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Synthesis of the Aziridinomitosene Skeleton by Intramolecular Michael Addition: α-Lithioaziridines and Nonaromatic Substrates

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The bicyclic pyrrole ketone **16** has been prepared by using an oxaza-Claisen rearrangement, followed by nitrogen deprotection. Coupling with the stannylaziridine mesylate **15a** or nosylate **15b** affords **17**. Conversion to **40** provides a substrate for generation of an α-lithioaziridine **41** by tin lithium exchange. An intramolecular Michael addition pathway for **41** has been demonstrated by the isolation of **46** in 20% yield under conditions where the intermediate enolate **43** is trapped by selenenylation, but competing proton transfer gives **42**. The synthetic potential of the process is limited by stability problems at the stage of the enolate **43** or the protonated product **44**.

There has been considerable interest in the "FR" compounds **1** and **2** due to their potent antitumor activity.[1,2] However, clinical trials of a related structure (FK973) encountered vascular leak syndrome (VLS).[3] Subsequent efforts to develop a drug candidate lacking this side effect have resulted in the discovery of FK317, a semisynthetic substance that retains high potency without inducing VLS.[4] This observation has revived interest in the "FR" series, and has refocused attention on the mode of action of these unusual molecules. A multistage activation mechanism has been proposed for the "FR" compounds, featuring reductive N−O bond cleavage followed by cyclization and aromatization to the labile tetracyclic intermediates **4** and **5**.[5] These structures bear a close resemblance to the leucoaziridinomitosenes that play an important role as intermediates in the reductive activation of mitomycins, and in DNA cross-linking events that are responsible for their antitumor activity.[6] Strong evidence has been advanced to support a similar mode of action by **4** and **5**,[7] and it is likely that analogous structures such as **6** and **7** may be involved in the activation sequence from FK317 (**3**).[4] So far, none of the proposed structures **4**−**7** have been observed directly or generated by total synthesis, although progress toward the tetracyclic skeleton has been reported.[2]

We have initiated a program designed to prepare **6** and **7** for the eventual study of their role in the activation cascade from FK317. Two closely related approaches have been investigated in parallel studies, based on the proposition that intramolecular nucleophilic addition starting from α-tributylstannylaziridines **8** or **10** may allow synthetic access to the tetracyclic structures **9** or **11**. The key cyclization step in the aromatic series (**8** to **9**) has been achieved, as described in a preliminary report from our laboratory, and detailed in the accompanying paper.[8] Here, we report our earlier efforts to develop an approach based on nonaromatic precursors related to **10**. The synthesis exploits prior methodology developed in our group for the generation of α-lithioaziridines.[9] While our work was under way,[10] Ziegler et al. described a strategically similar approach to tetracyclic aziridinomitosanes such as **14**, based on the cyclization of aziridinyl radicals generated from the intermediates **12** and **13**.[11] The sequence is similar for its timing of bond-forming events leading to the key tetracycle **14**. However, product **14** does not have the indole double bond that is essential for activation of potential leaving groups (CH_2-$OC(O)NH_2$; aziridine C−N) and for DNA cross-linking. Because of this difference, **14** is a relatively stable molecule compared to **11** and related structures where the allylic aziridine C−N bond is activated for heterolysis by the pyrrole subunit.

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(1) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 594. Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1989**, *42*, 145.

(2) Review: Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475. A summary and listing of key references is provided in the following article.

(3) Pazdur, R.; Ho, D. H.; Daugherty, K.; Bradner, W. T.; Krakoff, I. H.; Raber, M. N. *Invest. New Drugs* **1991**, *9*, 337.

(4) Naoe, Y.; Inami, M.; Matsumoto, S.; Nishigaki, F.; Tsujimoto, S.; Kawamura, I.; Miyayasu, K.; Manda, T.; Shimomura, K. *Cancer Chemother. Pharmacol.* **1998**, *42*, 31.

(5) Fukuyama, T.; Goto, S. *Tetrahedron Lett.* **1989**, *30*, 6491.

