Radical initiated reactions of artemisinin derivatives

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J. CHEM. SOC. PERKIN 1

Heating the propynyldihydroartemisinin derivatives 4 and 5 with Bu_3SnH–AIBN in toluene gave the stereoisomers 18 and 20 (5-*exo trig* products) respectively. The allyl ether 6 gave 21, a 1,2-*cis* 1,5-*trans* product under similar conditions, whereas the ether 7 gave two compounds, 22 (1,2-*cis* 1,5-*cis*) and 23 (1,2-*cis* 1,5-*trans*). The bromo ethers 8–12 gave their corresponding debrominated products whereas the bromo ether 14 and the bromo sulfides 15 and 16 gave the olefin 30.

Artemisinin (quinghaosu, arteannuin), an antimalarial agent isolated from the plant Artemisia annua, is an endoperoxide-containing sesquiterpene lactone.[1] It has shown very potent activity especially in the case of cerebral malaria. The use of artemisinin as an antimalarial agent has been hampered however by its poor solubility in oil and water and by its poor efficacy on oral administration. Therefore, the synthesis of new, stucturally modified derivatives of artemisinin is essential.[2–4] Though there are a number of methods reported for C–C bond formation in the literature, the use of the radical-mediated ring closure becomes more prominent in the synthesis of many natural products, because of its simplicity and high stereoselectivity.[5] We reported recently the synthesis of a novel ring system based on artemisinin using tin-mediated radical cyclisations involving an exclusive 1,5-*trans* (with regard to the newly formed 1,5-bond) ring cyclisation.[6] In order to appreciate the synthetic scope and limits of the radical cyclisations, we synthesised various 9-bromo-10-substituted dihydroartemisinin derivatives and studied their radical initiated reactions.

Results and discussion

Synthesis of 9-bromo-10-substituted dihydroartemisinin

The starting material for our present study was the bromo acetal, 9-bromodihydroartemisinin **1**, which was prepared conveniently as reported.[7] Treatment of the bromoacetal **1** with primary alcohols in the presence of BF_3–Et_2O gave the bromo ethers **2**–**14**. In the preparation of the compounds **2**–**7** and **12**–**13**, two diastereoisomers were formed in the ratio of approximately 4:1, the major compound having a higher R_f value by TLC, and were separated by flash column chromatography on silica gel. In the preparation of the compounds **8**–**11** and **14**, only the major diastereoisomer having a higher R_f value was isolated. The other isomer having a lower R_f value was formed in a negligible amount. Treatment of the bromo acetal **1** with allylthiol and benzenethiol gave only one diastereoisomer, **15** and **16**, respectively (Scheme 1).

Stereochemistry of 10-substituted dihydroartemisinin

In the ^1H NMR spectrum of 10-*O*-ethyldihydroartemisinin[8] the signals for 11a-H, 10-H and OCH_2 for the 10β-isomer, having a higher R_f value, appeared at δ_H 5.41 (s), 4.8 (s) and 3.68 (m) respectively whereas for the 10α-isomer they appeared at δ_H 5.33 (s), 4.43 (s) and 3.76 (m) respectively. In the β-isomer, the signal for OCH_2 appeared upfield and the signal for 10-H and 11a-H appeared downfield compared to those in the α-isomer. In this way, the major compounds **2**, **4**, **6** and **12**, having higher R_f values by TLC, were also assigned the β-configuration at the 10-position (Table 1).

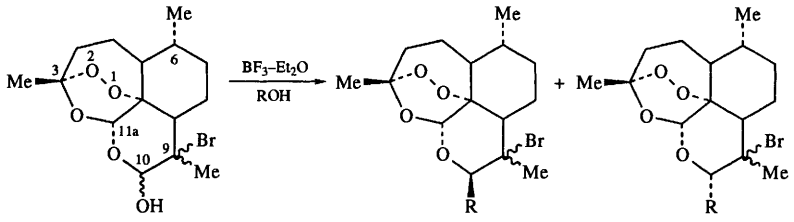
In the case of the compounds **8**–**11** and **14**, the 10β-configuration was assigned on the basis of their higher R_f values by TLC. The above assignment was further confirmed by the following experiment. 9-Bromo-10β-ethyldihydroartemisinin **2**, the major isomer having a higher R_f value, was debrominated using Bu_3SnH–AIBN to give arteether **17**, a known derivative,[8] thus confirming the relative stereochemistry at the 10-position to be β (Scheme 2). In the cases of 10-allylsulfanyl and phenylsulfanyl derivatives **15** and **16**, having a single spot on TLC, the relative stereochemistry at the 10-position was not assigned as the other diastereoisomers could not be isolated for comparison. However, in all the cases, the relative stereochemistry at the 9-position was not confirmed because it was not essential at this point.

Table 1 Selected δ_H values ($CDCl_3$) of the 9-bromo-10-substituted dihydroartemisinin derivatives

Compound	OCH_2	10-H	11a-H
Arteether (β)	3.68	4.80	5.41
(α)	3.76	4.43	5.33
2	3.72	4.80	5.44
3	3.80	4.70	5.32
4	4.38	5.10	5.44
5	4.47	5.00	5.36
6	4.20	4.88	5.44
7	4.22	4.84	5.32
8	3.90	4.84	5.54
9	4.44	4.92	5.44
10	3.52	4.70	5.40
11	5.28	5.12	5.52
12	3.90	4.76	5.38
13	3.95	4.72	5.24
14	—	5.36	5.52
15	3.36	5.00	5.20
16	—	5.56	5.74

