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A new route to 3-(2-vinylphenyl)-2-methyl-2*H*-isoquinolin-1-ones and benzo[*c*]phenanthridines: total synthesis of fagaronine

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Abstract—Treatment of *N*-carbethoxy-1-benzylideneisoquinolines with LDA gives *N*-ethoxycarbonyl-1-amino-1-(2-vinylphenyl)-2-phenylethylenes, which can be transformed into 3-(2-vinylphenyl)-2-methyl-2*H*-isoquinolin-1-ones by Bischler–Napieralski reactions, and thence into benzo[*c*]phenanthridin-6-ones. The use of this route for a new total synthesis of fagaronine is described.

Benzo[*c*]phenanthridines are attractive synthetic targets because of their widespread occurrence in nature and broad range of biological activities.[1,2] In the cases of nitidine (**6a**) and other 8,9-disubstituted planar benzophenanthridinium salts such as fagaronine (**6b**), antitumour activity in animal models has been traced to inhibition of DNA topoisomerase, an action that has been attributed to their conformationally rigid embedded 2-phenylnaphthalene subunit.[3,4] The toxicity of the most active members of these groups, and the consequent desire to study structure–activity relationships, has led to a search for new synthetic methods that would make it easy to prepare appropriate series of compounds.[5] Among the many methods developed for this aim, those in which the key step is the annelation of a 3-(2-vinylphenyl)isoquinolin-1-one[6] are specially interesting because compound **3c** has a strong antitumour activity[7] and can be considered as a bioisostere of the benzo[*c*]phenanthridine chelerythrine (**6c**). However, most of the few reported preparations of 3-vinylphenylisoquinolinones **3** are onerous and/or low-yielding.[8]

We recently described the first direct transformation of 1-benzylisoquinolines into benzo[*c*]phenanthridines by a route in which C–N cleavage of 1-benzylidine derivatives **1** gave the novel stilbene-like compounds **2**, in which rings C and B of the benzo[*c*]phenanthridine skeleton were then sequentially constructed.[9] Here we describe a modification of this approach that provides an easy, efficient access to vinylphenylisoquinolinones **3**, and hence a new method for the total synthesis of benzophenanthridinones **5** and we report the application of the new method to the synthesis of fagaronine (**6b**) (Scheme 1).

When the previously obtained[9] *N*-methyl derivative **2b** was reacted with Tf_2O and DMAP in CH_2Cl_2, the expected Bischler–Napieralski cyclization afforded vinylphenylisoquinolinone **3a**,[10] which was directly converted into benzo[*c*]phenanthridinone **5a** by oxidation[11] with thallium trinitrate and subsequent reaction of the resulting acetal **4a** with aqueous HCl.

The utility of this new approach to benzo[*c*]phenanthridines was corroborated by the analogous synthesis of fagaronine (**6b**) starting from the readily available *N*-ethoxycarbonylbenzylideneisoquinoline **1b**,[12] in which the OH group of fagaronine is protected as an isopropoxy group. Proceeding as for **5a**, treatment of **1b** with LDA at 0°C cleaved the C–N bond as expected, and the resulting styrylurethane **2c** was converted into its *N*-methyl derivative **2d** by treatment with MeI. Compound **2d** was next transformed into benzophenanthridinone **5b** via 3-vinylphenylisoquinolinone **3b** and acetal **4b**. After reduction of **5b** with lithium aluminium hydride and oxidation of the resulting dihydroderivative with DDQ had given the quaternary salt **6d**, this latter was *O*-dealkylated with sulfuric acid, furnishing fagaronine (**6b**).[13]

To sum up, this paper presents the first fruits of a new strategy toward the synthesis of potentially antitumoral 3-(2-vinylphenyl)-2-methyl-2*H*-isoquinolin-1-ones **3**

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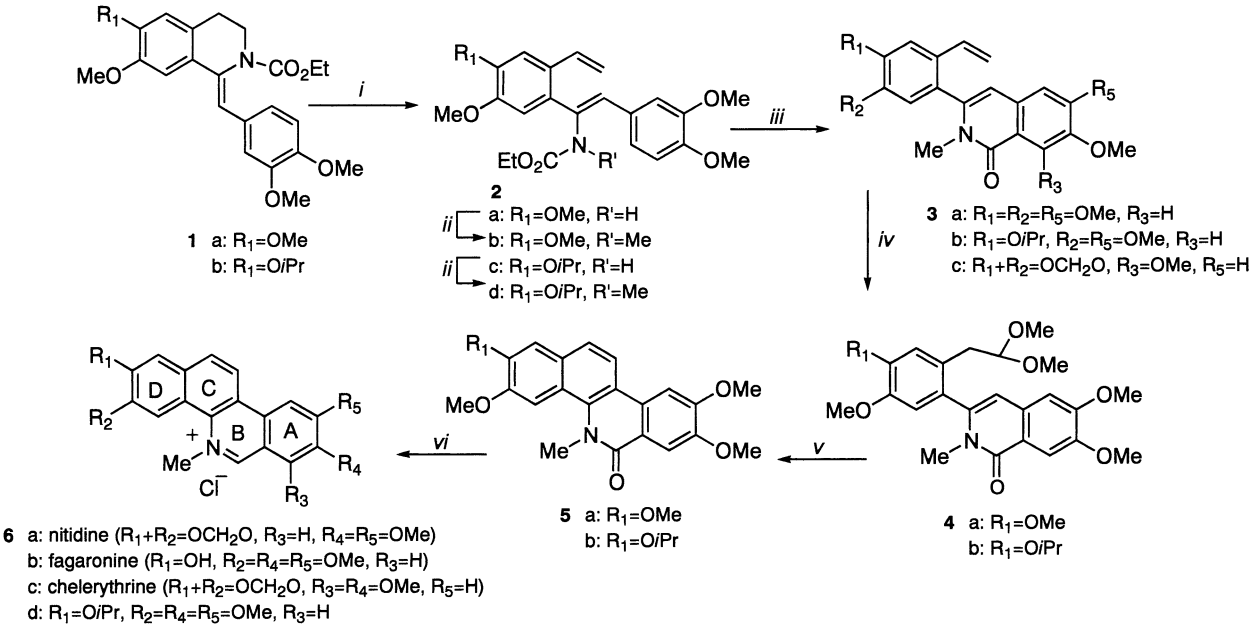

