*J. Am. Chem. Soc.* **1992**, *114*, 2560–2567

# Synthetic and Mechanistic Studies on the Antitumor Antibiotics Esperamicin $A_1$ and Calicheamicin $\gamma_1$. Oxidative Functionalization of the 13-Ketobicyclo[7.3.1]tridecenediyne Core Structure: Construction of the Allylic Trisulfide Trigger

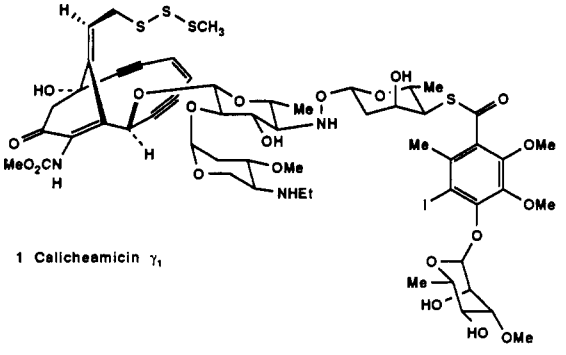
**Philip Magnus,*,† Richard Lewis,‡ and Frank Bennett‡**

*Contribution from the Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, and Department of Chemistry, Indiana University, Bloomington, Indiana 47405.* *Received August 26, 1991*

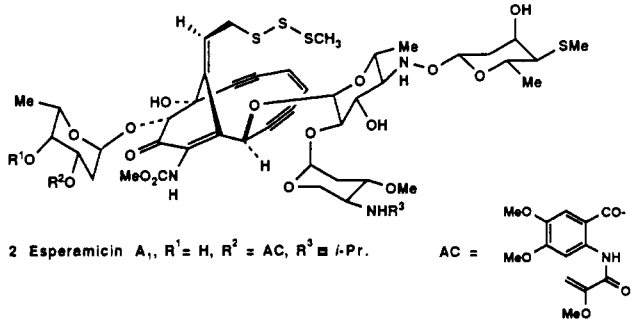
**Abstract:** The simple 13-ketobicyclo[7.3.1]tridecenediyne **3** core structure of the esperamicins/calicheamicin can be readily functionalized in an oxidative manner to introduce the 1,2 double bond and 3β-oxygen substituent. The 3β-hydroxyl substituent allowed the intramolecular introduction of a nitrogen functionality at C2, but the resulting cyclic carbamate was too resistant to hydrolysis to be synthetically useful. The allylic trisulfide trigger can be installed in a straightforward manner via Wittig chemistry on the 13-keto group. The relatively simple chemistry needed to functionalize the core system should allow access to a wide variety of analogues for biological evaluation of these potent antitumor agents.

## Introduction

In the accompanying paper the synthesis of the core structure of calicheamicin **1** and esperamicin **2**, namely, 13-ketobicyclo-



1 Calicheamicin $\gamma_1$



2 Esperamicin $A_1$, $R^1$ = H, $R^2$ = AC, $R^3$ = *i*-Pr. AC =

[7.3.1]tridecenediyne **3** is described.[1] It is readily made from the commercially available components (*Z*)-dichloroethylene, acetylene, propargyl alcohol, and cyclohexane-1,2-dione. Scheme I summarizes the overall route. The propargylic alcohol **4** was regiospecifically complexed with $Co_2(CO)_8$ to give the $\eta^2$ $Co_2(CO)_6$ adduct **5** (84%), which on treatment with $Tf_2O/CH_2Cl_2$/2,6-di-*tert*-butyl-4-methylpyridine (BMP) gave **6** (77%). Decomplexation of **6** by oxidation with iodine/benzene gave **3** (82%) as a stable crystalline compound.

The 13-ketobicyclo[7.3.1] enediyne **3** undergoes Bergman cycloaromatization at 79 °C in the presence of 1,4-cyclohexadiene to give **7** (>70%), $t_{1/2}$ 45 min; $k = 2.56 \times 10^{-4}$ s$^{-1}$, $\Delta G^{\ddagger} = 26.3$ kcal mol$^{-1}$ (37 °C).[2] Thus **3** provides a stable prototype model core enediyne structure upon which to examine the introduction of an oxygen functionality at C3, C4, and C12 and nitrogen at C2, and installation of the allylic trisulfide trigger. This nonconvergent strategy was adopted in order to investigate the types of transformations (particularly oxidative) that can be conducted on the intact enediyne core without destroying it. In this way it was hoped that a corpus of knowledge of enediyne chemistry could be accumulated which would be applicable to other members of this expanding new class of natural products.[3]

## C1–C13 Bridgehead Enolate Chemistry

The cyclohexanone ring in **3** adopts a boat conformation (the C1, C12 bond is equatorial to accommodate the enediyne in the 10-membered ring), and consequently the axial C1 hydrogen atom is in the plane of the carbonyl π-system. This results in increased kinetic acidity since the developing carbanion at C13 enjoys direct resonance delocalization without the necessity for geometric changes.

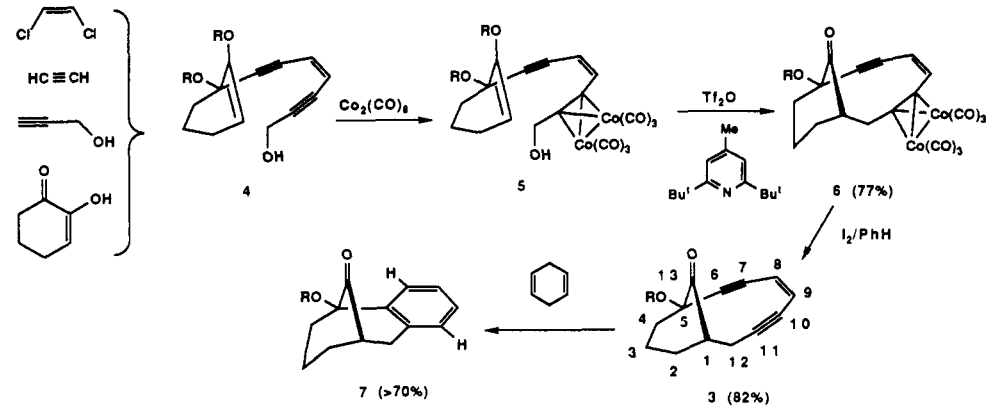
Treatment of **3** with $Et_3N/t$-$BuMe_2SiOTf/CH_2Cl_2$ at 20 °C for 5 days gave the bridgehead *tert*-butyldimethylsilyl enol ether **9** (54%) as a stable crystalline compound. More conveniently, **9** can be made from **3** by treatment with KHMDS/THF/*t*-$BuMe_2SiOTf$ at −78 °C for 0.5 h in 100% yield. If LiHMDS is used instead of KHMDS, the bridgehead alkylated compound **11** (70%) is formed. Presumably the solvent tetrahydrofuran is cleaved by *t*-$BuMe_2SiOTf$ to generate the alkylating agent **10** more rapidly than **8** is O-silylated. Treatment of **8** with *i*-$Pr_3SiOTf$/THF at −78 °C followed by warming to 0 °C gave the

† University of Texas at Austin.
‡ Indiana University.

(1) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986.
(3) Dynemicin-Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. Neocarzinostatin chromophore A: Napier, M. A.; Holmquist, B.; Strydom, D. J.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 635. Koide, Y.; Ishii, F.; Hasuda, K.; Koyama, Y.; Edo, K.; Katamine, S.; Kitame, F.; Ishida, N. *J. Antibiot.* **1980**, *33*, 342. Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Calicheamicin-Lee, M. D.; Dunne, T. S.; Seigel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Seigel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. Esperamicins-Golik, J.; Dubay, G.; Groenwold, G.; Kawaguchi, M.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462. Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, M.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. Konishi, M.; Ohkuma, H.; Saitoh, K.; Kawaguchi, H.; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T. W. *J. Antibiot.* **1985**, *38*, 1605.

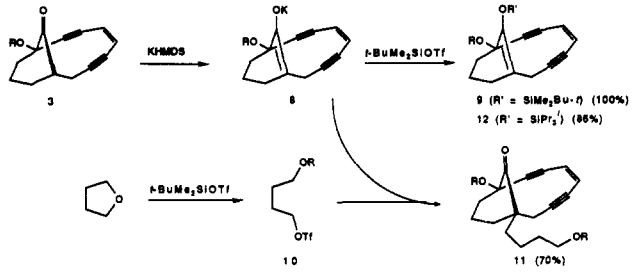
0002-7863/92/1514-2560$03.00/0 

**Scheme I**[a]



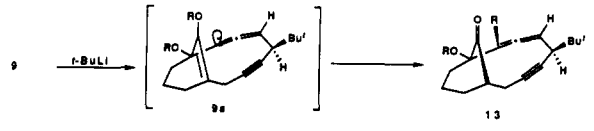
[a] R = TBDMS.

**Scheme II**[a]



[a] R = TBDMS.

**Scheme III**[a]

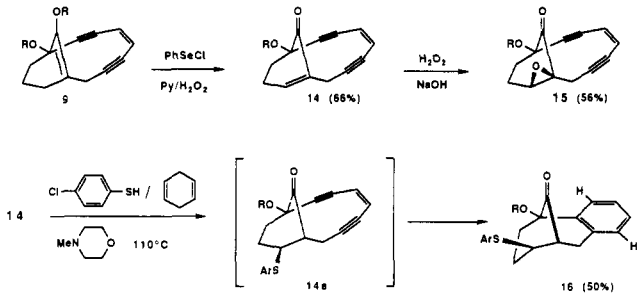


[a] R = TBDMS.

corresponding triisopropylsilyl enol ether **12** (86%). In an attempt to generate the propargylic–allylic anion derived from **9** in order to examine its reaction with oxygen electrophiles (introduction of C12 oxygen), we treated **9** with a variety of bases. In the cases of *n*-BuLi, *s*-BuLi, and *t*-BuLi, the enol ether was rapidly consumed and the only product isolated was **13** (7%), which when *t*-BuLi was used gave suitable crystals for X-ray crystallography (Figure 1, supplementary material, shows an ORTEP representation of **13**). The structure of **13** shows that the *t*-BuLi has added to the C9 position to form the allenyl anion **9a** (the propargyl resonance form is not shown). The anion **9a** can transfer the $SiMe_2Bu$-*t* group (intramolecularly or intermolecularly) to generate the enolate derivative of **13**, which upon work-up (protonation) gives **13**.

