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A Synthetic Approach toward the Proposed Tetracyclic Aziridinomitosene Derived from FK317

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A synthesis of the FK317 derivative **25** is described using internal Michael addition. Tin−lithium exchange of the deuterated stannylaziridine **18** generated the key lithioaziridine intermediate, followed by cyclization and aromatization of the pyrrole ring to give **7**. Ester reduction from **7** to **23** was effected via temporary aldehyde protection as the silylimidazole adduct **22**, and conversion to the carbamate **25** was carried out using FmocNCO and FMOC cleavage. Structure **25** is the *N*-trityl-protected derivative of the proposed intermediate from bioactivation of FK317 that is responsible for DNA cross-linking. Attempted nitrogen deprotection of **25** using MsOH/*i*-Pr_3SiH resulted in replacement of the C(10) carbamate by hydride. Deprotection of the more stable **21** gave the desired aziridine **26**.

Mitomycin C (**1**; Figure 1) has long been used against a variety of solid tumors despite significant side effects.[1] The related aziridine-containing antitumor agents **2** and **3** were isolated more recently from *Streptomyces sandaensis*, and the semisynthetic derivative FK973 (**4**) was found to have potent antitumor activity.[2,3] However, attempts to develop FK973 were terminated due to toxicity from vascular leak syndrome (VLS).[4] In 1998, FK317 (**5**)[5] was shown to have improved antitumor activity compared to FK973 or mitomycin C, but without the VLS side effects. The mode of action of FK317 is believed to involve a sequence of metabolic activation steps, including deacylation, reductive N−O bond cleavage, and cyclization to give the mitosene-like intermediate **6** as the activated form responsible for DNA−DNA cross-linking.[6]

Although FK317 has not yet lived up to its early promise,[7] it has attracted considerable interest due to the structural similarity between the proposed intermediate **6** and the aziridinomitosene intermediates responsible for the antitumor activity of mitomycins. We have therefore initiated a synthetic effort to prepare **6** and to learn whether structures containing the sensitive substitution pattern can be isolated. Here we report our first attempts to synthesize the fully functionalized **6** using an internal Michael addition approach based on lithiated aziridines.[8]

Results and Discussion

Our strategy involves the convergent synthesis of **8** via the intermediates **9** and the known **10**[8] (Scheme 1). In

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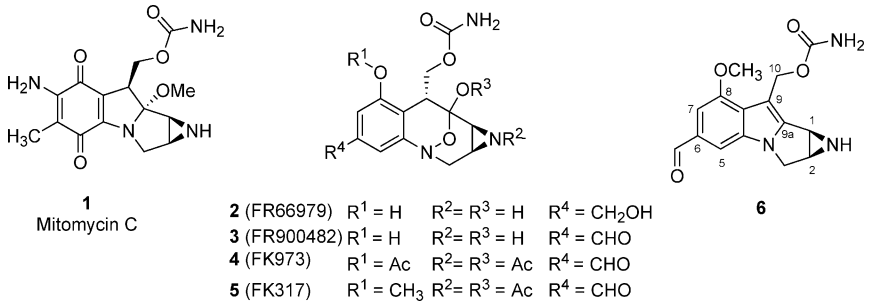
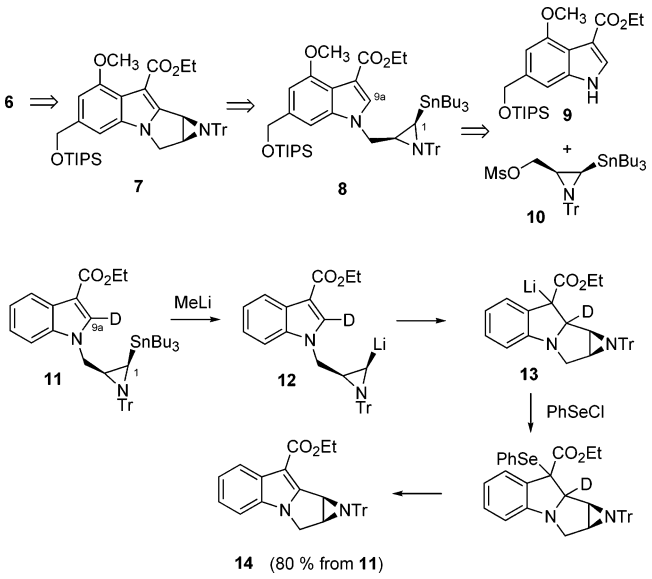


FIGURE 1.

