Perspective

Observations in the Chemistry and Biology of Cyclic Enediyne Antibiotics: Total Syntheses of Calicheamicin γ_1^I and Dynemicin A

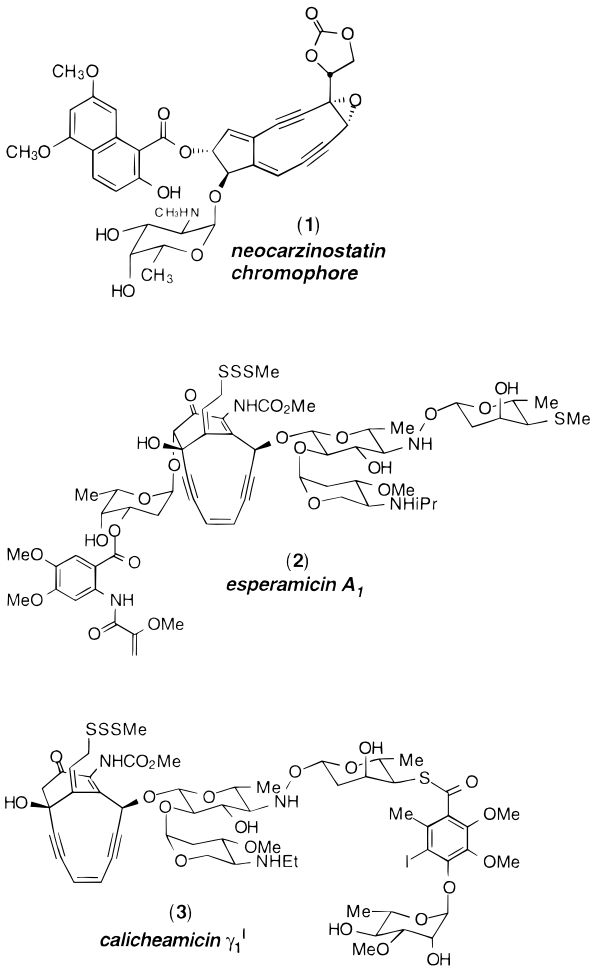
Samuel J. Danishefsky*,†,‡ and Matthew D. Shair†,‡

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, Box 106, New York, New York 10021, and Department of Chemistry, Havemeyer Hall, Columbia University, New York, New York 10027

Received August 25, 1995

For sheer structural audacity, complexity, and chemical novelty, few classes of natural products can rival the cyclic enediynes.[1] While there might have been a tendency to dismiss compounds such as neocarzinostatin choromophore (**1**),[2] esperamicin (**2**),[3] and calicheamicin (**3**)[4] as bizarre secondary metabolites (Scheme 1), arising

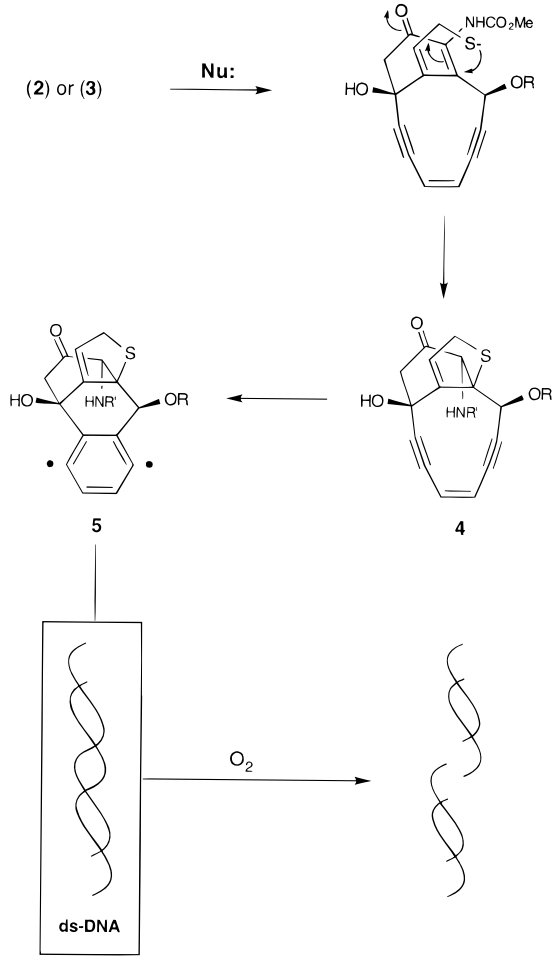
Scheme 1. Enediyne Antibiotics



from biosynthetic aberrations, their high double-stranded DNA cleaving ability (in some instances with significant sequence selectivity) ensured that they would receive serious attention.[5] Moreover, interest was augmented by reports of the cytotoxicity of such agents. In fact, these compounds are among the most potent prospective anticancer drugs from the natural products domain known to date.[6] There was certainly a perception, though not yet realized, that such substances, or analogs thereof, might be useful in oncology. Clearly, the goal of selectively directing these small molecule cell killers to diseased cells would pose no small challenge to the science of pharmacology.[7]

Further drawing many in organic chemistry to enlist to do combat in the "enediyne theater" was the mechanism of the DNA cleaving properties of esperamicin and calicheamicin. In a highly original insight following early observations of Sondheimer[8] and of Masamune,[9] Robert Bergman[10] had perceived and demonstrated the feasibility of electronic reorganization of a cis related 1,5-diyn-

Scheme 2. Mode of Action of Calicheamicin (3) and Esperamicin (2)



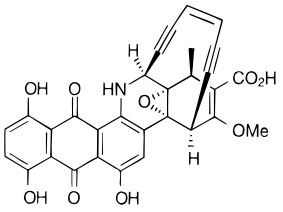
† Sloan-Kettering Institute for Cancer Research. Tel: 212-639-5502. Fax: 212-772-869.
‡ Columbia University. Tel: 212-854-6195. Fax: 212-854-7142.

0022-3263/96/1961-0016$12.00/0

3-ene to provide a 1,4-aryl diyl. Accordingly, when the extraordinary cytotoxicity and DNA cleaving abilities of esperamicin and calicheamicin were appreciated (even before the structures were fully formulated), a mechanism accounting for their activity could already be surmised. Thus, for either drug, cleavage of the trisulfide (Scheme 2) could set the stage for conjugate addition of a thiyl species to the "anti-Bredt" double bond. This accomplished, the setting would be in place for an enediyne → diyl tranformation (see **4** → **5**). It is diyl **5** which is presumed to be the active DNA cleaving agent starting with hydrogen abstraction from 2-deoxyribose residues. This simple, inspired concept of a "bio-Bergman" rearrangement to account for the mechanism of action of **2** and **3** was supported by voluminous backup studies. These included nonexperimental molecular modeling,[11] chemical modeling via syntheses of simple congeners,[12] and theoretical argumentations as to the relationship of diyl formation with precise molecular structure. There thus arose an intellectually pleasing framework in which chemists could contribute in a detailed way.

Another highly inspired insight, this time by Andrew Myers, served to include the older DNA cleaving agent neocarzinostatin chromophore (**1**) in a more generalized catechism.[13] A unifying theme emerges wherein a "cumulene drug" (which exists in nature in pro-drug form) upon suitable priming suffers transformation to a diyl which, through the medium of hydrogen atom transfer, functions as a DNA cleaving agent leading to cell death.

The repertoire of such "enediyne drugs" was further broadened by the discovery of dynemicin A (**6**)[14] as depicted in Figure 1. The combination of highly limited availability, lability, and difficult solubility considerably dims the prospects for dynemicin itself to emerge as a useful drug.



dynemicin A

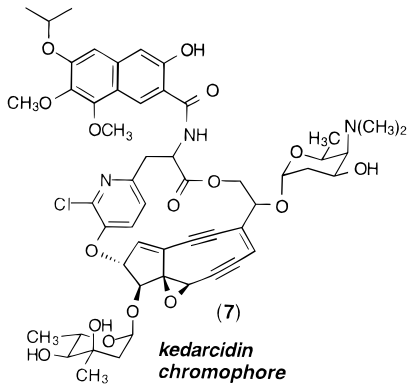
(**6**)

Figure 1. Dynemicin A.

At the level of chemical understanding, Semmelhack contributed the basic idea around which much of the dynemicin bioorganic investigations have been centered.[15] He argued, quite sensibly, that the quinone substructure provides the stabilizing element which protects dynemicin from a virtually spontaneous self-destruct pathway. This will be discussed later. For the moment, suffice it to say that Semmelhack's insight prompted the search for a variety of other ways to store and to unleash dynemicin-like activity. More recently, the list of enediyne drugs has been expanded with some further interesting additions (see **7**[16] and **8**[17] in Scheme 3).

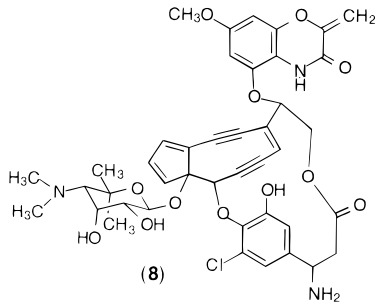
The background discussion provided above is certainly not presented in the spirit of a general review of cumulene or enediyne drugs. It is offered to provide an understanding of the stimulation and excitement which these agents provided to organic chemists, including those in our laboratory.

Scheme 3. Recently Discovered Members of the Enediyne Class of Antibiotics



(**7**)

kedarcidin chromophore



(**8**)

C-1027 chromophore

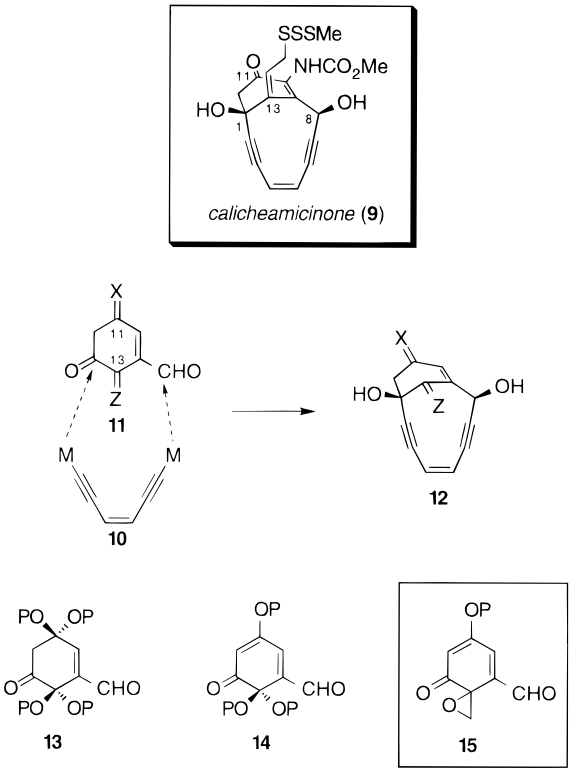
There are many vantage points from which novel and biologically potent chemical agents can be investigated. The quest for total synthesis can be one of the most illuminating. The scientific group undertaking a prospective total synthesis must concern itself with the complete "molecular personality" of its target. While, at any particular point in time, the focus is likely to be directed to a particular locale, or even a specific bond of the target, these efforts must be choreographed within the context of a comprehensive view of the problem. Insights garnered form such "total molecule" undertakings can be quite revealing. However, quite aside from bioorganic and medicinal (analog synthesis) motivations, members of our laboratory were enticed by the sheer novelty and, even, beauty of the structures and, yes, by the captivating challenge associated with the prospect of the total synthesis of such natural products.

Below, we relate an account of the activities of our laboratory which led to total synthesis of both calicheamicin (**2**)[18−21] and dynemicin (**6**).[22,23] This essay is not intended as a review of the enediyne or cumulene drug field. Many excellent coverages of the enediynes, including total synthesis in the case of **2**, have been provided.[24] Rather, what we present is a personalized reminiscence of our involvement, and the involvement of our colleagues, in two rather special research projects.

Our calicheamicin effort started first. We began by investigating the synthesis of a "core-structure" construct of an aglycon version of calicheamicin (we called the fully functional, but then unknown, aglycon calicheamicinone (**9**, Scheme 4). In the opening phase, we were willing to deal with a solution in which the urethan was deleted. We would, however, set as a requirement that our core construct contain the bridgehead double bond and that it have sound provision for the eventual ketone at C_{11} and for the two hydroxyl groups at carbons C_1 and C_8, and a credible modality for eventual installation of the

allylic trisulfide at C_{13}. Keeping in mind the need for a "global molecular solution", we were wary of alluring short term successes which upon subsequent analysis lacked plausibility for evolving into a fully comprehensive program of total synthesis.

Scheme 4. Initial Synthetic Perceptions of a Calicheamicinone (9) Synthesis



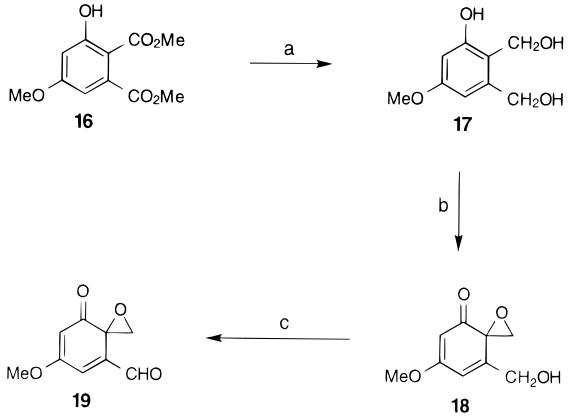
A concept which was captivating in its formal simplicity virtually imposed itself for putting together a core structure which meets the specifications outlined above. Such a core might be assembled by interpolating a (*Z*)-hex-3-ene-1,4-diyne unit (**10**) as a "double nucleophile" between "ketonic" and "aldehydic" centers in a domain of the type **11**. At this stage, we were not necessarily committed to the delivery of **10** as a single six-carbon unit. Perhaps, the overall unit would be delivered in modular form (see dotted lines). Even if the diynene segment were to be presented as a six-carbon unit, we maintained an open mind as to the issue of timing. The two nucleophilic attacks could be delivered in a single strike or staged in staccato-like steps, as appropriate.

Closer analysis of hypothetical construct **11** helped to sharpen the specificity of the thought process. There was obvious concern about equipping **11** with functionality implements which would serve the needs of the project over the long haul. The groups X and Z must not be competitive as electrophiles with the ketonic and aldehydo centers designated for the bridging strategy. Two perceptions of the nature of X were considered. In the most obvious view, "X" represents a type of ketal protecting group. Alternatively, X might represent an enol ether function. Again, the most obvious view of Z would be that of an acetal type of linkage. There was concern that prototype structures of the type **13** or **14** might be difficultly accessible and chemically unwieldy, particularly in regard to differential exposure of functionality at future carbons 11 and 13.

It seemed that the Becker–Adler reaction[25] *might provide the basis for a solution to several of the interactive problems posed by the approach of* ***10*** *+* ***11*** *→* ***12***. Thus, it was hoped that in a spiro dienone of the type **15** the future C_{13} functionality could be stored as an epoxide while an enol ether would guard the future C_{11} ketone. It was even hoped, though not realized in practice (vide infra), that the methylene group of the spiroepoxide in **15** could be exploited to serve as a member of the two-carbon appendage that must eventually be added to C_{13}.

The journey began with diester **16** (Scheme 5) which, upon reduction, gave rise to diol **17**. Becker–Adler oxidation of **17** served to differentiate the hydroxymethyl groups ortho and meta to the phenolic hydroxyl, thereby affording **18** and then, after Dess Martin oxidation, **19**.

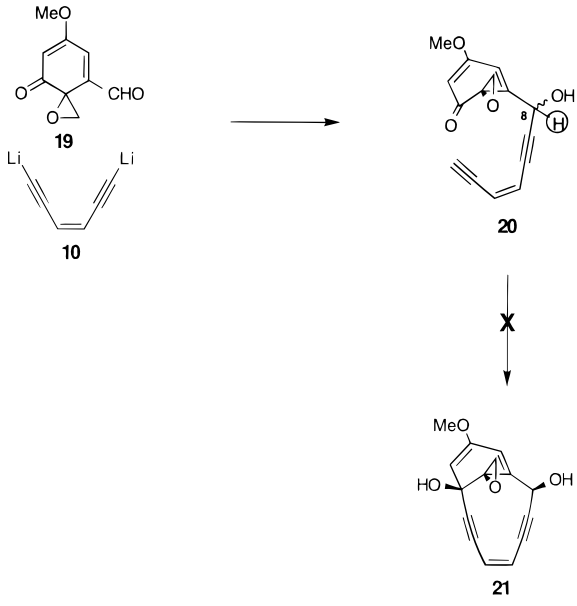
Scheme 5. Synthesis of Keto Epoxide (19)[a]



[a] (a) DIBAH, THF; (b) $NaIO_4$, THF–H_2O, 75% overall; (c) Dess–Martin periodinane, CH_2Cl_2, 70%.

Dennis Yamashita, who initiated this project, first learned how to prepare and condense the dilithio enediyne **10** with excess benzaldehyde.[26] He also found it possible to deliver the dilithio agent to the aldehyde function of **19** (Scheme 6). However, there was no sign

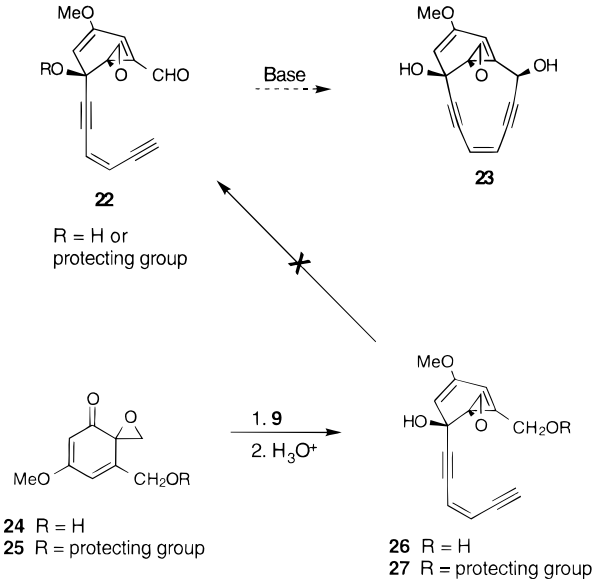
Scheme 6. Addition of Dilithio Enediyne 10 to Keto Aldehyde 19



of cyclization to the ketone. All attempts to accomplish the cyclization of **20** to **21** in a separate step were unsuccessful. Although confirmatory products were never characterized, we began to suspect the chemical lability of the proton at C_8 of adduct **20** (see circle).

We wondered about the possibility of conducting the cyclization (Scheme 7) in the reverse sense (cf. **22** → **23**). The logic was that in the case at hand the intramolecular step (i.e., the cyclization) may actually be more demanding than the first coupling. In that case, it would be better to reserve the aldehydo electrophile for the most problematic phase. This line of thinking first led us to explore addition to reduced versions of the future aldehyde group (cf. **24** and **25**). Addition was indeed achieved, but the lability of **26** and **27** was such that we were never able to make our way to enediyne aldehyde **22** to attempt cyclization.

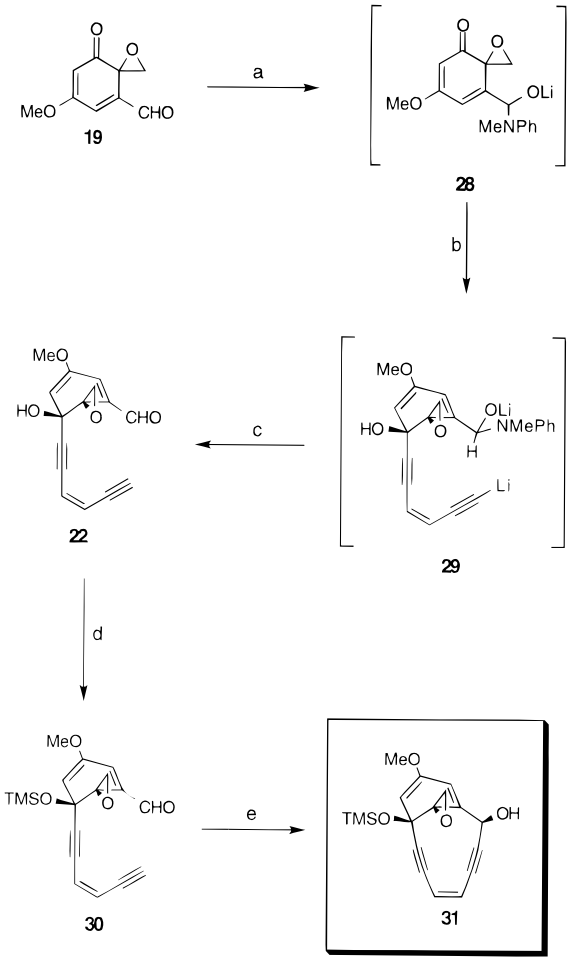
Scheme 7. Attempted Synthesis of Aldehyde 22



Given these disappointing results, the only recourse for reaching a system of the type **22** called for delivery of **10** to the ketone of keto aldehyde **19**. At this stage Dr. Nathan Mantlo had joined the project. Indeed, following the chemistry of the in situ protection of aldehydes (originally developed by Comins for the purpose of lithiation of aryl bromides in the presence of resident "aldehydes" [27]) Mantlo accomplished (Scheme 8) this goal (see presumed intermediates **28** and **29** and product **22**). Moreover, the addition of **10** was quite stereoselective. The resultant **22** corresponds to the acetylide having added to the ketone syn to the oxygen face of the spiroepoxide. After nontrivial protection of the tertiary alcohol, silyl ether **30** was in hand. In the event, deprotonation of **30** with lithium hexamethyldisilazide and warming to rt led to a 40−60% yield of core system **31**. When the cyclization was conducted under the strictly defined conditions shown, this compound was obtained with high stereoselectivity. It is the product which would formally arise from addition of the acetylide to the s-trans version of the enal.

