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Synthetic Studies on the Compounds Related to Neocarzinostatin Chromophore. 2.[1] Synthesis of the Open-Chain (E)- and (Z)-Dienediyne Systems and Its Application to the Synthesis of a Strain-released Cyclic Analogue[2]

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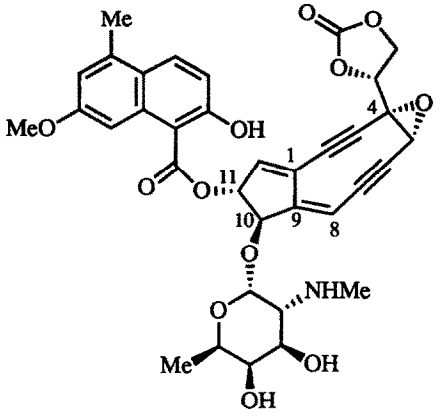
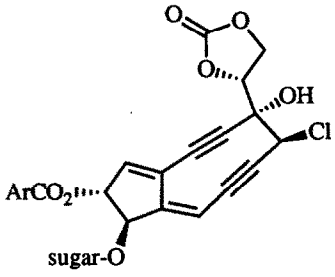
Abstract: The "double coupling" reaction of the (*E*)- and (*Z*)-dienol ditriflates (**5** and **6**) with various propargyl alcohols was found to give the (*E*)- and (*Z*)-dienediyne diols, the open-chain analogues of neocarzinostatin chromophore, stereospecifically. Those (*E*)- and (*Z*)-dienediyne diols exhibited comparable cytotoxicity against P388 murine leukemia. The "single coupling" reaction of **6** took place preferentially at the *exo*-cyclic position to give the mono enol triflate, which could be further elaborated to dienediyne compounds by second coupling reaction with acetylenes. Application of this synthetic scheme could afford the novel and strain-released cyclic dienediyne acetal (**33**).

Neocarzinostatin (NCS),[4] the antitumor antibiotic isolated from a culture filtrate of *Streptomyces carzinostaticus* var. F-41, consists of the apo-protein (apo-NCS) and the labile nonprotein chromophore (**1**) (NCS-Chr). The latter chromophore (**1**) has been revealed to be responsible for the biological activities of NCS such as DNA strand scission.[5,6] The role of apo-NCS has been recognized mainly as the stabilization of highly reactive **1**. In 1985, the chemical structure of **1** was elucidated to possess a novel and highly strained bicyclo[7.3.0]dodecadienediyne epoxide in its core system as shown below.[7] After the structure determination, Myers proposed the activation mechanism of **1** which includes the conjugate addition of a thiol, resulting in the formation of the eneyne cumulene (**3**). Subsequent Bergman-type cyclization of **3** generates the diradical species (**4**), which can abstract hydrogen(s) from DNA backbone to cause DNA cleavage.[8] This proposal stimulated extensive investigations toward synthesis of analogues of **1** which could undergo Bergman-type cyclization.[9] However, only a few analogues carrying (*E*)- and (*Z*)-open-chain dienediyne systems have so far been reported due to the lack of effective methodology to construct such molecules.[1,2,10]

The instability of **1** observed when **1** was treated under highly acidic conditions, heated or exposed to ultraviolet light was recognized mainly due to existence of the highly strained epoxide. Edo and Goldberg independently reported that the derivative of **1** (such as **2**) in which the epoxide ring was opened with a halide



neocarzinostatin chromophore
1 (NCS-Chr)



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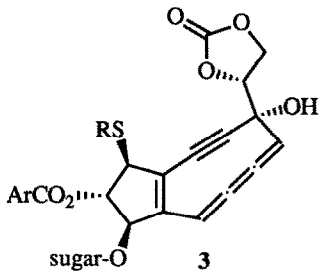

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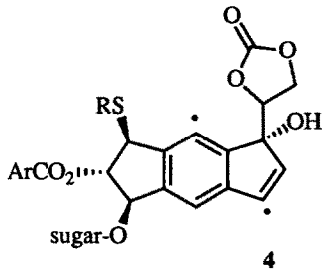

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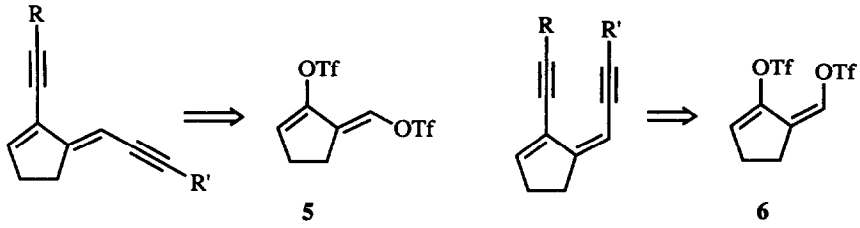
exhibits much improved stability than **1** while it still retains almost the same level of biological activity as **1**.[11,12] These observations obviously suggest that the strain inherent in the epoxide ring in **1** might not be the essential factor for the biological activity of **1**. Taking into account these facts, an epoxide analogue with much released strain is envisioned to be a promising candidate for stable but still active NCS-Chr substitute requiring no stabilization by the apo-protein. Such a stable NCS-Chr analogue may be utilized without the risks inherent in clinical uses of NCS consisting of **1** and the peptide (apo-NCS) derived from microorganisms.

In our previous communication,[2] we have demonstrated the efficient synthesis of the stereo-defined (*E*)- and (*Z*)-open-chain dienediyne systems by means of the palladium-catalyzed coupling of (*E*)- or (*Z*)-dienol ditriflates with propargyl alcohols. Herein, we would like to disclose the details of their preparations and its successful application to the synthesis of a strain-released analogue of **1**.

For a rapid access to the stereo-defined open-chain dienediyne systems, the two alkene-alkyne bonds are the coupling positions of choice since the simple dienediyne compounds bearing the same acetylenic functionalities (R = R') can be prepared in one operation. (**Scheme 1**) In our previous studies,[10a] it was found that the



Scheme 1

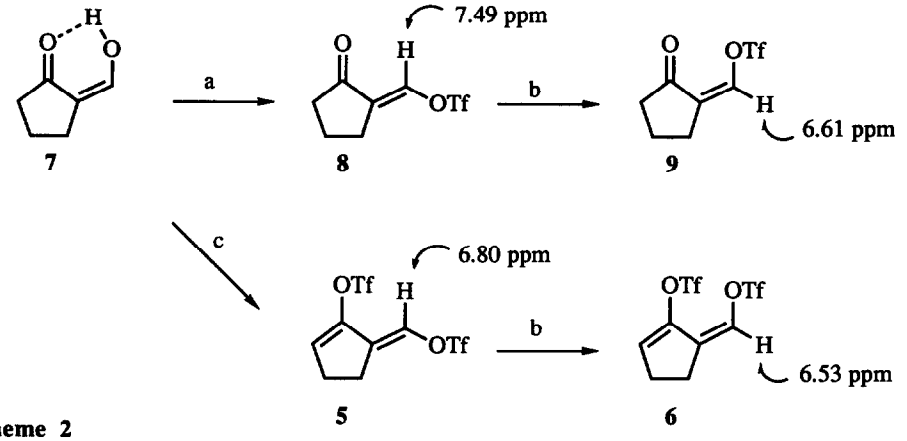
stereochemistry of trisubstituted double bond could be retained during the palladium-catalyzed coupling reaction of enol triflates and acetylene derivatives. Considering these informations as well as facile preparations of various enol triflates from carbonyl compounds,[13] the (*E*)- and (*Z*)-dienol ditriflates (**5** and **6**) were chosen as the precursors for the diene portions of stereo-defined (*E*)- and (*Z*)-dienediyne diols.