Radical cyclisations

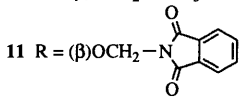
Heating the propynyl ether **4** with Bu_3SnH–AIBN in toluene at 110 °C for 18 h gave the single stereoisomer **18** (82%) as a solid. The other isomer **5** underwent a smooth radical cyclisation under similar conditions to give **20** (30%) as a solid. Stereochemical assignment of these pentacyclic derivatives rested on their ^1H NMR spectra, and nuclear Overhauser effect (NOE) experiments. The δ_H values of 15-H and 13-H for the compounds **18** and **20** are comparable to those of the corresponding protons of arteether,[8] thus confirming that the artemisinin ring skeleton had remained intact. Irradiation of the 9-methyl group in the ^1H NMR spectra of both the compounds **18** and **20** showed NOE enhancements for 13-H. For the compound **18**, the relative configuration of 9-methyl is α, since the relative configuration of 13-H is α as in the bromo ether **4**. For the compound **5**, the relative configuration of the 9-methyl is β, since the relative configuration of 13-H is β as in the bromo ether **5**. In the above cases, the bromo ethers **4** and **5** gave the 5-



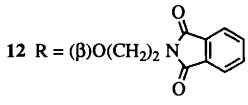
1

2 R = (β)OEt
3 R = (α)OEt
4 R = (β)$OCH_2C{\equiv}CH$
5 R = (α)$OCH_2C{\equiv}CH$
6 R = (β)$OCH_2CH{=}CH_2$
7 R = (α)$OCH_2CH{=}CH_2$
8 R = (β)OCH_2CH_2CN
9 R = (β)OCH_2CN

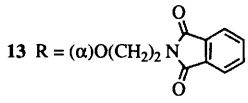
10 R = (β)OCH_2COCH_3



11 R = (β)OCH_2–N



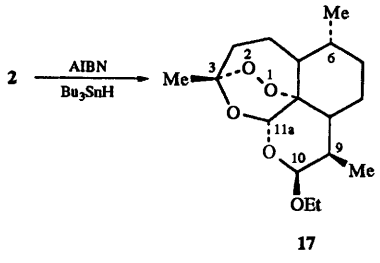
12 R = (β)$O(CH_2)_2$N



13 R = (α)$O(CH_2)_2$N

14 R = (β)OPh
15 R = (α or β)$SCH_2CH{=}CH_2$
16 R = (α or β)SPh

Scheme 1



17

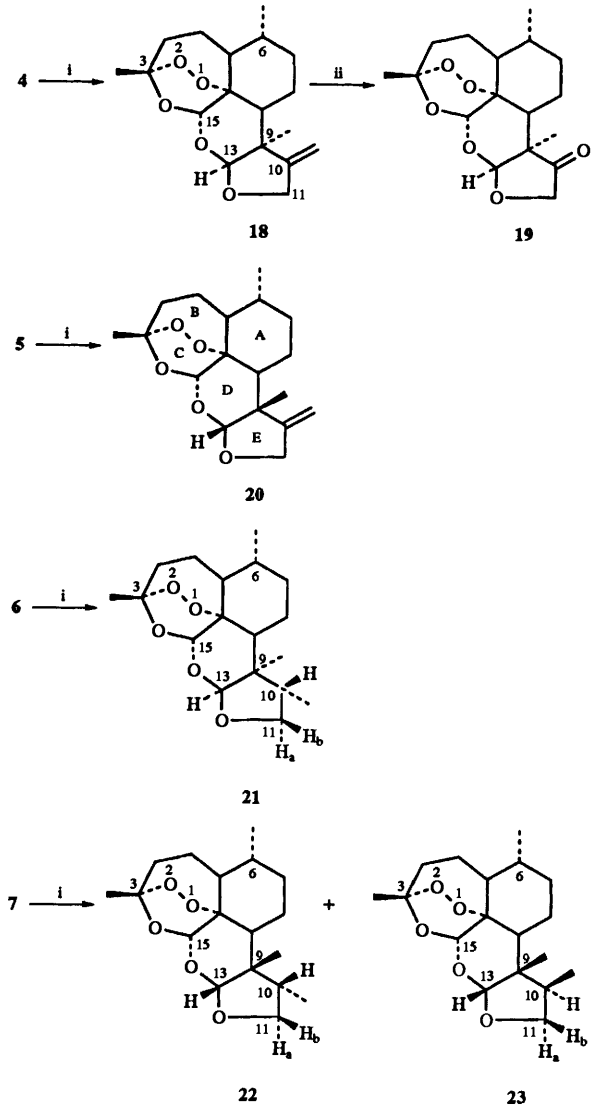
Scheme 2

exo trig products having *cis* fused D- and E-rings as predicted.[9] The exomethylene derivative **18** underwent oxidation in the presence of OsO_4 to give the keto compound **19** (30%).

