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Progress towards the total synthesis of the enediyne anticancer antibiotics

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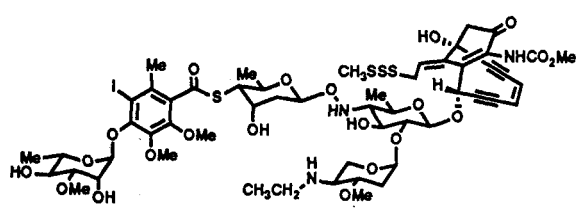
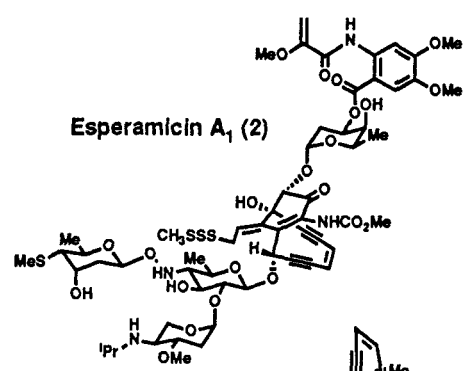
Abstract: *Progress towards the synthesis of two of the enediyne antibiotics, calicheamicin γ_1^I and dynemicin A, is outlined. The enantioselective total synthesis of the oligosaccharide and aglycone portions of calicheamicin γ_1^I have been achieved, as has a synthesis of a functioning model of dynemicin A. A key reaction in the oligosaccharide synthesis involved a [3,3]-sigmatropic rearrangement of an allylic thionoimidazolide, whilst the aglycone synthesis relied upon an intramolecular alkenyl nitrile oxide dipolar cycloaddition reaction to lead directly to the introduction of the full functionality of the molecule.*

INTRODUCTION

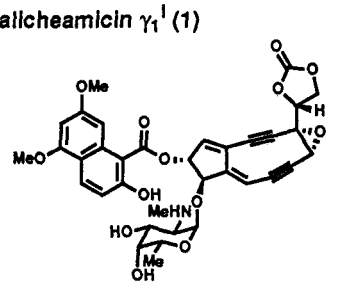
In 1987 the announcement of a new class of antitumour antibiotics, the enediynes (ref. 1), generated considerable interest within the chemical and biological communities. Calicheamicin γ_1^I (**1**) (ref. 2) and esperamicin A_1 (**2**) (ref. 3) are representative of the first two sub-classes to be recognised as such, the calicheamicins and esperamicins. The previously identified neocarzinostatin chromophore (**3**) (ref. 4) was later recognised as an enediyne antibiotic due to the similarity of its mode of action, and in 1989 the dynemicins, represented by dynemicin A (**4**) (ref. 5), were reported as a new series of enediynes. Not only do these compounds display extremely potent antitumour activity with IC_{50} values in the ng/mL range against a number of murine and human tumour cell lines, but they contain an array of structural features which were hitherto unseen.



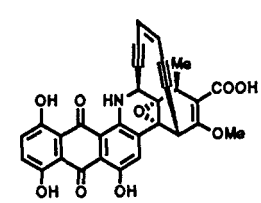
Calicheamicin γ_1^I (1)



Esperamicin A_1 (2)



Neocarzinostatin Chromophore (3)



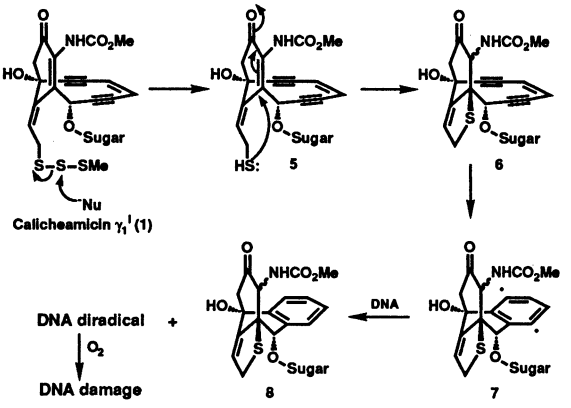
Dynemicin A (4)

At the heart of calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**) are rigid bicylic cores, the aglycone portions of the molecules. The cores are composed of a cyclohexenone ring bridged by a 1,5-diyn-3-ene unit contained within a 10-membered ring. Exocyclic to the cyclohexenone ring is an allylic trisulphide moiety, 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.

