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SYNTHETIC STUDY OF AN INTERMEDIATE TOWARDS PARACENTRONE*

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Abstract – Paracentrone (**1**), the second naturally occurring C_{31}-methyl ketone apocarotenoid from fucoxanthin (**2**), was first isolated from the sea urchin *Paracentrotus lividus*. In this study, we focused on this carotenoid metabolite and report on a synthetic approach towards (3*E*)-(5*R*)-[(2*R*,4*S*)-2-hydroxy-4-(*tert*-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-1-iodo-4-methyl-1,3,5-hexatriene (**5**), a synthetic intermediate towards **1**. This was obtained from epoxy acetylene (**11**) *via* (2*E*)-(4*R*)-[(2*R*,4*S*)-2-hydroxy-4-(*tert*-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-3-methylpenta-2,4-dien-1-ol (**7**).

As a research group, we are very interested in the chemical compounds that form food and food metabolites. We have already investigated the synthesis and activity of flavonoids and their metabolites.[1,2] Thus, we turned our focus towards carotenoids and their metabolites. Herein, we report the synthetic study of the carotenoid metabolite paracentrone (**1**). Paracentrone (**1**) was first isolated from the sea urchin *Paracentrotus lividus* by Galasko and co-workers in 1969.[3] It is the second naturally occurring C_{31}-methyl ketone apocarotenoid from fucoxanthin (**2**). Fucoxanthin (**2**) is a major carotenoid found in edible seaweeds, such as *Undaria pinnatifida* and *Hijikia fusiformis*.[4] The Hora group reported that fucoxanthin (**2**) was converted into paracentrone (**1**) *in vivo* through natural animal digestion.[5] Hydrolysis of the acetyl group in **2** results in fucoxanthinol (**3**), and oxidation of the alcohol to a

*This paper is dedicated to Dr. Tohru Fukuyama on the occasion of his 70th Birthday.

keto-compound yields amarouciaxanthin A (**4**). A base-induced retro-aldol cleavage of **4** ultimately yields paracentrone (**1**). The Miyashita group investigated the suppressive effects of fucoxanthin (**2**) and its metabolite, fucoxanthinol (**3**), on the differentiation of 3T3-L1 preadipocytes to adipocytes.[6] We were very interested in whether **1** also had suppressive effects on the differentiation of 3T3-L1 preadipocytes to adipocytes just like **2** and **3**.

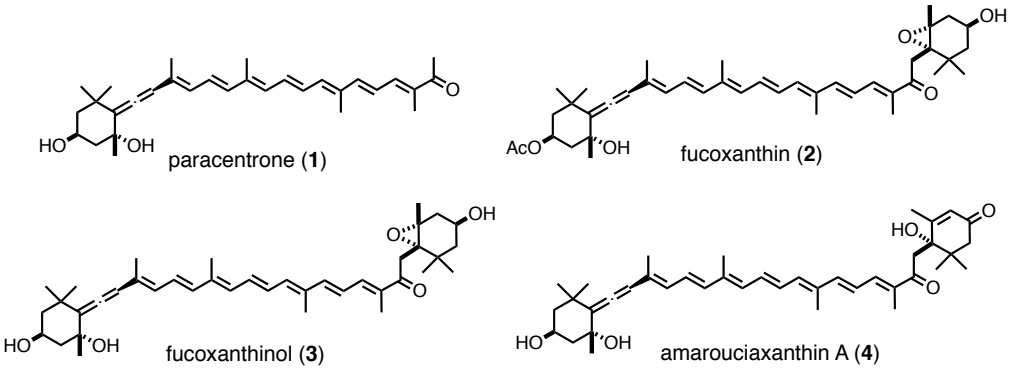
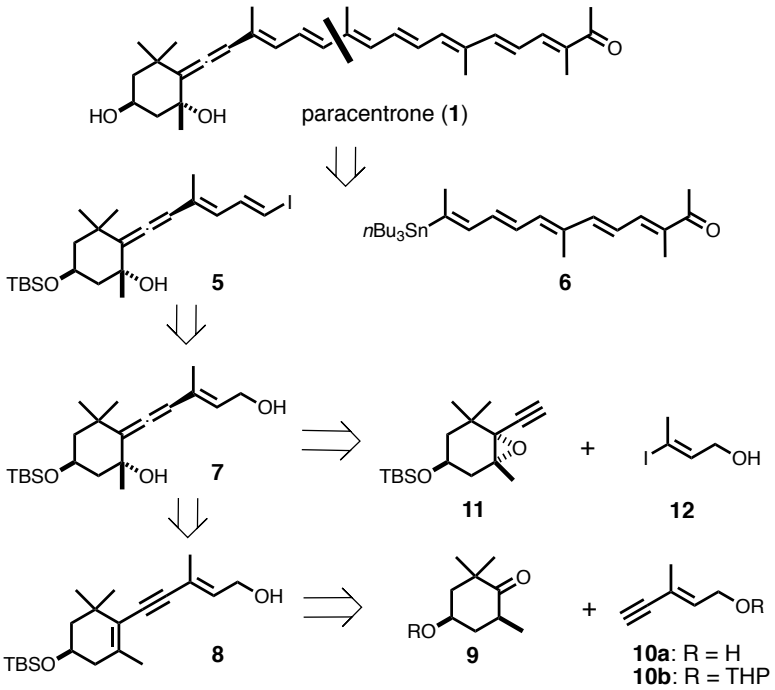


Figure 1. Chemical structures of **1**-**4**

Three groups have reported the synthesis of **1**. A synthesis of **1** was reported from the allenic diol (**7**) in five steps by the Haugan group.[7] Communications describing the total synthesis of optically active **1** was published by both the Katsumura[8] and the Nishioka[9] groups independently. **Scheme 1** summarizes our synthetic strategy. Migita-Kosugi-Stille cross-coupling[10] of iodide (**5**) and stannane (**6**) would

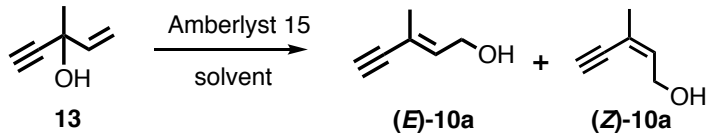


Scheme 1. Retrosynthetic scheme for the synthesis of **1**

furnish the polyene chain of **1**. In this study, we describe two different routes for the synthesis of allenic diol (**7**), an intermediate towards key compound (**5**). The key towards our first synthetic strategy is

coupling of ketones (4*R*,6*R*)-**9** and (4*R*,6*S*)-**9** with (*E*)-enyne units (**10a** and **10b**). Thereafter, a regioselective stereoselective epoxidation of dienyne compound (**8**) would furnish **7**. Unfortunately, the preparation of (*E*)-**10a** from commercially available 3-methylpent-1-en-4-yn-3-ol (**13**) by isomerization under strong acidic conditions[11] failed. The isomerization reaction proceeded in 60-70% yield; however, the obtained product was an inseparable mixture of (*E*)- and (*Z*)-**10a** (**Table 1**).

