Synthesis of a Protected (±)-Calicheamicinone Derivative by Sequential Introduction of Functionality into the Bicyclo[7.3.1]enediyne Core Structure

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Abstract: The core bicyclo[7.3.0]enediyne **3** has been synthesized from the protected cyclohexane-1,2-dione **6** and enediyne component **9**. Conversion of **20** into more highly functionalized enediynes was accomplished by oxidation and amination to give **27**. Protection of **27**, and conversion into **31**, gave on treatment with $(MeO)_2P(O)CH_2CO_2Me$ the lactone **32**, which was transformed into the trisulfide **39**. All attempts to deprotect **39**, using conditions that other workers successfully applied to similar substrates, only resulted in the cyclic sulfides **42** and **43**.

Introduction

The enediyne antitumor antibiotics have attracted a great deal of attention because of their unusual structures and potent biological activity.[1] Notable contributions to their synthesis and *in vitro* mechanism of action have been made by Danishefsky,[2] Nicolaou,[3] Clive,[4] and others.[5] We have adopted an approach to their synthesis that uses $\eta^2Co_2(CO)_6$-propargylic cation complexes to form the bicyclo[7.3.1]enediyne core structure.[6] Here is reported the culmination of this strategy, resulting in the synthesis of a protected version of (±)-calicheamicinone **2**, the aglycon of calicheamicin γ_1 **1**. The essence of our overall strategy has been to devise a sequence of reactions to convert the bicyclo[7.3.1]enediyne core compound **3** into **2**, Scheme 1.

Retrosynthetic Analysis

Our initial research indicated that the bicyclo[7.3.1] enediyne core structure **3** could be assembled *via* the retrosynthetic pathway shown in Scheme 2. Addition of the lithioenediyne **5** to the mono-*tert*-butyldimethylsilyl enol ether of cyclohexane-1,2-dione **6** followed by oxidation should allow access to **4**. An aldol reaction, initiated by conjugate addition to **4**, leads to **3**. We anticipated that a Lewis acid mediated aldol reaction would result in a synclinal intermediate through chelation and give the correct 12β-hydroxyl stereochemistry shown in **3**.[7] The remaining steps involve the introduction of the carbamate at C-2, a carbonyl at C-3, and the allylic trisulfide at C-13.

We considered that allylic oxidation of **3** to give **7** would allow an amination process to take place *via* an addition−elimination mechanism to give **8**. The trisulfide functionality can be introduced using Wadsworth−Emmons chemistry, reduction and conversion into **2** using the sequence we published in 1989.[8] This sequence of transformations has been used successfully by Danishefsky, Nicolaou, and Clive in their respective syntheses of calicheamicinone. In all cases they had to make modifications to prevent participation by the 12β-hydroxyl group.[9]

The key step in Scheme 2 is the introduction of the nitrogen functionality at C-2. In a more general sense there are relatively few methods for the direct introduction of nitrogen functionality into the α-position of a carbonyl group. We decided that the examination of methodology for the amination of ketone enol derivatives that operate under mild conditions would be a

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

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(2) Shair, M. D.; Danishefsky, S. J. *J. Org. Chem*. **1996**, *61*, 16 and references therein. Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1990**, *112*, 3253. 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.

(3) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1377, and references therein. Nicolaou, K. C.; Hummel, W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082.

(4) Clive, D. L. J.; Bo, Y.; Tao, Y.; Daigneault, S.; Wu, Y-J.; Meignan G. *J. Am. Chem. Soc*. **1996**, *118*, 4904.

(5) For a recent extensive review, see: Lhermitte, H.; Grierson, D. S. *Contemporary Organic Synthesis* **1996**, *3*, 41 and **1996**, *3*, 93. Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc*. **1988**, *110*, 631. Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, *30*, 433. Maier, M. E.; Brandstetter, T. *Tetrahedron Lett*. **1992**, *33*, 7511. Maier, M. E.; Brandstetter, T. *Liebigs Ann. Chem.* **1993**, 1009. Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851.

(6) For a review of our previous work in this area, see: Magnus, P. *Tetrahedron* **1994**, *50*, 1397. Magnus, P. *The Use of* $\eta^2Co_2(CO)_6$-Acetylene Complexes for the Synthesis of Enediyne Antitumor Antibiotics. SmithKline Beecham Research Symposium, *Organometallic Reagents in Organic Synthesis*; Academic Press Ltd.: 1994; Chapter 1, p 1.

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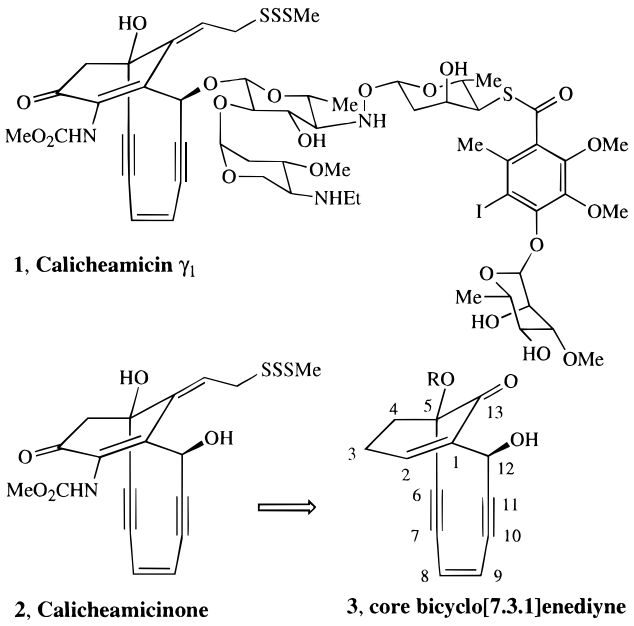
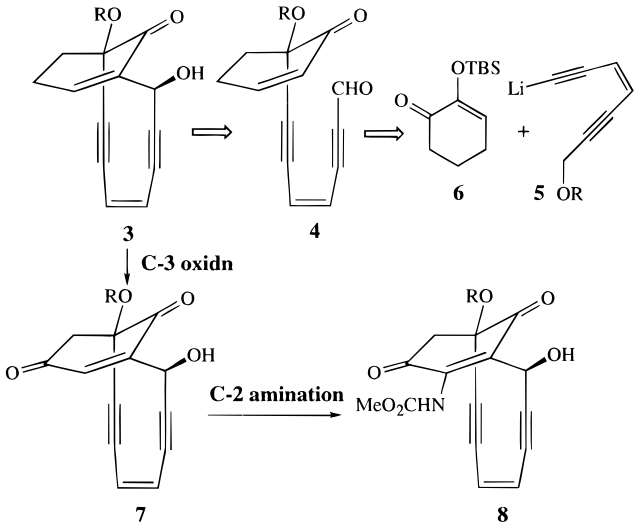
Scheme 1



Scheme 2



worthwhile endeavor in itself, regardless of its eventual applicability to the synthesis of calicheamicinone.[10]

Synthesis of Bicyclo[7.3.1]enediyne Core (Scheme 3)

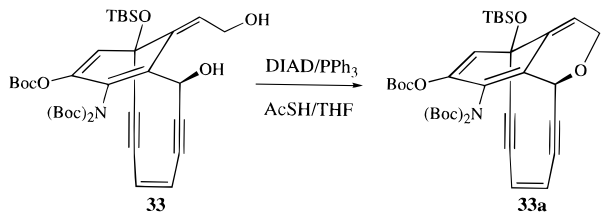
Coupling of propargyl alcohol-THP ether to *cis*-1,2-dichloroethylene under the usual conditions [$Pd(Ph_3P)_4$/CuI/$BuNH_2$/PhH] followed coupling to trimethylsilylacetylene under the same conditions, and desilylation gave the enediyne **9**.[11,12] Treatment of **9** with lithium bis(trimethylsilyl)amide and addition to the enone **6** followed by quenching the mixture with allyl chloroformate gave **11**. In this sequence of transformations the initially formed adduct **10** must undergo silyl migration to give **10a**, which is trapped by the chloroformate. Palladium diacetate catalyzed oxidation of **11** gave the enone **12**.[13] This very convenient procedure could be operated on a large scale (>40 g) in good yields. Removal of the THP group in **12** was achieved using Amberlyst H-15 acid resin in methanol to give the alcohol **13** (97%). Complexation of **13** with $Co_2(CO)_8$ was not entirely regiospecific and resulted in a mixture of the required adduct **15** and **14** (6:1). The adducts were separated, and **14** was recycled to **13** by oxidative removal of the cobalt complex with ceric(IV) ion. Oxidation of **15** using the Saigo procedure gave the aldehyde cobalt complex **16**.[14] This sequence of reactions can be carried out on >100 gram scale. Treatment of **16** with $PhSAlMe_2$ at −78 °C followed by Ti(OPr^i)$_4$ and warming to −10 °C gave the cyclized adduct **17**.[15] We have spent a great deal of time trying to optimize this reaction and make it reproducible on a convenient scale (ca. 5−10 g). The reagent $PhSAlMe_2$ rapidly adds to **16** to give two diastereomeric β-sulfides (*via* **16a**). Only one of these adducts proceeds to form the product **17**, presumably *via* the chelate **16b**. The reaction is worked-up by quenching with cold (−78 °C) silica gel to prevent retro-aldol reaction to **18**. It was found that it was best to oxidize the sulfide **17** with MCPBA to give directly **19**, which is far more stable since it cannot undergo a retro-aldol reaction. Cobalt decomplexation of **19** provides the crystalline enone **20** (12 steps from propargyl alcohol). Protection of the 12β-ol **20** as the derived TBS ether **21** was necessary for the next step to be successful.

Introduction of C-3 Oxygen and C-2 Nitrogen Functionality (Scheme 4)

While there are a number of allylic oxidation procedures that, in principle, are capable of converting **21** directly into **22**, only the Nicoloau reagent proved successful.[16] Surprisingly,[17] when **21** was treated with *N*-(phenylselenenyl)phthalimide the bisselenide **22** was formed. This turned out to be ideal, since **22** was readily oxidized to the desired enedione **23**. It is essential that the *N*-(phenylselenenyl)phthalimide be freshly recrystallized for this reaction to be successful.[18]

Conjugate addition of azide anion to the enedione **23** at C-2 should be a possible method for the introduction of an amine

(9) Treatment of the diol **33** with thiolacetic acid under Mitsunobu conditions gave the cyclic ether **33a** (70%). Using the modified reaction conditions reported by Danishefsky (ref 2) also gave **33a**. Consequently, we were forced to proceed by the protection deprotection sequence depicted in Scheme 4, as were both Nicolaou and Clive (refs 3 and 4), but using different protecting groups.



(10) The efforts to introduce the C2-amino group into **7** has lead to a number of new reactions involving PhIO/trimethylsilyl azide chemistry and other electrophilic aminating species. Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc*. **1996**, *118*, 3406. Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 3993. Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron*, **1995**, *51*, 11087. Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075. Magnus, P.; Lacour, J.; Weber, W. *J. Am. Chem. Soc*. **1993**, *115*, 9347. Magnus, P.; Hulme, C.; Weber, W. *J. Am. Chem. Soc*. **1994**, *116*, 4501.

(11) Magnus, P.; Eisenbeis, S. A.; Fairhurst, R. A.; Iliadis, T.; Magnus, N. A.; Parry, D. *J. Am. Chem. Soc*. **1997**, *119*, 5591−5605.

