A New Synthetic Route to Furofuranoid Lignans *via* the Intramolecular Mukaiyama Reaction

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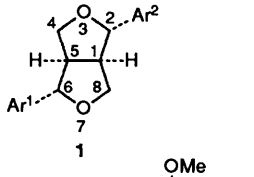
The sequence set out in Scheme 1 provides a short and expedient synthesis of a number of (±)-furofuranoid lignans, including styraxin **3** (antitumour), aptosimon **5**, asarinin **6**, pluviatilol **7**, 'MEL' **4** (inhibitor of germination) and related compounds.

Aryl substituted furofuranoid lignans **1** (2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes), comprise the major sub-group of the natural lignan family.[1] A wide range of biological activities, *e.g.* insect growth inhibition, and effects on the central nervous system, are exhibited within the group,[2] and there has been substantial interest in their synthesis.[3] A satisfactory synthesis would permit Ar^1 and Ar^2 to differ, and to carry free hydroxy groups. The relative stereochemistry at the four contiguous centres would be controlled; the *exo-exo* **1** and the *exo-endo* **2**



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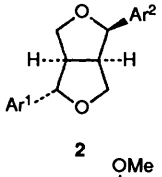

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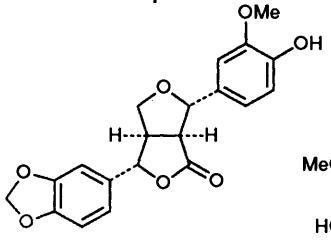
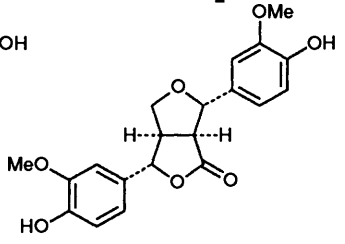
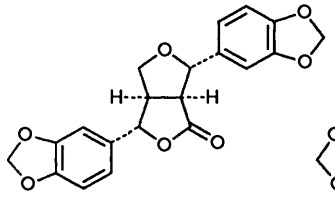


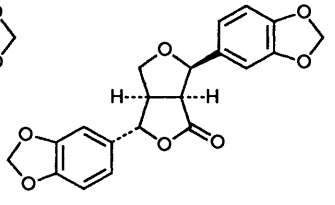
3 Styraxin



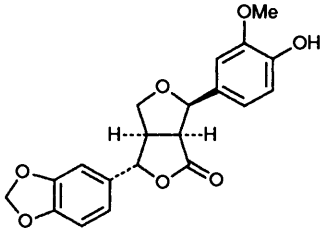
4 MEL



5 Aptosimon



6 Asarinin

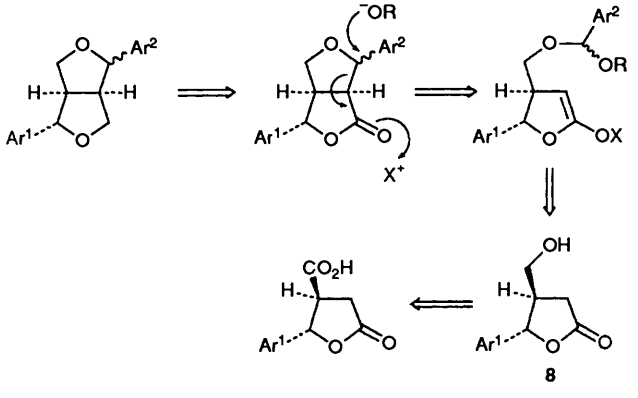


7 Pluviatilol

geometries are most common in natural systems. Further the methods should have potential for control of chirality. The oxidative coupling approach is unsatisfactory in several respects, and indeed only one synthesis has been reported which allows separate choice of aryl groups.[4]

This group also includes a few lactones (8-oxo compounds), *e.g.* styraxin **3**, showing antitumour activity,[5] and MEL **4**, displaying plant growth inhibition.[6] We were attracted to these compounds, not only as worthwhile targets in their own right, but as intermediates to unsymmetrical lignans types **1** and **2** ($Ar^1 \neq Ar^2$). In this paper we outline a new approach to the formation of these lignans, based on an intramolecular Mukaiyama cyclisation, which has allowed short syntheses of (±)-styraxin **3**, (±)-MEL **4**, (±)-aptosimon **5**, (±)-asarinin **6**, and (±)-pluviatilol **7**.

The general approach was based on the disconnections of Scheme 1, which proposes formation of the tetrahydrofuran ring by cyclisation onto a γ-lactone; a *trans*-4,5-disubstituted lactone **8** is central to the plan.



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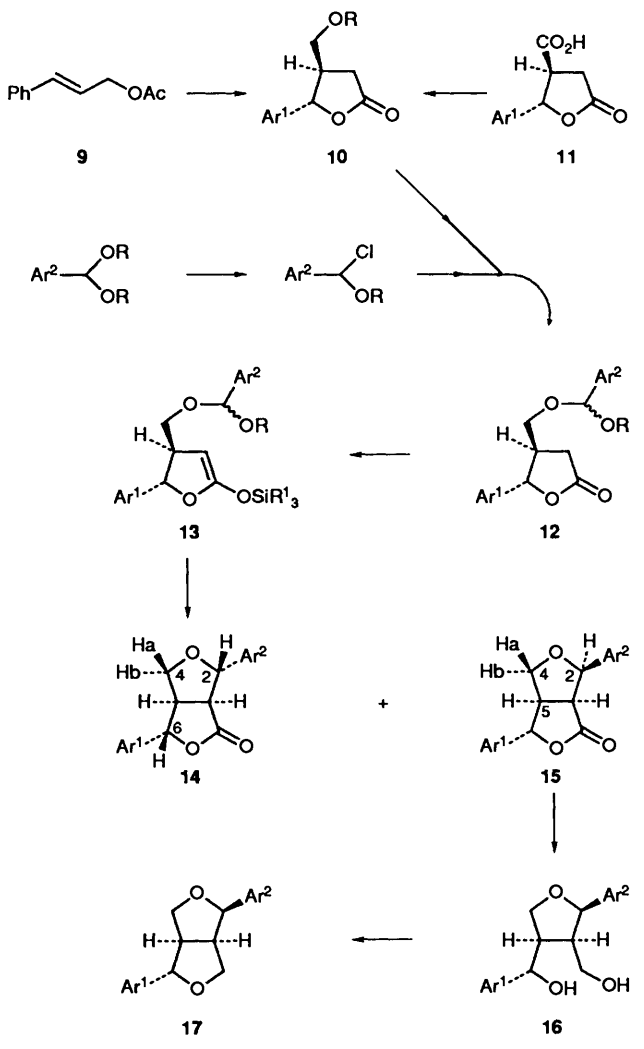
Scheme 1