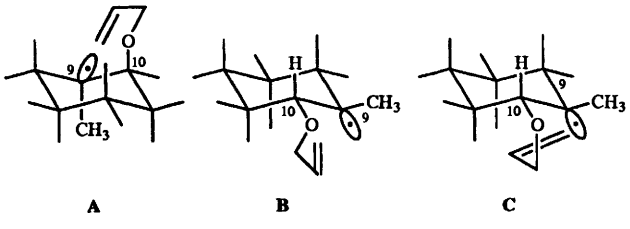
The allyl ether **6** underwent radical cyclisation to give exclusively **21** (75%) as a solid. The proton 13-H of the cyclic product **21** displayed an NOE upon irradiation of the 9-methyl group, thus confirming the relative configuration of 13-H and 9-CH_3 to be α. The signal for the protons 11a-H and 11b-H appeared at δ_H 3.44 and 4.09 respectively. The signal at δ_H 3.44 appeared as a doublet of doublets [J_{gem} 9 Hz; $J_{11a,10}$(*trans*) 12.5 Hz], and the other downfield signal at δ_H 4.09 appeared as a triplet. Irradiation of the signal at δ_H 3.44 (11a-H) showed NOE enhancements for the 13-H and 10-methyl signals. Similar selective NOE experiments (irradiation of 10-methyl and of 11a-H) confirm the relative configuration at 13-H, 10-methyl and 11a-H. On this basis, the structure **21** (a 1,2-*cis* 1,5-*trans* product), was assigned to the product. On the other hand, the radical cyclisation of **7** gave two isomers by TLC. On the basis of the spectral data, the structure **22** (1,2-*cis* 1,5-*cis* product) was assigned to the isomer with the higher R_f value. In its ^{1}H NMR spectrum, the signals at δ_H 3.5 and 4.16 appear as a doublet of doublets and a triplet respectively in similar fashion to the signals for compound **21**, confirming that 10-H is in the axial position. The structure **23** (1,2-*cis* 1,5-*trans* product) was assigned to the product having a lower R_f value by TLC. Its ^{1}H NMR showed two triplets at δ_H 3.46 and 4.12, thus confirming that 10-H is in an equatorial position.

The D-ring of the 10-ethers of dihydroartemisinin exists in a chair form and the 10β-OR group occupies an axial position while the 10α-OR group occupies an equatorial position as shown by NMR and X-ray data.[10] In the case of the radical generated by the bromo ether **6**, a transition state **A** can be invoked where the axial allyloxy group is attacked by the equatorially orientated radical and the 9-methyl group is in the axial position, in a 'chair-like' fashion[11] (Scheme 4). This would lead to the 1,5-*trans* product (with regard to the newly formed bond) **21** in which the D- and E-rings are *cis*-fused and the 10- and 9-methyl groups and 13-H are all *cis* as shown in Scheme 3. Similarly in the case of the radical generated by the bromo ether **7**, a transition state **B**, where the allyloxy group in the equatorial position is attacked by the axially oriented radical with the 9-methyl group in the equatorial position in a 'chair-like' fashion[12,13] would lead to the 1,2-*cis*, 1,5-*cis* product **22**. On the other hand if the cyclisation of the radical occurs in a 'boat like' fashion,[13] in the transition state **C** it would give rise to the 1,2-*cis* 1,5-*trans* product **23**.

Although the intramolecular radical addition of carbon radicals to enol ethers has been reported, the corresponding radical addition to carbonyl groups is unknown. However a product arising from the intramolecular addition of a carbon radical to a cyano group has been isolated in poor yield.[14] This prompted us to investigate the radical reaction of the 9-bromo-10-*O*-acetonyl derivative **10** and the 9-bromo-10-cyanoalkyl derivatives **8** and **9**. In all the cases only the 10β-substituted alkyl derivatives were subjected to the radical initiated reaction as the corresponding 10α isomers were



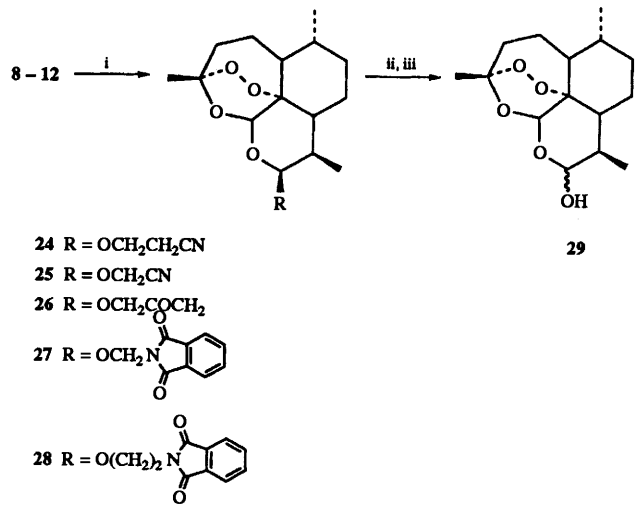
Scheme 3 *Reagents and conditions:* i, AIBN–Bu_3SnH, toluene, reflux; ii, OsO_4



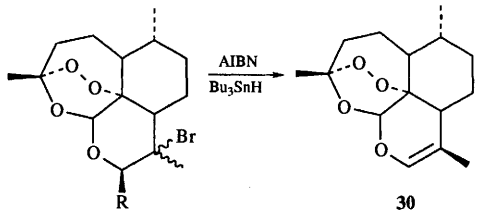
Scheme 4

available in very small quantities. Heating 9-bromo-10β-*O*-acetonyldihydroartemisinin **10** with Bu_3SnH–AIBN in toluene at 70 °C for 3 h gave the corresponding debrominated product **26** (59%) as a solid. The structure **26** was confirmed by comparing its IR and NMR spectra and mp with a sample prepared by the treatment of dihydroartemisinin **29** with hydroxyacetone[15] in the presence of BF_3–Et_2O. Similarly, bromocyanoethyl derivative **8**, bromocyanomethyl derivative **9**, phthalimidomethyl **11** and phthalimidoethyl derivative **12** gave the corresponding debrominated products **24**, **25**, **27** and **28** respectively and they were alternatively prepared from dihydroartemisinin **29** for structural confirmation as shown in Scheme 5.

