## Supporting Information

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

<br>${ }^{\dagger}$ Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen, 518055,China,<br>${ }^{\dagger}$ Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), and Peking-Tsinghua Center for Life Sciences, Peking University. Beijing 100871, China<br>${ }^{\S}$ Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao 266003, China

*E-mail: tuopingluo@pku.edu.cn.
*E-mail: zyang@pku.edu.cn.

Table of Contents
General Information ..... S2
Experimental Data ..... S3
Reference ..... S18
Spectra for the synthesized compounds ..... S19

## 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 ( $60 \mathrm{~F}-254$ ) 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 $0.040-0.063 \mathrm{~mm}$ ) 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 $500\left({ }^{1} \mathrm{H}: 500 \mathrm{MHz},{ }^{13} \mathrm{C} 125\right.$ $\mathrm{MHz})$ and Brüker Advance $400\left({ }^{1} \mathrm{H}: 400 \mathrm{MHz},{ }^{13} \mathrm{C} 100 \mathrm{MHz}\right)$. 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: $\mathrm{s}=\operatorname{singlet}, \mathrm{d}=\operatorname{doublet}, \mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, $\mathrm{m}=$ multiplet.

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


(-)-Carvone


S1

To a solution of $\mathrm{CuBr} \cdot \mathrm{Me}_{2} \mathrm{~S}(5.5 \mathrm{~g}, 27 \mathrm{mmol})$ in dry $\mathrm{THF}(200 \mathrm{~mL})$ was added the solution of vinyl Grignard reagent ( 1.0 M in THF, $135 \mathrm{~mL}, 135 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$, and the reaction mixture was then stirred at the same temperature for 10 minutes. To this solution was added a solution of (-)-carvone ( $13.5 \mathrm{~g}, 90$ mmol ) in dry THF ( 50 mL ) at $-78{ }^{\circ} \mathrm{C}$, and the mixture continuesely stirred for 1 more hour, and then quenched with a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(100 \mathrm{~mL})$. The miaxure was extracted with ethyl acetate $(2 \times 100 \mathrm{~mL})$, and the combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The extracts were filtered off, and then evaporated under vacuum. The residue was purified by a flash chromatography on silica gel $($ EtOAc/hexanes $=1 / 40)$ to give compound $\mathbf{S 1}(15.05 \mathrm{~g})$ as a yellow oil in $94 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.65$ $($ EtOAc/hexanes $)=1 / 20 ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.60(\mathrm{dt}, J=16.8,9.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.14-5.04(\mathrm{~m}$, $2 \mathrm{H}), 4.75(\mathrm{~d}, ~ J=19.5 \mathrm{~Hz}, 2 \mathrm{H}), 2.89-2.77(\mathrm{~m}, 1 \mathrm{H}), 2.66-2.58(\mathrm{~m}, 2 \mathrm{H}), 2.46(\mathrm{dd}, J=13.1,3.4 \mathrm{~Hz}, 1 \mathrm{H})$, $2.32(\mathrm{t}, J=13.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.03-1.88(\mathrm{~m}, 2 \mathrm{H}), 1.73(\mathrm{~s}, 3 \mathrm{H}), 0.96(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 212.3,147.6,136.9,117.6,110.0,47.5,47.0,46.7,41.6,37.2,20.6,12.5$; IR (neat, $\mathrm{cm}^{-1}$ ): 3078, 2973, 2933, 2874, 1713, 1674, 1643, 1450, 1429, 1209, 1153, 1093; HRMS-APCI calcd. for $\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{O}$ [M $\left.+\mathrm{H}^{+}\right]:$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 $\mathbf{S 1}(15.05 \mathrm{~g}, 84.4 \mathrm{mmol})$ in KOH solution $(10 \%$ in $\mathrm{MeOH}, 85 \mathrm{~mL})$ was added a solution of formalin ( $37 \%, 19 \mathrm{~mL}, 253 \mathrm{mmol}$ ) in a dropwise manner at $0^{\circ} \mathrm{C}$, and the mixture was then stirred at the same temperature for 15 minutes. The reaction was quenched by addition of a solution of $\mathrm{NH}_{4} \mathrm{Cl}(6.7 \mathrm{~g})$ in water $(100 \mathrm{~mL})$. After removal of the Methanol under vacuum, the mixture was then extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \times 100 \mathrm{~mL})$, and the combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $9(9.87 \mathrm{~g})$ as a yellow oil in $56 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.36(\mathrm{EtOAc} /$ hexanes $=1 / 6) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.82-5.53(\mathrm{~m}, 1 \mathrm{H}), 5.09(\mathrm{~d}, J=$ $3.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.06(\mathrm{~s}, 1 \mathrm{H}), 4.85(\mathrm{~s}, 1 \mathrm{H}), 4.68(\mathrm{~s}, 1 \mathrm{H}), 3.63(\mathrm{dd}, J=11.4,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.47(\mathrm{dd}, J=11.3,7.2$ $\mathrm{Hz}, 1 \mathrm{H}), 2.75-2.60(\mathrm{~m}, 3 \mathrm{H}), 2.60-2.50(\mathrm{~m}, 2 \mathrm{H}), 2.09-1.93(\mathrm{~m}, 1 \mathrm{H}), 1.91-1.81(\mathrm{~m}, 1 \mathrm{H}), 1.71(\mathrm{~s}, 3 \mathrm{H})$,
$0.99(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (125 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 217.1,146.4,136.9,117.3,112.3,77.4,77.1,76.9,66.2,52.7$, 42.2, 41.4, 40.5, 29.5, 21.9, 15.8; IR (neat, $\mathrm{cm}^{-1}$ ): 3440, 2975, 2940, 2875, 2364, 2331, 1714, 1705, 1699, 1456, 1377, 1045, 999, 895; HRMS-ESI calcd. for $\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{NaO}_{2}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 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 $9(4 \mathrm{~g}, 19 \mathrm{mmol})$ in $\mathrm{MeOH}(100 \mathrm{~mL})$ was added $\mathrm{TsNHNH}_{2}(3.35 \mathrm{~g}, 18$ mmol ) at room temperature, and the reaction mixture was stirred heated at $50^{\circ} \mathrm{C}$ for 12 h . The methanol was removed under vacuum to give the crude hydrzone; $\mathrm{R}_{\mathrm{f}}=0.52$ ( $\mathrm{EtOAc} /$ 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 $\mathrm{Et}_{2} \mathrm{O}, 47.5 \mathrm{~mL}, 76 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$. The mixture was warmed to room temperature and then stirred for 2 h . The reaction was quenched by addition of a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(50 \mathrm{~mL})$, and the mixture was extracted with ethyl acetate ( $2 \times 50 \mathrm{~mL}$ ), and the extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The solvent was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel $(\mathrm{EtOAc} /$ hexanes $=1 / 8)$ to give compound $\mathbf{1 0}(2.96 \mathrm{~g})$ as a yellow oil in $81 \%$ overall yield for 2 steps; $\mathrm{R}_{\mathrm{f}}=$ $0.54(\mathrm{EtOAc} /$ hexanes $=1 / 6) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.84-5.74(\mathrm{~m}, 1 \mathrm{H}), 5.70(\mathrm{dd}, J=10.0,4.3 \mathrm{~Hz}$, $1 \mathrm{H}), 5.52(\mathrm{~d}, J=10.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.03(\mathrm{dd}, J=13.3,12.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.83(\mathrm{~s}, 1 \mathrm{H}), 4.70(\mathrm{~s}, 1 \mathrm{H}), 3.38(\mathrm{~d}, J=3.2$ $\mathrm{Hz}, 2 \mathrm{H}), 2.72(\mathrm{~s}, 1 \mathrm{H}), 2.46-2.37(\mathrm{~m}, 1 \mathrm{H}), 1.76(\mathrm{~s}, 3 \mathrm{H}), 1.75-1.72(\mathrm{~m}, 1 \mathrm{H}), 1.61(\mathrm{~d}, J=13.4 \mathrm{~Hz}, 1 \mathrm{H})$, $0.83(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 147.6,134.0,134.4,130.4,115.5,111.8,69.9,41.1,40.4$, $39.0,28.6,22.1,18.9$; IR (neat, $\mathrm{cm}^{-1}$ ): 3416, 3075, 2963, 2933, 2872, 2350, 1643, 1453, 1373, 1039, 911, 895; HRMS-APCI calcd. for $\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{O}\left[\mathrm{M}+\mathrm{H}^{+}\right]$: 193.1587; Found: 193.1585.


