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A concise stereoselective total synthesis of (+)-artemisinin

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ABSTRACT

A protective group free, concise, and stereoselective total synthesis of (+)-artemisinin, starting from readily available (*R*)-(+)-citronellal, is described. Asymmetric 1, 4-addition, Aldol condensation, Ene reaction, regioselective hydroboration are the key steps involved in the total synthesis of the target molecule.

1. Introduction

Malaria continues to be one of the most widespread health hazards affecting over 500 million people and causing over two million deaths every year.[1] The adverse reactions/side effects in patients suffering with malaria caused from quinine, chloroquine has overwhelmed their utility and increased the demand for better therapeutic drugs. The identification of the sesquiterpenoid lactone endoperoxide (+)-Qinghaosu, also called as (+)-artemisinin having unusual trioxane structure with seven stereogenic centers and tetracyclic framework from the Chinese medicinal herb[2] has been a major break-through in malarial therapy.[3] Intrigued by the architectural complexity, pharmacological properties and scarcity of the material, artemisinin as well as its derivatives have become an attractive target molecules for synthetic organic chemists toward its total synthesis.[4,5] The significant importance of this natural product has also led to focus on the semisynthesis from other naturally occurring precursors, such as arteannuic acid **2** and arteannuin B **3** (Fig. 1).[6]

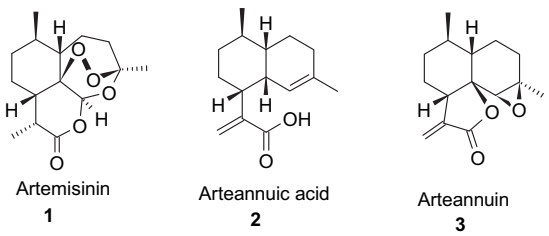
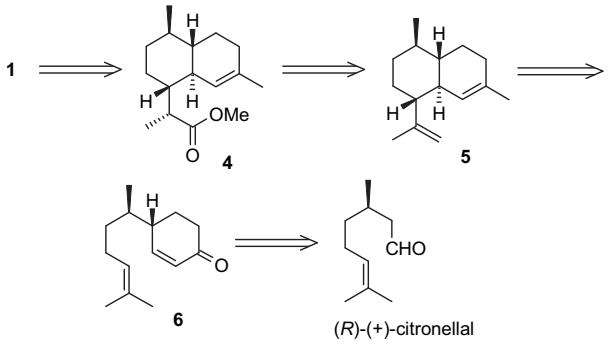


Figure 1. Natural products.

Recently, we have reported a chiron approach for the total synthesis of artemisinin starting from isolimonene.[7] In continuation, we herein wish to report an efficient, concise protective group free total synthesis of artemisinin.

Earlier synthetic strategies comprised of protective group manipulations, which lead to lengthy synthesis resulting in reduced reaction efficiency. In our synthetic design, we identified the well known ester **4** as the key precursor, which can be photooxygenated to obtain target compound. Key precursor **4** was proposed to be obtained by regioselective oxidation followed by esterification of **5**. Ene cyclization of the product obtained after methyl Grignard reaction on **6** was presumed to give **5** and **6** in turn could be easily synthesized from (*R*)-citronellal (Scheme 1).



Scheme 1. Retrosynthesis.

2. Results and discussion

The synthesis began with an enamine mediated 1, 4-addition of (*R*)-citronellal to methyl vinyl ketone (MVK) in presence of proline-derived catalyst[8] and ethyl 3,4-dihydroxybenzoate as a co-catalyst[9]

