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Note

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Total Synthesis of Nominal *ent*-Chlorabietol B

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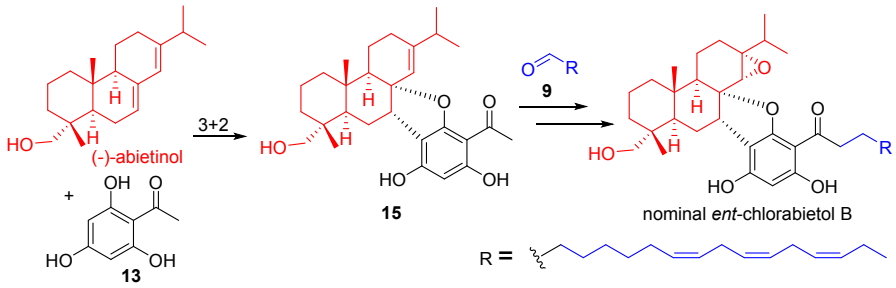
Abstract:



The nominal enantiomer of chlorabietol B was regio- and stereoselectively synthesized from (-)-abietic acid in 13 steps. Key features of the synthesis involved an oxidative [3+2] cycloaddition to install the dihydrobenzofuran moiety, and an Aldol reaction followed by elimination and reduction steps to introduce the long chain with three *cis* double bonds. However, obvious differences in the NMR spectra of the synthetic and natural samples suggested that the proposed structure of chlorabietol B should be revised carefully.

Chlorabietol A-C (**1-3**) were isolated by Hu and co-workers[1] from the extract of the roots of *Chloranthus oldhamii*, which is a rare species native to China.[2] (Figure 1) These compounds represent a new class of natural products, featuring an abietane-type diterpenoid coupled with different alkenyl phloroglucinol moiety by forming a 2,3-dihydrofuran ring. Bioactivity research showed that chlorabietols A-C have moderate inhibitory activities against protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 12.6, 5.3, 4.9 μM, respectively. As the compounds **4-7** were isolated together with chlorabietols A-C from the same collected plant sample, these compounds were envisioned to be the biogenetic precursors of the chlorabietols A-C. (Figure 1)

Their biosynthetic paths were proposed as an abietane-type diterpenoid such as compound **4**,

coupled with different alkenyl phloroglucinol moieties (such as compounds **5**-**7**) by an oxidative [3+2] cycloaddition reaction,[3] which has been proven to be a powerful method for the preparation of 2,3-dihydrofuran moiety with conjugated diene and phenol.[4] The challenges for this biomimetic [3+2] cycloaddition were reflected in two aspects. First, the methylene units positioned between two double bonds on an aliphatic side chains are sensitive to oxidative conditions. Second, the diene should be a conjugated one and distribute in a same ring. However, in this case the conjugated diene of **4** are dispersed into two rings. The challenge of biomimetic synthesis, unprecedented structures and the bioactivities stimulated our interest in their total synthesis. Herein, we report the biomimetic total synthesis of nominal enantiomer of chlorabietol B by an oxidative [3+2] cycloaddition reaction from (-)-abietic acid.

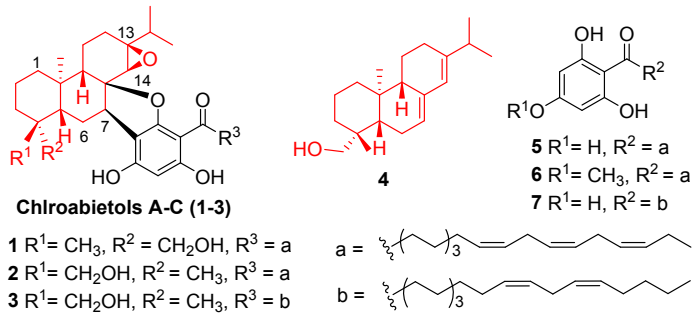
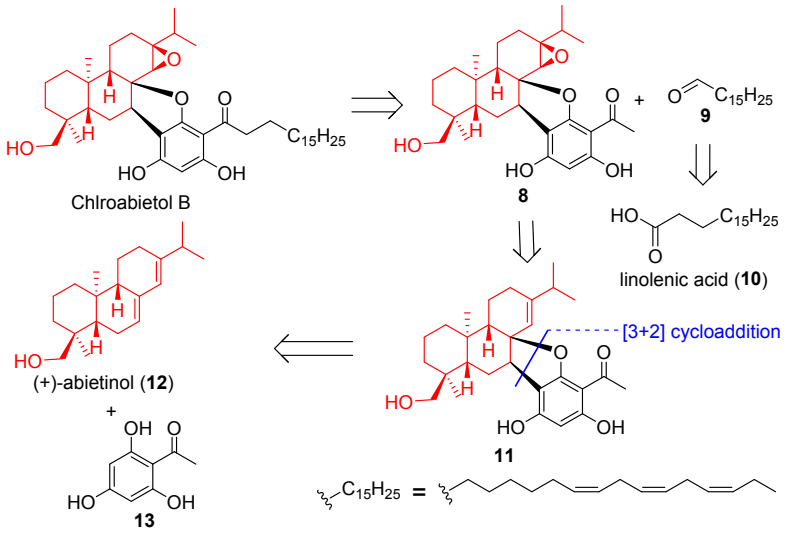


Figure 1. Proposed structures of chlorabietols A-C and their biosynthetic precursors 4-7 from C. *oldhamii*.

Scheme 1 outlines our retrosynthetic analysis of chlorabietol B (**2**). We favored the total synthesis of chlorabietol B (**2**) to involve the late-stage coupling of the ketone **8** with C_{16} synthon **9** to introduce the long aliphatic chain, so that the oxidative [3+2] cycloaddition and epoxidation procedure would proceed as hoped. The C_{16} building block **9** could be derived from commercially available linolenic acid (**10**). The compound **8**, contained all the stereocenters of the target

molecule, could be achieved via a stereoselective epoxidation of compound **11**. The key intermediate **11** was envisioned to be synthesized via the powerful oxidative [3+2] cycloaddition reaction between (+)-abietinol (**12**) and **13** to install the 2,3-dihydrofuran ring skeleton.

Scheme 1. Retrosynthetic Analysis of Chlorabietol B (2)

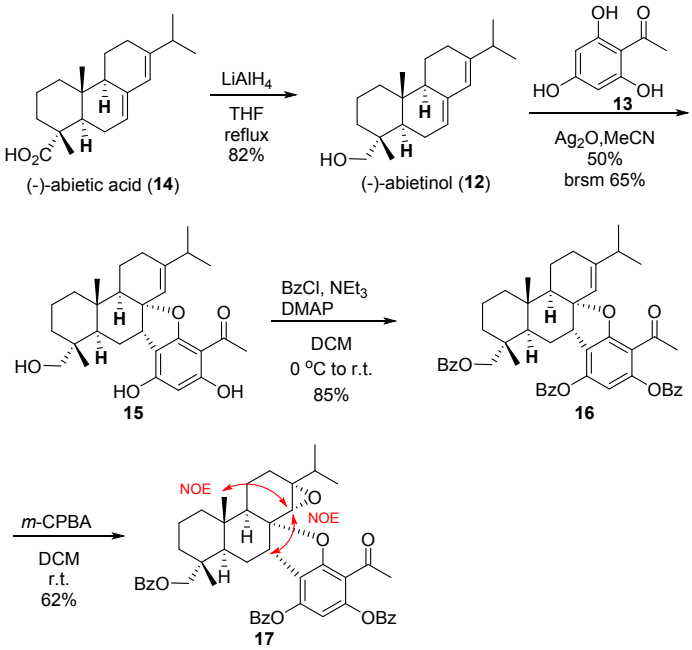


As shown in Scheme 2, (+)-abietinol (**12**) was unavailable in commercial sources. However, its enantiomer, (-)-abietinol (**12**) was easily obtained from commercially available (-)-abietic acid (**14**) by treating with $LiAlH_4$ in THF.[5] Using available (-)-abietinol (**12**) as starting material, the ent-chlorabietol B should be synthesized. Thus, we focused on the key oxidative [3+2] cycloaddition reaction between diene **12** and 2',4',6'-trihydroxylacetophenone (**13**) for the synthesis of enantiomer of chlorabietol B. Based on our previous work,[4d] Ag salts should be benefit for getting the desired product which resulted from the ortho phenol group involved in the cycloaddition process. So, Ag_2O was chosen as oxidation reagent to initiate the reaction. Pleasingly, treatment of (-)-abietinol (**12**) and **13** with Ag_2O in MeCN gave the desired [3+2] product **15** in moderate yield.

