

0.33 mmol). After the mixture had been stirred for 30 min at room temperature, ferrocene **3** (12 mg, 0.025 mmol) was added, and the resulting solution was then cooled to 10 °C. Stirring was continued for an additional 10 min at this temperature, and the aldehyde (0.25 mmol) was then added directly in one portion. The Schlenk flask was sealed, and the reaction mixture was stirred at 10 °C overnight. Quenching with water followed by extracting with dichloromethane, drying of the combined organic phase over MgSO₄, and evaporating the solvent under reduced pressure gave the crude product. Column chromatography (silica gel; eluents: hexanes/diethyl ether) afforded the pure secondary alcohol (for *ee* analyses by HPLC see Supporting Information).

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A Synthetic Azinomycin Analogue with Demonstrated DNA Cross-Linking Activity: Insights into the Mechanism of Action of this Class of Antitumor Agent**

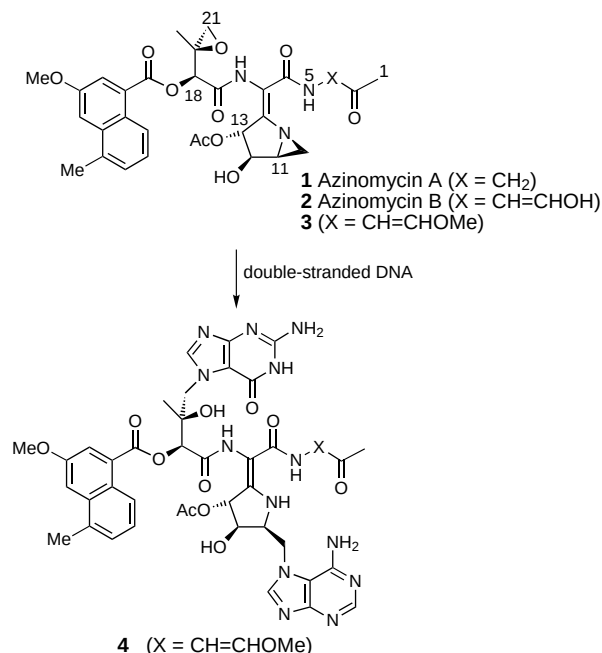
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Chemical agents capable of inducing DNA interstrand cross-links (ISCs) comprise an extremely important class of clinical cancer chemotherapeutic agents.^[2] The azinomycins (**1**

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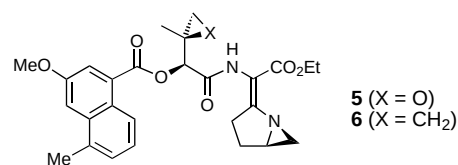
and **2**, Scheme 1) are a unique class of antibiotic which possess potent in vitro cytotoxic activity, significant in vivo antitumor activity, and which appear to act by ISC formation.^[3] Two reports have been published which provide insights into how



Scheme 1. Mechanism of action of the azinomycins, the azinomycins bind to two purine residues.

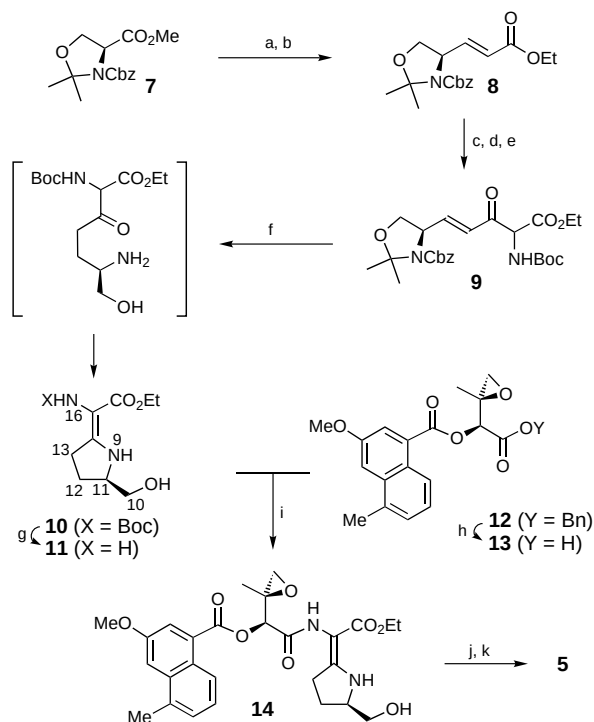
these natural products induce ISCs in double-stranded DNA. By using synthetic oligonucleotide duplexes, Armstrong et al. demonstrated that azinomycin B causes ISCs in the major groove of DNA by alkylation at N-7 of guanine (G) and reaction with another purine residue (A or G) two bases along on the complementary DNA strand.^[4] Recently, Fujiwara et al. isolated and partially characterized adduct **4**, produced upon treatment of the 4-methyl azinomycin B derivative **3** with the self-complementary oligodeoxynucleotide [d(TAGC-TA)₂], work which provided the first direct evidence of the involvement of the electrophilic epoxide and aziridine moieties in the DNA cross-linking event (Scheme 1).^[5]

