Diastereospecific approach to (±)-samin and 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane (furofuran) lignans using the Ireland–Claisen rearrangement of unsaturated oxamacrolides

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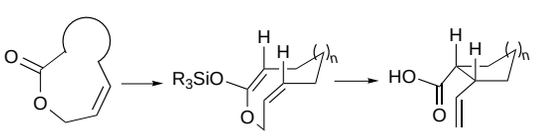
Enolate Claisen rearrangement of the unsaturated oxamacrolide 28 leads specifically, after reduction, to the tetrahydro-3-furylmethanol 30, *via* a boat-like transition state 29. Initial attempts to obtain a macrolide related to 28 by O-alkylation of the model β-hydroxy ester 12 using acetimidate 13 were inefficient. Key steps in the successful preparation of the macrolide 28 are Michael addition of a mono-protected (*Z*)-but-2-ene-1,4-diol 23 to an α-sulfonyl cinnamate 26 and lactonization of the derived hydroxy acid 27c using Mukaiyama's reagent. Subsequent oxidative cleavage of the vinyl group in the tetrahydrofuran 30 gives (±)-samin 9, a precursor of both symmetrical and unsymmetrical furofuran lignans 8.

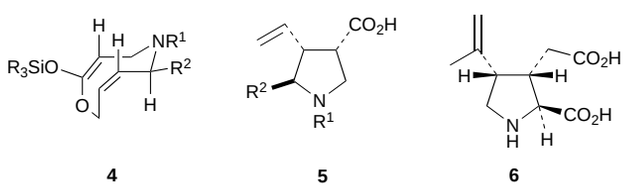
The Ireland ester enolate version of the classical Claisen rearrangement has greatly enhanced the utility of this valuable synthetic transformation, primarily because the ether linkage in the precursor allyl vinyl ethers is effectively obtained by an esterification rather than an etherification reaction.[1] This advance has allowed further extensions of Claisen rearrangement methodology to be realized; one of these was first introduced by Danishefsky and involves rearrangements of enolates derived from a variety of unsaturated lactones in a highly stereocontrolled approach to carbocycles.[2] Further studies showed that when unsaturated macrolides **1** were subjected to the enolate Claisen rearrangement, the intermediate silyl enolates were forced to adopt a less conventional boat-like geometry **2** when the ring contained eleven atoms or less, ensuring specific formation of *cis*-disubstituted cycloalkanoic acids **3** (Scheme 1).[3,4]



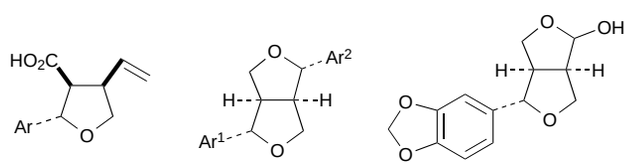
1 **2** **3**

Scheme 1

This is because the enolate geometry must be *cis* with respect to the ring [*i.e.* (*Z*)-lithio and (*E*)-silyl enolates], due to the constraints imposed by the ring size and the existing (*Z*)-alkene. Hence the more usual chair-like conformation would require a *trans*-diaxial bridge of five or less atoms, which would clearly be highly unfavourable. Given such a well-defined transition state geometry, our idea was that this could be exploited in the elaboration of single isomers of a variety of saturated heterocycles by two additions to the foregoing: firstly, inclusion of an additional heteroatom in the macrolide ring and secondly, positioning a substituent at one of the sp^3 carbons, which would be expected to adopt a pseudoequatorial position in the enolate (*cf.* **4**) and hence act as a predictive control feature. This is illustrated in our approaches to pyrrolidines **5** and (−)-α-kainic acid **6** by rearrangements of silyl enolates **4** derived from nine-membered azamacrolides.[5] We reasoned that a similar tactic might be suitable for the elaboration of tetrahydrofurans **7**, which would be especially suited to the synthesis of furofuran lignans **8**.[6] In particular, we focussed on the naturally occurring lactol samin **9**,[7] found in sesame oil, as our target, because it has

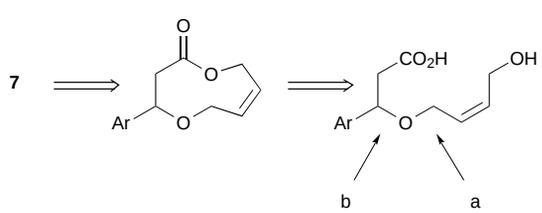


4 **5** **6**



7 **8** **9**

been converted into examples of furofurans **8** by sequential addition of an aryl Grignard reagent and cyclodehydration.[8] Retrosynthetic analysis then led to the macrolides **10** and thence to the hydroxy acids **11** (Scheme 2). These we hoped to



10 **11**

Scheme 2

obtain by O-alkylation of a chiral, non-racemic β-hydroxy ester (bond a) or, failing this, by Michael addition to a (activated) cinnamate (bond b). Given that the anticipated problems of β-elimination could be overcome, especially during lactone formation and the subsequent key rearrangement, this approach could lead to samin **9** and relatives thereof, and thence to unsymmetrical examples of the furofuran lignans **8**, by changing either the Grignard reagent or the starting aryl precursor.

To date, synthetic approaches to furofuran lignans which are suitable for the unambiguous synthesis of unsymmetrical examples **8** include those based on butyrolactone intermediates, accessed in rather different ways by the Pelter[9] and Whiting groups,[10] the Kraus photochemical approach,[11] rearrangements of 5-alkenyl-4,7-dihydro-1,3-dioxepines developed by Ogasa-

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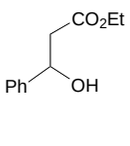
wara and his colleagues,[12] intramolecular radical cyclizations onto an acetylene to create the 3,4-tetrahydrofuran bond[13] and an alternative version of the Claisen rearrangement method described herein.[14,15] Approaches which deliver non-racemic material are rarer; to date, these include a somewhat protracted route featuring a hetero-Diels–Alder reaction with a homochiral ylidene Meldrum's acid as the diene,[8] an asymmetric version of the Ogasawara dioxepine method[16] and a very recent intramolecular radical cyclization of a chiral selenide.[17]

We began with a model sequence using ethyl (±)-3-hydroxy-3-phenylpropanoate **12**. A particularly useful method for the



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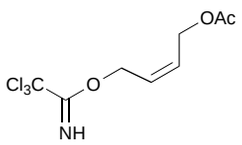
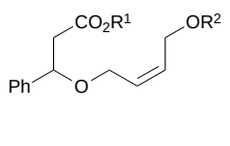
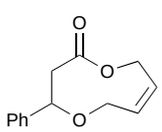


13



14a R^1 = Et, R^2 = Ac
b R^1 = R^2 = H



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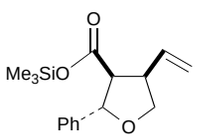

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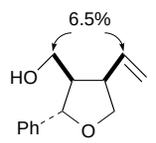

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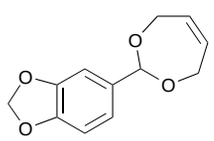
difficult O-alkylation of β-hydroxy esters features (Lewis) acid-catalysed reaction with a trichloroacetimidate; perhaps surprisingly, reaction between hydroxy ester **12** and benzyl 2,2,2-trichloroacetimidate, catalysed by triflic (trifluoromethanesulfonic) acid, delivers >70% of the O-benzyl ether, along with only *ca.* 8% of the elimination product, ethyl cinnamate.[18] For our sequence, we chose to use the acetimidate **13**, which was readily obtained in two steps from (*Z*)-but-2-ene-1,4-diol. However, we were never able to secure greater than a 38% return of the desired adduct **14a** in capricious reactions, when using triflic acid as the catalyst. Alternatives including aluminium trichloride, zinc chloride, magnesium bromide–diethyl ether complex, boron trifluoride–diethyl ether complex and silyl triflates were even less effective, as was replacement of the acetoxy group by various silyl functions, which caused problems in the acetimidate formation step. We reasoned that these low yields could be due to cyclization of the acetimidate **13** to 2,5-dihydrofuran and therefore turned to the corresponding alkynyl acetiminates; these, however, failed to provide any significant improvement in the yields of the desired O-alkylated derivatives of hydroxy ester **12**.

