Pergamon

Tetrahedron 55 (1999) 119–132

TETRAHEDRON

Novel *seco*-Cycloartanes from *Kadsura coccinea* and the Assisted Autoxidation of a Tri-Substituted Alkene

Lai-King Sy and Geoffrey D. Brown*

Chemistry Department, The University of Hong Kong, Pokfulam Rd., Hong Kong

Received 29 July 1998; revised 13 October 1998; accepted 29 October 1998

Abstract: Eight novel *seco*-cycloartanes (**1-8**) have been isolated from the medicinal plant *Kadsura coccinea*. The major component of the extract, coccinetane A (**1**), undergoes extremely facile autoxidation to yield tertiary and secondary allylic hydroperoxides **2** and **3**. Evidence is presented that such autoxidation of the Δ^{24}-tri-substituted double bond is assisted by the presence of the 3-carboxylic acid group or its methyl ester. © 1998 Elsevier Science Ltd. All rights reserved.

Kadsura coccinea (Lem.) A.C. Smith (Schisandraceae) is used in traditional Chinese medicine for treating gastritis and duodenal ulcers.[1] Previous chemical investigations of *K. coccinea* have yielded a number of dibenzocyclooctadiene lignans,[2] a variety of triterpenes (including lanostanes, *seco*-lanostanes, cycloartanes and *seco*-cycloartanes)[3] and eudesmane sesquiterpenes.[4]

RESULTS AND DISCUSSION

Extraction of the aerial parts of *K. coccinea* with CH_2Cl_2 followed by separation by CC and HPLC has yielded eight novel 3,4-*seco*-cycloartanes (**1-8**). HREIMS of coccinetane A (**1**), which was the major component of the extract, established the molecular formula $C_{30}H_{48}O_2$. Inspection of the 1D-NMR spectra demonstrated a carboxylic acid functional group (δ_C 179.6), a terminal alkene (δ_C 149.5 C; 111.6 CH_2; δ_H 4.81, *d*, J=0.7 Hz; 4.74, s), a tri-substituted alkene (δ_C 125.3 CH, 130.9 C; δ_H 5.10, *t*, J=7.0 Hz) and the methylene protons of a cyclopropane ring (δ_H 0.73, *d*, J=4.2 Hz, 0.41, *d*, J = 4.2 Hz). These various functional groups were incorporated into the 3,4-*seco*-cycloartane skeleton by means of 2D-NMR experiments such as HSQC, HMBC and ^1H-^1H COSY (Table 1). The relative stereochemistry for coccinetane A was established from NOESY correlations (Table 1). Although 3,4-*seco*-cycloartanes are very rare in nature the assignments given in Table 1 received support from comparison with recently reported NMR data for *seco*-cycloartanes isolated from *Illicium dunnianum* and *I. verum*.[5]

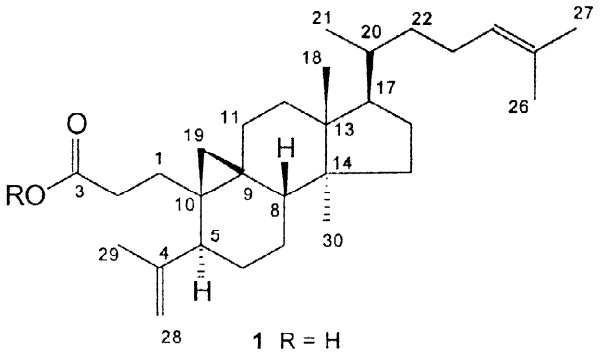
PII: S0040-4020(98)01021-7

Table 1 NMR data for compound **1**

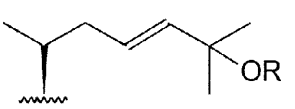
Assign -ment	δ_C+	δ_H	HMBC correlation from ^{13}C to ^1H	^1H-^1H COSY correlation from ^1H to ^1H	NOESY correlation from ^1H to ^1H
1	28.9 (CH_2)	2.08 1.40	-	2.53, 2.31, 1.40 2.53, 2.31, 2.08	1.66, 0.92 0.41
2	31.4 (CH_2)	2.53 2.31	-	2.31, 2.08, 1.40 2.53, 2.08, 1.40	2.43, 2.31 2.53
3	179.6 (C)	-	2.53, 2.31	-	-
4	149.5 (C)	-	2.43, 1.68	-	-
5	45.9 (CH)	2.43	4.81, 4.74, 1.68, 0.73, 0.41	1.52, 1.10	4.81, 2.53, 1.68, 1.52, 1.10
6α 6β	27.8 (CH_2)	1.10 1.52	-	2.43, 1.52 2.43, 1.10	2.43, 1.52 2.43, 1.10
7α 7β	25.0 (CH_2)	1.31 1.11	-	1.11 1.57, 1.31	1.57 1.68, 0.73
8	47.7 (CH)	1.57	0.73, 0.41	1.11	1.31, 0.96, 0.73
9	21.5 (C)	-	2.10, 1.25, 0.73, 0.41	-	-
10	27.1 (C)	-	0.73, 0.41	-	-
11α 11β	27.0 (CH_2)	2.10 1.25	0.73, 0.41	1.66, 1.25 2.10, 1.66	1.66, 1.25 2.10, 0.41
12	33.1 (CH_2)	1.66,1.66	0.96	2.10, 1.25	2.10, 2.08, 0.96, 0.92
13	45.2 (C)	-	0.96, 0.92	-	-
14	49.0 (C)	-	0.96, 0.92	-	-
15	35.7 (CH_2)	1.27 1.27	0.92	-	-
16	28.1 (CH_2)	1.91 1.32	-	1.59, 1.32 1.91, 1.59	1.32 1.91
17	52.3 (CH)	1.59	0.96, 0.88	1.91, 1.32	-
18	18.1 (CH_3)	0.96	-	-	1.66, 1.57
19α 19β	30.0 (CH_2)	0.41 0.73	-	0.73 0.41	1.25, 0.73 1.68, 1.57, 1.11, 0.41
20	35.9 (CH)	1.39	0.88	0.88	2.05, 0.88
21	18.3 (CH_3)	0.88	-	1.39	1.39
22	36.4 (CH_2)	1.45 1.08	0.88	2.05, 1.88, 1.08 2.05, 1.88, 1.45	1.08 1.45
23	25.0 (CH_2)	2.05 1.88	-	5.10, 1.88, 1.45, 1.08 5.10, 2.05, 1.45, 1.08	1.88, 1.39 2.05
24	125.3 (CH)	5.10	1.68, 1.61	2.05, 1.88, 1.68, 1.61	1.68
25	130.9 (C)	-	1.68, 1.61	-	-
26	17.6 (CH_3)	1.61	1.68	5.10	-
27	25.7 (CH_3)	1.68	1.61	5.10	5.10
28a* 28b*	111.6 (CH_2)	4.74 4.81	1.68	4.81, 1.68 4.74, 1.68	4.81, 1.68 4.74, 2.43
29	19.8 (CH_3)	1.68	4.81, 4.74, 2.43	4.81, 4.74	4.74, 2.43, 1.11, 0.73
30	19.3 (CH_3)	0.92	-	-	2.08, 1.66

+ Multiplicity established from DEPT; *28a proton *cis* to 29-methyl group; 28b proton *trans* to 29-methyl group.

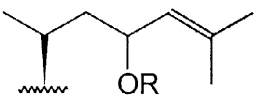
Seven other *seco*-cycloartanes (**2-8**), of closely related structure to **1** were also isolated from the extract and their structures rigorously established by 2D-NMR as for compound **1**. NMR assignments for the allylic tertiary hydroperoxide coccinetane B (**2**) were comparable to those for compound **1**, with significant differences noted only for resonances associated with the 2-methyl-hept-2-ene side-chain (i.e. C_{20}-C_{27}).



