Pergamon

Tetrahedron Vol. 50, No. 5, pp. 1519-1538, 1994

0040-4020/94 $6.00+0.00

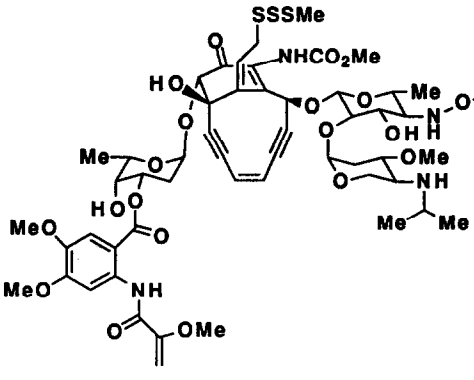
0040-4020(93)E0214-Z

Facile Synthesis of a Simplified Bicyclo[7.3.1] Esperamicin-Calicheamicin Enediyne Core

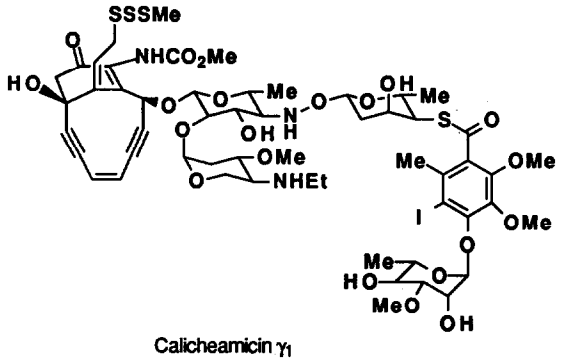
John F. Kadow*, Donald J. Cook, Terrence W. Doyle, David R. Langley, Kahnie M. Pham, Dolatrai M. Vyas, and Mark D. Wittman.

Bristol-Myers Squibb Company, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660

Abstract: An efficient non cobalt mediated route for the synthesis of a simplified bicyclo [7.3.1]enediyne core of the naturally occurring calicheamicins and esperamicins is described. The key cyclization provides a single propargylic alcohol stereoisomer which is in the same relative configuration as that found in the naturally occurring calicheamicins and esperamicins. Selective functionalizations of the cyclized core via selenium dioxide oxidations are described. Installation of an enone chemical trigger provides a hydroxylated analog of a previously described biologically active synthetic enediyne.



esperamicin A_1

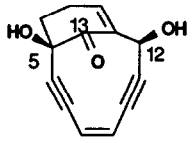


Calicheamicin γ_1

INTRODUCTION

The esperamicins[1], calicheamicins[2], dynemicins[3], kedarcidins[4], and neocarzinostatins[5] are all members of a growing class of naturally occurring enediyne antibiotics. Selected compounds from each group exhibit activity against distally implanted solid tumors in murine tumor models[6]. The preclinical biological activity for esperamicin A_1 was sufficiently impressive and unique from a mechanistic point of view, that phase I and II clinical trials in man were conducted. Unfortunately, due to its erratic toxicity profile the results were not promising enough to warrant continued studies[7]. In spite of their substantial biological activity, the chemical

instability and extreme potency of these naturally occurring compounds seems likely to preclude their broad use as antitumor agents. We have been involved in a program to synthesize enediynes with greater chemical stability and enhanced antitumor efficacy. To achieve greater stability we reasoned that nonessential, reactive chemical functionalities should be omitted from target analogs. For example, the trisulfide trigger in the natural products could be substituted with an alternate intermolecular trigger which results in a more stable enediyne molecule. Therefore, it is reasonable to suggest that future biologically active enediynes may possess considerably simplified structures than the naturally occurring compounds. Preliminary reports from our laboratory [8] and others[9] have shown that simple enediyne cores designed as potential synthetic mimics of natural products have displayed interesting activity in early preclinical models.



1

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In our studies, we have found the simple enone core **1**, which is totally devoid of any DNA recognition appendage but which has the potential to undergo a Bergman cycloaromatization upon thiol activation[8], to have substantial antitumor activity in some but not all *in vivo* murine tumor models.[10] In some models, the antitumor activity of **1** was comparable or better than that of the natural products. In light of our recent findings, it is possible that the cytotoxicity of **1** and the natural enediynes may not be due to the same mode of action. Despite these anomalous but encouraging results, we believe that further improvements in the biological profile of **1** are required for a viable clinical candidate. During the course of the search for such an improved analog of **1**, we have developed a facile, non-cobalt mediated route for the synthesis of core **11** which contains both the bicyclo [7.3.1] enediyne core system and the desired C_{12} ß hydroxy epimer found in the naturally occurring esperamicins and calicheamicins. Chemistry for the functionalization of the cyclized core was also developed. The synthesis of a hydroxylated analog of **1** is described as an example.

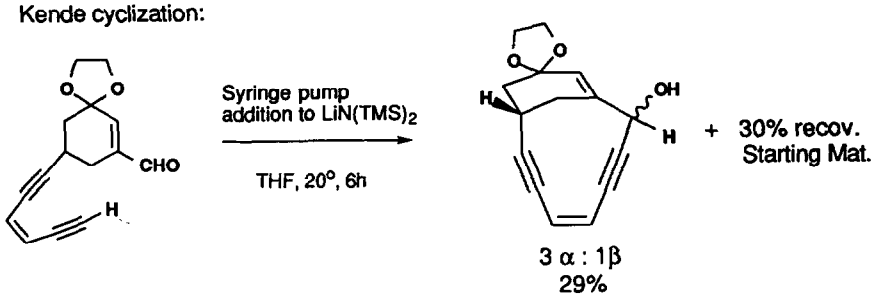
BACKGROUND

The first demonstrations that the carbon skeleton of the bicyclic enediyne aglycone core of the calicheamicins or esperamicins could be constructed by an intramolecular cyclization of an enediyne acetylide with a nonenolizable, unsaturated aldehyde to form the endiyne containing 10 membered ring of the complete bicyclic core were provided by the groups of Danishefsky[11] and Kende[12] and are shown in Scheme 1. A novel aldol approach to core synthesis which utilized a dicobalt hexacarbonyl acetylene complex to favor cyclization was reported at nearly the same time by Magnus and coworkers[13](Scheme 1). Since that time considerable synthetic activity has been reported[14] and two total syntheses of calicheamicin aglycone have been achieved[15]. The initial synthesis of simplified enediyne core **1** utilized modifications of the original Magnus cobalt approach[16]. Our need for a more practical synthesis of simple core molecules for analog

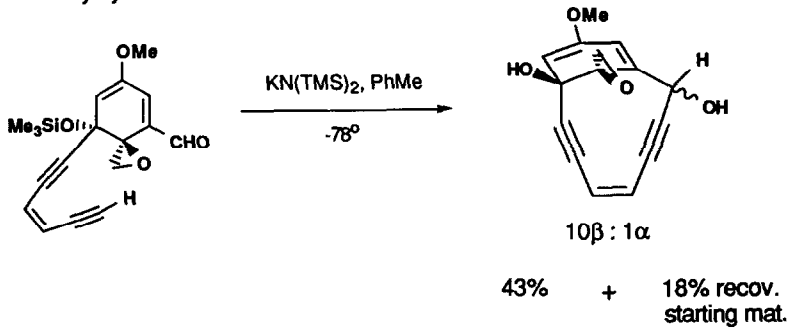
studies, eventually led us to examine the feasibility of the cyclization shown in Scheme 2 using molecular modeling.

SCHEME 1

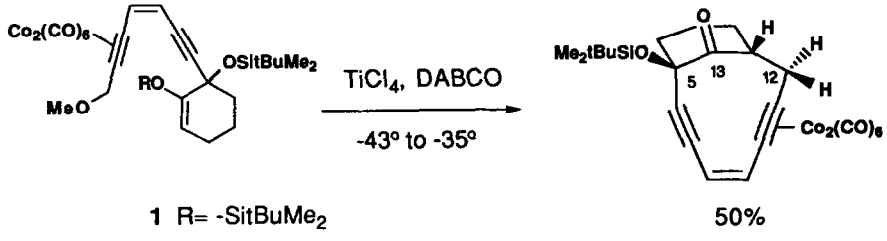
Kende cyclization:



Danishefsky cyclization:



Magnus cyclization



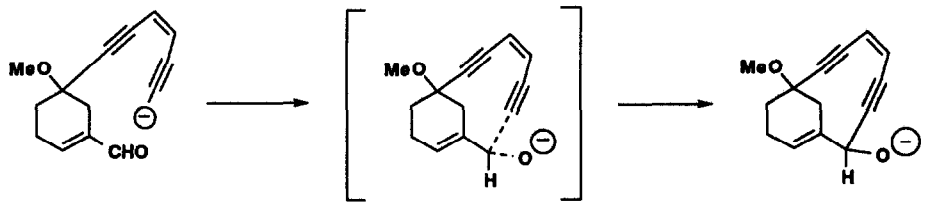
1 R= -SitBuMe$_2$ 50%

MOLECULAR MODELING

The ground state structures and energies for the possible reactants and products were determined using AM1[17] calculations. The transition state structure and energy for both reaction pathways were calculated

using the TS[18] routine in MOPAC 6.0[19] The resulting calculations determined the proposed cyclization to be thermodynamically favorable ($\Delta Hf_{reaction}$=-13.72 Kcal/mol)and to have an accessible transition state ($\Delta Hf_{transition\ state}$=3.80 Kcal/mol). The same calculations were carried out on the original cyclization of Kende and coworkers. That reaction, while elegantly providing one of the first demonstrations of cyclization, suffers from poor diasterosectivity, modest yield, and returns substantial amounts of recovered starting material even after a slow addition of substrate to base over 6h. Calculations predicted that the Kende cyclization should be at least as favorable as the cyclization proposed in Scheme 2 once the enediyne moiety adopts an axial orientation. However, since intuition and calculations also predicted that the enediyne in the Kende substrate would exist mainly in an equatorial conformer, it seemed that the cyclization depicted in Scheme 2 could be be more efficient.