Having achieved the first synthesis of a core structure of an enediyne drug,[28] attentions were directed to elaborating C_{13} by opening of the spiroepoxide with a carbon-centered nucleophile. Experiments were conducted on the core system containing the enol ether linkage present in the enone **32**, or on the ketal **33** (Scheme 9). While we were able to open the epoxide linkage with cyanide as the nucleophile, the β-cyanohydrin thus obtained did not lend itself to dehydration. Difficulties ranged from general decomposition to nonreactivity. A range of other

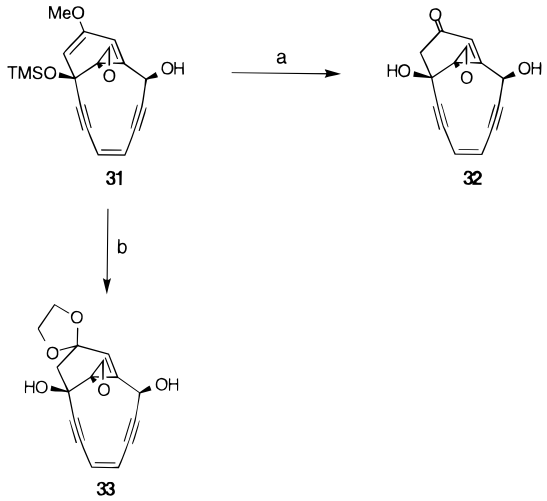
Scheme 8. Synthesis of Cyclic Enediyne 31[a]



[a] (a) LiNMePh, THF; (b) **10**; (c) H_3O^+, 40% overall; (d) TMS(O-$COCF_3$), Et_3N, CH_2Cl_2, 72%; (e) KHMDS, $PhCH_3$, 39%.

nucleophiles failed at the level of the ring-opening reaction. This was certainly one of the low points of the project.

Scheme 9[a]

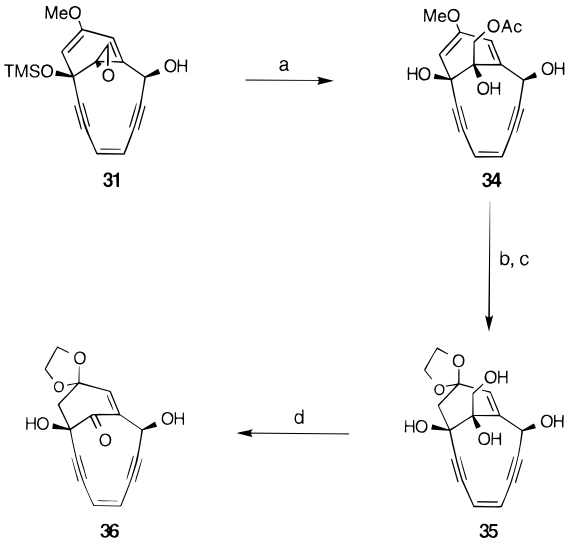


[a] (a) $(CO_2H)_2$, 95%; (b) $(CH_2OH)_2$, PPTS.

In the 11th hour of his stay at Yale, Mantlo (who was Merck bound) discovered that enol ether epoxide **31** (Scheme 10) could be subjected to high-yielding acetolysis to afford **34**. The diol function in the derived **35** could

be cleaved to produce a ketone (cf. **36**). While the hope of exploiting the methylene carbon of the spiroepoxide had been frustrated, the Becker−Adler chemistry in conjunction with the enediyne interpolation concept (after significant on-site modification) had proved to be workable. At this stage, Dr. John Haseltine (currently at Georgia Tech) replaced Dr. Mantlo on the project.

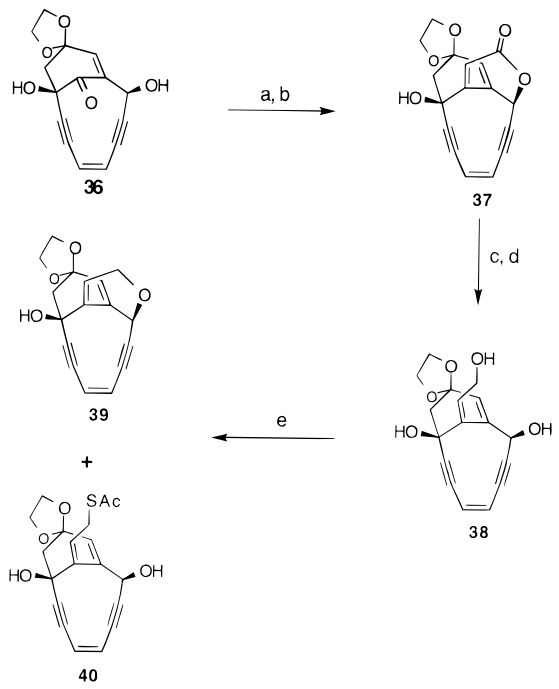
Scheme 10. Installation of the C_{13} Ketone of 36[a]



[a] (a) KOAc, HOAc, DMSO, 95%; (b) $(CH_2OH)_2$, CSA, 80%; (c) NH_3, MeOH; (d) HIO_4, THF, 84%.

Yamashita began our first explorations directed toward incorporating the urethane linkage, looking toward the synthesis of a fully equipped aglycon. Haseltine undertook the not inconsiderable challenge of charting a line of chemistry to proceed from **36** to reach descarbamoyl-

Scheme 11. Synthesis of Thioacetate 40[a]

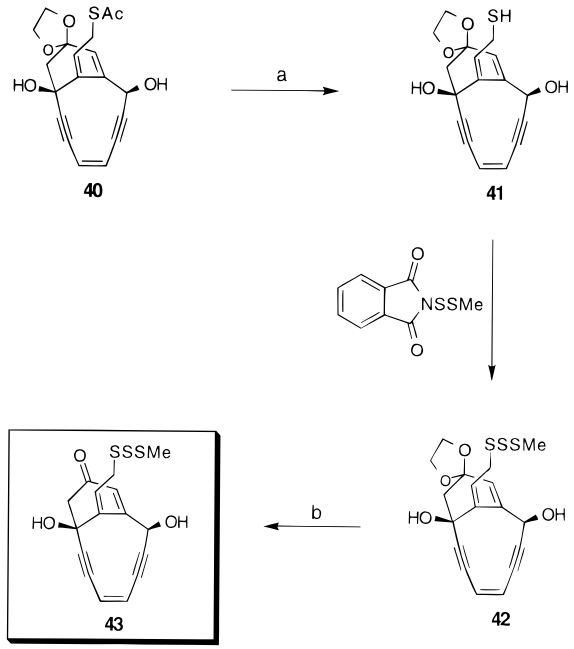


[a] (a) DCC, $(EtO)_2P(O)CH_2CO_2H$; (b) LiBr, Et_3N, THF, 76%; (c) DIBAH, CH_2Cl_2; (d) $NaBH_4$, MeOH, 69% overall; (e) DIAD, PPh_3, AcSH, 52%.

calicheaminone. After continuing trial, error, and retrofitting, Haseltine worked out a viable route (Scheme 11). His elegant intramolecular Emmons reaction afforded **37** which, after two stage reduction, gave rise to **38**.

In attempting to set the stage for installation of the allylic trisulfide, a very serious setback in terms of yield was sustained. All attempts to carry out displacement of the primary allylic alcohol (cf. **38**) with thiyl-based nucleophiles were severely complicated by formation of a cyclic ether in competition with the desired intermolecular displacement product. The formation of **39** and **40** under the conditions shown is illustrative. Not withstanding this setback, Haseltine showed how thioacetate **40** could be cleaved reductively (Scheme 12) to

Scheme 12. Synthesis of Descarbamoylcalicheamicinone 43[a]



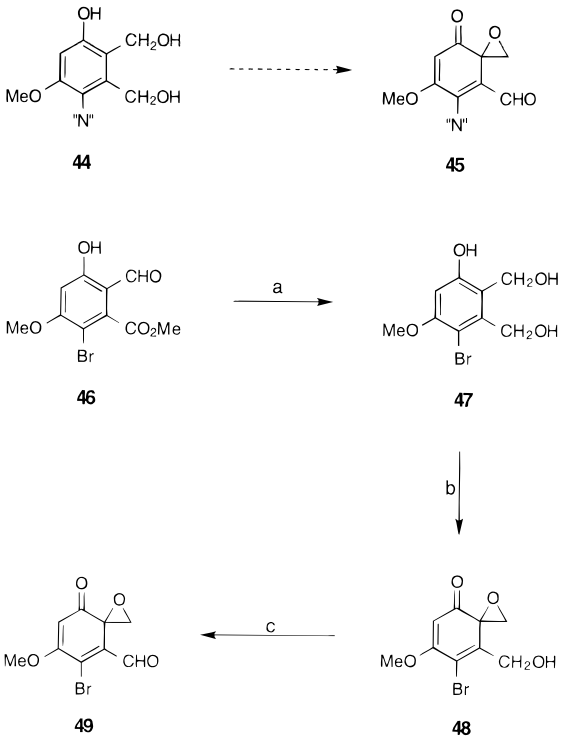
[a] (a) DIBAH, CH_2Cl_2; (b) CSA, THF−H_2O, 100%.

generate thiol **41**. The latter was converted to trisulfide **42**,[29] which, remarkably, could be readily deprotected to provide descarbmoylcalicheamicinone **43**.[30]

Following these critical experiments, the campaign to reach calicheamicinone was intensified. With Haseltine leaving for Georgia Tech, the cause was taken on by Dr. Maria Paz Cabal (currently at SUNY−Buffalo) and Dr. Robert Coleman (currently at the University of South Carolina). The thought was to include provision for the eventual urethane linkage in our aromatic precursor (Scheme 13) and then conversion to a spiroepoxide similar to **19** (Scheme 5). Two possibilities were entertained at the experimental level. In one version, the interim goal system would be **45**, which contains either the intact urethane, some form of an amino group, or, less likely, a nitro precursor. The other route, with system **49** as its interim target, involved placing a bromine atom where the urethane would eventually appear. These possibilities were investigated concurrently.

Unfortunately, no pathway leading to any version of the system corresponding to **45** was validated in practice. Attempts in this direction broke down even at the stage of projected early aromatic intermediates en route to the Becker−Adler reaction. The problem of installing and maintaining various amino permutations (or even a

Scheme 13. Synthesis of Bromide 49[a]



[a] (a) NaH, then DIBAH, THF; (b) $NaIO_4$, THF−H_2O; (c) Dess−Martin periodinane, CH_2Cl_2, 40% overall.

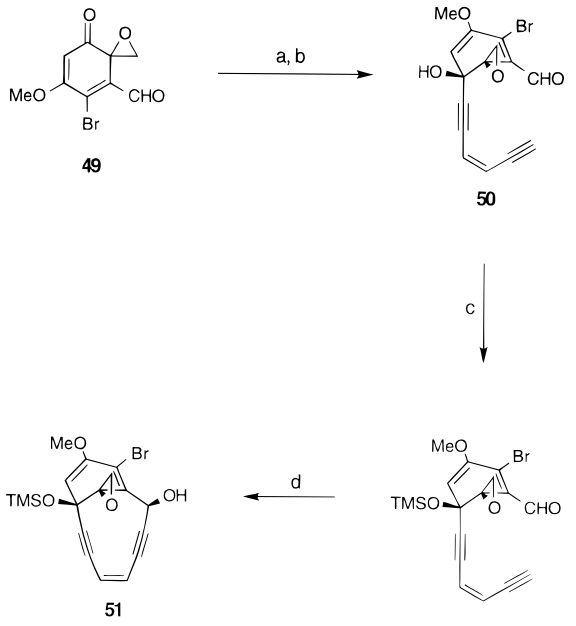
precursor nitro group) through the steps required to reach diol **44** did not prove to be manageable in an acceptable time frame.

More workable, though far from simple, was a route centered around a bromine handle. This goal was eventually achieved starting with the bromo ester aldehyde **46**. The inclusion of the bromine caused several serious technical problems. Particularly frustrating was the matter of retaining the bromine atom while reducing the ester aldehyde (**46** → **47**). The use of lithium aluminum hydride led to extensive debromination in addition to the desired reduction. This problem could be circumvented through the agency of diisobutylaluminum hydride as the reducing agent. Unfortunately, the workup protocols necessitated by this reducing agent proved to be difficultly manageable on a large scale, and yields of desired bromo diol suffered. The Becker−Adler oxidation of crude **47** was successful and provided the desired spiroepoxy dienone **48** containing the bromine. Again, Dess−Martin oxidation gave rise to **49**.

Here again, the yield of addition (Scheme 14) of compound **10** to aldehyde **49** seems to suffer from the presence of the bromine group. Once more, the hydroxyl group of the resultant and unstable **50** had to be protected as its silyl ether. In the event, cyclization of this compound gave the desired **51**. In this case, in contrast to the desbromo series, the intramolecular addition of the acetylide to the aldehyde seemed to be stereospecific, producing only **51**. This finding could be rationalized. The presence of the ortho bromo function likely favors the s-trans enal form required to produce the desired *S* configuration at C_8. Thus, we had in hand **51** (a modified version of **31**), where the bromine would serve as the eventual access point for introducing the urethane.

Two routes were now pursued for this conversion. In one route, the vinyl bromide would be lithiated and the

Scheme 14. Synthesis of Enediyne 51[a]



[a] (a) LiNMePh, THF; (b) enediyne **10**; (c) TMS($OCOCF_3$); (d) KHMDS, $PhCH_3$, 60%.

resultant vinyllithium reagent would be carboxylated, thus, setting into motion a possible Curtius degradation en route to the desired urethane. Surprisingly, some progress in this regard was realized in that the lithiation and carbomethoxylation steps could actually be accomplished on compound **51** in this multifunctional setting, though in poor yield. However, several attempts at Curtius and related degradations failed.

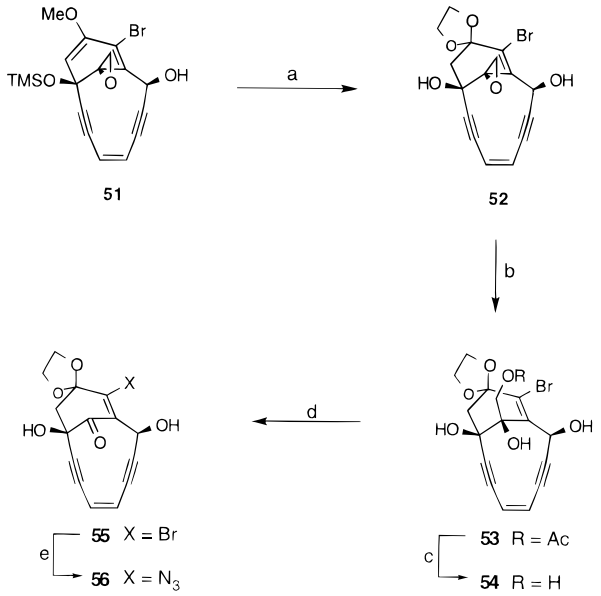
The alternative possibility was to find a point in the progression wherein the vinyl bromide might be displaced by an azido nucleophile. The idea was to take advantage of a niche in the synthesis in which the electronic character at C_{13} would favor addition by azide ion and displacement of bromide ion. At an appropriate stage, the azide would be reduced to an amine which, following carbomethoxylation, would provide the urethane.

We proceeded as follows (Scheme 15). The spiroepoxide **51** was converted to hydroxy acetate **53** in accordance with precedent in the descarbomyl series. (We shall return to this compound shortly in dealing with the synthesis of the optically pure aglycon). Compound **53** was converted to diol **54** and then to ketone **55**. In this substrate, it was possible to achieve addition of azide and elimination of bromide (see compound **56**). We processed compound **56** onward (Scheme 16), reaching unsaturated lactone **57** by intramolecular Emmons reaction. In this substrate, the azide function underwent reduction to a vinyl amine (stabilized no doubt by vinylogous conjugation to the lactonic carbonyl center). Two-stage acylation of the crude amine via "diphosgene" led to **58**. Thus was the urethane installed.

Reduction of the unsaturated lactone, through the previously described two-stage protocol, afforded **59**. Once again, we were not spared from the ravages of the low-yield Mitsonobu-type conversion of **59** to **60**. Compound **60** did, indeed, respond, albeit in lower yield, to the same protocol used in the model descarbamoylcalicheamicinone series to provide the aglycon calicheamicinone (**9**).[20]

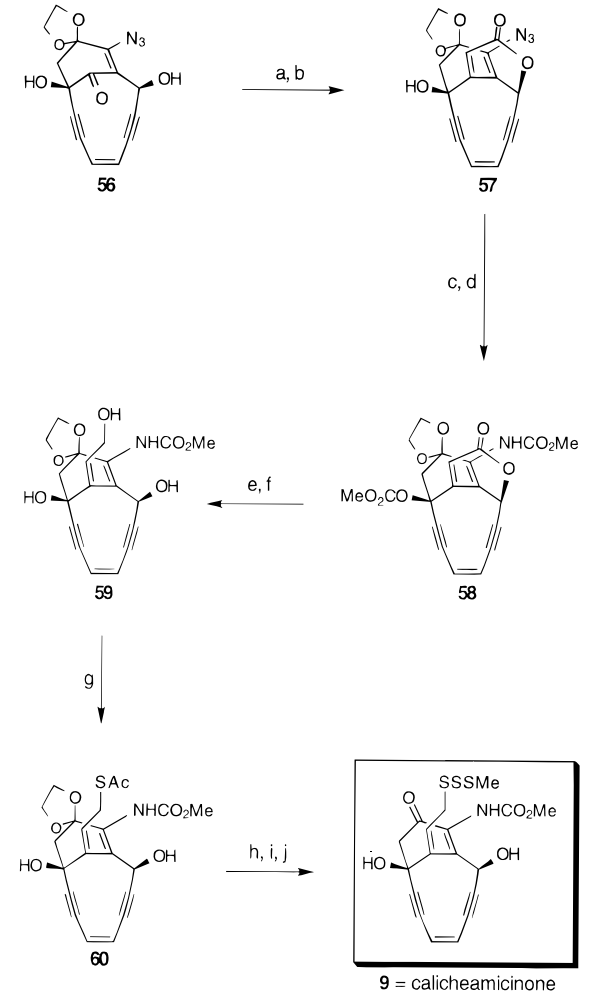
Before returning to the total synthesis project, it is worth recalling some insights gathered into the mode of

Scheme 15. Synthesis of Azide 56[a]



[a] (a) $(CH_2OH)_2$, THF, CSA, 89%; (b) KOAc, HOAc, DMSO, 88%; (c) NH_3, MeOH; (d) $NaIO_4$, acetone−H_2O, 80% overall; (e) NaN_3, MeOH, H_2O, 82%.

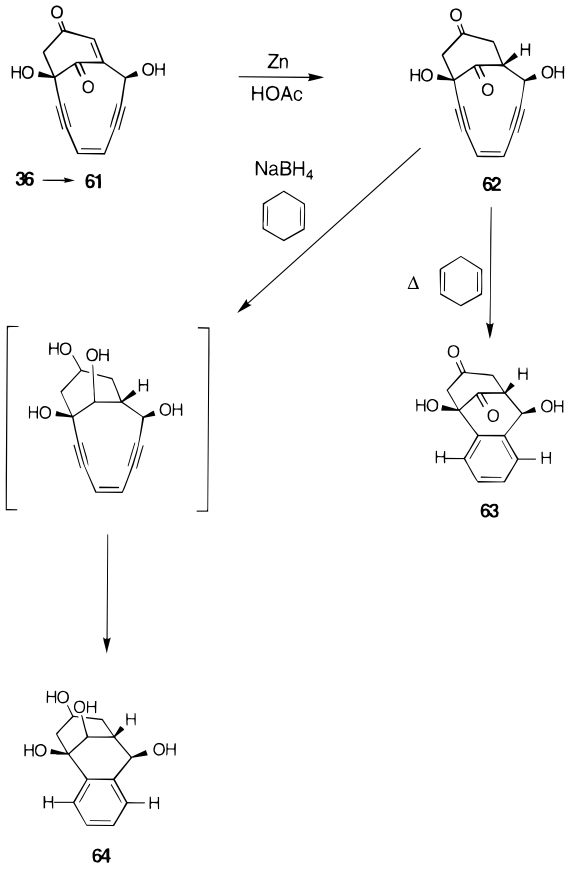
Scheme 16. Synthesis of Calicheamicinone (9)[a]



[a] (a) $ClC(O)CH_2PO(OEt)_2$, pyridine, THF, 64%; (b) LiBr, Et_3N, THF, 92%; (c) H_2S, piperidine, MeOH, 85%; (d) $(Cl_3C)_2CO$, pyridine, then MeOH, 82%; (e) DIBAH, CH_2Cl_2; (f) $NaBH_4$, MeOH, H_2O, 65%; (g) DIAD, (3-OMe)Ph_3P, AcSH, THF, 60%; (h) DIBAH, CH_2Cl_2; (i) Harpp reagent, CH_2Cl_2, 46%; (j) CSA, THF, H_2O, (65%).

action of calicheamicin which were rendered possible by the exercises described above. Thus, an early demonstration proceeded via enedione **61** (Scheme 17) obtained from **36**. The latter was reduced to the dihydro compound **62**, as shown. This compound would, in principle, be a candidate for spontaneous Bergman cyclization. As it turned out, Bergman cyclization occurred only upon thermolysis. Following a precedent of Magnus,[31] **62** was reduced to a diol. The latter underwent virtually spontaneous Bergman cyclization in the presence of 1,4-cyclohexadiene to produce **64**.[32] Thus, in a fully elaborated series, a new triggering mechanism for diol formation was established via reduction of the bridgehead double bond. Furthermore, in keeping with the precedent of Magnus, the role of the hybridization at C_{13} was verified in the more fully equipped system.