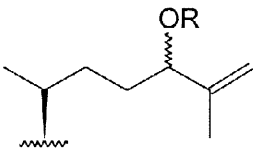
1 R = H
12 R = Me



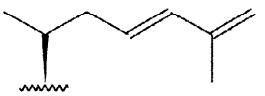
2 R = OH; 5 R = H



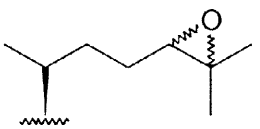
7 R = H; 8 R = Ac



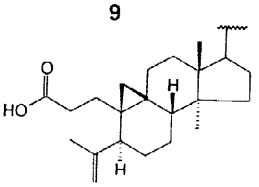
3a/3b R = OH; 6a/6b R = H



9



4a/4b



NMR assignments for this "side-chain" are reported in Table 2: all other assignments were essentially unchanged by comparison with compound **1** (see Table 1). Coccinetane C (**3a/3b**) which contains a new chiral centre at C-24 was isolated as a diastereoisomeric mixture of allylic secondary hydroperoxides. The structures of tertiary hydroperoxide **2** and secondary hydroperoxides **3a** and **3b** are suggestive of formation by autoxidation of the tri-substituted double bond in **1** (see later). Coccinetane D (**4a/4b**) was an inseperable mixture of diastereoisomeric epoxides also perhaps derived from oxygenation of the tri-substituted double bond in **1**. The allylic tertiary alcohol group in coccinetane E (**5**) may be viewed as being formed either by acid-catalysed ring-opening of this epoxide group or by reduction of **2**; such mechanisms would also account for the presence of coccinetane F (which was isolated as an inseperable mixture of diastereoisomers **6a/6b**), containing an allylic secondary alcohol group, which might be formed either from the diastereoisomeric epoxides **4a/4b** or by reduction of **3a/3b**. For both allylic alcohols **5** and **6** the chemical shift for the oxygen bearing carbon in the functionalized 2-methyl-heptyl side-chain is more than 10 ppm upfield as compared to the allylic hydroperoxide analogues **2** and **3**, which is consistent with the greater electron-withdrawing effect of a hydroperoxide when compared with an alcohol group. The allylic secondary alcohol system of **6** is transposed in coccinetane G (**7**) and the corresponding acetate, coccinetane H (**8**), both of which were isolated as single diastereoisomers.

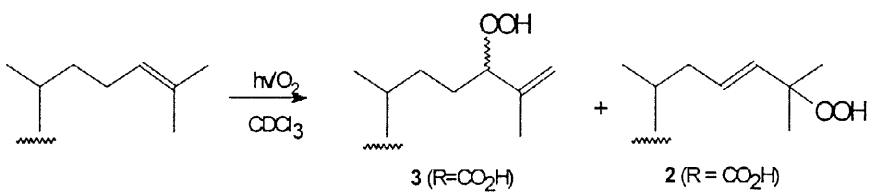
The structures of all novel natural products **2-8** are clearly suggestive of formation *via* oxidation of the double bond in the 2-methyl-hept-2-ene side-chain of **1**. Our suspicion that **2** and **3** might be derived from **1** by straightforward "ene-type" addition of molecular oxygen to the Δ^{24}-double bond was confirmed by the observation that a $CDCl_3$ solution of **1** when left at room temperature under natural illumination was cleanly converted into compounds **2** and **3** (Scheme 1) together with smaller amounts of the diene **9**. No reaction was observed in the dark indicating that singlet oxygen is the reactive species involved in this autoxidation. Although such autoxidation reactions of double bonds are well documented, what is remarkable about this particular transformation is that it was completed within a matter of hours under conditions of ambient light and temperature and in the absence of an external photo-sensitizer. By comparison, the tri-substituted double bond in natural products **10**[6] and **11**[7] (chosen because of close structural similarities to **1** in the composition

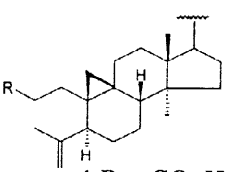
Table 2 ^{13}C and ^{1}H NMR assignments for compounds **2-8**[a]

	δ_C								δ_H							
Assign-ment	2	3a/3b+	4a	4b%	5	6a/6b+	7	8	2	3a/3b+	4a	4b%	5	6a/6b+	7	8
20	36.4	36.1/ 35.9	35.9	35.9	36.4	36.0/ 35.9	32.7	32.9	1.49	1.39/ 1.39	1.44	1.44	1.47	1.40/1.40	1.60	1.44
21	18.3	18.24/ 18.26	18.3	18.2	18.3	18.3/ 18.3	18.3	18.5	0.86	0.87/ 0.87	0.89	0.89	0.86	0.88/0.88	0.95	0.93
22	39.4	31.98/ 32.03	32.6	32.8	39.1	31.91/ 31.89	44.4	41.9	2.23, 1.79	1.15, 0.98/ 1.15, 0.98	1.52, 1.23	1.52, 1.23	2.19, 1.74	1.12, 0.95/ 1.12, 0.95	1.66, 1.04	1.82, 1.09
23	130.7	27.4/ 27.1	25.7	26.0	125.6	28.1/ 28.0	66.2	69.7	5.68	1.65, 1.52/ 1.48, 1.35	1.66, 1.40	1.66, 1.40	5.60	1.64, 1.45/ 1.64, 1.45	4.49	5.61
24	134.4	90.4/ 90.2	65.0	64.8	139.4	76.8/ 76.4	129.0	124.8	5.52	4.27/ 4.27	2.69	2.69	5.60	4.02/4.02	5.20	5.10
25	82.3	143.9/ 143.6	58.4	59.3	70.8	147.7/ 147.4	133.9	135.7	-	-	-	-	-	-	-	-
26	24.38*	17.0/ 17.2	18.8	18.7	29.9*	17.6/ 17.2	18.1	18.3	1.34	1.73/ 1.72	1.27	1.25	1.32	1.73/1.73	1.69	1.73
27	24.44*	114.7/ 114.2	24.9	24.9	30.0*	111.4/ 111.0	25.7	25.7	1.34	5.03, 5.01/ 5.02, 5.01	1.30	1.27	1.32	4.92, 4.84/ 4.93, 4.84	1.71	1.70
CH_3CO								21.4								2.02
CH_3CO								170.7								-

* Assignments interchangeble within column; ' Assignments within diastereoisomeric pair (approx. 1:1 ratio) interchangeable; % Minor diastereoisomer; [a] Assignments for ^{13}C and ^{1}H at positions 1-19, 28-30 identical to within ±0.01 ppm for ^{1}H and ±0.1 ppm for ^{13}C with compound **1**.

of the tri-substituted alkene-containing side-chain and for their availability in these laboratories) required a period of 1-2 months to undergo an analagous autoxidation reaction to the corresponding secondary and tertiary allylic hydroperoxides under identical conditions (Table 4).