In our initial exploration of this route, the manganese(III)-induced radical addition of acetic acid to olefins[7] was applied to *trans*-cinnamyl acetate to afford a single *trans*-lactone **10a** (R = Ac) (49%). Acid hydrolysis gave the corresponding alcohol **10a** (R = H) (78%), which was allowed to react with 1-ethoxy-1-(*p*-methoxyphenyl)chloromethane (prepared from anisaldehyde diethyl acetal by treatment with acetyl chloride–thionyl chloride)[8] at 0 °C, with triethylamine, to provide the mixed acetal **12a** (R = Et) (53%), as a mixture of diastereoisomers. The lactone enol trimethylsilyl ether **13a** (R = Et, R^1 = Me) was generated (92%) by successive treatments with lithium diisopropylamide (LDA) and trimethylsilyl chloride. Treatment of this ketene acetal with titanium tetrachloride at −78 °C gave the desired dioxabicycle **14a** (40%) as a single stereoisomer. The intramolecular Mukaiyama reaction impresses the *cis*-ring fusion, and the stereochemistry at the fourth chiral centre was controlled by transition state conformation. Chair-like cyclic enol titanium species[9] have been postulated for this type of reaction; such an intermediate, with the C-2 aryl equatorial, might seem to explain the observed stereochemistry. However, a further experiment shows that a more cautious view must be taken. Thus, the hydroxymethylene-



Scheme 2

a, Ar^1 = phenyl, Ar^2 = 4-methoxyphenyl; **b**, Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = phenyl; **c**, Ar^1 = Ar^2 = 3,4-methylenedioxyphenyl; **d**, Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3-benzyloxy-4-methoxyphenyl; **e**, Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3-hydroxy-4-methoxyphenyl; **f**, Ar^1 = Ar^2 = 3-benzyloxy-4-methoxyphenyl; and **g**, Ar^1 = Ar^2 = 3-hydroxy-4-methoxyphenyl.

lactone **10b**, see below, was allowed to react with 1-methoxy-1-phenylchloromethane to afford the acetal **12b** (R = Me); conversion into the ketene acetal **13b** (R = R^1 = Me) and cyclisation with titanium tetrachloride as above gave the 2-*endo*-6-*exo* lactone **15b**; the yield was poor (27%) but none of the *exo,exo*-form **14b** was isolated, in contrast to the case above. Clearly, further investigations are needed to clarify the mechanisms of these reactions. However it does seem likely that product epimerization is not involved in either case, since it is known that the *exo,exo*/*exo,endo* equilibrium is not heavily biased in either direction, and mixtures result from equilibration.[10]

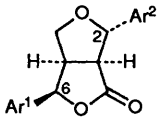
Ring closure of the ketene acetal **13a** (R = Et, R^1 = Me) with trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave a mixture of lactones **14a** and **15a**. In this case a cyclic transition state cannot be envisaged. The stereochemistry of these product lactones was determined by comparison of ^{1}H and ^{13}C NMR measurements with the substantial literature data (refs. 1, 3) and by examination of proton NOE. Thus, in lactone **14a** irradiation of 4-Ha led to signal enhancements at 2-H (5%), 6-H (5%) and 4-Hb (17%), while in lactone **15a** irradiation at 4-Hb augmented 2-H (6%), 5-H (9%) and 4-Ha (23%). It is not apparent whether the formation of two C-2 epimers derived from the presence of two diastereoisomers in the acetal **13a**, or from other mechanistic factors. The lability of **13a** renders difficult the separation of its isomers. The formation of both C-2 epimers in this sequence is not without advantage, since both the *exo-exo* and the *exo-endo* series are common. At the time of preliminary publication of these results[11] only one related application of the intramolecular Mukaiyama reaction had been described;[12] other applications have since appeared.[13]

We then turned our attention to the application of these methods to natural products. An attempt to prepare the lactone **10c** using oxidative addition of acetic acid to 3,4-methylenedioxycinnamyl alcohol led to a complex product mixture and it appeared that this method was not compatible with aromatic oxygenation. We therefore turned to the paraconic acids **11** as starting materials, prepared by the method of Lawlor and McNamee.[14] Zinc chloride–triethylamine catalysed condensation of piperonal and succinic anhydride afforded the desired *trans*-lactone acid **11c**, together with its *cis*-isomer (3:2, overall 75%). The isomers were readily separated by crystallization, and convincingly distinguished by NOE studies; the *cis*-form showed NOEs of 11.3 and 10.7% on irradiation of 5-H and 4-H respectively. Reduction of the acid **11c** with borane–dimethyl sulfide proceeded efficiently to yield the lactone alcohol **10c** (85%); on irradiation of 5-H, an NOE (3.2%) was noted at the 6-methylene signal, confirming the stereochemistry. α-Chloro-3,4-methylenedioxybenzyl methyl ether was prepared essentially quantitatively, from piperonal dimethyl acetal, and allowed to react with the alcohol **10c** in the presence of triethylamine to yield the mixed acetal **12c** (R = Me) (93%) as a pair of diastereoisomers. Treatment of this product with trimethylsilyl trifluoromethanesulfonate at 0 °C with triethylamine initially generated the silyl ketene acetal **13c** (R = R^1 = Me) and then induced cyclisation to give the lactones **14c** and **15c** (47%, 1:1.4).

