Synthesis of the Aziridino[1,2-*a*]pyrrolidine Substructure of the Antitumor Agents Azinomycin A and B

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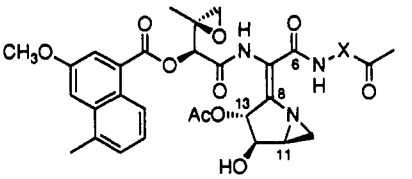
Summary: A stereoselective synthesis of the central aziridino[1,2-*a*]pyrrolidine substructure (**19**) of the antitumor agents azinomycin A and B is reported and featured as the key step an intramolecular Michael addition–elimination reaction between the aziridine and β-bromo acrylate of intermediate **18**; this compound was efficiently constructed via aldehyde **14**, which was prepared from D-glucosamine.

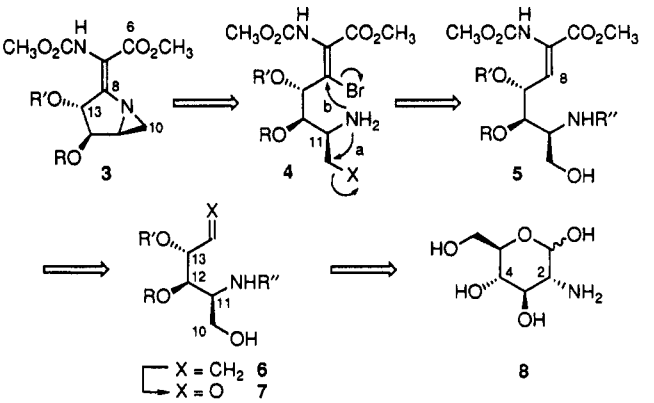
Azinomycins A (**1**) and B (**2**) are antitumor–antibiotic agents that were isolated from culture broths of *Streptomyces griseofuscus* S42227[2,3] and were shown to contain the unprecedented aziridino[1,2-*a*]pyrrolidine (1-azabicyclo[3.1.0]hexane) ring system.[4] Azinomycins A and B exhibit potent in vitro cytotoxic activity and significant, effective in vivo antitumor activity in mice.[2] Although the biological mechanism of action of the azinomycins is unknown, the presence of an electrophilic epoxide and aziridine implies that the azinomycins act by covalent alkylation and cross-linking of DNA[5a] in a manner reminiscent of mitomycin C.[5b] The intriguing structure, intricate functionalization, and potent, effective antitumor activity make the azinomycins exceptionally attractive and timely targets for total synthesis.[6] Herein, we detail an enantioselective synthesis of the densely functionalized C6–C13 aziridino[1,2-*a*]pyrrolidine substructure of the azinomycins that provides for the stereoselective introduction of the C7–C8 *E*-double bond and C12–C13 selectively protected diol of **1** and **2**.

The synthetic approach to the targeted substructure **3** is outlined below. The pyrrolidine ring of **3** was envisioned to arise by an intramolecular Michael addition–elimination reaction sequence between a C11-amine (azinomycin numbering) and the electrophilic β-bromoacrylate of



Azinomycin A (**1**) X = CH_2
Azinomycin B (**2**) X = CH=CHOH

acyclic precursor **4** (process b), whereas the fused aziridine ring could be introduced conceptually by cyclization of the amine onto a C10 electrophile (process a); the order of these two steps was not obvious at the inception of the synthesis. Introduction of the C8-vinyl bromide necessary for pyrrolidine ring formation would use the nucleophilic enamine character of olefin **5**.[7] A notable feature of this synthetic plan employs the mutable reactivity of systems such as **5**, wherein the dehydroamino acid functionality must react as both a nucleophilic enamine and an electrophilic acrylate. Olefin **5** would arise from aldehyde **7** by a stereoselective Wadsworth–Horner–Emmons olefination using an appropriate amino acid-derived phosphonate.[8] A synthesis of aldehyde **7** was proposed that was based on an observation that the C11, C12, and C13 stereogenic centers of the proposed structures of the azinomycins[2] can be superpositioned onto the C2, C3, and C4 stereogenic centers, respectively, of D-glucosamine (**8**). In this strategy,[9] C5 of D-glucosamine (**8**) emerges as the aldehyde carbonyl of **7**, while C1 of **8** is transposed to C10 of **7**; C6 of D-glucosamine is excised in conversion of olefin **6** to aldehyde **7**.



