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A NEW APPROACH TO 1,7-DIOXASPIRO[5.5]UNDEC-4-ENES *VIA* METALLATED ALLENOL ETHERS. SYNTHESIS OF LACRIMIN A.

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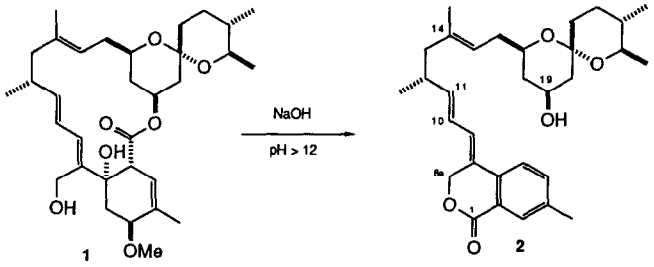
Abstract Key steps in the first total synthesis of Lacrimin A (**2**) include (a) the use of methoxyallene as an enone-1,3-dianion equivalent; (b) the use of a new copper-catalysed migratory insertion reaction to construct a tri-substituted alkene stereoselectively; and (c) the use of a Pd(0)-catalysed coupling reaction to generate an isochromanone ring.

Lacrimin A (**2**) is a member of a series of three related compounds first reported in 1983 by workers at Sankyo Co Ltd.[2] The Lacrimins, which are said to have antihypotensive activity, were obtained by chemical modification of the corresponding Milbemycins. Thus treatment of Milbemycin β_1 (**1**) with NaOH at pH >12 followed by silica gel chromatography caused cleavage of the macrolactone, relactonisation to the C8a[3] hydroxyl group and aromatisation to occur with the formation of Lacrimin A (**2**). We now give details[4] of a synthesis of Lacrimin A which was first reported at the Sheffield Stereochemistry Symposium in December 1988 at the invitation of Professor W David Ollis to whom we respectfully dedicate this paper

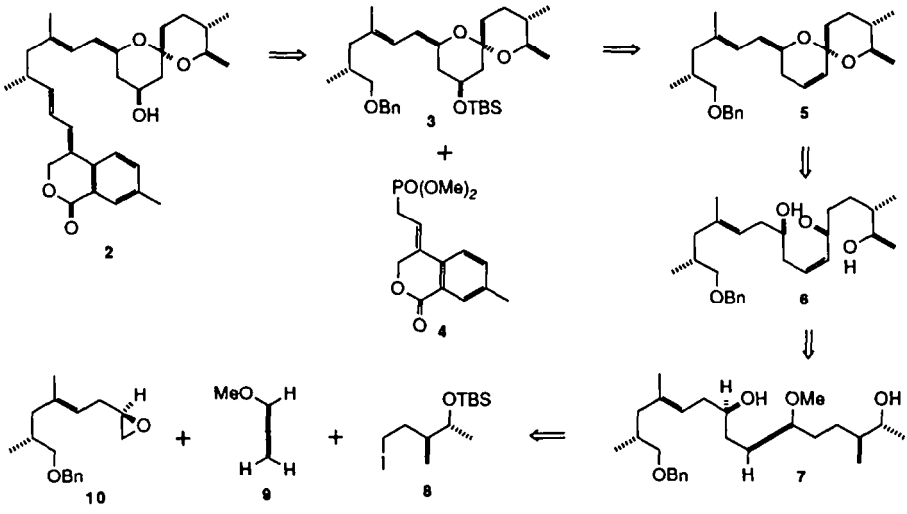


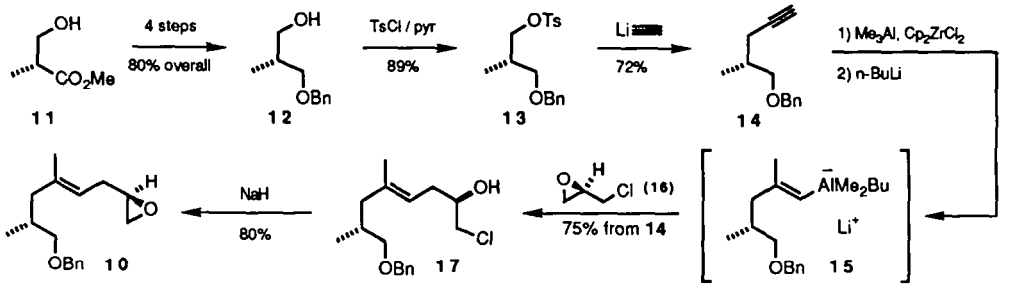
According to our retrosynthetic analysis of Lacrimin A (Scheme 1) disconnection at the C10-C11 alkene gave the spiroacetal derivative **3** and the isochromanone **4** Spiroacetal **3**, in turn, was assembled from three key fragments oxirane **10**, methoxyallene **9**, and iodoalkane **8** In the ensuing discussion we wish to emphasise the chemistry used to solve some of the stereochemical problems posed by Lacrimin A Particularly noteworthy are (a) the first synthetic application of a novel copper-catalysed migratory insertion reaction recently discovered in our laboratory[5] for the stereoselective construction of the C14-C15 tri-substituted alkene in fragment **10a**, (b) the stereoselective protonation of an alkoxyallene intermediate **7** to generate a *cis*-enone precursor **6** to the 1,7-dioxaspiro [5 5]undec-4-ene ring system of intermediate **5**, (c) the stereo- and regioselective hydration of the unsaturated spiroacetal **5** to introduce the C19 hydroxyl function; and (d) the use of a Stille cross-coupling reaction to construct the heterocyclic ring of isochromanone **4**

Synthesis of Oxirane 10. Our first approach to oxirane **10** (Scheme 2) was accomplished in 9 steps (31% overall yield). The requisite stereogenic centres were derived from commercially available (*R*)-(–)-methyl 3-hydroxy-2-methylpropionate (**11**) and (*R*)-epichlorohydrin (**16**) The latter compound was prepared in three steps from allyl alcohol (24% overall yield) according to procedures described by Sharpless and Baldwin and their co-workers[6] Negishi carboalumination[7] of the alkyne **14** proceeded smoothly and with high stereoselectivity to the alkenylalane which was converted to the aluminate complex **15** with *n*-BuLi Subsequent reaction with (*R*)-epichlorohydrin then gave the chlorohydrin **17** in 75% overall yield from **14** Finally treatment with sodium hydride effected ring closure to the desired oxirane **10** in 80% yield

Dedicated to Professor W. David Ollis on the occasion of his 65th birthday.

SCHEME 1. Retrosynthetic Analysis of Lacrimin A

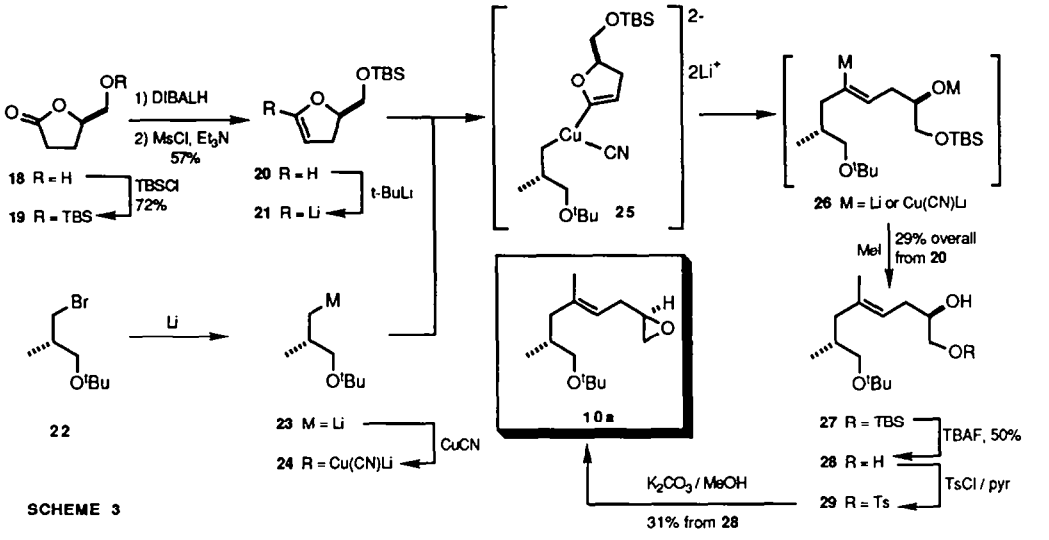




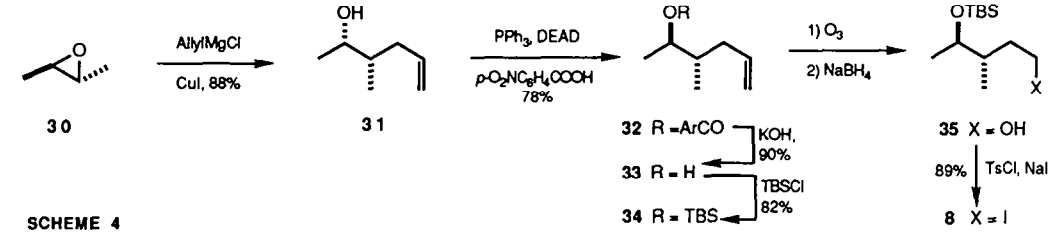
SCHEME 2

An alternative approach to the analogous *t*-butyl-protected oxirane **10a** (Scheme 3) began with the known homochiral intermediates **18** (prepared from D-glutamic acid according to known procedures[8]) and the bromoalkane **22** previously described by a Hoffmann-LaRoche group[9]. Lactone **18** was converted to the dihydrofuran **20** (3 steps; 41% overall yield) which underwent smooth and efficient deprotonation on treatment with *t*-BuLi in Et_2O at low temperature. The resultant lithiated dihydrofuran **21** was then added at -70°C to an excess of the cyanocuprate **24**, prepared from bromoalkane **22**, to give the putative higher order cyanocuprate intermediate **25**. On warming to 0°C, intermediate **25** underwent a novel migratory insertion reaction to yield the alkenyl cyanocuprate **26**[10]. Addition of MeI then accomplished the requisite alkylation affording tri-substituted alkene **27** in 29% overall yield from dihydrofuran **20**. High field ^1H and ^{13}C NMR analysis of the product revealed a single diastereoisomer confirming the high stereoselectivity previously observed in analogous simpler systems[5]. Standard transformations were then used to achieve the target **10a**. Owing to the mediocre yields attending some of the key reactions outlined in Scheme 3[11], the more traditional route depicted in Scheme 2 was adopted.

Synthesis of Iodoalkane 8. The homochiral iodoalkane **8** was prepared from *trans*-(2*S*,3*S*)-2,3-epoxybutane (**30**) (Scheme 4), itself readily available from (2*R*,3*R*)-(+)-tartaric acid[12]. Copper-catalysed opening of **30** with allylmagnesium chloride, followed by Mitsunobu inversion[13] of the resultant alcohol **31** and protection, gave rise to **34** in 54% overall yield. Ozonolysis of **34**, followed by an *in situ* $NaBH_4$ work-up, afforded **35** which was then converted to **8** in 77% yield *via* a halogen exchange reaction.



SCHEME 3

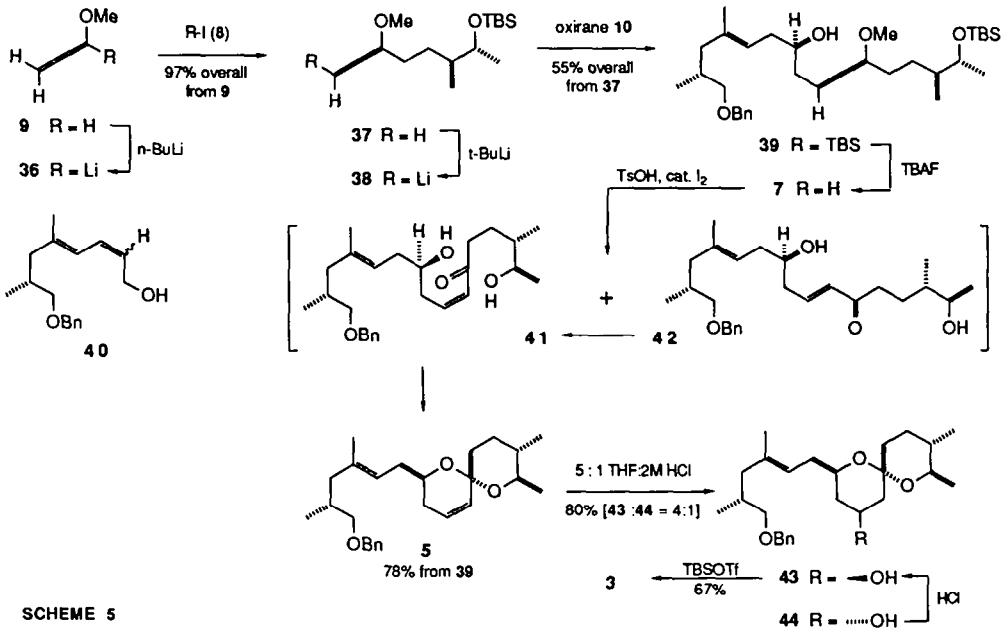


SCHEME 4

Synthesis of Spiroacetal 3. All 6 of the stereogenic centres of Lacrimin A are located in the spiroacetal fragment **3**. Four of the requisite stereogenic centres were derived from readily available "chiral pool" precursors used in the elaboration of fragments **8** and **10**. We now show how these fragments were linked and demonstrate how the remaining two stereogenic centres of the final product were introduced using thermodynamically-controlled reactions.