(6) DNA alkylation reviews: (a) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723. (b) Tomasz, M.; Palom, Y. *Pharmacol. Ther.* **1997**, *76*, 73. (c) Tomasz, M. *Chem. Biol.* **1995**, *2*, 575. For a review of synthetic approaches see ref 2.

(7) Huang, H.; Pratum, T. K.; Hopkins, P. B. *J. Am. Chem. Soc.* **1994**, *116*, 2703. Paz, M. M.; Hopkins, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 5999. Judd, T. C.; Williams, R. M. *Org. Lett.* **2002**, *4*, 3711.

(8) Companion paper : Vedejs, E.; Little, J. D. *J. Org. Chem.* **2003**, *68*, 1794.

(9) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607.

(10) Seaney, L. M. Ph.D. Dissertation, University of Wisconsin, 1995.

(11) (a) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962. (b) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083. (c) Ziegler, F. E.; Berlin, M. Y. *Tetrahedron Lett.* **1998**, *39*, 2455.

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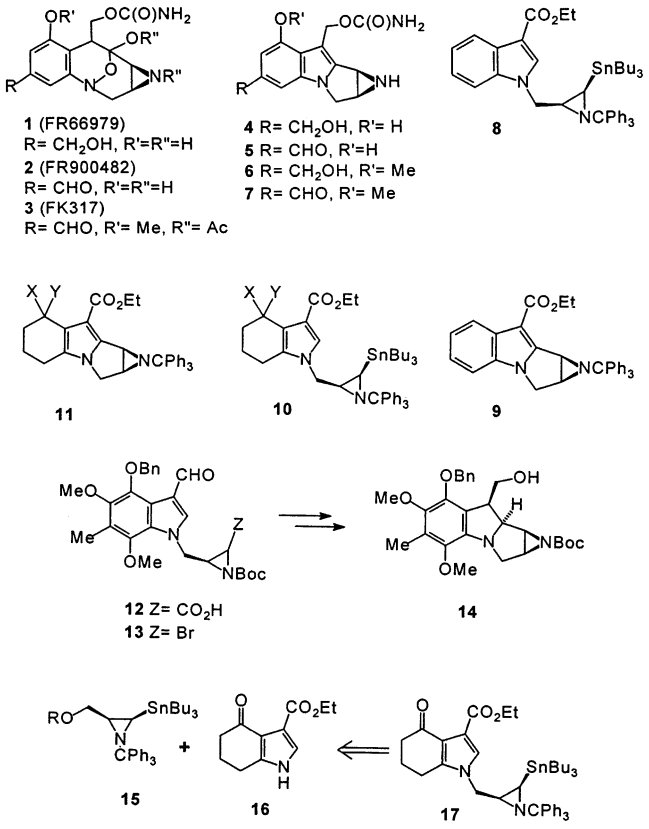
SCHEME 1



Our initial goal was to learn whether derivatives of **11** (X, Y = carbonyl equivalent) might be accessible by intramolecular Michael addition of an α-metalloaziridine. Eventually, we plan to evaluate the synthetic potential of related compounds for the preparation of the proposed FK317 metabolites **6** or **7**. The strategy is similar to Ziegler's in that **17** would be assembled by *N*-alkylation, using an aziridinyl-containing alkylating agent **15** and a bicyclic pyrrole derivative **16**. Earlier and later steps would be quite different, however, due to the planned cyclization sequence based on tin−lithium exchange, and the reliance on nonaromatic precursors.

The synthetic effort began with an adaptation of the oxaza-Claisen method[12] for synthesis of a bicyclic pyrrole, as outlined in Scheme 2. The main difference in this route compared to the precedent was in the use of a potentially removable nitrogen substituent, the *N*-benzenesulfonylethyl group. Thus, the known oxime **18**[13] was reduced with $NaCNBH_3$ to afford hydroxylamine **19** and condensation of the crude **19** with 1,3-cyclohexanedione (**20**) afforded the vinylogous hydroxamic acid **21**. Treatment of **21** with ethyl propiolate and *i*-Pr_2NEt at room temperature then produced aminal **24** via Michael addition of **21**, oxaza-Claisen rearrangement of **22**, and ring closure of the aldehyde intermediate **23**.