To a solution of $\mathrm{CuBr} \cdot \mathrm{Me}_{2} \mathrm{~S}(615 \mathrm{mg}, 3 \mathrm{mmol})$ in dry $\mathrm{THF}(50 \mathrm{~mL})$ was added a solution of vinyl Grignard reagent ( 1.0 M in THF, $30 \mathrm{~mL}, 30 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$, 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 $(1.5 \mathrm{~g}, 10 \mathrm{mmol})$ in dry THF $(20 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$, and the reaction mixture then stirred at the same temperature for 0.5 h . To the above mixture was added a solution of $\mathbf{1 1}(2.09 \mathrm{~g}, 14 \mathrm{mmol})$ in THF ( 20 mL ), and the resultant mixture was then stirred at $-20^{\circ} \mathrm{C}$ for 2 h . The reaction was quenched by addition of a
saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(50 \mathrm{~mL})$, and the mixture was extracted with ethyl acetate $(2 \times 50 \mathrm{~mL})$. The combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $9(1.66 \mathrm{~g}, \alpha-\mathrm{Me}: \beta-\mathrm{Me}=3: 10)$. The diastereoselectivity was confirmed by ${ }^{1} \mathrm{H}-\mathrm{NMR}$ spectrum of mixture.

To a solution of diastereomers $9(1.66 \mathrm{~g}, \alpha-\mathrm{Me}: \beta-\mathrm{Me}=3: 10)$ in $\mathrm{MeOH}(80 \mathrm{~mL})$ was added $\mathrm{TsNHNH}_{2}$ $(1.41 \mathrm{~g}, 7.6 \mathrm{mmol})$ at room temperature, and the resultant mixture was stirred at $50{ }^{\circ} \mathrm{C}$ 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 $\mathrm{Et}_{2} \mathrm{O}, 17.5 \mathrm{~mL}, 28 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$, 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 $\mathrm{NH}_{4} \mathrm{Cl}(20$ mL ), and the mixture was extracted with ethyl acetate $(2 \times 20 \mathrm{~mL})$. The combined organic extracts were first dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $\mathbf{1 0}$ $(1.06 \mathrm{~g})$ as a yellow oil in $55 \%$ overall yield for 3 steps.

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


10

toluene, $45{ }^{\circ} \mathrm{C}$ 85\%


14

To a solution of $\mathrm{Pd}_{2}(\mathrm{dba})_{3}(915.7 \mathrm{mg}, 1 \mathrm{mmol})$, DPE-Phos ( $\left.1.077 \mathrm{~g}, 2 \mathrm{mmol}\right)$ and $\mathrm{NaO}^{t} \mathrm{Bu}(1.44 \mathrm{~g}, 15$ mmol ) in dry toluene ( 80 mL ) was added a solution of compound $\mathbf{1 0}(1.92 \mathrm{~g}, 10 \mathrm{mmol})$ and alkynyl bromide ( $3 \mathrm{~g}, 11.5 \mathrm{mmol}$ ) in toluene $(20 \mathrm{~mL})$ at room temperature, and the mixture was then stirred at $45^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(40 \mathrm{~mL})$, and the mixture was extracted with ethyl acetate $(2 \times 20 \mathrm{~mL})$. The combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $\mathbf{1 4}(3.15 \mathrm{~g})$ as a colorless oil in $85 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.36(\mathrm{EtOAc} /$ hexanes $=1 / 20) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.99(\mathrm{~d}, J$ $=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.46(\mathrm{dd}, J=9.8,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.76(\mathrm{~s}, 1 \mathrm{H}), 4.71(\mathrm{~s}, 1 \mathrm{H}), 3.75-3.68(\mathrm{~m}, 1 \mathrm{H}), 3.63(\mathrm{~d}, J=$ $6.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.52(\mathrm{~d}, J=6.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.94-2.89(\mathrm{~m}, 1 \mathrm{H}), 2.64-2.52(\mathrm{~m}, 2 \mathrm{H}), 2.03-1.94(\mathrm{~m}, 1 \mathrm{H}), 1.87$ $-1.80(\mathrm{~m}, 2 \mathrm{H}), 1.78(\mathrm{~s}, 3 \mathrm{H}), 1.11-0.99(\mathrm{~m}, 21 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 148.4,132.8,130.0$, 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, $\mathrm{cm}^{-1}$ ): 2957,

