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Synthetic Studies on the Compounds Related to Neocarzinostatin Chromophore. 3.[1,2] Novel Synthesis of a Chiral Cyclic Dienediyne System

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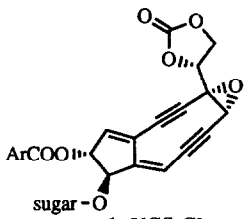
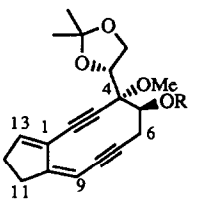
Key Words· neocarzinostatin chromophore; cyclic dienediyne; D-xylose; epoxide; Pd-catalyzed coupling

Abstract: Novel synthesis of the chiral 10-membered dienediynes (**2** and **3**) related to neocarzinostatin chromophore was accomplished by utilizing cyclization of an epoxy acetylene as a key step. The epoxy acetylene was prepared from the (Z)-dienediyne diol which could be obtained by coupling reaction of the (Z)-enol triflates (**5**) with the optically active acetylene diol (**25**) derived from D-xylose.

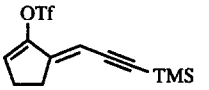
The compounds having characteristic ene-yne structures such as calicheamicin,[4] esperamicin,[5] dynamicin A,[6] and neocarzinostatin chromophore (NCS-Chr) (**1**)[7] have been drawing significant attention because of their potential antitumor activity as well as their novel structures, which are now recognized to deeply relate to their activation mechanisms.[8] Among them, **1**, the active component of antitumor antibiotic neocarzinostatin (NCS), is unique in that it involves the unprecedented bicyclo[7.3.0]dodecadienediyne core system.[7] Furthermore, it is known to exist as a form of the complex with protein (apo-NCS), which is supposed to stabilize extremely labile **1**.[9] Although NCS has been in clinical uses for curing various tumors,[10] apo-NCS, the non-human originated protein, has been pointed out that it might be a potential source of antigen.[11] Thus, evaluation of stable but still active analogues of **1** which do not require the stabilization by apo-NCS, might explore their utility as an anticancer agent without the risks inherent in clinical uses of non-human peptide.



1 NCS-Chr



2 ; R = H
3 ; R = Ac



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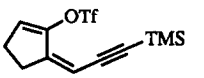

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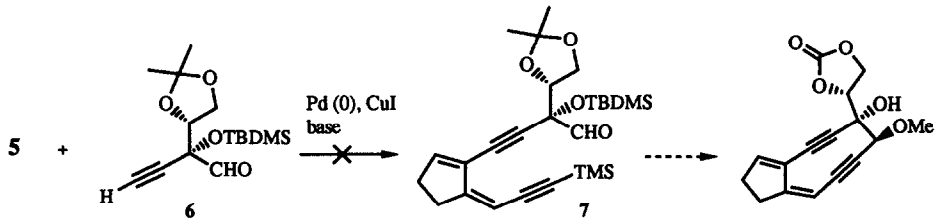
While much synthetic works have been devoted to construct the highly strained dienediyne core system of **1**, the synthetic sequence employing cyclization-dienediyne system formation initially developed by Wender et al.[12a,b] later by others has so far been the only promising route for cyclic analogues of **1**.[12,13] From the synthetic viewpoint of various types of analogues of **1** as well as **1** itself, construction of stereo-defined (Z)-

† This paper is dedicated to Professor Shun-ichi Yamada, Professor Emeritus of the University of Tokyo, on the occasion of his 77th birthday.

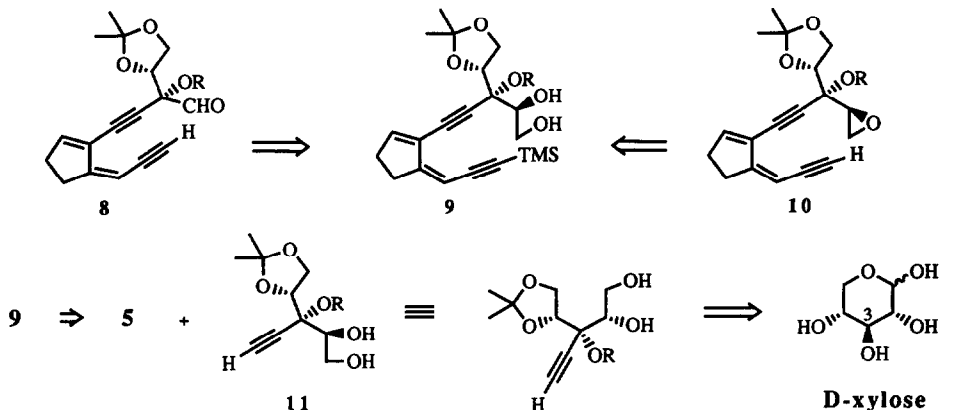
dienediyne system prior to ring formation was the general strategy of choice in our synthetic studies on the compounds related to **1**. Accordingly, we have reported the synthesis of the stereo-defined (E)- and (Z)-dienediyne systems[1,2,14] featuring two different types of the (E)- and (Z)-enol triflates as key intermediates.[15] We, herein, wish to disclose details of our recent results on the synthesis of optically active 10-membered dienediyne compounds (**2** and **3**) including the C_{13}-C_{14} portion of **1** with correct absolute configuration.[2] Furthermore, attempts to obtain 9-membered dienediyne compounds were also discussed.

The synthetic scheme for stereo-defined (E)- and (Z)-dienediyne systems which we have previously developed, utilizes the palladium-catalyzed coupling reaction of both (E)- and (Z)-enol triflates (**4** and **5**) with acetylene derivatives.[11b] The (Z)-dienediyne aldehyde (**7**) required for the proposed 9-membered dienediyne formation, however, could not be obtained by the direct coupling reaction of **5** and the acetylenic aldehyde (**6**) derived from D-isoascorbic acid.[1a] (**Scheme 1**)



Scheme 1

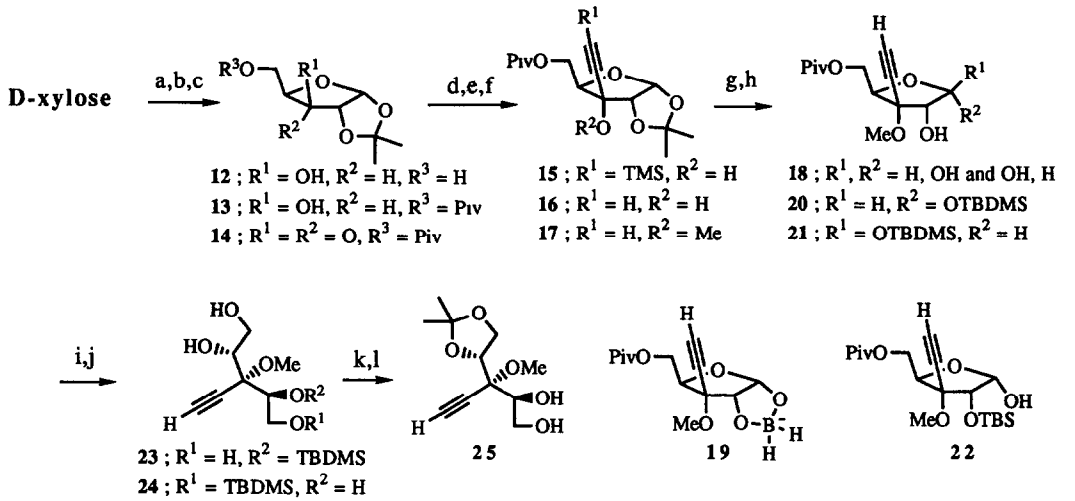
To circumvent this problem, oxidative cleavage of the glycol portion of the dienediynediol (**9**) was designed to obtain the aldehyde (**8**) as shown in **Scheme 2**. **9** was expected to be obtained by the coupling of **5** with the acetylenic diol (**11**), which could be derived from D-xylose. Assuming **9** as the key intermediate, another possibility for the synthesis of cyclic dienediyne compounds was realized. Thus, the dienediyne epoxide (**10**) anticipated to be derived from **9** might be a precursor for 10-membered cyclic dienediynes by taking into account the nucleophilic attack of acetylide anion toward the terminus of the epoxide ring. Since stability of 10-membered cyclic dienediyne compounds was reported to be much more improved than that of the corresponding 9-membered compounds,[12c] our initial goal was set at the cyclization of **10**.



