Cobalt-Assisted Claisen Rearrangement of Enediyne Lactones at Ambient Temperature. Studies toward a Synthetic Application of the Myers Cycloaromatization†

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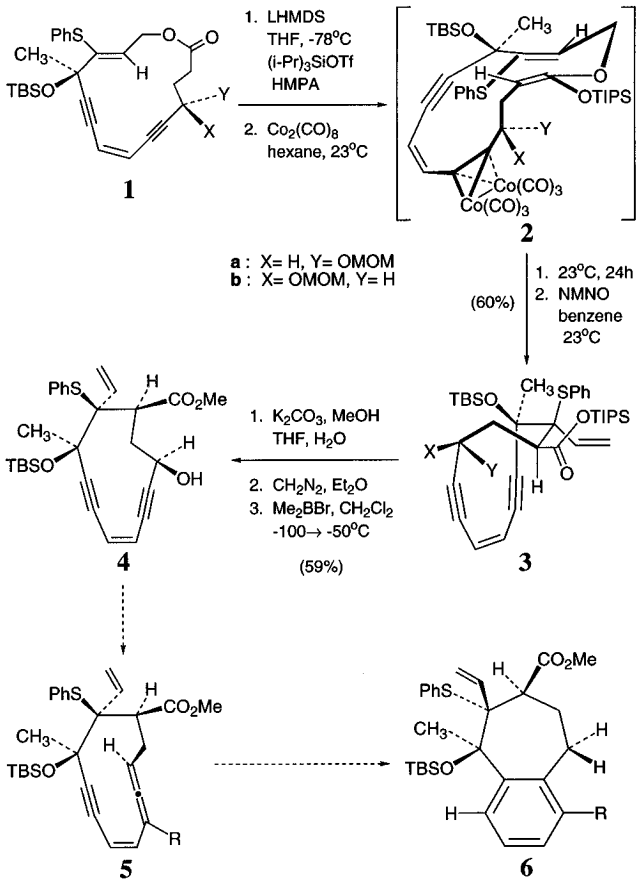
Introduction

The discovery of enediyne antibiotics neocarzinostatin, calicheamicin, esperamicin, and dynemicin triggered a plethora of mechanistic studies on their fascinating biological action.[1] These investigations indicated the importance of the enediyne [(*Z*)-1,5-diyn-3-ene] to 1,4-diyl transformation (Bergman cycloaromatization)[2] giving rise to the DNA-cleaving properties and cytotoxicity of the natural products. They also led to the discovery of a more facile process, namely the rearrangement of the parent enyne allene [(*Z*)-1,2,4-heptatrien-6-yne] to α,3-didehydrotoluene (Myers cycloaromatization).[3] We have recently reported the first stereoselective synthetic application involving the Bergman reaction, in the form of a tandem Claisen−Bergman rearrangement strategy for stereocontrolled tetrahydronaphthalene synthesis from nonaromatic precursors.[4] In a similar fashion, we envisioned that propargylic rearrangement of enediyne alcohol **4** would give rise to enyne allene **5** which could in turn undergo Myers cycloaromatization to deliver seven-membered benzannulated ring system **6** stereoselectively (Scheme 1). In this note, we report the stereochemical results of a novel cobalt-assisted Ireland−Claisen rearrangement of complexed silyl ketene acetals **2** to provide the desired 11-membered enediyne alcohol **4**. As indicated, the strategic placement of the secondary hydroxyl group adjacent to the enediyne moiety of **4** would serve in the formation of the enyne allene functionality.

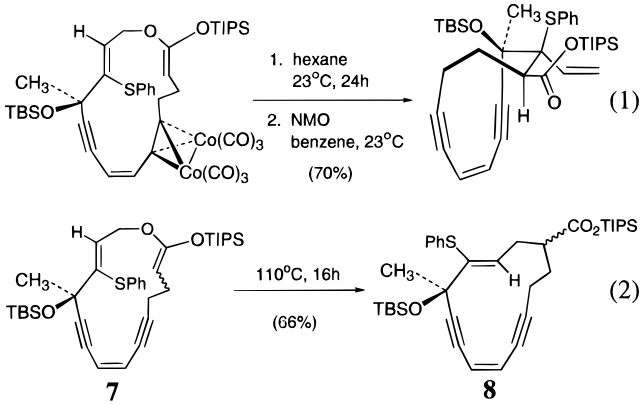
Results and Discussion

Since our tandem Claisen−Bergman strategy did not allow for the isolation of 10-membered enediyne intermediates, cobalt-complexation of the less hindered triple bond represented an attractive solution for the separation

Scheme 1



of the two processes.[5] Unfortunately our attempts to induce the Ireland−Claisen rearrangement to the cobalt-complexed 14-membered (*E*)- or (*Z*)-ketene acetals were unsuccessful. However, a prior model study with the 15-membered analog revealed a cobalt-assisted Ireland−Claisen rearrangement that proceeds in high yields at ambient temperature (eq 1). It is noted that thermolysis of (*E*)- or (*Z*)-ketene acetals **7** at 110 °C for 16 h produced 13-membered enediyne **8** (2:1 diastereomeric ratio) via a [1,3] sigmatropic rearrangement (eq 2).[4] It is this unprecedented conformational control of [3,3] vs [1,3] sigmatropic reactivity that we exploit for the synthesis of the target enediyne **4**.



The requisite diastereoisomeric lactones **1** (Scheme 1) were prepared from the corresponding hydroxy acids in

† Dedicated to Professor E. J. Corey with respect, affection, and happy birthday wishes.

