Pergamon

Tetrahedron 55 (1999) 3233–3244

TETRAHEDRON

The Enantioselective Total Synthesis of Epoformin and Analogues

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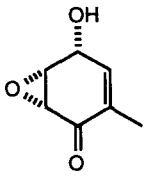
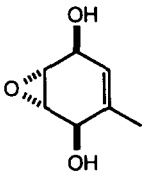
Received 13 April 1998; revised 29 May 1998; accepted 8 June 1998

Abstract: The enantioselective synthesis of epoformin, an antibiotic and cytotoxic natural compound, has been achieved via a remote hydroxyl directed epoxidation of an α,β-unsaturated ketone derived from quinic acid.

(+)-Epoformin **1** and (-)-theobroxide **2** belong to a family of highly oxygenated cyclohexane-based metabolites, mainly epoxides, that have been isolated from bacteria, fungi, higher plants and molluscs.[1-5] These compounds have stimulated several synthetic efforts[6-9] due to their biological activities, which range from antifungal, antibacterial, antitumor, phytotoxic and enzyme inhibitory.[1-9]



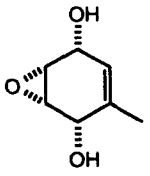
(+)-Epoformin **1**



(-)-Theobroxide **2**

Epoformin **1** is an antibiotic and cytotoxic substance isolated from the culture broth of *Penicillium claviforme*,[1] that to our knowledge, has not previously been synthesised in an optically active form.[6] The structurally related compound theobroxide **2** has recently been synthesised.[7] Compound **2** is a potato (*Solanum tuberosum* L.) micro-tuber growth inducing substance isolated from the fungus *Lasiodiplodia theobromae*.[2] Our interest in the enantioselective synthesis of the stereoisomers of theobroxide, and derivatives, remains in their potential practical applications in agriculture[2] and in the study of tuber-inducing mechanisms of plants in general.

We report here the enantioselective syntheses of epoformin **1** and our attempts to synthesise **2**. From these studies we obtained compounds **3**, a new diastereoisomer of theobroxide and **4**,[7] *via* common intermediates.



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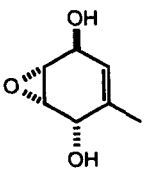

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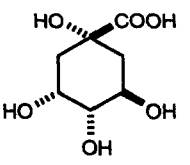

(-)-Quinic acid **5**

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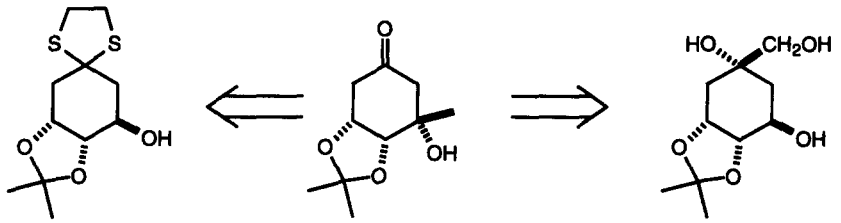
PII: S0040-4020(98)01136-3

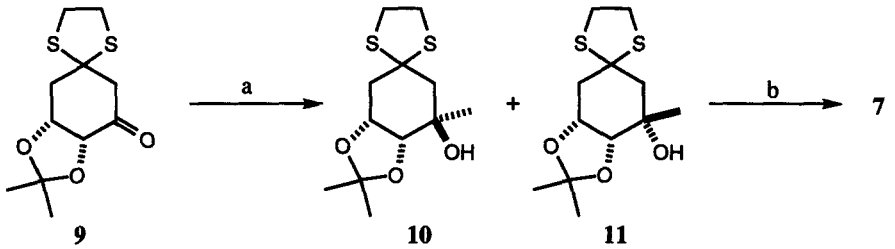
We chose (-)-quinic acid **5** as the starting material since it is a readily available cyclohexane based natural compound which has recently been used for several total syntheses.[9-16]



6 **7** **8**

Our first objective was to reach an intermediate that could originate the two double bonds required, one of them for the epoxidation and the other to remain in the final structure of **1** and **2**. Compound **7** has all of the necessary functionality to create selectively and sequencially the two necessary double bonds.

Two possible quinic acid derived starting materials **6** and **8** were available.[11] Initially we chose **10** or its epimer **11**, precursors to the key intermediate **7** or its epimer, as our first target compounds and these would be derived from compound **6**. This unfortunately proved to be the least viable route.



9 **10** **11**

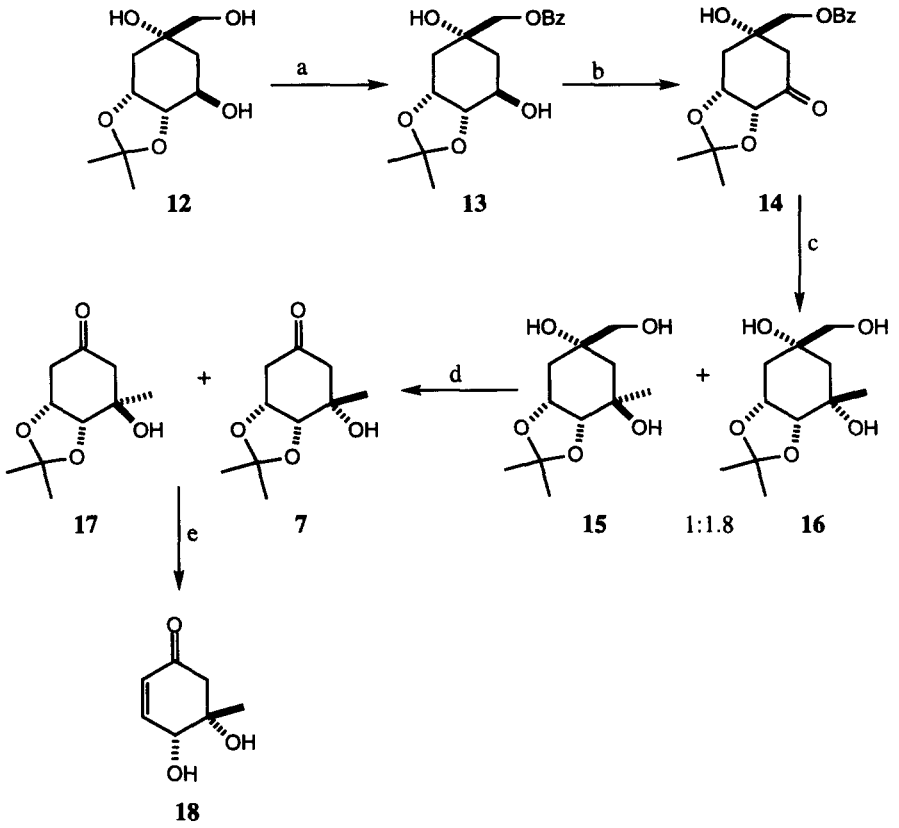
2.7:1

Scheme 1: a) $MeCeCl_2$, THF, -78 °C, 87%. b) $HgO/HgCl_2$, $MeCN/H_2O$ (8/2), rt, 30%.

