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Tetrahydroxy 10-Membered Cyclic Enediynes

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The preparation of cyclic 10-membered tetrahydroxy enediynes is reported. The synthesis starts from tartaric acid and allows the control of the relative stereochemistry. Acetal protection of the 2,3-hydroxy groups stabilizes the enediyne during synthesis. Removal of the cyclic protecting group with EtSH/TFA transforms the stable compounds into reactive enediynes, and the rate constants of their cyclization were determined in benzene and water. The cytoxicity of the activated compounds was assayed against tumor cells in vitro, but the growth inhibitory effect was weak compared to cisplatin.

Introduction

The cytotoxic properties of natural products such as calicheamicin γ_1^I, dynemicin A, or neocarzinostatin[1] have their origin in strained cyclic enediyne or cumulene-eneyne structures. Their spontaneous thermal cyclization yields reactive aryl or benzyl diradicals, which abstract hydrogen atoms, leading to DNA strand cleavage and ultimately to cell death.[2] To fulfill their biological function, the reactivity of the unsaturated macrocycles must be regulated. In the natural products this is achieved either by trigger mechanisms that unlock conformationally constrained precursors[3] or by proteins, which tightly bind and stabilize the enediyne or cumulene-eneynes chromophore.[4] To control the reactivity in synthetic enediyne model compounds, several strategies have been reported: release of a conformational constrain that prohibits spontaneous cyclization,[5] isomerization of enediynes to the more reactive cumulene-eneynes,[6] generation of the enediyne system by retro-Diels−Alder,[7] S_N2' reaction,[8] or alkyne deprotection[9] or the induction of the cyclization by catalytic antibodies,[10] metal cations,[11] oxidation,[12] or light.[13] Hydroxylated enediynes are well suited to reversibly lock their conformation and therefore modulate their reactivity by cyclic hydroxy protecting

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(2) Initially formed diradical is less reactive than the phenyl radical, which is obtained after one hydrogen abstraction. This fact is of importance for efficient DNA-strand cleavage by enediyne antibiotics. Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896−4903.

(3) In most cases, a strained, and therefore even at room temperature highly reactive, cyclic enediyne or cumulene-eneyne is held in a conformation that kinetically disfavors the cyclization reaction. A small change in conformation, caused, e.g., by a nucleophile that adds to a double bond or an epoxide, releases the constraint, and the cyclization to the arene diradical proceeds instantaneously. (a) 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*, 3850−3866. (b) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908−8921.

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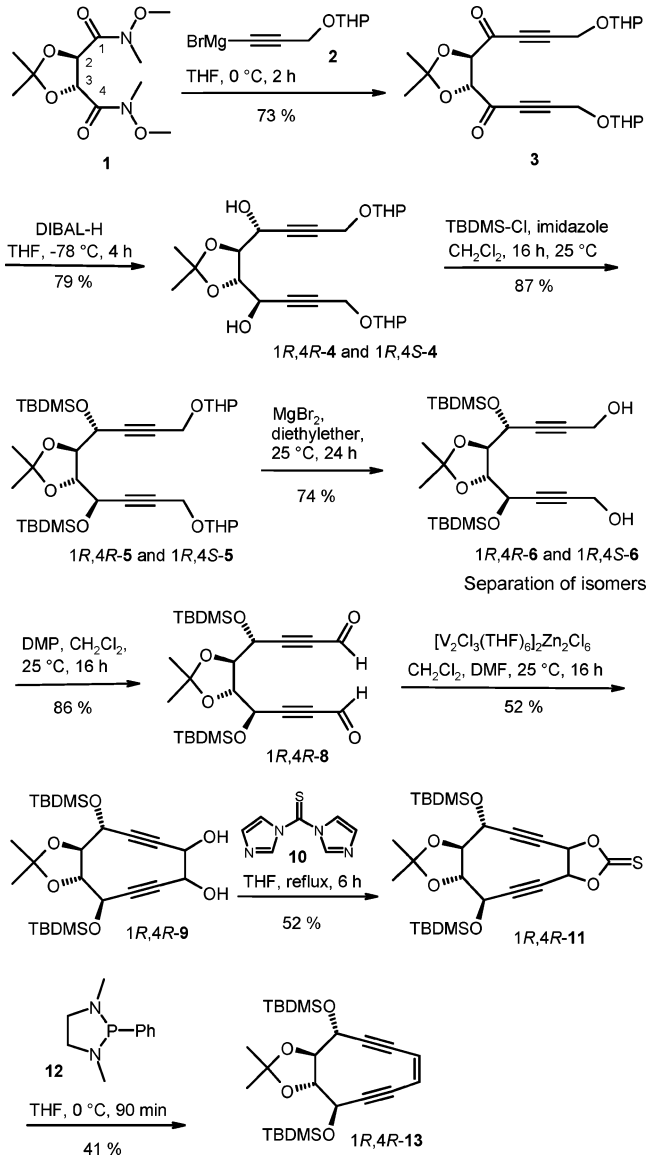
groups.[14] Nicolaou et al. reported an enediyne diol and its carbonate as the first example of this kind.[5a,15] We present here the stereodefined synthesis of enediyne tetraols. The cyclic enediynes become water soluble[16] by the additional hydroxy groups and still can be regulated in their reactivity by cyclic protecting groups.

