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Synthetic Studies on the Compounds Related to Neocarzinostatin Chromophore. 1. Synthesis of the Acyclic (E)- and (Z)-Dienediyne Systems

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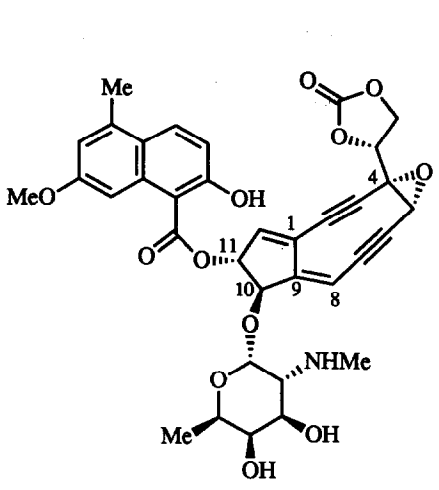
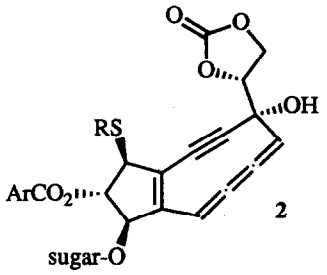
Abstract: The stereo-defined (E)- and (Z)-dienediyne systems related to neocarzinostatin chromophore (1) could be prepared by the coupling reaction of (E)- and (Z)-enol triflates with optically active acetylynes bearing the correct absolute stereochemistries as found in 1. Comparison of cytotoxic level of the (E)- and (Z)-dienediyne diols (32 and 33) revealed that the stereochemistry of exo-trisubstituted double bond might have a posibility to control the cytotoxicity of the acyclic analogues related to 1.

Neocarzinostatin chromophore (NCS-Chr) (**1**), the non-protein chromophore of the antitumor antibiotic neocarzinostatin (NCS) produced by *Streptomyces carzinostaticus*,[2] has been recognized to be responsible for the biological activities of NCS.[3,4] The role of apo-protein (apo-NCS) was recognized to stabilize the highly labile **1**. In 1985, it was revealed that the chemical structure of **1** involved novel bicyclo[7.3.0]dodecadienediyne system as shown below.[5] This novel ring system has been believed to relate deeply with its biological activities. Thus, in the proposed mechanism for activation of **1**,[6] vinylogus addition of a thiol to the highly strained dienediyne epoxide followed by Bergman-type cyclization of the resulting eneynecumulene (**2**) affords the diradical species (**3**) which can abstract hydrogen(s) from DNA backbone to cause a strand scission of DNA.

Recent model studies on the diradical generation from simple eneyneallene[7] or eneynecumulene[8] systems suggest that not only the strain energy but also the ring system involved in **1** may not be essential factors for the diradical generation. In connection with this remarkable mechanism of **1**, we became interested in the synthesis of the stereo-defined acyclic (E)- and (Z)-dienediyne systems (e.g. **4** and **5**) related to **1**.[9] Since both systems can produce the same intermediate [e.g. eneyneallene (**6**)] due to free rotation of the C_8-C_9 bond after the initial



neocarzinostatin chromophore
1 (NCS-Chr)



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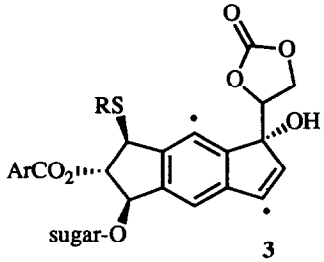

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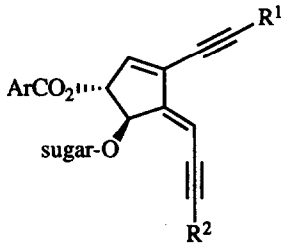
activation proposed for **1**, they might show comparable behavior in chemical reactivity and/or biological property. Furthermore, the synthetic scheme to these acyclic systems was envisioned to provide an opportunity to examine possibilities to construct the cyclic dienediyne system by the C_5-C_6 (NCS-Chr numbering) bond formation after installation of the acyclic (Z)-dienediyne system completed. In this report, we would like to describe details of the synthesis of several acyclic (E)- and (Z)-dienediyne compounds[10] related to **1** and an attempt to produce a dienediynealdehyde, the potential precursor for nine membered cyclic dienediyne analogues of **1**.[12]



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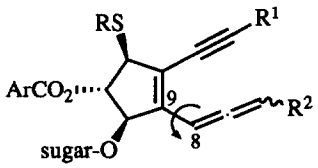

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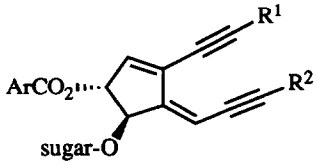

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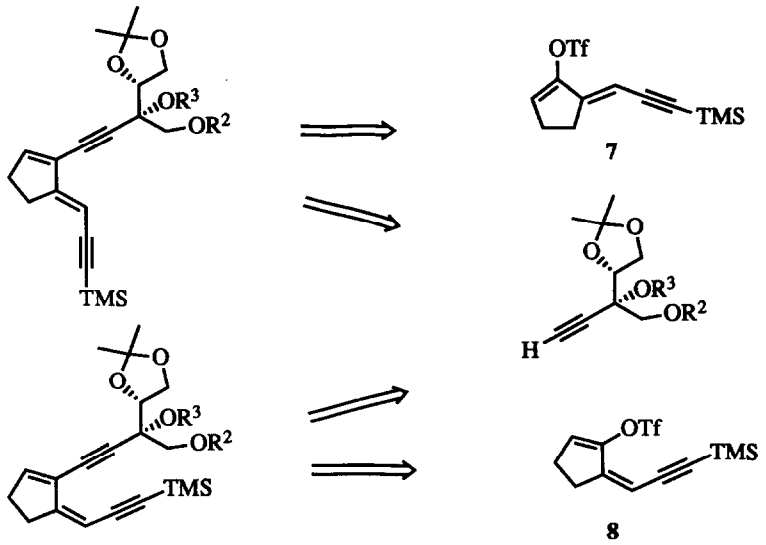
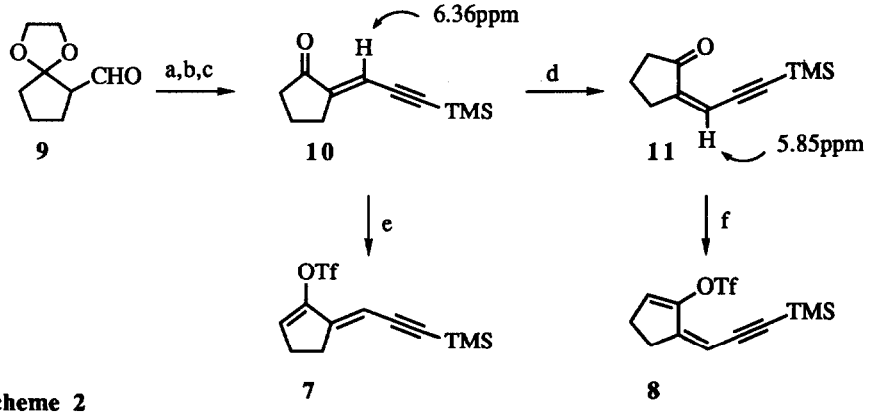
To synthesize the stereo-defined acyclic dienediyne compounds corresponding to **4** and **5**, the (E)- and (Z)-enol triflates (**7** and **8**) were anticipated to be the key intermediates, respectively. Final installation of the dienediyne system would be accomplished by the C_1-C_2 (NCS-Chr numbering) bond formation employing the well known palladium-catalyzed coupling reaction of enol triflates with optically active acetylenes involving the C_2-C_5 and C_{13}-C_{14} portions. (**Scheme 1**)



Scheme 1

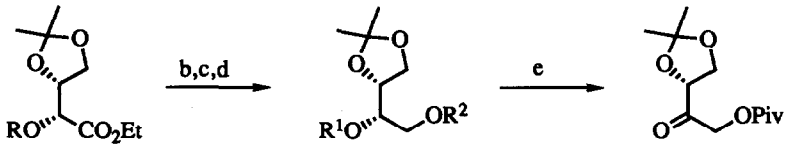
Preparation of the (E)- and (Z)-enol triflates

