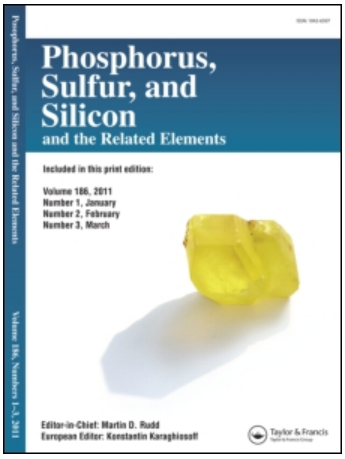

Phosphorus, Sulfur, and Silicon and the Related Elements

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Sulfur and the Enediyne Antibiotics

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SULFUR AND THE ENEDIYNE ANTIBIOTICS

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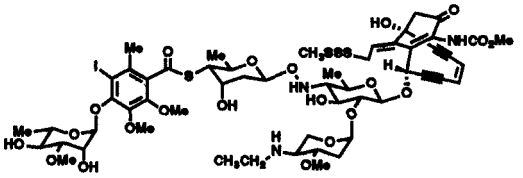
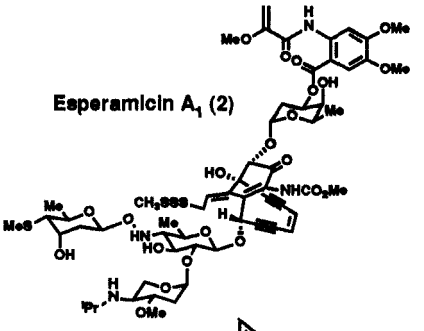
Abstract: *Some of our studies in the area of the enediyne antibiotics are discussed, with particular emphasis on the involvement of sulfur in these compounds. First, a model study for the ABC-ring system of the calicheamicin γ_1^I oligosaccharide involving a [3,3]-sigmatropic rearrangement is described which enabled the stereoselective installation of the 4-thio substituent on the B-ring and which served as the cornerstone for the first synthesis of the entire oligosaccharide fragment. The first enantioselective synthesis of (–)-calicheamicinone is then described. Finally, a novel triggering device for a dynemicin mimic based upon a 2-(phenylsulfonyl)ethyl carbamate is described which led to the synthesis of an extremely potent antitumor agent.*

INTRODUCTION

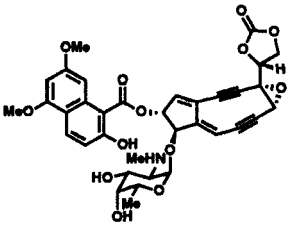
The enediyne antibiotics (ref. 1), represented by calicheamicin γ_1^I (**1**) (ref. 2), esperamicin A_1 (**2**) (ref. 3), the neocarzinostatin chromophore (**3**) (ref. 4) and dynemicin A (**4**) (ref. 5), are amongst the most potent antitumor agents known to date with IC_{50} values in the ng/mL range against a number of murine and human tumor cell lines. At the heart of calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**) are rigid bicyclic cores, the aglycone portions of the molecules. The cores are composed of a cyclohexenone ring bridged by a 1,5-diyne-3-ene unit contained within a 10-membered ring. Exocyclic to the cyclohexenone ring is an allylic trisulfide moiety which acts as the triggering device for the molecules, and attached to the aglycones are highly unusual oligosaccharide fragments. The single oligosaccharide fragment of calicheamicin γ_1^I (**1**) includes a hydroxylamine glycosidic linkage and an iodinated hexasubstituted thiobenzoate. Both the aglycone and sugar portions of this molecule therefore contain sulfur substituents,



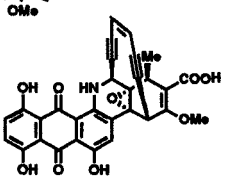
Calicheamicin γ_1^I (1)



Esperamicin A_1 (2)



Neocarzinostatin Chromophore (3)

