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Aziridinomitosenes by Anionic Cyclization: Deuterium as a Removable Blocking Group

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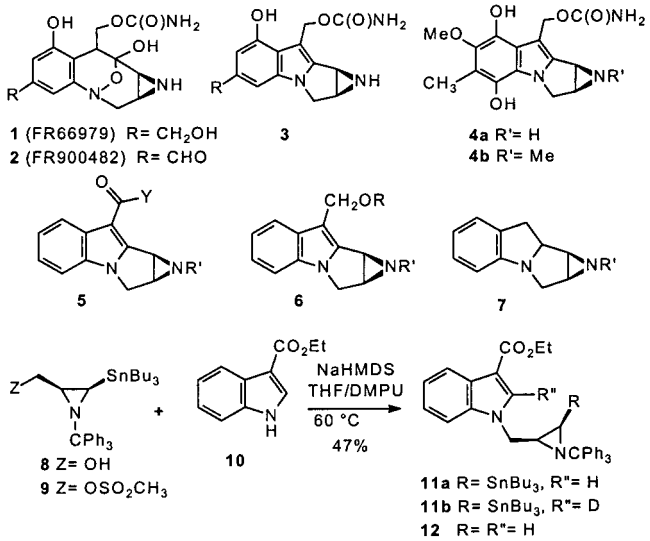
Metabolic activation of FR66979 (**1**) and FR900482 (**2**) is believed to generate transient intermediates **3** that have the ability to cross-link DNA.[1−3] The structurally related leucoaziridinomitosenes **4** play a similar role as the species responsible for the antitumor activity of the mitomycin antiobiotics.[4] Danishefsky and Egbertson were able to observe **4b** in solution using NMR methods, but the molecule was too labile for isolation and decomposed within minutes in the presence of water.[5] So far, there have been no reports of the direct observation of **3,** although derivatives resulting from aziridine ring cleavage have been characterized.[3]

Synthetic access to the tetracyclic skeleton common to **3** and **4** has been achieved,[6] and aziridinomitosene A, the quinone corresponding to hydroquinone **4a**, has been prepared by total synthesis.[6a] The quinone is considerably more stable than is **4a** because the carbonyls participate in vinylogous amide delocalization, a factor that is important for survival of the aziridine. Similar delocalization helps to stabilize carbonyl derivatives such as **5**, and several examples of related aldehydes, esters, or quinones are known.[6b] Lactam analogues of the leucoaziridinomitosenes are also well characterized.[6c] However, analogues of **3** or **4** that lack carbonyl stabilization for the indole nitrogen are virtually unknown. As far as we are aware, the bis-triethylsilyl ether of naturally derived **4b** is the only reported leucoaziridinomitosene that has been isolated.[5] No other examples containing the nonstabilized core structure **6** (basic indole nitrogen; alcohol oxidation state in the side chain) could be found in the literature. In contrast, leucoaziridinomitosane analogues containing the subunit **7** are well-known (indoline subunit in place of indole).[6e,7] These observations reflect the activating role of the indole double bond on heterolysis of adjacent C−N and C−O leaving groups, a factor that destabilizes **3**−**6** and leads to DNA cross-linking by **1**−**4**.[3,4]

We have been interested in the possibility that **5** might be available from a stannyl aziridine precursor **8**[8,9] by coupling with **10** followed by metal exchange and intramolecular Michael addition. While our studies were in progress, Ziegler and Belema reported a closely related intramolecular radical cyclization that affords substituted derivatives of **7**.[7] We anticipated that the anionic (internal Michael) variation would prove better suited for access to sensitive leucoaziridinomitosene derivatives **5**, assuming that the intermediate enolate could be intercepted by electrophiles that can undergo facile elimination to the indole.

To test the above proposition, **11a** was prepared from the serine-derived aziridine alcohol **8**[8,9] via the mesylate **9** and coupling with the indole carboxylate **10**. Preliminary attempts to effect metal exchange and internal Michael addition from **11a** revealed a complex situation. Typical experiments using excess methyllithium at −65 °C followed by aqueous quench produced a mixture of starting material **11a**, the destannylated **12**, as well as two stereoisomeric products that could not be separated. Since the initial



structural assignments had to be made based on NMR spectra of the mixtures, it proved helpful to evaluate the product ratios after workup with deuterated ethanol, as shown in experiment (1). Deuterium quench simplified the spectra, and allowed the tentative conclusion that **11a** had been converted into its monodeuterio derivative **11b**, the corresponding de-stannylated dideuterio structure **13**, and a small amount of the desired tetracyclic **14**. The identity of **11b** was easily confirmed by comparison of NMR signals with **11a**, and by the observation that **11b** is formed cleanly if **11a** is treated with phenyllithium with subsequent quenching of the C-lithio indole intermediate with deuterated ethanol.