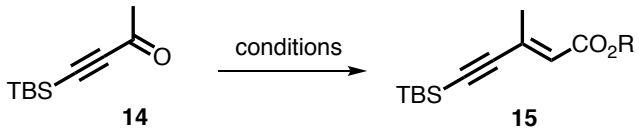
Table 1. Isomerization of a 3-methylpent-1-en-4-yn-3-ol (**13**) under acidic conditions



13 **(*E*)-10a** **(*Z*)-10a**

entry	solvent	temp., °C	yield, %	*E*:*Z* ratio of **10a**
1	*i*Pr$_2$O-H$_2$O (2:1)	60	63	1.0:3.4
2	H$_2$O	60	65	1.0:4.2
3	H$_2$O	50	68	1.0:5.6
4	H$_2$O	70	13	0:1.0
5	THF-H$_2$O (1:4)	55	70	1.0:4.3

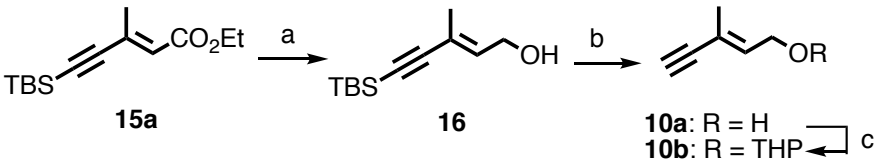
Table 2. Wittig olefination of propargyl ketone (**14**)



14 **15**

entry	phosphorus ylide	R	solvent	temp,°C	yield, %	*E*:*Z*	product
1	Ph_3PCHCO_2R	Et	THF	66	55	1.0:1.6	**15a**
2	〃	〃	toluene	110	68	2.3:1.0	**15a**
3	〃	〃	xylene	144	73	3.0:1.0	**15a**
4	〃	Me	〃	144	73	1.0:1.0	**15b**
5	〃	*n*propyl	〃	144	80	2.0:1.0	**15c**
6	〃	*i*propyl	〃	144	65	2.0:1.0	**15d**
7	〃	*t*butyl	〃	144	55	1.0:1.0	**15e**

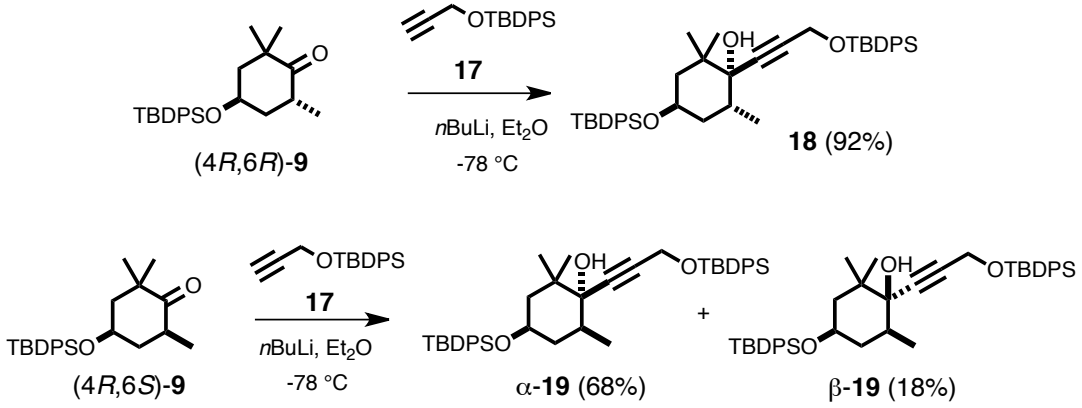
To obtain the (*E*)-**10a** exclusively, Wittig olefination of methyl propargyl ketone (**14**) was studied next. The treatment of **14** with various types of stable phosphorus ylides at reflux yielded the desired (*E*)-olefination enyne esters products (**15a**-**15e**) in 55% to 80% yields (**Table 2**).[12] After separation of (*E*)-ester (***E*-15a**), it was converted in the THP-ether (**10b**), by diisobutylaluminium hydride (DIBAL-H) reduction, TBAF treatment and THP protection in 68% yield over 3 steps, as shown in **Scheme 2**.



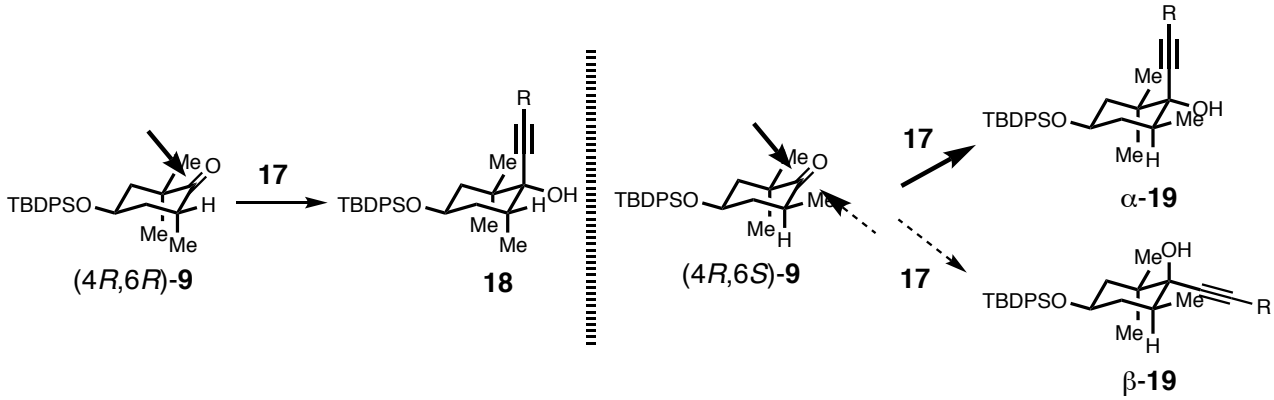
Reagents and conditions: (a) DIBAL-H, Et_2O, -78 °C (91%);
(b) TBAF, THF, rt (90%): (c) PPTS, DHP, CH_2Cl_2, rt (83%).

