Asymmetric Synthesis of Dibenzylbutyrolactones and Aryltetralin Lignan Lactones by Tandem Conjugate Addition to a Chiral Butenolide

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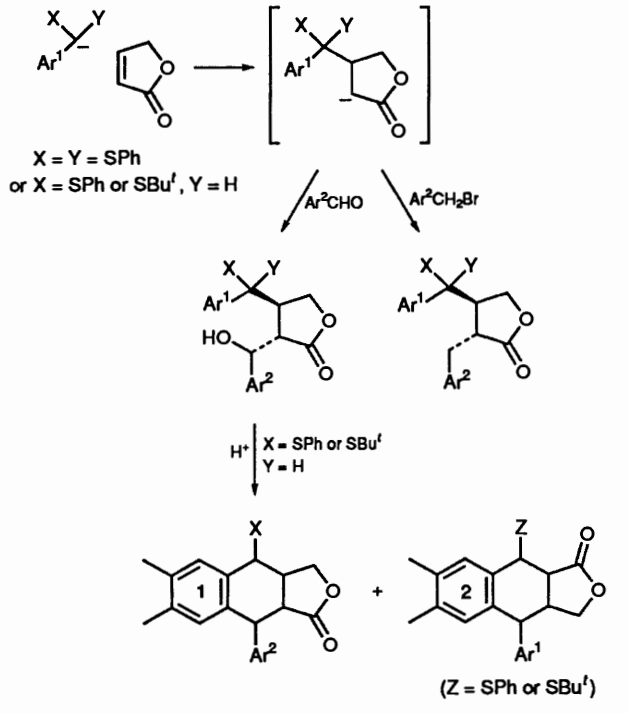
Addition of sulfur-stabilised carbanions to (−)-5-(1-menthyloxy)furan-2(5*H*)-one followed by reaction with an aromatic aldehyde affords a short synthesis of enantiomerically pure dibenzylbutyrolactone derivatives. Desulfurisation with $NaBH_4/NiCl_2$ proceeds in almost quantitative yield, and reduction with $NaBH_4$/KOH gives the parent dibenzylbutyrolactones including (−)-6-*epi*-podorhizol. These undergo cyclisation with acid to give homochiral aryltetralins including (−)-deoxyisopodophyllotoxin in high yield.

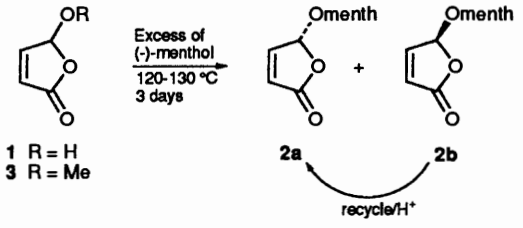
Lignans display a wide range of biological activity.[1–4] Thus, podophyllotoxin and its demethyl derivatives show powerful and specific cytotoxic activity,[5,6] and derivatives of these compounds are used clinically against small cell lung cancer and testicular cancer.[7,8]

We have previously shown that tandem conjugate addition reactions to butenolide provide an efficient route for the synthesis of *trans*-dibenzylbutyrolactone derivatives, and that these can be cyclised to afford aryltetralin lactones including analogues of podophyllotoxin (Scheme 1).[9,10]



