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A Simple and Efficient Synthetic Route to Benzo[c]phenanthridines

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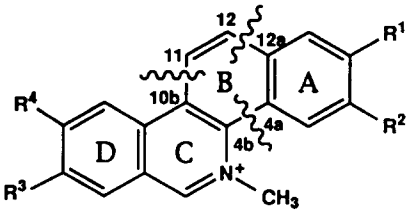
Abstract: The benzo[c]phenanthridine nucleus has been prepared in an overall yield of 52-58% in five stages. Synthetic route employs as key steps the intramolecular cyclisation of vinyl alcohols followed by a novel one pot double oxidation using iodine in ethanol.

Recently, the isoquinoline alkaloid fagaronine **1** (R^1=OH, R^2=R^3=R^4=OCH_3) has been shown to influence the cellular differentiation on human leukaemia K562[1] cells and to inhibit topoisomerases I and II.[2] This alkaloid has been chosen as a reference compound for the assessment of HIV-RT inhibition by natural product extracts[3]. As a part of our synthetic program for the preparation of benzo[c]phenanthridines with potential pharmacological activities, an area which has attracted considerable attention from synthetic chemists[4], we now wish to present an expeditious access to the benzo[c]phenanthridine nucleus.

Most of the methods which have been used for the synthesis of benzo[c]phenanthridines can be described by the single bond-forming strategies summarized in figure 1, where the B ring is built through the formation of bonds between carbons 4a and 4b, 10b and 11 or 12 and 12a[5].

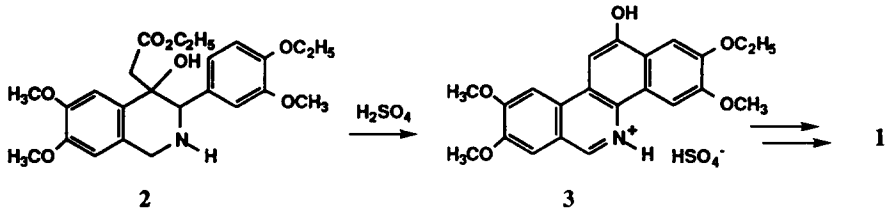


1

Figure 1

Following our recent synthesis of fagaronine **1**[6], we focused our efforts on reducing the number of steps involved in the preparation of benzo[c]phenanthridines.

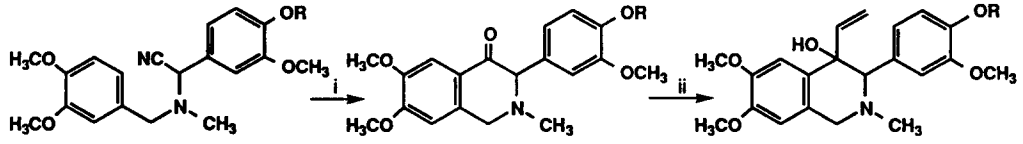
In our previous method, the β-hydroxyester 2 was cyclised to the fully aromatic benzo[c]phenanthridine 3 with a hydroxyl group at the C-12 position on the B ring (Scheme 1), which has to be removed by two subsequent steps. Looking for a more direct synthesis, we reasoned that lowering the oxidation state of the two-carbon fragment originating from the addition of organometallic reagents to aminoketones would eliminate these two extra steps and that the vinylic equivalent of 2, namely 6, would serve as an appropriate candidate.



2 3

Scheme 1

The viability of this method was first explored by performing Grignard reactions on secondary aminoketones. In all cases, no vinyl alcohols could be detected after mild acidic hydrolysis of reaction mixtures. To avoid this problem, we carried out an identical reaction on a tertiary aminoketone, obtained in very high yield by cyclisation of the aminonitrile 4[7] in anhydrous hydrofluoric acid[8] (Scheme 2). In this case, the Grignard addition of vinylmagnesium bromide to the aminoketone 5 proceeded as expected, furnishing the desired vinyl alcohol 6[9] (Scheme 2). An advantage of choosing this particular precursor was that the tertiary amine could be conveniently handled as its free base, unlike its secondary amine equivalent which spontaneously oxidized in air to a substituted isoquinolol which was of no further synthetic value.



