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Stereoselective total synthesis of (+)-artemisinin☆

J. S. Yadav,* R. Satheesh Babu and G. Sabitha

Organic Chemical Sciences, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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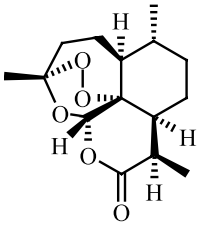
Dedicated to Dr. Sukh Dev on the occasion of his 80th birthday

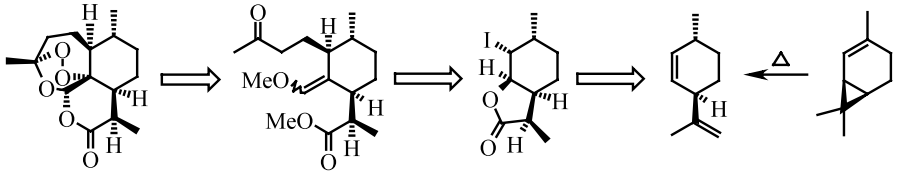
Abstract—The total synthesis of the novel antimalarial drug, a sesquiterpene endoperoxide, (+)-artemisinin is described. The approach is flexible and stereoselective. The use of an intermolecular radical reaction on an intermediate iodolactone and a Wittig reaction on a ketone were employed for the synthesis. © 2002 Published by Elsevier Science Ltd.

Malaria remains an important health problem all over the world (tropics and subtropics), which affects over 400 million people especially in Africa and South East Africa, causing deaths in excess of 2 million each year.[1,2] Increasing resistance of the malaria parasite *Plasmodium falciparum*, toward contemporary antimalarials is a cause for concern. The highly oxygenated sesquiterpene lactone endoperoxide (+)-artemisinin **1** (Qinghaosu) emerged as a potent antimalarial against several resistant strains of malaria without obvious adverse reaction or side effects in patients. Artemisinin, which has been isolated[3,4] from *Artemisia annua* L. *Compositae* (Qinghao), is an active constituent of traditional Chinese herbal medicine which has been used for the treatment of malaria in China for more than 1000 years. The unprecedented unique chemical structure, modest potency and the limited availability of this important natural product delineated the need for a ready synthetic entry to the tetracyclic framework of artemisinin. Though many valuable contributions[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.



(+)-Artemisinin 1

In our retrosynthetic analysis (Scheme 1), we believed that the key intermediate would be an α-hydroperoxy aldehyde which can be easily obtained by photo-oxygenation from methyl vinyl ether **2** because, in a ketalization-like process, simple cyclodehydration of the α-hydroperoxy aldehyde should readily furnish the tetracyclic natural product **1**. Thus, the next intermediate in our analysis was the iodolactone **3** which has the required stereochemistry and further, it can be easily prepared from the starting (+)-isolimonene **4**.



1 **2** **3** **4** Δ^2 Carene

Scheme 1.

Keywords: artemisinin; stereoselective; iodolactone; tris(trimethylsilyl)silane.

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* Corresponding author. Fax: +91-40-716 0512; e-mail: yadav@iict.ap.nic.in

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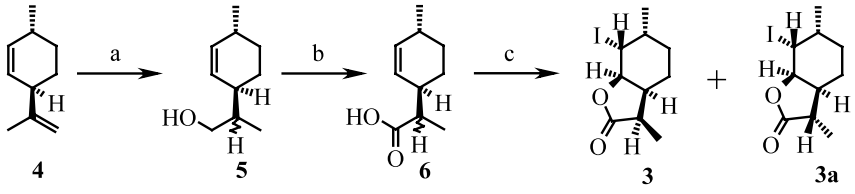
As shown in Scheme 2, (+)-isolimonene **4** was subjected to regioselective hydroboration using dicyclohexylborane[10] to give the required alcohol **5** in 82% yield, which was converted to the corresponding acid **6** in 80% yield by Jones' oxidation.[11] The γ,δ-unsaturated acid **6** was subjected to iodolactonization[12] using KI, I_2 in aq. $NaHCO_3$ to afford iodolactones **3** and **3a** as separable diastereomers, isomeric at C3 in a 68:32 (β:α) ratio in 70% yield. While this work was in progress, the iodolactones were reported by Chavan et al.[13] for the synthesis of wine lactone.