Addition of lithium trimethylsilylacetylide to the aldehyde (**9**)[15] afforded the addition products as a mixture of diastereoisomers. After hydrolysis of ethylene acetal, the (E)-ketoeneyne (**10**) was obtained predominantly by dehydration of the resulting aldol with mesyl chloride and triethylamine. The (Z)-isomer (**11**), however, could be easily obtained by photo-induced isomerization of **10** although the isomerization reaction did not complete. Assignment of the stereochemistries of **10** and **11** was based on the comparison of their ^{1}H-NMR spectra. Thus, in the case of **10**, the vinyl hydrogen was observed at 6.36 ppm, while in **11** it was found at as high as 5.85 ppm. From these observations, it was concluded that the vinyl hydrogen in **10** was deshielded by the carbonyl group, indicating the (E)-configuration of the exocyclic double bond. Formation of **7** was achieved by treating **10** with triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine,[16] although **11** gave



Scheme 2

a) LiC≡CTMS, THF, -78°C b) PPTS, acetone, H_2O, reflux c) MsCl, Et_3N, CH_2Cl_2, 67% (3 steps) d) hv (254nm) acetone, 36% (the recovery of **10**, 55%) e) Tf_2O, 2,6-di-^{t}Bu-4-MePy, CH_2Cl_2, 80% f) LDA, Tf_2NPh, THF, 80%



a { **12** ; R = H, **13** ; R = EE

14 ; R^1 = EE, R^2 = H
15 ; R^1 = EE, R^2 = Piv
16 ; R^1 = H, R^2 = Piv

17

EE = 1-ethoxy-1-ethyl

Scheme 3

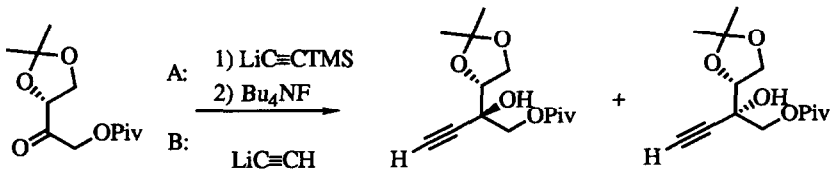
a) Ethyl vinyl ether, PPTS, CH_2Cl_2 b) $LiAlH_4$, Et_2O c) PivCl, Py d) PPTS, MeOH, 79% (4 steps) e) PDC, 4A-MS, CH_2Cl_2, 86%

polymeric products upon treatment under the same conditions. The (Z)-enol triflate (**8**), however, was cleanly obtained from **11** by successive treatments with LDA and N-phenyl-trifluoromethanesulfonimide.[17] The 400 MHz ^{1}H-NMR spectra clearly established that more than 95% of stereochemical integrities were kept at the stage of **7** and **8**. (**Scheme 2**)

Preparation of the optically active acetylenes

The optically active acetylenes with (***4S***)- and (***13R***)-configurations[6c] (NCS-Chr numbering) were anticipated to be prepared from D-isoascorbic acid. The hydroxy ester (**12**)[18] prepared from D-isoascorbic acid was converted into the ketone (**17**) in 5 steps. (**Scheme 3**) Introduction of the acetylenic functionality was examined by employing either lithium trimethylsilylacetylide or lithium acetylide under the conditions shown in **Table 1**. In the case of using lithium trimethylsilylacetylide as a nucleophile, the initial products were desilylated

Table 1 Reaction of the ketone **17** with Lithium Trimethylsilylacetylide or Lithium Acetylide



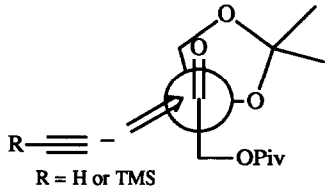
17 **18** **19**

Method	Solvent	Additive	ratio of **18** and **19**[a]			
	THF	-------	2.6		1	
A:		TMEDA	1.9	60%[b]	1	32%[b]
		HMPA	16.4		1	
		DABCO	2.7		1	
	Hex - Ether	-------	9.4		1	
B:	THF	-------	4.9		1	
		TMEDA	6.1		1	
	Hex - Ether	-------	2.4		1	

a) Determined by the 90 MHz ^{1}H-NMR spectrum. b)Isolated yield (see the experimental section).

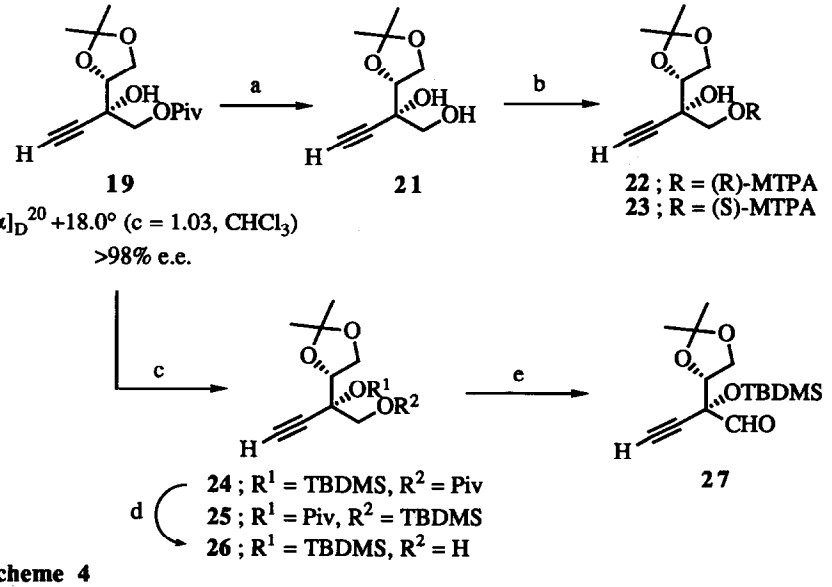
with TBAF before examining the ratio of two isomers. In all cases studied, the less polar isomer (**18**) was obtained as a major product. The stereochemistries of both isomers were determined as shown above by single X-ray crystallography of the more polar isomer (**19**).[19] The yield of the desired isomer (**19**) could be maximized by carrying out the reaction with lithium trimethylsilylacetylide in THF in the presence of TMEDA. Since the undesired isomer (**18**) was obtained as a major product, the addition reaction seems to proceed via the Felkin-Anh like model transition state (**20**) as in the nucleophilic addition to glyceraldehyde[20] although effects of both solvents and additives remained unclear. (**Fig. 1**)

Since **17** involved only one asymmetric center at the α position to carbonyl group, the possible racemisation was concerned during the oxidation and the nucleophilic addition reaction of acetylide anion.[21] To determine the optical purity of **19**, both the (*R*)- and (*S*)-MTPA esters (**22** and **23**), were prepared by treating the diol (**21**) obtained from **20** with (*R*)- and (*S*)-MTPA chlorides, respectively. Comparing their ^{1}H-NMR spectra, it appeared that the enantiomeric purity of **19** was more than 98%. (**Scheme 4**)



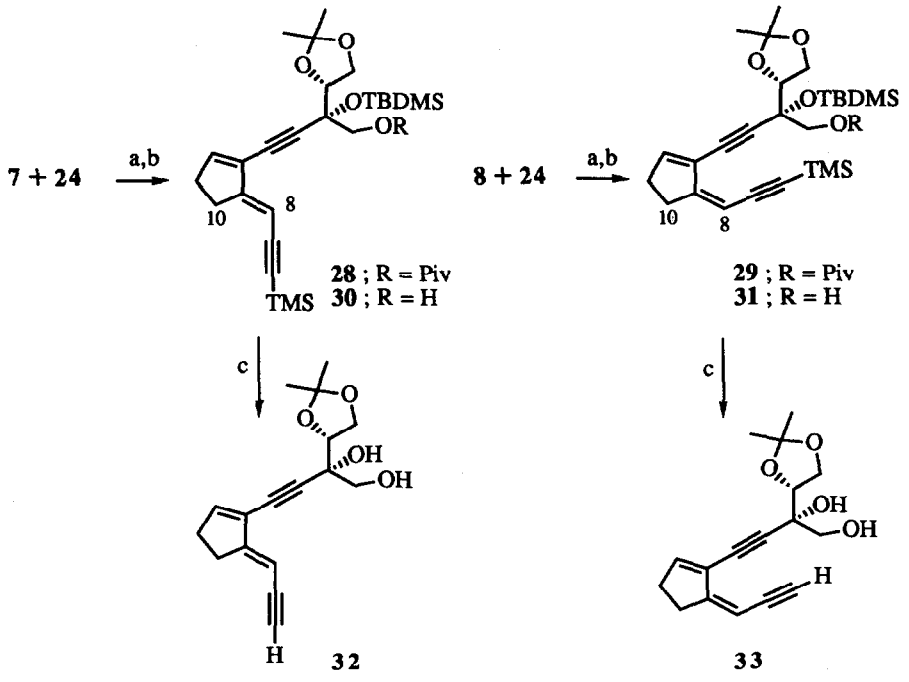
20 **Fig. 1**

Having established the stereochemistry and optical purity of **19**, its conversion into the aldehyde (**27**) was next examined. Silylation of the tertiary alcohol in **19** with *t*-butyldimethylsilyl triflate in the presence of 2,6-lutidine afforded the desired silyl ether (**24**) along with the compound (**25**) in which pivaloyl and TBDMS groups were transposed. The minor product (**25**) was desilylated to starting **19**. The major product (**24**) was transformed into **27** by reductive removal of the pivaloyl group and oxidation of the resulting alcohol (**26**) with sulfur trioxide-pyridine complex.



