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A SYNTHESIS OF LACRIMIN A

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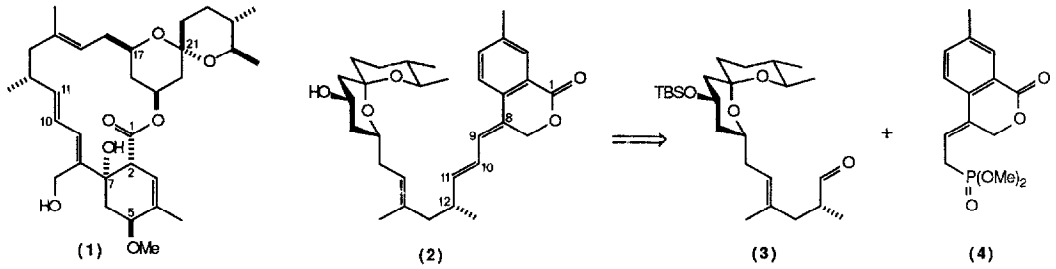
Abstract: A convergent synthesis of Lacrimin A (2) is described in which a Wadsworth-Emmons reaction was used to construct the C10-C11 double bond and link the isochroman-1-one phosphonate (4) to the spiroacetal aldehyde (3)†.

Lacrimin A (2) is an antihypotensive agent formed by treatment of Milbemycin β_1 (1) with NaOH at pH >12[1]. We report the first total synthesis of (2) from the known spiroacetal aldehyde (3)[2] and the isochroman-1-one phosphonate (4).

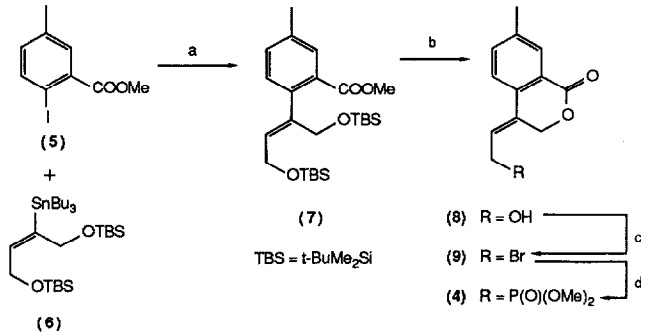


A. Synthesis of the isochroman-1-one phosphonate (4)(Scheme 1). The tri-substituted alkene of the isochroman-1-one was constructed with high stereoselectivity by a Pd-catalysed coupling[3] of the aryl iodide (5)[4] and the alkenylstannane (6)[5]. Subsequent hydrolysis of intermediate (7) and lactonisation gave the alcohol (8) [mp 93-5°C, CH_2Cl_2 - hexane] as a single stereoisomer assigned structure (8)[6] on the basis of nOe difference spectroscopy. The best conditions for the coupling step involved running the reaction in the presence of $ZnCl_2$ and LiCl in refluxing dioxane. An Arbuzov reaction on the corresponding bromide (9) furnished the desired phosphonate (4).

SCHEME 1

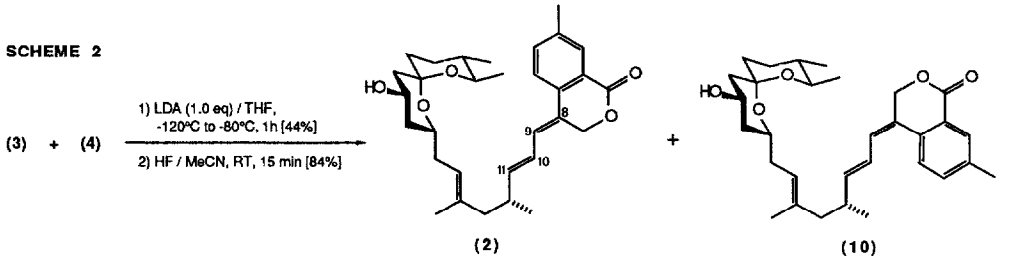
Reagents and Yields

(a) (43%): $Pd(PPh_3)Cl_2$ (0.08 eq), $ZnCl_2$ (2 eq) LiCl (2 eq) / dioxane, reflux, 48h;
(b) (83%): 2M HCl / THF (1:5), RT, 1.75h;
(c) (81%): NBS (1.05 eq), PPh_3 (1.05 eq) / CH_2Cl_2, 0°C-RT, 4.5h;
(d) (60%): $(MeO)_3P$ (4 eq) / benzene, reflux, 16h.



