Synthesis of the Azabicyclic Core of the Azinomycins: Introduction of Differentiated *trans*-Diol by Crotylstannane Addition to Serinal

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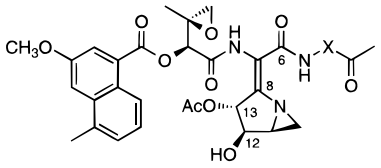
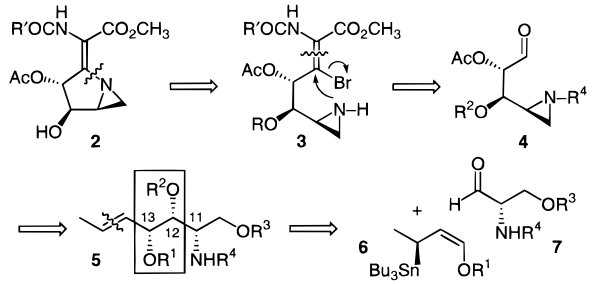
Azinomycins A (**1a**) and B (**1b**) are antitumor agents isolated from cultures of *Streptomyces*.[1] These agents contain a highly functionalized aziridino[1,2-*a*]pyrrolidine ring system, which presents perhaps the most significant synthetic challenge of these natural products. Synthetic issues presented by this substructure include the tetrasubstituted (*E*)-dehydroamino acid double bond, of the selectively acylated C12−C13 *vic*-diol, and of the electrophilic aziridine ring system. Herein, we detail a short synthesis of the aziridino[1,2-*a*]pyrrolidine substructure of the azinomycins that addresses these synthetic objectives.



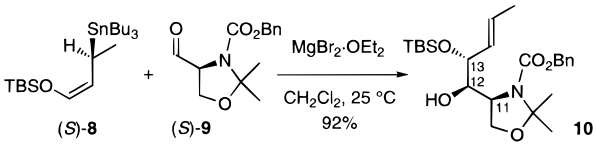
Azinomycins A and B exhibit potent in vitro cytotoxic activity and significant in vivo antitumor activity,[2] and the electrophilic epoxide and aziridine rings suggest that the azinomycins act by covalent cross-linking of DNA.[3] The azinomycins are attractive targets for synthetic efforts,[4] but with the exception of our work, there are no reports of azabicyclic systems containing a differentiated C12/C13 diol system, and no total synthesis of the natural products has been reported.

A number of less than optimal features of our original synthetic plan[5,6] led us to devise alternative routes to the core heterocyclic system.[7] A feature common to our synthetic work is the stereospecific cyclization of the aziridine of **3** onto the (*E*)-*β*-bromoacrylate to form the pyrrolidine ring of target **2**. Furthermore, the dehydroamino acid of **3** is introduced from aldehyde **4** by Wadsworth−Horner−Emmons olefination. Thus, aldehyde **4** in suitably protected form is the cornerstone intermediate in our synthetic plans. Herein, we detail a synthetic approach to the core aziridino-[1,2-*a*]pyrrolidine system **2** of the azinomycins that is based on chelation-controlled addition of *γ*-alkoxycrotylstannane **6** to serine aldehyde **7** for the stereoselective introduction of the differentiated C12/C13 *syn*-diol of intermediate **5**, and hence aldehyde **4**.



Marshall and co-workers[8] have demonstrated that *γ*-alkoxy stannanes **6** (R^1 = $SiMe_2$-*t*-Bu or CH_2OCH_3) undergo Lewis acid-promoted addition to α-amino aldehydes **7** with high syn stereoselectivity. In the context of the azinomycins, this strategy would produce intermediate **5** with the emergent C12 position *unprotected* (R^2 = H) and so would allow the divergent introduction hydroxyl protecting groups at this position. Stereoselection for the C11/C12 syn/C12/C13 syn diastereomer **5** in the addition of **6** to **7** is a consequence of a chelated aldehyde (C11/C12 bond) and the anti-S_E' transition state for crotylstannane addition (C12/C13 bond).[9]