(12) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001. Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1986**, *27*, 5857. Guillerm. D.; Linstumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.

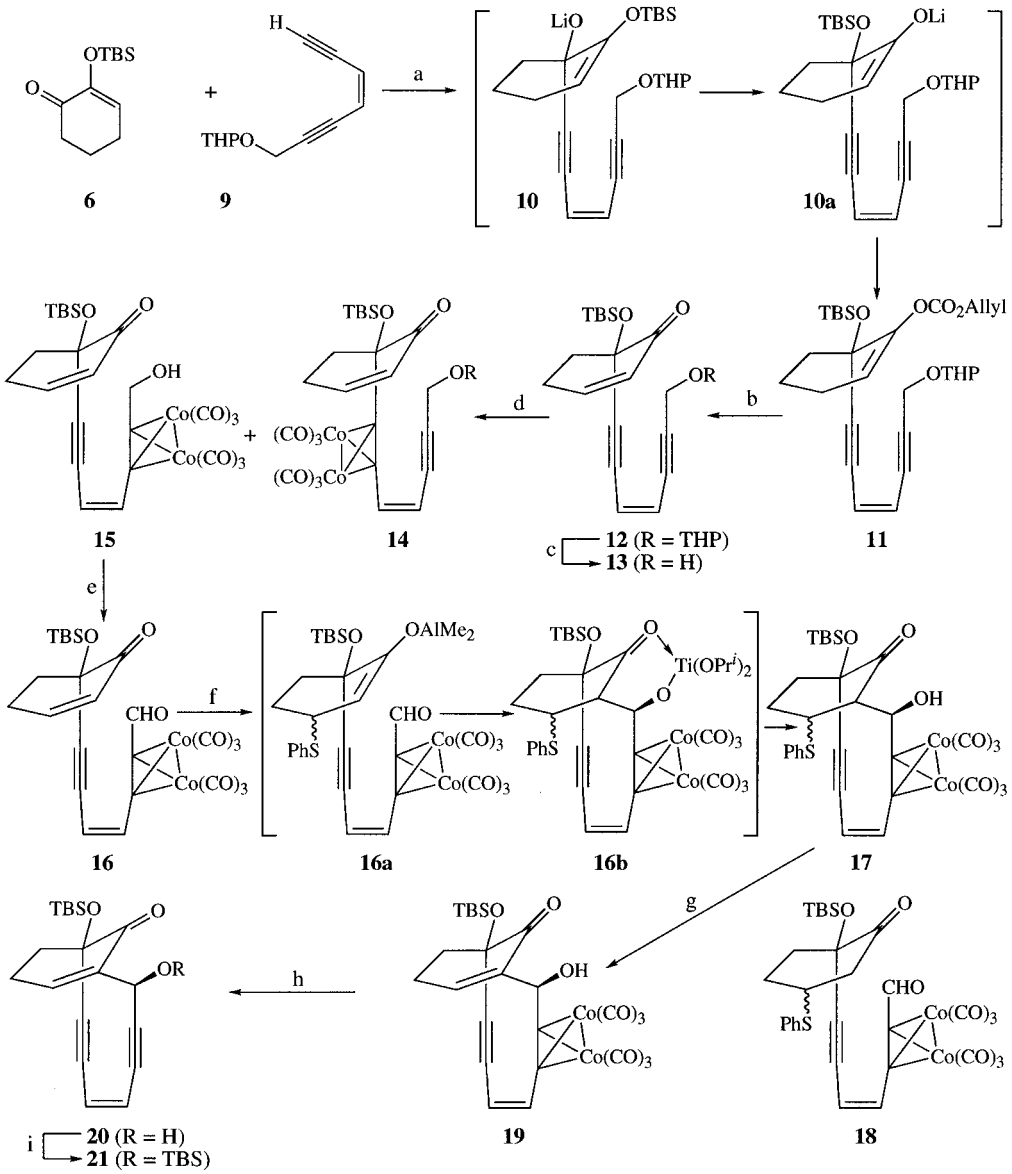
(13) Tsuji, J.; Minami, I.; Shimizu, I.; Kataoka, H. *Chem. Lett*. **1984**, 1133. Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc*. **1982**, *104*, 5844.

(14) For an example of the Saigo oxidation on a $\eta^2Co_2(CO)_6$-properglic alcohol see: Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett*. **1989**, *30*, 309. Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 2773. Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc*. **1978**, *101*, 7104.

(15) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 274.

(16) 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.

Scheme 3[a]

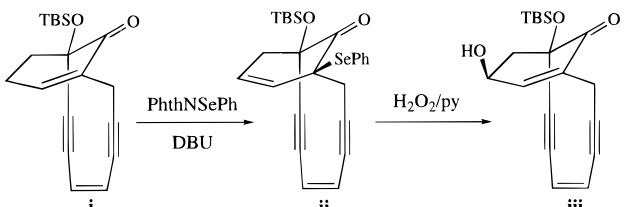


[a] Conditions: (a) LiN(TMS)$_2$/THF/−78 to −30 °C/recool to −78 °C add **6**, warm to 25 °C, recool to −78 °C, add allylchloroformate, **11** (90%). (b) Pd(OAc)$_2$ (cat)/MeCN reflux, **12** (76%). (c) Amberlyst H-15, MeOH, **13** (97%). (d) $Co_2(CO)_8/CH_2Cl_2$/0 °C **15** (85%), **14** (14%). (e) *t*-BuOMgBr/THF/1,1′-azodicarbonyldipiperidine/THF/0 °C, **16** (81%). (f) $PhSAlMe_2$/THF/CH_2Cl_2 at −78 °C, followed by Ti(OPr^i)$_4$ −78 to 10 °C, recool to −78 °C, workup with SiO_2 quench, **17** (45−71%). (g) MCPBA/CH_2Cl_2, **19** (64%). (h) Ce(NH$_4$)$_2$(NO$_2$)$_6$/acetone/−10 °C, **20** (76%). (i) TBSOTf/CH_2Cl_2/NEtPr$_2^i$/0 °C, **21** (93%).

group at this position.[19] It was found that treatment of **23** with NaN_3 in CF_3CH_2OH/DMF gave the amine **24**, albeit in low yield (<10%), which became even lower on a larger scale (>10 mg).[20]

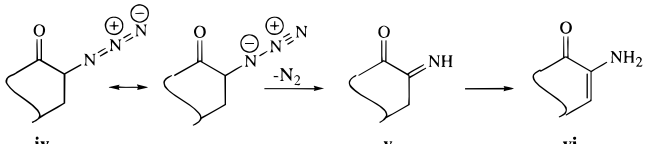
Diphenylsulfilimine ($Ph_2S{=}NH$) is known to add to enediones to produce aziridines in a protic solvent (MeOH) and enamines in benzene.[21] Exposure of **23** to $Ph_2S{=}NH{\cdot}H_2O$ in CF_3CH_2-OH only gave the 1,2-aziridine **25** (isolated as the -NCO_2Me derivative). Eventually, it was discovered that the 12β-alcohol **26** reacted with $Ph_2S{=}NH$ in tetrahydrofuran to give the 2-amino adduct **27** (65−85%).[22] Presumably, the success of this procedure is due to intramolecular protonation of the C1−

(17) Our earlier work on the 12-desoxy series had shown that treatment of **(i)** with *N*-(phenylselenenyl)phthalimide/DBU gave the monoselenide **(ii)**, which on oxidation provided access to the 3β-ol **(iii)**. Magnus, P.; Lewis, R.; Bennett, F. *J. Am. Chem. Soc.* **1992**, *114*, 2560.

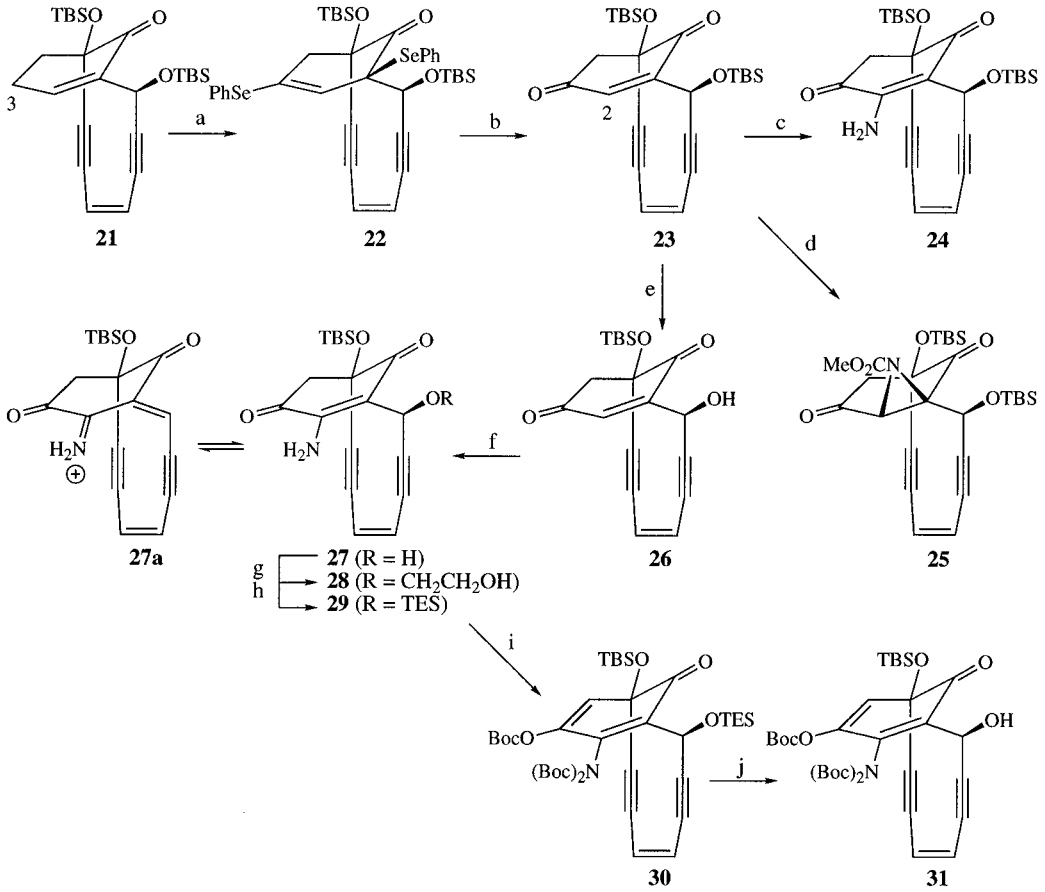


(18) The best results were obtained with *N*-(phenylselenenyl)phthalimide that was crystallized to constant melting point. While we could not detect impurities by TLC and NMR, the yields with unpurified reagent were <30%, and sometimes the substrate **21** was completely destroyed.

(19) Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075. Patonay, T.; Hoffman, R. V. *J. Org. Chem.* **1995**, *60*, 2368. Effenberger, F.; Beisswenger, T.; Az, R. *Chem. Ber.* **1985**, *118*, 4869. Effenberger, F.; Beisswenger, T. *Chem. Ber.* **1984**, *117*, 1497. α-Azidoketones **(iv)** undergo elimination of nitrogen to give an imine **(v)**, which usually tautomerizes to the enamine **(vi)**.



