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Biomimetic Synthesis of Arteannuin H and the 3,2-Rearrangement of Allylic Hydroperoxides

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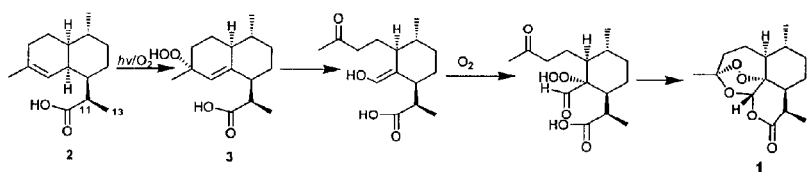
Abstract: The acyl endoperoxide arteannuin H, recently reported as a novel natural product from *Artemisia annua*, has been obtained in two steps from the photooxidation of dihydroartemisinic acid, thereby confirming biogenetic speculation regarding its derivation from a secondary allylic hydroperoxide. The little studied 3,2-rearrangement reaction of such allylic hydroperoxides is also discussed.

INTRODUCTION

In 1972, Chinese scientists isolated the unusual endoperoxide artemisinin (qinghaosu) (**1**) from *Artemisia annua*.[1] This compound has since become very important for the treatment of malaria in south east Asia and elsewhere and extensive investigations into its biogenesis have suggested a complex derivation from dihydroartemisinic acid (**2**) (or its 11,13-unsaturated analogue, artemisinic acid) *via* autoxidation to a tertiary allylic hydroperoxide (**3**) (Scheme 1).[2-4] In 1998 we reported a second endoperoxide, arteannuin H[4] (**4**), from *A. annua* with a structure clearly suggestive of direct derivation from a secondary allylic hydroperoxide (**5**). Although the photooxidation chemistry of dihydroartemisinic acid and artemisinic acid have been extensively studied by several investigators[2-8] only the tertiary allylic hydroperoxide **3** has ever been reported; no references exist in the literature concerning secondary allylic hydroperoxides such as **5** and **6** which would be expected from the "ene"-type reaction of molecular oxygen with the tri-substituted double bond in **2**.



Scheme 1. Proposed biogenesis of artemisinin (**1**) from dihydroartemisinic acid (**2**) *via* autoxidation reactions involving a tertiary allylic hydroperoxide **3**.

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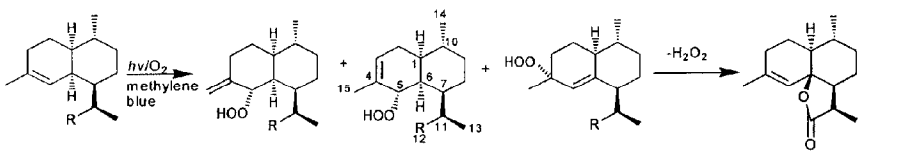
RESULTS AND DISCUSSION

Dihydroartemisinic acid used in this study was obtained as a natural product from *A. annua*,[4] although several syntheses[9-13] of this and closely related compounds have been reported. Photooxidation of dihydroartemisinic acid (**2**) in the presence of methylene blue as photosensitizer[5] resulted in isolation of the known tertiary allylic hydroperoxide **3** as the major product (58%) together with smaller amounts of the novel isomeric secondary allylic hydroperoxides **5** (8%) and **6** (4%) which are formed from two alternative "ene"-type reactions of molecular oxygen with the tri-substituted double bond in **2** (Scheme 2).



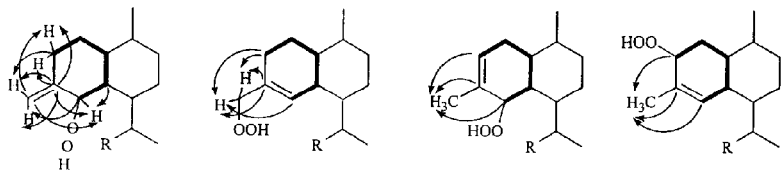
2 R=CO_2H **5** R=CO_2H **6** R=CO_2H **3** R=CO_2H **7** (from **3** only)
10 R=CO_2Me **11** R=CO_2Me **12** R=CO_2Me **13** R=CO_2Me
14 R=CH_2OH **17** R=CH_2OH **18** R=CH_2OH **19** R=CH_2OH
16 R=CH_3 **20** R=CH_3 **21** R=CH_3 **22** R=CH_3

Scheme 2. Photooxidation of dihydroartemisinic acid (**2**) and analogues **10**, **14** and **16** resulting in secondary and tertiary allylic hydroperoxides.

This reaction is best effected quickly in the presence of a strong light source (in this case, a 500 W tungsten lamp) in order to reduce the extent of decomposition of the tertiary allylic hydroperoxide **3** to dihydroepideoxyarteannuin B[4] (**7**), which is formed in appreciable yield if longer reaction times are used (for example, a 5% yield of **7** was obtained in addition to hydroperoxides **3**, **5** and **6** after 12 hours irradiation of a solution of **2** with a 100 W lamp). Complete NMR assignments for novel secondary allylic hydroperoxides **5** and **6** were made by 2D-NMR experiments such as HSQC, HMBC and ^1H-^1H COSY (Figure 1) and are reported in Table 1 (assignments for the tertiary allylic hydroperoxide **3** have been reported previously).[4] All other compounds reported in this paper were assigned in the same way. These assignments were then useful in determining the 5α-stereochemistry of the new secondary hydroperoxide functional group in **5** and **6** from NOESY experiments; this stereochemistry in the products is almost certainly a consequence of "ene"-type addition of molecular oxygen occurring from the less sterically hindered α-face of dihydroartemisinic acid.

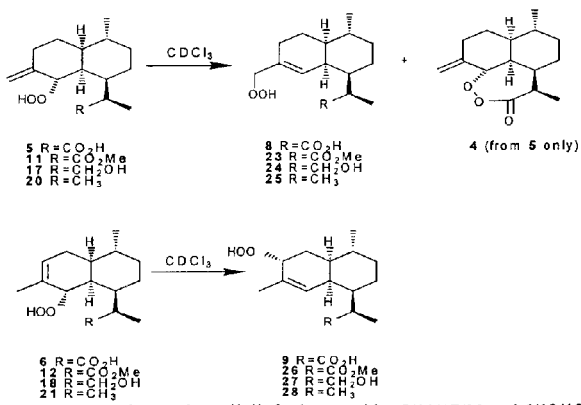
When allowed to stand in $CDCl_3$ solution over a period of several days, secondary allylic hydroperoxide **5** was converted into arteannuin H[4] (**4**) and the primary allylic hydroperoxide **8** (Table 1 and Figure 1) in approximately equal amounts (Scheme 3). Study of the rate of transformation of **5** into **4** and **8**, by determination of integrals for clearly resolved signals corresponding to the starting material and products in ^1H NMR spectra acquired at discrete time intervals over the course of the reaction (see Experimental), revealed that these two products were formed at approximately the same rate (-5.2 x 10^{-3} hr^{-1} for **4** and –6.5 x 10^{-3} hr^{-1} for **8**).

