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TRANSFORMATION OF ISOGERMACRONE WITH LEAD TETRAACETATE. FORMATION OF A NEW CYCLONONANE SKELETON

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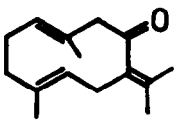
Abstract - The reaction of isogermacrone 2 with LTA under different conditions is described. In the presence of AcOH 2 undergoes mainly intramolecular cyclisation yielding the selinane-type products 4 - 6. When MeOH is used as a solvent ring contraction occur predominantly affording the compounds 13 and 14 with a new cyclononane skeleton. The mechanism of the reactions is discussed.

Recently we have described a new type of oxidative intramolecular cyclisation of germacrone 1 with lead tetraacetate (LTA) predominantly leading to cis-guaiane derivatives[1]. This result encouraged us to apply the same reaction to isogermacrone 2[2], as its endocyclic double bonds are in suitable position for forming the isovetivane skeleton 3[3]. Surprisingly, none of the products has been found to possess the skeleton 3. When the reaction was carried out in AcOH the selinane-type compounds 4 - 6 were mainly formed. In contrast, when MeOH was used as a solvent, 2 underwent predominantly ring contraction giving rise to the compounds 13 and 14 possessing a new cyclononane carbon skeleton.



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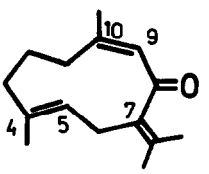

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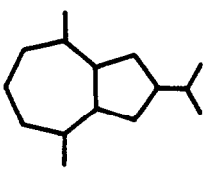

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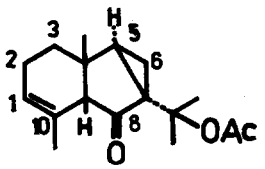
RESULTS

Treatment of 2 with equimolar quantity of LTA in AcOH at room temperature for 60 h furnished the selinane sesquiterpenoids 4-6 in the ratio of 6:2:1 (a total yield of 68%) together with four minor products 7-10 (a total yield of 13%). The selinane skeleton of the major product 4 was deduced

by the NMR spectra (Table 1 and 3). They showed the presence of the angular Me group (δ 1.05), an acetoxy group (δ 1.92) adjacent to the quaternary C-11 (δ 79.8 s) and a trisubstituted double bond (δ 5.52 s,H-1* ; δ 122.8 d and 128.6 s) with a Me group attached to it (δ 1.85). The lack of another double



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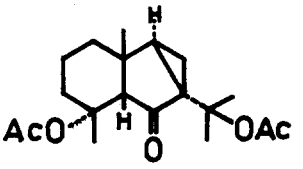

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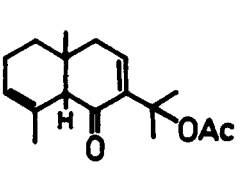

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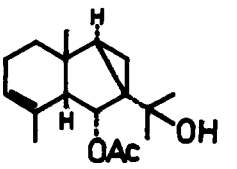

11

bond coupled with the MS data led to the structure 4, having a cyclopropane ring. However, the H-5 and H-6 signals appear at unusually low fields (δ 1.2 - 1.9) which could be explained by the deshielding effect of the neighbouring carbonyl group. In order to verify this presumption the compound 4 was subjected to reduction with $NaBH_4$. The cyclopropane protons of the resulting product 11 gave signals in the region of δ 0.5 - 0.7. The chemical shift of H-8 (δ 5.74) and the methyl groups at C-11 (δ 1.03, 1.32) clearly showed that an intramolecular transesterification had occurred during the reduction. The NMR data of the compound 5 (Table 1 and 3) were very similar to those of 4 except for the signals revealing the replacement of the C-10,1 double bond in 4 by the acetoxy group at C-10 in 5. Next, the relative configuration of 5 and 11 was investigated by NOE difference spectra. Irradiation of 15-Me (δ 1.06) in 5 produced a signal enhancement for H-9 (δ 3.20) and H-6ax (δ 0.84) of 10% and 6%, respectively, thereby placing the cyclopropane ring and both 15-Me and H-9 on the same side of the molecule (Fig.1). Irradiation of 15-Me (δ 0.91) in 11 gave an increase of 12% for H-9 (δ 1.65) which confirmed the cis-decalin system. Furthermore, an 8% increase for both H-8 (δ 5.73) and H-6ax (δ 0.49) established their proximity (Fig 1)