Benzylidene acetal **9** (Ar = *p*-$(CH_3O)C_6H_4$) was prepared in three steps from D-glucosamine[10] and served as an ap-

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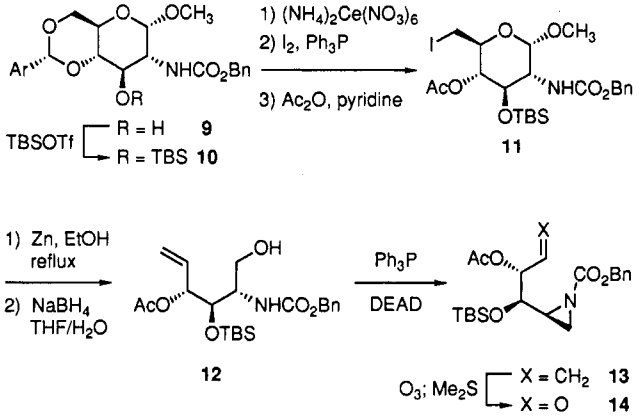
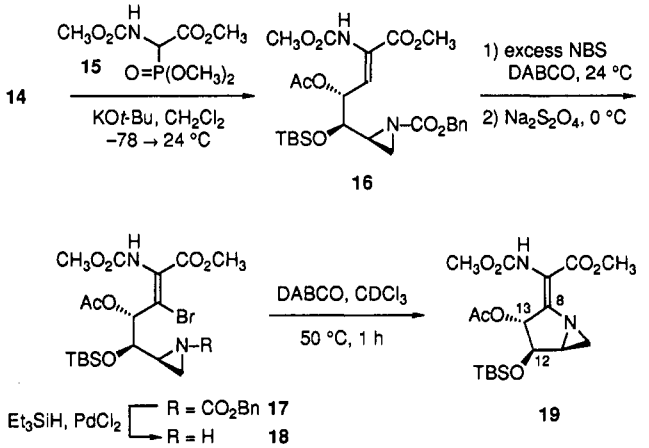
propriate starting point for the efficient construction of a selectively protected form of aldehyde **7**. Protection of **9** as the *tert*-butyldimethylsilyl (TBS) ether (*t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 90%) afforded **10**. Cleavage of the benzylidene acetal of **10** (2.0 equiv of $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O, 25 °C, 1 h, 73%)[11] was followed by selective iodination[12] of the newly liberated primary C6-hydroxyl group (I_2, Ph_3P, pyridine, toluene, 70 °C, 88%) and acylation of the remaining secondary C4-alcohol (Ac_2O, pyridine, CH_2Cl_2, cat. DMAP, 24 °C, 98%) to provide 6-iodo-6-deoxy-D-glucosamine **11**. Intermediate **11** possesses the emergent, selectively protected 1,2-diol functionality characteristic of the azinomycins.[13] Vasella fragmentation[14] of iodide **11** (activated Zn, 95% EtOH, 78 °C, 1 h) was followed by immediate reduction of the resulting labile aldehyde ($NaBH_4$, THF/H_2O, −43 °C), and provided alcohol **12** in excellent yields (84% overall from **11**).[9] Aziridine introduction was opted for at this juncture in the synthesis[15] and was achieved by Mitsunobu cyclization[16] of hydroxy urethane **12** (Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 23 °C, 12 h) to afford aziridine **13** in 85% yield. Ozonolysis of olefin **13** (O_3, CH_2Cl_2, −78 °C; 20 equiv $(CH_3)_2S$, 23 °C) provided aldehyde **14** in quantitative yield, and in 40% overall yield from **9**.



Wadsworth–Horner–Emmons olefination of aldehyde **14** with the potassium salt of phosphonate **15** (KO-*t*-Bu, CH_2Cl_2, 24 °C)[8] afforded dehydroamino acid **16** in good yield with ≥10:1 *Z*/*E* diastereoselectivity.[8e] Introduction of the vinyl bromide[7] necessary for the Michael addition–elimination reaction sequence was attempted by treatment of **16** with 1 equiv of *N*-bromosuccinimide (NBS) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH_2Cl_2 (24 °C, 2 h).[17] In conflict with expectations,[17b] this reaction selectively afforded the undesired *Z*-olefin isomer of **17** in ≥10:1 ratio to the desired *E*-isomer. Solution of this problem was attained by treatment of **16** with an excess of NBS in the presence of DABCO (CH_2Cl_2, 24 °C, 8 h), which cleanly afforded the corresponding *gem*-dibromoimine;[17b] reduction of this dibromide with sodium dithionite in aqueous THF (0 °C, 15 min) afforded the desired *E*-bromide **17**[18] along with the undesired *Z*-isomer, which were readily separable by silica gel chromatography.



