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Alkynyliodonium Salts in Organic Synthesis. Application to the Total Synthesis of (−)-Agelastatin A and (−)-Agelastatin B

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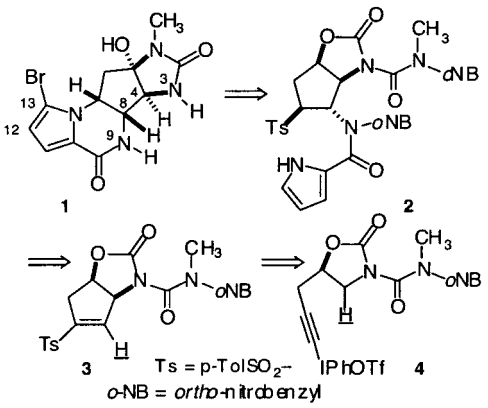
Alkynyliodonium salts have demonstrated utility in the synthesis of functionalized five-membered heterocyclic and carbocyclic systems by virtue of their ability to initiate a reaction sequence proceeding through both nucleophile/electrophile capture chemistry and carbene chemistry to fashion three, and even four, new bonds in a single operation.[1] Whereas these two-carbon reagents can be conveniently prepared by treatment of alkynylstannanes with PhI(CN)OTf (Stang's reagent)[2a] among other procedures,[2] the inherent thermal instability of the more functionally elaborate iodonium salts cautioned against their use in complex molecule synthesis. Ongoing in-house efforts to expand the scope of alkynyliodonium salt chemistry have led to successful protocols for exploiting these conjunctive reagents in increasingly more challenging contexts.[3] The culmination of one such study, the total synthesis of the functionally and stereochemically rich marine alkaloid (−)-agelastatin A (**1**),[4] is described below. This potent antileukemic principle isolated from the sponge *Agelas dendromorpha* features a central cyclopentane ring bearing four nitrogen-substituted stereogenic centers and a sensitive bromopyrrole unit. Facile generation of the pivotal cyclopentane core endowed with suitable functionality for further elaboration of the nitrogen appendages relies on the cyclopentene-forming sequence that initiates with alkynyliodonium salt **4** and proceeds through a putative alkylidenecarbene intermediate to deliver the bicyclic oxazolidinone template **3** (Scheme 1). The concave/convex framework of **3** should enforce the desired stereochemical outcome upon amine addition to C(8). The choice of amide protecting group in **2** is an area of some concern, given the difficulties encountered during its attempted removal in an earlier agelastatin A effort.[5a]

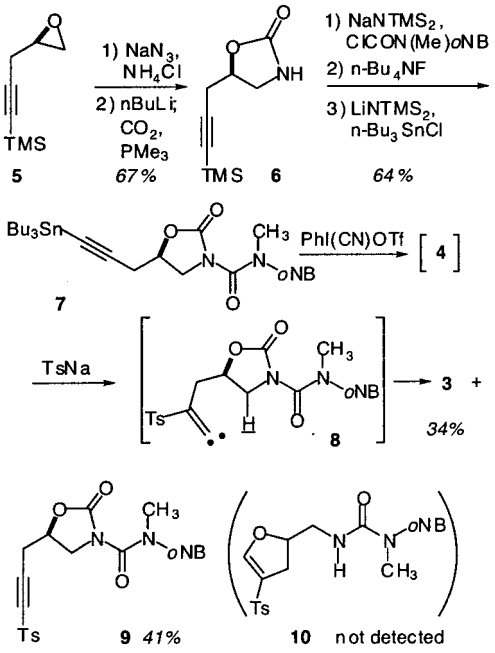
The synthesis of **4** commences with chiral epoxyalkyne **5**, which is readily available through BF_3·THF-mediated[6] addition of LiC≡CTMS to chiral epichlorohydrin.[7,8] Opening the epoxide with azide at the least hindered carbon followed standard procedures,[9] and application of Vilarrasa's oxazolidinone synthesis[10] to the intermediate hydroxyazide delivered **6** in good yield. Conversion of the alkynylsilane to the requisite stannane **7** set the stage for the key transformation in the synthesis route. Exposure of alkynylstannane **7** to Stang's reagent at −42 °C, followed by concentration in vacuo at −42 °C, dissolution of the crude alkynyliodonium salt in DME (−42 → 0 °C), and rapid cannulation of this chilled solution into a refluxing suspension of $TolSO_2Na$ (1 equiv) in DME, led to the isolation of two characterizable products, Scheme 2. The desired cyclopentene **3** was formed in modest yield as a single stereoisomer via 1,5 C−H insertion of the presumed intermediate alkylidenecarbene of **8** into the otherwise unactivated secondary C−H bond of the oxazolidinone unit. The sulfonylalkyne **9**, which plausibly arises from a 1,2-shift within carbene **8**, proved to be the major product. No further information is available at present which addresses the question of S versus C migration in this step, but earlier work by Ochiai et al. on a related alkylidenecarbene indicated that the sulfone and not the alkyl group migrated.[11] No product(s) resulting from alkylidenecarbene insertion into the lone pair of the oxazolidinone's oxygen (i.e., **10**) was observed despite earlier precedent that suggested this possibility.[12]

