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TOTAL SYNTHESIS OF VARIOUS ELEMANOLIDES

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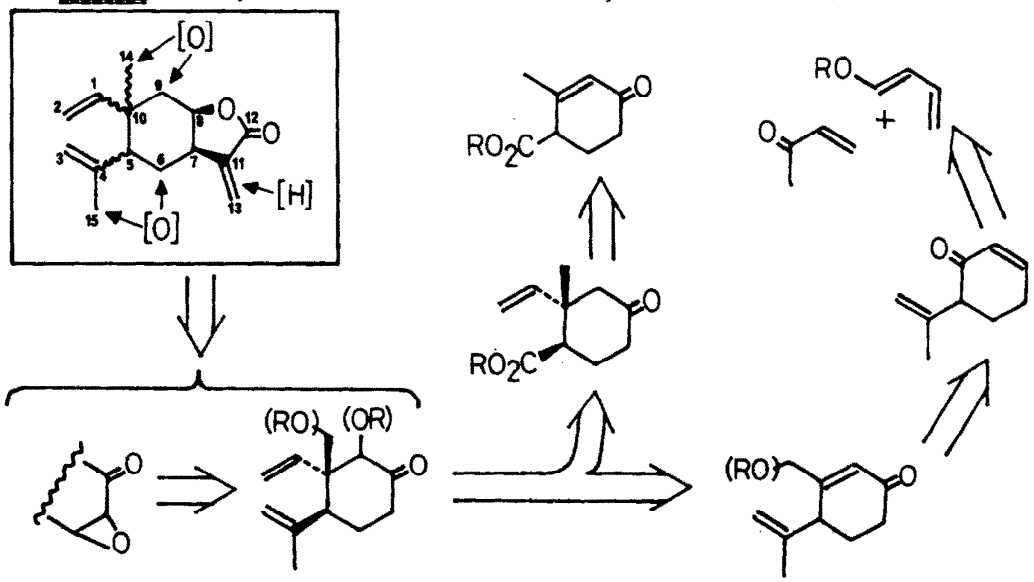
Abstract - Starting with a suitable substituted divinyl cyclohexanone, eleven naturally occurring 12.8-elemanolides bearing exo-methylene or methyl groups at C-11 and differing in substitution as well as in relative configuration, have been synthesized in racemic form. An approach to elemanolides with additional oxygen functionalities is principally possible by modification of the basic concept. Methods for the oxidative generation of terpenoid exo-methylene lactone and furan units are exemplified by synthesis of menthofuran and the *p*-menthenolides from isopulegols.

The plant family Compositae is rich in sesquiterpene lactones. Among other classes, also the elemanolides have now raised to a considerable number of representatives. In addition to vernolepin and related cytotoxic lactones [1], several 12.8-*cis*-elemanolides were reported mainly in the last ten years [2-9]. As shown in Scheme A, these compounds differ in the configuration at C-10 [10] and C-11 as well as in the oxygenation pattern at C-6, C-9, C-14 and C-15. As in some cases the assignment of their relative stereochemistry caused difficulties, a total synthetic approach to these lactones was desirable. Previous synthetic work was mainly focused on the synthesis of vernolepin [11] and related 12.6-*trans*-lactones [12].

SCHEME A: Retrosynthetic considerations for the synthesis of eleman-8.12-olides



Retrosynthetic considerations led to the proposal, that for the simpler members of this class lacking additional oxygen functions the known divinyl cyclohexanone 1 should be a suitable precursor, as it allows introduction of the essential C-7-substituent as an electrophile. Ketone 1 itself can be referred to a corresponding 3.4-disubstituted 2-cyclohexenone via conjugate addition of a vinyl unit. In course of this addition it also should be possible to introduce an additional C-9-function by enolate oxygenation. On the other hand, an additional C-14-function had to be present already in the enone precursor, which in either case could be obtained via a cycloaddition route. Generation of an additional C-6-function should be possible using a 6.7-epoxide derived from 1, the C-7-substituent having to be introduced as a nucleophile now. Finally, a regioselective allylic oxidation could serve for the functionalisation of C-15. These considerations are briefly outlined in Scheme A. Of course in all cases the stereochemistry, particularly of C-7 relative to that at C-10, had to be controlled.

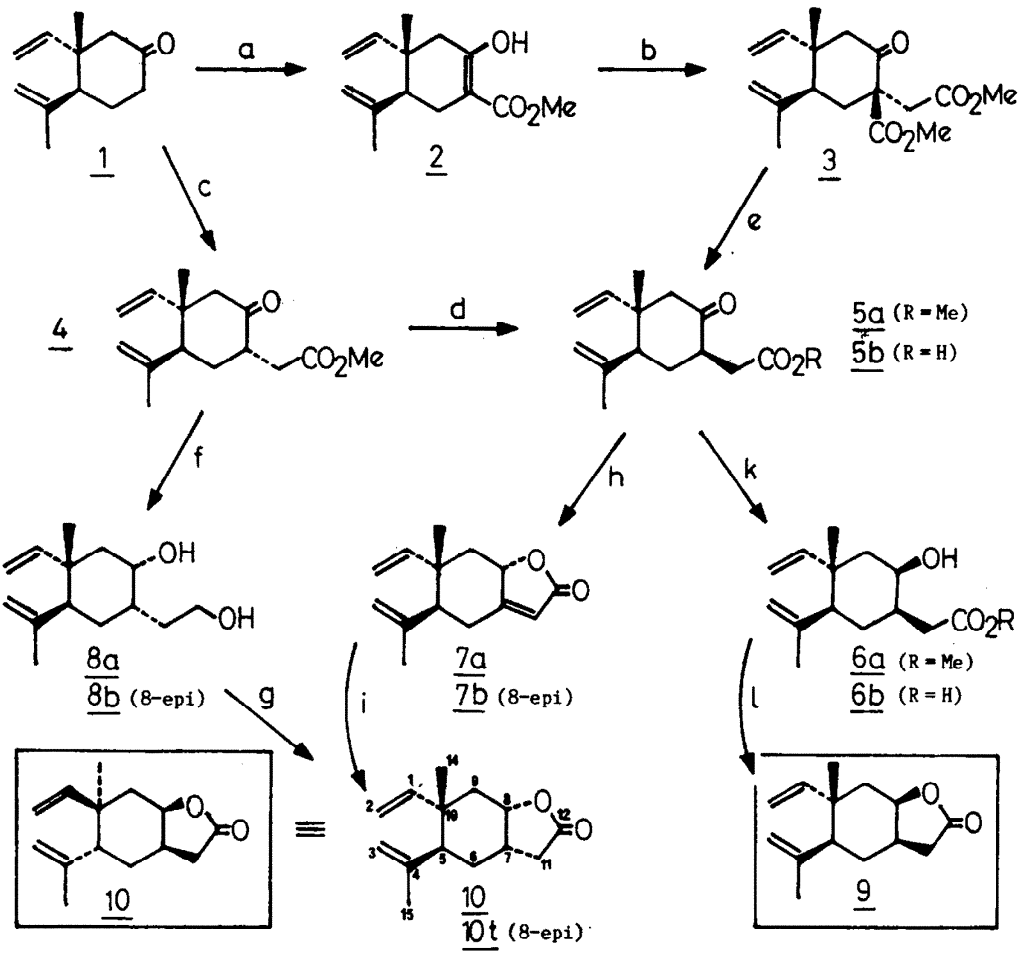
As a precursor for elemenone, ketone 1 has been prepared previously by different routes [13], the most convenient of these [13b] starting with the well known Hagemann ester [14]. A slight modification of the latter procedure raised the overall yield of 1 to 59%. For the transformation of 1 to the corresponding sesquiterpene lactones an additional C_3-unit is required. Since initial attempts to direct introduction (by alkylation of 1 or the related β-ketoester 2 with 2-bromo- or 2-oxo-propionate) were not very promising, a stepwise mode was chosen, which consists in methylation or methylenation respectively of preformed 13-nor-lactones obtained by coupling of 1 with a C_2-unit. Moreover, control of the final substitution and stereochemistry at C-11 respectively, seemed to be easier in this way.

Thus, 1 was transformed to the ketoester 4 by treatment with lithium diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) at -78°C followed by addition of methyl bromoacetate (Scheme B). As could be deduced from the ^{1}H-NMR-spectrum, only one product was obtained. The observed couplings (see Table 1) clearly indicated the presence of the kinetically controlled product 4, resulting from quasi-axial alkylation, but preferring a final conformation with axial H-7 and equatorial H-5. Complete conversion to the thermodynamically more stable epimer 5a occurred on treatment of 4 with methoxide in methanol, the observed couplings now being in agreement with an axial orientation of both H-5 and H-7. Reduction of 5a with lithium tri-tert-butoxyaluminum hydride (LATBH) gave a single hydroxyester 6a, which on heating with p-toluenesulfonic acid (p-TsOH) in benzene afforded nor-lactone 9 in 53% overall yield related to 1. This compound was also obtained by saponification of 6a and lactonisation of the resulting hydroxyacid 6b by heating in benzene without acid catalysis. Three small couplings of H-8 in compounds 6a/b and 9 verified that hydride had attacked specifically from the α-face.

Transformation of 1 into the bis-epimeric nor-lactone 10 proved to be more difficult. Initial attempts to reduce the keto group in 4 chemoselectively ($NaBH_4$ or LATBH at 0°C) afforded mixtures, obviously due to partial isomerisation at C-7. This isomerisation was completely suppressed by using diisobutylaluminum hydride (DIBAH) at low temperature, but these conditions led to a mixture of diols 8a and 8b (ca. 60:40 ratio), still epimeric at C-8, as could be deduced from their ^{1}H-NMR-spectra (see Table 1). Only slight different ratios of C-8-epimers were obtained by use of $LiAlH_4$, LATBH or even L-selectride at low temperatures. While diol 8a is smoothly converted to the desired cis-lactone 10 by Ag_2CO_3-oxidation [15], in the case of 8b only minor amounts of the corresponding trans-lactone 10t are produced besides a mixture of more polar products resulting from a fast initial C-8-oxidation. Thus, after Ag_2CO_3-oxidation of the diol mixture 8a/b ready purification of lactone 10 was possible, the overall yield of 29% from 1 being unsatisfactory, however.

An improved yield of 10 was obtained in a different approach starting from ketoacid 5b, obtainable by saponification of 5a, or simply by performing the C-7-isomerisation of 4 with aqueous base. Alternatively, condensation of 1 with dimethyl carbonate [16] and subsequent alkylation of the obtained β-ketoester 2 with methyl bromoacetate gave ketodiester 3 as a single diastereomer, the configuration at C-7 following from the observed nOe between H-5 and one of the side chain methylene protons. Saponification-decarboxylation of 3 then also led to ketoacid 5b by means of the already mentioned C-7-isomerisation. Heating of 5b with sodium acetate in acetic anhydride [17] afforded the

SCHEME B*: Synthesis of nor-lactones 9 and 10



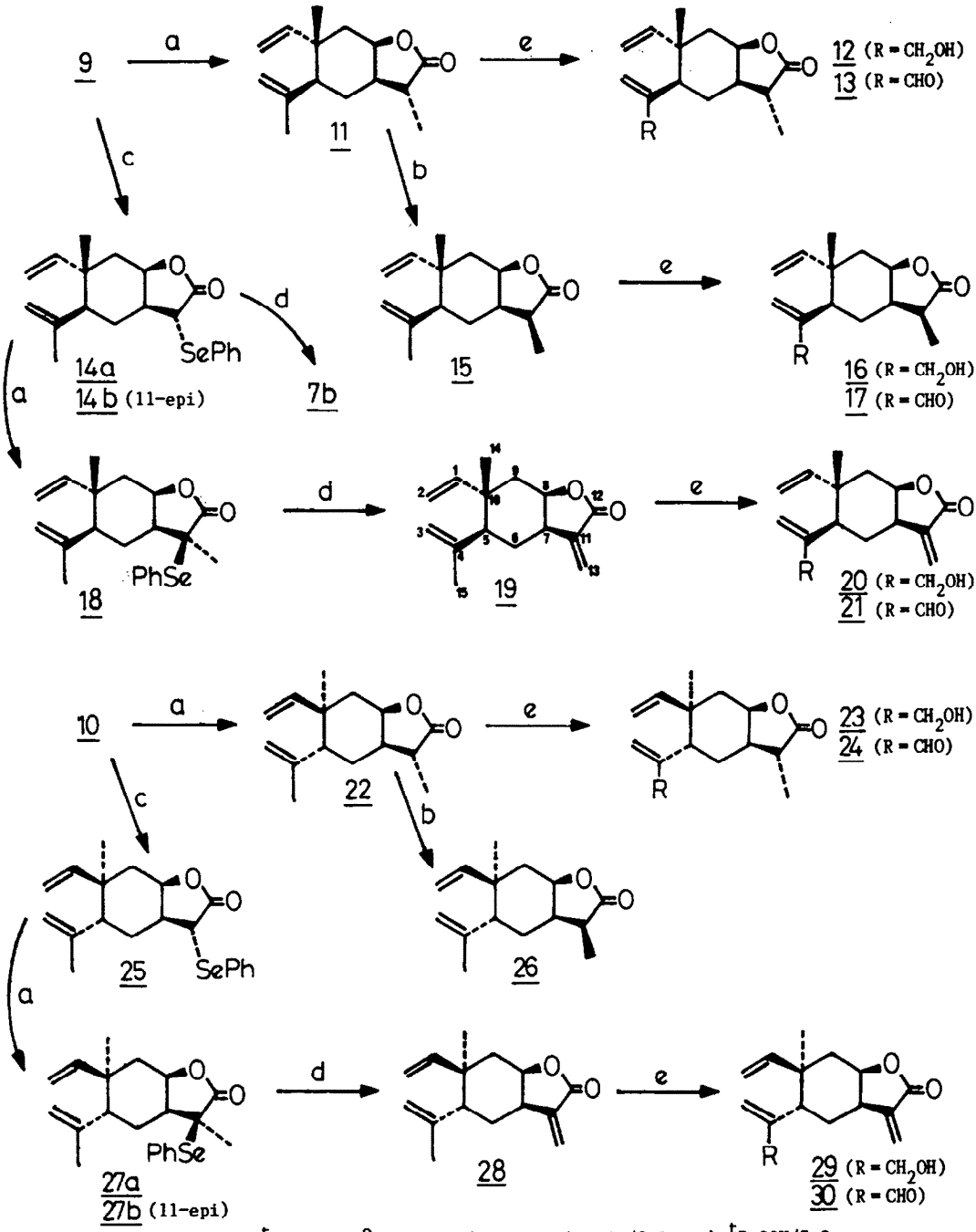
* Usual sesquiterpene numbering is used throughout this paper (cf. Scheme A)

a) NaH/Me_2CO_3 b) $NaH/BrCH_2CO_2Me$ c) $LDA/BrCH_2CO_2Me$ d) NaOMe or KOH e) $Ba(OH)_2$ f) DIBAH g) Ag_2CO_3 h) $NaOAc/Ac_2O$ i) DIBAH/[MeCu] k) LATBH l) $[H^+]$ or ΔT

thermodynamically more stable butenolide 7a in 50% overall yield related to 1 after separation from a small amount of epimer 7b formed as a byproduct. Assignment of stereochemistry was confirmed by the fact that 7b could be also obtained from the selenides 14a/b (vide infra) by oxidative elimination. Finally, conjugate reduction of 7a with DIBAH in the presence of methylcopper and HMPA [18] took place specifically from the less hindered α-side giving a virtually quantitative yield of the desired bis-epimeric nor-lactone 10. Thus, the precursors for several natural compounds of both diastereomeric series were obtained in good yields.

Methylation of the lithium enolates of 9 and 10 at low temperatures occurred stereoselectively from the α-side, affording the α-methyl lactones 11 and 22, respectively (Scheme C). The latter was identical with the natural lactone callitrin [4,6], while in the case of 11 only the C-11-epimer 15 had been isolated recently [8]. However, epimerisation of 11 could be achieved effectively. Thus, deprotonation of 11 followed by quenching with tert-butanol at -110°C afforded essentially pure epimer 15 which was identical with the natural lactone [8]. Similarly, lactone 22 could be epimerised to 26, although in this case even under optimized conditions only a partial conversion was achieved, the separation of 26 from recovered 22 being easy, however. The spectral data of 26 were superimposable with those of a third natural dihydrolactone [8].

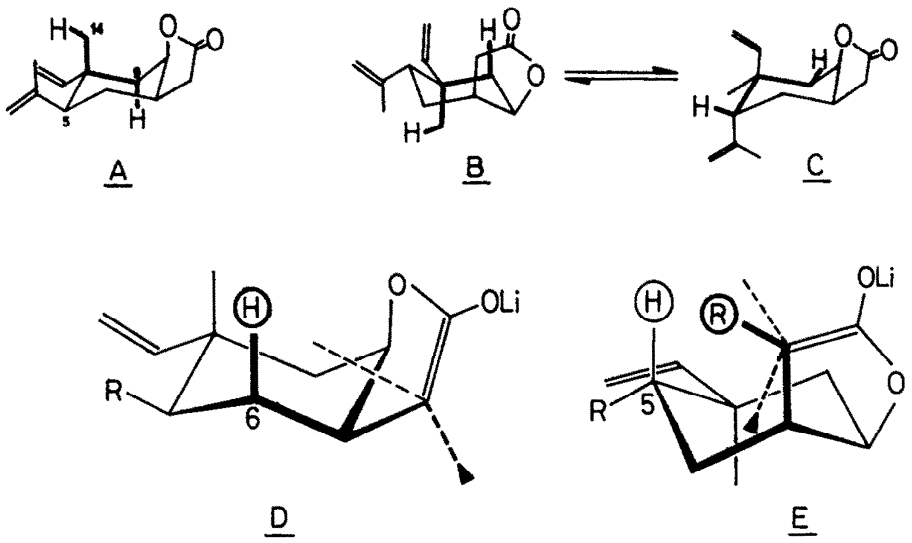
SCHEME C: Synthesis of eleman-8β,12-olides



a) LDA/MeI b) 1)LDA 2)^{t}BuOH/-110°C c) LDA/PhSeCl d) H_2O_2/SeO_2 e) ^{t}BuOOH/SeO_2

The transformation of 11 and 22 to the corresponding exo-methylene derivatives 19 and 28 should be possible via the phenylseleno derivatives [19]. However, in both cases the latter group had to be β-orientated to achieve the required regiospecific selenoxide syn-elimination. Reaction of the lithium enolate of 11 with phenylselenyl chloride afforded the undesired epimer 37 (vide infra) with an α-orientated phenylseleno group, as expected from the methylation results. Consequently, the desired isomer 18 was obtained by changing the order of the methylation and selenylation steps [20]. Oxidative elimination was performed with hydrogen peroxide in the presence of selenium dioxide, adapting conditions reported for the very fast oxidation of thioethers [21]. In this way a very smooth, high yield conversion to the exo-methylene lactone 19 was achieved, which was identi-

SCHEME D: Conformational behaviour of eleman-8β,12-olides



cal with the natural compound [5,6]. By an analogous sequence lactone 10 was transformed to the naturally occurring compound 28 [5,6]. Having sufficient amounts of 28 in hand, its identity with the previously isolated lactone igalan [22] of undefined stereochemistry could be established, though only a 60 MHz-^{1}H-NMR-spectrum was reported. It should be noted that 28 was recently identified as the most active component of a sesquiterpene lactone mixture isolated from a South American tree, and showing significant leaf cutter ant-repellent activity [23].

