An alternative diastereospecific approach to (±)-samin and 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane [furanofuran] lignans based on the Ireland–Claisen rearrangement of unsaturated oxa-macrolides

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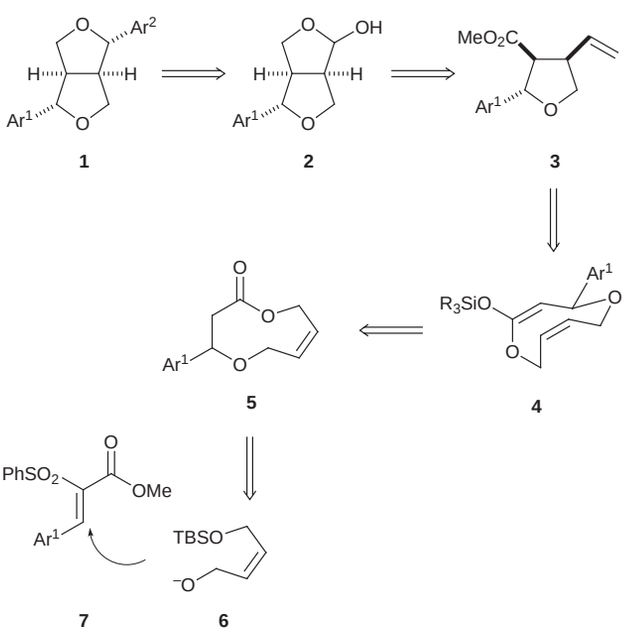
Ireland–Claisen rearrangement of the nine-membered macrolide 22 leads stereospecifically to the tetrahydrofurancarboxylate 23, *via* the boat-like transition state 9. The hydroxy-acid precursor 21c to the macrolide 22 has been prepared by Michael addition of the sodium alkoxide of (*Z*)-allylic alcohol 20 to methyl acrylate in the presence of dimethyl sulfoxide. Subsequent conversion into the corresponding aldehyde 29, Grignard addition, cleavage of the alkene and acid-catalysed cyclisation gives (±)-sesamin 32. The epimeric ester 33 has been converted into (±)-samin 37 by related functional group manipulations, but excluding the Grignard coupling, and a final isomerisation.

The naturally occurring lactol samin [**2**; Ar^1 = 1,3-benzodioxol-5-yl], and related structures containing other aryl substituents, have been shown by the Takano–Ogasawara group to be useful precursors to furanofuran lignans **1**, specifically with the two aryl groups in equatorial positions, following coupling with an aryl Grignard reagent [Ar^2MgX] and acid-catalysed cyclodehydration.[1,2] Hence, this approach allows for the incorporation of different aryl substituents into such lignans. The approach to the lactol intermediates **2** developed by the Japanese group also delivers homochiral products but does, however, rely on a somewhat convoluted route, based around an intramolecular Diels–Alder cycloaddition, to access the required precursors. Previous approaches, albeit shorter, have delivered racemic products and have mainly proceeded *via* butyrolactone intermediates,[3] with the exception of the Kraus photocyclisation method,[4] while more recent methods have proven capable of producing homochiral products,[5] as well as both axial–equatorial and diaxial furanofurans.[6] These methods have featured a range of key steps, including dioxepin rearrangements,[7] β-scission of alkoxy radicals,[8] radical cyclisation[9] and homochiral carbohydrate starting materials[10] to access these targets. We have exploited the excellent levels of stereoselection available from Ireland enolate Claisen rearrangements of medium-sized macrolides in a brief approach to the tetrahydrofurancarboxylic acid ester [**3**; Ar^1 = 1,3-benzodioxol-5-yl], which was then readily converted into samin [**2**; Ar^1 = 1,3-benzodioxol-5-yl].[11]

This strategy (Scheme 1) required the nine-membered macrolide **5** which upon enolization and *O*-silylation, underwent smooth rearrangement, presumably through the boat-like transition state **4** with the aryl group positioned equatorially, and hence delivered the required stereochemistry in the resulting tetrahydrofuran.[12] Our original plan was to prepare the hydroxy-acid precursor to macrolide **5** in homochiral form by selective *O*-alkylation of a β-hydroxy-ester. However, this route proved impractical; we were finally able to achieve a synthesis of racemic samin **2** by using a Michael addition of a mono-protected but-2-ene-1,4-diol **6** to the activated acceptor **7**. As yet, this approach has not proven capable of delivering homochiral products. We therefore contemplated an alternative but similarly brief strategy (Scheme 2) in which an isomeric tetrahydrofuran ester **8** would be a key intermediate. This implied the intermediacy of the transition state **9**, expected[12] from



Scheme 1

enolisation and *O*-silylation of the macrolide **10**, which we anticipated could be obtained in turn by Michael addition of an alkoxide **11**, potentially available in optically active form, to an acrylate ester **12** or an equivalent thereof. Herein, we report in full the outcome of this idea.[13]

We initially carried out a model study using the phenyl-substituted acetylenic alcohol **13a**,[14] Lindlar reduction of which led smoothly to the corresponding (*Z*)-alkene **14a**. Various attempts at effecting Michael addition of the derived alkoxide to either ethyl acrylate or acrolein failed. In the ester case, little reaction occurred at ambient temperature and more forcing conditions led to both transesterification and polymerisation; in the case of the aldehyde, polymerisation was the main reaction. However, the sodium alkoxide of alcohol **14a** added very cleanly to acrylonitrile giving an excellent yield of the nitrile **15**. Unfortunately, all attempts to hydrolyse the tetrahydropyranyl group, even using the mild pyridinium toluene-*p*-sulfonate (PPTS) method,[15] resulted in elimination of the ether side chain and alkene migration into conjugation with the phenyl ring. We therefore turned to the corresponding silyl ether derivative **13b**, as this protecting group can be removed under mildly basic

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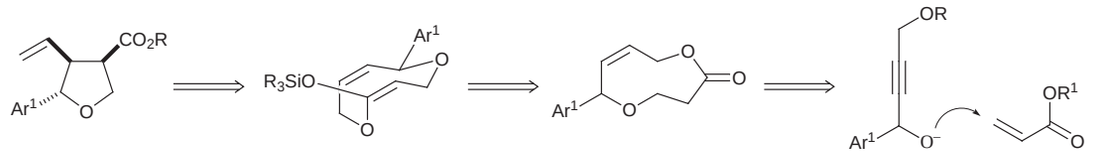
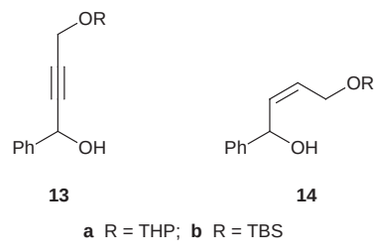


8 **9** **10** **11** **12**

Scheme 2



13 **14**

a R = THP; **b** R = TBS

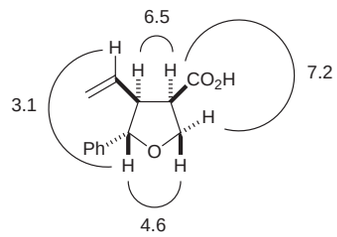
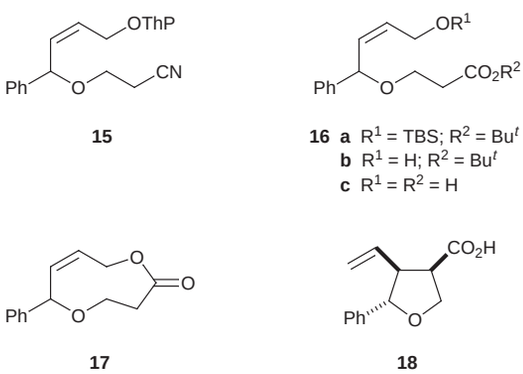


Fig. 1 NOE measurements on tetrahydrofuran **18**



15

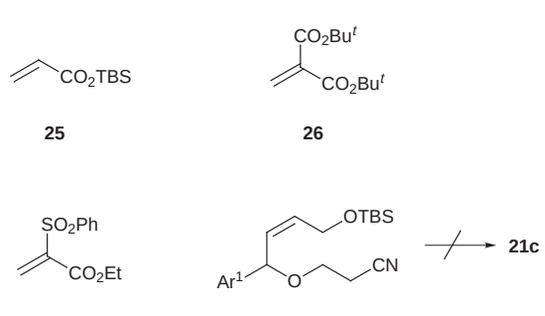
16 **a** R^1 = TBS; R^2 = Bu^t
b R^1 = H; R^2 = Bu^t
c R^1 = R^2 = H

17 **18**

(fluoride) conditions. Again, Lindlar reduction smoothly gave the (*Z*)-alkene (**14b**) and subsequent conjugate addition to acrylonitrile gave the expected nitrile (*cf*. **15**). Sadly, although desilylation was successful using tetrabutylammonium fluoride (TBAF), all attempts to hydrolyse the nitrile function, under either acidic or basic conditions led to destruction of the substrate. We then returned to the original idea of using an acrylate, reasoning that a more hindered ester might encourage the desired Michael addition. We were pleased to find that heating the sodium alkoxide of alcohol **14b** with *tert*-butyl acrylate gave a reasonable 53% yield of the required homologue **16a** and desilylation again proceeded smoothly to give the hydroxy-ester **16b**. Not surprisingly, attempts to hydrolyse the *tert*-butyl ester under acidic conditions led again to elimination of the ether side chain and alkene isomerisation to conjugated products. We were fortunate to find that hydrolysis under basic conditions (NaOH, MeOH, reflux) gave an acceptable yield of the desired hydroxy-acid **16c**. *tert*-Butyl esters are usually inert to such conditions; it may be that the distal hydroxy group provides anchiomeric assistance to this hydrolysis. In any event, we were then able to obtain a small sample of the key macrolide **17**, using the Keck method,[16] albeit in poor yield.

