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New Synthetic Strategies Towards (+)-Artemisinin+

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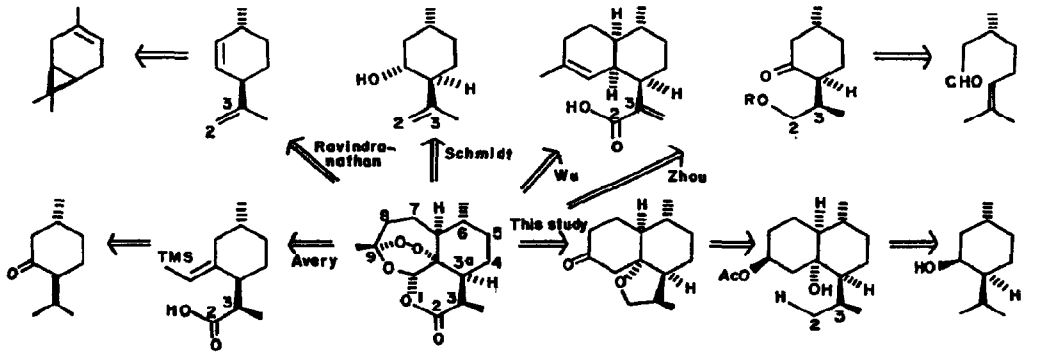
Abstract : Starting from (-)-menthol, two useful precursors for the formal total synthesis of (+)-Artemisinin, involving novel OH-assisted chemo and stereoselective C-H functionalisation and subsequent acid/base induced chemo-selective ring opening as key steps, have been synthesised.

(+)-Artemisinin (1) is a sesquiterpene endoperoxide and is the antimalarial principle of *Artemisia annua L.* herb (qinghao) used in traditional chinese medicine.[1,2] Recently, extensive clinical trials in China have shown that 1 can treat otherwise drug-resistant forms of malaria, notably *Plasmodium falciparum*.[3,4] This discovery has triggered world-wide interest into the synthesis, biosynthesis and biological action of 1 and its analogues.[3,4] The rather unusual highly oxygenated structure of (+)-artemisinin (1) with seven asymmetric centers constitutes a stimulating synthetic challenge and a number of chiron approaches have appeared in recent past for its partial and/or total synthesis.[5-9] Many of these synthetic strategies utilise readily available terpenes eg. (-)-isopulegol (Schimdt et al)[5], (+)-citronellal (Zhou et al)[6], (+)-car-3-ene (Ravindranathan et al)[7], arteannuic acid (Ye et al)[8] and (+)-pulegone (Avery et al)[9], where functionalisation at C-2 position (refer to numbering in (+)-Artemisinin (1) in Scheme 1) was relatively easy. This communication reports a novel OH-assisted chemo- and stereoselective C-H functionalisation for C-2 position and subsequent acid/base induced ring opening, which ultimately provides two useful precursors for the total synthesis of 1, from readily available (-)-menthol (Scheme 1).

SCHEME - 1



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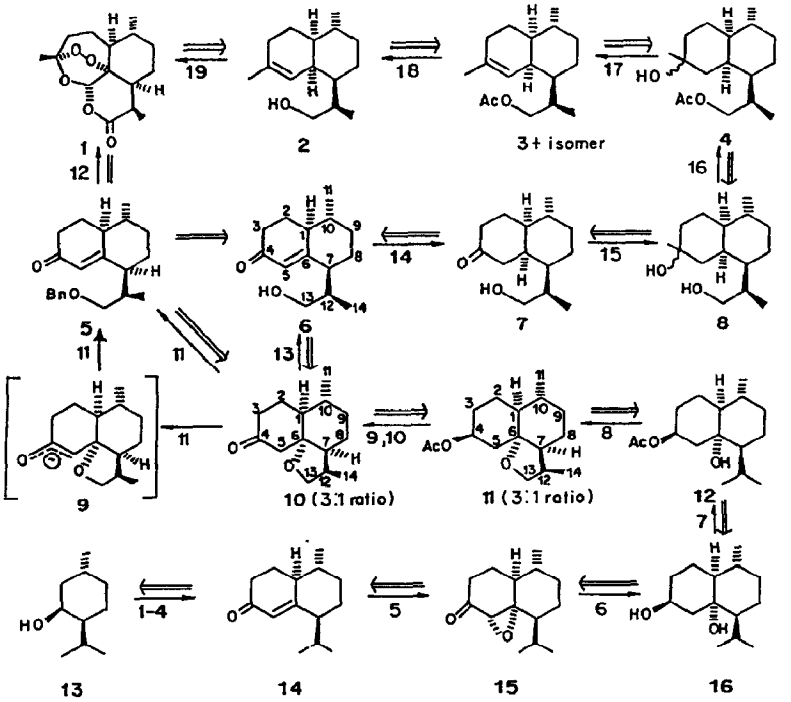
The retro-synthesis and synthesis of two useful precursors 5 and (+)-artemisiol (2) for the total synthesis of (+)-artemisinin (1) is shown in Scheme 2,[6,11] alongwith various reagents and reaction