The key to the biological activity of calicheamicin γ_1^I (**1**) is believed to be a highly elegant series of events leading to DNA destruction in tumour cells. It is widely accepted that the oligosaccharide fragment serves as a recognition and delivery system, binding the molecule with remarkable specificity within the minor groove of duplex DNA at 5'-TCCT and, to a lesser extent, CTCT and ACCT sequences (ref. 6). There is thought to be a significant hydrophobic interaction between the lipophilic oligsaccharide and the minor groove of duplex DNA, with binding being facilitated by substantial preorganisation of the oligosaccharide in an extended conformation (ref. 7). Calculations by Schreiber *et al.* suggest that a significant proportion of the sequence selectivity for 5'-TCCT arises from a favourable interaction between the large and polarisable iodo substituent of the hexasubstituted aromatic ring and the N^2 amino substituents of the two guanines of the CC•GG tetrad (ref. 8).

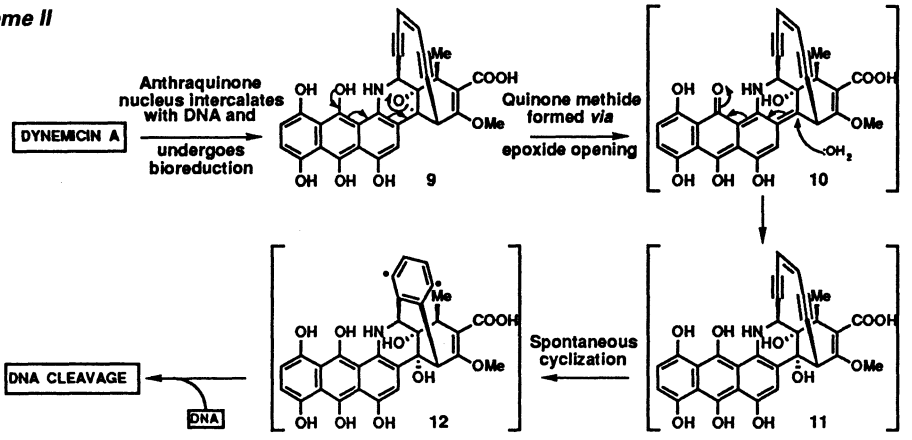
Once bound in the minor groove of DNA, a bionucleophile or reducing agent cleaves the trisulphide moiety of the aglycone generating a thiolate species which adds in a 1,4- fashion to the adjacent enone functionality (**1** → **5** → **6**, **Scheme I**). The proximity of the ethylamino residue of the oligosaccharide to the allylic trisulphide may play a role in this activation process. The resulting change in hybridisation from sp^2 to sp^3 at the bridgehead position facilitates a cycloaromatisation, commonly known as a Bergman cyclisation, of the enediyne system generating a reactive benzenoid diradical (**7**) (ref. 9). It has been demonstrated (ref. 10) that the calicheamicin diradical abstracts hydrogen atoms from duplex DNA at the C-5' position of the cytidine in 5'-TCCT and the C-1' position of the nucleotide 3 base pairs removed on the 3' side of the complimentary strand, leading to cleavage of both strands and hence cell death.

Scheme I



The dynemicins are unique amongst the enediyne antibiotics in combining the enediyne unit with the anthraquinone chromophore of the anthracycline antibiotics (ref. 11). A mechanism for the antitumour activity of dynemicin A (**4**) has been proposed (refs. 12,13) which combines elements of the mechanisms of action of the esperamicin/calicheamicin, neocarzinostatin and anthracycline classes of antibiotics and that is supported by the observation that DNA strand cleavage by dynemicin A 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 or Cl^-) 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

Scheme II



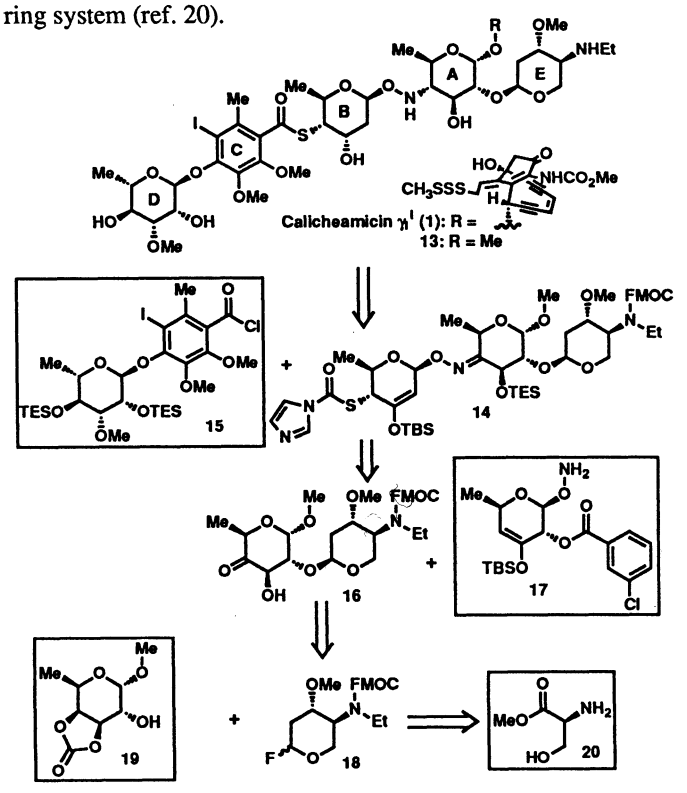
conformational change in the molecule facilitating cycloaromatisation of the endiyne to give the DNA-damaging benzenoid diradical **12**.