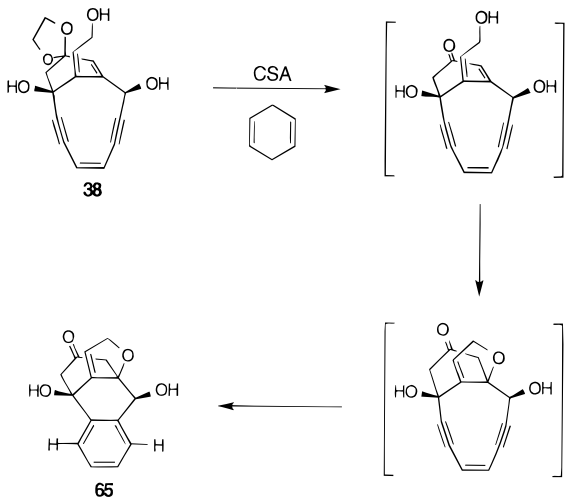
Scheme 17. Exploration of Various Triggering Mechanisms for Enedione 61



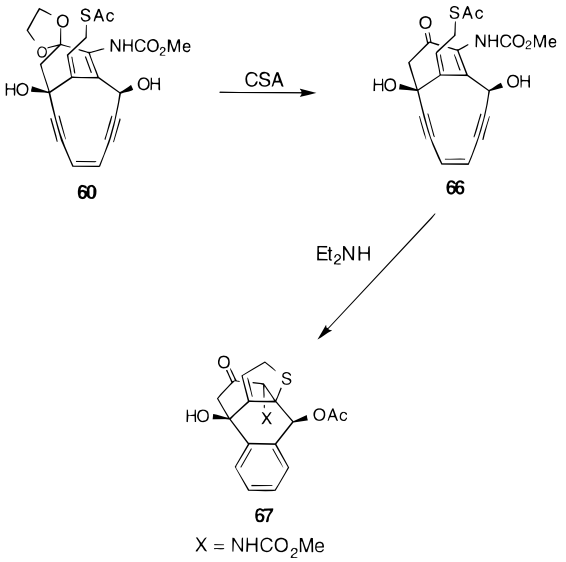
Moreover, allylic alcohol **38** (Scheme 18) provided another opportunity for triggering a Bergman reaction. Cleavage of the ketal linkage led to a ketone which, in the presence of 1,4-cyclohexadiene, afforded **65**. We had shown for the first time that an allyllic alcohol Michael addition reaction will inaugurate the bioactivation cascade. Similarly, thioacetate **60**, upon deketalization, gave rise to **66** (Scheme 19). Exposure of **66** to diethylamine sets into motion a Bergman-like process leading to **67**.[20b] These demonstrations, in the context of fully elaborated structures, provided more persuasive, though still suggestive, evidence to their pertinence to the drug itself.

Another important observation involved the capacity of the thioacetate and the trisulfide, both in the urethane-containing series and the descarbamoyl series, to effect cleavage of DNA. It was found that the aglycons themselves are quite cytotoxic and do induce cleavage of

Scheme 18. Michael Addition of 38 as a Triggering Device



Scheme 19. Activation by Cleavage of Thioacetate 66



oligonucleotide constructs. The cleavage included a residual double-stranded cleaving capacity of about 10−15% in the racemate, which is considerably less than that of the drug itself, with suitably chosen oligonucleotide targets.

Indeed, it was found that DNA cleavage is more readily realized from the thioacetates than via the trisulfide. This trend was subsequently confirmed by Nicolaou and coworkers in the context of the fully synthetic drug analog and drug.[24]

Moreover, the aglycon retained, to only a limited extent, the capacity to participate in direct hydrogen atom transfer from the oligonucleotide. This was established by conducting reactions in a deuterated medium. An experimentally reproducible and meaningful amount of aromatized aglycon containing proteo functions at carbons 3 and 4 was obtained by Nobuharu Iwasawa. However, once again, the efficiency of this transfer was far less than that of the native drug. These studies taught us *for the first time* that the bulk of the molecular recognition which leads to double-stranded cleavage capacity and hydrogen atom transfer resides in the carbohydrate entity rather than in the aglycon itself. This point was further corroborated by the fact that the aglycon lacks any semblance of sequence selectivity. *This study utilizing synthetic aglycon was the first to pinpoint the critical importance of the carbohydrate domain in mediating DNA cutting properties of the drug.*[33]

These findings, once again, underscored the unique role of synthesis in providing systems which are not available from the natural product. All previous attempts to retrieve aglycon from deglycosylation of natural calicheamicin were unsuccessful. Indeed, such hydrolysis was also not a viable way of producing the carbohydrate domain. That, too, has to be fashioned by total synthesis (vide infra).

Another important step in moving toward a total synthesis of calicheamicin itself was that of obtaining the aglycon in optically pure form. A key step in this regard was accomplished by Dr. Vincent Rocco (currently at Eli Lilly) via an enzymatically specific acetylation, following protocols of Wong conducted on intermediate **54** (vide infra).[34] This gave rise, eventually, to the two antipodes of calicheamicinone ketal and calicheamicinone itself. It was instructive to compare the DNA cleaving capacity of the two antipodes.[35] Surprisingly, the unnatural antipode exhibited greater double-stranded cleaving capacity than did the natural one. In the unnatural series, approximately 25% double-stranded cleavage was noted. Once again, the unique role of this sugar in modulating drug−DNA recognition of the drug had been illustrated through the medium of synthesis.

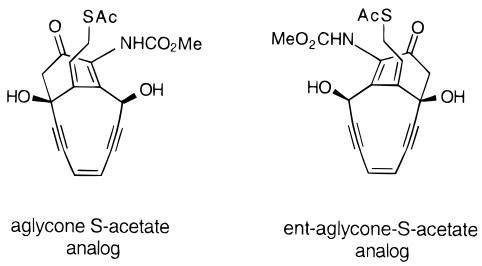


Figure 2.

Naturally, as the importance of the carbohydrate domains was becoming apparent, and as success in the synthesis of calicheamicinone was becoming more probable, our horizons began to shift toward its carbohydrate sector and that of esperamicin. There were several considerations involved in taking on this challenge. First, it was emerging that only synthesis could provide the fully operational carbohydrate entity.[19] All attempts to wean this intact domain from the drug were unsuccessful. One of the sources of this vulnerability was to emerge as a major issue in our synthetic work (vide infra).

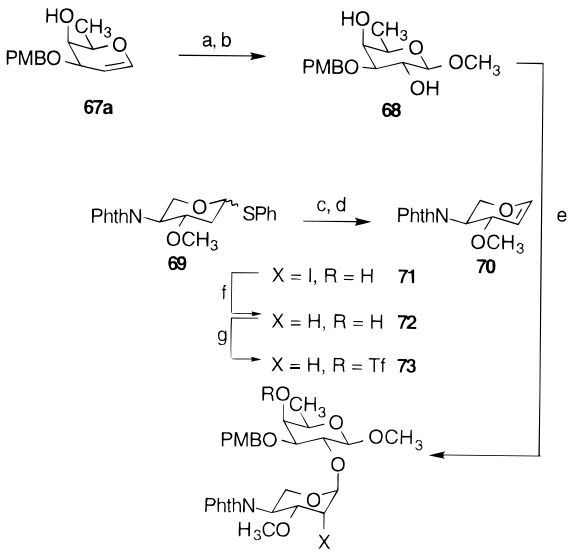
Insofar as we were interested in the biological properties of the carbohydrate sector itself, which in fact turned out to be fascinating, we would have to assemble it. Furthermore, this goal was, in itself, a synthetic challenge of some scope. Part of our agenda was its encouragement to extend our synthetic concepts in glycal assembly to some new structural types.[36] In addition, we began to think about the possibility of achieving a total synthesis of calicheamicin γ_1^{I} [21] itself. If the carbohydrate domain could be assembled, perhaps it could be delivered in a suitable form to a workable version of calicheamicinone.

Assuming the chemical issues could be negotiated, several questions could be addressed. For instance, it would be necessary to ascertain the stability limits of the

carbohydrate domain of either calicheamicin or esperamicin if the "reducing end" terminates in a free hydroxyl. What would be the minimum protection required to stabilize a molecule with a free reducing end? Assuming such protection were possible, could a viable glycosylation donor function be installed from such a free anomeric hydroxyl? Assuming this were achieved, could glycosylation with aglycon actually be achieved? Finally, assuming this were all feasible, could the coupling be executed at a sufficiently advanced stage such that deprotection and retrieval of the final product could be managed?

The conceptual framework for synthesizing the carbohydrate domains (both for esperamicin and calicheamicin γ_1^I) was that of glycal assembly. A review of the overall logic and practice of glycal assembly is beyond the scope of this report. Moreover, various facets of glycal assembly have been reviewed elsewhere.[37] Thus, here we confine ourselves to the sequences which were successfully implemented to attain the goals enumerated above. Randall Halcomb (currently at the University of Colorado, Boulder), Dr. Mark Wittman (currently at Bristol Myers), and Steven Olson first probed the issue of the stability of the aglycon-free carbohydrate domain in the less elaborate esperamicin series. Epoxidation of rhamnal derivative **67a** (Scheme 20), followed by methanolysis, afforded **68**. Compound **68** was used as the glycosyl acceptor in Thiem-like[38] iodoglycosylation with glycal **70** (prepared form the previously known phenyl thioglycoside **69**) to give **71**. De-iodination gave **72** and eventually triflate **73**.

Scheme 20. Synthesis of Triflate 73[a]

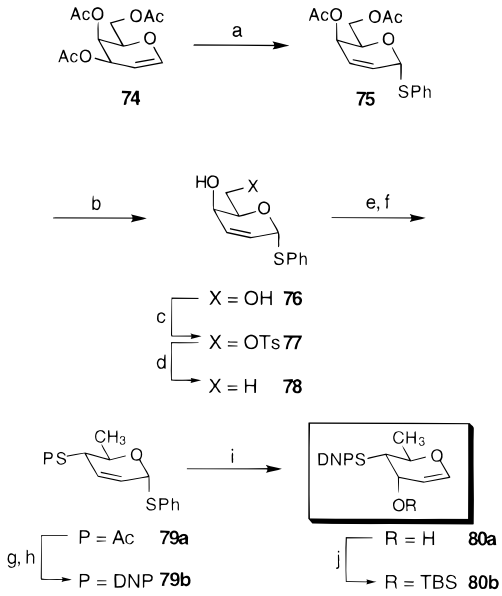


[a] (a) 2,2-Dimethyldioxirane, CH_2Cl_2; (b) MeOH, 68%; (c) *m*-CPBA, CH_2Cl_2; (d) benzene, reflux; (e) $I^+ClO_4^-$ (sym-collidine)$_2$, CH_2Cl_2, 49%; (f) Ph_3SnH, AIBN, benzene, reflux, 84%; (g) Tf_2O, pyridine.

The preparation of the coupling partner (**80b**) for the triflate required a fairly lengthy sequence. It started with D-galactal triacetate (**74**), employing a phenylthio version of the Ferrier rearrangement (Scheme 21). The plan was to install the C_{3a} hydroxyl group by 2,3-sigmatropic rearrangement of a derived pseudo glycal α-sulfoxide. Indeed, it was for the esperamicin carbohydrate that this chemistry for reaching glycals with 3-axial alcohols was developed (vide infra).

It would of course have been much preferable to conduct the desired sequence directly in the D-fucal series. However, in our hands, the projected thio-Ferrier rearrangement failed with 6-deoxy substrates. Accordingly, it was necessary to conduct this reaction in the galactose series bearing an oxygen function at C_6. Subsequent deoxygenation at C_6 was followed by installation of an α-methylthio group at C_4 (see **78** → **79a**). Inversion of the triflate was accomplished with thioacetate to afford **79a** and then the 2,4-dinitrophenylthiolate **79b**.

Scheme 21. Synthesis of Thiosugar 80b[a]

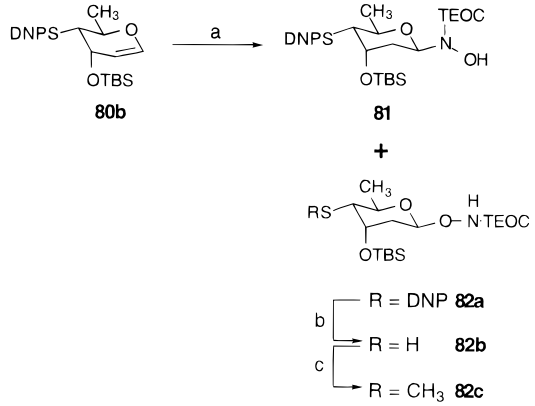


[a] (a) PhSH, $SnCl_4$, CH_2Cl_2, 96%; (b) NaOMe, MeOH; (c) TsCl, $CHCl_3$, TBAB, 86%; (d) LAH, THF, 91%; (e) MsCl, Et_3N; (f) KSAc, DMF, 95%; (g) LAH, THF; (h) DNP−F, 89%; (i) *m*-CBA, CH_2Cl_2, then Et_2NH, THF, 76%; (j) TBSOTf, pyridine, CH_2Cl_2.

It was at this stage that the rearrangement of the sulfoxide corresponding to **79b** was carried out. The axial alcohol of the resultant **80a** was protected as its silyl ether (see compound **80b**).

At approximately the time these investigations were progressing, Falck had described a useful direct conversion of glycals to 2-deoxyglycosides.[39] The Falck logic proved applicable to the case at hand. Treatment of **80b** with *N*-(trimethylsilylethoxycarbonyl)hydroxylamine (TEOC-NHOH, Scheme 22) in the presence of $Ph_3P{\cdot}HBr$

Scheme 22. Synthesis of Hydroxylamine 82c[a]



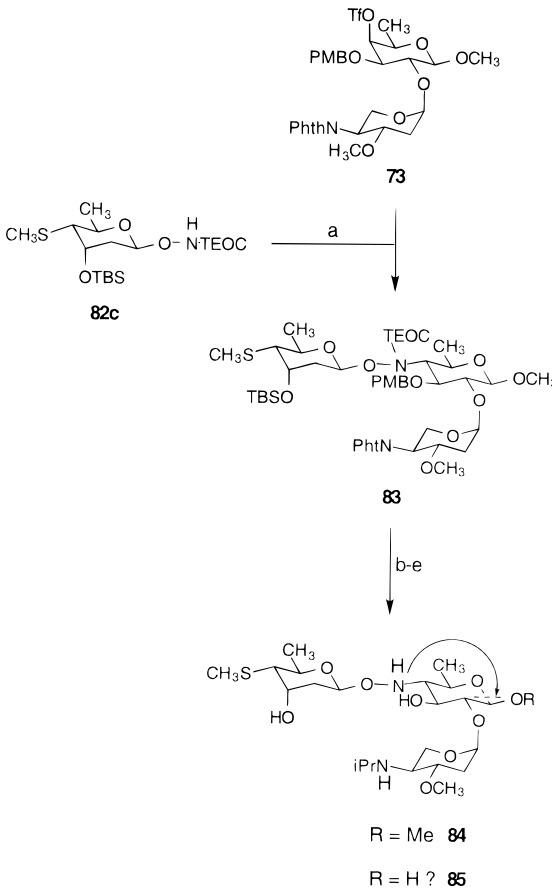
[a] (a) TEOC-NHOH, Ph_3P-HBr, CH_2Cl_2, 57%; (b) EtSH, K_2CO_3, MeOH; (c) MeI, DBU, benzene, 87%.

afforded only 2-deoxy-β-glycoside product **82a**. Given Falck's less than favorable precedents at the level of stereochemistry, this stereospecificity presumably reflects the substantial hindrance provided by the 3-α (axial)

OTBS group to glycoside formation. Unfortunately, however, the addition to **80b** produced a 3:2 mixture of desired **82a** and *N*-glycosylated **81**. The next phase involved conversion of the 2,4-dinitrophenyl protecting group on sulfur to the required S-methyl function (see compound **82c**, R = CH_3).

Coupling of deprotonated **82c** and **73** under the conditions worked out by Kahne and co-workers afforded **83**[40] (Scheme 23). Hydrazinolytic cleavage of the *N*-phthaloyl

Scheme 23. Synthesis of Esperamicin Trisaccharide 84[a]

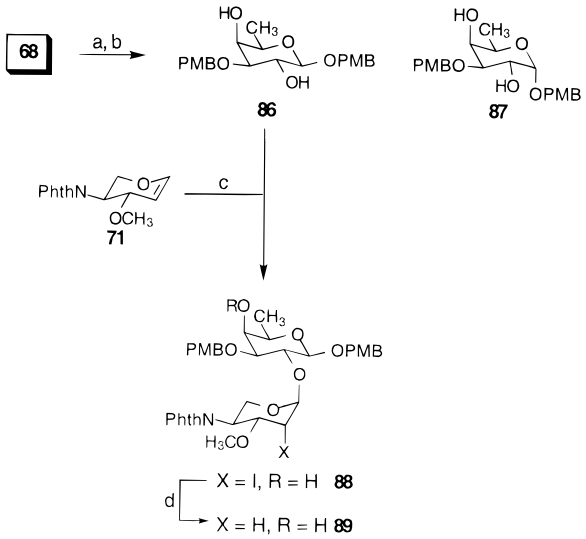


[a] (a) NaH, DMF, 78%; (b) N_2H_4, EtOH; (c) acetone, $NaCNBH_3$, iPrOH, 85%; (d) DDQ, $CH_2Cl_2-H_2O$, 99%; (e) TBAF, THF, 92%.

function and introduction of the isopropyl unit on nitrogen was followed by cleavage of the *O*-silyl protecting groups to afford **84**. This compound corresponds to the full trisaccharide carbohydrate sector of esperamicin with the reducing end blocked as a methyl glycoside. Pleasing as was this demonstration, it left unaddressed the matter of fashioning this type of domain to serve as a competent glycosyl donor. Since we had reached the aglycon of calicheamicin by total synthesis, we were, of course, aiming at solving this problem with the calicheamicin carbohydrate sector. However, it seemed that the somewhat simpler esperamicin domain would serve as a convenient model. The specific question to be faced was the protection levels needed throughout the domain as the donor element was being installed via a construct bearing a free (OH) reducing end. In particular, we had learned from our collaborators at Bristol-Myers about an apparent incompatiblity in a fully unprotected construct, i.e., **85** (vide infra).

To probe this area, we started with the same rhamnal derivative **68** (Scheme 24). This time, after epoxidation with dimethyldioxirane, the product was subjected to the action of *p*-methoxybenzyl alcohol. Once again, the epoxide opened to give **86**. Unfortunately, in this instance, with *p*-methoxybenzyl alcohol as the acceptor, significant erosion of stereoselectivity occurred and **86** was accompanied by a substantial amount of α-glycoside **87**. As will be seen in the calicheamicin series, each of these two compounds could be advanced equally well in the synthesis, but the need for partitioning, so as to operate with homogenous materials, was certainly a large inconvenience. In this orienting phase of the esperamicin work, we only operated with the *β*-glycoside **86**.

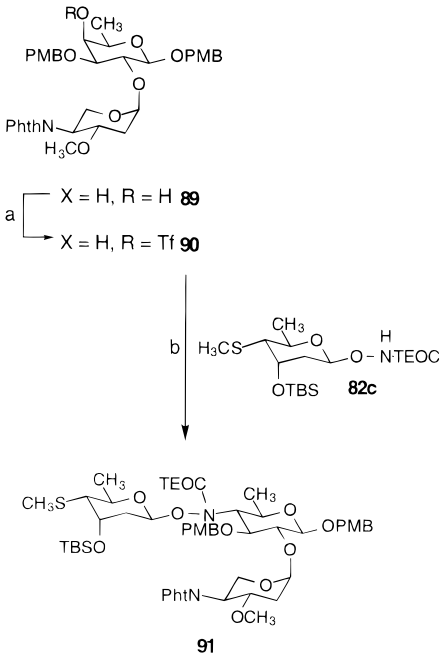
Scheme 24. Synthesis of Disaccharide 89[a]



[a] (a) 2,2-Dimethyldioxirane, CH_2Cl_2; (b) PMB-OH; (c) $I^+ClO_4^-$-(*sym*-collidine)$_2$, CH_2Cl_2; (d) Ph_3SnH, AIBN, benzene, reflux.

