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# Synthesis of the Aziridinomitosene Skeleton by Intramolecular Michael Addition of α-Lithioaziridines: An Aromatic Route Featuring Deuterium as a Removable Blocking Group

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A convergent synthetic route to the 1,2-aziridinopyrrolo(1,2-*a*)indole **34** has been developed. Key features of this route include the deuterium kinetic isotope effect to block undesired indole lithiation during tin−lithium exchange from **27a** to **30a**, the intramolecular Michael addition to generate the enolate **31a**, and conversion into **34** by trapping with phenylselenenyl chloride. Reductive cleavage of the *N*-trityl group in **34** allows access to tetracyclic aziridinomitosenes containing the aziridine N−H subunit. Reduction of the C(9) ester in **34** with LAH gives the primary alcohol **35** with the correct C(9), C(9a), C(10) oxidation state corresponding to the aziridinomitosenes, and deprotection of **34** affords **37**.

The unusual oxygen-bridged benzoazocine antitumor agents FR66979 (**1**) and FR900482 (**2**) form interstrand DNA cross-links upon reductive activation.[1,2] Solvolytically labile intermediates **5** and **6** are believed to explain the activity,[3] by analogy to the mode of action of mitomycin C.[4] The semisynthetic **3** (FK973) is no longer regarded as a promising drug candidate due to vascular leak syndrome (VLS),[5] but renewed interest in related compounds has been stimulated by reports that the closely related FK317 (**4**) retains activity, but does not have the VLS side effect.[6−8]

Both **5** and **6** contain the aziridinopyrrolo(1,2-*a*)indole ring system, a tetracyclic nucleus that was originally encountered in the mitomycin antibiotics.[9,10] Many synthetic approaches to the tetracyclic skeleton of aziridinomitosenes have been reported,[10−26] including several

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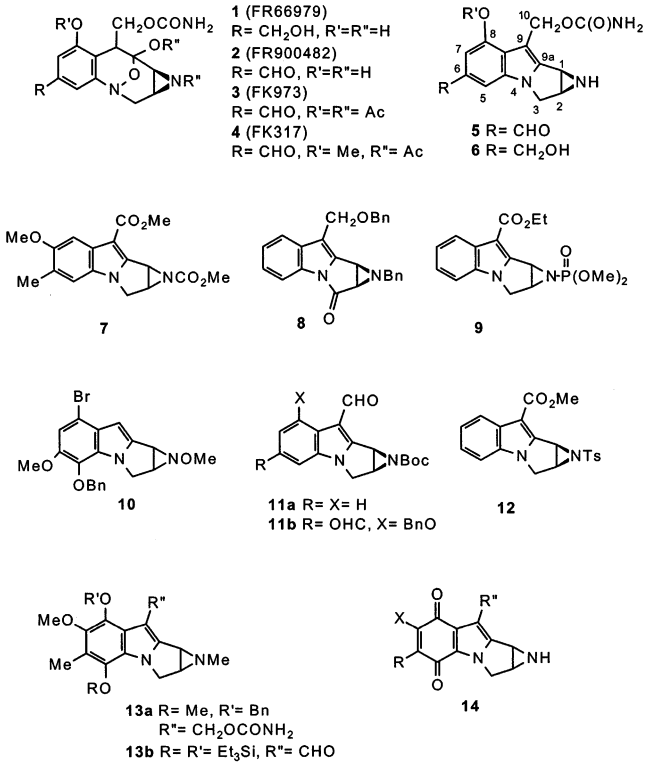
indole structures **7**−**12** that resemble **5** or **6**.[12−22] However, highly reactive indoles containing the natural substitution pattern of **5** or **6** have rarely been observed, and none have been prepared by total synthesis. The only isolable substance having the correct oxidation state at C(3), C(5), C(8), and (especially) C(9a)−C(9)−C(10) is the semisynthetic **13a** reported by Danishefsky and Egbertson.[16] Among the fully synthetic structures **7**−**12**, difficulties in removing the protecting groups at aziridine nitrogen may be inferred from the absence of reports where deprotection has been accomplished at the indole stage. Most of the synthetic structures also contain stabilizing carbonyl groups, as in the vinylogous carbamates **7**,[12] **9**,[22] or **12**,[21] the lactam **8**,[13] and the vinylogous formamides **13b**[17] or **11**.[19,20] These compounds have lower solvolytic reactivity at the "benzylic" aziridine C(1)−N bond because of the electron-withdrawing effect of the conjugated carbonyl group.

