Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Synthesis Of Fully-Substituted Enediynes by the Corey-Winter Reaction

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Published online: 17 Sep 2007.

To cite this article: D. Crich , A. B. Pavlovic & D. J. Wink (1999) Synthesis Of Fully-Substituted Enediynes by the Corey-Winter Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:3, 359-377, DOI: 10.1080/00397919908085778

To link to this article: http://dx.doi.org/10.1080/00397919908085778

SYNTHETIC COMMUNICATIONS, 29(3), 359-377 (1999)

# SYNTHESIS OF FULLY-SUBSTITUTED ENEDIYNES BY THE COREY-WINTER REACTION

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Functionalized alkynes are oxidized to the corresponding α-diketones with catalytic $RuO_4$ and $NaIO_4$. Treatment of these diones with metal acetylenides then gives mixtures of *erythro*- and *threo*-1,5-hexadiyne-3,4-diols with good *erythro*-selectivity. Reaction of the *erythro*-diols with thiophosgene in the presence of *n*-BuLi or KH as base results in the formation of the corresponding cyclic thionocarbonates in moderate to good yields. Reaction of the cyclic thionocarbonates with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine at 40 °C results in the formation of enediynes substituted at the 3- and 4-positions. As anticipated fom the mechanism of the pericyclic syn-elimination, the *erythro*-thionocarbonates provide pure *Z*-enediynes.

## Introduction

The continually expanding enediyne group of natural products, as exemplified by the original members calicheamicin $\gamma_1$' and esperamicin, are some of the most potent antitumor antibiotics known. This potency is thought to arise from their ability to achieve double stranded DNA cleavage by a sequence of reactions involving activation, Bergman rearrangement[1] to 1,4-benzenediyls, and hydrogen atom abstraction from the sugar-phosphate backbone of DNA.

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The highly unusual molecular architecture of these antibiotics and their novel mode of action and potency stimulated a great deal of ongoing interest in the synthesis community which rapidly resulted in several landmark total syntheses.[2-7] The associated renewed interest in the Bergman cyclization has also resulted in the use of enediynes as triggers for interesting series of cascade radical cyclizations.[8] The enediyne moiety also features prominently in the synthetic materials field.[9] Perusal of the numerous reviews on the chemistry of the enediynes[10-15] reveals that the field is dominated by palladium catalyzed cross coupling reactions of alkynes with vinyl halides, or their equivalents, as a rapid convergent entry into the 3-ene-hexa-1,5-diyne moiety. Exceptions are the use of the Ramburg Backlund reaction,[16] carbenoid couplings,[17] Norrish type II photoeliminations,[18] DDQ oxidation of 2-(4-anisyl)-1,5-hexadiynes,[19], retro Diels-Alder reactions,[20,21] and various eliminations from 3-substituted-1,5-hexadiynes.[10]

In the context of an ongoing synthetic and mechanistic investigation we became interested in the synthesis of fully substituted enediynes, carrying functional appendages at the 3, and 4-positions. Diederich and coworkers have reported the synthesis of representatives of this class by means of palladium (0) mediated coupling of alkynes to derivatives of mucobromic and mucochloric acid,[22] but we were interested in developing a protocol which did not rely on transition mediated coupling reactions, nor require the synthesis of the *cis*-vicinal dihalides or their analogs. In particular, we were interested in a strategy involving the double nucleophilic attack of acetylide anions on α-diketones,[23] followed by derivatization of the diol as a thionocarbonate, and eventual Corey-

Winter elimination.[24-26] This stereospecific fragmentation reaction has mostly been applied for the synthesis of 1,2-disubstituted and strained cyclic alkenes.[27,28] Nevertheless, we were encouraged in our endeavors by a report on the synthesis of simple enediynes, from the Semmelhack group,[29] by application of the Corey-Winter protocol to carbohydrate derived 1,5-diyn-3,4-diols, and by several reports of the smooth preparation of tetrasubstituted alkenes using this reaction.[24,30-32]

**Results and Discussion**

We began our study by conversion of 2-butyn-1,4-diol to the derivatives **1** and **2** by standard means. These were then oxidized to the functionalized diones **3** and **4** in 78 and 87% yields, respectively, with $NaIO_4$ and catalytic $RuO_4$.[33] In a similar manner 2-butyn-1-ol was tritylated giving **5**, which was converted to **6** in 89% yield by the catalytic oxidation protocol. Diones **3** and **4** were allowed to react with two molar equivalents of phenylacetylenyl cerium dichloride or TMS-acetylenyl cerium dichloride in THF with the results indicated in Table 1 (entries 1 - 3). One of these reactions, that between **4** and TMS-acetylenyl cerium dichloride (Table 1, entry 3), was extremely selective (25:1) in favor of the *erythro*-diol **11** whose stereochemistry was assigned crystallographically (Fig. 1). The other two (Table 1, entries 1 and 2) show a much smaller preference for the *erythro*-isomers (**7** and **8**), whose stereochemistry is based on analogy. A further example involved reaction of phenylacetylenyl cerium dichloride with dione **6**. In this case (Table 1, entry 4) good selectivity for the *erthyro*-diol **13** was observed, with stereochemistry being assigned by nOe difference spectroscopy on a subsequent derivative (vide infra). We note that for the diastereomeric pairs **11/12**, and **13/14**, whose

stereochemistries were rigorously assigned, the *threo*-isomer was found to be slower moving on silica gel chromatography. The same was found to be true for the pairs **7/9**, and **8/10**, which lends some weight to the stereochemical assignments of these pairs.

