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A route to the structure proposed for puetuberosanol and approaches to the natural products marshrin and phebalosin

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Abstract—Synthesis of the structure claimed for puetuberosanol **1** (using the Juliá–Colonna oxidation in a key step) showed that the natural product was a different material. The isomeric epoxy alcohols **16**–**18** can be discounted from the alternatives. An analogue **19** of marshrin **2** was prepared but the synthesis of the natural product was thwarted by failure of a Juliá–Colonna oxidation in the key step. The epoxy ketone **29** was prepared by Darzens condensation and was converted into (±)-phebalosin **3**.

1. Introduction

The Juliá–Colonna oxidation of α,β-unsaturated ketones can be employed to prepare a wide range of optically active epoxyketones (Scheme 1).[1]

Such easy access to these useful chiral building blocks has encouraged us to apply the methodology to the preparation of natural products[2] and biologically active compounds[3] in single enantiomer form. In this paper we have used products from Juliá–Colonna oxidations in explorations of the structure of puetuberosanol **1** and in the synthesis of an analogue of marshrin **2**. The preparation of marshrin itself was not accomplished but a route to the closely related natural product, phebalosin **3** is described below (Fig. 1).

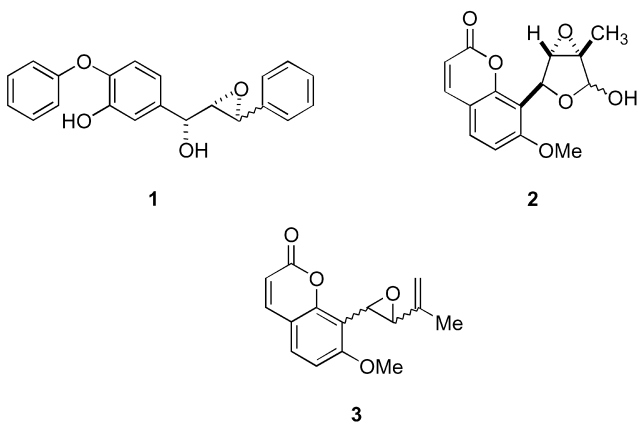
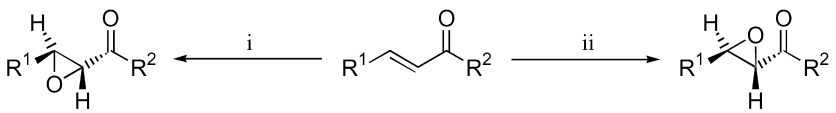


Figure 1. Structures of puetuberosanol, marshrin and phebalosin.

2. Part 1: synthesis of the structure proposed for puetuberosanol

2.1. Background information

In 1996, Khan and co-workers isolated a novel epoxychalcanol (that they called puetuberosanol) from the tubers of the deciduous climbing plant *Pueraria tuberosa*.[4] NMR studies suggested that the two substituents on the epoxide moiety were *cis*-oriented and that the epoxide ring and the hydroxy group had a *syn*-relationship. The absolute configuration of the compound was not recorded and the objective of our study was to clarify this particular issue.



Scheme 1. Juliá-Colonna epoxidation of α,β-unsaturated ketones. *Reagents and conditions*: (i) poly-(L)-leucine [PLL], urea hydrogen peroxide (UHP), diazabicycloundecene [DBU], tetrahydrofuran [THF]; (ii) poly-(D)-leucine, UHP, DBU, THF.

Keywords: asymmetric epoxidations; Juliá–Colonna catalyst; marshrin analogue, synthesis; phebalosin, synthesis; puetuberosanol structure.

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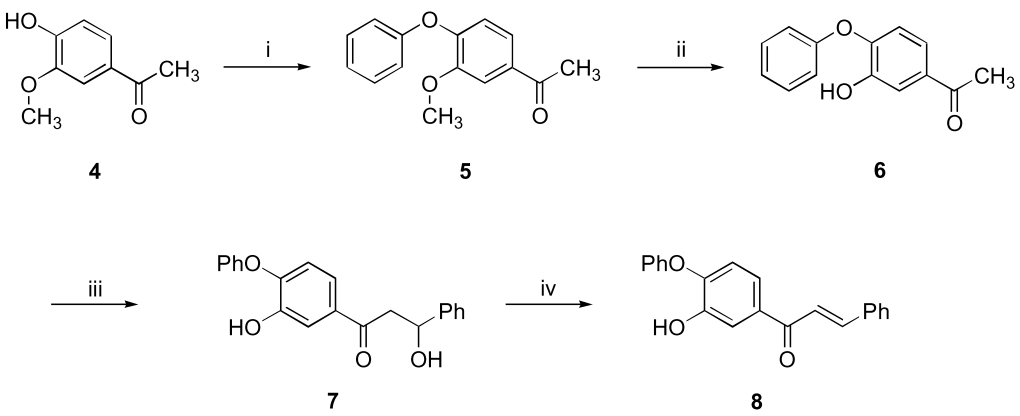


Scheme 2. Preparation of *E*-enone (**8**). *Reagents and conditions*: (i) $Cu(OAc)_2$, $PhB(OH)_2$, Et_3N, CH_2Cl_2, air (78%); (ii) BBr_3, CH_2Cl_2, −78 to 0°C, 3 h (98%); (iii) LDA, THF, 0°C, 45 min then PhCHO, −78°C, 2 h (81%); (iv) PTSA, CH_2Cl_2, 40°C, 15 h (81%).

2.2. Results and discussion

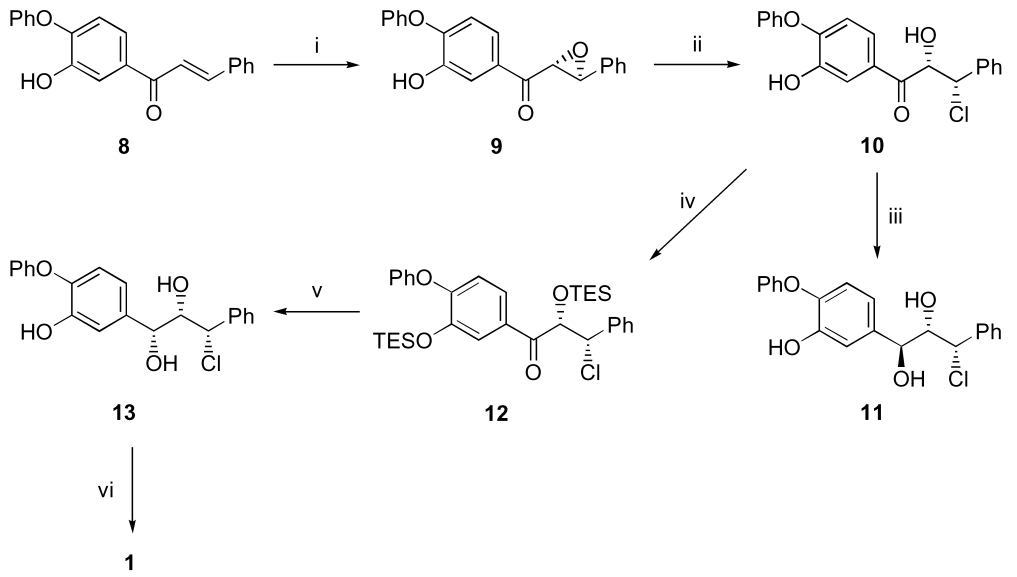
The enone required as the substrate for Juliá–Colonna oxidation was prepared as illustrated in Scheme 2. Thus, acetovanillone **4** and phenylboronic acid were coupled using the procedure recommended by Evans et al. employing copper(II) acetate, triethylamine in a dichloromethane solution saturated with air.[7]

The methyl group was removed from the ether unit in compound **5** using boron tribromide to yield the phenol **6** in almost quantitative yield. Conversion of this material into the required α,β-unsaturated ketone was achieved most efficiently using a two-step procedure. Thus the phenol **6** was reacted with lithium diisopropylamide (LDA) and then benzaldehyde to give the β-hydroxyketone **7**; this compound was dehydrated to the *E*-enone **8** using *para*-toluenesulfonic acid (PTSA). Care was taken not to expose the enone **8** to light over a long period, in order to avoid contamination of the sample with the *Z*-isomer.

Oxidation of enone **8** under the biphasic conditions prescribed for the Juliá–Colonna reaction[8] afforded the epoxyketone **9** in 85% yield (>99% ee) after recrystallization from dichloromethane (Scheme 3).

Formation of the *syn*-chlorohydrin **10** was accomplished by reacting the epoxide with gaseous HCl. Note that the *syn*-isomer is formed with retention of configuration at the participating carbon centre, a phenomenon that has ample literature precedent.[9] The small amount (ca. 7%) of the *anti*-isomer that was formed concurrently was removed by flash column chromatography.

Direct reduction of the chlorohydrin **10** with zinc borohydride gave the *anti*-diol **11** in excellent yield and high diastereoisomeric excess (>98%). In order to access the *syn*-diol series, both the hydroxy groups were protected as the triethylsilyl derivatives and then the bis-silyl ether **12** was reduced with sodium borohydride to furnish mainly the *syn*-diol **13** (80%), after brief treatment with tetrabutylammonium fluoride (TBAF) to take off the silyl protecting groups. The *anti*-diol **11** (9%) was removed by chromatography over silica.



Scheme 3. Synthesis of the structure proposed for puetuberosanol. *Reagents and conditions*: (i) PLL, UHP, DBU, THF, 15 h, 94% crude yield, 86% ee, recrystallization (CH_2Cl_2) gave 85% yield, >99% ee; (ii) HCl gas, CH_2Cl_2, 0°C, 30 min, 77%; (iii) $ZnBH_4$, THF, 20 min, 95%; (iv) Et_3SiCl, imidazole, DMF, rt, 2.5 h (100%); (v) $NaBH_4$, MeOH/CH_2Cl_2 (2.5:1), 0°C 50 min then TBAF, THF, rt, 1 min, (80%); (vi) TBAF, THF, rt, 30 h (72%).

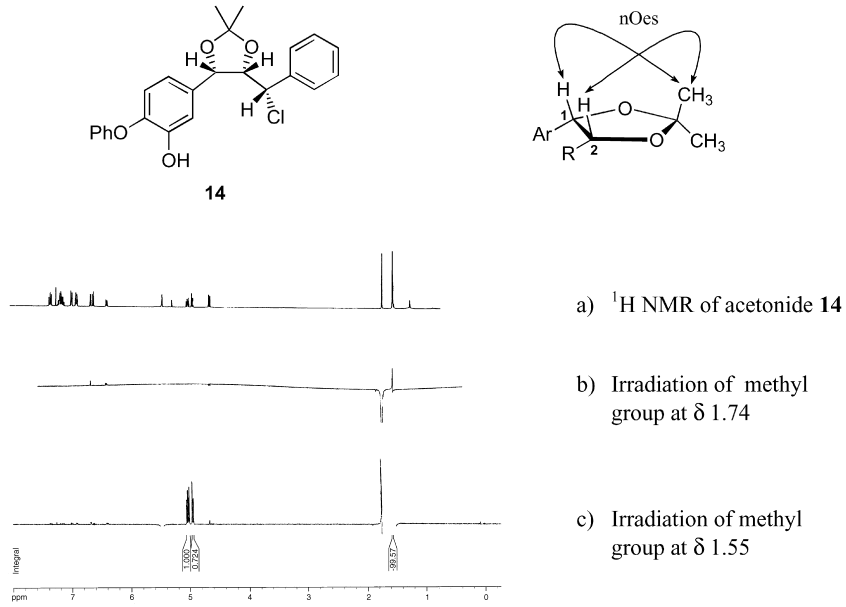


Figure 2. nOe experiments of acetonide **14**.

Confirmation of the *anti*/*syn* relationships between the hydroxy groups of diols **11** and **13** was obtained by formation of the corresponding acetonides **14** and **15** and subsequent nOe experiments on these derivatives. Upon irradiation of the methyl signal at δ 1.55 of **14**, nOes were observed at δ 4.94 and δ 5.02 corresponding to C(1)H and C(2)H respectively (Fig. 2, spectrum c). However, no nOes were observed upon irradiation of the second methyl group at δ 1.74 (Fig. 2, spectrum b). This result confirmed the *syn* relationship of C(1)H and C(2)H in **14**, and correspondingly the *anti* relationship of C(1)H and C(2)H in diol *anti*-**11**.