Conversion of the crude aminal **24** to **25** could be achieved by heating in toluene with azeotropic removal of water, or by room temperature treatment with TsOH (90% isolated overall from **21**). The TsOH conditions were

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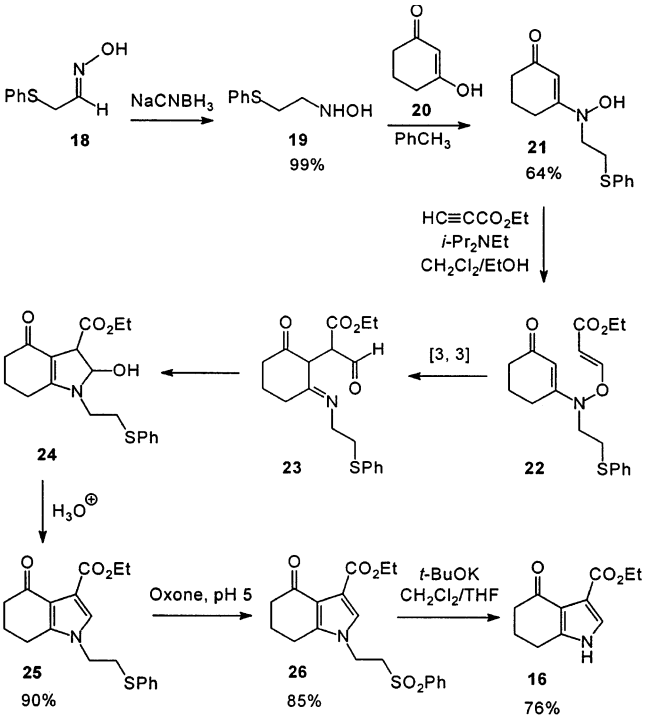
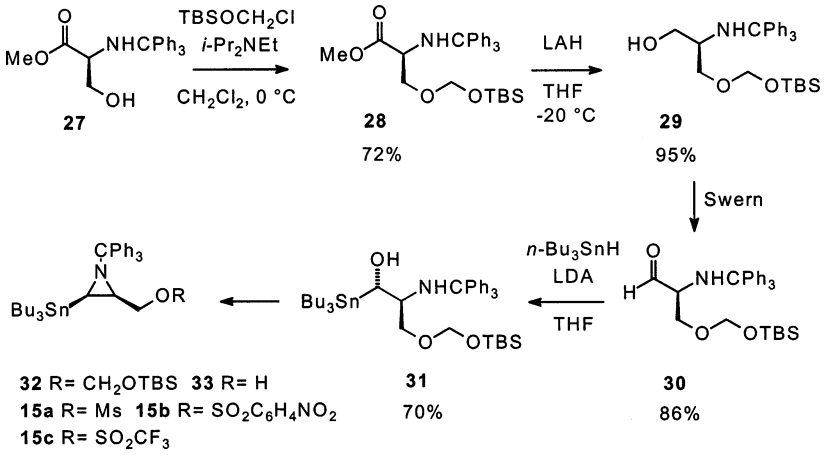


more convenient for monitoring the reaction, but they were complicated by competing hydrolysis of the ester upon prolonged exposure to the water released during cyclization. Conversion was minor on the 3 h time scale of the reaction, but facile ester hydrolysis proved to be more problematic in the next stage, during attempts to oxidize the sulfide **25** to the sulfone **26**. Although the sulfide was cleanly oxidized with oxone in an $EtOH/H_2O$ mixture, hydrolysis of the ester to the acid occurred under these conditions. Fortunately, buffering the oxone with a pH 5 NaOAc/HOAc buffer[14] resulted in rapid (15 min) oxidation to the sulfone **26**. Deprotection of the benzenesulfonylethyl functionality[15] was then accomplished with excess *t*-BuOK in THF/CH_2Cl_2 (−45 °C to room temperature). A 76% yield of the deprotected **16** was obtained.