The synthesis continued with the conjugate addition of *o*-nitrobenzylamine to the unsaturated sulfone moiety within **3** to furnish the secondary amine as the anticipated (vide supra) single diastereomer (Scheme 3). Acylation of this secondary amine with

Scheme 1



Scheme 2



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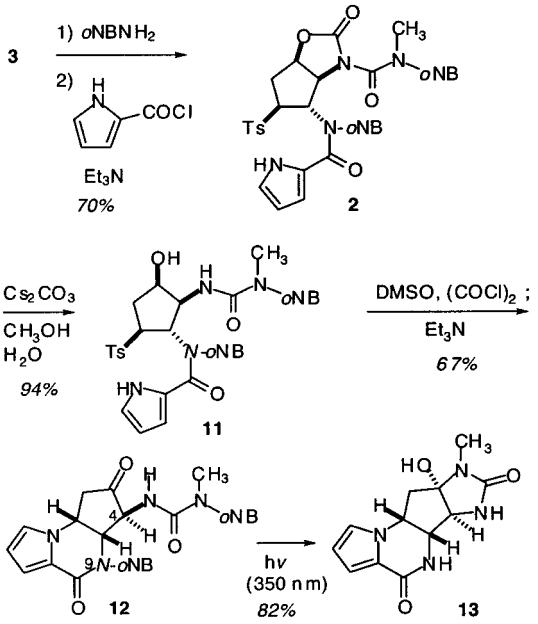
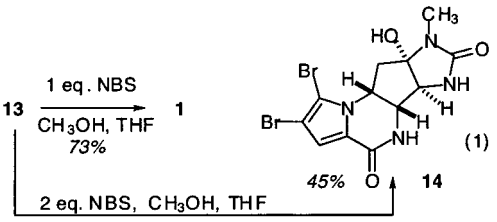
10.1021/ja027121e CCC: $22.00

Scheme 3



the parent pyrrole 2-carboxylic acid chloride furnished amide **2** and presaged bromine addition in the final step of the synthesis. In this way, complications that might arise from carrying a more functionalized pyrrole unit through several steps of the route can be avoided. Facile oxazolidinone hydrolysis without interference from the urea unit led to alcohol **11** in excellent yield. In the second complex transformation of the plan, treatment of alcohol **11** under standard Swern oxidation conditions afforded a single product, tricycle **12**, in good yield. This multistep sequence presumably passes through an unobserved cyclopentenone intermediate. Deprotection of this bis *o*-nitrobenzyl protected species by long wavelength irradiation under strictly neutral conditions led cleanly to debromoagelastatin A (**13**). Earlier exploratory studies with an N(1)-benzyl protected analogue of **12** indicated that when N(9) is substituted, C(4) is quite prone to epimerization.

Completion of the synthesis requires only selective monobromination of the pyrrole moiety at C(13), eq 1.[13] Careful titration of **13** with NBS in a polar solvent mixture afforded (−)-agelastatin A (**1**) essentially free of other brominated products in good yield. Use of excess electrophilic bromine led to the C(12), C(13) dibrominated product agelastatin B (**14**), itself an isolate of *A. dendromorpha*. The identity of the synthesized agelastatin A was confirmed by comparison of ^{1}H NMR and TLC data with that of an authentic sample of the naturally occurring material provided by the Università di Trento group, and by comparison of the ^{13}C NMR spectrum and optical rotation with published data.



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Supporting Information Available: Characterization data ($[\alpha]^{20}_D$, ^{1}H and ^{13}C NMR, IR, LRMS, HRMS, or elemental analysis) and copies of ^{1}H and ^{13}C NMR spectra for **1**−**3**, **6**, **7**, **9**, and **11**−**14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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