Enantiocontrolled Synthesis of (1*S*,2*S*)-6-Desmethyl-(methylaziridino)mitosene

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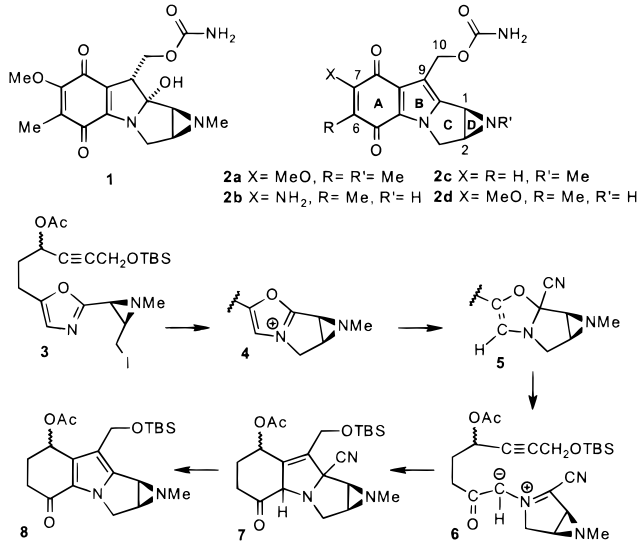
Aromatization of the pyrroline subunit of mitomycin B (**1**) results in the formation of the corresponding pyrrole, the aziridinomitosene **2a**.[1] A similar elimination occurs in the sequence of events that causes DNA cross-linking and is associated with the antitumor effects of the mitomycin antiobiotics. One of the alkylation steps involved in cross-linking occurs at the allylic aziridine C−N bond, and the ease of this process is reflected in the high solvolytic reactivity of **2a** or **2b**.[2] As a consequence, it has been difficult to access the aziridinomitosene skeleton including the correct C_1,C_{10} functionality. Several syntheses of mitomycins have been completed,[3] and there are a number of examples where the tetracyclic core of the aziridinomitosenes has been prepared.[4] Only one of the prior studies was able to incorporate the sensitive natural substitution pattern in rings B, C, D in a structure that also contains the fully elaborated ring A quinone,[4b] resulting in the total synthesis of racemic aziridinomitosene **2d**.



We have investigated a route to aziridinomitosenes that assembles the six-membered carbocycle from nonaromatic precursors. This approach was designed to allow greater potential for the variation of substituents at C_6,C_7 than is possible from the natural products, and specifically to target the 6-desmethyl-(methylaziridino)mitosene **2c** (nomenclature: see ref 1). The latter has no C_6,C_7 substituents and therefore has additional electrophilic sites compared to **2a**. The strategy relies on early introduction of the aziridine and ensures the absolute configuration shown in the key oxazole intermediate **3** if subsequent events occur without disruption of the aziridine C−N bonds. According to precedents for generation of azomethine ylides from oxazoles,[5] **3** would be converted into an oxazolium salt **4** by internal alkylation, followed by nucleophilic addition of cyanide to afford the 4-oxazoline **5**. Electrocyclic ring opening to the azomethine ylide **6** and internal 2+3 trapping would then produce the tetracyclic product **8** via the 3-pyrroline **7**.[6] None of these steps had been demonstrated in the presence of an aziridine, so it was difficult to anticipate whether intermediates such as **4** and **6** would be viable. Our prior work had also not explored the issue of dipolarophile reactivity with the eventual C_{10} carbon at the correct alcohol oxidation state. Ester-activated acetylenic dipolarophiles had been shown to intercept simpler azomethine ylides,[6] but reduction of a C_{10} ester in the aziridinomitosene setting would pose a difficult challenge because of the presence of vinylogous amide and quinone functionality. It was therefore necessary to test an unactivated alkyne as the dipolarophile for ylide trapping from **6** to **8**.

