Total Synthesis of Calicheamicin γ_1^I. 2. Development of an Enantioselective Route to (-)-Calicheamicinone[1]

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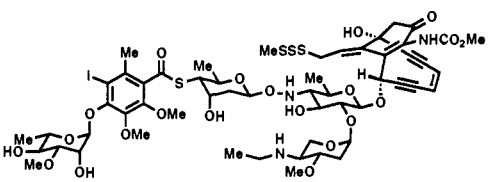
Abstract: The first enantioselective total synthesis of (-)-calicheamicinone (**3**), the naturally occurring antipode of the calicheamicin aglycon, has been achieved. The key elements of the synthesis are as follows: (i) the use of an asymmetric allylboration reaction to introduce asymmetry into the molecule (**13** + **17** → **18**), (ii) the incorporation of the nitrogen atom of the urethane through an intramolecular 1,3-dipolar cycloaddition reaction of an alkenyl nitrile oxide (**22** → **24**), (iii) the apparently stereospecific introduction of the enediyne moiety through alkylation of ketone **34**, (iv) an unusual one-pot double oxidation of hydroxy isoxazoline **39** to keto isoxazole **41**, (v) the apparently stereospecific introduction of the alkylidene side chain through Wittig olefination of **41**, (vi) the unveiling of key enamine-aldehyde functionalities through reductive ring opening of isoxazole **67**, (vii) the bridging of the enediyne residue through intramolecular alkylation of an aldehyde (**71** → **72**), and (viii) an unusual lactonization (**72** → **76**) to correct an errant stereocenter.

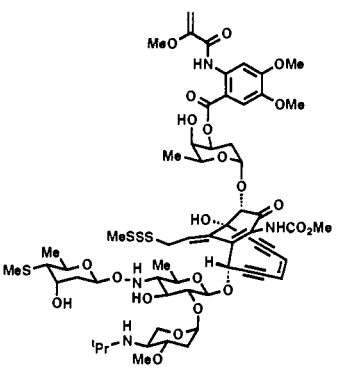
Introduction

In the preceding paper,[2] we described the synthesis of the oligosaccharide domain of calicheamicin γ_1^I (**1**)[3] (Figure 1), a member of the enediyne class of antitumor antibiotics[4] which also includes esperamicin A_1 (**2**),[5] the neocarzinostatin chromophore,[6] dynemicin A,[7] and the recently discovered kedarcidin chromophore.[8]

At the heart of calicheamicin γ_1^I (**1**) is a rigid bicyclic aglycon, calicheamicinone, composed of a cyclohexenone ring bridged by a 1,5-diyn-3-ene unit contained within a 10-membered ring. Attached to the cyclohexenone ring are an exocyclic allylic trisulfide moiety and a vinylic methyl carbamate. It should be noted that since the structure was first reported, the stereochemistry of the secondary hydroxyl group at C-8 has been revised on the basis of an NMR analysis of model systems[9,3c] and an X-ray crystal structure obtained for a derivative of the related esperamicin.[5b] It is to this hydroxyl group that the oligosaccharide fragment is attached.



1: calicheamicin γ_1^I



2: esperamicin A_1

Figure 1. Structures of naturally occurring enediyne anticancer antibiotics.

DNA destruction in tumor cells by calicheamicin γ_1^I (**1**) is believed to be the key to its biological activity. The oligosaccharide fragment is generally viewed as a recognition and delivery system, binding the molecule with remarkable specificity within the minor groove of duplex DNA.[10-12] A bionucleophile or reducing agent cleaves the trisulfide moiety of the aglycon, generating a thiolate species which adds in a 1,4-fashion to the adjacent enone

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functionality. The timing of this event in relation to binding is not certain. The resulting change in hybridization from $sp^2 \rightarrow sp^3$ at the bridgehead position facilitates a cycloaromatization of the enediyne system, generating a reactive benzenoid diradical.[13] It has been demonstrated[14] that the calicheamicin diradical abstracts hydrogen atoms from duplex DNA at the C-5′ position of the cytidine in 5′-TCCT and at the C-4′ position of the nucleotide three base pairs removed on the 3′-side of the complimentary strand, leading to cleavage of both strands of DNA.

The potent cytotoxicity of calicheamicin γ_1^I (**1**) combined with its unique and challenging structure has generated considerable interest among both biologists[15] and chemists[9a,16-19] in an effort to better understand the activity of the molecule and to possibly develop useful therapeutic agents.

Important synthetic goals are the total synthesis of calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**). The oligosaccharides of calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**) have been synthesized independently in our[20] and Danishefsky's[21] laboratories (see the preceding paper in this issue for details of our synthesis of the calicheamicin γ_1^I oligosaccharide).[2] Furthermore, Danishefsky has reported a synthesis of racemic calicheamicinone.[22] In this paper, we report details of the first enantioselective synthesis of (−)-calicheamicinone (**3**), the naturally occurring antipode of the calicheamicin aglycon,[23] and in the following paper,[24] we disclose details of the successful completion of the first total synthesis of calicheamicin γ_1^I (**1**).

Synthetic Strategy

The ultimate goal of this project was to achieve the coupling of the aglycon and oligosaccharide portions of calicheamicin γ_1^I (**1**) in order to complete a total synthesis of the natural product. This placed the constraint on any proposed synthesis of calicheamicinone (**3**) that it must be amenable to producing sufficient quantities of the aglycon and in a state of high enantiomeric purity in order to avoid the formation of diastereomers which would inevitably result from coupling a racemic aglycon with a chiral oligosaccharide fragment. Thus, a generalized plan of attack was formulated which would hopefully satisfy these requirements, as outlined in retrosynthetic form in Scheme I.

Many model studies from various groups,[9a,16a-o] including Danishefsky's successful racemic synthesis of calicheamicinone,[22] strongly suggested that an intramolecular addition of a metalated enediyne to an aldehyde functionality (**4**) would be the most efficient and synthetically flexible means of generating the rigid bicyclic structure. Because we assumed that the aldehyde group would be obtained by oxidation of a suitable primary allylic alcohol (**5**), the unique arrangement of nitrogen, double bond, and primary alcohol invited the use of an isoxazoline precursor (**6**) in the belief that it would be possible to induce the double bond to shift position. According to this strategy, the requirement of producing calicheamicinone (**3**) of high enantiomeric purity would be met if the absolute stereochemistry of the quaternary acetylenic center could be controlled, since any other chiral centers in the precursors of **4** would eventually be removed. Thus, compound **6** seemed to provide the perfect opportunity for controlling the absolute stereochemistry of this quaternary center if the chirality of the adjacent center could itself be controlled and used to direct facial attack of an acetylide anion on a ketone. This would then bring us down to the relatively simple task of making the fused bicyclic structure **6**, which should be directly accessible from the acyclic precursor **8** *via* the intramolecular 1,3-dipolar cycloaddition reaction of alkenyl nitrile oxide **7**. As noted previously, this would leave the retrosynthetic task of finding a short, efficient synthesis of **8** which would control the absolute stereochemistry at the

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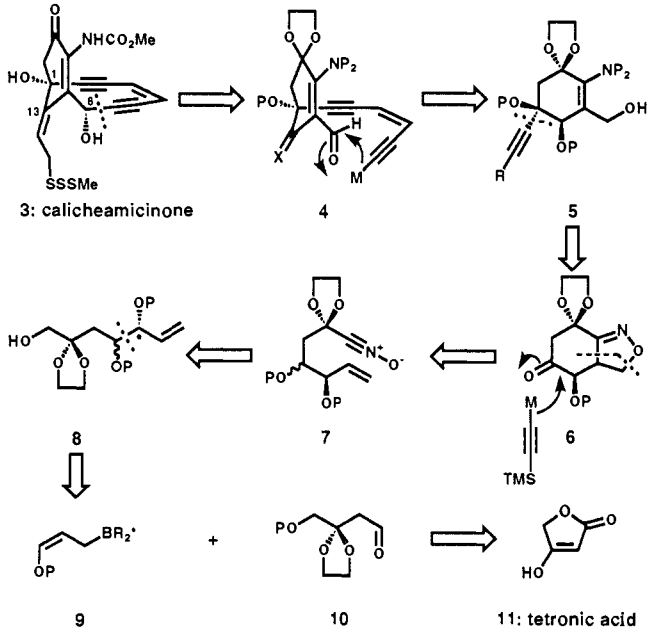
Scheme I.[a] Retrosynthetic Analysis of Calicheamicinone (3)



[a] M = metal, P = protecting group.

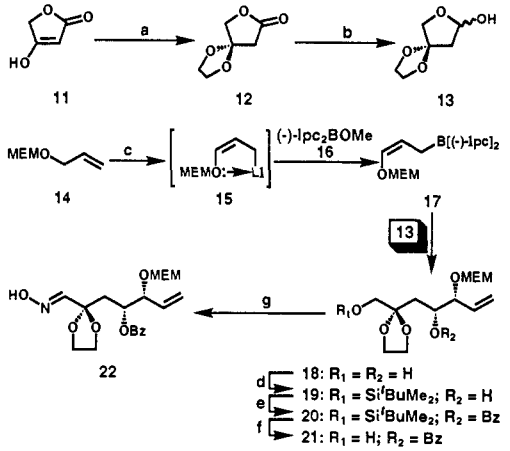
indicated (*) allylic center. While a number of possibilities for doing this presented themselves (*e.g.*, enantioselective reduction of a corresponding acetylenic ketone[25] or kinetic resolution of a racemate using Sharpless technology[26]), the asymmetric allylboration chemistry of Brown[27] seemed most appropriate (**9** + **10** → **8**) due to its simplicity and ease of operation, while at the same time providing a means of controlling the stereochemistry of the adjacent superfluous chiral center and thus avoiding the handling of diastereomeric mixtures. Further thought then suggested tetronic acid (**11**)[28] as a suitably functionalized and readily available starting material for the synthesis, and we thus embarked upon our synthetic studies, leaving the question of how best to stereoselectively introduce the allylic trisulfide moiety until a later date.

Results and Discussion

The reputation of tetronic acid (**11**) for being difficult to handle caused us some initial trepidation which, as it turned out, proved to be unfounded. Ketalization with ethylene glycol under standard conditions[29] readily provided **12** in 60% yield (Scheme II), and this, in turn, could be cleanly reduced with DIBAL to lactol **13**. The spectroscopic data for **13** indicated that, while existing predominantly in the closed lactol form, approximately 4% of the hydroxy aldehyde form (corresponding to **10**, Scheme I) was present in chloroform solution. This observation fueled our hopes that it might be used directly as the aldehyde component in the asymmetric allylboration reaction.

Brown had reported that either methoxy- or MOM-protected allyl alcohol could be stereospecifically converted to a (*Z*)-diisopinocampheylallylborane and then reacted with suitable aldehydes to provide *syn*-diols of high diastereomeric and enantiomeric purity.[27,30] However, the use of methoxy and MOM protecting groups concerned us since their use in syntheses has often caused problems at the deprotection stage. We therefore

Scheme II[a]



[a] Reagents and conditions: (a) 1 equiv of $(CH_2OH)_2$, TsOH (catalytic), PhH, Δ, 12 h, 60%; (b) 1.7 equiv of DIBAL, CH_2Cl_2, −78 °C, 1 h, 84%; (c) 1.1 equiv of **14**, 1.0 equiv of *s*-BuLi, THF, −78 °C, 10 min, then 1.1 equiv of **16**, −78 °C, 1 h, then −78 → 25 °C, (fast), 1.5 h, then 1.0 equiv of **13**, −95 °C (3 h) → 25 °C, slowly, and then excess 30% H_2O_2, NaOH (catalytic), 25 °C, 12 h, 87%; (d) 1.0 equiv of ^{t}BuMe$_2$SiCl, 2.1 equiv of imidazole, CH_2Cl_2, 25 °C, 2 h; (e) 2.0 equiv of PhCOCl, 4.4 equiv of pyr, DMAP (catalytic), CH_2Cl_2, 25 °C, 12 h; (f) 2 equiv of ^{n}Bu$_4$NF, 1.5 equiv of AcOH, THF, 50 °C, 4 h; (g) Swern oxidation, and then 2.2 equiv of NH_2OH·HCl, 2.2 equiv of NaOAc, EtOH–H_2O (2:1), 25 °C, 1 h, 88% overall from **18**.

settled for a MEM protecting group[31] which should be compatible with the proposed chemistry while being somewhat easier to remove. Thus, lithiation of MEM-protected allyl alcohol (**14**) with *sec*-butyllithium at −78 °C stereospecifically produced the canary-yellow (*Z*)-enol ether **15** which was treated with commercially available and enantiomerically pure (−)-*B*-methoxydiisopinocampheylborane (**16**). The resulting colorless borate was decomposed to the corresponding allylborane **17** upon treatment with BF_3·OEt_2. *In situ* treatment of allylborane **17** with lactol **13** at *ca.* −95 °C led to a remarkably smooth reaction producing, upon oxidative workup, diol **18** in 87% yield with extremely high diastereoselectivity (>98% de as judged by ^{1}H NMR analysis). The reaction proved amenable to large-scale synthesis,[32] making it feasible to produce the multigram quantities of compound necessary for developing the latter stages of the synthesis. While the high diastereoselectivity of the reaction bode well for the enantioselectivity, determination of the enantiomeric purity of the product would wait until the success of the proposed 1,3-dipolar cycloaddition reaction had been assured.

At this stage, it was necessary to selectively oxidize the primary hydroxyl group of **18** to the corresponding aldehyde in order for it to serve as a suitable precursor for the required nitrile oxide. However, all attempts to do this directly were thwarted by cyclization of the unprotected secondary hydroxyl group, resulting in 5-membered lactol and/or lactone formation. It was thus necessary to first selectively protect the offending secondary hydroxyl group, and this was rendered straightforward by its fairly hindered position which enabled a diprotection–deprotection sequence (**18** → **19** → **20** → **21**) to achieve this in virtually quantitative yield and with no necessity for chromatographic purification of intermediates. With the secondary hydroxyl group now protected as its benzoate ester (**21**), Swern oxidation[33] and trapping of the aldehyde as its oxime during workup gave aldoxime **22** as a single geometrical isomer in excellent yield.