Additionally, no nOes were observed between C(1)H and C(2)H of acetonide **15**, confirming the *syn* relationship of C(1)H and C(2)H in diol *syn*-**13** (Fig. 3).

Exposure of the chlorodiol **13** to TBAF over an extended period of time afforded the target epoxydiol **1**. The NMR spectrum of this compound revealed a 4.5 Hz coupling between the two protons (δ 3.35 and δ 4.18 ppm) attached to the oxirane ring, in accord with the expected value. Unfortunately these and other physical data proved to be distinctly different from the data reported for puetuberosanol.

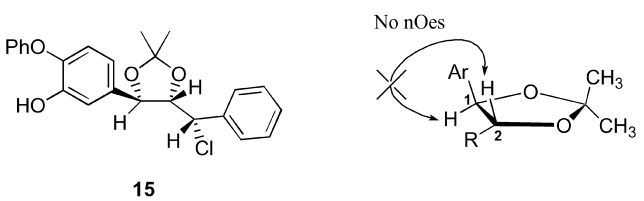


Figure 3. nOe experiments of acetonide **15**.

Three isomers of compound **1** were synthesised for the sake of comparison (Fig. 4). Treatment of the chlorodiol **11** with potassium carbonate in methanol gave the *cis*-epoxide **16** in 97% yield. (The ^{1}H NMR spectrum showed a coupling constant of 3.9 Hz between the oxiranyl protons.)

The two *trans*-epoxides **17** and **18** were formed as the major products on reduction of the epoxyketone **9** with zinc borohydride (ratio **17/18**, >95:<5, yield 95%) and tri-*n*-butyltin hydride and TBAF[10] (ratio **17/18**, 15:85, yield 60%), respectively.

None of these compounds gave NMR data corresponding to the natural compound (Table 1). However, it can be seen from Table 1 that the signals due to C(1)H in the epoxides **1**, **16**–**18** appear at higher field [$\Delta\delta$ 0.89–1.61] than that for the natural product. Conversely signals due to C(3)H in the synthesised epoxides are seen at lower field [$\Delta\delta$ 0.48–0.71]. It is possible that, in the structure of the natural material, the two aryl groups are transposed, with the hydroxy group adjacent to the phenyl ring. This speculation can only be put on a sure footing by further synthetic work: at this stage all that is definite is that the structure of puetuberosanol is not that represented by formula **1**.

3. Part 2: an approach to the natural product marshrin

3.1. Background information

(+)-Marshrin **2** was reported in 1999 by Takemura et al. having been extracted from the roots of the marsh grapefruit

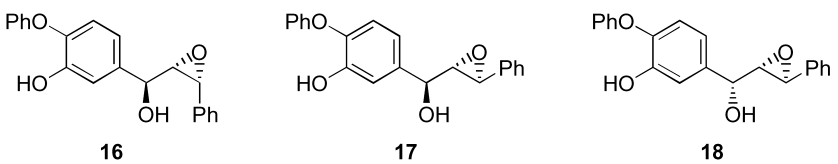
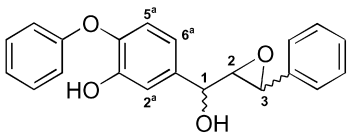


Figure 4. Preparation of isomers of puetuberosanol.

Table 1. NMR shifts observed for puetuberosanol and the synthesised epoxy alcohols **1**, **16**–**18**

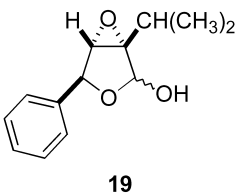


Nucleus	Puetuberosanol	**1**	**16**	**17**	**18**
C(1)H	5.49 (d, *J*=2.4 Hz)	4.10 (d, *J*=8.6 Hz)	3.88 (d, *J*=8.5 Hz)	4.60 (d, *J*=4.7 Hz)	4.54 (d, *J*=5.8 Hz)
C(2)H	3.54 (dd, *J*=2.4, 4.1 Hz)	3.35 (dd, *J*=4.5, 8.6 Hz)	3.24 (dd, *J*=8.5, 3.9 Hz)	3.15 (dd, *J*=4.7, 2.0 Hz)	3.20 (dd, *J*=5.8, 2.2 Hz)
C(3)H	3.47 (d, *J*=4.1 Hz)	4.18 (d, *J*=4.5 Hz)	4.18 (d, *J*=3.9 Hz)	3.99 (d, *J*=2.0 Hz)	3.95 (d, *J*=2.2 Hz)
C(2^a)H	7.06 (d, *J*=2.0 Hz)	6.60 (d, *J*=2.0 Hz)	6.97 (d, *J*=1.5 Hz)	7.06 (d, *J*=1.9 Hz)	7.10 (d, *J*=2.0 Hz)
C(5^a)H	6.95 (d, *J*=7.8 Hz)	6.68 (d, *J*=8.2 Hz)	6.79–6.84 (m)	6.85 (d, *J*=8.2 Hz)	6.85 (d, *J*=8.2 Hz)
C(6^a)H	6.96 (dd, *J*=7.8, 2.0 Hz)	6.26 (dd, *J*=2.0, 8.2 Hz)	6.79–6.84 (m)	6.85–6.90 (m)	6.87–6.93 (m)
C3	51.7	58.7	59.8	58.0	57.9
C2	54.5	64.6	63.5	66.9	67.5
C1	61.6	72.6	70.2	77.8	74.9

(*Citrus paradisi*).[5] The relative stereochemistry of marshrin was elucidated by nOe studies but the Japanese authors did not disclose the absolute configuration of the natural product. Once again a total asymmetric synthesis of the material would allow this point to be settled. Phebalosin **3**, which also possesses a 7,8-disubstituted coumarin skeleton, has been isolated in optically active and racemic forms from a variety of sources.[6] The stereochemistry about the epoxide ring is known to be *trans* but the absolute configuration was not elucidated.

3.2. Results and discussion

Before embarking on the synthesis of the natural product **2** and analogues, appropriate reaction conditions were sought using a simple model compound **19** (marshin analogue) as the target species.(Fig. 5)

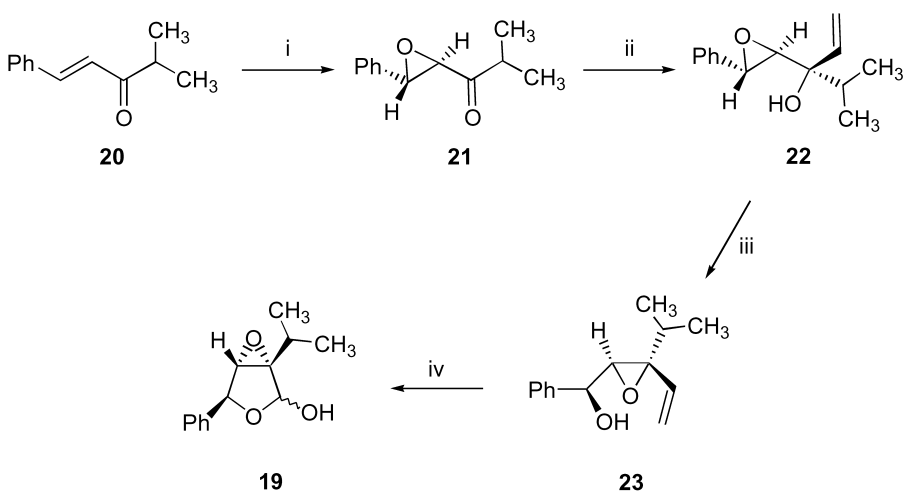


19

Figure 5. Structure of a marshrin analogue.

Thus the enone **20** was oxidised under Juliá–Colonna biphasic conditions to afford the epoxide **21** as white needles in 57% yield (Scheme 4). Reaction with vinylmagnesium bromide was highly diastereoselective giving the tertiary alcohol **22** as the only isolable product in 69% yield. The key step in the projected synthesis of marshrin derivative **19** entailed Payne rearrangement of the epoxyalcohol **22** and this was achieved using sodium hydroxide in *tert*-butanol. The major component in the mixture of epoxyalcohols (ratio ca. 7:1) was the secondary alcohol **23**, which was subjected to chromatography over silica to give the pure compound **23** in 72% yield. Ozonolysis of the oxirane **23**, employing dimethylsulfide in the work-up procedure, afforded the lactol **19** (51% yield after recrystallization).

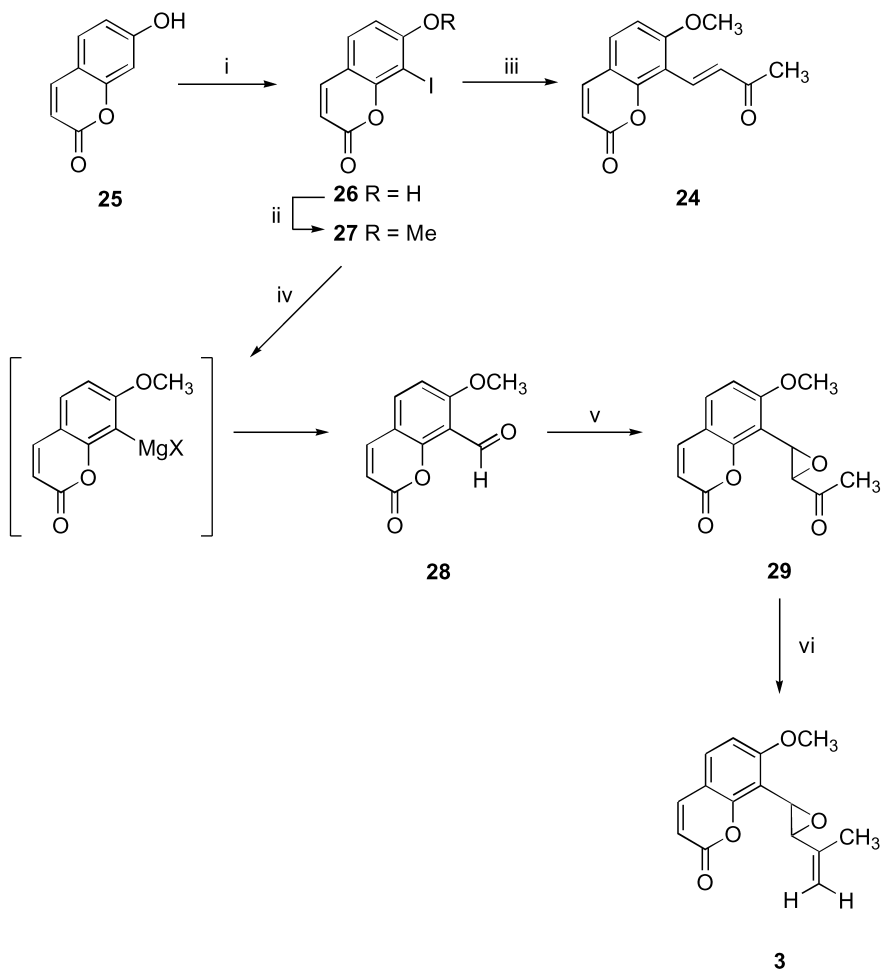
Attention then focused on the synthesis of the coumarin derivative **24** that was to be the starting material en route to marshrin (Scheme 5). This material (which has the trivial name osthenon) was synthesised using the method described by Furukawa et al.[11] Thus treatment of umbelliferone **25**



20 **21** **22**

19 **23**

Scheme 4. Preparation of marshrin analogue (**19**). *Reagents and conditions*: (i) PLL, THF, UHP, 18 h rt (57% after recrystallization from hexane); (ii) $CH_2CHMgBr$, THF, −78°C, 1.5 h (69%); (iii) NaOH, *tert*-BuOH, 30°C, 6 h (72%); (iv) O_3, CH_2Cl_2, −78°C, 30 min then Me_2S, 18 h, rt (51% after recrystallization from hexane).