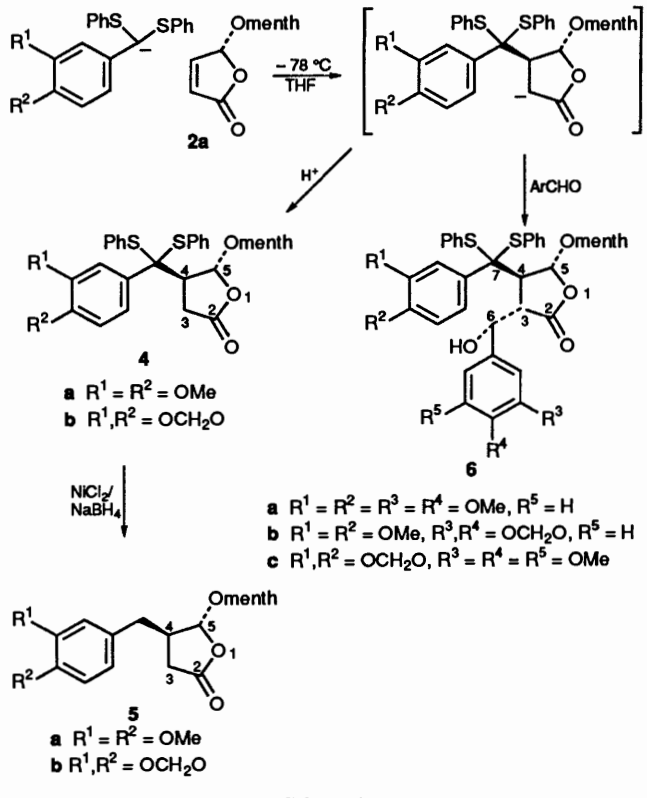
Scheme 1

As part of our studies of the asymmetric synthesis of lignans,[11] we decided to extend this strategy by making use of a chiral butenolide.[12,13] We chose to use (−)-5-(1-menthyloxy)-furan-2(5*H*)-one **2a** which had earlier been prepared by Feringa *et al.*[14–16] starting from 5-hydroxyfuran-2(5*H*)-one **1** which, in turn, can be obtained by photooxygenation of furfural or furoic acid. We now show that **2** can be prepared very conveniently from commercially available 5-methoxyfuran-2(5*H*)-one **3** (Scheme 2). Both diastereoisomers of the 5-menthyloxyfuran-2(5*H*)-one **2** are obtained as a 60:40 mixture which can be

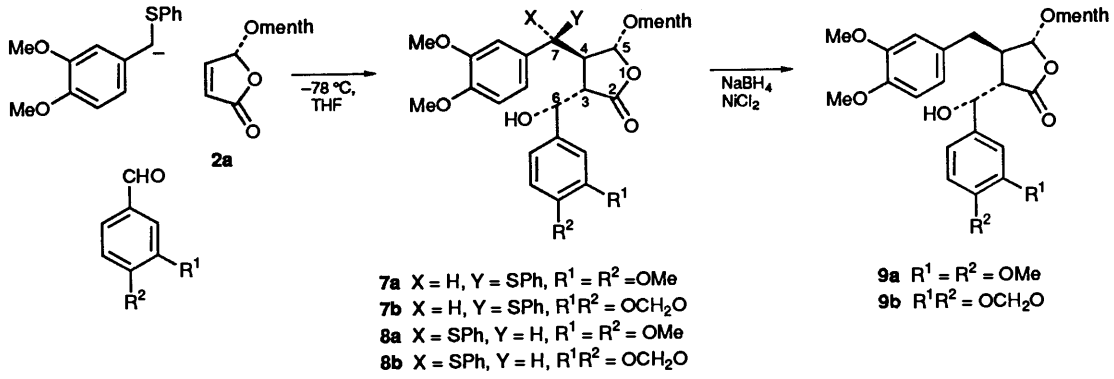


Scheme 2

separated by recrystallisation from light petroleum (b.p. 40–60 °C) at −25 °C to −30 °C to give the major diastereoisomer **2a**[15] as white needles $[\alpha]_D^{20}$ −137 (EtOH, *c* 1.00), m.p. 70.4–71.2 °C (lit.,[15] 70.5–70.7 °C). Furthermore, additional quantities of **2a** can be obtained by re-equilibration of the mother liquor (mainly **2b**) by heating with toluene-*p*-sulfonic acid (PTSA) (0.3 mol%) in benzene at reflux, followed again by recrystallisation from light petroleum.[15]