In the light of the above observation, it was of interest to study the radical reaction of the other bromo derivatives **14**–**16**. Heating 10-*S*-allyl-9-bromo-10-thiodihydroartemisinin **15** with Bu_3SnH–AIBN in toluene at 70 °C for 2 h gave dehydro-



Scheme 5 *Reagents and conditions:* i, AIBN, Bu_3SnH; ii, BF_3–Et_2O, ROH; iii, flash column chromatography



14 R = OPh
15 R = $SCH_2CH{=}CH_2$
16 R = SPh

Scheme 6

artemisinin[16] **30** (56%) as the only isolable product. The 9-bromo-10-phenyl derivative **14** and 9-bromo-10-*S*-phenyl-10-thio derivative **16** also gave dehydroartemisinin **30** under similar conditions. The substrates that have stabilised-radical leaving groups (like SR and OAr groups in the compounds **14**–**16**) at the α-position undergo 1,2-elimination to provide olefins rather than the cyclised product as reported in the literature.[17]

Biological activity

The bromo ethers **2**–**14**, bromo sulfides **15**–**16** and the pentacyclic derivatives **18**–**23** were found to be devoid of antimalarial activity when tested subcutaneously against *Plasmodium berghei* K-173 infected mice at a dose of 5 mg kg^{-1} × 5. However, the ethers **26**–**28** showed very mild antimalarial activity in *Plasmodium berghei* K-173 infected mice at a dose of 5 mg kg^{-1} × 5. The detailed biological activity of these and other analogous derivatives will be published elsewhere.

Experimental

All melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra of solid samples were obtained as KBr discs on a Perkin-Elmer spectrophotometer. ^1H NMR spectra were run on a JEOL FX 90Q (90 MHz) spectrophotometer in $CDCl_3$ using Me_4Si as an internal standard; *J* values are given in Hz. Elemental analyses were performed on a Heraeus micro-elemental analyser. Mass spectrum were recorded on a Kratos MS 80 RFA mass spectrometer. 9-Bromodihydroartemisinin **1** was prepared according to the reported procedure.[7]

Preparation of 9-bromo-10β-*O*-ethyldihydroartemisinin 2

Boron trifluoride–diethyl ether (3 drops) was added to a solution of bromoacetal **1** (200 mg, 0.055 mmol) in chloroform

(3 cm^3) and ethanol (4 drops) at 0–5 °C and the reaction mixture was heated at 50 °C for 10 h. After the reaction was complete, the mixture was extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (5:95) as eluent to give 9-bromo-10β-*O*-ethyl dihydroartemisinin **2** as a solid (150 mg, 70%), mp 120–122 °C (Found: C, 52.4; H, 7.15; Br, 20.4. $C_{17}H_{27}BrO_5$ requires C, 52.18; H, 6.95; Br, 20.42%); δ_H 5.44 (s, 1 H, 11a-H), 4.80 (s, 1 H, 10-H), 3.72 (m, 2 H, CH_2), 2.32 (s, 3 H, CH_3), 1.6 (s, CH_3), 1.48 (s, CH_3) and 1.28 (t, CH_3). Subsequent elution with ethyl acetate–light petroleum (5:95) gave 9-bromo-10α-*O*-ethyldihydroartemisinin **3** as a colourless oil (50 mg, 23%) (Found: C, 52.1; H, 7.0; Br, 20.3. $C_{17}H_{27}BrO_5$ requires C, 52.18; H, 6.95; Br, 20.42%); δ_H 5.32 (s, 1 H, 11a-H), 4.70 (s, 1 H, 10-H), 3.8 (m, 2 H, OCH_2), 2.2 (s, CH_3), 1.6 (s, CH_3), 1.48 (s, CH_3) and 1.32 (t, CH_3).

The compounds **4**–**16** were prepared using the corresponding alcohols or thiols in place of ethanol in the above reaction. In some cases both 10α and 10β derivatives were isolated and in other cases only 10β derivatives were isolated.

9-Bromo-10β-*O*-prop-2-ynyldihydroartemisinin 4. [160 mg (from 200 mg of **1**), 72%], mp 114–115 °C (Found: C, 53.8; H, 6.2; Br, 20.2. $C_{18}H_{25}BrO_5$ requires C, 53.87; H, 6.28; Br, 19.91%); δ_H 5.44 (s, 1 H, 11a-H), 5.10 (s, 1 H, 10-H), 4.38 (d, *J* 1.5, 2 H, OCH_2), 2.48 (t, *J* 1.5, 1 H, CH), 2.32 (s, CH_3), 1.56 (s, CH_3) and 1.48 (s, CH_3).

9-Bromo-10α-*O*-prop-2-ynyldihydroartemisinin 5. [42 mg (from 200 mg of **1**), 18%], colourless oil (Found: C, 53.6; H, 6.1; Br, 20.1. $C_{18}H_{25}BrO_5$ requires C, 53.87; H, 6.28; Br, 19.91%); δ_H 5.36 (s, 1 H, 11a-H), 5.00 (s, 1 H, 10-H), 4.47 (d, *J* 1.5, 2 H, CH_2), 2.48 (t, *J* 1.5, 1 H, CH), 2.24 (s, CH_3), 1.6 (s, CH_3) and 1.48 (s, CH_3).

9-Bromo-10β-*O*-prop-2-enyldihydroartemisinin 6. [67 mg (from 100 mg of **1**), 60%], mp 107–108 °C (Found: C, 53.6; H, 6.6; Br, 19.9. $C_{18}H_{27}BrO_5$ requires C, 53.60; H, 6.75; Br, 19.81%); δ_H 5.88 (m, 1 H, CH), 5.44 (s, 1 H, 11a-H), 5.16 (m, 2 H, CH_2), 4.88 (s, 1 H, 10-H), 4.20 (m, 2 H, OCH_2), 2.32 (s, CH_3), 1.58 (s, CH_3) and 1.46 (s, CH_3).