Scheme 2. Synthesis of the THP ether (**10b**)

The coupling of (4*R*,6*R*)- and (4*R*,6*S*)-ketone (**9**)[13] with nucleophiles was studied next.[14,15] The treatment of ketone (4*R*,6*R*)-**9** with the lithium salt of the TBDPS-propargyl alcohol (**17**) (*n*BuLi treatment in Et_2O at -78 °C) provided the alcohol (**18**) in 92% yield as a single diastereomer. On the other hand, the reaction of ketone (4*R*,6*S*)-**9** with **17** produced two alcohols, α-OH (α-**19**) in 68% and β-OH (β-**19**) in 18% yield (**Scheme 3**). This diastereomeric outcome can be explained by considering the preferred axial attack by nucleophile (**17**) on the less hindered side of ketone-**9** as shown in **Scheme 4**.

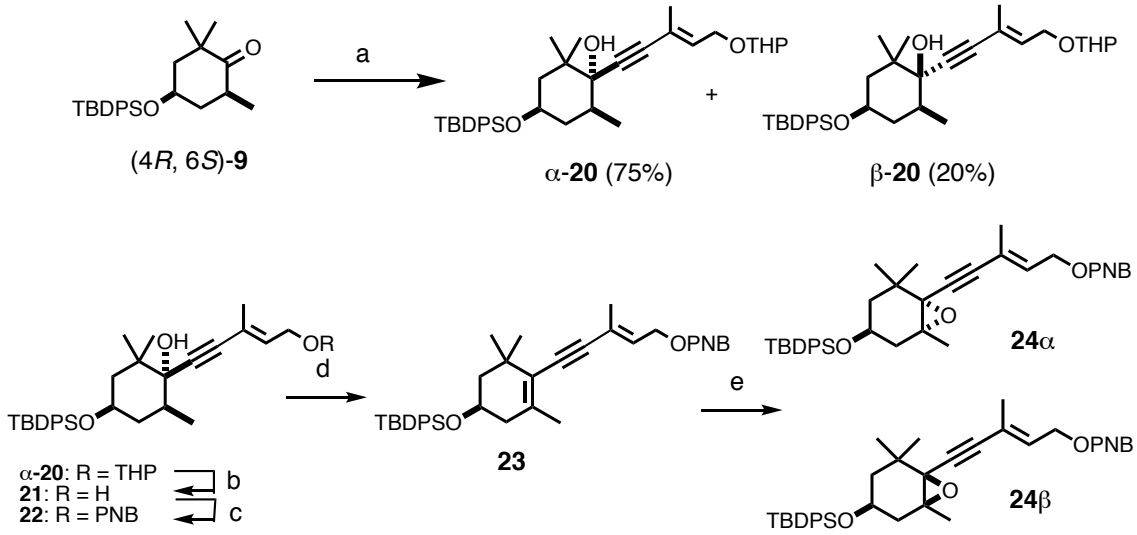


Scheme 3. Coupling of ketone (**9**) with the TBDPS-protected propargyl alcohol (**17**)



Scheme 4. Nucleophilic axial attack in the reaction

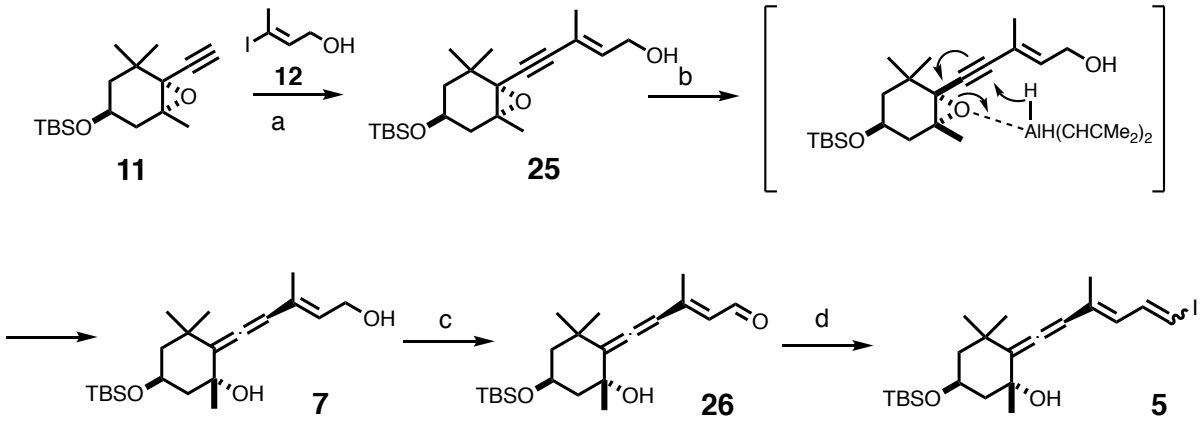
The treatment of (4*R*,6*S*)-**9**[16] with the lithium salt of **10b** (*n*BuLi treatment in Et_2O at -78 °C to 25 °C) produced the two alcohols, α-OH (α-**20**) and β-OH (β-**20**), in 75% and 20% yields, respectively. After separation of α-**20**, the THP protecting group of allylic alcohol was changed to a PNB (4-nitrobenzoyl) group *via* diol (**21**). Dehydration of **22** with phosphoryl ehloride in 2,4,6-collidine under reflux conditions gave the dienyne compound (**23**) in 51% yield.[17] The epoxidation of dienyne compound (**23**) with *m*-chloroperoxybenzoic acid (*m*CPBA) afforded two epoxides, α-epoxide (**24α**) in 35% and β-epoxide (**24β**) in 28% yield. By using the PNB protecting group for allylic alcohol, regioselective epoxidation at the tetra-substituted alkene was achieved.[17] Because the necessary stereoselectivity could not obtained by epoxidation, we were forced to abandon this route towards paracentrone synthesis.[18]



Reagents and conditions: (a) **10b**, *n*BuLi, Et_2O, -78 °C to 0 °C (95%); (b) 80% aq. AcOH, THF/H_2O, rt (82%); (c) *p*-$NO_2C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, rt (83%); (d) $POCl_3$, 2,4,6-collidine, reflux (51%); (e) *m*CPBA, CH_2Cl_2, 0 °C (63%).