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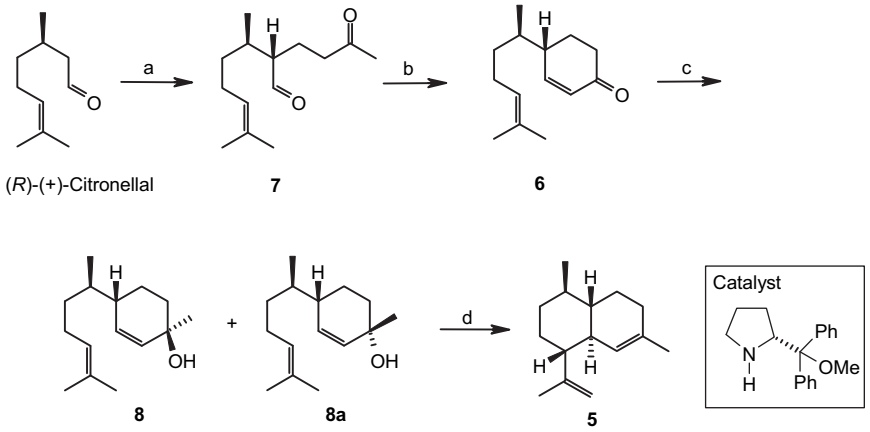


Scheme 2. Reagents and conditions: (a) MVK, catalyst (5 mol %), ethyl 3,4-dihydroxybenzoate (20 mol %), neat, 0–4 °C, 48 h, 70%. (b) KOH (0.1 N aq, 1.0 equiv), *n*-Bu_4NOH (40% aq, cat.), Et_2O: THF: H_2O (3:1:3), reflux, 8 h, 84%. (c) CH_3MgI, Et_2O, 2 h, rt, 92%. (d) $SnCl_4$, benzene:Et_2O (4:1), 0 °C, 65%.

by following Nicoloau's[10] procedure to obtain **7** in 70% yield with 83% *de* (based on ^1H NMR). Intramolecular Aldol condensation of **7** with aq KOH under reflux condition afforded compound **6** in 84% yield. The enone **6** was treated with methyl magnesium iodide to yield **8** and **8a** as a mixture of diastereomers.[11] As the stereochemistry at C4 was not the critical parameter for us, we proceeded further with this mixture for cyclization. Thus, treating diastereomeric mixtures of **8** and **8a** with $SnCl_4$ in benzene–diethyl ether (4:1) gave required ene product **5** (purified by column chromatography using silica gel impregnated with $AgNO_3$ and analyzed by 1D & 2D NMR studies) in 65% yield (Scheme 2).[12]

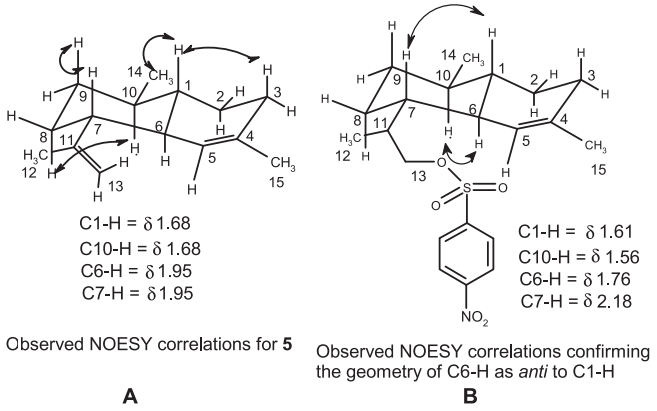
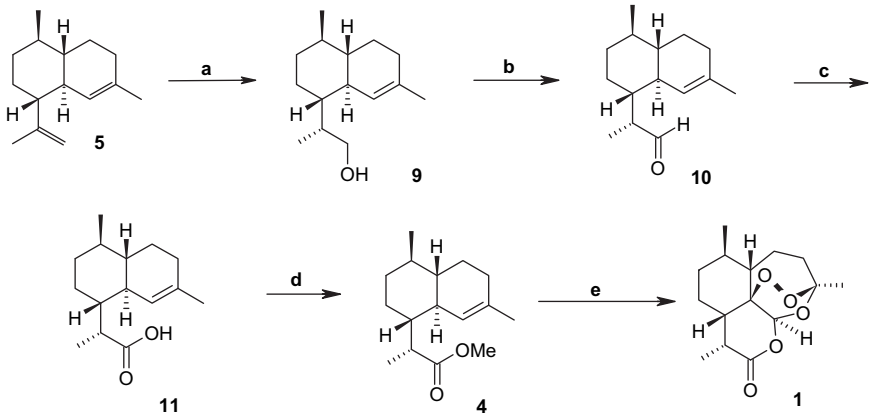


Figure 2. NOESY correlations.