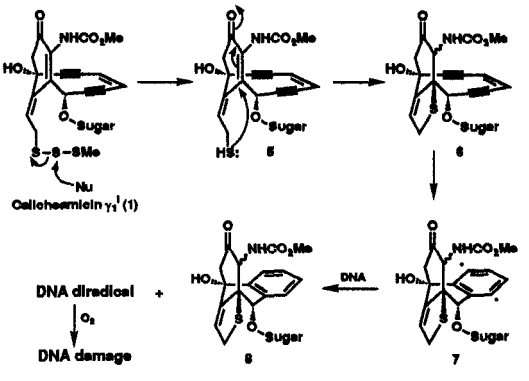


Dynemicin A (4)

and in this account we shall describe how these were approached in our syntheses of these fragments.

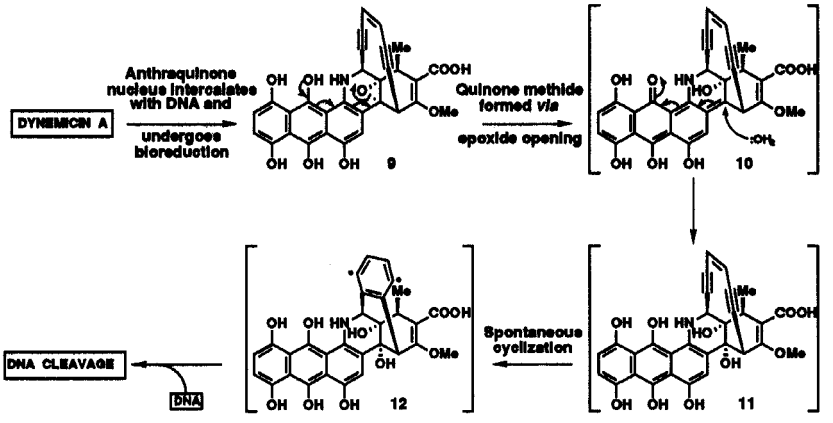
The key to the biological activity of calicheamicin γ_1^I (1) is a highly elegant series of events leading to DNA destruction in tumor cells, and includes the use of some unusual sulfur chemistry. Following the binding of the oligosaccharide portion within the minor groove of DNA (refs. 6, 7), a bionucleophile or reducing agent cleaves the trisulfide moiety of the aglycone at the central sulfur atom generating a thiolate species (1 → 5, Scheme I). The thiol then adds in a 1,4- fashion to the adjacent enone functionality (5 → 6). The resulting change in hybridization from sp^2 to sp^3 at the bridgehead position facilitates a cycloaromatization, commonly known as a Bergman cyclization (ref. 8), of the enediyne system generating a reactive benzenoid diradical (7). It has been demonstrated that the calicheamicin diradical abstracts hydrogen atoms from

Scheme I



duplex DNA, leading to cleavage of both strands and hence cell death (ref. 9).

Scheme II



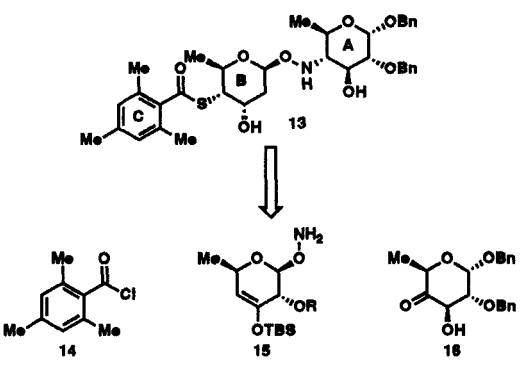
The dynemicins are unique amongst the enediyne antibiotics in combining the enediyne unit with the anthraquinone chromophore of the anthracycline antibiotics (ref. 10). A mechanism for the antitumor activity of dynemicin A (4) has been proposed (refs. 11, 12) which combines elements of the mechanisms of action of the esperamicin / calicheamicin, neocarzinostatin and anthracycline classes of antibiotics and which is supported by the observation that DNA strand cleavage by dynemicin A (4) is enhanced by the presence of reducing agents such as NADPH and thiols. In this mechanism (**Scheme II**), the anthraquinone nucleus intercalates with the DNA and undergoes bioreduction to give the 9,10-anthraquinol **9**. This rearranges *via* epoxide opening to give the quinone methide **10**, which is trapped by a nucleophile (e.g. H_2O) to give a *cis*-opened epoxide such as **11**. The strategically located nitrogen atom may also facilitate epoxide opening, either directly by electron donation or indirectly by acting as a base to deprotonate the adjacent acidic phenol in **9**. Opening of the epoxide moiety causes a dramatic conformational change in the molecule facilitating cycloaromatization of the enediyne to give the DNA-damaging benzenoid diradical **12**. Whilst there is no direct involvement of sulfur with dynemicin A itself, we will describe the use of a phenylsulfone group as a triggering device for some designed dynemicin mimics with potent antitumor activity.