The stereochemical course of the various substitution processes agrees well with the preferred conformations of the parent compounds, which follow from the ^{1}H-NMR data, if one assumes similar conformational behaviour of the corresponding enolates (see Tables 3/5 and Scheme D). As followed from the observed couplings, all compounds derived from 9 are present in a chair conformation represented by A, with axial H-5, H-7 and 8-OR, an informative W-coupling always being observed between the axial 10-methyl and H-9α. The compounds related to 10 in most cases adopt the chair conformation represented by B, with axial H-5 and H-8, H-7 and H-9α being equatorial and the axial 10-methyl now showing a W-coupling to H-9β. However, with a large 11β-substituent present, a different conformation C is preferred with axial 8-OR and a W-coupling occuring between H-5 and H-9β, being both equatorial now. Inspection of models showed that these conclusions also explain the observed preference for α-attack on the derived enolates, as shown in D and E. However, in the case of derivatives of 10 bearing a large C-11-substituent, β-attack can compete, as the tetragonalisation at C-11 becomes sterically hindered presumably by influence of the axial H-5. This view can explain the formation of some 27b in the methylation of 25, as well as the finding that 22 could be only partially epimerised to 26.

Allylic oxidation of 11, 15, 19, 22 and 28 was achieved under the mild conditions developed by Umbreit and Sharpless [24], which recently have also been used in a partial synthesis of melitensin [12d]. Even in the presence of the exo-methylene double bonds, high yield regiospecific oxidation at C-15 was observed. The resulting alcohols 12, 16, 20, 23 and 29 were accompanied by varying amounts of the corresponding aldehydes, which could easily be separated from the alcohols. Complete conversion to these aldehydes occurs smoothly on treatment with active manganese dioxide. So far only two of the carbinols have been isolated from nature, the spectral data of synthetic 23 and 29 being identical with those of the natural compounds [7].

As compounds related to the lactones already synthesized, the butenolides 33a, 34 and 36a as well as the furan 35 are known as natural products. Also these elemane derivatives could be prepared (Scheme E) starting from ketoester 5a, which first was ketalised to 31. After methylation of the corresponding lithium enolate, subsequent hydrolysis and saponification afforded ketoacid 32 as

Table 1: ^{1}H-NMR data of compounds 2 - 10 (400 MHz, $CDCl_3$), δ-values and coupling-constants J (Hz)

	2	3	4	5a **	6a **	7a	7b	8a	8b	9	10	10t	multiplicity
H-1	5.79	5.84	5.72	5.85	5.76	5.73	5.88	5.82	5.78	5.75	5.78	5.77	dd
H-2 E	4.98	5.00	5.00	4.98	4.91	5.02	5.19	4.92	4.99	4.97	4.96	5.08	d
H-2 Z	4.97	4.94	4.96	4.91	4.89	4.98	5.22	4.91	5.01	4.95	4.93	5.09	d
H-3 E	4.88	4.97	5.03	4.92	4.83	4.99	4.85	4.84	4.88	4.86	4.90	5.00	br s
H-3 Z	4.76	4.76	4.91	4.66	4.61	4.72	4.73	4.60	4.83	4.61	4.67	4.84	br s
H-5	2.17	2.43	2.31	2.55	2.04	2.12	2.60 d	2.08	2.16	1.98	2.11	2.36	dd
H-6α	2.37 dd	2.06 dd	2.04	2.00	1.33	2.73 dd	2.78 dd	1.95	1.66	1.60 m #	2.02	1.77	ddd
H-6β	2.31 dd	2.80 dd	1.82	1.81	1.83	2.66 dd	2.76 d	1.50	1.50		1.69	1.71	ddd
H-7	----	----	3.07 dddd	2.95 dddd	1.99	----	----	2.16	1.75	2.44 dddd	2.86	2.38	ddddd
H-8	----	----	----	----	3.98	4.93 dd	4.95 dd	4.04	3.55	4.58	4.71	4.04	ddd
H-9α	2.08	2.67	2.52 s *	2.57	1.64 m	1.42	2.34	1.40	1.64	1.69	1.90	1.91	dd
H-9β	2.45 d	2.22 d		2.12 d		2.25	1.76	1.67	1.83	2.05	1.47	2.16	dd
H-11	----	3.09 d	2.73	2.79	2.50	5.76 s	5.78 s	2.03 dddd	1.65 dddd	2.72	2.55	2.46	dd
H-11'	----	2.83 d	2.24	2.21	2.35	----	----	1.52 dddd	1.54 dddd	2.30 d	2.41	2.17	dd
H-14	1.03	1.05	1.06	0.96	1.17	1.18	1.02	1.03	1.00	1.07	1.02	1.08	s
H-15	1.75	1.77	1.89	1.77	1.71	1.75	1.77	1.70	1.82	1.71	1.73	1.84	br s
CO_2Me	3.76 s	3.69 s 3.78 s	3.68 s	3.68 s	3.68 s		H-12 H-12'	3.80 3.82	3.76 3.62	---- ----	---- ----	---- ----	ddd ddd
5,6α	6.5	3.5	5.5	3.5	3	4.5	6.5	13.5	4.5	3	13.5	2	
5,6β	9	13	5	12.5	13	12.5	2	3	5	13	3.5	5.5	
7,6α	--	--	6	6	3.5	--	--	4	4	6.5	5.5	3.5	
7,6β	--	--	12.5	12.5	12	--	--	3	10.5	12.5	1.5	12	
7,8	--	--	--	--	3	--	--	5	9	5	7	11	
7,11	--	--	7	6.5	8	--	--	7	7.5	7	12.5	6	
7,11'	--	--	7	6	6.5	--	--	5	4.5	<1	8.5	12.5	
8,9α	--	--	--	--	3	11.5	6.5	4	10	4	6	12	
8,9β	--	--	--	--	3	6.5	12	12	4.5	2.5	11	4	
6α,6β	16	14.5	14	13	13	14	15	13.5	13.5	14	14	13.5	
9α,9β	18	13	14.5	13	14.5	12.5	13	13	13.5	15.5	13.5	12.5	
11,11'	--	16	16	16.5	15	--	--	14.5	14.5	16.5	17	15.5	

further couplings: all compounds: 1,2E = 10.5 - 11; 1,2Z = 17 - 17.5; 3E,3Z = 15, 3E = 1.5; 15,3Z = 5, 3Z < 1; compound 2: 6β,9β = 2; 6α,9α < 1; compound 3: 14,9α = 11,6β < 1; compound 4: 5,9β = 1; 7,9α < 1; compound 5a: 14,9α = 7,9α < 1; compound 6a: 8,6α < 1; compound 7a: 11,6β = 1; 8,11 = 1; 14,9α < 1; compound 7b: 5,9α = 8,6α = 8,11 = 1; 11,6α = 2; compound 8a: 11,12 = 5; 11,12' = 9.5; 11',12 = 5; 11',12' = 4; 12,12' = 10; 7,9α = 1; 14,9β < 1; compound 8b: 11,12 = 4.5; 11,12' = 9.5; 11',12 = 5; 11',12' = 4; 12,12' = 10.5; 5,9β < 1; compound 9: 14,9α < 1; compound 10: 14,9β < 1; cpd. 10t: 5,9β < 1;

* in C_6D_6: H-9 2.31 d, H-9 2.42 d; # in C_6D_6: H-6 1.12 ddd, H-6 1.35 ddd;

** the corresponding acids 5b and 6b show essentially identical spectra, differing only by some insignificant shifts and of course lacking the CO_2Me-singlets.

Table 2: ^{13}C-NMR data of compounds 1 - 8 and 42 (67.5 or 100 MHz, $CDCl_3$, δ-values)

	1	2	3	4	5a **	6a	7a	7b	8a	8b	42	
C-1	146.8	146.4	146.2	147.0	146.5	150.2	146.2	146.0	149.3	148.8	143.3	d
C-2	110.0	112.8*	111.6	112.8	111.1	110.3	112.0	113.2	110.2	111.3	113.0*	t
C-3	113.3	113.3*	114.3	113.6	113.4	112.4	114.0	114.3	112.8	113.2	114.0*	t
C-4	145.6	146.3	144.0	145.6	145.0	146.8	144.4	146.7	146.5	147.5	145.1	s
C-5	51.6	48.7	47.3	48.0	51.7	52.6	53.3	49.4	45.8	47.8	50.7	d
C-6	27.9	25.9	37.0*	34.8*	34.7*	37.3	30.1	30.4	32.9*	37.8*	28.2	t
C-7	41.2 t	96.3 s	59.8 s	43.5 d	46.6 d	39.1 d	173.4*s	173.3*s	39.0 d	39.2 d	40.4 t	
C-8	210.7 s	172.6 s	206.2 s	210.8 s	209.4 s	68.4 d	79.2 d	79.5 d	68.3 d	71.7 d	210.2 s	
C-9	53.6	41.5	50.4	48.5	53.4	45.7	45.9	39.0	42.7	42.1	48.2	t
C-10	44.1	38.7	44.6	44.3	44.8	39.4	40.6	40.5	41.3	40.3	47.0	s
C-11	--	--	33.9*t	32.8*t	33.6*t	28.3 t	112.8 d	113.7 d	30.3*t	32.5*t	--	
C-12	--	--	171.4*s	172.5 s	172.8 s	173.7 s	171.5*s	171.4*s	62.7 t	61.8 t	--	
C-14	17.6 q	19.1 q	18.0 q	23.9*q	17.2 q	19.1 q	17.0 q	27.8*q	17.8 q	26.1*q	71.0 t	
C-15	25.0	24.6	24.8	26.0*	24.9	24.5	24.6	25.8*	24.6	26.2*	25.1	q
OMe	--	--	52.0*q	51.8 q	51.7 q	51.5 q				OR	96.7 t	
CO_2Me	--	170.4 s	170.6*s	--	--	--					55.5 q	
	--	51.4 q	52.6*q	--	--	--						

* these assignments are ambiguous by pairs ** the corresponding acid 5b shows essentially identical shifts except C-12 (178.2 s), but is of course lacking the OMe-quartet.

Table 3: ^{1}H-NMR-data of eleman-8β,12-olides (400 MHz, $CDCl_3$), δ-values and coupling constants J

	11 **	13	15 **	17	22 **	24	26	19 **	21	28 **	30	multi-plicity
H-1	5.77	5.57	5.73	5.56	5.75	5.56	5.97	5.80	5.58	5.71	5.51	dd
H-2 E	4.97	4.86	4.96	4.86	4.95	4.85	4.95	4.99	4.88	4.94	4.85	br d
H-2 Z	4.95	4.80	4.94	4.97	5.05	4.77	4.99	4.97	4.82	4.89	4.77	br d
H-3 E	4.85	6.16 s	4.87	6.18 s	4.95	6.22 s	4.90	4.85	6.14 s	4.91	6.23 s	br s
H-3 Z	4.58	6.08 s	4.61	6.09 s	4.67	6.12 s	4.69	4.50	6.08 s	4.68	6.12 s	br s
H-5	1.96	2.86	1.95	2.86	} 2.05 m #	2.99	2.18	2.04	2.90	1.97 m ##	2.52	dd
H-6α	1.67	1.54	} 1.48 m *	1.41		2.09	1.60	1.76	1.60	2.17 m ##	2.22	ddd
H-6β	1.57	1.64		1.52	1.68 m #	1.62 dd	1.67	1.57	1.75	1.97 m ##	1.92	ddd
H-7	2.11	2.17 ddd	2.38	2.47	2.35 br ddd	2.36 br ddd	2.72	3.03 ddddd	3.05 ddddd	3.28 m ##	3.31 ddddd	dddd
H-8	4.69	4.74	4.48	4.52	4.65	4.67	4.66	4.48	4.57	4.80	4.82	ddd
H-9α	1.68	1.75	1.69	1.77	1.90	1.94	1.86	1.77	1.82	1.93	1.97	dd
H-9β	1.97	2.12	2.05	2.11	1.41	1.51	1.98	1.89	2.10	1.30	1.36	dd
H-11	2.41	2.43 q	2.81	2.84	2.56	2.66	2.78	----	----	----	----	dq
H-13	1.09	1.31	1.22	1.20	1.22	1.21	1.20	5.58	5.59	5.56	5.56	d
H-13'	----	----	----	----	----	----	----	6.17	6.16	6.34	6.38	d
H-14	1.05	1.01	1.07	1.00	1.03	0.98	1.00	1.03	1.00	1.05	0.99	s
H-15	1.69	9.38 s	1.72	9.38 s	1.73	9.39 s	1.76	1.69	9.38 s	1.72	9.40 s	br s
5,6α	3.5	3	2.5	3	14	14	5	3	3	12.5	14	
5,6β	13	13	13	13	4	4	7.5	13	13.5	4.5	4	
7,6α	6.5	7	6	6	6	6	7.5	7.5	7	6	6	
7,6β	12	12	12	12	1	1	6.5	11.5	11.5	2	1.5	
7,8	5	5	4	4	7.5	7	6	5.5	5	7.5	7.5	
7,11	2	<1	6.5	6.5	12	12.5	8	--	--	--	--	
11,13	7.5	7.5	7	7	7	7	7	--	--	--	--	
6α,6β	14	14	13.5	14	15	15	14.5	14	14	15	15	
9α,9β	15	15.5	15.5	15.5	13	13.5	15	15	15.5	13	13.5	

* in C_6D_6: H-6α 1.15 ddd, H-6β 1.33 ddd; # in C_6D_6: H-6α 1.50 ddd, H-6β 1.25 ddd, H-5 1.72 dd;

in C_6D_6: H-6α 1.55 ddd, H-6β 1.48 ddd, H-5 1.77 dd, H-7 2.56 ddddd;

** the corresponding 15-hydroxy compounds 12, 16, 23, 20 and 29 are characterised by a pair of broadened doublets (δ=4.04 and 3.95 ppm, J = 14 Hz for all compounds) replacing the H-15 methyl signals. The remaining signals appear essentially unchanged compared with the parent compounds, being only somewhat shifted in the following cases: H-3 E (+0.25 - 0.35 ppm), H-3 Z (+0.20 - 0.30 ppm), H-5 (ca. +0.05 ppm), H-1 (ca. -0.05 ppm; in 29: -0.15 ppm), H-13 (+0.20 ppm in 12, -0.07 ppm in 16) and H-9β (+0.06 ppm in 12 and 20). All couplings are unchanged except: 3E,3Z=1 Hz.

further couplings: all compounds: 1,2E = 10.5 - 11; 1,2Z = 17 - 17.5; 2E,2Z$\leq$1; compounds 11, 15, 19, 22, 26 and 28: 3E,3Z = 15,3E = 1.5; 15,3Z = 5,3Z<1; compound 19: 7,13 = 7,13' = 1.5; compound 21: 7,13 = 7,13' = 1; compound 28: 7,13 = 3; 7,13' = 3.5; compound 30: 7,13 = 7,13' = 3.5; compounds 11, 13, 15, 17, 19 and 21: 14,9α<1; compounds 22, 24, 28 and 30: 14,9β<1; compound 26: 5,9β<1; compound 30: 7,9β<1; compound 28: 7,9α = 8,13'<1;

Table 4: ^{13}C-NMR-data of eleman-8β,12-olides and of nor-lactones 9, 10 and 10t (67.5 or 100 MHz, $CDCl_3$, δ-values)*

	9	10	10t	11	12	15	16	22	23	26	19	20	28	29
C-1	148.4	147.4	148.1	148.4	147.9	148.8	148.1	147.5	146.7	148.4	148.0	147.6	147.3	146.7
C-2	110.8	110.9	112.1	111.1	112.0	111.2	111.9	110.0	111.5	110.9	111.2	112.0	111.0	111.8
C-3	112.6	113.1	113.9	112.7	111.9	113.0	112.0	113.2	111.6	112.6	112.8	111.9	113.0	111.6
C-4	145.9	145.5	146.1	146.1	150.0	146.6	150.3	145.5	149.1	146.6	145.9	149.8	145.7	149.3
C-5	49.4	45.8	48.4	49.4	44.5	49.8	44.5	46.3	41.0	46.8	48.9	43.9	46.0	41.2
C-6	28.9	27.2	28.9	29.5	30.0	24.5	25.1	26.5	26.9	24.0	30.1	30.5	26.5	27.1
C-7	35.3	34.0	39.1	42.4	42.5	40.3	40.2	42.0	41.8	35.2	40.1	40.2	39.1	39.2
C-8	78.8	77.3	82.3	76.6	76.6	77.3	77.2	75.6	75.3	77.6	76.1	76.0	75.8	75.6
C-9	39.6	40.7	37.8	39.8	39.8	39.9	39.6	41.2	40.8	38.0	40.0	39.8	42.8	42.5
C-10	38.3	39.6	41.1	38.6	38.5	38.8	38.7	40.0	39.8	37.9	38.3	38.2	39.6	39.6
C-11	37.6	31.5	35.8	43.7	43.9	41.7	41.6	35.7	35.4	39.6	141.0	141.0	137.3	137.0
C-12	176.8	176.6	176.6	180.0	180.0	179.4	179.3	179.3	179.3	179.6	170.5	170.5	170.5	170.4
C-13	----	----	----	14.3	14.3	9.2	9.1	13.4	13.2	10.6	120.8	120.9	120.3	120.5
C-14	17.8	16.5	27.9	18.6	17.9	18.0	17.3	16.3	15.6	23.3	19.2	18.3	16.4	15.9
C-15	24.4	24.8	26.4	24.5	67.4	24.6	67.5	24.9	67.2	25.8	24.4	67.2	24.8	67.4

* all assignments in this table have been proved in ambiguous cases by selective decoupling or GATED-, INEPT- and heteronuclear 2D-shift correlation experiments.