In order to construct the carbon backbone of the spiroacetal target, we required a means for linking oxirane **10** and iodoalkane **8** with a three-carbon enone bridge. This was accomplished (Scheme 5) by exploiting the d^1, d^3 properties of methoxyallene amply precedented in the work of Brandsma and Linstrumelle and their co-workers[14]. Thus efficient metallation of methoxyallene[15] with *n*-BuLi produced the lithio derivative **36** which was alkylated in 97% yield with iodoalkane **8** to give the allene **37**. A second metallation, this time with *t*-BuLi, was likewise efficient and produced the lithiated allene **38** which underwent alkylation with oxirane **10** to give the 1,3-dialkylated methoxyallene **39** as an inseparable mixture of diastereoisomers in 55% yield (79% based on recovered **37**). The second alkylation was complicated by a base-catalysed elimination of the oxirane ring resulting in a stereoisomeric mixture of dienes **40** as the only other major products. Curiously the second alkylation was best achieved under comparatively concentrated reaction conditions; dienes **40** were the predominant products when dilute conditions were employed. Attempts to alleviate the problem of elimination by using various organocuprate derivatives with or without Lewis acid catalysts was fruitless.

After careful chromatographic purification of **39** and removal of the silyl protecting group, the sensitive diol **7** was treated with *p*-toluenesulphonic acid and a catalytic amount of iodine in THF at room temperature for 5 h to give the



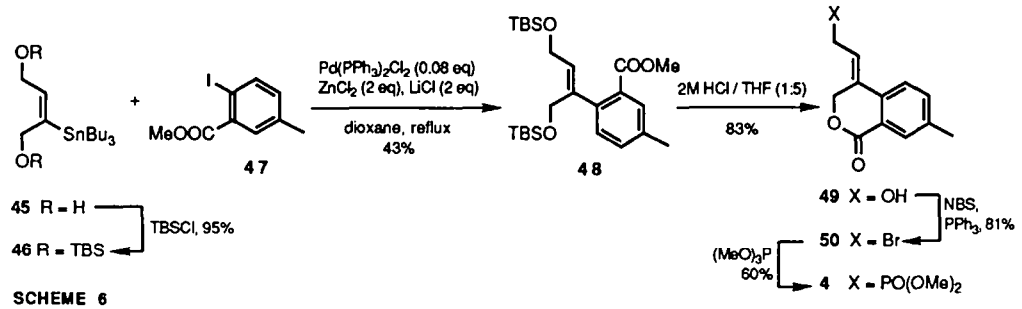
SCHEME 5

unsaturated spiroacetal **5** in 78% yield. Protonation of the methoxyallene was rapid and stereoselective[16] leading to spiroacetal **5** presumably *via cis*-enone intermediate **41**[17]. However, varying amounts of the isolable *trans*-enone **42** were also formed under the reaction conditions but this was slowly isomerised in the presence of the iodine to the the *cis*-enone and thence to spiroacetal **5**. High field ^1H and ^{13}C NMR analysis of **5** indicated a single diastereoisomer which was assigned the stereochemistry depicted in structure **5** based on the reasonable expectation that thermodynamically-controlled spirocyclisation led to a 1,7-dioxaspiro[5.5]undec-4-ene ring sytem[18] benefiting from equatorial disposition of the three appendages and maximisation of anomeric stabilisation[19].

The sixth and final stereogenic centre corresponding to C19 in the final product was likewise introduced using a thermodynamically controlled reaction. Prolonged exposure of the unsaturated spiroacetal **5** to aqueous HCl in THF at reflux resulted in regio- and stereoselective hydration of the alkene[18b] to give a 4:1 mixture of the alcohols **43** and **44**. The major isomer **43** was readily separated from **44** by column chromatography [Rf(SiO_2) 0.1 and 0.3 respectively; 30% Et_2O/hexane] and the minor isomer isomerised to a 4:1 mixture of **43** and **44** respectively thus confirming that hydration had reached equilibrium. Once again the stereochemistry of the product was governed by the preferred equatorial disposition of all 4 ring appendages reinforced by the anomeric effect. The structure and stereochemistry of the intermediate **3**, derived from **43** by silylation, was unambiguously confirmed by comparison of high field ^1H and ^{13}C NMR spectra with those previously recorded for **3** prepared by two independent routes[20].

Synthesis of Isochromanone 4. 1,1 and 1,2-Disubstituted alkenylmetallics are reported to react unsatisfactorily in palladium-catalysed coupling reactions in the absence of $ZnCl_2$ or $CdCl_2$[21, 22]. This was also found to be the case in the reaction of iodoarene **47**[23] with the unprotected alkenylstannane **45**[24] (Scheme 6) in the presence of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ as catalyst. In the absence of $ZnCl_2$ no coupling was observed, but if the reaction was carried out in the presence of $ZnCl_2$ (2 eq.) a 38% yield of impure isochromanone **49** could be obtained, in one step, after 72 h reflux in THF. Unfortunately, **49** prepared by this method could not be isolated in pure form.

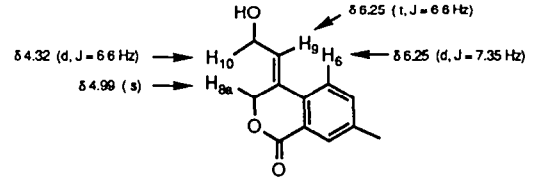
In an attempt to reduce the reaction time, the coupling of **45** with **47** was carried out in refluxing dioxane. This resulted in decomposition of the catalyst, as shown by the formation of a palladium mirror. However, by running the reaction in the presence of added LiCl, low yields of the isochromanone **49** could be obtained. The role of the LiCl, other than the apparent stabilisation of the catalyst, is not understood. LiCl is known to be essential in the palladium catalysed coupling of enol triflates with organotin reagents[25]. In this case organopalladium triflate intermediates are unable to enter the catalytic cycle but the corresponding chlorides can participate. The role of the LiCl in the case at



SCHEME 6

hand is difficult to assess since iodoarenes are known to readily take part in palladium-catalysed cross-coupling reactions[26].

The optimum conditions for the formation of pure **49** are summarised in Scheme 6. Reaction of iodoarene **47** with the protected alkenylstannane **46** in the presence of $ZnCl_2$ (2 equiv), LiCl (2 equiv), and $Pd(PPh_3)_2Cl_2$ (0.08 equiv), in refluxing dioxane, gave the pure coupled product **48** in 43% yield after 48 h at reflux. Conversion of **48** to **49** could then be readily achieved on treatment with 2M HCl in THF (1 : 5) affording **49** as a white crystalline solid (mp 93-95 °C) in 83% yield. ^1H and ^{13}C NMR showed the presence of only one double bond isomer, the (*Z*)-geometry of which was assigned on the basis of nOe difference spectroscopy (Table 1).

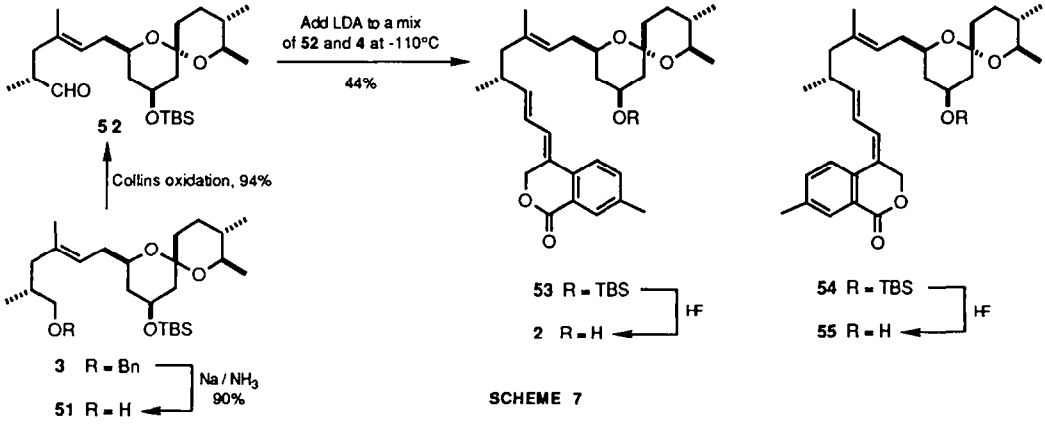


Irradiate	Observed Enhancement
H8a	H10 (12.6%)
H9	H6 (28.9%)
H10	H8a (11.1%)

Table 1. Differential n O e data observed for **49**

To complete the sequence, the hydroxyl function in **49** was converted to the corresponding bromide **50** which underwent an Arbuzov reaction with trimethyl phosphite to give the desired phosphonate **4**.

Synthesis of Lacrimin A: Finale. The last hurdle in our synthesis of Lacrimin A involved construction of the C10-C11 alkene bond. It was a hurdle which was not easily surmounted. After much experimentation a successful protocol was devised which is outlined in Scheme 7. The standard conditions for effecting the Wadsworth-Emmons reaction between phosphonate **4** and aldehyde **52** were fruitless owing in part to the instability of the lithio derivative of phosphonate **4**. Successful union of **4** and **52** was finally achieved by adding a pre-cooled (-70°C) solution of



SCHEME 7

lithium di-isopropylamide in THF to a *mixture* of **4** and **52** in THF at -110°C (bath temperature) followed by warming to -80°C whereupon a mixture of dienes was obtained in a disappointing yield of 44% at best.

Removal of the C19 silyl protecting group with HF in acetonitrile revealed a three-component mixture which was separated by HPLC. The major component eluted first[27] and gave high field ^1H and ^{13}C NMR data consistent with the data reported by the Sankyo group[2] for naturally-derived Lacrimin A. The second component was very minor (≤10%) and was not identified owing to insufficient pure material. The third and final component was assigned the structure **55** based on the spectroscopic data summarised in Figure 1.

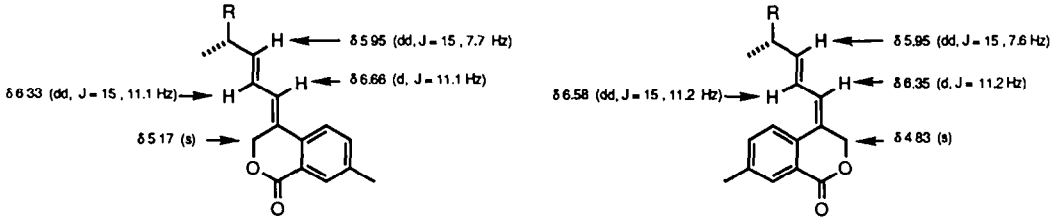
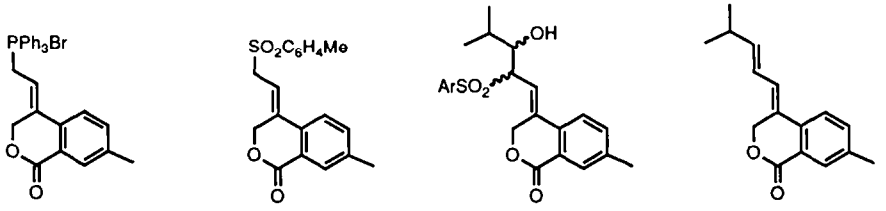


FIGURE 1. Selected NMR Data (270 MHz) for Lacrimin A and Isolacrimin A

Alternative coupling protocols based on the Julia olefination[28] and the Wittig reaction failed completely. Model studies directed toward the synthesis of diene **59** showed that the phosphonium salt **56**, prepared from bromide **50** in the usual way, produced an ylide which was too stable to react with isobutanal under a wide range of conditions including acid catalysis. The Julia approach was thwarted on two counts: first by the instability of the sulphone anion derived from **57** and secondly by the ease with which β-hydroxysulphone adduct **58** reverted to the sulphone anion and the aldehyde. Consequently good yields (81%) of the diastereomeric mixture of β-hydroxysulphone adducts **58** could only be obtained by adding a pre-cooled solution of LDA in THF to a mixture of isobutanal and sulphone **57** in THF at -110°C *in the presence of* $MgBr_2$. Unfortunately, the lability of **58** was such that it could not even be acylated with benzoyl chloride in the presence of pyridine. The mediocre yield and lack of stereocontrol in the Wadsworth-Emmons coupling of phosphonate **4** and aldehyde **52** was surprising in light of the results of a model study involving reaction of **4** and isobutanal to give **59**[68% yield of a single (*E*)-isomer]. These results suggest that, with further effort, the penultimate step of our synthesis of Lacrimin A could be greatly improved in efficiency and stereoselectivty.



56 **57** **58** **59**

In conclusion we have demonstrated once again[17, 29] the value of metallated allenol ethers in the synthesis of unsaturated spiroacetals and the utility of metallated cyclic enol ethers for the stereoselective synthesis of tri-substituted alkenes[30].

ACKNOWLEDGEMENTS. We thank Dr. Sjoerd Wadman and Dr. Richard Whitby for experimental advice and Pfizer Central Research for generous financial support. This is a contribution from the Southampton University Institute of Biomolecular Science.

Experimental

All reactions requiring anhydrous conditions were carried out in oven- or flame-dried apparatus under a static atmosphere of dry argon or nitrogen . Organic extracts were washed with the stated saturated aqueous solutions, dried over $MgSO_4$ and concentrated at aspirator pressure using a rotary evaporator unless otherwise stated. Column chromatography, under pressure, was carried out

on Colpak Sorbsil C60 (40/60) silica or on basic alumina (Brockmann grade 1) deactivated with 5% water. Column dimensions are quoted as diameter x length. Thin layer chromatography (tlc) was carried out on Camlab Alugram Sil. G/UV$_{254}$ plates coated to a depth of 0.25 mm.