We were, however, able to prepare sufficient of the acetoxy ester **14a** by the initial method to proceed with simultaneous saponification of both ester functions, leading to a good yield of the required hydroxy acid **14b**. This was then lactonized using Funk's modification[4] of the Mukaiyama method,[19] which gave a moderate yield of the desired macrolide **15**. Saponification of a mixture of the remaining isolates from this reaction failed to produce a significant return of the hydroxy acid **14b**, indicating that these other products were not simply polyesters or diolides *etc.* Although not further investigated, we presume that competing pathways include ketene formation by elimination from the intermediate acyloxypyridinium species[20] and β-elimination from either the starting material or the macrolide; resonances due to cinnamates were visible in the ^{1}H NMR spectra of the crude product. β-Elimination could also occur during formation of the required O-silyl enolates from macrolide **15**; fortunately, Ireland and Norbeck had already provided a solution to this potential problem with the introduction of the 'premix' method. In this, a substrate sensitive to such an elimination is added to a mixture of the base [often lithium diisopropylamide (LDA)] and the trapping agent [usually trimethylsilyl chloride (TMSCl) or *tert*-butyldimethylsilyl chloride (TBDMSCl)].[21] We were gratified to find that addition of the macrolide **15** to a solution of LDA and TMSCl in tetrahydrofuran at −100 °C, followed by warming to ambient temperature and *in situ* reduction of the presumed silyl ester **16** using lithium aluminium hydride gave the tetrahydro-3-furylmethanol **17** as a single diastereoisomer in 71% overall yield. Evidently, as in related macrolides,[3–5] the central Claisen rearrangement occurs as the reaction mixture is warmed to ambient temperature. The reduction step was included at this stage to avoid any epimerization during manipulations of the corresponding esters. The stereochemistry of the tetrahydrofuran was determined by a comparison of coupling constant values from NOE data with those previously reported,[5,6] especially a 6.5% enhancement between the hydroxymethyl and vinylic protons, as well as the expected absences of enhancements. This assignment is entirely consistent with the predictions made on the basis of a boat-like transition state (*cf.* **4**). It is likely that this approach could be generalized and also used to obtain optically active trisubstituted tetrahydrofurans, as the starting hydroxy esters (*e.g.* **12**) can be obtained in homochiral forms in a number of ways. However, we reluctantly abandoned it due to the poor and unreproducible yields obtained at the O-alkylation stage and turned instead to the alternative Michael addition strategy (*cf.* **11**, bond b).

Prior to this, we did briefly examine one alternative approach to the required β-alkoxy esters, based on Johnson's method[22] wherein silylketene acetals are condensed with 1,3-dioxanes. For our purpose, we required the dioxepine **18**, which was



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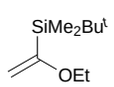

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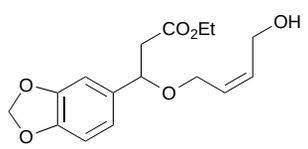

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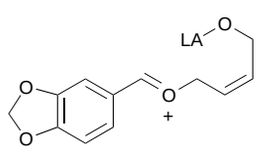

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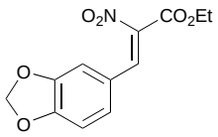
readily prepared by an established method,[23] and the acetal **19**.[24] However, despite many attempts using a variety of temperatures and Lewis acids (LA), including titanium tetrachloride, zinc chloride, boron trifluoride–diethyl ether complex and trimethylsilyl trifluoromethanesulfonate, we failed to isolate the target alkoxy ester **20** (Scheme 2). Instead, only piperonal was isolated, presumably because the likely intermediate **21** undergoes ring closure to give 2,5-dihydrofuran more rapidly than attack by the acetal **19**.

We therefore turned to the alternative Michael strategy and our first choice as the activated acceptor was the α-nitrocinnamate **22**, prepared by a Knoevenagel condensation.[25] This, we were pleased to find, reacted with the sodium alkoxide of the monoprotected but-2-ene-1,4-diol **23** to give a moderate yield



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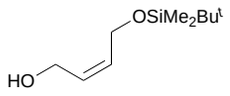

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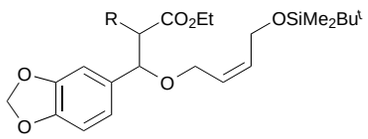
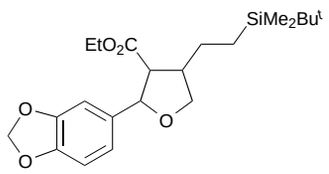


24a R = NO_2
b R = H



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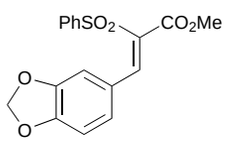

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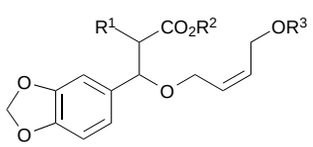
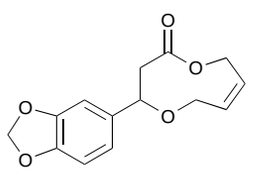


27a R^1 = SO_2Ph, R^2 = Me, R^3 = $SiMe_2Bu^t$
b R^1 = H, R^2 = Me, R^3 = $SiMe_2Bu^t$
c R^1 = R^2 = R^3 = H



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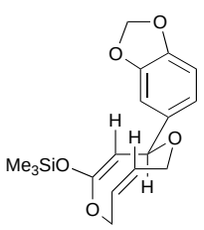

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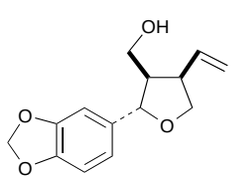

