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MELIANE*–MELIACIN RELATIONSHIP[1]

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Abstract—A direct relationship between the melianes and meliacins (limonoids) was established through opening of the 7α,8α-epoxide ring of a melianone derivative. The isolation and elucidation of the structure of a compound from *Melia azedarach* L. having a meliacin skeleton and meliane side chain lent further support to their postulated biogenetic relationship. Finally, in an attempt to convert the meliacin to a dammarane type skeleton the effect of opening the 14β,15β-epoxide ring in a few meliacin derivatives was also studied.

IN VIEW of the possible role played by epoxides in nature as demonstrated by the enzymatic conversion of squalene-2,3-oxide to lanosterol and cholesterol,[2] as well as by the conversion of simpler terpenes with terminal epoxides producing cyclic compounds[3] when reacted with $SnCl_4$, it has been anticipated that epoxides could also be involved in various secondary elaborations and transformations in the plant. Thus, a rearrangement induced by the opening of a 7α,8α-epoxide in an euphane–tirucallane type carbon skeleton may lead to an apoeuphol structure as in the meliacin (limonoid) series, whereby a migration of the C-14β Me to C-8 would take place with formation of a C-7 OH group having the correct α-orientation, and of a double bond at C-14, 15.[1,4] Such a sequence was performed using a melianone derivative as a model (reduction product of melianone[5] I). Thus, the isolation from the fruits of *Melia azedarach* L. of compound XII having an unaltered tirucallane side chain (characteristic of the melianes)* and an apo-euphol type skeleton (characteristic of the meliacins) clearly indicates that such a compound may be looked upon as a link between the melianes and the meliacins, and is probably due to different combinations of oxidative degradation reactions taking place in the plant.

The LAH reduction product IIa of melianone (I) (Δ^7 and C-14β Me) was selected for conversion to an apo-euphol structure. The tetrol (IIa) which was produced shows a broad unresolved complex signal in the NMR, ranging from δ 3·00 to 4·15 (4 × H) for 3α-H, 21-H (2 × H) and 23-H. The vinylic 7-H appears as a multiplet at δ 5·35, whereas the two side chain Me groups are at δ 1·25 and 1·21 in agreement with a hydroxyisopropyl system, determining thereby the direction of the epoxide opening taking place during the reduction. Furthermore, in its IR spectrum IIa shows a strong absorption at 3475 cm^{-1} for the four OH functions. Evidence for the structure of IIa was obtained from its mass spectrum in which the fragment *m/e* 404 corresponding to $M^+ - 72$ (4 × H_2O) is observed. Acetylation of IIa yielded the expected triacetate IIb in the NMR spectrum of which the signals corresponding to the four protons geminal to the acetoxy groups are now well resolved: multiplets for 3α-H at σ 4·52,

* The name of *melianes* is proposed for the group of compounds having a tirucallane type skeleton with an oxygenated ring system in the side chain as found in the Meliaceae.

21-H at δ 4·00 (2 × H) and 23-H at δ 5·29, the latter overlapping with the vinylic 7-H. The Me signals of the three acetate groups are as expected (Table 1), while those of the hydroxyisopropyl system are unchanged.

Treatment of IIb with perbenzoic acid afforded the 7α,8α-epoxy derivative III having an NMR spectrum basically similar to that of IIb (Table 1) with the exception of the epoxidic 7β-H signal a triplet at δ 2·89 (the 23-H signal at δ 5·29 now integrating