The synthesis of the stannylaziridine coupling partner was based on an earlier report from our laboratory describing analogous structures,[9] as shown in Scheme 3. The primary alcohol group of *N*-tritylserine methyl ester (**27**)[16] was protected with (*tert*-butyldimethylsiloxy)methyl chloride[17] and the resulting ester **28** was reduced with LAH to yield alcohol **29**. Oxidation of **29** under Swern conditions provided aldehyde **30** in 86% yield and incorporation of the tributylstannyl functionality was accomplished via addition of Bu_3SnLi to **30** to afford the amino alcohol **31**. The stereochemistry of this addition follows the earlier precedent,[9] as evidenced by conversion of crude **31** to the *cis*-aziridine **32** under Mitsunobu conditions (70% yield for the two steps). Attempted

(12) Reis, L. V.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1994**, *35*, 2747.
(13) Kanemasa, S.; Norisue, Y.; Suga, H.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3973.
(14) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(15) Gonzalez, C.; Greenhouse, R.; Tallabs, R.; Muchowski, J. M. *Can. J. Chem.* **1983**, *61*, 1697.
(16) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309.
(17) Benneche, T.; Gundersen, L.; Undheim, K. *Acta Chem. Scand.* **1988**, *B42*, 384.

SCHEME 3



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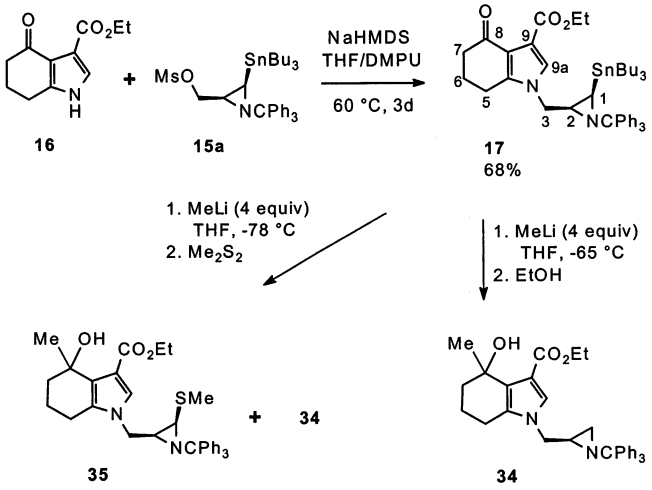


purification of **31** by column chromatography was not successful due to facile conversion to 3-(*tert*-butyldimethylsiloxy)methoxypropanal on silica gel. For this reason, **31** was used directly in the Mitsunobu cyclization (2 equiv of both DEAD and PPh_3) and purification was performed at the stage of the aziridine **32**. Deprotection of **32** occurred readily upon treatment with TBAF at room temperature, affording aziridinol **33** (91%), and subsequent reaction with methanesulfonyl chloride/triethylamine gave the mesylate **15a** in 91% yield.

Direct DIBAL reduction of ester **28** to the aldehyde **30** was also possible, although the product was contaminated with ca. 9% unreacted **28**. The mixture was sufficiently pure for conversion to **31**, **32**, and **33** in a sequence where only the final product was purified by chromatography. This approach was more convenient on preparative scale, and provided the aziridine alcohol **33** in 45% overall yield from **28**.