Treatment of the bridgehead *tert*-butyldimethylsilyl enol ether **9** with phenylselenyl chloride followed by pyridine/$H_2O_2$ gave the $\alpha,\beta$-unsaturated ketone **14** (66%).[4] It should be borne in mind that highly unsaturated molecules such as **14** have very simple $^1H$ NMR and $^{13}C$ NMR spectra and as a consequence do not contain so much information (connectivity); thus it is important to be cautious when assigning structures. The enone **14** has unexceptional IR and UV spectral properties and undergoes reactions typically associated with an $\alpha,\beta$-unsaturated ketone. For example, treatment of **14** with sodium peroxide gave the exceedingly stable epoxide **15** (56%, inert to PhSeNa, $NaN_3/ZnI_2$, $4\text{-}ClC_6H_4SH$, $BF_3\cdot OEt_2$). Heating **14** at 110 °C in 1,4-cyclohexadiene in the presence of 4-chlorothiophenol/*N*-methylmorpholine (cat.) provided the cycloaromatized adduct **16** (50%), convincingly demonstrating that formation of the putative 1,4-diyl can be triggered intermolecularly by thiol addition to C2 (change of C1 hybridization from $sp^2$ to $sp^3$).[5]

**Scheme IV**[a]



[a] R = TBDMS.

### Introduction of the C3 Oxygen Substituent

Treatment of **14** with trimethylsilyl triflate/$NEt_3$ gave the dienyl ether **17** (53%), which was directly treated with phenylselenenyl chloride to give a mixture of C1 and C3 phenylselenenyl adducts **18**/**19** (1:4.5), respectively. It was found that the enone **14** could be converted into the C1 phenylselenenyl adduct **18** (52%) without deleterious formation of **19** by treatment with the Nicolaou reagent *N*-(phenylseleno)phthalimide,[6] whereas treatment of **14** with phenylselenenyl chloride only gave products resulting from addition to the 10,11 acetylene, namely, **21**. Oxidation of **18** with $H_2O_2$/pyridine gave the 3$\beta$-hydroxy 1,2-enone **20** (76%) via [2.3] sigmatropic rearrangement of the resulting selenoxide.[7]

The 3$\beta$-hydroxybicyclo[7.3.1] enediyne system **20** is available in two oxidative steps, both involving selenium chemistry. At this stage in the development of this research we did not have a method to introduce the 12$\beta$-hydroxy substituent.[8] In a completely empirical manner we decided to treat the enol ether **9** with a variety of oxidizing agents with the expectation of observing either C12 functionalization (propargylic) or C3 functionalization (allylic). Without belaboring the fact, after the enol ether **9** was treated with a range of oxidants that only led to complex mixtures or complete destruction of **9**, it was found that treatment of **9** with $SeO_2$ (1.1 equiv)/dioxane at 25 °C for 3 h gave the hemiketal **22** (53%) as a stable crystalline material, mp 114–116 °C, along with the enone **14** (14%).[9]

(4) For numerous references to the $\alpha$-selenenylation of ketones, see: Back, T. G. In *Electrophilic Selenium Reagents in Organoselenium Chemistry*; Liotta, D., Ed.; Wiley-Interscience: New York, 1987.

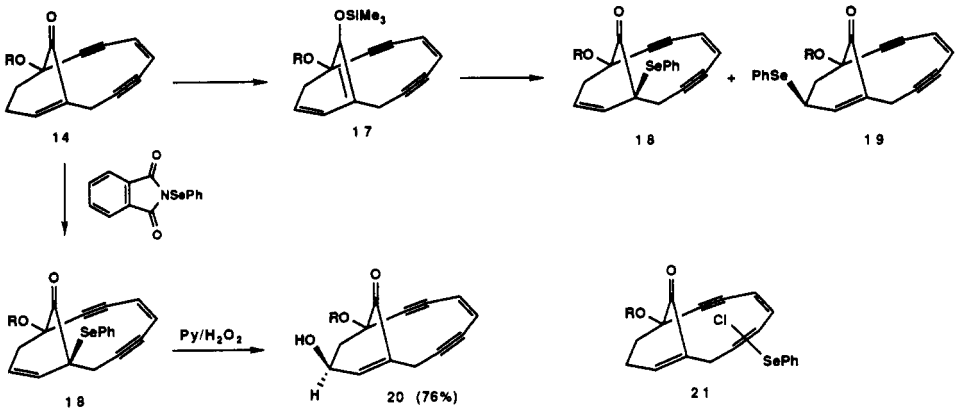
(5) Magnus, P.; Lewis, R. T. *Tetrahedron Lett.* **1989**, *30*, 1905.

(6) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835.

(7) For a review of [2.3] sigmatropic rearrangements, see: Reich, H. J. In *Electrophilic Selenium Reagents in Organoselenium Chemistry*; Liotta, D., Ed.; Wiley-Interscience: New York, 1987.

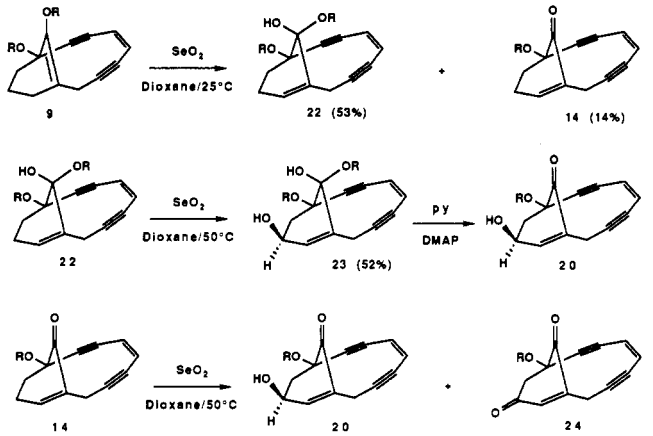
(8) Synthesis of the 12$\beta$-hydroxybicyclo[7.3.1]tridecenediyne core structure: Magnus, P.; Annoura, H.; Harling, J. *J. Org. Chem.* **1990**, *55*, 1709.

**Scheme V**[a]



[a] R = TBDMS.

**Scheme VI**[a]



[a] R = TBDMS.

The structure and relative stereochemistry of **22** was determined by single-crystal X-ray crystallography. (Figure 2, supplementary material, shows an ORTEP representation of **22**). Further exposure of **22** to $SeO_2$ (1.1 equiv)/dioxane at 50 °C for 16 h gave the 3β-hydroxy compound **23** (45%) along with starting material. Treatment of the hemihydrate **23** in pyridine with (*N*-dimethylamino)pyridine cleanly converted it into the 3β-hydroxy enone **20** (89%). The structure and relative stereochemistry of **23** was verified by single-crystal X-ray crystallography. (Figure 3, supplementary material, shows an ORTEP representation of **23**.)

It was further found that $SeO_2$ (73 °C for 21 h) cleanly converted the enone **14** into the 3β-hydroxy enone **20** (75%) along with smaller amounts of the dienone **24** and the starting enone **14**. This is a practical procedure that can be conducted on a 1-g scale to provide 788 mg of **20**.

### Introduction of the C2 Nitrogen Substituent

Treatment of the 3β-hydroxy enone **20** with ethoxycarbonyl isocyanate gave the carbamate **25**, which readily underwent intramolecular conjugate addition upon chromatography over silica gel to give the cyclic carbamate **26**. The reversible nature of this cyclization was demonstrated by treatment of **26** with potassium bis(trimethylsilyl)amide at −78 °C to give a mixture of **25** and **26** (1:1). As expected, the additional heterocyclic ring imposes increased strain in the transition state for cycloaromatization. Heating **26** at 90 °C for 16 h in 1,4-cyclohexadiene resulted in 50% conversion into the aromatized adduct **28**.

The cyclic carbamate **26** proved to be very resistant to hydrolysis without complete destruction. The only selective deprotection that could be achieved was the removal of the ethoxycarbonyl functionality by treatment with sodium carbonate in methanol, resulting in the formation of **27** (63%). Treatment of the alcohol **20** with sodium cyanate in the presence of trifluoroacetic acid gave the carbamate **29** (89%). Interestingly, if potassium cyanate is used, the alcohol **20** is recovered unchanged![10] The carbamate **29** was readily N-silylated by treatment with *tert*-butyldimethylsilyl triflate/$NEt_3$/$CH_2Cl_2$ to give **30** (95%). Treatment of the N-silylated derivative **30** with potassium bis(trimethylsilyl)amide at −78 °C followed by *N*-(phenylseleno)phthalimide gave a mixture of the bridgehead selenide **31** and the protonated compound **32** (2:1). Oxidation of the mixture with hydrogen peroxide/pyridine resulted in elimination of the intermediate selenoxide into the 10-membered ring to give the torsionally strained enone **33** (40% from **30**). The infrared spectrum of **33** exhibits two carbonyl stretching frequencies at 1759 (carbamate) and 1744 $cm^{-1}$ (C13 enone carbonyl). The $^1H$ NMR spectrum shows the C12 enone proton at δ 5.67 with a small coupling of 1.5 Hz to the C9 olefinic proton. The bridgehead protonated compound **32** can be converted into the enone **33** (44%) by the same procedure used to convert **30** into **33**. Mild acid hydrolysis of **33** removed the *N*-silyl protection resulting in the carbamate **34**. Ring opening of the cyclic carbamate **34** could not be achieved without complete destruction of the molecule.

Consequently, while the transformations described above provide a simple way to introduce the nitrogen functionality at C2, and may be of value for the synthesis of analogues, this route was not pursued further.