Stability is significantly improved in the absence of the activating C(9),C(9a) double bond, as in the indoline (aziridinomitosane) structures prepared by Ziegler and Belema,[25] or in the natural mitomycins and related molecules encountered in total synthesis efforts.[10,26] A number of aziridinomitosene quinones of the general structure **14** are also known.[11,24] Because of the strong electron-withdrawing effect of the quinone carbonyl groups and vinylogous amide delocalization, the quinones **14** are relatively stable compared to **13**. Nevertheless, all of the aziridines having an adjacent pyrrolic double bond are easily cleaved in acidic hydroxylic media. This is the reason synthetic analogues of **5** or **6** have been so difficult to prepare. Accordingly, we have initiated a program designed to access structures **5** and **6**. Progress toward this goal is described below in the context of a synthesis of tetracyclic indole derivatives having the correct oxidation pattern at C(9a)−C(9)−C(10).

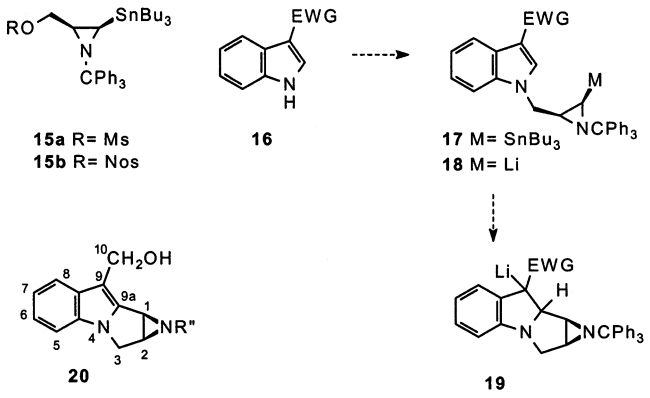
## Results and Discussion

Initial studies focused on determining the feasibility of the intramolecular Michael addition of an α-lithioaziridine **18** to a suitably activated indole subunit (Scheme 2). A parallel approach with nonaromatic precursors has been evaluated in the preceding article, and has encountered partial success as well as major difficulties in the cyclization step.[23] In the current approach, a fully aromatic (indole) precursor **17** was to be prepared from the same aziridinyl mesylate **15a** or nosylate **15b** alkylating agents used in the nonaromatic approach.[23b] The key issue was whether the internal Michael addition from **18** would generate an enolate **19** that might be captured by external electrophiles en route to potential targets **20**. Success was not assured in view of the competing lithiation adjacent to the pyrrolic nitrogen that had been observed in the nonaromatic series.[23b] Other important issues to be resolved include removal of the *N*-trityl protecting group and reduction of the C(10) ester to the correct alcohol oxidation state. Neither conversion has been reported in aziridinomitosenes containing an indole subunit.

**SCHEME 1**




**SCHEME 2**




The indole ester **16a** was conveniently prepared from the commercially available acid **21** by *O*-alkylation of the cesium salt with ethyl iodide (73% isolated; Scheme 3).[27] Subsequent coupling with nosylate **15b** followed the precedent developed in the nonaromatic series.[23b] Thus, a THF/DMPU solution of **16a** was deprotonated at −78 °C with $NaN(TMS)_2$ and addition of **15b** in THF gave a deep purple solution. After warming to room temperature and heating at 60 °C, **17a** was obtained in 40% yield, together with ca. 20% of the alcohol corresponding to nosylate S−O bond cleavage in **15b**. Marginally higher yields of **17a** (47%) were achieved when the mesylate **15a** was used in place of **15b**, but the coupling was slower and heating for 3 days at 60 °C was required. The same procedures were also used to prepare the nitrile and sulfone analogues **17b** and **17c** with similar results, starting from the commercially available nitrile **16b** and

