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Alkynyliodonium Salts in Organic Synthesis. Application to the Total Synthesis of the Tropoloisoquinoline Alkaloid Pareitropone

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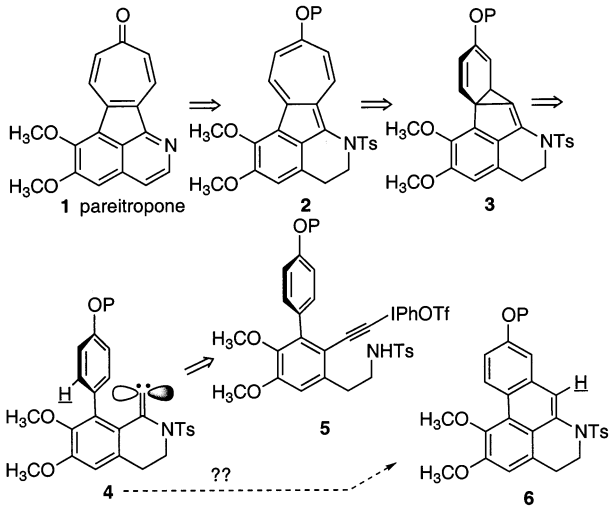
The emergence of alkynyliodonium salts as useful reagents in organic synthesis can be traced to their ready conversion into reactive alkylidenecarbenes upon exposure to weakly basic polarizable nucleophiles.[1] These monovalent carbenes are among the most energetic organic fragments known,[2] and discharge of this energy via a variety of decomposition pathways can result in the formation of new structural frameworks with significant increases in molecular complexity.[3] Nowhere is this paradigm more evident, perhaps, than in the nucleophilic addition of 1-tosylamido-2,4-pentadienes to the simple alkynyliodonium salt phenyl(propynyl)iodonium triflate to furnish bicyclic dihydropyrrole products in a single operation.[4] This sequence involves a pivotal intramolecular cycloaddition of a derived alkylidenecarbene to a proximal alkene that generates a severely strained methylenecyclopropane product. The successful utilization of an electronically unactivated olefin raises the related question of whether an arene ring might be reactive enough to substitute for the alkene in this transformation. Examples of alkylidenecarbene cycloaddition to aromatic rings are scarce,[5,7] but enforced proximity of reactive entities and the availability of a low-energy decomposition pathway for the first-formed methylenecyclopropane may suffice to facilitate this process.

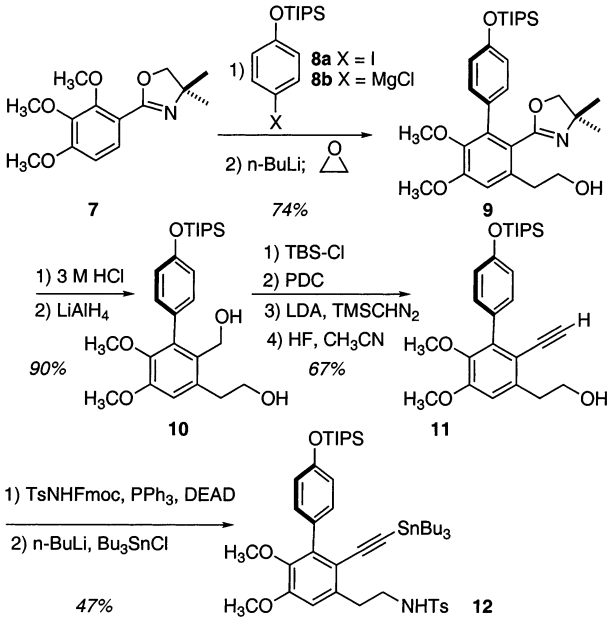
The motivation for pursuing this line of inquiry stems from an interest in the synthesis of the tropoloisoquinoline alkaloid pareitropone (**1**),[6a] Scheme 1. Pareitropone is the most potent anticancer agent among the relatively small family of tropoloisoquinoline alkaloids, with a reported IC_{50} of 2.7 nM versus the P388 leukemia cell line.[6a] Successful syntheses (or attempts at synthesis) of other members of this class (for example, grandirubrine, imerubrine, isoimerubrine),[6b−e] which differ structurally from **1** by the position and extent of oxygenation, have been reported,[8] but the strategies employed in those efforts do not lend themselves to a ready solution for the particular oxygenation pattern of **1**. However, a concise approach to this target structure, which passes through the alkynyliodonium salt **5** and alkylidenecarbene **4** en route to the cycloheptanoid product **2**, can be envisioned.[8f] This strategy is not without risk, as direct 1,6 C−H insertion within carbene **4** to furnish phenanthrene product **6** cannot be dismissed, given the similar alkylidenecarbene-based phenanthrene synthesis reported by Harrington et al.[7] and our own earlier work on this topic.[9] Nevertheless, the successful implementation of this strategy has been realized, leading to the first total synthesis of this potent antileukemic principle.

