Total synthesis of (+) Artemisinin

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Dedicated to Professor Sukh Dev on his 80th birthday
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Abstract
(+)-Artemisinin is a sesquiterpene endoperoxide lactone with an unprecedented structure is a natural medicine for the treatment of malaria in particular drug against drug resistant malaria and cerebral malaria. The total synthesis of this novel sesquiterpene is described using an intermolecular radical reaction on important intermediate iodolactone starting from terpene (+)-isolimonene.

Keywords: Artemisinin, iodolactone, selenolactone, tris(trimethylsilyl)silane

Introduction

Malaria is probably as old as mankind and continues to affect millions of people throughout the world.1 Today some 500 million people in Africa, India, South East Asia and South America are exposed to endemic malaria and it is estimated to cause two and half million deaths annually, one million of which are children.2 Certainly malaria is a serious problem all over the globe. As a consequence, effective therapeutic agents against malaria are continuously being sought, especially against those strains of Plasmodium falciparum, which are resistant to conventional quinine and acridine based drugs. Artemisinin, which has been isolated3,4 from Artemisia Annua L. Compositae (Qinghao), is an active constituent of traditional Chinese herbal medicine which is used for the treatment of malaria in China for more than 1000 years.
(+) Artemisinin 1, a sesquiterpene endoperoxide lactone with an unprecedented structure is a natural medicine for the treatment of malaria, in particular drug against drug resistant and cerebral malaria. The exceptional pharmacological potential and extreme scarcity of the natural material together with its complex structure prompted us to study the total synthesis of (+) Artemisinin. The architectural complexity is attributed to the presence of 7 chiral centers with tetracyclic framework with an endoperoxide unit. Though many valuable contributions\textsuperscript{5-9} have been made towards the total synthesis of this unique structurally complex molecule, the need for a simple strategic route still remains, encouraging us to take up the total synthesis of this potent antimalarial drug.

**Results and Discussion**

In the retrosynthetic analysis (scheme 1), among all the valuable contributions for the total synthesis of Artemisinin, we believe that the key intermediate would be $\alpha$-hydroperoxy aldehyde which can be easily photo oxygenated from methylvinylether 2 because, in a ketalization-like process, simple cyclodehydration of $\alpha$-hydroperoxy aldehyde should readily furnish the tetracyclic natural product 1. Thus, the next intermediate in our analysis was the iodolactone 3 which has required stereochemistry and further it can be easily prepared from the starting (+) isolimonene 4 which has two asymmetric carbon atoms having the same absolute configuration as the target molecule.
Iodolactone 3, a key intermediate in the synthesis with five asymmetric centers was elaborated from (+) isolimonene 4 by successive regioselective hydroboration, Jones oxidation followed by the iodolactonization (Scheme 2, 3).

(+)-Isolimonene 4 with exocyclic and endocyclic double bonds, was subjected to regioselective hydroboration. The regioselective exocyclic hydroboration was achieved using dicyclohexyl borane to get the required alcohol 5 in 82% yield. The resulting alcohol 5 was oxidized with Jones reagent in acetone at 0°C to the corresponding acid 6 in 80% yield. The γ,δ-unsaturated acid 6 was subjected to iodolactonization using KI, I₂ in aq. NaHCO₃ to afford iodolactone 3, 3a as separable diastereomers, isomeric at C3 in 68:32 (β:α) ratio in 70% yield. While this work was under progress the iodolactones were reported by Chavan et. al. for the synthesis of Wine lactone.

The next step in the synthesis called for the introduction of the side-chain appendage at carbon bearing iodine on intermediate 3 with the four requisite stereo centers embedded within its cyclohexane ring. Michael addition reaction was attempted with methylvinyl ketone using Bu₃SnH and a catalytic amount of AIBN in refluxing toluene. The reduced product 8 was the major product from the reaction and the desired product 7 was isolated in 10% yield (scheme 4). Use of Ph₃SnH in the place of Bu₃SnH also gave the same results.

Since homologation was essential for proceeding further in the synthesis of Artemisinin, we envisioned cyclofuncionalisation of \( \gamma,\delta \)-unsaturated acid with bezeneselenyl bromide for construction of selenolactone in place of iodolactone. Phenyl selenyl bromide\(^\text{15} \) was prepared from diphenyl diselenide\(^\text{16} \) using bromine in CH$_2$Cl$_2$ at 0°C, and treated with unsaturated acid 6 to afford selenolactone 9, 9a as 1:1 diasteriomic mixture in good yield. But attempted reaction of the selenolactone 9 with methylvinyl ketone using tri-n-butyltin hydride and catalytic amount of AIBN gave the same product distribution as observed with 3 (scheme 5).