With compound **15** in hand, we tried to oxidize the double bond to achieve the epoxide product. When using compound **15** or compound **15** protected OH groups by TBS or MOM, as substrates,

the double bond were failed to epoxidize by using H_2O_2[6a], *m*-CPBA[6b, 6c], $^tBuOOH/VO(acac)_2$[6d], $^tBuOOH/DBU$[6e], DMDO[6f] as oxidants. The stepwise epoxidation synthesis methods[4b,7] were also ineffective. We speculated that the benzene moiety in this kind of structure might be too electron-rich to be untouched under the oxidative conditions.[4a] Thus, the phenols should be protected by an electron-withdrawing group to lower the electron density of the benzene moiety for epoxidation of double bond. So, compound **15** was treated with benzoyl chloride, NEt_3 and catalytic DMAP to afford benzoyl protected compound **16** smoothly in 85% yield.[8] To our delight, a single crystal of **16** was obtained, which allowed us to unambiguously confirm regioselectivity and stereoselectivity of the oxidative [3+2] cycloaddition reaction by single crystal X-ray diffraction. (for X-ray crystallography and detailed crystallographic data see SI) As hoped, compound **16** was smoothly transferred to **17** by applying *m*-CPBA in DCM at room temperature. The relative stereochemistry of this epoxide was confirmed by NOE analysis. (Scheme 2)

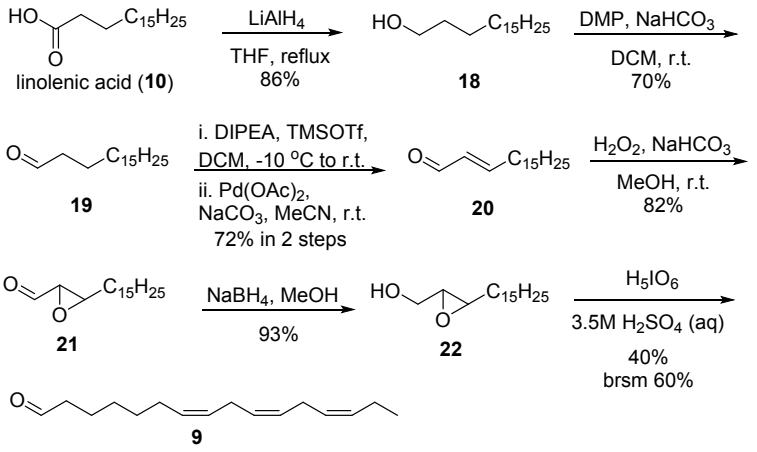
Scheme 2. Synthesis of the Core 17 with All Stereocentras



At this stage of our synthetic route, the next mission was to prepare the long C_{16} aliphatic chain. Scheme 3 outlined the synthetic route of this chain. The commercially available linolenic

acid (**10**) was reduced by $LiAlH_4$ in THF to produce the primary alcohol **18**, which was oxidized to deliver the aldehyde **19**. Compound **19** was treated with DIPEA, TMSOTf in DCM to give the silyl enol ether intermediate, followed by adding $Pd(OAc)_2$ and Na_2CO_3 to take part in a Saegusa oxidation reaction to afford the α, β-unsaturated aldehyde **20**.[9] The electron deficient double bond of **20** was selectively oxidized to deliver the desired epoxide product **21** in good yield using H_2O_2 under basic condition.[10] Attempts to directly cleave the epoxide moiety of **21** was unsuccessful. However, epoxide **21** was reduced by $NaBH_4$ to give the epoxide primary alcohol **22**, which was successfully transferred to the C_{16} aldehyde **9** via cleaving C-C bond of the epoxide moiety with applying H_5IO_6 under acid condition.[11]

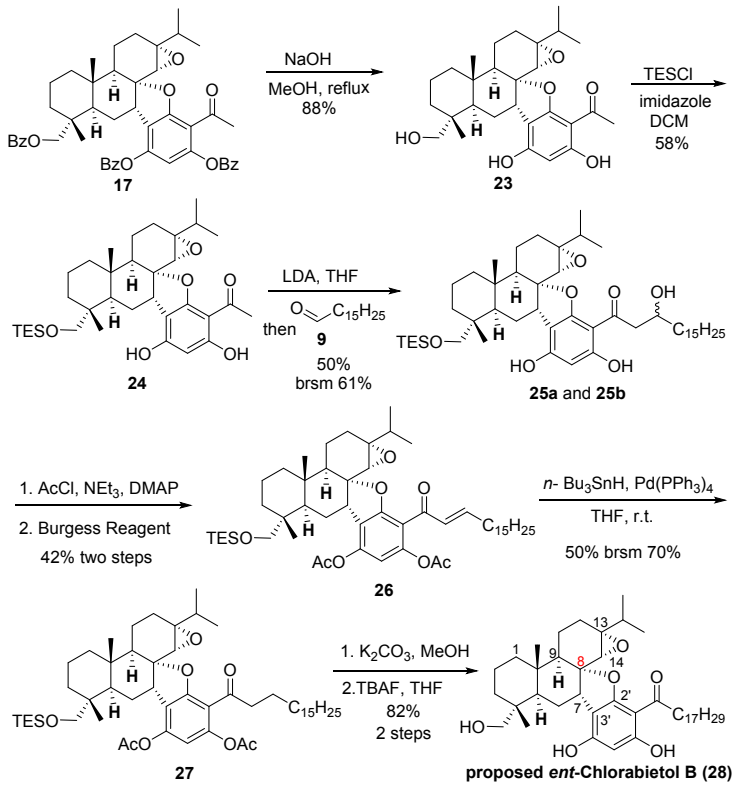
Scheme 3. Synthesis of C16 Long Aliphatic Aldehyde 9



With the C_{16} building block **9** in hand, we then turned our attention to couple ketone **17** with aldehyde **9**. Treating with LDA or LiHMDS, the compound **17** underwent a Baker-Venkataraman rearrangement[12] instead of an aldol reaction with **9**. Thus, the benzoyl group in compound **17** should be switched to another protecting group before attaching the long aliphatic chain. As shown in Scheme 4, three benzoyl groups were removed by treating with NaOH in MeOH to deliver alcohol **23** in high yield. The TES was chosen to replace benzoyl group. Treating with TESCl, imidazole in DCM, the primary hydroxyl and two phenol hydroxyls were protected by

TES. However, the TES group on the phenol in this compound turned out to be unstable. So, the TES protected primary alcohol species **24** was obtained in moderate yield. Fortunately, treating with LDA, the compound **24** was coupled with aldehyde **9** to produce a pair of diastereoisomers **25a** and **25b**,[13] which could not be isolated by column chromatography. Following direct deoxygenation of the β-hydroxyl group in **25a** and **25b** via Barton-McCombie deoxygenation procedure[14] did not work as expected. And attempts to eliminate the β-hydroxyl group to produce the corresponding elimination product under different conditions such as p-TSA,[15a, 15b] $MsCl/NEt_3$,[15c] $py{\cdot}SO_3$,[15d] TsCl/pyridine,[15e] $SOCl_2/NEt_3$[15f] also failed to produce corresponding elimination products. It was envisioned that the phenol groups in the compounds **25a** and **25b** should be protected before elimination step. Thus, the phenol groups in compounds **25a** and **25b** were selectively protected with acetyl chloride and NEt_3 to produce the corresponding desired products, which was dehydrated with Burgess Reagent[16] to obtain the compound **26**.