SYNTHETIC STRATEGY FOR FUNCTIONALIZATION OF THE CALICHEAMICIN γ_1^I OLIGOSACCHARIDE B-RING

During the course of our synthesis of the calicheamicin γ_1^I oligosaccharide it rapidly became apparent that the most challenging portion of this molecule would be the synthesis of the central B-ring subunit. This subunit contains a highly unusual array of functionality, including the presence of the very unusual hydroxylamino glycoside, the sulfur atom in the 4-position, and the 2,6-dideoxy nature of the sugar. These features posed a unique synthetic challenge which was solved during the course of the synthesis of a model for the ABC ring system of the oligosaccharide (ref. 13).

The model **13** (Scheme III) was chosen for its similarity to the ABC ring system of the calicheamicin γ_1^I oligosaccharide. The B-ring of this model is identical to the natural sugar and would be available from fragment **15** (ref. 13) *via* a [3,3]-sigmatropic rearrangement; however, the A and C rings were chosen for convenience. The A-ring fragment was available from the ketone **16** (ref. 13), and the C-ring fragment was modeled after a hindered benzoate ester and was directly available from the acid chloride **14** (ref. 14).

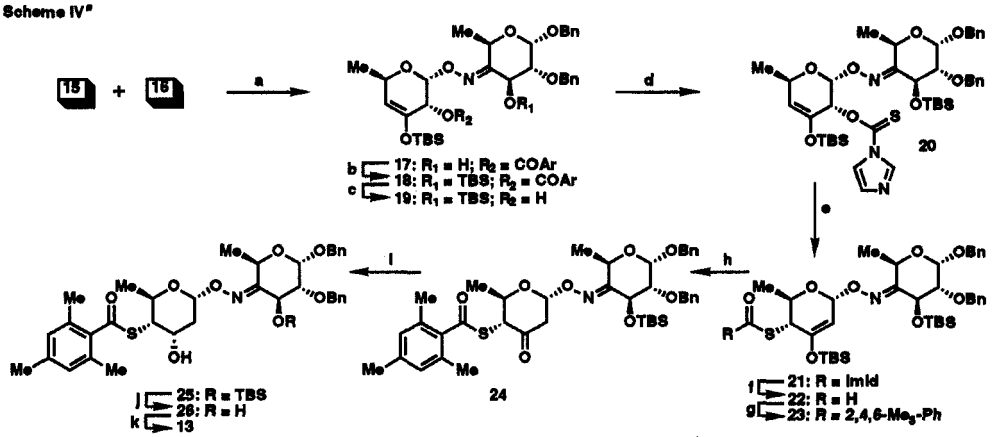
Scheme III[a]



[a]Retrosynthetic analysis of 13, a model for the ABC rings of the calicheamicin γ_1^I oligosaccharide