All commercial reagents and solvents were used as obtained except for the following which were purified by distillation from the drying agents stated in parentheses: THF (Na / benzophenone), Et_2O (Na / benzophenone), benzene (Na wire), toluene (Na wire), MeOH [$Mg(OMe)_2$], CH_2Cl_2 (P_2O_5), dioxane (Na / benzophenone), pentane (CaH_2), 1,2 dichloroethane (CaH_2), ethylene glycol (Na wire), HMPA (CaH_2), Et_3N (CaH_2), *i*-Pr_2NH (CaH_2), pyridine (CaH_2), MsCl (CaH_2), 2,6 lutidine (CaH_2), $P(OMe)_3$ (Na wire), BF_3.OEt_2. N-Bromosuccinimide was recrystallised from water and TsCl from petrol; CuI was purified by continuous extraction with THF. NaH was used as a dispersion in mineral oil which was washed with petrol prior to use. Petrol refers to the 40-60°C fraction of petroleum ether.

^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard (δ 0.00). Signals are assigned as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br); n.O.e experiments were carried out on a Bruker AM 360 spectrometer.^{13}C NMR were recorded using the central peak of the $CDCl_3$ signal as an internal standard (δ 77.2). The multiplicities of ^{13}C NMR signals are assigned as being singlet (s), doublet (d), triplet (t) or quartet (q) depending on the number of attached protons (0, 1, 2 or 3 respectively), as determined by off resonance decoupling or DEPT techniques. Infra red spectra were obtained as liquid films or in solution using a polystyrene film as an external standard. Absorptions are described as strong (s), medium (m), weak (w) or broad (br). Unless otherwise stated, mass spectra were recorded in the EI mode on samples judged to be ≥90% pure by tlc and high field ^{1}H and ^{13}C NMR spectroscopy. Optical rotations were measured on an Optical Activity AA-100 polarimeter using 5 or 50 mm cells.

(2*S*)-3-Benzyloxy-2-methyl-1-*p*-(toluenesulphonyloxy)propane (13). To an ice-cooled solution of **12** (4.0 g, 22.2 mmol) and pyridine (4.5 ml, 55.5 mmol) in CH_2Cl_2 (50 ml) under nitrogen, was added solid TsCl (5.08 g, 26.6 mmol) . The reaction mixture was stirred with cooling for 15 minutes then at room temperature for 24 h. The excess TsCl was destroyed with 1,3-dimethylaminopropylamine (1.7 ml, 13.5 mmol) and the reaction mixture washed with 2M HCl, water and $NaHCO_3$, dried and concentrated to afford a yellow liquid (7.27 g). The crude material was chromatographed (SiO_2, 60 x 70mm, 20% Et_2O in petrol) affording **13** (6.59 g, 89%) : $[\alpha]_D$(25°C)+7.3° (*c*. 1.0 in MeOH); IR (film) 3090 w, 3070 m, 3040 m, 2980 m, 2930 m, 2870 m, 1600 m, 1455 m, 1365 s, 1195 s, 1185 s, 1100 s, 980 s, 950 m, 840 m, 820 m, 670 m cm^{-1}; ^{1}H NMR (360 MHz) 7.83 (2H, d, J = 8.1 Hz), 7.34 (7H, m), 4.45 (2H, s), 4.06 (1H, dd, J = 9.3, 5.7 Hz) , 4.01 (1H, dd, J = 9.3, 5.7 Hz) , 3.36 (1H, dd, J = 9.3, 5 3 Hz), 3.32 (1H, dd, J = 9.3, 6.7 Hz), 2.41 (3H, s), 2.12 (1H, m), 0.95 (3H, d, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) 144.79 s, 138.32 s, 133.09 s, 129.91 d, 128.44 d, 128.01 d, 127.67 d, 127.54 d, 73.15 t, 72.35 t, 71.18 t, 33.78 d, 21.72 q, 13.73 q; m/z 334 (M$^+$, 3%), 243 (1), 227 (2), 179 (2), 155 (13), 139 (2), 107 (42), 91 (100), 56 (26).

(4*R*)-5-Benzyloxy-4-methyl-1-pentyne (14). To an ice-cooled suspension of lithium acetylide ethylenediamine complex (3.25 g, 90%, 31.8 mmol) in THF (50 ml) under argon was added **13** (5.31 g, 15.9 mmol) in THF (25 ml) followed by HMPA (5.5 ml, 31.8 mmol) . The resulting brown suspension was stirred with cooling for 30 minutes then at room temperature for a further 9 h. After quenching with water, the two phase mixture was separated and the aqueous phase re-extracted with Et_2O. The combined organic phases were dried and concentrated affording a colourless liquid (5.58 g). Chromatography of the crude material (SiO_2 , 50 x 75 mm, 10% Et_2O in petrol) afforded **14** (2.16 g, 72%) : $[\alpha]_D$ +16° (c. 1.2 in $CHCl_3$) [Lit.[20b] +16.3 ° (*c*. 0.95 in $CHCl_3$)] identical by IR and NMR spectroscopy with a sample previously prepared by an alternative route.

(2*R*)-1-Chloro-2,3-epoxypropane (16) The title compound was prepared by a modification of a procedure of Baldwin and co-workers[8b] from (2*R*)-(-)-glycidyl *p*-toluenesulphonate which was prepared according to Sharpless and co-workers[14] by asymmetric epoxidation of allyl alcohol. Thus, concentrated HCl (15 ml) was added to solid (2*R*)-(-)-glycidyl *p*-toluenesulphonate (10.6 g, 46.4 mmol) and the mixture stirred at room temperature for 24 h. The mixture was then extracted into Et_2O, washed with $NaHCO_3$, dried and concentrated to afford a colourless oil (11.7 g). The crude oil was treated with sodium ethyleneglycolate (100 ml) and stirred at room temperature for 30 minutes. The pressure was then reduced to 0.1 mm Hg and the volatile materials trapped on a cold finger (-78°C). The crude distillate was redistilled (b. p. 114-8 °C / 760 mm Hg; Lit.[8b] 115-7°C / 760 mm Hg) from calcium hydride to give pure **16** (2.31 g, 54%) : $[\alpha]_D$(20°C) -27.5 ° (*c*. 2.9 in MeOH) [Lit.[8b] -34.3 ° (*c*. in MeOH)]; IR (film) 3080 m, 3020 s, 2980 m, 2940 m, 1430 s, 1400 m, 1280 s, 1270 s, 1250 s, 960 s, 925 s, 850 s, 760 s, 720 s cm^{-1}; ^{1}H NMR (60 MHz) 3 6 (2H, d, J = 6 Hz), 3.3 (1H, m), 2.9 (1H, t, J = 4 Hz), 2.2 (1H, dd, J = 5, 2 Hz).

(4*E*)-(2*R*,7*R*)-8-Benzyloxy-1-chloro-5,7-dimethyl-4-octene-2-ol (17). Trimethylaluminium (13.2 ml, 2.0M in hexanes, 26.4 mmol) was added to a solution of zirconocene dichloride (1.29 g, 4.4 mmol) in 1,2-dichloroethane (25 ml) under argon and the resultant green solution stirred at room temperature for 15 minutes. A solution of **14** (1.66 g , 8.8 mmol) in 1,2-dichloroethane (5 ml) was then added and the solution stirred at room temperature for a further 66 h. The solvent and excess trimethylaluminium were removed by distillation (25 to 50°C, 0.9 mm Hg, 4 h) and the resultant yellow residue extracted into pentane (5 x 10 ml) and transferred, *via* syringe, to another flask cooled to -78° C under nitrogen. The mechanically stirred suspension was then treated with *n*-BuLi (4.4 ml, 2.5M in hexanes, 10.0 mmol) causing a white precipitate to form. The mixture was then stirred for 1.5 h during which time the temperature was allowed to rise to -30°C. (*R*)-epichlorohydrin (**16**) (1.06 g, 11.4 mmol) in pentane (5 ml) was then added and the reaction mixture transferred to an ice bath (0°C). After stirring for 2.5 h the reaction was quenched by the careful addition of water and the mixture acidified to pH 2 (2M HCl) and extracted into Et_2O. The ethereal extracts were dried and concentrated to afford an orange oil (2.94 g). The crude material was purified by chromatography (SiO_2, 60 x 80 mm, 30% Et_2O in petrol) affording **17** (1.96 g, 75%) : $[\alpha]_D$(20°C) -2.3° (*c*. 2.2 in MeOH) ; IR (film) 3450 m, 3110 w, 3090 w, 3060 w, 2980 s, 2940 s, 2890 s, 1510 w, 1465 m, 1380 m, 1100 s, 1085 s, 750 s, 710 s cm^{-1}; ^{1}H NMR (360 MHz) 7.25-7.45 (5H, m) , 5.11 (1H, tq, J = 7.4, 1 Hz), 4.47 (2H, s), 3.76-3.85 (1H, m), 3.57 (1H, ddd, J = 11.1, 3.7, 2.2 Hz), 3.44 (1H, ddd, J = 11.1, 6.6, 3.1 Hz), 3.28 (1H, dd, J = 9.1, 5.8 Hz), 3.21 (1H, ddd, J = 9.1, 6.6, 1.6 Hz), 2.56 (1H, br s, OH), 2.28 (2H, apparent t, J = 7 Hz), 2.16 (1H, dd, J = 13.1, 5.7 Hz), 1.93-2.05 (1H, m), 1.77 (1H, dd, J = 13.1, 8.2 Hz), 1.59 (3H, s),

0.86 (3H, d, J = 6.6 Hz); ^{13}C NMR (90 MHz) 138.97 s, 137.94 s, 128.47 d, 127.68 d, 127.60 d, 120.25 d, 75.84 t, 73.23 t, 71.61 d, 49.72 t, 44.52 t, 33.21 t, 31.81 d, 17.23 q, 16.43 q; m/z 298 (M$^+$, 0.2%), 296 (0.8), 260 (1), 242 (2), 205 (4), 169 (8), 148 (100), 135 (13), 110 (10), 91 (90); (Found : M$^+$ ^{35}Cl, 296.1530 . $C_{17}H_{25}{}^{35}ClO_4$ requires 296.1545) .

(4*E*)-(2*R*,7*R*)-1-Benzyloxy-2,4-dimethyl-7,8-epoxy-4-octene (10). To an ice-cooled, pre-washed, suspension of NaH (0.64 g, 50% in oil, 13.2 mmol) in THF (50 ml) under nitrogen was added **17** (1.96 g, 6.6 mmol) in THF (10 ml) followed by HMPA (2.3 ml, 13.2 mmol). The resultant mixture was stirred, with cooling, for 45 minutes and then at room temperature for a further 18h. The reaction was quenched by the careful addition of water and extracted into Et_2O The ethereal extracts were dried and concentrated to afford an oil (2.15 g). The crude material was purified by chromatography (SiO_2, 60 x 35 mm, 10% Et_2O in petrol) affording **10** (1.37 g, 80%) : $[\alpha]_D$(20°C) +1.9° (*c*. 2.1 in MeOH) ; IR (film) 3100 w, 3050 m, 2990 s, 2980 s, 2930 s, 2870 s, 1460 s, 1370 m, 1105 s, 1035 m, 970 m, 840 m, 745 s, 705 s cm^{-1}; ^{1}H NMR (360 MHz) 7.45-7.3 (5H, m), 5.18 (1H, tq, J = 7.3, 1 Hz), 4.51 (2H, s), 3.36 (1H, dd, J = 9.0, 5.7 Hz), 3.26 (1H, dd, J = 9.0, 6.6 Hz), 2.84-2.90(1H, m), 2.73 (1H, dd, J = 4.5, 4.4 Hz), 2.50 (1H, dd, J = 5.0, 2.7 Hz), 2.38 (1H, apparent dt, J = 14.3, 6.3 Hz), 2.10-2.23 (2H, m incorporating a 1H, dd, J = 13.1, 6.0 Hz), 1.84-1.98 (1H, m), 1.74 (1H, dd, J = 13.1, 8.7 Hz), 1.62 (3H, s), 0.91 (3H, d, J = 6.7 Hz) ;^{13}C NMR (90 MHz) 138.98 s, 136.84 s, 128.33 d, 127.52 d, 127.42 d, 119.74 d, 75.78 t, 73.09 t, 51.74 d, 46.48 t, 44.23 t, 31.70 d, 30.95 t, 17.04 q, 16.21 q; m/z 260 (M$^+$, 0.5%), 242 (1), 201 (1), 169 (5), 151 (7), 148 (39), 111 (14), 91 (100).

(5*R*)-5-(*tert*-Butyldimethylsiloxy)methyltetrahydrofuran-2-one (19). TBSCl (1.88 g, 12.5 mmol) in CH_2Cl_2 (10 ml) was added to a solution of **18** (1.32 g, 11.4 mmol) and imidazole (1.16 g, 17.1 mmol) in CH_2Cl_2 (10 ml) under nitrogen . The resultant white suspension was stirred at room temperature for 17 h and then diluted with CH_2Cl_2 , washed with 2M HCl, water and $NaHCO_3$, dried, and concentrated to give an oil (2.8 g). The crude material was chromatographed (SiO_2 , 65 x 40 mm , 40% Et_2O in petrol) affording **19** (1.88 g , 72%) : $[\alpha]_D$(24°C) -11.8°C (*c*. 2 in $CHCl_3$); IR (film) 2970 s, 2940 s, 2900 m, 2870 s, 1780 s, 1470 m, 1370 m, 1265 s, 1180 s, 1130 s, 1090 s, 1040 m, 1000 m, 950 s, 845 s, 790 s cm^{-1}; ^{1}H NMR (90 MHz) 4.55 (1H, m), 3.85 (1H, dd, J = 11.2, 3.4 Hz) , 3.65 (1H, dd, J = 11.2, 3.4 Hz) , 2.50 (2H, m), 2.20 (2H, m), 0.9 (9H, s), 0.1 (6H, s).

