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BIOMIMETIC SYNTHESIS OF 1,10-SEC-EUDESMANOLIDES

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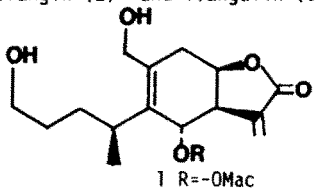
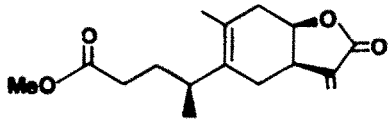
Abstract- The 1-hydroperoxy-eudesmanolides 9,10,21 and 22 were prepared, then converted to 1,10-sec-eudesmanolides via hydroperoxide transposition and/or homolytic fragmentation.The possible biogenetic significance of these processes is discussed.

The 1,10-sec-eudesmanolides are a small group of sesquiterpene lactones,three of which, eriolanin (1),eriolangin (2)[1] and ivangulin (3)[2] have already been synthesized.[3]



1 R=-OMac
2 R=-OTig



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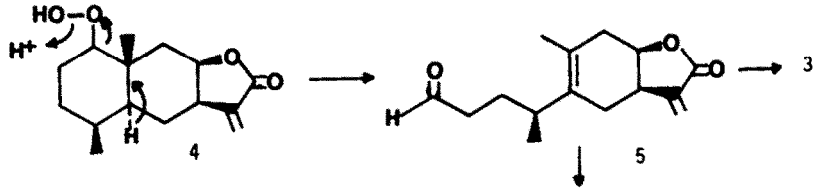
Herz suggested[4] that the biogenesis of the 1,10-sec-eudesmanolides could develop along the lines shown in Scheme I:

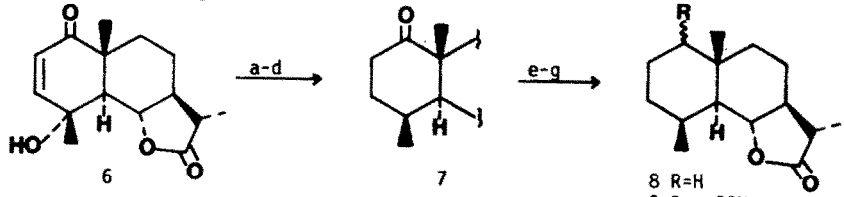
SCHEME I



4 5 1 (2)

To check if this is so[5],the 1-hydroperoxy-eudesmanolides 9 and 10 were prepared from vulgarin (6)[6] which was treated with Zn-HOAc,followed by reduction,hydrogenation and oxidation,to yield 7 (48%).[7] The method described by Cagliotti *et al*[8] was then applied to 7 which was treated with tosylhydrazine,diborane and sodium peroxide-hydrogen peroxide to give the epimers 9 and 10 (8:10, 46%),which,when reduced with Ph_3P,gave the alcohols 11 and 12 (Scheme II).

SCHEME II



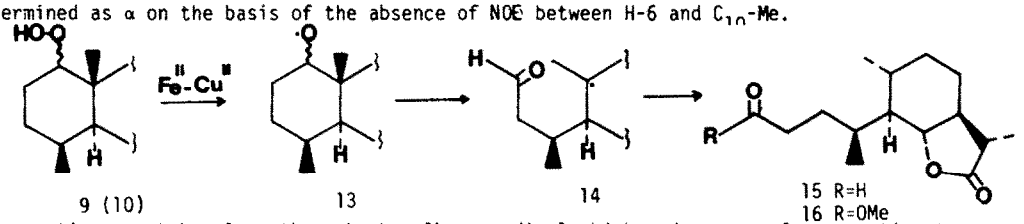
6 7

a)Zn-HOAc;b)$NaBH_4$;c)H_2-Pd;d)Jones
e)NH_2.NHTs;f)B_2H_6;g)H_2O_2-Na_2O_2

8 R=H
9 R=α-OOH
10 R=β-OOH
11 R=α-OH
12 R=β-OH

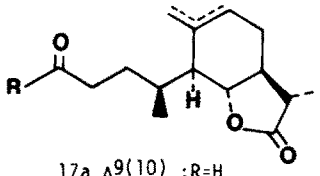
If 9 was treated with Ac_2O-py or $HClO_4$-HOAc, ketone 7 was obtained in 87% or 62% yields, respectively, the result of a hydroperoxide transposition, with a hydride migration instead of the desired σ[1,10] migration[9]. Its epimer, 10, reacted identically, and neither showed any signs of fragmentation products, in apparent contradiction of Herz' hypothesis.

