The enediyne and dienediyne based antitumour antibiotics. Methodology and strategies for total synthesis and construction of bioactive analogues. Part 2

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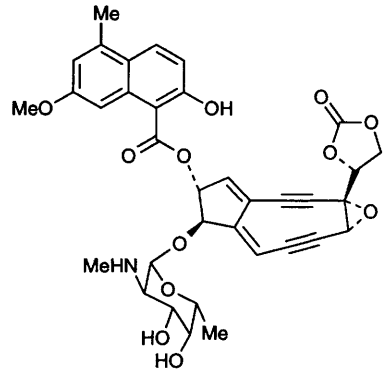
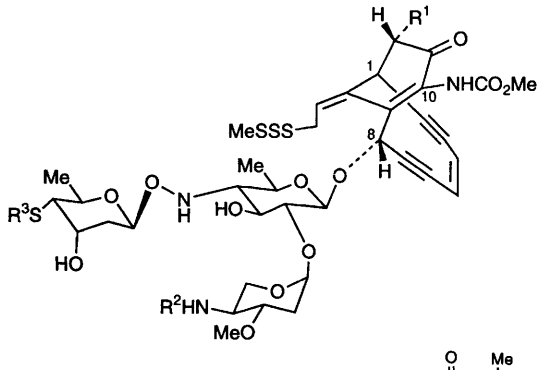
Reviewing the literature published up to 15 November 1995
Concluding the coverage which commenced in Part 1, *Contemporary Organic Synthesis*, 1996, **3**, 41

1 Introduction

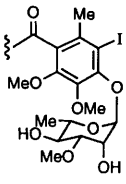
The discovery and structure elucidation of the highly potent antitumour antibiotics neocarzinostatin **1**,[1] calicheamicin γ_1^I **2**,[2] esperamicin A_1 **3**[3] and dynemicin A **4**[4] (**Scheme 1**) created a wave of wonder and amazement amongst scientists as to the neverending power of nature to innovate in the constitution of complex multifunctional molecules, and the mechanism through which they exert their biological activity. Antibiotics **1**–**4** associate with their intracellular target DNA and are converted to high energy diradical species which effect single and/or double strand cleavages through hydrogen abstractions from the deoxyribose backbone.[5] These multistep processes are unprecedented. In response to this stimulus, the chemical community quickly set out to demonstrate that modern synthetic methodology and thinking could rise to the



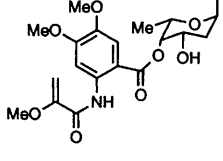
neocarzinostatin chromophore **1**

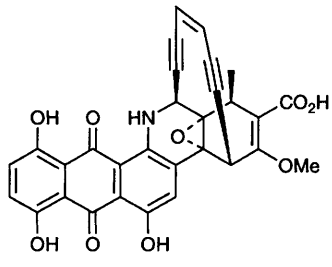


2 calicheamicin-γ_1^I R^1 = H, R^2 = Et, R^3 =



3 esperamicin-A_1^b R^1 = O, R^2 = Pr^i, R^3 = Me





dynemicin A **4**

Scheme 1

challenge that efficient construction of these sensitive and complex molecules represents.

In part 1 of this review,[6] an overview was given of the research that was initiated to synthesize simpler, more readily accessible enediyne–dienediyne systems and to examine their capacity to undergo Bergman or Myers type cycloaromatization[7,8] to diradical and polar intermediates.

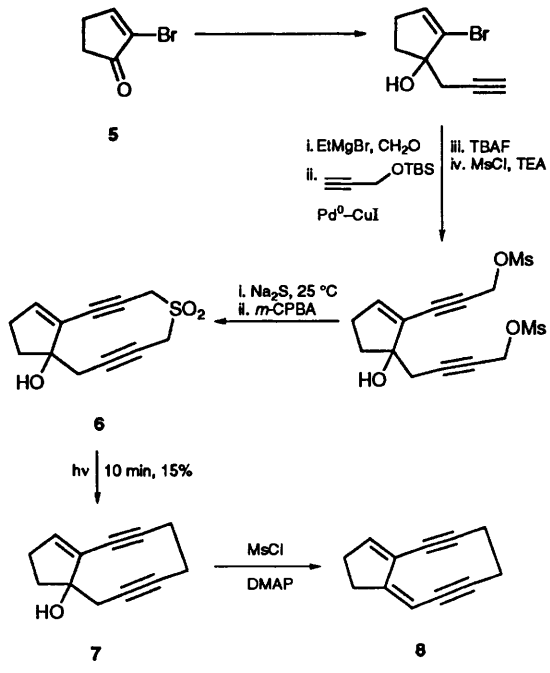
Concurrent with these studies, have been equally intense efforts to attain the natural products themselves by total synthesis. To date, significant progress has been made to construct the labile core structure of neocarzinostatin **1** and esperamicin **3**, and two successful approaches to the aglycone of calicheamicin have been developed. Several routes to the sugar components of **2** and **3** have similarly been devised, and through the coupling of advanced intermediates to both the aryl tetrasaccharide of calicheamicin and its aglycone (calicheamicinone) both Nicolaou and Danishefsky have achieved the total synthesis of natural (−)-**2**. A considerable body of work has also gone into constructing simplified bioactive analogues of dynemicin A **4**, and these efforts have formed a solid basis for the two syntheses of this enediyne antibiotic that have very recently appeared. A description of these ground breaking achievements, in conjunction with many other approaches and strategies that are under development for the total synthesis of the enediyne–dienediyne antitumour antibiotics is given here in Part 2 of this review.

2 Approaches to the total synthesis of the neocarzinostatin chromophore

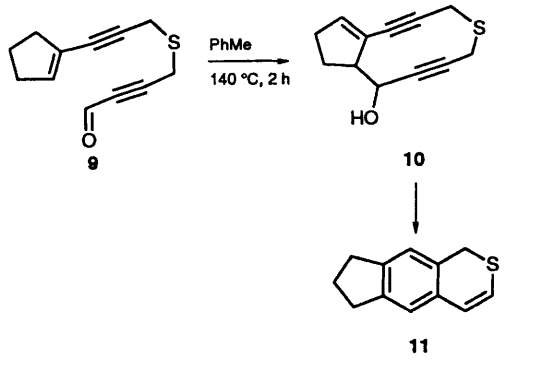
Wender's group was the first to achieve the construction of the neocarzinostatin chromophore skeleton. In this work they popularized the use of 2-bromocyclopent-2-enone **5** as an A-ring synthon onto which the B-ring propargyl and acetylene units can be conveniently attached (**Scheme 2**).[9,10] Also central to their strategy is the photochemically induced extrusion of SO_2 from **6**, which effects ring contraction to the strained 9-membered neocarzinostatin intermediate **7**. This choice was made in view of the sensitivity of **1** to high pH and certain nucleophiles, as well as to decouple the enthalpic and entropic problems which otherwise combine to make direct closure of the 9-membered ring difficult. The fragile bicyclic dienediyne **8** was obtained by treatment of alcohol **7** with MsCl and DMAP.

Elements of this strategy appear in Mikami's ene reaction approach to the construction of **10** from aldehyde **9** (**Scheme 3**). However, under the thermal conditions employed this intermediate undergoes dehydration and cycloaromatization giving tricycle **11**.[11]

Wender also explored the intramolecular Nozaki reaction of an allyl chromium reagent, generated from **12**, as a means to achieve 9-membered ring formation (77–88% yields) (**Scheme 4**),[12–14] as well as the 2,3-Wittig ring contraction of the



Scheme 2

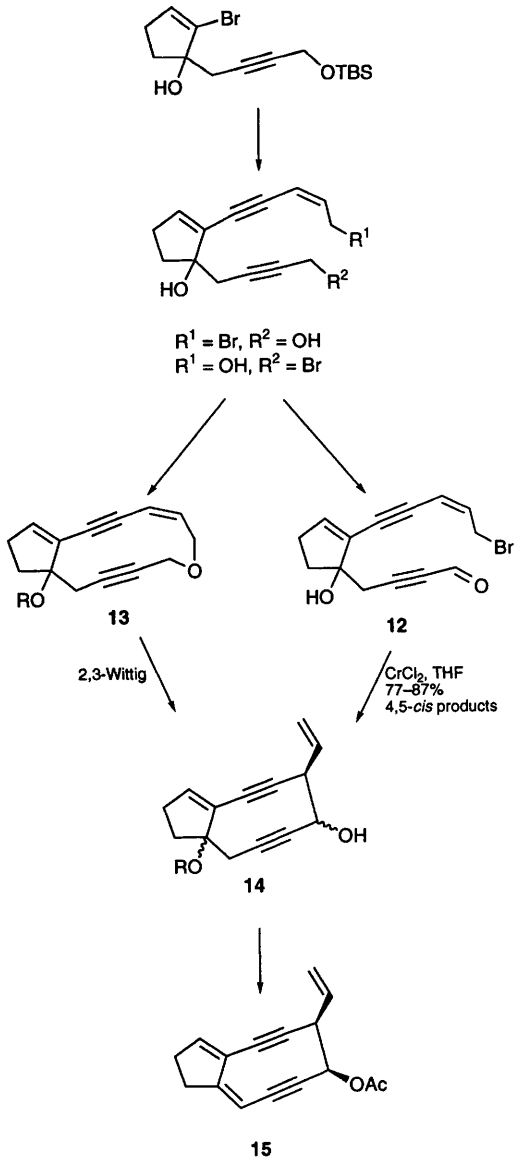


Scheme 3

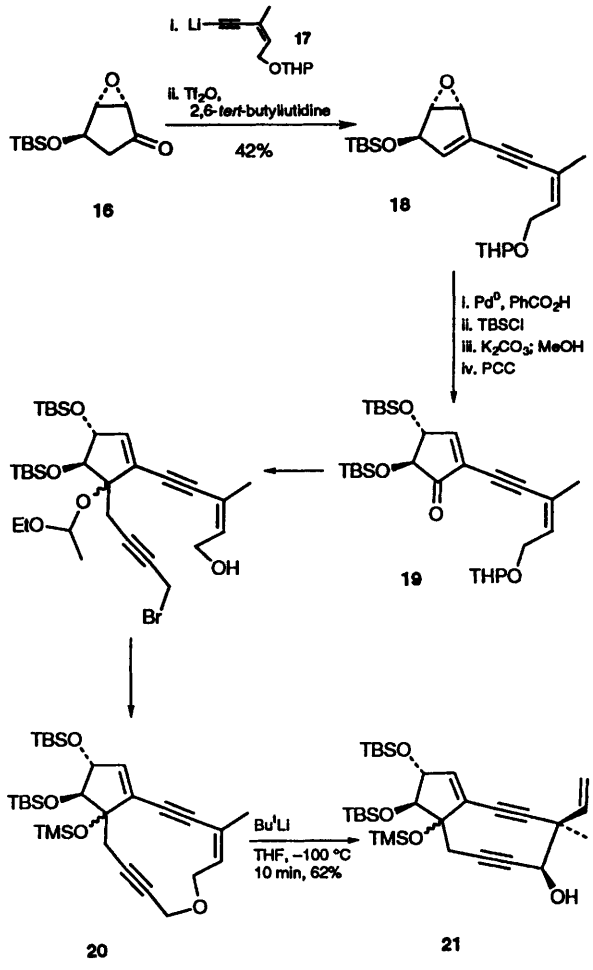
12-membered ether **13** (R = H) to compound **14**.[12] However, the yields in the latter study were only moderate, and difficulties were encountered during purification of the mixture of diastereoisomeric products.

Krebbs *et al.* found that the corresponding *O*-MEM protected ether **13** (R = MEM) fails to undergo the 2,3-Wittig ring contraction.[15] In contrast, Doi and Takahashi showed that ether **13** (R = TBS) does rearrange efficiently (Bu^tLi, THF, −100 °C, 10 min), and with a high degree of '*cis*' selectivity to give the neocarzinostatin derivative **14** (66% yield).[16] Further, simple, but delicate transformations gave the dienediyne **15**.

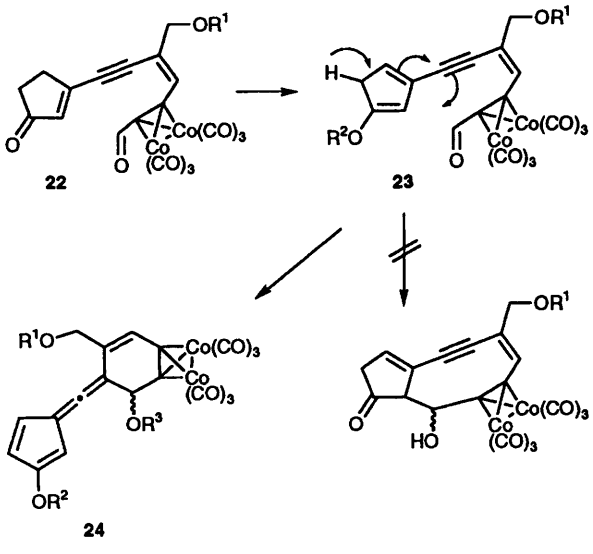
Takahashi's group have built upon this result to synthesize compound **21** in which the two hydroxy groups are present in the cyclopentene ring with the correct relative stereochemistry (**Scheme 5**).[17,18] This involved reaction of epoxy ketone **16** with the lithium acetylide **17**, followed by dehydration, regioselective Pd(0) catalysed opening of allylic



Scheme 4



Scheme 5

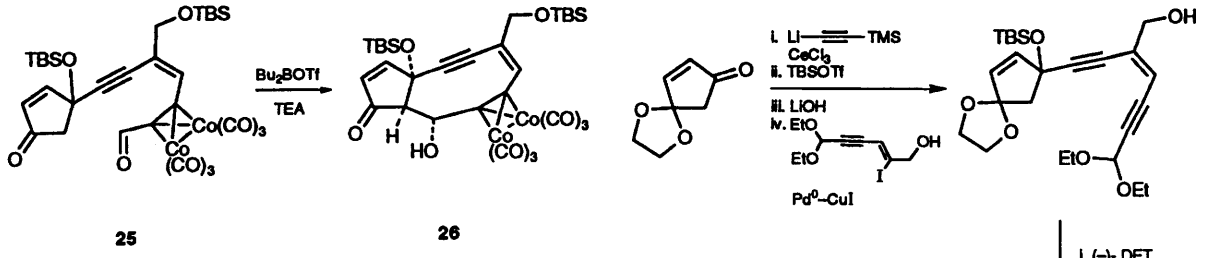


Scheme 6

epoxide **18** in the presence of benzoic acid, and elaboration of ketone **19**. 2,3-Wittig rearrangement of ether **20** produced the neocarzinostatin analogue **21** in greater than 60% yield.

Magnus and collaborators have shown that their strategy employing η^2-dicobalt hexacarbonyl alkyne complexes can be applied to the synthesis of the bicyclic skeleton of neocarzinostatin **1** (**Schemes 6–8**).[19,20] Their initial plan was to close the C_8–C_9 bond in an intramolecular aldol reaction involving the enol (enolate) form **23** of the masked enediyne **22**. However, exploratory experiments revealed an unexpected reaction pathway leading to **24** (**Scheme 6**). This problem could be countered through cyclization of intermediate **25**, but in this case, subsequent decomplexation of **26** was accompanied by cycloaromatization of the highly reactive 9-membered enediyne product (**Scheme 7**).

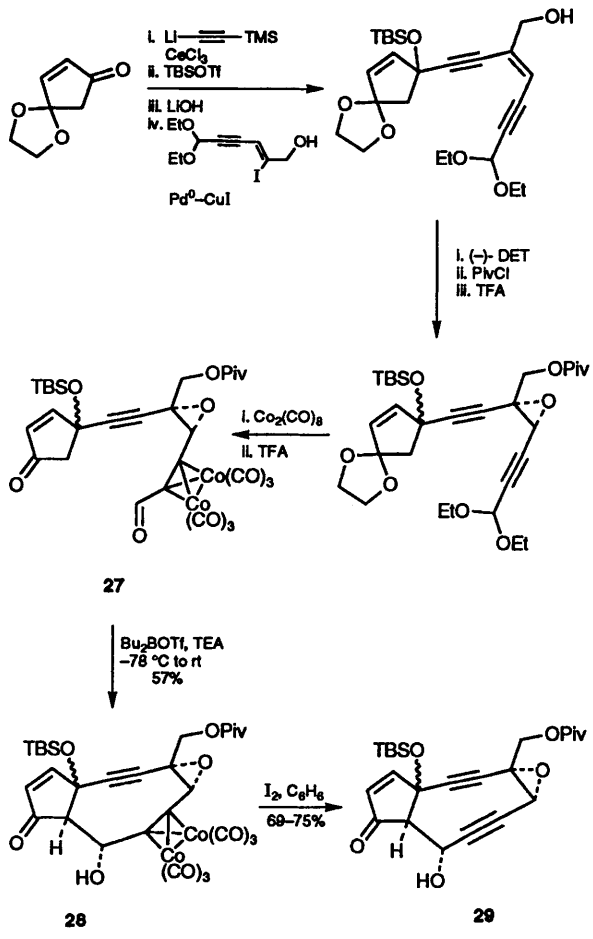
Analysis of the situation led to the audacious plan to install the sensitive epoxide trigger of **1** prior to the Lewis acid promoted aldol type cyclization step (**Scheme 8**). Fortunately, it was found that aldehyde **27**, obtained as a mixture of monochiral diastereoisomers, underwent smooth ring closure on treatment with Bu_2BOTf and Et_3N to give **28** in



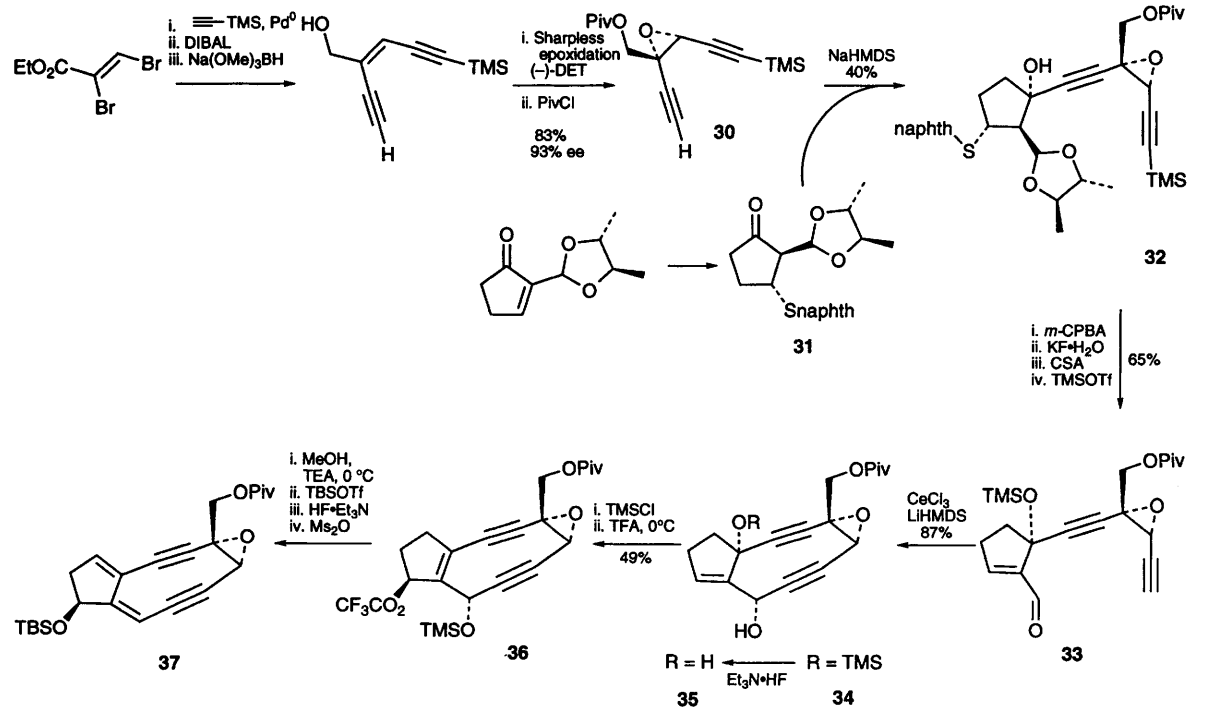
Scheme 7

57% yield. Oxidative decomplexation then gave the desired 9-membered diyne epoxide **29** (69–75% yield), which was a stable product!

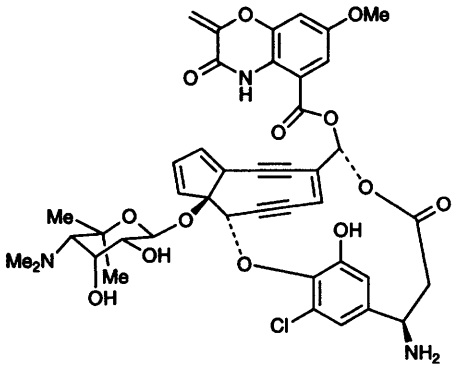
The most significant progress toward construction of the neocarzinostatin chromophore **1** in enantiomerically pure form has been made by Myers *et al.* (**Scheme 9**).[21,22] They showed that condensation of the chiral epoxy functionalized 1,5-diyne unit **30** with optically pure keto acetal **31** led to selective (18:1) formation of the desired 1,2-addition product **32**. Subsequent ring closure of aldehyde **33** to **34** was achieved using LHMDS in the presence of $CeCl_3$ (87%). The remarkable aspect of this, and similar ring closures discussed further on, is that the highly strained 9-membered ring is formed via a reaction which is potentially reversible. At this stage it was found that the delicate allylic transposition of **35** to **36** could be effected by brief exposure to trifluoroacetic acid. Hydrolysis of trifluoroacetate **36** was then followed by hydroxy protection and vinylogous elimination of MsOH to give the dienediyne product **37**.