2941, 2864, 2171, 1645, 1462, 1371, 1018, 993, 883, 677; HRMS-ESI calcd. for $\mathrm{C}_{24} \mathrm{H}_{41} \mathrm{OSi}\left[\mathrm{M}+\mathrm{H}^{+}\right]$: 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 $14(2.23 \mathrm{~g}, 6 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}(60 \mathrm{~mL} / 1.94 \mathrm{~mL})$ was continuously bubbled with ozone at $-98^{\circ} \mathrm{C}$ 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 $0{ }^{\circ} \mathrm{C}$. To this solution was added $\mathrm{Et}_{3} \mathrm{~N}(10 \mathrm{~mL}, 72 \mathrm{mmol})$, DMAP ( $73 \mathrm{mg}, 0.6 \mathrm{mmol}$ ) and $\mathrm{Ac}_{2} \mathrm{O}(6.8 \mathrm{~mL}, 72 \mathrm{mmol})$, and the reaction mixture was stirred at $40{ }^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched by addition of $\mathrm{Me}_{2} \mathrm{~S}(6 \mathrm{~mL})$ and water $(6 \mathrm{~mL})$, and the mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 20 \mathrm{~mL})$. The extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The extract was filtered off, and the filtrate was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel $(\mathrm{EtOAc} /$ hexanes $=1 / 8)$ to give a couple of diastereomers $15($ d.r. $=2.5: 1) ; \mathrm{R}_{\mathrm{f}}=0.36$ and 0.35 $($ EtOAc/hexanes $=1 / 6)$. The diastereomeric ratio (between $20: 1$ and $1: 1$ ) was deduced by ${ }^{1} \mathrm{H}-\mathrm{NMR}$ spectrum and it was variable from batch to batch.

To a solution of diastereomers $\mathbf{1 5}$ in $\mathrm{MeOH}(30 \mathrm{~mL})$ was added $\mathrm{K}_{2} \mathrm{CO}_{3}(3.26 \mathrm{~g}, 18.3 \mathrm{mmol})$ at $0^{\circ} \mathrm{C}$, and the mixture was stirred the same temperature for 1.5 h . The reaction was quenched by addition of a solution of $\mathrm{NH}_{4} \mathrm{Cl}(3.26 \mathrm{~g})$ in water $(20 \mathrm{~mL})$, and the methanol in the mixture was removed under vacuum. The mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 10 \mathrm{~mL})$, and the combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The extract was filtered off, and the filtrate was evaporated under vacuum to give crude products.

To a solution of above crude product in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(35 \mathrm{~mL})$ was added DMP $(2.97 \mathrm{~g}, 7 \mathrm{mmol})$ 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 $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(10 \mathrm{~mL})$, and the resultant mixture was extracted with ethyl acetate $(2 \times 10 \mathrm{~mL})$, and the combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $16(1.0 \mathrm{~g})$ as a colorless oil in $48 \%$ overall yield for 3 steps; $\mathrm{R}_{\mathrm{f}}=0.40(\mathrm{EtOAc} /$ hexanes $=1 / 4) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.07(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.92(\mathrm{~d}$,
$J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.95-3.82(\mathrm{~m}, 1 \mathrm{H}), 3.73(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.66(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.71(\mathrm{dd}, J=$ $17.0,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.61(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.56-2.48(\mathrm{~m}, 1 \mathrm{H}), 2.46-2.34(\mathrm{~m}, 1 \mathrm{H}), 1.18(\mathrm{~s}, 3 \mathrm{H}), 1.07-$ 0.95 (m, 23H); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 198.4,152.5,129.9,103.5,83.6,75.4,49.0,43.7,36.2$, 25.1, 19.3, 18.6, 11.3; IR (neat, $\mathrm{cm}^{-1}$ ): 2941, 2864, 2172, 1862, 1674, 1464, 1456, 1381, 1373, 1244, 1016, 881; HRMS-ESI calcd. for $\mathrm{C}_{21} \mathrm{H}_{34} \mathrm{NaO}_{2} \mathrm{Si}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 369.2220; Found: 369.2229. $[\alpha]^{26}{ }_{589}-41.2(c$ $=0.48, \mathrm{CHCl}_{3}$ ).

## Synthesis of ( $\mathbf{3 S , 3 a R}, 4 R, 7 \mathrm{a} R$ )-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 $\mathbf{1 6}(0.35 \mathrm{~g}, 1 \mathrm{mmol})$ in dry THF $(10 \mathrm{~mL})$ was added a solution of NaHMDS ( 2.0 M in THF, $1.1 \mathrm{~mL}, 2.2 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$, and the mixture was then stirred at the same temperature for 1 h . To this solution was added ethyl cyanoformate ( $0.13 \mathrm{~mL}, 1.3 \mathrm{mmol}$ ), 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 $(2 \times 10 \mathrm{~mL})$, and the combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel ( $\mathrm{EtOAc} /$ hexanes $=1 / 6$ ) to give product $\mathbf{1 8}$ and unreacted 16.

To a solution of above mixture of $\mathbf{1 6}$ and $\mathbf{1 8}$ made above in dry THF ( 10 mL ) was added a solution of NaHMDS ( 2.0 M in THF, $0.5 \mathrm{~mL}, 1 \mathrm{mmol}$ ) at $-78^{\circ} \mathrm{C}$, and the mixture was then stirred at the same temperature for 1 h . To this solution was added ethyl cynoformate ( $0.65 \mathrm{~mL}, 0.65 \mathrm{mmol}$ ), 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 $(2 \times 10 \mathrm{~mL})$, and the combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $\mathbf{1 8}(0.33 \mathrm{~g})$ as colorless oil in $79 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.40(\mathrm{EtOAc} /$ hexanes $=1 / 4) ;{ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 7.17(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.01(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.32-4.14(\mathrm{~m}, 2 \mathrm{H}), 4.04-3.94(\mathrm{~m}, 1 \mathrm{H})$, $3.78(\mathrm{q}, 2 \mathrm{H}), 3.44(\mathrm{~d}, J=13.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.20-3.01(\mathrm{~m}, 1 \mathrm{H}), 2.78(\mathrm{dd}, J=17.5,3.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.24(\mathrm{dd}, J=$ $17.6,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.31(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H}), 1.09-1.02(\mathrm{~m}, 23 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 193.7,168.9,153.0,129.0,104.0,83.2,76.5,75.3,61.6,54.3,48.8,44.0,25.0,20.5,18.7,14.1$,
11.4; IR (neat, $\mathrm{cm}^{-1}$ ): 2941, 2865, 2174, 1740, 1682, 1464, 1385, 1259, 1020, 914, 883, 748; HRMS-ESI calcd. for $\mathrm{C}_{24} \mathrm{H}_{38} \mathrm{NaO}_{4} \mathrm{Si}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 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 $(0.87 \mathrm{~g}, 125.8 \mathrm{mmol})$ in dry THF $(74 \mathrm{~mL})$ was added $\mathrm{PhMe}{ }_{2} \mathrm{SiCl}(6.1 \mathrm{~mL}$, 37 mmol ) under argon atmosphere at $0{ }^{\circ} \mathrm{C}$, and the mixture was then stirred at the same temperature for 12 h .

