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Mechanistic Considerations in the Synthesis of 2-Aryl-Indole Analogues under Bischler-Mohlau Conditions

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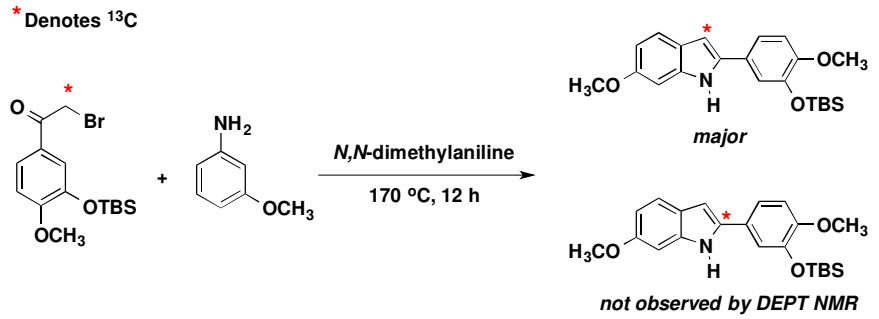
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Graphical Abstract



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Abstract

Mechanistic insight into the pathway of the Bischler-Mohlau indole formation reaction is provided by isotopic labeling utilizing judicious incorporation of a ^{13}C atom within the α-bromoacetophenone analogue reactant. The resulting rearranged 2-aryl indole, isolated as the major product, located the ^{13}C isotope label at the methine carbon of the fused five-membered heterocyclic ring, which suggested that the mechanistic pathway of cyclization, in this specific example, required two equivalents of the aniline analogue reactant partner and proceeded through an imine intermediate rather than by direct formation of the corresponding 3-aryl indole accompanied by a concomitant 1,2-aryl shift rearrangement.

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Keywords

Bischler-Mohlau Indole Synthesis

Indole Synthesis

Mechanistic Investigation

^{13}C Atom Incorporation

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Introduction

In the context of a long-standing program focused on the design, synthesis, and biological evaluation of diversely functionalized small-molecule anticancer agents, a series of benzo[*b*]thiophene,[1-3] benzo[*b*]furan,[4-5] and indole-based[6-8] analogues emerged as promising potential pre-clinical candidates (Fig. 1). These compounds were designed to function as inhibitors of tubulin polymerization (assembly) that bind to the colchicine site on the tubulin heterodimer and certain of these compounds demonstrated a dualistic mechanism of action functioning both as potent antiproliferative agents and as pronounced vascular disrupting agents (VDAs).[9-10] In each case, the heterocyclic fused ring was introduced synthetically through an efficient ring-closing step, and it proved intriguing to consider whether this reaction in the indole series of analogues mirrored that of the benzo[*b*]thiophene series or was mechanistically distinct.

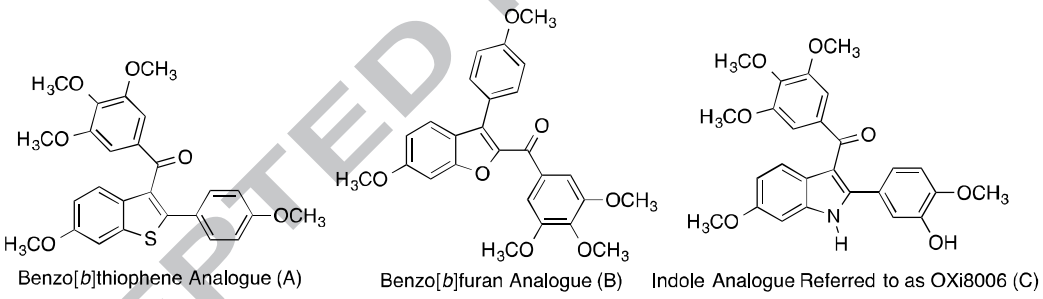
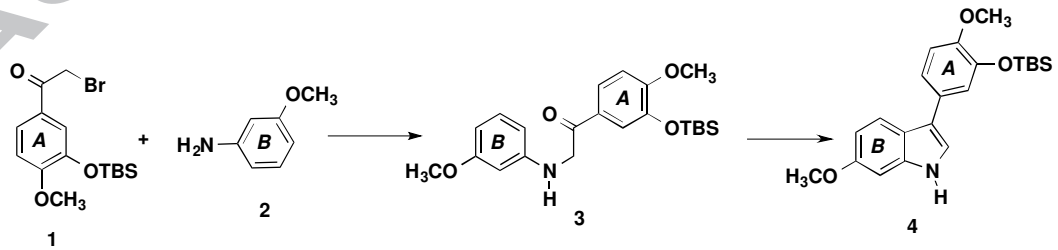