Results and Discussion

Fallis et al.[17] reported the first synthesis of a protected tetrahydroxy enediyne[18] using Cr(II)/Ni(II)-mediated coupling of an iodoalkyne to an aldehyde for ring closure. In their route, the sensitive enediyne was taken through the synthesis, while we intended to build up the enediyne in the last steps. Starting material **1** was prepared from *L*-tartaric acid. The reaction of (−)-dimethyl-2,3-*O*-isopropylidene-*L*-tartrate[19] with *N*,*O*-dimethylhydroxylamine hydrochloride and $AlMe_3$ gave the 2-fold Weinreb amide in 85% yield.[20] The reaction of compound **1** with the lithium salt of THP-protected propargylic alcohol gave single substitution as the major product pathway. Using the magnesium salt **2** yielded **3** in 73% yield by clean 2-fold substitution. Initial attempts to continue the enediyne synthesis at the oxidation level of the diketone were not successful.[21] Therefore, reduction was performed at this stage using DIBAL-H at −78 °C. The diol was obtained in good chemical yield but as an equal mixture of two out of the three possible diastereomers. To improve the diastereoselectivity of the reduction, several alternative reagents and conditions were tested, but the selectivity did not improve and chemical yields decreased. The isomeric mixture was carried through two further steps, TBDMS protection and THP deprotection, to facilitate separation and determination of configuration.[22] Selective THP deprotection requires magnesium dibromide in diethyl ether as a reagent. Methanol/acidic ion-exchange resin or methanol/iodine[23] leads to partial TBDMS deprotection. The two isomers of compound **6** were separated by column chromatography on silica gel. ^1H and ^{13}C NMR spectra of one isomer reveal a full set of resonances not reduced by symmetry, which corresponds to the nonsymmetric (1*R*,4*S*)-**6** isomer. The NMR spectra of the second

SCHEME 1. Synthesis of Protected Tetrahydroxy Enediyne 13



isomer show a symmetry reduced half set of resonances, which agrees with (1*R*,4*R*)-**6** and (1*S*,4*S*)-**6** but allows no distinction. An X-ray structure analysis (see Supporting Information) of the compound confirmed its structure to be (1*R*,4*R*)-**6**. The pure isomers were taken separately through the following synthetic steps to complete the synthesis (only one isomer reaction is shown in Scheme 1). Oxidation of (1*R*,4*R*)-**6** using the Dess−Martin reagent gave dialdehyde (1*R*,4*R*)-**8** in good yield. A pinacol-type reaction was used in the next step for ring closure. The Pederson vanadium(II) reagent is suitable to mediate the reaction as shown in earlier reports,[24] because it favors the formation of the desired *cis*-diol,[25] presumably by a cyclic chelate transition state.[26] Diol (1*R*,4*R*)-**9** was

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(21) Diketodialdehyde analogous to compound **8** is not stable.

(22) Additional racemic stereocenters of the THP groups lead to a complex mixture of possible stereoisomers.