The evident sensitivity of the oxamacrolide **17** with respect to β-elimination was also of prime concern in the projected enolate Claisen rearrangement step.[12] This has already been addressed by Ireland and Norbeck[17] who, when faced with a similar problem, used a cold 'pre-mix' method in which the silylating reagent and the base are mixed at low temperature before addition of the sensitive ester or lactone, resulting in rapid enolate *O*-silylation before the unwanted β-elimination occurs. We were delighted to find that such enolisation and trapping of the macrolide **17**, followed by warming to ambient temperature, gave the anticipated tetrahydrofurancarboxylic acid **18**, in excellent yield and as a single diastereoisomer, according to both ^{1}H and ^{13}C NMR analysis. The stereochemistry of acid **18** could not be determined with certainty using coupling constants alone, as is usually the case with five-membered rings, but NOE measurements (Fig. 1) confirmed the stereochemistry shown which had been anticipated on the basis of the transition state model **9**. Despite some low yields associated with this route, we next embarked upon a similar approach to representative lignans.

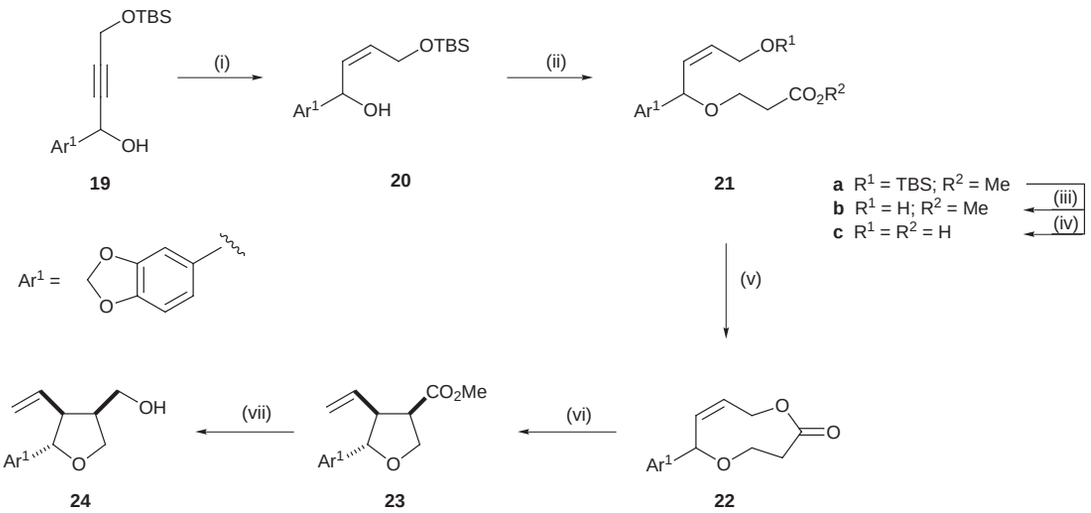
In the first step (Scheme 3), the *tert*-butyldimethylsilyl (TBS) ether of prop-2-ynyl alcohol was deprotonated using butyllithium and condensed with piperonal to give the mono-protected alcohol **19** in excellent yield which was then partly reduced to the (*Z*)-alkene **20** using Lindlar catalyst and hydrogen, again very efficiently. The subsequent Michael addition (Scheme 2; **11** and **12**), aimed at producing hydroxy-acid **21c**, was re-examined in the light of the foregoing results. Initial attempts using the sodium salt of the alcohol **20**, generated using sodium hydride and with or without THF as a solvent, and *tert*-butyl acrylate proved rather capricious and isolated yields of the required Michael adduct were poor, despite a number of changes to solvent, base and temperature. As expected, acidic hydrolysis of the resulting adduct failed; worse, the base hydrolysis method used to obtain the model hydroxy-acid **16c** also gave highly variable but generally much poorer yields with this substrate. More labile silyl esters (*e.g*. **25**) also



25 **26**

27 **28**

gave poor yields and silyl exchange with the alkoxide appeared to be a side reaction, while the more reactive Michael acceptors **26**[18] and **27**[19] also gave very poor returns of the desired products, using the NaH–THF base-solvent combination. As attack at the ester function in some of these acceptors was a problem, we turned again to acrylonitrile and were rewarded with an excellent yield (>90%) of the Michael adduct **28** (1 equiv. NaH, THF, 0–20 °C, 1 h). However, as before, all attempts to hydrolyse the nitrile group failed, giving unreacted starting material, partially hydrolysed products (*e.g*. the *N*-hydroxy-amide using KOH–H_2O_2) or decomposition under more forcing conditions. Attempted hydrolysis using a nitrilase enzyme led only to the isolation of piperonal(!).[20]



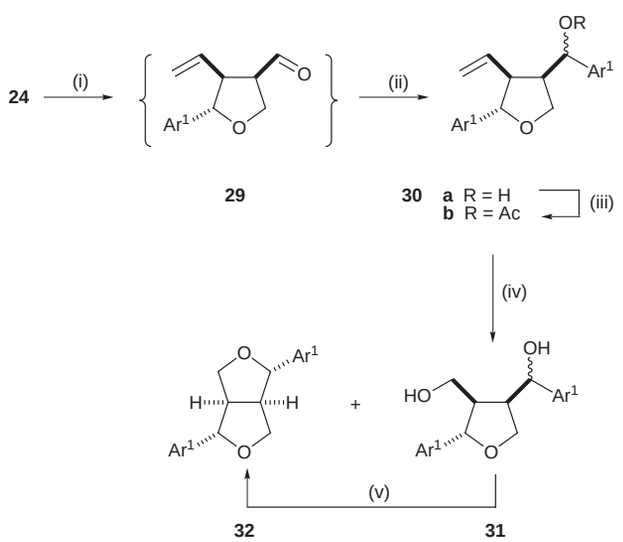
Scheme 3 *Reagents and conditions*: (i) Lindlar catalyst, H_2, EtOAc (95%); (ii) NaH (cat.), DMSO, methyl acrylate, 0–20 °C, 0.5 h (65%); (iii) TBAF, THF, 0.5 h, 20 °C (77%); (iv) KOH, MeOH, 2.5 h, 20 °C (84%); (v) 2-chloro-1-methylpyridinium iodide, Et_3N, MeCN, (slow addition), 80 °C (66%); (vi) LDA, THF, −100 °C, TMSCl, warm to +20 °C, MeOH then CH_2N_2 (86%); (vii) $LiAlH_4$, THF, 20 °C (93%)

The plan was saved by using dimethyl sulfoxide (DMSO) as a solvent, inspired by a previous report.[21] The best method found, a slightly unconventional one, was to mix the neat alcohol **20** with 10 mol% of sodium hydride and, after 30 min, dilute the resulting oil with a little DMSO, add methyl acrylate and work-up after a further 30 min. In this way, we routinely and reliably obtained at least a 60% isolated yield of the required ester **21a**. To our relief, subsequent removal of the silyl group, to give **21b**, and ester hydrolysis proceeded uneventfully and gave the required hydroxy-acid **21c** in good overall yield.

A number of lactonisation methods were then examined, in view of the relatively poor return of macrolide **17** using the Keck method.[16] However, the methods developed by Corey and Nicolaou (pyridine-2-thiol ester),[22] Palomo-Coll [bis(2-oxooxazolidin-3-yl)phosphinic chloride (BOPCl)][23] and Mukaiyama (2-chloro-1-methylpyridinium iodide, CH_2Cl_2)[24] all gave poor yields of the expected macrolide **22**. Fortunately, the latter method, when run in refluxing acetonitrile,[12c,e] gave a highly respectable 66% isolated yield of the required product **22**, considering that this is a nine-membered macrolide which could easily undergo a reverse-Michael cleavage; doubtless, the presence of a (*Z*)-alkene assists in the cyclisation. Only traces of the corresponding diolide were observed and saponification of the reaction residues did not deliver significant quantities of the starting hydroxy-acid **21c**, from presumed acyclic polyesters. Elimination of the intermediate activated ester to give a ketene and subsequent reactions,[25] together with reverse-Michael elimination probably accounts for the material balance.

The key enolate Claisen rearrangement of macrolide **22** proceeded smoothly using the pre-mix method, as in the model study, and gave, after esterification using diazomethane, a good overall yield of the tetrahydrofuran **23**, again as a single diastereoisomer. Reduction then gave the corresponding alcohol **24**.

