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SYNTHESIS OF CIS HEXAHYDROBENZOPYRANONES : BICYCLIC PRECURSOR LACTONES TO THE TRICHOTHECENES

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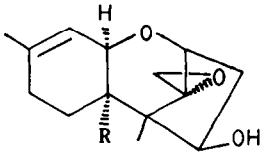
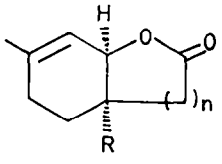
Abstract : Synthesis of bicyclic lactones **4** - **6**, potential precursors to trichothecenes is described. These incorporate the cis AB ring juncture and double bond in proper position in ring A. Luche reduction of **7** followed by hydrolysis furnished lactone **9**. Reaction of **7** with MeMgI and subsequent hydrolysis led to lactone **11** and was transformed to **4**. Reduction of **14** and hydrolysis produced pyran carboxylic acid **15** which was converted to **20**. Protection as epoxide **21** and oxidation with RuO_4 furnished epoxylactone **22**. Attempted deoxygenation afforded **5** which could not be obtained in pure form. Hydrolysis of primary ester in **14** and reduction of the sodium salt and subsequent acid treatment afforded lactone **6** and was converted to unsaturated lactone **23**.

The isolation and structure elucidation of trichothecenes[1], the highly oxygenated and intriguing sesquiterpenes, have led to one of the most intensive efforts directed towards their chemical synthesis[2]. This has mainly been due to their complex structural network and associated physiological properties. Trichodermol **1** and verrucarol **2** are the representative members of this group. This group of compounds present a major synthetic challenge, particularly in terms of the stereo- and regio- control required for their successful construction. The important points to be taken into account in the synthetic



1, R=CH_3
2, R=CH_2OH



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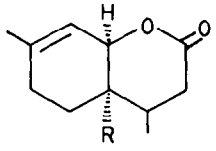
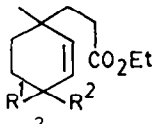


4, R=CH_3
5, R=CH_2OAc
6, R=CO_2Et

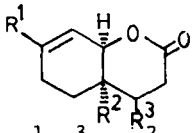
efforts are the cis fusion of the AB rings incorporating the oxa-octalin unit and the position of the double bond in proper position in ring A. In earlier syntheses the cis fusion had been brought about through mode of formation involving a Diels-Alder reaction[2f,j] or a biomimetic pathway[2a-e,g-k] which has been established to lead to the desired ring fusion. Bicyclic lactones of the type **3** (R=CH_3,n=1)[2a] and variations[2f,3] have also been demonstrated as potential precursors for the development of trichothecene carbocyclic framework. The strategically placed double bond in ring A and the stereochemistry at the ring juncture as found in the natural compounds underscores the

importance of these lactones. In an earlier occasion we had reported[4] convenient methods for the synthesis of lactones **3** ($R=CH_3, CO_2H, n=1$) which had previously[2a] been transformed to the trichothecene natural products. In this report we describe the synthesis of the homologous bicyclic lactones **4-6** incorporating the oxa-octalin unit with the cis ring juncture and double bond in proper position in ring A which can serve as potential synthons in the development of trichothecene synthesis.

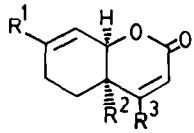
The unsaturated keto-ester **7**[5] was reduced under Luche[6] conditions to furnish the hydroxy-ester **8** as a mixture of epimers. Basic hydrolysis of this epimeric mixture followed by acidification in the cold with dilute HCl afforded only the corresponding hydroxy acid. However when this hydroxy acid was stirred at ambient temperature with dilute sulphuric acid in aqueous THF it cleanly cyclised to produce the lactone **9**, containing only traces of the other isomer. The assignment of cis ring junction to the lactone **9** stemmed from analogies in earlier trichothecene synthesis[2] where biomimetic type cyclisation through similar allylic cationic intermediate generates ring B with the desired cis fusion. However we have also secured more corroborative evidence in favour of



7, $R^1=R^2=O$
8, $R^1=H, R^2=OH$



9, $R^1=R^3=H, R^2=Me$
10, 7,8-dihydro $R^1=R^3=H, R^2=Me$
11, $R^1=R^2=Me, R^3=H$
4, $R^1=R^2=R^3=Me$