Preparation of the (*E*)- and (*Z*)-Dienol Ditriflates (5 and 6)

For the preparation of **5** and **6**, 2-formylcyclopentanone[14] (**7**) is the starting material of choice because two carbonyl groups reside at the desired positions and the hydrogen bond governing the stereochemistry of (**Z**)-*exo*-cyclic enol is expected to control the stereochemistry of the corresponding *exo*-cyclic enol triflate. (**Scheme 2**)

Treatment of **7** with triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine[13a] afforded the keto enol triflate (**8**). Contrary to our expectation, its stereochemistry could be assigned as (*E*)-configuration based on the chemical shift of vinyl hydrogen observed at 7.49 ppm in the ^{1}H-NMR spectrum. The reaction of the lithium enolate of **7** with N-phenyltrifluorosulfonimide was also examined to obtain the (**Z**)-keto enol triflate (**9**). In spite of the expectation that the stereochemistry of the enolate ion could be fixed to (**Z**)-configuration by chelation of the lithium cation with the carbonyl oxygen, only **8** was found to be produced in a low yield. After experimentations, it was found that the photo-induced isomerization of **8** could afford a mixture of **8** and **9**, which could be easily separated by flash chromatography. Observation of vinyl hydrogen at 6.61 ppm in the ^{1}H-NMR spectrum of **9** confirmed its stereochemistry as (**Z**)-configuration. With **9** in hand, the second enol triflate formation of **9** was further attempted to obtain the (**Z**)-dienol ditriflate (**6**). However, treatment of **9** with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave rise to the (*E*)-dienol ditriflate (**5**) instead of the desired **6**. Since the stereochemical outcome of the second enol triflate formation could be explained by the fact that **5** is thermodynamically more stable than **6**, we then focused on the photo-induced isomerization of pre-formed **5** into **6**.

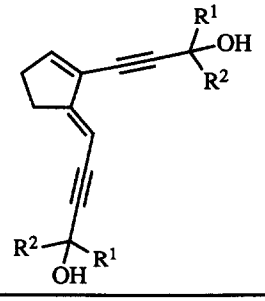
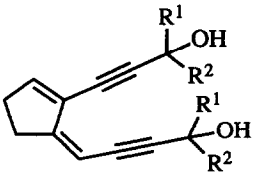
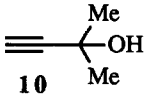
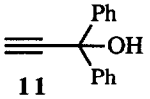
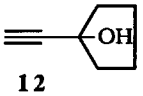
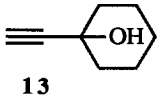
The reaction of **7** with excess of triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine underwent the double enol triflate formation, affording **5** in 63% yield. Irradiation of **5** in acetone with a high pressure mercury lamp effected isomerization of the *exo*-cyclic double bond to give **6** in 37% yield along with **5** in 48% recovery. The stereochemical assignments of **5** and **6** was based on the comparison of their ^{1}H-NMR spectra. Thus, the *exo*-cyclic olefinic hydrogen of **5** was observed at 6.80 ppm while **6** obtained by the photo-



Scheme 2

a) Tf_2O (1 eq), 2,6-di-^{t}Bu-4-MePy, CH_2Cl_2, 63% b) hν, acetone, **8**→**9** 28% (recovery of **8**, 55%), **5**→**6** 37% (recovery of **5**, 48%) c) Tf_2O (excess), 2,6-di-^{t}Bu-4-MePy, CH_2Cl_2, rt, 1day, 63%

Table 1 Double coupling reaction of **5** and **6** with propargyl alcohols

5 or **6** + **10**, **11**,**12** or **13**		
 **10**	**14**; $R^1 = R^2$ = Me, 91%	**15**; $R^1 = R^2$ = Me, 73%
 **11**	**16**; $R^1 = R^2$ = Ph, 98%	**17**; $R^1 = R^2$ = Ph, 63%
 **12**	**18**; R^1, R^2 = -$(CH_2)_4$-, 79%	**19**; R^1, R^2 = -$(CH_2)_4$-, 72%
 **13**	**20**; R^1, R^2 = -$(CH_2)_5$-, 91%	**21**; R^1, R^2 = -$(CH_2)_5$-, 71%

Condition; $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_2NH (2 eq), DMF, rt

induced isomerization showed its *exo*-cyclic olefinic hydrogen at 6.53 ppm. Other hydrogens of **6** were observed at almost the same chemical shifts as those of **5**. Difference of the chemical shifts could be rationalized by deshielding effect of the oxygen atom in the cyclic enol triflate, establishing the stereochemistries of **5** and **6** as (*E*)- and (*Z*)-configurations, respectively.[15,16]

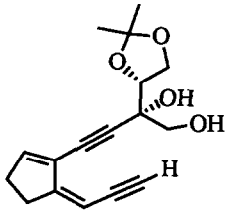
Formation of the Open-chain (*E*)- and (*Z*)-Dienediyne Systems

With completion of the synthetic scheme toward **5** and **6** the coupling reactions with acetylenic compounds, especially with propargyl alcohols were next attempted since the proposed activation mechanism of **1** requires a leaving group at the propargylic position. The reaction of **5** with a slightly excess amount of 2-methyl-3-butyn-2-ol (**10**) in DMF in the presence of 5 mol% of $PdCl_2(PPh_3)_2$, 10 mol% of CuI, and 2 equivalents of diethylamine cleanly produced the (*E*)-dienediyne diol (**14**) in 91% yield. The (*Z*)-dienediyne diol (**15**) could be similarly produced in 73% yield by the reaction of **6** with **10**. The *exo*-cyclic olefinic hydrogens of **14** and **15** were observed at 5.58 and 5.44 ppm in their ^{1}H-NMR spectra, respectively. It is evident that the hydrogen observed at lower field should be deshielded by the neighboring acetylenic group. Based on this spectral analysis as well as the expected high stereospecificity of the coupling reactions, the stereochemistries of **14** and **15** could be definitely assigned as (*E*)- and (*Z*)-configurations, respectively.