†Milbemycin numbering has been used in referring to the position of carbon atoms in various intermediates.

SCHEME 2



(2) (10)

B. Synthesis of Lacrimin A from isochroman-1-one (4) and spiroacetal aldehyde (3)(Scheme 2). Union of the spiroacetal aldehyde (**3**) and various activated forms of the isochroman-1-one was not easy. For example, a Wittig olefination was prevented by the failure of the triphenylphosphorane, prepared from bromide (**9**), to react with aldehyde (**3**) under a variety of conditions. Similarly, a Julia olefination sequence was thwarted by the instability of the anion of the sulphone analogue of (**4**) and the extremely easy retroaldolisation of the ß-hydroxysulphone adduct. Successful construction of the C10-C11 double bond was eventually achieved in 44% yield by adding a solution of LDA to a mixture of aldehyde (**3**) and phosphonate (**4**) at -120°C (bath temperature) followed by warming to -80°C. Under these conditions the unstable phosphonate anion was generated and trapped *in situ* before serious decomposition occurred. Unfortunately isomerisation of the C8-C9 double bond occurred under these conditions to give variable mixtures of the TBS ethers of Lacrimin A (**2**) and Isolacrimin A (**10**)[(**2**):(**10**) = 1.3 - 4.7:1]. After hydrolysis of the TBS ethers, the mixture of Lacrimin A and Isolacrimin A[7] was separated by HPLC on Zorbax SiO_2 (9.4 x 250 mm, 50% t-butyl methyl ether in hexane, 5 ml/min). The sample of Lacrimin A thus obtained was identical by IR, ^1H and ^{13}C NMR analysis, and mass spectrometry with data reported in the Sankyo patent[1]: $[\alpha]_D$(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 nm (log ε 4.06) , 243 (3.89) , 285 (4.12) ; ^1H NMR ($CDCl_3$, 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 , 11.1 Hz) , 5.95 (1H, dd, J = 15 , 7.7 Hz) , 5.23 (1H, t, J = 6.8 Hz) , 5.17 (2H, s) , 4.10 (1H, dddd, J = 11 , 11 , 5 , 5 Hz) , 3.51 (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 ($CDCl_3$, 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).

C. Synthesis of the spiroacetal aldehyde (3)(Scheme 3). We recently reported a new approach to unsaturated spiroacetals[8] which has now been applied to a highly convergent synthesis of (**26**) – a key intermediate in the preparation of (**3**). Noteworthy features of this Scheme are 1) the use of methoxyallene[9] as a $d^{1,3}$ reagent in the conjunction of chiral fragments (**16**) and (**23**); 2) the stereoselective protonation[10] of the allenol ether (**24**) to generate the *cis*-enone of intermediate (**25**) ; and 3) the regio- and stereoselective hydration[11] of the unsaturated spiroacetal (**26**) in order to introduce the C19 hydroxyl group[12]. Thus two of the six chiral centres in (**27**) (spiroacetal centre C21[13] and the hydroxyl function at C19) were derived from thermodynamically controlled reactions.

The principal chiral fragments in this Scheme were alcohol (**11**)[14] and acetylene (**19**)[2a]. Alcohol (**11**) was converted to the iodide (**16**) in 7 steps (46% overall). The oxirane (**23**)[15] was prepared in 4 steps (60% overall) *via* carboalumination[16] of (**19**) followed by alkylation with (*R*)-(-)-epichlorohydrin (**21**)[17]. The only refractory step in the sequence was the alkylation of the lithiated methoxyallene derivative (**18**). Considerable difficulty was encountered in suppressing the base-catalysed elimination of the oxirane (**23**) to the corresponding allylic dienol. By careful manipulation of the reaction temperature and by working under rather concentrated reaction conditions [0.18 M in (**18**) and 0.22 M in (**23**)] we were able achieve a 79% yield of the desired alkylation product (**24**) based on recovered allene (**17**) or 55% absolute yield.