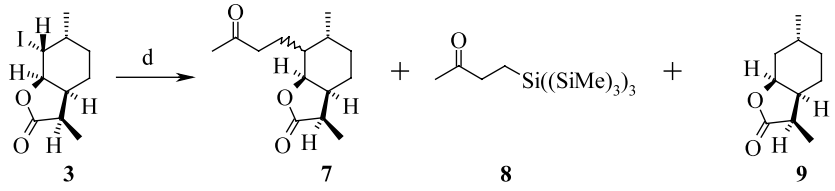
The iodolactone **3** was subjected to an intermolecular radical reaction with methyl vinyl ketone using tris(trimethylsilyl)silane[14] (TTMSS) and AIBN in toluene to yield the corresponding alkylated lactone **7** in 72% yield (Scheme 3) as an inseparable epimeric mixture at C7 (8:2 β/α) along with **8** (~10%) and the reduced product **9** (<5%).

The keto group of lactone **7** was reacted (Scheme 4) with ethanedithiol and $BF_3{\cdot}Et_2O$ in DCM at 0°C to afford thioketal lactones **10**, **11** in quantitative yield.[6] Thioketalization facilitated the separation of the major isomer **11**,[15] which was further subjected to hydrolysis and esterification with diazomethane providing hydroxy ester **12** in 50% yield. (The thioketal lactone **11** was also isolated due to competing lactonization of the hydroxy acid.) The hydroxy methyl ester **12** was transformed into the keto ester **13**[16] using PCC as the oxidizing agent in DCM at room temperature. A two dimensional ^1H NMR study of compound **13** revealed a strong NOE between the two diaxial protons adjacent to the carbonyl group. These observations confirmed its structure.

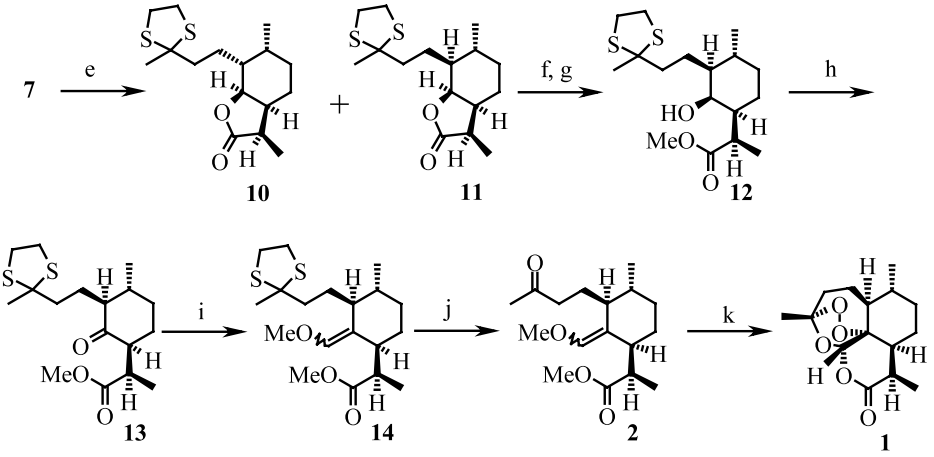
The ketone **13** was subjected to Wittig reaction[17] with methoxymethyl triphenylphosphonium chloride, KHMDS to furnish the required methyl vinyl ether **14** in 45% yield. The deprotection of thioketal **14** using



Scheme 2. *Reagents and conditions*: a. Dicyclohexylborane, THF, 0°C, 7 days, 82%. b. CrO_3, H_2SO_4 in acetone at 0°C, 80%. c. I_2, KI, aq. $NaHCO_3$ 48 h in the dark, 70%.