In scheme 1 our first approach to ketone **7**, or its epimer, is described. Starting from the known ketone **9** we made several attempts to introduce the methyl group by a 1,2-addition to the carbonyl group. Using the Grignard reagent, methylmagnesium iodide, we obtained the two diastereoisomers **10** and **11** in a ratio of about 1/2.5 respectively, in only 48% yield. The reaction of ketone **9** with methyllithium afforded selectively compound **11**, but the yield was only 34%. Since starting material was recovered we assumed that enolisation of the ketone by the organometallic had deactivated the system.[17] To improve the yield of this step we attempted the addition with the organocerium reagent $MeCeCl_2$.[18] Great care is needed in the preparation of these reagents,[18] but they have the advantage of being less basic than the organolithium and Grignard reagents. Thus, we obtained a mixture of the diastereoisomers in good yield (87%), but the diastereoselectivity was inverted (2.7/1, **10/11**).

Owing to their similar chromatographic properties, the diastereoisomers **10** and **11** were not routinely separated. Using this mixture, attempts were made to hydrolyse the dithiolane using $HgO/HgCl_2$, in order to obtain the ketone **7** and/or its epimer. The yield of this deprotection reaction was low (20-30%) and we obtained only one diastereoisomer, **7**. This diastereoisomer was obviously produced from compound **11**, and we assume that the other isomer is destroyed probably by aromatisation after exposure of the ketone. In face of these results,

we were obliged to devise a more efficient route to compound **7** which did not involve the dithiolane protecting group (scheme 2).

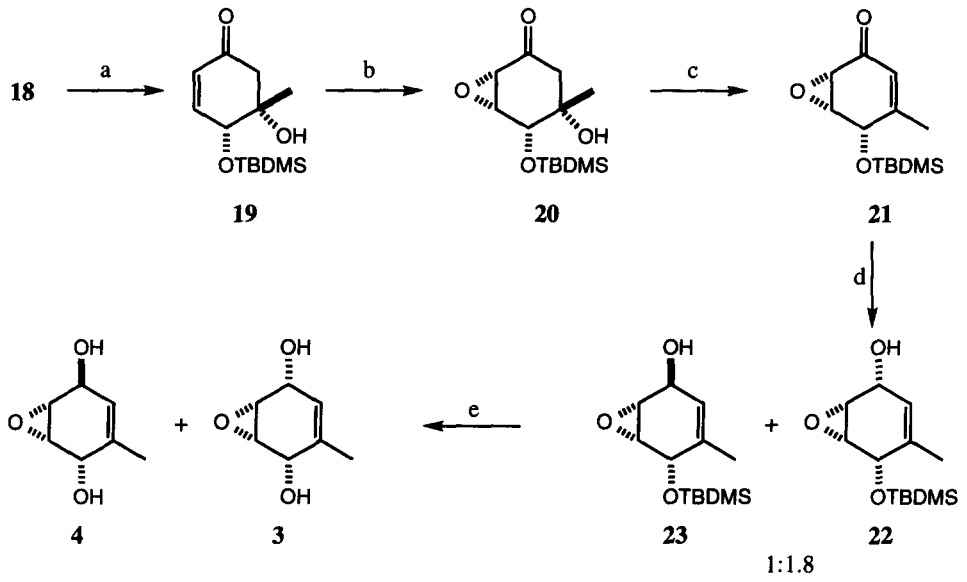


Scheme 2: a) BzCl, pyridine, 82%. b) periodinane, pyridine, CH_2Cl_2, rt, 88%. c) $MeCeCl_2$ THF, -78 °C. d) $NaIO_4$, H_2O, 5<pH<6. e) NaOH 0.5 N cat., THF, 0 °C, 60% (3 steps).

The selective protection of the primary hydroxyl of triol **12** with benzoyl chloride needed special precautions, in order to avoid the acylation of the secondary alcohol. Thus 0.87 eq of the benzoyl chloride was added very slowly over about 15 min to a strongly stirred solution of the triol and the temperature was maintained below 0 °C during the whole reaction period. Compound **13** resulted in 82% yield.

Oxidation of **13** was accomplished using periodinane,[19] in the presence of pyridine, to assure mild reaction conditions, and this afforded ketone **14** in good yield. Treatment of the unpurified product, **14**, with $MeCeCl_2$ afforded the two diastereoisomers **15** and **16**, (1.8/1 **16/15**), in good yield. Under these conditions the major diastereoisomer resulted from attack at the opposite diastereoface of the carbonyl group to that observed previously (scheme 1). We also tried the addition with MeLi, to see if there would be an inversion of the diastereoselectivity as had happened with the thioacetal protected compound **9**. Under these conditions, the only diastereoisomer obtained was triol **16**. In some way, the dithiolane group exerted a different steric effect to that of the methylbenzoate group. Unfortunately the yield of the reaction with MeLi wasn't good on scale up so the use of this reagent was not a practical solution to the selectivity problem and subsequently only the organocerium

reagent was used for this addition. Compounds **15** and **16** were difficult to separate and the oxidative cleavage (scheme 2) was therefore performed without further purification to yield a mixture of both diastereoisomers **7** and **17**. A sample of **17** was isolated for characterisation. Again without purification, the base catalysed elimination reaction was carried out on this mixture using aqueous 0.5 N NaOH[9] to obtain a mixture of unsaturated compound **18** and starting acetal **17**. After chromatography, **18** was obtained in 60% yield from **14**.



Scheme 3: a) TBDMSCl, DMF, imidazole, rt, 79%. b) H_2O_2, Triton B, THF, 0 °C, 92%. c) $(CF_3SO_2)_2O$, $(i\text{-Pr})_2NEt$, DMAP, CH_2Cl_2, 0 °C, 57%. d) DIBAL-H, THF, -78 °C, 99%. e) Bu_4NF, THF, H_2O (trace), rt, 92%.