Scheme IV shows the synthesis of the ABC ring model **13** (ref. 13). Coupling of the keto-alcohol **16** with hydroxylamine **15** proceeded smoothly under mildly acidic conditions to generate oxime ether **17**. Although only one geometrical isomer of the oxime was obtained, the geometry was not defined. It should also be noted that attempts to couple the 3-O-*tert*-butyldimethylsilyl protected ketone system failed under forcing conditions, presumably for steric reasons. The free alcohol was readily protected as the *tert*-butyldimethylsilyl ether **18**, and the ester group was removed under reductive conditions (DIBAL) in order to avoid base-catalyzed silyl migration from the silyl enol ether onto the adjacent hydroxyl group. Treatment of alcohol **19** with thiocarbonyldiimidazole then produced the required thionoimidazolide **20**, the substrate for a proposed [3,3]-sigmatropic rearrangement (ref. 15) which would simultaneously

Scheme IV[a]

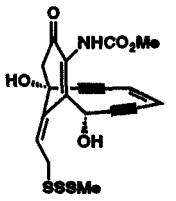


[a]**Reagents and conditions.** (a) 0.1 equiv. of PPTS, PhH, 25 °C, 3 h, 92%; (b) 1.4 equiv. of $^tBuMe_2SiOTf$, 2.5 equiv. of 2,6-lutidine, CH_2Cl_2, -25 °C, 30 min, 99%; (c) 2 equiv. of DIBAL, CH_2Cl_2, -78 °C, 45 min, 90%; (d) 2.0 equiv. of thiocarbonyl diimidazole, MeCN, 25 °C, 16 h; (e) PhMe, Δ, 1 h, 100%; (f) 6 equiv. of DIBAL, CH_2Cl_2, -78 °C, 2 h; (g) 2 equiv. of 2,4,6-trimethyl-benzoyl chloride, 1 equiv. of Et_3N, DMAP (catalytic), CH_2Cl_2, 25 °C, 12 h, 91%; (h) 1.0 equiv. of TBAF, AcOH, THF, H_2O, 0 °C, 15 min; (i) 3 equiv. of K-selectride, THF, -70 °C, 45 min, 68% from 23; (j) 1.5 equiv. of TBAF, THF, 0 °C, 30 min, 98%; (k) 3 equiv. of $BH_3.NH_3$, 0.5 equiv. of PPTS, THF, 25 °C, 1 h, 81%.

introduce the sulfur stereoselectively at the 4-position and deoxygenate at the 2-position. Thus heating **20** in toluene smoothly resulted in the desired transformation to give the rearranged product **21**. Sodium methoxide catalyzed hydrolysis of the thioimidazolide **21** led to the corresponding thiol, although in modest yield (<50%). However, treatment of **21** with DIBAL was found to produce an intermediate which was not purified, but treated directly with 2,4,6-trimethylbenzoyl chloride (**14**) in the presence of triethylamine and DMAP to yield the desired thioester **23**. The exact nature of the intermediate was later determined to be the thioformate **22** resulting from partial reduction of the thioimidazolide. *In situ* formation and trapping of the labile thiol proved to be a highly efficient method (91%) for the formation of the thioester.

Hydrolysis of the silyl enol ether **23** with TBAF in the presence of a proton source produced the labile ketone **24**. Upon extended reaction time, or atttempted column chromatography, a greater proportion of an isomerized product was formed which was tentatively assigned as the epimer α to the ketone. Reduction with K-selectride in DME then produced the desired α-alcohol as the major isomer (>8:1), and deprotection of the remaining silyl ether then proceeded in nearly quantitative yield with TBAF to produce **26**. Finally, stereoselective reduction of the oxime ether was successfully achieved using excess $BH_3.NH_3$ complex and pyridinium *p*-toluenesulfonate to give the targeted ABC ring model **13**. These results laid the foundations for our synthesis of the entire calicheamicin γ_1^I oligosaccharide fragment, as has been reported elsewhere (ref. 16).