Scheme 4

a) NaOMe, MeOH, 89% b) (R)- and (S)-MTPACl, DMAP, py c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, **24** 59%, **25** 32% d) DIBAL-H, CH_2Cl_2, -78°C, 91% e) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 80%

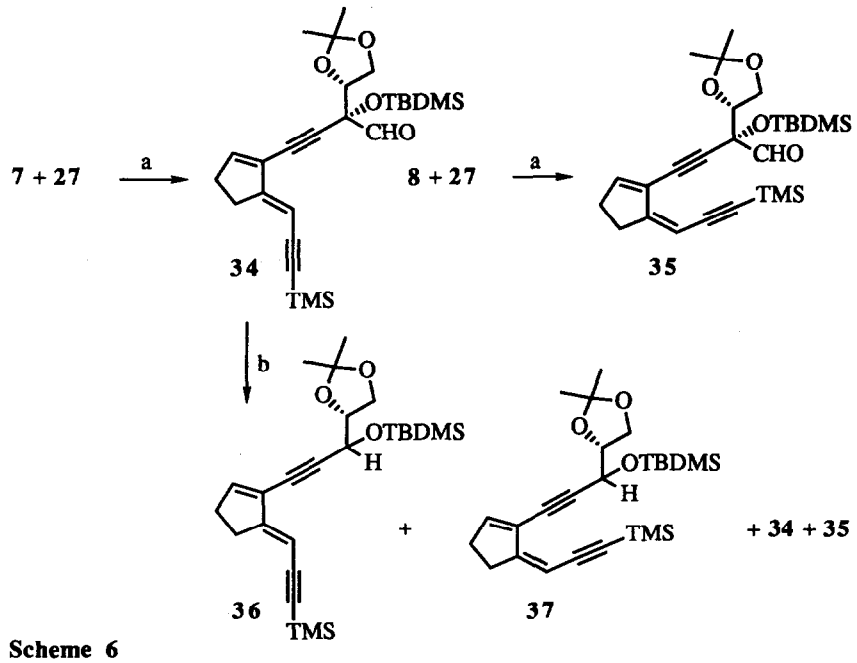


Scheme 5
a) $Pd(PPh_3)_4$, CuI, Et_2NH, DMF, **28** 88%, **29** 73% b) DIBAL-H, CH_2Cl_2, -78°C, **30** 84%, **31** 68%
c) TBAF, THF, 0°C, **32** 84%, **33** 89%

Synthesis of the acyclic (E)- and (Z)-dienediyne systems

With both enol triflates and optically active acetylenes in hands, formation of the acyclic dienediyne systems was next examined. The coupling reaction of the (E)-enol triflate (**7**) with **24** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium (0), copper (I) iodide and 2.0 equivalents of diethylamine in DMF afforded the (E)-dienediyne (**28**) in a good yield. The (Z)-dienediyne (**29**) could be also cleanly obtained by the reaction of the (Z)-enol triflate (**8**) and **24** under the same condition as above. By comparing their ^{1}H-NMR spectra, the stereochemistries at the exocyclic double bond were found not to be affected at all during the coupling reaction. Thus, the methylene at C_{10} and the vinyl hydrogen at C_8 in **28** were observed at 2.77 and 5.67 ppm, while in **29** they were found at 2.67 and 5.57 ppm, respectively. The differences of chemical shifts of both metheylene and vinyl hydrogens might be explained by the deshielding effect of acetylenic bond, confirming the stereochemical assignments for **28** and **29**, respectively. (**Scheme 5**)

Those (E)- and (Z)-dienediynes (**28** and **29**) obtained were deprotected to the corresponding dienediyne diols (**32** and **33**) to examine whether they might show a comparable biological activity. Reductive cleavages of the pivaloyl groups in both **28** and **29** with diisobutylaluminum hydride gave the alcohols (**30** and **31**), respectively. Two silyl groups in **30** and **31** were removed with TBAF in one operation to result in the formations of (E)- and (Z)-dienediyne diols (**32** and **33**) as unstable solids, respectively. These samples (**32** and **33**) were then subjected to *in vitro* cytotoxicity assay against P388 murine leukemia.[22] The IC_{50} values of $>10^{-1}$ mM (adriamycin: IC_{50} 1×10^{-6} mM) and 3.1×10^{-2} mM (8.9 ng/ml)(adriamycin: IC_{50} 3×10^{-6} mM) were recorded



Scheme 6

a) $Pd(PPh_3)_4$, CuI, Et_2NH, DMF, **34** 76%, **35** low yield b) hν, hexane

for **32** and **33**, respectively. Correcting the cytotoxicity of adriamycin used as a reference compound, the cytotoxicity of **33** was found to be at least 10 times stronger than that of **32**. It is noteworthy that the difference of cytotoxicities of **32** and **33** was caused only by their stereochemistries at the C_8-C_9 double bond although the cytotoxicity of **33** was relatively weak.

Attempt to synthesize the (Z)-dienediyne aldehyde, a potential precursor for the cyclic analogues of 1

Having established the synthetic scheme to both acyclic (E)- and (Z)-diendiynesystems, we then focused on the synthesis of an (Z)-dienediyne aldehyde to study whether the cyclization to 9-membered ring by forming the C_5-C_6 bond was possible. The coupling reaction of **27** with the (E)-enol triflate (**7**) cleanly gave the (E)-dienediye aldehyde (**34**) under the same reaction conditions as mentioned above. On the other hand, the reaction with the (Z)-enol triflate (**8**) gave a complex mixture of products. By comparing the products with the authentic sample prepared by photo-induced isomerization of **34**, it was later found that the desired (Z)-dienediyne aldehyde (**35**) was obtained at best as a very minor product (*vide infra*). Change of either solvent (from DMF to THF) or base (from diethylamine to triethylamine or 2,6-di-*t*-butyl-4-methylpyridine) did not alter the reaction course. To study if **35** was stable enough to be isolated, the photo-induced isomerization of **34** was then examined. Upon irradiation of **34** either with a high or a low pressure mercury lamp in hexane or acetone, a small amount of **35** was found to be produced along with the corresponding decarbonyl products (**36** and **37**) (the stereochemistries of both compounds were not established). Although we could not obtain an enough

amount of **35** to carry out following studies on the cyclization to nine-membered cyclic analogues of **1**, it was found that (Z)-dienediyne aldehydes such as **35** could exist as a fairly stable compound. Accordingly, it appeared that selection of an appropriate method to produce an aldehyde functionality would make it possible to produce a large amount of **35** required for studies on the cyclization.

Conclusion

We have succeeded in developing an efficient synthetic scheme to the acyclic (E)- and (Z)-dienediynes such as **32** and **33** and in disclosing that the stereochemistry of the C_8-C_9 double bond may play an important role for the cytotoxicity of acyclic analogues of **1**. From the viewpoint to explore prominent anticancer agents, one of the goals in the synthesis and testing of analogues of **1** is the separation of antitumor activity from its extreme chemical instability since 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. Taking into account these aspects, our findings may have values for designing various structural types of NCS-Chr analogues.

Experimental Section

All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. 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 are expressed in ppm downfield from tetramethylsilane, using tetramethylsilane or residual chloroform as an internal standard. Splitting patterns are 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 under an atomosphere of dry argon using anhydrous solvents. Especially, tetrahydrofuran and ethyl ether were distilled from sodium benzophenone ketyl. For thin layer chromatographic (TLC) analyses throught out this work, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25mm, Art 5715) were used. Wako Gel C-200 and C-300 were used as an adsorbent for flash column chromatography. The following abbreviations were used for solvents and reagents: tetrahydrofuran (THF), diethyl ether (Et_2O), ethyl acetate (EtOAc), n-butyllithium (n-BuLi), pyridinium p-toluenesulufonate (PPTS), pyridinium chlorochromate (PCC), tetrabutylammonium fluoride (TBAF).