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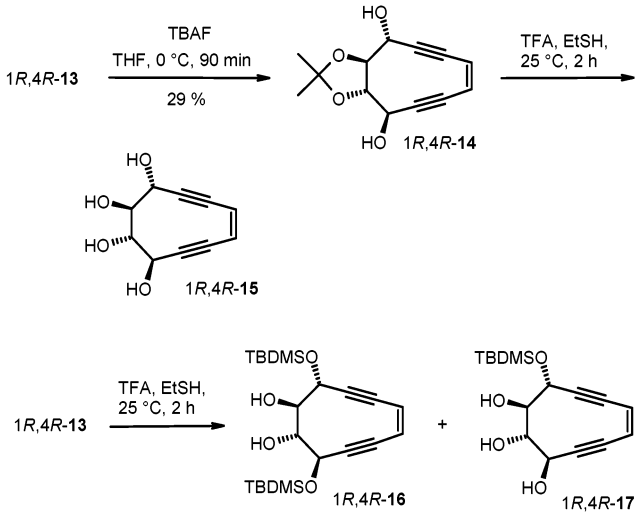
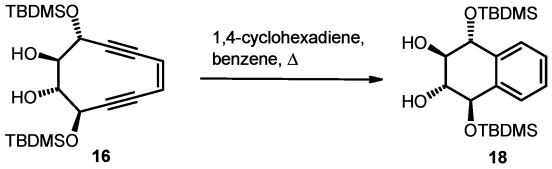
SCHEME 2. Deprotection of Enediyne 13



obtained in 52% yield as a mixture of diastereomers, which were not separated but reacted with *N*,*N*-thiocarbonylbisimidazole (**10**) to give thiocarbonate (1*R*,4*R*)-**11**. The Corey−Hopkins elimination[27] is completed by treatment of the thiocarbonate with 1,3-dimethyl-2-phenyl-[1,3,2]diazaphospholidine (**12**) to give enediyne (1*R*,4*R*)-**13** in 41%. Analogously, compound (1*R*,4*S*)-**6** was converted into (1*R*,4*S*)-**13** in 15% overall yield (see Supporting Information for yields of the individual reactions).

To investigate the properties of enediyne **13**, the protecting groups have to be removed under mild conditions. Selective TBDMS deprotection is possible using standard conditions, but the high polarity of the product makes its isolation difficult and low yielding. The enediyne will become reactive after cleavage of the isopropylidene diol protecting group, so heating must be strictly avoided. Removal of the isopropylidene protecting group at room temperature requires treatment with EtSH and concentrated TFA. Under these conditions, a partial loss of the TBDMS groups cannot be avoided.The thermal reactivity of enediynes (1*R*,4*R*)-**13**, (1*R*,4*R*)-**16**, and (1*R*,4*R*)-**15** was investigated by thermolysis and monitored by HPLC analysis[28] to derive kinetic data. The cyclization of (1*R*,4*R*)-**16** was performed in benzene/cyclohexadiene at 69 °C, and the formation of the expected Bergman cyclization product was confirmed by HPLC-MS. Data analysis revealed pseudo-first-order kinetics with a reaction rate constant of $k = 6.4 \times 10^{-4}$ s^{-1} and a half-life $t_{1/2} = 18$ min. The isopropylidene-protected compound (1*R*,4*R*)-**13** showed no reaction under these conditions. Tetrahydroxy enediyne (1*R*,4*R*)-**15** is water soluble. Therefore, the thermal cyclization of this compound was investigated in aqueous solution. Again the data fit to pseudo-first-order kinetics with a rate constant of $k = 4.3 \times 10^{-3}$ s^{-1} and a half-life $t_{1/2} = 3$ min at 60 °C.[29] The thermolysis data confirm that removal of

SCHEME 3. Thermal Cyclization of Enediyne 16



the isopropylidene group transforms the stabilized enediynes into thermally reactive compounds.To investigate if the concept of enediyne stabilization and activation holds in vitro, the cytoxicity of compounds (1*R*,4*R*)-**13**, (1*R*,4*R*)-**14**, (1*R*,4*R*)-**15**, and (1*R*,4*R*)-**16** was tested against human breast cancer cells MDA-MB-231 in the crystal violet assay[30] (see Supporting Information for data). Compounds (1*R*,4*R*)-**13** and (1*R*,4*R*)-**14**, stabilized by the isopropylidene protecting group, had no effect on cell growth, while for (1*R*,4*R*)-**15** and (1*R*,4*R*)-**16** a weak growth inhibition was observed. However, in comparison to cisplatin, a clinically widely used cytostatic, the inhibitory concentrations of enediynes **15** and **16** are high.

