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Aziridinomitosanes via Lactam Cyclization

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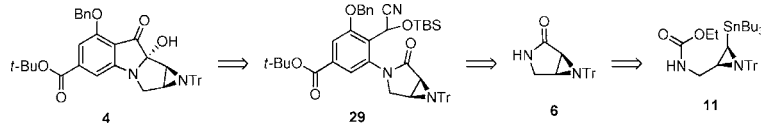
ABSTRACT

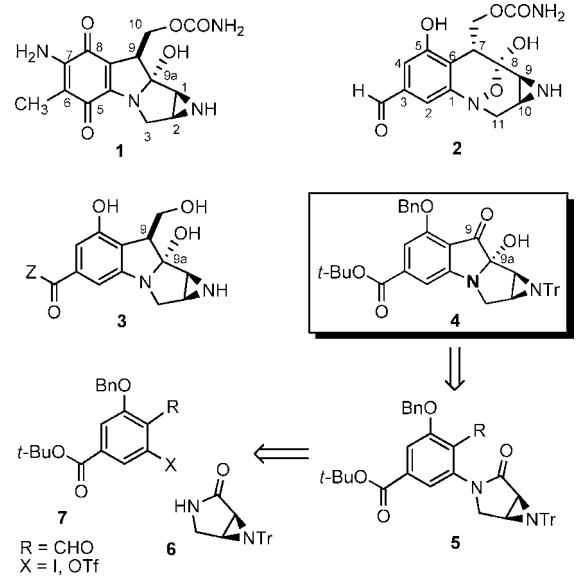


Aziridinomitosane ketones 4 and 24 are accessed by internal acyl anion equivalent-lactam cyclization of 29 in a convergent route. The key aziridinolactam 6 is prepared by tin−lithium exchange via the lithiated aziridine 11.

Mitomycin C (**1**) and FR900482 (**2**) are known for their anticancer activity[1] and for their remarkable reductive activation pathway via bis-electrophilic aziridino-mitosenes that cross-link DNA.[2] It has been hypothesized that these structurally distinct heterocycles not only share key functionality and mode of activation but also have partially overlapping biosynthetic pathways.[3] Early common biosynthetic intermediates have been identified using isotopic labeling studies,[4] but the point where the biosynthetic pathways diverge is still unknown. In principle, the point of divergence can be investigated using pyrrolo[1,2a]indole-derived aziridines such as **3**; however, synthetic access to derivatives of **3** is challenging due to the expected facile aromatization to the indole.[5] With the ultimate goal of synthesizing analogues of **3**, we have developed an enantiocontrolled route to the more stable[6] 9-oxo-pyrrolo[1,2a]indole **4** as described below. The new route also allows access to the ring system of FR900482 (**2**) by oxidative ring expansion.[7]

A convergent synthetic strategy designed to access the tetracyclic ketol **4** is outlined in Scheme 1, based on the

Scheme 1. Strategies Leading to Mitosane Ketol **4** via C9−C9a Bond Formation



(1) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723.
(2) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.
(3) Chamberland, S.; Grüschow, S.; Sherman, D. H.; Williams, R. M. *Org. Lett.* **2009**, *11*, 791.
(4) (a) Hornemann, U.; Kehrer, J. P.; Nunez, C. S.; Ranieri, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 320. (b) Hornemann, U.; Eggert, J. H. *J. Antibiot.* **1974**, *28*, 841. (c) Anderson, M. G.; Kibby, J. J.; Rickards, R. W. *Chem. Commun.* **1980**, 1277. (d) Fujita, T.; Takase, S.; Otsuka, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 392.
(5) For examples of nonstabilized aziridinomitosenes, see: (a) Feigelson, G. B.; Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 3390. (b) Feigelson, G. B.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 3393.
(6) (a) Wang, Z.; Jimenez, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 4977. (b) Papioannou, N.; Blank, J. T.; Miller, S. J. *Org. Lett.* **2001**, *3*, 2879.

