Stereocontrolled Synthesis of the Fully Elaborated Aziridine Core of the Azinomycins

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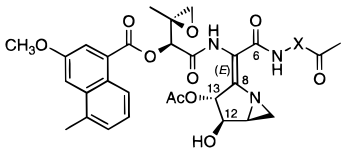
Azinomycins A (**1a**) and B (**1b**) are antitumor agents isolated from cultures of *Streptomyces griseofuscus*.[1] The azinomycins possess an intricate structure that contains the unprecedented aziridino[1,2-*a*]pyrrolidine ring system, which presents the most significant synthetic challenge of these natural products. The azinomycins exhibit potent in vitro cytotoxic activity and significant *in vivo* antitumor activity against P388 leukemia in mice.[2] Biological evaluation of these agents has been hampered by instability and poor availability from natural sources.[3]

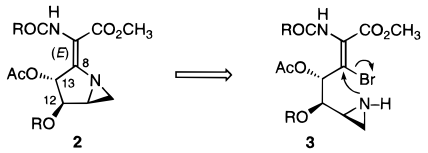


Azinomycin A (X = CH_2) **1a**
Azinomycin B (X = CH=CHOH) **1b**

The epoxide and aziridine rings of the agents suggest that the azinomycins act by covalent alkylation and cross-linking of DNA. Studies on azinomycin/oligonucleotide interactions by Armstrong and co-workers[4] were interpreted to show cross-link formation between the agent and DNA within the major groove.

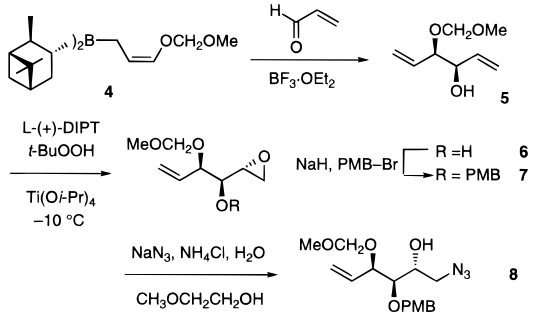
The unprecedented structure, complex molecular mechanism of action, and effective antitumor activity make the azinomycins particularly attractive targets for synthetic efforts. While there has been a significant amount of activity in the area,[5−8] no total synthesis of these agents has been reported,[6] largely due to difficulties surrounding the selectively acylated C12/C13 diol system. With the exception of our original work, there are no reports of azabicyclic ring systems containing a differentiated C12/C13 diol system, nor are there reports of systems containing a free C12 hydroxyl group. We now report the first synthesis of the fully elaborated aziridino[1,2-*a*]pyrrolidine substructure of the azinomycins including a solution to the selectively protected 1,2-diol of the agents, and we have discovered the potential origin of the instability of the natural agents.

Synthetic challenges presented by substructure **2** include (1) diastereocontrolled introduction of the C7−C8 (*E*)-dehydroamino acid double bond, (2) incorporation of the differentially acetylated C12−C13 *vic*-diol, and (3) the presence of the electrophilic aziridine ring, particularly as part of the densely functionalized system. The key transformation in our synthesis was pyrrolidine introduction by an addition−elimination reaction sequence **3** → **2**.[7,8]



2 **3**

Transformation of **5**, prepared as shown in 66% yield (>95% ee) from **4** according to Brown et al.,[9] to the key aldehyde **13** proceeded in over 35% yield for the eight-step conversion. The two double bonds of **5** were differentiated with a Sharpless asymmetric epoxidation[10] to afford epoxide **6** in 90% yield (≥98% ee). Faced with the choice of the C12-hydroxyl protecting group, and given our considerable experience from our earlier studies, we opted for a *p*-methoxybenzyl (PMB) ether, which can be removed under neutral, mildly oxidizing conditions. Protection of the remaining alcohol of **6** as the PMB ether (NaH, 4-$MeOC_6H_4$-CH_2Br, 25 °C) afforded **7** (84%) without rearrangement of the epoxide. Addition of azide to the terminal carbon of the epoxide **7** (NaN_3, $MeOCH_2CH_2OH/H_2O$, NH_4Cl(s), 25 °C)[11] provided a good yield of primary azide **8** (74%).