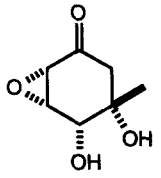
Selective protection of the secondary hydroxyl group of diol **18** (scheme 3), to obtain the silyl ether **19** in 79% yield, was followed by epoxidation with 30% H_2O_2 and Triton B to give exclusively the epoxide **20**, in excellent, 92%, yield. When employing the bulky *t*-BuOOH as the epoxidizing agent we only recovered starting material. Based upon our previous studies, epoxidations of structurally similar compounds without the tertiary hydroxyl group,[9,20] we expected that the epoxide would have been introduced *trans* to the adjacent silyloxy group. It appears, however, that the unprotected tertiary hydroxyl group directs the epoxidation such that we obtain the all *cis* compound **21**. We attempted unsuccessfully to block the tertiary hydroxyl in order to show that without this hydrogen bonding site the expected product would be produced.

Elimination of the elements of water from compound **20** was achieved using triflic anhydride and diisopropylethylamine, and compound **21** was obtained as an oil, in 57% yield. Variations on the reaction conditions did not produce better yields. With milder activating reagents such as acetic anhydride, mesyl chloride and mesyl anhydride, the elimination was too slow and decomposition competed effectively.

Reduction of the carbonyl group of **21** with DIBAL-H gave the two diastereoisomers **22** and **23**, with a diastereoselectivity of 1.8:1 respectively, in essentially quantitative yield. The two diastereoisomers were very difficult to separate and the removal of the TBDMS group was performed on the mixture. For this we employed

Bu_4NF in THF with a trace amount of water, which has proved to be the best conditions for epoxides[9] for this purpose, and compound **3** and known compound **4** were formed, the latter being identical by proton ^1H NMR spectroscopy comparison with the data previously reported.[7]

Our attempts to obtain the epoxide with inverted configuration were not successful. Mitsunobu reactions on **18** gave only decomposition products, and on compound **24**, obtained by epoxidation of **18** with hydrogen peroxide and Triton B, afforded the eliminated product **25** among other unidentified products. This latter thus did not constitute a practical route to **25**. Curiously, compound **20** under Mitsunobu conditions did not form the elimination product, which suggests that either the bulky TBDMS group prevented direct attack at the tertiary hydroxyl or that the secondary hydroxyl group of **24** had reacted with the activated phosphorus reagent first. Cyclisation then occurred at the tertiary hydroxyl followed by ring opening elimination in the resulting strained bicyclic system.



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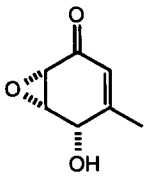

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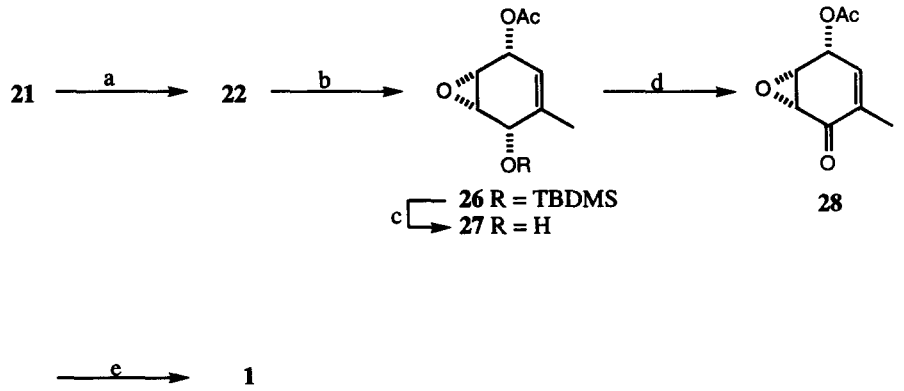
In principle using the strategy outlined below for the latter stages of the synthesis of epoformin, it should be possible to convert compound **4** to epiepoformin. Similarly a protection/deprotection strategy aimed at inverting the configuration of the appropriate hydroxyl group of **4** (see also epoformin synthesis) should also produce (-)-theobroxide **2**.

Compound **4** is a diastereoisomer of **2** only differing in the configuration at one of the hydroxyl groups. We plan to test the effect of both **3** and **4** on potato microtubercules to compare their biological activity with that of (-)-theobroxide.



Scheme 4: a) L-Selectride, THF, -78 °C. b) Ac_2O, $(i\text{-}Pr)_2NEt$, DMAP, CH_2Cl_2, 0 °C/rt, 73% (2 steps). c) Bu_4NF, THF, H_2O (trace), rt, 98%. d) periodinane, pyridine, CH_2Cl_2, 0 °C/rt, 99%. e) 10% KOH, THF, 0 °C, 95%.

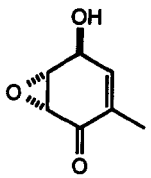
This work provided the basis for the synthesis of our other target compound epoformin **1** (scheme 4) which was successfully prepared by a slight variation of the above strategy. Reduction of ketone **21** with L-Selectride®[21] afforded exclusively the diastereoisomer **22**, which was normally protected without further purification to give the acetate **26**, 73% overall yield.

Removal of the TBDMS group was performed using fluoride as described above, and we obtained the alcohol **27** in 98% yield. Oxidation of **27** with periodinane afforded epoformin acetate **28** in quantitative yield.

Finally, hydrolysis of **28** was accomplished by careful addition of a 10% aqueous solution of potassium hydroxide, with TLC monitoring, to give epoformin **1** in 95% yield. Remarkably, the epoxide survived these basic reaction conditions. We have previously shown[9] that these epoxides were able to resist Grignard reagents, if it was carefully added to the reaction mixture. The spectroscopic data of **1** are identical to those described in the literature.[1] This appears to be the first reported enantioselective total synthesis of epoformin.

Our synthetic methodology should allow the stereoselective and efficient preparation of other structural related metabolites[5,8] belonging to this large and expanding family of biologically active natural compounds.

Interestingly, the ^{1}H NMR spectra of epoformin **1** (desoxyepoxydon) and epiepoformin **29** (desoxyepiepoxydon) show characteristic chemical shifts for their vinylic protons. Thus epoformin presents a resonance signal at about 6.27 ppm and epiepoformin a signal at about 6.46.[4,6,7] This implies that the compound isolated by Scott et al.[3] and Nagasawa et al.[4] is in fact the same compound and that it corresponds to epiepoformin (desoxyepiepoxydon).



