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The Intramolecular Addition of an Aryl Radical to a Pyridine Provides a Short Entry to Toddaquinoline

David C. Harrowven* and Michael I.T. Nunn

Department of Chemistry, The University, Southampton, S017 1BJ.

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Abstract: The paper describes a synthetic approach to toddaquinoline, an unusual alkaloid from the root bark of Formosan *Toddalia asiatica*. Key steps are a *cis*-selective Wittig coupling and a trialkyltin mediated, intramolecular cyclisation of an aryl radical to C-6 of a pyridine. © 1998 Elsevier Science Ltd. All rights reserved.

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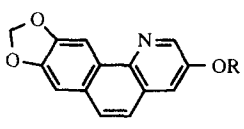
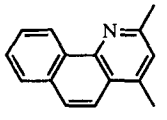
For centuries the root bark of Formosan *Toddalia asiatica* has been used in Asian folk medicine.[1] During an investigation into its chemical constituents, Chen and his co-workers discovered a new alkaloid which they named toddaquinoline.[2] The structure of toddaquinoline **1** and its methyl ether **2** were elucidated by NMR and shown to feature a unique tetracyclic skeleton. Indeed, its closest relatives in Nature are benzo[h]quinoline and some methylated analogues *e.g.* **3**, asimicilone **4** and a few condensed derivatives such as noravicine **5**.[3]



1 R = H, **2** R = Me



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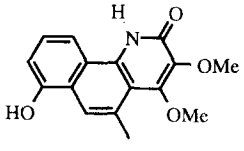

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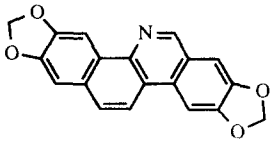

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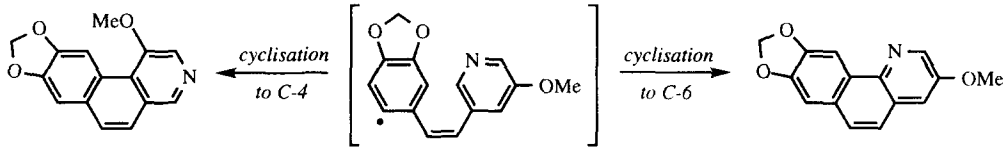
Our interest in the addition of carbon centred radicals to heteroaromatics prompted us to embark on a synthesis of toddaquinoline based on the radical cyclisation **7** to **2**.[4] For although radical additions to pyridine are well documented the intramolecular variant has received scant attention.[5] Moreover, we were keen to see whether cyclisation would occur preferentially to C-4 or C-6 of the pyridine (Scheme 1) and whether the reducing conditions would give the heteroaromatic directly or lead to a dihydroquinoline.

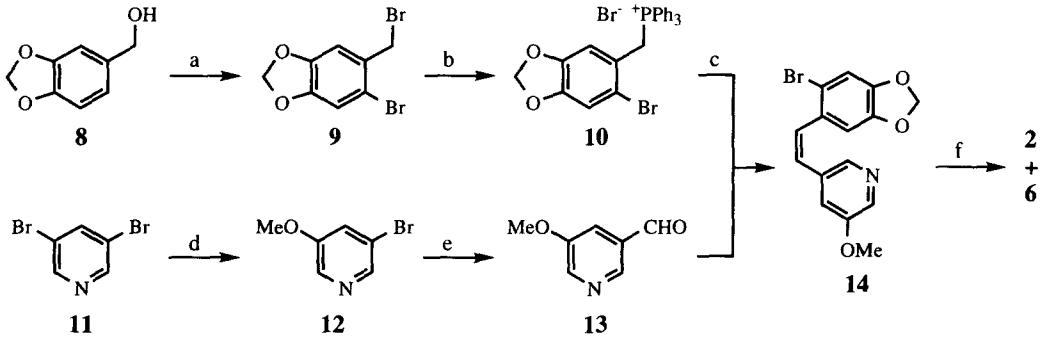


6 **7** **2**

Scheme 1

PII: S0040-4039(98)01187-3

The synthesis of the radical precursor **14** was achieved in a straight forward manner from piperonyl alcohol **8** and 3,5-dibromopyridine **11**. Thus, treatment of **8** with bromine in acetic acid gave dibromide **9** which was readily transformed into phosphonium salt **10** through the action of triphenylphosphine.[6] Similarly, exposure of **11** to a warmed solution of NaOMe in DMF/MeOH first gave **12** which was transformed into aldehyde **13** by transmetallation and quenching with DMF.[7] Union of **10** and **13** was then achieved using a standard Wittig coupling to give **14** as a partially separable 3:1 mixture of *cis*- and *trans*- diastereoisomers.



Reagents and Conditions: **a.** Br_2, AcOH, 0°C, 1h, 84%; **b.** PPh_3, xylene, 80°C, 1h, 54%; **c.** NaH, THF, 0°C, 10 min; r.t., 1h; **13**, 0°C, 10 min; r.t., 2h, 72% (*E*:*Z* - 1:3); **d.** 5 eq. NaOMe, MeOH, DMF, reflux, 100h, 78%; **e.** BuLi, THF, -90°C, 25 min; DMF, -90°C to -60°C, 30 min; brine, 67%; **f.** Bu_3SnH, AIBN, PhMe, 80°C, 4h, 58%.

Scheme 2

At this juncture we were in a position to examine the key step. Treatment of **14** under standard radical cyclisation conditions led to a separable 1:1 mixture of the two benzoquinolines **2** and **6** in 58% yield. The less polar product was shown to be toddaquinoline methyl ether **2** through comparison of our spectral and physical data with those reported in the isolation paper.

In conclusion, our synthesis of toddaquinoline methyl ether **2** has shown that intramolecular additions of aryl radical to pyridines provide a useful entry to benzoquinolines. Cyclisation occurs to C-4 and C-6 of the pyridine ring with equal propensity and yields heteroaromatic products rather than the dihydroquinolines.

References and Notes

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