Completion of the furanofuran lignan synthesis then required the addition of an aryl Grignard reagent and reductive removal of one carbon from the alkene substituent. This was achieved as shown in Scheme 4. Swern oxidation[26] of alcohol **24** gave the aldehyde **29** which was not characterised but immediately reacted with the Grignard reagent from 5-bromo-1,3-benzodioxole to give the alcohol **30a** in reasonable yield, as a mixture of epimers at the newly created secondary alcohol centre. Temporary protection as the corresponding acetate **30b** was followed by alkene cleavage using the Lemieux–Johnson one-pot procedure[27] and reduction of the resulting aldehyde using sodium borohydride. To our delight, the product was not the expected hydroxy-acetate but rather a 4:1 mixture of the target

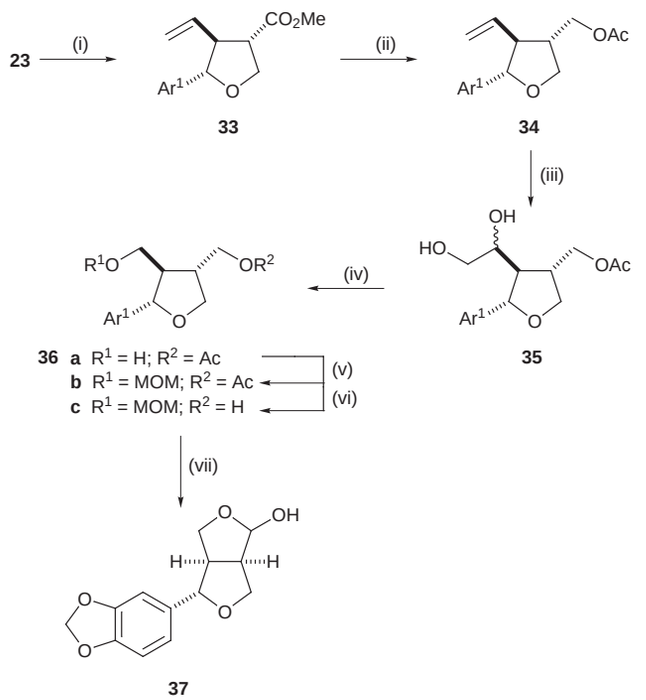


Scheme 4 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 to 20 °C; (ii) Ar^1MgBr, THF, 20 °C (53% for two steps); (iii) Ac_2O, pyridine, 20 °C (95%); (iv) OsO_4, $NaIO_4$, Et_2O–H_2O, 20 °C then $NaBH_4$, EtOH, 20 °C; (v) PPTS, CH_2Cl_2, 40 °C, 2 h

(±)-sesamin **32** and the diols **31**, although the yield was not as good as expected (see below). Quite why cyclisation had occurred under apparently basic conditions was not clear. Completion of the synthesis was achieved by heating this mixture with PPTS in dichloromethane,[1] which cleanly delivered the target **32** which showed spectroscopic and analytical data identical to that previously recorded for the racemic material.[8] By using a Grignard reagent derived from a different aryl bromide, this route could therefore be used to obtain unsymmetrical examples of such lignans. Despite a number of attempts, we were not able to increase the yields at the Grignard addition or alkene cleavage steps.

With a view to using this approach for a synthesis of samin **37** (*cf.* **2**),[1,5,9,11] not only a natural product but also a useful and stable precursor to these lignans, we returned to a stored sample of the initial tetrahydrofuran ester **23**. To our chagrin, we found that this had undergone almost complete epimerisation at the ester centre to give the 3*SR*-isomer **33**. Upon further investigation, we discovered that a freshly prepared sample of the ester **23**, having the initial stereochemistry delivered by the Claisen rearrangement, underwent this epimerisation upon standing in chloroform at ambient temperature. The progress of the

epimerisation could be easily followed by ^{1}H NMR analysis: the benzylic methine protons were especially clear at δ_H 4.75 (d, *J* 7.8) for ester **23** and δ_H 4.47 (d, *J* 9.2) for the epimer **33**. Evidently, we were fortunate to have quickly reduced the ester **23** during the sesamin synthesis. Undeterred, we continued with the synthesis (Scheme 5), in the hope that we could effect a necessary epimerisation at a later stage.



Scheme 5 *Reagents and conditions*: (i) $CHCl_3$, 24 h, 20 °C (98%); (ii) $LiAlH_4$, THF, 0–20 °C then AcCl, pyridine, 20 °C (84% for two steps); (iii) OsO_4, NMMO, acetone, Bu^{t}OH, H_2O, 20 °C, 16 h (83%); (iv) $NaIO_4$, Bu_4NIO_4, CH_2Cl_2, H_2O then $NaBH_4$, MeOH, 0 °C (58%); (v) $ClCH_2OMe$, Pr$^i_2$NEt, THF, 20 °C, 72 h (83%); (vi) KOH, MeOH, 0–20 °C, 2 h (83%); (vii) TPAP, NMMO, 4 Å mol. sieves, CH_2Cl_2, MeCN, 20 °C, 24 h (81%) then 1 M aq. HCl, 20 °C, 48 h (73%)

Reduction of ester **33** as before smoothly led to the expected alcohol which was isolated as the corresponding acetate **34**, in excellent yield. Rather than use the direct, one-flask Lemieux–Johnson procedure for cleavage of the alkene, which turned out to be very slow in this case, we found a two-step procedure[28] with isolation of the intermediate diol slightly cleaner. Thus, osmylation led to an epimeric mixture of the diols **35** which was converted into the hydroxy acetate **36a** by sequential periodate oxidation and borohydride reduction. Protection of the new hydroxy function as the MOM ether **36b**[29] and acetate hydrolysis then gave the alcohol **36c** in good yield. Oxidation using tetrapropylammonium perruthenate (TPAP)[30] then led to the corresponding aldehyde which, fortunately, upon exposure to mineral acid underwent both MOM hydrolysis and epimerisation to give samin **37**. Milder acid sources such as PPTS were ineffective [*cf*. ref. 9]. More recently, it has been demonstrated that this epimerisation can also be effected under basic conditions.[9] The sample of samin **37** proved to be identical to a sample previously prepared by ourselves,[11] and displayed data identical to that previously recorded elsewhere[1,9] for racemic samples of this compound.

Hence, this alternative approach could also be used to obtain both symmetrical and unsymmetrical examples of the furanofuran lignans **1**, despite the epimerisation problem associated with the initial ester **23**. Additionally, the likelihood that the starting alcohol **19** can be obtained in chiral, non-racemic forms, potentially by a number of methods, suggests that this approach could be used to prepare enantiomers of the lignans **1** in a relatively straightforward manner.

Experimental

For general details, see ref. 11.

(±)-(*Z*)-1-Phenyl-4-(tetrahydropyran-2-yloxy)but-2-en-1-ol 14a
The acetylenic alcohol **13a**[14] (9.76 g, 39.6 mmol) was dissolved in ethyl acetate (90 ml) containing Lindlar catalyst (0.2 g) and the resulting suspension was shaken under 1 atmosphere of hydrogen until gas uptake slowed significantly then filtered through kieselguhr. The filtrate and washings were evaporated to leave the (*Z*)-alcohol **14a** (9.47 g, 96%) as a pale yellow oil, ν_{max}/cm^{-1} 3420; δ_H 1.38–1.98 (6H, m, 3 × CH_2), 3.39–3.74 (2H, m, OCH_2), 4.20–4.52 (2H, m, CH_2OTHP), 4.52–4.86 (1H, m, OCHO), 5.60 (1H, d, *J* 8.0, PhCH), 5.70–5.98 (2H, m, 2 × =CH) and 7.27–7.64 (5H, m, 5 × ArH); *m*/*z* 160 (13%), 146 (64), 129 (21), 107 (14), 105 (90), 101 (12), 91 (16), 85 (100), 77 (41) and 56 (25).

(±)-(*Z*)-4-Oxa-5-phenyl-8-(tetrahydro-2*H*-pyran-2-yloxy)oct-6-enenitrile 15
Sodium (0.15 g, 6.15 mmol; one piece) was added to the alcohol **14a** (1.00 g, 4 mmol) and the resulting red mixture stirred at ambient temperature for 0.5 h. Freshly distilled acrylonitrile (0.5 ml, 7.6 mmol) was added and the mixture stirred for a further 1.5 h. The unreacted sodium was removed, the mixture diluted with diethyl ether (50 ml) then washed with water (2 × 50 ml), dried and evaporated to leave the nitrile **15** (1.12 g, 92%) as a yellow oil, ν_{max}/cm^{-1} 2250; δ_H 1.41–1.93 (6H, m, 3 × CH_2), 1.61 (2H, t, *J* 7.0, CH_2CN), 3.41–3.80 (4H, m, 2 × OCH_2), 4.23–4.42 (2H, m, CH_2OTHP), 4.54–4.80 (1H, m, OCHO), 5.27 (1H, d, *J* 8.0, PhCH), 5.74–5.98 (2H, m, 2 × =CH) and 7.28–7.54 (5H, m, 5 × ArH); *m*/*z* 199 (6%), 160 (100), 129 (32), 117 (35), 115 (63), 107 (15), 105 (16), 91 (25), 85 (75), 79 (26), 77 (22) and 55 (28).

(±)-(*Z*)-1-Phenyl-4-*tert*-butyldimethylsilyloxybut-2-en-1-ol 14b
The acetylenic alcohol **13b** (7.35 g) was partly reduced, as described for the tetrahydropyran (THP) analogue **13a**, to give the (*Z*)-alcohol **14b** (7.03 g), ν_{max}/cm^{-1} 3360; δ_H 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, $SiCMe_3$), 4.25–4.61 (2H, m, CH_2OSi), 5.41–5.78 (3H, m, PhCH and 2 × =CH) and 7.14–7.46 (5H, m, 5 × ArH); *m*/*z* 260 ($M^+ - H_2O$, 8%), 146 (19), 129 (78), 117 (15), 107 (13), 105 (32), 91 (10), 77 (18), 75 (100) and 57 (52) [Found: $M^+ - H_2O$, 260.1580. $C_{16}H_{24}OSi$ requires C, 63.72; H, 7.56%; *M*, 260.1565].