### Construction of the Allylic Trisulfide Trigger

While the allylic trisulfide[11] might appear to be a formidable challenge, there is in fact a reasonable body of literature, particularly the work of Harpp, that shows the construction of allylic trisulfides to be a relatively straightforward task.[12] At least in the case of the intermolecular version, the key issue is controlling the stereochemistry of the allylic substituent. On steric grounds alone, it may be predicted that the reaction of the enone **14** with a stabilized phosphonate carbanion should position the more

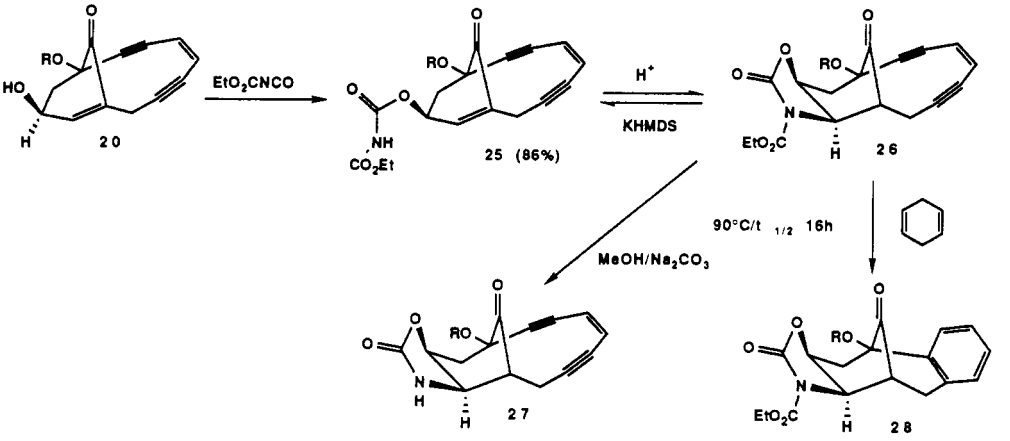
(9) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154. Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 7917. Jensen, H. P.; Sharpless, K. B. *J. Org. Chem.* **1975**, *40*, 264. Sharpless, K. B.; Gordon, K. M. *J. Am. Chem. Soc.* **1976**, *98*, 300. Magnus, P.; Bennett, F. *Tetrahedron Lett.* **1989**, *30*, 3637. Stable hydrates of bridged ketones have been isolated, the most recent being: Bonjoch, J.; Quirante, J.; Serret, I.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 1861.

(10) Loev, B.; Kormendy, M. F. *J. Org. Chem.* **1963**, *28*, 3421.

(11) General reviews on polysulfides: Harpp, D. N. *Perspectives in The Organic Chemistry of Sulfur*; Studies in Organic Chemistry 28; Zwanenburg, B., Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987. Kuthey, G. W.; Turnbull, K. *Chem. Rev.* **1982**, *82*, 333. Diallyl trisulfide and methyl allyl trisulfide are natural products: Augusti, K. T.; Mathew, P. T. *Experientia* **1974**, *30*, 468. Ariga, S.; Oshiba, S.; Tamada, T. *Lancet* **1981**, *1*, 150.

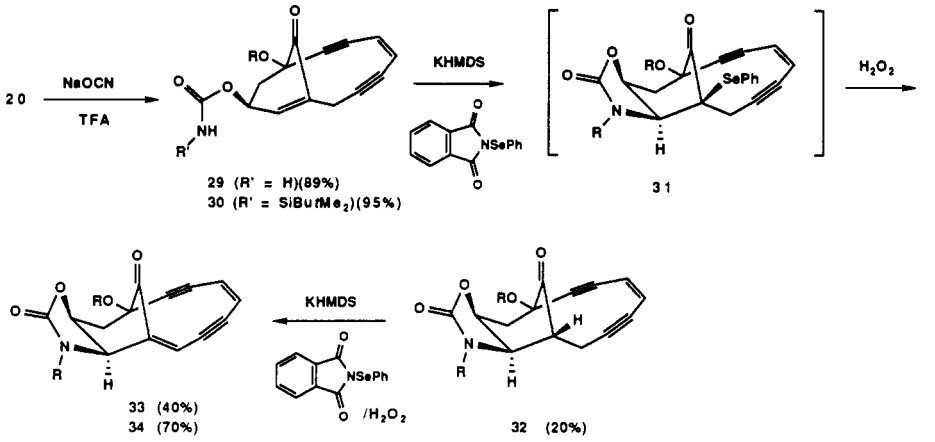
(12) Harpp, D. N.; Steliou, K.; Chen, T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1222. Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 211. Sullivan, A. B.; Boustany, K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 207. Mott, A. W.; Barany, G. *Synthesis* **1984**, 657.

**Scheme VII**[a]



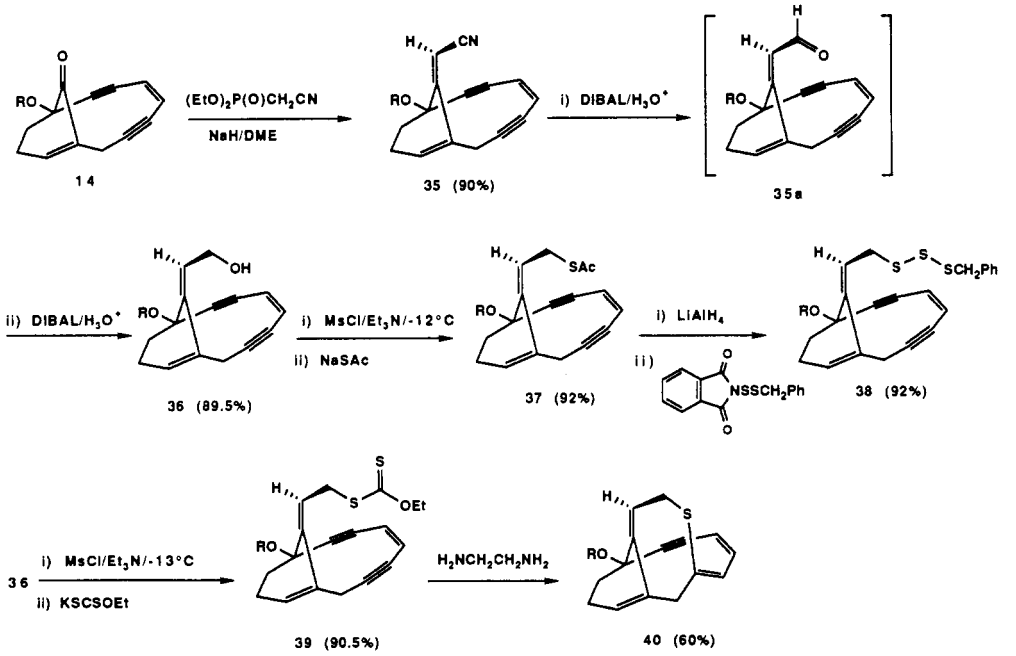

[a] R = TBDMS.

**Scheme VIII**[a]




[a] R = TBDMS.

**Scheme IX.** Allylic Trisulfide Chemistry[a]




[a] R = TBDMS.

sterically bulky groups toward the enone double bond. This then leads to the correct relative stereochemistry required for esperamicin/calicheamicin. Indeed treatment of the enone **14** with diethyl cyanomethylphosphonate/NaH/DME gave the $\alpha,\beta$-unsaturated nitrile **35** (90%), as a single stereoisomer. At this stage we did not know the relative stereochemistry of **35**, but as will

be seen later, the configuration of the double bond was shown to be that depicted. The nitrile was reduced using diisobutylaluminum hydride, first to give the aldehyde **35a** (after hydrolysis of the intermediate the imine), and repetition of the same reduction gave the allylic alcohol **36** (89.5% overall yield from **35**). The derived mesylate was converted into the thioacetate **37** (92%) by treatment with freshly prepared sodium thioacetate in methanol. If commercial sodium thioacetate is used, the yield of **37** is substantially reduced.

Subsequent reduction of the thioacetate **37** with lithium aluminum hydride in ether followed by quenching the intermediate thiolate with *N*-(benzylthiosulfenyl)phthalimide[12] gave the *S*-benzyl trisulfide **38** (92%). The *S*-benzyl derivative was chosen [(-$SCH_2Ph$) is large enough to detect, for example, the corresponding disulfide (-$SCH_2Ph)_2$] in order to examine the thermal stability of **38** with respect to potential [2.3] sigmatropic rearrangement processes[13] and potential disproportionation processes.[14] In the event thermolysis of **38** in toluene at reflux for several days only resulted in complete recovery of **38**, and no evidence for any decomposition.[14] The SMe analogue can be made in the same way. The sequence of transformations from the allylic alcohol to the trisulfide was used by Danishefsky[15] in his synthesis of calicheamicinone, demonstrating that it is completely compatible with the more highly functionalized bicyclo[7.3.1] enediyne systems.

We also examined more nucleophilic sources of thiolate, and it was in the course of this study, by chance, that unequivocal chemical evidence for the assigned stereochemistry of the 13,14 double bond was found. When the xanthate **39** was hydrolyzed using ethylenediamine, the cyclic sulfide **40** (60%) was isolated, thus confirming the stereochemical assignments.

## Summary

The simple 13-ketobicyclo[7.3.1]tridecenediyne **3** core structure can be readily functionalized in an oxidative stepwise manner to introduce the 1,2 double bond and 3-oxygen substituent. While the 4$\beta$-hydroxyl substituent allowed the intramolecular introduction of the nitrogen functionality at C2, the resulting cyclic carbamate was too resistant to hydrolysis to be synthetically useful. The allylic trisulfide can be installed in a straightforward manner via Wittig chemistry on the 13-keto group. The relatively simple chemistry needed to functionalize the core system should allow access to a wide variety of analogues for biological evaluation. We are currently applying the above chemistry to a 13-ketobicyclo[7.3.1]tridecenediyne core in which the 12$\beta$-hydroxyl substituent is present from an early stage in the synthesis.[8]

## Experimental Section

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer or a 881 grating spectrophotometer either neat or in $CHCl_3$ as indicated. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3B UV/vis spectrophotometer in the indicated solvents. Proton NMR spectra were recorded on a General Electric QE-300, 300-MHz spectrometer or a Bruker 500-MHz spectrometer in the indicated solvent and are reported in ppm downfield from TMS. Carbon-13 NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated and are also reported in ppm downfield from TMS. Elemental analyses were performed by Midwest Microlab in Indianapolis, IN. Routine monitoring of reactions was performed using Merck 60 $F_{254}$ silica gel, aluminum-backed TLC plates. Preparative layer chromatography was performed using Merck 60 $F_{254}$ silica gel, glass-supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H $F_{254}$ silica gel. Gas–liquid chromatography was performed on a Hewlett-Packard 5890 system, using an HP-1 capillary column. Air- and moisture-sensitive reactions were performed under the 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 THF were distilled from sodium benzophenone ketyl; $CH_2Cl_2$ and benzene were distilled from calcium hydride under argon.