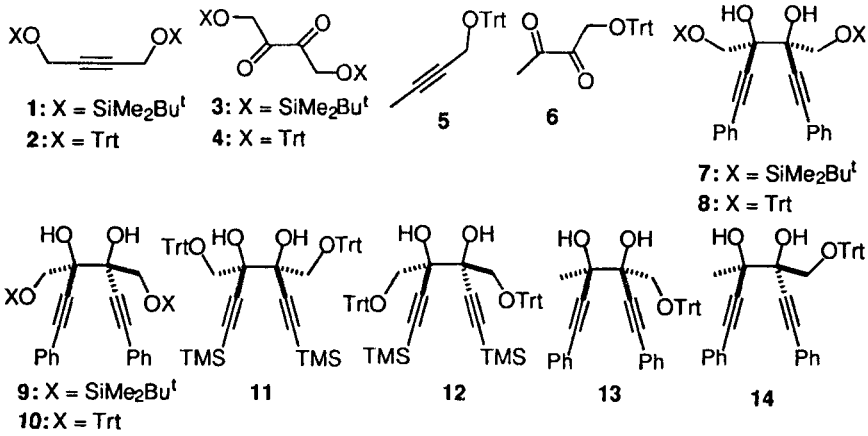
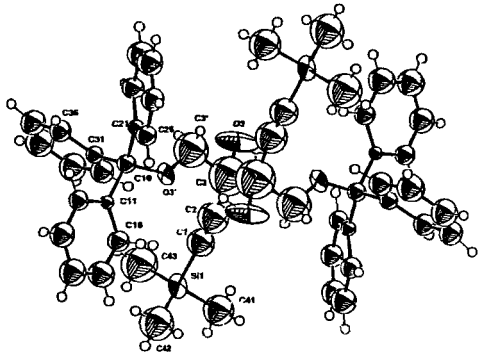



Table 1. Reaction of Diones with Metal Acetylides in THF

| Entry | Dione | Alkyne Subs. | Overall Yield (%) | Products (ratio) |
|---|---|---|---|---|
| 1 | **3** | Ph | 44 | **7:9** = 3:1 |
| 2 | **4** | Ph | 72 | **8:10** = 2:1 |
| 3 | **4** | TMS | 64 | **11:12** = 25:1 |
| 4 | **6** | Ph | 85 | **13:14** = 7:1 |

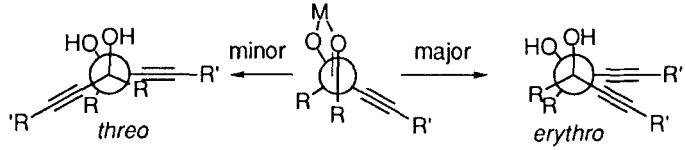
The selectivities observed in these additions to α-diketones are consistent with the operation of a Cram chelation model,[34] in which the $CH_2OCPh_3$ or $CH_2OTBDMS$ moieties are the large groups, with preferential attack of the second acetylide adjacent to the first one (Scheme 1). In full agreement with this

Fig 1. X-Ray crystal Structure of **11**



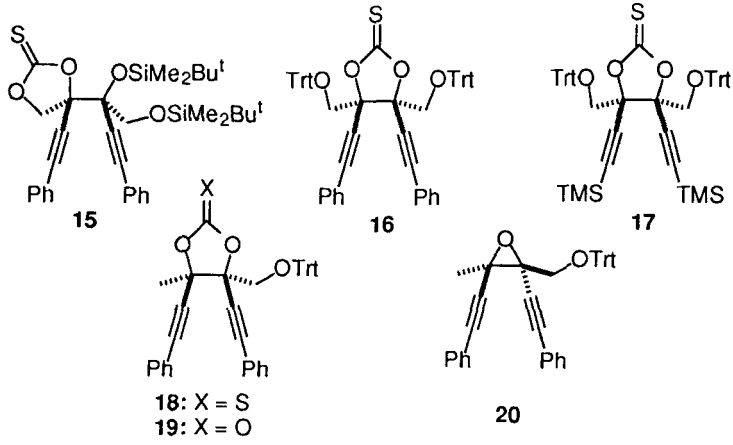
hypothesis and the smaller A-value of a TMS group (10.5 kJ.mol$^{-1}$)[35] than a phenyl group (11.7 kJ.mol$^{-1}$),[35] maximum *erythro* -selectivity is seen for attack of the cerium salt of TMS acetylene on dione **13** when the steric interactions in the transition state leading to the *erythro*-isomer are minimized (Scheme 2; Table 1, entry 8). A more extensive survey of conditions and additives was not conducted as the *erythro*- isomers are generally more useful than the *threo*-series.