The ^{1}H NMR and mass spectra (MS) of our sample of the *exo,exo*-lactone **14c** were indistinguishable from those of natural aptosimon, kindly supplied by Professor Brieskorn. Aptosimon is of interest in having been originally assigned a 2,4-diarylepoxylignanolide structure,[15] rather than the usual 2,6-diaryl pattern, chiefly on the basis of a MS fragment ion M − 85 arising from 1,2/4,5 cleavage. However this evidence has been shown to be inconclusive.[16] The present synthesis clearly shows aptosimon to have the 2,6-diaryl structure **14c**. No isomeric 2,4-diarylepoxylignanolides are known in Nature (at present), although the structure contains the well known framework of the bisbenzylbutyrolactone lignans.

The major lactone **15c**, m.p. 158–159 °C, was reduced with lithium aluminium hydride to the diol **16c** which cyclised very readily on exposure to acid to the dioxabicyclooctane **17c** (62%) from **15c**. This product proved to be (±)-asarinin, m.p. 132–133 °C, with *exo-endo* stereochemistry, by spectroscopic comparisons with authentic (−)-asarinin.

The reactions used in this short sequence are compatible with protected phenolic hydroxy groups. Thus, the lactone alcohol **10c** was treated with *O*-(α-chlorobenzyl)vanillyl methyl ether to provide the acetal **12d** (R = Me). Cyclisation with TMSOTf gave the furolactones **14d** and **15d** (34%, 1:1.9). Hydrogenolysis of the *exo,exo*-isomer gave (±)-styraxin **14e**, m.p. 108 °C. The ^{1}H NMR spectrum was indistinguishable from that of natural styraxin supplied by Professor Ulubelen; styraxin is a tumour inhibitory lignan isolated from *Styrax officinalis*. Reduction of benzyl epistyraxin **15d** with lithium aluminium hydride to the diol **16d**, followed by brief acid treatment afforded benzylpluviatilol **17d** (47%). Hydrogenolysis (81%) then provided (±)-pluviatilol **17e**, m.p. 142–145 °C, with NMR, IR and MS data parallel to those reported for the natural product. As



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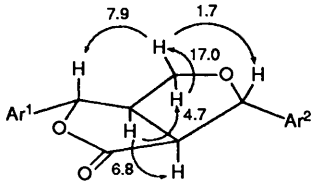

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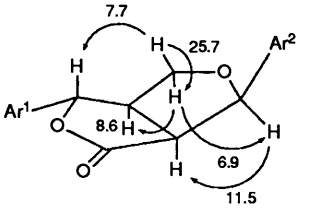
Selected NOE data for benzylstyraxin



20

Selected NOE data for epiaptosimon

above, the **16**→**17** ring closure proceeds with retention of configuration, under conformational control.

The stereochemistry of the key lactones **14** and **15** can be directly demonstrated by homonuclear NOE spectra. Thus, in the *exo-exo* group such measurements clearly show 2-H, 4-Hax and 6-H to be on one face, with 1-H, 4-Heq, and 5-H on the other, as, *e.g.*, **19**; while in the *exo-endo* series 4-Hax and 5-H are adjacent, with 1-H, 2-H, 4-Heq, and 5-H opposed, *e.g.* **20**.

One other natural lignan[6] was investigated, in connection with an interesting biological observation. The grains of *Aegilops ovata* have been noted to inhibit germination of lettuce achenes more in the light than in the dark. Search for the active principle led to the isolation of a new lignan, 'MEL', initially assigned a 2,4-diaryl structure, but later reassigned to the 2,6-diaryl constitution **4** on the basis of comparison with a synthetic 2,4-diphenyl compound, and on a synthesis based on oxidative cross coupling (7% yield). This synthesis is not, in fact, unambiguous, since either isomer could result. Irradiation of MEL with incandescent light gave rise to an 'isomeric photoproduct' which was isolated and shown to act co-operatively with MEL to inhibit germination. The structure of the photoproduct was not established, nor its relationship to 'iso-MEL', another product from the oxidative coupling synthesis.

In view of the interesting and unsolved photochemistry, and phytochemical relevance, it appeared worthwhile to synthesise MEL to supply material for further study. To this end, benzylvanillin was converted into the paraconic acid **11e** (57%), *trans*:*cis* = 3:2. The lactone alcohol **10e** (R = H) was prepared as above and converted into the acetal **12e** (R = Me) (34%). The latter apparently formed quantitatively (TLC) but decomposed on column chromatography. Cyclization with TMSOTf afforded the *exo,exo* lactone **14e** (21%), together with a trace of the *exo,endo* isomer **15e** (2%). A direct one-pot sequence gave the lactone **14e** in 26% yield from the lactone alcohol **10e** (R − H). Hydrogenolysis then provided (±)-MEL **14f**, with spectroscopic data closely similar to those reported for the natural product.

The *cis*-isomer of the lactone **10e** (R = H), treated in parallel fashion, yielded the 2-*exo*,6-*endo* product, 'iso-MEL' **18e** (8%), together with the 2-*exo*,6-*exo* isomer **14e** (12%). Acid-catalysed epimerization at C-2 has thus occurred in this process. Some preliminary photochemical experiments with MEL were disappointing; irradiation with several light sources lead either to no change or to drastic decomposition, and conditions for clean photoisomerization could not be found. Further work is required to clarify this problem.

In conclusion, the methods described here, although not ideal, provide short and effective routes to a number of natural lignans in racemic form. Enantiospecific synthesis can be envisaged using single enantiomers of the paraconic acids, derived either by resolution, or chiral synthesis. Investigation of the last possibility is in hand.