9-Bromo-10α-*O*-prop-2-enyldihydroartemisinin 7. [18 mg (from 100 mg of **1**), 16%], mp 118 °C (decomp.) (Found: C, 53.4; H, 6.7; Br, 19.9. $C_{18}H_{27}BrO_5$ requires C, 53.60; H, 6.75; Br, 19.81%); δ_H 5.72 (m, 1 H, CH), 5.32 (s, 1 H, 11a-H), 5.20 (m, 2 H, CH_2), 4.84 (s, 1 H, 10-H), 4.22 (m, 2 H, CH_2), 2.24 (s, CH_3), 1.6 (s, CH_3) and 1.48 (s, CH_3).

9-Bromo-10β-*O*-(2-cyanoethyl)dihydroartemisinin 8. [20 mg (from 50 mg of **1**), 35%], oil (Found: C, 51.9; H, 6.1; N, 3.3; Br, 19.1. $C_{18}H_{26}BrNO_5$ requires C, 51.93; H, 6.30; N, 3.36; Br, 19.19%); δ_H 5.54 (s, 1 H, 11a-H), 4.84 (s, 1 H, 10-H), 3.99 (m, 2 H, OCH_2), 2.7 (t, *J* 5, 2 H, CH_2), 2.27 (s, CH_3), 1.56 (s, CH_3) and 1.44 (s, CH_3).

9-Bromo-10β-*O*-(cyanomethyl)dihydroartemisinin 9. [12 mg (from 50 mg of **1**) 21%], oil (Found: C, 50.7; H, 6.0; N, 3.4; Br, 19.7. $C_{17}H_{24}BrNO_5$ requires C, 50.75; H, 6.01; N, 3.48; Br, 19.86%); δ_H 5.44 (s, 1 H, 11a-H), 4.92 (s, 1 H, 10-H), 4.44 (s, 2 H, CH_2), 2.32 (s, CH_3), 1.40 (s, CH_3) and 1.28 (s, CH_3).

10β-*O*-Acetonyl-9-bromodihydroartemisinin 10. [14 mg (from 80 mg of **1**), 15%], oil (Found: C, 51.4; H, 6.6; Br, 19.0. $C_{18}H_{28}BrO_6$ requires C, 51.43; H, 6.72; Br, 19.01%); δ_H 5.4 (s, 1 H, 11a-H), 4.7 (s, 1 H, 10-H), 3.52 (s, 2 H, CH_2), 2.3 (s, CH_3), 1.54 (s, CH_3) and 1.44 (s, CH_3).

9-Bromo-10β-*O*-(phthalimidomethyl)dihydroartemisinin 11. [15 mg (from 25 mg of **1**), 42%], oil (Found: C, 55.1; H, 5.3; N, 2.5; Br, 15.1. $C_{24}H_{28}BrNO_7$ requires C, 55.18; H, 5.40; N, 2.68; Br, 15.30%); δ_H 7.75 (m, 4 H, ArH), 5.52 (s, 1 H, 11a-H), 5.28 (s, 2 H, OCH_2), 5.12 (s, 1 H, 10-H), 2.24 (s, CH_3), 1.56 (s, CH_3) and 1.36 (s, CH_3). The corresponding 10α-isomer was present in negligible amount and hence it was not characterised.

9-Bromo-10β-*O*-[2-(phthalimido)ethyl]dihydroartemisinin 12. [50 mg (from 50 mg of **1**), 68%], oil (Found: C, 55.7; H, 5.6; N, 2.4; Br, 14.7. $C_{25}H_{31}BrNO_7$ requires C, 55.87; H, 5.81; N, 2.61; Br, 14.87%); δ_H 7.7 (m, 4 H, ArH), 5.38 (s, 1 H, 11a-H), 4.76 (s, 1 H, 10-H), 3.90 (m, 4 H, OCH_2 and NCH_2), 2.24 (s, 3 H, CH_3), 1.6 (s, CH_3) and 1.4 (s, CH_3).

9-Bromo-10α-*O*-[2-(phthalimido)ethyl]dihydroartemisinin 13. [10 mg (from 50 mg of **1**), 13%], oil (Found: C, 55.55; H, 5.5; N, 2.3; Br, 14.7. $C_{25}H_{31}BrNO_7$ requires C, 55.87; H, 5.81; N, 2.61; Br, 14.87%); δ_H 7.65 (m, 4 H, ArH), 5.24 (s, 1 H, 11a-H), 4.72 (s, 1 H, 10-H), 3.95 (m, 4 H, OCH_2 and NCH_2), 2.08 (s, CH_3), 1.36 (s, CH_3) and 1.28 (s, CH_3).

9-Bromo-10β-phenyldihydroartemisinin 14. [35 mg (from 50 mg of **1**), 58%], mp 88–90 °C (Found: C, 57.2; H, 6.1; Br, 18.2. $C_{21}H_{27}BrO_5$ requires C, 57.41; H, 6.19; Br, 18.19%); δ_H 7.06 (m, 5 H, ArH), 5.52 (s, 1 H, 11a-H), 5.36 (s, 1 H, 10-H), 1.4 (s, CH_3) and 1.2 (s, CH_3).

10-*S*-Allyl-9-bromo-10-thiodihydroartemisinin 15. [30 mg (from 50 mg of **1**), 53%], mp 138–139 °C (Found: C, 51.75; H, 6.6; Br, 19.3. $C_{18}H_{27}BrO_4S$ requires C, 51.56; H, 6.49; Br, 19.06%); δ_H 5.9 (m, 1 H, CH), 5.2 (s, 1 H, 11a-H), 5.14 (m, CH_2), 5.0 (s, 1 H, 10-H), 3.36 (m, 2 H, CH_2), 2.32 (s, CH_3), 1.84 (s, CH_3) and 1.44 (s, CH_3).

