Tetrahedron Vol. 49, No. 30, pp. 6581-6590, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Chemoselective Introduction of Acetylene into Hindered Carbonyl Group using Alkynyltrifluoroborate, A Solution as one Step to (-)-Tetrodotoxin

Noboru Yamamoto and Minoru Isobe*

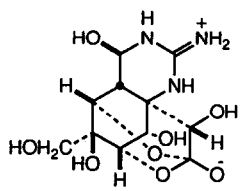
Laboratory of Organic Chemistry, School of Agriculture, Nagoya University,
Chikusa, Nagoya 464-01, Japan

(*Received in Japan* 8 *April* 1993)

Key Words: tetrodotoxin, Diels-Alder, levoglucosenone, lithium alkynyltrifluoroborate

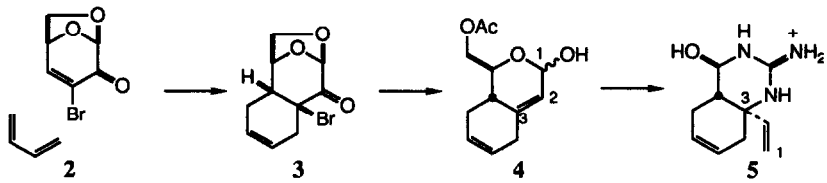
Abstract Optically active cyclohexane moiety precursor for tetrodotoxin molecule was synthesized by Diels-Alder cycloaddition between a bromo derivative of levoglucosenone and Danishefsky type diene. The unstable product, bromo-ketone, was converted into vinylphosphinate and then the carbonyl compounds, to which the critical carbon nucleophile was predominantly introduced with alkynyltrifluroborate. The Lewis acid played an important role for switching the selectivity toward the carbonyl carbon or phosphorous atom.

Tetrodotoxin **1** is one of the major biotoxins found in the ovaries and livers of many species of *Tetraodontidae*, esp. the puffer fish.[1] This toxin is responsible for blocking the ion current of sodium channels in mammalian nerve cell membrane.[2] Recent finding of tetrodotoxin analogs from various species suggests metabolic and catabolic pathways of **1**, that remain to uncover.[3] In 1972, Kishi *et al.* accomplished the total synthesis of (±)-tetrodotoxin.[4] Several attempts have been reported on the synthesis directed toward (-)-**1** as challenging problem as well as supplying sample for biological studies.[5]



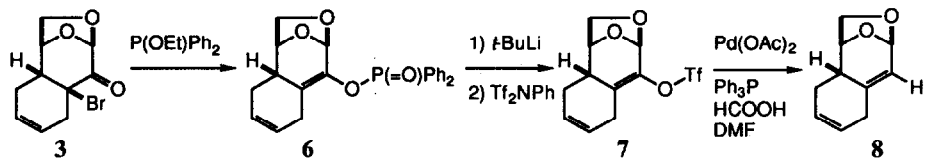
tetrodotoxin (1)

We have reported stereo controlled partial synthesis of **1**, that included Diels-Alder cycloaddition between levoglucosenone derivative and butadiene for the formation of the chiral cyclohexane ring (**2**→**3**) .[6] The more recent study included the guanidine ring through a [3,3]-sigmatropic rearrangement as shown in Scheme 1. Reduction of the bromoketone afforded the Δ^2-olefinic compound **4**, that was achieved through the reductive elimination of the corresponding bromohydrin (not shown in the scheme) and then the critical rearrangement gave the guanidine product **5**.[7]



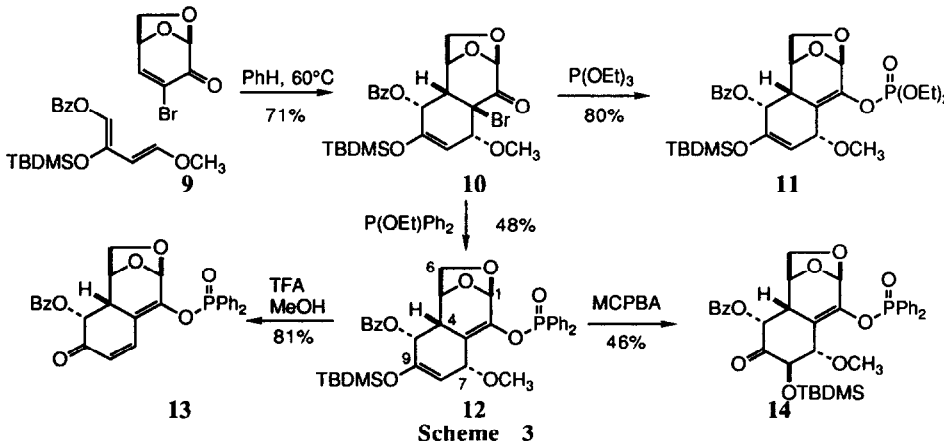
Scheme 1

In this paper we describe further studies toward (-)-tetrodotoxin (**1**) with more functionalized cyclohexane moiety in **4** in the optically active form under the same Diels-Alder strategy (**2**→**3**). Requirement of the Δ^2-olefinic moiety from **3** led us to convert into the vinyl phosphinate **6**, since it is further convertible to **7** and then to the reduction product **8** [nmr H-1 δ 5.49 ppm (J= 4 Hz); H-2 δ 5.74 (m); m/z 164 (M^+)].[8]