The orientation of proton H-6 at this stage could not be resolved due to complexity (merging of H-1 and H-10 (δ 1.68)), and H-6 and H-7 at (δ 1.95) in the NMR spectrum (Fig. 2A). As the H-6 proton orientation does not affect the further steps toward the total synthesis,[13] we proceeded further with this bicyclic skeleton for oxygenation toward the target synthesis.

The olefin **5** was subjected to regioselective hydroboration[4f] using 9-BBN following a known protocol[14] to get the required primary alcohol **9** in 85% yield with 90% *de* as judged by GC–MS. 2D NMR studies of compound **9** also did not reveal the exact orientation of H-6. Attempts to get a solid compound by derivatization of **9** as the corresponding ester with benzoic acid, 4-nitrobenzoic acid, 3,5-dinitrobenzoic acid, 4-chlorobenzenesulfonyl chloride, and 4-nitrobenzenesulfonyl chloride were not successfull. However, the 4-nitrobenzene sulfonate derivative showed significant NOESY correlations confirming the stereochemistry of the H-6 to be *anti* to that of H1 (Fig. 2B). The **9** was oxidized to corresponding aldehyde **10** by Swern oxidation[15] and subsequentially to acid **11** using $NaClO_2$, NaH_2PO_4[16] in 80% yield. The **11** was esterified with methyl iodide in presence of K_2CO_3 to get key precursor **4**. The **4** was subjected to photooxidation following Haynes protocol[5f] (DCM, rose bengal, copper triflate) to achieve the total synthesis of artemisinin (Scheme 3). The product was recrystallized and its structure (Fig. 3) was confirmed by X-ray analysis.[17] The spectral data of the synthetic compound was compared with the natural product and found to be identical.



Scheme 3. Reagents and conditions: (a) 9-BBN, 3 N NaOH, H_2O_2, 85%. (b) Swern oxidation, 94%. (c) $NaClO_2$, NaH_2PO_4, 0 °C, 80%. (d) CH_3I, K_2CO_3, acetone, rt 89%. (e) (i) O_2, rose bengal, −30 °C, 6 h, CH_3CN, 500 W tungsten filament lamp, (ii) O_2, $Cu(OTf)_2$, CH_3CN, −20 °C, (iii) TsOH (cat.), CH_2Cl_2, 4 h, rt, 25%.

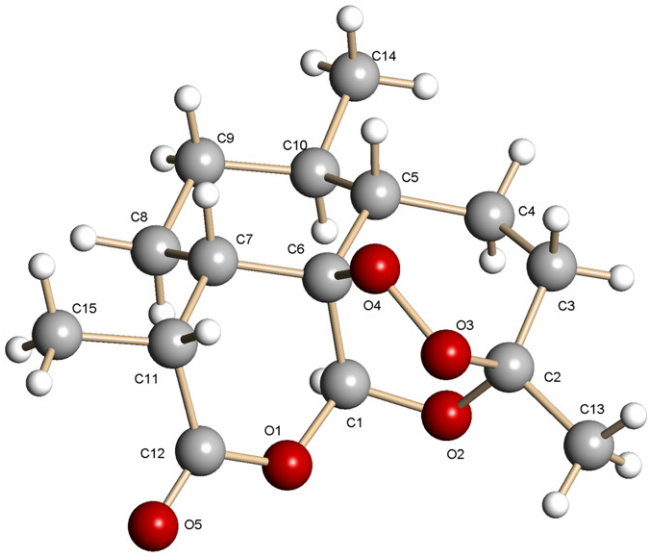


Figure 3. ORTEP diagram of artemisinin.

3. Conclusions

In conclusion, we have achieved a concise and an efficient total synthesis of potent antimalarial drug (+)-artemisinin. The key precursor **4** was synthesized with an overall yield of 13.0% starting from (*R*)-citronellal in eight steps. This strategy is found to be the shortest of the syntheses known so far in the literature. This strategy involves no protective groups[18] and presents several advantages, such as readily accessible starting materials and high yielding reactions. Further studies toward process development are currently being investigated.