Conclusions

Cyclic tetrahydroxy enediynes were synthesized from tartaric acid in enantiomerically pure form. Each sp^3-hybridized carbon of the compounds is functionalized. The hydroxy substituents make the compounds water soluble and at the same time lock the ring conformation and control enediyne reactivity by cyclic diol protecting groups. The preparation of enediynes, which can be activated by enzymes, light, or acid in vitro, can be envisaged, choosing a suitable protecting method.

Experimental Section

2,3-*O*-Isopropylidene-*L*-tartaric acid,[17] 2,2-dimethyl-[1,3]-dioxolane-4,5-bis(methoxymethyl-carboxamide) **1**,[18] vanadium tris(tetrahydrofuran) trichloride,[31] and magnesiumbromide Et_2O[32] were prepared according to reported procedures.

1-{2,2-Dimethyl-5-[4-(tetrahydropyran-2-yloxy)-but-2-inoyl]-[1,3]dioxolane-4-yl}-4-(tetrahydropyran-2-yloxy)-but-2-in-1-one (3). A mixture of 2-prop-2-inyloxy-tetrahydropyran (3.22 g, 23.0 mmol) and EtMgBr, prepared from Mg turnings (0.61 g, 25.0 mmol) and bromoethane (2.51 g, 23.0 mmol) in 10 mL of dry THF, was refluxed for 1 h. After cooling to room temperature, the reaction mixture was added dropwise to a solution of 2,2-dimethyl-[1,3]-dioxolane-4,5-bis-(methoxymethylcarboxamide) **1** (1.00 g, 3.62 mmol) in 40 mL of THF, refluxed for 4 h, poured into aqueous KH_2PO_4 (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed twice with brine, dried over Na_2SO_4, and evaporated to dryness in vacuo. Column chromatography (petroleum ether/EtOAc, 3:1) gave 1.15 g (73%) of **3** ($R_f = 0.32$) as a yellow oil. IR (neat): $\tilde{\nu} =$ 2944, 2872, 2216, 1688, 1386, 1345, 1241, 1122, 1033, 968, 941, 902, 871, 816 cm^{-1}. UV (CH_3-

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CN): λ_{max} (lg ϵ) = 224 nm (4.114). ^{1}H NMR: δ 1.40−1.88 (m, 18 H), 3.50−3.61 (m, 2 H), 3.76−3.90 (s, 2 H), 4.48 (m, 4 H), 4.84 (m, 4 H). ^{13}C NMR: δ 18.8 (−), 25.2 (−), 26.8 (+), 30.0 (−), 53.7 (−), 62.0 (−), 82.5 (C_{quat}), 82.7 (+), 94.6 (C_{quat}), 97.2 (+), 114.6 (C_{quat}), 183.8 (C_{quat}). MS (CI), *m*/*z* (%): 85 (12) [DHP], 102 (70), 118 (100), 368 (7) [M + NH_4 − DHP$^+$], 453 (40) [M + NH_4^+]. Anal. Calcd for $C_{23}H_{30}O_8$ (434.49): C, 63.58; H, 6.96. Found: C, 63.18; H, 7.00.

1-{5-[1-Hydroxy-4-(tetrahydropyran-2-yloxy)but-2-inyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-4-(tetrahydropyran-2-yloxy)but-2-in-1-ole ((1*R*,4*S*)-4, (1*R*,4*R*)-4). To a solution of **3** (5.40 g, 12.4 mmol) in THF (130 mL) was added DIBAL-H (50 mL, 50 mmol, 1 M solution in THF) at −78 °C over 1 h. The reaction mixture was stirred for 24 h; methanol (25 mL) was added, and the solvent was removed in vacuo. The residue was redissolved in saturated K/Na tartrate solution (340 mL) and EtOAc (310 mL) and stirred for 30 min; the organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo; column chromatography (petroleum ether/EtOAc, 1:1) yielded 4.31 g (79%) of **4** as a stereoisomeric mixture (R_f = 0.45), yellow oil. IR (neat): $\tilde{\nu}$ = 3415, 2942, 2871, 1738, 1455, 1373, 1243, 1119, 1025, 903, 872, 815 cm^{-1}. ^{1}H NMR: δ 1.34−1.92 (m, 18 H), 3.04 (s, 2 H), 3.45−3.61 (m, 2 H), 3.71−3.91 (m, 2 H), 4.10−4.43 (m, 6 H), 4.53−5.07 (m, 4 H). MS (CI), *m*/*z* (%): 85 (100) [DHP$^+$], 102 (49), 118 (85), 288 (10) [M + NH_4 − 2DHP$^+$], 372 (10) [M + NH_4 − DHP$^+$], 456 (17) [M + NH_4^+]. Anal. Calcd for $C_{23}H_{34}O_8$ (438.52): C, 63.00; H, 7.81. Found: C, 62.68; H, 7.65.