The structural elegance and synthetic challenge of calicheamicin γ_1^I (**1**) and dynemicin A (**4**) prompted us and others to initiate synthetic programmes directed at the synthesis of these molecules, and in this paper we describe our progress to date in this field, which includes the first enantioselective syntheses of the oligosaccharide (refs. 14,15) and aglycone (refs. 16,17) portions of calicheamicin γ_1^I (**1**), and the first synthesis of functioning models for dynemicin A (**4**) (refs. 18,19).

SYNTHESIS OF THE CALICHEAMICIN γ_1^I OLIGOSACCHARIDE

Following some initial model studies (ref. 20), we devised a synthetic strategy for the calicheamicin γ_1^I oligosaccharide which is outlined in retrosynthetic form in **Scheme III**. The cornerstone of the synthesis was the B-ring precursor **17** which had shown its synthetic utility in the synthesis of a model for the ABC ring system (ref. 20).

Scheme III[a]



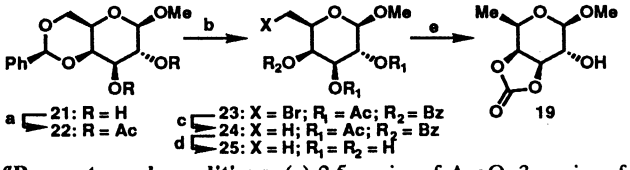
[a]Retrosynthetic analysis of the calicheamicin γ_1^I carbohydrate fragment

Retrosynthetic cleavage of the thioester of the oligosaccharide gave two main fragments, **14** and **15**. The aryl-glycoside **15** was obtained by glycosidation of a D-ring glycosyl donor and a hexasubstituted phenol (ref. 21). The remaining fragment **14** contained oxime, silyl enol ether and thio-imidazolide functionalities, in addition to several protecting groups which were chosen for their ease of removal.

Disconnection of **14** gave the hydroxylamine **17** and a disaccharide ketone **16**. Further disconnection led to the D-fucose derived A-ring, **19**, and an L-serine derived E-ring, **18**. The use of L-serine as a starting material was, in part, dictated by the uncertainty of the absolute configuration of the ethylamino substituent at the time of conception of this work and the ready availability of both enantiomers.

The synthesis of the A-ring subunit, alcohol **19**, is outlined in **Scheme IV**. The β-methyl glycoside **25** is available directly from D-fucose; however, it was more conveniently prepared on large scale from the known galactose derivative **21**. Although the next two steps would not be encumbered by the free hydroxyl groups, they were protected to facilitate product isolation. A two-step procedure (ref. 22) for transposition of the benzylidene ring **22** through the bromide **23** to the deoxy system **24** proceeded in good overall yield (73%). Hydrolysis followed by treatment with carbonyldiimidazole in refluxing acetonitrile then gave a 76% yield of the A-ring fragment **19**.

Scheme IV[a]

