Synthesis of the Antitumor Agent Aglycon (±)-Calicheamicinone Using an *o*-Quinone Monoketal Strategy

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Abstract: Commercially available 5-methoxysalicylic acid **16** was converted into the *o*-quinone monoketal **21**, which was attached to the enediyne **22**, resulting in **23**. After protection of the *tert*-alcohol **24** and conversion of the ester **25** to aldehyde **28**, treatment with $LiN(TMS)_2$ gave a 1:4 mixture of the 12α- and 12β-ols **29** and **30**, respectively. Oxidation of the mixture **29**/**30** followed by DIBAL-H reduction resulted in exclusive formation of **29**. Deprotection of **29** gave **34**, which on treatment with $Ph_2S{=}NH$ gave the 2-amino adduct **35**. Protection of **35** as the tris-Boc derivative **37** followed by intermolecular Wadsworth−Emmons reaction gave the lactone **38**. The lactone **38** was converted into the bis-methyl carbamate derivative **52**, which was reduced with $NaBH_4$/$CeCl_3$ to give **55**. Conversion of the allylic alcohol **55** into the thiol acetate **58** and then to the trisulfide **61** followed previous precedent. Finally, removal of the enol Boc protecting group and the alcohol protecting groups gave (±)-calicheamicinone (**2**).

Introduction

The majority of antitumor antibiotics inhibit cell division by interfering with the synthesis or use of nucleic acids,[1] and there is a constant need to discover new agents that interact with DNA in a mechanistically definable manner.[2] In 1987, the Lederle group reported the structure of calicheamicin γ_1 (**1**), isolated from fermentations of *Micromonospora echinospora* sp. calichensis,[3] the first example, along with esperamicin, of a new class of natural products known as enediynes (Scheme 1).[4] There are now several other members of this family, and they all exhibit potent antitumor activity.[5]

While calicheamicin exhibits a number of unusual structural features such as the allylic trisulfide, a hydroxylamino sugar, and C1−C2 bridgehead double bond, it is the *Z*-enediyne that imbues these molecules with a unique mechanism for cleaving DNA. Due to the novel structure of **1**, and its unique in vitro mode of action, the esperamicins and calicheamicins immediately initiated a substantial amount of interest in the chemistry and synthesis of these enediynes,[6] culminating in the synthesis of the aglycon calicheamicinone **2** by the groups of Danishefsky,[7] Nicolaou,[8] and Clive (2).[9] The former two groups have also synthesized calicheamicin.[10,11] Our earlier synthetic studies were based upon an η^2-$Co_2(CO)_6$-propargylic aldol reaction of **3** via the intermediate **4**, which underwent a stereoselective cyclization to give **5** (Scheme 2). Oxidation of **5** to its derived sulfoxide, elimination, and removal of the dicobalthexacarbonyl ligand gave an enone which was oxidized to provided **6** as the pivotal intermediate. Unfortunately, this sequence did not scale-up well and was often difficult to reproduce consistently. As a result, **6** was not available in sufficient quantities to readily explore the full range of protection−deprotection options that were necessary to complete the synthesis of **2**.[12] Consequently, it was decided to examine an

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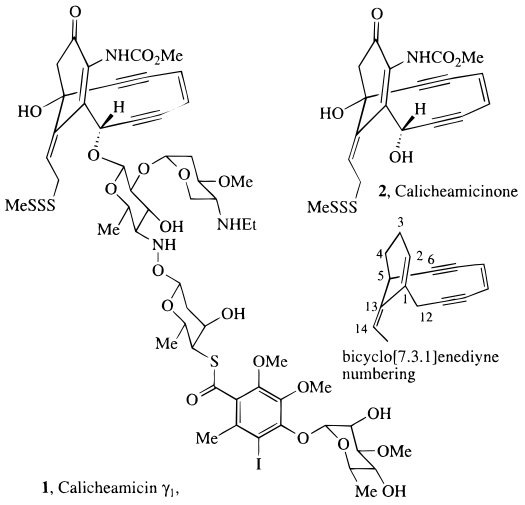
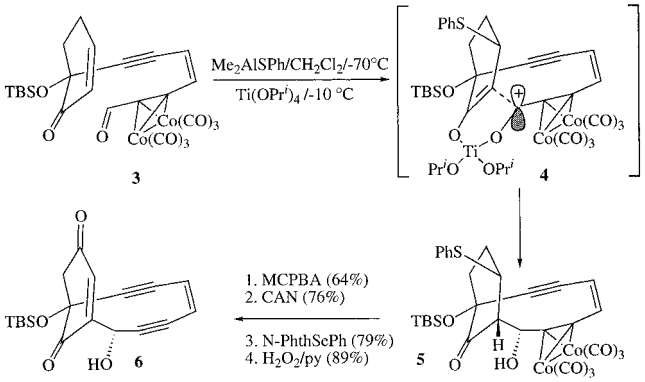
Scheme 1



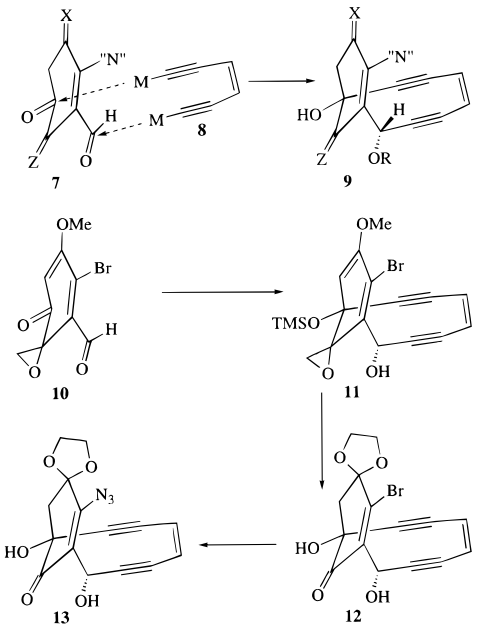
alternative route that would supply multigram amounts of **6**. Furthermore, since we had experienced difficulties removing the C-5 *tert*-butyldimethylsilyl protecting group in advanced intermediates (the trisulfide function was found to be incompatible with typical fluoride ion deprotection conditions), we also opted to replace it with a more labile triethylsilyl group that had successfully served the Nicolaou synthesis.[8]

While there is a substantial literature describing the various strategies that have been developed for the synthesis of **2**, it is notable that the potentially most direct approach, namely one based upon an *o*-quinone monoketal, has not been reported.[13] The original Danishefsky depiction of a generalized strategy to the enediyne core structure involved the addition of **8** to **7** to give **9** (Scheme 3). This conceptually simple strategy was successfully implemented through the stepwise conversion of **10** into **11**. The spiroepoxide **11** was converted into the derived 13,14-diol and cleaved with periodate, resulting in **12**, which underwent addition−elimination with NaN_3 to give **13**, into which the C-14/C-15 carbon atoms were subsequently introduced by means of an intramolecular Wadsworth−Emmons reaction. Overall, the route closely parallels a quinone monoketal strategy, but it uses the Becker−Adler spiro-epoxide reaction[14] to construct **10** and subsequently excises the C-14 carbon. We were interested in examining the simplest version of this strategy that did not require additional manipulations, and directly arrived at the ketal **15** (or equivalent) via **14** (or equivalent), (Scheme 4). This approach would also allow for the rapid construction of the key bicyclo[7.3.1]enediyne core structure.

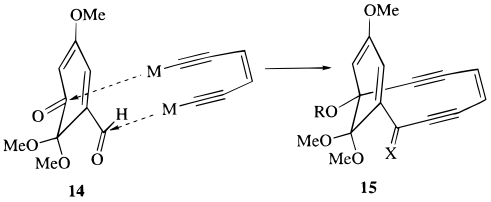
Scheme 2



Scheme 3



Scheme 4



Synthesis of the Bicyclo[7.3.1]enediyne Core. The first requirement was to develop a convenient, large-scale synthesis of the *o*-quinone monoketal **21**. The known salicylic acid derivative **17**[15] made by bromination of commercially available **16**, was converted into the ester **18** and exposed to 8% aqueous NaOH in the presence of copper bronze at 90 °C for 12 days to give **19** (80%) (Scheme 5). Attempts to increase the rate of this reaction by operating at higher temperatures gave diminished yields of **19** as well as substantial amounts of reduction to 2,5-dimethoxybenzoic acid. The derived ester **20** was treated with $PhI(OAc)_2$ in methanol[16] to give **21** as yellow crystals with no purification necessary over the five steps.

(8) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612.