Figure 1. Representative Examples of Inhibitors of Tubulin Polymerization Incorporating Fused Heterocyclic Ring Systems: Benzo[*b*]thiophene (A);[1-3] Benzo[*b*]furan (B);[4-5] and Indole (C)[6-8]

The indole core ring system continues to be utilized as an abundant molecular scaffold in medical chemistry[11] and represent an important class of heterocycles.[12] The mechanistic pathways and synthetic routes available towards the indole platform are well established and vary greatly.[13] One established approach, referred to as the Fischer indole synthesis, involves a [3,3]-sigmatropic rearrangement followed by closure to the fused five-membered ring. This method was first pioneered by Fischer in 1883[14] and continues to be

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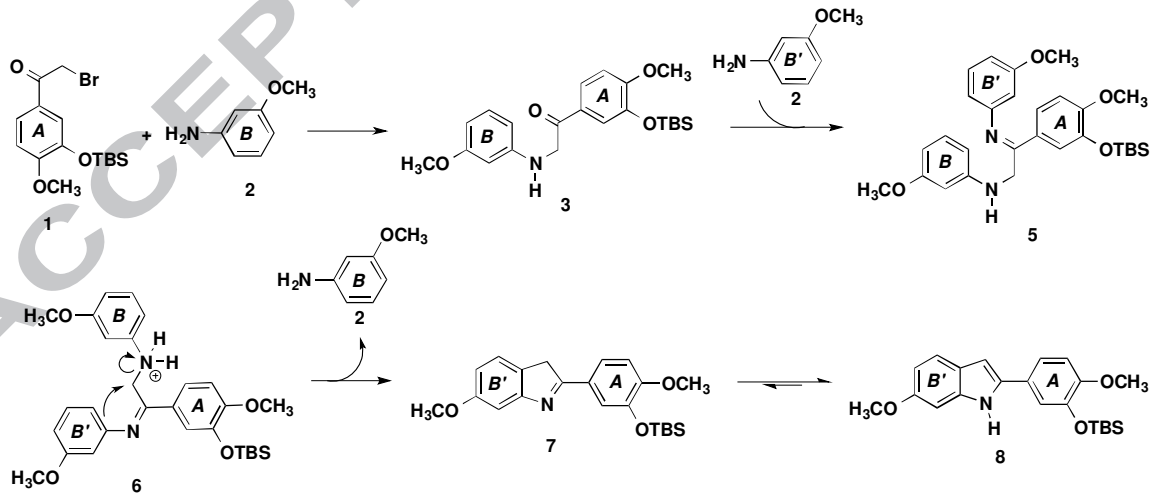
explored today.[15] Another frequently utilized approach is the Bischler-Mohlau indole synthesis[16-18] that involves the reaction between aniline analogues and α-halogenated ketone analogues and results in both 2-aryl and 3-aryl indole regioisomers. While the Bischler-Mohlau reaction[19-24] accommodates a wide-range of functionalized α-bromoketones and aniline analogues as starting materials, low isolated yields and unpredictable regiochemistry[25-26] remain potentially problematic. The reaction is heavily substrate dependent (in terms of yield and regiochemical outcome) and modifications in reaction conditions, including microwave heating,[25] can dramatically influence the overall process.[26] The perceived simplicity of the Bischler-Mohlau reaction somewhat disguises the complex mechanistic pathways which can lead to both 2-aryl and 3-aryl indole analogues. The indole product (2-aryl or 3-aryl) is dependent on one of several potential mechanistic pathways. These pathways were further investigated by Vara and co-workers by assessing the activation energies associated with intermediates and transition states.[26] Pathway A (Scheme 1) involves initial displacement of a bromine atom from 2-bromoacetophenone or an appropriately functionalized 2-bromoacetophenone analogue by aniline or an analogous aniline analogue. The pathway proceeds through intramolecular cyclization and subsequent re-aromatization to afford non-rearranged 3-aryl indole **4**.