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of the alkoxy ester **24a**. Removal of the nitro group to give the required hydroxy acid precursor **24b** was accomplished using tributyltin hydride–AIBN.[26] However, the reactions were capricious, despite a number of optimization attempts, and the product **24b** was always accompanied by varying amounts of the tetrahydrofuran **25**, as a stereochemical mixture, presumably formed by a 5-*exo*-*trig* radical cyclization of a type previously reported for related tertiary nitro precursors.[27] Other denitration methods[28] gave lower yields or complete decomposition. As an alternative, the corresponding phenylsulfonyl derivative **26**[29] was used and we were pleased to find that the Michael addition was now more efficient and reproducible, routinely giving an 80% yield of the adduct **27a**. Removal of the sulfonyl group proved problematic until we found that use of 1% sodium amalgam at −50 °C in buffered methanol led smoothly to the protected hydroxy ester **27b**; reactions with the more conventional 6% Na–Hg[30] caused extensive decomposition. Subsequent hydrolysis of the ester group using methanolic potassium hydroxide was accompanied by complete removal of the silicon group to give excellent yields of the hydroxy acid **27c**. Attemts to remove only the silicon group using various fluoride sources resulted in partial or essentially complete β-elimination back to the cinnamate. Macrolactonization, again using Mukaiyama's reagent, then gave a respectable yield of the macrolide **28**. As in the foregoing model studies, this was then rearranged to the expected tetrahydrofuran-3-carboxylic acid, *via* enolate **29**, following enolization and trapping using the premix method and Claisen rearrangement during warming to ambient temperature. This compound was not characterized but immediately esterified using diazomethane and reduced using lithium aluminium hydride to the tetrahydro-3-furylmethanol **30**. This was isolated as a single diastereoisomer; no trace of other isomers was detected. Finally, the alkene group in alcohol **30** was oxidatively cleaved using the two-step Ishibashi protocol[31] (the usual Lemieux–Johnson one-step method proved too slow) to give (±)-samin **9** which displayed spectral data identical to those provided by the Ogasawara group for (−)-**9**.[8] As samin has been shown to react efficiently with aryl Grignard reagents leading to 2,6-diaryl furofuran lignans **8**, following stereoselective, acid-catalysed ring closure,[8] this approach therefore represents a formal synthesis of both symmetrical and unsymmetrical examples of these compounds. The success of this route also shows the veracity of the predictions made on the basis of transition state geometry **29** and that, overall, this approach could be useful in the stereospecific elaboration of many other highly substituted tetrahydrofuran targets. The incorporation of homochiral starting materials into the overall sequence and more efficient routes to the central macrolides would greatly enhance this approach, however.

Experimental

General

Infrared spectra were obtained using a Perkin-Elmer 1720 FTIR spectrometer using liquid films on sodium chloride plates or, if solids, chloroform solutions. ^{1}H NMR Spectra were obtained using a Perkin-Elmer R32a instrument operating at 90 MHz or a Bruker WM-250 instrument operating at 250 MHz. A JEOL EX270 spectrometer operating at 67.5 MHz was used to obtain ^{13}C NMR spectra. All spectra were recorded using dilute solutions in deuteriochloroform, with tetramethyilsilane as the internal standard; *J* values are given in Hz. Mass spectra were obtained in the EI mode using either an AEI MS 902 or a VG 7070E instrument operating at 70 eV. Unless stated otherwise, all reactions were performed under dry mitrogen and all organic solutions from aqueous work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. CC refers to column chromatography using silica gel [SORBSIL® C60-H (40–60 μm)] and the eluents specified. Petrol refers to light petroleum with bp 60–80 °C, and ether refers to diethyl ether.

Ethyl (±)-3-hydroxy-3-phenylpropanoate 12

Ethyl benzoylacetate (4.00 g, 21 mmol) was added to an ice-cooled, stirred solution of sodium borohydride (0.39 g, 10 mmol) in dry ethanol (40 ml). After 1 h, the ethanol was evaporated, the residue dissolved in water (30 ml) and the resulting solution extracted with ether (3 × 30 ml). The combined extracts were washed with water (2 × 30 ml), then dried and evaporated to give the crude hydroxy ester (3.85 g, 95%). Distillation at 110 °C and 3 mmHg gave pure hydroxy ester **12** (3.45 g, 85%) as a colourless oil; ν_{max}/cm^{-1} 3450, 2995, 2945 and 1729; δ_H 1.28 (3 H, t, *J* 7.0, OCH_2CH_3), 2.77 (2 H, d, *J* 7.0, $CH_2C{=}O$), 3.06 (1 H, br, s, OH), 4.22 (2 H, q, *J* 7.0, OCH_2), 5.29 (1 H, t, *J* 7.0, C*H*OH) and 7.44 (5 H, m, Ph).

(*Z*)-4-Acetoxybut-2-en-1-yl trichloroacetimidate 13

Acetyl chloride (3.93 g, 50 mmol) was added to an ice-cooled, stirred solution of (*Z*)-but-2-ene-1,4-diol (22.03 g, 250 mmol) in dry pyridine (100 ml). No further coolant was added as the

resulting mixture was stirred for 15 h, then diluted with water (100 ml) and extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with water (2 × 100 ml), then dried and evaporated. CC [hexanes–ether (3:1)] of the residue gave (*Z*)-4-hydroxybut-2-en-1-yl acetate (4.49 g) as a colourless oil; δ_H 2.10 (3 H, s, MeC=O), 2.68 (1 H, br, s, OH), 4.32 (2 H, d, *J* 6.0, CH_2OH), 4.74 (2 H, d, *J* 6.0, CH_2OAc) and 5.55–6.07 (2 H, m, 2 × =CH); δ_C 20.47 (CH_3C=O), 57.64 (CH_2OH), 59.97 (CH_2OAc), 124.65 (=CH), 133.42 (=CH) and 170.81 (C=O).

A solution of the monoacetate (4.49 g, 35 mmol) in dry ether (5 ml) was added to sodium hydride (0.138 g of a 60% dispersion in oil; washed with dry hexane; *ca.* 3.5 mmol) and the resulting mixture stirred at ambient temperature for 20 min then cooled to *ca.* −5 °C.[32] While maintaining the temperature below 0 °C, trichloroacetonitrile (4.99 g, 35 mmol) was added over 15 min. The mixture was then allowed to warm to ambient temperature and the volatile components were evaporated. The residue was shaken with pentane [50 ml, containing methanol (1 drop)] for 1 min and the resulting suspension filtered. The solid was washed with pentane (2 × 10 ml) and the combined filtrates evaporated to leave the *trichloroacetimidate* **13** (8.34 g, 89%) as a yellow oil; ν_{max}/cm^{-1} 3342, 3034, 2951, 1741 and 1666; δ_H 2.15 (3 H, s, MeC=O), 4.70 (2 H, app. t, *J* 5.0, CH_2OAc), 4.94 (2 H, app. t, *J* 5.0, CH_2OC=N), 5.80–5.86 (2 H, m, 2 × =CH) and 8.39 (1 H, br s, NH); δ_C 20.90 (CH_3C=O), 60.14 (CH_2OAc), 64.95 (CH_2OC=N), 91.39 (Cl_3C), 127.63 (=CH), 128.58 (=CH), 162.35 (C=N) and 170.53 (C=O).

Ethyl (*Z*)-(±)-3-(4-acetoxybut-2-en-1-yloxy)-3-phenylpropanoate 14a

Trifluoromethanesulfonic acid (0.16 ml) was added to a stirred solution of the hydroxy ester **12** (2.34 g, 12 mmol) and trichloroacetimidate **13** (3.96 g, 14 mmol) in a mixture of cyclohexane (16 ml) and dichloromethane (8 ml) at ambient temperature.[18] After 0.5 h, the mixture was filtered and the filtrate washed with saturated aqueous sodium hydrogen carbonate (40 ml) and water (40 ml), then dried and evaporated. CC [hexanes–ether (4:1)] of the residue gave the *acetoxy ester* **14a** (1.38 g, 38%) as a pale yellow oil (Found: M^+, 306.145. $C_{17}H_{22}O_5$ requires *M*, 306.147); ν_{max}/cm^{-1} 3030, 2985, 2940, 1740 and 1730; δ_H 1.23 (3 H, t, *J* 7.0, OCH_2CH_3), 2.03 (3 H, s, MeC=O), 2.71 (2 H, d, *J* 7.0, CH_2C=O), 3.92–4.26 (4 H, m, OCH_2CH= and OCH_2CH_3), 4.66 (2 H, d, *J* 5.0, CH_2OAc), 5.10–5.16 (1 H, m, PhCH), 5.73–5.84 (2 H, m, 2 × =CH) and 7.32 (5 H, app. br s, Ph); *m/z* 306 (M^+, <1%), 120 (8), 113 (7), 106 (18), 77 (22), 70 (5) and 43 (100).