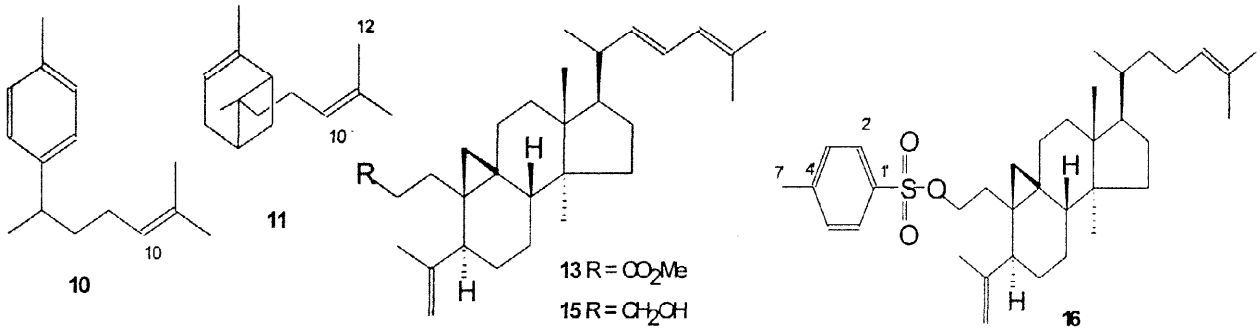




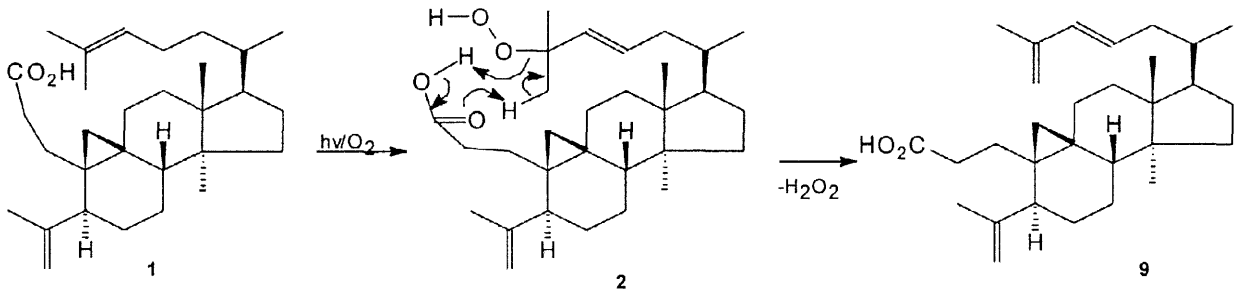
1 R = CO_2H
12 R = CO_2Me
14 R = CH_2OH
17 R = CH_3

Scheme 1 Autoxidation of compounds **1**, **12**, **14** and **17** to secondary and tertiary hydroperoxides (e.g. **2** and **3** from **1**)

In order to explain the remarkable facility with which the Δ^{24}-double bond in compound **1** undergoes autoxidation by singlet molecular oxygen, we hypothesised that the 3-carboxylic acid group might be able to assist this reaction in some way. Although the $\Delta^{4(28)}$-double bond would at first sight appear to be the preferred site for such assisted autoxidation, given its proximity to the carboxylic acid, there are precedents in the literature for expecting di-substituted double bonds to be much less susceptible to attack by singlet oxygen than tri-substituted double bonds.[8] In addition, model building studies of compound **1** showed that the 3-carboxylic acid and Δ^{24}-double bond functional groups are able to approach one another closely.



In order to test the foregoing hypothesis, the carboxylic acid group in **1** was first converted into a methyl ester (**12**) (Table 3). Compound **12** underwent autoxidation to the corresponding secondary and tertiary allylic hydroperoxides (as determined by appearance of characteristic resonances in the ^{1}H NMR spectral region of 4-6 ppm - see Experimental) at a rate more than double that of compound **1** in $CDCl_3$ under conditions of ambient light and temperature (Table 4), although no terminal diene analogous to compound **9** could be detected. When d_4-MeOH was substituted for $CDCl_3$ as solvent no hydroperoxides were obtained as products from the autoxidation of **12**: instead compound **13** was formed transiently and reaction ceased with the production of an unidentified compound in which NMR resonances corresponding to the 2-methyl-hept-2-ene side-chain had disappeared entirely, whilst resonances for the tricyclic triterpene nucleus remained. We speculate that the conjugated diene **13** is the product of facile elimination in protic solvent (d_4-MeOH) of hydrogen peroxide from allylic hydroperoxide autoxidation products derived from **12**, whilst the thermodynamically less favoured terminal diene **9**, formed from **1** in $CDCl_3$, is the result of a concerted elimination of hydrogen peroxide, which is intramolecularly assisted by the 3-carboxylic acid group, as depicted in Scheme 2.



Scheme 2 Possible mechanism for formation of diene **9** from autoxidation products of **1** in aprotic solvent.

Reduction of **12** with $LiAlH_4$[9] yielded the primary alcohol **14**, together with small amounts of the conjugated diene **15**; compound **15** was believed to have arisen as an elimination product of hydroperoxides formed by autoxidation during the course of the $LiAlH_4$ reduction in a manner similar to that discussed above. (In support of this compound **15** was not detected when the reaction was repeated under conditions excluding light). Complete reduction at the 3-position was effected by conversion of **14** into a tosylate (**16**)[10] and

Table 3 ^{13}C and ^{1}H NMR assignments for compounds **12** and **14-17** (from 2D-NMR).

Assignment	δ_C					δ_H				
	12	**14**	**15**	**16**	**17**	**12**	**14**	**15**	**16**	**17**
1	29.0	29.9	29.9	29.6	36.39	2.06, 1.36	1.50, 1.02	1.50, 1.02	1.65, 0.95	1.71, 0.90
2	31.5	29.9	29.9	26.2	19.8	2.51, 2.26	1.77, 1.52	1.80, 1.52	1.80, 1.58	1.51, 1.22
3	174.5	63.6	63.3	71.2	14.7	-	3.56, 3.56	3.56, 3.56	3.98, 3.93	0.83
4	149.5	150.1	150.1	150.1	150.3	-	-	-	-	-
5	45.9	45.7	45.7	45.8	45.6	2.44	2.53	2.52	2.38	2.53
6	27.8	27.8	27.8	27.8	27.9	1.52, 1.08	1.50, 1.09	1.50, 1.09	1.47, 1.04	1.49, 1.04
7	24.9	24.97	25.0	25.0	25.1	1.30, 1.09	1.30, 1.11	1.30, 1.10	1.27, 1.05	1.29, 1.11
8	47.7	47.7	47.8	47.7	47.8	1.57	1.58	1.58	1.53	1.57
9	21.5	21.9	21.9	21.3	21.2	-	-	-	-	-
10	27.1	27.5	27.5	27.2	28.0	-	-	-	-	-
11	27.0	27.1	27.1	27.1	27.1	2.08, 1.25	2.10, 1.24	2.10, 1.29	1.97, 1.13	2.10, 1.24
12	33.1	33.2	33.1	33.1	33.18	1.65, 1.65	1.65, 1.65	1.65, 1.65	1.61, 1.61	1.65, 1.65
13	45.1	45.2	45.2	45.2	45.2	-	-	-	-	-
14	48.9	49.0	49.2	49.0	49.0	-	-	-	-	-
15	35.6	35.7	35.7	35.7	35.67	1.29, 1.29	1.28, 1.28	1.27, 1.27	1.27, 1.27	1.29, 1.29
16	28.0	28.1	28.1	28.1	28.1	1.91, 1.32	1.89, 1.29	1.76, 1.29	1.89, 1.27	1.89, 1.29
17	52.3	52.3	52.2	52.3	52.3	1.58	1.59	1.65	1.58	1.59
18	18.0	18.0	18.2	18.0	18.0	0.96	0.97	1.00	0.94	0.97
19	29.9	30.1	30.1	29.9	30.1	0.72, 0.41	0.71, 0.34	0.71, 0.35	0.66, 0.29	0.67, 0.30
20	35.9	35.9	40.7	35.9	35.92	1.39	1.39	2.12	1.38	1.38
21	18.2	18.3	20.2	18.3	18.2	0.88	0.88	1.00	0.89	0.89
22	36.3	36.4	138.8	36.4	36.36	1.43, 1.05	1.45, 1.08	5.42	1.43, 1.05	1.43, 1.05
23	25.0	25.02	124.2	25.0	25.0	2.04, 1.88	2.05, 1.88	6.16	2.05, 1.88	2.05, 1.85
24	125.3	125.3	125.3	125.3	125.3	5.10	5.11	5.75	5.10	5.10
25	130.9	130.9	132.6	130.9	130.9	-	-	-	-	-
26	17.6	17.6	17.8	17.6	17.6	1.60	1.61	1.74	1.61	1.61
27	25.7	25.7	25.8	25.7	25.7	1.68	1.68	1.75	1.68	1.69
28	111.4	111.1	111.2	111.3	110.9	4.81, 4.73	4.80, 4.72	4.81, 4.72	4.72, 4.67	4.79, 4.71
29	19.7	19.8	19.8	19.8	19.9	1.68	1.68	1.69	1.63	1.69
30	19.3	19.3	19.3	19.3	19.3	0.93	0.94	0.94	0.88	0.94
-OMe	51.4	-	-	-	-	3.64	-	-	-	-
1'				133.6					-	
2'/6'				129.7					7.33	
3'/5'				127.9					7.77	
4'				144.6					-	
7'				21.6					2.45	