Scheme 1




Treatment of diol **7** with KH, followed by thiophosgene resulted in the isolation of cyclic thionocarbonate **15** as the only significant isolable product (Table 2, entry 1). Evidently, this product arises from a dynamic system with migration of TBDMS[36] groups and thioacylation on the less hindered alkoxide. No such problem was anticipated or observed with the corresponding trityl protected derivative **8** when the symmetric thionocarbonate was isolated in good

yield (Table 2, entry 2). Subsequently, diols **11**, and **13** were also converted to the corresponding cyclic thionocarbonates in satisfactory yield (Table 2, entries 3 and 4). However, we note that with the bistrimethylsilyl system (**11**) much higher yields were obtained when butyllithium was used as base in place of potassium hydride (Table 2, entry 3). We also draw attention to the formation of two minor byproducts formed in the derivatization of **13**. The less important one (7%), which was not obtained pure, is tentatively identified as the cyclic carbonate **19** given that its $^{1}H$ and $^{13}C$ NMR spectra closely resemble those of **18**, except that the resonance for the thiocarbonyl carbon has been replaced by a signal corresponding to a carbonate type carbonyl carbon at δ 152.3 in the $^{13}C$ spectrum. We speculate that this product is formed by attack of thiophosgene on **18**, leading to salt which is hydrolyzed on work up (Scheme 2). $^{13}C$-NMR spectroscopy of the thiophosgene employed revealed a unique signal at δ 170.4 ppm ($CDCl_3$)[37] and so ruled out the possibility of contamination by phosgene. The more significant byproduct (20%) was identified as an epoxide (**20**). We

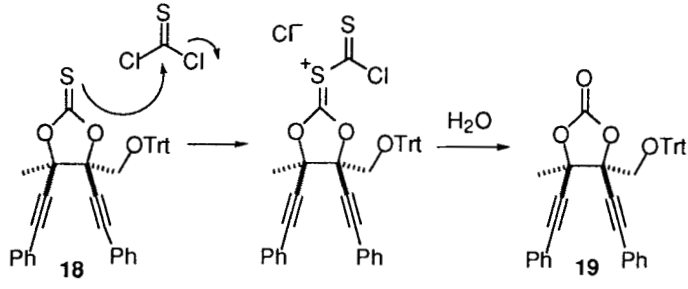


suggest that this product is formed, as indicated in Scheme 3, by a competing inversion process following the initial thioacylation. No such products were obtained in the reactions of diols **7**, **8**, and **11** with thiophosgene suggesting that the increased steric bulk shielded the thiocarbonyl group of the product cyclic thiocarbonates and retarded the type of backside attack advanced in Scheme 3.

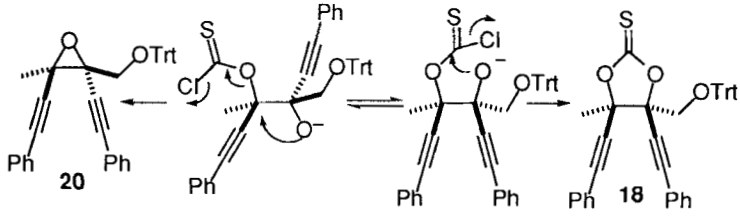
Table 2. Formation of Cyclic Thionocarbonates

| Entry | Diol | Base | Thionocarbonate |
|---|---|---|---|
| 1 | **7** | KH | **15** (68) |
| 2 | **8** | KH | **16** (68) |
| 3 | **11** | BuLi | **17** (66) |
| 4 | **13** | KH | **18** (53) |

Scheme 2




Scheme 3



Finally, with a range of cyclic thionocarbonates in hand, we turned to the elimination reaction. These reactions were conducted with the diazaphospholidine **21**[26] as reagent and solvent at 45 °C. As is evident from Table 3, all proceeded in moderate to good yield. Moreover, and in full agreement with the usual stereospecific syn-elimination mechanism for this reaction, isomerically pure enediynes were produced. The configuration of enediynes **24** was not established rigorously but is assigned according to the syn-elimination mechanism. Enediyne **23** was converted to the diol **26** by treatment with concentrated HCl in 89% yield. The spectral characteristics of **26** were entirely in accord with the assigned structure, yet markedly different from those of the E-isomer described by Diederich.[22] Diol **26**, and its immediate precursor **23** were therefore assigned the Z-configuration in full agreement with the stereospecific syn-elimination mechanism for the Corey-Winter reaction. The *Z*-geometry of

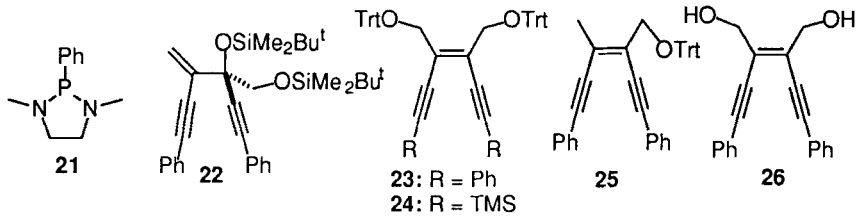



Table 3. Formation of Enediynes from Cyclic Thionocarbonates

| Entry | Substrate | Product |
|---|---|---|
| 1 | **15** | **22** (60) |
| 2 | **16** | **23** (60) |
| 3 | **17** | **24** (57) |
| 4 | **18** | **25** (69) |

the disymmetric enediyne **25**, established through the obvious NOE difference correlation, again confirms the syn-elimination process.

In summary we have provided a three step protocol for the synthesis of fully substituted enediynes from α-diketones, which themselves are prepared in high yield from readily available acetylenes. Given that the more standard palladium catalyzed couplings of alkynes to vicinal dihaloalkenes require, for all but the simplest cases, the prior preparation of isomerically pure of the dihaloalkenes, this method deserves consideration for the synthesis of such ramified enediynes.