The monosubstituted oxazole **9**[7] was converted into the borane complex **10** to allow lithiation at C_2 without complications due to ring opening.[8] Deprotonation produced **11** and trapping with the protected serinal **12**[9] gave the adduct **13** as a 6:1 diastereomer mixture, 93% from **9**. The isomers could not be separated, but Mitsunobu cyclization afforded a major aziridine **14** that was relatively easy to purify and was obtained in 71% yield based on the mixture of precursors **13**. The cis stereochemistry of **14** follows from the 6.1 Hz coupling between aziridine protons, and the absolute configuration is assured if the serinal precursor **12** couples with **11** without racemization. For confirmation, racemic **14** was prepared, and HPLC comparisons on a chiral stationary phase established 98.1% ee for **14** prepared from methyl (*S*)-*N*-tritylserinate (Scheme 1).

Exploratory work had shown that the bulky *N*-trityl group is important for diastereoselectivity in the addition of **11** to **12**, and that removal of the trityl group late in the synthesis is problematic. Therefore, **14** was deprotected to give **15** using the combination of trifluoroacetic acid and trimethylamine borane, a procedure where trityl cation is generated and is intercepted reductively to give triphenylmethane. A related method has been reported for *O*-trityl cleavage in nucleosides using silane-reducing agents,[10a] but the amine borane variation gave cleaner results.[10b] The aziridine **15** (82%) proved easy to *N*-methylate (BuLi; MeI) and gave **16** in 91% yield. Subsequent *O*-allyl cleavage[11] to **17** and conversion to the iodide **18** using modified Mitsunobu conditions[12] worked well after considerable optimization,[13] and cleared the way for the incorporation of a tethered alkyne dipolarophile. This was accomplished by cleavage of the TBS ether to afford the alcohol **19**, Dess−Martin oxidation to the aldehyde, and addition of a TBS-protected propargyllithium reagent. The resulting secondary alcohol was protected as the acetate **3** to avoid complications at the stage of ylide generation.

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(9) (a) Prepared from methyl *N*-tritylserinate[9b] by *O*-allylation with allyl bromide/NaH in DMF followed by DIBAL reduction at −78 °C, 94% yield. (b) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309.
(10) (a) Ravikumar, V. T.; Krotz, A. H.; Cole, D. L. *Tetrahedron Lett.* **1995**, *36*, 6587. Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739. (b) The use of the Et_3SiH (TES-H) reagent in place of amine borane risks scrambling of TES with the TBS-protecting group.
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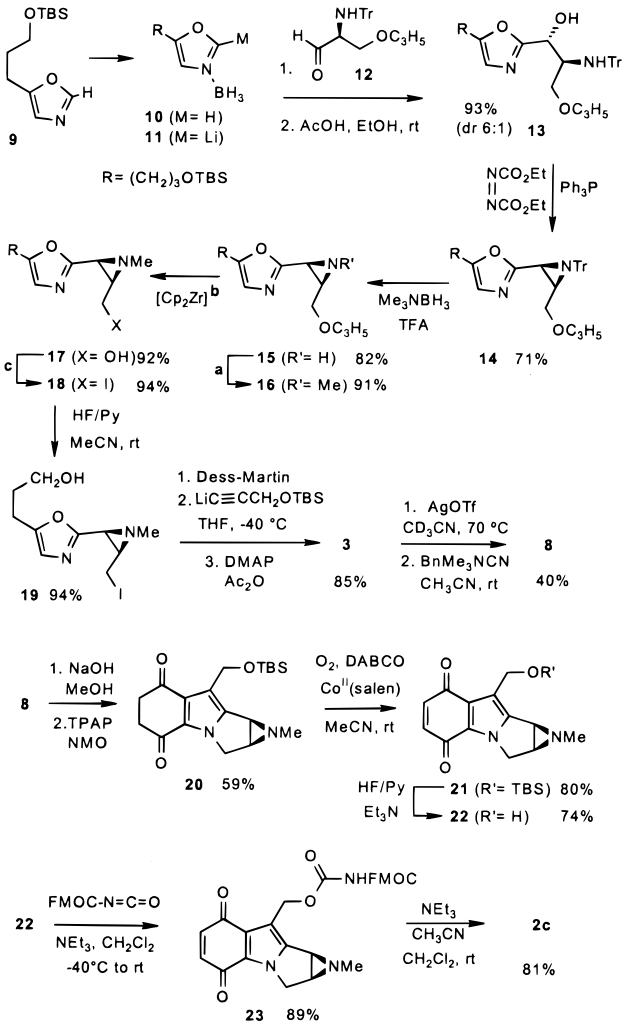
Scheme 1[a]



