# **Supporting Information**

## Synthetic Progress towards Azadirachtins, Part 1:Enantio- and Diastereo-selective Synthesis of the Left-Wing Fragment of 11-epi-Azadirachtin I

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#### **General Information**

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, toluene was distilled from sodium, dichloroethane and dichloromethane were distilled from calcium hydride. Yields refer to chromatographically.

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. NMR spectra were recorded on Brüker Advance 500 (<sup>1</sup>H: 500 MHz, <sup>13</sup>C 125 MHz) and Brüker Advance 400 (<sup>1</sup>H: 400 MHz, <sup>13</sup>C 100 MHz). Mass spectrometric data were obtained using Brüker Apex IV RTMS. Infrared spectra were recorded on a Shimadzu IRPrestige21. Optical rotations were measured with a Jasco P-1020 polarimeter. Chiral HPLC analysis was performed on Shimadzu Prominence Modular HPLC using Daicel ChiralpakTM columns.

The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

#### Synthesis of (3S,5R)-2-methyl-5-(prop-1-en-2-yl)-3-vinylcyclohexanone (S1):



To a solution of CuBr•Me<sub>2</sub>S (5.5 g, 27 mmol) in dry THF(200 mL) was added the solution of vinyl Grignard reagent (1.0 M in THF, 135 mL, 135 mmol) at -78 °C, and the reaction mixture was then stirred at the same temperature for 10 minutes. To this solution was added a solution of (-)-carvone (13.5 g, 90 mmol) in dry THF (50 mL) at -78 °C, and the mixture continuesely stirred for 1 more hour, and then quenched with a saturated solution of NH<sub>4</sub>Cl (100 mL). The miaxure was extracted with ethyl acetate (2×100 mL), and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off, and then evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes) = 1/20; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.60 (dt, *J* = 16.8, 9.9 Hz, 1H), 5.14 – 5.04 (m, 2H), 4.75 (d, *J* = 19.5 Hz, 2H), 2.89 – 2.77 (m, 1H), 2.66 – 2.58 (m, 2H), 2.46 (dd, *J* = 13.1, 3.4 Hz, 1H), 2.32 (t, *J* = 13.0 Hz, 1H), 2.03 – 1.88 (m, 2H), 1.73 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.3, 147.6, 136.9, 117.6, 110.0, 47.5, 47.0, 46.7, 41.6, 37.2, 20.6, 12.5; IR (neat, cm<sup>-1</sup>): 3078, 2973, 2933, 2874, 1713, 1674, 1643, 1450, 1429, 1209, 1153, 1093; HRMS-APCI calcd. for C<sub>12</sub>H<sub>19</sub>O [M + H<sup>+</sup>]: 179.1430; Found: 179.1432.

#### Synthesis of (2R,3S,5R)-2-(hydroxymethyl)-2-methyl-5-(prop-1-en-2-yl)-3-vinylcyclohexanone (9):



To a solution of **S1** (15.05 g, 84.4 mmol) in KOH solution (10% in MeOH, 85 mL) was added a solution of formalin (37 %, 19 mL, 253 mmol) in a dropwise manner at 0 °C, and the mixture was then stirred at the same temperature for 15 minutes. The reaction was quenched by addition of a solution of NH<sub>4</sub>Cl (6.7 g) in water (100 mL). After removal of the Methanol under vacuum, the mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×100 mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off, and the solvent was removed under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give compound **9** (9.87 g) as a yellow oil in 56% yield; R<sub>f</sub> = 0.36 (EtOAc/hexanes = 1/6); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.82 – 5.53 (m, 1H), 5.09 (d, *J* = 3.7 Hz, 1H), 5.06 (s, 1H), 4.85 (s, 1H), 4.68 (s, 1H), 3.63 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.47 (dd, *J* = 11.3, 7.2 Hz, 1H), 2.75 – 2.60 (m, 3H), 2.60 – 2.50 (m, 2H), 2.09 – 1.93 (m, 1H), 1.91 – 1.81 (m, 1H), 1.71 (s, 3H),

0.99 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  217.1, 146.4, 136.9, 117.3, 112.3, 77.4, 77.1, 76.9, 66.2, 52.7, 42.2, 41.4, 40.5, 29.5, 21.9, 15.8; IR (neat, cm<sup>-1</sup>): 3440, 2975, 2940, 2875, 2364, 2331, 1714, 1705, 1699, 1456, 1377, 1045, 999, 895; HRMS-ESI calcd. for C<sub>13</sub>H<sub>20</sub>NaO<sub>2</sub> [M + Na<sup>+</sup>]: 231.1356; Found: 231.1354.

#### Synthesis of ((1R,4R,6S)-1-methyl-4-(prop-1-en-2-yl)-6-vinylcyclohex-2-en-1-yl)methanol (10):



To a solution of compound **9** (4 g, 19 mmol) in MeOH (100 mL) was added TsNHNH<sub>2</sub> (3.35g, 18 mmol) at room temperature, and the reaction mixture was stirred heated at 50 °C for 12 h. The methanol was removed under vacuum to give the crude hydrzone;  $R_f = 0.52$  (EtOAc/hexanes= 1/2).