(*E*)-2-[3-(Trimethylsilyl)-2-propynylidene]-cyclopentanone (10)

To a solution of trimethylsilylacetylene (9.88 g, 14.2 ml, 0.10 mol) in THF (100 ml) was added n-BuLi (1.6 M in hexane, 60 ml, 97 mmol) at -78 °C. After stirring for 30 min, a solution of **9** (12.1 g, 77 mmol) in THF (20 ml) was added and the mixture was stirred for 1 h. The reaction was quenched with sat. NH_4Cl at 0 °C, then diluted with ether and hexane. The organic phase was washed successively with water, sat. NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was dissolved in acetone (120 ml) and H_2O (40 ml) containing PPTS (400 mg , 1.6 mmol), and the mixture was refluxed for 5 h. After cooling, acetone was removed *in vacuo*. The residue was extracted with ether and hexane. The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (150 ml) and triethylamine (13.8 g, 19.0 ml, 0.14 mol) and methanesulfonyl chloride (7.82

g, 5.3 ml, 68 mmol) were successively added to the dichloromethane solution at 0 °C. After being stirred for 2 h, the mixture was diluted with ether and hexane, then with water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:15) of the residue gave **10** (10.2 g, 68% from **9**) as light yellow plates. An analytical sample of **10** was obtained by recrystallization from hexane. m.p. 51 - 52.5 °C. IR ($CHCl_3$) 2970, 2140, 1710, 1610, 1095, 990, 845 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.23 (s, 9H, -Si*Me3*), 1.97 (quint, 2H, J = 7.6 Hz, -$COCH_2$*CH_2*CH_2-), 2.39 (t, 2H, J = 7.8 Hz, -CO*CH_2*CH_2CH_2-), 2.79 (dt, 2H, J = 7.4, 2.9 Hz, -$COCH_2CH_2$*CH_2*-), 6.36 (t, 1H, J = 2.9 Hz, =*CH*-). MS (m/e) (%) 192 (M^+) (29), 177 [$(M\text{-}Me)^+$] (100), 121 (23), 75 (31), 43 (31). Anal. Calcd. for $C_{11}H_{16}OSi$: C, 68.69; H, 8.38%. Found: C, 68.62; H, 8.46%.

(*Z*)-2-[3-(Trimethylsilyl)-2-propynylidene]-cyclopentanone (11)

A degassed solution of **10** (2.93 g, 15.3 mmol) in acetone (160 ml) was irradiated with a low pressure merrcury lamp through vycor filter under argon for 2 h. After concentration *in vacuo*, flash chromatography (SiO_2, EtOAc:hexane=40:1) of the residue gave **10** (1.64 g, 56% recovery) and **11** (1.22 g, 41%) as yellow plates. An analytical sample of **11** was obtained by recrystallization from hexane. m.p. 99 - 100.5 °C. IR ($CHCl_3$) 2960, 2120, 1710, 1605, 1050, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.24 (s, 9H, -Si*Me3*), 1.92 (quint, 2H, J = 7.5 Hz, -$COCH_2$*CH_2*CH_2-), 2.37 (t, 2H, J = 7.8 Hz, -CO*CH_2*CH_2CH_2-), 3.73 (dt, 2H, J = 7.2, 2.4 Hz, -$COCH_2CH_2$*CH_2*-), 5.85 (t, 1H, J = 2.5 Hz, =*CH*-). MS (m/e) (%) 192 $(M)^+$ (29), 177 [$(M\text{-}Me)^+$] (100), 121 (12), 75 (39). Anal. Calcd. for $C_{11}H_{16}OSi$: C, 68.69; H, 8.38%. Found: C, 68.49; H, 8.40%.

(*E*)-5-[3-(Trimethylsilyl)-2-propynylidene]-1-cyclopenten-1-yl Trifluoromethanesulfonate (7)

To a solution of **10** (77.7 mg, 0.40 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (166 mg, 0.8 mmol) in CH_2Cl_2 (2 ml) was added trifluoromethanesulfonic anhydride (137 mg, 0.08 ml, 0.49 mmol) at 0 °C and the mixture was stirred for 2 h. After concentration *in vacuo*, the residue was extracted with pentane and the combined extracts were concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:30) of the residue gave **7** (105 mg, 80%) as a pale brown oil. IR (neat) 2975, 2130, 1610, 1420, 1210, 1140, 840, 600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.20 (s, 9H, -Si*Me3*), 2.60 (m, 2H, =CH*CH_2*CH_2-), 2.81 (m, 2H, =$CHCH_2$*CH_2*-), 5.52 (m, 1H, =*CH*-), 6.17 (m, 1H, =*CH*CH_2CH_2-). MS (m/e) (%) 324 (M^+) (45), 309 [$(M\text{-}Me)^+$] (100), 176 (77), 161 (34), 141(37). HRMS Calcd. for $C_{12}H_{15}F_3O_3SSi$: 324.0462. Found: 324.0454.

(*Z*)-5-[3-(Trimethylsilyl)-2-propynylidene]-1-cyclopenten-1-yl Trifluoromethanesulfonate (8)

To a solution of diisopropylamine (173 mg, 0.24 ml, 1.7 mmol) in THF (8 ml) was added n-BuLi (1.6 M in hexane, 0.79 ml, 1.3 mmol) at -78 °C. After being stirred for 15 min, a solution of **11** (219 mg, 1.1 mmol) in THF (2 ml) was slowly added and the mixture was further stirred for 20min. A solution of N-phenyltrifluoromethanesulfoneimide (449 mg, 1.3 mmol) in THF (2 ml) was added and the reaction mixture was slowly warmed up to 0 °C over 5 h. The reaction was quenched with sat. NH_4Cl, and the resulting mixture was

extracted with ether and hexane. The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, hexane:benzene=15:1) of the residue gave **8** (317 mg, 86%) as colorless plates. m.p. 37 - 38 °C. IR (CCl_4) 2975, 2130, 1600, 1430, 1210, 1140, 1090, 850, 600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.18 (S, 9H, -Si*Me*$_3$), 2.52 (m, 2H, =CH*C*H_2CH$_2$-), 2.72 (m, 2H, =CHCH$_2$*C*H_2-), 5.49 (m, 1H, =*C*H-), 6.23 (m, 1H, =*C*HCH$_2$CH$_2$-). MS (m/e) (%) 324 $(M)^+$, (70), 309 $[(M\text{-}Me)^+]$ (84), 240 (15), 176 (100), 161 (51), 141 (75), 77 (72). HRMS Calcd. for $C_{12}H_{15}F_3O_3SSi$: 324.0462. Found: 324.0456.

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethyl 2,2-Dimethylpropanoate (16)

To a solution of **12**[18] (5.02 g, 25 mmol) and ethyl vinyl ether (14.7 g, 19.5 ml, 0.20 mol) in CH_2Cl_2 (80 ml) was added PPTS (62 mg, 0.25 mmol) at 0 °C and the mixture was stirred for 3 h at room temperature. After dilution with hexane and ether, the mixture was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The crude product obtained was dissolved in ether (50 ml). The etheral solution was slowly added to a suspension of $LiAlH_4$ (2.05 g, 54 mmol) in ether (30 ml) at 0 °C and stirring was continued for 40 min at room temperature. The reaction was carefully quenched by successive additions of water (2.1 ml), 15% NaOH (2.1 ml) and water (6.3 ml). After dilution with ether, white precipitates were filtered off and the filtrate was concentrated *in vacuo*. To a solution of the crude product in pyridine (10 ml) was added pivaloyl chloride (4.45 g, 4.5 ml, 37 mmol) at 0 °C. After stirring at 0 °C for 1 h and at room temperature for another 1 h, the mixture was diluted with ether and hexane. The organic phase was washed with water and brine, filtered, then concentrated *in vacuo*. The residue was dissolved in methanol (50 ml) and the methanolic solution was stirred in the presense of PPTS (1.24 g, 4.9 mmol) at 0 °C for 1 h and at room temperature for 24 h. Methanol was evaporated *in vacuo* and the residue was dissolved in ether and hexane. This solution was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:4) of the residue gave **16** (4.76 g, 79%) as colorless prisms. $[\alpha]_D^{20}$ -3.2° (c = 1.00, $CHCl_3$). m.p. 42 - 44 °C. IR (nujol) 3525, 3010, 1730, 1160, 1070, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.23 (s, 9H, ^{t}*Bu*), 1.36, 1.42 (sx2, 3Hx2, C*Me*$_2$), 2.50 (br, 1H, -*OH*), 3.85 (m, 1H), 3.98-4.10 (3H), 4.13 (dd, 1H, J = 11.8, 6.0 Hz, -*C*H_2OPiv), 4.33 (dd, 1H, J = 11.8, 3.2.Hz, -*C*H_2OPiv). MS (m/e) (%) 231 $[(M\text{-}Me)^+]$ (15), 101 (100), 73 (29), 57 (97). Anal. Calcd. for $C_{11}H_{22}O_5$: C, 58.52; H, 9.00%. Found: C, 58.64; H, 9.10%.