+ Dedicated to Dr. S.N. Kulkarni on the ocassion of his 65th birthday.

conditions employed with usual work-up and the yields obtained. Initially, the enone **14** was prepared from (-)-menthol (**13**) by Jones oxidation, N,N-dimethyl α-formylation, quaternisation of dimethyl amine with MeI in dry ether, followed by condensation with ethyl acetoacetate in the presence of sodium ethoxide in ethanol at room temperature for 9 hrs and subsequent reflux for 5 hrs to give quantitative yields of **14**[10] (See Scheme 1, steps 1-4). Epoxidation of **14** with H_2O_2 and NaOH gave mainly the α-epoxide **15**, which on reduction with lithium aluminium hydride led to regioselective reduction of the epoxide, alongwith reduction of the ketone to give ß-secondary alcohol **16**. Chemoselective oxidation of the secondary alcohol **16** with PCC and NaOAc in CH_2Cl_2 at room temperature gave a quantitative yield of *cis*-junctioned keto-alcohol **17**, the structure of which was confirmed by X-ray,[12] besides other spectroscopic ^{1}H-NMR and positive CD data[14]. Based on these evidences, non-steroidal *cis*-junction of **16** was established. Chemoselective acetylation of secondary ß-OH of **16** with Ac_2O and pyridine gave **12**, the structure of which was established on the basis of coupling constants in ^{1}H-NMR.[14]

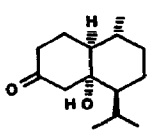
SCHEME - 2



Reagents, Reaction Conditions and Yields :

1. Jones oxidation, (97%); 2. Me_2NH_2Cl, $(CH_2O)_n$, HCl, EtOH, reflux, 10h (99%); 3. MeI, Ether, RT, 3h (98%); 4. $CH_3COCH_2CO_2Et$, NaOEt, EtOH, RT, 9h; then reflux 5h (42%); 5. 30% H_2O_2, NaOH, MeOH, -10° - 0°C, 7h (94%); 6. $LiAlH_4$, ether, reflux, 10h; RT, 7days (99%); 7. Ac_2O, Py, RT, 9h (94%); 8. LTA, I_2, C_6H_{12}, hμ (500W tungsten lamp), reflux, 2h; then Zn-dust, AcOH, Steam bath, 4h (85%); 9. KOH, EtOH, H_2O, RT, 4h (95%); 10. PCC, NaOAc, CH_2Cl_2, RT, 1h (85%); 11. NaH, DMF, -10° C, 45 min; then $PhCH_2Br$ in DMF, -10° C, 3h (28%); 12. Ref. 6; 13. Acidic Alumina (pH 4), elution with 40:60 EtOAc:Benzene (68%); 14. H_2 (20 PSI), 10% Pd-C, MeOH, 6h, RT (90%); 15. 2.5 eq MeMgI, ether, 0 - 5° C; 9h, RT (95%); 16. Ac_2O, Py, RT, 9h (96%); 17. $POCl_3$, Py, 10h, RT (94%); 18. KOH, EtOH, 4h, RT (95%); 19. Ref 8 & Ref 11.

