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A DIRECTED METALATION ROUTE TO THE ZWITTERIONIC INDOLE ALKALOIDS. SYNTHESES OF INDOLO[2,3-*a*]QUINOLIZINE, FLAVOPEREIRINE, FLAVOCARPINE, AND DIHYDROFLAVOPEREIRINE

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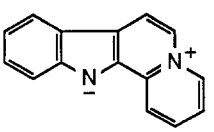
Summary: *A protocol involving beta-lithiation of 2-(2-pyridinyl)indoles (**4** → **5**) and subsequent reaction with bromoacetaldehyde or oxirane has led to syntheses of the alkaloids indolo[2,3-a]quinolizine (**1**), flavopereirine (**2**), flavocarpine (**21**), and dihydroflavopereirine (**24**).*

The small group of biogenetically-interesting[1] indole alkaloids that incorporate the zwitterionic indolo[2,3-*a*] - quinolizine ring system **1** has received relatively limited attention in the synthesis arena[2]. The recent discovery that some of these alkaloids, such as flavopereirine (**2**) and sempervirine (**3**), possess antitumor activity,[3] and our continued interest in exploring the use of lithiated heterocycles in synthesis[4] led us to devise an expedient metala - tion route to several members of this alkaloid class, which is the subject of this Letter.



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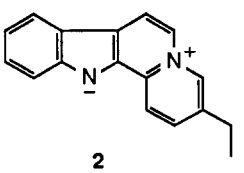

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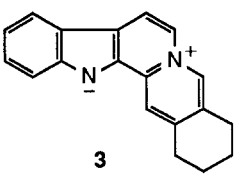
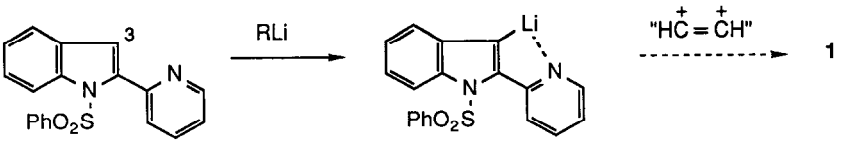


3

Our strategy exploits the marked *beta*-lithiating ability of the 2-pyridinyl moiety[4d,5] and, to our knowledge, represents the first time that this tactic has been utilized in natural product synthesis. Thus, we envisioned that the indolo[2,3-*a*]quinolizine ring system (**1**) could be constructed from a 3-lithio-1-phenylsulfonyl-2-(2-pyridinyl) - indole (**5**) and a suitable two-carbon bis(1,2)electrophile (Scheme I).[6]