SCHEME 2



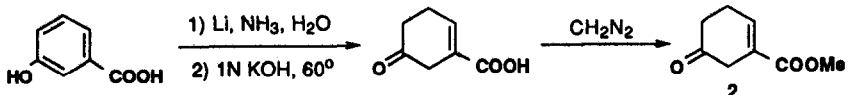
Hf = 60.02753 Kcal/mol Hf= 63.82424 Kcal/mol Hf = 46.30755 Kcal/mol

The Danishefsky cyclization of a more functionalized substrate (Scheme 1) proceeds in better yield probably due to the fact that the trimethylsilyloxy group helps maintain the enediyne in the axial orientation required for cyclization. Interestingly, the diastereoselectivity of this cyclization at C_{12} is quite good. The outcome of the molecular modeling study further fueled efforts to pursue this chemistry in the laboratory.

ENEDIYNE CORE SYNTHESIS

The ketoester starting material **2**, methyl 3-oxo-6-cyclohexene carboxylate, was prepared by the method of Silverstein and Webster[20] as shown in Scheme 3. This procedure, which was used without modification, describes a one pot preparation of the free acid of **2** from 50g of commercially available m-anisic acid. Esterification of the acid using diazomethane as described proceeded without complication.

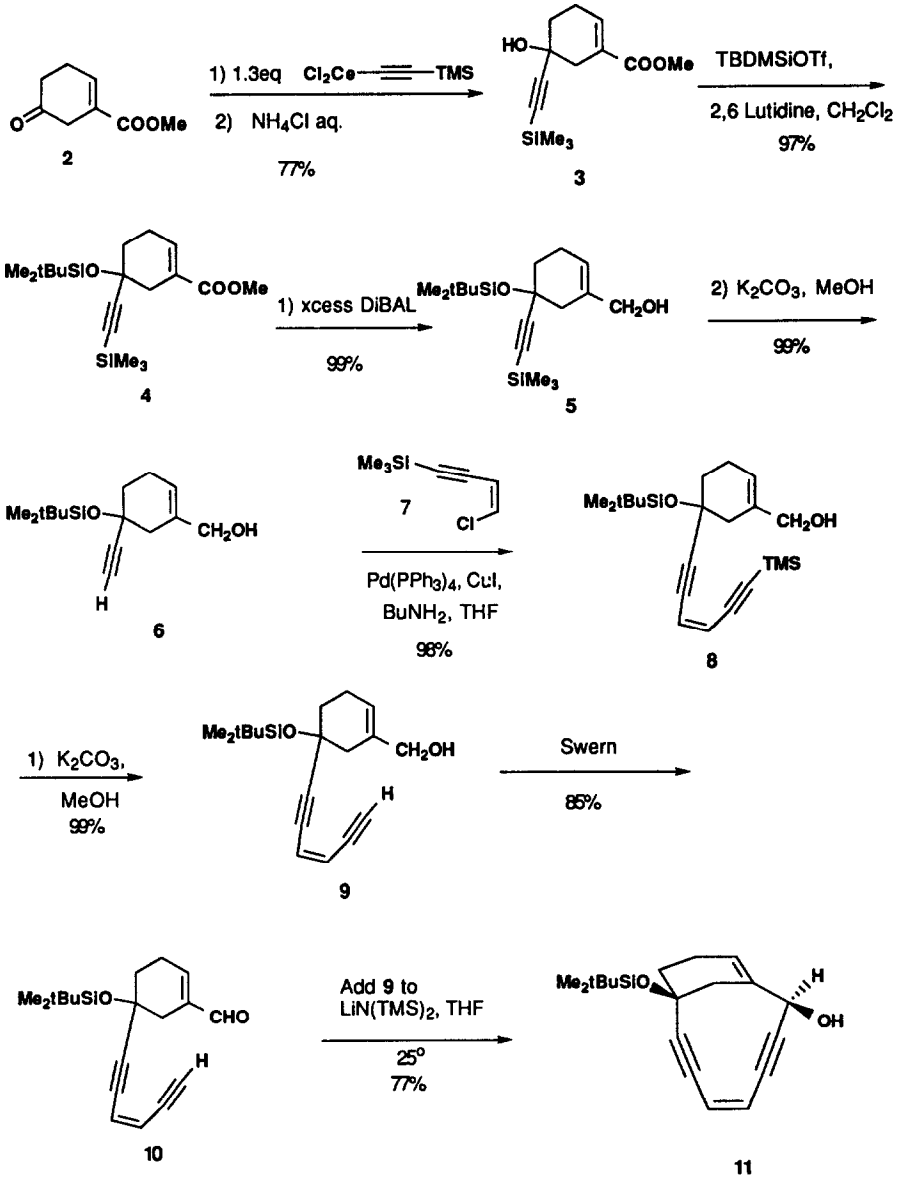
SCHEME 3



m- anisic acid reference 20 1 Pot, 50g scale **2** 94% overall

Trimethylsilylacetylene cerium dichloride was prepared from the corresponding lithium acetylide and cerium trichloride using standard conditions developed for the preparation of cerium acetylides[21]. Addition of the ketoester **2** to the preformed cerium acetylide provided the desired tertiary propargylic alcohol **3** in 77% yield after workup and chromatographic purification (Scheme 4). Use of the lithium trimethylsilylacetylide in

SCHEME 4



THF at temperatures of either -78° or 2° provided reduced yields of product along with considerable quantities of recovered keto ester most likely due to excessive enolization. The use of unprotected cerium acetylide was not explored and may be an alternative.

Silylation of the tertiary alcohol **3** using tert-butyl dimethylsilyl trifluoromethane sulfonate and 2,6-lutidine in dichloromethane provided a 97% yield of the desired silyl ether **4**. The efficiency of these silylation conditions for similar propargylic alcohols has been described.[22]

The methyl ester **4** was reduced to the primary alcohol **5** in 99% yield using diisobutyl aluminum hydride in dichloromethane at -78° . The relatively lipophilic alcohol **5** was obtained essentially quantitatively from this reaction under these conditions. However, undesired reduction of the acetylene moiety was observed in alternate runs when the reaction was permitted to reach higher temperatures in the presence of unreacted DIBAL.

Potassium carbonate in methanol removed the trimethylsilyl protecting group to provide the desired free alkyne **6** in 99% isolated yield. This alkyne was coupled to (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne[23] **7** using $Pd(PPh_3)_4/CuI/nBuNH_2$ to provide enediyne **8** in 98% yield on multigram scale. Alkyne **6** is an extremely good partner for this reaction as this particular Castro-Stephens[24] coupling was unusually efficient. Resorting to potassium carbonate in methanol once again for removal of the alkynyl trimethylsilyl group from **8** provided the deprotected enediyne **9** in 99% yield.

In principle, addition of a complete enediyne anion to keto ester **2** would result in a more convergent route to enediyne alcohol **9**. For example, the cerium reagent corresponding to the known magnesio acetylide anion of (Z) 1-dimethyl thexyl-hex-3-ene-1,5-diyne[25] could be considered. Alternatively, (Z)-6-lithio 1-triisopropylsilyl-hex-3-ene-1,5-diyne has been recently reported[26]. However, due to the consistent efficiency of the stepwise synthesis of enediyne **9** from keto ester **2** (71% overall) we have not explored these alternate routes.

Oxidation of alcohol **9** to the desired aldehyde **10** was best accomplished using either Swern[27] conditions or TPAP oxidation[28]. Both methods provided 85% yields of **10** from 10g of alcohol **9**.

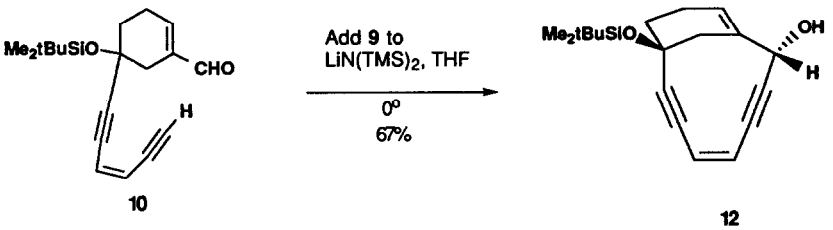
With the cyclization substrate **10** in hand, our efforts were focussed on the key cyclization. The literature examples shown in Scheme 1 had demonstrated the feasibility of an intramolecular cyclization between an enediyne acetylide and a nonenolizable aldehyde. In the course of a marine cembranoid synthesis, Tius and coworkers had demonstrated that slow addition of an acetylenic aldehyde to a solution of lithium bistrimethylsilylamide generated an acetylide anion which effected an intramolecular cyclization on an enolizable unsaturated aldehyde[29]. To the best of our knowledge, only one example of an intramolecular cyclization of an enediyne acetylide and an enolizable aldehyde has been reported and was used to produce a simple cyclic enediyne in a ten membered ring[30]. In this example, the Tius conditions mentioned above provided only trace amounts of the desired cyclic product so in order to achieve useful cyclization yields, it was necessary to generate the acetylide by exposure of an iodo acetylene precursor to chromium(II)-nickel salts.