Scheme 4[a]



[a] Conditions: (a) *N*-(phenylselenenyl)phthalimide/DBU/CH_2Cl_2/25 °C, **22** (79%). (b) H_2O_2/CH_2Cl_2/0−25 °C, **23** (89%). (c) NaN_3/CF_3CH_2OH/DMF, **24** (<10%). (d) $Ph_2S{=}NH{\cdot}H_2O$/CF_3CH_2OH, followed by triphosgene/$NEtPr_2^i$/MeOH, **25** (95%). (e) CF_3SO_3H/H_2O/THF, **26** (87%). (f) $Ph_2S{=}NH$/THF/25 °C, **27** (65%). (g) Camphor sulfonic acid/dioxane/ethylene glycol, **28** (65%). (h) **27**/TESOTf/NEt_3/CH_2Cl_2, **29** (90%). (i) $(Boc)_2O$/DMAP/NEt_3/CH_2Cl_2, **30** (95%). (j) CF_3SO_3H/H_2O/THF, **31** (95%).

C13 enolate by the 12β-hydroxyl, competing with the 1,3-elimination of Ph_2S.

Attempted ketalization of **27** was unsuccessful due to an unexpected reaction resulting in **28**, presumably *via* the iminium ion **27a**. The structure of **28** was established by X-ray crystallography, Figure 1. Since we could not use the C-3 ethylene ketal protecting group (that could have successfully completed the synthesis),[2−4] we explored various enol derivatives that could be made under neutral to basic conditions. It was found that treatment of **27** with TESOTf/Et_3N gave **29**, and both the 2-amino group and the C-3 carbonyl could be protected as the *tris*-Boc derivative **30**. Selective deprotection of **30** (TfOH/THF/H_2O) gave the 12β-alcohol **31**.

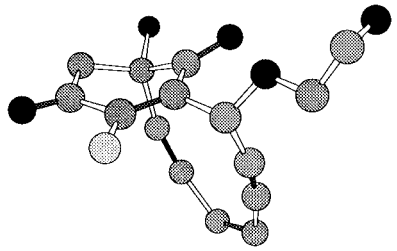


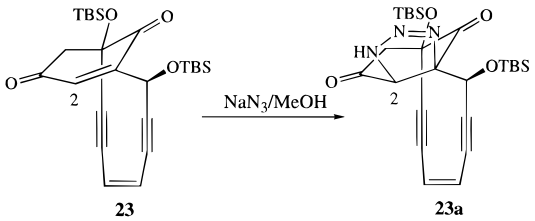
Figure 1. Chem 3D of **28** from X-ray coordinates (-TBS).

Introduction of the Trisulfide and Final Complications (Scheme 5)

The introduction of the C14 and C15 carbon atoms of the allylic trisulfide can be achieved by Wadsworth−Emmons phosphonate chemistry.[23] Since Danishefsky has conducted this transformation intramolecularly,[2] we converted **31** into the derived the β-phosphono-ester, but using the Rathke conditions[24] (or NaH and LiHMDS), we did not observe any lactone **32**.[25] Only slow conversion into **31** took place. Fortunately, the classical intermolecular Wadsworth−Emmons conditions cleanly converted **31** into **32** (88%). We could not detect the other stereoisomer (^{1}H NMR).

Both Nicolaou and Danishefsky have reduced lactones similar to **32** (3-ethylene ketal and 2-NPhth) in their respective syntheses of **2**, using DIBAL-H (lactol) followed by $NaBH_4$ to give the

(20) The solvent system CF_3CH_2OH/DMF was the only medium that gave **24**. If we treated **23** with NaN_3/MeOH a low yield of the triazole **23a** resulted.



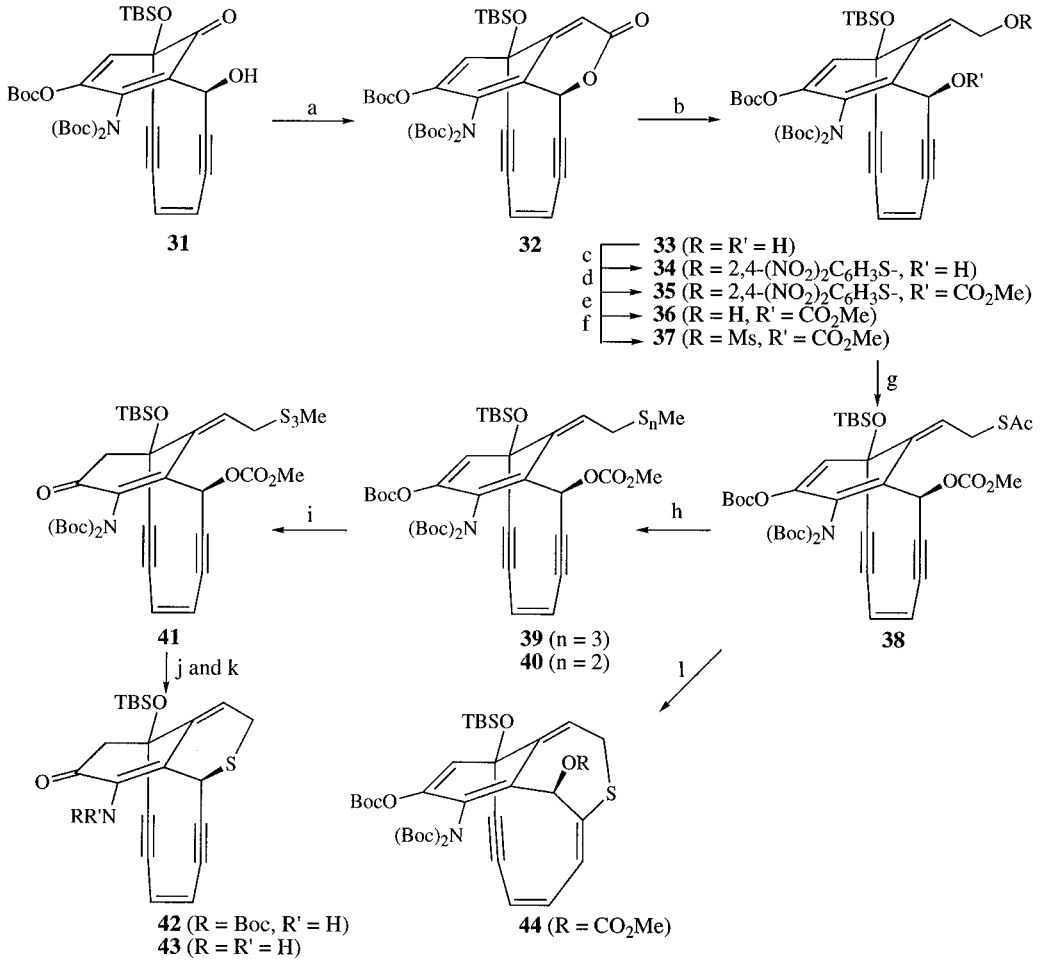
(21) Furukawa, N.; Yoshimura, T.; Ohtsu, M.; Akasaka, T.; Oae, S. *Tetrahedron* **1980**, *36*, 73. Yoshimura, T.; Omata, T.; Furukawa, N.; Oae, S. *J. Org. Chem.* **1976**, *41*, 1728.

(22) During the course of this work it was reported that $Ph_2S{=}NH$ reacts with similar enones to give an aziridine. Clark, D. A.; De Riccardis, F.; Nicolaou, K. C. *Tetrahedron* **1994**, *50*, 11391. Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1995**, *60*, 2753.

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

(24) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.

Scheme 5[a]



[a] Conditions: (a) $(MeO)_2P(O)CH_2CO_2Me/LiN(TMS)_2/THF/0$ °C, **32** (88%). (b) $NaBH_4/MeOH/H_2O$, **33** (81%). (c) $2,4\text{-}(NO_2)_2C_6H_3SCl/py/CH_2Cl_2$, **34** (73%). (d) MeOCOCl/py/CH_2Cl_2, **35** (74%). (e) PhSH/py/THF, **36** (87%). (f) $Ms_2O/NEt_3/CH_2Cl_2$, **37** (83%). (g) KSAc/acetone, **38** (81%). (h) DIBAL-H/THF/−78 °C, workup with Rochelle's salt, followed by PhthSSMe, **39** (90%). (i) TESOTf/CH_2Cl_2/NEt_3, **41** (39%) and **42** (49%). (j) **39**/$MeSO_3H/CH_2Cl_2$, **42** (86%). (k) TESOTf/2,6-lutidine/CH_2Cl_2, **43** (76%). (l) $NaBH_4$/MeOH, **44** (42%).

respective diol. We found this two-step procedure to be unreliable and low yielding.

The lactone **32** was readily reduced to the diol **33** (81%) by treatment with $NaBH_4$/MeOH. Selective protection of the primary alcohol was achieved by sulfenylation with $2,4\text{-}(NO_2)_2C_6H_3SCl$ to give **34**,[26] and the propargylic hydroxyl group was converted into the carbonate derivative **35**. Treatment of **35** with thiophenol gave **36**. The derived mesylate **37** was converted into the thiol acetate **38**, and its structure and relative stereochemistry were confirmed by single crystal X-ray analysis, Figure 2.

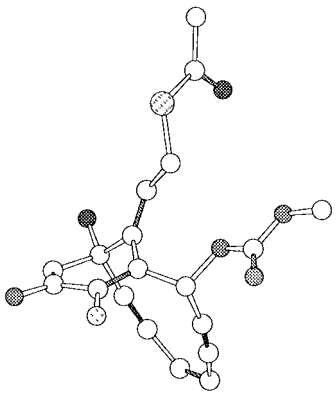
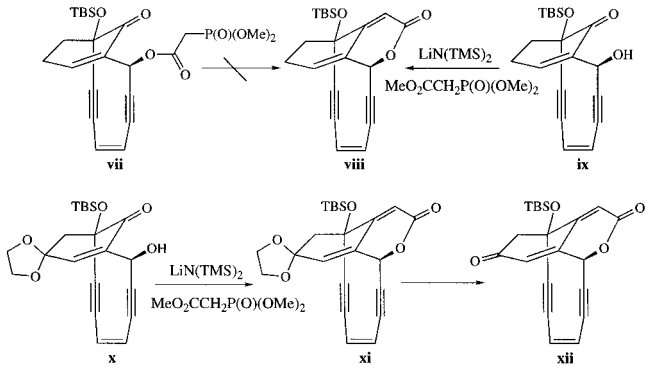


Figure 2. Chem 3D of **38** from X-ray coordinates (-TBS, -3 Boc's).