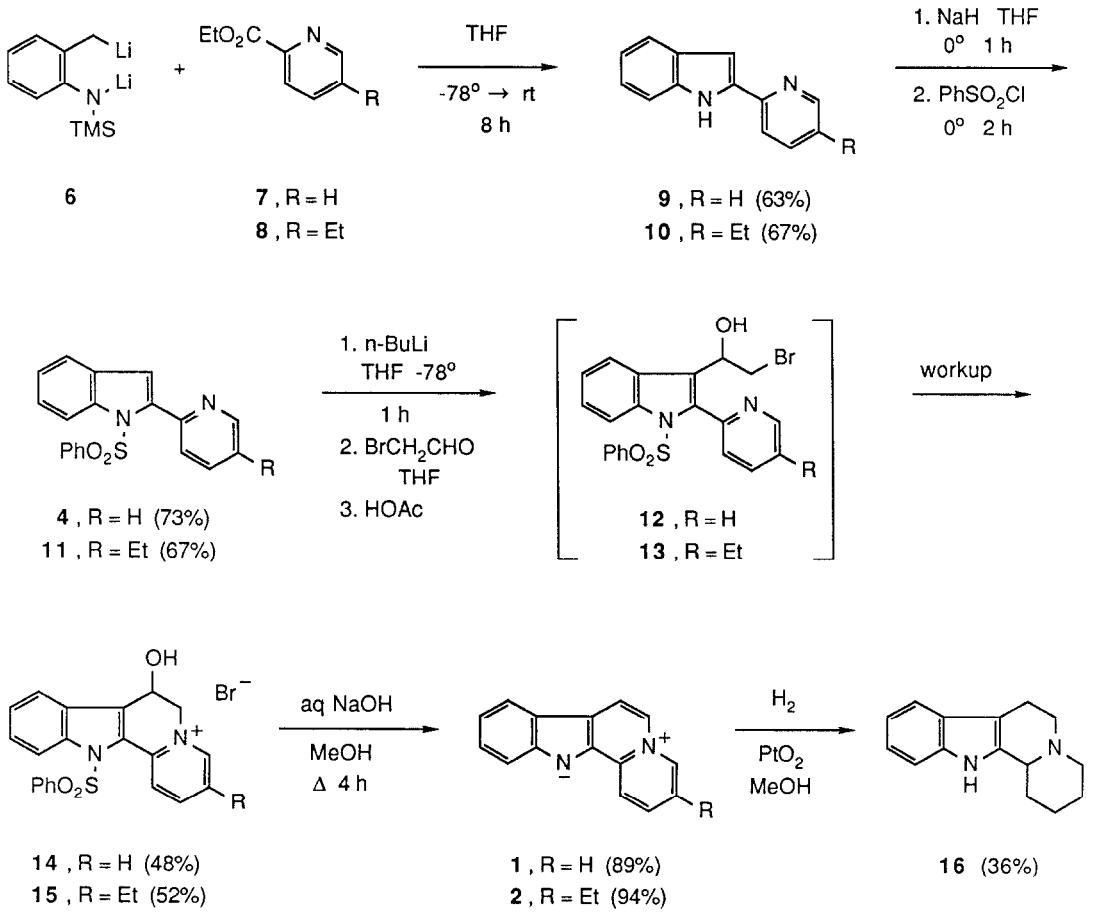
Scheme I



4 **5**

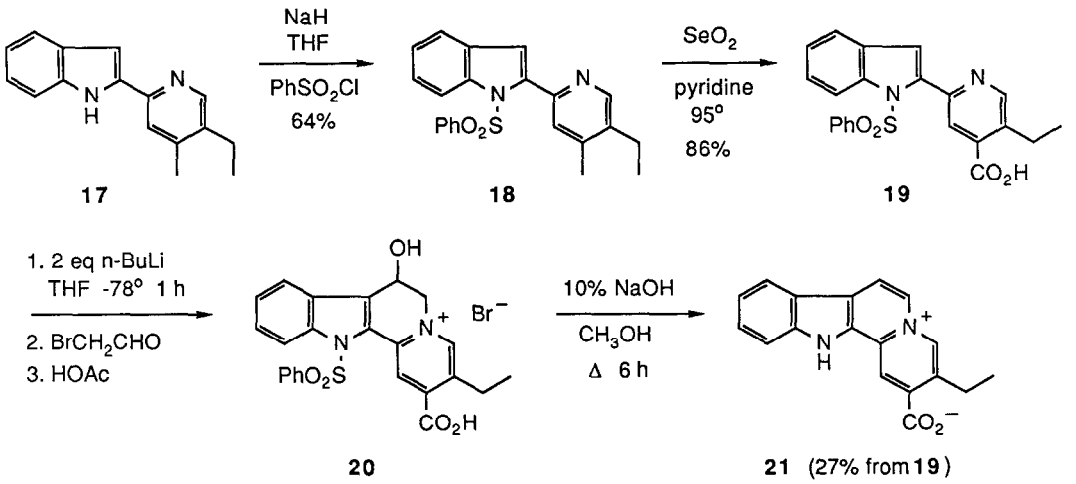
Accordingly, the requisite pyridinylindoles **9** and **10** were prepared[7] from ethyl picolinates **7** and **8** with the dianion of *N*-trimethylsilyl-*o*-toluidine (**6**),[8] and then protected[4d] as the *N*-phenylsulfonyl derivatives **4**[4d] and **11**[9] (Scheme II). Treatment of **4** and **11** with *n*-butyllithium and quenching the resulting 3-lithio species (e.g., **5**) with anhydrous bromoacetaldehyde[10] provided the indoloquinolizinium bromides **14** (mp 216.5-217°C) and **15**[9b] (mp 217-8°C). Hydrolysis of the *N*-phenylsulfonyl protecting group in **14** and **15** was accompanied by dehydration to give directly indolo[2,3-*a*]quinolizine (**1**) and flavopereirine (**2**) in 31% and 33% overall yield from **9** and **10**, respectively. The UV spectrum and melting point of the hydrochloride salt of **1** (mp 291-5°C dec) were in agreement with those reported,[11] and hydrogenation of **1** afforded the octahydro derivative **16**, which was identical (TLC, mp, IR, ^{1}H NMR) with known material.[12] The perchlorate salt of **2** was identical (TLC, IR, UV, ^{1}H NMR, MS, mixed mp 311-2°C dec) with a known sample of flavopereirine perchlorate.