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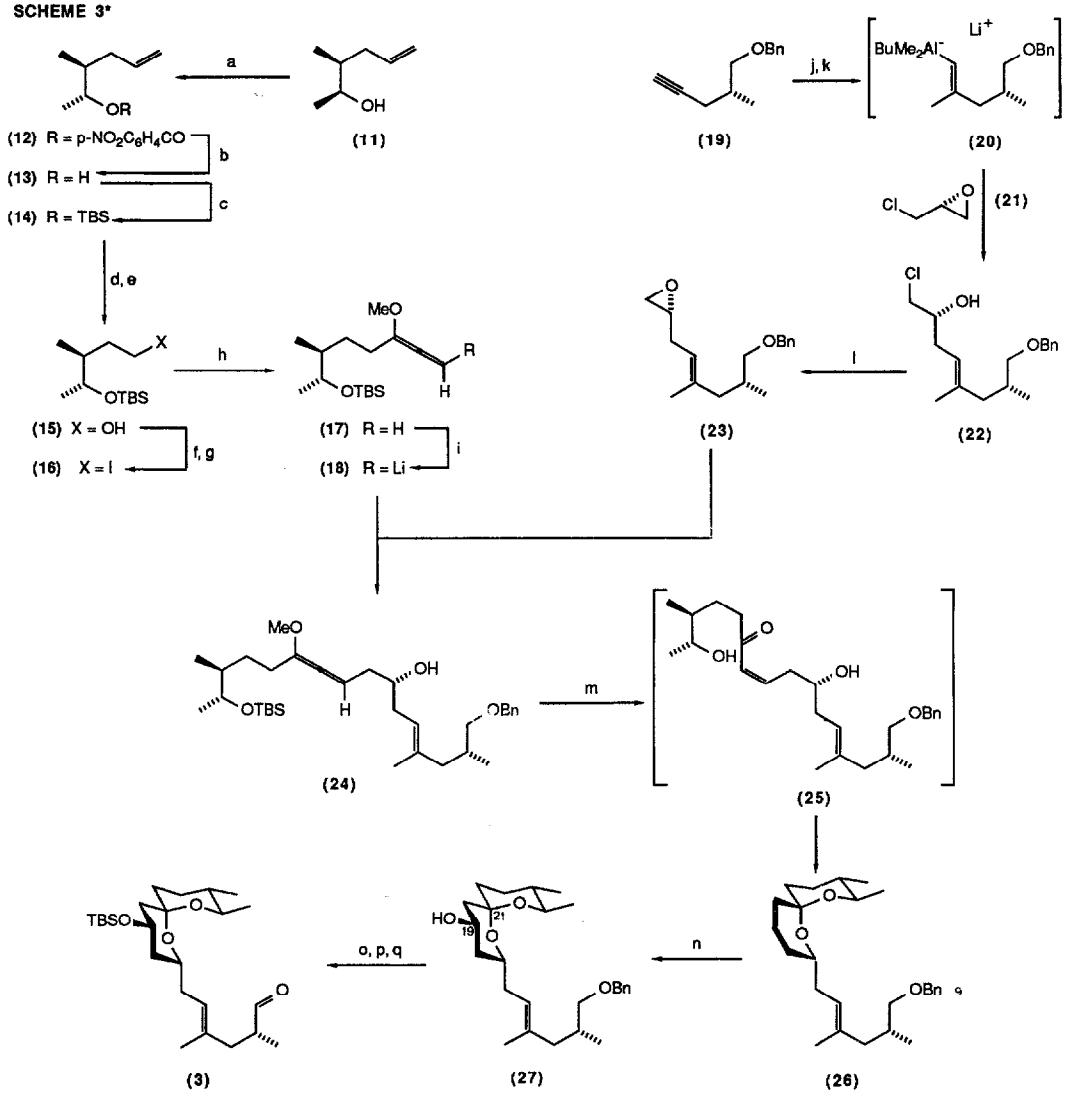
SCHEME 3*