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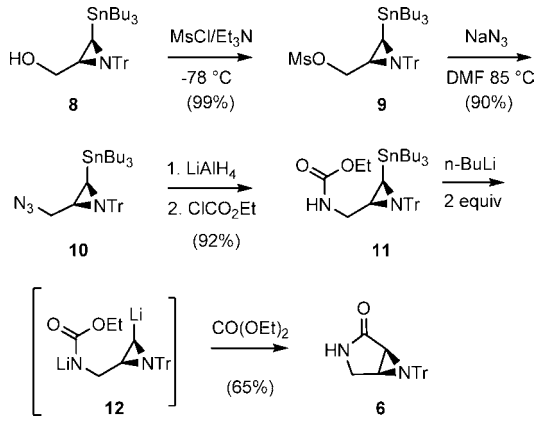
coupling of an aromatic subunit **7** with the bicyclic aziridinolactam **6** followed by C(9)−C(9a) bond formation (mitomycin numbering) using intramolecular nucleophilic addition to the lactam carbonyl group of **5**. The aziridine stereochemistry of **5** might be expected to control hemiaminal configuration in **4** based on kinetic or thermodynamic factors. Depending on the outcome of the cyclization step, the C(9a) hemiaminal stereochemistry might then be exploited as one of the factors that set configuration at C(9) corresponding to either the mitomycin or the FR900482 series.

First, the chiral bicyclic aziridinolactam **6** was targeted (Scheme 2). Although a number of related bicyclic aziridines

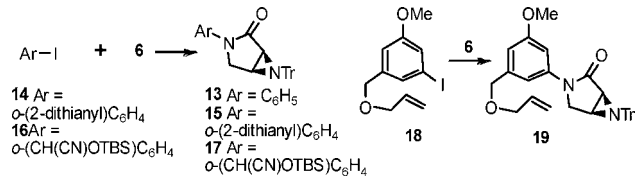
Scheme 2. Construction of the Bicylic Aziridine **6**



are known,[8] no bicyclic NH lactam analogue of **6** has been reported. We sought to establish convenient access to **6** and to obtain the aziridine stereocenters from the chiral pool, starting with the known chiral aziridinol **8**.[9] Conversion into mesylate **9** (MsCl, Et_3N, 99%) and azide **10** (91%) was followed by reduction and subsequent treatment of the unstable amine with ethyl chloroformate to provide **11** (81%, 2 steps). Carbamate **11** was converted to dianion **12**, which was then trapped with diethyl carbonate to afford aziridinolactam **6** (65% isolated; gram scale). Complete deprotonation of the carbamate nitrogen prior to tin−lithium exchange was essential to avoid significant protodestannylation in this sequence[10] (see Supporting Information for details).

With bicyclic aziridinolactam **6** in hand, conditions were screened for coupling with aryl iodides containing functionality that might eventually be used to form the tetracycle C(9)−C(9a) bond. The best yields of coupling products were obtained using CuI with K_3PO_4 and the highly active *trans-N,N′*-dimethyl-1,2-cyclohexanediamine ligand[11] upon heating in toluene (100−110 °C). Although the yields were generally modest (57−73%; Table 1), the reactions were very clean,

Table 1. Copper-Catalyzed Coupling of Aryl Iodides and **6**[a]



entry	substrate	CuI	time	product	yield
1	C_6H_5I	0.1	4 h	**13**	63%
2	**14**	0.30	20 h	**15**	61%[b]
3	**16**	1.0	20 h	**17**	57%
4	**18**	0.30	48 h	**19**	73%

[a] 1.2 equiv of **6** and 1.0 equiv of aryl iodide were dissolved in toluene with K_3PO_4 and *trans-N,N′*-dimethyl-1,2-cyclohexanediamine and heated to 100 °C. [b] Reaction conducted at 110 °C.