Scheme 5. Synthesis of (±)-phebalosin (**3**). *Reagents and conditions*: (i) I_2, KI, NH_3 (aq), rt, 24 h. (37%); (ii) MeI, K_2CO_3, acetone, reflux, 5 h (82%); (iii) $MeCOCHCH_2$, Bu_4NBr, Et_3N, $Pd(OAc)_2$, DMF, 100°C, 56 h, (65%); (iv) *i*-PrMgCl, THF, −78°C, 45 min, then *N*-formylmorpholine, 0°C to rt, 2.5 h, (75%); (v) $ClCH_2COCH_3$, K_2CO_3, 30 h, rt (65%); (vi) $^{+}Ph_3PCH_3^{-}Br$, diisopropylamine, *n*-BuLi, THF, 0°C to rt, 20 h (78% based on consumed starting material).

with iodine and potassium iodide in aqueous ammonia gave 7-hydroxy-8-iodocoumarin **26**. Formation of the methyl ether **27** using standard conditions was achieved in 82% yield. Coupling of the coumarin **27** to methylvinyl ketone used the Jeffery modification of the Heck reaction[12] such that after 56 h at 100°C in DMF containing palladium(II) acetate, tetrabutylammonium bromide and triethylamine, the enone **24** was obtained in 65% yield. Additionally the aldehyde **28** was prepared from the iodide **27** by an extension of the methodology recently pioneered by Knochel.[13] Thus treatment of the iodide **27** with *iso*-propylmagnesium chloride followed by *N*-formylmorpholine gave the aldehyde **28** (75% yield) together with a trace of 7-methoxycoumarin.

The first sample of racemic epoxyketone **29** was obtained by Darzens condensation of the coumarin **28** with chloroacetone (65% yield) and this epoxide was transformed into racemic phebalosin **3** by a Wittig reaction. The analytical data for **3** were identical to those reported for the natural material.[14]

Sadly all attempts to convert the enone **24** into optically active epoxide using Juliá–Colonna reactions were unsuccessful. Three factors contribute to this failure, we believe. First alkyl vinyl ketones are oxidized more slowly than aryl ketones in any circumstance. Secondly the aryl group is electron rich, decreasing the electrophilic nature of the β-carbon centre. Thirdly the Michael reaction of the hydroperoxide moiety and the β-arylenone may be sterically inhibited by the substituents at both *ortho*-positions on the aryl ring. It is noteworthy that asymmetric epoxidation using Shibasaki's conditions was also unsuccessful even though the Japanese team has reported the transformation of a closely related 6,7-disubstituted coumarin.[15]

4. Conclusion/closing remarks

Juliá–Colonna oxidation was employed to prepare the epoxide **9**. While the original purpose for making optically active material was subsequently rendered invalid, it is noteworthy that the polyleucine-catalysed reaction is more high-yielding and cleaner than that using standard Weitz–Scheffer conditions. Polyleucine-catalysed epoxidation of the enone **24** could not be effected. The target epoxide **29** was prepared in racemic form (as a standard) by a different method and this material was converted into (±) phebalosin **3**. Progress towards the determination of the absolute

configurations of phebalosin and marshrin will require further work to prepare the epoxide **29** in optically active form. These studies are on-going in the Liverpool laboratories.

5. Experimental

5.1. General

Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were determined using a Carlo Elba elemental analyser instrument. Nominal and accurate mass spectra were recorded on a VG7070E, CIPOS, Kratos Profile HV3 and TRIO1000. Specific optical rotations were measured at ambient temperature (22±3°C), using a 1 cm^3 cell with 0.1 dm path length, on an Optical Activity Ltd AA-1000 polarimeter, operating at λ=589 nm corresponding to the sodium D line, and are recorded in units of 10^{-1} deg cm^2 g^{-1} (concentrations are quoted in g/100 cm^3). Infrared spectra were recorded on a Perkin–Elmer 881 infrared spectrophotometer, over the range 4000–800 cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC200 (200 MHz), Varian 300 Gemini 2000 (300 MHz) or a Bruker 400 Avance (400 MHz) instrument. ^{13}C NMR spectra were recorded on a Varian 300 Gemini 2000 (75.5 MHz) or a Bruker 400 Avance (100 MHz) instrument. All chemical shifts are quoted in ppm relative to tetramethylsilane (TMS). The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants (*J*) are measured in hertz (Hz). Chiral High Pressure Liquid Chromatography was performed on a Gilson chromatograph equipped with a Chiracel OD column with UV detection at 254 nm.

Unless otherwise specified, all solvents used were dried by the appropriate technique and all reactions were carried out under a nitrogen atmosphere, in dried glassware, with exclusion of water and oxygen.

Reactions were monitored by thin layer chromatography (TLC), performed on glass backed silica gel Merk 60F-254 Plate in a variety of solvents using the ascending technique. The Plate were visualised by UV light (254 nm) and by application of cerium ammonium molybdate (CAM), *p*-anisaldehyde, potassium permanganate or 2,4-dinitrophenylhydrazine and baked with a heat gun. Column chromatography was conducted with Merk Kieselgel 60: 230–400 mesh for flash chromatography, using the technique described by Still.[16]

5.1.1. 3-Methoxy-4-phenoxyacetophenone (5). Activated molecular sieves (4 Å, 5 g), phenylboronic acid (44.9 g, 361.0 mmol, 2.0 equiv.), copper(II) acetate (36.8 g, 180.5 mmol, 1.0 equiv.) and anhydrous pyridine (59 cm^3, 722.0 mmol, 4.0 equiv.) were successively added to a stirred solution of 4-hydroxy-3-methoxy-acetophenone (**4**) (30 g, 180.5 mmol) in anhydrous dichloromethane (900 cm^3) at rt. This resulting black mixture was stirred vigorously at rt for 48 h (note: oxygen is necessary for the reaction to reach completion, and therefore air must be allowed to saturate the solution). The reaction mixture was filtered through celite. The filtrate was washed with aqueous Na_2–EDTA solution (5%, 500 cm^3), dilute aqueous hydrochloric acid solution (2 M, 500 cm^3), and extracted with dichloromethane (1000 cm^3, 2×500 cm^3). The combined organic extracts were washed with brine (500 cm^3), dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a dark brown gum (55.7 g). The crude material was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 9:1) to give the title compound **5** as a pale cream solid (33.5 g, 79%); mp 85–86°C (from EtOAc/*n*-hexane); R_f 0.57 (EtOAc/*n*-hexane, 1:1). (Found: C, 74.2; H, 5.8 $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%); ν_{max} (film, NaCl Plate)/cm^{-1} 3000–3050 (w, Ar-H), 2830 (OCH_3), 1674 (ketone CO); δ_H (300 MHz, $CDCl_3$) 2.58 (3H, s, $COCH_3$), 3.94 (3H, s, OCH_3), 6.88 (1H, d, *J*=8.4 Hz, C(5^a)H), 7.03 (2H, ddd, *J*=8.7, 2.1, 1.2 Hz, C(2^b)H and C(6^b)H), 7.14 (1H, tt, *J*=7.5, 1.2 Hz, C(4^b)H), 7.36 (2H, m, C(3^b)H and C(5^b)H), 7.49 (1H, dd, *J*=8.4, 2.1 Hz, C(6^a)H), 7.64 (1H, d, *J*=2.1 Hz, C(2^a)H); δ_C (75.5 MHz, $CDCl_3$) 26.3 ($COCH_3$), 56.2 (OCH_3), 111.8 (C2^a), 118.2 (C5^a), 118.9 (C2^b and C6^b), 122.7 (C6^a), 123.4 (C4^b), 129.9 (C3^b and C5^b), 133.2 (C1^a), 150.7 and 150.8 (C3^a and C4^a), 156.4 (C1^b), 196.9 ($COCH_3$); *m/z* (EI) 242 ([M]$^+$). (Found: [M]$^+$, 242.09373. $C_{15}H_{14}O_3$ requires [M]$^+$, 242.09429), 227 (100%), 77, 43.

5.1.2. 3-Hydroxy-4-phenoxyacetophenone (6). A solution of 3-methoxy-4-phenoxy acetophenone (**5**) (13 g, 54.0 mmol) in dichloromethane (40 cm^3) was added dropwise to a solution of boron tribromide (1.0 M in dichloromethane, 200 cm^3, 3.0 equiv.) in anhydrous dichloromethane (300 cm^3), at −78°C, under N_2. The resulting dark green solution was stirred for 1 h at −78°C and 2 h at 0°C. The reaction mixture was subsequently transferred very slowly, via cannula and at 0°C, into a vigorously stirring saturated aqueous solution of sodium hydrogen carbonate (1500 cm^3) (caution: on neutralization HBr gas is evolved). The resulting red mixture was stirred for 1 h at 0°C, and more sodium hydrogen carbonate was added until no more gas was evolved. The mixture was extracted with dichloromethane (3×1000 cm^3), the combined organic extracts were washed with brine (1000 cm^3), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to afford an orange oil (15 g), which crystallized on standing. The crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:5) to give the title compound **6** as a pale cream solid (14.5 g, 98%); mp 84–85°C; R_f 0.29 (EtOAc/*n*-hexane, 1:3). (Found: C, 73.6; H, 5.3 $C_{14}H_{12}O_3$ requires C, 73.7; H, 5.3 %); ν_{max} (film, NaCl Plate)/cm^{-1} 3215 (bd, OH), 1660 (ketone CO); δ_H (400 MHz, $CDCl_3$) 2.56 (3H, s, OCH_3), 5.92 (1H, bs, OH), 6.82 (1H, d, *J*=8.5 Hz, C(5^a)H), 7.07–7.09 (2H, m, C(6^b)H and C(2^b)H), 7.21 (1H, tt, *J*=7.5, 1.1 Hz, C(4^b)H), 7.37–7.43 (2H, m, C(5^b)H and C(3^b)H), 7.46 (1H, dd, *J*=2.2, 8.5 Hz, C(6^a)H), 7.65 (1H, d, *J*=2.2 Hz, C(2^a)H); δ_C (100 MHz, $CDCl_3$) 26.9 ($COCH_3$), 116.8 (C2^a), 117.3 (C5^a), 119.7 (C2^b and C6^b), 121.9 (C6^a), 125.0 (C4^b), 130.5 (C3^b and C5^b), 133.4 (C1^a), 147.4 and 149.2 (C4^a and C3^a), 155.8 (C1^b), 197.9 ($COCH_3$); *m/z* (EI) 228 ([M]$^+$). (Found: [M]$^+$, 228.07857. $C_{14}H_{12}O_3$ requires [M]$^+$, 228.07864), 213 (100%).

5.1.3. 3-Hydroxy-1-(3-hydroxy-4-phenoxyphenyl)-3-phenylpropan-1-one (7). *n*-Butyllithium (1.6 M in

tetrahydrofuran, 0.6 cm^3, 0.92 mmol, 2.4 equiv.) was added dropwise to a stirred solution of anhydrous diisopropylamine (0.13 cm^3, 0.92 mmol, 2.4 equiv.) in anhydrous tetrahydrofuran (2 cm^3) at −78°C, under N_2. After stirring for 45 min the temperature was raised to 0°C and a solution of 3-hydroxy-4-phenoxy acetophenone (**6**) (84.3 mg, 0.38 mmol) in tetrahydrofuran (2 cm^3) was added dropwise to the solution to give a milky mixture. Stirring was continued for an additional 45 min at 0°C. The solution was then cooled down to −78°C and benzaldehyde (0.05 cm^3, 0.46 mmol, 1.2 equiv.) was added dropwise over 5 min. The reaction mixture was allowed to stir for 2 h at −78°C, under N_2, and was neutralised with an aqueous phosphate buffer solution (pH=7, 2 cm^3) and acetic acid (0.2 cm^3, 3.5 mmol) and allowed to warm up to rt. Water (5 cm^3) was added and the mixture was extracted with ethyl acetate (3×10 cm^3). The combined organic extracts were washed with brine (30 cm^3), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford a creamy solid (180 mg). The crude material was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:3) to give the title compound **7** as white needles (100 mg, 80%). [Alternatively, when carrying out the reaction on a larger scale (15 g, 66 mmol of 3-hydroxy-4-phenoxyacetophenone), the crude product could be purified by trituration with cold ethyl acetate to afford the title compound as a white powder (17.7 g, 81%)]; mp 142–143°C; R_f 0.14 (EtOAc/*n*-hexane, 1:3). (Found: C, 75.4; H, 5.4 $C_{21}H_{18}O_4$ requires C, 75.4; H, 5.4%); ν_{max} (film, NaCl Plate)/cm^{-1} 3502 (sh, OH), 3301 (bd, OH), 3039 (w, Ar-H), 1660 (ketone CO); δ_H (300 MHz, MeOD) 3.21 (1H, dd, *J*=16.0, 4.5 Hz, C(2)H), 3.43 (H, dd, *J*=16.0, 8.4 Hz, C(2)H), 5.27 (1H, dd, *J*=4.5, 8.4 Hz, C(3)H), 6.83 (1H, d, *J*=8.4 Hz, C(5^a)H), 6.97–7.02 (2H, m, C(2^b)H and C(6^b)H), 7.13 (1H, tt, *J*=7.5, 1.2 Hz, C(4^b)H), 7.23 (1H, tt, *J*=7.2, 1.5 Hz, C(4^c)H), 7.28–7.41 (6H, m, C(3^b)H, C(5^b)H and Ph^c), 7.44 (1H, dd, *J*=8.4, 2.4 Hz, C(6^a)H), 7.54 (1H, d, *J*=2.4 Hz, C(2^a)H); δ_C (100 MHz, MeOD) 48.9 (C2), 71.9 (C3), 117.9, 119.9, 120.1, 122.6, 125.2, 127.4, 128.8, 129.8, 131.3 (Ph^a, Ph^b and Ph^c), 135.0 ($C1^a$), 146.0 ($C1^c$), 150.0 and 151.1 ($C3^a$ and $C4^a$), 158.3 ($C1^b$), 199.6 (C1); *m/z* (EI) 334 ($[M]^+$), 228, 213 (100%), 106, 105, 77.