## Experimental

**General.** Melting points were recorded on a Thomas hotstage microscope and are uncorrected. Unless otherwise noted, $^{1}H$ and $^{13}C$ spectra were run in $CDCl_3$ at 300 and 75 respectively. $^{1}H$ and $^{13}C$ chemical shifts are downfield from tetramethylsilane as internal standard; coupling constants are in Hz. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. THF was distilled, under $N_2$, immediately prior to use from sodium benzophenone ketyl. Ether refers to diethyl ether. All extracts were dried over $MgSO_4$ and concentrated under vacuum. Microanalyses were conducted by Midwest Microanalytical, Indianapolis.

**1,4-Bis (*tert*-butyldimethylsiloxy)-2-butyne (1).** To a stirred solution of 2-butyn-1,4-diol (4 g, 46.5 mmol), $Et_3N$ (13.6 $cm^{-3}$, 97.6 mmol), and DMAP (0.227 g, 1.86 mmol) in dichloromethane (100 $cm^{-3}$) at 0 °C, TBDMSCl (14.7 g, 97.6 mmol) in dichloromethane (50 $cm^{-3}$) was added dropwise. The reaction mixture was then stirred at room temperature for 5h before the solvent was removed by rotary evaporation and the residue extracted with ethyl acetate. After concentration the extracts were chromatographed on silica gel (gradient elution with hexane and ethyl acetate) to afford the title compound (14.2 g, 97.2%) as a

clear syrup. $\delta_H$: 4.34 (4 H, s); 0.91 (18 H, s); 0.12 (12 H, s); $\delta_C$: 83.2, 51.7, 25.7, 18.2, -5.3. Anal. Calc. for $C_{16}H_{34}O_2Si_2$: C, 61.08; H, 10.89 %. Found: C, 61.30; H, 11.01 %.

**1,4-Bis-(triphenylmethoxy)-2-butyne (2).** A mixture of trityl chloride (64.76 g, 0.232 mol), DMAP (0.709 g, 5.8 mmol), pyridine (19 $cm^{-3}$, 0.235 mol), and butyn-1,4-diol (10 g, 0.116 mol) was dissolved in dichloromethane (250 $cm^{-3}$) and stirred at room temperature until TLC indicated complete reaction (ca. 6h). Flash chromatography (1:1 to 1:2 hexane/dichloromethane) gave the crystalline bistrityl ether (47.07 g, 71%). mp. 212 °C (dichloromethane/ petroleum ether); $\delta_H$: 7.55 (12 H, d, *J* 8.5); 7.29-7.39 (18 H, m); 3.67 (4 H, s); $\delta_C$: 143.3; 128.6; 127.9; 127.1; 87.4; 82.0; 53.3. Anal. Calc. for $C_{42}H_{34}O_2$: C, 88.39; H, 6.00 %. Found: C, 88.11; H, 5.93 %.

**1-(Triphenylmethoxy)-2-butyne (5).** A mixture of 2-butyn-1-ol (3g, 42.8 mmol), trityl chloride (11.93 g, 42.8 mmol), pyridine (3.5 $cm^{-3}$, 43.2 mmol), and DMAP (0.261 g, 2.1 mmol) was dissolved in dichloromethane (80 $cm^{-3}$) and stirred in room temperature until TLC indicated complete reaction. After concentration, flash chromatography on silica gel (1:1 hexane/ dichloromethane) afforded the white, crystalline product (9.28 g, 89%). mp. 104-105 °C (dichloromethane/petroleum ether); $\delta_H$: 7.54 (6 H, d, *J* 7.1), 7.28-7.38 (9 H, m), 3.77 (2 H, d, *J* 2.3), 1.89 (3 H, s); $\delta_C$: 143.6, 128.6, 127.9, 127.1, 87.2, 81.6, 75.6, 53.4, 3.8. Anal Calc. for $C_{23}H_{20}O$: C, 88.43; H, 6.45 %. Found: C, 88.26; H, 6.45 %.

**General Protocol A. Oxidation of Alkynes to 1,2-Diones: 1,4-(*tert*-Butyldimethylsiloxy)-2,3-butanedione (3).** Alkyne **1** (4.63 g, 14.73. mmol) was dissolved in a 1:1 mixture of MeCN and $CCl_4$ (138 $cm^{-3}$) and treated with $NaIO_4$ (12.92 g, 60.39 mmol) dissolved in water (103 $cm^{-3}$), followed by $RuO_2$ (0.059 g, 0.44 mmol). The reaction mixture was vigorously stirred at room temperature until completion, as determined by TLC (90 % hexane, 10 % ethyl acetate), when water (348 $cm^{-3}$) was added to dissolve inorganic salts. The organic layer was separated and the water layer was extracted with dichloromethane (2 x 100 $cm^{-3}$). The organic layers were combined, washed with diluted sodium hydroxide (200 $cm^{-3}$), and brine (150 $cm^{-3}$), and, after drying, filtered through Celite and evaporated to give the crude

diketone **3** (3.98 g, 78 %) as a yellow syrup, which was used as such in the next step. $\delta_H$: 4.67 (4 H, s), 0.88 (18 H, s), 0.06 (12 H, s); $\delta_C$: 198.2, 66.2, 25.7, 18.3, -5.6. Anal. Calc. for $C_{16}H_{34}O_4Si_2.{}^1/_2H_2O$: C, 54.04; H, 9.92 %. Found: C, 54.46; H, 10.06 %.