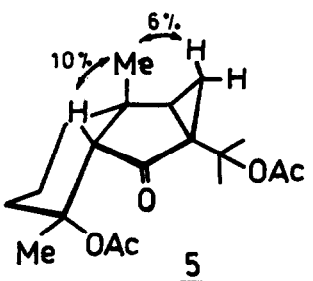

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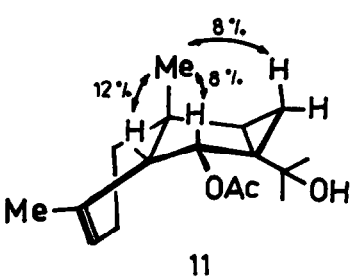
Fig 1



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*the numbering of 2 is preserved in the selinane type products.

Table 1. PMR (250 MHz) of compounds 4 - 6 and 11 ($CDCl_3$, ppm, J in Hz)

	4	4*	5*	6	11
H-1	5.52 sbr	5.45 sbr	-	5.50 sbr	5.50 sbr
H-5	1.95 dd (8, 5)	1.76 dd (8, 5)	1.76 dd (7, 5)	2.62 dd# (18 4)	1.53 dd (9, 5)
H-6	1.40 dd (8, 5)	1.32 dd (8, 5)	1.02 dd (7, 5)	6.71 dd (5, 4)	0.73 dd (9, 6)
H-6'	1.20 dd (5, 5)	0.78 dd (5, 5)	0.84 dd (5, 5)	-	0.49 dd (6, 5)
H-9	2.18 sbr	1.93 sbr	3.20 s	2.64 s	1.65 d (5.4)
H-12	1.69 s	1.72 s	1.84 s	1.64 s	1.32 s
H-13	1.63 s	1.58 s	1.53 s	1.64 s	1.03 s
H-14	1.85 s	1.97 sbr	1.66 s	1.60 s	1.58 s
H-15	1.05 s	0.80 s	1.06 s	1.03 s	0.91 s
OAc	1.92 s	1.91 s	1.84 s	2.07 s	2.13 s
miscellaneous				H-5': 2.62 dd# (18, 5)	H-8: 5.73 d (5.4)

* run in C_6D_6, # the assignment is based on decoupling experiments

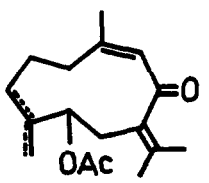
The structure of 6 again followed from the NMR spectra (Table 1 and 3) which were in part close to that of 4. However, the presence of an additional double bond, in the place of the cyclopropane ring in 4, was clearly indicated by the PMR (δ 6.71, H-6) and CMR data (δ 141.9 d and 138.8 s). The IR and UV absorption (1670 cm^{-1}, 238 nm) attributable to a conjugated carbonyl group confirmed the presence of the C-6,7 double bond. Because of the overlapping of the H-5 and H-9 signals, even when different solvents were used, the NOE experiments were unsuccessful and the cis-decalin system in 6 was assigned on mechanistic grounds only (Scheme 1).

According to the UV and IR spectra (see Experimental), as well as the PMR date (Table 2), the crossed enone system of the starting isogermacrone is preserved in the minor reaction products 7-10. Furthermore, the PMR spectra revealed the presence of an additional double bond - C-3,4 in 7, C-4,15 in 8 and C-5,6 in 9. The cis-configuration of the latter followed from the coupling constant $J_{5,6}$= 8 Hz. The mass spectrum of 10 indicated the presence of two acetoxy groups, which was reinforced by the PMR data (δ 2.06, 6H). Of note is the lack of signals for protons geminal to the acetoxy groups implying that the latter are adjacent to a quaternary C-atom, namely C-4. It

Table 2. PMR (250 MHz) of compounds 7-10 and 12- 14 ($CDCl_3$, ppm, J in Hz)