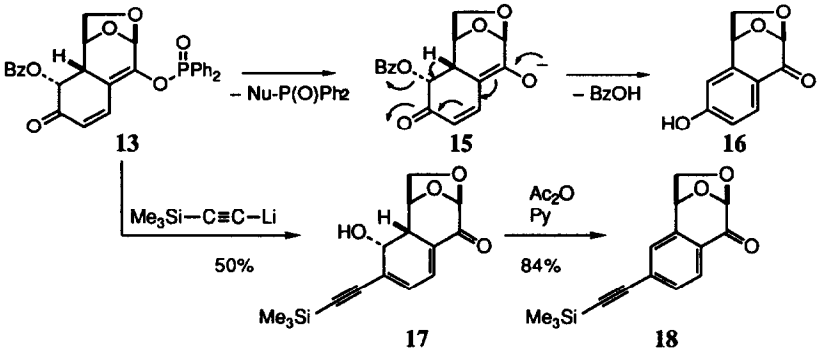
Scheme 2

Employment of the diene **9** and the bromolevoglucosenone afforded the adduct **10** under relatively milder condition at 60°C for 12 hr.[9] This bromoketone (**10**), when concentrated and kept as neat oil in a refrigerator, was not stockable because of its unstable nature. Diluted benzene solution of the product **10**, however, turned out to be stockable at -20°C without decomposition for a few months. Perkov reaction of **10** afforded the vinyl phosphate **11** and the vinyl phosphinate **12**, both of which were enough stable for purification on SiO_2 and for further reactions.[10] The diethyl phosphate **11** formed (after few more attempted steps to cleave the 1,6-anhydro bridge, though not shown in scheme) a cyclic phosphate between C-1 OH, that had to be avoided. The diphenyl phosphinate **12** did not have this problem. For introduction of carbon atom at the C-9 position, the vinyl silyl ether of **12** was converted into the corresponding carbonyl group such as the enone **13** or the ketone **14**.



Scheme 3

Attempted addition of nucleophile to the ketone **13**, obtained in 81% yield by hydrolysis of **12**, in fact, afforded the aromatized product **16**, that occurred during the addition of nucleophiles such as methyl magnesium bromide, trimethylsilyl cyanide or others. An example (with lithium trimethylsilylacetylide) afforded the alcohol **17**. After acetylation, **17** aromatized to **18**. To avoid such aromatization of the enone **13**, particularly during addition of the same carbon nucleophiles, the ketone **14** was examined as the electrophile. But it did not receive any nucleophile due to the steric congestion around the carbonyl group. The higher chemoselectivity of the nucleophile is requested for the predominant addition to the carbonyl carbon but not to the phosphorous atom.



Scheme 4

The chemoselective addition to the carbonyl moiety in **13** should avoid the formation of aromatization product, that would occur through reaction to the phosphorous atom. We fortunately found that lithium alkynylborate complex[11] did selectively attack the carbonyl group under limited conditions; thus, the relative ratio of the lithium acetylide and boron trifluoride etherate was quite critical. Excess acetylide was used to be the molar ratio 2:1 of the acetylide to the substrate **13**.

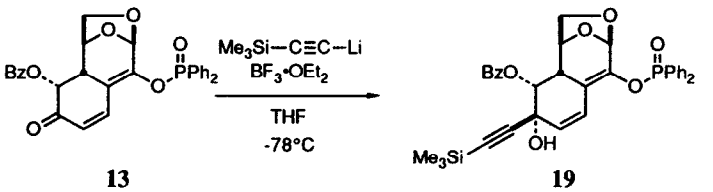
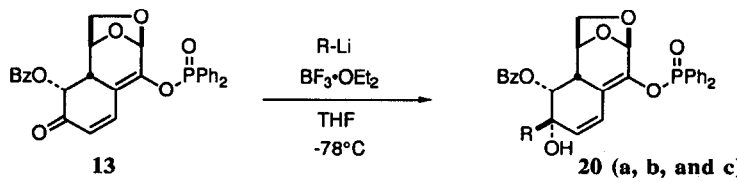


Table 1 Addition of alkynyltrifluoroborate using trimethylsilylacetylene

Entry	BF_3•OEt_2 : acetylide	Yield of **19**
1	0 : 1.0	13%
2	0.5 : 1.0	48%
3	0.7 : 1.0	50%
4	0.9 : 1.0	69%
5	1.0 : 1.0	72%
6	1.1 : 1.0	60%
7	1.5 : 1.0	53%
8	3.0 : 1.0	55%

Table 1 indicates that the equivalent amount of acetylide and BF_3•OEt_2 recorded the best result as 72% yield of **19**, while less or larger equivalents of the Lewis acid to the acetylide afforded lower yields. These experiments suggested that the relative electrophilicity between the carbonyl and phosphono groups changed with or without Lewis acid. This may be due to the difference of participation of BF_3 between the carbonyl oxygen and phosphinate oxygen atoms. Diminishing basicity of acetylide by the action of BF_3 would prohibit the formation of non-identified products.

The acetylenic nucleophiles (shown in Table 2) to **13** afforded the products **20a**,**b**,**c** only in the presence of BF_3•OEt_2. Three examples are summarized in Table 2 with more functionalized acetylides. The experiments involved mixing of Lewis acid and the lithium acetylide for 30 min prior to the addition to **13**. Product yields with 1 equivalent of Lewis acid in entries 1 and 3 are not the maxima, while the yields with 2 equivalents in entries 2 and 4 are better and maximum. On the other hand, comparison of entries 6 and 7 indicates the one equivalent is the best result. The table, thus, suggests that the oxygen atoms in the nucleophile molecule changed the stoichiometry of the Lewis acid to the acetylide due to the participation of oxygen as ligands. The acetylenic group was selectively added from the beta face of the carbonyl of the enone **13**.[12] About 50% excess acetylide was used to the substrate **13**.