Scheme 1. Mechanistic Pathway A Associated with the Bischler-Mohlau Reaction

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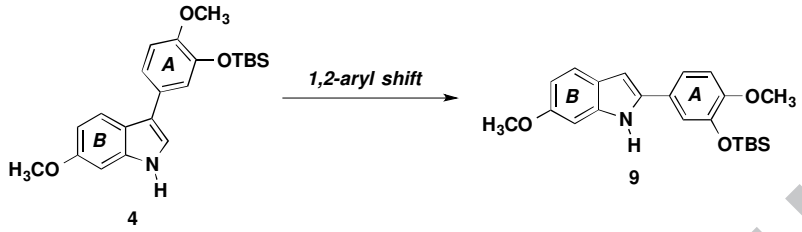
A well-recognized competing Pathway B (Scheme 2), which most often is invoked as being predictive of the major product of the Bischler-Mohlau indole synthesis, initiates in a similar fashion with the aniline analogue (3-methoxyaniline in this example) displacing the bromine atom on the alpha-bromoacetophenone analogue (compound **1** in this example). Condensation with a second molecule of 3-methoxyaniline results in the formation of imine intermediate **5**, which upon intramolecular cyclization involving displacement of the initial aniline molecule and subsequent tautomerization of 2-aryl indole **7,** generates the stable 2-aryl indole tautomer **8**. Previous computational and experimental studies have suggested that pathway B is preferred when an excess of aniline is used.[26] It should be noted that Vara and co-workers have evaluated another mechanistic possibility leading to formation of rearranged indole products (such as **8**), through an interesting carbonyl-shift rearrangement of a ketone (such as **3**) to an aldehyde prior to cyclization.[26-28]



Scheme 2. Mechanistic Pathway B Associated with the Bischler-Mohlau Reaction.

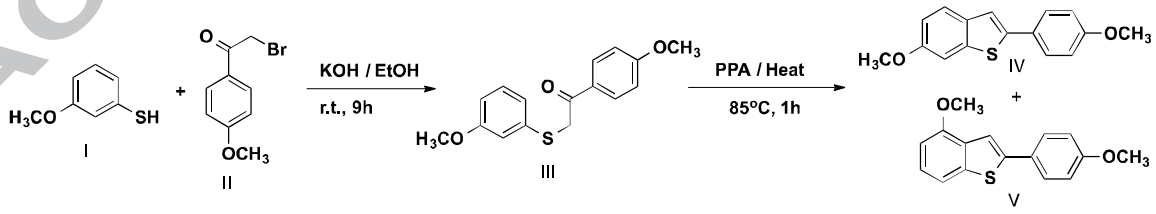
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We were intrigued by the possibility that a 3-aryl-indole analogue formed through pathway A could perhaps undergo a subsequent 1,2 aryl shift (pH dependent) resulting in a rearranged 2-aryl-indole analogue as the thermodynamic sink under these reaction conditions (Scheme 3).[29-30]



Scheme 3. Postulated 1,2-Aryl Shift Resulting in Rearranged Indole Analogue.

