvent was evaporated and the residue dissolved in acetonitrile (2 ml). Benzyl bromide (51 mg, 0.036 ml, 0.30 mmol) was added and the solution was refluxed for 16 h, cooled to room temperature, then potassium carbonate (100 mg) and methanol (0.5 ml) added, and the solution stirred for 30 min, filtered, and concentrated. The residue was purified by column chromatography (ether) to give **6a** as a colourless oil (15 mg, 21%), υ_{max} (cm^{-1}) 2952, 1738, 1683, 1629; δ_H 7.16-7.38 (5H, m, ArH), 4.89 (2H, q, *J* 3.0 Hz, $PhCH_2N$), 4.33 (1H, d, *J* 1.8 Hz, one of CH_2=C), 4.29 (1H, d, *J* 1.8Hz, one of CH_2=C), 4.05 (1H, s, MeNC*H*CH=CH_2), 3.78 (1H, d, MeNC*H*C=O, partially obscured by signal at 3.74 ppm), 3.74 (3H, s, CO_2Me), 2.98 (1H, dd, *J* 5.6, 10.2 Hz, $CHCO_2Me$), 2.68 (1H, m, *exo* MeNCHCH_2), 2.50 (3H, s, NCH_3), 2.38 (1H, dd, *J* 10.0, 13.3 Hz, *endo* MeNCHCH_2); *m/z* (EI) (relative intensity, %) 300 (M^+, 9), 214 (100), 209 (28), 186 (20), 166 (12), 91 (20) (Found: M^+, 300.1466. $C_{17}H_{20}N_2O_3$ requires *M*, 300.1474), further elution gave recovered starting material (18 mg, 35%).

Methyl 3-(1-phenylethyl)-8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-exo-6-carboxylate (6b).– To a stirred solution of methyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylate[6] (**5a**) (100 mg, 0.48 mmol) in DMF (10 ml) was added sodium hydride (80% oil dispersion, 16 mg, 0.53 mmol). The solution was stirred for 30 min, then 1-bromoethylbenzene (0.21 ml, 278 mg, 1.50 mmol) was added and the solution stirred at 40°C for 16 h. Saturated aqueous ammonium chloride solution (0.5 ml) was then added, the solution concentrated, then the residue extracted from water (50 ml) into dichloromethane (3x50 ml), the organic extracts dried and concentrated. The resultant brown oil was purified by column chromatography to give some starting material (108 mg, 39%) followed by **6b** as a colourless oil (80 mg, 54%), υ_{max} (cm^{-1}) 2951, 1739, 1680, 1627; δ_H 7.14-7.38 (5H, m, ArH), 6.21 (0.5H, q, *J* 7.3 Hz, PhCH(Me)N), 6.08 (0.5H, q, *J* 6.9 Hz, PhCH(Me)N), 4.24 (0.5H, d, *J* 1.5 Hz, one of CH_2=C), 4.18 (1H, bs, one of CH_2=C), 4.04 (0.5H, d, *J* 1.5 Hz, one of CH_2=C), 3.92 (1H, s, MeNC*H*C=CH_2), 3.73 (1.5H, s, CO_2CH_3), 3.71 (1.5H, s, CO_2CH_3), 3.67 (1H, d, MeNCHC=O, partially obscured by signal at 3.71 ppm), 3.01 (0.5H, dd, *J* 6.2, 10.0 Hz, $CHCO_2Me$), 2.95 (0.5H, dd, *J* 5.7, 9.9 Hz, $CHCO_2Me$), 2.61 (1H, m, *exo* MeNCHCH_2), 2.52 (1.5H, s, NCH_3), 2.48 (1.5H, s, NCH_3), 2.39 (0.5H, dd, *J* 10.1, 13.2 Hz, *endo* MeNCHCH_2), 2.27 (0.5H, dd, *J* 9.8, 13.2 Hz, *endo* MeNCHCH_2); *m/z* (relative intensity, %) 314 (M^+, 30), 228 (59), 209 (100), 140 (20), 124 (21), 105 (33) (Found: M^+, 314.1633. $C_{18}H_{22}N_2O_3$ requires *M*, 314.1630).