9-Bromo-10-*S*-phenyl-10-thiodihydroartemisinin 16. [35 mg (from 50 mg of **1**), 56%], mp 130–132 °C (Found: C, 55.1; H, 6.3; Br, 17.8. $C_{21}H_{27}BrO_4S$ requires C, 55.39; H, 5.98; Br, 17.55%); δ_H 7.6 (m, 3 H, ArH), 7.2 (m, 2 H, ArH), 5.74 (s, 1 H, 11a-H), 5.56 (s, 1 H, 10-H), 2.28 (s, CH_3), 1.6 (s, CH_3) and 1.28 (s, CH_3).

Radical reaction of 9-bromo-10β-*O*-ethyldihydroartemisinin 2

Azobisisobutyronitrile (AIBN; 21 mg, 0.13 mmol) and tributyltin hydride (0.35 cm^3, 0.13 mmol) were added to a solution of 9-bromo-10β-*O*-ethyldihydroartemisinin **2** (51 mg, 0.13 mmol) in dry toluene (5 cm^3). The reaction mixture was heated under reflux for 3 h. Aqueous potassium fluoride was added and the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was then extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (60–80 °C, 5:95) as eluent to give arteether **17** (24 mg, 60%) as a solid, mp 80–81 °C; ^1H NMR, IR spectra and TLC were identical to that of a sample prepared by the reported procedure.[8]

Radical cyclisation of 9-bromo-10β-*O*-prop-2-ynyldihydroartemisinin 4

Azobisisobutyronitrile (AIBN; 21 mg, 0.13 mmol) and tributyltin hydride (0.35 cm^3, 0.13 mmol) were added to a solution of 9-bromo-10β-*O*-prop-2-ynyldihydroartemisinin **4** (50 mg, 0.13 mmol) in dry toluene (50 cm^3). The reaction mixture was heated under reflux for 20 h and then cooled to room temperature. Aqueous potassium fluoride was added and the mixture stirred for 15 min. The reaction mixture was then extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (60–80 °C, 5:95) as eluent to give product **18** (34 mg, 82%) as a solid, mp 137 °C (Found: C, 67.2; H, 8.1. $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13%); δ_H 5.56 (s, 1 H, 15-H), 5.45 (s, 1 H, 13-H), 5.08 (t, *J* 2.5, 1 H, olefinic H), 4.72 (t, *J* 2.5, 1 H, olefinic H), 4.4 (m, 2 H, 11a-, 11b-H), 1.42 (s, 3 H, 3-CH_3), 1.4 (s, 3 H, 9-CH_3) and 1.0 (br d, 3 H, 6-CH_3); *m*/*z* 322 (M^+).

Radical cyclisation of 9-bromo-10α-*O*-prop-2-ynyldihydroartemisinin 5. Under similar conditions 9-bromo-10α-*O*-prop-2-ynyldihydroartemisinin **5** (50 mg, 0.13 mmol) gave product **20** (26 mg, 63%) as a colourless oil (Found: C, 67.3; H, 8.1. $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13%); δ_H 5.34 (s, 1 H, 15-H), 5.10 (s, 1 H, 13-H), 4.9 (m, 1 H, olefinic H), 4.7 (m, 1 H, olefinic H), 4.45 (m, 2 H, 11-H), 1.42 (s, 3 H, 3-CH_3), 1.4 (s, 3 H, 9-CH_3) and 1.0 (br d, 3 H, 6-CH_3); *m*/*z* 322 (M^+).

Radical cyclisation of 9-bromo-10β-*O*-prop-2-enyldihydroartemisinin 6

Azobisisobutyronitrile (40 mg, 0.24 mmol) and tributyltin hydride (0.67 cm^3, 0.25 mmol) were added to a solution of 9-bromo-10β-*O*-prop-2-enyldihydroartemisinin **6** (0.1 g, 0.25 mmol) in dry toluene (10 cm^3). The reaction mixture was heated under reflux at 70 °C for 6 h under a nitrogen atmosphere and then cooled to room temperature, after which aqueous potassium fluoride was added to the mixture, which was stirred for 15 min. The reaction mixture was extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (3:97) as eluent to give product **21** (56 mg, 70%) as a solid, mp 126–128 °C (Found: C, 66.7; H, 8.7. $C_{18}H_{28}O_5$ requires C, 66.64; H, 8.58%); δ_H 5.51 (s, 1 H, 15-H), 5.28 (s, 1 H, 13-H), 4.09 (dd, *J* 9.0, 7.5, 1 H, 11b-H), 3.44 (dd, *J* 10, 7.5, 1 H, 11a-H), 1.36 (s, 3-CH_3), 1.2 (s, 9-CH_3), 0.95 (br d, 10-CH_3) and 0.84 (br d, 6-CH_3).

Radical cyclisation of 9-bromo-10α-*O*-prop-2-enyldihydroartemisinin 7

Azobisisobutyronitrile (21 mg, 0.13 mmol) and tributyltin hydride (0.35 cm^3, 0.13 mmol) were added to a solution of 9-bromo-10α-*O*-prop-2-enyldihydroartemisinin **7** (0.05 g, 0.125 mmol) in dry toluene (5 cm^3). The reaction mixture was heated under reflux at 70 °C for 2 h under a nitrogen atmosphere and then cooled to room temperature, aqueous potassium fluoride was added and the mixture was stirred for 15 min. The reaction mixture was extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (3:17) as eluent to give 1,2-*cis* 1,5-*cis* product **22** (12 mg, 30%) as a solid, mp 132–135 °C (Found: C, 66.5; H, 8.5. $C_{18}H_{28}O_5$ requires C, 66.64; H, 8.70%); δ_H 5.5 (s, 1 H, 15-H), 5.3 (s, 1 H, 13-H), 4.12 (dd, *J* 9, 7.5, 1 H, 11b-H) and 3.42 (dd, *J* 10, 7.5, 1 H, 11a-H). Subsequent elution with ethyl acetate–light petroleum (3:17) gave 1,2-*cis* 1,5-*trans* product **23** (8 mg, 21%) as a solid, mp 118–120 °C (Found: C, 66.3; H, 8.5. $C_{18}H_{28}O_5$ requires C, 66.64; H, 8.70); δ_H 5.1 (s, 1 H, 15-H), 4.9 (s, 1 H, 13-H), 4.12 (t, *J* 7.5, 1 H, 11b-H) and 3.48 (t, *J* 7.5, 1 H, 11a-H).