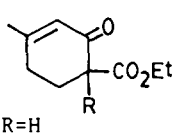


12 $R^1=R^2=Me$, $R^3=H$
23 $R^1=R^3=Me$, $R^2=CO_2Et$

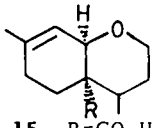
assigned stereochemistry to lactone **9**. To this end this was hydrogenated with tris-triphenylphosphine rhodium chloride (Wilkinson catalyst)[7] and furnished the saturated lactone **10** in quantitative yield. Comparison (^1H NMR and GC) of this with an authentic sample prepared by a reported[8] procedure conclusively established the cis fusion of the lactone **10** and thus confirming the stereochemistry assigned to **9**. Having thus a ready route to a cis fused bicyclic lactone we proceeded to incorporate the methyl group in ring A. To achieve this, the keto-ester **7** was reacted with methyl magnesium iodide and the product subjected to basic hydrolysis followed by treatment with sulphuric acid (4N) and afforded the desired lactone **11** in good yield. ^1H NMR spectrum revealed the presence of essentially a single isomer assigned cis following previous observation, with the other present to the extent of ca. 4%. The bicyclic lactone **11** incorporates two crucial aspects connected with trichothecene synthesis, the cis AB ring fusion and the double bond in proper position in ring A. Introduction of a methyl group in ring B next door to the angular methyl to furnish the lactone **4** was achieved in the following way. Lactone **11** was first converted to the α,β-unsaturated lactone **12** through the two-step sequence involving phenyl selenenation followed by oxidation[9], in good yield. This underwent ready conjugate addition with lithium dimethyl copper to furnish **4** as a single isomer. This bicyclic

lactone has all the potential for transformation to the trichothecene compounds represented by trichodermol **1** .

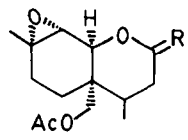
For the synthesis of the more oxygenated compounds represented by **2**, we envisaged the bicyclic lactone **5** with an angular functionalised methyl group. Michael reaction of the β -keto-ester[10] **13** with methyl crotonate afforded the adduct **14** in excellent yield. The configuration of the secondary methyl group is not defined and was not considered important at this point in view of the later requirement to involve the attached carbon in bridge formation. Following previous results it was anticipated that reduction followed by hydrolysis will lead to a bicyclic lactone where the angular ester function can be transformed to a hydroxymethyl. However, under these conditions it unexpectedly furnished the pyran carboxylic acid **15** as a crystalline solid in 50% yield. In the IR it showed only a peak due to the acid (1700 cm^{-1}) and in the ^1H NMR a triplet at δ 3.62 for two protons assignable to the $-O-CH_2-$ group. Clearly this has arisen from the primary ester in **14** also undergoing reduction. Change of experimental conditions, particularly



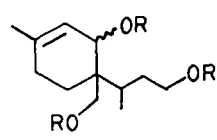
13, R=H
14, R=CH(Me)CH_2-CO_2Me



15, R=CO_2H
16, R=CO_2Me
17, R=CH_2OH
20, R=CH_2OAc



21, R=H_2
22, R=O



18, R=H
19, R=Ac

shortening reaction time did not lead to any improvement in the situation and hence we decided to harness the pyran carboxylic acid itself for conversion to the required lactone. The assigned cis ring junction for **15** followed from analogy in the preparation of lactones **9,11** as well as from earlier precedents[2]. Further in the ^1H NMR spectrum of the methyl ester **16** the angular C-8a hydrogen appeared as a doublet with a coupling constant of ca. 5 Hz in accordance with observed for same hydrogen in the trichothecenes. Reduction of the methyl ester **16** with LAH furnished alcohol **17** in excellent yield. This alcohol was subsequently prepared in a two-step sequence in high yield directly from the keto-diester **14**. Reduction of this with LAH furnished the triol **18** as a mixture of epimers. Brief treatment of this triol in benzene at reflux with a catalytic amount of p-TsOH afforded the bicyclic alcohol **17** in excellent yield, and was converted to the acetate **20**. For functionalisation of ring B in this pyranyl acetate through oxidation to a lactone, we decided to use the method developed by Smith et al[11] for oxidation of ethers with RuO_4 to lactones in a monophase system as it has been established that under these conditions oxidation proceeds only upto the lactone stage even after extended reaction time. Before that it became imperative to protect the double bond in **20**. Protection as the epoxide appeared as the suitable choice since this will expectedly remain stable during the

oxidation procedure and there are excellent methods[12] for the regeneration of olefins from epoxides without fear of isomerisation. Treatment of **20** with m-CPBA furnished an epoxide **21** in very good yield as a single isomer. The configuration of the epoxide is not important in the synthetic perspective, however, based on expected delivery of oxygen from the less hindered α-face it is designated the α-epoxide **21**. In the ^{1}H NMR the protons adjacent to the pyranyl oxygen and the epoxide appeared as singlets, arising out of no coupling (dihedral angle ~ 90°) in the situation of an α-epoxide in the cis-fused oxa-decalin system. This epoxy-ether was next subjected to oxidation with stoichiometric RuO_4 following reported[11] conditions and afforded the epoxy-lactone **22** cleanly in excellent yield. Yields of 80% proved to be general and no other side reaction was observed. Having obtained the bicyclic epoxy-lactone **22**, the crucial deoxygenation was next explored. The method involving sodium iodide and p-TsOH[13], or the Sharpless[14] procedure which has been successfully employed also in the trichothecenes[15], did not prove helpful and led to only difficult mixture of products. The Ganem[12] procedure involving dimethyl diazomalonate and rhodium acetate proved successful but was attended with other difficulties. The product obtained after extensive p.l .c. in a yield of ca. 30% though was very encouraging from the ^{1}H NMR spectrum showing the presence of the regenerated double bond, also showed a broad singlet at δ 3.78 and a broad peak at δ5.75 arising from a contaminant (possibly some decomposition product of dimethyl diazomalonate) which could not be completely eliminated. Cooling below 0°C of a solution of this product in hexane led to separation of the contaminant as colourless crystals. The solution was decanted and the process repeated a few times. The ^{1}H NMR of the product still revealed the presence of the contaminant besides the desired peaks due to the unsaturated lactone **5**. GC-MS of this showed the presence of lactone **5** to the extent of 70% (m/z 252) with the contaminant ca. 24% and a more polar impurity (ca. 5%).

