

Formal Synthesis of 7-Methoxymitosene and Synthesis of its Analog via a Key PtCl₂-Catalyzed Cycloisomerization

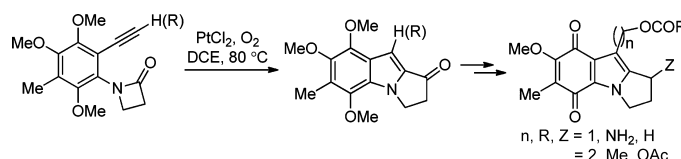
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ABSTRACT



A formal synthesis of 7-methoxymitosene is achieved via a key platinum-catalyzed cycloisomerization. The precursor for the Pt catalysis, a fully functionalized benzene intermediate, was prepared via a regioselective electrophilic bromination followed by a chemoselective Sonogashira cross-coupling. It underwent the PtCl₂-catalyzed cycloisomerization smoothly despite its hindered and highly electron-rich nature. Analogs of 7-methoxymitosene can be accessed in an expedient manner by following a similar synthetic sequence.

Mitomycins were isolated originally from *Streptomyces caespitosus* in the 1950s¹ and later from *Streptomyces verticillatus*.² They are members of a few aziridine-ring-containing natural products³ and possess potent antibiotic and antitumor activities (Figure 1). Mitomycin C is currently in clinical use and cross-links DNA upon in vivo activation. The more stable aziridinomitosenes, different from mitomycins by the formal loss of MeOH, possess activities against tumor cells similar to mitomycin C.⁴ Among various analogs of these pharmacologically important mitosenes, 7-methoxymitosene, a compound lacking the aziridine ring of **1**, has shown to be effective against

Gram positive bacteria.⁵ Its total synthesis has been realized by various creative approaches targeting the tricyclic pyrrolo-[1,2-*a*]indole skeleton.⁶ In this manuscript, we describe a new

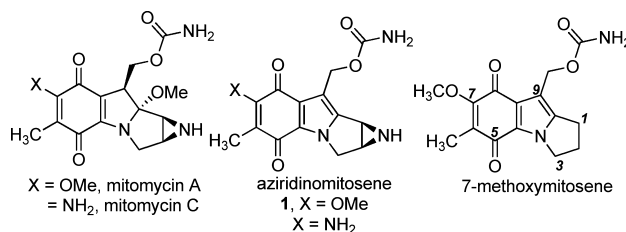


Figure 1. Mitomycins, aziridinomitosenes, and 7-methoxymitosene.

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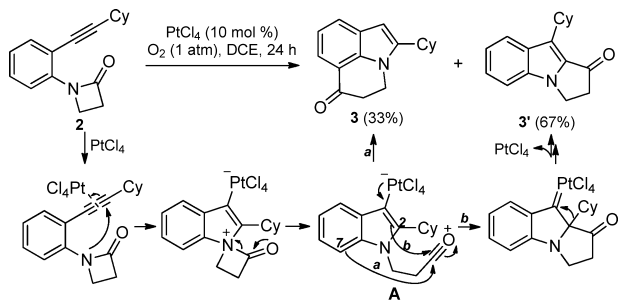
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synthetic approach to this compound, where its tricyclic core is constructed via a key PtCl_2 -catalyzed cycloisomerization reaction; in addition, a designed structural analog, which might possess interesting biological activities, is easily prepared by following a similar synthetic route.

A few years ago we reported a platinum-catalyzed formation of cyclic ketone-fused indoles from *N*-(2-alkynyl-phenyl)lactams.⁷ For example, when the β -lactam **2** was the substrate, the dihydropyrrolo[1,2-*a*]indolone **3'** was formed as the major product (Scheme 1). Mechanistically, the reaction likely begins with an initial Pt-promoted cyclization of the β -lactam nitrogen onto the C–C triple bond and then undergoes heterolytic fragmentation of the amide bond; the acylium intermediate **A** thus formed then cyclizes to either the 7- or 2-position of the indole moiety. In the case of the former, it leads to the minor tricyclic product **3**; in the case of the latter, a Pt carbene is formed, which would promote a 1,2-alkyl migration, eventually yielding **3'**. This rapid access to the pyrrolo[1,2-*a*]indole skeleton provides us with an opportunity to study the synthesis of mitosenes and in particular 7-methoxymitosene, while testing the Pt catalysis under more demanding scenarios.