Reductive cleavage of the thiolacetate **38** with DIBAL-H and *in situ* treatment of the thiolate anion with the Harpp reagent PhthSSMe[27] gave a mixture of the trisulfide **39** and disulfide **40**.[28] Whereas, workup of the above reaction with MeOH/

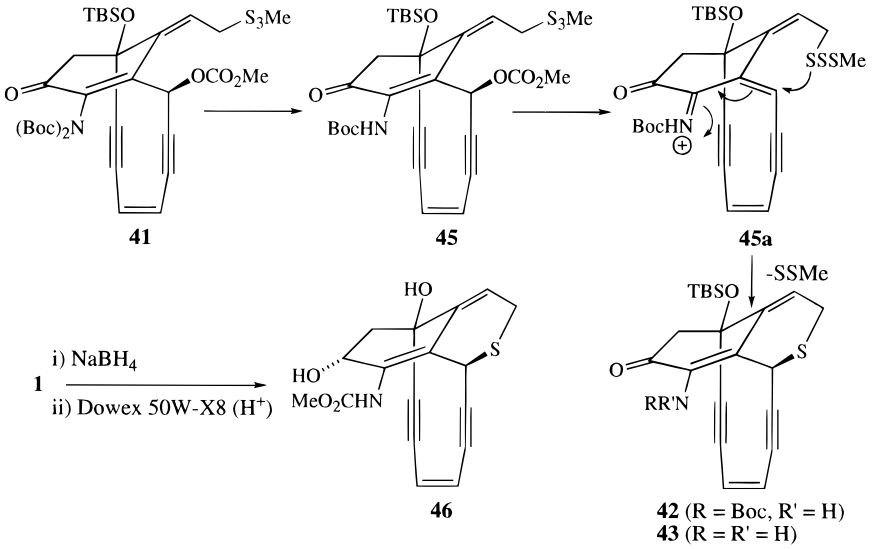
(25) The ketophosphonate **(vii)** did not undergo intramolecular cyclization to give **(viii)** under a variety of conditions [NaH, $LiN(TMS)_2$, DBU/LiCl, Et_3N/LiBr] and was slowly converted into the alcohol **(ix)**. In contrast, treatment of **(ix)** with the standard Wadsworth−Emmons reagent under intermolecular reaction conditions proceeded cleanly to give the lactone **(viii)** in >80% yield.



Ketalization of **26** gave **(x)** which underwent intermolecular Wadsworth−Emmons reaction to give **(xi)** (83%). Hydrolysis of **(xi)** gave **(xii)**, which would *not* undergo C-2 amination with $Ph_2S{=}NH$ under the conditions that worked well for the enedione **26**. More vigorous reaction conditions gave extensive decomposition.

(26) Letsinger, R. L.; Fontaine, J.; Mahadevan, V.; Schexnayder, D. A.; Leone, R. E. *J. Org. Chem.* **1964**, *29*, 2615.

Scheme 6



Rochelle's salt and addition of Harpp's reagent (now to the thiol) only gave the trisulfide **39**.[29] If the thiolacetate **38** is reductively cleaved with $NaBH_4$, the cyclic sulfide **44** was formed. We have observed this type of cyclic sulfide in earlier model work.[8]

Treatment of **39** with camphor sulfonic acid/THF/H_20 at 25 °C (conditions used by Danishefsky, Nicoloau, and Clive) gave no reaction, and warming the mixture resulted in extensive decomposition. Exposure of **39** to TESOTf/Et_3N cleanly gave **41** (39%) and **42** (49%). Excess TESOTf/2,6-lutidine resulted in the completely deprotected cyclic sulfide **43** (76%). More vigorous deprotection conditions ($MeSO_3H$) gave **42** (86%), Scheme 5. Apparently, the enol-Boc group is removed first to give **41**, which upon removal of one of the *N*-Boc groups results in **45**, which allows the iminium ion **45a** to form (see **27a**, Scheme 4), and sulfide participation to give **42** and **43**, Scheme 6. It is instructive to recall that the Lederle group had observed that **1** on treatment with $NaBH_4$, followed acid catalyzed methanolysis, isolated the cyclic sulfide **46**.[30] These results vividly illustrate that calicheamicinone precursors are delicately poised to be either converted into **2** or proceed down the pathway of iminium ion chemistry in the same manner as observed in the original structure/degradation studies.

Summary

The conversion of a simple bicyclo[7.3.1]enediyne core structure such as **20** into a fully functionalized system **39** has been accomplished and demonstrates that a variety of unusual reactions can be conducted on the core in an efficient manner. One of the most difficult problems in the above approach has been the conjugate addition−aldol reaction to convert **16** into **20**. This reaction does not scale-up well and drastically reduces the amount of material needed for the more detailed investigation of protecting group options, and exploring, for example, the potential uses of the aziridine **25** as an isomeric analogue of calicheamicinone. Consequently, as a realization of the limitations imposed by the above we have devised a much more efficient synthesis of theenedione **23**.[31]

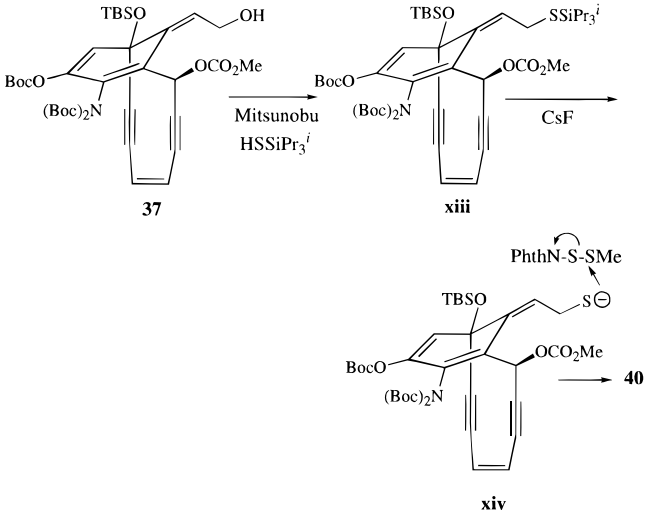
Experimental Section[32]

6-[(*Z*)-7-[(Tetrahydropyranyl)oxy]hept-1,5-diyn-3-ene]-6-[(*tert*-butyldimethylsilyl)oxy]-1-[carboallyloxy]cyclohex-1-ene (11). A solution of **9** (17.5 g, 92 mmol) in anhydrous tetrahydrofuran (275 mL) was cooled to −78 °C under argon. Lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 110 mL, 110 mol, 1.2 equiv) was added over 5 min, and the mixture stirred for 5 min at −78 °C and for 15 min at −30 °C. The solution was cooled to −78 °C, and a solution of **6** (24.9 g, 110 mmol, 1.2 equiv) in anhydrous tetrahydrofuran (25 mL) was added *via* cannula over 10 min. The mixture was stirred for 15 min at −78 °C, allowed to warm to room temperature, and stirred at ambient temperature for 3 h. The mixture was recooled to −78 °C, and allyl chloroformate (15.6 mL, 147 mmol, 1.6 equiv) was added over 5 min. The mixture was stirred at −78 °C for 5 min, allowed to warm to room temperature and stirred for a further 2 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (300 mL), the layers

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

(28) McGahren, W. J.; Ding, W-D.; Ellestad, G. A. Disulfide Calicheamicins and the Chemistry of the Allylic Trisulfide group. *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Dekker, Inc.: New York, 1995; Chapter 5, p 75.

(29) Exposure of **37** to the standard Mitsunobu reaction conditions (PPh_3/DEAD) in the presence of the Soderquist thiol ($HSSiPr_3^i$), (Miranda, E. I.; Diaz, M. J.; Rosado, I.; Soderquist, J. A. *Tetrahedron Lett*. **1994**, *35*, 3221) resulted in clean conversion into the protected sulfide **xiii** (45%). Exposure of **xiii** to HF/pyridine in the presence of the Harpp reagent (PhthNSSMe) gave the trisulfide **39** in low yield. Whereas, treatment of **xiii** with CsF/DMF resulted in clean formation of the disulfide **40** (70%). Presumably, in the latter process the thiolate **xiv** attacks the terminal sulfur atom with PhthNS- as the leaving group, and in the former reaction (HF/pyridine) the thiol displaces PhthN-.



(30) Lee, M. D. Identification, Isolation, and Structure Determination. *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Dekker, Inc.: New York, 1995; Chapter 4, p 49.

(31) Hallett, D. Unpublished results from this laboratory.

were separated, and the aqueous phase was extracted with Et_2O (300 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude product by chromatography over silica gel eluting with 95:5 hexanes/Et_2O gave **11** as a pale yellow oil (41.45 g, 90%). IR (thin film) 2930, 2855, 1768, 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.82−5.96 (2H, m), 5.80 (1H, s), 5.53 (1H, t, J = 4 Hz), 5.34 (1H, dd, J = 17, 1 Hz), 5.22 (1H, dd, J = 11, 1 Hz), 4.79 (1H, br s), 4.57−4.65 (2H, m), 4.30−4.47 (2H, m), 3.77−3.85 (1H, m), 3.47−3.53 (1H, m), 2.01−2.22 (4H, m), 1.45−1.84 (8H, m), 0.82 (9H, s), 0.18 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 147.4, 131.5, 119.5, 119.2, 118.9, 117.4, 98.2, 96.9, 92.9, 83.0, 82.4, 68.6, 68.2, 61.9, 54.8, 40.6, 30.2, 25.6, 25.3, 24.0, 19.0, 18.9, 18.0, −3.0, −3.5. HRMS calcd for $C_{28}H_{41}O_6Si$ (M^+ + 1) 501.2672. Found 501.2663.

6-[(*Z*)-7-[(Tetrahydropyranyl)oxy]hept-1,5-diyn-3-ene]-6-[(*tert*-butyldimethylsilyl)oxy]cyclohex-2-en-1-one 12. To a solution of **11** (41.7 g, 83.3 mmol) in anhydrous acetonitrile (420 mL) heated at reflux under argon was added palladium(II) acetate (375 mg, 1.67 mmol, 2 mol %), and the mixture heated at 80 °C for 4 h until TLC (hexanes/Et_2O, 80:20) showed complete reaction. Celite 545 (15 g) was added, and the mixture was allowed to cool with vigorous stirring over 30 min. The solution was filtered through a pad of Celite, and the solvent evaporated *in vacuo* to give the crude product, which was immediately purified by chromatography over silica gel eluting with 80:20 hexanes/Et_2O to give **12** as a colorless oil (26.2 g, 76%). IR (thin film) 2928, 2854, 1706, 1620 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.84−6.89 (1H, m), 5.95 (1H, bd), 5.77−5.88 (2H, m), 4.78 (1H, bt), 4.32−4.46 (2H, m), 3.78−3.84 (1H, m), 3.46−3.55 (1H, m), 2.50−2.66 (1H, m), 2.35−2.47 (1H, m), 2.17−2.41 (2H, m), 1.50−1.83 (6H, m), 0.86 (9H, s), 0.20 (3H, s), 0.18 (3H, s). ^{13}C NMR δ (75 MHz, $CDCl_3$) δ 193.6, 149.8, 126.9, 120.2, 118.9, 96.9, 94.4, 93.2, 84.4, 82.9, 73.2, 62.0, 54.7, 38.8, 30.2, 25.8, 25.3, 25.1, 19.0, 18.3, −3.2, −3.1. HRMS calcd for $C_{24}H_{35}O_4Si$ (M^+ + 1) 415.2315. Found 415.2305.