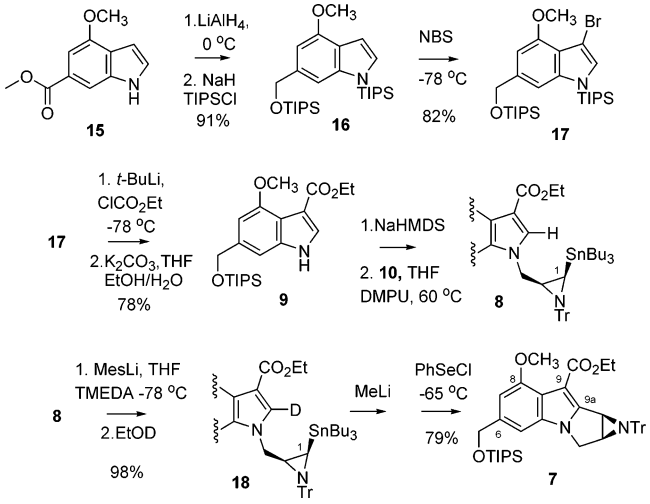
SCHEME 1



earlier studies, we had demonstrated the key bond formation between C(1) and C(9a) (mitomycin numbering) using a model substrate **11**. Treatment of **11** with methyllithium generated an aziridinyllithium intermediate **12**, followed by cyclization via internal Michael addition to give the tetracyclic enolate **13**. Enolate trapping with PhSeCl then gave the desired tetracyclic indole **14** in good yield. The presence of C(9a) deuterium at the stage of tin−lithium exchange was essential. Without the kinetic isotope effect of a deuterium blocking group, competing lithiation at C(9a) was the major pathway and effectively prevented the internal Michael addition step.

The more highly functionalized indole **15**[9] (Scheme 2) required to access aziridinomitosene-like structures related to **6** was prepared in four steps from pyrrole-2-carboxaldehyde using a recently optimized procedure as described elsewhere.[10,11] The ester side chain of **15** was reduced with $LiAlH_4$ and subsequent silylation afforded **16** in 91% yield. Carboxylation at the C(9) position of indole **16** was carried out by bromination, lithium halogen exchange, and quenching of the resulting anion with ethyl chloroformate.[12] Selective N-desilylation with

SCHEME 2



potassium carbonate in ethanol/THF/water (3:1:1) then afforded the desired indole **9** (78% from **17**).[13]

Indole **9** was deprotonated with NaHMDS and coupled with the aziridine mesylate **10**. To force the reaction of the mesylate **10** to completion, it was necessary to use indole **9** in excess. When 3 equiv of **9** was used, **8** was obtained in 95% yield based on **10**, and 64% of **9** was recovered (97% material balance) and could be reused in subsequent experiments.

In preparation for the key internal Michael cyclization, the C(9a) position of indole **8** was deprotonated using freshly prepared mesityllithium (MesLi),[14] and the resulting lithiated indole was quenched with EtOD to give **18** in excellent yield. In our model study where there were no substituents at C(6) or C(8), PhLi had been used as the base to prepare **11** with no complications.[8] However, in the case of **8**, significant addition of PhLi to the ethyl ester was observed under the same conditions. Although TMEDA[15] suppressed the undesired addition of PhLi to the ester, MesLi gave the best result (98% yield with >95% D_1 by ^1H NMR). The deuterated indole **18**