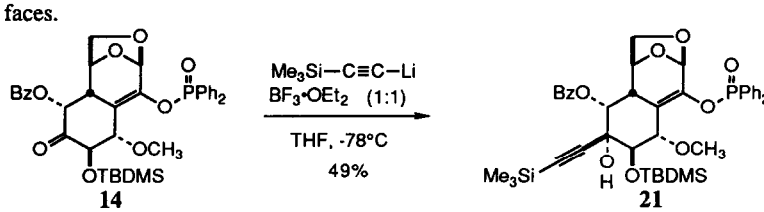


13 **20 (a, b, and c)**

Table 2 Addition of alkynyltrifluoroborates using other acetylenes

Entry	R	BF_3•OEt_2 : acetylide	Yield	Adduct
1	TBDMSO—C≡C-	1.0 : 1.0	24%	**20a**
2		2.0 : 1.0	60%	
3	MOMO—C≡C-	1.0 : 1.0	44%	
4		2.0 : 1.0	74%	**20b**
5		3.0 : 1.0	72%	
6	C_6H_{13}—C≡C-	1.0 : 1.0	61%	**20c**
7		2.0 : 1.0	47%	

The condition exhibited in Scheme 5, in fact, allowed the addition of an alternative compound **14** (having non-conjugated carbonyl group for the introduction of acetylenic nucleophile) to give **21**. In this case, both upper- and lower-sides of the carbonyl group are hindered by the protected alcohols that extend alpha and beta faces.



14 **21**

Scheme 5

The major product **21** selectively received the nucleophile on the carbonyl group but not on the phosphono group. It should be noted that the change of the chemoselectivity happened due to the Lewis acid, which would predominantly participate to the carbonyl group.

EXPERIMENTAL SECTION

General: Melting points were determined on a Yanaco MP-S3 and are uncorrected. Infrared spectra were determined on a JASCO FT/IR-7000S spectrophotometer and are reported in wave number (cm^{-1}). Proton NMR spectra were recorded on a JEOL EX270 or a GSX270. All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as internal standard. Data are reported as follows: chemical shift (integrated intensity or assignment, multiplicity, coupling constants in Hz, assignment). Carbon NMR spectra were recorded on a JEOL EX270 or a GSX270. All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million relative to $CDCl_3$ (δ 77.0) as internal standard. Data are reported as follows: chemical shift (assignment, coupling constants with phosphorous in Hz). The symbols (*) represent interchangeable assignments. Low-resolution EI and FAB mass spectra were obtained with a JEOL D-100 and a DX-705, respectively. High-resolution mass spectra (HRMS) were measured with a JEOL DX-705. Optical rotation was determined 26°C or 27°C with a JASCO DIP-370 digital polarimeter. Elemental analyses and HRMS were performed by Analytical Laboratory of this School.

Analytical thin-layer chromatography (tlc) was conducted on precoated tlc plates: silica gel 60 F-254 [E. Merck (Art 5715) Darmstadt, Germany], layer thickness 0.25mm; preparative layer chromatography (plc) was conducted on precoated silica gel 60 F-254 (Art 5774), layer thickness 0.5mm or prepared silica gel 60 FP-254 (Art 7747), layer thickness 2.0mm. Silica gel columns for open-column chromatography utilized Fuji Devison (BW 820-MH). Kieselgel 60 (Art 7734, 70-230mesh ASTM) supplied by E. Merck Darmstadt, Germany, used for medium-pressure column chromatography.

Tetrahydrofuran (THF) was distilled from potassium metal in the presence of potassium benzophenone ketyl as an indicator. Dichloromethane was dried over alumina and used without distillation. Pyridine was dried over KOH pellet and used without distillation.

Model Phosphinate 6: Ethyl diphenyl phosphinite (2.58 ml, 11.9 mmol) was added to the acetonitrile solution (10 ml) of bromoketone **3** (2.40 g, 7.88 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr, then room temperature for 1 hr. Column chromatography (silica gel 100 g, Et_2O) of the crude product afforded 2.36 g of **6** (9.40 mmol, 79 %). IR (KBr) ν 1227 (P=O) cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.90-2.60 (4H, m), 2.92-3.14 (1H, m), 3.48 (H-6, dd, *J*= 7, 2), 3.86 (H-6, dd, *J*= 7, 6), 4.30 (H-5, brd, *J*= 6), 5.50 (H-1, s), 5.40-5.62 (2H, m, olefin), 7.32-7.92 (10H, m). $[\alpha]^{26}_D$ -10.0° (*c* 0.66, $CHCl_3$). EI-MS m/z 380 (M^+); HRMS calcd for $C_{22}H_{21}O_4P_7$: 380.1177, found 380.1162.

Model Triflate 7: Under argon atmosphere, a solution of *t*-butyllithium in toluene (0.39 ml, 0.584 mmol) was slowly added to THF solution (7.0 ml) of the phosphinate **6** (222 mg, 0.584 mmol) at -78 °C. The reaction mixture was stirred for 35 min at -78 °C, 20 min at -28 °C and 20 min at 0 °C. $PhNTf_2$ (229 mg, 0.642 mmol) dissolved in THF (5.0 ml) was added to the solution and stirring was continued for 15 hr at rt. After removal of the solvent under reduced pressure, the obtained crude triflate **7**, which was unstable on

silica gel, was successively used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.23-2.37 (2H, m), 2.40-2.51 (1H, m), 2.79 (1H, brd, *J*= 21), 3.05 (1H, brd, *J*= 21), 3.74 (H-6, dd, *J*= 8, 2), 4.04 (H-6, dd, *J*= 8, 6), 4.42-4.48 (H-5, m), 5.46 (H-1, s), 5.58-5.81 (2H, m, olefin). EI-MS m/z 312 (M^+), 179 (M^+-Tf).

