Synthesis of 6,7-dehydroartemisinic acid

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The natural product 6,7-dehydroartemisinic acid from *Artemisia annua* has been synthesized in four steps from artemisitene, which was in turn prepared in four steps from commercially available artemisinin. The forward synthesis involves the acid degradation of artemisitene and some comparisons are made between the products from this reaction and the more extensively studied acid degradation reaction of its 11,13-dihydro analogue, artemisinin.

Introduction

The Chinese medicinal plant *Artemisia annua* has been the subject of intensive phytochemical investigation following the discovery of the potent anti-malarial sesquiterpene artemisinin (qinghaosu) over twenty years ago.[1] Around thirty-five further cadinane and amorphane sesquiterpenes have now been isolated from this species.[2,3] Several total[4–12] and partial[13–17] syntheses have been described for artemisinin (**1**), and total[5,18] and partial[6,19–30] syntheses of some of the other natural products from *A. annua*, including artemisitene (**2**),[19] deoxyartemisinin (**3**),[5,6,13,20,21] dihydroartemisinic acid (**4**),[22] artemisinic acid (**5**),[23] arteannuin B (**6**)[6,24] (and its analogues),[18] deoxyarteannuin B (**7**),[25] dihydro-*epi*-deoxyarteannuin B (**8**),[22,26,27] *epi*-deoxyarteannuin B (**9**),[25] arteannuin A (**10**),[6,28] epoxyarteannuic acid (**11**)[29] and artemisilactone (**12**)[30] (also referred to as arteannuins E and F)[6] are now also reported in the literature (Fig. 1).

We herein describe the synthesis in eight steps of another natural product from *A. annua*, 6,7-dehydroartemisinic acid (**13**), which was first isolated by El-Feraly *et al.* in 1989.[31] A reconstructive strategy, based on commercially available artemisinin as the starting material, has been employed.

Results and discussion

Our retrosynthetic design for the synthesis of the target 11,13-dehydroamorphane, compound **13**, required the preparation of the $\Delta^{11,13}$-unsaturated decalenone† methyl ester, compound **14** (Scheme 1). The selection of this intermediate was based on recent work in which we have shown that the free acid form of the 11,13-dihydro analogue of **14**, compound **15a**‡ [obtained from acid degradation of artemisinin (**1**) *via* compound **16a**‡], could be converted into **13a**,‡ the 11,13-dihydro analogue of the target molecule, in good yield by Grignard reaction (Scheme 2).[22] According to close precedents in the literature[32,33] we expected that **14** (or its free acid form **15**) might in turn be prepared from artemisitene (**2**) by an acid degradation reaction. Two methods are reported in the literature for the preparation of $\Delta^{11,13}$-unsaturated artemisitene (**2**) from commercially available artemisinin (**1**). El-Feraly and McPhail have adopted a photochemical route, involving the ene-type reaction of $^1O_2$ with an enol ether;[34] while Chinese workers have chosen an oxidative selenation procedure to introduce unsaturation at the 11,13-position both for artemisinin itself[35] and for other 11,13-dihydro natural products[6,23] from *A. annua*. In practice, we have found the procedure of El-Feraly and McPhail for desaturating the 11,13-position of artemisinin to be the more effective.

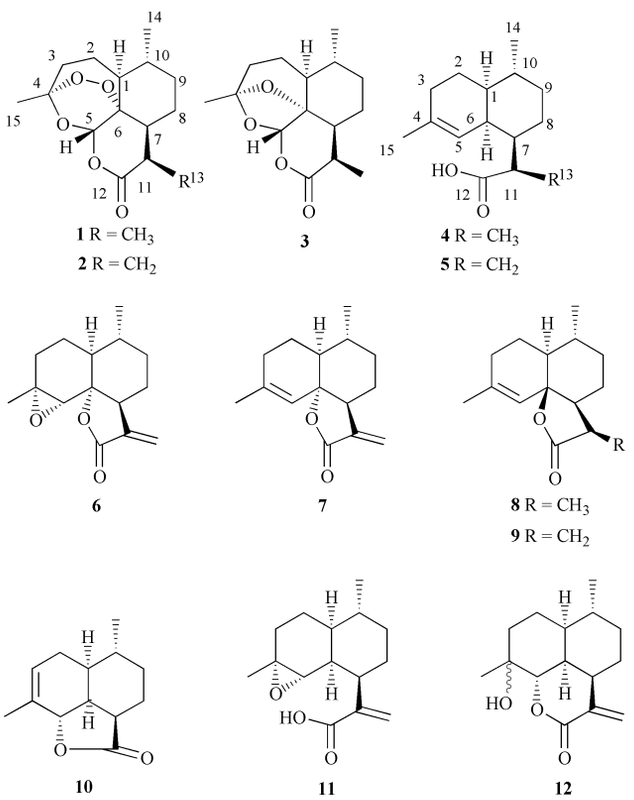

Fig. 1 Natural products from *A. annua* which have been obtained by either partial or total synthesis.

In the forward synthesis, treatment of artemisinin with sodium borohydride resulted in smooth transformation of the ester functionality in **1** to a mixture of α- and β-lactol epimers in dihydroartemisinin (**17**),[36] as expected (Scheme 3). Enol ether **18**,[37–40] obtained by dehydration of **17**, was a surprisingly stable compound, which could be stored for up to two years without any significant autoxidation being noted. The only side-product from the dehydration of **17** to **18** was the natural product deoxyartemisinin (**3**), which became the major product if the reaction was refluxed. Full NMR assignments for deoxyartemisinin (**3**) are reported in Tables 1 and 3 for the first time. Deoxyartemisinin may be formed by a Kornblum–de la

† The IUPAC name for decalenone is 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one.
‡ The suffix "**a**" is used herein to indicate the 11,13-dihydro analogue of a compound.

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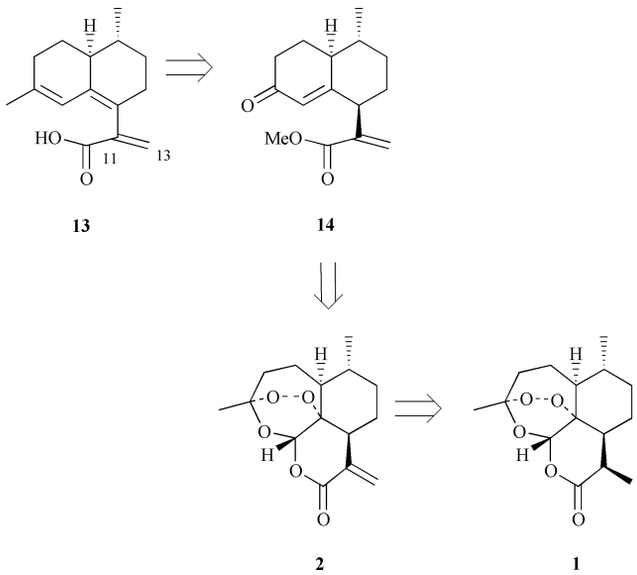
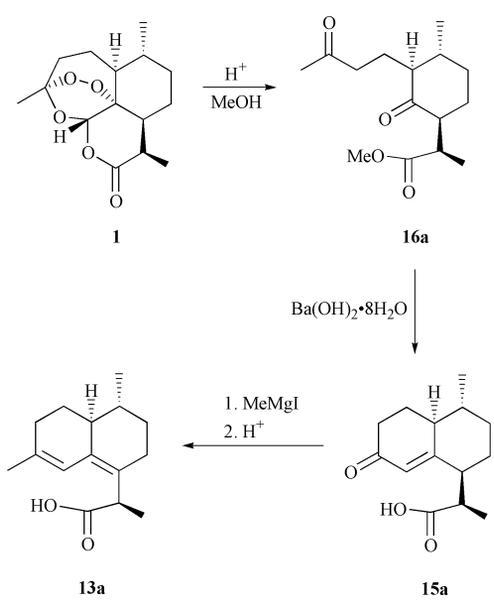