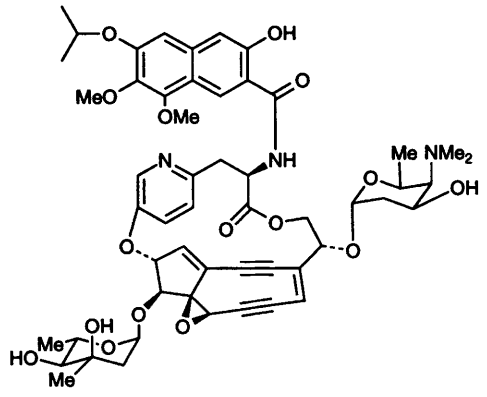
Scheme 8



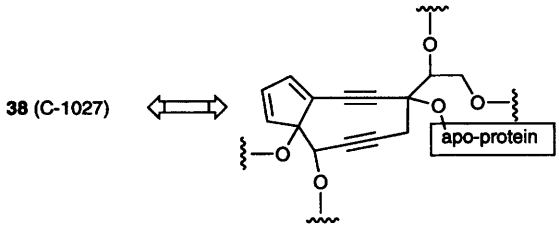
Scheme 9



C-1027 **38**



kedarcidin **39**



Scheme 10

3 Nine-membered enediynes: kedarcidin and C-1027

Recently, Hirama *et al.* have reported an approach to the 9-membered enediyne core of the enediyne C-1027 **38**[23] and kedarcidin **39**[24] (**Schemes 10 and 11**).[25,26] Fundamental to their strategy is the idea that these highly unstable molecules may exist as nucleophilic addition adducts (Serine–OH) in the apoprotein (**Scheme 10**), and that liberation of the chromophores is accompanied by enediyne double bond formation.[25]

As the absolute stereochemistry of the two antibiotics is unknown, racemic **40** was condensed with optically pure diyne **41** to give **42** (and its C-9 diastereomer as shown in **Scheme 11**). Both diastereomers were separately carried through to aldehydes **43** and reacted with LHMDS in the presence of $CeCl_3$. Interestingly, ring closure to **43** was succeeded by a facile Cope rearrangement to the bis-allene **44**.[27] This undesired transformation was suppressed during the corresponding cyclization of the enyne intermediate **45** to the point where the target compound **46** could be isolated and characterized (**46** can be stored at −20 °C).

By a short sequence of reactions this intermediate was converted to the enediynes **47** and **48** (**Scheme 11**). Compound **47** underwent rapid cycloaromatization ($t_{\frac{1}{2}}$ at 20 °C = 11 min), but epoxide **48** could be purified by silica column chromatography. The pronounced dependency of the cycloaromatization rate of **48** on solvent [$t_{\frac{1}{2}}$ (CD_2Cl_2) = 680 min; $t_{\frac{1}{2}}$ (CD_2Cl_2/CHD) = 23 min] led to the suggestion that **48** may be virtually in equilibrium with the diradical intermediate **49** due to a very low energy barrier to interconversion, and to a higher barrier to radical neutralization by hydrogen abstraction.

Several reports have also appeared concerning preparation of the aromatic and sugar components present in **38** and **39**.[28,29]

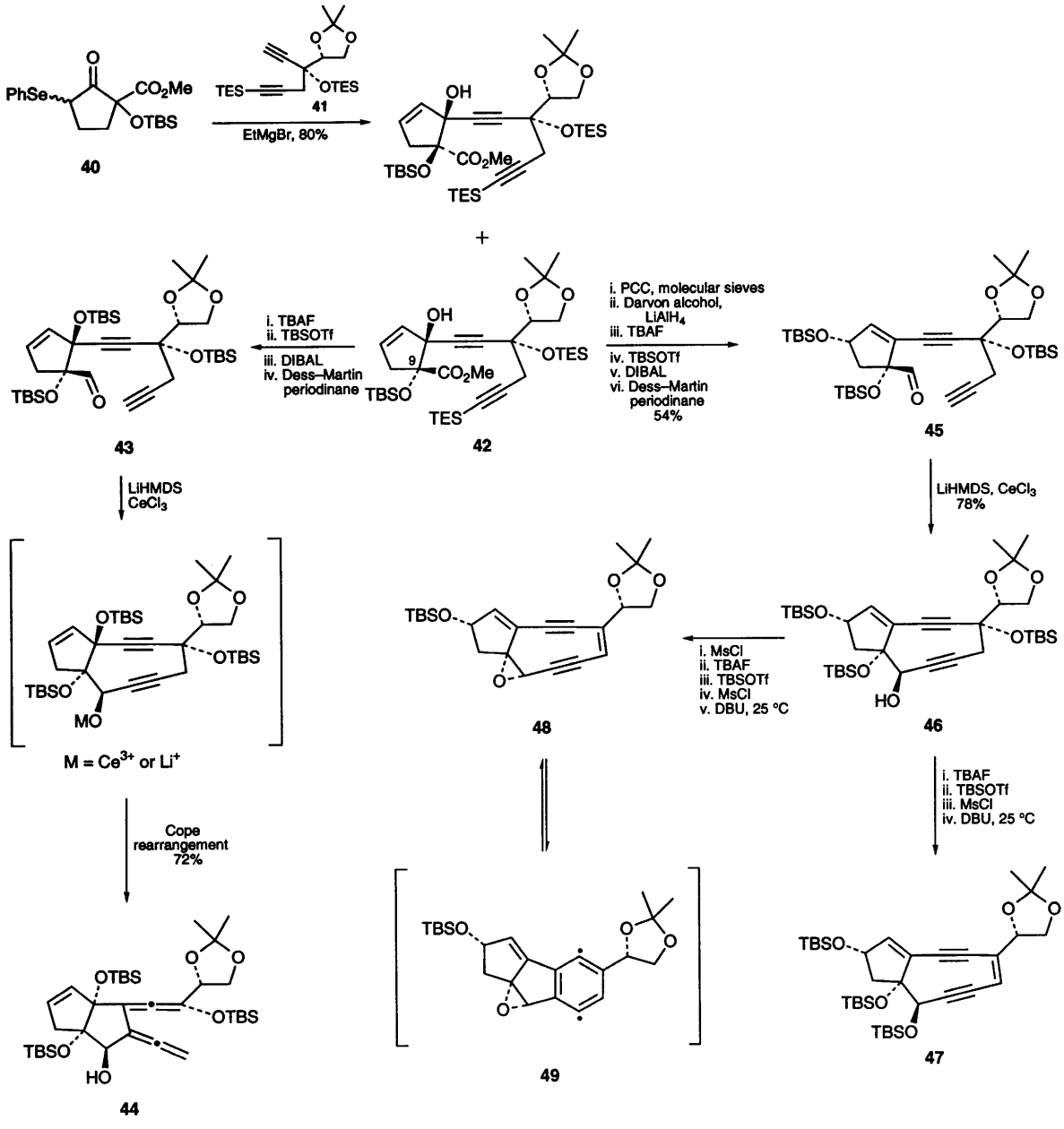
4 The total synthesis of calicheamicin/esperamicin

4.1 Central core structure

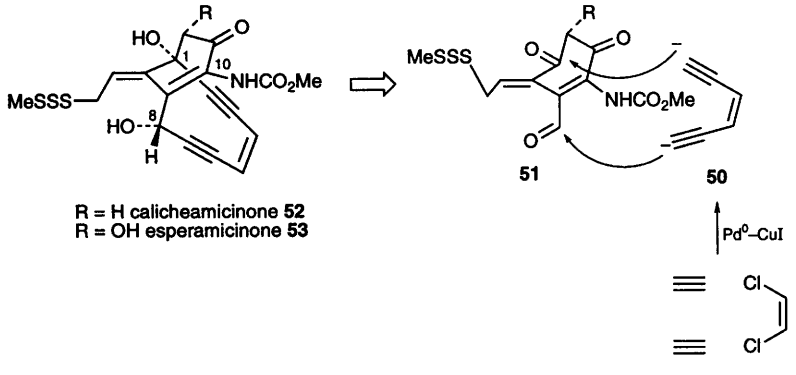
As with any large molecule, a vast number of retrosynthetic pathways can be envisaged for the preparation of calicheamicin/esperamicin. However, in view of the ready availability of enediyne **50**,[30] the bond disconnection shown in **Scheme 12**, involving condensation of its dianion across a keto aldehyde platform synthon **51**, has attracted particular attention. Given this choice, the problem of constructing the aglycones calicheamicinone **52** and esperamicinone **53** can be reduced to deciding how much of the molecules functionality (and in what form) should be present in the starting platform synthon, and at what moment either direct condensation or stepwise construction of the bridging enediyne system should intervene.

Kende achieved the synthesis of the bicyclo[7.3.1]tridecane compound **56**, possessing the crucial C_9–C_{10} bridgehead double bond of calicheamicinone which prevents cycloaromatization (**Scheme 13**).[31] In this work the aldehyde function in **54** served as a latent ethynyl substituent, and the keto group was elaborated into the α,β-unsaturated aldehyde system found in **55**. In the final step the enediyne bridge was successfully buckled together to produce **56** along with its C-8 epimer. Detailed NMR studies of these products permitted reattribution of the stereochemistry initially proposed for the C-8 centre in **2**.

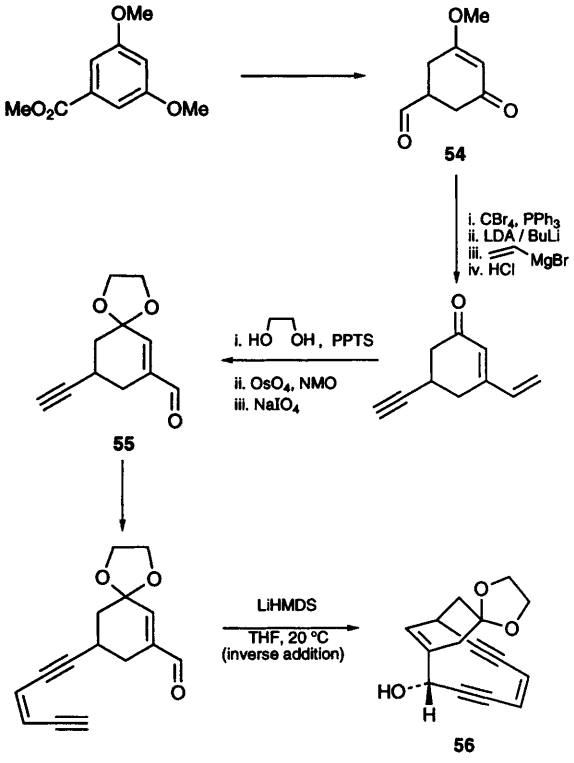
In the first synthesis of calicheamicinone by Danishefsky *et al.*, the concept of reacting the dianion of enediyne **50** with a fully functionalized platform structure was taken to the letter (**Scheme 14**).[32] Indeed a projected key step was the condensation of **50** with the keto aldehyde synthon **59**, obtained by Becker–Alder[33] dearomatization of the phenol intermediate **57** and a Dess–Martin periodinane mediated oxidation[34] of the resultant alcohol **58**. Preliminary studies of this process pointed to the inescapable necessity of having the



Scheme 11



Scheme 12

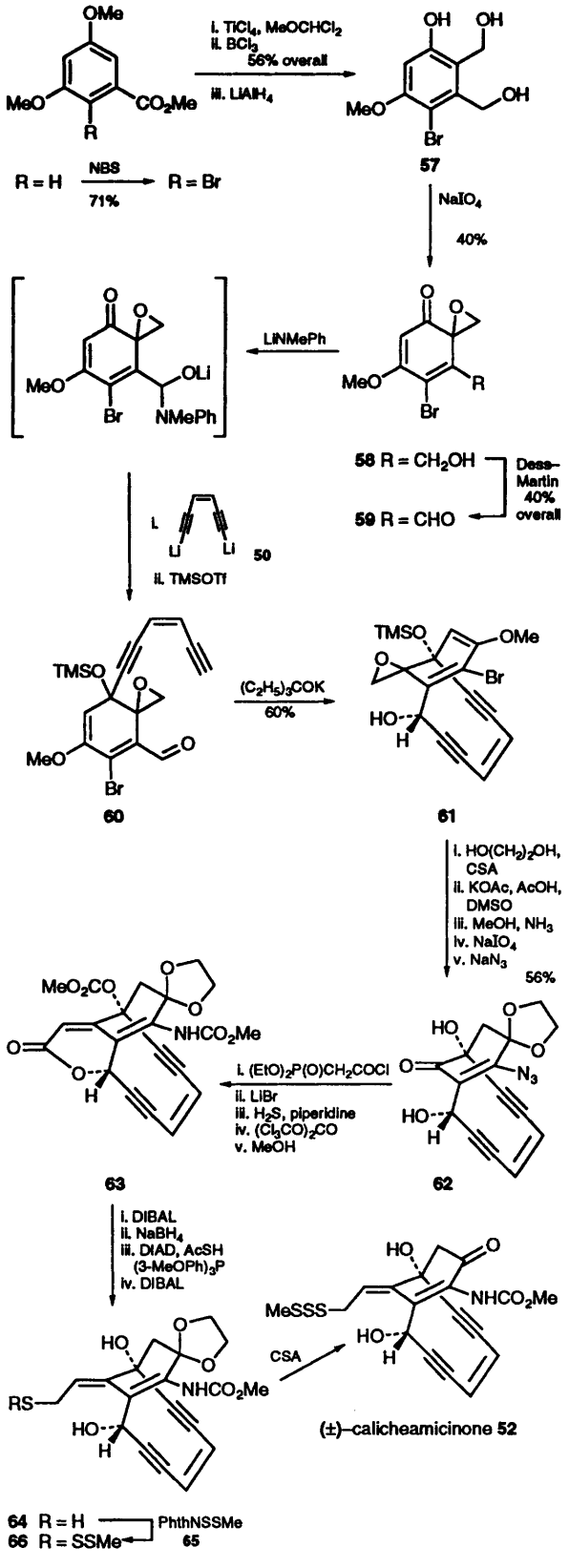


Scheme 13

dianion react first with the less reactive keto group in **59**. This was achieved by a clever application of the Comins procedure for *in situ* aldehyde protection[35] wherein the 1,2-addition product **60** was formed regio- and stereo-selectively. Despite the large distance between the reacting centres in this acyclic intermediate (~6.5 Å) ring closure was extraordinarily efficient giving the strained enediyne intermediate **61** with the correct C-8 hydroxy stereochemistry in 60% yield.

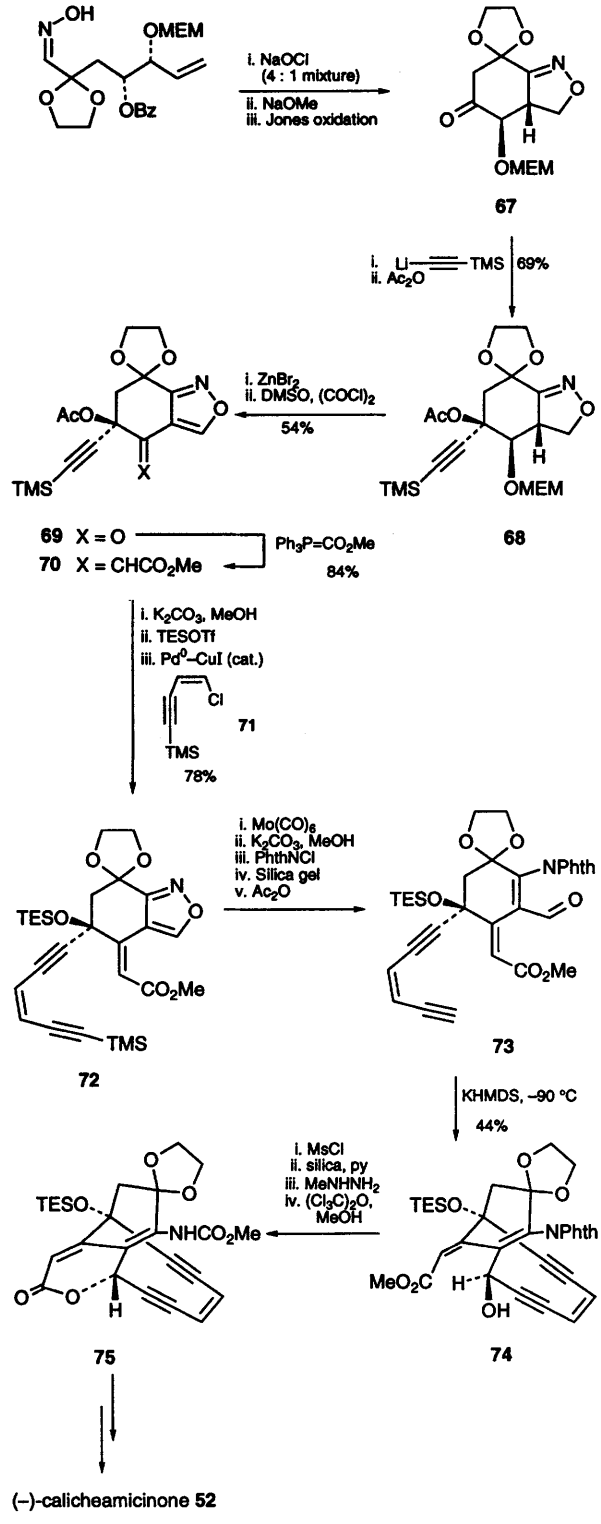
Subsequent steps involved conversion of the enol ether function to the corresponding ketal, elaboration of the C-13 ketone function through epoxide ring opening and oxidative cleavage of the resultant diol, and introduction of azide ion at C-10 in a Michael reaction process. At this stage the exocyclic double bond was stereospecifically introduced into **62** by an intramolecular Wittig reaction, and the azido group was reduced and carbomethoxylated giving lactone **63**. The final operations included reductive opening of the lactone ring, and conversion of the derived alcohol to thiol **64**, which on treatment with Harpp's disulfide reagent **65**[36] gave the allylic methyl trisulfide intermediate **66**. Selective reaction of **66** with CSA at room temperature touched only the ketal function, completing the synthesis of (±)-calicheamicinone **52**.

The essential elements of the strategy depicted in Scheme 12 are also found in Nicolaou's first synthesis of (−)-calicheamicinone (**Scheme 15**).[37] Particularly appealing in this work is the idea of capturing in latent form the urethane nitrogen and the C-9 aldehyde function within the

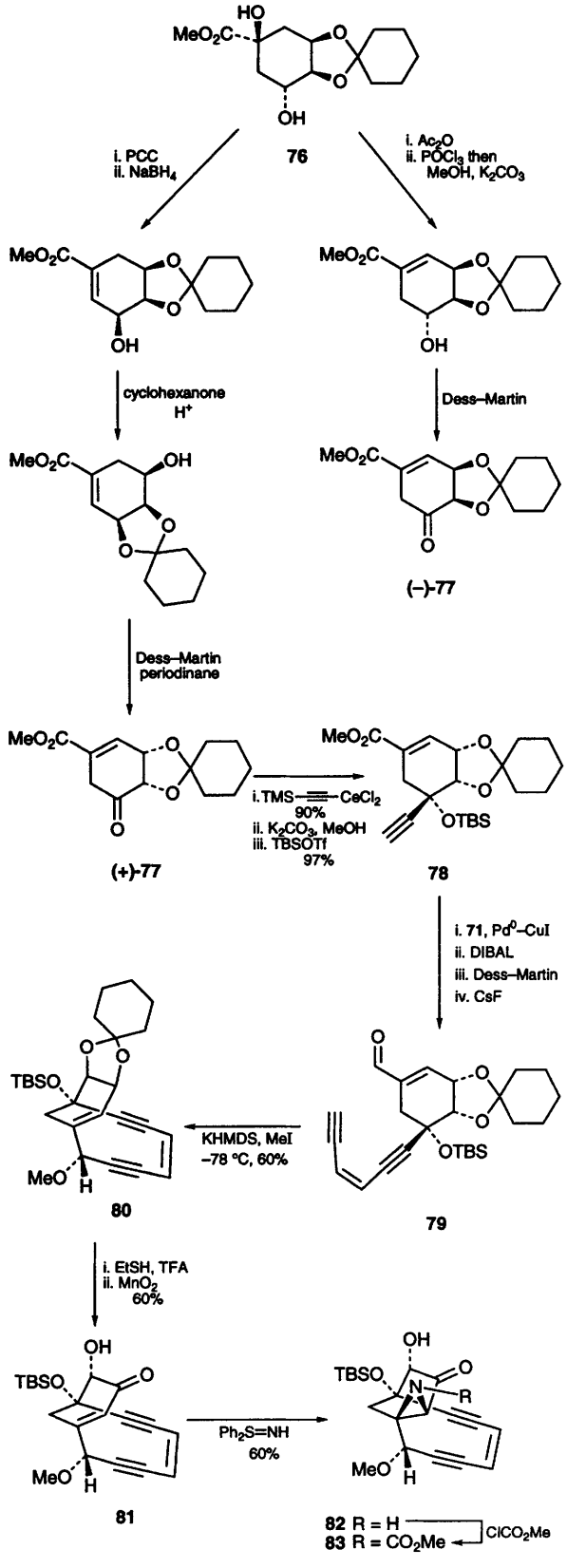


Scheme 14

dihydroisoxazole ring of the highly functionalized monochiral intermediate **67**. Note also that stereoselective reaction of the keto group in **67** with lithium (trimethylsilyl)acetylide to give **68**



Scheme 15



Scheme 16

established the chirality at C-1 of the target molecule.