2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-oxoethyl 2,2-Dimethylpropanoate (17)

To a suspension of **16** (452 mg, 1.8 mmol), powdered molecular sieves 3Å (0.9 g) and florisil (2.7 g) in CH_2Cl_2 (16 ml) was added PCC (1.73 g, 4.5 mmol) at 0 °C. The mixture was stirred for 16 h at room temperature. After the mixture was diluted with ether, another amount of florisil (*ca.* 10 g) was added. After stirring for 30 min, the mixture was filtered through a pad of celite and florisil and the filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:Hexane=1:8) of the residue gave **17** (385 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ +70.3° (c = 1.07, $CHCl_3$). IR (neat) 3000, 1730, 1140, 1065, 845 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.26 (s, 9H, ^{t}*Bu*), 1.39, 1.51 (sx2, 3Hx2, C*Me*$_2$), 4.13 (dd, 1H, J = 8.9, 5.4 Hz, -CHCH_2-), 4.22 (dd, 1H, J = 8.9, 7.8 Hz, -CHCH_2-), 4.53 (dd, 1H, J = 5.4, 7.8 Hz, -*C*HCH$_2$-) 4.89, 4.99 (dx2, 1Hx2, J = each 17.7 Hz, -*C*H_2OPiv). MS (m/e) (%) 229 $[(M\text{-}Me)^+]$ (4), 101 (100), 57 (43), 43 (34).

(2*R*)-2-Hydroxy-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1-yl 2,2-Dimethylpropanoate (18) and (2*S*)-2-Hydroxy-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1-yl 2,2-Dimethylpropanoate (19)

To a solution of trimethylsilylacetylene (1.85 g, 2.7 ml, 19 mmol) in THF (20 ml) was slowly added n-BuLi (1.6 M in hexane, 9.4 ml, 15 mmol) at -78 °C. After stirring for 20 min, N,N,N',N'-tetramethylethylenediamine (2.19 g, 2.8 ml, 19 mmol) was added and stirring was continued for 30 min. A solution of **17** (3.06 g, 13 mmol) in THF (5 ml) was then added and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with sat. NH_4Cl. The mixture was diluted with ether and hexane, and allowed to warm up to room temperature. The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was dissolved in THF (30 ml) and cooled to 0 °C. TBAF (1 M in THF, 13.8 ml, 13.8 mmol) was added and the mixture was stirred for 5 min. After dilution with ether and hexane, the mixture was 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 less polar **18** (2.04 g, 60%) and more polar **19** (1.08 g, 32%) both as colorless prisms. Analytical samples of **18** and **19** were obtained by recrystallization from hexane. The stereostructure of more polar **19** was determined by single crystal X-ray analysis.[19] **18**: $[\alpha]_D^{20}$ +7.3° (c = 0.90, $CHCl_3$). m.p. 56 - 58 °C. IR ($CHCl_3$) 3575, 3325, 2990, 2130, 1730, 1150, 1065, 850, 645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.24 (s, 9H, *t-Bu*), 1.38, 1.47 (sx2, 3Hx2, C*Me*$_2$), 2.47 (s, 1H, *HC*≡C-), 2.85 (s, 1H, *-OH*), 4.11, 4.33 (dx2, each 1H, J = 11.2 Hz, *-CH*$_2$OPiv), 4.15 (m, 2H, -CH*CH*$_2$-), 4.24 (dd, 1H, J = 7.1, 6.1 Hz, *-CH*CH$_2$-). MS (m/e) (%) 255 [(M-Me)$^+$] (5), 101 (50), 57 (100). Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%. Found: C, 62.24; H, 8.21%. **19**: $[\alpha]_D^{20}$ +18.0° (c = 1.03, $CHCl_3$). m.p. 120.5 - 121 °C. IR ($CHCl_3$) 3600, 3330, 3000, 2125, 1730, 1150, 1070, 850, 645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.25(s, 9H, *t-Bu*), 1.37, 1.48 (sx2, each 3H, C*Me*$_2$), 2.50 (s, 1H, *HC*≡C-), 2.90 (br, 1H, *-OH*), 4.11-4.17 (3H, -CH*CH*$_2$- and *-CH*CH$_2$-), 4.19, 4.41 (dx2, 1Hx2, J = each 11.6 Hz, *-CH*$_2$OPiv). MS (m/e) (%) 255[(M-Me)$^+$] (16), 101 (100), 57 (87), 43 (51). Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%. Found: C, 62.04; H, 8.29%.

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-butyn-1,2-diol (21)

To a solution of **19** (68.3 mg, 0.25 mmol) in MeOH (2 ml) was added NaOMe (5 mg, 0.09 mmol) and the whole mixture was heated at reflux for 2 h. After dilution with ether and hexane, the solution was washed with brine. The water phase separated was saturated with NaCl and extracted with EtOAc. The organic phases were combined, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:1) of the residue gave **21** (42.1 mg, 89%). An analytical sample of **21** was obtained by recrystallization from hexane. $[\alpha]_D^{20}$ +13.4° (c = 0.25, $CHCl_3$). m.p. 75.5 - 76 °C. IR ($CHCl_3$) 3625, 3340, 3010, 2150, 1370, 1070, 850, 650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.38, 1.48 (sx2, 3Hx2, C*Me*$_2$), 2.16 (t, 1H, J = 6.5 Hz, -CH$_2$*OH*), 2.53 (s, 1H, *HC*≡C-), 2.87 (s, 1H, *-OH*), 3.74 (dd, 1H, J = 11.4, 7.1 Hz, *-CH*$_2$OH), 3.80 (dd, 1H, J = 11.4, 5.0 Hz, *-CH*$_2$OH), 4.12 (dd, 1H, J = 8.6, 6.9 Hz, -CH*CH*$_2$-), 4.15 (dd, 1H, J = 8.5, 6.0 Hz, -CH*CH*$_2$-), 4.20 (dd, 1H, J = 6.9, 6.0 Hz, *-CH*CH$_2$-). MS (m/e) (%) 187 [(M+1)$^+$], 171 [(M-Me)$^+$] (16), 101 (56), 43 (100). Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58%. Found: C, 58.18; H, 7.72%.

(2*S*)-2-Hydroxy-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1-yl (2*R*)-2-Methoxy-2-phenyl-3-trifluoropropanoate (22)

To a solution of **21** (18.9 mg, 0.10 mmol) in pyridine (0.2 ml) was added (*R*)-α-methoxy-α-trifluoromethyl-phenylaceticacid chloride [(*R*)-MTPA chloride] (49.4 mg, 0.04 ml, 0.14 mmol) at 0 °C and the mixture was stirred for 3 h. After dilution with EtOAc, the mixture was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Without purification, this sample was used for ^{1}H-NMR mesurment. ^{1}H-NMR ($CDCl_3$) δ = 1.34, 1.46 (sx2, 3Hx2, C*Me*$_2$), 2.48 (s, 1H, *HC*≡C-), 3.50 (br, 1H, -OH), 3.57 (d, 3H, J = 1.0 Hz, -*OMe*), 4.06 - 4.14 (m, 3H, -CH*CH*$_2$- and -*CH*CH$_2$-), 4.42, 4.59 (dx2, 1Hx2, J = 11.3 Hz, -*CH*$_2$OPiv), 7.38 - 7.42 (m, 3H), 7.54 - 7.60 (m, 2H). MS (m/e) (%) 387 [(M-Me)$^+$] (2), 189 (7), 101 (19), 43 (12).