Scheme 4. Synthesis of the Proposed Enantiomer of Chlorabietol B



The last challenge was to selectively reduce the electron deficient double bond in the presence of three *cis* C=C bonds in the long side chain. In previous reports[17] different metal hydrides species were used to selectively reduce electron deficient double bonds via a 1,4-conjugated addition mechanism. However, in this case different metal hydrides species such as Stryker's Reagent[17a], MeCu/DIBAL-H[17b], $CuCl_2 \cdot 2H_2O$/PMHS[17c], *n*-Bu_3SnH[17d] could not reduce the electron deficient double bond. Other reductive conditions such as $NiCl_2 \cdot 6H_2O/NaBH_4$,[18a] $(Ph_3P)RhCl/Et_3SiH$[18b] and $[IrCp^*Cl_2]_2$/*i*-PrOH[18c] led to over reduction: the electron deficient double bond was reduced along with one of the three C=C bonds in the side chain. Reducing both the deficient double bond and the epoxide apparently occurred by $HSiCl_3$ under Lewis base Ph_3P=O or HMPA.[19] Gratifyingly, the desired reducing compound **27** was achieved in an acceptable yield by using $Pd(PPh_3)_4$/*n*-Bu_3SnH.[20] (Scheme 4) Finally, deprotecting all the hydroxyl groups in **27** afforded the proposed *ent*-chlorabietol B (**28**).

To our disappointment, the ^1H and ^{13}C NMR spectra of our synthetic sample **28** were not coincident in all respects with the data reported by Hu and co-workers for the "natural" chlorabietol B (**2**).[1] Moreover, we carefully checked the effects of pH, concentration, temperature, and impurities and excluded these reasons. By HMQC and HMBC experiment of the synthetic sample **28** along with the previous compounds in our synthetic route, we confirmed which carbons and hydrogens was different from the natural chlorabietol B (**2**). Significant differences ($\Delta\delta$> 0.08 ppm) in the ^1H NMR chemical shifts were observed between the synthesized *ent*-chlorabietol B (**28**) and the "natural" chlorabietol B (**2**) for the hydrogen atoms at C1, C2, C6, C9, C11, C12, C15 and some clear discrepancies ($\Delta\delta$>1.0 ppm) were also observed in the ^{13}C NMR chemical shifts for C2, C7, C8, C9, C11, C12, C20 and C3'. (See the part III in Supporting Information for details)

And more, a positive specific rotation ($[\alpha]_D^{23}$ = +26.0° (c 1.00, MeOH)) of synthetic sample was correlated with the reported specific rotation ($[\alpha]_D^{25}$ = +18.7° (c 0.08, MeOH)). According to the isolated paper,[1] the only uncertainty of proposed structure of chlorabietol B (**2**) was the configuration of C8. Therefore, we speculated that the original isolated sample of chlorabietol B (**2**) structure was more likely to have difference at C8 with our synthetic sample's structure which was reported in the isolation paper. But unfortunately, the oxidative [3+2] cycloaddition between (-)-abietinol (**12**) and compound **13** gave the sole product **15**. Further studies on synthesis of C-8 epimer by new strategy are ongoing in our group.

In summary, we have accomplished the total synthesis of nominal *ent*-chlorabietol B (**28**) in 13 steps with an overall yield of 3% (as the longest linear route from linolenic acid **10**). An oxidative [3+2] cycloaddition was applied to construct the main core of natural product. And the long side chain was attached to the core by aldol reaction, followed by elimination and selective reduction of electron deficient double bond. This synthetic strategy should pave a way to the synthesis of natural products featuring a 2,3-dihydrofuran ring moiety. Additionally, this work should be helpful to determine the real structure of chlorabietols.

EXPERIMENTAL SECTION

General Experimental Details: Unless otherwise noted, reactions were performed under an atmosphere of argon with magnetic stirring and commercially available materials were used without further purification. Solvents used for moisture sensitive operations were conducted according to *Purification of Laboratory Chemicals* (W. L. Armarego, C. L. Chai, Elsevier Press: Oxford, 2013). Flash chromatography (FC) was performed by using *Yantai Chemicals* (200–300 mesh). Reactions were monitored by thin-layer chromatography on plates (GF_{254}), which were purchased from *Energy chemcal* and visualized by UV or stained with the ethanolic solution of phosphomolybdic acid and ferric chloride hexahydrate. Infrared spectra were recorded on a

Nicolet Nexus 670 FT-IR spectrometer with wavenumbers expressed in cm^{-1} using samples prepared as thin films between salt plates. Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Mercury-600BB*, *Brüker Advance III-400* and *Brüker AVANCE CEO 600* spectrometer equipped with a *BB-H&F-D-05 Z ET* CryoProbe at operating frequencies of 400/600 MHz (^{1}H NMR) or 100/150 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ 7.27 for ^{1}H NMR or δ 77.0 for proton decoupled ^{13}C NMR), and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved and br when the signal in question is broadened. HR-ESI-MS data were performed on a *Bruker APEX-II* mass spectrometer. Optical rotations were measured on a *Rudolph Autopol IV* polarimeter. The X-ray single-crystal determination was performed on an *Agilent SuperNova* single crystal X-ray diffractometer.

(-)-Abietinol (12) To a mixture of $LiAlH_4$ (4.13 g, 108.8 mmol) and THF (80 ml) in a round bottom flask under 0 ^oC was slowly added abietic acid (**14**) (4.63 g, 15.32 mmol) which solved in THF (120 ml). The resulting reaction mixture was stirred at 0 ^oC for 10 min, and then heated to reflux for another one hour. After the abietic acid (**14**) was consumed confirmed by TLC analysis, saturated potassium sodium tartrate solution was added to reaction mixture under 0 ^oC. After gas releasing ceased, the mixture was stirred at room temperature overnight. This mixture was extracted by ethyl acetate. And the combined organic extract was washed with 2N HCl, saturated $NaHCO_3$ solution and brine. Separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification was performed by column chromatography (petroleum ether/ethyl acetate = 4:1) and afforded **(-)-**abietinol[5] (**12**) (3.62 g, 12.56 mmol, 82%) as a colorless oil: $[\alpha]_D^{24}$ = -141.0^o (c 1.00, DCM); **IR** (thin film, ν cm^{-1}): 3385, 2930, 2870, 1739, 1718, 1460, 1384, 1241, 1044 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.77 (s, 1H), 5.40 (s, 1H), 3.35 (d, J = 10.9 Hz, 1H), 3.12 (d, J = 10.9 Hz, 1H), 2.22 (dt, J = 13.6, 6.8 Hz, 1H), 2.14 – 1.94 (m, 4H), 1.94 – 1.70 (m, 5H), 1.65 –

1.48 (m, 3H), 1.45 – 1.30 (m, 2H), 1.28 – 1.14 (m, 1H), 1.02 (d, J = 3.9 Hz, 3H), 1.00 (d, J = 4.0 Hz, 3H), 0.87 (s, 3H), 0.83 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 145.1, 135.5, 122.4, 120.9, 72.0, 50.7, 43.5, 38.8, 37.4, 35.6, 34.8, 34.6, 27.5, 23.7, 22.6, 21.4, 20.8, 18.1, 17.6, 14.2; **HRMS** (ESIMS) m/z: $[M + K]^+$ Calcd for $C_{20}H_{32}OK$ 327.2085; Found 327.1927.