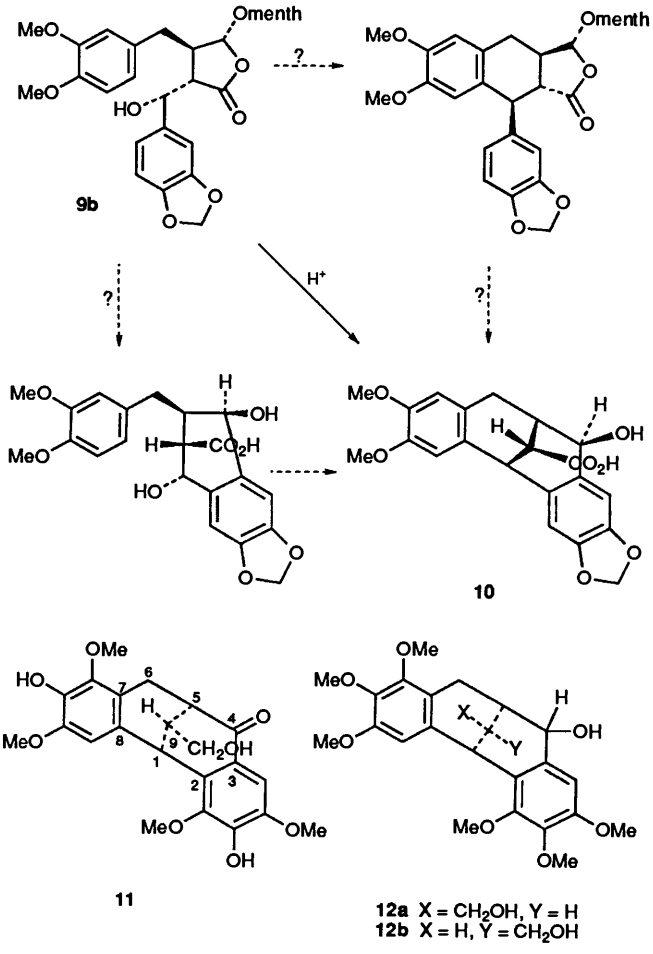
Scheme 3



Scheme 4

Treatment of the furanone **2a** with the lithio derivative of 3,4-dimethoxybenzaldehyde diphenyl thioacetal, followed by quenching with water, gave the monobenzylbutyrolactone **4a** in high yield (Scheme 3). Similarly, treatment of **2a** with the lithio derivative of 3,4-methylenedioxybenzaldehyde diphenyl thioacetal gave **4b**. Treatment of **4a** and **4b** with nickel boride (see below) gave the desulfurised products **5a** and **5b**. The ^{1}H and ^{13}C NMR spectra of **4a**, **b** and **5a**, **b** are listed in Tables 1 and 2. The small coupling constant observed between 4-H and 5-H in both **4a**, **b** and **5a**, **b** proves that the benzyl group has been introduced *trans* to the menthyloxy substituent.

Treatment of the furanone **2a** with the lithio derivative of 3,4-dimethoxybenzaldehyde diphenyl thioacetal, followed by reaction with 3,4-dimethoxybenzaldehyde or 3,4-methylenedioxybenzaldehyde gave, in each case, a single adduct **6a** and **6b** in 81 and 99% yield, respectively (Scheme 3). Similarly, treatment of the furanone **2a** with the lithio derivative of 3,4-methylenedioxybenzaldehyde diphenyl thioacetal followed by reaction with 3,4,5-trimethoxybenzaldehyde gave a single adduct **6c** in 80% yield. The ^{1}H and ^{13}C NMR spectra of the dibenzylbutyrolactone derivatives **6a–c** are listed in Tables 3 and 4.



Scheme 5

The all-*trans* arrangement of the three substituents on the butyrolactone ring in **6a–c** was again assigned on the basis of the ^{1}H NMR spectra and by analogy with previous work on conjugate addition to butenolide.[9–11] This was later confirmed by X-ray crystallography (see below). The OH stretching frequency in the IR spectrum was unaffected by dilution, which was indicative of intramolecular hydrogen bonding between the benzylic hydroxy and the lactone carbonyl group. The *threo* configuration of the benzylic hydroxy group at C-6 was then assigned on the basis of the observed coupling constant (8.4 Hz) between 3-H and 6-H.[17,18] The stereoselectivity of the reaction including the control of stereochemistry at C-6 is consistent with a chelated six-membered cyclic transition state (Fig. 1).[19,20]

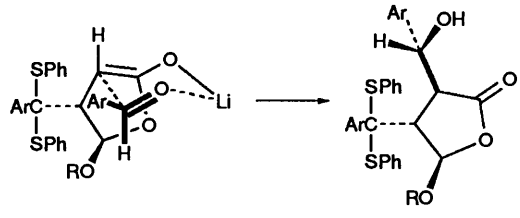


Fig. 1 Stereoselectivity of formation of **6a–c**

Treatment of the furanone **2a** with the lithio derivative of 3,4-dimethoxybenzyl phenyl sulfide followed by reaction with 3,4-dimethoxybenzaldehyde or 3,4-methylenedioxybenzaldehyde gave, in each case, a readily separable 1:1 mixture of two diastereoisomeric adducts **7** and **8** in 81 and 86% combined isolated yield, respectively (Scheme 4).