4a R=CH_3 **5a** 95% **6a** 86%

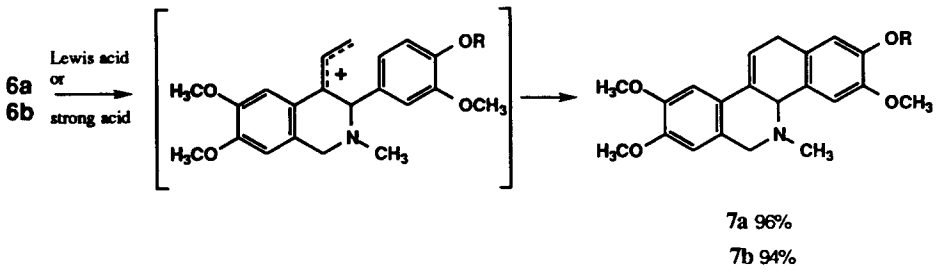
4b R=C_2H_5 **5b** 96% **6b** 84%

(i) HF; (ii) CH_2=MgBr, THF/CH_2Cl_2

Scheme 2

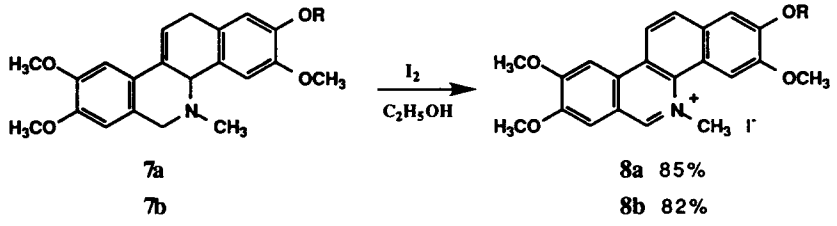
Several unsuccessful attempts were made to cyclise the vinyl precursor, using classical methods for cation generation from vinylic or benzylic alcohols in strong protic or Lewis acid media[10]. In trifluoroacetic acid, the starting material was recovered unchanged, whereas in the presence of $TiCl_4$ at low temperature (-78°C), the starting material decomposed. In the presence of $SnCl_4$ however, the desired product 7 was recovered but in low yield (49%). Prompted by the use of polar aprotic solvents in cationic cyclisations[11], optimal conditions were found by stirring a nitromethane solution of the vinyl alcohol 6 in presence of methanesulphonic acid. The reaction proceeded smoothly and rapidly, presumably via the stabilized tertiary

α-vinyl cation (Scheme 3), delocalized over three carbon atoms, leading to the desired benzo[c]phenanthridine precursor 7[12] in high yield (94-96%) and as a single product.



Scheme 3

By incorporating N-methyl group at the beginning of the synthetic sequence, quaternary benzo[c]phenanthridine target molecules 8 were directly obtained by iodine oxidation of the B and C rings of 7 in boiling ethanol[13]. This simultaneous oxidation of both B and C rings has never been reported on this heterocyclic system (Scheme 4). An advantage over existing methods is the ease of formation of quaternary alkaloids, as the need for a final N-methylation step is circumvented.



Scheme 4

In conclusion, this method provided a relatively straightforward and high yielding route to benzo[c]phenanthridine alkaloids. From the present reaction sequence, using readily available materials, quaternary alkaloids were isolated with overall yield of 58% (R=CH_3), 52% (R=C_2H_5). This current development represents to date one of the most effective totally synthetic route to these species . We are currently engaged in the application of this strategy towards the synthesis of other derivatives.

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9. Selected spectral data: **6a**, m.p.152-153°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 2.70 (broad s, 1H), 3.46 (s, 1H), 3.58 (AB system, 1H, J=15 Hz), 3.82 (s, 3H), 3.83 (AB system, 1H, J=15 Hz), 3.84 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 5.10 (dd, 1H, J= 2 and 10 Hz), 5.19 (dd, 1H, J=2 and 18 Hz), 5.91 (dd, 1H, J=11 and 18 Hz), 6.56 (s, 1H), 6.77 (m, 2H), 6.92 (m, 2H).
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12. Selected spectral data: **7b**, m.p.166-167°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.49 (t, 3H, J=7 Hz), 2.01 (s, 3H), 3.55 (m, 2H), 3.79 (AB system, 1H, J=17 Hz), 3.89 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.10 (q, 2H, J=7 Hz), 4.60 (AB system, 1H, J=17 Hz), 4.63 (m, 1H), 6.51 (m, 1H), 6.56 (s, 1H), 6.65 (s, 1H), 7.15 (s, 1H), 7.21 (s, 1H).
13. The physical and spectral characteristics of **8b** were identical to those of the benzo[c]phenanthridine prepared following the method described in reference 6.

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