5.1.4. (2*E*)-1-(3-Hydroxy-4-phenoxyphenyl)-3-phenylprop-2-en-1-one (8). *p*-Toluenesulfonic acid (1.95 g, 10.3 mmol, 0.2 equiv.) was added in one portion to a mixture of hydroxy ketone **7** (17.1 g, 51.2 mmol) in anhydrous dichloromethane (700 cm^3), at rt and under N_2. The temperature was raised to 40°C, and the mixture was stirred for 15 h, under N_2, care being taken to ensure the reaction mixture was shielded from light. The resulting transparent orange reaction mixture was quenched by the addition of water (200 cm^3). The aqueous layer was separated, neutralised with a saturated aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane (3×200 cm^3). The combined organic extracts were washed with brine (1000 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford an orange solid (17.5 g). The crude mixture was recrystallised (methyl *tert*-butyl ether/*n*-hexane) to afford the title product **8** as fine white needles (13.15 g, 81%), mp 104–105°C (from EtOAc/*n*-hexane); R_f 0.28 (EtOAc/*n*-hexane, 1:3). (Found: C, 79.6; H, 5.1 $C_{21}H_{16}O_3$ requires C, 79.7; H, 5.1%); ν_{max} (film, NaCl Plate)/cm^{-1} 3341 (bd, OH), 3056 (w, Ar-H), 1657 (ketone CO); δ_H (300 MHz, $CDCl_3$) 6.08 (1H, bs, OH), 6.87 (1H, d, *J*=8.4 Hz, C(5^a)H), 7.07–7.11 (2H, m, C(2^b)H and C(6^b)H), 7.15–7.27 (2H, m, C(4^b)H and C(4^c)H), 7.36–7.43 (4H, m, C(3^b)H, C(5^b)H, C(3^c)H and C(5^c)H), 7.49 (1H, d, *J*=15.6 Hz, C(2)H), 7.53 (1H, dd, *J*=8.4, 2.4 Hz, C(6^a)H), 7.59–7.69 (2H, m, C(2^c)H and C(6^c)H), 7.75 (1H, d, *J*=2.4 Hz, C(2^a)H), 7.81 (1H, d, *J*=15.6 Hz, C(3)H); δ_C (75.5 MHz, $CDCl_3$) 116.5, 116.9, 119.4, 121.7, 121.9, 124.8, 128.5, 129.0, 130.2, 130.6 (Ph^a, Ph^b and Ph^c), 134.3 and 135.0 ($C1^a$ and $C1^c$), 144.7 (C3), 147.1 and 148.5 ($C3^a$ and $C4^a$), 155.6 ($C1^b$), 189.1 (C1); *m/z* (EI) 316 ($[M]^+$), 315 (100%, $[M-H]^+$), 223, 103, 77, 51.

5.1.5. (3-Hydroxy-4-phenoxyphenyl)[(2*R*,3*S*)-3-phenyloxiran-2-yl]methanone (9). A mixture of urea hydrogen peroxide (114 mg, 1.2 mmol, 1.25 equiv.), immobilized poly-L-leucine (396 mg) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.29 cm^3, 1.9 mmol, 2.0 equiv.) in anhydrous tetrahydrofuran (5 cm^3) was stirred vigorously at rt, for 5 min. Enone **8** (300 mg, 0.95 mmol) subsequently added to give a bright orange mixture and stirring was maintained for 15 h (the colour of the reaction mixture turned yellow when the reaction was complete). The catalyst was removed by filtration and was washed with ethyl acetate (3×20 cm^3). The filtrate was washed with saturated sodium sulfite solution (2×10 cm^3), water (2×10 cm^3), and brine (10 cm^3) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to afford a yellow gum (350 mg) which was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:2) to give the title compound **9** as a creamy solid (297 mg, 94%, 86% ee). The product could be further recrystallised (dichloromethane) to give white needles (265 mg, 85%, >99.9% ee); mp 163–165°C (from CH_2Cl_2); R_f 0.22 (EtOAc/*n*-hexane, 1:3). (Found: C, 75.8; H, 4.9 $C_{21}H_{16}O_4$ requires C, 75.9; H, 4.8%); $[\alpha]_D^{25}=-154$ (*c*=1, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3366 (sh, OH), 3045 (w, Ar-H), 1684 (ketone CO); δ_H (400 MHz, $CDCl_3$) 4.06 (1H, d, *J*=1.8 Hz, C(3)H), 4.22 (1H, d, *J*=1.8 Hz, C(2)H), 5.83 (1H, bs, OH), 6.81 (1H, d, *J*=8.5 Hz, C(5^a)H), 7.07–7.10 (2H, m, C(2^b)H and C(6^b)H), 7.23 (1H, tt, *J*=7.5, 1.0 Hz, C(4^b)H), 7.34–7.43 (7H, m, C(3^b)H, C(5^b)H and Ph^c), 7.52 (1H, dd, *J*=8.5, 2.1 Hz, C(6^a)H), 7.71 (1H, d, *J*=2.1 Hz, C(2^a)H); δ_C (100 MHz, $CDCl_3$) 59.7 (C3), 61.3 (C2), 116.3 ($C2^a$), 116.8 ($C5^a$), 120.0 ($C2^b$ and $C6^b$), 122.0 ($C6^a$), 125.5 ($C4^b$), 126.2, 129.1, 129.4 and 130.6 (C(3^b)H, C(5^b)H and Ph^c), 131.7 ($C1^a$), 135.9 ($C1^c$), 147.3 ($C4^a$), 149.9 ($C3^a$), 155.3 ($C1^b$), 192.0 (C1); *m/z* (EI) 332 ($[M]^+$). (Found: $[M]^+$, 332.10521. $C_{21}H_{16}O_4$ requires $[M]^+$, 332.10486), 213 (100%), 77; ee >99.9% (Chiracel OD; *n*-hexane/*i*-PrOH, 1:1, 254 nm; major enantiomer 12.6 min, minor enantiomer 10.6 min).

5.1.6. (2*S*,3*S*)-3-Chloro-2-hydroxy-1-(3-hydroxy-4-phenoxyphenyl)-3-phenylpropan-1-one (10). Hydrochloric acid was bubbled through a suspension of epoxy ketone **9** (950 mg, 2.86 mmol) in anhydrous dichloromethane (25 cm^3), at 0°C, for 30 min. The excess gas and the solvent were evaporated under reduced pressure to afford a yellow foam. The crude residue diluted with dichloromethane (10 cm^3), washed with water (2×10 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting crude mixture was purified by flash column

chromatography (SiO_2; EtOAc/*n*-hexane, 1:6) to provide the title compound **10** as a hydroscopic pale green gum (800 mg, 77%, >99:1 [*syn*-**10**/*anti*-**10**]); R_f 0.61 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}=-50$ ($c=1$, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3446 (bd, OH), 3064 (w, Ar-H), 1682 (ketone CO); δ_H (300 MHz, $CDCl_3$) 4.1 (1H, bs, C(2)HO*H*), 5.26–5.35 (2H, m, C(2)H and C(3)H), 6.02 (1H, bs, ArO*H*), 6.85 (1H, d, $J=8.5$ Hz, C(5^a)H), 7.09–7.14 (2H, m, C(2^b)H and C(6^b)H), 7.26 (1H, tt, $J=7.8$, 1.2 Hz, C(4^b)H), 7.33–7.56 (8H, m, C(6^a)H, C(5^b)H, C(3^b)H and Ph^c), 7.61 (1H, d, $J=2.1$ Hz, C(2^a)H); δ_C (75.5 MHz, $CDCl_3$) 64.1 (C3), 75.9 (C2), 116.2 (C5^a), 116.4 (C2^a), 119.9 (C2^b and C6^b), 121.9 (C6^a), 125.4 (C4^b), 128.8 (C4^c), 128.0, 128.6 and 130.4 (C5^b, C3^b and Ph^c), 129.1 and 138.3 (C1^a and C1^c), 147.0 and 150.0 (C3^a and C4^a), 154.8 (C1^b), 196.3 (C1); *m/z* (CI) 386 ($[M+NH_4]^+$), 369 ($[M+H]^+$) (Found: $[M+H]^+$, 369.08843. $C_{21}H_{18}O_4Cl$ requires $[M+H]^+$, 369.08932), 350, 336, 317 (100%), 213.

5.1.7. (1*S*,2*S*,3*S*)-3-Chloro-1-(3-hydroxy-4-phenoxyphenyl)-3-phenylpropane-1,2-diol (11). A solution of zinc borohydride in ether (0.13 M, 2.2 cm^3, 0.27 mmol, 1.0 equiv.) was added dropwise to a solution of chlorohydrin **10** (100 mg, 0.27 mmol) in anhydrous tetrahydrofuran (3 cm^3), at 0°C and under N_2. The yellow transparent solution turned colourless and was stirred for 20 min. The reaction was quenched by the addition of water (5 cm^3) and the mixture was extracted with ethyl acetate (3×5 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:5, then 1:3) to afford the title product **11** as a transparent gum (95 mg, 95%, >99:1 [*anti*-(**11**)/*syn*-(**13**)]); R_f 0.50 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}=+43$ ($c=2$, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3527 (OH), 3423 (OH), 3061 (w, Ar-H); δ_H (400 MHz, $CDCl_3$) 2.76 (1H, bs, C(2)O*H*), 3.21 (1H, bs, C(1)O*H*), 4.05 (1H, dd, $J=4.2$, 6.8 Hz, C(2)H), 4.55 (1H, d, $J=6.8$ Hz, C(1)H), 5.23 (1H, d, $J=4.2$ Hz, C(3)H), 6.44 (1H, bs, Ar-O*H*), 6.73 (1H, dd, $J=1.8$, 8.2 Hz, C(6^a)H), 6.77 (1H, d, $J=8.2$ Hz, C(5^a)H), 6.94–6.96 (2H, m, C(2^b)H and C(6^b)H), 7.02 (1H, d, $J=1.8$ Hz, C(2^a)H), 7.06–7.10 (1H, m, C(4^b)H), 7.27–7.33 (5H, m, C(3^b)H, C(5^b)H, C(4^c)H, C(3^c)H and C(5^c)H), 7.39 (2H, dd, $J=8.1$, 2.1 Hz, C(2^c)H and C(6^c)H); δ_C (100 MHz, $CDCl_3$) 65.0 (C3), 74.6 (C1), 78.2 (C2), 115.6 (C2^a), 118.6 (C2^b and C6^b), 118.8 (C6^a), 120.1 (C5^a), 124.2 (C4^b), 128.4 (C2^c and C6^c), 129.0 (C3^c and C5^c), 129.1 (C4^c), 130.3 (C3^b and C5^b), 137.2 (C1^a), 138.9 (C1c), 144.0 (C4^a), 147.7 (C3^a), 156.8 (C1^b); *m/z* (CI) 370 ($[M+NH_4\text{-}H_2O]^+$) (Found: $[M+NH_4-H_2O]^+$, 370.12088. $C_{21}H_{21}O_3ClN$ requires $[M+NH_4-H_2O]^+$, 370.12100), 336, 232, 215 (100%), EI 370 ($[M]^+$), 352, 316, 213, 199, 120, 91 (100%), 77.

