SYNTHETIC STUDY OF AN INTERMEDIATE TOWARDS PARACENTRONE*

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Abstract – Paracentrone (1), the second naturally occurring C31-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 (3E)-(5R)-[(2R,4S)-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 (2E)-(4R)-[(2R,4S)-2-hydroxy-4-(tert-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-3-methylpent-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 C31-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. 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. Communications describing the total synthesis of optically active 1 was published by both the Katsumura and the Nishioka groups independently. Scheme 1 summarizes our synthetic strategy. Migita-Kosugi-Stille cross-coupling of iodide (5) and stannane (6) would 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 \((4R,6R)-9\) and \((4R,6S)-9\) 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

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp., °C</th>
<th>yield, %</th>
<th>(E:Z) ratio of (10a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(iPr_2O-H_2O) (2:1)</td>
<td>60</td>
<td>63</td>
<td>1.0:3.4</td>
</tr>
<tr>
<td>2</td>
<td>(H_2O)</td>
<td>60</td>
<td>65</td>
<td>1.0:4.2</td>
</tr>
<tr>
<td>3</td>
<td>(H_2O)</td>
<td>50</td>
<td>68</td>
<td>1.0:5.6</td>
</tr>
<tr>
<td>4</td>
<td>(H_2O)</td>
<td>70</td>
<td>13</td>
<td>0:1.0</td>
</tr>
<tr>
<td>5</td>
<td>THF-H_2O (1:4)</td>
<td>55</td>
<td>70</td>
<td>1.0:4.3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>entry</th>
<th>phosphorus ylide</th>
<th>R</th>
<th>solvent</th>
<th>temp, °C</th>
<th>yield, %</th>
<th>(E:Z)</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Ph_3PCHCO_2R)</td>
<td>Et</td>
<td>THF</td>
<td>66</td>
<td>55</td>
<td>1.0:1.6</td>
<td>15a</td>
</tr>
<tr>
<td>2</td>
<td>”</td>
<td>”</td>
<td>toluene</td>
<td>110</td>
<td>68</td>
<td>2.3:1.0</td>
<td>15a</td>
</tr>
<tr>
<td>3</td>
<td>”</td>
<td>”</td>
<td>xylene</td>
<td>144</td>
<td>73</td>
<td>3.0:1.0</td>
<td>15a</td>
</tr>
<tr>
<td>4</td>
<td>”</td>
<td>Me</td>
<td>”</td>
<td>144</td>
<td>73</td>
<td>1.0:1.0</td>
<td>15b</td>
</tr>
<tr>
<td>5</td>
<td>”</td>
<td>propyl</td>
<td>”</td>
<td>144</td>
<td>80</td>
<td>2.0:1.0</td>
<td>15c</td>
</tr>
<tr>
<td>6</td>
<td>”</td>
<td>ipropyl</td>
<td>”</td>
<td>144</td>
<td>65</td>
<td>2.0:1.0</td>
<td>15d</td>
</tr>
<tr>
<td>7</td>
<td>”</td>
<td>tbutyl</td>
<td>”</td>
<td>144</td>
<td>55</td>
<td>1.0:1.0</td>
<td>15e</td>
</tr>
</tbody>
</table>

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, Et₂O, -78 °C (91%); (b) TBAF, THF, rt (90%): (c) PPTS, DHP, CH₂Cl₂, rt (83%).

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

The coupling of (4R,6R)- and (4R,6S)-ketone (9) with nucleophiles was studied next. The treatment of ketone (4R,6R)-9 with the lithium salt of the TBDPS-propargyl alcohol (17) (nBuLi treatment in Et₂O at -78 °C) provided the alcohol (18) in 92% yield as a single diastereomer. On the other hand, the reaction of ketone (4R,6S)-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 (4R,6S)-9\textsuperscript{16} with the lithium salt of 10b (nBuLi treatment in Et\textsubscript{2}O 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 chloride in 2,4,6-collidine under reflux conditions gave the dienyne compound (23) in 51% yield.\textsuperscript{17} The epoxidation of dienyne compound (23) with m-chloroperoxybenzoic acid (mCPBA) 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.\textsuperscript{17} Because the necessary stereoselectivity could not obtained by epoxidation, we were forced to abandon this route towards paracentrone synthesis.\textsuperscript{18}