In the following steps Swern oxidation of the *O*-MEM deprotected derivative of **68** effected both oxidation of the liberated secondary alcohol and aromatization of the isoxazole ring giving **69**. Reaction of this intermediate with methyl(triphenylphosphoranylidene) acetate produced the α,β-unsaturated ester **70** as a single isomer. The enediyne system was then assembled by Pd^0–CuI catalysed coupling with *cis* chloro enyne **71**, and the amino aldehyde functionality contained in the

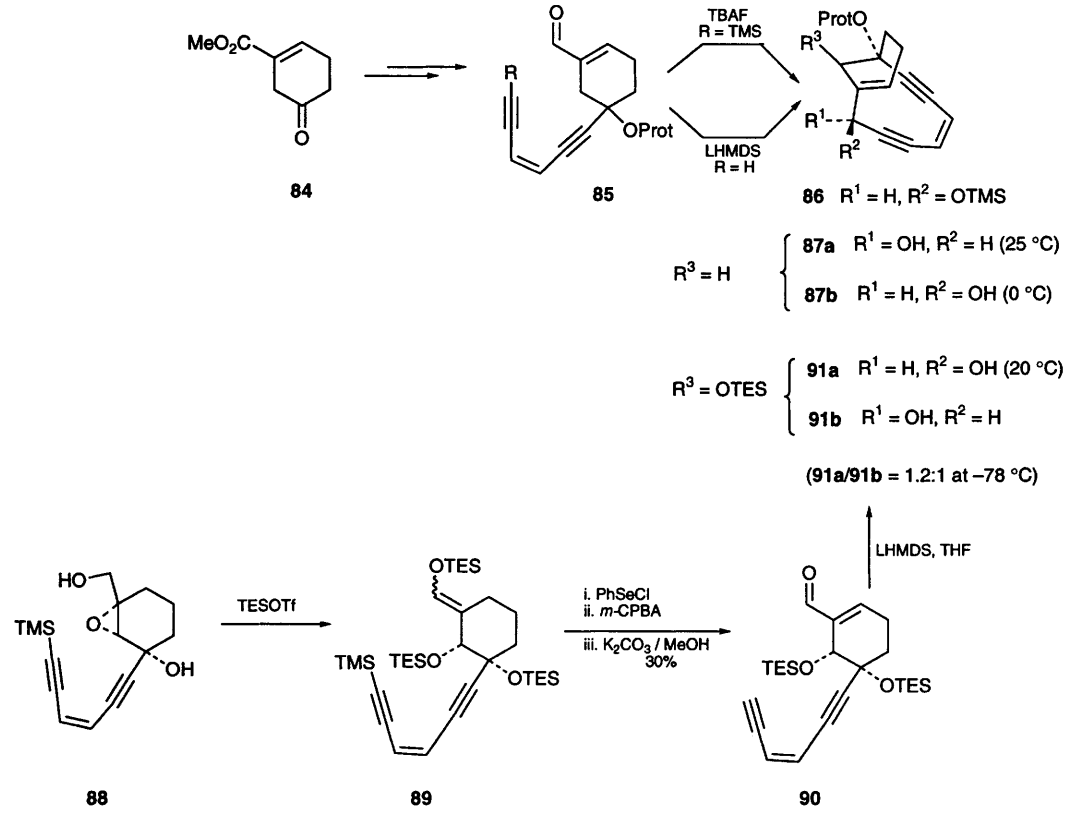
isoxazole ring of **72** was released by N–O bond cleavage using molybdenum hexacarbonyl. Ring closure of phthalamide derivative **73** to a 9:1 mixture of alcohol **74** and lactone **75** (44% combined yield) was achieved through reaction with KHMDS in toluene at −90 °C. Taking advantage of proximity effects, alcohol **74** possessing the incorrect stereochemistry at C-8 was converted via its mesylate derivative to lactone **75**. Reductive ring opening of this lactone, and its elaboration to (−)-calicheamicinone **52** was achieved using the chemistry developed by Danishefsky and Magnus.

To gain access to esperamicinone **53** in both its natural (1*S*,8*R*)[38] and antipodal forms for biological testing,[39] Grierson and co-workers employed the two enantiomers of keto ester **77**, obtained from the quinic acid derivative **76**, as the pivotal intermediate (**Scheme 16**).[40,41] For the natural series, elaboration of seco aldehyde **79** began by stereospecific acetylene addition to (+)-**77** using weakly basic dichlorocerium (trimethylsilyl)acetylide, and *O*-silylation of the derived alcohol to block intermediate **78** in the conformation having the acetylene function axial.

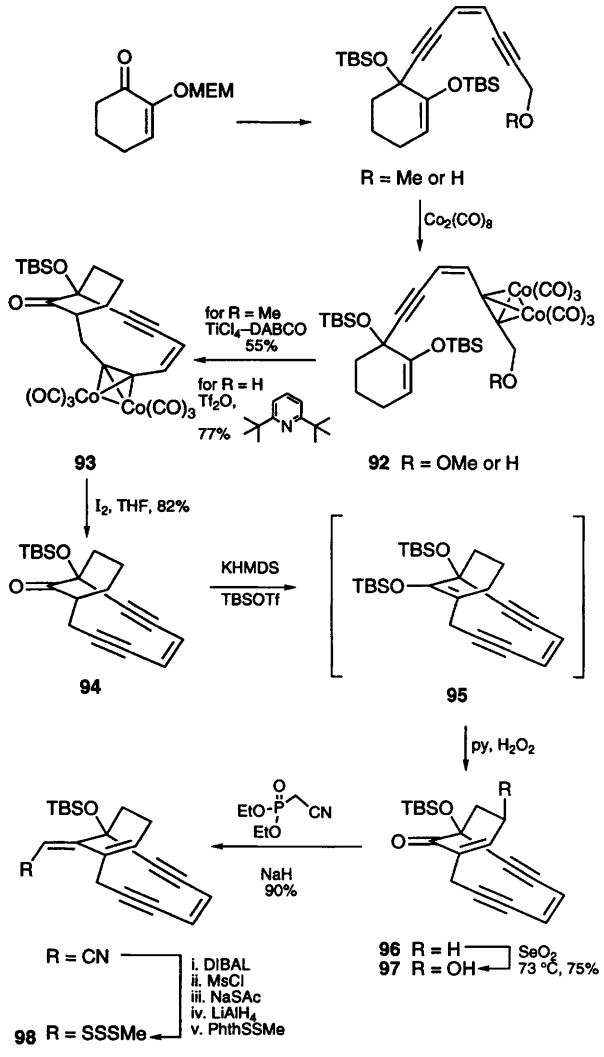
Cyclization of **79** gave the desired bicyclic enediyne product having the correct C-8 stereochemistry (>60%). However, to avoid retrocondensation during subsequent operations the cyclized alcohol was converted to its methyl ether **80** before work-up. Introduction of the urethane nitrogen was then achieved by reaction of enone **81** with $Ph_2S{=}NH$. In this transformation cyclization of the presumed intermediate Michael addition adduct to aziridine **82** is sufficiently rapid that cycloaromatization does not occur. Various conditions can be envisaged to effect ring opening of the *N*-carbomethoxylated aziridine derivative **83** such that the C_9–C_{10} double bond is reinstalled, and the C-13 centre is activated with respect to construction of the allylic trisulfide system.

In a closely related fashion Kadow and Isobe have elaborated the simpler esperamicin intermediates **86** and **87** from keto ester **84** (**Scheme 17**).[42,43] Interesting in Kadow's study is the contrasting dependence of product C-8 stereochemistry on reaction temperature in the ring closure of aldehyde **85**, and the analogous cyclization of **90** to **91**. Aldehyde **90** was obtained in four steps from Isobe's epoxide **88** (see Scheme 36) by TESOTf induced ring opening to the exocyclic enol ether **89** and regioselective thermal selenoxide *cis* elimination.[44]

With respect to the strategy depicted in Scheme 12, Magnus and co-workers approached the problem of synthesizing **52** from almost the opposite viewpoint, *i.e.* by introducing the functionality onto the 6-membered ring platform *after* assembly of the bicyclic enediyne skeleton (**Scheme 18**). In particular, from their work on the preparation of different cobalt complexed bicyclic enediyne structures (see Scheme 12 in Part 1 of this review[6]), it was observed that the ketone **94** obtained after decomplexation of **93** was sufficiently stable to permit chemical manipulation.[45–47] This result is remarkable, in view of the fact that the crucial



Scheme 17



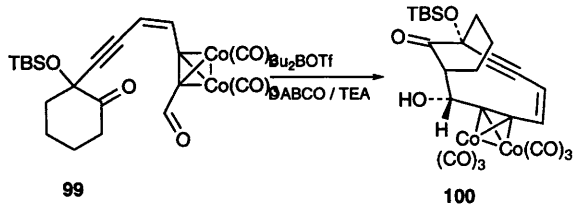
Scheme 18

bridgehead double bond is absent in enediyne **94**. The cobalt complexed enediyne **93** was prepared via a ring closure reaction involving reaction of the enol ether system in **92** with a formal carbocation generated by departure of the OMe or OH group under Lewis acid conditions (the Nicholas reaction).

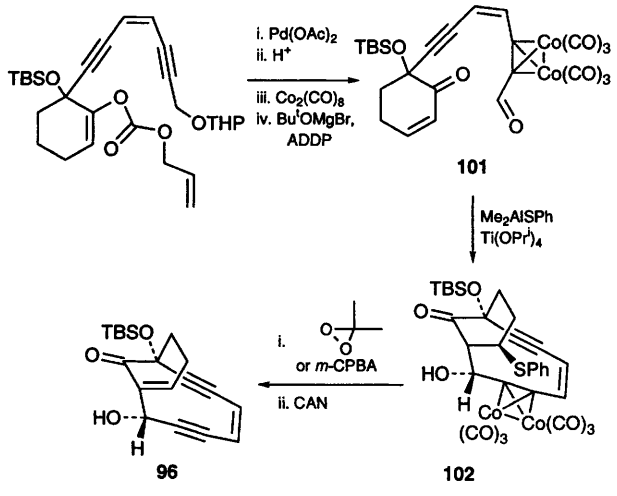
Since **94** adopts preferentially a boat conformation in which the C-9 hydrogen is in the plane of the carbonyl system, the enol silyl ether **95** could be generated. This opened the way to a selenium based protocol for creation of the C_9–C_{10} double bond in **96**.[48,49] At this point oxygen functionality can be further introduced at C-11 under SeO_2 allylic oxidation conditions giving **97**, and through a stereocontrolled Wittig–Horner reaction using diethyl cyanomethylphosphonate elaboration of the allylic trisulfide unit in **98** was achieved.[48,50]

To incorporate the C-8 alcohol function in the molecule the cobalt complexed aldehyde **99** was cyclized through an aldol reaction to **100** (**Scheme 19**).[51] Kadow,[52] and subsequently Roth[53] and Magnus,[46] have modified this approach showing that treatment of **101** with $PhS^-/Ti(OPr^i)_4$ initiates ring closure through a Michael addition–enolate trapping mechanism to give alcohol **102** (**Scheme 20**). Subsequent oxidative elimination of PhSOH and decomplexation then provides a simple alternative means to access compound **96**. At a later stage it was shown that diketone **103** can be converted to the enaminoketone **104** through reaction with either $Ph_2S{=}NH$ or the azide ion in DMF (**Scheme 21**).[46]

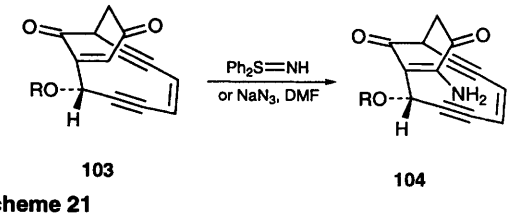
Having succeeded in obtaining calicheamicinone, Nicolaou's group turned to synthesizing esperamicinone **53**.[54] The main emphasis in the approach that was ultimately developed (**Scheme 22**) was to create the 1,2-*trans*-diol system in the late stage intermediate **110** via Sharpless epoxidation of **108** (90% ee) and acid catalysed ring opening of the epoxide unit in acetylene **109**. Key operations in the elaboration of allylic alcohol **108** involved nitration of the ketal **105**, oxidation of the aromatic ring in **106** to give quinone **107**, and ketone to cyanoethylene conversion (65% overall, $Z{:}E = 10{:}1$).



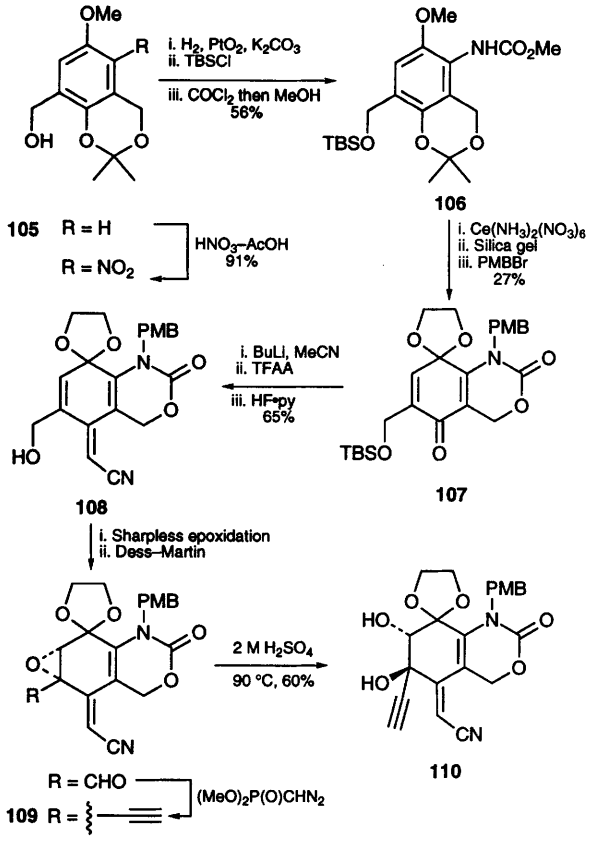
Scheme 19



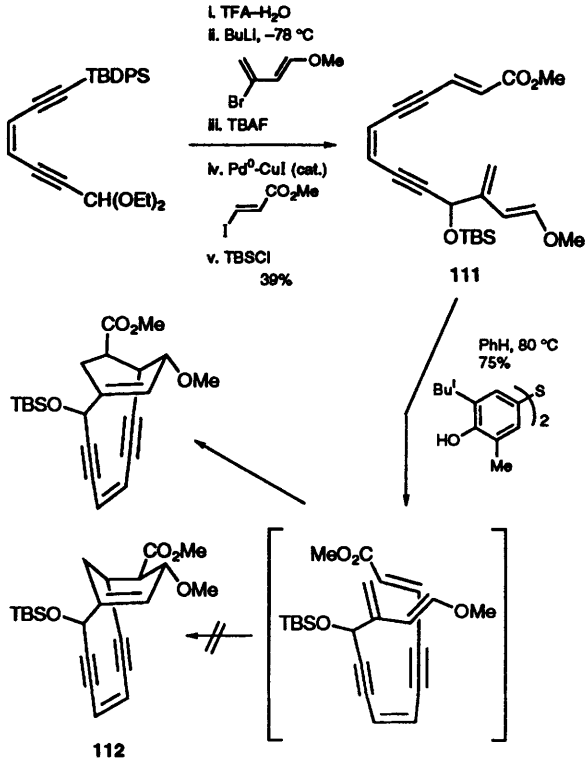
Scheme 20



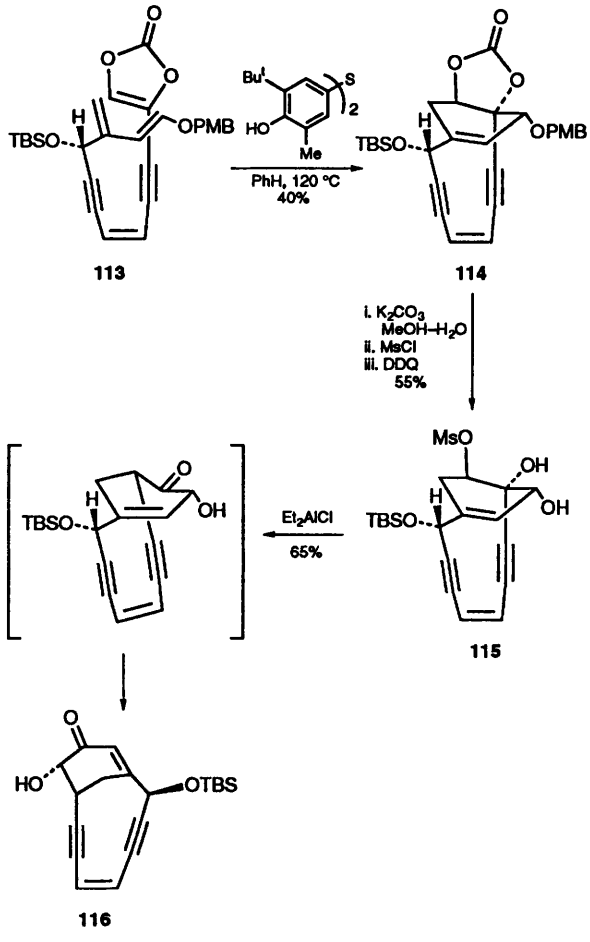
Scheme 21



Scheme 22



Scheme 23



Scheme 24

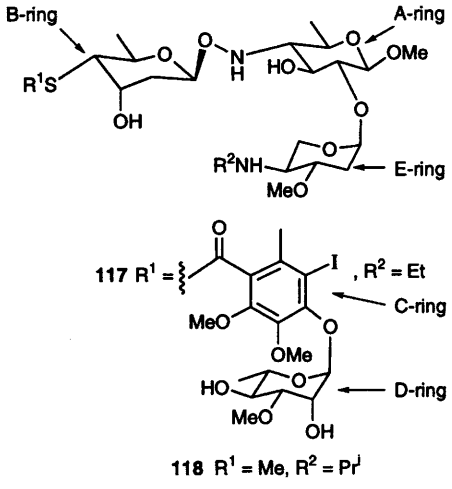
Schreiber *et al.* have adopted yet another entirely different strategy for the synthesis of the calicheamicin/esperamicin aglycone based upon an intramolecular Diels–Alder reaction in which the enediyne system acts as a structurally rigid chain connecting the diene and dienophile components (**Schemes 23 and 24**).[55] This approach to the platform ring is astute in that the bridgehead double double bond is created during the Diels–Alder step rendering the cycloadduct thermally stable. Contrary to expectation, compound **111** did not cycloadd via a geometry imposed *exo* transition state to give the desired product **112** (**Scheme 23**). However, it was found that the cycloadduct **114** obtained from Diels–Alder reaction of **113** could be readily converted to the mesylate derivative **115**, and that Lewis acid promoted pinacol type rearrangement of this intermediate produces the esperamicin analogue **116** (>15:1, 65%) (**Scheme 24**).

4.2 Synthesis of the glycone

Sophisticated NMR, molecular modelling, and (bio)chemical studies have revealed much about how the oligosaccharide fragment in calicheamicin, and the trisaccharide and fucosyl anthranilate units in esperamicin, contribute to the interaction of these antibiotics with the minor groove of duplex DNA.[56] From this work a detailed picture at the molecular level concerning the differences in site selectivity and capacity of the two compounds to

effect single versus double strand breaks in DNA through abstraction of specific hydrogens from the deoxyribose backbone has emerged. In particular, these studies point to the important role played by the hydroxylamino glycoside linkage between the A and B monosaccharide units in preorganizing the oligosaccharide into a conformation that compliments the shape of the minor groove.

The development of strategies for the stereocontrolled formation of the β-N–O linkage, which joins the anomeric centre in the novel sulfur containing 2-deoxy B-ring sugar and C-4 of the A (or A–E) ring fragment, is therefore a central issue that must be addressed in any effort to construct the A–(E)–B trisaccharide structure common to calicheamicin **2** and esperamicin **3**. The discussion will consequently be focused upon the problem of constructing the respective methyl glycosides **117** and **118** (**Scheme 25**).[57–70]



Scheme 25

Considering the presence of two 1,2-aminoalcohol systems in the otherwise sparsely functionalized E-ring of **117**, Nicolaou, and more recently Roush, chose to construct this sugar from L-serine.[61–63] The key step in both routes is the reaction of a serine derived aldehyde intermediate with a chiral allyl borane reagent. In Nicolaou's synthesis (**Scheme 26**) this led to formation of compound **119** as a single isomer (75%). Methylation and subsequent ozonolysis gave a methoxy aldehyde intermediate, which was converted to acetal **120** (68% overall yield for the four steps). Cyclization of **120** in dry HCl–MeOH produced a mixture of separable methyl glycosides which were converted to the *N*-Fmoc (9-fluorenylmethoxycarbonyl) protected glycosyl fluoride **121** by treatment with Fmoc-chloride followed by reaction of the anomeric acetate derivatives with DAST. Coupling of **121** with the methyl D-fucopyranoside derivative **122** followed by deprotection and selective oxidation of the axial C-4 alcohol gave the A–E ketone **123**.[64]

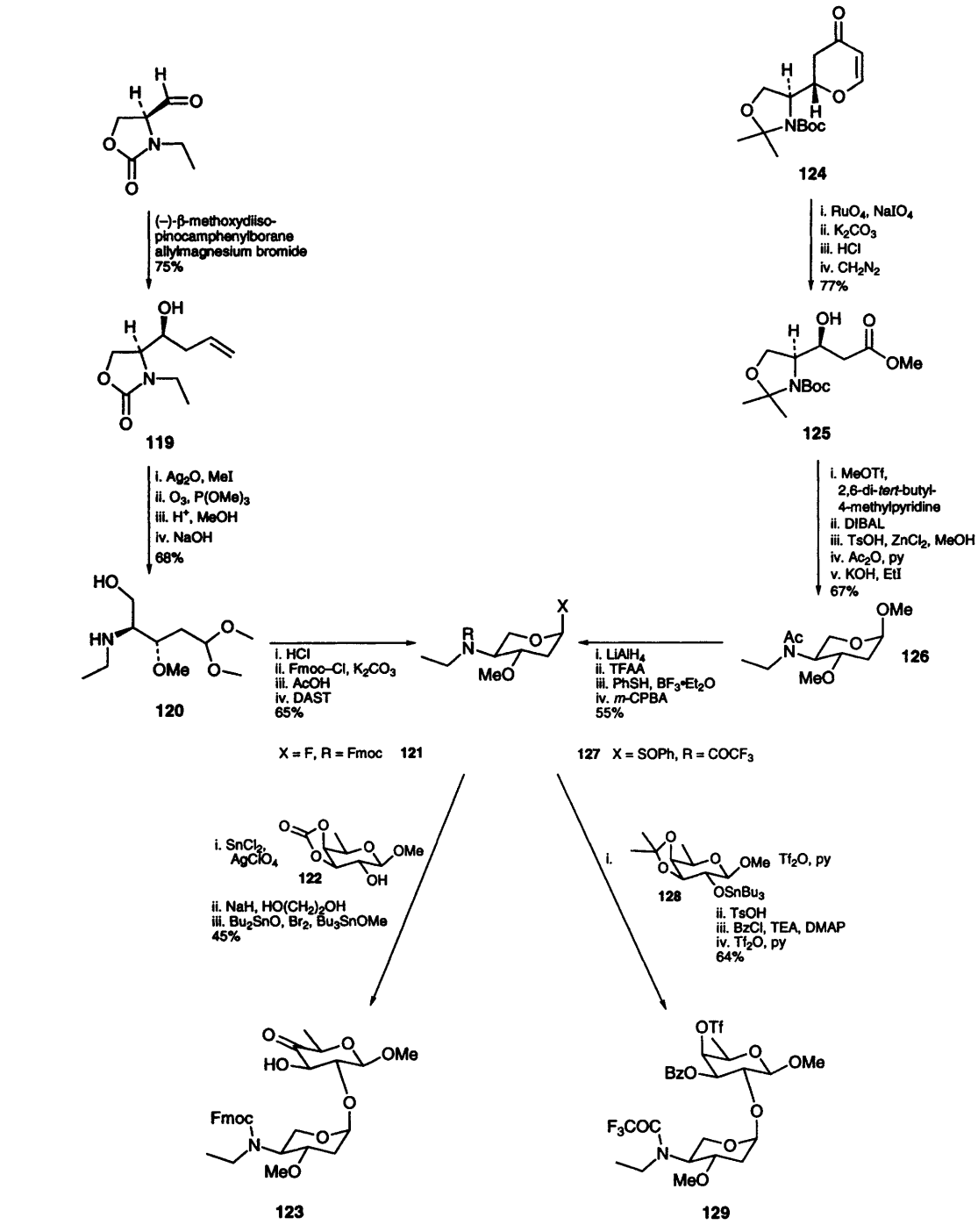
In Kahne's approach to the E-ring the Diels–Alder **124**, obtained from reaction of the *N*-Boc-*N,O*-isopropylidene derivative of serine aldehyde with Danishefsky's diene, was oxidatively cleaved giving the β-hydroxy ester **125** in 77% overall yield (**Scheme 26**).[65] Methylation of the secondary alcohol, DIBAL reduction, deprotection under acidic methanolic conditions, and sequential *N*-acetylation and alkylation then gave **126**. Anomeric activation involved OMe→SPh exchange and conversion of the derived thioglycoside to the corresponding sulfoxide **127**. Reaction of this sulfoxide with methyl glycoside **128** in the presence of triflic anhydride in pyridine (the Kahne reaction[66]) gave a disaccharide intermediate which was elaborated to the A–E ring triflate intermediate **129** (64% overall yield).[67]