To fully elucidate the mechanism of action of the azinomycins, work which might ultimately lead to the development of new clinically useful ISC agents, further studies are needed to determine the timing of the alkylation events that lead to ISC formation and to ascertain the role of other functional groups within the azinomycins (e.g. naphthyl residue, C-12/C-13 hydroxy groups) in DNA sequence recognition. One powerful way to address these issues would be to make simplified yet mechanistically fully functional analogues of the natural products. Surprisingly, despite the large volume of work that has been directed towards realizing the first total synthesis of the azinomycins,^[6] no reports have appeared on the ISC activity of any synthetic azinomycin derivatives. Herein we describe a flexible and efficient approach for the assembly of the basic C-6 to C-21 carbon skeleton of the azinomycins and demonstrate that this approach can be used to prepare simplified azinomycin analogues such as epoxy aziridine **5** and cyclopropyl aziridine **6**. Furthermore the analogue **5** is an ISC



agent and acts by a similar mechanism to that of the natural products.

Our synthesis of epoxy aziridine **5** is depicted in Scheme 2. Homochiral ester **7**,^[7] readily obtained from L-serine in three steps, was transformed into α,β -unsaturated ester **8** by DIBAL

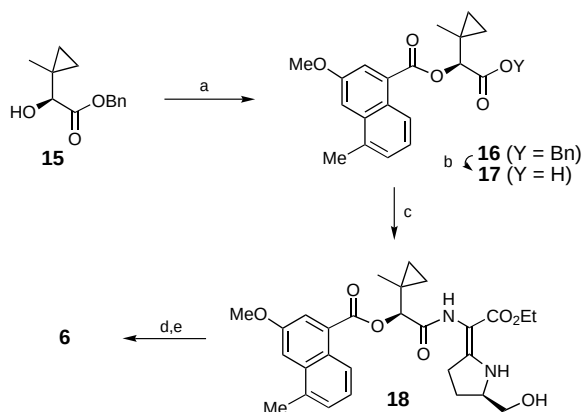


Scheme 2. Synthesis of the azinomycin analogue **5**. a) DIBAL, toluene, -78°C , 95%; b) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, toluene, 77%; c) NaOH, THF, H_2O ; d) $(\text{COCl})_2$, DMF (catalyst), CH_2Cl_2 ; e) $\text{EtO}_2\text{CCH}(\text{CO}_2\text{H})(\text{NHBoc})$, $\text{Mg}(\text{OEt})_2$, CCl_4 , 54% from **8**; f) H_2 , Pd/C, EtOH, HCl(aq), 68%; g) TFA, CH_2Cl_2 ; h) H_2 , Pd/C, MeOH; i) PyBOP, HOBT, Et_3N , DMF, 67% from **12**; j) MsCl , Et_3N , -78°C , CH_2Cl_2 , 91%; k) TBAF, 4 Å sieves, THF, 15 min, TLC, 45%. PyBOP = benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate, HOBT = 1-hydroxy-1H-benzotriazole, TBAF = tetrabutylammonium fluoride, MsCl = methanesulfonyl chloride, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl, DIBAL = diisobutylaluminum hydride.

