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Synthesis of 6-Chloro-1,3,4,5-tetrahydro-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline from a Quinoline; Formal Total Syntheses of Batzelline C, Isobatzelline C, Discorhabdin C and Makaluvamine D

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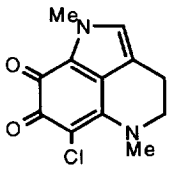
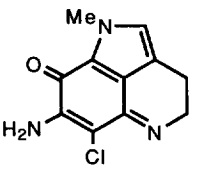
This Letter is dedicated to the memory of Professor Félix Serratosa (1925-1995)

Abstract: 6,7-Dimethoxy-4-methyl-5-nitroquinoline has been transformed in eight steps into 6-chloro-1,3,4,5-tetrahydro-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline, **7** (previously converted into the marine alkaloids batzelline C and isobatzelline C), and in five steps into 1*H*-3,4-dihydro-7-methoxy-pyrrrolo[4,3,2-*de*]quinolin-8-one, **8** (previously converted into discorhabdin C and makaluvamine D).


batzelline C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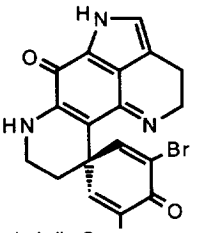
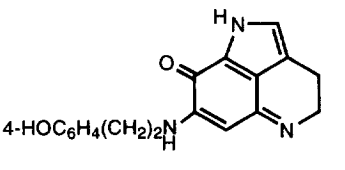
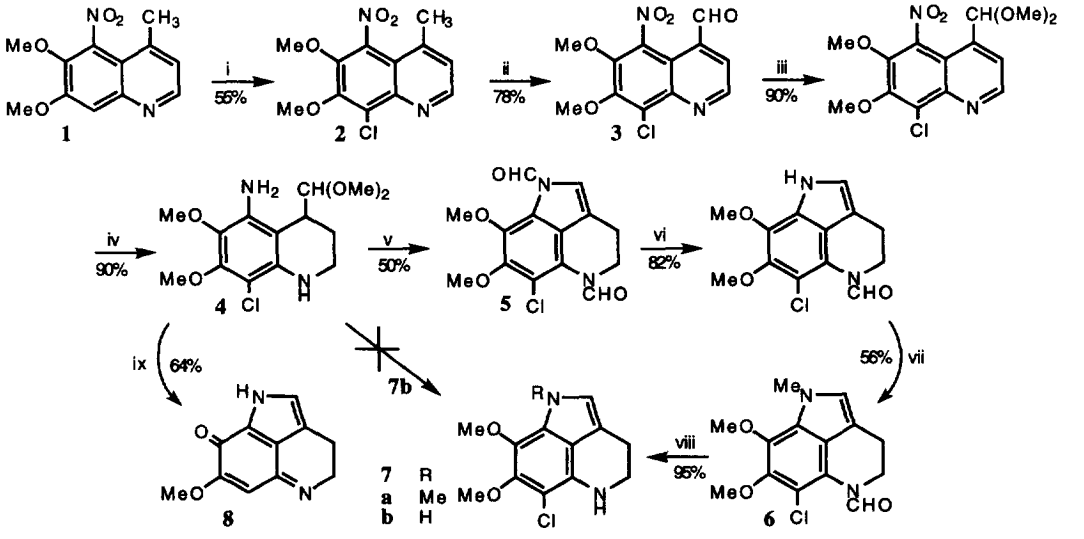

discorhabdin C


makaluvamine D

Several marine alkaloids[1] such as the tricyclic batzellines,[2] isobatzellines,[3] and damirones,[4] and more complex molecules such as the discorhabdins,[5] prianosins,[6] wakayin,[7] and the makaluvamines[8] share a common tricyclic nucleus – a 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline. Many[9] 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 most synthetic work relating to these natural products, except our own,[10] and recent Polish model work,[11] including early work relating to the toad-poison, dehydrobufotenine,[12] then later, syntheses of batzelline C and isobatzelline C,[13,14a,15] discorhabdin C,[14,16,17] damirones A and B,[15,18,19] makaluvamine D,[17,20] and makaluvamines A-D,[21] the tricyclic heterocycle was constructed *from an indole*, *i.e.* by forming the six-membered nitrogen-containing ring as a late step. Our approach[10] to these systems takes a quinoline as starting point.

6,7-Dimethoxy-4-methyl-5-nitroquinoline,[10] **1**, underwent chlorination at C-8 giving **2**. Vismara oxidation[22] to aldehyde **3**,[23] then acetal protection and reduction of both the nitro group and the pyridine ring produced **4**.[24] Treatment of **4** with HCO_2H/Ac_2O cleanly brought about double *N*-formylation, acetal deprotection, and pyrrole ring closure giving tricyclic bisformamide **5**.[25] Mild base selectively removed the pyrrole-*N*-formyl group to allow pyrrole-*N*-methylation and formation of **6**, requiring simply alkaline hydrolysis to produce **7a**[26] which has been transformed[14a] by Yamamura *et al.* in two steps into batzelline C and in two steps into isobatzelline C.