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(1) For reviews describing mechanistic, synthetic, and DNA-cleaving studies of neocarzinostatin, calicheamicin, esperamicin, and dynemicin, see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235. (c) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191. (d) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; VCH Publishers, Inc.: New York, 1995; pp 203−283.

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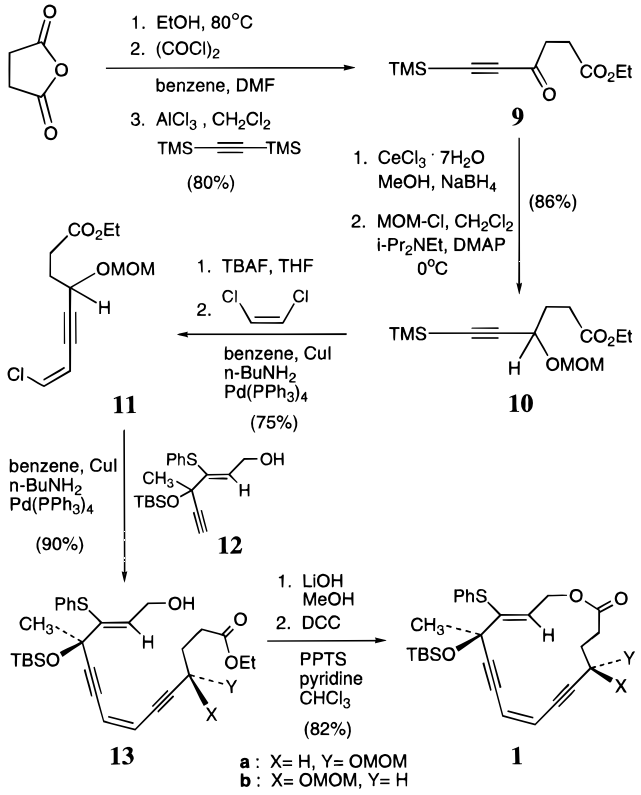
(5) The thiophenyl substituent was selected to serve as a handle in a projected [2,3] allyl sulfoxide−sulfenate rearrangement for the installation of a calicheamicin-type exocyclic double bond.

S0022-3263(95)02050-0 CCC: $12.00

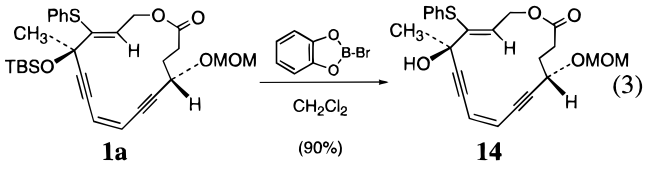
Scheme 2



82% yield, using the reagent combination DCC (4 equiv), pyridine (6 equiv), and PPTS (4 equiv).[6,7] In turn, the hydroxy acids were derived by hydrolysis of the enediyne ethyl esters **13**, obtained by coupling of the known enynol **12**[4,8] and chloroenyne ester **11** (Scheme 2). Specifically, heating succinic anhydride and ethanol (2 equiv) at reflux temperature, treating the concentrated reaction mixture with oxalyl chloride in the presence of a catalytic amount of DMF, and acylating bis(trimethylsilyl)acetylene with the resulting acid chloride[9a] furnished keto ester **9** in 80% overall yield after chromatographic purification.[7,9] Luche reduction[10] of ketone **9**, followed by protection of the secondary hydroxyl group,[11] provided MOM ether **10** (86% yield for two steps) which was desilylated and coupled with *cis*-1,2-dichloroethylene to produce chloroenyne ester **11** in 75% isolated yield from **10**.[7,12] After separation of the two diastereoisomeric lactones **1a** and **1b** by preparative HPLC,[13] **1a** was isolated in crystalline form suitable for X-ray analysis. Thus, the relative stereochemical identity of **1b** was also unequivocally established.

We had previously shown that the combination of lithium bis(trimethylsilyl)amide (LHMDS), triisopropylsilyl triflate (TIPS-OTf), and HMPA is an effective protocol for forming and handling (*Z*)-lactonic ketene acetals.[4,14] In addition, we have found that lowering the reaction temperature to −100 °C provides an exclusive control over the (*Z*)-geometrical outcome. Thus, both isomeric lactones **1a** and **1b** (Scheme 1) were subjected to the above reaction conditions, forming the corresponding (*Z*)-silyl ketene acetals. The (*Z*)-geometry was verified based on their NMR NOE-difference spectra which clearly indicated a correlation between the vinyl hydrogens of the trisubstituted double bonds.[13] Bending the linear geometry induced by complexation of the less hindered alkyne with $Co_2(CO)_8$, as shown in **2** (Scheme 1),[15] reduced dramatically the strain of the chairlike transition state for the Ireland−Claisen rearrangement[16] and allowed the completion of the reaction at ambient temperature (24 h). Subsequent oxidative decomplexation with NMO (benzene, 23 °C, 3 h) provided 11-membered enediynes **3a** and **3b** in 50−60% isolated yield from **1a** and **1b**, respectively.[7]

Since the TIPS ester functionality in **3a** and **3b** proved to be very sensitive to the reaction conditions used for the selective removal of the MOM ether (Me_2BBr, CH_2Cl_2, −100 → −50 °C),[17] its transformation to the corresponding methyl ester was performed by a hydrolysis−esterification sequence. Accordingly, the methyl ester resulting from **3b** was treated with dimethylbromoborane to produce crystals of enediyne alcohol **4** in 59% overall yield.[7] The selectivity of this deprotection could not be realized for epimer **3a** due to the increased lability of its TBDMS ether moiety under these conditions. To further illustrate this complication, treatment of **1a** with the more selective reagent catechol bromoborane led to only tertiary hydroxy lactone **14** in 90% isolated yield (eq 3).[7,18] Therefore, a different alcohol protection strategy utilizing the THP group is currently under consideration.