On account of the difficulty in obtaining the desired lactone in pure form and in good yield, we explored modifications in the reduction of the keto-diester **14** to lead to a bicyclic lactone with an angular ester function which can be suitably modified at an appropriate stage. Eventually the synthesis of **6** was realised as follows. The keto-diester was subjected to controlled hydrolysis to hydrolyse only the primary ester and the derived acid as the sodium salt was reduced under Luche conditions. Subsequent acid treatment of the product furnished the bicyclic lactone **6** in a satisfactory yield, thus consummating the original objective of synthesis of a bicyclic lactone precursor related to **2**. The assigned stereochemistry at the ring juncture followed analogy in other bicyclic lactones. This lactone **6** was further functionalised to provide the α,β-unsaturated lactone **23** through phenyl selenenation followed by oxidation.

The methodology reported here provides ready access to usefully functionalised bicyclic lactones possessing a cis ring juncture and double bond in proper position in ring A as found in the natural trichothecenes and expected to serve as potential precursors in the synthesis of these compounds. Some viable methods for incorporation of the bridged C-ring in such lactones have previously been demonstrated[3]. Experiments addressed to this problem are currently under way and will be reported in due course.

EXPERIMENTAL SECTION

Melting points and boiling points are uncorrected and melting points were taken in open capillary in sulphuric acid bath or Reichert hot stage. Preparative layer chromatography was performed using silica gel 60 HF_{254} (E.Merck), plate thickness 1 mm, UV spectra were measured in 95% ethanol solution on a Hitachi model 200-20 spectrophotometer. IR spectra were recorded in $CHCl_3$ solution on a Perkin-Elmer 298 instrument. ^1H NMR spectra were recorded against TMS as internal standard in CCl_4 solution at 60 MHz on a Varian T-60A and in $CDCl_3$ solution at 100 MHz on Jeol FX-100 and at 200 MHz on a Varian XL-200 spectrometers. Gas chromatography was carried out on a Shimadzu GC-9A model using OV-17 on 1.5% shimalite W 80-100 silanized column (6 m x 3 mm). GC-MS was performed on a Hewlett Packard model 5890 gas chromatograph using Hewlett Packard Ultra 2 column (0.33 um x 0.2 mm x 25 m) of fused silica with a crosslinked 5% phenyl methyl silicone (similar to DB-5 and OV-73) and mass on a model 5970 mass selective detector and an RTE-6/VM data system. Petroleum ether refers to fraction boiling in the range 60-80°C unless otherwise mentioned. Solvent extracts were dried over anhydrous Na_2SO_4.

(4aα,8aα)-4a-Methyl-3,4,4a,5,6,8a-hexahydro-2H-benzopyran-2-one (9):- To 25 ml of 0.4 M solution of cerium (III) chloride hexahydrate in ethanol at room temperature, the unsaturated keto-ester **7** (2.1 g, 10 mmol) was added, followed by sodium borohydride (0.38 g, 10 mmol) in portions with stirring. The reaction mixture was stirred at room temperature for 0.5 h, diluted with water, extracted with ether. The ethereal solution was washed well with water, dried and concentrated to afford a crude hydroxy ester **8** (2.1 g, 99%), which was directly used in the next step, IR 3600-3200, 1725 cm^{-1}, ^1H NMR δ CCl_4 0.95; 1.03 (2s, 3H), 1.25 (t, J = 7 Hz, 3H), 3.43-4.2 (m, with a q at 4.03, J = 7 Hz, 4H), 5.13-5.76 (m, 2H).

The above hydroxy-ester was added to a solution of KOH (2.54 g, 45 mmol) in water (25 ml). Enough ethanol was added to make a clear solution and the reaction mixture was stirred overnight at room temperature under N_2 and extracted once with ether. The aqueous alkaline fraction was acidified with dilute HCl (3%) and extracted with ether. The ethereal solution was washed with saturated brine, dried and concentrated. The residual oil was distilled to afford a hydroxy acid (1.6 g, 90%), b.p. 110°C/0.2 mm (bath temperature), IR 1700 cm^{-1}, ^1H NMR δ CCl_4 0.94, 1.03 (2s, 3H, 1:2 proportion), 4.2 (br s, 1H), 5.23-5.86 (m, 2H), 6.16 (s, 1H).