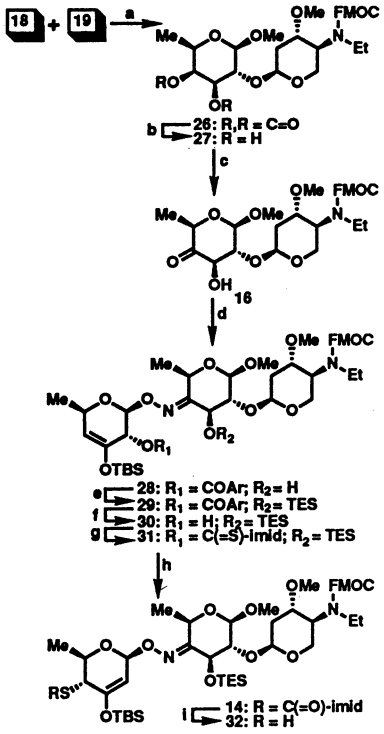


[a]**Reagents and conditions.** (a) 2.5 equiv. of Ac_2O, 3 equiv. of Et_3N, DMAP (catalytic), CH_2Cl_2, 25 °C, 3 h, 100%; (b) 1.0 equiv. of NBS, 0.6 equiv. of $BaCO_3$, AIBN (catalytic), CCl_4, Δ, 10 min, 100%; (c) 1.1 equiv. of *n*-Bu_3SnH, AIBN (catalytic), PhH, Δ, 20 min, 73%; (d) NaOMe (catalytic), MeOH, 25 °C, 4 h, 99%; (e) 2.5 equiv. of CDI, MeCN, Δ, 1 h, *then* 2 N HCl, H_2O, Δ, 15 min, 76%.

Coupling of the A- and E-ring subunits **18** and **19** proceeded smoothly using standard conditions ($AgClO_4$, $SnCl_2$) developed for glycosyl fluorides (ref. 23) (**Scheme V**). The coupled product **26** was obtained in 86% yield as a 4.5:1 mixture of α/β anomers in which the desired α-anomer predominated. The next stage of the synthesis required functionalisation of the A-ring in order to allow coupling of the B-ring subunit. The first requirement was deprotection of the cyclic carbonate in the presence of the FMOC protecting group to provide diol **27**. Initial attempts using sodium methoxide in methanol led to nearly equal rates of deprotection of the two protecting groups. It was observed by TLC analysis that when using low concentrations of sodium methoxide, the only products generated were the intermediate methyl carbonates as two regioisomers. Thus the acyclic methyl carbonate was less reactive than the cyclic form and required a higher concentration of base for hydrolysis. This observation led to the use of ethylene glycol to promote the transesterification of the carbonate by facilitating the second stage of the hydrolysis through a proximity effect. This allowed for clean differentiation between the carbonate and FMOC, giving a 93% yield of the diol.

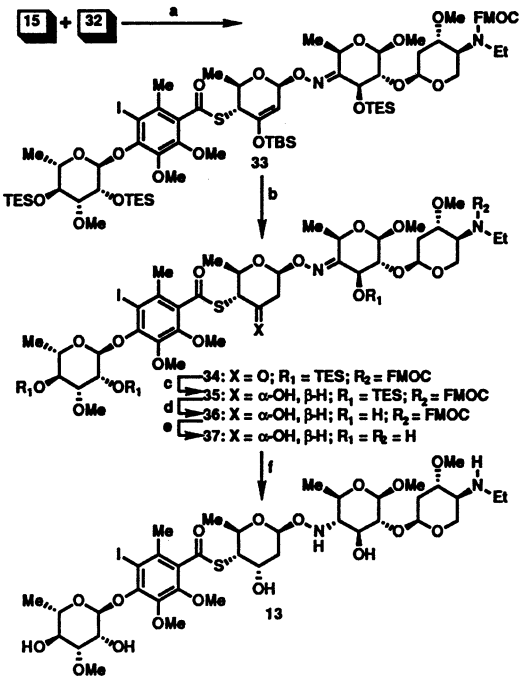
Regiospecific oxidation of the diol **27** to the hydroxyketone **16** proceeded cleanly in 70% yield using bromine oxidation of the stannylene acetal in the presence of *n*-Bu_3SnOMe to absorb HBr (ref. 24). The unstable ketone was successfully coupled with hydroxylamine **17** using catalytic PPTS in benzene to give the trisaccharide **28** as a single (unassigned) geometrical isomer. Silylation and DIBAL deprotection of the ester cleanly provided the alcohol **30** in 91% yield with no observable cleavage of the

Scheme V[a]