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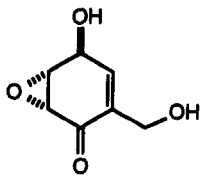
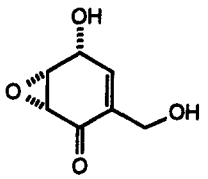


(+)-epiepoxydon



(+)-epoxydon

Experimental Section

General. Melting points were determined with a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with chemical shift values (δ) in ppm downfield from tetramethylsilane, and ^{13}C NMR spectra were obtained at 100.61 Mhz in $CDCl_3$. DEPT was used as an aid to structure elucidation and carbon assignments but the data are not reported here. Microanalyses were performed by the ITQB analytical services using a combustion apparatus. IR (v, cm^{-1}): measured on an FTIR spectrophotometer. Medium pressure preparative column chromatography: silica gel Merck 60 H. Preparative TLC: silica gel Merck 60 GF_{254}. Analytical TLC: Aluminum-backed silica gel Merck 60 F_{254}. Specific rotations ($[\alpha]_D^t$) were measured on an automatic polarimeter. Reagents and solvents were purified and dried according to ref 22. All the reactions were carried out in an inert atmosphere (argon), unless otherwise indicated.

(1S,2R,3R)-2,3-Isopropylidenedioxy-5,5-(1,2-ethanedithio)-1-methyl-1-cyclohexanol (11). (With methyllithium). To a solution of **9** (0.100 g, 0.38 mmol) in THF (7 mL), at 0 °C, was slowly added 1.6 M methylllithium in diethyl ether (0.264 mL, 0.42 mmol). The temperature was allowed to rise to room temperature. After stirring for 1 h at room temperature, saturated aqueous NH_4Cl solution (4 mL) was added, and the aqueous layer was extracted first with ethyl ether (5 mL) and then with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a viscous residue which was purified by preparative TLC

(AcOEt/hexane 4/6). This afforded 0.036 g of **11** (34%) as white crystals and 0.050 g of the starting material was also recovered (50%). Compound **11**: $[\alpha]_D^{20}$ -15.1 (c 1.04, CH_2Cl_2). mp 39-41 °C. ^1H NMR ($CDCl_3$): δ 4.42-4.34 (1H, m, H-3); 3.94 (1H, d, J=6.7 Hz, H-2); 3.36-3.27 (4H, m, $S(C\underline{H}_2)_2S$); 2.62-2.52 (2H, m, H-4, H-6); 2.39 (1H, dd, J= 13.5 Hz, J= 5.7 Hz, H-4); 2.18 (1H, d, J=3.2 Hz, H-6); 2.13 (1H, s, OH); 1.53 (3H, s, $C\underline{H}_3$); 1.38 (3H, s, $C\underline{H}_3$); 1.30 (3H, s, $C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 108.9 (O$\underline{C}$O); 78.3, 73.7 (C-2, C-3); 70.4 (C-1); 61.6 (C-5); 49.9, 43.1 (C-4, C-6); 39.4 ($S(\underline{C}H_2)_2S$); 28.1, 27.0, 24.9 (3x$\underline{C}H_3$). FT-IR (KBr): 3421 (O-H). Anal. Calcd. for $C_{12}H_{20}O_3S_2$ (276.4114): C 52.14, H 7.29. Found: C 52.41, H 7.28.

(1R,2R,3R)-2,3-Isopropylidenedioxy-5,5-(1,2-ethanedithio)-1-methyl-1-cyclohexanol (10) and (1S,2R,3R)-2,3-Isopropylidenedioxy-5,5-(1,2-ethanedithio)-1-methyl-1-cyclohexanol (11). (With organocerium $MeCeCl_2$). $CeCl_3.H_2O$ (7.157 g, 19.2 mmol) was pulverised and then dried at 135-140 °C, under vacuum for 6 h. Argon was then introduced and at 0 °C THF (30 mL) was added all at once to the stirred powder. The suspension was stirred overnight at rt. The mixture was cooled to -78 °C, and 1.6 M methyllithium in diethyl ether (11.78 mL, 19.2 mmol) was added. The yellow suspension was stirred for 1 h between -78 °C and -40 °C. At -78 °C, a solution of ketone **9** (1.0 g, 3.84 mmol) in THF (45 mL) was added. Saturated NH_4Cl solution (10 mL) was added, followed by extractions with ethyl ether (3 x 40 mL). The organic extracts were dried ($MgSO_4$), and the solvent was evaporated to yield a viscous residue. Purification by column chromatography (AcOEt/hexane 15/85) afforded a mixture (0.92 g) of the diastereoisomers **10** and **11** (87% yield, dr 2.7:1). Compound **10**: ^1H NMR ($CDCl_3$): δ 3.99 (2H, m, H-2, H-3); 3.37-3.26 (4H, m, $S(C\underline{H}_2)_2S$); 2.37-2.12 (4H, m, 2xH-4, 2xH-6); 1.49 (3H, s, $C\underline{H}_3$); 1.47 (3H, s, $C\underline{H}_3$); 1.37 (3H, s, $C\underline{H}_3$). Compound **11**: the characterisation data for **11** is described in the previous experiment.

(3S,4R,5R)-4,5-Isopropylidenedioxy-3-hydroxy-3-methyl-1-cyclohexanone (7). (By deprotection of the dithioacetal). To a solution of a mixture of **10** and **11** (0.984 g, 3.6 mmol) in acetonitrile/H_2O (8/2 11 mL/3 mL), at rt, was added $HgCl_2$ (1.24 g, 4.5 mmol) and HgO (0.96 g, 4.5 mmol). After stirring for 1.5 h, the suspension was filtered through a pad of celite. Water (10 mL) was added to the filtrate, and it was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt/hexane 2/8) gave 0.214 g of **7** (30%) as white needles. $[\alpha]_D^{20}$ -58.5 (c 1.30, CH_2Cl_2). mp 56-58 °C. ^1H NMR ($CDCl_3$): δ 4.60 (1H, q, J=6.0 Hz, H-5); 4.14 (1H, d, J=7.6 Hz, H-4); 2.87 (1H, dd, J=17.6 Hz, J=5.9 Hz, H-6); 2.69-2.61 (2H, m, H-2, H-6); 2.25 (1H, d, J=17.6 Hz, H-2); 1.53 (3H, s, $C\underline{H}_3$); 1.42 (3H, s, $C\underline{H}_3$); 1.30 (3H, s, $C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 207.0 (C-1); 109.0 (O$\underline{C}$O); 78.4, 71.5 (C-4, C-5); 69.7 (C-3); 48.3, 41.9 (C-2, C-6); 26.4, 26.2, 24.0 (3x$\underline{C}H_3$). FT-IR (KBr): 3462 (O-H); 1707 (C=O). Anal. Calcd. for $C_{10}H_{16}O_4$ (200.23662): C 59.98, H 8.05. Found: C 60.13, H 8.15.