5.1.8. (2*S*,3*S*)-3-Chloro-3-phenyl-2-triethylsilyloxy-1-(3-triethylsilyloxy-4-phenoxyphenyl)-propan-1-one (12). Imidazole (78 mg, 1.08 mmol, 4.0 equiv.) was added to a solution of chlorohydrin **10** (100 mg, 0.27 mmol) in anhydrous dimethylformamide (1 cm^3) at rt. Triethylsilyl chloride (0.14 cm^3, 0.81 mmol, 3.0 equiv.) was added dropwise, an evolution of HCl gas was immediately observed and the slight yellow solution became colourless. The reaction was stirred for 2.5 h and quenched by the addition of water (2 cm^3). The resulting mixture was extracted with ethyl acetate (3×5 cm^3). The combined organic extracts were washed with brine (15 cm^3), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:6) to give the title compound **12** as a transparent oil (170 mg, 100 %); R_f 0.67 (EtOAc/*n*-hexane, 1:6); $[\alpha]_D^{25}=+26$ ($c=1$, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 2876–2855 (CH stretch, Et_3Si), 1684 (ketone CO); δ_H (400 MHz, $CDCl_3$) 0.54 (6H, q, $J=8.1$ Hz, $(CH_3CH_2)_3SiOAr$), 0.70 (6H, q, $J=8.1$ Hz, $(CH_3CH_2)_3SiOC(2)H$), 0.88 (9H, t, $J=8.1$ Hz, $(CH_3CH_2)_3SiOAr$), 0.94 (9H, t, $J=8.1$ Hz, $(CH_3CH_2)_3$-SiOC(2)H), 4.93 (1H, d, $J=6.8$ Hz, C(2)H), 5.27 (1H, d, $J=6.8$ Hz, C(3)H), 6.85 (1H, d, $J=8.5$ Hz, C(5^a)H), 6.95–6.98 (2H, m, C(2^b)H and C(6^b)H), 7.12 (1H, tt, $J=7.6$, 1.0 Hz, C(4^b)H), 7.23–7.27 (5H, m, Ph^c), 7.27–7.36 (2H, m, C(5^b)H and C(3^b)H), 7.54 (1H, dd, $J=8.5$, 2.0 Hz, C(6^a)H), 7.57 (1H, d, $J=2.0$ Hz, C(2^a)H); δ_C (100 MHz, $CDCl_3$) 5.1 $(CH_3CH_2)_3SiOAr$), 5.5 $(CH_3CH_2)_3SiOC(2)H$), 6.8 $(CH_3CH_2)_3SiOAr$), 6.95 $(CH_3CH_2)_3SiOC(2)H$), 66.1 (C2), 82.6 (C3), 118.8 (C2^b and C6^b), 119.2 (C5^a), 122.8 (C2^a), 123.9 (C4^b), 124.2 (C6^a), 128.5, 128.7 and 129.1 (Ph^c), 130.1 (C3^b and C5^b), 131.8 (C1^a), 137.6 (C1^c), 146.8 (C3^a), 152.6 (C4^a), 156.7 (C1^b), 197.4 (C1); *m/z* (FAB) 599 ($[M+H, {}^{37}Cl]^+$), 597 ($[M+H, {}^{35}Cl]^+$), 569, 567, 327, 234, 87 (100%), HRMS could not be determined for neither $[M+H]^+$ nor $[M-C_2H_5]^+$.

5.1.9. (1*R*,2*S*,3*S*)-3-Chloro-1-(3-hydroxy-4-phenoxyphenyl)-3-phenylpropan-1,2-diol (13). A solution of sodium borohydride (6 mg, 0.28 mmol, 1.7 equiv.) in water (0.5 cm^3) was added dropwise to a solution of protected hydroxy ketone **12** (53 mg, 0.09 mmol) in methanol: dichloromethane (2 cm^3/0.5 cm^3) at 0°C. The mixture was stirred for 30 min, quenched with water (3 cm^3) and extracted with ethyl acetate (3×5 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford a mixture of isomeric products. The crude was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 2:98). A mixture of three isomeric products (40 mg) was isolated together and subjected to the next step. Tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 2 drops) was added to a solution of the previously obtained mixture (20 mg) in anhydrous tetrahydrofuran (1 cm^3) at rt. The mixture was stirred for one minute and was subsequently quenched by filtration through a short pad of silica. The silica was washed several times with dichloromethane (3×5 cm^3) and the combined filtrate was evaporated under reduced pressure to afford the pure product as a mixture of *syn*-**13** and *anti*-**11** diastereomers (17 mg, 90% over two steps, 90:10 [*syn*-(**13**)/*anti*-(**11**)], determined by ^1H NMR). The two diastereomers were separated by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 2:3) to give *anti*-**11** in 9% yield and *syn*-**13** as a white solid (15 mg, 80%); mp 80–81°C; R_f 0.25 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}=+30$ ($c=0.5$, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3382 (bd, OH); δ_H (400 MHz, $CDCl_3$) 2.75 (1H, d, $J=5.3$ Hz, C(1)O*H*), 2.77 (1H, d, $J=5.1$ Hz, C(2)O*H*), 4.03 (1H, ddd, $J=5.5$, 5.1, 4.7 Hz, C(2)H), 4.55 (1H, dd, $J=4.7$, 5.3 Hz, C(1)H), 4.97 (1H, d, $J=5.5$ Hz, C(3)H), 5.67 (1H, bs, ArO*H*), 6.83 (1H, dd, $J=1.8$, 8.3 Hz,

C(6[a])H), 6.86 (1H, d, J=8.3 Hz, C(5[a])H), 7.01–7.04 (2H, m, C(2[b])H and C(6[b])H), 7.05 (1H, d, J=1.8 Hz, C(2[a])H), 7.14 (1H, tt, J=7.4, 1.0 Hz, C(4[b])H), 7.33–7.45 (7H, m, C(3[b])H, C(5[b])H and Ph[c]); δ_C (100 MHz, $CDCl_3$) 65.2 (C3), 73.3 (C1), 79.1 (C2), 114.2 (C2[a]), 118.6 (C2[b] and C6[b]), 118.6 (C5[a] and C6[a]), 123.9 (C4[b]), 127.7 (C2[c] and C6[c]), 128.8 (C3[c] and C5[c]), 128.9 (C4[c]), 137.1 (C1[a]), 138.2 (C1[c]), 143.4 (C4[a]), 147.4 (C3[a]), 156.4 (C1[b]); m/z (CI) 372 ([M+NH_4−H_2O, ^{37}Cl]$^+$) 370 ([M+NH_4−H_2O, ^{35}Cl]$^+$) (Found: [M+NH_4−H_2O, ^{35}Cl]$^+$, 370.12120. $C_{21}H_{21}O_3ClN$ requires [M+NH_4−H_2O, ^{35}Cl]$^+$, 370.12100), 334, 232, 215 (100%).

5.1.10. 5-{(4*S*,5*S*)-5-[(*S*)-Chloro(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2-phenoxyphenol (14). Dimethoxypropane (0.02 cm^3, 0.18 mmol, 3.0 equiv.) and *p*-toluenesulfonic acid (a few crystals) were added to a solution of diol *anti*-**11** (20 mg, 0.06 mmol) in dichloromethane (1 cm^3) at rt. The mixture was stirred for 15 h and was quenched by the addition of water (1 cm^3). The organic layer was separated, washed with brine (2 cm^3), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford a gummy residue (30 mg). The crude product was purified by filtration through a short pad of silica to give the pure acetonide **14** as a white solid (25 mg, 100%), mp 129–130°C; R_f 0.78 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}$=−83.3 (c=1.9, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3420 (bd, OH), 3064 (m, Ar-H); δ_H (400 MHz, $CDCl_3$) 1.55 (3H, s, CH_3), 1.74 (3H, s, CH_3), 4.64 (1H, d, J=9.3 Hz, C(3)H), 4.94 (1H, d, J=6.9 Hz, C(1)H), 5.02 (1H, dd, J=6.9, 9.3 Hz, C(2)H), 5.46 (1H, bs, Ar-O*H*), 6.39 (1H, dd, J=2.0, 8.3 Hz, C(6[a])H), 6.62 (1H, d, J=8.3 Hz, C(5[a])H), 6.66 (1H, d, J=2.0 Hz, C(2[a])H), 6.83 (2H, dd, J=8.0, 1.4 Hz, C(2[c])H and C(6[c])H), 6.92 (2H, dd, J=8.6, 1.0 Hz, C(2[b])H and C(6[b])H), 7.06–7.12 (4H, m, C(3[c])H, C(5[c])H, C(4[b])H and C(4[c])H), 7.28 (2H, t, J=8.6 Hz, C(3[b])H and C(5[b])H); δ_C (100 MHz, $CDCl_3$) 23.7 (CH_3), 25.9 (CH_3), 61.1 (CH, C3), 78.2 (CH, C1), 80.7 (CH, C2), 108.1 (Q, $C(CH_3)_2$), 114.7 (CH, C2[a]), 116.9 (2×CH, C2[b] and C6[b]), 117.3 (CH, C5[a]), 119.1 (CH, C5[a]), 122.7 (CH, C4[b]), 126.7 (2×CH, C2[c] and C6[c]), 127.4 (2×CH, C3[c] and C5[c]), 127.5 (CH, C4[c]), 128.9 (2×CH, C3[b] and C5[b]), 132.4 (Q, C1[a]), 137.0 (Q, C1[c]), 142.2 (Q, C4[a]), 146.1 (Q, C3[a]), 155.7 (Q, C1[b]); m/z (CI) 430 ([M+NH_4, ^{37}Cl]$^+$), 428 ([M+NH_4, ^{35}Cl]$^+$) 413 ([M+H, ^{37}Cl]$^+$), 411 ([M+H, ^{35}Cl]$^+$). (Found: [M+H, ^{35}Cl]$^+$, 411.13608. $C_{24}H_{24}O_4Cl$ requires [M+H, ^{35}Cl]$^+$, 411.13632), 412–410 ([M]$^+$), 372–370 ([M+NH_4−$(CH_3)_2CO$]$^+$), 317 (100%, [M−$(CH_3)_2CO$, −Cl]$^+$), 256, 214 ([M−PhCHClCHOC$(CH_3)_2$]$^+$), 161; nOe experiments: by the irradiation of the methyl signal at δ 1.55, nOes were observed at δ 4.94 and δ 5.02 for C(1)H and C(2)H, respectively, whereas no nOes were observed for the other methyl signal at δ 1.74, confirming the *syn*-relationship between C(1)H and C(2)H.