4. Experimental section

4.1. General methods

IR spectra were recorded on Perkin–Elmer Infrared 683 spectrophotometer.^{1}H (200 MHz and 300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on Varian Gemini (200 MHz) or Bruker Avance (300 MHz) spectrometers using $CDCl_3$ as solvent at ambient temperature. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Optical rotations were measured using Perkin–Elmer model no.343 digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and High (HRMS) resolution, *m*/*z* ratios are reported as values in atomic mass units. Mass analysis was done in APCI mode or EI mode. All reagents and solvents were reagent grade and used without further purification unless specified otherwise. Column chromatography was carried out using Acme's silica gel (60–120 mesh or 100–200 mesh) packed in glass columns (20–25 g per 1 g of the crude product). All reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. GC–MS was performed using DB5 column of size 30 cm×0.25 mm.

4.1.1. (2S,3R)-3, 7-Dimethyl-2-(3-oxobutyl) oct-6-enal **7**. The pre-cooled mixture of (*R*)-(+)-citronellal (2.5 g, 16.2 mmol) and methyl vinyl ketone (1.97 mL, 24.3 mmol) was added to the mixture of proline-derived catalyst (0.216 g, 0.8 mmol, 5 mol %) and ethyl 3, 4-dihydroxybenzoate (0.590 g, 3.2 mmol, 20 mol %) at 0 °C. The resulting homogeneous solution was stirred at 4 °C for 48 h and the reaction mixture was directly subjected to flash column chromatography (silica gel, 8% EtOAc–hexane) to obtain **7** as a colorless oil (2.52 g, 70%, ca. 16:1 dr). R_f=0.60 (silica gel, 20% EtOAc–hexane). $[\alpha]_D^{27}$ −27.9 (*c* 2.4, $CHCl_3$). IR (neat): ν 2964, 2923, 2718, 1718, 1632, 1384 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.99 (d, *J*=7.0 Hz, 3H), 1.18–1.33 (m, 1H), 1.34–1.52 (m, 1H), 1.60 (s, 3H), 1.68 (s, 3H), 1.69–1.78 (m, 2H), 1.81–2.08 (m, 3H), 2.13 (s, 3H), 2.15–2.25 (m, 1H), 2.37 (ddd, *J*=7.3, 7.9, 17.7 Hz, 1H), 2.52 (ddd, *J*=5.8, 8.7, 17.7 Hz, 1H), 5.02–5.11 (m, 1H), 9.64 (d, *J*=2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.9, 17.6, 19.7, 25.5, 25.6, 29.9, 33.3, 33.9, 41.4, 56.2, 123.8, 131.9, 205.2, 208.0. ESI-MS: *m*/*z* 247 $(M+Na)^+$. HRMS (ESI-MS) calcd. For $C_{14}H_{24}NaO_2$ $(M+Na^+)$ 247.1669, found 247.1679.

4.1.2. (S)-4-((R)-6-Methylhept-5-en-2-yl) cyclohex-2-enone **6**. To a solution of **7** (2.1 g, 9.37 mmol) in Et_2O (100 mL) and THF (30 mL) was added KOH (100 mL, 0.1 N aq) and *n*-Bu_4NOH (1.70 mL, 40% aq). The reaction mixture was heated to reflux with vigorous stirring for 8 h. Upon cooling to room temperature, the reaction mixture was extracted with Et_2O (3×100 mL). The combined organic phase was washed with brine (1×100 mL) and dried over anhydrous Na_2SO_4. The solvent was filtered and then evaporated under vacuum to obtain the crude residue, which was subjected to flash column chromatography (silica gel, 4% EtOAc–hexane) to yield **6** as a colorless oil (1.63 g, 84%, ca. 8:1 dr). R_f=0.56 (silica gel, 10% EtOAc–hexane). $[\alpha]_D^{25}$ −44.8 (*c* 1.5, $CHCl_3$). IR (neat): ν 2960, 2924, 1682, 1452, 1381, cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.94 (d, 3H, *J*=6.8 Hz), 1.19–1.33 (m, 1H), 1.34–1.49 (m, 1H), 1.61 (s, 3H), 1.69 (s, 3H), 1.72–1.76 (m, 1H), 1.77–1.89 (m, 1H), 1.90–2.15 (m, 3H), 2.35 (ddd, *J*=5.1, 13.4, 16.6 Hz, 1H), 2.42–2.47 (m, 1H), 2.52 (dt, *J*=3.9, 16.6 Hz, 1H), 5.05–5.14 (m, 1H), 6.02 (ddd, *J*=0.9, 2.8, 10.4 Hz, 1H), 6.88 (dt, *J*=1.9, 10.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.9, 16.4 17.6, 23.9, 25.6, 25.7, 33.8, 34.0, 35.9, 36.0, 37.4, 37.6, 40.9, 41.5, 124.0, 129.5, 129.8, 131.6, 131.7, 154.2, 155.3, 199.9. ESI-MS: *m*/*z* 207 $(M+H)^+$. HRMS calcd for $C_{14}H_{22}ONa$ $(M+Na^+)$ 229.1568, found 229.1579.