To a solution of $\mathrm{ZnEt}_{2}$ ( 1.5 M in Toluene, 16.7 mL , 25 mmol ) in dry THF ( 39 mL ) was added the reagent $\mathrm{PhMe}_{2} \mathrm{SiLi}$ made above $(54 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$, and the mixture was first stirred at the same temperature for 10 minutes. To this solution was added a solution of compound $\mathbf{1 8}(4.78 \mathrm{~g}, 11.4 \mathrm{mmol})$ in THF (20 mL ) at $-78^{\circ} \mathrm{C}$ 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 $\mathrm{NH}_{4} \mathrm{Cl}(40 \mathrm{~mL})$, and mixture was extracted with ethyl acetate $(2 \times 40 \mathrm{~mL})$, and the combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $\mathbf{S 2} ; \mathrm{R}_{\mathrm{f}}=0.53(\mathrm{EtOAc} /$ hexanes $=1 / 6)$.

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

1941, 2864, 2171, 1734, 1732, 1726, 1462, 1454, 1427, 1254, 1230; HRMS-ESI calcd. for $\mathrm{C}_{34} \mathrm{H}_{50} \mathrm{NaO}_{4} \mathrm{Si}_{2}\left[\mathrm{M}+\mathrm{Na}^{+}\right]:$601.3140; Found: 601.3140. $[\alpha]^{26}{ }_{589}-67.1\left(c=0.033, \mathrm{CHCl}_{3}\right)$.

## Synthesis of

(3S,3aR,4S,7R,7aR)-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 $\mathbf{2 0}(1.75 \mathrm{~g}, 3.03 \mathrm{mmol})$ in dry THF ( 30 mL ) was added $\mathrm{LiAlH}_{4}(0.11 \mathrm{~g}$, 3.03 mmol ) at $-90^{\circ} \mathrm{C}$, 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 $(25 \mathrm{~mL})$ slowly, and the resultant mixture was stirred until a clear solution was obtained. The mixture was extracted with ethyl acetate ( $3 \times 25 \mathrm{~mL}$ ), and the combined extracts were dried with $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $21(1.26 \mathrm{~g}, \alpha-\mathrm{OH}: \beta-\mathrm{OH}=1: 9)$ in $77 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.30(\mathrm{EtOAc} /$ hexanes $=1 / 2)$. The diastereomeric ratio was deduced by ${ }^{1} \mathrm{H}-\mathrm{NMR}$ spectrum.
$\beta-\mathrm{OH} 21:{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.50-7.46(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.33(\mathrm{~m}, 3 \mathrm{H}), 4.14-4.07(\mathrm{~m}$, 2H), 3.98 - 3.93 (m, 1H), 3.70 (d, $J=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.63$ (d, $J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 312(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H})$, $2.99(\mathrm{dd}, J=17.3,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.73(\mathrm{dd}, J=17.3,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.37(\mathrm{~s}, 1 \mathrm{H}), 2.18(\mathrm{~d}, J=10.7 \mathrm{~Hz}, 1 \mathrm{H})$, $2.03-1.98(\mathrm{~m}, 1 \mathrm{H}), 1.94-1.89(\mathrm{~m}, 1 \mathrm{H}), 1.39(\mathrm{dd}, J=5.8,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.23(\mathrm{~s}, 3 \mathrm{H}), 1.09(\mathrm{~d}, J=2.9 \mathrm{~Hz}$, $21 \mathrm{H}), 0.46(\mathrm{~s}, 3 \mathrm{H}), 0.40(\mathrm{~d}, J=5.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 138.7,133.6,129.3,128.1$, $105.8,86.4,82.5,79.5,77.2,73.8,73.1,61.5,52.4,44.0,43.8,29.3,28.6,26.1,25.5,18.8,11.5$.

Diastereomers 21 ( $\alpha-\mathrm{OH}: \beta-\mathrm{OH}=1: 9$ ): IR (neat, $\mathrm{cm}^{-1}$ ): 3416, 3308, 2943, 2890, 2864, 2170, 1738, 1464, 1427, 1283 1111, 1055; HRMS-ESI calcd. for $\mathrm{C}_{32} \mathrm{H}_{50} \mathrm{O}_{3} \mathrm{NaSi}_{2}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 561.3191; Found: 561.3191 .

