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CYCLIC CONJUGATED ENEDIYNES VIA ELIMINATION OF A THIONOCARBONATE IN A LATENT Z-HEX-3-ENE-1,5-DIYNE UNIT

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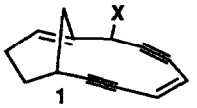
Summary: The common sugar dulcitol is transformed into a hex-1,5-diyne with 3,4-dihydroxyls modified as an acetonide; this serves as a building block for the cyclic ene-diynes and allows mild and efficient introduction of the key ene unit at a late stage in ene-diyne synthesis using the reactive Corey-Winter reagent.

The enediyne family is an important new class of antitumor antibiotics all containing the Z-hex-3-ene-1,5-diyne unit in a novel bicyclo [7.3.1] core, as represented by **1**.[1] The special activity and structures have generated interest in the synthesis of the natural structures, the synthesis of functional models, and the development of synthesis methodology for the key enediyne unit. The trigger for biological activity is thought to be saturation of a bridgehead alkene unit (calicheamicin, esperamicin) or opening of an angular epoxide (dynemicin).[1] Construction of the delicate enediyne unit is required for a complete synthesis, and also may serve as an alternative chemical trigger which initiates the cascade of thermal reactions resulting in DNA damage. Mild techniques for the preparation of this unsaturated unit would be valuable.[2]

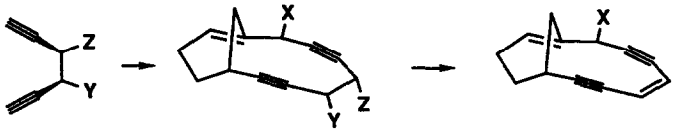
common core structure for the enediyne antibiotics



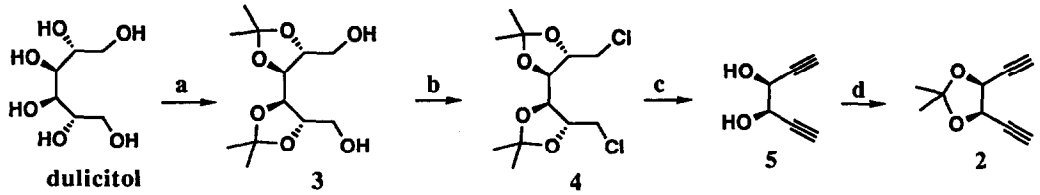
1

X = N or O linked to DNA association unit

One possibility is to develop a latent Z-hex-3-ene-1,5-diyne, the geometry of which might facilitate a key cyclization step to form the strained [7.3.1] bicyclo system. While one might imagine introducing one of the alkyne units at a late stage, the introduction of the alkene unit is more attractive based on the variety of general techniques for alkene synthesis by elimination. Two examples of this strategy have appeared in the literature, oxidative introduction of the ene unit using a phenyl substituent for activation[3a] and enediyne formation by anthraquinone reductive elimination-tautomerization.[3b]



With the goal of a low temperature technique operating under relatively neutral conditions, we considered variations on the Corey-Winter reaction for direct elimination of 1,2-diols via thionocarbonates.[4] We chose *meso*-

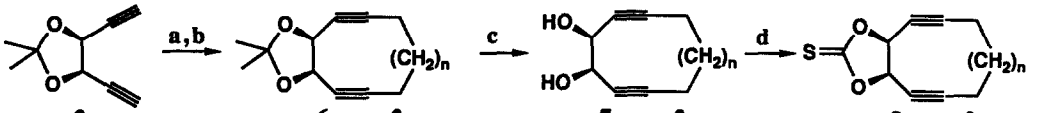


dulicitol 3 4 5 2

(a) 10% camphor sulfonic acid, 4 mol-eq 2,2-dimethoxypropane (DMP), benzene, Δ, 17.5 h, 57%.
(b) CCl_4, 4 mol-eq Ph_3P, Δ, 10 h, 73%. (c) 10-12 mol-eq LDA, THF, -78 °C, 3 h, 0 °C, 17 h 72-76%.
(d) 10% camphor sulfonic acid, 6 mol-eq DMP, benzene, 20 °C, 8.3 h, 96% yield of **2**.