Somewhat unexpectedly, the isomeric secondary allylic hydroperoxide **6** did not yield any acyl endoperoxide product analogous to **4** under these conditions, but was instead converted entirely to the rearranged allylic hydroperoxide **9** (Table 2 and Figure 1) at a somewhat faster rate (-9.8 x 10^{-3} hr^{-1}) than was observed in the rearrangement of **5** to **8**. The stereochemistry for the rearranged hydroperoxide group in **9** was confirmed to be 3α- by NOESY.



5, 11, 17, 20 **8, 23, 24, 25** **6, 12, 18, 21** **9, 26, 27, 28**

Figure 1. Critical two- and three-bond ^{13}C-^{1}H correlations (determined by HMBC and indicated by arrows from ^{13}C to ^{1}H) and ^{1}H-^{1}H correlations (determined by COSY and indicated by heavy lines) used in determining the structures and NMR assignments for allylic hydroperoxides **5/11/17/20**; **8/23/24/25**; **6/12/18/21** and **9/26/27/28**.



Scheme 3. Further reactions of secondary allylic hydroperoxides **5/11/17/20** and **6/12/18/21** in $CDCl_3$ solution.

We reasoned that if the acyl endoperoxide linkage of arteannuin H (**4**) was formed from secondary allylic hydroperoxide **5** by intramolecular nucleophilic attack of the hydroperoxide group at the carboxylic acid group, as would seem to be intuitively obvious, then it might be possible to improve the yield of **4** by increasing the rate of this reaction relative to the competing 3,2-rearrangement of the allylic hydroperoxide. One means of achieving this would be to utilise the methyl ester of **5**, which should be more susceptible to such nucleophilic attack. Accordingly, we obtained the methyl ester (**10**) of **2** (Table 3, Scheme 4) and subjected it to photooxidation (Scheme 2) which, as expected, yielded the three allylic hydroperoxide products **11** (Table 1;

Table 1. ^{13}C and ^{1}H NMR assignments for secondary allylic hydroperoxides **5**, **11**, **17** and **20** containing an exocyclic double bond and their rearrangement products **8**, **23**, **24** and **25**.

	$\delta^{13}C$								$\delta^{1}H$							
	5	**11**	**17**	**20**	**8**	**23**	**24**	**25**	**5**	**11**	**17**	**20**	**8**	**23**	**24**	**25**
1	45.6	45.5	45.4	45.2	41.6	41.5	41.8	41.8	1.44	1.43	1.36	1.32	1.34	1.32	1.32	1.24
2α	28.7	28.7	28.1	27.9	25.4	25.3	25.4	25.5	1.95	1.96	1.93	1.93	1.59	1.60	1.60	1.58
2β									1.42	1.41	1.41	1.42	2.04	2.03	2.01	2.01
3α	28.9	28.9	28.4	28.2	22.8	22.7	22.8	22.7	2.25	2.25	2.27	2.28	2.02	2.03	2.03	2.02
3β									2.18	2.16	2.17	2.18	2.02	2.03	2.03	2.02
4	148.0	148.0	148.1	148.1	135.1	134.9	134.2	133.7	-	-	-	-	-	-	-	-
5	85.5	85.6	86.0	86.1	126.2	126.5	128.0	128.7	4.73	4.72	4.71	4.67	5.54	5.54	5.64	5.66
6	43.2	43.3	44.0	44.6	36.6	36.6	37.2	38.1	1.94	1.92	1.94	1.97	2.59	2.57	2.56	2.59
7	45.6	46.0	45.2	50.9	43.4	43.7	42.4	48.3	1.66	1.67	1.30	0.97	1.69	1.68	1.29	0.97
8α	26.1	26.0	24.7	25.1	27.7	27.7	26.6	26.8	1.57	1.56	1.78	1.78	1.48	1.32	1.68	1.68
8β									1.57	1.42	1.39	1.26	1.10	1.01	0.96	0.88
9α	35.9	36.0	36.2	36.4	35.1	35.1	35.5	35.8	1.08	1.05	1.02	0.98	0.99	0.97	0.96	0.92
9β									1.82	1.79	1.81	1.71	1.63	1.60	1.64	1.65
10	28.9	29.0	29.1	29.1	27.9	27.9	28.0	28.1	1.74	1.71	1.69	1.70	1.43	1.40	1.42	1.37
11	43.7	43.8	37.8	30.1	41.7	42.1	36.6	28.8	2.87	2.84	1.93	1.81	2.53	2.51	1.64	1.57
12	182.9	178.3	67.0	22.2[a]	180.8	177.7	66.6	21.7[a]	-	-	3.71	0.88[a]	-	-	3.74	0.93[a]
											3.54				3.55	
13	16.5	16.6	16.4	21.9[a]	15.2	15.2	15.1	20.8[a]	1.22	1.17	1.02	0.91[a]	1.20	1.14	1.00	0.90[a]
14	19.9	20.0	20.1	20.1	19.6	19.6	19.7	19.8	0.86	0.86	0.85	0.84	0.89	0.88	0.88	0.88
15	107.2	107.2	107.9	108.1	81.9	81.9	82.1	82.3	5.06[b]	5.06[b]	5.05[b]	5.04[b]	4.38	4.37	4.38	4.38
									4.92[c]	4.92[c]	4.94[c]	4.93[c]	4.34	4.34	4.35	4.34
OMe	-	51.4	-	-	-	51.5	-	-	-	3.68	-	-	-	3.68	-	-

[a] Interchangeable within column
[b] *cis* to –OOH; [c] *trans* to -OOH

Table 2. ^{13}C and ^{1}H NMR assignments for isomeric secondary allylic hydroperoxides **6**, **12**, **18** and **21** containing an endocyclic double bond and their rearrangement products **9**, **26**, **27** and **28**.