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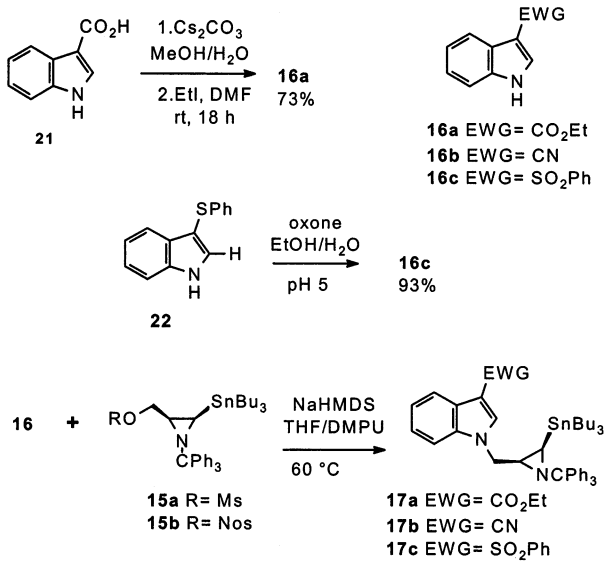
**SCHEME 3**

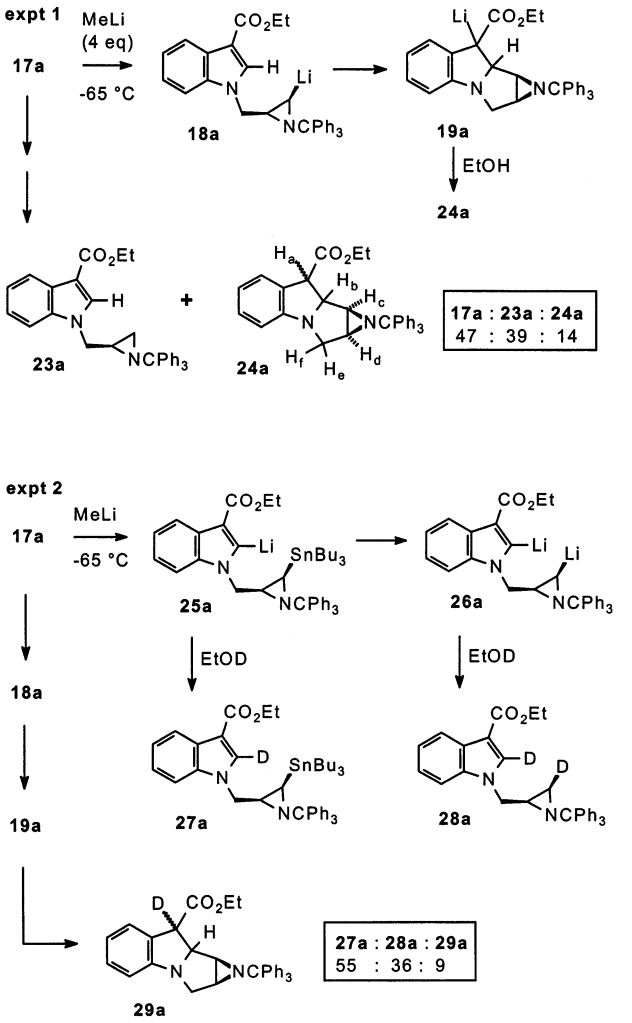



the known sulfone **16c**, prepared from **22** by oxidation with oxone.[28,29]

With a route to cyclization substrates **17** in place, studies of the tin−lithium exchange and internal Michael addition were initiated in the ester series, Scheme 4, expt 1. Treatment of a cold solution of **17a** in THF with excess methyllithium (4 equiv, 15 min) followed by an ethanol quench resulted in a mixture of starting material (**17a**), destannylated **23a**, and the desired tetracycle **24a**, in a 47:39:14 ratio, respectively. The two diastereomers **24** could not be separated from **23** and the NMR spectrum of the mixture proved difficult to interpret. Eventually, the NMR signals for one diastereomer of **24** were deduced from a combination of decoupling studies and insights gained from deuterium labeling as discussed below. Specific signals were identified corresponding to $H_e$ ($\delta$ 3.85 ppm, d, $J = 11$ Hz) and $H_f$ ($\delta$ 3.25 ppm, d, $J = 11$, 4 Hz), the aziridine protons $H_c$ ($\delta$ 2.12 ppm, d, $J = 5$ Hz) and $H_d$ ($\delta$ 2.35 ppm, dd, $J = 5$, 4 Hz), the C-9 proton $H_a$ ($\delta$ 4.05 ppm, d, $J = 7$ Hz), and the C-9a proton $H_b$ ($\delta$ 4.78 ppm, d, $J = 7$ Hz), and confirmed the tetracyclic skeleton as well as retention of configuration at the aziridine.