**5,13-Bis[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]trideca-8,13-diene-6,10-diyne (9).** To a solution of the ketone **3** (2.53 g, 8.05 mmol) in dry tetrahydrofuran (100 mL) at −78 °C was added a toluene solution of 0.5 M potassium bis(trimethylsilyl)amide (17.7 mL, 1.1 equiv). The solution was stirred for 5 min and *tert*-butyldimethylsilyl triflate (2.25 mL, 1.2 equiv) added dropwise. After 20 min at −78 °C the mixture was quenched with saturated aqueous sodium bicarbonate solution (100 mL) and extracted with pentane (2 × 50 mL). The dried ($MgSO_4$) solution was evaporated in vacuo to give an oil which was purified by chromatography over silica gel, eluting with 10% ether/petroleum ether to give **9**: 3.63 g 100%; mp 82–85 °C; IR ($CHCl_3$) 2355, 2331, 2167, 1637 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 5.43 (2 H, s), 3.35 (1 H, d, $J$ = 16.3 Hz), 2.19 (1 H, d, $J$ = 16.3 Hz), 2.15–2.00 (4 H, m), 1.83 (1 H, m), 1.57 (1 H, m), 1.02 (18 H, s), 0.41 (3 H, s), 0.39 (3 H, s), 0.22 (6 H, s). Anal. Calcd for $C_{25}H_{40}O_2Si_2$: C, 70.03; H, 9.40. Found: C, 69.85; H, 9.35.

Carrying out the same reaction as above using triisopropylsilyl triflate to quench the potassium enolate gave **12** (73.3 mg, 86% from 57.2 mg of **3**): mp 79–81 °C (ether/hexane); IR ($CHCl_3$) 2179, 1661, 1631 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 5.42 (1 H, d, $J$ = 9.3 Hz), 5.38 (1 H, d, $J$ = 9.3 Hz), 3.48 (1 H, d, $J$ = 16.5 Hz), 2.14 (1 H, d, $J$ = 16.5 Hz), 2.13–1.97 (4 H, m), 1.81 (1 H, m), 1.53 (1 H, m), 1.27 (3 H, m), 1.21 (12 H, d, $J$ = 9.5 Hz), 1.80 (6 H, d, $J$ = 9.5 Hz), 0.96 (9 H, s), 0.34 (3 H, s), 0.29 (3 H, s); HRMS calcd for $C_{28}H_{46}O_2Si_2$ 470.3036, found $m/e$ 470.3036. The derived $\eta^2$ $Co_2(CO)_6$ adduct has $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 6.22 (1 H, d, $J$ = 10.8 Hz), 5.13 (1 H, d, $J$ = 10.8 Hz), 4.62 (1 H, d, $J$ = 15.5 Hz), 3.18 (1 H, d, $J$ = 15.5 Hz), 2.28–1.92 (6 H, m), 1.56 (1 H, m), 1.37 (2 H, m), 1.24 (12 H, d, $J$ = 2.2 Hz), 1.21 (6 H, d, $J$ = 2.2 Hz), 0.99 (9 H, s), 0.37 (3 H, s), 0.31 (3 H, s).

Conducting the above experiment with lithium bis(trimethylsilyl)amide gave the bridgehead alkylated adduct **11**: 70%; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 5.45 (1 H, dd, $J$ = 1.2, 9.4 Hz), 5.36 (1 H, d, $J$ = 9.4 Hz), 3.41 (2 H, t, $J$ = 5.9 Hz), 2.88 (1 H, d, $J$ = 17.1 Hz), 2.81 (1 H, m), 2.18 (1 H, m), 1.96 (1 H, dd, $J$ = 17.1, 1.2 Hz), 1.85 (2 H, m), 1.5–1.04 (8 H, m), 1.1 (9 H, s), 0.96 (9 H, s), 0.47 (3 H, s), 0.44 (3 H, s), 0.03 (6 H, s); $^{13}C$ NMR (75 MHz, $C_6D_6$) $\delta$ 206.80, 124.70, 121.05, 100.43, 97.96, 91.86, 83.20, 74.29, 62.64, 53.84, 39.20, 34.74, 33.06, 30.75, 26.83, 25.94, 25.89, 20.32, 18.35, 18.31, 16.29, −2.95, −3.14, −5.29; HRMS calcd for $C_{29}H_{48}O_3Si$ 500.3142, found $m/e$ 500.3142.

**13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]-6-(*tert*-butyldimethylsilyl)-9$\beta$-*tert*-butylbicyclo[7.3.1]trideca-6,7-dienyne (13).** To a solution of the enol ether **9** (38.8 mg, 0.091 mmol) in dry tetrahydrofuran (1 mL) at −78 °C was added a solution of *t*-BuLi (64 $\mu$L of a 1.7 M solution in pentane). After 30 min at −78 °C trimethylsilyl chloride (35 mL, 0.27 mmol) was added and the mixture held at −78 °C for an additional 30 min. The solution was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with pentane (10 mL). The dried ($MgSO_4$) pentane solution was evaporated in vacuo to give an oil. Purification by plate layer chromatography on silica gel, eluting with hexane, gave recovered **9** (8.2 mg, 21%) and a polar component **13**: 3.1 mg, 7%; mp 144–147 °C (from hexane); IR ($CHCl_3$) 1919 (m), 1742 (w), 1701 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 5.03 (1 H, d, $J$ = 4.8 Hz), 2.92 (1 H, dt, $J$ = 4.8, 3.2 Hz), 1.20–2.73 (9 H, m), 1.11 (9 H, s), 1.03 (9 H, s), 0.94 (9 H, s), 0.67 (3 H, s), 0.49 (3 H, s), 0.28 (3 H, s), 0.07 (3 H, s); HRMS calcd for $C_{29}H_{50}O_2Si_2$ 486.3349, found $m/e$ 486.3351. Crystals suitable for single-crystal X-ray crystallography were grown from hexane.

**13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]trideca-1,8-diene-6,10-diyne (14).** To a solution of the enol ether **9** (3.63 g) in dichloromethane (50 mL) at −78 °C was added dropwise with stirring a solution of phenylselenenyl chloride (1.84 g, 1.1 equiv) in dichloromethane (25 mL). After 15 min at −78 °C pyridine (8.5 mL) was added to the above mixture followed by hydrogen peroxide (15 mL, 30% aqueous solution). The cooling bath was removed and the mixture allowed to warm to room temperature. After 1 h saturated aqueous $NaHCO_3$ solution (10 mL) was added and the resulting mixture stirred for a further 6 h. The mixture was poured on to saturated aqueous $NaHCO_3$ solution (100 mL), the layers were separated, and the aqueous phase was extracted with ether (2 × 100 mL). The dried ($MgSO_4$) extracts evaporated in vacuo to give an oil which was purified by chro-

(13) Barnard, D.; Houseman, H.; Porter, M.; Tidd, B. K. *Chem. Commun.* **1969**, 371. Hofle, G.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 6307. Baechler, R. D.; Hummel, J. P.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 4442.

(14) Pickering, T. L.; Saunders, K. J.; Tobolsky, K. *J. Am. Chem. Soc.* **1967**, *89*, 2364. Trivette, C. D.; Coran, A. Y. *J. Org. Chem.* **1966**, *31*, 100.

(15) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850. Haseltine, J. N.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2576. Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253. Magnus, P.; Lewis, R. T.; Bennett, F. *J. Chem. Soc., Chem. Commun.* **1989**, 916. Ellestad, G. A.; Hamann, P. R.; Zein, N.; Morton, G. O.; Siegel, M. M.; Pastel, M.; Borders, D. B.; McGahren, W. J. *Tetrahedron Lett.* **1989**, *30*, 3033.

matography over silica gel, eluting with 10% ether/petroleum ether to give **14**: 1.75 g, 66%; IR ($CCl_4$) 2950, 2030, 2855, 2194, 1710, 1250, 1156, 978, 836, 780 $cm^{-1}$; $\lambda_{max}$ ($\epsilon$ MeOH) 237 (4140), 272 (3880) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.35 (1 H, ddd, $J$ = 0.55, 1.5, 3.7 Hz), 5.82 (2 H, s, ABXY in $C_6D_6$), 3.67 (1 H, dd, $J$ = 16.5, 1.25 Hz), 3.01 (1 H, d, $J$ = 16.5 Hz), 2.46–2.51 (2 H, m), 2.32 (1 H, m), 2.15 (1 H, m), 0.92 (9 H, s), 0.21 (3 H, s), 0.17 (3 H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 192.45, 138.46, 136.78, 124.24, 120.90, 100.58, 95.96, 91.57, 74.45, 34.86, 25.88, 25.30, 24.00, 18.38, –2.94, –3.27; HRMS calcd for $C_{19}H_{24}O_2Si$ ($M^+$ – Bu'$C_{15}H_{15}O_2Si$) 255.0847, found $m/e$ 255.0838.