As before, in the methyl glycoside series, compound **86** reacted with the phthalimido glycal **71** to give, in this instance, **88** and then **89** (Scheme 24). Following closely the protocols described above, triflate **90** (Scheme 25) was

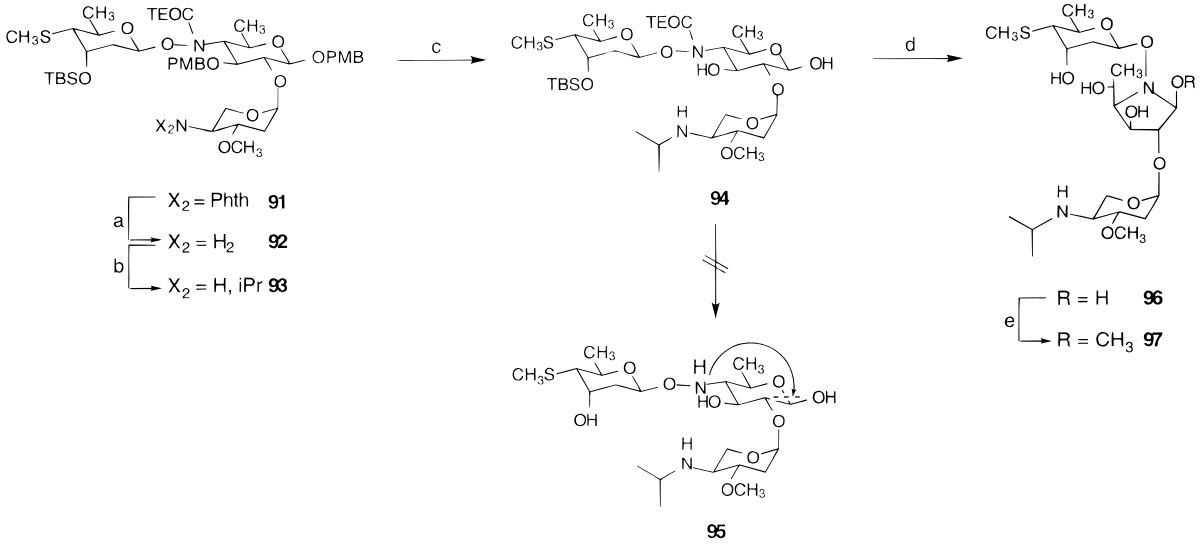
Scheme 25. Synthesis of Trisaccharide 91[a]



[a] (a) Tf_2O, pyridine; (b) NaH, DMF.

produced and coupled with the previously described **82c**. This gave rise to the fully protected system (**91**) in which a *p*-methoxybenzyl group protects the latent anomeric

Scheme 26. Synthesis of 97[a]



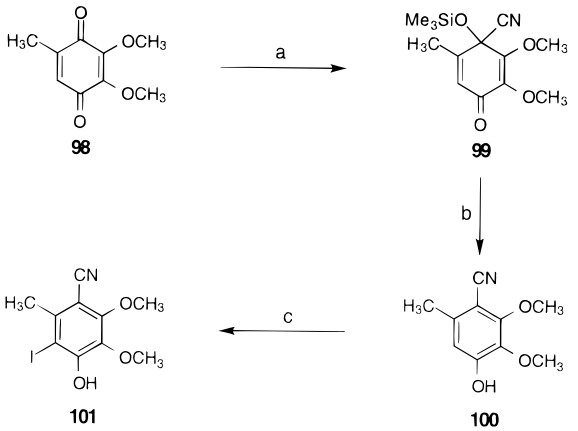
[a] (a) N_2H_4, EtOH; (b) acetone, $NaCNBH_3$, iPrOH; (c) DDQ, $CH_2Cl_2-H_2O$; (d) TBAF, THF; (e) MeOH, AcOH.

hydroxyl while a TEOC function guards the hydroxylamine "linker". Again, we first proceeded with cleavage of the phthalimide group (Scheme 26) and installation of an *N*-isopropyl function (cf. **93**). This was followed by full deprotection, including the TEOC group, leading to the formation of **96**. Once again, as with the case of methyl glycoside **84**, capping of the reducing end stabilizes the otherwise fully deprotected system in unrearranged form (vide infra). Similarly, cleavage of the two *p*-methoxybenzyl groups resulted in the formation of **94** where the domain terminates in a free anomeric hydroxyl on the A ring sugar. The substance was well characterized and appeared to be a stable entity. However, upon treatment of **91** with tetra-*N*-butylammonium flouride (for purposes of cleavage of the TEOC function), there was isolated not **95** but, in its stead, the pyrrolidine derivative **96**, best characterized as its methyl glycoside **97**. This compound proved to be identical with a specimen obtained from the Bristol-Myers Company. Hence, we had demonstrated two important features of the tricyclic esperamicin domain. With the reducing end capped, the system was quite stable even in the absence of protection of the hydroxylamine spacer. Conversely, with the hydroxylamine spacer in place in blocked (TEOC) form, the reducing end could be liberated in the form of a free hydroxyl. What did not appear to be feasible was retention of the core carbohydrate domain, in the face of simultaneous deprotection of the *N*-Teoc and anomeric *p*-methoxybenzyl groups. This combination (see hypothetical compound **95**) leads to very rapid rearrangement, presumably by ring opening and reclosure to the *N*-hydroxypyrrolidine type of valence isomer (see **96**).[41,42]

These lessons were not lost upon us as we embarked on the calicheamicin carbohydrate domain. This departure seemed to be preferable to continuing in the esperamicin series, in that we had learned to assemble the calicheamicin aglycon but not the esperamicin aglycon bearing the additional hydroxyl group. Furthermore, from a biological standpoint, the calicheamicin system which exhibits such striking sequence selectivity in its double-stranded DNA cleavage constituted the more exciting synthetic target. Fortunately, the calicheamicin problem was significantly simplified by our previous findings in the esperamicin area. The AEB system, at the fully protected stage, was in fact identical with the one used in the esperamicin series (see triflate **90**).

For calicheamicin, only a modest modification was necessary in the construction of the thiosugar. Thus, it would be presented in the form of the free thiol derivative **82b**. The CD system, however, had to be constructed *de novo* since it has no counterpart in the esperamicin domain. Actually, some strikingly new chemistry was employed in the construction of the B ring of this subdomain by Steven Olson. His synthesis started with the commercially available quinone derivative **98** (Scheme 27) which was converted, according to precedents of Evans, to cyanohydrin **99**. Treatment of **99** with samarium diiodide produced **100**. This chemistry has been used as a general synthesis of extensively substituted *p*-hydroxybenzonitrile groups, but here we confine ourselves to the calicheamicin connection. Iodination of the single available site was carried out with iodonium chloride to give **101**.[43]

Scheme 27. Synthesis of the Aryl Portion of Calicheamicin[a]

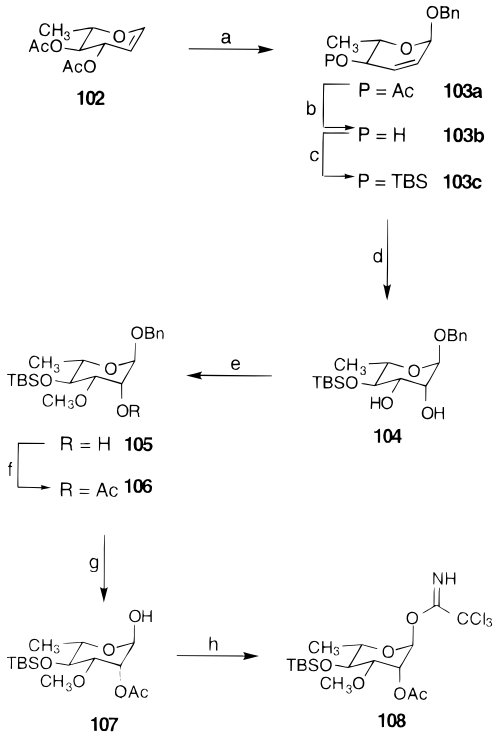


[a] (a) TMSCN, KCN, 18-C-6; (b) SmI_2, THF, MeOH, 82%; (c) ICl, MeCN, 93%.

There remained, also, the need to construct the carbohydrate E ring which also has no counterpart in the

esperamicin system. Randall Halcomb and Serge Boyer took up this problem in earnest. Their synthesis started with L-rhamnal diacetate **102** (Scheme 28) which was

Scheme 28. Synthesis of Trichloroacetimidate 108[a]

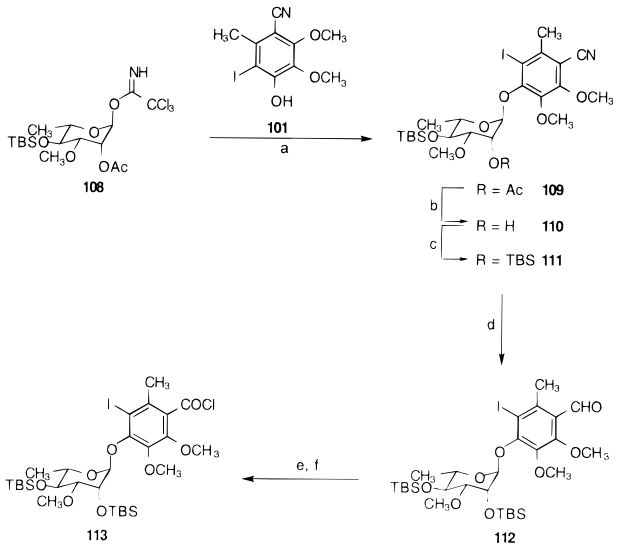


[a] (a) BnOH, CH_2Cl_2, $BF_3{\cdot}OEt_2$; (b) NaOMe, MeOH; (c) TBSCl, imidazole, CH_2Cl_2, 91%; (d) OsO_4, NMO, acetone−H_2O, 96%; (e) Bu_2SnO, MeOH, then MeI, TBAB, benzene; (f) Ac_2O, pyridine; (g) H_2, $Pd(OH)_2$, MeOH; (h) Cl_3CCN, NaH, CH_2Cl_2.

converted to **103a** by benzyloxy Ferrier rearrangement and protected via free alcohol **103b** as the TBS derivative **103c**. Reaction of **103c** with osmium tetraoxide gave, substantially, **104**, which could be selectively methylated at the equatorial center via stannylation (see compound **105**). Upon acetylation, **105** was converted to **106**. Cleavage of the anomeric benzyl glycoside was accomplished through hydrogenolysis. The anomeric hydroxyl group of **107** thus unveiled was activated as its trichloroacetimidate **108** through the action of sodium hydride and trichloroacetonitrile. Coupling of **108** with **101** (Scheme 29) was accomplished via the Schmidt methodology to produce **109**. This substance was, in turn, converted to bis-TBS derivative **111** via the monoalcohol **110**. In model systems related to **111**, it had been shown that the nitrile group (or even a methyl ester) was very sluggish with respect to hydrolysis. Accordingly, we proceeded via reduction of the nitrile function in **111** to aldehyde **112** followed by oxidation to the free carboxylic acid and activation as its acid chloride **113**. At this stage, we could couple the CD segment to the aforementioned B ring thiol **82b** to give rise to the tricyclic system **114** (Scheme 30). The stage was then set for coupling CD substructure **114** with the previously described AE system **90**. Once again, Kahne coupling was successful and the full "penta domain" was in hand (see compound **115**).[44]

At this stage, we could selectively deprotect the anomeric *p*-methoxybenzyl function to give rise to **116**. We were now in a position to explore the possibility of

Scheme 29. Synthesis of Aryl Saccharide 113[a]



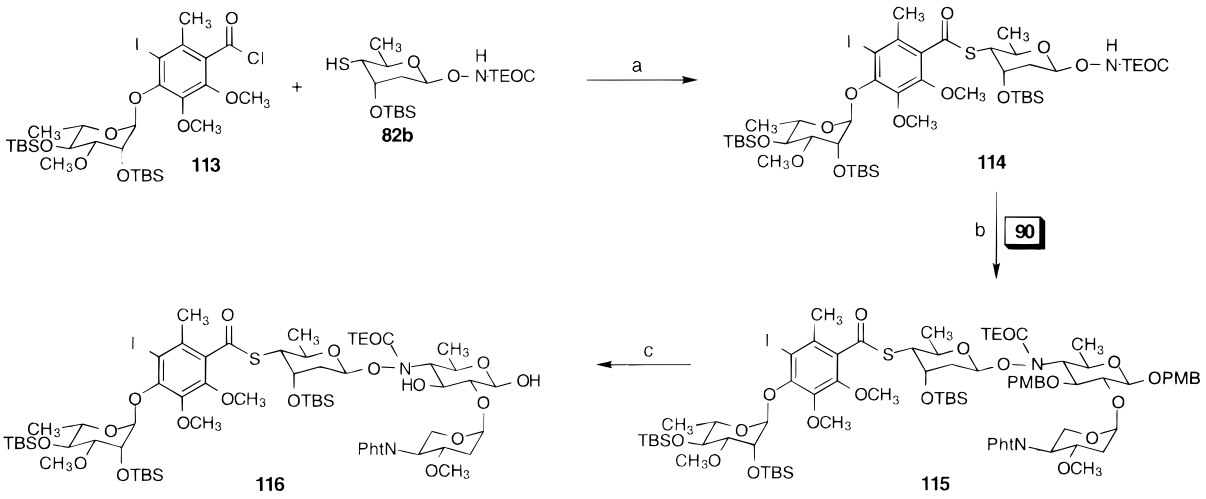
[a] (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 95%; (b) NaOMe, MeOH; (c) TBSOTf, pyridine, CH_2Cl_2, 87%; (d) DIBAH, CH_2Cl_2, 77%; (e) $NaClO_2$, H_2O, tBuOH, $NaHPO_4$; (f) $(COCl)_2$.

coupling a calicheamicin aglycon with an advanced carbohydrate model. We turned to the use of a trichloroacetimidate as the donor function, using the very powerful Schmidt protocol. It seemed that the trichloroacetimidate method would give us the best combination of a proven donor type which could be fashioned under mild conditions and which came with a long track record of couplings with rather hindered acceptors. The acceptor, in this instance, would be aglycon **56**. Before proceeding to such coupling steps, it would be necessary to produce the aglycon as a single enantiomer.

Fortunately this series of compounds was easily accessed by going back to the total synthesis of racemic calicheamicinone at the stage of compound **54** (Scheme 31). Treatment of this compound under the Wong conditions with vinyl acetate and lipase PS-30 indeed led to high enantioselectivity in the acetylation of the primary alcohol. Elsewhere we have described this process in greater detail.[32] Suffice it to say here that. building on the key Wong method, we could gain access to both the calicheamicinone and the *ent*-calicheamicinone series.[18b] After some initial confusion in the proper absolute configurational assignment of these aglycons, the matter was clarified and each of these series could be converted to their final glycosyl acceptor versions, i.e., the calicheamicinone ketal and the *ent*-calicheamicinone ketal (vide infra). It was our hope that there would be sufficient chemical distinction between the secondary and tertiary alcohols that it would not be necessary to protect the latter as a prelude to glycosylation.

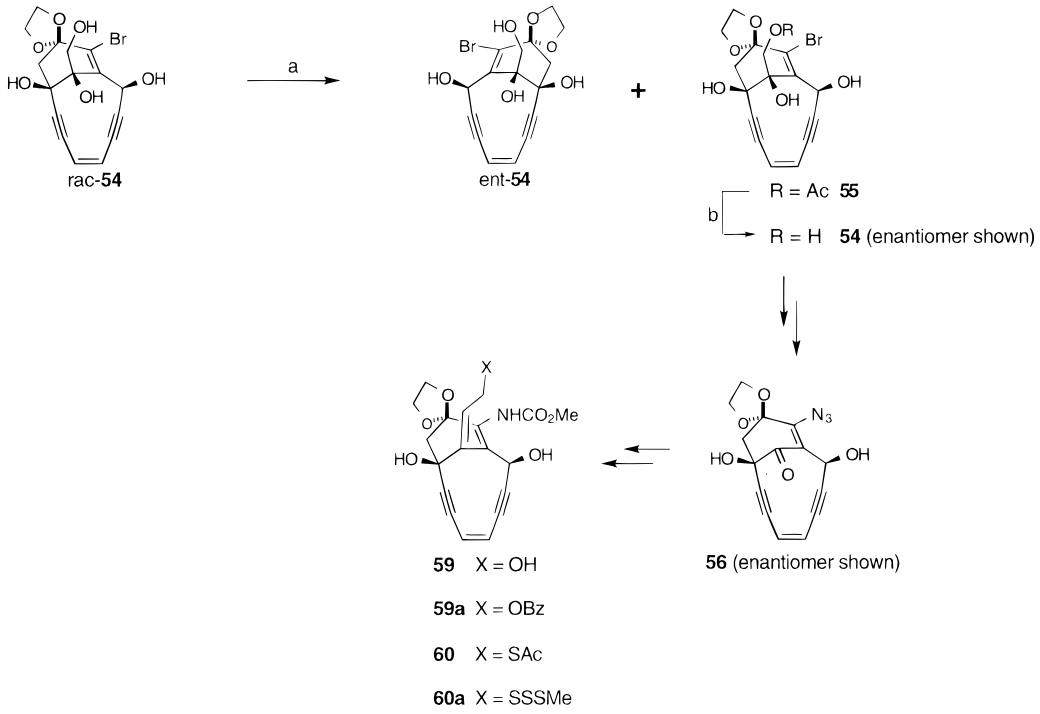
In a major advance in the area (Scheme 32), it was shown by Randall Halcomb *for the first time that it was indeed possible by trichloroacetimidate coupling to join an advanced, fully synthetic, aglycon construct to an advanced fully synthetic carbohydrate domain.*[45] While it was gratifying to demonstrate that such a coupling could be conducted, the sense of triumph was tinged with considerable concern in regard to total synthesis. For instance, the first step in developing the principal *β*-product **118** would involve cleavage of the phthalolyl group. Unfortunately, it soon became clear that substrates bearing the enediyne functionality, including **118**, were unstable to various conditions attempted in

Scheme 30. Synthesis of Calicheamicin Pentasaccharide 116[a]



[a] (a) Et_3N, DMAP, CH_2Cl_2, 85%; (b) NaH, DMF, then 90, 80%; (c) DDQ, CH_2Cl_2, H_2O.

Scheme 31. Enzymatic Resolution of 54[a]



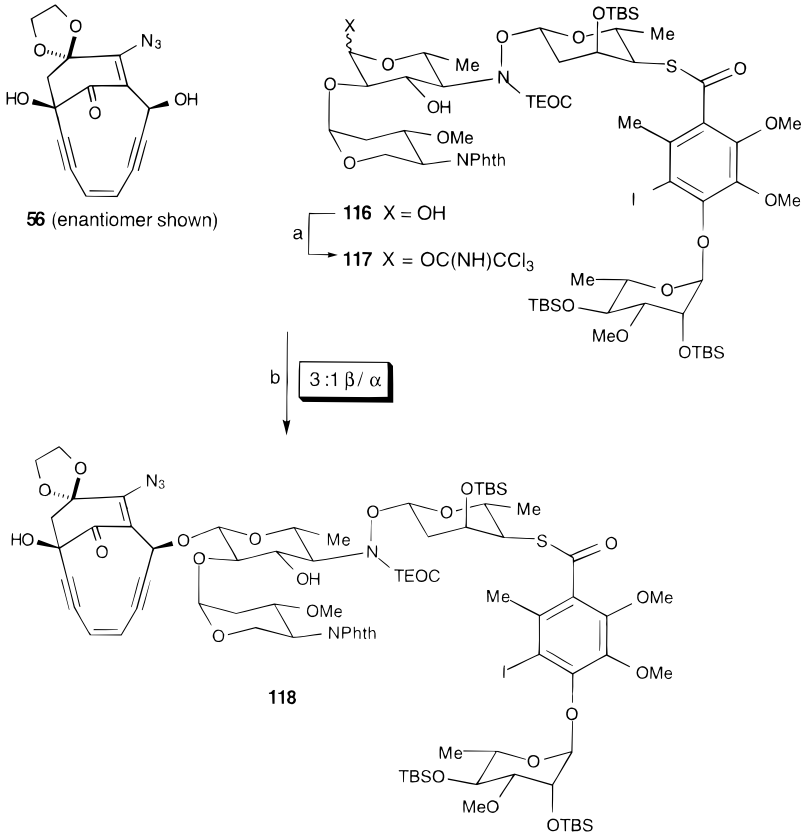
[a] (a) Lipase PS-30, DME, vinyl acetate; (b) 7 N NH_3, MeOH.

dephthaloylation. Thus, it became obligatory that the carbohydrate domain be introduced at an even more advanced level than is represented by compound **118**. We took this to mean that it would be necessary to advance the E ring nitrogen of the donor structure to the point where it had already incorporated its ethyl group and was protected with a readily dischargable function such as an Fmoc function.

It also seemed unlikely that the steps necessary to traverse the gap between the C_{13} ketone in the acceptor which was used and the final vinyl trisulfide would probably be too extensive to be feasible in a structure of this complexity. Accordingly, it would also be necessary to introduce the acceptor at a more advanced stage. Some early efforts using the benzoate **59a** (natural enantiomer) as the glycosyl acceptor were explored by Margaret Chu-Moyer with good indications of feasibility. However, in our series, we were somewhat skeptical about the possibility of conducting the advancement of the allylic benzoate to the allylic thioacetate with survival of the Fmoc function alluded to above. Hence, Dr. Stephen Hitchcock opted to examine the bolder possibility where the thioacetate would already be included in the structure of the acceptor molecule undergoing glycosylation (see compound **60**, Scheme 31).

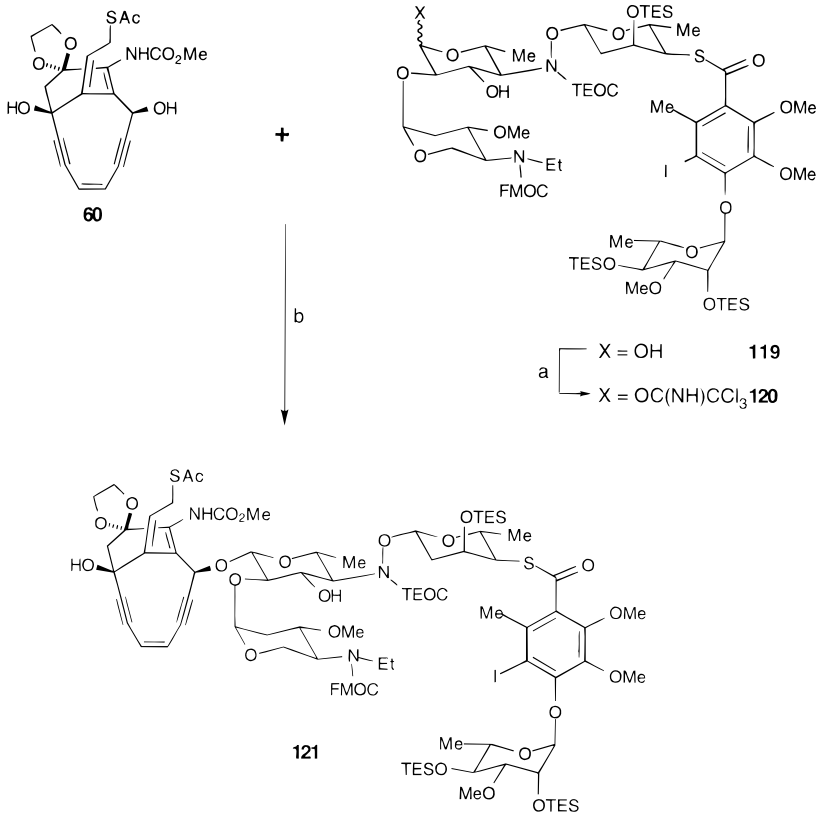
Returning again to the total synthesis of calicheamicinone, this time carried out on the natural (as well as the unnatural) enantiomer, we examined glycosylation of compound **60** (Scheme 33). We also effected changes in the donor system. Our in-house research had indicated that the cleavage of the TBS protecting groups post-glycosylation would be highly problematic in the setting of the full panoply of calicheamicin functionality. A particular source of vulnerability would be the slowness of the removal of the TBS function from the D ring sugar. This deprotection was possible in the methyl glycoside

Scheme 32. First Glycosylation of a Calicheamicinone Congener with a Full Penta Domain[a]



[a] (a) DBU, Cl_3CCN, CH_2Cl_2; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 28%.