Model Olefin 8: Under argon atmosphere, $Pd(OAc)_2$ (6.5 mg, 0.029 mmol), PPh_3 (15.3 mg, 0.0584 mmol), and the crude triflate **7** was dissolved in DMF (7.0 ml) at rt. After 5 min of stirring, to the solution was added Et_3N (0.33 ml, 2.34 mmol) and HCO_2H (0.066 mmol, 1.8 mmol). The reaction mixture was stirred for 20 min at rt , 19 hr at 62 °C and 20 min at 0 °C. After cooling to rt, the mixture was diluted with ethyl acetate, washed with water, and dried (Na_2SO_4). The solution was concentrated *in vacuo* and column chromatography (silica gel 15 g, 4:1 hexane/Et_2O) of the crude product afforded 482 mg of mixture of alkene **8** and 2-ketone as by-product (84 mg, 6:1 by ^{1}H NMR). ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.08 (1H, ddd, *J*= 11, 6 and 1), 2.18-2.32 (1H, m), 2.39-2.50 (1H, m), 2.59 (1H, brd, *J*= 19), 2.89 (1H , brd, *J*= 19), 3.71 (H-6, dd, *J*= 7, 2), 3.98 (H-6, dd, *J*= 7, 6), 4.39 (H-5, brd, *J*= 6), 5.49 (H-1, d, *J*= 4), 5.62-5.71 (2H, m), 5.74 (H-2, m). EI-MS m/z 164 (M^+).

Diels Alder Adduct, Bromoketone 10: The crude diene mixture **9** (23.4 g, desired 3,4-(E) diene was contained in 57 % (34.0 mmol) by measurement of ^{1}H-NMR), 1-(benzoyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-1,3-butadiene, prepared from (E)-1-(benzoyloxy)-4-methoxy-3-butene-2-one (see ref. 9) was dissolved in 200 ml of benzene. To the solution was added bromolevoglucosenone (8.38 g, 40.9 mmol). The reaction mixture was stirred for 12 hr at 60 °C under nitrogen, then the solution was concentrated *in vacuo* to give the crude cycloadduct. Flash column chromatography (silica gel 300 g, 9:1 hexane/ethyl acetate) of the crude product afforded 13 g of bromoketone as the product (24.1 mmol, 71 %). Because the bromoketone **10** was extremely unstable, it was used immediately after purification. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.2 (3H, s, CH_3Si), 0.25 (3H, s, CH_3Si), 0.85 (9H, s, *t*-BuSi), 3.00 (H-4, m), 3.30 (3H, s, CH_3O), 3.89 (H-6, dd, *J*= 6, 5), 3.98 (H-6, d, *J*= 6), 4.55 (H-7, brd, *J*= 4), 4.85 (H-5, d, *J*= 5), 5.30 (H-8, d, *J*= 4), 5.35 (H-1, s), 5.90 (H-10, dd, *J*= 5, 1), 7.35-8.10 (5H, m, BzO). FAB-MS (positive) m/z 539 (M[Br^{79}]+1), 541 (M[Br^{81}]+1).

Diethyl phosphate 11: Triethyl phosphite [$(EtO)_3P$, 1.16 ml, 6.75 mmol] was added to syrup of the bromoketone **10** (1.21 g, 2.25 mmol) at rt under nitrogen. After stirring for 12 hr, the reaction mixture was concentrated *in vacuo*. Column chromatography (silica gel 80 g, Et2O) of the crude product afforded 1.07 g of diethyl phosphate **11** (5.40 mmol, 80 %). IR (KBr) ν 1727, 1274 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3Si), 0.20 (3H, s, CH_3Si), 0.84 (9H, s, t-BuSi), 1.30-1.45 (6H, m, CH_3CH_2OP), 2.43 (H-4, m), 3.30 (3H, s, CH_3O), 3.63 (H-6, dd, *J*= 7, 1.5), 3.88 (H-6, dd, *J*= 7, 6), 4.05-4.40 (4H, m, CH_3CH_2OP), 4.90 (H-5, dd, *J*= 6, 1.5), 4.98 (H-7, d, *J*= 4), 5.23 (H-8, m) 5.30 (H-1, s), 5.78 (H-10, d, *J*= 5), 7.30-8.00 (5H, m, Bz). $[\alpha]^{26}_D$ -8.8° (*c* 0.89, $CHCl_3$). EI-MS m/z 596 (M^+).

Diphenyl phosphinate 12 The ethyl diphenyl phosphinite (2.07 ml, 9.57 mmol) was added to syrup of the bromoketone **10** (4.69 g, 8.70 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr, then at rt for 1 hr. Column chromatography (silica gel 200 g, 1:1 hexane/ethyl acetate) of the crude product afforded 2.75 g of **12** (4.17 mmol, 48 %). Mp 78 - 81 °C. IR (KBr) ν 1719, 1270 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (3H, s, CH_3Si), 0.15 (3H, s, CH_3Si), 0.85 (9H, s, t-BuSi), 2.28 (H-4, m), 3.25 (3H, s, CH_3O), 3.29 (H-6, dd, *J*= 7, 1), 3.76 (H-6, dd, *J*= 7, 6), 4.79 (H-5, dd, *J*= 6, 1), 4.93 (H-7, d, *J*= 4), 5.05 (H-8, m), 5.50 (H-1, s), 5.74 (H-10, d, *J*= 3), 7.35-8.10 (15H, m, arom.). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.9 (*Me*Si), -4.2 (*Me*Si), 15.3 (Me_3CSi), 25.3 (Me_3CSi), 45.8 (C-4),