Scheme 5. Synthesis of α-epoxide (**23α**)

To achieve the regio- and stereoselective epoxidation, a Katsuki-Sharpless asymmetric epoxidation[19] was employed. An alternative approach starting from epoxy acetylene (**11**)[20] reported by the Katsumura group[21] was successfully employed. The cross-coupling reaction of **11** with vinyl iodide (**12**)[22] was accomplished under standard Sonogashira conditions,[23] tetrakis(triphenylphosphine)palladium and copper(I) iodide in diisopropylamine ($Pd(PPh_3)_4$, CuI, DIPA), to afford the TBS ether of propargylic oxirane (**25**) in 92% yield. The S_N2' reduction of the **25** through a stereospecific hydride reduction with DIBAL-H, produced the allene moiety in 88% yield. Oxidation of **7** with MnO_2 in Et_2O furnished aldehyde (**26**)[24] in 92% yield. The carbon chain extension from aldehyde (**26**) by the Takai-Utimoto reaction[25] produced vinyl iodide (**5**) in 41% yield as a stereoisomeric mixture (*E*:*Z* = 1:2)[26] (**Scheme 6**).



Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, DIPA, rt (92%); (b) DIBAL-H, Et_2O, 0 °C (88%); (c) MnO_2, Et_2O, rt (92%); (d) CHI_3, $CrCl_2$, THF, 0 °C, *E*:*Z* = 1:2 (41%).

Scheme 6. Synthesis of intermediate (**5**)

In conclusion, we presented a synthetic route for paracentrone synthetic intermediate (**5**) from epoxy acetylene (**11**). The synthesis of *E* and *Z* mixture of (3*E*)-(5*R*)-[(2*R*,4*S*)-2-hydroxy-4-(*tert*-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-1-iodo-4-methyl-1,3,5-hexatriene (**5**) was successfully accomplished starting from (2*E*)-(4*R*)-[(2*R*,4*S*)-2-hydroxy-4-(*tert*-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-3-methylpenta-2,4-dien-1-ol (**7**).

EXPERIMENTAL

General. All reagents used were of commercial quality. Anhydrous THF and CH_2Cl_2 (Kanto Chemical) were used without purification. All air- and moisture-sensitive reactions were performed under an inert gas (nitrogen or argon). Analytical TLC was conducted on precoated TLC plates (silica gel $60F_{254}$, Merck) and column chromatography was performed using silica gel 60N (70-230 mesh, Kanto Chemical). ATR-IR spectra were measured using a PerkinElmer Spectrum 100 spectrometer equipped with a Universal ATR accessory. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Biospin AVANCE II 400 spectrometer using TMS or a solvent peaks as an internal standard (chemical shift in ppm). LR-ESI-MS spectra were recorded on an Agilent Technology 1100 LC-MSD spectrometer using MeOH or MeCN solutions in water or 0.5% HCO_2H as effluents. HR-ESI-MS spectra were acquired on a Bruker Dartonics micrOTOF focus spectrometer. Specific rotation values were measured with a Horiba polarimeter.

(2*E*)-[(1*S*,4*R*,6*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-1-hydroxy-2,2,6-trimethylcyclohexyl]-3-methyl-1-(tetrahydro-2*H*-pyran-2-yl)oxypent-2-en-4-yne

To a solution of (*E*)-2-((3-methylpent-2-en-4-yn-1-yl)oxy)tetrahydro-2*H*-pyran (**10b**, 189 mg, 1.05 mmol) in Et_2O (2.5 mL) was added *n*BuLi (2.69 M in hexane, 390 mL, 1.05 mmol) at −78 °C. The mixture was stirred for 20 min at the same temperature. To this mixture, **10b** (298 mg, 0.76 mmol) in THF (2.5 mL) was added at −78 °C. The mixture was stirred for 1.5 h at room temperature. We quenched the reaction with sat. aq. NH_4Cl and extracted the mixed solution with EtOAc. The organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10/1 to 3/1) to give a coupling product α-**20** (324 mg, 0.563 mmol, 75%) and β-**20** (84 mg, 0.15 mmol, 20%) as a colorless oil. Data for α−**20**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 7.68 (m, 4H, Ph), 7.394 (m, 6H, Ph), 5.85 (tt, *J*=7.7, 1.4 Hz, 1H, H-10), 4.71 (t, br, *J*=3.4Hz, 1H, O-CH-O), 4.32 (m, 2H, H-11), 3.85 (m, 2H, H-3, O-CH2), 3.52 (m, dt-like, 1H, O-CH2), 2.45 (d, *J*=5.3 Hz, 1H,), 1.94 (d, *J*=0.6, 3H, 9-Me), 1.87-1.37 (m, 10H, H-2,4-THP), 1.26 (s, 2H), 1.05 (s, 9H, Si-^{t}Bu), 1.01 (d-like, 3H,1-Me), 0.99 (t-like, 3H, 5-Me), 0.69 (s, 3H, 1-Me); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 135.9 (Si-Ph), 134.7 (C-10), 132.9 (C-9), 129.7 (Si-Ph), 127.6 (Si-Ph), 97.1 (THP), 94.4 (C-8), 86.2 (C-7), 78.2 (C-6), 67.9 (C-3), 65.0 (THP), 62.0 (C-11), 47.1 (C-2), 41.9 (C-5), 39.8 (C-1), 36.0 (C-4), 30.6 (THP), 29.9 (THP), 27.1 (Si-^{t}Bu), 25.6 (5-Me), 23.5 (1-Me), 20.7 0(1-Me), 19.3 (Si-^{t}Bu), 16.6 (THP), 1.16 (9-Me); IR (neat, cm^{-1}) ν : 3453.9 (w, br), 2931.8 (w), 2857.9 (w), 1741.7 (w), 1472.9 (w), 1427.8 (w), 1373.8 (w), 1238.7 (w), 1200.8 (w), 1184.9 (w), 1110.6 (m), 1073.6 (m), 1021.5 (m), 975.7 (w), 904.8 (w), 866.8 (w), 847.8 (w), 821.7 (w), 777.9 (w), 740.7 (w), 701.4 (m); LRMS (ESI) *m/z* : 597.34 $(M+Na)^+$; ESI-HRMS *m/z* : 597.3361 (calcd for $C_{36}H_{50}NaO_4Si$, 597.3371).