ENANTIOSELECTIVE SYNTHESIS OF (–)-CALICHEAMICINONE

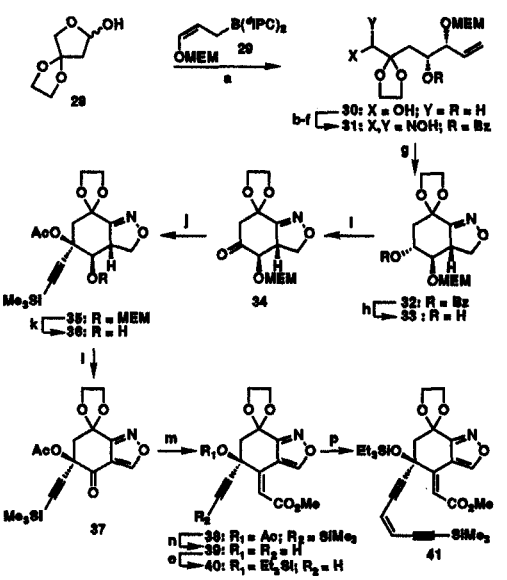


(–)-Calicheamicinone (27)

Numerous approaches to model systems of the calicheamicin aglycone (calicheamicinone, 27) have appeared in the literature (ref. 17), an impressive landmark in the area being the first synthesis of (±)-calicheamicinone recently reported by the Danishefsky group (ref. 18). However, our program for the synthesis of calicheamicin γ_1^I (1) required an enantioselective synthesis in order to avoid the inevitable formation of diastereomers which would result from coupling a racemic aglycone with a chiral sugar. We therefore conceived a new approach to the aglycone based upon an intramolecular alkenyl nitrile oxide cycloaddition reaction which would lead directly to the incorporation of the full functionality of the molecule and, in addition, be amenable to enantioselective synthesis (ref. 19). The synthesis is summarized in Schemes V and VI.

Asymmetry was introduced into the molecule *via* an asymmetric allylboration of the lactol 28 (readily prepared from tetronic acid) giving 30 according to a general procedure of Brown (ref. 20) in a highly stereo- and enantioselective manner (95% ee, >98% de). Compound 31 was then converted to the precursor for the dipolar cycloaddition reaction, oxime 31, using conventional transformations. Oxidation of the oxime with sodium hypochlorite

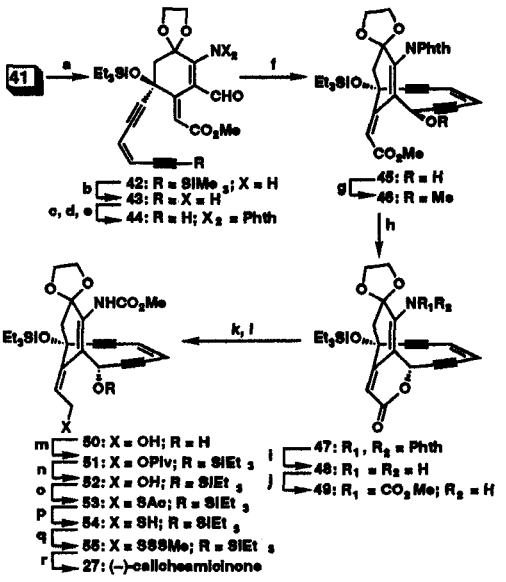
Scheme V[a]