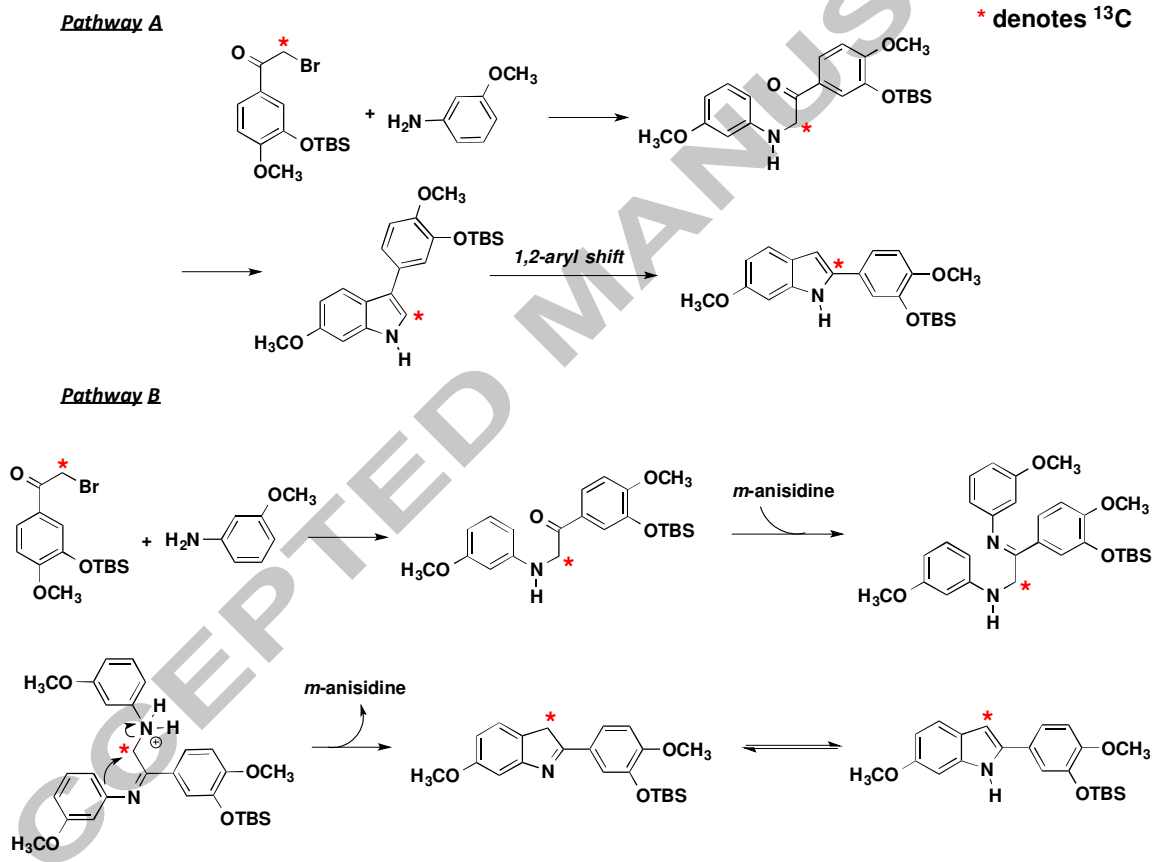
This postulated methodology (1,2-aryl shift in the indole system under Bischer-Mohlau conditions) is somewhat reminiscent of previous studies with related benzo[*b*]thiophene ring systems in which alpha-thio-ketone III (Scheme 4), for example, was converted to benzo[*b*thiophene regioisomers **IV** and **V** upon treatment with PPA.[1,31-32] The mechanism is widely thought to involve concomitant cyclization and 1,2 aryl ring migration. The regioisomers in this example result from initial cyclization occurring either *ortho* or *para* to the methoxy group on the aryl ring of the sulfide. [1,31-32]



Scheme 4. Formation of Benzo[*b*]thiophene Regioisomers Via Cyclization and Concomitant 1,2-Aryl Ring Migration.

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In an effort to further explore the Bischler-Mohlau reaction pathways a ^{13}C isotopic labeleling strategy was developed in which the α-carbon (to the carbonyl) was selectively labeled with ^{13}C. This labeled carbon atom can be readily traced through the identification of key distinct ^{13}C NMR signatures, specifically ^{13}C DEPT NMR, thus providing evidence for which mechanistic pathway predominates in this specific indole-forming reaction sequence (Scheme 5).