Methyl 3-(2-bromophenylmethyl)-8-benzyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-exo-6-carboxylate (6c).– To sodium hydride (80% wt. mineral oil dispersion, 63 mg, 2.1 mmol.), washed with dry hexane (5 x 5ml) under nitrogen, was added a solution of **5a**[6] (500 mg, 1.75 mmol) in dry DMF (10 ml). The solution was stirred at room temperature for 0.5 h then a solution of 2-bromobenzyl bromide (480 mg, 1.92 mmol) in dry DMF (2 ml) was added, then the whole stirred at 40°C for 5 h. The DMF was removed under high vacuum, water (10 ml) added to the residue, and organic material extracted with chloroform (3 x 50 ml). The chloroform extracts were combined, washed with water (3 x 50 ml), dried and evaporated in vacuo to give an oil. This was purified by flash column chromatography (ethyl acetate: hexane 1:3) over silica to give **6c** as an oil (170 mg, 21%), ν_{max} (cm^{-1}) 2952, 1738, 1687, 1630; δ_H ($CDCl_3$, 300 MHz) 7.58 (1H, dd, *J* 8, 1 Hz, ArH), 7.29 (6H, m, ArH), 7.15 (1H, dt, *J* 1.5, 7.5 Hz, ArH), 7.03 (1H, dd, *J* 8, 1.5 Hz, ArH), 5.17 (1H, d, *J* 16 Hz, one of $C_6H_4BrCH_2$), 4.87 (1H, d, *J* 16 Hz, one of $C_6H_4BrCH_2$), 4.19 (1H, d, *J* 1 Hz, one of CH_2=C), 4.16 (1H, d, *J* 1 Hz, one of CH_2=C), 4.10 (1H, s, BnNC*H*C=CH_2), 3.89 (1H, d, *J* 14 Hz, one of $PhCH_2N$), 3.78 (1H, d, *J* 14 Hz, one of $PhCH_2N$), 3.86 (1H, d, *J ca.* 8 Hz, partially hidden, BnNC*H*C=O), 3.72 (3H, s, OCH_3), 3.03 (1H, dd, *J* 10, 6 Hz, $CHCO_2Me$), 2.74 (1H, ddd, *J* 13, 8, 6 Hz, *exo*-BnNCHCH_2), 2.43 (1H, dd, *J* 13, 10 Hz, *endo*-BnNCHCH_2); *m/z*, (relative intensity, %) (EI) 365 (30), 363 (30), 171 (34), 169 (35), 91 (100); (CI) (reagent ammonia) 458 (35), 457 (97, $MH^+(^{81}Br)$), 456 (36), 455 (100, $MH^+(^{79}Br)$), 199 (71) (Found: M^+, 454.0904. $C_{23}H_{23}N_2O_3{}^{79}Br$ requires *M*, 454.0892).

Methyl 3-(2-bromophenylmethyl)-8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-exo-6-carboxylate (6d).– To sodium hydride (80% wt. mineral oil dispersion, 38 mg, 1.6 mmol) under nitrogen was added, with stirring, a solution of **5b**[6] (300 mg, 1.4 mmol) in dry DMF (10 ml). The solution was stirred at room temperature for 0.5 h then a solution of 2-bromobenzyl bromide (393 mg, 1.57 mmol) in dry DMF (2 ml) was added, then the whole stirred at 40°C for 3 h. The DMF was removed under high vacuum, water (10 ml) added to the residue and organic material extracted using chloroform (3 x 50 ml). The chloroform extracts were combined, washed with water (3 x 50 ml), dried and evaporated *in vacuo* to give an oil which was purified by flash column chromatography (gradient elution; ethyl acetate-hexane) to give **6d** as an oil (460 mg, 85%), ν_{max} (cm^{-1}) 2951, 1739, 1686, 1630; δ_H ($CDCl_3$, 200 MHz) 7.56 (1H, dd, *J* 7.5, 1 Hz, ArH), 7.25 (1H, dt, *J* 7.5, 1 Hz, ArH), 7.10 (1H, dt, *J* 7.5, 1 Hz, ArH), 6.96 (1H, dd, *J* 7.5, 1 Hz, ArH), 5.12 (1H, d, *J* 15 Hz, one of $C_6H_4BrCH_2$), 4.81 (1H, d, *J* 15 Hz, one of $C_6H_4BrCH_2$), 4.28 (1H, d, *J* 1.5 Hz, one of CH_2=C), 4.17 (1H, d, *J* 1.5 Hz, one of CH_2=C), 4.08 (1H, s, MeNC*H*C=CH_2), 3.79 (1H, d, *J ca.* 8 Hz, MeNC*H*C=O), 3.75 (3H, s, CO_2CH_3), 3.03 (1H, dd, *J* 6, 10 Hz, $CHCO_2Me$), 2.70 (1H, m, *exo*-MeNCHCH_2), 2.55 (3H, s, NCH_3), 2.41 (1H, m, *endo*-MeNCHCH_2); *m/z* (rel. abundance, %) (EI) 213 (66), 137 (59), 106 (58), 91 (62), 82, (100); (CI) (reagent ammonia) 381 (4, MH^+ (^{81}Br)), 379 (4, MH^+ (^{79}Br)), 211 (33), 138 (45) (Found: M^+, 378.3530. $C_{17}H_{19}N_2O_3{}^{79}Br$ requires *M*, 378.3536).