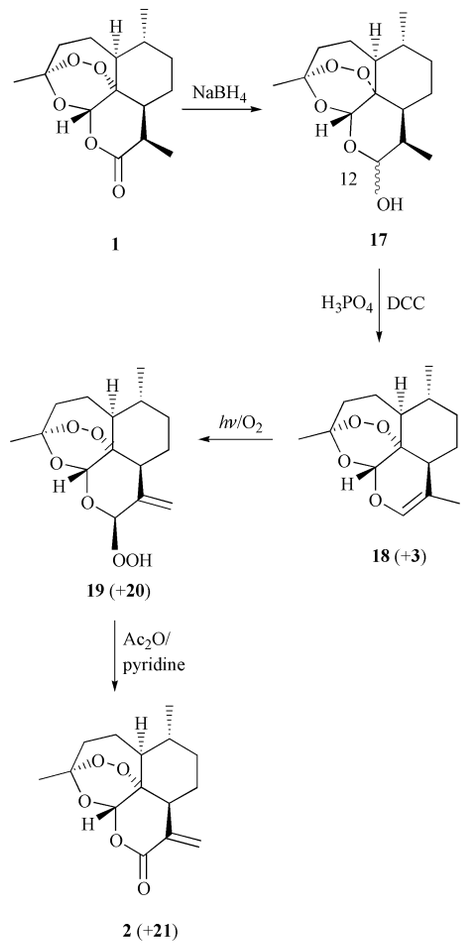
Scheme 1 Retrosynthetic scheme for the preparation of 6,7-dehydroartemisinic acid **13** from artemisinin **1**.



Scheme 2 Recently reported preparation of **13a** from the acid degradation of **1**.

Mare process operating on a peroxyhemiacetal intermediate,[41] following "unzipping" of the 1,2,4-trioxane system of dihydroartemisinin in the presence of acid (Fig. 2).

Photo-oxygenation of the enol ether functional group in **18** yielded the secondary allylic hydroperoxide **19**, accompanied by the cleavage product **20**[40] (estimated at about 5% by ^{1}H NMR analysis of the crude mixture). The amount of formaldehyde-substituted acetal **20** appeared to increase when attempts were made to separate **19** and **20** by column chromatography on silica gel; we propose that Hock cleavage is responsible for the formation of **20** from **19** (Fig. 3) and that this reaction is catalysed by the acidic properties of the stationary phase. Because of the problems encountered when attempting to purify **19**, the crude photo-oxygenation reaction product was generally used for conversion into artemisitene (**2**), in the next step. Dehydration of **19** to **2** proceeded in good yield, resulting in only one minor side-product, **21**,[38,41,42] which is also believed to be formed by "unzipping" of the 1,2,4-trioxane ring in **19** (following homolytic cleavage of the secondary allylic hydroperoxide functional group) under basic conditions (Fig. 4). Full NMR assignments for artemisitene (**2**) are reported in Tables 1 and 3 for the first time.



Scheme 3 Forward synthesis of artemisitene **2** from artemisinin **1**.

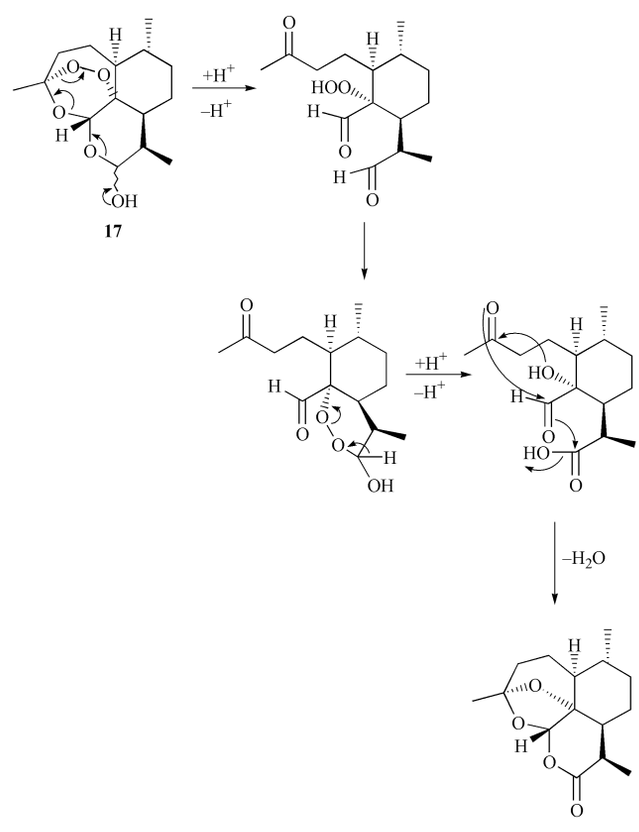


Fig. 2 Proposed mechanism for the formation of side-product **3** in the photochemical conversion of artemisinin **1** to artemisitene **2**.

Table 1 ^{13}C NMR data (δ, ppm) for compounds **2**, **3**, **13**, **14**, **16** and **18**–**23**

Position	**2**	**3**	**13**	**14**	**16**	**18**	**19**	**20**	**21**	**22**	**23**
1	50.1	44.5	42.4	45.0	56.5	51.6	51.9	52.7	49.1	56.8	54.0
2	24.6	22.0	27.6	25.6	20.1	24.6	24.5	24.8	21.3	26.8	21.5
3	35.8	33.9	31.1	35.2	41.1	36.4	36.3	35.7	43.6	40.8	41.7
4	105.4	109.2	137.3	199.9	209.1	104.7	104.6	105.4	208.7	208.4	209.0
5	93.5	99.6	121.6	122.5	30.0	89.9	88.3	86.6	204.4	30.1	29.9
6	79.4	82.4	134.0	168.2	210.4	79.2	80.7	85.0	92.0	212.9	210.0
7	46.1	42.3	127.0	45.8	52.4	44.6	47.5	57.1	42.8	49.0	53.1
8	31.6	23.5	30.9	32.2	31.0	30.2	31.3	23.8	21.7	25.6	27.7
9	33.7	33.4	31.5	34.8	34.4	34.3	34.0	33.6	34.3	26.9	32.3
10	37.7	35.3	34.3	39.1	40.1	37.7	37.5	37.4	33.8	37.0	37.5
11	134.9	32.7	141.2	140.5	138.6	108.3	138.6	208.2	140.6	138.6	138.5
12	162.8	171.9	172.1	167.0	167.3	135.2	105.5	159.4	100.4	167.1	167.6
13	130.4	12.6	130.0	126.8	125.4	16.4	119.8	32.3	111.2	125.8	125.6
14	19.9	18.6	20.3	20.2	20.6	20.5	20.2	19.9	20.4	19.5	13.4
15	25.4	23.9	23.9	—	—	26.1	25.9	25.3	30.0	—	—
12-OMe	—	—	—	52.1	52.0	—	—	—	—	51.9	51.9

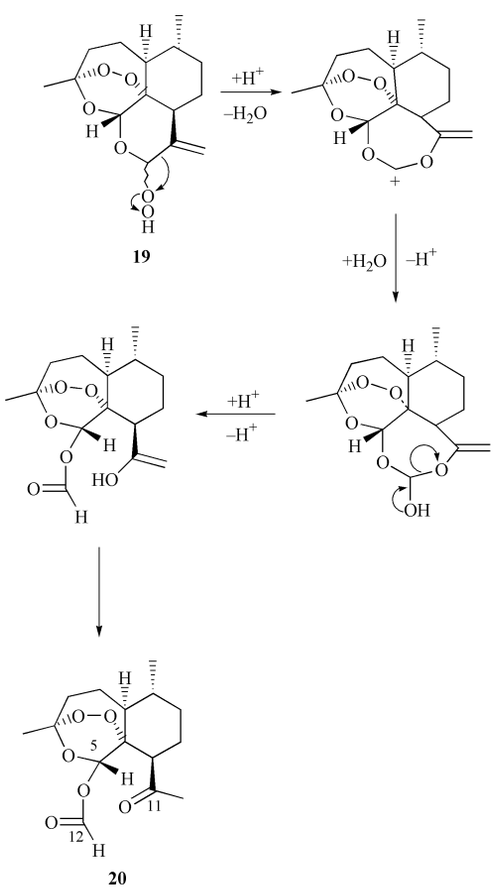


Fig. 3 Proposed mechanism for the formation of side-product **20** in the photochemical conversion of artemisinin **1** to artemisitene **2**.