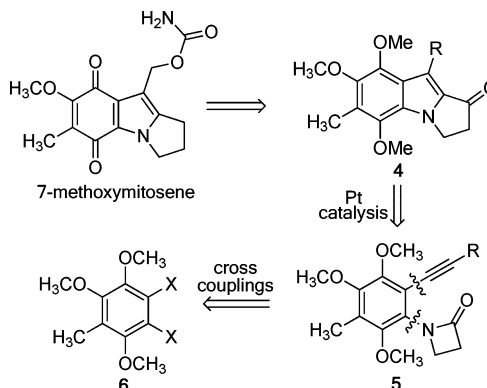
Scheme 1. Example of Pt-Catalyzed Formation of Pyrrolo[1,2-*a*]indolones



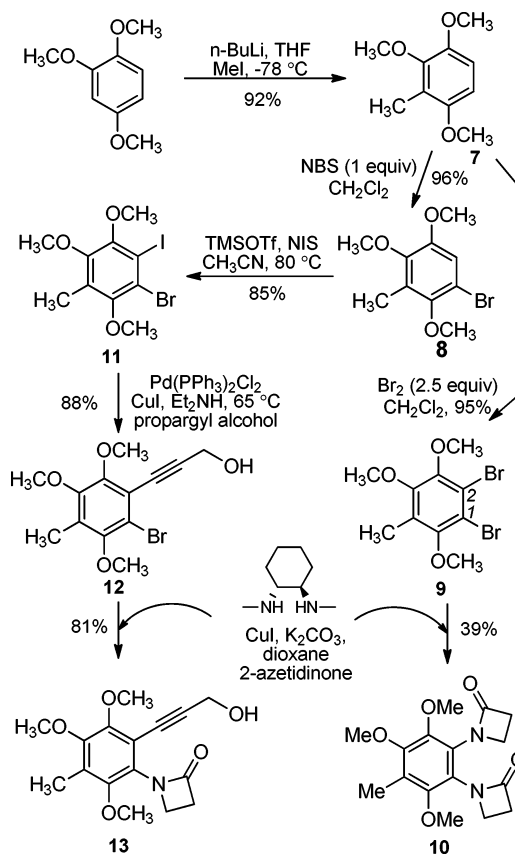
Scheme 2 shows the retrosynthetic analysis of 7-methoxymitosene. This mitosene could be accessed through oxidation and other manipulations of dihydropyrrolo[1,2-*a*]indolone **4**, the precursor of which would be the fully substituted benzene **5** based on our Pt chemistry. The side product of type **3** should be avoided due to substitution at the 7-position of the nascent indole ring. Elaboration of dihalogenated benzene **6** to the sterically congested **5** would rely on regio- or chemoselective sequential coupling reactions.

At the onset, 2,3,6-trimethoxytoluene (i.e., **7**) was prepared in an excellent yield from commercially available 1,2,4-trimethoxybenzene by following a known procedure (Scheme 3).⁸ Treatment of **7** with excess Br_2 results in efficient double bromination, yielding dibromobenzene **9**. Attempts to achieve regioselective mono-cross-coupling of **9** with the parent β -lactam (i.e., 2-azetidinone) surprisingly

Scheme 2. Retrosynthetic Analysis of 7-Methoxymitosene



Scheme 3. Preparation of the Precursor for Pt Catalysis



led to the double coupling product **10**, and neither mono-coupling product was observed at all even with azetidinone as the limiting reagent, suggesting that the second coupling was much faster than the first one. Alternatively, a mono-Sonogashira reaction with **9** was not successful. To achieve regiocontrol in the desired double couplings, we decided to install two different halogens onto **7**. Fortunately, the targeted *ortho*-bromoaryl iodide **11** could be prepared easily via sequential bromination and iodination. Of note, the initial

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bromination was highly regioselective and efficient, yielding the monobromide **8** in 96% yield. A subsequent chemoselective Sonogashira reaction of **11** followed by a Cu-catalyzed C–N bond formation⁹ was delightfully uneventful, providing the propargyl alcohol **13**, the precursor for the key platinum catalysis, in a combined 71% yield.