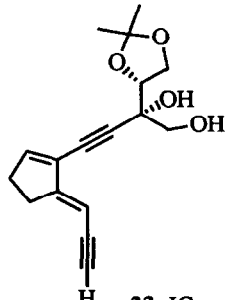
Table 2 Cytotoxicity of the (*E*)- and (*Z*)-dienediyne diols against P388 murine leukemia*

(*E*)-dienediyne diol	IC_{50} (mM)	(*Z*)-dienediyne diol	IC_{50} (mM)
14	4.8×10^{-3}	**15**	4.2×10^{-3}
16	4.1×10^{-3}	**17**	4.2×10^{-3}
18	2.6×10^{-3}	**19**	1.5×10^{-2}
20	2.8×10^{-3}	**21**	2.4×10^{-3}

*Adriamycin was used as a standard compound.



22; $IC_{50} = 3.1\times10^{-2}$mM

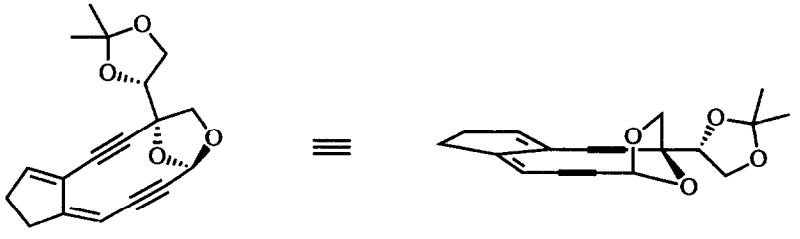


23; $IC_{50} = >10^{-1}$mM

Generality of this "double coupling" reaction employing **5** and **6** was also demonstrated by the successful synthesis of the (*E*)- and (*Z*)-dienediyne diols (**14** - **21**) from various propargyl alcohols (**10** - **13**) in good to excellent yields. These results are summarized in **Table 1**.

Cytotoxicity of the Open-chain (*E*)- and (*Z*)-Dienediyne Diols

With stereo-defined **14** - **21** in hand, we next looked at their cytotoxicity against P388 murine leukemia cells whether there were any relationships between their stereochemistries at the *exo*-cyclic olefinic bonds and their cytotoxicity. As shown in **Table 2**, all compounds except **19** exhibited the comparable cytotoxicity. In our previous study[10a] it was disclosed that (*E*)- and (*Z*)-diene diyne systems showed different cytotoxicity depending upon the stereochemistries of the *exo*-cyclic olefinic bonds. Thus, the (*Z*)-dienediyne diol (**22**) was found to be at least 10 times more potent than the (*E*)-dienediyne diol (**23**). Taking into account the fact that the (*E*)- and (*Z*)-dienediyne diols prepared in this work exhibited comparable cytotoxicity, it appeared that the existence of hydroxy groups at both ends of propargylic side chains might overweigh the effect of stereochemistry of *exo*-cyclic olefin. In accordance with this hypothesis, the cytotoxicity of **22** was found to be obviously 10 times less potent than that of **14**.



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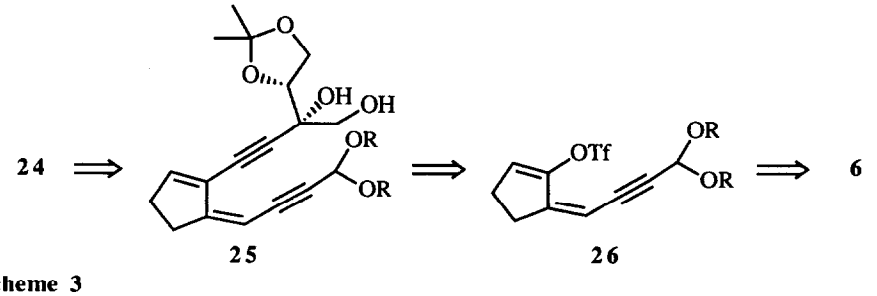


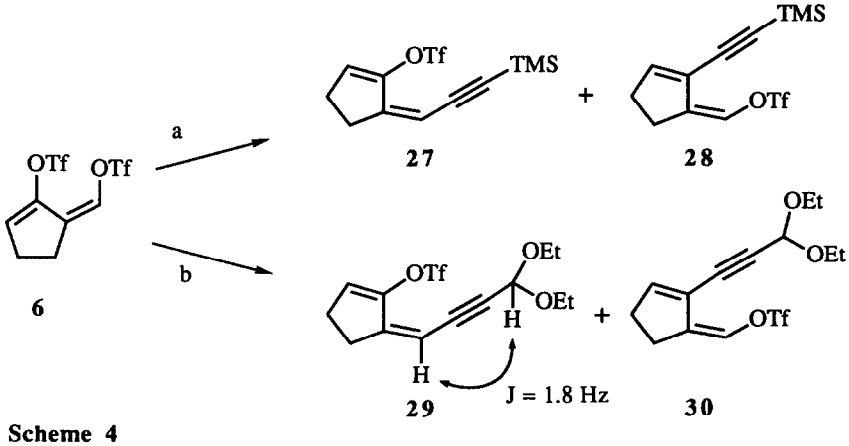
25 **26**

Scheme 3

Synthetic Studies on the Strain-released Cyclic Analogue of 1

As discussed earlier, it became apparent that the existence of highly strained epoxide ring in **1** made itself unstable and stabilization of **1** was brought about by the apo-protain. Accordingly, we became interested in designing and synthesizing strain-released cyclic analogues of **1** to examine their chemical and biological properties. It was envisioned that replacement of the epoxide ring with a larger cyclic ether ring such as tetrahydrofuran could release the strain energy inherent in the three-membered ring (*ca.* 20 kcal/mol). On the other hand, the compound bearing bicyclo[8.3.0]tridecadienediyne system, the 10-membered-ring analogue of **1**, has been reported to be relatively stable under inert atmosphere.[8d] Taking into account these facts, the tricyclic acetal (**24**) was designed as a strain-released analogue of **1**. (**Scheme 3**)