The formation of **23a** as the major product in expt 1 was initially taken to mean that some form of competing proton transfer had compromised the experiment. When conversion to **24** could not be improved by minimizing hydroxylic contaminants, nor by optimizing time or temperature variables, an experiment was performed with EtOD to quench the reaction and to test for the survival of organolithium intermediates, expt 2. This procedure revealed that lithiated species **25a** and **26a** are formed in competition with the desired tin−lithium exchange from **17a** to **18a**. A mixture of deuterium-labeled products **27a**, **28a**, and **29a** was obtained in a ratio of 55:36:9 according to $^1$H NMR assay. Significantly, the destannylated product **28a** was obtained with the indole proton completely replaced by deuterium, while the tetracyclic **29a** was formed with the original indole

**SCHEME 4**




proton intact. By implication, cyclization to **29a**, or **24a** in expt 1, is possible only to the extent that tin−lithium exchange to **18a** precedes competing events such as the formation of **25a**. The latter process dominates, as evidenced by the isolation of **27a** as the major product in expt 2. The desired intramolecular Michael addition from **18a** to **19a** may well be an efficient process, but the overall conversion from **17a** would be practical only if the competing lithiation to **25a** can be suppressed.

Optimization of the organolithium reagent was investigated with the aim of improving the ratio of tin−lithium exchange to **18a** vs indole lithiation to **25a**. After considerable effort, no better reagent for the intended purpose was found. Instead, an efficient procedure for the indole lithiation was encountered. Thus, treatment of **17a** with phenyllithium (PhLi) at −65 °C for 15 min, followed by subsequent trapping with EtOD, resulted in the deuterated product **27a** in 89% yield (Scheme 5). No evidence for tin−lithium exchange was seen in this reaction, even though PhLi has been used in analogous exchange reactions.[30] Similarly, tin−lithium exchange did not occur with *n*-butyllithium, the reagent most commonly used for such transformations,[31] nor with *sec*-

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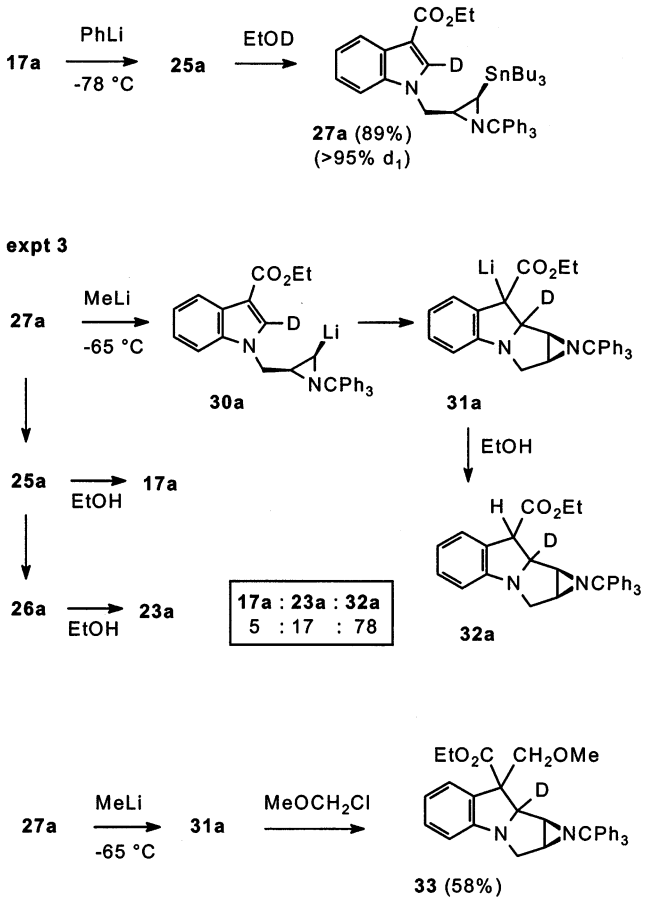
**SCHEME 5**




butyllithium or *tert*-butyllithium. Evidently, the stannylaziridine environment is too hindered for facile tin−lithium exchange with reagents other than MeLi, a trend that was also observed in the nonaromatic series.[23b]