Numerous attempts to improve the conversion to **14** gave no more than 10−15% of the tetracyclic product, and prolonged reaction times or higher temperatures increased the relative amount of destannylation to **13**. A key observation was made in the course of the deuterioethanol quenching experiments starting from **11a**. Destannylated **13** was always obtained with the indole proton completely replaced by deuterium, within the limits of NMR assay, while **14** was formed with the original indole proton intact (δ 4.80 ppm). This suggested that formation of **15** prevents Michael addition, and that the 10:1 ratio of (**11b** + **13**):**14** reflects the relative rates of indole C−H lithiation vs tin−lithium exchange. If this is correct, then monodeuterated **11b** (easily available from the PhLi; EtOD experiment, above) should be a better substrate for cyclization because it is protected from the undesired indole lithiation by a kinetic isotope effect, and might be used in place of **11a**. Accordingly, **11b** was treated with 4 equiv of methyllithium at −65 °C (15 min), followed by quenching with EtOH. This gave a dramatically altered ratio of products, including recovered **11a** (5%, from quenching of the undesired **15**), **12** (17%, from **15** followed by tin−lithium exchange), and **18** (78%, from the desired cycliza-

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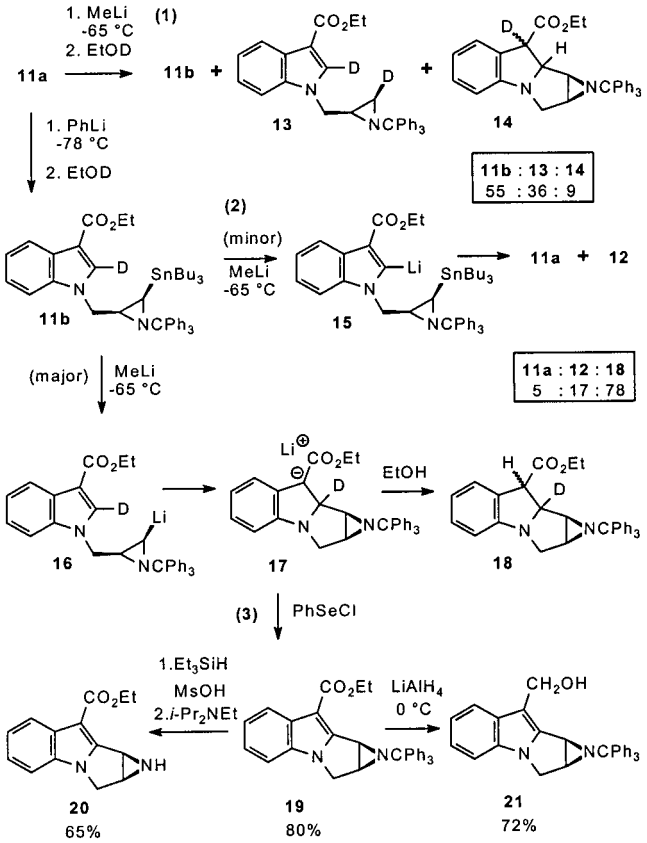

tion of **16** to form enolate **17**). A comparison of NMR signals confirmed the isomeric relationship between **14** and **18**, but the tetracyclic product could not be obtained free of **12**. We therefore repeated the cyclization sequence from **11b** using phenylselenenyl chloride to quench the intermediate enolate **17**, experiment (3). The presumed selenide intermediate was not detected, but the elimination product **19** was obtained in 80% yield based on **11b**, 71% for the two steps (deuteration; cyclization) from **11a**, or 19% overall (7 steps from *N*-tritylserinal). If the tricyclic side products **11b** and **13** in experiment (1) and **11a** + **12** in experiment (2) are formed only from the lithiated indole **15**, then the kinetic deuterium isotope effect is responsible for the inversion of tetracyclic:tricyclic product ratios from 1:10 in experiment (1) to ca. 4:1 in experiments (2) or (3), and k_H/k_D for generation of **15** is ca. 35.

A similar anionic cyclization sequence leading to **3** may be feasible if *N*-trityl cleavage and reduction of the ester can be achieved. The prospects were evaluated with **19** as a test case. Reductive de-tritylation with triethylsilane/MsOH under the recently optimized conditions[10] gave the parent N−H aziridine **20** (65%). This is the first example of aziridine deprotection in the presence of the activating indole. Also surprising was the relative ease of reductive conversion of **19** into the isolable aziridinomitosene alcohol **21** using lithium aluminum hydride (4 h, 0 °C). No special precautions were used in the reduction or the aqueous workup at 0 °C, although chromatographic purification of **21** required buffered silica gel to prevent solvolytic aziridine ring opening. The absence of a phenolic hydroxyl group in **21** compared to structures such as **3** or **4** should substantially increase stability, but the relative ease of handling **21** was unexpected and suggests that isolation of **3** may be an attainable synthetic goal in ongoing studies.

There are a number of prior reports where substantial deuterium isotope effects have been encountered in lithiations, and were used to address issues of selectivity.[11] A value of k_H/k_D of ca. 35 for indole ring lithiation implies tunneling, as discussed in related examples where considerably larger k_H/k_D values have been observed.[11c,d,g,h,12] Clive et al. have also described a case where a deuterium isotope effect helps protect against an undesired C−H abstraction by a radical intermediate,[12] and Clayden et al. have commented on the protecting group implications of deuterium in lithiations.[11g] However, the conversion from **11b** to **19** is unique in that deuterium serves as a blocking group in the tin−lithium exchange step and is removed in the subsequent cyclization, selenenylation, elimination sequence. The strategic benefits are reflected in a concise synthesis of sensitive aziridinomitosene derivatives.

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Supporting Information Available: Characterization of isolable intermediates and key experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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