Scheme 33. Synthesis of Protected Calicheamicin Thioacetate 121[a]



[a] (a) Cs_2CO_3, Cl_3CCN, CH_2Cl_2, 91%; (b) AgOTf, 4 Å MS, CH_2Cl_2, 58%.

series, upon prolonged treatment with TBAF. Unfortunately, it was demonstrated by model studies that such multihour exposure would not be feasible in the context of the fully developed, advanced, precalicheamicinone

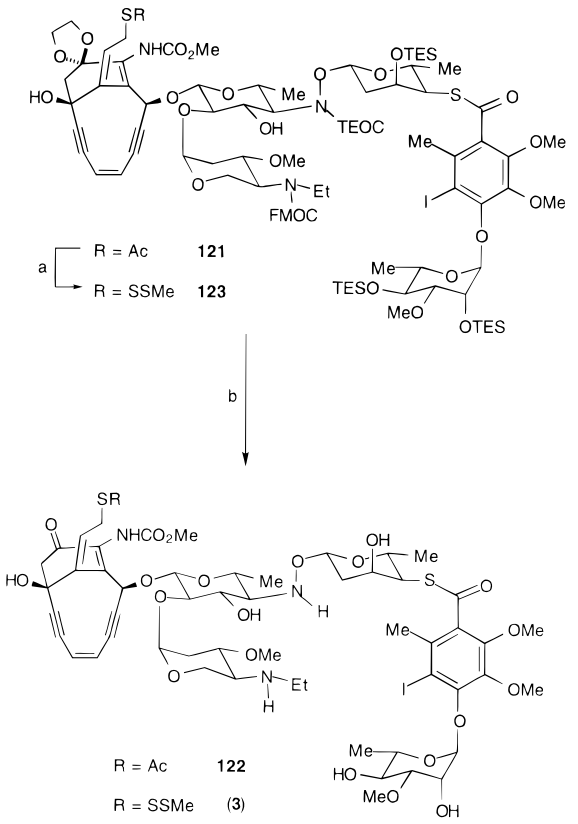
functionality. In fact, our studies indicated that the tolerance of such advanced constructs toward TBAF would be feasible only if exposure would be confined to a few minutes. While recourse to room temperature exposure to TBAF would shorten the time necessary for deprotection, even the carbohydrate domain did not tolerate these conditions well. Attempts to carry out such deprotections led to loss of the entire D ring from the domain by cleavage of the aryl glycoside bond. Accordingly, it became necessary to modify the carbohydrate domain such that the hydroxyl groups were protected as triethylsilyl (TES) ethers. Here, it seemed likely that deprotection could be accomplished under much milder conditions which might be compatible with survival of the sensitive resident functionality (vide infra). The schemes which had initially been used in construction of the per-TBS-protected glycosyl donor were now reconstituted using triethylsilyl protection groups for the carbohydrate domain hydroxyls. The coupling reaction types described above were carried out using triethylsilyl protecting groups, and the E ring nitrogen was protected as its *N*-ethyl Fmoc carbamoyl group. The feasibility of using this group had been earlier demonstrated by Nicolaou in his total synthesis in the context of an oxime ether linking strategy.[19] We were, of course, most thankful to have a documented precedent albeit on a different construct. The adaptation of our earlier chemistry for synthesizing donor **120** is shown in Scheme 33.

In the event, coupling at the stage of optically pure thioacetate **60** with trichloroacetimidate **120** was successful under the conditions shown. A 50% yield of glycoside **121** was obtained. Removal of the triethylsilyl and TEOC protecting groups was accomplished (Scheme 34) with HF·pyridine, and the ketal function was cleaved with aqueous acid to afford **122**. The fully deprotected thioacetate had also been prepared during the Nicolaou synthesis,[21] and upon receipt of an NMR spectrum of an authentic sample from the La Jolla workers, it was clear that our totally synthetic product **122** was correctly formulated. Therefore, the total synthesis of the thioacetate, itself a biologically active substance, had been accomplished by a highly convergent strategy.

We returned to the protected compound **121** (Scheme 34). Cleavage of the acetyl group was effected via diisobutylaluminum hydride. Installation of the trisulfide linkage was carried out under modified Harpp conditions to give **123**. After cleavage of the ketal with aqueous acetic acid, a reaction which also led to some silyl deprotection, the molecule was subjected to short term treatment with anhydrous TBAF. This led to complete deprotection of all silyl groups as well as the TEOC and the Fmoc functions, giving rise to fully synthetic calicheamicin γ^1_1 (**3**) identical with an authentic sample provide by the Lederle group.

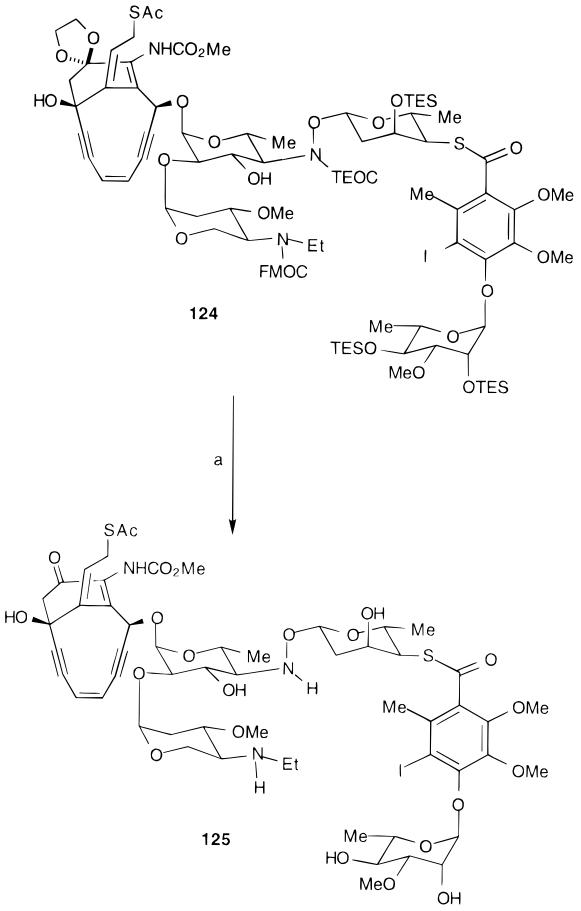
The ratio of β:α glycosylation in the natural series was approximately 3:1. The minor α product **124** could be processed (Scheme 35), as above, to give rise to the fully synthetic "allo" calicheamicin thioacetate construct **125**, differing from **122** only in the stereochemistry of the anomeric bond joining the carbohydrate domain to the C_8 hydroxyl of the aglycon thioacetate sector. We also coupled aglycon acceptor (*ent*-**60**) to glycosyl donor **120** (Scheme 36). Remarkably, in this case there was a striking reversal in the sense of glycosylation. The ratio of glycosides **126** and **127** produced in this reaction was 18:1 favoring the α-glycoside. We take this result as a striking reaffirmation of the concept that glycosidation

Scheme 34. Synthesis of Calicheamicin γ_1^I [a]



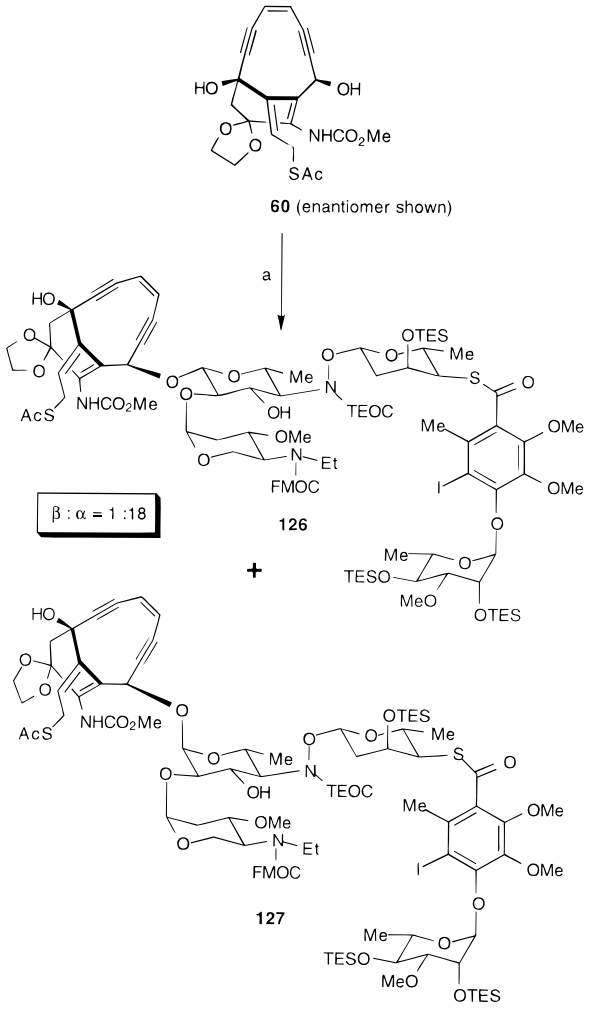
[a] (a) DIBAH, CH_2Cl_2, −78 °C, then *N*-(methyldithio)phthalimide (54%); (b) CSA, THF−H_2O, then TBAF, THF, R = Ac (40% overall), R = SSMe (37% overall).

Scheme 35. Synthesis of 125[a]



[a] (a) CSA, THF−H_2O, then TBAF, THF, 40%.

Scheme 36. Synthesis of 127[a]

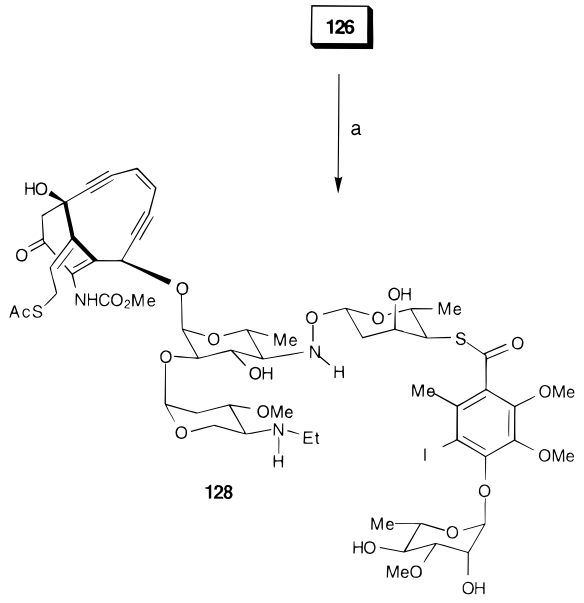


[a] (a) AgOTf, 4 Å MS, CH_2Cl_2, 38%.

ratios exhibited by a particular glycosyl donor are not an independent property of the leaving group and protecting group ensemble but also reflect a high order of interactivity with the acceptor system. We would argue that in the case of acceptor *ent*-**60** the formation of a β-equatorial glycoside giving rise to **127** cannot be accomplished without considerable abutments between donor and acceptor in the transition state of the emerging glycoside. However, α-glycosidation with formation of an axial bond allows for a much greater autonomy of the two sectors, even at the transition state level of their bond formation (see α-glycoside **126**). Full deprotection was carried out only on the prevalent α-glycoside to give the ent (aglycon domain) and epimeric thioacetate **128** (Scheme 37).

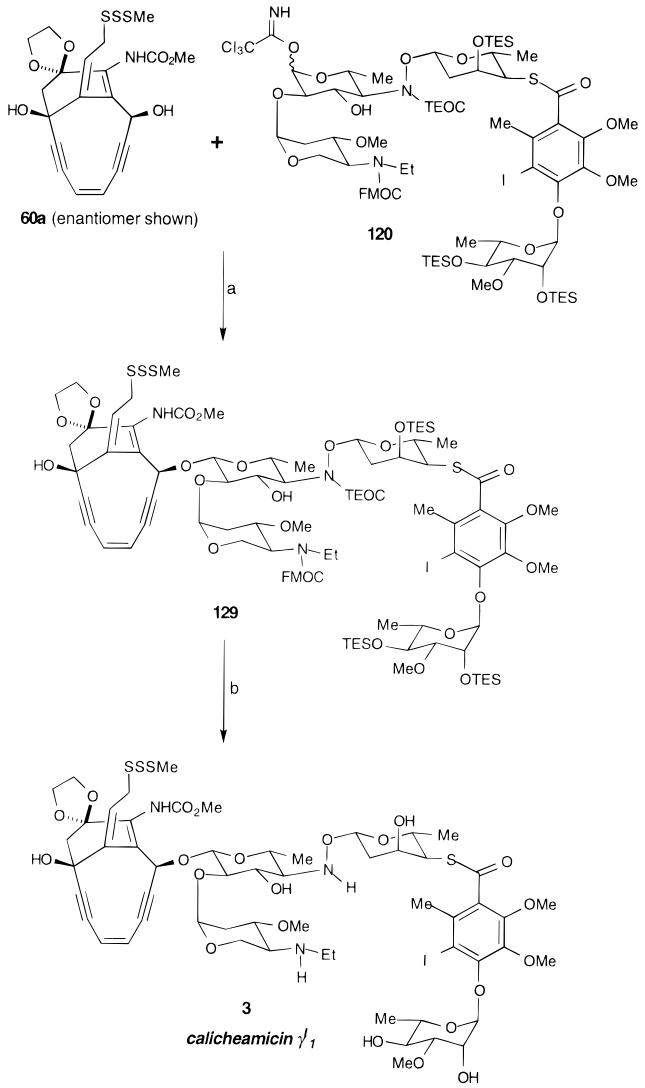
Having accomplished glycosidation at a rather advanced level, both in terms of glycosyl donor and glycosyl acceptor, we were unable to resist the temptation to explore the possibility of achieving maximal convergence in the synthesis. For that purpose the glycosyl acceptor would have to include the full trisulfide functionality. Accordingly, the optically pure natural calicheamicinone series was advanced to the point of calicheamicinone ketal **60a** itself, following chemistry previously carried out in the racemic series. In the event, coupling of donor **120** (Scheme 38) with calicheamicinone ketal **60a** (natural antipode), under very specified conditions developed by Dr. Stephen Hitchcock (silver triflate, 4 Å molecular

Scheme 37. Synthesis of 128[a]



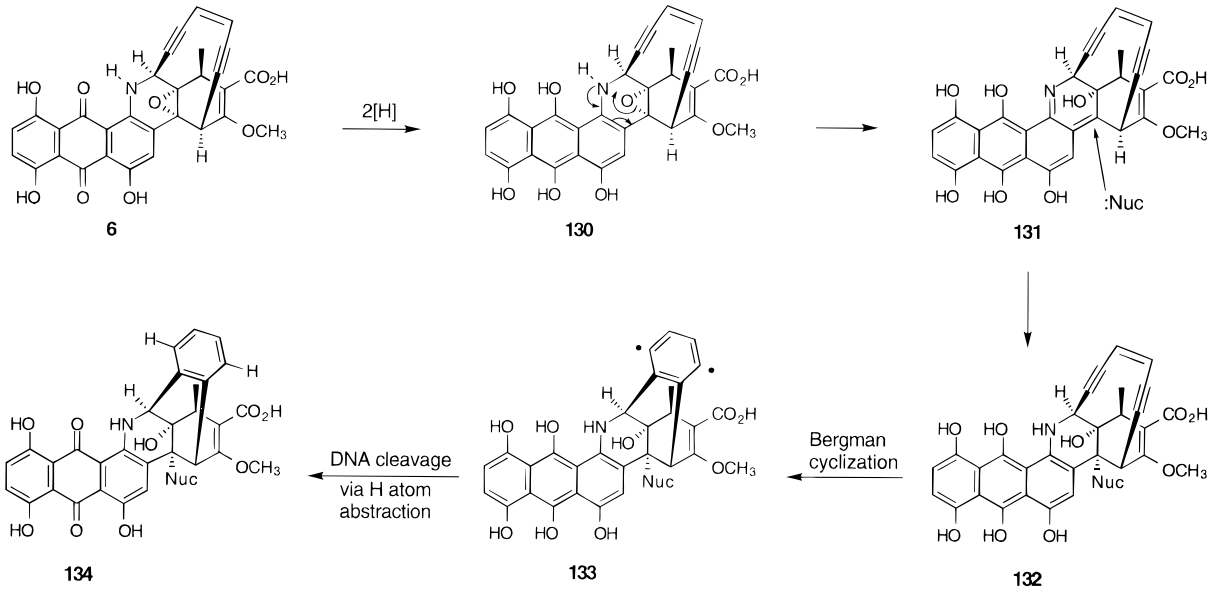
[a] (a) CSA, THF−H_2O, then TBAF, THF, 40%.

Scheme 38. A Highly Convergent Synthesis of Calicheamicin γ_1^I (two steps post-glycosylation)[a]



[a] (a) AgOTf, 4 Å MS, CH_2Cl_2, 34%; (b) CSA, THF−H_2O, then TBAF, THF, 32%.

Scheme 39. Mode of Action of Dynemicin A (6)



sieves, methylene chloride, room temperature), gave rise to a glycoside (**129**) as the only detectable product, albeit in only 34% yield. We attribute the somewhat disappointing yield to the relatively small amounts of acceptor which were available to us at this phase of the study. Nonetheless, it was remarkable that sufficiently mild glycosylation conditions had been developed such that it was possible to join the aglycon and donor entities of the fully functionalized calicheamicin system. A two-tep deprotection protocol involved camphorsulfonic acid which cleaved the ketal as well as some of the silyl groups and brief exposure to TBAF which led to completion of the silyl deprotection as well as cleavage of the TEOC and Fmoc functions. *A maximally convergent total synthesis of calicheamicin (two steps post coupling!) had in fact been accomplished*.[18]

Even while the calicheamicin project was occupying our attentions, there appeared in the literature another enediyne natural product, dynemicin A (see **6**, figure 1), isolated from *micromonospora chersina*.[14] Its structure was established via crystallographic means. Dynemicin A exhibits potent cytotoxicity and double-strand DNA cleavage capacity although lacking the sequence specificity of calicheamicin.[46]

In comparing dynemicin with calicheamicin, an obvious similarity in the presence of a cyclic enediyne in each structure is perceived as is a major difference. Thus, dynemicin lacks the carbohydrate domain which is central in establishing a molecular rapport between the enediyne and DNA. The anthraquinone sector of dynemicin presumably provides some of the DNA contacts which are furnished by the relatively lipophilic carbohydrate domain of calicheamicin.[44]

In a very early, but still influential position paper concerning the bioorganic chemistry of dynemicin, Semmelhack proposed that the bioactivation steps for dynemicin involves reduction of quinone to hydroquinone (Scheme 39).[15] At this point, the lone pair on the quinoline nitrogen, no longer part of a vinylogus amide linkage as in dynemicin, is more capable of manifesting internal nucleophilic character in participating in solvolytic displacement of the epoxide (see arrows: **130** → **131**). Without specifying the nature of the nucleophile (Nuc:) in detail (hydroxyl, cystine-based thiol, or amino functions), it is seen that overall front side displacement would give rise to **132**. The latter structure type emerges as a likely substrate for Bergman-type rearrangement to a 1,4-diyl (**133**) which inaugurates the DNA cleavage and cytotoxicity cascades.

This Semmelhack formulation, while unsupported by any chemical experiments, seemed so intuitively reasonable as to be persuasive and was also of great teaching value at the level of synthesis. From it followed the perception that, during the course of building dynemicin, once the epoxy enediyne system was in place it would be necessary to downregulate the nucleophilic character of the quinoline nitrogen either through acylation, through electronic connectivity to an anthraquinone moiety, or to an equivalent thereof.

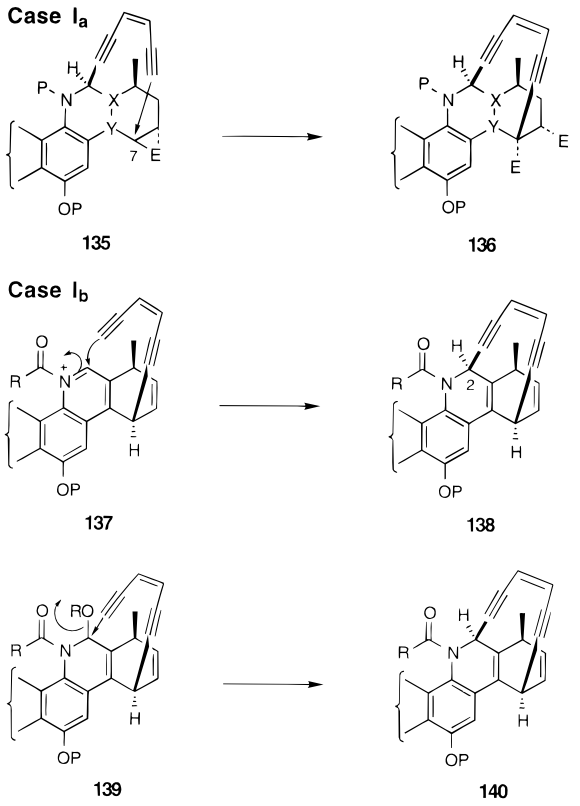
Indeed, it was compellingly clear that the opportunities and challenges posed by the novel metabolite dynemicin could not be overlooked or bypassed by our laboratory. As is our custom, we would become engaged at the level of total synthesis.[47,48] The interesting chemical issues posed by dynemicin were reason enough to institute an exploratory effort in synthesis. However, we further hoped that out of such synthetic studies might follow opportunities to garner some new insights regarding drug design in this area.[49]

Given our involvements in calicheamicinone and calicheamicin, we naturally came to consider the possibility of closing the enediyne ring by coupling of acetylide ion to a suitable electrophilic center. Clearly, two possibilities can be entertained for such a closure (Scheme 40).