1-((4aR,4bS,8R,8aR,9aS,14aS)-10,12-Dihydroxy-8-(hydroxymethyl)-2-isopropyl-4b,8-dimethyl-4,4a,4b,5,6,7,8,8a,9,9a-decahydro-3H-phenanthro[8a,9-b]benzofuran-13-yl)ethan-1-one (15) To a round bottom flask containing 2',4',6'-trihydroxylacetophenone (**13**) (1.52 g, 8.19 mmol) and Ag_2O (1.74 g, 7.51 mmol) equipped a magnetic stir bar was added **(-)-**abietinol (**12**) (1.97 g, 6.83 mmol) solved in MeCN (27 ml) under Ar atmosphere. After addition completion, the reaction mixture was stirred at ambient temperature for 7 days. And then the mixture was filtered through a pad of silica gel. The resulting organic solution was concentrated in vacuo. And the crude mixture was purified by column chromatography (petroleum/ethyl acetate = 8:1) to afford the [3+2] compound **15** (1.55 g, 3.41 mmol, 50%, brsm 65%) as a yellow solid: $[\alpha]_D^{21}$ = 157.0^o (c 1.00, MeOH); m.p. 157–164 ^{o}C; **IR** (thin film, ν cm^{-1}): 3430, 2928, 1740, 1614, 1433, 1364, 1298, 1262, 1181, 1062, 901 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.12 (s, 1H), 9.58 (brs, 1H), 5.85 (s, 1H), 5.61 (s, 1H), 3.70 (d, *J* = 11.8 Hz, 1H), 3.48 (s, 1H), 2.98 (d, *J* = 11.8 Hz, 1H), 2.56 (s, 3H), 2.48 (d, *J* = 13.4 Hz, 1H), 2.30 (ddd, *J* = 26.9, 15.9, 7.8 Hz, 2H), 2.17 – 1.89 (m, 4H), 1.82 (d, *J* = 12.8 Hz, 1H), 1.72 – 1.46 (m, 6H), 1.18 (d, *J* = 8.5 Hz, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.92 – 0.83 (m, 1H), 0.76 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 202.1, 164.6, 163.3, 158.9, 154.2, 122.0, 106.8, 103.3, 96.2, 90.3, 71.4, 49.1, 48.7, 41.0, 39.4, 37.5, 37.3, 35.3, 35.3, 31.4, 24.8, 21.4, 20.9, 20.0, 18.0, 17.9, 17.8, 15.6; **HRMS** (ESIMS) m/z: $[M + H]^+$ Calcd for $C_{28}H_{39}O_5$ 455.2792; Found 455.2796.

(4aR,4bS,8R,8aR,9aS,14aS)-13-Acetyl-8-((benzoyloxy)methyl)-2-isopropyl-4b,8-dimethyl-4,4a, 4b,5,6,7,8,8a,9,9a-decahydro-3H-phenanthro[8a,9-b]benzofuran-10,12-diyl dibenzoate (16) To a round bottom flask contained the triol compound **15** (1.88 g, 4.14 mmol) was added DMAP (303.4 mg, 2.48 mmol). And then the flask was capped with a rubber stopper. Under Ar atmosphere DCM (30 ml) was added to the flask in one portion, followed by NEt_3 (2.6 ml, 1.89 g, 18.64 mmol). The resulted pale yellow reaction mixture was cooled to 0 ^oC. At this temperature, BzCl (1.9 ml, 2.27 g, 16.15 mmol) was added dropwisely to the flask. After addition completion, the reaction mixture was allowed to warm to the room temperature and stirred over night. After completely consumption of triol compound **15** monitored by TLC, the reaction was quenched with saturated NH_4Cl solution. The aqueous layer was extracted by ethyl acetate three times. And the combined organic layer was washed with saturated $NaHCO_3$ solution, water, brine in sequence and dried over Na_2SO_4. The separated organic solution was concentrated in vacuo to give the crude product which was purified by column chromatography (petroleum/ethyl acetate = 8:1) to afford pure compound **16** (2.70 g, 3.52 mmol, 85%) as a colorless solid: $[\alpha]_D^{24}$ = +77.0^o (c 1.00, DCM); m.p. 132–135 ^oC; **IR** (thin film, ν cm^{-1}): 3407, 2960, 1741, 1601, 1465, 1404, 1244, 1084, 708 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (t, *J* = 7.7 Hz, 4H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.62 (dd, *J* = 6.4, 1.8 Hz, 2H), 7.51 (dd, *J* = 8.9, 6.6 Hz, 5H), 7.43 (t, *J* = 7.4 Hz, 2H), 6.17 (s, 1H), 5.68 (s, 1H), 4.00 (d, *J* = 11.0 Hz, 1H), 3.77 (dd, *J* = 15.1, 7.3 Hz, 2H), 2.60 (s, 3H), 2.29 (ddd, *J* = 24.9, 13.6, 6.2 Hz, 2H), 2.11 (dt, *J* = 22.1, 11.0 Hz, 4H), 1.89 (d, *J* = 12.7 Hz, 1H), 1.78 – 1.49 (m, 5H), 1.44 (s, 2H), 1.09 (dd, *J* = 6.6, 4.5 Hz, 6H), 1.03 (s, 3H), 1.00 – 0.94 (m, 1H), 0.82 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.6, 166.5, 164.8, 163.5, 160.2, 153.8, 149.5, 149.2, 134.1, 133.4, 132.7, 130.4, 130.4, 130.1, 130.1, 129.5, 129.3, 129.3, 128.8, 128.8, 128.5, 128.5, 128.4, 128.4, 128.0, 122.3, 122.2, 114.7, 109.3, 90.3, 72.3, 51.1, 48.9, 43.4, 39.5, 36.9, 36.5, 35.6, 35.1, 35.1, 32.1, 24.6, 21.3, 20.8, 20.4, 18.1, 17.6, 17.5, 15.7; **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{49}H_{50}O_8Na$ 789.3398; Found 789.3395.

CCDC 1972686 contains the supplementary crystallographic data for **16** and is available free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(2aR,2bS,6R,6aR,7aS,12aS,12bS,13aR)-11-Acetyl-6-((benzoyloxy)methyl)-13a-isopropyl-2

b,6-dimethyl-2,2a,2b,3,4,5,6,6a,7,7a,12b,13a-dodecahydro-1H-oxireno[2',3':7,8]phenanthro[8a,9-b]benzofuran-8,10-diyl dibenzoate (17) The compound **16** (1.93 g, 2.51 mmol) was solved in DCM (42 ml). The resulted clear solution was added *m*-CPBA (75 %, 927.3 mg, 4.03 mmol) in one portion. After *m*- CPBA was added, the reaction mixture was stirred at room temperature for 8h. Saturated $NaHCO_3$ aqueous solution was applied to quench the reaction. The resulted mixture was extracted with ethyl acetate three times. The combined organic layer was washed by water and brine in sequence and dried over Na_2SO_4. The organic solution was concentrated in vacuo and resulted crude product which was purified by column chromatography (petroleum/ethyl acetate = 6:1) to afford epoxide compound **17** (1.22 g, 1.56 mmol, 62%) as a colorless viscous oil: $[\alpha]_D^{24}$ = +10.0° (c 1.00, DCM); **IR** (thin film, ν cm^{-1}): 3424, 2930, 1727, 1462, 1071, 987, 725 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.4 Hz, 2H), 8.15 (d, *J* = 7.3 Hz, 2H), 7.87 (d, *J* = 7.3 Hz, 2H), 7.70 – 7.59 (m, 2H), 7.53 (dt, *J* = 14.7, 7.6 Hz, 5H), 7.43 (t, *J* = 7.5 Hz, 2H), 6.22 (s, 1H), 3.98 (d, *J* = 11.1 Hz, 1H), 3.88 (d, *J* = 5.5 Hz, 1H), 3.80 (d, *J* = 11.0 Hz, 1H), 3.16 (s, 1H), 2.64 (s, 3H), 2.16 (d, *J* = 14.2 Hz, 1H), 1.98 – 1.73 (m, 6H), 1.73 – 1.64 (m, 1H), 1.56 (d, *J* = 11.8 Hz, 3H), 1.45 (s, 3H), 1.28 (t, *J* = 12.8 Hz, 1H), 1.08 (s, 3H), 1.02 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.5, 166.5, 164.8, 163.4, 159.3, 149.6, 149.4, 134.2, 134.2, 133.4, 132.8, 130.5, 130.5, 130.2, 130.0, 129.5, 129.3, 129.3, 128.9, 128.9, 128.5, 128.5, 128.5, 128.5, 128.0, 121.8, 114.6, 109.8, 89.8, 72.1, 64.0, 63.0, 51.1, 47.5, 42.8, 39.6, 36.5, 36.1, 35.5, 33.9, 32.3, 21.6, 21.2, 19.0, 18.3, 17.7, 17.7, 17.3, 15.7; **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{49}H_{50}O_9Na$ 805.3347; Found 805.3352.