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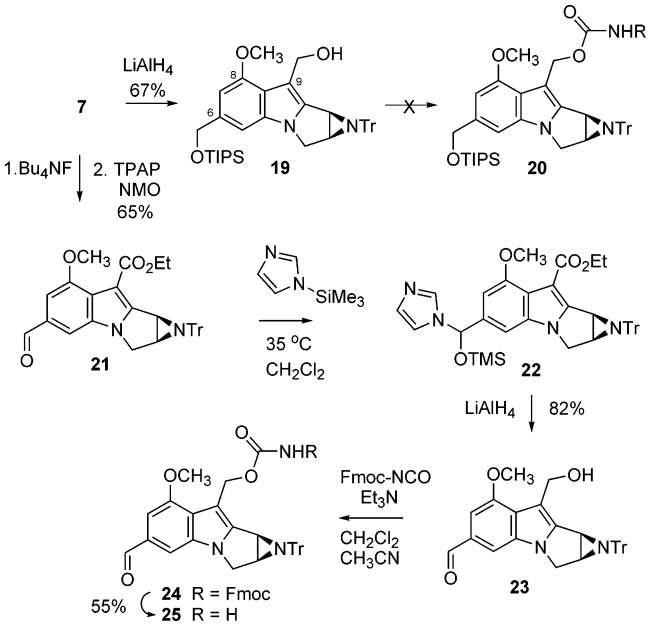
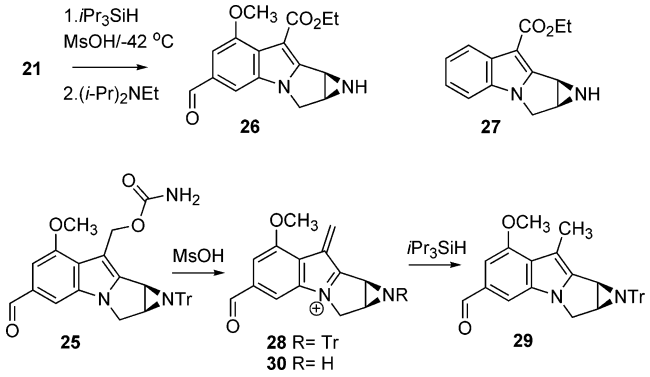
SCHEME 3



was then reacted with MeLi followed by PhSeCl to give tetracycle **7** in an overall yield of 79% via the same sequence of tin−lithium exchange, internal Michael addition, and aromatization steps as in the model study.[8]

The most direct strategy at this point would be to attach the C(10) carbamate and then to deprotect and modify the C(6) hydroxymethyl ether group of tetracycle **7**. Ester **7** was reduced with $LiAlH_4$ to give hydroxy indole **19** with relative ease (Scheme 3). However, all attempts to install the carbamate moiety from **19** using precedented methods[16] failed due to the sensitivity of the desired product **20**. This was no surprise because **20** contains potential leaving groups at C(1) (aziridine C−N) and C(10) (carbamate C−O) that are activated by donation from the electron-rich indole nitrogen. To suppress leaving group reactivity, an alternative sequence was followed from **7** via initial deprotection of the C(6) silyl ether with TBAF followed by TPAP oxidation to the aldehyde **21** (65% from **7**). The electron-withdrawing CHO group in **21** was expected to improve stability by a delocalization effect due to the conjugated, vinylogous formamide subunit, resulting in lower electron density in the indole and a higher barrier for leaving group departure. On the other hand, the presence of a C(6) aldehyde would not be compatible with reduction of the C(10)-ester. Fortunately, temporary protection of the CHO group was possible using TMS-imidazole[17] in refluxing CH_2Cl_2 to give the N,O acetal **22**. Without purification of **22**, the ester group was reduced with $LiAlH_4$, followed by workup using solid $Na_2SO_4 \cdot 10H_2O$.