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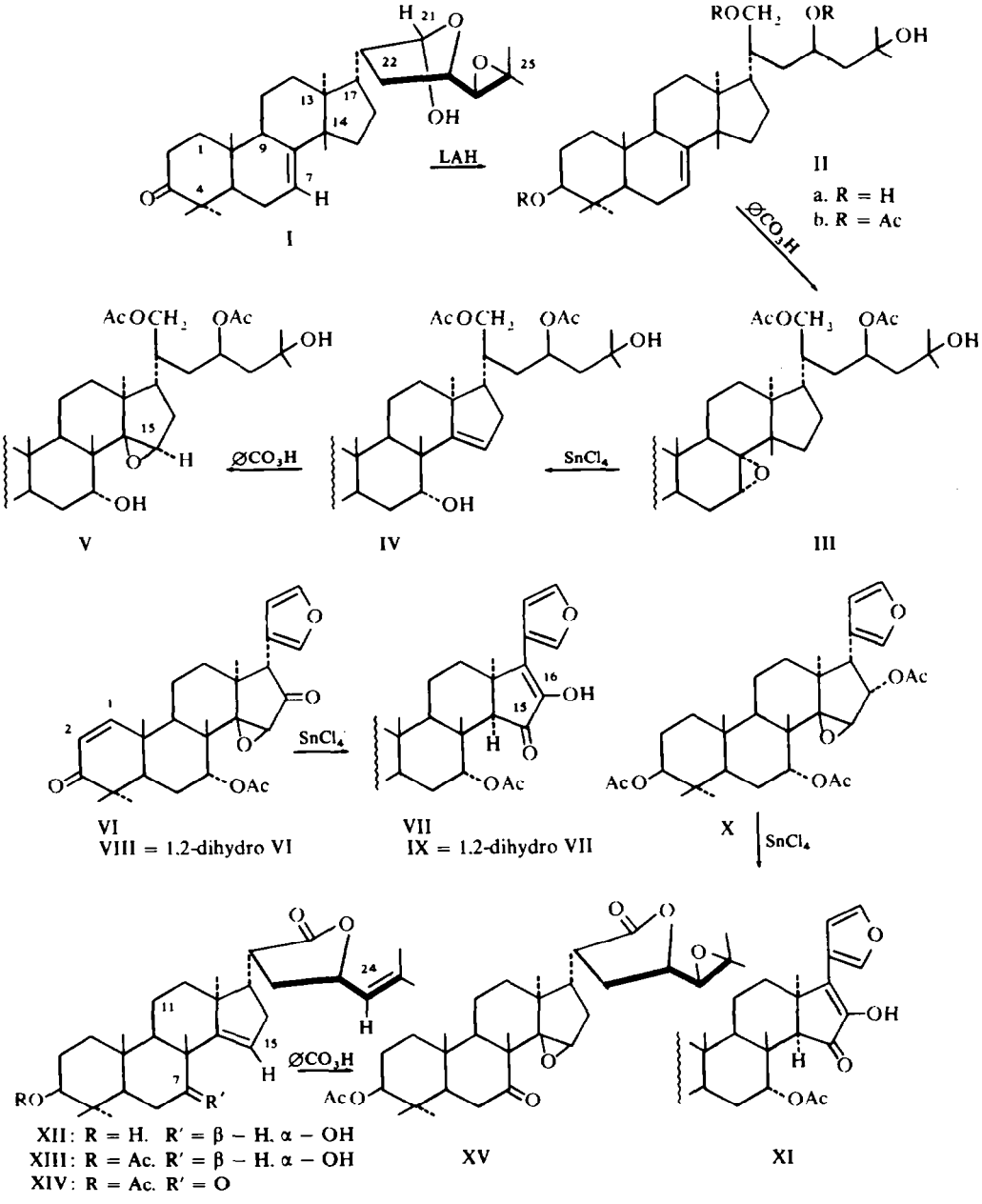


TABLE 1. CHEMICAL SHIFTS OF PROTONS OF THE COMPOUNDS (δ UNITS)

Compound	3-H	7-H	15-H	21-H	23-H	24-H	OAc	Me-groups					at 25	
I		5·38 t		5·38	3·90 m	2·90 d *J* 7·5 Hz		1·12 (2 × Me)	1·04 (2 × Me)	0·86			1·30 (2 × Me)	
IIa								1·00	0·97	0·90	0·85	0·74	1·25	121
IIb	4·52 m	5·29 t		4·00 m	5·29 m		2·03 (2 × Me) 2·08	0·92 (2 × Me)	0·84 (2 × Me)	0·76			1·25	1·20
III	4·55 m	2·89 t		4·00 m	5·29 m		2·03 (2 × Me) 2·08	1·16	1·11 (2 × Me)	1·01 (2 × Me)			1·24	121
								at 4α	4β	8	10	13	25	
IV	4·54 m	3·94 t	5·50 t	4·00 m	5·28 m		2·03 (2 × Me) 2·08	0·88	0·88	1·05	0·93	1·06	1·23 (2 × Me)	
V	4·56 m	3·88 t	3·45 s	4·01 m	5·29 m		2·01 (2 × Me) 2·07	0·87	0·87	1·01	0·93	1·06	1·23 (2 × Me)	
					22-H	23-H								
VI*		4·68 t	3·33 s	7·52 m	7·35 m	6·18 m	1·98	1·02	1·02	1·00	1·20	1·90		
VII†		5·28 t		8·05 m	7·52 m	6·94 m	2·06	1·05	1·05	0·95	1·21	1·45		
VIII		4·70 t	3·38 s	7·53 m	7·35 m	6·18 m	2·02	1·02	1·02	1·02	1·06	1·18		
IX		5·28 t		8·05 m	7·52 m	6·94 m	2·08	1·01	1·01	0·91	1·11	1·41		
X	4·59 m	4·84 t	3·45 s	7·45 m	7·40 m	6·37 m	2 × 2·05 21·2	0·78	0·85	1·03	0·95	1·25		
XI	4·59 m	5·25 t		8·05 m	7·52 m	6·94 m	2 × 2·05	0·78	0·86	0·86	0·97	1·41		
					23-H	24-H								
XIII	4·50 m	4·10 m	5·35 t		4·10 m	5·15 m	2·07	0·80	0·83	0·95	0·87	0·91	1·70	1·65
XIV	4·55 m		5·49 t		4·10 m	5·15 m	2·07	0·80	0·88	1·10	1·10	0·91	1·70	1·65
XV	4·52 m		2·95 s		4·15 m	2·85 d *J* 7 Hz	2·08	0·88	0·90	1·28	1·11	0·98	1·31 (2 × Me)	