The assembly of the alkynylstannane cyclization precursor **12** commenced with functionalization of the known oxazoline **7**,[11a] Scheme 2. Fundamental advances in arene addition chemistry from the Meyers laboratory[10] were exploited for the introduction of both the *p*-silyloxyaryl moiety and the ethyl alcohol fragment as shown in the conversion of **7** into **9**.[11] The Grignard reagent **8b** was conveniently prepared from the iodide **8a** using the procedure of Knochel et al.[12] Acid-mediated hydrolysis of the oxazoline unit in **9** required assistance from the pendant alcohol, and the intermediate lactone so formed was reduced cleanly to the diol **10**. Attempts to hydrolyze or reduce the oxazoline ring in a model system (with OTIPS = OCH_3 in **8**) lacking the alcohol unit were frustrated by either recovery of starting material or compound destruction.[13] Thus, combination of the aryl anion derived from lateral metalation of

Scheme 1



Scheme 2



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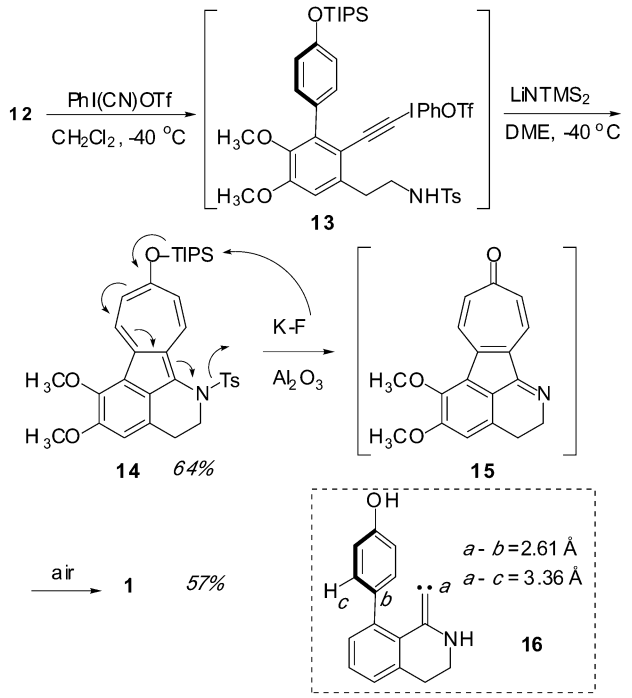
10.1021/ja0277430 CCC: $22.00

Scheme 3



the oxazoline with tosylaziridine (in lieu of ethylene oxide) afforded excellent yields of the desired ethyltosylamide appendage, but this promising intermediate proved to be a dead end.

A more indirect approach to tosylamide introduction, which passed through the alkynol **11**, was pursued. Mitsunobu-type displacement of the alcohol in **11** with TsNHFmoc led to the secondary tosylamide directly, as apparently the Fmoc tosylimide intermediate suffers decarboxyfluorenylation under the mildly basic reaction conditions.[14] Stannylation of the terminal alkyne in the intermediate tosylamide proceeded uneventfully, delivering the cyclization precursor **12** in moderate yield.

Exposure of this alkynylstannane **12** to Stang's reagent (PhI(CN)OTf)[15] at −40 °C followed by solvent removal at this temperature resulted in formation of the iodonium salt **13** as a yellow oily solid which decomposed upon warming to ca. 0 °C, Scheme 3. Dissolution of this residue in DME at −40 °C preserved the integrity of this sensitive species, and subsequent treatment with $LiNTMS_2$ triggered a cascade of reactions that presumably pass through intermediates of the type illustrated in Scheme 1 to deliver the cycloheptatrienylidene product **14** in good yield as the only isolable material. No evidence for an alternative phenanthrene-type product (cf. **6**) could be gleaned from inspection of the crude reaction mixture's ^{1}H NMR spectrum. Perhaps this alkylidenecarbene reaction selectivity can be attributed simply to proximity, as a comparison of the key carbene−arene carbon and carbene−hydrogen distances, revealed by an electronic structure calculation on the model system **16**,[16] argues for reaction at the former site. Unexpectedly, the dark blue-green tetraene **14** could be converted to the natural product pareitropone (**1**) by simple treatment with KF on Al_2O_3 at −78 °C with subsequent warming to ambient temperature. A plausible sequence of events that describes this conversion might include initial fluoride-induced elimination of the elements of Ts-TIPS to afford an unobserved dihydropareitropone intermediate **15**. Apparently, air oxidation of **15** is facile, and the fully aromatic isoquinoline core of **1** provides enough of a thermodynamic sink to drive the reaction to the desired target. The spectral data (^{1}H NMR, ^{13}C NMR) for synthetic pareitropone matched those reported in the literature for the naturally derived material.[6a]

In summary, the tropoloisoquinoline alkaloid pareitropone has been synthesized for the first time in a 14-step route from commercially available 2,3,4-trimethoxybenzoic acid (7% overall yield). The chemistry features a rather cryptic use of alkynyliodonium salts in the context of cycloheptatrienylidene synthesis from aryl ring precursors.

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Supporting Information Available: Characterization data (^{1}H and ^{13}C NMR, IR, LRMS, HRMS, or elemental analysis) and copies of ^{1}H and ^{13}C NMR spectra for **1**, **9**−**12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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