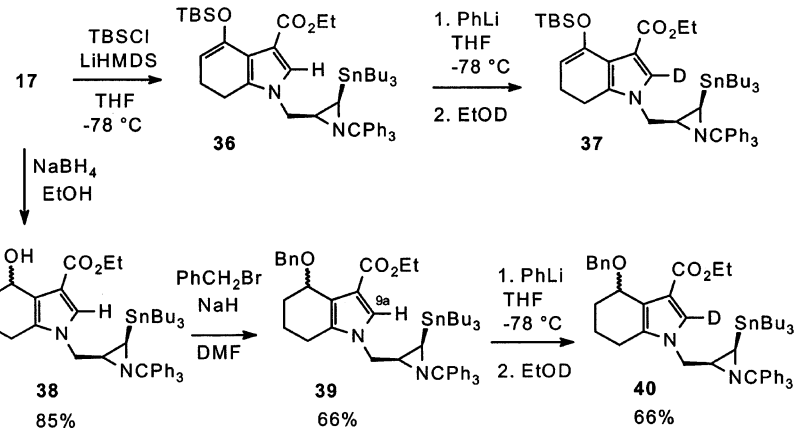
The coupling of bicyclic ketone **16** with mesylate **15a** proved to be challenging (Scheme 4). After considerable optimization, it was found that deprotonation of **16** with sodium hexamethyldisilazide (NaHMDS) in THF/DMPU (2:1) at room temperature followed by addition of **15a**, concentration of the resulting solution to 0.6 M, and heating at 60 °C for 3 days afforded the desired coupling product **17** in 68% yield.

In view of the long reaction time required in the coupling reaction between **16** and **15a**, the use of more reactive leaving groups in place of the mesylate was investigated. Treatment of aziridinol **33** with 4-nitrobenzenesulfonyl chloride (NosCl) in the presence of NEt_3/DMAP afforded the crude nosylate **15b** (Scheme 3). The nosylate was not stable to flash chromatography and was therefore used directly in the coupling step. Deprotonation of **16** with $NaN(TMS)_2$ in THF/DMPU (2:1) at −78 °C as before, followed by addition of crude **15b** in THF and warming to 60 °C for 24 h resulted in consumption of **15b**. After flash chromatography, **17** was isolated in 56% yield, somewhat lower than using the mesylate **15a**. However, the reaction was more convenient due to the shorter time scale, and was preferred for preparative experiments. To further improve the rate for the coupling process, the aziridinyltriflate **15c** was considered, as in the analogous reaction reported by Ziegler et al. with use of an *N*-alkoxycarbonyl protected aziridinyl fragment.[11c] Unfortunately, attempts to prepare **15c** resulted in decomposition, and an experiment where **15c** was generated in situ and coupling was attempted as before gave none of the coupling product **17**.

Sufficient **17** was in hand for a preliminary test of the proposed tin lithium exchange; internal Michael addition sequence (Scheme 4). We were interested in knowing whether metal exchange might be faster than addition to the presumably deactivated vinylogous amide carbonyl group. However, treatment of stannylaziridine **17** with methyllithium at −65 °C followed by quenching with ethanol gave the destannylated tertiary alcohol **34** (71%), but no products that could be attributed to the formation of tetracyclic structures related to **11**. According to trapping experiments, tin−lithium exchange had indeed occurred. Thus, treatment of **17** with methyllithium as before, followed by addition of Me_2S_2, gave **35** as well as **34**, together with complex decomposition products. This result indicates that the C-lithioaziridine is formed and survives long enough to undergo intermolecular sulfenylation, but for some reason does not cyclize. One possible interpretation of the data is that the undesired 1,2-carbonyl addition interferes with cyclization. Attention was therefore turned to preparation of suitably protected derivatives of **17**.

Temporary protection of the carbonyl group by conversion to a silyl enol ether was investigated first (Scheme

SCHEME 5



5). Addition of $LiN(TMS)_2$ (LiHMDS) to a cooled solution of **17** and *tert*-butyldimethylchlorosilane (TBSCl) in THF resulted in 87% conversion to silyl enol ether **36** based on assay by ^{1}H NMR integration. However, **36** proved to be exceptionally sensitive to hydrolysis and could not be purified nor fully characterized. The characteristic doublet of doublets at δ 4.8 ppm ($CDCl_3$), along with the *tert*-butyldimethyl resonances, left little doubt that the silyl enol ether had been formed, so tin−lithium exchange with the crude **36** was attempted under conditions that had induced the destannylation of **33**.