Table 5: ^{1}H-NMR-data of phenylseleno lactones (400 MHz, C_6D_6), δ -values and coupling-constants J

	14a	14b	18	37	25	27a	27b	multiplicity
H-1	5.50	5.55	5.63	5.56	5.54	5.78	6.06	dd
H-2 E	4.89	4.90	4.93	4.92	4.86	4.93	4.95	d
H-2 Z	4.81	4.84	4.87	4.85	4.75	4.92	4.91	d
H-3 E	4.83	4.85	4.88	4.83	4.89	4.97	4.81	br s
H-3 Z	4.49	4.55	4.63	4.50	4.56	4.72	4.52	br s
H-5	1.47	1.57	1.65	1.55	1.66	2.57	2.03	dd
H-6α	1.12	1.70	1.81	1.25	1.41	1.62	1.49	ddd
H-6β	1.35	1.64	1.99	1.43	1.73	1.87 br dd	1.31	ddd
H-7	1.91 br ddd	1.88 dddd	1.70	1.85	2.16 dddd	2.14 br dd	2.38	ddd
H-8	4.42	3.81	4.07	4.87	3.90	4.29	4.69	ddd
H-9α	1.10	1.18	1.29	1.62	1.54	1.89	1.37	dd
H-9β	1.78	1.83	1.88	1.91	1.03	2.28	1.81	dd
H-11	3.55 br s	3.96	----	----	3.29	----	----	d
H-13	----	----	1.37	1.55	----	1.37	1.50	s
H-14	1.05	1.07	1.04	1.08	0.57	0.77	0.78	s
H-15	1.56	1.60	1.64	1.60	1.59	1.74	1.55	br s
PhSe-o	7.67	7.67	7.94	7.74	7.79	7.80	7.75	m (2H)*
-m/p	7.05	7.05	7.08	7.09	7.01	7.08	7.06	m (3H)**
5,6α	2.5	3	2.5	2.5	13.5	14	4	
5,6β	13	12	13	13	3.5	4.5	8.5	
7,6α	6.5	6	6.5	6	6	8	7	
7,6β	12	11	13	12	1	<1	6.5	
7,11	<1	6	—	—	13	--	—	
7,8	4.5	4	4.5	4.5	8	8.5	6	
8,9α	4	4	4.5	2	6	6.5	4.5	
8,9β	2.5	2	4.5	4.5	11	12	5	
6α,6β	14	13	13.5	13	14.5	15.5	15	
9α,9β	15	15.5	15	15.5	13.5	13	15	

* width ca. 20 Hz

** width ca. 40 Hz

further couplings: all compounds: 1,2E = 10.5 - 11; 1,2Z = 17 - 17.5; 2E,2Z = 1; 3E,3Z = 15,3E = 1.5; 15,3Z = 5,3Z <1; compound 14a: 14,9α = 11,6α = 11,9β <1; compounds 14b, 18 and 37: 14,9α <1; compounds 25 and 27a: 14,9β <1; compound 27b: 5,9β <1;

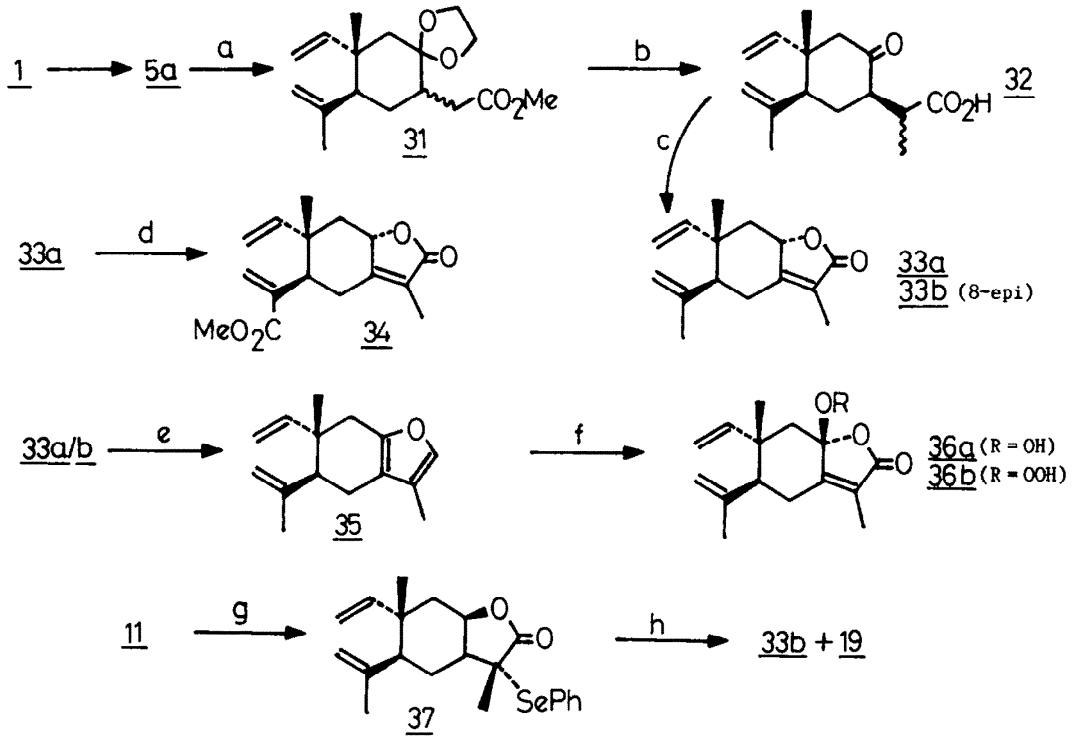
Table 6: ^{1}H-NMR-data of compounds 33 - 36 (400 MHz, $CDCl_3$), δ -values and coupling-constants J

	33a	33a*	33b *	34	35	36a	36b	multiplicity
H-1	5.73	5.43	5.41	5.63	5.88	5.70	5.69	dd
H-2 E	5.00	4.84	4.88	4.92	4.97	5.00	5.00	d
H-2 Z	4.97	4.75	4.80	4.89	5.00	4.97	4.97	d
H-3 E	4.99	4.89	4.64	6.32 s	4.87	4.98	4.99	br s
H-3 Z	4.73	4.53	4.53	5.53 s	4.76	4.74	4.74	br s
H-5	2.04	1.59	2.15 d	2.68	2.30 t	2.05	2.07	dd
H-6α	2.67	2.15	2.04 d	2.95	2.42 d	2.56	2.58	dd
H-6β	2.55	1.84	2.20	2.57		2.72	2.68	dd
H-8	4.83	4.25	4.45	4.84	----	----	----	br dd
H-9α	1.33	0.98	1.97	1.41	2.37 d	1.76 d	1.75 d	dd
H-9β	2.20	1.86	1.48	2.23	2.68 d	2.14 d	2.24 d	dd
H-12	----	----	----	----	7.06	----	----	br s
H-13	1.83	1.67	1.68	1.83	1.93	1.83	1.87	br s
H-14	1.17	0.72	0.74	1.09	1.07	1.27	1.22	s
H-15	1.76	1.55	1.42	----	1.75	1.77	1.77	br s
				CO_2Me 3.71 s		3.01 OH	8.42 OOH	br s
5,6α	4		7.5	4	7	3.5	3.5	
5,6β	13.5		<1	14		13	13	
8,9α	11.5		6	11.5	--	--	--	
8,9β	6		11.5	6	--	--	--	
6α,6β	14		14.5	13.5	--	13.5	13.5	
9α,9β	12		12.5	12.5	16	14	14.5	

further couplings: all compounds: 1,2E = 10.5 - 11; 1,2Z = 17 - 17.5; 2E,2Z ≤1; compounds 33a/b, 35 and 36a/b: 3E,3Z = 15,3E = 1.5; 15,3Z <1; compound 33a: 8,13 = 8,6β = 13,6β = 1.5; 14,9α <1; compound 33b: 8,13 = 8,6α = 13,6α = 1.5; 5,9α = 1; compound 34: 13,8 = 13,6β = 1.5; 8,6β = 1; 14,9α <1; compound 35: 12,13 = 1; 6,9β ≈1.5; 6,9α ≈1; compounds 36a/b: 13,6β = 1.5; 14,9α <1;

* in C_6D_6

Scheme E: Synthesis of butenolide- and furan-type compounds



a) 2-methoxy-1.3-dioxolane/$[H^+]$ b) 1)LDA/MeI 2)H_3O^+ 3)HO^- c) NaOAc/Ac_2O d) 1)$^tBuOOH/SeO_2$ 2)MnO_2 3)CrO_3/ H^+ 4)CH_2N_2 e) 1)DIBAH 2)H_3O^+ f) $O_2/[PtO_2]$ g) LDA/PhSeCl h) H_2O_2/SeO_2

a mixture of C-11-epimers. A temporary loss of stereochemical integrity at C-7 observed in the ketalisation step was compensated by the equilibrating conditions of the saponification. By heating with sodium acetate in acetic anhydride, ketoacid 32 was transformed to an unexpectedly unfavorable mixture of butenolides 33a and 33b (ca. 60:40 ratio). After separation of this mixture, it could be shown that the spectroscopic data of 33a were identical with those of natural isogermafurenolide [25]. Confirmation of the stereochemistry assigned to 33a and 33b was gained from the identity of 33b with a butenolide obtained by selenoxide elimination from the already mentioned selenylation product 37 of lactone 11. By allylic oxidation of 33a, subsequent Jones oxidation and esterification with diazomethane, compound 34 was obtained, its spectral data being identical with those of natural desoxysericealactone [26]. Reduction of the butenolide mixture 33a/b with DIBAH followed by acid treatment [27] afforded furan 35, its spectral data being identical with those of isofuranogermacrene [28]. Finally, by stirring a solution of 35 under oxygen in the presence of platinum dioxide [26], low yields of 36a and the corresponding hydroperoxide 36b were obtained, the spectral data of 36a being identical with those of hydroxyisogermafurenolide [25]. Assignment of stereochemistry was confirmed by the observed nOe between 10-methyl and OH in 36a, and the fact that 36b was immediately transformed to 36a by reduction with triphenylphosphine.

With regard to the introduction of further oxygen functions into the elemane skeleton, a number of model reactions were undertaken following the considerations mentioned in the beginning. At first, a C-14-function can be established in the course of an alternative approach to the required divinyl cyclohexanone precursor (Scheme F). Thus, cyclohexenone 39 was prepared by cycloaddition of diene 38 [29] and methyl vinyl ketone (100°C, neat), followed by Wittig olefination and Jones oxidation [30]. It should be mentioned that an analogous sequence allows the convenient preparation of isopiperitenones, which are valuable synthetic intermediates [31]. Thus isopiperitenone 47 [32] and its derivative 48 were obtained, starting with diene 46 [33] and methyl vinyl ketone or methoxymethyl vinyl ketone [34], in 51% (47) and 48% (48) overall yield from diene 46, respectively. Reaction of enone 39 with the lithio derivative 40 [37] followed by Jones oxidation afforded enone 41, which by

Table 7: ^{1}H-NMR-data of compounds 1, 42 - 45 and 49 - 52 (400 MHz, $CDCl_3$), δ-values and coupling constants J

	1 *	42 **	44	45b	49 ***	50	51	52	multiplicity
H-1	5.61	5.63	5.90	5.81	5.84	5.86	5.85	5.81	dd
H-2 E	4.84	4.94	5.06	5.18	4.98	5.00	5.00	4.93	d
H-2 Z	4.75	4.82	5.08	5.13	4.92	4.98	4.94	4.91	d
H-3 E	4.88	4.96	} ##	4.94	4.94	5.08	5.09	5.03	br s
H-3 Z	4.54	4.75		4.70	4.67	4.79	4.71	4.78	br s
H-5	1.97	2.06	1.89	2.12	2.68	3.03	2.82 s	2.45 br s	dd
H-6α	1.48	1.56	1.55 dd	} 1.68 m #	1.97 ddd	} 6.70 dd	----	----	dddd
H-6β	1.66	2.14	1.42 dd		2.47 ddd		3.55 d	3.27 br d	dddd
H-7α	1.89 ddd	1.97 ddd	2.37	2.50	----	----	----	----	ddddd
H-7β	2.25	2.38	----	----	3.22 ddd	} 6.05 dd	3.30 br d	3.19 d	dddd
H-8	----	----	4.68	4.65	----	----	----	4.28 dd	ddd
H-9α	2.07 d	2.13 d	2.33	1.62	3.32 d	} 2.45 s	2.87 d	1.78	dd
H-9β	2.11	2.56	1.67	2.52	1.89		1.86 br d	1.45	dd
H-11	----	----	2.82	2.75	----	----	----	----	dd
H-11'	----	----	2.24	2.31	----	----	----	----	dd
H-14	0.87 s	3.66	3.75	3.80	0.99 s	1.05 s	0.96 s	1.04 s	d
H-14'	----	3.41	3.57	3.65	----	----	----	----	d
H-15	1.62	1.69	##	1.76	1.76	1.85	1.84	1.83	br s
5,6α	3.5	3	5.5	3	3.5	} 4	----	----	
5,6β	13	12	13	13	13.5		<1	1	
6α,7α	7	6.5	4	6	----	} 10	----	----	
6α,7β	2.5	3	----	----	2		----	----	
6β,7α	13.5	11	13	12	----		----	----	
6β,7β	4.5	5	----	----	5.5		4	3.5	
8,9α	----	----	7	4	----	----	----	6	
8,9β	----	----	10.5	4	----	----	----	6	
6α,6β	14	13	13.5	14	14.5	----	----	----	
9α,9β	13.5	14	13.5	15	14	----	----	14	
14,14'	----	9.5	9	11	----	----	----	----	

* in C_6D_6; ** in C_6D_6; OCH_2OMe: 4.42 AB-m (2H) and 3.24 s (3H); *** SMe: 2.05 s (3H);
\# in C_6D_6: H-6α 1.05 ddd, H-6β 1.35 ddd; ## H-3 / H-15: 1.28 s and 1.18 s;

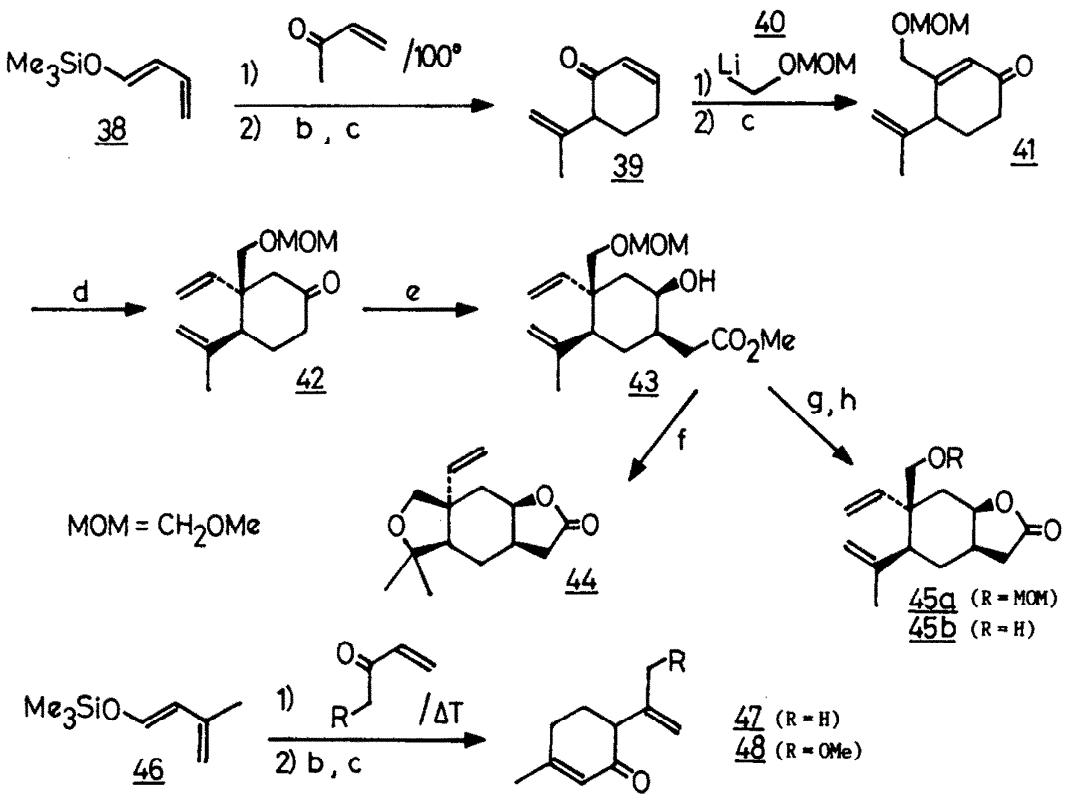
further couplings: all compounds: 1,2E = 10.5 - 11; 1,2Z = 17 - 17.5; 2E,2Z $\leq$ 1;
all compounds except 44: 3E,3Z = 1.5 - 2; 15,3E = 1.5; 15,3Z = 5,3Z < 1; compound 1: 7α,7β = 14; 7β,9β = 2; 7α,9α = 14,9α < 1; compound 42: 7α,7β = 14.5; 7β,9β = 2; compound 44: 7,8 = 7.5; 7,11 = 9.5; 7,11' = 2.5; 11,11' = 18; compound 45b: 7,8 = 4.5; 7,11 = 7; 7,11' = 1; 11,11' = 17; 14',9α < 1; compound 49: 7,9β = 1.5; 14,9α < 1; compound 50: 5,7 = 2; compound 51: 7,9β = 1; 5,7 = 14,9α < 1; compound 52: 6,8 = 7,8 = 14,9α < 1;

Table 8: ^{13}C-NMR-data of compounds 33 - 36, 44, 45b and 49 - 52 (67.5 or 100 MHz, $CDCl_3$, δ-values)

	33a	33b	34	35	36a	36b	44	45b	49	50	51	52	
C-1	146.5	146.2	144.9	147.0	147.4	147.1	144.5	144.5	146.5	146.1	146.0	148.2	d
C-2	111.8	113.1	112.5	110.9	112.0	112.3	112.1	113.9 *	111.2	112.5	112.1	110.8	t
C-3	113.9	113.9	125.4	112.7	114.2	114.4	**	114.0 *	113.5	116.4	115.8	114.9	t
C-4	144.8	147.1	140.8	147.1	144.7	144.5	83.1	145.6	145.1	142.4	143.1	144.5	s
C-5	52.9	49.4	44.8	49.9	54.2	54.0	51.5	49.1	46.6	52.7	51.1	50.4	d
C-6	28.3 t	28.6 t	27.7 t	24.1 t	27.1 t	27.2 t	26.8 t	29.4 t	33.3 t	150.6 d	61.3 d	56.9 d	
C-7	161.9 s	161.9 s	160.9 s	116.4 s	160.1 s	157.1 s	32.0 d	35.0 d	52.4 d	128.6 d	54.9 d	55.3 d	
C-8	77.9 d	78.1 d	77.5 d	149.4 s	102.8 s	108.5 s	77.2 d	78.8 d	207.2 s	199.2 s	206.2 s	64.2 d	
C-9	45.7	39.2	45.3	36.1	49.3	45.7	34.8 *	37.5	48.0	47.5	47.1	38.7	t
C-10	40.8	40.7	40.8	40.1	40.6	40.4	48.1	42.9	44.3	42.4	45.3	36.7	s
C-11	120.1 s	120.7 s	120.7 s	119.3 s	122.0 s	124.2 s	33.5 t*	32.5 t	—	—	—	—	
C-12	174.7 s	174.7 s	174.5 s	137.1 d	171.9 s	171.7 s	176.6 s	176.6 s	—	—	—	—	
C-13	8.2	8.3	8.3	8.1	8.2	8.3	—	—	—	—	—	—	
C-14	17.0 q	27.9 q	15.0 q	19.4 q	17.7 q	17.8 q	76.9 t	63.5 t	17.1 q	22.5 q*	20.3 q	24.2 q	
C-15	24.7 q	25.3 q	167.9 s	25.4 q	24.4 q	24.4 q	**	24.6 q	25.1 q	24.5 q*	25.2 q	25.7 q	
		OMe	52.1 q					SMe	15.2 q				

* these assignments are ambiguous by pairs ** C-3 / C-15: 28.2 q and 22.9 q

SCHEME F: Approach to 14-oxygenated eleman-8β,12-olides



b) $Ph_3P{=}CH_2$ c) CrO_3/H^+ or PCC d) Vinyl-MgBr/$[CuI{\cdot}P(NEt_2)_3]$ e) 1)LDA/$BrCH_2CO_2Me$ 2)NaOMe 3)$LiAlH(O^tBu)_3$ f) $[H^+]$ g) 1)KOH 2)ΔT h) $[H^+]$/MeOH

treatment with vinyl magnesiumbromide in the presence of $CuI / P(NEt_2)_3$ [38] afforded the desired functionalised divinyl ketone 42 with virtually complete stereoselectivity [39]. Transformation of 42 to the corresponding nor-lactone 45a was now tried, in analogy to the preparation of 9 from 1. However, application of the acid catalysed conditions for lactonisation of hydroxyester 43, which was obtained from 42 by alkylation, epimerisation and reduction, led to the exclusive formation of compound 44 (42% yield from 42) by simultaneous deprotection and cyclisation. Hence, lactone 45a was prepared via saponification of 43 and lactonisation of the resulting hydroxyacid in refluxing benzene. While no formation of cyclisation product 44 was observed under these conditions, attempts at subsequent removal of the protecting group from 45a (pyridinium p-toluenesulfonate [40]/ methanol, thiophenol/BF_3-etherate [41]) led again to substantial formation of 44. Best results were finally obtained by refluxing 45a in methanol containing a trace of aqueous HCl, giving hydroxylactone 45b in only 27% yield from ketone 42, however. An improvement of this approach to C-14-oxygenated elemane derivatives should be possible by choice of a more suitable protection group. In connection with an allylic oxidation at C-15 followed by lactonisation, also compounds of the 14,15-δ-lactone type should be accessible avoiding the usual exo-methylenation step of a preformed 15-nor-δ-lactone unit [56].