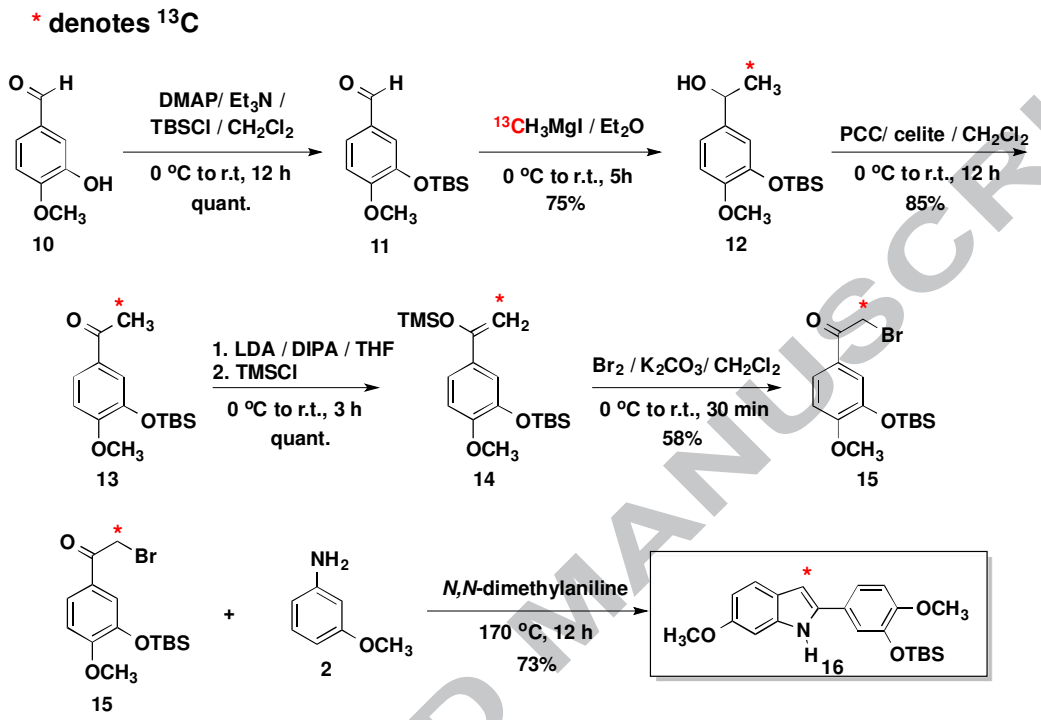


Scheme 5. Potential Mechanistic Pathways Leading to ^{13}C Labeled Indole Analogues

The synthetic route to ^{13}C-labeled bromoacetophenone intermediate **16** followed a similar sequence as the non-labeled bromoacetophenone intermediate from our previous studies with the indole based vascular disrupting agent (VDA) OXi8006[6-7,33] along with related

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work by von Angerer and co-workers,[34] and simply replaces the transitional methylation step reagents to install the ^{13}C carbon atom at the alpha position (Scheme 6).



Scheme 6. Synthesis of ^{13}C Labeled Bromoacetophenone **16**

Protection of 3-hydroxy-4-methoxybenzaldehyde (*iso*vanillin) with TBSCl in the presence of Et_3N and catalytic DMAP afforded TBS-aldehyde **11** which was subsequently treated with *in situ* generated $^{13}CH_3MgI$ (from commercially available $^{13}CH_3I$) to yield ^{13}C-labeled secondary alcohol **12**. PCC mediated oxidation generated ^{13}C-labeled acetophenone **13**, which after enolization was trapped as its corresponding silyl enol ether **14** upon reaction with TMSCl. Bromination of ^{13}C-labled enol ether **14** afforded requisite ^{13}C-labeled bromoacetophenone intermediate **15**, which was treated with three molar equivalents of 3-methoxyaniline (*m*-anisidine) **2** in *N*,*N*-dimethylaniline

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at 170 °C (Bischler-Mohlau conditions) for 12 h to afford rearranged ^{13}C-labeled 2-aryl indole **16** (Scheme 6).