(5*R*)-5-(*tert*-Butyldimethylsiloxy)methyl-4,5-dihydrofuran (20). Dibal-H (3.7 ml, 1.5M in toluene , 5.6 mmol) was added to a solution of **19** (1.0 g, 4.3 mmol) in CH_2Cl_2 (5 ml) cooled to -70°C under nitrogen and the solution stirred for 30 minutes. The reaction mixture was then poured into 0.2M HCl and extracted into CH_2Cl_2 . The combined extracts were washed with $NaHCO_3$, dried and concentrated affording an oil (0.96 g). The crude lactol was taken up in CH_2Cl_2 (10 ml), cooled to -20°C under nitrogen, and treated with Et_3N (1.8 ml, 1.31 g, 12.9 mmol) followed by MsCl (0.45 ml, 0.64 g, 5.6 mmol). The resultant white suspension was stirred at -20°C for 30 minutes and then refluxed for a further 2.5 h. The mixture was then diluted with CH_2Cl_2 , washed with water, dried (Na_2SO_4) and concentrated affording a brown oil (1.1 g). The crude material was chromatograhed (basic Al_2O_3 / 5% water, 40 x 90 mm, 2% Et_3N in petrol) affording **20** (520 mg, 57%) : $[\alpha]_D$(24°C) -57.6° (*c*. 1.9 in MeOH) ; IR (film) 3110 w, 2960 s, 2940 s, 2900 m, 2870 s, 1625 s, 1475 m, 1470 m, 1390 m, 1365 m, 1260 s, 1145 s, 1060 s, 845 s, 780 s, 710 m cm^{-1}; ^{1}H NMR (270 MHz) 6.26 (1H, q, J = 2.4 Hz) , 4.85 (1H, q, J = 2.6 Hz), 4.60 (1H, dddd, J = 10, 7, 6, 5 Hz), 3.71 (1H, dd, J = 10.8, 6.0 Hz) , 3.61 (1H, dd, J = 10.8, 6.0 Hz) , 2.63 (1H, ddt, J = 15.1, 10.3, 2.3 Hz), 2.39 (1H, ddt, J = 15.1, 7.3, 2.4 Hz), 0.91 (9H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (67.5 MHz) 145.29 d, 99.11 d, 81.55 d, 65.51 t, 31.36 t, 26.09 q, 18.54 s, -5.09 q, -5.14 q.

(4*E*)-(2*R*,7*R*)-8-*tert*-Butoxy-1-(*tert*-butyldimethylsiloxy)-5,7-dimethyl-4-octen-2-ol (27). A solution of **22** (1.5 g, 7.2 mmol) in pentane (5 ml) was added to a pre-washed suspension of lithium dispersion (0.8 g, 25 wt.%, 28.7 mmol) in pentane (10 ml) under argon. The mixture was then sonicated for 7 h with the formation of a yellow solution and a brown sediment. Pentane was added periodically to keep the volume at 15 ml. Titration against 1,3-diphenylacetone *p*-tosylhydrazone showed the molarity, of the oganolithium **23** to be approximately 0.25 M.

To a solution of **20** (0.46 g, 2.1 mmol) in Et_2O (12 ml) cooled to -70°C under argon was added *t*-BuLi (1.3 ml, 1.7 M in pentane, 2.2 mmol). The resultant solution was stirred at -70°C for 5 minutes and then with ice-cooling for 50 minutes. Meanwhile **23** (11.2 ml, 0.25 M in pentane, 2.8 mmol) was added to a suspension of CuCN (0.19 g, 2.1 mmol) in Et_2O (10 ml) cooled to -70°C under argon. After stirring for 5 minutes the cyanocuprate **24** was transferred to an ice bath and stirred for a further 30 minutes.

The solution of the lithiated dihydrofuran **21** was transferred *via* syringe to the cyanocuprate **24** and the mixture stirred with ice-cooling for 4 h. Methyl iodide (0.65 ml, 1.49 g, 10.5 mmol) was then added and the mixture stirred at room temperature for a further 10 h. The mixture was then poured into saturated NH_4Cl / 10% NH_3 and extracted into Et_2O. The extracts were dried and concentrated affording a yellow oil (0.91 g). The crude material was chromatographed (SiO_2, 50 x 65 mm, 10-20% Et_2O in petrol) affording **27** (0.20 g , 29%) : $[\alpha]_D$(24°C) -3.5° (*c*. 1.1 in $CHCl_3$) ; IR (film) 3460 m, 3000 s, 2980 s, 2950 s, 2880 s, 1605 w, 1590 w, 1470 m, 1400 m, 1370 s, 1265 s, 1210 s, 1110 s, 1090 s, 850 s, 790 s cm^{-1}; ^{1}H NMR (270 MHz) 5.16 (1H, t, J = 7.1 Hz) , 3.64 (2H, m), 3.44 (1H, m), 3.18 (1H, dd, J = 8.6, 5.5 Hz), 3.06 (1H, dd, J = 8.6, 6.8 Hz), 2.42 (1H, br s), 2.17 (3H, m), 1.74 (2H, m), 1.60 (3H, s), 1.17 (9H, s), 0.90 (9H, s), 0.83 (3H, d, J = 6.4 Hz), 0.07 (6H, s); ^{13}C NMR (67.5 MHz) 136.78 s, 121.06 d, 72.52 s, 72.12 d, 67.25 t, 66.75 t, 44.63 t, 32.09 d, 31.86 t, 27.74 q, 26.06 q, 18.47 s, 17.19 q, 16.28 q, -5.19 q; m/z 330 (M$^+$, 10%), 314 (40), 302 (82), 273 (2), 215 (100), 199 (8), 171 (18), 108 (59), 75 (47), 57 (97).

(4*E*)-(2*R*,7*R*)-8-*tert*-Butoxy-5,7-dimethyl-4-octene 1,2-diol (28). TBAF (1.7 ml, 1.0M in THF, 1.7 mmol) was added to a solution of **27** (190 mg , 0.57 mmol) in THF (5 ml) under argon and the resultant brown mixture stirred at room temperature for 15 minutes. The mixture was then diluted with brine and extracted into Et_2O. The ethereal extracts were dried and concentrated affording a brown oil (196 mg). The crude material was chromatographed (SiO_2, 30 x 30 mm, 90% Et_2O in petrol) affording **28** (69 mg, 50%) : $[\alpha]_D$(25°C) +1° (*c*. 1 in $CHCl_3$); IR (film) 3380 m, 3000 s, 2940 s, 2900 s, 1470 m, 1400 m, 1370 s, 1250 m, 1210 s, 1090 s, 1050 m, 1030 m, 890 m cm^{-1}; ^{1}H NMR (270 MHz) 5.14 (1H, t, J = 7.1 Hz), 3.71 (1H, m), 3.64 (1H, dd, J = 11.2, 2.9 Hz), 3.44 (1H, dd, J = 11.1, 7.2 Hz), 3.18 (1H, dd, J = 8.6, 5.5 Hz), 3.06 (1H, dd, J = 8.5, 6.8 Hz), 2.99 (1H, br s), 2.18 (3H, m), 1.74 (2H, m),1.59 (3H, s), 1.15 (9H, s), 0.82 (3H, d, J = 6.2 Hz); ^{13}C NMR (67.5 MHz) 137.56 s, 120.64 d, 72.59 s, 72.35 d, 67.19 t, 66.36 t, 44.62 t, 32.19 t, 32.05 d, 27.68 q, 17.20 q, 16.32 q.

(4*E*)-(2*R*,7*R*)-1-*tert*-Butoxy-2,4-dimethyl-7,8-epoxy-4-octene (10a). TsCl (59 mg, 0.31 mmol) in CH_2Cl_2 (2 ml) was added to a solution of **28** (69 mg, 0.28 mmol), pyridine (0.07 ml, 0.84 mmol) and DMAP (a few crystals) in CH_2Cl_2 (3 ml) under nitrogen and the solution stirred at room temperature for 17 h. The mixture was then diluted with CH_2Cl_2 , washed with 2M HCl, water and $NaHCO_3$, dried and concentrated affording an oil (142 mg). Chromatography (SiO_2, 30 x 30 mm , 50-100% Et_2O in petrol) afforded in order of elution the monotosylate **29** (53 mg, 48-68% based on recovered **28**) : IR (film) 3440 m, 3000 s, 2950 s, 1615 m, 1470 m, 1375 s, 1205 s, 1195 s, 1110 m, 1090 m, 990 m, 830 m, 680 m cm^{-1}; ^1H NMR (270 MHz) 7.79 (2H, d, J = 7.9 Hz), 7.34 (2H, d, J = 7.9 Hz), 5.05 (1H, t, J = 7 Hz), 4.04 (1H, dd, J = 6.8, 2 Hz), 3.90 (2H, m), 3.10 (2H, m), 2.45 (3H, s), 2.2 (4H, m), 1.7 (2H, m), 1.56 (3H, s), 1.16 (9H, s), 0.77 (3H, d, J = 6.4 Hz); followed by recovered **28** (21 mg , 30%). The recovered diol was recycled affording the monotosylate **29** (22 mg).

The monotosylate **29** (75 mg , 0.19 mmol) was taken up in MeOH (5 ml) and treated with solid K_2CO_3 (53 mg , 0.38 mmol). After stirring at room temperature for 1.5 h, the mixture was concentrated, taken up in water and extracted into Et_2O. The combined ethereal extracts were dried and concentrated affording an oil (56 mg). The crude material was chromatographed (SiO_2 , 30 x 40 mm, 15% Et_2O in petrol) affording **10a** (28 mg , 65-31% overall) : $[\alpha]_D$(25°C) +7° (*c*. 0.7 in $CHCl_3$); IR (film) 3050 w, 2980 s, 2910 s, 1480 m, 1460 m, 1395 m, 1365 s, 1260 m, 1240 m, 1200 s, 1080 s, 1025 m, 840 m cm^{-1}; ^1H NMR (270 MHz) 5.16 (1H, t, J = 7.0 Hz), 3.18 (1H, dd, J = 8.5, 5.4 Hz), 3.07 (1H, dd, J = 8.5 , 6.8 Hz), 2.98-2.90 (1H, m), 2.73 (1H, t, J = 4.5 Hz), 2.50 (1H, dd, J = 5.0 , 2.7 Hz), 2.38 (1H, dt, J = 15, 6.4 Hz), 2.26 (1H, apparent t, J = 6.4 Hz), 2.17 (1H, dd, J = 12, 5 Hz), 1.75 (2H, m), 1.61 (3H, s), 1.17 (9H, s), 0.84 (3H, d, J = 6.2 Hz); ^{13}C NMR (67.5 MHz) 137.33 s, 119.46 d, 72.51 s, 67.18 t, 52.05 d, 46.81 t, 44.53 t, 32.00 d, 31.03 t, 27.74 q, 17.19 q, 16.27 q; m/z 226 (M^+,4%), 225 (18), 183 (4), 169 (7), 153 (10), 147 (38), 115 (10), 109 (28), 73 (36), 69 (34), 57 (100), 43 (37).

(2*S*,3*S*)-3-Methyl-5-hexen-2-ol (31). To a suspension of CuI (2.3 g, 12 mmol) in THF (40 ml) cooled to -70°C under nitrogen was added allylmagnesium chloride (130 ml, 1.5 M in THF , 195 mmol), keeping the internal temperature below -55°C. The resultant thick green suspension was recooled to -70°C before the addition of **30** (3.5 g, 48.5 mmol) in THF (20 ml). The temperature was then allowed to rise to -40°C and the reaction mixture stirred for 12 h. After warming to room temperature, the mixture was poured into NH_4Cl and extracted into Et_2O. The combined ethereal extracts were dried and concentrated to afford a slightly yellow liquid (5.59 g). The crude material was Kugelrohr-distilled [100 °C (bath) / 20 mm Hg] affording **31** (4.89 g , 88%) : $[\alpha]_D$(19°C) +5.5° (*c*. 4.1 in MeOH); IR (film) 3360 s, 3090 m, 2990 s, 2940 s, 2890 s, 1640 s, 1460 s, 1380 s, 1300 m, 1150 s, 1085 s, 995 s, 915 s cm^{-1} ; ^1H NMR (360 MHz) 5.74-5.87 (1H, m), 4.96-5.06 (2H, m), 3.73 (1H, dq, J = 4.3, 6.4 Hz), 2.25 (1H, ddd with further fine splitting, J = 13.6, 6.7, 6.7 Hz), 1.97 (1H, br s, OH), 1.90 (1H, ddd with further fine splitting, J = 13.6, 8.7, 8.7 Hz), 1.55 (1H, m), 1.15 (3H, d, J = 6.3 Hz), 0.90 (3H, d, J = 6.9 Hz); ^{13}C NMR (90 MHz) 137.56 d, 115.83 t, 70.87 d, 39.77 d, 37.49 t, 20.32 q, 14.01 q; m/z 96 (M -H_2O, 26%), 82 (3), 72 (28), 55 (52), 41 (25); (Found : M -H_2O, 96.0907. $C_7H_{12}O$ requires 96.0936) .