To a well stirred solution of the above hydroxy acid (1.5 g, 8 mmol) in THF (15 ml) dilute H_2SO_4 (6N) was added slowly and reaction mixture stirred overnight. This was next diluted with water and extracted with ether. The combined organic layer was washed with saturated brine, dried and ether distilled off to obtain an oil (1.4 g) which was chromatographed over silica gel. Elution with ethyl acetate-petroleum ether (1:9) furnished the lactone **9**. Further elution with ethyl acetate-petroleum ether (1:5) furnished some recovered acid. This was stirred again with dilute H_2SO_4 as above and chromatographed to afford the lactone in a total amount of (1.1 g, 85%), b.p. 100-105°C/0.3 mm, IR 1730 cm^{-1}, ^1H NMR δ $CDCl_3$ 1.06 (s, 3H), 2.5 (t, J = 6 Hz, 2H), 4.36 (br s, 1H), 5.66-6.12 (m, 2H), GC, R_t 8.41 min at 150°C (single peak). Anal. calcd. for $C_{10}H_{14}O_2$; C, 72.26; H, 8.49 . Found: C, 72.22; H, 8.19.

(4aα,8aα)-4a-Methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-1-benzopyran-2-one (10) :- The unsaturated lactone **9** (166 mg, 1 mmol) in benzene (8 ml) was hydrogenated in presence of tris-triphenyl phosphine rhodium chloride as catalyst. The calculated amount of hydrogen was smoothly consumed. After removal of the solvent the residue was evaporatively distilled to afford **10** (165 mg, 99%), b.p. 100-105°C/0.4 mm (bath temperature) (lit[8], b.p.102-104°C/0.8 mm), IR 1725 cm^{-1}, ^1H NMR δ $CDCl_3$ 1.04 (s, 3H), 2.52 (t, J = 6 Hz, 2H), 4.1 (t, J = 5 Hz, 1H), GC R_t 7.81 min at 150°C (single peak).

A mixture of lactone **10** and the trans isomer was prepared by procedure of House et al[8] and showed the following features, GC, R_t, 7.93 and 8.79 min at 150°C in proportion of ca 60:40, IR 1720 cm^{-1}, ^1H NMR δ $CDCl_3$ 0.96, 1.04 (2s, 3H, ca. 40:60 proportion), 2.54-2.62 (2 coalesced t, J = 6 Hz, 2H), 3.92-4.28 (m, 1H).

Co-injection of our lactone **10** with this mixture of lactones showed in GC pronounced increase in the predominant peak (R_t, 7.76 min).

(4a α,8a α)-4a,7-Dimethyl-3,4,4a,5,6,8a-hexahydro-2H-benzopyran-2-one (11) :- To a stirred and cooled (ice-bath) solution of MeMgI prepared from Mg (1.92 g, 0.08 g atom), an ethereal solution of keto-ester **7** (10.5 g, 50 mmol) was added over 2-3 min under N_2. After further 15 min saturated aqueousNH_4Cl solution was added dropwise with stirring. The ether layer was separated and aqueous portion extracted with ether. The combined organic extract was washed with saturated brine, dried and concentrated. Distillation of residual oil furnished the hydroxy-ester (7.42 g, 70%), b.p. 110°C/0.1 mm, IR 1720 cm^{-1}, ^1H NMR δ (200 MHz), 0.92 and 1.0 (2s, 3H), 1.27, 1.28 (2s, 3H), 5.38-5.62 (m, 2H).

The above hydroxy-ester (7.4 g, 35 mmol) was added to a solution of KOH (19.6 g, 350 mmol) in water (200 ml). Enough ethanol was added to make a clear solution and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. The alkaline aqueous part was acidified with dilute H_2SO_4 (4N) and stirred for 30 min at room temperature. The reaction mixture was saturated with NaCl and extracted with ether. The combined organic extract was washed with saturated brine and dried. The solvent was evaporated off, the residual oil was subjected to chromatography over silica gel and eluted with ethyl acetate-petroleum ether (1:9) and distilled to furnish the lactone **11** (4.4 g, 70%), b.p. 110-115°C/0.3 mm, IR 1725 cm^{-1}, ^1H NMR δ $CDCl_3$ (200 MHz) 0.90 (very small s), 1.04 (s, 3H), 1.75 (s, 3H), 2.52, 2.53 (2 coalesced t, J = 6 Hz, 2H), 4.38 (br s, 1H), 5.52 (br s, 1H), GC, R_t 11.47 min at 150°C (single peak). Anal. calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found : C, 73.03, H, 9.28.