Several blocking strategies were contemplated that might prevent the competing formation of **25a** and **26a**. By far the simplest method emerged when we realized that a potential "blocking group" had already been introduced in the sequence where **17a** was treated with phenyllithium, followed by quenching with EtOD to give **27a**. The stronger C−D bond in **27a** should resist lithiation due to the well-known kinetic isotope effect.[32]

In the key experiment (3), Scheme 5, **27a** was reacted with excess MeLi at −65 °C, followed by quenching with EtOH. This gave a mixture of **17a**, **23a**, and **32a** in a 5:17:78 ratio (Scheme 5), corresponding to a dramatically improved 71% yield of the desired tetracycle **32a**. Analysis of the starting material zone recovered by chromatography revealed that the deuterium blocking group had been lost (as in **17a**). The destannylated **23a** had also lost the deuterium label, as expected if lithiation of the indole ring prior to tin−lithium exchange had occurred to some extent, and had prevented cyclization of ca. 20% of the material. However, this process was now the minor pathway, in striking contrast to the results of experiments 1 or 2, Scheme 4. If the tricyclic byproducts **27a** and **28a** in expt 2 and the analogous products **17a** and **23a** in expt 3 are formed only via the lithiated indole **25a**, then the kinetic deuterium isotope effect for indole lithiation can be estimated as $k_H/k_D$ = ca. 35. This kinetic effect is responsible for the inversion in tetracyclic:tricyclic product ratios from 1:10 in expt 2 to ca. 4:1 in expt 3.

Another cyclization experiment was performed to confirm that the internal Michael reaction affords a long-lived enolate intermediate as we have assumed in the above discussion. Treatment of **27a** with MeLi at −65 °C, followed by addition of methoxymethyl chloride and warming to room temperature gave an alkylation product **33** in 58% yield (2:1 diastereomer mixture). Although this compound was not elaborated further, its formation demonstrates that the deuterium-containing enolate **31a** is the intermediate in the cyclization, and can be trapped by typical electrophiles as expected.

With the feasibility of the Michael addition strategy demonstrated for ester **17a**, studies were extended to evaluate other electron-withdrawing groups (CN, $SO_2$-Ph) in the analogous substrates **17b** and **17c** that had been prepared as described earlier in connection with Scheme 3. A preliminary attempt to achieve cyclization from **17b** with methyllithium was not promising, so the deuterium blocking strategy was employed. However, unexpected complications were encountered in the lithiation of **17b** with PhLi (Scheme 6). Quenching the organolithium intermediates with EtOD gave the expected product **27b** (46%), but a substantial amount of destannylated **28b** (27%) was also formed via premature tin−lithium exchange to generate **26** as well as **25**.

Although a clean indole ring deuteration was not achieved, sufficient **27b** was obtained after chromatographic separation to explore tin−lithium exchange and conversion to tetracyclic products. Reaction of **27b** with 2 equiv of MeLi at −65 °C followed by ethanol quenching produced a mixture of **23b** and **32b** in a 1:3 ratio in favor of the cyclized product (67% combined yield). Under the conditions optimized for the ester analogue **27a** (4 equiv of MeLi), nitrile **27b** gave relatively more of the destannylated product **23b**. This result reflects facile conversion from **25b** to **26b** in the nitrile series, as also observed in the phenyllithium experiment starting from **17b**. In view of this disadvantage compared to the ester sequence from **17a** or **27a**, the nitrile series was not pursued further.

Attention was turned to the sulfone **17c** as a potential substrate for cyclization (Scheme 6). Given the large change in steric and electronic variables for the phenylsulfonyl group of **17c** compared to the carboethoxy (**17a**) or nitrile (**17b**) analogues, the cyclization of **17c** was attempted without prior deuteration of the indole ring. However, the usual conditions with excess MeLi followed by quenching with EtOD gave no cyclized product.