Amazingly, addition of aldehyde **10** to a solution of freshly prepared $LiN(TMS)_2$ in THF at 25° resulted in a fast, clean conversion to what appeared by TLC to be a single, more polar product. Workup and chromatographic purification provided a 75% yield of the desired cyclized product **11** as a single alcohol stereoisomer at the propargylic C_{12} position. Furthermore, the presence of an NOE enhancement between the

C_2 vinyl hydrogen and the C_{12} hydrogen, plus the lack of any NOE enhancement between the bridgehead hydrogens and the C_{12} hydrogen confirmed that the propargyylic hydroxy group of **11** was in the desired ß position on the outside of the bicyclic system. This orientation corresponds to the same relative stereochemistry as that found in the cores of the esperamicin and calicheamicin natural products. In the course of our analog program, cyclized alcohol **11** was eventually converted into an enediyne core whose structure was unambiguously confirmed.[31]

In contrast, cyclization of **10** at 0° C using a shorter reaction time provided a 67% yield of the cyclization product **12** which is epimeric at the C_{12} propargylic alcohol center (Scheme 5). ^1H NMR of the crude reaction product showed only **12** and a small amount of unreacted **10**. None of the other alcohol epimer

SCHEME 5



10 **12**

11 was visible in the proton spectrum. Surprisingly, exposure of pure **12** to excess $LiN(TMS)_2$ in THF at 25° for a reaction time similar to the initial cyclization returned only recovered **12**. The reaction temperature therefore plays a critical role in determining the relative stereochemistry of the C_{12} alcohol moiety of the cyclization product[32].

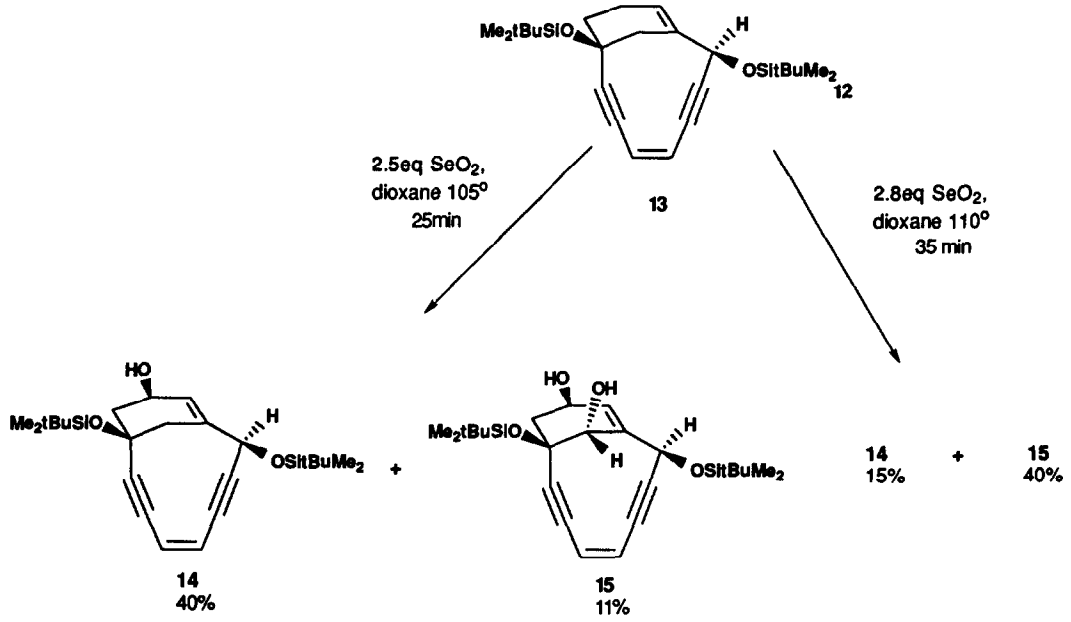
Because our initial conditions for production of **11** proved to be ideal, we have not further investigated the effects of reaction parameters on the cyclization. However, extensive attempts to use fluoride sources[33] to induce cyclization of the trimethylsilyl protected enediyne corresponding to **10** failed to provide more than traces of cyclized products. Under mild conditions, acetylene desilylation to provide aldehyde **10** was the major product.

ENEDIYNE CORE FUNCTIONALIZATION

Silylation of cyclized core **11** using $tBuMe_2SiCl$ and imidazole in DMF provided bis silyl ether **13** in 88% yield. Compound **13** could be hydroxylated fairly selectively to provide either mono allylic alcohol **14** or diol **15** as shown in Scheme 6. The best conditions for somewhat selective formation of either compound each used greater than stoichiometric amounts of SeO_2, however variations in the reactant's concentration, reaction time, and reaction temperature could be utilized to favor formation of either the mono or bis alcohol. Portionwise addition of 2.58 equivalents of SeO_2 to **13** in dioxane at 105° for 25 min provided a 40% yield of the allylic alcohol **14** along with 11% of the easily separable diol **15**. Attempts to prepare compound **14** using stoichiometric SeO_2 or lower reaction temperatures afforded no improvement in yield as these conditions

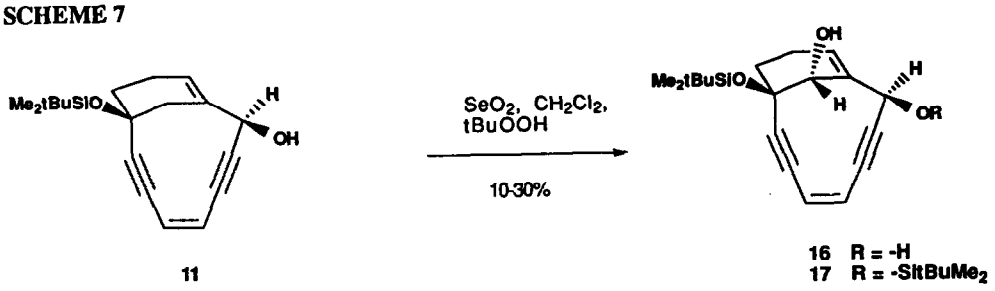
required longer reaction times and the product was harder to purify due to more sideproduct formation. Alternatively, portionwise addition of 2.8 equivalents of SeO_2 to a solution of **13** in dioxane at 110° for 35 minutes provided a 40% yield of the diol **15** and 15% of monoalcohol **14**. Monitoring the reaction by thin layer chromatography suggested that the reaction proceeded via the mono oxidation product **14** which was subsequently oxidized at the bridgehead position.

SCHEME 6



Selective selenium dioxide oxidation at the bridgehead position of alcohol **11** could be achieved, albeit in modest yield. Oxidation of **11** with tBuOOH and SeO_2 in dichloromethane, conditions developed by Sharpless and coworkers[34], provided a single isomer of the desired bridgehead alcohol **16** as the only identifiable product along with recovered starting material (Scheme 7). Typical runs yielded 10% of **16** (and 55% of the recovered **11**) but yields of **16** as high as 30% (along with 15% recovered **11**) occasionally were realized. Unfortunately, attempts to increase the efficiency and reliability of this reaction have met with little success. Under the same oxidation conditions, the bis silyl ether **13** was no longer oxidized preferentially at the bridgehead position. C_{12} esters of **11** were inert at 25° and heating to higher temperatures resulted in the formation of complex product mixtures presumably arising from oxidative side reactions due to the presence of tBuOOH. However, NMR analysis of crude and isolated products suggested selectivity for oxidation at the desired bridgehead position. Preliminary attempts to achieve oxidation of protected derivatives of **11** with SeO_2 and tert butyl alcohol in dichloromethane or 1,2-dichloroethane at reflux were frustrated by a sluggish reaction rate although further studies are contemplated.

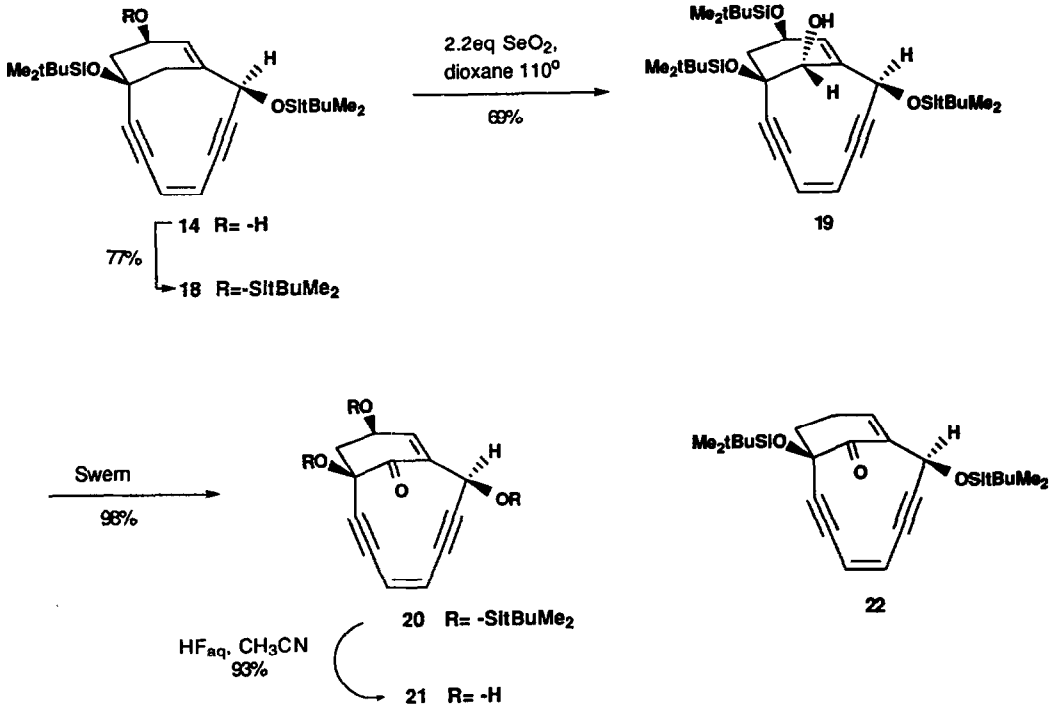
SCHEME 7



11

16 R = -H
17 R = -SitBuMe2

SCHEME 8



SYNTHESIS OF A HYDROXYLATED CORE WITH ENONE TRIGGER

The enone moiety of **1** has been shown to be an effective trigger for formation of a benzene diradical after conjugate addition of thiol at physiological pH. Installation of a bridgehead ketone moiety into allylic alcohol **14** provided an operational hydroxylated analog of **1** and was carried out using the sequence shown in Scheme 8. Silylation, bridgehead hydroxylation (SeO_2, dioxane), and Swern oxidation provided the protected keto

