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OXIDATIVE CYCLISATION OF GERMACRONE

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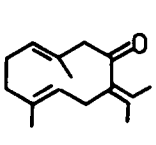
Abstract - The oxidative intramolecular cyclisation of germacrone with LTA is found to lead predominantely to cis-guaiane derivatives. The mechanism of the reaction is discussed briefly.

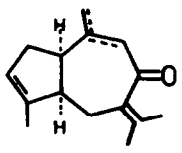
It has been postulated that selinanes and guaianes derive from E,E-1,5-germacradiene precursors[1]. However, the formation of guaianes has so far been performed only by photolysis[2] or electrophile induced cyclisation of the 4,5-monoepoxygermacrenes[3]. In the present paper we wish to report a new type of intramolecular cyclisation of germacrone, 1 with lead tetra-acetate (LTA) predominantely leading to cis-guaiane derivatives. To the best of our knowledge, this is the first example of a direct conversion of an E,E-germacradiene into guaianes.

RESULTS

The reaction of germacrone, 1 with equimolar quantity of LTA in benzene at room temperature required 18 h for the total consumption of the starting material. After chromatographic separation of the resulting complex reaction mixture and repeated PTLC purification the products 2 - 7, 10 and 12 were isolated in the ratio of 6:5:25:4:3:3:1:1, accounting for a total yield of 76%. Furthermore, the presence of 8 and 11 was detected by ^{1}H NMR signals in mixtures with 7 and 10, respectively. The structure of the reaction products was established on the basis of their spectral data, in particular ^{1}H NMR spectra with double resonance experiments aiding the assignment. The IR and UV absorption (1660 - 1680 cm^{-1}; 250 - 254 nm) indicate the presence of the enone system in all reaction products. The

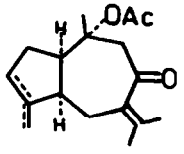


1



2 $\Delta^{9,10}$

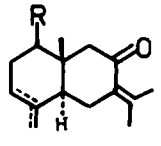
3 $\Delta^{10,14}$



4 $\Delta^{3,4}$

5 $\Delta^{4,15}$

6 $\Delta^{4,5}$

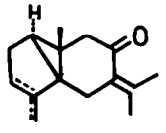


7 R=OAc $\Delta^{3,4}$

8 R=OAc $\Delta^{4,15}$

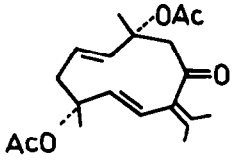
9 R=H $\Delta^{3,4}$

^{1}H NMR data (Table 1) clearly show the guaiane skeleton of the compounds 2 - 6 and the cis-ring junction was deduced from the coupling $J_{1,5}$= 7.5-8.5 Hz. The anti-orientation of H-1 and the C-10 methyl group in the products 4 - 6 was based on the lack of NOE between them. Irradiation of the C-10 methyl group affected one of the C-9 protons only. Of note is the difference in the chemical shift of the C-9 methylene protons (0.38 - 0.50 ppm) which seems to be characteristic for the cis-guaiane compounds 3 - 6. The nonequivalency of these protons do not appear to be due to the neighbouring carbonyl group for in 7 the natural products 9[4] and its 10-epimer[5] the same protons give a singlet in the region of δ 2.20 - 2.30. The very close ^{1}H NMR features of 7 and 9 together with mechanistic reasons allowed the assignment of the trans-fused decalin system in 7. The presence of 10 among the cyclisation products is of interest, as the same tricyclic system and stereochemistry has been found in the natural products anastreptene[6], trinoranastreptene[7] and clavukerin-B[8]. The similarity of their ^{1}H NMR data with those of 10 was a further support for the structure of the latter. Finally, the structure of the monocyclic diacetate 12 was given from the analysis of the spectral data. The trans nature of the two endocyclic double bonds followed from the couplings $J_{1,2}$=$J_{5,6}$=16.4 Hz. The orientation of the acetoxy groups at C-4 and C-10 is tentatively assigned on mechanistic grounds only (see Scheme 3).