(2*S*)-2-Hydroxy-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1-yl (2*S*)-2-Methoxy-2-phenyl-3-trifluoropropanoate (23)

To a solution of **21** (23.2 mg, 0.12 mmol) in pyridine (0.2 ml) was added (*S*)-α-methoxy-α-trifluoromethyl-phenylaceticacid chloride [(*S*)-MTPA chloride] (52.3 mg, 0.04 ml, 0.15 mmol) at 0 °C and the mixture was stirred for 3 h. After dilution with EtOAc, the mixture was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Without purification, this sample was used for ^{1}H-NMR mesurment. ^{1}H-NMR ($CDCl_3$) δ = 1.33, 1.47 (sx2, 3Hx2, C*Me*$_2$), 2.50 (s, 1H, *HC*≡C-), 3.50 (br, 1H, -OH), 3.59 (d, 3H, J = 1.0 Hz, -*OMe*), 4.04 - 4.10 (m, 2H, -CH*CH*$_2$- and -*CH*CH$_2$-), 4.12 (dd, 1H, J = 5.0, 3.3 Hz, -*CH*CH$_2$-), 4.39, 4.61 (dx2, 1Hx2, J = 11.3 Hz, -*CH*$_2$OPiv), 7.38 - 7.42 (m, 3H), 7.54 - 7.60 (m, 2H). MS (m/e) (%) 387 [(M-Me)$^+$] (3), 189 (9), 101 (22), 43 (13). Compareing the ^{1}H-NMR spectra of **22** and **23**, the optical purity of **21** was determined at least 98%.

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1-yl 2,2-Dimethylpropanoate (24) and (2*S*)-1-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-2-yl 2,2-Dimethylpropanoate (25)

To a solution of **19** (549 mg, 2.0 mmol) in CH_2Cl_2 (5 ml) were added 2,6-lutidine (653 mg, 0.71 ml, 6.1 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (1.07 g, 0.93 ml, 4.1 mmol) and the mixture was stirred over night at room temperature. After dilution with ether and hexane, the resulting mixture was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:30) of the residue gave **24** (458 mg, 59%) and **25** (247 mg, 32%), both as oils.
24: $[\alpha]_D^{20}$ +4.6° (c = 1.36, $CHCl_3$). IR (neat) 3275, 2950, 2125, 1735, 1150, 1085, 840, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.22, 0.23 (sx2, 3Hx2, Si*Me*$_2$), 0.84 (s, 9H, Si*t-Bu*), 1.23 (s, 9H, *t-Bu*), 1.34, 1.45 (sx2, 3Hx2, C*Me*$_2$), 2.55 (s, 1H, *HC*≡C-), 4.08 (dd, 1H, J = 8.3, 7.0 Hz, -CH*CH*$_2$-), 4.11 (dd, 1H, J = 8.3, 6.1 Hz, -CH*CH*$_2$-), 4.19 (t, 1H, J = 6.5 Hz, -*CH*CH$_2$-), 4.13, 4.29 (dx2, 1Hx2, J = each 11.5 Hz, -*CH*$_2$OPiv). MS (m/e) (%) 369 [(M-Me)$^+$] (3), 327 [(M-*t*Bu)$^+$] (4), 269 (5), 159 (30), 101 (61), 57 (100). **25**: $[\alpha]_D^{20}$ +14.5° (c = 0.79, $CHCl_3$). IR (neat) 3330, 2970, 2860, 2930, 1480, 1255, 1075, 840, 780 cm^{-1}. This compound was

found to exist as a mixture of two rotamers (*ca.* 2.3:1) by its ^{1}H-NMR spectrum. The signals of the minor isomer were indicated by asterisks. ^{1}H-NMR ($CDCl_3$) δ = 0.16, 0.17 (sx2, Si*Me*$_2$) and 0.25*, 0.26* (sx2, Si*Me*$_2$) total 6H, 0.91 (s, Si^t*Bu*) and 0.92*, (s, Si^t*Bu*) total 9H, 1.03 (s, ^{t}*Bu*) and 1.00* (s, ^{t}*Bu*) total 9H, 1.36, 1.46 (sx2, C*Me*$_2$) and 1.34*, 1.46* (sx2, C*Me*$_2$) total 6H, 2.49 (s, *HC*≡C-) and 2.56* (s, *HC*≡C-) total 1H, 4.10-4.36 (m, 5H).

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butyn-1-ol (26)

To a solution of **24** (71.8 mg, 0.19 mmol) in CH_2Cl_2 (3 ml) was added diisobutyl aluminumhydride (0.93 M in hexane, 0.44 ml, 0.41 mmol) at -78 °C and the mixture was stirred for 1 h. After dilution with ether, a small amount of water was added to quench the reaction. The mixture was stirred for 30 min at room temperature. The resulting white precipitates were filtered off through a pad of celite and the filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:8) of the residue gave **26** (50.9 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ +5.8° (c=0.94, $CHCl_3$). IR ($CHCl_3$) 3460, 3300, 2920, 2100, 1460, 1370, 1250, 1075, 830, 770 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.22, 0.23 (sx2, 3Hx2, Si*Me*$_2$), 0.87 (s, 9H, Si^t*Bu*), 1.36, 1.46 (sx2, 3Hx2, C*Me*$_2$), 2.14 (dd, 1H, J = 9.7, 4.0 Hz, -CH_2*OH*), 2.57 (s, 1H, *HC*≡C-), 3.69 (dd, 1H, J = 11.2, 4.0 Hz, -*CH*$_2$OH), 3.74 (dd, 1H, J = 11.2, 9.7 Hz, -*CH*$_2$OH), 4.10 (m, 2H, -CH*CH*$_2$-), 4.19 (dd, 1H, J = 7.0, 6.0 Hz, -*CH*CH$_2$-). MS (m/e) (%); 285 [(M-Me)$^+$] (3), 269 [(M-CH_2OH)$^+$] (1), 211 (2), 185 (12), 155 (26), 101 (61), 75 (100), 73 (59), 43 (72).

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butynal (27)

To a solution of **26** (45.8 mg, 0.15 mmol) and triethyl amine (309 mg, 0.43 ml, 3.1 mmol) in dry DMSO (1 ml) was added sulfur trioxide-pyridine complex (258 mg, 1.6 mmol) in one portion at room temperature and the mixture was stirred for 3 h at the same temperture. The mixture was diluted with hexane and ether, and washed with water and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:10) of the residue gave **27** (36.6 mg, 80%) as a colorless oil. $[\alpha]_D^{28}$ +62.5° (c=0.70, hexane). IR ($CHCl_3$) 3310, 2940, 2110, 1745, 1410, 1375, 1255, 1090, 910, 845 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.17, 0.18 (sx2, 3Hx2, Si*Me*$_2$), 0.90 (s, 9H, Si^t*Bu*), 1.34, 1.48 (sx2, 3Hx2, C*Me*$_2$), 2.72 (s, 1H, *HC*≡C-), 4.12 (dd, 1H, J = 8.5, 7.0 Hz, -CH*CH*$_2$-), 4.14 (dd, 1H, J = 8.5, 5.3 Hz, -CH*CH*$_2$-), 4.19 (dd, 1H, J = 7.0, 5.3 Hz, -*CH*CH$_2$-), 9.52 (s, 1H, -*CHO*). MS (m/e) (%); 283 [(M-Me)$^+$] (3), 269 [(M-CHO)$^+$] (3), 155 (7), 101 (100), 73 (52), 43 (46).

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(5*E*)-5-(3-trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl]-3-butyn-1-yl 2,2-Dimethylpropanoate (28)

To a degassed DMF solution (1.5 ml) of **7** (105 mg, 0.33 mmol), **24** (138 mg, 0.36 mmol) and diethylamine (47 mg, 0.067 ml, 0.65 mmol) were added tetrakistriphenylphosphine palladium (0) (188 mg, 0.16 mmol) and copper (I) iodide (61.9 mg, 0.33 mmol) and the mixture was stirred for 30 min at room temperature. The mixture was diluted with hexane and ether, and washed with water and brine. The organic phase was dried

over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=1:10) of the residue gave **28** (155 mg, 86%) as a pale brown oil. $[\alpha]_D^{20}$ +22.1° (c=0.83, hexane). IR (CCl_4) 3000, 2170, 1742, 1150, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.19 (s, 9H, Si*Me*$_3$), 0.20 (s, 3Hx2, Si*Me*$_2$), 0.85 (s, 9H, Si^t*Bu*), 1.23 (s, 9H, ^{t}*Bu*), 1.34, 1.41 (sx2, 3Hx2, C*Me*$_2$), 2.61 (m, 2H, =CHC*H*$_2$CH$_2$-), 2.77 (m, 2H, =CHCH$_2$C*H*$_2$-), 4.09 (m, 2H, -CHC*H*$_2$-), 4.22 (t, 1H, J = 6.5Hz, -C*H*CH$_2$-), 4.15, 4.33 (dx2, 1Hx2, J = each 11.4 Hz, -C*H*$_2$OPiv), 5.67 (m, 1H, =C*H*-), 6.54 (m, 1H, =C*H*CH$_2$CH$_2$-). MS (m/e) (%) 543 [(M-Me)$^+$] (2), 501 (8), 457 (22), 341 (14), 159 (46), 101 (100), 73 (85), 57 (96), 43 (18).