(9Z,12Z,15Z)-octadeca-9,12,15-trien-1-ol (18) To a round bottom flask containing $LiAlH_4$ (5.96 g, 157.1 mmol) and THF (180 ml) equipped with a magnetic stir bar was added commercial

available linolenic acid **10** (6.16 g, 22.13 mmol) in THF (110 ml) slowly at 0 °C. After all the acid was added, the reaction mixture was heated to reflux for 1h. Then the reaction was cooled to 0 °C. At this temperature, saturated potassium sodium tartrate aqueous solution was applied to quench the reaction. Then the mixture was stirred overnight at ambient temperature. The mixture was extracted with ethyl acetate. Combined organic extracts were washed by 2N HCl, sat. $NaHCO_3$ and brine in sequence, dried over Na_2SO_4. The volatile was evaporated in vacuo to give the crude product which was purified by column chromatography (petroleum/ethyl acetate = 8:1) to afford alcohol **18**[21] (5.03 g, 19.03 mmol, 86%) as a colorless viscous oil: **IR** (thin film, ν cm^{-1}): 3341, 2927, 2374, 1655, 1461, 1056, 722 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.42 – 5.28 (m, 6H), 3.61 (t, *J* = 6.7 Hz, 2H), 2.85 – 2.75 (m, 4H), 2.11 – 2.02 (m, 4H), 1.82 (brs, 1H), 1.59 – 1.52 (m, 2H), 1.38 – 1.25 (m, 10H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 131.9, 130.3, 128.2, 128.2, 127.6, 127.0, 63.0, 32.7, 29.6, 29.5, 29.4, 29.2, 27.2, 25.7, 25.6, 25.5, 20.5, 14.2; **HRMS** (ESIMS) m/z: $[M + H]^+$ Calcd for $C_{18}H_{33}O$ 265.2526; Found 265.2527.

(9Z,12Z,15Z)-octadeca-9,12,15-trienal (19) To a round bottom flask containing alcohol **18** (1.09 g, 4.11 mmol) equipped with a stir bar was added DCM (21 ml), followed by $NaHCO_3$ (691.3 mg, 8.23 mmol). This mixture was stirred at room temperature. And then DMP (2.62 g, 6.17 mmol) was added to the reaction vow in portions. After the substrate **18** was consumed, monitored by TLC analysis, the reaction was quenched by sat. sodium thiosulfate aqueous solution. The resulted mixture was extracted by DCM. Combined organic layer was washed with water and brine in sequence, followed by drying over Na_2SO_4. The extract was concentrated in vacuo to give the crude product. The crude product was purified by flash column chromatography (petroleum/ethyl acetate = 60:1) to afford aldehyde **19**[22] (755.8 mg, 2.88 mmol, 70%) as a

colorless oil: **IR** (thin film, ν cm^{-1}): 3433, 2960, 1727, 1461, 1269, 1069, 727 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 5.43 – 5.28 (m, 6H), 2.82 – 2.79 (m, 4H), 2.42 (td, *J* = 7.4, 1.6 Hz, 2H), 2.11 – 2.03 (m, 4H), 1.64 (dd, *J* = 14.3, 7.4 Hz, 2H), 1.32 (m, 8H), 0.98 (t, *J* = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 202.7, 131.9, 130.1, 128.2, 128.2, 127.7, 127.1, 43.8, 29.5, 29.2, 29.1, 29.0, 27.1, 25.6, 25.5, 22.0, 20.5, 14.2; **HRMS** (ESIMS) m/z: $[M + H]^+$ Calcd for $C_{18}H_{31}O$ 263.2369; Found 263.2367.

(2E,9Z,12Z,15Z)-octadeca-2,9,12,15-tetraenal (20). To a round bottom flask equipped a magnetic stir bar was added aldehyde **19** (714.4 mg, 2.72 mmol) in DCM (30 ml). This flask was placed in a – 10 °C ice-salt bath. After the aldehyde solution was cooled to – 10 °C, DIPEA (1.9 ml, 1.41 g, 10.89 mmol) and TMSOTf (0.99 mol, 1.21 g, 5.44 mmol) was added via a syringe in sequence. Then the reaction mixture was allowed to warm to room temperature and stirred overnight. And sat. $NaHCO_3$ aqueous solution was added to quench the reaction. The resulted mixture was extracted by DCM three times. Combined organic layer was washed by H_2O and brine in sequence and dried over Na_2SO_4. The extract was concentrated in vacuo to afford the desired crude silyl enol ether product which was used in the next transformation without any purification.

To a round bottom flask containing the obtained silyl enol ether was added MeCN (39 ml) to form a solution followed by addition of Na_2CO_3 (577.1 mg, 5.44 mmol) and $Pd(OAc)_2$ (611.2 mg, 2.72 mmol). The resulted reaction mixture was stirred at room temperature for 8h. After the total consumption of substrate monitored by TLC, the reaction mixture was filtered through a pad of silica gel. The filtration was concentrated in vacuo to give the crude α, β-unsaturated aldehyde which was purified by flash column chromatography (petroleum/ethyl acetate = 60:1) to afford desired aldehyde **20** (510.4 mg, 1.96 mmol, 72% over 2 steps) as a colorless oil: **IR** (thin film, ν cm^{-1}): 3365, 2931, 1693, 1460, 1267, 1129, 976, 717 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 7.9 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.14 – 6.08 (m, 1H), 5.39 – 5.32 (m, 6H), 2.80 (m, 4H), 2.33 (dd, *J* = 13.5, 6.7 Hz, 2H), 2.14 – 2.00 (m, 4H), 1.60 – 1.47 (m, 2H), 1.46 – 1.30 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 194.0, 158.7, 133.0, 131.9, 129.8, 128.3, 128.1, 128.0, 127.0, 32.6, 29.2, 28.7, 27.7, 27.0, 25.6, 25.5, 20.5, 14.2; **HRMS** (ESIMS) m/z: [M

+ Na]$^+$ Calcd for $C_{18}H_{28}ONa$ 283.2032; Found 283.2032.

3-((6Z,9Z,12Z)-pentadeca-6,9,12-trien-1-yl)oxirane-2-carbaldehyde (21). The α, β-unsaturated aldehyde **20** (323.7 mg, 1.24 mmol) was solved in MeOH (5.0 ml) followed by adding $NaHCO_3$ (104.4 mg, 1.24 mmol) and H_2O_2 (30%, 0.38 ml, 126.8 mg, 3.73 mmol) in sequence. The resulting reaction was stirred at room temperature for 2h. After the adehyde substrate consumed, sat. sodium thiosulfate aqueous solution was added to quench the reaction. The resulted mixture was extracted by ethyl acetate. Combined organic solvents were washed with water and brine in sequence, followed by drying over Na_2SO_4. This washed extract was concentrated in vacuo to give the crude epoxide product which was purified by flash column chromatography (petroleum/ethyl acetate = 60:1) to afford the desired epoxide **21** (281.7 mg, 1.02 mmol, 82%) as a colorless oil: **IR** (thin film, ν cm^{-1}): 3432, 2929, 1729, 1460, 1265, 1070, 851, 722 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 6.3 Hz, 1H), 5.46 – 5.30 (m, 6H), 3.23 (dd, *J* = 7.6, 3.3 Hz, 1H), 3.14 (dd, *J* = 6.2, 1.7 Hz, 1H), 2.87 – 2.70 (m, 4H), 2.14 – 2.01 (m, 4H), 1.76 – 1.61 (m, 2H), 1.53 – 1.36 (m, 6H), 0.98 (t, *J* = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 198.4, 132.0, 129.9, 128.3, 128.1, 128.0, 127.0, 59.0, 56.7, 31.2, 29.4, 28.8, 27.0, 25.7, 25.6, 25.5, 20.5, 14.3; **HRMS** (ESIMS) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{28}O_2Na$ 299.1982; Found 299.1983.

