19 (0.141 g, 94%) as a syrup: IR (neat) ν_{max} 2960, 2873, 1716, 1450, 1313, 1279, 1113, 1099, 1070, 1026, 710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.94 (3 H, br t, J = 6.0 Hz), 1.40 (3 H, d, J = 6.4 Hz), 1.2-2.0 (4 H, m), 2.10 (2 H, t, J = 6.0 Hz), 5.29 (2 H, sextet, J = 6.1 Hz), 7.2-7.6 (6 H, m), 7.97 (4 H, br d, J = 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.96, 18.49, 20.56, 36.76, 40.36, 68.45, 71.41, 128.20, 128.23, 129.51, 129.56, 130.52, 130.62, 132.67, 132.71, 166.00, 166.07; UV (hexane) λ_{max} 227.4 nm (ϵ 25 700). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.12. Found: C, 74.17; H, 7.15.

(2*S*,4*R*)-2,4-Heptanediyl Dibenzoate (20). Olefin (2*S*,4*R*)-**7** (0.221 g, 0.445 mmol) was similarly reduced to yield **20** (0.145 g, 96%) as a syrup: IR (neat) ν_{max} 2960, 2873, 1716, 1450, 1313, 1275, 1099, 1070, 1026, 712 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.92 (3 H, br t, J = 6.1 Hz), 1.41 (3 H, d, J = 6.2 Hz), 1.2-2.4 (6 H, m), 5.2-5.6 (2 H, m), 7.2-7.6 (6 H, m), 8.02 (4 H, br d, J = 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.91, 18.46, 20.28, 36.52, 40.23, 69.01, 71.84, 128.27, 128.31, 129.55, 129.60, 130.46, 130.55, 132.78, 132.83, 165.98, 166.16; UV (hexane) λ_{max} 227.6 nm (ϵ 26 200). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.12. Found: C, 74.34; H, 7.12.

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Supplementary Material Available: Synthetic procedure and spectral data of compounds which are not described in the Experimental Section (9 pages). Ordering information is given on any current masthead page.

Total Synthesis of Calicheamicinone: New Arrangements for Actuation of the Reductive Cycloaromatization of Aglycon Congeners

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Abstract: The total synthesis of *dl*-calicheamicinone (**1**) has been accomplished. The key elements of the synthesis were (i) an application of the Becker-Adler reaction to reach compound **91**, (ii) an application of the concept of in situ protection to deliver lithiated enediyne **35** to a ketone group in the nominal presence of an aldehyde, (iii) an apparently stereospecific aldol-like cyclization of **93** to reach **94**, (iv) intramolecular Emmons-like closure (cf. **102** to **103**), (v) exploitation of vinylogous urethane character to provide stabilization to an otherwise labile primary enamine (see compound **104**), and (vi) generation of an allylic thiolate and its conversion to the allylic trisulfide emanating from the C_1 bridge (see transformation **111** → **112**). Much of the strategy used in the synthesis of **1** had been worked out in a synthesis of the descarbamate system **9**. The propensity for reductive cycloaromatization of calicheamicin has been simulated with these simpler substrates (see compounds **9**, **68**, **115**, **117**, **124**, and its unstable reduction product).

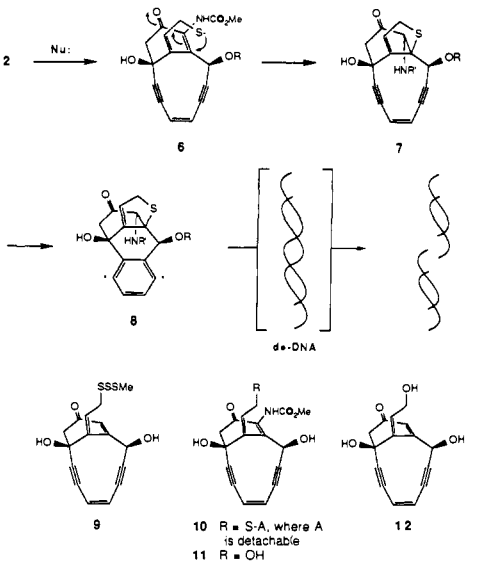
Background and Synthetic Strategy

It is not uncommon for the discovery of a class of compounds of novel structure to provide impetus for new research in organic chemistry. One need only reflect on the enormous impact occasioned by the discovery of steroids, terpenes, and alkaloids (not to mention carbohydrates, proteins, and nucleic acids) to appreciate this connectivity.[1] The recent advent of a new class of antibiotics featuring a confluence of olefinic and acetylenic functionality is likely to provide new challenges for organic chemists. Four such compounds (**2-5**) have been fully characterized, and they all exhibit remarkably potent cytotoxicity.[2] The possibility of exploiting the high cell-killing potential of **2-5** for cancer chemotherapy has evoked interdisciplinary efforts in the biomedical sciences (Chart I).

The cytotoxic properties of these substances are perceived to involve a bionucleophile-induced series of bond reorganizations leading to aromatic diyl species (vide infra) with DNA-damaging ability via cleavage of carbon-hydrogen bonds of deoxyribose residues. The resultant DNA species, bearing anomalous carbon appendages, could well be less subject to normal repair mechanisms.[3]

One might question whether such drugs can exhibit useful indices of selectivity based solely on the increased vulnerability of rapidly proliferating cells to cytotoxic agents.[4a] Conceivably, a better understanding of the way in which these compounds are

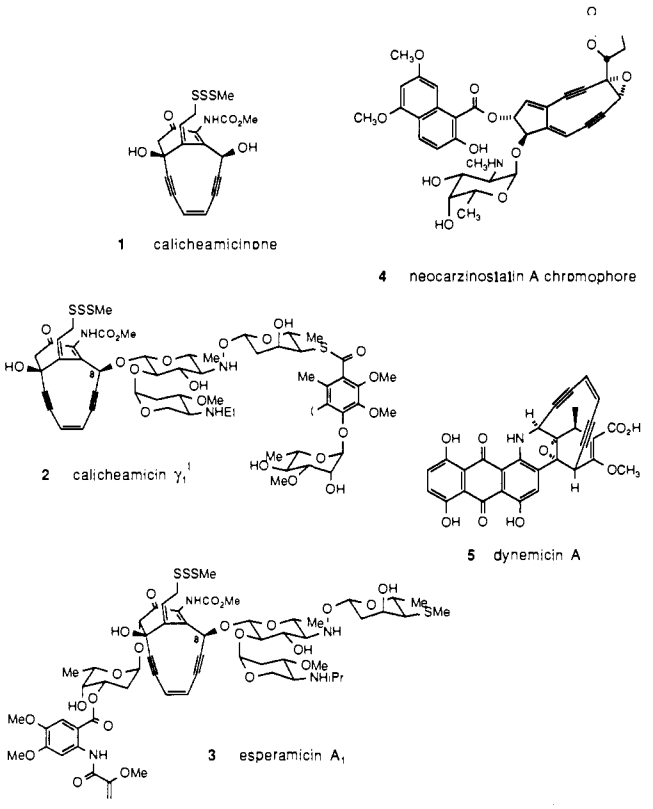
Scheme I



† Department of Chemistry, Yale University.
‡ Yale University Center for Chemical Instrumentation.

0002-7863/91/1513-3850$02.50/0

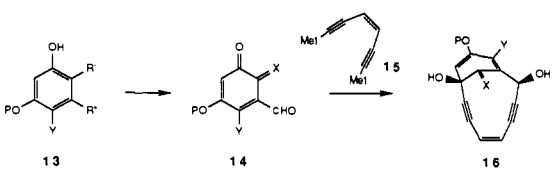
Chart I



maintained in their host systems might provide a clue for channeling such enynes for medical application. Also under consideration are targeting devices such as covalent attachment of the drugs to cell-specific carrier systems.[4b]

Here we focus on calicheamicin (**2**) obtained from *Micromonospora echinospora*[2a-c] and esperamicin (**3**) derived from *Actinomadura verrucosospora*.[2d-f] The two drugs share obvious structural features both in their aglycon and carbohydrate domains. In each case, it is proposed that a bionucleophile or reducing agent cleaves the trisulfide, generating a thiolate species

Scheme II[a]



[a] P = protecting group.

(**6**), which adds to the proximal bridgehead double bond. System **7**, thus unveiled, suffers a bond reorganization[5] to generate the effector diyl species **8** (Scheme I).

Though calicheamicin and esperamicin cause double-strand cleavage of duplex DNA, a significant difference in the nature of the interactions of the two drugs has been revealed. For instance, with a 144-base-pair restriction fragment (*Eco*RI–*Pvu*-II from plasmid pUC18), calicheamicin favored cleavage with remarkable specificity at one of two cytosine residues in a TCCT sequence on one strand, with the site of the second cleavage being three base pairs removed toward the 5′ end.[6] The sequence specificity of the double-stranded cutting of esperamicin is rather more diffuse.[7] Since the carbohydrate residues presumably have no direct DNA-cleavage potential, the rather sharp difference of compounds **2** and **3**, at the level of sequence specificity, probably reflects differing recognition properties of their carbohydrate domains.[8,9]

It would be of interest to examine the DNA-cleaving potential of the aglycon sectors, independent of the sugars. *However, at this writing, no one has succeeded in removing the carbohydrate section from 2 or 3 while retaining the structural integrity of the aglycon.* The total synthesis of the aglycon of calicheamicin, which we call calicheamicinone (**1**), became the first major focus of our investigation.[10]

Moreover, a successful total synthesis program leading to aglycon **1** might allow for deletion of the urethane residue. One could then ascertain, at least qualitatively, its role in diyl formation. Thus, compound **9** emerged as a subgoal. More broadly, we hoped to address some other structural possibilities for actuating the progression leading to bond reorganization. For instance, could the trisulfide form of housing the thiyl or thiolate trigger (cf. species **6**) be replaced by a functional group that is less cumbersome from a synthetic standpoint (see **10**, where A is a suitably detachable group)? Moreover, would the related allylic alcohols **11** or **12** (corresponding to aglycons **1** and **9**) undergo the same chemistry?

Quite aside from any biomechanistic insights that might be garnered by the synthesis of **1**, the enterprise would constitute

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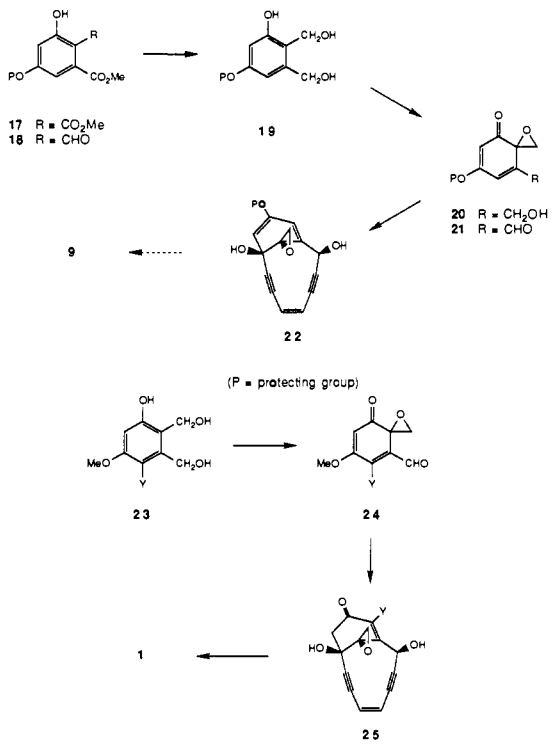
Scheme III[a]



[a] Y = urethane precursor.

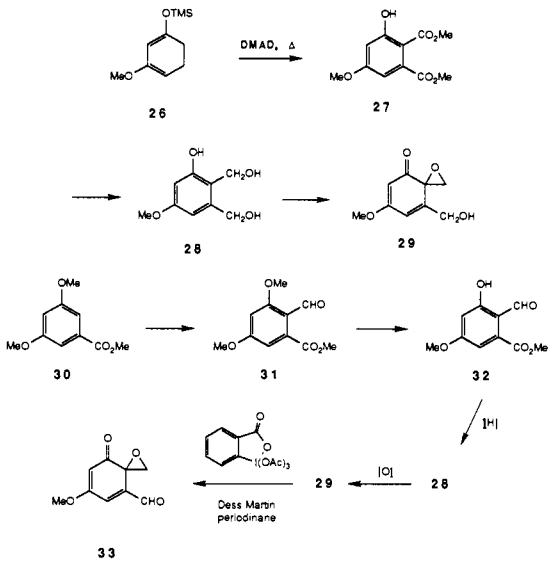
a significant challenge at the purely chemical level. Given the difficulty predictable multicomponent nature of the total problem, two policies were adopted. A direct attack on our most challenging goal (calicheamicinone (**1**)) would await model studies directed to the descarbamate analogue **9**. This simplification would facilitate the screening of some general possibilities for assembling the rest of the system. However, we insisted on the constraint that *any program followed in pursuit of 9 must in principle be expandable to reach 1*.

In approaching a synthesis of **9**, we focused on an intermediate that might be assembled in a few steps and that would have sufficient access points for further explorations in this region of the molecule. The hypothetical progression **14** (X and Y unspecified) + **15** → **16** seemed to have the virtue of a concise entry to the desired ring system containing the enediyne and the requisite oxygenation pattern. Of course, this formalism postpones several issues. While we would start with Y = H in **14**, it would be necessary for the overall design to accommodate a suitable implement for installation of the urethane. In this connection, it seemed attractive if **14** were derived from a generalized aromatic precursor **13** (R′ is unspecified). An aromatic ring seemed to be an ideal depot for assembly and storage of the functionalized array required in **14** (Scheme II).

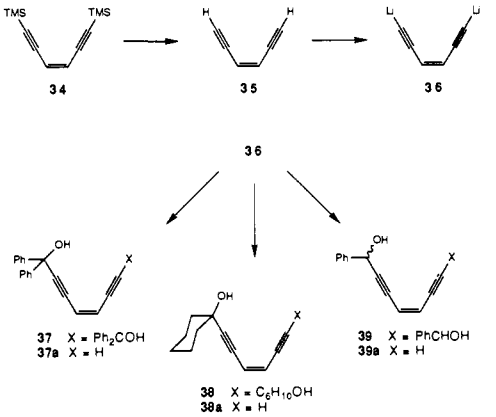
In considering the nature of X in **16**, we favored a system that offered considerable flexibility for conversion to **9** and that could be obtained from an aromatic precursor such as **13**. Given these considerations, we came to favor **22** as a more specific type of intermediate en route to **9**. This system might arise from **21**, in turn derived from **19**. Central to the plan was a projected Becker–Adler reaction[11] to progress from **19** to **20**. This was to be followed by oxidation of **20** → **21**. Similarly, the route to **1** itself could be envisioned as starting from **23**, passing through **24**, en route to **25**. It would be necessary for Y in **23** to be convertible to a urethane (Scheme III).

To reach diol **19**, we would start with precursors of the type **17** or **18**. It is from this level of strategy that our experiments began.[12]

Scheme IV



Scheme V



Discussion of Results

Following the protocols of McMurry,[13] diester **27** was prepared from a Diels–Alder reaction of 1-[(trimethylsilyl)oxy]-3-methoxycyclohexa-1,3-diene (**26**) with dimethyl acetylenedicarboxylate. Reduction of **27** to diol **28** was carried out with diisobutylaluminum hydride. The crude and unstable product was oxidized with sodium metaperiodate (Becker–Adler reaction), thereby providing the spiroepoxydiene **29** in 66% overall yield from **27**. Unfortunately, this method did not response well to scale-up. Difficulties were encountered in the multigram-level preparation of **26** and in the Diels–Alder reaction leading to **27** (Scheme IV).

By contrast, the aldehyde **32**[14] is preparable on large scale from commercially available methyl 3,5-dimethoxybenzoate (**30**) by sequential formylation ($TiCl_4$/dichloromethyl methyl ether) and regioselective demethylation (BCl_3). Reduction of **32** with lithium aluminum hydride afforded crude **28**, which was subjected to the Becker–Adler oxidation[11] to provide **29** as before. The overall yield for converting **32** to **29** was 71%. Of a variety of methods surveyed for the oxidation of **29** to **33**, the Dess and Martin procedure was the only one that gave reproducible and acceptable (70%) yields.[15]

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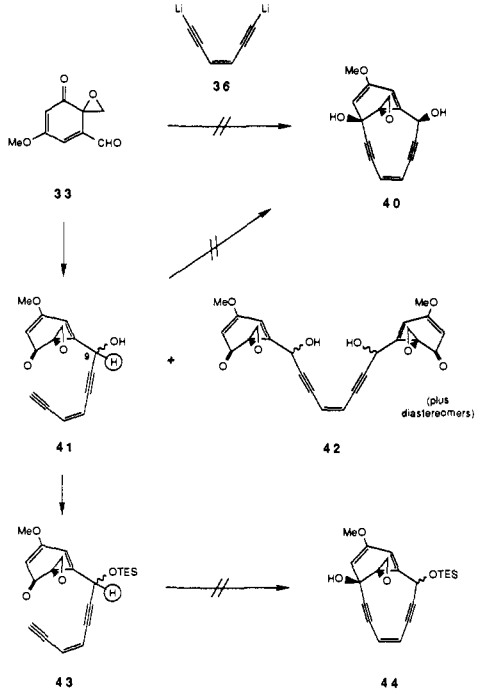
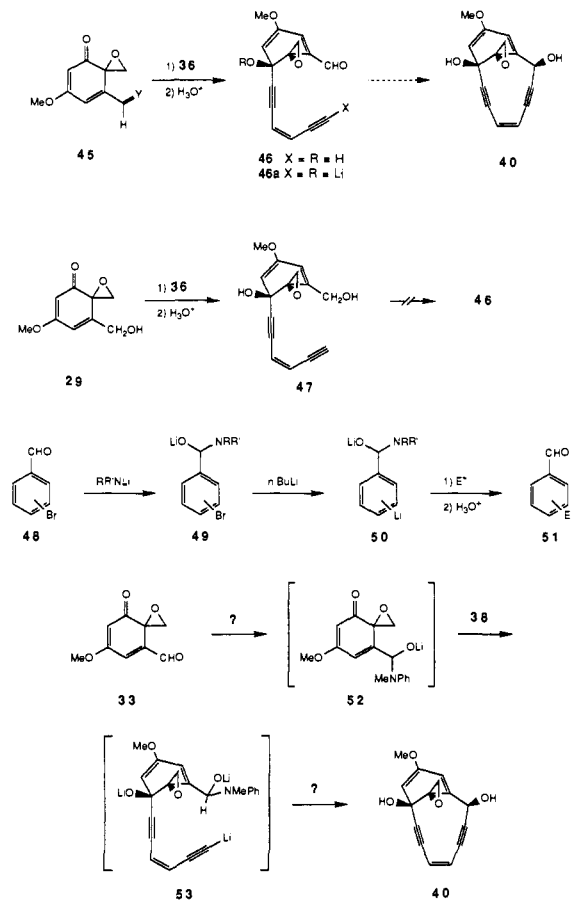
Scheme VI



Scheme VII



We first considered a one-step coupling of ketoaldehyde **33** with a dilithiodiacetylide such as **36** in turn to be prepared from the parent (*Z*)-enediyne **35**. The *Z* isomer had earlier been obtained by gas chromatographic purification of a mixture of *Z* and *E* isomers.[16] Since we envisioned the need for substantial amounts of this volatile hydrocarbon, we took advantage of Vollhardt's practical synthesis of the (*Z*)-bis(trimethylsilyl) derivative **34**.[17] A procedure was soon developed wherein **35** could be generated from **34** and converted to dilithio salt **36** by titration with *n*-butyllithium[12a] (Scheme V). This treatment achieved both the final drying of the hydrocarbon and the 2-fold deprotonation.

That the dilithio salt **36** had in fact been generated was strongly suggested by condensation studies with several carbonyl compounds. Indeed, quenching of a THF solution of the presumed **36** with benzophenone and cyclohexanone afforded **37**[12a] and **38**, in yields of 64 and 35%, respectively. Similarly, reaction with benzaldehyde gave rise to **39** (73%). In each case, some monoadducts (**37a**, **38a**, and **39a**) were also isolated.

Compound **39** would presumably be obtained as a mixture of diastereomers arising from stereorandomness in the second coupling process. Our chromatographic and spectroscopic data (see Experimental Section) failed to reveal the expected inhomogeneity. Since the formation of a single product at this stage would involve a most remarkable instance of asymmetric induction, we prefer to leave this matter open.