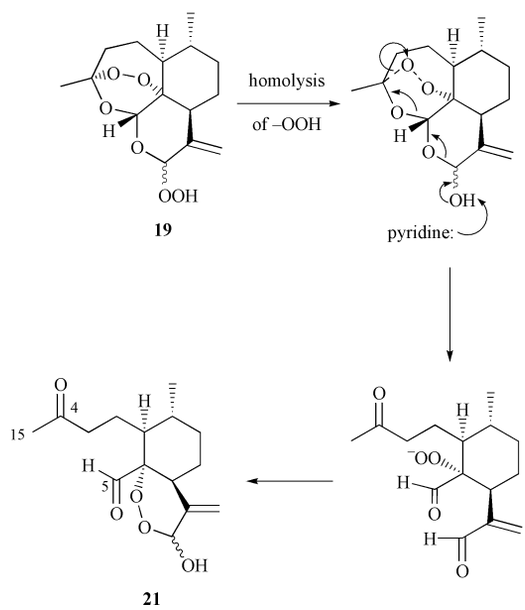


Fig. 4 Proposed mechanism for the formation of side-product **21** in the photochemical conversion of artemisinin **1** to artemisitene **2**.

The solubility of artemisitene in the sulfuric acid–methanol medium, which we have previously used for effecting acid degradation of **1** to **16a** in good yield, was greatly reduced as compared to artemisinin itself, and this may be one of the reasons why little reaction was observed when **2** was subjected to the same conditions as those which are reported to give a high yield of **16a** from **1** (Scheme 2).[22,26] Artemisitene (**2**) was much more soluble in a methanolic medium incorporating acetic acid in addition to sulfuric acid, which has previously been reported to yield the 7-epimerized product **24a** when applied to artemisinin.[6,32] However, under these conditions, **2** was converted into a complex mixture of products, including **14** and **22**–**29** in addition to **16** (Figs. 5 and 7).

11,13-Dihydro analogues for all of the 1,7-epimeric cyclohexanones (**16a**, **22a** and **23a**) and the decalenone lactone (**24a**) isolated from acid degradation of **2**, have been reported previously from acid degradation of **1** (Fig. 6), and the mechanisms suggested for their formation from artemisitene in Fig. 5 parallel those previously proposed for the formation of these products from the acid degradation of artemsinin.[32,43] 11,13-Dihydro analogues of the remaining decalenone reaction products (**14a**, **25a** and **26a**) shown in Fig. 5 have also been isolated from further reactions of **16a** and **24a**,[32,44] although such cyclized products have not been reported directly from the acid degradation of **1** (the 11,13-dihydro analogue of **27** is not known).

The 11,13-dihydro analogues of the two tricyclic products shown in Fig. 7 (**28a** and **29a**) have been reported on one occasion from the acid degradation of **1**.[45] The relative ease of formation of these two products from artemisitene may be the result of the enhanced acidity of the H-7 proton in compound **16**, which can form a more stable extended enolate on proton abstraction, allowing the intramolecular aldol reaction shown in Fig. 7 to proceed more readily. The two-dimensional NMR results which were used to determine the unusual structures of **28/29** are shown explicitly in Fig. 8. (NB Complete ^{13}C and ^{1}H assignments for all compounds reported in Tables 1–4 were rigorously determined in the same way.)

Thus, although acid degradation reactions of **2** can yield a wide variety of products, most of which have parallels in the

Table 2 ^{13}C NMR data (δ, ppm) for compounds **24**–**33**

Position	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**
1	45.7	46.5	42.4	41.6	51.8	50.2	44.7[a]	44.6[a]	47.3	42.5
2	21.5	24.2	26.8	25.6	29.0	32.3	24.2[b]	24.5[b]	20.2	27.7
3	35.9	40.6	36.6	36.1	32.0	32.5	35.3[c]	36.0[c]	26.3	31.2
4	207.0	206.4	199.8	199.9	90.4	90.1	68.9	68.1	136.8	137.0
5	46.8	53.0	127.8	124.8	24.3	24.1	125.8	125.3	123.3	121.8
6	87.9	85.7	165.8	165.8	208.9	208.6	142.1	142.4	79.2	133.6
7	46.3	45.3	44.5	45.9	60.7	60.5	44.3[a]	44.2[a]	52.1	127.6
8	22.7	28.9	28.7	26.7	27.2	21.3	32.3[b]	31.7[b]	22.2	30.9
9	29.6	31.3	29.8	33.2	26.1	27.8	35.9[c]	35.1[c]	35.0	31.6
10	30.8	30.2	38.4	35.4	38.3	38.1	38.9[a]	40.0[a]	30.5	34.3
11	137.4	141.4	142.4	140.4	137.4	138.1	143.9	144.8	159.0	141.6
12	169.2	169.1	167.2	127.4	168.2	168.1	167.9	167.9	80.8	167.6
13	120.1	121.3	125.3	166.8	124.2	124.6	125.2	125.7	100.8	127.7
14	19.0	20.0	20.2	14.7	20.3	18.5	20.0	20.2	19.8	20.3
15	—	—	—	—	—	—	28.5	29.9	23.7	23.9
12-OMe	—	—	52.1	52.1	—	—	52.0	51.9	—	52.0
16	—	—	—	—	—	—	—	—	28.8[d]	—
17	—	—	—	—	—	—	—	—	31.7[d]	—

[a] Assignments interchangeable within column. [b] Assignments interchangeable within column. [c] Assignments interchangeable within column. [d] Assignments interchangeable within column.