However, when $FeSO_4$-$Cu(OAc)_2$[10] was applied to 9 or 10, aldehyde 15 was obtained (59%) and could be converted to ester 16 by oxidation and diazomethane esterification. The C_{10}-Me stereochemistry was determined as α on the basis of the absence of NOE between H-6 and C_{10}-Me.

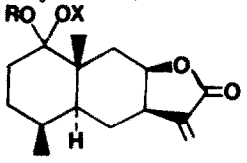


9 (10) 13 14 15 R=H 16 R=OMe

The reaction may take place through the alkoxy radical which undergoes β-fragmentation to generate aldehyde 15. This possibility is favoured by the fact that alcohol 12, when treated with LTA-I_2[11] or with iodosobenzene diacetate-I_2[12], yields the unsaturated aldehyde 17a (72 and 56%, respectively).



17a $\Delta^{9(10)}$;R=H
17b $\Delta^{9(10)}$;R=OMe
18 $\Delta^{10(14)}$;R=OMe



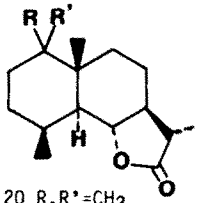
19 X=leaving group

Enzymatic transformations of hydroperoxides to aldehydes in various plants[13] have been observed and may be the pathway to the formation of 1,10-sec-eudesmanes. However it is difficult to reconcile the results given above with the hydroperoxide-type transpositions provoked by the "hydroperoxy cleavage enzyme or lyase" in linoleic acid 9- or 13-hydroperoxides, since only the volatile aldehydes, cis-3-nonenal or hexanal, are generated in these processes, together with the corresponding 9-oxo-nonanoic and 12-oxo-cis-dodecenoic fragments[14], which would appear to rule out the possibility of a homolytic fragmentation.

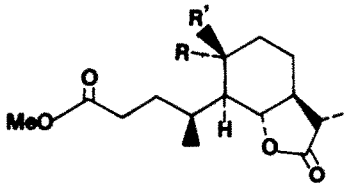
A second hypothesis of Herz[2] is that the 1,10-sec-eudesmanolides may be formed from a eudesmane precursor such as 19 by a process similar to that proposed by Barton et al for the biogenesis of nycthantic and dammarenolic acids[15].

We therefore decided to prepare an analog of 19 and test the feasibility of its transformation to 1,10-sec-eudesmanolides.

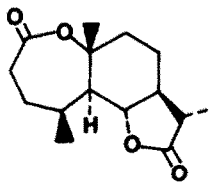
It is well known that geminal hydroxyhydroperoxides have variable stability[16], while alkoxy-hydroperoxides are considerably more stable. The compound chosen as model was 21 (X=OH, R=Me), and it was thought that it could be prepared by ozonolysis of the olefin 20 in the presence of methanol[17]. This olefin was prepared from ketone 7 by the Wittig reaction and was then subjected to ozonolysis (CH_2Cl_2-anhydrous MeOH, 5:1, -78°C). The crude from the reaction was treated with Ac_2O-py and after concentration at low temperature[18], the hydroxymethyl ester 23 was obtained in 43% yield and its structure was established by a detailed spectroscopic study and comparison with an authentic sample prepared from 7 by treatment with MCPBA and subsequent methanolysis of the ε-lactone 24 with K_2CO_3 in methanol.