Attempts to achieve a direct synthesis of **40** by coupling of **33** with **36** resulted instead in formation in low yield of the monoadduct **41**, apparently accompanied by diadduct **42**. Attempts to achieve cyclization of **41** to **40** by treatment with lithium diisopropylamide were unsuccessful, leading to extensive decomposition. It was hoped that a more favorable result might be forthcoming if the secondary alcohol function of **41** were protected. Silylation of **41** thus gave rise to **43**. Reaction of **43** with lithium diisopropylamide resulted in a complex mixture of products that contained no detectable amounts of **44** (Scheme VI).

We reconsidered our tactical approach. In the route that we were following, the aldehyde function of **33** was the electrophile for the intermolecular, first-stage coupling with **36**. The ketonic function was to serve as the electrophile for the intramolecular, second-stage step. A priori, this timing seemed to be reasonable. First-stage attack at the aldehyde, which was in any case to be expected on grounds of chemoselectivity, would reserve perceived entropic advantages of intramolecularity for the more demanding attack on the ketone.

In practice, however, bond constructions from **41** and **43** based on this premise failed. We considered the possibility that the aldehyde would serve as the internal electrophile. *This would be a logical response to the possibility that we were dealing with a rare situation where the cyclization was more demanding than the intermolecular step.*

While this reappraisal was forced upon us by necessity, the new plan did have several favorable features. First, based on an important precedent from the work of Corey,[18] there was the possibility of achieving stereoselectivity if the acetylide were delivered to the ketone in the intermolecular step. Diastereofacial guidance would be provided by the spiroepoxide. The facial sense of intramolecular attack on the aldehyde would then be controlled strictly by its rotameric state with respect to the C4=C5 double bond (see structure **46**). Also, in the failed cyclization attempts of **41** → **40** and **43** → **44**, the projected acetylide deprotonation was potentially complicated by competing abstraction of the C9 proton (circled in **41** and **43**), vinylogously activated by the carbonyl function. In the projected reaction of **46**, arising from acetylide attack on the keto group of **45** (Y is unspecified), there would be no competitive enolization sites to interfere with cyclization to **40**.

The obvious possibility for reaching **46** involved delivery of the acetylide not to **33** but to a modified version thereof (cf. **45**). System **45** might be generated from **33** by selective protection of the aldehyde. Alternatively, **46** might be derived from intermediates en route to the aldehyde (cf. **29** or derivatives thereof). For instance, reaction of **36** with **29** could be followed by oxidation. Indeed, the first addition did occur to produce **47** (Scheme VII). Unfortunately, a variety of oxidation reactions intended to convert

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(17) Vollhardt, K. P. C.; Winn, L. S. *Tetrahedron Lett.* **1985**, *26*, 709.
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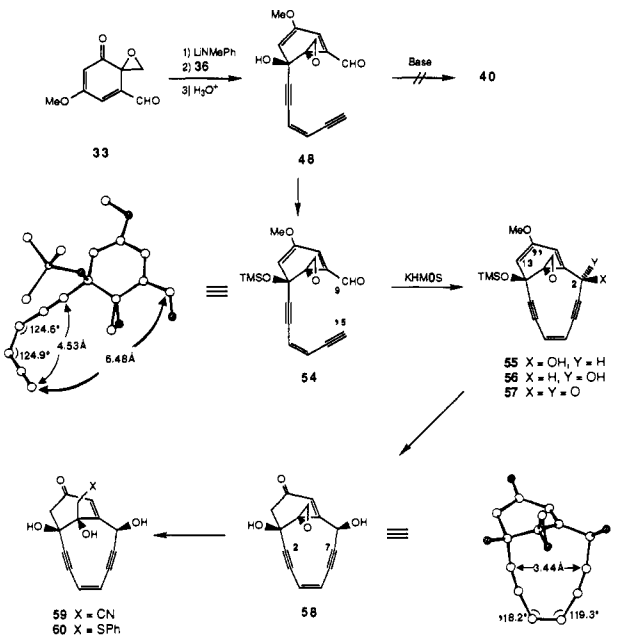
Scheme VIII



47 to **46** were unsuccessful. Of course, these reactions were complicated by the presence of a potentially labile tertiary alcohol. However, the prospects for a straightforward route to a derivative in which the tertiary alcohol was protected while the primary alcohol would be free were none too promising.

Mindful of the concept of in situ protection that had been introduced by Comins,[19] we turned to a more interesting strategem. The ability to generate stoichiometric or near stoichiometric equivalents of tetrahedral geminal *C*-oxido *C*-amino structures (see structure **49**) by the addition of lithio-*sec*-amides to aldehydes at −78 °C had been reported. In a remarkable exploitation of this finding, Comins had demonstrated the capacity to lithiate an aryl bromide in the nominal presence of an aldehyde, which presumably existed in a geminal *C*-oxido *C*-amino linkage under the conditions of lithiation. The lithio derivative **50** thus produced reacts with a variety of electrophiles. The Comins discovery is represented in the sequence **48**–**51**.

Our projected extension is implied in the progression **33** → **52** → **53** → **40**. Addition of **36** to "protected" aldehyde **52** would lead to **53**. It was our hope that, upon warming, **53** would revert to **46a**, which would cyclize to **40**.

To reduce this construct to practice, a THF suspension of compound **33** was treated at −40 °C with lithium *N*-methylanilide. To the resultant solution at −78 °C was administered 2 equiv of dilithioenediyne **36**. The alkoxide thus presumably generated showed only major decomposition upon being allowed to warm to room temperature. Since spontaneous cyclization did not occur, the reaction mixture was worked up to provide adduct **46**. Yields in the range of 60–70% were realized when the transformation was conducted on the millimolar level. In attempts at scale-up, this yield was reduced to ca. 40%. By both TLC and NMR criteria, the compound appeared to be substantially a single entity, though the possibility of the presence of small amounts of a stereoisomer could not be excluded. On the basis of analogy,[18] we assign to this adduct the stereochemistry shown wherein the acetylide had attacked the ketone syn to the oxygen atom of the spiroepoxide. The correctness of this proposition would soon be proven. We next attempted to carry out the long awaited cyclization of **46** → **40** under a variety of basic conditions. Such reactions gave complex mixtures of unidentified products.

We surveyed the possibility that protection of the tertiary alcohol might prove to be of advantage. Toward this end, **46** was treated with trimethylsilyl trifluoroacetate in the presence of triethylamine. There was obtained a 72% yield of the trimethylsilyl ether **54** (Scheme VIII). *Reaction of* ***54*** *in toluene at −78 °C with potassium hexamethyldisilazide did indeed bring about cyclization, producing* ***55*** *and* ***56*** *in a 9:1 ratio.*

We anticipated that the cyclization step, realized on the silyl derivative **54**, would produce the correct stereoisomer at C2, wherein the secondary hydroxyl is cis to the C_1 bridge. Of course, the bonds from the enediyne to the tertiary and secondary alcohols must be cis vis à vis the six-membered ring. Accordingly, the stereochemistry of the secondary alcohol at C2 follows strictly from the rotameric state of the aldehyde undergoing attack. The s-trans rotameric state is generally more stable in enals,[20] and barring some special reactivity effect this conformer would be expected to determine the stereochemical outcome. Given this assumption, as well as the precedent-based assumption about the facial sense of attack of acetylide **36** on the ketone of **52**, the major product was provisionally formulated as **55**, while the minor one is shown as **56**. The minor component was oxidized via the Dess–Martin periodinane[15] to the very unstable ketone **57**, which upon reduction with potassium triisopropoxyborohydride afforded alcohol **55** in an apparently highly stereoselective process. Thus, even the minor alcohol **56** can be channeled into the synthetic scheme.

Hydrolyses of the enol ether and silyl ether linkages were accomplished with oxalic acid to afford a 95% yield of **58**, mp 211–212 °C. Fortunately, it was possible to achieve X-ray crystallographic verification of this structure. In addition to its value in supporting our two stereochemical assignments, the crystallographic study provided the first hard structural data relevant to the core of this class of enediyne antibiotics. We note particularly that the distance between C2 and C7 is compressed to 3.44 Å. Presumably, it is the formation of a bond between corresponding carbon centers in calicheamicin that results in generation of the diyl species (cf. **7**). Also noteworthy are the deviation from coplanarity[12b] of the enediyne and the quasi-boatlike tendencies of the cyclohexenone ring. Not surprisingly, the angle strain of the enediyne linkage is born almost entirely by acetylenic rather than ethylenic carbons.[21]

Some time after we had achieved the cyclization leading to **55**, its precursor **54** was obtained in crystalline form (mp 94–95 °C). The three-dimensional structure of the molecule was determined by crystallographic measurements. The terminal carbons of the acyclic enediyne moiety in **54** are separated by a distance of 4.53 Å in the crystalline state, implying an enediyne compression of approximately 1.09 Å in **58**. Bond angles involving the acetylenes deviate only slightly from 180° (maximum of 2.7°). The X-ray data also indicated a C9–C15 interatomic distance of 6.48 Å, which had to be compressed to achieve cyclization. Finally, the s-trans enal conformation that was the basis of our strategy to establish the stereochemistry at the secondary alcohol did in fact pertain, at least in crystalline **54**.

With compound **58** in hand, we began to pursue some possibilities for progress toward the allylic trisulfide group of **1**. Two seemingly promising possibilities were encountered. Thus, reaction of **58** with diethylaluminum cyanide[22] afforded a 1:1 adduct formulated as **59**. Similarly, reaction of **58** with diethylaluminum thiophenoxide[23] provided **60**. Unfortunately, we were unsuccessful in a variety of ventures to exploit either compound. For instance, **59** could not be converted to the corresponding α,β-unsaturated

(19) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213.

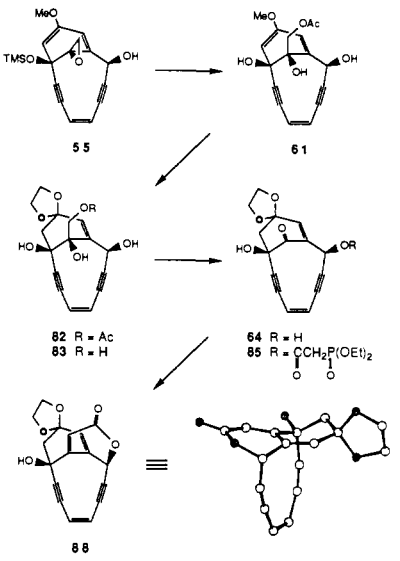
(20) (a) Cherniak, E. A.; Costain, C. C. *J. Chem. Phys.* **1966**, *45*, 104. (b) Wiberg, K. B.; Rosenberg, R. E.; Rauben, P. Submitted for publication.

(21) This assertion is based on a hypothetical value of 120° for unstrained sp^2 angles in a cis-disubstituted olefin. We resist the alternative comparison of the sp^2 angles in **58** with the corresponding angles of acyclic *cis*-olefins (e.g., **54**) on the grounds that the latter structures should experience some angle strain arising from van der Waals repulsion of the vicinal olefin substituents. An acyclic olefin, therefore, cannot be considered as an unstrained reference system.

(22) (a) Nagata, W.; Yoshioka, M. *Tetrahedron Lett.* **1966**, 1913. (b) Nitrile **59** was characterized by ^{1}H NMR and low-resolution mass spectroscopy.

(23) (a) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361. (b) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274. (c) Adduct **60** was characterized by ^{1}H NMR spectroscopy.

Scheme IX



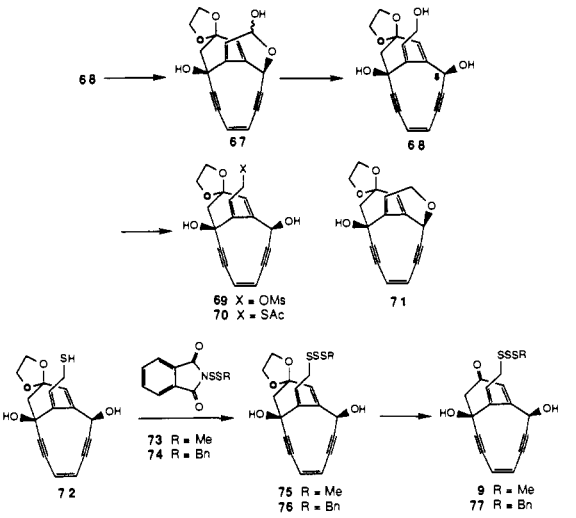
nitrile under numerous dehydrating conditions. Similarly unsuccessful were several undertakings that contemplated Pummerer-type transformations of the (phenylthio)methyl function.

While the possibilities for development of these compounds were by no means exhausted, a fresh departure presented itself. In principle, all attempts to salvage the exocyclic carbon of the spiroepoxide would entail some uncertainty as to the geometry of the resultant double bond.[24] We now proposed a tactic where the stereochemical issue would inevitably be resolved in a favorable way, provided that the olefin could be generated. To put this plan into action, we had to excise the exocyclic carbon of the spiroepoxide, thereby generating a ketone at the C_1 bridge. During this exercise, it would be important to maintain the differentiation of the potential carbonyl groups at C13 and C11.

Progress in this respect arose from the finding that compound **55** reacts with potassium acetate and acetic acid in DMSO to provide the acetoxyhydrin **61**. Reaction of **61** with dry ethylene glycol and camphorsulfonic acid (CSA) served to convert the enol ether linkage to an ethylene ketal. Compound **62**, thus available in 76% overall yield from **55**, was treated with methanolic ammonia to provide tetraol **63** (Scheme IX). Upon treatment of **63** with periodic acid in THF, the ketone–ketal **64** was in hand in 84% overall yield from **62**. Acylation of **64** with (diethoxyphosphinyl)acetic acid[25] in the presence of dicyclohexylcarbodiimide afforded the monoester **65**. A critical advance was registered upon reaction of **65** with lithium bromide and triethylamine[26] in THF at room temperature whereby there was obtained the crystalline dienyllactone **66**, mp >95 °C dec. The structure of **66** was verified by a single crystal X-ray determination. The near coplanarity of the $\alpha,\beta,\gamma,\delta$-dienyllactone was to play a significant role during installation of the urethane in the series leading to calicheamicinone itself (vide infra).

We focused next on opening the lactone by reductive means. Accordingly, **66** was subjected to the action of diisobutylaluminum hydride. A reaction occurred in methylene chloride at −78 °C. Workup revealed the product to be the hemiacetal **67** (Scheme X). Attempts to reduce **67** further by reaction with DIBAH were not successful. However, a favorable result was obtained upon treatment of hemiacetal **67** with sodium borohydride. This reaction gave rise to the triol **68** (69% yield from **66**). As will be seen, compound **68** was an interesting substrate for assessing the feasibility of an alternative triggering mechanism for the Bergman reaction.[5] Its role as an intermediate in the synthesis of **9** was critically dependent on a workable program to activate the allylic

Scheme X



alcohol and to achieve thiylation at some suitable stage.

We were not unmindful that in activating the primary allylic alcohol of **68** for displacement by a thiolate species we were incurring vulnerability to intramolecular displacement by the secondary alcohol at C8. However, attempts to obtain derivatives wherein the secondary alcohol is selectively protected were not successful. Accordingly, **68** itself was treated with methanesulfonyl chloride in pyridine. To this mixture, presumably containing the mesylate **69**, was added thiolacetic acid. There was produced the thioacetate **70**, though only in 23% yield. The major product was indeed the dihydropyran **71**.[27] An improved yield (50–60%) of thioacetate was realized by direct Mitsunobu reaction of **68** with thiolacetic acid under conditions similar to those described by Volante.[28]

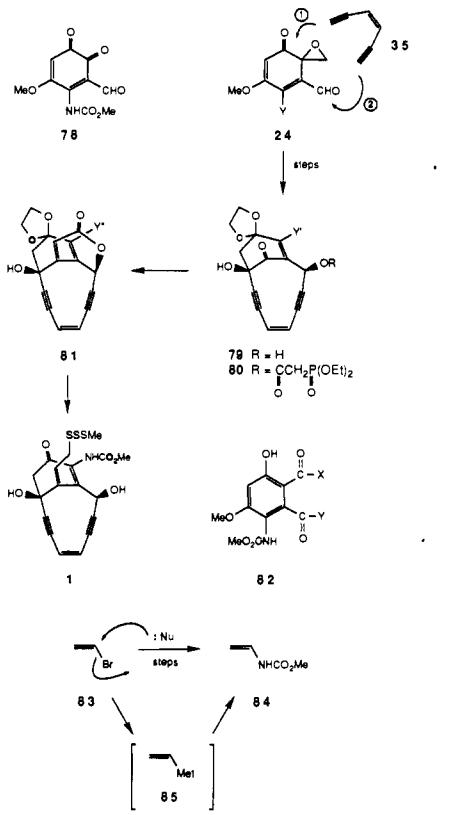
Compound **70** was reduced with diisobutylaluminum hydride. The crude thiol **72** reacted with homogeneous disulfide reagents **73**[10f] and **74**.[29] The corresponding trisulfides **75** and **76** were obtained in yields of 84 and 61%, respectively. Related chemistry had been reported by Magnus et al. prior to our own disclosure.[10f] In their conversion of an allylic thiol to the corresponding methyl trisulfide (through the use of **73**), a significant amount of the undesired methyl disulfide was formed. In our work, we do not encounter competition from disulfide formation. We believe that, when these Harpp-type reagents[29] are used in pure form, the amount of disulfide formation is sharply minimized.

The removal of the ketal, which was the last step in the synthesis of **9**, was approached with some concern since we had no experience to help in predicting the extent of lability of the trisulfide linkage. However, *in* practice, exposure of **75** or **76** to the action of camphorsulfonic acid in aqueous THF provided the bridgehead enones. Compound **77** was available in high yield, as was the long awaited **9**.

The campaign leading to the synthesis of descarbamate aglycon **9** had provided the context and framework for planning the next effort. The lessons learned from the synthesis of **9** were the following: (i) a spiroepoxide could serve as an accessible and viable equivalent of an orthoquinone (compare structures **78** and **24**, Scheme XI) (ii) a direct annulation with use of metalated enediyne **36** could well be possible provided that the ketone in the hypothetical structure **24** were involved in the intermolecular step, saving the aldehyde as the electrophile for the more demanding cyclization step; (iii) a differentiated enone (cf. structure **79**) would be a desirable intermediate for reaching **81** via intramolecular Emmons condensation of **80**; (iv) the *E* geometry at the one-carbon

(24) For an example of a stereoselective olefination that addresses this problem, see ref 10f.
(25) Cooke, M. P., Jr.; Biciunas, K. P. *Synthesis* **1981**, 283.
(26) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.
(27) Magnus and co-workers had previously described an efficient introduction of the thioacetate function in a simpler aglycon analogue that did not have the potential for pyran formation as a side reaction. See ref 10f.
(28) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
(29) (a) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem. Part A* **1971**, *1*, 57. (b) Sullivan, A. B.; Boustany, K. *Ibid.* **1971**, *1*, 207. (c) Harpp, D. N.; Ash, D. K. *Ibid.* **1971**, *1*, 211.

Scheme XI



bridge imposed by structure **81** could be exploited to reach our goal system; and (v) the installation of the allylic methyl trisulfide was probably feasible from an allylic alcohol to be derived from **81**.

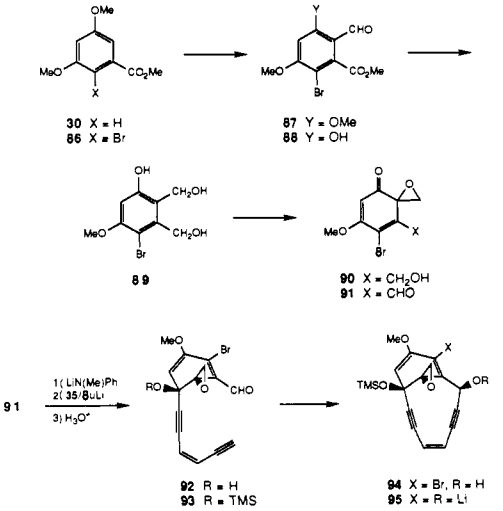
Of course, left unaddressed in this formalistic analysis was the nature of Y → Y″ in intermediates **24** → **81**, leading eventually to **1**. Also to be decided was the way in which the nature of Y would be changing as the ring system to which it is anchored was evolving. Unsuccessful forays in the direction of compounds of the type **82** suggested that such systems might not be readily available. Moreover, there was considerable doubt as to whether an early installation of the urethane group would be consistent with the chemistry that would be required to proceed toward **1**.