[a]**Reagents and conditions:** (a) 1.1 equiv. of **29**, THF, -78 °C, 3 h → 25 °C, 87%; (b) 1.0 equiv. of ^{t}BuMe$_2$SiCl, 2.0 equiv. of imidazole, CH_2Cl_2, 25 °C, 2 h; (c) 2.0 equiv. of PhCOCl, pyr., DMAP (catalytic), CH_2Cl_2, 25 °C, 12 h; (d) 3 equiv. of ^{n}Bu$_4$NF, THF, 50 °C, 3 h; (e) Swern oxidation; (f) 3 equiv. of $NH_2OH.HCl$, 3 equiv. of NaOAc, EtOH - H_2O (2 : 1), 25 °C, 30 min, 98% overall from **30**; (g) excess aqueous NaOCl, CH_2Cl_2, 0 °C, 2 h, 65% as a 4:1 mixture; (h) NaOMe (catalytic), MeOH, 0 °C, 12 h, 100%; (i) 1.5 equiv. of Jones' reagent, acetone, 0 °C, 12 h, 95%; (j) 1.5 equiv. of lithium trimethylsilylacetylide, THF, -78 °C, 30 min; then 5 equiv of Ac_2O, -78 → 25 °C, 3 h, 67%; (k) 10 equiv. of $ZnBr_2$, CH_2Cl_2, 25 °C, 2 h; (l) Swern oxidation, 54% overall from **35**; (m) 5 equiv. of $Ph_3P{=}CHCO_2Me$, toluene, 90 °C, 16 h, 84%; (n) NaOMe (catalytic), MeOH - CH_2Cl_2 (1:1), 0 °C, 12 h, 80%; (o) 1.5 equiv. of Et_3SiOTf, 2.0 equiv. of 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 96%; (p) 1.5 equiv. of (*Z*)-(4-chloro-3-buten-1-ynyl)trimethylsilane, 0.07 equiv. of $Pd(PPh_3)_4$, 0.20 equiv. of CuI, 1.5 equiv. of ^{n}BuNH$_2$, PhH, 0 °C, 2 h, 91%.

generated the required nitrile oxide, which rapidly underwent the desired intramolecular cycloaddition reaction (ref. 21) giving the isoxazoline 32. The MEM group was then used to direct the facial addition of lithium trimethylsilylacetylide on the ketone 34, which occurred with complete stereoselectivity delivering, upon quenching with acetic anhydride, the alkylated product 35. The stereochemistry at the newly generated quaternary center was confirmed by a single crystal X-ray analysis, thus ensuring the high overall enantioselectivity of the synthesis.

Scheme VI [a]



[a] **Reagents and conditions:** (a) 1.0 equiv. of $Mo(CO)_6$, MeCN - H_2O (20:1), 80 °C, 1.5 h, 76%; (b) NaOMe (catalytic), CH_2Cl_2-MeOH (1:1), 0 °C, 12 h, 92%; (c) 1.4 equiv. of phthaloyl chloride, 4 equiv. of pyr., $MeNO_2$, 0 °C, 30 min; (d) Silica gel, CH_2Cl_2, 25 °C, 2 h; (e) excess Ac_2O, $MeNO_2$, 25 °C, 1 h, 78% from 43; (f) 1.1 equiv. of KHMDS, toluene, -90 °C, 5 min, 44%; (g) 10 equiv. of MsCl, 20 equiv. of pyr., DMAP (catalytic), CH_2Cl_2, 0 °C, 2 h; (h) silica gel, 2 equiv. of pyridine, PhH, 25 °C, 5 h, 90% from 45; (i) 10 equiv. of $MeNHNH_2$, PhH, 25 °C, 30 min, 99%; (j) 3 equiv. of triphosgene, 15 equiv. of pyridine, CH_2Cl_2, 25 °C, 40 min; *then* 15 equiv. of pyridine, excess MeOH, 0 °C, 30 min, 82%; (k) 3 equiv. of DIBAL, CH_2Cl_2, -78 °C, 30 min, 95%; (l) Excess $NaBH_4$, MeOH, 0 °C, 1 h, 88%; (m) 3 equiv. of *PivCl*, 15 equiv. of pyr., CH_2Cl_2, 25 °C, 4 h; *then* 3 equiv. of TESOTf, 0 °C, 10 min, 67%; (n) 3 equiv. of DIBAL, CH_2Cl_2, -78 °C, 1 h, 84%; (o) 8 equiv. of DEAD, 10 equiv. of PPh_3, 8 equiv. of AcSH, THF, 0 °C, 30 min, 93%; (p) 5 equiv. of DIBAL, CH_2Cl_2, -78 °C, 30 min; (q) 5 equiv. of *N*-(methyldithio)phthalimide, CH_2Cl_2, 25 °C, 30 min, 71% from 53; (r) TsOH (catalytic), aqueous THF, 25 °C, 16 h, 66%.