## Synthesis of



To a solution of mixture $21(\alpha-\mathrm{OH}: \beta-\mathrm{OH}=1: 9,1.25 \mathrm{~g}, 2.32 \mathrm{mmol})$ in THF ( 20 mL ) was added a solution of TBAF ( 1.0 M in THF, $4.6 \mathrm{~mL}, 4.6 \mathrm{mmol}$ ) at room temperature, and the reaction mixture was stirred at $50{ }^{\circ} \mathrm{C}$ overnight. The reaction was quenched by addition of a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(20$ $\mathrm{mL})$, and the mixture was then extracted with ethyl acetate ( $2 \times 20 \mathrm{~mL}$ ). The combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 ( $0.85 \mathrm{~g}, \alpha-\mathrm{OH}: \beta-\mathrm{OH}=1: 9$ ) as yellow solids in $96 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.31$ (EtOAc/hexanes= $1 / 1)$. The diastereomeric ratio was determined by ${ }^{1} \mathrm{H}-\mathrm{NMR}$ spectrum.
$\beta-\mathrm{OH} 22:{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.50-7.46(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.33(\mathrm{~m}, 3 \mathrm{H}), 4.14(\mathrm{~d}, J=11.5$ $\mathrm{Hz}, 1 \mathrm{H}), 4.08-4.03(\mathrm{~m}, 2 \mathrm{H}), 3.71-3.66(\mathrm{~m}, 2 \mathrm{H}), 3.17(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.88(\mathrm{~d}, J=17.1 \mathrm{~Hz}, 1 \mathrm{H})$, $2.65(\mathrm{dd}, J=17.1,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.39(\mathrm{~s}, 1 \mathrm{H}), 2.07-2.00(\mathrm{~m}, 2 \mathrm{H}), 1.95-1.90(\mathrm{~m}, 1 \mathrm{H}), 1.39-1.36(\mathrm{~m}$, $1 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H}), 0.47(\mathrm{~s}, 3 \mathrm{H}), 0.40(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 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 ( $\alpha-\mathrm{OH}: \beta-\mathrm{OH}=1: 9$ ): IR (neat, $\mathrm{cm}^{-1}$ ): 3416, 3304, 3069, 3048, 2927, 2885, 1427, 1418, 1254, 1170, 1055, 1028; HRMS-ESI calcd. for $\mathrm{C}_{23} \mathrm{H}_{31} \mathrm{O}_{3} \mathrm{Si}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 383.2037; Found: 383.2036.

## Synthesis of

(2aS,2a1R,4aS,5R,7aS,8R,10R,10aR)-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 $22(\alpha-\mathrm{OH}: \beta-\mathrm{OH}=1: 9,35 \mathrm{mg}, 0.091 \mathrm{mmol})$ in dry $\mathrm{DCM}(1.8 \mathrm{~mL})$ were sequentially added 2-(trimethylsilyl)ethanol ( $14 \mu \mathrm{~L}, 0.1 \mathrm{mmol}$ ), ( IPr ) $\mathrm{AuCl}(2.8 \mathrm{mg}, 0.0046 \mathrm{mmol})$ and $\mathrm{AgSbF}_{6}(1.6 \mathrm{mg}, 0.0046 \mathrm{mmol})$ 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 $(\mathrm{EtOAc} /$ hexane $=1 / 8)$ to give compound $23(20 \mathrm{mg})$ in $49 \%$ yield (base on $\beta-\mathrm{OH} 9)$.

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

## Synthesis of

(2aS,2a1R,4aS,5R,7aS,10R,10aR)-10-(dimethyl(phenyl)silyl)-10a-methyl-4-methylene-5-(2-(trimethy Isilyl)ethoxy)decahydronaphtho[1,8-bc:4,4a-c']difuran-8(2aH)-one (S3):


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

## Synthesis of

(2aS,2a1R,4aS,5R,7aS,8S,10R,10aR)-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 $\mathbf{S 3}(135 \mathrm{mg}, 0.37 \mathrm{mmol})$ in $\mathrm{MeOH} / \mathrm{THF}(2.5 / 0.5 \mathrm{~mL})$ was added $\mathrm{NaBH}_{4}$ $(10 \mathrm{mg}, 0.27 \mathrm{mmol})$ at $-10^{\circ} \mathrm{C}$, and the mixture was stirred at the same temperature for 0.5 h . The reaction was quenched by addition of a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(3 \mathrm{~mL})$, the mixture was extracted with EtOAc $(3 \times 3 \mathrm{~mL})$. The combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel ( $\mathrm{EtOAc} /$ hexane $=1 / 10$ ) to give compound $24(110 \mathrm{mg})$ as a white solid in $82 \%$ yield, $\mathrm{R}_{\mathrm{f}}=0.69$ (silica gel, EtOAc/hexanes $=1 / 4$ ) and compound $23(10 \mathrm{mg})$ in $7 \%$ yield.

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

## Synthesis of

(2aS,2a1S,4aS,5R,7aS,8S,10R,10aR)-10a-methyl-4-methylene-5-(2-(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 $24(55 \mathrm{mg}, 0.11 \mathrm{mmol})$ in dry THF $(1.2 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$, followed by addition of $\mathrm{Na}(12.7 \mathrm{mg}, 0.55 \mathrm{mmol})$, 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 $\mathrm{NH}_{4} \mathrm{Cl}(2 \mathrm{~mL})$, and the mixture was extracted with EtOAc $(3 \times 2 \mathrm{~mL})$. The combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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, $0.24 \mathrm{~mL}, 0.24 \mathrm{mmol}$ ) at room temperature, and the reaction mixture was tirred at the same temperature for 1 h . To this solution was sequentially added $\mathrm{MeOH}(0.5 \mathrm{~mL}), \mathrm{KHCO}_{3}(16.5 \mathrm{mg} 0.165 \mathrm{mmol})$ and $30 \% \mathrm{H}_{2} \mathrm{O}_{2}$ solution $(0.125 \mathrm{~mL}, 1.1 \mathrm{mmol})$ 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 $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ ( 2 mL ), and the resultant mixture was extracted with EtOAc ( $3 \times 2 \mathrm{~mL}$ ), and the combined organic extracts dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $\mathbf{2 5}(40 \mathrm{mg})$ as a white solid in $95 \%$ overall yield for 2 steps; $\mathrm{R}_{\mathrm{f}}=0.38$ (silica gel, EtOAc/hexanes $=1 / 1$ ); ${ }^{1} \mathrm{H}$ NMR ( 500 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.23(\mathrm{~s}, 1 \mathrm{H}), 5.09(\mathrm{~s}, 1 \mathrm{H}), 4.97(\mathrm{~s}, 1 \mathrm{H}), 4.25(\mathrm{~s}, 1 \mathrm{H}), 4.11(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.84-3.77$ (m, 2H), $3.67-3.57(\mathrm{~m}, 3 \mathrm{H}), 3.54(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.49-3.43(\mathrm{~m}, 1 \mathrm{H}), 2.94-2.74(\mathrm{~m}, 4 \mathrm{H}), 2.36(\mathrm{~d}$, $J=11.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.19-2.12(\mathrm{~m}, 2 \mathrm{H}), 2.08-2.01(\mathrm{~m}, 1 \mathrm{H}), 0.98-0.82(\mathrm{~m}, 5 \mathrm{H}), 0.02(\mathrm{~s}, 9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 141.7,113.9,102.5,76.4,73.7,71.3,71.2,69.3,64.9,52.6,50.1,44.2,44.2,43.3$, 32.6, 18.9, 18.7, -1.3; IR (neat, $\mathrm{cm}^{-1}$ ): 3400, 2950, 2892, 1457, 1248, 1080, 1015, 860, 835; HRMS-ESI calcd. for $\mathrm{C}_{20} \mathrm{H}_{34} \mathrm{O}_{5} \mathrm{NaSi}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 405.2068; Found: 405.2068.