* 1-H 7·10 d. 2-H 5·76 d (*J* 10 Hz).
† 1-H 7·07 d. 2-H 5·80 d (*J* 10 Hz).

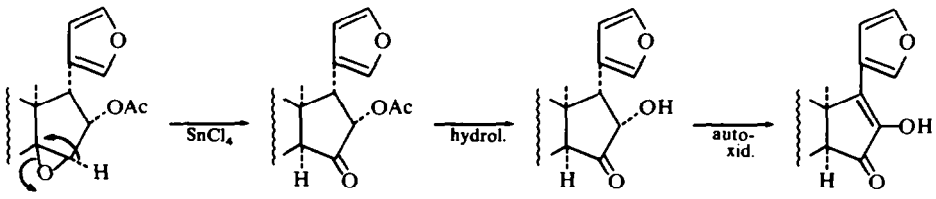
for one proton only). Opening of the epoxide III in dry benzene with $SnCl_4$ yielded the expected 7α-hydroxy-14-ene derivative (IV), product of the 14 → 8 Me migration, with generation of a double bond at 14–15. The presence of this double bond was disclosed in the NMR spectrum as a narrow triplet at δ 5·50 in addition to the new multiplet at δ 3·94 having a 1/2 W of 6 Hz, a value similar to that of 1,2-dihydro-7-deacetoxy-7α-hydroxy-epoxyazadiradione.[6] Hence the orientation of the OH group in IV is as expected from the opening of a 7α,8α epoxide ring. Further support for this structure was adduced by epoxidation of IV to the corresponding 14β,15β-epoxy-derivative (V) having now the characteristic[7] epoxidic 15α-H at δ 3·45.

Epoxyazadiradione[6] (VI) was the second model compound selected for the study of the effect of epoxide ring opening with concomitant Me migration, in this case from 13 → 14, producing thereby a dammarane type skeleton. It has previously been reported[8] that when cedrelone acetate was treated with BF_3 etherate, migration of a Me group from C-13 to C-14 took place with generation of a 13–17 double bond. However, treatment of VI with $SnCl_4$ gave a product to which structure VII was assigned on the following grounds. UV spectrum shows absorptions at λ_{max} 225 and 307 nm (ε 14,300 and 15,500), addition of alkali brought about a bathochromic shift of the latter to 343 nm (ε 11,500).[9] The IR shows absorption maxima at ν 1764 (—C(=O)—C(=O)— in a 5-membered ring),[10] 1736 (acetate), 1700 (cyclohexenone) and 886 (furan) cm^{-1}. Additional information concerning the structure of VII was obtained from its NMR spectrum in which the two singlets corresponding to the epoxidic 15-H as well as that of the 17-H originally present in VI are now missing, whereas the furanic proton signals suffer a paramagnetic shift due to the formation of the Δ^{16} bond: δ 8·05 for the α proton, 6·94 and 7·52 for the α′ and β′ protons respectively, all being multiplets. The singlet at δ 2·57 was assigned to the 14α-H being adjacent to the C-15 ketone function and thus at lower field than is normal for such a proton. The enolic 16-OH signal (singlet δ 6·55) disappears upon exchange with D_2O. Compound VII gave a positive test with $FeCl_3$. All these properties are clearly indicative of the presence of a diosphenol system which could only be located in ring D and its formation could be explained through a cleavage of the C_{14}—O bond concerted with 1,2-hydride shift from 15 → 14 with retention of configuration. The product being a diketone, is then enolised to form the keto–enol system. A similar sequence was also observed when 1,2-dihydro-epoxyazadiradione[6] (VIII) was treated with $SnCl_4$ giving the 1,2-dihydro-derivative IX.