***tert*-Butyl (±)-(*Z*)-8-(*tert*-butyldimethylsilyloxy)-4-oxa-5-phenyloct-6-enoate 16a**
To a stirred mixture of the alcohol **16a** (1.37 g, 4.9 mmol) and sodium hydride (25 mg of a 40% dispersion in oil; 0.63 mmol) was added freshly distilled *tert*-butyl acrylate (1.5 ml, 10 mmol) and the resulting dark red mixture heated to 100 °C for 18 h. The cooled mixture was diluted with diethyl ether (100 ml) and 2 M hydrochloric acid (25 ml). The separated ether phase was washed with water (2 × 50 ml) then dried and evaporated. Column chromatography (CC) [ether : petrol (1 : 19)] gave the ester **16a** (1.06 g, 53%) as a colourless oil, ν_{max}/cm^{-1} 1730; δ_H 0.06 (6H, s, $SiMe_2$), 0.91 (9H, s, $SiCMe_3$), 1.46 (9H, s, $OCMe_3$), 2.52 (2H, t, *J* 6.5, CH_2CO_2), 3.52–3.87 (2H, m, OCH_2CH_2), 4.33–4.49 (2H, m, CH_2OSi), 5.17 (1H, d, *J* 8.0, PhCH), 5.61–5.93 (2H, m, 2 × =CH) and 7.13–7.45 (5H, m, 5 × ArH); *m*/*z* 260 (23%), 147 (100), 129 (22), 105 (30), 77 (6), 75 (71) and 57 (41) [Found: C, 67.6; H, 9.5. $C_{23}H_{38}O_4Si$ requires C, 67.9; H, 9.4%].

***tert*-Butyl (±)-(*Z*)-8-hydroxy-4-oxa-5-phenyloct-6-enoate 16b**
Tetrabutylammonium fluoride (TBAF; 2.0 ml of a 1 M solution in THF, 2.0 mmol) was added to the foregoing ester **16a** (0.66 g, 1.62 mmol) and the resulting solution stirred at ambient temperature for 0.5 h. The bulk of the THF was evaporated and the

residue dissolved in ethyl acetate (25 ml). The resulting solution was washed with water (2 × 25 ml) then dried and evaporated. CC {ether : petrol [(1 : 19) increasing to (1 : 1)]} of the residue separated the alcohol **16b** (0.31 g, 65%) as an oil, ν_{max}/cm^{-1} 3420 and 1730; δ_H 1.49 (9H, s, $OCMe_3$), 1.61 (1H, br s, OH), 2.51 (2H, t, *J* 6.5, CH_2CO_2), 3.52–3.85 (2H, m, OCH_2CH_2), 4.35 (2H, t, *J* 6.5, CH_2OSi), 5.21 (1H, d, *J* 7.5, PhCH), 5.69–6.02 (2H, m, 2 × =CH) and 7.35–7.66 (5H, m, 5 × ArH); *m*/*z* 274 ($M^+ - H_2O$, 2%), 179 (37), 147 (46), 146 (49), 145 (58), 129 (39), 117 (100), 115 (65), 107 (37), 105 (30), 91 (39), 77 (18), 75 (28), 57 (94) and 55 (28) [Found: $M^+ - H_2O$, 274.1580. $C_{17}H_{12}O_3$ requires *M*, 274.1569].

(±)-(*Z*)-4-Oxa-5-phenyloct-6-en-8-olide 17

The foregoing hydroxy-ester **16b** (0.31 g, 1.06 mmol) was dissolved in methanol (25 ml) containing sodium hydroxide (0.27 g, 6.75 mmol) and the resulting solution stirred and refluxed for 2.5 h. The cooled solution was evaporated and the residue partitioned between ethyl acetate (10 ml) and water (10 ml). The separated aqueous layer was acidified using solid citric acid then extracted with ethyl acetate (3 × 15 ml). The combined extracts were washed with water (2 × 10 ml) then dried and evaporated to leave the hydroxy-acid **16c** (0.21 g, 85%) as a viscous oil, ν_{max}/cm^{-1} 3570–2200 and 1710; δ_H 2.62 (2H, t, *J* 7.0, CH_2CO_2), 3.60–3.84 (2H, m, OCH_2CH_2), 4.29–4.49 (2H, m, CH_2OH), 5.24 (1H, d, *J* 7.0, PhCH), 5.60–5.95 (2H, m, 2 × =CH), 6.80 (2H, br s, 2 × OH) and 7.34–7.60 (5H, m, 5 × ArH); *m*/*z* 188 (3%), 147 (17), 146 (99), 129 (22), 117 (69), 115 (40), 107 (33), 105 (100), 91 (20), 77 (44), 55 (20) and 43 (96).

To a stirred, refluxing solution of *N*,*N*-dicyclohexylcarbodiimide (0.42 g, 2 mmol), 4-dimethylaminopyridine (0.37 g, 3 mmol) and 4-dimethylaminopyridinium hydrochloride (0.34 g, 2 mmol) in dry chloroform (220 ml) was added, *via* motor-driven syringe during 20 h, a solution of the foregoing hydroxy-acid **16c** (0.21 g, 0.90 mmol) in chloroform (30 ml).[16] The cooled solution was treated with acetic acid (0.5 ml) and methanol (0.5 ml) and stirred for an additional 0.5 h then evaporated to *ca*. 5 ml. Diethyl ether (25 ml) was added and the resulting precipitate removed by filtration. Evaporation of the filtrates left an oily residue, CC [ether : petrol (1 : 19)] of which separated the lactone **17** (0.044 g, 22%) as an oil, ν_{max}/cm^{-1} 1745; δ_H 2.81 (2H, app. t, *J* 7.0, CH_2CO_2), 3.86–4.43 (2H, m, OCH_2CH_2), 4.90 (2H, d, *J* 6.0, $=CHCH_2O$), 5.43 (1H, m, PhCH), 5.74–5.98 (2H, m, 2 × =CH) and 7.38–7.64 (5H, m, 5 × ArH); *m*/*z* 218 (M^+, 4%), 159 (34), 147 (18), 146 (57), 145 (98), 130 (36), 129 (37), 128 (32), 115 (44), 105 (100), 91 (98), 77 (32), 55 (26) and 43 (54) [Found: M^+, 218.0935. $C_{13}H_{14}O_3$ requires *M*, 218.0943].

(3*RS*,4*SR*,5*SR*)-4-Ethenyl-5-phenyltetrahydrofuran-3-carboxylic acid 18

A stirred solution of lithium diisopropylamide [from BuLi (0.4 ml of a 1.6 M solution in hexanes, 0.64 mmol) and diisopropylamine (0.1 ml, 0.7 mmol)] in THF (10 ml) was cooled to −100 °C and treated sequentially with trimethylsilyl chloride (0.1 ml, 0.8 mmol) and a solution of the lactone **17** (0.04 g, 0.18 mmol) in THF (1 ml), the latter added dropwise during 10 min. No further coolant was added and the reaction mixture was allowed to warm slowly to −30 °C then the cooling bath was removed and stirring continued for 1 h. Methanol (1 ml) was added and, after 10 min, the solvents were evaporated. The residue was partitioned between ethyl acetate (10 ml) and water (10 ml) and the resulting mixture acidified using solid citric acid. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 10 ml). The combined organic solutions were washed with water (2 × 15 ml) then dried and evaporated. The residue crystallised slowly from diethyl ether–petrol to give the acid **18** as colourless prisms (0.035 g, 88%), mp 91–92 °C, ν_{max}/cm^{-1} 3340–2200 and 1710; δ_H 2.98 (1H, ddd, *J* 9.0, 8.8 and 7.6, 4-H), 3.37 (1H, ddd, *J* 8.8, 7.5 and 6.3, 3-H), 4.27 (1H, dd, *J* 9.3 and 7.5, 2-H_a), 4.35 (1H, dd, *J* 9.3 and 6.3, 2-H_b), 4.88 (1H, d, *J* 7.6, 5-H), 5.07 (1H, dd, *J* 17.0 and 1.5, $=CH_tH_c$), 5.15 (1H, dd, *J* 10.2 and 1.5, $=CH_tH_c$), 5.87 (1H, ddd, *J* 17.0, 10.2 and 9.0, $CH=CH_2$) and 7.22–7.39 (5H, m, 5 × ArH); δ_C 49.1, 55.2 (3- and 4-CH), 69.8 (2-CH_2), 84.7 (5-CH), 119.6 ($=CH_2$), 124.4, 126.0, 127.8, 133.3 (all =CH), 140.4 (C) and 177.6 (CO); *m*/*z* 218 (M^+, 12%), 146 (30), 129 (13), 115 (14), 112 (71), 107 (25), 105 (37), 97 (47), 91 (17), 77 (29), 70 (25) and 67 (100) [Found: M^+, 218.0960].