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(7) Satisfactory NMR (^1H and ^{13}C) and IR data were obtained for all new compounds described herein. For details see the Experimental Section and supporting information.

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(13) For specific data see the supporting information.

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(15) For precedent on selective complexation of enediynes, see: Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544 and earlier work.

(16) For an excellent recent review of the Claisen rearrangement, see: Frauenrath, H. In *Houben-Weyl, Methods of Organic Chemistry*; 4th ed.; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; G. Theime: Stuttgart, 1995; Vol. E 21d, pp 3301−3547. For key papers on the lactonic variation of the Ireland−Claisen process, see: (a) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (b) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. (c) Cameron, A. G.; Knight, D. W. *Tetrahedron Lett.* **1982**, *23*, 5455. (d) Brunner, R. K.; Borschberg, H.-J. *Helv. Chim. Acta* **1983**, *66*, 2608. (e) Reference 4. (f) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229.

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Conclusion

In summary, X-ray crystallographic analyses of enediyne compounds **1a** and **4**,[19] which are stereochemically related to the (*Z*)-ketene acetal starting material **2** and the product $Co_2(CO)_6$-complexed **3** of the Ireland−Claisen rearrangement, suggest that such a stereospecific process must proceed through a single chairlike transition state structure with respect to the local conformation of the six participating atoms as approximated in **2** (Scheme 1). It can thus be inferred that the previously believed as prohibitive pseudo-1,3-diaxial interaction between PhS and OTIPS substituents does not raise the energy of the preferred chairlike transition state significantly.[4] Apparently, the other three possible transition state structures (two boatlike and one chairlike) are energetically inaccessible due to transannular interactions and the antiperiplanar effect requiring that the allylic C−O bond be nearly perpendicular to the vinyl sulfide plane and *anti* to the incipient C−C bond, respectively.[4,20] The successful construction of enediyne **4** renders the stereoselective synthesis of benzannulated derivative **6** via enyne allene **5** possible.

Experimental Section

^{1}H (270 MHz) and ^{13}C (67.9 MHz) NMR spectra were recorded on a 270 NMR spectrometer with $CDCl_3$ as solvent and $CHCl_3$ (^{1}H δ 7.26), $CDCl_3$ (^{13}C δ 77.02) as internal standard. ^{1}H NMR multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The coupling constant is designated as *J* and is given in Hz. NOEDIF spectra were recorded on a 300 MHz NMR spectrometer. IR spectra were recorded on a FT-IR spectrometer using sodium chloride plates and reporting in wavenumbers (cm^{-1}). Melting points were taken on a MEL-TEMP apparatus and are uncorrected. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates using UV-light detection and either 7% ethanolic phosphomolybdic acid−heat or 5% *p*-anisaldehyde and 5% sulfuric acid−heat as the developing reagent. Preparative thin-layer chromatography (prep TLC) was performed on 0.25 mm (or 0.5 mm) x 20 cm x 20 cm glass supported silica-gel plates. E. M. Science silica gel 60 (230−400 mesh ASTM) was used for flash column chromatography. Tetrahydrofuran (THF), benzene, diethyl ether, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride, hexane and diisopropylamine were distilled from calcium hydride under argon prior to use. Triisopropylsilyl trifluoromethansulfonate (TIPS-OTf), palladium tetrakis(triphenylphosphine) ($Pd(PPh_3)_4$), copper iodide (CuI), and 1,3-dicyclohexylcarbodiimide (DCC) were purchased from Aldrich Chemical Co. and used directly. *n*-Butyllithium (*n*-BuLi), and lithium bis(trimethylsilyl)amide (LHMDS) were obtained from Aldrich Chemical Co. and used as received after their concentrations were determined by titration.

Ethyl 6-(Trimethylsilyl)-4-oxohex-5-ynoate (9). A suspension of succinic anhydride (5.0 g, 0.05 mol) in ethanol (2 equiv, 0.1 mol, 4.60 g, 5.86 mL) was heated with stirring at reflux temperature. The succinic anhydride dissolved after 5 min, and the light-yellow solution was further stirred at that temperature for 2 h. The reaction mixture was cooled, and ethanol was evaporated under reduced pressure to provide the desired monoethyl ester, which was used in the next step without further purification. To a solution of this acid (0.05 mol, 7.32 g) in benzene (30 mL) was added one drop of DMF followed by oxalyl chloride (1.06 equiv, 0.053 mol, 6.73 g, 4.62 mL), and the reaction mixture was allowed to stir for 2.5 h at ambient temperature. The end of the reaction was established by IR monitoring, and the solvent was evaporated under reduced pressure, providing 7.4 g (90% crude yield) of the desired acid chloride, which was sufficiently pure to be used in the acylation step. To this end, the acid chloride (7.0 g, 0.043 mol) and bis(trimethylsilyl)-acetylene (1.1 equiv, 0.047 mol, 7.9 g) were dissolved in methylene chloride (70 mL). In another flask, equipped with a magnetic stirring bar and a nitrogen inlet (through septum cap), were added aluminum trichloride (1.2 equiv, 0.05 mol, 6.79 g) and methylene chloride (150 mL), and the suspension was cooled at 0 °C. The solution of acid chloride and bis(trimethylsilyl)-acetylene was slowly cannulated into the aluminum trichloride suspension, and stirring was continued at 0 °C for 15 min. After that time the ice bath was removed and the reaction mixture was allowed to stir for 3 h at ambient temperature. The resulting yellow solution was cooled at 0 °C, treated with HCl (250 mL, 2.5 M), and stirred at that temperature for 15 min. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic phase was treated with saturated aqueous ammonium chloride, washed with brine, and dried over anhydrous magnesium sulfate. Purification by flash chromatography provided the desired keto ester **9** in 93% yield (8.95 g): R_f (50% diethyl ether/50% hexane) 0.52; IR (neat) 2150.0, 2093.5, 1736.8, 1681.5; ^{1}H NMR ($CDCl_3$) δ 4.04 (q, J = 7.15, 2H), 2.80 (t, J = 6.78, 2H), 2.53 (t, J = 6.78, 2H), 1.16 (t, J = 7.15, 3H) 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 185.23, 171.92, 101.37, 98.43, 60.68, 39.73, 27.79, 14.05, −0.91.

