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MODEL SYNTHETIC STUDIES TOWARDS PALITANTIN TOTAL SYNTHESIS

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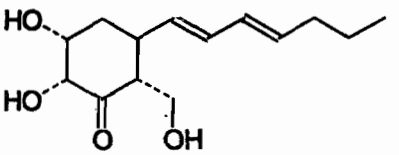
ABSTRACT. Synthesis of palitantin, 5-(1'*E*, 3'*E*-heptadienyl)-*cis*-2,3-dihydroxy-6-hydroxymethylcyclohexan-1-one (**1**), model compounds, 6-carbethoxy-2,3-dihydroxy-5-methylcyclohexan-1-one (**3**), *cis*-2,3-dihydroxy-6-hydroxymethyl-5-methylcyclohexan-1-one (**4**) and 6-carbethoxy-*cis*-2,3-dihydroxy-5-(1'-propenyl)cyclohexan-1-one (**5**) have been accomplished via a 3+3 ring annulation followed by standard fuctionalisations. The effect of carbethoxyl group in regioselectivity of the dihydroxylation of 6-carbethoxy-5-(1'-propenyl)-2-cyclohexen-1-one (**5**) and the corresponding alcohol was investigated. The apparent high dihydroxylation reaction rate for *E*-propenyl pendant double bond as compared to the *Z*-isomer in the presence of the β-carbethoxyl group was noted in cyclohexenones. Substitution of the β-carbethoxyl with an β-hydroxymethyl group revealed loss of the regioselectivity in dihydroxylation of the pendant double bond in both *Z*- and *E*-isomers.

INTRODUCTION

Palitantin, 5-(1'*E*,3'E-heptadienyl)-*cis*-2,3-dihydroxy-6-hydroxymethylcyclohexan-1-one (**1**), is a polyketide derived secondary metabolite of *Penicillium palitans, P. cyclopium, P. frequentans* and *P. brefeldianum* [1-4]. It is structurally and biosynthetically related to frequentin (**1**), another polyketide antibiotic, which has also been isolated from *P. palitans* and *P. brefeldianum*. It is believed that the two fungal metabolites are produced by the same biosynthetic pathway, with one as a progenitor of the other. Since palitantin was isolated 60 years ago, only one total synthesis [5] has been achieved. Although this report confirmed the structure of palitantin, the steps involved are too many for use in the commercial preparation of the compound.

In our efforts to find a short and convinient synthetic route to palitantin (**1**), we envisioned a retrosynthetic approach based on a one-pot Michael-Wittig reactions followed by standard functionalisations and *cis*-dihydroxylation (Scheme 1). We therefore undertook syntheses of 6-carbethoxy-*cis*-2,3-dihydroxy-5-methylcyclohexan-1-one (**3**), *cis*-2,3-dihydroxy-6-hydroxymethyl-5-methylcyclohexan-1-one (**4**), 6-carbethoxy-*cis*-2,3-dihydroxy-5-(1'-propenyl)cyclohexan-1-one (**5**) and *cis*-2,3-dihydroxy-6-hydroxy-methyl-5-(1'-propenyl)cyclohexan-1-one (**6**) as model compounds. Compounds **3** and **4** were chosen to study the stereochemistry of the dihydroxylation of the enone while compounds **5** and **6** were chosen to study the regioselectivity of dihydroxylation of the dienone.



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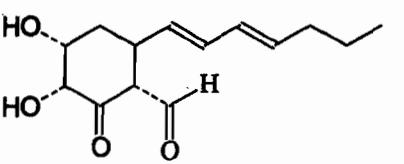

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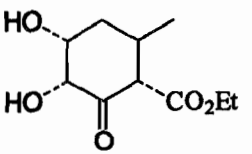

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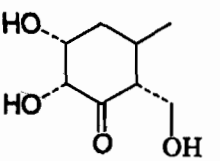

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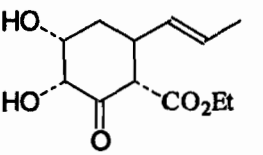

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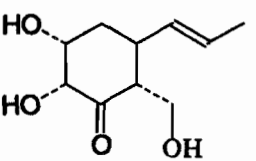

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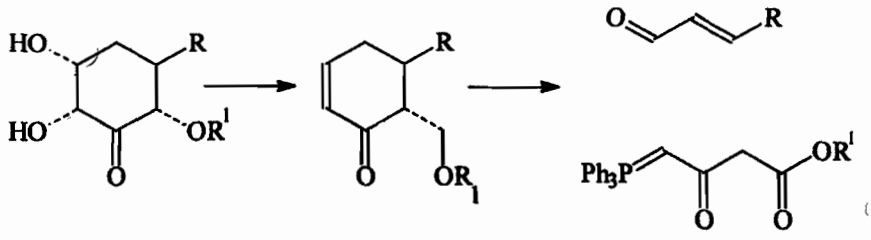
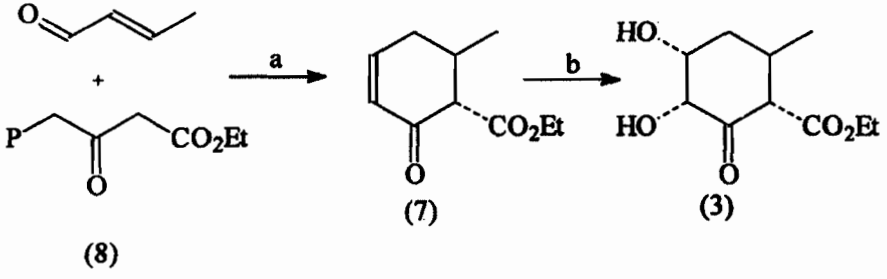
RESULTS AND DISCUSSION