51.2 (*Me*O), 65.8 (C-7), 71.2 (C-6), 72.7 (C-5), 72.8 (C-10), 97.4 (C-1), 107.0 (C-8), 111.2 (C-3, *J*= 6.2 with γ-P), 128.1*, 128.3*, 128.4 (BzO), 128.5*, 128.6*, 129.7 (BzO), 130.17 (BzO), 130.27*, 130.30*, 131.7*, 131.86*, 131.89*, 132.0*, 132.1*, 132.2*, 132.3*, 132.39*, 132.42*, 133.0 (BzO), 144.8 (C-2, *J*= 11.2 with β-P), 152.0 (C-9), 166.8 (BzO). $[\alpha]^{27}_D$ +30.6° (*c* 0.31, $CHCl_3$). EI-MS m/z 660 (M^+). Anal. Calcd for $C_{36}H_{41}O_8PSi$: C, 65.44; H, 6.25. Found: C, 65.41; H, 6.17.

Enone 13: The silyl vinyl Et2O **12** (675 mg, 0.995 mmol) was dissolved in methanol (12 ml) at 0 °C. To this solution was added trifluoroacetic acid (TFA, 3 ml) dropwise. After stirring at 0 °C for 1 hr, the reaction mixture was diluted with toluene (20 ml), and concentrated *in vacuo* to afford the crude product. Column chromatography (silica gel 20 g, Et2O) of the crude product afforded 414 mg of **13** (0.806 mmol, 81 %). IR (KBr) ν 1725, 1684 1270 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.84 (H-4, brs), 3.62 (H-6, dd, *J*= 7, 1), 3.87 (H-6, dd, *J*= 7, 6), 4.89 (H-5, dd, *J*= 6, 1), 5.50 (H-1, s), 5.63 (H-10, dd, *J*= 4, 1), 5.96 (H-8, d, *J*= 10), 7.67 (H-7, d, *J*= 10), 7.37-8.05 (15H, m, arom.). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 47.4 (C-4), 69.8 (C-6), 72.9 (C-5 and C-10, overlap), 96.8 (C-1), 112.3 (C-3, *J*= 7.3 with γ-P), 125.3 (C-8), 128,1*, 128.2 (BzO), 128.4*, 128.5*, 128.6*, 128.7*, 129.3*, 129.8*, 130.1*, 130.58 (BzO), 131.3*, 131.39*, 131.44*, 131.5*, 131.7*, 131.89*, 131.93*, 133.0*, 133.1*, 149.7 (C-2, *J*= 11 with β-P), 165.6 (BzO), 191.0 (C-9). FAB-MS (positive) m/z 515 (M+1). HRMS calcd for $C_{29}H_{23}O_7P$: 515.1260, found 515.1254.

Ketone 14 : The silyl vinyl Et2O **12** (1.02 g, 1.55 mmol) was dissolved in CH_2Cl_2 (50 ml) and cooled to 0 °C in an ice bath under nitrogen. To this solution was added anhydrous Na_2HPO_4 (571 mg, 4.02 mmol) and MCPBA [433 mg (80 % purity)], 2.01 mmol). The reaction mixture was stirred for 12 hr at rt and then quenched at 0 °C with saturated $NaHCO_3$ solution and warmed to rt. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). The solution was concentrated *in vacuo* and the residual oil was purified by column chromatography (silica gel 40 g, 1:1 hexane/ethyl acetate) to give 482 mg of **14** (0.713 mmol, 46 %). IR (KBr) ν 1727, 1260 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$Si), 0.10 (3H, s, C*H*$_3$Si), 0.66 (9H, s, t-BuSi), 2.19 (H-4, m), 3.26 (3H, s, C*H*$_3$O), 3.57 (H-6, dd, *J*= 7, 1), 3.80 (H-6, dd, *J*= 7, 6), 3.87 (H-7, dd, *J*= 10, 3), 4.17 (H-8, d, *J*= 10), 4.85 (H-5, brd, *J*= 6), 5.27 (H-1, s), 6.67 (H-10, d, *J*= 2), 7.32-8.07 (15H, m, arom.). $[\alpha]^{26}_D$ +8.0° (*c* 0.46, $CHCl_3$). FAB-MS (positive) m/z 677 (M+1). HRMS calcd for $C_{36}H_{42}O_9PSi$: 677.2335, found 677.2347.

Phenol 16: *Method A* ; $CeCl_3 \cdot 7H_2O$ (90.5 mg, 0.243 mmol) was placed in a two-necked flask. The flask was immersed in an oil bath and heated to 135 - 140 °C *in vacuo*. The cerium chloride was dried by stirring at the same temperature for 3 hr. After cooled under argon atmosphere, distilled THF (4.0 ml) was added with stirring at 0 °C for 5 min. The ice bath was removed and the suspension was stirred overnight under argon atmosphere at rt. The flask was again immersed at 0 °C and vinyl Grignard reagent (H_2C=CHMgBr, 1.0 M solution in THF, 0.20 ml, 0.20 mmol) was added. After stirring for 2 hr at 0 °C, **13** (50 mg, 0.0973 mmol) dissolved in THF (1.0 ml) was added at -78 °C. After stirring for 0.5 hr at -78°C, the cooling bath was removed. The reaction mixture was stirred for 10 hr and then quenched at 0 °C with saturated NH_4Cl solution. The mixture was diluted with Et2O, washed with saturated NH_4Cl solution and dried (Na_2SO_4). The solution was concentrated *in vacuo* and the residue was chromatographed on plc (silica gel, Et2O) to give 17.8 mg of **16** (0.093 mmol, 96 %).