Reaction of **36** with methyllithium in THF at −65 °C resulted in extensive degradation to give a complex mixture that could not be separated. In the course of optimization attempts, it was observed that treatment of crude **36** with phenyllithium at −78 °C was less destructive than was the analogous methyllithium experiment. Although tetracyclic products were not detected and the NMR signals due to the tributylstannyl group were still present, there were indications that the phenyllithium reagent had been consumed. The reason became clear when the reaction was quenched with d_1-ethanol (EtOD). This gave the deuterated enol silane **37**, as determined from the disappearance of the signal at δ 6.99 ppm in the NMR spectrum.

The formation of **37** demonstrates that lithiation of the pyrrole ring is faster than tin−lithium exchange in the phenyllithium; DOEt quenching experiment. It also suggests that ring lithiation α to the pyrrole nitrogen may have been a complicating factor in the methyllithium experiments, and may have prevented the intramolecular Micheal addition. By this time, we had completed preliminary experiments in the aromatic series (**8** to **9**) and had confirmed that ring lithiation is the major pathway in that series if methyllithium is used for the tin−lithium exchange.[8] Furthermore, we had observed that the undesired pyrrole lithiation can be minimized by taking advantage of the kinetic deuterium isotope effect during the metalation step.[8,18] In the first attempt to probe this possibility in the aliphatic series, the deuterated silyl enol ether **37** was reacted with methyllithium at −65 °C. However, once again a complex product mixture was obtained from which little could be learned. The silyl enol ether did not survive the reaction conditions, judging from the disappearance of the δ 4.9 ppm signal in the ^{1}H NMR spectrum, but the complexity of the product mixture obscured the outcome and further conclusions were not possible.

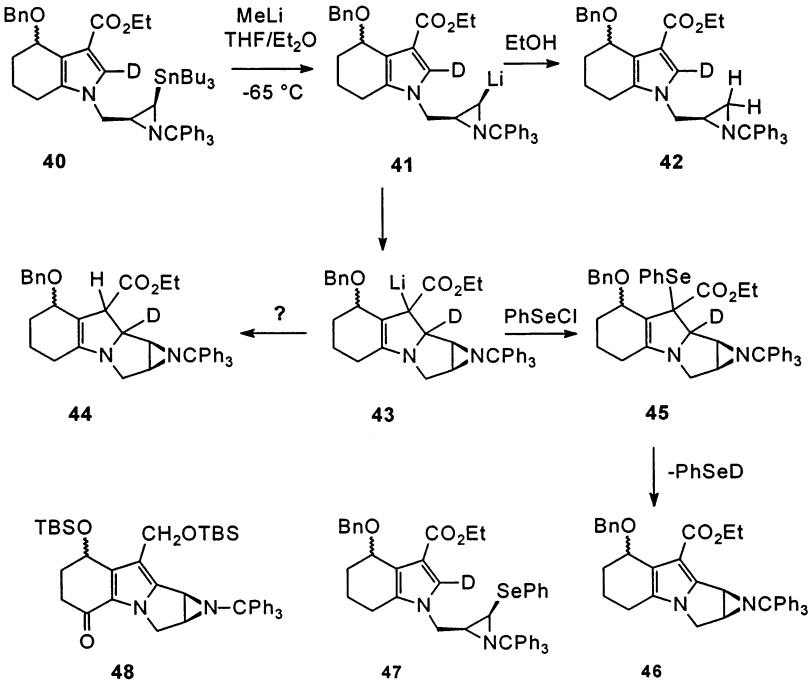
Encouraged by the finding that at least the selective deuterium incorporation had occurred without destruction of the stannylaziridine, we explored a more conventional protecting group strategy for the problematic ketone carbonyl group. Treatment of **17** with excess $NaBH_4$ at room temperature in ethanol afforded alcohol **38** in 85% yield as a 1:1 mixture of diastereomers (Scheme 5). The alcohol **38** was then protected as the benzyl ether by treatment with excess sodium hydride in DMF, followed by addition of benzyl bromide to give **39** (66% isolated).