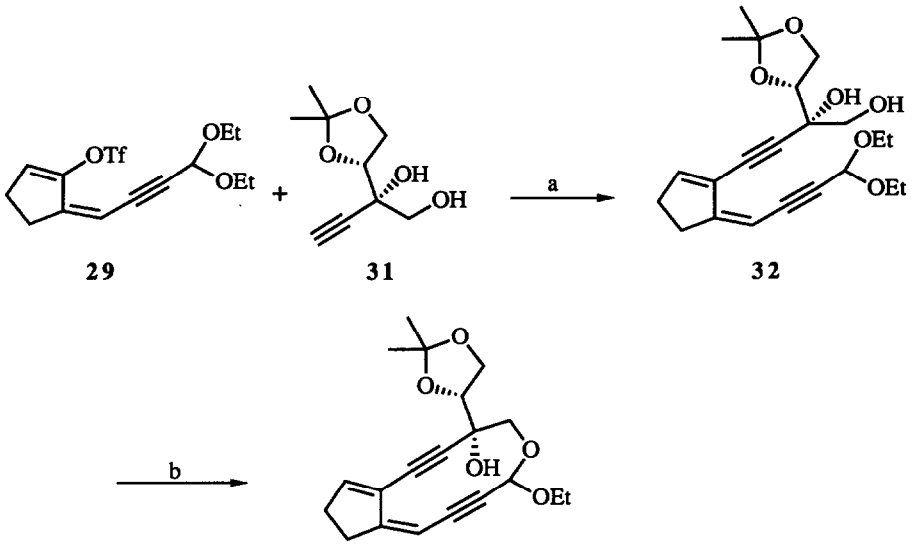
Retrosynthetic analysis of **24** suggested that the site selective coupling of **6** with an acetylenic acetal at the *exo*-cyclic position and the subsequent coupling of the resulting enol triflate (**26**) with the optically active acetylenic diol (**31**)[17] would give the diol acetal (**25**). This might be elaborated to **24** by the following intramolecular acetal exchange. In the intramolecular acetal exchange, it was expected that the initial formation of 11-membered acetal might facilitate the subsequent cyclic acetal formation, readily producing the 10-membered dienediyne system.



Scheme 4
a) trimethylsilylacetylene, $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_2NH (2 eq), DMF, **27** and **28**, 56%. b) 3,3-diethoxy-1-propyne, $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_2NH (2 eq), DMF, **29**, 50%; **30**, 10%.

To realize this synthetic scheme, the site selectivity of "single-coupling" reaction of **6** was first investigated. The coupling reaction of **6** with 1 molar equivalent of trimethylsilylacetylene in the presence of $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), and diethylamine (2 eq) in DMF afforded an inseparable mixture of the regioisomers (**27** and **28**) as coupling products. (**Scheme 4**) Judging from the ^{1}H-NMR spectrum the ratio of two regioisomers could be established as *ca.* 4:1. The major product was identified as **27** resulting from the coupling reaction at the *exo*-cyclic enol triflate, by comparing its ^{1}H-NMR spectrum with that of the authentic sample.[10a] Since the *exo*-

cyclic enol triflate of **6** was found to preferentially react with an acetylene, the coupling reaction with an acetylenic acetal was next attempted. Thus, treatment of **6** with 3,3-diethoxy-1-propyne under the same conditions as mentioned above afforded a mixture of two regioisomers (**29** and **30**). Fortunately, they could be separated by silica gel chromatography to give **29** and **30** in 50 and 10% yields, respectively. In this case, the structures of those two regioisomers were determined by their ^{1}H-NMR spectra. Thus, the hydrogen presented in the acetal carbon was observed as a sharp singlet in **30** while that of **29** appeared as a doublet due to long range coupling (J = 1.8 Hz) with the *exo*-olefinic hydrogen.



29 **31** **32** **33**

Scheme 5
a) $Pd(PPh_3)_4$ (20 mol%), CuI (50 mol%), Et_2NH (2 eq), DMF, 92%. b) *d*-CSA, molecular sieves 4A, benzene

The second coupling of **29** with **31**[17] under the usual conditions proceeded smoothly to afford the (**Z**)-dienediyne diol acetal (**32**) in 92% yield. (**Scheme 5**) Upon treatment of **32** with *d*-camphor sulfonic acid (*d*-CSA) in dry benzene in the presence of powdered molecular sieves 4A at room temperature, formation of a fairly unstable product could be observed after usual extractive isolation followed by column chromatography.[18] However, the ^{1}H-NMR spectrum of the isolated product was found not to be compatible with desired **24** but with the bicyclic acetal (**33**).[19] Furthermore, in the ^{1}H-NMR spectrum recorded in C_6D_6, it appeared that the reaction product consisted of two isomers (either diastereoisomers or rotamers). Attempts to convert **33** into **24** under the forcing conditions (e.g. *d-CSA* in refluxing benzene) simply resulted in the decomposition of **33**. While our initial objective to produce **24** turned out to be fruitless, the facile intramolecular acetal exchange observed for **32** should obviously expand the scope of utility of **6** for preparing novel cyclic dienediyne acetals to which it is not easy to access by conventional methodologies.

Conclusion

We have succeeded in developing an expeditious synthetic method of stereo-defined (*E*)- and (*Z*)-dienediyne systems by means of Pd-catalyzed double coupling reaction of (*E*)- and (*Z*)-dienol ditriflates with various propargyl alcohols. Being independent upon the stereochemistries of the *exo*-cyclic double bonds, the dienediyne diols so obtained were found to exhibit comparable cytotoxicity. Sequential coupling reactions of **6** with different acetylenic compounds enabled rapid access to the novel cyclic dienediyne acetal such as **33**. In the future, these synthetic methods explored in this work might contribute to produce a stable but still active NCS-Chr substitute.

Experimental Section

Optical rotations were measured with a Horiba SEPA-200 automatic digital polarimeter. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured with Hitachi R-90H (90 MHz) and Brucker AM 400 (400MHz) spectrometers. The chemical shifts were expressed in parts per million downfield from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.25) and benzene (δ=7.20) as an internal standard. Splitting pattern were indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Unless otherwise noted, all experiments were carried out using anhydrous solvents under an atmosphere of dry argon. Especially, tetrahydrofuran and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Throughout this work, Merck pre-coated TLC plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used for thin layer chromatographic (TLC) analyses. Wako Gel C-200, C-300 and florisil were used as an adsorbent for flash column chromatography.

(*E*)-(2-Oxo-cyclopentylidene)-methyl Trifluoromethanesulfonate (8)

To a solution of **7** (196 mg, 1.8 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (575 mg, 2.8 mmol) in CH_2Cl_2 (5 ml) was added trifluoromethanesulfonic anhydride (741 mg, 0.44 ml, 2.6 mmol) at 0 °C and the mixture was stirred for 1 hr at the same temperature. The reaction mixture was diluted with pentane and the resulting precipitates were filtered off. The filtrate was carefully concentrated *in vacuo*. The residue was dissolved in pentane and the resulting precipitates were again filtered off. After concentration of the filtrate *in vacuo*, flash chromatography (SiO_2, EtOAc:hexane=1:10) of the residue gave **8** (271 mg, 63%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ = 2.03 (quint, 2H, J = 7.6 Hz, -$COCH_2$*CH_2*CH_2-), 2.42 (t, 2H, J = 7.7 Hz, -CO*CH_2*CH_2CH_2-), 2.77 (dt, 2H, J = 7.3 , 2.9 Hz, -$COCH_2CH_2$*CH_2*-), 7.49 (t, 1H, J = 2.8 Hz, =*CH*-). IR (neat): 2970, 1740, 1660, 1430, 1215, 1140, 1080, 990, 815, 755 cm^{-1}. MS (m/e) (%): 244 (M^+) (15), 216 [$(M-CO)^+$] (8), 124 (44), 69 (100).