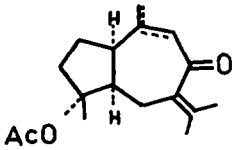


10 $\Delta^{3,4}$

11 $\Delta^{4,15}$



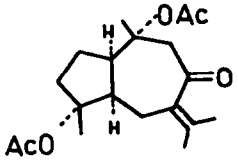
12



13 $\Delta^{9,10}$

14 $\Delta^{10,14}$

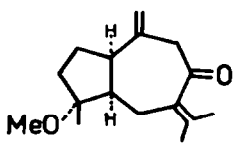
15 $\Delta^{10,1}$



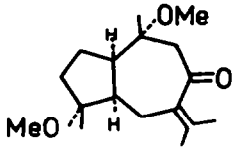
16

When acetic acid was used as a solvent, the reaction of 1 with LTA proceeds much more rapidly (2 h) and again afforded a complex mixture. Nine products were isolated, 2 - 6 and 13 - 16, in the ratio of 1:2:6:1:3:1:2:3:2, accounting for a total yield of 87%. The ^{1}H NMR data of the new guaiane derivatives 13 - 16 (Table 1) are very similar to those of 4 - 6 as the two sets of compounds actually differ in the location of the acetoxy group only. The shape of the H-1 signal and the coupling $J_{1,5}$=7.8-8.1 Hz showed the presence of the cis-guaiane skeleton and NOE experiments revealed the anti-orientation of the C-4 methyl group and H-1.

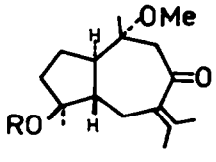
Finally, the cyclisation of 1 with LTA was carried out in methanol. The reaction was completed within 50 min and provided only four products, 17 - 20, in the ratio of 2:3:1:2 in total yield of 80%. The ^{1}H NMR spectra (Table 1) clearly show that the products 17 and 18 belong to the cis- guaiane series. In contrast, the



17

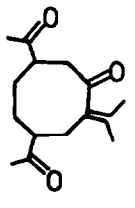


18



19 R=Me

21 R=H



20

Table 1. ^{1}H NMR data of the products with guaiane skeleton

compound	H-1	H-6	H-6'	H-9		H-12	H-13	H-14	H-15	miscellaneous
2	3.00 q (8.5)	2.34 dd (14,5)	2.56 dd (14,4)	6.00 d (0.7)	-	1.91 s	1.81 s	2.01 d (0.7)	1.76 s	H-3: 5.40 brs
3	3.17 q (8.3)	2.20-2.30*	2.53 dd (14,3)	3.05 d (15.5)	3.55 d (15.5)	1.91 s	1.81 s	4.86 s 4.95 s	1.74 s	H-3: 5.40 brs
4	3.16 q (8)	2.20-2.27*	2.54 dd (14.2,4)	2.90 d (16)	3.27 d (16)	1.87 s	1.87 s	1.55 s	1.77 d (1)	H-3: 5.36 brs OAc: 1.98 s
5	3.10 q (8)	2.25-2.50*		2.87 d (16)	3.17 d (16)	1.90 s	1.86 s	1.57 s	4.90 brs 4.98 brs	OAc: 1.98 s
6	3.46 t (7.5)	3.36 d (16)	2.89 d (16)	2.78 d (15)	3.66 d (15)	1.92 s	1.85 s	1.27 s	1.64 s	OAc: 1.96 s
13	3.04 q (7.8)	1.80-2.10*	2.75 dd (14,3.5)	5.98 s	-	1.94 s	1.89 s	1.97 s	1.67 s	OAc: 2.01 s
14	3.15 q (8.1)	1.85-2.00*	2.55 brd (13.3)	2.99 d (15.6)	3.53 d (15.6)	1.92 s	1.86 s	4.83 s 4.96 s	1.61 s	OAc: 2.01 s
15	-	2.25-2.50*	2.80 dd (14.2,2)	2.88 d (15)	3.58 d (15)	1.97 s	1.84 s	1.67 s	1.35 s	H-5: 2.57 dd (12,2) OAc: 1.99 s
16	3.20 q (6)	1.70-1.80*	2.51 brd (14.4)	2.87 d (16.5)	3.18 d (16.5)	1.90 s	1.84 s	1.66 s	1.53 s	OAc: 1.98 s, 2.01 s
17	3.18 ddd (9,7,7)	1.60-1.85*	2.43 brd (13.5)	3.00 d (15.5)	3.53 d (15.5)	1.92 s	1.81 s	4.88 s 4.96 s	1.28 s	OMe: 3.20 s
18	2.76 q (6)	1.70-1.90*	2.39 brd (14.6)	2.50 d (16)	3.16 d (16)	2.01 s	1.85 s	1.12 s	1.32 s	OMe: 3.14 s, 3.19 s H-5: 2.20 dd (12,6)
19	2.00-2.15*	1.73 dd (15,4.5)	2.78 brd (15)	2.66 d (12)	2.84 d (12)	1.94 s	1.82 s	1.11 s	1.16 s	OMe: 3.21 s (6H)