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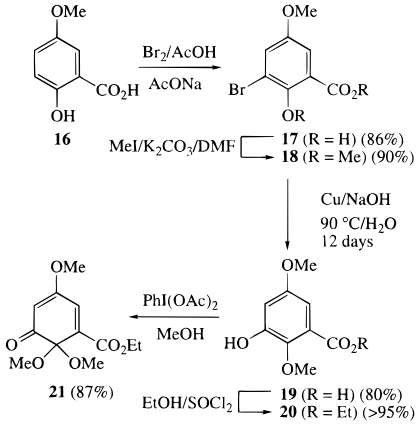
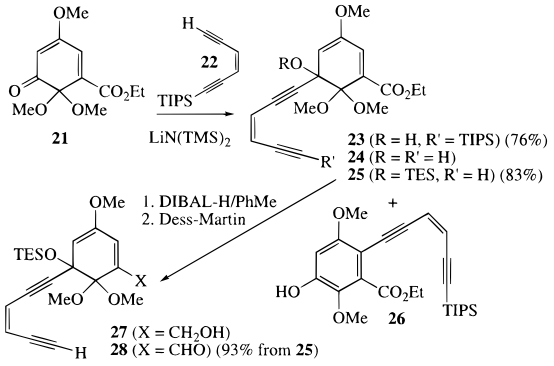
Scheme 5. Synthesis of Quinone Monoketal **21**



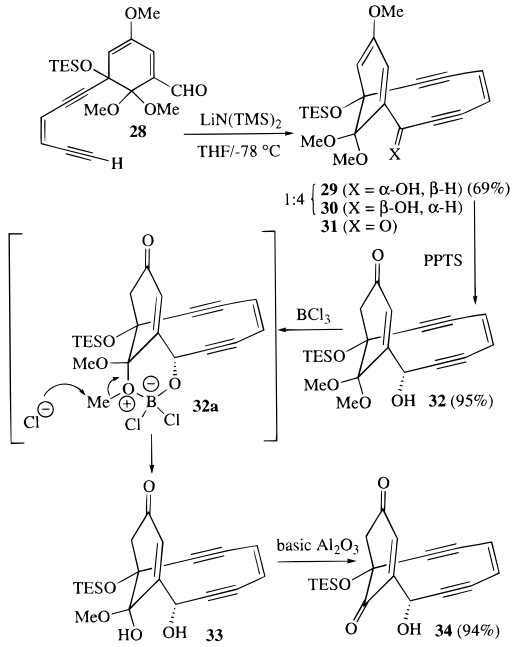
Scheme 6. Addition of Enediyne to **21**



It was discovered that introduction of the enediyne was best accomplished in a single operation making use of the known silyl enediyne **22**.[17] Treatment of **22** with $LiN(TMS)_2$ followed by addition of **21** at −78 °C and warming to −30 °C gave **23**, along with the product of conjugate addition **26** (ca. 10%) as the only major byproduct (Scheme 6).[18] Exposure of **23** to tetra-*n*-butylammonium fluoride/THF at −78 °C gave **24**, which was immediately converted into **25** by treatment with triethylsilyl trifluoromethanesulfonate/2,6-lutidine. During the conversion of **23** into **24** it was imperative to keep the temperature at −78 °C; otherwise, rearrangement took place to give an *o*-cyclohexadienone.[19] Reduction of **25** using DIBAL-H in dichloromethane or THF did not give **27**; instead, only an incompletely characterized aromatized compound, thought to result from reduction of an oxonium ion, was obtained. Use of DIBAL-H in toluene, however, cleanly gave **27**, which could be oxidized with Dess−Martin (D−M) periodinane[20] to give the aldehyde **28** (93% from **25**). Typically **28** was made in 10−20-g batches and used immediately in the next stage.

Exposure of **28** to $LiN(TMS)_2$/THF at −78 °C gave **29** and **30** (1:4), which were directly oxidized (D−M) to the stable crystalline ketone **31** (Scheme 7). Reduction of **31** with DIBAL-H (toluene, −78 °C) produced the desired 12α-alcohol

Scheme 7. Cyclization to the Bicyclo[7.3.1]enediyne Core

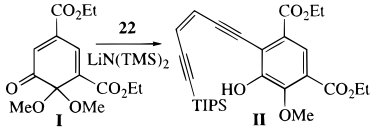


29 (69% over three steps from **28**; **30** could not be detected by ^{1}H NMR). Attempted modification of the base-induced ring closure in order to improve the amount of desired α-alcohol **29** produced an equimolar mixture of epimers at best. This cyclization represents one of the most efficient methods for closure of the 10-membered ring; in addition to the yield observed here (69% over three steps; **28** to **30**), model studies using an analogue of **28** lacking the 5-methoxyl substituent gave the cyclized product in 98% isolated yield as a 1:1 mixture of epimers. Molecular models show that, with the bulky protected tertiary alcohol forcing the pendant enediyne into a pseudoaxial orientation, the reactive termini during the ring closure may be close in space and that only a small amount of ring strain is introduced during the cyclization.

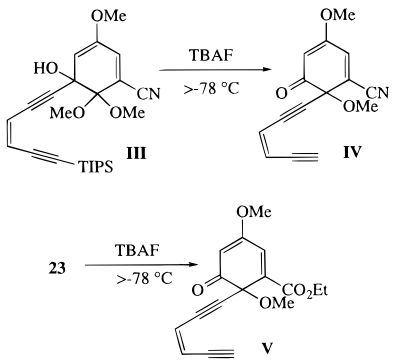
To correlate with previously prepared enedione **6**, removal of the ketal and enol ether protecting groups was necessary, and this was most efficiently accomplished in a stepwise manner. Thus, treatment of **29** with PPTS in aqueous dioxane at 60 °C gave **32** (95%), which on exposure to BCl_3/CH_2Cl_2/heptane gave the hemi-ketal **33**, presumably via S_N2-type *O*-alkyl cleavage. The isolation of similar stable hemi-ketals has been noted in our previous work.[21] Although the configuration at C-13 was not established unequivocally, it is likely that intramolecular

(17) Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *J. Org. Chem.* **1994**, *58*, 4202.

(18) In related studies, *o*-quinone monoketal **I** was shown to give only poor yields of the desired 1,2-adduct. The major product **II** had arisen from attack at the 6-position, demonstrating the high degree of electrophilicity associated with many sites in these systems.



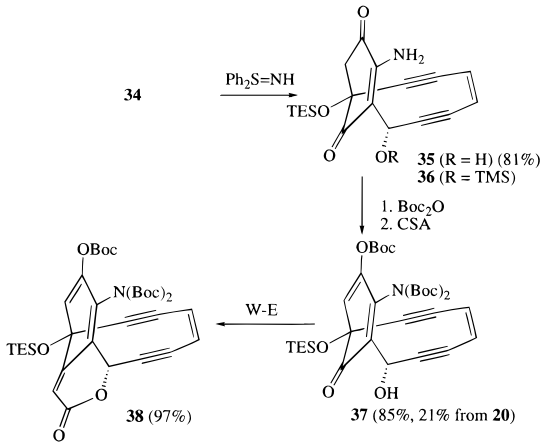
(19) This unwanted migration was noted both with the conversion of **III** to **IV** and of **23** to **V**.



(20) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(21) Magnus, P.; Bennett, F. *Tetrahedron Lett.* **1989**, *30*, 3637.

Scheme 8. C2-Amination and Lactone Formation



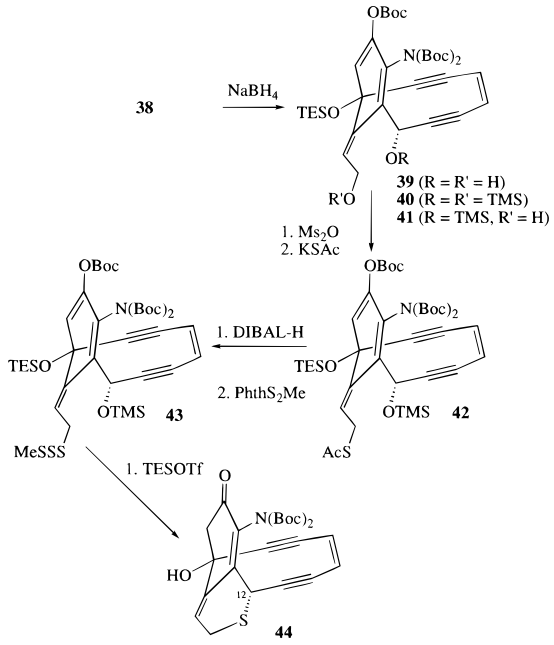
chelation of the Lewis acid allowed cleavage of the methoxyl proximal to the secondary alcohol. Subsequent treatment of **33** with deactivated basic Al_2O_3/CH_2Cl_2 gave **34** (94% from **32**).

C2-Amination and Lactone Formation. In accord with our previously published observations, treatment of **34** with $Ph_2S{=}NH$/THF gave the 2-amino adduct **35** (81%, on 4-g scale) (Scheme 8).[22] The yield of **35** was found to be consistently high only with the use of freshly prepared diphenylsulfilimine, which could be made on a large scale by modification of the literature procedures[23] (see Supporting Information). The purification of enamine **35** represents the first recourse to chromatography required in the synthesis. All previous intermediates could be satisfactorily used with minimal purification. The development of solvent extraction protocols, together with the use of filtrations through shallow beds of alumina or Florisil, meant that large quantities of material could be easily brought through the sequence, making the entire process practically straightforward and rapid as well as chemically efficient.