Methyl 3-(2-bromo-6-methoxyphenylmethyl)-8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]-octane-6-exo-6-carboxylate (6e).– To a stirred solution of **5b**[6] (1.16 g, 7.62 mmol) in DMF (100 ml)

at 0°C was added sodium hydride (60% oil dispersion, 312 mg, 7.80 mmol). The mixture was stirred for 30 min, then 2-bromo-6-methoxybenzyl bromide (2.20 g, 7.86 mmol) in DMF (20 ml) was added dropwise. After stirring at 0°C for a further 2 h, then at room temperature overnight, the solution was poured into water (300 ml) and organic material extracted with dichloromethane (4x250 ml). The dried extract was evaporated and the residue recrystallised from ethyl acetate-petrol to give **6e** as a cream coloured solid (2.36 g, 76%), mp 126-128°C, υ_{max} (cm^{-1}) 2951, 1738, 1687, 1630, 1589, 1572; δ_H ($CDCl_3$) 7.18 (1H, dd, *J* 1.5, 8.1 Hz, ArH), 7.10 (1H, t, *J* 8.0 Hz, ArH), 6.82 (1H, dd, *J* 1.5, 7.9 Hz, ArH), 5.59 (1H, d, *J* 15.3 Hz, one of $ArCH_2N$), 4.76 (1H, d, *J* 15.2 Hz, one of $ArCH_2N$), 4.40 (1H, d, *J* 1.7 Hz, one of CH_2=C), 4.21 (1H, d, *J* 1.7 Hz, one of CH_2=C), 3.96 (1H, s, MeNC*H*C=CH_2), 3.82 (3H, s, CH_3OAr), 3.71 (3H, s, CO_2CH_3) 3.69 (1H, d, MeNCHC=O, partially obscured by signal at 3.71 ppm), 2.95 (1H, dd, *J* 6.3, 9.8 Hz, $CHCO_2Me$), 2.56 (1H, m, *exo* MeNCHCH_2), 2.47 (3H, s, NCH_3), 2.40 (1H, m, *endo* MeNCHCH_2); δ_C ($CDCl_3$, 50 MHz) 175.73, 171.32, 160.97, 144.03, 131.37, 127.68, 127.20, 125.90, 112.03, 95.12, 69.32, 68.24, 57.93, 54.46, 49.94, 41.67, 37.42, 35.39; *m/z* (relative intensity, %) (CI) 411 (14, MH^+ (^{81}Br)), 409 (14, MH^+ (^{79}Br)), 106 (35), 55 (41), 44 (42), 32 (67), 30 (100) (Anal.Calcd for $C_{18}H_{21}N_2O_4Br$: C, 52.8; H, 5.1; N, 6.8; Br, 19.6. Found: C, 53.0; H, 5.4; N, 6.9; Br, 19.3).