Scheme 5. a. PhSeBr, CH$_2$Cl$_2$, 0°C, 78%. b. Bu$_3$SnH, AIBN, toluene reflux.

In another approach, iodolactone 3 was treated with Na$_2$CO$_3$ in refluxing methanol for 8 hours to afford epoxide 10. Biscyclopentadienyl titanium chloride Cp$_2$TiCl\(^\text{17} \) was generated in situ from biscyclopentadienyl titanium dichloride Cp$_2$TiCl$_2$\(^\text{18} \) with Zn, ZnCl$_2$ in dry THF at -15°C and attempted reductive ring opening with low valent titanium in the presence of methyl vinyl ketone to access hydroxy ketone 11 met with success but yield was very less (Scheme 6).

Scheme 6. a. Na$_2$CO$_3$, CH$_3$OH, reflux, 72%. b. Cp$_2$TiCl, Zn, ZnCl$_2$, THF, 0°C, 10%.
Since intermolecular C-C bond formation reactions have been increasingly achieved by radical addition to alkenes. But in efforts, alkylation reaction on iodolactone 3 and selenolactone 9 with methylvinyl ketone met with failure using Bu$_3$SnH, Ph$_3$SnH. We therefore, selected the silane functionality as mediator in the formation of intermolecular C-C bond. Using Chatgilialoglu’s reagent$^{19}$ tris(trimethylsilyl)silane ((CH$_3$)$_3$Si)$_3$SiH, the reaction of iodolactone 3 with methylvinyl ketone, with AIBN in refluxing toluene gave product 7 in very good yield by slow addition of tris(trimethylsilyl)silane using syringe pump (Scheme 7). The product 7 was obtained in 72 % yield as an inseparable epimeric mixture at C 7 (8:2 $\beta/\alpha$) along with 12 (10 %) and the reduced product 8 (5 %).

Scheme 7. a. methylvinyl ketone, ((CH$_3$Si)$_3$)$_3$SiH, AIBN, toluene reflux, 72%.

To proceed further towards the synthesis of Artemisinin 1, the ketogroup of lactone 7 has to be protected. Ethane diol and propane diol were used for protecting the ketone using PTSA in refluxing benzene but decomposition of starting material was observed. The keto group of lactone 7 was treated (scheme 8) with ethane dithiol and BF$_3$Et$_2$O in CH$_2$Cl$_2$ at 0$^\circ$C to afford thioketal lactone 13, 14 in quantitative yield.$^6$ Thioketalization reaction facilitated the separation of the major isomer 14 in pure form, which was expected as all three side chains are in equitorial position. Which was further subjected to hydrolysis and esterification with diazomethane provided hydroxyl ester 15 in 50% yield (The thioketal lactone 14 was also isolated due to competent lactonization of the hydroxy acid.). The hydroxy methylester 15 was transformed to the keto ester 16 using PCC as the oxidizing agent in CH$_2$Cl$_2$ at room temperature (Scheme 8).

In a two dimensional $^1$H NMR study of compound 16 revealed the strong nOe between the two di axial protons adjacent to the carbonyl group. These observations confirmed its structure.
Scheme 8. a. Ethanedithiol, BF$_3$Et$_2$O in CH$_2$Cl$_2$ at 0°C, 98%. b. 10% NaOH in MeOH reflux, 1% HCl to congeored pH at -24°C, 50%. c. CH$_2$N$_2$ in Et$_2$O. d. PCC, DCM at 0°C, 89%.

The second key intermediate methylvinyl ether 17 was achieved by Wittig reaction using methoxymethyl triphenylphosphonium chloride and KHMDS in THF, HMPA at 50°C. The reaction was also carried out using n-butyl lithium in THF, n-butyl lithium in ether, NaH in DMSO, NaH in DMSO at benzene reflux conditions as reported in the literature. But due to hindrance at the two sides of the carbonyl group yields were moderate. These reactions were successful with high yields when attempted on the unhindered ketone such as menthone 18 (Scheme 9).