20 R,R'=CH_2
21 R=β-OOH;R'=α-OMe
22 R=β-OTBDMS;R'=α-OOH



23 R=OH;R'=Me



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When 21 was fragmented by treatment with $FeSO_4$-$Cu(OAc)_2$,the methyl ester 16 and the olefins 17b and 18 (10:8) were obtained and identified by comparison with authentic samples prepared from 23 by dehydration with $SOCl_2$-py.

As it proved impossible to isolate the intermediate alkoxyhydroperoxide 21,all attempts to do so only affording the starting ketone,7, a compound analogous to 21 was prepared.The t-butyldimethylsilyl enol ether of 7 was prepared[19] (97%) and then treated with anhydrous hydrogen peroxide and TFA[20] to yield the 1-silyloxy-1-hydroperoxy derivative 22 (79%) which,when treated with Ac_2O-py, gave the dilactone 24 (84%).When 21 was cleaved with $FeSO_4$-$Cu(OAc)_2$[11,12],methyl ester 16 (50%) was obtained after esterification with diazomethane.

The results obtained seem to support the hypothesis that the 1,10-sec-eudesmanolides may be derived from 1-hydroperoxy-1-hydroxy-eudesmanes via a hydroperoxide transposition essentially equivalent to a Baeyer-Villiger oxidation[14].Less likehood attaches to the implication of the 1-hydroperoxy-eudesmanes as precursors,due to the preferred migration of the hydrogen on the $\sigma^{1,10}$ b nd.However it is necessary to add that mono-oxygenases capable of converting ketones to lactones are known[21],with some discrepancies between the chemical and enzymatic results,as Chapman et al[22] have shown in the microbial conversion of fenchone by the action of species of Coryneabacterium.

EXPERIMENTAL

Mp's were determined using a Kofler hot-plate and are uncorrected.I.r. spectra were recorded on a Perkin-Elmer 257 and n.m.r. spectra were taken at 90 MHz on a Perkin-Elmer R-123 and at 200 MHz on a Bruker 200SY,with $CDCl_3$ as solvent.Mass spectra were measured on a VG Micromass ZAB-2F.Unless otherwise stated,column chromatography was carried out using Merck silica gel (0.065-0.2 mm).

Preparation of 7 a)A solution of dihydrosantamarin (prepared from vulgarin as described in reference 23) (1.64 g) in EtOAc was hydrogenated for 24 h at room temperature and atm. pressure using Pd-C (10%,100 mg) as catalyst.After filtration of the catalyst through celite,the resulting solution was concentrated and chromatographed.Elution with a 1:1 hexane-EtOAc mixture afforded tetrahydrosantamarin (12) (1.61 g,97%),mp=165-167° (hexane-CH_2Cl_2) (lit[24] 169°);$[\alpha]_D$+36.5 ($CHCl_3$, 0.23). H nmr:δ ppm 4.02(1H,dd,J=9.9 and 9.8 Hz,H-6),3.33(1H,br s,H-1),1.23(3H,d,J=6.9 Hz,C_{11}-Me), 1.02(3H,s,C_{10}-Me),1.00(3H,d,J=7.6 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},3600(OH),1760(γ-lactone).H.r.m.s., m/z 237.1498 (M^+-Me,$C_{14}H_{21}O_3$),234.1498 (M^+-H_2O,$C_{15}H_{22}O_2$).

b)A solution of tetrahydrosantamarin (1.26 g) in acetone (20 ml) was oxidized at 0° with Jones' reagent until the orange colour persisted.The resulting solution was poured over ice and $NaHCO_3$-saturated solution,extracted with CH_2Cl_2,washed with water, dried over anhydrous Na_2SO_4, concentrated and chromatographed with hexane-EtOAc (7:3) as eluent.7 (1.14 g,91%) was obtained: mp=195-197° (hexane-CH_2Cl_2);$[\alpha]_D$+64.5° ($CHCl_3$,0.20).H nmr:δ ppm 4.04(1H,dd,J=9.8 and 9.7 Hz,H-6), 1.25(3H,s,C_{10}-Me),1.23(3H,d,J=7.4 Hz,C_4-Me),1.22(3H,d,J=6.9 Hz,C_{11}-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},1765 (γ-lactone),1700(carbonyl).H.r.m.s.,m/z 235.1305 (M^+-Me,$C_{14}H_{19}O_3$),250.1560 (M^+,$C_{15}H_{22}O_3$).