Ethyl 6-(Trimethylsilyl)-4-[(methoxymethyl)oxy]hex-5-ynoate (10). To a suspension of cerium chloride heptahydrate (1.3 equiv, 0.026 mol, 9.67 g) in methanol (250 mL) was added ketone **9** (4.5 g, 0.02 mol), and the mixture was stirred for 15 min at ambient temperature. Sodium borohydride (3 equiv, 0.06 mol, 2.271 g) was added slowly while stirring was continued, and an exothermic reaction was observed. The reaction mixture was allowed to stir for 20 min after the end of the addition. Quenching with saturated aqueous ammonium chloride solution and further acidification with cold HCl (0.5 M) to pH 1.0 was followed by extraction with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure and purification of the resulting yellow residue by flash chromatography (30% diethyl ether/70% hexane) provided the desired alcohol in 92% yield (4.2 g): R_f (50% diethyl ether/50% hexane) 0.3. A solution of the alcohol (3.56 g, 0.016 mol) in methylene chloride (0.3 M, 50 mL), containing diisopropylethylamine (1.6 equiv, 0.026 mol, 3.31 g, 4.46 mL) and a catalytic amount of 4-(dimethyamino)pyridine (0.15 equiv, 0.0024 mol, 0.3 g), was treated at 0 °C with methoxymethyl chloride (2.1 equiv, 0.034 mol, 2.705 g, 2.55 mL), and the reaction mixture was stirred at ambient temperature for 12 h. After establishing the end of the reaction by TLC, ice cold HCl (60 mL, 1.0 M) was added and the two-phase solution was stirred for 20 min. The organic layer was separated, extracted with methylene chloride, washed with brine, and dried over anhydrous magnesium sulfate. Purification by flash chromatography provided 4.0 g (92% yield) of the desired MOM ether **10**: R_f (50% diethyl ether/50% hexane) 0.55; ^{1}H NMR ($CDCl_3$) δ 4.83 (d, J = 6.78, 1H), 4.47 (d, J = 6.78, 1H), 4.28 (t, J = 6.23, 1H), 4.04 (q, J = 7.14, 2H), 3.27 (s, 3H), 2.40 (t, J = 7.33, 2H), 1.96 (q, J = 7.33, 2H), 1.16 (t, J = 7.14, 3H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.43, 103.09, 93.59, 90.27, 64.43, 60.07, 55.25, 30.30, 29.54, 13.86, −0.52; HRMS calcd for $C_{13}H_{24}O_4Si$ 272.1444, found 272.1440.

(7*Z*)-Ethyl 8-Chloro-4-[(methoxymethyl)oxy]octen-5-ynoate (11). A solution of trimethylsilyl alkyne **10** (4.0 g, 0.015 mol) in THF (60 mL, 0.25 M) was cooled at 0 °C and treated with tetrabutylammonium fluoride (1.5 equiv, 0.022 mol, 21.9 mL). After 15 min, the reaction mixture was poured into water and extracted with diethyl ether. The combined organic phase was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by filtration through a silica gel pad to furnish the desired free alkyne (2.85 g, 95%) as a dark brown oil: R_f (70% diethyl ether/30% hexane) 0.22. To a flame-dried, pear-shaped flask were added the free alkyne (2.6 g, 0.013 mol) and freshly distilled benzene (15 mL). In another flame-dried, round-bottomed flask were placed *cis*-1,2-dichloroethylene (3.0 equiv, 0.039 mol, 3.8 g, 2.95 mL), distilled benzene (25 mL), palladium tetrakis(triphenylphosphine) (5 mol %, 0.65 mmol,

(19) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(20) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788 and relevant citations found in ref 4.

0.75 g), copper(I) iodide (15 mol %, 1.95 mmol, 0.37 g), and *n*-butylamine (5.0 equiv, 0.065 mol, 4.75 g, 6.41 mL). The resulting suspension was degassed by four freeze-thaw cycles and was gently stirred at room temperature until it became a pale, yellow clear solution (10−20 min). After degassing by four freeze-pump-thaw cycles, the alkyne solution was cannulated dropwise to the yellow solution of *cis*-1,2-dichloroethylene and catalysts, and the reaction mixture was allowed to stir for 12 h under nitrogen. It was then poured into saturated aqueous ammonium chloride (50 mL) and extracted with diethyl ether. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, and the residue was purified by gradient flash chromatography (diethyl ether/hexane mixtures) to afford enyne ester **11** (2.69 g) as a light yellow oil in 79% yield: R_f (25% diethylether/75% hexane) 0.3; IR (neat) 2252.2, 1732.5, 1589.2; ^{1}H NMR ($CDCl_3$) δ 6.33 (d, J = 6.96, 1H), 5.80 (dd, J = 7.51, J = 1.65, 1H), 4.89 (d, J = 6.78, 1H), 4.48 (dd, overlapping, J = 7.14, J = 1.65, 1H), 4.50 (d, J = 6.78, 1H), 4.05 (q, J = 7.15, 2H), 3.29 (s, 3H), 2.46 (t, J = 7.88, 2H), 2.03 (dt, J = 7.51, J = 7.14, 2H), 1.17 (t, J = 7.15, 3H); ^{13}C NMR ($CDCl_3$) δ 172.66, 129.00, 111.20, 95.06, 93.84, 79.66, 64.47, 60.17, 55.51, 30.33, 29.67, 13.95; HRMS calcd for $C_{12}H_{17}ClO_4$ 260.0815, found 260.0822.