To a solution of the crude product made above in dry THF (190 mL) was added a solution of MeLi (1.6 M in Et<sub>2</sub>O, 47.5 mL, 76 mmol) at -78 °C. The mixture was warmed to room temperature and then stirred for 2 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (50 mL), and the mixture was extracted with ethyl acetate (2×50 mL), and the extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give compound **10** (2.96 g) as a yellow oil in 81% overall yield for 2 steps; R<sub>f</sub> = 0.54 (EtOAc/hexanes= 1/6); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.84 – 5.74 (m, 1H), 5.70 (dd, *J* = 10.0, 4.3 Hz, 1H), 5.52 (d, *J* = 10.1 Hz, 1H), 5.03 (dd, *J* = 13.3, 12.1 Hz, 2H), 4.83 (s, 1H), 4.70 (s, 1H), 3.38 (d, *J* = 3.2 Hz, 2H), 2.72 (s, 1H), 2.46 – 2.37 (m, 1H), 1.76 (s, 3H), 1.75 – 1.72 (m, 1H), 1.61 (d, *J* = 13.4 Hz, 1H), 0.83 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  147.6, 134.0, 134.4, 130.4, 115.5, 111.8, 69.9, 41.1, 40.4, 39.0, 28.6, 22.1, 18.9; IR (neat, cm<sup>-1</sup>): 3416, 3075, 2963, 2933, 2872, 2350, 1643, 1453, 1373, 1039, 911, 895; HRMS-APCI calcd. for C<sub>13</sub>H<sub>21</sub>O[M + H<sup>+</sup>]: 193.1587; Found: 193.1585.



To a solution of CuBr•Me<sub>2</sub>S (615 mg, 3 mmol) in dry THF(50 mL) was added a solution of vinyl Grignard reagent (1.0 M in THF, 30 mL, 30 mmol) at -78 °C, and the reaction mixture was then stirred at the same temperature for 10 minutes. To this reaction mixture was slowly added a solution of (-)-carvone (1.5 g, 10 mmol) in dry THF (20 mL) at -78 °C, and the reaction mixture then stirred at the same temperature for 0.5 h. To the above mixture was added a solution of **11** (2.09 g, 14 mmol) in THF (20 mL), and the resultant mixture was then stirred at -20 °C for 2 h. The reaction was quenched by addition of a

saturated solution of NH<sub>4</sub>Cl (50 mL), and the mixture was extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off, and the filtrate was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give diastereomers **9** (1.66 g,  $\alpha$ -Me: $\beta$ -Me = 3:10). The diastereoselectivity was confirmed by <sup>1</sup>H-NMR spectrum of mixture.

To a solution of diastereomers **9** (1.66 g,  $\alpha$ -Me: $\beta$ -Me = 3:10) in MeOH (80 mL) was added TsNHNH<sub>2</sub> (1.41 g, 7.6 mmol) at room temperature, and the resultant mixture was stirred at 50 °C for 12 h. The methanol was evaporated under vacuum to get the crude hydrazone product.

To a solution of crude hydrazon made above in dry THF (80 mL) was added a solution of MeLi (1.6 M in Et<sub>2</sub>O, 17.5 mL, 28 mmol) at -78 °C, and the reaction mixture was warmed to room temperature, followed by stirring for additional 2 h. The reaction was quenched with a saturated solution of NH<sub>4</sub>Cl (20 mL), and the mixture was extracted with ethyl acetate (2×20 mL). The combined organic extracts were first dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off, and then concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give compound **10** (1.06 g) as a yellow oil in 55% overall yield for 3 steps.

Synthesis of triisopropyl(3-((1*S*,3*aR*,6*R*,7*aR*)-3a-methyl-6-(prop-1-en-2-yl)-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl)prop-1-yn-1-yl)silane (14):



To a solution of Pd<sub>2</sub>(dba)<sub>3</sub> (915.7 mg, 1 mmol), DPE-Phos (1.077 g, 2 mmol) and NaO'Bu (1.44g, 15 mmol) in dry toluene (80 mL) was added a solution of compound **10**(1.92 g, 10 mmol) and alkynyl bromide (3 g, 11.5 mmol) in toluene (20 mL) at room temperature, and the mixture was then stirred at 45 °C for 3 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (40 mL), and the mixture was extracted with ethyl acetate (2×20 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off, and the filtrate was evaporated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/50) to give compound **14** (3.15 g) as a colorless oil in 85% yield;  $R_f = 0.36$  (EtOAc/hexanes = 1/20); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.99 (d, *J* = 9.8 Hz, 1H), 5.46 (dd, *J* = 9.8, 3.2 Hz, 1H), 4.76 (s, 1H), 4.71 (s, 1H), 3.75 – 3.68 (m, 1H), 3.63 (d, *J* = 6.9 Hz, 1H), 3.52 (d, *J* = 6.9 Hz, 1H), 2.94 – 2.89 (m, 1H), 2.64 – 2.52 (m, 2H), 2.03 – 1.94 (m, 1H), 1.87 – 1.80 (m, 2H), 1.78 (s, 3H), 1.11 – 0.99 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  148.4, 132.8, 130.0, 111.2, 104.7, 82.4, 77.5, 76.5, 47.3, 43.0, 42.2, 25.5, 23.9, 21.7, 20.6, 18.7, 11.4; IR (neat, cm<sup>-1</sup>): 2957,

2941, 2864, 2171, 1645, 1462, 1371, 1018, 993, 883, 677; HRMS-ESI calcd. for  $C_{24}H_{41}OSi [M + H^+]$ : 373.2921; Found: 373.2921.

#### **Synthesis**

(3S,3aR,7aR)-7a-methyl-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,3a,4,7a-tetrahydro-iso-benzofuran -5(3H)-one (16):



To a solution of compound 14 (2.23 g, 6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub>/MeOH (60 mL/1.94 mL) was continuously bubbled with ozone at -98 °C till the starting materials was fully consumed by monitoring with TLC, and the reaction mixture was then warmed up to room temperature, and stirred for additional 0.5 h. Then reaction mixture was then cooled to 0 °C. To this solution was added Et<sub>3</sub>N (10 mL, 72 mmol), DMAP (73 mg, 0.6 mmol) and Ac<sub>2</sub>O (6.8 mL, 72 mmol), and the reaction mixture was stirred at 40 °C for 3 h. The reaction was quenched by addition of Me<sub>2</sub>S (6 mL) and water (6 mL), and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×20 mL). The extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extract was filtered off, and the filtrate was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give a couple of diastereomers 15 (d.r. = 2.5:1); R<sub>f</sub> = 0.36 and 0.35 (EtOAc/hexanes = 1/6). The diastereometric ratio (between 20:1 and 1:1) was deduced by <sup>1</sup>H-NMR spectrum and it was variable from batch to batch.