We settled instead on inclusion of a bromine atom at the arene carbon destined to house the urethane. The bromine (cf. structure **83**) offered two kinds of options for eventual introduction of the required functionality. At a suitable stage, the bromine might be displaced by a nucleophile that could translate eventually to the urethane. Alternatively, the vinylic bromide might be metalated, and the resultant organometallic species, generalized as **85**, might react with appropriate electrophiles, thus providing a route to ene urethane **84**.

The synthesis of calicheamicinone[12e] started with the commercially available **30** used in the synthesis of **9**. After considerable experimentation, conditions were developed (*N*-bromosuccinimide/acetonitrile) that produced **86** in good yield, contaminated by traces of a dibromo compound. Formylation of **86** was carried out with dichloromethyl methyl ether in the presence of titanium tetrachloride. The aldehyde function of the resultant **87** directed regiospecific demethylation via the action of BCl_3. The substituted salicylaldehyde **88** was available in 56% yield from **30** (Scheme XII).

The reduction of **88** to produce **89** proved to be rather more difficult than was the case with **32**. In our hands, the use of lithium aluminum hydride led to considerable reductive debromination, thus necessitating a nontrivial chromatographic separation of **89** from **28**. To avoid this problem, we employed diisobutylaluminum hydride as the reducing agent. While debromination was indeed avoided, workup of this reaction proved to be quite troublesome. Eventually, conditions were devised wherein the unstable triol **89**

Scheme XII



was, without prior purification, subjected to Becker oxidation.[11] Compound **90**, obtained in crude form, was oxidized with the Dess–Martin periodinane[15] to afford **91**. The yield of homogeneous **91** following a multigram scale reaction sequence was typically 40% from **88**. The annulation stage was at hand.

Some modifications were introduced in the three-step annulation procedure. In the first step, we no longer used stoichiometric dilithio derivative **36**. Instead, the enediyne **35** was treated with 1.3 equiv of *n*-butyllithium, and the resultant lithium acetylide served as the nucleophile after in situ protection of the aldehyde with lithium *N*-methylanilide.[19] The resultant adduct **92** was silylated, again using trimethylsilyl trifluoroacetate. Cyclization of **93** was conducted with potassium 3-ethyl-3-pentoxide.[30] The core system **94** was obtained in ca. 35–40% overall yield from **91**.

Early probes indicated that the bromine atom of **94** could be exchanged for lithium (see structure **95**) through the successive action of phenyllithium (1 equiv) and *tert*-butyllithium (2 equiv). Proton-quenching experiments produced the desbromo compound **55**, already well-known to us. Quenching the presumed vinyllithium derivative **95** with *p*-toluenesulfonyl azide[31] did in fact provide the desired vinyl azide in 70% yield, although attempts to reductively acylate this azide with use of triphenylphosphine and methyl chloroformate[32] were unsuccessful in providing the desired vinyl urethane. Similarly, carboxylation of the presumed **95** likewise gave rise to the corresponding unsaturated acid. This matter was not pursued extensively since attempted Curtius rearrangement for installation of the urethane gave, at best, low yields of the required product in an inhomogeneous state.

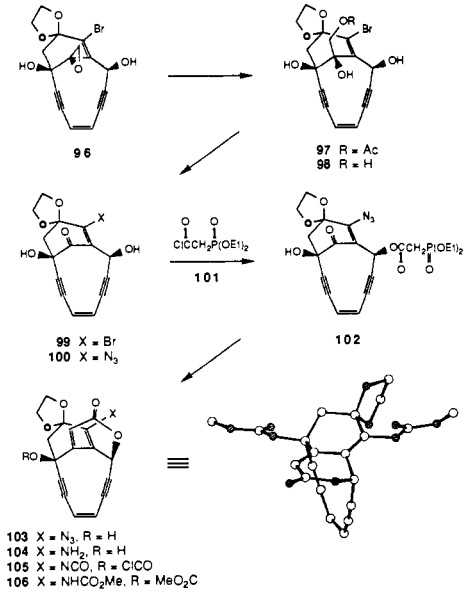
The possibilities inherent in the remarkable vinyllithium compound **95** were by no means surveyed in detail. However, since several preliminary attempts in this direction were not productive and since we were in any case skeptical as to whether this timing was optimal for installation of the urethane, we proceeded along a different course.

Treatment of enol ether **94** with camphorsulfonic acid and ethylene glycol afforded ketal **96** (89% yield). Acetolysis of the epoxide led to **97**, albeit in impure form (Scheme XIII). Deacylation was conducted with ammonia in methanol. Oxidative cleavage of the diol was accomplished with sodium periodate. The keto ketal **99** was thus in hand in 70% overall yield from **96**.

Mindful of the precedents of Magnus,[10e,g,33] which identified the possibility of Michael-type addition to the bridgehead double bond conjugated to a C_1 bridge ketone, we sought to exploit the β-bromoenone function of **99** as a target for attack by a nitro-

(30) Brown, H. C.; Moritani, I. *J. Am. Chem. Soc.* **1953**, *75*, 4112.
(31) Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* **1982**, *47*, 3177. Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795.
(32) Bachi, M. D.; Vaya, J. *J. Org. Chem.* **1979**, *44*, 4393. Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1988**, *53*, 1580.
(33) Magnus, P.; Lewis, R. T. *Tetrahedron Lett.* **1989**, *30*, 1905.

Scheme XIII



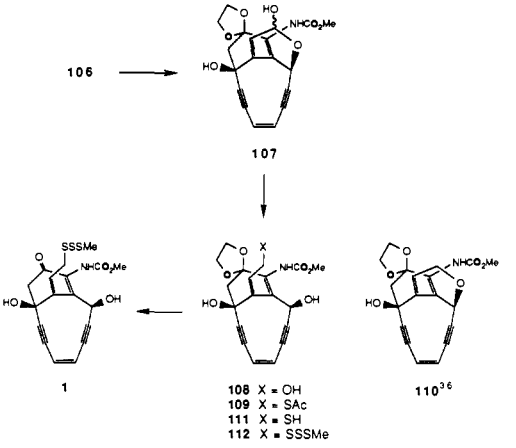
gen-based nucleophile. In the event, reaction of **99** with sodium azide in methanol did indeed afford the desired azidoenone **100** in 82% yield. Preliminary small-scale probes indicated that reduction of the azido group at this stage might not be a simple matter. Instead, we explored acylation of the secondary alcohol. The C8 hydroxyl function in **100** was, not surprisingly, less nucleophilic than was the corresponding group in the desazido analogue **64**. Accordingly, acylation was carried out with (diethoxyphosphinyl)acetyl chloride (**101**) rather than by carbodiimide coupling of the corresponding acid. Ester **102** thus obtained did indeed give rise to **103** (59% from **100**) by recourse to the lithium bromide/triethylamine conditions of Rathke.[26]

It was at the stage of **103** that we attempted to generate the primary vinylamine linkage en route to the urethane. The crystal structure of the unsubstituted analogue **66** (vide supra) bolstered our hopes that electronic conjugation of the amine to the lactonic carbonyl group would endow the nitrogen with overriding vinylogous urethane character, thus mitigating hydrolysis of an otherwise labile primary enamine linkage. Happily, treatment of **103** with H_2S and piperidine in methanol gave rise to vinylamine **104** as a remarkably stable compound. Indeed, the nearly neutral character of this "amine" group conferred some resistance to nitrogen acylation. However, treatment of **104** with bis(trichloromethyl) carbonate[34] and pyridine in CH_2Cl_2 led to the vinylisocyanate–chloroformate **105**. Presumably, the same conjugation factors that stabilized vinylamine **104** were operative in promoting the rapid methanolysis of **105** with methanol and pyridine to afford **106**. The structure of this compound (mp >105 °C dec) was verified crystallographically.

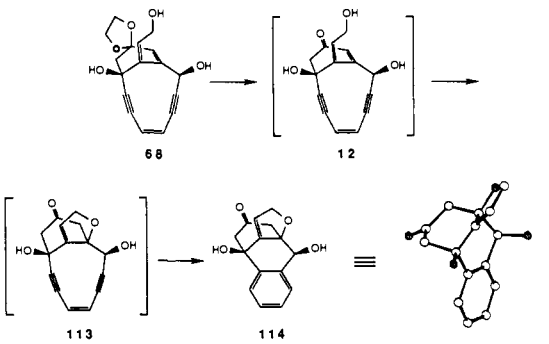
The urethane linkage proved to be stable to the remaining required steps. Thus, treatment of **106** with DIBAH resulted in deprotection of the carbonate as well as reduction of the lactone to the hemiacetal level. Further reduction of **107**, now with sodium borohydride, gave rise to triol **108** (64%, two steps). The Mitsunobu coupling of **108** with thiolacetic acid under modified conditions (see Experimental Section for the use of tri-*m*-anisylphosphine)[35] provided a 60% yield of **109**[36] (Scheme XIV).

As before (cf. compound **70**), the thioacetate was subjected to the action of DIBAH. The crude thiol thus generated was treated with disulfide **73**. There was thus obtained a 46% yield of the ketal **112**. The prospective final step, i.e., the deprotection of the ketal, again evoked some apprehension. The concern was that

Scheme XIV



Scheme XV

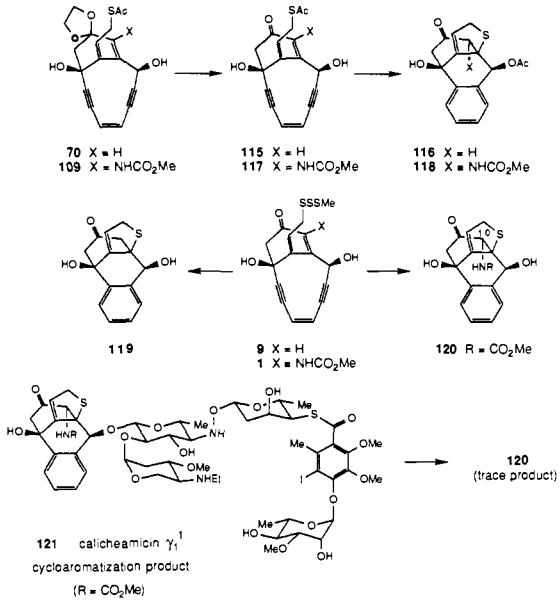


the presence of the vicinal urethane linkage would serve to retard the rate of acid-catalyzed deketalization. More vigorous reaction conditions or longer times might lead to damage of the trisulfide moiety. In the event, treatment of **112** with CSA for 8 h at room temperature did indeed lead to deprotection of the ketone and the formation of *dl*-calicheamicinone (**1**). While, as noted at the outset, an authentic sample of calicheamicinone is not available from natural sources (or via chemistry on the natural product), the claim of a total synthesis of **1** can be registered with high confidence. The structure of **106** is securely supported by a crystallographic determination. Spectroscopic and molecular weight determinations of the subsequent products through **1** sustain the claim that the last few steps occurred as expected. Furthermore, the conversion of **1** → **120** (vide infra) and the comparison of that aglycon with a trace specimen generated from the cycloaromatization product of calicheamicin γ_1^I also support the claim.

Concurrent with the synthetic studies, we examined the feasibility of reductive aromatization of various enediyne derivatives discussed above. Early experiments were conducted in the descarbamate series. For instance, it was of interest to explore the possibility of using an allylic alcohol as the internal Michael nucleophile.[12d] In an attempt to generate compound **12**, the allylic alcohol ketal **68** was subjected to camphorsulfonic acid in aqueous THF (Scheme XV). The process was closely monitored by TLC. While the formation of a new primary product was indicated, the isolation of this material proved to be problematic since it seemed to be unstable. We hypothesized that the primary product might be the allylic alcohol enone that could be undergoing Michael addition, producing **113**. The latter might in turn undergo Bergman-type bond reorganization followed by extensive polymerization or disproportionation of the diyl thus generated. Mindful of previous reports wherein diyls had been trapped with 1,4-cyclohexadiene,[5,10e,33] the deketalization of **68** was carried out in the presence of this hydrocarbon. This procedure led to a 58% yield of dihydrofuran derivative **114**, mp >215 °C dec, whose structure was corroborated crystallographically. Presumably, this transformation passed through the triol **12**, which undergoes

(34) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.
(35) Substitution of this reagent for triphenylphosphine allowed for a simpler chromatographic purification of thioacetate **109**.
(36) In addition to **109**, minor amounts of a side product tentatively identified as pyran **110** were generated under the Mitsunobu conditions (see also **68** → **70** + **71**).

Scheme XVI



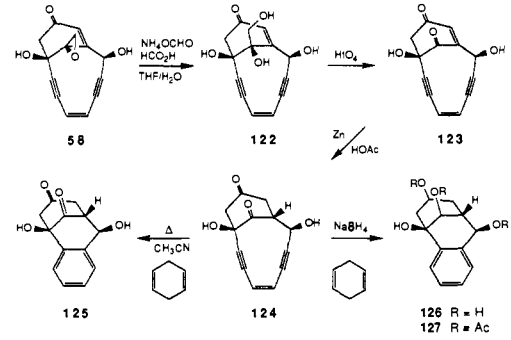
Michael addition of the hydroxyl group to the double bond. Given several failures to realize conjugate addition of various external nucleophiles to enone **58** (vide supra), the feasibility of the Michael reaction could not necessarily have been assumed. It is also well to note that, while the pre-Bergman cyclization step of calicheamicin (cf. **6** → **7**) is formulated for simplicity as a Michael addition, there is in fact no evidence against a thiyl radical equivalent of **6** functioning as the active intermediate. Since the effector species is not detected and since it is generated by reduction of the chemically novel trisulfide, it would be difficult to define with confidence the nature of the sulfur species undergoing cyclization. The cyclization leading from **68** would appear to be most confidently interpreted in terms of an even-electron species.

It was of interest to develop a sulfur-based cyclization precursor that was simpler than the trisulfide. For this purpose, we first turned to the thioacetate **70**. Cleavage of the ketal linkage was accomplished, again with camphorsulfonic acid in aqueous THF. The enone **115**[12d] was produced in 89% yield.

An interesting result was realized upon treatment of **115** with diethylamine in the presence of 1,4-cyclohexadiene. After 15 h, at room temperature, there was isolated a 71% yield of dihydrothiophene **116** (Scheme XVI). It seems likely that this transformation is initiated by deprotonation of the secondary hydroxyl followed by S → O migration of the acetyl function. Intramolecular thiol addition then triggers the bond reorganization of the enediyne, generating the diyl that, upon reduction with 1,4-cyclohexadiene, becomes **116**. While this model reaction certainly does not clarify the fine details of the in vivo bioactivation of calicheamicin itself, it does suggest that intramolecular Michael addition of an even-electron thiolate species is a viable method of activating diyl formation. In a process that is mechanistically less clear than but perhaps more closely related to the in vivo activation of the drugs, trisulfide **9**[12f] was treated with benzyl mercaptan in the presence of triethylamine and 1,4-cyclohexadiene. This led to a 49% yield of dihydrothiophene **119** that, upon acetylation, gave rise to **116**.

Actuations were also demonstrated in the urethane series. Treatment of **109** with camphorsulfonic acid afforded enone **117**. This compound reacted with diethylamine to afford **118** in 40% yield. Finally, in this series, the actuation of calicheamicinone (**1**) itself was demonstrated. Treatment of **1** under the same conditions as were employed for **9** afforded **120**, albeit in only 16% yield. With compound **120** in hand, there emerged an opportunity to correlate the synthetic and natural series. For this purpose, we obtained a specimen sample of calicheamicin γ_1^I cycloaromatization product **121**[37] and studied its deglycosylation under

Scheme XVII



a variety of conditions. Unfortunately, with the amounts of material on hand, we could not define conditions for a preparatively useful conversion of **121** → **120**. However, upon treatment of **121** with concentrated HCl/MeOH, there were obtained traces of a product whose TLC properties were the same as those of **120**. Moreover, the 250-MHz ^{1}H spectrum of the nonhomogeneous aglycon thus obtained displays all of the peaks present in *dl*-**120** while also exhibiting signals arising from impurities. We note that this comparison does not define the stereochemistry at C10 in compounds **118** and **120**. We favor the assignment indicated for the carbamate linkage on the basis of NMR data. In the ^{1}H NMR spectra of the descarbamate analogues **116** and **119**, we observe a W coupling (1.5–1.9 Hz) between the equatorial protons flanking the carbonyl of the cyclohexanone ring. This coupling is absent in **118** and **120**. Assuming that this ring occupies a chair conformation in all four compounds, the loss of coupling is most consistent with the urethane being disposed equatorially (i.e., α).

We also studied a Bergman-type bond reorganization that was not initiated through conventional Michael-type addition as the device for dissipating the bridgehead double bond. Solvolysis of spiroepoxide **58**[12c] afforded **122** which, upon treatment with periodic acid, afforded enedione **123** (Scheme XVII). Previous efforts to trigger diyl formation by reduction of the double bond of **58** and related compounds had been unsuccessful. However, enedione **123** suffered smooth reduction with zinc and acetic acid to provide dihydro product **124** as a stable entity.

Heating **124** in acetonitrile in the presence of 1,4-cyclohexadiene at 82 °C for 7 h afforded a dihydro product whose spectral properties clearly reveal it to be **125**. In the light of arguments concerning the rate of bond reorganization of *cis*-enediynes as a function of structural factors such as strain[38] and distance between the terminal acetylenic carbons,[10k] it was of interest to investigate a substrate analogous to **124**, except that the C_1 bridge would have a tetrahedral rather than trigonal carbon. Upon treatment of **124** with sodium borohydride, an unstable product was produced. It seemed possible that reduction was being quickly followed by cyclization and disproportionation. Accordingly, the reaction was carried out in the presence of 1,4-cyclohexadiene. There was thus obtained a 54% yield of a hexahydro product that underwent triacetylation upon treatment with triethylamine and acetic anhydride. The tetraol and triacetate are formulated as **126** and **127**, respectively. In contrast to **124** itself, its reduction product had undergone spontaneous bond reorganization at room temperature, a result very much in keeping with precedent.[10e]

Summary. The calicheamicin aglycon **1** was synthesized. A great deal was learned from an earlier study that led to the 10-descarbamate analogue **9**. A key element of the construction was the use of the Becker–Adler reaction as a device for advancing a relatively easily assembled aromatic system to a viable electrophile for annulation. In the effort shown here, the Becker–Adler-derived spiroepoxides served in essence as equivalents of differentiated orthoquinones (see synthetic equivalencies **78** and

(37) We are grateful to Dr. George Ellestad of American Cyanamid for a sample of this material.
(38) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986.

24). One can well imagine other applications of this type of intermediate wherein the spiroepoxide would be exploited differently. In achieving the annulations, it was possible to enter the full enediyne unit as a single entity. The logic of in situ protection[19] was expanded upon to include the case where an acetylenic nucleophile is directed to a ketone in the nominal presence of an aldehyde (see annulations leading to **55** and **94**).

Bond reorganizations resulting in reductive aromatization of constrained enediynes were demonstrated in both the descarbamate and fully substituted aglycon series. The effects of changing the nature of the C_1 bridging group from a keto carbon to a carbinol were strikingly demonstrated (see formation of compounds **125** and **126**). As previously reported,[12c] these differential rates of reductive aromatization were mirrored in the efficiency of oligonucleotide cleavage of *ϕX174* form I DNA.[39]

The next logical step in the program would be an investigation of the DNA-cleaving abilities of the aglycons which have been shown to undergo reductive aromatization (presumably via diyl intermediates). Studies along these lines in conjunction with corresponding studies on calicheamicin itself could help to define the role of the carbohydrate in the potency and sequence specificity of DNA cleavage. Such studies are in fact well in progress, and their results will be disclosed shortly.[40]

Experimental Section

8-(Hydroxymethyl)-6-methoxy-1-oxaspiro[2.5]octa-5,7-dien-4-one (29) from 27. Diisobutylaluminum hydride (95 mL, 1.0 M in toluene, 95 mmol) was added to a solution of diester **27**[13] (4.30 g, 19.0 mmol) in THF (70 mL) at −78 °C. The reaction was stirred for 30 min at ambient temperature and quenched with a saturated solution of potassium sodium tartrate (50 mL). EtOAc (100 mL) was added, and the mixture was stirred for 2 h and then filtered through Celite. The aqueous layer was well-extracted, and the combined organics were concentrated to an approximately 15-mL volume. THF (150 mL) was added, followed by $NaIO_4$ (63 mL, 0.30 M in H_2O, 19 mmol). After it was stirred for 9 h, the mixture was filtered and extracted with EtOAc. Flash column chromatography (EtOAc) gave the epoxide (2.30 g, 66%). Crystallization (EtOAc) produced yellow needles: mp 109–110 °C; IR ($CHCl_3$) 3660–3100, 3590, 3010, 1665, 1640, 1580 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.49–6.47 (m, 1 H), 5.62 (d, J = 2.6 Hz, 1 H), 4.27 (dd, J = 1.2, 14.9 Hz, 1 H), 4.10 (d, J = 14.9 Hz, 1 H), 3.82 (s, 3 H), 3.29 (ABq, J = 7.7, $\Delta\nu$ = 21.4 Hz), 2.29 (s, 1 H); electron impact mass spectrum, m/e 182.0580, calcd for $C_9H_{10}O_4$ 182.0579. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.08; H, 5.36.