Methyl 5,7,8,9,10,11-hexahydro-13-benzyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylate (7a).– To a solution of **6c** (157 mg, 0.35 mmol) and triphenylphosphine (36 mg, 0.138 mmol) in dry THF (10 ml) was added palladium (II) acetate (8 mg, 0.035 mmol) and silver carbonate (193 mg, 0.69 mmol). This mixture was refluxed with stirring for 8 h. The solution was filtered and the eluate concentrated *in vacuo* to give an oil. The oil was taken up in ether (15 ml), washed with saturated aqueous ammonium chloride (10 ml), dried, filtered and evaporated *in vacuo* to give an oil, purified by flash column chromatography (ethyl acetate-hexane, 1:3) to give some unchanged starting material (30 mg) and **7a** as an oil (80 mg, 0.21 mmol, 62%), ν_{max} (cm^{-1}) 2953, 1738, 1683, 1647; δ_H ($CDCl_3$, 300 MHz) 7.2 - 6.9 (9H, m, ArH), 5.01 (1H, s, ArCH=C), 5.06 (1H, d, *J* 13 Hz, one of $ArCH_2N$), 4.98 (1H, d, *J* 14 Hz, one of $ArCH_2N$), 4.15 (1H, s, BnNC*H*C=CH), 3.8 - 3.6 (3H, m, $PhCH_2N$ and BnNCHC=O), 3.70 (3H, s, CO_2CH_3), 3.02 (1H, dd, *J* 10, 5 Hz, $CHCO_2Me$), 2.65 (1H, ddd, *J* 14, 9, 5 Hz, *exo* BnNCHCH_2), 2.31 (1H, dd, *J* 14, 10 Hz, *endo* BnNCHCH_2); δ_C ($CDCl_3$, 50 MHz) 175.24, 171.33, 139.52, 137.61, 132.18, 130.47, 130.36, 130.29, 129.84, 129.38, 129.15, 127.93, 126.89, 106.97, 66.37, 64.87, 54.51, 50.65, 45.51, 35.14; *m/z* (rel. abundance, %) (EI) 374 (25, M^+), 289 (40), 288 (93), 198 (31), 197 (88), 169 (37), 168 (33), 91 (100); (CI) (reagent ammonia) 376 (30), 375 (100), 91 (28).

Methyl 5,7,8,9,10,11-hexahydro-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylate (7b).– To a solution of **6d** (132 mg, 0.35 mmol) and triphenylphosphine (36 mg, 0.14 mmol) in dry THF (10 ml) was added palladium (II) acetate (16 mg, 0.07 mmol) and silver carbonate (193 mg, 0.7 mmol). This mixture was refluxed with stirring for 4 h. The solution was filtered and the eluate concentrated *in vacuo* to give an oil which was taken up in ether (15 ml) and, after

washing with saturated aqueous ammonium chloride (10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil, purified by flash column chromatography (ethyl acetate: hexane 1:1) to give **7b** as an oil (84 mg, 76%), ν_{max} (cm^{-1}) 2952, 1737, 1682, 1641; δ_H ($CDCl_3$, 300 MHz) 7.15 (2H, m, ArH), 7.08 (1H, d, *J* 7.5 Hz, ArH), 6.98 (1H, dd, *J* 1.5, 7.5 Hz, ArH), 5.65 (1H, s, ArCH=C), 5.02 (1H, d, *J* 17 Hz, one of $ArCH_2N$), 4.92 (1H, d, *J* 17 Hz, one of $ArCH_2N$), 4.12 (1H, s, MeNC*H*C=CH), 3.75 (3H, s, CO_2CH_3), 3.68 (1H, d, *J* 7 Hz, MeNCHC=O), 3.05 (1H, dd, *J* 10, 5.5 Hz, $CHCO_2Me$), 2.55 (1H, ddd, *J* 14, 7, 5.5 Hz, *exo* MeNCHCH_2), 2.45 (3H, s, NCH_3), 2.28 (1H, dd, *J* 14, 10 Hz, *endo* MeNCHCH_2); δ_C ($CDCl_3$, 50 MHz) 175.30, 171.17, 137.56, 132.12, 130.67, 130.24, 129.80, 129.71, 129.11, 127.88, 126.83, 106.93, 68.11, 67.28, 54.63, 50.89, 45.39, 37.44, 35.39; *m/z* (rel. abundance, %) (EI) 299 (20), 298 (11, M^+), 213 (36), 212 (97), 197 (32), 55 (100); (CI) 299 (100, MH^+).