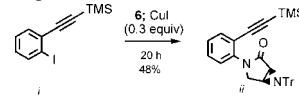
and unreacted **6** could be recovered along with the products **13**, **15**, **17**, or **19**. The reaction was faster with the unhindered iodobenzene (entry 1), and 10 mol % of CuI catalyst was sufficient for conversion over several hours. In the other examples, increased catalyst loading and longer reaction times were necessary (see entries 2−4).[12]

Lactams **15** and **17** offer several options for C(9)−C(9a) bond formation, one of which (cyclization via acyl anion equivalent generation) was investigated in detail. Initial attempts to deprotonate dithiane **15** with *n*-BuLi resulted in alkyllithium addition to the lactam carbonyl group, while LDA treatment caused unproductive bimolecular side reactions. Furthermore, reaction of **15** or **17** with KHMDS afforded no products of cyclization, and quenching the reaction mixtures with a deuterium source did not result in deuterium incorporation (assay by ^{1}H NMR spectroscopy). Attempts to close the C(9)−C(9a) bond therefore focused on lithium amide bases with the silylated cyanohydrin lactam **17** as substrate.

Choice of temperature, base, and solvent proved critical for successful cyclization of **17**. The first hints of cyclization were observed using LDA/THF at low temperatures, but the product mixture was complex, and the presumed cyclization product did not survive chromatography. Better control was achieved by switching from LDA to LiHMDS for deprotonation at −78 °C and by allowing the reaction temperature to reach 0 °C prior to quenching. Improved conversion was observed when the THF was replaced by ether, and the best experiments could be monitored visually as the cloudy

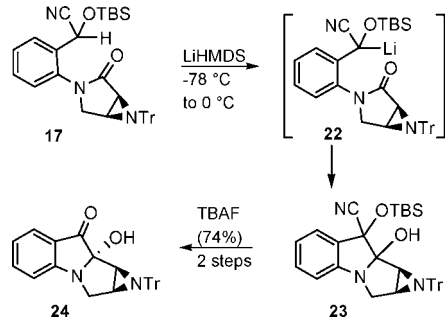
(7) Dmitrienko, G. I.; Denhar, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705.
(8) (a) Kametani, T.; Kigawa, Y.; Ihara, M. *Tetrahedron* **1979**, *35*, 313. (b) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369.
(9) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 7.
(10) Goswami, R.; Corcoran, D. E. *Tetrahedron Lett.* **1982**, *23*, 1463.
(11) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(12) Conversion of i to ii was also demonstrated using the conditions of Table 1. However, attempted cyclization following Cha's alkene analogy[13] (modified Kulinkovich conditions) gave predominant alkyne reduction. Tetracyclic products derived from ii were not detected.



reaction mixture of the presumed intermediate **22** became clear over time. These optimized conditions produced a 3:1 mixture of two diastereomeric products corresponding to structure **23** according to NMR assay of the crude product. The minor isomer was identical by NMR comparisons with the unstable product from low temperature LDA experiments, but attempted purification at the stage of **23** resulted in significant decomposition.[14] On the other hand, treatment of the crude cyclization mixture with TBAF provided the stable and easily purified ketol **24** in 74% yield over the two steps (Scheme 3). Only one dominant diastereomer was