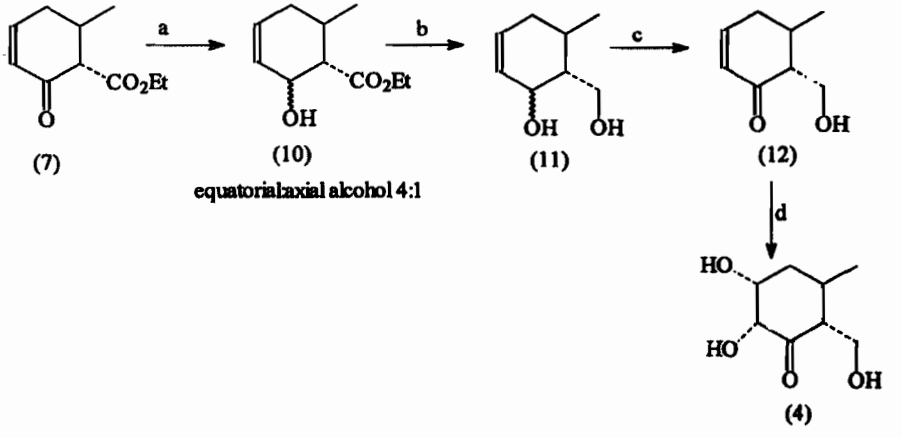
Both 6-carbethoxy-*cis*-2,3-dihydroxy-5-methylcyclohexan-1-one (**3**) and *cis*-2,3-dihydroxy-6-hydroxymethyl-5-methylcyclohexan-1-one (**4**) were envisaged to be accessible by the retrosynthetic Scheme 1. Preparation of the enone (**7**) was achieved in 67% yield according to Scheme 2 [6]. The pseudo-equatorial relationship between the methyl and the carbethoxyl groups in **7** was evident from ^{1}H NMR chemical shifts and coupling constant values [δ 3.10 (1H, d, $J_{H5\text{-}H6}$ 11.7 Hz, H-6) and 2.17 (1H, m, H-5)] for the methine protons [6]. Dihydroxylation of the enone (**7**) was accomplished in 62% yield [7] to give the desired diol (**3**). The stereochemistry of the dihydroxlated product was evident from the ^{1}H NMR chemical shifts, coupling constants [δ 4.20, (1H, d, $J_{H2ax\text{-}H3}$ 3.50 Hz, H-2) and 4.38 (1H, m, H*eq*-3)]. NOE difference pattern also confirmed the axial relationship between H-2, H-4 and H-6, which was found to be similar to the pattern observed in palitantin (**1**). This observation confirmed the equatorial relationship between the methyl and the carbethoxyl groups in **3**. The stereoselective dihydroxylation of the enone (**7**) can be explained if it is assumed that the enone (**7**) adopts a half-chair conformation making only one face of the double bond accessible to OsO_4 approach. Examples of stereoselective dihydroxlation of cyclohexenes with OsO_4 have been reported elsewhere [5, 7, 8, 9]. Other examples where fused heterocyclic unsaturated medium-size rings and unsaturated macrocyclic rings have been used to control the stereochemistry of double bond during dihydroxylation have been reported [10-12]. Asymmetric induction during dihydroxylation of acyclic alkenes with OsO_4 in the presence of optically pure ligands (amines and chinchona alkaloids) has also been achieved [13-17].



Scheme 1. **1** R^1 = H, R = heptadienyl



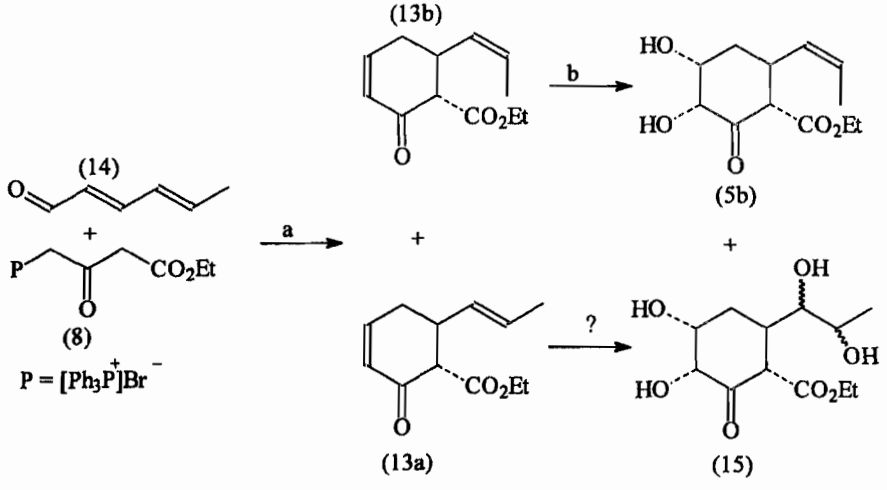
Scheme 2. P = $[Ph_3P^+]Br^-$, (a) 2 eq NaH/THF, (b) OsO_4/THF.



Scheme 3. (a) $NaBH_4/CeCl_3$/MeOH, 60%, (b) DIBAL-H/CH_2Cl_2/-78 °C, 33%, (c) MnO_2/ CH_2Cl_2/RT, 55%, (d) $NaClO_3$/THF,cat OsO_4, 50%.

Synthesis of the triol (**4**) was accomplished according to Scheme 3. Regiospecific reduction of the enone (**7**) to the β-hydroxyester (**10**) was achieved in 60% yield according to the established procedures [18]. The ratio of equatorial:axial alcohols was determined to be 4:1 from ^{1}H NMR analysis. The reduction of the β-hydroxyester (**10**) was achieved in 33% yield [19]. Regioselective oxidation of the enediol (**11**) to the enone alcohol (**12**) was accomplished in 55% yield [20]. Dihydroxylation of the enone alcohol (**12**) to the triol (**4**) was done using $NaClO_3$ and catalytic amounts of OsO_4 [7].