Preparation of 9 and 10 a)To a solution of 7 (750 mg) in absolute MeOH (20 ml) and dry $CHCl_3$ (5 ml), tosylhydrazine (586 mg) and concentrated HCl (35%,0.05 ml) were added.The mixture was slowly distilled and 20 ml of distillate was collected.Removal of the remaining solvent at reduced pressure yielded tosylhydrazone as a pale yellow oil.Attempts to crystallize produced significant decomposition to the ketone 7.H nmr:δ ppm 8.10(1H,s,-NH-),7.68(2H,d,J=8.3 Hz,aromatics),7.35 (2H, d,J=8.1 Hz,aromatics),3.96(1H,dd,J=9.8 and 11.3 Hz,H-6),2.43(3H,s,Me-C_6H_4-),1.22(3H,d,J=6.8 Hz, C_{11}-Me),1.13(3H,s,C_{10}-Me),1.10(3H,d,J=7.4 Hz,C_4-Me).Ir:ν_{max} (film)cm^{-1},3290(-NH-),1760(γ-lactone).

b)Tosylhydrazone in tetrahydrofuran (6 ml) was treated with 1 M diborane solution in THF (6 ml) for 35 min at 0° and under argon.EtOH (15 ml) was added and after 30 min,the solvent was removed at reduced pressure.The oily residue was dissolved in Et_2O (30 ml),and H_2O_2 (30%,30 ml) and Na_2O_2 (351 mg) were added.The mixture was stirred at r.t. for 24 h,then diluted with water and extracted with Et_2O.The soln was dried over Na_2SO_4 and evaporated under reduced pressure.The oily residue was chromatographed with hexane-EtOAc mixtures (9:1 and 7:3) as eluents.8 (72 mg,10% based on 7): mp=153-155° (hexane-CH_2Cl_2);$[\alpha]_D$+57.6° ($CHCl_3$,0.30).H nmr:δ ppm 3.92(1H,dd,J=11.7 and 9.6 Hz,H-6), 1.20(3H,d,J=6.9 Hz,C_{11}-Me),1.02(3H,s,C_{10}-Me),0.99(3H,d,J=7.5 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},1750 (γ-lactone).H.r.m.s.,m/z 236.1174 (M^+,$C_{15}H_{24}O_2$),221.1545(M^+-Me,$C_{14}H_{21}O_2$).Compounds 9 and 10 (8:10 based on mixture reduction to the corresponding alcohols;370 mg,46% overall yield based on 7). Compound 9 was obtained from the mixture by crystallization with hexane-CH_2Cl_2:mp=156-159°;$[\alpha]_D$ +101° ($CHCl_3$,0.20).H nmr:δ ppm 7.79(1H,br s,HOO-,removed by D_2O exchange),3.90(1H,dd,J=9.9 and 9.8 Hz,H-6),3.68(1H,br s,H-1),1.17(3H,d,J=6.7 Hz,C_{11}-Me),1.07(3H,s,C_{10}-Me),1.00(3H,6.7 Hz,C_4-Me).Ir: ν_{max} ($CHCl_3$)cm^{-1},3520(OOH),1760(γ-lactone).H.r.m.s.,m/z 235.1579(M^+-OOH,$C_{15}H_{23}O_2$).Mother-liquor chromatography with hexane-EtOAc (7:3) as eluent yielded compound 10 as an oil:H nmr:δ ppm 8.02 (1H,br s,HOO-,removed by D_2O exchange),3.98(1H,dd,J=9.9 and 9.9 Hz,H-6),3.67(1H,m,H-1),1.20(3H,d, J=6.8 Hz,C_{11}-Me),0.99(3H,d,J=7.5 Hz,C_4-Me),0.99(3H,s,C_{10}-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},3520(OOH),1760 (γ-lactone).H.r.m.s.,m/z 235.1554 (M^+-OOH,$C_{15}H_{23}O_2$).