triol **20** in 52% overall yield. Desilylation of **20** using aqueous HF in CH_3CN[35] for extended reaction times at ambient temperature provided compound **21**, a hydroxylated analog of **1** in 93% yield. Similar methodology provided the bis silyl ketone **22** from bridgehead alcohol **17**.

CONCLUSION

A facile synthesis of **11** which contains the carbon core skeleton of the esperamicins and calicheamicins has been achieved. The overall yield of **11** from keto ester **2** on multigram scale is 46%. The key step is a high yielding cyclization which occurrs at ambient temperature and normal dilution. The relative stereochemistry of the C_{12} alcohol formed during the cyclization is dependent on the reaction temperature. Methods for selective functionalization of the core have been developed. The biological evaluation of simple core analogs prepared by this methodology will be described in the future. It is hoped that this methodology will find application in future attempts to prepare more stable and efficacious enediyne anti tumor antitumor agents.

ACKNOWLEDGEMENTS

We are grateful to Stella Huang for NMR spectroscopy support, Rich Dalterio for IR spectra, and to Steve Klohr for providing timely high resolution mass spectral data.

EXPERIMENTAL SECTION

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recored on a Perkin Elmer 1800 FTIR spectrophotometer either neat as a capillary film, as a KBr pellet, or in $CHCl_3$ as indicated. Proton NMR and carbon NMR spectra were recorded on a Varian Gemini 300MHz spectrometer or a Bruker 30MHz AC 300 in the indicated solvent and are reported in ppm downfield from tetramethylsilane. Elemental analysis was performed by Oneida Research Services Inc. Whitesboro, NY. Routine monitoring of reactions was performed using Whatman silica gel 60 MK6F glass backed TLC plates. Flash chromatography was performed with the indicated solvents using EM C60 silica gel. Air and miosture sensitive reactions were performed using the usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried in an oven at 140° and then cooled under nitrogen or in the case of palladium coupling reactions, argon. Aldrich anhydrous grade solvents and reagents were generally used without further purification with the exception of THF and diethyl ether which were distilled from sodium benzophenone ketal prior to use.

Computations The modeling studies were conducted with Quanta/CHARMM[36] software (version 3.1)[37] running on an IBM Risk 6000/540 workstation and MOPAC 6.0[19] running on a Cray Y-MP2E. The Chemnote molecular drawing routine was used to generate 3-dimentional coordinants for each reactant and product. The molecules were than relaxed with an adopted-basis Newton Raphson (ABNR) minimizer[36] to a RMS gradient force of ≤ 0.01. The non-bonded interactions were smoothed to zero with the shift/vswitch

functions between 10.0Å - 14.0Å with a 15.0Å cutlist. The force field minimized structures were then minimized using the AM1[17], PRECISE, EF, NODIIS, XYZ and CHARGE=-1 keywords to obtain their ground state conformations and energies. The transition state structure for each reaction was estimated using the SADDLE[38] routine. The transition state conformations and energies were optimized with the TS[18] routine. Each transition state was tested by diagonalising the Hessian matrix with a FORCE calculation to ensure that only one negative eigenvalue exists.

5-Hydroxy-5-trimethylsilanylethynyl-cycohex-1-enecarboxylic acid methyl ester (3).
Cerium trichloride heptahydrate (33.76g, 91.43mmol) was heated at 140-150°C in a 500mL flask under a vaccuum of 1 torr for 2h. the heat source was then removed and the solid was allowed to stir under vaccuum at ambient temperature for 16h. Nitrogen and then 250 mL of dry tetrahydrofuran were added to the flask and the suspension was stirred vigorously for two hours at 25°. The stirred suspension was then cooled to -78°.
A solution of 1.0 M lithium bistrimethylsilylamide 77.3 mL (77.3mmol) was added over 10 minutes to a separate flask which contained a stirred solution of 7.8g (79.4 mmol) trimethylsilylacetylene in 100 mL of tetrahydrofuran stirring at -78°. The solution was allowed to stir for an additional 30 minutes and then was added via cannula over over 5 minutes to the vigorously stirred cerium trichloride suspension.
A solution of 10.0g (70.3mmol) of ketoester **2** in 50 mL of dry THF at 2° was added dropwise over 5 minutes via cannula. The reaction was stirred for 20 minutes at -78° and then the cooling bath was removed. The reaction was allowed to stir for an additional 20 minutes and then 400 mL of a saturated aqueous ammonium chloride solution was added. The reaction was filtered by suction through celite accompanied by liberal washing with 1:1 ethyl acetate/diethyl ether. The layers were separated and the aqueous phase was rextracted with two 100 mL portions of ethyl acetate. The combined organic extracts (~1600mL) were washed with 150 mL of saturated aqueous NaCl, dried over anhydrous sodium sulfate, and concentrated in vacuo. Flash chromatography over silica gel using a gradient of 10-15% ethyl acetate hexane as eluent provided 13.6g (77%) of the desired product (TLC rf just above starting material in 15% EtOAc/hexane on SiO_2) as a colorless oil: IR (neat) :3438 (br), 2166 (w), 1716, 1250, 1038, 878 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (m, 1H), 3.75 (s, 3H), 2.66 (d of ABq, J=2.0Hz, J_{AB} =18.7Hz, 2H), 2.42 (m, 2H), 2.03 (s, 1H), 1.87 (t, J=3.6Hz, 2H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) d 167.17, 138.70, 126.83, 108.53, 87.68, 65.85, 51.63, 38.58, 34.08, 23.72, 0.00; DCI MS (isobutane) :M+H=253; Anal. calcd. for $C_{13}H_{20}O_3Si$: C, 61.87; H, 7.99. Found: C, 61.74; H, 7.90.

5-[(tert-butyldimethylsilyl)oxy]-5-trimethylsilanylethynyl-cyclohex-1-enecarboxylic acid methyl ester (4). Neat tertbutyl dimethylsilyl trifluoromethanesulfonate 2.6 mL (11.24 mmol) was added to a stirred solution of 2.58g (10.22 mmol) tertiary alcohol **3** and 1.8 mL (15.33 mmol) 2,6 Lutidine in 35 mL of dichloromethane at 2°. The reaction was stirred for 1 minute and then the cooling bath was removed. The reaction was allowed to stir for 5h and then was diluted with approximately 65 mL dichloromethane and washed sequentially with 50 mL of water and then 50 mL of saturated aqueous brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel using a gradient of 2 to 5% ethyl acetate/hexane provided 3.62g (97%) of a colorless oil which solidified in the freezer: IR (neat) :2956, 2162, 1712, 1270, 1252, 1240, 1086, 838 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 6.97 (m, 1H), 3.74 (s, 3H), 2.58 (ABq, J_{AB}=18.7Hz, 2H), 2.33 (m, 2H), 1.81 (t, J=6.4Hz, 2H), 0.83 (s, 9H),

0.18 (s, 6H), 0.15 (s, 9H); ^{13}C NMR (300MHz, $CDCl_3$) d 167.45, 138.80, 127.01, 109.29, 88.51, 66.77, 51.57, 39.67, 35.49, 25.69, 23.72, 18.05, -0.24, -3.07; DCI MS (isobutane) :M+H=367; Anal. calcd. for $C_{19}H_{34}O_3Si_2$: C, 62.24; 9.35. Found: C, 62.13; H, 9.26. M.P. 50.2 -51.8°

2-Hydroxymethyl-4-[(tert-butyldimethylsilyl)oxy]-4-trimethylsilanylethynyl-cyclohex-1-ene (5).