## Synthesis of

(2aS,2a1S,4aS,5R,7aS,8S,10R,10aR)-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 $25(38 \mathrm{mg}, 0.1 \mathrm{mmol})$ in dry DCE $(2.5 \mathrm{~mL})$ was added $\mathrm{Ac}_{2} \mathrm{O}(38 \mu \mathrm{~L}, 0.4$ mmol) and DMAP ( $73 \mathrm{mg}, 0.6 \mathrm{mmol}$ ) at room temperature, and the mixture was stirred at $90^{\circ} \mathrm{C}$ for 12 h . To ensure the conversion, second batch of $\mathrm{Ac}_{2} \mathrm{O}(38 \mu \mathrm{~L}, 0.4 \mathrm{mmol})$ and DMAP ( $73 \mathrm{mg}, 0.6 \mathrm{mmol}$ ) was added to the reaction mixture, and the reaciton was stirred at at $90^{\circ} \mathrm{C}$ for additional 6 h . The reaction was quenched by addition of a saturated solution of $\mathrm{NH}_{4} \mathrm{Cl}(2.5 \mathrm{~mL})$, and the mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 2.5 \mathrm{~mL})$, and the combined extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $26(41 \mathrm{mg})$ as a colorless oil in $89 \%$ yield; $\mathrm{R}_{\mathrm{f}}=0.82$ (silica gel,

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

## Synthesis of

( $2 \mathrm{a} R, 2 \mathrm{a} 1 S, 3 S, 4 \mathrm{aS}, 5 R, 7 \mathrm{aS}, 8 S, 10 R, 10 \mathrm{aR}$ )-3-hydroxy-10a-methyl-4-methylene-5-(2-(trimethylsilyl)eth oxy)dodecahydronaphtho[1,8-bc:4,4a-c' $]$ difuran-8,10-diyl diacetate (27):


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

Since there was no obvious signal between H-7 with other hydrogen on NOESY spectrum, the relative configuration of C 7 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 $174.7^{\circ}$ and $54.9^{\circ}$, respectively, whereas in $\mathbf{B}$, the dihedral angles were $173.7^{\circ}$ and $179.4^{\circ}$. With a consideration of the coupling constants between the protons $(12.3 \mathrm{~Hz}$ and 2.5 Hz ) in compound $\mathbf{2 7}, \mathbf{A}$ is in more agreement with the experimental result. Therefore, the $\mathrm{H}-7$ was assigned as $\alpha$-oriented.


A


Calculation Type $=$ FOPT
Calculation Method $=$ RB3LYP
Basis Set $=6-31+G(d)$
Charge $=0$
Spin $=$ Singlet
$E($ RB3LYP $)=-1828.78510883$ a.u.

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

Scheme S1: Molecular modeling study of compound 27

| A: |  |  |  |
| :---: | :---: | :---: | :---: |
| C | 1.67391800 | 1.20269800 | -1.74731500 |
| C | 3.06758200 | 0.98183700 | -1.11881600 |
| C | 3.27386700 | -0.50835700 | -0.74699000 |
| C | 2.01680300 | -0.97995400 | -0.00250200 |
| C | 0.64678500 | -0.89760600 | -0.65890400 |
| C | 0.44935900 | 0.60748500 | -1.01166300 |
| C | 2.43667000 | -2.28847200 | 0.61429300 |
| C | 1.44801600 | -2.67171900 | 1.71923700 |
| C | 0.06546500 | -2.73947600 | 1.07147700 |
| C | -0.43180800 | -1.48623300 | 0.32812300 |
| C | 4.31235100 | -0.86808000 | 0.35276000 |
| O | 3.76153000 | -2.00117800 | 1.09474400 |
| C | 0.36790400 | -1.76251900 | -1.90574100 |
| O | -1.03425400 | -2.07003500 | -1.88263300 |
| C | -1.60967600 | -1.73840500 | -0.62124400 |
| O | -2.39364900 | -0.56759700 | -0.68235000 |
| C | -3.50581900 | -0.65720700 | -1.58675700 |
| C | -4.42866600 | 0.54026100 | -1.37400700 |
| C | -0.61848600 | -3.88570600 | 1.18024200 |
| O | 1.44197900 | -1.70423000 | 2.77029600 |
| C | 3.61938100 | -1.28722500 | -2.03496400 |
| O | 3.16306300 | 1.85263500 | 0.04308400 |
| O | 5.33820100 | 2.31123600 | -0.41671600 |
| C | 4.34547400 | 2.48058100 | 0.26177700 |
| C | 4.25016600 | 3.41465900 | 1.44394900 |
| Si | -5.31874500 | 0.67582500 | 0.31142500 |
| C | -5.96913600 | -1.02862900 | 0.83378600 |
| C | -4.17878900 | 1.36094900 | 1.65824900 |
| C | -6.78378600 | 1.86083200 | 0.08530000 |
| O | 0.22738100 | 1.31502300 | 0.23544600 |
| O | -0.80272900 | 3.02202200 | -0.84262500 |
| C | -0.41083000 | 2.50592200 | 0.18524600 |
| C | -0.55684000 | 3.09462200 | 1.56750600 |
| H | 1.69409300 | 0.77700300 | -2.75777100 |
| H | 1.50839000 | 2.27571700 | -1.88139100 |
| H | 3.83560800 | 1.30689800 | -1.82504600 |
| H | -0.43711200 | 0.74884000 | -1.63169500 |
| H | 4.47124100 | -0.05245500 | 1.06327500 |