All attempts to ketalize the C-3 carbonyl group of **35**, and closely related intermediates, were unsuccessful (preventing correlation with the other syntheses), necessitating recourse to an enol carbonate protecting group strategy.[12] To allow the introduction of the C-14 and C-15 carbon atoms by way of a Wadsworth−Emmons reaction, the 3-keto and 2-amino functions had first to be selectively protected. This was possible by treatment of **35** with TMSCN to give **36**, which was immediately exposed to $Boc_2O/Et_3N/DMAP/CH_2Cl_2$ followed by citric acid/MeOH to give the adduct **37** (85%). The use of methyl carbonate/carbamate protecting groups, which would be desirable considering the difficulty with which the *N-tert*-butoxycarbonyl groups were removed in late-stage intermediates (vide infra), was precluded at this stage due to their lability under the Wadsworth−Emmons reaction conditions.[24] Intermolecular Wadsworth−Emmons[25] reaction [$(MeO)_2POCH_2CO_2$-Me/$LiN(TMS)_2$/THF, −78 °C to 25 °C] of tris-Boc protected **37** smoothly gave **38** (97%) (Scheme 8).[26]

Closely paralleling earlier work,[12] the lactone **38** was readily reduced to the diol **39** by treatment with $NaBH_4$/MeOH.

Scheme 9. Cyclic Sulfide Formation



Selective protection of the secondary alcohol in order to allow trisulfide introduction was achieved by persilylation to give **40**, followed by mild acid hydrolysis affording **41** (Scheme 9). The derived mesylate was converted into the thiol acetate **42**, reductive cleavage of which (DIBAL-H), followed by in situ treatment of the thiol with the Harpp reagent PhthSSMe,[27] gave the trisulfide **43**. However, attempted deblocking of **43** by exposure to TESOTf/Et_3N afforded the cyclic sulfide **44**. Thus, even though **43** bears more labile silyl ether protecting groups than previously prepared advanced intermediates, it would appear that the Boc groups are not removed before ionization at C-12 and formation of **44**. This result both mandates that the Boc protecting groups must be removed at an earlier point in the synthesis and amply demonstrates the readiness with which the functionalized calicheamicinone skeleton undergoes vinylogous iminium ion formation.

The failure of the Wadsworth−Emmons reaction on substrates other than **37** forced us to consider the modification of the protecting groups at a later stage. Considering the likely harshly acidic conditions required for removal of the three Boc groups, and the observed propensity for the system to enter into unwanted extended iminium ion chemistry and the possibility

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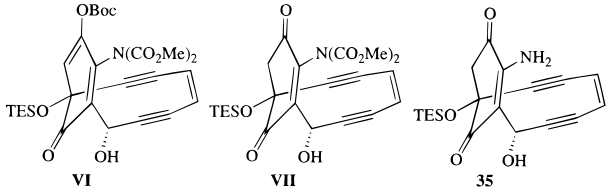
(23) Tsujihara, K.; Furukawa, N.; Oae, K.; Oae, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2631. Yoshimura, T.; Omata, T.; Furukawa, N.; Oae, S. *J. Org. Chem.* **1976**, *41*, 1728.

(24) Ketone **35** as well as **VI** and **VII** (easily prepared from **35**) gave only low yields of the respective lactones under a variety of conditions.

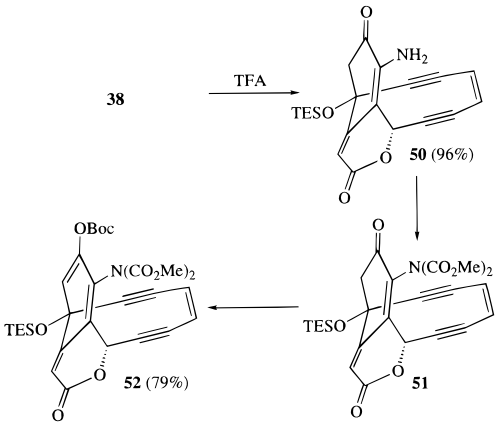


(25) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

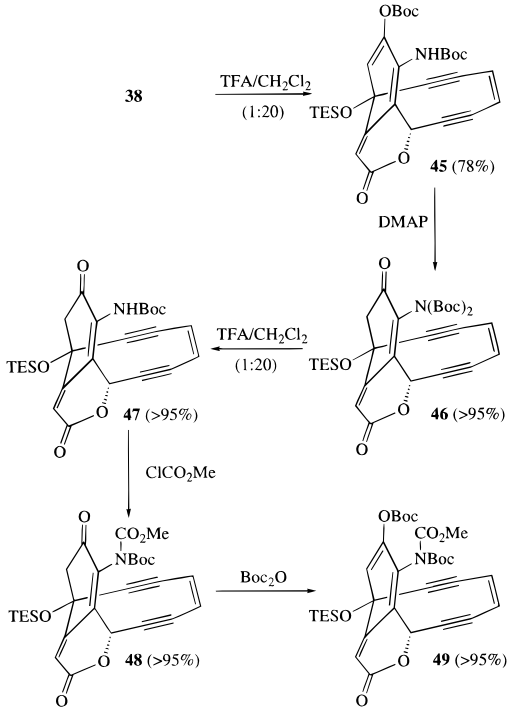
(26) Magnus, P.; Lewis, R.; Bennett, F. *J. Am. Chem. Soc.* **1992**, *114*, 2560.

(27) Harpp, D. N. In *Studies in Organic Chemistry 28. Perspectives in The Organic Chemistry of Sulfur*; Zwanenburg, B., Klunder, A. H., Eds.; Elsevier: Amsterdam, 1987. Harpp, D. N.; Steliou, K.; Chen, T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1222. Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem. A* **1971**, *1*, 211. Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem. A* **1971**, *1*, 57. Sullivan, A. B.; Boustany, K. *Int. J. Sulfur Chem. A* **1971**, *1*, 207. Mott, A. W.; Barany, G. *Synthesis* **1984**, 657.

Scheme 10. Change Protecting Groups



Scheme 11. Boc-*O* to -*N* Migration

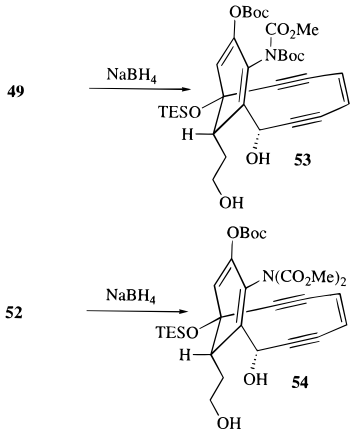


of subsequent cyclization of any pendant C-14 nucleophile, it was decided that lactone **38** itself would be the best candidate for deprotection.

In the event, complete removal of all of the Boc protecting groups was accomplished by treatment of **38** with a large excess of TFA in CH_2Cl_2 (1:1 v/v) to give **50** as vivid yellow crystals (Scheme 10). Use of trifluoromethanesulfonic acid also afforded **50** but now lacking the tertiary silyl ether. This potentially advantageous process was found to be inferior due to the relative difficulty with which compounds bearing a free C-5 alcohol may be subsequently handled. Reprotection was carried out by treatment of **50** with methyl chloroformate/Et_3N/DMAP to give **51**, which was immediately treated with di-*tert*-butyl dicarbonate/Et_3N/DMAP, efficiently giving **52**.

While examining the deprotection of **38**, it was observed that treatment of **38** under less harsh conditions (TFA/CH_2Cl_2 1:20 v/v) selectively removed only one of the *N*-Boc groups to give **45** (Scheme 11). Exposure of **45** to mildly basic conditions (catalytic DMAP) resulted in rapid migration of the enol Boc group onto the adjacent nitrogen atom, giving ketone **46**. The ease with which this acyl transfer reaction is seen to occur lends persuasive evidence that the unusually fast acylation reaction

Scheme 12. Anomalous $NaBH_4$ Reductions



of **36** with *tert*-butyl pyrocarbonate may proceed by way of initial *O*-acylation, followed by intramolecular acyl transfer onto the relatively unreactive enamine nitrogen. This acyl transfer is observed only under basic conditions and represents a reaction pathway (and one that needed to be borne in mind in subsequent manipulations) characteristic of the calicheamicinone skeleton. Further hydrolysis of **46** (TFA/CH_2Cl_2 1:20 v/v) gave **47**, which on treatment with methyl chloroformate afforded **48** and, in turn, (*tert*-butyl pyrocarbonate/Et_3N) **49** as an alternative intermediate to overcome the protecting group problems.

Whereas reduction of the lactone **38** had proceeded without any difficulties to give **39**, treatment of **52** under identical conditions ($NaBH_4$/MeOH) resulted in substantial amounts of conjugate reduction to give **54** (Scheme 12). Similarly, reduction of **49** gave predominantly **53**, denoting a marked dichotomy in the behavior of **38** and **49**, despite their close structural relations.