In one broad category, the enediyne is encased in the quinoline sector, presumably at the dihydro or tetrahydro stages (X−Y may correspond to an epoxide, to the second bond of a double bond, or to sp^3-bound functional groups which might become, through some sequence, an epoxide). The electrophile E would be positioned at C_7, and bond formation with the acetylide would occur. The electrophile might be the carbonyl carbon of a ketone or an epoxide joining C_7 and C_6 (cf. **135** → **136**). Alternatively, the enediyne might be moored to C_7. Bond formation might involve attack of the acetylide on carbon 2. The electrophilic center might arise from an intermolecular variant of a Reissert-like reaction.[50]

To pursue the Reissert analogy further, the nitrogen

Scheme 40. Initial Synthetic Perceptions for Cyclic Enediyne Formation (Case Ia and Ib)

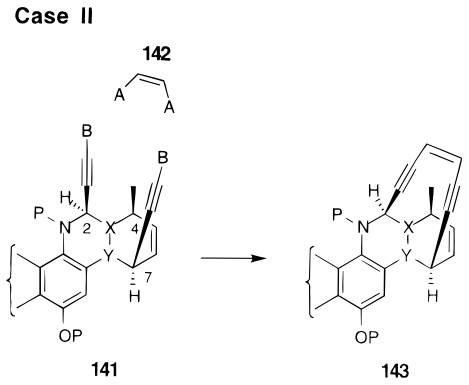


might be suffering acetylation as the ring is being closed (cf. **137** → **138**). In this way, in keeping with the Semmelhack teaching discussed above, amide-like character is introduced even as the enediyne ring system is being fashioned. Alternatively, one could readily imagine a potential carbinolamide-based leaving group being displaced by the nucleophilic acetylide center of the enediyne (cf. **139** → **140**). Bond formation would thus correspond to amidoalkylation. Again, amide-like character of the nitrogen coincides with establishment of the cyclic enediyne systems.

Of the two acetylide−electrophile closures, the case I_b was, for us, the more interesting. Case I_a, while certainly far from trivial in leading to an actual synthesis of dynemicin, represented at the conceptual level a relatively modest extension of the calicheamicinone approach. Happily, many other groups were now practicing this chemistry throughout the enediyne field. In fact, with the notable exception of the Schreiber approach to dynemicin (which led to a synthesis of methylated versions of dynemicin via transannular Diels−Alder reaction)[46] every route to either calicheamicin or dynemicin was utilizing, in one form or another, an acetylide−electrophile bond connection for fashioning the cyclic enediyne. While this motif also pervaded attempts to close a bond to C_2, the challenges associated with organizing the requisite functionality and the likelihood that they would bring in their wake greater opportunities for chemical innovation served to tilt us in the direction of case I_b.

We also wanted to examine an unprecedented approach (Scheme 41), i.e., closure of the enediyne by interpolating a generic cis-disubstituted ethylene (**142**) between two acetylides as shown in the structure (**141** + **142** → **143**). Once again, we leave unspecified the nature of X, Y and A, B in the cyclization precursor. We refer to the interpolative approach as case II.

Scheme 41. Synthetic Perceptions of an Interpolative Approach to the Cyclic Enediyne (Case II)

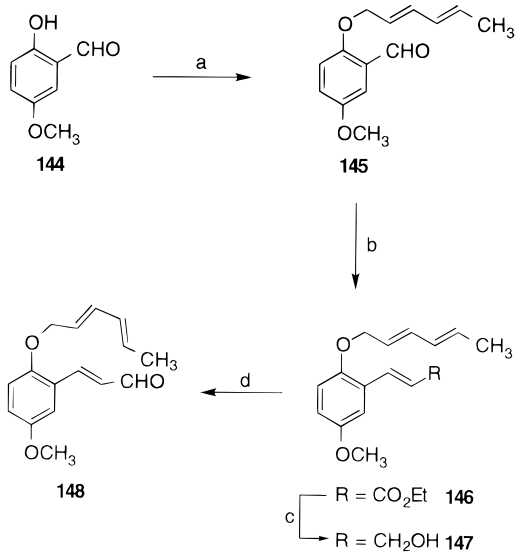


It will be noted that, from a stereochemical perspective, case II represents the greater challenge in preassembly. In either version of case I, a single cis relationship between the secondary methyl center at C_4 and an enediyne arm of a suitable seco precursor must be fashioned. In essence, the cyclization (in whichever order) implements the second cis acetylide−methyl relationship. This is in contrast to case II where two cis methyl−acetylide relationships governing C_2, C_4, and C_7 must in place before interpolative cyclization between bisalkyne and olefin can be considered.

We elected to pursue concurrently case I_b and case II. In each instance, a need for fashioning a cis relationship between the secondary methyl at C_4 and the propynyl arm at C_7 would be necessary. Obviously, the solution for this requirement must be melded into a comprehensive synthetic program. *As in calicheamicin, our aim with dynemicin was the full natural product in all its structural detail.* Solutions which seemed to solve regional issues without the promise of extendibility to a total molecular solution were of less interest. It is with the matter of a solution to the cis C_4−C_7 relationship in a realistic setting appropriate for reaching dynemicin that our explorations began. For establishing this relationship, Tae-young Yoon turned to one of the most reliable precepts in organic chemistry, i.e., the suprafacial governance of the Diels−Alder cycloaddition reaction (vide infra).

Commercially available aldehyde **144** (Scheme 42) was *O*-alkylated with sorbyl bromide to afford **145**. Through sound chemical steps, **145** was converted to **147** and then to trienal **148**. The asterisks at the butadienyl carbons (cf. **148**, Scheme 43) direct attention to the cisoid relationship of the methyl and methylene groups projecting from prochiral centers corresponding respectively to C_4 and C_7 of the future dynemicin target. Under catalysis by zinc chloride, a highly stereoselective Diels−Alder reaction occurred, affording **149a**, the product of endo addition. The next steps involved treatment of **149a** with ceric ammonium nitrate (CAN). A great deal of precedent could be marshaled for the use of this reagent to achieve oxidative dealkylation of diethers of hydroquinones. Ordinarily both alkyl carbons constitute C_1 or C_2 reaction "throwaways". In the case at hand, the role of the methoxy carbon is indeed relegated to that of a "throwaway" carbon. However, the methylene etheral carbon had undergone conversion to a hydroxymethyl

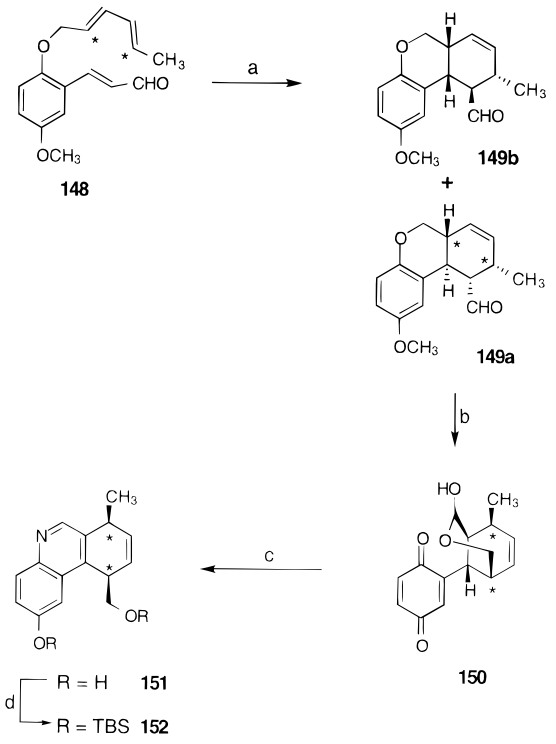
Scheme 42. Synthesis of Triene Aldehyde 148[a]



[a] (a) Sorbol bromide, K_2CO_3, acetone, 96%; (b) $(EtO)_2P(O)$-CH_2CO_2Et, NaH, THF, 95%; (c) DIBAH, CH_2Cl_2, 99%; (d) Swern oxidation, 91%.

group during the same oxidative dealkylation. This cis relationship of the hydroxymethyl group and the aldehyde need not have been critical to the total synthesis plan but turned out to be important. It allowed for containment of these groups in the form of a hemiacetal linkage (see compound **150**) which stabilizes the functionality to the oxidative conditions. We note parenthetically that the exo IMDA product **149b** formed as a minor product in the strictly thermal cyclization of **148** suffered virtually complete destruction upon treatment with CAN. This difference of outcomes presumably reflects the crucial stabilization role of the hemiacetal linkage.

Scheme 43. Synthesis of Dihydrophenanthradine 152[a]

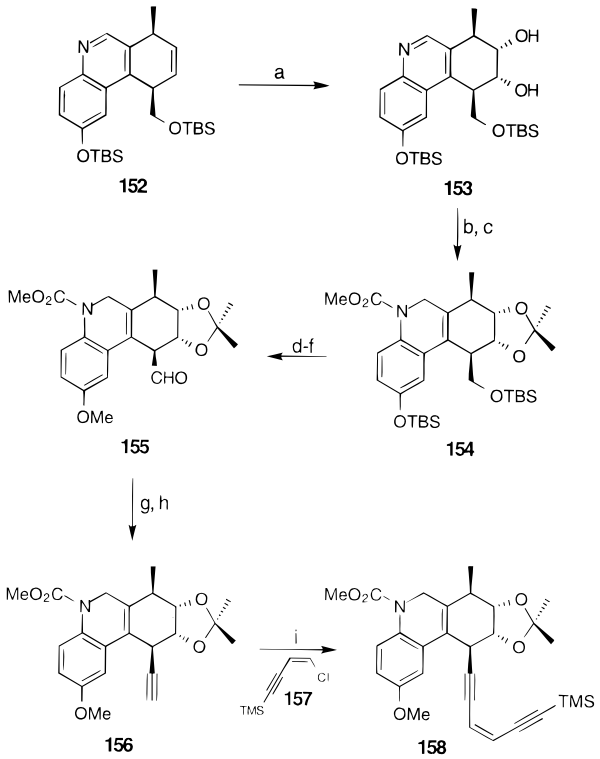


[a] (a) $ZnCl_2$, CH_2Cl_2, 60%; (b) $Ce(NH_4)_2(NO_3)_6$, MeCN, H_2O, 90%; (c) NH_4OAc, HOAc, 100 °C, 89%; (d) TBSCl, IMID, CH_2Cl_2, 98%.

Treatment of **150** with ammonium acetate in acetic acid at 100 °C afforded **151** and, following bis silylation, **152** in which the quinoline structure had been installed.[51] This matrix in which the necessary C_4-C_7 cis relationship had been put into place was to serve both cases I_b and II. The latter would lead to dynemicin A (vide infra).[22]

Before detailing the progression which did bring success, we digress to describe the highlights of our efforts, albeit unsuccessful, to realize an intramolecular Reissert reaction.[52] To pursue this possibility, compound **152** (Scheme 44) was subjected to osmylation to produce diol

Scheme 44. Synthesis of Seco Enediyne 158[a]

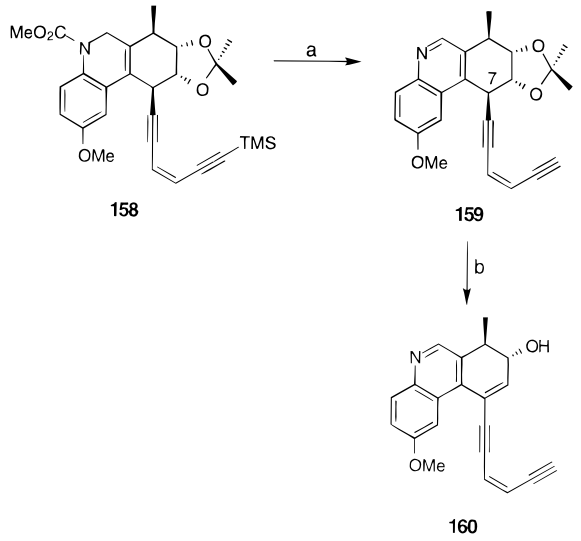


[a] (a) Catalytic OsO_4, NMO, THF$-H_2O$, 90%; (b) nBu_3SnH, $ClCO_2Me$; (c) $Me_2C(OMe)_2$, catalytic pTsOH, 95% (two steps); (d) K_2CO3, MeOH; (e) K_2CO_3, Me_2SO4; (f) TBAF, THF, then Swern oxidation, 81% (three steps); (g) PPh_3, CBr_4, CH_2Cl_2, 79%; (h) nBuLi, $PhCH_3$, −78 °C, 77%; (i) **157**, $Pd(PPh_3)_4$, CuI, $BuNH_2$, PhH, 93%.

153 as shown. The resultant **153** was exposed to reductive carbomethyoxylation to deliver **154** following formation of the acetonide. At this stage, functional and protecting group differentiation afforded **155**. The derived aldehyde **155**, when taken through a Corey−Fuchs protocol,[53] afforded terminal acetylide **156**. Elongation of the latter by Castro−Stephens coupling[54] to **157** gave rise to **158**. The scenario for attempting intermolecular Reissert bond closure was then set (Scheme 45) by oxidative decarbomethoxylation of **158** with DDQ followed by desilylation with TBAF to afford enediyne **159**.

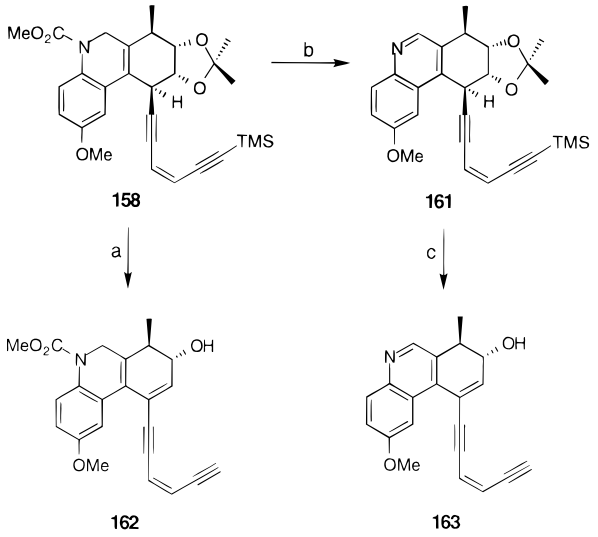
Cyclization of **159** was attempted with lithium hexamethyldisilazide. The reaction afforded the β-eliminated product **160**. Clearly, reaction had occurred through deprotonation of the C_7-H bond with ejection of acetone. The acidity of the C_7 center and its undermining effect on our proposed cyclization had not been properly anticipated. Other experiments pointed to the same problem. Thus, attempted desilylation of **158** (Scheme 46) with TBAF led instead to **162**. Another sequence also

Scheme 45. Synthesis of Quinoline 159 and Attempted Cyclization[a]



[a] (a) DDQ, TMSCN, then TBAF, 68%; (b) LHMDS, THF, −78 °C.

Scheme 46. Attempted Enediyne Cyclizations[a]



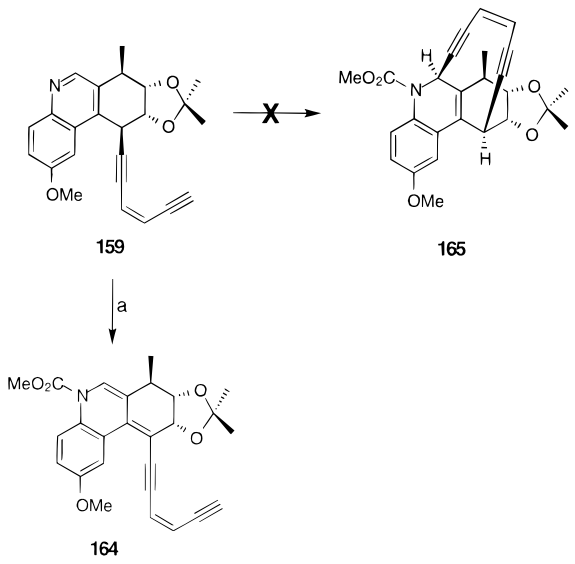
[a] (a) TBAF; (b) DDQ, TMSCN; (c) $ClCO_2Ph$, CsF.

supported this trend. Treatment of **158** with DDQ in the presence of TMSCN afforded **161**. We then hoped to achieve carbamoylative cyclization through joint treatment of **161** with phenyl chloroformate and cesium fluoride (for disylylation). Once again, these conditions led to compound **163**. We then returned to compound **159** in which the acetylenic silyl group had already been cleaved (Scheme 47).

The thought was to deprotonate the acetylene while carbamoylating the quinoline nitrogen as a protocol to favor cyclization. We hoped to bring this result about by treatment of **159** with isopropylmagnesium bromide in the presence of methyl chloroformate. Unfortunately, this reaction afforded not the cyclic enediyne **165** but **164**, in which the same type of elimination, by deprotonation from C_7, had occurred.

At this stage, we despaired of achieving cyclization in the intended sense, unless the problem of the C_7 acidity had been countered. One progressive way of dealing with this problem was to install the epoxide at the C_8−C_9 double bond prior to projected cyclization. We proceeded

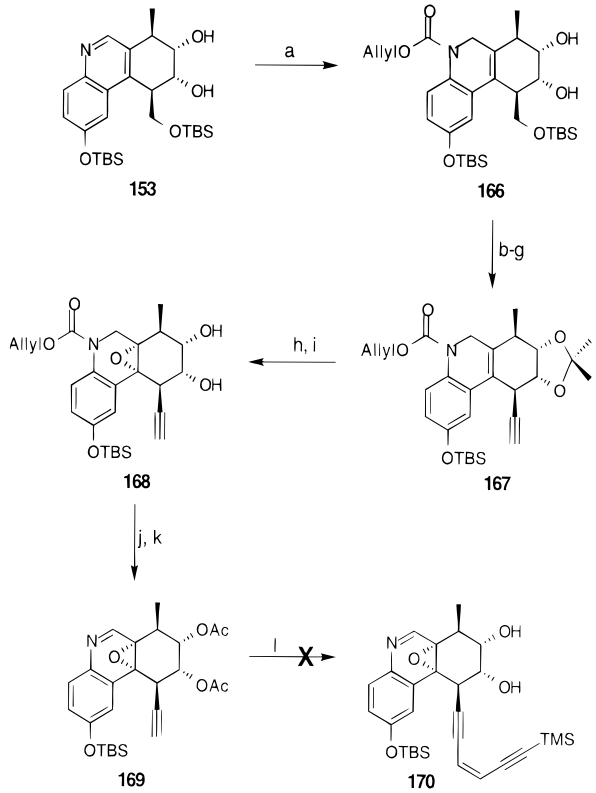
Scheme 47. Attempted Cyclization of 159[a]



[a] (a) iPrMgBr, $ClCO_2Me$.

as follows (Scheme 48). Compound **153** was successfully subjected to reductive allyloxycarbomylation to afford

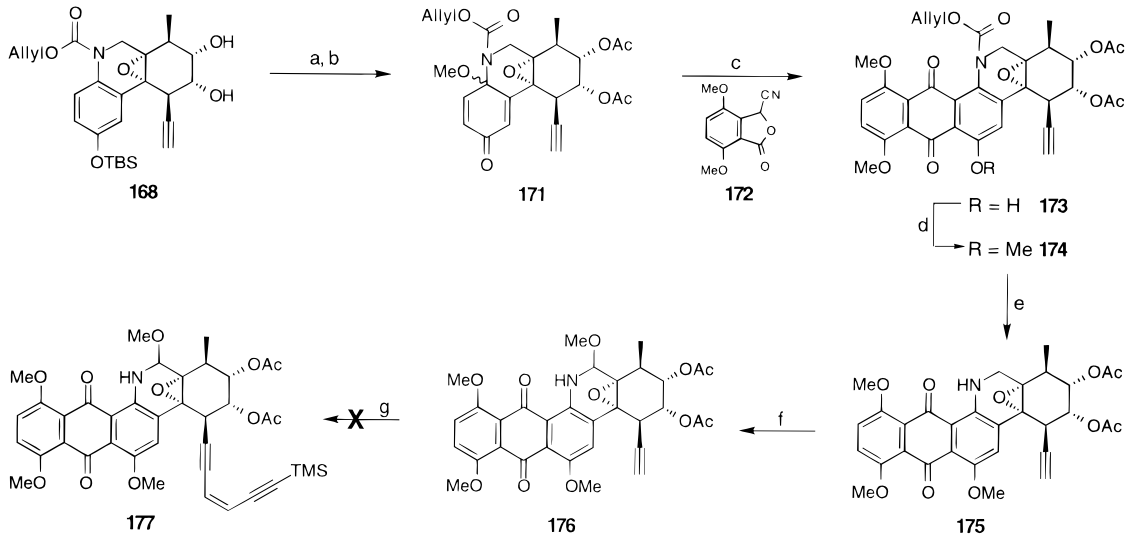
Scheme 48. Synthesis of Imino Epoxide 169 and Attempted Enediyne Formation[a]



[a] (a) nBu_3SnH, $ClCO_2Allyl$; (b) 2-methoxypropene, PPTS; (c) TBAF, THF, 96%; (d) NaH, TBSCl, 79%; (e) Swern oxidation; (f) PPh_3, CBr_4, CH_2Cl_2; (g) nBuLi, $PhCH_3$, −78 °C, 74% (three steps); (h) aqueous TFA, CH_2Cl_2; (i) $VO(acac)_2$, tBuOOH, PhH, 83% (two steps); (j) Ac_2O, Et_3N, DMAP; (k) $Pd(PPh_3)_4$, nBu_3SnH, then DDQ, CH_2Cl_2, 56%.