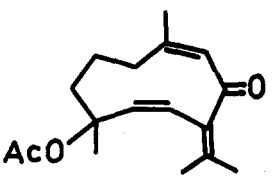
	7	8	9	10	12	13	14
H-5	5.42 dd (12, 4)	5.07 dd (9, 6)	6.29 d (8)	2.50 ddd (12, 5, 3)	6.28 d (17.5)	1.97 dd (9, 4)	2.34 ddd (12, 6, 2)
H-6	2.85 dd (14, 12)	2.89 dd (14, 9)	5.74 d (8)	2.73 d (13)	5.51 d (17.5)	2.85 dd (14, 9)	2.75 d (14)
H-6'	2.73 dd (14, 4)	2.81 dd (14, 6)	-	1.9-2.0#	-	1.9-2.0#	1.8-1.9#
H-9	6.09 sbr	6.02 sbr	6.08 s	6.15 s	5.82 s	6.07 sbr	6.09 s
H-12	1.87 s	1.89 s	1.88 s	1.80 s	1.89 s	1.76 s	1.74 s
H-13	1.70 s	1.76 s	1.73 s	1.74 s	1.78 s	1.64 s	1.69 s
H-14	1.89 sbr	1.97 s	2.00 s	1.94 s	1.89 s	1.92 sbr	1.93 s
H-15	1.60 s	4.91 s 5.09 s	1.73 s	1.64 s	1.32 s	1.20 s	2.17 s
OAc	2.07 s	2.04 s	2.02 s	2.06 s(6H)	-	-	-
OMe	-	-	-	-	3.22 s	3.19 s 3.15	-

the location is based on decoupling experiments



7 $\Delta^{3.4}$

8 $\Delta^{4.15}$



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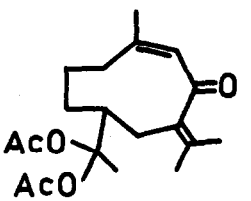
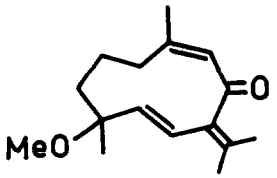


10

was presumed, therefore, that the reaction product 10 has a 9-membered carbon skeleton.

Having failed to get any products of the isovetivane skeleton 3 from the above reaction, we decided to change the reaction conditions, in particular, to replace the acetic acid with the better nucleophilic solvent methanol (see Discussion). The reaction of 2 with LTA in MeOH was completed in shorter time giving a much simpler mixture of products. After chromatographic separation, the compounds 12 - 14 were isolated in a ratio of 2:3:4, accounting for a total yield of 72%. The spectral data of 12 and 13 (Table 2) are very similar to those of 9 and 10, as the two sets of compounds actually differ only in the nature of the substituent at C-4 - acetoxy and methoxy

group, respectively. However, in contrast to 9 the C-5,6 double bond in 12 is with trans-configuration as judged from the coupling $J_{5,6}$= 17,5 Hz. The PMR of 14 (Table 2) showed signals due to three olefinic and one acyl methyl group (δ 1.69, 1.74, 1.93 and 2.17). The IR absorption at 1708 and 1620 cm^{-1} also revealed the presence of the acyl group together with the crossed conjugated carbonyl group. These data together with CMR (Table 3) were only consistent with the constitution of 14.



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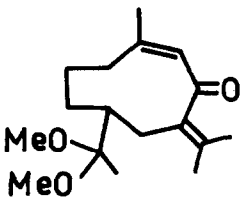

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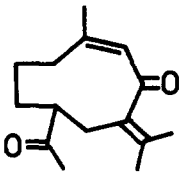
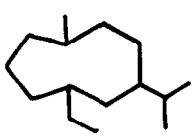


14

To the best of our knowledge, the compounds 10, 13 and 14 are the first representatives of a new skeletal type sesquiterpenoids.It is noteworthy that the skeleton 15 is arranged according to the isoprene rule and could be regarded as a plausible precursor of the known cyperane skeleton 16 . The presence of the endocyclic enone system in 14 and the acyl group located in a suitable position for intramolecular Michael addition prompted us to attempt its cyclisation. When treated with t-BuOK/t-BuOH 14 was quantatively converted into the bicyclic product 17. The IR spectrum showed absorptions typical for the acyl group (1694 cm^{-1}) and the conjugated carbonyl group (1680 cm^{-1}). Alongside the signals due to the methyl groups (δ 0.97, 1.80, 2.10 and 2.22), the PMR (see Experimental) exhibited two pairs of doublets in the region δ 2.30-2.90 which were assigned to the methylene protons at C-6 and C-9. The cis-ring junction was deduced from NOE experiments - irradiation of 14-Me (δ 0.97) gave an increase of 6% and 10% for 15-Me (δ 2.22) and H-9



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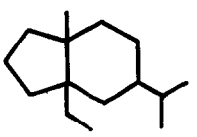

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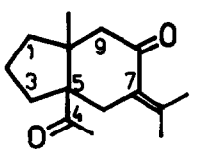

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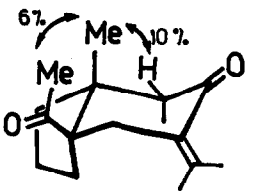

17A

(δ 2.50),respectively. It is of note, that the same is the stereochemistry of the ring junction in the so far isolated natural products possessing the cyperane skeleton 16[4-7].