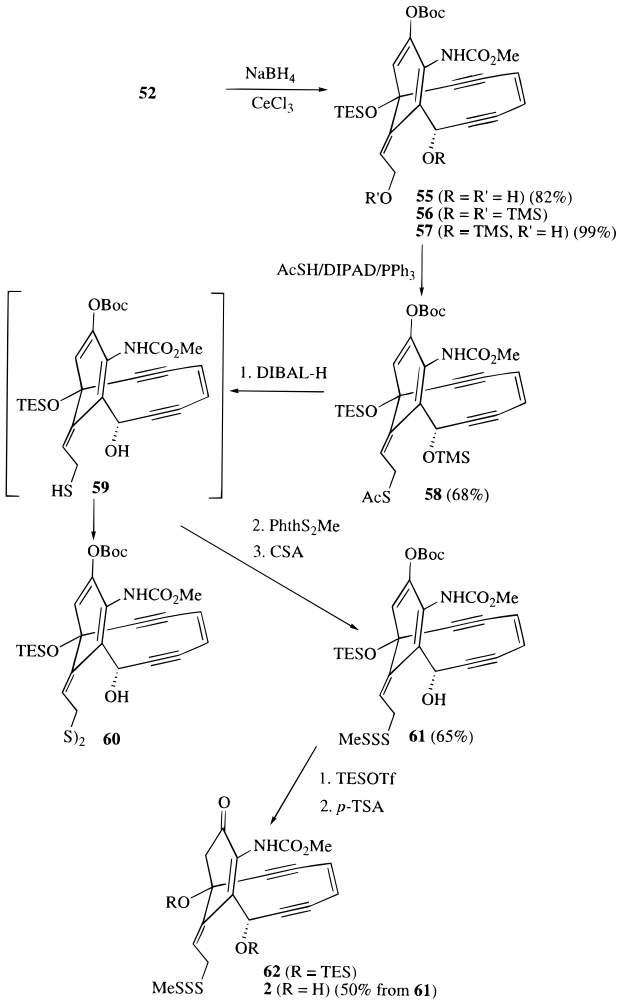
Resort to Luche conditions ($NaBH_4/CeCl_3 \cdot 7H_2O$)[28] did allow exclusive 1,2-reduction but also additionally cleaved one of the *N*-methyl carbamate functions to give **55** (82%) (Scheme 13). The latter result may be viewed either as an advantageous selective deprotection or else as a problematic access to the *O*- to *N*-acyl migration pathway. Should this migration occur in advanced intermediates, the unmasking of the C-3 ketone would labilize C-1 toward intramolecular conjugate addition, which would initiate Bergman cycloaromatization. Clearly, the base sensitivity of these intermediates would need to be considered carefully.

Introduction of the trisulfide was next addressed. While selective secondary alcohol protection to yield **57** (via **56**) proceeded without event (AcOH/H_2O/THF, 99%), mesylation and displacement with potassium thioacetate as a method of accessing the allylic thiol acetate was found to be unsuitable with this substrate due to the instability of the intermediate mesylate. Instead, use of standard Mitsunobu conditions (AcSH/PPh_3/DIPAD/THF/0 °C) provided the desired thiol acetate **58** in good (68%) yield. Use of much smaller excesses of reagents in this reaction than those previously utilized greatly simplified the purification of the product.

Reductive cleavage of the thiol ester used (DIBAL-H/THF/-78 to -10 °C, and the resultant thiol was quenched in situ with the Harpp reagent (PhthSSMe) to give **61** (65% after desilylation). The thiol intermediate in this sequence, when isolated, was seen to be particularly prone to aerial oxidation and is rapidly converted into the disulfide **60**. Cleavage or other transformations of **60** were found to be problematic but its

(28) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Scheme 13. Completion of Synthesis



formation could be avoided by its in situ quench and the use of degassed solvents.

We were now in a position to once again address the final deprotection sequence, but crucially this time lacking the *tert*-butyl carbamate functions that had been the cause of the previous failings. It was found that the enol carbonate and silyl ether were best hydrolyzed in a stepwise fashion. Treatment of **61** with triethylsilyl trifluoromethanesulfonate (2,6-lutidine, CH_2Cl_2) cleaved the enol carbonate to give **62**, and subsequent *p*-toluenesulfonic acid treatment (THF/H_2O/23 °C) provided calicheamicinone **2** (50% over two steps from **61**) as a colorless powder. The synthetic calicheamicinone was found to be moderately stable but degraded significantly upon standing in $CDCl_3$ at ambient temperature for 12 h. Much darkening was observed well below its melting point (93−95 °C).

In summary, we have described the synthesis of (±)-calicheamicinone from 5-methoxysalicylic acid in 28 chemical steps (2% overall yield) with the chromatographic purification of only nine intermediates. The synthesis offers rapid access to large quantities of key building blocks, such as **34** and **35**, which may be of use for the preparation of simpler analogues of the enediyne natural products in the continuing search for useful antitumor compounds. The elaboration of these key intermediates to calicheamicinone has demonstrated the wide range of chemical transformations which may be carried out on the intact bicyclo[7.3.1]enediyne skeleton while at the same time highlighting characteristic reaction pathways (i.e., vinylogous iminium ion formation and *O*- to *N*-acyl transfer) that the calicheamicinone skeleton undergoes.

Experimental Section[29]

Ethyl 2,2,5-Trimethoxy-3-oxocyclohexa-4,6-diene-1-carboxylate (21). A solution of **20** (34.0 g, 0.15 mol) in methanol (400 mL) at 0 °C was treated with iodobenzene diacetate (51 g, 0.16 mol) added in one portion. The mixture was stirred at 0 °C for 30 min, pH 7.4 buffer (50 mL) was added, and the methanol was evaporated in vacuo. The residue was dissolved in EtOAc (700 mL), washed with pH 7.4 buffer (500 mL), water (500 mL), and brine (500 mL), and dried ($MgSO_4$). Filtration and evaporation in vacuo afforded a brown oil which solidified under high vacuum. The solid was triturated with a 5% solution of Et_2O in pentane and filtered to give **21** (25.4 g) as a yellow powder. Purification of the filtrate by chromatography over silica gel, eluting with 0−30% EtOAc/hexanes, gave further **21** (8.1 g, combined yield 87%): mp 65−66 °C, IR (film) 2944, 1733, 1660, 1594 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.09 (1H, d, J = 2.5 Hz), 5.24 (1H, d, J = 2.5 Hz), 4.04 (2H, q, J = 7.0 Hz), 3.42 (6H, s), 2.73 (3H, s), 0.94 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 192.8, 166.8, 163.1, 140.3, 133.7, 102.1, 93.6, 61.1, 55.4, 51.2, 14.0; HRMS (CI) calcd for $C_{12}H_{16}O_6$ (M^+) 256.0947, found 256.0948.

Ethyl 2,2,5-Trimethoxy-3-hydroxy-3-[(*Z*)-6-triisopropylsilylhexa-1,5-diyn-3-ene]cyclohexa-4,6-diene-1-carboxylate (23). A solution of hexamethyldisilazane (8.4 mL, 40 mmol) in THF (150 mL) was cooled to −20 °C and treated with *n*-BuLi (15.9 mL of a 2.5 M solution in hexanes, 40 mmol). After the solution was stirred at −20 °C for 5 min, it was cooled to −78 °C and treated with a precooled (−78 °C) solution of **22** (8.65 g, 37 mmol) in THF (50 mL). The mixture was stirred at −78 °C for 30 min, and a precooled (−20 °C) solution of **21** (5.8 g, 23 mmol) in THF (50 mL) was added to the solution of the lithioacetylide by means of a double-ended needle over a period of 5 min. The mixture was stirred at −78 °C for 30 min and then at −45 °C for 1.5 h before the reaction was quenched with saturated aqueous NH_4Cl (100 mL). After stirring to ambient temperature, the mixture was diluted with Et_2O (150 mL) and water (50 mL) and separated. The organic layer was washed with citric acid (100 mL of a 0.5 M aqueous solution) and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to afford a dark brown oil (18.6 g), which was applied to a bed of neutral alumina (12% w/w water). Excess **22** was first recovered by washing the filter cake with pentane (1 L). Further washing with a 30% solution of EtOAc/hexanes (2.5 L) afforded **23** (8.4 g, 76%) as a brown oil: IR (film) 3488, 2944, 2866, 2143, 1727, 1655, 1610 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.85 (1H, d, J = 2.5 Hz), 5.51 (1H, d, J = 11.0 Hz), 5.49 (1H, d, J = 11.0 Hz), 5.11 (1H, d, J = 2.5 Hz), 3.96−3.85 (2H, m), 3.59 (3H, s), 3.58 (3H, s), 3.32 (1H, s), 3.04 (3H, s), 1.21−1.14 (21H, m), 0.94−0.84 (3H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 170.2, 165.0, 151.5, 133.5, 120.3, 119.7, 106.0, 104.5, 100.4, 99.3, 98.1, 82.3, 73.9, 60.8, 54.5, 52.4, 51.9, 18.9, 14.0, 11.6; HRMS (CI) calcd for $C_{27}H_{40}O_6Si$ (M^+) 488.2594, found 488.2584.