**13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]-1,2$\beta$-oxabicyclo[7.3.1]tridec-8-ene-6,10-diyne (15).** A solution of the enone **14** (23 mg) in methanol (1 mL) at 5 °C was treated with basic hydrogen peroxide solution (300 $\mu$L, 1.5 mL of $H_2O_2$/130 mg of NaOH) for 3 h. The mixture was poured into water (10 mL) and extracted with ether (10 mL). The dried ($MgSO_4$) ether layer was evaporated in vacuo and the residue purified by PLC (10% ether/petroleum ether) to give **15**: 13.6 mg, 56%; IR ($CCl_4$) 2958, 2936, 2895, 2860, 2200, 1748, 1462, 1335, 1170, 1084, 952, 910, 800 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.92 (1 H, dd, $J$ = 0.6, 9.8 Hz), 5.89 (1 H, d, $J$ = 9.8 Hz), 3.67 (1 H, d, $J$ = 16.9 Hz), 3.36 (1 H, m), 2.37 (1 H, dddd, $J$ = 1.8, 5.8, 12.8, 15.6 Hz), 2.30 (1 H, d, $J$ = 15.6 Hz), 2.07 (1 H, dd, $J$ = 1.4, 16.9 Hz), 1.98 (1 H, dt, $J$ = 5.1, 13 Hz), 1.88 (1 H, dddd, $J$ = 0.8, 2.1, 5.7, 13.3 Hz), 0.90 (9 H, s), 0.18 (3 H, s), 0.16 (3 H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 194.61, 124.32, 121.27, 96.80, 94.80, 93.06, 86.35, 74.74, 61.51, 59.46, 25.77, 23.54, 22.36, 18.30, –3.10, –3.32; HRMS calcd for $C_{19}H_{24}O_3Si$ ($M^+$ – Bu', $C_{15}H_{15}O_3Si$) 271.0791, found $m/e$ 271.0799.

**1-[(*tert*-Butyldimethylsilyl)oxy]-10$\beta$-thiophenyltricyclo[7.3.1$0^{2,7}$]-trideca-2,4,6-trien-13-one (16).** A solution of 4-chlorothiophenol (31 mg, 3.36 equiv), *N*-methylmorpholine (21 $\mu$L), and the enone **14** (20 mg) in 1,4-cyclohexadiene (1 mL) was heated in a sealed ampule under argon. After heating at 110 °C for 44 h the mixture was evaporated and the residue purified by PLC (10% ether/petroleum ether to give **16**: 16 mg, 50%; IR ($CCl_4$) 2930, 2855, 1738, 1450, 1160, 1082, 918 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.24 (3 H, s), 1.75–1.93 (3 H, m), 2.54 (1 H, m), 2.96 (1 H, m), 3.09 (1 H, d, $J$ = 17.8 Hz), 3.50 (1 H, dd, $J$ = 7.7 and 17.8 Hz), 3.73 (1 H, m), 7.04 (1 H, dd, $J$ = 0.8, 7.6 Hz), 7.21 (1 H, dt, $J$ = 1.4, 7.4 Hz), 7.28 (1 H, m), 7.32 (2 H, d, $J$ = 7 Hz), 7.41 (2 H, d, $J$ = 8.7 Hz), 7.60 (1 H, dd, $J$ = 1.3, 7.9 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ –2.28 (q), –2.32 (q), 18.91 (s), 26.29 (q), 25.04 (t), 30.30 (t), 41.20 (t), 49.98 (d), 55.12 (d), 80.30 (s), 127.52 (d), 129.40 (d), 131.80 (s), 133.23 (s), 134.26 (s), 134.94 (d), 142.90 (s), 208.81 (s); HRMS calcd for $C_{25}H_{31}O_2SiSCl$ ($M^+$ – Me, $C_{24}H_{28}O_2SiSCl$) 443.1268, found $m/e$ 443.1262.

**3$\beta$-Hydroxy-13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (20).** To a mixture of the enone **14** (15 mg) and *N*-(phenylseleno)phthalimide (16 mg, 1.1 equiv) in dry tetrahydrofuran (1.0 mL) was added DBU (14 $\mu$L, 2 equiv). After 18 h at 20 °C TLC indicated approximately 50% conversion to a less polar material. A further quantity of *N*-(phenylseleno)phthalimide (14 mg) was added and the mixture stirred for a further 24 h. The solution was evaporated and the residue purified by PLC (silica gel/10% ether/petroleum ether to give **18** (11.8 mg, 52%; 68% based on recovered **14**) and recovered enone **14** (3.5 mg). To a solution of the allylic selenide **18** (11.8 mg) in dichloromethane (1.0 mL) and pyridine (500 $\mu$L) at –20 °C was added hydrogen peroxide (1.0 mL of a 30% aqueous solution). The mixture was allowed to warm to 20 °C; saturated aqueous $NaHCO_3$ (1.5 mL) added was and stirring continued for a further 4 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with dichloromethane (2 × 5 mL) and ether (1 × 5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by PLC (silica gel, 40% ether/petroleum ether to give the 3$\beta$-hydroxy enone **20**: 6.3 mg, 76%; IR ($CCl_4$) 3410, 2940, 2855, 2190, 1710, 1255, 1150, 975 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.38 (1 H, dd, $J$ = 2.3, 3.0 Hz), 5.84 (1 H, dd, $J$ = 0.7, 9.7 Hz), 5.81 (1 H, dd, $J$ = 0.5, 9.7 Hz), 4.55 (1 H, m), 3.70 (1 H, dt, $J$ = 0.7, 16.6 Hz), 3.04 (1 H, dd, $J$ = 1.1, 16.6 Hz), 2.78 (1 H, ddd, $J$ = 2.0, 6.1, 12.9 Hz), 2.08 (1 H, dd, $J$ = 9.7, 12.9 Hz), 1.91 (1 H, m, exchanged), 0.92 (9 H, s), 0.21 (3 H, s), 0.18 (3 H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 11191.25, 139.58, 136.97, 124.62, 120.82, 100.05, 95.44, 91.48, 87.77, 74.53, 67.00, 25.81, 23.90, 18.33, –2.95, –3.24; HRMS calcd for $C_{19}H_{24}O_3Si$ 328.1488, found $m/e$ 328.1480.

**13$\beta$-Hydroxy-5,13-bis[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (22).** Freshly sublimed selenium dioxide (5.7 mg, 0.051 mmol) was added to a stirred solution of **9** (20 mg, 0.047 mmol) in dioxane (1.0 mL). The resulting suspension was stirred at 20 °C for 3 h. The mixture was diluted with ether and poured in saturated aqueous $NaHCO_3$ solution (5 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo to give a residue, which was purified by PLC on silica gel using ether/hexane 1:20) to give the enone **14** (2.0 mg, 14%) and the hemiketal **22**: 11.0 mg, 53%; mp 114–116 °C (ethanol/water); IR ($CHCl_3$) 3505, 2190 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.82 (1 H, dd, $J$ = 5.4, 2.9 Hz), 5.76 (1 H, dt, $J$ = 9.5, 0.8 Hz), 5.71 (1 H, ddd, $J$ = 9.53, 0.90, 0.70 Hz), 3.30 (1 H, d, $J$ = 16.8 Hz), 2.98 (1 H, dt, $J$ = 16.8, 0.7 Hz), 2.34–2.41 (1 H, m), 2.02–2.20 (3 H, m), 0.94 (9 H, s), 0.93 (9 H, s), 0.34 (3 H, s), 0.24 (3 H, s), 0.21 (3 H, s), 0.19 (3 H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 140.04, 129.30, 123.18, 121.52, 103.78, 99.34, 98.39, 85.91, 85.34, 76.21, 34.56, 26.32, 26.06, 25.61, 23.10, 18.24, 18.08, –0.31, –2.45, –2.61, –2.88; HRMS calcd for $C_{25}H_{40}O_3Si_2$ 444.2516, found $m/e$ 444.2481. Anal. Calcd for $C_{25}H_{40}O_3Si_2$: C, 67.53; H. 9.07. Found: C, 67.40; H, 8.88.

**3$\beta$,13$\beta$-Dihydroxy-5,13-bis[(*tert*-butyldimethylsilyl)oxy]bicyclo-[7.3.1]trideca-1,8-diene-6,10-diyne (23).** Selenium dioxide (26.4 mg, 0.24 mmol) was added to a stirred solution of the hemiketal **22** (58.8 mg, 0.13 mmol) in dioxane (4 mL). The resulting suspension was stirred at 50 °C for 16 h and worked up as for **22** to give **23**: 26.9 mg, 45%; mp 143–145 °C (dioxane/water); IR ($CHCl_3$) 3589, 3507, 1472, 1467 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.76 (1 H, d, $J$ = 9.5 Hz), 5.71 (1 H, dd, $J$ = 9.5, 1.4 Hz), 4.20 (1 H, br s), 4.16 (1 H, ddd, $J$ = 7.6, 5.9, 4.5 Hz), 3.32 (1 H, d, $J$ = 16.6 Hz), 3.01 (1 H, dd, $J$ = 16.6, 1.4 Hz), 2.64 (1 H, dd, $J$ = 14.4, 7.6 Hz), 2.10 (1 H, dd, $J$ = 14.4, 4.5 Hz), 1.60 (1 H, br s), 0.92 (9 H, s), 0.918 (9 H, s), 0.34 (3 H, s), 0.23 (3 H, s), 0.20 (3 H, s), 0.17 (3 H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 220.5, 143.66, 130.67, 123.39, 121.62, 102.51, 99.47, 98.16, 85.74, 85.66, 63.89, 46.29, 26.31, 25.95, 25.47, 18.18, 18.04, –0.42, –2.55, –2.70, –2.83; HRMS calcd for $C_{25}H_{40}O_4Si_2$ 460.2464, found $m/e$ 460.2458. Anal. Calcd for $C_{25}H_{40}O_4Si_2$: C, 65.18; H, 8.76. Found: C, 65.02; H, 8.66.