[a] (a) i. *n*-BuLi, −78 °C. ii. MeI. (b) Cp_2ZrCl_2, *n*-BuLi, THF, −78 °C to rt. (c) PPh_3, diisopropyl azodicarboxylate, MeI, PhMe, 70 °C.

Extensive exploratory work had established that there are two critical stages in the one-pot sequence from **3** to **8**. The first is the conversion to an oxazolium salt **4** without destruction of the aziridine. This step was carried out from the iodide using AgOTf activation, 3 h in acetonitrile at 70 °C. Attempts to perform the internal alkylation thermally, without silver ion assistance, resulted in aziridine degradation in related structures. The other key was to use a soluble cyanide source, $BnMe_3N(+)CN(-)$ for ylide generation, as reported in a model study.[6c] When a solution of **4** in acetonitrile was added to the $BnMe_3N(+)CN(-)$ reagent at room temperature, each drop produced a transient yellow color, tentatively attributed to the ylide **6**. The color faded within seconds, and the desired **8** was obtained in 40% yield after chromatographic purification. No evidence for the 3-pyrroline intermediate **7** was found.

Compared to the aziridine-containing precursors **14**−**18**, the tetracyclic **8** and all subsequent intermediates were sensitive to nucleophiles and to acidic reagents, presumably due to the presence of C−O and C−N bonds activated by pyrrole nitrogen. The cycloaddition product **8** was sufficiently stable for chromatographic purification and subsequent saponification and tetrapropylammonium perruthenate (TPAP) oxidation to give the diketone **20**. Chromatography was more difficult and significant decomposition occurred on a time scale of ∼1 h on unbuffered silica gel, and considerably faster in the presence of Et_3N buffer. A possible explanation is that initial enolization would result in a monoenol that should be highly activated for a second enolization to afford the aromatized hydroquinone. The latter is a leucoaziridinomitosene[14] and is expected to undergo especially facile aziridine solvolysis. Fortunately, it was possible to intercept the hydroquinone oxidatively by treatment with DABCO/oxygen/Co(II)−salen. The resulting quinone **21** could be deprotected to **22** with the HF−pyridine reagent, provided that triethylamine was also present to control acidity.

All of the tetracyclic intermediates were sensitive and difficult to handle, so that it was not a total surprise when conversion of **22** to **2c** using the standard $Cl_3CC(O)N{=}C{=}O$ method failed.[15] NMR analysis suggested that the aziridine ring had not survived exposure to the strongly electrophilic reagent, and therefore the reaction was repeated using a somewhat deactivated carbamoylating agent FMOCN=C=O/triethylamine. This gave a protected carbamate **23** at −40 °C to room temperature, and deprotection with triethylamine at room temperature afforded **2c**. A comparison with the reported UV and NMR characteristics for **2a** leaves no doubt regarding the structure, and the absolute configuration is defined by the starting methyl serinate.

These findings confirm that the azomethine ylide strategy is viable, and establish a route to C_6,C_7-unsubstituted aziridinomitosenes. The isolation of the diketone **20** also suggests that it may be possible to access natural leucoaziridinomitosenes from relatively stable precursors if the corresponding diketone tautomers can be prepared. Studies designed to address these issues and to probe the in vitro activity of **2c** are under way.

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

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