Scheme 2

Preparation of the optically active acetylene diol (25) from D-xylose

The requisite acetylene diol (**25**) bearing (*3S, 4'R*) configuration was expected to be obtained by introducing an acetylene unit at C_3 position of D-xylose. The newly formed stereogenic center at C_3 position could be controlled by assuming that an acetylide anion approaches from the convex face of 1,2-O-isopropylidene-α-D-xylofuranose (**12**).[16] (**Scheme 3**) According to the literature, D-xylose was transformed into **12**,[17] whose primary alcohol was, then, protected as a pivaloate to give the alcohol (**13**). Swern oxidation of **13** followed by treatment with lithium trimethylsilylacetylide produced the addition product (**15**). This was, without purification, desilylated using tetrabutylammonium fluoride (TBAF) to give the highly crystalline terminal acetylene (**16**) as a sole addition product. After protection of the tertiary alcohol in **16** as a methyl ether, the 1,2-O-isopropylidene group was hydrolyzed with trifluoroacetic acid to give the hemiacetal (**18**). Although the next task was the reduction of **18**, direct reduction of **18** with sodium borohydride resulted in the recovery of **18**. Formation of the cyclic boronic ester such as **19** which might be stable under the reaction condition seemed to be



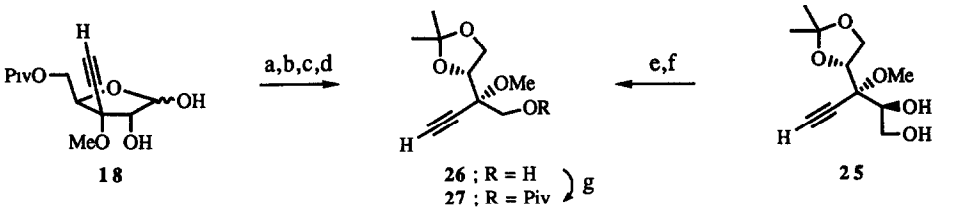
Scheme 3

a) acetone, cat. H_2SO_4 b) Me_3CCOCl, Py, rt, 74% (2 steps) c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C d)LiC≡CTMS, THF, -78°C e) TBAF, THF, 0°C, 72% (3 steps) f) MeI, K_2CO_3, acetone, sealed tube, 75°C, 77% g) CF_3CO_2H-H_2O (5:1), rt, 88% h) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -78°C, **20** (62%), **21** (11%) i) $NaBH_4$, THF-H_2O (1:1), rt j) NaOMe, MeOH, rt , 82% (2 steps) k) acetone, $CuSO_4$, rt l) TBAF, THF, rt, 63% (2 steps)

rapid. Various reaction conditions were examined, the direct reduction of **18** was, however, unsuccessful. To avoid the formation of **19**, protection of the hydroxy group at C_2 position was next attempted. Thus, treatment of **18** with TBDMSOTf in the presence of 2,6-lutidine afforded a mixture of the C_1-α- and C_1-β-silyl ethers (**20** and **21**). The desired C_2-silyl ether (**22**) was found to be the minor product in the above reaction mixture. It was, however, found that separated **20** could be cleanly reduced upon treatment with $NaBH_4$ in THF-H_2O. During this reduction, a rapid equilibrium between **20** and **22** was observed on TLC analysis. Accordingly, this reduction was considered to proceed via **22** after initial 1,2-migration of the silyl group from C_1 to C_2 position in the basic reaction condition. Without purification, the reduction product was allowed to react with NaOMe in MeOH to effect solvolysis of the pivaloate to give a mixture of the triol (**23**) and (**24**). The latter product (**24**)

was anticipated to be produced via the 1,2-silyl migration of initially formed **23**. This mixture was treated with acetone in the presence of $CuSO_4$ to form the acetonide, which was then desilylated with TBAF to furnish **25**.

In this synthetic scheme, a similar 1,3-silyl migration across the quaternary center which might cause partial racemization of **23** and **24**, was concerned. It was, however, ascertained that such 1,3-silyl migration was negligible in this case, by comparing the values of optical rotations of the pivaloate (**27**) derived from both **18** and **25**, respectively. (**Scheme 4**) Thus, oxidative cleavage of **18** with sodium periodate followed by reduction



18 **26** ; R = H, **27** ; R = Piv (g) **25**

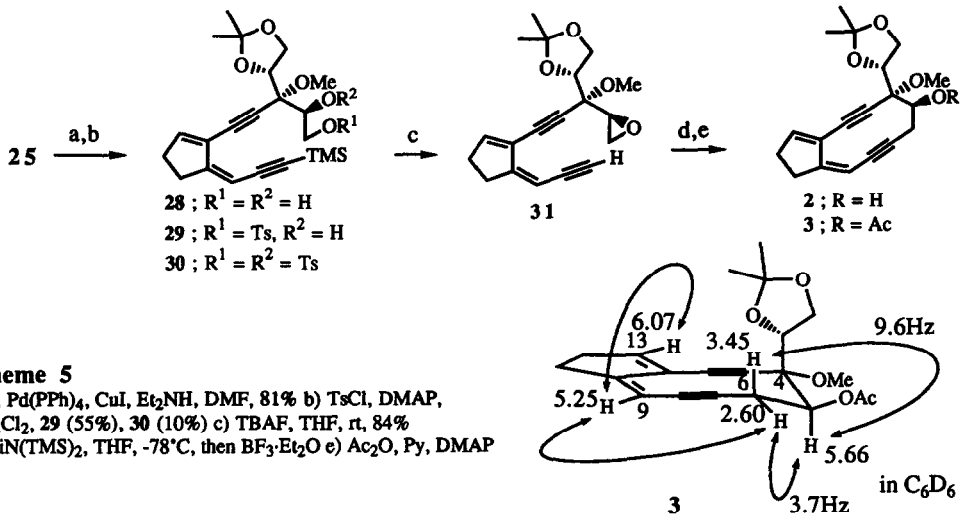
Scheme 4

a) $NaIO_4$, acetone-H_2O (9:1) b) $NaBH_4$, EtOH c) NaOMe, MeOH d) $CuSO_4$, acetone, 51% (4 steps) e) $NaIO_4$, acetone-H_2O (9:1) f) $NaBH_4$, EtOH, 82% (2 steps) g) Me_3CCOCl, Py, 89% (from **26** derived from **18**), 67% (from **26** derived from **25**)

of the resulting aldehyde with $NaBH_4$ and methanolysis in the presence of NaOMe afforded the triol, which was then converted into the acetonide (**26**). The primary alcohol in **26** was acylated with pivaloyl chloride to give **27**. In this sequence, there is no possibility to induce any racemization of **27**. Similarly, **25** was converted into **27** by sequential oxidative cleavage with $NaIO_4$, reduction with $NaBH_4$, and acylation with pivaloyl chloride. The optical rotations of each **27** derived from **18** and **25** were found to be $[\alpha]_D^{20}$ -7.2° (c=0.64, $CHCl_3$) and $[\alpha]_D^{20}$ -7.5° (c=0.81, $CHCl_3$) , respectively. These experiments definitely established that possible racemization by 1,3-silyl migration during the reaction sequence from **20** to **25** is negligible.