[(1S,3R,4S,5R)-1,5-Dihydroxy-3,4-isopropylidenedioxycyclohex-1-yl]-methyl benzoate (13). To a strongly stirred solution of **12** (1.50 g, 6.9 mmol) in pyridine (7.5 mL), at –5 °C, was added dropwise benzoyl chloride (0.846 g, 6.02 mmol). The reaction was immediatly quenched with saturated aqueous $NaHCO_3$ (8 mL), to avoid formation of the dibenzoate. The mixture was extracted with ethyl acetate (3 x 5 mL), dried ($MgSO_4$) and evaporated to give a viscous residue which was purified by column chromatography. Elution with AcOEt/hexane 6/4 afforded **13** (2.105 g, 82%, 2 steps), as a white foam that solidified as white crystals on standing. $[\alpha]_D^{20}$ -48.2 (c 2.0, CH_2Cl_2). mp 54-56 °C. ^1H NMR ($CDCl_3$): δ 8.06 (1H, dd, J=6.9 Hz, Ar H orto); 7.58 (1H, dd, J=7.4 Hz, Ar H para); 7.45 (1H, dd, J=7.6 Hz, Ar H meta); 4.49 (1H, broad s, H-3 or H-4 or H-5 or $C\underline{H}_2OBz$); 4.29-4.18 (3H, m, H-3 and/or H-4 and/or H-5 and/or $C\underline{H}_2OBz$); 3.97 (1H, t, J=6.0 Hz, H-3 or H-4 or H-5 or $C\underline{H}_2OBz$); 2.33 (1H, d, J=15.5 Hz, H-2 or H-6); 2.11 (1H, m, J=11.8 Hz, H-2 or H-6); 1.97 (1H, dd, J= 15.6 Hz, J=4.1 Hz, H-2 or H-6); 1.61-1.53 (1H, m, H-2 or H-6); 1.56 (3H, s, $C\underline{H}_3$); 1.38 (3H, s,

CH_3). ^{13}C NMR ($CDCl_3$): δ 166.3 (C=O, Bz); (133.1, 130.0, 129.6, 128.4, Ar); 109.3 (OCO); 80.6, 74.2 (C-3, C-4); 71.7 (C-1); 71.1 (CH_2OBz); 69.0 (C-5); 38.5, 33.7 (C-2,C-6); 28.3, 25.8 (2xCH_3). FT-IR (KBr): 3447 (O-H); 1718 (C=O). Anal. calcd. for $C_{17}H_{22}O_6$ (322.36063): C 63.34, H 6.88. Found: C 63.20, H 7.12.

[(1S,4R,5R)-1-Hydroxy-4,5-isopropylidenedioxy-3-oxocyclohex-1-yl]-methyl benzoate (14). To a solution of **13** (1.749 g, 5.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C, was added periodinane (2.868 g, 6.8 mmol) and pyridine (16.0 mL). The reaction mixture was stirred at rt for 30 min, and more periodinane (1.59 g, 3.7 mmol) was added. After all the starting material had been consumed, the mixture was poured into saturated aqueous $NaHCO_3$ (40 mL) containing a sevenfold excess of $Na_2S_2O_3$, and it was stirred to dissolve the solid. The aqueous layer was then extracted with ethyl acetate (3 x 20 mL), and the combined extracts dried and concentrated. Purification by column chromatography (AcOEt/hexane 4/6) yielded ketone **14** (1.53 g, 88%) as white crystals. $[\alpha]_D^{20}$ -21.4 (c 1.24, CH_2Cl_2). mp 83-85 °C. ^1H NMR ($CDCl_3$): δ 8.06 (2H, d, J=7.5 Hz, Ar H orto); 7.62-7.57 (1H, m, Ar H para); 7.49-7.44 (2H, m, Ar H meta); 4.77 (1H, s, H-4 or H-5); 4.43 (1H, d, J=5.1 Hz, H-4 or H-5); 4.34-4.23 (2H, m, CH_2OBz); 2.82-2.68 (2H, m, H-2 and/or H-6); 2.58 (1H, d, J=15.6 Hz, H-2 or H-6); 2.34 (1H, dd, J=15.6 Hz, J=3.3 Hz, H-2 or H-6); 1.50 (3H, s, CH_3); 1.41 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 205.3 (C-3); 166.0 (C=O, Bz); 133.4, 129.6, 129.5, 128.5 (Ar); 110.6 (OCO); 78.8, 76.7 (C-4, C-5); 75.0 (C-1); 70.0 (CH_2OBz); 49.0, 33.5 (C-2, C-6); 27.2, 25.8 (2xCH_3). FT-IR (KBr): 3495 (O-H); 1734 (C=O). Anal. Calcd. for $C_{17}H_{20}O_6$ (320.34475): C 63.74, H 6.29. Found: C 63.73, H 6.37.