(*Z*)-(±)-4-Oxa-3-phenyloct-6-en-8-olide 15

Potassium hydroxide (7.0 ml of a 2 M solution in ethanol; 14 mmol) was added to the acetoxy ester **14a** (1.38 g, 4.5 mmol) and the resulting solution stirred at ambient temperature for 4 h before removal of the bulk of the volatile components. The residue was partitioned between ethyl acetate (50 ml) and water (50 ml) and the separated aqueous layer acidified using 2 M hydrochloric acid and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water (2 × 50 ml) then dried and evaporated to leave the *hydroxy acid* **14b** (0.74 g, 70%) as a pale yellow oil; δ_H 2.74–2.78 (2 H, m, CH_2C=O), 3.97 (2 H, d, *J ca.* 5, CH_2O), 4.17 (2 H, d, *J* 5, CH_2O), 4.88 (1 H, dd, *J* 9 and 5, PhCH), 5.78–5.84 (2 H, m, 2 × =CH), 7.16 (2 H, br s, 2 × OH) and 7.46 (5 H, app. br s, Ph). This was used in the next step without further purification.

The hydroxy acid **14b** (0.304 g, 1.43 mmol) and triethylamine (1.15 g, 11.5 mmol) in dry dichloromethane (50 ml) were added dropwise over 40 h, *via* a motor driven syringe, to a stirred and refluxing solution of 2-chloro-1-methylpyridinium iodide (1.47 g, 5.98 mmol) in dry dichloromethane (270 ml).[19] After a further 4 h reflux, the mixture was cooled and evaporated. CC [hexanes–ether (3:1)] of the residue separated the *macrolide* **15** (0.113 g, 36%) as a pale yellow oil (Found: C, 71.7; H, 6.6. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%); ν_{max}/cm^{-1} 3025, 2925, 1745 and 1575; δ_H 2.75 (1 H, dd, *J* 14.7 and 10.8, CH_AH_BC=O), 3.03 (1 H, dd, *J* 14.7 and 5.0, CH_AH_BC=O), 4.23–4.29 (1 H, m, OCH_AH_BCH=), 4.40–4.46 (1 H, m, OCH_AH_BCH=), 4.68 (1 H, d, *J* 14.9, CH_AH_BOC=O), 5.02 (1 H, dd, *J* 10.8 and 5.0, PhCH), 5.26–5.30 (1 H, m, CH_AH_BOC=O), 5.81–5.83 (2 H, m, 2 × =CH) and 7.23–7.40 (5 H, m, Ph); δ_C 44.69 (CH_2C=O), 62.58 (OCH_2CH=), 70.67 (CH_2OC=O), 83.69 (PhCH), 125.60, 127.75, 128.52, 128.62, 131.64 (all CH), 142.09 (C) and 170.93 (C=O).

(2*SR*,3*RS*,4*RS*)-2-Phenyl-4-vinyltetrahydro-3-furylmethanol 17

Lithium diisopropylamide was prepared by the addition of butyllithium (1.35 ml of a 1.6 M solution in hexanes, 2.2 mmol) to a cooled (*ca.* −30 °C) solution of diisopropylamine (0.35 ml, 2.5 mmol) in dry tetrahydrofuran (8.3 ml). After 0.5 h, 3.2 ml of the resulting solution was transferred *via* syringe to a dry flask and cooled to −100 °C. Trimethylsilyl chloride (0.10 g, 0.93 mmol) was added followed by a solution of the macrolide **15** (0.050 g, 0.23 mmol) in dry tetrahydrofuran (3 ml), added dropwise over 10 min.[21] The resulting solution was warmed to −30 °C over 1 h then stirred without cooling for a further 1 h. A solution of lithium aluminium hydride (0.02 g, 0.45 mmol) in tetrahydrofuran (2 ml) was added dropwise *via* syringe and the resulting solution stirred for 1 h, after which water (6 ml) was added. The resulting suspension was filtered and the filtrate extracted with ether (3 × 10 ml). The combined extracts were washed with water (2 × 10 ml), then dried and evaporated. CC [hexane–ether (1:2)] separated the *alcohol* **17** (0.033 g, 71%) as a colourless oil (Found: M^+, 204.114. $C_{13}H_{16}O_2$ requires *M*, 204.115); ν_{max}/cm^{-1} 3470, 2935 and 1620; δ_H 2.42 (1 H, dddd, *J* 9.3, 7.8, 6.7 and 5.8, 4-H), 3.12 (1 H, dddd, *J* 7.8, 7.4, 7.2 and 5.8, 3-H), 3.70 (1 H, dd, *J* 11.1 and 5.8, CH_AH_BOH), 3.80 (1 H, dd, *J* 11.1 and 7.4, CH_AH_BOH), 3.87 (1 H, dd, *J* 8.6 and 5.8, 5-H_A), 4.27 (1 H, dd, *J* 8.6 and 6.7, 5-H_B), 4.79 (1 H, d, *J* 7.2, 2-H), 5.17–5.23 (2 H, m, $=CH_2$), 5.98 (1 H, ddd, *J* 17.1, 10.1 and 9.3, =CH) and 7.30–7.38 (5 H, m, Ph); δ_C 45.82 (CH), 53.97 (CH), 61.05 (CH_2OH), 72.92 (5-CH_2), 82.63 (PhCH), 117.50 ($=CH_2$), 125.83, 127.56, 128.48, 135.75 (all CH) and 142.53 (C); *m/z* 204 (M^+, 12%), 203 (23), 127 (36), 106 (88), 105 (100), 77 (74) and 69 (43).

2-(2*H*-1,3-Benzodioxol-5-yl)-4,7-dihydro-2*H*-1,3-dioxepine 18

A solution of piperonal (3.00 g, 20 mmol), (*Z*)-but-2-ene-1,4-diol (1.85 g, 21 mmol) and camphorsulfonic acid (0.023 g, 0.1 mmol) in dry toluene (100 ml) was held at reflux under a Dean and Stark water separator for 18 h.[23] The cooled solution was washed with water (3 × 30 ml) and brine (40 ml) then the volatile components were evaporated. Crystallization of the residue from hexane gave the *acetal* **18** (3.87 g, 88%) as a colourless solid, mp 48–50 °C (Found: C, 65.6; H, 5.5. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.5%) (Found: M^+, 220.071. $C_{12}H_{12}O_4$ requires *M*, 220.073); ν_{max}/cm^{-1} 3031, 2941, 2896 and 1605; δ_H 4.35–4.41 (4 H, m, 2 × OCH_2), 5.86 (3 H, app. br s, 2-H and 2 × =CH), 6.05 (2 H, s, OCH_2O) and 6.86–7.14 (3 H, m, 3 × CH); *m/z* 220 (M^+, 43%), 166 (11), 149 (100), 134 (5), 121 (22) and 70 (11).