Experimental

For experimental generalisations see *J. Chem. Soc., Perkin Trans. 1*, 1991, 1901.

trans- *and* cis-*Paraconic Acids* **11**.—(*a*) Piperonal (16.0 g, 66.6 mmol) and succinic anhydride (10.0 g, 100 mmol) were added to powdered zinc chloride (18.15 g, 133.2 mmol) (dried *in situ* with thionyl chloride) in dry dichloromethane (80 cm^3) under nitrogen. Triethylamine (13.5 g, 133 mmol) was added dropwise with stirring over 30 min; the mixture became warm and nearly homogeneous. After being stirred overnight the mixture was treated with 2 mol dm^{-3} hydrochloric acid (80 cm^3), and the solution was extracted with ethyl acetate. The organic phase was washed with 2 mol dm^{-3} hydrochloric acid and brine, and then extracted with aq. sodium hydrogencarbonate (3 × 100 cm^3). The alkaline extracts were washed with chloroform and then acidified, to yield the product acids as a mixture (12.4 g, 75%) of isomers (*cis*:*trans* = 2:3). These were separated by trituration with ether, followed by recrystallization from ethyl acetate–hexane, chloroform, or methanol–water, to provide trans-4-*carboxy*-5-(3,4-*methylenedioxyphenyl*)*dihydrofuran*-2(3H)-*one* **11b**, m.p. 160–161 °C (lit.,[17] m.p. 164–165 °C for a sample made by another route) (Found: C, 57.3; H, 4.1%; M^+, 250.048. $C_{12}H_{16}O_6$ requires C, 57.6; H, 4.0%; *M*, 250.048); ν_{max}(KBr)/cm^{-1} 3300–2900, 1740, 1720, 1500, 1255, 1225, 1180, 1160, 1035 and 965; δ_H(250 MHz, [$^2H_6$]acetone) 2.98 (2 H, m, 3-H_2), 3.5–3.6 (1 H, m, 4-H), 5.55 (1 H, d, *J* 8.5, 5-H), 6.04 (2 H, s, OCH_2O) and 6.85–7.02 (3 H, m, ArH).

The isomeric cis-*lactone acid*, m.p. 163–165 °C (lit.,[17] m.p. 160–163 °C) (Found: C, 57.5; H, 4.0%; M^+, 250.045); ν_{max}(KBr)/cm^{-1} 3410, 1770, 1740, 1690, 1500, 1260, 1090, 1040, 930 and 825; δ_H(400 MHz, [$^2H_6$]acetone) 2.9 (2 H, m, 3-H_2), 3.80 (1 H, dt, *J* 5.4, 7.3, 4-H), 5.80 (1 H, d, *J* 7.4, 5-H), 5.99 (2 H, ABq, *J* 1, OCH_2O) and 6.78–6.92 (3 H, m, Ar-H).

(*b*) The methods in expt. 1a were applied to *O*-benzylvanillin to provide the title acids as a *cis*:*trans* (2:3) mixture (57%). Separation was effected by trituration with ether followed by recrystallization from ethyl acetate and then aq. methanol. The trans-(4-*benzyloxy*-3-*methoxyphenyl*)-4-*carboxydihydrofuran*-2(3H)-*one* **11f** had m.p. 125 °C (Found: C, 66.4; H, 5.5%; M^+, 342.111. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%; *M*, 342.110); δ_H(400 MHz, [$^2H_6$]acetone) 2.96 (2 H, d, *J* 9.3, 3-H_2), 3.59 (1 H, m, 4-H), 3.84 (3 H, s, OMe), 5.13 (2 H, s, OCH_2Ph), 5.57 (1 H, d, *J* 7.7, 5-H), 6.96–7.14 (3 H, m, ArH) and 7.3–7.5 (5 H, m, Ph).

The isomeric cis-*lactone acid* had m.p. 171–172 °C (Found: C, 66.7; H, 5.3%; M^+, 342.112); δ_H(250 MHz, [$^2H_6$]acetone) 2.91 (2 H, d, *J* 6.4, 3-H_2), 3.79 (3 H, s, OMe), 3.80 (1 H, m, 4-H), 5.09 (2 H, s, OCH_2Ph), 5.81 (1 H, d, *J* 7.4, 5-H), 6.87–7.03 (3 H, ArH) and 7.32–7.51 (5 H, m, PhH).

4-*Hydroxymethyl*-5-*aryl*-*dihydrofuran*-2(3H)-*ones* **10** (R = H).—(*a*) Cinnamyl acetate (1.00 g, 5.67 mmol), manganese(III) acetate (3.80 g, 14.2 mmol), and potassium acetate (2.78 g, 28.3 mmol) were refluxed together in acetic acid for 4 h, when the brown colour had disappeared. The cooled solution was diluted with ethyl acetate and washed with water, aq. sodium carbonate, and brine. Drying, evaporation, and chromatography on silica (ethyl acetate, hexane) gave trans-4-*acetoxymethyl*-5-*phenyldihydrofuran*-2(3H)-*one* **10a** (R = Ac) (0.53 g,

40%) as an oil (Found: M^+, 234.089. $C_{13}H_{14}O_4$ requires *M*, 234.089); ν_{max}(film)/cm^{-1} 3050, 1795, 1745, 1680 and 1240; δ_H 2.06 (3 H, s, Me), 2.40–2.95 (3 H, m, 3-H_2, 4-H), 4.26 (2 H, d, *J* 5.0, CH_2OAc), 5.31 (1 H, d, *J* 6.5, 5-H) and 7.44 (5 H, br s, ArH).

A solution of the acetate (4.4 g) was dissolved in tetrahydrofuran (20 cm^3) with 4 mol dm^{-3} hydrochloric acid (10 cm^3), and set aside at ambient temperature overnight. The product was isolated through ether extraction, and chromatographed on silica to yield trans-4-*hydroxymethyl*-5-*phenyldihydrofuran*-2(3H)-*one* **10a** (R = H), as an oil (Found: M^+, 192.079. $C_{11}H_{12}O_3$ requires M, 192.079); ν_{max}/cm^{-1} 3500 and 1770; δ_H(90 MHz) 2.67 (2 H, br s, 3-H_2), 3.27 (1 H, OH), 3.72 (2 H, br d, *J* 5.5, CH_2OH), 5.40 (1 H, br d, *J* 5.5, 5-H) and 7.39 (5 H, ArH).

(b) The lactone acid **11b** (4.75 g, 19.0 mmol) in dry tetrahydrofuran (THF) (80 cm^3) under nitrogen at 0 °C was treated with borane–dimethyl sulfide (28.5 mmol), added dropwise over 10 min. The mixture was allowed to warm to ambient temperature overnight, when it was diluted with methanol and evaporated. The residue was partitioned between brine (50 cm^3) and ethyl acetate (50 cm^3). The organic phase was washed, dried, and evaporated to yield trans-4-*hydroxymethyl*-5-(3,4-*methylenedioxyphenyl*)-*dihydrofuran*-2(3H)-*one* **10b** (3.85 g, 86%), m.p. 82–83 °C from ethyl acetate–light petroleum (Found: C, 61.2; H, 5.1%; M^+, 236.068. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%; *M*, 236.069); ν_{max}(KBr)/cm^{-1} 3440, 1745, 1505, 1210, 1039, 973, 934, 827 and 709; δ_H(250 MHz) 2.33 (1 H, br s, OH), 2.59–2.75 (3 H, m, 3-H_2, 4-H), 3.73 (2 H, m, CH_2OH), 5.28 (1 H, d, *J* 6.6, 5-H), 5.97 (2 H, s, OCH_2O) and 6.79–6.81 (3 H, m, ArH).