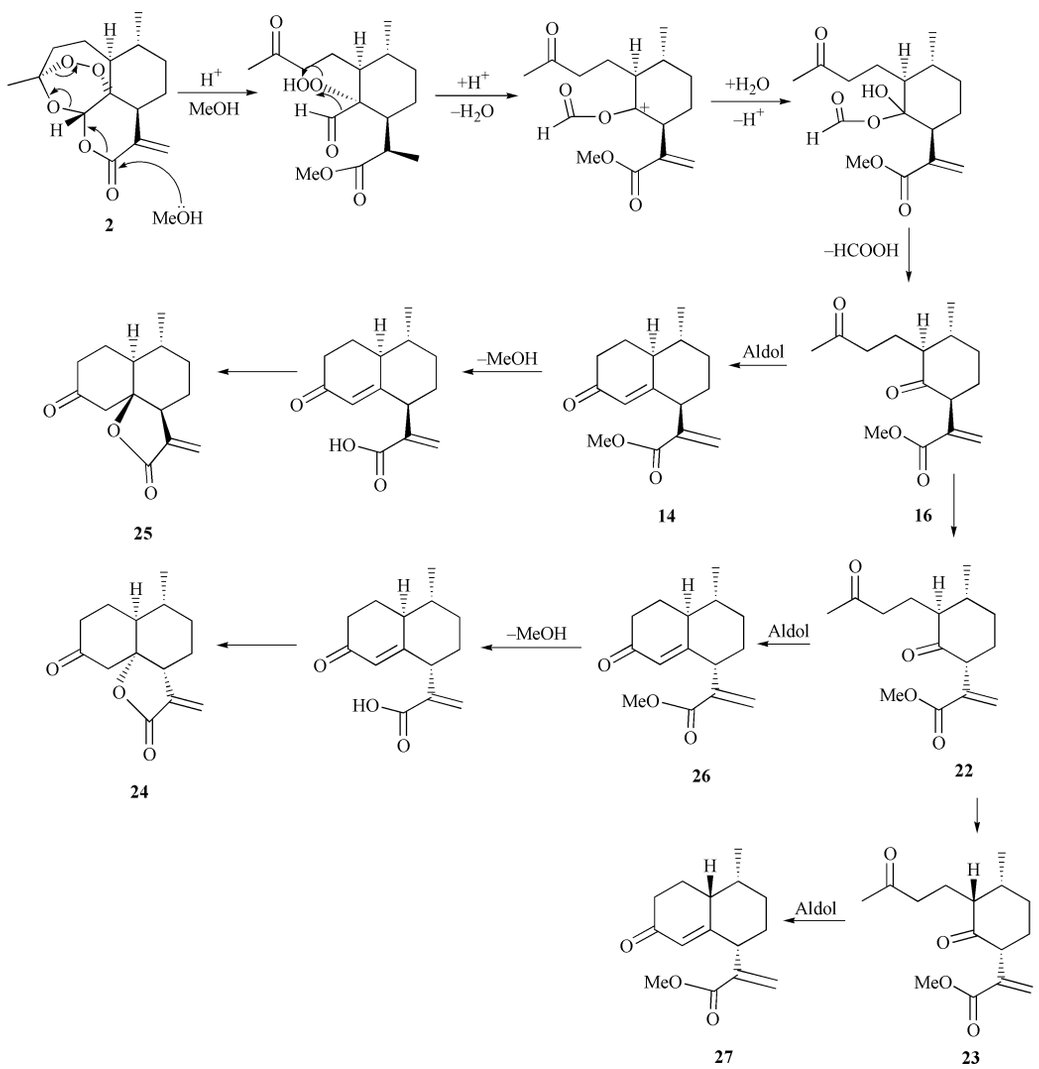


Fig. 5 Proposed mechanism for the formation of **14**, **16** and **22**–**27** in the acid degradation of **2**.

chemistry of its 11,13-dihydro analogue **1**, the conditions required for obtaining a clean reaction of **2** were clearly not the same as for **1**. Our attempts to find conditions which would result in a better yield of **16** from **2** by systematic modifications of the various acid degradation procedures for **1** [32,33,40,42,44] which have been reported in the literature were unsuccessful. However, it did prove possible to find conditions which resulted directly in the desired decalenone methyl ester **14** (presumably derived from the *in situ* intramolecular aldol reaction of **16**—see Fig. 5) in reasonable yield and with little contamination by side-products formed by either epimerization at C-1/C-7 or as a result of methyl ester cleavage. This was fortuitous, as

Table 3 ^{1}H NMR data (δ, ppm) for compounds **2**, **3**, **13**, **14**, **16** and **18**–**23**

Position	**2**	**3**	**13**	**14**	**16**	**18**	**19**	**20**	**21**	**22**	**23**
1	1.45	1.28	1.70	2.07	2.21	1.44	1.31	1.47	1.38	2.17	2.65
2α	1.97	1.92	2.11	2.26	1.85	1.93	1.92	1.97	1.75	2.07	1.97
2β	1.49	1.28	1.16	1.76	1.74	1.56	1.50	1.51	1.75	1.94	1.41
3α	2.41	1.78	2.00	2.29	2.55	2.41	2.38	2.48	2.67	2.49	2.57
3β	2.07	1.63	2.12	2.35	2.38	2.04	2.06	2.06	2.55	2.46	2.32
5	5.99	5.70	5.88	5.59	2.12	5.59	5.76	6.51	9.97	2.14	2.12
7	2.55	2.00	—	3.41	3.56	1.71	2.25	2.33	2.75	3.65	3.52
8α	1.77	1.92	2.20	1.93	2.08	2.06	1.84	1.84	2.11	2.07	2.07
8β	1.58	1.01	2.20	1.64	1.77	1.18	1.64	1.37	1.70	1.92	2.00
9α	1.21	1.09	1.36	1.41	1.62	1.12	1.09	0.99	1.21	1.58	1.78
9β	1.75	1.81	1.70	1.91	1.94	1.66	1.64	1.75	1.88	2.15	2.07
10	1.46	1.28	1.34	1.52	1.62	1.43	1.40	1.49	1.64	2.13	2.43
11	—	3.18	—	—	—	—	—	—	—	—	—
12	—	—	—	—	—	6.19	5.77	7.88	5.54	—	—
13a[a]	6.56	1.20	6.46	6.44	6.35	1.59	5.33	2.45	5.04	6.35	6.33
13b[b]	5.67		5.63	5.62	5.54		5.20		4.88	5.58	5.56
14	1.02	0.94	1.02	1.07	1.12	0.98	0.98	0.99	0.95	0.99	0.80
15	1.46	1.53	1.71	—	—	1.43	1.46	1.41	2.15	—	—
12-OMe	—	—	—	3.74	3.74	—	—	—	—	3.74	3.57

[a] Proton *cis* with 12-functional group. [b] Proton *trans* with 12-functional group.

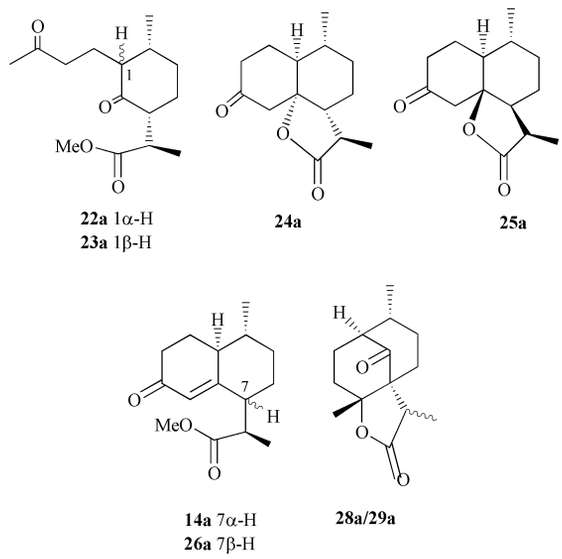


Fig. 6 Some alternative products, **22a**, **23a**, **24a**, **28a** and **29a**, which have been reported in the literature from the acid degradation of **1**. Compounds **14a**, **25a** and **26a** have been reported from further reactions of **16a** and **24a**.

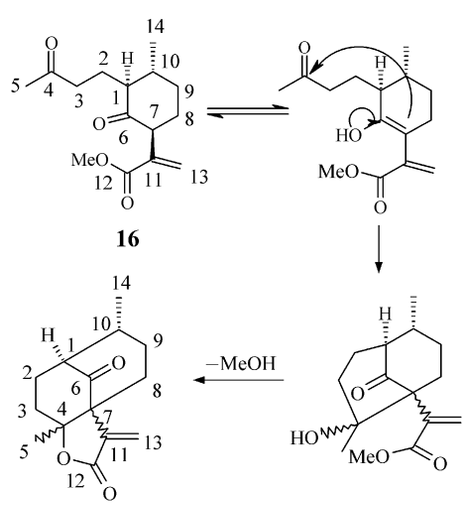


Fig. 7 Proposed mechanism for the formation of **28** and **29** *via* intermediate **16** (see Fig. 5) in the acid degradation of **2**.