As a prelude to cyclization studies, the feasibility of replacing the pyrrole ring proton with deuterium was investigated. It was hoped that this precaution would help protect against the complexity of product mixtures that had been observed in previous cyclization attempts. Treatment of **39** with phenyllithium at −78 °C in THF followed by EtOD quench resulted in **40** containing 90% deuterium according to ^{1}H NMR integration. In contrast to the enol silane experiments, the deuterated **40** could be purified by chromatography, but complex minor byproducts were also formed, resulting in significant material loss after purification (66% of **40** isolated). However, sufficient material was obtained to explore cyclization conditions with use of the deuterated substrate **40** (Scheme 6).

Treatment of **40** with excess MeLi in THF/Et_2O at −65 °C (15 min) followed by quenching with ethanol gave the uncyclized product **42** (67%), together with yet another complex array of minor, unknown byproducts. Analysis by HRMS and ^{1}H NMR revealed that **42** still contains

(18) (a) Knaus, G.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1192. Warmus, J. S.; Rodkin, M. A.; Barkley, R.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1993**, 1357. Kopach, M. E.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 6764. (b) Clive, D. L. J.; Khodabocus, A.; Cantin, M.; Tao, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1755. Clive, D. L. J.; Cantin, M.; Khodabocus, A.; Kong, X.; Tao, Y. *Tetrahedron* **1993**, *49*, 7917. Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 11275. (c) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. Hoppe, D.; Kaiser, B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323. (d) Laplaza, C. E.; Davis, W. M.; Cummins, C. C. *Organometallics* **1995**, *14*, 577. (e) Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103. (f) Mathieu, J.; Gros, P.; Fort, Y. *Chem. Commun.* **2000**, 951. (g) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Terahedron Lett.* **2002**, *43*, 5605.

SCHEME 6



the original deuterium label, indicating that no significant pyrrole ring lithiation had occurred prior to formation of **42**. The desired intermediate **41** must therefore have been generated, suggesting that perhaps the cyclization to **43** is unexpectedly slow. However, it was now clear that all of the methyllithium cyclization attempts afford exceptionally complex product mixtures, an observation that could be taken to imply a stability problem for the key intermediate **43** or for the desired product **44**. We therefore considered ways to convert **43** directly into the presumably stable, aromatic pyrrole **46**.

The usual tin−lithium exchange of **40** was carried out, followed by a quenching with PhSeCl in place of ethanol. This gave the desired pyrrole **46** in 20% yield, isolated as an inseparable 3:2 mixture of diastereomers, and provided, at last, clear evidence that some of the lithiated aziridine **41** survives long enough to cyclize to the lithium enolate **43**. Trapping with excess PhSeCl affords the labile tetracycle **45**, and spontaneous aromatization occurs with expulsion of PhSeD to give **46**. This result demonstrates that slow cyclization by the lithiated aziridine **41** is not the reason cyclized products were not isolated in the prior experiment (simple protic quench of **43**). More likely, the protonated product **44** is unstable, perhaps because it contains a benzyloxy leaving group adjacent to an electron-rich enamine double bond.

The structure of tetracycle **46** was assigned based on ^{1}H NMR data and extensive homonuclear decoupling studies, along with IR and HRMS evidence. A summary of the key ^{1}H NMR data for **46** (400 MHz, $CDCl_3$) is shown in Figure 1 along with data for the known tetracycle **48**.[19] In general, chemical shifts for protons H_a−H_d appear at somewhat lower field for **48**, consistent with the increased electron demand in the vinylogous amide **48**. In the two diastereomers of **46**, the aziridine