**Selenium Dioxide Oxidation of the Enone 14 To Give 20.** A mixture of **14** (1.0 g) and selenium dioxide (0.608 g) in dioxane (11 mL) was stirred at 73 °C for 21 h. The cooled mixture was poured into water (50 mL) and extracted with ether (3 × 20 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by column chromatography (silica gel with 55% ether/petroleum ether) to give **20** (526 mg), **14** (421 mg), and **24** (58 mg). The recovered enone **14** (421 mg) was cycled through another selenium dioxide reaction to give **20** (174 mg) and **14** (212 mg), which on further recycling gave **20** (88.4 mg) and **14** (75 mg). The overall yield of 3$\beta$-hydroxy enone **20** is 788 mg, 75% after three cycles.

**Conversion of the Hemiketal 23 into the 3$\beta$-Hydroxy Enone 20.** To a stirred solution of the hemiketal **23** (4.4 mg, 0.01 mmol) in dry pyridine (0.5 mL) was added 4-(dimethylamino)pyridine (3.5 mg, 0.03 mmol) and the mixture stirred at 25 °C for 48 h. The mixture was evaporated in vacuo and the residue purified by PLC, eluting with ether to give **24** (2.9 mg, 89%).

**3$\beta$-[(*N*-Ethoxycarbonyl)carbamoyl]-13-keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]trideca-1,8-diene-6,10-diyne (25).** A solution of the 3$\beta$-alcohol **20** (62 mg, 0.188 mmol) in dichloromethane (1.0 mL) was treated with ethoxycarbonyl isocyanate (26 $\mu$L, 1.2 equiv) at 25 °C for 1 h. The mixture was evaporated to give **25** (80 mg, 95%) as an unstable oil: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 (1 H, br s), 6.33 (1 H, m), 5.86 (1 H, d, $J$ = 9.5 Hz), 5.80 (1 H, d, $J$ = 9.5 Hz), 5.53 (1 H, m), 4.22 (2 H, q, $J$ = 7.1 Hz), 3.67 (1 H, d, $J$ = 16.4 Hz), 3.03 (1 H, d, $J$ = 16.4 Hz), 2.83 (1 H, ddd, $J$ = 12.8, 6.5, 1.9 Hz), 2.16 (1 H, dd, $J$ = 12.8, 9.5 Hz), 1.27 (3 H, t, $J$ = 7.1 Hz), 0.89 (9 H, s), 0.18 (3 H, s), 0.15 (3 H, s).

When the above product was chromatographed over silica gel the, cyclic *N*-ethoxycarbonyl carbamate **26** was isolated (216 mg from 186 mg of **20**, 86%): $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.99 (1 H, d, $J$ = 9.4 Hz), 5.93 (1 H, d, $J$ = 9.4 Hz), 5.39 (1 H, t, $J$ = 8.1 Hz), 5.02 (1 H, q, $J$ = 9.4 Hz), 5.39 (1 H, t, $J$ = 8.1 Hz), 5.02 (1 H, q, $J$ = 8.0, 8.1 Hz), 4.36 (2 H, q, $J$ = 7.1 Hz), 3.28 (1 H, dd, $J$ = 18.5, 4.3 Hz), 2.99 (2 H, m), 2.82 (1 H, dd, $J$ = 13.9, 8.2 Hz), 2.25 (1 H, dd, $J$ = 13.9, 9.0 Hz), 1.38 (3 H, t, $J$ = 7.1 Hz), 0.90 (9 H, s), 0.19 (3 H, s), 0.17 (3 H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.50, 151.43, 150.83, 126.25, 120.40, 99.66, 93.56, 92.40, 84.42, 71.67, 71.24, 64.00, 54.59, 51.40, 38.75, 25.67, 23.32, 18.30, 14.09, –3.13, –3.41; HRMS calcd for $C_{23}H_{29}NO_6Si$ $M^+$ 443.1768, found $m/e$ 443.1764.

To a solution of the cyclic carbamate **26** (34 mg) in THF (2 mL) at –78 °C was added potassium hexamethyldisilazide (40 $\mu$L, 2.3 equiv of a 1 M solution in THF). After 40 min the mixture was quenched with $NaHCO_3$ to give after work-up 23 mg (68%) of a 1:1 mixture ($^1H$ NMR) of **25** and **26**.

**Cycloaromatization of the Cyclic Carbamate 26 to 30.** A solution of the carbamate **26** (2 mg) in freshly distilled 1,4-cyclohexadiene (3 mL) was heated at 90 °C under an argon atmosphere for 15.5 h. The mixture was evaporated in vacuo and the residue purified by PLC (eluting with 60% ether/petroleum ether to give the aromatized adduct **28** (1 mg) and **26** (1 mg): $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.61 (1 H, dd, $J$ = 7.7, 1.2 Hz), 7.37 (1 H, t, $J$ = 7.5 Hz), 7.29 (1 H, dt, $J$ = 7.4, 1.3 Hz), 7.14 (1 H, d, $J$ = 7.6 Hz), 4.52 (1 H, d, $J$ = 7.5 Hz), 4.39 (2 H, q, $J$ = 7.3 Hz), 4.24 (1 H, m), 3.75 (1 H, br d, $J$ = 4.8 Hz), 3.49 (1 H, dd, $J$ = 17.2,

5.7 Hz), 3.24 (1 H, dd, $J$ = 17.2, 2.0 Hz), 2.72 (1 H, dd, $J$ = 13.0, 7.0 Hz), 2.31 (1 H, m), 1.40 (3 H, t, $J$ = 7.1 Hz), 0.95 (9 H, s), 0.14 (3 H, s), 0.00 (3 H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.10, 151.89, 151.12, 141.60, 131.11, 128.64, 128.34, 127.65, 126.48, 76.79, 71.06, 64.73, 64.23, 47.84, 47.67, 37.78, 26.24, 14.15, -2.47, -2.74; HRMS calcd for $C_{22}H_{28}NO_6Si$ requires 430.1686, found $m/e$ 430.1680.

Treatment of **26** (32 mg) in methanol (3 mL) with sodium carbonate (500 mg) at 25 °C for 2 h gave the deprotected cyclic carbamate **27**: 17 mg, 63%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.23 (1 H, br s, NH), 5.92 (1 H, d, $J$ = 9.4 Hz), 5.85 (1 H, d, $J$ = 9.4 Hz), 5.09 (1 H, m), 4.83 (1 H, t, $J$ = 9 Hz), 3.30 (1 H, dd, $J$ = 17.9, 3.0 Hz), 2.82 (1 H, m), 2.78 (1 H, dd, $J$ = 13.7, 7.9 Hz), 2.63 (1 H, ddd, $J$ = 1.5, 4.2, 17.9 Hz), 2.28 (1 H, dd, $J$ = 9.4, 13.7 Hz), 0.89 (9 H, s), 0.18 (3 H, s), 0.16 (3 H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.59, 159.15, 125.69, 120.84, 98.85, 93.56, 92.26, 84.42, 73.26, 72.36, 52.05, 51.52, 39.32, 25.72, 21.83, 18.29, -3.06, -3.33; HRMS calcd for $C_{20}H_{25}NO_4Si$ requires 371.1553, found $m/e$ 371.1550.

**3$\beta$-Carbamoyl-13-keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-1,8-diene-6,10-diyne (29).** To the alcohol **20** (526 mg, 1.6 mmol) and sodium cyanate (440 mg) suspended in dichloromethane (14 mL) was added dropwise trifluoroacetic acid (500 $\mu$L, 4.0 equiv) and the mixture stirred at 25 °C for 4 h. The mixture was poured onto saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with ether (3 × 15 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by chromatography over silica gel, eluting with 60% ether/petroleum ether to give **29**: 530 mg, 89%; mp 168-170 °C dec; IR ($CCl_4$) 3555, 3440, 3330, 3266, 1736, 1725, 1580, 1320, 1250, 1165, 1050, 983, 840 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.37 (1 H, dd, $J$ = 3.0, 2.1 Hz), 5.83 (2 H, s), 5.49 (1 H, ddd, $J$ = 3.3, 6.4, 9.6 Hz), 4.77 (2 H, br s), 3.68 (1 H, d, $J$ = 16.4 Hz), 3.06 (1 H, d, $J$ = 16.4 Hz), 2.82 (1 H, ddd, $J$ = 1.8, 6.4, 12.9 Hz), 2.17 (1 H, dd, $J$ = 9.8, 12.9 Hz), 0.92 (9 H, s), 0.21 (3 H, s), 0.18 (3 H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 190.91, 155.52, 138.57, 135.76, 124.63, 120.90, 99.65, 94.99, 91.87, 87.90, 74.99, 69.08, 41.58, 25.79, 23.93, 18.32, -2.97, -3.27; HRMS calcd for $C_{20}H_{25}NO_4Si$ 371.1553, found $m/e$ 371.1556. Anal. Calcd for $C_{20}H_{25}NO_4Si$: C, 64.66; H, 6.78; N, 3.77. Found: C, 64.67; H, 6.85; N, 3.82.

**Silylation and Cyclization of 30 to give the Enone 31.** To a solution of the carbamate **29** (62.3 mg) in dichloromethane (3 mL) and triethylamine (600 $\mu$L) was added *tert*-butyldimethylsilyl triflate (80 $\mu$L). After 10 min at 25 °C the solution was poured into saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ether (10 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by PLC, eluting with 40% ether/petroleum ether to give the N-silylated derivative **30**: 77 mg, 95%; IR ($CHCl_3$) 3490, 2929, 2856, 1723, 1703, 1471, 1343, 1305, 1279, 1255, 1165, 1115 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.36 (1 H, br s), 5.80 (1 H, d, $J$ = 10 Hz), 5.78 (1 H, d, $J$ = 10 Hz), 5.52 (1 H, m), 3.67 (1 H, d, $J$ = 16.4 Hz), 3.02 (1 H, d, $J$ = 16.4 Hz), 2.77 (4 H, m), 2.12 (1 H, m), 0.90 (9 H, s), 0.88 (9 H, s), 0.21 (6 H, br s), 0.18 (3 H, s), 0.15 (3 H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 191, 158, 138, 136, 125, 121, 99, 95, 92, 88, 75, 42, 27, 26, 24, 20, 18, -3, -3.5. This product was used directly in the next step.