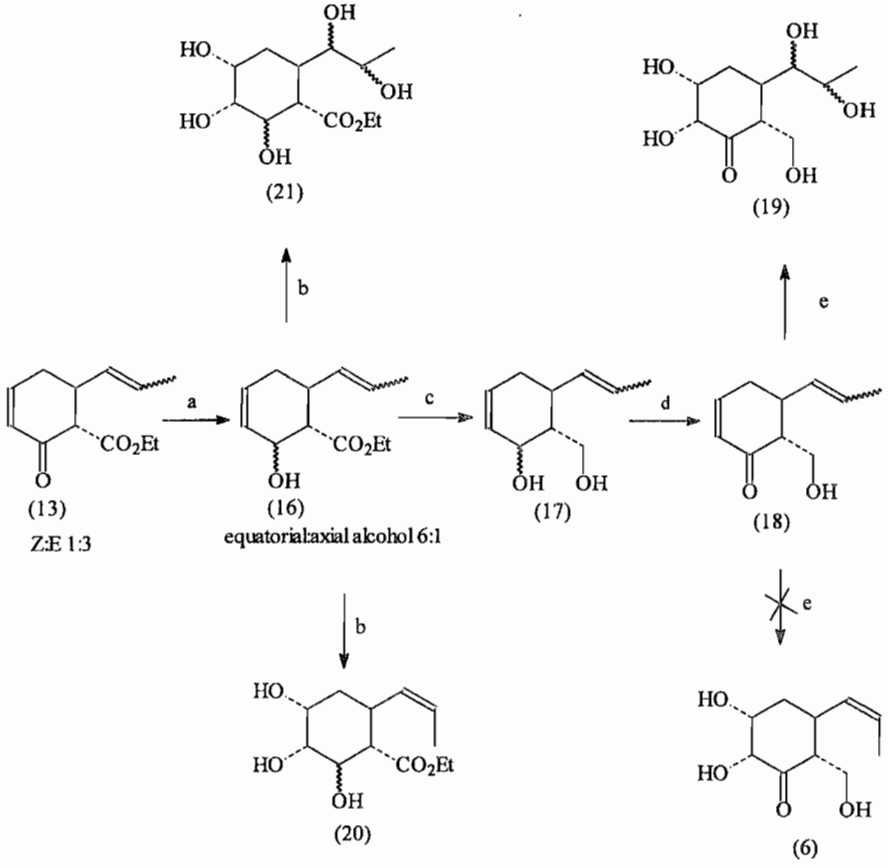
The triol (**4**) was achieved in 50% yield. Again ^{1}H NMR chemical shifts and coupling constants for the two methinecarbinol protons [δ 4.19 (1H, d, J 3.70 Hz, H-2) and 4.35 (1H, m, H-3)], NOE difference experiments (axial relationship between H-2, H-4 and H-6) confirmed similar stereochemical relationship to palitantin (**1**). The stereoselectivity of the otherwise regioselective $NaBH_4/CeCl_3$ reduction has also been noted elsewhere [21] for substituted cyclohexanones and can be explained here by the adoption of the half-chair conformation leading to the preferential approach of the borohydride from one face of the carbonyl group in the enone (**7**) to give the equatorial alcohol. The triol (**4**) may be regarded as palitantin in which the 1,3-heptadienyl residue has been replaced with a methyl group.



Scheme 4. (a) 2 NaH/THF/cat KH, (b) $NaClO_3$/cat OsO_4/THF, 8% **5b** only.

With the stereoselectivity of the dihydroxylation ascertained, we shifted our attention to the regioselectivity of the dihydroxylation of dienones **13** and **18**. The dienone (**13**) was prepared according to the standard reaction [22] in 38% yield (scheme 4). The ratio of the *Z:E*-isomer was calculated as 1:3 from ^{1}H NMR chemical shifts and coupling constants [δ 3.24 (1H, d, $J_{H5\text{-}H6}$ 11.99 Hz, H-6) for the major isomer [22] and δ 3.22 (1H, d, $J_{H5\text{-}H6}$ 12.18 Hz, H-6) for the minor isomer] confirmed the pseudo-equatorial relationship. Dihydroxylation of the mixture of the enones (**13**) to the dihydroxy compound (**5**) was achieved in very poor yields (8%). ^{1}H NMR chemical shift analysis for the olefinic protons in the product (**5b**) confirmed that the pendant double bond in the product was not dihydroxylated but had exclusively *Z*-stereochemistry. The observed regioselectivity of dihydroxlation may be due to the steric hindrance to the osmylation of the pendant *Z*-double bond in **13**. This implies that the pendant *E*-double bond is more accessible to the OsO_4 and hence easily dihydroxylated leading to polyhydroxylated products which could not be easily isolated from the aqueous phase. Attempts to improve the regioselectivity of the dihydroxlation of the dienes by converting the carbethoxyl group to the hydroxymethyl group as in 18 gave the wrong compound in poor yields (scheme 5). The ^{1}H NMR spectrum of the isolated compound confirmed the absence of olefinic protons (δ 4.5-6.0). However, many unresolved signals were observed in the range δ 3.0-4.3 suggesting that the dihydroxylation of **18** may have resulted in the