Formation of the 10-membered cyclic dienediynes (2 and 3)

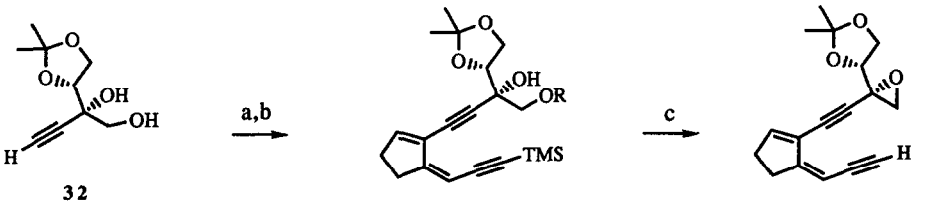
Next task was the coupling of **25** with **5** to obtain the key epoxide (**31**) for the proposed 10-membered dienediyne formation. (**Scheme 5**) Thus, palladium-catalyzed coupling reaction of **25** with **5** cleanly produced the dienediynediol (**28**). Tosylation of **28** afforded the monotosylate (**29**) along with the undesired ditosylate (**30**). Upon treatment of separated **29** with TBAF at room temperature, simultaneous desilylation and epoxide formation were effected to give the desired epoxy acetylene (**31**). With the key epoxide **31** in hand, cyclization to the cyclic dienediyne system was next examined. Treatment of **31** with lithium bistrimethylsilylamide ($LiN(TMS)_2$) in THF at -78 to 0°C resulted in complete recovery of the starting material (**31**). However, upon addition of $BF_3{\cdot}Et_2O$[18] after base treatment at -78°C, a single product immediately appeared on TLC analysis. After usual work-up and separation by column chromatography, the compound (**2**) exhibiting its molecular ion peak (M^+) at 314 in the mass spectrum could be obtained. Since separation of the signals in the 400 MHz ^1H-NMR spectrum of **2** measured in C_6D_6 was found not to be enough for structure elucidation, **2** was subjected to acetylation to give the monoacetate (**3**) [MS m/e: 356 (M^+)]. Decoupling and 2D-NMR experiments definitely disclosed the structure of **3** as a cyclic dienediyne since the long range couplings between $C_{6\alpha}$-H and C_9-H and C_9-H and C_{13}-H were observed as depicted. While preparation of stable 10-membered cyclic dienediynes had been reported by Hirama *et al.*,[12c,d,f] **2** and **3** were found to be extremely labile for concentration and could be treated only in a solution.



Scheme 5
a) **5**, $Pd(PPh)_4$, CuI, Et_2NH, DMF, 81% b) TsCl, DMAP, CH_2Cl_2, **29** (55%), **30** (10%) c) TBAF, THF, rt, 84% d) $LiN(TMS)_2$, THF, -78°C, then $BF_3{\cdot}Et_2O$ e) Ac_2O, Py, DMAP

Attempts on the formation of 9-membered cyclic dienediyne (38)

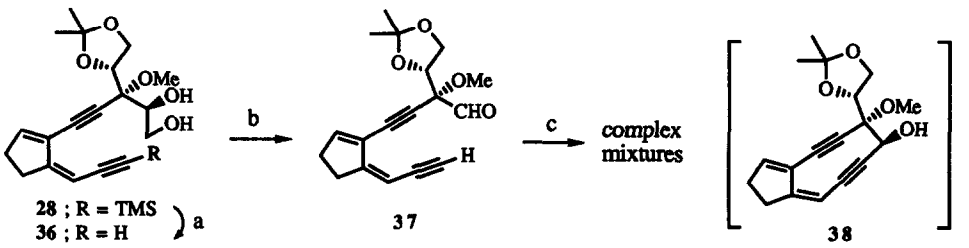
With completion of the synthesis of 10-membered dienediynes (**2** and **3**), our effort was next focused on the synthesis of 9-membered dienediyne compounds. We at first looked at the similar epoxide-ring opening strategy for 9-membered ring formation employing the dienediyne epoxide (**35**). Thus, the acetylene diol (**32**)[1a] derived from D-isoascorbic acid was coupled with **5** to give the dienediyne diol (**33**), which was converted to **35** by successive tosylation and desilylative epoxide formation. It was, however, found that **35** did not react in the same way as for **31**. Treatment of the lithium salt of **35** with $BF_3{\cdot}Et_2O$ gave no cyclized product but resulted in



Scheme 6
a) **5**, $Pd(PPh_3)_4$, CuI, Et_2NH, DMF, 75% c) TsCl, Py, 94% d) TBAF, THF, 61%

the recovery of **35**. It is well known for the epoxide ring opening reaction that incoming nucleophile and carbon-oxygen bond cleaved are required to be collinear for efficient S_N2 displacement.[19] In the case of **31** such alignment could be easily adopted, however, serious bending of acetylenic bonds in **35** would be required for the back side attack of acetylide anion. On the other hand, studies using molecular models obviously suggested that nucleophilic addition of acetylide anion with aldehyde carbonyl does not accompany such a serious bending of acetylenic bonds. Then, we looked at the cyclization of the aldehyde (**37**) featuring the nucleophilic addition of acetylide anion with aldehyde carbonyl.

The aldehyde (**37**) which could not be previously obtained by direct coupling of **5** with an acetylenic aldehyde was derived from **28**. Thus, desilylation of **28** followed by oxidative cleavage of the resulting diol



Scheme 7
a) TBAF, THF, 61% b) $NaIO_4$, acetone-H_2O (9:1) c) $LiN(TMS)_2$, THF, -78°C

(**36**) afforded **37** as an unstable compound. Upon treatment of **37** with excess amount of $LiN(TMS)_2$ in THF at -78 °C, **37** immediately disappeared, however, many spots of products were observed on TLC analysis. Although this reaction was also attempted in the presence of 1,4-cyclohexadiene as a hydrogen radical donor, no change of the reaction was detected on TLC analysis. Although production of the cyclized compound (**38**) was not detected at all, formation of the complex reaction products might suggest possible decomposition of **38** under strongly basic conditions. From these studies, however, it appeared that milder reaction conditions without use of highly nucleophilic species would be essential to obtain 9-membered dienediyne compounds.

Conclusion

As mentioned above, we have succeeded in the synthesis of optically active 10-membered cyclic dienediynes (**2** and **3**) having the C_{13}-C_{14} portion of **1** with correct absolute configurations by employing novel dienediyne construction - cyclization strategy. The synthetic scheme explored in these studies might facilitate to access various types of the cyclic compounds related to **1**. Furthermore, the acetylene diol (**25**) easily obtainable from D-xylose was demonstrated to be highly promising as a potential subunit of **1**.

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 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 and C-300 were used as an adsorbent for flash column chromatography.

5-(2,2-Dimethylpropanoyl)-1,2-O-isopropylidene-α-D-xylofuranose (13)

To a suspension of finely powdered D-xylose (30.0 g, 0.20 mmol) in anhydrous acetone (1 L) was slowly added concentrated sulfuric acid (20 ml) and the mixture was stirred for 2 hr at room temperature. A solution of potassium hydroxide (43 g, 0.77 mmol) in water (45 ml) was then added and the resulting precipitate was filtered off. After concentration of the filtrate *in vacuo*, the residue was dissolved in water (200 ml) and the aqueous solution was washed with hexane. The aqueous phase was concentrated *in vacuo* to give a syrup, which was dissolved in water (20 ml). After being saturated with sodium chloride, the resulting solution was extracted with ethyl acetate. The combined organic extracts were concentrated *in vacuo* to give crude 1,2-O-isopropylidene-α-D-xylofuranose (**12**). After azeotropical evaporation with toluene, crude **12** was treated with 2,2-dimethylpropanoyl chloride (24.1 g, 0.20 mol) in pyridine (16.6 g, 0.21 mol) at 0 °C for 1 hr. After dilution

with ether, the resulting mixture was washed with water and brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give **13** as colorless prisms (40.3 g, 74%). An analytical sample was obtained by recrystallization from hexane. $[\alpha]_D^{20}$ +28.8° (c=1.42, $CHCl_3$) and m.p. 36.0-38.0 °C. IR (CCl_4): 3525, 3000, 2950, 1720, 1485, 1285, 1165, 1080, 1020, 860cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 1.22 (s, 9H, $OCOCMe_3$), 1.32, 1.51 (sx2, each 3H, CMe_2), 3.2 (br, 1H, -OH), 4.04 (d, 1H, J=2.4 Hz, C_3-H), 4.14 (dd, 1H, J=11.3, 4.5 Hz, -CHOPiv), 4.22 (ddd, 1H, J=8.2, 4.5, 2.5 Hz, C_4-H), 4.53 (dd, 1H, J=11.3, 8.3 Hz, -CHOPiv), 4.56 (d, 1H, J=3.6Hz, C_2-H), 5.91 (d, 1H, J=3.6 Hz, C_1-H). MS (m/e) (%): 259 [(M-Me)$^+$] (15), 217 [(M-^{t}Bu)$^+$] (1), 159 (7), 145 (8), 129 (11), 85 (22), 57 (^{t}Bu)$^+$ (100). *Anal.* Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%. Found: C, 56.90; H, 8.21%.