[a]**Reagents and conditions.** (a) 1.0 equiv. of **19**, 1.5 equiv. of **18**, 2 equiv. of $AgClO_4$, 2 equiv. of $SnCl_2$, 4 Å molecular sieves, THF, -78 °C, 3 h, 70%; (b) NaH (catalytic), THF – $(CH_2OH)_2$ (20:1), 0 °C, 1 h, 93%; (c) 1.1 equiv. of *n*-Bu_2SnO, MeOH, Δ, 45 min *then* 1 equiv. of Br_2, 1.1 equiv. of *n*-Bu_3SnOMe, CH_2Cl_2, 25 °C, 5 min, 70%; (d) 1.0 equiv. of **16**, 1.2 equiv. of **17**, PPTS (catalytic), PhH, 25 °C, 1 h, 83%; (e) 1.5 equiv. of 2,6-lutidine, 1.2 equiv. of TESOTf, CH_2Cl_2, 0 °C, 30 min, 100%; (f) 3 equiv. of DIBAL, CH_2Cl_2, -78 °C, 20 min, 91%; (g) 3.0 equiv. of thiocarbonyldiimidazole, MeCN, 25 °C, 1.5 h, 87%; (h) PhMe, Δ, 30 min, 98%; (i) 1.0 equiv. of NaSMe, 40 equiv. of EtSH, CH_2Cl_2, 0 °C, 5 min, 96%.

Scheme VI[a]



[a]**Reagents and conditions.** (a) 1.0 equiv. of **32**, 1.2 equiv. of **16**, 2 equiv. of Et_3N, DMAP (catalytic), CH_2Cl_2, 0 °C, 1 h, 60%; (b) 1.0 equiv. of TBAF, 0.05 M AcOH in THF, -23 °C, 15 min; (c) 3 equiv. of K-selectride, DME, -78 °C, 2 h, 75% from **33**; (d) HF.Py, CH_2Cl_2, THF, 0 °C, 45 min, 72%; (e) Et_2NH – THF (1:1), 25 °C, 2 h, 85%; (f) 10 equiv. of $NaCNBH_3$, $BF_3.OEt_2$, CH_2Cl_2, -50 °C, 2 h, 86%.

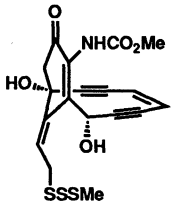
FMOC protecting group. Treatment with thiocarbonyldiimidazole gave the corresponding thionoimidazolide **31** in 87% yield. In one of the key steps of the synthesis, thermolysis of **31** cleanly induced a [3,3]-sigmatropic rearrangement (ref. 25) in nearly quantitative yield, providing multigram quantities of trisaccharide **14** for coupling with the arylsaccharide unit.

Coupling of the trisaccharide subunit with the CD-subunit **15** proved to be rather difficult. The best procedure turned out to be cleavage of the thioimidazolide with sodium thiomethoxide in the presence of EtSH to give a near quantitative yield of the thiol **32**. Coupling of the thiol with acid chloride **15** (ref. 21) to give pentasaccharide **33** (**Scheme VI**) required fairly forcing conditions and the yield was modest (60%). This is in part explained by the low reactivity of the acid chloride **15** due to the electron rich nature of the aromatic ring which deactivates the carbonyl towards nucleophilic attack. Hydrolysis of the silyl enol ether than gave the unstable ketone **34**. Reduction of the crude mixture with K-selectride at -78 °C selectively gave the desired alcohol **35** in 75% overall yield. Deprotection of the silyl ethers was accomplished with HF.Py complex in good yield (72%) to reveal the tetrol **36**. Removal of the FMOC protecting group proved straightforward using diethylamine in THF to produce the free amine **37** in 85% yield. With the oligosaccharide skeleton functionalised and fully deprotected, the only remaining step was reduction of the oxime functionality to the desired α-hydroxylamine **13**. This was best achieved with

sodium cyanoborohydride in the presence of $BF_3.OEt_2$ at -50 °C, giving an 86% yield of an epimeric mixture of hydroxylamines in an α/β ration of 6:1 in which the desired α-component predominated.