(4*S*,5*R*)-4-Methyl-5-(*p*-nitrobenzoyloxy)-1-hexene (32). To a stirred suspension of triphenylphosphine (6.89 g, 26.3 mmol) and *p*-nitrobenzoic acid (4.4 g, 26.3 mmol) in toluene (70 ml), cooled to -35°C under nitrogen, was added **31** (2.5 g , 21.9 mmol) in toluene (20 ml). The resultant suspension was stirred for 10 minutes before the slow addition of diethyl azodicarboxylate (4.58 g , 26.3 mmol) in benzene (20 ml), keeping the internal temperature below -30°C. The resultant orange solution was then allowed to warm to room temperature over a period of 2 h and stirred for a further 2 h. The reaction mixture was poured into $NaHCO_3$ and extracted into Et_2O . The combined extracts were washed with brine, dried and concentrated affording a heterogeneous mixture (28.3 g). The mixture was taken up in 1 : 1 Et_2O / petrol and filtered, the residue washed with 1 : 1 Et_2O / petrol, and the combined filtrate and washings concentrated to afford an oil (8.92 g). The crude material was chromatographed (SiO_2 , 60 x 130 mm, 1-50% Et_2O in petrol) affording **32** (4.52 g, 78%) : $[\alpha]_D$(22°C) -40.1° (*c*. 1.4 in $CHCl_3$); IR (film) 3130 w, 3100 w, 3000 m, 2950 m, 2900 m, 1725 s, 1650 m, 1610 m, 1530 s, 1360 s, 1280 s, 1110 s, 1020 m, 920 m, 880 m, 850 m, 725 s cm^{-1}; ^1H NMR (360 MHz) 8.29 (2H, d, J = 8 Hz), 8.21 (2H, d, J = 8 Hz), 5.73-5.86 (1H, m), 5.13 (1H, dq, J = 6, 6.3 Hz), 5.03-5.07 (2H, m), 2.20-2.32 (1H, m), 1.92-2.06 (2H, m), 1.33 (3H, d, J = 6.4 Hz), 1.05 (3H, d, J = 6.6 Hz); ^{13}C NMR (90 MHz) 164.20 s, 150.74 s, 136.45 s, 136.37 d, 130.68 d, 123.58 d, 116.55 t, 75.97 d, 37.60 d, 37.27 t, 16.30 q, 14.88 q; m/z 263 (M^+, 0.5%), 222 (2), 121 (1), 96 (100), 56 (3).

(2*R*,3*S*)-3-Methyl-5-hexen-2-ol (33). To a solution of **32** (8.17 g, 31 mmol) in THF (40 ml) was added KOH (5.2 g , 93 mmol) in water (20 ml) followed by MeOH (15 ml), until the mixture was homogeneous. The solution was stirred at room temperature for 16 h , diluted with brine and extracted into CH_2Cl_2 . The combined extracts were dried and concentrated to afford a pale yellow liquid (5.7 g). The crude material was Kugelrohr-distilled (100 °C (bath) / 20 mm Hg) affording a colourless liquid **33** (3.17 g , 90%) : $[\alpha]_D$(25°C) +0.3° (*c*. 2.1 in $CHCl_3$) ; IR (film) 3390 s, 3090m, 3000 s, 2940 s, 2900 s, 1650 m, 1460 m, 1390 m, 1105 s, 1070 s, 1000 s, 920 s, 750 m cm^{-1}; ^1H NMR (360 MHz) 5.80-5.67 (1H, m), 5.03-4.90 (2H, m), 3.58 (1H, dq, J = 6.2, 6.2 Hz), 2.42 (1H, br s, OH), 2.20 (1H, ddd with further fine splitting, J = 13.5, 5.1, 5.1 Hz), 1.85 (1H, ddd, 13.5, 8.3, 8.3 Hz), 1.60-1.47 (1H, m), 1.08 (3H, d, J = 6.3 Hz), 0.82 (3H, d, J = 6.8 Hz); ^{13}C NMR (90 MHz) 137.49 d, 115.77 t, 71.34 d, 40.06 d, 37.39 t, 19.69 q, 14.74 q .

(4S,5R)-5-(*tert*-Butyldimethylsiloxy)-4-methyl-1-hexene (34). To an ice-ccoled solution of **33** (3.06 g, 26.8 mmol) and imidazole (2.74 g, 40.2 mmol) in CH_2Cl_2 under nitrogen was added TBSCl (4.45 g, 29.5 mmol) in CH_2Cl_2 (20 ml). The resultant white suspension was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was then washed with 1M HCl and $NaHCO_3$ and dried and concentrated to afford an oil (6.14 g). The crude material was purified by chromatography (SiO_2, 50 x 65 mm , 2% Et_2O in petrol) affording **34** (5.37 g, 82%) as a colourless oil : $[\alpha]_D$(25°C) -11.7° (*c*. 2.1 in $CHCl_3$) ; IR (film) 3080 m, 2970 s, 2940 s, 2900 s, 2870 s, 1645 m, 1475 m, 1470 m, 1385 m, 1260 s, 1110 s, 1080 s, 1040 s, 1000 s, 970 s, 915 s, 845 s, 780 s cm^{-1}; ^1H NMR (360 MHz) 5.80 (1H, ddt, J = 17.1, 10.1, 7.0 Hz), 5.06-4.96 (2H, m), 3.68 (1H, dq, J = 6, 6.2 Hz), 2.25 (1H, ddd with further fine splitting, J = 12.9, 6.0, 5.9 Hz) , 1.83 (1H, ddd with further fine splitting, J = 12.9, 7.8, 7.8 Hz) , 1.63-1.50 (1H, m) , 1.10 (3H, d, J = 6.3 Hz) , 0.93 (9H, s) , 0.87 (3H, d, J = 6.8 Hz), 0.10 (6H, s); ^{13}C NMR (90 MHz) 138.16 d, 115.48 t, 71.92 d, 40.63 d, 37.37 t, 26.09 q, 19.88q, 18.27 s, 14.82 q, -4.13 q, - 4.62 q; m/z 171 (M^+ - *t*-Bu, 22%), 153 (3),

115 (7), 75 (100), 41 (6); (Found : M - *t*-Bu , 171.1222 . $C_9H_{19}OSi$ requires 171.1205).

(3*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3-methylpentan-1-ol (35). Ozone was passed through a solution of **34** (5.3 g, 23.2 mmol) in CH_2Cl_2 (80 ml) and MeOH (50 ml), cooled to -70°C, until a blue colour persisted. The system was then purged with nitrogen until the blue colouration had completely disappeared. $NaBH_4$ (1.75 g, 46 mmol) was then added followed by two further (1.75 g) portions when the temperature had risen to -60°C and -40°C (after approximately 40 and 100 minutes) . After warming to room temperature the reaction mixture was poured into brine and extracted into CH_2Cl_2. The combined extracts were dried and concentrated to afford a colourless oil (5.65 g). The crude material was chromatographed (SiO_2, 60 x 75 mm, 25% Et_2O in petrol) affording **35** (4.7 g, 87%) : IR (film) 3340 m, 2980 s, 2950 s, 2900 s, 2880 s, 1475 m, 1390 m, 1270 s, 1115 s, 1060 s, 850 s, 785 s cm^{-1}; ^1H NMR (360 MHz) 3.73-3.63 (2H, m), 3.54 (1H, dt, J = 10.9, 6.3 Hz), 2.86 (1H, br s, OH), 1.68-1.56 (2H, m),1.51 (1H, dt, J = 6.6, 6.5 Hz), 1.09 (3H, d, J = 6.3 Hz), 0.88 (3H, d, J = 6.7 Hz), 0.86 (9H, s), 0.05 (6H, s); ^{13}C NMR (90 MHz) 72.42 d, 60.52 t, 37.47 d, 34.85 t, 25.96 q, 20.37 q, 18.15 s, 15.64q, -4.31 q, -4.73 q; m/z 175 (M^+ -*t*-Bu, 9.1%), 157 (9), 117 (2), 115 (14), 99 (4), 75 (100); (Found : M -*t*-Bu, 175.1174 . $C_8H_{19}O_2Si$ requires 175.1154).

(3*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-1-Iodo-3-methylpentane (8). To an ice-cooled solution of **35** (4.49 g, 19.3 mmol) and pyridine (3.1 ml, 38.6 mmol) in CH_2Cl_2 (40 ml) under nitrogen was added solid TsCl (5.52 g, 28.9 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. After washing with 1M HCl and $NaHCO_3$, drying and concentration afforded an oil (9.7 g). The crude tosylate was taken up in acetone (75 ml) and treated with NaI (14.5 g , 96.5 mmol). After refluxing for 1.5 h, the heterogeneous mixture was concentrated and the residue taken up in water and extracted into Et_2O. The combined ethereal extracts were washed with $Na_2S_2O_3$, dried and concentrated to afford an oil (6.49 g). The crude material was chromatographed (SiO_2, 60 x 70 mm, 2% Et_2O in petrol) affording **8** (5.87 g, 89%) : $[\alpha]_D$(24°C) 28.3° (*c*. 2.2 in MeOH); IR (film) 2970 s, 2940 s, 2890 s, 2860 s, 1465 m, 1385 m, 1260 s, 1195 m, 1120 s, 840 s, 780 s cm^{-1}; ^1H NMR (270 MHz) 3.67 (1H, dq, J = 4.5, 6.2 Hz), 3.32 (1H, ddd , J = 9.4, 8.6, 5 Hz), 3.14 (1H, ddd, J = 9.4, 7.9, 7.8 Hz), 2.09-1.94 (1H, m), 1.69-1.50 (2H, m), 1.08 (3H, d, J = 6.2 Hz), 0.89 (9H, s), 0.87 (3H, d, J = 6.5 Hz), 0.05 (6H, s); ^{13}C NMR (67.5 MHz) 71.68 d, 41.38 d, 36.45 t, 25.97 q, 20.32 q, 18.14 s, 14.64 q, 5.94 t, -4.22 q, -4.71 q; m/z 341 (M^+-H , 0.1%), 285 (17), 157 (12), 127 (5), 115 (15), 75 (54); (Found : M-H , 341.0820. $C_{12}H_{26}IOSi$ requires 341.0799).

(6*S*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-3-methoxy-6-methyl-1,2-octadiene (37). To a solution of **9** (1.23 g, 17.5 mmol) in THF (15 ml) cooled to -35 °C under argon was added *n*-BuLi (6.3 ml, 2.5M in hexane, 15.8 mmol) at such a rate as to keep the internal temperature below -25°C . The resultant yellow solution was stirred at -25°C for 1.25 h before the addition of **8** (2.0 g , 5.8 mmol) in THF (15 ml). The solution was then stirred at -25°C for 2.5 h, poured into $NaHCO_3$ and extracted into Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and concentrated affording an oil (2.34 g). The crude material was purified by chromatography (basic Al_2O_3 / 5% H_2O, 50 x50 mm, 5% Et_3N in petrol) affording **37** (1.6 g, 97%) : $[\alpha]_D$(24°C) -14.1° (*c*. 1.3 in $CHCl_3$); IR (film) 2970 s, 2940 s, 2900 s, 2870 s, 1965 m, 1470 m, 1385 m, 1260 s, 1195 m, 1105 s, 840 s, 780 s cm^{-1}; ^1H NMR (270 MHz) 5.40 (2H, apparent t, J = 2.8 Hz), 3.68 (1H, dq, J = 4.9, 6.1 Hz), 3.40 (3H, s), 2.34-2.18 (1H, m), 2.16-2.02 (1H, m), 1.68-1.44 (3H, m), 1.04 (3H, d, J = 6.4 Hz), 0.89 (9H, s), 0.86 (3H, d, J = 6.8 Hz), 0.04 (6H, 2xs); ^{13}C NMR (67.5 MHz) 199.12 s, 134.45 s, 90.26 t, 72.05 d, 56.21 q, 39.97 d, 29.97 t, 29.62 t, 26.09 q, 19.54 q, 18.32 s, 14.49 q, -4.19 q, - 4.63 q; m/z 284 (M^+, 1%) , 252 (3), 227 (34), 199 (84), 195 (18), 159 (59), 153 (10), 93 (42), 75 (97), 73 (100).

(4*E*)-(2*R*,7*R*,9*RS*,14*S*,15*R*)-1-Benzyloxy-15-(*tert*-butyldimethylsiloxy)-11-methoxy-2,4,14-trimethyl-4,9,10-hexadecatrien-7-ol (39). To a solution of **37** (0.37 g, 1.3 mmol) in THF (3 ml) cooled to -55°C under argon was added *t*-BuLi (0.85 ml, 1.7M in pentanes, 1.4 mmol) keeping the internal temperature below -50°C. The resultant yellow solution was stirred at -55°C for 1 h before the addition of **10** (0.41 g, 1.57 mmol) in THF (3 ml) keeping the temperature below -45°C. The resultant pale yellow solution was stirred for 1 h during which time the temperature was allowed to rise to -25°C before the addition of HMPA (0.47 g, 2.7 mmol). The orange solution was stirred at -25°C for 4 h, during which time the colour changed to red and then cleared. The mixture was poured into $NaHCO_3$ and extracted into Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and concentrated to afford a yellow oil (1.15 g). The crude material was chromatographed (basic Al_2O_3 deactivated with 5% H_2O, 50 x 90 mm, 0-30% Et_2O in 95 : 5 petrol : Et_3N) affording **39** (0.39 g, 55% : 79% based on recovered **37**) : IR (film) 3460 m, 3100 w, 3080 w, 3040 w, 2970 s, 2940 s, 2870 s, 1965 m, 1670 m, 1615 m, 1470 s, 1385 s, 1260 s, 1105 s, 845 s, 780 s cm^{-1}; ^1H NMR (270 MHz) 7.36-7.28 (5H, m), 5.90-5.80 (1H, m), 5.19 (1H, t with further fine splitting, J = 7.3 Hz), 4.51 (2H, s), 3.82-3.72 (1H, m), 3.72-3.62 (1H, m), 3.39 (3H, s), 3.32 (1H, dd, J = 9.1, 5.8 Hz), 3.25 (1H, dd, J = 9.1, 6.6 Hz), 2.31-1.77 (11H, m), 1.63 (3H, s), 1.60-1.45 (2H, m), 1.04 (3H, d, J = 6.4 Hz), 0.90 (3H, m), 0.89 (9H, s), 0.85 (3H, d, J = 6.8 Hz), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (67.5 MHz) 192.71* s, 138.88 s, 137.32* s, 135.40* s, 128.49 d, 127.68 d, 127.62 d, 121.58* d, 102.85* d, 75.89 t, 73.17 t, 72.03* d, 71.25 d, 56.09 q, 44.57 t, 39.97* d, 39.55 t, 35.66* t, 31.66 d, 30.35* t, 29.74* t, 26.07q, 19.60* q, 18.28 s, 17.20 q, 16.41 q, 14.53* q, -4.21 q, -4.64 q [* denotes signals split by < 0.12 ppm due to allene diastereomers].