5-(2,2-Dimethylpropanoyl)-3-ethynyl-1,2-O-isopropylidene-α-D-ribofuranose (16)
To a solution of oxalyl chloride (18.5 g, 12.8 ml, 0.15 mol) in CH_2Cl_2 (1 L) was slowly added a solution of DMSO (28.7 g, 26.0 ml, 0.29 mol) in CH_2Cl_2 (50 ml) at -78 °C over 15 min. After stirring for 15 min, a solution of **13** (20.0 g, 73 mmol) in CH_2Cl_2 (50 ml) was slowly added over 15 min and the mixture was stirred at -78 °C for another 30 min. Triethylamine (29.5 g, 0.29 mol, 40.6 ml) was then slowly added over 15 min and the mixture was gradually warmed up to -20 °C and stirred for another 1 hr. After the reaction was quenched with water (500 ml), the resulting mixture was extracted with ether and hexane. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give the crude ketone (**14**) (*ca.* 20.0 g). **14** was used for the next reaction without purification. To a solution of trimethylsilylacetylene (9.50 g, 96.7 mmol, 13.5 ml) in THF (140 ml) was added n-butyllithium (54.7 ml, 1.6 M in hexane, 91.8 mmol) at -78 °C over 15 min. After stirring for 30 min , a solution of **14** (*ca.* 73 mmol) in THF (50 ml) precooled at -78 °C was added over 20 min and the mixture was stirred at -78 °C for another 30 min. After the reaction was quenched with saturated NH_4Cl solution, the reaction mixture was extracted with ether and hexane. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give the crude addition product (**15**). This crude product was subjected to the next reaction without purification. To a solution of the crude addition product in THF (100 ml) was added TBAF (73 ml, 1M in THF, 73 mmol) at 0 °C and the reaction was continued for 1 hr with stirring. The reaction mixture was poured into water and extracted with ether and hexane. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. **16** (13.7 g) was obtained as colorless needles by recrystallization of the crude concentrated residue from hexane. Another crop of **16** (2.0 g) was obtained from the mother liquor of recrystallization by concentration *in vacuo* followed by flash chromatography (SiO_2; EtOAc:hexane=1:6 to 1:4) and recrystallization from hexane. The total yield of **16** (15.7 g) was 72% from **13**. $[\alpha]_D^{20}$ +35.2° (c=0.76, $CHCl_3$) and m.p. 93.0-95.0 °C. IR (CCl_4): 3575, 3330, 3000, 2140, 1735, 1160, 875cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 1.22 (s, 9H, $OCOCMe_3$), 1.39, 1.59 (sx2, each 3H, CMe_2), 2.61 (s, 1H, CCH), 2.92 (br, 1H, -OH), 4.06 (dd, 1H, J=7.3, 4.0 Hz, C_4-H), 4.33 (dd, 1H, J=11.9, 7.3 Hz, -CHOPiv), 4.46 (dd, 1H, J=11.9, 4.0 Hz, -CHOPiv), 4.60 (d, 1H, J=3.8 Hz, C_2-H), 5.90 (d, 1H, J=3.8 Hz, C_1-H). MS (m/e) (%): 283 [(M-Me)$^+$] (5), 241 (3), 182 (17), 145 (38), 85 (36), 57 (^{t}Bu)$^+$ (100). *Anal.* Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43%. Found: C, 60.12; H, 7.58%.

5-(2,2-Dimethylpropanoyl)-3-ethynyl-3-O-methyl-1,2-O-isopropylidene-α-D-ribofuranose (17) A suspension of **16** (5.00 g, 16.8 mmol), anhydrous K_2CO_3 (4.64 g, 33.6 mmol), and iodomethane (23.8 g, 168 mmol) in acetone (30 ml) was placed in a sealed tube and heated at 70 °C for 6 days under vigorous stirring. After cooling, the reaction mixture was filtered through a pad of celite, and concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:6) of the residue gave **17** as colorless needles (4.02 g, 77%) along with recovered **16** (2.28 g, 23% recovery). An analytical sample was obtained by recrystallization from hexane. $[\alpha]_D^{20}$ +36.0° (c=0.54, $CHCl_3$) and m.p. 115.0-116.0 °C. IR (CCl_4): 3330, 2980, 2120, 1730, 1280, 1160, 1055, 870cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 1.20 (s, 9H, ^{t}Bu), 1.37, 1.59 (sx2, each 3H, CMe_2), 2.65 (s, 1H, -CCH), 3.50 (s, 3H, -OMe), 4.24 (dd, 1H, J=7.6, 3.2 Hz, C_4-H), 4.30 (dd, 1H, J=11.5, 7.6 Hz, -CHOPiv), 4.40 (dd, 1H, J=11.5, 3.2 Hz, -CHOPiv), 4.61 (d, 1H, J=3.6 Hz, C_2-H), 5.86 (d, 1H, J=3.6 Hz, C_1-H). MS (m/e) (%): 297 [(M-Me)$^+$] (5), 255 [(M-^{t}Bu)$^+$] (1), 196 (51), 95 (79), 57 (^{t}Bu)$^+$ (100). *Anal.* Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74%. Found: C, 61.66; H, 7.83%.

5-(2,2-Dimethylpropanoyl)-3-ethynyl-3-O-methyl-α- and β-D-ribofuranose (18)
A solution of **17** (10.2 g, 32.8 mmol) in trifluoroacetic acid (15 ml) and water (3 ml) was kept standing at room temperature for 2 days. After removal of volatile material *in vacuo*, the residue was extracted with EtOAc. The combined organic extracts were washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:2 to 1:1) of the residue gave oily **18** as a diastereomeric mixture (7.81 g, 88%) along with recovered **17** (0.92 g, 9% recovery). IR (neat): 3460, 3270, 2980, 2115, 1730, 1280, 1135, 1080cm^{-1}. ^{1}H-NMR ($CDCl_3$) (major:minor= *ca.* 5.4:1): δ= 1.22 (major) and 1.23 (minor) (each s, total 9H, $-OCOCMe_3$), 2.71 (major) and 2.80 (minor) (each s, total 1H, -CCH), 2.90 (br, 1H, -OH), 3.50 (minor) and 3.52 (major) (each s, total 3H, -OMe), 3.63 (br, 1H, -OH), 4.15-

4.43 (m, 5H), 5.25 (minor) and 5.33 (major) (each br, total 1H, C_1-H). MS (m/e) (%): 255 [(M-OH)+] (37), 145 (19), 111 (31), 57 (^{t}Bu)+ (100).