For the C-2 functionalisation of C-H of primary methyl in isopropyl group in **12** (Scheme 1 & 2) a lead tetraacetate (LTA) + I_2 combination alongwith photolysis was carried out.[15,16] This step was chemo- and stereoselective. Thus, 3:1 ratio of stereoisomers were obtained, where major isomer is depicted as **11**. However, these stereoisomers could not be seperated at this step. Saponification, followed by PCC-oxidation gave quantitative yields of a mixture of stereoisomers (3:1 ratio), where both isomers were seperated (major isomer depicted as **10**).[13,14] Thus elution with 12% ethylacetate in benzene gave the *cis* isomer whereas elution with 18% ethylacetate in benzene gave the *trans* isomer in column chromatography. The preferential formation of *trans* stereoisomer over the *cis* (3:1 ratio) during cyclisation has been rationalised in terms of initial conformational preference shown in **20**, where clock-wise rotation of isopropyl group is restricted due to steric reasons.[14] Additional proof for getting the desired stereoisomer has been obtained by comparison with reported data (spectroscopic and optical rotation) for **2** and **5**. Cleavage of ether C-O bond in **10** was planned by generating α-carbanion by base.[17,18] Various basic conditions eg. NaOH, KOH, K_2CO_3, NaH in dry DMF, LDA or basic alumina were attempted.[14] However, the reaction did not yield the desired product **6**. Subsequently, the cleavage of C-O in **10** followed by benzylation of incipient anion was attempted with above bases. However, **18** was found to be a major product.[19] A highly selective reaction condition, where sodium hydride treatment of **10** in DMF at -10° to -5°C and subsequent addition of benzyl bromide in DMF also at -10°C gave the kinetic benzylation product **5**.[14] Since the synthesis of (+)-artemisinin (**1**) from **5** is already reported by Zhou et al[6], the synthesis of **5** constitutes, a formal total synthesis of **1**.



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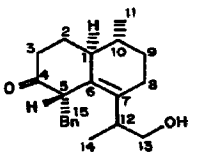
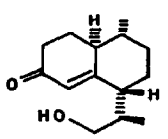


18



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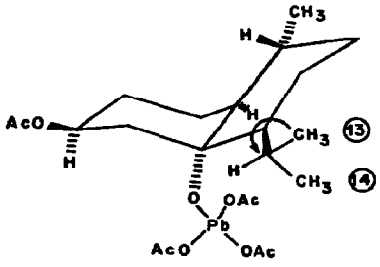

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To circumvent the problem of base induced cleavage of C-O bond in **10**, use of Lewis acid such as $BF_3.Et_2O$ was attempted. However, reaction with $BF_3.Et_2O$ was not clean and a major product **19** was invariably isolated, where isopropyl group had undesired stereochemistry. Indeed, the epimerisation of isopropyl group in **14** under $BF_3.Et_2O$ condition was found to be a facile process.[14] Alternatively, treatment of **10** with acidic alumina (pH 4) in 40:60 ethylacetate : benzene gave 68% isolated yield of **6**. Benzylation of **6**, once again, under basic conditions gave problems in obtaining clean transformation to **5**. Having obtained **6**, we wondered whether (+)-artemisiol (**2**) coud be obtained, which is known to give **1** in three steps.[8,11] Indeed, catalytic reduction of **6** with 10% Pd on charcoal was stereoselective and only the *cis*-junctured non-steriodal keto-alcohol **7** was obtained.[14] Treatment of the keto-alcohol **7** with 2.5 eq MeMgI gave quantitative yields of the Grignard product **8**. Subsequently, the primary alcohol of **8** was selectively acetylated to give **4** which on treatment with $POCl_3$ and pyridine gave a 50:50 mixture of regioisomeric double bonds of **3**. The separation of the desired isomer was possible after saponification of **3** to give **2**.[14]

In summary, an efficient chemo- and stereoselective OH-assisted cyclisation of **12** to **11** has been achieved, which could lead to two useful precursors **2** and **5** for (+)-artemisinin (**1**) by base or acid induced ring opening of **10**. Thus, this study reports two formal syntheses of **1**.