A 1.0M solution of diisobutylaluminumhydride in hexanes (21.7 mL, 21.7 mmol) was added over 15 seconds to a stirred solution of 3.62g (9.88 mmol) methyl ester 4 in 25 mL of dichloromethane at -78° under N_2. The reaction was stirred for ten minutes and then the cooling bath was removed. The reaction was allowed to stir for an additional 15 minutes and was washed with several portions of saturated potassium sodium tartrate solution. The combined aqueous washes were rextracted with three portions of dichloromethane and then the organic extracts were combined and dried over anhydrous magnesium sulfate. Concentration in vacuo followed by flash chromatography over silica gel using 10 through 20% EtOAc/hexane as eluent provided 3.34g (100%) of a colorless oil which solidified in the freezer: IR (neat) : 3320 (b), 2164 (w), 1252, 1088, 840 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.67 (m, 1H), 3.99 (bs, 2H), 2.35 (ABq, J_{AB}=15.6Hz, 2H), 2.19 (m, 2H), 1.78 (t, J=6.3Hz, 2H), 0.82 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (300MHz, $CDCl_3$) δ 134.12, 121.82, 109.95, 87.84, 67.37, 67.03, 41.45, 36.38, 25.67, 22.88, 18.04, -0.21, -2.94, -3.06; FAB mass spectrum, m/e 339.2189, M+H calcd for $C_{18}H_{34}O_2Si_2$ 339.2176. Anal. calcd. for $C_{18}H_{34}O_2Si_2$: C, 63.84; H, 10.12. Found: C, 63.56; H, 10.18. M.P. 47.8 to 49.6°.

4-Ethynyl-2-hydroxymethyl-4-[(tert-butyldimethylsilyl)oxy]cyclohex-1-ene (6).

Solid potassium carbonate (0.45g, 3.25 mmol) was added to a solution of 2.22g (6.55 mmol) of the trimethylsilyl alkyne 5 stirring in 45 mL of methyl alcohol at 25° under an atmosphere of N_2. The reaction was stirred for 16h and was then concentrated on a rotary evaporator at bath temperature 25°. The residue was dissolved in 120mLdichloromethane and approximately 60 mL of water and the layers were separated. The organic layer was washed with approximately 60 mL of saturated brine and then dried over anhydrous sodium sulfate. Flash chromatography over silica gel using 5-20% ethyl acetate/hexane as eluent provided 1.72g (99%) of a colorless oil: IR (neat) :3310 (b), 1472, 1464, 1252, 838, 778 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.67 (m, 1H), 3.99 (d, J= 6.1Hz, 2H), 2.38 (ABq, J_{AB}=15.6Hz, 2H), 2.22 (m, 2H), 1.82 (m, 2H), 1.23 (t, J=6.2Hz, 1H), 0.85 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 134.2, 122.0, 87.6, 72.0, 67.3, 67.0, 41.5, 36.4, 25.7, 23.2, 18.0, -2.93, -2.99; FAB mass spectrum, m/e 267.1785, M+H calcd for ($C_{15}H_{26}O_2Si$) 267.1780.

2-Hydroxymethyl-4-[(tert-butyldimethylsilyl)oxy]-4-(6-trimethylsilanyl-hex-3-ene-1,5-diynyl)-cyclohex-1-ene (8).

Note: All reagents and solutions utilized in this experiment were degassed by bubbling a stream of argon through the liquid material. All operations were conducted under a positive pressure of argon.

Neat vinyl chloride 7 (8.50g, 43.8 mmol) followed by 7.75 mL (78.2 mmol) of n-butylamine were added by cannula to a stirred semi solution of 1.49g (7.82 mmol) CuI and 2.26g (1.95 mmol) $Pd(PPh_3)_4$ in 32 mL of dry tetrahydrofuran at 25°. Then a solution of 10.42g (39.1 mmol) acetylenic alcohol 6 in 16 mL of tetrahydrofuran was added via cannula over 3 minutes. The reaction became relatively warm and was briefly cooled by blowing a stream of air into the empty flask surrounding the bath. After about 45 minutes the

reaction began to slowly cool and the flow of air was dicontinued. The reaction was stirred for a total time of 2.23 h and then a stream of air was bubbled through the reaction for 15 minutes. 1l of 1:1 diethyl ether: pentane was added and the reaction was filtered through a fritted funnel by suction. The organic filtrate was washed with three 300 mL portions of saturated ammonium chloride and one 300 mL portion of saturated sodium chloride and then dried over anhydrous sodium sulfate. The Flash chromatography over SiO_2 using 5% thru 15% ethyl acetate / hexane as eluent provided 14.51g (96%) of the desired product as a brown oil: IR (neat) :3330(b), 2146 (w), 1472 (w), 1462 (w), 1252, 1088, 842 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.83 (s, 2H), 5.66 (m,1H), 3.99 (d, J=4.5Hz, 2H), 2.42 (ABq, J_{AB}= 15.6Hz, 2H), 2.25 (m, 2H), 1.86 (m, 2H), 1.22 (t, J=4.5Hz, 1H), 0.86 (s, 9H), 0.21 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 134.2, 122.1, 119.9, 119.4, 102.4, 101.9, 101.1, 81.3, 67.9, 67.1, 41.6, 36.6, 25.7, 23.3, 18.0, -0.15, -2.79, -2.85; Anal. calcd. for $C_{22}H_{36}O_2Si_2$: C, 67.98; H, 9.33. Found: C, 67.69; H, 9.22. DCIMS (isobutane) :M+H=389.

4-(Hex-3-ene-1,5-diynyl)-2-hydroxymethyl-4-[(tert-butyldimethylsilyl)oxy]-cyclohex-1-ene (9).
Solid potassium carbonate (2.62g, 18.97mmol) was added in one portion to a solution of 14.67g (37.9 mmol) trimethylsilyl acetylenic alcohol **8** in 431 mL of methyl alcohol stirring under an atmosphere of nitrogen at 25°. The reaction was stirred for 2.8h and then concentrated on a rotary evaporator at 30°. The residue was dissolved in 500 mL diethyl ether and 250 mL of water. The water layer was drawn off and the organic layer was washed with 150 mL saturated aqueous NaCl and then dried over anhydrous sodium sulfate. Flash chromatographic purification over silica gel using 10% to 15% ethyl acetate as eluent provided 10.3g (86%) of nearly colorless oil: IR (neat) :3302 (b), 1472 (w), 1462(w), 1252, 1090, 834, 778 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.92 (d, J=11.2Hz, 1H), 5.78 (dd, J= 11.0, 2.5Hz, 1H), 5.66 (m, 1H), 3.98 (d, J=6.0Hz, 2H), 3.28 (d, J=2.4Hz, 1H), 2.43 (ABq, J_{AB}=16.6Hz, 2H), 2.25 (m, 2H), 1.88 (m, 2H), 1.26 (m, 1H), 0.858 (s, 9H), 0.203 (s, 3H), 0.196 (s,3H); ^{13}C NMR (300MHz, $CDCl_3$) d 134.13, 121.99, 121.15, 118.20, 101.17, 84.48, 80.90, 80.69, 67.98, 66.87, 41.53, 36.48, 25.64, 25.58, 23.25, 17.94, -2.90, -2.96; FAB mass spectrum, m/e 317.1948, M+H calcd for ($C_{19}H_{28}O_2Si$) 317.1937.

5-(Hex-3-ene-1,5-diynyl)-5-[(tert-butyldimethylsilyl)oxy]-cyclohex-1-enecarboxaldehyde (10).
Swern Oxidation
A solution of 13.36mL, 0.188mol DMSO in 98 mL of CH_2Cl_2 was added over 5 min to a solution of 8.2 mL, 0.112 mol oxalyl chloride in 197mL of CH_2Cl_2 stirring in a -78° dry ice/ acetone cooling bath. The reaction was stirred for 10 min and then a solution of 9.87g, 0.0314 mol of alcohol **9** in 97mL of CH_2Cl_2 was added over 5 min. The reaction was stirred for 10 min and then 21.88mL, 0.157 mol of neat triethylamine was added via syringe in one portion. The cooling bath was removed and the reaction was allowed to stir for 10 min. the reactioon was diluted with approximately 600mL of Et_2O and then washed successively with 100ml portions of 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography over silica gel using 18:1 hexane:EtOAc as eluent provided 8.38g (85%) of a colorless oil:
IR (neat) :3300 (w), 1686, 1090, 838 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 9.47 (s, 1H), 6.81 (m, 1H), 5.90 (d, J=11.1Hz, 1H), 5.80 (dd, J=11.0, 2.3Hz, 1H), 3.28 (d, J=2.5Hz, 1H), 2.61 (ABq, J_{AB}=16.0Hz, 2H), 2.57 (m, 2H), 1.96 (t, J=6.3Hz, 2H), 0.83 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 193.5,

150.0, 138.6, 120.8, 118.8, 100.1, 84.7, 81.6, 80.6, 66.8, 37.1, 36.2, 25.6, 24.7, 18.0, -3.0; FAB mass spectrum, m/e 315.1787, M+H calcd for ($C_{19}H_{26}O_2Si$) 315.1780m/e 315.1787.

TPAP Oxidation

Molecular sieves , 4A, activated powder, (16.2g) followed by 5.7g (48.6 mmol) of 4-methylmorpholine-N-oxide were added to a solution of 10.2g (32.43 mmol) alcohol stirring at 25 in 130 mL of anhydrous acetonitrile under an atmosphere of nitrogen. Solid tetrapropylammoniumperruthenate (TPAP), (0.57g, 1.62 mmol) was added in a single portion. The reaction was allowed to stir vigorously for 75 minutes and was then concentrated on a rotary evaporator (bath temp 25°). The residue was dissolved in a minimal amount of dichloromethane and placed atop a silica gel column which had a pad of celite on the top. Elution with 5% EtOAc/hexane provided 8.34g (86%) of nearly colorless oil which had the same properties as the product arising from the Swern oxidation.

12ß-Hydroxy-5-[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (11).