1-O-(*tert*-Butyldimethylsilyl)-5-(2,2-dimethylpropanoyl)-3-ethynyl-3-O-methyl-α-D-ribofuranose (20) and 1-O-(*tert*-Butyldimethylsilyl)-5-(2,2-dimethylpropanoyl)-3-ethynyl-3-O-methyl-β-D-ribofuranose (21) To a solution of **18** (4.11 g, 15.1 mmol) and 2,6-lutidine (1.94 g, 18.1 mmol, 2.1 ml) in CH_2Cl_2 (30 ml) was added *t*-butyldimethylsilyl triflate (3.99 g, 15.1 mmol, 3.5 ml) at -78 °C and the mixture was stirred for 2 hr. After being warmed up to 0 °C, the reaction was quenched with water and the resulting mixture was extracted with ether and hexane. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, then concentrated *in vacuo* . Flash chromatography (SiO_2; EtOAc:hexane=1:15 to 2:1) of the residue gave **20** as a colorless oil (3.59 g, 62%) and **21** as colorless crystals (0.64 g, 11%) along with recovered **18** (0.37 g, 9% recovery). An analytical sample of **21** was obtained by recrystallization from hexane. **20**: $[\alpha]_D^{20}$ +106.5° (c=0.74, $CHCl_3$). IR (neat): 3570, 3280, 2980, 2890, 2125, 1730, 1285, 1260, 1135, 840cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 0.15, 0.16 (sx2, each 3H, -$SiMe_2$), 0.92 (s, 9H, -Si^{t}Bu), 1.20 (s, 9H, -OCOCMe_3), 2.61 (s, 1H, -CCH), 3.16 (d, 1H, J=8.9 Hz, -OH), 3.49 (s, 3H, -OMe), 4.17 (dd, 1H, J=8.9, 4.5 Hz, C_2-H), 4.20 (dd, 1H, J=10.9, 7.1 Hz, -CHOPiv), 4.25 (dd, 1H, J=7.1, 2.8 Hz, C_4-H), 4.34 (dd, 1H, J=10.8, 2.8 Hz, -CHOPiv), 5.44 (d, 1H, J=4.4 Hz, C_1-H). MS (m/e) (%): 329 [(M-^{t}Bu)+] (9), 255 [(M-OSi$Me_2{}^t$Bu)+] (2), 227 (12), 185 (44), 159 (22), 111 (42), 57 (^{t}Bu)+ (100). **21**: $[\alpha]_D^{20}$ -25.6° (c=0.81, hexane) and m.p. 69.5-70.5 °C. IR (CCl_4): 3500, 3330, 2970, 2950, 2870, 2120, 1730, 1460, 1390, 1280, 1160, 850, 830, 770cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 0.13 (sx2, 6H, -$SiMe_2$), 0.91 (s, 9H, -Si^{t}Bu), 1.24 (s, 9H, -OCOCMe_3), 2.70 (s, 1H, -CCH), 2.82 (d, 1H, J=5.8 Hz, -OH), 3.50 (s, 3H, -OMe), 4.09 (dd, 1H, J=5.8, 2.2 Hz, C_2-H), 4.18-4.24 (m, 2H), 4.37 (m, 1H), 5.23 (d, 1H, J=2.2 Hz, C_1-H). MS (m/e) (%): 371 [(M-Me)+], 329 [(M-^{t}Bu)+] (3), 255 [(M-OSi$Me_2{}^t$Bu)+] (2), 227 (13), 185 (41), 159 (51), 75 (50), 57 (^{t}Bu)+ (100). *Anal.* Calcd. for $C_{19}H_{34}O_6Si$: C, 59.04; H, 8.87%. Found: C, 59.07; H, 9.03%.

(2*S*,3*R*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-ethynyl-3-methoxypentan-1,4,5-triol (23) and (2*S*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-3-ethynyl-3-methoxypentan-2,4,5-triol (24)

To a suspension of **20** (6.14 g, 15.9 mmol) in THF (25 ml) and H_2O (25 ml) was added $NaBH_4$ (1.05 g, 27.8 mmol) under vigorous stirring and the mixture was stirred overnight at room temperature. An excess amount of $NaBH_4$ was decomposed with saturated NH_4Cl solution and the resulting mixture was concentrated *in vacuo* to remove THF. The residue was dissolved in EtOAc. The ethyl acetate solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo* . To a solution of the crude reduction products in anhydrous MeOH (50 ml) was added NaOMe (0.52 g, 9.6 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of AcOH (0.58 g, 9.6 mmol, 0.55 ml). After concentration *in vacuo*, the residue was dissolved in EtOAc and insoluble materials were filtered off. The filtrate was concentrated *in vacuo* to give a crude triol, which was then purified by flash chromatography (SiO_2; EtOAc:hexane=1:1 to 3:2) to give a mixture of **23** and **24** as a bright yellow oil (4.00 g, 82%, *ca.* 4:1). IR ($CHCl_3$): 3440, 3330, 2975, 2900, 2880, 2130, 1470, 1265, 1090, 850cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 0.11 (major) and 0.14 (minor) (s, total 6H, $SiMe_2$), 0.91 (major) and 0.92 (minor) (s, total 9H, Si^{t}Bu), 2.67 (major) and 2.70 (minor) (s, 1H, -CCH), 3.44 (s, 3H, -OMe), 3.8-4.0 (m, 6H). Ms (m/e) (%): 305 [(M+1)+], 197 (8), 155 (44), 75 (100).

(2*S*,3*S*)-3-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-methoxy-4-pentyn-1,2-diol (25)

A solution of the mixture of **23** and **24** (601 mg, 2.0 mmol) in acetone (10 ml) was stirred with anhydrous $CuSO_4$ (3.02 g, 19 mmol) overnight at room temperature. After filtration through a pad of celite, the acetone solution was concentrated *in vacuo* to give the crude product. To a solution of this crude product in THF (2 ml) was added TBAF (2.0 ml, 1 M in THF, 2.0 mmol) at room temperature. After 2 hr, THF was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=2:1) of the residue gave **25** as a solid (285mg, 63% in 2 steps), which was recrystallized from EtOAc-hexane to give an analytical sample as colorless needles. $[\alpha]_D^{20}$ -16.2° (c=0.35, $CHCl_3$) and m.p. 121.5-123.0 °C. IR ($CHCl_3$): 3480, 3320, 3000, 2120, 1385, 1090, 850cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1,17, 1.39 (sx2, each 3H, CMe_2), 1.95 (s, 1H, -CCH), 2.50 (dd, 1H, J=8.8, 4.2 Hz, -OH), 2.71 (d, 1H, J=5.1 Hz, -OH), 3.20 (s, 3H, -OMe), 3.86 (m, 2H, -CH_2OH), 3.99 (dd, 1H, J=8.5, 6.7 Hz), 4.00 (m, 1H, -CHOH), 4.18 (dd, 1H, J=8.5, 6.8 Hz), 4.28 (t, 1H, J=6.7 Hz). MS (m/e) (%): 231 [(M+1)+] (15eV in beam method), 215 [(M-Me)+] (7), 101 (75), 43 (100). *Anal.* Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%. Found: C, 57.15; H, 7.99%.

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methoxy-3-butyn-1-ol (26)

a) Preparation from **18** To a solution of **18** (236 mg, 0.87 mmol) in acetone (2 ml) and H_2O (0.2 ml) was added $NaIO_4$ (223 mg, 1.0 mmol) and the mixture was stirred for 2 hr at room temperature. After concentration *in vacuo*, the residue was diluted with H_2O. The resulting aqueous solution was extracted with EtOAc. The

combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The crude aldehyde obtained was then dissolved in EtOH (2 ml) and treated with $NaBH_4$ (19.6 mg, 0.5 mmol) at 0 °C for 2 hr. After an excess amount of $NaBH_4$ was decomposed with saturated NH_4Cl solution, the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and the ethylacetate solution was washed with brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The crude diol was dissolved in MeOH (2 ml) containing NaOMe (10 mg, 0.02 mmol) and the resulting solution was stirred overnight at room temperature, then at 50 °C for 3 hr. After addition of AcOH (0.1 ml), the mixture was diluted with toluene, then concentrated *in vacuo*. The residue was dissolved with EtOAc and the resulting suspension was filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue was dissolved in anhydrous acetone. The acetone solution was treated with anhydrous $CuSO_4$ (80 mg, 0.5mmol) under vigorous stirring at room temperature. After 4 hr, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:1) of the residue gave **26** as a colorless oil (89.0 mg, 51%). $[\alpha]_D^{20}$ -1.9° (c=0.64, $CHCl_3$). IR (CCl_4): 3630, 3330, 3010, 2950, 2900, 2850, 2125, 1385, 1375, 1085, 850, 660, 640cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=1.33, 1.45 (sx2, each 3H, CMe_2), 2.14 (br, 1H, -OH), 2.55 (s, 1H, -CCH), 3.42 (s, 3H, -OMe), 3.77, 3.83 (dx2, each 1H, J=12.2 Hz, $-CH_2OH$), 4.09 (m, 2H), 4.25 (t, 1H, J=6.7 Hz). MS (m/e) (%): 185 [(M-Me)$^+$] (15), 169 [(M-OMe)$^+$] (6), 141 (13), 111 (21), 101 (88), 99 (55), 43 (100).