subsequent reduction by $LiAlH_4$[9] to yield compound **17**. Compounds **14** and **17** were found to undergo autoxidation reactions of the Δ^{24}-double bond in $CDCl_3$ at rates which were respectively one and two orders of magnitude slower than the methyl ester of coccinetane A (**12**) under conditions of ambient light and temperature (Table 4). The rate of autoxidation for fully reduced compound **17** was comparable to that of the sesquiterpene hydrocarbons **10** and **11**, which is consistent with our hypothesis that the functional group at the 3-position is in some way able to assist the autoxidation of the Δ^{24}-double bond. In addition, no diene products analogous to **9** could be detected from autoxidation of either **14** or **17**, which supports the proposition that the 3-carboxylic acid group is required to promote further elimination reactions of hydroperoxide autoxidation products in aprotic solvents (Scheme 2).

Having established that autoxidation of the tri-substituted double bond in **1** is assisted by the presence of an oxygen-containing functional group at the 3-position (effectiveness in the order CO_2Me > CO_2H >> CH_2OH >> CH_3), we next attempted to establish whether this assistance was intramolecular or intermolecular in nature. Under controlled conditions of light and temperature (see Experimental), it was found that the rate of autoxidation of **1** to each of the products **2**, **3** and **9** as determined by ^1H NMR spectroscopy was essentially independent of substrate concentration in dilute solution (over the range 0.25 mg- 2 mg per NMR tube (0.6 ml); Figure 1 - autoxidation to **2** only shown). However, more concentrated solutions - e.g. 5 mg and 7.5 mg - showed progressively slower reaction rates, which we attribute to be due to a limitation in the rate of dissolution of oxygen into solution in the NMR tube. Thus, it would appear that self-catalysis of autoxidation of the Δ^{24}-double bond in **1** by the 3-carboxylic acid group is an intramolecular process.

Table 4 Rate$^+$ of autoxidation of compounds **1**, **10**, **11**, **12**, **14** and **17** to corresponding secondary and tertiary hydroperoxides in $CDCl_3$ under conditions of ambient light and temperature.

Compound	Rate of formation of tertiary hydroperoxide (e.g. **2**)*	Rate of formation of secondary hydroperoxide (e.g. **3**)*	Rate of formation of diene **9***
1	-0.16	-0.17	-0.089
10	-0.0029	-0.0048	-
11	-0.0038	-0.0047	-
12	-0.46	-0.43	-
14	-0.038	-0.040	-
17	-0.0076	-0.0080	-

*See Experimental section for calculation of rate constants; $^+$ Rate expressed as hr^{-1}

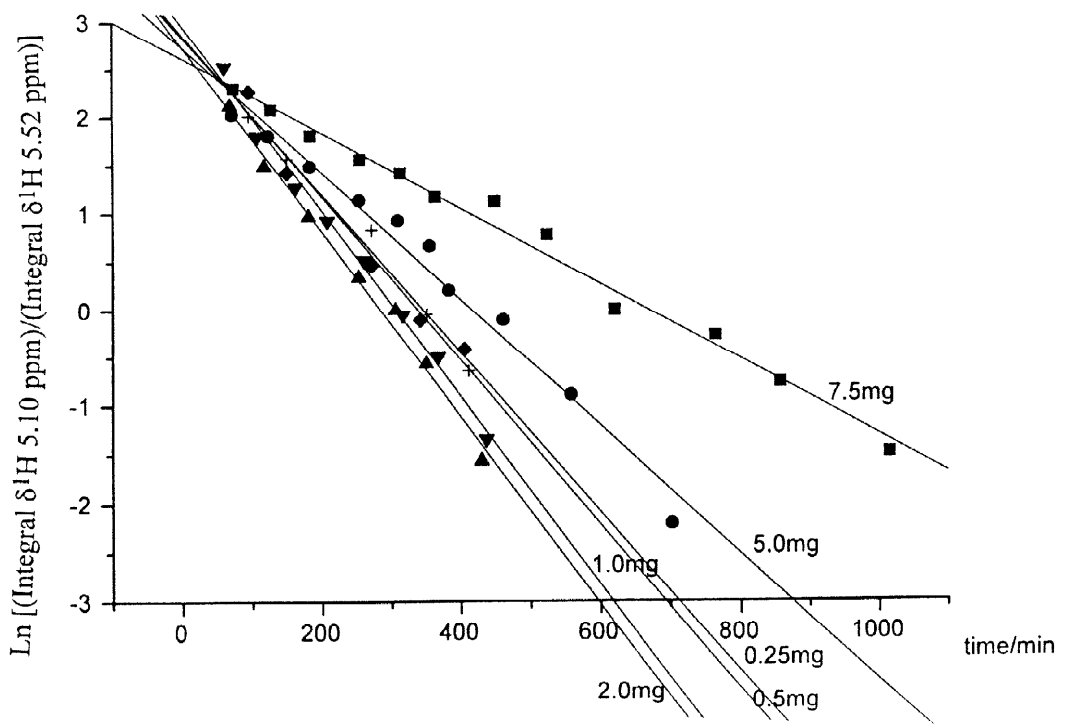


Figure 1. The autoxidation reaction of **1** to **2** at various concentrations (relative rates of production of **3** and **9** were similar to those of **2**).