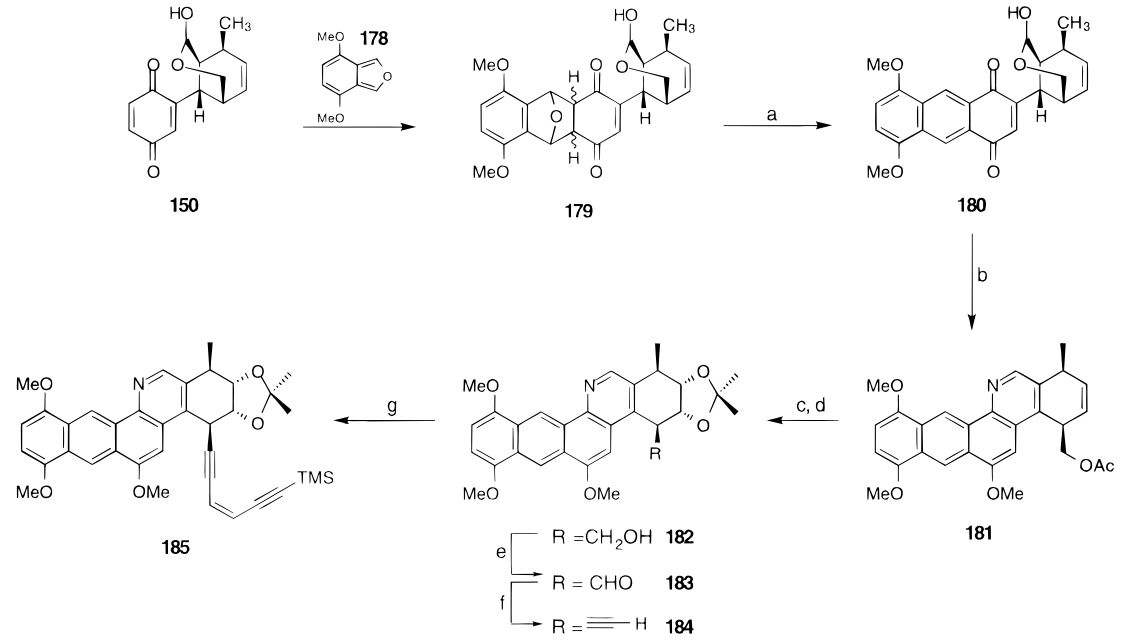
166. We hoped that the Alloc group (allyl carbamate) could be cleaved under very mild conditions after installation of the C_8−C_9 epoxide. It seemed likely that such an epoxide would itself be quite labile. In the event, a

Scheme 49. Synthesis of Anthraquinone 176 and Attempted Enediyne Formation[a]



[a] (a) K_2CO_3, MeOH, then $PhI(OAc)_2$, MeOH; (b) Ac_2O, Et_3N, DMAP, 72%; (c) **172**, tBuOLi, LiCl, 37%; (d) Me_2SO_4, K_2CO_3, 84%; (e) $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, 96%; (f) DDQ, MeOH, CH_2Cl_2, 87%; (g) **157**, $Pd(PPh_3)_4$, CuI, $BuNH_2$, PhH. In one instance, we were able to reach a promising pentacyclic domain, containing a fully extended enediyne side chain at C7.

Scheme 50. Synthesis of Pentacyclic Seco Enediyne 185[a]



[a] (a) NaOAc, HOAc, 100 °C. (b) NH_4OAc, HOAc, 100 °C, then K_2CO_3, Me_2SO_4, then Ac_2O, Et_3N, 25% overall; (c) OsO_4, NMO, THF; (d) 2-methoxypropene, catalytic pTsOH, then K_2CO3, MeOH; (e) Swern oxidation; (f) PPh_3, CBr_4, then nBuLi, THF; (g) **157**, $Pd(PPh_3)_4$, CuI, $BuNH_2$, PhH.

significant part of the scheme was accomplished. Compound **166** could be advanced to **167** and, remarkably, epoxidized, as shown to afford **168**. Even more remarkable was the feasibility of transforming **168** → **169**.

Here, however, our good fortune ran out. All attempts to carry out Castro−Stephens-like elongation of imine epoxide **169** to gain access to enediyne **170** were unsuccessful. We attribute this noncorrectable difficulty to the instability of the imine epoxide in the presence of the palladium(0) reagents necessary for extension of the propynyl group to the enediyne.

We returned to compound **168** and investigated the possibility of building up a pentacyclic domain prior to the acetylide activated imine cyclization step (Scheme 49). Following bisacetylation, the TBS ether group was cleaved and the resultant phenol was oxidized with phenyliodosobenzene diaceteate to afford compound **171**. It then proved to be possible to annulate the system with the dimethoxycyanophthalide **172**, as shown,[55] in a Swenton-like reaction.[56,57] Curiously, only one stereoisomer of **171** functioned in this reaction (probably the epimer with the β-methoxy group). The other methoxy aminal was impervious to the Swenton reaction under a variety of conditions. While this steric dependence was certainly a serious incovenience in moving large amounts of material forward, we did reach compound **173** and then to **174** as shown. Presumably, the viability of the epoxide owes much to the carbamoyl group and to the quinone. Such conjugation attenuates the internal nucleophilicity

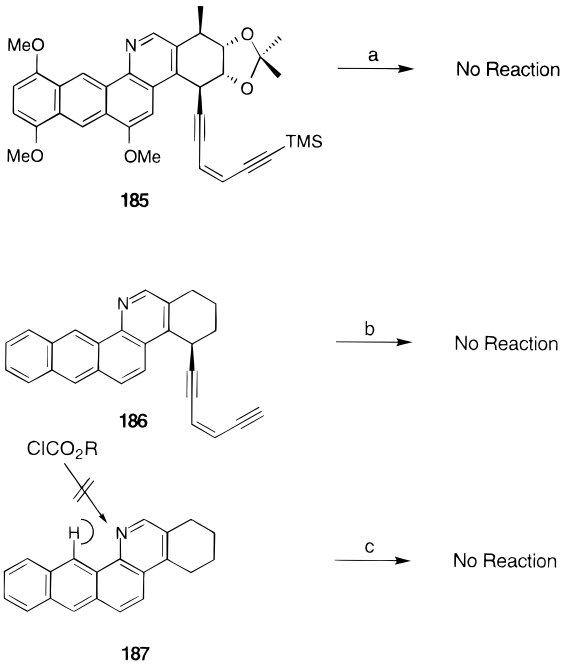
of the tetrahydroquinoline type of nitrogen, thereby lessening solvolytic threats to the epoxide.

Indeed, quinone substitution itself suffices for this purpose. Thus, the Alloc group was cleaved with tetrakis(triphenylphosphine)palladium(0) to afford **175**. Furthermore, oxidation of **175** led to the sensitive, but still viable, **176**. However, attempts to chain extend **176** in the direction of **177** failed. It seemed that there was an incompatibility between the presence of the quinone (and possibly the epoxide) with the insertion chemistry necessary to bring about the Castro−Stephens chemistry needed for elongation to the seco enediyne.

For this purpose, we went back to the virtual beginning of the synthesis. Thus, treatment of compound **150** (Scheme 50) with presumed isobenzofuran **178** afforded **179**. The latter, on aromatization (cf. **179** → **180**) provided the labile, poorly characterized **180** which was converted to **181** via aminolysis. Once again, the oxidation of the isolated double bond and protection of the α diol could be accomplished (see compound **182**). Oxidation of **182** afforded aldehyde **183** which lent itself to conversion to acetylene **184** and then to enediyne **185**.

Unfortunately, this system could not be cyclized by acylative (Reissert) activation of the azomethine linkage (Scheme 51). Indeed, even a much simpler model,

Scheme 51. Attempted Inter- and Intramolecular Reissert Reactions of Pentacyclic Compounds[a]

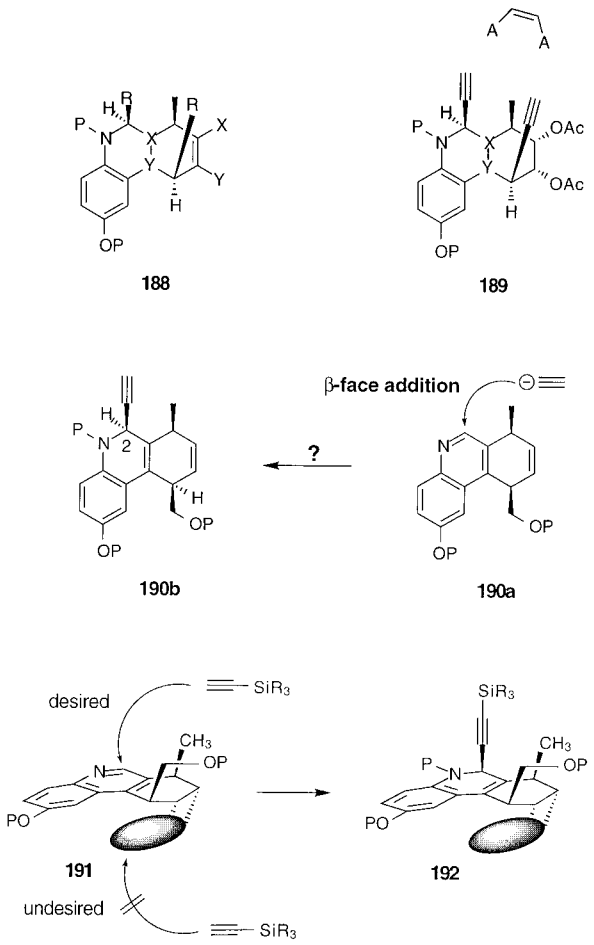


[a] (a) base, $ClCO_2Me$; (b) EtMgBr, $ClCO_2Me$; (c) ethynylmagnesium bromide, $ClCO_2Me$.

compound **186**, failed to cyclize in the Reissert mode. Moreover, substrate **187**, lacking the enediyne appendage, failed to afford even an intermolecular addition of ethynyl Grignard under Riessert conditions. We can only conclude that the steric hindrance of the pendant naphthalene system prevents the acylative activation phase of the Riessert-like sequence (see depiction of bay region type of interference in **187**). At this point, we were confronted with a major dilemma. Tricyclic intermediates lacking the putative C_8-C_9 epoxide but containing the fully developed enediyne side chain could be synthesized but were interdicted en route to cyclization by the acidity of the C_7 proton (see compounds **159**, **161**). With the epoxide in place, the C_7 acidity problem would probably not pertain. However, in such intermediates (see **169** and **176**) we could not elaborate the enediyne. In pentacyclic intermediates, where the enediyne could be installed, acylation of the azomethine linkage as a first step in the Reissert sequence failed (cf. **185**−**187**).

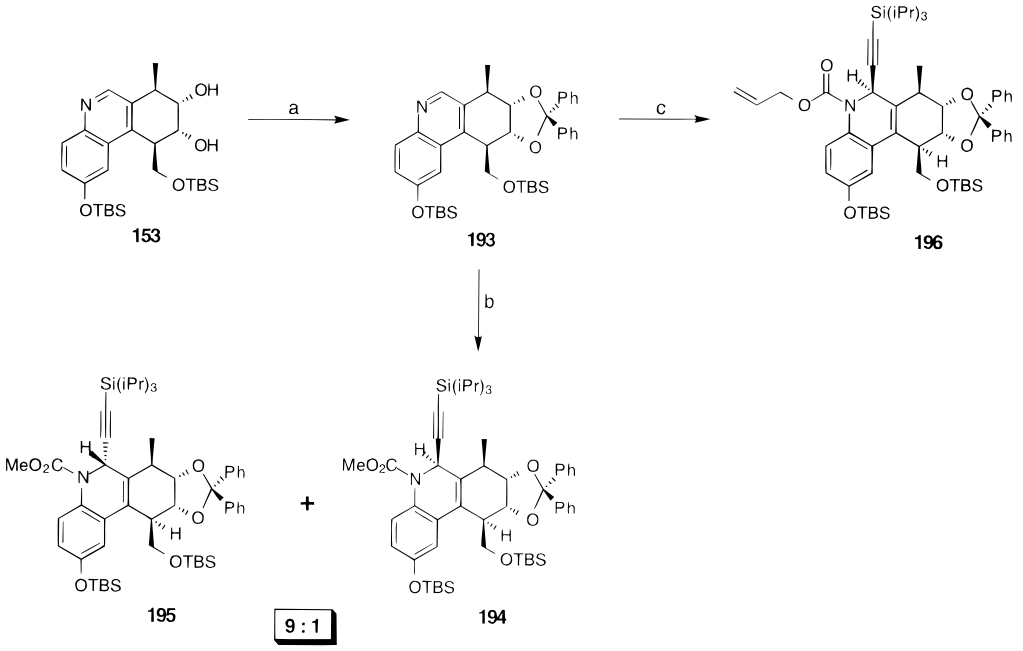
Of course, in any undertaking of this level of complexity, one can always point to possibilities which had not yet been excluded. However, the accumulated and serious setbacks which we had suffered served to focus our attentions on the prospects of implementing case II. For this purpose, we returned once again to compound **152**. Our goal structure (Scheme 52) emerged as compound **188** or, more specifically, diyne **189** (vide infra). With such a substrate in hand, attempt an interpolative cyclization by insertion of a *Z*-ethylene linkage inserted between the cis-related acetylenes would be undertaken.[58] As an interim goal, we sought to gain access to a generic structure of the type **190a**. The problem was obvious. How could one direct introduction of a group at C_2 from the *β*-face of the azomethine linkage in the presence of the two *β*-resident functions (**190a** → **190b**)? It seemed likely that intermolecular addition of a nucleophile in a Reissert-like reaction to a structure of the type **190a** would occur from the α-face, given the *β*-disposed resident groups at C_4 and C_7.

Scheme 52. Synthetic Perceptions for Case II Approach



At this point, a bold possibility surfaced. If the double bond of **190a** could be substituted on its α-face with sterically demanding groups (cf. **191**), nucleophilic attack

Scheme 53. Synthesis of Alkyne 196[a]



[a] (a) $Ph_2C(OMe)_2$, H_2SO_4, CH_2Cl_2, 40 °C, 83%; (b) (TIPS)ethynylmagnesium bromide, $ClCO_2Me$, THF, −20 °C, 95%; (c) (TIPS)ethynylmagnesium bromide, allyl chloroformate, THF, −20 °C, 75%.

on the azomethine linkage might occur from the β-face (see **191** → **192**). This was to be our guiding paradigm.

Compound **153** (Scheme 53), which we had prepared earlier, appeared to us to be an excellent starting point for the examination of the above-discussed theory. The two hydroxyls of **153** were engaged in the form of a benzophenone acetal through an exchange reaction with its dimethyl acetal. There was thus obtained an 83% yield of **193**. Happily, treatment of **193** with the Grignard reagent derived from TIPS acetylene in the presence of methyl chloroformate gave rise to **194** and **195** in a ratio of 9:1 favoring the desired β-isomer. The structure of **194** was proven crystallographically.

In a similar vein, anticipating future needs (vide infra), the acylating agent was changed to allyl chloroformate and compound **196** bearing the β-vinyl linkage was in hand. Thus, an important milestone had been passed in that the three stereogenic centers at positions 2, 4, and 7 had been properly emplaced.

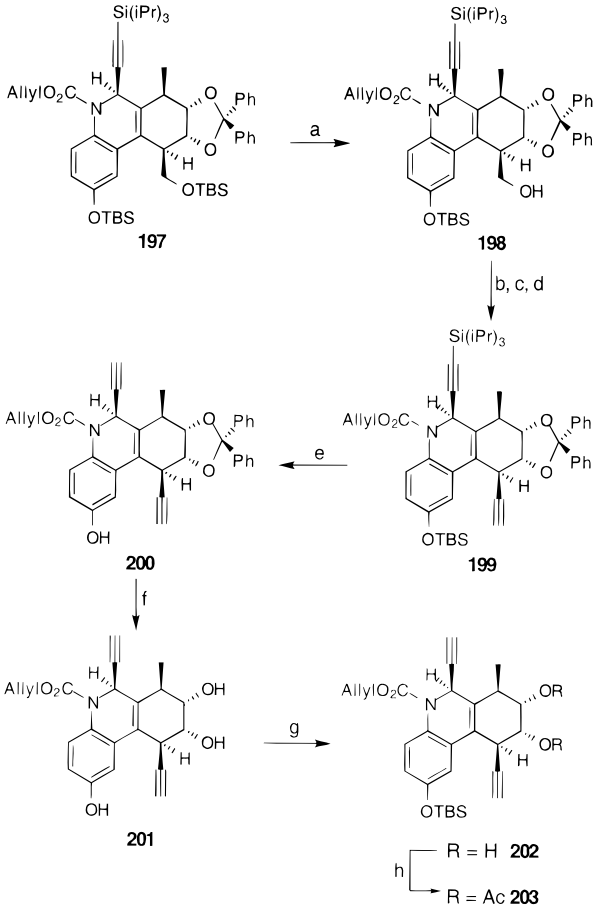
The time was now at hand to advance the hydroxymethyl group at C_7 toward the acetylene linkage, projected to appear in compound **207** (vide infra). This goal was smoothly accomplished.

The sequence started (Scheme 54) with selective cleavage of the aliphatic TBS group (without concomitant loss of the phenolic TBS group and without forfeiture of the benzophenol ketal). Compound **198** upon oxidation and Corey−Fuchs elongation was converted to acetylide **199**.

Finally, discharge of the TIPS group was achieved through the action of TBAF to produce the free diyne **200**. The benzophenone ketal function was cleaved with methanolic HCl to give rise to **201**. A TBS group was reinstalled on the phenolic hydroxyl through the agency of sodium hydride and TBS chloride to afford **202** and then diacetate **203**.

It became appropriate to direct our attentions to the precise nature of the carbamoyl protecting device. What we would need, of course, is that the urethane linkage, in fact, shield the nitrogen from undesirable chemical changes which might occur through the steps which would be required to finish the synthesis. Furthermore,

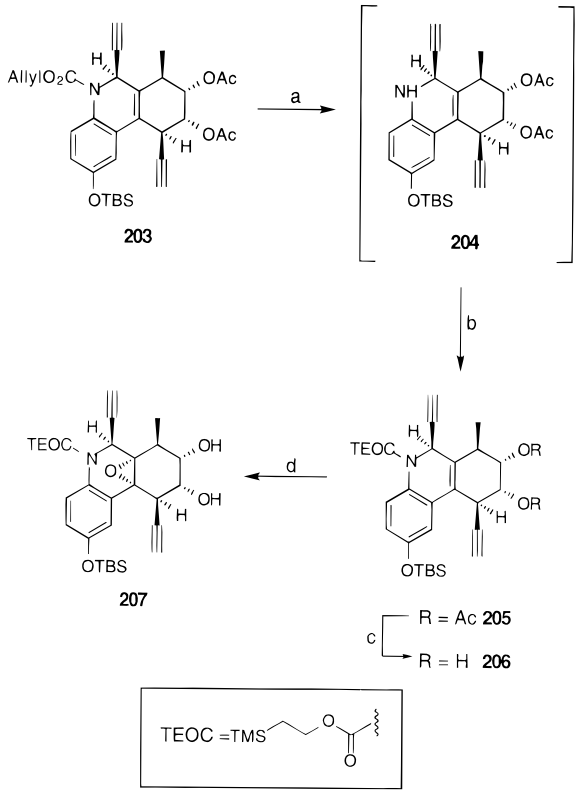
Scheme 54. Synthesis of Diyne 203[a]



[a] (a) Concentrated HCl, THF, 86%; (b) Swern oxidation; (c) PPh_3, CBr_4, CH_2Cl_2, 84%; (d) nBuLi, $PhCH_3$, −78 °C, 74%; (e) TBAF, THF; (f) HCl, MeOH, 74%; (g) NaH, TBSCl, THF, 85%; (h) Ac_2O, Et_3N, DMAP, 95%.

we required the carbamoyl group to be cleavable at a strategic point. Finally, it is a group whose stability must be consistent with the anticipated use of Pd(0) in the cyclization step. With the issue of the removal of the carbon-bound silyl functionality having been established, it was no longer necessary that the urethane linkage be stable to desilylating conditions. If all went well, the only desilylation which would be necessary would be that of the phenolic TBS function. What could *almost certainly* not be tolerated was the continued use of the Alloc protecting device. It was critical that the protective arrangement survive the action of Pd(0) which we perceived to be necessary to mediate cyclization (vide infra), although the precise form of the interpolation had not even been decided. Accordingly, the Alloc group of **203** was discharged (Scheme 55) through the agency of

Scheme 55. Synthesis of Epoxy Diyne 207[a]

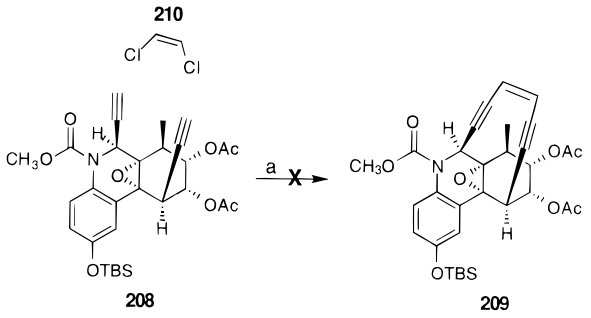


[a] (a) $Pd(PPh_3)_4$, morpholine, THF, 0 °C; (b) TEOCCl, NaH, THF; (c) NH_3, MeOH, 90% (two steps); (d) *m*-CPBA, CH_2Cl_2, 87%.

tetrakis(triphenylphosphine)palladium(0) in the presence of morpholine. This reaction undoubtedly passed through compound **204**, which was immediately protected as the TEOC urethane **205**, and following deacetylation with ammonia, diol **206** was in hand. A large step forward was accomplished when it was shown that epoxidation of the double bond, even in the presence of the ethynyl linkages, could be conducted. Anticipating a result proven later, this oxidation was assumed to have produced α-epoxide **207**.