**1,4-Bis-(triphenylmethoxy)-2,3-butanedione (4).** Prepared from **2** according to general protocol A. A yellow solid (87%) mp. 199-201 °C (dichloromethane/petroleum ether) with loss of water of crystallization at about 175 °C; $\delta_H$: 7.26-7.49 (30 H, m), 4.22 (4 H, s); $\delta_C$: 196.0, 142.9, 128.5, 128.0, 127.3, 87.6, 66.5. Anal. Calc. for $C_{42}H_{34}O_4.{}^1/_2H_2O$: C, 82.46; H, 5.76 %. Found: C, 82.46; H, 5.57 %.

**1-Triphenymethoxy-3,4-butanedione (6).** A light yellow solid (75%) prepared from **5** by protocol A. mp.110-111 °C (diethyl ether/petroleum ether);. $\delta_H$: 7.48 (6 H, d, *J* 6.0), 7.27-7.36 (9 H, m), 4.38 (2 H, s), 2.26 (3 H, s); $\delta_C$: 197.2, 193.9, 143.1, 128.5, 128.0, 127.3, 87.4, 66.0, 23.8. Anal. Calc. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85 %. Found: C, 80.14; H, 5.83 %.

**General Protocol B. Addition of Cerium Acetylides to Diones.** $CeCl_3.7H_2O$ (5.81 g, 15.6 mmol) is placed in a round bottom flask and dried at 100-110 °C overnight, under high vacuum. After cooling to 0 °C, THF (48 $cm^3$) is added and the heterogeneous mixture is then stirred at room temperature for 2h. The suspension is then cooled to –78 °C and lithium phenylacetylide (15.6 mmol) in THF (31 $cm^{-3}$) is added via a cannula. After 0.5 h, the dione (6.0 mmol) in THF (12 $cm^{-3}$) is added dropwise and the reaction mixture was stirred for 4 h before quenching with dilute aqueous ammonium chloride (20 $cm^{-3}$) at – 78 °C. The reaction mixture is allowed to warm to room temperature and filtered through Celite, and the cake washed with ethyl acetate. The organic layer is separated and the water layer extracted with ethyl acetate and the combined organic layers are dried and concentrated. The products are isolated by silica gel chromatography.

***erythro*- and *threo*-3,4-Bis(*tert*-butyldimethylsiloxy)methyl-3,4-dihydroxy-1,6-diphenyl-1,5-hexadiyne (7) and (9).** Prepared from **3** by protocol B (44%) as a 3/1 mixture of *erythro*/*threo* isomers. *Erythro* (**7**): white crystalline solid mp. 86-87 °C (diethyl ether and hexane); $\delta_H$: 7.45-7.47 (4 H, m), 7.31- 7.33 (6 H, m), 4.91 (2 H, s), 4.36 (2 H, d, *J* 9.6), 4.00 (2 H, d, *J*

9.6), 0.94 (18 H, s), 0.17 (12 H, d, *J* 2.7); $\delta_C$: 131.8, 128.3, 128.1, 122.6, 88.6, 86.1, 74.4, 69.1, 25.7, 18.1, -5.5. Anal. Calc. for $C_{32}H_{46}O_4Si_2$: C, 69.78; H, 8.42 %. Found: C, 69.68, H 8.52 %. The minor, *threo*-isomer (**9**) is identified in the reaction mixture by diagnostic signals in the $^1H$ and $^{13}C$ NMR spectra. $\delta_H$: 4.83 (2 H, s), 4.42 (2 H, d, *J* = 10.3), 4.05 (2 H, d, *J* 10.3); $\delta_C$: 131.6, 128.3, 128.1, 122.4, 88.0, 86.3, 74.7, 69.9, 25.7, 18.3, -5.5.

***erythro-* and *threo*-3,4-Dihydroxy-3,4-di(triphenylmethoxymethyl) -1,6-diphenyl-1,5-hexadiyne (8) and (9).** A mixture of 1.6/1 *erythro-* and *threo* diastereomers were prepared in 73% yield by protocol B, and separated chromatographically. *Erythro*-diol (**8**): mp. 279-280 °C (dichloromethane/petroleum ether); $\delta_H$: 7.50-7.53 (12 H, m), 7.33-7.7.38 (10 H, m), 7.19-7.27 (18 H, m), 4.84 (2 H, s), 3.78 (2 H, d, *J* 4.3), 3.71 (2 H, d, *J* 4.3); $\delta_C$: 142.9, 132.0, 128.5, 128.0, 127.2, 122.3, 88.4, 87.9, 86.7, 74.4, 68.6. Anal. Calc. for $C_{58}H_{46}O_4$: C, 86.32; H, 5.75 %. Found: C, 86.40; H, 5.82 %. *Threo*-diol (**9**): mp 85-87 °C; $\delta_H$: 7.37 (12 H, d, *J* 4.7), 7.28 (18 H, m), 4.54 (2 H, s), 3.84 (2 H, d, *J* 9.4), 3.75 (2 H, d, *J* 9.2); $\delta_C$: 143.2, 131.8, 128.7, 128.0, 127.0, 122.2, 87.6(2), 86.3, 75.3, 69.1. anal. Calcd for $C_{58}H_{46}O_4$: C, 86.32; H, 5.75 %. Found: C, 86.25; H, 5.89 %.