Treatment of bromide **17** with Et_3SiH in the presence of $PdCl_2$ and Et_3N[19] (25 °C, 30 min) effected quantitative removal of the *N*-benzoxycarbonyl protecting group to afford the corresponding free aziridine **18**. The isolated and purified aziridine **18** so obtained could be induced to undergo the desired intramolecular Michael addition–elimination reaction upon warming in the presence of base (1 equiv DABCO, $CDCl_3$, 50 °C) and thereby afforded the targeted aziridino[1,2-*a*]pyrrolidine **19**. Complete retention of configuration of the olefin was observed.[6a,20] Sub-

(10) Compound **9** was synthesized from D-glucosamine hydrochloride (Aldrich) by the following reaction sequence: (1) $ClCO_2Bn$, $NaHCO_3$, dioxane/H_2O, 24 °C; (2) 2% HCl in CH_3OH, reflux, 24 h; (3) *p*-$(CH_3O)C_6H_4CH(OCH_3)_2$, cat. CSA, DMF, 80 °C. Overall yields for this three-step conversion ranged from 40–50%.[9] See also: Chargaff, E.; Bovarnick, M. *J. Biol. Chem.* **1937**, *118*, 421. Neuberger, A.; Rivers, R. P. *J. Chem. Soc.* **1939**, 122.

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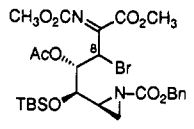
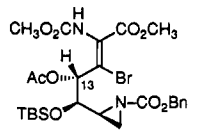
(17) (a) If the bromination was performed in the absence of base (1 equiv of NBS, CH_2Cl_2, 23 °C), the intermediate α-bromoimine **i** could be isolated.[7] α-Bromoimine **i** exhibited a characteristic resonance in the ^1H NMR (300 MHz, $CDCl_3$) at δ 5.64 (d, *J* = 5.9 Hz) corresponding to C8-H. Treatment of **i** with base (DABCO or Et_3N, CH_2Cl_2, 23 °C, 15–30 min) effected quantitative conversion to the undesired *Z*-isomer of **17**. (b) Full details of our observations on the bromination of dehydroamino acids will be communicated separately (Coleman, R. S.; Carpenter, A. J., unpublished observations).



i

(18) Assignment of *E*-olefin geometry to **17** was based primarily on correlation of spectral data with related compounds and was confirmed by the observation of a strong positive nuclear Overhauser enhancement of the NH in the NOE difference spectrum of **17** when C13-H was irradiated (500 MHz, $CDCl_3$).



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structure **19** contains the intact, completely functionalized, stereochemically elaborated C6–C13 bicyclic ring system of the azinomycins, including the C7–C8 tetrasubstituted *E*-double bond[21] and C12–C13 selectively acylated *trans*-1,2-diol characteristic of this family of antitumor agents. Spectral characterization of **19**[21,22] was in accord with literature precedent.[2,6a,b]

(21) The *E*-geometry of the double bond of **19** was confirmed by the observation of a strong positive nuclear Overhauser enhancement of C13-H in the NOE difference spectrum of **19** when the NH was irradiated (500 MHz, $CDCl_3$). No enhancement was seen in similar experiments with the isomeric aziridino[1,2-*a*]pyrrolidine.

(22) Compound **19** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (br s, 1 H, NH), 5.25 (br s, 1 H, C13-H), 4.51 (br d, J = 4.4 Hz, 1 H, C12-H), 3.81 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 3.16 (apparent q, J = 4.5 Hz, 1 H, C11–H), 2.62 (br m, 1 H, C10–H_{exo}), 2.56 (d, J = 3.7 Hz, 1 H, C10-H_{endo}), 2.10 (s, 3 H, CH_3CO), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); IR (neat) ν_{max} 3324, 1734, 1251, 838, 779 cm^{-1}; HRMS *m/e* calcd for $C_{18}H_{30}N_2O_7Si$ 414.1822, found 414.1819.

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Supplementary Material Available: Detailed experimental procedures and full spectral characterization for **10–14** and **16–19** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Allium Chemistry: Simple Syntheses of Antithrombotic Cepaenes from Onion and Deoxycepaenes from Oil of Shallot by Reaction of 1-Propenethiolate with Sulfonyl Halides

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Summary: Stereoisomers of MeCH=CHSLi from Li/NH_3 reduction of MeCH=CHSPr react with varying proportions of MsCl giving the respective stereoisomers of either bis(1-propenyl) disulfide (**1**), *S*-1-propenyl methanesulfonothiate (**2a**), or 6-ethyl-4,5,7-trithiadeca-2,8-diene (**3**); oxidation of **3**, a shallot oil component, gives 6-ethyl-4,5,7-trithiadeca-2,8-diene 7-oxide (cepaene, **4**), an antithrombotic compound from onion.