SCHEME 4



This resulted in the neutralization of alkoxides as well as hydrolysis of the N,O acetal to give **23** (82% from **21**). The indole **23** was then treated with freshly prepared Fmoc-NCO[16c] to give the Fmoc-carbamate **24**, and cleavage of Fmoc with Et_3N in a one-pot procedure afforded the desired **25** (55% from **23**).[16e]

The challenging removal of the *N*-trityl group could now be explored in the highly sensitive environment. Preliminary attempts to deprotect the most sensitive substrate **25** were not promising, so deprotection of the ester aldehyde **21** was studied in the expectation that the electron-withdrawing substituents would help to stabilize the product **26** (Scheme 4). Electrospray mass spectroscopy (ES/MS) was used to monitor events in small scale experiments based on the observation that all of the tetracyclic structures prepared up to this point had given distinct peaks for the M + Na^+ ions, characteristic of the expected structures. We anticipated the same behavior for **26** because removal of the trityl group was not expected to adversely affect the stability of the aziridine. However, the recently optimized deprotection conditions (MsOH/Et_3SiH at 0 °C)[18] gave no mass peak for the desired aziridine **26**, and identifiable components could not be separated from the complex product mixture.

Attempts to control the deprotection of **21** with the Et_3-SiH/MsOH reagent at lower temperatures were not successful, but a similar experiment using the bulkier triisopropylsilane at −42 °C (10 min) gave the desired aziridine **26** (41%) together with recovered **21** (16%). The structure of **26** was supported by ES/MS and NMR data and by comparisons with the simpler structure **27** prepared earlier in our laboratory.[8]

The reoptimized detritylation procedure (−42 °C) was then applied to **25** with monitoring by ES/MS. However, no clear evidence to support the formation of the deprotected aziridine **6** was obtained, and an alternative reductive pathway was encountered. The major product (65%) still contained an *N*-trityl group, as well as the characteristic ^1H NMR signals for the bridgehead protons of an intact aziridine and the adjacent CH_2 protons in the five-membered ring. Structure **29** was assigned, based on the presence of a new methyl singlet at δ 2.52 ppm, together with the disappearance of the characteristic AB pattern for the C(10) protons. In contrast to the tetracyclic structures **21**, **23**, or **25**, no M + Na^+ ion was observed in the ES/MS output for **29**. Instead, a strong

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peak corresponding to M + MeOH + Na^+ was found, suggesting that **29** undergoes solvolytic aziridine ring opening under electrospray sampling conditions due to increased electron density in the pyrrole ring of **29** compared to **26**.

Analysis of the minor chromatography fractions by NMR was uninformative, but ES/MS assay revealed the characteristic mass of an iminium ion **28**. The same ion was observed in the electrospray mass spectrum of the carbamate **25** as well as the precursor alcohol **23**, so this ion can be taken as evidence for the presence of a C(10)-heteroatom that is capable of heterolysis, as well as for the survival of the *N*-trityl group. Weak ions were also detected in several fractions corresponding to the adduct of **28** + Na + OMe or **28** + MeOH, but these peaks were always small compared to that of **28**.

Detritylated products were detected in trace amounts based on a weak ion corresponding to **30**, but no products were found having the characteristic mass of the deprotected carbamate **6**. When detritylation was attempted on the alcohol **23** in small scale test experiments, the formation of the same over-reduction product **29** was indicated by ES/MS. Evidently, the C(10) hydroxyl group of **23** is also easily activated for heterolysis and reduction, presumably via the acid-induced formation of the iminium ion **28**. We conclude that the reductive detritylation of **25** via *N*-protonation and cleavage to give the trityl cation cannot compete with the undesired conversion into the iminium ion **28**.

From the above evidence, it is likely that the late stage deprotection of **25** will not be feasible. On the other hand, detritylation is possible earlier, prior to reduction of the ester group, as demonstrated in the conversion from **21** to **26**. Although the earlier deprotection would require adjustments in the carbamoylation chemistry and the timing of redox events, the stability of **25** under carefully controlled conditions suggests that **6** will also prove to be an isolable substance. Prior synthetic efforts have accessed tetracyclic aziridinomitosene derivatives stabilized by the presence of the quinone ring,[16b,c,19] but reports describing the isolation of solvolytically sensitive analogues of **6** or **25** have been rare.[8c,20] Further studies toward this goal are underway.

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

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