**Conversion of 30 into 31/32 and 33.** To a solution of **30** (15 mg) in dry THF (1.0 mL) under argon at -78 °C was added potassium bis(trimethylsilyl)amide (145 $\mu$L, 0.5 M solution, 2.5 equiv) and the resultant mixture was stirred for 15 min. A solution of *N*-(phenylseleneno)phthalimide (40 mg) in THF (0.5 mL) was added and the resulting mixture stirred at -78 °C for 1 h and allowed to warm to 20 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ether (2 × 10 mL). The dried ($MgSO_4$) extract was evaporated and the residue purified by PLC (20% ether/petroleum ether to give a mixture of **31/32** (15.9 mg, 2:1). The mixture of **31/32** was dissolved in dichloromethane (3 mL)/pyridine (20 $\mu$L) at -35 °C and treated with hydrogen peroxide (200 $\mu$L, 30% aqueous solution). Work-up as above gave **33**: 6 mg, 40% overall; IR ($CCl_4$) 2954, 2030, 2858, 1759, 1744 (8 h), 1472, 1369, 1346, 1255, 1197, 1166, 1123 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.78 (1 H, d, $J$ = 9.7 Hz), 5.74 (1 H, dd, $J$ = 9.7, 1.5 Hz), 5.67 (1 H, d, $J$ = 1.5 Hz), 5.31 (1 H, ddd, $J$ = 8.75, 2.5, 3.1 Hz), 4.66 (1 H, d, $J$ = 8.75 Hz), 2.88 (1 H, dd, $J$ = 15.8, 2.5 Hz), 2.59 (1 H, dd, $J$ = 15.8, 3.1 Hz), 0.23, 0.24, 0.28 (12 H), 0.89, 0.96 (18 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 196.36, 159.33, 155.81, 124.76, 124.31, 112.75, 99.91, 98.56, 96.85, 91.6, 80.21, 74.96, 62.68, 26.69, 25.52, 19.26, 18.17, -3.24, -3.54, -4.59, -5.03; HRMS calcd for $C_{26}H_{37}NO_4Si_2$ 483.226, found $m/e$ 483.2237.

For **32**: 3 mg, 20% overall; IR ($CCl_4$) 2956, 2930, 2897, 2885, 1755, 1743, 1472, 1325, 1256, 1193, 1177, 1109, 950, 865 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.94 (1 H, d, $J$ = 9.2 Hz), 5.86 (1 H, d, $J$ = 9.7 Hz), 4.90 (1 H, m), 4.70 (1 H, dd, $J$ = 9.8, 7.1 Hz), 3.29 (1 H, dd, $J$ = 17.8, 3.0 Hz), 2.78 (1 H, m), 2.67 (1 H, ddd, $J$ = 17.8, 4.2, 1.7 Hz), 2.76 (1 H, dd, $J$ = 14.2, 9.2 Hz), 2.24 (1 H, dd, $J$ = 14.2, 7.0 Hz), 0.98 (9 H, s), 0.88 (9 H, s), 0.34, 0.29, 0.16, 0.13 (12 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.65, 161.05, 125.58, 121.14, 98.96, 93.58, 92.61, 85.51, 73.58, 71.80, 55.76, 52.03, 38.47, 21.80, 27.31, 25.72, 19.43, 18.27, -3.08, -3.36, -3.88, -4.18; HRMS calcd for $C_{26}H_{39}NO_4Si_2$ 485.2418, found $m/e$ 485.2402.

**Conversion of 32 into 33.** A solution of the ketone **32** (95 mg, 0.19 mmol) in THF (4 mL) at -78 °C was treated with potassium bis(trimethylsilyl)amide (780 $\mu$L, 0.5 M in toluene) and the resulting dark brown solution stirred at -78 °C for 15 min. A solution of *N*-(phenylseleneno)phthalimide (200 mg, 3.5 equiv) in THF (2 mL) was added dropwise and the mixture warmed to -10 °C over 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extracts were evaporated in vacuo and the residue was dissolved in dichloromethane (2 mL) and pyridine (350 $\mu$L). The solution was cooled to -78 °C and hydrogen peroxide (1000 $\mu$L, 30% aqueous solution) added. After 1 h at 20 °C the mixture was worked up as above and the residue purified by PLC, eluting with ether/petroleum ether (60%) to give the enone **33** (42 mg, 44%, 75% based on recovered starting material) and **32** (35 mg, 37%).

**Conversion of 33 into 34.** The enone **33** (40 mg) in THF (3 mL) and water (750 $\mu$L) was treated with trifluoroacetic acid (300 $\mu$L) at 20 °C for 6 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with ether (5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by PLC, eluting with ether to give **34**: 25 mg 70%; IR ($CH_2Cl_2$) 3683, 3448, 2955, 2955, 2931, 1775, 1738, 1225, 1167 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.76 (3 H, br m, $J$ = 10, 1.6 Hz), 5.45 (1 H, dt, $J$ = 9.0, 2.8 Hz), 5.25 (1 H, br s), 4.73 (1 H, d, $J$ = 9.0 Hz), 2.93 (1 H, ABX, $J$ = 16, 2.8 Hz), 2.63 (1 H, ABX, $J$ = 16, 2.8 Hz), 0.91 (9 H, s), 0.24 (3 H), 0.25 (3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.0, 156.49, 154.08, 124.78, 124.37, 113.23, 99.39, 98.35, 97.07, 92.35, 81.12, 74.99, 57.26, 40.36, 25.52, 18.14, -3.25, -3.48; HRMS calcd for $C_{20}H_{23}NO_4Si$ 369.1396, found $m/e$ 369.1388.

**(*E*)-14-Cyano-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]trideca-1,8,13-triene-6,10-diyne (35).** To a suspension of NaH (23 mg, 960 $\mu$mol) in dimethoxyethane (2 mL) at 0 °C was added diethyl cyanomethylphosphonate (150 $\mu$L, 880 $\mu$mol) dropwise, and the mixture stirred until the evolution of hydrogen was complete. The solution was warmed to 25 °C and transferred via a syringe to a solution of the ketone **14** (285 mg, 91 $\mu$mol) in dimethoxyethane (2 mL) at -45 °C ($CO_2/CH_3CN$). After 5 min the mixture was warmed to 25 °C and kept at this temperature for 4 h. The orange solution was poured into saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give a residue which was purified by chromatography over silica gel, eluting with 10% ether/petroleum ether, to give **35** (274 mg, 90%) as a colorless oil: IR ($CCl_4$) 2922, 2884, 2858, 2220, 1642, 1462, 1428, 1246, 1130, 800 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.91 (1 H, br t, $J$ = 4 Hz), 5.80 (1 H, ddd, $J$ = 9.5, 1.3, 0.7 Hz), 5.77 (1 H, d, $J$ = 9.5 Hz), 5.75 (1 H, m), 4.12 (1 H, dd, $J$ = 17.8, 1.3 Hz), 3.27 (1 H, d, $J$ = 17.8 Hz), 2.46 (1 H, m), 2.39 (1 H, m), 2.18 (1 H, dddd, $J$ = 13.1, 6.7, 1.6, 0.9 Hz), 1.88 (1 H, ddd, $J$ = 13.1, 10.0, 7.5 Hz), 0.92 (9 H, s), 0.25 (3 H, s), 0.22 (3 H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 162.58 (s), 133.40 (d), 132.81 (s), 124.48 (d), 121.15 (d), 117.60 (s), 101.40 (s), 97.3 (s), 88.1 (d), 85.8 (s), 88.8 (s), 71.32 (s), 35.24 (t), 26.61 (t), 25.7 (q), 25.2 (t), 18.1 (s), -2.97 (q), -3.18 (q); HRMS calcd for $C_{21}H_{25}NOSi$ 335.1705, found $m/e$ 335.1712.

**(*E*)-14-(Hydroxymethyl)-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo-[7.3.1]trideca-1,8,13-triene-6,10-diyne (36).** To a solution of the cyanide **35** (141.5 mg, 0.422 mmol) in toluene (6.4 mL) at -78 °C was added DIBAL-H in toluene (507 $\mu$L, 1.2 equiv of a 1.0 M solution). After 10 min at -78 °C the mixture was allowed to warm to 20 °C for 20 min and recooled to -78 °C. The mixture was quenched by the dropwise addition of 2 N HCl (5 mL), warmed to room temperature, poured into 1 M aqueous sodium tartrate solution (5 mL), and extracted with ether (10 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by chromatography over silica gel, eluting with 12% ether/petroleum ether, to give the aldehyde: 134 mg, 93%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.07 (1 H, d, $J$ = 7.40 Hz), 6.29 (1 H, d, $J$ = 7.40 Hz), 5.98 (1 H, t, $J$ = 3.7 Hz), 5.82 (1 H, d, $J$ = 9.6 Hz), 5.78 (1 H, d, $J$ = 9.6 Hz), 3.52 (1 H, d, $J$ = 17.3 Hz), 3.32 (1 H, d, $J$ = 17.3 Hz), 2.43 (2 H, m), 2.22 (1 H, m), 1.89 (1 H, m), 0.93 (9 H, s), 0.25 (3 H, s), 0.23 (3 H, s). The aldehyde **35a** (134 mg, 0.396 mmol) in toluene (6.4 mL) at -78 °C was treated with DIBAL-H (476 $\mu$L, 1.0 M in toluene, 1.2 equiv). After 10 min at -78 °C the mixture was rapidly (2 min) warmed to room temperature, cooled to -78 °C, and quenched with 2 N HCl (4.5 mL). Work-up, as above, gave the allylic alcohol **36** (120.7 mg, 89.5%) as a colorless oil: IR ($CCl_4$) 3624, 3500, 2964, 2938, 2860, 2190, 1662, 1468, 1250, 1130, 1080, 892, 780 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.96 (1 H, t, $J$ = 6.9 Hz), 5.78 (1 H, dt, $J$ = 9.4, 0.8 Hz), 5.74 (1 H, dt, $J$ = 9.4, 1.2 Hz), 5.73 (1 H, m), 4.34 (1 H, dd, $J$ = 12.7, 6.5

Hz), 4.26 (1 H, dd, $J$ = 12.7, 7.3 Hz), 3.26 (2 H, AB, $J$ = 18.0 Hz), 2.25-2.42 (2 H, m), 2.14 (1 H, ddd, $J$ = 13.0, 7.2, 2.0 Hz), 1.83 (1 H, m), 1.6 (1 H, br s), 0.94 (9 H, s), 0.24 (3 H, s), 0.23 (3 H, s); $^{13}$C NMR (125.8 MHz, $CDCl_3$) $\delta$ 143.5 (s), 133.9 (s), 129.6 (d), 123.5 (d), 122.0 (d), 119.5 (d), 102.0 (s), 100.9 (s), 85.3 (s), 85.1 (s), 77.4 (s), 59.9 (t), 36.8 (t), 29.0 (t), 25.9 (q), 24.9 (t), 18.3 (s), -2.7 (q), -2.9 (q); HRMS calcd for $C_{21}H_{28}O_2Si$ - $t$Bu ($C_{17}H_{19}O_2Si$) 283.1154, found $m/e$ 283.1156.