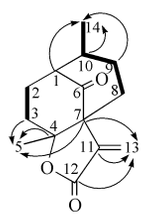


Fig. 8 Critical 2D-NMR correlations used in determining the planar structures of **28**/**29** from the acid degradation of **2**. Arrows from ^{13}C to ^{1}H indicate two- and three-bond ^{13}C–^{1}H correlations observed in HMBC; bold lines indicate ^{1}H–^{1}H correlations observed in ^{1}H–^{1}H COSY.

conversion of **16** to **14** by Robinson annulation would have required an additional synthetic step [*cf.* Scheme 2, in which, in order to obtain **15a** (the free acid 11,13-dihydro analogue of **14**), the immediate product of acid degradation of artemisinin **1**, compound **16a**, must first be subjected to cyclization in the presence of $Ba(OH)_2 \cdot 8H_2O$].[32] From the above results, we conclude that the presence of unsaturation at the 11,13-position in **2** results in a greater tendency to undergo intramolecular aldolization reactions further to the opening of the 1,2,4-trioxane ring and accompanying loss of formic acid, which are normally associated with the treatment of **1** with strong acid. This tendency leads to the direct isolation of decalenones **14**, **25**, **26** and **27**, which have no analogies in the known acid degradation reactions of **1**. The explanation for this effect is not immediately obvious.

Addition of the Grignard reagent from methyl iodide to the ketone group in **14** resulted in the expected approximately 1 : 1 epimeric mixture of tertiary allylic hydroxides **30** and **31**. An alternative addition product **32** was also formed if Grignard reagent was used in excess (**32** appears to be the product of two successive Grignard reactions with the methyl ester group, forming a tertiary alcohol, which then participates in S_N2' addition to the allylic alcohol group—itself formed by attack of a third equivalent of methyl Grignard reagent at the 4-position of the α,β-unsaturated ketone in **14**—resulting in a five-membered lactone ring, see Scheme 4). Although this epimeric mixture of **30**–**31** could be separated by HPLC, it was generally found more expedient simply to treat the crude mixture with acid in order to induce dehydration, which cleanly yielded the methyl ester of 6,7-dehydroartemisinic acid **33**. The methyl ester group in **33** could then be hydrolysed to the free acid by treatment with base, thereby resulting in the target compound, 6,7-dehydroartemisinic acid **13** in good yield. The physical properties of **13** obtained by synthesis were identical with those

Table 4 ^{1}H NMR data (δ, ppm) for compounds **24**–**33**

Position	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**
1	1.31	1.55	2.11	2.65	2.45	2.55	[c]	[c]	1.39	1.69
2α	2.18	2.19	2.27	2.07	2.15	2.09	[c]	[c]	2.04	2.12
2β	2.02	1.90	1.65	1.90	1.97	1.99	[c]	[c]	1.79	1.16
3α	2.38	2.33	2.30	2.32	2.03	1.98	[c]	[c]	1.83	2.00
3β	2.28	2.56	2.47	2.43	2.19	2.06	[c]	[c]	1.89	2.13
5α	2.53	2.38	5.94	5.70	1.46	1.45	5.04	5.07	5.17	5.88
5β	2.83	2.51								
7	2.75	2.71	3.68	3.40	—	—	3.14	3.14	2.37	—
8α	2.14	1.93	2.03	1.93	2.19	1.99	[c]	[c]	1.76	2.17
8β	1.88	1.40	1.77	1.71	1.99	1.96	[c]	[c]	1.12	2.17
9α	1.24	1.17	1.35	1.74	1.54	1.65	[c]	[c]	1.11	1.35
9β	1.66	1.71	1.60	1.89	2.24	1.77	[c]	[c]	1.76	1.70
10	1.63	1.47	1.39	2.22	2.41	2.21	[c]	[c]	1.41	1.33
13a [a]	6.30	6.17	6.22	6.40	6.49	6.51	6.35	6.33	4.84	6.32
13b [b]	5.50	5.57	5.47	5.66	5.51	5.52	5.55	5.55	4.70	5.49
14	0.99	1.02	1.04	0.98	1.04	1.09	0.97	0.99	0.94	1.02
15	—	—	—	—	—	—	1.20	1.20	1.62	1.71
12-OMe	—	—	3.76	3.75	—	—	3.74	3.75	—	3.74
16	—	—	—	—	—	—	—	—	1.38 [d]	—
17	—	—	—	—	—	—	—	—	1.27 [d]	—

[a] Proton *cis* with 12-functional group. [b] Proton *trans* with 12-functional group. [c] Not assigned. [d] Interchangeable within column.

reported for the natural product (full ^{13}C and ^{1}H assignments for **13**, made by 2D-NMR as elsewhere, appear in Tables 1 and 3 for the first time and should replace some of the unassigned and erroneous assignments (*e.g.* C-6 was previously wrongly assigned as C-4) made in the initial report of **13** as a natural product).[31]

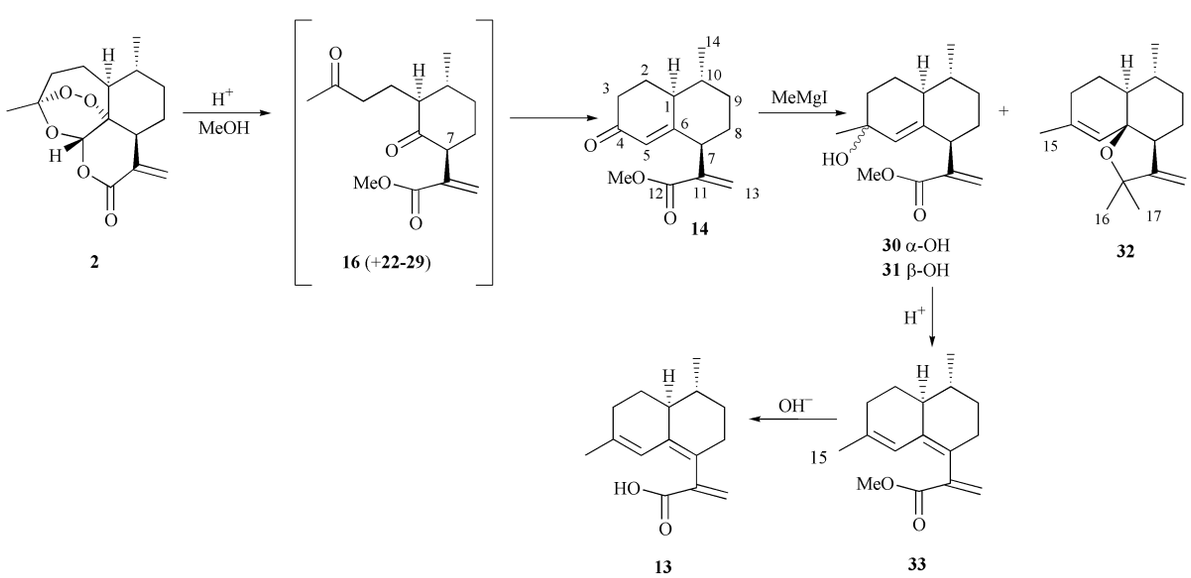
Experimental

General

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 one-dimensional ^{1}H NMR without recourse to 2D-NMR analysis (see Tables 1–4 for 2D-NMR analysis). All NMR experiments were run on a Bruker DRX 500 instrument. HSQC, HMBC, ^{1}H–^{1}H COSY and NOESY spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. High-resolution mass spectra were recorded in EI mode at 70 eV 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 either a normal phase Intersil PREP-SIL 20 mm × 25 cm column or a YMC diol 20 mm × 25 cm column, flow rate 8 ml min^{-1}. Melting points were recorded by a Perkin-Elmer differential scanning calorimeter 7 (DSC7). Optical rotations were measured by a Perkin-Elmer 343 Polarimeter (Na 589 nm); $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and $CHCl_3$ was used as solvent.