As a precursor for 6α-oxygenated eleman-8,12-olides, epoxy alcohol 52 was prepared from ketone 1 (Scheme G). Transformation of 1 to the α-methylthio derivative 49 [42], subsequent oxidation [21] and elimination afforded enone 50, which by alkaline epoxidation gave epoxy ketone 51 by exclusive attack from the less hindered α-side. Reduction of 51 with sodium borohydride in the presence of cerium trichloride [43] afforded 52 with almost complete stereoselectivity. The further transformation of 52 to the naturally occuring lactones zempoalin A / B 53a/b [3] via nucleophilic epoxide opening has been realised meanwhile [44].

Table 9: ^{1}H-NMR-data of p-menthane derivatives (400 MHz, $CDCl_3$), δ-values and coupling constants J

	55a	55b	56a	56b	57a	57b	58a	58b	59a	59b	60	61	62	multiplicity
H-1	1.87	##	2.09	1.96	1.90	2.18	2.45	2.68	2.36 ddddd	2.83 ddddd	2.95 dd	##	——	ddd
H-2	3.45	3.98	4.79	5.25	3.49	3.96	3.56	3.96	3.73	4.51	——	4.32 dd	——	ddd
H-3α	0.94	1.11	1.02	1.16	0.99	1.18	1.05	1.29	1.34	1.29	2.04	1.05	2.16 dddd	ddd
H-3β	2.03	1.97	1.99	1.91	1.98	1.80	2.05	##	2.26 ddd	2.18	2.41 ddd	1.87	2.65 dd	dddd
H-4	1.47	##	1.55	##	1.50	##	1.55	##	1.54	1.63	##	1.80	1.92	ddddq
H-5α	0.90	0.92	0.95	0.99	0.91	0.97	0.99	1.05	1.12	0.97	##	0.91	1.35	dddd
H-5β	##	##	##	1.79 dddd	1.65	##	##	##	1.84 dddd	1.65	1.91	1.73	1.83	ddddd
H-6α	##	1.44 ddddd	##	1.57 ddddd	1.69	1.44 ddddd	##	1.41	2.11	1.84	2.04	##	2.39 ddddd	dddd
H-6β	1.30	##	1.38	##	1.32	##	1.37	##	1.36	1.35	1.78	##	2.31	dddd
H-8	1.69	1.78	1.76	1.74	4.07 br d	4.11 br d	9.58 s	9.53 s	——	——	1.74	2.80 d	7.04	br s
H-8'	——	——	——	——	4.01	4.05	——	——	——	——	——	2.49 d	——	br d
H-9 E	4.88	4.95	4.73	4.77	5.05	5.17	6.36 s	6.38 s	5.38 d	5.52 d	4.93	1.40 s	1.93	br s
H-9 Z	4.84	4.78	4.72	4.67	4.90	4.99	6.12 s	6.14 s	6.06 d	6.09 d	4.71	——	——	br s
H-10	0.91	0.86	0.93	0.89	0.93	0.89	0.97	0.92	1.04	0.94	1.01	0.87	1.08	d
Ac	——	——	1.98	1.99	——	——	——	——	——	——	——	——	——	s
##	1.61 -1.72	1.64 -1.86	1.65 -1.75	1.62 -1.77	——	1.73 -1.86	1.65 -1.75	1.75 -1.92	——	——	1.84 -1.98	1.37 -1.57	——	m

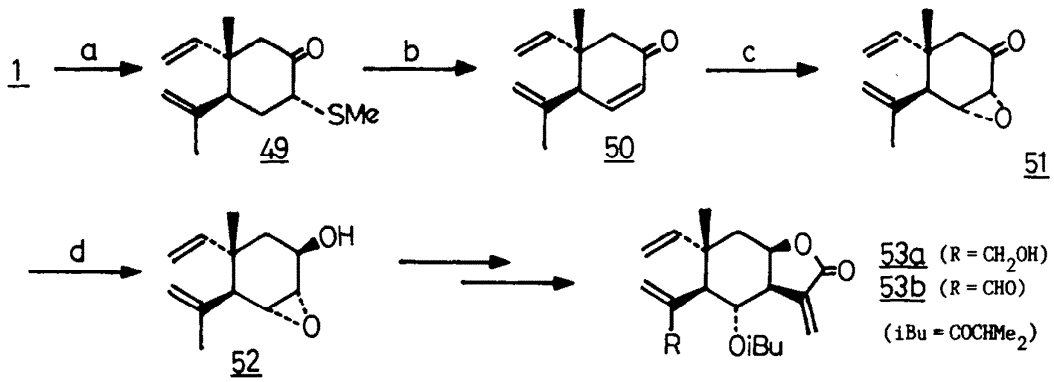
J (Hz): compounds 55a, 56a, 57a, 58a: 3α,3β = 1,6β = 4,3α = 12 - 12.5; 1,2 = 2,3α = 10.5; 4,10 = 6.5; 2,3β = 4.5; 4,3β = 1,6α = 3.5; 3β,5β = 2; compounds 55b, 56b, 57b, 58b, 61: 4,3α = 1,6β = 12 - 12.5; 3α,3β = 14; 4,10 = 6.5; 2,3β = 4,3β = 1,6α = 3.5; 1,2 = 2,3α = 2.5; 3β,5β = 2; 2,6α = 1; compounds 57a, 57b: 8,8' = 12.5; compound 61: 8,8' = 4.5; 9,8 < 1; compound 59a: 3α,3β = 15; 4,3α = 12; 1,2 = 1,6β = 2,3α = 11; 4,10 = 6.5; 2,3β = 4,3β = 3.5; 1,6α = 1,9E = 1,9Z = 3; 3β,5β = 1; compound 59b: 3α,3β = 15; 4,3α = 1,6β = 12; 4,10 = 6.5; 1,6α = 6; 1,2 = 5; 2,3α = 4; 4,3β = 3.5; 2,3β = 3; 3β,5β = 2; 1,9E = 1,9Z = 1; compound 60: 3α,3β = 13.5; 1,6β = 4,5α = 13; 4,3α = 12.5; 4,10 = 6.5; 1,6α = 5.5; 4,3β = 4; 4,5β = 3.5; 3β,5β = 2; 1,3α = 1; compound 62: 3α,3β = 6α,6β = 16; 5α,5β = 13; 4,5α = 5α,6β = 10; 4,3α = 9.5; 4,10 = 6.5; 5α,6α = 6; 4,3β = 5.5; 4,5β = 5; 5β,6α = 5β,6β = 3; 3α,6α = 3α,6β = 2; 6α,3β = 3β,5β = 9,8 = 1;

Table 10: ^{13}C-NMR-data of p-menthane derivatives (67.5 or 100 MHz, $CDCl_3$, δ-values)

	55a	55b	57a	57b	59a	59b	60	61	62	
C-1	54.1 d	48.3 d	49.8 d	46.2 d	48.6 d	39.4 d	57.6 d	44.2 d	117.3 s	
C-2	70.3 d	66.3 d	73.1 d	68.3 d	82.6 d	77.1 d	210.1 s	67.8 d	150.6 s	
C-3	42.6	40.9	43.4	41.3	38.5	35.6	50.5	41.9	31.4	t
C-4	31.4	25.7	31.4	25.6	31.4	25.5	35.3	25.4	29.6	d
C-5	34.3	34.7	34.4	34.7	33.8	31.2	33.8	34.4	31.3	t
C-6	29.6	23.9	31.2	24.0	25.0	28.3	31.1	22.1	19.8	t
C-7	146.6	147.3	150.7	150.5	139.5	141.2	143.4	60.2	119.6	s
C-8	19.1 q	22.7 q	65.3 t	64.7 t	170.8 s	170.9 s	21.3 q	51.3 t	136.7 d	
C-9	112.7 t	111.2 t	112.3 t	113.3 t	117.1 t	119.5 t	112.7 t	21.7 q	8.1 q	
C-10	22.2	22.2	22.0	22.2	22.0	21.7	22.3	22.1	21.5	q

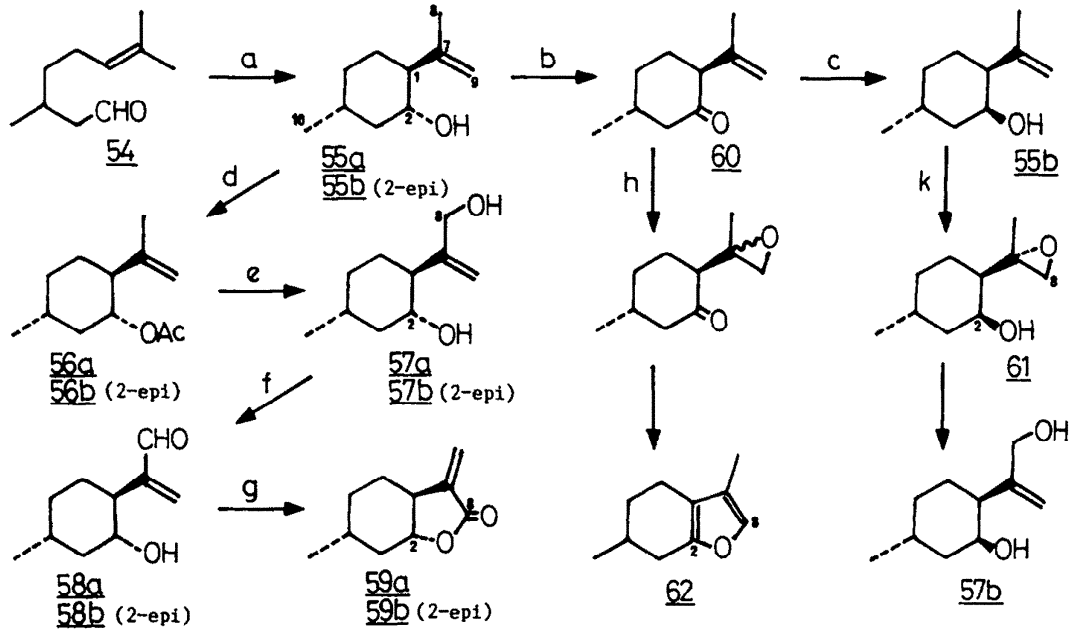
Finally, a study aimed at the oxidative transformation of an α-isopropenylcarbinol moiety into exo-methylene lactone and furan units under mild conditions was undertaken [45]. Such a process may be a useful tool for terpene synthesis, in cases where the appropriate precursor is readily available. The objective chosen for this study is the transformation of isopulegols to menthofuran and the p-menthenolides, which already has been achieved by others [46,47], but in a somewhat different manner. The required isopulegol-epimers were obtained (Scheme H) by $SnCl_4$-induced ene-cyclisation of citronellal 54 [48], affording in good yield a mixture of isopulegol 55a and neoisopulegol 55b (ca. 75:25 ratio) conveniently isolated by steam distillation. Treatment of this mixture with less than one equivalent of acetic anhydride / pyridine cleanly effected selective acetylation of the more reactive equatorial alcohol 55a to its acetate 56a, which could easily be isolated by flash chromatography. On the other hand, pure neoisopulegol acetate 55b was obtained by Jones oxidation of 55a/b to isopulegone 60, stereoselective reduction with L-selectride to axial alcohol 55b, and acetylation assisted by 4-dimethylaminopyridine (DMAP).

SCHEME G: Approach to 6α-oxygenated eleman-8β,12-olides



a) LDA/$MeSSO_2Me$ b) 1)H_2O_2/SeO_2 2)$BaCO_3/\Delta T$ c) $H_2O_2/[HO^-]$ d) $NaBH_4/CeCl_3$

SCHEME H: Synthesis of menthofuran and p-menthenolides



a) $[SnCl_4]$ b) CrO_3/H^+ c) L-selectride d) 0.6eq Ac_2O/Py (for 56a) or Ac_2O/Py/[DMAP] (for 56b)
e) 1)$^tBuOOH/SeO_2$ 2)$LiAlH_4$ f) MnO_2 g) Ag_2CO_3 (for 59a) h) MCPBA i) KOH k) $^tBuOOH/[VO^{2+}]$ l) LDA

While regioselective allylic oxidation of trans-acetate 56a with tert-butylhydroperoxide /SeO_2 [24] occurred smoothly, giving a 68% yield of diol 57a after subsequent $LiAlH_4$-treatment, in the case of cis-acetate 56b only a 16% yield of diol 57b was obtained as a consequence of competing oxidation at the tertiary allylic position. Fortunately, cis-alcohol 55b suffers fast vanadium-catalysed epoxidation [49] to a single epoxy alcohol 61, which is smoothly transformed to diol 57b by treatment with LDA in diethylether, while trans-alcohol 55a is only slowly epoxidised and also partially oxidised to isopulegone under these conditions.

Oxidation of cis-diol 57b with active MnO_2 afforded cis-p-menthenolide 59b in 65% overall yield from neoisopulegol, the intermediate hydroxy aldehyde 58b being isolable only by using less MnO_2 for a short reaction time. Trans-diol 57a was only transformed to hydroxy aldehyde 58a by active MnO_2, just traces of trans-p-menthenolide 59a being produced even with excess MnO_2 and after prolonged time. Hence, transformation to 59a was completed by Ag_2CO_3-oxidation [15] in 48% overall yield from isopulegol acetate.

Finally, transformation of isopulegone 60 to menthofuran 62 was achieved in 52% yield by epoxidation with m-chloroperbenzoic acid followed by treatment with a methanolic KOH-solution, avoiding the acidic conditions usually employed [46] for this kind of transformation.

In summary, we described the first total synthetical access to several eleman-cis-8.12-olides and related compounds of both diastereomeric series, which also offers possibilities for elaboration into more highly oxygenated members of this class, as shown by some model reactions. Methods for the generation of terpenoid exo-methylene lactone and furan units using regioselective oxidation reactions were exemplified by syntheses of menthofuran and the p-menthenolides [55].

EXPERIMENTAL SECTION

General remarks — Solvents were distilled prior to use (ether from KOH/$SnCl_2$; petrol, bp 30-70°C, from KOH). Dry solvents were obtained by distillation from Na-wire (ether, THF, benzene, toluene), K_2CO_3 (CH_2Cl_2), P_4O_{10} (CCl_4, acetone), CaH_2 (HMPA), Mg (MeOH) or KOH (pyridine, diisopropylamine). Small amounts of THF were distilled from $LiAlH_4$ immediately prior to use. Reactions requiring exclusion of air and moisture were run under dry N_2. For small scale reactions the flasks were flushed with N_2, sealed with serum caps and rinsed with dry solvent prior to use, employing syringes for addition of reagents and withdrawing of samples. Solutions of LDA were prepared at 0°C by adding commercial n-BuLi/hexane soln to diisopropylamine in dry THF and stirring for 30 min. All reactions were monitored by thinlayer chromatography (TLC) on silica gel 60 (Merck F254 aluminum foils, development by $KMnO_4$ soln or I_2 vapours). Workup was usually performed by partitioning between the specified organic solvents and aqueous solutions, several reextractions of the latter, washing of the combined organic phases with brine, drying over anhydrous $MgSO_4$, evaporation of solvents in vacuo and removal of last traces of volatile material by short application of high vacuum. Flash chromatography (50) was performed on silica gel (Woelm 32-63 μm), which was reused several times after flushing with acetone and ether. Preparative thinlayer chromatography (PTLC) was performed on silica gel 60 (Merck PF_{254}). Boiling points (bp) are uncorrected, for bulb-to-bulb distillations only bath temperatures are given. Melting points (mp) were determined on a Mettler FP-1 microscope-desk. Microanalyses were obtained with a Hewlett-Packard CHN-analyser.
IR-spectra (Beckman IR 9 or Beckman IR 4320): ν_{max} in cm^{-1}, solvent CCl_4 unless otherwise specified. UV-spectra (Cary 118): λ_{max} in nm, solvent MeOH. Low resolution MS-spectra (Varian MAT 44S, EI 70 eV; isobutane used for CI): signals given in m/z with relative intensity (%) in brackets, fragments marked with an asterisk are main peaks of a characteristic isotopic pattern. High resolutions (Varian MAT 711) were obtained with perfluorokerosene as standard. ^{1}H-NMR-spectra (Bruker WM 400, 400 MHz) and ^{13}C-NMR-spectra (Bruker WM 400, 100 MHz or Bruker AM 270, 67.5 MHz): chemical shifts in ppm (δ-scale) relative to tetramethylsilane as internal standard, ^{1}H-coupling constants in Hz, solvents $CDCl_3$ or C_6D_6 as specified. Nontrivial ^{1}H-assignments were confirmed by extensive spin-decoupling and by use of nOe-difference spectroscopy. ^{13}C-multiplicities were determined under BB-decoupling using DEPT-pulse sequences.