| C | 0.64517800 | 0.77871300 | 0.69155700 |
| :---: | :---: | :---: | :---: |
| C | 0.42016500 | -0.74000100 | 0.95743900 |
| C | 2.45752400 | 2.20153200 | -0.50908900 |
| C | 1.47987800 | 2.61191200 | -1.60406800 |
| C | 0.10559700 | 2.72703600 | -0.94078300 |
| C | -0.41970700 | 1.44779200 | -0.25894100 |
| C | 4.31321900 | 0.74306600 | -0.31171200 |
| O | 3.79382700 | 1.93725300 | -0.97057800 |
| C | 0.38602000 | 1.57775000 | 1.98659700 |
| O | -1.00748600 | 1.91994600 | 1.98236700 |
| C | -1.59012200 | 1.67834400 | 0.70545200 |
| O | -2.40612100 | 0.52691100 | 0.70080600 |
| C | -3.52168800 | 0.60213400 | 1.60242800 |
| C | -4.46617300 | -0.56768300 | 1.33776500 |
| C | -0.54883800 | 3.89264000 | -0.99355400 |
| O | 1.84155400 | 3.83506100 | -2.23010000 |
| C | 3.61715900 | 1.04863000 | 2.09088900 |
| Si | -5.34468600 | -0.62164500 | -0.35788400 |
| C | -4.20263500 | -1.27016700 | -1.72189700 |
| C | -6.82892800 | -1.79287200 | -0.19495900 |
| C | -5.96637900 | 1.11093700 | -0.81810000 |
| O | 0.19220200 | -1.37142300 | -0.33112600 |
| O | -0.84703100 | -3.13272500 | 0.64638200 |
| C | -0.45222700 | -2.56088700 | -0.34977700 |
| C | -0.60609200 | -3.06733800 | -1.76369200 |
| O | 3.12075100 | -1.96946600 | -0.15445000 |
| O | 5.27976500 | -2.50347200 | 0.30111000 |
| C | 4.29359300 | -2.60731700 | -0.39917000 |
| C | 4.19633200 | -3.45615100 | -1.64373300 |
| H | 1.65271600 | -1.03021100 | 2.69579700 |
| H | 1.44857700 | -2.47282300 | 1.73400300 |
| H | 3.79119200 | -1.53901500 | 1.74478600 |
| H | -0.47223400 | -0.90214700 | 1.56360000 |
| H | 4.44670500 | -0.02944600 | -1.07442800 |
| H | 5.28967000 | 0.99058100 | 0.11473400 |
| H | 0.97395800 | 2.50256200 | 2.01642600 |
| H | 0.58527500 | 1.01240400 | 2.90237600 |
| H | -2.22011000 | 2.54598000 | 0.48588200 |
| H | -3.14692300 | 0.58506500 | 2.63391900 |
| H | -4.03525600 | 1.56635700 | 1.45475700 |
| H | -5.24921000 | -0.53633200 | 2.11097800 |
| H | -3.92342800 | -1.50999900 | 1.49909300 |
| H | -0.11421800 | 4.73473900 | -1.52066800 |
| H | -1.51798800 | 4.05242400 | -0.53433600 |
| H | 2.76311200 | 3.74373500 | -2.52221000 |
| H | 3.73412700 | 2.12744400 | 1.94807800 |
| H | 4.57114000 | 0.66331700 | 2.47020800 |
| H | 2.86712800 | 0.89531900 | 2.87172900 |
| H | 2.48920100 | 3.00863000 | 0.23720800 |
| H | -0.71886800 | 0.73546400 | -1.03411000 |
| H | 1.93316100 | 0.22506800 | -0.84499500 |
| H | 1.45267200 | 1.80871800 | -2.36104700 |
| H | -3.84565400 | -2.28025000 | -1.48418400 |
| H | -3.32666100 | -0.62247200 | -1.84151100 |
| H | -4.72548000 | -1.31984500 | -2.68611200 |
| H | -7.36299500 | -1.89231900 | -1.14892500 |
| H | -7.54933000 | -1.43056200 | 0.54998500 |
| H | -6.51484500 | -2.79907800 | 0.11201900 |
| H | -5.13760000 | 1.81264400 | -0.97524500 |
| H | -6.61532900 | 1.53035100 | -0.03817100 |
| H | -6.54912000 | 1.08049400 | -1.74789100 |
| H | -1.27340900 | -2.40531600 | -2.32618200 |
| H | -1.02589800 | -4.07437500 | -1.74593000 |
| H | 0.36318000 | -3.07109200 | -2.27269200 |
| H | 3.46147500 | -4.25487100 | -1.49253400 |
| H | 5.17144800 | -3.89323600 | -1.86330400 |
| H | 3.85668100 | -2.85274400 | -2.49212800 |

## Synthesis of

## (2aR,2a1S,4aS,5R,7aS, $8 S, 10 R, 10 a R)-4,10 a-d i m e t h y l-3-0 x 0-5-(2-(t r i m e t h y l s i l y l) e t h o x y) d o d e c a h y d r o$ naphtho[1,8-bc:4,4a-c']difuran-8,10-diyl diacetate (6):



To a solution of compound $27(17 \mathrm{mg}, 0.035 \mathrm{mmol})$ in EtOAc $(0.7 \mathrm{~mL})$ was added $\mathrm{Pd} / \mathrm{C}(10 \%$ on carbon, 3 mg ), and the mixture was then degassed with $\mathrm{H}_{2}$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}(0.7 \mathrm{~mL})$ was sequentially added $4 \AA$ molecular sieve ( 17 mg ), $\operatorname{TPAP}(1.5 \mathrm{mg}, 0.0043 \mathrm{mmol})$ and NMO $(8.3 \mathrm{mg}, 0.07 \mathrm{mmol})$ 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 $\mathbf{6}$ as a pair of diastereomers ( $14 \mathrm{mg}, \alpha-\mathrm{Me}: \beta-\mathrm{Me}=10: 3$ ) in $82 \%$ overall yield for 2 steps; $\mathrm{R}_{\mathrm{f}}=0.61$ and 0.51 (silica gel, EtOAc/hexanes $=1: 1$ ). The ratio was confirmed by ${ }^{1} \mathrm{H}-\mathrm{NMR}$ spectrum.