Oxidation of compound 18

Osmium tetroxide (8 mg, 0.0314 mmol) and sodium periodate (26 mg, 0.12 mmol) were added to a solution of the compound **18** (40 mg, 0.12 mmol) in dioxane (1 cm^3) and water (0.5 cm^3) at 0 °C. The reaction mixture was brought to room temperature and stirred for 18 h. The reaction mixture was poured into water and extracted with chloroform and the extracts were dried and concentrated. The product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (3:97) as eluent to give product **19** (12 mg, 30%) as a colourless oil (Found: C, 62.9; H, 7.4. $C_{17}H_{24}O_6$ requires C, 62.95; H, 7.46%); δ_H 5.80 (s, 1 H, 15-H), 5.36 (s, 1 H, 13-H) and 4.0 (s, 2 H, 11-H); *m/z* 346 (M^+).

Reaction of tributyltin hydride–AIBN with 10β-*O*-acetonyl-9-bromodihydroartemisinin 10

Azobisisobutyronitrile (21 mg, 0.13 mmol) and tributyltin-hydride (0.35 cm^3, 0.13 mmol) were added to a solution of 10β-*O*-acetonyl-9-bromodihydroartemisinin **10** (55 mg, 0.13 mmol) in dry toluene (5 cm^3). The reaction mixture was heated under reflux at 70 °C for 3 h under a nitrogen atmosphere and then cooled to room temperature, aqueous potassium fluoride was added and the mixture was stirred for 15 min. The reaction mixture was extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (5:95) as eluent to give 10β-*O*-acetonyldihydroartemisinin **26** (22 mg, 50%) as a solid, mp 106–107 °C; ^{1}H NMR, IR spectra and TLC were identical to that of a sample prepared from the reaction of dihydroartemisinin **29** with hydroxyacetone. Under similar conditions, the compounds **8**–**12** gave their corresponding reduced products **24**–**28** respectively.

Preparation of 10β-*O*-acetonyldihydroartemisinin 26

Boron trifluoride–diethyl ether (4 drops) was added to a solution of dihydroartemisinin **29** (284 mg, 1 mmol) and hydroxyacetone (250 mg, 1.25 mmol) in chloroform (5 cm^3) at 0 °C and stirred for 1 h. After the reaction was complete (as seen by TLC), aqueous sodium acetate was added to the reaction mixture, which was extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (3:97) as eluent to give 10β-*O*-acetonyldihydroartemisinin **26** (80 mg, 23%) as a solid, mp 106–107 °C (Found: C, 63.5; H, 8.2. $C_{18}H_{29}O_6$ requires C, 63.32; H, 8.56%); δ_H 5.4 (s, 1 H, 11a-H), 4.8 (d, *J* 3.5, 1 H, 10-H), 4.22 (q, *J* 18, 2 H, CH_2), 1.36 (s, CH_3) and 1.44 (s, CH_3).

The compounds **24**–**28** were prepared following the procedure described for the preparation of the compound **26**, using 2-cyanoethanol, cyanomethanol, 2-(phthalimido)ethanol and 2-(phthalimido)methanol in place of hydroxyacetone respectively.

10β-*O*-(2-Cyanoethyl)dihydroartemisinin 24. [80 mg (from 100 mg of **29**), 67%], mp 137–138 °C (Found: C, 64.1; H, 7.9; N, 4.1. $C_{18}H_{27}NO_5$ requires C, 64.06; H, 8.07; N, 4.15%); δ_H 5.44 (s, 1 H, 11a-H), 4.98 (d, *J* 3.6, 1 H, 10-H), 3.9 (m, 2 H, OCH_2), 2.6 (t, *J* 5.4, 2 H, CH_2CN), 1.40 (s, CH_3) and 1.24 (s, CH_3).

10β-*O*-Cyanomethyldihydroartemisinin 25. [25 mg (from 100 mg of **29**), 22%], mp 150–152 °C (Found: C, 63.0; H, 7.8; N, 4.4. $C_{17}H_{25}NO_5$ requires C, 63.14; H, 7.79; N, 4.43%); δ_H 5.36 (s, 1 H, 11a-H), 4.90 (d, *J* 3.6, 1 H, 10-H), 4.4 (s, 2 H, CH_2), 1.48 (s, CH_3), 1.04 (s, CH_3) and 0.96 (s, CH_3).

10β-*O*-(Phthalimidomethyl)dihydroartemisinin 27. [46 mg (from 120 mg of **29**), 25%], oil (Found: C, 65.2; H, 6.9; N, 3.1. $C_{24}H_{29}NO_7$ requires C, 65.00; H, 6.59; N, 3.16%); δ_H 7.8 (m, 4 H, ArH), 5.44 (s, 1 H, 11a-H), 5.22 (q, *J* 9, 2 H, OCH_2N), 5.06 (d, *J* 3.6, 1 H, 10-H), 1.6 (s, CH_3), 1.4 (s, CH_3) and 1.24 (s, CH_3).