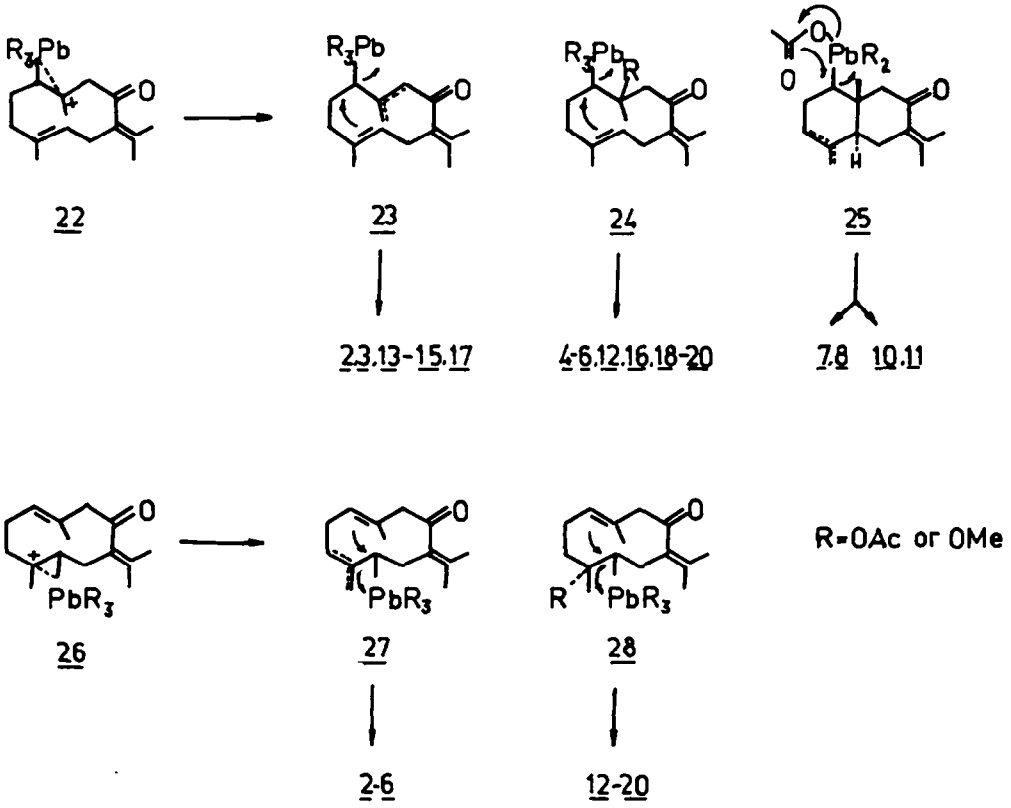
*The location is based on decouplig experiments.

compound 19 was suggested to belong to the trans-fused guaianes. Although the MS, IR and UV spectra of 18 and 19 are almost identical, their ^{1}H NMR data differ to a certain extent. The H-1 signal in 19 does not appear in the typical for the cis-products region (δ 2.80-3.20) but is concealed in the envelope at δ 1.80 - 2.00; the geminal coupling constant for the C-9 methylene protons and the difference in their chemical shift are smaller when compared to 18. Similarly, the ^{13}C NMR spectra of 18 and 19 (Table 2) revealed a more significant difference. The final support for the trans-ring junction in 19 and also for the relative stereochemistry at C-4 and C-10 came from the complete coincidence of the recorded in C_6D_6 ^{1}H NMR spectra of 19 and 21 (Table 3), the stereochemistry of the latter being established by X-ray analysis[9].