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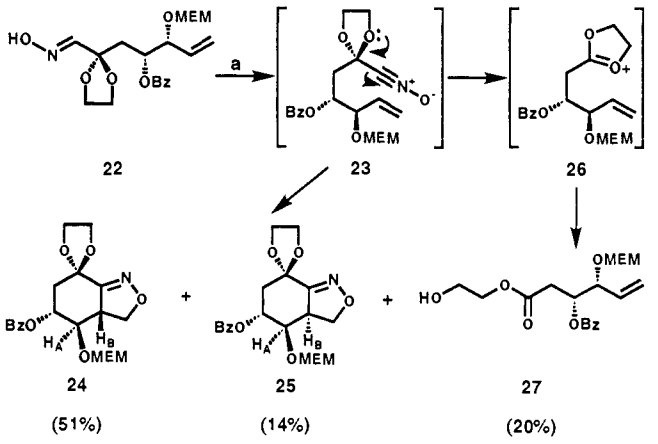
(32) The large scale synthesis required that the intermediate borate of **17** be decomposed by allowing the reaction to warm to room temperature (over ~1.5 h) instead of treating it with BF_3·OEt_2 at −78 °C. This facilitated the workup without compromising yield or diastereoselectivity.
(33) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme III[a]



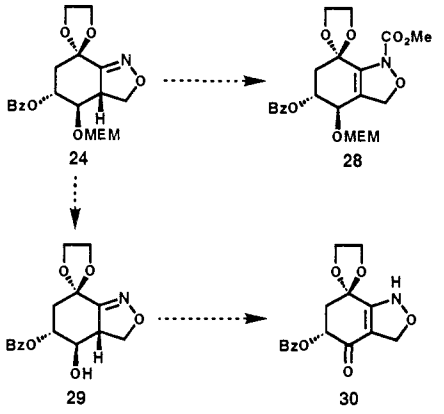
[a] Reagents and conditions: (a) NaOCl, CH_2Cl_2/H_2O, 0° C.

The scene was now set for the key intramolecular 1,3-dipolar cycloaddition reaction upon which the successful continuation of the synthesis depended (Scheme III).[34] The substrate for the reaction, **22**, is more heavily functionalized than most substrates which have been reported for this reaction, and the heavy oxygenation pattern, particularly the ethylene ketal α to the proposed nitrile oxide **23**, caused a certain amount of apprehension. Gratifyingly, treatment of aldoxime **22** with aqueous sodium hypochlorite solution in CH_2Cl_2 at 0 °C gave a 65% yield of isoxazolines **24** and **25** (epimeric at the ring-fusion position) in a ratio of about 4:1 in favor of **24**, the structures being assigned on the basis of coupling constants in the ^1H NMR spectra (J_{AB} = 9.2 Hz for **24**, J_{AB} = 3.6 Hz for **25**). Although both epimers were theoretically useful for the synthesis since the epimeric chiral center would eventually be destroyed, the two isomers were separated chromatographically at this stage and the minor isomer **25** was set aside so that the subsequent chemistry could be developed on a single isomer. Also identified in the reaction mixture was a small amount (*ca.* 20%) of ester **27** resulting from oxidative cleavage of aldoxime **22**, cleavage occurring at the stage of either nitrile oxide **23** (see arrows) or the precursor α-chloro aldoxime (neither of which were observed while monitoring the reaction by TLC).

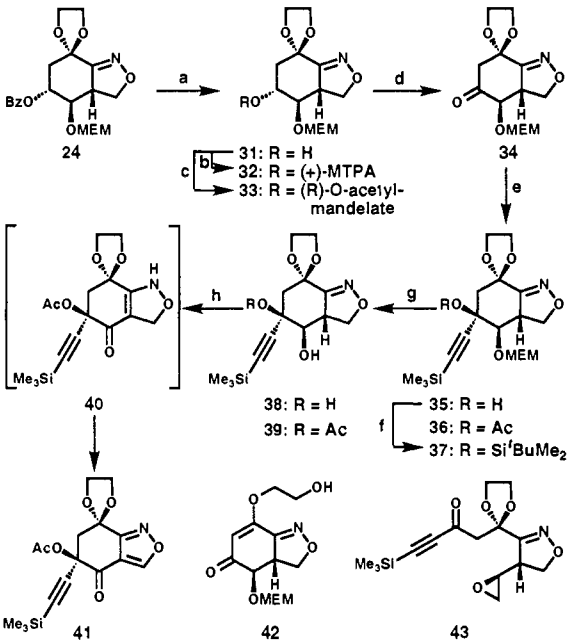
In an attempt to optimize this step, a variety of different protocols, reported for the transformation of aldoximes to nitrile oxides,[35] were tested. However, they were inferior to aqueous sodium hypochlorite. Use of triethylamine or tetrabutylammonium fluoride (as a phase-transfer catalyst) did not improve the reaction profile, while changing the solvent from dichloromethane to ethanol resulted in ester **27** being the sole product.

Our thoughts now turned to the matter of how to induce the double bond in **24** to migrate in order to install the vinyl urethane functionality present in calicheamicinone (Scheme IV). All attempts to do this directly from **24**, *e.g.*, by treatment with base and methyl chloroformate to give **28**, were completely unsuccessful, giving either recovered **24** or decomposition depending upon the conditions employed. It was therefore hoped that removal of the MEM group (**24** → **29**) and oxidation (**29** → **30**) would induce the double bond to migrate into conjugation with the ketone to give vinylogous amide **30**. However, such a process would necessarily involve destruction of the very chiral center which was anticipated to control the overall asymmetry of the synthesis and so it became clear that we would have to introduce the quaternary acetylenic center first.

Scheme IV. Proposed Strategies for the Migration of the Isoxazoline Double Bond



Scheme V[a]



[a] Reagents and conditions: (a) NaOMe (catalytic), MeOH, 0 °C, 12 h, 100%; (b) 2 equiv of (+)-Mosher acid, 2 equiv of DCC, DMAP (catalytic), CH_2Cl_2, 25 °C, 2 h, 88%; (c) 1.2 equiv of (*R*)-(−)-*O*-acetylmandelic acid, 1.5 equiv of DCC, DMAP (catalytic), CH_2Cl_2, 0 → 25 °C, 12 h, 77%; (d) 1.5 equiv of Jones reagent, acetone, 0 °C, 12 h, 95%; (e) 1.5 equiv of lithium (trimethylsilyl)acetylide, THF, −78 °C, 30 min, and then 5 equiv of E^+, −78 → 25 °C (for **35**, $E^+ = H_2O$, 69% and for **36**, $E^+ = Ac_2O$, 69%); (f) 2 equiv of ^{t}BuMe$_2$SiOTf, 4 equiv of 2,6-lutidine, CH_2Cl_2, 25 °C, 3 h, 72%; (g) for **36** → **39**, 10 equiv of $ZnBr_2$, CH_2Cl_2, 25 °C, 12 h; (g) Swern oxidation, 54% overall from **36**.

To this end, the benzoate group of **24** was removed to give the secondary alcohol **31** (Scheme V). Compound **31** provided a convenient opportunity for determining the enantiomeric purity of the material derived from the asymmetric allylboration reaction (Scheme II) and so the (+)-Mosher's ester derivative **32** was prepared.[36] ^1H NMR analysis clearly indicated the presence of a minor amount of an impurity in a ratio of 97.6:2.4, and the identity of the impurity was confirmed as being derived from *ent*-**31** by preparation of and comparison with *ent*-**31** obtained from (+)-*B*-methoxydiisopinocampheylborane. The enantiomeric purity of the material was thus determined to be 95% ee. Furthermore, comparison of the 500-MHz ^1H NMR spectra of the two diastereomeric esters suggested[37] that compound **31**

(34) For an excellent review of nitrile oxide cycloaddition reactions, see: Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley–Interscience: New York, 1984; Vol. 1, Chapter 3, pp 291–392.

(35) (a) Grundmann, C.; Richter, R. *J. Org. Chem.* **1968**, *33*, 476. (b) Just, G.; Dahl, K. *Tetrahedron* **1968**, *24*, 5251. (c) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916. (d) Lee, G. A. *Synthesis* **1982**, 508. (e) Peake, C. J.; Strickland, J. H. *Synth. Commun.* **1986**, *16*, 763. (f) Hassner, A.; Rai, K. M. L. *Synthesis* **1989**, 57. (g) Kim, J. N.; Ryu, E. K. *Synth. Commun.* **1990**, *20*, 1373.

(36) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

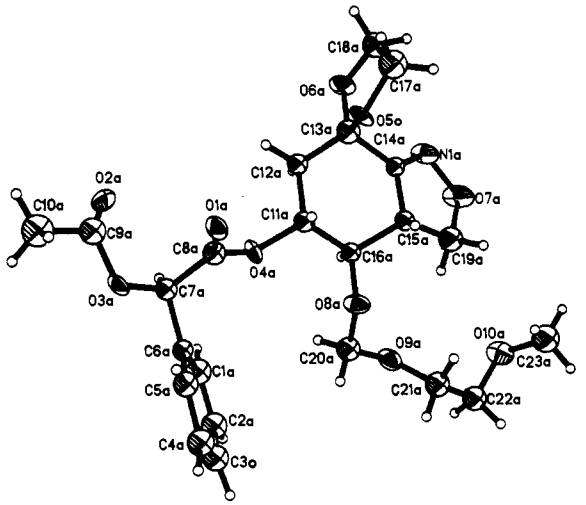


Figure 2. ORTEP drawing of compound 33.

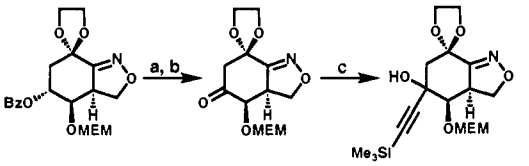
possessed the indicated absolute stereochemistry which was also proven by X-ray crystallographic analysis carried out on the (*R*)-*O*-acetylmandelate derivative[38] **33** (see ORTEP drawing, Figure 2).

Oxidation of the secondary hydroxyl group of **31** to ketone **34** was hampered by two factors—the hindered nature of the hydroxyl group and the sensitivity of the product. However, oxidation with Jones reagent[39] gave a remarkably clean reaction, though taking a full 12 h to go to completion at 0 °C with 1.5 equiv of the reagent. Ketone **34** required careful handling, being readily converted to enone **42** by both silica gel and base *via* β-elimination. Once formed, **42** could not be induced to close and re-form **34**.

All systems were now ready for the all-important stereoselective introduction of an acetylenic unit to generate the chiral quaternary center which would govern the overall enantioselectivity of the synthesis. Conformational analysis of **34**[40] suggested the desired isomer **35** (Scheme V) as the favored product of nucleophilic attack on the carbonyl group. Our previous synthetic exploits into the area of dynemicin A[19] suggested that it would be more convenient experimentally to introduce the enediyne unit in a stepwise manner rather than as a single entity as Danishefsky did in his synthesis of (±)-calicheamicinone.[22] Thus, **34** was treated with freshly prepared lithium (trimethylsilyl)acetylide at −78 °C in THF, providing **35** in what proved to be a highly stereoselective reaction with absolutely no sign of the epimeric product being observed (for proof of stereochemistry at the newly generated center, see below). The corresponding reaction with the analogous acetylenic Grignard reagent was far less satisfactory, being sluggish and less stereoselective and producing a significant amount of material derived from **42**.

Now that the question of stereochemistry had been worked out for the major isomer **24** from the 1,3-dipolar cycloaddition reaction, we focused upon the minor isomer **25** (Scheme VI). Thus, **25** was smoothly converted to ketone **44** according to the previously described chemistry. Our conformational analysis[40] of **44** predicted that alkylation of **44** would tend to be even more stereoselective than alkylation of **34**; however, this was not the result we obtained. Addition of lithium (trimethylsilyl)acetylide at −78 °C in THF gave an inseparable 3.8:1 mixture of diastereomers **45a,b** of undetermined stereochemistry. In light of the perfect stereoselectivity obtained with the major diastereomer **24** from the 1,3-dipolar cycloaddition reaction, work on the minor isomer was discontinued.

Scheme VI[a]



[a] Reagents and conditions: (a) NaOMe (catalytic), MeOH, 0 °C, 12 h, 100%; (b) 1.5 equiv of Jones reagent, acetone, 0 °C, 12 h, 92%; (c) 1.5 equiv of lithium (trimethylsilyl)acetylide, THF, −78 °C, 30 min, 72%.

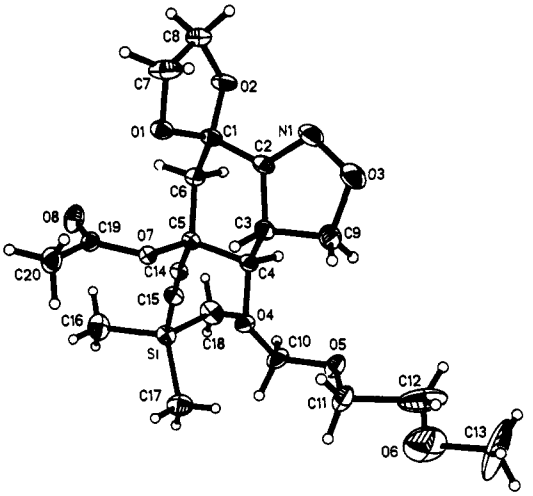


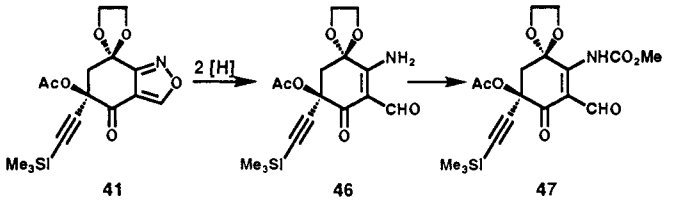
Figure 3. ORTEP drawing of compound 36.

Having established the single, important asymmetric center in the molecule, we could now return our thoughts to the matter of inducing double-bond migration, as outlined in Scheme IV (**24** → **29** → **30**). Accordingly, the MEM ether was removed from **36** with $TiCl_4$ to give **38** (Scheme V). However, all attempts to oxidize **38** were unsuccessful, presumably due to oxidative cleavage of the 1,2-diol. It would therefore be necessary to first protect the tertiary hydroxyl group, and for a number of protecting groups tried, this was most conveniently achieved by *in situ* trapping of the alkoxide produced during the acetylide addition reaction. Thus, trapping with Ac_2O provided a 69% overall yield of acetate **36** from ketone **34**. Acetate **36** readily yielded good quality crystals, and this enabled an X-ray structure determination to be carried out in order to confirm that the stereochemistry we had predicted for the newly created quaternary center was correct, as indeed it was (see ORTEP drawing, Figure 3). Besides the acetate, a fair number of other protecting groups were tried for the tertiary hydroxyl group, but the acetate was the only one which worked reasonably well over the next couple of steps. In particular, it should be noted that the use of a silyl ether, such as **37**, was unsuitable since removal of the MEM ether under Lewis acid conditions was accompanied by an unusual fragmentation of the 6-membered ring to produce what is believed to be **43**. Removal of the MEM ether from **36** was best achieved with $ZnBr_2$ in CH_2Cl_2 to provide **39** in a fairly clean reaction.[31] Once produced, **39** required careful handling to avoid migration of the acetate onto the neighboring secondary hydroxyl group (a reaction which occurred with remarkable ease both on silica gel and under basic conditions).

We were now arranged to oxidize the secondary hydroxyl group and, in the process, isomerize the double bond to give the vinylogous amide **40**, and so, we subjected **39** to Swern oxidation conditions.[33] We were totally unprepared for what happened next. What we isolated from the reaction mixture was a 54%

(37) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(38) (a) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548. (b) Breitholle, E. G.; Stammer, C. H. *J. Org. Chem.* **1974**, *39*, 1311.
(39) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.
(40) Calculations were carried out using the modeling program Sybyl on a Silicon Graphics IRIS personal workstation.