In practice, when serine aldehyde (*S*)-**9**[10] was treated with $MgBr_2$·OEt_2 in CH_2Cl_2 at −20 °C followed by stannane (*S*)-**8**[11] and warming to 25 °C, selectively protected diol **10** was produced in near-quantitative yield with >10:1 selectivity for the syn diastereomer.[12] Performing the addition to (*S*)-**9** with the racemic stannane *rac*-**8** (2.5 equiv) effected useful levels of kinetic resolution (>10:1 *S*/*R*) and obviated the need for tedious and expensive preparation of enantiomerically pure *γ*-alkoxy stannane (*S*)-**8**.



At this point, we selected an enzymatically removable phenylacetate ester[13] for C12 hydroxyl group protection. The sterically crowded hydroxyl group of **10** was unreactive

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(1) Nagaoka, K.; Matsumoto, M.; Oono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527. Yokoi, K.; Nagaoka, K.; Nakashima, T. *Chem. Pharm. Bull.* **1986**, *34*, 4554.

(2) Ishizeki, S.; Ohtsuka, M.; Irinoda, K.; Kukita, K.-I.; Nagaoka, K.; Nakashima, T. *J. Antibiot.* **1987**, *40*, 60.

(3) (a) Lown, J. W.; Majumdar, K. C. *Can. J. Biochem.* **1977**, *55*, 630. (b) Armstrong, R. W.; Salvati, M. E.; Nguyen, M. *J. Am. Chem. Soc.* **1992**, *114*, 3144.

(4) (a) Bryant, H. J.; Dardonville, C. H.; Hodgkinson, T. J.; Shipman, M.; Slawin, A. M. *Synlett* **1996**, *10*, 973. (b) Bryant, H. J.; Dardonville, C. Y.; Hodgkinson, T. J.; Hursthouse, M. B.; Malik, K. M. A.; Shipman, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1249. (c) Armstrong, R. W.; Tellew, J. E.; Moran, E. J. *Tetrahedron Lett.* **1996**, *37*, 447. (d) Moran, E. J.; Tellew, J. E.; Zhao, Z.; Armstrong, R. W. *J. Org. Chem.* **1993**, *58*, 7848. (e) Armstrong, R. W.; Moran, E. J. *J. Am. Chem. Soc.* **1992**, *114*, 371. (f) Combs, A. P.; Armstrong, R. W. *Tetrahedron Lett.* **1992**, *33*, 6419. (g) Armstrong, R. W.; Tellew, J. E.; Moran, E. J. *J. Org. Chem.* **1992**, *57*, 2208. (h) Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 3807. (i) England, P.; Chun, K. H.; Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett.* **1990**, *31*, 2669. (j) Hashimoto, M.; Terashima, S. *Heterocycles* **1998**, *47*, 59. (k) Hashimoto, M.; Terashima, S. *Tetrahedron Lett.* **1994**, *35*, 9409. (l) Hashimoto, M.; Terashima, S. *Chem. Lett.* **1994**, *6*, 1001. (m) Hashimoto, M.; Matsumoto, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1994**, *35*, 2207. (n) Hashimoto, M.; Yamada, K.; Terashima, S. *Chem. Lett.* **1992**, *6*, 975. (o) Konda, Y.; Machida, T.; Sasaki, T.; Takeda, K.; Takayanagi, H.; Harigaya, Y. *Chem. Pharm. Bull.* **1994**, *42*, 285. (p) Ando, K.; Yamada, T.; Shibuya, M. *Heterocycles* **1989**, *29*, 2209. (q) Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2053. (r) Shibuya, M.; Terauchi, H. *Tetrahedron Lett.* **1987**, *28*, 2619. (s) Shibuya, M. *Tetrahedron Lett.* **1983**, *24*, 1175.

(5) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813.

(6) Coleman, R. S.; Carpenter, A. J. *Tetrahedron* **1997**, *53*, 16313.