Oil of shallot (*Allium ascalonicum*) contains α,β-unsaturated organosulfur compounds such as bis(1-propenyl) disulfide (**1**), *S*-1-propenyl methane- and propanesulfonothioate (MeCH=CHSSO$_2$R, **2a/2b**, R = Me/Pr), and (*E,E*)-6-ethyl-4,5,7-trithiadeca-2,8-diene ((*E,E*)-**3**, a "deoxycepaene").[1] The 7-oxide of (*E,E*)-**3** ((*E,E*)-**4**), termed a "capaene," has been isolated from extracts of onion (*Allium cepa*) and shows significant biological activity.[2] We describe here simple stereospecific syntheses of **1–4**, notable in involving 1-propenethiolate and sulfonyl halides, RSO_2Cl, in the first step of each synthesis! Our work demonstrates the unusual reactions that can occur with enethiols.

We required pure samples of (*E,Z*)-**1** as well as (*E,E*)- and (*Z,Z*)-**1** for our continuing study of *Allium* chemistry.[3] While (*E,E*)- and (*Z,Z*)-**1** could be prepared by oxidation of lithium (*E*)- and (*Z*)-1-propenethiolate ((*E*)-**5** and (*Z*)-**5**), respectively, synthesis of (*E,Z*)-**1** required a more indirect route, e.g, reaction of (*E*)-**5**, or the corresponding potassium salt, with (*Z*)-**2** (eq 1). While (*Z*)-**2** should be available

(1)

by regiospecific S,S-dioxidation of (*Z*)-MeCH=CHSSR, this approach suffers from difficulty in controlling the regiochemistry of oxidation, unexpected side products and C=C isomerization.[4] In the course of exploring synthesis of **2** by reaction of **5** with RSO_2Cl, we discovered remarkable one-step syntheses of **1–3**, described herein.

Slow addition of (*E*)-**5** (Li/NH_3 cleavage of (*E*)-1-propenyl propyl sulfide ((*E*)-**6**)[5]) to 20 equiv of MsCl in THF at −78 °C gives (*E*)-**2a**, in 22% yield, along with (*E,E*)-**1** (Table I).[6] Similarly, MsCl and $PrSO_2Cl$ give (*Z*)-**2a** and (*Z*)-**2b** in 34% and 30% yield, respectively, from (*Z*)-**5**.[5,6] Addition of 0.8 equiv of MsCl in THF to (*E*)- or (*Z*)-**5** at −65 °C affords (*E,E*)- or (*Z,Z*)-6-ethyl-4,5,7-trithiadeca-2,8-diene ((*E,E*)- or (*Z,Z*)-**3**; 27% and 20% yield) and (*E,E*)- or (*Z,Z*)-5,8-diethyl-4,6,7,9-tetrathiadodeca-2,10-diene, as pairs of diastereomers ((*E,E*)- or (*Z,Z*)-**7a,b**; 15% and 10% yield, respectively),[7] and 2,4,6-triethyl-1,3,5-trithiane isomers (**8**, trace).[6] Addition of 2 equiv of MsCl in ether to (*E*)- or (*Z*)-**5** at −78 °C, followed after 5 min by quenching with water and rapid warming to 5 °C, gives (*E,E*)- and (*Z,Z*)-**1** (>95% isomeric purity;

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(5) Preparation of (*Z*)- and (*E*)-**6**: base-induced isomerization of propyl 2-propynyl sulfide (from propanethiol and propargyl bromide or chloride) to propyl 1-propynyl sulfide (95% yield) followed by $LiAl(OMe)_3H$ reduction giving (*Z*)-**6** (75%) or by $LiAlH_4$ reduction giving (*E*)-**6** (60%).[4]

(6) New compounds have been fully characterized by spectroscopic means; mass spectra of compounds **1–3** matched the spectra of the shallot oil components.[1]

(7) Oxidation of MeCH=CHSCHEtSLi (**11**) prepared from MeCH=CHSCHEtSAc/MeLi gives a product identical by GC–MS to **7a,b**, supporting the structure proposed for **7a,b**.

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