To a solution of diastereomers 15 in MeOH (30 mL) was added K<sub>2</sub>CO<sub>3</sub> (3.26 g, 18.3 mmol) at 0 °C, and the mixture was stirred the same temperature for 1.5 h. The reaction was quenched by addition of a solution of NH<sub>4</sub>Cl (3.26 g) in water (20 mL), and the methanol in the mixture was removed under vacuum. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×10 mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extract was filtered off, and the filtrate was evaporated under vacuum to give crude products.

To a solution of above crude product in CH<sub>2</sub>Cl<sub>2</sub> (35 mL) was added DMP (2.97 g, 7 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL), and the resultant mixture was extracted with ethyl acetate (2×10 mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered off, and the filtrate was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/5) to give compound 16 (1.0 g) as a colorless oil in 48% overall yield for 3 steps;  $R_f = 0.40$  (EtOAc/hexanes = 1/4); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.07 (d, J = 9.8 Hz, 1H), 5.92 (d,

of

J = 9.8 Hz, 1H), 3.95 - 3.82 (m, 1H), 3.73 (d, J = 7.2 Hz, 1H), 3.66 (d, J = 7.2 Hz, 1H), 2.71 (dd, J = 17.0, 3.8 Hz, 1H), 2.61 (d, J = 5.0 Hz, 2H), 2.56 - 2.48 (m, 1H), 2.46 - 2.34 (m, 1H), 1.18 (s, 3H), 1.07 - 0.95 (m, 23H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  198.4, 152.5, 129.9, 103.5, 83.6, 75.4, 49.0, 43.7, 36.2, 25.1, 19.3, 18.6, 11.3; IR (neat, cm<sup>-1</sup>): 2941, 2864, 2172, 1862, 1674, 1464, 1456, 1381, 1373, 1244, 1016, 881; HRMS-ESI calcd. for C<sub>21</sub>H<sub>34</sub>NaO<sub>2</sub>Si [M + Na<sup>+</sup>]: 369.2220; Found: 369.2229. [ $\alpha$ ]<sup>26</sup><sub>589</sub>-41.2 (c = 0.48, CHCl<sub>3</sub>).

#### Synthesis of (3S,3aR,4R,7aR)-ethyl

7a-methyl-5-oxo-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carb oxylate (18):



To a solution of compound **16** (0.35 g, 1 mmol) in dry THF (10 mL) was added a solution of NaHMDS (2.0 M in THF, 1.1 mL, 2.2 mmol) at -78 °C, and the mixture was then stirred at the same temperature for 1 h. To this solution was added ethyl cyanoformate (0.13 mL, 1.3 mmol), and the reaction mixture was stirred at the same temperature for 20 minutes. The reaction was quenched by addition of water (10 ml), and the resultant mixture was extracted with ethyl acetate ( $2 \times 10$  mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes= 1/6) to give product **18** and unreacted **16**.

To a solution of above mixture of **16** and **18** made above in dry THF (10 mL) was added a solution of NaHMDS (2.0 M in THF, 0.5 mL, 1 mmol) at -78 °C, and the mixture was then stirred at the same temperature for 1 h. To this solution was added ethyl cynoformate (0.65 mL, 0.65 mmol), and the resultant mixture was stirred at the same temperature for 20 minutes. The reaction was quenched by addition of water (10 ml), and the mixture was extracted with ethyl acetate (2×10 mL), and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes= 1/6) to give compound **18** (0.33 g) as colorless oil in 79% yield; R<sub>f</sub> = 0.40 (EtOAc/hexanes= 1/4); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.17 (d, *J* = 9.8 Hz, 1H), 6.01 (d, *J* = 9.8 Hz, 1H), 4.32 – 4.14 (m, 2H), 4.04 – 3.94 (m, 1H), 3.78 (q, 2H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.20 – 3.01 (m, 1H), 2.78 (dd, *J* = 17.5, 3.7 Hz, 1H), 2.24 (dd, *J* = 17.6, 3.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 3H), 1.09 – 1.02 (m, 23H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  193.7, 168.9, 153.0, 129.0, 104.0, 83.2, 76.5, 75.3, 61.6, 54.3, 48.8, 44.0, 25.0, 20.5, 18.7, 14.1,

11.4; IR (neat, cm<sup>-1</sup>): 2941, 2865, 2174, 1740, 1682, 1464, 1385, 1259, 1020, 914, 883, 748; HRMS-ESI calcd. for  $C_{24}H_{38}NaO_4Si [M + Na^+]$ : 441.2432; Found: 441.2429.

#### Synthesis of (3S,3aR,4R,7R,7aR)-ethyl

7-(dimethyl(phenyl)silyl)-4-ethynyl-7a-methyl-5-oxo-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydr oisobenzofuran-4-carboxylate (20):



To a suspension of lithium (0.87 g, 125.8 mmol) in dry THF (74 mL) was added PhMe<sub>2</sub>SiCl (6.1 mL, 37 mmol) under argon atmosphere at 0 °C, and the mixture was then stirred at the same temperature for 12 h.