Ethyl 2,2,5-Trimethoxy-3-hydroxy-3-[(*Z*)-hexa-1,5-diyn-3-ene]-cyclohexa-4,6-diene-1-carboxylate (24). A solution of **23** (33.2 g, 68 mmol) in THF (400 mL) was cooled to −78 °C and treated with

(29) Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer or a Perkin-Elmer 1600 FT-IR spectrometer either neat or in $CHCl_3$ as indicated. ^1H NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer as solutions in the specified solvent and are reported in ppm downfield from TMS. ^{13}C NMR spectra were recorded on a General Electric QE-300 (75 MHz) instrument as solutions in the specified solvent. Low-resolution chemical ionization (CI) mass spectra were obtained on a TSQ 70 instrument, and the exact mass determinations were obtained on a VG analytical ZAB2-E instrument. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel and aluminum-backed TLC plates. Preparative layer chromatography (PLC) was performed using Merck 60H F_{254} silica gel and glass-supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel. Air- and moisture-sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C, and then cooled under argon and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use: Et_2O and tetrahydrofuran were distilled from sodium benzophenone ketyl; dichloromethane and benzene were distilled from calcium hydride under argon.

tetra-*n*-butylammonium fluoride (100 mL of a 1.0 M solution in THF, 100 mmol) added dropwise by syringe over 5 min. Stirring at −78 °C was continued for a further 16 h before MeOH (10 mL) and water (10 mL) were added. After the mixture was stirred to ambient temperature, the solvent was evaporated in vacuo and the residue dissolved in EtOAc (900 mL), washed with 0.1 N hydrochloric acid (600 mL), water (600 mL), and brine (600 mL), and then dried (Na_2SO_4). The solution was filtered, concentrated to half volume, and diluted with hexanes (500 mL). The solution was filtered through a pad of neutral alumina (400 g containing 10% w/w water), washing the filter cake with a 50% solution of EtOAc/hexanes (500 mL). Evaporation to dryness gave a brown oil which was dissolved in acetonitrile (900 mL) and washed with pentane (5 × 400 mL). Evaporation of the acetonitrile fraction in vacuo gave **24** (23.0 g) as a brown oil contaminated with traces of silicon containing residues, used without further purification: IR (film) 3472, 3272, 2978, 2943, 2837, 2097, 1719, 1661, 1613 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.84 (1H, d, J = 2.5 Hz), 5.52 (1H, dd, J = 11.0, 1.0 Hz), 5.34 (1H, dd, J = 11.0, 2.5 Hz), 5.09 (1H, d, J = 2.5 Hz), 3.96−3.87 (2H, m), 3.60 (3H, s), 3.58 (3H, s), 3.38 (1H, s), 2.98 (1H, m), 2.96 (3H, s), 0.93−0.84 (3H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 165.1, 151.5, 133.7, 133.4, 121.4, 119.2, 106.2, 102.1, 100.4, 98.0, 85.5, 81.9, 74.0, 60.8, 54.5, 52.4, 52.0, 13.9; HRMS (CI) calcd for $C_{18}H_{20}O_6$ (M^+) 332.1260, found 332.1270.

Ethyl 2,2,5-Trimethoxy-3-(triethylsilyl)oxy-3-[(*Z*)-hexa-1,5-diyn-3-ene]cyclohexa-4,6-diene-1-carboxylate (25). A suspension of K_2CO_3 (20.0 g) in dichloromethane (150 mL) at 0 °C was treated with triethylsilyl trifluoromethanesulfonate (39 mL, 172 mmol). The mixture was stirred for 15 min, and then stirring was stopped. A solution of crude **24** (23.0 g) and 2,6-lutidine (32 mL, 275 mmol) in dichloromethane (300 mL) was stirred at −78 °C and treated with triethylsilyl trifluoromethanesulfonate (ca. 100 mL of the solution in dichloromethane prepared above, 115 mmol), and the mixture was stirred at −78 °C for 2 h. The reaction was quenched by the addition of MeOH (20 mL) and water (100 mL). After warming to ambient temperature, the solvent was evaporated in vacuo and the residue dissolved in EtOAc (1 L). The solution was washed with 0.1 N hydrochloric acid (2 × 750 mL), water (750 mL), and brine (750 mL) and dried ($MgSO_4$). Filtration and concentration afforded a dark brown oil which was applied to a 3.5-kg bed of neutral alumina (10% w/w water) contained in a 5-L sinter funnel. The filter cake was washed with pentane (4 L) followed by a 5% solution of EtOAc/hexanes (4 l) to give **25** (4.1 g) as a colorless oil contaminated with ca. 5% triethylsilanol. Further washing with 10% EtOAc/hexanes (5 l) gave pure **25** (21.1 g, combined yield ca. 83% over two steps) as a yellow oil: IR (film) 2943, 1727, 1655 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.70 (1H, d, J = 2.5 Hz), 5.57 (1H, dd, J = 11.0, 1.0 Hz), 5.36 (1H, dd, J = 11.0, 2.5 Hz), 5.21 (1H, d, J = 2.5 Hz), 3.96−3.89 (2H, m), 3.82 (3H, s), 3.61 (3H, s), 3.05 (3H, s), 2.90 (1H, m), 1.11 (9H, t, J = 8.0 Hz), 0.94−0.79 (9H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 165.4, 152.6, 136.6, 130.7, 121.4, 118.8, 105.6, 101.2, 100.9, 84.9, 83.1, 81.2, 72.9, 60.7, 54.4, 52.5, 51.4, 14.0, 7.3, 6.8; HRMS (CI) calcd for $C_{24}H_{35}O_6Si$ (M + 1) 447.2203, found 447.2200.

2,2,5-Trimethoxy-3-(triethylsilyl)oxy-3-[(*Z*)-hexa-1,5-diyn-3-ene]cyclohexa-4,6-diene-1-carbinol (27). A solution of **25** (21.1 g, 47.2 mmol) in toluene (300 mL) at −78 °C was treated with precooled (−78 °C) diisobutylaluminum hydride (118 mL of a 1.0 M solution in toluene, 118 mmol) added by means of a double-ended needle. After 90 min, MeOH (15 mL) was added, followed by powdered $Na_2SO_4 \cdot 10H_2O$ (100 g), and the mixture was stirred vigorously to ambient temperature over 45 min. The mixture was filtered through Celite, and the filter cake was washed with EtOAc (200 mL). The solvent was evaporated in vacuo to afford an oil which was dissolved in EtOAc (750 mL) and washed with 0.1 N hydrochloric acid (500 mL), water (500 mL), and brine (500 mL) and dried (Na_2SO_4). Filtration and evaporation in vacuo gave **27** (18.6 g) as a brown oil which was used without further purification: ^1H NMR (300 MHz, C_6D_6) δ 6.11 (1H, m), 5.57 (1H, dd, J = 11.0, 1.0 Hz), 5.35 (1H, dd, J = 11.0, 2.5 Hz), 5.00 (1H, d, J = 2.5 Hz), 4.42 (1H, ddd, J = 14.0, 4.5, 1.5 Hz), 4.10 (1H, ddd, J = 14.0, 8.0, 1.5 Hz), 3.65 (3H, s), 3.10 (3H, s), 3.09 (3H, s), 2.91 (1H, dd, J = 2.5, 1.0 Hz), 2.02 (1H, dd, J = 8.0, 4.5 Hz), 1.18−1.06 (9H, m), 0.92−0.76 (6H, m); HRMS (CI) calcd for $C_{22}H_{33}O_5Si$ (M + 1) 405.2097, found 405.2100.

2,2,5-Trimethoxy-3-(triethylsilyl)oxy-3-[(*Z*)-hexa-1,5-diyn-3-ene]-cyclohexa-4,6-diene -1-carboxaldehyde (28). A solution of crude **27** (18.6 g) in dichloromethane (500 mL) was cooled to 0 °C and treated with $NaHCO_3$ (8.0 g, 95 mmol), followed by 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (21.1 g, 49.42 mmol). The mixture was stirred at 0 °C for 30 min and quenched with 1 N aqueous sodium thiosulfate (100 mL), followed by saturated aqueous $NaHCO_3$ (100 mL). The solvent was evaporated in vacuo, and the residue was shaken with EtOAc (500 mL) and filtered through a pad of neutral alumina (containing 10% w/w water), washing the filter cake with EtOAc (500 mL). The filtrate was washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). Filtration and evaporation to dryness gave **28** (17.7 g, 93% over 2 steps) as a brown oil which was used without further purification: ^1H NMR (300 MHz, C_6D_6) δ 10.11 (1H, s), 7.07 (1H, d, J = 2.5 Hz), 5.54 (1H, dd, J = 11.0, 1.0 Hz), 5.35 (1H, dd, J = 11.0, 2.5 Hz), 5.22 (1H, d, J = 2.5 Hz), 3.68 (3H, s), 3.01 (3H, s), 2.98 (3H, s), 2.91 (1H, m), 1.04 (9H, t, J = 8.0 Hz), 0.82−0.69 (6H, m); HRMS (CI) calcd for $C_{22}H_{31}O_5Si$ (M + 1) 403.1941, found 403.1950.