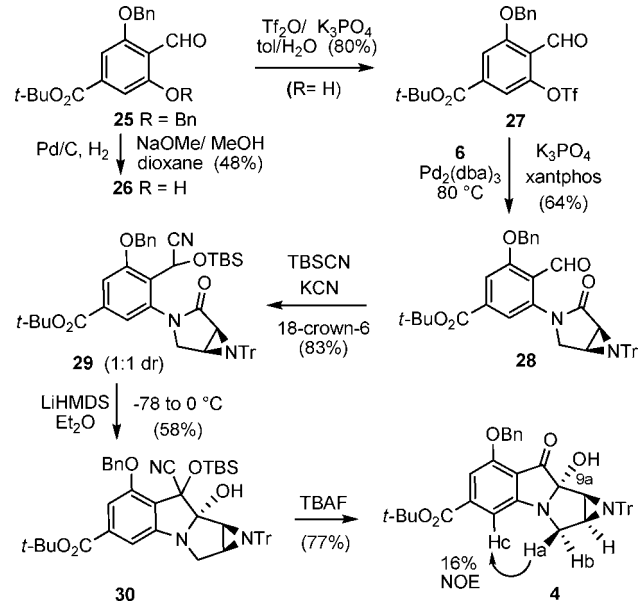
Scheme 3. Model of Ketol **24**



detected after OTBS deprotection. Presumably, the unstable diastereomer differs at the hemiaminal carbon, but its fate under the conditions of silyl ether cleavage is not clear. The C(9a) stereochemistry of **24** was initially assigned based on NOE data and was eventually confirmed by X-ray crystallography. The preferred formation of the corresponding diastereomer **23** in the cyclization step from **17** is tentatively attributed to decreased lone pair repulsion compared to the unstable hemiaminal isomer having the C(9a)−O bond and aziridine nitrogen on the same face of the tetracycle. According to this interpretation, the major diastereomer of **23** is formed under thermodynamic control (hemiaminal anion equilibration at 0 °C).

Having successfully demonstrated construction of the C(9−C(9a) bond in the model tetracycle **24**, we turned to the synthesis of an appropriately functionalized aryl halide **7** that might be used in a route similar to **4**. The known aldehyde **25**, obtained in 4 steps from commercially available 4-bromo-3,5-dihydroxybenzoic acid,[15] was selectively monodebenzylated under hydrogenolysis conditions to provide phenol **26** (Scheme 4).[16] Treatment of

Scheme 4. Coupling and Cyclization



26 with triflic anhydride/K_3PO_4 afforded triflate **27**,[17] but attempts to convert **27** to the analogous iodide required for copper -catalyzed amidation were unsuccessful. Therefore, alternative catalytic procedures were evaluated that might allow coupling of the aziridinolactam **6** directly with the triflate **27**, and conditions developed by Buchwald et al. using $Pd_2(dba)_3$/xantphos worked well after optimization.[18] The commonly used Cs_2CO_3[19] gave poor yields of the desired product **28**, and a carbonylamide byproduct was obtained by amide addition to the aldehyde group. However, a similar experiment using K_3PO_4 as base provided the lactam **28** in acceptable (64%) yield.[11,20] Subsequent treatment of **28** with TBSCN and catalytic KCN in the presence of 18-crown-6 then gave a 1:1 diastereomeric mixture of **29** (83%), setting the stage for the key cyclization (Scheme 5).[21]

Deprotonation of the cyanohydrin **29** was performed with LiHMDS in ether, the same conditions that were used in the model study from **17**. Unlike the model system, the cyclization gave only one diastereomer of aminal **30** (58%) along with unreacted starting material (25−30%). Extended reaction time at 0 °C (>40 min) was needed for good conversion to **30**, but unreacted starting material was always recovered after aqueous quench even after 1.5 h. The differences between cyclization of **17** and **29** are attributed to the *para* electron-withdrawing ester substituent of **29**. The ester would help stabilize the intermediate carbanion, resulting in the higher reaction temperature and lower conversion to the alkoxide precursor of **30**. Subsequent removal of the cyanohydrin with TBAF afforded the desired ketol **4** (77%). Analysis of **4** by NOE spectroscopy showed a 16% correlation between H_a and H_c, consistent with the same stereochemistry at C(9a) as in the model **24**.

(13) Lee, J.; Du Ha, J.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127.
(14) The major diastereomer of **23** survived chromatography, but purification at the stage of the stable **24** was more efficient. The relative proportion of the minor (unstable) diastereomer of **23** increased if the reaction mixture was quenched at −12 °C but did not affect the yield of **24**.
(15) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572.
(16) (a) Curtis, W. D.; Stoddart, F. *J. Chem. Soc., Perkin Trans. I* **1977**, 220. (b) Hendrickson, J. B.; Ramsay, M. V. J.; Kelly, T. R. *J. Am. Chem. Soc.* **1972**, *94*, 6834.
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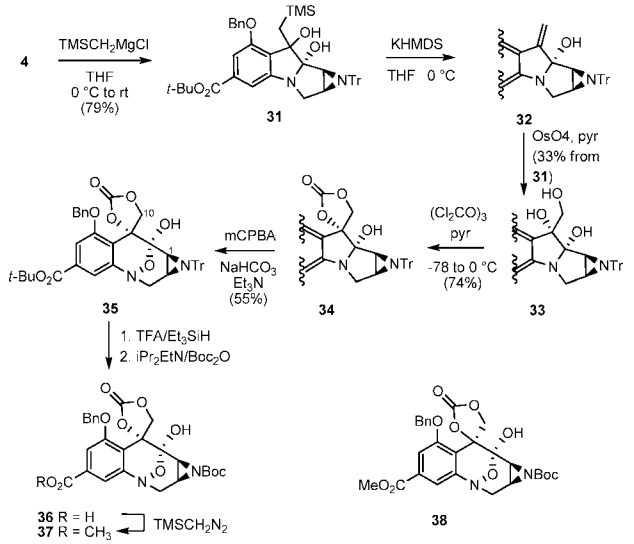
Scheme 5. Correlation of Stereochemistry