(7) Concurrent with the present work, we developed a complementary synthesis of the core substructure **2** (R′ = CH_3): Coleman, R. S.; Kong, J.-S. *J. Am. Chem. Soc.* **1998**, *120*, 3538.

(8) Marshall, J. A.; Seletsky, B.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139.

(9) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239.

(10) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18.

(11) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

(12) For the syn-selective addition of a vinylzinc reagent to α-amino aldehydes in a similar context, see: Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697.

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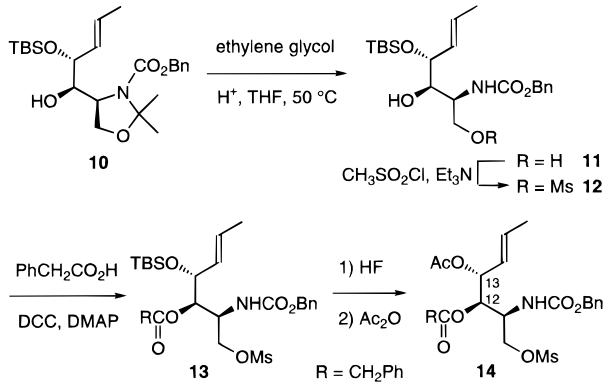
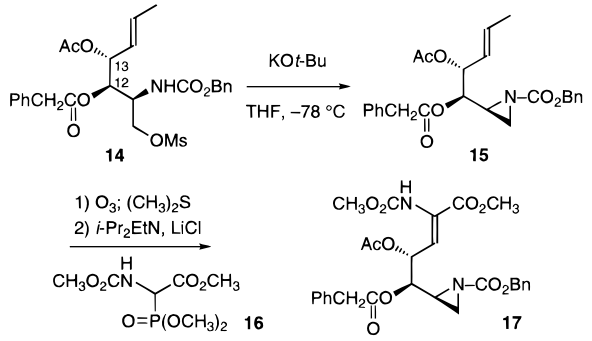
toward even forcing acylation conditions, so the *N*,*O*-acetonide was removed prior to acylation. Cleavage of the oxazolidine ring of **10** occurred upon treatment with ethylene glycol and camphorsulfonic acid, and the resulting diol **11** was selectively acylated at the primary hydroxyl group with methanesulfonyl chloride (Et_3N, CH_2Cl_2, −20 °C) to afford **12**. The secondary hydroxyl group of **12** was protected as the phenylacetate ester by treatment with the carboxylic acid and dicyclohexylcarbodiimide (DCC) to afford **13**.

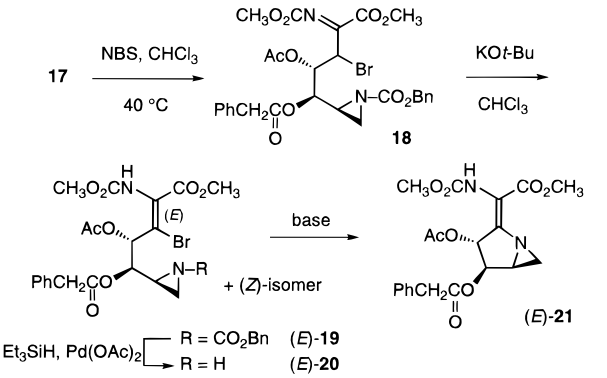


Interchange of C13 hydroxyl protecting groups was accomplished by removal of the silyl group from **13** (5% aqueous HF/CH_3CN, 25 °C) and acetylation of the resulting alcohol (Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 25 °C) to afford **14**. In six high-yielding steps (57% overall yield), the advanced intermediate **14** was generated with complete control of absolute stereochemistry and effective introduction of suitable protecting groups. Aziridine installation was achieved by treatment of methanesulfonate **14** with potassium *tert*-butoxide at −78 °C, which afforded aziridine **15** in good yields. Ozonolysis of the double bond of **15** followed by olefination of the resulting aldehyde with the glycine phosphonate **16**[14] afforded dehydroamino acid **17** as a 2.5:1 ratio of *Z*/*E* isomers in good yields under carefully optimized reaction conditions (LiCl, *i*-Pr_2NEt).[15] The ratio of olefin