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(5*E*)-5-(3-trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl]-3-butyn-1-ol (30)

To a solution of **28** (105 mg, 0.18 mmol) in CH_2Cl_2 (2 ml) was slowly added diisobutylaluminum hydride (1 M in hexane, 0.54 ml, 0.54 mmol) at -78 °C and the mixture was stirred for 5 h at the same temperature. After the reaction was quenched with a small amount of water, the mixture was diluted with ether and stirred for 15 min at room temperature. The resulting white precipitates were filtered off through a pad of celite and the filtrate was concentrated *in vacuo* to give the crude products. Flash chromatography (SiO_2, EtOAc:hexane=1:10) of this sample gave **30** (74.8 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ +18.3° (c=1.06, hexane). IR (CCl_4) 3525, 2950, 2160, 1260, 1090, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.19 (s, 9H, Si*Me*$_3$), 0.20 (s, 3Hx2, Si*Me*$_2$), 0.86 (s, 9H, Si^t*Bu*), 1.35, 1.42 (sx2, 3Hx2, C*Me*$_2$), 2.15 (dd, 1H, J = 10.1, 3.4 Hz, -CH$_2$*OH*), 2.60 (m, 2H, =CHC*H*$_2$CH$_2$-), 2.77 (m, 2H, =CHCH$_2$C*H*$_2$-), 3.75 (m, 2H, -C*H*$_2$OH), 4.10 (m, 2H, -CHC*H*$_2$-), 4.22 (t, 1H, J = 6.5 Hz, -C*H*CH$_2$-), 5.68 (m, 1H, =C*H*-), 6.55 (m, 1H, =C*H*CH$_2$CH$_2$-). MS (m/z) (%) 443 [(M-CH$_2$OH)$^+$] (1), 417 [(M-^{t}Bu)$^+$] (4), 373 (10), 147 (10), 101 (100), 73 (93), 59 (13), 43 (21).

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-[(5*E*)-5-(2-propynylidene)-1-cyclopenten-1-yl]-3-butyn-1,2-diol (32)

To a solution of **30** (41.9 mg, 0.09 mmol) in THF (5 ml) was added TBAF (1 M in THF, 0.18 ml, 0.18 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature. After dilution with hexane and ether, the mixture was washed with water and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc:hexane=2:1) of the residue gave **32** (21.5 mg, 84%) as an unstable solid. $[\alpha]_D^{20}$ +46.3° (c=0.19, MeOH). IR (KBr) 3325, 3000, 2950, 2225, 2106, 1620, 1065, 1035, 855 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.37, 1.47 (sx2, 3Hx2, C*Me*$_2$), 2.14 (dd, 1H, J = 7.7, 6.0 Hz, -CH$_2$*OH*), 2.61 (m, 2H, =CHC*H*$_2$CH$_2$-), 2.73 (m, 2H, =CHCH$_2$C*H*$_2$-), 2.83 (s, 1H, -*OH*), 3.22 (d, 1H, J = 2.3 Hz, *HC*≡C-), 3.79 (dd, 1H, J = 11.4, 7.7 Hz, -C*H*$_2$OH), 3.84 (dd, 1H, J = 11.4, 5.9 Hz, -C*H*$_2$OH), 4.14 (dd, 1H, J = 8.6, 6.8 Hz, -CHC*H*$_2$-), 4.17 (dd, 1H, J = 8.6, 6.0Hz, -CHC*H*$_2$-), 4.24 (t, 1H, J = 6.4 Hz, -C*H*CH$_2$-), 5.63 (m, 1H, =C*H*-), 6.57 (m, 1H, =C*H*CH$_2$CH$_2$-). Ms (m/z) (%) 288 (M$^+$) (2), 273 [(M-Me)$^+$] (3), 128 (18), 101 (100), 73 (11), 43 (47). HRMS calcd for $C_{17}H_{20}O_4$: 288.1360. Found: 288.1373.

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(5*Z*)-5-(3-trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl]-3-butyn-1-yl 2,2-Dimethylpropanoate (29)

To a degassed DMF solution (0.3 ml) of **8** (15.4 mg, 0.05 mmol), **24** (33.5 mg, 0.09 mmol) and diethylamine (7 mg, 0.01 ml, 0.10 mmol) were added tetrakistriphenylphosphine palladium (0) (27.5 mg, 0.02 mmol) and copper (I) iodide (9.1 mg, 0.05 mmol) and the mixture was stirred for 10 min at room temperature. The mixture was worked up in the same manner as described for the preparation of **28**, giving **29** (19.3 mg, 73%) as a pale brown oil after flash chromatography (SiO_2, EtOAc:hexane=1:10) of the residue. $[\alpha]_D^{20}$ +10.6° (c=0.66, hexane). IR (neat) 2975, 2180, 2125, 1735, 1140, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.20 (s, 9H, Si*Me*$_3$), 0.25 (sx2, 3Hx2, Si*Me*$_2$), 0.90 (s, 9H, Si^t*Bu*), 1.23 (s, 9H, ^{t}*Bu*), 1.35, 1.45 (sx2, 3Hx2, C*Me*$_2$), 2.53 (m, 2H, =CHC*H*$_2$CH$_2$-), 2.67 (m, 2H, =CHCH$_2$C*H*$_2$-), 4.08-4.15 (m, 2H, -CHC*H*$_2$-), 4.27 (t, 1H, J = 6.7 Hz, -*CH*CH$_2$-), 4.18, 4.48 (dx2, 1Hx2, J = each 11.6 Hz, -*CH*$_2$OPiv), 5.57 (m, 1H, =*CH*-), 6.66 (m, 1H, =*CH*CH$_2$CH$_2$-). MS (m/z) (%); 501 [(M-^{t}Bu)$^+$] (2), 457 (3), 341 (3), 159 (29), 101 (46), 57 (100), 43 (17).

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(5*Z*)-5-(3-trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl]-3-butyn-1-ol (31)

To a solution of **29** (33.6mg, 0.06mmol) in CH_2Cl_2 (3 ml) was slowly added diisobutylaluminum hydride (1 M in hexane, 0.70 ml, 0.70 mmol) at -78 °C and mixture was stirred for 1 h. After the reaction was quenched with a small amount of water, the mixture was diluted with ether and stirred for 15 min at room temperature. The mixture was worked up in the same manner as described for the preparation of **30**, giving **31** (19.4 mg, 68%) as a colorless oil after flash chromatography (SiO_2, EtOAc:hexane=1:10) of the residue. $[\alpha]_D^{20}$ +32.6° (c=1.05, hexane). IR (CCl_4) 2920, 2140, 1250, 1080, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.25 (s, 9H, Si*Me*$_3$), 0.27, 0.28 (s, 3Hx2, Si*Me*$_2$), 0.90 (s, 9H, Si^t*Bu*), 1.36, 1.45 (sx2, 3Hx2, C*Me*$_2$), 2.18 (t, 1H, J = 7.2 Hz, -CH$_2$*OH*), 2.53 (m, 2H, =CHC*H*$_2$CH$_2$-), 2.67 (m, 2H, =CHCH$_2$C*H*$_2$-), 3.75 (m, 2H, -*CH*$_2$OH), 4.10 (m, 2H, -CHC*H*$_2$-), 4.24 (t, 1H, J = 6.7 Hz, -*CH*CH$_2$-), 5.59 (m, 1H, =*CH*-), 6.68 (m, 1H, =*CH*CH$_2$CH$_2$-). MS (m/z) (%) 443 [(M-CH$_2$OH)$^+$] (1), 417 [(M-^{t}Bu)$^+$] (1), 373 (4), 285 (2), 241 (5), 195 (3), 101 (53), 73 (100), 43 (20).