Furthermore, the monocyclic triketone 20 was isolated in 20% yield when 1 was treated with LTA in MeOH. The mass spectrum (with i-butane) exhibited a pseudomolecular ion corresponding to the molecular formula $C_{15}H_{22}O_3$. The IR and ^{1}H NMR spectra (see Experimental) revealed the presence of the two acetyl groups besides the enone system. Hence, the product 20 possesses an eight-membered ring. The Dreiding model showed that at least six of the ten protons of the ring should be deshielded and the ^{1}H NMR spectrum exhibits two sets of uninterpretable multiplets at δ 2.45-2.62 and 2.78-2.96, each integrated to four protons.

DISCUSSION

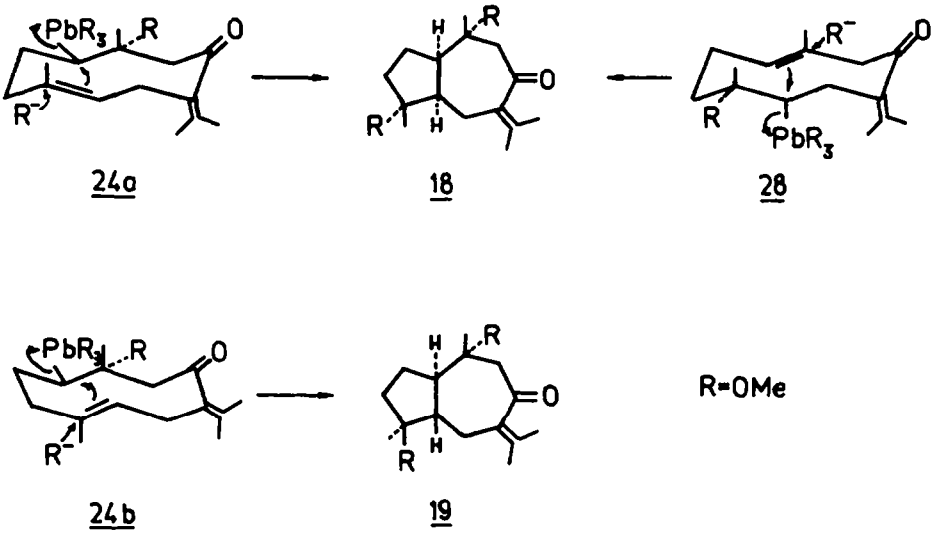
The formation of the products from the oxidative intramolecular cyclisation of germacrone, 1 with lead tetra-acetate could be explained in terms of the ionic mechanism shown in Scheme 1. After the initial electrophilic attack at the



Scheme 1

endocyclic double bond* and Markovnikov cleavage of the resulting π-complex, two competitive reactions appear to be possible - proton elimination and nucleophilic addition. The former would lead to allylic organolead intermediates of the type 23/27, and the latter - to the acetoxy, respectively methoxy**, intermediates 24/28. As the endocyclic double bond in 22 could play the role of an intramolecular nucleophile the cyclisation to the selinane-type intermediate 25 may also occur. Subsequent deplumbilation of the latter could proceed through a concerted S_Ni process, thus accounting for the stereochemistry of the acetoxy group in 7 and 8, or through 1,3-proton elimination giving the tricyclic compounds 10 and 11. It is worth noting that the cyclisation of germacrone with mercury-II-acetate has been considered to proceed via a metallic adduct of the type 25[11].

The second stage of the reaction includes the decomposition of the unstable organolead adducts 23/27 and 24/28 with the participation of the endocyclic double bond. Deplumbilation with concomitant C-1/C-5 bond formation resulted in the cis-guaiane derivatives. Their stereochemistry suggested that the reacting conformation of 23/27 and 24/28 is with syn-oriented methyl groups (Scheme 2, 24a). The following equatorial attack at C-4 or C-10, respectively, fully determines the reaction stereospecifity. In contrast, the trans-guaiane compound 19 should derived from the conformation with anty-oriented methyl groups, 24b. The latter has been found to be the reacting conformation in the acid catalyzed cyclisation of 4S,5R-epoxygermacrone[9].