Ketone 1 from Hagemann ester [13b] (improved preparation)

To a soln of vinylmagnesium bromide — prepared from Mg (7.0 g, 2.4 eq) and vinyl bromide (33.0 g, 2.6 eq) in dry THF (650 ml) — is added a soln of CuI (2.0 g, 0.09 eq) and $P(NEt_2)_3$ (52) (5.0 g, 0.17 eq) in THF (20 ml) at -78°C. After 15 min Hagemann ester (14) (25.0 g, 1.0 eq) in THF (50 ml) is slowly added to the vigorously stirred mixture (to suppress any 1.2-addition, the solution is precooled by rinsing down the flask wanding). As soon as all starting material is consumed (30 min - 1 h) the reaction is quenched with sat NH_4Cl soln at -78°C. Evaporation of THF and workup of the residue (ether/dil HCl) leaves crude 1.4-adduct as an oil (27.5 g; R_f=0.25, ether/petrol 1:2), which after dissolution in dry CH_2Cl_2 (140 ml) is treated with 2-methoxy-1.3-dioxolane (53) (17.0 g, 1.2 eq) and p-TsOH (0.75 g) at -10°C. After stirring at RT overnight the reaction is quenched with sat $NaHCO_3$ soln and worked up (CH_2Cl_2/H_2O). The resulting crude ketal (32.4 g; R_f=0.31, ether/petrol 1:2) in ether (50 ml) is slowly added at RT to a soln of methylmagnesium iodide (ca. 6.5 eq), prepared from Mg (20 g) and Me (118 g) in dry ether (600 ml). After stirring until complete consumption of starting material (24 - 48 h) careful hydrolysis (H_2O/0°C) and workup (ether/dil HCl) leaves crude tertiary alcohol as a colourless oil (28.7 g), which after dissolution in dry CH_2Cl_2 (250 ml) and pyridine (160 ml) is treated with $POCl_3$ (43 ml, 3.9 eq) at -78°C. The mixture is slowly warmed to RT overnight and then carefully hydrolysed (H_2O/0°C). After evaporation of CH_2Cl_2, workup (ether/dil HCl) leaves an oil (22.5 g), which is stirred at RT with p-TsOH (3.0 g) and H_2O (40 ml) in acetone (300 ml) until complete deprotection (ca. 48 h). After quenching with sat $NaHCO_3$ soln and evaporation of acetone, workup (ether/H_2O) leaves crude ketone 1, which is purified by bulb-to-bulb distillation (ca. 90°C/5mm).
Yield: 14.5 g 1 (59% from Hagemann ester) as a pale yellow oil; R_f=0.42 (ether/petrol 1:1);

An analytically pure sample was obtained as a colourless oil by flash chromatography and subsequent redistillation; found: C 80.55 H 10.45 (calc. C 80.85 H 10.18); IR: 1720 (satd ketone); MS (RT): 178(1/M^+·)163(2)160(0.5)150(6)136(2.5)110(10)68(100)67(76); H-NMR: table 7; C-NMR: table 2.

13-Nor-eleman-8β.12-olide (9)

To a soln of LDA — prepared from HN(i-Pr)$_2$ (3.0 ml, 1.91 eq) and 2.5m-BuLi/hexane soln (3.0 ml, 1.6 eq) in dry THF (40 ml) — ketone 1 (2.0 g, 1.0 eq) in some THF is slowly added during 10 min at -78°C. After 30 min a soln of $BrCH_2CO_2Me$ (1.8 ml, 1.70 eq) and HMPA (3.0 ml) in some THF is added during 10 min at -78°C. After stirring for 3 h the soln is warmed to 0°C during 30 min and then quenched with sat NH_4Cl soln. Workup (ether/dil HCl) leaves crude ketoester 4 as an oil, containing only traces of epimer 5a as judged by ^{1}H-NMR. A spectroscopically pure sample of 4 was obtained by PTLC (ether/petrol 1:1, R_f=0.39) as a colourless oil; IR: 1743 (satd ester), 1718 (satd ketone); MS (RT): 250(4/M$^+$·)218(16)182(20)150(28)122(25)114(50)108(100); H-NMR: table 1; C-NMR: table 2.

The crude 4 obtained above is stirred at RT with NaOMe (0.6 g, 1.0 eq) in dry MeOH (30 ml) for 24 h. Workup (ether/dil HCl) leaves crude epimeric ketoester 5a as an oil, containing only traces of starting material as judged by ^{1}H-NMR. A spectroscopically pure sample was obtained by PTLC (ether/petrol 1:1, R_f=0.33) as a colourless oil; IR: 1742 (satd ester), 1720 (satd ketone); MS (60°C): 250(3/M$^+$·)218(16)182(6)151(25)150(19)122(24)114(34)109(100)108(85); H-NMR: table 1; C-NMR: table 2.

The crude 5a obtained above is slowly added at 0°C to a suspension of LATBH (12.0 g, 3.56 eq) in dry THF (100 ml). After stirring at RT for 3 h, careful hydrolysis (H_2O/0°C) and evaporation of THF, workup (ether/dil HCl) leaves crude hydroxyester 6a as an oil, yet containing varying amounts of lactone 9. A spectroscopically pure sample of 6a was obtained by PTLC (ether/petrol 1:1, R_f=0.30) as a colourless oil; H-NMR: table 1; C-NMR: table 2.

Lactonisation is completed by refluxing the crude reduction product obtained above for 2 h in dry benzene (60 ml) containing p-TsOH (40 mg). After washing with sat $NaHCO_3$ soln and evaporation of benzene, the residue is purified by flash chromatography (ether/petrol 2:1).
Yield: 1.22 g 9 (53% from 1) as a colourless syrup; R_f=0.19 (ether/petrol 1:1).

9 crystallised only slowly on prolonged standing. An analytically pure sample was obtained by sublimation (60°C/0.05 mm) as colourless crystals, mp 47-48°C; found: C 76.36 H 9.40 (calc. C 76.33 H 9.15); IR: 1787 (γ-lactone); MS (RT): 220.1463(6/M$^+$·; calc. 220.1463)205(12)192(2)191(3)187(2)179(10)178(10)161(14)160(16)145(29)121(34)119(36)94(50)79(50)68(78)61(100); H-NMR: table 1; C-NMR: table 4.

9 is also obtained in comparable yield by saponification of the crude reduction product (excess KOH in MeOH/H_2O 10:1 at RT overnight), workup by acidification and exhaustive ether extraction, complete lactonisation of the obtained mixture of hydroxyacid 6b (R_f=0.20-0.30, ether/petrol 3:1) and lactone 9 by refluxing in dry benzene overnight, and purification by flash chromatography.

13-Nor-elemasteiractinolide (10) (via reduction of ketoester 4)

The crude alkylation product 4 obtained (vide supra) from ketone 1 (4.0 g) is dissolved in dry toluene (200 ml) and treated with 1.2m-DIBAH/hexane soln (85 ml, 1.5 eq) during 15 min at -78°C. The soln is slowly warmed to RT overnight, then carefully hydrolysed (sat NH_4Cl soln), acidified (5% H_2SO_4) and worked up by thorough ether extraction. The crude diol mixture 8a/b obtained (vide infra) is refluxed with 10% Ag_2CO_3/celite (15) (40 g) in dry benzene (140 ml) until complete consumption of starting material. After filtration through a $MgSO_4$ layer and evaporation, lactone 10 is isolated by flash chromatography (ether/petrol 1:1, R_f=0.30).
Yield: 1.42 g 10 (29% from 1) as a colourless crystal mass.

Recrystallisation (twice from pentane) gave colourless crystals, mp 76-76.5°C; found: C 76.51 H 8.71 (calc. C 76.33 H 9.15); IR: 1790 (γ-lactone); MS (RT): 220.1463(3/M$^+$·; calc. 220.1463)205(12)192(4)191(6)187(2)179(10)178(16)161(17)160(20)145(32)121(26)119(42)94(44)79(51)68(100)61(26); H-NMR: table 1; C-NMR: table 4.

Isolation of diols 8a, 8b and of trans-lactone 10t

Ketone 1 (347 mg) was transformed to diol mixture 8a/b (417 mg of colourless syrup) as described above. Separation by flash chromatography (ether/MeOH 40:1) afforded the following fractions:

A) 37 mg 8b as a colourless syrup; R_f=0.20 (ether); IR: 3600 and 3100-3500 (OH); MS (90°C): 224.1776(0.5/M$^+$·; calc. 224.1776)206(23)191(20)188(6)161(35)119(45)97(100); H-NMR: table 1; C-NMR: table 2.

B) 156 mg 8a/8b (63:37 as judged by ^{1}H-NMR) as a colourless semicrystalline mass.

C) 33 mg 8a as colourless crystals; R_f=0.17 (ether); recrystallisation (ether, some pentane added) gave mp 112.5-113.5°C; IR: 3620 and 3100-3500 (OH); MS (100°C): 224.1776(2/M$^+$·; calc. 224.1776)209(5)206(9)193(10)191(9)161(14)155(20)149(20)119(24)97(100); MS (CI/130°C): 225(30/M+H$^+$)207(100)189(23); H-NMR: table 1; C-NMR: table 2.

Yield: 226 mg 8a/8b (ca. 58:42; 52% from 1), distributed into ca. 30% 8a and ca. 22% 8b.

Fractions B) and C) were then separately oxidised with Ag_2CO_3/celite as described above. Fraction C) afforded crystalline lactone 10 (31 mg, 96%) after purification by flash chromatography. Fraction B) afforded a mixture, which in addition to 10 and more polar material, contained only small amounts of epimeric lactone 10t. Separation by flash chromatography (ether/petrol 1:1) gave:

1) 10 mg 10t (ca. 18% based on 8b contained in starting material) as a colourless oil; R_f=0.40 (ether/petrol 1:1); IR: 1800 (γ-lactone); MS (70°C): 220.1460(1/M$^+$·; calc. 220.1463)205(3)122(10)68(100); H-NMR: table 1; C-NMR: table 4.

2) 91 mg 10 (ca. 94% based on 8a contained in starting material).

The polar fractions contained a mixture of C-8-oxidised products (as indicated by the absence of low field H-8 resonances in the ^{1}H-NMR), which obviously are formed from 8b,and were not further investigated.

13-Nor-elemasteiractinolide (10) (via conjugate reduction of butenolide 7a)

To a suspension of NaH (700 mg of 80% dispersion, 2.08 eq; washed with petrol) in dimethyl carbonate (25 ml) ketone 1 (2.0 g, 1.0 eq) is added and the mixture refluxed for 5 h, during which time it solidifies to an off-white mass. Workup (ether/dil HCl) affords ketoester 2 (2.67 g) as a pale yellow oil, being almost completely enolised in solution. A spectroscopically pure sample was obtained by PTLC (ether/petrol 1:4) as a colourless oil; IR: 1670 and 1622 (enolised β-ketoester), 1752 and 1720 (weak; satd ester and ketone of ketoform); MS (RT): 236(15/$M^+\cdot$)204(23)168(22)108(65) 61(100); H-NMR: table 1; C-NMR: table 2.

The crude 2 obtained above is dissolved in dry THF (20 ml) and slowly added at RT to a suspension of NaH (860 mg of 80% dispersion, 2.54 eq; washed with petrol) in THF (60 ml). After 30 min methyl bromoacetate (3.80 g, 2.20 eq) is added and the mixture refluxed for 12 h. Workup (ether/dil HCl) leaves crude ketodiester 3 as an oil. A spectroscopically pure sample was obtained by PTLC (ether/petrol 1:1) as a colourless oil; IR: 1750 (satd esters), 1720 (satd ketone); MS (85°C): 308(2/$M^+\cdot$) 276(17)245(27)208(66)61(100); H-NMR: table 1; C-NMR: table 2.

The crude 3 obtained above is refluxed with a soln of $Ba(OH)_2 \cdot 8H_2O$ (15.6 g, 4.4 eq) in H_2O (100 ml) and EtOH (40 ml) for 24 h. Workup (ether/dil HCl) affords crude ketoacid 5b as an oil. A spectroscopically pure sample was obtained by PTLC (ether/petrol 3:1) as a colourless oil; IR: 2800-3200 (acid), 1711 (broad; acid and satd ketone); MS (70°C): 236(1/$M^+\cdot$)168(2)73(29)61(100); H-NMR: table 1; C-NMR: table 2.

The crude 5b obtained above is heated with NaOAc (5.0 g, 5.4 eq) in Ac_2O (25 ml) at 120°C for 4 h. Evaporation of Ac_2O and workup (ether/dil $NaHCO_3$ soln) affords a mixture of butenolides 7a/b. Separation by flash chromatography (ether/petrol 3:2) yields:

1) 202 mg 7b (8% from 1) as a pale yellow sirup; R_f=0.27 (ether/petrol 1:1); IR: 1788, 1772 and 1760 (butenolide); MS (70°C): 218.1305(10/$M^+\cdot$; calc. 218.1307)203(14)189(16)121(100); H-NMR: table 1; C-NMR: table 2.

2) 1.21 g 7a (50% from 1) as a pale yellow crystal mass; R_f=0.22 (ether/petrol 1:1); recrystallisation (twice from ether/pentane) gave colourless crystals, mp 91-91.5°C; found: C 77.12 H 8.31 (calc. C 77.03 H 8.31); IR: 1795 and 1765 (butenolide); MS (85°C): 218(15/$M^+\cdot$)203(19)189(17) 121(100); H-NMR: table 1; C-NMR: table 2.

To a suspension of CuI (35 mg) in dry THF (15 ml) 1.6m-MeLi/ether soln (0.1 ml) is added at -50°C, followed after 10 min by HMPA (2.5 ml) and 1.2m-DIBAH/toluene soln (3.0 ml, 1.57 eq). After 30 min butenolide 7a (500 mg, 1.0 eq) in some THF is slowly added. The mixture is slowly warmed to -30°C during 4 h, then quenched with sat NH_4Cl soln and worked up (ether/dil HCl). Filtration through a celite layer and evaporation of solvents leaves spectroscopically pure lactone 10.
Yield: 502 mg 10 (quantitative from 7a) as a colourless crystal mass.

11β,13-Dihydroelemasteiractinolide (22) (callitrin)

To a soln of LDA -- prepared from HN(i-Pr)$_2$ (1.0 ml, 1.57 eq) and 2.5m-BuLi/hexane soln (2.55 ml, 1.40 eq) in dry THF (20 ml) -- lactone 10 (1.0 g, 1.0 eq) in some THF is slowly added at -78°C. After 30 min a soln of MeI (0.42 ml, 1.49 eq) and HMPA (1.0 ml) in some THF is slowly added. After 1 h the reaction is quenched with sat NH_4Cl soln and worked up (ether/dil HCl). The main portion of the product is isolated by crystallisation (petrol, some ether added), giving 22 (792 mg) as white crystals. The residue is flash chromatographed (ether/petrol 2:3), giving a further crop of 22 (135 mg) besides some recovered 10 (56 mg).
Yield: 927 mg 22 (92% based on unrecovered 10); R_f=0.43 (ether/petrol 1:1).

Recrystallisation (twice from pentane) gave colourless crystals, mp 116-116.5°C; found: C 77.29 H 9.42 (calc. C 76.88 H 9.46); IR: 1790 (γ-lactone); MS (RT): 220.1463(3/$M^+\cdot$; calc. 220.1463) 205(12)192(4)191(6)187(2)179(19)178(16)161(17)160(20)145(32)121(26)119(42)94(44)79(51)68(100)61(26); H-NMR: table 3; C-NMR: table 4.

11β,13-Dihydroeleman-8β.12-olide (11)

Analogous to the preparation of 22, methylation of 9 (300 mg) gave raw 11 as an oil. Purification by flash chromatography (ether/petrol 5:6) afforded:

1) 258 mg 11 as a colourless crystal mass; R_f=0.39 (ether/petrol 1:1).

2) 26 mg recovered 9 as a colourless oil.

Yield: 258 mg 11 (88% based on unrecovered 9).

Recrystallisation (twice from pentane) gave colourless crystals, mp 60.5-61°C; found: C 77.13 H 9.55 (calc. C 76.88 H 9.46); IR: 1790 (γ-lactone); MS (60°C): 234.1620(13/$M^+\cdot$; calc. 234.1620)219(11) 206(2)205(2)201(1)193(12)192(8)173(7)161(32)160(26)145(28)134(42)121(41)119(38)108(41)93(66)68(100); H-NMR: table 3; C-NMR: table 4.

11α,13-Dihydroeleman-8β.12-olide (15)

To a soln of LDA -- prepared from HN(i-Pr)$_2$ (1.0 ml, 15.0 eq) and 2.5m-BuLi/hexane soln (1.3 ml, 6.8 eq) in dry THF (15 ml) -- lactone 11 (112 mg, 1.0 eq) in some THF is slowly added at -78°C. After 30 min the soln is cooled to -115°C (ether/liquid N_2), a soln of tert-BuOH (800 mg, 22.6 eq)

in some THF is added during 1 min,and after a further 5 min the reaction is quenched by addition of sat NH_4Cl soln. Workup (ether/dil HCl) affords crude lactone 15, which is purified by flash chromatography (ether/petrol 2:3).
Yield: 100 mg 15 (89% from 11) as a colourless crystal mass; R_f=0.31 (ether/petrol 1:1).

Recrystallisation (twice from pentane) gave colourless crystals, mp 92.5-93.5°C; found: C 77.19 H 9.13 (calc. C 76.88 H 9.46); IR: 1780 (γ-lactone); MS (70°C): 234.1620(9/M^+·; calc. 234.1620) 219(12)206(2)205(2)201(2)193(14)192(13)173(8)161(38)160(27)145(40)134(63)121(53)119(58)108(53) 93(100)68(90); H-NMR: table 3; C-NMR: table 4.

11α,13-Dihydroelemasteiractinolide (26)

Under the conditions described for the preparation of 15, lactone 22 (250 mg) was epimerised to a mixture of 22 and 26 (ca. 75:25 as judged by ^{1}H-NMR), which on separation by flash chromatography (ether/petrol 1:1) afforded:

1) 177 mg recovered 22 (71%) as colourless crystals.

2) 61 mg 26 (24%; 83% based on unrecovered 22) as a colourless syrup, which could not be induced to crystallize; R_f=0.30 (ether/petrol 1:1); found: C 77.34 H 9.71 (calc. C 76.88 H 9.46); IR: 1783 (γ-lactone); MS (90°C): 234.1620(3/M^+·; calc. 234.1620)219(8)206(5)205(5)201(2)193(6) 192(8)173(7)161(29)160(23)145(24)134(15)121(28)119(44)108(40)93(67)68(70); H-NMR: table 3; C-NMR: table 4.

Eleman-8β,12-olide (19)

To a soln of LDA — prepared from HN(i-Pr)$_2$ (0.65 ml, 2.9 eq) and 2.5m-BuLi/hexane soln (1.5 ml, 2.4 eq) in dry THF (15 ml) -- lactone 9 (350 mg, 1.0 eq) in some THF is slowly added at -78°C, followed after 40 min by a soln of PhSeCl (490 mg, 1.6 eq) in some THF. After 2 h at -78°C the cooling bath is removed and stirring continued for 30 min after RT has been reached. Workup (ether/dil HCl) and separation by flash chromatography (ether/petrol 2:5, then ether) affords after a yellow forerun (Ph_2Se_2):

1) 248 mg 14a as a colourless crystal mass; R_f=0.44 (ether/petrol 1:2); recrystallisation from pentane gave colourless crystals, mp 115-116°C; IR: 1777 (γ-lactone); MS (125°C): 376*(33)219(94) 105(100); H-NMR: table 5.

2) 210 mg 14b as a colourless crystal mass; R_f=0.25 (ether/petrol 1:2); recrystallisation from pentane gave colourless crystals, mp 100-101°C; IR: 1785 (γ-lactone); MS (150°C): 376*(15/M^+·) 299*(6)219(24)105(76)77(100); H-NMR: table 5.

3) 45 mg unreacted 9 as a colourless oil.

Yield: 458 mg 14a/b (88% based on unrecovered 9), which were combined for subsequent methylation.