3-Hydroxy-5-methoxy-1,2-benzenedimethanol (28) from 32. Lithium aluminum hydride (8.49 g, 0.224 mol) was added in portions over 5 min to a solution of phenol **32**[14b] (23.44 g, 0.112 mol) in 700 mL of THF at 0 °C. The reaction was stirred for 1 h at 0 °C and then quenched slowly with 40 mL of 1 N HCl. The triol was usually not isolated but exposed directly to the Becker oxidation conditions. Spectroscopically pure material could be obtained by extraction of a reaction aliquot that had been quenched with saturated sodium potassium tartrate solution. Drying and concentrating gave the triol as an unstable solid: IR ($CHCl_3$) 3570, 3520–3140, 3000, 1610, 1575, 1430, 1315, 1145, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 6.44 (d, J = 2.5 Hz, 1 H), 6.39 (d, J = 2.5 Hz, 1 H), 4.86 (s, 2 H), 4.59 (s, 2 H), 3.77 (s, 3 H); electron impact mass spectrum, m/e 184.0736, calcd for $C_9H_{12}O_4$ 184.0735.

Preparation of 29 from 28. Sodium periodate (47.69 g, 0.223 mol) and 140 mL of 1 N HCl were added to the above acidified solution of triol at ambient temperature. The oxidation was stirred for 18 h and then vacuum filtered, washing with THF and EtOAc in succession. The filtrate was washed with brine, saturated $NaHCO_3$ solution, and brine. The combined aqueous layers were saturated with NaCl and extracted with EtOAc (5×). The latter extracts were washed with saturated $NaHCO_3$ and brine. All organic layers were combined, dried over $MgSO_4$, concentrated in vacuo, redissolved in 50 mL of EtOAc, seeded, and allowed to stand at −20 °C. Filtration gave epoxide **29** (14.35 g, 70.6%) as orange prisms. Flash column chromatography (acetone/hexanes, 1:1) of the mother liquor and crystallization (EtOAc) provided a further 1.01 g (5.0%) of product (total yield of 15.36 g, 75.6%).

6-Methoxy-8-oxo-1-oxaspiro[2.5]octa-4,6-diene-4-carboxaldehyde (33). Dess–Martin periodinane[15] (62.0 g, 0.146 mol) was added to a solution of alcohol **29** (20.5 g, 0.113 mol) in 750 mL of CH_2Cl_2 at 0 °C. The oxidation was stirred for 30 min at 0 °C, and 15 g of K_2CO_3 was added. After another 4 min of stirring, the reaction mixture was vacuum-filtered through 100 mL of SiO_2, washing with EtOAc. The filtrate was concentrated in vacuo, redissolved in 200 mL of MeOH, and heated at reflux for 5 min. The cooled solution was concentrated in vacuo, redissolved in 400 mL of CH_2Cl_2, stirred for 1 h, and chromatographed [1 L of SiO_2, hexanes/EtOAc/CH_2Cl_2, 1:0:1 (200 mL) → 3:2:5]. Product fractions were crystallized from 125 mL of THF to give 13.4 g of crude product. This material was redissolved in 175 mL of CH_2Cl_2, filtered, concentrated, and recrystallized from THF to afford aldehyde **33** (10.27 g, 50.6%) as bright yellow needles. Mother liquors of several trials were combined, concentrated, redissolved in CH_2Cl_2, filtered, reconcentrated, and crystallized from THF to obtain a second crop. In this way, 87.1 g of alcohol **29** provided 60.5 g (four trials, 70% overall) of aldehyde **33**: mp 139–141 °C; IR ($CHCl_3$) 3015, 1700, 1655, 1630, 1575, 1345, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.50 (d, J = 0.5 Hz, 1 H), 7.15 (d, J = 2.5 Hz, 1 H), 5.88 (d, J = 2.5 Hz, 1 H), 3.89 (s, 3 H), 3.62 (ABq, J = 8.3, $\Delta\nu$ = 109.7 Hz, 2 H); electron impact mass spectrum, m/e 180.0438, calcd for $C_9H_8O_4$ 180.0422. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.47. Found: C, 60.28; H, 4.60.

α-3(*Z*)-Hexene-1,5-diynyl-α-phenylbenzenemethanol (37a). A solution of dilithioenediyne **36** (8.3 mL, 0.025 M in THF/pentane, 0.21 mmol)[12a] was added by cannula to a solution of benzophenone (30 mg, 0.16 mmol) in 5 mL of THF at −78 °C. After it was stirred for 30 min, the reaction was warmed to 0 °C and stirred for another 30 min. Extractive aqueous workup and flash column chromatography (hexanes/EtOAc) afforded alcohol **37a** (23 mg, 53%) as a colorless oil: IR ($CHCl_3$) 3580, 3300, 3040, 3000, 2960, 2920, 2850, 2250, 2100, 1600, 1490, 1450, 1330, 1140, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.62–7.58 (m, 4 H), 7.29–7.18 (m, 6 H), 5.96 (dd, J = 0.7, 10.8 Hz, 1 H), 5.82 (dd, J = 2.2, 10.8 Hz, 1 H), 3.31 (dd, J = 0.7, 2.2 Hz, 1 H), 2.77 (s, 1 H); electron impact mass spectrum m/e 258.1036, calcd for $C_{19}H_{14}O$ 258.1045.

1,1′-(3(*Z*)-Hexene-1,5-diyne-1,6-diyl)biscyclohexanol (38) and 1-(3-(*Z*)-Hexene-1,5-diynyl)cyclohexanol (38a). A solution of dilithioenediyne **36** (7.3 mL, 0.035 M, 0.26 mmol) was added by cannula to a solution of cyclohexanone (50 mg, 0.51 mmol) in THF (3 mL) at −78 °C. After it was stirred for 30 min, the reaction was warmed to 0 °C and stirred for another 10 min. Extractive aqueous workup and flash column chromatography (EtOAc/hexane) afforded diol **38** (25 mg, 35%) and alcohol **38a** (13 mg, 29%) as colorless oils.

Data for **38**: IR ($CHCl_3$) 3360, 3000, 2930, 2850, 2190, 1440, 1060, 960 cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 5.85 (s, 2 H), 2.77 (s, 2 H), 2.05–1.89 (m, 4 H), 1.75–1.51 (m, 14 H), 1.32–1.19 (m, 2 H); electron impact mass spectrum, m/e 272.1762, calcd for $C_{18}H_{24}O_2$ 272.1776.

Data for **38a**: IR ($CHCl_3$) 3570, 3390, 3290, 3000, 2930, 2840, 2200, 2090, 1445, 1060, 1050, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.96 (d, J = 11.0 Hz, 1 H), 5.81 (dd, J = 2.2, 11.0 Hz, 1 H), 3.35 (d, J = 2.2 Hz, 1 H), 2.06 (s, 1 H), 2.00–1.94 (m, 2 H), 1.73–1.55 (m, 8 H); electron impact mass spectrum, m/e 174.1061, calcd for $C_{12}H_{14}O$ 174.1045.

Preparation of 38a. Cyclohexanone (20 mg, 0.20 mmol) was added to a solution of dilithioenediyne **36** (13.5 mL, 0.045 M in THF/pentane, 0.61 mmol) at −78 °C, and the reaction was allowed to warm to ambient temperature. Extractive aqueous workup and flash column chromatography (EtOAc/hexanes) afforded alcohol **38a** (24 mg, 68%) and diol **38** (2 mg, 4%).

1,8-Diphenyl-4-octene-2,6-diyne-1,8-diol (39) and α-3(*Z*)-Hexene-1,5-diynylbenzenemethanol (39a). To a solution of bis(trimethylsilyl)-enediyne **34** (253 mg, 1.14 mmol) in THF (5 mL) was added LiOH-H_2O (153 mg, 3.67 mmol) dissolved in H_2O (1 mL). After the mixture was stirred for 1.5 h, pentane (10 mL) was added, the layers were separated, and the aqueous layer was extracted with pentane (2 × 2 mL). The combined organic layers were dried briefly over K_2CO_3, decanted onto 4-Å molecular sieves (1 h), and then added via cannula to a 100-mL round-bottom flask. 1,10-Phenanthroline (1 mg) and 20 mL of THF were added, the mixture was cooled to 0 °C, and *n*-BuLi (2.5 M solution in hexanes) was added until a dark brown color persisted. The mixture was then cooled to −78 °C, and *n*-BuLi (0.73 mL, 1.8 mmol) was added. After 30 min, benzaldehyde (0.19 mL, 1.9 mmol) was added and the mixture was warmed to 0 °C and quenched with pH 8 buffer. Extractive workup and flash column chromatography (EtOAc/hexanes, 1:9) gave alcohol **39a** (20 mg, 7.5%) and diol **39** (240 mg, 73%) as colorless glasses.

Data for **39**: IR ($CHCl_3$) 3570, 3360, 3100, 3000, 1490, 1450, 990 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57–7.54 (m, 4 H), 7.38–7.32 (m, 6 H), 5.95 (s, 2 H), 5.60 (d, J = 2.7 Hz, 2 H), 2.88–2.85 (m, 2 H); chemical ionization mass spectrum, m/e 289.1233, M + H calcd for $C_{20}H_{17}O_2$ 289.1229.

(39) For the first documentation of cyclic enediynes as synthetic DNA cleaving agents, see: Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247.

(40) Iwasawa, N.; Drak, J.; Haseltine, J. N. Unpublished results.

Data for **39a**: IR ($CHCl_3$) 3570, 3440, 3290, 1490, 1450, 1130, 990 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2 H), 7.44–7.35 (m, 3 H), 5.99 (dd, J = 1.0, 11.0 Hz, 1 H), 5.88 (dd, J = 2.2, 11.0 Hz, 1 H), 5.68 (d, J = 5.2 Hz, 1 H), 3.38 (dd, J = 0.7, 2.2 Hz, 1 H), 2.46 (s, 1 H); electron impact mass spectrum, m/e 182.0722, calcd for $C_{13}H_{10}O$ 182.0732.

Preparation of 39a. Benzaldehyde (20 mg, 0.19 mmol) was added to a solution of dilithioenediyne **36** (12.4 mL, 0.045 M, 0.56 mmol) at −78 °C, and the solution was warmed to room temperature. Extractive aqueous workup and chromatography (EtOAc/hexanes) afforded alcohol **39a** (26 mg, 76%) and diol **39** (5 mg, 9%).

8-(3-Hexene-1,5-diynyl)-8-hydroxy-6-methoxy-1-oxaspiro[2.5]octa-4,6-diene-4-carboxaldehyde (46). Generation of 1,6-Dilithiohexenediyne. A mixture of 1,6-bis(trimethylsilyl)hex-3-ene-1,5-diyne (**34**) (4.92 g, 22.3 mmol) and lithium hydroxide hydrate (5.06 g, 121 mmol) in 80 mL of THF and 17 mL of water was stirred vigorously for 2 h. Pentane (20 mL) was added, the layers were separated, and the aqueous layer was extracted with 20 mL of THF/pentane (1:1). Combined organic layers were dried over K_2CO_3 (−20 °C, 3 h), filtered through 10 mL of SiO_2, washing with 15 mL of THF, and concentrated under a stream of nitrogen to approximately 125 mL. A few milligrams of 1,10-phenanthroline (as indicator) were added, and the solution was cooled to 0 °C. n-Butyllithium (2.5 M in hexanes) was added until a dark color persisted (21 mL), the solution was cooled to −78 °C, a second portion of n-butyllithium was added (16.25 mL, 41 mmol), and the solution was stirred at −78 °C for 15 min.

In situ Protection of the Aldehyde Carbonyl. N-Methylaniline (1.34 mL, 12.4 mmol) in 60 mL of THF was cooled to 0 °C and treated with n-butyllithium (4.73 mL, 2.5 M in hexanes, 12 mmol). After 5 min, the resulting slurry was transferred via cannula to a −78 °C slurry of aldehyde **33** (2.03 g, 11.3 mmol) in 120 mL of THF. The −78 °C bath was removed, and the reaction was allowed to warm until complete solution was achieved. After 2 more min, the −78 °C bath was returned.

Addition of Dilithiohexenediyne to the Protected Substrate. The above solution of dilithiohexenediyne was transferred via cannula to the −78 °C solution of protected **33**, and the reaction was stirred for 30 min at −78 °C and for 20 min at −40 °C. The bath was removed, and 100 mL of 20% NH_4Cl solution was added rapidly. The mixture was extracted with Et_2O, and combined extracts were washed with water, 100 mL of 0.1 N HCl, water (2×), and brine. Drying (Na_2SO_4), concentration, and flash column chromatography (loading crude product into a sand trap at the head of the column to minimize exposure to SiO_2; eluting with EtOAc/hexane, 1:2) provided alcohol **46** (1.13 g, 39%) as an unstable yellow glass: IR ($CHCl_3$) 3600–3100, 3545, 3280, 3005, 1685, 1640, 1580 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.52 (s, 1 H), 6.92 (d, J = 2.5 Hz, 1 H), 5.94 (d, J = 11.0 Hz, 1 H), 5.88 (dd, J = 1.9, 11.0 Hz, 1 H), 5.34 (d, J = 2.4 Hz, 1 H), 3.76 (ABq, J = 5.5 Hz, $\Delta\nu$ = 95.9 Hz, 2 H), 3.71 (s, 3 H), 3.39 (d, J = 1.8 Hz, 1 H), 2.45 (s, 1 H); mass spectrum (20 eV) m/e 256 (molecular ion, 4.8), 238 (11.8), 139 (100.0).

8-(3-Hexene-1,5-diynyl)-6-methoxy-8-[(trimethylsilyl)oxy]-1-oxaspiro[2.5]octa-4,6-diene-4-carboxaldehyde (54). Trimethylsilyl trifluoroacetate (3.02 mL, 17.5 mmol) was added to a 0 °C solution of alcohol **46** (1.13 g, 4.41 mmol) and triethylamine (4.93 mL, 35.4 mmol) in 60 mL of CH_2Cl_2. The solution was stirred for 1 h at ambient temperature and then poured into saturated $NaHCO_3$ solution. Extraction with CH_2Cl_2, drying (Na_2SO_4), concentration, and flash column chromatography (loading in sand as above; eluting with EtOAc/hexanes, 3:17) provided silyl ether **54** (1.04 g, 72%) as an unstable slightly yellow glass. Low-temperature crystallization gave prisms: mp 94–95 °C (EtOAc/hexanes); IR ($CDCl_3$) 3300. 2960, 2255, 1695, 1650, 1590, 1270, 1255, 1045, 1035, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 6.89 (d, J = 2.5 Hz, 1 H), 5.94 (d, J = 11.2 Hz, 1 H), 5.86 (dd, J = 2.2, 11.0 Hz, 1 H), 5.31 (d, J = 2.5 Hz, 1 H), 3.74 (ABq, J = 5.7 Hz, $\Delta\nu$ = 136.2 Hz, 2 H), 3.69 (s, 3 H), 3.35–3.34 (m, 1 H), 0.19 (s, 9 H); chemical ionization mass spectrum, m/e 329.1206, M + H calcd for $C_{18}H_{21}O_4Si$ 329.1209.

11-Methoxy-9-[(trimethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-5,10,12-triene-3,7-diyne-13,2′-oxiran]-2-ol (55) and Its C2 Epimer (56). Potassium bis(trimethylsilyl)amide (12.69 mL, 0.5 M in toluene, 6 mmol) was added to a −78 °C solution of aldehyde **54** (1.04 g, 3.17 mmol) in 250 mL of toluene. The cyclization was stirred 45 min at −78 °C, and a solution of acetic acid (0.54 mL, 9.51 mmol) in 18 mL of toluene was added rapidly. The warmed solution was poured into saturated $NaHCO_3$ solution and extracted with EtOAc. Drying (Na_2SO_4), concentration, and flash column chromatography (EtOAc/hexanes, 3:17) provided alcohol **55** (430 mg, 39%) and its C2 epimer (**56**) (46 mg, 4.4%) as slightly yellow glasses.

Data for **55**: IR ($CDCl_3$) 3600–3380, 2950, 2240, 1650, 1605, 1390, 1240, 1120, 1020, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.09 (d, J = 9.6 Hz, 1 H), 5.97 (dd, J = 1.7, 9.7 Hz, 1 H), 5.79 (d, J = 2.2 Hz, 1 H), 5.18 (dd, J = 1.2, 11.6 Hz, 1 H), 4.71 (d, J = 2.3 Hz, 1 H), 3.61 (s, 3 H), 3.28 (d, J = 11.7 Hz, 1 H), 3.15 (ABq, J = 5.9 Hz, $\Delta\nu$ = 166.5 Hz, 2 H), 0.25 (s, 9 H); electron impact mass spectrum, m/e 328.1122, calcd for $C_{18}H_{20}O_4Si$ 328.1131.

Data for **56**: IR ($CHCl_3$) 3700–3200, 3590, 3020, 1660, 1610, 1380, 1125, 1100, 1030, 875, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (dd, J = 1.5, 2.3 Hz, 1 H), 6.03 (dd, J = 0.7, 9.6 Hz, 1 H), 5.93 (dd, J = 1.0, 9.6 Hz, 1 H), 4.84 (d, J = 2.0 Hz, 1 H), 4.70 (d, J = 2.3 Hz, 1 H), 3.62 (s, 3 H), 3.06 (ABq, J = 5.7 Hz, $\Delta\nu$ = 450.2 Hz, 2 H), 0.24 (s, 9 H); chemical ionization mass spectrum, m/e 329.1185, M + H calcd for $C_{18}H_{21}O_4Si$ 329.1209.

11-Methoxy-9-[(trimethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-5,10,12-triene-3,7-diyne-13,2′-oxiran]-2-one (57). Dess–Martin periodinane[15] (3.6 mg, 8.3 μmol) was added to a stirred solution of alcohol **56** (2.5 mg, 7.6 μmol) in CH_2Cl_2 (0.5 mL) at room temperature. After 1 h, 2% aqueous $NaHCO_3$ was added and the product was extracted into ether (20 mL). The organic extract was dried (Na_2SO_4) and concentrated to give ketone **57** (2.5 mg, 100%) as a glass. This product was not stable upon standing in concentrated form.

Data for **57**: IR ($CDCl_3$) 3600–3100, 2950, 1665, 1600, 1245, 1125, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.43 (d, J = 9.7 Hz, 1 H), 6.19 (d, J = 9.6 Hz, 1 H), 6.04 (d, J = 2.2 Hz, 1 H), 4.79 (d, J = 2.2 Hz, 1 H), 3.63 (s, 3 H), 3.03 (ABq, J = 5.8 Hz, $\Delta\nu$ = 207.9 Hz, 2 H), 0.26 (s, 9 H); mass spectrum (20 eV) m/e 326 (molecular ion, 2.1), 73 (100).

Preparation of 55 from 57. Potassium triisopropoxyborohydride (8.3 μL of a 1.0 M solution in THF, 8 μmol) was added to a stirred solution of ketone **58** (2.5 mg, 7.7 μmol) in THF (1 mL, 8 μmol) at 0 °C. After 20 min, 20% aqueous NH_4Cl (3 mL) was added and the product was extracted into EtOAc. The organic extract was dried (Na_2SO_4) and concentrated to give 1 mg of diastereomer **55**, which was judged pure by TLC and ^1H NMR.

1,8-Dihydroxyspiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-13,2′-oxiran]-11-one (58). Oxalic acid (3 mL, 5% solution in H_2O) was added to a solution of **55** (40 mg, 120 μmol) in THF (10 mL), and this solution was stirred at ambient temperature for 6 h. An excess of saturated sodium bicarbonate solution was then added. Extraction and flash column chromatography (hexanes/EtOAc, 1:1) gave the enone (28 mg, 95%) as a colorless solid. Crystallization from EtOAc/hexanes gave prisms: mp 211–212 °C; IR ($CHCl_3$) 3660, 3530, 3005, 2910, 1710, 1670, 1285, 1060, 1030, 920 cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 6.13 (s, 1 H), 5.94 (app s, 2 H), 5.25 (d, J = 11.7 Hz, 1 H), 3.46 (ABq, J = 5.2 Hz, $\Delta\nu$ = 108.1 Hz, 2 H), 3.27 (d, J = 11.6 Hz, 1 H), 3.13 (dd, J = 1.3, 7.3 Hz, 1 H), 2.75 (d, J = 7.3 Hz, 1 H), 2.61 (s, 1 H); chemical ionization mass spectrum, m/e 243.0662, M + H calcd for $C_{14}H_{11}O_4$ 243.0657.