Scheme 3. *Reagents and conditions*: d. methyl vinyl ketone, $((CH_3Si)_3)_3SiH$, AIBN in refluxing toluene using a syringe pump, 72%.



Scheme 4. *Reagents and conditions*: e. Ethanedithiol, $BF_3{\cdot}Et_2O$ in DCM at 0°C, 98%. f. 10% NaOH in MeOH reflux, 1% HCl to congo red pH at −24°C. g. CH_2N_2 in Et_2O, 50% for two steps. h. PCC, DCM at 0°C, 89%. i. methoxymethyl triphenylphosphonium chloride, 2 M KHMDS, THF:HMPA (8:2) 50°C 24 h, 45%. j. $HgCl_2$, $CaCO_3$ in CH_3CN:H_2O (9:1), 80%. k. O_2, Rose Bengal in MeOH at −78°C, *hv*, 4 h, dry HCl, 70% $HClO_4$ in ether 28 h, 10%.

$HgCl_2$, $CaCO_3$ resulted in the key intermediate **2** in 80% yield. Compound **2** was transformed to the target molecule **1**[18] by photooxidation followed by acid hydrolysis with 70% $HClO_4$ as reported by Zhou et al.[6] The synthetic material was found to be identical with natural artemisinin in every respect (^{1}H NMR, IR, Mass, TLC and $[\alpha]_D$).

In conclusion, we have accomplished a highly efficient and stereoselective total synthesis of (+)-artemisinin **1**. Our approach presents several advantages such as stability and availability of the starting material, high yielding reactions and high stereoselectivity. Further, the approach involves less steps compared to other reported methods; hence we believe that the method can be a valuable route for the synthesis of (+)-artemisinin **1**.