	$\delta^{13}C$								$\delta^{1}H$							
	6	**12**	**18**	**21**	**9**	**26**	**27**	**28**	**6**	**12**	**18**	**21**	**9**	**26**	**27**	**28**
1	45.3	45.2	45.7	45.6	44.3	44.2	44.6	44.6	1.41	1.40	1.37	1.32	1.51	1.51	1.46	1.42
2α	27.8	27.8	27.8	27.9	30.7	30.6	30.8	30.8	2.13	2.13	2.10	2.08	1.89	1.87	1.87	1.85
2β									2.16	2.13	2.15	2.14	2.40	2.39	2.40	2.39
3	127.2	127.3	127.4	127.4	82.3	82.3	82.6	82.7	5.69	5.68	5.71	5.69	4.40	4.40	4.42	4.42
4	131.3	131.3	131.5	131.6	134.4	134.2	133.8	132.7	-	-	-	-	-	-	-	-
5	83.2	83.2	83.6	83.7	126.2	126.4	127.8	128.3	4.39	4.37	4.38	4.34	5.41	5.41	5.51	5.52
6	35.9	35.9	37.0	36.9	36.7	36.7	37.8	38.2	2.61	2.58	2.58	2.61	2.61	2.60	2.58	2.62
7	45.2	45.5	45.1	49.9	43.5	43.7	42.5	48.5	1.71	1.72	1.44	1.09	1.63	1.60	1.21	0.89
8α	26.3	26.3	24.9	25.1	27.5	27.5	26.4	26.5	1.57	1.57	1.78	1.77	1.46	1.28	1.67	1.67
8β									1.41	1.39	1.30	1.12	1.11	1.05	0.96	0.88
9α	35.4	35.4	35.8	36.0	35.2	35.2	35.6	35.8	1.05	1.02	1.02	0.96	0.96	0.94	0.89	0.88
9β									1.70	1.67	1.74	1.70	1.62	1.58	1.62	1.64
10	28.9	28.9	28.9	28.8	28.9	28.8	28.9	28.9	1.32	1.31	1.32	1.31	1.36	1.35	1.37	1.37
11	43.1	43.3	37.2	29.6	42.0	42.3	36.7	28.8	2.69	2.68	1.87	1.73	2.50	2.49	1.62	1.57
12	182.1	178.1	66.7	21.4[a]	182.0	177.8	66.6	21.7[a]	-	-	3.70	1.04[a]	-	-	3.73	0.93[a]
											3.60				3.55	
13	16.0	15.9	16.1	21.6[a]	15.1	15.2	15.0	20.7[a]	1.35	1.29	1.12	0.88[a]	1.19	1.13	0.99	0.89[a]
14	20.2	20.3	20.4	20.4	19.6	19.6	19.7	19.8	0.80	0.79	0.79	0.78	0.93	0.92	0.92	0.92
15	19.8	19.8	20.0	19.9	19.9	20.0	20.0	20.0	1.78	1.77	1.78	1.77	1.78	1.77	1.77	1.76
OMe	-	51.3	-	-	-	51.5	-		-	3.67	-	-	-	3.68	-	

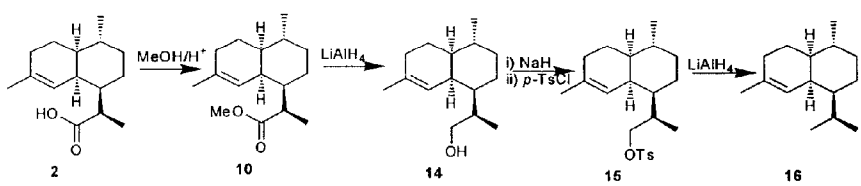
[a] Interchangeable within column

Table 3. ^{13}C and ^{1}H NMR assignments for derivatives of dihydroartemisinic acid (**2**)[a] modified at the 12-position: methyl ester **10**, primary alcohol **14** and fully reduced compound **16** and tertiary hydroperoxides **13, 19** and **20** formed by autoxidation of these derivatives.

	$\delta^{13}C$						$\delta^{1}H$					
Atom	**10**	**14**	**16**	**13**	**19**	**22**	**10**	**14**	**16**	**13**	**19**	**22**
1	41.7	42.1	42.1	45.1	45.1	45.1	1.25	1.21	1.17	1.57	1.56	1.55
2α	25.8	25.9	25.9	22.6	23.4	23.4	1.55	1.54	1.54	1.48	1.42	1.43
2β							1.94	1.95	1.93	1.93	1.97	1.97
3α	26.6	26.7	26.7	28.8	29.3	29.4	1.91	1.90	1.92	1.92	1.88	1.88
3β							1.80	1.80	1.80	1.48	1.53	1.53
4	135.9	135.2	134.7	80.6	81.2	81.3	-	-	-	-	-	-
5	119.5	120.7	121.1	120.0	120.1	119.8	5.12	5.22	5.23	5.22	5.35	5.26
6	36.4	37.5	37.9	146.7	147.5	148.5	2.50	2.48	2.51	-	-	-
7	44.0	42.7	48.6	47.6	47.3	49.8	1.62	1.63	0.91	2.10	1.83	1.66
8α	27.5	26.4	26.5	32.8	29.6	28.8	1.25	1.61	1.63	1.69	1.90	1.84
8β							1.08	1.00	0.91	1.18	0.99	1.00
9α	35.3	35.7	35.9	35.5	35.7	35.7	0.94	0.92	0.91	1.20	1.16	1.15
9β							1.59	1.61	1.63	1.75	1.77	1.77
10	27.7	27.7	27.7	38.6	39.0	38.9	1.41	1.43	1.41	1.29	1.22	1.22
11	42.2	36.7	28.8	41.2	35.2	27.1	2.50	1.63	1.57	2.73	2.04	2.01
12	178.0	66.8	21.7[b]	177.0	65.6	22.3[b]	-	3.77, 3.50	0.91[b]	-	3.77 3.46	0.95[b]
13	15.1	15.0	20.7[b]	15.9	16.7	18.5[b]	1.13	0.99	0.89[b]	1.22	1.06	087[b]
14	19.7	19.8	19.9	20.0	20.1	20.1	0.86	0.86	0.85	0.93	0.92	0.93
15	23.8	23.9	23.9	24.5	24.5	24.5	1.63	1.63	1.62	1.30	1.31	1.31
OMe	51.4	-	-	51.4	-	-	3.68	-	-	3.67	-	-

[a] For NMR assignments of **2** see ref. 4; [b] Interchangeable within column.

Figure 1), **12** (Table 2; Figure 1) and **13**. To our surprise, secondary allylic hydroperoxide **11**, which is the desired methyl ester analogue of **5**, underwent conversion to the primary hydroxyl rearrangement product **23** in $CDCl_3$ solution (Scheme 3; Table 1), without any detectable formation of arteannuin H; the isomeric secondary allylic hydroperoxide **12** also only underwent rearrangement and was cleanly converted to **26** (Scheme 3). Similarly, secondary allylic hydroperoxides **17** and **20** (Table 1) incorporating a primary alcohol and a methyl group respectively in place of the 12-carboxylic acid group of **5** and 12-methyl ester of **11** also underwent only rearrangement reactions (Scheme 3); compounds **17** and **20** were obtained by photooxidation of **14** and **16** (Scheme 2), which were in turn derived from further reduction of the methyl ester group in **10** (Scheme 4). It is



Scheme 4. Synthesis of 12-derivatives **10**, **14** and **16** of dihydroartemisinic acid, which are used as substrates for photooxidation reactions.

interesting to note that of the eight compounds investigated (**5/6, 11/12, 17/18** and **20/21**), only compound **5**, which contains a carboxylic acid at the 12-position, is able to "trap" the hydroperoxide group as an acyl endoperoxide before it rearranges under the mild conditions employed. Acyl endoperoxides are rare in nature, and if, as has been proposed,[4] arteannuin H is indeed formed from dihydroartemisinic acid by analogous chemical reactions occurring in the plant, then the biogenesis of this unusual structural motif might be ascribed to a fortuitous combination of two functional groups (the Δ^4 tri-substituted double bond and the 12-carboxylic acid) occuring in an appropriate spatial relationship with one another in the substrate dihydroartemisinic acid.