(*Z*)-(2-Oxo-cyclopentylidene)-methyl Trifluoromethanesulfonate (9)

A degassed solution of **8** (240 mg, 1.0 mmol) in acetone (200 ml) was irradiated at 0 °C with a high pressure mercury lamp (100W) through pyrex filter for 40 min. After concentration *in vacuo*, flash chromatography (SiO_2, EtOAc:hexane=1:10) of the residue gave **9** (68.0 mg, 28%) and recovered **8** (132 mg, 55%) both as a pale

yellow oil. ^{1}H-NMR ($CDCl_3$) δ = 2.02 (quint, 2H, J = 7.5 Hz, -$COCH_2CH_2CH_2$-), 2.40 (t, 2H, J = 7.8 Hz, -$COCH_2CH_2CH_2$-), 2.70 (dt, 2H, J = 7.2, 2.3 Hz, -$COCH_2CH_2CH_2$-), 6.61 (t, 1H, J = 2.2 Hz, =*CH*-). IR (neat): 2970, 1735, 1650, 1430, 1210, 1140, 1025, 915, 850 cm^{-1}. MS (m/e) (%): 244 (M^+) (32), 216 [(M-CO)$^+$] (13), 124 (43), 69 (100).

(*E*)-5-Trifluoromethanesulfonyloxymethylidene-1-cyclopenten-1-yl Trifluoromethanesulfonate (5)

To a solution of **7** (997 mg, 8.9 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (5.48 g, 27 mmol) in CH_2Cl_2 (80 ml) was slowly added trifluoromethanesulfonic anhydride (6.28 g, 3.7 ml, 22 mmol) at 0 °C and the mixture was stirred at room temperature for 24 hr. After removing the solvent *in vacuo* the residue was dissolved in pentane. The resulting precipitates were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was again dissolved in pentane and the formed precipitates were further filtered off. After concentration of the filtrate *in vacuo*, flash chromatography (SiO_2, EtOAc:hexane=1:20) of the residue gave **5** (2.12 g, 63%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ = 2.66 (m, 2H, =CHCH_2-), 2.81 (m, 2H, =CHCH$_2CH_2$-), 6.20 (t, 1H, J = 2.9 Hz, =*CH*CH_2CH_2-), 6.80 (m, 1H, *CH*OTf). IR (neat): 3120, 2940, 1680, 1620, 1430, 1210, 1140, 1080, 1030, 1000, 860 cm^{-1}. MS (m/e) (%): 376 (M^+) (19), 243 [(M-CF_3SO_2)$^+$] (3), 179 (7), 151 (16), 85 (64), 69 (CF_3^+) (100), 65 (45), 55 (31). HRMS calcd for $C_8H_6F_6O_6S_2$: 375.9508, Found: 375.9506.

(*Z*)-5-Trifluoromethanesulfonyloxymethylidene-1-cyclopenten-1-yl Trifluoromethanesulfonate (6)

A degassed solution of **5** (1.30 g, 3.5 mmol) in acetone (200 ml) was irradiated with a high pressure mercury lamp (400W) through pyrex filter at 0 °C for 25 min. After concentration *in vacuo*, flash chromatography (SiO_2; Et_2O:hexane=1:8) of the residue gave **6** (0.48 g, 37%) and recovered **5** (0.63 g, 48%) both as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ = 2.63 (m, 2H, =CHCH_2-), 2.74 (m, 2H, =CHCH$_2CH_2$-), 6.22 (t, 1H, J = 2.9 Hz, =*CH*CH_2CH_2-), 6.53 (m, 1H, *CH*OTf). IR (neat): 3120, 2940, 1680, 1615, 1430, 1210, 1140, 1090, 1025, 920, 850 cm^{-1}. MS (m/e) (%): 376 (M^+) (15), 243 [(M-CF_3SO_2)$^+$] (2), 179 (6), 151 (15), 85 (66), 69 (CF_3^+) (100), 65 (49), 55 (39). HRMS calcd for $C_8H_6F_6O_6S_2$: 375.9509, Found 375.9518.

4-[(*E*)-5-(4-Hydroxy-4-methyl-2-pentynylidene)-1-cyclopenten-1-yl]-2-methyl-3-butyn-2-ol (14)

To a degassed solution of **5** (95.0 mg, 0.25 mmol), diethylamine (55.0 mg, 0.08 ml, 0.75 mmol) and **10** (85.0 mg, 1.0 mmol) in DMF (0.4 ml) was added $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol) and CuI (9.6 mg, 0.051 mmol) and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated NH_4Cl and the mixture was extracted with ether. The organic phases were combined, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (florisil, EtOAc:hexane=1:4) gave **14** (55.8 mg, 91%) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ = 1.57 (s, 3Hx4, *CH*$_3$x4), 1.9-2.2 (br, 2H, -*OH*), 2.58 (m, 2H, =CHCH_2-), 2.73 (m, 2H, =CHCH$_2CH_2$-), 5.58 (m, 1H, =*CH*-), 6.47 (t, 1H, J = 3.0 Hz, =*CH*CH_2CH_2-). IR (neat): 3400, 3000, 2220, 1375, 1245, 1170, 965 cm^{-1}.

MS (m/e) (%): 244 (M^+), 229 [$(M-Me)^+$], 211, 151 (8), 105 (7), 43 (100). HRMS calcd for $C_{16}H_{20}O_2$: 244.1463, found 244.1477.

4-[(*Z*)-5-(4-Hydroxy-4-methyl-2-pentynylidene)-1-cyclopenten-1-yl]-2-methyl-3-butyn-2-ol (15)

To a degassed solution of **6** (62.0 mg, 0.16 mmol), diethylamine (36.0 mg, 0.05 ml, 0.49 mmol) and **10** (69.0 mg, 0.82 mmol) in DMF (0.4 ml) was added $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol) and CuI (6.3 mg, 0.033 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was worked up in the same manner as described for the preparation of **14**, giving **15** (29.2 mg, 73%) as a pale brown oil after separation by flash chromatography (florisil, EtOAc:hexane=1:4). ^{1}H-NMR ($CDCl_3$) δ = 1.56 (s, 3Hx2, CH_3x2), 1.58 (s, 3Hx2, CH_3x2), 2.50 (m, 2H, =CH$CH_2$$CH_2$-), 2.65 (m, 2H, =CH$CH_2$$CH_2$-), 3.3-3.8 (br, 2H, -$OH$x2), 5.44 (m, 1H, =$CH$-), 6.53 (m, 1H, =$CH$$CH_2$$CH_2$-). IR (neat): 3370, 3000, 2230, 1375, 1240, 1160, 955 cm^{-1}. MS (m/e) (%): 244 (M^+) (9), 229 [$(M-Me)^+$] (4), 211 (11), 153 (15), 128 (18), 115 (12), 43 (100). HRMS calcd for $C_{16}H_{20}O_2$: 244.1463, found 244.1480.

