An Enantioselective 1,2-Aziridinomitosene Synthesis via a Chemoselective Carbon−Hydrogen Insertion Reaction of a Metal Carbene

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Several concise routes to assembling the 1,2-aziridinomitosene ring system common to the mitomycin antitumor antibiotics (cf. mitomycin C (**1**)) have been published.[1] Few of these synthetic routes have led to the production of nonracemic products.[2] Earlier we reported an enantioselective approach to 1,2-disubstituted mitosenes which relied on the desymmetrization of a meso diazoester by way of an asymmetric intramolecular carbon−hydrogen insertion reaction.[3] Unfortunately, the levels of enantioselectivity in this process were disappointingly low. Herein, we describe a second generation strategy which ultimately provides a 1,2-aziridinomitosene in high optical purity.

The key elements of our synthetic strategy are outlined in Figure 1 which shows metal carbene **5** may undergo an intramolecular carbon−hydrogen insertion reaction by one of two pathways (labeled a and b). Cyclization by way of path a leads to azido ether **3** while the alternate cyclization (path b) leads to **4**. Subsequent closure of the azido alcohols derived from **3** and **4** would lead to 1,2-aziridinomitosene **2** and *ent*-**2** respectively. *Thus, depending on the chemoselectivity of the insertion reaction (path a versus path b), either enantiomer of aziridinomitosene* ***2*** *may be derived from a common metal carbene (****5****).*[4]

Our investigations started with the synthesis of ester **10** from pyrrolidine **6** (Scheme 1). Jacobsen has described the efficient preparation of azido alcohol **6** by the asymmetric ring opening of a meso epoxide with $TMSN_3$ catalyzed by a chiral (salen)Cr(III) complex.[5] Following silylation of **6** and removal of the Boc-protecting group, we determined the enantiomeric excess of **8** to be 94.7% using capillary electrophoresis as the analytical method.[6] Palladium-catalyzed cross-coupling of **8** with 2-bromoiodobenzene using Buchwald−Hartwig conditions[7,8] gave aryl bromide **9** which was

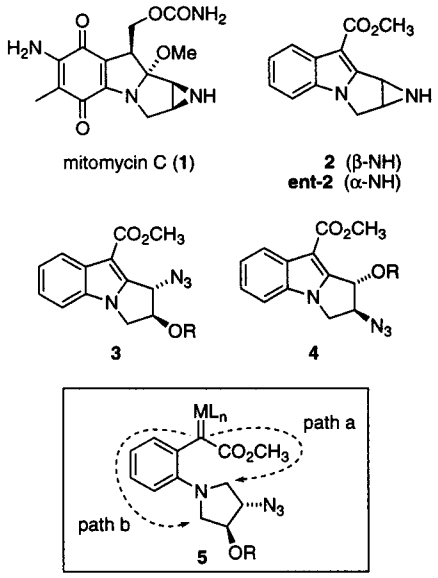

Figure 1.

subsequently coupled with the silylketene acetal derived from *tert*-butyl acetate in the presence of tributyltin fluoride to afford aryl acetate **10**.[9] At this point we examined a series of diazotransfer reactions to produce a forerunner to metal carbene **5**. Unfortunately, all attempts to effect a diazotransfer upon aryl acetate **10** and other derivatives failed; the only detectable product in these cases was undesired azide transfer.[10] On the basis of experience with similiar substrates, we determined the difficulty in effecting a diazotransfer to lie in the trans relationship of the azido and silyl ether groups. This led us to convert azido ether **10** to carbamate **18** starting with a reaction sequence develped by Jacobsen for the conversion of trans azido alcohols to cis amino alcohols.[11] To this end, hydrogenation of **10** gave amine **11** which following acetylation and desilylation yielded amide alcohol **13**. Mesylation of **13** followed by DBU treatment gave oxazoline **14**, completing inversion of stereochemistry at the oxygen-bearing carbon. Hydrolysis of **14** followed by tosylation and phosgene treatment gave carbamate **17**. Finally, methanolysis provided methyl ester **18** which underwent diazotransfer without any observed azide transfer to afford diazoester **19**.

Cyclization of diazoester **19** was examined under three sets of reaction conditions. In each case the carbon−hydrogen insertion products were not separated but instead oxidized (chloranil, CH_2Cl_2, 23 °C) to the corresponding mitosenes and the ratio of **20** and **21** determined by HPLC analysis. Photolysis of **19** in benzene followed by oxidation provided **20** and **21** in a 3:1 ratio (79% yield). Addition of a solution of **19** in dichloromethane to a suspension of rhodium(II) acetate in dichloromethane afforded a 4:1 ratio (96% yield) of **20** and **21** following oxidation with chloranil. Optimal selectivity was realized using the copper(I) complex derived from 2,2′-(1-methylethylidene)bis(5,5-dimethyl-4,5-