4.1.3. (S)-1-Methyl-4-((R)-6-methylhept-5en-2-yl) cyclohex-2-enol ***8*** *and* ***8a***. To a mixture of Mg turnings (0.524 g, 21.8 mmol) and diethyl ether (5 mL) was added methyl iodide (1.36 mL, 21.8 mmol) at 0 °C under N_2 atmosphere and stirred at room temperature for 2 h. To this Grignard reagent, the enone compound **6** (1.5 g, 7.28 mmol) dissolved in diethyl ether (15 mL) was added drop wise at 0 °C and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) at 0 °C and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic phase was washed with brine (1×25 mL), dried over anhydrous Na_2SO_4. Filtration followed by evaporation of the solvent under vacuum afforded crude residue, which was subjected to column chromatography (silica gel, 7% EtOAc–hexane) to give **8** and **8a** as colorless oils (1.52 g, 95%). R_f=0.55 (silica gel, 20% EtOAc–hexane). IR (neat): ν 3367, 2963, 2863, 1455, 1377, 1117 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.79–0.91 (m, 3H), 1.06–1.23 (m, 1H), 1.28 (s, 3H), 1.30–1.76 (m, 6H), 1.61 (s, 3H), 1.69 (s, 3H) 1.78–2.17 (m, 4H), 5.05–5.15 (m, 1H), 5.47–5.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.7, 16.4, 17.6, 22.0, 22.3, 24.1, 25.7, 26.0, 28.4, 29.6, 33.7, 34.1, 36.3, 37.4, 38.3, 40.1, 40.6, 41.1, 69.8, 124.7, 130.9, 131.3, 132.0, 133.0, 133.7, 134.5, 134.8. ESI-MS: *m*/*z* 245 $(M+Na)^+$. HRMS calcd for $C_{15}H_{26}ONa$ $(M+Na^+)$ 245.1881, found 245.1887.

4.1.4. (1R,4R,4aS,8aS)-4,7-Dimethyl-1-(prop-1en-2-yl)-1,2,3,4,4a,5,6,8a-octahydronphthalene ***5***. To a stirred solution of compounds **8** and **8a** (0.350 g, 1.57 mmol) in benzene and diethyl ether (4:1, 8 mL) was added stannic chloride (0.18 mL, 1.57 mmol)

at 0 °C under nitrogen atmosphere. After 15 min the reaction mixture was quenched with aq saturated $NaHCO_3$ solution (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2×10 mL). The combined organic phase was washed with brine (1×10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum, followed by column chromatography of the crude residue (silica gel impregnated with silver nitrate, hexane) gave **5** as a colorless oil (0.208 g, 65%). R_f=0.3 (silica gel impregnated with silver nitrate, hexane). $[\alpha]_D^{28}$−107 (*c* 1.1, $CHCl_3$). IR (neat): *ν* 3072, 2924, 1643, 1448, 1375, 885 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 0.93 (d, 3H, *J*=6.6 Hz), 1.08–1.49 (m, 4H), 1.50–1.59, (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 1.64–1.76 (m, 2H), 1.90–2.01 (m, 4H), 4.66–4.73 (m, 2H), 5.34 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 17.2, 19.6, 19.7, 23.6, 29.4, 31.2, 33.0, 35.4, 39.4, 40.0, 47.9, 110.2, 125.3, 133.3, 149.0. APCI: *m*/*z* 205 $(M+H)^+$. HRMS calcd for $C_{15}H_{24}$ $(M+H^+)$ 205.1951, found 205.1959.