Reduction of mixture of 9 and 10 A mixture of 9 and 10 (18 mg) in acetone (2 ml) was treated with Ph_3P (17 mg) for 30 min at room temperature.Chromatography with hexane-EtOAc (7:3) as eluent gave compounds 11 (6 mg) and 12 (5 mg).Compound 11:mp=110-111° (hexane CH_2Cl_2);$[\alpha]_D$+77.8° ($CHCl_3$,0.20). H nmr:δ ppm 3.96(1H,dd,J=9.8 and 9.8 Hz,H-6),3.43(1H,br s,H-1),1.20(3H,d,J=6.8 Hz,C_{11}-Me),1.03(3H, s,C_{10}-Me),1.02(3H,d,J=7.5 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},3600(OH),1760(γ-lactone).H.r.m.s.,m/z 237.1497(M^+-Me,$C_{14}H_{21}O_3$).

Treatment of 9 and 10 with Ac_2O-py A solution of 9 (30 mg) in dry pyridine (0.5 ml) was treated

with Ac_2O (0.5 ml) for 24 h at r.t.The mixture was poured onto ice and water,extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4,concentrated and chromatographed with hexane-EtOAc (1:1) as eluent. Ketone 7 (87%) was obtained.
When compound 10 was subjected to identical treatment,compound 7 was also obtained.
Acid treatment of 9 and 10 To a solution of 9 (20 mg) in HOAc (3 ml),$HClO_4$ (70%,1 ml) was added. After being stirred at r.t. for 24 h,water was added,the mixture was neutralized with a saturated-$NaHCO_3$ solution,extracted with CH_2Cl_2,dried over anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.From the hexane-CH_2Cl_2 crystallization, 7 (13 mg) was obtained.When 10 was treated in the same way, 7 was also produced.
Homolytic fragmentation of 9 and 10 To a solution of 9 (115 mg) in abs. MeOH (15 ml),$Cu(OAc)_2.H_2O$ (132 mg) was added.When all the Cu salt was dissolved,$FeSO_4.7H_2O$ (185 mg) in abs. MeOH (10 ml)was added under argon.After 2 h at r.t. the soln was diluted with EtOAc,filtered through silica gel, concentrated at reduced pressure and chromatographed with hexane-EtOAc as eluent.Compound 15 was obtained (63 mg,59%) as an oil: H nmr:δ ppm 9.79(1H,br s,-CHO),3.69(1H,dd,J=10.6 and 10.4 Hz,H-6), 1.20(3H,d,J=6.8 Hz,C_{11}-Me),1.05(3H,d,J=7.1 Hz,C_4-Me),1.00(3H,d,J=6.3 Hz,C_{10}-Me).Ir:ν_{max} ($CHCl_3$) cm^{-1},2800,2700,1720(aldehyde),1760(γ-lactone).M.S.,m/z 252(M^+),251(M^+-1),223(M^+-29).Compound 7 was also obtained (19 mg,17.7%).
Oxidation and esterification of 15 To a solution of 15 (55 mg) in EtOH (10 ml),$AgNO_3$ (100 mg) and distilled water (2.5 ml) were added.NaOH (1.5 M,2.5 ml) was added dropwise while stirring.After 2 h at r.t.,the mixture was filtered,the solid material was washed with more distilled water.The aqueous soln was acidified with HCl (10%),extracted with CH_2Cl_2 and dried over Na_2SO_4.Removal of the solvent afforded crude carboxylic acid as an oil: H nmr:δ ppm 3.68(1H,dd,J=10.6 and 10.3 Hz,H-6), 1.20(3H,d,J=6.8 Hz,C_{11}-Me),1.07(3H,d,J=7.1 Hz,C_4-Me),0.99(3H,d,J=6.2 