(2*E*)-[(1*S*,4*R*,6*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-1-hydroxy-2,2,6-trimethylcyclohexyl]-3-methylpent-2-en-4-yn-1-ol (21)

The coupling product (α−**20**, 117 mg, 0.2 mmol) was dissolved in the 2 mL solution mixture of AcOH/THF/H_2O (4:2:1). The mixture was stirred for 24 h at 48 °C. The reaction was quenched with sat. aq. $NaHCO_3$, and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/1 to 1/1) to give **21** (78 mg, 0.16 mmol, 82%) as a colorless oil and α−**20** (21 mg, 0.036mmol, 18%) was recovered. Data for **21**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 7.66 (m, 4H, Ph), 7.40 (m, 6H, Ph), 5.90 (dt, *J*=5.3, 1.5Hz, 1H, H-10), 4.90 (s, br, 1H, 6-OH), 4.36 (d, *J*=6.6 Hz, 2H, H-11), 3.83 (m, 1H, H-3), 2.78 (s, br, 1H, 11-OH), 1.93 (d, *J*=1.2 Hz, 3H, 9-Me), 1.88-1.38 (m, 5H, H-2,4,5), 1.05 (s, 9H, Si-tBu), 1.01 (s, 3H, 1-Me), 0.99 (d, *J*=6.4 Hz, 3H, 5-Me), 0.69 (s, 3H, 1-Me); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 135.8 (Si-Ph), 134.6 (C-10),

129.6 (Si-Ph), 127.5 (Si-Ph), 120.8 (C-9), 94.5 (C-8), 85.7 (C-7), 78.3 (C-6), 67.7 (C-3), 60.5 (C-11), 46.9 (C-2), 41.7 (C-5), 39.7 (C-1), 35.9 (C-4), 27.0 (Si-^{t}Bu), 23.4 (5-Me), 20.6 (1-Me), 20.30 (1-Me), 19.2 (Si-^{t}Bu), 16.5 (9-Me); IR (neat, cm^{-1}) ν : 3398.9 (w, br), 2931.8 (w), 2857.9 (w), 1713.7 (w), 1472.8 (w), 1427.8 (w), 1374.7 (w), 1239.7 (w), 1104.6 (m), 1072.6 (m), 1041.6 (m), 1007.6 (m), 976.6 (m), 916.8 (w), 846.8 (w), 821.79(w), 777.9 (w), 740.7 (w), 701.3 (s); LRMS (ESI) *m/z* : 513.3 $(M+Na)^+$; ESI-HRMS *m/z* : 513.2833 (calcd for $C_{31}H_{42}NaO_3Si$, 513.2795).

(2*E*)-[(1*S*,4*R*,6*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-1-hydroxy-2,2,6-trimethylcyclohexyl]-1-hydroxy-3-methylpent-2-en-4-ynyl 4-nitrobenzoate (22)

To a mixture of alcohol (**21**, 125 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) were added Et_3N (110 μl, 0.79 mmol), DMAP (32 mg, 0.26 mmol), and 4-nitrobenzoyl chloride (49 mg, 0.26 mmol) at 0 °C. The mixture was stirred for 1.0 h at 0 °C. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to give **22** (140 mg, 0.29 mmol, 83%) as a colorless oil. Data for **22**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 8.27 (d, *J*=8.0 Hz, 2H, NO_2-Ph), 8.21 (d, *J*=8.0 Hz, 2H, NO_2-Ph), 7.65 (m, 4H, Si-Ph), 7.34 (m, 6H, Si-Ph), 5.96 (dt, *J*=7.0, 1.5 Hz, 1H, H-10), 5.10 (d, *J*=7.0 Hz, 2H, H-11), 3.84 (m, 1H, H-3), 2.00 (s, 3H, 9-Me), 1.86-1.41 (m, 5H, H-2, 4, 5), 1.04 (s, 3H, 1-Me), 1.03 (s, 9H, Si-^{t}Bu), 1.01 (s, 3H, 1-Me), 0.71 (s, 3H, 5-Me); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 164.5 (11-O-C=O), 150.5 (NO_2-Ph), 135.8 (Si-Ph), 135.7 (Si-Ph), 135.6 (NO_2-Ph), 134.5 (Si-Ph), 134.5 (Si-Ph), 130.8 (NO_2-Ph), 129.6 (Si-Ph), 129.6 (Si-Ph), 129.3 (C-10), 124.8 (C-9), 123.5 (NO_2-Ph), 95.8 (C-8), 85.2 (C-7), 78.3 (C-6), 67.6 (C-3), 64.1 (C-11), 46.9 (C-2), 41.7 (C-5), 39.7 (C-1), 35.9 (C-4), 29.7 (Si-^{t}Bu), 27.0 (Si-^{t}Bu), 23.5 (5-Me), 20.5 (1-Me), 19.1 (1-Me), 16.5 (9-Me); IR (neat, cm^{-1}) ν : 3515.0 (w, br), 3072.0 (w), 2960.9 (w), 2930.8 (w), 2857.9 (w), 1726.6 (m), 1608.9 (w), 1530.6 (m), 1472.9 (w), 1461.8 (w), 1427.8 (w), 1373.8 (w), 1347.8 (w), 1267.4 (w), 1240.6 (m), 1186.9 (w), 1100.5 (m), 1073.6 (m), 1040.6 (m), 1015.7 (w), 975.7 (w), 936.8 (w), 916.8 (w), 873.8 (w), 846.7 (w), 821.7 (w), 784.8 (w), 774.8 (w), 740.7 (w), 719.6 (m), 701.3 (m), 690.6 (m); LRMS (ESI) *m/z* : 662.3 $(M+Na)^+$; ESI-HRMS *m/z* : 662.2902 (calcd for $C_{38}H_{45}NNaO_4Si$, 662.2980).