(±)-1-(1,3-Benzodioxol-5-yl)-4-*tert*-butyldimethylsilyloxybut-2-yn-1-ol 19

A stirred solution of the *O*-(*tert*-butyldimethylsilyl)prop-2-yn-1-ol (3.20 g, 19 mol)[31] in dry tetrahydrofuran (THF) (70 ml) was cooled to −78 °C and butyllithium (11.8 ml of a 1.6 M solution in hexanes; 20 mmol) was added dropwise. After 10 min, a solution of piperonal (3.0 g, 20 mmol) in dry THF (5 ml) was added slowly *via* syringe. The reaction mixture was then warmed to ambient temperature during 0.5 h. Saturated aqueous ammonium chloride (70 ml) was then added and the organic layer separated. The aqueous phase was extracted with diethyl ether (2 × 70 ml) and the combined organic phases washed with water (2 × 70 ml) then dried and evaporated to leave the alcohol **19** (5.60 g, 93%) as an oil, ν_{max}/cm^{-1} 3380; δ_H 0.11 (6H, s, $SiMe_2$), 0.92 (9H, s, $SiCMe_3$), 3.31 (1H, br s, OH), 4.33 (2H, s, CH_2OSi), 5.42 [1H, br s, ArCH(OH)], 5.91 (2H, s, OCH_2O), 6.83 (1H, m, ArH) and 7.01 (2H, m, 2 × ArH); *m*/*z* 320 (M^+, 5%), 263 (4) and 75 (100) [Found: C, 63.67; H, 7.69; M^+, 320.1443. $C_{17}H_{24}O_4Si$ requires C, 63.72; H, 7.56%; *M*, 320.1444].

(±)-(*Z*)-1-(1,3-Benzodioxol-5-yl)-4-*tert*-butyldimethylsilyloxybut-2-en-1-ol 20

To the foregoing alcohol **19** (5.62 g, 18 mmol) in ethyl acetate (50 ml) was added Lindlar catalyst (130 mg; Aldrich) and the resulting suspension stirred vigorously under an atmosphere of hydrogen until gas uptake slowed to a negligible rate (*ca*. 360 ml; ~3 h). The suspension was filtered through kieselguhr and the combined filtrate and washings evaporated to leave the (*Z*)-alcohol **20** (5.39 g, 95%) as a pale yellow oil showing ν_{max}/cm^{-1} 3400; δ_H 0.13 (6H, s, $SiMe_2$), 0.92 (9H, s, $SiCMe_3$), 3.42 (1H, br s, OH), 4.28–4.33 (2H, m, CH_2OSi), 5.37–5.43 [1H, m, ArC*H*(OH)], 5.60–5.65 (2H, m, 2 × =CH), 5.93 (2H, s, OCH_2O) and 6.83–6.91 (3H, m, 3 × ArH); δ_C *ca*. −6.00 (2 × MeSi), 18.36 (SiC), 25.96 ($SiCMe_3$), 59.66 (CH_2O), 69.68 [ArCH(OH)], 101.04 (OCH_2O), 106.81, 108.17, 119.42 (all ArCH), 130.60, 133.49 (both =CH), 137.41, 146.95 and 147.86 (all ArC).

Methyl (±)-(*Z*)-5-(1,3-benzodioxol-5-yl)-8-(*tert*-butyldimethylsilyloxy)-4-oxaoct-6-enoate 21a

Sodium hydride (21 mg of a 60% dispersion in oil; 0.5 mmol) was added to the alcohol **20** (1.70 g, 5 mmol) and the resulting suspension stirred for 0.5 h. The resulting red oil was cooled in ice and diluted with dry DMSO (5 ml) followed by freshly distilled methyl acrylate (0.70 g, 8 mmol). The cooling bath was removed and the solution stirred for 0.5 h then diluted with diethyl ether (25 ml) and water (25 ml). The mixture was neutralized using 2 M hydrochloric acid and the organic layer separated. The aqueous phase was further extracted with diethyl ether (2 × 25 ml) and the combined organic solutions washed with water (2 × 25 ml) then dried and evaporated. CC [hexane : diethyl ether (2 : 1)] then separated the methyl ester **21a** (1.33 g, 65%) as a yellow oil showing ν_{max}/cm^{-1} 1740; δ_H 0.07 (6H, s, $SiMe_2$), 0.90 (9H, s, $SiCMe_3$), 2.59 (2H, t, *J* 6.5, CH_2CO), 3.66 (2H, m, OCH_2CH_2), 3.68 (3H, s, OMe), 4.31 (2H, m, CH_2OSi), 5.02 (1H, d, *J* 8.4, ArCHO), 5.52–5.70 (2H, m, 2 × =CH), 5.93 (2H, s, OCH_2O) and 6.75–6.81 (3H, m, 3 × ArH); δ_C *ca*. −6.0 (2 × MeSi), 18.37 (SiC), 25.97 ($SiCMe_3$), 35.08 (CH_2CO), 51.70 (OMe), 59.69 (CH_2OSi), 63.70 (CH_2O), 76.78 (ArCHO), 101.04 (OCH_2O), 107.11, 108.13, 120.09 (all

ArCH), 130.91, 131.95 (both =CH), 135.33, 147.09, 147.93 (all ArC) and 172.01 (CO); *m/z* 305 ($C_{17}H_{25}O_3Si$, 6%), 189 (69) and 161 (100) [Found: C, 61.90; H, 8.10. $C_{21}H_{32}O_6Si$ requires C, 61.76; H, 7.94%].

Methyl (±)-(*Z*)-5-(1,3-benzodioxol-5-yl)-8-hydroxy-4-oxaoct-6-enoate 21b

Tetrabutylammonium fluoride (1.2 ml of a 1.0 M solution in THF; 1.2 mmol) was added to the foregoing ester **21a** (0.50 g, 1.2 mmol) and the resulting solution stirred for 0.5 h at ambient temperature then the volatiles evaporated. The residue was dissolved in ethyl acetate (20 ml) and the resulting solution washed with water (2 × 20 ml) then dried and evaporated. CC [hexane : diethyl ether (2 : 1)] gave the hydroxy-ester **21b** (0.28 g, 77%) as a yellow oil, showing ν_{max}/cm^{-1} 3452 and 1739; δ_H 2.11 (1H, br s, OH), 2.59 (2H, t, *J* 6.3, CH_2CO), 3.59–3.72 (2H, m, OCH_2CH_2), 3.69 (3H, s, OMe), 4.21 (1H, dd, *J* 13.3 and 5.9, CH_aH_bOH), 4.35 (1H, dd, *J* 13.3 and 7.0, CH_aH_bOH), 5.06 (1H, d, *J* 8.0, ArCHO), 5.64 (1H, dd, *J* 11.2 and 8.0, 6-H), 5.77 (1H, m, 7-H), 5.94 (2H, s, OCH_2O) and 6.76–6.83 (3H, m, 3 × ArH); δ_C 34.99 (CH_2CO), 51.82 (OMe), 58.90 (CH_2OH), 63.66 (CH_2O), 77.71 (ArCHO), 101.11 (OCH_2O), 107.09, 108.22, 120.24 (all ArCH), 131.00, 132.67 (both =CH), 135.10, 147.24, 148.03 (all ArC) and 172.23 (CO); *m/z* 294 (M^+, 1%), 237 (10), 191 (21) and 173 (100) [Found: C, 61.48; H, 6.38; M^+, 294.1095. $C_{15}H_{18}O_6$ requires C, 61.22; H, 6.12%; *M*, 294.1103].

(±)-(*Z*)-5-(1,3-Benzodioxol-5-yl)-4-oxaoct-6-en-8-olide 22

Potassium hydroxide (1.5 ml of a 2 M solution in methanol; 2.9 mmol) was added to the foregoing hydroxy-ester **21b** (0.60 g, 1.9 mmol) and the resulting solution stirred at ambient temperature for 2.5 h then the bulk of the solvent was evaporated. The residue was dissolved in a mixture of ethyl acetate (10 ml) and water (10 ml) and the separated aqueous layer acidified with ice-cold 2 M hydrochloric acid and extracted with ethyl acetate (3 × 10 ml). The combined extracts were washed with water (2 × 10 ml) then dried and evaporated to leave the hydroxy-acid **21c** (0.45 g, 84%) as a viscous yellow oil showing ν_{max}/cm^{-1} 3400 (br) and 1710; δ_H 2.66 (2H, t, *J* 6.0, CH_2CO), 3.66–3.81 (2H, m, OCH_2CH_2), 4.37 (2H, app. t, *J* 6.0, CH_2OH), 5.14 (1H, d, *J* 7.0, ArCHO), 5.73–5.89 (2H, m, 2 × =CH), 6.04 (2H, s, OCH_2O), 6.72 (2H, br, 2 × OH) and 6.90–6.97 (3H, m, 3 × ArH); δ_C 36.58 (CH_2CO), 64.10 (CH_2O), 65.24 (CH_2O), 87.66 (ArCHO), 101.05 (OCH_2O), 107.00, 108.16, 120.00 (all ArCH), 130.73, 133.39 (both =CH), 135.83, 147.68, 148.07 (all ArC) and 176.02 (CO); *m/z* 263 ($M^+ - OH$, 3%), 190 (28), 121 (9) and 60 (100) [Found: $M^+ - OH$, 263.0951. $C_{14}H_{15}O_5$ requires *M*, 263.0919]. Samples of the hydroxy-acid were not further purified but immediately subjected to lactonisation. A solution of the foregoing hydroxy-acid **21c** (1.04 g, 3.7 mmol) and dry triethylamine (3.0 g, 30 mmol) in dry acetonitrile (50 ml) was added dropwise, *via* motor-driven syringe, during 40 h to a refluxing solution of 2-chloro-1-methylpyridinium iodide (3.79 g, 14.8 mmol) in dry acetonitrile (550 ml). The resulting dark solution was refluxed for an additional 4 h then cooled and the bulk of the solvent evaporated. CC [hexane : diethyl ether (2 : 1)] separated the lactone **22** (0.64 g, 66%) as a yellow oil showing ν_{max}/cm^{-1} 1748 and 1503; δ_H 2.63–2.70 (2H, m, 2-CH_2), 3.86 (1H, ddd, *J* 11.9, 8.4 and 6.9, 3-H_a), 4.10 (1H, ddd, *J* 11.9, 6.1 and 4.3, 3-H_b), 4.59 (1H, ddd, *J* 15.3, 3.0 and 1.9, 8-H_a), 5.21 (1H, dd, *J* 5.3 and 0.9, 5-H), 5.23 [1H, ddd (partly obscured), *J* 15.3, 4.1 and 0.7, 8-H_b], 5.47–5.65 (2H, m, 2 × =CH), 5.86 (2H, s, OCH_2O), 6.68 (2H, app. s, 2 × ArH) and 6.76 (1H, s, ArH); δ_C 36.72 (2-CH_2), 62.61 (3-CH_2), 68.31 (8-CH_2), 81.18 (5-CH), 100.98 (OCH_2O), 106.41, 108.02, 119.18 (all ArCH), 129.46, 134.24 (both =CH), 137.21, 146.89, 147.95 (all ArC) and 171.68 (CO); *m/z* 262 (M^+, 100%), 232 (44), 190 (31), 174 (50), 150 (50), 115 (37) and 57 (26) [Found: C, 64.30; H, 5.67; M^+, 262.0827. $C_{14}H_{14}O_5$ requires C, 64.10; H, 5.38%; *M*, 262.0841].