Methyl 5,7,8,9,10,11-hexahydro-4-methoxy-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylate (7c).– The ester (**6e**) (2.35 g, 5.75 mmol), triphenylphosphine (705 mg, 2.69 mmol), silver carbonate (3.20 g, 11.6 mmol) and palladium (II) acetate (259 mg, 1.15 mmol) were refluxed in THF (250 ml) for 48 h. The solution was then filtered through celite, the solvent evaporated, then the resulting brown oil purified by column chromatography (ethyl acetate-hexane, 3:2) to give **7c** as a pale yellow foam (1.33 g, 71%), υ_{max} (cm^{-1}) 2952, 1737, 1682, 1647, 1601, 1581; δ_H ($CDCl_3$, 300 MHz) 7.15 (1H, t, *J* 7.7 Hz, ArH), 6.70 (1H, d, *J* 8.4 Hz, ArH), 6.61 (1H, d, *J* 7.7Hz, ArH), 5.60 (1H, s, ArCH=C), 4.90 (2H, q, *J* 20.0 Hz, $ArCH_2N$), 4.12 (1H, s, MeNC*H*C=CH), 3.82 (3H, s, $ArOCH_3$), 3.77 (3H, s, CO_2CH_3), 3.75 (1H, d, *J* 6.1 Hz, MeNCHC=O, partially obscured by signal at 3.77 ppm), 3.06 (1H, dd, *J* 5.5, 9.5 Hz, $CHCO_2Me$), 2.67 (1H, m, *exo* MeNCHCH_2), 2.49 (3H, s, NCH_3), 2.34 (1H, dd, *J* 10.0, 13.3 Hz, *endo* MeNCHCH_2); *m/z* (relative intensity, %) (EI) 328 (M^+, 13), 242 (100), 227 (15), 99 (15) (Found: M^+, 328.1436. $C_{18}H_{20}N_2O_4$ requires *M*, 328.1423).

1-(5,7,8,9,10,11-Hexahydro-4-methoxy-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinolin-10-yl)pentan-1-one, (8a)– To a stirred solution of **7c** (110 mg, 0.34 mmol) in THF (25 ml) at -78°C was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.22 ml, 0.36 mmol). The solution was stirred for 30 min, then chlorotrimethylsilane (39 mg, 0.36 mmol, 0.046 ml) was added, and stirring continued at -78°C for 30 min. The solvent was evaporated and the residue extracted from water (50 ml) into dichloromethane (3x50 ml). The combined organic extracts were dried, concentrated and the residue purified by column chromatography (ethyl acetate) over silica to give **8a** as a colourless oil (26 mg, 22%) υ_{max} (cm^{-1}) 2956, 1683, 1647, 1601, 1580; δ_H ($CDCl_3$, 300 MHz) 7.15 (1H, t, *J* 7.7 Hz, ArH), 6.70 (1H, d, *J* 8.0 Hz, ArH), 6.60 (1H, d, *J* 8.0 Hz, ArH), 5.52 (1H, s, ArCH=C), 4.92 (2H, s, $ArCH_2N$), 4.04 (1H, s, MeNC*H*C=CH), 3.82 (3H, s, $ArOCH_3$), 3.72 (1H, d, *J* 8.4 Hz, MeNCHC=O), 3.10 (1H, dd, *J* 6.8, 9.7Hz, CHCO-*n*-Bu), 2.55 (1H, m, *exo* MeNCHCH_2), 2.49 (3H, s, NCH_3), 2.40 (1H, m, *endo* MeNCHCH_2), 1.65 (2H, m, $COCH_2$), 1.35 (4H, m, $COCH_2(CH_2)_2Me$), 0.95 (3H, t, *J* 8.4 Hz, $CO(CH_2)_3CH_3$); *m/z* (relative intensity, %) (FAB) 355 (MH^+, 34), 325 (48), 242 (75), 227 (21), 156 (68) (Found: M^+, 355.2016. $C_{21}H_{26}N_2O_3$ requires *M*, 355.2022), further elution gave recovered starting material (32 mg, 29%).

1-(5,7,8,9,10,11-Hexahydro-4-methoxy-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-yl)-2,2-dimethylpropan-1-one (8b).– To a stirred solution of **7c** (31 mg, 0.095 mmol) in THF (5 ml) at -78°C was added dropwise *t*-butyllithium (1.7 M solution in pentane, 0.059 ml, 0.10 mmol). The solution was stirred for 15 min then chlorotrimethylsilane (13.0 mg, 0.12 mmol, 0.016 ml) was added and stirring continued at -78°C for 30 min. The solvent was evaporated and the residue extracted from water (50 ml) into dichloromethane (3x50 ml). The combined organic extracts were dried and concentrated and the residue purified by column chromatography (ethyl acetate) to give **8b** as a colourless oil (7 mg, 21%), υ_{max} (cm^{-1}) 2956, 1682, 1647, 1601, 1581; δ_H 7.15 (1H, t, *J* 7.6 Hz ArH), 6.70 (1H, d, *J* 8.3 Hz, ArH), 6.60 (1H, d, *J* 7.6 Hz, ArH), 5.44 (1H, s, ArCH=C), 4.93 (2H, d, J 26.0 Hz, $ArCH_2N$), 3.83 (3H, s, $ArOCH_3$), 3.75 (1H, d, *J* 6.2 Hz, MeNCHC=O), 3.71 (1H, s, MeNC*H*C=CH), 3.50 (1H, dd, *J* 6.9, 9.2 Hz, CHCO-*t*-Bu), 2.49 (3H, s, NCH_3), 2.17-2.47 (2H, m, MeNCHCH_2), 1.19 (9H, s, $C(CH_3)_3$); *m/z* (relative intensity, %) 354 (M^+, 7), 242 (100), 227 (34) (Found: M^+, 354.1940. $C_{21}H_{26}N_2O_3$ requires *M*, 354.1943), further elution gave recovered starting material (4 mg, 13%).