(2*E*)-[(4*S*)-(4-((*tert*-Butyldiphenylsilyl)oxy)-2,6,6-trimethylcyclohex-1-en-1-yl)-1-hydroxy-3-methyl-pent-2-en-4-ynyl 4-nitrobenzoate (23)

To a mixture of 4-nitrobenzoate (**22**, 140 mg, 0.22 mmol) in 2,4,6-trimethylpyridine (2.0 mL) was added $POCl_3$ (60 μL, 66 mmol) at 0 °C. The mixture was stirred for 3 h at 170 °C. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O. The organic layer was washed with 1 N HCl, H_2O,

and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 12/1) to give **23** (70 mg, 0.11 mmol, 51%) as a colorless oil. Data for **23**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 8.27 (d, *J*=8.8 Hz, 2H, NO_2-Ph), 8.19 (d, *J*=8.8 Hz, 2H, NO_2-Ph), 7.67 (m, 4H, Si-Ph), 7.40 (m, 6H, Si-Ph), 5.83 (t, br, *J*=7.0 Hz, 1H, H-10), 5.03 (d, *J*= 7.0 Hz, 2H, H-11), 3.91 (m, 1H, H-3), 2.21 (m, 2H, H-4), 1.96 (s, 3H, 9-Me), 1.82 (s, 3H, 5-Me), 1.63 (m, 2H, H-2), 1.10 (s, 3H, 1-Me), 1.07 (s, 9H, Si-^{t}Bu), 0.78 (s, 3H, 1-Me); ^{13}C-NMR(100MHz, $CDCl_3$) δ : 164.7 (11-O-C=O), 150.6 (NO_2-Ph), 139.7 (NO_2-Ph), 135.9 (Si-Ph), 135.9 (Si-Ph), 134.5 (Si-Ph), 134.4 (Si-Ph), 130.9 (C-5), 129.8 (NO_2-Ph), 127.7 (Si-Ph), 127.4 (C-10), 125.7 (C-6), 123.6 (NO_2-Ph), 123.6 (C-9), 94.5 (C-8), 91.3 (C-7), 66.3 (C-3), 64.7 (C-11), 46.6 (C-2), 41.8 (C-4), 36.5 (C-1), 30.5 1(1-Me), 29.8 (1-Me), 28.3 (Si-^{t}Bu), 27.1 (Si-^{t}Bu), 23.7 (5-Me), 19.2 (9-Me); IR (neat, cm^{-1}) ν : 3072.0 (w), 2959.8 (w), 2928.8 (w), 2857.9 (w), 2185.0 (w), 1725.6 (m), 1608.9 (w), 1529.6 (m), 1471.8 (w), 1427.8 (w), 1375.8 (w), 1360.8 (w), 1343.7 (w), 1318.9 (w), 1267.4 (m), 1241.7 (w), 1209.8 (w), 1176.9 (w), 1101.5 (m), 1077.5 (m), 1014.7 (w), 998.8 (w), 985.8 (w), 938.8 (w), 872.7 (w), 832.7 (w), 821.7 (w), 784.8 (w), 770.8 (w), 739.6 (w), 719.5 (w), 700.3 (s); LRMS (ESI) *m/z* : 644.3 $(M+Na)^+$; ESI-HRMS *m/z* : 660.2529 (calcd for $C_{38}H_{43}KNO_5Si$, 660.2542); $[\alpha]_D^{25}$ -31.6 (*c* 1.26, $CHCl_3$).

(2*E*)-((1*R*,4*S*,6*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl]-1-hydroxy-3-methylpent-2-en-4-ynyl 4-nitrobenzoate (24α)

To a mixture of **23** (**23**, 70 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (27 mg, 0.11 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction was quenched with sat. aq. $NaHCO_3$, and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel TLC plate (hexane/EtOAc, 10/1) to give **24** (48 mg, 0.076 mmol, 67%) as a 5:4 mixture. Data for **24α**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 8.28 (m, 2H, NO_2-Ph), 8.20 (m, 2H, NO_2-Ph), 7.65 (m, 4H, Si-Ph), 7.40 (m, 6H, Si-Ph), 5.91 (dd-like, 2H, H-10), 4.96 (d, *J*=6.9 Hz, 2H, H-11), 3.82 (m, 1H, H-3), 2.19 (ddd, *J*=14.6, 5.0, 1.2 Hz, 1H, H-4), 1.90 (d, *J*=0.9 Hz, 3H, 9-Me), 1.74 (m, 1H, H-4), 1.49 (t-like, 1H, H-2), 1.39 (s, 3H, 5-Me), 1.26 (s, 9H, Si-^{t}Bu), 1.23 (s, 3H, 1-Me), 1.04 (s, 3H, 1-Me); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 164.6 (11-O-C=O), 150.7 (NO_2-Ph), 135.9 (Si-Ph), 135.9 (NO_2-Ph), 130.9 (NO_2-Ph), 129.8 (C-10), 129.8 (Si-Ph), 127.7 (Si-Ph), 124.1 (C-9), 123.7 (NO_2-Ph), 92.8 (C-8), 83.3 (C-9), 67.1 (C-6), 64.3 (C-3), 63.7 (C-5), 45.4 (C-2), 38.7 (C-4), 32.1 (C-1), 29.5 (Si-^{t}Bu), 27.0 (Si-^{t}Bu), 24.5 (1-Me), 23.3 (1-Me), 22.8 (9-Me), 14.3 (5-Me); IR (neat, cm^{-1}) ν : 3073.0 (w), 2961.9 (w), 2931.9 (w), 2858.9 (w), 1727.6 (m), 1608.9 (w), 1529.6 (w), 1472.8 (w), 1447.9 (w), 1427.8 (w), 1410.9 (w),

1373.8 (w), 1362.8 (w), 1342.7 (w), 1318.9 (w), 1267.4 (m), 1239.6 (m), 1101.5 (m), 1080.5 (m), 1063.6 (m), 1046.6 (m), 1014.7 (w), 998.8 (w), 937.8 (w), 894.8 (w), 872.8 (w), 857.8 (w), 844.8 (w), 821.6 (w), 784.8 (w), 772.8 (w), 740.7 (w), 719.5 (m), 701.3 (s), 690.6 (m) ; LRMS(ESI) *m/z* : 660.3 $(M+Na)^+$; ESI-HRMS *m/z* : 660.2764 (calcd for $C_{38}H_{43}N_1Na_1O_6Si$, 660.2752).