(c) The *trans*-lactone acid **11f** was reduced by the method described above to yield trans-5-(4-*benzyloxy*-3-*methoxyphenyl*)-4-*hydroxymethyldihydrofuran*-2(3H)-*one* **10f** (85%), m.p. 113 °C from ethyl acetate–hexane (Found: C, 69.45; H, 6.2%; M^+, 328.130. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%; M, 328.131); ν_{max}/cm^{-1} 3530, 3100–3030, 1775, 1600, 1515, 1405, 1270, 1230, 1170, 1020, 820, 760 and 720; δ_H(400 MHz) 2.54–2.70 (4 H, m, 3-H_2, 4-H, OH), 3.64–3.69 (2 H, m, CH_2OH), 3.86 (3 H, s, OMe), 5.12 (2 H, s, OCH_2Ph), 5.27 (1 H, d, *J* 6.4, 5-H), 6.77–6.86 (3 H, m, ArH) and 7.26–7.42 (5 H, m, Ph). The isomeric cis-*alcohol* was prepared (83%) in parallel fashion from the *cis*-lactone acid; m.p. 97–98 °C from chloroform–hexane (Found: C, 69.6; H, 6.2%; M^+, 328.131); δ_H(250 MHz) 1.83 (1 H, br s, OH), 2.57–2.90 (3 H, m, 3-H_2, 4-H), 3.29 (2 H, m, CH_2OH), 3.87 (3 H, s, OMe), 5.12 (2 H, s, OCH_2Ph), 5.60 (1 H, d, *J* 6.5, 5-H), 6.72–6.89 (3 H, m, ArH) and 7.27–7.44 (5 H, m, Ph).

Preparation of Mixed Acetals **12**.—(i) 1-*Aryl*-1-*alkoxychloromethanes*. The appropriate arylaldehyde dimethyl acetal (40 mmol) in acetyl chloride (freshly distilled; 10 cm^3) was treated with thionyl chloride (0.1 cm^3), and stirred under nitrogen overnight. The product mixture was then evaporated under reduced pressure to yield the required α-chloro ether as an air-sensitive oil in essentially quantitative yield as indicated by ^{1}H NMR spectrometry. In view of the relative instability of these compounds, they were used without further purification. α-Chloro-3,4-methylenedioxybenzyl methyl ether had δ_H(90 MHz) 3.72 (2 H, s), 6.07 (2 H, s), 6.51 (1 H, s) and 6.8–7.2 (3 H, m); α-chlorobenzyl methyl ether displayed δ_H(90 MHz) 3.62 (3 H, s), 6.47 (1 H, s) and 7.2–7.7 (5 H, m); α-chloro-4-benzyloxy-3-methoxybenzyl methyl ether showed δ_H(90 MHz) 3.61 (3 H, s), 3.89 (3 H, s), 5.14 (2 H, s), 6.38 (1 H, s) and 6.89–7.50 (8 H, m); and α-chloro-4-methoxybenzyl) ethyl ether had δ_H(90 MHz) 3.32 (3 H, t, *J* 7), 3.81 (3 H, s), 3.94 (2 H, q, *J* 7), 6.58 (1 H, s) and 6.95, 7.51 (4 H, ABq).

(ii) *Mixed acetals* **12**. (a) The lactone alcohol **10b** (1.39 g, 5.88 mmol) was dissolved in dry dichloromethane (50 cm^3) under nitrogen at 0 °C. Triethylamine (5 cm^3) was added followed by dropwise addition of α-chlorobenzyl methyl ether (1.38 g, 8.82 mmol) in dry dichloromethane (5 cm^3). After being stirred for 15 min the solution was washed with aq. sodium hydrogen carbonate, dried and evaporated. The residue was chromatographed on alumina (grade III; ether–light petroleum, 1:1, containing a trace of triethylamine) to yield the *acetal* **12b** as two diastereoisomers (1.93 g, 92%), m.p. 90 °C (Found: C, 67.6; H, 5.8%; M^+, 356.126. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.7%; *M*, 356.126); ν_{max}/cm^{-1} 1770, 1250, 1110 and 1050; δ_H(250 MHz, [$^2H_6$]acetone) 2.6–2.86 (3 H, m, 3-H_2, 4-H), 3.28 (3 H, s, OMe), 3.55–3.72 (2 H, m, OCH_2), 5.25–5.29 (1 H, m, 5-H), 5.51–5.53 (1 H, 2 × s, OCHO), 6.00 (2 H, s, OCH_2O), 6.79–6.93 (3 H, m, ArH) and 7.30–7.45 (5 H, m, Ph).