(3-((6Z,9Z,12Z)-pentadeca-6,9,12-trien-1-yl)oxiran-2-yl)methanol (22). To a round bottom flask containing $NaBH_4$ (109.3 mg, 2.89 mmol) was added MeOH (4.1 ml) and placed in an ice-warter bath. After cooling to 0 ^{o}C the epoxide **21** (228.1 mg, 0.83 mmol) in MeOH (10.3 ml) was added dropwisely. The reaction was maintained at 0 ^{o}C for 10 min. Sat. NH_4Cl aqueous solution was added to quench the reaction. The resulted mixture was extracted with ethyl acetate. Combined organic layer was washed by water and brine in sequence followed by drying over Na_2SO_4. The dried extract was concentrated in vacuo to give a crude desired reduction product which was purified by column chromatography (petroleum/ethyl acetate = 4:1) to afford primary alcohol **22** (183.0 mg, 0.77 mmol, 93%) as a colorless oil: **IR** (thin film, ν cm^{-1}): 3401, 2928, 1655, 1460, 1029, 885, 717 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.43 – 5.27 (m, 6H), 3.90 (ddd, *J* = 12.5, 5.3, 2.1 Hz, 1H), 3.65 – 3.55 (m, 1H), 2.98 – 2.89 (m, 2H), 2.85 – 2.70 (m, 4H), 2.19 – 2.13 (m, 1H), 2.12 – 2.02 (m, 4H), 1.62 – 1.52 (m, 2H), 1.48 – 1.34 (m, 6H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 131.9, 130.0, 128.3, 128.1, 127.8, 127.0, 61.7, 58.5, 55.9, 31.5, 29.4, 29.0, 27.0, 25.8, 25.5, 25.5, 20.5, 14.2; **HRMS** (ESIMS) m/z: [M + Na]$^+$ Calcd for

$C_{18}H_{30}O_2Na$ 301.2138; Found 301.2138.

(7Z,10Z,13Z)-hexadeca-7,10,13-trienal (9). To a round bottom flask equipped a magnetic stir bar, primary alcohol **22** (181.9 mg, 0.43 mmol) in Et_2O (7.0 ml) was added followed by adding H_2SO_4 (3.5 M, 2.0 ml) and H_5IO_6 (1.36 g, 5.98 mmol) in sequence. The resulted two phase solution was stirred vigorously at room temperature for 4h. Then sat. $NaHCO_3$ aqueous solution was added to the solution until gas releasing ceased. The aqueous phase was separated and extracted with Et_2O. The combined organic extracts were washed by water and brine in sequence and dried over $MgSO_4$. The dried extract was concentrated in vacuo to give the desired crude aldehyde which was purified by column chromatography (petroleum/ethyl acetate = 60:1 to 4:1) to afford aldehyde **9**[23] (40.1 mg, 0.17 mmol, 40%, brsm 60%) as a colorless oil: **IR** (thin film, ν cm^{-1}): 3431, 2932, 2370, 1727, 1461, 1392, 1242, 1069, 918, 713 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1.7 Hz, 1H), 5.43 – 5.27 (m, 6H), 2.87 – 2.73 (m, 4H), 2.42 (td, J = 7.4, 1.7 Hz, 2H), 2.11 – 2.02 (m, 4H), 1.77 – 1.59 (m, 2H), 1.43 – 1.33 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 202.6, 131.9, 129.8, 128.3, 128.1, 128.0, 127.0, 43.8, 29.3, 28.7, 26.9, 25.6, 25.5, 21.9, 20.5, 14.2; **HRMS** (ESIMS) m/z: $[M + H]^+$ Calcd for $C_{16}H_{27}O$ 235.2056; Found 235.2056.

1-((2aR,2bS,6R,6aR,7aS,12aS,12bS,13aR)-8,10-Dihydroxy-6-(hydroxymethyl)-13a-isopropyl-2b,6-dimethyl-2,2a,2b,3,4,5,6,6a,7,7a,12b,13a-dodecahydro-1H-oxireno[2',3':7,8]phenanthro [8a,9-b]benzofuran-11-yl)ethan-1-one (23). To a round bottom flask containing epoxide compound **17** (1.21 g, 1.55 mmol) was added MeOH (52 ml) and NaOH (644.3 mg, 16.11 mmol). And then the reaction mixture was heated to reflux for 6h. After the compound **17** was consumed completely monitored by TLC, 1N HCl was applied to quench the reaction. The mixture was extracted by ethyl acetate three times. Combined organic layer was washed with sat. $NaHCO_3$, H_2O and brine sequencelly, dried over Na_2SO_4. The organic solution was concentrated in vacuo to give crude product. The crude product was purified by column chromatography (petroleum/ethyl acetate = 2:1) to afford compound **23** (641.4 mg, 1.36 mmol, 88%) as a yellowish solid: $[\alpha]_D^{24}$ = +56.0^o (c 1.00, DCM)**;** m.p. 115–118 ^{o}C; **IR** (thin film, ν cm^{-1}): 3338, 2926, 1614, 1438, 1366, 1300, 1263, 1183, 1065, 822 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.17 (s, 1H), 9.41 (s, 1H), 5.81 (s, 1H), 3.62 (s, 1H), 3.53 (d, *J* = 11.6 Hz, 1H), 3.11 – 3.00 (m, 2H), 2.60 (s, 3H), 2.54 (d, *J* = 14.0 Hz, 1H), 1.93 (m, 2H), 1.80 – 1.61 (m, 5H), 1.61 – 1.32 (m, 6H), 1.23 (dd, *J* = 19.7, 9.8 Hz,

1H), 1.05 (s, 3H), 1.00 (dd, *J* = 11.8, 6.9 Hz, 6H), 0.96 – 0.86 (m, 1H), 0.80 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 202.3, 164.6, 162.2, 159.2, 106.6, 103.0, 96.4, 89.4, 71.8, 64.1, 62.7, 49.1, 47.6, 41.2, 39.3, 37.2, 36.6, 35.0, 34.0, 31.3, 22.0, 20.4, 18.9, 18.3, 18.0, 17.6, 17.6, 15.4; **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{38}O_6Na$ 493.2561; Found 493.2563.

1-((2aR,2bS,6R,6aR,7aS,12aS,12bS,13aR)-8,10-Dihydroxy-13a-isopropyl-2b,6-dimethyl-6-(((triethylsilyl)oxy)methyl)-2,2a,2b,3,4,5,6,6a,7,7a,12b,13a-dodecahydro-1H-oxireno[2',3':7,8] phenanthro[8a,9-b]benzofuran-11-yl)ethan-1-one (24). To a round bottom flask containing compound **23** (136.5 mg, 0.29 mmol) was added imidazole (177.7 mg, 2.61 mmol) and DCM (5.0 ml). And then the flask was placed in a ice-water bath and treated with TESCl (0.12 ml, 104.9 mg, 0.70 mmol). The resulted reaction mixture was allowed to warm to room temperature and stirred overnight. After the consumption of substrate **23** monitored by TLC analysis, 2N HCl was added and stirred for 20 min. The mixture was extracted by ethyl acetate. The combined organic solvent was washed with sat. $NaHCO_3$, water and brine in sequence. Separated organic layer was dried over Na_2SO_4 and concentrated in vacuo to give crude product **24.** The crude product was purified by column chromatography (petroleum/ethyl acetate = 8:1) to afford compound **24** (98.4 mg, 0.17 mmol) as a colorless oil: $[\alpha]_D^{25}$ = +45.0° (c 1.00, DCM); **IR** (thin film, ν cm^{-1}): 3324, 2956, 1740, 1614, 1437, 1366, 1301, 1263, 1183, 1097, 822, 742 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.14 (s, 1H), 6.94 (s, 1H), 5.91 (s, 1H), 3.58 (d, *J* = 5.0 Hz, 1H), 3.24 (d, *J* = 9.9 Hz, 1H), 3.13 (d, *J* = 9.9 Hz, 1H), 3.04 (s, 1H), 2.63 (s, 3H), 2.38 (d, *J* = 14.3 Hz, 1H), 1.96 – 1.87 (m, 2H), 1.85 – 1.71 (m, 4H), 1.64 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.51 (m, 2H), 1.45 – 1.38 (m, 2H), 1.33 – 1.18 (m, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 – 0.84 (m, 13H), 0.61 – 0.43 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 202.5, 164.9, 161.8, 159.6, 108.3, 102.8, 97.4, 89.7, 72.6, 64.7, 63.2, 50.4, 45.6, 42.6, 39.9, 37.6, 37.6, 36.3, 35.5, 34.1, 31.4, 22.8, 21.6, 19.1, 18.3, 17.7, 17.7, 16.1, 6.7, 6.7, 6.7, 4.3, 4.3, 4.3; **HRMS** (ESIMS) m/z: $[M + H]^+$ Calcd for $C_{34}H_{53}O_6Si$ 585.3606; Found 585.3606.