4,5-Bis-[1-(*tert*-butyldimethylsilanyloxy)-4-(tetrahydropyran-2-yloxy)but-2-inyl]-2,2-dimethyl-[1,3]dioxolane ((1*R*,4*S*)-5, (1*R*,4*R*)-5). Diol **4** (745 mg, 1.70 mmol), imidazole (748 mg, 11.0 mmol), and *tert*-butylchloro dimethylsilane (TBDMS−Cl, 640 mg, 4.25 mmol) were dissolved in 20 mL of CH_2Cl_2 and stirred for 16 h at room temperature. The reaction mixture was washed with aqueous $NaHCO_3$ and brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Column chromatography (petroleum ether/EtOAc, 4:1) gave 980 mg (87%) of **5** as a mixture of stereoisomers (R_f = 0.52), colorless oil. IR (neat): $\tilde{\nu}$ = 2931, 2857, 1742, 1464, 1370, 1253, 1217, 1121, 1078, 1027, 945, 903, 838, 779, 669 cm^{-1}. ^{1}H NMR: δ 0.06−0.19 (m, 12 H), 0.80−0.98 (m, 18 H), 1.36−1.96 (m, 18 H), 3.43−3.56 (m, 2 H), 3.75−3.89 (m, 2 H), 4.00−4.09 (m, 1 H), 4.14−4.22 (m, 1 H), 4.24−4.32 (m, 4 H), 4.58−4.69 (m, 2 H), 4.75−4.85 (m, 2 H). MS (CI), *m*/*z* (%): 85 (36) [DHP$^+$], 118 (19), 499 (11), 516 (9) [M + NH_4 − 2DHP$^+$], 600 (3) [M + NH_4 − DHP$^+$], 685 (100) [M + NH_4^+]. Anal. Calcd for $C_{35}H_{62}O_8Si_2$ (667.04): C, 63.02; H, 9.37. Found: C, 62.74; H, 9.56.