The rates of the 3,2-rearrangement reactions of secondary allylic hydroperoxides **5**, **11**, **17** and **20** (Table 4) as determined by ^{1}H NMR spectroscopy were all very similar; the rates of rearrangement for isomeric secondary allylic hydroperoxides **6**, **12**, **18** and **21** were also largely independent of the functional group present at the 12-position, although this series of compounds, for which the allylic double bond is endocyclic, reacted significantly faster than did their exocyclic double bond counterparts. It is possible that the driving force for this rearrangement is the relief of congestion in the molecule when the hydroperoxide group is shifted away from the vicinity of the bulky 7β-substituent, and this may be the reason for the faster reaction of the series **6/12/18/21** for which the hydroperoxyl group is more conformationally restricted by the endocyclic nature of the allylic double bond.

Table 4. Rate of rearrangement of **5/11/17/20** into **8/23/24/25** and of **6/12/18/21** into **9/26/27/28** as determined by ^{1}H NMR in $CDCl_3$ solution (see Experimental), expressed as x 10^{-3} hr^{-1}.

Exocyclic allylic secondary hydroperoxides		Endocyclic allylic secondary hydroperoxides	
5 → 8	-6.5	**6 → 9**	-9.8
11 → 23	-4.7	**12 → 26**	-10
17 → 24	-5.2	**18 → 27**	-18
20 → 25	-7.0	**21 → 28**	-14

Such 3,2-rearrangement reactions of allylic hydroperoxides have been only infrequently reported,[14-18] and it has been proposed that the mechanism involves a five-membered ring transition state.[19-21] This would certainly be consistent with our results, in which the rearrangement was in all cases found to be suprafacial. Factors governing the rate of the reaction have not been well defined,[22] although such 3,2-rearrangements apparently require initial hydrogen abstraction from the hydroperoxyl group assisted by the presence of radical initiators or ultraviolet light[14,23] in order to generate peroxyl radicals, which then participate in the five-membered ring transition state.[14,24] It has been suggested that such hydrogen abstraction should be more difficult when the hydroperoxyl group is involved in hydrogen bonding. However, we found no conclusive evidence for this since the rate of rearrangement was largely independent of the nature of the 12-functional group which certainly would be expected to be capable of participating in such hydrogen bonding. We were also disappointed to

discover that repeating the reactions in the dark led to no significant decrease in the rate of rearrangement in all cases. More encouraging was the observation that, as expected from precedents in the literature, the rearrangement of **6** to **9** could be completely prevented by addition of the free-radical inhibitor 2,6-di-^{t}butyl-4-methylphenol to $CDCl_3$ solution; this strategy was also successful in preventing the competing rearrangement reaction of **5** to **8** observed in the formation of arteannuin H. Inhibition of the 3,2-rearrangement is thus a slow but effective way to achieve a clean conversion of secondary hydroperoxide **5** to endoperoxide **4**. A far better approach was to increase the rate of acyl endoperoxide formation by the addition of trifluoroacetic acid (TFA) (2 μl) to $CDCl_3$ solution, which resulted in clean conversion of **5** to **4** within 30 minutes. Interestingly, the rearranged hydroperoxide **8** can also be cleanly converted to arteannuin H over several days by the same procedure. Presumably, although the equilibrium position for 3,2-allylic rearrangement of all the compounds we have studied lies heavily in favour of the less sterically hindered products **8**, **9** and **23-28** (see above), the reverse reaction from primary hydroperoxide **8** does still manage to maintain a small percentage of secondary hydroperoxide **5** in the thermal equilibrium mixture: this hydroperoxide is effectively "trapped" by the 12-carboxylic acid group in the presence of acid, thereby perturbing the equilibrium and resulting in the observed slow conversion of **8** to arteannuin H.

In conclusion, we have been able to prepare arteannuin H (4) from dihydroartemsinic acid (**1**) in an improved but still low yield (8%) by photooxidation of **1** to secondary allylic hydroperoxide **5** followed by quantitative conversion of this compound to arteannuin H in TFA/$CDCl_3$. In order to further improve the yield of arteannuin H from this biomimetic synthesis, it would be necessary to alter the percentage composition of allylic hydroperoxides which are formed from the initial photooxidation in order to favour the secondary allylic hydroperoxide products over the tertiary allylic hydroperoxide product: however, to the best of our knowledge, there are no precedents available in the literature to suggest how this might be achieved.

EXPERIMENTAL

Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. Proton chemical shifts, multiplicities, coupling constants and integrals reported in this section are those which are clearly resolved in ^{1}H 1D-NMR without recourse to 2D-NMR analysis (see Tables for 2D-NMR). All NMR experiments were run on a Bruker DRX 500 instrument. HSQC and HMBC spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. High-resolution MS were recorded in EI mode at 70 e.v. on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a Shimadzu FT-IR-8201 PC instrument. Column chromatography was performed using silica gel 60-200 μm (Merck). HPLC separations were performed using a Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and a normal phase Intersil PREP-SIL 20 mm x 25 cm column, flow rate 8 mL/min. The rates of reactions for 3,2-allylic rearrangements of allylic

hydroperoxides were determined from ^{1}H NMR spectra which were recorded daily during the conversion of starting material (1 mg) in $CDCl_3$ solution (0.6 ml) into product(s) under ambient conditions. Integrals were measured for a well-resolved characteristic ^{1}H NMR signal associated with both starting material and product and the rate of reaction was determined by plotting the logarithm of the ratio for the integral for the characteristic signal chosen for starting material to the integral of the characteristic signal chosen for product against time (in hours) and determining the slope of the resulting line.