Scheme VII. Proposed Reductive Cleavage of the Isoxazole Ring System to the Required Vinylogous Urethane Aldehyde

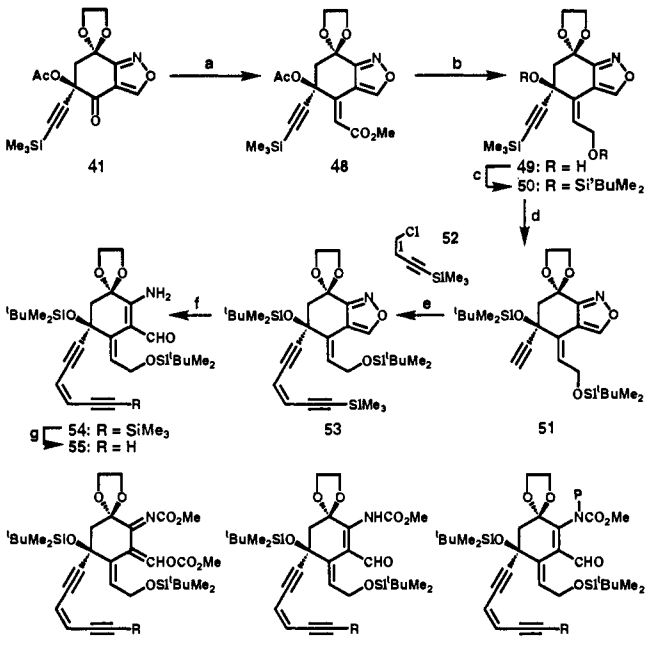


yield of keto isoxazole **41** rather than the expected vinylogous amide **40**! A number of other oxidizing agents (*e.g.*, Jones reagent, Dess–Martin periodinane,[41] and TPAP[42]) gave a similar result, although in less satisfactory yield, and at no time was there any evidence of **40** being observed. Although the exact mechanism of this double oxidation is open to speculation, it seems likely that rapid aromatization is occurring through aerial oxidation of initially formed **40**. Our initial frustration soon turned to hope when we realized that, far from being a disaster, this result might actually be fortuitous. Embedded within the isoxazole ring are the very amine, aldehyde, and double-bond functionalities we required for the cyclization substrate **4** in our initial retrosynthetic analysis (see Scheme I). Some preliminary small scale experiments were therefore carried out to test the validity of this hope (Scheme VII). Thus, reductive cleavage of the weak N–O bond in **41** (*e.g.*, $Mo(CO)_6$, MeCN, H_2O, Δ)[43] provided enamino aldehyde **46** (perhaps better thought of as a vinylogous formamide), and acylation with LDA/MeOCOCl installed the methyl carbamate functionality in **47**. Buoyed by these results, the time was now ripe to consider how best to establish the allylic trisulfide of calicheamicinone.

The reactive keto functionality contained in **41** provided us with an unexpected window of opportunity for introduction of a suitable exocyclic alkylidene unit which would serve as a handle for the later introduction of the trisulfide. Accordingly, ketone **41** was treated with methyl (triphenylphosphoranylidene)acetate at 90 °C in toluene and, to our delight, provided an 84% yield of the olefinated product **48** as a single geometrical isomer (Scheme VIII). DIBAL reduction of **48** gave a 94% yield of diol **49**, which was protected as *bis*(silyl) ether **50** (TBSOTf, 2,6-lutidine, CH_2Cl_2, 87%). The correct geometry of the alkylidene unit was confirmed at this stage by the observation of a large NOE between the isoxazole and allylic protons in the ^1H NMR spectrum of **50** (15% enhancement of the isoxazole proton upon irradiating the allylic protons), while no corresponding NOE was observed between the isoxazole and vinylic protons. Incorporation of the full enediyne moiety was readily achieved by selective removal of the TMS group from the acetylene in the presence of silyl ethers (LiOH, THF, H_2O, 90%) followed by a palladium(0)–copper(I)-mediated coupling[44] with (*Z*)-chloro enyne **52**, giving enediyne **53** in 76% yield. Reductive cleavage of the isoxazole N–O bond of **53** was best achieved by heating with molybdenum hexacarbonyl in acetonitrile containing a trace of water,[43] providing the vinylogous amide **54** in 70% yield. The TMS group could be conveniently removed from the enediyne in 95% yield using LiOH in aqueous THF. Installation of the urethane onto **54** or **55** proved problematic since all electrophiles preferentially reacted at the oxygen atom of the vinylogous amide system first. Though far from satisfactory, the best method for introducing the methyl carbamate was to treat **54** or **55** with a large excess of methyl chloroformate and triethylamine to give **56** or **57** and then to hydrolyze the enol carbonate under mildly acidic or basic conditions to give **58** or **59**. Under no conditions could the acidic N*H* proton be masked to give **60** or **61** since all electrophiles reacted exclusively at the formyl oxygen atom. Thus, all extensive efforts to induce cyclization and bridging of enediynes **54–59** met with failure due to the presence of acidic N*H* protons (methods tried included treatment with base, Lewis acid, and anhydrous fluoride and the Ni(II)–Cr(II)-mediated cyclization of terminally iodinated enediynes[45]).

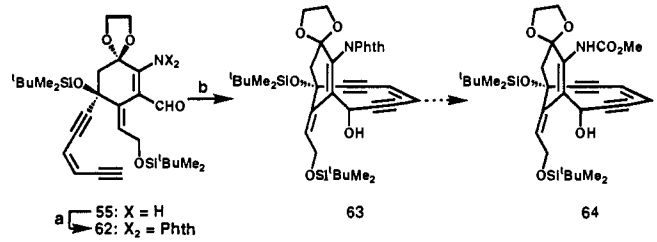
It therefore became clear to us that the best chance for progress would come from diprotecting the nitrogen as a cyclic protecting group, and after considerable experimentation, success came with the phthalimido protecting group which we could introduce in rather low and variable yield with phthaloyl chloride/pyridine to give **62** (Scheme IX). Indeed, once the nitrogen was fully protected, treatment of **62** with potassium hexamethyldisilazide at –78 °C in toluene provided us with a 30% yield of the bridged enediyne **63** with a single (undetermined) stereochemistry at the newly generated secondary hydroxyl center. However, it was

Scheme VIII[a]



[a] Reagents and conditions: (a) 5 equiv of $Ph_3P{=}CHCO_2Me$, toluene, 90 °C, 16 h, 84%; (b) 4 equiv of DIBAL, THF, –78 → 0 °C, 30 min, 94%; (c) 4 equiv of ^{t}BuMe$_2$SiOTf, 6 equiv of 2,6-lutidine, CH_2Cl_2, 25 °C, 1 h, 87%; (d) 5 equiv of LiOH, aqueous THF, 25 °C, 1 h, 90%; (e) 2 equiv of **52**, 2 equiv of ^{n}BuNH$_2$, 0.05 equiv of $Pd(OAc)_2$, 0.25 equiv of PPh_3, 0.20 equiv of CuI, PhH, 25 °C, 2 h, 76%; (f) 1.0 equiv of $Mo(CO)_6$, MeCN–H_2O (20:1), 80 °C, 1.5 h, 70%; (g) 5 equiv of LiOH, aqueous THF, 25 °C, 1 h, 95%.

Scheme IX[a]



[a] Reagents and conditions: (a) 2 equiv of phthaloyl chloride, 6 equiv of pyridine, CH_2Cl_2, 0 °C, 30 min, 25%; (b) 1.0 equiv of KHMDS, toluene, –78 °C, 15 min, 30%.

(41) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(42) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(43) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877.
(44) (a) Stephans, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (b) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315. (c) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.
(45) Crévisy, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 3171.

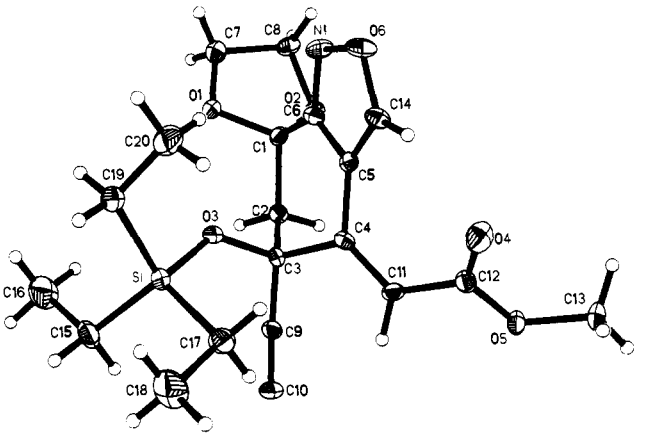
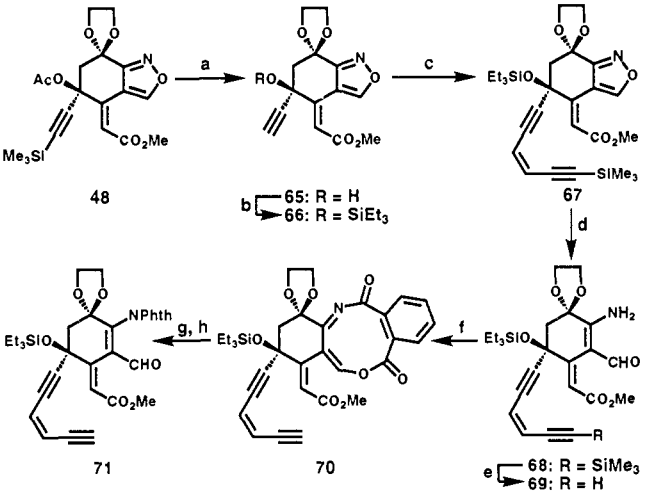


Figure 4. ORTEP drawing of compound **66**.

Scheme X[a]

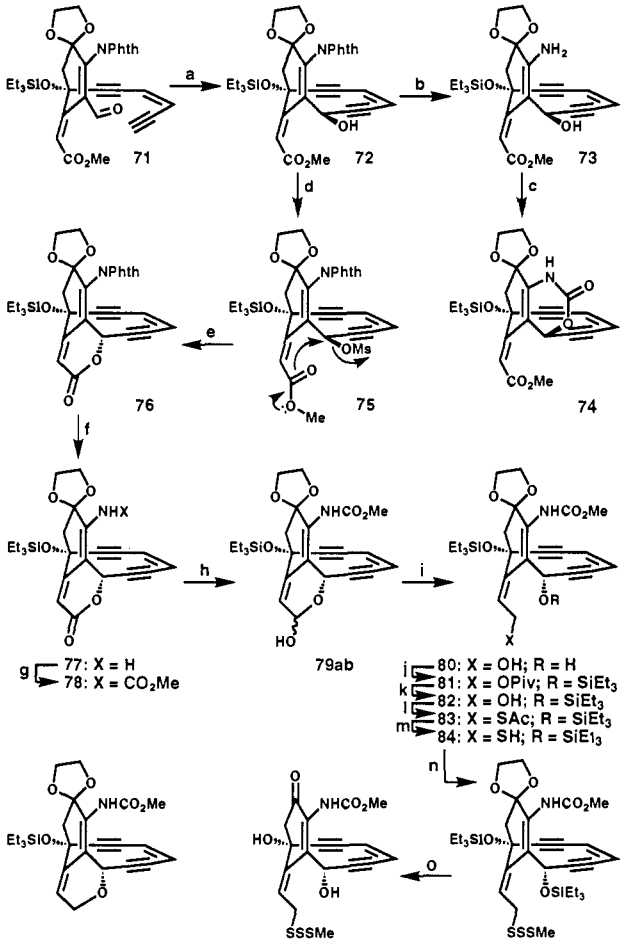


[a] Reagents and conditions: (a) 1.0 equiv of K_2CO_3, MeOH–CH_2Cl_2 (1:1), 0 °C, 6 h, 90%; (b) 2.0 equiv of Et_3SiOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 96%; (c) 1.5 equiv of **52**, 0.1 equiv of $Pd(PPh_3)_4$, 0.20 equiv of CuI, 1.5 equiv of $^nBuNH_2$, PhH, 0 °C, 2 h, 91%; (d) 1.0 equiv of $Mo(CO)_6$, MeCN–H_2O (5:1), 80 °C, 1.5 h, 82%; (e) 1.0 equiv of K_2CO_3, MeOH–THF (2:1), 0 °C, 2 h, 92%; (f) 1.4 equiv of phthaloyl chloride, 4 equiv of pyr, $MeNO_2$, 0 °C, 30 min; (g) silica gel, CH_2Cl_2, 25 °C, 2 h; (h) excess Ac_2O, $MeNO_2$, 25 °C, 1 h, 78% from **69**.

obvious that exchanging the phthalimide of **63** for the urethane of **64** would be no easy task since it would require the intermediacy of a labile primary enamine. Therefore, it would be necessary to retrace our steps slightly in order to retain the alkylidene ester functionality of **48** which would hopefully confer stability to the primary enamine by endowing it with vinylogous urethane character.

Double deprotection of **48** (K_2CO_3, MeOH) gave a 90% yield of acetylenic alcohol **65**. Silylation (TESOTf, 2,6-lutidine) gave the highly crystalline ester **66** which gave us the opportunity to reconfirm (by X-ray analysis) absolute stereochemistry (see ORTEP drawing, Figure 4). Subsequent coupling to (*Z*)-chloro enyne **52** (Pd(0)–Cu(I) catalysis)[44] gave a 91% yield of enediyne **67** (Scheme X). Cleavage of the isoxazole with molybdenum hexacarbonyl[43] then gave an 82% yield of vinylogous amide **68** from which the TMS group was removed (K_2CO_3, MeOH) in 92% yield, providing the unprotected enediyne **69**. Reinvestigation of the phthaloylation reaction with phthaloyl chloride/pyridine revealed that while a minor amount of the required phthalimide **71** was produced, virtually all of the remaining material was accounted for in the formation of the labile, novel 9-membered heterocycle **70**. Fortunately, it was found that hydrolysis of the enol ester on silica gel and activation of the resulting phthalamic acid with acetic anhydride produced a mixture of the desired

Scheme XI[a]



[a] Reagents and conditions: (a) 1.1 equiv of KHMDS, toluene, –90 °C, 5 min, 48%; (b) 10 equiv of $MeNHNH_2$, PhH, 25 °C, 2 h, 85%; (c) 3 equiv of triphosgene, 15 equiv of pyr, CH_2Cl_2, 25 °C, 40 min, and then 15 equiv of pyr, excess MeOH, 0 °C, 30 min, 64%; (d) 10 equiv of MsCl, 20 equiv of pyr, DMAP (catalytic), CH_2Cl_2, 0 °C, 2 h; (e) silica gel, 2 equiv of pyr, PhH, 25 °C, 5 h, 90% from **72**; (f) 12 equiv of $MeNHNH_2$, PhH, 25 °C, 30 min, 99%; (g) 3 equiv of triphosgene, 15 equiv of pyr, CH_2Cl_2, 25 °C, 40 min, and then 15 equiv of pyr, excess MeOH, 0 °C, 30 min, 82%; (h) 3 equiv of DIBAL, CH_2Cl_2, –78 °C, 30 min, 95%; (i) excess $NaBH_4$, MeOH, 0 °C, 1 h, 88%; (j) 3 equiv of PivCl, 15 equiv of pyr, CH_2Cl_2, 25 °C, 4 h, and then 3 equiv of TESOTf, 0 °C, 10 min, 67%; (k) 3 equiv of DIBAL, CH_2Cl_2, –78 °C, 1 h, 84%; (l) 8 equiv of DEAD, 10 equiv of PPh_3, 8 equiv of AcSH, THF, 0 °C, 30 min, 93%; (m) 5 equiv of DIBAL, CH_2Cl_2, –78 °C, 30 min; (n) 5 equiv of *N*-(methyldithio)phthalimide, CH_2Cl_2, 25 °C, 30 min, 71% from **83**; (o) TsOH (catalytic), aqueous THF, 25 °C, 16 h, 66%.

phthalimide **71** together with **70**. The use of polar solvents such as nitromethane greatly favored *N*-acylation over *O*-acylation in this second step so that recycling of **70** twice provided a 78% overall yield of phthalimide **71** from **69**.