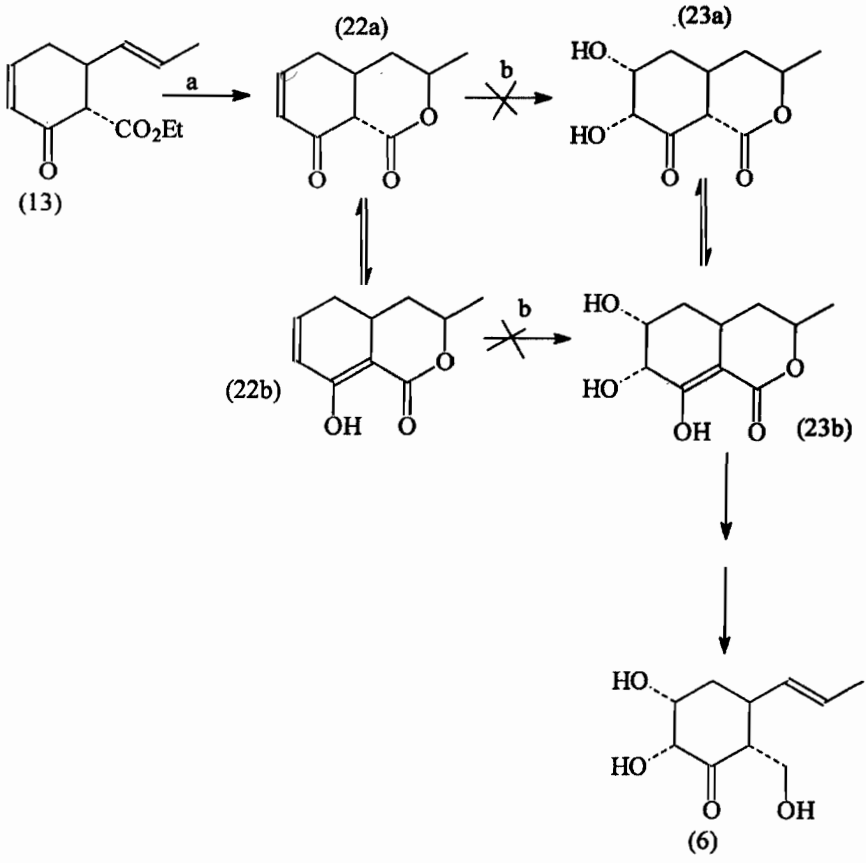
polyhydroxylated product **19**. Conversion of the keto group in **13** to the hydroxyl group gave the β-hydroxy ester (**16**). Attempts to regioselectively dihydroxylate **16** resulted in low yields (<1%) of the trihydroxyester (**20**). Again, it may be assumed that the rest of the material may have been converted to the polyhydroxylated ester (**21**). The loss of regioselectivity of dihyhydroxylation due to conversion of the carbethoxyl to the hydroxylmethyl group can be explained by reduced steric hindrance (to OsO_4 approach to the pendant double bond) by the hydroxymethyl leading to intramolecular osmylation and therefore the increased accessibility. The loss of regioselectivity when the keto group is changed to the hydroxyl group as in **16** and **17** can be explained by coordination of OsO_4 to the hydroxyl group leading to intramolecular osmylation. The carbethoxyl group is therefore a much better group in directing the dihydroxylation of these dienes than the hydroxymethyl and hydroxyl groups.



Scheme 5. (a) $CeCl_3.7H_2O/NaBH_4/MeOH$, (b) $NaClO_3$/cat OsO_4/THF, (c) DIBAL-H/CH_2Cl_2/-78 °C, (d) MnO_2/CH_2Cl_2/RT, (e) $NaClO_3$/cat OsO_4/THF.

It was envisaged that protection of the pendant double bond in **13** would ensure that the remaining double bond is dihydroxlated without any complications. The acid catalysed lactonisation of the dienone gave one diastereoisomer of the lactone (**22**) in

20% yield (scheme 6) unlike the 74% yield of both diastereoisomers as reported for the methylester analogue [22]. No optimisation of this reaction was done. The ^{1}H NMR spectrum of the lactone confirmed the existence of the compound in the enol form (**22b**). Attempted dihydroxylation of the lactone (**22**) did not give the required dihydroxylated product. Infact, neither the product nor the starting material was recovered suggesting that the OsO_4 may have caused decomposition of the starting material.



Scheme 6. (a) H_2SO_4/CH_2Cl_2, (b) cat $OsO_4/NaClO_3$/THF.

CONCLUSIONS

Syntheses of new palitantin model compounds, 6-carbethoxy-*cis*-2,3-dihydroxy-5-methylcyclohexan-1-one (**3**), *cis*-2,3-dihydroxy-6-hydroxymethyl-5-methylcyclohexan1-one (**4**) and 6-carbethoxy-*cis*-2,3-dihydroxy-5-(1'*Z*-propenyl)cyclohexan-1-one (**5b**) have been accomplished through one-pot Michael-Wittig reactions followed by standard functionalisations. The revelation of the steric hindrance caused by carbethoxyl group on the osmylation of the adjacent pseudo-equatorial pendant 1'*Z*-propenyl substituent in

cyclohexenones has a potential use in regioselective dihydroxylation of dienes in organic synthesis.

EXPERIMENTAL

General Procedures. M.P's were done on a Koepfler hot-stage apparatus and are uncorrected. ^{1}H NMR were recorded on Bruker WM-250, WH-400 or AM-400 spectrometers. ^{13}C NMR were done on Bruker AM-400 at 100 MHz. IR spectra were recorded on Perkin-Elmer 297, 983 or 1310 instruments. NMR and IR solvents were first passed through basic alumina to remove any traces of acid. MS analyses were done on Kratos AEI 30 or 50. Dry solvents were used in all reactions. Anhydrous Na_2SO_4 was used in drying organic solvent extracts. The reported yields are from either preparative TLC or flash column chromatographic purification [23] of the product.

6-Carbethoxy-5-methyl-2-cyclohexen-1-one (7). Sodium hydride (140 mg, 50% dispersion in oil) was washed with dry THF (2 x 2 mL) then suspended in dry THF (5 mL) and cooled to 0 °C. To the cooled suspension, a solution of the phosphonium salt (**8**) (472 mg, 1 mmol) [prepared according to reference 6] in dry THF (5 mL) was added followed by 70 mg (1 mmol) of croton aldehyde in dry THF (2 mL). One drop of H_2O was then added and the mixture stirred at 35 °C for 2 h. The reaction mixture was cooled to 0 °C and quenched with 2 M HCl to pH 1 and extracted with Et_2O (5 x 50 mL). The organic extracts were combined, dried, solvent removed and the oily residue purified by column chromatography (silica, CH_2Cl_2) to give 117 mg (67%) of the cyclohexenone (**7**) as an oil. HRMS found 182.0927 (M^+), $C_{10}H_{14}O_3$ requires 182.0943; MS *m/z* 182, 167, 137, 136, 121, 110, 109, 95, 86, 68 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 1725, 1665, 1616; ^{1}H NMR ($CDCl_3$) δ 6.97 (1H, ddd, J 10.3, 5.5, 2.6 Hz, $CH_2C\underline{H}$=), 6.06 (1H, d, J 10.3 Hz, =CHCO-), 4.24 (2H, q, J 7.1 Hz, -OCH_2-), 3.10 (1H, d, J 11.7 Hz, -$COCHCO_2$-), 2.63-2.44 (2H, m, -$C\underline{H}_2CH$=), 2.17 (1H, m, -$C\underline{H}CH_3$), 1.28 (3H, t, J 7.1 Hz, -$CH_2C\underline{H}_3$), 1.07 (3H, d, J 6.4 Hz, -$CHC\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 194.5 (C-1), 169.9 (-CO_2-), 149.7 (C-3), 128.4 (C-2), 61.7 (C-6), 61.0 (-CH_2O-), 33.1 (C-4), 32.8 (C-5), 19.7 (-$CH\underline{C}H_3$), 14.2 (-$CH_2\underline{C}H_3$).