1,5-hexadyne-3,4-diol acetonide (**2**) as our starting reagent. It was prepared from dulicitol,a readily available inexpensive sugar, by a four-step procedure[5] which is amenable to 100-g scale. The product diyne **2** was obtained as a colorless liquid after chromatography and short path distillation.[6]

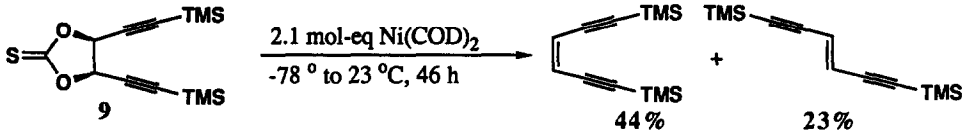
A simple approach to cyclic ene-diynes involves alkylation of the dianion of **2**, for example with 1,n-diiodoalkanes, followed by conversion to the diol **7**, and then the thionocarbonate, **8**. Fragmentation of thionocarbonates to give alkenes is well-established as the Corey-Winter reaction,[4] and can also be accomplished with Ni(0).[7]



2 **6a: n=2** **6b: n=3** **7a: n=2** **7b: n=3** **8a: n=2** **8b: n=3**

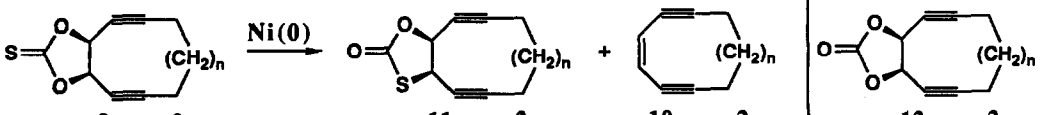
(**a**) 2 mol-eq *n*-BuLi, THF, -78°-0 °C, 25 min. (**b**) 2-10 mol-eq HMPA, 1.2 mol-eq $ICH_2(CH_2)_nCH_2I$, 0°-23 °C, 12 h, **6a**: 40%; **6b**: 53%. (**c**) 10% camphor sulfonic acid, MeOH, water, Δ, 2 h, **7a**: 79%; **7b**: 95%. (**d**) 1-1.2 mol-eq 1.1'-thiocarbonyldiimidazole, toluene, Δ, 5-15 min, **8a**: 92%; **8b**: 94%.

The first method tested for disassembling of the thionocarbonate was based on earlier general results with Ni(0).[8] Ni(1,5-cyclooctadiene)$_2$ [Ni(COD)$_2$] reacts with thionocarbonates in various solvents at ca -30 °C to give a black solid which then decomposes upon warming to give alkenes in high yield.[7] Initially, the reaction of Ni(COD)$_2$ with thionocarbonate **9** was examined. While reaction occurred at a low temperature (-30 °C), and the yield of alkene was good (67% after isolation), a mixture of Z- (44%) and E- isomers (23%) was produced. The reaction of Ni(COD)$_2$ with simple acyclic thionocarbonates was reported to proceed stereospecifically.[7]



9 44% 23%

The reactions of **8a** and **8b** with Ni(COD)$_2$ were studied systematically. Treatment of **8b** with Ni(COD)$_2$ (2 mol-eq) at -78 °C and slow warming to 19 °C over 21 h led to the sudden appearance of a black precipitate when the temperature reached ca. -30°C, and to the formation of enediyne **10b** in 16% yield with no recovered unreacted thionocarbonate. Expecting that the black precipitate was a precursor to **10b**, H_2S was added before the isolation procedure in order to separate the Ni as NiS. Under these conditions the yield of **10b** increased to 48%.[8] The use of just 1 mol-eq of Ni(COD)$_2$ led to a mixture of **10b** (23% yield), thiolocarbonate **11b** (37% yield), and recovered starting thionocarbonate (8%). Apparently, Ni(COD)$_2$ facilitates the isomerization of the thionocarbonate to the thermodynamically more stable thiolocarbonate. We were able to demonstrate that thiolocarbonate **11b** is converted to enediyne **10b** in comparable yield upon treatment with Ni(COD)$_2$, but at a slower rate. Somewhat revealing was the result when **8b** was treated with 1.1 mol-eq of Ni(COD)$_2$ and quenched with oxygen just after reaching 20 °C; enediyne **10b** and thiolocarbonate **11b** (16% and 26% yields, respectively) were isolated along with the oxidation product, the carbonate **12b** (10% yield). Similar experiments with **8a** were less successful. In the best example, treatment of **8a** with 1.0 mol-eq of Ni(COD)$_2$ gave **10a** in 8% yield accompanied by **11a** (22%), **12a** (3%) and the Bergman rearrangement[9] product, tetralin (5%). It was also determined that the enediynes