Method B ; Enone **13** (22.8 mg, 0.0443 mmol) was dissolved in CH_2Cl_2 (2.0 ml) at rt. To this solution was added zinc iodide (2.8 mg, 0.0089 mmol) and trimethylsilyl cyanide (0.01 ml, 0.076 mmol). After 12 hr

stirring, the reaction mixture was concentrated *in vacuo* and chromatographed on preparative tlc (silica gel, 1:1 hexane/ethyl acetate) to gave 4.7 mg of **16** (0.025 mmol, 55 %). IR (KBr) ν 1699, 1604, 1306 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 3.78 (H-6, d, *J*= 7), 4.08 (H-6, dd, *J*= 7, 5), 5.38 (H-5, d, *J*= 5), 5.52 (H-1, s), 6.76 (H-10, d, *J*= 2), 6.89 (H-8, dd, *J*= 8.5, 2), 7.97 (H-7, d, *J*= 8.5). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 68.6, 75.9, 101.6, 110.5, 116.1, 128.8, 130.5, 145.7, 160.8, 197.3. EI-MS m/z 192 (M^+). HRMS calcd for $C_{10}H_8O_4$: 190.0422, found 190.0409.

Alcohol 17: Under argon atmosphere, a solution of *n*-BuLi in hexane (0.19 ml, 0.38 mmol) was slowly added to THF solution (8.0 ml) of trimethylsilylacetylene (0.06 ml, 0.4 mmol) at -78 °C. The reaction mixture was stirred for 1.5 hr at -78 °C. A solution of **13** (94.8 mg, 0.184 mmol) in THF (2.0 ml) that was preliminary cooled to -78 °C. This solution of **13** was added dropwise to the prepared acetylide solution. After stirring at -78 °C for 30 min, the reaction mixture was poured into saturated NH_4Cl solution. The mixture was warmed to rt and extracted with Et2O. The organic phase was separated and washed with water and brine, and then dried over Na_2SO_4. After removal of the solvent, 26.5 mg of **17** (0.0914 mmol, 50%) was obtained by plc (silica gel, 1:3 hexane/Et2O), and 10.3 mg of the adduct **19** was obtained (0.0168 mmol, 9.1 %). IR (KBr) ν 3478, 2955, 2914, 2364, 1695, 1616 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.23 (9H, s, CH_3Si), 2.82 (H-4, dd, *J*= 5.5, 3), 3.93 (H-6, dd, *J*= 7, 1), 3.96 (H-6, dd, *J*= 7, 4), 4.17 (H-10, brd, *J*= 5.5), 5.01 (H-5, d, *J*= 4), 5.30 (H-1, s), 6.57 (H-8, d, *J*= 6), 7.22 (H-7, dd, *J*= 6, 3). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.3 (Me_3Si), 44.6 (C-4), 68.3 (C-6), 70.8 (C-10), 73.2 (C-5), 99.9 (C-1), 103.8 (acetylene), 104.2 (acetylene), 126.5 (C-3), 126.9 (C-9), 130.2 (C-8), 132.5 (C-7), 188.6 (C-2). EI-MS m/z 290 (M^+).

Aromatic Acetylene 18: The alcohol **17** (19.4 mg, 0.0668 mmol) was dissolved in Ac_2O (1.0 ml) at rt under nitrogen. To this solution was added pyridine (1.0 ml) and it was stirred for 15.5 hr. The reaction mixture was diluted with toluene, and concentrated *in vacuo* to afford crude product. Chromatography on plc (silica gel, 1:1 hexane/Et2O) gave 15.3 mg of the aromatic compound **18** (0.0563 mmol, 84 %). IR (KBr) ν 2151, 1715 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.27 (9H, s, CH_3Si), 3.77 (H-6, d, *J*= 6.7), 4.08 (H-6, dd, *J*= 6.7, 4.6), 5.40 (H-5, d, *J*= 4.6), 5.54 (H-1, s), 7.41 (H-10, d, *J*= 1.4), 7.53 (H-8, dd, *J*= 8, 1.4), 7.99 (H-7, d, *J*= 8). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.3 (Me_3Si), 68.6 (C-6), 75.5 (C-5), 99.5 (acetylene), 101.3 (C-1), 103.4 (acetylene), 127.4, 127.5 (C-7), 128.9, 132.2 (C-8), 142.6 (C-9), 187.1 (C-2). EI-MS m/z 272 (M^+). HRMS calcd for $C_{15}H_{16}O_3Si$: 272.0868, found 272.0876.

Typical procedure of **Alkynyl adducts 19, 20 and 21**: Under argon atmosphere, a solution of *n*-BuLi in hexane (1.5 equiv.) was slowly added to THF solution of the acetylene compound (1.8 equiv.) at -78 °C. The reaction mixture was stirred for 1.5 hr at -78 °C. $BF_3{\cdot}OEt_2$ (1.5 or 3.0 equiv.) was added to this solution and stirring was continued for 0.5 hr at -78 °C. Cold solution of **13** (or **14**) (1.0 equiv.) at -78 °C in THF was added dropwise. After stirring for 15 min at -78 °C, the reaction mixture was poured into saturated NH_4Cl solution. The reaction mixture was warmed to rt and extracted with Et2O. The organic phase was washed with water and brine, and then dried over Na_2SO_4. After removal of the solvent, the adduct was obtained by column chromatography (silica gel).

