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Synthesis of Azacridone A

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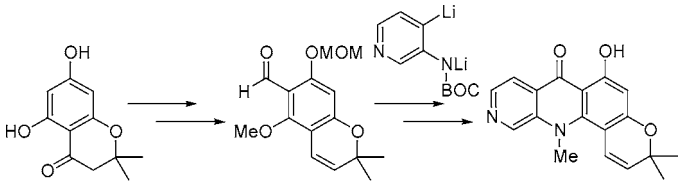
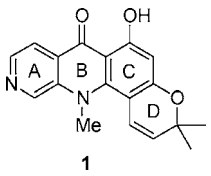
ABSTRACT

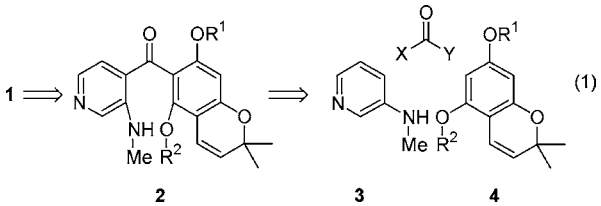


The first total synthesis of the only known naturally occurring azaacridone alkaloid (1) has been achieved in 10 steps from phloroglucinol. A variety of ortholithiation reactions are described, and a method for overcoming the originally unfavorable regiochemistry of one of them is provided.

In 1993, a team of Japanese scientists reported the isolation of the first naturally occurring azaacridone alkaloid.[1] The compound, aptly named azacridone A, was assigned structure **1** on the basis of its spectroscopic properties. Since azacridone A is the only known representative of the [1]-benzopyrano[5,6-*b*][1,7]naphthyridine ring system and since no independent confirmation of the structure determination has been recorded, the synthesis of **1** was undertaken. We now report the first synthesis of azacridone A and the affirmation of the original structure assignment.

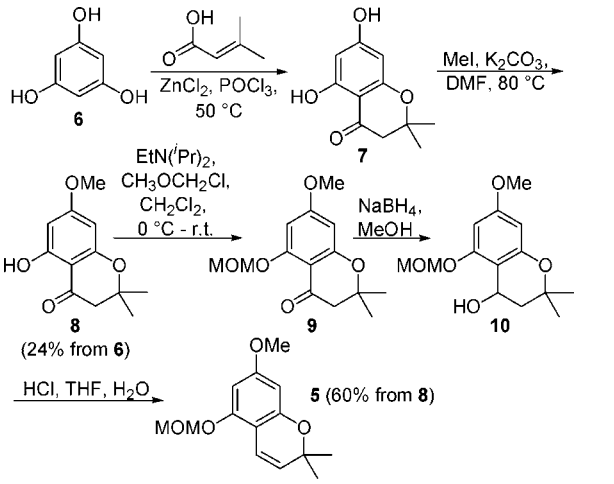


Retrosynthetic analysis suggested (eq 1) that **1** might be secured by cyclization of **2**. The latter should be accessible from **3**, **4**, and a carbonyl synthon. In principle, the carbonyl synthon could be incorporated initially attached to either the pyridine or the benzopyran unit. While both possibilities were examined, in practice initial attachment to the benzopyran entity provided the solution.



A specific embodiment (**5**) of differentially protected benzopyran **4** was prepared as shown in Scheme 1. Thus,

Scheme 1



the known annelation of phloroglucinol (**6**) with β,β-dimethylacrylic acid afforded **7**.[2] The two hydroxyl groups