1,1-Diphenyl-3-[(*E*)-5-(4,4-diphenyl-4-hydroxy-2-butynylidene)-1-cyclopenten-1-yl]-2-propyn-1-ol (16)

To a degassed solution of **5** (88.0 mg, 0.23 mmol), diethylamine (51.4 mg, 0.07 ml, 0.70 mmol) and **11** (188 mg, 0.59 mmol) in DMF (0.5 ml) was added $PdCl_2(PPh_3)_2$ (8.2 mg, 0.012 mmol) and CuI (4.5 mg, 0.023 mmol) and the mixture was stirred at room temperature for 3 hr. The mixture was worked up in a similar manner to that described for the preparation of **14**, giving **16** (110 mg, 96%) as a pale brown oil after separation by flash chromatography (florisil, EtOAc:hexane=1:8). ^{1}H-NMR ($CDCl_3$) δ = 2.56 (m, 2H, =CH$CH_2$$CH_2$-), 2.71, 2.75 (sx2, 1Hx2, -OHx2), 2.75 (m, 2H, =CH$CH_2$$CH_2$-), 5.68 (m, 1H, =$CH$-), 6.53 (t, 1H, J = 3.0 Hz, =$CH$$CH_2$$CH_2$-), 7.15-7.29 (m, 12H), 7.51-7.58 (m, 8H). IR (CCl_4): 3630, 3475, 3090, 2210, 1610, 1490, 1450, 1340, 1160, 1030, 910, 700, 620 cm^{-1}. MS (m/e) (%): 492 (M^+), 474 (2), 414 (2), 396 (7), 309 (12), 262 (11), 231 (10), 203 (9), 182 (21), 105 (100), 77 (62), 51 (19).

1,1-Diphenyl-3-[(*Z*)-5-(4,4-diphenyl-4-hydroxy-2-butynylidene)-1-cyclopenten-1-yl]-2-propyn-1-ol (17)

To a degassed solution of **6** (116 mg, 0.31 mmol), diethylamine (67.8 mg, 0.09 ml, 0.93 mmol) and **11** (161 mg, 0.77 mmol) in DMF (0.5 ml) was added $PdCl_2(PPh_3)_2$ (10.8 mg, 0.015 mmol) and CuI (5.9 mg, 0.031 mmol) and the mixture was stirred at room temperature for 3 hr. The mixture was worked up in the same manner as described for the preparation of **14**, giving **17** (95.9 mg, 63%) as a pale brown oil after separation by flash chromatography (florisil, EtOAc:hexane=1:4). ^{1}H-NMR ($CDCl_3$) δ = 2.57 (m, 2H, =CH$CH_2$$CH_2$-), 2.73 (m, 2H, =CH$CH_2$$CH_2$-), 3.45, 3.65 (sx2, 1Hx2, -OHx2), 5.63 (m, 1H, =CH-), 6.69 (m, 1H, =$CH$$CH_2$$CH_2$-), 7.15-7.36 (m, 12H), 7.47-7.58 (m, 8H). IR (CCl_4): 3560, 3470, 3090, 2210, 1600, 1490, 1440, 1340, 1160, 1030, 880, 700, 640 cm^{-1}. MS (m/e) (%): 492 (M^+), 474, 414, 396 (2), 309 (3), 231 (4), 203 (4), 182 (26), 105 (94), 77 (55), 43 (40), 18 (100).

1-[2-[(*E*)-5-[3-(1-Hydroxycyclopent-1-yl)-2-propynylidene]-1-cyclopenten-1-yl]-ethynyl]-cyclopentan-1-ol (18)

To a degassed solution of **5** (103 mg, 0.27 mmol), diethylamine (60.2 mg, 0.09 ml, 0.82 mmol) and **12** (78.6 mg, 0.71 mmol) in DMF (0.6 ml) was added $PdCl_2(PPh_3)_2$ (9.6 mg, 0.014 mmol) and CuI (5.2 mg, 0.027 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was worked up in a similar manner to that described for the preparation of **14**, giving **18** (64.1 mg, 79%) as a pale brown oil after separation by flash chromatography (florisil, Et_2O:hexane=2:3). ^{1}H-NMR ($CDCl_3$) δ = 1.7-2.1 (m, 18H, *OH*x2 and CH_2x8), 2.58 (m, 2H, =CH$CH_2$$CH_2$-), 2.73 (m, 2H, =CH$CH_2$$CH_2$-), 5.60 (m, 1H, =*CH*-), 6.46 (t, 1H, J = 3.0 Hz, =*CH*$CH_2$$CH_2$-). IR (neat): 3660, 3100, 3000, 2220, 1100, 1000 cm^{-1}. MS (m/e) (%): 296 (M^+) (70), 277 (29), 249 (28), 235 (24), 221 (23), 211 (100), 207 (49), 161 (43), 91 (48), 55 (86). HRMS calcd for $C_{20}H_{24}O_2$: 296.1776, found 296.1778.

1-[2-[(*Z*)-5-[3-(1-Hydroxycyclopent-1-yl)-2-propynylidene]-1-cyclopenten-1-yl]-ethynyl]-cyclopentan-1-ol (19)

To a degassed solution of **6** (95.9 mg, 0.26 mmol), diethylamine (56.0 mg, 0.08 ml, 0.77 mmol) and **12** (70.2 mg, 0.64 mmol) in DMF (0.5 ml) was added $PdCl_2(PPh_3)_2$ (9.0 mg, 0.013 mmol) and CuI (4.9 mg, 0.026 mmol) and the mixture was stirred at room temperature for 2.5 hr. The mixture was worked up in the same manner as described for the preparation of **14**, giving **19** (54.1 mg, 72%) as a pale brown oil after separation by flash chromatography (florisil, EtOAc:hexane=1:8). ^{1}H-NMR ($CDCl_3$) δ = 1.7-2.1 (m, 16H, CH_2x8), 2.50 (m, 2H, =CH$CH_2$$CH_2$-), 2.65 (m, 2H, =CH$CH_2$$CH_2$-), 3.13, 3.40 (brx2, 1Hx2, -*OH*x2), 5.46 (m, 1H, =*CH*-), 6.52 (m, 1H, =*CH*$CH_2$$CH_2$-). IR (neat): 3625, 3350, 2980, 2225, 1090, 1000 cm^{-1}. MS (m/e) (%): 296 (M^+) (4), 278 (100), 250 (48), 235 (26), 221 (37), 211 (94), 207 (63), 165 (72), 95 (66), 41 (45). HRMS calcd for $C_{20}H_{24}O_2$: 296.1776, found 296.1760.