(4a α ,8a α)-4a,7-Dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-2-one (12):- To a well stirred solution of LDA in THF (50 ml) [prepared from n-BuLi (26 mmol of 1.2 M solution in hexane, 27 mmol) and diisopropylamine (2.7 g, 27 mmol)] at -78°C under N_2, a solution of the lactone **11** (4.05 g, 22.5 mmol) in THF (5 ml) was added in drops and the solution stirred for 15 min. In a separate pot diphenyl diselenide (4.2 g, 13.5 mmol) was dissolved in THF (10 ml) under N_2. To the selenide solution, bromine (2.16 g, 13.5 mmol) was added dropwise and the mixture was agitated briefly. The phenyl selenide bromide solution was added rapidly to the above enolate solution of the lactone at -78°C. Instantaneously decolourisation occurred and the cold reaction mixture was poured into a mixture of dilute HCl (0.5 N, 100 ml) and ether-petroleum ether (50%, 100 ml). The organic phase was washed with aqueous $NaHCO_3$ solution, saturated brine, dried and evaporated affording a yellow oil. This was chromatographed on silica gel eluting with ethyl acetate-petroleum ether (1:19) furnished the selenate lactone as a yellow solid (5.2 g), m.p. 154-155°C, ^1H NMR δ CCl_4 0.88 (s, 3H), 1.63 (s, 3H), 3.83-4.28 (m, 2H, angular H and -CH-SePh), 5.18 (br s, 1H), 6.73-7.5 (m, 5H, SePh), MS, m/z, 335 M^+.

A solution of the above α-phenyl selenated lactone (5.0 g, 15 mmol) in THF (25 ml) containing acetic acid (2.25 ml) was cooled to 0°C and H_2O_2 (10.5 ml, 30%) added. The reaction mixture was stirred for 30 min at 0°C. Then it was poured into cold saturated aqueous $NaHCO_3$ solution and extracted with ether (x 3). Combined extracts was washed well with saturated brine, dried and solvent removed. Column chromatography of the crude product over silica gel and elution with ethyl acetate-petroleum ether (1:9) furnished the unsaturated lactone **12** (2.6 g, 98%), b.p. 110°C/0.2 mm, IR 1710 cm^{-1}, UV λ_{max} 224.4 nm ε 2859, ^1H NMR δ $CDCl_3$ 1.12 (s, 3H), 1.72 (s, 3H), 4.58 (br s, 1H), 5.5 (br s, 1H), 5.88 (d, J = 10 Hz, 1H), 6.58 (d, J = 10 Hz, 1H), GC, R_t 9.37 min at 150°C (single peak). Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found : C, 74.25; H, 8.15.

(4a α ,8a α)-4a-Methyl-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran-2-one (4):- MeLi-LiI complex (1.4 M in ether, 41 ml) was added slowly to a stirred suspension of CuI (5.13 g, 27 mmol) in anhydrous ether (40 ml) at 0°C until the initially formed yellow precipitate had just disappeared. The resulting clear solution was stirred for 5 min at 0°C, then the lactone **12** (1.06 g, 6 mmol) in ether (5 ml) was added slowly

and stirred for further 30 min. Then it was poured to a stirred ice-cold saturated aqueous NH_4Cl solution (50 ml) and left for 5 min. The resulting mixture was filtered and the layer separated. The aqueous layer was extracted with ether and combined organic extract dried and concentrated. The residual oil was chromatographed on silica gel eluting with ethyl acetate-petroleum ether (1:9) and furnished the methylated lactone **4** (760 mg, 65%), b.p. 110°C/0.1 mm, IR 1720 cm^{-1}, ^1H NMR δ (200 MHz), 0.94 (s, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.71 (s, 3H), 4.49(br s, 1H), 5.45 (br s, 1H), GC R_t 5.28 at 180°C (single peak).

Metyl-3-[1-ethoxycarbonyl-2-oxo-4-methylcyclohex-3-enyl]-butyrate (14):- Potassium (100 mg) was dissolved in dry t-butanol (40 ml), cooled with ice water and the unsaturated keto-ester **13** (13.65 g, 75 mmol) added in drops under N_2. After 15 min, methyl crotonate (9 g, 9.5 ml, 90 mmol) was added dropwise with cooling and stirred for 20 h at room temperature. The reaction mixture was then diluted with water, extracted with ether, washed with saturated brine, dried and solvent removed. Distillation of the residue afforded the keto-diester **14** (19 g, 90%), b.p. 130°C/0.3 mm, IR 1725,1680 cm^{-1}, ^1H NMR δ CCl_4, 0.95 (d, J = 6 Hz, 3H), 1.2 (t, J = 7 Hz, 3H), 1.96 (s, 3H), 3.6 (s, 3H). 4.08 (q, J = 7 Hz, 2H), 5.7 (s, 1H). Anal. calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found : C, 63.60; H, 8.39.