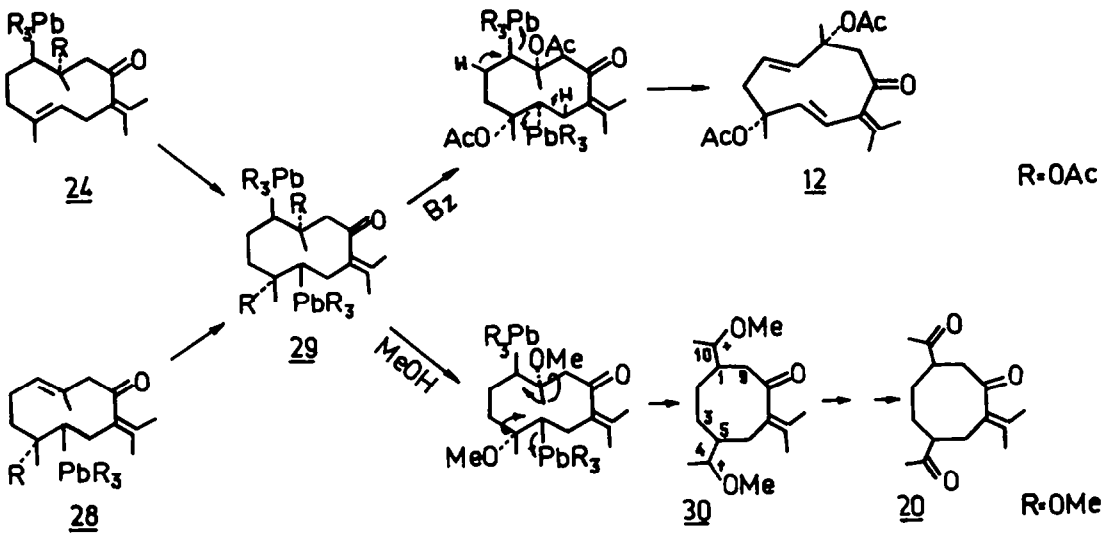


Scheme 2

Finally, we believe that the formation of the monocyclic compounds 12 and 20 could be rationalized as shown in Scheme 3. Deplumbilation of the intermediate 29, which could easily arise from 24 or 28 would proceed in benzene with the elimina-

*The attack at 4,5- and 1,10-double bonds in the molecule of germacrone should be considered as equally probable. We have no evidence of a preference in the attack of LTA.

**The lack of any acetoxy products when the reaction is performed in MeOH is most likely due to a rapid ligand exchange which Pb^{IV} undergoes with nucleophilic solvents[10]. The replacement of acetoxy by methoxy increases the electrophilicity of the Pb^{IV}, thus accounting for the greater rate of the reaction in MeOH.



Scheme 3

tion of protons from the C-2 and C-6 methylene groups, thus leading to the formation of the trans endocyclic double bonds in 12. The decomposition of the same intermediate in MeOH should occur with C-9/C-10 and C-3/C-4 bond cleavage. The driving force of the ring contraction could be the formation of the tertiary carbonium ions in 30 which are additionally stabilized by the geminal methoxy groups. The subsequent nucleophilic attack by the solvent on C-4 and C-10, and decomposition of the resulting diketal would lead to the cyclooctane triketone 20.

EXPERIMENTAL

M.ps are uncorrected; UV: in EtOH; IR: film or KBr pellets; ^{1}H NMR: in $CDCl_3$ (unless indicated otherwise) at 250 MHz, chemical shifts in δ from TMS, J values in Hz; ^{13}C NMR: in $CDCl_3$ at 62.9 Hz; MS: EI at 70 eV, CI with i-butane; flash chromatography[12]: on Kieselgel 60 (Merck, No 9385); PTLC: on Kieselgel 60 PF_{254} (Merck); TLC: on Alufolien 60 PF_{254} (Merck); "work-up in the usual way" implies dilution with H_2O, extraction with ether, washing, drying (Na_2SO_4) and removal of the solvent under reduced pressure.