4-(*tert*-Butyldimethylsilanyloxy)-4-{5-[1-(*tert*-butyldimethylsilanyloxy)-4-hydroxybut-2-inyl]-2,2-dimethyl-[1,3]-dioxolan-4-yl}but-2-in-1-ol ((1*R*,4*S*)-6 and (1*R*,4*R*)-6). Compound **5** (1.8 g, 2.7 mmol) and $MgBr_2$·Et_2O, prepared in situ from Mg turnings (0.58 g, 24 mmol) and 1,2 dibromoethane (1.8 mL, 3.93 g, 21 mmol), in dry diethyl ether (30 mL) was stirred at room temp for 24 h. The organic phase was washed with water (three times) and dried over Na_2SO_4, and the solvent was removed in vacuo. Column chromatography gave two fractions: (1) (1*R*,4*S*)-**6** (0.52 mg, 39%) (R_f = 0.39), yellow oil, and (2) (1*R*,4*R*)-**6** (0.47 mg, 35%) (R_f = 0.24), colorless soft solid. **(1*R*,4*S*)-6:** [α]$^{25}_D$ −18 (*c* 0.84 in CH_3CN). IR (neat): $\tilde{\nu}$ = 3406, 2931, 2896, 2858, 1742, 1253, 1135, 1072, 1026, 977, 940, 838, 779, 670 cm^{-1}. ^{1}H NMR: δ 0.13 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.17 (s, 3 H), 0.92 (s, 18 H), 1.45 (s, 6 H), 1.91 (s, 2 H), 4.09 (dd, ^3J = 7.3 Hz, 3.2 Hz, 1 H), 4.18 (dd, ^3J = 7.3 Hz, 4.0 Hz, 1 H), 4.29 (d, ^5J = 1.7 Hz, 2 H), 4.31 (d, ^5J = 1.7 Hz, 2 H), 4.60 (dt, ^3J = 4.0 Hz, ^5J = 1.7 Hz, 1 H), 4.64 (dt, ^3J = 7.3 Hz, ^5J = 1.7 Hz, 1 H). ^{13}C NMR: δ −5.0 (+), −4.8 (+), −4.6 (+), −4.4 (+), 18.3 (C_{quat}), 18.4 (C_{quat}), 25.8 (+), 25.9 (+), 27.3 (+), 27.6 (+), 51.1 (−), 51.2 (−), 63.6 (+), 64.2 (+), 79.9 (+), 80.5 (+), 84.1 (C_{quat}), 84.2 (C_{quat}), 84.3 (C_{quat}), 84.5 (C_{quat}), 110.6 (C_{quat}). MS (CI), *m*/*z* (%): 516.3 (100) [M + NH_4^+]. HRMS $C_{25}H_{47}O_6Si_2$ calcd 499.2911, found 499.2915 ±0.5 ppm. **(1*R*,4*R*)-6:** Mp 116−118 °C. IR (neat): $\tilde{\nu}$ = 3400, 2956, 2956, 2896, 2886, 2859, 2361, 2342, 1472, 1381, 1254, 1131, 1131, 1075, 1023, 838, 784 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.12 (s, 6 H), 0.16 (s, 6 H), 0.91 (s, 18 H), 1.46 (s, 6 H), 2.35 (s, 2 H), 4.21 (dd, ^3J = 2.3 Hz, 1.3 Hz, 2 H), 4.31 (d, ^5J = 1.7 Hz, 2 H), 4.58−4.60 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.9 (+), −4.4 (+), 18.2 (C_{quat}), 25.8 (+), 27.6 (+), 51.0 (−), 64.1 (+), 80.2 (+), 84.3 (C_{quat}), 84.4 (C_{quat}), 111.0 (C_{quat}). MS (CI), *m*/*z* (%): 499 (4) [M + H$^+$], 516 (100) [M + NH_4^+]. Anal. Calcd for $C_{25}H_{46}O_6Si_2$ (498.81): C, 60.20; H, 9.30. Found C, 60.19; H, 9.47.

4-(*tert*-Butyldimethylsilanyloxy)-4-{5-[1-(*tert*-butyldimethylsilanyloxy)-4-oxobut-2-inyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}but-2-inal ((1*R*,4*R*)-8). To a solution of (1*R*,4*R*)-**6** (498 mg, 1.00 mmol) in dry CH_2Cl_2 (20 mL) was added Dess−Martin periodinane (1.28 g, 3 mmol) at room temperature, and the suspension was stirred for 17 h. The reaction mixture was filtered, washed with aqueous $Na_2S_2O_5$ (100 mL, 0.4 M), and dried over Na_2SO_4, and the solvent was removed in vacuo. Column chromatography (petroleum ether/EtOAc, 1:1) gave 425 mg (86%) of (1*R*,4*R*)-**8** (R_f = 0.87), as an oil. IR (neat): $\tilde{\nu}$ = 3054, 2987, 2360, 2411, 1671, 1422, 896, 740 cm^{-1}. UV (CH_3-CN): λ_{max} (lg ϵ) = 218 nm (3.867). ^{1}H NMR: δ 0.15 (s, 6 H), 0.20 (s, 6 H), 0.93 (s, 18 H), 1.48 (s, 6 H), 4.28 (dd, ^3J = 2.0 Hz, 1.2 Hz, 2 H), 4.76−4.80 (m, 2 H), 9.26 (s, 2 H). ^{13}C NMR: δ −4.9 (+), −4.5 (+), 18.2 (C_{quat}), 25.7 (+), 27.3 (+), 64.0 (+) 79.2 (+), 84.8 (C_{quat}), 93.9 (C_{quat}), 111.7 (C_{quat}), 176.1 (+). MS (CI), *m*/*z* (%): 115 (33), 117 (26), 133 (49), 173 (11), 197 (18), 205 (11), 269 (12), 297 (11), 305 (10), 437 (14), 495 (100) [M + H$^+$], 296 (37). Anal. Calcd for $C_{25}H_{42}O_6Si_2$ (494.78): C, 60.69; H, 8.56. Found: C, 59.61; H, 8.54.