Photooxidation of **2** *in the presence of methylene blue.* Methylene blue (11 mg) was added to dihydroartemisinic acid (**2**) in acetone (100 mg/ 200 ml) and the mixture maintained at ice-bath temperature under irradiation with a tungsten lamp (500 W) for 1 h after which solvent was removed by a rotary evaporator and the residue taken up in Et_2O (200 ml). After filtration to remove the dye, solvent was rotary evaporated to yield a crude product (98 mg; 86%) which was subjected to preparative HPLC (30% EtOAc/hexane): **5** (9 mg, 8%, R_f 15.2 min); **6** (5 mg, 4 %, R_f 14.2 min); **3** (66 mg, 58%, R_f 17.0 min). *5α-Hydroperoxy-amorph-4(15)-en-12-oic acid (5):* Oil. $[\alpha]_D$ -92.1 (*c* 0.6 $CHCl_3$); IR υ_{max} ($CHCl_3$) 3522, 3292 (br), 2928, 2870, 1705, 1456 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) ppm: 8.50 (1H, br s, -OOH), 5.06 (1H, s), 4.92 (1H, s), 4.73 (1H, d, *J* = 10.7 Hz), 2.87 (1H, m), 1.22 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.3 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 250.1572 [M^+ - H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (40), 235 (70), 205 (20), 177 (85), 161 (100), 121 (30), 109 (25). *5α-Hydroperoxy-amorph-3-en-12-oic acid (6):* Oil. $[\alpha]_D$ -29.8 (*c* 0.3, $CHCl_3$); IR υ_{max} ($CHCl_3$) 3514, 3329 (br), 2928, 2872, 1709, 1603, 1456 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) ppm: 7.20 (1H, br s, -OOH), 5.69 (1H, br s), 4.39 (1H, d, *J* = 8.9 Hz), 2.69 (1H, m), 2.61 (1H, m), 1.78 (3H, s), 1.35 (3H, d, *J* = 6.6 Hz), 0.80 (3H, d, *J* = 6.2 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 250.1560 [M^+ - H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (15), 235 (100), 205 (25), 177 (20), 161 (70), 149 (35), 121 (10), 109 (20). *4α-Hydroperoxy-amorph-5-en-12-oic acid* (**3**) – Physical data for **3** identical with reference 4. *Dihydroepideoxyarteannuin B* (**7**) –Physical data for **7** identical with reference 25.

Transformation of **5** *into* **4** *and* **8** *in* $CDCl_3$ *solution.* Compound **5** (6 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 4 weeks. When the reaction was complete solvent was removed and the mixture was separated by HPLC (20% EtOAc/hexane): **4** (1.2 mg, R_f 9.1 min); **8** (1.6 mg, R_f 40.6 min). *Arteannuin H (4)* – see ref. 4 for physical data. *15-Hydroperoxy-amorph-4-en-12-oic acid (8):* Oil. IR υ_{max} ($CHCl_3$) 3364 (br), 3028, 2930, 2855, 1717, 1684, 1456 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) ppm: 9.42 (1H, s, -OOH), 5.54 (1H, s), 4.36 (2H, m), 2.59 (1H, s), 2.53 (1H, m), 1.20 (3H, d, *J* = 7.0 Hz), 0.89 (3H, d, *J* = 6.1 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 250.1571 [M^+ - H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (8), 234 (12), 177 (100), 161 (30), 147 (15), 133 (5). *Calculation of the rate of conversion of* **5** *into* **4** *and* **8** *in* $CDCl_3$ *solution by* ^{1}*H NMR spectroscopy.* See general procedure at beginning of experimental: **4**, δ_H 3.52, 1H, q, *J* = 7.0 Hz, H-11; **5**, δ_H 4.92, 1H, s, H-15; **8**, δ_H 5.54, 1H, s, H-5.

Rearrangement of ***6*** *to* ***9*** *in* $CDCl_3$ *solution.* Compound **6** (3.3 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 3 weeks, resulting in clean conversion into compound **9** (3.0 mg). *3α-Hydroperoxy-amorph-4-en-12-oic acid* ***(9)****:* Oil. $[\alpha]_D$ +2.5 (*c* 0.2, $CHCl_3$); IR υ_{max} ($CHCl_3$) 3530, 3321 (br), 3022, 2928, 2855, 1709, 1670, 1456 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.41 (1H, s), 4.40 (1H, d, *J* = 7.2 Hz), 2.61 (1H, s), 2.50 (1H, m), 1.78 (3H, s), 1.19 (3H, d, *J* = 6.9 Hz), 0.93 (3H, d, *J* = 6.4 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 250.1572 [M^+ - H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (12), 234 (30), 177 (100), 161 (55), 149 (25), 119 (15). *Calculation of the rate of conversion of* ***6*** *into* ***9*** *in* $CDCl_3$ *solution by* ^1H *NMR spectroscopy.* See general procedure at beginning of experimental: **6**, δ_H 5.69, 1H, s, H-3; **9**, δ_H 5.41, 1H, s, H-5.

Conversion of dihydroartemisinic acid (2) to dihydroartemisinic acid methyl ester ***(10)****.* Dihydroartemisinic acid was dissolved in CH_3OH (296 mg/3 ml). HCl (conc., 0.15 ml) was added and the mixture stirred overnight. When the reaction was complete solvent was removed under reduced pressure to yield a crude product (276 mg, 93 %) which was further purified by HPLC (5% EtOAc/hexane) to yield the methyl ester of dihydroartemisinic acid (**10**) (150 mg, 51%, R_f 12.2 mins): Oil. $[\alpha]_D$ –9.6 (*c* 1.6, $CHCl_3$); IR ν_{max} ($CHCl_3$) 2924, 2872, 2851, 1728, 1456, 1437 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 5.12 (1H, s), 3.68 (3H, s), 1.63 (3H, d, *J* = 0.7 Hz), 1.13 (3H, d, *J* = 6.9 Hz), 0.86 (3H, d, *J* = 6.5 Hz); ^{13}C NMR, see Table 3; HREIMS *m/z* (rel. int.) 250.1939 [M^+, $C_{16}H_{26}O_2$ requires 250.1933] (10), 219 (7), 201 (5), 162 (100).

Reduction of the methyl ester in ***10*** *to a primary alcohol in* ***14****.* To a stirred solution of $LiAlH_4$ in anhydrous Et_2O (26 mg/4 ml) was added a solution of methyl ester **10** in anhydrous Et_2O (88mg/2 ml) under a nitrogen atmosphere. The reaction mixture was refluxed (2.5 h), then cooled in an ice-bath before addition of Na_2SO_4 (sat., 5 ml) to hydrolyse excess hydride. After filtering and washing with Et_2O (3 x 10 ml) the combined organic layers were dried ($MgSO_4$) and solvent removed by rotary evaporation to yield 4-amorphen-12-ol (**14**) (72 mg, 82%) with no need for further purification: Oil. $[\alpha]_D$ –20.7 (*c* 0.9, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3616, 3445 (br), 3018, 2964, 2924, 2872, 1448 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 5.22 (1H, s), 3.77 (1H, dd, *J* = 10.6, 3.3 Hz), 3.50 (1H, dd, *J* = 10.6, 6.3 Hz), 1.63 (3H, s), 0.99 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.6 Hz); ^{13}C NMR, see Table 3; HREIMS *m/z* (rel. int.) 222.1983 [M^+, $C_{15}H_{26}O$ requires 222.1984] (15), 191 (18), 163 (100), 135 (10), 107 (20), 99 (25).