reduction and subsequent olefination by using (carboethoxymethylene)triphenylphosphorane. Further homologation of ethyl ester **8** to α -amino- β -ketoester **9** was accomplished by conversion to the acid chloride and coupling with $\text{EtO}_2\text{CCH}(\text{CO}_2\text{H})(\text{NHBoc})$ in the presence of magnesium ethoxide.^[8] Then, a pivotal step in the synthesis was executed by the hydrogenation of **9** in EtOH in the presence of aqueous hydrochloric acid to give dehydroamino acid **10** in 68% yield. We suggest that these reaction conditions produce the γ -amino ketone which undergoes spontaneous cyclization to the corresponding cyclic imine which then tautomerizes to the

thermodynamically more stable **10**. Dehydroamino acid **10** is produced as a variable mixture of geometric isomers in favor of the desired *E* isomer (*E*:*Z*; 10:1 to 6:1 (in CDCl₃)) as determined by NOE measurements,^[9] and in reproducibly high enantiomeric excess (*E* isomer = 90 % *ee*; *Z* isomer = 89 % *ee*) as established by chiral HPLC analysis.^[10] As yet, we have been unable to ascertain the source of the small amount of racemization observed in the conversion of **8** into **10**. Coupling of carboxylic acid **13**, produced by hydrogenation of benzyl ester **12**,^[6b] with 1.5 equivalents of amine **11** (formed by removal of the *N*-Boc group from **10**) yielded **14** in 67 % yield, as a mixture of geometric isomers (9:1 (in CDCl₃)). Finally, ring closure to give 1-azabicyclo[3.1.0]hexane **5** was accomplished via the corresponding mesylate according to methodology originally devised by Terashima and co-workers.^[11] In our hands, this ring closure was best performed with TBAF^[6c] which provides the bicyclic compound **5** in 45 % yield after rapid preparative thin-layer chromatography (TLC) on plates pretreated with triethylamine.

To study the mechanism of DNA cross-link formation by using simplified azinomycin analogues, we have also prepared **6**, containing a “left-hand” domain in which the electrophilic epoxide moiety has been replaced by the chemically inert cyclopropane ring. This was achieved by esterification of homochiral alcohol **15**^[12] with 5-methyl-3-methoxy-1-naphthoyl chloride to give benzyl ester **16** (Scheme 3). Subsequent



Scheme 3. Synthesis of the azinomycin analogue **6**. a) 5-Methyl-3-methoxy-1-naphthoyl chloride, DMAP (catalyst), Et₃N, CH₂Cl₂, 85 %; b) H₂, Pd/C, MeOH; c) PyBOP, HOBT, Et₃N, DMF, **11**, 65 % from **16**; d) MsCl, Et₃N, –78 °C, CH₂Cl₂, 80 %; e) TBAF, 4 Å molecular sieves, THF, 15 min, TLC, 34 %. DMAP = 4-dimethylaminopyridine

hydrogenolysis of this ester gave the corresponding acid **17**, which was coupled with amine **11** and further converted into **6** via **18** as described above for **5**. Whilst the gross structure of the bicyclic compounds **5** and **6** have been established unambiguously, the stereochemical assignment about the tetrasubstituted double bond can only be tentatively assigned as *trans*, based on comparisons with the earlier synthetic intermediates (e.g. **10**, Scheme 2).^[13]

By using an agarose gel assay,^[14] we have studied the interstrand cross-linking activity of three of our synthetic azinomycin compounds (**5**, **6**, **14**). We have determined that

epoxy aziridine **5** produces DNA cross-links (100 % cross-link formation at 100 μM after 1.5 h), whereas **6** and **14**, devoid of the epoxide or the aziridine, respectively, show little more than background-level activity (Figure 1). Thus, the presence

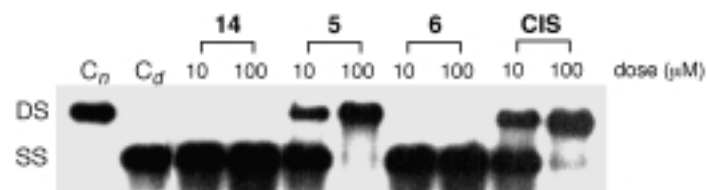


Figure 1. Agarose cross-linking gel for the synthetic azinomycin analogues (**5**, **6**, **14**). Plasmid DNA was treated with the agents at two separate concentrations (10 and 100 μM) for 1.5 h prior to denaturation and gel electrophoresis. CIS is the cross-linking drug cisplatin which was used for comparative purposes. C_n and C_d are control non-denatured and denatured samples, respectively. DS and SS indicate the positions of double- and single-stranded DNA, respectively.

of both functional groups is essential for ISC formation and indicates that **5** is acting on DNA in a similar manner to the natural products (see above). In an effort to elucidate the sequence specificity of these agents, we have evaluated them in a Taq DNA polymerase stop assay.^[15] All three analogues (**5**, **6**, **14**) induce Taq stops preferentially at G residues indicating alkylation at these bases, an observation which lends further credence to the idea that these compounds mimic the azinomycins (data not shown).^[4, 5]

The cytotoxicity of derivatives (**5**, **6**, **14**) was determined against a small panel of human tumor cell lines (SKOV-3, CH1, A2780 (all ovarian), HT-29 (colon), K-562 (leukemia)) using the SRB^[16] or MTT^[17] assay (Table 1). Significantly,

Table 1. Cytotoxicity data for **5**, **6**, and **14**.