(2*S*,6*S*,8*R*,9*S*)-2-[(5*R*)-(2*E*)-6-Benzyloxy-3,5-dimethyl-2-hexen-1-yl]-8,9-dimethyl-1,7-dioxaspiro [5.5]undec-4-ene (5). To a solution of **39** (0.176 g, 0.32 mmol) in THF (3 ml) under nitrogen was added TBAF (2 ml, 1.0M in THF, 2 mmol) and the resultant brown solution stirred at room temperature for 90 h. *p*-Toluenesulphonic acid (0.38 mg, 2 mmol) and I_2 (*ca*. 5 mg) were then added and the mixture stirred for 5 h before washing with $NaHCO_3$ and $Na_2S_2O_3$. The organic portion was dried (Na_2SO_4) and concentrated to afford an orange oil (0.2 g). The crude material was purified by chromatography (SiO_2, 40 x 50 mm, 10-20% Et_2O in petrol) affording **5** (100 mg, 78%) : $[\alpha]_D$(25°C) -23° (*c*. 1.0 in $CHCl_3$); IR (film) 3100 w, 3080 w, 3050 m, 2970 s, 2940 s, 2880 s, 1660 w, 1460 m, 1380 m, 1250 m, 1205 m, 1095 s, 1010 s, 980 m, 740 m, 705 m cm^{-1}; ^1H NMR (270 MHz) 7.40-7.28 (5H, m), 5.91 (1H, ddd, J = 9.5, 4, 3 Hz), 5.63 (1H, dt, J = 9.5, 2 Hz), 5.24 (1H, t, J = 7.2 Hz), 4.51 (2H, s), 3.98-3.85 (1H, m), 3.56 (1H, dq, J = 9.7, 6.2 Hz), 3.34 (1H, dd, J = 9.1, 5.6 Hz), 3.25 (1H, dd, J = 9.1, 6.8 Hz), 2.1-2.4 (3H,

m), 2.03-1.85 (3H, m), 1.85-1.45 (6H, m), 1.64 (3H, s), 1.16 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.6 Hz), 0.86 (3H, d, J = 6.6 Hz); ^{13}C NMR (67.5 MHz) 138.86 s, 135.41 s, 130.74 d, 128.38 d, 127.99 d, 127.55 d, 127.49 d, 122.11 d, 94.43 s, 75.90 t, 73.04 t, 71.68 d, 67.21 d, 44.35 t, 36.57 d, 35.36 t, 34.30 t, 31.59 d, 30.70 t, 27.81 t, 19.71 q, 18.13 q, 17.24 q, 16.32 q; m/z 398 (M$^+$, 2.5%), 307 (1), 181 (100), 121 (2), 113 (2), 107 (2), 105 (2), 91 (27), 81 (3), 69 (6); (Found : M$^+$, 398.2820. $C_{26}H_{38}O_3$ requires 398.2820).

(2*S*,4*S*,6*S*,8*R*,9*S*)-2-[(5*R*)-(2*E*)-6-Benzyloxy-3,5-dimethyl-2-hexen-1-yl]-8,9-dimethyl-4-hydroxy-1,7-dioxaspiro[5.5]undecane (43). To a solution of **5** (40 mg, 0.1 mmol) in THF (2.5 ml) was added 2M HCl (0.5 ml, 1.0 mmol) and the resultant solution refluxed for 22 h. Solid K_2CO_3 was then added until the mixture was basic, followed by water and the two phase mixture then extracted into CH_2Cl_2. The combined extracts were dried and concentrated to afford an oil (80 mg). The crude material was purified by chromatography (SiO_2, 30 x 35 mm, 10-80% Et_2O in petrol) affording, in order of elution, recovered **5** (4 mg, 10%), **44** (6.8 mg, 16%) : $[\alpha]_D$(25°C) +41.6° (*c*. 0.7 in $CHCl_3$) ; IR (film) 3520 sharp m, 3090 w, 3070 w, 3040 w, 2960 s, 2940 s, 2880 s, 1460 m, 1385 m, 1130 s, 1095 s, 1045 s, 995 m, 970 m, 950 m, 740 m, 700 m cm^{-1}; ^{1}H NMR (270 MHz) 7.37-7.24 (5H, m), 5.23 (1H, t, J = 6.6 Hz), 4.51 (2H, s), 4.11-4.0 (1H, m), 3.92-3.80 (1H, m), 3.39 (1H, dq, J = 9.9, 6.4 Hz), 3.34 (1H, dd, J = 8.9, 5.6 Hz), 3.24 (1H, dd, J = 8.9, 6.8 Hz), 2.30-2.10 (3H, m), 2.05-1.90 (1H, m), 1.80-1.75 (4H, m), 1.65-1.35 (7H, m), 1.62 (3H, s), 1.16 (3H, d, J = 6.4 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.83 (3H, d, J = 6.6 Hz) ; ^{13}C NMR (67.5 MHz) 138.93 s, 135.40 s, 128.46 d, 127.64 d, 127.57 d, 122.08 d, 98.25 s, 76.02 t, 73.11 t, 72.03 d, 65.54 d, 64.39 d, 44.40 t, 40.28 t, 38.11 t, 36.45 d, 35.78 t, 34.52 t, 31.67 d, 27.37 t, 19.77 q, 18.05 q, 17.29 q, 16.40 q ; followed by **43** (26.5 mg, 64%) : $[\alpha]_D$(25°C) +26.8° (*c*. 0.8 in $CHCl_3$) ; IR (film) 3395 br m, 3100 w, 3070 w, 3040 w, 2960 s, 2940 s, 2890 s, 1460 m, 1385 m, 1120 s, 1100 s, 1075 s, 1035 m, 1000 s, 740 m, 705 m cm^{-1}; ^{1}H NMR (270 MHz) 7.35-7.24 (5H, m), 5.21 (1H, t, J = 6.9 Hz), 4.51 (2H, s), 4.11 (1H, dddd, J = 11, 11, 5, 5 Hz), 3.60-3.44 (1H, m), 3.34 (1H, dd, J = 5.8, 9.1 Hz), 3.25 (1H, m), 3.24 (1H, dd, J = 6.6, 9.1 Hz), 2.35-2.1 (3H, m), 2.05-1.90 (3H, m), 1.85-1.45 (7H, m), 1.62 (3H, s), 1.27-1.1 (2H, m), 1.11 (3H, d, J = 6.2 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.83 (3H, d, J= 6.6 Hz); ^{13}C NMR (67.5 MHz) 138.94 s, 135.48 s, 128.47 d, 127.62 d, 127.58 d, 122.09 d, 97.57 s, 76.01 t, 73.11 t, 71.23 d, 68.23 d, 65.01 d, 44.93 t, 44.39 t, 40.56 t, 36.77 d, 35.99 t, 34.54 t, 31.67 d, 27.94 t, 19.55 q, 18.11 q, 17.29 q, 16.40 q .

To a solution of **44** (40 mg, 0.096 mmol) in THF (2.5 ml) was added 2M HCl (0.5 ml, 1.0 mmol) and the resultant solution refluxed for 29 h. Solid K_2CO_3 was added until the mixture was basic, followed by water, and the two phase mixture extracted into CH_2Cl_2. After drying and concentration the resulting oil (70 mg) was chromatographed (SiO_2, 30 x 50 mm, 50% Et_2O) affording **43** (36 mg, 90%) : spectral data as above.

(2*S*,4*S*,6*S*,8*R*,9*S*)-2-[(5*R*)-(2*E*)-6-Benzyloxy-3,5-dimethyl-2-hexen-1-yl]-4-(*tert*-butyldimethylsiloxy)-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane (3). To a solution of **43** (110 mg, 0.26 mmol) and 2,6-lutidine (92 mg, 0.86 mmol) in CH_2Cl_2 (4 ml) cooled to -25°C under nitrogen was added TBSOTf (0.092 ml, 106 mg , 0.4 mmol). The solution was stirred at -25°C for 45 minutes before diluting with CH_2Cl_2 and washing with 1M HCl, water and $NaHCO_3$. Drying and concentration afforded a yellow oil (0.3 g). The crude material was chromatographed (SiO_2, 30 x 25 mm, 10% Et_2O in petrol) affording **3** (92 mg , 67%) : $[\alpha]_D$(23°C) +31° (*c*. 0.8 in $CHCl_3$) [Lit.[20] + 27.1° (*c*. 0.94 in $CHCl_3$)]; IR (film) 3100 w, 3080 w, 3040 w, 2970 s, 2940 s, 2880 s, 1460 m, 1390 m, 1265 m, 1200 m, 1130 m, 1080 m, 1000 m, 845 m, 780 m, 705 m cm^{-1}; ^{1}H NMR (270 MHz) 7.38-7.25 (5H, m), 5.22 (1H, t, J = 6.7 Hz), 4.51 (2H, s) , 4.09 (1H, dddd, J = 11, 11, 5, 5 Hz), 3.56-3.40 (1H, m), 3.33 (1H, dd, J = 9.1, 5.8 Hz), 3.26 (1H, dd, J = 9.0, 6.7 Hz), 3.24 (1H, m), 2.30-2.10 (3H, m), 2.06-1.70 (4H, m), 1.69-1.40 (4H, m), 1.61 (3H, s), 1.35-1.14 (3H, m), 1.10 (3H, d, J = 6.2 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.88 (9H, s), 0.82 (3H, d, J = 6.6 Hz), 0.06 (6H, s); ^{13}C NMR (67.5 MHz) 138.98 s, 135.27 s, 128.47 d, 127.65 d, 127.59 d, 122.38 d, 97.63 s, 76.06 t, 73.14 t, 71.05 d, 68.11 d, 65.68 d, 45.34 t, 44.40 t, 41.35 t, 36.78 d, 36.08 t, 34.64 t, 31.73 d, 28.06 t, 26.07 q, 19.58 q, 18.25 s, 18.19 q, 17.29 q, 16.43 q, -4.21 q, -4.30 q ; m/z 530 (M$^+$, 1.3%), 473 (4), 398 (9), 313 (29), 295 (100), 181 (6), 91 (47), 73 (8); (Found : M$^+$, 530.3784 . $C_{32}H_{54}O_4Si$ requires 530.3791).

(*Z*)-1,4-Bis-(*tert*-butyldimethylsiloxy)-2-tri-*n*-butylstannyl-2-butene (46). To a solution of **45** (6.34 g, 16.8 mmol) and imidazole (3.43 g, 50.4 mmol) in CH_2Cl_2 (40 ml) under nitrogen was added TBSCl (5.57 g, 37 mmol) in CH_2Cl_2 (25 ml) and the resultant white suspension stirred at room temperature for 14 h. The mixture was then washed with 1M HCl, water and $NaHCO_3$, and then dried and concentrated to afford a colourless liquid (10.62 g). The crude material was purified by chromatography (SiO_2, 60 x 80 mm, 5% Et_2O in petrol) affording **46** as a colourless oil (9.62 g, 95%) : IR (film) 2970 s, 2940 s, 2870 s, 1470 m, 1370 m, 1265 s, 1080 s, 845 s, 790 s cm^{-1}; ^{1}H NMR (270 MHz) 5.78-5.45 (1H, m, $J_{Sn,H}$ = 35 Hz), 4.42-4.25 (2H, m, $J_{Sn,H}$ = 17 Hz), 4.20 (2H, d, J = 5.2 Hz), 1.6-1.4 (6H, m), 1.4-1.2 (6H, m), 0.9 (33H, m), 0.08 (12H, s); ^{13}C NMR (67.5 MHz) 148.03 s, 137.49 d, 64.82 t, 61.16 t ($J_{C,Sn}$ = 27 Hz), 29.44 t ($J_{C,Sn}$ = 10 Hz), 27.66 t ($J_{C,Sn}$ = 30 Hz), 26.36 q, 26.14 q, 18.77 s, 18.54 s, 13.92 q, 10.48 t ($J_{C,Sn}$ = 160, 170 Hz), -4.87 q, -5.12 q; m/z 549 (M-*t*-Bu, 3%), 435 (1), 365 (100), 281 (39), 225 (20), 195 (17),73 (36), 57 (12).