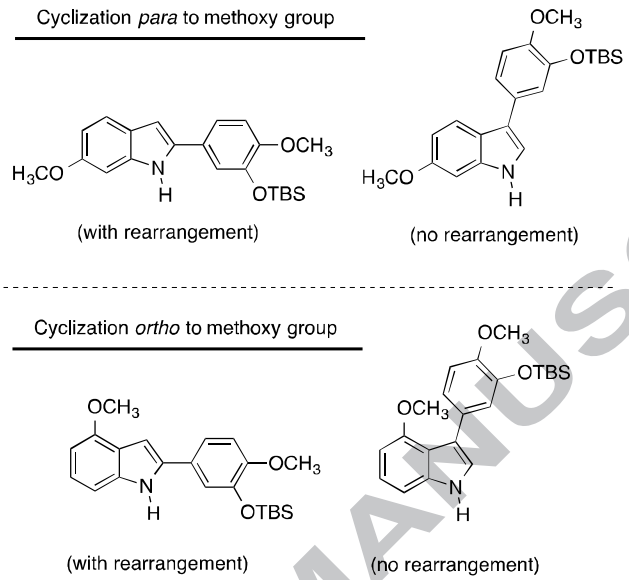


Figure 2. Four Possible Indole Regioisomers from Representative Bischler-Mohlau Reaction

It is important to note that there are four possible indole regioisomers that can result from this transformation (Fig. 2) depending on whether the initial cyclization takes place *para* or *ortho* to the methoxy group, with or without rearrangement. In our hands, with this specific set of reactants and these reaction conditions, only one regioisomer was isolated and it was identified as the regioisomer in which the ^{13}C atom label was located at the methine carbon (C-3 position of the indole core), suggesting that the system proceeded mechanistically through pathway B (imine intermediate formation) to generate the rearranged 2-aryl indole analogue **16**. The Bischer-Mohlau reaction to form indole analogue **16** was repeated twice for verification. In the first case, the isolated/purified yield of indole **16** was somewhat low (23%), however in the repeated experiment this yield rose to 73% (91% pure by HPLC), and a subsequent recrystallization afforded a

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highly pure sample (see Supplementary data for pertinent spectra). Initial comparison of the ^{13}C-NMR of indole regioisomer **16** (Fig. 3) with the predicted spectra (ChemBioDraw Ultra, Version 13.0.2.3020) for each of the four regioisomers, also taking into account the differences in the ^{1}H-NMR coupling patterns in the A-ring between the *para* and *ortho* ring closed possible products, strongly suggested regioisomer **16** as the major (and only identified and characterized) product of this reaction (both the intial reaction and the repeated reaction). DEPT ^{13}C NMR analysis (Fig. 3) confirmed that the ^{13}C atom label was located on a methine carbon, thus providing further evidence in support of regioisomer **16**. X-ray crystallographic analysis[35] of indole regioisomer **16** provided unequovical confirmation of its structural assignment (see Supplementary data).