To a solution of ZnEt<sub>2</sub> (1.5 M in Toluene, 16.7 mL, 25 mmol) in dry THF (39 mL) was added the reagent PhMe<sub>2</sub>SiLi made above (54 mL) at 0 °C, and the mixture was first stirred at the same temperature for 10 minutes. To this solution was added a solution of compound **18** (4.78 g, 11.4 mmol) in THF (20 mL) at -78 °C in a dropwise manner, and the mixture was then stirred at the same temperature for 45 minutes. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (40 mL), and mixture was extracted with ethyl acetate (2×40 mL), and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes= 1/8) to give product **S2**;  $R_f = 0.53$  (EtOAc/hexanes= 1/6).

To a solution of product **S2** made above in dry THF (110 mL) was added a solution of iodonium **19** (4.32 g, 12.54 mmol), followed by addition of TBAF solution (1.0 M in THF, 28.5 mL, 28.5 mmol) at -78 °C. The mixture was then warmed up to 0 °C and stirred for additional 3.5 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (20 mL), and the mixture was extracted with ethyl acetate (2×20 mL), and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (Et<sub>2</sub>O/toluene= 1/60) to give compound **20** (4.68 g) as yellow oil in 50% overall yield for 2 steps; R<sub>f</sub> = 0.32 (Et<sub>2</sub>O/toluene= 1/20); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.49 – 7.42 (m, 2H), 7.38 – 7.33 (m, 3H), 4.26 – 4.21 (m, 1H), 3.72 (d, *J* = 8.0 Hz, 1H), 3.33 (d, *J* = 7.9 Hz, 1H), 3.09 – 3.02 (m, 1H), 2.97 (dd, *J* = 17.3, 3.3 Hz, 1H), 2.69 (dd, *J* = 15.4, 3.2 Hz, 1H), 2.60 (dd, *J* = 17.4, 5.2 Hz, 1H), 2.53 (s, 1H), 2.49 (d, *J* = 10.0 Hz, 1H), 1.58 – 1.55 (m, 1H), 1.31 – 1.27 (m, 3H), 1.09 – 1.05 (m, 11H), 0.41 (s, 1H), 0.37 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  201.1, 167.5, 137.5, 133.7, 129.5, 128.2, 108.6, 105.6, 82.4, 77.8, 76.0, 74.9, 62.8, 56.4, 55.1, 44.2, 37.0, 31.5, 25.7, 22.5, 18.8, 18.7, 13.8, 11.5, -1.7, -1.7; IR (neat, cm<sup>-1</sup>): 3312,

1941, 2864, 2171, 1734, 1732, 1726, 1462, 1454, 1427, 1254, 1230; HRMS-ESI calcd. for  $C_{34}H_{50}NaO_4Si_2 [M + Na^+]$ : 601.3140; Found: 601.3140.  $[\alpha]^{26}_{589}$ -67.1 (c = 0.033, CHCl<sub>3</sub>).

#### Synthesis of

(3*S*,3a*R*,4*S*,7*R*,7a*R*)-7-(dimethyl(phenyl)silyl)-4-ethynyl-4-(hydroxymethyl)-7a-methyl-3-(3-(triisopr opylsilyl)prop-2-yn-1-yl)octahydroisobenzofuran-5-ol (21):



To a solution of compound **20** (1.75 g, 3.03 mmol) in dry THF (30 mL) was added LiAlH<sub>4</sub> (0.11 g, 3.03 mmol) at -98 °C, and the mixture was first stirred at the same temperature for 0.5 hour, and then warmed up to room temperature, and the mixture was then stirred for additional 1 h. The reaction was quenched with a saturated solution of Seignette salt (25 mL) slowly, and the resultant mixture was stirred until a clear solution was obtained. The mixture was extracted with ethyl acetate (3×25 mL), and the combined extracts were dried with Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 2/3) to give inseparable diastereomers **21** (1.26 g,  $\alpha$ -OH: $\beta$ -OH = 1:9) in 77% yield; R<sub>f</sub> = 0.30 (EtOAc/hexanes = 1/2). The diastereomeric ratio was deduced by <sup>1</sup>H-NMR spectrum.

β-OH **21** : <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.50 – 7.46 (m, 2H), 7.37 – 7.33 (m, 3H), 4.14 – 4.07 (m, 2H), 3.98 – 3.93 (m, 1H), 3.70 (d, J = 11.3 Hz, 1H), 3.63 (d, J = 7.6 Hz, 1H), 312 (d, J = 7.6 Hz, 1H), 2.99 (dd, J = 17.3, 3.6 Hz, 1H), 2.73 (dd, J = 17.3, 4.4 Hz, 1H), 2.37 (s, 1H), 2.18 (d, J = 10.7 Hz, 1H), 2.03 – 1.98 (m, 1H), 1.94 – 1.89 (m, 1H), 1.39 (dd, J = 5.8, 4.6 Hz, 1H), 1.23 (s, 3H), 1.09 (d, J = 2.9 Hz, 21H), 0.46 (s, 3H), 0.40 (d, J = 5.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 138.7, 133.6, 129.3, 128.1, 105.8, 86.4, 82.5, 79.5, 77.2, 73.8, 73.1, 61.5, 52.4, 44.0, 43.8, 29.3, 28.6, 26.1, 25.5, 18.8, 11.5.

Diastereomers **21** ( $\alpha$ -OH: $\beta$ -OH = 1:9): IR (neat, cm<sup>-1</sup>): 3416, 3308, 2943, 2890, 2864, 2170, 1738, 1464, 1427, 1283 1111, 1055; HRMS-ESI calcd. for C<sub>32</sub>H<sub>50</sub>O<sub>3</sub>NaSi<sub>2</sub> [M + Na<sup>+</sup>]: 561.3191; Found: 561.3191.