That **7a**, **b** and **8a**, **b** only differed in their configuration at C-7 was established by desulfurisation using nickel boride[21] which gave the same products **9a** and **9b** in almost quantitative yield from both diastereoisomers (Scheme 4). Furthermore, **9a** and **9b** were also obtained by desulfurisation of the diphenyl thioacetal adducts **6a** and **6b**, demonstrating that **6**, **7** and **8** have the same configuration at C-3, C-4, C-5 and C-6. X-Ray crystallography of **8b**[12,29] confirmed the absolute configuration at all of the chiral centres in these adducts. Desulfurisation of **6c** gave **9c** in 92% yield. The ^{1}H and ^{13}C NMR spectra of **7a–c** and **8a–c** are listed in Tables 3 and 4.

Attempts to cyclise compounds **6**, **7** and **8** under acidic conditions were unsuccessful, giving either no reaction or a complex mixture of products. Attempts were also made to cyclise the desulfurised compound **9b**. These reactions were also unsuccessful, although in one difficultly reproducible reaction

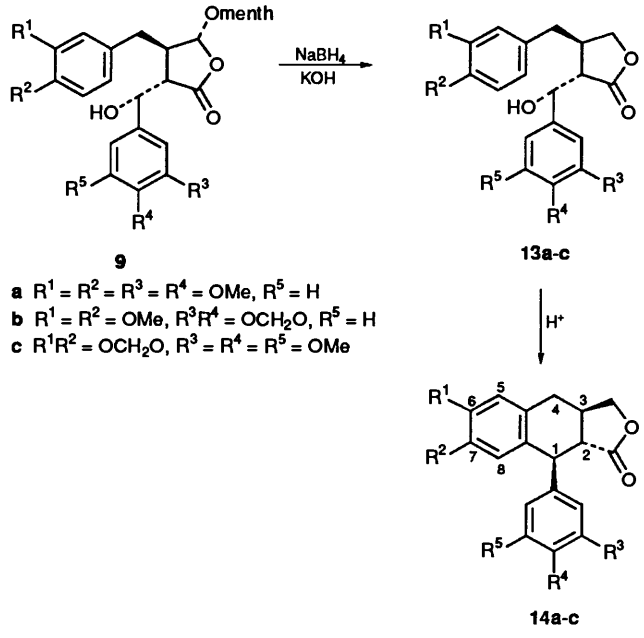
Table 1 ^{1}H NMR spectra of monobenzylbutyrolactone derivatives*

	4a	4b	5a	5b
3a-H	2.93dd (3.1, 18.7)	2.97dd (18.7, 2.7)	2.74dd (8.2, 17.4)	2.68dd (8.0, 17.6)
3b-H	2.84dd (9.9, 18.7)	2.79dd (10.0, 18.7)	2.21dd (2.1, 17.4)	2.14dd (2.8, 17.6)
4-H	3.07dd (3.1, 9.9)	2.96dd (2.7, 10.0)	2.61m	2.50m
5-H	5.85s	5.81s	5.39s	5.30s
7a-H	—	—	2.73m	2.67m
7b-H	—	—	2.58d (11.0)	2.48d (10.9)
H-A†	3.46dt (3.3, 10.3)	3.45dt (4.0, 11.0)	3.46dt (4.2, 11.0)	3.39dt (4.1, 10.7)
OMe	3.87s	—	3.86s	—
OMe	3.74s	—	3.85s	—
OCH_2O	—	5.98d (1.4)	—	5.87s (2 H)
	—	5.97d (1.4)	—	
Me	0.90d (7.4)	0.90d (6.5)	0.89d (6.5)	0.83d (7.1)
Me	0.85d (7.2)	0.86d (7.1)	0.87d (6.9)	0.79d (7.0)
Me	0.75d (6.9)	0.73d (6.9)	0.77d (7.1)	0.72d (7.6)
	7.17–7.37m (11 H)	7.20–7.40m (11 H)	6.70s	6.58d (1.6)
Arom.	6.95dd (2.4, 8.9)	7.70dd (2.0, 8.3)	6.82d (8.1)	6.68d (7.8)
	6.67d (8.9)	6.65d (8.3)	6.70d (8.1)	6.54dd (1.7, 7.9)

* All spectra recorded in $CDCl_3$ solution. † H–A is 1-H of menthyloxy group.

an interesting compound tentatively assigned structure **10** was obtained. This is related to the natural product lirionol (**11**).[22] The formation of this compound would involve a double cyclisation leading to the formation of two new carbon–carbon bonds and represents a very short synthesis of the lirionol group of compounds (Scheme 5). The ^{1}H NMR spectra of **10** and similar compounds **12a** and **12b** related to **11**[22] are listed in Table 5.