6-Carbethoxy-cis-2,3-dihydroxy-5-methylcyclohexan-1-one (3). The cyclohexenone (**7**) (17 mg, 0.13 mmol) was dissolved in dry THF (2 mL), the solution cooled to 0 °C and OsO_4 solution (0.25 mL, solution of 10 mg of OsO_4 in 10 mL H_2O, 0.1 eqv.) added slowly. A solution of $NaClO_3$ (25 mg in 0.5 mL H_2O, 1.1 eqv.) was added and the mixture stirred for 48 h at 25 °C. The reaction mixture was subsequently cooled to 0 °C and sodium metabisulphite (250 mg in 1 mL H_2O) added. The reaction mixture was stirred for another 18 h, diluted with H_2O (5 mL), filtered through celite and extracted with Et_2O (5 x 50 mL). The Et_2O extracts were combined, dried solvent removed to give 17 mg (75%) of the crude diol. The crude diol was purified further by preparative TLC (silica, EtOAc, R_f 0.45) to give 13 mg (62%) of the pure diol (**3**) as a white flaky solid. HRMS found 216.0980 (M^+), $C_{10}H_{16}O_5$ requires 216.0998; MS *m/z* 216,198,169, 146 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3450 (br), 3350, 1720, 1700; ^{1}H NMR ($CDCl_3$) δ 4.38 (1H, m, J 3.5 Hz, -$CH_2C\underline{H}$(OH)-), 4.25 (2H, q, J 7.2 Hz, -OCH_2-), 4.20 (1H, d, J 3.5 Hz, -$COC\underline{H}$(OH)-), 3.10 (1H, d, J 12.2 Hz, -$COCHCO_2$-), 2.81 (1H, m, -$C\underline{H}CH_3$), 2.18 (1H, dt, J 12.7, 3.8 Hz, -$C\underline{H}_{2eq}$CH(OH)-), 1.65 (1H, ddd, J 13.7, 12.7, 1.8 Hz, -CH_{2ax}-), 1.20

(3H, t, J 7.2 Hz, -$CH_2\underline{CH_3}$), 1.08 (3H, d, J 6.7 Hz, -$CHC\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 204.8 (C-1), 168.1 (-CO_2-), 76.7 (C-2), 71.3 (C-3), 62.4 (C-6), 61.2 (-OCH_2-), 35.9 (C-4), 31.2 (C-5), 20.2 (-$CH\underline{C}H_3$), 14.1 (-$OCH_2\underline{C}H_3$).

6-Carbethoxy-5-methyl-2-cyclohexen-1-ol (10). The cyclohexanone (**7**) (159 mg, 0.87 mmol) was dissolved in CH_3OH (5 mL), $CeCl_3.7H_2O$ (325 mg, 1 eqv) added and the mixture cooled to 0 °C. To the cold mixture, $NaBH_4$ (17 mg, 0.33 eqv.) was added and the mixture stirred at that temperature for 1 h, then quenched with H_2O (5 mL). The mixture was filtered through celite and the filterate extracted with Et_2O. The Et_2O extracts were combined, dried, solvent removed and the oily residue purified by column chromatography (silica, petrol:Et_2O 7:3) to give 98 mg (61%) of the β-hydroxyester (**10**) as a colourless oil. HRMS found 184.1094 (M^+), $C_{10}H_{16}O_3$ requires 184.1099; MS *m/z* 184, 139, 123, 115, 110, 69 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3450, 1705, 1605; ^{1}H NMR ($CDCl_3$) δ 5.85-5.61 (2H, m, -C$\underline{H}$=C$\underline{H}$-), 4.51 (1H, dm, J 9.3 Hz, -C$\underline{H}$(OH)-), 4.20 (2H, q, J 7.1 Hz, -OCH_2-), 2.15 (1H, dd, J 11.4, 9.3 Hz, -$CHCO_2$-), 2.17-2.06 (1H, m, -$C\underline{H}_{2eq}$CH=), 1.95 (1H, m, -C$\underline{H}CH_3$), 1.83-1.69 (2H, m, -OH and -$C\underline{H}_{2ax}$CH=), 1.28 (3H, t, J 7.1 Hz, -$CH_2C\underline{H_3}$), 0.95 (3H, d, J 6.3 Hz, -$CHC\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 174.7 (-CO_2-), 129.8, 128.1 (C-2 and C-3), 70.1 (C-1), 60.5 (-OCH_2-), 56.6 (C-6), 33.7 (C-4), 30.9 (C-5), 19.2 (-$CH\underline{C}H_3$), 14.3 (-$CH_2\underline{C}H_3$) for the major alcohol as confirmed by ^{1}H decoupling experiments. The ratio of the equatorial to axial alcohols was found to be 4:1 from ^{1}H NMR analysis.