ENANTIOSELECTIVE SYNTHESIS OF (−)-CALICHEAMICINONE

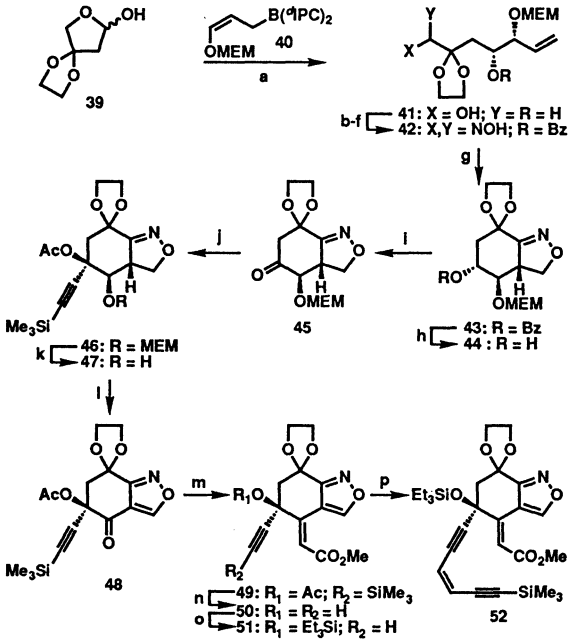
Several approaches to model systems of the calicheamicin aglycone (calicheamicinone) have appeared in the literature (ref. 26), an impressive landmark in the area being a total synthesis of racemic calicheamicinone (**38**) recently recorded by the Danishefsky group (ref. 17). However, any total synthesis of calicheamicin γ_1^I (**1**) would preferably involve an enantioselective synthesis of the aglycone in order to avoid diastereomer formation upon coupling to the oligosaccharide portion. We therefore embarked upon a conceptually different approach to calicheamicinone based upon an intramolecular alkenyl nitrile oxide dipolar cycloaddition reaction (ref. 27) which led directly to the incorporation of the full functionality of the molecule and which was amenable to enantioselective synthesis, culminating in a highly enantio- and stereoselective total synthesis of (–)-calicheamicinone (**38**) (ref. 16).



(–)-Calicheamicinone (38)

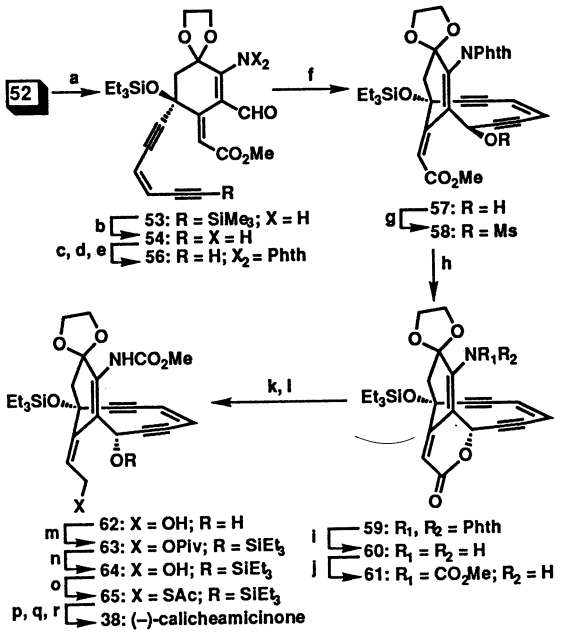
The execution of the synthesis proceeded as summarized in Schemes **VII** and **VIII**. Lactol **39**, readily prepared from tetronic acid *via* ketalisation and DIBAL reduction, was treated with the allyl borane **40** according to a general procedure of Brown (ref. 28) to give **41** in a highly stereo- and enantioselective manner (95% ee, >98% de). Compound **41** was converted to aldoxime **42** by standard chemistry. Generation of the nitrile oxide with aqueous sodium hypochlorite was accompanied by spontaneous cyclisation resulting in a 4:1 mixture of isoxazoline diastereomers from which the major isomer **43** was isolated by flash chromatography. Addition of lithium trimethylsilylacetylide to the

Scheme VII[a]



[a]**Reagents and conditions:** (a) 1.1 equiv. of **40**, 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 **41**; (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 **46**; (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%.

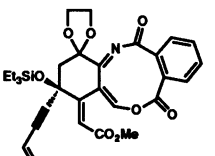
Scheme VIII[a]



[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 **54**; (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 **57**; (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 **65**; (r) TsOH (catalytic), aqueous THF, 25 °C, 16 h, 66%.

sensitive ketone **45** at -78 °C proceeded with complete stereoselectivity delivering the incoming nucleophile from the face opposite to the MEM ether to give, after quenching with acetic anhydride, acetate **46**. Removal of the MEM group followed by Swern oxidation (ref. 29) and concomitant aromatisation gave the keto-isoxazole **48**. Stereocontrolled olefination of **48** proceeded smoothly upon heating with methyl (triphenylphosphoranylidene)acetate resulting in exclusive formation of the desired geometrical isomer of the alkylidene side chain in **49** which would become the allylic trisulphide trigger of calicheamicinone. Coupling of **51** with (Z)-(4-chloro-3-buten-1-ynyl)trimethylsilane by Pd(0)–Cu(I) catalysis completed the construction of the enediyne moiety (ref. 30) leading to compound **52**. Unmasking of the aminoaldehyde functionality was then realised by reductive opening of the isoxazole ring with molybdenum hexacarbonyl (ref. 31) furnishing **53** (**Scheme VIII**).