Several attempts to conduct a conventional Castro–Stephens reaction (Scheme 56) for insertion of the *cis*-dichloroethylene (**210**) which were conducted in the related methyl carbamate series (see compound **208**) were unsuccessful (**208** ↛ **209**) and could never be accomplished in our hands. At that point, we resorted to the possibility of a Stille-like coupling, with the caveat that it would accomplish interpolation of an ethylenic

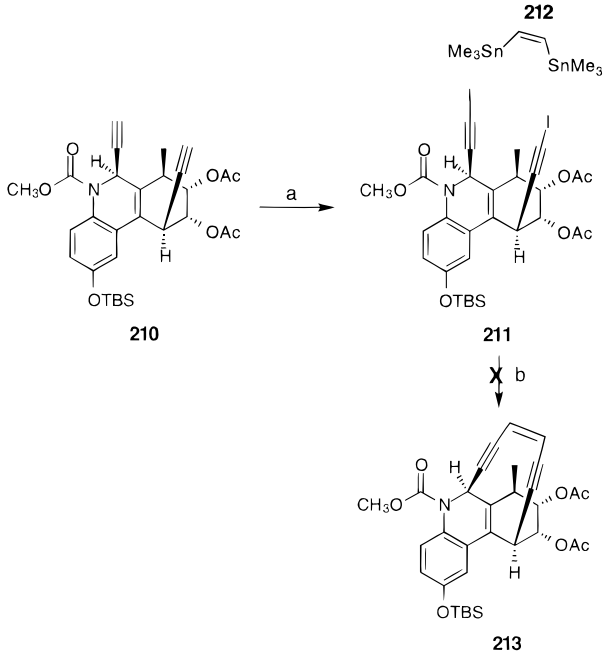
Scheme 56. Attempted Sonogashira Cyclization of 208[a]



[a] (a) **210**, $Pd(PPh_3)_4$, CuI, $nBuNH_2$, PhH.

moiety between two acetylenes. Returning to compound **210a** (Scheme 57), the two ethynyl groups were oxidized with *N*-iodosuccinimide in the presence of silver nitrate to give the bis-iodo system **211**.[59]

Scheme 57. Attempted Cyclization of Bisiodoalkyne 211[a]



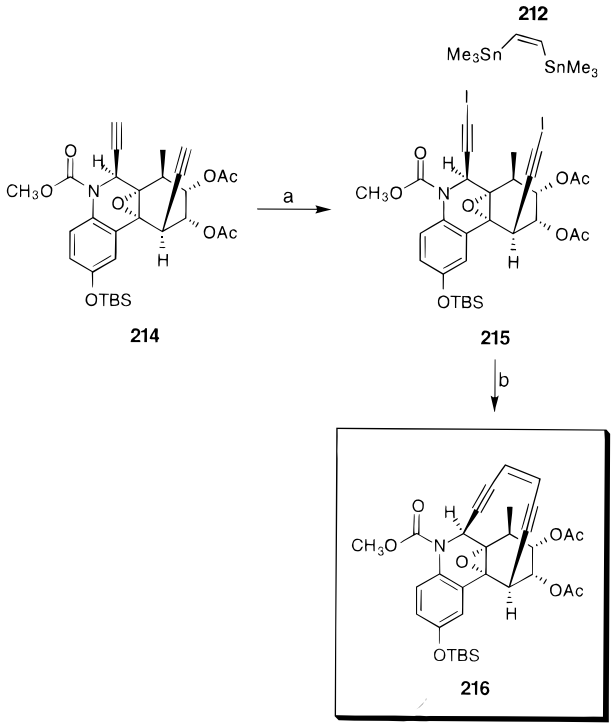
[a] (a) $AgNO_3$, NIS, THF, 75%; (b) **212**, $Pd(PPh_3)_4$, DMF, 70 °C.

Once again, this compound (**211**) failed to undergo interpolative cyclization with the (*Z*)-1,2-bis(trimethylstannyl)ethylene (**212**).[60] It was hoped, however, that cyclization could be accomplished if the epoxide were in place. The presence of the C_8-C_9 epoxido linkage would serve to bring the two ethynyl functions closer together and to remove some of the steric strains associated with the projected cyclization. In the event (Scheme 58), treatment of compound **215** with the bis-stannyl ethylene agent **212** did indeed give rise to the epoxy enediyne **216**![61]

We returned to the TEOC-protected epoxy diacetylene **207** (Scheme 59). This compound was iodinated to give **217**. *In the defining step of the synthesis,* ***217*** *cyclized in the presence of tetrakis(triphenylphosphine)palladium-(0) (5 mol %) and delivered an 81% yield of the epoxy enediyne* ***218****.*

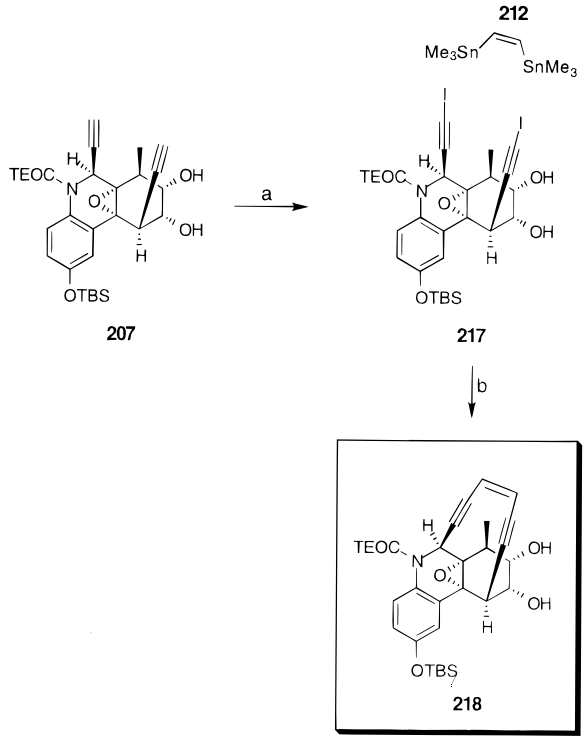
At this point, a clear strategy to reach dynemicin itself surfaced. Many detours and failed initiatives still awaited

Scheme 58. Interpolative Cyclization of 215 To Deliver Cyclic Enediyne 216[a]



[a] (a) $AgNO_3$, NIS, THF, 98%; (b) **212**, $Pd(PPh_3)_4$, DMF, 70 °C, 78%.

Scheme 59. Interpolative Cyclization of 217 To Deliver Cyclic Enediyne 218[a]

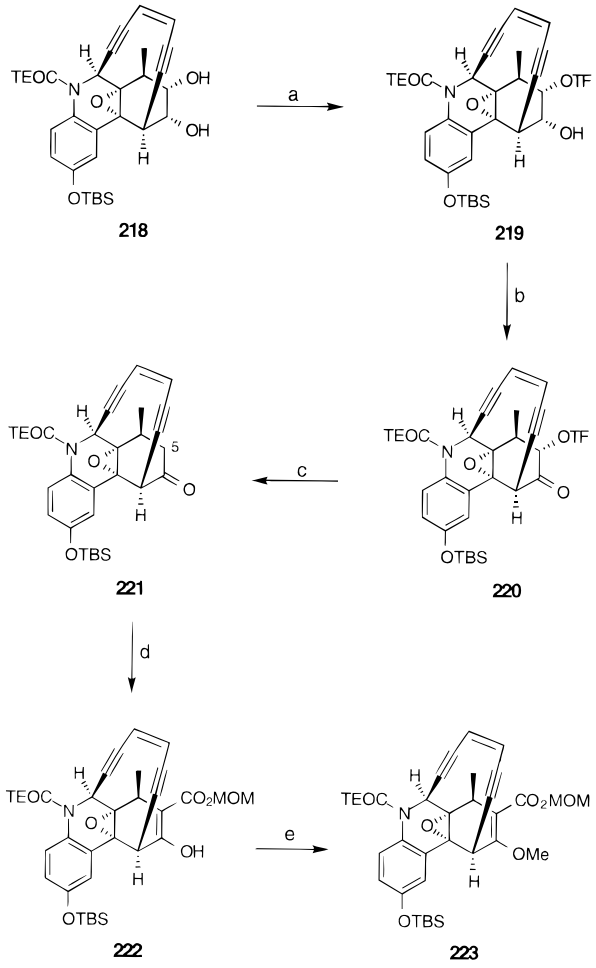


[a] (a) $AgNO_3$, NIS, THF, 95%; (b) **212**, $Pd(PPh_3)_4$, DMF, 70 °C, 81%.

us. Here we relate the route which did indeed lead to dynemicin A.

The first stage of that progression involved the proper development of the vinylogous carbonate functionality (Scheme 60). An important step in this regard was the capacity to differentiate the two hydroxyl groups of **218** by triflation at the equatorial site. This success was followed by oxidation of the axial alcohol to the ketone (see compound **220**) and reductive excision of the trifyloxy function (see ketone **221**).

Scheme 60. Conversion of Diol 218 to Vinylogous Carbonate 223[a]



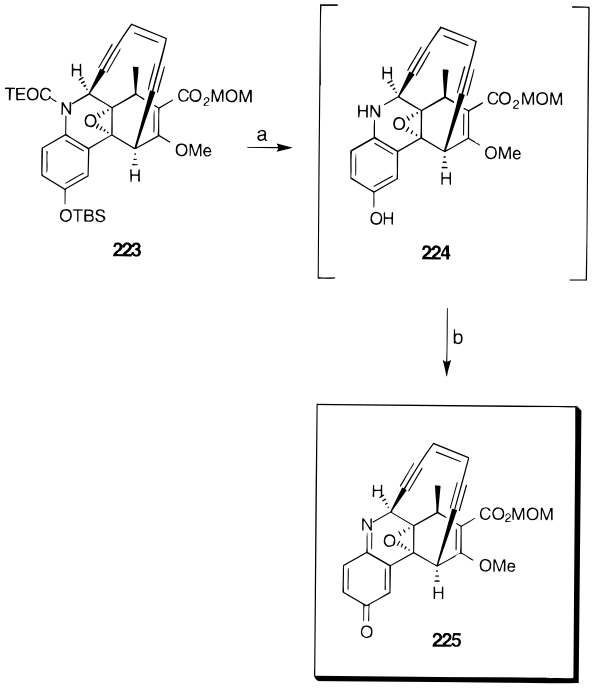
[a] (a) Tf_2O, Pyr, CH_2Cl_2, −20 °C, 95%; (b) Dess−Martin periodinate, CH_2Cl_2, 95%; (c) $CrCl_2$, THF, 75%; (d) $MgBr_2$, CO_2, Et_3N, MeCN; (e) MOMCl, iPr_2NEt, THF, 61% (over two steps).

At this point, we thought it would be appropriate to introduce the carboxyl group at carbon 5. A variety of possibilities were surveyed with a view toward enolization of the C_6 ketone. Apparently, enolates derived from such full scale deprotonation are quite unstable. We were, however, able to achieve the same result through a pathway which had been developed for the carboxylation of ketones by Rathke and associates.[62] In the event, compound **221**, upon treatment with magnesium bromide under an atmosphere of carbon dioxide, gave a rather unstable β-keto acid which on treatment with MOMCl in the presence of Hunig's base, under carefully controlled conditions, progressed to the MOM protected enol version of the β-keto ester (**222**) in 61% yield. The latter could be converted to the required methyl enol ether **223** through the agency of diazomethane. Model reactions indicated (see compound **223**) that the cleavage of the MOM function would produce the required carboxyl group and that it should prove to be feasible at a rather late stage of the synthesis.[63]

Returning, then, to compound **223**, it was possible to cleave the TEOC function with TBAF (Scheme 61). This,

in turn gave rise to an unstable and ill-characterized intermediate (**224**) in which the full vulnerability of the epoxide would be manifest. However, product **224** was immediately oxidized to give quinone imine **225** which was in fact a stable entity and turned out to be a critical intermediate in the eventual total synthesis.[23b,64]

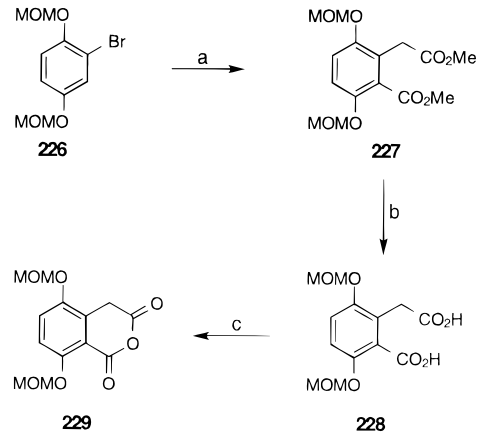
Scheme 61. Synthesis of Imino Quinone 225[a]



[a] (a) TBAF, THF, 0 °C; (b) $PhI(OAc)_2$, THF, 0 °C, 60% from **223**.

Chronicled elsewhere are a variety of approaches which were used to take advantage of the functionality of the quinone imine to install the fully deprotected anthraquinone system.[65] Here we content ourselves with that route which brought success. The coupling partner for a quinone imine was prepared from bis-MOM-protected bromo hydroquinone **226** (Scheme 62) which was converted through the action of lithiomalonate in the presence of LiTMP to the homophthallate **227**. Hydrolysis of the latter followed by cyclization with (trimethylsilyl)ethoxyacetylene gave rise to **229**.[66]

Scheme 62. Synthesis of Homophthalic Anhydride 229[a]



[a] (a) Lithium dimethylmalonate, LiTMP, THF, −78 °C, 71%; (b) KOH, MeOH, H2O, 95%; (c) (trimethylsilyl)ethoxyacetylene, CH_2Cl_2, 100%.

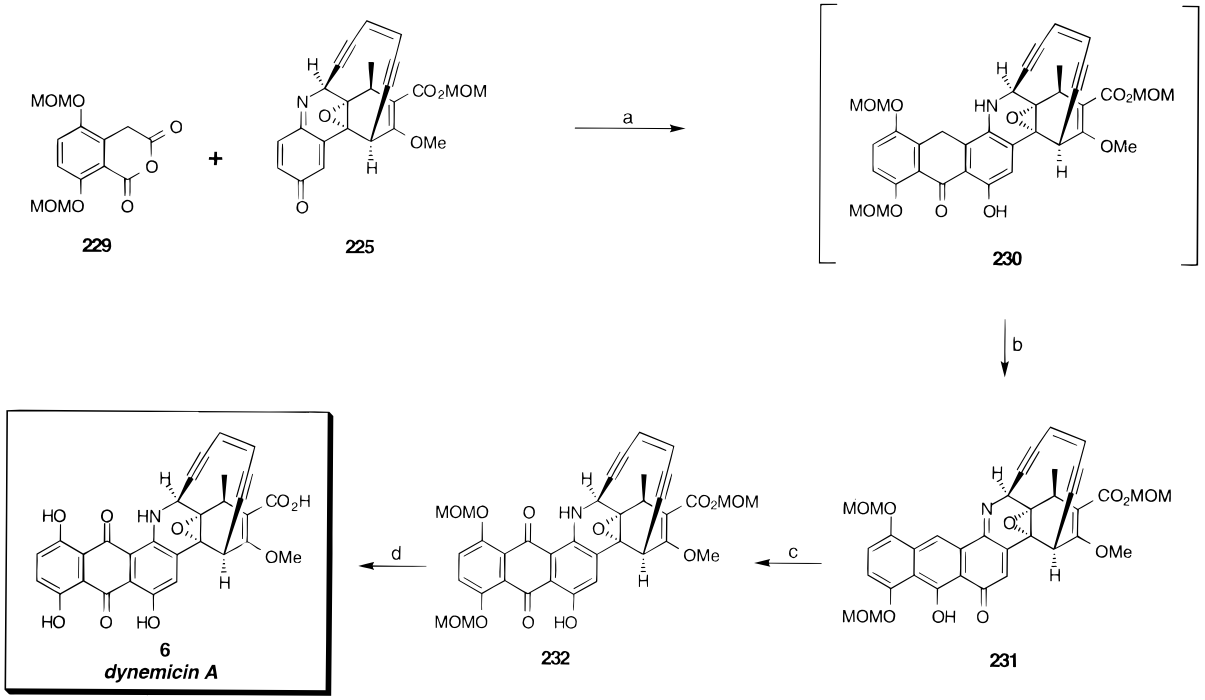
Finally, the elusive anthraquinone was installed by exposure of the quinone imine **225** (Scheme 63) to the enolate generated from deprotonation of **229**. There was thus generated an adduct which we believe corresponds to structure **230**. In the formation of **230** a formal cycloaddition followed by decarboxylation would have occurred.[67] Compound **230** would, in itself, be likely to be an unstable compound, and its formation was followed immediately by oxidation with bis(trifluoroacetoxy)iodobenzene leading to **231** in which the quinone imine ring had been restored, thereby stabilizing, at least to some extent, the C_8-C_9 epoxide against solvolytic attack for reasons discussed above. The structure of **231** has not been fully established, but it is consistent with spectral data provided elsewhere.[65] Exposure of **231** to the action of air, under daylight conditions, produced quinone system **232** which in fact corresponds to tris-MOM-protected dynemicin A. In the concluding step of the synthesis, the MOM functions were cleaved through the action of magnesium bromide in ether. *There was thus isolated, albeit in rather low yield, the long sought after dynemicin A (15% from structure **225**).*[22] We attribute this disappointing yield not so much to the chemical inefficiency of the transformations themselves but to the instability of dynemicin A and to the difficulties in handling this compound. Similar findings were registered by Myers using a totally different, but still logical, annulation scheme. In the Myers annulation, at the end of the sequence, dynemicin A could be isolated in 14% yield, also reflecting the extreme difficulty encountered in dealing with the anthraquinone system.[23] In any case, the total synthesis of dynemicin A has now been accomplished in our laboratory.

We also note that the quinone imine concept as a stabilizing device for epoxide solvolysis was used in a new concept for elaboration of a new kind of dynemicin drug analog. In this connection, compound **233** (Scheme 64) has been prepared by a route similar to those shown above.[23b] It has been shown to be a potent DNA cleaving agent and to be a compound of high cytotoxicity. In fact, during in vivo investigations in mice, it has outperformed standard clinically used anticancer drugs such as mitomycin C.[64,68] It is presumed that the mechanism of action of compound **233** involves in vivo reduction of the quinone imine linkage or in vivo Michael addition of a bionucleophile to the quinone imine linkage. In either case, there would be generated a *p*-hydroxytetrahydroquinoline of the type **234** which would then become a major prospect for entering the bio-Bergmann manifold discussed at the outset of this manuscript. Interestingly, a compound related to **234** had been generated and observed spectroscopically by Nicolaou and associates.[49]

Conclusions

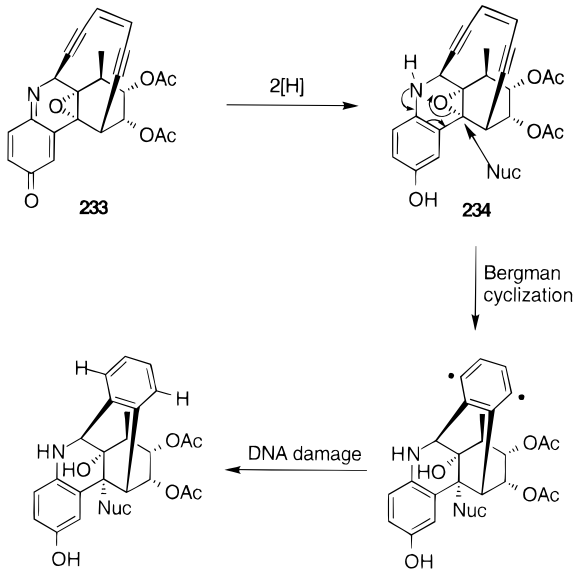
In the preceding text, we have described the total synthesis of two complex enediyne drugs, calicheamicin γ_1^I and dynemicin A. These goals were accomplished through totally different strategies. During this work there was learned a great deal about enediynes as well as about the feasibility of various routes to reach them. The calicheamicinone synthesis revealed the potentiality of using enediyne anions for cyclization reactions. (In one fashion or another, not always with full scholarly attribution, the chemistry has found wide application in the field.) The total synthesis of calicheamicin itself also involved the development of some very new methodology

Scheme 63. Annulation of Anthraquinone and Synthesis of Dynemicin A (6)[a]



[a] (a) LHMDS, **229**, then **225**, THF, 0 °C; (b) $PhI(OCOCF_3)_2$, THF, 0 °C, 5 min; (c) air, daylight, THF, high concentration; (d) $MgBr_2$, Et_2O, 24 h, 15% (overall from **225**).

Scheme 64. Development of Enediyne Quinone Imines (233) as Biologically Active Dynemicin Congeners



in glycal assembly of rare carbohydrate types. The eventual synthetic mastery over the carbohydrate domains of esperamicin and calicheamicin, in conjunction with appropriate binding and spectroscopic investigations, led to a much enhanced perception of the critical role of the carbohydrate domain in the drugs. This domain is what seems to provide the basic recognition motif in mediating the encounter between the drug and DNA. While much modeling and interpretation is still necessary, it is clear that the sequence selectivity of calicheamicin γ_1^I arises from drug−carbohydrate interactions of a type which had not been fully appreciated.

We note parenthetically that the concept of using relatively hydrophobic sugars to bind to stretches of oligonucleotides has recently been exploited in exerting transcriptional control.[69] This concept may yet have further extensions as a device in mediating DNA−protein interactions. Such interactions are of course critical for protein expression.

In the total synthesis of dynemicin, a new paradigm for enediyne synthesis has been demonstrated. Already, it has found application in another laboratory.[70] Also, while following quite a related line of reasoning, the dynemicin effort has led to a new type of enediyne drug stabilized as a quinone imine linkage (see compound **233**). The clinical usefulness of such an agent awaits definition following quite favorable preliminary in vivo experiments in animals.

As first hand witnesses and participants in these exciting explorations we can attest to the captivating nature of the problems and to the special motivations which these different quests provided for finding solutions. We are confident that the two expeditions were fruitful in developing new chemistry and even hopeful that the insights thus garnered will find application in future drug design. Ultimately, the goal must be to improve upon these fascinating metabolites.

Why do *Micromonospora echinospora* spp. *calichensis* and *M. chersina* manufacture, respectively, calicheamicin γ_1I and dynemicin A? For those with a positivist view of life, it seems not unlikely that these compounds serve a useful purpose in promoting the well being of their biological inventors. Our task as chemists is to draw from the genius of these biological inventions and to apply it to the much more demanding needs of human application. We remain confident that as time goes on, the role of synthesis in fostering productive coalitions between chemistry and biology in such grand pursuits will become even more apparent.

Acknowledgment. This work was supported by NIH Grant CA 28824. A predoctoral fellowship from

Memorial Sloan−Kettering Cancer Center to M.D.S. is gratefully acknowledged. It is a pleasure to acknowledge the dedication of our graduate student and postdoctoral colleagues, mentioned throughout the text, whose work provided the basis for this review. In particular, we thank Dr. Taeyoung Yoon (currently at Cal Tech), Dr. Stephen A. Hitchcock (currently at Eli Lilly), Dr. Margaret Chu-Moyer (currently at Pfizer), Dr. Serge H. Boyer (currently at Gensia), Dr. Stephen H. Olson (currently at U.C. Berkeley), who were involved in a critical way in the very demanding "end-games" of these syntheses.

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JO951560X