(7*Z*,12*Z*)-Ethyl-14-hydroxy-11-[(*tert*-butyldimethylsilyl)oxy]-11-methyl-4-[(methoxymethyl)oxy]-12-(phenylthio)-tetradecadiene-(5,9)-diynoate (13). According to the above procedure for the synthesis of **11**, palladium (0)-catalyzed coupling of free alkyne **12** (8.0 mmol, 2.8 g) with chloroenyne ester **11** (1.1 equiv, 8.8 mmol, 2.3 g) in a benzene solution (10 mL) containing palladium tetrakis(triphenylphosphine) (5 mol %, 0.4 mmol, 0.46 g), copper(I) iodide (10 mol %, 0.8 mmol, 0.152 g), and *n*-butylamine (3 equiv, 0.024 mol, 1.75 g, 2.4 mL) generated enediyne **13** (3.2 g) in 93% isolated yield (flash chromatography) as a mixture of two diastereomers: R_f (50% diethyl ether/50% hexane) 0.20; IR (neat) 3450.1, 2247.4, 1732.3, 1582.2; ^{1}H NMR ($CDCl_3$) δ 7.23−6.92 (m, 5H), 6.81 (dd, J = 6.95, J = 5.49, 1H for one diastereomer), 6.79 (dd, J = 6.96, J = 5.49, 1H for other diastereomer), 5.78 (s, 2H for one diastereomer), 5.75 (s, 2H for other diastereomer), 4.89 (d, J = 3.66, 1H), 4.87 (d, J = 3.66, 1H), 4.48 (ddd, J = 6.95, J = 5.4, J = 3.1, 2H), 4.06 (t, J = 7.51, 1H), 4.02 (q, J = 7.15, 2H), 3.28 (s, 3H for one diastereomer), 3.26 (s, 3H for other diastereomer), 2.42 (t, J = 7.51, 2H), 2.03 (dt, J = 7.51, J = 1.28, 2H), 1.63 (s, 3H for one diastereomer), 1.61 (s, 3H for other diastereomer), 1.14 (t, J = 7.15, 3H), 0.77 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.90, 137.61, 137.49, 137.21, 136.85, 136.83, 128.67, 126.46, 124.95, 119.25, 99.04, 94.29, 83.52, 82.97, 72.93, 64.65, 61.13, 60.35, 55.42, 30.84, 30.44, 29.86, 25.60, 18.04, 13.99, −3.00, −3.32.

(4*Z*,9*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-13-[(methoxymethyl)oxy]-5-(phenylthio)tetradecadiene-(7,-11)-diynolides (1a and 1b). To a solution of water (64 mL) in methanol (100 mL) was added *n*-butyllithium (5 equiv, 0.028 mol, 12.17 mL from a 2.3 M solution in hexane) dropwise while stirring. To the resulting lithium hydroxide solution was added ester **13** (3.2 g, 5.6 mmol) in methanol (100 mL) slowly at room temperature. The reaction mixture was allowed to stir vigorously until hydrolysis was complete (5 h) as indicated by TLC analysis. Concentration under reduced pressure and treatment of the residue with HCl solution (0.5 M) was followed by extraction with diethyl ether. The combined ether layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to furnish the desired hydroxy acid in quantitative yield (3.05 g). This material was used for the macrolactonization without further purification. To a solution of DCC (4 equiv, 0.014 mol, 2.96 g), pyridine (6 equiv, 0.021 mol, 1.7 g, 1.74 mL), and pyridinium *p*-toluenesulfonate (4 equiv, 0.14 mol, 3.52 g) in dry, ethanol-free chloroform (350 mL) was infused a solution of crude hydroxy acid (1.95 g, 3.5 mmol) in dry chloroform (40 mL) via a syringe pump during 50 h. After this time, methanol (10 equiv, 0.035 mol, 1.15 g, 1.45 mL) and acetic acid (8 equiv, 0.028 mol, 1.72 g, 1.64 mL) were added and stirring was continued for 30 min, until no DCC was detected by TLC analysis. The mixture was concentrated to about 30 mL, diluted with 30 mL of diethyl ether, filtered and concentrated. The residual oil was purified by flash chromatography with diethyl ether/hexane to furnish the desired macrolactones **1a** and **1b** as a mixture of two diastereomers in 82% yield (1.54 g): R_f (50% diethyl ether/50% hexane) 0.60. The mixture was separated by preparative HPLC. Diastereoisomer **1a**: ^{1}H NMR ($CDCl_3$) δ 7.31−6.86 (m, 5H), 6.80 (dd, J = 6.60, J = 3.85, 1H), 5.82 (dd, J = 10.99, J = 1.83, 1H), 5.79 (d, J = 10.99, 1H), 4.81 (dd, J = 6.60, J = 14.11, 1H), 4.76 (d, J = 6.59, 1H), 4.75 (dt, overlapping, 1H), 4.49 (d, J = 6.59, 1H), 4.12 (dd, J = 3.85, J = 14.11, 1H), 3.28 (s, 3H), 2.59−1.78 (m, 4H), 1.63 (s, 3H), 0.80 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.72, 141.28, 136.36, 133.33, 128.21, 127.24, 125.44, 120.25, 118.89, 98.28, 94.85, 94.30, 84.63, 83.90, 73.01, 65.43, 62.45, 55.56, 30.75, 30.64, 30.22, 25.70, 18.17, −3.19, −3.58; mp 84−85 °C; HRMS calcd for $C_{29}H_{38}O_5SSi$ 526.2209, found 526.2218. Diastereoisomer **1b**: IR (neat) 2251.0, 1739.6, 1582.1; ^{1}H NMR ($CDCl_3$) δ 7.32−6.93 (m, 5H), 6.81 (dd, J = 6.41, J = 4.21, 1H), 5.79 (s, 2H), 4.84 (d, J = 6.78, 1H), 4.73 (t, J = 6.22, 1H), 4.53 (dd, J = 4.21, J = 14.28, 1H), 4.48 (d, J = 6.78, 1H), 4.44 (dd, J = 6.41, J = 14.28, 1H), 3.29 (s, 3H), 2.58−2.3 (m, 2H), 2.18−1.98 (m, 2H), 1.65 (s, 3H), 0.78 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.77, 140.73, 136.21, 133.29, 128.21, 127.10, 125.43, 119.15, 118.54, 98.56, 95.16, 94.12, 84.73, 83.84, 73.31, 65.20, 62.40, 55.59, 31.06, 30.73, 30.59, 25.63, 18.14, −3.02, −3.36; HRMS calcd for $C_{29}H_{38}O_5SSi$ 526.2209, found 526.2206.