b) Preparation from **25** To a solution of **25** (38.0 mg, 0.17 mmol) in ^{t}BuOH (1.0 ml), THF (0.8 ml) and H_2O (0.2 ml) was added $NaIO_4$ (223 mg, 1.0 mmol) and the mixture was stirred for 2 hr at room temperature. After concentration *in vacuo*, the residue was diluted with H_2O. The resulting aqueous solution was extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The crude aldehyde obtained was then dissolved in EtOH (0.5 ml) and treated with $NaBH_4$ (2.3 mg, 0.06 mmol) at 0 °C for 2 hr. After an excess amount of $NaBH_4$ was decomposed with saturated NH_4Cl solution, the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and the ethyl acetate solution was washed with brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:1) of the residue gave **26** as a colorless oil (27.1 mg, 82%).

(*2S*)-2-[(*4R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(2,2-dimethylpropanoyl)-2-methoxy-3-butyne (27) To a solution of **26** (84.0 mg, 0.42 mmol) prepared from **18** in pyridine (1 ml) was added 2,2-dimethylpropanoyl chloride (106 mg, 0.88 mmol, 0.11 ml) at 0 °C and the mixture was stirred for 1 hr at room temperature. After dilution with ether and hexane, the resulting mixture was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:10) of the residue gave **27** as colorless prisms (106 mg, 89%). An analytical sample of **27** was obtained by recrystallization from hexane. The same treatment of **26** (27.1 mg, 0.14 mmol) prepared from **25** as described above gave **27** as colorless prisms (25.8 mg, 67%) after flash chromatography. **27** (derived from **18** *via* **26**): $[\alpha]_D^{20}$ -7.2° (c=0.64, $CHCl_3$) and m.p. 50.0-51.5 °C. **27** (derived from **25** *via* **26**) (not recrystallized): $[\alpha]_D^{20}$ -7.5° (c=0.81, $CHCl_3$) and m.p. 50.5-51.0 °C. IR (CCl_4): 3350, 3000, 2960, 2860, 2225, 1740, 1156cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 1.23 (s, 9H, $-OCOCMe_3$), 1.35, 1.47 (sx2, each 3H, CMe_2),2.54 (s, 1H, -CCH), 3.40 (s, 3H, -OMe), 4.07, 4.62 (dx2, each 1H, J=12.1 Hz, $-CH_2OPiv$), 4.11 (dd, 1H, J=8.6, 7.1 Hz), 4.13 (dd, 1H, J=8.6, 5.6 Hz), 4.20 (dd, 1H, J=7.1, 5.6 Hz). MS (m/e) (%): 269[(M-Me)$^+$] (11), 101(100), 57 (82), 43 (50). *Anal.* Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%. Found: C, 63.36; H, 8.69%.

(*2S,3S*)-3-[(*4R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-methoxy-5-[(5*Z*)-5-[(3-trimethylsilyl)-2-propynylidene]-1-cyclopenten-1-yl]-4-pentyn-1,2-diol (28) To a degassed solution of **5** (103 mg, 0.32 mmol) and **25** (73.3 mg, 0.32 mmol) in DMF (2 ml) was added $Pd(PPh_3)_4$ (73.6 mg, 0.06 mmol) and the mixture was stirred for 15 min at room temperature. Diethylamine (46.6 mg, 0.64 mmol, 0.066 ml) and CuI (24.3 mg, 0.13 mmol) was then added and the reaction mixture was stirred for 30 min at the same temperature. The reaction was quenched by the addition of saturated NH_4Cl solution. After dilution with H_2O and EtOAc, the resulting mixture was vigorously stirred for another 15 min at room temperature. The organic phase was separated and washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:benzene=1:2) of the residue gave **28** as a pale yellow oil (104 mg, 81%). $[\alpha]_D^{20}$ -33.4° (c=1.06, MeOH). IR (neat): 3470, 2980, 2120, 1380, 1250, 1080, 845cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 0.30 (s, 9H, $SiMe_3$), 1.25, 1.47 (sx2, each 3H, CMe_2), 1.83 (m, 2H, C_{12}-H_2), 2.07 (m, 2H, C_{11}-H_2), 2.68 (br dd, 1H, J=9.6, 3.2 Hz, C_6-OH), 3.20 (br d, 1H, J=4.6 Hz, C_5-OH), 3.53 (s, 3H, -OMe), 4.08 (m, 1H), 4.14 (m, 1H), 4.23 (m, 2H), 4.44 (m, 2H), 5.47 (m, 1H, C_9-H), 6.29 (m, 1H, C_{13}-H). MS (m/e) (%): 404 (M)$^+$, 389 [(M-Me)$^+$], 373 [(M-CH_2OH)$^+$], 343 [[M-CH(OH)CH_2OH]$^+$] (5), 303 (1), 286 (4), 271 (4), 255 (8), 242 (5), 197 (5), 165 (7), 101 (100), 73 (87), 43 (48). High resolution mass spectrum for $C_{22}H_{32}O_5Si$: Calcd. 404.2019. Found 404.2045.

(*2S,3S*)-3-[(*4R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-3-methoxy-5-[(5Z)-5-[(3-trimethylsilyl)-2-propynylidene]-1-cyclopenten-1-yl]-4-pentyn-1-yl *p*-toluenesulfonate (29) A solution of **28** (103 mg, 0.25 mmol), TsCl (63.2 mg, 0.33 mmol) and DMAP (40.5 mg, 0.33 mmol) in CH_2Cl_2 (4 ml) was stirred overnight at room temperature. Additional amounts of TsCl (14.6 mg, 0.07 mmol) and DMAP (9.3 mg, 0.07 mmol) were then added and the mixture was stirred for another 6 hr at room temperature. The reaction mixture was diluted with EtOAc and the ethylacetate solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:benzene=1:20) of the residue gave **29** as a pale yellow oil (78.6 mg, 55%) along with **30** (18.2 mg, 10%) and recovered **28** (13.4 mg, 13% recovery). $[\alpha]_D^{20}$ -29.8° (c=0.90, MeOH). IR (neat): 3500, 2980, 2130, 1600, 1370, 1180, 1090, 845cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 0.30 (s, 9H, -$SiMe_3$), 1.20, 1.45 (sx2, each 3H, CMe_2), 1.81 (s, 3H, C_4-Me), 1.84 (m, 2H, C_{12}-H_2), 2.05 (m, 2H, C_{11}-H_2), 2,65 (br d, 1H, J=3.2 Hz, C_5-OH), 3.35 (s, 3H, -OMe), 4.06 (dd, 1H, J=8.0, 6.3 Hz), 4.34 (t, 1H, J=6.3 Hz), 4.40 (dd, 1H, J=8.0, 6.3 Hz), 4.48 (ddd, 1H, J=8.0, 3.1, 2.1 Hz, C_5-H), 4.66 (dd, 1H, J=11.0, 8.0 Hz, C_6-H), 4.96 (dt, 1H, J=10.9, 1.7 Hz, C_6-H), 5.44 (m, 1H, C_9-H), 6.49 (m, 1H, C_{13}-H), 6.69 (d, 2H, J=8.1 Hz, $C_{3'}$ and $C_{5'}$-H), 7.86 (d, 2H, J=8.3 Hz, $C_{2'}$ and $C_{6'}$-H). MS (m/e) (%): 558 (M)$^+$, 543 [(M-Me)$^+$], 457, 343 (3), 285 (6), 229 (54), 165 (18), 101 (48), 73 (100), 43 (45).