\[\text{Reagents and conditions:} \quad \text{a) 10b, nBuLi, Et}_2\text{O, -78 °C to 0 °C (95%); b) 80% aq. AcOH, THF/H}_2\text{O, rt (82%); c) p-NO}_2\text{C}_6\text{H}_4\text{COCl, Et}_3\text{N, DMAP, CH}_2\text{Cl}_2, \text{rt (83%); d) POCl}_3, 2,4,6\text{-collidine, reflux (51%); e) mCPBA, CH}_2\text{Cl}_2, 0 °C (63%).}\]

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

To achieve the regio- and stereoselective epoxidation, a Katsuki-Sharpless asymmetric epoxidation\textsuperscript{19} was employed. An alternative approach starting from epoxy acetylene (11)\textsuperscript{20} reported by the Katsumura group\textsuperscript{21} was successfully employed. The cross-coupling reaction of 11 with vinyl iodide (12)\textsuperscript{22} was accomplished under standard Sonogashira conditions,\textsuperscript{23} tetrakis(triphenylphosphine)palladium and copper(I) iodide in diisopropylamine (Pd(PPh\textsubscript{3})\textsubscript{4}, CuI, DIPA), to afford the TBS ether of propargylic oxirane (25) in 92% yield. The S\textsubscript{N}2’ reduction of the 25 through a stereospecific hydride reduction with DIBAL-H, produced the allene moiety in 88% yield. Oxidation of 7 with MnO\textsubscript{2} in Et\textsubscript{2}O furnished aldehyde (26)\textsuperscript{24} in 92% yield. The carbon chain extension from aldehyde (26) by the Takai-Utimoto reaction\textsuperscript{25} produced vinyl iodide (5) in 41% yield as a stereoisomeric mixture (E:Z = 1:2)\textsuperscript{26} (Scheme 6).
Reagents and conditions: (a) Pd(PPh₃)₄, CuI, DIPA, rt (92%); (b) DIBAL-H, Et₂O, 0 °C (88%); (c) MnO₂, Et₂O, rt (92%); (d) CHI₃, CrCl₂, 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 (3E)-(5R)-[(2R,4S)-2-hydroxy-4-(tert-butyldimethylsilyl)oxy-2,6,6-trimethylcyclohexylidene]-1-iodo-4-methyl-1,3,5-hexatriene (5) was successfully accomplished starting from (2E)-(4R)-[(2R,4S)-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 CH₂Cl₂ (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 60F₂₅₄, 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. ¹H- and ¹³C-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% HCO₂H as effluents. HR-ESI-MS spectra were acquired on a Bruker Dartonics micrOTOF focus spectrometer. Specific rotation values were measured with a Horiba polarimeter.

(2E)-[(1S,4R,6S)-4-(tert-Butyldiphenylsilyl)oxy-1-hydroxy-2,2,6-trimethylcyclohexyl]-3-methyl-1-(tetrahydro-2H-pyran-2-yl)oxypent-2-en-4-yne
To a solution of (E)-2-((3-methylpent-2-en-4-yn-1-yl)oxy)tetrahydro-2H-pyran (10b, 189 mg, 1.05 mmol) in Et₂O (2.5 mL) was added nBuLi (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. NH₄Cl and extracted the mixed solution with EtOAc. The organic layer was washed with H₂O and brine, and dried over Na₂SO₄. 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. ¹H-NMR (400MHz, CDCl₃) δ: 7.68 (m, 4H, Ph), 7.39 (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-tBu), 1.01 (d-like, 3H,1-Me), 0.99 (t-like, 3H, 5-Me), 0.69 (s, 3H, 1-Me); ¹³C-NMR (100MHz, CDCl₃) 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), 29.9 (THP), 27.1 (Si-tBu), 25.6 (5-Me), 23.5 (1-Me), 20.7 0(1-Me), 19.3 (Si-tBu), 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 C36H50NaO4Si, 597.3371).