Forward synthesis of artemisitene (2) from artemisinin (1)

Reduction of artemisinin (1). To a solution of **1** (2.4 g, 8.5 mmol) (*ex* Kunming pharmaceuticals, Kunming, China) in MeOH (120 ml) cooled in an ice–salt bath was added $NaBH_4$ (2.4 g) over a period of 100 min. The temperature of the reaction was maintained below 0 °C and stirring continued for a further 75 min, before CH_3COOH was added to neutralize the mixture. HCl (3 M) was then added dropwise to precipitate the product. The reaction mixture was left in the fridge overnight, then filtered and the solid precipitate was re-dissolved in $CHCl_3$, dried ($MgSO_4$) and solvent removed under reduced pressure to yield **17** as a 1 : 1 mixture of 12α- and 12β-



Scheme 4 Forward synthesis of 6,7-dehydroartemisinic acid **13** from artemisitene **2**.

diastereoisomers (2.3 g, 96% w/w) without the need for further purification. The physical properties of **17** were identical with those reported previously.[36]

Dehydration of 17. Dry H_3PO_4 was freshly prepared by overnight azeotropic distillation of a solution of H_3PO_4 (5.02 g) in dry C_6H_6 (60 ml) in a Dean–Stark apparatus. To a solution containing H_3PO_4 (0.20 g) and *N*,*N*′-dicyclohexylcarbodiimide (DCC; 4.4 g, 21.2 mmol) in dry C_6H_6–DMSO (24 ml–3 ml), was added **17** (2.0 g, 7.04 mmol). The mixture was stirred at room temperature for 21 h and completion of the reaction was determined by TLC. Aqueous oxalic acid solution (5%, 100 ml) was then added and stirring was continued for a further 30 min before addition of H_2O (100 ml) and extraction by Et_2O (4 × 250 ml). The combined organic layers were washed with brine (3 × 50 ml), dried (anhydrous Na_2SO_4) and solvent was removed under reduced pressure. The residue was taken up in EtOAc–*n*-hexane (3 : 7; 50 ml) and filtered to remove insoluble dicyclohexylurea. Following removal of solvent, the crude product (1.6 g; 80% w/w) was purified by column chromatography (20% EtOAc–*n*-hexane) to yield **18** (1.28 g; 68%) and **3** (0.20 g; 11%).

Compound **18**: Oil; $[\alpha]_D$ +124.6 (*c* 6.5, $CHCl_3$); IR ν_{max}($CHCl_3$): 3028, 2999, 2930, 1686, 1456 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.19 (1H, d, *J* = 1.1 Hz), 5.54 (1H, s), 1.59 (3H, d, *J* = 0.8 Hz), 1.43 (3H, s), 0.98 (3H, d, *J* = 6.0 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 266.1517 [M^+, $C_{15}H_{22}O_4$, requires 266.1518] (42%), 237 (10), 166 (31), 162 (100), 133 (53).

Compound **3**: Oil; $[\alpha]_D$ −42.8 (*c* 5.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3020, 2930, 2876, 1744, 1459 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 5.70 (1H, s), 3.18 (1H, dq, *J* = 4.5, 7.3 Hz), 2.00 (1H, ddd, *J* = 14.0, 4.5, 4.0 Hz), 1.53 (3H, s), 1.20 (3H, d, *J* = 7.3 Hz), 0.94 (3H, d, *J* = 5.9 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 266.1521 [M^+, $C_{15}H_{22}O_4$, requires 266.1518] (10%), 234 (10), 221 (100), 210 (18), 180 (25), 163 (100), 152 (50).

Photo-oxygenation of 18. A stirred solution of **18** (1.2 g, 4.51 mmol) in acetone (100 ml) containing Methylene Blue (5.0 mg) was subjected to strong light (500 W bulb) and maintained at 25 °C. After 4 h, when TLC showed the complete disappearance of the starting material, acetone was removed under reduced pressure and replaced by Et_2O (100 ml) in order to precipitate the photosensitizer. Insoluble Methylene Blue was filtered off and the crude product mixture (1.15 g; 96% w/w) was separated by column chromatography (25% EtOAc–*n*-hexane) to yield **19** (1.06 g, 79%) and **20** (0.14 g, 10%) as a minor side-product.

Compound **19**: Solid; mp 148–150 °C; $[\alpha]_D$ +158 (*c* 0.8, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3387 (br), 3028, 2932, 2854, 1456, 1379 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 9.39 (1H, s, -OOH), 5.77 (2H, s), 5.33 (1H, s), 5.20 (1H, s), 2.38 (1H, ddd, *J* = 13.6, 13.6, 4.0 Hz), 2.25 (1H, dd, *J* = 11.5, 4.2 Hz), 2.06 (1H, ddd, *J* = 13.6, 4.3, 4.3 Hz), 1.84 (1H, dddd, *J* = 12.9, 4.2, 3.4, 3.4 Hz), 1.46 (3H, s), 1.09 (1H, dddd, *J* = 12.9, 11.9, 11.9, 3.6 Hz), 0.98 (3H, d, *J* = 6.3 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; CIMS: *m*/*z* (rel. int.) 281 [$M^+ + 1 - H_2O$] (6%), 265 (82), 235 (50), 219 (100), 177 (78).

Compound **20**: Oil; $[\alpha]_D$ −54 (*c* 1.0, $CHCl_3$); IR ν_{max}($CHCl_3$): 2987, 2874, 1730, 1706 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 7.88 (1H, d, *J* = 0.9 Hz), 6.51 (1H, s), 2.45 (3H, s), 2.33 (1H, dd, *J* = 13.1, 3.4 Hz), 1.41 (3H, s), 0.99 (3H, d, *J* = 5.8 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 266.1514 [$M^+ - O_2$, $C_{15}H_{22}O_4$ requires 266.1518] (1%), 237 (16), 219 (100), 177 (22), 163 (90), 159 (40), 124 (82).

Dehydration of 19. Compound **19** (1.0 g, 3.36 mmol) was dissolved in Ac_2O–pyridine (6 ml–0.3 ml) and the solution was stirred at room temperature for 50 min. Completion of the reaction was determined by TLC and the reaction mixture was then taken up in $CHCl_3$ (3 × 100 ml), washed with H_2SO_4 (5%, 3 × 10 ml), $NaHCO_3$ (5%, 3 × 10 ml) and brine (3 × 50 ml), then dried (anhydrous Na_2SO_4) and solvent removed under reduced pressure to yield a crude product (0.91 g, 91% w/w) consisting of **2** (0.83 g; 88%) and a little of **21** (0.03 g; 3%).

Compound **2**: Solid; mp 159–161 °C; $[\alpha]_D$ +85.2 (*c* 3.5, $CHCl_3$); IR ν_{max}($CHCl_3$): 3028, 2959, 2932, 2876, 1724, 1629, 1456 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.56 (1H, s), 5.99 (1H, s), 5.67 (1H, s), 2.55 (1H, dd, *J* = 14.6, 4.5 Hz), 1.46 (3H, s), 1.02 (3H, d, *J* = 5.8 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; CIMS: *m*/*z* (rel. int.) 281 [$M^+ + 1$] (81%), 263 (89), 245 (78), 235 (91), 217 (100), 177 (95); HREIMS: *m*/*z* (rel. int.) 248.1421 [$M^+ - O_2$, $C_{15}H_{20}O_3$, requires 248.1412] (3%), 230 (40), 190 (100).