Hz,C_{10}-Me).Ir:ν_{max} ($CHCl_3$) cm^{-1},3500,1700(carboxyl),1760(γ-lactone).This carboxylic acid was esterified with excess ether soln of diazomethane.Chromatography with hexane-EtOAc 1:1 as eluent gave ester 16 as an oil. H nmr: δ ppm 3.68(1H,dd,J=9.9 and 10 Hz,H-6),3.65(3H,s,-OMe),1.19(3H,d,J.6.9 Hz,C_{11}-Me),1.05(3H,d,J=7 Hz, C_4-Me),0.98(3H,d,J=6.4 Hz,C_{10}-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},1760(γ-lactone),1725(ester).H.r.m.s.,m/z 251.1628(M^+-OMe,$C_{15}H_{23}O_3$).
Homolytic fragmentation of alcohol 12 a)A suspension of $CaCO_3$ (1.8 g) and LTA (5.3 g) in dry cyclohexane (80 ml) was refluxed under argon for 10 min.Alcohol 12 (504 mg) and iodine (508 mg) were added and the mixture refluxed and irradiated with a 500 watt tungsten lamp for 1 h.The mixture was cooled,filtered,the solid material washed with more cyclohexane.The organic soln was washed with concentrated-$Na_2S_2O_7$ solution and water,dried over anhydrous Na_2SO_4,concentrated and chromatographed.With a 8:2 hexane-EtOAc eluent,aldehyde 17a was obtained (362 mg,72%):mp=112-114°; $[\alpha]_D$ -28.3° ($CHCl_3$,0.30). H nmr:δ ppm 9.78(1H,s,-CHO),5.55(1H,br s,H-9),3.95(1H,dd,J=10 and 10 Hz, H-6),1.69(3H,br s,C_{10}-Me),1.22(3H,d,J=7 Hz,C_{11}-Me),1.11(3H,d,J=7 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1}, 1760(γ-lactone),1716(aldehyde).H.r.m.s.,m/z 250.1550(M^+,$C_{15}H_{22}O_3$),206.1253(M^+-C_2H_4O,McLafferty, $C_{13}H_{18}O_3$).No exo isomer ($\Delta^{10,14}$) was detected.
b)To a solution of 12 (378 mg) in dry cyclohexane-CH_2Cl_2 (9:1,50 ml),iodosobenzene diacetate (531 mg) and iodine (127 mg) were added and the mixture irradiated under argon for 2½ h with a 500 watt tungsten lamp at r.t.The organic soln was washed with water,HCl (5%),concentrated-$Na_2S_2O_7$ solution and water,dried over anhydrous Na_2SO_4,concentrated and chromatographed with hexane-EtOAc 8:2 as eluent.Aldehyde 17a was obtained (210 mg,56%).No exo isomer was detected.
Oxidation and esterification of 17a Oxidation and esterification of aldehyde 17a,as above for aldehyde 15,provided methylester 17b:mp=78-80°(hexane-CH_2Cl_2).$[\alpha]_D$-28.1° ($CHCl_3$,0.30). H nmr:δ ppm 5.55(1H,br s,H-9),3.95(1H,dd,J=10 and 10 Hz,H-6),3.67(3H,s,-OMe),1.70(3H,s,C_{10}-Me),1.23(3H,d,J=6.9 Hz,C_{11}-Me),1.12(3H,d,J=7 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},1760(γ-lactone),1725(ester).H.r.m.s.,m/z 249.1445(M^+-OMe,$C_{15}H_{21}O_3$).