Scheme 9. methoxymethyl triphenylphosphonium chloride, 2M KHMDS, THF:HMPA (8:2) 50°C 24 hours.
The deprotection of thioketal 17 using HgCl₂, CaCO₃ resulting the key intermediate 2 in 80% yield. Compound 2 has been transformed to the target molecule 1 by photooxidation using an ordinary tungsten light source (250 V, 500W), followed by acid hydrolysis reaction with 70 % HClO₄ (scheme 10). Photooxidation of methyl vinyl ether 2 with O₂ with Rose Bengal forms 1,2 dioxetane and which on acid hydrolysis with HCl gives the hydroperoxy-aldehyde, thereafter, cyclization with HClO₄ forms the final product 1. The synthetic material was found to be identical with natural Artemisinin in every respect (¹H NMR, IR, Mass, TLC and OR).

Scheme 10. a. HgCl₂, CaCO₃ in CH₃CN:H₂O (9:1), 80%. b. O₂, Rose Bengal in MeOH, hυ 4h at -78°C, dry HCl. c. 70% HClO₄ in ether 28 hours, 10%.

Conclusions

In conclusion, a stereoselective total synthesis of the highly potent antimalarial drug (+) Artemisinin has been achieved in the shortest possible route. Synthetic intermediate iodolactone and its inter molecular C-C bond formation using silane functionality as the mediator have been achieved as key steps in the total synthesis with very good yields. Further, the synthetic route is very much useful for the large-scale synthesis of structurally diverse natural sesquiterpene endoperoxide lactone (+) Artemisinin 1 (Qinghaosu).
Experimental Section

**General Procedures.** Infrared spectra were recorded on a GC-FTIR spectrometer. $^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectra were recorded using a Varian-Gemini 200 or Varian Unity 400 MHz spectrometer. Mass spectra were recorded on Finningan Mat 1020B mass spectrometer. Column chromatography refers to silica gel chromatography using Acme 60-120 mesh. Analytical thin layer chromatography was performed on pre-coated E-Merck silica glass plates. Acetonitrile was used as it is purchased from E-Merck.

3-Isopropenyl-6-methyl-(3R, 6R)-1-cyclohexene (4). This material was obtained in enantiomerically pure form $\Delta^3$ carene, which is available abundantly in India. (+) Isolimonene is also commercially available. $^1\text{H}$ NMR (200 MHz, CDCl$_3$): $\delta$ 0.98 (d, $J = 7.2$ Hz, 3H), 1.10-1.51 (m, 2H), 1.70 (s, 3H), 1.76-1.93 (m, 2H), 2.06-2.24 (m, 1H), 4.70 (s, 2H), 5.43-5.61 (m, 2H). MS (EI): 137 (M+1). Optical rotation $[\alpha]_D$: (+) 159.82 (c=1.0, CHCl$_3$).

2-(4-Methyl-2-cyclohexenyl)-1-propanol (5). A 250 mL flask equipped with a septum inlet, a magnetic stirring bar was charged with 5.05 mL of BH$_3$SMe$_2$ (50 mmol) and 18 mL of freshly distilled THF. It was cooled to 0°C and 18.3 mL (115 mmol) of cyclohexene (neat) was added drop wise. After the mixture was stirred at 0°C for 1 hour (C$_6$H$_5$)$_2$BH separated as white solid during this time), the flask was stored at 0°C in a refrigerator for 7 days.

To the (C$_6$H$_5$)$_2$BH (solid, 50 mmol) was added (18.3 g, 75 mmol) of neat olefin 4. The reaction mixture was stirred at -25°C for 1 hour and kept in the refrigerator for a day. The trialkyl borane was treated with 50 mL of 3N sodium hydroxide, 7.5 mL of 30% hydrogen peroxide and stirred at 25°C for 5 hours. This was extracted with ether, dried (Na$_2$SO$_4$) and the ether was evaporated. The residue was filtered through silica gel (pet.ether-ethyl acetate 9:1 used as eluent) to remove the olefin and cyclohexyl alcohol and then eluted with pet.ether-ethylacetate (1:1) mixture to give the pure alcohol 5 in (17.0 g) 82% yield. $^1\text{H}$ NMR (200MHz, CDCl$_3$): $\delta$ 0.86 (d, $J = 7.3$ Hz, 3H), 0.95 (d, $J = 7.2$ Hz, 3H), 1.10-1.40 (m, 3H), 1.46-1.94 (m, 3H), 2.02-2.30 (m, 1H), 3.40-3.78 (m, 2H), 5.40-5.58 (m, 2H). MS (EI): m/z 155 (M+1). IR (neat): 3380 cm$^{-1}$. Optical rotation $[\alpha]_D$: (+) 70.0 (c=2.0, CHCl$_3$).