Treatment of **71** with potassium hexamethyldisilazide in toluene at –90 °C produced **72**, contaminated with approximately 10% of **76**, in yields of up to 48% (56% based upon recovered **71**) (Scheme XI). It should be noted that the use of freshly prepared reagent (from KH and $HN(SiMe_3)_2$ in THF) consistently provided slightly better results than the use of a fresh bottle of commercially available reagent, and it was important to quench the reaction at low temperature with acetic acid in order to minimize hydrolysis of the phthalimide by the neighboring alkoxide anion. The use of other bases in this cyclization reaction was less satisfactory.

We were initially uncertain of the stereochemistry of the newly generated secondary hydroxyl center in **72**, but an attempt to

install the methyl carbamate unequivocally confirmed that it was of the incorrect stereochemistry for calicheamicinone (**3**). Thus, removal of the phthalimide from **72** with methylhydrazine (hydrazine hydrate caused the undesired reduction of the enediyne) gave the rather labile enamine **73**. Treatment with triphosgene/pyridine followed by MeOH then resulted in the isolation of the cyclic carbamate **74**, a result which would be geometrically impossible for the epimeric alcohol. Thus, we would need to invert the secondary hydroxyl group of **72**.

Because the secondary hydroxyl group of **72** was too hindered for traditional intermolecular inversion techniques such as that of Mitsunobu,[46] it was reasoned that since propargylic mesylates have a strong tendency to ionize, this might provide an opportunity for the neighboring ester group to accomplish the inversion in an intramolecular lactonization. Thus, mesylate **75** was prepared from **72** (MsCl, pyridine), and we were pleased to observe that the proposed lactonization (**75** → **76**) cleanly took place on a silica gel TLC plate (observed by two-dimensional TLC). On a preparative scale, stirring **75** with a slurry of silica gel in benzene converted it to **76** but the process was complicated by partial hydrolysis of the silyl ether and ethylene ketal. These side reactions were readily eliminated by the addition of 2 equiv of pyridine to neutralize the generated methanesulfonic acid which was the presumed culprit, providing a 90% yield of lactone **76** from **72**.

Removal of the phthalimide from **76** with methylhydrazine gave a 99% yield of the stable enamine **77**, which was converted to methyl carbamate **78** in 82% yield by treatment with triphosgene/pyridine followed by MeOH. The conclusion of the synthesis then followed along the lines of Danishefsky's synthesis of (±)-calicheamicinone.[22] Thus, DIBAL reduction of **78** gave a 4:1 mixture of lactol epimers **79a,b** (95% yield) which were further reduced with $NaBH_4$ to diol **80** (88% yield). Direct introduction of the primary allylic thioacetate group at this stage through a Mitsunobu reaction with thiolacetic acid[47] was badly complicated by intramolecular etherification to give dihydropyran **86** as the major product in a ratio of *ca.* 2:1. Therefore, a diprotection–deprotection sequence (**80** → **81** → **82**) was carried out to selectively protect the secondary hydroxyl group in 56% overall yield. Mitsunobu reaction with thiolacetic acid[47] then introduced the thioacetate of **83** (93% yield) which was deacylated (DIBAL) and converted to trisulfide **85** with *N*-(methyldithio)-phthalimide[48] in 71% yield, following the methodology developed by Magnus on a model system.[16i] A final deprotection of the ethylene ketal and two silyl ethers was accomplished in one pot with TsOH in aqueous THF in 66% yield, thus completing the first asymmetric synthesis of calicheamicinone (**3**). The material thus obtained was spectroscopically identical to the (±)-calicheamicinone previously obtained by Danishefsky[49] and had a rotation of $[\alpha]^{25}_D$ –472° (*c* 0.21, CH_2Cl_2) (estimated weighing error = ±5%). No sample of natural calicheamicinone is available for comparison purposes since it has not been possible to isolate the intact aglycon from degradation studies.

Conclusion

The first enantioselective total synthesis of (–)-calicheamicinone (**3**), the naturally occurring antipode of the calicheamicin aglycon, has been achieved. This result, combined with our synthesis of the oligosaccharide of calicheamicin γ_1^I, had paved the way for completion of the total synthesis of the natural product **1** itself (see the following paper).[24] This strategy should also be amenable to the construction of the aglycon of esperamicin A_1 (**2**), facilitating the synthesis of that natural product.

(46) Mitsunobu, O. *Synthesis* **1981**, 1.
(47) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
(48) (a) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 57. (b) Sullivan, A. B.; Boustany, K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 211.
(49) We thank Prof. S. Danishefsky for providing us with IR and ^{1}H NMR spectra of (±)-calicheamicinone.

Future developments in this program will be to tether aglycon analogs, perhaps with synthetically more convenient triggering devices than the trisulfide, to other specific delivery systems for the development of novel DNA-cleaving molecules and anticancer agents.

Experimental Section

General Techniques. NMR spectra were recorded on a Bruker AMX-500 instrument. IR spectra were recorded on Nicolet 205 or Perkin-Elmer 1600 series FT-IR spectrophotometers. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light, 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere with anhydrous, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

1,4,7-Trioxaspiro[4,4]nonan-8-one (12). Tetronic acid (100 g, 1.0 mol), ethylene glycol (56 mL, 1.0 mol), and TsOH (2 g, catalytic) in benzene (1 L) were refluxed (Dean–Stark trap) for 12 h. The solution was poured into saturated aqueous sodium bicarbonate solution (500 mL) and extracted with CH_2Cl_2 (2 L) utilizing a continuous extraction apparatus; the organic extracts were dried (Na_2SO_4), concentrated, and purified by low-pressure distillation (bp 115 °C, 0.02 Torr) to give ketal **12** (86.6 g, 60%) as a low-melting solid: R_f = 0.32 (Et_2O); IR (thin film) ν_{max} 1781 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (s, 2H, C*H*$_2$-O-C=O), 3.98 (s, 4 H, OC*H*$_2$C*H*$_2$O), 2.73 (s, 2 H, C*H*$_2$-C=O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 110.1, 75.2, 65.2, 38.7; FAB HRMS (NBA/CsI) *m/e* 276.9477, M + Cs^+ calcd for $C_6H_8O_4$ 276.9477.

1,4,7-Trioxaspiro[4.4]nonan-8-ol (13). A solution of **12** (86.6 g, 0.60 mol) in dichloromethane (600 mL) at –78 °C was treated with 32 mL of 1.0 M DIBAL in dichloromethane (1.0 mol). The mixture was stirred for 1 h and the reaction quenched at –78 °C with EtOAc (60 mL total); water (45 mL total) was added and the solution stirred at 25 °C until complete decomposition of the aluminum complex (12 h). The granular precipitate of alumina was filtered off and the product purified by flash chromatography (ether) to give **13** (73.7 g, 84%) as a low-melting solid: R_f = 0.16 (Et_2O); IR (thin film) ν_{max} 3446 (b s), 1720 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (b d, *J* = 4.7 Hz, 1 H, OC*H*OH), 3.96–3.73 (m, 7 H, C*H*$_2$-O, OC*H*$_2$C*H*$_2$O, O*H*), 2.27 (dd, *J* = 13.7, 5.4 Hz, 1 H, C*H*H), 2.05 (dd, *J* = 13.7, 1.8 Hz, 1 H, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.8, 98.2, 72.5, 64.8, 64.7, 43.1; FAB HRMS (NBA/NaI) *m/e* 169.0477, M + Na^+ calcd for $C_6H_{10}O_4$ 169.0477.

2-Hydroxymethyl-2-[(2*R*,3*R*)-2-hydroxy-3-[(2-methoxyethoxy)methoxy]-pent-4-enyl]-1,3-dioxolane (18). 1-[(2-Methoxyethoxy)methoxy]-2-propene (**14**) (54 g, 370 mmol) in THF (220 mL) was cooled to –78 °C. *s*-BuLi was added dropwise (250 mL of a 1.3 M solution in cyclohexane, 325 mmol), giving a canary-yellow solution. The reaction mixture was stirred for 10 min at –78 °C, and then (–)-*B*-methoxydiisopinocampheylborane (116 g, 367 mmol) in THF (370 mL) was added dropwise (the yellow color discharged upon addition of the last few drops to give a colorless solution). The reaction mixture was stirred for 30 min at –78 °C, the cooling bath was removed, and the reaction mixture was allowed to stir for 1.5 h at 25 °C. Then it was cooled back down to –95 °C. Hemiacetal **13** (47.5 g, 325 mmol) in THF (330 mL) was then slowly added dropwise. The colorless solution was maintained at –95 °C for 3 h and then allowed to slowly warm to 25 °C over several hours. The solvent was removed *in vacuo* and the residue dissolved in ether (1.3 L). The solution was treated with a mixture of 30% hydrogen peroxide (96 mL) and 250 mL of 3 N NaOH (NB exothermic). The reaction mixture was stirred overnight and separated, and the aqueous layer was extracted with dichloromethane (5 × 500 mL); the organic extracts were concentrated, and the residue was purified by flash chromatography (50% ether/petroleum ether → ether → EtOAc → 4% methanol/EtOAc) to give **18** (82.7 g, 87%) as a colorless oil: R_f = 0.28 (4% MeOH in EtOAc); $[\alpha]^{25}_D$ –60.2° (*c* 3.6, CH_2Cl_2); IR (thin film) ν_{max} 3420, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (m, 1 H, C*H*=CH$_2$), 5.25–5.21 (m, 2 H, CH=C*H*$_2$), 4.65 (AB q, *J* = 6.9 Hz, Δν = 36 Hz, 2 H, OC*H*$_2$O), 3.93–3.86 (m, 7 H, C*H*-OH, *ethylene ketal*, C*H*-OMEM, O-C*H*H-CH$_2$-

OMe), 3.79 (m, 1 H, OCH*H*-CH_2OMe), 3.74 (m, 1 H, O-CH_2-C*H*H-OMe), 3.56 (m, 1 H, O-CH_2-CH*H*-OMe), 3.51–3.43 (m, 4 H, CH_2OH, O*H*), 3.29 (s, 3 H, O*Me*), 1.80 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 119.9, 109.8, 93.8, 80.7, 71.5, 69.4, 67.1, 65.0, 65.0, 64.8, 58.8, 37.4; FAB HRMS (NBA/CsI) *m/e* 425.0590, M + Cs^+ calcd for $C_{13}H_{24}O_7$ 425.0576.

2-[((*tert*-Butyldimethylsilyl)oxy)methyl]-2-[(2*R*,3*R*)-2-hydroxy-3-[(2-methoxyethoxy)methoxy]pent-4-enyl]-1,3-dioxolane (19). A solution of **18** (82.7 g, 283 mmol) in dichloromethane (600 mL) at 0 °C was treated with imidazole (40 g, 588 mmol) and then with *tert*-butyldimethylsilyl chloride (43 g, 285 mmol) in dichloromethane (290 mL) and stirred for 2 h. The mixture was poured into saturated aqueous sodium bicarbonate solution (1 L), extracted with dichloromethane (4 × 500 mL), and concentrated, and the residue was purified by flash chromatography (ether) to give **19** (112 g, 98%) as a colorless oil: R_f = 0.51 (Et_2O); $[\alpha]^{25}_D$ −33.3° (*c* 5.3, CH_2Cl_2); IR (thin film) ν_{max} 3490 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (m, 1 H, C*H*=CH_2), 5.30–5.26 (m, 2 H, CH=CH_2), 4.73 (AB q, *J* = 6.5 Hz, Δν = 40 Hz, 2 H, OCH_2O), 4.03–3.95 (m, 5 H, C*H*-OH, *ethylene ketal*), 3.93 (dd, *J* = 10.0, 5.4 Hz, 1 H, C*H*-OMEM), 3.82 (m, 1 H, OC*H*H-CH_2-OMe), 3.61 (m, 1 H, OCH*H*-CH_2-OMe), 3.55 (AB q, *J* = 10.4 Hz, Δν = 23 Hz, 2 H, CH_2-OTBS), 3.53 (m, 2 H, OCH_2CH$_2$-OMe), 3.48 (b s, 1 H, O*H*), 3.37 (s, 3 H, O*Me*), 1.94 (dd, *J* = 14.9, 1.4 Hz, 1 H, C*H*H), 1.83 (dd, *J* = 14.9, 10.0 Hz, 1 H, CH*H*), 0.88 (s, 9 H, *t-Bu*), 0.04 (s, 6 H, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 119.3, 110.4, 92.9, 80.2, 71.7, 69.5, 67.0, 66.2, 65.5, 65.1, 58.9, 37.2, 25.8, 18.2, −5.5; FAB HRMS (NBA/CsI) *m/e* 539.1430, M + Cs^+ calcd for $C_{19}H_{38}O_7Si$ 539.1441.

2-[(2*R*,3*R*)-2-(Benzoyloxy)-3-[(2-methoxyethoxy)methoxy]pent-4-enyl]-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-dioxolane (20). Silyl ether **19** (112 g, 275 mmol) was dissolved in dichloromethane (200 mL), and pyridine (94 mL, 1.2 mol) and benzoyl chloride (64 mL, 551 mmol) plus 1.7 g of DMAP were added. The solution was stirred at 25 °C for 12 h, diluted with dichloromethane (2 L), and washed with saturated copper sulfate solution (3 × 600 mL). The aqueous layers were extracted with additional dichloromethane (3 × 600 mL), and the combined organic layers were concentrated *in vacuo* to give a colorless oil. The product was sufficiently pure for the next step: R_f = 0.60 (Et_2O); $[\alpha]^{25}_D$ −26.7° (*c* 3.0, CH_2Cl_2); IR (thin film) ν_{max} 1719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2 H, *Bz*), 7.50 (t, *J* = 8.2 Hz, 1 H, *Bz*), 7.39 (t, *J* = 8.2 Hz, 2 H, *Bz*), 5.72 (m, 1 H, C*H*=CH_2), 5.52 (m, 1 H, C*H*-OBz), 5.32–5.27 (m, 2 H, CH=CH_2), 4.69 (AB q, *J* = 6.8 Hz, Δν = 32 Hz, 2 H, O-CH_2-O), 4.22 (dd, *J* = 6.8, 6.8 Hz, 1 H, C*H*-OMEM), 3.98–3.82 (m, 4 H, *ethylene ketal*), 3.71–3.36 (m, 4 H, O-CH_2CH_2-OMe), 3.48 (AB q, *J* = 10.2 Hz, Δν = 39 Hz, 2 H, CH_2-OTBS), 3.32 (s, 3 H, O*Me*), 2.17–2.08 (m, 2 H, CH_2), 0.84 (s, 9 H, *t-Bu*), 0.00 (2 × s, 6 H, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 133.9, 132.7, 130.6, 129.6, 128.2, 120.0, 109.6, 92.8, 78.3, 71.6, 70.7, 66.9, 66.2, 65.4, 65.3, 58.9, 34.4, 25.8, 18.2, −5.5; FAB HRMS (NBA/CsI) *m/e* 643.1703, M + Cs^+ calcd for $C_{26}H_{42}O_8Si$ 643.1703.