(6*Z*)-2-Ethynyl-3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-10-[(methoxymethyl)oxy]-2-(phenylthio)-1-[[(triisopropylsilyl)oxy]carbonyl]-cycloundecene-(4,8)-diynes (3a and 3b). To a stirred solution of lactone **1a** (350 mg, 0.69 mmol) in dry THF (12 mL) containing HMPA (3.5 equiv, 2.3 mmol, 0.42 g, 0.40 mL) at −100 °C (hexane−liquid nitrogen bath) was added lithium bis(trimethylsilyl)amide (LHMDS, 1.2 equiv, 0.8 mmol, 0.80 mL from a 1.0 M solution in THF) immediately followed by triisopropylsilyl trifluoromethansulfonate (1.2 equiv, 0.8 mmol, 0.245 g, 0.22 mL). Subsequently the reaction mixture was warmed quickly to 23 °C and allowed to stir for 5 min (TLC analysis). Gradual replacement of almost all THF with dry hexane under high vacuum while stirring was continued induced the precipitation of insoluble salt (LiOTf) which was removed by filtration through a triethylamine pretreated silica gel microcolumn (Pasteur pipette). The filtrate was concentrated in *vacuo* to give uncomplexed (*Z*)-ketene acetal **2a** as the only isomer in quantitative yield: R_f (50% diethyl ether/50% hexane) 0.80; ^{1}H NMR ($CDCl_3$) δ 7.38−7.05 (m, 5H), 6.97 (dd, J = 5.86, J = 4.4, 1H), 5.92 (dd, J = 10.81, J = 1.46, 1H), 5.82 (d, J = 10.81, 1H), 4.93 (d, J = 6.77, 1H), 4.63 (d, J = 6.77, 1H), 4.61 (dt, J = 4.03, J = 1.46, 1H), 4.47 (dd, overlaping, 1H), 4.42 (dd, J = 15.94, J = 4.40, 1H), 4.38 (dd, J = 15.94, J = 5.86, 1H), 3.39 (s, 3H), 3.38 (t, J = 7.03, 1H), 2.77−2.31 (m, 2H), 1.70 (s, 3H), 1.08 (m, 3H), 1.05 (dd, J = 6.22, J = 1.25, 18H), 0.90 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.63, 138.57, 136.15, 134.34, 128.77, 126.25, 125.02, 120.83, 117.38, 97.77, 96.93, 93.74, 83.87, 82.45, 72.56, 69.51, 67.05, 64.94, 55.03, 31.39, 30.12, 25.54, 17.68, 12.47, 11.20, −3.26, −3.57. To a carbon monoxide-purged solution of the (*Z*)-ketene acetal (450 mg, 0.66 mmol) in dry hexane (10 mL) was added $Co_2(CO)_8$ (1.3 equiv, 0.85 mmol, 293 mg) at 23 °C. After stirring for 24 h, the resulting solution was passed through a silica gel microcolumn (Pasteur pipette). Concentration of the appropriate fractions provided $Co_2(CO)_6$-complexed **3a** as a deep crimson oil in 81% yield (518 mg): R_f (5% diethyl ether/95% hexane) 0.80; IR (neat) 1725.1; ^{1}H NMR ($CDCl_3$) δ 7.69−7.19 (m, 5H), 6.72 (d, J = 10.45, 1H), 5.75 (d, J = 10.45, 1H), 5.70 (d, J = 17.6, 1H), 5.67 (dd, J = 17.60, J = 9.16, 1H), 5.30 (d, J = 9.16, 1H), 5.27 (t, overlaping, 1H), 5.01 (d, J = 6.78, 1H), 4.68 (d, J = 6.78, 1H), 4.03 (t, J = 3.48, 1H), 3.67 (dd, J = 15.94, J = 3.48, 1H), 3.47 (s, 3H), 2.33 (m, 1H), 1.45 (s, 3H), 1.32 (m, 3H), 1.12 (d, J = 7.15, 18H), 0.91 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.06, 173.89, 138.45, 137.74, 135.73, 132.63, 128.64, 128.42, 119.79, 108.55, 100.33, 97.25, 95.79, 84.62, 82.32, 80.04, 76.22, 66.86, 56.25, 51.12, 43.54, 27.92, 25.86, 18.49, 17.91, 12.10, −2.19, −2.64. To a solution of $Co_2(CO)_6$-complexed **3a** (450 mg, 0.46 mmol) in dry benzene (6 mL) was added *N*-methylmorpholine *N*-oxide (5 equiv, 2.3 mmol, 0.272 g) at 23 °C in two equal portions with a time interval of 1.5 h. After this time, the resulting reaction mixture was passed through a silica gel microcolumn and the filtrate was directly purified by flash chromatography (6% diethyl ether/94% hexane) to provide 11-membered enediyne **3a** in 74% yield (232 mg): R_f (25% diethyl ether/75% hexane) 0.40; IR (neat) 2091.6, 2054.5, 2027.8, 1709.9;