(4a α ,8a α)-4a-(Carboxy)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran (15):- To 50 ml of 0.4 (M) solution of cerium (III) chloride hexahydrate in methanol, the keto-ester **14** (2.82 g, 10 mmol) was added, followed by sodium borohydride (0.76 g, 20 mmol) in portions (5 min) with stirring. The reaction mixture was stirred at room temperature for 1 h, diluted with water and extracted with ether. The ether layer was washed with water and dried. Removal of the solvent furnished 2.8 g, of an oil which was used directly in the next step, IR 3600-3200, 1725 cm^{-1}. The above crude product was added to a solution of potassium hydroxide (56 ml, 10%). Enough methanol was added to make a clear solution and the reaction mixture was stirred overnight at room temperature. Next day the reaction mixture was diluted with water and extracted once with ether. The alkaline part was cooled and acidified with dilute H_2SO_4 (6N) and stirred for 30 min at room temperature. The reaction mixture was then saturated with NaCl and extracted with ether, washed thoroughly with saturated brine and dried. Removal of the solvent furnished the pyranocarboxylic acid **15** as a solid compound (1.1 g, 50%). Crystallised from ether, m.p. 90°C, IR 1700 cm^{-1}, ^1H NMR δ $CDCl_3$, 1.04(d, J = 6 Hz, 3H), 1.6 (s, 3H), 3.62 (t, J = 5 Hz, 2H), 4.38 (br s, 1H), 5.42 (br s, 1H), 6.72 (br s, 1H), GC R_t 1.52 min at 200°C (single peak, 98%). Anal. calcd. for $C_{12}H_{18}O_3$: C, 69.21; H, 7.74. Found : C, 69.47; H, 8.73.

The value for hydrogen did not further improve.

The corresponding methyl ester **16** was prepared from diazomethane, b.p. 130°C/0.1 mm, IR 1720 cm^{-1}, ^1H NMR δ $CDCl_3$, 1.0 (d, J = 6 Hz, 3H), 1.64 (s, 3H), 3.44-4.14 (m, with a s, 3.64, 5H), 4.27 (d, J = 5 Hz, 1H), 5.54 (br s, 1H). Anal. calcd. for $C_{13}H_{20}O_3$: C, 69.62; H, 8.99. Found : C, 70.12; H, 9.05.

(4a α,8a α)-4a-(Hydroxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran (17):- To a stirred suspension of LAH (230 mg, 6 mmol) in dry ether (10 ml) a solution of ester **16** (670 mg, 3 mmol) in ether (2 ml) was added dropwise. When addition was complete, the reaction mixture was refluxed for 3 h. It was cooled and decomposed with saturated aqueous Na_2SO_4 solution. The ethereal layer was decanted, dried and concentrated and the residue distilled to afford the alcohol **17** (465 mg, 80%), b.p. 110°C/0.2 mm. This subsequently solidified, m.p. 52-54°C, IR 3600-3200, 1670 cm^{-1}, ^1H NMR δ $CDCl_3$ 0.92 (d, J = 6 Hz, 3H), 1.68 (s, 3H), 3.38,3.89 (AB q, J = 12 Hz), 3.50-3.78 (m, 2H), 4.34 (br s, 1H), 5.28 (br s, 1H). GC R_t 3.68 min at 170°C (single peak, 98%). Anal. calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found : C, 73.76; H, 10.28.

3-[1-Hydroxymethyl-2-hydroxy-4-methylcyclohex-3-enyl]-butan-1-ol (18):- To a well stirred slurry of LAH (2.28 g, 60 mmol) in dry ether (100 ml) was added dropwise, a solution of the keto-ester **14** (5.66 g, 20 mmol) in ether (20 ml). When addition was complete, a further quantity of ether (30 ml) was added and the whole mixture refluxed

ior 3 h. It was then decomposed with saturated aqueous Na_2SO_4 solution. The ethereal layer was decanted, dried and the product crystallised from ethyl acetate. This furnished the triol **18** (3.4g, 80%), m.p. 125°C. Anal. calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found : C, 67.04; H, 10.61.

On account of insolubility in CCl_4, $CDCl_3$, ^1H NMR spectrum could not be obtained.

3-[1-Acetoxymethyl-2-acetoxy-4-methylcyclohex-3-enyl]-butyl acetate (19):- A mixture of the triol **18** (200 mg, 0.9 mmol) acetic anhydride (4 ml) and pyridine (8 ml) was left overnight. Nexy day, it was heated in an oil bath at 100°C for 1 h. The product was then cooled, diluted with water and extracted with ether. Ether layer was washed with dilute HCl, saturated with brine and dried. The residue after removal of solvent was evaporatively distilled to provide the triacetate **19** (310 g, 94%), b.p. 120°C/0.2 mm, IR 1720 cm^{-1}, ^1H NMR δ CCl_4 0.92 (d, J = 6 Hz, 3H), 1.73 (s, 3H), 2.0 (s, 9H), 3.7-4.23 (m, 4H), 5.0 (br s, 1H), 5.5 (br s, 1H); GC R_t 4.16 and 4.91 min at 200°C in proportions of 35:65 respectively. Anal. calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.17; H, 8.44.