13-[(Acetyloxy)methyl]-11-methoxybicyclo[7.3.1]trideca-4,9,11-triene-2,6-diyne-1,8,13-triol (61). A mixture of epoxide **55** (1.05 g, 3.20 mmol), potassium acetate (800 mg, 8.15 mmol), and acetic acid (0.54 mL, 9.4 mmol) in dry DMSO (40 mL) was heated at 50 °C (bath temperature) for 4 h. Extractive aqueous workup and flash column chromatography (acetone/hexanes, 7:13) afforded acetate **61** (961 mg, 95%) as a colorless glass: IR ($CHCl_3$) 3540, 3500, 3600–3120, 1740, 1655, 1615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.10 (d, J = 9.5 Hz, 1 H), 5.99 (dd, J = 1.7, 9.6 Hz, 1 H), 5.72 (dd, J = 0.6, 2.2 Hz, 1 H), 5.30 (dd, J = 1.5, 10.1 Hz, 1 H), 4.80 (d, J = 2.4 Hz, 1 H), 4.77 (dd, J = 1.7, 11.9 Hz, 1 H), 4.30 (d, J = 11.8 Hz, 1 H), 3.60 (s, 3 H), 3.48 (d, J = 1.5 Hz, 1 H), 3.44 (d, J = 10.1 Hz, 1 H), 3.00 (s, 1 H), 2.08 (s, 3 H); chemical ionization mass spectrum, m/e 317.1042, M + H calcd for $C_{17}H_{17}O_6$ 317.1025.

13-[(Acetyloxy)methyl]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolane]-1,8,13-triol (62). Camphorsulfonic acid (35 mg, 0.15 mmol) was added to a solution of acetate **61** (961 mg, 3.04 mmol) in dry ethylene glycol (25 mL) and THF (1 mL) with stirring at 50 °C (bath temperature). After 2.5 min at 50 °C, pyridine (0.1 mL) was added and the oil bath was removed. Aqueous extractive workup and flash column chromatography (acetone/hexanes, 7:13) provided ketal **62** (836 mg, 80%) as a colorless glass: IR ($CHCl_3$) 3500, 3610–3120, 1740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.94 (d, J = 9.6 Hz, 1 H), 5.85 (dd, J = 1.5, 9.6 Hz, 1 H), 5.57 (s, 1 H), 5.22 (br s, 1 H), 4.47 (ABq, J = 11.7 Hz, $\Delta\nu$ = 20.4 Hz, 1 H), 4.05–3.89 (m, 5 H), 3.83 (br s, 1 H), 3.18 (br s, 1 H), 2.53 (d, J = 14.6 Hz, 1 H), 2.49 (dd, J = 1.2, 14.7 Hz, 1 H), 2.11 (s, 3 H); chemical ionization mass spectrum, m/e 347.1113, M + H calcd for $C_{18}H_{19}O_7$ 347.1131.

13-(Hydroxymethyl)spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolane]-1,8,13-triol (63). A solution of ketal–acetate **62** (1.90 g, 5.49 mmol) in 100 mL of MeOH at 0 °C was saturated with gaseous ammonia and allowed to stir for 20 min at ambient temperature. Nitrogen was bubbled through the solution for 10 min, and the resulting solution was stirred under reduced pressure (aspirator) until the reaction volume had decreased to approximately 100 mL. Removal of methanol

by rotary evaporator provided tetraol **63** as a colorless glass. This material was usually not purified but used directly in the next reaction. Analytically pure prisms could be obtained by crystallization from EtOAc/hexanes: mp 154.0–157.0 °C dec; IR (KBr) 3485, 3620–2060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.95 (d, J = 9.5 Hz, 1 H), 5.86 (dd, J = 1.5, 9.5 Hz, 1 H), 5.55 (dd, J = 0.7, 1.3 Hz, 1 H), 5.15 (dd, J = 0.8, 9.4 Hz, 1 H), 4.10–3.89 (m, 9 H), 2.98 (app t, J = 6.5 Hz, 1 H), 2.61 (dd, J = 1.4, 14.8 Hz, 1 H), 2.48 (d, J = 14.9 Hz, 1 H); chemical ionization mass spectrum, m/e 305.1043, M + H calcd for $C_{16}H_{17}O_6$ 305.1025. Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.95; H, 5.14.

1,8-Dihydroxyspiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-13-one (64). Tetraol **63**, obtained from the previous reaction, was dried by concentration from benzene in vacuo and redissolved in 150 mL of dry THF. Periodic acid dihydrate (1.38 g, 6.06 mmol) was then added to the solution. After 5 min, the reaction was halted by the addition of saturated $NaHCO_3$ solution and extracted with EtOAc. Drying over Na_2SO_4, concentration, and flash column chromatography (hexanes/EtOAc, 1:1) gave enone **64** (1.26, 84% for two steps) as a slightly yellow glass. Colorless prisms could be obtained by crystallization from EtOAc/hexanes: mp >141 °C dec; IR (KBr) 3580–3100, 1705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.21 (d, J = 1.9 Hz, 1 H), 5.93 (d, J = 9.7 Hz, 1 H), 5.87 (dd, J = 1.4, 9.8 Hz, 1 H), 5.24 (dd, J = 1.0, 11.1 Hz, 1 H), 4.19 (d, J = 11.3 Hz, 1 H), 4.15–3.96 (m, 4 H), 3.82 (s, 1 H), 2.73 (dd, J = 2.0, 14.1 Hz, 1 H), 2.43 (d, J = 14.2 Hz, 1 H); chemical ionization mass spectrum, m/e 273.0773, M + H calcd for $C_{15}H_{13}O_5$ 273.0763.

(Diethoxyphosphinyl)acetic Acid, 9-Hydroxy-13-oxospiro[bicyclo-[7.3.1]trideca-5,12-diene-3,7-diyne-11,2′-[1,3]dioxolan]-2-yl Ester (65). Dicyclohexylcarbodiimide (1.43 g, 6.93 mmol) was added to a solution of enone **64** (1.26 g, 4.63 mmol) and (diethoxyphosphinyl)acetic acid[25] (1.9 mL, 6.88 mmol) in 85 mL of dry THF at 0 °C. This mixture was stirred for 1.5 h at ambient temperature (followed closely by TLC analysis). Extractive aqueous workup and flash column chromatography (acetone/hexanes, 1:1) provided the desired product (contaminated with dicyclohexylurea). This material was sufficiently pure for use in the next reaction, but a spectroscopically pure colorless glass could be obtained by repeating the chromatography: IR ($CHCl_3$) 3600–3100, 1745, 1720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.40 (d, J = 1.9 Hz, 1 H), 6.15 (d, J = 1.1 Hz, 1 H), 5.99 (d, J = 9.8 Hz, 1 H), 5.87 (dd, J = 1.5, 9.7 Hz, 1 H), 4.26–3.95 (m, 9 H), 3.12 (dABq, J = 14.7, 21.4 Hz, $\Delta\nu$ = 16.0 Hz, 2 H), 2.73 (dd, J = 1.9, 14.2 Hz, 1 H), 2.40 (d, J = 14.2 Hz, 1 H), 1.35 (app t, J = 7.1 Hz, 6 H); chemical ionization mass spectrum, m/e 451.1180, M + H calcd for $C_{21}H_{24}O_9P$ 451.1158.

5′,6′-Dihydro-5′-hydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene-[1,5]diyno[1*H*-2]benzopyran]-3′-one (66). The preceding phosphinylacetate **65** was dissolved in 170 mL of THF. Lithium bromide (1.70 g, 19.6 mmol) and triethylamine (5.09 mL, 36.5 mmol) were added in succession, and the resulting solution was stirred for 3 h at ambient temperature. The reaction was then diluted with hexanes (100 mL) and CH_2Cl_2 (50 mL) and filtered through SiO_2 (50 mL), washing with acetone/hexanes (2:3). Concentration of the resulting solution and flash column chromatography (acetone/hexanes, 1:3) afforded lactone **66** (1.04 g, 76% for two steps) as a slightly yellow glass. Crystallization from THF/hexanes provided colorless prisms: mp >95 °C dec; IR (KBr) 3580–3110, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.18 (d, J = 1.6 Hz, 1 H), 5.94 (d, J = 9.5 Hz, 1 H), 5.84 (dd, J = 1.3, 9.8 Hz, 1 H), 5.760 (s, 1 H), 5.755 (s, 1 H), 4.17–3.94 (m, 4 H), 2.89 (s, 1 H), 2.54 (dd, J = 0.9, 13.6 Hz, 1 H), 2.37 (d, J = 13.6 Hz, 1 H); chemical ionization mass spectrum, m/e 297.0770, M + H calcd for $C_{17}H_{13}O_5$ 297.0763. Anal. Calcd for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08. Found: C, 68.87; H, 4.16.

13-((*E*)-2-Hydroxyethylidene)spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolane]-1,8-diol (68). Lactone **66** (271 mg, 0.916 mmol) was dissolved in 30 mL of dry CH_2Cl_2 and cooled to −78 °C. Diisobutylaluminum hydride (2.74 mL, 1.0 M solution in cyclohexane, 2.7 mmol) was added, and the solution was stirred for 20 min at −78 °C. The reaction was quenched with EtOAc (0.5 mL) and saturated $NaHCO_3$ solution. Extraction with EtOAc, drying (Na_2SO_4), and flash column chromatography (product loaded in CH_2Cl_2/THF, 9:1; eluted with acetone/hexane, 0:1 → 2:3) gave the lactol as a colorless solid. This material was redissolved in 12 mL of MeOH containing 240 μL of water. The solution was cooled to 0 °C, sodium borohydride (240 mg, 6.34 mmol) was added, and the mixture was stirred for 45 min at 0 °C. Acetic acid (0.6 mL) was added dropwise, and the solution was concentrated in vacuo. The resulting mixture was redissolved in a minimal amount of THF/MeOH (1:1) and reconcentrated (repeat 1×) in order to solvolyze the apparent substrate–boron complex. The material was then resuspended in THF/MeOH (95:5) and filtered through a plug of SiO_2, washing with THF. Concentration in vacuo followed by concentration from 12 mL of toluene/EtOH (1:1) and flash column chromatography (acetone/hexanes, 2:3 → 3:2) afforded triol **68** (190 mg, 69% for two steps) as a colorless glass. Needles could be obtained by crystallization from THF/hexanes: mp >125 °C dec; IR (KBr) 3495, 3660–3000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.27 (app t, J = 6.9 Hz, 1 H), 5.88 (d, J = 8.4 Hz, 1 H), 5.84 (s, 1 H), 5.81 (d, J = 8.2 Hz, 1 H), 5.39 (br s, 1 H), 4.59 (br s, 1 H), 4.30 (app d, J = 6.6 Hz, 2 H), 4.07–3.89 (m, 4 H), 2.83 (br s, 1 H), 2.71 (br s, 1 H), 2.41 (ABq, J = 13.7 Hz, $\Delta\nu$ = 92.8 Hz, 2 H); chemical ionization mass spectrum, m/e 301.1088, M + H calcd for $C_{17}H_{17}O_5$ 301.1076.

Ethanethioic Acid, (*S*)-2-(1,8-dihydroxyspiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-13-ylidene)ethyl Ester (70) and Spiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]-(*E*)-hexene[1,5]diyno[1*H*-2]-benzopyran]-5′(6′*H*)-ol (71). Diisopropyl azodicarboxylate (0.21 mL, 1.1 mmol) was added dropwise to a 0 °C solution of triphenylphosphine (280 mg, 1.07 mmol) in 6 mL of THF. The resulting mixture was stirred at 0 °C for 30 min, when thiolacetic acid (0.11 mL, 1.5 mmol) and a solution of triol **68** (64 mg, 0.21 mmol, in 3 mL of THF plus 1.5 mL wash) were added dropwise in succession. The reaction was stirred for 1 h at 0 °C and then poured into saturated $NaHCO_3$ solution and extracted with EtOAc. Drying, concentration, and flash column chromatography (acetone/hexanes, 3:7) afforded pyran **71** (12 mg, 20%) as a colorless solid and impure thioacetate **70**. Contaminant triphenylphosphine oxide could be removed from the latter by flash column chromatography (EtOAc/hexanes, 1:1), affording pure **70** as an unstable colorless solid (40 mg, 52%; best stored in THF solution, −20 °C).

Data for **70**: IR ($CHCl_3$) 3570, 3600–3120, 1680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.04 (app t, J = 8.0 Hz, 1 H), 5.89 (d, J = 9.5 Hz, 1 H), 5.82 (dd, J = 1.4, 11.1 Hz, 1 H), 5.80 (s, 1 H), 5.37 (d, J = 7.7 Hz, 1 H), 4.13–3.89 (m, 5 H), 3.73 (dd, J = 7.1, 14.3 Hz, 1 H), 3.12 (d, J = 7.7 Hz, 1 H), 2.58 (dd, J = 1.0, 13.6 Hz, 1 H), 2.34 (s, 3 H), 2.33 (s, 1 H), 2.20 (d, J = 13.5 Hz, 1 H); chemical ionization mass spectrum, m/e 359.0859, M + H calcd for $C_{19}H_{19}O_5S$ 359.0954.

Data for **71**: mp >145 °C dec; IR (KBr) 3600–3100, 2975, 2885, 2835, 1325, 1180, 1075, 1025, 985, 950, 770 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.95 (dd, J = 2.5, 4.2 Hz, 1 H), 5.85 (d, J = 9.6 Hz, 1 H), 5.76 (dd, J = 1.4, 9.5 Hz, 1 H), 5.40 (s, 1 H), 5.18 (d, J = 1.1 Hz, 1 H), 4.54 (dd, J = 3.1, 18.0 Hz, 1 H), 4.45 (dd, J = 2.6, 18.0 Hz, 1 H), 4.12–3.87 (m, 4 H), 2.48 (dd, J = 1.5, 13.3 Hz, 1 H), 2.39 (s, 1 H), 2.32 (d, J = 13.3 Hz, 1 H); chemical ionization mass spectrum, m/e 283.0990, M + H calcd for $C_{17}H_{15}O_4$ 283.0971. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 71.87; H, 4.77.

***N*-(Methyldithio)phthalimide (73).** Preparation of this reagent was based on the general procedure of Sullivan and Boustany.[29b] A suspension of phthalimide (7.36 g, 0.050 mol) and Et_3N (6.97 mL, 0.050 mol) in 120 mL of CH_2Cl_2 was added over 40 min to a vigorously stirred solution of SCl_2 (5.15 g, 0.050 mol) in 25 mL of CH_2Cl_2 at 0 °C. Methanethiol (2.78 mL, 0.050 mol, condensed at −78 °C) was added to Et_3N (6.97 mL, 0.050 mol) in 10 mL of CH_2Cl_2 at 0 °C, and this solution was added over 12 min to the above reaction mixture at 0 °C. The resulting mixture was stirred for 8 h at 0 °C and for 40 min at room temperature, then washed successively with H_2O (40 mL), 5% Na_2CO_3 solution (20 mL), and H_2O (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The derived solid was extracted with hot benzene (80 mL) and filtered, washing with benzene (remaining solid was discarded). The filtrate was then concentrated and the residue dissolved in a minimal amount of hot ethanol. After this solution had been cooled to −23 °C, the slightly yellow precipitate was collected by filtration and washed successively with ethanol, water, and ethanol. This procedure provided 3.05 g of crude product, which could be conveniently purified by flash column chromatography (hexanes/Et_2O/CH_2Cl_2, 60:35:5) to deliver disulfide **73** (2.10 g, 19%) as a colorless solid. The reagent was so employed in subsequent transformations; a small portion was crystallized from CH_2Cl_2/ethanol to obtain needles: mp 157–9 °C; IR ($CHCl_3$) 3020, 1785, 1740, 1705, 1340, 1275, 1055, 870 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.95 (dd, J = 3.1, 5.5 Hz, 2 H), 7.80 (dd, J = 3.0, 5.5 Hz, 2 H), 2.77 (s, 3 H); chemical ionization mass spectrum, m/e 226.0015, M + H calcd for $C_9H_8NO_2S_2$ 225.9997. Anal. Calcd for $C_9H_7NO_2S_2$: C, 47.98; H, 3.13; N, 6.22; S, 28.46. Found: C, 47.96; H, 2.96; N, 6.38; S, 28.58.

13-((*E*)-2-Mercaptoethylidene)spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolane]-1,8-diol (72). Diisobutylaluminum hydride (1.00 mL, 1.0 M in cyclohexane, 1.0 mmol) was added to a −78 °C solution of thioacetate **70** (25 mg, 0.070 mmol) in 10 mL of CH_2Cl_2. The reaction was stirred for 30 min at −78 °C and then quenched with EtOAc (0.5 mL) and saturated sodium potassium tartrate solution (5 mL). EtOAc (5 mL) was added, and the mixture was stirred vigorously for 20 min at 0 °C. Extraction with EtOAc, drying (Na_2SO_4), and concentration gave the thiol as an unstable, slightly yellow glass. This compound was usually not purified but used directly in the next reaction.

Spectroscopically pure **72** could be obtained by flash column chromatography (acetone/hexanes, 2:3): IR (CH_2Cl_2) 3560, 3610–3180, 3045, 2970, 2880, 1330, 1150, 1110, 1070, 1050, 1015, 950 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.17 (app t, J = 8.2 Hz, 1 H), 5.89 (d, J = 9.5 Hz, 1 H), 5.82 (d, J = 1.4, 9.5 Hz, 1 H), 5.82 (s, 1 H), 5.36 (d, J = 7.8 Hz, 1 H), 4.06–3.89 (m, 4 H), 3.62–3.50 (m, 1 H), 3.46–3.35 (m, 1 H), 2.73 (d, J = 8.0 Hz, 1 H), 2.41 (ABq, J = 13.7 Hz, $\Delta\nu$ = 92.4 Hz, 2 H), 2.39 (s, 1 H), 1.67 (dd, J = 6.7, 7.3 Hz, 1 H); chemical ionization mass spectrum, m/e 317.0857, M + H calcd for $C_{17}H_{17}O_4S$ 317.0848.

13-[(*E*)-2-(Methyltrithio)ethylidene]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolane]-1,8-diol (75). Crude thiol **72** from the preceding reaction was dissolved in 3 mL of CH_2Cl_2 containing 0.2 mL of THF. *N*-(Methyldithio)phthalimide (68 mg, 0.30 mmol) was added, and the resulting solution was allowed to stand at −20 °C for 10 min. The reaction was loaded directly onto a column for flash chromatography, eluting with hexanes/Et_2O/CH_2Cl_2 (4:3:3) to afford trisulfide **75** (23 mg, 84%) as a colorless glass: IR ($CHCl_3$) 3610–3160, 3580, 3010, 1330, 1150, 1075, 1050, 1020, 950 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.26 (app t, J = 7.9 Hz, 1 H), 5.90 (d, J = 9.5 Hz, 1 H), 5.82 (dd, J = 1.3, 9.4 Hz, 1 H), 5.82 (s, 1 H), 5.37 (d, J = 7.8 Hz, 1 H), 4.07–3.82 (m, 6 H), 2.64 (d, J = 7.9 Hz, 1 H), 2.64–2.57 (m, 1 H), 2.57 (s, 3 H), 2.44 (s, 1 H), 2.27 (d, J = 13.6 Hz, 1 H); FAB mass spectrum, m/e 395.0442, M + H calcd for $C_{18}H_{19}O_4S_3$ 395.0446.