1-[2-[(*E*)-5-[3-(1-Hydroxycyclohex-1-yl)-2-propynylidene]-1-cyclopenten-1-yl]-ethynyl]-cyclohexan-1-ol (20)

To a degassed solution of **5** (108 mg, 0.29 mmol), diethylamine (63.1 mg, 0.09 ml, 0.86 mmol) and **13** (143 mg, 1.2 mmol) in DMF (0.8 ml) was added $PdCl_2(PPh_3)_2$ (10.1 mg, 0.014 mmol) and CuI (5.5 mg, 0.029 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was worked up in a similar manner to that described for the preparation of **14**, giving **20** (84.4 mg, 91%) as a pale brown oil after separation by flash chromatography (florisil, EtOAc:hexane=1:4). ^{1}H-NMR ($CDCl_3$) δ = 1.5-2.1 (m, 22H, -*OH*x2 and CH_2x10), 2.60 (m, 2H, =CH$CH_2$$CH_2$-), 2.76 (m, 2H, =CH$CH_2$$CH_2$-), 5.63 (m, 1H, =*CH*-), 6.49 (t, 1H, J = 3.0 Hz, =*CH*$CH_2$$CH_2$-). IR ($CCl_4$): 3640, 3450, 2950, 2880, 2210, 1455, 1070, 960 cm^{-1}. MS (m/e) (%): 324 (M^+) (1), 306, 277, 228 (4), 203 (2), 175 (4), 146 (5), 98 (3), 86 (63), 84 (100).

1-[2-[(*Z*)-5-[3-(1-Hydroxycyclohex-1-yl)-2-propynylidene]-1-cyclopenten-1-yl]-ethynyl]-cyclohexan-1-ol (21)

To a degassed solution of **6** (104 mg, 0.28 mmol), diethylamine (60.6 mg, 0.09 ml, 0.83 mmol) and **13** (85.7 mg, 0.69 mmol) in DMF (0.5 ml) was added $PdCl_2(PPh_3)_2$ (9.7 mg, 0.014 mmol) and CuI (5.3 mg, 0.028 mmol) and the mixture was stirred at room temperature for 3 hr. The mixture was worked up in the same manner as described for the preparation of **14**, giving **21** (63.6 mg, 71%) as a pale brown oil after separation by flash chromatography (florisil, EtOAc:hexane=1:4). ^{1}H-NMR ($CDCl_3$) δ = 1.5-2.0 (m, 20H, CH_2x10), 2.50 (m, 2H, =CH$CH_2$$CH_2$-), 2.66 (m, 2H, =CHCH$_2$$CH_2$-), 3.57, 3.88 (brx2, 1Hx2, -OHx2), 5.48 (m, 1H, =CH-), 6.54 (m, 1H, =CHCH$_2$CH$_2$-). IR (neat): 3375, 2960, 2900, 2260, 1450, 1070, 970, 910, 730 cm^{-1}. MS (m/e) (%): 324 (M^+) (11), 306 (11), 277 (6), 263 (14), 235 (13), 228 (41), 221 (19), 203 (20), 175 (40), 165 (16), 146 (48), 91 (43), 81 (31), 77 (31), 55 (94), 41 (100). HRMS calcd for $C_{22}H_{28}O_2$: 324.2089, found 324.2105.

(*Z*)-5-(3-Trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl Trifluoromethanesulfonate (27) and (*Z*)-[2-(2-Trimethylsilyl-1-ethynyl)-2-cyclopentenylidene]-methyl Trifluoromethanesulfonate (28)

To a degassed solution of **6** (30.0 mg, 0.08 mmol) and trimethylsilylacetylene (7.1 mg, 0.07 mmol) in DMF (0.5 ml) was added $Pd(PPh_3)_4$ (4.2 mg, 0.004 mmol) and the mixture was stirred at room temperature for 5 min. Diethylamine (10.6 mg, 0.02 ml, 0.14 mmol) and CuI (1.4 mg, 0.007 mmol) was then added and the reaction mixture was further stirred at the same temperature for 15 min. The reaction was quenched with saturated NH_4Cl and the mixture was diluted with water and EtOAc. The organic phase was separated, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:10) of the residue gave an inseparable mixture of **27** and **28** (13.1 mg, 56% yield, *ca.* 4:1) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) (The signals of **28** were marked with the asterisk.) δ = 0.18 (s, 9H, -SiMe_3), 2.4-2.8 (m, 4H), 5.49 and 6.42* (mx2, 1H, =CH-), 6.23 and 6.53* (mx2, 1H, =CHCH$_2$-). The ^{1}H-NMR spectrum of **27** was identical with that of the authentic sample.

(*Z*)-5-(4,4-Diethoxy-2-butynylidene)-1-cyclopenten-1-yl Trifluoromethanesulfonate (29) and (*Z*)-[2-(3,3-Diethoxy-1-propynyl)-2-cyclopentenylidene]-methyl Trifluoromethanesulfonate (30)

To a degassed solution of **6** (213 mg, 0.57 mmol) and 3,3-diethoxy-1-propyne (69.1 mg, 0.54 mmol) in DMF (1 ml) was added $Pd(PPh_3)_4$ (31.1 mg, 0.02 mmol) and the mixture was stirred at room temperature for 5 min. Diethylamine (78.9 mg, 0.11 ml, 1.1 mmol) and CuI (10.3 mg, 0.05 mmol) were then added and the reaction mixture was stirred at room temperature for 15 min. The reaction was quenched with saturated NH_4Cl and the mixture was diluted with water and EtOAc. The organic phase was separated, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; benzene:hexane=1:1) of the residue gave **29** (100 mg, 50%) and **30** (20.1 mg, 10%) both as a pale yellow oil. **29**; ^{1}H-NMR (C_6D_6); δ = 1.21 (t, 6H, J = 7.0 Hz, CH$_2$$CH_3$x2), 1.60 (m, 2H, =CH$CH_2CH_2$-), 1.89 (m, 2H,

=CHCH$_2$*CH$_2$*-), 3.65 (dq, 2H, J = 7.0, 9.2 Hz, -*CH$_2$*CH$_3$x2), 3.86 (dq, 2H, J = 7.0, 9.2 Hz, -*CH$_2$*CH$_3$x2), 5.18 (m, 1H, =*CH*-), 5.61 (br s, 1H, =*CH*CH$_2$CH$_2$-), 5.71 (d, 1H, J = 1.8 Hz, -*CH*(OEt)$_2$). IR (C_6H_6): 2970, 2910, 2210, 1430, 1330, 1210, 1140, 1700, 870, 850 cm^{-1}. MS (m/e) (%): 354 $(M)^+$ (12), 325 $[(M-Et)^+]$ (18), 309 $[(M-OEt)^+]$ (100), 281 (22), 148 (18), 120 (35), 82 (36), 55 (16). HRMS calcd for $C_{14}H_{17}F_3O_5S$: 354.0749, found 354.0777. **30**; ^{1}H-NMR (C_6D_6); δ = 1.21 (t, 6H, J = 7.0 Hz, CH$_2$*CH$_3$*x2), 1.72-1,82 (m, 4H), 3.64 (dq, 2H, J = 7.0, 9.2 Hz, -*CH$_2$*CH$_3$x2), 3.85 (dq, 2H, J = 7.0, 9.2 Hz, -*CH$_2$*CH$_3$x2), 5.61 (s, 1H, -*CH*(OEt)$_2$), 6.05 (br, 1H, =*CH*-), 6.11 (br, 1H, J = 1.8 Hz, =*CH*CH$_2$CH$_2$-), IR (C_6H_6): 2980, 2940, 2230, 1430, 1330, 1210, 1140, 1060, 925, 850 cm^{-1}. MS (m/e) (%): 354 $(M)^+$ (16), 325 $[(M-Et)^+]$ (23), 309 $[(M-OEt)^+]$ (100), 281 (24), 192 (17), 148 (28), 120 (53), 91 (31). HRMS calcd for $C_{14}H_{17}F_3O_5S$: 354.0749, found 354.0774.