(9Z,12Z,15Z)-1-((2aR,2bS,6R,6aR,7aS,12aS,12bS,13aR)-8,10-dihydroxy-13a-isopropyl-2b,6-dimethyl-6-(((triethylsilyl)oxy)methyl)-2,2a,2b,3,4,5,6,6a,7,7a,12b,13a-dodecahydro-1H-oxireno[2',3':7,8]phenanthro[8a,9-b]benzofuran-11-yl)-3-hydroxyoctadeca-9,12,15-trien-1-one (25a and 25b). To a flame-dried round bottom flask equipped with a magnetic stir bar was added THF (freshly distilled, 1.0 ml) followed by diisopropylamine (0.16 ml, 111.3mg, 1.1 mmol)

under Ar atmosphere. After this mixture was cooled to 0 °C, *n*-BuLi (2.5M in hexane, 0.4 ml, 1.0 mmol) was added through a syringe. The resulted mixture was stirred at the same temperature for 30 min. The LDA solution formed here was used directly in the next procedure.

The compound **24** (158.2 mg, 0.23 mmol) was solved in THF (0.8 ml) and added to another flame-dried flask under Ar atmosphere. After this solution was cooled to -78 °C, the freshly prepared LDA (1.2 ml, 0.70 mmol) was added via a syringe dropwisely. The reaction mixture was stirred for 50 min at -78 °C. And then aldehyde **9** (63.6 mg, 0.27 mmol) solved in THF (0.8 ml) was added to the flask by syringe. The reaction mixture was kept at -78 °C for another 1h. Then sat. NH_4Cl aqueous solution was used to quench the reaction. The mixture was extracted with ethyl acetate. Combined organic layer was washed with water and brine in sequence, dried over Na_2SO_4. The organic solution was concentrated in vacuo to give a crude product. The crude product was purified by column chromatography (petroleum/ethyl acetate = 8:1 to 4:1) to afford compound **25a and 25b** (1:1.1, inseparable) contained two diastereoisomers (94.2 mg, 0.12 mmol, 50 %, brsm 61%) as a colorless oil. Compounds **25a** and **25b**: $[\alpha]_D^{25}$ = +50.0° (c 1.00, DCM); **IR** (thin film, ν cm^{-1}): 3195, 2961, 2927, 1638, 1612, 1431, 1261, 1095, 1020, 800, 739, 568 cm^{-1}. **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{50}H_{78}O_7SiNa$ 841.5409; Found 841.5416.

Compound **25a: ^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.09 (s, 1H), 7.06 (brs, 1H), 5.91 (s, 1H), 5.44 – 5.27 (m, 6H), 4.18 (brs, 1H), 4.05 – 4.03 (m, 1H), 3.64 (d, *J* = 4.6 Hz, 1H), 3.48 – 3.38 (m, 1H), 3.27 (d, *J* = 4.9 Hz, 1H), 3.15 (d, *J* = 6.0 Hz, 1H), 3.10 (s, 1H), 2.94 (d, *J* = 8 Hz, 1H), 2.82 – 2.77 (m, 4H), 2.48 (d, *J* = 16 Hz, 1H), 2.12 – 2.05 (m, 4H), 1.94 – 1.87 (m, 2H), 1.86 – 1.71 (m, 5H), 1.66 (d, *J* = 8 Hz, 1H), 1.60 – 1.55 (m, 3H), 1.53 – 1.47 (m, 3H), 1.42 – 1.20 (m, 8H), 1.04 (s, 3H), 1.01 – 0.96 (m, 9H), 0.91 – 0.85 (m, 12H), 0.57 – 0.50 (m, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 203.9, 165.5, 161.5, 159.9, 131.9, 130.3, 128.3, 127.6, 127.1, 108.3, 102.9, 98.0, 89.8, 72.7, 69.9, 68.4, 65.3, 64.6, 63.4, 51.5, 50.3, 49.5, 46.1, 42.8, 39.8, 37.6, 37.0, 36.3, 35.5, 34.2, 29.7, 29.4, 27.3, 25.6, 25.5, 22.7, 21.5, 20.5, 19.1, 18.3, 17.7, 17.6, 16.0, 14.3, 6.7, 6.7, 6.7, 4.3, 4.3, 4.3.

Compound **25b: ^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.91 (s, 1H), 7.06 (brs, 1H), 5.90 (s, 1H), 5.44 – 5.27 (m, 6H), 4.02 (brs, 1H), 3.59 (d, *J* = 4.6 Hz, 1H), 3.51 (brs, 1H), 3.48 – 3.38 (m, 1H), 3.25 (d, *J* = 4.9 Hz, 1H), 3.13 (d, *J* = 6.0 Hz, 1H), 3.02 (s, 1H), 2.90 (d, *J* = 8.0 Hz, 1H), 2.82 – 2.77 (m, 4H), 2.41 (d, *J* = 16 Hz, 1H), 2.12 – 2.05 (m, 4H), 1.94 – 1.87 (m, 2H), 1.86 – 1.71 (m,

5H), 1.62 (d, *J* = 8 Hz, 1H), 1.60 – 1.55 (m, 3H), 1.53 – 1.47 (m, 3H), 1.42 – 1.20 (m, 8H), 1.04 (s, 3H), 1.01 – 0.96 (m, 9H), 0.91 – 0.85 (m, 12H), 0.57 – 0.50 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 203.2, 165.1, 161.1, 159.9, 131.9, 130.3, 128.3, 127.6, 127.1, 108.1, 102.9, 97.7, 89.6, 72.7, 69.9, 68.4, 65.3, 64.6, 63.1, 51.5, 50.2, 49.5, 45.7, 42.8, 39.7, 37.6, 37.0, 36.3, 35.5, 34.2, 29.7, 29.4, 27.3, 25.5, 25.4, 22.4, 21.4, 20.5, 19.1, 18.3, 17.7, 17.6, 15.9, 14.3, 6.7, 6.7, 6.7, 4.3, 4.3, 4.3.

(2E,9Z,12Z,15Z)-1-((2aR,2bS,6R,6aR,7aS,12aS,12bS,13aR)-8,10-Dihydroxy-13a-isopropyl-2b,6-dimethyl-6-(((triethylsilyl)oxy)methyl)-2,2a,2b,3,4,5,6,6a,7,7a,12b,13a-dodecahydro-1H-oxireno[2',3':7,8]phenanthro[8a,9-b]benzofuran-11-yl)octadeca-2,9,12,15-tetraen-1-one (26). The adol products **25a** and **25b** (67.9 mg, 0.083 mmol) were solved in DCM (3.0 ml) and transferred to a round bottom flask containing DMAP (2.0 mg, 0.01658 mmol) via syringe. After the reaction mixture was cooled to 0 °C, NEt_3 (34.6 μl, 25.2 mg, 0.25 mmol) and AcCl (23.6 μl, 26 mg, 0.33 mmol) were added in sequence. The resulted mixture was stirred at 0 °C for another 1h. After the totally consumption of compounds **25a** and **25b**, sat. $NaHCO_3$ aqueous solution was used to quench the reaction. The aqueous phase was extracted by DCM. The combined organic layer was washed with water and brine in sequence, dried over Na_2SO_4 followed by concentrating in vacuo to give crude product. The crude product was purified by column chromatography (petroleum/ethyl acetate = 16:1 to 8:1) to afford corespoding diacetyl protected products (49.7 mg, 0.055 mmol, 66%) as a colorless oil.