Methyl (3*RS*,4*SR*,5*SR*)-5-(1,3-benzodioxol-5-yl)-4-ethenyltetrahydrofuran-3-carboxylate 23

A solution of the lactone **22** (0.226 g, 0.87 mmol) in dry THF (4 ml) was added to a cooled (−100 °C), stirred solution of lithium diisopropylamide (LDA) (1.73 ml of a 1.5 M solution in THF; 2.60 mmol) and trimethylsilyl chloride (0.34 g, 3.02 mmol) in dry THF (50 ml). With the cooling bath still in place, the resulting solution was slowly warmed to −30 °C then the bath was removed and stirring continued for 1 h. Methanol (4 ml) was added and, after a further 10 min, the bulk of the solvents were evaporated. The residue was partitioned between ethyl acetate (40 ml) and water (40 ml) and the whole acidified by the addition of solid citric acid. The separated aqueous layer was further extracted using ethyl acetate (2 × 40 ml) and the combined organic solutions washed with water (2 × 20 ml) then dried and evaporated to leave an acid fraction (0.19 g, 84%) as a yellow oil which showed ν_{max}/cm^{-1} 3500–2500 and 1705 and which was immediately esterified by treatment with excess ethereal diazomethane for 1 h at ambient temperature. Excess diazomethane was destroyed by the addition of a few drops of acetic acid, then the solution diluted to a volume of 50 ml using diethyl ether and washed with water (2 × 30 ml), then dried and evaporated. CC [hexane : diethyl ether (2 : 1)] separated the THF-ester **23** (0.17 g, 86%) as a yellow oil which showed ν_{max}/cm^{-1} 2890 and 1730; δ_H 2.86–2.92 (1H, app. br q, *J ca*. 8.5, 3-H), 3.37 (1H, ddd, *J* 8.9, 7.8 and 6.4, 4-H), 3.70 (3H, s, OMe), 4.21 (1H, dd, *J* 9.1 and 6.2, 2-H_a), 4.27 (1H, dd, *J* 9.1 and 7.2, 2-H_b), 4.75 (1H, d, *J* 7.8, 5-H), 5.04 (1H, ddd, *J* 17.1, *ca*. 1.5 and 0.8, $=CH_cH_t$), 5.12 (1H, ddd, *J* 10.2, 1.1 and 0.8, $=CH_cH_t$), 5.73–5.81 (1H, m, =CH), 5.93 (2H, s, OCH_2O) and 6.73–6.89 (3H, m, Ar-H); δ_C 48.98 [3- (or 4-) CH], 51.76 (OMe), 55.21 [4- (or 3-) CH], 69.70 (2-CH_2), 84.58 (5-CH), 101.02 (OCH_2O), 106.43, 107.98 (both ArCH), 119.33 (=CH_2), 119.66 (ArCH), 133.48 (=CH), 134.26, 147.13, 147.78 (all C) and 172.68 (CO); *m/z* 276 (M^+, 24%), 150 (100) and 67 (32) [Found: C, 65.29; H, 6.05; M^+, 276.0995. $C_{15}H_{16}O_5$ requires C, 65.19; H, 5.84%; *M*, 276.0998].

(3*SR*,4*SR*,5*SR*)-5-(1,3-Benzodioxol-5-yl)-4-ethenyltetrahydrofuran-3-methanol 24

A solution of the 3*RS*-ester **23** (0.418 g, 1.5 mmol) in dry THF (10 ml) was added dropwise during 15 min to an ice-cold suspension of lithium aluminium hydride (0.12 g, 3 mmol) in dry THF (50 ml) and the resulting mixture stirred vigorously for 1 h. Ethyl acetate (0.2 ml) followed by water (10 ml) were then carefully added and the resulting suspension filtered. The filtrate was concentrated to *ca*. 15 ml and extracted with diethyl ether (3 × 20 ml). The combined organic solutions were washed with water (2 × 10 ml) then dried and evaporated. CC [hexane : diethyl ether (1 : 2)] of the residue separated the 3*SR*-alcohol **24** (0.349 g, 93%) as a colourless oil, ν_{max}/cm^{-1} 3420 and 1600; δ_H 1.59 (1H, br s, OH), 2.60–2.66 (1H, m, 3-H), 2.78–2.84 (1H, m, 4-H), 3.67 (1H, dd, *J* 10.8 and 7.0, CH_aH_bOH), 3.82 (1H, dd, *J* 10.8 and 6.0, CH_aH_bOH), 3.89 (1H, dd, *J* 8.8 and 6.0, 2-H_a), 4.27 (1H, dd, *J* 8.8 and 7.0, 2-H_b), 4.68 (1H, d, *J* 7.4, 5-H), 5.09 (1H, ddd, *J* 17.1, *ca* 0.8 and 0.8, $=CH_cH_t$), 5.16 (1H, ddd, *J* 10.2, *ca*. 0.8 and 0.8, $=CH_cH_t$), 5.87–6.00 (1H, m, =CH), 5.94 (2H, s, OCH_2O), 6.75 (2H, app. s, 2 × ArH) and 6.82 (1H, app. s, Ar-H); δ_C 45.68 [3- (or 4-) CH], 54.63 [4- (or 3-) CH], 61.95 (CH_2), 70.95 (CH_2), 84.71 (5-CH), 100.94 (OCH_2O), 106.25, 107.97 (both ArCH), 118.58 (=CH_2), 119.20 (ArCH), 134.86 (=CH), 135.77, 146.65 and 147.68 (all C); *m/z* 248 (M^+, 19%), 150 (100), 98 (5), 93 (15), 67 (14) and 54 (18) [Found: C, 67.80; H, 6.45; M^+, 248.1031. $C_{14}H_{16}O_4$ requires C, 67.71; H, 6.50%; *M*, 248.1049].

(±)-2,6-Bis-(1,3-benzodioxol-5-yl)-3,7-dioxabicyclo[3.3.0]octane [(±)-sesamin] 32

Dimethyl sulfoxide (0.182 g, 2.25 mmol) was added to a stirred solution of oxalyl chloride (0.127 g, 1.0 mmol) in dry dichloro-

methane (2 ml) maintained at −78 °C. After 10 min, a solution of the 3*SR*-alcohol **24** (0.12 g, 0.48 mmol) in dichloromethane (2 ml) was added dropwise and the resulting solution stirred for 1 h at the same temperature. Triethylamine (0.25 g, 2.5 mmol) was then added dropwise and the solution allowed to warm to ambient temperature. The solvent was evaporated and the resulting aldehyde **29** dissolved in dry THF (4 ml). This solution was stirred and treated with a solution of the Grignard reagent prepared from 5-bromo-1,3-benzodioxole (0.20 g, 1.0 mmol) and magnesium (0.024 g, 1.0 mmol) in THF (5 ml) after stirring for 2 h, when the bulk of the magnesium had reacted. After 4 h, saturated aqueous ammonium chloride (10 ml) was carefully added and the resulting mixture extracted with diethyl ether (3 × 10 ml). The combined extracts were washed with water (2 × 10 ml) then dried and evaporated. CC [hexane : diethyl ether (2 : 1)] separated the alcohols **30a** (0.096 g, 53%), ν_{max}/cm^{-1} 3400 and 1600; δ_H 2.58–3.95 (2H, m, 3- and 4-H), 4.09–4.27 (2H, m, 2-CH_2), 4.73–4.90 (2H, m, =CH_2), 5.06–5.23 (2H, m, 5-H and C*H*OH), 5.84–5.89 (1H, m, =CH), 5.92 and 5.94 (total 4H, both s, OCH_2O) and 6.73–6.81 (6H, m, 6 × ArCH).