A number of acidic reductions (*e.g.* Et_3SiH/BF_3) for removing the menthyloxy substituent from **9a** and **9b** were investigated, but these were largely unsuccessful. We therefore adopted the conditions reported by Vandewalle *et al.*[23] for carrying out this step. Thus, treatment of **9a** and **9b** with $NaBH_4$/KOH gave the dibenzylbutyrolactones **13a** and **13b** in 50 and 38% yield, respectively (Scheme 6). Treatment of these compounds with trifluoroacetic acid gave the aryltetralins **14a** and **14b** in 91 and 96% yields, respectively. Similarly, removal of the menthyloxy group from **9c** afforded (−)-epipodorhizol **13c**[24] in 43% yield and this underwent cyclisation with trifluoroacetic acid to give (−)-deoxyisopodophyllotoxin **14c**[25] in 92% yield. The ^{1}H and ^{13}C NMR spectra of **14a–c** are listed in Tables 6 and 7.



a $R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = H$
b $R^1 = R^2 = OMe$, $R^3R^4 = OCH_2O$, $R^5 = H$
c $R^1R^2 = OCH_2O$, $R^3 = R^4 = R^5 = OMe$

Scheme 6

Table 2 ^{13}C NMR spectra of monobenzylbutyrolactone derivatives*

Carbon atom	4a	4b	5a	5b
C-2	175.56s	175.61s	176.12s	176.09s
C-3	32.20t	32.00t	33.20t	33.17t
C-4	47.90d	47.79d	47.67d	47.64s
C-4a	70.58s	70.31s	37.23t	37.36t
C-5	101.57d	101.51d	104.10d	104.10s
C-1′	131.15s	132.54s	130.30s	131.51s
C-2′	109.85d	107.30d	111.30d	108.33d
C-3′	148.42s	147.35s	147.85s	146.39s
C-4′	148.89s	147.82s	149.06s	147.94s
C-5′	113.63d	110.10d	111.81d	109.04d
C-6′	120.86d	122.63d	120.86d	121.83d
OMe	55.90q	—	55.84q	—
OMe	55.81q	—	55.84q	—
OCHO	—	101.44t	—	101.00t

* All spectra recorded in $CDCl_3$ solution. OMenth and SPh carbons not included.

Experimental

IR spectra were recorded on a Pye Unicam SP1050 spectrometer. UV spectra were recorded on a Philips PU8720 scanning spectrometer. ^{1}H NMR spectra were recorded on a Bruker 250WM spectrometer at 250 MHz and, where indicated, an Hitachi Perkin-Elmer R24B spectrometer at 60 MHz. The highfield spectra were recorded using Bruker spectrometers at 300, 360 and 400 MHz. ^{13}C NMR spectra were recorded on a Bruker 250WM spectrometer at 62.5 MHz. All spectra used tetramethylsilane as the internal standard, and were run in deuteriated chloroform, unless otherwise stated. The mass spectra were recorded on a VG-12-250 low-resolution quadruple mass spectrometer, whilst accurate mass measurements were obtained from a ZAB-E high-resolution, double-focusing mass spectrometer. M.p.s were recorded on an Electrothermal digital melting point apparatus, and are uncorrected. Optical rotation values were obtained from a Perkin-Elmer 141 polarimeter, using a sodium lamp at 589 nm and values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

The analytical HPLC work was carried out on a Milton Roy 3100 SpectroMonitor, 3000 constaMetric pump, CI-4100 integrator, and used an Apex II ODS 5 μm column. Preparative HPLC work was carried out on a Gilson 806 manometric module, 305 pump, 115 UV detector, and used a L. Chrosorb BP18 10 μm Knauer preparative column. Thin layer chromatography was carried out on Merck 5735 Kieselgel $60F_{254}$

