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Synthesis of Damirones A and B from a Quinoline

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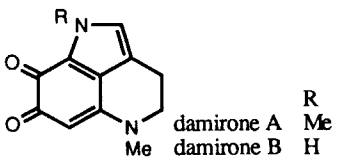
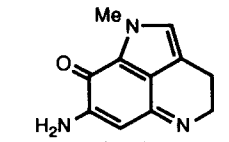
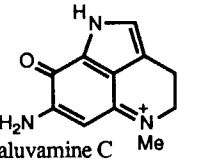
Abstract: 6,7-Dimethoxy-4-methylquinoline has been transformed in seven steps into the *ortho*-quinone, 1,3,4,5-tetrahydro-5-methyl-1-(4-methylphenylsulphonyl)-pyrrolo[4,3,2-*de*]quinoline-7,8-dione, **7**, an intermediate which has previously beeen converted into the marine alkaloids damirone A and damirone B.



	R
damirone A	Me
damirone B	H



makaluvamine A



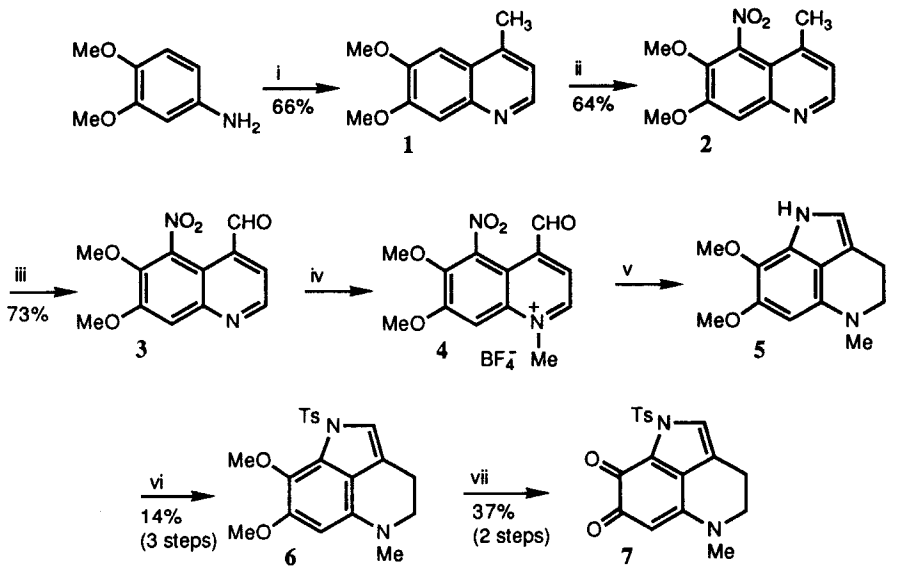
makaluvamine C

The first natural 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline was the toad poison, dehydrobufotenine.[1] More recently, several marine alkaloids[2] such as the tricyclic batzellines,[3] isobatzellines,[4] and damirones,[5] and more complex molecules such as the discorhabdines,[6] prianosines,[7] wakayin,[8] and the makaluvamines[9] have been described which are also based on a 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus. Many[10] possess potentially valuable biological activity – the makaluvamines and wakayin, for example, exhibit potent *in vitro* cytotoxicity against human colon tumour cell line HCT116; they are topoisomerase II inhibitors.[8,9]

In all previous synthetic work relating to these natural products, except our own,[11] including preparations of the unsubstituted[12,13] and 1-methyl-[14] tricyclic system, of *O*-methylnordehydrobufotenine,[15] of dehydro-bufotenine itself[16], and then later of batzelline C and isobatzelline C,[17,18] discorhabdin C,[18,19] damirones A and B,[20] and makaluvamines A-D,[21] the tricyclic heterocycle has been constructed *from an indole*, *i.e.* by forming the six-membered nitrogen-containing ring as a late step, by cyclisation either of a 4-aminoindole carrying a two-carbon chain at its C-3,[12-18,21] or of a tryptamine quinone.[19,20,22] Our approach[11] to these systems takes a quinoline as starting point: we show here how 6,7-dimethoxy-4-methylquinoline can be converted into the damirones.