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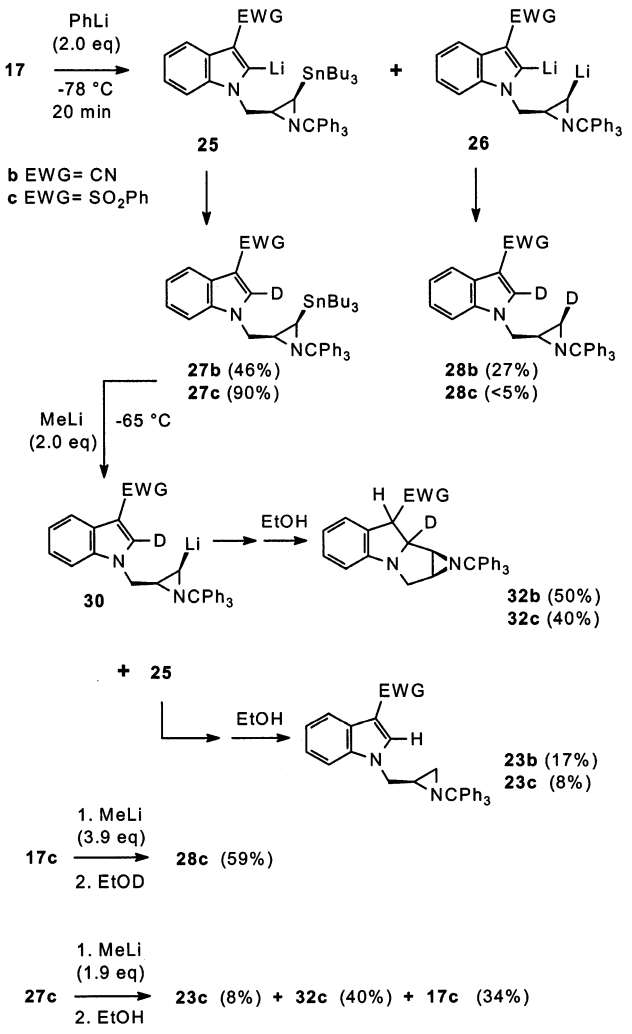
**SCHEME 6**

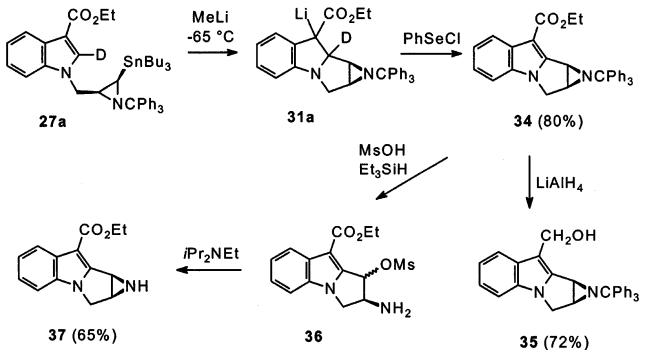



Instead, **28c** was isolated in 59% yield. Clearly, the undesired indole lithiation was even more dominant than in the ester series (**17a**) and it was necessary to use the deuterium blocking effect. Accordingly, **17c** was treated with PhLi (2 equiv) at −78 °C, followed by EtOD to afford **27c** in 90% yield. The use of more than 2 equiv of PhLi for deuterium incorporation in this system gave lower yields of **27c**, but destannylation products were not detected.

Tin−lithium exchange experiments with **27c** proved to be difficult and required re-optimization. The best result was obtained at −65 °C with 1.9 equiv of MeLi (15 min), followed by EtOH quench. This afforded a mixture of tetracyclic **32c**, recovered **17c**, and destannylated **23c** (40%, 34%, and 8%, respectively). Thus, the sulfonyl series proved to be the most susceptible to indole lithiation (to **25c**), although the deuterium blocking effect was still sufficient to favor tin−lithium exchange to **30c** and eventual cyclization.[33]

The nitrile and sulfone cyclization experiments demonstrated no preparative advantage over the ester substrate **27a** in the critical tin−lithium exchange process,

**SCHEME 7**




and separation of the diastereomers of tetracyclic **32** from the destannylated **23** was not feasible in any of the cyclization reactions. No further experiments were attempted with **27b** or **27c**, and attention was turned to the redox and deprotection steps that would be needed to convert **27a** into tetracyclic indole alcohols having the substitution pattern of structure **20**, mentioned earlier (Scheme 3).