Without further characterisation or purification, the foregoing alcohols **30a** (0.09 g, 0.24 mmol) were dissolved in dry pyridine (2 ml) containing DMAP (*ca*. 5 mg) and the resulting solution stirred while acetic anhydride (50 μl, 0.5 mmol) was added. The solution was stirred at ambient temperature for 15 h then diluted with water (10 ml) and extracted with dichloromethane (3 × 5 ml). The combined extracts were washed with water (2 × 5 ml) then dried and evaporated to leave the acetates **30b** (0.095 g, 95%) as a colourless semi-solid, ν_{max}/cm^{-1} 1740 and 1590; δ_H 1.98 and 1.96 (3H, 2 × s, Ac), 2.34–2.61 (1H, m, 3-H), 2.77–2.98 (1H, m, 4-H), 3.90–4.19 (2H, m, 2-CH_2), 4.70–4.74 (2H, m, =CH_2), 4.93–5.14 (1H, m, 5-H), 5.77–6.01 (6H, m, =CH, CHOAc and 2 × OCH_2O) and 6.65–6.73 (6H, m, 6 × ArH).

Osmium tetroxide (*ca*. 2 mg) was added to a vigorously stirred solution of the foregoing acetates **30b** (0.09 g 0.22 mmol) in diethyl ether (5 ml) and water (5 ml) followed by sodium metaperiodate (0.188 g, 0.88 mmol). After 24 h, the solution was extracted with ethyl acetate (3 × 5 ml) and the combined extracts dried and evaporated. The residue was dissolved in ethanol (1 ml) and the resulting solution and washings added to a stirred solution of sodium borohydride (7 mg) in ethanol (2 ml). After 3 h at ambient temperature, the solvent was evaporated and the residue partitioned between ethyl acetate (5 ml) and water (5 ml). The separated aqueous phase was extracted with ethyl acetate (2 × 5 ml) and the combined organic solutions washed with water (2 × 5 ml) then dried and evaporated. The residue was dissolved in hexane–diethyl ether (1 : 2) and the resulting solution filtered through a short plug of silica gel. Evaporation of the filtrates left a residue (0.051 g) which, according to ^{1}H NMR spectroscopy, was a mixture of (±)-sesamin **32** (see below) and the diols **31**, in an approximate ratio of 4 : 1. The latter was identified by δ_H 2.70–2.80 (m, 3-H), 4.58 (d, *J* 6.5), 4.85 (d, *J* 8.9), 4.92 (d, *J* 6.5) and 5.06 (d, *J* 3.9) for the methine protons, 5-H and C*H*OH, along with complex multiplets between δ_H 3.7 and 4.2. Small traces (<5%) of what could have been the acetates related to diols **31** [δ_H 2.05 and 2.10 (both s)] were visible. No trace of the starting alkene function was present.

The foregoing sample (0.05 g) was dissolved in dry dichloromethane (3 ml) containing pyridinium toluene-*p*-sulfonate (PPTS; 10 mg) and the resulting solution refluxed for 2 h. The cooled solution was diluted with dichloromethane (5 ml), washed with water (2 × 2 ml) then dried and filtered through a plug of silica and evaporated. Crystallisation of the residue from hexane–dichloromethane gave (±)-sesamin **32** (0.028 g) as a colourless solid, mp 125–126 °C [lit.[8] mp 129–130 °C]; δ_H 2.96–3.01 (2H, m, 1- and 5-H), 3.80 (2H, dd, *J* 9.2 and 3.6, 4- and 8-H_a), 4.17 (2H, dd, *J* 9.1 and 6.8, 4- and 8-H_b), 4.65 (2H, d, *J* 4.3, 2- and 6-H), 5.88 (4H, s, 2 × OCH_2O) and 6.72–6.78 (6H, m, 6 × ArH); δ_C 54.3 (1- and 5-CH), 71.7 (4- and 8-CH_2), 85.8 (2- and 6-CH), 101.1 (2 × OCH_2O), 106.5, 108.2, 119.4 (all 2 × ArCH), 135.1, 147.1 and 148.0 (all 2 × ArC); *m*/*z* 354 (M^+, 20%), 203 (23), 161 (31), 149 (100), 135 (40), 122 (19) and 69 (20) [Found: M^+, 354.1095. $C_{20}H_{18}O_6$ requires *M*, 354.1103].

Methyl (3*SR*,4*SR*,5*SR*)-5-(1,3-benzodioxol-5-yl)-4-ethenyltetrahydrofuran-3-carboxylate 33

A solution of the 3*RS*-ester **23** (0.30 g) in chloroform (20 ml) was left for 24 h then evaporated. The residue was filtered through a plug of silica using hexane–diethyl ether (2 : 1) as eluent to give the 3*SR*-ester **33** (0.29 g) as a pale yellow oil, ν_{max}/cm^{-1} 1732; δ_H 2.86–2.92 (1H, m, 3-H), 3.14 (1H, ddd, *J* 9.1, 8.8 and 7.4, 4-H), 3.72 (3H, s, OMe), 4.18 (1H, dd, *J* 9.0 and 8.6, 2-H_a), 4.29 (1H, dd, *J* 9.0 and 7.5), 4.47 (1H, d, *J* 9.2, 5-H), 5.04 (1H, ddd, *J* 17.1, *ca*. 1.5 and 0.8, =CH_cH_t), 5.11 (1H, ddd, *J* 10.3, 1.2 and 0.7, =CH_cH_t), 5.74 (1H, ddd, *J* 17.1, 10.3 and 8.2, =CH), 5.94 (2H, s, OCH_2O) and 6.73–6.88 (3H, m, Ar-H); δ_C 50.76 [3- (or 4-) CH], 52.15 (OMe), 56.30 [4- (or 3-) CH], 69.99 (2-CH_2), 86.22 (5-CH), 101.02 (OCH_2O), 106.76, 107.98 (both ArCH), 118.39 (=CH_2), 120.07 (ArCH), 133.59 (C), 135.01 (=CH), 147.32, 147.78 (both C) and 173.02 (CO); *m*/*z* 276 (M^+, 22%), 150 (100) and 67 (26) [Found: M^+, 276.0996].

(3*SR*,4*SR*,5*SR*)-3-Acetoxymethyl-5-(1,3-benzodioxol-5-yl)-4-ethenyltetrahydrofuran 34

Reduction of the 3*SR*-ester **33** (0.35 g) using lithium aluminium hydride, exactly as outlined above, gave the corresponding 3*RS*-alcohol (0.29 g) which was not characterised but immediately converted into the 3*SR*-acetate **34**.

To an ice-cold solution of the 3*RS*-alcohol (0.29 g, 1.2 mmol) in dry pyridine (5 ml) was added acetyl chloride (0.14 g, 1.7 mmol) and the resulting solution was stirred at ambient temperature for 15 h, then diluted with water (15 ml) and extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with water (2 × 20 ml) then dried and evaporated. CC [hexane : diethyl ether (1 : 1)] gave the 3*SR*-acetate **34** (0.28 g, 84%) as a colourless oil showing ν_{max}/cm^{-1} 1732; δ_H 2.05 (3H, s, OAc), 2.34 (1H, app. q, *J ca*. 8.9, 4-H), 2.51–2.61 (1H, m, 3-H), 3.90 (1H, dd, *J* 8.7 and 7.1, 2-H_a), 4.02 (1H, dd, *J* 11.1 and 7.9, CH_aH$_b$OAc), 4.13 (1H, dd, *J* 8.7 and 8.2, 2-H_b), 4.21 (1H, dd, *J* 11.1 and 5.1, CH$_a$CH_bOAc), 4.48 (1H, d, *J* 9.0, 5-H), 4.98 (1H, br d, *J* 17.1, =CH_cH_t), 5.09 (1H, br dd, *J* 10.2 and 1.4, =CH_cH_t), 5.69–5.77 (1H, m, =CCH), 5.94 (2H, s, OCH_2O) and 6.75–6.83 (3H, m, 3 × Ar-H); δ_C 20.79 (*C*H$_3$CO), 45.07 (4-CH), 55.83 (3-CH), 64.78 (CH_2), 70.77 (CH_2), 85.82 (5-CH), 100.94 (OCH_2O), 106.40, 107.94 (both ArCH), 118.13 (=CH_2), 119.59 (ArCH), 134.36 (=CH), 135.89, 147.04, 147.67 (all C) and 170.96 (CO); *m*/*z* 290 (M^+, 37%), 150 (100) and 140 (53) [Found: C, 65.97; H, 6.45; M^+, 290.1193. $C_{16}H_{18}O_5$ requires C, 66.18; H, 6.25%; *M*, 290.1154].

(2*SR*,3*RS*,4*SR*)-4-Acetoxymethyl-2-(1,3-benzodioxol-5-yl)-tetrahydrofuran-3-methanol 36a

A solution of the 3*SR*-acetate **34** (0.072 g, 0.25 mmol), osmium tetroxide (10 mg) and *N*-methylmorpholine *N*-oxide (0.037 mg, 0.27 mmol) in acetone (7.5 ml), *tert*-butyl alcohol (2 ml) and water (2 ml) was stirred for 16 h.[28] Celite and sodium sulfite (0.23 g in 4 ml of water) were added and the solution filtered, the solid washed with acetone and the combined filtrates evaporated. The residue was taken up in ethyl acetate (5 ml) and the resulting solution washed with brine (2 × 5 ml) then dried and evaporated to leave the crude diols **35** (0.067 g, 83%); ν_{max}/cm^{-1} 3564, 3378, 2913, 2855 and 1731. The complex ^{1}H NMR spectrum (mixture of diastereoisomers) showed the absence of resonances due to the 4-ethenyl group in the starting material **34**.