6-Hydroxymethyl-5-methyl-2-cyclohexan-1-ol (11). The β-hydroxyester (**10**) (87 mg, 0.47 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and the solution cooled to -78 °C. To the cold mixture, DIBAL-H (1.38 mL eqv.) was added slowly and the reaction mixture stirred at that temperature for 2 h. The reaction mixture was left to warm to 0 °C, quenched carefully with H_2O (10 mL), filtered through celite and the filterate extracted with Et_2O (5 x 20 mL). The Et_2O extracts were combined, dried, solvent removed and the oily residue purified by column chromatography (silica, Et_2O) to yield 22 mg (33%) of the diol (**11**) as an oil. HRMS found 142.1001 (M^+), $C_8H_{14}O_2$ requires 142.0994; MS *m/z* 142, 124, 112, 109, 97, 92, 70 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3450 (br), 1600, 1610; ^{1}H NMR ($CDCl_3$) δ 5.89-5.62 (2H, m, -C$\underline{H}$=C$\underline{H}$-) , 4.57 (1H, m, =CHC$\underline{H}$(OH)-), 3.90 (1H, m, -C$\underline{H}_2$OH), 3.72 (1H, m, -C$\underline{H}_2$OH), 2.67 (2H, br s, -OH), 2.13 (1H, m, -(OH)CHC$\underline{H}$-CH_2OH), 2.04-1.52 (3H, m, -C$\underline{H}CH_3$ and -C$\underline{H}_2$CH=), 1.02 (3H, d, J 6.9 Hz, -$CHC\underline{H_3}$).

6-Hydroxymethyl-5-methyl-2-cyclohexen-1-one (12). The diol (**11**) (15 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and MnO_2 (150 mg, 1.7 mmol) added. The mixture was stirred at 25 °C for 18 h, filtered through celite, the solvent removed and the residue purified by preparative TLC (silica, Et_2O, R_f 0.42) to give 8 mg (55%) of the enone alcohol (**12**) as a colourless oil. HRMS found 140.0828 (M^+), $C_8H_{12}O_2$ requires 140.0838; MS *m/z* 140, 125, 122, 111, 94, 84 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3440 (br), 1650, 1610; ^{1}H NMR ($CDCl_3$) δ 6.97 (1H, ddd, J 10.0, 5.0, 1.6 Hz, -$CH_2C\underline{H}$=), 6.0 (1H, d, J 10.0 Hz, =CHCO-), 3.99 (1H, dd, J 11.0, 8.3 Hz, -C$\underline{H}_2$OH), 3.74 (1H, dd, J 11.0, 5.3 Hz, -CH_2OH), 2.96 (1H, br t, -OH), 2.44 (1H, m, -C$\underline{H}CH_2$OH), 2.46-2.10 (3H, m, -C$\underline{H}CH_3$ and -C$\underline{H}_2$CH=), 1.07 (3H, d, J 5.7 Hz, -$CHC\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 203.0 (C-1), 150.4 (C-3), 129.5 (C-2), 60.0 (-CH_2OH), 54.9 (C-6), 34.7 (C-4), 31.4 (C-5), 19.32 (CH_3-).

cis-2,3-Dihydroxy-6-hydroxymethyl-5-methylcyclohexan-1-one (4). The enone alcohol (**12**) (13.4 mg, 0.1 mmol) was dissolved in THF (2 mL) and the solution cooled to 0 °C. To the cold solution, catalytic amounts of OsO_4 (0.25 mL, solution of 100 mg in 10 mL H_2O) followed by $NaClO_3$ (25 mg in 1 mL H_2O) was added slowly and the mixture stirred at 25 °C for 48 h. The reaction mixture was cooled to 0 °C, sodium metabisulphite (250 mg in 0.5 mL H_2O) added and then stirred for a further 18 h at 25 °C. The mixture was diluted with H_2O (5 mL), filtered through celite and the filterate extracted with EtOAc (5 x 10 mL). The EtOAc extracts were combined, dried, solvent removed and the residue purified by flash column chromatography (silica, EtOAc:CH_3OH 99:1). The triol (**4**) was recovered as a colourless oil (8 mg, 50%). HRMS found 156.0779 (M^+-H_2O), $C_8H_{12}O_3$ requires 156.0786; MS *m/z* 156, 138, 112, 109, 86 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3600, 3400 (br), 2962, 1708; ^1H NMR ($CDCl_3$) δ 4.35 (1H, m, J 3.7 Hz, -CH_2C<u>H</u>(OH)-), 4.19 (1H, dd, J 3.7, ^2J 1.1 Hz, -C<u>H</u>(OH)CO-), 3.90 (1H, dd, J 11.9, 2.6 Hz,-CH_2OH), 3.80 (1H, dd, J 11.9, 6.2 Hz, -CH_2OH), 2.25 (2H, m, -C<u>H</u>CH_2OH), 2.13 (1H, dt, J 14.0, 3.7 Hz, -CH_{2eq}-), 1.70 (1H, ddd, J 14.0, 12.0, 2.1 Hz, -CH_{2ax}-), 1.1 (3H, d, J 6.1 Hz, -CH_3); ^{13}C NMR ($CDCl_3$) δ 212.3 (C-1), 77.0 (C-2), 71.9 (C-3), 59.0 (-CH_2OH), 56.5 (C-6), 37.0 (C-4), 29.7 (C-5), 19.5 (CH_3-).