1,1,1,3,3,3-Hexamethyldisilazane (3.1 mL, 14.7 mmole) and 5.5 mL, 13.8 mmole of 2.5 molar n-butyl lithium were added sequentially by syringe to 125 mL of freshly distilled tetrahydrofuran stirring at 25° under an atmosphere of N_2. The base solution was stirred vigorously for 5 min at 25° and then a solution of 3.80 grams (12.1 mmole) of aldehyde in 35 mL of anhydrous THF was added via cannula over 4.5 min. The reaction mixture took on a brown coloration as the addition was initiated. The continuously darkening reaction was allowed to stir for an additional 8 minutes after the completion of aldehyde addition. At this time TLC (20% ethyl acetate/hexane on silica) indicated that starting material had been consumed so 200mL of saturated ammonium chloride was added. The reaction was extracted sequentially with one 600 mL portion of diethylether, one 100 mL portion of diethyl ether, and then 120mL of 9:1 ethyl acetate : diethyl ether. The combined organic extracts were washed with one 150mL portion of saturated aqueous NaCl, dried over anhydrous sodium sulfate, and concentrated in vacuo. Flash chromatography over SiO_2 using 5 through 20% ethyl acetate/hexane as eluent provided 2.95 grams (77.4%) of the desired product as a colorless viscous oil. This material eventually solidified into low melting white rosettes upon storage in a freezer: IR (neat) :3854(b)3320, 3054, 2954, 2930, 2894, 1472, 1462, 1088,838, 760 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.85 (d, J=9.5Hz, 1H), 5.76 (dd, J=9.5, 1.5Hz, 1H), 5.61 (q, J=3.1Hz, 1H, 5.22 (d, J=4.0Hz, 1H), 3.08 (dd, J=2.5, 14.4Hz, 1H), 2.40 (m, 1H), 2.35 (m, 1H), 2.40-2.20 (m, 1H), 2.03-1.95 (m, 1H), 1.91 (d, J=4.7Hz, 1H), 1.87-1.76 (m, 1H), 0.89 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 137.5, 124.6, 122.6, 121.9, 103.6, 100.8, 86.0, 85.1, 70.4, 69.0, 44.0, 35.0, 25.7, 24.7, 17.9, -2.8, -2.9; FAB mass spectrum, m/e 315.1784, M+H calcd for ($C_{19}H_{27}O_2Si$) 315.1780.

12α-Hydroxy-5-[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (12).

A 1.0M solution of $LiN(TMS)_2$ in THF (0.5mL, 0.5mmol) was added in one portion to 5 mL of dry THF stirring under N_2. The solution was cooled in an ice, water salt bath to 0°. A solution of 0.135g, 0.429mmol of aldehyde **10** in 7mL of THF which had been precooled to 0° was added over 30 seconds via cannula. The reaction was stirred for an additional 4 min and then was poured into 50 mL of sat. aq. NH_4Cl and 50mL of diethyl ether. The mixture was extracted and then rextracted with an additional 50 mL prtion of ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography over SiO_2 using 2through 5% EtOAc/hexane as eluent provided 9.8 mg (7%) of recovered **10** and then 91mg

(67%) of a viscous colorless oil. This material solidified into low melting white rosettes upon storage in the freezer. ^{1}H NMR indicated the presence of a just detectable amount of inseparable unidentified contaminant. IR (neat) 3344 b, 3054, 2954, 2930, 2896, 2858, 1472, 1462, 1434, 1250, 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) 5.84 (d, J=9.5Hz, 1H), 5.75 (dd, 9.5, 1.5Hz, 1H), 5.60 (q, J=3.3Hz, 1H), 5.22 (s, 1H), 3.08 (dd, J=14.4, 2.5Hz, 1H), 2.40 (m, 1H), 2.34 (m, 1H), 2.32-2.10 (m, 1H), 2.03-1.95 (m, 1H), 1.88-1.76 (m, 1H), 0.89 (s, 9H), 0.206 (s, 3H), 0.193 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 137.57, 124.56, 122.62, 121.88, 103.68, 100.80, 86.00, 85.10, 70.42, 68.98, 43.96, 34.99, 25.70, 24.70, 17.94, –2.80, –2.92; DCI MS (isobutane) :M+H=315. Anal. calcd. for $C_{19}H_{26}O_2Si$: C, 72.56; H. 8.33. Found: C, 72.20; H, 8.10. M.P. 74.5-77.8°.

Attempted Equilibration of **12**

A 1.0M solution of $LiN(TMS)_2$ in THF (0.10mL, 0.1mmol) was added to a solution of 13.5mg, 0.043mmol alcohol **12** in 2mL of THF at 25°. The The reaction was stirred for 5min and then an additional 0.40 mL, 0.40mmol of base solution was added. The reaction was stirred for 3 min and then poured into sat. aq NH_4Cl. The reaction was extracted with three portions of ether, dried over Na_2SO_4 and concentrated in vacuo. ^{1}H NMR of the crude product showed no new products and clean, unchanged starting material **12.**

5,12ß-Bis[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (13).

Solild tert-butyl dimethylsilyl chloride (1.38g, 9.15 mmol) was added to a solution of 1.12g, 16.45 mmol of imidazole and 2.07g, 6.58 mmol of alcohol **11** in 25mL of DMF stirring at 2°. The reaction was stirred for 5 min and then the cooling bath was removed. Stirring was continued for 5h at ambient temperature and then the reaction was poured into 100mL of hexane and 100 mL of water. The mixture was extracted and the aqueous layer was rextracted with an additional 50mL portion of hexane. The combined organic extracts were washed with 50mL of brine, dried over Na_2SO_4, and concentrated in vacuo to provide a yellow oil. Flash chromatographic purification over silica gel using a gradient of 0 to 3% EtOAc/hexane provided 2.48g (88%) of the desired product as an off white amorphous solid:

IR (neat) 3050, 2956, 2930, 2886, 2856, 1472, 1464 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 5.80 (d, J=9.5Hz, 1H), 5.73 (dd,J=9.51,1.4Hz, 1H) 5.49 (m, 1H), 5.15 (s, 1H), 3.11 (dd, J= 14.8, 2.7Hz,1H), 2.38-2.10 (m, 3H), 1.98 (m, 1H), 1.79 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 139.002, 123.90, 122.976, 120.04, 103.45, 102.19, 85.077, 70.539, 69.586, 44.131, 35.152, 25.754, 24.770, 18.195, 17.97, -2.757, -2.890, -4.744, -4.901; FAB mass spectrum, m/e 429.2659, M+H calcd. for $C_{25}H_{41}O_2Si_2$ 429.2645. Anal. Calcd. for $C_{25}H_{40}O_2Si_2$: C, 70.03; H, 9.40. Found: C, 70.14; H, 9.39. M.P. 47.3-51.5°.

3ß-Hydroxy-5,12ß-bis[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (14).

Solid SeO_2 (50mg, 0.45mmol) was added to a stirred solution of 152.2 mg, 0.355 mmol bissilyl ether **13** in 5 mL of dioxane. The reaction was immersed in an oil bath which had been preheated to 100°. After 15 minutes TLC showed the presence of two new products of low rf but starting material still predominated. An additional 52mg, 0.468 mmol of SeO_2 was added and the reaction was carefully monitored by TLC. After ten minutes, the nearly complete consumption of starting material was observed and the reaction was removed from the oil bath, diluted with approximately 100 mL Et_2O and washed consecutively with 30 mL portions of sat. aq. $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated in

vacuo, and purified by flash chromatography using CH_2Cl_2 as eluent to provide 64mg (40%) of an offwhite solid which was the desired mono allylic alcohol:
IR (neat) 3356, 2956, 2930, 2886, 2858, 1472, 1464, 1362, 1256 , 1130 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.81 (d, J=9.5Hz, 1H), 5.75 (dd, J=9.5, 1.4Hz, 1H), 5.56 (t, J=3.4Hz, 1H), 5.17 (s, 1H), 4.33 (bm, 1H), 3.08 (dd, J=15.0, 3.0Hz, 1H), 2.52-2.44 (m, 1H), 2.37 (dt, J=15.0, 3.1Hz), 1.77 (dd, J=12.3,9.7 Hz, 1H), 1.60 (bs, 1H), 0.91 (s,9H), 0.89 (s, 9H), 0.20 (s, 6H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 141.87, 123.85, 123.186, 121.847, 102.37, 101.624, 85.597, 85.252, 71.825, 69.199, 68.511, 45.679, 44.568, 25.673, 25.495, 18.145, 17.922, -2.819, -2.977, -4.759, -4.953; FAB mass spectrum, m/e 445.2609, M+H calcd for $C_{25}H_{41}O_3Si_2$ 445.2594. A second product (17mg, 11%) eluted later and was isolated as a light yellow solid which was the diol **15**.