3,13,13-Trimethoxy-5-(triethylsilyl)oxy-12α/*β*-hydroxybicyclo-[7.3.1]trideca-6,10-diyne-1,3,8-triene (29 and 30). A solution of hexamethyldisilazane (6.5 mL, 31 mmol) in THF (300 mL) was cooled to −78 °C and treated with *n*-BuLi (12.0 mL of a 2.5 M solution in hexanes, 30 mmol). After being stirred at −78 °C for 10 min, the solution was treated with a precooled (−78 °C) solution of **28** (10.8 g, 27 mmol) in THF (150 mL). The mixture was stirred at −78 °C for 15 min and quenched by the addition of a 10% solution of water in THF (100 mL). After being stirred to ambient temperature, the solvent was evaporated in vacuo, and the residue was dissolved in EtOAc (750 mL). The solution was washed with 0.1 N hydrochloric acid (500 mL), water (500 mL), and brine (500 mL) and dried (Na_2SO_4). Filtration through a pad of Florisil (to remove some of the color) and concentration gave **29** and **30** (10.0 g) as a brown oil. ^1H NMR analysis of this crude product indicated a 1:4 mixture of α:*β* alcohols **29** and **30**, respectively, used without further purification.

3,13,13-Trimethoxy-5-(triethylsilyl)oxy-12-oxobicyclo[7.3.1]trideca-6,10-diyne-1,3,8-triene (31). A solution of crude alcohols **29** and **30** (10.0 g, 25 mmol) in dichloromethane (300 mL) was cooled to 0 °C and treated with $NaHCO_3$ (4.5 g, 54 mmol) followed by 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (11.1 g, 26 mmol). The mixture was stirred at 0 °C for 1 h and quenched with 1 N aqueous sodium thiosulfate (10 mL), followed by saturated aqueous $NaHCO_3$ (10 mL). The solvent was evaporated in vacuo, and the residue was dissolved in EtOAc (200 mL) and filtered through Celite, washing the filter cake with EtOAc (200 mL). The filtrate was washed with water (300 mL) and brine (300 mL) and dried (Na_2SO_4). Filtration and evaporation to dryness gave **31** (10.0 g) as a brown solid which was used without further purification: ^1H NMR (300 MHz, C_6D_6) δ 5.88 (1H, d, J = 2.0 Hz), 5.57 (1H, d, J = 10.0 Hz), 5.26 (1H, d, J = 10.0 Hz), 4.82 (1H, d, J = 2.0 Hz), 3.44 (3H, s), 3.24 (3H, s), 3.01 (3H, s), 1.09 (9H, t, J = 8.0 Hz), 0.88−0.72 (6H, m); HRMS (CI) calcd for $C_{22}H_{28}O_5Si$ (M^+) 400.1706, found 400.1703.

3,13,13-Trimethoxy-5-(triethylsilyl)oxy-12α-hydroxybicyclo[7.3.1]-trideca-6,10-diyne-1,3,8-triene (29). A solution of crude **31** (10.0 g, 25 mmol) in toluene (300 mL) was stirred and cooled to −78 °C before being treated with precooled (−78 °C) diisobutylaluminum hydride (40 mL of a 1.0 M solution in toluene, 40 mmol) added by means of a double-ended needle. Stirring at −78 °C was continued for 90 min, MeOH (10 mL) was added followed by powdered $Na_2SO_4 \cdot 10H_2O$ (50 g), and the mixture was stirred vigorously to ambient temperature over 45 min. The mixture was filtered through Celite, and the filter cake was washed with EtOAc (100 mL). The solvent was evaporated in vacuo to afford an oil which was dissolved in EtOAc (500 mL), washed with 0.1 N hydrochloric acid (500 mL), water (500 mL), and brine (500 mL), and dried (Na_2SO_4). Filtration and evaporation to dryness gave a brown oil which was purified by filtration through a pad of Florisil, eluting with 5−20% EtOAc/hexanes to give **29** (7.5 g, 69% over three steps) as pale yellow crystals: mp 109−111 °C; IR (thin film) 3520, 2952, 2199, 1657, 1617 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 6.13 (1H, d, J = 10.0 Hz), 5.98 (1H, dd, J = 10.0, 1.5 Hz), 5.84 (1H, dd, J = 2.0, 0.5 Hz), 5.26 (1H, m), 4.78 (1H, d, J = 2.0 Hz), 3.57 (3H, s), 3.52 (3H, s), 3.27 (3H, s), 2.82 (1H, s), 0.98−0.90 (9H, m),

0.82−0.72 (6H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 153.3, 144.8, 124.6, 124.2, 122.1, 103.5, 102.7, 102.5, 99.9, 87.7, 84.9, 78.8, 67.9, 54.2, 51.9, 50.9, 7.4, 7.0; HRMS (CI) calcd for $C_{22}H_{30}O_5Si$ (M^+) 402.1863, found 402.1862.

13,13-Dimethoxy-5-(triethylsilyl)oxy-12α-hydroxy-3-oxobicyclo-[7.3.1]trideca-6,10-diyne-1,8-diene (32). A solution of **29** (5.4 g, 13 mmol) in 1,4-dioxane (100 mL) and water (10 mL) was treated with pyridinium *p*-toluenesulfonate (250 mg, 1 mmol), and the mixture was heated at 60 °C overnight. After the solution was cooled to ambient temperature, solid $NaHCO_3$ (500 mg) was added, and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc (300 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), and dried ($MgSO_4$). Filtration and evaporation afforded a yellow oil which was purified by filtration through a pad Florisil, eluting with 5−20% EtOAc/hexanes, to give **32** (5.0 g, 95%) as a pale yellow oil: IR (thin film) 3499, 2960, 2870, 1677 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.08 (1H, s), 6.07 (1H, d, J = 9.5 Hz), 5.97 (1H, dd, J = 9.5, 1.5 Hz), 5.38 (1H, m), 4.39 (1H, d, J = 12.0 Hz), 3.72 (3H, s), 3.39 (3H, s), 3.00 (1H, dd, J = 17.0, 0.5 Hz), 2.83 (1H, br s), 2.71 (1H, dd, J = 17.0, 1.0 Hz), 1.08−0.97 (9H, m), 0.82−0.71 (6H, m); ^{13}C NMR (75 MHz, acetone-d_6) δ 195.6, 161.1, 127.6, 124.4, 123.9, 104.2, 102.5, 99.6, 88.6, 86.1, 78.5, 68.0, 52.9, 52.2, 50.0, 7.1, 6.6; HRMS (CI) calcd for $C_{21}H_{29}O_5Si$ (M + 1) 389.1784, found 389.1774.

3,13-Dioxo-5-(triethylsilyl)oxy-12α-hydroxybicyclo[7.3.1]trideca-6,10-diyne-1,8-diene (34). To a solution of **32** (5.0 g, 13 mmol) in dichloromethane (500 mL) at −20 °C was added cooled (−20 °C) boron trichloride (80 mL of 1.0 M solution in heptane, 80 mmol), and the resulting yellow solution was stirred at −20 °C for 3 h. To the mixture was added Et_2O (300 mL), and the mixture was poured into saturated aqueous $NaHCO_3$ (500 mL) and stirred to ambient temperature. A further quantity of Et_2O (300 mL) was added, and the organic phase was separated, washed with saturated aqueous $NaHCO_3$ (300 mL), water (300 mL), brine (300 mL), and dried (Na_2SO_4). Filtration and evaporation in vacuo gave a solid, **33**: ^{1}H NMR (300 MHz, C_6D_6) δ 5.57 (1H, d, J = 1.0 Hz), 5.21 (2H, s), 5.07 (1H, d, J = 11.0 Hz), 3.66 (1H, d, J = 11.0 Hz), 3.51 (3H, s), 3.08 (1H, d, J = 16.0 Hz), 2.91 (1H, dd, J = 16.0, 1.0 Hz), 0.92 (9H, t, J = 7.5 Hz) 0.54 (6H, m) The solid was dissolved in dichloromethane (200 mL) and treated with basic alumina (25 g, 10% w/w water). The suspension was stirred at ambient temperature for 1 h and filtered through a pad of Florisil, washing the filter cake with Et_2O. Evaporation in vacuo gave **34** (4.5 g, 94%) as a pale yellow solid: mp 101−104 °C dec; IR (thin film) 3508, 2953, 1709, 1674 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 5.64 (1H, d, J = 1.5 Hz), 5.14 (1H, dd, J = 10.0, 1.5 Hz), 5.09 (1H, d, J = 10.0 Hz), 4.92 (1H, dd, J = 11.0, 1.5 Hz), 4.54 (1H, d, J = 11.0 Hz), 3.06 (1H, dd, J = 17.0, 1.5 Hz), 2.47 (1H, d, J = 17.0 Hz), 1.04 (9H, t, J = 7.5 Hz), 0.79 (6H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 194.7, 192.5, 147.7, 132.2, 124.4, 122.6, 100.2, 96.0, 93.0, 89.1, 75.4, 67.7, 50.4, 7.1, 6.4; HRMS (CI) calcd for $C_{19}H_{23}O_4Si$ (M + 1) 343.1367, found 343.1356.