Two diastereomers could be separated by flash chromatography, and the relative stereochemistry of the major isomer $6(\alpha-\mathrm{Me})$ was determined by 2D-NMR spectra.
$\alpha$-Me $6:{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.24(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.96(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.82(\mathrm{~s}, 1 \mathrm{H})$, $4.42(\mathrm{~d}, J=14.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.22(\mathrm{~d}, J=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.86(\mathrm{~d}, J=9.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.78-3.71(\mathrm{~m}, 1 \mathrm{H}), 3.66(\mathrm{~s}$, $2 \mathrm{H}), 3.38-3.30(\mathrm{~m}, 1 \mathrm{H}), 2.74(\mathrm{~d}, J=14.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.45(\mathrm{~d}, J=11.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.40-2.30(\mathrm{~m}, 2 \mathrm{H}), 2.10-$ $2.01(\mathrm{~m}, 7 \mathrm{H}), 1.23(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H}), 1.07(\mathrm{~s}, 3 \mathrm{H}), 0.90-0.83(\mathrm{~m}, 2 \mathrm{H}),-0.00(\mathrm{~s}, 9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (100 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 206.5,170.1,169.5,105.6,77.3,71.8,70.6,69.3,65.0,59.4,47.9,47.5,43.7,43.0,28.5$, $21.3,21.1,18.0,17.8,13.0,-1.3$; IR (neat, $\mathrm{cm}^{-1}$ ): 2925, 2855, 1738, 1732, 1377, 1250, 1058, 1024, 999, 860, 837, 802; HRMS-ESI calcd. for $\mathrm{C}_{24} \mathrm{H}_{38} \mathrm{O}_{8} \mathrm{NaSi}\left[\mathrm{M}+\mathrm{Na}^{+}\right]$: 505.2228; Found: 505.2228; $[\alpha]^{26}{ }_{589}$ $+96.1\left(c=0.25, \mathrm{CHCl}_{3}\right)$.

## Reference:

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

Reference 4e: S. V. Ley, A. Abad-Somovilla, J. C. Anderson, C. Ayats, R. Bänteli, E. Beckmann, A. Boyer, M. G. Brasca, A. Brice, H. B. Broughton, B. J. Burke, E. Cleator, D. Craig, A. A. Denholm, R. M. Denton, T. Durand-Reville, L. B. Gobbi, M. Gçbel, B. Lawrence Gray, R. B. Grossmann, C. E. Gutteridge, N. Hahn, S. L. Harding, D. C. Jennens, L. Jennens, P. J. Lovell, H. J. Lovell, M. L. de la Puente, H. C. Kolb, W.-J. Koot, S. L. Maslen, C. F. McCusker, A. Mattes, A. R. Pape, A. Pinto, D. Santafianos, J. S. Scott, S. C. Smith, A. Q. Somers, C. D. Spilling, F. Stelzer, P. L. Toogood, R. M. Turner, G. E. Veitch, A. Wood, C. Zumbrunn, Chem.-Eur. J. 2008, 14, 10683-10704.

${ }^{1}$ H NMR of compound S1


${ }^{13} \mathrm{C}$ NMR of compound $\mathbf{S 1}$


${ }^{1} \mathrm{H}$ NMR of compound 9

$-217.068$



${ }^{13} \mathrm{C}$ NMR of compound 9


${ }^{1} \mathrm{H}$ NMR of compounds 9 ([]-Me;[-Me $\left.=3: 10\right)$





${ }^{13} \mathrm{C}$ NMR of compounds 9 (回-Me: $-\mathrm{Me}=3: 10$ )


${ }^{1} \mathrm{H}$ NMR of compound 10


${ }^{13} \mathrm{C}$ NMR of compound 10


${ }^{1} \mathrm{H}$ NMR of compound 14


${ }^{13} \mathrm{C}$ NMR of compound 14



${ }^{1} \mathrm{H}$ NMR of compounds 15 （回－OAc：回－OAc．$=2.5: 1$ ）

－
\％
4.5
4
＂

运

${ }^{1} \mathrm{H}$ NMR of compound 16


${ }^{13} \mathrm{C}$ NMR of compound 16



${ }^{1} \mathrm{H}$ NMR of compound 18


| \％ | 玉 | 종 | \％ | 或 |  | \％ | 5 | \％ | ํํ |  | Б |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| \％ | 家 | 骂 | ๕ | $\stackrel{\rightharpoonup}{1}$ | MEERQ | $\bar{\square}$ | $\stackrel{5}{5}$ |  |  | ＋ |  |
| 1 | 1 | － |  |  | 4 |  |  |  |  | 1 |  |


${ }^{13} \mathrm{C}$ NMR of compound 18

| 210 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 |  | $(\mathrm{ppm})^{100}$ |  | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 等贸易 |  |  |  |  |  |  |  | ご5 | ¢ | $\stackrel{3}{3}$ | \％－ | 5988 |  | \％ |  |  |  |  | $\begin{aligned} & \text { Yiv } \\ & 0.0 \\ & i 0 \end{aligned}$ |  |  |


${ }^{1} \mathrm{H}$ NMR of compound 20


${ }^{13} \mathrm{C}$ NMR of compound 20




${ }^{1} \mathrm{H}$ NMR of compounds 21 ( $\mathrm{B}-\mathrm{OH}:$ [OH $=1: 9$ )



${ }^{13} \mathrm{C}$ NMR of compounds 21 （回－OH：国－OH＝1：9）



##  <br> tutititity <br> 


${ }^{1} \mathrm{H}$ NMR of compounds 22 （回－OH： $\mathrm{OH}=1: 9$ ）





 - ヘivi

${ }^{1} \mathrm{H}$ NMR of compound 23


${ }^{13} \mathrm{C}$ NMR of compound 23


\$

$\mathrm{PhMe}_{2} \mathrm{Si}^{\text {' }}$

${ }^{1}$ H NMR of compound S3


${ }^{13} \mathrm{C}$ NMR of compound $\mathbf{S 3}$


$\mathrm{PhMe}_{2} \mathrm{Si}$

${ }^{1} \mathrm{H}$ NMR of compound 24



${ }^{13} \mathrm{C}$ NMR of compound 24


${ }^{1} \mathrm{H}$ NMR of compound 25


${ }^{13} \mathrm{C}$ NMR of compound 25


${ }^{1} \mathrm{H}$ NMR of compound 26



${ }^{13} \mathrm{C}$ NMR of compound 26


## $\stackrel{8}{9}$

##  

## 下. <br> oiojigic


${ }^{1} \mathrm{H}$ NMR of compound 27




Dept135 NMR of compound 27




${ }^{89} \mathrm{C}^{2}-$


${ }^{1} \mathrm{H}$ NMR of compounds 6 ( -Be - Me 雨- $\mathrm{Me}=10: 3$ )






Dept 135 NMR of compound 6 (?-Me)