2-[(2*R*,3*R*)-2-(Benzoyloxy)-3-[(2-methoxyethoxy)methoxy]pent-4-enyl]-2-(hydroxymethyl)-1,3-dioxolane (21). Crude **20** (275 mmol) was dissolved in THF (550 mL); 550 mL of 1.0 M TBAF in THF and 24 mL of glacial acetic acid were added, and the reaction mixture was heated at 50 °C for 4 h. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography (ether → EtOAc) to give **21** (109 g, 100% over 2 steps) as a colorless oil: R_f = 0.20 (Et_2O); $[\alpha]^{25}_D$ −30.0° (*c* 0.55, CH_2Cl_2); IR (thin film) ν_{max} 3465, 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.2 Hz, 2 H, *Bz*), 7.53 (t, *J* = 7.2 Hz, 1 H, *Bz*), 7.41 (t, *J* = 7.2 Hz, 2 H, *Bz*), 5.73 (ddd, *J* = 17.2, 10.8, 6.8 Hz, 1 H, C*H*=CH_2), 5.51 (ddd, *J* = 10.3, 6.4, 5.0 Hz, 1 H, C*H*-OBz), 5.34–5.29 (m, 2 H, CH=CH_2), 4.71 (AB q, *J* = 8.1 Hz, Δν = 30 Hz, 2 H, O-CH_2-O), 4.26 (dd, *J* = 6.8, 5.0 Hz, 1 H, C*H*-OMEM), 4.03–3.88 (m, 4 H, *ethylene ketal*), 3.74 (m, 1 H, OC*H*H-CH_2-OMe), 3.56–3.41 (m, 6 H, O-CH*H*-CH_2-OMe, CH_2-O*H*), 3.34 (s, 3 H, O*Me*), 2.19–2.17 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 133.8, 132.9, 130.2, 129.7, 128.2, 120.0, 109.2, 93.0, 78.0, 71.6, 70.8, 67.0, 65.2, 65.2, 65.1, 58.9, 34.4; FAB HRMS (NBA/CsI) *m/e* 529.0861, M + Cs^+ calcd for $C_{20}H_{28}O_8$ 529.0839.

(*E*)-2-[(2*R*,3*R*)-2-(Benzoyloxy)-3-[(2-methoxyethoxy)methoxy]pent-4-enyl]-1,3-dioxolane-2-carboxaldehyde Oxime (22). Oxalyl chloride (31.2 mL, 358 mmol) in 600 mL of dichloromethane at −78 °C was treated dropwise with DMSO (49 mL, 691 mmol) in 10 mL of dichloromethane. The mixture was stirred for 30 min at −78 °C, and then alcohol **21** (109 g, 275 mmol) in dichloromethane (275 mL) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C, and then triethylamine was added (240 mL, 1.7 mol). The reaction mixture was stirred for 30 min at −60 °C and then allowed to warm slowly to 25 °C over 30 min. The reaction mixture was poured into sodium bicarbonate solution (1 L) and extracted with dichloromethane (3 × 600 mL), and the extracts were concentrated. The residue was dissolved in ethanol (920 mL), and hydroxylamine hydrochloride (42 g, 2.2 equiv) and sodium acetate trihydrate (82 g, 2.2 equiv) dissolved in 470 mL of water were added. The solution was stirred for 1 h, poured into brine (2 L), and extracted with dichloromethane (3 × 600 mL). The organic extracts were concentrated, and the residue was purified by flash chromatography (ether) to give oxime **22** (101 g, 90% over 2 steps) as a colorless oil: R_f = 0.29 (70% Et_2O in petroleum ether); $[\alpha]^{25}_D$ −32.0° (*c* 0.44, CH_2Cl_2); IR (thin film) ν_{max} 3380, 1718 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.1 Hz, 2 H, *Bz*), 7.99 (b s, 1 H, CH=N-O*H*), 7.52 (t, *J* = 7.1 Hz, 1 H, *Bz*), 7.41 (t, *J* = 7.1 Hz, 2 H, *Bz*), 7.29 (s, 1 H, C*H*=N), 5.73 (ddd, *J* = 17.1, 10.4, 6.8 Hz, 1 H, C*H*=CH_2), 5.60 (m, 1 H, C*H*-OBz), 5.34–5.29 (m, 2 H, CH=CH_2), 4.71 (AB q, *J* = 6.8 Hz, Δν = 29 Hz, 2 H, O-CH_2-O), 4.27 (dd, *J* = 6.8, 5.1 Hz, 1 H, C*H*-OMEM), 4.06–3.83 (m, 4 H, *ethylene ketal*), 3.76 (m, 1 H, O-C*H*H-CH_2-OMe), 3.57–3.42 (m, 3 H, OCH*H*-CH_2-OMe), 3.35 (s, 3 H, O*Me*), 2.32–2.30 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 149.2, 133.6, 132.8, 130.3, 129.7, 128.2, 120.1, 105.8, 92.9, 77.8, 71.6, 70.0, 67.0, 65.1, 65.1, 58.9, 36.1; FAB HRMS (NBA/CsI) *m/e* 542.0776, M + Cs^+ calcd for $C_{20}H_{27}NO_8$ 542.0791.

(3a*S*,4*R*,5*R*)-5-(Benzoyloxy)-3,3a,4,5,6,7-hexahydro-4-[(2-methoxyethoxy)methoxy]spiro[2,1-benzisoxazole-7,2′-[1,3]dioxolane] (24) and (3a*R*,4*R*,5*R*)-5-(Benzoyloxy)-3,3a,4,5,6,7-hexahydro-4-[(2-methoxyethoxy)methoxy]spiro[2,1-benzisoxazole-7,2′-[1,3]dioxolane] (25). A solution of oxime **22** (33.7 g, 82.3 mmol) in dichloromethane (1.6 L) was treated at 0 °C with sodium hypochlorite (490 mL of a 5% aqueous solution) and vigorously stirred for 2 h. The reaction mixture was separated and the aqueous layer extracted with dichloromethane (3 × 250 mL); the organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (70% ether in petroleum ether) to give **24** (17.1 g, 51%) followed by **25** (4.7 g, 14%).

Data for **24**: colorless crystals; mp = 97–98 °C (from Et_2O); R_f = 0.38 (Et_2O); $[\alpha]^{25}_D$ −20.4° (*c* 2.1, CH_2Cl_2); IR (thin film) ν_{max} 1726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.6 Hz, 2 H, *Bz*), 7.57 (t, *J* = 8.6 Hz, 1 H, *Bz*), 7.43 (t, *J* = 8.6 Hz, 2 H, *Bz*), 5.47 (ddd, *J* = 12.0, 9.2, 4.6 Hz, 1 H, C*H*-OBz), 4.77 (AB q, *J* = 7.3 Hz, Δν = 106 Hz, 2 H, O-CH_2-O), 4.68 (dd, *J* = 10.8, 8.3 Hz, 1 H, C*H*H-O-N), 4.33 (dd, *J* = 9.8, 8.3 Hz, 1 H, CH*H*-O-N), 4.21 (m, 1 H, *ethylene ketal*), 4.12 (m, 1 H, *ethylene ketal*), 4.04 (m, 1 H, *ethylene ketal*), 3.93 (m, 1 H, *ethylene ketal*), 3.84 (dd, *J* = 9.2, 9.2 Hz, 1 H, C*H*-OMEM), 3.69 (ddd, *J* = 10.8, 9.8, 4.6 Hz, 1 H, C*H*-C=N), 3.67–3.46 (m, 4 H, O-CH_2-CH_2-OMe), 3.34 (s, 3 H, O*Me*), 2.43 (dd, *J* = 13.1, 4.6 Hz, 1 H, C*H*H), 2.10 (dd, *J* = 13.1, 12.0 Hz, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 155.1, 133.3, 129.7, 128.6, 128.2, 102.5, 95.9, 81.1, 74.1, 72.9, 71.4, 67.6, 65.9, 64.7, 59.1, 51.5, 39.1; FAB HRMS (NBA/CsI) *m/e* 540.0678, M + Cs^+ calcd for $C_{20}H_{25}NO_8$ 540.0635.

Data for **25**: oil; R_f = 0.33 (Et_2O); $[\alpha]^{25}_D$ +34.7° (*c* 5.3, CH_2Cl_2); IR (thin film) ν_{max} 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2 H, *Bz*), 7.54 (t, *J* = 8.7 Hz, 1 H, *Bz*), 7.42 (t, *J* = 8.7 Hz, 2 H, *Bz*), 5.51 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1 H, C*H*-OBz), 4.83 (AB q, *J* = 7.1 Hz, Δν = 57 Hz, 2 H, O-CH_2-O), 4.42 (dd, *J* = 11.8, 7.6 Hz, 1 H, C*H*H-O-N), 4.32 (dd, *J* = 7.6, 7.6 Hz, 1 H, CH*H*-O-N), 4.17 (m, 1 H, *ethylene ketal*), 4.05 (m, 1 H, *ethylene ketal*), 4.00 (dd, *J* = 3.6, 3.6 Hz, 1 H, C*H*-OMEM), 3.98–3.90 (m, 3 H, C*H*-C=N, *ethylene ketal*), 3.76–3.68 (m, 2 H, O-CH_2CH$_2$-OMe), 3.54–3.50 (m, 2 H, O-CH$_2$CH_2-OMe), 3.34 (s, 3 H, O*Me*), 2.54 (dd, *J* = 15.2, 3.6 Hz, 1 H, C*H*H), 2.29 (ddd, *J* = 15.2, 2.6, 0.9 Hz, 1 H, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 154.8, 133.2, 129.9, 129.8, 128.3, 103.1, 96.0, 74.3, 71.5, 70.3, 68.8, 68.0, 65.1, 64.8, 59.0, 44.1, 35.7; FAB HRMS (NBA/CsI) *m/e* 540.0671, M + Cs^+ calcd for $C_{20}H_{25}NO_8$ 540.0635.

Data for **27**: oil; R_f = 0.21 (Et_2O); $[\alpha]^{25}_D$ −36.0° (*c* 3.0, CH_2Cl_2); IR (thin film) ν_{max} 3480, 1736, 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9 Hz, 2 H, *Bz*), 7.53 (t, *J* = 7.9 Hz, 1 H, *Bz*), 7.41 (t, *J* = 7.9 Hz, 2 H, *Bz*), 5.73 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1 H, C*H*=CH_2), 5.68 (ddd, *J* = 9.0, 6.1, 3.9 Hz, 1 H, C*H*-OBz), 5.39–5.32 (m, 2 H, CH=CH_2), 4.71 (AB q, *J* = 7.2 Hz, Δν = 31 Hz, 2 H, O-CH_2-O), 4.36 (dd, *J* = 7.0, 5.9 Hz, 1 H, C*H*-OMEM), 4.22–3.69 (m, 4 H, O-CH_2CH_2-OH), 3.68–3.41 (m, 4 H, O-CH_2CH_2-OMe), 3.33 (s, 3 H, O*Me*), 2.84 (dd, *J* = 16.1, 3.9 Hz, 1 H, C*H*H), 2.75 (dd, *J* = 16.1, 9.0 Hz, 1 H, CH*H*), 2.57 (b s, 1 H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 166.1, 133.3, 133.0, 129.7, 129.5, 128.4, 120.7, 93.0, 71.7, 71.6, 67.2, 66.5, 60.7, 60.7, 59.0, 36.0; FAB HRMS (NBA/CsI) *m/e* 515.0682, M + Cs^+ calcd for $C_{19}H_{26}O_8$ 515.0682.

(3a*S*,4*R*,5*R*)-5-Hydroxy-3,3a,4,5,6,7-hexahydro-4-[(2-methoxyethoxy)methoxy]spiro[2,1-benzisoxazole-7,2′-[1,3]dioxolane] (31). A solution of **24** (17.1 g, 42.0 mmol) in anhydrous methanol (330 mL) at 0 °C was treated with sodium methoxide (*ca.* 500 mg, catalytic) and stirred at 0 °C for 12 h. The solution was poured into brine (300 mL) and extracted with dichloromethane (3 × 300 mL); the organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (ether) to give **31** (12.7 g, 100%) as a white solid: mp = 55–56 °C (from Et_2O); R_f = 0.13 (Et_2O); $[\alpha]^{25}_D$ –69.1° (*c* 1.1, CH_2Cl_2); IR (thin film) ν_{max} 3440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (AB q, *J* = 7.4 Hz, $\Delta\nu$ = 52 Hz, 2 H, O-C*H*$_2$-O), 4.58 (dd, *J* = 11.0, 8.5 Hz, 1 H, C*H*H-O-N), 4.18 (dddd, *J* = 11.9, 6.8, 4.8, 2.4 Hz, 1 H, C*H*-OH), 4.17 (dd, *J* = 8.5, 8.5 Hz, 1 H, CH*H*-O-N), 4.12 (d, *J* = 2.4 Hz, 1 H, O*H*), 4.05 (m, 2 H, *ethylene ketal*), 3.89 (ddd, *J* = 11.0, 8.5, 7.3 Hz, 1 H, C*H*-C=N), 3.89 (dd, *J* = 7.3, 6.8 Hz, 1 H, C*H*-OMEM), 3.78 (m, 1 H, *ethylene ketal*), 3.69 (m, 1 H, *ethylene ketal*), 3.53 (m, 2 H, O-CH$_2$C*H*$_2$-OMe), 3.48 (m, 1 H, O-C*H*HCH$_2$-OMe), 3.36 (s, 3 H, O*Me*), 3.31 (m, 1 H, O-CH*H*CH$_2$-OMe), 2.27 (dd, *J* = 13.8, 4.8 Hz, 1 H, C*H*H), 1.95 (dd, *J* = 13.8, 11.9 Hz, 1 H, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 103.9, 96.4, 87.9, 73.8, 71.3, 70.0, 67.9, 65.7, 64.6, 59.0, 51.3, 40.9; FAB HRMS (NBA) *m/e* 304.1371, M + H$^+$ calcd for $C_{13}H_{21}NO_7$ 304.1396.