**Conversion of the Allyl Alcohol 36 into Its Derived Thioacetate 36.** To a solution of the alcohol **36** (106 mg) in dichloromethane (10 mL) was added $Et_3N$ (450 $\mu$L) and the mixture cooled to -12 °C. Methanesulfonyl chloride (90 $\mu$L) was added and the mixture stirred for 15 min. A solution of freshly prepared sodium thioacetate (300 mg, 10 equiv) in methanol (2 mL) was added to the above mixture. After 1 h at 20 °C the mixture was poured into water (5 mL) and extracted with dichloromethane (2 × 5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue chromatographed over silica gel, eluting with 20% ether/petroleum ether, to give **37** (114.2 mg, 92%) as a colorless oil: IR (film) 2958, 2930, 2860, 1695, 1255, 1130, 840, 780 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.73-5.79 (4 H, m), 3.60-3.70 (2 H, ABX, $J_{AB}$ = 13.5 Hz), 3.31 (1 H, d, $J$ = 17.2 Hz), 3.25 (1 H, d, $J$ = 17.2 Hz), 2.33 (3 H, s), 2.32 (2 H, m), 2.12 (1 H, m), 1.80 (1 H, ddd, $J$ = 13.0, 9.5, 7.9 Hz), 0.91 (9 H, s), 0.22 (3 H, s), 0.20 (3 H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 195.5 (s), 144.0 (s), 133.6 (s), 130.3 (d), 123.6 (d), 121.9 (d), 115.2 (d), 102.0 (s), 100.9 (s), 85.3 (s), 85.0 (s), 71.5 (s), 37.1 (t), 30.4 (q), 28.6 (t), 28.2 (t), 25.9 (q), 24.9 (t), 18.3 (s), -2.8 (q), -3.0 (q); HRMS calcd for $C_{23}H_{30}O_2SiS$ 398.1736, found $m/e$ 398.1718.

***S*-Benzyl Trisulfide Adduct 38.** Treatment of a solution of the thioester **37** (11.4 mg) in ether (1.5 mL) with lithium aluminum hydride (35 $\mu$L, 1 M solution) at 0 °C for 10 min followed by warming to 20 °C for 0.5 h gave intermediate thiol **37a**, which was not isolated but used directly. Treatment of the thiol with *N*-(benzylthiosulfenyl)phthalimide (20 mg) in dichloromethane (0.8 mL) at 20 °C for 1 h gave the trisulfide **38** (13.4 mg, 92%) after purification by PLC, eluting with 10% ether/petroleum ether: IR (film) 2960, 2935, 2858, 1458, 1252, 1138, 1112, 836, 780 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.26 (5 H, m), 5.89 (1 H, m), 5.78 (1 H, d, $J$ = 9.4 Hz), 5.75 (1 H, d, $J$ = 9.4 Hz), 5.75 (1 H, m), 4.08 (2 H, $J_{AB}$ = 2.7 Hz), 3.56-3.65 (2 H, ABX, $J_{AB}$ = 12.7 Hz), 3.40 (1 H, d, $J$ = 17.1 Hz), 3.26 (1 H, d, $J$ = 17.1 Hz), 2.24-2.40 (2 H, m), 2.13 (1 H, m), 1.85 (1 H, ddd, $J$ = 13.0, 9.3, 7.9 Hz), 0.93 (9 H, s), 0.23 (3 H, s), 0.21 (3 H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 145.1 (s), 136.6 (s), 133.8 (s), 130.4 (d), 129.5 (d), 128.6 (d), 127.6 (d), 123.6 (d), 121.9 (d), 115.4 (d), 102.2 (s), 100.9 (s), 85.3 (s), 85.1 (s), 71.7 (s), 43.1 (t), 37.24 (t), 37.23 (t), 28.7 (t), 25.9 (q), 24.9 (t), 18.3 (s), -2.7 (q), -2.9 (q); HRMS calcd for $C_{28}H_{34}OSiS_3$ 510.1540, found $m/e$ 510.1525. *S*-Methyl derivative: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.91 (1 H, m), 5.78 (3 H, m), 3.40 (1 H, d, $J$ = 17 Hz), 3.28 (1 H, d, $J$ = 17 Hz), 2.43 (3 H, s), 2.36 (2 H, m), 2.36 (2 H, m), 2.17 (1 H, m), 1.86 (1 H, m), 0.95 (9 H, s), 0.23 (3 H, s), 0.21 (3 H, s).

**Cyclic Sulfide 40.** To a solution of the alcohol **36** (11.9 mg, 36.8 $\mu$mol) in dichloromethane (1.5 mL) at -15 °C were added triethylamine (50 $\mu$L) and methanesulfonyl chloride (10 $\mu$L). After 15 min potassium ethylxanthate (50 mg) was added and the mixture warmed to 20 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (2 × 5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by PLC, eluting with 20% ether/petroleum ether, to give the xanthate **39** (12.5 mg, 80.5%). The xanthate **39** (11.8 mg) in dichloromethane (0.5 mL) was treated with ethylenediamine (0.5 mL) at 20 °C for 1 h. Evaporation in vacuo and chromatography of the residue over silica gel gave the cyclic sulfide **40**: 6 mg, 60%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.22 (1 H, dd, $J$ = 10.9, 3.0 Hz), 6.14 (1 H, ddd, $J$ = 3.4, 2.1, 0.7 Hz), 5.96 (1 H, ddd, $J$ = 8.9, 8.0, 1.1 Hz), 5.52 (1 H, m), 5.44 (1 H, dd, $J$ = 10.9, 2.1 Hz), 3.75 (1 H, dd, $J$ = 13.2, 5.9 Hz), 3.48 (2 H, m), 2.92 (1 H, dd, $J$ = 13.2, 8.0 Hz), 2.33 (2 H, m), 2.05 (1 H, m), 1.83 (1 H, dt, $J$ = 13.2, 3.4 Hz), 0.93 (9 H, s), 0.22 (3 H, s), 0.19 (3 H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 148.3, 140.6, 137.3, 129.6, 129.5, 127.2, 114.0, 113.4, 104.8, 90.7, 72.5, 39.9, 35.5, 26.5, 25.9, 24.0, 18.2, -3.0, 3.1; HRMS calcd for $C_{21}H_{28}OSiS$ 356.1630, found $m/e$ 356.1624.

**Acknowledgment.** The National Institutes of Health (CA 50512), National Science Foundation, and Robert A. Welch Foundation are thanked for their support of this research. Dr. Jason Elliott is thanked for earlier contributions to this work.

**Supplementary Material Available:** Details of the X-ray structure determination of **13**, **22**, and **23** and tables of fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond lengths, bond angles (58 pages). Ordering information is given on any current masthead page.

# Applications of an Asymmetric [2 + 2]-Photocycloaddition. Total Synthesis of (-)-Echinosporin. Construction of an Advanced 11-Deoxyprostaglandin Intermediate

**Amos B. Smith, III,* Gary A. Sulikowski, Michelle M. Sulikowski, and Katsumi Fujimoto**

*Contribution from the Department of Chemistry, the Monell Chemical Senses Center, and the Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104.* *Received September 16, 1991*

**Abstract:** The first total synthesis of the novel antitumor metabolite (-)-echinosporin (**1**) has been achieved. Asymmetric [2 + 2]-photocycloaddition of dihydrofuran acetonide (+)-**8** to 2-cyclopentenone (**7**) constituted the cornerstone of the synthetic strategy. Mitsunobu lactonization of hemiacetal acid **43** generated the tricyclic framework of **1**, which embodies a strain energy of ca. 17 kcal/mol as estimated by MNDO calculations. The successful synthetic venture permitted assignment of the absolute configuration of echinosporin. Construction of the Corey 11-deoxyprostaglandin intermediate (+)-**49** further demonstrated the utility of (+)-**8** as a chiral building block.

The isolation of (-)-echinosporin (XK-213) from the fermentation broth of *Streptomyces echinosporus* was reported by a group from the Kyowa Hakko Kogyo Co. (Japan) in 1981.[1] The structure of **1**, initially deduced via spectroscopic and chemical methods, was later confirmed by a single-crystal X-ray analysis.[2] Although **1** displays modest activity against Gram-negative bacteria, its efficacy against several rodent tumor models appears promising.[3] Moreover, in vitro studies have implicated the in-

(1) (a) Iida, T. N.; Hirayama, N.; Shirahata, K. *Abstr. Papers, 44th Annu. Meeting Jpn. Chem. Soc.*, October 12, 1981, 1E-18, pp 403. Kyowa Hakko Kogyo Co., Ltd. *Jpn. K. Tokkyo Koho* **1981**, *59*, 777. (b) Sato, T.; Kawamoto, I.; Oka, T.; Okachhi, R. *J. Antibiot.* **1982**, *35*, 266.

(2) Hirayama, N.; Iida, T.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 287.

(3) Morimoto, M.; Imai, R. *J. Antibiot.* **1985**, *38*, 490.

0002-7863/92/1514-2567$03.00/0 