(2E)-[(1S,4R,6S)-4-(t-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/H₂O (4:2:1). The mixture was stirred for 24 h at 48 °C. The reaction was quenched with sat. aq. NaHCO₃, and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, H₂O, and brine, and then dried over Na₂SO₄. 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. ¹H-NMR (400MHz, CDCl₃) 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); ¹³C-NMR (100MHz, CDCl₃) δ: 135.8 (Si-Ph), 134.6 (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), 29.9 (THP), 27.1 (Si-tBu), 25.6 (5-Me), 23.5 (1-Me), 20.7 0(1-Me), 19.3 (Si-tBu), 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 C₃₆H₅₀NaO₄Si, 597.3371).
(2E)-[(1S,4R,6S)-4-(tert-Butyldiphenylsilyl)oxy-1-hydroxy-2,6,6-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$_2$Cl$_2$ (2.0 mL) were added Et$_3$N (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$_2$O, and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, H$_2$O, and brine, and then dried over Na$_2$SO$_4$. 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. 1H-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-2Bu), 1.01 (s, 3H, 1-Me), 0.71 (s, 3H, 5-Me); 13C-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-2Bu), 27.0 (Si-2Bu), 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$_4$Si, 662.2980).

(2E)-[(4S)-4-((tert-Butyldiphenylsilyl)oxy)-2,6,6-trimethylcyclohex-1-en-1-yl]-1-hydroxy-3-methylpent-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$_2$O, and the mixture was extracted with Et$_2$O. The organic layer was washed with 1 N HCl, H$_2$O,
and brine, and then dried over Na₂SO₄. 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. ¹H-NMR (400MHz, CDCl₃) δ : 8.27 (d, J=8.8 Hz, 2H, NO₂-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); ¹³C-NMR(100MHz, CDCl₃) δ : 164.7 (11-O-C=O), 150.6 (NO₂-Ph), 139.7 (NO₂-Ph), 135.9 (Si-Ph), 135.9 (Si-Ph), 134.5 (Si-Ph), 134.4 (Si-Ph), 130.9 (C-5), 129.8 (NO₂-Ph), 127.7 (Si-Ph), 127.4 (C-10), 125.7 (C-6), 123.6 (NO₂-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-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 (m), 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), 1210.9 (w), 1176.9 (m), 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), 703.0 (s); LRMS (ESI) m/z : 644.3 (M+Na)+; ESI-HRMS m/z : 660.2529 (calcd for C₃₈H₄₃KNO₅Si, 660.2542); [α]D²⁵ -31.6 (c 1.26, CHCl₃).

(2E)-(1R,4S,6R)-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 CH₂Cl₂ (1 mL) was added mCPBA (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. NaHCO₃, and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, H₂O, and brine, and then dried over Na₂SO₄. 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. ¹H-NMR (400MHz, CDCl₃) δ : 8.28 (m, 2H, NO₂-Ph), 8.20 (m, 2H, NO₂-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 (dd, 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); ¹³C-NMR (100MHz, CDCl₃) δ : 164.6 (11-O-C=O), 150.7 (NO₂-Ph), 135.9 (Si-Ph), 135.9 (NO₂-Ph), 130.9 (NO₂-Ph), 129.8 (C-10), 129.8 (Si-Ph), 127.7 (Si-Ph), 124.1 (C-9), 123.7 (NO₂-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), 2958.9 (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),
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$_4$Cl, and the mixture were extracted with EtOAc. The organic layer was washed with 1 N HCl, H$_2$O, and brine, and then dried over Na$_2$SO$_4$. 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. ¹H-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 (dd, $J$=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), 1.23 (overlapped, 1H, H-2), 1.23 (s, 3H, 1-Me), 1.09 (s, 3H, 1-Me), 0.86 (s, 9H, Si-tBu), 0.03(d, $J$=2.0Hz, 6H, Si-Me$_2$); ¹³C-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-tBu), 26.0 (Si-tBu), 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$_3$Si, 387.2326); [$\alpha$]$_D^{26}$ -10.6 (c 0.94, MeOH).