Reaction of 1 with LTA in benzene. To a well stirred suspension of LTA (520 mg, 1 mmol) in dry benzene (8 ml) was added at room temperature a soln of 1 (218 mg, 1 mmol) in dry benzene (2 ml) and the stirring was continued for 18 h. Work-up in the usual way gave the crude product (200 mg) which was separated by flash chromatography (SiO_2, 90 g, ether/petrol ether 6/1 mixture as eluent) to give 5 main fractions. Subsequent separation of each of them by PTLC yielded:

2 (18 mg), oil, UV:252 nm; IR:1660, 1640 cm^{-1}; MS-EI (m/e,%):216 (M^+,50), 201 (60), 188 (85).

3 (15 mg), oil, UV:250 nm; IR:1675, 1650, 900 cm^{-1}; MS-EI (m/e,%): 216 (M^+, 40), 201 (45), 188 (90).

4 (75 mg), m.p. 78-80°(hexane); UV:250 nm; IR:1730, 1680, 1620, 1235 cm^{-1}; MS-CI: 277 (M^++1); MS-EI (m/e,%):216 (M^+-60, 25), 201 (30).

5 (12 mg), oil, UV:250 nm; IR:1730, 1675, 1648, 1230, 900 cm^{-1}; MS-CI:277 (M^++1); MS-EI (m/e,%): 216(80), 201 (20), 173 (60).

6 (9 mg), oil, UV:250 nm; IR:1725, 1660, 1608, 1235 cm^{-1}; MS-CI: 277 (M^++1); MS-EI (m/e,%): 216 (100), 201 (20), 173 (50).

^{1}H NMR of 2 - 6: in Table 1.

7 (9 mg), oil, UV:254 nm; IR:1730, 1670, 1230 cm^{-1}; MS-EI (m/e,%):276 (M^+, 30), 216 (20), 201 (30); ^1H NMR: 0.92 (3H, s, H-14), 1.71 (3H, s, H-15), 1.85 (3H, s, H-13), 2.05 (3H, s, H-12), 2.09 (3H, s, OAc), 2.20 (2H, brs, H-9), 2.83 (1H, dd, J=15, 6 Hz, H-6), 4.82 (1H, dd, J=10.5, 6 Hz, H-1), 5.38 (1H, brs, H-3).

10 (3 mg), oil, UV:254 nm; IR:1660, 1100 cm^{-1}; MS-EI (m/e,%):216 (M^+,25), 175 (15); ^1H NMR: 0.86 (3H, s, H-14), 1.23 (1H, d, J=7.5 Hz, H-1), 1.72 (3H, q J=2 Hz, H-15), 1.83 (3H, s, H-13), 2.00 (1H, brd, J=17 Hz, H-2), 2.10 (3H, brs, H-12), 2.40 (1H, ddq, J=17, 7.5, 2 Hz, H-2'), 2.60 (1H, d, J=15 Hz, H-9), 2.71 (1H, d, J=15 Hz, H-9'), 2.85 (1H, d, J=16 Hz, H-6), 3.03 (1H, d J=16 Hz, H-6'), 5.17 (1H, brs, H-3).

12 (3 mg), oil, UV:247 nm; IR:1730, 1725, 1235, 1228 cm^{-1}; MS-CI: 335 (M^++1); MS-EI (m/e,%):275 (8), 215 (80), 151 (42); ^1H NMR: 1.62 (3H, s, H-14), 1.67 (3H, s, H-15), 1.83 (3H, s, H-13), 1.93 (3H, s, H-12), 2.02 (3H, s, OAc), 2.09 (3H, s, OAc), 2.20 (1H, dd, J=12, 8 Hz, H-3), 2.58 (1H, d, J= 13 Hz, H-9), 2.65 (1H, dd, J=12, 5 Hz, H-3'), 3.17 (1H, d, J=13 Hz, H-9'), 5.26 (1H, ddd, J=16.4, 8, 5 Hz, H-2), 5.29 (1H, brd, J=16.4 Hz, H-1), 5.46 (1H, d, J=16.4 Hz, H-6), 5.66 (1H, d, J=16.4 Hz, H-5).