(3a*S*,4*R*,5*R*)-3,3a,4,5,6,7-Hexahydro-4-[(2-methoxyethoxy)methoxy]-spiro[2,1-benzisoxazole-7,2′-[1,3]dioxolan]-5-one (34). A solution of **31** (7.67 g, 25.3 mmol) in acetone (200 mL) was cooled to 0 °C and treated with Jones reagent (19.0 mL of a 2.0 M solution, 1.5 equiv). The mixture was stirred at 0 °C for 12 h, the reaction was quenched with excess isopropyl alcohol, and the mixture was poured into brine (300 mL) and extracted with dichloromethane (3 × 300 mL). The organic extracts were dried (Na_2SO_4) and concentrated to give ketone **34** (7.24 g, 95%) as a white solid: mp = 80–82 °C (from Et_2O); R_f = 0.28 (Et_2O); $[\alpha]^{25}_D$ +42.6° (*c* 0.44, CH_2Cl_2); IR (thin film) ν_{max} 1735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (AB q, *J* = 7.6 Hz, $\Delta\nu$ = 33 Hz, 2 H, O-C*H*$_2$-O), 4.68 (dd, 1 H, *J* = 10.6, 8.3 Hz, 1 H, C*H*H-O-N), 4.40 (dd, *J* = 8.3, 8.3 Hz, 1 H, CH*H*-O-N), 4.33 (d, *J* = 11.4 Hz, 1 H, C*H*-OMEM), 4.23 (m, 1 H, *ethylene ketal*), 4.10 (m, 1 H, *ethylene ketal*), 3.93 (m, 1 H, *ethylene ketal*), 3.78 (ddd, *J* = 11.4, 10.6, 8.3 Hz, 1 H, C*H*-C=N), 3.65 (m, 2 H, O-C*H*$_2$CH$_2$-OMe), 3.52 (m, 2 H, O-CH$_2$C*H*$_2$-OMe), 3.38 (s, 3 H, O*Me*), 2.93 (AB q, *J* = 14.4 Hz, $\Delta\nu$ = 112 Hz, 1 H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 154.8, 103.0, 94.8, 80.6, 74.1, 71.4, 67.8, 66.1, 65.0, 59.1, 50.9, 49.8; FAB HRMS (NBA) *m/e* 302.1251, M + H$^+$ calcd for $C_{13}H_{19}NO_7$ 302.1240.

(3a*S*,4*R*,5*R*)-5-Acetoxy-3,3a,4,5,6,7-hexahydro-4-[(2-methoxyethoxy)methoxy]-5-[2-(trimethylsilyl)ethynyl]spiro[2,1-benzisoxazole-7,2′-[1,3]-dioxolane] (36). A solution of (trimethylsilyl)acetylene (6.8 mL, 48.2 mmol) in THF (30 mL) was treated at 0 °C with *n*-butyllithium (14.5 mL of a 2.5 M solution in hexanes, 36.2 mmol). This solution was added dropwise to a solution of **34** (7.24 g, 24.1 mmol) in THF (150 mL) at –78 °C. After 30 min at –78 °C, acetic anhydride (11.4 mL, 120 mmol) was added, the cooling bath was removed, and the solution was stirred at 25 °C for 3 h. The solution was poured into brine (200 mL) and extracted with dichloromethane (3 × 300 mL); the organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (70% ether in petroleum ether) to give **36** (7.14 g, 67%) as a white solid: mp = 154.5–155.0 °C (from Et_2O); R_f = 0.35 (70% Et_2O) in petroleum ether); $[\alpha]^{25}_D$ +1.0° (*c* 1.4, CH_2Cl_2); IR (thin film) ν_{max} 1751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (AB q, *J* = 7.6 Hz, $\Delta\nu$ = 194 Hz, 2 H, O-C*H*$_2$-O), 4.61 (dd, *J* = 10.6, 8.1 Hz, 1 H, C*H*H-O-N), 4.29 (dd, *J* = 10.6, 8.2 Hz, 1 H, CH*H*-O-N), 4.11 (m, 1 H, *ethylene ketal*), 4.00 (m, 1 H, *ethylene ketal*), 3.93–3.85 (m, 3 H, *ethylene ketal* (2 H), O-C*H*HCH$_2$-OMe), 3.79 (ddd, *J* = 10.1, 8.2, 8.1 Hz, 1 H, C*H*-C=N), 3.72 (d, *J* = 10.1 Hz, 1 H, C*H*-OMEM), 3.58–3.51 (m, 3 H, O-CH*H*CH$_2$-OMe), 3.37 (s, 3 H, O*Me*), 3.33 (d, *J* = 15.5 Hz, 1 H, C*H*H), 2.11 (d, *J* = 15.5 Hz, 1 H, CH*H*), 2.06 (s, 3 H, O*Ac*), 0.12 (s, 9 H, Si*Me*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 154.9, 101.9, 101.0, 97.1, 92.0, 84.1, 75.0, 73.2, 71.3, 67.9, 65.1, 65.0, 59.1, 49.8, 40.8, 21.9, –0.4; FAB HRMS (NBA/CsI) *m/e* 574.0879, M + Cs$^+$ calcd for $C_{20}H_{31}NO_8Si$ 574.0873.

(5*R*)-5-Acetoxy-4,5,6,7-tetrahydro-5-[2-(trimethylsilyl)ethynyl]spiro-[2,1-benzisoxazole-7,2′-[1,3]dioxolan]-4-one (41). A solution of **36** (7.14 g, 16.2 mmol) in anhydrous dichloromethane (200 mL) was treated with zinc bromide (36.4 g, 162 mmol), and the mixture was stirred at 25 °C for 12 h. The mixture was poured into brine (200 mL) and extracted with dichloromethane (3 × 200 mL), the organic extracts were dried (Na_2SO_4) and concentrated, and the residue was rapidly filtered through a short plug of silica gel, eluting with ether to give the sensitive crude alcohol **39** (5.91 g).

A solution of oxalyl chloride (5.7 mL, 65.5 mmol) in dichloromethane (40 mL) at –78 °C was treated with a solution of DMSO (9.3 mL, 131 mmol) in dichloromethane (40 mL) at –78 °C. The solution was stirred for 30 min, and then the above crude alcohol **39** in dichloromethane (40 mL) was added dropwise. The solution was stirred for 30 min at –78 °C, and then Et_3N (36.4 mL, 260 mmol) was added. The solution was stirred for 30 min at –78 °C and then allowed to warm up to –20 °C. The solution was poured into brine (200 mL) and extracted with dichloromethane (3 × 200 mL), the organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (30% ether in petroleum ether) to give isoxazole **41** (3.07 g, 54%) as a white solid: mp = 132–133 °C dec (from Et_2O); R_f = 0.36 (30% Et_2O in petroleum ether); $[\alpha]^{25}_D$ +26.8° (*c* 2.3, CH_2Cl_2); IR (thin film) ν_{max} 1747, 1722, 1581 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1 H, C=C*H*-O), 4.36 (m, 1 H, *ethylene ketal*), 4.23 (m, 2 H, *ethylene ketal*), 4.11 (m, 1 H, *ethylene ketal*), 3.44 (d, *J* = 13.8 Hz, 1 H, C*H*H), 2.63 (d, *J* = 13.8 Hz, 1 H, CH*H*), 2.14 (s, 3 H, O*Ac*), 0.14 (s, 9 H, Si*Me*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.7, 169.2, 162.0, 161.5, 115.6, 100.6, 97.8, 97.3, 77.1, 65.2, 64.9, 43.6, 21.1, –0.8; FAB HRMS (NBA) *m/e* 350.1065, M + H$^+$ calcd for $C_{16}H_{19}NO_6Si$ 350.1060.

(*E*)-2-[(5*R*)-5-Acetoxy-4,5,6,7-tetrahydro-5-[2-(trimethylsilyl)ethynyl]-spiro[2,1-benzisoxazole-7,2′-[1,3]dioxolan]-4-ylidene]acetic Acid, Methyl Ester (48). A solution of **41** (3.02 g, 8.65 mmol) in toluene (80 mL) was treated with methyl (triphenylphosphoranylidene)acetate (14.5 g, 43.3 mmol) and stirred at 90 °C for 16 h. The solution was concentrated, and the residue was purified by flash chromatography (30% ether in petroleum ether) to give **48** (2.94 g, 84%) as a colorless oil: R_f = 0.41 (30% Et_2O in petroleum ether); $[\alpha]^{25}_D$ +29.7° (*c* 2.7, CH_2Cl_2); IR (thin film) ν_{max} 1759, 1722, 1644, 1581 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1 H, C=C*H*-O), 6.86 (s, 1 H, C=C*H*-CO$_2$), 4.30 (m, 2 H, *ethylene ketal*), 4.15–4.07 (m, 2 H, *ethylene ketal*), 3.78 (s, 3 H, CO$_2$*Me*), 3.39 (d, *J* = 13.9 Hz, 1 H, C*H*H), 2.53 (d, *J* = 13.9 Hz, 1 H, CH*H*), 1.92 (s, 3 H, O*Ac*), 0.21 (s, 9 H, Si*Me*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 166.1, 161.6, 160.3, 138.4, 119.2, 111.4, 100.3, 99.6, 96.3, 76.0, 65.3, 64.8, 51.8, 44.1, 21.7, –0.4; FAB HRMS (NBA/CsI) *m/e* 538.0298, M + Cs$^+$ calcd for $C_{19}H_{23}NO_7Si$ 538.0298.

(*E*)-2-[(5*R*)-5-Ethynyl-4,5,6,7-tetrahydro-5-hydroxyspiro[2,1-benz-isoxazole-7,2′-[1,3]dioxolan]-4-ylidene]acetic Acid, Methyl Ester (65). A solution of **48** (2.94 g, 7.26 mmol) in dichloromethane–methanol (1:1, 40 mL) was treated with anhydrous potassium carbonate (1.00 g, 7.26 mmol) and stirred at 0 °C for 6 h. The solution was poured into brine (100 mL) and extracted with dichloromethane (3 × 100 mL). The organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (ether) to give **65** (1.68 g, 90%) as a white foam: R_f = 0.32 (50% Et_2O in petroleum ether); $[\alpha]^{25}_D$ +14.8° (*c* 3.3, CH_2Cl_2); IR (thin film) ν_{max} 3444, 3285, 2117, 1717, 1642, 1582 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1 H, C=C*H*-O), 6.80 (s, 1 H, C=C*H*-CO$_2$), 4.43 (m, 1 H, *ethylene ketal*), 4.33 (m, 1 H, *ethylene ketal*), 4.24 (m, 1 H, *ethylene ketal*), 4.17 (m, 1 H, *ethylene ketal*), 3.78 (s, 3 H, CO$_2$*Me*), 3.68 (s, 1 H, O*H*), 2.79 (s, 1 H, C≡C-*H*), 2.73 (s, 2 H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 162.3, 159.6, 141.4, 117.0, 111.3, 100.4, 82.8, 76.2, 71.1, 65.3, 65.2, 51.8, 47.1; FAB HRMS (NBA/CsI) *m/e* 423.9797, M + Cs$^+$ calcd for $C_{14}H_{13}NO_6$ 423.9797.

(*E*)-2-[(5*R*)-5-Ethynyl-4,5,6,7-tetrahydro-5-[(triethylsilyl)oxy]spiro-[2,1-benzisoxazole-7,2′-[1,3]dioxolan]-4-ylidene]acetic Acid, Methyl Ester (66). A solution of **65** (1.657 g, 5.69 mmol) in dichloromethane (10 mL) was treated with 2,6-lutidine (2.00 mL, 17.1 mmol) and triethylsilyl trifluoromethanesulfonate (2.58 mL, 11.4 mmol) at 0 °C. The solution was stirred for 30 min, anhydrous methanol (2 mL) was added, and the mixture was poured into brine (50 L) and extracted with dichloromethane (3 × 50 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (20% Et_2O in petroleum ether) to give **66** (2.204 g, 96%) as a white solid: mp = 108–109 °C (from CH_2Cl_2); R_f = 0.43 (30% Et_2O in petroleum ether); $[\alpha]^{25}_D$ –15.4° (*c* 2.8, CH_2Cl_2); IR (thin film) ν_{max} 3307, 2116, 1721, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1 H, C=C*H*-O), 6.57 (s, 1 H, C=C*H*-CO$_2$), 4.38–4.31 (m, 2 H, *ethylene ketal*), 4.18–4.10 (m, 2 H, *ethylene ketal*), 3.74 (s, 3 H, CO$_2$*Me*), 2.66 (s, 1 H, C≡C-*H*), 2.61 (AB q, *J* = 14.0 Hz, $\Delta\nu$ = 34 Hz, 2 H, C*H*$_2$), 0.92 (t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 0.70 (q, *J* = 7.9 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 161.3, 160.7, 143.8, 114.5, 111.9, 100.6, 83.2, 76.9, 70.9, 65.0, 64.8, 51.6, 49.8, 6.8, 5.9; FAB HRMS (NBA/CsI) *m/e* 538.0652, M + Cs$^+$ calcd for $C_{20}H_{27}NO_6Si$ 538.0662.

(*E*)-2-[(5*R*)-4,5,6,7-Tetrahydro-5-[(triethylsilyl)oxy]-5-[(3*Z*)-6-(tri-

methylsilyl)-3-hexene-1,5-diynyl]spiro[2,1-benzisoxazole-7,2′-[1,3]dioxolan]-4-ylidene]acetic Acid, Methyl Ester (67). (*Z*)-(4-Chloro-3-buten-1-ynyl)trimethylsilane (**52**) (1.41 mL, 8.16 mmol) and *n*-butylamine (0.81 mL, 8.16 mmol) were added to a solution of $Pd(PPh_3)_4$ (628 mg, 0.54 mmol) in benzene (25 mL). The solution was stirred at 25 °C for 15 min and then added to a mixture of **66** (2.204 g, 5.44 mmol) and CuI (207 mg, 1.09 mmol) in benzene (25 mL) at 0 °C. The solution was stirred for 2 h at 0 °C, poured into brine (100 mL), and extracted with dichloromethane (3 × 100 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (10% Et_2O in petroleum ether) to give **67** (2.606 g, 91%) as a colorless oil: R_f = 0.46 (30% Et_2O in petroleum ether); $[\alpha]^{25}_D$ +17.4° (*c* 2.7, CH_2Cl_2); IR (thin film) ν_{max} 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1 H, C=C*H*-O), 6.65 (s, 1 H, C=C*H*-CO_2), 5.86 (AB q, *J* = 11.0 Hz, Δν = 30 Hz, 2 H, C*H*=C*H*), 4.38–4.29 (m, 2 H, *ethylene ketal*), 4.15–4.09 (m, 2 H, *ethylene ketal*), 3.74 (s, 3 H, CO_2Me), 2.67 (AB q, *J* = 14.1 Hz, Δν = 61 Hz, 2 H, CH_2), 0.89 (t, *J* = 7.3 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.66 (m, 6 H, Si(CH_2CH_3)$_3$), 0.17 (s, 9 H, SiMe_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 161.2, 161.0, 143.7, 121.2, 118.6, 114.9, 112.0, 103.5, 101.3, 100.7, 95.5, 85.7, 72.1, 65.0, 64.6, 51.5, 50.0, 6.8, 5.9, –0.4; FAB HRMS (NBA/CsI) *m/e* 660.1213, M + Cs^+ calcd for $C_{27}H_{37}NO_6Si_2$ 660.1214.