3,13-Dioxo-2-amino-5-(triethylsilyl)oxy-12α-hydroxybicyclo[7.3.1]-trideca-6,10-diyne-1,8-diene (35). Diphenylsulfilimine monohydrate (7.8 g, 36 mmol, freshly prepared, see Supporting Information) was dried in vacuo for 2 h at 70 °C, cooled to ambient temperature under argon, dissolved in THF (300 mL), and cooled to 0 °C. To this solution was added a solution of **34** (3.26 g, 9.5 mmol) in THF (150 mL) via cannula, and the mixture was stirred for 5 h at 23 °C. Petroleum ether (500 mL) was added and the mixture filtered through a pad of silica gel, washing with Et_2O (500 mL). The filtrate was evaporated in vacuo and the residue chromatographed over silica gel, eluting with 20−50% Et_2O/petroleum ether to give **35** (2.75 g, 81%) as colorless crystals: mp 124−125 °C dec; IR (thin film) 3450, 3354, 2956, 2877, 2818, 1697, 1660, 1633 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 6.11 (1H, d, J = 10.0 Hz), 5.19 (1H, dd, J = 8.0, 1.5 Hz), 5.11 (1H, d, J = 8.0 Hz), 5.02 (1H, dd, J = 10.0, 1.5 Hz), 3.87 (2H, br s), 3.10 (1H, d, J = 18.5 Hz), 2.51 (1H, d, J = 18.5 Hz), 1.10 (9H, t, J = 8.0 Hz), 0.89 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 190.3, 142.1, 124.3, 123.2, 114.3, 99.9, 96.8, 91.1, 85.0, 74.2, 63.1, 48.9, 6.9, 6.0; HRMS (CI) calcd for $C_{19}H_{24}NO_4Si$ (M + 1) 358.1475, found 358.1472.

13-Oxo-2-[bis(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)oxy]-5-(triethylsilyl)oxy-12α-hydroxybicyclo[7.3.1]trideca-6,10-diyne-1,3,8-triene (37). A solution of **35** (1.50 g, 4.2 mmol) in trimethylsilyl cyanide (5 mL) was stirred for 30 min. The solvent was distilled in vacuo and the residue dissolved in dichloromethane (100 mL). To this solution was added successively Et_3N (2.9 mL, 21 mmol), di-*tert*-butyl dicarbonate (3.9 mL, 17 mmol), and 4-*N*,*N*-(dimethylamino)pyridine (1.0 g, 8 mmol), and the mixture was stirred for 30 min, after which time Et_2O (200 mL) was added. The solution was washed with water (150 mL) and citric acid (2 × 150 mL of a 0.5 M solution), dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was dissolved in MeOH (40 mL), and citric acid monohydrate (880 mg, 4.2 mmol) was added. The mixture was stirred for 2 h, diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 75 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to leave a residue which was chromatographed over silica gel, eluting with 30% Et_2O/petroleum ether to give **37** (2.35 g, 85%) as a colorless foam: mp 135−137 °C dec (Et_2O/petroleum ether); IR (thin film) 3509, 2959, 1800, 1770, 1698 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 6.24 (1H, s), 5.73 (1H, dd, J = 10.0, 2.0 Hz), 5.31 (2H, m), 4.66 (1H, d, J = 10.0 Hz), 1.43 (9H, s), 1.37 (9H, s), 1.27 (9H, s), 1.07 (9H, t, J = 8.0 Hz), 0.84 (6H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 196.6, 150.6, 148.3, 148.2, 142.3, 136.1, 132.7, 127.9, 126.0, 123.5, 101.3, 94.5, 92.6, 87.8, 84.1, 83.9, 83.3, 75.2, 63.5, 27.4, 26.9, 26.8, 6.9, 6.0; HRMS (CI) calcd for $C_{34}H_{48}NO_{10}Si$ (M + 1) 658.3048, found 658.3043.

Tris-(*tert*-Butyloxycarbonyl)-Protected Lactone 38. To a solution of hexamethyldisilazane (2.72 mL, 13 mmol) in THF (250 mL) at −78 °C was added dropwise *n*-BuLi (5.4 mL of a 2.40 M solution in hexanes, 13 mmol), and the solution was stirred at −78 °C for 30 min. A solution of trimethylphosphonoacetate (2.1 mL, 13 mmol) in THF (50 mL) was added via cannula and the mixture stirred for 1 h. A solution of **37** (2.12 g, 3.2 mmol) in THF (100 mL) was added via cannula, and the mixture was stirred at 0 °C for 30 min, and then at 23 °C for 2 h, and quenched by the addition of saturated aqueous NH_4Cl (100 mL). To the mixture was added Et_2O (200 mL) and water (100 mL), and the layers were separated. The aqueous layer was washed with Et_2O (100 mL), and the combined extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to leave a residue which was dissolved in Et_2O (25 mL) and filtered through a pad of silica gel, washing with Et_2O. Evaporation in vacuo gave **38** (2.14 g, 97%) as a pale yellow foam: IR (thin film) 2979, 1800, 1762, 1736 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 6.45 (1H, s), 6.15 (1H, s), 6.00 (1H, d, J = 2.0 Hz), 5.47 (1H, d, J = 9.5 Hz), 5.35 (1H, dd, J = 9.5, 2.0 Hz), 1.34 (9H, s), 1.33 (9H, s), 1.27 (9H, s), 0.90 (9H, t, J = 8.0 Hz), 0.67 (6H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 160.8, 154.4, 150.7, 148.7, 148.4, 144.0, 125.6, 125.0, 123.3, 119.9, 114.9, 98.2, 97.1, 95.2, 90.3, 84.1, 83.8, 83.1, 70.3, 67.9, 27.6, 27.5, 27.4, 7.0, 6.2; HRMS (CI) calcd for $C_{36}H_{48}NO_{10}Si$ (M + 1) 682.3048, found 682.3060.

Enamine Lactone 50. To a solution of **38** (1.33 g, 1.95 mmol) in dichloromethane (60 mL) was added trifluoroacetic acid (30 mL), and the mixture was stirred for 45 min. The solution was diluted with Et_2O (250 mL), and the mixture was cautiously washed with saturated aqueous $NaHCO_3$ (5 × 100 mL). The combined aqueous layers were extracted with Et_2O (100 mL), and the combined Et_2O extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give **50** (717 mg, 96%) as yellow crystals: mp 146−150 °C dec (Et_2O/petroleum ether); IR (thin film) 3458, 3340, 2956, 2877, 1696, 1622 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (1H, s), 5.99 (1H, d, J = 1.5 Hz), 5.90 (1H, d, J = 9.5 Hz), 5.81 (1H, dd, J = 9.5, 1.5 Hz), 4.67 (2H, br s), 3.14 (1H, d, J = 16.5 Hz), 2.97 (1H, d, J = 16.5 Hz), 1.02 (9H, t, J = 8.0 Hz), 0.79 (6H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 189.6, 162.7, 154.5, 133.8, 125.1, 123.5, 113.0, 107.5, 99.1, 95.6, 88.8, 86.9, 70.8, 67.3, 49.1, 6.9, 5.8; HRMS (CI) calcd for $C_{21}H_{24}NO_4Si$ (M + 1) 382.1474, found 382.1464.

Enol Carbonate 52. To a solution of **50** (693 mg, 1.8 mmol), Et_3N (2.54 mL, 18 mmol), and 4-*N*,*N*-(dimethylamino)pyridine (890 mg, 7.3 mmol) in dichloromethane (150 mL) was added methyl chloroformate (850 μL, 11 mmol) as a solution in dichloromethane (75 mL) via cannula, and the reaction was stirred for 1 h. The mixture was diluted with Et_2O (250 mL), and the solution was washed with water (200 mL), citric acid (2 × 150 mL of a 0.5 M aqueous solution), and brine (100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give **51** (850 mg, 94%) as brown crystals. The crystals were dissolved in dichloromethane (100 mL), and Et_3N (720 μL, 5.1 mmol), di-*tert*-butyl

dicarbonate (1.18 mL, 5.1 mmol), and 4-*N*,*N*-(dimethylamino)pyridine (630 mg, 5.1 mmol) were added successively. The mixture was stirred for 1 h, diluted with Et_2O (250 mL), washed with water (150 mL), citric acid (2 × 100 mL of a 0.5 M aqueous solution), brine (100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give dark brown crystals. The crystals were dissolved in 10% dichloromethane/Et_2O (10 mL) and filtered through a pad of silica, washing with Et_2O. Evaporation in vacuo gave pale yellow crystals which were triturated with petroleum ether (100 mL) to give **52** (805 mg, 79%) as a colorless powder: mp 140−141 °C dec; IR (thin film) 2958, 1808, 1770, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (1H, d, J = 10.0 Hz), 6.21 (1H, s), 6.04 (3H, m), 3.86 (3H, s), 3.59 (3H, s), 1.49 (9H, s), 1.04 (9H, t, J = 8.0 Hz), 0.82 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 153.2, 150.9, 150.4, 150.0, 142.2, 125.8, 124.3, 123.3, 121.8, 114.9, 97.1, 95.3, 94.3, 90.5, 84.7, 67.0, 54.5, 54.0, 27.4, 6.7, 5.7; HRMS (CI) calcd for $C_{30}H_{36}NO_{10}Si$ (M + 1) 598.2109, found 598.2103.

