Friedel–Crafts Cyclodehydration Approach toward the Synthesis of Ellipticine and 9-Methoxyellipticine

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Abstract: An expedient synthesis of biologically important pyrido[4,3-*b*]carbazole alkaloids, ellipticine and 9-methoxyellipticine, is reported. Our synthetic approach applies a key H_3PO_4-mediated Friedel–Crafts cyclodehydration to construct the pyridine core.

Key words: alkaloids, nitrogen heterocycles, natural products, total synthesis, cyclization

Natural products belonging to the pyrido[4,3-*b*]carbazole family of alkaloids are well represented in the chemical literature.[1–12] Examples of such pyridocarbazole alkaloids are depicted in Figure 1, each of which possesses a pyridine ring fused to a carbazole moiety. Since the initial isolation of ellipticine (**1**) and 9-methoxyellipticine (**2**) in 1959 by Goodwin et al.,[2] several other compounds in this family have been isolated from *Apocynaceae* plants.[3] The interesting structures of these molecules, and their wide biological properties,[4,6] have prompted a number of synthetic investigations.[5,8] The antineoplastic property of ellipticine was established to be largely due to DNA intercalation and inhibition of topoisomerase II.[6] Successful clinical trials and commercialization of derivatives have provoked significant interest in the chemistry and biology of pyrido[4,3-*b*]carbazole alkaloids.[7] This is highlighted by several reviews covering the synthesis and biological properties of ellipticine derivatives.[8]

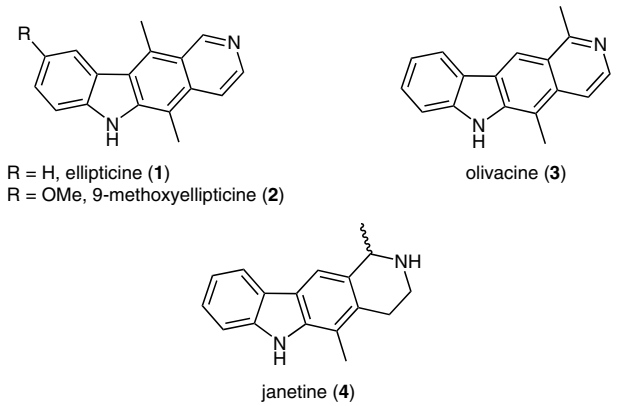
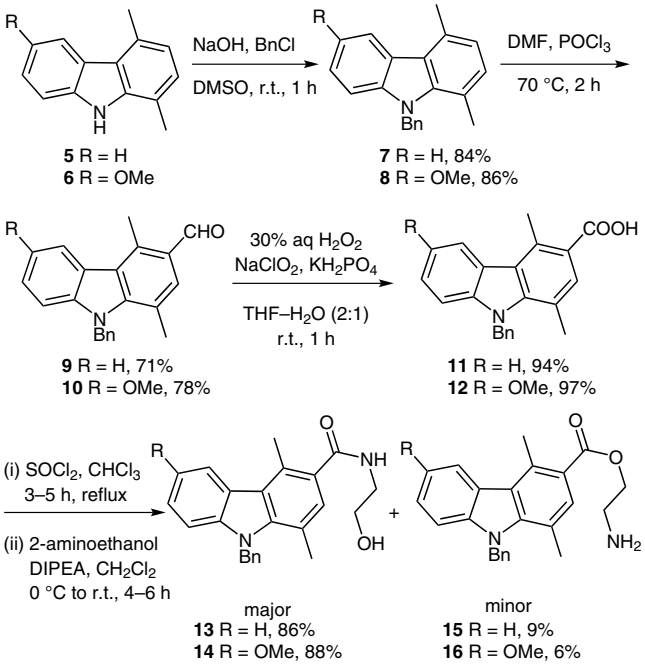


Figure 1 Representative pyrido[4,3-*b*]carbazole alkaloids **1**–**4**

Previous syntheses of ellipticine and 9-methoxyellipticine have been accomplished from known 1,4-dimethylcarbazole-3-aldehyde precursors using a Pomeranz–Fritsch cyclization as key step; reported individually by Saxton,[9] Jackson,[10] Chern,[11] and Dračínský.[12] However, acid-catalyzed Friedel–Crafts-type cyclodehydration reactions have been less explored in the total synthesis of natural products.[13]