13-[(*E*)-2-[(Phenylmethyl)trithio]ethylidene]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2'-[1,3]dioxolane]-1,8-diol (76). Thioacetate **70** (15 mg, 0.042 mmol) was converted to thiol **72** as described above. The crude thiol was dissolved in 3 mL of CH_2Cl_2 containing 0.20 mL of THF and treated with *N*-(Benzyldithio)phthalimide **74**[29a] (80 mg, 0.27 mmol). The resulting solution was allowed to stand for 20 h at −20 °C. Flash column chromatography of the reaction mixture (hexanes/Et_2O/CH_2Cl_2, 4:3:3) afforded benzyl trisulfide **76** (12 mg, 61%) as a colorless glass: IR ($CHCl_3$) 3610–3150, 3580, 3010, 1335, 1150, 1075, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34–7.28 (m, 5 H), 6.24 (app t, J = 7.8 Hz, 1 H), 5.89 (d, J = 9.5 Hz, 1 H), 5.81 (dd, J = 1.4, 9.5 Hz, 1 H), 5.80 (s, 1 H), 5.35 (d, J = 7.8 Hz, 1 H), 4.11 (app s, 2 H), 4.09–3.75 (m, 6 H), 2.62–2.56 (m, 2 H), 2.39 (s, 1 H), 2.26 (d, J = 13.4 Hz, 1 H); FAB mass spectrum, m/e 471.0779, M + H calcd for $C_{24}H_{23}O_4S_3$ 471.0760.

1,8-Dihydroxy-13-[(*E*)-2-(methyltrithio)ethylidene]bicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-11-one (9). Camphorsulfonic acid (25 mg, 0.11 mmol) was added to a solution of ketal **75** (23 mg, 0.058 mmol) in 3 mL of THF containing 90 μL of water. The solution was stirred for 1.75 h at ambient temperature and was then diluted with 3 mL of hexanes and filtered through 1 mL of SiO_2, washing with EtOAc/hexanes (1:1). Concentration and flash column chromatography (EtOAc/hexanes, 2:3) afforded enone **9** (21 mg, 100%) as a colorless glass: IR ($CHCl_3$) 3610–3150, 3580, 3020, 1665, 1125, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.47–6.40 (m, 1 H), 6.12 (s, 1 H), 5.92 (d, J = 9.5 Hz, 1 H), 5.86 (dd, J = 1.4, 9.5 Hz, 1 H), 5.52 (d, J = 7.9 Hz, 1 H), 3.95 ($^1/_2$ ABX, J_{AB} = 13.6, J_{AX} = 8.8 Hz, 1 H), 3.85 ($^1/_2$ ABX, J_{BA} = 13.6, J_{BX} = 7.5 Hz, 1 H), 3.10 (dd, J = 1.0, 17.0 Hz, 1 H), 2.74 (d, J = 16.9 Hz, 1 H), 2.68 (s, 1 H), 2.66 (d, J = 8.0 Hz, 1 H), 2.55 (s, 3 H); FAB mass spectrum, m/e 351.0172, M + H calcd for $C_{16}H_{15}O_3S_3$ 351.0184.

1,8-Dihydroxy-13-[(*E*)-2-[(phenylmethyl)trithio]ethylidene]bicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-11-one (77). Camphorsulfonic acid (25 mg, 0.11 mmol) was added to a solution of ketal **76** (26.5 mg, 0.056 mmol) in 3 mL of THF containing 90 μL of water. The solution was stirred for 1.5 h at ambient temperature, then diluted with 3 mL of hexanes, and filtered through 1 mL of SiO_2, washing with EtOAc/hexanes (1:1). Concentration and flash column chromatography (EtOAc/hexanes, 2:3) provided enone **77** (24 mg, 100%) as a colorless glass. Crystallization from CH_2Cl_2 gave slightly yellow prisms: mp >130 °C dec; IR ($CHCl_3$) 3610–3150, 3570, 3010, 1665, 1125, 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5 H), 6.44–6.37 (m, 1 H), 6.09 (s, 1 H), 5.91 (d, J = 9.6 Hz, 1 H), 5.85 (dd, J = 1.4, 9.5 Hz, 1 H), 5.49 (d, J = 8.0 Hz, 1 H), 4.08 (app s, 2 H), 3.89 ($^1/_2$ ABX, J_{AB} = 13.5, J_{AX} = 8.8 Hz, 1 H), 3.79 ($^1/_2$ ABX, J_{BA} = 13.5, J_{BX} = 7.5 Hz, 1 H), 3.08 (dd, J = 1.0, 17.1 Hz, 1 H), 2.71 (d, J = 17.1 Hz, 1 H), 2.62 (s, 1 H), 2.58 (d, J = 8.1 Hz, 1 H); FAB mass spectrum, m/e 427.0478, M + H calcd for $C_{22}H_{19}O_3S_3$ 427.0556.

Methyl 2-Bromo-3,5-dimethoxybenzoate (86). An acetonitrile solution (700 mL) of **30** (102 g, 0.52 mol) was treated with *N*-bromosuccinimide (111 g, 0.62 mol) in one portion at 0 °C, and the reaction mixture was stirred overnight at room temperature. Saturated Na_2SO_3 solution (300 mL) was added, and most of the acetonitrile was removed under vacuum. The products were extracted with ether (4 × 500 mL), and the combined extracts were dried over $MgSO_4$. After most of the solvent was removed, a precipitate was filtered off and the filtrate was concentrated under vacuum. The residue was distilled (144–49 °C (1 mm Hg)) to give 101 g (71%) of **86** as a slightly yellow oil, which slowly solidified on standing: mp 57–59 °C; IR ($CDCl_3$) 2954, 1732, 1587, 1453, 1341, 1212, 1164, 1057 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.81 (d, 1 H, J = 2.7 Hz, CH arom), 6.59 (d, 1 H, J = 2.7 Hz, CH arom), 3.94 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3); electron impact mass spectrum, m/e 275.9814, calcd for $C_{10}H_{11}BrO_4$ 275.9820. Anal. Calcd for $C_{10}H_{11}BrO_4$: C, 43.64; H, 4.03; Br, 29.06. Found: C, 43.38; H, 4.00; Br, 29.35.

Methyl 2-Bromo-6-formyl-3,5-dimethoxybenzoate (87). To a CH_2Cl_2 solution (500 mL) of **86** (54.8 g, 0.20 mol) at −25 °C was added a solution of $TiCl_4$ (44 mL, 0.40 mol) in CH_2Cl_2 (200 mL) over 20 min. After the mixture was stirred at this temperature for 10 min, Cl_2CHOMe (25 mL, 0.28 mol) was slowly added over 25 min at −20 °C and the mixture was stirred at this temperature for another 30 min. Aqueous HCl (1 N, 150 mL) was slowly added to the mixture at −20 °C, followed by H_2O (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL), and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude solid was crystallized from EtOAc/THF to give 47.8 g of **87**. Concentration of the mother liquor and chromatography (hexanes/ethyl acetate, 3:1) gave an additional 3.8 g of **87** as a colorless solid: total yield of 51.6 g, 85%; mp 187–188 °C; IR ($CDCl_3$) 2954, 1740, 1682, 1598, 1343, 1215, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.23 (s, 1 H, CHO), 6.51 (s, 1 H, CH arom), 4.01 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3); EIMS, m/e 302 (M^+); electron impact mass spectrum, m/e 301.9786, calcd for $C_{11}H_{11}BrO_5$ 301.9789.

Methyl 2-Bromo-6-formyl-5-hydroxy-3-methoxybenzoate (88). To a CH_2Cl_2 suspension (260 mL) of **87** (52.3 g, 0.17 mol) was slowly added a 1.0 M CH_2Cl_2 solution of BCl_3 (260 mL, 0.26 mol) over 30 min at 0 °C. The mixture was stirred for 10 h at room temperature. Aqueous HCl (1 N, 250 mL) was added very slowly, followed by H_2O (500 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was crystallized from ethyl acetate to give 37.4 g of **88** as colorless needles. The mother liquors were concentrated and purified by flash SiO_2 chromatography (methylene chloride) to give 9.1 g of **88** (total yield of 46.5 g, 93%). Crystallization gave colorless needles: mp 128–130 °C (ethyl acetate); IR (film) 3085, 2960, 1712, 1633, 1204, 1026, 834 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.09 (s, 1 H, CHO), 9.66 (s, 1 H, OH), 6.52 (s, 1 H, CH arom), 4.02 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3); EIMS, m/e 288 (M^+); electron impact mass spectrum, m/e 287.9622, calcd for $C_{10}H_9BrO_5$ 287.9633. Anal. Calcd for $C_{10}H_9BrO_5$: C, 41.53; H, 3.14; Br, 27.65. Found: C, 41.66; H, 3.10; Br, 27.35.

7-Bromo-8-(hydroxymethyl)-6-methoxy-1-oxaspiro[2.5]octa-5,7-dien-4-one (90). To a THF solution (240 mL) of **88** (10.43 g, 36.0 mmol) at −10 °C was added NaH (97%, 912 mg, 37.0 mmol), and the mixture was stirred at −5 °C to +0 °C for 15 min to give a yellow clear solution. Diisobutylaluminum hydride (120 mL, 1.5 M solution in toluene, 180 mmol) was added over 10 min to the above mixture at −5 °C to +0 °C, and the reaction was stirred at this temperature for 1 h. The solution was cooled to −20 °C and carefully quenched with MeOH (6 mL), followed by aqueous HCl (1 N, 50 mL) and THF/H_2O (4:1, 250 mL). $NaIO_4$ (20.6 g, 96.3 mmol) was added to the above mixture at room temperature, followed by the addition of aqueous HCl (1 N, 50 mL). After 30 min, additional aqueous HCl (1 N, 50 mL) was added and the reaction was stirred for 3 h. The mixture was filtered through Celite, washing successively with THF/H_2O (4:1, 200 mL) and ethyl acetate, (500 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (300 mL), followed by brine (150 mL), and dried over $MgSO_4$. Solvents were evaporated at room temperature, and a yellow solid was obtained. This was used in the next reaction without further purification. A sample of crude **90** was purified by flash SiO_2 chromatography (hexanes/ethyl acetate, 1:1) to give a colorless solid: mp 47–49 °C (ethyl acetate); IR ($CDCl_3$) 3593, 3376, 2943, 1656, 1561, 1365, 1250, 898, 742 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.72 (s, 1 H, =CH—), 4.29 (br s, 2 H, CH_2O), 3.90 (s, 3 H, OCH_3), 3.82 (s, 1 H, OH), 3.37 (ABq, 2 H, J = 7.6 Hz, $\Delta\nu$ = 47.6 Hz, CH_2 spiroepoxide); EIMS, m/e 260 (M^+); electron impact mass spectrum, m/e 259.9686, calcd for $C_9H_9BrO_4$ 259.9683.

5-Bromo-6-methoxy-8-oxo-1-oxaspiro[2.5]octa-4,6-diene-4-carboxaldehyde (91). Dess–Martin periodinane[15] (18.3 g, 43.2 mmol) was added under nitrogen to a solution of the above **90** in dry CH_2Cl_2 at 0 °C. The reaction was stirred for 1 h at 0 °C and for 1 h at room temperature (room temperature sometimes unnecessary). The mixture was successively treated with K_2CO_3/H_2O (40 g, ~4 mL, respectively), filtered through Celite (3×), and finally filtered through a plug of SiO_2, washing with ethyl acetate. The resulting clear yellow solution was concentrated and purified by flash SiO_2 chromatography (hexanes/ethyl acetate/methylene chloride, 5:3:2) to give 3.70 g of **91** (40% overall yield from **88**) as a yellow solid: mp 134–136 °C (CH_2Cl_2); IR ($CDCl_3$) 1692,

1654, 1603, 1327, 1251, 1226 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.96 (s, 1 H, CHO), 5.89 (s, 1 H, =CH), 3.95 (s, 3 H, OCH_3), 3.68 (ABq, 2 H, J = 8.7 Hz, $\Delta\nu$ = 192.5 Hz, spiroepoxide CH_2); EIMS, m/e 258 (M^+); electron impact mass spectrum, m/e 257.9515, calcd for $C_9H_7BrO_4$ 257.9527. Anal. Calcd for $C_9H_7BrO_4$: C, 41.71; H, 2.72; Br, 30.86. Found: C, 41.53; H, 2.77; Br, 30.87.

5-Bromo-8-(3-hexene-1,5-diynyl)-8-hydroxy-6-methoxy-1-oxaspiro-[2.5]octa-4,6-diene-4-carboxaldehyde (92). Generation of Lithiated Hexenediyne. A solution of 1,6-bis(trimethylsilyl)hexenediyne (6.00 g, 27.2 mmol) in THF/H_2O (3:1; 100 mL) at 20 °C was treated with $LiOH:H_2O$ (5.90 g, 140 mmol). The reaction was stirred for 2 h at 20 °C, diluted with pentane (200 mL), washed with brine (2 × 100 mL), dried over $MgSO_4$, and filtered through $CaSO_4$ under nitrogen. The filtrate was concentrated to approximately 60 mL under a stream of nitrogen. 1,10-Phenanthroline (10–15 mg) was added, and the solution was cooled to 0 °C. *n*-Butyllithium (2.5 M solution in hexane) was added until indicator change occurred and then another 14.8 mL (37.0 mmol) was added, giving a brown-purple solution. The mixture was cooled to −78 °C.

In situ Protection of the Aldehyde Carbonyl. *n*-Butyllithium (3.60 mL, 2.5 M hexane solution, 9.0 mmol) was added under nitrogen to a solution of *N*-methylaniline (1.00 mL, 9.2 mmol) in dry THF (20 mL) at 0 °C. This mixture was cooled to −78 °C and added via cannula to a slurry of aldehyde **91** (2.06 g, 7.95 mmol) in dry THF (50 mL) at −78 °C. The cold bath was removed, and the reaction was allowed to warm until the aldehyde dissolved completely (yellow suspension → orange solution).

Addition of Lithiated Hexenediyne to the Protected Substrate. The above reaction mixture was recooled to −78 °C and treated with the solution of lithiated hexenediyne via cannula. The mixture was stirred for 1 h at −78 °C and for 15 min at −43 °C, then quenched with saturated NH_4Cl solution (30 mL), and diluted with ether (600 mL). The organic layer was washed successively with aqueous HCl (1 N, 100 mL), aqueous HCl (0.1 N, 100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL) and then dried over $MgSO_4$. Solvents were evaporated, and the residue was subjected to flash SiO_2 chromatography (hexanes/ethyl acetate, 4:1) to give **92** as an unstable brown oil, which was used without further purification in the next reaction. Thus, a solution of this material in dry CH_2Cl_2 (100 mL) at 0 °C was treated under nitrogen with Et_3N (6.00 mL, 43.0 mmol) and trimethylsilyl trifluoroacetate (3.60 mL, 20.8 mmol), stirring for 30 min at 0 °C and then for 1.5 h at room temperature. The reaction was quenched by the addition of saturated NH_4Cl solution (30 mL) and diluted with ether (600 mL). The organic layer was washed with aqueous HCl (0.1 N, 30 mL), saturated $NaHCO_3$ solution (30 mL), and brine (30 mL), drying over $MgSO_4$. The solvents were evaporated and the residue was purified by flash SiO_2 chromatography (hexanes/ethyl acetate, 10:1) to afford 1.95 g of **93** (60% from **91**) as a yellow oil: IR ($CHCl_3$) 3302, 2962, 1681, 1267, 1250, 1046 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.04 (s, 1 H, CHO), 5.96–5.87 (m, 2 H, CH=CH), 5.37 (s, 1 H, CH enol ether), 3.75 (br s, 3 H, OCH_3), 3.72 (ABq, 2 H, J = 5.4 Hz, $\Delta\nu$ = 116.5 Hz, spiroepoxide CH_2), 3.37 (d, 1 H, J = 1.8 Hz, =CH), 0.18 (br s, 9 H, Me_3Si–); EIMS, m/e 406 (M^+); electron impact mass spectrum, m/e 408.0234, calcd for $C_{18}H_{19}Si^{81}BrO_4$ 408.0216.

12-Bromo-11-methoxy-9-[(trimethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-5,10,12-triene-3,7-diyne-13,2′-oxiran]-2-ol (94). Potassium hexamethyldisilazide (7.20 mL, 1.4 M solution in THF, 10 mmol) was added under nitrogen to a solution of 3-ethyl-3-pentanol (1.80 mL, 12.8 mmol) in dry toluene (200 mL) at 0 °C. After 10 min, the mixture was cooled to −78 °C. A solution of **93** (1.95 g, 4.79 mmol) in dry toluene (30 mL) was added to the above mixture via syringe, affording a yellow-orange solution. After 20 min at −78 °C, the reaction was quenched by the addition of pH 7 buffer solution (50 mL), followed by ethyl acetate (300 mL). The aqueous layer was extracted with ethyl acetate (4 × 100 mL); the combined extracts were dried over $MgSO_4$. The solvents were evaporated, and the residue was purified by flash SiO_2 chromatography (hexanes/ethyl acetate, 8:1) to give 1.17 g of **94** (60%) as a colorless foam: IR (film) 3508, 2956, 1621, 1237, 1122, 846, 738 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.10 (d, 1 H, J = 9.5 Hz, CH=CH), 5.99 (dd, 1 H, J = 9.5, 1.7 Hz, CH=CH), 5.83 (dd, 1 H, J = 11.8, 1.7 Hz, CH proparg), 4.84 (s, 1 H, =CH enol ether), 3.75 (d, 1 H, J = 11.8 Hz, OH), 3.67 (s, 3 H, OCH_3), 3.15 (ABq, 2 H, J = 5.8, $\Delta\nu$ = 148.2 Hz, spiroepoxide CH_2), 0.26 (br s, 9 H, $Si(CH_3)_3$); EIMS, m/e 406 (M^+); chemical ionization mass spectrum m/e 407.0307, M + H calcd for $C_{18}H_{20}BrSiO_4$ 407.0314. Anal. Calcd for $C_{18}H_{19}BrSiO_4$: C, 53.20; H, 4.72. Found: C, 52.84; H, 4.55.

10-Bromo-spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]-dioxolane-13,2″-oxirane]-1,8-diol (96). A solution of bicycle **94** (2.24 g, 5.50 mmol) in 38 mL of ethylene glycol and 10.0 mL of dry THF was treated under nitrogen with camphorsulfonic acid (48 mg, 0.21 mmol). After it was stirred at 50 °C for 45 min, the mixture was cooled and quenched with pyridine (1 mL). The solution was diluted with ethyl acetate (800 mL) and washed with H_2O (2 × 75 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of approximately 150 mL. The latter was filtered through a plug of SiO_2, washing with hexanes/ethyl acetate (3:2). The filtrate was concentrated to give 1.78 g of ketal **96** (89%) as a colorless amorphous solid: mp >180 °C dec; IR (film) 3379, 2897, 1169, 1093, 1028, 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.97–5.87 (m, 2 H, CH=CH), 5.76 (dd, 1 H, J = 11.8, 1.3 Hz, CH proparg), 4.33–4.01 (m, 4 H, ethylene ketal), 3.62 (d, 1 H, J = 11.8 Hz, OH proparg), 3.33 (ABq, 2 H, J = 5.1 Hz, $\Delta\nu$ = 80.8 Hz, spiroepoxide CH_2), 2.48 (ABq, 2 H, J = 13.6 Hz, $\Delta\nu$ = 83.6 Hz, CH_2 six-membered ring), 2.47 (s, 1 H, OH); chemical ionization mass spectrum, m/e 365.0040, M + H calcd for $C_{16}H_{14}BrO_5$ 365.0024. Anal. Calcd for $C_{16}H_{13}BrO_5$: C, 52.63; H, 3.59; Br, 21.88. Found: C, 52.55; H, 3.43; Br, 21.58.

13-[(Acetyloxy)methyl]-10-bromo-spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolane]-1,8,13-triol (97). A solution of ketal **96** (1.50 g, 4.11 mmol) in anhydrous DMSO (40 mL) was treated under nitrogen with KOAc (1.30 g, 13.1 mmol) and AcOH (0.85 mL, 15 mmol). After the reaction was stirred at 55 °C for 3 h, the mixture was cooled and poured into saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with ethyl acetate (2 × 500 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of approximately 150 mL. The latter was filtered through a plug of SiO_2, washing with hexanes/ethyl acetate (1:1), and the solvents were evaporated in vacuo to afford 1.54 g (88%) of acetate **97** as a colorless glass: IR ($CDCl_3$) 3490, 2961, 2897, 1735, 1236, 1161, 1039 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.97–5.92 (m, 2 H, CH=CH), 5.83 (dd, 1 H, J = 9.6, 1.6 Hz, CH proparg); 4.60 (s, 1 H, OH); 4.46 (ABq, 2 H, J = 12.0 Hz, $\Delta\nu$ = 26.3 Hz, CH_2OAc), 4.30 (d, 1 H, J = 9.6 Hz, OH proparg), 4.27–3.96 (m, 4 H, ethylene ketal), 3.47 (s, 1 H, OH), 2.53 (ABq, 2 H, J = 14.1 Hz, $\Delta\nu$ = 24.9 Hz, CH_2 six-membered ring), 2.12 (s, 3 H, OCH_3); EIMS, m/e 426 (M + H); chemical ionization mass spectrum, m/e 425.0215, M + H calcd for $C_{18}H_{18}BrO_7$ 425.0235.