In another set of experiments VI was reduced with $NaBH_4$ and acetylated to the corresponding 3α–16α diacetoxy epoxyazadiradione[6] X (for NMR see Table 1). Treatment of X with $SnCl_4$ afforded a product XI having the same disphenol system in ring D as in VII and IX. The mechanism for such a reaction is illustrated in Scheme a. Opening of the epoxide ring with concomitant 1,2-hydride shift from 15α → 14 would lead to the 15-oxo-16α-acetoxy intermediate (**1**) which upon hydrolysis and autoxidation[11] would yield the desired diosphenol (**2**) (for NMR see Table 1).

Having chemically demonstrated the relationship between the melianes and meliacins through conversion of the 7α,8α-epoxy-melianone derivative III to a meliacin type skeleton, the isolation of a compound from natural sources having the side chain of the former and the skeleton of the latter, is a supporting evidence for the

SCHEME *a*



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postulated biogenetic pathway. Such a compound may be looked upon as a link between the melianes and melacins.[12] It could be assumed that during the various enzymatic processes, oxidation of the hemiacetal to a lactone could take place, blocking the possibility of further degradation of the chain to form a furan ring, while the migration of the methyl group 14 → 8 would still take place.

Since compound XII could not be obtained in a pure form from the fruits of *Melia azedarach* L., purification was accomplished through acetylation and separation on thick layer chromatoplates to yield the pure crystalline acetyl derivative XIII. Elemental analysis and the molecular ion peak in the mass spectrum, M^+ 512, indicates an empirical formula $C_{32}H_{48}O_5$. The NMR spectrum of XIII shows signals corresponding to seven tertiary Me groups in the molecule, two of which being at lower field δ 1·70 and 1·65 are related to the vinylic 26,27-Me groups as is the case in flindissol,[13] while the vinylic 24-H is a multiplet at σ 5·15. That XIII is the monoacetyl derivative is clearly indicated from its NMR spectrum: one Me signal of the acetate group at δ 2·07. The rest of the signals are: 3α-H multiplet centred at δ 4·50, the vinylic 15-H triplet at δ 5·35, 23-H and 7β-H overlap as a complex signal at δ 4·10. The UV spectrum of XIII shows end absorption, at 200 nm (ε 11,300), while in the IR an absorption at 1776 cm^{-1} was attributed to the 5-membered ring lactone of the side chain.

Oxidation of XIII (Jones reagent) afforded the 7-oxo derivative XIV, for which the 15-H vinylic signal appears now as a triplet at lower field δ 5·49, while of the two overlapping 7β-H and 23-H, only that of the latter remains. Thus, of the two signals at δ 4·10 in XIII one is related to the proton geminal to a hydroxy group, which being secondary and not acetylatable has to be in a hindered position.

Hence, the problem at this stage was to locate this OH group and determine its relationship to the double bond. It has previously been shown that oxidation of a Δ^7-11-OH or alternatively $\Delta^{9(11)}$-7-OH compound, under the acidic conditions of the reaction, would have obviously led to the corresponding α,β-unsaturated ketone with the double bond at C-8, C-9 being tetrasubstituted (CO at 7 or 11).[14] Thus, in the NMR spectrum of XIV the second vinylic proton, in either of the proposed cases, would have disappeared. Since this signal continues to persist after oxidation, it can only be concluded that the relationship of the OH group to the double bond is not as proposed above. Further evidence was obtained through the elimination of the OH group with $SOCl_2$ in dry pyridine solution. In this reaction no diene derivative ($\Delta^{7,9(11)}$) with its characteristic absorption in the UV spectrum was formed. There

remains only two other possibilities, the double bond being at C-14 C-15 with the OH group either at C-7 or C-11. Oxidation of the OH group to the corresponding ketone XIV induced a downfield shift in the NMR spectrum of the 15-H signal from δ 5·35 in XIII to 5·49 in XIV, and therefore an OH group at C-11 has to be eliminated, since such a shift can be expected only when a C-7 OH is oxidized to the ketone.[15] Epoxidation of XIV with perbenzoic acid afforded the diepoxy derivative XV in which the 23-H is a multiplet at δ 4·15 and the epoxidic 15-H a narrow doublet at 2·95, in agreement with a 14β, 15β epoxide.[7] The second epoxidic proton in the molecule was shown to be located at position 24–25 of the side chain, doublet at δ 2·85 (J = 7 Hz) identical with that present in melianone[6] (I). The 26,27-Me signals are also in the expected positions.