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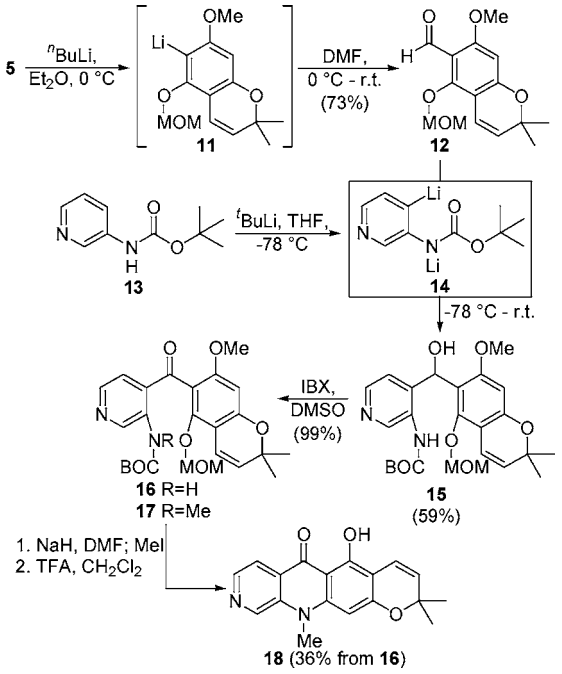
were selectively protected (**7** → **8** → **9**) by exploiting the hydrogen-bonding interaction between the carbonyl oxygen and the peri hydroxyl. Reduction to **10** and dehydration then provided **5**.

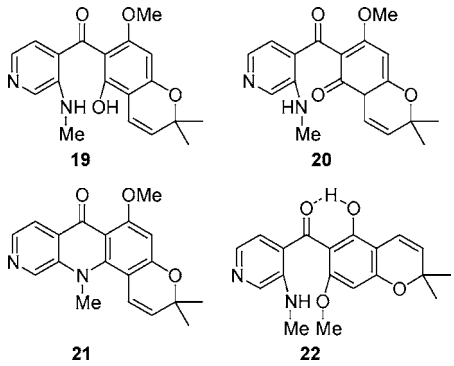
It was anticipated that the greater chelating properties of the methoxymethoxy (MOMO) group would cause it to dominate the regiochemical outcome of ortholithiation of **5**.[3] That expectation was borne out: D_2O-quench studies combined with NOESY measurements revealed that lithiation of **5** is regiospecific, giving **11**. Reaction of **11** with *N*,*N*-dimethylformamide (DMF) gave aldehyde **12** in 73% yield from **5** (Scheme 2).

Scheme 2



As expected based on the work of Hands et al.,[4] and confirmed by the ^{1}H NMR spectrum of the product, double lithiation of the *t*-BOC derivative (**13**)[5] of 3-aminopyridine gives **14**, which affords **15** upon reaction with aldehyde **12**. Oxidation[6] of the benzhydryl alcohol followed by *N*-methylation provides **17**.

It had been anticipated that treatment of **17** with acid would deprotect both the *t*-BOC and MOM groups, giving **19**. Subsequent cyclization of **19**, perhaps via its minor keto tautomer **20**, should then generate **21**. Exposure of **17** to trifluoroacetic acid (TFA) in dichloromethane did, as expected, achieve both deprotections, but unfortunately also led to regiospecific cyclization to the unwanted **18** (Scheme 2).

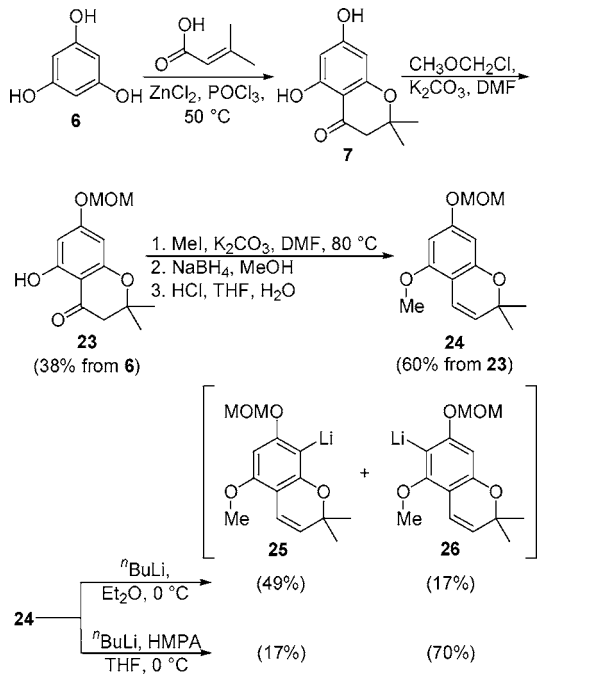


The preferential—but undesired—formation of **18** rather than **21** was ascribed to hydrogen bonding (see **22**), which by that argument, imposes a conformation on **19** that ordains the regiochemical outcome.