The precise mechanism by which a carboxylic acid/methyl ester functional group (and to a lesser extent a primary alcohol group) is able to assist in the autoxidation of a tri-substituted double bond, as observed in this study, remains unclear. It seems certain that this reaction involves participation of the excited state of molecular oxygen -$^1O_2$ (autoxidation by $^3O_2$ being exceedingly rare).[11] Production of $^1O_2$ normally requires the presence of an external photosensitizer such as Rose Bengal or methylene blue, although there are a few examples of highly conjugated molecules, such as fullerenes and carotenes, which are able to act as their own $^1O_2$-sensitizers during autoxidation reactions.[12] However, we are unaware of any reports in which an isolated carboxylic acid or methyl ester has been shown to be able to act as an "internal" photosensitizer. On the other hand, there is considerable evidence for functional groups (in particular -OH) exerting a "directing" or "steering" effect on the "ene-type" reaction of singlet oxygen with a double bond, leading to a high degree of regio- and stereoselectivity in the products.[13] It is now generally assumed that such selectivity is the result of initial formation of a perepoxide intermediate between O_2 and the alkene which is stabilized by interaction with the allylic oxygen-containing functional group. Although there is quite strong evidence for the intermediacy of perepoxides in such singlet oxygen addition reactions,[14] it is experimentally difficult to distinguish several alternative mechanisms which have been proposed (including concerted [4+2] reactions, mechanisms involving diradicals, zwitterionic intermediates or exciplexes).[15] We propose that that the oxygen atom in the 3-functional group which is common to compounds **1**, **12** and **14** may also be able to exert some kind of analogous "steering" effect, thereby facilitating the "ene-type" reaction of molecular oxygen which leads to the observed autoxidation products at the Δ^{24}-double bond. Although the assisted autoxidation reactions reported herein appear to be unique, there is no lack of precedents for such "long-distance" intramolecular functionalization reactions from the steroid literature.[16]

Finally, we note that oxygenated steroids similar in the composition of the side-chain to **2-6** have been reported on several ocassions from natural sources[17] and that their biogenetic origins, as either artifacts from autoxidation or *bona fide* natural products arising from biosynthesis, have been the subject of debate. Clearly, the observation that (apparently) quite remote functional groups are able to promote autoxidation of double bonds in the steroid side-chain will have a bearing on deciding for or against the authenticity of such oygenated steroidal products.

EXPERIMENTAL

NMR chemical shifts, expressed in ppm (δ) relative to TMS as int. standard, for those resonances which are clearly resolved in 1-dimensional ^1H NMR spectra are listed herein. Fully assigned ^1H and ^{13}C data were determined by 2D-NMR techniques and are listed in Tables in the text. All NMR experiments were run on a Bruker DRX 500 instrument. Two dimensional spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. HREIMS were recorded at 70 ev on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in solution on a BIO-RAD FT S-7 IR spectrometer.

Extraction and Separation. K. coccinea (1.51 kg) was collected in Hong Kong (a voucher specimen GDBROWN 97/5 has been deposited in the University of Hong Kong Herbarium) and exhaustively extracted with CH_2Cl_2 over a period of several days. The organic layer was dried and evaporated under reduced pressure to yield a green solid (9.53g, 0.63% w/w). Gradient column chromatography was performed using silica gel 60-200 μm (Merck). TLC plates were developed using *p*-anisaldehyde. Further HPLC purification of crude fractions from the column was performed using a PREP-SIL 20 mm x 25 cm column, flow rate 8 ml/min.

Coccinetane A (**1**): Oil (809 mg, R_t 10.4 min in 20% ethyl acetate/hexane); $[\alpha]_D$ +167.5° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3034, 2928, 2860, 1732, 1466, 1375, 1250, 1045 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.10 (1H, *t*, J=7.0 Hz), 4.81 (1H, *d*, J=0.7 Hz), 4.74 (1H, *s*), 1.68 (6H, *s*), 1.61 (3H, *s*), 0.96 (3H, *s*), 0.92 (3H, *s*), 0.88 (3H, *d*, J=6.3 Hz), 0.73 (1H, *d*, J=4.2 Hz), 0.41 (1H, *d*, J=4.2 Hz); ^{13}C NMR -see Table 1; HREIMS *m/z* (% intensity) 440.3640 (54) [M^+, calc. 440.3654 for $C_{30}H_{48}O_2$], 425 (100), 397 (5), 356 (10), 329 (22), 313 (2), 273 (10), 235 (10), 205 (10), 175 (10), 147 (10), 121 (10), 109 (22), 95 (18).

Coccinetane B (**2**): Oil (8.1 mg, R_t 14.2 min in 30% ethyl acetate/hexane); $[\alpha]_D$ +51.9° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3020, 2934, 2874, 1709, 1458, 1308, 1219 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.68 (1H, *ddd*, J=15.6, 8.2, 6.0 Hz), 5.52 (1H, *d*, J=15.6 Hz), 4.82 (1H, *s*), 4.74 (1H, *s*), 1.68 (3H, *s*), 1.34 (6H, *s*), 0.97 (3H, *s*), 0.93 (3H, *s*), 0.86 (3H, *d*, J=6.4 Hz), 0.74 (1H, *d*, J=4.3 Hz), 0.41 (1H, *d*, J=4.3 Hz); ^{13}C NMR - see Table 2; HREIMS *m/z* (% intensity) 472.3546 (1) [M^+, calc. 472.3553 for $C_{30}H_{48}O_4$], 454 (5), 439 (15), 423 (35), 399 (10), 385 (15), 357 (20), 329 (55), 313 (20), 287 (20), 247 (20), 235 (28), 187 (20), 175 (42), 161 (50), 147 (70), 121 (80), 107 (100), 79 (50).

Coccinetane C (**3a/3b**): Oil (13.8 mg, R_t 13.6 min in 30% ethyl acetate/hexane); $[\alpha]_D$ +38.4° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3400-2600 (br), 2930, 2854, 1711, 1644, 1450, 1308, 1223, 1220 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.03 (1H, *d*, J=1.5 Hz)/5.02 (1H, *t*, J=1.5 Hz), 5.01 (1H, *s*), 4.81 (1H, *s*), 4.73 (1H, *s*), 4.27/4.26 (1H, *t*, J=6.0 Hz), 1.73/1.72 (3H, *s*), 1.68 (3H, *s*), 0.96 (3H, *s*), 0.92 (3H, *s*), 0.87 (3H, *d*, J=6.6 Hz), 0.73 (1H, *d*, J=4.3 Hz), 0.41 (1H, *d*, J=4.3 Hz); ^{13}C NMR - see Table 2; HREIMS *m/z* (% intensity) 454.3450 (6) [M^+-H_2O, calc. 454.3447 for $C_{30}H_{46}O_3$], 439 (27), 423 (35), 397 (5), 357 (10), 329 (50), 313 (20), 273 (20), 219 (25), 187 (25), 175 (50), 147 (62), 121 (68), 95 (100), 81 (85).

Coccinetane D (**4a/4b**): Oil (12.9 mg, R_t 16.3 min in 20% ethyl acetate/hexane); $[\alpha]_D$ +66.9° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3018, 2932, 2854, 1715, 1454, 1375, 1221, 1219 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 4.81 (1H, *s*), 4.73 (1H, *s*), 2.69 (1H, *t*, J=6.2), 1.69 (3H, *s*), 1.30/1.27 (3H, *s*), 1.27/1.25 (3H, *s*), 0.96 (3H, *s*), 0.94 (3H, *s*), 0.89 (3H, *d*, J=6.2 Hz), 0.73 (1H, d, J=4.4 Hz), 0.41 (1H, *d*, J=4.4 Hz); ^{13}C NMR - see Table 2; HREIMS *m/z* (% intensity) 456.3613 (19) [M^+, calc. 456.3603 for $C_{30}H_{48}O_3$], 441 (63), 423 (40), 395 (8), 355 (10), 329 (53), 287 (15), 273 (20), 235 (20), 203 (22), 175 (48), 147 (60), 121 (65), 107 (90), 95 (100).