2-(4-Methyl-2-cyclohexenyl)proanoic acid (6). Jones reagent was prepared by drop wise addition of sulfuric acid (17 mL) to a cooled solution of CrO$_3$ (20 g, 200 mmol) in water (30 mL) and the resulting solution was diluted with water until the total volume of this solution 60 mL.

The alcohol 5 (10g, 65.25 mmol) was dissolved in acetone (150 mL) and cooled to 0°C. Jone’s reagent was added drop wise through dropping funnel over a period of 2 hours until orange brown colour of the reagent persisted. The reaction mixture was stirred for another 2 hours. Ether (100 mL) was added to precipitate out the chromous salts, the reaction mixture was filtered and the residue was washed with ether. The organic layer was dried over anhydrous Na$_2$SO$_4$, concentrated and purified by addition of 5% aq. NaOH and washed with ether to
remove the impurities and the aq. layer was further acidified and extracted with ethyl acetate. This extract was dried over anhydrous Na$_2$SO$_4$ and concentrated to get pure acid 6 (8.73 g) in 80 % yield. $^1$H NMR (200MHz, CDCl$_3$): δ 0.95 (d, J = 7.2, 3H), 1.12 (d, J = 7.1, 3H), 1.18-1.42 (m, 2H), 1.60-1.95 (m, 2H), 2.02-2.22 (m, 1H), 2.28-2.54 (m, 2H), 5.36-5.60 (m, 2H). MS (EI): m/z 169 (M+1). IR (neat): 3000 cm$^{-1}$. Optical rotation $[\alpha]_D$: (+) 59.39 (c=2.0, CHCl$_3$).

7-Iodo-3,6-dimethylperhydrobenzo[b]furan-2-one (3). To the solution of unsaturated acid formula III (10 g, 59.5 mmol) in 360 mL of 0.5M aq. NaHCO$_3$ was added a solution of I$_2$ (15.1 g, 119.04 mmol) and KI (59.2 g, 357.14 mmol) in 180 mL water. The resulting reaction mixture was allowed to stand in the dark for 48 hours with occasional swirling. The reaction mixture was extracted with DCM, the combined organic layers were washed with aq. Na$_2$S$_2$O$_3$ and dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The residual crude lactone was subjected to column chromatography on silica gel using eluent (96:4 hexane/ethyl acetate) to provide iodolactones formula 3, 3a (12.323 g) as separable diastereomers at C3 in (68:32 β/α) in 70 % yield as brown solid.

7-Iodo-3,6-dimethyl-(3R,3aS,6R,7R,7aR)-perhydrobenzo[b]furan-2-one (3) $^1$H NMR (500MHz, CDCl$_3$): δ 0.94 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.24-1.42 (m, 2H), 1.67-1.71 (m, 2H), 1.82-1.87 (m, 1H), 2.74-2.81 (m, 2H), 4.73 (m, 2H). $^{13}$C NMR (200MHz, CDCl$_3$): δ 179.80, 96.18, 42.22, 36.28, 32.11, 29.16, 26.60, 16.42, 13.53, 9.10. MS (EI): 294 (M$^+$). IR (neat): 1782 cm$^{-1}$. Optical rotation $[\alpha]_D$: (+) 22.12 (c=3.0, CHCl$_3$).

7-Iodo-3,6-dimethyl-(3S,3aS,6R,7R,7aR)-perhydrobenzo[b]furan-2-one (3a) $^1$H NMR (500MHz, CDCl$_3$): δ 1.00 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 7.4 Hz, 3H), 1.34-1.47 (m, 4H), 1.84-1.89 (m, 1H), 2.37-2.80 (m, 2H), 4.66 (t, J = 3.0 Hz, 1H), 4.94 (t, J = 4.1, 1H). $^{13}$C NMR (200MHz, CDCl$_3$): δ 178.36, 81.90, 42.16, 35.10, 30.44, 26.75, 23.05, 21.74, 13.55, 8.71. MS (EI): 294 (M$^+$). IR (neat): 1780 cm$^{-1}$. Optical rotation $[\alpha]_D$: (-) 36.89 (c=3.0, CHCl$_3$).