#### Synthesis of

(3*S*,3a*R*,4*S*,7*R*,7a*R*)-7-(dimethyl(phenyl)silyl)-4-ethynyl-4-(hydroxymethyl)-7a-methyl-3-(prop-2-yn -1-yl)octahydroisobenzofuran-5-ol (22):



To a solution of mixture **21** ( $\alpha$ -OH: $\beta$ -OH = 1:9, 1.25 g, 2.32 mmol) in THF (20 mL) was added a solution of TBAF (1.0 M in THF, 4.6 mL, 4.6 mmol) at room temperature, and the reaction mixture was stirred at 50 °C overnight. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (20 mL), and the mixture was then extracted with ethyl acetate (2×20 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes= 1/1) to give inseparable diasteroisomers **22** (0.85 g,  $\alpha$ -OH: $\beta$ -OH = 1:9) as yellow solids in 96% yield; R<sub>f</sub> = 0.31 (EtOAc/hexanes= 1/1). The diastereomeric ratio was determined by <sup>1</sup>H-NMR spectrum.

β-OH **22** : <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.50 – 7.46 (m, 2H), 7.37 – 7.33 (m, 3H), 4.14 (d, J = 11.5 Hz, 1H), 4.08 – 4.03 (m, 2H), 3.71 – 3.66 (m, 2H), 3.17 (d, J = 7.6 Hz, 1H), 2.88 (d, J = 17.1 Hz, 1H), 2.65 (dd, J = 17.1, 2.4 Hz, 1H), 2.39 (s, 1H), 2.07 – 2.00 (m, 2H), 1.95 – 1.90 (m, 1H), 1.39 – 1.36 (m, 1H), 1.24 (s, 3H), 0.47 (s, 3H), 0.40 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 138.6, 133.6, 129.3, 128.1, 86.1, 81.6, 79.7, 73.6, 73.1, 70.5, 61.3, 52.3, 44.2, 43.9, 29.9, 28.8, 25.2, 25.0, -0.9.

Diastereomers **22** ( $\alpha$ -OH: $\beta$ -OH = 1:9): IR (neat, cm<sup>-1</sup>): 3416, 3304, 3069, 3048, 2927, 2885, 1427, 1418, 1254, 1170, 1055, 1028; HRMS-ESI calcd. for C<sub>23</sub>H<sub>31</sub>O<sub>3</sub>Si [M + Na<sup>+</sup>]: 383.2037; Found: 383.2036.

#### Synthesis of

# (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*R*,10*R*,10a*R*)-10-(dimethyl(phenyl)silyl)-10a-methyl-4-methylene-5-(2-(trim ethylsilyl)ethoxy)dodecahydronaphtho[1,8-bc:4,4a-c']difuran-8-ol (23):



To a solution of diasteroisomers **22** ( $\alpha$ -OH: $\beta$ -OH = 1:9, 35 mg, 0.091 mmol) in dry DCM (1.8 mL) were sequentially added 2-(trimethylsilyl)ethanol (14  $\mu$ L, 0.1 mmol), (IPr)AuCl (2.8 mg, 0.0046 mmol) and AgSbF<sub>6</sub> (1.6 mg, 0.0046 mmol) at room temperature. The reaction mixture was then stirred at the same temperature for 1.2 h. The reaction mixture was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/8) to give compound **23** (20 mg) in 49% yield (base on  $\beta$ -OH **9**).

Compound **23**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 – 7.49 (m, 2H), 7.38 – 7.34 (m, 3H), 5.24 (s, 1H), 5.05 (s, 1H), 5.02 (s, 1H), 4.10 (d, *J* = 8.6 Hz, 1H), 3.93 – 3.84 (m, 2H), 3.77 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.63 (d, *J* = 8.6 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.39 (d, *J* = 8.1 Hz, 1H), 2.83 (dd, *J* = 12.5, 4.3 Hz, 1H), 2.46 (s, 1H), 2.07 – 2.02 (m, 1H), 2.01 – 1.94 (m, 1H), 1.89 (t, *J* = 11.5 Hz, 1H), 1.60 (d, *J* = 11.3 Hz, 1H), 1.38 (d, *J* = 6.1 Hz, 1H), 1.06 – 0.94 (m, 5H), 0.47 (s, 3H), 0.03 (s, 9H).<sup>: 13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  142.0, 139.1, 133.8, 129.3, 128.1, 114.7, 104.5, 80.47, 75.8, 72.7, 66.3, 65.4, 58.2, 54.1, 51.1, 44.0, 42.9, 32.2, 31.3, 22.3, 18.2, -0.4, -0.8, -1.4; IR (neat, cm<sup>-1</sup>): 3395, 2952, 2889, 1426, 1251, 1083, 1014, 859, 835, 814, 774, 701; HRMS-ESI calcd. for C<sub>28</sub>H<sub>44</sub>O<sub>4</sub>NaSi<sub>2</sub> [M + Na<sup>+</sup>]: 523.2670; Found: 523.2668. [ $\alpha$ ]<sup>26</sup><sub>589</sub> +43.1 (*c* = 0.13, CHCl<sub>3</sub>).