Ethyl (*Z*)-3-(2*H*-1,3-benzodioxol-5-yl)-2-nitropropenoate 22

A mixture of piperonal (4.70 g, 31 mmol), ethyl nitroacetate (5.05 g, 38 mmol), diethylammonium chloride (6.90 g, 63 mmol) and potassium fluoride (0.27 g, 4.7 mmol) in dry toluene (160 ml) was heated at reflux under a Dean and Stark water separator for 24 h.[25] After cooling, the solvent was evaporated and the residue partitioned between water (30 ml) and dichloromethane (100 ml). The organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 40 ml). The combined organic solutions were dried and evaporated and the residue stirred with hexane (50 ml) for 3 h. The hexane was decanted and the residue separated by CC [hexanes–ether (2:1)] to give the *nitro ester* **22** (2.60 g, 31%) as an orange oil; ν_{max}/

cm^{-1} 2986, 2909, 1754, 1603, 1569 and 1360; δ_H 1.04–1.32 (3 H, m, OCH_2CH_3), 4.07–4.33 (2 H, m, OCH_2), 4.78–4.04 (1 H, m, =CH), 6.00 (2 H, s, OCH_2O) and 6.90–6.96 (3 H, m, 3 × CH); δ_C 14.78 (CH_3), 63.66 (OCH_2), 101.42 (OCH_2O), 108.36, 109.23, 123.04 (all CH), 124.67 (C), 124.94 (3-C), 147.98 (C), 148.29 (C), 162.21 (=CNO_2) and 162.64 (C=O); *m/z* 265 (M^+, 7%), 220 (5), 86 (30), 84 (46), 58 (60), 44 (10) and 43 (100).

(*Z*)-4-*tert*-Butyldimethylsilyloxybut-2-en-1-ol 23

A solution of *tert*-butyldimethylsilyl chloride (7.54 g, 50 mmol) in dry dichloromethane (10 ml) was added dropwise to an ice-cooled, stirred solution of (*Z*)-but-2-ene-1,4-diol (11.01 g, 125 mmol), triethylamine (5.06 g, 50 mmol) and 4-dimethylaminopyridine (*ca.* 10 mg) in dry dichloromethane (90 ml). The cooling bath was removed and stirring continued for 16 h before water (100 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 100 ml). The combined organic solutions were washed successively with water (100 ml) and brine (100 ml), then dried and evaporated. The residue was purified by CC [hexanes–ether (2:1)] to give the silyl ether **23** (8.64 g, 86% based on silyl chloride) as a colourless oil (Found: $M^+ - OH$, 185.133. $C_{10}H_{21}OSi$ requires $M - OH$, 185.136); ν_{max}/cm^{-1} 3356, 3025, 2929, 2857 and 1472; δ_H 0.11 (6 H, 2 × MeSi), 0.94 (9 H, Bu^{t}Si), 2.45 (1 H, br s, OH), 4.27–4.33 (4 H, m, 2 × CH_2O) and 5.77–5.81 (2 H, m, 2 × =CH); δ_C −0.04 (SiMe), −0.01 (SiMe), 18.58 (SiC), 26.16 (SiCMe_3), 59.04 (CH_2O), 59.86 (CH_2O), 130.39 (=CH) and 131.64 (=CH); *m/z* 185 (6), 159 (13), 145 (16), 129 (10), 115 (8), 75 (100), 71 (7) and 57 (16).

Ethyl (*Z*)-3-(2*H*-1,3-benzodioxol-5-yl)-3-(4-*tert*-butyldimethylsilyloxybut-2-en-1-yloxy)-2-nitropropanoate 24a

A solution of the monosilylated diol **23** (1.01 g, 5.0 mmol) in dry tetrahydrofuran (5 ml) was added to sodium hydride (0.20 g of a 60% suspension in oil, washed with tetrahydrofuran, *ca.* 5.0 mmol) and the mixture stirred at ambient temperature for 0.5 h. Additional tetrahydrofuran (10 ml) was added and the resulting solution cooled to 0 °C before the dropwise addition of a solution of the nitro ester **22** (1.30 g, 5.0 mmol) in dry tetrahydrofuran (5 ml). The cooling bath was then removed and stirring continued for a further 0.5 h at which point water (20 ml) was added. The resulting mixture was neutralized using 2 M hydrochloric acid and extracted with ether (3 × 20 ml). The combined extracts were washed with water (2 × 20 ml), then dried and evaporated. CC [hexane–ether (2:1)] gave the *nitro ether* **24a** (0.75 g, 32%) as an orange oil; ν_{max}/cm^{-1} 2956, 2886, 2857, 1753, 1571 and 1374; δ_H 0.09 (6 H, s, 2 × MeSi), 0.92 (9 H, s, Bu^{t}Si), 1.03–1.32 (3 H, m, OCH_2CH_3), 4.14–4.32 (6 H, m, 3 × OCH_2), 4.62–4.80 (2 H, m, ArC*H* and $CHNO_2$), 5.70–5.87 (2 H, m, 2 × =CH), 5.98 (2 H, s, OCH_2O) and 6.82–6.87 (3 H, m, 3 × CH); δ_C −0.03 (SiMe), −0.01 (SiMe), 14.45 (CH_3), 18.21 (SiC), 25.85 (SiCMe_3), 58.25 and 58.57 (CH_2O), 59.49 (CH_2O), 63.39 and 63.77 (CH_2O), 87.77 (CH), 88.53 and 88.91 (CH), 101.53 (OCH_2O), 108.58, 109.50, 123.15 (all CH), 129.97 (C), 130.89, 131.17 (both =CH), 148.12, 148.50 (both C) and 162.75 (C=O); *m/z* 351 (13%), 266 (14), 220 (62), 204 (27), 160 (59), 121 (13), 88 (44) and 75 (100).

The NMR data indicated a diastereoisomer ratio of 3:2.

Ethyl (*Z*)-3-(2*H*-1,3-benzodioxol-5-yl)-3-(4-*tert*-butyldimethylsilyloxybut-2-en-1-yloxy)propanoate 24b

Tributyltin hydride (1.37 g, 4.7 mmol) was added dropwise to a refluxing solution of the nitro ether **24a** (0.44 g, 0.9 mmol) and AIBN (31 mg) in dry benzene (10 ml).[26] After 2 h, the solution was cooled to ambient temperature and the solvent evaporated. The residue was partitioned between ether (10 ml) and water (10 ml). The separated aqueous layer was extracted with ether (2 × 10 ml) and the combined organic solutions were then dried and evaporated. CC [hexane–ether (1:1)] gave the *ester* **24b** (0.33 g, 83%) as a yellow oil; ν_{max}/cm^{-1} 2930, 2857 and 1732; δ_H 0.09 (6 H, s, 2 × MeSi), 0.91 (9 H, s, Bu^{t}Si), 1.08 (3 H, t, *J* 8.0, OCH_2CH_3), 2.53–2.59 (2 H, m, CH_2C=O), 4.02 (2 H, q, *J* 8.0, OCH_2), 4.14–4.20 (4 H, m, 2 × OCH_2CH=), 4.66 (1 H, dd, *J* 8.7 and 4.9, ArCH), 5.63–5.69 (2 H, m, 2 × =CH), 5.90 (2 H, s, OCH_2O) and 6.68–6.74 (3 H, m, 3 × CH); δ_C −0.03 (SiMe), −0.01 (SiMe), 14.04 (SiC), 14.36 (CH_3), 25.85 (SiCMe_3), 40.91 (CH_2C=O), 58.57 (CH_2O), 59.49 (CH_2O), 62.80 (CH_2O), 76.97 (ArCH), 100.83 (OCH_2O), 107.60, 108.14, 120.38 (all CH), 129.97 (C), 130.81, 131.11 (both =CH), 146.34, 147.64 (both C) and 171.53 (C=O).