6-Carbethoxy-5-(1'-propenyl)-2-cyclohexen-1-one (13). Sodium hydride (200 mg, 50% dispersion in oil) was washed with (2 x 2 mL) and suspended in dry THF. The phosphonium salt (**8**) (1.88 g, 4 mmol) was added followed by catalytic amounts of KH and the reaction mixture stirred until evolution of H_2 gas stopped. Sorbaldehyde (**14**) (0.53 mL, 1.25 eqv.) was added and the mixture stirred at 25 °C for 18 h. The reaction mixture was cooled to 0 °C, carefully quenched with 2 M HCl to pH 4 and extracted with CH_2Cl_2 (5 x 50 mL). The CH_2Cl_2 extract were combined, dried, solvent removed and the oily residue purified by column chromatography (silica, CH_2Cl_2) to give 310 mg (38%) of the dienone ester as a yellowish oil. HRMS found 208.1103 (M^+), $C_{12}H_{16}O_3$ requires 208.1099; MS *m/z* 208, 163, 162, 147, 135, 107, 68 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 1720, 1665, 1610; ^1H NMR ($CDCl_3$) δ 6.79 (1H, ddd, J 10.2, 5.7, 2.6 Hz, -CH_2C<u>H</u>=), 6.10 (1H, d, J 10.2 Hz, =CHCO-), 5.60 (1H, dq, J 15.2, 6.3 Hz, =C<u>H</u>CH_3), 5.30 (1H, dd, J 15.2, 7.3 Hz, -CHC<u>H</u>=), 4.20 (2H, q, J 7.2 Hz, -OCH_2-), 3.24 (1H, d, J 12.0 Hz, -COC<u>H</u>CO_2-), 3.10 (1H, m, -C<u>H</u>CH=), 2.50 (1H, br dt, J 19.1, 5.2 Hz, -C<u>H</u>$_2$CH=), 2.25 (1H, ddd, J 19.1, 10.1, 2.6 Hz, -C<u>H</u>$_2$CH=), 1.63 (3H, d, J 6.3 Hz =CHC<u>H</u>$_3$), 1.24 (3H, t, J 7.2 Hz, -CH_2C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 194.1 (C-1), 169.5 (-CO_2-), 149.5 (C-3), 130.7, 128.9, 127.9 (C-1', C-2' and C-2), 60.9 (-OCH_2-), 60.0 ((C-6), 41.3 (C-5), 31.5 (c-4), 17.8 (C-3'), 14.2 (-CH_2CH_3) for the *E*-isomer. The NMR data was consistent with the presence of both the *E*- and *Z*-isomers in a ratio of 3:1.

6-Carbethoxy-cis-2,3-dihydroxy-5-(1'-propenyl)cyclohexan-1-one (5b). The γ,δ-unsaturated-β-ketoester (**13**) (136 mg, 0.67 mmol, 3:1 *E:Z*) was dissolved in THF (5 mL), the solution cooled 0 °C and OsO_4 solution (1.2 mL, 100 mg in 100 mL H_2O, 0.1 eqv.) added. A solution of $NaClO_3$ (78 mg in H_2O, 1.2 eqv.) was added and the mixture stirred at 25 °C for 48 h. Sodium metabisulphite (400 mg in H_2O) was subsequently added and the mixture stirred at 25 °C for a further 18 h. The mixture was diluted with H_2O (3 mL), filtered through celite and the filterate extracted with EtOAc (5 x 20 mL). The EtOAc extracts were combined, dried, solvent removed and the oily residue purified by column chromatography (silica, Et_2O) to give 11 mg (8%) of the diol (**5b**) as an oil.

HRMS found 242.1150 (M^+), $C_{12}H_{18}O_5$ requires 242.1154; MS *m/z* 242, 224, 196, 99(100%); ^{1}H NMR ($CDCl_3$) δ 5.54 (1H, dq, J 10.5, 6.9 Hz, =C<u>H</u>CH$_3$), 5.17 (1H, dd, J 10.4, 10.2 Hz, -CHC<u>H</u>=), 4.38 (1H, m, J 3.6 Hz, -CH$_2$C<u>H</u>(OH)-), 4.20 (1H, d, J 3.0 Hz, -C<u>H</u>(OH)CO-), 4.19 (2H, q, J 7.1 Hz, -OCH$_2$-), 3.80 (1H, br s, -OH), 3.72 (1H, m, -C<u>H</u>CH=), 3.25 (1H, d, J 11.8 Hz, -COCHCO$_2$-), 2.61 (1H, br s, -OH), 2.10 (1H, dt, J 14.7, 3.9 Hz, -CH$_{2eq}$-), 1.76 (1H, ddd, J 14.6, 12.6, 2.0 Hz, -CH$_{2ax}$-), 1.66 (3H, d, J 6.8 Hz, C<u>H</u>$_3$CH=), 1.25 (3H, t, J 7.1 Hz, -CH$_2$C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 204.3 (C-1), 167.7 (-CO$_2$-), 130.0 (C-1'), 127.2 (C-2'), 77.0 (C-2), 71.5 (C-3), 61.2 (-OCH$_2$-), 60.9 (C-6), 34.5 (C-5), 34.2 (C-4), 14.1 (-CH$_2$<u>C</u>H$_3$), 13.2 (C-3'). The NMR data was consistent with the presence of the *Z*-isomer only.

6-Carbethoxy-5-(1'-propenyl)2-cyclohexen-1-ol (16). The γ,δ-unsaturated-β-ketoester (**13**) 213 mg, 1 mmol) was dissolved in CH_3OH (5 mL), the solution cooled to 0 °C and $CeCl_3.7H_2O$ (381 mg, 1 mmol) added. To the cold mixture, $NaBH_4$ (41 mg, 1 eqv.) was added and the mixture stirred for 1 h. The mixture was diluted with H_2O (3 mL), filtered through celite and the filterate extracted with Et_2O (5 x 20 mL). The Et_2O extracts were combined, dried, solvent removed and the oily residue purified by column chromatography (silica, petrol:Et_2O 3:2) to give 154 mg (72%) of the β-hydroxyester (**16**) as a colourless oil. HRMS found 210.1266 (M^+), $C_{12}H_{18}O_3$ requires 210.1256; MS *m/z* 210, 192, 182, 142, 136, 119 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3600, 3400 (br), 1715, 1600; ^{1}H NMR ($CDCl_3$) δ 5.57-5.52 (2H, m, -CH$_2$C<u>H</u>=C<u>H</u>-), 5.48 (1H, dq, J 15.1, 6.3 Hz, =C<u>H</u>CH$_3$), 5.28 (1H, dd, J 15.1 7.0 Hz, -CHC<u>H</u>=), 4.56 (1H, dm, J 7 Hz, -C<u>H</u>(OH)-), 4.15 (2H, q, J 7.1 Hz, -OCH$_2$-), 2.52-2.35 (1H, m, -C<u>H</u>CH=), 2.30 (1H, dd, J 11.7, 9.7 Hz, -CHCO$_2$-), 2.10 (1H, dm, J 17.3 Hz, -C<u>H</u>$_2$CH=), 1.99-1.84 (1H, m, -C<u>H</u>$_2$CH=) 1.61 (3H, d, J 6.3 Hz, C<u>H</u>$_3$CH=), 1.22 (3H, t, J 7.1 Hz, -CH$_2$C<u>H</u>$_3$) for the equatorial alcohol (major). The ^{1}H NMR data was consistent with the presence of both the equatorial and axial alcohol in a ratio of 6:1, respectively.