Coccinetane E (**5**): Oil (13.2 mg, R_t 23.2 min in 30% ethyl acetate/hexane); $[\alpha]_D$ +54.7° (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3071, 2934, 2870, 1703, 1458, 1375, 1286 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.60 (2H, *m*), 4.81 (1H, *s*), 4.73 (1H, *s*), 1.69 (3H, *s*), 1.321 (3H, *s*), 1.319 (3H, *s*), 0.97 (3H, *s*), 0.93 (3H, *s*), 0.86 (3H, *d*, J=6.5 Hz), 0.73 (1H, *d*, J=4.5 Hz), 0.41 (1H, *d*, J=4.5 Hz); ^{13}C NMR - see Table 2; HREIMS *m/z* (% intensity) 456.3602 (4) [M^+, calc. 456.3603 for $C_{30}H_{48}O_3$], 438 (39), 423 (100), 395 (10), 357 (38), 329 (30), 273 (12), 259 (18), 219 (20), 203 (35), 175 (32), 161 (40), 147 (66), 121 (65), 109 (99), 95 (88).

Coccinetane F (**6a/6b**): Oil (29.7 mg, R_t 17.9 min in 30% ethyl acetate/hexane); $[\alpha]_D$ +86.5° (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3071, 2943, 2872, 1709, 1454, 1375, 1224 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 4.93 (1H, *s*)/4.92 (1H, *s*), 4.84 (1H, *d*, J=1.3 Hz), 4.81 (1H, *s*), 4.73 (1H, *s*), 4.02 (1H, *t*, J=6.3 Hz), 1.73 (3H, *s*), 1.68 (3H, *s*), 0.96 (3H, *s*), 0.93 (3H, *s*), 0.88 (3H, *d*, J=6.4 Hz), 0.72 (1H, *d*, J=4.4 Hz), 0.41 (1H, *d*, J=4.4 Hz); ^{13}C NMR -see Table 2; HREIMS *m/z* (% intensity) 456.3608 (26) [M^+, calc. 456.3603 for $C_{30}H_{48}O_3$], 441 (47), 423 (98), 395 (18), 355 (20), 329 (81), 302 (30), 273 (30), 235 (35), 203 (35), 175 (65), 161 (63), 147 (75), 121 (100), 95 (85), 81 (70).

Coccinetane G (**7**): Oil (27.4 mg, R_t 15.1 min in 30% ethyl acetate/hexane); $[\alpha]_D$ +71.1° (*c* 2.74, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3069, 3018, 2941, 2874, 1709, 1636, 1452, 1377, 1306, 1215 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.20 (1H, *d*, J=8.4 Hz), 4.81 (1H, *s*), 4.73 (1H, *s*), 4.49 (1H, *ddd*, J=9.8, 8.4, 3.2 Hz), 1.71 (3H, *d*, J=1.1 Hz), 1.69 (6H, *s*), 0.99 (3H, *s*), 0.95 (3H, *d*, J=6.1 Hz), 0.93 (3H, *s*), 0.73 (1H, *d*, J=4.4 Hz), 0.41 (1H, *d*, J=4.4 Hz); ^{13}C NMR -see Table 2; HREIMS *m/z* (% intensity) 456.3595 (2) [M^+, calc. 456.3603 for $C_{30}H_{48}O_3$], 438 (20), 423 (38), 400 (10), 385 (25), 357 (20), 341 (25), 329 (37), 287 (10), 259 (10), 235 (15), 219 (18), 187 (20), 175 (30), 159 (35), 147 (70), 121 (75), 109 (100), 95 (80).

Coccinetane H (**8**): Oil (428.4 mg, R_t 13.9 min in 20% ethyl acetate/hexane); $[\alpha]_D$ +62.1° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) ν_{max} : 3400-2600 (br), 3030, 2937, 2874, 1709, 1639, 1452, 1375, 1256, 1211, 1016 cm^{-1}; ^1H NMR δ ($CDCl_3$) ppm: 5.61 (1H, *ddd*, J=9.6, 8.9, 3.3 Hz), 5.10 (1H, *d*, J=8.9 Hz), 4.81 (1H, *s*), 4.73 (1H, *s*), 2.02 (3H, *s*), 1.73 (3H, *d*, J=1.0 Hz), 1.70 (3H, *d*, J=0.8 Hz), 1.68 (3H, *s*), 0.96 (3H, *s*), 0.93 (3H, *d*, J=6.0 Hz), 0.92 (3H, *s*), 0.73 (1H, *d*, J=4.4 Hz), 0.41 (1H, *d*, J=4.4 Hz); ^{13}C NMR - see Table 2; HREIMS *m/z* (% intensity) 498.3710 (1) [M^+, calc. 498.3709 for $C_{32}H_{50}O_4$], 454 (2), 438 (42), 423 (100), 395 (5), 357 (38), 329 (37), 287 (10), 273 (10), 235 (10), 219 (15), 203 (30), 173 (30), 147 (20), 133 (20), 121 (50), 109 (99), 95 (74), 81 (82).

Compound 9. Inseparable from **1** by either CC or HPLC. ^1H and ^{13}C NMR assignments for positions 22-27 were determined by 2D-NMR (HSQC, HMBC, ^1H-^1H COSY) analysis of a mixture of **9** and **1** (other assignments for **9** were not distinguished for those from **1**) ^1H NMR δ (ppm): 6.12 (1H, *d*, J=15.6 Hz, H-24), 5.65 (1H, *dd*, J=15.6, 8.1 Hz, H-23), 4.86 (2H, *s*, H-27), 1.85 (3H, *s*, H-26), 2.30 (1H, *m*, H-22a), 1.72 (2H, *m*, H-22b). ^{13}C NMR 143.5 (C, C-25), 134.1 (CH, C-24), 130.0 (CH, C-23), 114.0 (CH_2, C-27), 18.1 (CH_3, C-26).

Compound 13. Inseparable from **12** by either CC or HPLC. ^{1}H NMR assignments for positions 22-27 of **13** could be resolved when present as a mixture with **12** (other assignments for **13** were not distinguished for those from **12**) ^{1}H NMR δ (ppm): 6.12 (1H, *dd*, J=14.8, 10.7 Hz, H-23), 5.69 (1H, *d*, J=10.7, H-24), 5.33 (1H, *dd*, J=14.8, 9.0 H-22), 1.64 (3H, *s*, H-27), 1.58 (3H, *s*, H-26).

Methylation of coccinetane A (**1**) Compound **1** (550 mg) was dissolved in MeOH (6 ml) and conc. HCl (0.3 ml) added. After stirring overnight, solvent was removed under reduced pressure to yield coccinetane A methyl ester (**12**) (530 mg) without further need for purification: Oil; IR ($CHCl_3$) ν_{max} : 2932, 2874, 1732, 1645, 1456, 1375, 1227, 1205, 1169 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) ppm: 5.10 (1H, *t*, *J*=7.0 Hz), 4.81 (1H, *s*), 4.73 (1H, *s*), 3.64 (3H, *s*), 1.68 (6H, *s*), 1.60 (3H, *s*), 0.96 (3H, *s*), 0.93 (3H, *s*), 0.88 (3H, *d*, J=6.3 Hz), 0.72 (1H, *d*, *J*=4.2 Hz), 0.41 (1H, *d*, *J*=4.2 Hz) ; ^{13}C NMR - see Table 3; HREIMS *m/z* (% intensity) 454.3810 (60) [M^+, 454.3811 calc. for $C_{31}H_{50}O_2$], 439 (100), 411 (10), 385 (10), 343 (15), 287 (5), 249 (10), 205 (10), 175 (10), 147 (10), 109 (15).