EXPERIMENTAL

M.p. were taken on a Fisher–Johns apparatus. Optical rotations refer to $CHCl_3$ solns. IR spectra were recorded on a Perkin–Elmer Infracord model 137 spectrophotometer equipped with a NaCl prism and were determined in KBr pellets. UV spectra were recorded on a Cary 14 in EtOH soln. NMR spectra were recorded on a Varian A-60 spectrometer, for 5–10% solns in $CDCl_3$ containing TMS as internal standard. Column chromatography was done using florisil (100–200 mesh), silica gel-H (Merck) or silica gel (0·05–0·2 mesh, Merck) as stationary phases. TLC was done on chromatoplates of silica gel G (Merck) irrigated with $CHCl_3$–acetone (9 : 1) unless otherwise stated, and spots were developed with I_2 vapour. M. wts were determined by mass spectrometry on an Atlas CH4 instrument by Mr. S. Gattegno.

Isolation procedure. The berries from *Melia azedarach* L. were collected in November, crushed and exhaustively extracted with $CHCl_3$. The $CHCl_3$ residue (after removal of the solvent) was suspended in 80%aq MeOH and extracted with hexane. Water (4 × volume of aq MeOH) was then added and the aq layer extracted with $CHCl_3$, dried over Na_2SO_4, filtered and the organic solvent removed *in vacuo*. The crude product was then chromatographed on florisil and eluted with hexane with increasing concentration of $CHCl_3$. The fraction eluted with hexane–$CHCl_3$ (6 : 4) containing the compound with R_f 0·5 $CHCl_3$–acetone (9 : 1), as the major component was further purified on thick layer chromatoplates irrigated with $CHCl_3$–acetone (8 : 2) yielding a single spot on TLC (400 mg) $CHCl_3$–acetone (8 : 2). NMR spectrum showed it to be a mixture in which compound XII is the major component. Acetylation with Ac_2O in pyridine afforded a product showing two spots on a chromatoplate ($CHCl_3$–acetone, 8 : 2). Separation by thick layer chromatoplates irrigated with the same solvent mixture afforded pure upper spot XIII (200 mg) crystallized from MeOH, m.p. 169–171°; $[\alpha]_D$ −30° (*c*, 0·1); UV end absorption at 200 nm (ε 11.300); ν_{max} 3350 (OH), 1776 (5-membered ring lactone), 1720 (OAc) cm^{-1}. (Found: M^+ 512. $C_{32}H_{48}O_5$ requires: M. wt 512·70).

Oxidation of XIII *to* XIV. To compound XIII (150 mg) in acetone (20 ml) a few drops of Jones reagent were added at room temp. After the usual work up and passing the crude product through silica gel, pure XIV (120 mg) was obtained, crystallized from MeOH, m.p. 206–208°; $[\alpha]_D$ −3·5° (*c*, 0·1); UV end absorption at 205 nm (ε 11.400); ν_{max} 1776 and 1720 (cyclohexanone and OAc) cm^{-1}. (Found: M^+ 510. $C_{32}H_{46}O_5$ requires: M. wt 510·69).

Epoxidation of XIV *to* XV. To compound XIV (80 mg) in dry benzene (20 ml) was added perbenzoic acid (4 ml of 60 mg/ml) and the soln left at room temp overnight. After the usual work up XV (70 mg) crystallized from $CHCl_3$–hexane, m.p. 238–240°; $[\alpha]_D$ −4·0° (*c*, 0·1); UV end absorption, at 200 nm (ε 5600); ν_{max} 1776 and 1720 cm^{-1}. (Found: M^+ 542. $C_{32}H_{46}O_7$ requires: M. wt 542·69).

LAH reduction of I *to* IIa. To melianone I (4·4 g) in pure dry dioxan (1 : 1) was added LAH (6 g) and the soln stirred at room temp overnight. To increase the yield of IIa this reduction had to be repeated 3 times. After the usual work up the crude product showing 3 spots on a chromatoplate ($CHCl_3$–acetone, 7 : 3) was chromatographed on a florisil column and elution with $CHCl_3$–hexane (9 : 1) yielded pure IIa (1·5 g) crystallized from $CHCl_3$–hexane, m.p. 133–135°; $[\alpha]_D$ −39° (*c*, 1·0); UV end absorption, at 200 nm (ε 8000), ν_{max} 3475, 1635, 1609, 980 and 830 cm^{-1}. (Found: M^+ 476. $C_{30}H_{52}O_4$ requires: M. wt 476·72).