(*E*)-2-[(9*R*)-6-Amino-7-formyl-9-[(triethylsilyl)oxy]-9-[(3*Z*)-6-(trimethylsilyl)-3-hexene-1,5-diynyl]-1,4-dioxaspiro[4.5]dec-6-en]-8-ylidene]acetic Acid, Methyl Ester (68). A solution of **67** (2.588 g, 4.91 mmol) in acetonitrile–water (10 mL, 5:1) was treated with molybdenum hexacarbonyl (1.30 g, 4.91 mmol) and heated to 80 °C for 90 min. Silica gel (20 g) was added, and the mixture was evaporated to dryness. The powder was applied to the top of a flash column and eluted with 50% Et_2O in petroleum ether → Et_2O to give **68** (1.962 g, 82%) as a colorless oil: R_f = 0.41 (Et_2O); $[\alpha]^{25}_D$ +4.9° (*c* 2.8, CH_2Cl_2); IR (thin film) ν_{max} 3381, 3280, 3195, 1704, 1643, 1597 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1 H, C*H*O), 6.25 (s, 1 H, C=C*H*-CO_2), 5.84 (AB q, *J* = 10.9 Hz, Δν = 30 Hz, 2 H, C*H*=C*H*), 4.09–4.02 (m, 4 H, *ethylene ketal*), 3.68 (s, 3 H, CO_2Me), 2.45 (AB q, *J* = 14.2 Hz, Δν = 42 Hz, 2 H, CH_2), 0.93 (t, *J* = 8.0 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.68 (q, *J* = 8.0 Hz, 6 H, Si(CH_2CH_3)$_3$), 0.19 (s, 9 H, SiMe_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 167.7, 158.3, 153.1, 120.8, 118.9, 109.8, 103.2, 103.2, 102.2, 101.5, 97.8, 83.7, 70.6, 65.5, 65.4, 51.2, 49.7, 7.0, 5.9, –0.3; FAB HRMS (NBA/CsI) *m/e* 662.1370, M + Cs^+ calcd for $C_{27}H_{39}NO_6Si_2$ 662.1370.

(*E*)-2-[(9*R*)-6-Amino-7-formyl-9-[(3*Z*)-3-hexene-1,5-diynyl]-9-[(triethylsilyl)oxy]-1,4-dioxaspiro[4.5]dec-6-en]-8-ylidene]acetic Acid, Methyl Ester (69). A solution of **68** (1.962 g, 3.71 mmol) in methanol–THF (60 mL, 2:1) was treated with anhydrous potassium carbonate (510 mg, 3.71 mmol) and stirred at 0 °C for 2 h. The solution was poured into brine (100 mL) and extracted with dichloromethane (3 × 100 mL); the organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (ether) to give **69** (1.567 g, 92%) as a white solid: mp = 109–110 °C (from Et_2O); R_f = 0.33 (Et_2O); $[\alpha]^{25}_D$ –29.9° (*c* 2.5, $CDCl_3$); IR (thin film) ν_{max} 3404, 3281, 3195, 1707, 1647, 1604 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (b s, 1 H, N*H*), 9.20 (s, 1 H, C*H*O), 6.29 (s, 1 H, C=C*H*-CO_2), 5.88 (d, *J* = 10.4 Hz, 1 H, C*H*=CH), 5.85 (b s, 1 H, N*H*), 5.81 (dd, *J* = 10.4, 2.4 Hz, 1 H, CH=C*H*), 4.09–4.01 (m, 4 H, *ethylene ketal*), 3.68 (s, 3 H, CO_2Me), 3.33 (d, *J* = 2.4 Hz, 1 H, C≡C-*H*), 2.42 (AB q, *J* = 13.9 Hz, Δν = 74 Hz, 2 H, CH_2), 0.93 (t, *J* = 7.6 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.69 (q, *J* = 7.6 Hz, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 167.9, 158.1, 153.0, 120.5, 119.8, 109.8, 103.2, 102.5, 98.0, 85.4, 83.2, 80.4, 70.5, 65.5, 65.4, 51.2, 49.5, 6.9, 5.8; FAB HRMS (NBA/CsI) *m/e* 590.0975, M + Cs^+ calcd for $C_{24}H_{31}NO_6Si$ 590.0975.

(*E*)-2-[(9*R*)-7-Formyl-9-[(3*Z*)-3-hexene-1,5-diynyl]-6-phthalimido-9-[(triethylsilyl)oxy]-1,4-dioxaspiro[4.5]dec-6-en]-8-ylidene]acetic Acid, Methyl Ester (71). A solution of **69** (1.543 g, 3.38 mmol) in nitromethane (130 mL) at 0 °C was treated with pyridine (1.09 mL, 13.5 mmol) followed by the dropwise addition of phthaloyl chloride (0.68 mL, 4.73 mmol) in nitromethane (10 mL) over 15 min. The solution was stirred at 0 °C for 30 min, poured into brine (200 mL), and extracted with dichloromethane (3 × 200 mL). The extracts were dried (Na_2SO_4), concentrated, azeotroped with toluene, and dissolved in dichloromethane (100 mL). Silica gel (*ca.* 20 g) was added and the mixture stirred at 20 °C for 2 h. The slurry was then concentrated to dryness and washed with 15% MeOH in EtOAc. The filtrate was dissolved in nitromethane (30 mL) and treated with Ac_2O (2.84 mL, 30 mmol). After being stirred for 1 h at 25 °C, the solution was concentrated and azeotroped with toluene (3 times) and the residue was dissolved in dichloromethane (100 mL). Silica gel (*ca.* 20 g) was added, and the slurry was stirred for 2 h at 25 °C and concentrated to dryness. The resulting powder was applied to the top of a flash column and eluted with 20% Et_2O in petroleum ether → 50% Et_2O in petroleum ether → 10% MeOH in EtOAc to give **71** (1.27 g) followed by the phthalamic acid (430 mg).

The phthalamic acid was azeotroped with benzene and dissolved in nitromethane (5 mL), and acetic anhydride (1 mL) was added. The solution was stirred for 1 h at 25 °C and worked up as above to give an additional 280 mg of **71** followed by the phthalamic acid (80 mg). Combined yield of **71** = 1.55 g (78%).

Data for **71**: white foam; R_f = 0.38 (70% Et_2O in petroleum ether); $[\alpha]^{25}_D$ +2.9° (*c* 3.2, $CDCl_3$); IR (thin film) ν_{max} 3296, 3274, 1733, 1716 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1 H, C*H*O), 7.92–7.87 (m, 2 H, *phth*), 7.75 (m, 2 H, *phth*), 6.63 (s, 1 H, C=C*H*-CO_2), 6.07 (d, *J* = 11.1 Hz, 1 H, C*H*=CH), 5.87 (dd, *J* = 11.1, 2.3 Hz, 1 H, CH=C*H*), 3.94–3.89 (m, 2 H, *ethylene ketal*), 3.84–3.75 (m, 2 H, *ethylene ketal*), 3.68 (s, 3 H, CO_2Me), 3.31 (d, *J* = 2.3 Hz, 1 H, C≡C-*H*), 2.54 (AB q, *J* = 13.5 Hz, Δν = 52 Hz, 2 H, CH_2), 0.98 (t, *J* = 7.6 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.78 (m, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 166.4, 166.3, 166.2, 148.0, 137.5, 136.8, 134.3, 134.3, 132.0, 132.0, 124.0, 123.9, 120.6, 119.6, 117.8, 105.3, 95.4, 85.3, 85.2, 80.7, 71.0, 71.0, 65.7, 65.7, 7.0, 5.9; FAB HRMS (NBA/CsI) *m/e* 720.1060, M + Cs^+ calcd for $C_{32}H_{33}NO_8Si$ 720.1030.

(*E*)-2-[(1*R*,8*R*)-8-Hydroxy-10-phthalimido-1-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-13-ylidene]acetic Acid, Methyl Ester (72). A solution of **71** (1.55 g, 2.64 mmol) in toluene (350 mL) was cooled in a methanol–dry ice–liquid nitrogen bath to just above the freezing point of the reaction mixture (*ca.* –90 °C), and KHMDS (2.90 mL of a freshly prepared 1.0 M solution in THF, 2.90 mmol) was added dropwise. The solution was stirred for 5 min and then quenched at –90 °C with acetic acid (8.7 mL of a 1.0 M solution in toluene). The mixture was poured into brine (300 mL) and extracted, and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (50 → 70% ether in petroleum ether) to give an inseparable 9:1 mixture of **72** and **76** (748 mg, 48%) as a white solid. **72**: mp > 200 °C dec (from CH_2Cl_2); R_f = 0.32 (70% Et_2O in petroleum ether); $[\alpha]^{25}_D$ –235° (*c* 2.4, CH_2Cl_2); IR (thin film) ν_{max} 3495, 1721 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2 H, *phth*), 7.70–7.68 (m, 2 H, *phth*), 6.26 (s, 1 H, C=C*H*-CO_2), 6.00 (dd, *J* = 9.6, 1.1 Hz, 1 H, C*H*=CH), 5.88 (dd, *J* = 9.6, 0.8 Hz, 1 H, CH=C*H*), 5.39 (b s, 1 H, C*H*-OH), 3.87–3.69 (m, 4 H, *ethylene ketal*), 3.77 (s, 3 H, CO_2Me), 3.21 (b s, 1 H, O*H*), 2.58 (AB q, *J* = 13.5 Hz, Δν = 300 Hz, 2 H, CH_2), 0.99 (t, *J* = 7.4 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.79–0.72 (m, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.1, 166.0, 156.2, 148.8, 133.9, 133.7, 132.3, 132.2, 131.1, 123.7, 123.7, 122.9, 122.7, 113.6, 105.3, 98.9, 98.5, 91.2, 86.3, 71.3, 66.0, 65.2, 64.9, 52.8, 52.1, 7.1, 5.9; FAB HRMS (NBA/CsI) *m/e* 720.1032, M + Cs^+ calcd for $C_{32}H_{33}NO_8Si$ 720.1030.

(1′*S*,5′*R*)-5′,6′-Dihydro-8′-phthalimido-5′-[(triethylsilyl)oxy]spiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-3′-one (76). A solution of **72** (686 mg, 1.17 mmol) in CH_2Cl_2 (15 mL) was treated with pyridine (1.90 mL, 26 mmol), methanesulfonyl chloride (0.89 mL, 11.5 mmol), and DMAP (20 mg, catalytic) at 0 °C. The solution was stirred at 0 °C for 2 h, poured into brine (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography, eluting with ether to give mesylate **75** as a white solid.

Mesylate **75** was dissolved in benzene (100 mL), and pyridine (0.19 mL, 2.6 mmol) followed by silica gel (4 g) was added. The suspension was stirred for 5 h at 25 °C, concentrated to give a powder, applied to the top of a flash chromatography column, and eluted with ether to give pure lactone **76** (585 mg, 90%) as a white foam: R_f = 0.43 (20% EtOAc in PhH); $[\alpha]^{25}_D$ –406° (*c* 0.82, CH_2Cl_2); IR (thin film) ν_{max} 1730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2 H, *phth*), 7.80–7.78 (m, 2 H, *phth*), 6.26 (s, 1 H, C=C*H*-CO_2), 6.06 (d, *J* = 9.7 Hz, 1 H, C*H*=CH), 5.90 (dd, *J* = 9.7, 1.6 Hz, 1 H, CH=C*H*), 5.73 (d, *J* = 1.6 Hz, 1 H, C≡C-C*H*O), 3.96–3.86 (m, 3 H, *ethylene ketal*), 3.58–3.54 (m, 1 H, *ethylene ketal*), 2.51 (AB q, *J* = 13.2 Hz, Δν = 24 Hz, 2 H, CH_2), 1.01 (t, *J* = 8.5 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.85–0.70 (m, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 165.7, 161.7, 153.1, 134.7, 134.6, 131.7, 131.6, 125.8, 125.4, 124.2, 124.1, 123.1, 111.7, 105.7, 98.8, 94.9, 91.6, 90.8, 69.5, 68.0, 65.6, 65.4, 46.4, 6.9, 5.9; FAB HRMS (NBA/CsI) *m/e* 688.0768, M + Cs^+ calcd for $C_{31}H_{29}NO_7Si$ 688.0768.

(1′*S*,5′*R*)-8′-Amino-5′,6′-dihydro-5′-[(triethylsilyl)oxy]spiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-3′-one (77), A solution of **76** (585 mg, 1.054 mmol) in benzene (50 mL) was treated

with methylhydrazine (0.70 mL, 13 mmol) and stirred for 30 min at 25 °C. The reaction mixture was concentrated and purified by flash chromatography (Et_2O) to give vinylogous urethane **77** (443 mg, 99%) as a yellow solid: mp = 118–120 °C dec (from CH_2Cl_2); R_f = 0.11 (20% EtOAc in PhH); $[\alpha]^{25}_D$ –654° (*c* 0.29, CH_2Cl_2); IR (thin film) ν_{max} 3425, 3342, 3237 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.41 (s, 1 H, C=C*H*-CO_2), 5.53 (b s, 1 H, N*H*), 5.44 (d, *J* = 1.7 Hz, 1 H, C*H*-C≡C), 5.28 (d, *J* = 9.6 Hz, 1 H, C*H*=CH), 5.15 (dd, *J* = 9.6, 1.7 Hz, 1 H, CH=C*H*), 4.39 (b s, 1 H, N*H*), 3.42–3.23 (m, 4 H, *ethylene ketal*), 2.37 (AB q, *J* = 13.0 Hz, $\Delta\nu$ = 57 Hz, 2 H, CH_2), 1.04 (t, *J* = 8.6 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.86–0.72 (m, 6 H, Si(CH_2CH_3)$_3$); FAB HRMS (NBA/CsI) *m/e* 558.0713, M + Cs^+ calcd for $C_{23}H_{27}NO_5Si$ 558.0713.

Methyl[(1′*S*,5′*R*)-5′,6′-Dihydro-3′-oxo-5′-[(triethylsilyl)oxy]spiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-8′-yl]carbamate (78). A solution of **77** (443 mg, 1.042 mmol) in CH_2Cl_2 (50 mL) at 0 °C was treated with pyridine (1.30 mL, 16.1 mmol) and triphosgene (936 mg, 3.22 mmol) and stirred at 25 °C for 40 min. The solution was then cooled to 0 °C, treated with pyridine (1.30 mL, 16.1 mmol) and MeOH (9.2 mL, excess), and stirred at 0 °C for 30 min. The solution was poured into brine (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (70% Et_2O in petroleum ether) to give carbamate **78** (414 mg, 82%) as a white foam: R_f = 0.39 (Et_2O); $[\alpha]^{25}_D$ –550° (*c* 2.9, CH_2Cl_2); IR (thin film) ν_{max} 3293, 1728, 1669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (s, 1 H, C=C*H*-CO_2), 6.09 (b s, 1 H, C*H*-C≡C), 5.98 (b s, 1 H, N*H*), 5.91 (d, *J* = 9.6 Hz, 1 H, C*H*=CH), 5.81 (dd, *J* = 9.6, 1.8 Hz, 1 H, C*H*=CH), 4.20–3.91 (m, 4 H, *ethylene ketal*), 3.73 (s, 3 H, CO_2Me), 2.34 (AB q, *J* = 13.5 Hz, $\Delta\nu$ = 102 Hz, 2 H, CH_2), 0.98 (t, *J* = 9.4 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.80–0.66 (m, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 154.4, 154.1, 128.1, 124.7, 124.7, 123.4, 110.8, 104.7, 99.2, 96.3, 90.7, 87.9, 69.2, 68.7, 65.9, 65.3, 53.3, 45.4, 6.9, 5.9; FAB HRMS (NBA/CsI) *m/e* 616.0760, M + Cs^+ calcd for $C_{25}H_{29}NO_7Si$ 616.0768.