Reduction of methyl ester 12 to alcohol 14 by $LiAlH_4$. To a stirred solution of $LiAlH_4$ (46mg) in anhydrous Et_2O (5 ml) was added dropwise a solution of compound **12** (510 mg) in anhydrous Et_2O (2 ml). Following further addition of Et_2O (3 ml), the reaction was refluxed (3 h), then cooled in an ice-bath and Na_2SO_4 (sat., 1 ml) added to destroy excess hydride. The mixture was stirred (2 h) and the resulting salt was filtered off and washed with Et_2O, after which the combined organic layers were dried and rotary evaporated. Compound **14** (414 mg) was obtained by column chromatography (15% ethyl acetate/hexane): Oil; IR ($CHCl_3$) ν_{max} : 3368 (br) 2932, 2873, 1645, 1456, 1437, 1375 cm^{-1}; ^{1}H NMR δ (ppm): 5.11 (1H, *tt*, J=7.1, 1.3 Hz), 4.80 (1H, *d*, J=1.3 Hz), 4.72 (1H, *dd*, J=2.5, 1.4 Hz), 3.56 (2H, *m*), 2.53 (1H, *dd*, J=11.7, 4.9 Hz), 1.68 (6H, *s*), 1.61 (3H, *s*), 0.97 (3H, *s*), 0.94 (3H, *s*), 0.88 (3H, *d*, J=6.4 Hz), 0.71 (1H, *d*, J=4.3 Hz), 0.34 (1H, *d*, J=4.3 Hz); ^{13}C NMR - see Table 3; HREIMS *m/z* (% intensity) 426.3847 (40) [M^+, 426.3862 calc. for $C_{30}H_{50}O$], 411 (100), 357 (5), 286 (8), 259 (10), 231 (5), 205 (10), 173 (10), 109 (10). Compound **15** (20 mg) was isolated as a minor product from the reaction: IR ($CHCl_3$) ν_{max} : 3351, 2932, 2874, 1645, 1370 cm^{-1}; ^{1}H NMR δ (ppm): 6.16 (1H, *dd*, J=15.1, 11.4 Hz), 5.75 (1H, *d*, J=11.4 Hz), 5.42 (1H, *dd*, J=15.1, 8.5 Hz), 4.81 (1H, *s*), 4.72 (1H, *s*), 3.56 (2H, *m*), 2.52 (1H, *dd*, J=11.7, 5.0 Hz), 1.75 (3H, *s*), 1.69 (3H, *s*), 1.00 (3H, *d*, J=6.4 Hz), 1.00 (3H, *s*), 0.94 (3H, *s*), 0.71 (1H, *d*, J=4.3 Hz), 0.35 (1H, *d*, J=4.3 Hz);^{13}C NMR - see Table 3.

Tosylation of alcohol **14**. Compound **14** (388mg) was dissolved in $CHCl_3$ (1 ml) and cooled in an ice-bath. Pyridine (0.15 ml) was added followed by *p*-toluenesulfonyl chloride (262 mg) in small portions with constant stirring. After 2.5 h the reaction was complete and Et_2O (3 ml) and water (0.7 ml) were added. The organic layer was washed successively with HCl (2N) and $NaHCO_3$ (5%) and then dried. Solvent was removed and compound **16** (325 mg) obtained by column chromatography (5% ethyl acetate/hexane): Oil; ^{1}H NMR δ (ppm): 7.77 (2H, *d*, J=8.0 Hz), 7.33 (2H, *d*, J=8.0 Hz), 5.10 (1H, *t*, J= 7.0 Hz), 4.72 (1H, *s*), 4.67 (1H, *s*), 4.00-3.90 (2H, *m*), 2.45 (3H, *s*), 2.38 (1H, *dd*, J=11.7, 4.9 Hz), 1.68 (3H, *s*), 1.63 (3H, *s*), 1.61 (3H, *s*), 0.94 (3H, *s*), 0.89 (3H, *d*, J=6.3 Hz), 0.88 (3H, *s*), 0.66 (1H, *d*, J=4.3 Hz), 0.29 (1H, *d*, J=4.3 Hz); ^{13}C NMR - see Table 3;

HREIMS *m/z* (% intensity) 580.3948 (1) [M^+, 580.3950 calc. for $C_{37}H_{56}SO_3$], 565 (5), 408 (10), 393 (18), 365 (2), 339 (2), 297 (5), 203 (10), 175 (10), 161 (10), 123 (20), 119 (30), 109 (40).

Reduction of compound 16 by $LiAlH_4$. Reduction of **16** (224 mg) by $LiAlH_4$ (identical procedure as described for compound **12**) yielded compound **17** (180 mg) with no need for further purification: Oil; IR ($CHCl_3$) ν_{max} : 2932, 2872, 1636, 1452, 1371 cm^{-1}; ^1H NMR δ (ppm): 5.10 (1H, *t*, J=6.9 Hz), 4.79 (1H, *s*), 4.71 (1H, *s*), 2.53 (1H, *dd*, J=11.0, 4.7 Hz), 1.69 (3H, *s*), 1.61 (6H, *s*), 0.97 (3H, *s*), 0.94 (3H, *s*), 0.89 (3H, *d*, J=6.4 Hz), 0.83 (3H, *t*, J=7.3 Hz), 0.67 (1H, *d*, J=4.0 Hz), 0.30 (1H, *d*, J=4.0 Hz); ^{13}C NMR -see Table 3; HREIMS *m/z* (% intensity) 410.3913 (4) [M^+, 410.3913 calc. for $C_{30}H_{50}$], 395 (100), 367 (5), 327 (8), 299 (12), 271 (10), 231 (10), 205 (18), 189 (10), 121 (10), 109 (40), 95 (36).

Study of autoxidation of compounds 1, 10, 11, 12, 14 and 17 in $CDCl_3$ under conditions of natural illumination and temperature (see Table 4). 1 mg of each compound was prepared in $CDCl_3$ (0.6 ml) in an NMR tube which was left on a laboratory windowsill. ^1H NMR spectra for compounds **1** and **12**, which underwent rapid autoxidation, were taken at approximately 1 h intervals throughout the day. Spectra for **14** were acquired at daily intervals over a period of two weeks and spectra of **10**, **11** and **17** were acquired every 3-5 days over a period of 1-2 months. Normally 8-15 time points were used to calculate the rate of autoxidation to secondary and tertiary hydroperoxides. The rate of formation of tertiary hydroperoxides was calculated by plotting the natural logarithm of the ratio of the integrals in ^1H NMR spectra for the alkene proton in the starting material (**1**, H-24, δ 5.10, *t*, J=7.0 Hz; **10**, H-10, δ 5.01, *t*, J=7.0 Hz; **11**, H-10, δ 5.16, *t*, J=7.0 Hz; **12**, H-24, δ 5.10, *t*, J=7.0 Hz; **14**, H-24, δ 5.11, *tt*, J=7.1, 1.3 Hz; **17**, H-24, δ 5.10, *t*, J=6.9 Hz) to the integral of the alkene proton adjacent to the tertiary hydroperoxide in the autoxidation product (from **1**, H-24, δ 5.52, *d*, J=15.6 Hz; from **10**, H-10, δ 5.29, *d*, J=16.3 Hz; from **11**, H-10, δ 5.58, *d*, J=15.7 Hz; from **12**, H-24, δ 5.53, *d*, J=15.8 Hz; from **14**, H-24, δ 5.52, *d*, J=15.6 Hz; from **17**, H-24, δ 5.52, *d*, J=15.8 Hz) against hours of exposure to daylight. The rate of formation of the secondary hydroperoxides was calculated by plotting the natural logarithm of the ratio of the integral in ^1H NMR spectra for the alkene proton in the starting material (as above) to half the value of the integral of the terminal alkene protons of the secondary hydroperoxide autoxidation product (or in the case of compound **10** the full value of the proton geminal with the secondary hydroperoxide group) (from **1**, H-27, δ 5.03-5.01, *m*, [2H]; from **10**, H-10, δ 4.25, *t*, J= 7.1 Hz [1H]; from **11**, H-12, δ 5.04 *m*, [2H]; from **12**, H-27, δ 5.03-5.01, *m*, [2H]; from **14**, H-27, δ 5.03-5.01 *m* [2H]; from **17**, H-27, δ 5.03-5.01, *m*, [2H]) against hours of exposure to daylight. The rate of formation of diene **9** was calculated by plotting the natural logarithm of the ratio of the integral in ^1H NMR spectra for the alkene proton in starting material **1** (H-24, δ 5.10, *t*, J=7.0 Hz) to the integral of the methine alkene proton of the diene autoxidation product (**9**, H-24, δ 6.12, *d*, J= 15.6 Hz) against hours of exposure to daylight.