Conversion of primary alcohol ***14*** *to tosylate 15.* Primary alcohol **14** was dissolved in $CHCl_3$ (50mg/1 ml) and cooled in an ice-bath prior to addition of pyridine (0.02 ml) and *p*-toluenesulfonyl chloride (*p*-TsCl) (86 mg) in small portions with constant stirring. After 36 hours water was added (1 ml) and the reaction was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed succesively with HCl (2N, 3 ml) and $NaHCO_3$ (5%, 3 ml), then dried ($MgSO_4$) and solvent removed by rotary evaporation to yield a crude mixture (110 mg, 85 %). Tosylate **15** (80 mg, 73 %, R_f 9.7 mins) was purified by HPLC (7% EtOAc/hexane): Oil. $[\alpha]_D$ –0.5 (*c* 0.9, $CHCl_3$); IR ν_{max} ($CHCl_3$) 2966, 2926, 2870, 2855, 1450, 1358 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 7.78 (2H, d, *J* = 8.2 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 5.08 (1H, s), 4.07 (1H, dd, *J* = 9.4, 3.1 Hz), 3.94 (1H,

dd, J = 9.4, 5.9 Hz), 2.45 (3H, s), 2.41 (1H, br s), 1.60 (3H, d, J = 0.6 Hz), 0.94 (3H, d, J = 6.7 Hz), 0.84 (3H, d, J = 6.4 Hz); ^{13}C NMR (δ $CDCl_3$) ppm: 144.6, 135.6, 133.1, 129.8 x 2, 127.9 x 2, 119.9, 74.4 , 42.1, 41.8, 37.2, 35.3, 34.2, 27.5, 26.6, 26.0, 25.7, 23.8, 21.6, 19.7, 15.0; HREIMS *m/z* (rel. int.) 376.2075 [M^+, $C_{22}H_{32}SO_3$ requires 376.2072] (8), 204 (45), 189 (18), 163 (35), 162 (100).

Reduction of the tosylate functional group in 15 to a methyl group in 16. The procedure for reduction of **15** (80 mg) by $LiAlH_4$ was identical to that described for compound **10**, yielding 4-amorphene (**16**) (40 mg) without the need for further purification: Oil. $[\alpha]_D$ –25.8 (*c* 2.8, $CHCl_3$); IR ν_{max} ($CHCl_3$) 2924, 2870, 2855, 1449, 1381 cm^{-1}; ^{1}H NMR (δ $CDCl_3$) ppm: 5.23 (1H, s), 2.51 (1H, br s), 1.62 (3H, s), 0.91 (3H, d, J = 7.4 Hz), 0.89 (3H, d, J = 7.4 Hz), 0.85 (3H, d, J = 6.5 Hz); ^{13}C NMR, see Table 3; HREIMS *m/z* (rel. int.) 206.2027 [M^+, $C_{15}H_{26}$ requires 206.2035] (15), 191 (2), 163 (100), 121 (10).

Photooxidation of 10 yielding 11, 12 and 13. Methylene blue (1.5 mg) was added to dihydroartemisinic acid methyl ester (**10**) in acetone (30 mg/ 25 ml) and the mixture maintained at ice-bath temperature under irradiation with a tungsten lamp (500 W) for 2 h after which solvent was removed by a rotary evaporator and the residue taken up in Et_2O (20 ml). After filtration to remove the dye, solvent was removed by rotary evaporation to yield a crude product (27 mg; 91 %) which was subjected to preparative HPLC (15% EtOAc/hexane): **11** (3 mg, R_f 17.2 min); **12** (1.5 mg, R_f 15.8 min); **13** (16 mg, R_f 25.4 min). *5α-Hydroperoxy-amorph-4(15)-en-12-oic acid methyl ester* (**11**): Oil. $[\alpha]_D$ –172.9 (*c* 0.2, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3280 (br), 2937, 2846, 1715, 1597, 1456 cm^{-1}; ^{1}H NMR (δ $CDCl_3$) ppm: 5.06 (1H, s), 4.92 (1H, s), 4.72 (1H, d, J = 11.0 Hz), 3.68 (3H, s), 2.84 (1H, dq, J = 9.9, 6.9 Hz), 1.17 (3H, d, J = 6.9 Hz), 0.86 (3H, d, J = 6.1 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 264.1726 [M^+ -H_2O, $C_{16}H_{24}O_3$ requires 264.1725] (7), 249 (53), 217 (31), 189 (32), 177 (44), 161 (100), 149 (31), 109 (48), 99 (63). *5α-Hydroperoxy-amorph-3-en-12-oic acid methyl ester* (**12**): Oil. $[\alpha]_D$ –53.0 (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3360 (br), 2926, 2853, 1730 cm^{-1}; ^{1}H NMR (δ $CDCl_3$) ppm: 7.23 (1H, s, -OOH), 5.68 (1H, d, J = 5.6 Hz), 4.37 (1H, d, J = 8.6 Hz), 3.67 (3H, s), 2.68 (1H, dq, J =10.6, 6.6 Hz), 1.77 (3H, s), 1.29 (3H, d, J = 6.5 Hz), 0.79 (3H, d, J = 6.2 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 264.1724 [M^+ - H_2O, $C_{16}H_{24}O_3$ requires 264.1725] (3), 249 (44), 234 (22), 233 (23), 217 (24), 205 (25), 189 (29), 161 (100), 109 (38). *4α-Hydroperoxy-amorph-5-en-12-oic acid methyl ester* (**13**): Oil. $[\alpha]_D$ –30.7 (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3300 (br), 3026, 2937, 2872, 1724, 1460, 1360, 1170 cm^{-1}; ^{1}H NMR (δ $CDCl_3$) ppm: 7.41 (1H, br s, -OOH), 5.22 (1H, s), 3.67 (3H, s), 2.73 (1H, dq, J =8.4, 6.8 Hz), 1.30 (3H, s), 1.22 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.3 Hz); ^{13}C NMR, see Table 3; HREIMS *m/z* (rel. int.) 282.1836 [M^+, $C_{16}H_{26}O_4$ requires 282.1831] (0.1), 264 (2), 249 (10), 217 (25), 189 (38), 161 (100), 133 (13), 119 (15), 105 (24).