(4R,5S)-4,5-Dihydroxy-5-methyl-2-cyclohexen-1-one (18). $CeCl_3.H_2O$ (8.718 g, 23.4 mmol) was pulverised and then dried at 135-140 °C, under vacuum, for 6 h. Argon was then introduced, and at 0 °C THF (40 mL) was added all at once to the stirred powder. The suspension was stirred overnight at rt. The mixture was cooled to -78 °C, and 1.6 M methyllithium in diethyl ether (14.67 mL, 23.9 mmol) was added. The yellow suspension was stirred for 1 h, between -78 °C and -40 °C. To this mixture, at -78 °C, a solution of ketone **14** (1.5 g, 4.7 mmol) in THF (3 mL) was slowly added. Saturated NH_4Cl solution (10 mL) was then added, followed by extractions with ethyl ether (1 x 25 mL) and ethyl acetate (3 x 25 mL). The organic extracts were dried ($MgSO_4$), and the solvent was evaporated to yield a mixture (1.42 g) of the diastereoisomers **15** and **16** (dr 1:1.8, by ^1H NMR), which were not separated. Compound **16**: ^1H NMR ($CDCl_3$): δ 4.46-4.42 (1H, m, H-5); 3.88 (1H, d, J=6.0 Hz, H-4); 3.40-3.32 (2H, m, CH_2OBz); 2.26 (1H, d, J=18.0 Hz, H-2 or H-6); 2.11 (1H, dd, J=15.0 Hz, J=3.0 Hz, H-2 or H-6); 1.82 (1H, dd, J=15.0 Hz, J=6.0 Hz, H-2 or H-6); 1.57 (3H, s, CH_3); 1.50-1.33 (1H, m, H-2 or H-6); 1.41 (3H, s, CH_3); 1.25 (3H, s, CH_3). Compound **15**: ^1H NMR ($CDCl_3$): δ 4.67 (1H, m, H-5); 4.29 (1H, s, OH); 3.89 (1H, d, J=6.0 Hz, H-4); 3.49-3.40 (2H, m, CH_2OBz); 2.31 (1H, dd, J=15.3 Hz, J=2.7 Hz, H-6); 2.05-1.93 (3H, m, H-6, 2xH-2); 1.50 (3H, s, CH_3); 1.36 (3H, s, CH_3); 1.26 (3H, s, CH_3). To a solution of a crude mixture of **15** and **16** in water (20 mL), was added $NaIO_4$ (1.70 g, 7.9 mmol), maintaining the pH between 5 and 6 by adding an aqueous solution of NaOH 2 N or HCl 6 N, as necessary. The reaction was stirred for 1 h, with continuous monitoring of the pH. It was then extracted with ethyl acetate (3 x 15 mL), dried (MgSO4), and concentrated to afford a mixture of the diastereoisomers **7** and **17**, which was used without further purification in the next step. To a solution of the crude mixture of **7** and **17** (1.201 g) in THF (6 mL), at 0 °C, was added a catalytic amount (5 drops) of aqueous NaOH (0.5 N). The mixture was stirred at 0 °C until all the starting material had been consumed (if the reaction slowed down, 5 more drops of aqueous NaOH 0.5 N was added). Saturated aqueous NH_4Cl was added (6 mL), and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The residue obtained was purified by column chromatography (AcOEt/hexane 7/3 to 100% AcOEt) to yield 0.801 g of **18** (0.40 g, 60%, 3 steps) as a viscous colourless oil, and 0.035 g of compound **17** were recovered. Compound **19**:

$[\alpha]_D^{20}$ -173.8 (c 1.71, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 6.76 (1H, dd, J=10.3 Hz, J=2.4 Hz, H-3); 6.04 (1H, dd, J=10.3 Hz, J=0.9 Hz, H-2); 4.31 (1H, dd, J=2.3 Hz, H-4); 2.85 (2H, broad s, 2xOH); 2.72 (1H, d, J=16.3 Hz, H-6); 2.51 (1H, d, J=16.5 Hz, H-6); 1.40 (3H, s, $C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 198.3 (C-1); 149.7 (C-3); 129.1 (C-2); 74.3 (C-5); 71.9 (C-4); 49.4 (C-6); 26.2 ($\underline{C}H_3$). FT-IR (Film): 3414 (O-H); 1676 (C=O, α,β-unsat. ketone). Anal. Calcd. for $C_7H_{10}O_3$ (142.15595): C 59.14, H 7.09. Found: C 58.93, H 7.39. Compound **17**: (3R,4R,5R)-4,5-Isopropylidenedioxy-3-hydroxy-3-methyl-1-cyclohexanone: $[\alpha]_D^{20}$+98.9 (c 1.17, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 4.73-4.70 (1H, m, H-5); 4.06 (1H, dd, J=7.2 Hz, J=1.8 Hz, H-4); 2.86 (1H, dd, J=17.4 Hz, J=3.9 Hz, H-2 or H-6); 2.64-2.57 (2H, m, H-2 and/or H-6); 2.29 (1H, dd, J=17.4 Hz, J=1.5 Hz, H-2 or H-6); 1.42 (3H, s, $C\underline{H}_3$); 1.36 (6H, s, 2x$C\underline{H}_3$). FT-IR (film): 3437 (O-H); 1710 (C=O).

(4R,5S)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-5-methyl-2-cyclohexen-1-one (19). Compound **18** (0.410 g, 2.9 mmol), imidazole (0.490 g, 7.2 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.520 g, 3.4 mmol) were dissolved in DMF (1.38 mL). The reaction mixture was stirred at rt until all the starting material had been consumed (6 h). Water (2.5 mL) was added, followed by extractions with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), and evaporated to give a residue which was purified by column chromatography (AcOEt/hexane 1/9). 0.740 g (79%) of **19** was obtained as a colourless oil that crystallized in the refrigerator. $[\alpha]_D^{20}$-43.1 (c 0.64, CH_2Cl_2). mp 54-55 °C. ^1H NMR ($CDCl_3$): δ 6.57 (1H, dd, J=10.3 Hz, J=2.4 Hz, H-3); 6.02 (1H, d, J=10.3 Hz, H-2); 4.31 (1H, dd, J=2.1 Hz, H-4); 2.73 (1H, d, J=16.4 Hz, H-6); 2.41 (1H, d, J=16.3 Hz, H-6); 1.29 (3H, s, $C\underline{H}_3$); 0.95 (9H, s, $SiC(C\underline{H}_3)_3$); 0.19 (3H, s, $SiC\underline{H}_3$); 0.18 (3H, s, $SiC\underline{H}_3$). FT-IR (KBr): 3437 (O-H); 1670 (C=O, α,β-unsat. ketone); 1643 (C=C).

(2R,3S,4R,5S)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-5-hydroxyl-5-methyl-1-cyclohexanone (20). To a solution of the enone **19** (0.220 g, 0.86 mmol) in THF (2 mL), at 0 °C, was added Triton B (N-benzyltrimethylammonium hydroxide (40 wt% solution in methanol), 0.021 mL, 0.007 mmol) and 30% H_2O_2 (0.731 mL, 0.22 mol). After 2 h at 0 °C, saturated aqueous NH_4Cl solution (3 mL) was added, and the mixture was extracted with ethyl ether (3 x 5 mL), the combined extracts dried ($MgSO_4$), and evaporated to give a liquid residue, which was purified by column chromatography. Elution with AcOEt/hexane 1.5/8.5 afforded the epoxide **20** (0.191 g, 92%) as a colourless oil. $[\alpha]_D^{20}$-91.3 (c 0.84, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 3.94 (1H, d, J=3.2 Hz, H-4); 3.56 (1H, dd, J=2.8 Hz, H-3); 3.34 (1H, d, J=3.1 Hz, H-2); 3.16 (1H, broad s, OH); 2.92 (1H, d, J=14.4 Hz, H-6); 2.15 (1H, d, J=14.6 Hz, H-6); 1.14 (3H, s, $C\underline{H}_3$); 0.99 (9H, s, $SiC(C\underline{H}_3)_3$); 0.24 (3H, s, $SiC\underline{H}_3$); 0.20 (3H, s, $SiC\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 203.5 (C-1); 72.9 (C-5); 71.4 (C-4); 57.1, 56.2 (C-2, C-3); 47.2 (C-6); 25.8 ($SiC(\underline{C}H_3)_3$); 25.2 ($\underline{C}H_3$); 18.2 ($Si\underline{C}(CH_3)_3$); -4.2, -4.9 (2x$Si\underline{C}H_3$). FT-IR (Film): 3541 (O-H); 1720 (C=O).