Methyl (*Z*)-3-(2*H*-1,3-benzodioxol-5-yl)-2-phenylsulfonylpropenoate 26

Reaction between piperonal (2.46 g, 16.4 mmol), methyl phenylsulfonylacetate (4.21 g, 19.7 mmol), diethylammonium chloride (2.67 g, 24.5 mmol) and potassium fluoride (0.14 g, 2.5 mmol) in dry toluene (100 ml) for 15 h, as described above for the corresponding 2-nitropropenoate **22**, gave a solid residue which was directly crystallized from dichloromethane to give the *sulfonyl ester* **26** (2.51 g, 44%) as yellow needles, mp 129–131 °C (Found: C, 58.7; H, 4.1. $C_{17}H_{14}O_6S$ requires C, 59.0; H, 4.1%) (Found: M^+, 346.050. $C_{17}H_{14}O_6S$ requires *M*, 346.051); λ_{max}/nm 241.6, 295.7 and 336.8; ν_{max}/cm^{-1} 2953, 2907, 1726, 1598, 1322 and 1151; δ_H 3.85 (3 H, s, OMe), 6.15 (3 H, app. br s, 3-H and OCH_2O), 7.06–7.12 (3 H, m, 3 × CH), 7.74–7.80 (2 H, m, 2 × CH) and 8.14–8.22 (3 H, m, 3 × CH); δ_C 52.88 (OMe), 101.97 (OCH_2O), 108.47, 108.74, 109.01, 125.59, 127.48, 128.40, 129.05 (all CH), 132.09, 133.50, 147.36, 148.12 (all C) and 163.29 (C=O); *m/z* 346 (45%), 315 (7), 205 (31), 204 (100) and 46 (54).

Methyl (*Z*)-3-(2*H*-1,3-benzodioxol-5-yl)-3-(4-*tert*-butyldimethylsilyloxybut-2-en-1-yloxy)-2-phenylsulfonylpropanoate 27a

A solution of the monoprotected diol **23** (0.97 g, 4.8 mmol) in tetrahydrofuran (1 ml) was added to a suspension of sodium hydride (0.193 g of a 60% suspension in oil; washed with tetrahydrofuran; 4.8 mmol) in tetrahydrofuran (10 ml). After 0.5 h, a solution of the sulfone **26** (1.67 g, 4.8 mmol) in tetrahydrofuran (5 ml) was added followed, after 0.5 h, by ether (50 ml). Water (50 ml) was added and the separated aqueous layer extracted with ether (3 × 50 ml). The combined organic solutions were washed with water (2 × 30 ml), then dried and the solvents evaporated. CC [hexane–ether (2:1)] of the residue gave the *sulfonyl ester* **27a** (2.12 g, 80%) as a yellow oil; ν_{max}/cm^{-1} 2950, 2855, 2782 and 1722; δ_H 0.08 (6 H, s, 2 × MeSi), 0.91 (9 H, s, Bu^{t}Si), 3.57 (3 H, s, OMe), 3.85–3.91 (2 H, m, CH_2OSi), 4.10–4.14 (2 H, m, OCH_2CH=), 5.01 (1 H, dd, *J* 11.1 and 3.0, ArCH), 5.69 (2 H, m, 2 × =CH), 5.96–6.01 (1 H, m, $CHSO_2$), 6.03 (2 H, s, OCH_2O), 6.83–6.87 (3 H, m, 3 × CH), 7.64–7.80 (2 H, m, 2 × CH) and 8.14–8.20 (3 H, m, 3 × CH); δ_C −0.02 (SiMe), 0.00 (SiMe), 18.04 (SiC), 25.68 (SiCMe_3), 52.72 and 52.86 (OMe), 59.23 and 59.19 (CH_2OSi), 63.69 and 64.15 (OCH_2C=), 75.83 and 76.52 (CH), 77.67 and 78.51 (CH), 101.04 and 101.13 (OCH_2O), 107.21 and 107.69, 107.98, 121.67, 125.78, 128.48, 128.64, 129.33 and 129.76, 133.05 and 133.45 (all CH), 133.39 and 133.75, 138.58 and 139.95, 147.69 and 147.92, 148.09 and 148.19 (all C) and 163.50 and 164.60 (C=O). These data indicated a diastereoisomer ratio of 3:2.

Methyl (*Z*)-3-(2*H*-1,3-benzodioxol-5-yl)-3-(4-*tert*-butyldimethylsilyloxybut-2-en-1-yloxy)propanoate 27b

A solution of the sulfone **27a** (0.20 g, 0.36 mmol) in dry tetrahydrofuran (2 ml) was added dropwise to a stirred suspension of 1% sodium amalgam [from 17 mg (0.7 mmol) of sodium] and sodium dihydrogen phosphate (0.21 g, 1.46 mmol) in dry methanol (4 ml),[30] maintained at −50 °C. The resulting mixture was allowed to warm slowly to ambient temperature, when ether (20 ml) was added. The resulting solution was washed with water (4 × 20 ml) and brine (20 ml), then dried and evaporated.

CC [hexane–ether (4:1)] of the residue gave the *ester* **27b** (0.10 g, 68%) as a colourless oil (Found: C, 61.9; H, 8.1. $C_{21}H_{32}O_6Si$ requires C, 61.7; H, 7.9%) (Found: M^+, 408.198. $C_{21}H_{32}O_6Si$ requires *M*, 408.197); ν_{max}/cm^{-1} 2952, 2930, 2856, 1735 and 1610; δ_H 0.02 (6 H, s, 2 × MeSi), 0.86 (9 H, s, Bu^{t}Si), 2.55 (1 H, dd, *J* 15.4 and 5.0, CH_AH$_B$C=O), 2.79 (1 H, dd, *J* 15.4 and 8.9, CH$_A$$H_B$C=O), 3.67 (3 H, s, OMe), 3.85–3.91 (2 H, m, CH$_2$C=), 4.07–4.11 (2 H, m, CH$_2$C=), 4.69 (1 H, dd, *J* 8.9 and 5.0, ArCH), 5.52–5.58 (1 H, m, =CH), 5.62–5.68 (1 H, m, =CH), 5.94 (2 H, s, OCH$_2$O) and 6.77–6.83 (3 H, m, 3 × CH); δ_C −0.02 (SiMe), 0.00 (SiMe), 18.32 (SiC), 25.94 (SiC*Me*$_3$), 43.42 (CH$_2$C=O), 51.73 (OMe), 59.53 (CH$_2$OSi), 64.30 (CH$_2$C=), 77.37 (CH), 101.12 (OCH$_2$O), 106.81, 108.19, 120.43, 126.60, 132.92 (all CH), 134.71, 147.45, 148.09 (all C) and 171.28 (C=O); *m/z* 408 (M^+, 2%), 208 (37), 207 (27), 165 (24), 148 (31) and 135 (100).