The use of glycals both as starting materials and intermediates in the sugar coupling reactions is a key feature of Danishefsky's synthesis of the calicheamicin/esperamicin oligosaccharides.[68,69] This is exemplified by the Theim type coupling ($I^+ClO_4^-$)[70] of glycal **130** with compound **131**, itself derived from D-fucal, to give ultimately the disaccharide intermediate **132** with the *O*-4 axial triflate function in 41% overall yield (**Scheme 27**). In a similar way Beau *et al.* showed that glycal **133**, prepared in six steps from D-arabinal, condenses with the A-ring precursor **134** in a Theim reaction to give the A–E ring intermediate **135** (**Scheme 28**).[71]

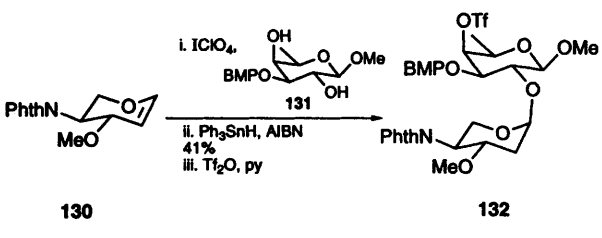
Three major strategies have evolved to date for the coupling of A–E-ring intermediates to the B-ring via the N–O bond such that the correct $A_4\alpha$–$B_1\beta$ configuration is obtained. In the initial phase of Nicolaou's synthesis of the calicheamicin glycone the idea was to use the C-2 oxygen substituent in compound **138** to direct selective formation of the β-glycoside **139** (**Scheme 29**).[64,72] Intermediate **138** was obtained in five steps from glycal **136**, the most important operation of which was the stereoselective $Zn(BH_4)_2$ reduction of ketone **137** from the β-face with concomitant ester migration. As planned, reaction of lactol **138** ($\alpha:\beta = 8:1$) with *N*-hydroxyphthalamide (Mitsunobu conditions) produced the required β-anomer **139** as the major product (5:1 to 7:1; 56% overall).

Liberation of the amino group and coupling of the derived hydroxylamine **140** with the A–E ring ketone **123** under acidic conditions proved highly efficient, giving oxime **141** as a single isomer (83%). Conversion of compound **141** to thioniomidazolide **142** then set the stage for a thermal [3,3]-sigmatropic rearrangement to **143**. In this step the B-ring C-4 sulfur substituent was introduced stereospecifically, and the C-2 position was deoxygenated. Subsequent condensation of **144** with the acid chloride derivative **145** gave the tetrasaccharide intermediate **146** in 80% yield.

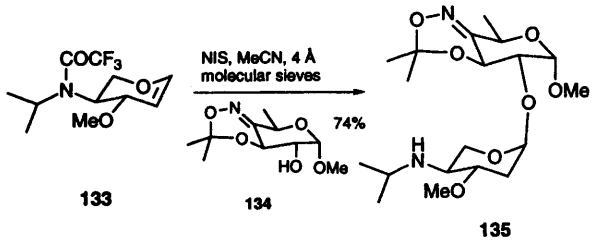
In the final steps to the calicheamicin methyl glycoside **117** the B-ring keto group was exposed and reduced, and the remaining protecting groups were removed. Most importantly, the oxime double



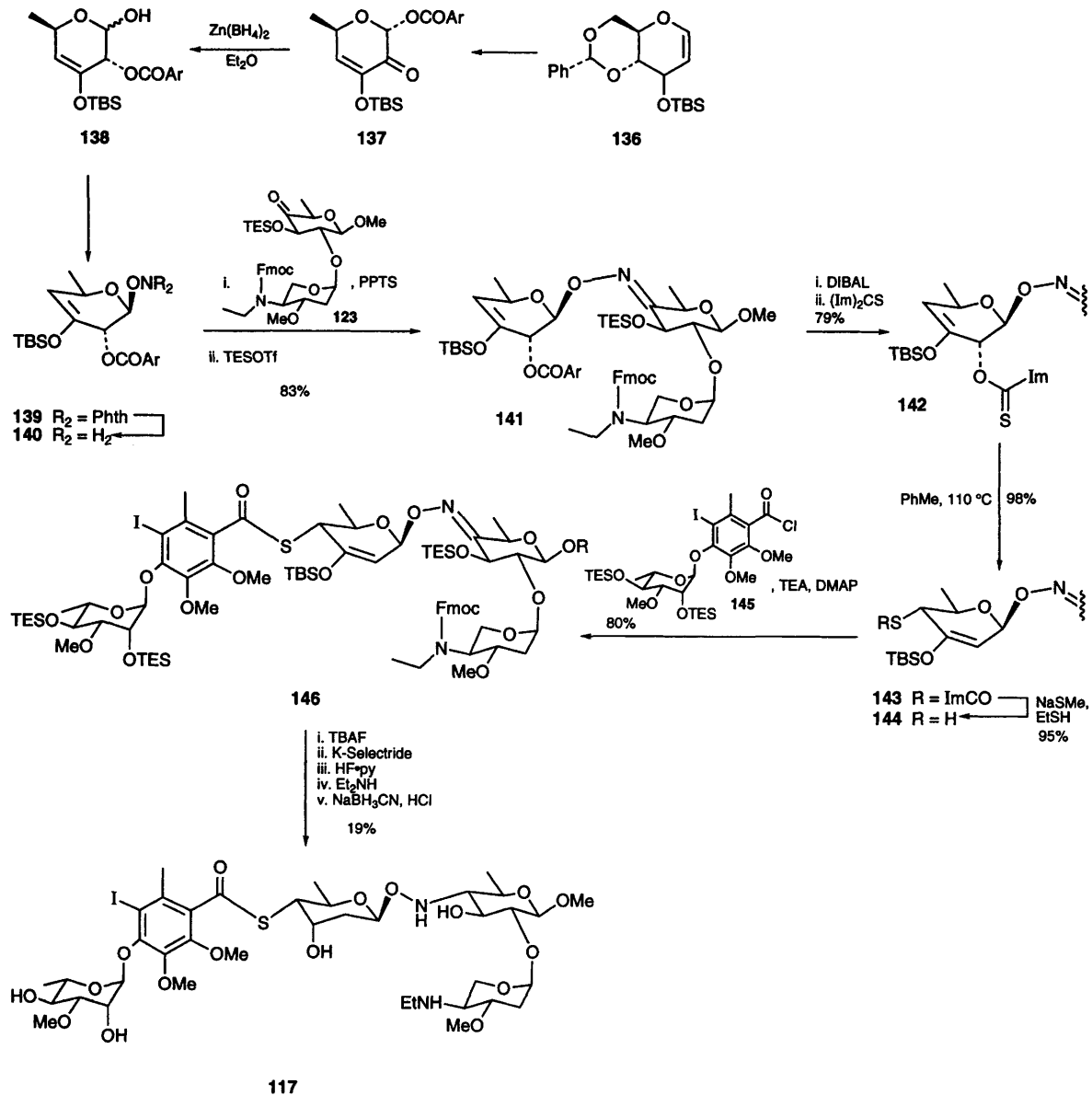
Scheme 26



Scheme 27



Scheme 28

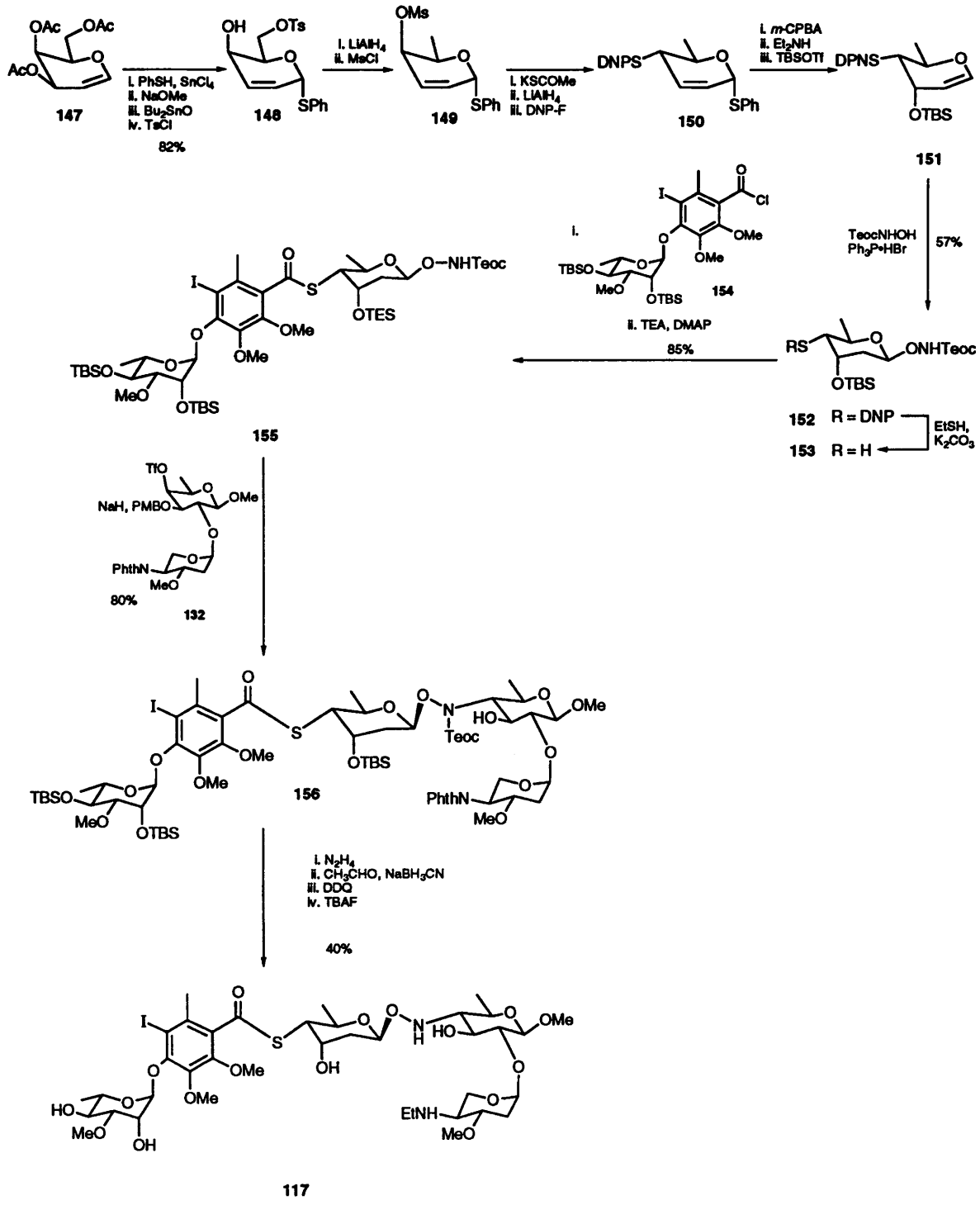


Scheme 29

bond was reduced selectively such that the required C–N equatorial stereochemistry was obtained (86%; $\alpha:\beta = 6:1$). By essentially the same route the esperamicin trisaccharide **118** was synthesized.[73]

The second approach to the calicheamicin aryl tetrasaccharide **117** was developed independently by Danishefsky and Kahne. Here, the B and A–E rings are joined through S_N2 displacement of the axial triflate substituent in the A–E fragment by the anion generated from *N*-acylated B-ring anomeric hydroxyalmine intermediates (**Schemes 30 and 31**). The *N*-Teoc derivative **155** employed by Danishefsky[68,69,74,75] was prepared by first converting tri-*O*-acetyl-D-galactal **147** to the α-phenylthio pseudoglycal **148** (82% overall) (**Scheme 30**). $LiAlH_4$ reduction and mesylation of the remaining hydroxy group then afforded compound **149**, which was converted to the disulfide **150**. Treatment of **150** with *m*-CPBA at −40 °C resulted in sulfoxidation of the less hindered anomeric thiophenyl residue only. At room temperature this intermediate underwent clean [2,3]-sigmatropic rearrangement giving **151** (76% after *O*-silylation). Reaction of this glycal with $TMSCH_2CH_2OC(O)NHOH$ (Teoc-NHOH) in the presence of $Ph_3P \cdot HBr$ gave urethane **152** (57%) along with 37% of the undesired *N*-linked glycoside. The C-4 thiol was then liberated through reaction with $EtSH/K_2CO_3$ giving the B-ring thiol **153** in high yield.[76] This intermediate was condensed with acid chloride **154** in the presence of Et_3N–DMAP to give the *N*-Teoc protected B–C–D fragment **155** (85%).

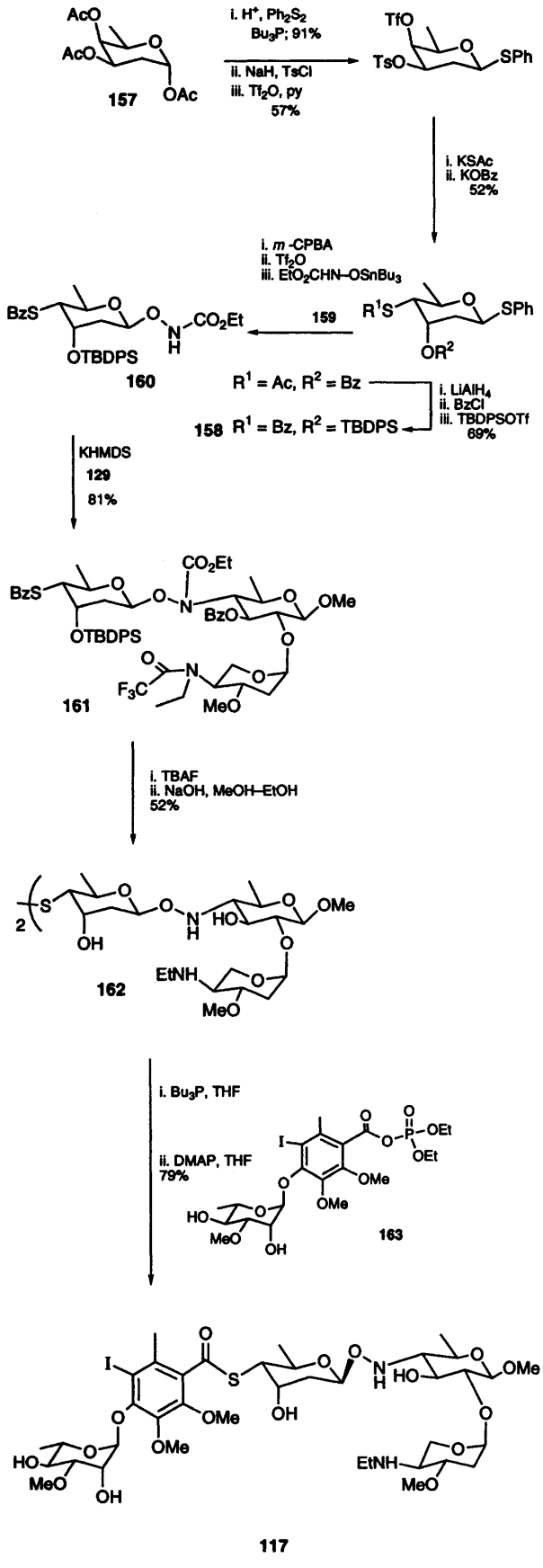
In the next step the crucial reaction of the urethane anion of **155** with the A–E ring triflate derivative **132** was effected producing the protected oligosaccharide intermediate **156** in 80% yield. Liberation of the E-ring amino function in **156**



Scheme 30

followed by reaction with acetaldehyde and $NaBH_3CN$ permitted introduction of the *N*-ethyl substituent (98%). Final cleavage of the *p*-methoxybenzyl, silyl and Teoc blocking groups through successive reaction with DDQ and TBAF provided the target glycone **117** in 40% overall yield. By the same sequence of reactions using the *S*-methyl derivative of thiol **153** the esperamicin glycone **118** was efficiently prepared.

The requisite B-ring substrate **160** in Kahne's synthesis was prepared in six steps from the readily available D-*lyxo*-pyranoside **157** (**Scheme 31**).[67] This involved two sequential displacement reactions, and stereoselective formation of the desired *β*-anomer in the reaction of the sulfoxide derived from **158** with *O*-stannyl-*N*-hydroxyurethane **159** (12:1; 39%). *N*-Alkylation of urethane **160** with the A–E triflate **129** was then effected producing **161** in 81% yield. This



Scheme 31

intermediate was fully deprotected by successive treatment with TBAF and NaOMe to give the (A–(E)–B trisaccharide as its disulfide **161**. Deprotection at this stage was judicious as the protected aryl tetrasaccharide otherwise obtained proved sensitive to base treatment, undergoing a number of interesting rearrangements. Selective formation of the calicheamicin methyl glycoside **117** from **162** was elegantly achieved by reacting the corresponding thiolate generated *in situ* (Bu_3P) with the phosphate derivative **163** according to Masamune (79% for the two steps).[77]

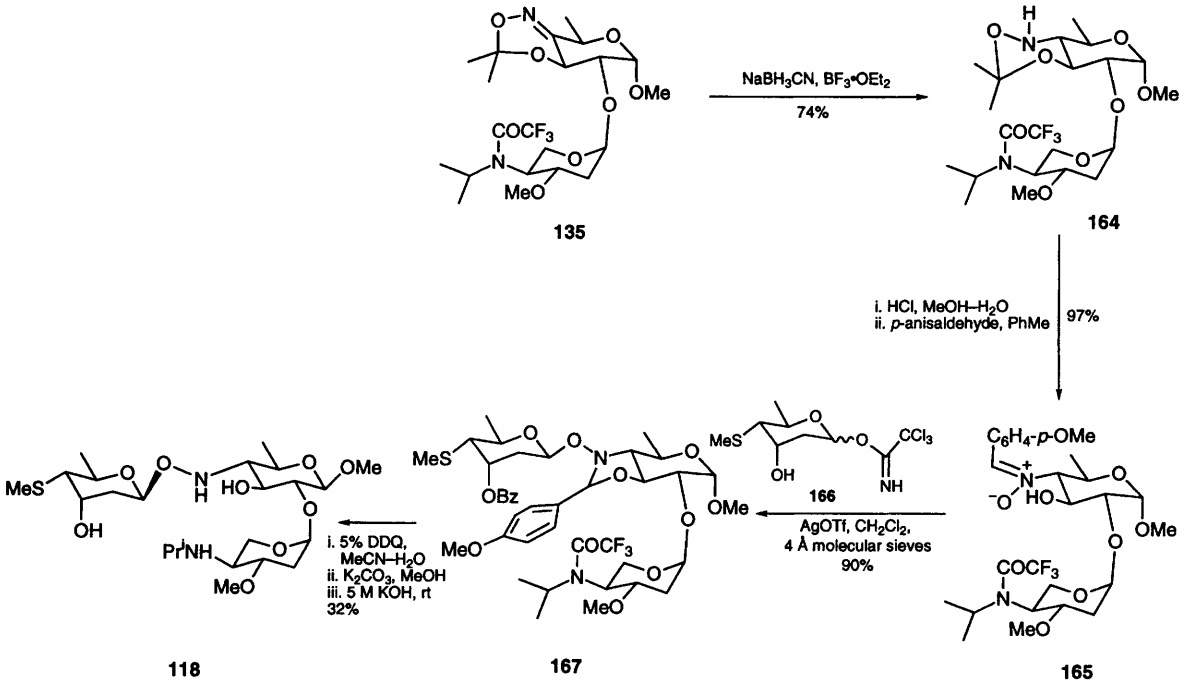
In the third strategy for A–(E)–B ring assembly, Beau *et al.* showed that $BF_3 \cdot OEt_2$ assisted cyanoborohydride reduction of the oxime ether double bond in the A–E ring derivative **135** occurs selectively from the β-face giving the hydroxylamine **164** (74%) (**Scheme 32**).[71,78] Preparation of this intermediate for attachment to the B-ring involved isopropylidene hydrolysis and conversion to the *N*-protected nitrone derivative **165**. *O*-Alkylation of this nitrone, achieved by reaction with trichloroacetimidate **166** in the presence of silver triflate, was accompanied by *N,O*-acetal formation giving the trisacccharide **167** in 90% yield ($\beta:\alpha = 5:1$). After three further deprotection steps the esperamicin methyl glycoside **118** was obtained.