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-[(5Z)-5-(2-propynylidene)-1-cyclopenten-1-yl]-3-butyn-1,2-diol (33)

To a solution of **31** (10.2mg, 0.02mmol) in THF (1 ml) was added TBAF (1 M in THF, 0.04 ml, 0.04 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature. After dilution with hexane and ether, the mixture was worked up in the same manner as described for the preparation of **32**, giving **33** (5.5 mg, 89%) as an unstable solid after flash chromatography (SiO_2, EtOAc:hexane=2:1) of the residue. $[\alpha]_D^{20}$ +16.2° (c=0.38, MeOH). IR (KBr) 3450, 3275, 2940, 2125, 1680, 1370, 1060, 1030, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.37, 1.48 (sx2, 3Hx2, C*Me*$_2$), 2.24 (dd, 1H, J = 9.0, 5.3 Hz, -CH$_2$*OH*), 2.54 (m, 2H, =CHC*H*$_2$CH$_2$-), 2.68 (m, 2H, =CHCH$_2$C*H*$_2$-), 2.93 (s, 1H, -*OH*), 3.15 (d, 1H, J = 2.9 Hz, *HC*≡C-), 3.72 (dd, 1H, J = 11.3, 8.9 Hz, -*CH*$_2$OH), 3.86 (dd, 1H, J = 11.4, 5.1 Hz, -*CH*$_2$OH), 4.16 (dd, 1H, J = 8.4, 7.1 Hz, -CHC*H*$_2$-), 4.19 (dd, 1H, J = 8.5, 5.7 Hz, -CHC*H*$_2$-), 4.23 (dd, 1H, J = 7.1, 5.7 Hz, -*CH*CH$_2$-), 5.45 (m, 1H, =*CH*-), 6.67 (m, 1H, =*CH*CH$_2$CH$_2$-). MS (m/z) (%) 273 [(M-Me)$^+$] (3), 199 (4), 128 (12), 101 (100), 73 (13), 43 (51). HRMS calcd for $C_{16}H_{17}O_4$ [(M-Me)$^+$]: 273.1125. Found: 273.1133.

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(5*E*)-5-(3-trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl]-3-butynal (34)

To a degassed DMF solution (0.3 ml) of **7** (18.1 mg, 0.06 mmol), **27** (10.3 mg, 0.04 mmol) and diethylamine (5 mg, 0.007 ml, 0.07 mmol) were added tetrakistriphenylphosphine palladium (0) (20.0 mg, 0.02 mmol) and copper (I) iodide (6.6 mg, 0.04 mmol) and the mixture was stirred for 25 min at room temperature. The mixture was diluted with hexane and ether, and washed successively with sat. NH_4Cl, sat. $NaHCO_3$ and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Purification of the residue by preparative thin layer chromatography (SiO_2, EtOAc:hexane=1:10) **34** (12.4 mg, 76%) as a colorless oil. $[\alpha]_D^{20}$ +103.4° (c=1.12, hexane). IR (neat) 2960, 2940, 2860, 2130, 1740, 1460, 1370, 1250, 1085, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.16 (s, 6H, Si*Me*$_2$), 0.21 (s, 9H, Si*Me*$_3$), 0.90 (s, 9H, Si^t*Bu*), 1.34, 1.45 (sx2, 3Hx2, C*Me*$_2$), 2.63 (m, 2H, =CH*C*H_2CH$_2$-), 2.79 (m, 2H, =CHCH$_2$*C*H_2-), 4.13 (dd, 1H, J = 8.6, 7.0 Hz, -CH*C*H_2-), 4.16 (dd, 1H, J = 8.6, 5.4 Hz, -CH*C*H_2-), 4.22 (dd, 1H, J = 6.9, 5.4 Hz, -*C*HCH$_2$-), 5.68 (m, 1H, =*C*H-), 6.60 (t, 1H, J = 3.1 Hz, =*C*HCH$_2$CH$_2$-), 9.55 (s, 1H, -*C*HO). MS (m/e) (%); 457 [(M-Me)$^+$], 443 [(M-CHO)$^+$] (2), 415 [(M-^{t}Bu)$^+$] (3), 372 (8), 357 (4), 315 (2), 241 (2), 227 (4), 101 (100), 73 (15).

(2*S*)-2-(*t*-Butyldimethylsilyloxy)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(5*Z*)-5-(3-trimethylsilyl-2-propynylidene)-1-cyclopenten-1-yl]-3-butynal (35)

a) Prepation from **8** and **27**. To a degassed solution of **8** (11.6 mg, 0.04 mmol) and **27** (10.7 mg, 0.04 mmol) and triethylamine (7.2 mg, 0.01 ml, 0.07 mmol) were added tetrakistriphenylphosphine palladium (0) (20.7 mg, 0.02 mmol) and copper (I) iodide (6.8 mg, 0.04 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was diluted with hexane and ether, and washed successively with sat. NH_4Cl, sat. $NaHCO_3$ and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Purification of this sample by preparative thin layer chromatography (SiO_2, EtOAc:toluene=1:50) of the residue gave a small amount of sample which indicated an aldehyde signal in its ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum of this compound was identical to that of **35** obtained by photo-induced isomerization of **34**.

b) Prepation from **34** by photo-induced isomerization. A hexane solution (3 ml) of **34** (8.8 mg, 0.02 mmol) was irradiated with low pressure mercury lamp through vycor filter for 40 min at room temperature. After concentration *in vacuo*, the crude products were separated by preparative thin layer chromatography pretreated with triethylamine (SiO_2, EtOAc:hexane=1:10) to give **36** (1.9 mg, 23%), **37** (1.4 mg, 17%), **35** (1.0 mg, 11%) and **34** (0.8 mg). **36**: ^{1}H-NMR ($CDCl_3$) δ = 0.13, 0.14 (sx2, 3Hx2, Si*Me*$_2$), 0.20 (s, 9H, Si*Me*$_3$), 0.91 (s, 9H, Si^t*Bu*), 1.36, 1.44 (sx2, 3Hx2, C*Me*$_2$), 2.59 (m, 2H, =CH*C*H_2CH$_2$-), 2.77 (m, 2H, =CHCH$_2$*C*H_2-), 4.01 (dd, 1H, J = 8.6, 5.9 Hz, -CH*C*H_2-), 4.09 (dd, 1H, J = 8.6, 6.5 Hz, -CH*C*H_2-), 4.17 (q, 1H, J = 6.1 Hz, -*C*HCHOSi), 4.62 (d, 1H, J = 5.7 Hz, -CHC*H*OSi), 5.62 (m, 1H, =*C*H-), 6.50 (t, 1H, J = 3.1 Hz, =*C*HCH$_2$CH$_2$-). MS (m/e) (%); 444 (M$^+$), 429 [(M-Me)$^+$], 387 [(M-^{t}Bu)$^+$] (11), 329 (11), 101 (89), 73 (100). **37**: ^{1}H-NMR ($CDCl_3$) δ = 0.15, 0.16 (sx2, 3Hx2, Si*Me*$_2$), 0.20 (s, 9H, Si*Me*$_3$), 0.92 (s, 9H, Si^t*Bu*), 1.35, 1.43 (sx2, 3Hx2, C*Me*$_2$), 2.50 (m, 2H, =CH*C*H_2CH$_2$-), 2.66 (m, 2H, =CHCH$_2$*C*H_2-), 4.02 (dd, 1H, J = 8.7, 5.9 Hz, -CH*C*H_2-), 4.09 (dd, 1H, J = 8.7, 6.6 Hz, -CH*C*H_2-), 4.21 (m, 1H, -*C*HCHOSi), 4.51 (d, 1H, J = 6.7 Hz, -CHC*H*OSi), 5.56 (m, 1H, =*C*H-), 6.67 (m, 1H, =*C*HCH$_2$CH$_2$-). MS (m/e) (%); 444 (M$^+$), 429 [(M-

Me)$^+$], 387 [(M-^{t}Bu)$^+$] (4), 343 (5), 329 (5), 255 (5), 147 (18), 101 (58), 73 (100). **35**: ^{1}H-NMR ($CDCl_3$) δ = 0.19 (sx2, 9H and 6H, Si*Me*$_3$ and Si*Me*$_2$), 0.91 (s, 9H, Si^t*Bu*), 1.34, 1.48 (sx2, 3Hx2, C*Me*$_2$), 2.54 (m, 2H, =CH*C*H_2CH$_2$-), 2.67 (m, 2H, =CHCH$_2$*C*H_2-), 4.14 (dd, 1H, J = 8.6, 6.8 Hz, -CH*C*H_2-), 4.18 (dd, 1H, J = 8.6, 5.8 Hz, -CH*C*H_2-), 4.24 (dd, 1H, J = 6.7, 5.8 Hz, -*C*HCH$_2$-), 5.58 (m, 1H, =*C*H-), 6.71 (m, 1H, =*C*HCH$_2$CH$_2$-), 9.63 (s, 1H, -*CHO*). MS (m/e) (%); 457 [(M-Me)$^+$], 443 [(M-CHO)$^+$], 415 [(M-^{t}Bu)$^+$] (1), 372 (2), 357 (5), 315 (4), 101 (69), 73 (100).

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