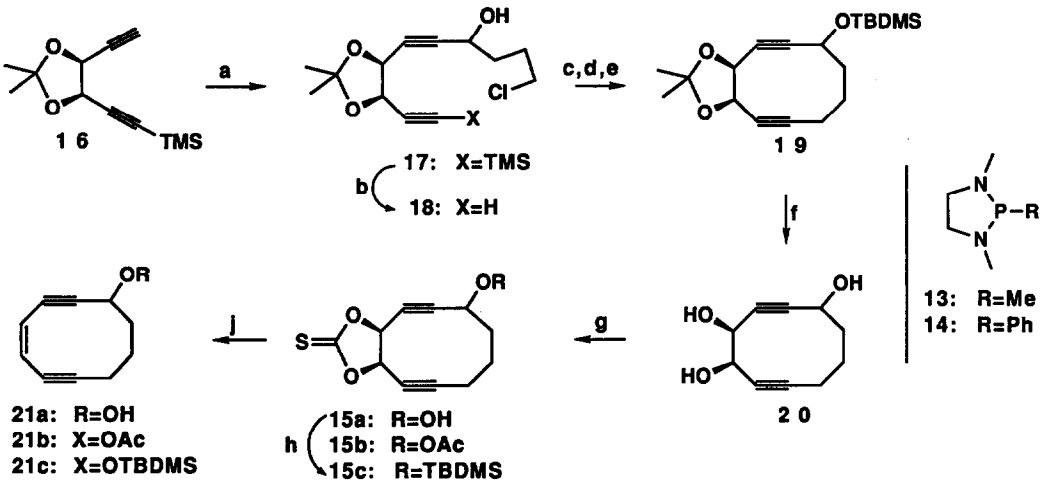


8a: n=2 **8b: n=3** **11a: n=2** **11b: n=3** **10a: n=2** **10b: n=3** **12a: n=2** **12b: n=3**

are reactive with the Ni(0) reagent, apparently suffering polymerization upon warming to 20 °C.

Attention was turned to the Corey-Winter reaction, conversion of thionocarbonates to alkenes with phosphines.[4] The optimum reaction would occur well below room temperature, requiring more electron-rich phosphines such as 1,2,3-trimethyl-1,3-diaza-2-phospholidine (**13**) or the 2-phenyl analog (**14**). While both phosphines successfully produce the enediynes from **8a** and **8b**, reagent **13** reacts at -20 ° to -5 °C and reagent **14** requires 20-25 °C for reasonable rates. The temperature difference is significant when producing more reactive enediynes. Using reagent **13**, the yields for formation of **10a** and **10b** were 65-80%.

With the need to attach a DNA delivery agent in mind, we prepared the series of hydroxyl-substituted versions, **15a-c**. The acetylide anion of mono-TMS derivative **16**[10] added to 4-chlorobutyraldehyde to give chloro alcohol **17**. Desilylation freed the other alkyne, in **18**. Protection of the hydroxyl group, conversion to the primary iodide, and base-induced ring closure produced **19**. A sequence of acetonide hydrolysis and thionocarbonate formation led to **15c**. The elimination process (Corey-Winter reaction) was optimized with **15c** (one of the two possible diastereoisomers; both gave the same result).[11] While several solvents are successful (THF, DMF, toluene, MeCN), a simple and reproducible procedure was developed in anhydrous ether.[12] After the usual extractive isolation procedure followed by simple chromatography on silica gel, the enediyne, **21c** was obtained in 84% yield. The free alcohol **21a**[13], which proved to be somewhat less stable than **21b**[13] or **21c**, was obtained by desilylation of **21c** or directly from **15a**.