Methyl[(1′*S*,5′*R*)-5′,6′-Dihydro-3′-hydroxy-5′-[(triethylsilyl)oxy]spiro-[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-8′-yl]carbamate (79a,b). A solution of **78** (57.0 mg, 0.118 mmol) in CH_2Cl_2 (5 mL) at –78 °C was treated with DIBAL (0.35 mL of a 1.0 M solution in CH_2Cl_2, 0.35 mmol) and stirred at –78 °C for 30 min. The reaction was quenched at –78 °C with MeOH (0.5 mL added dropwise), the cooling bath was removed, the reaction mixture was diluted with EtOAc (10 mL), and saturated aqueous Rochelle salt (10 mL) was added. The mixture was stirred vigorously for 30 min until the two phases became clear, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (Et_2O) to give lactols **79a,b** (54.4 mg, 95%) as a white solid consisting of a 4:1 mixture of 3′-epimers: mp = 90–102 °C (from PhH); R_f = 0.34 (Et_2O); $[\alpha]^{25}_D$ –477° (*c* 0.69, CH_2Cl_2); IR (thin film) ν_{max} 3400, 3315, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04–5.51 (m, 6 H), 4.17–3.87 (m, 4 H, *ethylene ketal*), 3.71 (s, 3 H, CO_2Me), 3.20 (b s, 1 H, O*H*), 2.42–2.23 (m, 2 H, CH_2), 1.01–0.97 (m, 9 H, Si(CH_2CH_3)$_3$), 0.81–0.68 (m, 6 H, Si(CH_2CH_3)$_3$); FAB HRMS (NBA/CsI) *m/e* 618.0930, M + Cs^+ calcd for $C_{25}H_{31}NO_7Si$ 618.0924.

Methyl [(1*R*,8*S*,13*E*)-8-Hydroxy-13-(2-hydroxyethylidene)-1-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]-dioxolan]-10-yl]carbamate (80). A solution of lactols **79a,b** (54.4 mg, 0.112 mmol) in MeOH (3 mL) was treated at 0 °C with $NaBH_4$ (64 mg, 1.7 mmol) and stirred at 0 °C until complete consumption of **79a,b** had occurred (*ca.* 2 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 then concentrated. THF (1 mL), MeOH (2 mL), and H_2O (2 drops) were added to the residue, and the solution was stirred for 15 min. The mixture was poured into saturated sodium bicarbonate solution (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (Et_2O) to give diol **80** (48.2 mg, 88%) as a colorless oil: R_f = 0.16 (Et_2O); $[\alpha]^{25}_D$ –221° (*c* 1.7, CH_2Cl_2); IR (thin film) ν_{max} 3362 (b s), 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.41 (b s, 1 H, N*H*), 6.28 (dd, *J* = 7.6, 6.4 Hz, 1 H, C=C*H*-CH_2), 5.85 (d, *J* = 9.5 Hz, 1 H, C*H*=CH), 5.79 (dd, *J* = 9.5, 1.5 Hz, 1 H, CH=C*H*), 5.67 (b s, 1 H, C*H*-C≡C), 4.63 (b s, 1 H, O*H*), 4.28 (dd, *J* = 13.7, 7.6 Hz, 1 H, C*H*H-OH), 4.19 (dd, *J* = 13.7, 6.4 Hz, 1 H, CH*H*-OH), 3.99–3.87 (m, 4 H, *ethylene ketal*), 3.73 (s, 3 H, CO_2Me), 2.33 (AB q, *J* = 13.6 Hz, $\Delta\nu$ = 173 Hz, CH_2), 0.97 (t, *J* = 7.8 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.80–0.68 (m, 6 H, Si(CH_2CH_3)$_3$); FAB HRMS (NBA/CsI) *m/e* 620.1086, M + Cs^+ calcd for $C_{25}H_{33}NO_7Si$ 620.1081.

Methyl [(1*R*,8*S*,13*E*)-1,8-Bis[(triethylsilyl)oxy]-13-[2-(trimethylacetoxy)ethylidene]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (81). A solution of diol **80** (48.2 mg, 99.0 μmol) in CH_2Cl_2 (1 mL) was treated at 25 °C with pyridine (120 μL, 1.5 mmol) and pivaloyl chloride (36 μL, 0.30 mmol) and stirred for 4 h. The solution was then cooled to 0 °C, and triethylsilyl trifluoromethanesulfonate (67 μL, 0.30 mmol) was added. The solution was stirred for 10 min, poured into brine (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (50% Et_2O in petroleum ether) to give **81** (45.2 mg, 67%) as a colorless oil: R_f = 0.21 (50% Et_2O in petroleum ether); $[\alpha]^{25}_D$ –162° (*c* 2.7, CH_2Cl_2); IR (thin film) ν_{max} 3334, 1737, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 8.9, 2.7 Hz, 1 H, C=C*H*-CH_2), 5.85 (b s, 1 H, N*H*), 5.85 (d, *J* = 9.5 Hz, 1 H, C*H*=CH), 5.76 (dd, *J* = 9.5, 1.7 Hz, 1 H, CH=C*H*), 5.75 (d, *J* = 1.7 Hz, 1 H, C*H*-C≡C), 4.96 (b d, *J* = 14.1 Hz, 1 H, C*H*H-OPiv), 4.58 (dd, *J* = 14.1, 8.9 Hz, CH*H*-OPiv), 4.10–3.82 (m, 4 H, *ethylene ketal*), 3.70 (s, 3 H, CO_2Me), 2.28 (AB q, *J* = 13.3 Hz, $\Delta\nu$ = 180 Hz, CH_2), 1.17 (s, 9 H, ^tBu), 0.96 (t, *J* = 7.7 Hz, 18 H, 2 × Si(CH_2CH_3)$_3$), 0.78–0.67 (m, 12 H, 2 × Si(CH_2CH_3)$_3$); FAB HRMS (NBA/CsI) *m/e* 818.2505, M + Cs^+ calcd for $C_{36}H_{55}NO_8Si_2$ 818.2521.

Methyl [(1*R*,8*S*,13*E*)-1,8-Bis[(triethylsilyl)oxy]-13-(2-hydroxyethylidene)spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (82). A solution of pivaloate **81** (45.2 mg, 66.0 μmol) in CH_2Cl_2 (3 mL) at –78 °C was treated with DIBAL (0.20 mL of a 1.0 M solution in CH_2Cl_2, 0.20 mmol) and stirred for 1 h. The reaction was quenched at –78 °C with MeOH (0.5 mL added dropwise), the cooling bath was removed, the reaction mixture was diluted with EtOAc (10 mL), and saturated aqueous Rochelle salt (10 mL) was added. The mixture was vigorously stirred for 30 min until the two phases became clear, poured into brine (15 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (70% Et_2O in petroleum ether) to give alcohol **82** (33.2 mg, 84%) as a colorless oil: R_f = 0.17 (70% Et_2O in petroleum ether); $[\alpha]^{25}_D$ –193° (*c* 1.8, CH_2Cl_2); IR (thin film) ν_{max} 3400, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (t, *J* = 6.6 Hz, 1 H, C=C*H*-CH_2), 5.90 (b s, 1 H, N*H*), 5.87 (d, *J* = 9.4 Hz, 1 H, C*H*=CH), 5.78 (b s, 1 H, C*H*-C≡C), 5.76 (dd, *J* = 9.4, 1.5 Hz, 1 H, CH=C*H*), 4.21 (t, *J* = 6.6 Hz, 2 H, CH_2-OH), 4.07–3.82 (m, 4 H, *ethylene ketal*), 3.70 (s, 3 H, CO_2Me), 2.29 (AB q, *J* = 13.5 Hz, $\Delta\nu$ = 195 Hz, 2 H, CH_2), 0.97 (t, *J* = 8.1 Hz, 18 H, 2 × Si(CH_2CH_3)$_3$), 0.79–0.68 (m, 12 H, 2 × Si(CH_2CH_3)$_3$); FAB HRMS (NBA/CsI) *m/e* 734.1945, M + Cs^+ calcd for $C_{31}H_{47}NO_7Si_2$ 734.1945.

Methyl [(1*R*,8*S*,13*E*)-13-[2-(Acetylthio)ethylidene]-1,8-bis[(triethylsilyl)-oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (83). A solution of triphenylphosphine (145 mg, 0.55 mmol) in THF (2 mL) at 0 °C was treated with diethyl azodicarboxylate (70 μL, 0.44 mmol) and stirred at 0 °C for 30 min. AcSH (31 μL, 0.44 mmol) was added followed by alcohol **82** (33.2 mg, 55.2 μmol) in THF (1 mL + 0.5 mL washing), and the solution was stirred at 0 °C for 30 min. The solution was poured into saturated sodium bicarbonate solution (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (30% Et_2O in petroleum ether) to give thioacetate **83** (33.8 mg, 93%) as a colorless oil: R_f = 0.18 (50% Et_2O in petroleum ether); $[\alpha]^{25}_D$ –96° (*c* 0.59, CH_2Cl_2); IR (thin film) ν_{max} 3314, 1729, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (b s, 1 H, N*H*), 5.97 (dd, *J* = 9.4, 6.2 Hz, 1 H, C=C*H*-CH_2), 5.86 (d, *J* = 9.2 Hz, 1 H, C*H*=CH), 5.79 (b s, 1 H, C*H*-C≡C), 5.76 (dd, *J* = 9.2, 1.4 Hz, 1 H, CH=C*H*), 4.08–3.76 (m, 6 H, CH_2-S and *ethylene ketal*), 3.71 (s, 3 H, CO_2Me), 2.30 (s, 3 H, S*Ac*), 2.25 (AB q, *J* = 13.1 Hz, $\Delta\nu$ = 204 Hz, 2 H, CH_2), 0.98–0.94 (m, 18 H, 2 × Si(CH_2CH_3)$_3$), 0.73–0.68 (m, 12 H, 2 × SiCH_2CH_3)$_3$); FAB HRMS (NBA/CsI) *m/e* 792.1839, M + Cs^+ calcd for $C_{33}H_{49}NO_7SSi_2$ 792.1823.

Methyl[(1*R*,8*S*,13*E*)-1,8-bis[(triethylsilyl)oxy]-13-[2-(methyltrithio)-ethylidene]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (85). A solution of thioacetate **83** (18.7 mg, 28.4 μmol) in CH_2Cl_2 (2 mL) at –78 °C was treated with DIBAL (0.14 mL of a 1.0 M solution in CH_2Cl_2, 0.14 mmol) and stirred at –78 °C for 30 min. The reaction was quenched at –78 °C with MeOH (0.5 mL added dropwise), the cooling bath was removed, and the reaction mixture was diluted with EtOAc (10 mL). Saturated aqueous Rochelle salt (10 mL) was added, and the mixture was vigorously stirred for 30 min until the two phases became clear. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to give crude thiol **84**.

Crude thiol **84** was dissolved in CH_2Cl_2 (2 mL) at 0 °C, and *N*-(methyldithio)phthalimide (32 mg, 0.14 mmol) was added. The solution was stirred for 30 min at 0 °C and then applied directly to a flash chromatography column and eluted with 30% Et_2O in petroleum ether to give trisulfide **85** (14.0 mg, 71%) as a colorless oil: R_f = 0.28 (50% Et_2O in petroleum ether); $[\alpha]^{25}_D$ −100° (*c* 0.49, CH_2Cl_2); IR (thin film) ν_{max} 3285, 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 4.9, 10.3 Hz, 1 H, C=C*H*-CH_2), 5.94 (b s, 1 H, N*H*), 5.86 (d, *J* = 9.3 Hz, 1 H, C*H*=CH), 5.79 (d, *J* = 1.4 Hz, 1 H, C*H*-C≡C), 5.75 (dd, *J* = 9.3, 1.4 Hz, 1 H, CH=C*H*), 4.10–3.63 (m, 6 H, CH_2S and *ethylene ketal*), 3.70 (s, 3 H, CO_2Me), 2.53 (s, 3 H, SSS*Me*), 2.33 (AB q, *J* = 13.3 Hz, Δν = 140 Hz, 2 H, CH_2), 1.00–0.95 (m, 18 H, 2 × $Si(CH_2CH_3)_3$), 0.75–0.67 (m, 12 H, 2 × $Si(CH_2CH_3)_3$); FAB HRMS (NBA/CsI) *m/e* 828.1355, M + Cs^+ calcd for $C_{32}H_{49}NO_6S_3Si_2$ 828.1315.

(−)-Calicheamicinone (3). A solution of **85** (14.0 mg, 20.1 μmol) in THF (1 mL) and H_2O (4 drops) was treated with TsOH (5 mg) and stirred at 25 °C for 16 h. The reaction mixture was diluted with petroleum ether (2 mL) and dichloromethane (2 mL) and applied to a flash chromatography column, eluting with 50% Et_2O in petroleum ether to give (−)-calicheamicinone (**3**; 5.6 mg, 66%) as a colorless gum: R_f = 0.30 (70% Et_2O in petroleum ether); $[\alpha]^{25}_D$ −472° (*c* 0.21, CH_2Cl_2); IR (thin film) ν_{max} 3340, 1711, 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (b s, 1 H, N*H*), 6.47 (dd, *J* = 9.2, 6.4 Hz, 1 H, C=C*H*-CH_2), 6.00 (b s, 1 H, C*H*-C≡C), 5.90 (dd, *J* = 9.4, 1.3 Hz, 1 H, C*H*=CH), 5.87 (d, *J* = 9.4 Hz, 1 H, CH=C*H*), 4.09 (dd, *J* = 14.1, 9.2 Hz, 1 H, C*H*HS), 3.84 (dd, *J* = 14.1, 6.4 Hz, 1 H, CH*H*S), 3.77 (s, 3 H, CO_2Me), 3.32 (b s, 1 H, O*H*), 3.01 (AB q, *J* = 17.1 Hz, Δν = 180 Hz, 2 H, CH_2), 2.83 (b s, 1 H, O*H*), 2.53 (s, 3 H, $SSSCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 154.6, 137.4, 130.5, 126.2, 124.4, 123.8, 100.2, 99.9, 87.9, 84.8, 72.6, 64.6, 53.5, 52.3, 38.7, 22.6 (1 olefinic signal hidden); FAB HRMS (NBA/CsI) *m/e* 555.9323, M + Cs^+ calcd for $C_{18}H_{17}NO_5S_3$ 555.9323.

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