Scheme II



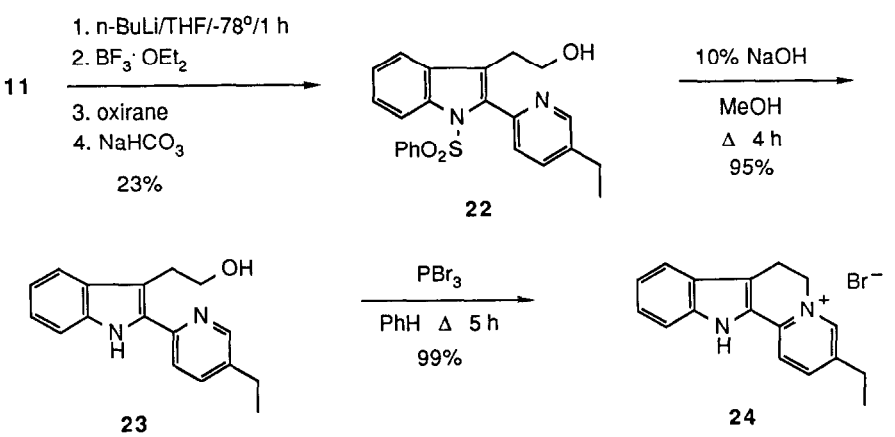
Application of this metalation-annulation protocol to isonicotinic acid derivative **19**[9] (mp 274-7°C dec) (Scheme III), prepared from **17**[9,13] (mp 160-3°C) via the usual *N*-protection[4d] to **18**[9] (mp 104.5-105°C) and selenium dioxide oxidation,[16] furnished flavocarpine (**21**) in 27% overall yield from **19**. This material was identical (TLC, IR, UV, ^{1}H NMR, mixed mp 323-5°C dec) with the known alkaloid.[17]

Scheme III



Our methodology is equally applicable to the synthesis of 6,7-dihydroindolo[2,3-*a*]quinolizine alkaloids (Scheme IV). Thus, treating the anion generated from **11** sequentially at -78°C with $BF_3{\cdot}Et_2O$,[18] oxirane, and saturated aqueous $NaHCO_3$ afforded the acid-sensitive alcohol **22**[9] (mp 149-150°C). Hydrolysis gave the known[19] indole **23** (mp 131-3°C), which was cyclized with PBr_3 to give dihydroflavopereirine hydrobromide (**24**)[19] (mp 317-320°C dec), identical (TLC, UV) with a sample of the perchlorate salt.

Scheme IV



Surprisingly, treatment of **22** with PBr_3 or, better, *p*-toluenesulfonyl chloride (1.2 equiv, CH_2Cl_2-pyridine, 0°C) produced flavopereirine (**2**) (ca. 100%), presumably via loss of benzenesulfinate from the initially formed indoloquinolizinium salt.

In summary, we have described a new annulation of 2-(2-pyridinyl)indoles leading to a general and reasonably efficient construction of the indolo[2,3-*a*]quinolizine ring system, exemplified by the synthesis of several alkaloids of this class.

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