Reduction of the azide of **8** to the amine **9** (Ph_3P, toluene/H_2O, 25 °C)[12] and N-acylation ($ClCO_2Bn$, Et_3N, CH_2Cl_2) afforded carbamate **10** in quantitative yield. Acylation of the secondary hydroxyl of **10** (CH_3SO_2Cl, Et_3N, 96%), cleavage of the acetal (anhydrous HCl, MeOH, 25 °C, 74%),[13] and introduction of the azinomycin C13-acetate (Ac_2O, pyridine, 99%) afforded **11**. Final closure of **11** to the aziridine **12** (KO*t*-Bu, THF, −78 °C, 100%) provided the pivotal intermediate **12** in an overall yield of >35% from **5**. This compound possesses all of the functionality for elaboration to the azinomycin core, including the essential C13-acetate ester and a readily removable *p*-methoxybenzyl ether at the emergent C12 position.

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(3) Azinomycin B is apparently identical to carzinophilin A, an antitumor agent isolated in 1954 from *Streptomyces sahachiroi*: Hata, T.; Koga, F.; Sano, Y.; Kanamori, K.; Matsumae, A.; Sugawara, R.; Hoshi, T.; Shima, T.; Ito, S.; Tomizawa, S. *J. Antibiot. Ser. A* **1954**, *7*, 107.

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(6) Recently, Hashimoto and Terashima[5c] reported the synthesis of the C12/C13 bis-benzyl ether of the natural products, although these workers were unsuccessful in effecting either differentiation or deprotection of the diol.

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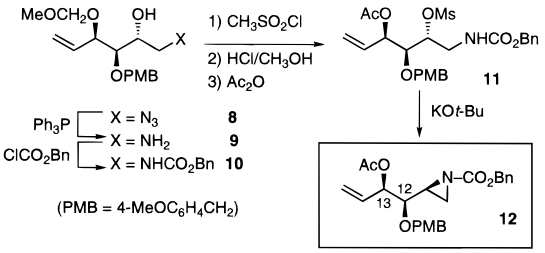
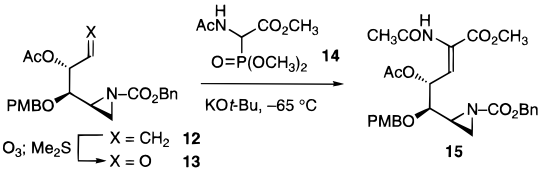
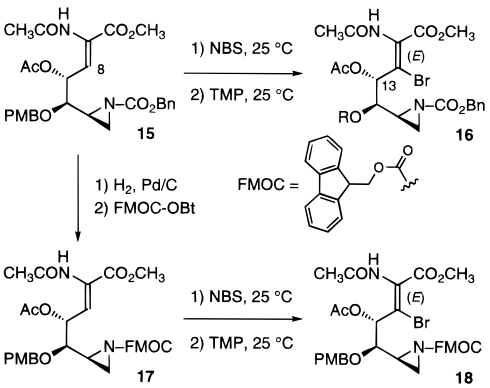


Installation of the dehydroamino acid was preceded by ozonolysis of the olefin of **12** (O_3; Me_2S) to afford aldehyde **13**. Wadsworth−Horner−Emmons olefination[14] with phosphonate **14**[15] (KO*t*-Bu, THF, −65 °C, 12 h) afforded olefin **15** in 67% yield (>4:1 Z/E). Under controlled reaction conditions the yield of **15** was satisfactory, an important fact given the delicacy of C13 protecting group manipulations on more elaborate systems.[8]



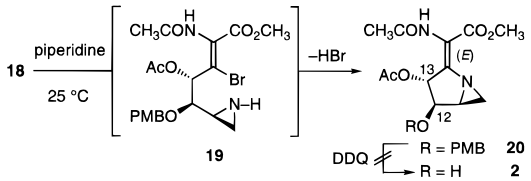
Treatment of **15** with *N*-bromosuccinimide ($CHCl_3$, 25 °C) afforded a mixture of the stereoisomeric α-bromoimines, which underwent tautomerization with base (2,2,6,6-tetramethylpiperidine, 25 °C) to the vinyl bromide (*E*)-**16** with >5:1 E/Z stereoselectivity.[16] Stereocontrol in this transformation is critical, since the cyclization used for pyrrolidine introduction is stereospecific.[8] Demonstration of stereochemistry was made by nuclear Overhauser enhancement between the NH and C13−H protons of (*E*)-**16**, and the lack of an enhancement with the Z-isomer.