If the hydrogen bonding interaction (e.g., **22**) is, in fact, the determining factor, then a simple cure is available: swap the Me and MOM protecting groups in **17**. It is hardly surprising to one skilled in the art of organic synthesis that accomplishing such a seemingly insignificant change proved nontrivial.

Switching the two protecting groups themselves at the bicyclic level to give **24** was straightforward (Scheme 3).

Scheme 3



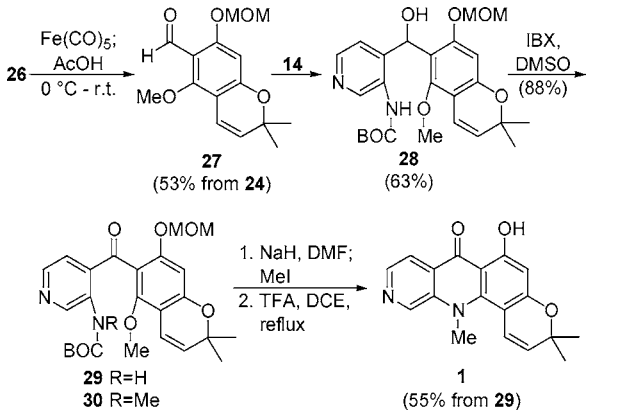
However, lithiation employing the conditions used in Scheme 2 (**5** → **11**) gave predominantly **25**, not the desired **26**, as established by D_2O-quench and NOESY studies, as before. Apparently, while the MOMO group is presumably still the

(1) Takemura, Y.; Isono, Y.; Ju-Ichi, M.; Omura, M.; Ito, C.; Furukawza, H. *Chem. Pharm. Bull.* **1993**, *41*, 789.
(2) (a) Sowmithran, D.; Prasad, K. J. R. *Synthesis* **1985**, 545. (b) Timar, T. *J. Heterocycl. Chem.* **1988**, *25*, 871.
(3) For a recent review, see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
(4) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877.
(5) Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003.
(6) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

dominant director, the conformationally constrained pyran oxygen wins out against the conformationally mobile methoxy oxygen. An extensive (see the Supporting Information) examination of the role of additives,[7] solvents, and reaction conditions revealed that in the presence of 2 equiv of HMPA (per equivalent of ^{n}BuLi), lithiation of **24** generates predominantly **26**, rather than **25**. We are not certain why the presence of HMPA changes the outcome, but ortholithiations can be complicated, with regioselectivity[8] being a function of the complex interactions of kinetics, thermodynamics, chelation, and aggregation.[9] In the event, a change in reaction conditions transforms a 3:1 regioisomer ratio to a 1:4 ratio.

With the ability to effect the desired lithiation of **24**, completion of the synthesis soon fell into place. Reaction of **26** with $Fe(CO)_5$[10,11] gave **27** (Scheme 4) in 53% yield (along with 18% of the **25**-derived regioisomer). A three-step sequence similar to before (Scheme 2), converted aldehyde **27** to ketone **30**. Treatment of **30** with TFA resulted in a cascade of reactions analogous to those in Scheme 2, but this time leading directly to the desired target, azacridone A. Spectra for synthetic **1** are in excellent agreement with those reported for naturally occurring azacridone A, confirming the structure originally assigned.

Scheme 4



In conclusion, we report the first synthesis of azacridone A, a synthesis that affirms the initially assigned structure.

Acknowledgment. We thank Mr. Jack Beierle for preliminary studies.

Supporting Information Available: Experimental procedures and characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331.

(8) For cases where lithiation regioselectivity has been reversed, see: (a) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815. (b) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430.

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(11) Anion **25** was largely unreactive toward DMF at 25 °C. We have previously shown (ref 10b) that $Fe(CO)_5$ exhibits greater reactivity toward aryllithium species than DMF.