We herein describe a novel route to the synthesis of ellipticine and 9-methoxyellipticine, starting from *N*-benzyl-1,4-dimethylcarbazole-3-aldehyde precursors. Our synthesis commenced with the preparation of 9-benzyl-1,4-dimethylcarbazoles **7** and **8** from the corresponding 1,4-dimethylcarbazoles, which can be readily prepared by literature methods[7] (Scheme 1). N-Benzylation of **5** and **6** afforded **7** and **8** in excellent yields. Next, Vilsmeier–Haack formylation of **7** and **8** with DMF and $POCl_3$ at 70 °C furnished aldehydes **9** and **10**. Subsequent Pinnick oxidation, using 30% aqueous H_2O_2, $NaClO_2$, and KH_2PO_4 in THF–H_2O (2:1), transformed **9** and **10** into acids **11** and **12** in 94% and 97% yields, respectively. Acids **11** and **12** were converted into the corresponding acid chlorides using $SOCl_2$, followed by amidation with 2-am-



Scheme 1 Synthesis of 9-benzyl-*N*-(2-hydroxyethyl)-1,4-dimethyl-9*H*-carbazole-3-carboxamides **13** and **14**

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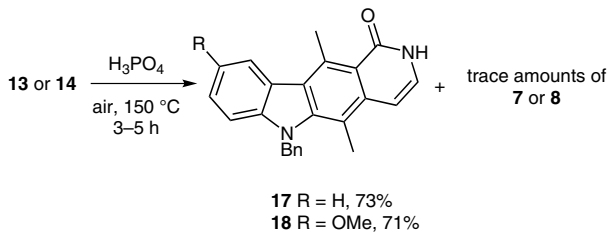
inoethanol afforded the desired amides **13** and **14** along with esters **15** and **16** in smaller amounts.

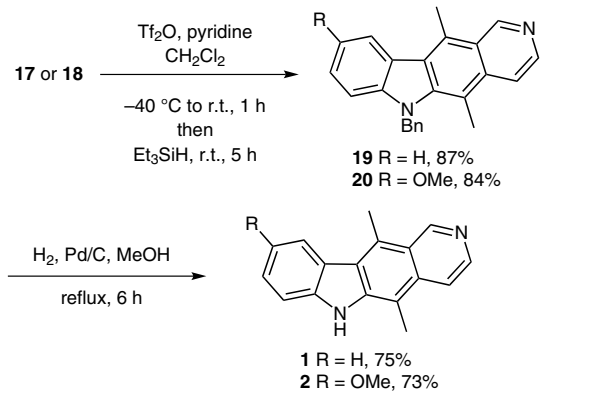
Following access to amides **13** and **14**, we explored the critical Friedel–Crafts cyclodehydration and ensuing pyridine ring formation, as summarized in Scheme 2. We were delighted to find that treatment of **13** or **14** with H_3PO_4 in air at 150 °C furnished dihydropyridocarbazolones **17** and **18** in 73% and 71% yields, respectively. Under these rather forcing conditions, we also observed the formation of the oxidative cleavage products **7** or **8** in trace amounts.



Scheme 2 The key H_3PO_4-mediated Friedel–Crafts cyclodehydration

Having assembled the tetracyclic scaffold of the natural products, two simple transformations remained in order to access ellipticine (**1**) and 9-methoxyellipticine (**2**). This would involve conversion of the amide group into an imine followed by the cleavage of the *N*-benzyl group in the intermediates **17** and **18**.

As shown in Scheme 3, the first of these challenges was achieved by reductive amination using mild reagents Tf_2O and Et_3SiH. This generated *N*-benzylellipticines **19**[14] and **20** in good yields. Next, the *N*-benzyl group was removed from **19** and **20** by using 10% palladium on carbon to furnish ellipticines **1** and **2** with analytical data consistent with those previously reported in literatures in all aspects.[8]



Scheme 3 Synthesis of ellipticine (**1**) and 9-methoxyellipticine (**2**)

In summary, we have completed an expedient synthesis of the pyrido[4,3-*b*]carbazole alkaloids, ellipticine (**1**) and 9-methoxyellipticine (**2**) over seven steps from known 1,4-dimethylcarbazoles (**5** and **6**) with 23% and 25% overall yields, respectively. For the first time, we have utilized the H_3PO_4-mediated Friedel–Crafts cyclodehydration as a key step to construct these pyrido[4,3-*b*]carbazole alkaloids and observed in situ aerial oxidation during the course of the reaction.

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(14) The CCDC deposition number for compound **19** is 994825. Formula: $C_{24}H_{20}N_2$. Unit cell parameters: a = 15.225 (8), b = 5.364 (3), c = 22.108 (12), α = 90, β = 101.789 (9), γ = 90, Space group $P2_1/c$.

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