(2R,3S,4R)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-5-methyl-5-cyclohexen-1-one (21). To a solution of **20** (0.114 g, 0.42 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C, was added a catalytic amount of 4-(dimethylamino)pyridine (DMAP), diisopropylethylamine (0.239 mL, 1.43 mmol) and trifluoromethanesulfonic anhydride (triflic anhydride) (0.14 mL, 0.83 mL). Monitoring the reaction by TLC, more reagents were added until almost all the starting material had been consumed and decomposition was not too relevant. Saturated aqueous $NaHCO_3$ (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 7 mL). After drying and concentrating the organic extracts, the dark residue was filtered through a pad of silica gel and this was washed several times with CH_2Cl_2. Again it was concentrated and purified by preparative TLC (AcOEt/hexane 2/8) to yield **21** (0.061 g, 57%) as a pale yellow oil that crystallized on standing. $[\alpha]_D^{20}$-149.0 °C (c 0.14, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 5.76 (1H, s, H-6); 4.60 (1H, dd, J=1.2 Hz, H-4); 3.68 (1H, dd, J=3.9 Hz,

J=2.7 Hz, H-3); 3.41 (1H, dd, J=3.9 Hz, J=2.1 Hz, H-2); 1.96 (3H, s, $C\underline{H}_3$); 0.98 (9H, s, $SiC(C\underline{H}_3)_3$); 0.23 (3H, s, $SiC\underline{H}_3$); 0.21 (3H, s, $SiC\underline{H}_3$). FT-IR (KBr): 1685 (C=O, α,β-unsat. ketone); 1631 (C=C).

(1R,2R,3S,4R)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-5-methyl-5-cyclohexen-1-ol (22) and (1S,2R,3S,4R)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-5-methyl-5-cyclohexen-1-ol (23). To a solution of **24** (0.080 g, 0.31 mmol) in THF (1.5 mL), at –78 °C, was added DIBAL-H (0.350 mL, 0.984 M in hexanes, 0.34 mmol). Saturated aqueous NH_4Cl (4 mL) was then added. The mixture was extracted with ethyl ether (3 x 5mL), the extracts dried ($MgSO_4$) and concentrated to afford a mixture of the two diastereoisomers **25** and **26** (0.080 g, 99%, 1.8/1 **22/23**) as a very viscous oil, that was used in the next reaction without purification. Compound **22**: $[\alpha]_D^{20}$ -8.8 (c 0.34, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 5.26 (1H, s, H-6); 4.36 (1H, s, H-1 or H-4); 4.31 (1H, m, H-1 or H-4); 3.55-3.52 (1H, m, H-2 or H-3); 3.46-3.44 (1H, m, H-2 or H-3); 1.74 (3H, s, $C\underline{H}_3$); 0.96 (9H, s, $SiC(C\underline{H}_3)_3$); 0.18 (3H, s, $SiC\underline{H}_3$); 0.16 (3H, s, $SiC\underline{H}_3$). FT-IR (film): 3435 (O-H); 2957, 2943, 2897, 2872, 2854 (C-H). Compound **23**: ^1H NMR ($CDCl_3$): δ 5.47 (1H, m, H-6); 4.52 (1H, s, H-1 or H-4); 4.43 (1H, d, J=4.8 Hz, H-1 or H-4); 3.38 (2H, s, H-2, H-3); 1,77 (3H, s, $C\underline{H}_3$); 0.95 (9H, s, $SiC(C\underline{H}_3)_3$); 0.17 (3H, s, $SiC\underline{H}_3$); 0.16 (3H, s, $SiC\underline{H}_3$).

(1R,2R,3S,4R)-2,3-Epoxy-1,4-dihydroxy-5-methyl-5-cyclohexene (3) and (1S,2R,3S,4R)-2,3-Epoxy-1,4-dihydroxy-5-methyl-5-cyclohexene (4). To a solution of a mixture of **22** and **23** (0.068 g, 0.26 mmol) in THF (1.5 mL) at rt, was added a trace amount (2 drops) of water followed by Bu_4NF (0.104 g, 0.39 mmol). The mixture was stirred at rt until all the starting material had been consumed. The solution was diluted with ethyl acetate (2 mL), and water (2 mL) was added. After stirring for 5 min, the mixture was quenched with saturated NaCl (5 mL) and extracted with ethyl acetate (3 x 5mL). The evaporation of the solvent gave a viscous residue that was purified by preparative TLC (AcOEt/EtOH 95/5) to yield a mixture of **3** and **4** (0.035 g, 92%). The two diastereoisomers were partially separated, in order to characterise them. Compound **3** (white solid): $[\alpha]_D^{20}$ -12.0 (c 0.25, EtOH). mp 94-96 °C. ^1H NMR ($CDCl_3$): δ 5.28 (1H, s, H-6); 4.35 (1H, d, J=3.0 Hz, H-1 or H-4); 4.20 (1H, d, J=9.0 Hz, H-1 or H-4); 3.63 (2H, s, H-2, H-3); 2.20-2.12 (2H, m, 2xOH); 1.80 (3H, s, $C\underline{H}_3$). FT-IR (KBr): 3369 (O-H); 1653 (C=C). Anal. Calcd. for $C_7H_{10}O_3$ (142.15595): C 59.14, H 7.09. Found: C 58.71, H 7.16. Compound **4** (colourless viscous oil): $[\alpha]_D^{28}$+48.57 (c 0.35, EtOH), (lit.[7] $[\alpha]_D^{28}$+47.52 (c 0.59, EtOH)). ^1H NMR ($CDCl_3$): δ 5.49 (1H, s, H-6); 4.40 (1H, broad s, H-1 or H-4); 4.30 (1H, broad s, H-1 or H-4); 3.54 (1H, s, H-2 or H-3); 3.50 (1H, s, H-2 or H-3); 2.23 (2H, broad s, 2xOH); 1.83 (3H, s, $C\underline{H}_3$).