***erythro-* and *threo*-3,4-Dihydroxy-3,4-di(triphenylmethoxymethyl) -1,6-di(trimethylsilyl)-1,5-hexadiyne (11) and (12).** A mixture of 25/1 *erythro-* and *threo*-isomers prepared according to protocol B in 64% yield. *Erythro*-diol (**11**): mp 250-251 °C (dichloromethane/petroleum ether); $\delta_H$: 7.51 (12 H, d, *J* 8.2), 7.23-7.33 (18 H, m), 4.34 (2 H, s), 3.69 (2 H, d, *J* 8.6), 3.54 (2 H, d, *J* 7.3), 0.20 (18 H, s); $\delta_C$: 143.1, 128.6, 127.9, 127.2, 104.3, 91.6, 87.6, 74.3, 67.6, -0.03. Anal. Calc. for $C_{52}H_{54}O_4Si_2$: C, 78.15; H, 6.81 %. Found: C, 77.91; H, 6.83 %. The minor *threo*-isomer (**12**) was identified by diagnostic signals at: $\delta_H$ 3.79 (2 H, s), 3.67 (2 H, d, *J* 8.1), 3.59 (2 H. d, *J* 8.1) in the $^1H$-NMR spectrum, and at $\delta_C$ 143.1, 128.7, 127.8, 103.7, 91.3, 87.2, 74.9, 67.7, -0.3 in the $^{13}C$-NMR spectrum.

***erythro-* and *threo*-3,4-Dihydroxy-4-methyl-3-(triphenylmethoxy-methyl)-1,6-diphenyl-1,5-hexadiyne (13) and (14).** Prepared from **6** by protocol B in 85% yield as a 7/1 *erythro/threo* mixture. The *erythro*-isomer (**13**) could be isolated pure by chromatography on silica gel. (**13**): mp 167-168

°C (diethyl ether/petroleum ether); $\delta_H$: 7.57 (6 H, d, *J* 7.0), 7.50 (4 H, d, *J* 7.0), 7.21- 7.37 (15 H, br. m), 3,75 (1 H, d, *J* 8.7), 3.74 (1 H, s), 3.62 (1 H, d, *J* 8.8), 3.07 (1 H, s), 1.71 (3 H, s); $\delta_C$: 143.2, 131.8, 131.7, 128.6, 128.3, 127.9, 127.2, 122.3, 122.2, 89.8, 88.2, 87.7, 86.6, 85.2, 75.3, 73.7, 67.8, 24.6. Anal. Calc. for $C_{39}H_{32}O_3$: C, 85.37; H, 5.88 %. Found: C, 84.98; H, 5.99 %. The minor *threo*-diol (**14**) was identified by diagnostic signals at: $\delta_H$: 4.08 (1 H, s), 3.68 (1 H, d, *J* 7.1), 3.82 (1 H, d, *J* 7.1), 3,57 (1 H, s) in the $^1H$ NMR spectrum and at $\delta_C$: 143.0, 88.0, 86.5, 77.2, 69.2, 25.0 in the $^{13}C$ NMR.

**General Protocol C. Formation of Cyclic Thionocarbonates using KH and Thiophosgene.** 1.18 mmol (1 mole eq) of vicinal diol, is dissolved in THF (17 $cm^{-3}$) and added to a suspension of 5.9 mmol (5 mole eq) KH and 0.059 mmol (0.05 mole eq) of imidazole in THF (17 $cm^{-3}$) with stirring at 0 °C. After 5 minutes of vigorous stirring, a solution of thiophosgene (1.36 mmol, 1.15 mol eq) in THF (20 $cm^{-3}$) is added dropwise. After the addition is complete, the reaction mixture is stirred at 0 °C for 0.25 h, then quenched with aqueous ammonium chloride. The aqueous layer is separated and the organic layer washed with water (20 $cm^{-3}$) and dried. The solvent is evaporated and the residue is purified by chromatography on silica gel, using gradient elution (hexane/ethyl acetate, or hexane/dichloromethane).

**(+/-)-4R-Phenylacetylenyl-4-[1-phenyl-3,4-bis(*tert*-butyldimethylsiloxy)-3S-butyl]-1,3-dioxolan-2-thione (15).** Application of protocol C to diol **7** gave the title compound as a light yellow oil in 68% yield. $\delta_H$: 7.45 (4 H, d, *J* 9.7), 7.38-7.35 (6 H, br. m), 5.37 (1 H, d, *J* 8.9), 4.68 (1 H, d, *J* 8.9), 4.26 (1 H, d, *J* 10.8), 3.88 (1 H, d, *J* 10.7), 0.94 (9 H, s), 0.92 (9 H, s), 0.38 (3 H, s), 0.30 (3 H, s), 0.11 (6 H, s); $\delta_C$: 190.3, 131.8, 131.7, 129.5, 129.1, 129.0, 128.4, 128.3, 121.5, 120.8, 90.1, 88.9, 88.7, 84.7, 83.3, 76.1, 69.5, 25.6, 18.3, 18.1, -3.1, -3.3, -5.6. Anal. Calc. for $C_{33}H_{44}O_4SSi_2$: C, 66.85; H, 7.48 %. Found: C, 66.91; H, 7.51 %.