The diastereoselective synthesis of the key mitosane ketol **4** was accomplished in 9 linear steps (11 total) in 12% overall yield from known aldehyde **25** and chiral aziridinol **8**. However, further confirmation of hemiaminal stereochemistry was desired, as well as added insight regarding the potential of **4** in the context of possible synthetic applications. We therefore initiated a correlation of stereochemistry with intermediates reported in prior synthetic studies. Following precedent from the work of Danishefsky and McClure,[22] **4** was treated with Me_3SiCH_2MgCl to afford diol **31** as one diastereomer (79%; Scheme 5), followed by Peterson elimination to **32**. Attempted purification of **32** by chromatography resulted in allylic alcohol rearrangement to the isomeric indole, so crude **32** was treated with stoichiometric OsO_4 in pyridine[3] to provide triol **33** (33% from **31**) followed by triphosgene/pyridine to afford the cyclic carbonate **34** (74%).[8b] The C(9) and C(9a) stereochemistry of **34** was eventually established by X-ray crystallography. Among several choices, we had opted to compare intermediates having the more stable FR900482 skeleton that should be accessible from **34** via Dmitrienko oxidation.[7] In the event, carbonate **34** was treated with buffered *m*-CPBA to provide the ring-expansion-derived acetal **35** (55%). An NOE correlation between the C(1) aziridine proton and one of the C(10) methylene protons supported the assignment as shown. Next, the trityl and *t*-butyl ester protecting groups of **35** were removed with excess TFA/triethylsilane;[23] addition of Hünig's base/Boc_2O provided the Boc-protected carboxylic acid **36**; and treatment with trimethylsilyl diazomethane gave a mixture of products including methyl ester **37**.

We had expected to obtain a diastereomer of **38**, an intermediate reported by O'Boyle and Trost in their synthesis of *epi*-FR900482,[8b] and were surprised to find that NMR signals of our material appeared to match those of **38**. Initially, this was concerning because the stereochemistry might conceivably have been altered during the correlation sequence from **34** to **37**. However, we soon learned that the structure of **38** had been reassigned in the PhD dissertation of O'Boyle to match **37**.[24] Comparison of NMR spectra established the identity of **37** obtained according to Scheme 5 with the major product reported by O'Boyle and Trost.

Because **37** is a precursor of **7**-*epi*-FR900482 rather than the natural diastereomer, we opted not to pursue further synthetic steps from **35** in the expectation that differences in the protecting groups would not alter the outcome of reductive deoxygenation at C(7). However, the concise, convergent route leading to **4** has interesting potential for accessing elusive mitosane-like structures such as **3**. Efforts toward this goal are underway that will exploit the superior stability profile of **4** as the key intermediate. The unusual intramolecular cyclization leading to acetals **23** and **30** holds considerable promise in this regard. We could find no prior report describing the cyclization of an acyl anion equivalent with the carbonyl group of a lactam, although analogous cyclizations involving lithiated substrates and the carbonyl group of lactams, amides, and imides are known,[25] including a related case of enolate−lactam cyclization.[25a] The chemistry described herein also demonstrates a convenient synthesis of the bicyclic lactam **6** via a lithiated aziridine intermediate.

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Supporting Information Available: Experimental procedures and characterization data for new substances. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (b) Ahman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.
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(22) McClure, K. F.; Benbow, J. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 8185.
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