(*2S*)-4-[(*Z*)-5-(4,4-Diethoxy-2-butynylidene)-1-cyclopenten-1-yl]-2-[(*4R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1,2-diol (32)

To a degassed solution of **29** (90.3 mg, 0.26 mmol) and **31** (56.9 mg, 0.31 mmol) in DMF (1.0 ml) was added $Pd(PPh_3)_4$ (58.9 mg, 0.05 mmol) and the mixture was stirred at room temperature for 15 min. Diethylamine (37.3 mg, 0.05 ml, 0.51 mmol) and CuI (24.3 mg, 0.13 mmol) were added and the reaction mixture was stirred at room temperature for 20 min. The reaction was quenched with saturated NH_4Cl and the mixture was diluted with water and EtOAc. The organic phase was separated, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:benzene=1:3) of the residue gave **32** (91.6 mg, 92%) as a pale yellow oil. $[\alpha]_D^{20}$ +20.9° (c=1.43, benzene). ^{1}H-NMR (C_6D_6) δ = 1.14 (t, 3H, J = 7.3 Hz, CH$_2$*CH$_3$*), 1.16 (t, 3H, J = 7.3 Hz, CH$_2$*CH$_3$*), 1.36, 1.62 (sx2, 3Hx2, *CMe$_2$*), 1.88 (m, 2H, =CH*CH$_2$*CH$_2$-), 2.11 (m, 2H, =CHCH$_2$*CH$_2$*-), 2.46 (m, 1H, -CH$_2$*OH*), 3.52, 3.56 (dqx2, 1Hx2, J = 9.8, 7.0 Hz, -*CH$_2$*CH$_3$), 3.76, 3.79 (dqx2, 1Hx2, J = 9.8, 7.0 Hz, -*CH$_2$*CH$_3$), 4.06 (m, 1H, -*CH$_2$*OH), 4.16 (br d, 1H, J = 10.1 Hz, -*CH$_2$*OH), 4,25 (dd, 1H, J = 8.6, 6.7 Hz, -CH*CH$_2$*-), 4.41 (t, 1H, J = 6.4 Hz, -CH*CH$_2$*-), 4.60 (dd, 1H, J = 8.6, 6.1 Hz, -*CH*CH$_2$-), 4.72 (s, 1H, -*OH*), 5.38 (br s, 1H, =*CH*-), 5.55 (s, 1H, -*CH*(OEt)$_2$), 6.35 (br s, 1H, =*CH*CH$_2$CH$_2$-). IR (C_6H_6); 3400, 2940, 2160, 1370, 1070, 720 cm^{-1}. MS (m/e) (%): 345 $[(M-OEt)^+]$, 243 (25), 215 (24), 101 (77), 85 (56), 71 (72), 57 (100).

(*4S*)-4-[(*4R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-7-ethoxy-4-hydroxy-6-oxabicyclo[9.3.0]tetradeca-10,14-dien-2,8-diyne (33)

A solution of **32** (10.5 mg, 0.03 mmol), *d*-camphorsulfonic acid (1 mg), and powdered molecular sieves 4A (*ca.* 20 mg) in anhydrous benzene (2 ml) was stirred for 1 hr at room temperature. This reaction mixture was directly poured onto silica gel column, which was then eluted with EtOAc and hexane (1:4). Fractions containing **33** were combined and carefully concentrated *in vacuo* to *ca.* 0.2 ml of volume. To the concentrated solution was added benzene (2 ml) and the resulting solution was then concentrated to 0.1 ml of volume. After this operation was repeated, d^6-benzene was used in stead of benzene to prepare a sample for ^{1}H-NMR spectrum. ^{1}H-NMR spectral measurement of this sample clearly indicated the formation of **33** as a mixture of either the diastereoisomers at C_7 or the possible rotamers.

^{1}H-NMR (C_6D_6) (Signals corresponding to the minor isomer were indicated by the asterisk.); δ = 1.03 (m, 3H, CH_2CH_3), 1.31, 1.55 and 1.33*, 1.46* (sx4, total 3Hx2, CMe_2), 1.83* and 1.87 (m, total 2H, =CHCH_2CH_2), 2.08 (m, 2H, =CHCH_2CH_2-), 2.91* and 3.17 (s, total 1H, -*OH*), 3.21 (m, 1H, CH_2CH_3), 3.56 (m, 1H, CH_2CH_3), 3.71 (d, 1H, J = 11.6 Hz, C_5H), 4.1-4.3 (total 2H), 4.58 (m, 1H), 4.58* and 4.82 (dx2, total 1H, J = 11.0 Hz, C_5H), 5.27 (br, 1H, C_{10}H), 5.37* and 5.50 (br sx2, total 1H, C_7H),6.20* and 6.25 (br sx2, total 1H, C_{14}H). IR (C_6H_6): 3500, 3350, 2940, 2840, 1360, 1065 cm^{-1}. MS (m/e) (%): 344 (M^+) (3), 329 [(M-Me)$^+$] (6), 299 [(M-OEt)$^+$] (2), 262 (4), 199 (20), 149 (22), 101 (100), 78 (35), 57 (37). HRMS calcd for $C_{20}H_{24}O_5$: 344.1622, found 344.1623.

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15. Recently, synthesis of (*E*)- and (*Z*)-dienediynes from **5** and **6** was also reported by Suffert *et al.* See references 10b,c.
16. The dienol ditriflates (**5** and **6**) were fairly unstable oils and slowly decomposed to form black polymeric products even kept in a refrigerator as a hexane solution.
17. The optically active acetylenic diol (**31**) was synthesized from *D*-isoascorbic acid. See ref. 1 and 10a.
18. In the absence of molecular sieves 4A, the reaction mainly afforded an unstable aldehyde derivatives (the stereochemistry of the *exo*-cyclic olefin was not certain) which might be produced by hydrolysis of the diethyl acetal moiety.
19. The yield of **33** could not be determined due to its extreme instability upon concentration *in vacuo*.