The immediate problem was to prepare an indole from the deuterium-containing enolate **31a** resulting from the intramolecular Michael addition (Scheme 7). To this end, the cyclization sequence from **27a** was repeated, and the enolate **31a** was reacted with phenylselenenyl chloride. No intermediates were detected. Instead, the indole product **34** was isolated in 80% yield based on **27a**, or 71% for the two steps from **17a** (including deuteration and cyclization), 19% overall (7 steps from *N*-tritylserinal). Side products were detected in the cyclization experiment, presumably derived from selenenylation of anionic intermediates such as **26a** and **30a**, but these minor products could not be separated or purified.

In contrast to the ethanol quench procedure used in the initial cyclization experiments from **27a**, the PhSeCl experiment produced a single dominant product **34** that was easy to separate from the side products. The 80% yield of **34** is consistent with the ratio of tetracyclic **24a** or **29a** compared to tricyclic products that had been deduced for the ethanol quenching experiments with NMR methods to analyze product mixtures, and confirms the estimated kinetic isotope effect responsible for the greatly improved efficiency of cyclization in the deuterated series from **27a**.

Contrary to expectations based on the lack of literature precedents in the aziridinomitosene series, reduction of **34** to **35** proved to be relatively easy with lithium aluminum hydride in diethyl ether at 0 °C (Scheme 7). Alcohol **35** was isolated in 72% yield with use of silica gel chromatography, although it was necessary to prewash the silica plates with hexane/$NEt_3$. Without this precaution, facile destruction of the aziridine occurred, presumably by heterolysis of the labile C(1)−N bond. By comparison, the starting ester **34** was considerably more stable, a consequence of vinylogous carbamate delocalization and the electron-withdrawing effect of the ester. For this reason, removal of the *N*-trityl group with use of our recently optimized method[34] was explored at the ester stage. When ester **34** was treated with 3 equiv of

(33) The sulfide series corresponding to the sulfone was also briefly investigated. No cyclization products were detected upon tin−lithium exchange, and destannylation was the exclusive pathway.

(34) Vedejs, E.; Klapars, A.; Warner, D. L.; Weiss, A. H. *J. Org. Chem.* **2001**, *66*, 7542.

$Et_3SiH$ and 3 equiv of MsOH, quenching the reaction with excess *i*-$Pr_2NEt$ (1.5 h) resulted in the deprotected aziridine **37** (65%).[35] Presumably, this reaction involves a labile ring-opened intermediate **36** that undergoes recyclization upon addition of the *i*-$Pr_2NEt$, a sequence of events that was observed in a model study of deprotection with a solvolytically sensitive aziridine substrate.[34] The conversion from **34** to **37** is the first example to our knowledge of successful aziridine nitrogen deprotection in the aziridinomitosene indole series.

In summary, a convergent synthetic route to 1,2-aziridinopyrrolo(1,2-*a*)indole derivatives has been developed. Key features of this route include the deuterium kinetic isotope effect to block undesired indole lithiation, as well as the intramolecular Michael addition of a configurationally stable *C*-lithioaziridine in the cyclization step. The deuterium blocking effect is precedented in prior work where similar or even larger isotope effects had been observed in lithiations,[32] but the current example from **27a** to **34** is unusual because the deuterium disappears in the next step after having served its blocking role.

Reductive cleavage of the *N*-trityl group allows access to tetracyclic structures containing the aziridine N−H subunit via a late-stage deprotection. Furthermore, reduction of the C(9) ester moiety with LAH demonstrates access to **35** containing the C(9) side chain at the oxidation state found in the DNA cross-linking agents **5** and **6**. Synthesis of these more highly substituted structures will require modified timing in the sequence of reduction and deprotection steps so that the C(10) carbamate group can be attached without interference by the aziridine. Experiments toward this goal are under way, and will be reported in due course.

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

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(35) According to NMR comparisons, structure **37** is identical with the major component obtained by Michael et al. using a different approach (ref 22). We thank Dr. Michael for providing copies of the NMR spectra.

(36) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
(37) Kašpárek, S.; Heacock, R. *Can. J. Chem*. **1966**, *44*, 2805.