5.1.11. 5-{(4*R*,5*S*)-5-[(*S*)-Chloro(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2-phenoxyphenol (15). Dimethoxypropane (0.01 cm^3, 0.081 mmol, 3.0 equiv.) and *p*-toluenesulfonic acid (a few crystals) were added to a solution of *syn*-**13** (10 mg, 0.027 mmol) in dichloromethane (1 cm^3) at rt under N_2. The pale yellow solution turned colourless and was stirred for 16 h. The solvent was evaporated under reduced pressure to afford a brown residue. The crude material was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:3) to give the title compound **15** as a pale cream gum (3 mg, 30%); R_f 0.60 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}$=+93.3 (c=0.3, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3423 (bd, OH); δ_H (400 MHz, $CDCl_3$) 1.57 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.28 (1H, dd, J=5.3, 8.2 Hz, C(2)H), 4.78 (1H, d, J=8.2 Hz, C(1)H), 4.89 (1H, d, J=5.3 Hz, C(3)H), 5.53 (1H, bs, Ar-O*H*), 6.55 (1H, dd, J=8.2, 2.0 Hz, C(6[a])H), 6.71 (1H, d, J=8.2 Hz, C(5[a])H), 6.83 (1H, d, J=2.0 Hz, C(2[a])H), 6.97 (2H, dd, J=8.7, 0.9 Hz, C(2[b])H and C(6[b])H), 7.13 (1H, t, J=7.3 Hz, C(4[b])H), 7.25–7.26 (3H, m, C(4[c])H and 2×H[c]), 7.31–7.37 (4H, m, C(3[b])H, C(5[b])H and 2×H[c]); δ_C (100 MHz, $CDCl_3$) 28.1 (CH_3), 28.6 (CH_3), 63.4 (CH, C2), 81.7 (CH, C1), 87.2 (CH, C3), 111.1 (Q, $C(CH_3)_2$), 115.8 (CH, C2[a]), 119.0 (2×CH, C2[b] and C6[b]), 119.9 (CH, C5[a]), 120.4 (CH, C6[a]), 124.8 (CH, C4[b]), 129.3 (2×CH), 129.6 (2×CH) and 131.0 (2×CH) (C2[c], C6[c], C3[c], C5[c], C3[b], C5[b]), 129.9 (CH, C4[c]), 134.9 (Q, C1[a]), 139.0 (Q, C1[c]), 144.4 (Q, C4[a]), 148.5 (Q, C3[a]), 157.7 (Q, C1[b]); m/z (CI) 412 ([M, ^{37}Cl]$^+$), 410 ([M, ^{35}Cl]$^+$). (Found: [M, ^{35}Cl]$^+$, 410.12870. $C_{24}H_{23}O_4Cl$ requires [M, ^{35}Cl]$^+$, 410.12845), 372 ([M+NH_4−$(CH_3)_2CO$, ^{37}Cl]$^+$), 370 ([M+NH_4−$(CH_3)_2CO$, ^{35}Cl]$^+$), 336 (100%, [M+NH_4−Cl, −C_3H_5O]$^+$), 319 ([M+H, −Cl, −C_3H_5O]$^+$), 256, 215 ([M+H−PhCHClCHOC$(CH_3)_2$]$^+$), 161, 91 ([C_7H_7]$^+$).

5.1.12. 5-{(*S*)-Hydroxy[(2*S*,3*R*)-3-phenyloxiran-2-yl]methyl}-2-phenoxyphenol (16). Potassium carbonate (25 mg, 0.18 mmol, 2.2 equiv.) was slowly added to a solution of chlorohydrin *anti*-**11** (30 mg, 0.081 mmol) in methanol (2 cm^3) at 0°C. The mixture was allowed to warm to rt and was stirred for 18 h. The reaction mixture was quenched by the addition of water (2 cm^3) and was extracted with ethyl acetate (5×5 cm^3). The combined organic extracts were washed with brine (15 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a creamy gum (35 mg). Flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:3) of the crude residue afforded the title compound **16** as a pale cream gum (26 mg, 97%); R_f 0.50 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}$=−211 (c=1, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3423 (bd, OH); δ_H (400 MHz, MeOD) 3.24 (1H, dd, J=8.5, 3.9 Hz, C(2)H), 3.88 (1H, d, J=8.5 Hz, C(1)H), 4.18 (1H, d, J=3.9 Hz, C(3)H), 6.79–6.84 (4H, m, C(5[a])H, C(6[a])H, C(2[b])H and C(6[b])H), 6.90–6.94 (1H, m, C(4[b])H), 6.97 (1H, d, J=1.5 Hz, C(2[a])H), 7.16–7.35 (7H, m, C(3[b])H, C(5[b])H and Ph[c]); δ_C (100 MHz, MeOD) 59.8 (C3), 63.5 (C2), 70.2 (C1) 116.7 (C2[a]), 118.6 (C2[b] and C6[b]), 119.5 (C6[a]), 122.2 (C5[a]), 123.9 (C4[b]), 128.1, 129.3 and 129.7 (Ph[c]), 130.9 (C3[b] and C5[b]), 136.8 (C1[c]), 141.3 (C1[a]), 144.9 (C4[a]), 150.5 (3[a]), 159.9 (C1[b]); m/z (CI) 352 ([M+NH_4]$^+$). (Found: [M+NH_4]$^+$, 352.15396. $C_{21}H_{22}O_4N$ requires [M+NH_4]$^+$, 352.15488), 335 ([M+H]$^+$), 317, 232, 215 (100%), 91.

5.1.13. 5-{(*S*)-Hydroxy[(2*S*,3*S*)-3-phenyloxiran-2-yl]methyl}-2-phenoxyphenol (17). A solution of zinc borohydride (0.13 M, 2.5 cm^3, 0.31 mmol, 1 equiv.) was added dropwise to a solution of epoxy ketone **9** (100 mg, 0.31 mmol) in anhydrous tetrahydrofuran (2 cm^3), at 0°C, and under N_2. The mixture was stirred for 2 h and was quenched with water (5 cm^3). The mixture was extracted with ethyl acetate (5×10 cm^3). The combined organic

extracts were washed with brine (30 cm^3), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford a creamy gum (150 mg). The crude mixture was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:6) to give the title compound **17** as a white solid (85 mg, 82%, >98:2 [*anti*-(**17**)/*syn*-(**18**)], as determined by ^1H NMR), mp 89–90°C; R_f 0.17 (EtOAc/*n*-hexane, 1:3); $[\alpha]_D^{25}=+5$ ($c=1$, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3421 (bd, OH), 3064 (w, Ar-H); δ_H (400 MHz, MeOD) 3.15 (1H, dd, $J=4.7$, 2.0 Hz, C(2)H), 3.99 (1H, d, $J=2.0$ Hz, C(3)H), 4.60 (1H, d, $J=4.7$ Hz, C(1)H), 6.85 (1H, d, $J=8.2$ Hz, C(5^a)H), 6.86–6.90 (3H, m, C(6^a)H, C(2^b)H and C(6^b)H), 6.97–7.01 (1H, tt, $J=7.3$, 1.0 Hz, C(4^b)H), 7.06 (1H, d, $J=1.9$ Hz, C(2^a)H), 7.20–7.32 (7H, m, C(3^b)H, C(5^b)H and Ph^c); δ_C (100 MHz, $CDCl_3$) 58.0 (C3), 66.9 (C2), 77.8 (C1), 116.9 (C2^a), 118.6 (C2^b and C6^b), 119.8 (C6^a), 122.2 (C5^a), 123.9 (C4^b), 127.2, 129.6 (C4^c), 129.9 and 130.9 (C3^b, C5^b and Ph^c), 138.9 (C1^a), 139.8 (C1^c), 145.1 (C4^a), 150.6 (C3^a), 159.9 (C1^b); *m/z* (CI) 352 ($[M+NH_4]^+$). (Found: $[M+NH_4]^+$, 352.15364. $C_{21}H_{22}O_4N$ requires $[M+NH_4]^+$, 352.15488), 335 ($[M+H]^+$), 317, 232, 215 (100%), 138, 91.

5.1.14. 5-{(*R*)-Hydroxy[(2*S*,3*S*)-3-phenyloxiran-2-yl]methyl}-2-phenoxyphenol (18). Tributyltin hydride (4.17 cm^3, 15.5 mmol, 5.0 equiv.) was added dropwise to a solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 15.5 cm^3, 15.5 mmol, dried over 4 Å molecular sieves) in anhydrous tetrahydrofuran (10 cm^3), at −78°C, under N_2. The mixture was allowed to stir for 10 min at −78°C (an evolution of gas was observed) and an additional 5 min at 0°C. Epoxy ketone **9** (1 g, 3.1 mmol) was added in one portion. The resulting bright yellow mixture was allowed to warm to rt slowly and stirred for 48 h. The reaction was quenched by the addition of methanol and was stirred for 5 min. Water (15 cm^3) was added and the mixture was extracted with ethyl acetate (3×15 cm^3), the combined organic extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and the solvent was evaporated to afford an orange oil. The crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:10, then 1:3) to give the title compound **18** as a yellow gum (675 mg, 65%, 8:1 [*syn*-(**18**)/*anti*-(**17**)]) which crystallised on standing; mp 116–117°C; R_f 0.46 (EtOAc/*n*-hexane, 1:1); ν_{max} (film, NaCl Plate)/cm^{-1} 3418 (bd, OH); δ_H (400 MHz, MeOD) 3.20 (1H, dd, $J=5.8$, 2.2 Hz, C(2)H), 3.95 (1H, d, $J=2.2$ Hz, C(3)H), 4.54 (1H, d, $J=5.8$ Hz, C(1)H), 6.85 (1H, d, $J=8.2$ Hz, C(5^a)H), 6.87–6.93 (3H, m, C(6a)H, C(2^b)H and C(6^b)H), 7.00 (1H, tt, $J=7.4$, 1.1 Hz, C(4^b)H), 7.10 (1H, d, $J=2.0$ Hz, C(2a)H), 7.23–7.33 (7H, m, C(3^b)H, C(5^b)H, Ph^c); δ_C (100 MHz, MeOD) 57.9 (C3), 67.5 (C2), 74.9 (C1), 116.5 (C2^a), 118.5 (C6^b and C2^b), 119.3 (C6^a), 122.0 (C5^a), 123.8 (C4^b), 127.0, 129.5, 129.7 and 130.8 (C3^b, C5^b and Ph^c), 138.5 (C1^a), 139.4 (C1^c), 144.9 (C4^a), 150.4 (C3^a), 159.6 (C1^b); *m/z* (EI) 334 ($[M]^+$). (Found: $[M]^+$, 334.11988. $C_{21}H_{18}O_4$ requires $[M]^+$, 334.12048), 213, 120, 91 (100%), 77.

5.1.15. 5-{(*R*)-Hydroxy[(2*S*,3*R*)-3-phenyloxiran-2-yl]methyl}-2-phenoxyphenol (1). Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 4 drops) was added to a solution of chlorohydrin *syn*-**13** (15 mg, 0.025 mmol) in anhydrous tetrahydrofuran (2 cm^3) at rt. The resulting yellow solution was stirred for 6 h and tetrabutylammonium fluoride (4 drops) was added. The reaction was stirred for an additional 24 h and the reaction was quenched by filtration through a short pad of silica. The pad of silica was washed several times with dichloromethane (3×5 cm^3) and the combined filtrate was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:3) to give the title compound **1** as a creamy gum (6 mg, 72%); R_f 0.39 (EtOAc/*n*-hexane, 1:1); $[\alpha]_D^{25}=+116.7$ ($c=0.6$, $CHCl_3$); ν_{max} (film, NaCl Plate)/cm^{-1} 3418 (bd, OH), 3062 (w, Ar-H); δ_H (400 MHz, MeOD) 3.35 (1H, dd, $J=4.5$, 8.6 Hz, C(2)H), 4.10 (1H, d, $J=8.6$ Hz, C(1)H), 4.18 (1H, d, $J=4.5$ Hz, C(3)H), 6.26 (1H, dd, $J=2.0$, 8.2 Hz, C(6^a)H), 6.60 (1H, d, $J=2.0$ Hz, C(2^a)H), 6.68 (1H, d, $J=8.2$ Hz, C(5^a)H), 6.86 (2H, m, C(6^b)H and C(2^b)H), 7.01 (1H, tt, $J=7.3$, 1.0 Hz, C4^b), 7.25–7.31 (2H, m, C(3^b)H and C(5^b)H), 7.34–7.39 (5H, m, Ph^c); δ_C (100 MHz, MeOD) 58.7 (C3), 64.6 (C2), 72.6 (C1), 116.5 (C2^a), 118.6 (C6^b and C2^b), 119.2 (C6^a), 121.8 (C5^a), 123.9 (C4^b), 127.9 (C2^c and C6^c), 129.3 (C4^c), 129.6 (C3^c and C5^c), 130.9 (C3^b and C5^b), 137.1 (C1^c), 139.1 (C1^a), 145.1 (C4^a), 150.4 (C3^a), 159.8 (C1^b); *m/z* (CI) 352 ($[M+NH_4]^+$) (Found: $[M+NH_4]^+$, 352.15396. $C_{21}H_{22}O_4N$ requires $[M+NH_4]^+$, 352.15488), 334 ($[M]^+$), 317 (100%), 228, 215, 120, 91.