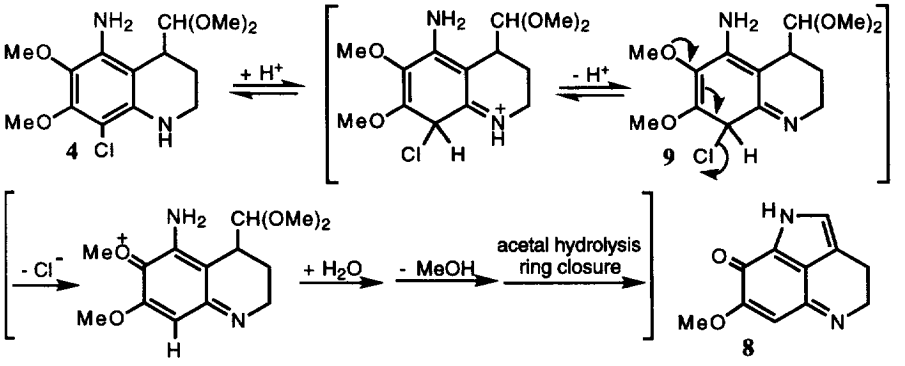


Reagents: i, NCS, DMF, 60°C; ii, I_2, *t*-BuI, $FeCl_2$, TFA, DMSO, 80°C; iii, MeOH, HCl, reflux; iv, 32x$NaBH_4$, 6x$NiCl_2.6H_2O$, MeOH, 0°C; v, HCO_2H, Ac_2O, rt; vi, aq. NaOH, MeOH, CH_2Cl_2, rt; vii, MeI, NaH, THF, rt; viii, aq. 2N NaOH, reflux; ix, aq. 1N HCl, THF, 40°C.

Interestingly, and serendipitously, on attempting the obvious direct transformation of **4** into **7b**, we found that mild treatment of amine-acetal **4** with hydrochloric acid produced quinone-imine **8**[27] in 64% yield. This substance has been transformed in two steps into discorhabdin C[14a] and in one step into makaluvamine D.[20] The present route to a substance, **8**, with the biologically important iminoquinone pharmacaphore[14b,28] is both short and efficient.

As an explanation for the synthetically valuable transformation of **4** into **8**, with loss of the chlorine substituent and an increase in ring oxidation level, we propose that *C*-protonation of the very electron-rich benzene ring,[29] followed by *N*-deprotonation, produces an intermediate, **9**, from which chloride loss is

facilitated, subsequent water addition then methanol loss producing[30] the observed product (Scheme 1).[31] Thus, in the transformation of **4** into **5** we believe that initial formylation at both nitrogen sites reduces the propensity for benzene ring protonation and allows the desired pyrrole closure, without loss of chlorine.



Scheme 1

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23 Solid, m.p. 132-134°C, δ_H ($CDCl_3$) 10.20 (1H, s, CHO), 9.19 (1H, d, J 4.2, ArH), 7.84 (1H, d, J 4.2, ArH), 4.15, 4.10 (2x3H, 2xs, 2xOCH_3); Found, M, 296.0208. $C_{12}H_9{}^{35}ClN_2O_5$ requires 296.0200.

24 Oil, δ_H ($CDCl_3$) 4.41 (1H, d, J 8.7, $CH(OMe)_2$) 4.38 (3H, bs, NH & NH_2) 3.87, 3.76, 3.39, 3.32 (4x3H, 4xs, 4xOCH_3), 3.35 (2H, m, H-4, H-2), 3.19 (1H, m, H-2), 2.10 (1H, m, H-3), 1.55 (1H, m, H-3); Found, M, 316.1200. $C_{14}H_{21}{}^{35}ClN_2O_4$ requires 316.1190.

25 Solid, m.p. 80-81°C, δ_H ($CDCl_3$) 9.69, 9.03 (2x1H, 2xs, 2NCHO), 7.54 (1H, s, H-2), 4.08 (2H, t, J 5.6, H_2-4) , 4.05, 3.95 (2x3H, 2xs, 2xOCH_3), 2.91 (2H, t, J 5.6, H_2-3); Found 308.0569. $C_{14}H_{13}{}^{35}ClN_2O_4$ requires 308.0564.

26 Gum, δ_H ($CDCl_3$) 6.51 (1H, s, H-2), 4.26 (1H, bs, NH), 3.91 (6H, s, 2xOCH_3), 3.48 (2H, t, J 5.8, H_2-4), 2.95 (2H, t, J 5.8, H_2-3); Found 266.0817. $C_{13}H_{15}{}^{35}ClN_2O_2$ requires 266.0822.

27 Compound **8** had spectroscopic properties identical with those previously described.[14b]

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29 One resonance contributor only shown.

30 An alternative is *O*-demethylation *via* chloride attack at the methyl group.

31 The timing of acetal hydrolysis and pyrrole ring closure might be other than that shown.

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