10-Bromo-1,8-dihydroxy-spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-13-one (99). A saturated solution of NH_3 in methanol (40 mL) was added to **97** (1.54 g, 3.60 mmol) at room temperature. After the reaction mixture was stirred for 1 h, the volatiles were removed in vacuo and the residue was dissolved in acetone/pH 7 phosphate buffer (1:1, 40 mL) at 0 °C. $NaIO_4$ (12.0 mL, 0.30 M solution in H_2O, 3.6 mmol) was added, and the reaction was stirred at 0 °C for 30 min. Ethyl acetate (50 mL) was added, and the mixture was filtered through a plug of SiO_2, washing with ethyl acetate. The aqueous layer was extracted with ethyl acetate (4 × 25 mL), and the combined organics layers were dried over $MgSO_4$, filtered, and concentrated to give 1.00 g of enone **99** (80%) as a yellow amorphous solid: mp >130 °C dec; IR (film) 3378,2899, 1702, 1168, 1114, 1099 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.96–5.84 (m, 3 H, CH=CH and CH proparg), 4.56 (d, 1 H, J = 11.4 Hz, OH proparg), 4.41–4.08 (m, 4 H, ethylene ketal), 3.77 (d, 1 H, J = 8.0 Hz, OH), 2.62 (ABq, 2 H, J = 14.0 Hz, $\Delta\nu$ = 94.0 Hz, CH_2 six-membered ring); EIMS, m/z 352 (M^+); chemical ionization mass spectrum, m/e 350.9889, M + H calcd for $C_{15}H_{12}BrO_5$ 350.9868. Anal. Calcd for $C_{15}H_{11}BrO_5$: C, 51.29; H, 3.16; Br, 22.76. Found: C, 51.54; H, 3.44; Br, 22.79.

10-Azido-1,8-dihydroxy-spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-13-one (100). A solution of enone **99** (1.16 g, 3.30 mmol) in MeOH (115 mL) and H_2O (4 mL) was treated with NaN_3 (539 mg, 8.28 mmol). After it was stirred at 55 °C (bath temperature) for 4 h, the mixture was cooled and diluted with ethyl acetate (50 mL). The solution was filtered through a plug of SiO_2, washing with ethyl acetate. The solvents were evaporated, and the residue was subjected to SiO_2 chromatography (hexanes/acetone, 1:1) to afford 0.84 g (82%) of **100** as a yellow solid: mp >118 °C dec; IR ($CDCl_3$) 3508, 2908, 2126 (int), 1678, 1610, 1343, 1314, 1111, 1031 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.94–5.85 (m, 2 H, CH=CH), 5.73 (dd, 1 H, J = 11.3, 1.0 Hz, CH proparg), 4.60 (d, 1 H, J = 11.3 Hz, OH proparg), 4.36–4.15 (m, 4 H, ethylene ketal), 3.89 (br s, 1 H, OH), 2.51 (ABq, 2 H, J = 13.8 Hz, $\Delta\nu$ = 129.1 Hz, CH_2 six-membered ring); chemical ionization mass spectrum, m/e 314.0762, M + H calcd for $C_{15}H_{11}N_3O_5$ 314.0778.

(Diethoxyphosphinyl)acetic Acid, 12-Azido-9-hydroxy-13-oxospiro-[bicyclo[7.3.1]trideca-5,12-diene-3,7-diyne-11,2′-[1,3]dioxolan]-2-yl Ester (102). A solution of (diethoxyphosphinyl)acetic acid[25] (2.50 g, 12.8 mmol) in 47 mL of dry benzene was treated under nitrogen at room temperature with oxalyl chloride (3.40 mL, 38.4 mmol), followed by DMF (0.21 mL). After the mixture was stirred for 1 h, the volatiles were removed in vacuo. The residue was dissolved in dry THF (30 mL) to give a 0.43 M solution of acid chloride. Pyridine (0.79 mL, 9.8 mmol) was added under nitrogen to a solution of alcohol **100** (1.02 g, 3.26 mmol)

in dry THF (80 mL) at 0 °C. A portion of the above acid chloride solution (11.4 mL, 4.89 mmol) was added, and the reaction mixture was stirred for 15 min at 0 °C. Ethyl acetate was added, and the solution was filtered through a plug of SiO_2, washing with ethyl acetate. Solvents were evaporated, and the residue was purified by flash SiO_2 chromatography (ethyl acetate) to give 1.02 g (64%) of **102** as a colorless solid: mp 109–11 °C (ethyl acetate); IR (film) 3270, 2987, 2134, 1746, 1700, 1609, 1339, 1254, 1109, 1024 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 1.5 Hz, CH proparg), 5.97 (d, 1 H, J = 9.5 Hz, CH=CH), 5.86 (dd, 1 H, J = 9.5, 1.5 Hz, CH=CH), 4.36–4.08 (m, 8 H, ethylene ketal, $(OCH_2Me)_2$), 3.11 (ABq, 2 H, J = 9.3 Hz, $\Delta\nu$ = 21.1 Hz, $CH_2P(O)$–), 2.48 (ABq, 2 H, J = 13.8 Hz, $\Delta\nu$ = 141.2 Hz, CH_2 six-membered ring), 1.35 (t, 6 H, J = 7.0 Hz, $(OEt)_2$); FAB mass spectrum (NOBA) m/e 492.1173, M + H calcd for $C_{21}H_{23}PN_3O_9$ 492.1165.

8′-Azido-5′,6′-dihydro-5′-hydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-3′-one (103). A solution of **102** (0.83 g, 1.7 mmol) in dry THF (85 mL) was cooled to 0 °C under nitrogen and treated with LiBr (473 mg, 5.44 mmol), followed by Et_3N (2.37 mL, 17.0 mmol). After it was stirred at 0 °C for 15 min, the reaction mixture was allowed to stir at room temperature for 4 h. The solution was then filtered through a plug of SiO_2, washing with ethyl acetate. The filtrate was concentrated, and the residue was chromatographed (hexanes/acetone, 1:1) to give 527 mg (92%) of **103** as a yellow solid: mp > 113 °C dec; IR (film) 3358, 2986, 2126, 1713, 1645, 1340, 1022 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.13 (s, 1 H, =CH enone), 6.09 (d, 1 H, J = 1.5 Hz, CH proparg), 5.93 (d, 1 H, J = 9.5 Hz, CH=CH), 5.85 (dd, 1 H, J = 9.5, 1.5 Hz, CH=CH), 4.35–4.15 (m, 4 H, ethylene ketal), 2.78 (br s, 1 H, OH), 2.44 (ABq, 2 H, J = 13.3 Hz, $\Delta\nu$ = 77.36 Hz, CH_2 six-membered ring): FAB mass spectrum (NOBA) m/e 338.0783, M + H calcd for $C_{17}H_{12}N_3O_5$ 338.0777.

8′-Amino-5′,6′-dihydro-5′-hydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-3′-one (104). Hydrogen sulfide was bubbled into a stirred solution of lactone **103** (0.68 g, 2.0 mmol) in MeOH (90 mL) containing piperidine (0.3 mL) over 20 min while the temperature was maintained at 0 °C. Ethyl acetate (50 mL) and H_2O (50 mL) were then added carefully, and the mixture was extracted with ethyl acetate (5 × 20 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was flash chromatographed (hexanes/acetone, 1:1) to give 534 mg (85%) of **104** as a yellow solid: mp >70 °C dec; IR (film) 3360 (br), 1642, 1609, 1409, 1177, 1011 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 6.14 (d, 1 H, J = 1.5 Hz, CH proparg), 5.97 (d, 1 H, J = 9.5 Hz, CH=CH), 5.83 (dd, 1 H, J = 9.5, 1.5 Hz, CH=CH), 5.76 (s, 1 H, =CH enone), 5.63 (br s, 1 H, NH), 5.49 (br s, 1 H, NH), 4.16–4.02 (m, 4 H, ethylene ketal), 2.80 (br s, 1 H, OH), 2.33 (ABq, 2 H, J = 13.4 Hz, $\Delta\nu$ = 88.8 Hz, CH_2 six-membered ring); EIMS, m/e 311 (M^+); chemical ionization mass spectrum, m/e 312.0883, M + H calcd for $C_{17}H_{14}NO_5$ 312.0872.

Methyl 5′-[(Methoxycarbonyl)oxy]-3′-oxospiro[1,3-dioxolane-2,7′-(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-8′-yl Carbamate (106). Bis(trichloromethyl) carbonate (1.01 g, 3.4 mmol) was added under nitrogen to a solution of vinyl amine **104** (365 mg, 1.17 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C followed by pyridine (1.40 mL, 17.4 mmol). After it was stirred for 40 min at room temperature, the reaction mixture was cooled to 0 °C. Pyridine (1.40 mL, 17.4 mmol) was added, followed by MeOH (10 mL). After 30 min at 0 °C, the reaction was quenched by the addition of pH 7 phosphate buffer (50 mL), followed by ethyl acetate (200 mL). The aqueous layers were extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash SiO_2 chromatography (hexanes/ethyl acetate, 2:3) to give 413 mg (82%) of **106** as a yellow solid: mp >105 °C dec; IR ($CDCl_3$) 3404, 2977, 2872, 1733 (br), 1275 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 (s, 1 H, =CH enelactone), 6.18 (d, 1 H, J = 1.5 Hz, CH proparg), 6.04 (br s, 1 H, NH), 5.96 (d, 1 H, J = 9.6 Hz, CH=CH), 5.89 (dd, 1 H, J = 9.6, 1.5 Hz, CH=CH), 4.23–4.14 (m, 1 H, ethylene ketal), 4.12–3.97 (m, 3 H, ethylene ketal), 3.87 (s, 3 H, $-OCH_3$ carbonate), 3.79 (s, 3 H, $-OCH_3$ carbamate), 2.75 (ABq, 2 H, J = 13.4 Hz, $\Delta\nu$ = 224.6 Hz, CH_2 six-membered ring); chemical ionization mass spectrum, m/e 428.0983, M + H calcd for $C_{21}H_{18}NO_9$ 428.0981. Anal. Calcd for $C_{21}H_{18}NO_9$: C, 59.00; H, 4.01; N, 3.28. Found: C, 58.60; H, 4.40; N, 2.86.

Methyl 3′,5′-Dihydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene-[1,5]diyno[1*N*-2]-benzopyran]-8′-yl Carbamate (107). Diisobutylaluminum hydride (4.08 mL, 1.5 M solution in toluene, 6.1 mmol) was added under nitrogen to a solution of **106** (433 mg, 1.01 mmol) in anhydrous CH_2Cl_2 (80 mL) at −78 °C. After 15 min, the reaction was quenched by the addition of MeOH (2 mL) at −78 °C. The cold bath was removed, and the reaction mixture was allowed to warm to room temperature. The solution was then diluted with ethyl acetate (50 mL). A saturated solution of potassium sodium tartrate (Rochelle's salt, 30 mL) was added, and the mixture was stirred until the two phases were clear (2 h). The aqueous layer was further extracted with ethyl acetate (3 × 50 mL), and combined organics were dried over $MgSO_4$. Purification of the crude product by SiO_2 flash chromatography (hexanes/ethyl acetate, 1:3) afforded 374 mg (99%) of lactol **107** as a colorless glass: IR (film) 3335, 1708, 1702, 1503, 1252, 1034 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 6.14 (d, 1 H), 5.65–5.27 (m, 4 H), 4.15–3.86 (m, 4 H, ethylene ketal), 3.64 (s, 3 H, OCH_3), 2.44 ($^1/_2$ ABX, 1 H, J_{AB} = 13.4, J_{AX} = 3.6 Hz, CH_2 six-membered ring), 2.12 ($^1/_2$ ABX, 1 H, J_{AB} = 13.4, J_{BX} = 5.4 Hz, CH_2 six-membered ring); FAB mass spectrum (NOBA/NaI) m/e 394.0934, M + Na calcd for $C_{19}H_{17}NO_7$ 394.0903.

Methyl 1,8-Dihydroxy-13-((*E*)-2-hydroxyethylidene)spiro[bicyclo-[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl Carbamate (108). $NaBH_4$ (64 mg, 1.7 mmol) was added to a solution of lactol **107** (39 mg, 0.10 mmol) in anhydrous MeOH (3.2 mL) and H_2O (4 drops) at 0 °C. After 1 h, the reaction was quenched by the dropwise addition of AcOH (1 mL) and H_2O (4 drops) at 0 °C. The mixture was stirred for 5 min and concentrated in vacuo. THF (1 mL), MeOH (1.8 mL), and H_2O (2 drops) were added to the residue, and it was allowed to stir for 5 min. The solvents were evaporated, THF (5 mL) followed by MeOH (5 drops) and H_2O (5 drops) was added to the residue, and the resulting solution was stirred for 5 min. The latter operation was repeated five times, adding Celite to make the solid more consistent. Finally, the mixture was filtered through a plug of SiO_2, washing with THF (5 × 2 mL). Solvents were evaporated, and the residue was subjected to SiO_2 flash chromatography (ethyl acetate → ethyl acetate/methanol, 95:5) to give 25.5 mg (65%) of triol **108** as a colorless glass: IR (film) 3313, 2924, 1704, 1503, 1242, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.72 (br s, 1 H, NH), 6.42 (dd, 1 H, J = 8.0, 7.0 Hz, vinyl CH), 5.84 (br s, 2 H, CH=CH), 5.61 (br s, 1 H, CH proparg), 4.74 (br s, 1 H, OH), 4.37–4.18 (m, 2 H, 1 H from allylic CH_2 and 1 H from ethylene ketal), 4.11–3.94 (m, 4 H, 1 H, from allylic CH_2 and 3 H from ethylene ketal), 3.80 (s, 3 H, OCH_3), 3.27 (br s, 1 H, OH), 2.72 (s, 1 H, OH), 2.46 (ABq, 2 H, J = 14.3 Hz, $\Delta\nu$ = 63.8 Hz, CH_2 six-membered ring); FAB mass spectrum (NOBA/NaI) m/e 396.1086, M + Na calcd for $C_{19}H_{19}NO_7$ 396.1060.

Methyl 13-[(*E*)-2-(Acetylthio)ethylidene]-1,8-dihydroxyspiro[bicyclo-[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl Carbamate (109). Diisopropyl azodicarboxylate (0.084 mL, 0.43 mmol) was added under nitrogen to a solution of tris(3-methoxyphenyl)phosphine (178 mg, 0.50 mmol) in dry THF (2 mL) at 0 °C. After it was stirred 30 min at 0 °C, the solution had turned yellow. Thiolacetic acid (0.032 mL, 0.44 mmol) was added to the above solution, followed by triol **108** (19.4 mg, 0.052 mmol) in dry THF (1.5 mL). After it was stirred 15 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL). The mixture was diluted with ethyl acetate (5 mL) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by SiO_2 flash chromatography (hexanes/ethyl acetate, 2:3) afforded 13.5 mg (60%) of thioacetate **109**: IR ($CDCl_3$) 3392, 2961, 2250, 1729, 1681, 1502, 1227 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.75 (br s, 1 H, NH), 6.21 (t, 1 H, J = 8.3 Hz, vinyl CH), 5.85 (d, 1 H, J = 9.7 Hz, CH=CH), 5.79 (d, 1 H, J = 9.7 Hz, CH=CH), 5.59 (d, 1 H, J = 1.5 Hz, CH proparg), 4.45 (br s, 1 H, OH), 4.19–3.94 (m, 6 H, CH_2S and ethylene ketal), 3.79 (s, 3 H, OCH_3), 2.44 (ABq, 2 H, J = 14.3 Hz, $\Delta\nu$ = 55.0 Hz, CH_2 six-membered ring), 2.48 (br s, 1 H, OH), 2.32 (s, 3 H, $C(O)CH_3$); FAB mass spectrum (NOBA/NaI) m/e 454.0951, M + Na calcd for $C_{21}H_{21}NO_7S$ 454.0937.

Methyl 1,8-Dihydroxy-13-[(*E*)-2-(methyltrithio)ethylidene]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl Carbamate (112). Diisobutylaluminum hydride (0.28 mL, 1.0 M sodium in cyclohexane, 0.28 mmol) was added under nitrogen to a solution of thioacetate **109** (12 mg, 0.028 mmol) in anhydrous CH_2Cl_2 (5 mL) at −78 °C. After 30 min, the reaction was quenched by the addition of MeOH (5 drops) at −78 °C. The cold bath was removed, and the reaction mixture was allowed to warm to room temperature. The solution was diluted with ethyl acetate (10 mL), and saturated aqueous potassium sodium tartrate (Rochelle's salt, 3 mL) was added. The mixture was stirred for 30 min until the two phases became clear. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). Combined organics were then dried over $MgSO_4$ and concentrated. *N*-(Methyldithio)phthalimide (30 mg, 0.13 mmol) was added to a solution of the above residue in dry CH_2Cl_2 (1.5 mL) and dry THF (3 drops) at room temperature. After it was stirred 30 min, the reaction mixture was subjected to SiO_2 flash chromatography (hexanes/acetone, 1:1) to afford 6 mg (46%) of trisulfide **112** as a colorless glass: IR ($CDCl_3$) 3396, 2923, 1736, 1502, 1235 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.81 (br s, 1 H, NH), 6.46 (dd, 1 H, J = 9.5, 6.1 Hz, vinyl CH), 5.84 (d, 1 H, J = 9.6 Hz, CH=CH), 5.80 (d, 1 H, J = 9.6 Hz, CH=CH), 5.57 (s, 1 H, CH proparg), 4.39 (dd, 1 H, J = 14.2, 9.5 Hz, CH_2S–), 4.12–3.81 (m, 5 H,

1 H from CH_2S– and 4 H from ethylene ketal), 3.80 (s, 3 H, carbamate OCH_3), 2.56 (s, 3 H, SCH_3), 2.48 (ABq, 2 H, J = 14.3 Hz, $\Delta\nu$ = 46.0 Hz, CH_2 six-membered ring); FAB mass spectrum (GLY) m/e 468.0606, M + H calcd for $C_{20}H_{22}NO_6S_3$, 468.0611.

Methyl 1,8-Dihydroxy-13-[(*E*)-2-(methyltrithio)ethylidene]-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-10-yl Carbamate (1). Camphorsulfonic acid (2 mg, 0.009 mmol) was added to a solution of trisulfide **112** (5 mg, 0.01 mmol) in THF (1 mL) and H_2O (3 drops) at room temperature. After it was stirred for 8 h, the reaction mixture was diluted with hexanes (1 mL) and subjected to SiO_2 flash chromatography (hexanes/ethyl acetate, 3:2) to give 3 mg (65%) of calicheamicinone (**1**) as a colorless glass: IR ($CDCl_3$) 3582, 3374, 2925, 1732, 1678, 1497, 1236 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 6.93 (br s, 1 H, NH), 6.48 (dd, 1 H, J = 9.3, 6.4 Hz, vinyl CH), 6.03 (br s, 1 H, CH proparg), 5.91 (d, 1 H, J = 9.3 Hz, CH=CH), 5.89 (d, 1 H, J = 9.3 Hz, CH=CH), 4.12 (dd, 1 H, J = 14.0, 9.3 Hz, CH_2S), 3.87 (dd, 1 H, J = 14.0, 6.4 Hz, CH_2S), 3.79 (s, 3 H, carbamate OCH_3), 3.21 (s, 1 H, OH), 3.03 (ABq, 2 H, J = 17.0 Hz, $\Delta\nu$ = 176.6 Hz, CH_2 six-membered ring), 2.64 (s, 1 H, OH), 2.55 (s, 3 H, SCH_3); FAB mass spectrum (NOBA) m/e 424.0359, M + H calcd for $C_{18}H_{18}NO_5S_3$ 424.0348.