4.3 Total synthesis of (−)-calicheamicin γ_1^I

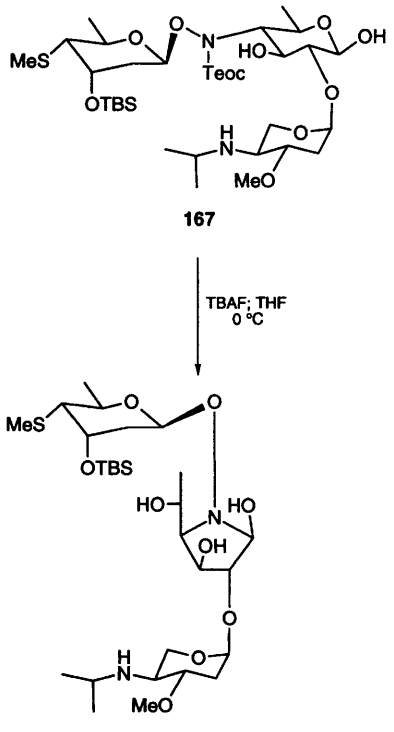
To complete the total synthesis of calicheamicin **2** in a convergent fashion required the coupling of an advanced stage optically pure central core intermediate with a suitably protected aryl oligosaccharide component, under conditions where both components and the derived product survive. Further, the coupled product must not be overly sensitive to any subsequent steps of deprotection and functional group elaboration. In particular, provision must be made to avoid the known rearrangement of *N*-unprotected free glycosides such as **167** to azafuranoses (**Scheme 33**).[60]

In Nicolaou's first synthesis of **2**, both the labile trisulfide system in the aglycone and the hydroxylamine system joining the A and B rings of the sugar component were elaborated after the coupling reaction (**Scheme 34**).[79] Important to the success of this approach was the use of the *O*-TES and *N*-Fmoc protected β-2-nitrobenzyl glycoside **168**,[80] which could be converted photolytically to lactols **169** (1:1 mixture) and coupled to the calicheamicinone derivative **171** via trichloroacetamide **170** using the exceptionally mild conditions of the Schmidt reaction (76%).[81]

With compound **172** in hand, the first of the three allylic sulfur atoms was introduced at C-15 in the aglycone. To effect the crucial reduction of the oxime double bond in **173** ($NaCNBH_3$, $4\alpha:4\beta = 2:1$; 80% yield) the silyl protecting groups had to be removed. However, temporary reprotection of the sugar hydroxyls subsequently proved necessary in order to elaborate the allylic trisulfide unit. This was achieved through reaction of **174** with TESOTf and



Scheme 32



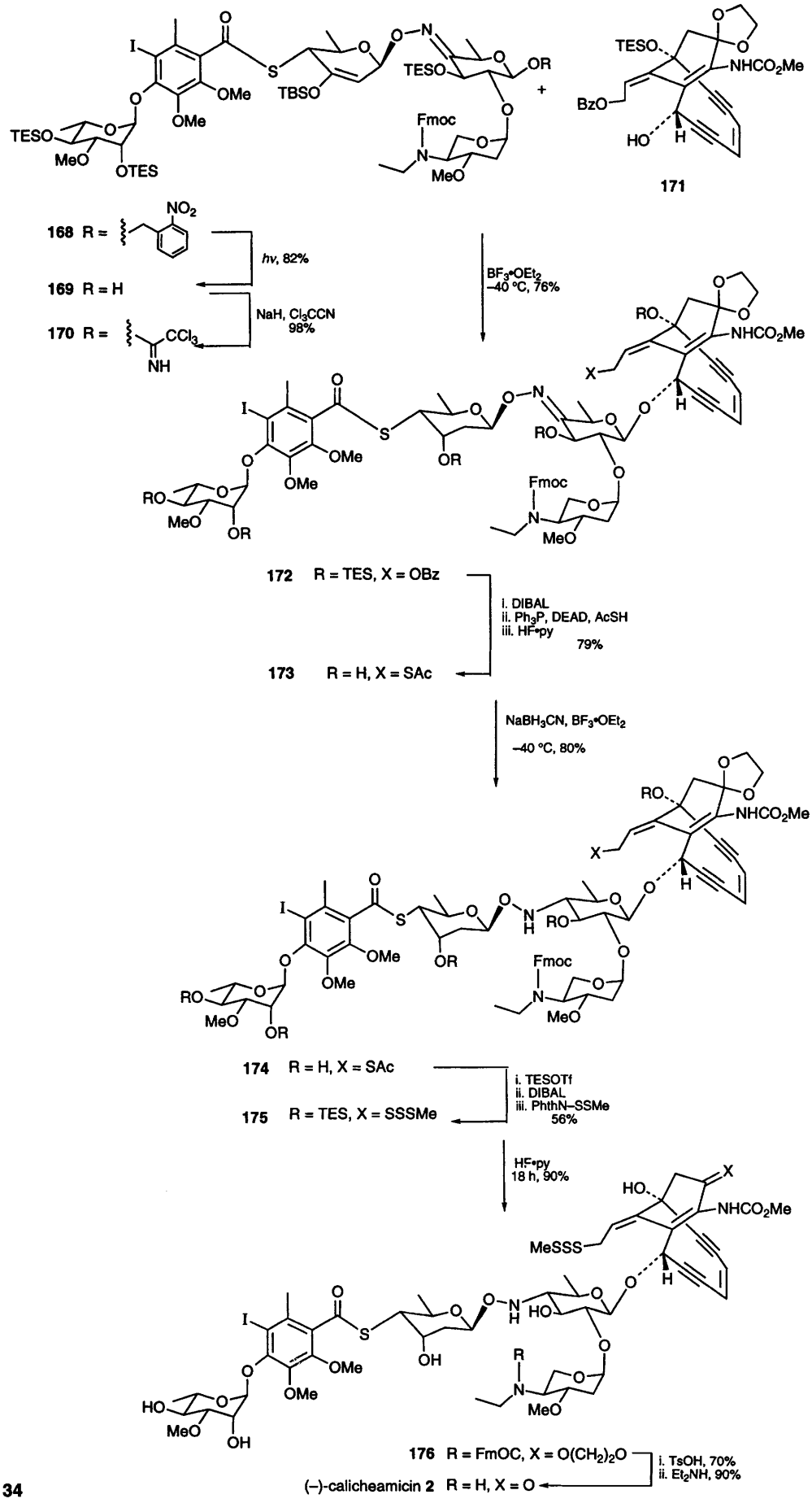
Scheme 33

Hünig's base followed by treatment of the crude product mixture with excess HOAc–H_2O. Reduction of the thioacetate group with DIBAL at −90 °C then gave the corresponding thiol which was reacted with Harpp's reagent giving **175** in 75% yield. Treatment of this intermediate with HF–pyridine afforded **176** (90%) which was further deprotected in the last two steps through sequential treatment with TsOH (70%) and Et_2NH (90%), completing the synthesis of (−)-calicheamicin **2**.

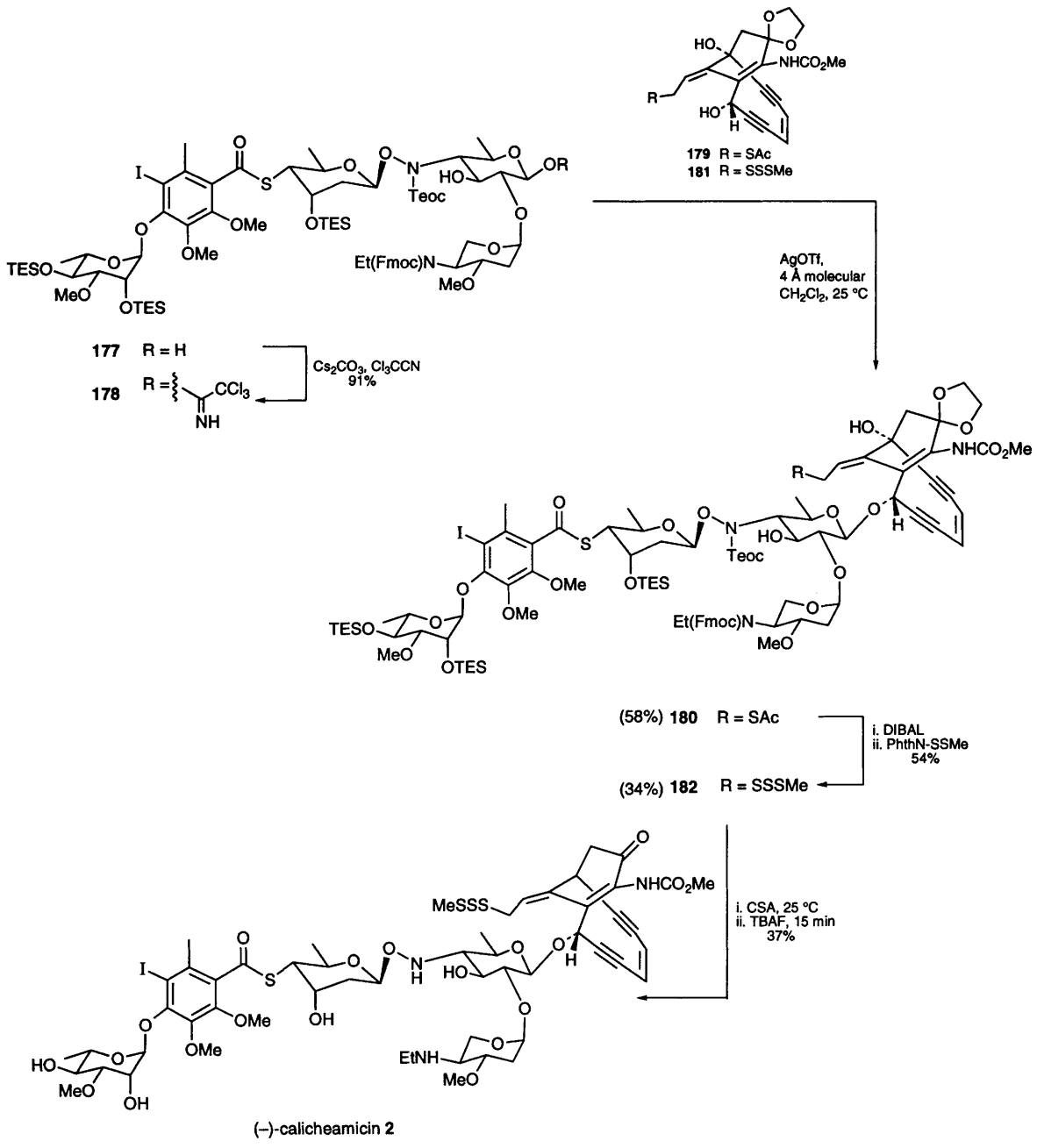
Exploratory studies by Danishefsky of the coupling of the free glycoside derivative of **155** with different forms of the calicheamicin aglycone revealed problems associated with the use of the *O*-TBS and *N*-phthalimide protecting groups, and the potential incompatibility of the allylic trisulfide (and other functionality) during fluoride promoted removal of the *N*-Teoc hydroxylamine protecting group.[69,74] In light of these findings and Nicolaou's precedent, they also settled upon use of a *O*-TES/*N*-FMOC substituted oligosaccharide as the glycone precursor to calicheamicin (**Scheme 35**).[82] Coupling of the trichloroacetimidate derivative **178** of lactol **177** with (−)-(*S*)-acetate **179** under modified Schmidt conditions (AgOTf catalyst) gave the desired β-configured product **180** along with the α-isomer in 58% combined yield.[83,84] Only four steps were required to convert this coupling product to (−)-**2**. However, more impressive was the finding that AgOTf catalysed Schmidt coupling of trichloroimidate **178** with the calicheamicinone ketal **181** was possible giving **182** in 34% yield (β-isomer only). From this intermediate (−)-calicheamicin **2** was obtained by successive treatment with CSA and TBAF.

5 Dynemicin analogues and the total synthesis of dynemicin A

Dynemicin A **4** possesses an intriguing hybrid structure composed of a calicheamicin/esperamicin enediyne core structure condensed to an


168 R =
169 R = H
170 R =
hv, 82%
NaH, Cl3CCN
98%
BF3•OEt2
–40 °C, 76%
171
172 R = TES, X = OBz
i. DIBAL
ii. Ph3P, DEAD, AcSH
iii. HF•py
79%
173 R = H, X = SAc
NaBH3CN, BF3•OEt2
–40 °C, 80%
174 R = H, X = SAc
175 R = TES, X = SSSMe
i. TESOTf
ii. DIBAL
iii. PhthN–SSMe
56%
HF•py
18 h, 90%
176 R = FmOC, X = O(CH2)2O
(–)-calicheamicin 2 R = H, X = O
i. TsOH, 70%
ii. Et2NH, 90%

Scheme 34



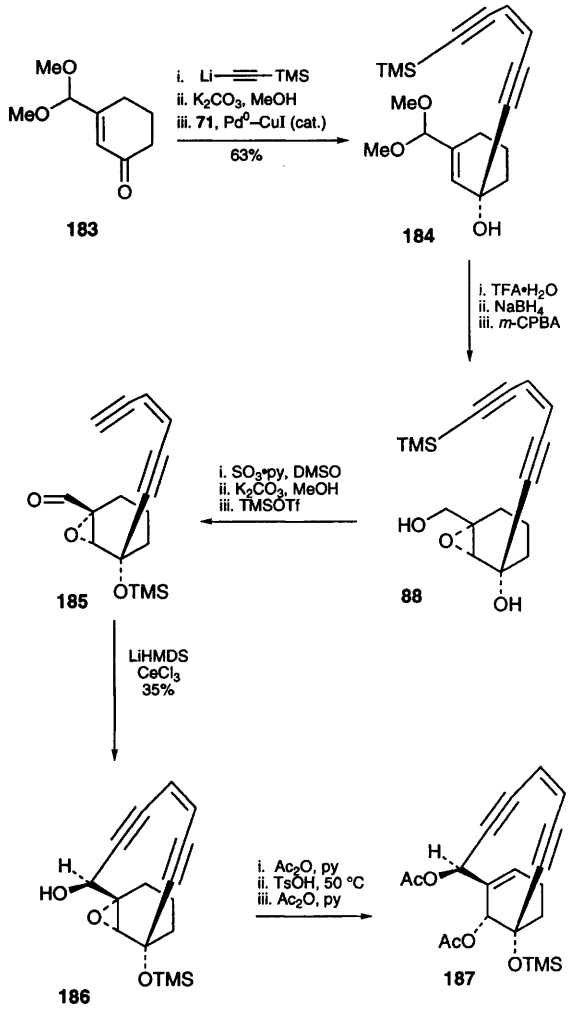
Scheme 35

anthraquinone unit characteristic of the anthracycline antibiotics. Between these two subunits is the epoxide trigger which is highly susceptible to ring opening in intermediates wherein the anthraquinone system is reduced to the hydroquinone level. Particular care must thus be taken during construction of dynemicin to either maintain the anthraquinone component in a protected form, and/or in the correct oxidation state.

The strategies which have evolved for the synthesis of antibiotic **4** include a linear approach in which the pentacyclic 'platform' structure (rings A–E) is elaborated before attempting introduction of the epoxide ring, the enediyne bridge and other functionality onto the A-ring, and a second, more convergent 'biomimetic' approach in which the enediyne core structure is joined to an anthraquinone derivative via formation of the C_8–C_9 and C_2–N_1 bonds. However, the approach which has been most extensively developed to access dynemicin and simplified fully functional analogues involves the use of quinoline or phenanthridine derivatives as B–C and A–B–C ring precursors onto which the enediyne/epoxide system can be elaborated, followed by the D–E rings. This later strategy was adapted by Myers and Danishefsky in their respective total syntheses of dynemicin A, and by Schreiber *et al.* in their synthesis of the di-*O*-methyl ether–methyl ester of **4**.

5.1 A-ring 'biomimetic' approach

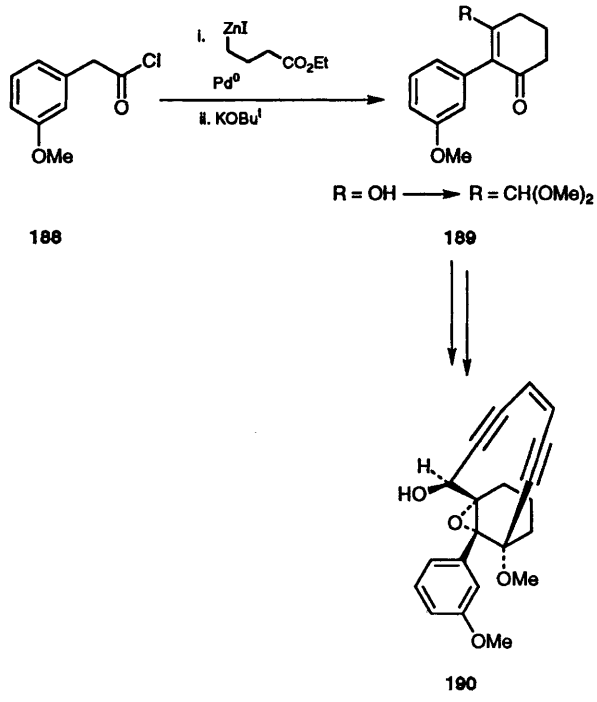
To access the enediyne core component of dynemicin equipped with the epoxide trigger, Isobe showed that the ketal enone **183** can be converted selectively via **184** to the epoxy diol intermediate **88** (**Scheme 36**).[85] Cyclization of the corresponding aldehyde **185** to the bicyclic dynemicin analogue **186** proved feasible using the LHMDS/$CeCl_3$ combination. Note that treatment of the acetate derivative of **186** with TsOH gives **187**, providing a convenient link to the calicheamicin series (see Scheme 17).



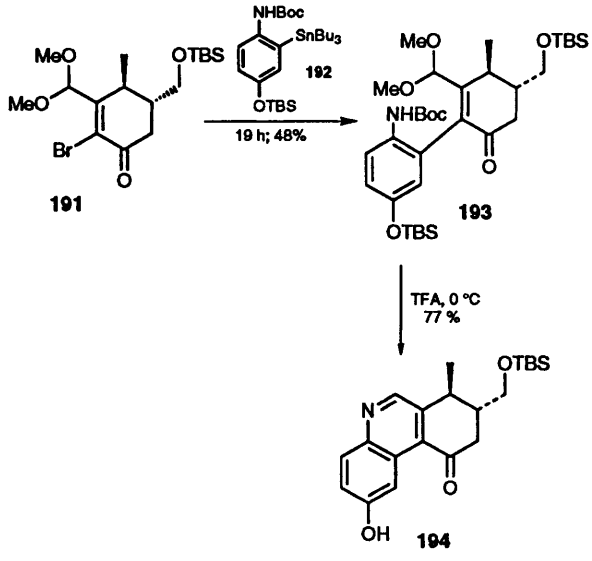
Scheme 36

In a more recent study Maier has synthesized the related enediyne **190** in which one of the connections is made to the oxygenated C-ring (**Scheme 37**).[86] The starting ketal enone **189** for this study was prepared in five steps from acid chloride **188**.

Addressing the problem of making the C_8–C_9 connection and closing the B-ring in a biomimetic type synthesis of **4**, Isobe showed that palladium based coupling of the more highly functionalized A-ring bromide **191** with the aryl tin derivative **192**



Scheme 37



Scheme 38

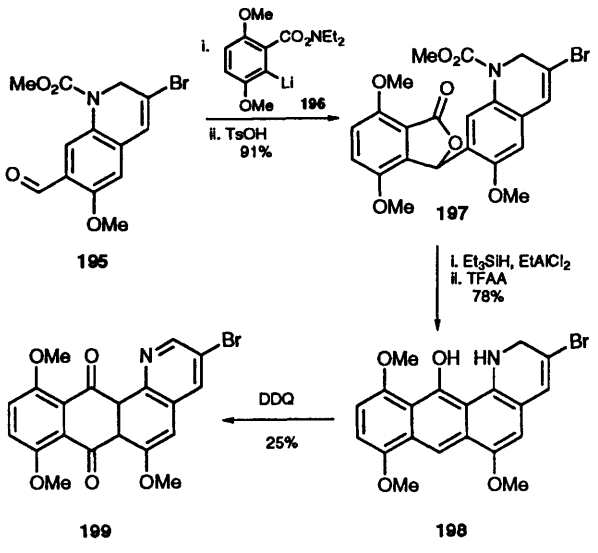
could be achieved (**Scheme 38**).[87] Treatment of intermediate **193** with TFA in CH_2Cl_2 then gave the A–B–C ring synthon **194** in 77% yield.

5.2 Anthraquinone 'platform' assembly

Construction of the anthraquinone portion of dynemicin A has been undertaken by several groups, with the idea in mind either to use this material as a synthetic intermediate on the way to **4**, or to evaluate methodology which will subsequently be applied for the elaboration of the D–E rings in late stage intermediates which already contain the

enediyne/epoxide moieties. The possibility that synthetically derived anthraquinones may themselves display antitumour properties is of further interest.

Within the latter synthetic context Schreiber developed a route to the angular anthraquinone **199**, involving condensation of the quinoline derived aldehyde **195** with the lithiated benzamide derivative **196**, followed by reduction of lactone **197** and intramolecular Friedel–Crafts cyclization to the air sensitive anthracenol **198** (**Scheme 39**).[88] Treatment of this intermediate with DDQ provided **199** in 25% yield.