6-((*Z*)-7-Hydroxyhepta-1,5-diyn-3-ene)-6-[(*tert*-butyldimethylsilyl)oxy]cyclohex-2-en-1-one 13. Amberlyst H-15 (5.2 g) was added to a stirred solution of **12** (11.4 g, 27.5 mol) in methanol (125 mL) at room temperature. After 3 h the reaction was complete by TLC (hexanes/EtOAc, 80:20). The mixture was filtered through a pad of silica gel (5 cm × 10 cm dia) and washed thoroughly with methanol (250 mL) and Et_2O (500 mL). The filtrate was concentrated *in vacuo*, and the residues were purified by chromatography over silica gel eluting with hexanes/Et_2O 80:20) to give **13** as a colorless oil (8.83 g, 97%). IR (thin film) 3428, 2928, 2885, 2855, 2708, 2206, 1697, 1620 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (1H, ddd, J = 10, 4.1, 4.0 Hz), 5.96 (1H, ddd, J = 10, 1.7, 1.6 Hz), 5.86 (1H, dt, J = 10.8, 1.7 Hz), 5.78 (1H, d, J = 10.8 Hz), 4.39 (2H, s), 2.41−2.65 (3H, m), 2.18−2.27 (2H, m), 0.84 (9H, s), 0.19 (3H, s), 0.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 150.5, 126.8, 120.9, 118.9, 95.8, 94.2, 84.8, 82.6, 73.0, 51.4, 38.4, 25.7, 24.7, 18.3, −3.2, −3.3. HRMS calcd for $C_{19}H_{27}O_3Si$ (M^+ + 1) 331.1730. Found 331.1728.

6-((*Z*)-7-Hydroxyhepta-1,5-diyn-5,6-η^2-hexacarbonyldicobaltio-3-ene)-6-[(*tert*-butyldimethylsilyl)oxy]cyclohex-2-en-1-one 15. Dicobalt octacarbonyl (16.45 g, 48.1 mmol, 1 equiv) was added in portions over 5 min to a stirred solution of **13** (15.9 g, 48.1 mmol) in dichloromethane (240 mL) at 0 °C under argon. The mixture was stirred until the evolution of gas ceased, and TLC (hexanes/EtOAc, 80:20) showed complete consumption of starting material. The solvent was evaporated *in vacuo*, and the mixture purified by chromatography over silica gel eluting with 80:20 hexanes/Et_2O to give **15** (25.2 g, 85%) and **14** (5.0 g, 14%). ^1H NMR spectroscopy on these compounds produced very broad-peaked spectra.

Recycling 14. A stirred solution of **14** (14 g, 22.7 mmol) in acetone (220 mL) and triethylamine (0.575 mL) was treated with cerium(IV) ammonium nitrate in small portions until the solution became light orange (total added: 40 g, 72.9 mmol, 3.2 equiv). Celite 545 (10 g) was added, and the mixture stirred vigorously for a further 15 min. The solids were filtered, the filtrate was concentrated to a volume of *ca.* 20 mL and diluted with EtOAc (200 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (250 mL). The aqueous layer was extracted with EtOAc (4 × 250 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by chromatography over silica gel eluting with 60:40 hexanes/Et_2O gave **13** (6.57 g, 87%).

6-((*Z*)-6-Formylhex-1,5-diyn-5,6-η^2-hexacarbonyldicobaltio-3-ene)-6-[(*tert*-butyldimethylsilyl)oxy]cyclohex-2-en-1-one 16. To a solution of **15** (16.8 g, 27.25 mmol) in anhydrous tetrahydrofuran (136 mL) at 0 °C under argon was added dropwise over 5 min *tert*-butoxymagnesium bromide (0.5 M in tetrahydrofuran, 65.4 mL, 32.7 mmol, 1.2 equiv), and the mixture stirred for a further 5 min. 1,1′-(Azodicarbonyl)dipiperidine (8.25 g, 32.7 mmol, 1.2 equiv) in anhydrous tetrahydrofuran (50 mL) was added over 5 min, and the mixture stirred at 0 °C until TLC (hexanes/EtOAc, 80:20) showed complete consumption of the starting material (*ca.* 30 min). The mixture was quenched with saturated aqueous NH_4Cl (250 mL), and the organic layer separated. The aqueous phase was extracted with Et_2O (2 × 250 mL), and the combined extracts were dried ($MgSO_4$). Concentration *in vacuo* left a dark red solid which was triturated with Et_2O and filtered through a 5 cm pad of florisil eluting with Et_2O. The filtrate was concentrated, and the residue purified by chromatography over silica gel eluting with 90:10 hexanes/Et_2O to afford **16** (13.6 g, 81%). IR (thin film) 2955, 2930, 2094, 2059, 2031, 1705, 1675 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 10.49 (1H, s), 6.17 (1H, m), 6.12 (1H, d, J = 10.7 Hz), 5.87 (1H, m), 5.44 (1H, d, J = 10.7 Hz), 2.21 (1H, m), 2.02 (3H, m), 1.01 (9H, s), 0.38 (3H, s), 0.32 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 192, 189, 150, 136, 127, 111, 101, 88, 85, 83, 74, 38, 26, 24, 19, −2.9, −3.0. HRMS calcd for $C_{25}H_{25}O_9SiCo_2$ (M^+ + 1) 614.9956. Found 614.9961.

13-Oxo-2β-thiophenyl-12β-hydroxy-5-[(*tert*-butyldimethylsilyl)-oxy]bicyclo[7.3.1]trideca-6,10-diyn-(10,11-η^2-hexacarbonyldicobaltio)-8-ene 17. Redistilled thiophenol (1.06 mL, 10.4 mmol) was added slowly to a solution of trimethyl aluminum (2 M in hexanes, 5.2 mL, 10.4 mmol) in anhydrous dichloromethane (21 mL) stirred at 0 °C under argon. The mixture was stirred at 0 °C for 20 min, after which time anhydrous tetrahydrofuran (845 μL, 10.4 mmol) was added. The mixture was cooled to −78 °C and stirred for 10 min. The aldehyde **16** (3.19 g, 5.2 mmol) in anhydrous dichloromethane (10 mL; stirred over 4Å molecular sieves for 24 h) was added dropwise over 5 min, and the mixture stirred for a further 10 min at −78 °C. Titanium tetraisopropoxide (12.36 mL, 41.5 mmol, 8 equiv) was added dropwise over 15 min. The mixture was stirred at −78 °C for 10 min, after which time the cold bath was replaced by an ice−water bath. The mixture was allowed to reach 10 °C over 2 h and was stirred for a further 45 min at 10 °C, after which time TLC showed almost all the starting material converted to product. The mixture was recooled to −78 °C, and precooled (−78 °C) silica gel (40 g) added slowly over 10 min *via* a solid addition funnel. The argon line was removed, and the mixture stirred for a further 45 min in air. The mixture was filtered through a plug of silica, and the plug washed with Et_2O. The filtrate was concentrated *in vacuo*, and the residue purified by chromatography over silica gel eluting with 95:5−80:20 hexanes/Et_2O to give a mixture of β-thiophenol adducts **18** (510 mg, 16%), starting material **16** (160 mg, 5%), and the cyclized material **17** (2.66 g, 71%). IR ($CHCl_3$) 3500, 2929, 2094, 2059, 2030, 1731 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.42 (2H, d, J = 7.3 Hz), 6.98 (3H, m), 6.34 (1H, d, J = 10 Hz), 5.22 (1H, d, J = 10 Hz), 5.17 (1H, m), 4.20 (1H, br. s), 3.11 (1H, d, J = 9.2 Hz), 2.47 (1H, m), 2.02 (2H, m), 1.62 (1H, m), 1.25 (1H, d, J =

(32) Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer or a Perkin-Elmer 1600 FT-IR spectrometer either neat or in $CHCl_3$ as indicated. ^1H NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer as solutions in deuterochloroform ($CDCl_3$) unless otherwise indicated and are reported in ppm downfield from TMS. ^{13}C NMR spectra were recorded on General Electric QE-300 (75 MHz) instrument as solutions in $CDCl_3$ unless otherwise indicated. Low resolution chemical ionization (CI) mass spectra were obtained on a TSQ 70 instrument, and the exact mass determinations were obtained on a VG analytical ZAB2-E instrument. Routine monitoring of reactions was performed using Merck 60 F254 silica gel, aluminum-backed TLC plates. Preparative layer chromatography (plc) was performed using Merck 60H F254 silica gel, glass supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F254 silica gel. Air and moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C, then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use: Et_2O and tetrahydrofuran were distilled from sodium benzophenone ketyl; dichloromethane and benzene were distilled from calcium hydride under argon.

7.4 Hz), 1.06 (9H, s), 0.39 (3H, s), 0.34 (3H, s). Anal. Calcd for $C_{31}H_{30}O_9SSiCo_2$: C, 51.38; H, 4.18. Found: C, 51.19; H, 4.26%.

13-Oxo-12β-hydroxy-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-6,10-diyn-(10,11-η^2-hexacarbonyldicobaltio)-1,8-diene 19. To a solution of **17** (849 mg, 1.2 mmol) in dichloromethane (50 mL) at −78 °C under argon was added *m*-chloroperoxybenzoic acid (242 mg, 1.4 mmol) in one portion, and the cooling bath removed. Stirring was continued at room temperature for 3 h. The mixture was poured into saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by chromatography over Florisil eluting with 80:20 hexanes/Et_2O to afford **19** (466 mg, 64%). IR ($CHCl_3$) 3500, 2929, 2094, 2059, 2030, 1731 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 6.27 (1H, d, J = 10.7 Hz), 5.50 (1H, br s), 5.23 (1H, d, J = 10.7 Hz), 4.91 (1H, d, J = 1.7 Hz), 4.87 (1H, d, J = 1.7 Hz), 1.78 (2H, m), 1.55 (2H, m), 0.94 (9H, s), 0.15 (3H, s), 0.13 (3H, s). ^{13}C NMR (75 MHz, CD_3OD) δ 200.0, 143.8, 133.4, 128.6, 110.5, 97.5, 93.4, 79.5, 70.1, 64, 38.4, 26.3, 23.7, −2.3, −2.6. LRMS (FAB) 613, 586, 530, 502, 473, 445, 305. See **20** for complete characterization.

13-Oxo-12β-hydroxy-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-6,10-diyn-1,8-diene 20. To a solution of **19** (468 mg, 0.76 mmol) in acetone (50 mL) at −10 °C was added cerium(IV) ammonium nitrate in small portions until the solution turned a light orange color. The mixture was diluted with Et_2O (150 mL), washed with saturated aqueous $NaHCO_3$ (200 mL), and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* and purification of the residue by chromatography over Florisil eluting with 75:25 hexanes/Et_2O gave **20** (190 mg, 76%). Mp 123−124 °C (Et_2O). IR ($CHCl_3$) 3457, 3024, 2959, 2856, 1698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.39 (1H, m), 5.87 (1H, d, J = 9.5 Hz), 5.84 (1H, d, J = 9.5 Hz), 5.24 (1H, d, J = 10.5 Hz), 2.53 (2H, m), 2.26 (1H, m), 2.14 (1H, m), 0.92 (9H, s), 0.22 (3H, s), 0.19 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197, 140, 137, 125, 123, 101, 96, 93, 88, 75, 69, 35, 26, 25, 18, −2.8, −3.1. Anal. Calcd for $C_{19}H_{24}O_3Si$: C, 69.48; H, 7.37. Found: C, 69.56; H, 7.40%.