(b) Using the same methods, the following acetals were prepared, each as two diastereoisomers: **12a** (53%) (Found: M^+, 356.161. $C_{21}H_{24}O_5$ requires *M*, 356.162), δ_H(90 MHz) 1.25 (3 H, t, *J* 7, CH_2CH_3), 2.55 (3 H, m, 3-H_2, 4-H), 3.45–3.75 (4 H, m, $CH_2OCHOCH_2$), 3.81 (3 H, s, OMe), 5.28 (1 H, m, 5-H), 5.54 (1 H, s, OCHO), 6.84 (2 H, d, ArH) and 7.34 (7 H, m, ArH, Ph); **12c** (93%) (Found: M^+, 400.113. $C_{21}H_{20}O_7$ requires *M*, 400.116); δ_H(250 MHz, [$^2H_6$]acetone) 2.60–2.71 (3 H, m, 3-H_2, 4-H), 3.32 (3 H, s, OMe), 3.47–3.70 (2 H, m, OCH_2), 5.23–5.27 (1 H, m, 5-H), 5.38–5.40 (1 H, 2 × s, OCHO), 5.97 (2 H, s, OCH_2O), 6.72–6.95 (6 H, m, ArH); **12d** (59%) (Found: M^+, 492.178. $C_{28}H_{28}O_8$ requires *M*, 492.178); δ_H(90 MHz) 2.60–2.70 (3 H, m, 3-H_2, 4-H), 3.31 (3 H, s, OMe), 3.50–3.55 (2 H, m, OCH_2), 3.86 (3 H, s, ArOMe), 5.13 (2 H, s, OCH_2Ph), 5.15–5.28 (1 H, m, 5-H), 5.42 (1 H, 2 × s, OCHO), 5.92 (2 H, s, OCH_2O), 6.70–6.90 (6 H, m, ArH) and 7.35–7.55 (5 H, Ph); and **12f** (34%); δ_H(90 MHz) 2.64–2.73 (3 H, m, 3-H_2, 4-H), 3.33 (3 H, s, OMe), 3.52–3.63 (2 H, m, OCH_2), 3.87 and 3.90 (each 3 H, s, ArOMe), 5.19 (4 H, s, 2 × OCH_2Ph), 5.27–5.37 (1 H, m, 5-H), 5.47 (1 H, s, OCHO), 6.81–7.07 (6 H, m, ArH) and 7.25–7.48 (5 H, Ph).

Cyclisation of Silyl Ketene Acetals with Titanium Tetrachloride.—(a) Lithium diisopropylamide (2.78 mmol) in dry THF (20 cm^3) was cooled to −78 °C under nitrogen, and the acetal **12b** (0.91 g, 2.53 mmol) in THF (3 cm^3) was added. After 30 min trimethylsilyl chloride (0.50 cm^3, 3.9 mmol) was added, and the mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was stirred with dry ether (20 cm^3). The mixture was filtered and the filtrate was evaporated to leave the silyl ketene acetal **13b** as an oil, which was dissolved in dichloromethane (20 cm^3). The solution was cooled to −78 °C and was treated with titanium tetrachloride (0.30 cm^3, 2.74 mmol) in dichloromethane (2 cm^3); the reaction mixture was stirred at −78 °C for 3 h, when it was quenched with water (20 cm^3). The resulting mixture was extracted with ethyl acetate, and the extracts were washed, dried, and evaporated. Chromatography of the residue on silica (ether–petroleum, 1:1) afforded 2-exo-*phenyl*-6-endo-(3,4-*methylenedioxyphenyl*)-3,7-*dioxabicyclo*[3.3.0]*octan*-8-*one* **15b** (0.22 g, 27%), m.p. 154–155 °C from ethyl acetate–hexane (Found: C, 70.2; H, 5.2%; M^+, 324.097. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.0%; *M*, 324.099); ν_{max}(KBr)/cm^{-1} 1780, 1495, 1260, 1245, 1030, 955, 930, 710; δ_H(250 MHz, [$^2H_6$]acetone) 3.29–3.37 (1 H, m, 5-H), 3.72 (1 H, dd, *J* 8.9, 8.9, 1-H), 3.92 (1 H, dd, *J* 9.5, 4.9, 4-Ha), 4.33 (1 H, d, *J* 9.5, 4-Hb), 5.12 (1 H, d, *J* 8.5, 2-H), 5.26 (1 H, d, *J* 6.4, 6-H), 6.01 (2 H, s, OCH_2O), 6.84–6.99 (3 H, m, ArH) and 7.22–7.43 (5 H, m, Ph).

A parallel sequence with the acetal **12a** *via* **13a** provided 2-exo-(4-*methoxyphenyl*-6-exo-*phenyl*-3,7-*dioxabicyclo*[3.3.0]*octan*-8-*one* **14a** as an oil (Found: C, 73.5; H, 5.45%; M^+, 310.119, $C_{19}H_{18}O_4$ requires C, 73.55; H, 5.81%; *M*, 310.121);

δ_H(90 MHz) 3.25 (1 H, m, 5-H), 3.44 (1 H, dd, *J* 3.5, 9.2, 1-H), 3.90 (3 H, s, OMe), 3.99 (1 H, dd, *J* 9.5, 4.5, 4-Ha), 4.34 (1 H, dd, *J* 9.5, 6.5, 4-Hb), 5.26 and 5.30 (each 1 H, d, *J* 3.5, 2-H, 6-H), 6.78 and 7.10 (each 2 H, d, *J* 9, ArH) and 7.2–7.45 (5 H, PhH).

Cyclisation of Mixed Acetals **12** *with Trimethylsilyl Trifluoromethanesulfonate.*—(a) The acetal **12c** (1.58 g, 3.94 mmol) in THF (15 cm^3) and ether (15 cm^3) at 0 °C under nitrogen was treated with triethylamine (1.21 cm^3, 2.2 equiv.) and trimethylsilyl trifluoromethanesulfonate (1.69 cm^3, 2.1 equiv.). The mixture was stirred for 3 h, when water was added. The mixture was extracted with ethyl acetate. Evaporation of the washed dried extracts gave a residue which was chromatographed on silica (ether–petroleum gradient), to yield *aptosimon* **14c** (0.28 g, 19%) (eluted first) as a pale yellow gum, followed by 2-*epiaptosimon* **15c** (0.4 g, 28%), as a crystalline solid, m.p. 158–159 °C (ethyl acetate–hexane). Aptosimon (Found: M^+, 368.086. $C_{20}H_{16}O_7$ requires *M*, 368.089) had δ_H(90 MHz) 3.23 (1 H, m, 5-H), 3.42 (1 H, dd, *J* 3.5, 9.2, 1-H), 4.01 (1 H, dd, *J* 9.5, 4.5, 4-Ha), 4.32 (1 H, dd, *J* 9.5, 6.5, 4-Hb), 5.28 and 5.29 (each 1 H, d, *J* 3.5, 2-H, 6-H), 5.95 (4 H, s, 2 × OCH_2O) and 6.79–6.98 (6 H, m, ArH); δ_C(250 MHz, [$^2H_6$]acetone) 50.4, 53.8, 73.5, 84.3, 85.3, 102.1, 102.3, 107.1, 108.8, 109.0, 120.0, 120.6, 135.0, 135.9, 148.8 and 177.4. Epiaptosimon (Found: C, 65.2; H, 4.55%; M^+, 368.09. $C_{20}H_{16}O_7$ requires *M*, C, 65.2; H, 4.4%) had ν_{max}/cm^{-1} 1765 and 1500; δ_H(250 MHz, [$^2H_6$]acetone) 3.33 (1 H, m, 5-H), 3.68 (1 H, dd, *J* 8.8, 8.8, 1-H), 3.90 (1 H, dd, *J* 4.8, 9.5, 4-Ha), 4.31 (1 H, d, *J* 9.5, 4-Hb), 5.07 (1 H, d, *J* 8.6, 2-H), 5.27 (1 H, d, *J* 6.5, 6-H), 5.99 (2 H, s, OCH_2O), 6.03 (2 H, s, OCH_2O) and 6.78–7.00 (6 H, m, ArH); δ_C(250 MHz, [$^2H_6$]acetone) 51.8, 52.3, 72.4, 84.2, 86.1, 101.9, 102.3, 107.2, 107.7, 108.5, 108.9, 120.7, 120.8, 132.3, 135.2, 148.1, 148.5, 149.1 and 174.7.