4,9-Dihydro-4,9-dihydroxy-2*H*-4,9a-propanonaphtho[2,3-*b*]furan-11-one (114). Camphorsulfonic acid (4 mg, 0.02 mmol) was added to a solution of triol **68** (22 mg, 0.073 mmol) in 3.5 mL of THF containing water (80 μL) and 1,4-cyclohexadiene (0.20 mL, 2.1 mmol). The solution was stirred for 11.5 h at ambient temperature. Pyridine (30 μL) was added, and the reaction mixture was filtered through 1 mL of SiO_2, washing with acetone/hexanes (1:2). Concentration and flash column chromatography (acetone/hexanes, 1:2) gave **114** (10.9 mg, 58%) as a colorless solid. Crystallization from THF gave prisms: mp >215 °C dec; IR (KBr) 3620–2990, 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.62 (d, J = 7.9 Hz, 1 H), 7.45–7.29 (m, 3 H), 5.97 (s, 1 H), 4.97 (d, J = 12.6 Hz, 1 H), 4.90 (dd, J = 1.3, 12.4 Hz, 1 H), 4.62 (s, 1 H), 2.90 (s, 1 H), 2.88–2.63 (m, 4 H), 2.60 (s, 1 H); chemical ionization mass spectrum, m/e 259.0965, M + H calcd for $C_{15}H_{15}O_4$ 259.0971. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.51; H, 5.49.

Ethanethioic Acid, (*S*)-2-(1,8-Dihydroxy-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-13(*E*)-ylidene)ethyl Ester (115). Camphorsulfonic acid (2 mg, 0.009 mmol) was added to a solution of ketal **70** (15 mg, 0.042 mmol) in 2 mL of THF containing 40 μL of water. The reaction was stirred at ambient temperature for 2.5 h and then diluted with 2 mL of hexanes and filtered through a plug of SiO_2, washing with EtOAc/hexanes (1:1). The resulting solution was concentrated, and flash column chromatography (EtOAc/hexanes, 2:3) provided enone **115** (11.7 mg, 89%) as a colorless solid. Crystallization from EtOAc/hexanes gave prisms: mp >145 °C dec; IR ($CHCl_3$) 3570, 3600–3100, 1675 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.21 (app dt, J = 1.0, 8.5 Hz, 1 H), 6.11 (s, 1 H), 5.91 (d, J = 9.5 Hz, 1 H), 5.87 (dd, J = 1.1, 9.5 Hz, 1 H), 5.53 (d, J = 8.1 Hz, 1 H), 4.06 ($^1/_2$ ABX, J_{AB} = 14.5, J_{AX} = 8.6 Hz, 1 H), 3.74 ($^1/_2$ ABX, J_{BA} = 14.4, J_{BX} = 7.5 Hz, 1 H), 3.38 (d, J = 8.2 Hz, 1 H), 3.06 (dd, J = 1.1, 17.1 Hz, 1 H), 2.72 (s, 1 H), 2.61 (d, J = 17.2 Hz, 1 H), 2.35 (s, 3 H); chemical ionization mass spectrum, m/e 315.0699, M + H calcd for $C_{17}H_{15}O_4S$ 315.0692.

9-(Acetyloxy)-4,9-dihydro-4-hydroxy-2*H*-4,9a-propanonaphtho[2,3-*b*]thiophen-11-one (116). Diethylamine (40 μL, 0.39 mmol) was added to a solution of enone **115** (13 mg, 0.041 mmol) and 1,4-cyclohexadiene (0.20 mL, 2.1 mmol) in 2 mL of THF. The resulting solution was stirred for 30 min at ambient temperature. Camphorsulfonic acid (2 mg, 0.009 mmol) was added, and stirring was continued for a further 15 h. The reaction was filtered through 1 mL of SiO_2, washing with THF. Concentration and flash column chromatography (acetone/hexanes, 3:7) afforded **116** (9.3 mg, 71%) as a colorless glass: IR ($CHCl_3$) 3555, 3600–3130, 1730, 1720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.62 (d, J = 7.6 Hz, 1 H), 7.46–7.40 (m, 1 H), 7.32–7.28 (m, 2 H), 6.11 (app t, J = 2.4 Hz, 1 H), 5.98 (s, 1 H), 3.92 ($^1/_2$ ABX, J_{AB} = 14.5, J_{AX} = 2.7, 1 H), 3.84 ($^1/_2$ ABX, J_{BA} = 14.5, J_{BX} = 2.2 Hz, 1 H), 3.19 (d, J = 16.8 Hz, 1 H), 2.93 (dd, J = 1.5, 16.8 Hz, 1 H), 2.90 (d, J = 13.8 Hz, 1 H), 2.73 (dd, J = 1.5, 13.8 Hz, 1 H), 2.65 (s, 1 H), 2.04 (s, 3 H); chemical ionization mass spectrum, m/e 317.0867, M + H calcd for $C_{17}H_{17}O_4S$ 317.0848.

Methyl 13-[(*E*)-2-(Acetylthio)ethylidene]-1,8-dihydroxy-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-10-yl Carbamate (117). Camphorsulfonic acid (2 mg, 0.009 mmol) was added to a solution of thioacetate **109** (3.4 mg, 0.008 mmol) in THF (1 mL) and H_2O (1 drop) at room temperature. After the mixture was stirred for 5 h, hexanes (0.5 mL) were added to the reaction mixture and the solution was filtered through a pad of SiO_2, washing with hexanes/ethyl acetate (1:2). Solvents were evaporated, and the residue was subjected to SiO_2 flash chromatography (hexanes/ethyl acetate, 1:1) to give 2.4 mg (78%) of enone **117** as a colorless glass: IR (CH_2Cl_2) 3565, 3370, 2958, 2928, 1737, 1678, 1500, 1236 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.91 (br s, 1 H), 6.21 (t, J = 8.3 Hz, 1 H), 5.98 (br s, 1 H), 5.88–5.82 (m, 2 H), 3.91 (t, J = 6.2 Hz, 2 H), 3.76 (s, 3 H), 3.38 (br s, 1 H), 3.14 (d, J = 17.0 Hz, 1 H), 2.76 (br s, 1 H), 2.70 (d, J = 17.0 Hz, 1 H), 2.32 (s, 3 H); chemical ionization mass spectrum, m/e 388.0859, M + H calcd for $C_{19}H_{17}NO_6S$ 388.0855.

Methyl 9-(Acetyloxy)-4,9-dihydro-4-hydroxy-11-oxo-2*H*-4,9a-propanonaphtho[2,3-*b*]thiophen-10-yl Carbamate (118). Diethylamine (3 drops) was added to a solution of enone **117** (1.2 mg, 0.003 mmol) in dry THF (1 mL) containing 1,4-cyclohexadiene (0.10 mL, 1.0 mmol). After it was stirred at room temperature overnight, the reaction mixture was filtered through a plug of SiO_2, washing with THF. Solvents were evaporated, and the crude was purified by SiO_2 flash chromatography (hexanes/ethyl acetate, 1:1) to give 0.5 mg of Bergman product **118** (40%) as a colorless glass: IR ($CDCl_3$) 3588, 3396, 2919, 1738, 1509, 1237 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.64 (app d, 1 H, J = 9.8 Hz, CH arom), 7.45 (dt, 1 H, J = 7.4, 1.7 Hz, CH arom), 7.33–7.22 (m, 2 H, 2 CH arom), 6.20 (t, 1 H, J = 2.5 Hz, =CH), 6.06 (s, 1 H, -CH-(OAc)), 5.31 (d, 1 H, J = 8.6 Hz, NH), 5.15 (d, 1 H, J = 8.6, CH carbamate), 3.94 ($^1/_2$ ABX, 1 H, J_{AB} = 14.6, J_{AX} = 2.8 Hz, CH_2S–), 3.85 ($^1/_2$ ABX, 1 H, J_{AB} = 14.6, J_{BX} = 2.3 Hz, CH_2S–), 3.73 (s, 3 H, carbamate), 2.92 (AB_q, 2 H, J = 12.5 Hz, $\Delta\nu$ = 61.5 Hz, CH_2 six-membered ring), 2.60 (br s, 1 H, OH), 2.18 (s, 3 H, acetate); FAB mass spectrum (NOBA/NaI) m/e 412.0831, M + Na calcd for $C_{19}H_{19}SO_6N$ 412.0832.

4,9-Dihydro-4,9-dihydroxy-2*H*-4,9a-propanonaphtho[2,3-*b*]thiophen-11-one (119). Triethylamine (60 μL, 0.43 mmol) was added to a solution of enone **9** (21 mg, 0.060 mmol) in 3 mL of MeOH containing benzyl mercaptan (60 μL) and 1,4-cyclohexadiene (0.30 mL, 3.2 mmol). The solution was then stirred for 2.75 h at ambient temperature. Concentration and flash column chromatography (hexanes/EtOAc, 1:1) afforded diol **119** (8 mg, 49%) as a colorless solid. Crystallization from the THF/hexanes gave slightly yellow prisms: mp 207–209 °C; IR (KBr) 3590–3100, 2880, 1700, 1235, 1075, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 1 H), 7.45–7.30 (m, 3 H), 6.03 (app t, J = 2.4 Hz, 1 H), 4.43 (d, J = 0.5 Hz, 1 H), 3.93 (app t, J = 1.8 Hz, 2 H), 3.59 (d, J = 1.2 Hz, 1 H), 3.20 (d, J = 16.6 Hz, 1 H), 2.88 (d, J = 13.6 Hz, 1 H), 2.87 (dd, J = 1.8, 16.6 Hz, 1 H), 2.73 (dd, J = 1.9, 14.0 Hz, 1 H), 2.63 (s, 1 H); electron impact mass spectrum, m/e 274.0659, calcd for $C_{15}H_{14}O_3S$ 274.0664.

Preparation of 119 from 77. Triethylamine (60 μL, 0.43 mmol) was added to a solution of enone **77** (20 mg, 0.047 mmol) in 3 mL of MeOH containing benzyl mercaptan (60 μL) and 1,4-cyclohexadiene (0.30 mL, 3.2 mmol). The solution was then stirred for 3 h at ambient temperature. Concentration and flash column chromatography (hexanes/EtOAc, 1:1) gave diol **119** (6.5 mg, 51%) as a colorless solid.

Preparation of 116 from 119. Acetic anhydride (0.50 mL) was added to a solution of diol **119** (6.5 mg, 0.024 mmol) in pyridine (0.50 mL). After it was stirred at ambient temperature for 2 h, the reaction was diluted with toluene (3 mL) and concentrated in vacuo (repeating azeotropic concentration twice). Flash column chromatography (acetone/hexanes, 3:7) afforded acetate **116** (7.3 mg, 97%) as a colorless solid.

Methyl 4,9-Dihydro-4,9-dihydroxy-11-oxo-2*H*-4,9a-propanonaphtho-[2,3-*b*]thiophen-10-yl] Carbamate (120). Synthetic calicheamicinone (3.3 mg, 0.0078 mmol) was dissolved in 1.5 mL MeOH containing 1,4-cyclohexadiene (0.15 mL, 1.6 mmol). Benzyl mercaptan (45 μL, 0.38 mmol) and triethylamine (45 μL, 0.32 mmol) were added in succession to this solution while it was stirred at ambient temperature. After 2.25 h, the mixture was concentrated in vacuo. Flash column chromatography (hexanes/EtOAc, 2:3) delivered tetracycle **120** (0.44 mg, 16%; determined by ^1H NMR integration in comparison with an internal standard) as a colorless glass: IR ($CHCl_3$) 3610–3210, 3415, 2930, 1718, 1499, 1084 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 1 H), 7.46–7.39 (m, 1 H), 7.32 (app d, J = 4.1 Hz, 2 H), 6.16 (app t, J = 2.4 Hz, 1 H), 5.19 (s, 2 H), 4.54 (s, 1 H), 3.95 (app t, J = 3.5 Hz, 2 H), 3.73 (s, 3 H), 3.44 (d, J = 0.7 Hz, 1 H), 2.90 (ABq, J = 12.5 Hz, $\Delta\nu$ = 52.1 Hz, 2 H), 2.64 (s, 1 H); MS (20 eV) m/e 329 (M – H_2O, 4.4), 311 (37.1), 254 (31.5), 236 (23.4), 217 (100).

1,8,13-Trihydroxy-13-(hydroxymethyl)bicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-11-one (122). A mixture of epoxide **58** (32 mg, 0.13 mmol), formic acid (0.5 mL), and ammonium formate (1.56 g, 24.7 mmol) in 10 mL of THF/H_2O (1:1) was heated at reflux for 6.5 h. The cooled reaction was saturated with NaCl and extracted with EtOAc. Drying of the extracts (Na_2SO_4), concentration, reconcentration from toluene, and flash column chromatography (acetone/ hexanes, 1:1) gave tetraol **122** (34 mg, 99%) as a slightly yellow solid. Crystallization from EtOAc/Et_2O gave colorless prisms: 199–203 °C dec; IR (thin film) 3660–2980, 2930, 1657, 1410, 1297, 1133, 1065 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6/D_2O, 5:1) δ 6.09 (s, 1 H), 6.08 (d, J = 9.6 Hz, 1 H), 5.99 (dd, J = 1.5, 9.6 Hz, 1 H), 5.52 (s, 1 H), 3.95 (ABq, J = 11.3 Hz,

$\Delta\nu$ = 93.1 Hz, 2 H), 3.11 (d, J = 18.0 Hz, 1 H), 2.74 (dd, J = 1.0, 18.1 Hz, 1 H); chemical ionization mass spectrum, m/e 261.0769, M + H calcd for $C_{14}H_{13}O_5$ 261.0763.

1,8-Dihydroxybicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,13-dione (123). Periodic acid (11.6 mg, 50 μmol) was added to a solution of tetraol **122** (11 mg, 42 μmol) in THF (1 mL) at 0 °C. After 5 min at 0 °C, the reaction was allowed to stir for 10 min at ambient temperature and was then quenched by the addition of ethylene glycol (100 μL) and saturated sodium bicarbonate solution (0.5 mL). Thorough extraction with EtOAc, drying over Na_2SO_4, and concentration at room temperature gave dione **123** (9.6 mg, 100%) as a slightly yellow glass, which was judged homogeneous by TLC and ^{1}H NMR: IR ($CDCl_3$) 3490, 2900, 2160, 1690, 1400, 1245, 1110, 1050 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.47 (d, 1 H, J = 1.5 Hz), 5.96 (s, 2 H), 5.43 (d, 1 H, J = 11.3 Hz), 4.15 (d, 1 H, J = 11.3 Hz (OH)), 3.98 (s, 1 H, (OH)), 3.43 (dd, 1 H, J = 17.6, 1.5 Hz), 3.02 (d, 1 H, J = 17.6 Hz); UV (CH_3CN) λ_{max} 232 nm (ϵ 10900), 259 (6700), 272 (6400), 286 (4900); MS (20 eV) m/e 228 (M^+, 25), 210 (15), 182 (30), 168 (76), 155 (36), 126 (74), 115 (100); electron impact mass spectrum, m/e 228.0411, calcd for $C_{13}H_8O_4$ 228.0422.

1,8-Dihydroxybicyclo[7.3.1]trideca-4-ene-2,6-diyne-11,13-dione (124). Zinc dust (100 mg, 1.53 mmol) was added to a solution of enone **125** (19 mg, 0.083 mmol) in 1 mL of acetic acid. The mixture was stirred for 13 min at ambient temperature and then filtered through Celite, washing with THF. Concentration from toluene and flash column chromatography (EtOAc/hexanes, 1:1) afforded dione **124** (16.8 mg, 88%) as a colorless glass: IR ($CHCl_3$) 3600–3150, 3500, 3020, 1715, 1250, 1080, 1045 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 6.00 (dd, J = 1.7, 9.6 Hz, 1 H), 5.95 (d, J = 9.6 Hz, 1 H), 4.68 (ddd, J = 1.7, 4.5, 11.5 Hz, 1 H), 4.12 (d, J = 11.5 Hz, 1 H), 3.91 (s, 1 H), 3.58 (dd, J = 13.3, 17.0 Hz, 1 H), 3.34 (ddd, J = 4.5, 7.0, 13.3 Hz, 1 H), 3.28 (d, J = 18.5 Hz, 1 H), 2.79 (dd, J = 7.0, 17.0 Hz, 1 H), 2.78 (d, J = 18.5 Hz, 1 H); chemical ionization mass spectrum, m/e 231.0657, M + H calcd for $C_{13}H_{11}O_4$ 231.0657.

5,8,9,10-Tetrahydro-5,10-dihydroxy-6*H*-5,9-methanobenzocyclooctene-7,11-dione (125). A degassed (freeze–thaw method) solution of dione **124** (5 mg, 21 μmol) and 1,4-cyclohexadiene (0.5 mL) in acetonitrile (1.5 mL) was heated at reflux under N_2 for 7 h. The reaction mixture was concentrated and purified (SiO_2, 1:1, EtOAc/hexanes) to give Bergman product **125** (2 mg, 40%) as a glass: IR (film) 3400, 2920, 1720, 1290, 1140, 1085, 1025 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (dd, 1 H, J = 8.0, 1.0 Hz), 7.50 (dt, 1 H, J = 8.0, 2.0 Hz), 7.44–7.35 (m, 2 H), 5.12 (d, 1 H, J = 3.5 Hz), 3.46 (ddd, 1 H, J = 7.5, 3.5, 1.2 Hz), 3.05 (dd, 1 H, J = 17.0, 7.5 Hz), 3.04 (d, 1 H, J = 8.0 Hz), 2.95 (dd, 1 H, J = 8.0, 3.0 Hz), 2.77 (ddd, 1 H, J = 17.0, 3.0, 1.2 Hz), hydroxyl protons not detected; MS (20 eV) m/e 232 (M^+, 7), 214 (45), 186 (25), 172 (32), 144 (100), 105 (40); chemical ionization mass spectrum, m/e 233.0813, M + H calcd for $C_{13}H_{13}O_4$ 233.0814.

7,8,9,10-Tetrahydro-6*H*-5,9-methanobenzocyclooctene-5,7,10,11-tetraol (126). Sodium borohydride (0.48 mL of a 1.0 M solution in diglyme, 480 μmol) was added to a stirred solution of dione **124** (5.5 mg, 24 μmol) and 1,4-cyclohexadiene (0.3 mL) in methanol (0.5 mL) at 0 °C. After 10 min, the reaction mixture was warmed to room temperature and glacial AcOH (0.5 mL) and MeOH (3 mL) were added. The mixture was allowed to stand at room temperature for 12 h (to solvolyze a putative borate ester), then concentrated, and purified (SiO_2, EtOAc) to give tetraol **126** (3 mg, 54%) as a solid: IR (film) 3350, 2910, 1055, 760 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70 (dd, 1 H, J = 6.0, 1.8 Hz), 7.48–7.35 (m, 3 H), 4.79 (s, 1 H), 4.10–3.98 (m, 1 H), 3.94 (d, 1 H, J = 3.7 Hz), 3.28 (s, 1 H, OH), 3.00 (s, 1 H, OH), 2.88 (s, 1 H, OH), 2.84–2.80 (m, 1 H), 2.19–1.98 (m, 5 H); MS (20 eV) m/e 236 (M^+, 5), 218 (10), 200 (100), 182 (20), 159 (82), 146 (70), 131 (45), 105 (25); chemical ionization mass spectrum, m/e 237.1116, M + H calcd for $C_{13}H_{17}O_4$ 237.1127.

7,8,9,10-Tetrahydro-7,10,11-triacetoxy-6*H*-5,9-methanobenzocyclooctene-5,7,10,11-tetraol (127). A solution of tetraol **126** (1 mg), Ac_2O (0.2 mL), Et_3N (0.4 mL), and 4-(dimethylamino)pyridine (0.5 mg) in CH_2Cl_2 (2 mL) was stirred at room temperature for 12 h. The mixture was concentrated and purified (SiO_2, EtOAc/hexanes) to give triacetate **127** (0.5 mg): IR (film) 3400, 2920, 1740, 1375, 1245, 1045 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 (dd, 1 H, J = 6.9, 1.7 Hz), 7.43–7.26 (m, 3 H), 6.11 (d, 1 H, J = 4.0 Hz), 5.94 (s, 1 H), 5.01–4.93 (m, 1 H), 3.17 (dd, 1 H, J = 14.1, 4.4 Hz), 3.06 (m, 1 H), 2.27–1.90 (m, 4 H), 2.14 (s, 3 H), 2.07 (s, 3 H), 1.97 (s, 3 H); MS (20 eV) m/e 362 (M^+, 4), 344 (15), 242 (30), 200 (100), 182 (90), 159 (28), 155 (25), 148 (24), 127 (20); electron impact mass spectrum, m/e 362.1378, calcd for $C_{19}H_{22}O_7$ 362.1366.

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Supplementary Material Available: Tables of fractional coordinates, bond distances, torsional angles, and anisotropic temperature factors and summary of the X-ray crystallographic determinations and structures of compounds **54**, **58**, **66**, **106**, and **114** (42 pages). Ordering information is given on any current masthead page.