^{1}H NMR ($CDCl_3$) δ 7.58−7.03 (m, 5H), 5.89 (dd, J = 10.99, J = 17.40, 1H), 5.88 (d, J = 9.90, 1H), 5.76 (dd, J = 9.90, J = 0.91, 1H), 5.45 (dd, J = 17.40, J = 0.73, 1H), 5.13 (dd, J = 10.99, J = 0.73, 1H), 4.77 (d, J = 6.96, 1H), 4.49 (d, J = 6.96, 1H), 4.40 (dd, J = 8.80, J = 5.68, 1H), 4.29 (m, 1H), 3.22 (s, 3H), 2.46 (m, 2H), 1.91 (s, 3H), 1.21 (m, 3H), 1.00 (dd, J = 7.33, J = 1.65, 18H), 0.65 (s, 9H), 0.04 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.16, 138.37, 134.07, 133.94, 128.13, 126.72, 122.76, 121.05, 116.54, 100.30, 97.30, 94.38, 86.06, 85.75, 79.11, 67.09, 66.51, 55.63, 53.54, 37.13, 32.17, 25.72, 18.17, 17.88, 12.09, −2.64, −3.15; HRMS calcd for $C_{38}H_{58}O_5SSi_2$ 682.3544, found 682.3531. Similarly, enediyne **3b** was obtained in 55% overall yield from **1b**: IR (neat) 2946.9, 1725.1; ^{1}H NMR ($CDCl_3$) δ 7.71−7.13 (m, 5H), 5.84 (s, 2H), 5.37 (dd, J = 10.80, J = 17.95, 1H), 5.28 (dd, J = 17.95, J = 1.46, 1H), 4.92 (dd, J = 10.80, J = 1.46, 1H), 4.78 (d, J = 6.78, 1H), 4.53 (m, 1H), 4.51 (m, 1H), 4.48 (d, J = 6.78, 1H), 3.22 (s, 3H), 3.17 (t, J = 11.72, 1H), 2.36 (ddd, J = 24.73, J = 13.01, J = 4.21, 1H), 1.50 (s, 3H), 1.18 (m, 3H), 0.96-(dd, J = 7.33, J = 5.13, 18H), 0.89 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.60, 138.19, 138.00, 132.75, 128.25, 123.07, 122.53, 117.16, 99.59, 98.36, 94.33, 85.24, 85.12, 79.22, 66.37, 63.89, 55.44, 51.34, 35.74, 26.85, 25.75, 18.57, 17.92, 17.88, 12.02, −2.34, −3.18; HRMS calcd for $C_{38}H_{58}O_5SSi_2$ 682.3544, found 682.3552.