13-Oxo-5,12β-bis[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]trideca-6,10-diyn-1,8-diene 21. To a solution of **20** (266 mg, 0.81 mmol) and diisopropylethylamine (700 μL, 4.02 mmol, 5 equiv) in anhydrous dichloromethane (8 mL) at 0 °C under argon was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (372 μL, 1.62 mmol, 2 equiv) by syringe over 5 min. The mixture was stirred for 10 min at 0 °C and at room temperature for a further 10 min to completion by TLC (hexanes/EtOAc, 80:20). The mixture was quenched with water (10 mL), and the aqueous phase extracted with dichloromethane (3 × 10 mL). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*, and the crude product was purified by chromatography over silica gel eluting with 95:5 hexanes/Et_2O to give **21** (333 mg, 93%). Mp 103−105 °C (Et_2O). IR ($CHCl_3$) 2955, 2929, 2856, 1722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (1H, m), 5.84 (1H, d, J = 9.8 Hz), 5.80 (1H, d, J = 9.8 Hz), 5.43 (1H, s), 2.46 (2H, m), 2.25 (1H, m), 2.11 (1H, m), 0.94 (9H, s), 0.91 (9H, s), 0.22 (3H, s), 0.18 (3H, s), 0.14 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 138.8, 137.4, 122.7, 101, 97.1, 90.9, 87.3, 74.9, 69.5, 34.6, 26, 25.9, 24.5, 18.4, −2.8, −3.2, −4.6, −4.7. Anal. Calcd for $C_{25}H_{38}O_3Si_2$: C, 67.84; H, 8.66. Found: C, 67.92; H, 8.71.

Bis-Selenide 22. A solution of **21** (600 mg, 1.35 mmol) in anhydrous dichloromethane (14 mL) was stirred at room temperature under argon in the dark (flask wrapped in foil). Freshly-prepared *N*-(phenylselenenyl)phthalimide (820 mg, 2.71 mmol, 2 equiv) was added in one portion, followed by DBU (4.05 mL, 27.1 mmol, 20 equiv). The mixture was stirred for 1.5 h at room temperature, after which time TLC (hexanes/EtOAc, 90:10) showed the complete consumption of starting material and formation of one new less polar product plus diphenyl diselenide. The mixture was concentrated *in vacuo* (water bath temperature *below* 30 °C), and the residue triturated with Et_2O and filtered through Florisil eluting with Et_2O. The filtrate was concentrated *in vacuo* (bath below 30 °C) to give the crude product, which was purified by chromatography over silica gel eluting with 95:5 hexanes/Et_2O to afford **22** (800 mg, 79%). ^1H NMR (300 MHz, C_6D_6) δ 7.57 (2H, m), 7.39 (2H, m), 7.03 (3H, m), 5.91 (1H, d, J = 2.9 Hz), 5.37 (1H, dd, J = 9.5, 1.5 Hz), 5.33 (1H, d, J = 9.5 Hz), 4.88 (1H, d, J = 1.5 Hz), 2.46 (1H, d, J = 16.4 Hz), 1.72 (1H, dd, J = 16.4, 2.9 Hz), 1.15 (9H, s), 0.97 (9H, s), 0.45 (3H, s), 0.31 (3H, s), 0.27 (3H, s), 0.25 (3H, s). Compound **22** was used immediately in the next step.

3,13-Dioxo-5,12β-bis[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]-trideca-6,10-diyn-1,8-diene 23. Pyridine (171 μL, 2.12 mmol, 2 equiv) was added to a solution of **22** (800 mg, 1.06 mmol) in dichloromethane (10 mL), and the mixture cooled to 0 °C. 30% Aqueous hydrogen peroxide solution (280 μL, 2.12 mmol, 2 equiv) was added, and the mixture stirred at 0 °C for 5 min and then at room temperature for 1 h. The mixture was quenched with water (10 mL), and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the crude product was purified by chromatography over silica gel eluting with Et_2O/hexanes (95:5−90:10) to give **23** (430 mg, 89%). IR (thin film) 2955, 2930, 2896, 2858, 1737, 1694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (1H, d, J = 1.75 Hz), 5.90 (1H, d, J = 9.5 Hz), 5.90 (1H, d, J = 9.5 Hz), 5.50 (1H, s), 3.23 (1H, dd, J = 17.4, 1.7 Hz), 2.93 (1H, d, J = 17.4 Hz), 0.95 (9H, s), 0.93 (9H, s), 0.23 (3H, s), 0.19 (3H, s), 0.16 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.5, 188.8, 151.8, 131.9, 123.8, 123.2, 99.1, 96.1, 90.9, 89.6, 75.9, 68, 51.2, 25.8, 25.7, 18.3, −3.0, −3.3, −4.7. HRMS calcd for $C_{25}H_{36}O_4Si_2$ (M^+) 456.2152. Found 456.2159.

3,13-Dioxo-5,12β-bis[(*tert*-butyldimethylsilyl)oxy]-1,2-iminobicyclo [7.3.1]trideca-6,10-diyn-8-ene 25. A solution of **23** (150 mg, 328 μmol) and diphenylsulfilimine monohydrate (216 mg, 984 μmol, 3 equiv) in 2,2,2-trifluoroethanol (33 mL) was heated to reflux under argon. After 1 h, TLC (hexanes/EtOAc, 80:20) showed the complete consumption of starting material and the formation of one new product plus diphenyl sulfide. The solvent was evaporated *in vacuo*, and the residue purified by flash column chromatography over silica gel eluting with Et_2O/hexanes (20:80) to give **25** (147 mg, 95%). Due to slow inversion of the imine and hydration of the C-13 carbonyl group it was difficult to obtain good spectral data. Consequently, **25** was converted into its $-NCO_2Me$ derivative by treatment with triphosgene/$NEtPr_2^i$ followed by methanol. IR ($CHCl_3$) 1735, 1715 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (1H, d, J = 10.1 Hz), 5.91 (1H, dd, J = 10.1, 1.2 Hz), 4.31 (1H, d, J = 1.2 Hz), 3.78 (3H, s), 3.20 (1H, d, J = 1.4 Hz), 3.02 (1H, d, J = 14.2 Hz), 2.77 (1H, dd, J = 14.2, 1.4 Hz), 0.95 (9H, s), 0.88 (9H, s), 0.15 (3H, s), 0.14 (3H, s), 0.12 (3H, s), 0.10 (3H, s). HRMS calcd for $C_{27}H_{39}NO_6Si_2$ (M^+) 529.2316. Found 529.2309.

3,13-Dioxo-5-[(*tert*-butyldimethylsilyl)oxy]-12β-hydroxybicyclo-[7.3.1]trideca-6,10-diyn-1,8-diene 26. To a solution of **23** (240 mg, 0.53 μmol) in tetrahydrofuran (4.9 mL) and water (1.8 mL) was added trifluoromethanesulfonic acid (610 μL), and the mixture stirred at 25 °C for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and diluted with Et_2O (5 mL). The dried ($MgSO_4$) extract was evaporated *in vacuo*, and the residue purified by chromatography over silica gel eluting with 20% Et_2O/hexanes to give **26** (157 mg, 87%). Mp 113−115 °C (Et_2O/hexanes). IR (thin film) 3509, 2957, 2929, 2858, 1712, 1692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (1H, d, J = 1 Hz), 5.90 (2H, s), 5.35 (1H, d, J = 11 Hz), 4.44 (1H, d, J = 11 Hz), 3.21 (1H, dd, J = 17.4, 1 Hz), 2.96 (1H, d, J = 17.4 Hz), 0.88 (9H, s), 0.19 (3H, s), 0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194, 193, 148, 132, 124, 123, 99, 95, 93, 89, 75, 68, 50, 26, 18, −3, −4. HRMS calcd for $C_{19}H_{22}O_4Si$ (M^+) 342.1287. Found 342.1288.

3,13-Dioxo-2-amino-5-[(*tert*-butyldimethylsilyl)oxy]-12β-hydroxybicyclo[7.3.1]trideca-6,10-diyn-1,8-diene 27. Freshly dehydrated diphenylsulfilimine (350 mg, 1.75 mmol, 2.0 equiv) was added to a solution of **26** (300 mg, 0.87 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) at room temperature. The mixture was stirred under argon for 12 h, diluted with hexanes (10 mL), filtered through a silica plug, and washed with Et_2O (10 mL). The crude amine was purified by chromatography over silica gel eluting with 40% Et_2O/hexanes to give **27** (204 mg, 65%). The amine slowly decomposes and is best stored in the freezer in petroleum ether. Mp 82−84 °C (Et_2O). IR (thin film) 3459, 3354, 2953, 2928, 2855, 1704, 1622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (2H, s), 5.74 (1H, d, J = 10.0 Hz), 5.37 (1H, d, J = 10.0 Hz), 4.93 (2H, bs), 3.22 (1H, ABq, J = 17.4 Hz), 2.98 1H, ABq, J = 17.4 Hz), 0.86 (9H, s), 0.19 (3H, s), 0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 190.2, 141.7, 124.8, 124.2, 123.3, 115.0, 99.7, 96.8, 91.3, 85.0, 74.6, 63.1, 48.9, 25.6, 18.3, 16.4, −3.0, −3.3. HRMS calcd for $C_{19}H_{24}NO_4Si$ ($M^+ + 1$) 358.1475. Found 358.1459.

3,13-Dioxo-2-amino-5-[(*tert*-butyldimethylsilyl)oxy]-12*β*-[(2-hydroxyethyl)oxy]bicyclo[7.3.1]trideca-6,10-diyn-1,8-diene 28. Camphor sulfonic acid (24 mg, 0.104 mmol, 2.5 equiv) was added in one portion to a dioxane (0.5 mL) solution of **27** (15 mg, 0.042 mmol, 1.0 equiv) containing ethylene glycol (0.5 mL). The mixture was stirred at room temperature for 90 min, quenched with triethylamine (2 drops), diluted with saturated aqueous NaCl, and extracted with EtOAc (5.0 mL). The extract was dried (Na_2SO_4) and evaporated *in vacuo*, and the residue purified by plc (70:30 $CHCl_3$/acetone) to give **28** (11 mg, 65%). Mp 205 °C (EtOAc/hexanes). IR (NaCl) 3436, 3349, 2928, 2860, 1693, 1620 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (1H, d, J = 9.5 Hz), 5.82 (1H, d, J = 9.7 Hz), 5.41 (1H, s), 5.01 (2H, bs), 3.87−3.62 (4H, m), 3.26 (1H, ABq, J = 17.6 Hz), 2.97 (1H, ABq, J = 17.6 Hz), 0.88 (9H, s), 0.22 (3H, s), 0.18 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 189.4, 143.7, 124.1, 123.5, 114.9, 97.4, 96.7, 89.9, 86.9, 75.5, 71.4, 71.3, 69.3, 61.9, 49.1, 25.8, 18.4, −3.4, −2.1. HRMS calcd for $C_{21}H_{28}NO_5Si$ (M^+ + 1) 402.1737. Found 402.1727.