(b) In a closely similar fashion the acetal **12d** (0.7 g) was cyclised to afford, after chromatography on silica (ethyl acetate–light petroleum, 1:2), *benzylstyraxin* **14d** (78 mg, 12%), m.p. 144 °C from ethyl acetate–hexane, and *benzylepistyraxin* **15d** (145 mg, 22%) m.p. 145 °C. Benzylstyraxin (Found: C, 70.2; H, 5.5%; M^+, 460.155. $C_{27}H_{24}O_7$ requires C, 70.4; H, 5.3%, *M*, 460.152) displayed δ_H(400 MHz) 3.20 (1 H, m, 5-H), 3.46 (1 H, dd, *J* 3.8, 9.2, 1-H), 3.90 (3 H, s, OMe), 4.02 (1 H, dd, *J* 4.7, 9.2, 4-Ha), 4.32 (1 H, dd, *J* 6.8, 9.4, 4-Hb), 5.12 (2 H, s, OCH_2Ph), 5.29 (1 H, d, *J* 3.8, 6-H), 5.34 (1 H, d, *J* 3.7, 2-H), 5.97 (2 H, s, OCH_2O) and 6.74–6.93 (6 H, ArH). Benzylepistyraxin (Found: C, 70.4; H, 5.4%; M^+, 460.152) showed δ_H($CDCl_3$, 250 MHz) 3.19 (1 H, m, 5-H), 3.53 (1 H, dd, *J* 8.8, 8.8, 1-H), 3.88 (1 H, dd, *J* 4.7, 9.6, 4-Ha), 3.89 (3 H, s, OMe), 4.27 (1 H, d, *J* 9.7, 4-Hb), 5.01 (1 H, d, *J* 8.7, 2-H), 5.14 (2 H, s, OCH_2Ph), 5.20 (1 H, d, *J* 6.6, 6-H), 5.97 (2 H, s, OCH_2O), 6.81 (3 H, s, ArH) and 6.89–6.91 (3 H, ArH).

(c) In a parallel experiment the acetal **12f** (1.04 g) with trimethylsilyltrifluoromethane sulfonate (0.87 g) yielded the 2-exo-6-exo-*lactone* **14f** (210 mg, 21%), m.p. 90–91 °C and the 2-endo-6-exo-*lactone* **15f** (17 mg, 2%), m.p. 194 °C. The former (Found: M^+, 552.215. $C_{34}H_{32}O_7$ requires *M*, 552.215) exhibited ν_{max}/cm^{-1} 1780; δ_H(250 MHz) 3.24 (1 H, m, 5-H), 3.45 (1 H, dd, *J* 9.3, 3.8, 1-H), 3.89, 3.90 (each 3 H, s, 2 × OMe), 4.02 (1 H, dd, *J* 9.4, 4.6, 4-Ha), 4.32 (1 H, dd, *J* 9.3, 6.8, 4-Hb), 5.15 (4 H, s, 2 × OCH_2Ph), 5.32 (1 H, d, *J* 3.3, 6-H), 5.34 (1 H, d, *J* 3.5, 2-H), 6.74–6.93 (6 H, m, ArH) and 7.25–7.43 (10 H, PhH). The latter (Found: C, 73.8; H, 5.95%; M^+, 552.215. $C_{34}H_{32}O_7$ requires C, 73.9; H, 5.8%) had ν_{max}/cm^{-1} 1780; δ_H(400 MHz) 3.24 (1 H, m, 5-H), 3.55 (1 H, dd, *J* 8.9, 8.9, 1-H), 3.90 (1 H, dd, *J* 9.5, 4.8, 4-Ha), 3.89, 3.90 (each 3 H, s, OMe), 4.29 (1 H, d, *J* 9.7, 4-Hb), 5.02 (1 H, d, *J* 8.7, 2-H), 5.14, 5.17 (each 2 H, s, OCH_2Ph), 5.23 (1 H, d, *J* 6.7, 6-H), 6.80–6.92 (6 H, m, ArH) and 7.25–7.44 (10 H, PhH).

(±)-*Styraxin.*—Benzylstyraxin (20 mg) in ethyl acetate (10 cm^3) was hydrogenated over 10% palladium on charcoal (2 mg) until no starting material could be detected by TLC. Filtration and evaporation gave the *title compound* **14e** (15.9 mg, 98%), m.p. 108 °C from chloroform–hexane or ethanol (Found: C, 64.5; H, 5.3%; M^+, 370.105. $C_{20}H_{18}O_7$ requires C, 64.9; H, 4.9%; *M*, 370.105); ν_{max}(KBr)/cm^{-1} 3500, 1750, 1605, 1510, 1040 and 940; δ_H(400 MHz) 3.22 (1 H, m, 5-H), 3.48 (1 H, dd, *J* 3.8, 9.2, 1-H), 3.91 (3 H, s, OMe), 4.03 (1 H, dd, *J* 4.6, 9.5, 4-Ha), 4.34 (1 H, dd, *J* 6.8, 9.5, 4-Hb), 5.31 (1 H, d, *J* 3.7, 6-H), 5.35 (1 H, d, *J* 3.5, 2-H), 5.64 (1 H, br s, OH), 5.99 (2 H, s, OCH_2O) and 6.76–6.92 (6 H, m, ArH). Essentially identical data were recorded for a natural sample.