5.1.16. 4-Methyl-1-phenyl-1-penten-3-one (20). Benzaldehyde (11 cm^3, 0.11 mol, 1.1 equiv.) was added to a stirred solution of 3-methyl-2-butanone (11 cm^3, 0.10 mol, 1.0 equiv.) in MeOH (100 cm^3) at 0°C. Aqueous sodium hydroxide (1 M, 50 cm^3, 0.05 mol, 0.5 equiv.) was added over 5 min and the mixture turned pale yellow. After 21 h water (50 cm^3) was added and the aqueous layer was extracted with TBME (3×50 cm^3). The combined organic extracts were washed with aqueous hydrochloric acid (1 M, 100 cm^3), water (2×100 cm^3) and brine (100 cm^3) before drying ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude product which was purified by Kügelrohr distillation of the impurities from the crude oil (65–70°C, 10 mm Hg) to afford title compound **20** (15.4 g, 0.09 mol, 86%) as a yellow oil; R_f 0.5 (cyclohexane/EtOAc 3:1); ν_{max} (thin film)/cm^{-1} 1685 and 1663 (C=O), 1612 (C=C), 1448, 1202, 1056, 980 and 762; δ_H (400 MHz, $CDCl_3$) 1.18 (6H, d, $J=6.9$ Hz, $CH(CH_3)_2$), 2.91 (1H, hept, $J=6.9$ Hz, C(4)H), 6.82 (1H, d, $J=16.0$ Hz, CH), 7.27–7.39 (3H, m, Ph), 7.54–7.57 (2H, m, Ph), 7.62 (1H, d, $J=16.0$ Hz, CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.8 ($CH(CH_3)_2$), 41.5 (C(4)H), 123.3, 130.7, 131.2 and 132.6 (CH), 137.0 (ipso), 144.7 (CH), 206.0 (C=O); HRMS (EI) $C_{12}H_{14}O$ $[M^+]$ requires 174.1045, found 174.1051; *m/z* (EI) 174 (M^+, 14%), 131 (M^+-C_3H_7, 100), 103 (39); (Chiralpak® AD; 5% EtOH in *n*-hexane; 254 nm; 7.1 min).

5.1.17. (−)-(1*S*,2*R*)-1,2-Epoxy-4-methyl-1-phenyl-3-pentanone (21). Enone **20** (1.0 g, 5.74 mmol), UHP (649 mg, 6.89 mmol, 1.2 equiv.), DBU (1.28 cm^3, 8.61 mmol, 1.5 equiv.) and scat (10.3 g) were stirred in dry THF (60 cm^3) until the reaction was complete by TLC (after 18 h). The catalyst was separated by filtration and washed with EtOAc (300 cm^3). The filtrate was washed with saturated sodium sulfite solution (2×100 cm^3), water (2×100 cm^3) and brine (100 cm^3) before drying ($MgSO_4$). Removal of the solvent under reduced pressure afforded the

crude product. Purification by flash column chromatography (SiO_2; petroleum ether; Et_2O 6:1) followed by recrystallisation from *n*-hexane furnished the title compound **21** (621 mg, 3.26 mmol, 57%) as white needles; mp 56–57°C (*n*-hexane); R_f 0.4 (petroleum ether/Et_2O 6:1). (Found: C, 75.8; H, 7.4 $C_{12}H_{14}O_2$ requires: C, 75.8; H, 7.4%); $[\alpha]_D^{22}=-208$ ($c=1.0$, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1711 (C=O), 1458, 1417 and 1052; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.16 (3H, d, $J=7.0$ Hz) and 1.17 (3H, d, $J=7.0$ Hz, $CH(CH_3)_2$), 2.83 (1H, hept, $J=7.0$ Hz, C(4)H), 3.61 (1H, d, $J=2.0$ Hz, CH), 3.93 (1H, d, $J=2.0$ Hz, CH) 7.29–7.38 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$; Me_4Si) 17.3 and 18.1 ($CH(CH_3)_2$), 37.0 (C(4)H), 58.4 and 61.9 (CH), 125.7, 128.7 and 129.0 (Ph), 135.4 (ipso), 208.7 (C=O); *m/z* (EI) 190 (M^+, 4%), 174 (57), 148 (88), 147 (77); ee >99% (Chiralpak® AD, 5% EtOH in *n*-hexane; major enantiomer 8.9 min, minor enantiomer 23.4 min).

5.1.18. (+)-(1*S*,2*R*,3*R*)-1,2-Epoxy-4-methyl-1-phenyl-3-vinyl-3-pentanol (22). To a stirred solution of vinylmagnesium bromide (1 M in THF, 6.5 cm^3, 6.5 mmol, 2.0 equiv.) in THF (45 cm^3) at −78°C was added the epoxyketone **21** (620 mg, 3.26 mmol) as a solution in THF (25 cm^3) under a nitrogen atmosphere. The reaction was stirred at −78°C for 1.5 h before quenching by addition of saturated, aqueous ammonium chloride (25 cm^3), warming to rt and extraction with EtOAc (3×60 cm^3). The combined organic extracts were washed with water (2×120 cm^3) and brine (120 cm^3) before drying ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude product with a *Re*/*Si* ratio of >99:1. The crude product was purified by flash column chromatography (SiO_2; petroleum ether; Et_2O 6:1), followed by recrystallisation from *n*-hexane to yield the title compound **22** (493 mg, 2.25 mmol, 69%) as white crystals, mp 36–39°C (*n*-hexane); R_f 0.31 (petroleum ether/Et_2O 6:1). (Found: C, 77.2; H, 8.45; $C_{14}H_{18}O_2$ requires: C, 77.0; H, 8.3%); $[\alpha]_D^{22}=+32$ ($c=1.0$, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3493 (O–H), 2971 (C–H), 1642 (unconjugated C=C), 1495, 1457 (O–H), 989 and 929, 744 and 699; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.96 (6H, d, $J=6.6$ Hz, $CH(CH_3)_2$), 1.84 (1H, hept, $J=6.6$ Hz, C(4)H), 2.06 (1H, br, s, OH), 3.08 (1H, d, $J=2.2$ Hz, CH), 3.99 (1H, d, $J=2.2$ Hz, CH), 5.29 (1H, dd, $J_{AX}=11.0$ Hz, $J_{AB}=1.2$ Hz, $C(7)H^AH^B$), 5.39 (1H, dd, $J_{BX}=17.6$ Hz, $J_{AB}=1.2$ Hz, $C(7)H^AH^B$), 5.97 (1H, dd, $J_{AX}+J_{BX}=28.6$ Hz, $C(6)H^X$), 7.29–7.31 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.95 and 17.0 ($CH(CH_3)_2$), 34.9 (C(4)H), 55.6 and 66.1 (CH), 74.9 (C(3)), 115.1 ($C(7)H_2$), 125.7, 128.3 and 128.6 (Ph), 137.0 (ipso), 140.4 (C(6)H); *m/z* (EI) 129 (6%), 120 (39), 112 (26), 105 (6), 91 (61), 77 (19), 55 (100).

5.1.19. (−)-(1*S*,2*S*,3*R*)-2,3-Epoxy-4-methyl-1-phenyl-3-vinyl-1-pentanol (23). Epoxyalcohol **22** (296 mg, 1.36 mmol) and solid sodium hydroxide (60 mg, 1.49 mmol, 1.1 equiv.) were stirred in dry *tert*-butanol (20 cm^3) at 30°C for 6 h. The reaction mixture was quenched by addition of saturated, aqueous ammonium chloride (20 cm^3) and extracted with EtOAc (3×50 cm^3). The combined organic extracts were washed with water (2×100 cm^3) and brine (100 cm^3) before drying ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude product which was purified by flash column chromatography (SiO_2; petroleum ether; Et_2O 6:1) to afford the title compound **23** (212 mg, 0.97 mmol, 72%) as a colourless oil; R_f 0.3 (petroleum ether: Et_2O 6:1); $[\alpha]_D^{22}=-126$ ($c=1.0$, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3405 (br, O–H), 1604 (phenyl C=C), 1494, 1453, 1085, 1047, 935 and 698; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.97 (3H, d, $J=6.9$ Hz) and 1.07 (3H, d, $J=6.9$ Hz, $CH(CH_3)_2$), 1.63 (1H, hept, $J=6.9$ Hz), 1.81 (1H, d, $J=3.2$ Hz, C(1)OH), 3.04 (1H, d, $J=8.0$ Hz, C(2)H), 4.45 (1H, dd, $J=8.0$, 3.2 Hz, C(1)H), 5.44 (1H, dd, $J_{AX}=10.2$ Hz, $J_{AB}=2.1$ Hz, $C(7)H^AH^B$), 5.48 (1H, dd, $J_{BX}=17.7$ Hz, $J_{AB}=2.1$ Hz, $C(7)H^AH^B$), 6.12 (1H, dd, $J_{AX}+J_{BX}=27.9$ Hz, $C(6)H^X$), 7.28–7.46 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.7 and 18.6 ($CH(CH_3)_2$), 34.4 (C(4)H), 66.8 (CH), 68.9 (C(3)), 70.9 (CH), 119.2 ($C(7)H_2$), 126.1, 128.0 and 128.6 (Ph) 131.1 (C(6)H), 141.7 (ipso); HRMS (CI): $C_{14}H_{22}NO_2$ $[M+NH_4]^+$ requires 236.1651, found 236.1652; *m/z* (EI) 120 (83%), 111 (40), 105 (61), 97 (24), 91 (41), 77 (100).

5.1.20. (3*R*,4*S*,5*S*)-3,4-Epoxy-2-hydroxy-3-(isopropyl)-5-phenyltetrahydrofuran (19). Through a stirred solution of epoxyalcohol **23** (88 mg, 0.40 mmol) in CH_2Cl_2 (10 cm^3) was bubbled ozone at −78°C (2×15 min at 150 V). The gas outlet was passed through a scrubber containing a mixture (1:1) of aqueous acetic acid (10%, 20 cm^3) and aqueous potassium iodide (5%, 20 cm^3). The reaction was flushed with a stream of nitrogen for 30 min before quenching (caution; fumes) by addition of dimethyl sulfide (0.2 cm^3, 2.7 mmol, 6.8 equiv.) and stirring overnight at rt. The reaction mixture was partitioned between water (25 cm^3) and CH_2Cl_2 (25 cm^3) and extracted with further portions of CH_2Cl_2 (2×25 cm^3). The combined organic extracts were washed with water (2×50 cm^3) and brine (50 cm^3) before drying ($MgSO_4$). Purification by flash column chromatography (SiO_2; petroleum ether; Et_2O 6:1+1% triethylamine) followed by recrystallisation from *n*-hexane gave title compound **19** (45 mg, 0.21 mmol, 51%) as white crystals, mp 74–75°C (*n*-hexane); R_f 0.2 (petroleum ether/Et_2O 6:1). (Found: C, 70.5; H, 7.6; $C_{13}H_{16}O_3$ requires: C, 70.9; H, 7.3%); ν_{max} (KBr)/cm^{-1} 3405 (O–H), 1495, 1456, 1205, 1090, 1024, 948, 854, 750, 700 and 629; δ_H (400 MHz; DMSO-d_6; Me_4Si) 0.79 (3H, d, $J=6.8$ Hz) and 1.03 (3H, d, $J=6.8$ Hz, $CH(CH_3)_2$), 2.45 (1H, hept, $J=6.8$ Hz, $CH(CH_3)_2$), 3.79 (1H, s, C(4)H), 5.03 (1H, s, C(5)H), 5.37 (1H, d, $J=4.6$ Hz, C(2)H), 7.08 (1H, d, $J=4.6$ Hz, exchangeable with D_2O, C(2)OH), 7.35–7.39 (3H, m, Ph), 7.56–7.58 (2H, m, Ph); δ_C (75 MHz; DMSO-d_6; Me_4Si) 17.5 and 18.5 ($CH(CH_3)_2$), 23.9 ($CH(CH_3)_2$), 63.1 (CH), 72.2 (C(3)), 80.3 and 96.6 (CH), 127.4, 127.8 and 128.3 (Ph), 139.6 (ipso); *m/z* (EI) 131 (100%), 120 (4), 103 (40), 91 (11), 77 (23).