3,13-Dioxo-2-amino-5-[(*tert*-butyldimethylsilyl)oxy]-12*β*-[(triethylsilyl)oxy]bicyclo[7.3.1]trideca-6,10-diyn-1,8-diene 29. A solution of **27** (105 mg, 0.294 mmol) in dichloromethane (2 mL) under argon at 0 °C was treated with triethylamine (70 μL), followed by triethylsilyl trifluoromethanesulfonate (100 μL). The mixture was stirred at 0 °C for 10 min and warmed to room temperature for a further 10 min. The mixture was diluted with Et_2O (5 mL) and washed with aqueous NH_4Cl (5 mL). After drying ($MgSO_4$) and evaporation *in vacuo*, the product was purified by plc, eluting with 30% Et_2O/hexanes to give **29** (125 mg, 90%). IR (film) 3371, 2954, 2880, 1695, 1614 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (1H, d, J = 9.5 Hz), 5.80 (1H, d, J = 9.5 Hz), 5.63 (1H, s), 4.67 (2H, s), 3.22 (1H, d, J = 17.2 Hz), 2.92 (1H, d, J = 17.2 Hz), 1.01−0.91 (9H, t, J = 7.9 Hz), 0.89 (9H, s), 0.68 (6H, q, J = 7.9 Hz), 0.23 (3H, s), 0.18 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 187.8, 141.1, 123.7, 123.5, 123.4, 118.4, 99.5, 97.7, 89.4, 85.6, 75.8, 62.5, 49.2, 26.1, 18.4, 6.9, 4.7. HRMS calcd for $C_{25}H_{37}NO_4Si_2$ (M^+) 471.2261. Found 471.2264.

13-Oxo-2-[bis(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)oxy]-5-[(*tert*-butyldimethylsilyl)oxy]-12*β*-[(triethylsilyl)oxy]bicyclo-[7.3.1]trideca-6,10-diyn-1,3,8-triene 30. A solution of **29** (292 mg, 0.62 mmol) in dichloromethane (1.78 mL) under argon was treated with triethylamine (180 μL), followed by Boc_2O (534 mg) and 4-(dimethylamino)pyridine (160 mg). After 5 min the mixture was loaded onto a column of silica gel and eluted with 15% Et_2O/hexanes to give **30** (453 mg, 95%) as a pale yellow foam. IR (film) 2955, 2879, 1798, 1768, 1729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (1H, s), 6.00 (1H, d, J = 7.1 Hz), 5.95 (1H, dd, J = 7.1, 1.3 Hz), 5.78 (1H, d, J = 1.3 Hz), 1.46 (9H, s), 1.45 (9H, s), 1.35 (9H, s), 0.96 (9H, t, J = 8 Hz), 0.92 (9H, s), 0.69 (6H, m), 0.20 (3H, s), 0.15 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 149.9, 149.0, 148.8, 141.0, 135.0, 134.1, 125.1, 124.3, 122.5, 100.4, 95.0, 91.1, 87.8, 84.1, 84.0, 75.5, 62.1, 27.6, 27.5, 25.9, 18.4, 6.8, 5.0, −3.1, -3.2. HRMS calcd for $C_{40}H_{62}NO_{10}Si_2$ (M^+ + 1) 772.3912. Found 772.3914.

13-Oxo-2-[bis(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)oxy]-5-[(*tert*-butyldimethylsilyl)oxy]-12*β*-hydroxybicyclo[7.3.1]-trideca-6,10-diyn-1,3,8-triene 31. To a solution of **30** (906 mg) in tetrahydrofuran (10.6 mL) under argon at room temperature was added aqueous trifluoromethanesulfonic acid [(1.37 mL) was added to water (3.87 mL)] with stirring. This solution was added dropwise by cannula to the substrate. The mixture was stirred for 10 min, diluted with Et_2O (50 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL). After drying ($MgSO_4$) and evaporation of solvents *in vacuo*, the product was purified by chromatography over silica gel eluting with 20% Et_2O/hexanes to yield **31** (730 mg, 95%). IR (film) 3499, 2932, 2858, 1798, 1768, 1730, 1694, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (1H, s), 6.02 (2H, s), 5.47 (1H, d, J = 11.2 Hz), 4.40 (1H, d, J = 11.2 Hz), 1.47 (9H, s), 1.46 (9H, s), 1.34 (9H, s), 0.93 (9H, s), 0.20 (3H, s), 0.17 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 197, 150.6, 148.4, 148.3, 142.3, 136.0, 132.8, 127.8, 126.0, 123.6, 101.2, 94.4, 92.7, 87.8, 84.2, 84.0, 83.4, 63.6, 27.5, 25.8, 18.6, −2.7, −3.0. HRMS calcd for $C_{34}H_{48}NO_{10}Si$ (M^+ + 1) 658.3047. Found 658.3057.

Lactone 32. To a solution of trimethylphosphonoacetate (450 μL) in tetrahydrofuran (5.1 mL) under argon at 0 °C was added dropwise 1 M lithium bis(trimethylsilyl)amide (2.74 mL), and the mixture stirred at 0 °C for 5 min. A solution of **31** (730 mg, 1.11 mmol) in tetrahydrofuran (17.6 mL) was added dropwise by cannula to the above solution at 0 °C. The mixture was stirred at 0 °C for 2 h and quenched with water (20 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography over silica gel to give **32** (665 mg, 88%). IR (film) 2980, 2931, 1798, 1768, 1732, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (1H, d, J = 9 Hz), 6.08 (1H, s), 6.02 (1H, d, J = 9 Hz), 6.01 (1H, s), 5.90 (1H, s), 1.47 (9H, s), 1.46 (9H, s), 1.31 (9H, s), 0.94 (9H, s), 0.28 (3H, s), 0.26 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 154.1, 150.1, 148.5, 142.8, 129.4, 124.8, 122.1, 120.1, 119.7, 114.3, 113.9, 97.5, 95.9, 94.9, 93.7, 90.1, 84.5, 84.0, 70.0, 67.5, 27.4, 25.8, 18.1, −3.0. HRMS calcd for $C_{36}H_{48}NO_{10}Si$ (M^+ + 1) 682.3047. Found 682.3037.

Allylic Alcohol 33. A solution of **32** (439 mg, 0.644 mmol) in MeOH (7.83 mL) and water (17 drops) at 0 °C under argon was treated with $NaBH_4$ (400 mg), the mixture stirred for 30 min, and further $NaBH_4$ (240 mg) added. The mixture was then stirred at 0 °C for 1.25 h, diluted with Et_2O (10 mL), and washed with saturated aqueous NH_4Cl (10 mL). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue taken up in MeOH (10 mL) and left for 15 min at room temperature. The solution was evaporated *in vacuo*, and the residue again taken up in MeOH (10 mL) and left for 10 min. After evaporation of the solution *in vacuo* the residue was purified by plc eluting with 60% Et_2O/hexanes to give **33** (356 mg, 81%). IR (film) 3414, 2932, 1786, 1764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (1H, dd, J = 5.2, 5.3 Hz), 6.05 (1H, d, J = 9.5 Hz), 5.94 (1H, dd, J = 9.5, 1.4 Hz), 5.77 (1H, s), 5.73 (1H, d, J = 1.4 Hz), 4.35 (1H, dd, J = 5.3, 13.2 Hz), 4.22 (1H, dd, J = 5.2, 13.2 Hz), 1.49 (9H, s), 1.44 (9H, s), 1.35 (9H, s), 0.93 (9H, s), 0.27 (3H, s), 0.21 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 150.2, 149.4, 143.2, 138.4, 136.9, 134.4, 128.0, 126.4, 125.2, 124.8, 124.5, 122.6, 120.5, 100.2, 99.5, 88.9, 87.2, 83.9, 83.5, 83.0, 71.4, 62.9, 60.3, 27.9, 27.6, 25.8, 18.4, −2.9. HRMS calcd for $C_{36}H_{51}NO_{10}Si$ (M^+) 685.3282. Found 685.3272.

2,4-Dinitrosulfenate Ester 34. To a solution of **33** (381 mg, 0.556 mmol) and 2,4-dinitrophenylsulfenyl chloride (157 mg) in dichloromethane (10.16 mL) under argon at 0 °C was added pyridine (15 drops), and the mixture stirred for 5 min, after which it was diluted with dichloromethane (10 mL). After washing with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $CuSO_4$ (10 mL), the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the residue by plc eluting with 45% Et_2O/hexanes gave **34** (359 mg, 73%). IR (film) 3448, 2933, 1787, 1760, 1593, 1521 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (1H, d, J = 2.3 Hz), 8.51 (1H, dd, J = 2.3, 9.1 Hz), 7.95 (1H, d, J = 9.1 Hz), 6.58 (1H, dd, J = 5.5, 8 Hz), 6.07 (1H, d, J = 9.5 Hz), 5.96 (1H, dd, J = 9.5, 1.6 Hz), 5.73 (1H, s), 5.70 (1H, dd, J = 1.6, 6.3 Hz), 4.72 (2H, m), 2.28 (1H, d, J = 6.3 Hz), 1.48 (9H, s), 1.41 (9H, s), 1.35 (9H, s), 0.86 (9H, s), 0.24 (3H, s), 0.18 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 149.3, 144.5, 143.5, 139.1, 132.6, 128.3, 127.1, 125.6, 124.6, 124.3, 122.5, 120.8, 120.7, 99.7, 89.0, 88.2, 83.9, 83.7, 74.7, 71.3, 65.8, 62.6, 27.8, 27.6, 25.6, 18.2, 15.2, −3.0. HRMS calcd for $C_{42}H_{54}N_3O_{14}SiS$ (M^+ + 1) 884.3096. Found 884.3108.

12*β*-Carbonate Derivative 35. A solution of **34** (264 mg, 0.3 mmol) in dichloromethane (6.4 mL) under argon at 0 °C was treated with methyl chloroformate (500 μL), followed by pyridine (500 μL), and the mixture stirred at 0 °C for 45 min. After dilution with dichloromethane (10 mL), the solution was washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $CuSO_4$ (10 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Purification by plc eluting with 40% Et_2O/hexanes gave **35** (208 mg, 74%). IR (film) 2981, 2933, 2858, 1798, 1767, 1594, 1520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (1H, d, J = 2.6 Hz), 8.52 (1H, dd, J = 2.3, 9.0 Hz), 7.89 (1H, d, J = 9.0 Hz), 6.57 (1H, dd, J = 3.9, 9.0 Hz), 6.39 (1H, d, J = 1.3 Hz), 6.11 (1H, d, J = 9.5 Hz), 5.96 (1H, dd, J = 9.5, 1.3 Hz), 5.78 (1H, s), 4.77 (1H, dd, J = 3.9, 12.9 Hz), 4.57 (1H, dd, J = 9.0, 12.9 Hz), 3.79 (3H, s), 1.49 (9H, s), 1.36 (9H, s), 1.33 (9H, s), 0.89 (9H, s), 0.26 (3H, s), 0.20 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 154.0, 150.4, 149.3, 148.9, 144.5, 143.2, 139.2, 137.6, 128.9, 128.4, 128.1, 126.4, 125.7, 124.4, 124.3, 123.4, 120.8, 120.7, 99.1, 95.9, 89.3, 88.9, 84.1, 83.9, 83.8, 74.8, 71.1, 67.2, 65.8, 55.4, 27.9, 27.6, 25.7, 18.3, 15.3, −2.9. HRMS calcd for $C_{44}H_{55}N_3O_{16}SiS$ (M^+) 941.3072. Found 941.3042.