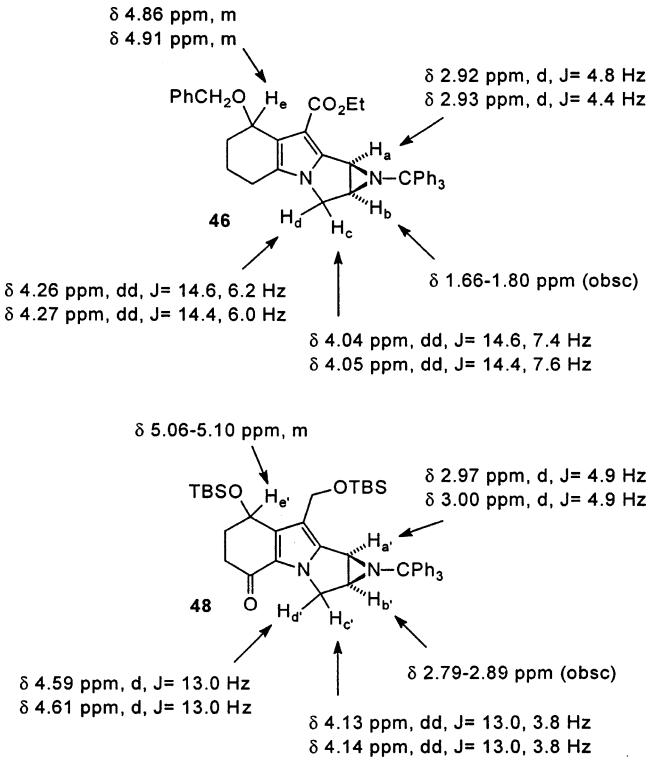


FIGURE 1. Selected ^{1}H NMR signals for **46** and **48**.

proton H_a appears at δ 2.92 ppm (0.4 H) and δ 2.93 ppm (0.6 H) with J values of 4.4 and 4.8 Hz, respectively. This is in close agreement with the shifts and J values of $H_{a'}$ in **48** (Figure 1), confirming that **46** is a cis-fused aziridine. The chemical shift of the second aziridine proton, H_b, is shifted to ca. 1 ppm higher field in **46** compared to **48**. The signal is obscured by a multiplet due to one of the cyclohexane protons (δ 1.66−1.80 ppm), but the assignment is clear from decoupling experiments.

(19) Vedejs, E.; Klapars, A.; Naidu, B. N.; Piotrowski, D. W.; Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401.

Differences in coupling constants between H_b and H_c or H_d of **46** compared to the analogous signals in **48** indicate differences in conformation between the two tetracyclic structures, but the connectivity is clearly the same.

In addition to tetracycle **46**, 20% of the protonated product **42** was also isolated in the PhSeCl quench experiment. The remainder of the reaction mixture was even more complex than in the protic quench, and material balance for products that could be purified was considerably lower (40%). Some of the minor products may be derived from the lithiated aziridine **41** via reaction with PhSeCl. NMR signals that might indicate the presence of the phenylselenenyl aziridine **47** were not detected. Other explanations for the complexity of the product mixture may be related to the reasons why **42** is formed in this experiment. Apparently, some of the lithiated aziridine **41** is protonated by potentially acidic protons derived from the substrate or its decomposition products. The resulting anions may be formed next to the pyrrole ring, and their selenenylation would afford solvolytically labile phenylselenenyl derivatives, activated by the same donor effect of pyrrole nitrogen that activates the aziridine C−N bond. This rationale is not fully satisfying, but it is consistent with the observation of numerous minor products from the cyclization experiment.

The proposed cyclization by intramolecular Michael addition of an α-lithio aziridine has been demonstrated, but the synthetic potential of the process is limited by stability problems at the stage of the enolate **43** or the protonated product **44**. Structure **44** was never observed, despite the effort invested to detect it. The exact reasons for these limitations remain unclear, but the principal source of difficulty resides in the cylohexane ring, and not in the aziridine. The conclusion follows from observations made in the aromatic series where cyclization products were obtained with much better efficiency. This work is described in the accompanying article,[8] along with a more detailed investigation of the kinetic deuterium isotope effect used to control pyrrole ring lithiation during the tin lithium exchange; cyclization steps.

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Supporting Information Available: Experimental procedures, characterization, and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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