AN APPROACH TO THE SYNTHESIS OF NOVEL 11-HYDROXYARTEMISININ DERIVATIVES

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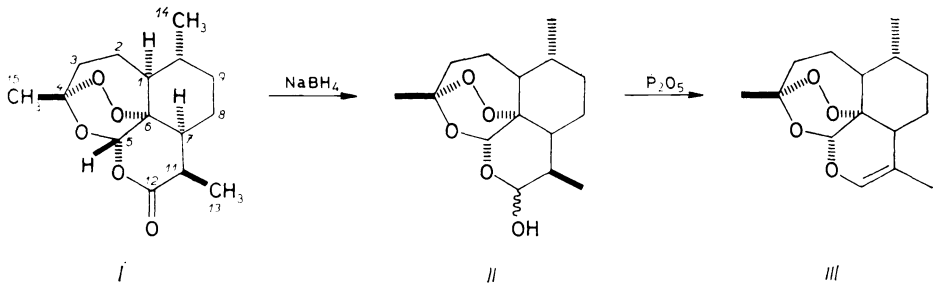
Received July 23, 1990
Accepted October 29, 1990

Dedicated to the memory of Professor František Šorm.

The conversion of artemisinin (*I*) to the epoxide *V* and its use for the preparation of novel artemisinin derivatives as potential antimalarial drugs is described.

Artemisinin (*I*), a sesquiterpene endoperoxide, isolated from *Artemisia annua* L., is one of the most promising antimalarials known (for recent reviews see refs[1,2]). Its clinical use is limited by the low solubility in water and oils. All attempts to improve the antimalarial activity and/or the bioavailability of *I* are based exclusively on derivatization of the hydroxyl group of its $NaBH_4$-reduction product – the lactol dihydroartemisinin (*II*) (refs[3–7]). According to a recent assumption[8] the antimalarial effect of *II* could be connected with the specific assembly of oxygen atoms in a rigid lipophilic molecule, favoring interactions mainly with the parasite membranes. In the light of this suggestion introduction of an additional oxygen substituent in the polar edge of the molecule may improve the selectivity and increase the antimalarial activity. Herein we report an approach to the synthesis of novel 11-hydroxydihydroartemisinin derivatives, using the epoxide *V* as a key intermediate.



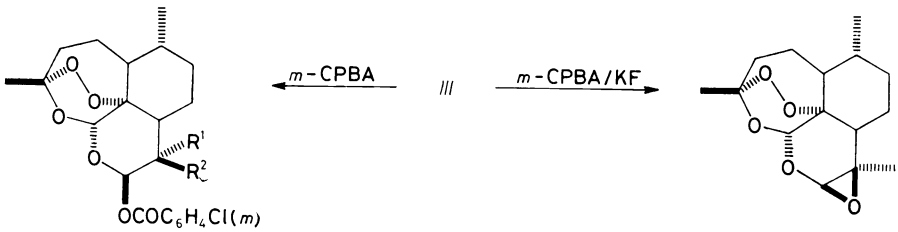
I *II* *III*

SCHEME 1

Artemisinin (*I*) was reduced with $NaBH_4$ in MeOH (ref.[5]) to dihydroartemisinin (*II*) and the latter dehydrated with P_2O_5 in CH_2Cl_2 to anhydrodihydroartemisinin (*III*) (refs[6,9]) in 90% yield (Scheme 1).

Attempted epoxidation of *III* with *m*-CPBA in CH_2Cl_2 at 0°C failed to produce an epoxide in acceptable yield. Instead, two diastereomeric products *IVa* (70%) and *IVb* (20%) were isolated. Obviously, they resulted from the reaction of the two initially formed diastereomeric epoxides with *m*-chlorobenzoic acid (produced by the reduction of *m*-CPBA). The stereochemistry of the newly created chiral centers in *IVa* and *IVb* was established by examination of their IR and NMR spectra (Table I). The IR-absorption of *IVb* (CCl_4, $1 . 10^{-3}$ mol l^{-1}) at 3 545 cm^{-1} (H bonded in a six membered ring hydroxyl) and at 1 743 cm^{-1} (free ester carbonyl) indicated the presence of a strong H-bond between the hydroxyl and the peroxide group, i.e. both have α-configuration. In contrast, the corresponding data of *IVa* (3 610, 1 745 and 1 725 cm^{-1}) are consistent with a weak H-bonding between the β-hydroxyl and the ester group. This assignment was further supported by the downfield shift (δ 1·72 ppm) of the α-methyl group at C-11 in the ^1H NMR spectrum of *IVa*. On the other hand, irradiation of the H-12 singlet lead to an NOE enhancement of the signal of the hydroxylic proton in *IVb* or of the methyl group at C-11 in *IVa*, respectively. The absence of an NOE between H-12 and H-5 also ruled out the α-configuration of the ester group in both *IVa* and *IVb*.