Reagents and Yields

(a)	(78%)	PPh_3, DEAD, p-$NO_2C_6H_4COOH$ / toluene, -35°C to RT, 4h;	(i)	(55%)	t-BuLi / pentane - THF, -55°C, 1h; then add **(23)** (1.1 eq), -45°C, 1h followed by HMPA (2 eq) , -25°C, 4h;
(b)	(90%)	KOH / MeOH - H_2O, RT, 10h;	(j)	-	Me_3Al, Cp_2ZrCl_2 / hexane-dichloroethane, RT, 66h;
(c)	(82%)	TBSCl, imidazole / CH_2Cl_2;	(k)	-	n-BuLi / hexane, -78°C to -30°C, 1.5h; then add **(21)**, 0°C, 2.5h;
(d)	-	O_3 / MeOH, -70°C;	(l)	(80%)	NaH / THF - HMPA, RT, 18h;
(e)	(87%)	$NaBH_4$ / MeOH, -60°C to RT, 2h;	(m)	(78%)	TBAF (6 eq) / THF, RT, 90h; then TsOH (6 eq), cat. I_2, RT, 5h;
(f)	-	TsCl / pyridine, 0°C;	(n)	(80%)	2M HCl / THF (1:5), reflux, 22h;
(g)	(89%)	NaI / acetone, reflux, 1.5h;	(o)	(67%)	TBSOTf / 2,6-lutidine - CH_2Cl_2 , -25°C, 45 min;
(h)	(97%)	$H_2C{=}C{=}C(Li)OMe$ / THF, -25°C, 2.5h;	(p)	(90%)	Na / Et_2O - NH_3(l), -78°C, 30 min;
			(q)	(94%)	Collins oxidation.

*All compounds were characterised by IR, ^1H (270 MHz) and ^{13}C(67.5 MHz) NMR spectroscopy. Yields refer to compounds purified by column chromatography and/or distillation. All compounds gave satisfactory high resolution mass spectra from samples judged to be ≥92% pure by NMR and TLC or GLC analysis.

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5. Prepared by silylation of (*E*)-2-(tri-n-butylstannyl)-but-2-en-1,4-diol: I. Fleming and M. Taddei, *Synthesis*, 1985, 898.
6. Spectroscopic data for (**8**): 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) 232nm (log ε 4.18) , 261 (4.01) , 312 (3.4) ; ^1H NMR ($CDCl_3$, 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) , 2.41 (3H, s) , 1.57 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 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).
7. By HPLC a third stereoisomer (presumably the C12 epimer of Lacrimin A) comprising ≤10% of the mixture was also detected. Order of elution: (**2**)[RT = 12.6 min], C12 epimer [RT = 13.6 min], (**10**) [RT = 13.8 min]. Analytical HPLC revealed that (**2**) was ≥92% pure and (**10**) was *ca.* 90% pure. Spectroscopic data for Isolacrimin A (**10**) : ^1H NMR ($CDCl_3$, 270 MHz) 7.96 (1H, br s) , 7.49 (1H, d, J = 7.9 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) , 3.51 (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 ($CDCl_3$, 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, 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, 18.15 q, 16.54 q.
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12. At equilibrium a 4:1 mixture of (**27**) and its C19 epimer was obtained. The isomers were easily separated by column chromatography on SiO_2 [10-80% ether - hexane] and the C19 epimer recycled.
13. For a discussion of the factors governing the stereochemistry of spiroacetal formation see: P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry', Pergamon, Oxford, 1983, pp. 4-53.
14. Alcohol (**11**) {$[\alpha]_D$ (19°C) +5.5° (c 4.1 in MeOH)}was prepared in 88% yield by the Cu(I)-catalysed cleavage of (2*S*, 3*S*)-2,3-dimethyloxirane with allylmagnesium chloride.
15. Spectroscopic data for oxirane (**23**): $[\alpha]_D$ (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; ^1H NMR (360 MHz, $CDCl_3$) 7.45-7.3 (5H, m) , 5.18 (1H, tq, J = 7.3 , 1Hz) , 4.51 (2H, s) , 3.36 (1H, dd, J = 9.0 , 5.7 Hz) , 3.26 (1H, dd, J = 9.1 , 6.6 Hz) , 2.94 (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 = 14.3 , 6.3 Hz) , 2.22 (2H, m) , 1.98 (1H, m) , 1.80 (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, $CDCl_3$) 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.
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