To a solution of propargylic oxirane (25, 80 mg, 0.22 mmol) in Et$_2$O (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$_3$O. The organic layer was washed with 30% Potassium sodium tartrate solution and then dried over Na$_2$SO$_4$. 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$_3$) $\delta$ : 5.93 (s, 1H, H-8), 5.58 (t, $J$=7.0 Hz, H-4), 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), 1.66 (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'-Bu), 0.09 (s, 6H, Si-Me$_2$); $^{13}$C-NMR (100MHz, CDCl$_3$) $\delta$ : 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'-Bu), 26.1 (Si'-Bu), 18.4 (1-Me), 13.7 (1-Me), -4.46 (Si-Me$_2$); IR (neat, cm$^{-1}$) $\nu$ : 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 (m), 993.7 (m), 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$_3$Si, 389.2482); [$\alpha$]$_D$$^{24}$ -40.0 (c 1.00, MeOH).

(2E)-(4R)-(2R,4S)-4-(tert-Butyldimethylsilyl)oxy-2-hydroxy-2,6,6-trimethylcyclohexylidene)-3-methylpent-2,4-dien-1-ol (26)

To a solution of allylic alcohol (7, 100 mg, 0.27 mmol) in CH$_2$Cl$_2$ (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 an aldehyde (26) (92 mg, 0.25 mmol, 92%) as an amorphous solid. $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ : 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), 1.35 (s, 3H, 1-Me), 1.08 (s, 3H, 1-Me), 0.91 (s, 9H, Si'-Bu), 0.10 (s, 6H, Si-Me$_2$); $^{13}$C-NMR (100MHz, CDCl$_3$) $\delta$ : 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'-Bu), 25.9 (Si'-Bu), 18.2 (1-Me), 14.2 (1-Me), -4.64 (Si-Me$_2$); IR (neat, cm$^{-1}$) $\nu$ : 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), 1306.8(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$_{38}$NaO$_3$Si, 387.2326); [$\alpha$]$_D$$^{25}$ -40.0 (c 0.70, MeOH).

(3E)-(5R)-(2R,4S)-4-(tert-Butyldimethylsilyl)oxy-2-hydroxy-2,6,6-trimethylcyclohexylidene)-1-ido-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$_2$SO$_4$). Filtration, concentration and silica gel column purification (hexane/EtOAc, 20/1) afforded an $E$/$Z$ 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$_3$) $\delta$ : 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-tBu), 0.10 (Si-Me$_2$); $^{13}$C-NMR (100MHz, CDCl$_3$) $\delta$ : 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-tBu), 26.1 (Si-tBu), 18.4 (1-Me), 14.1 (9-Me), -4.46 (Si-Me$_2$); IR (neat, cm$^{-1}$) $\nu$: 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$_2$Si, 511.1500).

REFERENCES AND NOTES


12. Wittig-Horner type olefination of methyl propargyl ketone (14) gave Z-rich compounds in 80% yields.

13. The 1:1 mixture of TBDPS-ether of (4R,6R)-9 and (4R,6S)-9 were synthesized from (-)-phorenol in 93% yield.


16. Under the alkaline conditions (K₂CO₃ in MeOH, 0 °C), 1:1 mixture of (4R,6R)-8 and (4R,6S)-8 were epimerized into 1:5 mixture of (4R,6R)-9 and (4R,6S)-9 in 78% yield. Stable (4R,6S)-9 was used for coupling reaction.

17. Unfortunately, the epoxidation of di-Ac compound with mCPBA in CH₂Cl₂ 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.


20. Epoxy acetylene (11) was synthesized from 9 in 6 steps and 37% yield.