1-(5,7,8,9,10,11-Hexahydro-4-methoxy-5-deuterio-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]-isoquinolin-10-yl)pentan-1-one (8c).– To a stirred solution of **7c** (44.0 mg, 0.13 mmol) in THF (5 ml) at -78°C was added dropwise *n*-butyllithium (1.6 M solution in hexane, 1.00 ml, 0.63 mmol): a deep blue colur developed; D_2O (1.0 ml) was added immediately then the solution was warmed to room temperature and the solvent evaporated. The residue was extracted from water (50 ml) into dichloromethane (3x50 ml), the combined organic extracts dried and concentrated, and the residue purified by column chromatography (ethyl acetate-hexane, 3:2) to give **8c** as a colourless oil (10.5 mg, 22%), δ_H 7.15 (1H, t, *J* 7.7 Hz ArH), 6.70 (1H, d, *J* 8.3 Hz, ArH), 6.60 (1H, d, *J* 7.3 Hz, ArH), 5.52 (1H, s, ArCH=C), 4.87 (1H, s, ArCHDN), 4.01 (1H, s, MeNC*H*C=CH), 3.82 (3H, s, $ArOCH_3$), 3.69 (1H, d, *J* 6.4 Hz, MeNCHC=O), 3.09 (1H, dd, *J* 6.7, 9.8 Hz, CHCO-*n*-Bu), 2.52 (1H, m, *exo* MeNCHCH_2), 2.45 (3H, s, NCH_3), 2.43 (1H, m, *endo* MeNCHCH_2), 1.61 (2H, m, $COCH_2$), 1.26 (4H, m, $COCH_2(CH_2)_2Me$), 0.91 (3H, t, *J* 7.2 Hz, $CO(CH_2)_3CH_3$); *m/z* (relative intensity, %) 355 (M^+, 1), 243 (19), 28 (100); (CI) 356 (MH^+, 57), 243 (8), 130 (23), 32 (100) (Found: M^+ 355.2009. $C_{21}H_{25}N_2O_3D$ requires *M*, 355.2006).

1-(5,7,8,9,10,11-Hexahydro-4-methoxy-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinolin-10-yl)methanol (10).- To a stirred solution of **7c** (90 mg, 0.27 mmol) in THF at -5°C was added dropwise lithium aluminium hydride (1.0 M solution in THF, 0.18 mmol, 0.18 ml). The solution was stirred at -5°C for 35 min, then water (0.5 ml) was added cautiously. The mixture was then poured into water (25 ml) and extracted with dichloromethane (3x25 ml), the combined organic extracts dried and concentrated, and the resultant pale brown oil purified by column chromatography (ethyl acetate-methanol, 20:1) to give **10** as a pale yellow oil (54 mg, 66%), υ_{max} (cm^{-1}) 3366, 2939, 1679, 1642; δ_H ($CDCl_3$, 300 MHz) 7.13 (1H, t, *J* 7.7 Hz, ArH), 6.69 (1H, d, *J* 8.5 Hz, ArH), 6.59 (1H, d, *J* 7.7 Hz, ArH), 5.52 (1H, s, ArCH=C), 4.90 (2H, q, *J* 29.1 Hz, $ArCH_2N$), 3.82 (3H, s,

$ArOCH_3$), 3.55-3.85 (4H, m, MeNCHC=O, MeNC*H*C=CH, and CH_2OH), 2.47 (3H, s, NCH_3), 2.1-2.45 (3H, m, $CHCH_2OH$ and $MeNCHCH_2$); *m/z* (relative intensity, %) 300 (M^+, 4), 259 (11), 243 (100), 165 (41), 105 (19), 45 (56) (Found: M^+, 300.1474. $C_{16}H_{18}N_2O_3$ requires *M*, 300.1473).

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