The foregoing diols **35** (0.067 g, 0.21 mmol), tetrabutylammonium periodate (5 mg) and sodium metaperiodate

(0.088 g, 0.41 mmol) were vigorously stirred in water (5 ml) and dichloromethane (5 ml) for 48 h (TLC monitoring). Ethyl acetate (10 ml) was added and the separated organic phase dried and evaporated to leave an aldehyde (0.057 g, 94%) as a pale yellow oil, ν_{max}/cm^{-1} 2948, 2854 and 1732, which was immediately used in the next reduction step.

A solution of the foregoing aldehyde (0.057 g, 0.19 mmol) in dry methanol (1 ml) was added to an ice-cold solution of sodium borohydride (10 mg) in methanol and the resulting solution stirred for 1 h. The bulk of the solvent was evaporated, the residue diluted with water (10 ml) and the product extracted into diethyl ether (3 × 10 ml). The combined extracts were washed with water (2 × 10 ml) then dried and concentrated to *ca*. 1 ml. This solution was filtered through a plug of silica gel, which was then washed with diethyl ether. Evaporation of the combined filtrates left the alcohol **36a** (0.034 g, 58%) as a colourless oil, ν_{max}/cm^{-1} 3457, 2882 and 1735; δ_H 2.06 (3H, s, OAc), 2.54–2.60 (2H, m, 3- and 4-H), 2.57 (1H, br s, OH), 3.66–3.74 (2H, m, C*H*$_2$OH), 3.91 (1H, dd, *J* 9.1 and 5.2, C*H*$_a$H$_b$OAc), 3.95–4.03 (1H, m, CH$_a$*H*$_b$OAc), 4.09 (1H, dd, *J* 10.9 and 8.0, 5-H$_a$), 4.17 (1H, dd, *J* 10.9 and 6.0, 5-H$_b$), 4.54 (1H, d, *J* 8.2, 2-H), 5.94 (2H, s, OCH$_2$O) and 6.76–6.84 (3H, m, 3 × Ar-H); δ_C 20.89 (*C*H$_3$CO), 30.91 (3-CH), 42.09 (4-CH), 62.25, 65.96, 70.48 (all CH$_2$), 83.54 (2-CH), 101.05 (OCH$_2$O), 106.61, 108.12, 119.73 (all ArCH), 135.25, 147.19, 147.92 (all C) and 171.11 (CO); *m*/*z* 294 (M^+, 40%), 263 (6), 251 (10), 235 (7), 204 (5), 190 (4), 164 (10), 134 (5), 121 (8) and 43 (100) [Found: M^+, 294.1095. $C_{15}H_{18}O_6$ requires *M*, 294.1103].

(2*SR*,3*RS*,4*SR*)-4-Acetoxymethyl-2-(1,3-benzodioxol-5-yl)-3-methoxymethoxymethyltetrahydrofuran 36b

Chloromethyl methyl ether (0.10 g, 1.2 mmol) was added to a solution of the foregoing alcohol **36a** (0.12 g, 0.4 mmol) in dry THF (15 ml) containing diisopropylethylamine (0.212 g, 1.6 mmol) and the resulting solution stirred for 72 h at ambient temperature (TLC monitoring).[29] Water (20 ml) was added and the solution extracted with diethyl ether (3 × 10 ml). The combined extracts were washed with water (2 × 15 ml) then dried and evaporated. CC [hexane : diethyl ether (1 : 1)] of the residue gave the ether **36b** (0.115 g, 83%) as a colourless oil showing ν_{max}/cm^{-1} 2949, 2854, 2777 and 1732; δ_H 1.95–2.03 (1H, m, 3-H), 2.06 (3H, s, OAc), 2.57–2.61 (1H, m, 4-H), 3.37 (3H, s, MeO), 3.56–3.62 (2H, m, C*H*$_2$OMOM), 3.92 (1H, dd, *J* 9.0 and 5.1, C*H*$_a$H$_b$OAc), 3.96–4.04 (1H, m, CH$_a$*H*$_b$OAc), 4.07 (1H, dd, *J* 10.9 and 8.2, 5-H$_a$), 4.18 (1H, dd, *J* 10.9 and 5.9, 5-H$_b$), 4.56 (1H, d, *J* 8.1, 2-H), 4.61 (2H, s, OC*H*$_2$OMe), 5.94 (2H, s, OCH$_2$O) and 6.77–6.85 (3H, m, 3 × Ar-H); δ_C 20.93 (*C*H$_3$CO), 42.31 (3-CH), 50.88 (4-CH), 55.46 (OMe), 65.91, 67.13, 70.52 (all CH$_2$), 83.55 (2-CH), 96.65 (OCH$_2$OMe), 101.06 (OCH$_2$O), 106.57, 108.14, 119.69 (all ArCH), 135.23, 147.18, 147.92 (all C) and 171.03 (CO); *m*/*z* 338 (M^+, 15%), 293 (12), 277 (5), 234 (5), 150 (49), 121 (4) and 43 (100) [Found: M^+, 338.1353. $C_{17}H_{22}O_7$ requires *M*, 338.1365].

(2*SR*,3*RS*,4*RS*)-2-(1,3-Benzodioxol-5-yl)-3-methoxymethoxymethyltetrahydrofuran-4-methanol 36c

Potassium hydroxide (0.2 ml of a 2 M solution in methanol; 0.4 mmol) was added to a stirred solution of the foregoing ether **36b** (0.081 g, 0.24 mmol) in ice-cold methanol (1 ml) and the resulting solution stirred without further cooling for 2 h then the solvent evaporated. The residue was mixed with water (10 ml) and dichloromethane (10 ml) and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 × 10 ml) and the combined organic solutions washed with water (2 × 10 ml) then dried and evaporated to leave the alcohol **36c** (0.059 g, 83%) as a colourless oil, ν_{max}/cm^{-1} 3504, 2948, 2855, 2774 and 1602; δ_H 1.63 (1H, br s, OH), 2.01–2.09 (1H, m, 3-H), 2.43–2.49 (1H, m, 4-H), 3.36 (3H, s, MeO), 3.50–3.62 (3H, m, 3 × CH.O), 3.68–3.72 (1H, m, CH.O), 3.84 (1H, dd, *J* 9.0 and 6.3, 5-H$_a$), 4.04 (1H, dd, *J* 9.0 and 6.1, 5-H$_b$), 4.45 (1H, d, *J* 8.9, 2-H), 4.63 (2H, s, OC*H*$_2$OMe), 5.95 (2H, s, OCH$_2$O) and 6.79–6.85 (3H, m, 3 × Ar-H); δ_C 47.53 (3-CH), 52.72 (4-CH), 55.65 (OMe), 64.71, 67.85, 70.24 (all CH$_2$), 84.02 (2-CH), 96.62 (OCH$_2$OMe), 101.16 (OCH$_2$O), 106.61, 108.10, 119.89 (all ArCH), 134.89, 147.31 and 147.92 (all C); *m*/*z* 296 (M^+, 14%), 252 (10), 251 (52), 235 (4), 222 (5), 221 (18), 164 (10), 132 (5) and 45 (100) [Found: M^+, 296.1266. $C_{15}H_{20}O_6$ requires *M*, 296.1260].

(±)-2-(1,3-Benzodioxol-5-yl)-6-hydroxy-3,7-dioxabicyclo[3.3.0]-octane [(±)-samin] 37

Tetrapropylammonium perruthenate (3 mg) was added to a stirred mixture of the foregoing alcohol **36c** (0.051 g, 0.17 mmol), *N*-methylmorpholine *N*-oxide (0.031 g, 0.26 mmol) and powdered 4 Å molecular sieves (0.090 g) in dry dichloromethane (5 ml) and dry acetonitrile (5 ml). After 24 h at ambient temperature, TLC indicated that no alcohol remained and the solvents were evaporated. The residue was suspended in dichloromethane (10 ml) and filtered through silica gel. The filtrate and washings were combined and evaporated to leave an aldehyde (0.042 g, 81%) as a colourless oil, ν_{max}/cm^{-1} 2927, 2853 and 1724, which was used in the final step without further purification or characterisation.

A solution of the foregoing aldehyde (0.042 g, 0.14 mmol) in THF (1 ml) and 1 M hydrochloric acid (1 ml) was stirred for 48 h (TLC monitoring), then the bulk of the THF evaporated. The resulting liquid was diluted with water (5 ml) and extracted with diethyl ether (3 × 10 ml). The combined extracts were washed with water (2 × 5 ml) then dried and evaporated. CC [diethyl ether] of the residue, followed by crystallisation from dichloromethane–petrol gave (±)-samin **37** (0.026 g, 73%), as a colourless solid, mp 111–112 °C [lit.,[1] mp 106 °C for (+)-**37**] [lit.,[11] mp 112–114 °C for (±)-**37**] [mixed mp with a previously prepared sample,[11] 110–111 °C] which displayed spectroscopic and analytical data identical to those previously reported.[1,9,11]

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