3,6-Dimethyl-7-(3-oxobutyl)perhydrobenzo[b]furan-2-one (7). A 500 mL round-bottomed flask equipped with a magnetic stirring bar, dry nitrogen inlet, reflux condenser, and septum was flushed with nitrogen and charged with 5 g (17.0 mmol) of iodolactone formula IV and 1.06 mL (12.75 mmol) of methylvinyl ketone in 150 mL of toluene. The mixture was brought to reflux; 3.96 g (12.75 mmol) of TTMSS and 279 mg (1.7 mmol) of AIBN dissolved in 20 mL of toluene were added over 4 hours through a long needle using a syringe pump. Similarly, second portion of 1.06 mL (12.75 mmol) of methylvinyl ketone was added and 3.96 g (12.75 mmol) of TTMSS and 279 mg (1.7 mmol) of AIBN dissolved in 6 mL of toluene were added over 4 hours through a long needle using a syringe pump. The reaction mixture was brought to room temperature, concentrated in vacuum. The residue was subjected to column chromatography on silica gel using eluent (80:20 hexane/ethyl acetate) to provide the pure ketolactone 7 (2.954 g, 73 % yield) as brown colour semisolid.

3,6-Dimethyl-7-(3-oxobutyl)-(3R,3aS,6R,7S,7aS)-perhydrobenzo[b]furan-2-one (7) $^1$H NMR (200MHz, CDCl$_3$): δ 0.96 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.35-1.43 (m, 2H), 1.58-
1.62 (m, 4H), 1.71-1.78 (m, 1H), 1.91-2.00 (m, 2H), 2.16 (s, 3H), 2.30-2.36 (m, 1H), 2.48-2.54 (m, 1H), 2.59-2.63 (m, 1H), 4.58 (t, J = 3.6 Hz, 1H).

3,6-Dimethyl-7-(3-oxobutyl)-(3R,3aS,6R,7R,7aS)-perhydrobenzo[b]furan-2-one (7a) \(^1\)H NMR (200MHz, CDCl\(_3\)): \(\delta\) 0.88 (d, J = 7.2 Hz, 3H), 1.08-1.34 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H), 1.50-1.98 (m, 4H), 2.06-2.37 (m, 3H), 4.60 (m, 1H). MS (EI): m/z 239 (M+1). IR (neat):1630, 1780 cm\(^{-1}\).

3,6-Dimethyl-(3R,3aS,6R,7aS)-perhydrobenzo[b]furan-2-one (8). \(^1\)H NMR (200MHz, CDCl\(_3\)): \(\delta\) 0.92 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.50-1.98 (m, 4H), 2.06-2.37 (m, 3H), 4.60 (m, 1H). MS (EI): m/z 169 (M+1). IR (neat): 1782 cm\(^{-1}\).

3,6-Dimethyl-7-phenylselanyl-(3aS,6R,7R,7aS)-perhydrobenzo[b]furan-2-one (9). Benzeneselenyl bromide (PhSeBr) 1.545 g, 6.54 mmol was prepared by dissolving Ph\(_2\)Se\(_2\) (1.021g, 3.27 mmol) in 3 mL THF and 0.16 mL (0.523g, 3.27 mmol) of bromine were added drop wise while stirring under N\(_2\) atmosphere. The reaction is essentially instantaneous and solution can be used directly for the next reaction.

To the solution of unsaturated acid 6 (1 g, 5.95 mmol) in 10 mL of dry methylene chloride under nitrogen at 0\(^\circ\)C was added a solution of PhSeBr (1.545 g, 6.547 mmol) and the resulting reaction mixture was allowed to stir at 0\(^\circ\)C for 2 hours. The completion of the reaction was signaled by the complete dissolution of the red-orange PhSeBr and was confirmed by TLC. The pale yellow solution was then allowed to reach room temperature, concentrated and chromatographed on silica gel using eluent (96:4 hexane/ethyl acetate) to provide the selenolactone 9, 9a as 1:1 diastereomeric mixture in (1.350 g) in 70 % yield. (9a)\(^1\)H NMR (200MHz, CDCl\(_3\)) mixture: \(\delta\) 1.10-1.38 (m, 12H), 1.40-1.60 (m, 4H), 1.84-2.45 (m, 2H), 2.65-2.80 (m, 2H), 3.60 (t, J = 3.0 Hz, 1H), 3.70 (t, J = 3.2 Hz, 1H), 4.58 (t, J = 3.6 Hz, 1H), 4.75 (t, J = 3.8 Hz, 1H), 7.38 (m, 6H), 7.55 (m, 2H). (9)\(^1\)H NMR (200MHz, CDCl\(_3\)): \(\delta\) 1.24 (d, J = 7.9 Hz, 3H), 1.24 (d, J = 7.9 Hz, 3H), 1.35-1.60 (m, 2H), 1.84-2.38 (m, 2H), 2.28-2.50 (m, 2H), 3.63 (t, J = 3.0 Hz, 1H), 4.78 (t, J = 3.6 Hz, 1H), 7.30 (m, 3H), 7.60 (m, 2H). MS (EI): m/z 324 (M\(^+\)). IR (KBr): 1782 cm\(^{-1}\).