(*2S,3S*)-3-[(*4R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,2-epoxy-3-methoxy-5-[(5Z)-5-(2-propynylidene)-1-cyclopenten-1-yl]-4-pentyne (31) To a solution of **29** (69.2 mg, 0.12 mmol) in THF (1.5 ml) was slowly added TBAF (0.15 ml, 1 M in THF, 0.15 mmol) at 0 °C and the reaction mixture was stirred for 24 hr at room temperature. After dilution with EtOAc, the ethylacetate solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc :benzene=1:9) of the residue gave **31** as a pale yellow oil (32.9 mg, 84%). $[\alpha]_D^{20}$ +68.0° (c=0.98, hexane). IR (neat): 3300, 3000, 2950, 2230, 2100, 1615, 1450, 1370, 1215, 1090, 855cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1.32, 1.56 (sx2, each 3H, CMe_2), 1.81 (m, 2H, C_{12}-H_2), 2.04 (m, 2H, C_{11}-H_2), 2.38 (dd, 1H, J=5.7, 3.9 Hz, C_{6a}-H), 2.98 (dd, 1H, J=5.7, 2.5 Hz, C_{6b}-H), 3.16 (d, 1H, J=2.7 Hz, C_7-H), 3.46 (dd, 1H, J=3.8, 2.5 Hz, C_5-H), 3.49 (s, 3H, -OMe), 4.15 (dd, 1H, J=8.5, 6.8 Hz), 4.37 (t, 1H, J=6.7 Hz), 4.51 (dd, 1H, J=8.4, 6.7 Hz), 5.29 (m, 1H, C_9-H), 6.25 (m, 1H, C_{13}-H). MS (m/e) (%): 299 [(M-Me)$^+$], 271, 213 (4), 184 (12), 153 (14), 101 (100), 43 (45).

(*4S,5S*)-4-[(*4R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-hydroxy-4-methoxybicyclo[8.3.0]trideca-9,13-dien-2,7-diyne (2) To a solution of **31** (20.9 mg, 0.067 mmol) in anhydrous THF (2 ml) was added $LiN(SiMe_3)_2$ (0.20 ml, 1 M in THF, 0.20 mmol) at -78 °C and the mixture was stirred for 30 min at the same temperature. BF_3·Et_2O (28.3 mg, 0.20 mmol, 0.025 ml) was then added and the reaction mixture was stirred for another 1 hr at -78 °C. The reaction was quenched with saturated $NaHCO_3$ solution and the mixture was extracted with ether. The combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$, then filtered. After addition of benzene (*ca.* 10ml), the filtrate was slowly concentrated *in vacuo* to *ca.* 0.5ml volume. The residual solution was charged onto a silica gel column, which was then eluted with benzene and ether (12:1). Fractions containing **2** were collected and carefully concentrated *in vacuo* to ca.0.5ml volume. d^6-Benzene (*ca.* 1.5ml) was added, then concentrated *in vacuo* to *ca.* 0.5ml volume. After this operation was repeated twice, almost all benzene could be substituted with d^6-benzene. This d^6-benzene solution was directly subjected to ^{1}H-NMR measurement to characterize **2**. IR (C_6D_6): 3600, 2850, 2120, 1535, 1400, 1380, 1295, 1245, 1060, 850, 735cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1.28, 1.53 (sx2, each 3H, CMe_2), 1.87 (m, 2H, C_{12}-H_2), 2.10 (m, 2H, C_{11}-H_2), 2.67 (br, 1H, C_5-OH), 2.96 (m, 2H, C_6-H_2), 3.41 (s, 3H, -OMe), 3.81 (br, 1H, C_5-H), 4.01 (dd, 1H, J=8.2, 6.8 Hz), 4.23 (dd, 1H, J=8.2, 7.0 Hz), 4.59 (t, 1H, J=6.9 Hz), 5.23 (m, 1H, C_9-H), 6.06 (m, 1H, C_{13}-H). MS (m/e) (%): 314 (M)$^+$, 299 [(M-Me)$^+$] (2), 225 (7), 213 (7), 197 (17), 183 (8), 167 (15), 101 (100).

(*4S,5S*)-5-Acetoxy-4-[(*4R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methoxybicyclo[8.3.0]trideca-9,13-dien-2,7-diyne (3) Fractions of flash chromatography containing **2** prepared from **31** (8.0 mg, 0.025 mmol) was concentrated *in vacuo* to *ca.* 1 ml volume. To the concentrated solution, pyridine (0.005 ml), acetic anhydride (0.005 ml), and DMAP (1 mg) were added and the mixture was stirred for 1 hr at room temperature. The reaction mixture was then diluted with benzene and ether. The organic solution was washed with H_2O, diluted HCl and saturated $NaHCO_3$, dried over $MgSO_4$, then filtered. The filtrate was carefully concentrated *in vacuo* to *ca.* 0.5 ml volume. By using parts of this solution, the solvent was substituted with d^6-benzene or CCl_4 as described above for ^{1}H-NMR and IR spectra measurements. IR (CCl_4): 3000, 2950, 2280, 1750, 1370, 1090, 1030, 850, 495cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1.29, 1.62 (sx2, each 3H, CMe_2), 1.65 (s, 3H, -$OCOCH_3$), 1.90 (m, 2H, C_{12}-H_2), 2.13 (m, 2H, C_{11}-H_2), 2.60 (br d, 1H, J=16.2 Hz, C_{6a}-H), 3.43 (s, 3H, -OCH_3), 3.45 (1H, obscured by the signal of OCH_3, C_{6b}-H), 4.13 (dd, 1H, J=8.5, 6.9 Hz), 4.42 (dd, 1H, J=8.5, 6.1 Hz), 4.59 (t, 1H, J=6.5 Hz), 5.25 (m, 1H, C_9-H), 5.66 (dd, 1H, J=9.6, 3.7 Hz,

C_5-H), 6.07 (m, 1H, C_{13}-H). MS (m/e) (%): 356 $(M)^+$ (2), 341 $[(M\text{-}Me)^+]$ (3), 255 (4), 239 (6), 196 (16), 152 (15), 101 (87), 43 $(COCH_3)^+$ (100).

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-[(5Z)-5-[(3-trimethylsilyl)-2-propynylidene]-1-cyclopenten-1-yl]-3-butyn-1,2-diol (33) To a degassed solution of **5** (60.9 mg, 0.19 mmol) and **32**[1a] (35.0 mg, 0.19 mmol) in DMF (1.5 ml) was added $Pd(PPh_3)_4$ (43.4 mg, 0.04 mmol) and the mixture was stirred for 15 min at room temperature. Diethylamine (27.5 mg, 0.38 mmol, 0.039 ml) and CuI (14.3 mg, 0.08 mmol) were then added and the reaction mixture was stirred for 30 min at the same temperature. The reaction was quenched by the addition of saturated NH_4Cl solution. The resulting mixture was diluted with H_2O and EtOAc and stirred vigorously for another 15 min. The organic layer was separated and washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:benzene=1:5) of the residue gave **33** as a pale yellow oil (50.6 mg, 75%). $[\alpha]_D^{20}$ +36.1° (c=1.07, CCl_4). IR (CCl_4): 3600, 2970, 2120, 1535, 1370, 1250, 1070, 845cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 0.32 (s, 9H, -$SiMe_3$), 1.27, 1.49 (sx2, each 3H, CMe_2), 1.80 (m, 2H, C_{11}-H_2), 2.04 (m, 2H, C_{10}-H_2), 2.15 (dd, 1H, J=9.2, 5.1 Hz, C_5-OH), 2.94 (s, 1H, C_4-OH), 3.83 (dd, 1H, J=11.2, 9.2 Hz, C_5-H), 3.99 (dd, 1H, J=11.2, 5.1 Hz, C_5-H), 4.10 (dd, 1H, J=8.4, 6.7 Hz), 4.22 (t, 1H, J=6.4 Hz), 4.40 (dd, 1H, J=8.4, 6.2 Hz), 5.46 (m, 1H, C_8-H), 6.25 (m, 1H, C_{12}-H). MS (m/e) (%): 360 $(M)^+$ (2), 345 $[(M\text{-}Me)^+]$ (2), 329 $[(M\text{-}CH_2OH)^+]$ (1), 271 (2), 241 (3), 212 (2), 152 (4), 101 (100), 43 (32).