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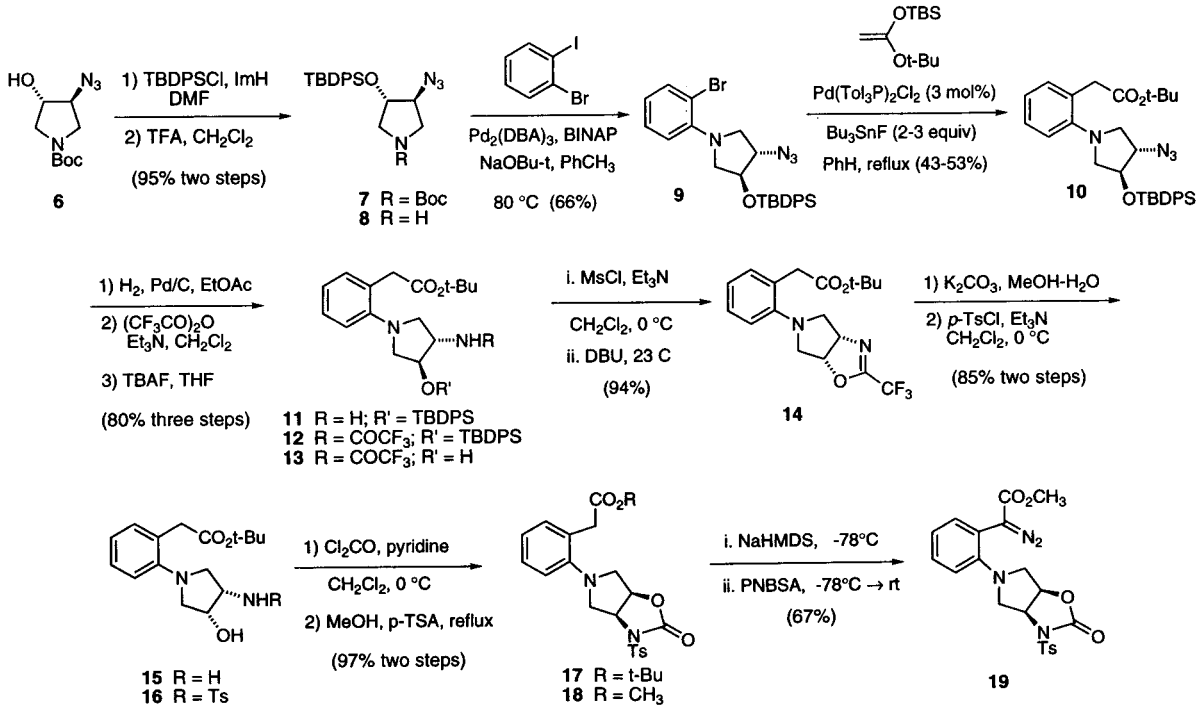
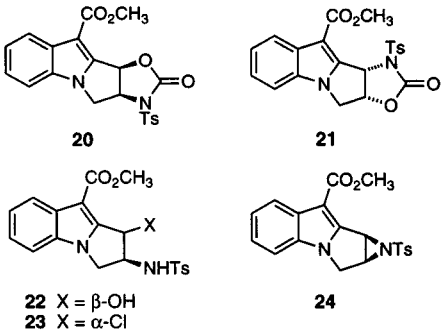
Scheme 1



dihydrooxazole)[12] and copper(I) triflate. Under these conditions a 9:1 ratio (73% yield) of **20** and **21** was realized. The major isomer **20** was hydrolyzed to amino alcohol **22**, which on treatment with $MsCl/Et_3N$ afforded chloride **23**.[13] The structure of **23** was confirmed by single-crystal X-ray analysis. Exposure of **23** to DBU in dichloromethane produced aziridine **24** (82% yield).



In conclusion, we have developed an enantioselective synthesis of a 1,2-aziridinomitosene (**24**), a key substructure of the mitomycin antitumor antibiotics. Unfortunately, our initial goal of generating either enantiomer from a common diazoester (cf. **5**, Figure 1) was derailed due to complications in effecting a diazotransfer onto ester **10**. Key transformations in the synthesis include the use of sequential palladium-mediated cross-coupling reactions to convert bromoiodobenzene to ester **10** and the application of a chemoselective carbon−hydrogen insertion reaction using a copper(I) catalyst to selectively produce mitosene **20** from diazoester **19**.

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Supporting Information Available: Experimental procedure and characterization data for all new compounds, and X-ray data for compound **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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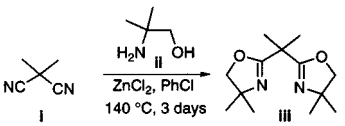
(12) 2,2′-(1-Methylethylidene)bis(5,5-dimethyl-4,5-dihydrooxazole) (iii) was prepared from dimethylmalonitrile (i) and amino alcohol **ii**.



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