14-Alcohol 36. To a solution of **35** (283 mg, 0.3 mmol) in tetrahydrofuran (2 mL) under argon at room temperature was added

thiophenol (100 μL) followed by pyridine (100 μL). After stirring at room temperature for 45 min, the mixture was diluted with Et_2O (10 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $CuSO_4$ (5 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give a residue which was purified by plc eluting with 60% Et_2O/hexanes to give **36** (195 mg, 87%). IR (film) 3544, 2988, 2933, 2858, 1796, 1762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (1H, dd, J = 7.2, 8.0 Hz), 6.48 (1H, d, J = 1.7 Hz), 6.12 (1H, d, J = 9.5 Hz), 5.95 (1H, dd, J = 9.5, 1.7 Hz), 5.78 (1H, s), 4.35−4.22 (1H, m), 4.12−3.98 (1H, m), 2.0 (1H, t, J = 5 Hz), 1.45 (9H, s), 1.43 (9H, s), 1.35 (9H, s), 0.94 (9H, s), 0.28 (3H, s), 0.23 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 150.2, 149.3, 149.2, 143.1, 134.7, 130.7, 128.9, 128.4, 126.7, 124.0, 123.2, 114.4, 99.8, 96.0, 88.9, 88.8, 83.8, 71.1, 67.3, 60.3, 55.6, 27.9, 27.6, 25.8, 18.4, −2.9. HRMS calcd for $C_{38}H_{53}NO_{12}Si$ (M^+) 743.3337. Found 743.3340.

14-Mesylate 37. A solution of **36** (153 mg, 0.205 mmol) in dichloromethane (2.52 mL) under argon at 0 °C was treated with methanesulfonic anhydride (115 mg) and triethylamine (140 μL), and the mixture stirred at 0 °C for 1 h. Purification by plc gave **37** (139 mg, 83%). IR (film) 2957, 2939, 1798, 1760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (1H, d, J = 1.4 Hz), 6.41 (1H, dd, J = 3.1, 8.2 Hz), 6.10 (1H, d, J = 9.5 Hz), 5.96 (1H, dd, J = 9.5, 1.4 Hz), 5.81 (1H, s), 5.08 (1H, dd, J = 3.1, 14 Hz), 4.87 (1H, dd, J = 8.2, 14 Hz), 3.84 (3H, s), 2.96 (3H, s), 1.46 (9H, s), 1.44 (9H, s), 1.36 (9H, s), 0.95 (9H, s), 0.28 (3H, s), 0.23 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 150.1, 149.1, 149.0, 143.0, 137.3, 129.1, 128.0, 126.4, 124.7, 124.3, 122.8, 99.2, 95.8, 89.5, 89.1, 84.1, 83.9, 71.2, 68.7, 67.2, 55.5, 37.7, 27.8, 27.6, 25.8, 18.3, 3.0, −2.9. HRMS calcd for $C_{39}H_{56}NO_{14}SiS$ (M^+ + 1) 822.3191. Found 822.3201.

14-Thioacetate 38. To a solution of **37** (139 mg, 0.17 mmol) in acetone (1.24 mL) under argon at 0 °C was added a suspension of potassium thioacetate (40 mg) in acetone (2.18 mL) in one portion by pipet. The mixture was warmed to room temperature, stirred for 2.5 h, diluted with Et_2O (5 mL), washed with water (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and dried ($MgSO_4$). Evaporation *in vacuo*, followed by purification of the residue by plc eluting with 60% Et_2O/hexanes, gave **38** (110 mg, 81%). Mp 170−171 °C (from Et_2O/hexanes, dec). IR (film) 2980, 2956, 2931, 1797, 1760, 1694 cm^{-1}. ^1H (300 MHz, $CDCl_3$) δ 6.53 (1H, d, J = 1.3 Hz), 6.26 (1H, dd, J = 7.2, 8.9 Hz), 6.06 (1H, d, J = 9.3 Hz), 5.93 (1H, dd, J = 9.3, 1.3 Hz), 5.77 (1H, s), 3.82 (3H, s), 3.73 (2H, dd, J = 9.2, 8.9 Hz), 2.28 (3H, s), 1.43 (9H, s), 1.42 (9H, s), 1.35 (9H, s), 0.91 (9H, s), 0.25 (3H, s), 0.18 (3H, s). ^{13}C (75 MHz, $CDCl_3$) δ 195.3, 172.3, 154.3, 150.1, 149.1, 142.7, 134.7, 129.2, 128.9, 127.2, 126.2, 124.2, 122.9, 99.9, 96.2, 89.1, 88.8, 83.7, 83.6, 71.4, 67.6, 55.3, 30.3, 29.1, 27.8, 27.6, 25.7, 18.4, −2.9. HRMS calcd for $C_{40}H_{55}NO_{12}SiS$ (M+) 801.3214. Found 801.3198.

Protected Trisulfide 39. To a solution of **38** (10.3 mg, 0.013 mmol) in tetrahydrofuran (370 μL) under argon at −78 °C was added DIBAL-H (200 μL of a 1 M solution in dichloromethane), and the mixture stirred at −78 °C for 1.3 h. The reaction was quenched by addition of MeOH (4 drops) and diluted with EtOAc (1 mL). The mixture was washed with Rochelle's salt (2 mL), and the organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in dichloromethane (1 mL), and Harpp's reagent (5 mg) added. After 30 min the mixture was concentrated *in vacuo*, and the residue purified by plc eluting first with 60% Et_2O/hexanes, reloaded, and eluted with Et_2O/dichloromethane/hexanes (10:20:70) to give **39** (5.7 mg, 52%, 90% based on 5.3 mg recovered starting material). IR (film) 2931, 1796, 1761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (1H, dd, J = 6.4, 8.9 Hz), 6.53 (1H, d, J = 1.3 Hz), 6.08 (1H, d, J = 9.4 Hz), 5.94 (1H, dd, J = 9.4, 1.3 Hz), 5.79 (1H, s), 3.87 (1H, dd, J = 6.4, 14.7 Hz), 3.82 (3H, s), 3.69 (1H, dd, J = 8.9, 14.7 Hz), 2.52 (3H, s), 1.44 (9H, s), 1.43 (9H, s), 1.36 (9H, s), 0.96 (9H, s), 0.28 (3H, s), 0.23 (3H, s). HRMS calcd for $C_{39}H_{55}NO_{11}SiS_3$ (M^+ + 1) 838.2785. Found 838.2774.

3-Oxotrisulfide 41 and 12,14-Cyclic Sulfide 42. To a solution of **39** (3 mg, 3.5 μmol) in dichloromethane (150 μL) under argon at room temperature was added triethylamine (1 drop), followed by triethylsilyl trifluoromethanesulfonate (2 drops). After 15 min the mixture was diluted with Et_2O (1.0 mL) and washed with water (1.0 mL). After drying ($MgSO_4$) and concentration the products were purified by plc, eluting with 50% Et_2O/hexanes to give **42** (1 mg, 49%) and the trisulfide **41** (1 mg, 39%). IR (film) 2959, 2929, 2855, 1799, 1764, 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, dd, J = 5.0, 9.0 Hz), 6.43 (1H, d, J = 1.3 Hz), 6.00 (1H, d, J = 9.4 Hz), 5.81 (1H, dd, J = 9.4, 1.3 Hz), 3.84 (3H, s), 3.79 (1H, dd, J = 5.0, 12.8 Hz), 3.60 (1H, dd, J = 9.0, 12.8 Hz), 3.16 (1H, d, J = 18 Hz), 2.70 (1H, d, J = 18 Hz), 2.51 (3H, s), 1.46 (9H, s), 1.40 (9H, s), 0.96 (9H, s), 0.28 (3H, s), 0.26 (3H, s). HRMS calcd for $C_{34}H_{47}NO_9SiS_3$ (M^+) 737.2182. Found 737.2176.

11,14-Cyclic Sulfide 44. To a solution of **38** (2.5 mg, 3.12 μmol) in MeOH (100 μL) at 0 °C under argon was added solid $NaBH_4$. The mixture was stirred for 2.5 h, quenched with acetone (1 mL), and purified by plc, eluting with 60% Et_2O/hexanes to give **44** (1 mg, 42%). IR (film) 2932, 1795, 1760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (1H, dd, J = 3.2, 10.7 Hz), 6.29−6.20 (2H, m), 6.04 (1H, s), 5.90 (1H, s), 5.59 (1H, dd, J = 2.1, 10.7 Hz), 3.78 (3H, s), 3.76 (1H, dd, J = 9.2, 12.2 Hz), 2.78 (1H, dd, J = 9.2, 12.2 Hz), 1.50 (9H, s), 1.44 (9H, s), 1.43 (9H, s), 0.93 (9H, s), 0.20 (6H, s). HRMS calcd for $C_{38}H_{54}NO_{11}SiS$ (M^+ + 1) 760.3187. Found 760.3193.

3-Oxo-12,14-cyclic Sulfide 42. A solution of **39** (2 mg, 2.4 μmol) in dichloromethane (135 μL) and dioxane (15 μL) under argon at room temperature was treated with methane sulfonic acid (2 drops). After 30 min, the mixture was diluted with Et_2O (0.5 mL) and washed with aqueous $NaHCO_3$ (1 mL). After drying ($MgSO_4$) and evaporation *in vacuo*, the product was purified by plc eluting with 20% Et_2O/hexanes to give **42** (1 mg, 86%). IR (film) 2919, 2850, 1727, 1673 1615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (1H, t, J = 4.3 Hz), 5.73 (2H, m), 4.58 (1H, s), 3.90 (1H, bs), 3.66 (1H, dd, J = 4.3, 18 Hz), 3.35 (1H, dd, J = 4.3, 18 Hz), 2.92 (2H, ABq, J = 16.3 Hz), 1.23 (9H, s), 0.94 (9H, s), 0.23 (6H, s). HRMS calcd for $C_{26}H_{33}NO_4SiS$ (M^+) 483.1900. Found 483.1900.

2-Amino-3-keto-12,14-cyclic Sulfide 43. A solution of **39** (9 mg, 0.011 mmol) in dichloromethane (200 μL) under argon was treated with 2,6-lutidine (1 drop) followed by triethylsilyl trifluoromethanesulfonate (2 drops). After 20 min at room temperature, further triethylsilyl trifluoromethanesulfonate (2 drops) was added. The mixture was stirred for another 20 min, extracted into Et_2O (2 mL), and washed with water (2 mL). After drying ($MgSO_4$) and evaporation *in vacuo*, the residue was purified by plc, eluting with 40% Et_2O/hexanes, to give **43** (3.1 mg, 76%). IR (film) 3371, 2929, 2856, 1732, 1667, 1615 cm^{-1}. ^1H (300 MHz, $CDCl_3$) δ 6.17 (1H, t, J = 4.4 Hz), 5.72 (2H, s), 4.58 (1H, s), 3.91 (2H, bs), 3.65 (1H, dd, J = 4.4, 18.3 Hz), 3.35 (1H, dd, J = 4.4, 18.3 Hz), 2.92 (2H, ABq, J = 16.4 Hz), 0.92 (9H, s), 0.22 (6H, s). HRMS calcd for $C_{21}H_{25}NO_2SiS$ (M^+ + 1) 384.1454. Found 384.1453.

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Supporting Information Available: Complete experimental details and spectral information for compounds **6** and **9** and X-ray crystallographic data for **28** and **38** (42 pages). See any current masthead page for ordering and Internet access instructions.

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