In contrast, the epoxidation of *III* with the 1 : 2 complex *m*-CPBA/KF (ref.[10]) in CH_2Cl_2 at 0°C proceeded with high stereoselectivity affording the epoxide *V* in 60% yield after purification by flash chromatography. The β-configuration of the epoxide ring was proven by reacting *V* with *m*-chlorobenzoic acid, resulting in *IVa* as a sole product. The highly preferred β-attack of the peracid on the enolether *III* is consistent with a recent observation[9] (see Scheme 2).



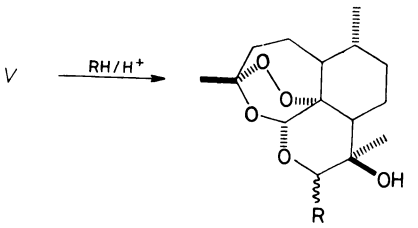
IV a, $R^1 = CH_3$; $R^2 = OH$
IV b, $R^1 = OH$; $R^2 = CH_3$

V

SCHEME 2

The peroxide *V* is highly sensitive to acids and even in the presence of wet SiO_2 is easily transformed to 11-hydroxydihydroartemisinin (*VI*). Similarly to other

alkoxysubstituted oxiranes[11], compound *V* smoothly undergoes regioselective oxirane opening (Scheme 3), when treated with alcohols or carboxylic acids, giving the corresponding C-12 derivatives of 11-hydroxydihydroartemisinin in quantitative yields.



IV a, R = *m*-ClC_6H_4COO (β)
VI, R = OH (α + β)
VII, R = CH_3COO (β)
VIII a, R = CH_3O (β)
VIII b, R = CH_3O (α)

SCHEME 3

Configuration assignment at C-12 of the new products *VII*, *VIIIa* and *VIIIb* (compounds *VIIIa* and *VIIIb* – ratio 3·3 : 1 as determined by ^{1}H NMR – were separated by flash chromatography on silica gel) was based on ^{1}H NMR NOE data. NOE's between H-5 and H-12 in the 12α-epimer *VIIIb* and between CH_3-13 and H-12 in the 12β-epimers *VII* and *VIIIa* were observed. It should be pointed out that only the 12β-acyl derivatives were obtained by this reaction, while the direct esterification of *II* afforded exclusively 12α-epimers[3].

TABLE I
Selected ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) and IR (CCl_4, 1 . 10^{-3} mol l^{-1}) data

Compound	^{1}H NMR		IR	
	H-12, ppm	CH_3-13, ppm	OH, cm^{-1}	CO, cm^{-1}
IVa	6·33	1·72	3 610	1 725, 1 745
IVb	6·32	1·20	3 545	1 743
VII	6·07	1·64	3 608	1 739, 1 768
VIIIa	4·58	1·56	3 581	—
VIIIb	4·50	1·53	3 602	—

The high reactivity of the epoxide *V* offers a wide range of possibilities for preparation of novel artemisinin derivatives as potential antimalarial drugs. Application of this approach for the synthesis of water soluble compounds is in progress.

EXPERIMENTAL

Flash chromatography: Merck silica gel 60 (40—60 μm). M.p. (uncorrected): Kofler microscope. IR spectra (cm^{-1}): Bruker IFS 113V and IR-20 (Zeiss, Jena). ^1H NMR spectra: Bruker WM-250 spectrometer at 250 MHz; δ values in ppm relative to internal TMS; coupling constants (J) in Hz. MS: JEOL JMS D300 instrument.

Epoxidation of Anhydrodihydroartemisinin

Compound *III* (refs[6,9]) was treated with the *m*-CPBA/KF complex (1 : 2) in CH_2Cl_2 at 0°C according to ref.[10]. The oxirane *V* was purified by flash chromatography (SiO_2, hexane/diethyl ether 3 : 1). Yield 60%. M.p. 117—120°C. ^1H NMR ($CDCl_3$, 250 MHz, δ): 5·28 (s, 1 H), 4·96 (s, 1 H), 2·39—0·88 (m, 11 H), 1·43 (s, 3 H), 1·32 (s, 3 H), 0·96 (d, 3 H, J = 5·8 Hz). MS (CI/2-methylpropan, *m/z*, %): 283 ($[M + H]^+$, 9), 265 (25), 237 (27), 219 (100), 192 (9).