Human tumor cell lines	14	5	6
A2780	0.06	0.076	5.2
A2780cisR ^[b]	0.14	0.28	10
CH1	0.058	0.078	8.6
CH1cisR ^[b]	0.035	0.087	5.8
SKOV-3	0.56	2.1	29
HT29	0.55	0.52	10
K562	0.52	0.143	1.9

[a] Dose of drug inhibiting growth by 50 % following a 96 h exposure (1 h in the case of K562) as determined by the SRB assay^[16] (MTT assay^[17] in the case of K562). [b] Cell line with acquired resistance to cisplatin. SRB = sulforhodamine blue, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

epoxide **5** displayed markedly greater potency (13–110 times) than the corresponding cyclopropane analogue **6**. Intriguingly, epoxide analogue **14**, devoid of the aziridine ring, showed potency comparable to that of **5**. These observations suggest that the epoxide moiety is largely responsible for the cytotoxic activity of these agents. This could indicate that whilst DNA cross-link formation has been demonstrated for both the azinomycins and the synthetic analogue **5**, in whole cells cytotoxicity may be induced by simple DNA alkylation

brought about by reaction with the epoxide center. Such a hypothesis would be consistent with earlier observations that simple azinomycin analogues based upon just the “left-hand” domain of the azinomycins are highly cytotoxic.^[12, 18] Additionally, it is notable that the synthetic agents **5**, and **6** retained activity in the two cell lines possessing acquired resistance to the widely used drug cisplatin, which forms a variety of intrastrand and interstrand bifunctional crosslinks on DNA.

In summary, our results suggest that synthetic azinomycin analogues such as **5** can be readily assembled, and induce ISC in double-stranded DNA along similar lines to the natural products. In view of the limited availability of the azinomycins, we believe that these and other analogues will prove useful in further addressing the molecular mechanism of action of this class of antitumor agent.

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- [10] HPLC retention times (Chiralpak AD column): (*E*)-**8** (98% *ee*, 5% isopropyl alcohol (IPA)/hexanes, 1.0 mL min⁻¹) = 14.27 min (*S*), 13.43 min (*R*); **10** (18% IPA/hexanes, 1.0 mL min⁻¹): *E* isomer (90% *ee*) = 8.35 min (*S*), 10.98 min (*R*); *Z* isomer (89% *ee*) = 7.74 min (*S*), 7.34 min (*R*). Racemic materials were prepared and used for comparison purposes.
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Fascinating Alkali Halide Structures of Different Dimensionalities Incorporated in Host Lattices

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Design and synthesis of supramolecular inorganic structures exhibiting novel host–guest interactions and molecular recognition have provided exciting new possibilities.^[1, 2] Some of these materials contain cages for ions or cation–anion aggregates, polyoxometalates with cages containing ions such as Cl⁻ and NO₃⁻, and ion-pairs such as NH₄⁺Cl⁻, being good examples.^[3] Several classes of inorganic–organic hybrid materials wherein the organic molecules subtly determine the structures of metal oxide lattices have also been prepared in recent years.^[4] Amongst these, metal–organic networks described in the recent literature^[5–7] are noteworthy, besides the large variety of inorganic open-framework structures, such as the metal phosphates^[8] and oxalates^[9] synthesized hydrothermally in the presence of organic amines. However, there is no report of materials to date, wherein extended structures of ionic compounds are incorporated in host lattices. Herein we report for the first time novel oxalate materials containing alkali halides with entirely new structures. The structures described include, a three-dimensional expanded KCl, a two-dimensional layered RbCl, and a one-dimensional KBr chain. The study makes an important addition to the chemistry of inorganic host–guest materials and suggests that many more such structures can indeed be synthesized.

To prepare materials incorporating new alkali halide structures, we have employed the hydrothermal method of synthesis, which is known to yield materials not obtained ordinarily.^[4, 10] The basic reaction employed is the simple exchange reaction between a cadmium halide and an alkali metal oxalate, carried out in the presence of an amine. The three new Cd oxalates containing alkali halides obtained by this means have the compositions **I–III**.

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