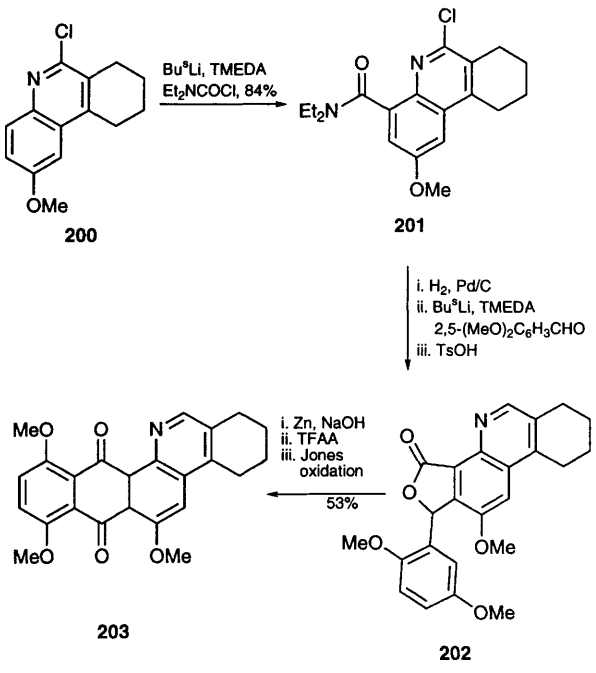


Scheme 39

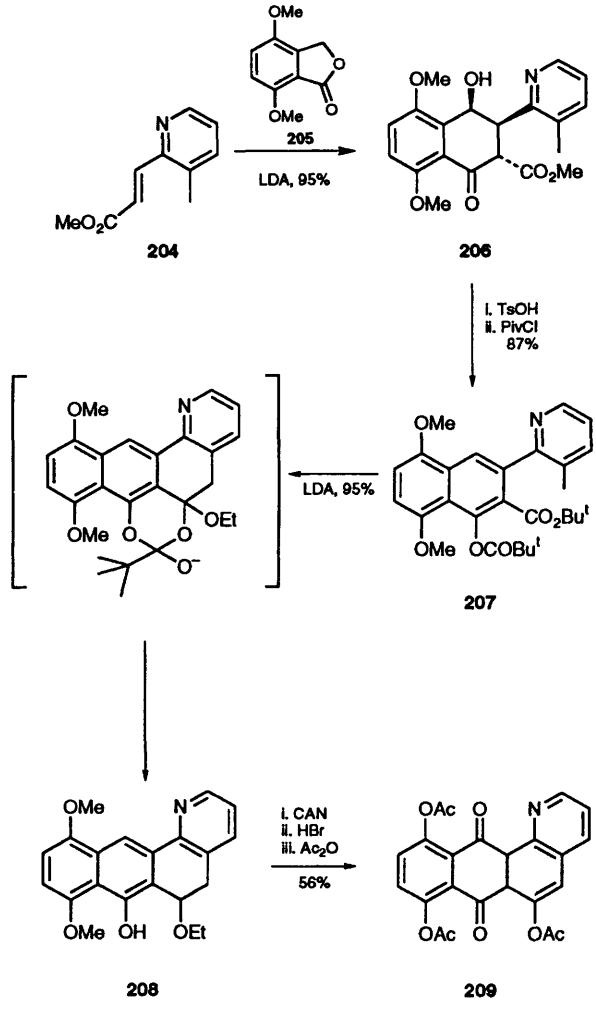
Nicolaou's route to the pentacyclic compound **203** (**Scheme 40**) began with directed metalation of the phenanthridine intermediate **200** and reaction with diethylcarbamoyl chloride (84%).[89] Hydrogenolysis of the C–Cl bond in **201** was then followed by a second metalation reaction with 2,5-dimethoxybenzaldehyde and lactonization. Reduction of lactone **202**, ring closure and oxidation with Jones reagent gave **203** (53% overall).

Magnus *et al.* have also devised a synthesis of the B to E rings of dynemicin (**Scheme 41**) via a seven step sequence in which compound **206** is obtained by conjugate addition of the anion of lactone **205** to the α,β-unsaturated ester **204** followed by aromatization and *O*-pivaloate formation (85% overall).[90] Reaction of **207** with LDA then leads to ethyl ether **208** which is converted to **209** after oxidation (CAN), deprotection and reaction with acetic anhydride.

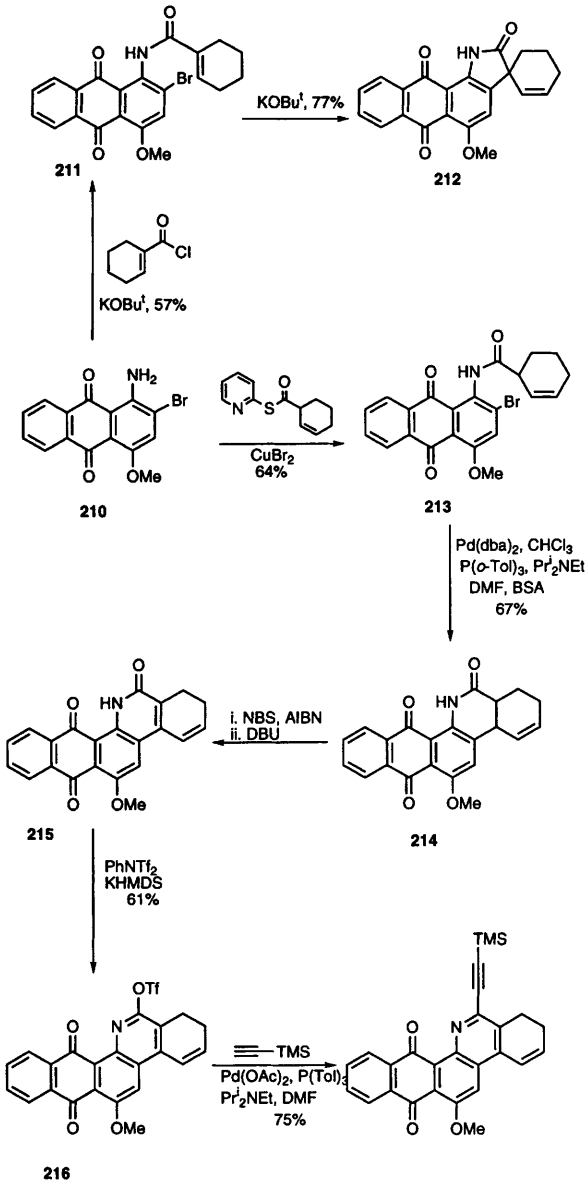
Starting from the readily available anthraquinone derivative **210**, Isobe and co-workers prepared the pentacycle **215** (**Scheme 42**).[91] Remarkably, all efforts to cyclize the conjugated amide intermediate **211** to a 6-membered ring product led instead to spirocycle **212**. This situation was countered by effecting a Pd catalysed Heck type reaction of the



Scheme 40



Scheme 41



Scheme 42

corresponding β,γ-unsaturated amide **213**, which proceeds through the preferred *exo-trig* pathway giving the pentacyclic amide **214** (9:1 with double bond isomer). Reaction of this product with NBS–AIBN and base then permitted conversion to pyridone **215**. Attempts to close the enediyne bridge across carbons 2 and 7 (dynemicin numbering) in this product through reaction at the amide carbonyl centre failed.[92] However, Isobe's group has recently developed Pd catalysis conditions for replacement of the triflate group in **216** by an acetylene function.[93] Note the mild conditions of this reaction, plus the fact that no inorganic salt additives are required.

5.3 Nor-D,E dynemicin analogues: the total synthesis of dynemicin A

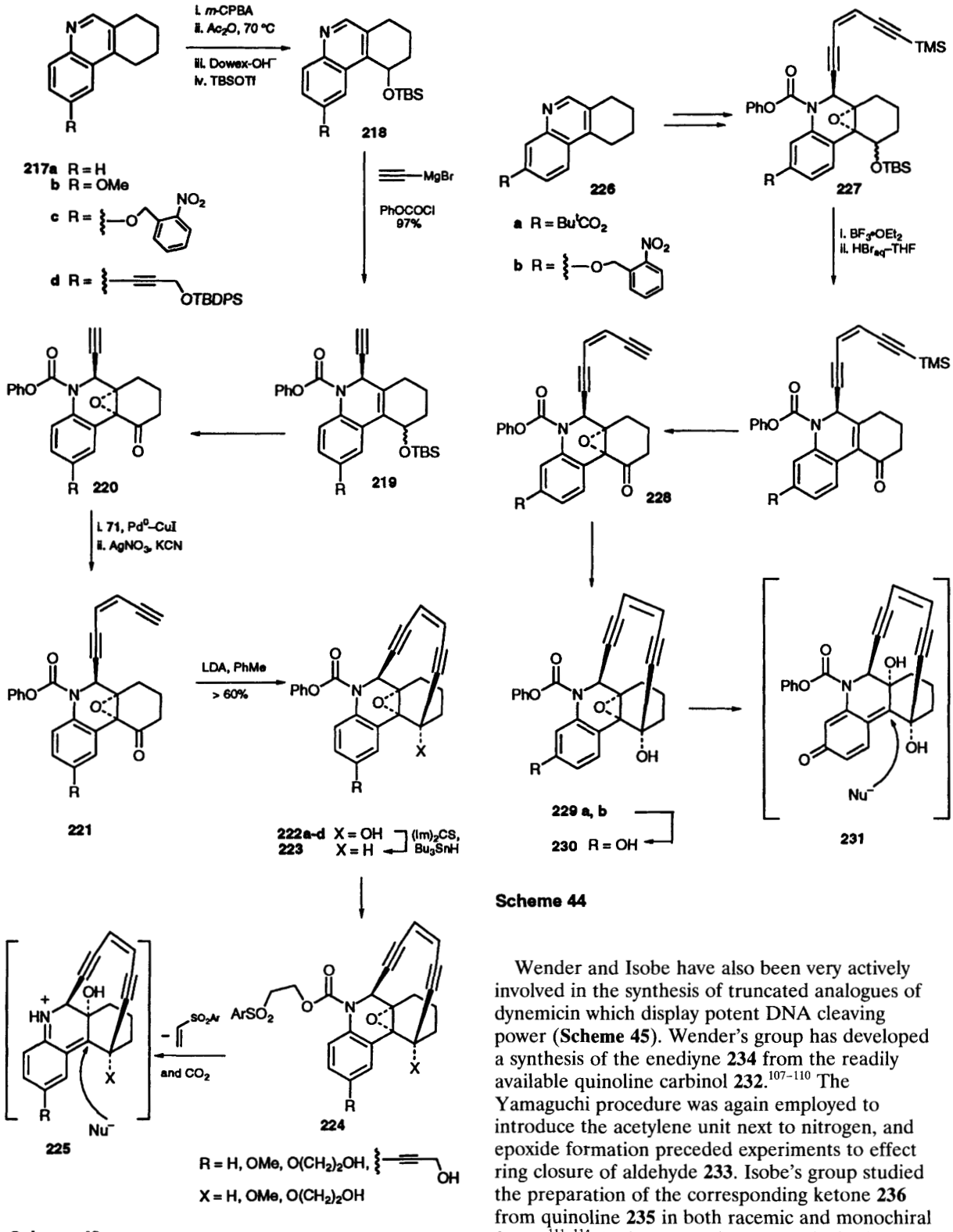
An impressive contribution to the chemistry and biological study of dynemicin has been made by Nicolaou and co-workers, who have focused their activity on the synthesis of dynemicin analogues lacking the D and E rings.[94–103] In many respects this effort has been fuelled by the fact that diversely functionalized derivatives of phenanthridines **217a–d** and **226a,b** could readily be obtained as starting substrates[104] (**Schemes 43 and 44**), and by the fact that the derived model compounds retain the capacity to undergo epoxide opening–Bergman cycloaromatization, displaying potent DNA cleaving power.

Introduction of oxygen functionality at C-10 in compounds **217a–d** was achieved by acetic anhydride promoted rearrangement of their *N*-oxide derivatives (**Scheme 43**).[94–96,105] For the next step, Yamaguchi type reaction of compounds **218** with ethynyl magnesium bromide and benzoyl chloride proved to be a very effective means for introduction of the acetylene unit at C-6 in **219** (3:1 mixture, 97%).[106] Epoxidation of this intermediate occurred uniquely from the face opposite the ethynyl group, giving ketone **220** (after *O*-desilylation and PCC oxidation). The acyclic enediyne unit was then constructed through Pd^0–CuI catalysed reaction with *cis*-chloro enyne **71** and TMS cleavage ($AgNO_3$–KCN). Cyclization of compounds **221** to the dynemicin analogues **222a–d** was achieved using LDA at −78 °C (>60%).

It should be emphasized that it was necessary to install the epoxide unit before this ring closure, otherwise a strained product would be formed in which the olefinic double bond is severely distorted. Notice also that, in contrast to studies on calicheamicin, the reactivity of the ketone carbonyl in **21** was sufficient for closure of the enediyne bridge to take place. In a similar manner the synthetic strategy was extended to include benzodiyne analogues of dynemicin in which the central double bond of the enediyne system in **222** was replaced by a phenyl and a naphthalene ring.[97,98] Reaction of the ketone derived from **219a** with (2*R*,3*R*)-butane-2,3-diol also permitted access to enediyne **222a** in enantiomerically pure form.[99] Further reductive removal of the C-7 hydroxy group in compounds **222** gave the analogues **223**.

Compound **222a** did not display any DNA cleavage activity when incubated with DNA. However, the corresponding free amine caused significant damage to DNA. This observation was pursued and confirmed in tumour culture assays using the base labile *N*-2-(phenylsulfonyl)-ethoxycarbonyl derivatives **224**.[100–102] These results indicate that in its free form the amine nitrogen assists epoxide ring opening producing an *o*-quinone methide type intermediate **225** which picks up a nucleophile and cycloaromatizes.

For preparation of the dynemicin analogues **229a,b** the synthetic plan had to be modified such that the enediyne system was assembled first, in order to allow for the sensitivity of the epoxide system to the presence of the C-12 oxygen substituent (**Scheme 44**).[103] In fact the epoxide system in **227** is opened and reformed giving **228**

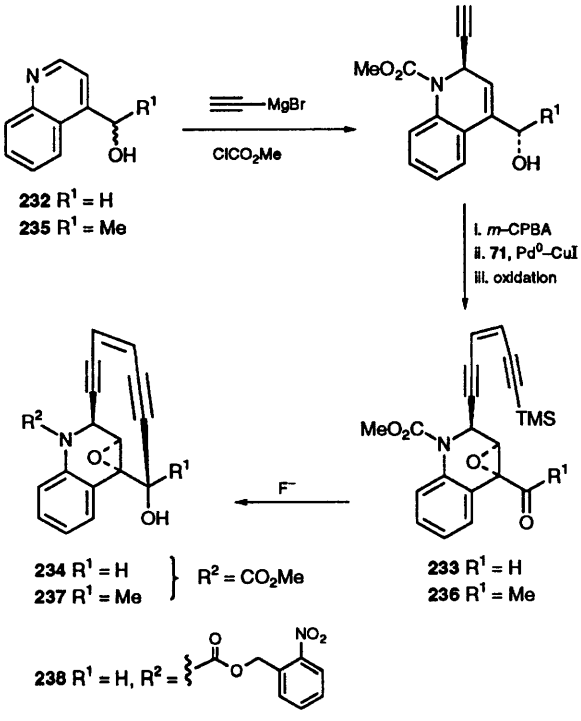


Scheme 43

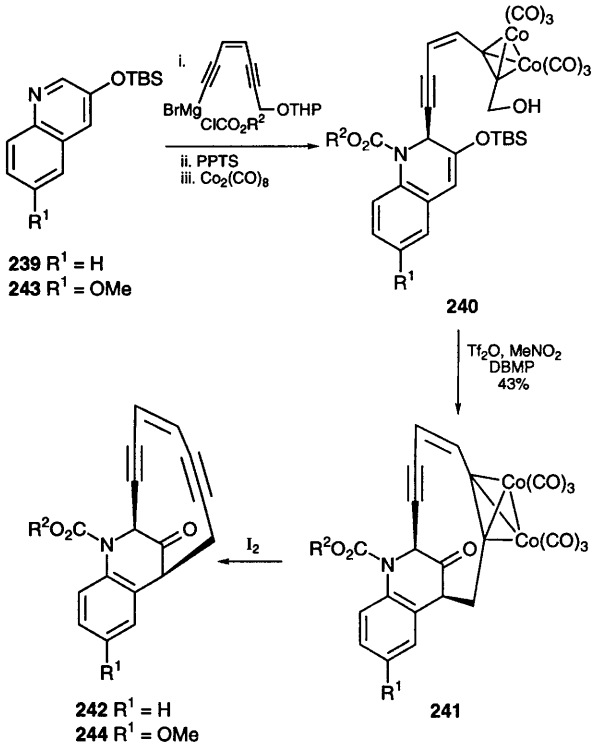
prior to cyclization. Compounds **229** were also shown to be mechanism based analogues of dynemicin, their free phenol form **230** rearranging to the *p*-quinone methide intermediate **231** which reacts with added nucleophiles giving a species which spontaneously cycloaromatizes.[100,102]

Scheme 44

Wender and Isobe have also been very actively involved in the synthesis of truncated analogues of dynemicin which display potent DNA cleaving power (**Scheme 45**). Wender's group has developed a synthesis of the enediyne **234** from the readily available quinoline carbinol **232**.[107–110] The Yamaguchi procedure was again employed to introduce the acetylene unit next to nitrogen, and epoxide formation preceded experiments to effect ring closure of aldehyde **233**. Isobe's group studied the preparation of the corresponding ketone **236** from quinoline **235** in both racemic and monochiral forms.[111–114] An important innovation by both groups in the enediyne field was the finding that direct condensation of the TMS protected acetylene with the carbonyl function in **233** and **236** could be achieved upon treatment with fluoride ion. Wender further showed that the yield of this transformation could be markedly improved by reacting the cyclized alkoxide intermediate with Ac_2O (or other electrophiles) prior to extractive work-up.[108]



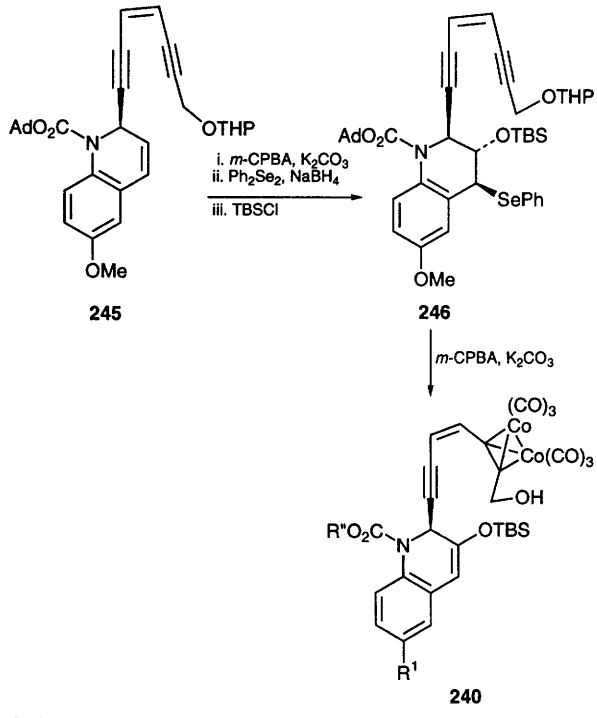
Scheme 45



Scheme 46

Photochemical cleavage of the *o*-nitrobenzyl-carbamate protecting group in **238** proved to be a very effective way to generate and study the cycloaromatization chemistry of the derived amine.[109,110]

Starting from the TBS ether **239** of 3-hydroxyquinoline, Magnus *et al.* achieved regioselective introduction of the entire enediyne chain giving **240** after cobalt carbonyl complexation (**Scheme 46**).[115] Providing nitromethane, a polar cation solvating solvent, was employed in the subsequent cyclization step (a Nicholas reaction), the desired product **241** was obtained in 43% yield. Liberation of the acetylene moiety gave the dynemicin analogue **242**, which proved to be remarkably stable to Bergman cyclization compared to **94**. In a closely related fashion formation of enediyne **244** from the 6-methoxyquinoline derivative **243** was achieved. However, the difficulty in accessing the starting material for this study led Magnus to conceive an alternative strategy involving epoxidation and selenoxide elimination (**245**→**246**) to introduce the C-3 oxygen substituent (**Scheme 47**).[116]



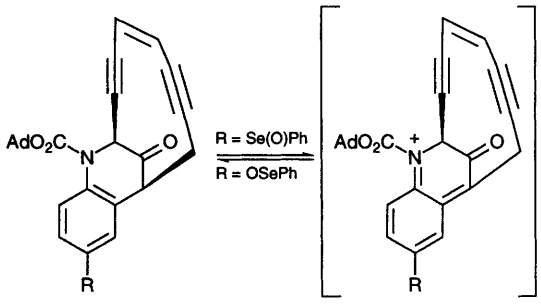
Scheme 47

Two other relevant aspects of the chemistry of these dynemicin systems is the observed isomerization of the bridgehead selenoxide **247** to the corresponding selenite ester **249**, via, most probably, the iminium quinomethide **248** (**Scheme 48**), and the discovery of a nonradical cycloaromatization pathway upon treatment of enediyne **242** with the thiolate ion (**242**→**250**, **Scheme 49**).[116,117]

Recently, Takahashi has developed a promising new approach to the dynemicin system in which the 2,3-Wittig rearrangement reaction of **251** is employed to generate the tetrahydroquinoline intermediate **252** (**Scheme 50**).[118] Dehydration of this intermediate to diene **253** (a *Z,E*:*Z,Z* mixture which is isomerized totally to *Z,Z*-**253** using I_2) opened the way to construction of compound **254**,

and its conversion to **255** in an intramolecular Diels–Alder reaction. Alternatively, compound **253** was reacted with dimethyl acetylenedicarboxylate in an intermolecular cycloaddition sequence to give the compound **256**. Notice that both routes permit control of the C-2,4,7 stereochemistry. In a manner similar to Danishefsky (see Scheme 53), the bis(iodoalkyne) intermediate **256** was coupled with *Z*-bis(trimethylstannyl)ethylene to give the dynemicin analogue **257**.