Methyl 2-[5-methyl-(1aR,2S,5R,5aS)-perhydrobenzo[b]oxiren-2-yl]- (2R)-propanoate (10). A 50 mL round-bottomed flask equipped with a magnetic stirring bar, dry nitrogen inlet, reflux condenser, and septum was flushed with nitrogen and charged with 2.0 g (6.80 mmol) of iodolactone 3 and finely powdered 865 mg (8.16 mmol) of Na\(_2\)CO\(_3\) in 20 mL of methanol. The mixture was refluxed for 8 hours. Completion of the reaction was monitored on TLC. The resulting solution was brought to room temperature, concentrated under reduced pressure and partitioned between 10 mL water and 10 mL ether. The organic layer was washed with brine and water, dried over Na\(_2\)SO\(_4\) and evaporated to give the crude product. The residue was subjected to column chromatography on silica gel using eluent (90:10 hexane/ethyl acetate) to provide the pure epoxide 10 (0.969 g, 72 % yield) as an oil. \(^1\)H NMR (200MHz, CDCl\(_3\)): \(\delta\) 1.05 (d, J = 7.2
Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.25-1.42 (m, 2H), 1.62-2.68 (m, 2H), 1.84-1.92 (m, 1H), 2.05-2.11 (m, 1H), 2.58-2.64 (m, 1H), 2.82 (d, J = 4.1 Hz, 1H), 3.05 (d, J = 3.6 Hz, 1H), 3.70 (s, 3H). MS (EI): m/z 199 (M+1). IR : 1200, 1680 cm⁻¹.

**Methyl 2-[2-hydroxy-4-methyl-3-(3-oxobutyl)-(1S,2S,4R)-cyclohexyl]-(2R)-propanoate (11).** Biscyclopentadienyl titanium chloride (Cp₂TiCl) was prepared by the addition of Zn (1.981 g, 30.30 mmol), freshly fused ZnCl₂ (2.064 g, 15.15 mmol) to the biscyclopentadienyl dichloride (Cp₂TiCl₂) (3.772 mg, 15.15 mmol) in dry THF (25 mL). It was stirred at ambient temperature till the red colour changed to dark blue. It was then cooled to -15 °C and added to a solution of epoxides 10 (1 g, 5.05 mmol) and methylvinyl ketone (4.20 mL, 50.50 mmol) in 20 mL of THF over 5 min, and the reaction mixture was stirred at -15 °C for 10 min. The reaction mixture was quenched with 10 % H₂SO₄ and extracted into ether. The ether extract was dried after being washed with NaHCO₃, and the product was isolated by column chromatography using silica gel using eluent (80:20 hexane/ethyl acetate) to give keto alcohol 11 (109 mg, 8 % yield) as an oil. ¹H NMR (200MHz, CDCl₃): δ 0.94 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 7.7 Hz, 3H), 1.20-1.92 (m, 7H), 1.62-2.68 (m, 2H), 1.84-1.92 (m, 1H), 2.12 (s, 3H), 2.52 (m, 1H), 3.48 (td, J = 4.8, 9.6 Hz, 1H), 3.66 (d, J = 7.6 Hz, 3H). MS (EI): m/z 271 (M+1). IR : 1200 cm⁻¹.

**3,6-Dimethyl-7-[2-(2-methyl-1,3-dithiolan-2-yl)ethyl]perhydrobenzo[b]furan-2-one (13).** A 250 mL two neck round-bottomed flask equipped with a magnetic stirring bar, dry nitrogen inlet, and septum was charged with ketolactone 7 (2.5 g, 10 mmol) in DCM (100 mL) was added drop wise 1,2 ethane dithiol (1.67 mL, 20 mmol) with stirring at 0 °C, then BF₃.Et₂O (2.5 mL, 20 mmol) was added drop wise. The reaction mixture was stirred at room temperature for 3 hours. After completion as indicated by TLC, the reaction mixture was diluted with DCM, washed successively with 5 % NaHCO₃, water, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using eluent (90:10 hexane/ethyl acetate) to provide the pure thioketal 13 (3.43 g) in 98 % yield as colorless semisolid. ¹H NMR (200MHz, CDCl₃): δ 0.98 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 7.1 Hz, 3H), 1.17-1.29 (m, 2H), 1.37-1.43 (m, 1H), 1.56-1.75 (m, 4H), 1.76 (s, 3H), 1.82-1.93 (m, 2H), 2.12-2.19 (m, 1H), 2.22-2.27 (m, 1H), 2.73-2.79 (m, 1H), 3.28-3.48 (m, 4H), 4.38 (t, J = 3.2 Hz, 1H). MS (EI):315 (M+1). IR (neat):1780 cm⁻¹. Optical rotation [α]D: (+) 32.10 (c=1.0, CHCl₃).