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-4-[(5Z)-5-[(3-trimethylsilyl)-2-propynylidene]-1-cyclopenten-1-yl]-3-butyn-1-yl *p*-toluenesulfonate (34) A solution of **33** (45.0 mg, 0.13 mmol), TsCl (47.7 mg, 0.25 mmol), and DMAP (45.8 mg, 0.38 mmol) in CH_2Cl_2 (2 ml) was stirred for 2 hr at room temperature. The mixture was diluted with ether and hexane and washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:2) of the residue gave **34** as a pale yellow oil (62.0 mg, 94%). $[\alpha]_D^{20}$ +7.5° (c=1.45, CCl_4). IR (neat): 3600, 3520, 2970, 2120, 1600, 1535, 1375, 1250, 1190, 1180, 1075, 845cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 0.31 (s, 9H, -$SiMe_3$), 1.18, 1.44 (sx2, each 3H, CMe_2), 1.78 (m, 2H, C_{11}-H_2), 1.80 (s, 3H, C_4-Me), 2.02 (m, 2H, C_{10}-H_2), 2.84 (s, 1H, C_4-OH), 4.02 (dd, 1H, J=8.6, 6.8 Hz), 4.20 (dd, 1H, J=6.7, 5.8 Hz), 4.42 (dd, 1H, J=8.6, 5.7 Hz), 4.50, 4.54 (dx2, each 1H, J=10.1 Hz, C_6-H_2), 5.44 (m, 1H, C_8-H), 6.22 (m, 1H, C_{12}-H), 6.64 (d, 2H, J=8.2 Hz, $C_{3'}$ and $C_{5'}$-H) , 7.74 (d, 2H, J=8.3 Hz, $C_{2'}$ and $C_{6'}$-H). MS (m/e) (%): 514 $(M)^+$, 499 $[(M\text{-}Me)^+]$ (1), 342 (2), 242 (14), 101 (100).

(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,2-epoxy-4-[(5Z)-5-(2-propynylidene)-1-cyclopenten-1-yl]-3-butyne (35) To a solution of **34** (58.0 mg, 0.11 mmol) in THF (2 ml) was slowly added TBAF (0.12 ml, 1 M in THF, 0.12 mmol) at 0 °C and the mixture was stirred overnight at room temperature. After dilution with EtOAc, the resulting solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=1:6) of the residue gave **35** as a pale yellow oil (18.6 mg, 61%). $[\alpha]_D^{20}$ +63.8° (c=1.86, CCl_4). IR (neat): 3340, 3010, 2950, 2240, 2110, 1370, 1215, 1070, 850cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1.25, 1.46 (sx2, each 3H, CMe_2), 1.84 (m, 2H, C_{11}-H_2), 2.06 (m, 2H, C_{12}-H_2), 2.64, 2.88 (dx2, each 1H, J=6.0 Hz, C_6-H_2), 3.04 (d, 1H, J=2.4 Hz, C_6-H), 3.88 (br t, 1H, J=6.5 Hz), 3.98 (br dd, 1H, J=8.4, 6.7 Hz), 4.20 (a pair of dd, total 1H, J=8.5, 6.3 Hz), 5.26 (m, 1H, C_8-H), 6.24 (m, 1H, C_{12}-H). MS (m/e) (%): 270 $(M)^+$ (1), 255 $[(M\text{-}Me)^+]$ (9), 225 (4), 212 (6), 183 (28), 153 (47), 101 (67), 43 (100).

(2*S*,3*S*)-3-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-methoxy-5-[(5Z)-5-(2-propynylidene)-1-cyclopenten-1-yl]-4-pentyn-1,2-diol (36) To a solution of **28** (63.1 mg, 0.16 mmol) in THF (2 ml) was slowly added TBAF (0.17 ml, 1 M in THF, 0.17 mmol) at 0 °C and the mixture was stirred for 1 hr at the same temperature. After dilution with EtOAc, the resulting solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography (SiO_2; EtOAc:hexane=2:3) of the residue gave **36** as an unstable pale yellow oil (18.6 mg, 61%). IR (neat): 3500, 2970, 2120, 1540, 1375, 1100, 1030, 855cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1.22, 1.46 (sx2, each 3H, CMe_2), 1.87 (m, 2H, C_{12}-H_2), 2.10 (m, 2H, C_{11}-H_2), 2.64 (br dd, 1H, J=9.7, 3.8 Hz, C_6-OH), 2.86 (d, 1H, J=5.0 Hz, C_5-OH), 3.14 (d, 1H, J=2.7 Hz, C_7-H), 3.40 (s, 3H, -OMe), 4.06-4.20 (2H, C_6-H_2), 4.16 (dd, 1H, J=8.3, 6.5 Hz), 4.26 (ddd, 1H, J=11.4, 5.1, 3.4 Hz, C_5-H), 4.43 (dd, 1H, J=8.3, 6.7 Hz), 4.49 (t, 1H, J=6.6 Hz), 5.32 (m, 1H, C_9-H), 6.30 (m, 1H, C_{13}-H). MS (m/e) (%): 332 $(M)^+$, 317 $[(M\text{-}Me)^+]$ (1), 271 $[[M\text{-}CH(OH)CH_2OH]^+]$ (10), 231 (3), 213 (6), 185 (16), 128 (7), 101 (100), 43 (57).

(2*R*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methoxy-4-[(5Z)-5-(2-propynylidene)-1-cyclopenten-1-yl]-3-butynal (37) To a solution of **36** (45.0 mg, 0.14 mmol) in acetone (2.7 ml) and H_2O (0.3 ml) was added $NaIO_4$ (58.0 mg, 0.27 mmol) and the mixture was stirred overnight. After dilution with benzene, acetone was removed *in vacuo* and the remaining solution was diluted with ether. The etheral solution

was washed with H_2O and brine, dried over anhydrous $MgSO_4$, then filtered. The filtrate was concentrated *in vacuo* to *ca.* 1 ml volume. This solution was directly charged onto a silica gel column, which was then eluted with benzene and ether (6:1). The fractions containing **37** were combined and carefully concentrated *in vacuo* to *ca.* 0.5ml volume. By using parts of this solution, the solvent was substituted with d6-benzene or CCl_4 to measure either ^{1}H-NMR or IR spectrum. IR (CCl_4): 3320, 3000, 2940, 2850, 2100, 1740, 1530, 1370, 1090, 845, 635, 595cm^{-1}. ^{1}H-NMR (C_6D_6): δ= 1.18, 1.49 (sx2, each 3H, CMe_2), 1.82 (m, 2H, C_{11}-H_2), 2.03 (m, 2H, C_{10}-H_2), 2.97 (d, 1H, J=2.4 Hz, C_5-H), 3.46 (s, 3H, -OCH_3), 4.03 (dd, 1H, J=7.8, 5.7 Hz), 4.35 (t, 1H, J=5.7 Hz), 4.42 (dd, 1H, J=7.7, 5.7 Hz), 5.27 (m, 1H, C_8-H), 6.28 (m, 1H, C_{12}-H), 9.74 (s, 1H, C_5-H). MS (m/e) (%): 300 $(M)^+$, 285 $[(M\text{-}Me)^+]$ (4), 271 $[(M\text{-}CHO)^+]$ (12), 213 (6), 185 (2), 128 (2), 101 (87), 43 (100).

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