#### Synthesis of

(2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,10*R*,10a*R*)-10-(dimethyl(phenyl)silyl)-10a-methyl-4-methylene-5-(2-(trimethy lsilyl)ethoxy)decahydronaphtho[1,8-bc:4,4a-c']difuran-8(2a*H*)-one (S3):



To a solution of compound **23** (0.25 g, 0.5 mmol) in dry DCM (5 mL) was added NaHCO<sub>3</sub> (84 mg, 1 mmol) and DMP (0.32 g, 0.75 mmol) at room temperature, and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by addition of a saturated solution of NaHCO<sub>3</sub> (4 mL), and the mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×4 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/7) to give compound **S3**(0.21 g) as a colorless oil in 84% yield;  $R_f = 0.53$  (silica gel, EtOAc/hexanes = 1/4); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.46 – 7.41 (m, 2H), 7.35 – 7.30 (m, 3H), 4.89 (s, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 4.28 (d, *J* = 9.1 Hz, 1H), 4.07 – 3.98 (m, 1H), 3.79 (d, *J* = 8.0 Hz, 1H), 3.74 (d, *J* = 9.1 Hz, 1H), 3.72 – 3.66 (m, 1H), 3.50 – 3.44 (m, 1H), 3.42 (d, *J* = 8.1 Hz, 1H), 3.39 (s, 1H), 2.80 (dd, *J* = 14.9, 8.3 Hz, 1H), 2.73 (dd, *J* = 15.4, 8.0 Hz, 1H), 2.53 (d, *J* = 14.9 Hz, 1H), 2.10 (dd, *J* = 15.5, 5.3 Hz, 1H), 1.81 (d, *J* = 11.8 Hz, 1H), 1.63 (d, *J* = 8.1 Hz, 1H), 1.40 (s, 3H), 0.98 – 0.86 (m, 2H), 0.33 (s, 3H), 0.29 (s, 3H), -0.00 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  207.8, 142.5, 137.6, 133.7, 129.4, 128.1, 117.3, 107.1, 80.2, 71.3, 67.5, 65.1, 58.3, 54.2, 54.0, 42.1, 38.8, 37.9, 34.4, 22.1, 18.0, -1.3, -1.6, -2.0; IR (neat, cm<sup>-1</sup>): 2953, 2892, 1715, 1427, 1250, 1109, 1033, 835, 775, 703; HRMS-ESI calcd. for C<sub>28</sub>H<sub>42</sub>O<sub>4</sub>NaSi<sub>2</sub> [M + Na<sup>+</sup>]: 521.2514; Found: 521.2513.

Synthesis of

(2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10-(dimethyl(phenyl)silyl)-10a-methyl-4-methylene-5-(2-(trime thylsilyl)ethoxy)dodecahydronaphtho[1,8-bc:4,4a-c']difuran-8-ol (24):



To a solution of compound **S3** (135 mg, 0.37 mmol) in MeOH/THF (2.5/0.5 mL) was added NaBH<sub>4</sub> (10 mg, 0.27 mmol) at -10 °C, and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (3 mL), the mixture was extracted with EtOAc (3×3 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/10) to give compound **24** (110 mg) as a white solid in 82% yield,  $R_f = 0.69$  (silica gel, EtOAc/hexanes = 1/4) and compound **23** (10 mg) in 7% yield.

**Compound 24** : <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 (dd, J = 6.4, 3.0 Hz, 2H), 7.38 – 7.32 (m, 3H), 5.24 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.05 (t, J = 2.9 Hz, 1H), 3.90 (d, J = 8.2 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.49 (dddd, J = 17.2, 11.2, 10.4, 5.2 Hz, 2H), 3.37 (d, J = 8.2 Hz, 1H), 2.86 (dd, J = 11.5, 4.3 Hz, 1H), 2.75 (s, 1H), 2.19 – 2.12 (m, 1H), 2.11 – 1.99 (m, 3H), 1.35 (dd, J = 6.7, 1.4 Hz, 1H), 1.02 – 0.88 (m, 5H), 0.53 (s, 3H), 0.39 (s, 3H), 0.04 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  142.0, 140.8, 133.9, 128.6, 127.7, 113.5, 102.5, 80.8, 73.9, 70.2, 69.8, 64.8, 52.4, 50.0, 48.8, 44.4, 41.9, 30.3, 28.5, 21.8, 18.7, -1.0, -1.3, -1.6; IR (neat, cm<sup>-1</sup>): 2953, 2926, 1260, 1250, 1090, 1017, 860, 835, 814, 702; HRMS-ESI calcd. for C<sub>28</sub>H<sub>44</sub>O<sub>4</sub>NaSi<sub>2</sub> [M + Na<sup>+</sup>]: 523.2670; Found: 523.2668.

#### Synthesis of

(2a*S*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10a-methyl-4-methylene-5-(2<sup>-</sup>(trimethylsilyl)ethoxy)dodecahy dronaphtho[1,8-bc:4,4a-c']difuran-8,10-diol (25):



To liquid ammonia (1.2 mL) was added a solution of compound **24** (55 mg, 0.11 mmol) in dry THF (1.2 mL) at -78 °C, followed by addition of Na (12.7 mg, 0.55 mmol), and the resultant mixture was then stirred at the same temperature for 1 minute. The reaction was quenched by addition of a saturated

solution of NH<sub>4</sub>Cl (2 mL), and the mixture was extracted with EtOAc ( $3 \times 2$  mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and concentrated under vacuum to afford the crude product.

To a solution of above crude product in THF (1 mL) was added a solution of TBAF (1.0 M in THF, 0.24 mL, 0.24 mmol) at room temperature, and the reaction mixture was tirred at the same temperature for 1 h. To this solution was sequentially added MeOH (0.5 mL), KHCO<sub>3</sub> (16.5 mg 0.165 mmol) and 30% H<sub>2</sub>O<sub>2</sub> solution (0.125 mL, 1.1 mmol) at room temperature, and the resultant mixture was stirred at the same temperature for 5 h. The reaction was quenched by addition of a saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 mL), and the resultant mixture was extracted with EtOAc ( $3 \times 2$  mL), and the combined organic extracts dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and concentrated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 2/3) to give compound **25** (40 mg) as a white solid in 95% overall yield for 2 steps; R<sub>f</sub> = 0.38 (silica gel, EtOAc/hexanes = 1/1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.23 (s, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 4.25 (s, 1H), 4.11 (d, *J* = 7.4 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.67 – 3.57 (m, 3H), 3.54 (d, *J* = 7.4 Hz, 1H), 3.49 – 3.43 (m, 1H), 2.94 – 2.74 (m, 4H), 2.36 (d, *J* = 11.6 Hz, 1H), 2.19 – 2.12 (m, 2H), 2.08 – 2.01 (m, 1H), 0.98 – 0.82 (m, 5H), 0.02 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  141.7, 113.9, 102.5, 76.4, 73.7, 71.3, 71.2, 69.3, 64.9, 52.6, 50.1, 44.2, 44.2, 43.3, 32.6, 18.9, 18.7, -1.3; IR (neat, cm<sup>-1</sup>): 3400, 2950, 2892, 1457, 1248, 1080, 1015, 860, 835; HRMS-ESI calcd. for C<sub>20</sub>H<sub>34</sub>O<sub>5</sub>NaSi [M + Na<sup>+</sup>]: 405.2068; Found: 405.2068.