**Methyl-2-{2-hydroxy-4-methyl-3-[2-methyl-1,3-dithiolan-2-yl]ethyl] cyclohexyl}propanoate (15).** In a 100 mL round-bottomed flask equipped with a magnetic stirring bar, with lactone 14 (3.15 g, 10 mmol) in methanol (20 mL) was added drop wise 0.5 N NaOH solution with stirring at 0°C, then the reaction mixture was stirred at room temperature for 3 hours. Methanol was removed under reduced pressure and the reaction mixture was acidified using 1% HCl using congeored pH paper. The solid separated was extracted with ether and was added freshly prepared diazomethane at -24°C, ether was concentrated and the residue was subjected to column chromatography on silica gel using eluent (90:10 hexane/ethyl acetate) to provide the pure hydroxyester 15 (1.73 mg) in 50 % yield as colorless semisolid. (Starting lactone was
isolated as remaining amount). $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 0.93 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 7.2 Hz, 3H), 1.30-1.58 (m, 8H), 1.76 (s, 3H), 1.80-2.14 (m, 3H), 2.54 (m, 1H), 3.22-3.38 (m, 5H), 3.67 (s, 3H), 3.85 (brs, 1H). $^{13}$C NMR (200MHz, CDCl$_3$): $\delta$ 177.10, 96.22, 77.61, 76.98, 76.81, 67.82, 67.39, 51.29, 48.87, 45.75, 42.99, 42.36, 39.86, 35.40, 32.45, 30.82, 27.03, 24.57, 20.57, 15.52. MS (EI): m/z 347 (M+1). IR (neat): 1755, 3400 cm$^{-1}$. Optical rotation $[\alpha]_D$: (+) 21.24 (c=2.0, CHCl$_3$).

Methyl-2-{4-methyl-[2-methyl-1,3-dithiolan-2-yl]ethyl}-2-oxocyclohexyl} propanoate (16). Pyridinium chlorochromate (PCC) (433 mg, 2 mmol) was added to a solution of hydroxyester 12 (350 mg, 1 mmol) in 1M DCM (1 mL) and NaOAc (8.2 mg, 0.1 mmol) in portions at 0°C. After stirring the reaction mixture for 3 hours isopropanol (1 mL) was added and the solvent was removed under reduced pressure. The residue was triturated with ether and filtered through celite. The precipitate was thoroughly washed with ether, and the organic layer was washed with dil. HCl, water and brine and dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using eluent (95:5 hexane/ethyl acetate) to provide the pure ketone 16 (383 mg, 89% yield) as colorless semi-solid.

$^1$H NMR (200MHz, CDCl$_3$): $\delta$ 1.01 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 7.4 Hz, 3H), 1.24-1.33 (m, 1H), 1.64-1.73 (m, 6H), 1.77 (s, 3H), 1.96-2.02 (m, 1H), 2.09-2.14 (m, 1H), 2.32-2.35 (m, 1H), 2.60-2.66 (m, 1H), 2.75-2.84 (m, 1H), 3.27-3.36 (m, 4H), 3.67 (s, 3H). MS (EI): m/z 344 (M$^+$). IR (neat): 1600, 1765 cm$^{-1}$. Optical rotation $[\alpha]_D$: (+) 18.31 (c=1.0, CHCl$_3$).