$AgNO_3$ column chromatography: To a solution of silver nitrate (3.0 g) in H_2O (5 mL) was added acetone (100 mL) and 12.0 g of silica gel (60–120 mesh). The reaction mixture was stirred and subjected to evaporation under vacuum (to remove water and acetone). Traces of water present in the slurry were removed by azeotropic distillation with acetone (2×75 mL) using rotavapor. The dry silica with $AgNO_3$ was directly utilized for column chromatography.

4.1.5. (R)-2-((1R,4R,4aS,8aR)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1-yl)propan-1-ol ***9***. Compound **5** (0.120 g, 0.59 mmol) in dry THF (3 mL) was charged into a (25 mL) two neck round bottomed flask equipped with a magnetic spin bar, nitrogen inlet, and a septum. To this was added 9-BBN (2.35 mL, 1.18 mmol, 0.5 M in THF) solution drop wise at 0 °C and stirred for 24 h at room temperature. Absolute ethanol was added (5 mL) at room temperature followed by 3 N NaOH (5 mL) and then cooled to 0 °C. Then 30% H_2O_2 (6 mL) was added drop by drop and the solution was stirred for 12 h at room temperature. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic phase was washed with brine (1×10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum followed by column chromatography (silica gel, 5% EtOAc–hexane) purification afforded **9** as a light yellow liquid. (0.110 g, 85% with 90% *de*). R_f=0.5 (20% EtOAc–hexane). $[\alpha]_D^{25}$−80.0 (*c* 1.0, $CHCl_3$). IR (neat): *ν* 3326, 2930, 1632, 1451, 1379, 1027 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 0.89 (d, 3H, *J*=6.6 Hz), 0.97 (d, 3H, *J*=6.9 Hz), 0.99–1.18 (m, 2H), 1.21–1.74 (m, 8H), 1.64 (s, 3H), 1.83–2.07 (m, 4H), 3.43 (dd, 1H, *J*=8.7, 10.4 Hz), 3.75 (dd, 1H, *J*=5.1, 10.5 Hz), 5.55–5.63 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 15.6, 16.9, 19.5, 23.7, 27.7, 29.8, 31.1, 35.5, 36.1, 39.7, 39.9, 42.9, 65.3, 125.2, 134.3. APCI: *m*/*z* 223 $(M+H)^+$. HRMS calcd for $C_{15}H_{26}O$ $(M+H^+)$ 223.2056, found 223.2064.

4.1.6. (R)-2-((1R,4R,4aS,8aR)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)propanal ***10***. Oxalyl chloride (0.79 mL, 9.0 mmol) was charged into a (50 mL) two neck round bottomed flask equipped with a magnetic stir bar, nitrogen inlet, and a septum. After addition of CH_2Cl_2 (5 mL), the solution was cooled to −78 °C. To this dimethyl sulphoxide (1.28 mL, 18.0 mmol) was added and the resulting white suspension was stirred for 30 min. Alcohol **9** (1.0 g, 4.50 mmol) in CH_2Cl_2 (10 mL) was added and the reaction mixture was stirred for 1.5 h at −78 °C. The reaction mixture was treated with Et_3N (3.75 mL, 27.0 mmol) and warmed to room temperature over a period of one hour. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (1×10 mL), brine (1×10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 2% EtOAc–hexane) to yield **10** as a light yellowish liquid. (0.930 g, 94%). R_f=0.7 (10% EtOAc–hexane). IR (neat): *ν* 2928, 2870, 1718, 1632, 1384 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 0.93 (d, 3H, *J*=6.8 Hz), 1.08 (d, 3H, *J*=6.8 Hz), 1.61 (s, 3H), 1.12–1.74 (m, 8H), 1.75–2.05 (m, 4H), 2.29–2.48 (m, 1H), 5.29 (*s*, 1H), 9.67 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 9.3, 16.8, 19.3, 23.4, 29.5, 30.8, 30.9, 35.1, 39.2, 39.4, 41.5, 49.4, 124.3, 135.8, 206.0. ESI-MS: *m*/*z* 243 $(M+Na)^+$. HRMS calcd for $C_{15}H_{24}NaO$ $(M+Na^+)$ 243.1719, found 243.1717.