Oxirane Opening

In a typical experiment to 0·5 mmol of *V* in 5 ml of CH_2Cl_2 a 10-fold excess of a carboxylic acid or a 10-fold excess of an alcohol and cat. amount of toluenesulfonic acid was added. The reaction mixture was left at room temperature until total disappearance (TLC) of the starting material, washed with $NaHCO_3$ solution and concentrated in vacuo.

11β-*Hydroxy*-12β-O-(3-*chlorobenzoyl*)*dihydroartemisinin* (IVa), M.p. 146—148°C. ^1H NMR ($CDCl_3$, 250 MHz, δ): 7·96 (br . s, 1 H), 7·86 (br . d, 1 H, J = 7·9 Hz), 7·57 (br . d, 1 H, J = = 7·9 Hz), 7·41 (dd, 1 H, J = 7·9; 7·9 Hz), 6·33 (s, 1 H), 5·60 (s, 1 H), 2·44—1·20 (m, 12 H), 1·72 (s, 3 H), 1·45 (s, 3 H), 1·00 (d, 3 H, J = 5·8 Hz). IR (KBr): 3 600, 3 580—3 200, 1 730. MS (CI/2-methylpropan, *m/z*, %): 437 (5), 435 (15, $[M - H]^+$), 421 (9), 381 (33), 379 (100), 283 (51), 265 (25), 223 (46).

11α-*Hydroxy*-12β-O-(3-*chlorobenzoyl*)*dihydroartemisinin* (IVb), M.p. 153—155°C. ^1H NMR ($CDCl_3$, 250 MHz, δ): 7·93 (br . s, 1 H), 7·84 (d, 3 H, J = 8 Hz), 7·58 (br . d, 1 H, J = 8 Hz), 7·42 (dd, 1 H, J = 8; 8 Hz), 6·32 (s, 1 H), 5·60 (s, 1 H), 4·91 (s, exchangeable with D_2O, OH), 2·44—1·32 (m, 11 H), 1·47 (s, 3 H), 1·20 (s, 3 H), 1·02 (d, 3 H, J = 5·6 Hz). IR (KBr): 3 530, 1 720. MS (CI/2-methylpropan, *m/z*, %): 421 (1), 379 (4), 283 (57), 267 (24), 265 (19), 237 (48), 219 (100).

11β-*Hydroxy*-12β-O-*acetyldihydroartemisinin* (VII), M.p. 125—127°C. ^1H NMR ($CDCl_3$, 250 MHz, δ): 6·07 (s, 1 H), 5·50 (s, 1 H), 2·42—1·26 (m, 12 H), 2·14 (s, 3 H), 1·64 (s, 3 H), 1·43 (s, 3 H), 0·97 (d, 3 H, J = 5·9 Hz). IR (KBr): 3 600—3 300, 1 730. MS (CI/2-methylpropan, *m/z*, %): 343 ($[M + H]^+$, 3), 325 (42), 297 (21), 283 (41), 265 (43), 237 (40), 219 (100).

11β-*Hydroxy*-12β-O-*methyldihydroartemisinin* (VIIIa), M.p. 94—96°C. ^1H NMR ($CDCl_3$, 250 MHz, δ): 5·39 (s, 1 H), 4·58 (s, 1 H), 3·52 (s, 3 H), 2·53 (br . s, exchangeable with D_2O, OH), 2·42—1·21 (m, 11 H), 1·56 (s, 3 H), 1·44 (s, 3 H), 0·95 (d, 3 H, J = 5·9 Hz). MS (CI/2-methylpropan, *m/z*, %): 297 (10), 283 (41), 269 (100), 237 (22), 219 (52).

11β-*Hydroxy*-12α-O-*methyldihydroartemisinin* (VIIIb), M.p. 87—89°C. ^1H NMR ($CDCl_3$, 250 MHz, δ): 5·35 (s, 1 H), 4·50 (s, 1 H), 3·57 (s, 3 H), 2·43—0·90 (m, 12 H), 1·53 (s, 3 H), 1·45

(s, 3 H), 0·96 (d, 3 H, $J = 5·8$ Hz). MS (CI/2-methylpropan, m/z, %): 297 (79), 283 (25), 269 (49), 265 (39), 237 (44), 219 (100).

We thank Miss B. Michova for performing the NOE *experiments and Dr D. Tsankov for the* IR *measurements and helpful discussion.*

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