DISCUSSION

The formation of the products of the reaction of isogermacrone with LTA could be rationalized in terms of the ionic mechanism presented in Scheme 1. After regioselective electrophilic attack of the metal salt at the C-4,5 double bond and Markovnikov cleavage of the resulting π-complex, three competitive reactions may occur: 1. proton elimination to allylic organolead intermediates of type 18, 2. exomolecular nucleophilic addition to the acetoxy, respectively methoxy intermediate 19 and 3. intramolecular nucleophilic addition with the participation of the C-9,10 bond to 20 and 21* . It is to be expected that the nature of the solvent could be a factor controlling the above three reactions. In the presence of AcOH the intramolecular cyclisation obviously proceeds preferentially, although the minor products 7-10 are apparently formed by elimination and exomolecular adddition reactions. Decomposition of the selinane-type intermediates 20 and 21 incorporating the C-7,11 double bond result in the formation of the cyclopropane ring in 4 and 5. The 1,2-hydride shift followed by migration of the isopropylidene double bond explains the presence of compound 6. Methanol, being a much better nucleophile than the acetic acid, favours the exomolecular addition reaction. Demetallation of the resulting intermediate 19 (R = OMe) furnished the secondary cation 22 which further underwent two different reactions-ring contraction and proton elimination. The former, path a, includes C-3,4 bond cleavage and the formation of the cyclononane tertiary cation 23 which is additionally stabilized by the geminal methoxy group. Subsequent attack by the solvent results in the ketal 13, the decomposition of which leads to the diketone 14. The proton elimination, path b, results in the compounds 9 and 12 which differ in the configuration of the newly formed C-5,6 double bond. This difference, most probably, is due to the ability of methanol to stabilize the cation 22, thus giving the energetically preferred trans-double bond in 12. So, it became clear that decomposition of neither 18 nor 19 proceed with the assistance of the C-9,10 bond, i.e. intramolecular cyclisation to isovetivane products does not occur. A very likely reason for this may be the quite large distance between C-5 and C-9 which prevents the corresponding C-C bond formation.

Finally, the high regioselectivity of the reaction of isogermacrone with metal salts should be mentioned. However, in contrast to LTA, which attacks the E-4,5 bond solely, mercury-II-acetate attacks predominantly the Z-9,10 bond[8].