(*Z*)-3-(2*H*-1,3-Benzodioxol-5-yl)-4-oxaoct-6-en-8-olide 28

Potassium hydroxide (3.1 ml of a 2 M solution in methanol; 5.4 mmol) was added to the ester **27b** (0.86 g, 2.03 mmol) and the resulting solution stirred overnight at ambient temperature. The methanol was evaporated and the residue dissolved in water (80 ml). The resulting solution was brought to pH 4 using 2 M hydrochloric acid and then extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with water (2 × 25 ml), then evaporated to leave the hydroxy acid **27c** (0.53 g, 92%); ν_{max}/cm^{-1} 3522, 3192, 2854, 2779 and 1715; δ_H 2.68–2.74 (2 H, m, CH$_2$C=O), 3.94 (2 H, d, *J* 5.1, CH$_2$C=), 4.10–4.16 (2 H, m, CH$_2$C=), 4.70–4.78 (1 H, m, ArCH), 5.69–5.75 (2 H, m, 2 × =CH), 6.00 (2 H, s, OCH$_2$O) and 6.87–6.93 (3 H, m, 3 × CH), which was immediately subjected to lactonization.

A solution of hydroxy acid **27c** (0.53 g, 1.9 mmol) and triethylamine (1.53 g, 15 mmol) in dry acetonitrile (40 ml) was added over 40 h, *via* motor-driven syringe, to a refluxing solution of 2-chloro-1-methylpyridinium iodide (1.93 g, 7.5 mmol) in acetontrile (380 ml).[19] After a further 4 h, the mixture was cooled and the solvent evaporated. CC [hexane–ether (2:1)] of the residue gave the *macrolide* **28** (0.25 g, 51%) as a colourless oil (Found: M^+, 262.083. $C_{14}H_{14}O_5$ requires *M*, 262.084); ν_{max}/cm^{-1} 2929, 2855 and 1749; δ_H 2.70 (1 H, dd, *J* 14.7 and 10.8, CH_AH$_B$C=O), 2.96 (1 H, dd, *J* 14.7 and 5.0, CH$_A$$H_B$C=O), 4.20–4.24 (1 H, m, OCH_AH$_B$), 4.36–4.40 (1 H, m, OCH$_A$$H_B$), 4.65 (1 H, br d, *J* 14.9, CH_AH$_B$OC=O), 4.90 (1 H, dd, *J* 10.8 and 5.0, ArCH), 5.25 (1 H, br d, *J* 14.9, CH$_A$$H_B$OC=O), 5.75–5.81 (2 H, m, 2 × =CH), 5.93 (2 H, s, OCH$_2$O) and 6.77–6.83 (3 H, m, 3 × CH); δ_C 44.74 (CH$_2$C=O), 62.57 (OCH$_2$), 70.48 (CH$_2$OC=O), 83.41 (ArCH), 101.13 (OCH$_2$O), 106.40, 108.17, 118.89 (all CH), 128.45, 131.56 (both =CH), 136.11, 147.11, 147.94 (all C) and 170.83 (C=O); *m/z* 262 (M^+, 13%), 208 (3), 164 (4), 121 (6), 112 (27) and 75 (100).

(±)-(2*SR*,3*RS*,4*RS*)-2-(2*H*-1,3-Benzodioxol-5-yl)-4-vinyltetrahydro-3-furylmethanol 30

Trimethylsilyl chloride (0.14 g, 1.3 mmol) was added dropwise to a stirred solution of lithium diisopropylamide (0.6 ml of a 1.5 M solution in cyclohexane, 0.9 mmol) in tetrahydrofuran (10 ml) maintained at −100 °C, followed by a solution of the lactone **28** (0.082 g, 0.3 mmol) in dry tetrahydrofuran (2 ml), added dropwise over 10 min. The resulting solution was allowed to warm to −30 °C over 1 h, then the cooling bath was removed and stirring continued for a further 1 h. Methanol (2 ml) was added and after a further 10 min the solvents were evaporated. The residue was partitioned between ethyl acetate (20 ml) and water (20 ml) and the whole neutralized by the addition of solid citric acid. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 20 ml). The combined organic solutions were washed with water (2 × 20 ml), then dried and evaporated to leave the crude tetrahydrofurancarboxylic acid as a yellow oil.

Excess ethereal diazomethane was added to this residue and the resulting solution left at ambient temperature for 1 h, when most of the excess diazomethane was destroyed by the dropwise addition of acetic acid. The resulting solution was filtered through a plug of silica, the filtrates evaporated and the residue dissolved in dry tetrahydrofuran (1 ml). This solution was added dropwise to an ice-cooled, stirred suspension of lithium aluminium hydride (5 mg) in tetrahydrofuran (5 ml). The cooling bath was removed and stirring continued for 1 h, at whch point water (5 ml) was slowly added. The resulting suspension was filtered and the solid washed with ether. The filtrate was separated and the aqueous phase extracted with ether (3 × 10 ml). The combined organic solutions were washed with water (2 × 5 ml), then dried and evaporated. CC [hexane–ether (1:2)] of the residue gave the *tetrahydro*-3-*furylmethanol* **30** (18.4 mg, 53%)[8] as a colourless, crystalline solid, mp 68–70 °C (from hexane–ether) (Found: C, 67.5; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%) (Found: M^+, 248.103. $C_{14}H_{16}O_4$ requires *M*, 248.105; ν_{max}/cm^{-1} 3467, 2936, 2677 and 1610; δ_H 1.55 (1 H, br s, OH), 2.29 (1 H, m, 4-H), 3.01–3.07 (1 H, m, 3-H), 3.58 (1 H, dd, *J* 11.1 and 5.8, CH_AH$_B$OH), 3.69 (1 H, dd, *J* 11.1 and 7.3, CH$_A$$H_B$OH), 3.75 (1 H, dd, *J* 8.6 and 5.8, 5-H$_A$), 4.16 (1 H, dd, *J* 8.6 and 6.7, 5-H$_B$), 4.60 (1 H, d, *J* 7.3, 2-H), 5.10–5.14 (2 H, m, =CH$_2$), 5.93–5.99 (1 H, m, =CH), 5.87 (2 H, s, OCH$_2$O) and 6.69–6.75 (3 H, m, 3 × CH); δ_C 45.84 (3-CH), 53.82 (4-CH), 61.01 (CH$_2$OH), 72.81 (5-CH$_2$), 82.59 (2-CH), 101.01 (OCH$_2$O), 106.40, 108.10 (both ArCH), 117.47 (=CH$_2$), 119.35 (ArCH), 135.75 (*C*H=CH$_2$), 136.37, 147.04 and 147.90 (all ArC); *m/z* 248 (M^+, 41%), 150 (100), 135 (12) and 67 (9).

(±)-2-(2*H*-1,3-Benzodioxol-5-yl)-3,7-dioxabicyclo[3.3.0]octan-6-ol [(±)-samin] 9

A solution of tetrahydrofuran **30** (18.4 mg, 0.07 mmol), osmium tetroxide (10 mg) and *N*-methylmorpholine *N*-oxide (11 mg, 0.08 mmol) in acetone (7.5 ml), *tert*-butyl alcohol (1.75 ml) and water (1.75 ml) was stirred at ambient temperature for 15 h (TLC monitoring). Celite (*ca.* 0.5 g) and sodium hydrogen sulfate [0.5 g in water (10 ml)] were added and the resulting suspension filtered and the solid thoroughly washed with acetone. The filtrate was evaporated and the residue extracted with ethyl acetate (2 × 20 ml). The combined extracts were dried and evaporated to leave the crude triol (*ca.* 15 mg, >70%); ν_{max}/cm^{-1} 3323, 2914, 2853 and 2778.