5,12ß-Bis[(tert-butyldimethylsilyl)oxy]-3ß,13ß-dihydroxy-bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (15). Solid SeO_2 (77mg, 0.697 mmol) was added in one portion to a solution of 0.249g, 0.581mmol of bis silyl ether **13** in 2 mL of dioxane at 25°. The reaction was placed under a condenser and immersed in an oil bath which had been preheated to 105°. The reaction was stirred for 15 min and then an additional 100mg, 0.91mmol of SeO_2 was added. The reaction was stirred for an 20 min more and then was transferred into a separatory funnel containing 40mL of sat. aq. $NaHCO_3$ using 50 mL of 1:1 Et_2O/ EtOAc total. The layers were separated and then the aqueous layer was reextracted with an additional 40 mL of 1:1 Et_2O/ EtOAc. The combined organic extracts were washed with 40 mL of brine and then dried over anhydrous Na_2SO_4. Flash chromatography over silica gel using a gradient of 10 to 30% EtOAc/hexane as eluent provided 38mg (15%) of mono alcohol **14** and 107 mg (40%) of the desired diol as an off white solid:
IR (neat) 3574, 3414, 2954, 2930, 2884, 2858, 1472, 1464, 1254, 838 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 5.84 (d, J=9.6Hz, 1H), 5.81-5.77 (m, 2H), 5.25 (s, 1H), 4.58 (s, 1H), 4.15 (bs, 1H), 2.82 (s, 1H), 2.33 (dd, J=12.5,7.8Hz, 1H), 2.26 (bs, 1H), 2.14 (dd, J= 12.8,8.2Hz, 1H), 0.94 (s, 9H), 0.913 (s, 9H), 0.24 (s, 3H), 0.22 (s,3H), 0.17 (s,3H), 0.15 (s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 143.167, 126.535, 123.524, 123.399, 101.775, 100.198, 86.902, 86.84, 72.744, 72.251, 68.457, 66.424, 39.251, 25.752, 18.325, 17.999, -3.003, -3.049, -4.872. FAB mass spectrum M+Na=483. Anal. calcd. for $C_{25}H_{40}O_4Si_2$: C, 65.17; H, 8.75. Found: C, 64.89, H, 8.75.

12ß,13ß-Diydroxy-5-[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (16). To SeO_2 (16 mg, 0.148 mmol) was added *t*-Butyl hydroperoxide (90%, 62 mg, 0.62 mmol) in 0.5 mL of methylene chloride. This solution was stirred 25 minutes until most of the SeO_2 had dissolved. Then the alcohol **11** (47 mg, 0.149mmol) in 1.5 mL of methylene chloride was added and stirred 39 hrs. The reaction was stirred with 0.65 mL of 1N NaOH diluted with ether and washed with water and brine. The etheral fraction was dried($MgSO_4$), concentrated and chromatographed over silica gel (3:1 hexane/ethyl acetate) to give 6 mg of recovered starting material (13%) along with 15 mg of allylic alcohol (30%) as a colorless oil.
IR (film) 3400 br, 1254, 1084, 838, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (m, 3H), 5.31 (s, 1H), 4.65 (s, 1H), 2.50 (br s, 2H), 2.37 (m, 1H), 2.16 (m, 1H), 2.13 (m, 1H), 1.79 (m, 1H) 0.90 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 3.1.DC139.4, 125.9, 123.7, 123.3, 101.2, 100.0, 87.7, 87.1, 72.4, 72.1, 68.7, 27.5, 25.8, 24.2, 18.0, -3.0, FAB mass spectrum, m/e 331.1718, M+H calcd for $C_{19}H_{27}SiO_3$ 331.1729.

13ß-Hydroxy-5,12ß-bis[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (17). To a solution of the allylic alcohol **16** (29 mg, 0.088 mmol) was added imidazole (17 mg, 0.249 mmol) follwed by *t*-Butyldimethylsilyl chloride (20 mg, 0.132 mmol). This solution was stirred for 19 hrs. The reaction was diluted with ether and washed with water, dried($MgSO_4$), concentrated and chromatographed over silica gel (19:1 hexane/ethyl acetate) to give 17 mg of the bis silyl derivative (43%) as a clear colorless oil. IR (film) : 3500-3400 br, 2202(w), 1254, 1126, 1078, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.79 (m, 2H), 5.65 (t, J = 3.1 Hz, 1H), 5.23 (s, 1H), 4.60 (s, 1H), 2.67 (br s, 1H), 2.33 (m, 1H), 2.15 (m, 2H), 1.76 (m, 1H) 0.94 (s, 9H), 0.90 (s, 9H), 0.21 (s, 6H), 0.16 (s, 3H), 0.141 (s, 3H); ^{13} C NMR ($CDCl_3$, 300 MHz) d 140.6, 124.4, 123.5, 123.3, 102.5, 100.5, 87.1, 86.4, 72.3, 72.2, 69.1, 27.7, 25.8, 24.2, 18.4, 18.0, -3.0, -3.0, -4.9; FAB mass spectrum, m/e 445.2603, M+H calcd for $C_{25}H_{41}Si_2O_3$ 445.2594.

13ß-Hydroxy-5,12ß-bis[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (18). To a solution of the allylic alcohol **14** (52 mg, 0.117 mmol) in 10 mL of methylene chloride at 0 °C was added 2,6 lutidine (20 mL, 0.172 mmol) followed by TBSOTf (30mL, 0.130 mmol) and stirred for 30 min and diluted with ether. The etheral solution was washed with bicarbonate and dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (99:1 hexane/ethyl acetate) to give 51 mg of the trisilyl ether (77%): IR(film) 1472, 1254, 1112, 1066, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78 (ABq, J = 17.4, 9.5 Hz, 2H), 5.44 (t, J = 3.2 Hz, 1H), 5.14 (s, 1H), 4.30 (m, 1H), 3.05 (dd, J = 14.8, 2.9 Hz, 1H), 2.41-2.27 (m, 2H), 1.82 (dd, J = 12.4, 9.4 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 18H), 0.19 (s, 6H), 0.14 (s, 6H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 140.6, 123.9, 122.6, 102.9, 101.9, 85.4, 85.0, 71.8, 69.2, 69.1, 45.7, 44.4, 25.9, 25.7, 18.2, 18.0, -2.7, -2.9, -4.5, -4.7; FAB mass spectrum, m/e 581.3266, M+H calcd for $C_{31}H_{54}O_3Si_3Na$ 581.3278.

13ß-Hydroxy-3ß,5,12ß-tris[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (19). To a solution of the trisilyl ether **18** (51 mg, 0.91 mmol) in 5 mL of 1,4 dioxane was added SeO_2 (12 mg, 0.108 mmol) and the solution heated to 110 °C for 1 hr. The solution was diluted with chloroform and washed with bicarbonate. The solution was dried over $MgSO_4$ and concentrated and the residue chromatographed over silica gel (99:1 hexane/ethyl acetate) to give 36 mg of allylic alcohol (69%) along with recovered starting material IR(film) 3572 (br), 1472, 1252, 1124, 1068, 836, 776 cm^{-1}; ^1H NMR (300Mz, $CDCl_3$, 300 MHz) δ 5.78 (ABq, J = 14.9, 9.6 Hz, 2H), 5.56 (d, J = 3.5 Hz, 1H), 5.21 (s, 1H), 4.52 (s, 1H), 4.16 (m 1H), 2.56 (s, 1H), 2.20 (dd, J = 12.2, 9.5 Hz, 1H), 2.03 (dd, J = 12.2, 7.1 Hz, 1H), 0.91 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 141.5, 127.1, 123.5, 123.4, 102.0, 100.3, 86.9, 86.8, 72.7, 72.2, 68.9, 67.9, 38.4, 25.8, 18.3, 18.1, -3.0, -4.4, -4.4, -4.9, -4.9; FAB mass spectrum, m/e 575.3392, M+H calcd for $C_{31}H_{55}O_4Si_3$ 575.3408.

13-keto-3ß, 5, 12ß-tris[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (20). To a solution of oxalyl chloride (100 mL, 1.15 mmol) in 8 mL of methylene chloride at -78°C was added DMSO (160 mL, 2.40 mmol) followed by the allylic alcohol **19** (116 mg, 0.20 mmol) in 3 mL of methylene chloride. After 10 min. at -78°C triethylamine (275 mL, 1.97 mmol) was addedand the cold bath removed. The solution was diluted with ether and washed with 0.5N HCl, bicarbonate and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (99:1 hexane/ethyl acetate) to give 109 mg of enone (98%): IR(film) 1730, 1256, 1126, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.17 (t, J = 2.5 Hz, 1H),

5.82 (s, 2H), 5.41 (s, 1H), 4.24 (m, 1H), 2.51 (ddd, J = 12.9, 6.2, 2.0 Hz, 1H), 2.06 (dd, J = 12.9, 9.4 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 189.5, 139.5, 137.7, 124.0, 122.7, 100.8, 97.0, 90.4, 87.7, 75.4, 69.1, 66.8, 45.3, 26.0, 25.8, 25.7, 18.4, 18.4, 18.0, -2.8, -3.2, -4.5, -4.6, -4.6, -4.6; FAB mass spectrum, m/e 595.3052, M+H calcd for $C_{31}H_{52}O_4Si_3Na$ 595.3071.

13-keto-3ß, 5, 12ß-trihydroxy bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (21)

To a solution of the trisilyl ether **20** (109 mg, 0.19 mmol) in 16 mL of acetonitrile was added 6 mL of 48% HF. The solution was stirred for a total of 30 h. The solution was diluted with ethyl acetate and washed with brine. The brine was extracted with 2x50 mL ethyl acetate and let stand over solid $NaHCO_3$ decanted and the solution dried with $MgSO_4$. The solution was concentrated and the residue dissolved in a minimal amount of DMF and placed on a column of silica gel and eluted (1:1 hexane/ethyl acetate) to give 41 mg of an oil which was diluted with water and lyophilized (93%): IR(film) 3500-3200, 2188, 1694, 1032, 748 cm^{-1}; ^1H NMR (d-6 acetone, 300 MHz) δ 6.67 (t, J = 2.4 Hz, 1H), 6.05 (ABq, J = 20.3, 16.7 Hz, 2H), 5.40 (d, J = 10.4 Hz, 1H), 5.38 (s, 1H), 4.76 (d, J = 6.4 Hz, 1H), 4.62 (d, J 10.4 Hz, 1H), 4.49 (m, 1H), 2.70 (ddd, J= 12.9, 5.9, 1.9 Hz, 1H), 2.00 (dd, J= 12.9, 9.7 Hz, 1H); ^{13}C NMR (d-6 acetone, 75.5 Hz) δ 196.6, 143.7, 136.6, 125.1, 123.9, 101.8, 97.4, 91.2, 88.1, 73.9, 68.6, 66.3, 43.4; FAB mass spectrum, m/e 231.0657, M+H calcd for $C_{31}H_{11}O_4$ 231.0657.