Photooxidation of 14 yielding 17, 18 and 19. Methylene blue (2 mg) was added to 4-amorphen-12-ol (**14**) in acetone (27 mg/ 25 ml) and the mixture maintained at ice-bath temperature under irradiation with a tungsten lamp (500 W) for 2 h after which solvent was removed by rotary evaporation and the residue taken up in Et_2O (20 ml). After filtration to remove the dye, solvent was rotary evaporated to yield a crude product (25

mg; 92%) which was subjected to preparative HPLC (25% EtOAc/hexane): **17** (3 mg, R_f 40.8 min); **18** (1.5 mg, R_f 31.2 min); **19** (14 mg, R_f 46.9 min). *5α-Hydroperoxy-amorph-4(15)-en-12-ol* (**17**): Oil. $[\alpha]_D$ –83.9 (*c* 0.3, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3285 (br), 2937, 2864, 1454, 1331 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 8.27 (1H, s, -OOH), 5.05 (1H, s), 4.94 (1H, s), 4.71 (1H, d, *J* = 10.0 Hz), 3.71 (1H, dd, *J* =10.6, 2.7 Hz), 3.54 (1H, dd, *J* = 10.6, 6.0 Hz), 1.02 (3H, d, *J* = 6.6 Hz), 0.85 (3H, d, *J* = 6.5 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 236.1781 [M^+-H_2O, $C_{15}H_{24}O_2$ requires 236.1776] (1), 211 (5), 155 (20), 99 (100). *5α-Hydroperoxy-amorph-3-en-12-ol* (**18**): Oil. $[\alpha]_D$ –30.1 (*c* 0.06, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3622, 3454 (br), 3009, 2966, 1392 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 7.24 (1H, s, -OOH), 5.71 (1H, d, *J* = 4.7 Hz), 4.38 (1H, d, *J* = 8.4 Hz), 3.70 (1H, dd, *J* = 10.5, 3.4 Hz), 3.60 (1H, dd, *J* = 10.5, 5.0 Hz), 1.78 (3H, s), 1.12 (3H, d, *J* = 6.6 Hz), 0.79 (3H, d, *J* = 6.0 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 236.1777 [M^+-H_2O, $C_{15}H_{24}O_2$ requires 236.1776] (1), 211 (10), 167 (3), 155 (22), 99 (100). *4α-Hydroperoxy-amorph-5-en-12-ol* (**19**): Oil. $[\alpha]_D$ –6.4 (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3622, 3466 (br), 3020, 2986, 2889, 1396, 1255, 1219 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 7.74 (1H, br s, -OOH), 5.35 (1H, s), 3.77 (1H, dd, *J* = 10.5, 3.7 Hz), 3.46 (1H, dd, *J* = 10.5, 7.6, Hz), 1.31 (3H, s), 1.06 (3H, d, *J* = 6.7 Hz), 0.93 (3H, d, *J* = 6.2 Hz); ^{13}C NMR, see Table 3; HREIMS *m/z* (rel. int.) 254.1880 [M^+, $C_{15}H_{26}O_3$ requires 254.1882] (0.1), 236 (10), 221 (100), 203 (30), 177 (5), 163 (100), 121 (65), 81 (80).

*Photooxidation of **16** yielding **20**, **21** and **22***. Methylene blue (10 mg) was added to 4-amorphene (**16**) in acetone (100 mg/ 100 ml) and the mixture maintained at ice-bath temperature under irradiation with a tungsten lamp (500 W). After the starting material had disappeared (2.5 h) solvent was removed by a rotary evaporator and the residue taken up in Et_2O (200 ml). After filtration to remove the dye, solvent was removed by rotary evaporation to yield a crude product which was subjected to preparative HPLC (3.5% EtOAc/hexane): **20** (8 mg, R_f 17.5 min); **21** (4 mg, R_f 15.0 min), **22** (88 mg, R_f 34.6 min). *5α-Hydroperoxy-amorph-4(15)-ene* (**20**): Oil. $[\alpha]_D$ –49.8 (*c* 0.5, $CHCl_3$); ^1H NMR (δ $CDCl_3$) ppm: 8.02 (1H, s, -OOH), 5.04 (1H, s), 4.93 (1H, s), 4.67 (1H, d, *J* = 9.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 0.84 (3H, d, *J* = 6.4 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 238.1931 [M^+, $C_{15}H_{26}O_2$ requires 238.1932] (1), 220 (35), 205 (60), 165 (20), 161 (25), 149 (30), 121 (25), 99 (100). *5α-Hydroperoxy-amorph-3-ene* (**21**): Oil. $[\alpha]_D$ +3.1 (*c* 0.2, $CHCl_3$); ^1H NMR (δ $CDCl_3$) ppm: 6.99 (1H, s, -OOH), 5.69 (1H, d, *J* = 5.1 Hz), 4.34 (1H, d, *J* = 8.4 Hz), 2.61 (1H, d, *J* = 8.9 Hz), 1.77 (3H, s), 1.04 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.6 Hz), 0.78 (3H, d, *J* = 5.9 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 220.1750 [M^+-H_2O, $C_{15}H_{24}O$ requires 220.1827] (10), 205 (100), 161 (30), 149 (40), 121 (25), 95 (45), 81 (50). *4α-Hydroperoxy-amorph-5-ene* (**22**): Oil. $[\alpha]_D$ –12.6 (*c* 8.8, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3531, 3340 (br), 1654, 1456, 1367, 1325, 1126 cm^{-1}; ^1H NMR (δ $CDCl_3$) ppm: 7.19 (1H, br s, -OOH), 5.26 (1H, s), 1.31 (3H, s), 0.95 (3H, d, *J* = 6.7 Hz), 0.93 (3H, d, *J* = 6.2 Hz), 0.87 (3H, d, *J* = 6.8 Hz); ^{13}C NMR, see Table 3; HREIMS *m/z* (rel. int.) 238.1928 [M^+, $C_{15}H_{26}O_2$ requires 238.1932] (0.1), 220 (5), 205 (10), 177 (18), 161 (36), 149 (30), 121 (65), 93 (25), 81 (39).

*Rearrangement of **11** to **23** in $CDCl_3$ solution.* Compound **11** (2.5 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 4 weeks, resulting in clean conversion into compound **23** (2.0 mg). *15-Hydroperoxy-amorph-4-en-12-oic acid methyl ester (**23**):* Oil. ^{1}H NMR δ ($CDCl_3$) ppm: 7.84 (1H, s, -OOH), 5.54 (1H, s), 4.37 (1H, d, J = 11.9 Hz), 4.34 (1H, d, J = 11.9 Hz), 3.68 (3H, s), 2.57 (1H, br s), 2.51 (1H, dq, J = 11.1, 6.9 Hz), 1.14 (3H, d, J = 6.9 Hz), 0.88 (3H, d, J = 6.4 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 264.1717 [M$^+$ - H_2O, $C_{16}H_{24}O_3$ requires 264.1725] (5), 251 (10), 248 (10), 204 (10), 191 (30), 177 (100), 161 (45), 145 (30), 133 (35), 105 (30). *Calculation of the rate of conversion of **11** into **23** in $CDCl_3$ solution by ^{1}H NMR spectroscopy.* See general procedure at beginning of experimental: **11** δ_H 5.06, 1H, s, H-15; **23** δ_H 5.54, 1H, s, H-5.