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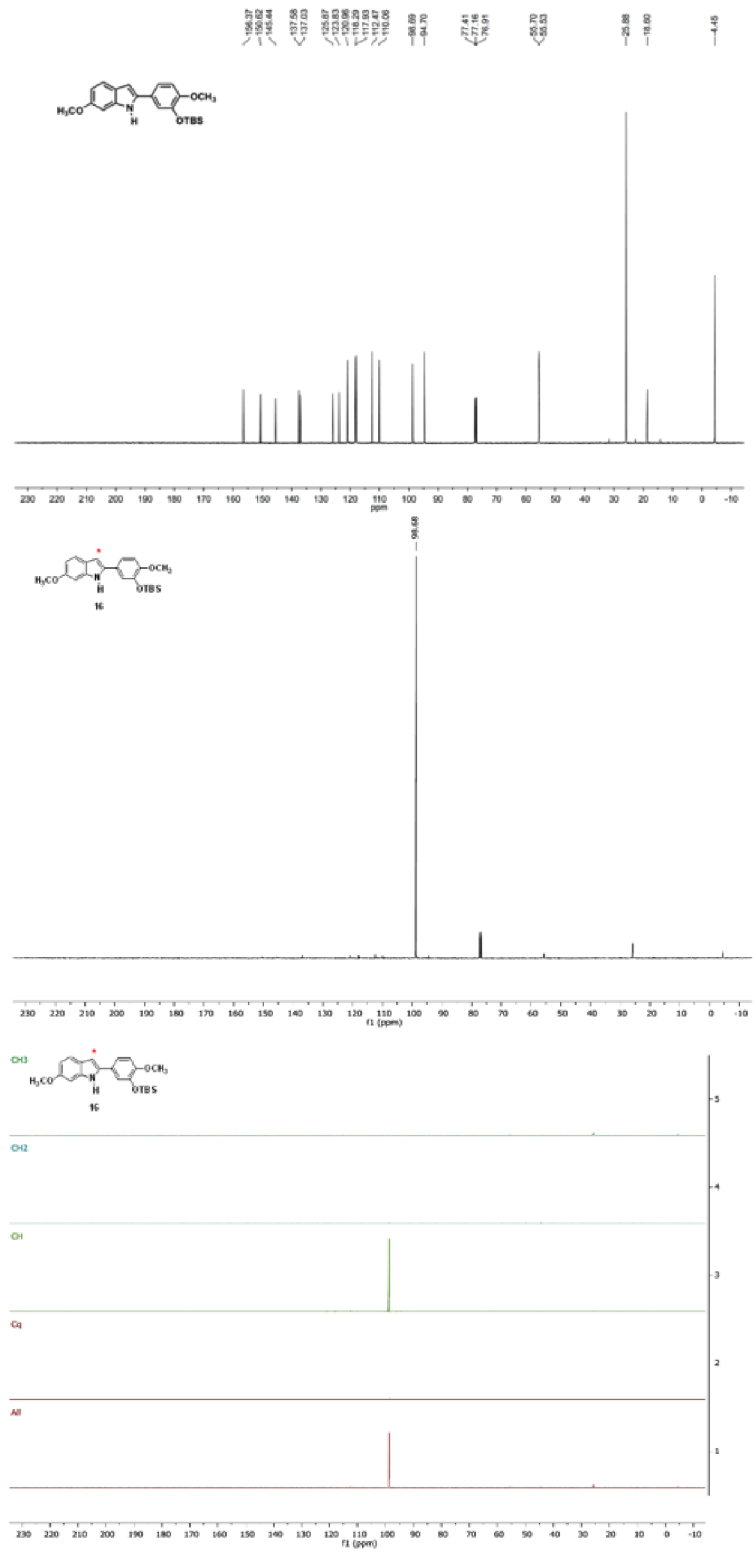


Figure 3. ^{13}C-NMR of Unlabeled Indole Analogue **8**, ^{13}C-NMR of ^{13}C Labeled Indole Analogue **16** (same as indole **8** but incorporating ^{13}C label), DEPT NMR of ^{13}C Labeled Indole Analogue **16**.

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Judicious incorporation of a ^{13}C label provided compelling evidence that the indole ring closure occurred (at least in this example) through a Bischler-Mohlau pathway rather than a Friedel-Crafts type ring closure, re-aromatization, accompanied by a concomitant aryl ring migration sequence that was envisioned as a potential competing pathway based on early studies suggesting that certain benzo[*b*]thiophene systems undergo ring-closure through this pathway under polyphosphoric acid (PPA) conditions. These results suggest that further inquiry into these and related systems may prove fruitful in delineating and predicting mechanistic pathways based (perhaps) on functional group incorporation and choice of reaction conditions, thus expanding the canopy of indole, benzo[*b*]thiophene, benzo[*b*]furan, and related small-molecule anticancer agents accessible under these synthetic protocols.

Acknowledgments.

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Supplementary data.

Supplementary data (Experimental procedures, ^{1}H NMR, ^{13}C NMR, DEPT NMR, HRMS, and HPLC data, along with X-ray crystallographic data) associated with this article can be found, in the online version, at {to be completed later}.

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35. Crystallographic data for ^{13}C labeled indole regioisomer **16** presented in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC deposition number 1041417). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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