Trimethylsilylacetylene Adduct 19, IR (KBr) ν 3060, 2158, 1721, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.19 (9H, s, CH_3Si), 2.89 (H-4, brd, *J*= 3), 3.57 (H-6, dd, *J*= 7, 1), 3.81 (H-6, dd, *J*= 7, 6), 4.76 (H-5, brd, *J*= 6), 5.42 (H-1, s), 5.61 (H-8, d, *J*= 10), 5.63 (H-10, s), 6.61 (H-7, d, *J*= 10), 7.36-8.08 (15H, m, arom.). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.3 (Me_3Si), 44.5 (C-4), 68.6 (C-9), 70.2 (C-6), 73.8 (C-5), 75.0 (C-10), 92.6 (acetylene), 97.3 (C-1), 103.5 (acetylene), 113.1 (C-3, *J*= 6.1 with γ-P), 122.4 (C-7), 128.4 (BzO), 128.5*, 128.7*, 129.1 (BzO), 129.5*, 129.7*, 129.8*, 130.1 (BzO), 131.1*,

131.5*, 131.55*, 131.57*, 131.6*, 131.7*,131.9*, 132.67*, 132.71*, 132.76*, 132.8*, 133.3 (BzO), 144.8 (C-2, J= 11.2 with β-P), 167.0 (BzO). $[\alpha]^{26}_{D}$ -173° (*c* 0.28, $CHCl_3$). EI-MS m/z 612 (M^+). HRMS calcd for $C_{34}H_{33}O_7PSi$: 612.1733, found 612.1732.

TBDMS-oxypropynyl Adduct 20a, IR (KBr) ν 3060, 2200, 1722, 1270 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.10 (3H, s, CH_3Si), 0.11 (3H, s, CH_3Si), 0.90 (9H, s, *t*-BuSi), 2.90 (H-4, brd, J= 4), 3.54 (H-6, dd, J= 7, 1), 3.81 (H-6, dd, J= 7, 6), 4.36 (2H, s, -$OCH_2C{\equiv}C$-), 4.73 (H-5, brd, J= 6), 5.45 (H-1, s), 5.60 (H-8, d, J= 10), 5.63 (H-10, s), 6.61 (H-7, d, J= 10), 7.36-8.08 (15H, m, arom.). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -5.3 (*Me*Si), -5.1 (*Me*Si), 18.2 (Me_3CSi), 25.8 (*Me*$_3$CSi), 44.4 (C-4), 51.7 (OCH2C≡), 68.3 (C-9), 69.9 (C-6), 73.9 (C-5), 76.5 (C-10), 83.3 (acetylene), 86.1 (acetylene), 97.3 (C-1), 112.9 (C-3, J= 7 with γ-P), 122.4 (C-7), 128.4 (BzO), 128.5*, 128.7*, 129.7 (BzO), 130.0 (BzO), 131.1*, 131.5*, 131.68*, 131.72*, 131.9*, 132.7*, 132.8*, 133.3 (BzO), 144.7 (C-2, J= 11 with β-P), 167.0 (BzO). FAB-MS (positive) m/z 685 (M+1), 663 (M-17), 627 (M-58). HRMS calcd for $C_{38}H_{42}O_8PSi$: 685.2386, found 685.2400.

MOM-oxypropynyl Adduct 20b, IR (KBr) ν 3064, 2198, 1721, 1271 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.91 (H-4, brd, J= 3), 3.35 (3H, s, CH_3O-), 3.57 (H-6, d, J= 7), 3.81 (H-6, dd, J= 7, 6), 4.26 (2H, s, -$OCH_2C{\equiv}$), 4.66 (2H, s, -OCH_2O-), 4.76 (H-5, brd, J= 6), 5.41 (H-1, s), 5.65 (H-8, d, J= 10), 5.61 (H-10, s), 6.63 (H-7, d, J= 10), 7.36-8.08 (15H, m, arom.). $[\alpha]^{27}_{D}$ -108.2° (*c* 2.4, $CHCl_3$). FAB-MS (positive) m/z 615 (M+1). HRMS calcd for $C_{34}H_{32}O_9P$: 615.1783, found 615.1774.

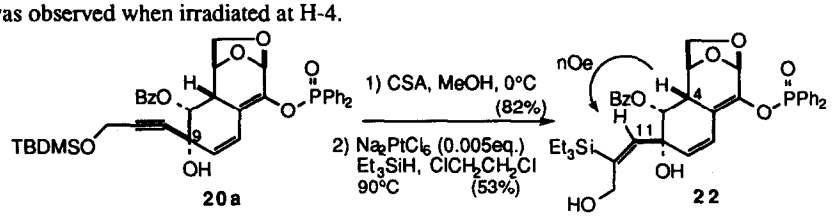
1-Octynyl Adduct 20c, IR (KBr) ν 3057, 2234, 1718, 1274 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, t, J= 6.7, CH_3-$(CH_2)_5$-), 1.22-1.58 (8H, m, CH_3-$(CH_2)_4$-CH_2-), 2.22 (2H, t, J= 7, CH_3-$(CH_2)_4$-CH_2-), 2.91 (H-4, brd, J= 3), 3.56 (H-6, d, J= 7), 3.81 (H-6, dd, J= 7, 6), 4.75 (H-5, brd, J= 6), 5.42 (H-1, s), 5.61 (H-10, s), 5.63 (H-8, d, J= 10), 6.58 (H-7, d, J= 10), 7.36-8.08 (15H, m, arom.). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.0, 18.8, 22.4, 28.2, 28.5, 31.1, 44.5 (C-4), 68.3 (C-9), 70.0 (C-6), 73.9 (C-5), 75.4 (C-10), 79.1 (acetylene), 88.5 (acetylene), 97.1 (C-1), 113.2 (C-3, J= 7.2 with γ-P), 121.6 (C-7), 128.37(BzO), 128.44*, 128.6*, 129.2*, 129.6 (BzO),129.8*, 130.0 (BzO), 130.5*, 131.2*, 131.5*, 131.6*, 131.7*, 131.8*, 132.59*, 132.64*, 132.7*, 133.1 (BzO), 144.5 (C-2, J= 10 with β-P), 166.9 (BzO). $[\alpha]^{26}_{D}$ -138.2° (*c* 0.55, $CHCl_3$). FAB-MS (positive) m/z 625 (M+1), 607 (M-17). HRMS calcd for $C_{37}H_{38}O_7P$: 625.2354, found 625.2364.