#### Synthesis of

(2a*S*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10a-methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)dodecahyd ronaphtho[1,8-bc:4,4a-c']difuran-8,10-diyl diacetate (26):



To a solution of compound **25** (38 mg, 0.1 mmol) in dry DCE (2.5 mL) was added Ac<sub>2</sub>O (38  $\mu$ L, 0.4 mmol) and DMAP (73 mg, 0.6 mmol) at room temperature, and the mixture was stirred at 90 °C for 12 h. To ensure the conversion, second batch of Ac<sub>2</sub>O (38  $\mu$ L, 0.4 mmol) and DMAP (73 mg, 0.6 mmol) was added to the reaction mixture, and the reaction was stirred at at 90 °C for additional 6 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (2.5 mL), and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×2.5 mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/2) to give compound **26** (41 mg) as a colorless oil in 89% yield; R<sub>f</sub> = 0.82 (silica gel,

EtOAc/hexanes = 1/1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.24 – 5.18 (m, 2H), 5.10 (s, 1H), 5.01 (s, 1H), 4.93 (t, J = 2.8 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.71 – 3.61 (m, 4H), 3.56 (d, J = 7.9 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.93 – 2.86 (m, 2H), 2.40 (d, J = 11.7 Hz, 1H), 2.36 – 2.30 (m, 1H), 2.21 (t, J = 11.1 Hz, 1H), 2.10 – 2.01 (m, 7H), 0.97 (s, 3H), 0.91 – 0.80 (m, 2H), -0.01 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.1, 169.6, 141.4, 114.4, 103.0, 76.3, 73.6, 71.6, 71.4, 69.1, 64.8, 52.1, 48.5, 45.8, 43.7, 42.7, 28.8, 21.3, 21.1, 19.1, 17.9, -1.3; IR (neat, cm<sup>-1</sup>): 2950, 2893, 2357, 2330, 1738, 1250, 1053, 1017, 835, 750; HRMS-ESI calcd. for C<sub>24</sub>H<sub>38</sub>O<sub>7</sub>NaSi [M + Na<sup>+</sup>]: 489.2279; Found: 489.2278.

#### Synthesis of

(2a*R*,2a1*S*,3*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-3-hydroxy-10a-methyl-4-methylene-5-(2-(trimethylsilyl)eth oxy)dodecahydronaphtho[1,8-bc:4,4a-c']difuran-8,10-diyl diacetate (27):



To a solution of compound **26** (40 mg, 0.086 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.7 mL) was added SeO<sub>2</sub> (48 mg, 0.43 mmol) and 'BuOOH solution (5.5 M in decane, 78  $\mu$ L, 0.43 mmol) at room temperature, and the mixture was stirred at the same temperature for 7 h. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 2/3) to give compound **27** (30 mg) as a colorless oil in 73% yield; R<sub>f</sub> = 0.40 (silica gel, EtOAc/hexanes = 1/1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.36 (s, 1H), 5.26 – 5.20 (m, 2H), 5.15 (s, 1H), 4.95 (s, 1H), 4.62 (d, *J* = 2.5 Hz, 1H), 3.80 – 3.60 (m, 6H), 3.38 – 3.30 (m, 1H), 3.25 (s, 1H), 3.15 (d, *J* = 12.3 Hz, 1H), 2.36 (d, *J* = 16.7 Hz, 1H), 2.11 – 2.03 (m, 7H), 0.97 (s, 3H), 0.89 – 0.84 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.2, 169.8, 143.3, 117.2, 103.0, 77.4, 77.1, 77.0, 76.9, 76.2, 74.9, 71.4, 68.8, 64.9, 48.4, 48.2, 42.3, 36.2, 28.8, 21.3, 21.1, 18.7, 17.9, -1.3; IR (neat, cm<sup>-1</sup>): 3445, 2953, 2929, 2894, 1738, 1732, 1377, 1248, 1053, 860, 837; HRMS-ESI calcd. for C<sub>24</sub>H<sub>38</sub>O<sub>8</sub>NaSi [M + Na<sup>+</sup>]: 505.2227; Found: 505.2228.

Since there was no obvious signal between H-7 with other hydrogen on NOESY spectrum, the relative configuration of C7 was deduced by coupling constant analysis and molecular modeling. The two lowest energy conformers of epimers **A** and **B** (Scheme S1), corresponding to the  $\alpha$ - and  $\beta$ -orientations of H-7, were generated using computational methods (MMFF94X force field calculations for energy minimization using MOE 2009.10 and further optimization using Gaussian 09 by B3LYP/6-31+G(d)). In **A**, the dihedral angles between H-6 and H-5, H-6 and H-7 were 174.7° and 54.9°, respectively, whereas in **B**, the dihedral angles were 173.7° and 179.4°. With a consideration of the coupling constants between the protons (12.3 Hz and 2.5 Hz) in compound **27**, **A** is in more agreement with the experimental result. Therefore, the H-7 was assigned as  $\alpha$ -oriented.