Having established the absolute stereochemistry at the single important chiral center (i.e. the quaternary acetylenic center), the remaining chiral centers could now be safely removed in a unique and efficient manner to provide the framework for the introduction of the remaining functionality of the molecule. Thus cleavage of the MEM ether (ref. 22) and oxidation of the resulting secondary alcohol to the corresponding ketone (ref. 23) was accompanied by spontaneous aromatization of the isoxazoline ring to give the keto isoxazole 37. Stereocontrolled olefination of 37 proceeded smoothly upon heating with methyl (triphenyl-phosphoranylidene)acetate resulting in exclusive formation of the desired geometrical isomer of the alkylidene side chain in 38 which would become the allylic trisulfide trigger of calicheamicinone. Following introduction of the complete enediyne moiety through a Pd(0)–Cu(I) catalyzed coupling reaction (ref. 24), the enaminoaldehyde functionality latent within the isoxazole ring was unmasked by reductive opening of isoxazole 41 to give 42 (ref. 25).

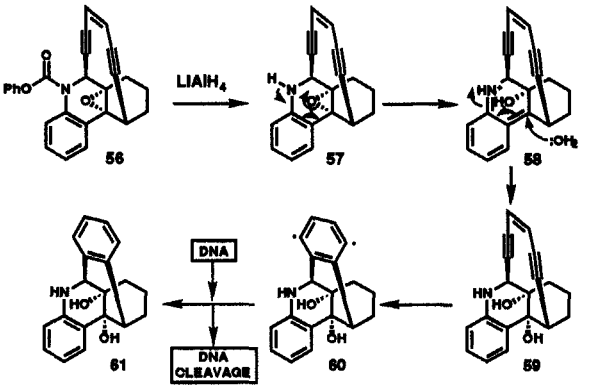
Following masking of the acidic nitrogen protons of 43 as the corresponding phthalimide 44 (ref. 19), the enediyne ring was bridged under basic conditions according

to ample literature precedent (refs. 17, 18) to give a 9:1 mixture of **45** and **47** in which the major component was of the incorrect stereochemistry at the newly generated secondary hydroxyl center. Inversion of this stereocenter was efficiently accomplished by taking advantage of the neighboring ester group and the propargylic nature of the center. Thus conversion to the corresponding propargylic mesylate **46** was followed by lactonization with inversion upon treatment with silica gel giving **47**, similar to an intermediate in Danishefsky's synthesis of (±)-calicheamicinone (ref. 18). The remaining few steps of the synthesis were therefore completed based upon chemistry previously described by Danishefsky (ref. 18) and Magnus (ref. 26). Particularly noteworthy is the chemistry used to introduce the trisulfide. Thus introduction of the first sulfur atom was achieved by a Mitsunobu reaction of alcohol **52** with thiolacetic acid (ref. 27) to give thioacetate **53**. Liberation of the free thiol **54** with DIBAL was then followed by treatment with *N*-(methyldithio)phthalimide (ref. 28) to introduce the methyltrisulfide in **55**. Finally, the simultaneous deprotection of the ketal and silyl protecting groups was achieved under acidic conditions to complete the first enantioselective synthesis of (–)-calicheamicinone (**27**) (ref. 19).