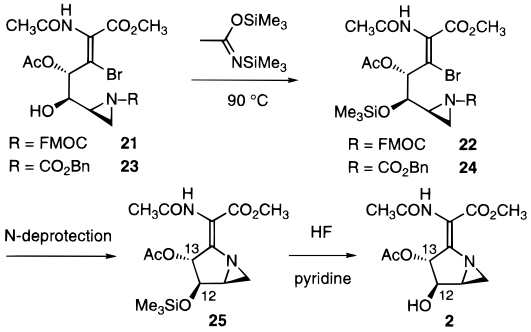
For nonobvious reasons the benzyl carbamate of **16** was resistant to cleavage with Et_3SiH and $PdCl_2$,[17] so we proceeded with a 9-fluorenylmethoxycarbonyl (FMOC) protecting group.[18] We could interchange the CO_2Bn for an FMOC group by hydrogenolysis of **15** followed by acylation of the aziridine nitrogen with FMOC−OBt to afford **17** in good yields. Bromination of **17** proceeded to afford (*E*)-**18** with 12:1 diastereoselection.

The FMOC carbamate was removed from **18** (piperidine, 25 °C, 30 min) to afford the intermediate aziridine **19**, which cyclized at room temperature to afford **20**. The *E*-stereochemistry of olefin **20** was confirmed by observation of a NOE between the C13−H and proximal NH, and by the characteristic chemical shift of the C13−H and NH protons.[8] Unfortunately, we were unable to remove the C12−PMB ether from **20** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone ($CHCl_3/H_2O$, 25 °C)[19] without causing concomitant destruction of the aziridine ring system.

The PMB ether of **18** could be removed with DDQ ($CHCl_3/H_2O$) to afford **21**, but acetate migration from C13 to C12 occurred in the course of aziridine deprotection and cyclization. This problem was solved by transient protection of the C12 alcohol of **21** as the labile trimethylsilyl ether **22**. Similarly, the benzyl



carbamate **23** (prepared from **16** by DDQ oxidation) could be silylated to afford **24**. Removal of the FMOC carbamate from **22** (piperidine, 25 °C), or the benzyl carbamate from **24** (Et_3SiH, $Pd(OAc)_2$, 25 °C)[17] (now this reaction worked well with the C12-trimethylsilyl ether), and cyclization afforded the aziridino[1,2-*a*]pyrrolidine system **25** as a stable, isolable intermediate.



Deprotection of the C12-silyl ether of **25** with HF/pyridine in THF afforded the target substructure **2**, which could not be isolated, but was characterized by ^{1}H NMR and HRMS. Repeated attempts to isolate **2** were unsuccessful, and in the end, we were able to obtain data from *in situ* ^{1}H NMR in d_8-THF sufficient to provide characterization of **2**.[20] The chemical shifts of the protons on the azabicyclic ring of **2** agreed well with those reported for the azinomycins in $CDCl_3$.[1b]

We have described the first synthesis of the fully elaborated core substructure **2** of the azinomycins, including a description of an effective protecting group strategy for the selectively acylated C12/C13 diol of the natural products. Our observations on the instability of the azinomycin core substructure **2** may provide at least a partial explanation of the unstable character of the natural products. It seems clear that the C12 hydroxyl group is potentially the cause of the instability of the natural agents. However, without clear evidence on the reaction pathway by which the C12 hydroxyl reacts, we can offer no rationale as to why this group effects the stability of the agents.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of synthetic intermediates (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(20) ^{1}H NMR (d_8-THF, 300 MHz) δ 8.42 (br s, 1H, NH), 5.36 (d, J = 0.4 Hz, 1H, C13−H), 4.40 (d, J = 4.6 Hz, 1H, C12−H), 3.67 (s, 3H, OCH_3), 3.04−2.97 (m, 1H, C11−H), 2.45−2.39 (m, 2H, C10−H), 2.05 (s, 3H, $COCH_3$), 1.87 (s, 3H, $COCH_3$); HRMS (EI) *m*/*z* 284.0996 ($C_{12}H_{16}N_2O_6$ requires 284.1008).