The propensity of the aldehyde group in **54** to enolise *via* the vinylogous amine led us to protect the later functionality as the phthalimide before proceeding further. Reaction with phthaloyl chloride occurred first prefentially at the oxygen atom of the vinylogous amide system resulting in the formation of predominantly the nine-membered heterocycle **55**. The use of polar solvents seemed to increase the proportion of reaction at nitrogen. However, acidic hydrolysis of the enol ester functionality and activation of the intermediate phthalamic acid with acetic anhydride resulted in formation of the desired phthalimide **56**. Treatment of **56** with KHMDS at low temperature then effected ring closure of the enediyne giving a 9:1 mixture of **57** and **59** in which the major product was of the incorrect stereochemistry at the newly generated secondary hydroxyl centre. However, it was posssible to correct this errant stereocentre in nearly quantitative yield using an unusual lactonisation – inversion procedure which took advantage of the propargylic nature of the hydroxyl centre. Thus conversion to the corresponding propargylic mesylate **58** was followed by lactonisation to give **59** upon treatment with silica gel. The completion of the synthesis was then based upon chemistry developed by Danishefsky (ref. 17) and Magnus (ref. 32), completing the first enantioselective synthesis of (–)-calicheamicinone (**38**).



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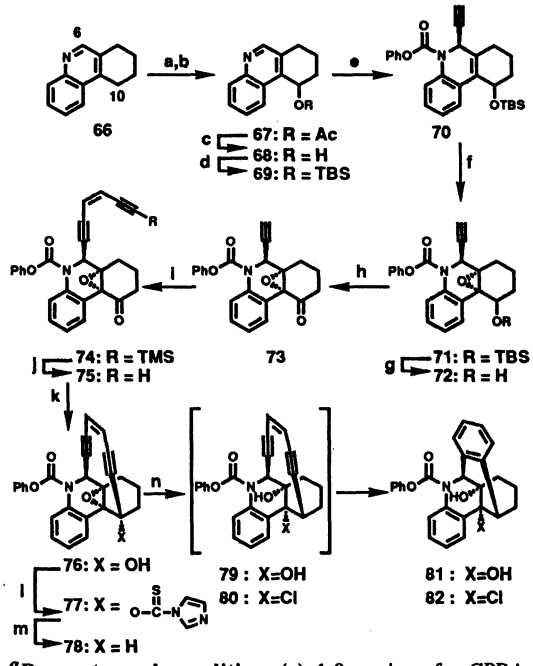
SYNTHESIS OF A DYNEMICIN A MODEL

The elegance and synthetic challenge of the dynemicin A structure, combined with its potent antitumour activity, prompted us to explore the synthesis and properties of models for dynemicin A (**4**) with a view to synthesizing dynemicin A itself and to shed further light upon the mechanism of action of this fascinating molecule.

A literature search revealed that 7,8,9,10-tetrahydrophenanthridine (**66**) is readily prepared on a large scale in a few steps (ref. 33), and the electronic properties of this molecule suggested that it should be possible to selectively functionalise at the C-6 and C-10 positions. **Scheme IX** summarises the construction of the dynemicin model **76** from 7,8,9,10-tetrahydrophenanthridine (**66**). Thus treatment of **66** with *m*-chloroperoxybenzoic acid (*m*CPBA) in dichloromethane gave the corresponding *N*-oxide, which underwent regiospecific rearrangement (ref. 34) upon heating in acetic anhydride to give the acetoxy derivative **67**. This was converted to the corresponding silyl ether **69** in 92% overall yield. Addition of phenyl chloroformate (ref. 35) to a mixture of compound **69** and ethynylmagnesium bromide at -78 °C led to the formation of compound **70** in 97% yield as a 3:1 mixture of isomers. Treatment of **70** with *m*CPBA then installed the epoxide functionality of the dynemicin model in **71**, and this was converted to ketone **73** *via* alcohol **72** by desilylation followed by oxidation (80% overall). Ketone **73** was obtained as a single isomer, indicating that epoxidation had taken place exclusively from the opposite face to the the acetylene. Coupling **73** with (*Z*)-(4-chloro-3-buten-1-ynyl)trimethylsilane under Pd(0)–Cu(I) catalysis followed by $AgNO_3$/KCN desilylation of the terminal acetylene then resulted in the formation of the requisite precursor for the cyclisation in 67% overall yield. Finally, treatment of **75** with LDA in toluene at -78 °C effected ring closure to complete the first synthesis of a dynemicin A model (**76**) in 59% yield together with 25% recovered **75** (presumably due to enolisation of the ketone).