Diol 55. To a solution of **52** (1.09 g, 1.82 mmol) and $CeCl_3 \cdot 7H_2O$ (3.40 g, 9.1 mmol) in a mixture of MeOH (125 mL) and dichloromethane (25 mL) at 0 °C was added portionwise $NaBH_4$ (347 mg, 9.1 mmol), and the solution was stirred at 0 °C for 4 h. Saturated aqueous NH_4Cl (150 mL), EtOAc (300 mL), and water (200 mL) were added, and the organic layer was separated. The dried (Na_2SO_4) extract was evaporated in vacuo to give a residue which was dissolved in MeOH (20 mL), allowed to stand for 30 min, and evaporated in vacuo. The residue was redissolved in MeOH (20 mL) and evaporate,d and the residue was chromatographed over silica gel, eluting with 50% EtOAc/petroleum ether to give **55** (810 mg, 82%) as an off-white solid foam: IR (thin film) 3354, 2972, 1762, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (1H, dd, J = 8.0, 6.0 Hz), 5.97 (4H, m), 5.80 (1H, s), 4.39 (2H, m), 4.21 (1H, br t, J = 5.0 Hz), 3.71 (3H, br s), 1.50 (9H, s), 0.98 (9H, t, J = 8.0 Hz), 0.78 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 150.6, 128.9, 124.7, 124.5, 124.3, 100.7, 99.3, 88.2, 88.1, 87.0, 84.2, 81.9, 71.2, 63.1, 59.9, 53.0, 27.4, 6.4, 5.6; HRMS (CI) calcd for $C_{28}H_{37}NO_8Si$ 543.2288, found 543.2277.

Trimethylsilyl Ether 57. A solution of **55** (465 mg, 0.85 mmol) in trimethylsilyl cyanide (1 mL) was stirred for 30 min and evaporated in vacuo. The residue was dissolved in a mixture of THF (50 mL), water (10 mL), and glacial AcOH (1 mL). The mixture was stirred for 30 min (with close monitoring by TLC, eluent 50% ether/petroleum ether), diluted with Et_2O (150 mL), washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give **57** (518 mg, 99%) as a pale yellow solid foam: IR (thin film) 3381, 3263, 2956, 1760, 1710 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.82 (1H, t, J = 6.5 Hz), 6.19 (1H, d, 1.5 Hz), 6.17 (1H, s), 5.56 (1H, d, J = 9.5 Hz), 5.48 (1H, br s), 5.47 (1H, dd, J = 9.5, 1.5 Hz), 4.45 (1H, br dd, J = 14.0, 6.5 Hz), 4.32 (1H, br dd, J = 14.0, 6.5 Hz), 3.24 (3H, br s), 1.90 (1H, br s), 1.24 (9H, s), 1.05 (9H, t, J = 7.5 Hz), 0.84 (6H, m), 0.25 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 142.9, 134.6, 130.6, 129.0, 124.8, 124.2, 101.1, 101.0, 99.5, 87.8, 86.7, 84.0, 71.2, 63.2, 60.3, 52.8, 27.3, 7.0, 6.0, 0.0; HRMS (CI) calcd for $C_{31}H_{46}NO_8Si_2$ (M + 1) 616.2762, found 616.2776.

Thioacetate 58. To a solution of triphenylphosphine (362 mg, 1.38 mmol) in THF (50 mL) at 0 °C was added diisopropylazodicarboxylate (226 μL, 1.15 mmol), and the mixture was stirred for 30 min, after which time the solution had become colorless. Freshly distilled thiolacetic acid (83 μL, 1.15 mmol) was added, followed by **57** (285 mg, 0.46 mmol, as a solution in THF, 50 mL, by cannula). The mixture was stirred at 0 °C for 4 h, diluted with Et_2O (50 mL), washed with saturated aqueous $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to leave a residue which was chromatographed over silica gel, eluting with 25−50% Et_2O/petroleum ether to give **58** (210 mg, 68%) as colorless crystals: mp 114−114.5 °C dec; IR (thin film) 3304, 2956, 2877, 1760, 1710, 1694 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.74 (1H, dd, J = 8.5, 8.0 Hz), 6.22 (1H, d, J = 1.0 Hz), 5.53 (1H, d, J = 9.5 Hz), 5.46 (1H, dd, J = 9.5, 1.0 Hz), 5.31 (1H, s), 4.21 (2H, m), 3.30 (3H, br s), 1.82 (3H, s), 1.24 (9H, s), 1.06 (9H, t, J = 8.0 Hz), 0.89 (6H, m), 0.32 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 150.6, 142.9, 134.9, 126.8, 124.7, 124.6, 124.4, 124.1, 99.4, 87.8, 86.7, 84.0, 71.3, 63.4, 52.8, 30.3, 29.6, 27.4, 6.9, 6.1, 0.1; HRMS (CI) calcd for $C_{33}H_{47}NO_8Si_2S$ 673.2561, found 673.2562.

Triethylsilyl-*tert*-butyloxycarbonyl calicheamicinone (61). To a solution of **58** (51 mg, 0.076 mmol) in THF (4 mL, degassed) at −78 °C was added DIBAL-H (1.14 mL of a 1.0 M solution in toluene, 1.14 mmol), and the mixture was stirred at −65 °C (±5 °C) for 3 h. The mixture was quenched with MeOH (800 μL, degassed) followed by crushed $Na_2SO_4 \cdot 10H_2O$ (600 mg), and the mixture was allowed to warm to room temperature over 30 min. Upon recooling to 0 °C, dichloromethane (4 mL, degassed), EtOAc (4 mL, degassed), and PhthSSMe (50 mg, 0.22 mmol) was added. The mixture was stirred for 50 min and then filtered through a pad of silica gel, washing with Et_2O (20 mL). The solvents were evaporated in vacuo to leave a residue which was dissolved in a mixture of THF (2 mL) and water (200 μL). Camphorsulfonic acid (32 mg, 0.15 mmol) was added, and the mixture was stirred for 25 min, diluted with ether (15 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was chromatographed over silica gel, eluting with 25−50% Et_2O/petroleum ether to give **61** (31.2 mg, 65%) as a colorless oil: IR (thin film) 3355, 2955, 1757, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, t, J = 8.0 Hz), 6.31 (1H, br s), 5.95 (3H, m), 5.80 (1H, s), 4.03 (2H, m), 3.72 (3H, br s), 2.56 (3H, s), 1.49 (9H, s), 1.02 (9H, t, J = 7.5 Hz), 0.82 (6H, m); HRMS (CI) calcd for $C_{29}H_{40}NO_7SiS_3$ 638.1736, found 638.1728.

(±)-Calicheamicinone (2). To a solution of **61** (15 mg, 23 μmol) in dichloromethane (2 mL) was added 2,6-lutidine (106 μL, 0.46 mmol) and triethylsilyl trifluoromethanesulfonate (82 μL, 0.69 mmol), and the mixture was stirred for 4 h. The mixture was quenched with Et_2O (10 mL) and the solution washed with citric acid (5 mL of a 0.5 M solution) and brine (5 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give **62** contaminated with silyl residues. This was used without further purification, although chromatography over silica gel, eluting with 20% Et_2O/petroleum, ether afforded pure **62**: IR (thin film) 3355, 2956, 1741, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, br s), 6.40 (1H, dd, J = 11.0, 4.5 Hz), 6.12 (1H, d, J = 1.5 Hz), 5.93 (1H, d, J = 9.5 Hz), 5.84 (1H, dd, J = 9.5, 1.5 Hz), 4.01 (1H, dd, J = 14.5, 11.0 Hz), 3.78 (3H, s), 3.63 (1H, dd, J = 14.5, 4.5 Hz), 2.55 (3H, s), 1.00 (18H, m), 0.79 (12H, m); HRMS (CI) calcd for $C_{30}H_{45}NO_5Si_2S_3$ 651.1998, found 651.1999. Crude **62** was dissolved in a mixture of dioxane (3 mL) and water (1 mL), *p*-toluenesulfonic acid monohydrate (4.4 mg, 23 μmol) was added, and the mixture was stirred at ambient temperature for 72 h. The mixture was diluted with Et_2O (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to leave a residue which was dissolved in acetonitrile (3 mL) and washed with pentane (2 × 3 mL). The acetonitrile layer was evaporated in vacuo and the residue dissolved in a small quantity of Et_2O and filtered through a pad of silica gel, washing with further Et_2O. Evaporation in vacuo afforded calicheamicinone **2** (4.9 mg, 50% from **61**) as a colorless powder: mp 93−95 °C dec; IR (thin film) 3351, 2921, 1713, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (1H, br s), 6.48 (1H, dd, J = 9.0, 6.5 Hz), 6.03 (1H, d, J = 6.5 Hz), 5.92 (1H, d, J = 9.5 Hz), 5.90 (1H, d, J = 9.5 Hz), 4.12 (1H, dd, J = 14.0, 9.5 Hz), 3.87 (1H, dd, J = 14.0, 6.5 Hz), 3.79 (3H, s), 3.26 (1H, d, J = 6.5 Hz), 3.21 (1H, d, J = 17.0 Hz), 2.85 (1H, d, J = 17.0 Hz), 2.73 (1H, s), 2.54 (3H, s); ^{13}C NMR (75 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, 52.4, 38.7, 22.6; HRMS (CI) calcd for $C_{18}H_{18}NO_5S_3$ (M + 1) 424.0347, found 424.0338.

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Supporting Information Available: Complete experimental details and spectral information for compounds **17**−**20**, **22,** diphenylsulfilimine monohydrate, **49**, and **54** (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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