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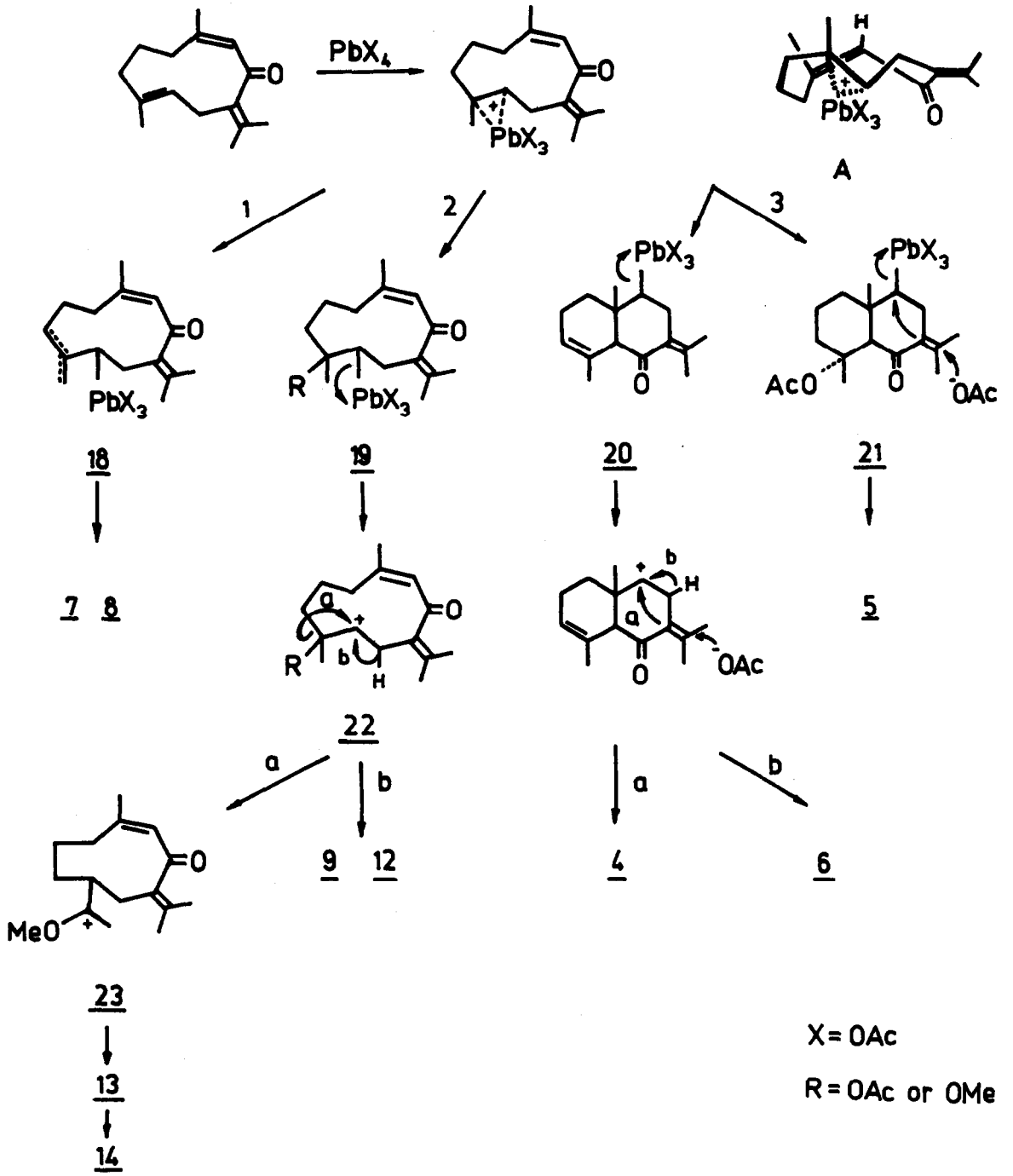
*the cis-ring junction of the products 4-6 suggested that the cyclisation proceeds via the conformer A.


PbX4
PbX3
A
1
2
3
18
19
20
21
7 8
5
22
a
b
9 12
4
6
MeO
23
13
14
X = OAc
R = OAc or OMe

Scheme 1

Table 3. CMR (69.2 MHz) of 4 -6, 13 and 14 ($CDCl_3$, ppm from TMS)

Carbons	4	5	6	13	14
- CH_3 (q)*	20.66	22.32	22.16	21.83	26.03
	22.35	22.67	22.51	26.29	27.27
	23.20	22.67	26.36	26.62	27.20
	23.82	23.11	26.83	27.86	27.70
	24.14	24.05	27.55	48.02	
		24.85		48.29	
- CH_2 (t)	16.00	15.61	22.79	17.09	19.80
	21.98	17.44	32.27	19.80	21.83
	33.21	35.23	34.59	29.92.	29.68
		36.76		34.68	34.19
- CH -(d)	37.19	38.14	59.92	43.95	53.03
	53.68	51.67	122.12	131.64,	130.19
	122.77		141.99		
- C - (s)	35.25	37.88	34.93	104.37	133.05
	44.11	43.26	80.76	130.04	135.63
	79.86	79.93	130.12	136.95	154.79
	128.56	82.90	138.80	155.83	201.00
	169.60	169.56	170.00	203.42	209.42
	210.00	170.65	206.07		
		207.79			

* Multiplicity confirmed by DEPT measurement

EXPERIMENTAL

M. ps are uncorrected; UV: in EtOH; IR: film, $CHCl_3$ soln or KBr pellets PMR: in $CDCl_3$ (unless indicated otherwise) at 250 MHz; chemical shifts in δ from TMS, J values in Hz; CMR: in $CDCl_3$ at 69.2 MHz; NOE experiments:on Bruker WM 250 spectrometer equipped with an ASPECT 2000 data system, data points 8K, sweep width 2000 Hz, flip angle 6μs (45°), decoupler power 45dB, repetition time 5s; the samples for the NOE experiments were degassed; MS: EI at 70 eV (m/z, %); column chromathography: on Merck Kieselgel 60; PTLC: on Merck Kieselgel 60 PF_{254}; TLC: on Merck Alufolien 60 F_{254}; "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 2 with LTA in AcOH. A soln of 2 (218 mg, 1 mmol) in AcOH