5.1.21. 7-Hydroxy-8-iodo-2*H*-chromen-2-one (26). A solution of iodine (31.3 g, 123.4 mmol, 1.0 equiv.) in aqueous potassium iodide (5%, 1000 cm^3) was added dropwise, via cannula, to a solution of umbelliferone (**25**) (20 g, 123.4 mmol) in aqueous ammonia (20%, 500 cm^3) over 60 min. The solution was stirred for 24 h, and sufficient aqueous sulphuric acid solution (2.5 M) was added to precipitate 8-iodoumbelliferone (**26**). The crude product was collected by filtration (32.8 g) and was purified by recrystallisation (acetone) to afford the title compound **26** as a pale brown powder (11.0 g, 31%), flash column chromatography of the mother liquor afforded additional

product (SiO_2; EtOAc) (13.12 g, 37%), mp 224–226°C (from acetone, lit.[17] 228–232°C); R_f 0.23 (EtOAc/*n*-hexane, 1:1). (Found: C, 37.6; H, 1.7 $C_9H_5O_3I$ requires C, 37.6; H, 1.7%); ν_{max} (film, NaCl Plate)/cm^{-1} 3396 (bs, OH), 1701 (lactone CO); δ_H (400 MHz, acetone d^6) 6.08 (1H, d, *J*=9.5 Hz, C(3)H), 6.84 (1H, d, *J*=8.5 Hz, C(6)H), 7.40 (1H, d, *J*=8.5 Hz, C(5)H), 7.71 (1H, d, *J*=9.5 Hz, C(4)H), 9.90 (1H, bs, OH); δ_C (100 MHz, acetone d^6) 74.5 (C8), 112.9 (C6), 113.8 (C3), 114.0 (C10), 130.8 (C5), 145.1 (C4), 156.9 (C9), 161.1 (C2), 162.0 (C7); *m/z* (EI) 288 (100%, $[M]^+$). (Found: $[M]^+$, 287.92830. $C_9H_5O_3I$ requires $[M]^+$, 287.92834), 260, 133, 105.

5.1.22. 8-Iodo-7-methoxy-2*H*-chromen-2-one (27). A mixture of 8-iodoumbelliferone (**26**) (600 mg, 2.08 mmol), methyl iodide (0.25 cm^3, 4.1 mmol, 2.0 equiv.) and anhydrous potassium carbonate (574 mg, 4.1 mmol, 2.0 equiv.) in anhydrous acetone (20 cm^3) was heated to reflux for 5 h. Dilute aqueous hydrochloric acid solution (5 cm^3) followed by water (20 cm^3) were added. The mixture was extracted with dichloromethane (3×20 cm^3), and the combined organic extracts were washed with brine (60 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:3) to give the title compound **27** as pale cream needles (520 mg, 82%), mp 160–161°C (from EtOAc, lit.[18] 155–157°C); R_f (EtOAc/*n*-hexane, 1:1). (Found: C, 40.1; H, 2.3 $C_{10}H_7O_3I$ requires C, 39.8; H, 2.3 %); ν_{max} (film, NaCl Plate)/cm^{-1} 3040–3076 (w, Ar-H), 2845 (O*CH*$_3$), 1732 (lactone CO); δ_H (300 MHz, $CDCl_3$) 3.99 (3H, s, OCH_3), 6.24 (1H, d, *J*=9.5 Hz, C(3)H), 6.81 (1H, d, *J*=8.5 Hz, C(6)H), 7.44 (1H, d, *J*=8.5 Hz, C(5)H), 7.58 (1H, d, *J*=9.5 Hz, C(4)H); δ_C (75.5 MHz, $CDCl_3$) 57.1 (O*C*H$_3$), 75.9 (C8), 107.5 (C6), 113.7 (C10), 113.8 (C3), 129.2 (C5), 143.2 (C4), 155.1 (C7), 160.5 and 161.8 (C9 and C2); *m/z* (EI) 302 (100%, $[M]^+$). (Found: $[M]^+$, 301.94386. $C_{10}H_7O_3I$ requires $[M]^+$, 301.94400), 274, 259, 132.

5.1.23. 7-Methoxy-8-[(1*E*)-3-oxobut-1-enyl]-2*H*-chromen-2-one (24). Methyl vinyl ketone (11.5 cm^3, 124.2 mmol, 7.5 equiv.) was added dropwise to a mixture of 8-iodo-7-methoxyumbelliferone (**27**) (5.0 g, 16.6 mmol), tetrabutylammonium bromide (18.52 g, 56.3 mmol, 3.4 equiv.), triethylamine (7.83 cm^3, 56.3 mmol, 3.4 equiv.) and palladium(II) acetate (373 mg, 1.7 mmol, 0.1 equiv.) in deoxygenated dimethylformamide (125 cm^3) at rt and under N_2. The mixture was heated to 100°C for 56 h, allowed to cool to rt and filtered through celite. Water (200 cm^3) was added and the mixture was extracted with ethyl acetate (4×500 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:2) to give the title compound **24** as colourless needles (2.64 g, 65%), mp 138–139°C (lit.[18] 140–141°C); R_f 0.28 (EtOAc/*n*-hexane, 2:1); ν_{max} (film, NaCl Plate)/cm^{-1} 3060–3091 (w, Ar-H), 1732 (lactone CO), 1667 (ketone CO); δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s, COC*H*$_3$), 4.00 (3H, s, OC*H*$_3$), 6.30 (1H, d, *J*=9.5 Hz, C(3)H), 6.91 (1H, d, *J*=8.6 Hz, C(6)H), 7.35 (1H, d, *J*=16.6 Hz, C(12)H), 7.45 (1H, d, *J*=8.6 Hz, C(5)H), 7.65 (1H, d, *J*=9.5 Hz, C(4)H), 7.98 (1H, d, *J*=16.6 Hz, C(11)H); δ_C (100 MHz, $CDCl_3$) 28.0 (CO*C*H$_3$), 57.4 (O*C*H$_3$), 108.1 (C6), 112.0 and 113.3 (C8 and C10), 113.9 (C3), 130.5 (C5), 131.7 (C11), 132.9 (C12), 143.9 (C4), 154.2, 160.4 and 162.1 (C7, C9 and C2), 200.0 (*C*OCH$_3$); *m/z* (EI) 244 ($[M]^+$). (Found: $[M]^+$, 244.07348. $C_{14}H_{12}O_4$ requires $[M]^+$, 244.07356), 229, 213 (100%), 201, 158, 115, 102, 63, 43.

5.1.24. 7-Methoxy-2-oxo-2*H*-chromene-8-carbaldehyde (28). A solution of *i*-propylmagnesium chloride (2 cm^3, 4.0 mmol, 1.2 equiv.) was added dropwise to a mixture of 7-iodo-8-methoxyumbelliferone (**27**) (1 g, 3.3 mmol) in anhydrous tetrahydrofuran (20 cm^3) at −78°C, under N_2. The mixture turned to a clear orange solution and was stirred at −78°C for 45 min. *N*-Formylmorpholine (3.3 cm^3, 33.0 mmol, 10.0 equiv.) was added dropwise. The mixture was allowed to stir at 0°C for 2 h, and 30 min at rt. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (10 cm^3) and water (10 cm^3). The mixture was extracted with ethyl acetate (5×20 cm^3). The combined organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting crude product was triturated with cold ethyl acetate and filtered to give the title compound **28** as a yellow solid (465 mg, 75%), mp 208–209°C; R_f 0.19 (EtOAc/*n*-hexane, 2:1); ν_{max} (film, NaCl Plate)/cm^{-1} 3000 (w, Ar-H), 1724 (lactone CO), 1694 (aldehyde CO); δ_H (400 MHz, $CDCl_3$) 4.02 (3H, s, OC*H*$_3$), 6.32 (1H, d, *J*=9.6 Hz, C(3)H), 6.95 (1H, d, *J*=8.8 Hz, C(6)H), 7.64 (1H, d, *J*=8.8 Hz, C(5)H), 7.65 (1H, d, *J*=9.6 Hz, H$_4$), 10.65 (1H, s, CO*H*); δ_C (100 MHz, $CDCl_3$) 57.1 (O*C*H$_3$), 108.5 (C6), 113.0 and 113.3 (C8 and C10), 114.5 (C3), 134.4 (C5), 143.3 (C4), 156.5 (C9), 159.7 (C2), 163.6 (C7), 187.1 (C11); *m/z* (CI) 222 ($[M+NH_4]^+$, 100%), 205 ($[M+H]^+$). (Found: $[M+H]^+$, 205.05018. $C_{11}H_9O_4$ requires $[M+H]^+$, 205.05008).

5.1.25. 8-(3-Acetyloxiran-2-yl)-7-methoxy-2*H*-chromen-2-one (29). Chloroacetone (0.13 cm^3, 1.6 mmol, 3.0 equiv.) and potassium carbonate (440 mg, 3.2 mmol, 6.0 equiv.) were added to a solution of aldehyde **28** (100 mg, 0.53 mmol) in anhydrous acetonitrile (5 cm^3) at rt under N_2. The mixture was stirred for 30 h and quenched by the addition of water (10 cm^3). The mixture was extracted with ethyl acetate (2×10 cm^3) followed by dichloromethane (3×10 cm^3). The organic extracts were washed with brine (30 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting pale yellow solid was triturated with cold ethyl acetate to afford the pure title compound **29** as a white solid (90 mg, 65%), mp 158–159°C; R_f 0.26 (EtOAc/*n*-hexane, 2:1). (Found: C, 64.2; H, 4.6. $C_{14}H_{12}O_5$ requires C, 64.5; H, 4.6%); ν_{max} (film, NaCl Plate)/cm^{-1} 3009–3083 (w, Ar-H), 1725 (br, lactone and ketone CO); δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, COC*H*$_3$), 3.95 (3H, s, OC*H*$_3$), 4.15 (1H, d, *J*=2.2 Hz, C(11)H or C(12)H), 4.27 (1H, d, *J*=2.2 Hz, C(11)H or C(12)H), 6.27 (1H, d, *J*=9.6 Hz, C(3)H), 6.87 (1H, d, *J*=8.6 Hz, C(6)H), 7.45 (1H, d, *J*=8.6 Hz, C(5)H), 7.63 (1H, d, *J*=9.6 Hz, C(4)H); δ_C (100 MHz, $CDCl_3$) 25.9 (CO*C*H$_3$), 51.4 (C11), 56.8 (O*C*H$_3$), 59.7 (C12), 108.1 (C3), 110.7 (C10), 113.2 (C8), 113.9 (C6), 130.0 (C5), 143.7 (C4), 154.5 and 160.3 (C9 and C7), 162.1 (C2), 205.5 (C13); *m/z* (EI) 260 ($[M]^+$). (Found: $[M]^+$, 260.06851. $C_{14}H_{12}O_5$ requires $[M]^+$, 260.06848), 218, 189 (100%), 131, 43.

5.1.26. 8-(3-Isopropenyloxiran-2-yl)-7-methoxy-2*H*-chromen-2-one (3). A mixture of methyl triphenylphosphonium bromide (70 mg, 0.2 mmol, 1.4 equiv.) and diisopropylamine (0.24 cm^3, 0.25 mmol, 1.6 equiv.) in anhydrous tetrahydrofuran (2 cm^3) was cooled down to −45°C, under N_2. *n*-Butyllithium (0.122 cm^3, 0.2 mmol, 1.4 equiv.) was added dropwise and the resulting clear solution was allowed to stir at −45°C for 1 h and an additional 1 h at 0°C. Epoxy ketone **29** (35 mg, 0.15 mmol) was then added and stirring was continued for 2 h at 0°C and for 18 h at rt. The reaction was quenched by the addition of water (2 cm^3) and the mixture was extracted with ethyl acetate (3×5 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford a yellow oil. The crude material was purified by flash column chromatography (SiO_2; EtOAc/*n*-hexane, 1:1) to give the title compound **3** as a white solid (10 mg, 28%), mp 119–120°C (lit.[19] 118–120°C); R_f 0.52 (EtOAc/*n*-hexane, 2:1); ν_{max} (film, NaCl Plate)/cm^{-1} 3050 (Ar-H), 1724 (lactone CO); δ_H (400 MHz, $CDCl_3$) 1.87 (3H, m, C(15)H_3), 3.92 (1H, d, *J*=2.2 Hz, C(11)H), 3.97 (3H, s, OCH_3), 3.99 (1H, d, *J*=2.2 Hz, C(12)H), 5.08 (1H, m, C(14)H), 5.30 (1H, m, C(14)H), 6.27 (1H, d, *J*=9.5 Hz, C(3)H), 6.87 (1H, d, *J*=8.7 Hz, C(6)H), 7.42 (1H, d, *J*=8.7 Hz, C(5)H), 7.62 (1H, d, *J*=9.5 Hz, C(4)H); *m/z* (EI) 258 ($[M]^+$), 229, 213, 199, 189, 131, 89 (100%).

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