(1R,2R,3S,4S)-4-[(*tert*-Butyldimethylsylil)oxy]-2,3-epoxy-5-methyl-5-cyclohexen-1-ol (22). To a solution of the α,β-unsaturated ketone **21** (0.057 g, 0.22 mmol) in THF (1.5 mL), at –78 °C, was added L-Selectride® (1.0 M solution in THF, 0.27 mL, 0.27 mmol). The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL), and extracted with ethyl ether (3 x 5 mL). After evaporation of the solvent the crude **22** (0.082 g, viscous oil) was used in the next reaction without further purification.

(1R,2R,3S,4S)-1-Acetyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-5-methyl-5-cyclohexene (26). To a solution of crude **22** (0.082 g) in CH_2Cl_2 (1.5 mL), at 0 °C, was added a catalytic amount of DMAP, diisopropylethylamine (0.112 mL, 0.64 mmol) and acetic anhydride (0.036 mL, 0.38 mmol). The reaction mixture was stirred at rt, and when it was completed, saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 4 mL), the combined extracts dried ($MgSO_4$), and concentrated to afford a viscous residue which was purified by preparative TLC (AcOEt/hexane 2/8). Compound **26** was obtained (0.049 g, 73%, 2 steps) as a colourless oil. $[\alpha]_D^{20}$–26.1 (c 0.64, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 5.50-5.47 (1H, m, H-6), 5.16 (1H, s, H-1); 4.39 (1H, s, H-4); 3.59-3.54 (1H, m, H-2 or H-3), 3.42-3.40 (1H, m,

H-2 or H-3); 2.13 (3H, s, $COCH_3$); 1.76 (3H, s, CH_3); 0.95 (9H, s, $SiC(CH_3)_3$); 0.18 (3H, s, $SiCH_3$); 0.16 (3H, s, $SiCH_3$). FT-IR (film): 1739 (C=O, acetate).

(1R,2S,3R,4S)-4-Acetyloxy-2,3-epoxy-6-methyl-5-cyclohexen-1-ol (27). To a solution of **26** (0.051 g, 0.17 mmol) in THF (1.5 mL) at rt, was added a trace amount of water (2 drops) followed by Bu_4NF (0.067 g, 0.26 mmol). The mixture was stirred at rt until all the starting material had been consumed. The solution was diluted with ethyl acetate (2 mL), and water (2 mL) was added. After stirring for 5 min, the mixture was quenched with saturated NaCl (5 ml) and extracted with ethyl acetate (3 x 5 mL). Evaporation of the solvent afforded a viscous residue which was purified by preparative TLC (AcOEt/hexane 6/4) to yield **27** (0.031 g, 98%) as white needles. $[\alpha]_D^{20}$ –16.0 (c 0.20, CH_2Cl_2). mp 64-66 °C. ^1H NMR ($CDCl_3$): δ 5.54-5-53 (1H, m, H-6); 5.20 (1H, s, H-1); 4.24 (1H, s, H-4); 3.68-3.65 (1H, m, H-2 or H-3); 3.62-3.60 (1H, m, H-2 or H-3); 2.15 (3H, s, $COCH_3$); 1.83 (3H, s, CH_3). FT-IR (KBr): 3514 (O-H); 3034, 2980, 2939, 2916, 2891(C-H); 1715 (C=O, acetate).

(2R,3R,4R)-4-Acetyloxy-2,3-epoxy-6-methyl-5-cyclohexen-1-one (28). To a solution of the alcohol **27** (0.027 g, 0.15 mmol) in CH_2Cl_2 (4.1 mL) at 0 °C, was added periodinane (0.075 g, 0.18 mmol), and pyridine (0.41 mL), and the reaction was stirred at rt. When all the starting material had been consumed, the mixture was diluted with ethyl ether (5 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred to dissolve the solid, and the layers were separated. After extractions with ethyl ether (3 x 5 mL), the combined organic layers was dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 4.5/5.5) gave ketone **28** (0.026 g, 99%) as white crystals. $[\alpha]_D^{22}$ +111.1 (c 0.28, EtOH), mp 45-46 °C, (lit.[1] $[\alpha]_D^{22}$ + 113.4 (c 1.0, EtOH), mp 62-63 °C). ^1H NMR ($CDCl_3$): δ 6.17 (1H, d, J=1.5 Hz, H-5); 5.76-5.74 (1H, m, H-4); 3.89-3.86 (1H, m, H-3); 3.51 (1H, d, J=3.9 Hz, H-2); 2.21 (3H, s, $COCH_3$); 1.84 (3H, t, J=1.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 193.3 (C-1); 170.3 ($\underline{C}OCH_3$); 135.9 (C-5); 133.9 (C-6); 66.8, 52.6, 51.4 (C-2, C-3, C-4); 20.8, 15.8 ($CO\underline{C}H_3$, $\underline{C}H_3$). FT-IR (KBr): 3408, 2953, 2926 (C-H); 1739 (C=O, ester); 1689 (C=O, α,β-unsat. ketone). Anal. Calcd. for $C_9H_{10}O_4$ (182,17765): C 59.34, H 5.53. Found: C 59.30, H 5.26.

(2R,3R,4R)-2,3-Epoxy-4-hydroxy-6-methyl-5-cyclohexene-1-one (1). To a solution of **28** (0.020 g, 0.11 mmol) in THF (1.5 mL), at 0 °C, was added 10% aqueous KOH dropwise with TLC monitoring. When all the starting material had been consumed, saturated aqueous NH_4Cl (3 mL) was added and the mixture was extracted with ether (5 mL) and ethyl acetate (3 x 5 mL) and the combined extracts dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by preparative TLC (AcOEt/hexane 1/1) to afford 0.015 g of **1** (95%) as a very viscous colourless oil, $[\alpha]_D^{22}$ +108.6 (c 0.21, EtOH), (lit.[1] $[\alpha]_D^{22}$+114.3 (c 1.0, EtOH)). ^1H NMR ($CDCl_3$): δ 6.27 (1H, s, H-5); 4.63 (1H, s, H-4); 3.84 (1H, d, J=3.0 Hz, H-3); 3.51 (1H, d, J=3.0 Hz, H-2); 1.82 (3H, s, CH_3). FT-IR (film): 3468 (O-H); 2924 (C-H); 1678 (C=O, α,β-unsat. ketone).

Acknowledgment: Two of us M.T.B. and C.D.M. are indebted to Prof. Barton for the enthusiasm and knowledge which he instilled in them during their respective periods of collaboration with him. His example is their continuing guide.

We thank Fundação para a Ciência e a Tecnologia for a grant (Praxis XXI/BD/4527/94) conceded to M. R. V..

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