2,9-Bis-(*tert*-butyldimethylsilanyloxy)-12,12-dimethyl-5,6-dihydroxy-11,13-dioxobicyclo-[8.3.0]trideca-3,7-diyne ((1*R*,4*R*)-9). To dry CH_2Cl_2 (12 mL) were added VCl_3·3THF (1.37 g, 3.7 mmol) and zinc powder (160 mg, 2.46 mmol) at room temperature, and the mixture was stirred for 30 min and diluted with CH_2Cl_2 (12 mL) and DMF (1.4 mL). Compound (1*R*,4*R*)-**8** (236 mg, 0.48 mmol), dissolved in CH_2Cl_2 (12 mL), was added by syringe pump over 120 min. The mixture was stirred for an additional 4 h and poured into water (30 mL); the organic phase was separated and washed with aqueous Na/K tartrate (40%) and brine. The solvent was removed in vacuo and the crude product purified by column chromatography (petroleum ether/EtOAc, 1:1) to yield 124 mg (52%) of (1*R*,4*R*)-**9** (R_f = 0.91), colorless solid. IR (neat): $\tilde{\nu}$ = 3380, 2931, 2896, 2858, 2251, 1739, 1473, 1372, 1255, 1109, 839, 780 cm^{-1}. ^{1}H NMR: δ −0.04−0.26 (m, 12 H), 0.76−1.03 (m, 18 H), 1.39 (m, 6 H), 4.02−4.17 (m, 4 H), 4.21−4.39 (m, 4 H), 4.41−4.64 (m, 2 H). MS (FI/FD), *m*/*z* (%): 439 (100) [M + $(CH_3)_2CO^+$], 497 (68) [M + H$^+$].

2,9-Bis-(*tert*-butyldimethylsilanyloxy)-12,12-dimethyl-5,6-(thiocarbonyldioxy)-11,13-dioxo-bicyclo-[8.3.0]trideca-3,7-diyne ((1*R*,4*R*)-11). A mixture of diol (1*R*,4*R*)-**9** (73 mg, 0.15 mmol) and *N*,*N*-thiocarbonyldiimidazole (**10**) (79 mg, 0.42 mmol) in 20 mL of dry THF was refluxed for 6 h. The solvent was removed in vacuo, and the crude product was purified by column chromatography (petroleum ether/EtOAc, 5:1) yielding 56 mg (71%) of (1*R*,4*R*)-**11** (R_f = 0.61), yellow oil. IR (neat): $\tilde{\nu}$ = 2956, 2858, 2240, 1825, 1727, 1472, 1347, 1168, 983, 844, 781, 670 cm^{-1}. UV (CH_3CN): λ_{max} (lg ϵ) = 237 nm (4.031). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13 (s, 6 H), 0.14 (s, 3 H), 0.15 (s, 3 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 1.39 (s, 3 H), 1.40 (s, 3 H), 3.99 (dd, ^3J = 9.0 Hz, 5.4 Hz, 1 H), 4.12 (dd, ^3J = 9.0 Hz, 5.4 Hz, 1 H), 4.32 (dd, ^3J = 9.0 Hz, ^5J = 2.0 Hz, 1 H), 4.37 (d, ^3J = 9.0 Hz, 1 H), 5.56 (dd, ^3J = 8.0 Hz, ^5J = 2.0 Hz, 1 H), 5.58 (d, ^3J = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.8 (+), −4.8 (+), −4.7 (+), 18.3 (C_{quat}), 25.7 (+), 27.6 (+), 66.6 (+), 66.7 (+), 74.6 (+), 74.8 (+), 82.4 (+), 82.6 (+), 93.3 (C_{quat}), 94.3 (C_{quat}), 110.9 (C_{quat}), 188.7 (C_{quat}). MS (CI), *m*/*z* (%): 556 (100) [M + NH_4^+].