Adduct 21, IR (KBr) ν 3033, 2173, 1724, 1273 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (3H, s, CH_3Si), 0.15 (3H, s, CH_3Si), 0.19 (9H, s, $(CH_3)_3Si$), 0.92 (9H, s, *t*-BuSi), 2.52 (H-4, m), 3.08 (3H, s, CH_3O), 3.65 (H-6, dd, J= 7, 1), 3.74 (H-7, dd, J= 10, 3), 3.87 (H-6, dd, J= 7, 6), 3.99 (H-8, d, J= 10), 4.73 (H-5, brd, J= 6), 5.57 (H-1, s), 5.66 (H-10, d, J= 2), 7.34-8.08 (15H, m, arom.). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.9 (*Me*Si), -4.0 (*Me*Si), -0.3 (TMS), 18.3 (Me_3CSi), 25.8 (*Me*$_3$CSi), 43.1 (C-4), 60.2 (C-6), 68.4 (C-5), 73.6, 74.2, 74.7 (C-7, 9 and 10), 83.7 (C-8), 93.9 (acetylene), 97.0 (C-1), 103.6 (acetylene), 113.3 (C-3, J= 7.2 with γ-P), 128.2 (BzO), 128.3*, 128.4*, 128.5*, 129.9 (BzO), 130.1 (BzO), 131.4*, 131.6*, 131.7*, 131.9*, 132.1*, 132.3*, 132.5*, 132.8 (BzO), 133.2*, 143.5 (C-2, J= 9.2 with β-P), 166.7 (BzO). $[\alpha]^{26}_{D}$ +25.1° (*c* 0.35, $CHCl_3$). FAB-MS (positive) m/z 775 (M+1), 743 (M-31), 717 (M-57). HRMS calcd for $C_{41}H_{52}O_9PSi_2$: 775.2887, found 775.2878.

Acknowledgements The authors are grateful to Dr. Stanislaw Pikul, Dr. A. Herunsalee, Mr. Toshio Nishikawa and the late Professor Toshio Goto for valuable discussions and help to persuade these experiments. The author thanks Mr. S. Kitamura of this department for HRMS measurements and elemental analyses.

REFERENCES AND NOTES

1. (a) Tsuda, K.; Tachikawa, R.; Tamura, C.; Amakasu, M.; Kawamura, M.; Ikuma, S. *Chem. Pharm. Bull.*, **1964**, *12*, 634, 642, 1357. (b) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron Lett.*, **1963**, 2105, 2115.; *ibid*, **1964**, 779. (c) Woodward, R. B. *et al. Pure and Appl. Chem.*, **1964**, *9*, 49.
2. Yoshida, E.; Nakayama, H.; Hatanaka, Y.; Kanaoka, Y. *Chem. Pharm. Bull.*, **1990**, *38*, 982.
3. Yotsu, M.; Yasumoto, T.; Kim, Y. H.; Naoki, H.; Kao, C. Y. *Tetrahedron Lett.*, **1990**, *31*, 3187.
4. Kishi, Y.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S., Kakoi, H. *J. Am. Chem. Soc.*, **1972**, *94*, 9217, 9219.
5. Isobe, M.; Nishikawa, T.; Pikul, S.; Goto, T. *Tetrahedron Lett.*, **1987**, *28*, 6485.
6. For Diels-Alder reaction with levoglucosenone and its derivatives; (a) Isobe, M.; Fukami, N; Goto, T. *Chem. Lett.*, **1985**, 71. (b) Isobe, M.; Fukami, N; Nishikawa, T.; Goto, T. *Heterocycles*, **1987**, *25*, 521. 3327.
7. Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P.; Goto, T. *Tetrahedron Lett.*, **1990**, *31*, 3327.
8. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.*, **1984**, *25*, 4821.
9. (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.*, **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Organic Syntheses collective volume 7*, **1990**, 312. (c) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.*, **1985**, *107*, 1269.
10. (a) Borowitz, I. J.; Anschel, M.; Firstenberg, S. *J. Org. Chem.*, **1967**, *32*, 1723. (b) Stork, G.; Isobe, M. *J. Am. Chem. Soc.*, **1975**, *97*, 4745.
11. (a) Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.*, **1984**, *25*, 2411. (b) Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.*, **1983**, 35. (c) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.*, **1983**, *24*, 391.
12. The stereochemistry of the acetylenic group was proven from the following experiments: first **20a** was converted to the olefin **22** through hydrosilylation under the condition cited below; thus, one of the two products (regioisomer, 1:1) was isolated as **22**. In the nmr spectrum of **22**, strong enhancement of H-11 was observed when irradiated at H-4.



20a **22**