Acetylation of IIa *to* IIb. Acetylation of IIa in the usual way gave crystalline IIb (from MeOH) (1·3 g), m.p. 161–162°; $[\alpha]_D$ −10° (*c*, 1·1); UV end absorption, at 205 nm (ε 7600); ν_{max} 3475 and 1750 (OAc) cm^{-1}. (Found: M^+ 602. $C_{36}H_{58}O_7$ requires: M. wt 602·82).

Epoxidation of IIb *to* III. To compound IIb (1·1 g) dissolved in dry benzene (60 ml) was added perbenzoic acid (16 ml of 60 mg/ml) and the soln left at room temp overnight. After the usual work up pure III (1·0 g) crystallized from MeOH. m.p. 70–71°; $[\alpha]_D$ −5° (*c*, 1·0); UV end absorption. at 200 nm (ε 4500); ν_{max} 3475 and 1750 cm^{-1}. (Found: M^+ 618. $C_{36}H_{58}O_8$ requires: M. wt 618·82).

Treatment of III *with* $SnCl_4$. To compound III (900 mg) dissolved in dry benzene (30 ml) was added a few drops of a soln of $SnCl_4$ in dry benzene (~1% v/v) and the soln left at 10° for 10 min. After the usual work up the crude product showing 3 spots on TLC. Chromatography on silica gel-H and elution with $CHCl_3$–hexane (1:1) afforded pure IV (200 mg) crystallized from $CHCl_3$–hexane. m.p. 118–120°; $[\alpha]_D$ +10° (*c* 0·1); UV end absorption. at 210 nm (ε 8000); ν_{max} 3475 and 1750 cm^{-1}. (Found: M^+ 618. $C_{36}H_{58}O_9$ requires: M. wt 618·82).

Epoxidation of IV *to* V. Treatment of IV (100 mg) with perbenzoic acid in a manner similar to that described above gave pure V (90 mg) crystallized from $CHCl_3$–hexane. m.p. 110–112°; $[\alpha]_D$ −15° (*c*, 0·1); UV end absorption at 200 nm (ε 5400); ν_{max} 3475 and 1750 cm^{-1}. (Found: M^+ 634. $C_{36}H_{58}O_9$ requires: M. wt 634·82).

Treatment of VI. VIII *and* X *with* $SnCl_4$. To compound VI (300 mg) dissolved in dry benzene (25 ml) was added a few drops of a soln of $SnCl_4$ in dry benzene (~1% v/v) and the mixture left at room temp for 25 min. The crude product, after the usual work up, showed five spots on a chromatoplate, one being the major spot. Chromatography on silica gel-H and elution with $CHCl_3$–hexane (7:3) yielded pure VII (150 mg) crystallized from $CHCl_3$–hexane mixture; m.p. 270–272° dec.; $[\alpha]_D$ +5° (*c*, 0·1); λ_{max} 225 and 307 nm (ε 14.300 and 15.500); (1% KOH) 225 and 343 nm (ε 14.300 and 11.500); ν_{max} 1764 (cyclopentenone), 1736 (OAc), 1700 (cyclohexenone) and 886 (furan) cm^{-1}. (Found: M^+ 466. $C_{28}H_{34}O_6$ requires: M. wt 466·55).

In a similar reaction compound VIII (300 mg) yielded pure IX (150 mg) crystallized from $CHCl_3$–hexane. m.p. 241–243°; $[\alpha]_D$ −3° (*c*, 0·1); λ_{max} 217 (furan) and 307 nm (ε 22.400); (1% KOH) 343 nm (ε 17.400); ν_{max} 1764, 1730, 1710 (cyclohexanone) and 886 cm^{-1}. (Found: M^+ 468. $C_{28}H_{36}O_6$ requires: M. wt 468·57).

Treatment of X (400 mg) with the same reagent, followed by chromatography on silica gel and elution with hexane–Et_2O (6:4) yielded pure XI (200 mg), crystallized from MeOH. m.p. 170° dec; $[\alpha]_D$ −5° (*c*, 0·1); λ_{max} 217 and 307 nm (ε 20.520); (1% KOH) 343 nm (ε 17.400); ν_{max} 1764, 1730 and 886 cm^{-1}. (Found: M^+ 512. $C_{30}H_{40}O_7$ requires: M. wt 512·62).

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