***erythro*-4,5-Bis(phenylacetylenyl)-4,5-(triphenylmethoxymethyl)-1,3-dioxolan-2-thione (16).** A white crystalline product isolated in 68 % yield from application of protocol C to diol **8**. mp.199-201 °C (decomp., ether/petroleum ether); $\delta_H$: 7.46 (4 H, d, *J* 6.9), 7.16-7.44 (36 H, m), 3.51 (2 H, d, *J* 10.2), 3.45 (2 H, d, *J* 10.3); $\delta_C$: 188.9, 142.7, 132.1, 129.5, 128.6,

128.4, 127.9, 127.1, 121.0, 91.8, 88.1, 87.6, 81.8, 63.7. Anal. Calc. for $C_{59}H_{44}O_4S$: C, 83.46; H, 5.22 %. Found: C, 83.25; H, 5.35 %.

***erythro*-5-Methyl-4,5-bis(phenylacetylenyl)-4-(triphenylmethoxymethyl)-1,3-dioxolan-2-thione (18).** A white solid product obtained in 53 % yield on application of protocol C to diol **13**. mp 147-148 °C (ether and petroleum ether); $\delta_H$: 7.21-7.57 (25 H, m), 3.74 (1 H, d, *J* 10.4), 3.52 (1 H, d, *J* 10.4), 1.78 (3 H, s); $\delta_C$: 189.0, 142.6, 132.0, 129.9, 129.4, 128.8, 128.5, 128.4, 128.3, 128.1, 127.8, 127.4, 127.2, 121.1, 120.7, 91.9, 90.2, 87.9, 87.0, 84.5, 81.1, 64.6, 21.1. Anal. Calc. for $C_{40}H_{30}O_3S$: C, 81.33; H, 5.12 %. Found: C, 81.28; H, 5.08 %. Double irradiation of the singlet at $\delta_H$ 1.78 in the $^1$H-NMR spectrum resulted in an enhancement of the doublets at 3.74 and 3,52 and so confirmed the stereochemistry.

***erythro*-5-Methyl-4,5-bis(phenylacetylenyl)-4-(triphenylmethoxymethyl)-1,3-dioxolan-2-one (19).** Although this minor byproduct product was not isolated pure, it s presence was discernible in the crude reaction mixture from treatment of diol **13** with KH and thiophosgene by diagnostic peaks in the NMR spectra. $\delta_H$: 3.72 (1 H, d, *J* 9.7); 3.54 (1 H, d, *J* 10.0); $\delta_C$: 152.3, 92.4, 91.8, 87.8, 87.7, 84.0, 82.8, 82.2, 64.7, 19.1.

***threo*-3-Methyl-2,3-bis(phenylacetylenyl)-2-(triphenylmethoxymethyl)-oxirane (20).** A clear syrup obtained in 20% yield on application of protocol C to diol **13**. $\delta_H$: 7.58 (6 H, d, *J* 6.5), 7.39-7.19 (19 H, m), 3.69 (1 H, d, *J* 9.1), 3.54 (1 H, d, *J* 9.5), 1.92 (3 H, s); $\delta_C$: 143.7, 131.9, 128.8, 128.4, 128.0, 127.9, 127.7, 127.2, 126.9, 122.6, 121.1, 86.8, 86.6, 85.5, 84.9, 84.8, 66.1, 60.7, 57.9, 21.5. Anal. Calc. for $C_{39}H_{30}O_2$: C, 88.27; H, 5.70 %. Found: C, 87.92; H, 5.93 %. No enhancement in the signals at $\delta_H$ 3.69 and 3.54 was observed in the $^1$H-NMR spectrum on double irradiation at $\delta_H$ 1.92 leading to the tentative assignment of the threo stereochemistry.

***erythro*-4,5-Bis(trimethylsilylacetylenyl)-4,5-bis(triphenylmethoxymethyl)-1,3-dioxolan-2-thione (17).** Diol **11** (1.10g, 1.38 mmol) was dissolved in THF (44 $cm^{-3}$) and cooled to –15 °C. BuLi (1.21 $cm^{-3}$ of 2.5 M, 3.03 mmol) was then added dropwise, and the reaction mixture stirred at –15 °C for an additional 5 min. Next, thiophosgene (0.13 $cm^{-3}$, 1.65 mmol) in THF (44 $cm^{-3}$) was added dropwise. When the addition was complete, water (20 $cm^{-3}$

$^3$) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (20 $cm^{-3}$). The combined organic layers were dried and concentrated and the residue purified by chromatography on silica gel by gradient elution with dichloromethane/hexane (hexane 100→90%, dichloromethane 0→10%) to give **17** (0.77 g, 66%) as a white crystalline solid. mp. 208-210 °C (ether); $\delta_H$: 7.28-7.31 (12 H, m), 7.18-7.20 (18 H, m), 3.24 (4 H, q, *J* 3.93), 0.24 (18 H, s); $\delta_C$: 188.8, 142.7, 128.5, 127.8, 127.0, 98.3, 96.2, 87.4, 87.2, 63.4, -0.5. Anal. Calc. for $C_{53}H_{52}O_4Si_2$: C, 75.67; H, 6.23 %. Found: C, 75.80; H, 6.44 %.

**General Protocol D. Corey-Winter Reaction.** To a 1 mole equivalent of thiocarbonate is added 3-mole equivalents of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (**21**) and the resulting mixture stirred at 40-45 °C until TLC indicates completion of the reaction. The reaction mixture is added directly to a silica gel column and the enediyne eluted with a gradient of solvents (hexane/ethyl acetate or hexane/dichloromethane). The reaction time varies from 20 min to 5h. More phospholidine compound may be used if the solubility of the thiocarbonate is a problem, but lower yields can then be expected.