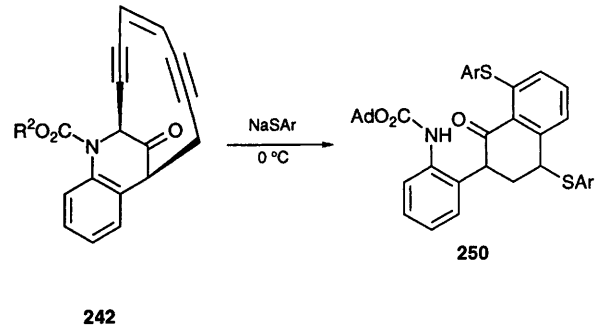
In a very elegant fashion, Schreiber and co-workers have adapted their Diels–Alder approach in the enediyne field to access di-*O*-methyl dynemicin methyl ester **271**. In the initial phase,



247 R = Se(O)Ph
249 R = OSePh

248

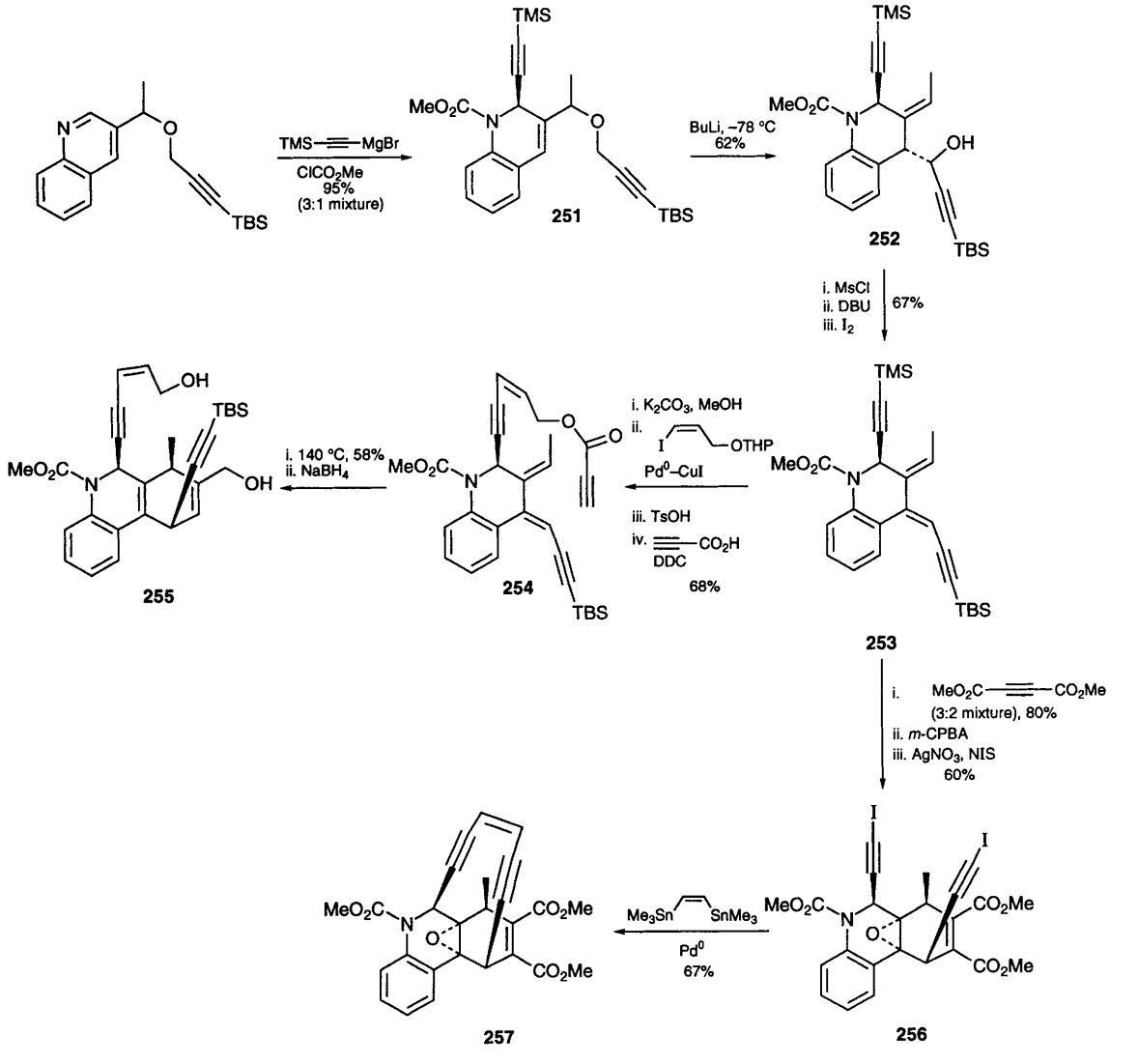
Scheme 48



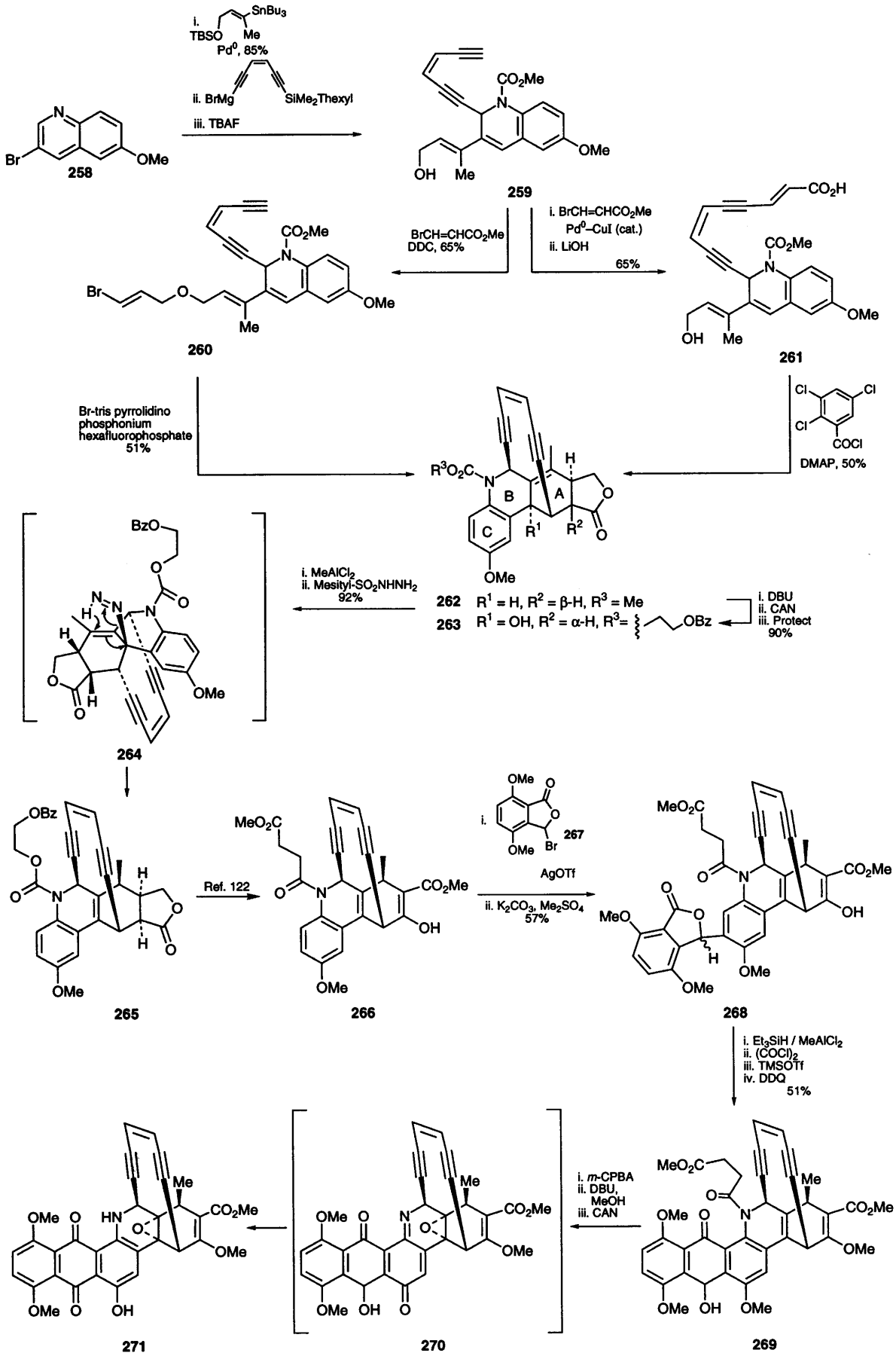
242

250

Scheme 49



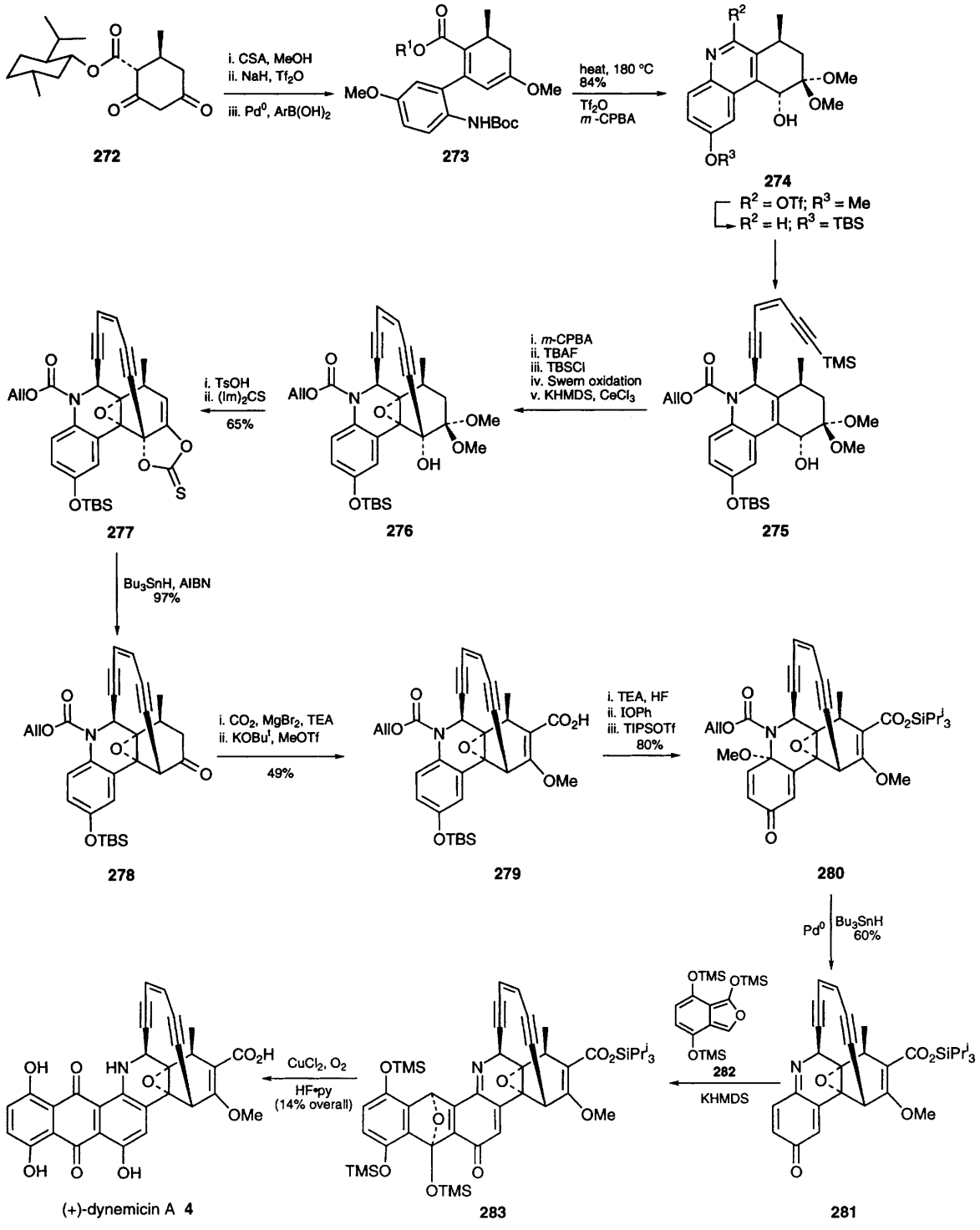
Scheme 50


i. TBSO SnBu3 Me Pd0, 85%
ii. BrMg SiMe2Thexyl
iii. TBAF
258
259
BrCH=CHCO2Me DDC, 65%
i. BrCH=CHCO2Me Pd0–CuI (cat.) ii. LiOH 65%
260
261
Br-tris pyrrolidino phosphonium hexafluorophosphate 51%
DMAP, 50%
i. MeAlCl2 ii. Mesityl-SO2NHNH2 92%
262 R1 = H, R2 = β-H, R3 = Me
263 R1 = OH, R2 = α-H, R3 = OBz
i. DBU ii. CAN iii. Protect 90%
264
Ref. 122
265
266
i. 267 AgOTf ii. K2CO3, Me2SO4 57%
268
i. Et3SiH / MeAlCl2 ii. (COCl)2 iii. TMSOTf iv. DDQ 51%
i. m-CPBA ii. DBU, MeOH iii. CAN
269
270
271

Scheme 51

3-bromo-6-methoxyquinoline **258** was converted to the acyclic enediyne intermediate **259**, which was in turn elaborated to compounds **260** and **261** (**Scheme 51**).[119] Subjection of these intermediates to conditions aimed at achieving macrocyclization led directly to formation of a common product **262**, resulting from an apparent room temperature [4+2] cycloaddition.

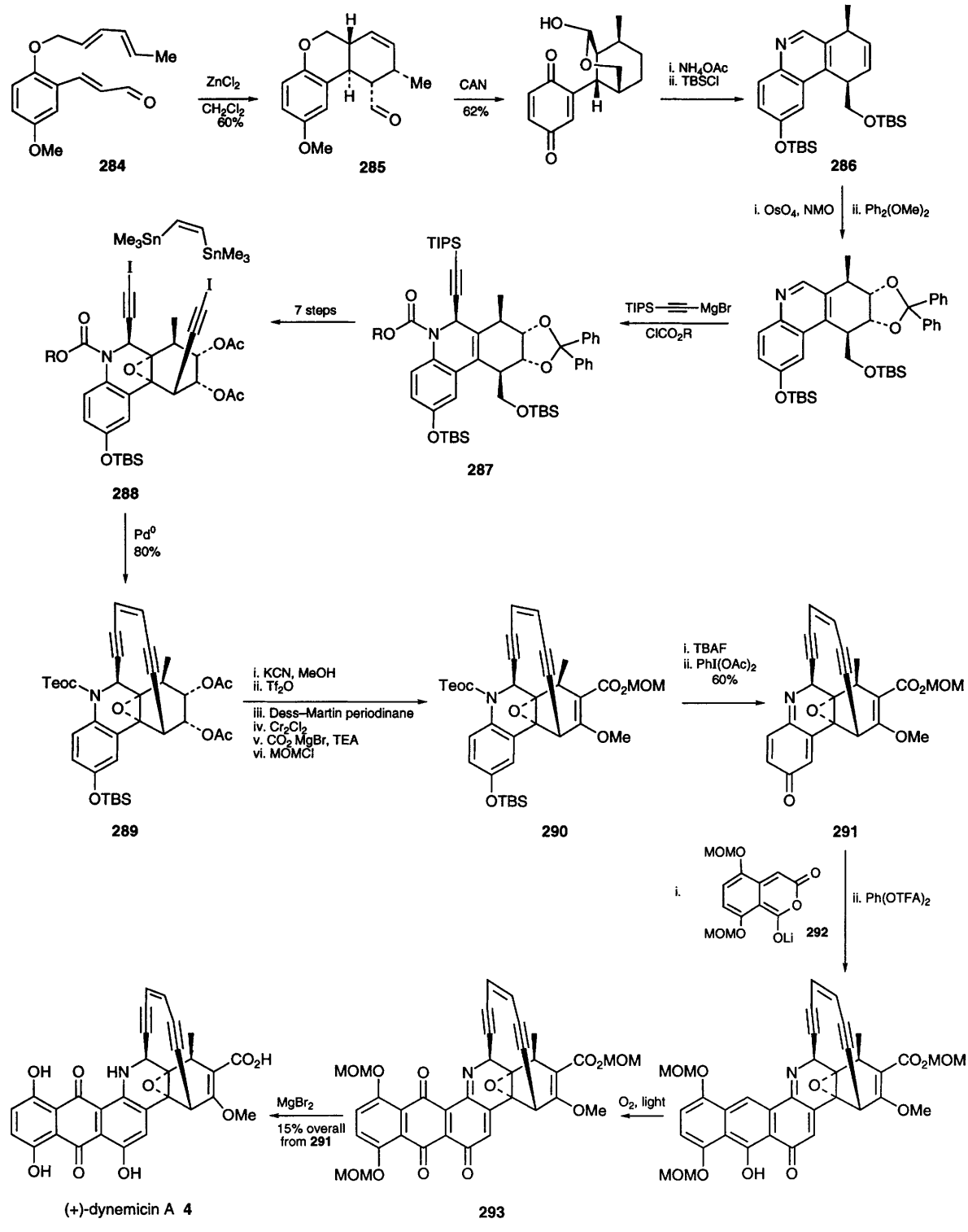
Further experimentation revealed the necessity to epimerize the lactone ring of **262** such that repositioning the double bond to the A–B ring junction position would produce the correct C-4 methyl stereochemistry. Thus, after *N*-protecting group modification, reaction with DBU and oxidation with CAN gave **263**, which was reacted with $EtAlCl_2$ at low temperature followed by quenching with mesitylenesulfonylhydrazide. In this way the desired product **265** was produced via a [1,5]-sigmatropic rearrangement of the diazene intermediate **264**. At this point the A-ring enol ester



Scheme 52

system of **266** was elaborated by oxidative cleavage of the lactone ring, and the *N*-protecting group was further modified to enhance its base lability.

Under precise conditions, the silver triflate promoted Freidel–Crafts reaction of **266** with **267** produced compounds **268** (1:1 mixture) in 57% yield. This intermediate was then converted to the hexacyclic ketol **269** (51% overall) exploiting technology developed for a model system (see Scheme 39). In the final, delicate steps of the synthesis the epoxide unit was introduced, the D-ring nitrogen was deprotected, and the resultant intermediate was oxidized using CAN to give the target molecule **271**. It is remarkable that the *N*-deprotected compound could be converted to the iminoquinone intermediate **270** before total loss of



Scheme 53

the molecule occurred through the competing dynemicin cycloaromatization pathway.

In their first synthesis of (+)-dynemicin A, Myers *et al.* settled the problem of the C-4 methyl stereochemistry in the first steps through the use of monochiral diketone **272** as the A-ring precursor (**Scheme 52**).[120] Pd^0 catalysed condensation of the enol triflate of this intermediate with *tert*-butyl-2-borono-4-methoxycarbinolate gave compound **273**, which was ring closed and converted to hydroxy ketal **274**. Introduction of the epoxide unit and enediyne bridge was then undertaken giving **276**. Note that the alcohol function and one of the methoxy oxygens played a critical role in directing acetylene addition to the same face of **275** as the methyl substituent.

At this juncture ketal deprotection and reaction of cyclic thiocarbonate **277** with tin hydride produced ketone **278**. In a very expeditious manner this ketone was converted in two steps (CO_2, $MgBr_2$, Et_3N then $KOBu^t$, MeOTf) to the enol methyl ether carboxylic acid **279**. Reaction of the desilylated phenol derivative of **279** with iodosobenzene afforded compound **280**, which on *N*-deprotection was transformed to the stable quinone imine **281**. To build up the A–B rings of dynemicin a series of different isobenzofurans derivatives were evaluated as Diels–Alder dienophiles. The combination which led to (+)-dynemicin A **4** involved cycloaddition of quinone imine **281** with the tris(trimethylsilyl-oxy)isobenzofuran **282** followed by air oxidation and deprotection of the derived Diels–Alder adduct **283**.

In Danishefsky's total synthesis of (±)-dynemicin, Diels–Alder chemistry was used in the initial steps to fix the stereochemistry of the C-4 and C-7 centres (**Scheme 53**).[121] This involved Lewis acid mediated intramolecular cycloaddition of compound **284**, oxidation of the derived hydroquinone **285** and B-ring closure giving **286**. *cis*-Dihydroxylation of **286** and ketal formation encumbered the lower face of the molecule, thereby directing introduction of the acetylene at C-2 in the required fashion (7:1 mixture) to give **287**. Seven steps were subsequently needed to construct the C-7 acetylene, modify the hydroxy protection and iodinate both alkyne units giving **288**. In a new innovation brought to the dynemicin field, the enediyne bridge was then installed by Pd^0 coupling of **288** with *Z*-bis(trimethylstannyl)ethylene producing the enediyne product **289**. After subsequent acetate cleavage and removal of the C-5 hydroxy group, the resultant intermediate, the C-5,6 enol ether–ester system of **290** was elaborated. *O*-TBS deprotection and treatment with $PhI(OAc)_2$ then produced the key iminoquinone product **291**. The D–E rings were built onto this substrate through reaction with the lithium anion of the homophthalic anhydride **292**, followed by oxidation of the derived adduct. Exposure of this product to oxygen and light followed by *O*-MOM deprotection of quinone **293** completed the synthesis of dynemicin A **4**.

6 Conclusion

The total synthesis of dynemicin A by Myers and Danishefsky, like the accomplishments in the calicheamicin/esperamicin and neocarzinostatin area, marks just the beginning of what will be a rich harvest of knowledge which synthetic chemists will employ in the construction of the enediyne- and dienediyne-containing molecules that nature still has in waiting.

7 References and notes

1 N. Ishida, K. Miyazaki, K. Kumagai and M. Rikimaru, *J. Antibiot.*, 1965, **18**, 68; K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Otake and N. Ishida, *Tetrahedron Lett.*, 1985, **26**, 331.

2 M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3464; M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3466.

3 J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K.-I. Saitoh and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3461; J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K.-I. Saitoh and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3462.

4 M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne and J. Clardy, *J. Am. Chem. Soc.*, 1990, **112**, 3715.

5 G. Pratviel, J. Bernadou and B. Meunier, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 746; *Enediyne Antibiotics as Antitumor Agents*, ed. D. B. Broders and T. W. Doyle, Marcel Dekker, New York, 1994.

6 See Part 1 of this review: H. Lhermitte and D. S. Grierson, *Contemp. Org. Synth.*, 1996, **3**, 41.

7 R. R. Jones and R. G. Bergman, *J. Am. Chem. Soc.*, 1972, **94**, 660; R. G. Bergman, *Acc. Chem. Res.*, 1973, **6**, 25; T. P. Lockhart, P. B. Comita and R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4082; T. P. Lockhart and R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4091.