*Rearrangement of **12** to **26** in $CDCl_3$ solution.* Compound **12** (1.4 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 3 weeks, resulting in clean conversion into compound **26** (1.2 mg). *3α-Hydroperoxy-amorph-4-en-12-oic acid methyl ester (**26**):* Oil. ^{1}H NMR δ ($CDCl_3$) ppm: 7.47 (1H, s, -OOH), 5.41 (1H, s), 4.40 (1H, m), 3.68 (3H, s), 2.60 (1H, br s), 2.49 (1H, dq, J = 11.7, 6.9 Hz), 1.77 (3H, s), 1.13 (3H, d, J = 6.9 Hz), 0.92 (3H, d, J = 6.5 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 264.1717 [M$^+$ - H_2O, $C_{16}H_{24}O_3$ requires 264.1725] (10), 211 (12), 177 (30), 149 (48), 136 (50), 106 (50), 89 (75), 77 (100). *Calculation of the rate of conversion of **12** into **26** in $CDCl_3$ solution by ^{1}H NMR spectroscopy.* See general procedure at beginning of experimental: **12** δ_H 5.68, 1H, d J = 5.6 Hz, H-3; **26** δ_H 5.41, 1H, s, H-5.

*Rearrangement of **17** to **24** in $CDCl_3$ solution.* Compound **17** (2.5 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 4 weeks, resulting in clean conversion into compound **24** (2.4 mg). *15-Hydroperoxy-amorph-4-en-12-ol (**24**):* Oil. ^{1}H NMR δ ($CDCl_3$) ppm: 7.85 (1H, s, -OOH), 5.64 (1H, s), 4.38 (1H, d, J = 11.9 Hz), 4.35 (1H, d, J = 11.9 Hz), 3.74 (1H, dd, J = 10.6, 3.3 Hz), 3.55 (1H, dd, J = 10.6, 6.2 Hz), 1.00 (3H, d, J = 6.7 Hz), 0.88 (3H, d, J = 6.4 Hz). HREIMS *m/z* (rel. int.) 236.1773 [M$^+$ - H_2O, $C_{15}H_{24}O_2$ requires 236.1776] (15), 220 (35), 205 (70), 177 (60), 165 (100), 161 (55), 153 (40), 106 (40), 89 (60), 77 (100). *Calculation of the rate of conversion of **17** into **24** in $CDCl_3$ solution by ^{1}H NMR spectroscopy.* See general procedure at beginning of experimental: **17** δ_H 5.05, 1H, s, H-15; **24** δ_H 5.64, 1H, s, H-5.

*Rearrangement of **18** to **27** in $CDCl_3$ solution.* Compound **18** (1.4 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 2 weeks, resulting in clean conversion into compound **27** (1.3 mg). *3α-Hydroperoxy-amorph-4-en-12-ol (**27**):* Oil. ^{1}H NMR δ ($CDCl_3$) ppm: 7.46 (1H, s, -OOH), 5.51 (1H, s), 4.42 (1H, d, J = 7.4 Hz), 3.73 (1H, dd, J = 11.5, 8.5 Hz), 3.55 (1H, dd, J = 11.5, 5.4 Hz), 2.58 (1H, br s), 1.77 (3H, s), 0.99 (3H, d, J = 6.8 Hz), 0.92 (3H, d, J = 6.4 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 236.1571 [M$^+$ - H_2O, $C_{15}H_{24}O_2$ requires 236.1776] (25), 220 (30), 205 (10), 177 (75), 165 (58), 161 (80), 137 (38), 119 (50), 109 (65), 99 (100). *Calculation of the rate of conversion of **18** into **27** in $CDCl_3$ solution by ^{1}H NMR spectroscopy.* See general procedure at beginning of experimental: **18** δ_H 5.71, 1H, d J = 4.7 Hz, H-3; **27** δ_H 5.51, 1H, s, H-5.

*Rearrangement of **20** to **25** in $CDCl_3$ solution.* Compound **20** (2.0 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 4 weeks, resulting in clean conversion into compound **25** (2.0 mg). *15-Hydroperoxy-amorph-4-ene (**25**):* Oil. ^{1}H NMR δ ($CDCl_3$) ppm: 7.79 (1H, s, -OOH), 5.66 (1H, s), 4.38 (1H, d, J = 11.7 Hz), 4.34 (1H, d, J = 11.7 Hz), 2.59 (1H, br s), 0.93 (3H, d, J = 6.7 Hz), 0.90 (3H, d, J = 6.7 Hz), 0.88 (3H, d, J = 6.4 Hz); ^{13}C NMR, see Table 1; HREIMS *m/z* (rel. int.) 220.1817 [M^+ - H_2O, $C_{15}H_{24}O$ requires 220.1827] (30), 191 (60), 177 (30), 150 (100), 135 (55), 107 (55), 77 (85). *Calculation of the rate of conversion of **20** into **25** in $CDCl_3$ solution by ^{1}H NMR spectroscopy.* See general procedure at beginning of experimental: **20** δ_H 5.04, 1H, s, H-15; **25** δ_H 5.66, 1H, s, H-5.

*Rearrangement of **21** to **28** in $CDCl_3$ solution.* Compound **21** (2.0 mg) was dissolved in $CDCl_3$ (0.6 ml) and left in an NMR tube under ambient conditions for 3 weeks, resulting in clean conversion into compound **28** (1.8 mg). 3α-*Hydroperoxy-amorph-4-ene (**28**):* Oil. ^{1}H NMR δ ($CDCl_3$) ppm: 7.45 (1H, s, -OOH), 5.52 (1H, s), 4.41 (1H, m), 1.76 (3H, dd, J = 2.5, 1.3 Hz), 0.93 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.89 (3H, d, J = 6.6 Hz); ^{13}C NMR, see Table 2; HREIMS *m/z* (rel. int.) 238.1928 [M^+, $C_{15}H_{26}O_2$ requires 238.1933] (1), 220 (20), 205 (90), 161 (90), 95 (90), 81 (100). *Calculation of the rate of conversion of **21** into **28** in $CDCl_3$ solution by ^{1}H NMR spectroscopy.* See general procedure at beginning of experimental: **21** δ_H 5.69, 1H, s, H-3; **28** δ_H 5.52, 1H, s, H-5.

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