Reaction of 1 with LTA in AcOH. A soln of 1 (218 mg) in AcOH (100%, 0.5 ml) was added at room temperature to a stirred soln of LTA (520 mg) in AcOH (2 ml). The mixture was stirred further for 2 h, worked-up in the usual way and chromatographic separation of the crude product (197 mg) under the same conditions as above gave besides 2 (8 mg), 3 (16 mg), 4 (50 mg), 5 (8 mg) and 6 (25 mg) the following products:

13 (8 mg), oil, UV:250 nm; IR:1730, 1640, 1600, 1230 cm^{-1}; MS-CI:277 (M^++1).

14 (16 mg), oil, UV:250 nm; IR:1730, 1680, 1230 cm^{-1}; MS-CI:277 (M^++1); MS-EI (m/e,%): 216 (65), 201 (70).

15 (25 mg), oil, UV:252 nm; IR:1735, 1660, 1230 cm^{-1}; MS-CI:277 (M^++1); MS-EI (m/e,%): 216 (55), 201 (50).

16 (16 mg), oil, UV:252 nm; IR:1730, 1725, 1680, 1230 cm^{-1}; MS-CI:337 (M^++1) MS-EI (m/e,%): 216 (20), 201 (25).

^1H NMR of 13 - 16: in Table 1.

Reaction of 1 with LTA in MeOH. When the reaction of 1 (218 mg) with LTA (520 mg) was carried out in dry MeOH (3 ml in total) the starting germacrone was consumed after 50 min stirring at room temperature. Work-up in the usual way gave the crude product (205 mg) which after chromatographic separation as above afforded:

17 (40 mg), oil, UV:253 nm; IR:1685, 1626, 910 cm^{-1}; MS-CI: 249 (M^++1); MS-EI (m/e,%): 248 (M^+, 10), 216 (25), 136 (75).

18 (60 mg), oil, UV:252 nm; IR:1680, 1630, 1100, 1090 cm^{-1}; MS-EI (m/e,%): 280 (M^+, 10), 248 (100), 216 (50).

19 (20 mg), oil, UV:252 nm; IR:1680, 1620, 1100 cm^{-1}; MS-EI (m/e,%): 280 (M^+, 5), 248 (40), 216 (55).

^1H NMR of 17 - 19: in Table 1; ^{13}C NMR of 18 and 19: in Table 2.

20 (40 mg), oil, UV:252 nm; IR:1720, 1680, 1620 cm^{-1}; MS-CI: 251 (M^++1); MS-EI (m/e,%): 250 (M^+,20), 207 (50), 164 (35), 43 (100); ^1H NMR: 1.86 (3H, s, H-13), 1.96 (3H, s, H-12), 2.19 and 2.21 (each 3H, s, H-14 and H-15), 2.45-2.62 (4H, m), 2.78-2.96 (4H, m).

Acknowledgements - the authors thank the UNDP (project BUL 77/009) for the partial support of this work.

Table 2. ^{13}C NMR of 18 and 19

Carbons		18	19
$-CH_3$	(q)	18.70	17.06
		22.10	19.09
		22.75	22.92
		25.46	28.86
		48.02	48.02
		49.10	49.02
$-CH_2$	(t)	24.84	22.18
		27.23	22.34
		34.71	33.84
		48.23	53.77
-CH	(d)	47.42	50.48
		49.10	53.05
-C-	(s)	77.33	76.73
		86.70	84.18
		134.27	134.27
		142.34	142.70
		203.23	203.23

Table 3. ^{1}H NMR of 19 and 21[9] in C_6D_6

Protons	19	21
H-1	1.99 ddd (J=12,9,9)	1.89 ddd (J=12,9,9)
H-6	1.72 dd (J=14.5,12)	1.66 dd (J=15.5,12)
H-6'	2.74 d (J=14.5)	2.70 d (J=15.5)
H-9	2.65 d (J=12)	2.61 d (J=12)
H-9'	2.76 d (J=12)	2.73 d (J=12)
H-12	1.58 s	1.58 s
H-13	2.03 s	2.03 s
H-14	1.11 s	1.11 s
H-15	0.94 s	0.91 s
OMe	2.93 s	2.92 s
	3.03 s	-

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