13-Keto-5,12ß-bis[(tert-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (22).

To a solution of the allylic alcohol **17** (15 mg, 0.33 mmol) in CH_2Cl_2 (2.5 mL) was added the Dess Martin periodinane (19 mg, 0.145 mmol) and stirred 2.5 h at ambient temperature. Another portion of oxidant was added (5 mg, 0.012 mmol) and stirring continued for 1 h. The solution was filtered through Celite and another 10 mg of oxidant (0.024 mmol) was added and stirred 1 h. The solution was diluted with ether and washed with saturated bicarbonate and dried over $MgSO_4$. The solution was filtered, concentrated and the residue chromatographed over silica gel (19:1, hexane/ether) to give 10 mg (68%) of the bis silyl ketone which was identical in all respects to material prepared from BMY-46108: IR (film) : 1720, 1254, 1157, 1126, 839, 779 cm^{-1}; ^1H NMR ^1H NMR ($CDCl_3$, 300 MHz) δ 6.30 (br t, J = 1 Hz, 1H), 5.82 (s, 2H), 5.43 (s, 1H), 2.46 (m, 2H), 2.22 (m, 1H), 2.12 (m, 1H), 0.94 (s, 9H), 0.91 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H), 0.14 (s, 6H): FAB mass spectrum, m/e 443.2435, M+H calcd for $C_{25}H_{39}O_3Si_2$ 443.2438.

REFERENCES

1. (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold,G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J.Am. Chem. Soc.* **1987**, *109*, 3461-3462. (b) Golik, J.; Clardy, J.; Dubay, G.; Groenewold,G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462 and references therein.
2. (a) Lee, M.C.; Dunne, T.S.; Siegel, M. M.; Chang, C. C.; Morton, G.O.; Borders, D.B. *J.Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M.C.; Dunne, T.S; Chang, C.C.; Ellestad, G. A.; Siegel, M.M.; Morton, G.O.; McGahren, W. J.; Borders, D.B. *J.Am. Chem. Soc.* **1987**, *109*, 3466 and references therein.
3. (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Kamei, H.; Miyaki, T.; Tsuno, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiotics* **1989**, *XLII*, 1449.

4. (a) Lam, K.S.; Hesler, G.A.; Gustavson, D.R.; Crosswell, A.R.; Veitch, J.M.; Forenza, S. *J. Antibiotics* **1991**,*44*, 472. (b) Hofstead, S. J.; Matson, J. A..; Malacko, A. R.; Marquardt, H. *J. Antibiotics* **1992**,*45*, 1250. (c) Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Golik, J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T.W.;Matson, J. A. *J. Am. Chem. Soc.* **1992**, *114* , 7946. (d) Zein, N.; Colson K.; Leet J., Schroeder D.; Solomon W.; Doyle T. W.; Casazza A. M. *Proc. Natl. Acad. Sci. USA* **1993**, in press.
5. (a) Goldberg, I. H. *Accts. Chem. Res.*, **1991**, *24*, 191 and references therein. (b) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Okate, N.; Ishida, N.; *Tetrahedron Lett.* **1985**, *26*, 331. (c) Hensons, O. D.; Goldberg, I. H. *J. Antibiot.* **1989**, *42*, 761. (d) Hensons, O. D.; Giner, J. L.; Goldberg, I. H. *J. Am. Chem. Soc.* **1989**,*111*, 3295.
6 (a) esperamicins: i) Schurig, J. E.; Rose, W. C.; Kamei, H.; Nishiyama, Y.; Bradner, W.T.; Stringfellow, D. A. ii) Doyle, T. W.; Golik, J.; Wong, H.; Lam, K. S.; Langley, D.; Forenza, S. L.; Vyas, D. M.; Kelley, S. in Baker, L.; Valeriote, F.; Corbett, T.; (Eds.)): *Proc. 22nd Ann. Cancer Symp. Anticancer Drug Discovery and Development-1*,, Kluwer Acad. Publishers, Boston, MA, USA, in press. (b) calicheamicins: i) ref 2. ii) Lee, M. D.; Manning, J. K.; Williams, D. R.; Kuck, N.; Testa, R. T.; Borders, D. B. *J. Antibiot.* **1989**, *42*, 1070; Maiese, W. M.; Lechevalier, M. P.; Lechevalier, H. A.; Korshalla, J.; Kuck, N.; Fantini, A.; Wildey, M. J.; Thomas, J.; Greenstein, M. *ibid.* **1989**, *42*, 558. (c) dynemicins i) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715; ii) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamada, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y.; *J. Antibiot.* **1990**, *43*, 1000; iii) ref 3, (d) kedarcidin: ref 4 (e) (e) neocarzinostatin: Unpublished results of William C. Rose.
7 Unpublished results Bristol-Myers Squibb Co..
8. Zein, N.; Solomon, W.; Casazza, A. M.; Kadow, J. F.; Krishnan, B. S.; Tun, M. M.; Vyas, D. M.; Doyle, T. W. *Biorg.and Med.Chem.Lett.* **1993**, *3(6)*, 1351-1356.
9. Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science*, **1992**, *256*, 1172 and references therein.
10. (11) Rose, W. C. Unpublished results from these laboratories.
11. Danishefsky, S.J.; Mantlo, N.B.; Yamashita, D.S.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 6980.
12. Kende, A.S.; Smith, C.A. *Tetrahedron Lett.* **1988**, *29*, 4217.
13. Magnus, P.; Lewis, R. *J. Am. Chem. Soc.* **1988**, *110*, 6921.
14. For recent reviews see: a)Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci.* **1993**, *90*, 5881-5888. (b) Nicolaou, K. C.; Dai, W. M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.
15. (a) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253-3255. (b) Smith, A. L.; Hwang, C.K.; Pitsinos, E.; Scarlato, G. R.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, *114*, 3134.
16. (a) Kadow, J. F.; Tun, M. M.; Vyas, D. M.; Wittman, M. D.; Doyle, T. W. *Tetrahedron Lett.* **1992**, *11*,1423. (b) Kadow, J.F.; Saulnier, M.G.; Tun, M.M.; Langley, D.R.; Vyas, D.M. *Tetrahedron Lett.* **1989**, *30*, 3499.
17. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.
18. Baker, J. *J. Comp. Chem.* **1986**, *7*, 385.

19. (a) Steward, J. J. P. *MOPAC, A Semi-Empirical Molecular Orbital Program, QCPE* **1983**, 455; (b) Seiler, F. J. *MOPAC* **1990**, *6.0*,
20. Webster, F. W.; Silverstein, R. M. *Synthesis* **1987**, *10*, 922-924.
21. Inamoto, T.; Sugiura, Y.; Takiyama, T. *Tetrahedron Lett.* **1984**, *25*, 4233.
22. Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851.
23. ref 12. This material was isolated via distillation at atmospheric pressure on large scale.
24. Stephens, R. D.; Castro, C. E. *J.Org. Chem.* **1963**, *28*, 3313.
25. (a) Porco, J. A.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410-7411. (b) for an alternate preparation of the free enediyne see Bharucha, K. N.; Marsh, R. M.; Minto, R. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 3120-3121.
26. Lu, Y. F.; Harwig, C. W.; Fallis, A. G. *J. Org. Chem.* **1993**, *58*, 4202-4204.
27. Kanji Omura and Daniel Swern Tetrahedron vol 34 pp1651-1660.
28. Griffith, W. P.; Ley, S.P.; *Aldrich Chimica Acta* **1990**, *23(1)*, 13 and references therein
29. Tius, M. A.; Cullingham, J. M. *Tetrahedron Lett.* **1989**, *30*, 3749-3752.
30. Crevisy, C.; Beau, J-M. *Tetrahedron Lett.* **1991**, *30*, 3171-3174.
31. An x-ray crystal structure of diol **1** which was synthesized as described in references 10 and 18 has been obtained (Unpublished results from Dr. Jack Z.Gougoutas and Dr. Jerzy Golik.) Bissilyl ether **20** was prepared from the literature route and this new route and were found to be identical.
32. Proton NMR spectra of the crude products resulting from a cyclization at a temperature between 25° and 0° (A solution of aldehyde at ambient temperature was added to a solution of base cooled in an ice water bath which contained no salt) provided an approximately 1:1 mixture of **11** and **12**.
33. Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975-982.
34. Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
35. Newton, R. F.; Reynolds, D. P.; Finch, M.; Kelly, D.R.; Roberts, S.M. *Tetrahedron Lett.* 1979, *41*, 1979.
36. Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187-217.
37. Molecular Simulations 16 New England Executive Park, Burlington, MA 01803, USA.
38. Dewar, M. J. S.; Healy, E. F.; Stewart, J. J. P. *J. Chem. Soc., Faraday Trans* **1984**, *80*, 227-233.

(*Received* 1 *September* 1993; *accepted* 24 *November* 1993)