Preparation of olefin 20 A solution of freshly prepared sodium t-amyloxide in toluene (1.5 N,5 ml) was added to a triphenylmethylphosphonium bromide (3.16 g) suspension in dry toluene (20 ml) and stirred under argon until a yellow precipitate was formed.Ketone 7 (1.6 g) in dry toluene (40 ml) was added and the mixture refluxed under argon for 24 h.The mixture was filtered,washed with Et_2O, concentrated at reduced pressure and chromatographed with hexane-EtOAc(7:3)as eluent.Olefin 20 (1.3 g,93%) was obtained and starting material 7 (190 mg) was recovered.Compound 20:mp=163-164° (hexane-CH_2Cl_2);$[\alpha]_D$+111.5° ($CHCl_3$,0.20). H nmr:δ ppm 4.69(1H,s,H-16),4.59(1H,s,H*-16),4.01(1H,dd, J=9.7 and 11.5 Hz,H-6),1.22(3H,d,J=7 Hz,C_{11}-Me),1.16(3H,s,C_{10}-Me),1.10(3H,d,J=7.4 Hz,C_4-Me).Ir: ν_{max}($CHCl_3$)cm^{-1},1760(γ-lactone),1634(double bond).H.r.m.s.,m/z 248.1781 (M^+,$C_{16}H_{24}O_2$).
Ozonolysis and fragmentation of 20 a)A current of ozone (750 mg/h) was passed through a solution of 19 (155 mg) in CH_2Cl_2-anhydrous MeOH (5:1;12 ml) for 30 min at -78°.The solvent was partially removed by a dry nitrogen stream and dry pyridine (4 ml) and Ac_2O (3 ml) were added,also at -78°. The reaction mixture was allowed to warm to r.t. and was stirred for 24 h,poured onto ice and water,washed with aqueous $NaHCO_3$ solution,extracted with CH_2Cl_2,dried over anhydrous Na_4SO_4, concentrated and chromatographed.With a 1:1 hexane-EtOAc eluent,compound 23 was obtained (80 mg, 43%) as an oil: H nmr:δ ppm 3.75(1H,dd,J=10.3 and 10.4 Hz,H-6),3.63(3H,s,-OMe),1.25(3H,s,C_{10}-Me), 1.19(3H,d,J=6.8 Hz,C_{11}-Me),1.04(3H,d,J=7 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},3500(OH),1770(γ-lactone), 1725(ester).H.r.m.s.,m/z 224.1370 (M^+-$C_3H_6O_2$,McLafferty,$C_{13}H_{20}O_3$).
b)Compound 20 (350 mg) was treated with ozone as above and $Cu(OAc)_2.H_2O$ (422 mg) and $FeSO_4.7H_2O$ (262 mg) were added under argon at -78°.The reaction mixture was allowed to warm to room temperature.After 14 h the solvents were evaporated at reduced pressure and the resulting mixture was chromatographed with silica gel-$AgNO_3$(10%) and hexane:EtOAc (8:2) as eluent.Methyl ester 16 and olefins 17b and 18 in a 30:10:8 relationship were obtained (39.5 overall yield).Compound 18, oil: H nmr:δ ppm 5.00(1H,br s,H-14),4.90(1H,br s,H*-14),3.95(1H,dd,J=9.9 and 10 Hz,H-6),3.57(3H, s,-OMe),1.22(3H,d,J=6.9 Hz,C_{11}-Me),1.09(3H,d,J=7 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},1760(γ-lactone), 1725(ester)1500(double bond).H.r.m.s.,m/z 249.1523 (M^+-OMe,$C_{15}H_{21}O_3$).
Baeyer-Villiger Oxidation of ketone 7 To 7 (500 mg) in CH_2Cl_2 (20 ml),$NaHCO_3$ (420 mg) and MCPBA (1 g) were added and stirred at r.t. for 24 h.The mixture was then filtered,the solvent was evaporated at reduced pressure and chromatographed with 7:3 hexane-EtOAc to give 24 (520 mg,91%): mp=238-239° (hexane-CH_2Cl_2);$[\alpha]_D$+88° ($CHCl_3$,0.20). H nmr:δ ppm 3.73(1H,dd,J=10.6 and 11.4 Hz,H-6), 1.59(3H,s,C_{10}-Me),1.24(3H,d,J=6.9 Hz,C_{11}-Me),1.17(3H,d,J=7.5 Hz,C_4-Me).Ir:ν_{max} ($CHCl_3$)cm^{-1},1770