Compound **21**: Oil; $[\alpha]_D$ −243 (*c* 0.2, $CHCl_3$); IR ν_{max}-($CHCl_3$): 3566, 2956, 2931, 2873, 1713 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 9.97 (1H, d, *J* = 1.2 Hz), 5.54 (1H, s), 5.04 (1H, s), 4.88 (1H, s), 2.75 (1H, d, *J* = 12.7 Hz), 2.67 (1H, ddd, *J* = 17.2, 9.7, 5.2 Hz), 2.55 (1H, ddd, *J* = 17.2, 7.8, 5.8 Hz), 2.15 (3H, s), 0.95 (3H, d, *J* = 6.5 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1.

Acid degradation of 2 in acetic acid–sulfuric acid–methanol. Compound **2** (0.80 g, 2.86 mmol) was stirred in AcOH–H_2SO_4–MeOH (10 ml–10 ml–10 ml) at 0 °C for 30 min. The reaction mixture was poured into iced water (200 ml) and extracted with $CHCl_3$ (3 × 50 ml). The combined organic layers were then washed with water (2 × 50 ml) and brine (50 ml), dried ($MgSO_4$) and the solvent removed on a rotary evaporator to yield a crude mixture (330 mg, 41% w/w), which was separated by HPLC (23% EtOAc–*n*-hexane): **14** (R_t 25.8 min, 6 mg, 1%); **16** (R_t 28.6 min, 92 mg, 12%); **22** (R_t 37.5 min, 8 mg, 1%); **23** (R_t 37.7 min, 37 mg, 5%); **24** (R_t 49.0 min, 15 mg, 2%); **25** (R_t 63.6 min, 73 mg, 11%); **28/29** (R_t 31.9 min, 12 mg, 2%).

Compound **14**: Oil; $[\alpha]_D$ −97.6 (*c* 4.6, $CHCl_3$); IR ν_{max}-($CHCl_3$): 3011, 2955, 2875, 1717, 1666, 1632, 1441 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.44 (1H, s), 5.63 (1H, s), 5.59 (1H, s), 3.74 (3H, s), 3.41 (1H, dd, *J* = 13.1, 3.5 Hz), 1.64 (1H, dddd, *J* = 13.4, 13.4, 13.1, 2.3 Hz), 1.41 (1H, dddd, *J* = 13.4, 12.9, 12.9, 3.7 Hz), 1.07 (3H, d, *J* = 6.4 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 248.1423 [M^+, $C_{15}H_{20}O_3$, requires 248.1412] (18%), 233 (4), 216 (100), 189 (29), 188 (30).

Compound **16**: Oil; $[\alpha]_D$ −46.7 (*c* 0.3, $CHCl_3$); IR ν_{max}-($CHCl_3$): 3120, 2926, 1767, 1713, 1438 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.35 (1H, s), 5.54 (1H, s), 3.74 (3H, s), 3.56 (1H, dd, *J* = 13.2, 5.2 Hz), 2.55 (1H, ddd, *J* = 17.4, 9.6, 5.2 Hz), 2.38 (1H, ddd, *J* = 17.4, 9.3, 6.2 Hz), 2.21 (1H, ddd, *J* = 10.5, 9.3, 5.2 Hz), 2.12 (3H, s), 1.12 (3H, d, *J* = 6.0 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 266.1516 [M^+, $C_{15}H_{22}O_4$, requires 266.1518] (1%), 248 (50), 234 (23), 191 (18), 176 (100).

Compound **22**: Oil; $[\alpha]_D$ +9.7 (*c* 0.3, $CHCl_3$); IR ν_{max}($CHCl_3$): 3011, 2955, 1715 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.35 (1H, s), 5.88 (1H, d, *J* = 0.4 Hz), 3.74 (3H, s), 3.65 (1H, dd, *J* = 11.4, 5.6 Hz), 2.14 (3H, s), 0.99 (3H, d, *J* = 7.1 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 266.1512 [M^+, $C_{15}H_{22}O_4$, requires 266.1518] (3%), 248 (56), 234 (32), 191 (20), 176 (100).

Compound **23**: Oil; $[\alpha]_D$ +16.3 (*c* 0.5, $CHCl_3$); IR ν_{max}-($CHCl_3$): 3034, 2955, 1713, 1438 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.33 (1H, s), 5.56 (1H, s), 3.75 (3H, s), 3.52 (1H, dd, *J* = 12.2, 5.9 Hz), 2.65 (1H, ddd, *J* = 9.1, 4.8, 4.8 Hz), 2.57 (1H, ddd, *J* = 17.6, 8.6, 5.7 Hz), 2.43 (1H, m), 2.32 (1H, ddd, *J* = 17.6, 13.5, 6.7 Hz), 2.12 (3H, s), 0.80 (3H, d, *J* = 7.2 Hz), see Table 3 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 266.1520 [M^+, $C_{15}H_{22}O_4$, requires 266.1518] (1%), 248 (60), 234 (25), 191 (12), 176 (100).

Compound **24**: Oil; $[\alpha]_D$ −1.5 (*c* 0.8, $CHCl_3$); IR ν_{max}($CHCl_3$): 3026, 2963, 1763, 1719, 1456 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 6.30

(1H, d, J = 3.4 Hz), 5.50 (1H, d, J = 3.4 Hz), 2.83 (1H, d, J = 16.3 Hz), 2.75 (1H, m), 2.53 (1H, ddd, J = 16.3, 1.8, 1.8 Hz), 2.38 (1H, dd, J = 15.1, 1.8 Hz), 2.28 (1H, ddd, J = 15.1, 14.8, 5.5 Hz), 0.99 (3H, d, J = 6.4 Hz), see Table 4 for full assignments; ^{13}C NMR: see Table 2; HREIMS: *m*/*z* (rel. int.) 234.1246 [M^+, $C_{14}H_{18}O_3$, requires 234.1256] (26%), 216 (26), 176 (80), 111 (100).

Compound **25**: Oil; ^{1}H NMR (δ, $CDCl_3$): 6.17 (1H, d, J = 1.2 Hz), 5.57 (1H, d, J = 1.2 Hz), 2.71 (1H, dd, J = 9.5, 6.8 Hz), 2.56 (1H, dddd, J = 15.6, 4.4, 2.5, 2.2 Hz), 2.51 (1H, dd, J = 15.0, 2.2 Hz), 2.38 (1H, d, J = 15.0 Hz), 2.33 (1H, ddd, J = 15.6, 12.8, 7.1 Hz), 2.19 (1H, m), 1.02 (3H, d, J = 6.5 Hz), see Table 4 for assignments; ^{13}C NMR: see Table 2; HREIMS: *m*/*z* (rel. int.) 234.1252 [M^+, $C_{14}H_{18}O_3$, requires 234.1256] (91%), 206 (100), 177 (65), 161 (65).

Compound **26**: Oil; $[a]_D$ +4.1 (*c* 0.3, $CHCl_3$); IR ν_{max}($CHCl_3$): 3028, 2957, 2872, 1719, 1668, 1624, 1439 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 6.22 (1H, s), 5.94 (1H, s), 5.47 (1H, d, J = 1.6 Hz), 3.76 (3H, s), 3.68 (1H, m), 2.47 (1H, ddd, J = 16.2, 4.8, 3.0 Hz), 1.04 (3H, d, J = 6.4 Hz), see Table 4 for assignments; ^{13}C NMR: see Table 2; HREIMS: *m*/*z* (rel. int.) 248.1410 [M^+, $C_{15}H_{20}O_3$, requires 248.1412] (100%), 233 (45), 216 (85), 201 (15), 188 (75).

Compound **27**: isolated as an inseparable mixture with **23**. Characterized as a mixture by 2D-NMR. ^{1}H NMR (δ, $CDCl_3$): 6.40 (1H, s), 5.70 (1H, s), 5.66 (1H, s), 3.75 (3H, s), 3.40 (1H, m), 0.98 (3H, d, J = 7.1 Hz), see Table 4 for assignments; ^{13}C NMR: see Table 2; HREIMS: as for **23**.