(*E*)-5-((1*R*,4*S*,6*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl)-3-methylpent-2-en-4-yn-1-ol (25)

To a solution of epoxy acetylene (**11**, 600 mg, 2.03 mmol) and (*E*)-3-iodobut-2-en-1-ol (**12**, 403 mg, 2.00 mmol) in DIPA (10 mL) were added $Pd(PPh_3)_4$ (115 mg, 0.10 mmol) and CuI (19 mg, 0.10 mmol) at room temperature. The mixture was stirred for 2 h at this temperature. The reaction was quenched with sat. aq. NH_4Cl, and the mixture were extracted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified the residual oil by silica gel column chromatography (hexane/EtOAc, 3/1) to give **25** (684 mg, 1.88 mmol, 93%). Data for **25**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 6.00 (dt, *J*=6.8, 1.4 Hz, 1H, H-10), 4.22 (dd, br, *J*=5.8 Hz, 2H, H-11), 3.77 (m, 1H, H-3), 2.22 (ddd, *J*=14.5, 5.0, 1.4Hz, 1H, H-4), 1.82 (s, 3H, 9-Me), 1.65 (dd, *J*=14.5, 8.0Hz, 1H, H-4), 1.47 (ddd, *J*=15.3, 3.3, 1.5Hz, 1H, H-2), 1.47 (s, 3H, 5-Me), 1.43 (s, br, 1H, 11-OH), 1.234 (overlapped, 1H, H-2), 1.234 (s, 3H, 1-Me), 1.09 (s, 3H, 1-Me), 0.86 (s, 9H, Si-^{t}Bu), 0.03(d, *J*=2.0Hz, 6H, Si-Me_2); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 136.0 (C-9), 120.4 (C-10), 87.96 (C-8), 84.93 (C-7), 67.1 (C-6), 64.5 (C-3), 63.9 (C-11), 59.2 (C-5), 45.9 (C-2), 40.5 (C-4), 34.5 (C-1), 29.9 (Si-^{t}Bu), 26.0 (Si-^{t}Bu), 25.9 (1-Me), 22.0 (1-Me), 18.2 (5-Me), 17.6 (9-Me), -4.61(Si-Me_2) ; IR (neat, cm^{-1}) ν : 3388.9 (w, br), 2956.8 (w), 2928.8 (w), 2857.8 (w), 1635.0 (w), 1471.8 (w), 1382.8 (w), 1362.8 (w), 1252.7 (w), 1183.9 (w), 1151.9 (w), 1083.5 (m), 1032.7 (w), 1005.7 (w), 978.8(w), 936.8 (w), 870.7 (w), 851.6 (m), 833.4 (m), 773.5 (m), 714.8 (w), 667.8 (w); LRMS (ESI) *m/z* : 387.2 $(M+Na)^+$; ESI-HRMS *m/z* : 387.2316 (calcd for $C_{21}H_{36}NaO_3Si$, 387.2326); $[\alpha]_D^{26}$ -10.6 (*c* 0.94, MeOH).

(2*E*)-(4*R*)-[(2*R*,4*S*)-2-Hydroxy-4-(*tert*-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-3-methylpenta-2,4-dien-1-ol (7)

To a solution of propargylic oxirane (**25**, 80 mg, 0.22 mmol) in Et_2O (15 mL) was added DIBAL-H (1.0 M in toluene, 1.1 mL, 1.1 mmol) at 0 °C. The mixture was stirred for 1.5 h at 0 °C. The reaction was quenched with MeOH (6.0 mL) and 30% Potassium sodium tartrate solution, and the mixture was extracted with Et_2O. The organic layer was washed with 30% Potassium sodium tartrate solution and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to give **7** (71 mg, 0.19 mmol, 88%) as a pale

yellow oil. Data for **7**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 5.93 (s, 1H, H-8), 5.58 (t, *J*=7.0 Hz, H-10), 4.28 (m, 1H H-3), 4.25 (d, *J*=7.0 Hz, H-11), 2.13 (ddd, *J*=13.2, 4.2, 2.1 Hz, 1H, H-4), 1.81 (ddd, *J*=12.6, 4.2, 2.1 Hz, 1H, H-4), 1.66 (s, 3H, 9-Me), 1.45-1.34 (m, 1H, H-2), 1.32 (s, 3H, 5-Me), 1.31 (s, 3H, 1-Me), 1.04 (s, 3H, 1-Me), 0.90 (s, 9H, Si-^{t}Bu), 0.09 (s, 6H, Si-Me_2); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 201.5 (C-7), 133.6 (C-9), 126.4 (C-10), 118.0 (C-6), 101.9 (C-8), 73.0 (C-5), 65.1 (C-11), 59.7 (C-3), 50.0 (C-4), 49.4 (C-2), 35.7 (C-1), 32.3 (5-Me), 31.5 (9-Me), 29.4 (Si-^{t}Bu), 26.1 (Si-^{t}Bu), 18.4 (1-Me), 13.7 (1-Me), -4.46 (Si-Me_2); IR (neat, cm^{-1}) ν : 3378.9 (w, br), 2956.8 (w), 2926.7 (w), 2854.8 (w), 1938.0 (w), 1641.0 (w), 1471.8 (w), 1461.8 (w), 1452.8 (w), 1379.8 (w), 1360.8 (w), 1302.9 (w), 1251.7 (w), 1180.9 (w), 1153.8 (w), 1072.4 (m), 1005.7 (w), 993.7 (w), 956.7 (w), 938.8 (w), 908.8 (w), 874.6 (w), 837.4 (m), 770.5 (m), 704.8 (w), 665.7 (w); LRMS (ESI) *m/z* : 389.2 $(M+Na)^+$; ESI-HRMS *m/z* : 389.2460 (calcd for $C_{21}H_{38}NaO_3Si$, 389.2482); $[\alpha]_D^{24}$ -40.0 (*c* 1.00, MeOH).