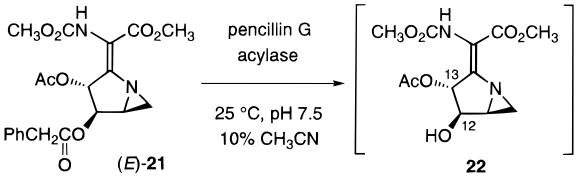
stereoisomers was irrelevant, since both isomers converge to the same mixture of stereoisomeric vinyl bromides in the subsequent bromination reaction sequence.[16]

At this point, the vinylic bromide necessary for pyrrolidine formation was introduced by treatment of **17** with *N*-bromosuccinimide ($CHCl_3$, 40 °C). We found that the intermediate α-bromo imine **18** so produced from either (*Z*)- or (*E*)-**17** underwent only a modestly stereoselective base-promoted tautomerization with KO-*t*-Bu in THF. The desired (*E*)-bromide **19** was obtained in typically a 1:1 ratio to the (*Z*)-bromide. This is a notable divergence from results in other systems,[6,7,16] wherein we obtained ≈10:1 E-selectivity in the tautomerization of systems related to **18** that was dependent on the use of sterically bulky bases.



Since we knew that a free C12 hydroxyl group could participate as the receiving partner in a thermodynamically driven acetate migration from the proximal C13 ester prior to cyclization, this necessitated that C12 deprotection await closure of the pyrrolidine ring. Triethylsilane-mediated removal of the aziridine N-protecting group[17] of **19** afforded the free aziridine **20**, which underwent cyclization upon warming in the presence of Dowex anion-exchange resin (carbonate form) to afford the pyrrolidine **21**. This cyclization was found to be stereospecific.[6]

Deprotection of the C12 phenylacetate ester of **21** occurred upon treatment with 5−10 mol % polymer-supported penicillin G acylase in a mixed solvent system of acetonitrile/aqueous buffer. Systems such as **22** where the C12 hydroxyl group is unprotected are not sufficiently stable to permit isolation,[7] and so we attempted to characterize **22** formed in situ using ^1H NMR (500 MHz, 9:1 D_2O/CD_3CN). The phenylacetate ester of **21** could be removed with an approximate half-life of 2 h, and **22** could be observed as at best the minor of several products of this reaction. Neither isolation nor further characterization of **22** could be achieved, and from the data we concluded that **22** was undergoing further reaction at rates similar to its production from **21**.



The source of the instability of **22** was not apparent from an examination of ^1H NMR spectra, as no clearly defined products from reaction(s) of **22** could be identified. We believe it resides in the unprotected C12 hydroxyl group since the penultimate C12 ester described herein and the corresponding *p*-methoxybenzyl ether[7] are sufficiently stable to permit isolation and storage. We conclude that problems with deprotection of the C12 hydroxyl group are not a result of inappropriate choice of protecting group but are the result of the instability of the natural agents.

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Supporting Information Available: ^1H and ^{13}C NMR spectra and detailed experimental procedures of synthetic intermediates (27 pages).

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(13) Waldmann, H.; Sebastian, D. *Chem. Rev.* **1994**, *94*, 911. Fuganti, C.; Grasselli, P.; Servi, S.; Lazzarini, A.; Casati, P. *Tetrahedron* **1988**, *44*, 2575. Fuganti, C.; Rosell, C. M.; Servi, S.; Tagliani, A.; Terreni, M. *Tetrahedron: Asymmetry* **1992**, *3*, 383.

(14) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863. Schmidt, U.; Lieberknecht, A.; Wild, S. *Synthesis* **1984**, 53.

(15) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(16) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1993**, *58*, 4452.

(17) Birkofer, L.; Bierwirth, E.; Ritter, A. *Chem. Ber.* **1961**, *94*, 821.