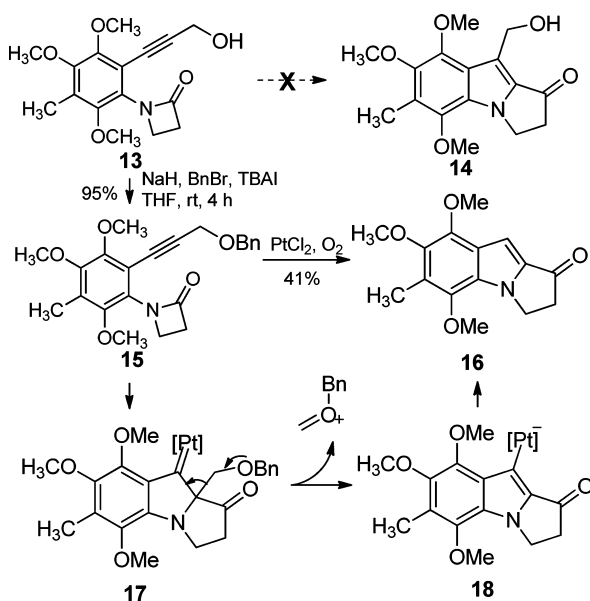
Treatment of the propargyl alcohol **13**, however, led to a messy reaction, and no desired product was detected (Scheme 4). We speculated that the free HO group might be the culprit; consequently, it was capped by a benzyl group. Treatment of the resulting benzyl ether **15** with PtCl₂ (5 mol %) under an oxygen atmosphere still did not afford the desired product; however, to our delight, the anticipated pyrrolo[1,2-*a*]indole skeleton was formed, as the tricyclic ketone **16** was isolated in a 41% yield. Notably, **16** has no substitution at its indole

3-position. The apparent loss of the benzyloxymethyl group during the reaction is rationalized in the same scheme. Apparently, the platinum carbene **17** undergoes C–C bond fragmentation preferentially over the desired Wagner–Meerwein-type rearrangement.

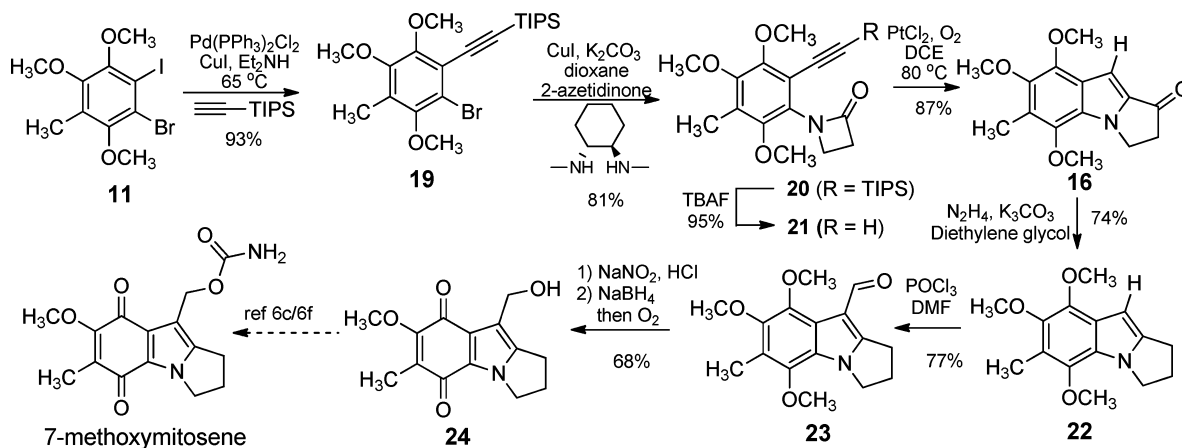
Knowing that the platinum catalysis could work with hindered substrates like **15**, we chose to avoid the problematic alkyl migration process and install the substituent at the indole 3-position at a later stage. The successful execution of this approach is detailed in Scheme 5. Starting from dihalide **11**, the desired arylacetylene **21** was prepared via similar sequential regiocontrolled cross-couplings and then a routine desilylation. The platinum catalysis, to our delight, occurred smoothly, converting **21** into the dihydropyrrolo[1,2-*a*]indolone **16** in 87% yield. With the core structure set, the penultimate structure, hydroxyquinone **24** was accessed via the following sequence: first, a Wolff–Kishner reductive deoxygenation, then a Vilsmeier–Haack reaction to install the formyl group, which was followed by an oxidation of the hydroquinone back to the desired quinone structure. Since the conversion of **24** to 7-methoxymitosene has been achieved previously,^{6c,f} the synthesis of **24** constitutes a formal synthesis of the mitosene.