Cyclisation of the triol (18):- To a warm solution of the triol **18** (6.42 g, 30 mmol) in benzene, toluene-p-sulphonic acid (300 mg) was added. The mixture was refluxed for 1 h. The reaction mixture was washed well with water and benzene removed in vacuo and the residue distilled to afford **17** (5.8g, 99%) identical with sample prepared by previous method. This also on trituration solidified, m.p. and m.m.p. with earlier sample 52-54°C.

(4a α,8a α)-4a-(Acetoxymethyl)-4,7-dimethyl,3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran (20):- A mixture of the hydroxy ether **17** (5.5 g, 28 mmol) acetic anhydride (40 ml, 420 mmol) and pyridine (80 ml) was left overnight. Next day the reaction mixture was heated on an oil bath at 100°C for 1 h. It was cooled, diluted with water and extracted with ether. The ether layer was washed with dilute HCl, saturated brine, dried and concentrated. The residue was distilled under vacuum to furnish the acetate **20** (6.3 g, 95%), b.p. 100°C/0.05 mm, ^1H NMR δ CCl_4 0.95 (d, J = 6 Hz, 3H), 1.7 (s, 3H), 2.0 (s, 3H), 3.33-3.66 (m, 2H), 3.97, 4.15 (AB q, J = 12 Hz, 3H, also including 1H), 5.23 (br s, 1H), GC R_t, 6.72 min at 180°C (single peak 96%). Anal. calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found : C, 70.67; H, 9.39.

(4a α,8a α)-4a-(Acetoxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-7,8-epoxy-2H-1-benzopyran (21):- A stirred mixture of acetate **20** (3.01 g, 12.5 mmol) in CH_2Cl_2 (60 ml) and dilute $NaHCO_3$ (0.5 N, 6 g, in 73 ml water) was cooled to 5-10°C and slowly treated with mCPBA (4.6 g) so that the temperature never rose above 10°C. Stirring was continued for 4 h more at the same temperature. Organic layer was separated, washed with water, dried and concentrated. The residue was subjected to column chromatography over silica gel, eluted with 5% ethyl acetate in petroleum ether and distilled to afford the epoxy acetate **21** (2.24 g, 70%), b.p. 120°C/0.2 mm. This epoxy acetate on subsequent trituration solidifed, m.p. 67-68°C, IR 1720 cm^{-1}, ^1H NMR δ $CDCl_3$ (200 MHz), 0.91 (d, J = 6.9 Hz, 3H), 1.39 (s, 3H), 2.05 (s, 3H), 3.03 (s, 1H), 3.42-3.61 (m, 2H), 3.93 (s, 1H), 4.02, 4.26 (AB q, J = 11 Hz, 2H), GC R_t, 11.24 min at 170°C (single peak). Anal. calcd. for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found : C, 66.3; H, 8.83.

(4a α,8a α)-4a-(Acetoxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-7,8-epoxy-2H-1-benzopyran-2-one (22):- A stirred solution of ruthenium trichloride trihydrate (600 mg) in CCl_4 (75 ml) was cooled to 10-15°C and treated with a solution of sodium metaperiodate (5.1 g) in water (75 ml). Vigorous stirring of the two layers was continued for 2 h. The CCl_4 layer containing ruthenium tetraoxide was separated as a deep yellow solution. To this layer the epoxy-ether **21** (762 mg, 3 mmol) in CCl_4 (5 ml) was added and stirred for 24 h. The precipitated black ruthenium dioxide was removed by filtration through filter paper and concentrated under vacuo. Careful distillation of the residue afforded the epoxy lactone **22** (710 mg, 90%), b.p. 160°C/0.07 mm, IR 1720 cm^{-1}, ^1H NMR δ $CDCl_3$ (200 MHz) 0.99 (d, J = 6.7 Hz, 3H), 1.39 (s, 3H), 2.06 (s, 3H), 3.06 (s, 1H), 4.08, 4.13 (AB q, J = 11.7 Hz, 2H), 4.58 (s, 1H), GC R_t, 3.0 min at 240°C (single peak). Anal. calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.49; H, 7.96.

(4aα,8aα)-4a-(Acetoxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran-2-one (5):- A solution of scrupulously pure dimethyl diazomalonate (316 mg, 2 mmol) in benzene (20 ml) was added dropwise to a mixture of rhodium acetate dimer (10 mg) and the epoxylactone **22** (108 mg, 0.4 mmol) in benzene (20 ml) at reflux. Upon completion of addition (10 min), the reaction mixture was refluxed another 1 h then cooled and filtered through a pipetteful of silica gel and solvent removed under reduced pressure. The residual oil was subjected to preparative layer chromatography and eluted with ethyl acetate-petroleum ether (1:3) to afford a product in 30% showing desired peaks in ^{1}H NMR due to lactone **5** alongwith strong peaks at δ 3.78 and 5.75. This was dissolved in petroleum ether (40-60°C) and cooled in freezing mixture (ice-salt), slowly some crystals separated out. This was decanted in the cold. The solid m.p. 130-132°C showed in the ^{1}H NMR peaks at only δ 3.78 and a broad hump at δ 5.75 and was not further investigated. This process of cooling, decanting was continued for a few times when no more solid separated. Removal of solvent left an oil which showed IR 1720 cm^{-1}, ^{1}H NMR δ $CDCl_3$ (200MHz) 1.4 (d, J = 7 Hz, 3H), 1.74 (br s, 3H), 2.06 (s, 3H), 3.78 (br s,), 4.06, 4.11 (AB q, J = 6 Hz, 2H), 4.80-4.88 (br s, 1H), 5.46-5.53 (br s, 1H), 5.75 (br s,), GC-MS, column temperature 230°C-10 min-15°C/min-260°C, R_t 4.22 min (70.3%), corresponding to lactone **5** MS, m/z 252, 5.38 min (23.9%), MS, m/z 274, 13.15 min (5.7%).