(±)-2-*Epistyraxin.*—Benzyl 2-epistyraxin (65.9 mg) was hydrogenolysed as in the previous experiment to afford the *title compound* **15e** (50.6 mg, 96%), m.p. 165–166 °C from ethyl acetate–hexane (Found: C, 64.7; H, 5.1%; M^+, 370.105); δ_H(250 MHz) 3.21 (1 H, m, 5-H), 3.54 (1 H, dd, *J* 8.8, 8.8, 1-H), 3.89 (3 H, s, OMe), 3.90 (1 H, dd, *J* 9.7, 4.7, 4-Ha), 4.29 (1 H, d, *J* 9.7, 4-Hb), 5.02 (1 H, d, *J* 8.7, 2-H), 5.21 (1 H, d, *J* 6.6, 6-H), 5.67 (1 H, br s, OH), 5.99 (2 H, s, OCH_2O) and 6.82–6.95 (6 H, m, ArH).

(±)-*Pluviatilol.*—Benzyl 2-epistyraxin (55.5 mg) and lithium aluminium hydride (50 mg) in dry THF (5 cm^3) were refluxed for 2 h. Methanol–THF was added, followed by dil. hydrochloric acid. The mixture was extracted with ethyl acetate, and the washed dried extracts were evaporated. Preparative TLC afforded *benzylpluviatilol* **17d** (25.1 mg) as a pale yellow oil (Found: M^+, 446.171. $C_{27}H_{26}O_6$ requires *M*, 446.173). This product (20.8 mg) was hydrogenolysed as above to form the *title compound* **17e** (13.5 mg, 81%), m.p. 142–145 °C (Found: M^+, 356.127. $C_{20}H_{20}O_6$ requires *M*, 356.126); ν_{max}(KBr)/cm^{-1} 3470, 1235, 1070 and 1030; δ_H(250 MHz) 2.88 (1 H, m, 5-H), 3.30–3.34 (2 H, m, 8-Ha, 1-H), 3.80–3.86 (2 H, m, 8-He, 4-Ha), 3.91 (3 H, s, OMe), 4.10 (1 H, d, *J* 9.4, 4-He), 4.42 (1 H, d, *J* 7.0, 6-H), 4.85 (1 H, d, *J* 5.3, 2-H), 5.62 (1 H, br s, OH), 5.95 (2 H, s, OCH_2O), and 6.73–6.94 (6 H, m, ArH).

(±)-*Asarinin.*—(±)-Epiaptosimon (31.7 mg) was treated with lithium aluminium hydride as in the previous experiment to afford the *title compound* **17c** (19.8 mg, 62%), m.p. 132–133 °C, spectroscopically identical with an authentic specimen.

Monoepoxylignanolide **14g** (*MEL*).—Dibenzyl MEL **14f** (67.2 mg) was hydrogenolysed over palladium as above. Chromatographic isolation (silica, ethyl acetate–light petroleum gradient) gave the *title compound* **14g** (35.5 mg, 78%) as an amorphous solid (Found: M^+, 372.120. $C_{20}H_{20}O_7$ requires *M*, 372.121); ν_{max}(KBr)/cm^{-1} 3400, 1750, 1610, 1505, 1120 and 1020; δ_H(400 MHz) 3.25 (1 H, m, 5-H), 3.48 (1 H, dd, *J* 9.0, 3.9, 5-H), 3.88 (6 H, s, 2 × OMe), 4.04 (1 H, dd, *J* 9.5, 4.5, 4-Ha), 4.33 (1 H, dd, *J* 9.4, 6.8, 4-Hb), 5.33 (1 H, d, *J* 4.0, 6-H), 5.35 (1 H, d, *J* 3.7, 2-H), 5.60–5.80 (2 H, br s, 2 × OH) and 6.77–6.92 (6 H, m, ArH).

6-*Iso-MEL.*—The *cis*-lactone alcohol **10f** (R = H) (1.07 g) in dry THF (75 cm^3) at 0 °C was treated with triethylamine (2.3 cm^3) and 4-benzyloxy-α-chloro-3-methoxybenzyl methyl ether [1.14 g, in THF (3 cm^3)] under nitrogen. After the mixture had been stirred for 30 min trimethylsilyl trifluoromethanesulfonate (1.39 cm^3) was added dropwise; stirring was then continued for 1 h. The mixture was quenched with dil. hydrochloric acid and extracted with ethyl acetate. The washed, dried, extracts were evaporated and the residue was chromatographed on silica (ethyl acetate–hexane gradient) to yield *dibenzyl* 6-*iso-MEL* **18f** (103 mg, 6%), m.p. 139–140 °C from ethyl acetate (Found: C,

73.6; H, 6.1%; M^+, 552.215. $C_{34}H_{32}O_7$ requires C, 73.9; H, 5.8%; *M*, 552.215); ν_{max}(KBr)/cm^{-1} 1770, 1595, 1520, 1145, 1020, 775 and 715; δ_H(400 MHz) 3.46–3.52 (3 H, m, 1-H, 4-Ha, 5-H), 3.82 (1 H, m, 4-Hb), 3.88, 3.89 (each 3 H, s, OMe), 5.13, 5.14 (each 2 H, s, OCH_2Ph), 5.30 (1 H, s, 2-H), 5.68 (1 H, d, *J* 4.7, 6-H), 6.74–6.91 (ArH) and 7.28–7.43 (PhH). Hydrogenolysis as above provided the title compound **18g** (89%), m.p. 128–131 °C (lit., m.p. 131–133 °C) (Found: M^+, 372.119. Calc. for $C_{20}H_{20}O_7$: *M*, 372.121); ^{1}H NMR data (400 MHz) were closely comparable to lit. values, although some minor impurities could be discerned.

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