**4-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-3-methylene-1,6-diphenyl-1,5-hexyne (22).** Application of protocol D to cyclic thionocarbonate **15** gave 60% of this soft yellowish solid. mp. 51-52 °C; $\delta_H$: 7.44-7.42 (4 H, m), 7.29-7.33 (6 H, m), 6.02 (1 H, d, *J* 1.7), 5.70 (1 H, d, *J* 1.7), 3.91 (1 H, d, *J* 9.5), 3.80 (1 H, d, *J* 9.5), 0.94 (9 H, s), 0.90 (9 H, s), 0.24 (3 H, s), 0.27 (3 H, s), 0.24 (3 H, s), 0.081(6 H, s). Anal. Calc. for $C_{32}H_{44}O_2Si_2$: C, 74.36; H, 8.58%. Found: C, 74.42; H, 8.77%.

**Z-1,6-Diphenyl-3,4-bis(triphenylmethoxymethyl)-3-hexen-1,5-diyne (23).** A white, crystalline solid isolated in 60% yield following application of protocol D to *erythro* thionocarbonate **16**. mp.202 °C; $\delta_H$: 7.64 (12 H, d, *J* 8.1), 7.27-7.36 (28 H, m), 4.16 (4 H, s); $\delta_C$: 144.0, 131.4, 128.8, 128.4, 128.2,128.0, 127.8, 126.9, 123.1, 100.9, 87.3, 86.8, 64.5. Anal. Calc. for $C_{58}H_{44}O_2$: C, 90.12; H, 5.74 %. Found: C, 89.74; H, 5.71 %.

**Z-1,6-Bis(trimethylsilyl)-3,4-bis(triphenylmethoxymethyl)-3-hexen-1,6-diyne (24).** A white crystalline product isolated in 57 % yield by

application of protocol D to *erythro*-thionocarbonate **17**. mp. 155-156 °C; $\delta_H$: 7.35-7.38 (12 H, m), 7.19-7.21 (18 H, m), 3.51 (4 H, s), 0.32 (18 H, s); $\delta_C$: 143.7, 129.0, 128.6, 127.6, 126.8, 104.2, 102.2, 86.7, 62.2, 0.02. Anal. Calc. for $C_{52}H_{52}O_2Si_2$: C, 81.63; H, 6.85 %. Found: C, 81.23; H, 7.22 %.

**Z-4-Methyl-1,6-diphenyl-3-(triphenylmethoxymethyl)-3-hexen-1,5-diyne (25).** A white, crystalline solid obtained in 69 % from **18** by protocol D. mp. 122-123 °C; $\delta_H$: 7.59-7.71 (10 H, m), 7.29-7.41 (15 H, m), 3.88 (2 H, s), 1.92 (3 H, s); $\delta_C$: 144.0, 131.6, 131.5, 128.9, 128.7, 128.4, 128.2, 127.9, 127.0, 126.9, 127.4, 125.9, 123.6, 123.4, 95.1, 94.9, 91.4, 90.4, 86.8, 62.4, 16.8. Anal. Calc. for $C_{39}H_{30}O$: C, 91.08; H, 5.87 %. Found: C, 90.73; H, 5.96 %. Double irradiation of the resonance at $\delta_H$ 1.92 in the $^1$H-NMR led to an enhancement of the signal at $\delta_H$ 3.88 and so established the *Z*-geometry.

**Z-3,4-Bis(hydroxymethyl)-1,6-diphenyl-3-hexene-1,5-diyne (26).** The bis(trityl) ether **23** (0.048 g, 0.06 mmol) was dissolved in 1:2 mixture of methanol and dichloromethane (1.5 $cm^{-3}$) followed by addition of two small drops of conc HCl. The reaction mixture was stirred at room temperature until TLC showed completion (about 30 min.) before it was diluted with ethyl acetate and neutralized with dilute aqueous $NaHCO_3$. The organic layer was separated and water layer extratced with ethyl acetate (2 x 5 $cm^{-3}$). The combined organic layers were dried, concentrated, and purified by chromatography on silica gel (eluent: hexane/ dichloromethane 1:2) yielding **26** (0.0153 g, 89 %) as a white, crystalline solid. mp. 54 °C (decomp.); $\delta_H$: 7.45-7.49 (4 H, m), 7.34-7.37 (6 H, m), 4.58 (4 H, s), 2.22 (2 H, bs); $\delta_C$: 131.5, 129.6, 129.0, 122.2, 102.1, 85.4, 63.6. FABMS (glycerol matrix): m/z: 381 ($M^{+\cdot}$ + glycerol). Anal. Calc. for $C_{20}H_{16}O_2 \cdot 1.25H_2O$: C, 77.59; H, 5.61 %. Found: C, 77.29; H, 5.47 %.

**X-ray Crystallographic Analysis of 11.**[38] Data were processed and the structure was refined on *F* using the XTAL 3.4[39,40] suite of programs. The structure was solved using SHELXS-86 in the $P2_1/n$ space group. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were located in idealized positions based on the carbon backbone and were given a fixed isotropic thermal parameter $U$ = 0.035. The molecule is situated on a crystallographic inversion center.

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(Received in the USA 06 July 1998)