ОН

TMS

AcO<sup>\</sup>

A: C

Ο AcO

> Ĥ Ó

> > Α

Calculation Type = FOPT Calculation Method = RB3LYP Basis Set = 6-31+G(d)Charge = 0Spin = Singlet E(RB3LYP) = -1828.78513520 a.u

#### *Scheme S1*: Molecular modeling study of compound 27

			Н	5.27954900	-1.17236500	-0.05786500
1.67391800	1.20269800	-1.74731500	Н	0.93254500	-2.70239600	-1.88257200
3.06758200	0.98183700	-1.11881600	Н	0.58081100	-1.25698700	-2.85286400
3.27386700	-0.50835700	-0.74699000	Н	-2.26458800	-2.57475300	-0.35560800
2.01680300	-0.97995400	-0.00250200	Н	-3.12525300	-0.68831300	-2.61583100
0.64678500	-0.89760600	-0.65890400	Н	-4.03864000	-1.60496000	-1.40443400
0.44935900	0.60748500	-1.01166300	Н	-5.20630800	0.49513200	-2.15198700
2.43667000	-2.28847200	0.61429300	Н	-3.86542500	1.46455700	-1.56624700
1.44801600	-2.67171900	1.71923700	Н	-0.21342100	-4.71624900	1.75325000
0.06546500	-2.73947600	1.07147700	Н	-1.58985200	-4.05678100	0.72910200
0.43180800	-1.48623300	0.32812300	Н	2.37382000	-1.54346300	3.00199800
4.31235100	-0.86808000	0.35276000	Н	2.87485400	-1.15897800	-2.82562800
3.76153000	-2.00117800	1.09474400	Н	3.71735400	-2.35992700	-1.84061600
0.36790400	-1.76251900	-1.90574100	Н	4.58146500	-0.93743800	-2.42809200
.03425400	-2.07003500	-1.88263300	Н	2.47960500	-3.12132400	-0.10306200
.60967600	-1.73840500	-0.62124400	Н	-0.70252400	-0.73243200	1.07200200
.39364900	-0.56759700	-0.68235000	Н	1.93445800	-0.29657100	0.85332700
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Н	5.1/144800	-3.89323600	-1.86330400
Н	3.85668100	-2.85274400	-2.49212800

#### Synthesis of

(2a*R*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-4,10a-dimethyl-3-oxo-5-(2-(trimethylsilyl)ethoxy)dodecahydro naphtho[1,8-bc:4,4a-c']difuran-8,10-diyl diacetate (6):



To a solution of compound **27** (17 mg, 0.035 mmol) in EtOAc (0.7 mL) was added Pd/C (10% on carbon, 3 mg), and the mixture was then degassed with  $H_2$  for 5 times. The mixture was then stirred at room temperature for 1.5 h. The reaction was worked up by filtration of the mixture through a celite pad, followed by washing the pad with EtOAc. The filtrate was concentrated under vacuum to give the crude hydrogenated products.

To a solution of the crude product made above in dry  $CH_2Cl_2$  (0.7 mL) was sequentially added 4Å molecular sieve (17 mg), TPAP (1.5 mg, 0.0043 mmol) and NMO (8.3 mg, 0.07 mmol) at room temperature, and then the mixture was stirred at the same temperature for 1 h. The reaction mixture was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/2) to give compounds **6** as a pair of diastereomers (14 mg,  $\alpha$ -Me: $\beta$ -Me = 10:3) in 82% overall yield for 2 steps;  $R_f = 0.61$  and 0.51 (silica gel, EtOAc/hexanes = 1:1). The ratio was confirmed by <sup>1</sup>H-NMR spectrum.

Two diastereomers could be separated by flash chromatography, and the relative stereochemistry of the major isomer **6** ( $\alpha$ -Me) was determined by 2D-NMR spectra.

α-Me **6** : <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.24 (t, J = 2.8 Hz, 1H), 4.96 (t, J = 2.8 Hz, 1H), 4.82 (s, 1H), 4.42 (d, J = 14.1 Hz, 1H), 4.22 (d, J = 9.4 Hz, 1H), 3.86 (d, J = 9.5 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.66 (s, 2H), 3.38 – 3.30 (m, 1H), 2.74 (d, J = 14.0 Hz, 1H), 2.45 (d, J = 11.2 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.10 – 2.01 (m, 7H), 1.23 (d, J = 6.4 Hz, 3H), 1.07 (s, 3H), 0.90 – 0.83 (m, 2H), -0.00 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 206.5, 170.1, 169.5, 105.6, 77.3, 71.8, 70.6, 69.3, 65.0, 59.4, 47.9, 47.5, 43.7, 43.0, 28.5, 21.3, 21.1, 18.0, 17.8, 13.0, -1.3; IR (neat, cm<sup>-1</sup>): 2925, 2855, 1738, 1732, 1377, 1250, 1058, 1024, 999, 860, 837, 802; HRMS-ESI calcd. for C<sub>24</sub>H<sub>38</sub>O<sub>8</sub>NaSi [M + Na<sup>+</sup>]: 505.2228; Found: 505.2228; [α]<sup>26</sup><sub>589</sub> +96.1 (c = 0.25, CHCl<sub>3</sub>).

#### **Reference:**

[1] T. B. Dunn, J. M. Ellis, C. C. Kofink, J. R. Manning, L. E. Overman, Org. Lett. 2009, 11, 5658-5661.

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-7.268

<sup>1</sup>H NMR of compound **S1** 































-207.845

 $^{13}\text{C}$  NMR of compound S3



<sup>1</sup>H NMR of compound **24** 







<sup>13</sup>C NMR of compound **24** 





