(6*Z*)-2-Ethynyl-3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-10-hydroxy-2-(phenylthio)-1-(methoxycarbonyl)cycloundecen-(4,8)-diyne (4). A solution of triisopropylsilyl ester **3b** (150 mg, 0.22 mmol) in methanol (3 mL), THF (1 mL), and water (1 mL) was stirred vigorously for 10 min after which time potassium carbonate (3 equiv, 0.66 mmol, 91 mg) was added and stirring was continued at ambient temperature (TLC control). When hydrolysis was judged complete, the reaction mixture was poured into saturated ammonium chloride solution, extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate to furnish the desired carboxylic acid in quantitative yield (116 mg). This product was used for the next step without further purification: R_f (50% diethyl ether/50% hexane/3 drops of AcOH) 0.25; IR (neat) 3500 (broad), 1711.8; ^{1}H NMR ($CDCl_3$) δ 7.63−7.12 (m, 5H), 5.90 (d, J = 14.9, 1H), 5.89 (d, J = 14.9, 1H), 5.42 (dd, J = 10.26, J = 16.61, 1H), 5.35 (d, J = 16.61, 1H), 5.08 (d, J = 10.26, 1H), 4.79 (d, J = 6.59, 1H), 4.61 (dd, overlaping, 1H), 4.57 (d, J = 6.59, 1H), 4.46 (dd, J = 11.96, J = 8.05, 1H), 3.31 (s, 3H), 3.23 (t, J = 11.96, 1H), 2.31 (m, 1H), 1.51 (s, 3H), 0.98 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.43, 137.94, 136.60, 130.78, 129.15, 123.53, 122.38, 118.34, 98.57, 98.30, 94.83, 85.41, 78.72, 66.69, 64.02, 55.58, 50.73, 34.95, 27.14, 25.74, 18.57, 17.67, 12.23, −2.36, −3.25. A solution of diazomethane in ether, prepared in 1.0 mmol scale from *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine,[21] was added dropwise with stirring to a solution of the above carboxylic acid (80 mg, 0.15 mmol) in diethyl ether (5 mL) until esterification was complete (TLC control). The reaction mixture was poured into water, extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate to provide after flash chromatography (20% diethyl ether/80% hexane) the desired methyl ester in 90% yield (71 mg): R_f (50% diethyl ether/50% hexane) 0.45; IR (neat) 2250.3, 1743.5; ^{1}H NMR ($CDCl_3$) δ 7.59−7.15 (m, 5H), 5.85 (s, 2H), 5.46 (dd, J = 11.36, J = 17.96, 1H), 5.24 (dd, J = 17.96, J = 0.74 , 1H), 4.96 (dd, J = 11.36, J = 0.74, 1H), 4.75 (d, J = 6.78, 1H), 4.52 (d, J = 6.78, 1H), 4.47 (dd, J = 11.72, J = 1.46, 1H), 4.26 (dd, J = 11.90, J = 3.84, 1H), 3.45 (s, 3H), 3.27 (s, 3H), 3.14 (m, 1H), 2.43 (ddd, J = 15.76, J = 13.01, J = 4.03, 1H), 1.55 (s, 3H), 0.88 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.82, 137.90, 137.86, 132.71, 128.32, 128.29, 123.26, 122.58, 117.18, 99.25, 98.60, 94.58, 85.41, 85.24, 79.02, 66.54, 63.99, 55.51, 51.21, 50.57, 35.77, 27.05, 25.74, 18.57, −2.35, −3.20. To a solution of the derived methyl ester (70 mg, 0.13 mmol) in methylene chloride (4 mL) at −100 °C (hexane−liquid nitrogen bath) was added dimethylbromoborane (2.3 equiv, 0.3 mmol, 0.197 mL from a 1.5 M solution in 1,2-dichloroethane) dropwise with stirring. After 30 min the reaction mixture was transferred into a 1:1 solution of THF (10 mL) and saturated sodium bicarbonate (10 mL) and stirred at ambient temperature for 5 min. Extraction with diethyl ether, drying over anhydrous magnesium sulfate, filtration, and concentration provided a dark-yellow residue which was purified by preparative HPLC (20% ethyl acetate/80% hexane) to yield 39 mg (61%) of the desired alcohol **4**: R_f (50% diethyl ether/50% hexane) 0.20; IR (neat) 3483.2, 1725.1; ^{1}H NMR ($CDCl_3$) δ 7.73−7.23 (m, 5H), 5.96 (s, 2H), 5.56 (dd, J = 11.35, J = 17.95, 1H), 5.32 (d, J = 17.95, 1H), 5.06 (d, J = 11.35, 1H), 4.51 (dd, J = 11.73, J = 1.65, 1H), 4.45 (s, 1H), 3.54 (s, 3H), 3.24 (dd, J = 12.82, J = 1.65, 1H), 3.19 (dd, J = 13.37, J = 1.65, 1H), 2.55 (ddd, J = 15.75, J = 12.82, J = 4.21, 1H), 1.66 (s, 3H), 0.98 (s, 9H), 0.27 (s, 3H), 0.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.66, 137.91, 137.88, 132.64, 128.37, 128.31, 123.08, 122.84, 117.19, 99.80, 99.37, 85.37, 84.87, 79.12, 63.86, 63.07, 50.99, 38.42, 29.69, 27.09, 25.75, 18.58, −2.32, −2.98; mp 97−98 °C; HRMS calcd for $C_{28}H_{36}O_4SSi$ 496.2104, found 496.2112.

(4*Z*,9*Z*)-6-Hydroxy-6-methyl-13-[(methoxymethyl)oxy]-5-(phenylthio)tetradecadiene-(7,11)-diynolide (14). To a stirred solution of lactone **1a** (50 mg, 0.1 mmol) in methylene chloride (0.5 mL, 0.25 M) was added catecholbromoborane (1.1 equiv, 0.11 mmol, 0.55 mL of a 0.2 M solution in CH_2Cl_2) dropwise at ambient temperature (TLC control). When deprotection was judged complete, water (1 mL) was added and the reaction mixture was stirred at ambient temperature for 20 min. Addition of sodium hydroxide (10% solution), extraction with methylene chloride, washing of the combined organic layer with brine, drying over anhydrous magnesium sulfate, concentration, and purification by preparative TLC furnished alcohol **14** in 90% yield (36 mg): R_f (50% diethyl ether/50% hexane) 0.50; ^{1}H NMR ($CDCl_3$) δ 7.31−6.97 (m, 6H), 5.91 (d, J = 11.17, 1H), 5.83 (dd, J = 11.17, J = 1.65, 1H), 5.56 (dd, J = 10.07, J = 4.21, 1H), 4.81 (d, J = 6.78, 1H), 4.77 (dd, J = 10.95, J = 4.21, 1H), 4.53 (d, J = 6.78, 1H), 4.17 (dd, J = 10.44, J = 10.6, 1H), 3.30 (s, 3H), 2.81−2.11 (m, 4H), 1.88 (s, 3H); HRMS calcd for $C_{23}H_{24}O_5S$ 412.1344, found 412.1351.

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Supporting Information Available: Reproductions of ^{1}H, ^{13}C NMR, and IR spectra for new compounds **1**, **3**, **4**, **9**, **10**, **11**, **13**, and **14**; HPLC trace of diastereoisomeric lactones **1a** and **1b**, NOE-difference spectrum of uncomplexed **2b**, and ORTEP presentations of enediyne structures **1a** and **4** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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