10β-*O*-[2-(Phthalimido)ethyl]dihydroartemisinin 28. [42 mg (from 100 mg of **29**), 26%], mp 139 °C (Found: C, 65.7; H, 7.0; N, 3.2. $C_{25}H_{31}NO_7$ requires C, 65.63; H, 6.83; N, 3.06%); δ_H 7.66 (m, 4 H, ArH), 5.24 (s, 1 H, 11a-H), 4.74 (d, *J* 3.8, 1 H, 10-H) and 3.98 (m, 4 H, CH_2).

Radical reaction of 10-*S*-allyl-9-bromo-10-thiodihydroartemisinin 15

Azobisisobutyronitrile (21 mg, 0.13 mmol) and tributyltin hydride (0.35 cm^3, 0.13 mmol) were added to a solution of 10-*S*-allyl-9-bromo-10-thiodihydroartemisinin **15** (54 mg, 0.13 mmol) in dry toluene (5 cm^3). The reaction mixture was heated at reflux at 70 °C for 2 h under a nitrogen atmosphere and then cooled to room temperature, aqueous potassium fluoride was added and the mixture was stirred for 15 min. The reaction mixture was extracted with chloroform, washed with water, dried and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using ethyl acetate–light petroleum (3:97) as eluent to give dehydroartemisinin **30** (20 mg, 59%) as a solid, mp 95–96 °C (lit.,[16] 95–97 °C) (Found: C, 67.3; H, 8.1. $C_{15}H_{22}O_4$ requires C, 67.64; H, 8.33%); δ_H 6.19 (br s, 1 H, olefinic H), 5.54 (s, 1 H, 11a-H), 1.58 (s, CH_3), 1.42 (s, CH_3) and 0.99 (d, CH_3).

The compounds **14** and **16** gave dehydroartemisinin **30** in 50% and 55% yields respectively under similar conditions.

Acknowledgements

Our thanks are due to Dr P. K. Inamdar and Dr D. K. Chatterjee, Hoechst India Ltd, for the spectral and biological data respectively.

References

1 (*a*) D. L. Klayman, *Science*, 1985, **228**, 1049; (*b*) X. O. Luo and C. C. Shen, *Med. Res. Rev.*, 1987, **7**, 29; (*c*) A. R. Butler and Y. I. Wu, *Chem. Soc. Rev.*, 1992, 85; (*d*) H. J. Woerdenbag, N. Pras, W. Uden, T. E. Wallaart, A. L. Beekman and C. B. Lugt, *Pharmacy World and Science*, 1994, **16**, 169.

2 G. H. Posner, D. J. McGarvey, C. H. Oh, N. Kumar, S. R. Meshnick and W. Asawamahasadka, *J. Med. Chem.*, 1995, **38**, 607.

3 Y. U. Pu and H. Ziffer, *J. Med. Chem.*, 1995, **38**, 613.

4 B. Venugopalan, C. P. Bapat and P. J. Karnik, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 751.

5 (*a*) B. Giess, *Radicals in Organic Synthesis: Formation of C–C bonds*, Pergamon, New York, 1986; (*b*) M. Ramaiah, *Tetrahedron*, 1987, **43**, 3541; (*c*) D. P. Curran, *Synthesis*, 1988, **417**, 489; (*d*) T. V. RajanBabu, *Acc. Chem. Res.*, 1991, **24**, 139.

6 B. Venugopalan, S. L. Shinde and P. J. Karnik, *Tetrahedron Lett.*, 1993, **34**, 6305.

7 B. Venugopalan, C. P. Bapat, P. J. Karnik, B. Lal, D. K. Chatterjee, S. N. Iyer and J. Blumbach, EP 456, 149/1991 (*Chem. Abstr.*, 1992, **116**, 837082).

8 A. Brossi, B. Venugopalan, G. L. Dominguez, H. J. C. Yeh, J. L. Flippen-Anderson, P. Buchs, X. D. Luo, W. Milhous and W. Peters, *J. Med. Chem.*, 1988, **31**, 645.

9 A. L. J. Beckwith, C. J. Easton and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 1980, 482.

10 X. Luo, H. J. C. Yeh, A. Brossi, J. L. Flippen-Anderson and R. Gilardi, *Helv. Chim. Acta.*, 1984, **67**, 1515.

11 (*a*) A. L. J. Beckwith, G. Phillipou and A. K. Serelis, *Tetrahedron Lett.* 1981, **22**, 2811; (*b*) A. L. J. Beckwith, *Tetrahedron* 1981, **37**, 3073.

12 A. L. J. Beckwith, T. Lawrence and A. K. Serelis, *Aust. J. Chem.*, 1983, **36**, 545; (*b*) E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821; (*c*) M. A. M. Brandney, A. D. Forbes and J. J. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1655.

13 T. V. RajanBabu, *J. Am. Chem. Soc.*, 1987, **109**, 609; (*b*) T. V. RajanBabu and T. Fukunaga, *J. Am. Chem. Soc.*, 1989, **111**, 296; (*c*) T. V. RajanBabu, T. Fukunaga and G. S. Reddy, *J. Am. Chem. Soc.*, 1989, **111**, 1759.

14 M. Ladlow and G. Pattenden, *Tetrahedron Lett.*, 1984, **25**, 4317.

15 P. A. Levene and A. Wati, *Org. Synth.*, 1975, **2**, 5.

16 A. J. Lin, M. Lee and D. L. Klayman, *J. Med. Chem.*, 1989, **32**, 1249.

17 B. Lythgoe and I. Waterhouse, *Tetrahedron Lett.*, 1977, 4223.

Paper 5/06763D
Received 12*th October* 1995
Accepted 1*st December* 1995