(γ-lactone),1710(ε-lactone).H.r.m.s.,m/z 266.1460(M^+,$C_{15}H_{22}O_4$).
Methanolysis of lactone 24 Anhydrous K_2CO_3 (690 mg) was added to 24 (266 mg) dissolved in abs. MeOH (30 ml) and stirred at r.t. for 24 h.After filtering and evaporation of the solvent at reduced pressure,chromatography with 7:3 hexane-EtOAc yielded 23 (205 mg,68.8%).
Dehydration of 23 $SOCl_2$ (0.5 ml) was added to 23 (196 mg) in dry pyridine (2 ml) at 0°.The soln was stirred for 30 min at 0°,water was added,it was extracted with CH_2Cl_2, washed with a saturated soln of $NaHCO_3$ and water,dried on anhydrous Na_2SO_4 and concentrated at reduced pressure. Chromatography with 8:2 hexane-EtOAc gave 17b (123 mg),18 (14 mg) and traces of $\Delta^{5,10}$ isomer.

Preparation of 22 a)Dry triethylamine (0.4 ml) and TBDMSTf (0.8 ml) were added to ketone 7 (500 mg) in dry CH_2Cl_2 (10 ml) and stirred for 3 h at r.t. under argon;more CH_2Cl_2 and a saturated soln of $NaHCO_3$ were added,the mixture was extracted with CH_2Cl_2,dried on anhydrous Na_2SO_2 and the solvent eliminated at reduced pressure.Chromatography with 1:1 CH_2Cl_2-hexane yielded the corresponding silylenol ether (710 mg,97.6%)which could not be crystallized: H nmr:δ ppm 4.52(1H, m,H-2),4.03(1H,dd,J=9.7 and 9.7 Hz,H-6),1.19(3H,d,J=7Hz,C_{11}-Me),1.17(3H,s,C_{10}-Me),1.00(3H,d,J=7.5 Hz,C_4-Me),0.91(9H,s,t-Bu),0.14(6H,d,J=2.7 Hz,Me_2-Si-).Ir:ν_{max} ($CHCl_3$)cm^{-1},1760(γ-lactone),1650 (enol).H.r.m.s.,m/z 364.2417(M^+,$C_{21}H_{26}O_3Si$).
b)An ether soln of hydrogen peroxide (0.8 N,15 ml),anhydrous $MgSO_4$ (950 mg) and TFA (7 μl) were added to the above silylenol ether (530 mg) and the resulting suspension was stirred for 3 h at r.t..A saturated soln of $NaHCO_3$ was then added,the mixture was extracted with ether,dried over anhydrous $MgSO_4$ and the solvent eliminated at reduced pressure.9:1 hexane-EtOAc chromatography gave starting material (345 mg,35% conversion) and 22 (160 mg,79%) as an oil: H nmr:δ ppm 7.41(1H, s,OOH,removed by D_2O exchange),3.94(1H,dd,J=10 and 10.1 Hz,H-6),1.19(3H,d,J=6.9 Hz,C_{11}-Me),1.12 (3H,s,C_{10} -Me),1.01(3H,d,J=7.5 Hz,C_4-Me),0.90(9H,s,t-Bu),0.18(6H,J=3.7 Hz,Me_2-Si-).Ir:ν_{max} ($CHCl_3$) cm^{-1},3520(OOH),1760(γ-lactone).
Fragmentation of 22 a)Ac_2O (0.5 ml) was added to 22 (60 mg) in dry pyridine (0.5 ml) and stirred for 24 h at r.t. Ice and a saturated soln of $NaHCO_3$ were added,the mixture was extracted with CH_2Cl_2 ,dried over anhydrous Na_2SO_4 and the solvent eliminated at reduced pressure.1:1 hexane-EtOAc chromatography gave the bilactone 24 (34 mg,85%).
b) $Cu(OAc)_2.H_2O$ (100 mg) was added to 22 (140 mg) in abs. MeOH (5 ml) and when it had dissolved, $FeSO_4.7H_2O$ (139 mg) was added and stirred at r.t. for 24 h.After the solvent had been eliminated at reduced pressure.Esterification with diazomethane gave methylester 16 (52 mg).

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