To a soln of LDA -- prepared from HN(i-Pr)$_2$ (0.52 ml, 3.25 eq) and 2.5m-BuLi/hexane soln (1.15 ml, 2.50 eq) in dry THF (20 ml) -- selenide mixture 14a/b (430 mg, 1.0 eq) in some THF is slowly added at -78°C. After 30 min a soln of MeI (0.38 ml, 5.3 eq) and HMPA (0.6 ml) in some THF is slowly added at -78°C. After 1 h the cooling bath is removed and stirring continued for 30 min after RT has been reached. Workup (ether/dil HCl) affords selenide 18 as the single product, which is purified by flash chromatography (ether/petrol 1:2).
Yield: 376 mg 18 (84% from 14a/b) as a pale yellow crystal mass; R_f=0.35 (ether/petrol 1:2).

Recrystallisation from pentane gave colourless crystals, mp 107.5-108.5°C; IR: 1782 and 1770 (γ-lactone) MS (170°C): 390*(17/M^+·)313*(8)233(38)161(53)91(80)77(88)55(100); H-NMR: table 5.

The solution of selenide 18 (375 mg, 1.0 eq) in THF (20 ml) is treated during 5 min with the soln of 30% H_2O_2 (0.80 ml, 8.1 eq), SeO_2 (100 mg, 0.94 eq) and HOAc (0.15 ml) in H_2O (3 ml). After complete consumption of starting material (< 1 h/0°C), workup (ether/sat $NaHCO_3$ soln) affords lactone 19, which is purified by flash chromatography (ether/petrol 1:1, R_f=0.39).
Yield: 199 mg 19 (89% from 18) as a colourless crystal mass.

Recrystallisation (twice from pentane) gave colourless crystals, mp 59-59.5°C; found: C 77.77 H 8.79 (calc. C 77.55 H 8.68); IR: 1778 (γ-lactone); MS (70°C): 232.1463(2/M^+·; calc. 232.1463) 217(6)204(2)203(3)199(4)191(12)190(10)187(7)171(7)161(19)160(18)145(22)134(27)121(40)119(29)93(58) 68(100); H-NMR: table 3; C-NMR: table 4.

Elemasteiractinolide (28) (igalan)

Lactone 10 (500 mg) was selenylated analogous to the preparation of 14a/b (vide supra), affording selenide 25 as the single product,besides some unreacted starting material. Separation by flash chromatography (ether/petrol 2:5, then 1:1) afforded:

1) 604 mg 25 as a colourless crystal mass; R_f=0.37 (ether/petrol 1:2); recrystallisation from pentane gave colourless crystals, mp 111-112°C; IR: 1785 (broad; γ-lactone); MS (150°C): 376*(19/M^+·)219(34)105(74)77(90)55(100); H-NMR: table 5.

2) 120 mg unreacted 10 as a colourless crystal mass.

Yield: 604 mg 25 (93% based on unrecovered 10).

Selenide 25 (600 mg) was methylated analogous to the preparation of 18 (vide supra), affording a mixture of selenides 27a and 27b,besides some unreacted starting material. The main portion of 27a was isolated by crystallisation (pentane, some ether added) to give 335 mg of colourless crystals. Flash chromatography (ether/petrol 2:3) of the residue afforded:

1) 113 mg 27b (18% from 25) as a colourless syrup; R_f=0.41 (ether/petrol 1:2); IR: 1775 (γ-lactone); MS (130°C): 390*(16/M^+·)233(57)187(20)91(64)77(80)55(100); H-NMR: table 5.

2) 35 mg unreacted 25 as a colourless syrup.

3) 98 mg 27a as a colourless crystal mass; R_f=0.20 (ether/petrol 1:2).

Yield: 433 mg 27a (74% based on unrecovered 25); recrystallisation from pentane afforded colourless crystals, mp 135–137°C; IR: 1769 (γ-lactone); MS (130°C): 390*(18/M^+·)233(51)187(21)91(72) 77(84)55(100); H-NMR: table 5.

Selenoxide elimination from 27a (433 mg) as described for the preparation of 19 (vide supra) afforded lactone 28, which was purified by flash chromatography (ether/petrol 1:1, R_f=0.39).

Yield: 246 mg 28 (95% from 27a) as a colourless crystal mass; recrystallisation (twice from pentane) gave colourless crystals, mp 93.5–94.5°C; found: C 77.22 H 8.85 (calc. C 77.55 H 8.68); IR: 1775 (γ-lactone); MS (80°C): 232.1463(6/M^+·; calc. 232.1463)217(20)204(3)203(6)199(8)191(26)190(22) 187(13)171(12)159(36)145(30)134(22)121(48)119(28)93(93)68(100); H-NMR: table 3; C-NMR: table 4.

Formation of butenolide 7b via selenoxide elimination

A sample of selenide mixture 14a/b (40 mg) was oxidised with H_2O_2/SeO_2 as described for the preparation of 19. Butenolide 7b was produced as the single product, which was identical (^{1}H-NMR- and TLC-comparison) with the minor epimer produced in the enollactonisation of ketoacid 5b (vide supra). Purification by PTLC (ether/petrol 1:1) gave 16 mg 7b (ca. 70%) as a colourless oil.

Formation of butenolide 33b via selenoxide elimination

Lactone 11 (231 mg, 1.0 eq) was selenylated following the procedure described for the preparation of 14a/b (vide supra), but using a soln of PhSeCl (280 mg, 1.49 eq) and HMPA (0.5 ml) in THF. Selenide 37 was obtained as the single product (raw yield 367 mg of a yellowish crystal mass). A pure sample was obtained by crystallisation (pentane, some ether added) as colourless crystals, mp 156.5–158.5°C; H-NMR: table 5.

The crude 37 (367 mg) obtained above was oxidised with H_2O_2/SeO_2 as described for the preparation of 19, affording an inseparable mixture of methylene lactone 19 and butenolide 33b, which was purified by flash chromatography (ether/petrol 2:3).
Yield: 116 mg 19/33b (51% from 11; ca. 70:30 as judged by ^{1}H-NMR) as a colourless syrup.

The butenolide produced in the above elimination is identical (^{1}H-NMR- and TLC-comparison) with the minor diastereomer produced in the enollactonisation of ketoacid 32 (vide infra).

C-15-allylic oxidation of eleman-8β,12-olides, general procedure

A soln of commercial tert-BuOOH (80% soln in tert-Bu_2O_2; 2.0 eq) in CH_2Cl_2 (20 ml/mmol of substrate) is dried by addition of enough $MgSO_4$ to obtain a clear solution. After addition of finely powdered SeO_2 (0.5 eq) and a soln of the elemane derivative (1.0 eq) in some CH_2Cl_2 the mixture is stirred at RT until complete consumption of starting material (2–6 h; prolonged reaction times or greater amounts of tert-BuOOH cause increased aldehyde formation). Workup by addition of ether and washing with H_2O, sat $NaHCO_3$ soln and brine affords a mixture of C-15-alcohol and -aldehyde, which is separated by flash chromatography (ether/petrol 4:1 for aldehyde elution, then ether/petrol 15:1 for alcohol elution). The results obtained in the oxidation of lactones 11, 15, 19, 22 and 28 are summarized as follows (R_f in ether/petrol 1:5; mp after recrystallisation from pentane (aldehydes) or ether/pentane (alcohols), colourless crystals; for ^{1}H-NMR-data see table 3):

educt	product alcohol	product aldehyde
11 (124 mg)	12 (96 mg, 72%); R_f=0.16; mp 72.5–73.5°C;	13 (18 mg, 14%); R_f=0.36; mp 126–128°C;
15 (90 mg)	16 (65 mg, 68%); R_f=0.16; mp 80.5–81°C;	17 (23 mg, 24%); R_f=0.39; mp 161–163°C;
19 (138 mg)	20 (97 mg, 66%); R_f=0.17; mp 87–87.5°C;	21 (33 mg, 23%); R_f=0.43; mp 115–117°C;
22 (260 mg)	23 (222 mg, 80%); R_f=0.19; mp 60.5–61.5°C;	24 (25 mg, 9%); R_f=0.38; mp 115.5–116°C;
28 (120 mg)	29 (91 mg, 71%); R_f=0.22; mp 98–99°C;	30 (20 mg, 16%); R_f=0.32; mp 124–125°C;

11β,13-Dihydro-15-hydroxy-eleman-8β,12-olide(12): found C 71.74 H 8.88 (calc. C 71.97 H 8.86); IR ($CHCl_3$): 3620 (OH), 1765 (γ-lactone); MS (80°C): 250.1569(3/M^+·; calc. 250.1569)235(4)232(5) 219(14)217(4)204(8)177(20)159(29)150(56)145(34)124(27)119(43)93(68)55(100); C-NMR: table 4.

11β,13-Dihydro-15-oxo-eleman-8β,12-olide(13): IR: 1777 (γ-lactone), 1696 (unsatd aldehyde); MS (100°C): 248.1411(9/M^+·; calc. 248.1412)233(3)230(2)219(9)202(10)175(38)98(100)97(79).

11α,13-Dihydro-15-hydroxy-eleman-8β,12-olide(16): found C 72.31 H 8.86 (calc. C 71.97 H 8.86); IR ($CHCl_3$): 3590 (OH), 1765 (γ-lactone); MS (125°C): 250.1560(3/M^+·; calc. 250.1569)235(4)232(4) 219(12)217(3)204(7)177(20)159(33)150(79)145(44)124(30)119(42)93(94)55(100); C-NMR: table 4.

11α,13-Dihydro-15-oxo-eleman-8β,12-olide(17): IR: 1788 and 1778 (γ-lactone), 1698 (unsatd aldeh.); MS (110°C): 248.1414(38/M^+·; calc. 248.1412)233(9)230(6)219(22)202(24)175(82)98(95)97(100).

15-Hydroxy-eleman-8β,12-olide (20): found C 72.61 H 7.93 (calc. C 72.55 H 8.12); IR ($CHCl_3$): 3600 (OH), 1765 (γ-lactone); MS (80°C): 248.1412(3/M^+·; calc. 248.1412)233(5)230(7)217(20)215(8) 176(25)148(38)91(100)53(80); C-NMR: table 4.

15-Oxo-eleman-8β,12-olide (21): IR: 1773 (γ-lactone), 1696 (unsatd aldehyde); MS (120°C): 246.1251 (10/M^+·; calc. 246.1256)231(2)228(8)217(22)200(14)122(39)121(38)96(100)91(54)68(50)53(47).

11β,13-Dihydro-15-hydroxy-elemasteiractinolide (23): found C 71.83 H 8.46 (calc. C 71.97 H 8.86); IR ($CHCl_3$): 3610 and 3350-3600 (OH), 1776 (γ-lactone); MS (60°C): 250.1569(1/M^+·; calc. 250.1569) 235(3)232(3)219(20)217(6)204(6)177(16)159(35)150(30)145(54)124(21)119(32)93(74)55(100).

11β,13-Dihydro-15-oxo-elemasteiractinolide (24): IR: 1790 (γ-lactone), 1710 (unsatd aldehyde); MS (90°C): 248.1411(7/M^+·; calc. 248.1412)233(3)230(2)219(10)202(10)175(42)98(100)97(71).

15-Hydroxy-elemasteiractinolide (29): found C 72.48 H 7.85 (calc. C 72.55 H 8.12); IR ($CHCl_3$): 3590 and 3300-3600 (OH), 1760 (γ-lactone); MS (110°C): 248.1410(1/M^+·; calc. 248.1412)233(4)230(5) 217(30)215(14)91(100)53(91).

15-Oxo-elemasteiractinolide (30): IR: 1782 (γ-lactone), 1707 (unsatd aldehyde); MS (150°C): 246.1253 (3/M^+·; calc. 246.1256)231(2)228(4)217(8)200(8)122(38)121(35)96(60)91(70)68(60)53(100).

Isogermafurenolide (33a) and 8-epi-isogermafurenolide (33b)

Ketone 1 (1.30 g) is transformed to crude ketoester 5a (vide supra), which is ketalised by stirring with 2-methoxy-1,3-dioxolane (53) (1.0 g, 1.32 eq) and p-TsOH (50 mg) in dry CH_2Cl_2 (20 ml) overnight (cf. preparation of 1). Purification by flash chromatography (ether/petrol 2:3) affords ketal ester 31 as a mixture of C-7-epimers.
Yield: 1.10 g 31 (51% from 1) as a pale yellow oil; found: C 69.13 H 8.60 (calc. C 69.36 H 8.90); IR: 1742 (satd ester); MS (RT): 294(2/M^+·)171(22)158(14)139(76)99(40)73(24)61(100); selected ^{1}H-NMR data (400 MHz, $CDCl_3$) are: 1.71 brs (H-15), 1.09 s (H-14), 2.65 dd (J=15+7;H-11), 2.29 dd (J=15+7.5;H-11'), 1.79 brd (J=14;H-9α), 1.34 dd (J=14+2;H-9β), 2.44 ddddd (J=7.5,7,4.5,2+2;H-7), 3.79-4.02 m (4H;ketal), 3.67 s (CO_2Me) for main diastereomer; 1.70 brs (H-15), 1.05 s (H-14), 2.57 dd (J=15+5.5;H-11), 2.12 dd (J=15+8;H-11'), 1.53 brd (J=13.5;H-9α), 1.57 d (J=13.5;H-9β), 2.28 ddddd (J=13,8,5.5+4;H-7), 3.89-4.04 m (4H;ketal), 3.66 s (CO_2Me) for minor diastereomer; a W-coupling (J=2) between H-7 and H-9α shows the ester residue to be axially orientated in the main diastereomer.

To a soln of LDA -- prepared from HN(i-Pr)$_2$ (0.35 ml, 1.75 eq) and 2.5m-BuLi/hexane soln (0.88 ml, 1.54 eq) in dry THF (12 ml) -- ester 31 (420 mg, 1.0 eq) in some THF is slowly added at -78°C, followed after 60 min by a soln of MeI (320 mg, 1.58 eq) and HMPA (1 ml) in some THF. After 2.5 h the reaction is quenched with sat NH_4Cl soln at -78°C and worked up (ether/dil HCl). The resulting oil (a mixture of four methylation products epimeric at C-7 and C-11 as judged by ^{1}H-NMR) is deketalised by refluxing for 12 h with pyridinium-p-toluenesulfonate (40) (100 mg) and H_2O (1 ml) in acetone (30 ml). After evaporation of acetone saponification and C-7-equilibration are effected by stirring with KOH (400 mg, 5 eq) in MeOH/H_2O (3:1, 40 ml) at RT for 12 h. After evaporation of MeOH and workup of the residue (ether/dil HCl) crude ketoacid 32 is obtained as a mixture of C-11-epimers. Selected ^{1}H-NMR-data (400 MHz, $CDCl_3$) of 32 are: 1.77 brs and 1.76 brs (H-15), 0.95 s and 0.99 s (H-14), 1.26 d (J=7) and 1.20 d (J=7) (H-13), 2.69-2.90 m (2 x 2H, H-7/H-11).

The crude 32 obtained above is heated with NaOAc (550 mg, 4.7 eq) in Ac_2O (10 ml) at 120°C for 4 h. After evaporation of Ac_2O and workup (ether/dil $NaHCO_3$ soln) the obtained mixture of butenolides 33a and 33b is purified by flash chromatography (ether/petrol 1:1).
Yield: 216 mg 33a/33b (ca. 61:39 as judged by ^{1}H-NMR; 65% from 31, distributed into ca. 40% 33a and ca. 25% 33b) as a pale yellow syrup; found: C 77.39 H 8.63 (calc. C 77.55 H 8.68).

Spectroscopically pure samples of both epimers were obtained by PTLC (ether/petrol 1:2; 33a: R_f= 0.21, 33b: R_f=0.24) as colourless oils; minor epimer 33b was identical (^{1}H-NMR- and TLC-comparison) with the butenolide obtained by oxidation of selenide 37 (vide supra).

33a: IR: 1770 (butenolide); MS (RT): 232.1463(10/M^+·; calc. 232.1463)217(13)176(13)121(100); H-NMR: table 6; C-NMR: table 8.

33b: IR: 1770 (butenolide); H-NMR: table 6; C-NMR: table 8.

Isofuranogermacrene (35)

A soln of butenolides 33a/b (66 mg, 1.0 eq) in dry THF (3 ml) is treated with 1.2m-DIBAH/toluene soln (0.40 ml, 1.69 eq) at -30°C during 10 min and the mixture slowly warmed to -10°C during 4 h. After addition of THF (2 ml) and 10% H_2SO_4 (2 ml) the mixture is vigorously stirred at 0°C for 30 min and then worked up (ether/brine, then sat $NaHCO_3$ soln). Removal of polar impurities by filtration over a pad of silica gel (Ø 60 x 5 mm; ether/petrol 1:4) and evaporation of solvents leaves pure furan 35, which is very sensitive to autoxidation.
Yield: 45 mg 35 (73% from 33a/b) as a colourless oil; R_f=0.67 (ether/petrol 1:4).

IR: 1648, 1454, 1427, 1389, 1129, 935, 915; MS (RT): 216.1510(13/M^+·; calc. 216.1514)201(6)148(26) 108(100); H-NMR: table 6; C-NMR: table 8.

8β-Hydroxy-isogermafurenolide (36a) and 8β-hydroperoxy-isogermafurenolide (36b)

A soln of furan 35 (22 mg) in dry benzene (2 ml) containing PtO_2 (10 mg) is stirred under O_2 (1 atm) at RT for 10 h. After filtration and evaporation of solvents the obtained mixture is separated by PTLC (ether/petrol 1:1) affording:

1) 4 mg 36a (ca. 16% from 35) as a white solid; R_f=0.09 (ether/petrol 1:2); recrystallisation (ether, some pentane added) gave colourless crystals, mp 155-157°C; IR: 3580 and 3300-3600 (OH), 1780 and 1750 (butenolide); MS (110°C): 248.1412(2/M^+·; calc. 248.1412)230(14)215(10)135(28) 123(32)107(100); H-NMR: table 6; C-NMR: table 8.

2) 2 mg 36b (ca. 8% from 35) as a white solid; R_f=0.24 (ether/petrol 1:2); MS (CI/130°C): 265(100/ M+H$^+$)249(50)247(33)233(36)231(58); H-NMR: table 6; C-NMR: table 8.

36b was immediately reduced to 36a (identical by ^{1}H-NMR- and TLC-comparison) by treatment of its $CDCl_3$-soln with some drops of a dilute triphenylphosphine/$CDCl_3$-soln.

Methylester 34 of desoxysericealactone

A pure sample of butenolide 33a was obtained by combining the more polar fractions of a chromatographic separation of the epimeric mixture 33a/b (vide supra). 33a (60 mg) is reacted with SeO_2 (20 mg, 0.70 eq) and 80% tert-BuOOH (50 mg, 1.7 eq) following the general procedure for C-15-allylic oxidation (vide supra). After 6 h a further portion of tert-BuOOH (200 mg, 6.9 eq) is added and stirring continued overnight. The crude allylic alcohol obtained after workup is oxidised by stirring with active MnO_2 (1.0 g) in ether for 3 h at RT. The crude aldehyde (50 mg of yellow oil) obtained after filtration and evaporation of ether is dissolved in acetone (10 ml) and treated with 2.5m-Jones reagent (2 ml, 20 eq) at 0°C. After stirring at RT for 18 h,workup (ether/brine; celite filtration) affords the carboxylic acid (40 mg of colourless oil), which is methylated by an excess of diazomethane in ether at RT. The residue obtained after evaporation of ether is purified by flash chromatography (ether/petrol 1:1).
Yield: 36 mg 34 (50% from 33a) as a colourless crystal mass; R_f=0.40 (ether/petrol 2:1).