4.1.7. (R)-2-((1R,4R4aS,8aR)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahyronaphthalen-1-yl)propanoic acid ***11***. 2-Methyl 2-butene (1 mL) was added to a stirred solution of aldehyde **10** (0.430 g, 1.95 mmol) in *tert*-butyl alcohol (8 mL) at 0 °C. To this solution was added NaH_2PO_4 (1.52 g, 9.72 mmol) and $NaClO_2$ (0.441 g, 4.83 mmol) dissolved in H_2O (5 mL) and the reaction mixture was stirred for half an hour. After completion of the reaction, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine (2×10 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography, (silica gel, 10% EtOAc–hexane) to give **11** as a yellow liquid (0.370 g, 80%). R_f=0.3 (20% EtOAc–hexane). $[\alpha]_D^{26}$−97 (*c* 1.1, $CHCl_3$). IR (neat): *ν* 3100, 2931, 1702, 1455, 1240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): *δ* 0.90 (d, 3H, *J*=7.0 Hz), 1.14 (d, 3H, *J*=7.0 Hz), 1.18–1.36 (m, 4H), 1.63 (s, 3H), 1.36–1.83 (m, 7H), 1.88–2.07 (m, 3H), 2.77 (dq, 1H, *J*=3.1, 7.0, Hz), 5.67 (d, 1H, *J*=5.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 14.4, 17.1, 19.6, 23.8, 28.1, 29.6, 31.1, 35.3, 39.8, 40.0, 43.6, 60.2, 124.9, 134.5, 182.2. APCI: *m*/*z* 237 $(M+H)^+$. HRMS calcd for $C_{15}H_{25}O_2$ $(M+H^+)$ 237.1849, found 237.1854.

4.1.8. (R)-Methyl2-((1R,4R,4aS,8aR)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octhydronaphthale-1-yl)propanoate ***4***. Methyl iodide (0.17 mL, 2.67 mmol) was added drop by drop to the suspension of acid compound **11** (0.210 g, 0.89 mmol) and K_2CO_3 (1.06 g, 4.45 mmol) in dry acetone (10 mL) at 0 °C, after addition of methyl iodide, the ice bath was removed and the reaction mixture was stirred at room temperature for 9 h. The solvent was removed under vacuum, and the residue was diluted with ethyl acetate (10 mL) and H_2O (5 mL), the organic layer was separated and aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layer was washed with the brine (1×10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification of the crude product (silica gel column chromatography, 3% EtOAc: hexane) afforded **4** as a light yellow liquid (0.20 g, 89%). R_f=0.6 (10% EtOAc–hexane). $[\alpha]_D^{26}$−87 (*c* 3.0, $CHCl_3$). IR (neat): *ν* 2930, 2859, 1735, 1454, 1196, 1171 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 0.90 (d, 3H, *J*=6.6 Hz), 1.13 (d, 3H, *J*=6.9 Hz), 1.20–1.36 (m, 3H), 1.37–1.78 (m, 7H), 1.64 (s, 3H), 1.79–2.11 (m, 3H), 2.76 (dq, 1H, *J*=3.0, 7.2 Hz), 3.65 (s, 3H), 5.62–5.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 14.2, 16.9, 19.4, 23.6, 28.3, 29.4, 31.0, 35.2, 39.7, 40.0, 40.1, 43.4, 51.0, 124.7, 134.6, 176.2. ESI-MS: *m*/*z* 273 $(M+Na)^+$. HRMS calcd for $C_{16}H_{27}O_2$ $(M+H)^+$ 251.2006, found 251.2000.