Although the hydroxymethyl group in **24** could not be secured directly via the Pt catalysis, other R groups might be possible. This approach (i.e., from **5** to **4**, R ≠ H, Scheme 2) would offer a succinct preparative route to various mitosene analogs with potential biological activities. To demonstrate feasibility, we targeted the bisacetate **29** (Scheme 6). Its 1-acetoxy group can act as a leaving group en route to generate a reactive alkylating moiety in a manner similar to the case of the aziridine ring in aziridinomitosenes,¹⁰ and its 9-acetoxyethyl group, though suspect in mimicking¹¹ the carbamoyloxymethyl moiety in aziridinomitosenes/mitomycins in the formation of the second alkylating site,¹² can demonstrate the feasibility of direct installation of functional groups at the 9-position via the Pt catalysis. As shown in Scheme 6, the synthesis of this designed structure commenced with the

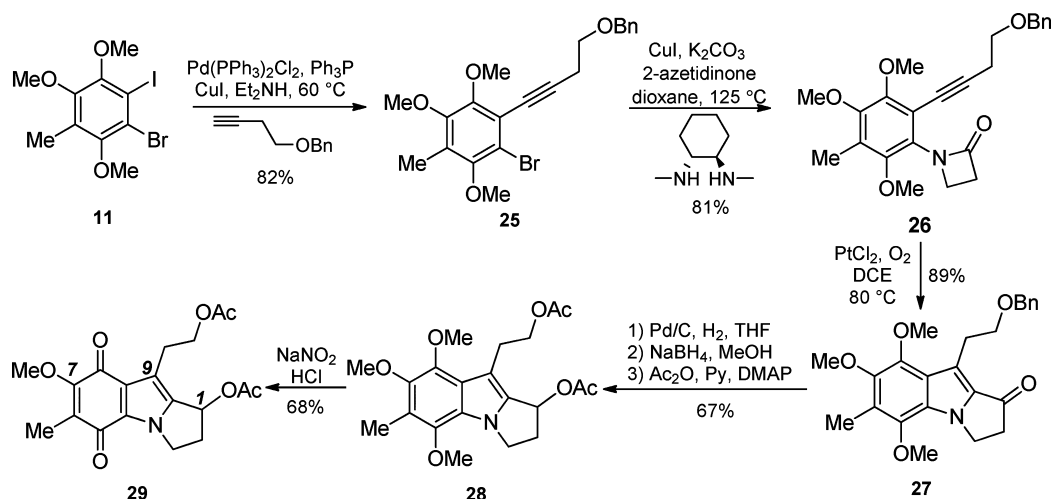
Scheme 4. Initial Studies with PtCl₂-Catalyzed Cycloisomerization: Access to the Pyrroloindole Skeleton



Scheme 5. Synthesis of 7-Methoxymitosene



Scheme 6. Succinct Synthesis of an 1-Acetoxy-7-methoxymitosene Analog



same sequential chemoselective cross-coupling reactions as those in Scheme 5, but but-3-yn-1-yl benzyl ether was used as the alkyne. Much to our delight, the platinum catalysis proceeded with excellent efficiency, delivering the dihydropyrrolo[1,2-*a*]indolone **27** with a 2-benzyloxyethyl substituted at its 9-position in 89% yield. Sequential one-pot hydrogenative debenzoylation, ketone reduction, and double acetylation readily converted **27** into bisacetate **28** in 67% overall yield, which in turn was oxidized to the targeted molecule in 68% yield. This short sequence constitutes a five-pot, seven-step synthesis of the mitosene analog from the dihalide **11** in 27% overall yield. Its biological activities will soon be studied.

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(11) Though we envisioned that a spirocyclopropane intermediate substituted with an iminium moiety could be formed via the expulsion of the acetoxy group by the indole ring, the related structures substituted with an imine moiety were previously shown not to be susceptible toward ring opening. For references, see: (a) Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 1072–1077. (b) Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2004–2007.

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In conclusion, we have successfully applied the platinum-catalyzed cycloisomerization, previously developed in our laboratory, as a key step in a formal synthesis of 7-methoxymitosene. The reaction precursor, a fully functionalized benzene intermediate, is prepared in a succinct manner featuring two highly selective events: a regioselective electrophilic bromination and a chemoselective Sonogashira cross-coupling. The Pt catalysis proceeds smoothly despite the hindered and highly electron-rich nature of the substrate. An analog of 7-methoxymitosene is prepared in an expedient manner by following a similar synthetic sequence.

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Supporting Information Available. Experimental procedures, NMR spectra, and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.