To a round bottom flask equipped with a stir bar was added Burgess reagent (24.3 mg, 0.10 mmol) solved in toluene (0.6 ml). And the diacetyl protected products (30.7 mg, 0.034 mmol) in toluene (0.8 ml) was added to the reaction system via syringe. The resulted mixture was placed in a 50 °C oil bath and stirred for 8h. After the total consumption of the substrates, water was added to quench the reaction. Resulted mixture was extracted by ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude product. The crude product was purified by column chromatography (petroleum/ethyl acetate = 16:1 to 8:1) to afford α, β-unsaturated ketone **26** (18.9 mg, 0.021 mmol, 63%) as a colorless oil: $[\alpha]_D^{25}$ = +13.0° (c 1.00, DCM); **IR** (thin film, ν cm^{-1}): 3395, 2928, 1775, 1670, 1617, 1461, 1413, 1367, 1192, 1096, 825, 728 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86 (dt, *J* = 15.4, 6.6 Hz, 1H), 6.69 (d, *J* = 15.6 Hz, 1H), 6.40 (s, 1H), 5.43 – 5.28 (m, 6H), 3.59 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.14 (q,

J = 9.5 Hz, 2H), 2.99 (s, 1H), 2.82 – 2.77 (m, 4H), 2.30 (s, 3H), 2.26 – 2.21 (m, 5H), 2.11 – 2.06 (m, 4H), 1.97 (d, *J* = 14.1 Hz, 1H), 1.87 – 1.69 (m, 6H), 1.60 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.55 – 1.44 (m, 4H), 1.39 – 1.23 (m, 9H), 1.03 (s, 3H), 1.00 – 0.95 (m, 8H), 0.90 – 0.83 (m, 13H), 0.56 – 0.47 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 188.7, 169.1, 167.3, 158.7, 149.8, 149.1, 148.6, 131.9, 130.5, 130.1, 128.3, 128.2, 127.7, 127.1, 121.9, 114.2, 109.5, 89.8, 71.7, 63.9, 62.9, 50.7, 46.0, 42.8, 39.6, 37.7, 35.9, 35.4, 34.0, 32.5, 29.5, 29.0, 27.8, 27.1, 25.6, 25.5, 22.3, 21.4, 20.9, 20.9, 20.5, 19.1, 18.3, 17.7, 17.6, 17.2, 15.9, 14.2, 6.8, 6.8, 6.8, 4.3, 4.3, 4.3; **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{54}H_{80}O_8SiNa$ 907.5515; Found 907.5516.

(9Z,12Z,15Z)-1-((2aR,2bS,6R,6aR,7aS,12aS,12bS,13aR)-8,10-Dihydroxy-13a-isopropyl-2b,6-dimethyl-6-(((triethylsilyl)oxy)methyl)-2,2a,2b,3,4,5,6,6a,7,7a,12b,13a-dodecahydro-1H-oxireno[2',3':7,8]phenanthro[8a,9-b]benzofuran-11-yl)octadeca-9,12,15-trien-1-one (27). To a round bottom flask equipped with a magnetic stir bar, $Pd(PPh_3)_4$ (1.0 mg, 0.00082 mmol) was added followed by adding unsaturated ketone **26** (24.3 mg, 0.02745 mmol) in THF (3.0 ml). After Pd-catalyst solved to give a pale yellow solution, *n*-Bu_3SnH (22.2 μl, 24.0 mg, 0.08234 mmol) was added via a syringe. The resulted reaction mixture was stirred at room temperature for 24h. And then water was added to quench. The aqueous phase was extracted with ethyl acetate three times. Combined organic layer was washed by brine and dried over Na_2SO_4, followed by concentrating in vacuo to provide a mixture of **26** and **27**. This mixture was purified by column chromatography (petroleum/ethyl acetate = 16:1) to afford selectively reduced product **27** (12.2 mg, 0.014 mmol, 50%, brsm 70%) as a colorless oil: $[\alpha]_D^{25}$ = +11.0° (c 1.00, DCM); **IR** (thin film, ν cm^{-1}): 3399, 2927, 1775, 1671, 1616, 1460, 1412, 1367, 1192, 1095, 727 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 5.44 – 5.27 (m, 6H), 3.61 (dd, *J* = 7.0, 1.7 Hz, 1H), 3.18 – 3.10 (m, 2H), 3.01 (s, 1H), 3.00 – 2.85 (m, 2H), 2.84 – 2.72 (m, 4H), 2.30 (s, 3H), 2.26 (s, 3H), 2.12 – 2.03 (m, 4H), 2.01 – 1.95 (m, 1H), 1.90 – 1.84 (m, 2H), 1.81 – 1.72 (m, 3H), 1.67 – 1.59 (m, 4H), 1.52 – 1.46 (m, 2H), 1.40 – 1.25 (m, 13H), 1.04 (s, 3H), 1.00 – 0.96 (m, 8H), 0.90 – 0.83 (m, 13H), 0.54 – 0.47 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 199.6, 169.4, 167.3, 158.9, 149.6, 148.8, 131.9, 130.4, 128.3, 128.2, 127.5, 127.1, 121.9, 114.2, 109.6, 89.9, 71.7, 64.1, 63.0, 50.8, 46.2, 43.9, 42.7, 39.6, 37.7, 35.9, 35.4, 34.0, 29.7, 29.4, 29.3, 29.2, 27.3, 25.6, 25.5, 24.0, 22.1, 21.4, 21.0, 20.9, 20.5, 19.2, 18.3, 17.7, 17.6, 17.2, 15.9, 14.3, 6.8, 6.8, 6.8, 4.3, 4.3, 4.3; **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{54}H_{82}O_8SiNa$ 909.5671; Found 909.5665.

Nominal *ent*-Chlorabietol B (28). The compound **27** (10 mg, 0.011 mmol) was solved in MeOH (1.6 ml) followed by addition of K_2CO_3 (9.3 mg, 0.068 mmol). The resulting reaction mixture was stirred at room temperature for 8h. After the complete consumption of substrate **27**, water was added to the reaction vow. The resulting aqueous solution was extracted with ethyl acetate. Combined organic layer was washed by brine, dried over Na_2SO_4. The organic solvent was evaporated in vacuo to give the crude deacetylation product which was used without any purification.

The crude deacetylation product was solved in THF (1.6 ml) followed by addition of TBAF (1.0M in THF, 11.0 µl, 0.11 mmol). The resulting solution was stirred at room temperature for another 3h. After the fully consumption of the substrate, water was added to quenching. The aqueous solution was extracted with ethyl acetate three times. Combined organic layer was washed with brine, dried over Na_2SO_4. The organic solution was concentrated in vacuo to give a crude product **28**. This crude product was purified by flash column chromatography (petroleum/ethyl acetate = 3:1) to afford compound **28** (6.2 mg, 0.0090 mmol, 82% over 2 steps) as a white solid: $[\alpha]_D^{23}$ = +26.0° (c 1.00, MeOH); m.p. 95–102 °C; **IR** (thin film, ν cm^{-1}): 3389, 2930, 2840, 1633, 1616, 1449, 1262, 1026, 824, 692 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.38 (s, 1H), 9.18 (brs, 1H), 5.85 (s, 1H), 5.42 – 5.31 (m, 6H), 3.66 (s, 1H), 3.61 (d, *J* = 12.0 Hz, 1H), 3.07 (s, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.99 (d, *J* = 12.0 Hz, 2H), 2.81 – 2.77 (m, 4H), 2.58 (d, *J* = 12.0 Hz, 1H), 2.11 – 2.02 (m, 4H), 1.98 – 1.89 (m, 2H), 1.80 – 1.72 (m, 4H), 1.71 – 1.63 (m, 4H), 1.61 – 1.57 (m, 1H), 1.57 – 1.50 (m, 2H), 1.42 (d, *J* = 12.0 Hz, 1H), 1.40 – 1.31 (m, 9H), 1.21 (d, *J* = 12.0 Hz, 1H), 1.08 (s, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.98 (t, *J* = 6.0 Hz, 3H), 0.91-0.89 (m, 1H), 0.82 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 205.2, 165.0, 162.0, 158.6, 131.9, 130.4, 128.3, 128.2, 127.6, 127.1, 106.3, 103.0, 96.5, 89.4, 71.7, 63.7, 62.6, 49.1, 47.7, 42.8, 40.9, 39.4, 37.3, 36.8, 35.0, 34.0, 29.7, 29.5, 29.4, 29.3, 27.3, 25.6, 25.5, 24.6, 22.2, 20.5, 20.3, 18.9, 18.4, 18.1, 17.7, 17.6, 15.4, 14.3; **HRMS** (ESIMS) m/z: $[M + Na]^+$ Calcd for $C_{44}H_{64}O_6Na$ 711.4595; Found 711.4600.

ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

CCDC 1972686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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