Recrystallisation from ether/pentane gave colourless crystals, mp 134-134.5°C; found: C 69.81 H 7.78 (calc. C 69.55 H 7.30); IR: 1773 (γ-lactone), 1733 (unsatd ester); MS (70°C): 276.1360 (34/M^+·; calc. 276.1362)244(32)176(80)149(55)148(57)121(64)91(100); H-NMR: table 6; C-NMR: table 8.

10-Nor-isopiperitenone (39) (6-(1-methylethenyl)-2-cyclohexenone)

A mixture of diene 38 (29) (90.0 g, 1.0 eq) and methyl vinyl ketone (50.0 g, 1.1 eq; freshly dried and distilled) is heated at 100°C until complete consumption of 38 is indicated by ^{1}H-NMR (2-4 h). Distillation through a 15cm-Vigreux column affords pure (2-trimethylsilyloxy-3-cyclohexen-1-yl)-ethanone as an epimeric mixture (cis/trans ratio ca. 75:25).
Yield: 97.2 g (72% from 38) as a colourless liquid; bp 70-73°C/5mm; IR: 1715 (satd ketone); MS (RT): 212(1.5/M^+·)197(68)142(43)127(81)75(100)73(90); C-NMR (67.5 MHz, $CDCl_3$): 210.0 s, 130.8 d, 128.0 d, 65.4 d, 53.6 d, 28.4 q, 25.0 t, 18.2 t, 0.4 q (main epimer); 211.7 s, 130.8 d, 127.8 d, 69.0 d, 55.0 d, 31.0 q, 24.5 t, 23.9 t, 0.1 q (minor epimer).

To a soln of methylenetriphenylphosphorane -- prepared from Ph_3PCH_3I (105 g, 1.20 eq) and 2.5m-BuLi/hexane soln (100 ml, 1.15 eq) in dry THF (500 ml) -- the above ketone (46.0 g, 1.0 eq) in THF (50 ml) is added at -10°C during 15 min. After warming to RT overnight the solvents are largely evaporated at RT and the residue is worked up (ether/H_2O; precipitated Ph_3P=O is removed by decantation) to leave an oil, which is dissolved in acetone (250 ml) and treated with 2.5m-Jones reagent (90 ml, 1.05 eq) at 0°C during 30 min. After stirring for 1 h and partial evaporation of acetone,workup (ether/H_2O, then 5% KOH soln and brine) leaves crude ketone 39, which after filtration through a pad of celite is purified by bulb-to-bulb distillation (ca. 60°C/5mm).
Yield: 16.3 g 39 (55%) as a pale yellow liquid; found: C 79.09 H 8.83 (calc. C 79.37 H 8.88); IR: 1685 (enone); UV: 224 (enone); MS (50°C): 136(9/M^+·)121(8)68(100); H-NMR ($CDCl_3$): 3.04 dd(H-1), 6.03 ddd(H-3), 6.95 ddd(H-4), 2.37-2.44 m(H-5/H-5'), 2.13 dddd(H-6), 2.03 dddd(H-6'), 4.95 brs(H-9E), 4.76 brs(H-9Z), 1.75 brs(H-8); J(Hz): 6,6'= 13; 1,6 = 11; 3,4 = 10; 1,6'= 5; 3,5/5'= 2+2; 4,5/5'=4.5+3.5; 6,5/5'= 8+6; 6',5/5'= 5+5; 9E,9Z = 8,9E = 1.5; 8,9Z = 1,9Z≤1; C-NMR ($CDCl_3$): 199.3 s(C-2), 149.7 d(C-4), 142.9 s(C-7), 129.7 d(C-3), 113.3 t(C-9), 54.7 d(C-1), 27.7 t and 25.1 t(C-5/C-6), 20.4 q(C-8).

Isopiperitenone (47) and 8-methoxy-isopiperitenone (48)

Following the procedure described for the preparation of 39, cycloaddition of diene 46 (33) (105 g, 1.0 eq) and methyl vinyl ketone (50 g, 1.05 eq) afforded (4-methyl-2-trimethylsilyloxy-3-cyclohexen-1-yl)-ethanone as an epimeric mixture (cis/trans ratio ca. 75:25).
Yield: 116.9 g (77% from 46) as a colourless liquid; bp 85-90°C/5mm; IR: 1720 (satd ketone); MS (60°C): 226(2/M^+·)211(14)183(10)167(10)153(10)141(23)136(17)121(18)117(14)93(28)81(23)75(60)73(100); C-NMR ($CDCl_3$): 210.2 s, 138.8 s, 122.8 d, 66.1 d, 53.4 d, 29.9 t, 28.5 q, 23.4 q, 18.7 t, 0.4 q (main epimer); 211.9 s, 135.9 s, 125.3 d, 69.5 d, 55.1 d, 31.1 q, 29.4 t, 24.1 t, 23.0 q, 0.1 q (minor epimer).

This ketone (40.0 g) by methylenation and oxidation afforded pure isopiperitenone 47 after purification by bulb-to-bulb distillation (< 100°C/5 mm).
Yield: 17.5 g 47 (66%) as a colourless liquid; found: C 79.80 H 9.65 (calc. C 79.96 H 9.39); IR: 1675 (enone); MS (60°C): 150(6/M^+·)135(8)82(100)54(26); H-NMR ($CDCl_3$): 2.94 ddd(H-1), 5.89 ddq (H-3), 2.36 ddddq(H-5), 2.30 ddddq(H-5'), 2.09 dddd(H-6), 2.00 dddd(H-6'), 1.73 dd(3H; H-8), 4.94 dq (H-9E), 4.75 ddq(H-9Z), 1.94 ddd(3H; H-10); J(Hz): 5,5'= 18.5; 6,6'= 13.5; 1,6 = 11; 1,6'=6',5 = 6',5'= 5; 6,5 = 8.5; 6,5'= 5.5; 9E,9Z = 2; 3,5 = 8,9E = 1.5; 3,5'= 3,10 = 1; 10,5 = 10,5'=8,9Z = 1,9Z≤1; C-NMR ($CDCl_3$): 199.2 s(C-2), 161.8 s(C-4), 143.2 s(C-7), 126.6 d(C-3), 113.4 t(C-9), 53.7 d(C-1), 30.2 t and 27.5 t(C-5/C-6), 24.1 q(C-10), 20.5 q(C-8).

Analogously, reaction of diene 46 (62.5 g, 1.03 eq) and methoxymethyl vinyl ketone (34) (38.9 g, 1.0 eq) afforded 2-methoxy-1-(4-methyl-2-trimethylsilyloxy-3-cyclohexen-1-yl)-ethanone as an epimeric mixture (cis/trans ratio ca. 75:25).
Yield: 71.9 g (72% from 46) as a colourless oil; bp 106-111°C/5mm; IR: 1718 (satd ketone); MS (CI/120°C): 257(11/M+H$^+$)239(50)167(100); C-NMR ($CDCl_3$): 208.1 s, 138.5 s, 122.5 d, 76.8 t, 65.6 d, 59.0 d, 50.2 q, 29.4 t, 23.2 q, 17.7 t, 0.3 q (main epimer); 210.4 s, 135.7 s, 125.1 d, 78.1 t, 69.4 d, 59.0 d, 50.4 q, 29.2 t, 24.0 t, 22.8 q, -0.1 q (minor epimer).

This ketone (19.0 g) after methylenation and oxidation, in this case using pyridinium chlorochromate (51) (50 g, 3.1 eq) in dry CH_2Cl_2 (200 ml) at 0°C, afforded enone 48 after bulb-to-bulb distillation (< 120°C/1mm).
Yield: 8.82 g 48 (66%) as a pale yellow oil; found: C 73.26 H 9.01 (calc. C 73.30 H 8.95); IR: 1685 (enone); UV: 234 (enone); MS (50°C): 180(100/M^+·)165(36)98(68)82(71); H-NMR ($CDCl_3$): 3.04 brdd(H-1), 3.95 brs(H-8), 5.21 brs(H-9E), 4.94 brs(H-9Z), 3.30 s(OMe); residual spectrum essentially identical compared with that of 47; C-NMR ($CDCl_3$): 198.4 s(C-2), 161.5 s(C-4), 143.7 s(C-7), 126.1 d(C-3), 113.5 t(C-9), 74.6 t(C-8), 57.4 q(OMe), 49.1 d(C-1), 30.0 t and 27.3 t(C-5/C-6), 23.7 q(C-8).

Alkoxyenone 41 (3-(methoxymethoxy)methyl-4-(1-methylethenyl)-2-cyclohexenone)

According to Still [37], but using chloromethyl methylether for protection, tri-n-butyltin hydride was transformed into (methoxymethoxy)methyl-tributylstannane, $Bu_3SnCH_2OCH_2OMe$, in 56% yield. To a soln of this stannane (18.3 g, 1.39 eq) in dry THF (150 ml) was added 2.5m-BuLi/hexane soln (19.3 ml, 1.34 eq) during 10 min at -78°C, followed after 15 min by a soln of enone 39 (4.90 g, 1.0 eq) in some THF. After 3 h the mixture was quenched (H_2O/-78°C) and worked up (ether/H_2O). The crude adduct obtained was purified by flash chromatography (ether/petrol 1:4 for elution of nonpolar tin compounds, then 1:1 for elution of product) to afford a colourless oil (6.33 g). A portion (5.84 g) of this oil was oxidised with 2.5m-Jones reagent (16.5 ml, 1.5 eq) in acetone (50 ml) at 0°C for 4 h (cf. preparation of 39). Workup and purification by flash chromatography (ether/petrol 3:1) afforded pure enone 41.
Yield: 3.82 g 41 (55% from 39) as a pale yellow oil; R_f=0.26 (ether/petrol 2:1); found: C 68.86 H 8.73 (calc. C 68.55 H 8.63); IR: 1685 (enone); UV: 230 (enone); MS (70°C): 210(23/$M^+\cdot$)195(6) 178(19)165(66)79(100); H-NMR ($CDCl_3$): 6.24 brs(H-2), 2.95 dd(H-4), 2.12 dddd(H-5), 2.03 dddd(H-5'), 2.47 ddd(H-6), 2.31 ddd(H-6'), 1.82 brs(H-8), 4.97 brs(H-9E), 4.73 brs(H-9Z), 4.10 s(2H; H-10), 4.64 s(2H) and 3.36 s(3H); J(Hz): 6,6'= 16.5; 5,5'= 14; 5,6 = 12;4,5 = 5',6 = 5',6'=5; 5,6'= 4.5; 4,5'= 4; 9E,9Z = 2; 8,9E = 2,10 = 2,10' = 1-1.5; 8,9Z = 2,4 < 1; C-NMR ($CDCl_3$): 199.4 s(C-1), 161.2 s(C-3), 142.4 s(C-7), 125.4 d(C-2), 113.5 t(C-9), 96.1 t(OCH_2O), 67.6 t(C-10), 55.4 q(OCH_3), 43.1 d(C-4), 34.0 t(C-5), 26.3 t(C-6), 22.0 q(C-8).

14-Alkoxyketone 42 ((3α,4β)-3-ethenyl-3-(methoxymethoxy)methyl-4-(1-methylethenyl)-cyclohexanone)

Following the procedure described for preparation of ketone 1 (vide supra), enone 41 (1.50 g, 1.0 eq) is reacted with a soln of vinylmagnesium bromide -- prepared from Mg (460 mg, 2.65 eq) and vinyl bromide (2.13 g, 2.79 eq) in dry THF (50 ml) -- in the presence of CuI (0.27 g, 0.20 eq) and $P(NEt_2)_3$ (0.44 g, 0.25 eq) for 2 h at -78°C. Workup and purification by flash chromatography (ether/petrol 1:1) affords pure ketone 42.
Yield: 1.01 g 42 (61% from 41) as a colourless oil; found C 70.12 H 9.22 (calc. C 70.56 H 9.30); IR: 1718 (satd ketone); MS (90°C): 238(1/$M^+\cdot$)206(7)193(9)176(16)163(21)135(19)67(100); H-NMR: table 7; C-NMR: table 2.

14-Hydroxy-13-nor-eleman-8β,12-olide (45b)

Following essentially the procedure described for the preparation of lactone 9 (vide supra), alkylation, epimerisation and reduction of ketone 42 (428 mg) afforded crude hydroxyester 43 as an oil, which was lactonised by saponification (40% KOH soln (1 ml) in MeOH (10 ml) at RT for 8 h) and subsequent refluxing in dry benzene (20 ml) for 12 h,to afford crude lactone 45a as an oil (480 mg). A portion (432 mg) of this product was refluxed for 2 h under careful TLC-control in MeOH (20 ml) containing 37% HCl (0.1 ml). After neutralisation with sat $NaHCO_3$ soln and evaporation of MeOH,workup (ether/dil HCl) afforded an oil, from which hydroxy lactone 45b was isolated as the major constituent by flash chromatography (ether/petrol 10:1).
Yield: 102 mg 45b (27% from 42) as a pale yellow syrup; R_f=0.13 (ether/petrol 3:1); found: C 70.98 H 8.72 (calc. C 71.16 H 8.53); IR: 3550 and 3350-3650 (OH), 1778 (γ-lactone); MS(90°C): 236(3/$M^+\cdot$) 221(5)218(6)206(19)191(13)159(25)147(96)131(88)119(51)105(93)91(98)79(100); H-NMR: table 7; C-NMR: table 8.

Formation of cyclisation product 44

As described above, ketone 42 (191 mg) was transformed to hydroxyester 43, which on refluxing for 1 h in dry benzene (15 ml) containing p-TsOH (15 mg) was smoothly transformed to a single product. Workup (ether/dil HCl) and purification by flash chromatography (ether/petrol 5:1) afforded pure 44.
Yield: 80 mg 44 (42% from 42) as a colourless oil; R_f=0.17 (ether/petrol 2:1); found: C 71.46 H 8.39 (calc. C 71.16 H 8.53); IR: 1782 (γ-lactone); MS (70°C): $M^+\cdot$ missing; 221(21)206(42)191(13) 178(47)147(79)131(86)119(89)118(100)105(46)91(63)79(84); H-NMR: table 7; C-NMR: table 8.

Compound 44 was unaffected by acetylation (Ac_2O/DMAP) and oxidation (PCC/CH_2Cl_2) conditions, which confirms the presence of a tetrahydrofuran moiety.

Preparation of epoxyalcohol 52 from ketone 1

To a soln of LDA -- prepared from HN(i-Pr)$_2$ (5.9 ml, 1.5 eq) and 2.5m-BuLi/hexane soln (15.0 ml, 1.35 eq) in dry THF (100 ml) — ketone 1 (5.0 g, 1.0 eq) in some THF is slowly added at -78°C, followed after 30 min by a soln of $MeSSO_2Me$ (42) (4.25 g, 1.2 eq) in some THF. After 6 h the reaction is quenched (H_2O/-78°C) and worked up (ether/dil HCl). Purification by flash chromatography (ether/petrol 1:6) affords:

1) 4.30 g 49 as a pale yellow crystal mass; R_f=0.41 (ether/petrol 1:4); sublimation (50°C/0.05 mm) afforded colourless crystals, mp 48-49°C; found: C 69.89 H 9.15 (calc. C 69.59 H 8.98); IR: 1705 (ketone); MS (RT): 224(27/$M^+\cdot$)209(10)177(33)176(23)156(30)88(100); H-NMR: table 7; C-NMR: table 8.

2) 698 mg unreacted 1 as a colourless oil.

Yield: 4.30 g 49 (81% based on unrecovered 1).

A soln of sulfide 49 (4.11 g, 1.0 eq) in MeOH (75 ml) is treated with a soln of 30% H_2O_2 (2.18 g, 1.05 eq) and SeO_2 (2.13 g, 1.05 eq) in H_2O (15 ml) at 0°C during 15 min. After complete consumption of starting material (< 1h/0°C) workup ($CHCl_3$/H_2O) affords crude sulfoxide, which is refluxed with $BaCO_3$ (4.0 g, 1.1 eq) in dry benzene (120 ml) for 24 h. Filtration and evaporation of solvents affords crude enone 50, which is purified by flash chromatography (ether/petrol 1:2).

Yield: 2.36 g 50 (73% from 49) as a pale yellow oil; an analytically pure sample was obtained by bulb-to-bulb distillation (ca. 100°C/5 mm) as a colourless oil; found: C 81.53 H 9.08 (calc. C 81.77 H 9.15); IR: 1690 (unsatd ketone); MS (90°C): 177(1/M+H$^+$)176(0.5/M$^+$·)161(1)148(1)133(1.5) 108(40)80(100); H-NMR: table 7; C-NMR: table 8.

To a soln of enone 50 (2.02 g, 1.0 eq) and 30% H_2O_2 (3.25 g, 2.50 eq) in MeOH (30 ml) a soln of 6m-NaOH (0.4 ml, 0.2 eq) in MeOH (4 ml) is added very slowly at 10°C. After complete consumption of starting material (ca. 6 h/RT), workup (ether/H_2O) affords crude 51, which is purified by flash chromatography (ether/petrol 1:5).
Yield: 1.59 g 51 (72% from 50) as a colourless oil; R_f=0.53 (ether/petrol 1:2); 51 afforded colourless crystals after some time, which after washing with pentane and drying gave mp 39–40°C; found: C 74.72 H 8.14 (calc. C 74.97 H 8.39); IR: 1735 (satd ketone); MS (CI/RT): 193(100(M+H$^+$)175(42)165 (25)147(40)121(38); H-NMR: table 7; C-NMR: table 8.

To a soln of 51 (1.09 g, 1.0 eq) and $CeCl_3 \cdot 6H_2O$ (1.8 g, 0.9 eq) in MeOH (35 ml), $NaBH_4$ (250 mg, 1.15 eq) is slowly added at 0°C. After stirring at RT for 1 h, careful hydrolysis (H_2O/0°C) and workup (ether/dil HCl) the residual oil is purified by flash chromatography (ether/petrol 1:2, R_f=0.35).
Yield: 960 mg 52 (87% from 51) as a colourless oil; IR: 3620 and 3350–3550 (OH), 1640 (C=C); MS (RT): 194.1308(1/M$^+$·; calc. 194.1307)179(2)176(2)161(8)135(17)133(14)121(28)119(22)97(100)69(92); H-NMR: table 7; C-NMR: table 8.

Preparation of trans-p-menthenolide (59a) and cis-p-menthenolide (59b) via allylic oxidation

To a soln of citronellal 54 (25.0 g) in dry CH_2Cl_2 (500 ml) is added a soln of $SnCl_4$ (0.6 ml, 0.03 eq) in CH_2Cl_2 (25 ml) at −10°C during 10 min. After 30 min at −10°C sat $NaHCO_3$ soln (100 ml) is added, CH_2Cl_2 evaporated and the residue exhaustively steam distilled. The organic portion of the distillate is isolated by saturation with NaCl and ether extraction, giving a mixture of isopulegol 55a and epiisopulegol 55b, which is finally bulb-to-bulb distilled (<100°C/5mm).
Yield: 19.3 g 55a/55b (77% from 54; ca. 75:25 as judged by ^{1}H-NMR) as a colourless liquid; spectroscopically pure samples of both epimers were obtained by PTLC (ether/petrol 1:2).