Methyl 2-iodo-5-methylbenzoate (47). AcCl (10 ml) was added to a solution of 2-iodo-5-methylbenzoic acid[23] (12.68 g, 48.4 mmol) in MeOH (100 ml) and the mixture refluxed for 14 h. The mixture was then concentrated and the residue taken up in CH_2Cl_2 and washed with 1M $Na_2S_2O_3$ and $NaHCO_3$ before being dried and concentrated to a brown oil (13.15 g). The crude material was Kugelrohr-distilled [180 °C (bath) / 0.7 mm Hg] affording **47** (11.81 g, 88%) : IR (film) 3040 m, 3010 m, 2960 m, 2930 m, 1725 s, 1600 m, 1470 s, 1440 s, 1300 s, 1310 s, 1210 s, 1110 s, 1020 s, 820 m, 790 m, 780 m cm^{-1}; UV (EtOH) 236 (log ε 3.8), 290 (3.2); ^{1}H NMR (60 MHz) 7.9 (1H, d, J = 8 Hz), 7.7 (1H, br s), 7.05 (1H, d, J = 8 Hz), 4.0 (3H, s), 2.45 (3H, s).

Methyl 2-[(*Z*)-bis-1,4-(*tert*-butyldimethylsiloxy)-2-buten-2-yl]-5-methylbenzoate (48). To a mixture of $ZnCl_2$ (2.54 g, 18.6 mmol), LiCl (0.79 g, 18.6 mmol) and $Pd(PPh_3)_2Cl_2$ (0.52 g, 0.74 mmol) in dioxane (80 ml), under nitrogen , was added **47** (2.5 g , 9.3 mmol) in dioxane (20 ml) followed by **46** (7.36 g, 12.2 mmol) in dioxane (30 ml). The mixture was then stirred at reflux for 48 h during which time the colour changed from yellow to brown. After cooling to room temperature the mixture was

poured into saturated aqueous KF and rapidly stirred for 24 h. The two phase mixture was filtered through cellite and extracted into Et_2O. The combined ethereal extracts were dried and concentrated to afford an orange oil (7.59 g). The crude material was chromatographed (SiO_2, 60 x 100 mm, 5% Et_2O in petrol) affording **48** (1.84 g, 43%) : IR (film) 2970 s, 2940 s, 2900 m, 2870 s, 1730 s, 1480 m, 1470 m, 1440 m, 1300 s, 1260 s, 1210 s, 1100 s, 845 s, 785 s cm^{-1}; UV (EtOH) 236 (log ε 3.8), 286 nm (3.2); ^1H NMR (270 MHz) 7.65-7.68 (1H, m), 7.26(1H, d with furhter fine splitting, J = 7.7 Hz), 7.16 (1H, d, J = 7.7 Hz), 5.49 (1H, t with further fine splitting, J = 5.9 Hz), 4.43 (2H, d, J = 6.0 Hz), 4.42 (2H, s), 3.82 (3H, s), 2.37 (3H, s), 0.92 (9H, s), 0.78 (9H, s), 0.11 (6H, s), -0.10 (6H, s); ^{13}C NMR (67.5 MHz) 168.30 s, 141.23 s, 140.41 s, 136.71 s, 132.26 d, 131.41 d, 130.27 d, 129.77 d, 129.62 s, 62.23 t, 60.33 t, 52.02 q, 26.13 q, 25.88 q, 21.08 q, 18.50 s, 18.31 s, -4.91 q, -5.43 q; m/z 464 (M^+, 1.7%), 433 (2), 407 (100), 376 (17), 375 (58), 332 (20), 275 (84), 201 (11), 147 (21), 75 (11); (Found : M^+, 464.2774. $C_{28}H_{44}O_3Si$ requires 464.2778).

(*Z*)-(2-Hydroxyethyliden-1-yl)-7-methylisochroman-1-one (49). To a solution of **48** (1.25 g, 2.68 mmol) in THF (10 ml) was added 2M HCl (2 ml, 4 mmol) and the resultant solution stirred at room temperature for 1.75 h. The mixture was then diluted with Et_2O and washed with water and $NaHCO_3$, and then dried and concentrated to afford an oil (1.2 g) which solidified on trituration with Et_2O. Recrystallisation (CH_2Cl_2 / petrol) gave **49** as a white solid (0.452 g , 83%) : mp 93-5 °C (CH_2Cl_2 / petrol); IR ($CHCl_3$) 3440 m, 3020 m, 2940 m, 2890 m, 1720 s, 1620 m, 1500 m, 1460 m, 1425 m, 1390 m, 1305 m, 1275 s, 1190 s, 1155 m, 1120 m, 1030 s, 910 m, 895 m, 830 m cm^{-1}; UV (EtOH) 232 (log ε 4.18), 261 (4.01), 312 nm (3.4); ^1H NMR (360 MHz) 7.95 (1H, br s) , 7.50 (1H, d, J = 8.0 Hz), 7.42 (1H, dd, J = 8.0, 1.5 Hz), 6.37 (1H, t, J = 6.6 Hz), 5.14 (2H, s), 4.46 (2H, d, J = 6.6 Hz), 3.4 (1H, br s, OH), 2.41 (3H, s), 1.57 (1H, br s); ^{13}C NMR (67.5 MHz) 165.29 s, 139.16 s, 135.21 d, 135.14 s, 130.36 d, 128.26 d, 127.84 s, 123.06 d, 122.92 s, 66.34 t, 58.41 t, 21.12 q; m/z 204 (M^+, 79.9%), 186 (49), 176 (76), 175 (70), 160 (10), 158 (80), 145 (100), 132 (37), 115 (71), 91 (36); (Found : M^+, 204.0796. $C_{12}H_{12}O_3$ requires 204.0786); (Found : C, 70.24 ; H, 5.93. $C_{12}H_{12}O_3$ requires C, 70.57 ; H, 5.92%).

(*Z*)-(2-Bromoethyliden-1-yl)-7-methylisochroman-1-one (50). To an ice-cooled solution of **49** (348 mg, 1.7 mmol) and PPh_3 (470 mg, 1.79 mmol) in CH_2Cl_2 (15 ml) under nitrogen was added solid NBS (318 mg, 1.79 mmol). The reaction mixture was warmed to room temperature and stirred for 4.5 h. The solution was then diluted with CH_2Cl_2 , washed with $NaHCO_3$, dried and concentrated to afford an orange oil (1.17 g). The crude material was chromatographed (SiO_2, 30 x 70 mm, 20% EtOAc in petrol) affording an off-white solid (409 mg). Recrystallisation (CH_2Cl_2 / petrol) afforded **50** (368 mg, 81%) : mp 92-4°C (CH_2Cl_2 / petrol); IR ($CHCl_3$) 3060 m, 3000 m, 2930 w, 1730 s, 1620 m, 1500 m, 1430 m, 1360 m, 1310 m, 1270 s, 1245 m, 1195 s, 1150 m, 1105 m, 1030 m, 915 m, 830 m, 780 m, 740 s, 710 s cm^{-1}; UV (EtOH) 235 (log ε 3.57), 271 (3.57), 311 nm (3.08); ^1H NMR (270 MHz) 7.94 (1H, br s), 7.49 (1H, d, J = 8.1 Hz), 7.43 (1H, dd, J = 8.0, 1 Hz), 6.43 (1H, tt, J = 8.7, 1 Hz), 5.12 (2H, d, J = 1 Hz), 4.17 (2H, d, J = 8.7 Hz), 2.42 (3H, s); ^{13}C NMR (67.5 MHz) 164.33 s, 140.09 s, 135.13 d, 134.06 s, 131.18 s, 130.68 d, 123.28 s, 123.18 d, 123.05 d, 65.42 t, 25.63 t, 21.23 q; m/z 267 (M^+ ^{81}Br , 10.7%) , 265 (M^+ ^{79}Br , 10.9%), 187 (100), 186 (34), 158 (29), 141 (10), 131 (31), 115 (27), 91 (10); (Found : M^+ ^{81}Br , 267.9918. $C_{12}H_{11}{}^{81}BrO_2$ requires 267.9921; Found : M^+ ^{79}Br, 265.9945. $C_{12}H_{11}{}^{81}BrO_2$ requires 265.9941); (Found : C, 53.63; H, 4.06. $C_{12}H_{11}BrO_2$ requires C, 53.96; H, 4.15%).

(*Z*)-2-(2-Dimethylphosphonatoethyliden-1-yl)-isochroman-1-one (4). A solution of **50** (370 mg, 1.39 mmol) and $(MeO)_3P$ (0.8 ml, 6.78 mmol) in benzene (5 ml) was refluxed for 16 h. The reaction was then diluted with water and extracted into Et_2O. The combined ethereal extracts were dried and concentrated to afford an oil (389 mg). The crude material was chromatographed (SiO_2, 30 x 30 mm, 0-10% MeOH in EtOAc) affording **4** (245 mg , 60%) as a colourless oil: IR (film) 3040 w, 2950 m, 2920 m, 2850 m, 1730 s, 1660 w, 1610 m, 1495 m, 1460 m, 1420 m, 1380 m, 1300 m, 1270 s, 1185 s, 1145 s, 1100 s, 1050 s, 860 m, 820 s, 780 m, 730 m cm^{-1}; UV (EtOH) 233 (log ε 3.90), 259 (3.71), 298 nm (3.05); ^1H NMR (270 MHz) 7.89 (1H, br s), 7.45 (1H, d, J = 8.3 Hz), 7.38 (1H, br d, J = 8.3 Hz), 6.15 (1H, apparent q, J = 7.5 Hz), 5.04 (2H, d, J = 3.3 Hz), 3.77 (3H, s), 3.73 (3H, s), 2.82 (2H, dd, J = 23, 8.3 Hz) , 2.39 (3H, s) ; ^{13}C NMR (67.5 MHz) 164.76 s, 139.44 s, 135.15 d, 134.92 s ($J_{P,C}$ = 4 Hz) , 130.95 s, 130.75 s, 130.62 d, 123.06 d ($J_{P,C}$ = 2 Hz) , 117.29 d ($J_{P,C}$ = 13 Hz) , 66.26 t ($J_{P,C}$ = 3 Hz) , 53.13 q ($J_{P,C}$ = 7 Hz) , 25.96 t ($J_{P,C}$ = 140 Hz) , 21.23 q; m/z 296 (M^+, 63%), 235 (2), 187 (80), 185 (74), 158 (100), 141 (13), 131 (27), 128 (28), 115 (37), 109 (10), 91 (13).

Lacrimin A (2) and Isolacrimin A (55). To a solution of **52** (53 mg, 0.12 mmol) and **4** (45 mg, 0.15 mmol) in THF (5 ml) cooled to -110°C (bath temperature) under argon was added LDA (0.6 ml, 0.25 M, 0.15 mmol) (pre-cooled to -70°C) over a period of 10 minutes . The resultant deep red solution was stirred for 1 h during which time the temperature was allowed to rise to -80°C. The mixture was then poured into brine and extracted into Et_2O. The combined ethereal extracts were dried and concentrated affording an oil (162 mg). The crude material was purified by chromatography (Basic Al_2O_3 / 5% water, 30 x 60 mm, 5-50% Et_2O in petrol) affording and inseparable mixture of **53** and **54** (44 mg , 44%) : IR (film) 3060 m, 2970 s, 2940 s, 2890 s, 2870 s, 1725 s, 1645 m, 1620 w, 1465 m, 1390 m, 1270 s, 1200 m, 1080 s, 995 s, 840 s, 780 s, 750 s, 710 s cm^{-1}; ^{13}C NMR (67.5 MHz) 165.32 s, 147.62 d, 146.89 d, 138.84 s, 138.65 s, 136.08 s, 135.08 d, 134.82 s, 134.71 s, 134.68 s, 134.29 d, 131.12 d, 130.86 s, 130.81 d, 127.90 d, 126.75 s, 124.50 s, 124.15 s, 123.19 d, 123.12 d, 122.68 d, 122.54 d, 97.62 s, 74.10 t, 71.07 d, 67.99 d, 66.68 t, 65.64 d, 47.40 t, 47.28 t, 41.32 t, 36.73 d, 36.06 t, 35.40 d, 35.23 d, 34.57 t, 28.03 t, 26.06 q, 21.39 q, 21.36 q, 19.74 q, 19.58 q, 18.22 q, 16.55 q, -4.25 q.