6,7-Dimethoxy-4-methylquinoline,[23] **1**, was prepared, in an adaptation of a reported method,[24] by the reaction of 3,4-dimethoxyaniline with methyl vinyl ketone in the presence of ferric chloride. Nitration of **1**

under normal conditions produced the 5,8-disubstitution product; however, by conducting the nitration in fuming nitric acid, and at low temperature, regioselective mono-nitration could be achieved, giving **2**.



Reagents: i, CH_2=CHCO.Me/$FeCl_3$/AcOH/reflux; ii, f. HNO_3/-50 °C to -40 °C; iii, I_2, *t*-BuI, $FeCl_2$, TFA, DMSO, 80 °C; iv, Me_3O^+ F_4B^-/CH_2Cl_2/20 °C; v, 80x$NaBH_4$/13x$NiCl_2.6H_2O$/MeOH/initially at 20 °C (no external cooling); vi, TsCl/NaOH/CH_2Cl_2/Bu_4N^+ HSO_4^-/20 °C; vii, BBr_3/CH_2Cl_2/-78 °C → -20 °C then air.

6,7-Dimethoxy-4-methyl-5-nitroquinoline, **2**, was oxidised to the 4-aldehyde, **3**[25] using Vismara's method.[26] In our model work,[11] at the comparable stage and before reduction of the pyridine ring, we protected the aldehyde as an acetal, expecting that this functional group would not survive the conditions required for pyridine ring reduction. In the present instance, however, this diversion proved to be unnecessary.

Quaternisation of quinoline-aldehyde, **3**, with iodomethane proved problematical, no doubt because the electron-withdrawing aldehyde and nitro groups on the pyridine and benzene rings respectively, reduce the nucleophilicity of the ring nitrogen; however, exposure to trimethyloxonium tetrafluoroborate, at room temperature, led to the formation of a precipitate of salt, **4**, which was utilised without purification. Treatment of the salt, **4**, with the combination $NaBH_4/NiCl_2$, led directly to an indole, **5**,[27] which was converted into its *N*-tosyl derivative, **6**.[28]

The completion of the synthesis of the damirones required an oxidation to quinone oxidation level. This was achieved by demethylation using BBr_3, then aerial oxidation of the presumed diphenol intermediate giving quinone, **7**.[29] Cava has already shown[20] that the tosyl group in *ortho*-quinone **7** can be hydrolysed, and the resulting product *N*-methylated to produce the two damirones.

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25 Yellow solid, δ_H ($CDCl_3$) 10.26 (1H, s, CH=O), 9.09 (1H, d, J 4.4 Hz, H-2), 7.77 (2H, s & d, H-8 & H-3), 4.16 & 4.14 (2x3H, 2xs, 2xCH_3O) (Found 262.0589. $C_{12}H_{10}N_2O_5$ requires 262.0590).

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27 Oil, δ_H ($CDCl_3$) 7.89 (1H, bs, NH), 6.69 (1H, bs, H-2), 6.03 (1H, s, H-6), 3.96 & 3.94 (2x3H, 2xs, 2xCH_3O), 3.30 (2H, t, J 5.3 Hz, H_2-4), 3.07 (2H, t, J 5.3 Hz, H_2-3), 2.97 (3H, s, CH_3N) (Found 232.1212. $C_{13}H_{16}N_2O_2$ requires 232.1212).

28 Oil, δ_H ($CDCl_3$) 7.89 (2H, d, J 8.4 Hz, ArH), 7.24 (2H, d, J 8.4 Hz, ArH), 7.21 (1H, s, H-2), 6.12 (1H, s, H-6), 3.90 & 3.86 (2x3H, 2xs, 2xCH_3O), 3.23 (2H, t, J 5.9 Hz, H_2-4), 2.98 (2H, t, J 5.9 Hz, H_2-3), 2.92 (3H, s, CH_3N), 2.37 (2H, s, $ArCH_3$) (Found 386.1307. $C_{20}H_{22}N_2O_4S$ requires 386.1300).

29 Red solid, δ_H ($CDCl_3$) 8.14 (2H, d, J 8.4 Hz, ArH), 7.56 (1H, s, H-2), 7.35 (2H, d, J 8.4 Hz, ArH), 5.34 (1H, s, H-6), 3.61 (2H, t, J 6.7 Hz, H_2-4), 3.08 (3H, s, CH_3N), 2.94 (2H, t, J 6.7 Hz, H_2-3), 2.45 (3H, s, CH_3Ar) (Found 357.0927. $C_{18}H_{17}N_2O_4S$ requires 357.0909).

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