Scheme 1. *Reagents and conditions*: (i) LDA, THF, 0°C, 30–60 min (100% yield); (ii) (a) NaH, THF, rt, 30 min, (b) MeI, rt, 45–60 min (74–100% yield); (iii) Tf_2O, DMAP, CH_2Cl_2, 0°C→rt, 1.5 h (40–50% yield); (iv) $Tl(NO_3)_3{\cdot}3H_2O$, MeOH, rt, 5 min; (v) 10% aq. HCl, rt, 40–60 min (80–95% yield); (vi) (a) $LiAlH_4$, THF, 35°C, 3 h (95% yield), (b) DDQ, benzene, 25°C, 2 h (80% yield), (c) H_2SO_4, AcOH, rt, 2.5 h (80% yield).

which is original and more efficient than the few previous syntheses of these compounds and may be suitable for large-scale work. Optimization of this new route, and its application to the synthesis of pharmacologically active benzo[*c*]phenanthridines other than fagaronine (**6b**), is now under investigation. Additionally, we are completing a systematic study of the chemical properties of *N*-ethoxycarbonyl-1-amino-1-(2-vinylphenyl)-2-phenylethylenes **2** with a view to the synthesis of other interesting anticancer compounds such as benzofuronaphthoquinones, indolonaphthoquinones and ellipticines.[14]

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10. All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data follow.
Compound **3a**. Mp 205–208°C (methanol). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.30 (s, 3H, -NCH_3), 3.90 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3), 4.00 (s, 3H, -OCH_3), 4.04 (s, 3H, -OCH_3), 5.15 (d, J=11 Hz, 1H, -C=CH_2), 5.63 (d, J=17.5 Hz, 1H, -C=CH_2), 6.40 (s, 1H, Ar-H), 6.46 (dd, J=17.5 Hz, J=11 Hz, 1H, -C*H*=CH_2), 6.77 (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 7.16 (s, 1H, Ar-H), 7.84 (s, 1H, Ar-H). MS (*m*/*z*, %): 381 (M^+, 100).
Compound **2c**. Mp 119–121°C (methanol). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.86 (t, J=7.1 Hz, 3H, -CH_3), 1.40 (d, J=6.1 Hz, 6H, 2×-CH_3), 3.03 (s, 3H, -NCH_3), 3.84–3.97 (m, 11H, 3×-OCH_3+-OCH_2-), 4.63 (h, J=6.1 Hz, 1H, -$CHMe_2$), 5.13 (dd, J=10.9 Hz, J=1.1 Hz, 1H, -C=CH_2), 5.52 (dd, J=17.4 Hz, J=1.1 Hz, 1H, -C=CH_2), 6.12 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 6.83–7.05 (m, 4H, 3×Ar-H+-C*H*=CH_2), 7.07 (s, 1H, Ar-H). MS (*m*/*z*, %): 455 (M^+, 32), 310 (100).

Compound **3b**. Mp 204–206°C (ethanol). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.43 (d, $J=6.1$ Hz, 6H, 2×-CH_3), 3.28 (s, 3H, -NCH_3), 3.85 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 4.02 (s, 3H, -OCH_3), 4.65 (h, $J=6.1$ Hz, 1H, -$CHMe_2$), 5.10 (d, $J=11$ Hz, 1H, -C=CH_2), 5.55 (d, $J=17.4$ Hz, 1H, -C=CH_2), 6.37 (s, 1H, Ar-H), 6.41 (dd, $J=17.4$ Hz, $J=11$ Hz, 1H, -C*H*=CH_2), 6.74 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 7.16 (s, 1H, Ar-H), 7.82 (s, 1H, Ar-H). MS (m/z, %): 409 (M^+, 100).

Compound **5b**. Mp 188–189°C (methanol). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.47 (d, $J=6.1$ Hz, 6H, 2×-CH_3), 3.98 (s, 3H, -CH_3), 4.00 (s, 3H, -CH_3), 4.01 (s, 3H, -CH_3), 4.05 (s, 3H, -CH_3), 4.75 (h, $J=6.1$ Hz, 1H, -$CHMe_2$), 7.15 (s, 1H, Ar-H), 7.48–7.52 (m, 2H, 2×Ar-H), 7.57 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.90 (d, $J=8.7$ Hz, 1H, Ar-H). MS (m/z, %): 407 (M^+, 89), 350 (100).

Compound **6b**. Mp 198–200°C (methanol/ethyl acetate). ^{1}H NMR (δ, ppm, CF_3COOD): 4.14 (s, 6H, 2×-OCH_3), 4.22 (s, 3H, -OCH_3), 4.93 (s, 3H, -NCH_3), 7.40 (s, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.88 (s, 2H, 2×Ar-H), 7.88 (d, $J=8.5$ Hz, 1H, Ar-H), 8.28 (d, $J=8.5$ Hz, 1H, Ar-H), 9.25 (s, 1H, Ar-H).

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