To a solution of **53** and **54** (24 mg, 0.039 mmol) in CH_3CN (1 ml) was added HF (0.1 ml, 40% in water) and the mixture stirred at room temperature for 15 minutes . After diluting with $NaHCO_3$ the mixture was extracted into Et_2O, dried and concentrated to afford a yellow oil (55 mg). The crude material was purified by chromatography affording **2** and **55** (16.4 mg , 84%) . The isomeric mixture was separated by hplc (Zorbax SiO_2, 9.4 x 250 mm, 50% MTBE in hexane, 5 ml / minute) affording, in order of elution **2** (5.6 mg, 29%) : $[\alpha]_D$(22°C) -49° (*c*. 0.26 in $CHCl_3$); IR (film) 3440 m, 3040 m, 2980 s, 2950 s, 2890 m, 1720 s, 1640 m, 1615 w, 1500 w, 1465 m, 1390 m, 1190 m, 1095 m, 1000 m, 980 m cm^{-1}; UV (EtOH) 214 (log ε 4.06) , 243 (3.89) , 285 nm (4.12); ^1H NMR (270 MHz) 7.93 (1H, br s), 7.49 (1H, d, J = 8.1 Hz), 7.39 (1H, dd, J = 8.1, 2 Hz), 6.66 (1H, d, J = 11.2 Hz), 6.33 (1H, dd, J = 15, 11.2 Hz), 5.95 (1H, dd, J = 15, 7.7 Hz), 5.23 (1H, br t, J = 6.8 Hz), 5.17 (2H, s), 4.10 (1H, dddd, J = 11, 11, 5, 5 Hz), 3.6-3.45

(1H, m), 3.26 (1H, dq, J = 9.7, 6.3 Hz), 2.52 (1H, m), 2.41 (3H, s), 2.24 (1H, dd, J = 15, 7 Hz), 2.15-1.90 (4H, m), 1.63 (3H, s), 1.75-1.45 (5H, m), 1.26 (4H, m), 1.10 (3H, d, J = 6.4 Hz), 1.04 (3H, d, J = 6.6 Hz), 0.83 (3H, d, J = 6.6 Hz); ^{13}C NMR (67.5 MHz) 165.30 s, 146.79 d, 138.71 d, 136.08 s, 135.11 d, 131.09 s, 130.83 d, 127.84 d, 124.28 s, 123.16 s, 122.79 d, 122.71 d, 122.68 s, 97.63 s, 71.28 d, 68.17 d, 66.69 t, 65.08 d, 47.54 t, 44.99 t, 40.44 t, 36.77 d, 35.99 t, 35.55 d, 34.55 t, 27.99 t, 21.32 q, 20.04 q, 19.59 q, 18.17 q, 16.58 q; m/z 494 (M$^+$, 13.8%), 476 (7), 267 (10), 227 (34), 199 (43), 181 (100), 166 (5), 155 (13), 113 (13), 109 (6), 91 (7); (Found : M$^+$, 494.3035 . $C_{31}H_{42}O_5$ requires 494.3032); followed by the C8-9 double bond isomer **55** (4.5 mg , 23%) : ^{1}H NMR (270 MHz) 7.96 (1H, br s), 7.49 (1H, d, J = 8.2 Hz), 7.44 (1H, dd, J = 8.2, 1.7 Hz), 6.58 (1H, dd, J = 15, 11.2 Hz), 6.35 (1H, d, J = 11.6 Hz), 5.95 (1H, dd, J = 15, 7.6 Hz), 5.22 (1H, t, J = 7.2 Hz), 4.83 (2H, s), 4.10 (1H, dddd, J 11, 11, 5, 5 Hz), 3.6-3.43 (1H, m), 3.26 (1H, dq, J = 9.7, 6.4 Hz), 2.49 (1H, m), 2.44 (3H, s), 2.40-1.90 (5H, m), 1.70-1.45 (5H, m), 1.62 (3H, s), 1.26 (4H, m), 1.11 (3H, d, J = 6.4 Hz), 1.02 (3H, d, J = 6.8 Hz), 0.82 (3H, d, J =6.6 Hz); ^{13}C NMR (67.5 MHz) 163.66 s, 147.57 d, 138.87 s, 135.11 d, 134.82 s, 134.30 d, 131.08 d, 130.82 s, 126.72 d, 125.00 s, 124.57 s, 123.32 d, 122.71 d, 97.62 s, 74.19 t, 71.27 d, 68.16 d, 65.08 d, t, 47.42 t, 44.99 t, 40.43 t, 36.74 d, 35.96 t, 35.33 d, 34.52 t, 27.97 t, 21.39 q, 20.02 q, 19.59 q, 18.1 q, 16.54 q.

(4*Z*)-7-Methyl-4-(2-triphenylphosphoniumethyliden-1-yl)-isochroman-1-one bromide (56). A solution of **50** (320 mg, 1.2 mmol) and PPh_3 (630 mg, 2.4 mmol) in benzene (10 ml) was refluxed for 1.5 h. The resultant white precipitate was filtered and washed with benzene to give a white crystalline solid. Recrystallisation (CH_2Cl_2 / petrol) afforded **56** (620 mg , 98%): mp 237-9°C (CH_2Cl_2 / petrol); IR ($CHCl_3$) 3080 w, 3040 w, 2980 m, 1720 s, 1610 w, 1585 w, 1435 s, 1380 m, 1220 m, 1120 m, 730 m, 700 m cm^{-1}; UV (MeOH) 225 (log ε 5.56) , 258 (416) , 310 nm (3.36) ; ^{1}H NMR (270 MHz) 7.96-7.89 (6H, m), 7.81-7.22 (4H, m), 7.71-7.69 (6H, m), 7.38 (1H, d, J = 8.1 Hz), 7.30 (1H, br d, J = 8.1 Hz), 6.20 (1H, dt, J = 7.8, 6 Hz), 5.28 (2H, dd, J = 16.0 , 8.3 Hz), 4.73 (2H, d, J = 3.1 Hz), 2.33 (3H, s); ^{13}C NMR (67.5 MHz) 164.25 s, 140.08 s, 135.43 d, 135.38 d, 135.24 d, 134.19 d, 134.03 d, 130.68 d, 130.49 d, 130.37 d, 123.62 d, 122.96 s, 118.34 s, 117.07 s, 114.39 d, 114.23 d, 66.84 t ($J_{P,C}$ = 3 Hz), 25.11 t ($J_{P,C}$ = 49 Hz), 21.26 q; m/z (glycerol matrix) 449 (M-Br, 5%), 369 (3), 293 (3), 277 (11), 262 (3), 185 (100); (Found: C, 67.72; H, 4.76; P, 5.81. $C_{30}H_{28}BrO_2P$ requires C, 68.06; H, 4.95; P, 5.85%).

(4*Z*)-7-Methyl-4-(2-*p*-toluenesulphonylethyliden-1-yl)-isochroman-1-one (57). To a solution of **50** (300 mg, 1.1 mmol) in DMF (10 ml) was added sodium *p*-toluenesulphinate (800 mg , 4.5 mmol) and the resultant mixture stirred at room temperature for 5 h. The mixture was then diluted with water, extracted into Et_2O, dried and concentrated to afford a colourless liquid (870 mg) composed of the desired sulphone **57** and some DMF. The crude material was chromatographed (SiO_2, 40 x 80 mm, 20% EtOAc in petrol) to give an oil (250 mg) which solidified on trituration with 1 : 2 Et_2O in petrol. Recrystallisation (CH_2Cl_2 / petrol) afforded **57** (250 mg, 61%) : mp 180-2°C (CH_2Cl_2 / petrol); IR ($CHCl_3$) 3030 m, 2940 m, 2880 w, 1720 s, 1610 m, 1600 w, 1330 s, 1310 s, 1285 m, 1230 m, 1195 m, 1160 s, 1150 s, 1095 m, 1030 m cm^{-1}; UV (EtOH) 231 (log ε 4.26), 264 (4.18), 308 nm (3.51); ^{1}H NMR (270 MHz) 7.91 (1H, br s), 7.74 (2H, d, J = 8.1 Hz), 7.44 (2H, s), 7.35 (2H, d, J = 8.1 Hz), 6.10 (1H, t, J = 8.2 Hz), 4.69 (2H, s), 4.03 (2H, d, J = 8.5 Hz), 2.45 (3H, s), 2.42 (3H, s); ^{13}C NMR (67.5 MHz) 164.08 s, 145.61 s, 140.35 s, 135.28 s, 135.26 s, 135.20 d, 134.02 s, 130.66 d, 130.12 d, 128.39 s, 123.18 d, 123.12 d, 113.95 d, 65.71 t, 55.63 t, 21.75 q, 21.26 q ; m/z 324 (M$^+$, 1.2%), 187 (100), 186 (20), 159 (27), 132 (5), 116 (11), 91 (16); (Found: M$^+$, 342.0912. $C_{19}H_{18}O_4S$ requires 342.0925); (Found : C, 66.23; H, 5.16; S, 9.39. $C_{19}H_{18}O_4S$ requires C, 66.65; H, 5.30; S, 9.36%).

(4*Z*)-7-Methyl-4-[(2*RS*,3*RS*)-3-hydroxy-4-methyl-2-*p*-toluenesulphonylethyliden-1-yl]-isochroman-1-one (58). A solution of **57** (100 mg, 0.29 mmol) and isobutanal (2 ml, 0.22M in THF, 0.44 mmol) in THF (2 ml) was cooled to -110°C (bath temperature) under argon. $MgBr_2$ (0.58 ml, 0.5M in THF, 0.29 mmol) was then added followed by the dropwise addition of LDA (0.58 ml , 0.5M in THF, 0.29 mmol), pre-cooled to -70°C. Addition of the LDA initially caused a red colour to form which rapidly changed to yellow before decolourising completely. After addition of all of the LDA, the solution remained slightly yellow . After stirring at -110°C for 30 minutes the reaction was quenched by the addition of brine before extracting into Et_2O. The combined ethereal extracts were dried and concentrated to give an off-white solid (128 mg). The crude material was purified by chromatography (SiO_2, 30 x 45 mm, 25% EtOAc in petrol) followed by recrystallisation (CH_2Cl_2 / petrol) to give **58** (97 mg, 81%): mp 143-6°C (CH_2Cl_2 / petrol); IR ($CHCl_3$) 3530 m, 3070 m, 2980 s, 2930 m, 2880 m, 1730 s, 1620 m, 1600 m, 1500 m, 1460 m, 1425 m, 1310 s, 1270 s, 1190 s, 1155 s, 1135 s, 1090 s, 1020 m, 820m, 740 s, 710 s, 670 m cm^{-1}; ^{1}H NMR (270 MHz) 7.90 (1H, br s), 7.68 (2H, d, J = 8.3 Hz), 7.45 (1H, br d, J = 8.1 Hz), 7.37 (1H, d, J = 8.1 Hz), 7.32 (2H, d, J = 7.9 Hz), 6.42 (0.25H, d, J = 10.6 Hz), 5.71 (0.75H, d, J = 11.2 Hz), 4.74 (1H, dd, J = 13.5, 1 Hz), 4.32-3.95 (3H, m), 4.12 (1H, dd, J = 13.5, 2 Hz), 2.45 (3H, s), 2.42 (3H, s), 1.67 (1H, m), 1.06 (0.7H, d, J = 6.9 Hz), 1.00 (0.3H, d, J = 6.6 Hz), 0.79 (3H, d, J = 6.7 Hz); ^{13}C NMR (67.5 MHz) 163.98 s, 146.30 s, 140.63 s, 135.38 d, 134.17 s, 133.92 s, 133.81 s, 133.68 s, 130.91 d, 130.70 d, 130.16 d, 129.19 d, 129.08 d, 123.56 d, 123.32 s, 123.17 s, 123.09 d, 117.43 d, 115.82 d, 73.66 d, 72.69 d, 69.22 d, 66.67 d, 66.23 t, 65.80 t, 32.48 d, 31.36 d, 21.90 q, 21.38 q, 21.22 q, 20.07 q, 19.20 q, 18.67 q, 14.35 q, 13.72q; m/z 415 (M$^+$H, 1%), 397 (1), 342 (13), 281 (3), 259 (67), 241 (31), 187 (81), 173 (60), 171 (100), 159 (43), 145 (29), 131 (46), 115 (35), 91 (48).

(4*Z*)-7-Methyl-4-[(2*E*)-4-methyl-2-pentenyliden-1-yl]-isochroman-1-one (59). To a solution of **4** (40 mg, 0.14 mmol) and isobutanal (0.9 ml, 0.22 M in THF, 0.2 mmol) in THF (2 ml) cooled to -110°C (bath temperature) under argon was added LDA (pre-cooled to -70°C) . The mixture was stirred for 1 h during which time the temperature was allowed to rise to -80°C , and the initially formed deep red colour disappeared. The reaction mixture was poured into brine and extracted into Et_2O. The combined ethereal extracts were dried and concentrated to give an oil (48 mg). The crude material was chromatographed (SiO_2, 20 x 30 mm, 20% Et_2O in petrol) to give **59** (23 mg , 68%) : IR (film) 3040 w, 2950 m, 2920 m, 2860 w, 1720 s, 1635 w, 1605 w, 1260 s, 1180 m, 1090 m, 1015 m, 780 m, 735 s, 700 m cm^{-1}; UV (MeOH) 214 (log ε 4.25), 248 (4.12), 286 (4.39), 324 nm (4.03); ^{1}H NMR (270 MHz) 7.94 (1H, d, J = 1 Hz), 7.48 (1H, d, J = 8.1 Hz), 7.40 (1H, dd, J = 8.0, 1 Hz), 6.67 (1H, br d, J = 11.2 Hz), 6.33 (1H, ddd, J = 14.9, 11.1, 1 Hz), 6.01 (1H, dd, J = 15.0, 6.9 Hz), 5.17 (2H, d, J = 1 Hz), 2.47 (1H, m), 2.41 (3H, s), 1.08 (6H, d, J =

6.8 Hz); ^{13}C NMR (67.5 MHz) 165.29 s, 148.10 d, 138.59 s, 136.59 s, 135.07 d, 130.73 d, 127.93 d, 124.11 s, 123.09 s, 122.66 d, 121.75 d, 66.66 t, 31.92 d, 22.30 q, 21.29 q; m/z 242 (M$^+$, 64%), 227 (6), 215 (18), 199 (24), 186 (37), 158 (29), 145 (51), 128 (31), 118 (100), 83 (25), 43 (76); (Found: M$^+$, 242.1291. $C_{16}H_{18}O_2$ requires 242.1307).

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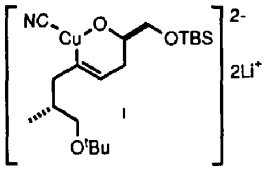

11. Since this work was completed we have accomplished similar transformations involving lithiated dihydrofurans and organocuprates derived from organolithium reagent **23** in much better yield (*ca.* 50% overall) by conducting the migratory insertion reaction at or near room temperature.

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