(2*E*)-(4*R*)-[(2*R*,4*S*)- 4-(*tert*-Butyldimethylsilyl)oxy-2-hydroxyl-2,6,6-trimethylcyclohexylidene]-3-methylpenta-2,4-dien-1-al (26)

To a solution of allylic alcohol (**7**, 100 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) was added MnO_2 (270 mg, 3.11 mmol) and reaction mixture was stirred for 12 h at room temperature. Filtration by Celite, concentration and silica gel column purification (hexane/EtOAc, 2/1) afforded a aldehyde (**26**) (92 mg, 0.25 mmol, 92%) as an amorphous solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 10.02 (d, *J*=8.0 Hz, 1H, H-11), 6.05 (s, 1H, H-8), 5.93 (d, *J*=8.0 Hz, 1H, H-10), 4.28 (m, 1H, H-3), 2.18 (m, 1H, H-4) 2.13 (d, *J*=1.0 Hz, 3H, 9-Me), 1.85 (ddd, *J*=12.8 Hz, 4.1Hz, 2.0Hz, 1H, H-4), 1.48-1.37 (m, 2H, H-2), 1.36 (s, 3H, 5-Me), 1.35 (s, 3H, 1-Me), 1.08 (s, 3H, 1-Me), 0.91 (s, 9H, Si-^{t}Bu), 0.10 (s, 6H, Si-Me_2); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 204.9 (C-7), 190.8 (C-11), 127.2 (C-9), 119.3 (C-10), 102.0 (C-6), 72.8 (C-8), 64.6 (C-5), 49.7 (C-3), 49.3 (C-4), 36.0 (C-2), 31.9 (C-1), 31.2 (5-Me), 29.1 (Si-^{t}Bu), 25.9 (Si-^{t}Bu), 18.2 (1-Me), 14,2 (1-Me), -4.64 (Si-Me_2); IR (neat, cm^{-1}) ν : 3428.9 (w, br), 2956.8 (w), 2927.7 (w), 2855.8 (w), 1930.9 (w), 1739.9 (w), 1651.6 (m), 1601.8 (w), 1472.8 (w), 1454.8 (w), 1383.8(w), 1362.8 (w),1328.9(w), 1303.88(w), 1250.7 (w), 1195.7 (w), 1180.7 (w), 1160.7 (w), 1132.7 (w), 1075.4 (m), 1023.8 (w), 1006.8 (w), 995.8 (w), 957.7 (w), 937.8 (w), 908.8 (w), 876.6 (m), 848.4 (m), 834.3 (m), 773.4 (m), 733.4 (w), 708.8 (w), 668.7 (w); LRMS (ESI) *m/z* : 387.2 $(M+Na)^+$; ESI-HRMS *m/z* : 387.2308 (calcd for $C_{21}H_{36}NaO_3Si$, 387.2326); $[\alpha]_D^{25}$ -42.7 (*c* 0.70, MeOH).

(3*E*)-(5*R*)-[(2*R*,4*S*)- 4-(*tert*-Butyldimethylsilyl)oxy-2-hydroxy-2,6,6-trimethylcyclohexylidene]-1-iodo-4-methyl-1,3,5-hexatriene (5)

To a solution of $CrCl_2$ (185 mg, 1.5 mmol) in THF (1 mL) was added the THF solution (1 mL) of

aldehyde (**26**, 55 mg, 0.15 mmol) and THF solution (0.5 mL) of CHI_3 (0.3 mmol). After stirring for 5 h at 0 °C, the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aq. solution was extracted with EtOAc and the organic phase was washed with water and brine and dried (Na_2SO_4). Filtration, concentration and silica gel column purification (hexane/EtOAc, 20/1) afforded a *E*:*Z* mixture of **5 (**31.5 mg, 0.062 mmol, *E*:*Z*=1:2, 41%). Data for *E*-isomer of **5**. ^{1}H-NMR (400MHz, $CDCl_3$) δ : 7.30 (dd, *J*=14.1, 11.4 Hz, 1H, H-11), 6.27 (d, *J*=12.8 Hz, 1H, H-12), 5.90 (s, 1H, H-8), 5.90 (d, *J*=11.0, 1H, H-10), 4.27 (m, 1H, H-3), 2.14 (m, 1H, H-4), 2.04 (s, 3H, 9-Me), 1.82 (m, 1H, H-4), 1.70 (d, *J*=0.7Hz, 3H, 5-Me), 1.49-1.35 (m, 2H, H-2), 1.31 (d, *J*=1.9 Hz, 3H, 1-Me), 1.03 (s, 3H, 1-Me), 0.90 (s, 9H, Si-^{t}Bu), 0.10 (Si-Me_2); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 202.8 (C-8), 142.1 (C-11), 133.2 (C-9), 126.9 (C-10), 118.4 (C-6), 102.2 (C-8), 78.6 (C-11), 73.0 (C-5), 50.0 (C-3), 49.4 (C-4), 35.8 (C-2), 32.2 (5-Me), 31.5 (1-Me), 29.4 (Si-^{t}Bu), 26.1 (Si-^{t}Bu), 18.4 (1-Me), 14.1 (9-Me), -4.46 (Si-Me_2); IR (neat, cm^{-1}) ν : 3460.0 (w, br), 2956.8 (w), 2927.8 (w), 2855.8 (w), 1931.9 (w), 1727.9 (w), 1603.9 (w), 1557.0 (w), 1471.8 (w), 1453.8 (w), 1373.8 (w), 1361.8 (w), 1289.8 (w), 1250.7 (w), 1179.8 (w), 1158.7 (w), 1074.5 (m), 1023.8 (w), 1005.7 (w), 995.8 (w), 956.8 (w), 938.8 (w), 908.8 (w), 876.7 (w), 848.5 (m), 834.4 (m), 815.6 (w), 773.4 (m), 733.8 (w), 693.7 (w), 672.7 (w); LRMS(ESI) *m/z* : 511.2 $(M+Na)^+$; ESI-HRMS *m/z* : 511.1501 (calcd for $C_{22}H_{37}INaO_2Si$, 511.1500).

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12. Wittig-Horner type olefination of methyl propargyl ketone (**14**) gave *Z*-rich compounds in 80% yields.
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16. Under the alkaline conditions (K_2CO_3 in MeOH, 0 °C), 1:1 mixture of (4*R*,6*R*)-**8** and (4*R*,6*S*)-**8** were epimerized into 1:5 mixture of (4*R*,6*R*)-**9** and (4*R*,6*S*)-**9** in 78% yield. Stable (4*R*,6*S*)-**9** was used for coupling reaction.
17. Unfortunately, the epoxidation of di-Ac compound with *m*CPBA in CH_2Cl_2 at 0 °C gave α-epoxide in 26% yield and β-epoxide in 25% yield, and 12% yield of di-epoxide was also obtained.
18. We succeed to obtain the allene structure from DIBAL-H reduction of the propargylic epoxide (di-TBDPS ether of **24)** within 37% yield.
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