Scheme IX[a]



[a]**Reagents and conditions.**(a) 1.0 equiv. of mCPBA, CH_2Cl_2, 25 °C, 1 h, 80%; (b) Ac_2O, reflux, 20 h, 77%; (c) K_2CO_3 (catalytic), MeOH, 25 °C, 1 h, 100%; (d) 1.2 equiv. of $^tBuMe_2SiOTf$, 1.4 equiv. of 2,6-lutidine, CH_2Cl_2, 0.5 h, 92%; (e) 3.0 equiv. of ethynylmagnesium bromide, 3.0 equiv. of PhOCOCl, THF, -78 Æ 25 °C, 1 h, 92%; (f) 2.0 equiv. of mCPBA, CH_2Cl_2, 25 °C, 3 h, 85%; (g) 1.2 equiv. of TBAF, THF, 42 °C, 3 h, 95%; (h) 3.0 equiv. of PCC, CH_2Cl_2, 4Å MS, 25 °C, 1 h, 81%; (i) 1.4 equiv. of (*Z*)-(4-chloro-3-buten-1-ynyl)trimethylsilane, 1.5 equiv. of *n*-$BuNH_2$, 0.25 equiv. of PPh_3, 0.05 equiv. of $Pd(OAc)_2$, 0.2 equiv. of CuI, PhH, 25 °C, 4 h, 88%; (j) 4.0 equiv. of $AgNO_3$, 7.0 equiv. of KCN, H_2O, EtOH, THF, 25 °C, 10 min, 90%; (k) 1.1 equiv. of LDA, toluene, -78 °C, 1 h, 80% based on 25% recovery of **75**. (l) 3 equiv. of thiocarbonyldiimidazole, 0.5 equiv. of DMAP, CH_2Cl_2, 25 °C, 48 h, 91%; (m) 2 equiv. of *n*-Bu_3SnH, AIBN (catalytic), toluene, 75 °C, 2 h, 75%; (n) (i) 0.05 M in benzene – 1,4-cyclohexadiene (4:1), 1.2 equiv. of $TsOH.H_2O$, 24 h, 25 °C, 86% (X=OH); or (ii) $HCl_{(g)}$, 40 equiv. of 1,4-cyclohexadiene, CH_2Cl_2, 1 min, 25 °C, 82% (X=Cl).

In order to obtain a closer model to dynemicin A (**4**), the tertiary hydroxyl group in **76** was removed to form **78**. Thus exposure of **76** to thiocarbonyldiimidazole in the presence of 4-(dimethylamino)pyridine (DMAP) resulted in the formation of thionoimidazolide **77** in 95% yield. This compound led to the formation of the desired deoxygenated compound **78** in 86% yield upon treatment with *n*-Bu_3SnH–AIBN (catalytic) in toluene at 80 °C.

The observed sensitivity of dynemicin A toward acid-induced epoxide opening and hence triggering of the Bergman cyclisation prompted us to examine the triggering of our model systems. Thus treatment of **78** with *p*-toluenesulphonic acid in

benzene–1,4-cyclohexadiene (3:1, 0.05 M) at 25 °C for 24 h led to the formation of product **81** in 86% yield. Protonation of the epoxide in **78** apparently initiates formation of diol **79** which undergoes spontaneous Bergman cyclisation to form a benzenoid diradical intermediate. This is, in turn, rapidly trapped by the hydrogen atom donor present (1,4-cyclohexadiene) to give the aromatised product **81**. The use of anhydrous HCl in dichloromethane in the presence of 1,4-cyclohexadiene also resulted in triggering of the cyclisation cascade leading to **82**, presumably *via* **80**. These cyclisations are analogous to those observed for dynemicin A itself, and support epoxide opening as a triggering mechanism for the action of dynemicin A.

CONCLUSION

The completion of the enantioselective syntheses of both the oligosaccharide and aglycone portions of calicheamicin γ_1^I (**1**) paves the way for the attainment of an important goal in the enediyne field, namely the total synthesis of calicheamicin γ_1^I (**1**) itself. During the course of these syntheses, novel and interesting chemistry has been developed to solve the unique synthetic problems posed by this fascinating molecule resulting in efficient, stereoselective syntheses. Together with the synthesis of the dynemicin A models, this work provides exciting avenues for the development of novel DNA-cleaving and anticancer agents.

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