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13. All the new compounds were characterised by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and elemental analysis. The data for selected compounds eg. **3**, **5**, **6** and **11** are being provided below. For numbering of atoms, see original structures.
    Compound **3** : bp 220° C (bath)/ 1 mm; α^{26}_D -52.8° (c, 0.174); GC, OV101, 200°C, r.t.= 5.64 min; IR (Neat) cm^{-1} : 3440 (m, O-H), 1675 (vs, C=O), 1615 (w, C=C), 1040 (s, C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.88 (3H, d, J=7 Hz, C-14 methyl), 1.04 (3H, d, J=7 Hz, C-11 methyl), 3.53 (2H, d, J=7 Hz, H-13), 5.88 (1H, s, H-5), 1.1 - 2.5 (13H, m, hydroxyl and rest of the methylene, methine protons); MS (m/z) : 222 (22, M^+), 207 (20, M^+-CH_3), 165 (base peak, M^+-CH_3CHCHO); $C_{14}H_{22}O_2$ (222.32), Calc : C, 75.67, H, 9.9; Found : C, 75.5, H, 10.05%.
    Compound **5** : α^{26}_D -49.21° (c, 0.532); GC, OV101, 200° C, r.t. = 3.03 min; IR (Neat) cm^{-1} : 1715 (vs, C=O), 1030, 1055 (s, C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ : 0.99 (3H, d, J=7 Hz, C-14 methyl), 1.04 (3H, d, J=7 Hz, C-11 methyl), 3.31 (1H, dd, J_1=9 Hz, J_2=8 Hz, H-13), 4.07 (1H, dd, J_1=9 Hz, J_2=8 Hz, H-13), 1.1 - 2.8 (14H, m, rest of the methylene and methine protons); MS (m/z) : 222 (30, M^+), 207 (20, M^+-CH_3), 165 (base peak, M^+-CH_3CHCHO); $C_{14}H_{22}O_2$ (222.32) Calc : C, 75.67, H, 9.90; Found : C, 75.59, H, 9.78 %.
    Compound **6** : bp 180° C (bath)/ 1 mm; α^{26}_D -48.9° (c, 1.3); GC, HP-1, 160° C, r.t. = 4.46 min; IR (Neat) cm^{-1} : 1740 (vs, C=O), 1010, 1035 (s, C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ : 0.92 (3H, d, J=7 Hz, C-14 methyl), 0.98 (3H, d, J=7 Hz, C-11 methyl), 2.0 (3H, s, acetoxy methyl), 3.3 (1H, t, J=8 Hz,H-13), 4.12 (1H, t, J=8 Hz, H-13), 5.02 (1H, m, H-4), 1.0 - 2.5 (17H, m, acetoxy methyl and rest of the methylene, methine protons); MS (m/z) : 266 (7, M^+), 206 (base peak, M^+-CH_3COOH), 191 (10, M^+-CH_3COOH-CH_3); $C_{16}H_{26}O_3$ (148.28) Calc : C, 72.18, H, 9.77; Found : C, 72.00, H, 9.8 %.
    Compound **11** : mp = 85 - 86° C; α^{26}_D -13.54° (c, 0.254); GC, OV101, 200°C, r.t.= 10.42 min; IR (Neat) cm^{-1} : 3420 (m, O-H), 1720 (vs, C=O), 3020 (m, aromatic C-H), 1615 (m, aromatic C=C), 1045 (s, C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.8 (3H, d, J=7 Hz, C-14 methyl), 1.1 (3H, d, J=7 Hz, C-11 methyl), 2.91 (1H, dd, J_{vic}=7 Hz, J_{gem}=11 Hz, H-13), 2.97 (2H, d, J=7 Hz, H-15), 3.12 (1H, dd, J_{vic}=7 Hz, J_{gem}=11 Hz, H-13), 3.68 (1H, t, J=7 Hz, H-5), 7.1-7.4 (5H, m, aromatic protons) and 1.15-2.8 (12H, m, hydroxyl and rest of the methylene, methine protons); MS (m/z) : 312 (70, M^+), 313 (8, M^++1), 294 (12, M^+-H_2O), 281 (47, M^+-CH_2OH), 253 (4, M^+-CH_3CHCH_2OH), 221 (base peak, M^+-CH_2Ph) and 91 (50, $C_7H_7^+$).
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