Compound **28**: Oil; $[a]_D$ +57.5 (*c* 0.2, $CHCl_3$); IR ν_{max}-($CHCl_3$): 3020, 2949, 1769, 1718 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 6.49 (1H, s), 5.51 (1H, s), 1.46 (3H, s), 1.04 (3H, d, J = 7.2 Hz), see Table 4 for full assignments; ^{13}C NMR: see Table 3; HREIMS: *m*/*z* (rel. int.) 234.1251 [M^+, $C_{14}H_{18}O_3$, requires 234.1256] (15%), 209 (15), 176 (100).

Compound **29**: isolated as an inseparable mixture with **28**. Characterized as a mixture by 2D-NMR. ^{1}H NMR (δ, $CDCl_3$): 6.51 (1H, s), 5.52 (1H, s), 1.45 (3H, s), 1.09 (3H, d, J = 6.9 Hz), see Table 4 for assignments; ^{13}C NMR: see Table 2; HREIMS: as for **28**.

Forward synthesis of 6,7-dehydroartemisinic acid (13) from artemisitene (2)

Acid degradation of 2 in sulfuric acid–methanol. To a solution of **2** (0.8 g, 2.86 mmol) in MeOH (18 ml) cooled in an ice bath, was added conc. H_2SO_4 (12 ml) and the reaction was stirred at room temperature for 3 h. H_2O (50 ml) and $CHCl_3$ (50 ml) were added to the reaction mixture, which was extracted by $CHCl_3$ (3 × 100 ml). The combined organic layers were washed by Na_2CO_3 solution (5%, 3 × 20 ml) and brine (3 × 50 ml), dried ($MgSO_4$) and solvent was removed under reduced pressure to obtain a crude product (0.74 g, 93% w/w), which was separated by CC (30% EtOAc–*n*-hexane) to yield **14** (0.50 g, 70%).

Reaction of 14 with a methyl Grignard reagent. To small Mg chips (0.044 g, 1.79 mmol) in anhydrous Et_2O (30 ml) was added MeI (0.132 ml, 1.43 mmol) in anhydrous Et_2O (10 ml) and the reaction mixture was refluxed under N_2 for 2 h. A solution of **14** (0.2 g, 0.81 mmol) in anhydrous Et_2O (20 ml) was added dropwise and reflux continued for a further 2.5 h until the reaction was complete, as determined by TLC. The reaction mixture was cooled by an ice bath and H_2O (20 ml) was added to destroy the excess Grignard reagent. The reaction mixture was then extracted by Et_2O (3 × 30 ml) and the combined organic layers were washed with brine (3 × 10 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield a crude mixture consisting of **30** and **31** (0.15 g, 75% w/w) which could be separated by HPLC (20% EtOAc–*n*-hexane–0.5% CH_3COOH).

Compound **32** was also obtained as a minor side-product when a larger excess of Grignard reagent was used in the reaction.

Compound **30** (R_t 22.1 min; 68 mg, 32%): Oil; $[a]_D$ −48.2 (*c* 1.2, $CHCl_3$); IR ν_{max}($CHCl_3$): 3460 (br), 3007, 2953, 2870, 1717, 1628, 1439 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 6.35 (1H, d, J = 1.0 Hz), 5.55 (1H, dd, J = 1.0, 1.0 Hz), 5.04 (1H, s), 3.74 (3H, s), 3.14 (1H, ddd, J = 11.6, 1.0, 1.0 Hz), 1.20 (3H, s), 0.97 (3H, d, J = 6.2 Hz); ^{13}C NMR: see Table 2 for partially assigned data; HREIMS: *m*/*z* (rel. int.) 264.1735 [M^+, $C_{16}H_{24}O_3$, requires 264.1725] (1%), 246 (78), 231 (20), 214 (11), 187 (100), 171 (23).

Compound **31** (R_t 19.3 min; 75 mg, 35%): Oil; $[a]_D$ −54.8 (*c* 1.3, $CHCl_3$); IR ν_{max}($CHCl_3$): 3420 (br), 3034, 2926, 2858, 1717, 1440 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 6.33 (1H, d, J = 1.0 Hz), 5.55 (1H, d, J = 1.0 Hz), 5.07 (1H, s), 3.75 (3H, s), 3.14 (1H, d, J = 13.1 Hz), 1.20 (3H, s), 0.99 (3H, d, J = 6.2 Hz); ^{13}C NMR: see Table 2 for partially assigned data; HREIMS: *m*/*z* (rel. int.) 264.1721 [M^+, $C_{16}H_{24}O_3$, requires 264.1725] (1%), 246 (90), 231 (23), 214 (12), 203 (16), 187 (100), 171 (27).

Compound **32** (R_t 9.8 min, 3% EtOAc–*n*-hexane; 12 mg, 6%): Oil; $[a]_D$ −4.3 (*c* 0.38, $CHCl_3$); IR ν_{max}($CHCl_3$): 3020, 2932, 2872, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 5.17 (1H, s), 4.84 (1H, d, J = 2.6 Hz), 4.70 (1H, d, J = 2.6 Hz), 2.37 (1H, d, J = 9.2 Hz), 1.62 (3H, s), 1.38 (3H, s), 1.27 (3H, s), 0.94 (3H, d, J = 6.2 Hz), see Table 4 for full assignments; ^{13}C NMR: see Table 2; HREIMS: *m*/*z* (rel. int.) 246.1979 [M^+, $C_{17}H_{26}O$, requires 264.1984] (36%), 231 (63), 228 (83), 213 (100), 201 (45), 171 (50).

Dehydration of 30 and 31. To the crude mixture of **30** and **31** (0.09 g, 0.34 mmol) in Et_2O (10 ml) was added H_2SO_4 (70%, 2 ml). The reaction mixture was stirred overnight at room temperature, extracted by Et_2O (3 × 20 ml), washed with brine (3 × 10 ml), dried ($MgSO_4$) and solvent was removed under reduced pressure to yield **33** (0.07 g; 83%) without the need for further purification.

Compound **33**: Oil; $[a]_D$ +13.5 (*c* 0.9, $CHCl_3$); IR ν_{max}-($CHCl_3$): 2930, 2874, 1713, 1618, 1456, 1437 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 6.32 (1H, d, J = 1.8 Hz), 5.88 (1H, s), 5.49 (1H, d, J = 1.8 Hz), 3.74 (3H, s), 1.71 (3H, s), 1.02 (3H, d, J = 5.9 Hz), see Table 4 for full assignments; ^{13}C NMR: see Table 2; HREIMS: *m*/*z* (rel. int.) 246.1623 [M^+, $C_{16}H_{22}O_2$, requires 246.1620] (12%), 203 (50), 187 (100), 111 (85).

Hydrolysis of the ester in 33. To a solution of **33** (0.02 g, 0.08 mmol) in MeOH–H_2O (10 ml–10 ml) was added KOH powder (0.05 g). The reaction mixture was refluxed overnight, then acidified by dropwise addition of HCl (10%) to pH 2, extracted by $CHCl_3$ (3 × 30 ml), washed with brine (3 × 10 ml), dried ($MgSO_4$) and solvent removed under reduced pressure to yield **13** (0.016 g; 85%) without the need for further purification.

Compound **13**: Oil; $[a]_D$ +160.0 (*c* 1.6, $CHCl_3$); IR ν_{max}-($CHCl_3$): 3400–2700 (br), 3020, 2928, 1693, 1435 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 6.46 (1H, d, J = 2.0 Hz), 5.88 (1H, br s), 5.61 (1H, d, J = 2.0 Hz), 1.71 (3H, s), 1.02 (3H, d, J = 6.1 Hz), see Table 3 for full analysis; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 232.1458 [M^+, $C_{15}H_{20}O_2$, requires 232.1463] (50%), 217 (16), 187 (100), 153 (35).

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