Methyl-2-{2-[1-methoxy-(E/Z)-methylidene]-4-methyl-3-[2-(2-methyl-1,3-dithiolan-2-yl)ethyl]cyclohexyl}propionate (17). A solution of methoxymethyltriphenylphosphonium chloride (296 mg, 0.867 mmol) in THF (1 mL) and HMPA (1 mL) was stirred at 0°C for 20 min with a solution of 0.5 M potassium bis(trimethylsilyl)amide (KHMD) (0.43 mL, 3 mmol) in toluene. To this solution was slowly added a solution of ketone 16 (100 mg, 0.289 mmol) in THF (1 mL) and the resulting reaction mixture was allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was cooled to 0°C and saturated NH$_4$Cl solution was added and extracted with diethyl ether, the combined organic layers were washed with H$_2$O, brine, dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using eluent (96:4 hexane/ethyl acetate) to provide the pure methylvinylether 17 (144 mg) in 45% yield as colorless semi-solid. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 0.86 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.18-1.53 (m, 10H), 1.72 (s, 3H), 2.21-2.43 (m, 1H), 2.62-2.70 (m, 1H), 3.24-3.34 (m, 4H), 3.49 (s, 3H), 3.67 (s, 3H), 5.76, 5.87 (2s, 1H). MS (EI): m/z 373 (M$^+$). IR (neat): 1650 (enol ether), 1730 (COOCH$_3$) cm$^{-1}$.

Methyl-2-{2-[1-methoxy-(Z)-methylidene]-4-methyl-3-(3-oxobutyl)cyclohexyl}propanoate (2). To a stirred solution of HgCl$_2$ (157 mg, 0.58 mmol) and powdered CaCO$_3$ (96 mg, 0.96 mmol) in acetonitrile and water (8:2, 6 mL), was added at 25°C a solution of thioketal 17 (144 mg, 0.38 mmol) in in acetonitrile and water (8:2, 4 mL). The resulting reaction mixture was stirred under N$_2$ atmosphere for 6 hours, cooled and filtered; the filtered cake was washed with DCM. The
organic layer was washed successively with 5M aqueous NH₄OAc and water, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using eluent (90:10 hexane/ethyl acetate) to provide the pure ketone 2 (73 mg) in 80% yield as colorless semi-solid. ¹H NMR (200MHz, CDCl₃): δ 0.88 (d, J = 7.2 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H), 1.18-1.40 (m, 10H), 2.06 (s, 3H), 2.22-2.40 (m, 1H), 2.60-2.72 (m, 1H), 3.46 (s, 3H), 3.66 (s, 3H), 5.72, 5.90 (2s, 1H). MS (EI): m/z 297 (M+1). IR (neat): 1650 (enol ether), 1710 (C=O), 1720 (COOCH₃) cm⁻¹. Optical rotation [α]D: (+) 12.82 (c=1.0, CHCl₃).

1,5,9-Trimethyl-(1R,4S,5R,8S,9R,12S,13R)-11,14,15,16-tetraoxatetracyclo [10.3.1.O₄,13.O₈,13]hexadecan-10-one (Artemisinin) (1). To a solution of enol ether 3 (70 mg, 0.23 mmol) in methanol (5 mL) was added Rose Bengal (5 mg). The resulting reaction mixture through which oxygen was bubbled was cooled to –78°C and irradiated, using an ordinary tungsten lamp (250V, 500W) for 4 hours. Then the HCl gas was passed to the reaction mixture until the red solution was decolorized. After further stirring at room temperature for 1.5 hours, the reaction solution was neutralized with 5% NaHCO₃ and concentrated under reduced pressure to give crude product.

To a solution of above crude product in ether (5 mL) was added a solution of 70% HClO₄ (1 mL) and water (5 mL). The resulting reaction mixture was stirred at 25°C for 28 hours. The ethereal layer was separated and the aqueous layer was further extracted with ether. The combined ethereal solution was washed, dried and concentrated to obtain the target compound. The crude product was purified on preparative TLC (eluent petroleum ether/ethyl acetate, 90/10) to give 1 (6 mg) in 10% yield. ¹H NMR (500MHz, CDCl₃): δ 1.00 (d, J = 6.0 Hz, 3H), 1.01-1.13 (m, 2H), 1.21 (d, J = 7.4 Hz, 3H), 1.34-1.43 (m, 3H), 1.44 (s, 3H), 1.74-1.79 (m, 2H), 1.86-1.90 (m, 1H), 1.97-2.07 (m, 2H), 2.40-2.46 (qxd, J = 3.8, 8.9 Hz, 1H), 3.36-3.41 (qxd, J = 1.7, 5.3, 5.4 Hz, 1H), 5.84 (s, 1H). MS (FAB): m/z 283 (M+1). IR (KBr): 1740 (δ-lactone) cm⁻¹. Optical rotation [α]D: (+) 87.94 (c=0.1, Dioxane).

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References