(100%, 1 ml) was added at room temperature to a stirred soln of LTA (520 mg, 1 mmol) in AcOH (100%, 5 ml) and the stirring was continued for 60 h. Work-up in the usual way gave the crude product (198 mg) which was chromatographed over SiO_2 (40 g) using a petrol ether-ether gradient solvent system (20:1 - 5:1) to give 7 fractions. Subsequent purification of each of them by PTLC yielded:

4 (90 mg), m.p. 95-97°C (hexane); IR-KBr: 1725, 1700, 1250 cm^{-1}; MS: 276 (M^+, 1), 216 (80), 201 (50), 188 (40).

5 (30 mg), m.p. 165-167°C (hexane); IR-$CHCl_3$: 1725, 1250 cm^{-1}; MS; 336 (M^+, 1), 276 (4), 201 (50), 188 (40).

6 (15 mg), m.p. 118-120°C (hexane); IR-$CHCl_3$: 1724, 1670, 1270 cm^{-1}; UV: 238 nm; MS: 276 (M^+, 2), 216 (45), 201 (10).

7 (6 mg), oil, IR-film: 1740, 1640, 1250 cm^{-1}; UV: 250 nm; MS: 276 (M^+, 20), 216 (40), 201 (20).

8 (6 mg), oil, IR-film: 1740, 1640, 1250, 920 cm^{-1}; UV: 255 mn; MS 276 (M^+, 5), 216 (35), 201 (15)

9 (5 mg), oil, IR-film: 1740, 1640, 1235 cm^{-1}; UV: 250 nm; MS: 276 (M^+, 7), 216 (60), 201 (55).

10 (5 mg), m.p. 103-105°C (hexane); IR-KBr: 1740, 1670, 1620, 1250 cm^{-1}; UV: 244 nm; MS-CI (with diethylamine): 410 (M^++74); MS: 276 (10), 234 (40). PMR of 4-10 in Table 1 and 2. CMR of 4-6 in Table 3.

Reduction of 4. Reduction of 4 (5 mg) with $NaBH_4$ (1 mg in 1 ml MeOH) for 10 min at room temperature gave 11 (4 mg), oil, IR-film: 3600, 1740, 1250 cm^{-1}; MS: 260 (M^+, 2), 200 (50); PMR in Table 1.

Reaction of 2 with LTA in MeOH. A soln of 2 (218 mg, 1 mmol) in dry MeOH (1 ml) was added to a soln of LTA (520 mg, 1 mmol) in MeOH (5 ml) and the mixture was kept at room temperature for 20 h. Work-up in the usual way gave the crude product (180 mg) which after chromatographic separation under the same conditions as above and PTLC purification gave the following products:

12 (27 mg), m.p. 58-60°C (hexane); IR-KBr: 1640 cm^{-1}; UV: 248 nm; MS: 280 (M^+, 1), 248 (30), 201 (25).

13 (45 mg), m.p. 85-87°C (hexane); IR-KBr: 1640, 1230, 1170, 1125 cm^{-1}; UV: 244 nm; MS: 280 (M^+, 1), 248 (30), 216 (50).

14 (58 mg), m.p. 66-68°C (hexane); IR-KBr: 1708, 1620 cm^{-1}; UV: 244 nm: MS: 234 (M^+, 12), 219 (60). PMR of 12-14 in Table 2. CMR of 13 and 14 in Table 3.

Cyclisation of 14. To a soln of 14 (20 mg, 8.10^{-5} mol) in t-BuOH (0.2 ml) was added a soln of t-BuOK (1 mg, 8.10^{-5} mol) in t-BuOH (0.5 ml) and the mixture was kept at room temperature for 10 min. Subsequent work-up in the

usual way and recrystallisation of the crude product from hexane gave 17 (14 mg), m.p. 72-74°C; IR-KBr: 1694, 1680, 1600 cm^{-1}: UV: 260nm; MS: 234 (M^+,30),6219 (50), 191 (60); PMR: 0.97 (s, 3H, H-14), 1.80 (s, 3H, H-13), 2.10 (s, 3H, H-12), 2.22 (s, 3H, H-15), 2.35 (d, J=15 Hz, 1H, H-9'), 2.45 (d, J=15 Hz, 1H, H-6'), 2.60 (d, J=15 Hz, 1H, H-9), 2.85 (d, J=15 Hz, 1H, H-6).

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