8 A. G. Myers, *Tetrahedron Lett.*, 1987, **28**, 4493; I. H. Goldberg, *Acc. Chem. Res.*, 1991, **24**, 191.

9 P. A. Wender, M. Harmata, D. Jeffrey, C. Mukai and J. Suffert, *Tetrahedron Lett.*, 1988, **29**, 909.

10 See Scheme 36 and reference 74 in Part 1 of this review.[6]

11 K. Mikami, H. Matsueda and T. Nakai, *Synlett*, 1993, 23.

12 P. A. Wender, J. A. McKinney and C. Mukai, *J. Am. Chem. Soc.*, 1990, **112**, 5369.

13 P. A. Wender, J. W. Grissom, U. Hoffmann and R. Mah, *Tetrahedron Lett.*, 1990, **31**, 6605.

14 Y. Okude, S. Hirano, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 3179.

15 A. Krebs, T. Wehlage and C.-P. Kramer, *Tetrahedron Lett.*, 1990, **31**, 3533.

16 T. Doi and T. Takahashi, *J. Org. Chem.*, 1991, **56**, 3465.

17 T. Takahashi, H. Tanaka, Y. Hirai, T. Doi, H. Yamada, T. Shiraki and Y. Sugiura, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1657.

18 See also: S. Caddick and S. Khan, *J. Chem. Soc., Chem. Commun.*, 1995, 1971.
19 P. Magnus and T. Pitterna, *J. Chem. Soc., Chem. Commun.*, 1991, 541.
20 P. Magnus and M. Davies, *J. Chem. Soc., Chem. Commun.*, 1991, 1522.
21 A. G. Myers, M. A. M. Fundy and P. A. Lindstrom Jr., *Tetrahedron Lett.*, 1988; **29**, 5609; A. G. Myers, M. M. Alauddin, M. A. M. Fuhry, P. S. Dragovich, N. S. Finney and P. M. Harrington, *Tetrahedron Lett.*, 1989, **30**, 6997; A. G. Myers, P. M. Harrington and E. Y. Kuo, *J. Am. Chem. Soc.*, 1991, **113**, 694; A. G. Myers, P. M. Harrington and B.-M. Kwon, *J. Am. Chem. Soc.*, 1992, **114**, 1086.
22 See also: N. A. Petasis and K. A. Teets, *Tetrahedron Lett.*, 1993, **34**, 805.
23 K.-I. Yoshida, Y. Minami, R. Azuma, M. Saeki and T. Otani, *Tetrahedron Lett.*, 1993, **34**, 2637.
24 J. E. Leet, D. R. Schroeder, F. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc.*, 1992, **114**, 4976; J. E. Leet, D. R. Schroeder, D. R. Langley, K. L. Colson, S. Huang, S. E. Klohr, M. S. Lee, J. Golik, S. J. Hofstead, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc.*, 1993, **115**, 8432.
25 K.-I. Iida and M. Hirama, *J. Am. Chem. Soc.*, 1994, **116**, 10310.
26 K.-I. Iida and M. Hirama, *J. Am. Chem. Soc.*, 1995, **117**, 8875.
27 K. C. Nicolaou, G. Zuccarello, C. Riemer, V. A. Estevez and W.-M. Dai, *J. Am. Chem. Soc.*, 1992, **114**, 7360.
28 K.-I. Iida, T. Ishii, M. Hirama, T. Otani, Y. Minami and K.-I. Yoshida, *Tetrahedron Lett.*, 1993, **34**, 4079.
29 T. Vuljanic, J. Kihlberg and P. Somfai, *Tetrahedron Lett.*, 1994, **35**, 6937.
30 D. Guillerm and G. Linstrumelle, *Tetrahedron Lett.*, 1985, **26**, 3811; K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467; K. P. C. Vollhardt and L. S. Winn, *Tetrahedron Lett.*, 1985, **26**, 709; S. J. Danishefsky, D. S. Yamashita and N. B. Mantlo, *Tetrahedron Lett.*, 1988, **37**, 4681; see also: K. Sonogashira, in *Comprehensive Organic Synthesis*; ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, **3**, pp. 521–549.
31 A. S. Kende and C. A. Smith, *Tetrahedron Lett.*, 1988, **29**, 4217.
32 J. N. Haseltine, M. P. Cabal, N. B. Mantlo, N. Iwasawa, D. S. Yamashita, R. S. Coleman, S. J. Danishefsky and G. K. Schulte, *J. Am. Chem. Soc.*, 1991, **113**, 3850; J. N. Haseltine and S. J. Danishefsky, *J. Org. Chem.*, 1990, **55**, 2576; M. P. Cabal, R. S. Coleman and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1990, **112**, 3253; J. N. Haseltine, S. J. Danishefsky and G. K. Schulte, *J. Am. Chem. Soc.*, 1989, **111**, 7638; N. B. Mantlo and S. J. Danishefsky, *J. Org. Chem.*, 1989, **54**, 2781; S. J. Danishefsky, N. B. Mantlo and D. S. Yamashita, *J. Am. Chem. Soc.*, 1989, **111**, 7638; N. B. Mantlo and S. J. Danishefsky, *J. Org. Chem.*, 1989, **54**, 2781; S. J. Danishefsky, N. B. Mantlo and D. S. Yamashita, *J. Am. Chem. Soc.*, 1988, **110**, 6890.
33 E. Alder, S. Brasen and H. Miyake, *Acta Chem. Scand.*, 1971, **25**, 2055; H.-D. Becker, T. Bremholt and E. Alder, *Tetrahedron Lett.*, 1972, 4205.
34 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277; D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.
35 D. L. Comins and J. D. Brown, *Tetrahedron Lett.*, 1981, **22**, 4213.
36 D. N. Harpp and J. G. Gleason, *J. Am. Chem. Soc.*, 1971, **93**, 2437; D. N. Harpp and D. K. Ash, *J. Chem. Soc., Chem. Commun.*, 1991, 541; D. N. Harpp and R. A. Smith, *J. Am. Chem. Soc.*, 1982, **104**, 6045.
37 A. L. Smith, E. N. Pitsinos, C.-K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scariato, T. Suzuki and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1993, **115**, 7612; A. L. Smith, C.-K. Hwang, E. Pitsinos, G. R. Scarlato and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1993, **115**, 7612; A. L. Smith, C.-K. Hwang, E. Pitsinos, G. R. Scarlato and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1992, **114**, 3134.
38 J. Golik, B. Krishnan, T. W. Doyle, G. VanDuyne and J. Clardy, *Tetrahedron Lett.*, 1992, **33**, 6049.
39 J. Aiyar, S. A. Hitchcock, D. Denhart, K. K. C. Liu, S. J. Danishefsky and D. M. Crothers, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 855.
40 T. Skrydstrup, H. Audrain, G. Ulibarri and D. S. Grierson, in *Recent Progress in the Chemical Synthesis of Antibiotics*, ed G. Lukacs, Springer-Verlag, Berlin, 1993, vol. II, pp. 213–292.
41 G. Ulibarri, T. Skrydstrup, H. Audrain and D. S. Grierson, *J. Org. Chem.*, 1995, **60**, 2753.
42 J. F. Kadow, D. J. Cook, T. W. Doyle, D. R. Langley, K. M. Pham, D. M. Vyas and M. D. Wittman, *Tetrahedron*, 1994, **50**, 1519.
43 T. Nishikawa, S. Shibuya and M. Isobe, *Synlett*, 1994, 482.
44 H. Mastalerz, T. Doyle, J. Kadow, K. Leung and D. Vyas, *Tetrahedron Lett.*, 1995, **36**, 4927.
45 P. Magnus, P. Carter, J. Elliott, R. Lewis, J. Harling, T. Pitterna, W. E. Bauta and S. Fortt, *J. Am. Chem. Soc.*, 1992, **114**, 2544; P. Magnus, R. T. Lewis and J. C. Huffman, *J. Am. Chem. Soc.*, 1988, **110**, 6921; P. Magnus and P. A. Carter, *J. Am. Chem. Soc.*, 1988, **110**, 1626.
46 General overviews: P. Magnus, *Tetrahedron*, 1994, **50**, 1397; P. Magnus, in *Organometallic Reagents in Organic Synthesis*, Academic Press, 1994, pp. 1–32.
47 For related work, see: K. Tomioka, H. Fujita and K. Koga, *Tetrahedron Lett.*, 1989, **30**, 851; J. F. Kadow, M. G. Saulnier, M. M. Tun, D. R. Langley and D. M. Vyas, *Tetrahedron Lett.*, 1988, **30**, 3499.
48 P. Magnus, R. T. Lewis and F. Bennett, *J. Am. Chem. Soc.*, 1992, **114**, 2560.
49 P. Magnus and F. Bennett, *Tetrahedron Lett.*, 1989, **30**, 3637; P. Magnus and R. T. Lewis, *Tetrahedron Lett.*, 1989, **30**, 1905.
50 P. Magnus, R. T. Lewis and F. Bennet, *J. Chem. Soc., Chem. Commun.*, 1989, 916.
51 P. Magnus, H. Annoura and J. Harling, *J. Org. Chem.*, 1990, **55**, 1709.
52 J. F. Kadow, M. M. Tun, D. M. Vyas, M. D. Wittman and T. W. Doyle, *Tetrahedron Lett.*, 1992, **33**, 1423.
53 G. P. Roth, D. R. Marshall, J. F. Kadow, S. W. Mamber, W. C. Rose, W. Solomon and N. Zein, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 711.
54 D. A. Clark, F. De Riccardis and K. C. Nicolaou, *Tetrahedron*, 1994, **50**, 11 391.
55 S. L. Schreiber and L. L. Kiessling, *J. Am. Chem. Soc.*, 1988, **110**, 631; S. L. Schreiber and L. L. Kiessling, *Tetrahedron Lett.*, 1989, **30**, 433; F. J. Schoenen, J. A. Porco Jr, S. L. Schreiber, G. D. VanDuyne and J. Clardy, *Tetrahedron Lett.*, 1989, **30**, 3765.
56 S. Walker, J. Murnick and D. Kahne, *J. Am. Chem. Soc.*, 1993, **115**, 7954; D. R. Langley, T. W. Doyle and D. L. Beveridge, *Tetrahedron*, 1994, **50**, 1379; D. R. Langley, J. Golik, B. Krishnan, T. W. Doyle and D. L. Beveridge, *J. Am. Chem. Soc.*, 1994, **116**, 15; S. Walker, D. Gange, V. Gupta and D. Kahne, *J. Am.*

Chem. Soc., 1994, **116**, 3197; T. Li, Z. Zeng, V. A. Estevez, K. U. Baldenius, K. C. Nicolaou and G. F. Joyce, *J. Am. Chem. Soc.*, 1994, **116**, 3709; L. G. Paloma, J. A. Smith, W. J. Chazin and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1994, **116**, 3697; M. Chatterjee, S. C. Mah, T. D. Tullius and C. A. Townsend, *J. Am. Chem. Soc.*, 1995, **117**, 8074.

57 Syntheses of the C-ring, the D-ring and the C–D ring fragment of calicheamicin **2** include: K. C. Nicolaou, T. Ebata, N. A. Stylianides, R. D. Groneberg and P. J. Carrol, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1097; K. V. Laak and H.-D. Scharf, *Tetrahedron*, 1989, **45**, 5511; K. V. Laak, H. Rainer and H.-D. Scharf, *Tetrahedron Lett.*, 1990, **31**, 4113; S. H. Olson and S. J. Danishefsky, *Tetrahedron Lett.*, 1994, **30**, 7901; see also: references 61, 69 and 74.

58 Two syntheses of the A-ring sugar equipped with the C-4 hydroxylamine substituent have also been developed: H. Rainer and H.-D. Scharf, *Liebigs Ann. Chem.*, 1993, 117; see also: Golik *et al.*, reference 60.

59 For preparation of the C–D aryl monosaccharide unit in esperamicin **3**; see reference 73.

60 In instances where the C-4 hydroxylamine nitrogen and the anomeric centre in ring A are unprotected, very facile rearrangement to a nitrone intermediate occurs: J. Golik, H. Wong, B. Krishnan, D. M. Vyas and T. W. Doyle, *Tetrahedron Lett.*, 1991, **32**, 1851; see also: reference 69.

61 K. C. Nicolaou, R. D. Groneberg, N. A. Stylianides and T. Miyazaki, *J. Chem. Soc., Chem. Commun.*, 1990, 1275.

62 W. R. Roush and J. A. Hunt, *J. Org. Chem.*, 1995, **60**, 798.

63 See also: J. Golik, H. Wong, D. M. Vyas and T. W. Doyle, *Tetrahedron Lett.*, 1989, **30**, 2497.

64 R. D. Groneberg, T. Miyazaki, N. A. Stylianides, T. J. Schultz, W. Stahl, E. P. Schreiner, T. Suzuki, Y. Iwabuchi, A. I. Smith and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1993, **115**, 7593; K. C. Nicolaou, R. D. Groneberg, T. MIyazaki, N. A. Stylianides, T. J. Schulze and W. Stahl, *J. Am. Chem. Soc.*, 1990, **112**, 8193.

65 D. Kahne, D. Yang and M. D. Lee, *Tetrahedron Lett.*, 1990, **31**, 21.

66 D. Kahne, S. Walker, Y. Cheng and D. Van Engen, *J. Am. Chem. Soc.*, 1989, **111**, 6881.

67 S.-H. Kim, D. Augeri, D. Yang and D. Kahne, *J. Am. Chem. Soc.*, 1994, **116**, 1766; D. Yang, S.-H. Kim and D. Kahne, *J. Am. Chem. Soc.*, 1991, **113**, 4715.

68 R. L. Halcomb, M. D. Wittman, S. H. Olson and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1991, **113**, 5080.

69 R. L. Halcomb, S. H. Boyer, M. D. Wittman, S. H. Olson, D. J. Denhart, K. K. C. Liu and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1995, **117**, 5720.

70 J. Theim, H. Karl and J. Schwentner, *Synthesis*, 1978, 696; D. Horton, W. Priebe and M. Sznaidman, *Carbohydr. Res.*, 1990, **205**, 71.

71 E. Da Silva, J. Pradi and J.-M. Beau, *J. Chem. Soc., Chem. Commun.*, 1994, 2127.

72 K. C. Nicolaou and R. D. Groneberg, *J. Am. Chem. Soc.*, 1990, **112**, 4085.

73 K. C. Nicolaou and D. Clark, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 855.

74 R. L. Halcomb, S. H. Boyer and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 338.

75 M. D. Wittman, R. L. Halcomb, S. J. Danishefsky, J. Golik and D. Vyas, *J. Org. Chem.*, 1990, **55**, 1979.

76 Other approaches to the B-ring thio sugar include: F.-Y. Dupradeau, S. Allaire, J. Prandi and J.-M. Beau, *Tetrahedron Lett.*, 1993, **34**, 4513; H.-D. Scharf and K. V. Laak, *Tetrahedron Lett.*, 1989, **30**, 4505; A. Classen and H.-D. Scharf, *Liebigs Ann. Chem.*, 1993, 183; J. Golik, T. W. Doyle, G. Van Duyne and J. Clardy, *Tetrahedron Lett.*, 1990, **31**, 6149.

77 G. O. Spessard, W. K. Chan and S. Masamune, *Org. Synth.*, 1983, **61**, 134.

78 T. Bamhaoud, J.-M. Lancelin and J.-M. Beau, *J. Chem. Soc., Chem. Commun.*, 1992, 1494.

79 K. C. Nicolaou, C. W. Hummel, M. Nakada, S. Shibayama, E. N. Pitsinos, H. Saimoto, Y. Mizuno, K.-U. Baldenius and A. L. Smith, *J. Am. Chem. Soc.*, 1993, **115**, 7625; K. C. Nicolaou, C. W. Hummel, E. N. Pitsinos, M. Nakada, A. L. Smith, K. Shibayama and H. Saimoto, *J. Am. Chem. Soc.*, 1992, **114**, 10 082.

80 K. C. Nicolaou, E. P. Schreiner and W. Stahl, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 585; K. C. Nicolaou, E. P. Schreiner, Y. Iwabuchi and T. Suzuki, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 340.

81 R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 212.

82 S. A. Hitchcock, S. H. Boyer, M. Y. Chu-Moyer, S. H. Olson and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 858; S. A. Hitchcock, M. Y. Chu-Moyer, S. H. Boyer, S. H. Olson and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1995, **117**, 5750.

83 For papers on the enzymatic resolution of synthetic intermediates toward calicheamicinone, see: D. S. Yamashita, V. P. Rocco and S. J. Danishefsky, *Tetrahedron Lett.*, 1991, **32**, 6667; V. P. Rocco, S. J. Danishefsky and G. K. Schulte, *Tetrahedron Lett.*, 1991, **32**, 6671.

84 Concerning the reactivity of compounds related to calicheamicin precursor **180**, see also: K. C. Nicolaou, T. Li, M. Nakada, C. W. Hummel, A. Hiatt and W. Wrasidlo, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 183.

85 T. Nishikawa, M. Isobe and T. Goto, *Synlett*, 1991, 393.

86 M. E. Maier and U. Abel, *Synlett*, 1994, 38.

87 T. Nishikawa and M. Isobe, *Tetrahedron*, 1994, **50**, 5621.

88 H. Chikashita, J. A. Porco Jr, T. J. Stout, J. Clardy and S. L. Schreiber, *J. Org. Chem.*, 1991, **56**, 1692.

89 K. C. Nicolaou, J. L. Gross, M. A. Kerr, R. H. Lemus, K. Ikeda and K. Ohe, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 781.

90 M. Magnus, S. A. Eisenbeis and N. A. Magnus, *J. Chem. Soc., Chem. Commun.*, 1994, 1545.

91 T. Okita and M. Isobe, *Tetrahedron*, 1994, **50**, 11 143.

92 M. Isobe, T. Nishikawa, N. Yamamoto, T. Tsukiyama, A. Ino and T. Okita, *J. Heterocycl. Chem.*, 1992, **29**, 619.

93 T. Okita and M. Isobe, *Synlett*, 1994, 589; T. Okita and M. Isobe, *Tetrahedron*, 1995, **51**, 3737.

94 K. C. Nicolaou, C.-K. Hwang, A. L. Smith and S. V. Wendeborn, *J. Am. Chem. Soc.*, 1990, **112**, 7416.

95 K. C. Nicolaou, A. L. Smith, S. V. Wendeborn and C.-K. Hwang, *J. Am. Chem. Soc.*, 1991, **113**, 3106.

96 K. C. Nicolaou, P. Maligres, T. Suzuki, S. V. Wendeborn, W.-M. Dai and R. K. Chadha, *J. Am. Chem. Soc.*, 1992, **114**, 8890.

97 K. C. Nicolaou, Y.-P. Hong, Y. Torisawa, S.-C. Tsay and W.-M. Dai, *J. Am. Chem. Soc.*, 1991, **113**, 9878.

98 K. C. Nicolaou, W.-M. Dai, Y. P. Hong, S.-C. Tsay, K. K. Baldridge and J. S. Siegel, *J. Am. Chem. Soc.*, 1993, **115**, 7944.

99 K. C. Nicolaou, Y. P. Hong, W.-M. Dai, Z.-J. Zeng and W. Wrasidlo, *J. Chem. Soc., Chem. Commun.*, 1992, 1542.

100 K. C. Nicolaou, W.-M. Dai, S. V. Wendeborn, A. L. Smith, P. Torisawa, P. Maligres and H.-K. Hwang, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1032.
101 K. C. Nicolaou, W.-M. Dai, S.-C. Tsay and W. Wrasidlo, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1155.
102 K. C. Nicolaou, W.-M. Dai, S.-C. Tsay, V. A. Estevez and W. Wrasidlo, *Science*, 1992, **256**, 1172.
103 K. C. Nicolaou and W.-M. Dai, *J. Am. Chem. Soc.*, 1992, **114**, 8908.
104 W.-M. Dai, *J. Org. Chem.*, 1993, **58**, 7581.
105 V. Voekelheide and W. J. Linn, *J. Am. Chem. Soc.*, 1954, **76**, 1286.
106 R. Yamaguchi, Y. Nakazono and M. Kawanisi, *Tetrahedron Lett.*, 1983, **27**, 1801.
107 P. A. Wender and C. K. Zercher, *J. Am. Chem. Soc.*, 1991, **113**, 2311.
108 P. A. Wender, S. Beckham and D. L. Mohler, *Tetrahedron Lett.*, 1995, **36**, 209.
109 P. A. Wender, C. K. Zercher, S. Beckham and E.-M. Haubold, *J. Org. Chem.*, 1993, **58**, 5867.
110 P. A. Wender, S. Beckham and J. G. O'Leary, *Synthesis*, 1994, 1278.
111 T. Nishikawa, A. Ino, M. Isobe and T. Goto, *Chem. Lett.*, 1991, 1271.
112 T. Nishikawa, M. Yoshikai, K. Obi and M. Isobe, *Tetrahedron Lett.*, 1994, **35**, 7997.
113 T. Nishikawa, A. Ino and M. Isobe, *Tetrahedron*, 1994, **50**, 1449.
114 T. Nishikawa, M. Isobe and T. Goto, *Synlett*, 1991, 99.
115 P. Magnus and S. M. Fortt, *J. Chem. Soc., Chem. Commun.*, 1991, 544.
116 P. Magnus, D. Parry, T. Iliadis, S. A. Eisenbeis and A. Fairhurst, *J. Chem. Soc., Chem. Commun.*, 1994, 1543.
117 P. Magnus and S. A. Eisenbeis, *J. Am. Chem. Soc.*, 1993, **115**, 12 627.
118 Y. Sakamoto and T. Takahashi, *Synlett*, 1995, 513; T. Takahashi, Y. Sakamoto, H. Yamada, S. Usui and Y. Fukazawa, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1345.
119 J. A. Porco Jr, F. J. Schoenen, T. J. Stout, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.*, 1990, **112**, 7410; J. L. Wood, J. A. Porco Jr, J. Taunton, A. Y. Lee, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 5898; J. Taunton, J. L. Wood and S. L. Schreiber, *J. Am. Chem. Soc.*, 1993, **115**, 10 378.
120 A. G. Myers, M. E. Fraley and N. J. Tom, *J. Am. Chem. Soc.*, 1994, **116**, 11 556; A. G. Myers, M. E. Fraley, N. J. Tom, S. B. Cohen and D. J. Madar, *Chem. Biol.*, 1995, **2**, 33.
121 M. D. Shair, T. Yoon and S. J. Danishefsky, *J. Org. Chem.*, 1994, **59**, 3755; T. Yoon, M. D. Shair, S. J. Danishefsky and G. E. Shulte, *J. Org. Chem.*, 1994, **59**, 3752; M. D. Shair, T. Yoon, T.-C. Chou and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2477; T. Yoon, M. D. Shair and S. J. Danishefsky, *Tetrahedron Lett.*, 1994, **35**, 6259; M. D. Shair, T.-Y. Yoon and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1721.