(4aα,8aα)-4a-(Ethoxycarbonyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran-2-one (6):- The unsaturated keto-ester **14** (2.82 g, 10 mmol) was added to a solution of KOH (340 mg, 12 mmol) in water (7 ml). Enough methanol was added to make a clear solution and the reaction mixture was stirred overnight at room temperature. The resultant mixture was diluted with water and extracted with ether. the alkaline aqueous part was acidified with dilute H_2SO_4, saturated with NaCl and extracted with ether (x 3). The combined organic extract was washed with saturated brine and dried. The solvent was distilled to afford an acid (2.5 g, 95%) as a light yellow solid, m.p. 86-88°C, IR 1725, 1700 cm^{-1}.

The sodium salt of the above crude acid (2.4 g, 9 mmol) was prepared from NaOH (400mg, 10 mmol) in few drops of water. The salt was dissolved in 0.4 M ceric chloride hexahydrate methanolic solution (28 ml) and $NaBH_4$ (430 mg, 11.3 mmol) was added slowly in portions (5 min), with stirring. The reaction mixture was stirred at room temperature for 1 h and methanol was evaporated under reduced pressure. The solid residue was acidified with dilute H_2SO_4 (4N) and stirred for 30 min at room temperature. The reaction mixture was saturated with NaCl and extracted with ether, washed with saturated brine, dried and the solvent removed. The residual oil was subjected to chromatography over silica gel and eluted with ethyl acetate-petroleum ether (1:9) furnished the lactone **6** (1.4 g, 62%), b.p. 120°C/0.1 mm, IR 1720 cm^{-1}, ^{1}H NMR δ $CDCl_3$ 1.04 (d, J = 7 Hz, 3H), 1.28 (t, J = 6 Hz, 3H), 1.74 (s, 3H), 4.22 (q, J = 7 Hz, 2H), 5.06-5.18 (br s, 1H), 5.33-5.43 (br s, 1H), GC R_t 5.87, 99% (single peak). Anal. calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found : C, 66.40; H, 8.05.

(4aα,8aα)-4a-(Ethoxycarbonyl)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-2-one (23):- To a well stirred solution of LDA in THF (20 ml) [prepared from n-BuLi (5.9 ml of 1 M solution in hexane, 6 mmol) and diisopropylamine 0.92 ml, 6 mmol)] at -78°C under N_2, a solution of the lactone **6** (1.26 g, 5 mmol) in THF (5 ml) was added dropwise. After 15 min, phenyl selenenyl bromide (1.42 g, 6 mmol) in THF (5 ml) was added rapidly to the enolate solution and stirring continued at -78°C. Instantaneously decolourisation occured and cold reaction mixture was poured into a mixture of 0.5 (N) HCl (50 ml) and ether-petroleum ether (1:1, 50 ml). The organic layer was separated. washed with aqueous $NaHCO_3$ solution, saturated brine, dried and concentrated. An yellow residue of selenated lactone (2 g) was obtained and it was directly oxidised without purification.

A solution of the above α-phenylseleno-lactone in THF (15 ml) containing acetic acid (8 ml) was cooled to 0°C and H_2O_2 (3 ml, 30%) was added. The reaction mixture was stirred for 30 min at 0°C. Then it was poured into cold saturated aqueous $NaHCO_3$ solution and extracted with ether. The ethereal extract was washed well with brine, dried and concentrated. The oily residue was purified by chromatography over silica gel and elution with ethyl acetate-petroleum ether (1:9) furnished the unsaturated lactone **23** (1 g, 80%), b.p. 130°C/0.2 mm, IR 1710 cm^{-1}, UV λ_{max} 244 nm, ε 2500, ^{1}H NMR δ $CDCl_3$ 1.26 (t, J = 6 Hz, 3H), 1.73 (s, 3H), 1.95 (s, 3H), 4.23 (q, J = 7 Hz, 2H), 5.22-5.30 (br s, 1H), 5.53-5.66 (br s, 1H), 5.92 (d, J = 2 Hz, 1H), GC R_t 5.8 min at 200°C (single peak). Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found : C, 67.33; H, 7.64.

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