A solution of the triol (*ca.* 15 mg), sodium metaperiodate (23 mg, 0.1 mmol) and tetrabutylammonium periodate (1 mg, 0.003 mmol) in ice-cold water (5 ml) and dichloromethane (5 ml) was stirred vigorously for 24 h (TLC monitoring).[31] The organic phase was separated and the aqueous phase extracted with dichloromethane (2 × 20 ml). The combined organic solutions were dried and evaporated. CC [hexane–ether (1:2)] gave (±)-samin **9** (9 mg, 68%) as a colourless solid, mp 112–114 °C [lit.,[8] mp 106 °C for (+)-**9**] (Found: M^+, 250.086. $C_{13}H_{14}O_5$ requires *M*, 250.084); ν_{max}/cm^{-1} 3597, 3020, 2930 and 2891; δ_H 1.46 (1 H, br s, OH), 2.87 (1 H, app. dd, *J* 15.3 and 6.1, 1-H), 3.08 (1 H, app. br q, *J* 8.9, 5-H), 3.57 (1 H, dd, *J* 9.2 and 7.4, 4-H$_A$), 3.91 (1 H, app. d, *J* 9.2, 4-H$_B$), 4.18 (2 H, app. dd, *J* 9.2 and 6.0, 8-CH$_2$), 4.33–4.39 (1 H, m, 2-H), 5.39 (1 H, s, 6-H), 5.95 (2 H, s, OCH$_2$O) and 6.77–6.85 (3 H, m, 3 × CH); δ_C 52.88 (1-CH), 53.70 (5-CH), 69.42 (4-CH$_2$), 71.33 (8-CH$_2$), 86.97 (2-CH), 101.15 (OCH$_2$O), 102.30 (6-CH), 106.63, 108.25, 119.71 (all ArCH), 134.65, 147.38 and 148.06 (all ArC); *m/z* 250 (M^+, 11%), 216 (11), 121 (3) and 57 (100). These data are identical to those supplied by Professor K. Ogasawara (Tohoku University) for a synthetic sample of (−)-samin.[8]

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References

1 R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.
2 S. Danishefsky, R. L. Funk and J. F. Kerwin, *J. Am. Chem. Soc.*, 1980, **102**, 6889; S. Danishefsky and K. Tsuzuki, *J. Am. Chem. Soc.*, 1980, **102**, 6891.
3 A. G. Cameron and D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1986, 161; R. L. Funk, T. A. Olmstead, M. Parvez and J. B. Stallmann, *J. Org. Chem.*, 1993, **58**, 5873 and references cited therein.
4 R. L. Funk, M. M. Abelman and J. D. Munger, *Tetrahedron*, 1986, **42**, 2831.
5 J. Cooper, D. W. Knight and P. T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1991, 705; J. Cooper, D. W. Knight and P. T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1992, 553; R. L. Funk and J. D. Munger, Jr., *J. Org. Chem.*, 1985, **50**, 707.
6 For reviews of this area in general, see D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 191; 1987, **4**, 499; D. C. Ayers and J. D. Loike, *Lignans: Chemistry, Biological and Clinical Properties*, Cambridge University Press, 1990; R. S. Ward, *Tetrahedron*, 1990, **46**, 5029; R. S. Ward, *Nat. Prod. Rep.*, 1993, **10**, 1. For recent work in the area of furofuran synthesis, see K. Mikami, H. Matsueda and T. Nakai, *Synlett*., 1993, 235; A. van Oeveren, J. F. G. A. Jansen and B. L. Feringa, *J. Org. Chem.*, 1994, **59**, 5999; T. Ogiku, S. Yoshida, H. Ohmizu and T. Iwasaki, *J. Org. Chem.*, 1995, **60**, 1148; S. Yoshida, T. Yamanaka, T. Miyake, Y. Moritani, H. Ohmizu and T. Iwasaki, *Tetrahedron Lett.*, 1995, **36**, 7271; H. Suginome, K. Orito, K. Yorita, M. Ishikawa, N. Shimoyama and T. Sasaki, *J. Org. Chem.*, 1995, **60**, 3052.
7 E. Haslam and R. D. Haworth, *J. Chem. Soc.*, 1955, 827; P. Budowski, *J. Am. Oil Chem. Soc.*, 1964, **41**, 280.
8 S. Takano, T. Ohkawa, S. Tamori, S. Satoh and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 189. See also Y. Fukuda, M. Isobe, M. Nagata, T. Osawa and M. Namiki, *Heterocycles*, 1986, **24**, 923.
9 A. Pelter, R. S. Ward, P. Collins, R. Venkateswarlin and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1*, 1985, 587 and references cited therein.
10 D. R. Stevens and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1990, 425 and references cited therein.
11 G. A. Kraus and L. Chen, *J. Am. Chem. Soc.*, 1990, **112**, 3464.
12 S. Takano, K. Samizu and K. Ogasawaara, *J. Chem. Soc., Chem. Commun.*, 1993, 1032; *Synlett*, 1993, 785.
13 G. Maiti, S. Adhikari and S. C. Roy, *Tetrahedron Lett.*, 1994, **35**, 6731; *Tetrahedron*, 1995, **51**, 8389.
14 H. M. Bradley, R. G. Jones and D. W. Knight, *Synlett*, 1992, 479.
15 For a preliminary communication, see H. M. Bradley and D. W. Knight, *J. Chem. Soc., Chem. Commun.*, 1991, 1641.
16 K. Shimizu and K. Ogasawara, *Chem. Lett.*, 1995, 543.
17 T. Wirth, K. J. Kulicke and G. Fragale, *J. Org. Chem.*, 1996, **61**, 2686.
18 U. Widmer, *Synthesis*, 1987, 568.
19 T. Mukaiyama, M. Usui and K. Saigo, *Chem. Lett.*, 1976, 49.
20 R. L. Funk, M. M. Abelman and K. M. Jellison, *Synlett*, 1989, 36.
21 R. E. Ireland and D. W. Norbeck, *J. Am. Chem. Soc.*, 1985, **107**, 3279.
22 J. D. Elliott, J. Steele and W. S. Johnson, *Tetrahedron Lett.*, 1985, **26**, 2535.
23 S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge and B. E. Segmuller, *J. Am. Chem. Soc.*, 1985, **107**, 3891.
24 C. H. Heathcock and L. A. Flippin, *J. Am. Chem. Soc.*, 1983, **105**, 1667.
25 D. Dauzonne and R. Royer, *Synthesis*, 1987, 399.
26 N. Ono, H. Miyake, R. Tamura and A. Kaji, *Tetrahedron Lett.*, 1981, **22**, 1705.
27 N. Ono, H. Miyake and A. Kaji, *Chem. Lett.*, 1985, 635; N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura and A. Kaji, *Tetrahedron*, 1985, **41**, 4013.
28 N. Kornblum, S. C. Carlson and R. G. Smith, *J. Am. Chem. Soc.*, 1979, **101**, 647; A. Lytko-Krasuska, H. Piotrowska and T. Urbanski, *Tetrahedron Lett.*, 1979, 1243; N. Ono, R. Tamura and A. Kaji, *J. Am. Chem. Soc.*, 1980, **102**, 2851; H. Suzuki, K. Takaoka and A. Osuka, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1067.
29 H. Dressler and J. E. Graham, *J. Org. Chem.*, 1967, **32**, 985.
30 B. M. Trost, H. C. Arndt, P. E. Strege and T. R. Verhoeven, *Tetrahedron Lett.*, 1976, 3477.
31 F. Ishibashi and E. Taniguchi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4361; *Chem. Lett.*, 1989, 313.
32 L. A. Clizbe and L. E. Overman, *Org. Synth.*, 1978, **58**, 4.

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