55a: R_f=0.40; IR: 3580 (OH); MS (RT): 154(12/M$^+$·)139(27)136(25)121(54)111(56)95(76)84(48)81(53) 69(100)55(95); H-NMR: table 9; C-NMR: table 10.

55b: R_f=0.26; IR: 3580 (OH); MS (RT): 154(12/M$^+$·)139(15)136(18)121(36)111(32)95(46)82(70)69(92) 55(100); H-NMR: table 9; C-NMR: table 10.

Isopulegol acetate 56a was obtained by reaction of the above 55a/b mixture (10.0 g, 1.0 eq) with Ac_2O (4.0 g, 0.6 eq) and pyridine (5.2 g, 1.0 eq) in dry benzene (50 ml) at RT for 36 h, workup (ether/dil HCl) and separation of the nonpolar 56a by flash chromatography (ether/petrol 1:10).
Yield: 6.31 g 56a (50% from 55a/b; ca. 65% based on 55a contained in starting material) as a colourless liquid; R_f=0.30 (ether/petrol 1:10); IR: 1740 (acetate); MS (80°C): 196(2/M$^+$·)136(46)121(28) 107(23)93(27)81(33)73(31)61(100); H-NMR: table 9.
The alcohol fraction obtained by further elution with ether can be utilized for the preparation of isopulegone 60 (vide infra).

Epiisopulegol acetate 56b was obtained by L-selectride reduction of isopulegone 60 (2.80 g) (vide infra) and reaction of the crude epiisopulegol 55b obtained with Ac_2O (2.5 g, 1.3 eq), pyridine (2.2 g, 1.5 eq) and DMAP (0.2 g, 0.2 eq) in dry benzene (30 ml) at RT for 48 h, followed by workup (ether/dil HCl) and purification by bulb-to-bulb distillation (<80°C/5mm).
Yield: 2.71 g 56b (75% from 60) as a colourless liquid; R_f=0.30 (ether/petrol 1:10); IR: 1740 (acetate); MS (RT): 196(2/M$^+$·)136(100)121(87)107(69)93(90); H-NMR: table 9.

To a soln of tert-BuOOH (80% soln in tert-Bu_2O_2; 2.2 g, 3.42 eq) in CH_2Cl_2 (20 ml) are added $MgSO_4$ (ca. 1 g) and finely powdered SeO_2 (0.15 g, 0.24 eq) followed after 30 min by acetate 56a (1.12 g, 1.0 eq). After stirring at RT for 36 h, workup (ether/brine, then sat $NaHCO_3$ soln) affords an oil, which is added at 0°C to a suspension of $LiAlH_4$ (300 mg, ca. 2.7 eq) in dry ether (25 ml). After warming to RT overnight, workup ($CHCl_3$/dil HCl) affords crude diol 57a, which is purified by crystallisation (ether, some pentane added).
Yield: 660 mg 57a (68% from 56a) as a white solid; R_f=0.15 (ether/petrol 5:1); recrystallisation from ether gave mp 97–97.5°C; IR ($CHCl_3$): 3600 and 3200–3600 (OH); MS (50°C): 170.1309(1/M$^+$·; calc. 170.1307)152(39)137(19)123(40)108(74)93(100)81(100)55(79); MS (CI/100°C): 171(41/M+H$^+$)153(66)151(13) 135(100); H-NMR: table 9; C-NMR: table 10.

Diol 57a (490 mg) was stirred with active MnO_2 (6.0 g) in ether (50 ml) at RT for 2 h. Filtration over a $MgSO_4$ layer and evaporation of ether afforded hydroxy aldehyde 58a as a colourless oil (406 mg; R_f=0.23, ether/petrol 3:1) containing only traces of lactone 59a as judged by TLC and NMR (see tables 9/10). Further oxidation by refluxing with 10% Ag_2CO_3/celite (15) (8.0 g) in dry benzene (40 ml) for 8 h, afforded pure trans-p-menthenolide 59a after filtration, evaporation and purification by bulb-to-bulb distillation (ca. 110°C/5mm).
Yield: 334 mg 59a (48% from 56a) as a colourless oil; R_f=0.32 (ether/petrol 1:2); found C 72.45 H 8.05 (calc. C 72.20 H 8.49); IR: 1787 (γ-lactone); MS (RT): 166(16/M$^+$·)138(80)123(22)120(18) 109(40)94(100); H-NMR: table 9; C-NMR: table 10.

In a completely analogous manner, acetate 56b (1.12 g) was transformed to a mixture of products, from which only a small amount of diol 57b was obtained by flash chromatography (ether).
Yield: 186 mg 57b (16% from 56b) as a white solid; R_f=0.23 (ether/petrol 5:1); recrystallisation from ether gave mp 115–116°C; IR ($CHCl_3$): 3600 and 3200–3550 (OH); MS (50°C): 170.1309(1/M$^+$·; calc. 170.1307)152(47)137(25)123(54)108(89)93(100)81(93)55(78); MS (CI/130°C): 171(34/M+H$^+$)153(20)151(44) 135(100); H-NMR: table 9; C-NMR: table 10.

Diol 57b (420 mg) was stirred with active MnO_2 (7.0 g) in ether (50 ml) at RT for 4h. Filtration over a $MgSO_4$ layer and evaporation of ether afforded cis-p-menthenolide 59b, which was homogeneous

by TLC and ^{1}H-NMR.
Yield: 341 mg 59b (83% from 57b) as a colourless oil; R_f=0.27 (ether/petrol 1:2); an analytically pure sample was obtained by bulb-to-bulb distillation (ca. 100°C/5mm); found C 72.23 H 8.87 (calc. C 72.20 H 8.49); IR: 1780 (γ-lactone); MS (RT): 166(46/M^+·)138(86)123(35)120(30)109(51)94(100); H-NMR: table 9; C-NMR: table 10.

Hydroxyaldehyde 58b could be obtained as a colourless oil by PTLC (ether/petrol 3:1, R_f=0.20) of a sample withdrawn from the oxidation reaction shortly after addition of MnO_2; H-NMR: table 9; C-NMR: table 10.

Preparation of cis-p-menthenolide (59b) via vanadium catalysed epoxidation

Isopulegol mixture 55a/b (25.5 g) is oxidised with 1.05 eq of Jones reagent at 0°C (cf. preparation of 39) to give pure isopulegone 60 after bulb-to-bulb distillation (< 80°C/5mm).
Yield: 20.8 g 60 (82% from 55a/b) as a colourless liquid; R_f=0.54 (ether/petrol 1:2); IR: 1717 (satd ketone); MS (RT): 152(23/M^+·)137(15)123(72)109(100)93(74)81(43)67(90); H-NMR: table 9; C-NMR: table 10.

To a soln of isopulegone 60 (3.81 g, 1.0 eq) in dry THF (80 ml), 1m-L-selectride/THF soln (36 ml, 1.44 eq) is added at -78°C during 15 min. After warming to RT overnight, organoboranes are destroyed (54) by treatment with H_2O_2/NaOH. Partial evaporation of THF, workup (ether/dil HCl) and purification by bulb-to-bulb distillation (< 100°C/5mm) affords pure epiisopulegol 55b, which is completely free of isopulegol 55a.
Yield: 3.40 g 55b (88% from 60) as a colourless liquid.

To a soln of epiisopulegol 55b (3.40 g, 1.0 eq) and $VO(acac)_2$ (100 mg) in benzene (40 ml), is added 80% tert-BuOOH (3.50 g, 1.41 eq) and the mixture stirred at RT for 4 h. Workup (ether/sat $NaHCO_3$ soln) affords crude epoxy alcohol 61 (R_f=0.22, ether/petrol 1:2; essentially a single diastereomer as judged by NMR, see tables 9/10), which with some ether is added to the soln of LDA -- prepared from HN(i-Pr)$_2$ (10.8 ml) and 2.5m-BuLi/hexane soln (27.0 ml, 3.05 eq) in dry ether (120 ml). After stirring for 60 h at RT, H_2O is added, ether is evaporated and the residue worked up ($CHCl_3$/dil HCl) to afford crude diol 57b (3.02 g raw yield) as a pale yellow syrup, which is stirred with active MnO_2 (50 g) in ether (150 ml) at RT for 4 h. Filtration, evaporation and bulb-to-bulb distillation (ca. 100°C/5mm) affords pure cis-p-menthenolide 59b.
Yield: 2.38 g 59b (65% from 55b) as a pale yellow liquid.

Preparation of menthofuran (62)

To a soln of isopulegone 60 (2.7 g, 1.0 eq) in dry benzene (120 ml) is added 85% m-chloroperbenzoic acid (4.8 g, 1.47 eq). After stirring at RT for 20 h the main portion of precipitated m-chlorobenzoic acid is separated by evaporation of benzene, taking up in petrol and filtration. Evaporation of solvents leaves crude epoxyketone as an oil, which after dissolution in MeOH (60 ml) is treated with 40% KOH soln (30 ml). After stirring at RT for 4 h, evaporation of MeOH and workup (ether/brine) leaves crude menthofuran 62, which is purified by bulb-to-bulb distillation (ca. 80°C/2mm).
Yield: 1.40 g 62 (52% from 60) as a colourless liquid, which is very susceptible to autoxidation; R_f=0.60 (ether/petrol 1:10); found: C 79.92 H 8.95 (calc. C 79.96 H 9.39); H-NMR: table 9; C-NMR: table 10.

REFERENCES AND NOTES

1) N.H.Fischer, E.J.Olivier and H.D.Fischer, Fortschr.Chem.Org.Naturst. 38, 48 (1979). F.C.Seaman, The Botanical Review 48, 323-326 (1982).
2) A.Ortega and E.Maldonado, Phytochemistry 24, 2635 (1985), and literature cited therein.
3) A.Ortega, E.Maldonado, F.R.Fronczec, T.J.Delord and G.Chiari, Phytochemistry 24, 1755 (1985).
4) D.J.Brecknell and R.M.Carman, Aust.J.Chem. 32, 2455 (1979).
5) F.Bohlmann and L.Dutta, Phytochemistry 18, 1228 (1979).
6) F.Bohlmann, J.Jakupovic, L.Hartono, R.M.King and H.Robinson, Phytochemistry 24, 1100 (1985).
7) F.Bohlmann, C.Zdero, R.M.King and H.Robinson, Liebigs Ann.Chem., 799 (1986).
8) J.Jakupovic, V.Castro and F.Bohlmann, Phytochemistry 26, 421 (1987).
9) G.Delgado, S.Guzman and A.Romo de Vivar, Phytochemistry 26, 755 (1987).
10) H-5 and C-14 always being in a trans-relationship as a consequence of the assumed biogenetic origin from (E,E)-germacranolides, the only exception being some compounds of a dihydrooxepine type, cf.: W.Herz, P.S.Subramaniam, P.S.Santhanam, K.Aota and A.L.Hall, J.Org.Chem. 35, 1453 (1970), F.Bohlmann, E.Tsankova, R.M.King and H.Robinson, Phytochemistry 23, 1099 (1984).
11) a) P.A.Grieco, M.Nishizawa, T.Oguri, S.D.Burke and N.Marinovic, J.Am.Chem.Soc. 99, 5773 (1977).
b) S.Danishefsky, P.F.Schuda, T.Kitahara and S.J.Etheredge, J.Am.Chem.Soc. 99, 6066 (1977).
c) F.Zutterman, H.DeWilde, R.Mijngheer, P.DeClerq and M.Vandevalle, Tetrahedron 35, 2389 (1979).
d) H.Iio, M.Isobe, T.Kawai and T.Goto, J.Am.Chem.Soc. 101, 6076 (1979).
e) G.R.Kieczykowski, M.L.Quesada and R.H.Schlessinger, J.Am.Chem.Soc. 102, 782 (1980).
f) see also: P.M.Wege, R.D.Clark and C.H.Heathcock, J.Org.Chem. 41, 3144 (1976).
12) a) P.A.Grieco and M.Nishizawa, J.Org.Chem. 42, 1717 (1977).
b) M.Nishizawa, P.A.Grieco, S.D.Burke and W.Metz, J.Chem.Soc., Chem.Commun., 78 (1978).
c) M.Ando, K.Tajima and K.Takase, J.Org.Chem. 48, 1210 (1983).
d) M.Arno, B.Garcia, J.R.Pedro and E.Seoane, Tetrahedron 40, 5243 (1984).
13) a) G.Majetich, P.A.Grieco and M.Nishizawa, J.Org.Chem. 42, 2327 (1977).
b) T.L.Ho and T.W.Hall, Synth.Commun., 97 (1982).
c) O.Soria and L.A.Maldonado, Synth.Commun., 1093 (1982).
d) T.Sato, Y.Gotoh, M.Watanabe and T.Fujisawa, Chem.Lett., 1533 (1983).
e) Ketone 1 has also been isolated in small amounts from an essential oil: A.F.Thomas, Helv.Chim.Acta 55, 2429 (1972).

14) B.A.McAndrew, J.Chem.Soc., Perkin Trans. I, 1837 (1979).
15) M.Fetizon,M.Golfier and J.M.Louis, Tetrahedron 31, 171 (1975).
Ag recycling from used reagent as $AgNO_3$ is easily effected by drying, treatment with concentrated HNO_3, filtration and evaporation of the combined H_2O-washings.
16) R.B.Miller and R.D.Nash, Tetrahedron 30, 2961 (1974).
17) cf.: J.A.Marshall and W.R.Snyder, J.Org.Chem. 40, 1656 (1975).
18) T.Tsuda, T.Hayashi,H.Satomi,T.Kawamoto and T.Saegusa, J.Org.Chem. 51, 537 (1986).
19) P.A.Grieco and M.Mijashita, J.Org.Chem. 39, 120 (1974).
20) cf.: P.A.Grieco and J.J.Reap, Tetrahedron Lett., 1097 (1974).
21) J.Drabowicz and M.Mikolajczyk, Synthesis, 758 (1978).
22) L.P.Nikonova and G.K.Nikonov, Khim.Prir.Soedin. 6, 508 (1970).
23) A.L.Okunade and D.F.Wiemer, Phytochemistry 24, 1199 (1984).
24) M.A.Umbreit and K.B.Sharpless, J.Am.Chem.Soc. 99, 5526 (1977).
25) K.Takeda, I.Horibe and H.Minato, J.Chem.Soc. C, 569 (1968).
26) S.Hayashi,N.Hayashi and T.Matsuura, Tetrahedron Lett., 2647 (1968).
27) H.Minato and T.Nagasaki, J.Chem.Soc. C, 377 (1966).
cf.: P.A.Grieco, C.S.Pogonowski and S.Burke, J.Org.Chem. 40, 542 (1975).
28) H.Ishii,M.Nakamura and K.Takeda, Tetrahedron 24, 625 (1968).
29) K.Krohn, Liebigs Ann.Chem., 2285 (1981).
30) A related cyclohexenone was prepared recently by an analogous sequence:
H.Hauptmann,G.Mühlbauer and N.P.C.Walker, Tetrahedron Lett., 1315 (1986).
31) cf.: W.C.Still, J.Am.Chem.Soc. 99, 4186 (1977).
32) 47 was also prepared recently in much lower yield by a similar sequence:
T.Mandai,K.Osaka,M.Kawagishi,M.Kawada and J.Otera, Synth.Commun., 797 (1984).
Previous methods for the preparation of 47 are inconvenient for large scale operation, see refs. 35) and 36).
33) H.S.South and L.S.Liebeskind, J.Org.Chem. 47, 3815 (1982).
34) E.Wenkert,N.F.Golob,S.S.Sathe and R.A.J.Smith, Synth.Commun., 205 (1973).
35) W.G.Dauben,M.Lorber and D.S.Fullerton, J.Org.Chem. 34, 3587 (1969).
36) T.C.T.Chang and M.Rosenblum, J.Org.Chem. 46, 4103 (1981).
37) W.C.Still, J.Am.Chem.Soc. 100, 1481 (1978).
W.C.Still, J.Am.Chem.Soc. 99, 4836 (1977).
38) cf.: E.J.Corey and D.J.Beames, J.Am.Chem.Soc. 94, 7210 (1972).
39) By using methyllithium instead of 40,also ketone 1 can be prepared by this route in 50% yield from enone 39, the preparation from Hagemann ester being more effective in this case, however.
40) N.Miyashita, A.Yoshikoshi and P.A.Grieco, J.Org.Chem. 42, 3772 (1977).
cf.: R.Sterzycki, Synthesis, 724 (1979).
41) cf.: R.H.Schlessinger et al. in ref. 11e).
42) D.Scholz, Synthesis, 944 (1983).
43) G.Rücker, H.Hörster and W.Gajewski, Synth.Commun., 623 (1980).
44) S.Bartel, Diplomarbeit, Technische Universität Berlin (1986).
45) For a similar study see: B.S.Bal and H.W.Pinnick in ref. 47).
46) Menthofuran from isopulegol or isopulegone:
a) H.Fritel and M.Fetizon, J.Org.Chem. 23, 481 (1958).
b) L.H.Zalkow and J.W.Ellis, J.Org.Chem. 29, 2626 (1964).
c) Z.U.Din,T.L.Ho and S.G.Traynor, Chem.Abstr. 95, P 7510m (1981).
d) S.C.Taneja,K.L.Dhar and C.K.Atal, Indian J.Chem. 19B, 714 (1980).
e) cf.: T.Sato,M.Tada and T.Takahashi, Bull.Chem.Soc.Jpn. 52, 3129 (1979).
f) see also: J.M.Fang and Y.W.Wang, Chem.Abstr. 105, 79170v (1986).
47) Menthenolides from isopulegol:
a) V.R.Tadwalkar and A.S.Rao, Indian J.Chem. 9, 1416 (1971).
b) B.S.Bal and H.W.Pinnick, Heterocycles 16, 2091 (1981).
c) see also: J.M.Fang and Y.W.Wang in ref. 46f)
48) Y.Nakatani and K.Kawashima, Synthesis, 147 (1978).
49) K.B.Sharpless and R.C.Michaelson, J.Am.Chem.Soc. 95, 6136 (1973).
50) W.C.Still,M.Kahn and A.Mitra, J.Org.Chem. 43, 2923 (1978).
51) E.J.Corey and J.W.Suggs, Tetrahedron Lett., 2647 (1975).
52) V.Mark, Org.Synth. 46, 42 (1966).
53) H.Baganz and L.Domaschke, Chem.Ber. 91, 650 (1958).
54) H.C.Brown and W.C.Dickason, J.Am.Chem.Soc. 92, 709 (1970).
H.C.Brown and S.Krishnamurthy, J.Am.Chem.Soc. 94, 7159 (1972).
55) This work is part of the Ph.D.Thesis of D.Friedrich, Technische Universität Berlin (1987).
56) Further work in this direction as well as efforts directed towards the additional functionalisation of C-9 by enolate oxygenation are in progress.