2,9-Bis-(*tert*-butyldimethylsilanyloxy)-12,12-dimethyl-11,13-dioxo-bicyclo-[8.3.0]trideca-5-en-3,7-diyne ((1*R*,4*R*)-13). To a solution of (1*R*,4*R*)-**11** (40 mg, 74.2 μmol) in 4 mL of dry dioxane was added 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (**12**, 96 μL, 101 mg, 520 μmol), and the reaction mixture was stirred for 4 h at 40 °C. The solvent was removed in vacuo and column chromatography (petroleum ether/EtOAc, 5:1) was performed on the crude product. Yield: 14 mg (41%) of (1*R*,4*R*)-**13** (R_f = 0.95), colorless oil. $[\alpha]^{25}_D$ −79 (*c* 0.67 in CH_3CN). IR (neat): $\tilde{\nu}$ = 2928, 2856, 1824, 1731, 1463, 1378, 1332, 1259, 1109, 1018, 840, 780, 752 cm^{-1}. UV (CH_3CN): λ_{max} (lg ϵ) = 271 nm (4.021). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (s, 6 H), 0.15 (s, 6 H), 0.91−0.99 (m, 18 H), 1.42 (s, 6 H), 4.10−4.15 (m, 2 H), 4.41−4.46 (m, 2 H), 5.94 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.7 (+), −4.7 (+), 18.4 (C_{quat}), 25.8 (+), 28.0 (+), 67.2 (+), 84.5 (+), 86.7 (C_{quat}), 100.3 (C_{quat}), 110.5 (C_{quat}), 123.4 (+). MS (EI, 70 eV), *m*/*z* (%): 73 (100), 75 (24) [Me_2SiOH^+], 347 (88) [$M^+ - Me_2SiC_4H_9$], 348 (25), 462 (8) [M^+]. HRMS $C_{25}H_{42}O_4Si_2$ calcd 462.2621, found 462.2621 ± 1.5 ppm.

2,3-*O*-Isopropylidencyclodec-7-en-5,9-diyne-1,2,3,4-tetraol ((1*R*,4*R*)-14). To a solution of (1*R*,4*R*)-**13** (110 mg, 0.24 mmol) in 20 mL of THF was added TBAF (1.1 mL, 1.1 mmol, 1 M solution in THF), and the mixture was stirred for 90 min at 0 °C, diluted with diethyl ether, washed with brine (three times), and dried over Na_2SO_4. The solvent was removed in vacuo, and column chromatography (petroleum ether/EtOAc, 1:1) gave 16 mg (29%) of (1*R*,4*R*)-**14** (R_f = 0.32), colorless oil. IR (neat): $\tilde{\nu}$ = 3996, 3429, 3428, 2884, 1807, 1730, 1639, 1467, 1354, 1280, 1114, 947, 843 cm^{-1}. UV (CH_3CN): λ_{max} (lg ϵ) = 269 nm (3.926). ^{1}H NMR (400 MHz, CD_3CN): δ 1.41 (s, 6 H), 3.67 (dd, ^3J = 4.6 Hz, 2 H), 4.00−4.05 (m, 2 H), 4.44−4.50 (m, 2 H), 6.05 (s, 2 H). ^{13}C NMR (100 MHz, CD_3CN): δ 28.0 (C12, C13), 66.7 (C1, C4), 85.2 (C2, C3), 87.6 (C6, C9), 100.5 (C5, C10), 111.7 (C11), 124.6 (C7, C8). MS (CI), *m*/*z* (%): 234 (28) [$M^+ - H_2O$], 252 (100) [$M + NH_4^+$]. HRMS $C_{13}H_{15}O_4$ calcd 235.0970, found 235.0969 ± 1.5 ppm.

General Procedure for Cleavage of the Isopropylidene Protecting Group. Enediyne (15 μmol) to be deprotected was dissolved in 1 mL of EtSH and 1 mL of concentrated TFA. The reaction mixture was stirred for 1 h at room temperature; the solvents were removed in vacuo at 0 °C, and the reaction products were used without further purification.

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Supporting Information Available: Structure of compound (1*R*,4*R*)-**6** in crystalline form; experimental procedures for the preparation of compound (1*R*,4*S*)-**13**; kinetic analyses of the thermolysis of (1*R*,4*R*)-**16** and (1*R*,4*R*)-**15**; in vitro cytoxicity cell assay; copies of proton and carbon NMR spectra of compounds **3**, (1*R*,4*S*)-**6**, (1*R*,4*R*)-**6**, (1*R*,4*S*)-**8**, (1*R*,4*R*)-**13**, (1*R*,4*S*)-**13**, and (1*R*,4*R*)-**14**; and copies of proton NMR spectra of compounds **4**, **5**, (1*R*,4*S*)-**9**, (1*R*,4*R*)-**9**, (1*R*,4*S*-)**11**, and (1*R*,4*R*)-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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