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References

1. Rogers, D. J.; Randolph, S. E. *Science* **2000**, *289*, 1763–1766.
2. White, N. J.; Nosten, F.; Looareesuwan, S.; Watkins, W. M.; Marsh, K.; Snow, R. W.; Kokwaro, G.; Ouma, J.; Hien, T. T.; Molyneux, M. E.; Newbold, C. I.; Ruebush, T. K.; Danis, M.; Greenwood, B. M.; Anderson, R. M.; Olliaro, P. *Lancet* **1999**, *353*, 1965–1967.
3. Liu, J. M.; Ni, M. Y.; Fen, J. F.; Tu, Y. Y.; Wu, Z. H.; Wu, Y. L.; Zhou, W. S. *Huaxue Xuebao* **1979**, *37*, 129–141.
4. Klayman, D. L.; Lin, A. J.; Acton, N.; Scovill, J. P.; Hoch, J. M.; Milhous, W. K.; Theoharides, A. D.; Dobek, A. S. *J. Nat. Prod.* **1984**, *47*, 715–717.
5. Schimid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624–625.
6. Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron* **1986**, *42*, 819–828.
7. (a) Avery, M. A.; Chong, W. K. M.; White, C. J. *J. Am. Chem. Soc.* **1992**, *114*, 974–979; (b) Avery, M. A.; White, C. J.; Chong, W. K. M. *Tetrahedron Lett.* **1987**, *28*, 4629–4632.
8. Ravindranathan, T.; Kumar, M. A.; Menon, R. B.; Hiremath, S. V. *Tetrahedron Lett.* **1990**, *31*, 755–758.
9. Liu, H. J.; Yeh, W. L.; Chew, S. Y. *Tetrahedron Lett.* **1993**, *34*, 4435–4438.
10. (a) Zweifel, G.; Ayyangar, N. R.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2072–2075; (b) Brown, H. C.; Kulkarni, S. V.; Khann, V. V.; Racherla, V. *J. Org. Chem.* **1992**, *57*, 6173–6177.
11. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedors, B. C. L. *J. Chem. Soc.* **1946**, 39–45.
12. House, H. O.; Carlson, R. G.; Babad, H. *J. Org. Chem.* **1963**, *28*, 3359–3361.
13. Chavan, S. P.; Kharul, R. K.; Sharma, A. K.; Chavan, S. P. *Tetrahedron: Asymmetry* **2001**, *12*, 2985–2988.
14. (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194; (b) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678–683.
15. Spectral data for **11**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (d, $J=6.2$ Hz, 3H, CH_3), 1.14 (d, $J=7.1$ Hz, 3H, CH_3), 1.17–1.29 (m, 2H, CH_2), 1.37–1.43 (m, 1H), 1.56–1.75 (m, 4H, CH_2), 1.76 (s, 3H, CH_3), 1.82–1.93 (m, 2H, CH_2), 2.12–2.19 (m, 1H, $CH_2CH(CH)CH$), 2.22–2.27 (m, 1H, $OCHCH$), 2.73–2.79 (m, 1H, $OCCHCH_3$), 3.28–3.48 (m, 4H, SCH_2CH_2S), 4.38 (t, $J=3.2$ Hz, 1H, OCH). MS (EI): 315 (M+1). IR (neat): 1780 cm^{-1}. Anal. calcd for $C_{16}H_{26}O_2S_2$: C, 61.11; H, 8.33. Found: C, 61.08; H, 8.28. Optical rotation $[\alpha]_D$: +32.10 (c 1.0, $CHCl_3$).
16. Spectral data for **13**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (d, $J=6.8$ Hz, 3H, CH_3), 1.14 (d, $J=7.4$ Hz, 3H, CH_3), 1.24–1.33 (m, 1H, CH_2), 1.64–1.73 (m, 6H, CH_2), 1.77 (s, 3H, CH_3), 1.96–2.02 (m, 1H, CH_2), 2.09–2.14 (m, 1H, $CHCH_3$), 2.32–2.35 (m, 1H, $CH_2CH(CO)CH$), 2.60–2.66 (m, 1H, $COOCHCH_3$), 2.75–2.84 (m, 1H, $COCH(CH_2)CH$), 3.27–3.36 (m, 4H), 3.67 (s, 3H, OCH_3). MS (EI): m/z 344 (M^+). IR (neat): 1600, 1765 cm^{-1}. Anal. calcd for $C_{17}H_{28}O_3S_2$: C, 59.27; H, 8.19, Found: C, 59.18; H, 8.24. Optical rotation $[\alpha]_D$: +18.31 (c 1.0, $CHCl_3$).
17. (a) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260–4262; (b) Cazelles, J.; Camuzat-Dedenis, B.; Provot, O.; Robert, A.; Mayrargue, J.; Meunier, B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1265–1270.
18. Spectral data for **1**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (d, $J=6.0$ Hz, 3H, CH_3), 1.01–1.13 (m, 2H, CH_2), 1.21 (d, $J=7.4$ Hz, 3H, CH_3), 1.34–1.43 (m, 3H, CH_2, CH), 1.44 (s, 3H, CH_3), 1.74–1.79 (m, 2H, CH_2), 1.86–1.90 (m, 1H, $CHCH_3$), 1.97–2.07 (m, 2H, CH_2), 2.40–2.46 (qd, $J=3.8$, 8.9 Hz, 1H, $COCHCH_3$), 3.36–3.41 (qd, $J=1.7$, 5.3, 5.4 Hz, 1H, $COCHCH_3$), 5.84 (s, 1H, OCHO). MS (FAB): m/z 283 (M+1). IR (KBr): 1740 (δ-lactone) cm^{-1}. $[\alpha]_D$: +87.9 (c 0.1, dioxane); lit.[5] $[\alpha]_D$: +89 (c 0.1, dioxane).