(**a**) i. 1.0 mol-eq *n*-BuLi, THF, -70 °C, 1 h; ii. 1.5 mol-eq $Cl(CH_2)_3CHO$, -55 °C, 20 h, 82% (86%conversion). (**b**) 1.0 mol-eq *n*-$Bu_4NF{\cdot}H_2O$, THF, -70° to 23 °C, 0.5 h, 100%. (**c**) 1.3 mol-eq TBDMS•triflate, 1.5 mol-eq 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 82%. (**d**) 20 mol-eq NaI, acetone, dark, 55 °C, 45 h, 92%. (**e**) i. 1.1 mol-eq LDA, THF, -78 °C, 1.5 h; ii. 5 mol-eq HMPA, -78° to 23 °C, 21 h, 85%. (**f**) 3.0 mol-eq camphor sulfonic acid, 4:1 MeOH:H_2O, 23 °C, dark, 165 h, 71%. (**g**) 1.0 mol-eq 1,1'- thiocarbonyldiimidazole, THF, 23 °C, dark, 48 h, 57%. (**h**) 2.0 mol-eq TBDMS•triflate, 2.5 mol-eq 2,6-lutidine, CH_2Cl_2, 0 °C, 2.3 h, 85%. (**j**) 2.8 mol-eq **13**, ether, 0 °C, 4 h, 84%.

Comparing **21a**, with the propargylic hydroxyl group, to related enediynes[1a] suggests a significantly higher reactivity in the Bergman cyclization. For example, the simple enediyne, cyclodeca-1,5-diyne-3-ene has a half lifetime of 18 h at 37 °C[2c], while **21a** disappears with a half lifetime of 4.5 h at 37 °C in deuterobenzene, with an excess of 1,4-cyclohexadiene present. However, the reaction is not simple, and at least five products appear in significant amounts. The attachment of **21a** through tethers to analogs of netropsin, a DNA minor groove binder, has been completed and a full description of the DNA cleaving ability of derivatives of **21a** will be reported in due course.[14]

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7. M. F. Semmelhack and R. D. Stauffer, *Tetrahedron Lett.*, **1973**, 2667.

8. Thionocarbonate **8b** (43.4 mg, 0.194 mmol) in THF (1 ml, dry, degassed) was added via syringe to $Ni(COD)_2$ (114.3 mg, 2.1 mol-eq) in THF (4 ml) at -78 °C. The temperature was allowed to rise to 20 °C slowly over 50 h. Then H_2S was bubbled in, the resulting black slurry was filtered through 2 cm of silica gel in a glass frit, the filtrate was concentrated on a rotary evaporator from a 0 °C bath, and the product was purified by chromatography on silica gel (98:2 pentane:ethyl acetate). Enediyne **10b**[1a] was obtained in 48% yield.

9. R. Bergman, *Acc. Chem. Res.*, **1973**, *6*, 25.

10. Compound **16** was prepared in 20-30% yield from **2** by deprotonation with *n*-butyl lithium (1 mol-eq) in pentane at 0 °C followed by addition of TMSCl (2 mol-eq). The other products of the reaction, unreacted **2** (50-60%) and the bis(trimethylsily) derivative (15-20%) could be recycled.

11. The diastereomers were separated by flash chromatography on silica gel (9:1 hexane:ethyl acetate).

12. Reagent **13** (210 ml, 2.8 mol-eq) was added via syringe over 1 min. to thionocarbonate **15c** (180.5 mg, 0.537 mmol) in dry ether (5.3 ml) under Ar at 0 °C, the mixture was allowed to stir at -5 to 0 °C for 4 h, and then the reaction was quenched by adding 3 ml water. Rapidly (ca. 1 h) the reaction mixture was extracted with ether, the ethereals were dried over Na_2SO_4, and the crude product was purified by flash chromatography on silica gel (98:2 n-pentane:ether). Enediyne **21c** was obtained as a pale yellow oil in 83.5% yield. The product decomposes only slowly at room temperature and can be stored for long periods of time at < -20 °C.

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