6-Hydroxymethyl-5-(1'-propenyl)-2-cyclohexen-1-ol (17). The β-hydroxyester (**16**) (146 mg, 0.7 mmol) was dissolved in dry CH_2Cl_2 (15 mL), the solution cooled to -78 °C and DIBAL-H (2.4 mL, 3 eqv.) added slowly. The reaction mixture was stirred at that temperature for 2 h., warmed to 0 °C and quenched with H_2O (5 mL). The mixture was filtered through celite, the filterate extracted with Et_2O (5 x 30 mL), the extracts combined, dried, solvent removed and the oily residue purified by column chromatography (silica, Et_2O). The diol (**17**) was recovered as a colourless oil 24 mg (21%). HRMS found 168.1144 (M^+), $C_{10}H_{16}O_2$ requires 168.1150; MS *m/z* 168, 150, 132, 81 (100%), IR ν_{max} ($CHCl_3$) cm^{-1} 3400, 1600; ^{1}H NMR ($CDCl_3$) δ 5.77-5.58 (2H, m, -CH$_2$C<u>H</u>=C<u>H</u>-), 5.46 (1H, dq, J 15.1, 6.3 Hz, =C<u>H</u>CH$_3$), 5.26 (1H, dd, J 15.1, 8.7 Hz, -CHC<u>H</u>=), 4.27 (1H, m, -C<u>H</u>(OH)-), 3.96, (1H, dd, J 11.1, 3.6 Hz, -CH$_2$O-), 3.63 (1H, dd, J 11.1, 8.4 Hz, -CH$_2$O-), 2.6 (1H, m, -C<u>H</u>CH=), 2.20-1.51 (8H, m, 2 x (-OH), C<u>H</u>$_3$CH= , C<u>H</u>$_2$CH= and -C<u>H</u>CH$_2$OH) for the equatorial alcohol (major).

6-Hydroxymethyl-5-(1'-propenyl)-2-cyclohexen-1-one (18). The diol (**17**) (21 mg, 0.13 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and MnO_2 (210 mg, 2.4 mmol) added. The reaction mixture was stirred at 25 °C for 18 h, filtered through celite, solvent removed and the residue purified by column chromatography (silica, Et_2O) to give 10 mg (50%) of the dienone (**18**) as a colourless oil. HRMS found 166.0979 (M^+), $C_{10}H_{14}O_2$ requires

166.0994; MS *m/z* 166, 149, 138, 137 (100%); IR ν_{max} ($CHCl_3$) cm^{-1} 3500 (br), 1650, 1610; ^1H NMR ($CDCl_3$) δ 6.97 (1H, ddd, J 10.0, 5.4, 2.7 Hz, -CH_2C<u>H</u>=), 6.02 (1H, d, J 10.0 Hz, =CHCO-), 5.57 (1H, dq, J 15.1, 6.4 Hz, =C<u>H</u>CH_3), 5.33 (1H, dd, J 15.1, 7.5 Hz, -CHC<u>H</u>=), 3.86 (1H, dd, J 11.8, 8.5 Hz, -CH_2O-), 3.72 (1H, dd, J 11.8, 6.9 Hz, -CH_2O-), 2.96 (1H, br t, -OH), 2.58 (1H, m, -C<u>H</u>CH=), 2.45-2.27 (3H, m, -C<u>H_2</u>CH= and -C<u>H</u>CH_2OH), 1.68 (3H, d, J 6.4 Hz, CH_3CH=) for the *E*-isomer (major).

8-Hydroxy-3-methyltetrahydroisocuomarin (22). The dienone (**13**) (161 mg, 0.76 mmol) was dissolved in dry CH_2Cl_2 and the solution cooled to 0 °C. To the cold solution, 0.6 mL of concentrated H_2SO_4 was added and and the reaction kept at that temperature for 18 h. The mixture was poured into ice, extracted with Et_2O (5 x 30 mL), the organic extract combined, washed with dilute $NaHCO_3$ solution, dried and concentrated. Column chromatography (SiO_2, 10% Et_2O in hexane) gave 28 mg (20%) of the white crystalline product (**22**). HRMS found 180.0789 (M^+), $C_{10}H_{12}O_3$ requires 180.0787; MS *m/z* 180, 139, 121 (100%), 107, 95, 94, 77, 41., IR ν_{max} ($CHCl_3$) cm^{-1} 3100, 2900, 2800, 1640, 1605, 1570; ^1H NMR ($CDCl_3$) δ 1.38 (3H, , d, J 6.3 Hz, CH_3-), 1.53 (1H, dt, J 13.5, 11.7 Hz, -C<u>H_{2ax}</u>CHO-), 1.95 (1H, tt, J 17.2, 2.8 Hz, -C<u>H_{2ax}</u>CH=), 2.0 (1H, ddd, J 13.5, 4.5, 2.2 Hz, -C<u>H_{2eq}</u>CHO-), 2.32 (1H, dt, J 17.2, 6.4 Hz, -C<u>H_{2eq}</u>CH=), 2.84 (1H, dddd, J 11.7, 4.5, 6.5, 17.2 Hz, -CH-), 4.38 (1H, dqd, J 11.7, 2.2, 6.5 Hz, -OCH-), 6.05 (1H, dd, J 10.0, 3.0 Hz, =C<u>H</u>-C(OH)-), 6.42 (1H, ddd, J 2.2, 6.6, 10.0 Hz, =C<u>H</u>CH_2-), 12.83 (1H, s, -OH); ^{13}C NMR ($CDCl_3$) δ 171.9 (C-8), 168.2 (C-1), 139.6 (C-6), 124.6 (C-7), 92.7 (C-8a), 75.6 (C-3), 36.8 (C-4), 30.41 (C-4a), 30.35 (C-5), 21.5 (-CH_3).

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