4.1.9. (+)-Artemisinin ***1***. The methyl ester **4** (0.1 g, 0.40 mmol) was dissolved in acetonitrile (15 mL) and irradiated with tungsten filament, 500 W in the presence of Rose Bengal sensitizer, under a slow stream of O_2, for 6 h at −30 °C. The solvent was evaporated under vacuum, and the residue was submitted to flash chromatography (8% EtOAc–hexane) to give the hydroperoxide compound (0.067 g, 60%). A solution of hydroperoxide compound (0.067 g, 0.23 mmol) in CH_3CN (5 mL) was cooled to −20 °C, under a slow stream of O_2 and treated with $Cu(OTf)_2$ (0.008 g, 0.023 mmol). After 8 h, the reaction mixture was poured into saturated $NaHCO_3$ solution (5 mL) and extracted with diethyl ether (15 mL). The combined organic layer was washed with brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the resulting crude mixture was redissolved in CH_2Cl_2 (5 mL) and to this was added *p*-TsOH (0.003 g) at 0 °C. After stirring for 5 h

at room temperature, the reaction mixture was quenched with solid $NaHCO_3$. The reaction mixture was filtered and the filtrate was dried over anhydrous Na_2SO_4. Evaporation of the solvent, followed by flash chromatography of the residue, (silica gel, 10% EtOAc–hexane) gave **1** as a colorless solid (0.027 g, 25% yield). R_f=0.6 (20% EtOAc–hexane). The obtained product was recrystallized with hexane to afford **1** as colorless needles. Mp=153–155 °C. $[\alpha]_D^{24}$+61 (*c* 0.2, $CHCl_3$) IR (KBr): ν 2921, 2854, 1738, 1115, 994 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (d, 3H, *J*=5.8 Hz), 1.02–1.13 (m, 1H), 1.21 (d, 3H, *J*=7.3 Hz), 1.45 (s, 3H), 1.33–1.54 (m, 4H), 1.69–1.83 (m, 2H), 1.84–1.94 (m, 1H), 1.95–2.11 (m, 2H), 2.36–2.53 (m, 1H), 3.34–3.46 (m, 1H), 5.86 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5, 19.8, 23.4, 24.8, 25.2, 32.9, 33.6, 35.9, 37.5, 45.0, 50.0, 79.5, 93.7, 105.4, 172.0. APCI: *m*/*z* 283 $(M+H)^+$. HRMS calcd for $C_{15}H_{22}NaO_5$ $(M+Na^+)$ 305.1359, found 305.1371.

4.1.10. Nosylate data. *p*-Nitrobenzenesulfonyl chloride (0.022 g, 0.10 mmol) was added to the stirred solution of alcohol **9** (0.015 g, 0.067 mmol) and triethylamine (0.01 mL, 0.08 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, catalytic amount of DMAP was added to this reaction mixture and allowed to stir for 30 min at 0 °C. The reaction was quenched with H_2O (3 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×4 mL) and the combined organic layers were washed with brine solution (1×5 mL). Solvent was evaporated under vacuum and the crude product was purified by silica gel column chromatography. R_f=0.3 (5% EtOAc–hexane), eluted with (2% EtOAc–hexane) to afford nosylate as a yellow sticky liquid (0.026 g, 95%). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.77–0.85 (m, 1H), 0.88 (d, 3H, *J*=6.6 Hz), 0.94 (d, 3H, *J*=7.0 Hz), 0.98–1.14 (m, 1H), 1.20–1.46 (m, 5H), 1.47–1.69 (m, 6H), 1.71–2.01 (m, 2H), 2.11–2.27 (m, 1H), 3.93 (m, 1H), 4.23 (dd, 1H, *J*=4.9,5.1 Hz), 5.32–5.39 (m, 1H), 8.12 (d, 2H, *J*=8.9), 8.42 (d, 2H, *J*=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ, 15.6, 16.7, 19.4, 23.7, 27.2, 26.5, 29.7, 30.9, 33.0, 35.3, 39.5, 39.6, 42.8, 74.6, 123.9, 124.4, 129.1, 135.2, 142.0. ESI-MS: *m*/*z* 430 $(M+Na)^+$. HRMS calcd for $C_{21}H_{29}NO_5NaS$ $(M+Na^+)$ 430.1660, found 430.1664.

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Supplementary data

Electronic Supplementary Information (ESI) copies of ^1H and ^{13}C NMR spectra are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.051.

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