DYNEMICIN MODELS WITH PHENYLSULFONE TRIGGERS

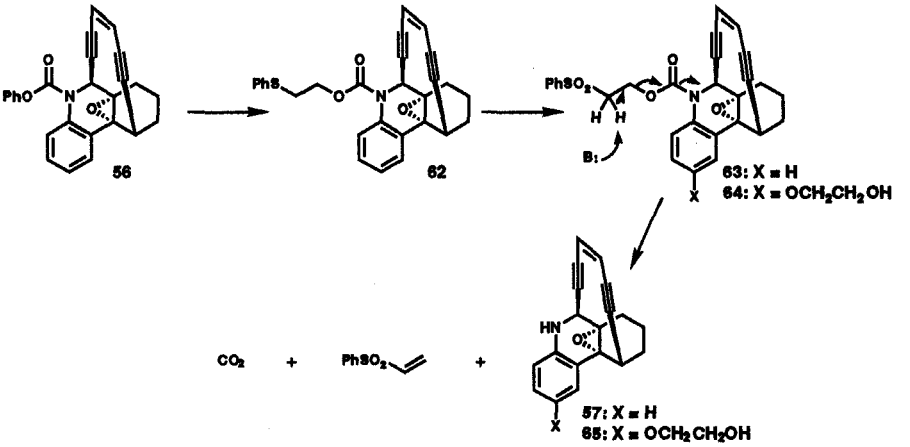
The potent antitumor activity of dynemicin A prompted us to investigate models which mimic the mode of action of the natural product with the aim of producing novel agents with potential antitumor activity. Our initial studies led to the synthesis of the model **56** (**Scheme VII**) (ref. 29) which, whilst capable of being triggered to undergo the Bergman cyclization under strongly acidic conditions sufficient to hydrolyze the epoxide, displayed no DNA cleavage ability at neutral pH and had limited cytotoxicity (ref. 30). By contrast, the free amine **57** not only displayed a marked ability to cause duplex DNA cleavage (ref. 29) but also had interesting cytotoxicity against a number of tumor cell lines (ref. 30), presumably due to the availability of the lone pair of electrons on the nitrogen atom to open the epoxide as shown in **Scheme VII**. However, the free amine **57** itself was too unstable to be of use for developing DNA cleavage / antitumor agents, and so a means was sought by which the free nitrogen could be liberated under mild, possibly physiological, conditions.

Scheme VII



The 2-(phenylsulfonyl)ethyl carbamate was therefore selected as a protecting group which could be removed under mildly basic conditions due to its ready ability to undergo a β-elimination reaction (Scheme VIII) (ref. 31). Thus transesterification of the phenylcarbamate **56** with 2-(phenylthio)ethanol followed by oxidation of **62** to the sulfone **63** with mCPBA gave the desired 2-(phenylsulfonyl)ethyl carbamate. Whilst being perfectly stable under neutral conditions, this compound was observed to undergo slow release of the free amine **57** and phenyl vinyl sulfone at pHs as low as 7.4. This had a profound effect on the cytotoxicity of the compound, having an IC_{50} of 2.5 x 10^{-11} M against Molt-4 leukemia cells. Further structural modifications led to the finding that compound **64** has an IC_{50} of 2.0 x 10^{-14} M against Molt-4 leukemia cells and also shows encouraging results in preliminary *in vivo* studies with animals infected with leukemia and solid tumors (ref. 30).

Scheme VIII



CONCLUSION

The synthesis of a model for the ABC ring system of the calicheamicin γ_1^I oligosaccharide is described in which the methodology for the functionalization of the B-ring was developed. This included a [3,3]-sigmatropic rearrangement which simultaneously introduced the 4-thio substituent in a stereoselective manner and deoxygenated the 2-position. This methodology was later successfully applied to the synthesis of the entire oligosaccharide. The first enantioselective synthesis of (–)-calicheamicinone is then described, relying upon an intramolecular alkenyl nitrile oxide cycloaddition reaction to lead to a fully functionalized skeleton. The completion of these two fragments opens the door for the completion of the synthesis of calicheamicin γ_1^I itself. Finally, some designed dynemicin models are described which contain a 2-(phenylsulfonyl)ethyl carbamate triggering device resulting in compounds with extremely potent antitumor activity.

ACKNOWLEDGEMENT

The contributions of our collaborators whose names are mentioned in the references are deeply appreciated. This work was financially supported by the National Institutes of Health, The Scripps Research Institute, and through a NATO fellowship (ALS).

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