Study of autoxidation of 1 at different concentrations under conditions of controlled illumination and temperature (Figure 1). Samples of **1** were prepared in $CDCl_3$ (0.6 ml) in an NMR tube at various concentrations (0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, 5.0 mg, 7.5 mg). NMR tubes were placed in an incubator

with constant illumination (25.5 °C; 300 ft candles) and ^{1}H NMR spectra acquired at 30-60 min intervals. The rate of formation of secondary and tertiary hydroperoxides **2** and **3** and diene **9** was calculated as in the preceding section.

ACKNOWLEDGEMENTS

Dr. R. Saunders of the Department of Ecology and Biodiversity, The University of Hong Kong collected and identified the sample of *K. coccinea*. This research was supported by the CRCG.

REFERENCES

1. Cheung, S.C.; Li, .H. *Chinese Medicinal Herbs of Hong Kong*. 1991, The Commercial Press, Hong Kong. Vol 6, p.26.
2. (a) Li, L.-N.; Qi, X.-J.; Ge, D.-L.; Man, K. *Planta Med.*, **1988**, *54*, 45. (b) Li, L.-N.; Xue, H. *Phytochemistry*, **1990**, *29*, 2730. (c) Liu, J.-S.; Li, L.; Yu., H.-G. *Can. J. Chem.* **1989**, *67*, 682. (d) Liu, J.-S.; Li, L. *Phytochemistry* **1993**, *32*, 1293. (e) Liu, J.-S.; Li, L. *Phytochemistry*, **1995**, *38*, 241. (f) Liu, J.-S.; Li, L. *Phytochemistry*, **1995**, *38*, 1009. (g) Li, L.-N.; Xue, H.; Tan, R. *Planta Med.*, **1985**, *51*, 296.
3. (a) Li, L.-N.; Xue, H. *Planta Med.*, **1986**, *52*, 492. (b) Tan, R.; Xue, H.; Li,. L.-N. *Planta Med.*, **1991**, *57*, 87.
4. Zou, C.; Pu X.-Y.; Zhou, J. *Acta Bot. Yunnanica*, **1993**, *15*, 196.
5. a) Sy, L.-K.; Saunders, R.M.K.; Brown, G.D. *Phytochemistry*, **1997**, *44*, 1099. b) Sy, L.-K.; Brown, G. D. *Phytochemistry* **1998**, *48*, 1169.
6. Sy, L-K.; Brown, G.D. *Phytochemistry*, **1997**, *45*, 537.
7. Sy, L.-K.; Brown, G.D. *Mag. Res. Chem.*, **1997**, *35*, 424.
8. Baeckstrom, P.; Koutek, B.; Saman, D.; Vrkoc, J. *Biorg. Med. Chem.*, **1996**, *4*, 419.
9. Stolow, R.D.; Sachdev, K. *Tetrahedron*, **1965**, *21*, 1889.
10. Kabalka, G.W.; Varma M.; Varma, R.S. *J. Org. Chem.*, **1986**, *51*, 2386.
11. Seip, M.; Brauer, H.-D. *J. Am. Chem. Soc.*, **1992**, *114*, 4486.
12. (a) An, Y.-Z.; Viado, A.L.; Arce M.-J.; Rubin, Y. *J. Org. Chem.*, **1995**, *60*, 8330. (b) Mordi, R.C.; Walton, J.C.; Burton, G.W.; Hughes, L.; Ingold, K.U.; Lindsay, D.A.; Moffatt, D.J. *Tetrahedron*, **1993**, *49*, 911.
13. (a) Adam, W.; Brunker, H.-G.; Kumar, A.S.; Peters, E.-M.; Peters, K.; Schneider, U.; von Schnering, H.G. *J. Am. Chem. Soc.*, **1996**, *118*, 1899. (b) Adam W.; Nestler, B. *Tetrahedron Lett.*, **1993**, *34*, 611. (c) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6550. (d) Matsumoto, M.; Kobayashi, H.; Matsubara, J.; Watanabe, N.; Yamashita, S.; Oguma, D.; Kitano Y.; Ikawa, H. *Tetrahedron Lett.*, **1996**, *37*, 397. (e) Adam, W.; Peters, E.M.; Peters, K.; Prein M.; von Schnering, H.G. *J. Am. Chem. Soc.*, **1995**, *117*, 6686. (f) Adam W.; Prein, M. *Tetrahedron*, **1995**, *51*, 12583. (g) Adam W.; Prein, M. *J. Am. Chem. Soc.*, **1993**, *115*, 3766. (h) Adam W.; Prein, M. *Tetrahedron Lett.*, **1994**, *35*, 4331.
14. (a) Poon, T.H.W.; Pringle K.; Foote, C.S. *J. Am. Chem. Soc.*, **1995**, *117*, 7611. (b) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.*, **1990**, *112*, 6417. (c) Davis, K.M.; Carpenter, B.K. *J. Org. Chem.*, **1996**, *61*, 4617. (d) Stratakis M.; Orfanopoulos, M. *Tetrahedron Lett.*, **1995**, *36*, 4291. (e) Orfanopoulos M.; Stratakis, M. *Tetrahedron Lett.* **1991**, *32*, 7321.
15. (a) Adam, W.; Richter, M.J. *Tetrahedron Lett.*, **1993**, *34*, 8423. (b) Clennan, E.L.; Chen X.; Koola, J.;

J. Am. Chem. Soc. **1990**, *112* , 5193. (c) Delogu, G.; Fabbri, D.; Fabris, F.; Sbrogio, F.; Valle, G.; de Lucchi, O. *J. Chem. Soc. Chem. Commun.*, **1995**, 1887. (d) Linker, T.; Rebien F.; Toth, G. *J. Chem. Soc. Chem. Commun.*, **1996**, 2585. (e) Aubry, J.-M.; Mandard-Cazin, B.; Rougee M.;Bensasson, R.V. *J. Am. Chem. Soc.*, **1995**, *117*, 9159.

16. a) Zhu, Y.; Schuster, G.B. *J. Am. Chem. Soc.*, **1993**, *115*, 2190. (b) Orito, K.; Satoh, S.;Suginome, H. *J. Chem. Soc. Chem. Commun.*, **1989**, 1829. (c) Wu, Z.-Z.; Morrison, H. *Tetrahedron Lett.*, **1990**, *31*, 5865. (d) Orito, K.; Ohto, M.; Sugawara N.; Suginome, H. *Tetrahedron Lett.*, **1990**, *31*, 5921. e) Kaufman, M.D.; Grieco, P.A.; Bougie, D.W. *J. Am. Chem. Soc.*, **1993**, *115*, 11648.
17. Sheu, J.-H.; Huang, S.-Y.; Wang, G.-H.; Duh, C.-Y. *J. Nat. Prod.*, **1997**, *60*, 900.