Table 3 ^{1}H NMR spectra of dibenzylbutyrolactone derivatives*

	6a	6b	6c	7a	7b	8a	8b
3-H	3.30d (8.1)	3.25d (8.5)	3.18d (8.7)	3.14dd (3.5, 8.4)	3.03dd (3.4, 8.6)	2.61dd (2.3, 9.4)	2.60dd (2.3, 9.6)
4-H	2.87br s	2.88br s	2.72br s	2.53ddd (1.4, 3.5, 9.3)	2.52ddd (1.4, 3.4, 8.7)	2.44dd (1.3, 10.8)	2.36dd (2.3, 11.0)
5a-H	5.88br s	5.85br s	5.99m	5.42d (1.4)	5.45d (1.4)	6.09s	6.12s
5b-H	—	—	—	—	—	—	—
6-H	4.84d (8.4)	4.79d (8.4)	4.77d (8.7)	4.96d (8.4)	4.88d (8.6)	4.84d (9.4)	4.75d (9.6)
7a-H	—	—	—	3.70d (9.3)	3.75d (8.6)	3.70d (10.8)	3.68d (11.0)
7b-H	—	—	—	—	—	—	—
H-A†	3.53m	3.51m (4.2)	3.57dt (3.9, 11.0)	3.40dt (3.9, 10.6)	3.41dt (4.0, 10.6)	3.58m	3.60dt (4.1, 10.6)
OMe	3.86s (6 H)	3.85s	3.94s	3.91s	3.84s	3.89s	3.83s
OMe	3.85s (6 H)	3.65s	3.93s	3.89s	3.76s	3.83s	3.64s
OMe	—	—	3.93s	3.83s	—	3.66s	—
OMe	—	—	—	3.74s	—	3.62s	—
OCH_2O	—	5.91d (1.8)	5.92d (1.3)	—	5.96d (1.2)	—	5.93d (1.6)
	—	5.95d (1.8)	5.95d (1.3)	—	5.98d (1.2)	—	6.00d (1.6)
Me	0.94d (6.8)	0.93d (6.8)	0.94d (7.4)	0.90d (7.2)	0.90d (7.0)	0.97d (6.8)	0.97d (6.6)
Me	0.86m	0.86m	0.85m	0.83d (6.6)	0.85d (6.5)	0.91d (6.2)	0.93d (7.0)
Me	0.78d (6.9)	0.76d (6.9)	0.78d (6.9)	0.77d (6.9)	0.77d (6.9)	0.84d (6.9)	0.82d (6.9)
Arom	6.6–7.3m	6.6–7.3m	6.4–7.3m	6.4–7.3m	6.4–7.2m	6.2–7.2m	6.3–7.2m

	9a	9b	9c	13a	13b	13c
3-H	2.58dd (4.0, 9.3)	2.54dd (3.6, 9.5)	2.52dd (4.0, 9.4)	2.63d (7.9)	2.57d (8.2)	2.61d (7.0)
4-H	2.22m	2.20m	2.20m	2.50m	2.46m	2.48m
5a-H	5.38d (1.8)	5.39d (1.5)	5.38d (1.8)	4.11dd (7.8, 9.1)	4.12dd (7.8, 9.0)	4.14dd (7.8, 9.1)
5b-H	—	—	—	3.85m	3.85m	3.85m
6-H	4.81d (9.3)	4.73d (9.5)	4.75d (9.4)	4.83d (7.9)	4.77d (8.2)	4.80d (7.0)
7a-H	2.54dd (6.3, 9.3)	2.56dd (6.0, 13.0)	2.50dd (3.9, 8.0)	2.20m (2 H)	2.20m (2 H)	2.20m (2 H)
7b-H	2.24d (9.3)	2.23d (12.9)	2.21d (8.0)			
H-A†	3.48dt (4.3, 10.7)	3.50dt (4.0, 10.0)	3.49d (4.2, 10.5)	—	—	—
OMe	3.88s	3.85s	3.82s	3.89s	3.83s	3.88s
OMe	3.85s	3.74s	3.81s	3.87s	3.81s	3.88s
OMe	3.80s	—	3.81s	3.83s	—	3.83s
OMe	3.76s	—	—	3.81s	—	—
OCH_2O	—	5.98d (1.4)	5.95d (1.5)	—	5.96d (1.9)	5.91s (2 H)
	—	5.93d (1.4)	5.90d (1.5)	—	5.94d (1.9)	
Me	0.92d (7.5)	0.91d (7.2)	0.91d (7.2)			
Me	0.87d (6.9)	0.86d (7.8)	0.90d (6.5)			
Me	0.80d (7.0)	0.79d (6.9)	0.80d (6.9)			
	6.81dd (2.9, 9.0)	6.77d (7.2)	6.60d (7.7)	6.97s	6.91s	6.65d (8.0)
Arom	6.76s (2 H)	6.71d (8.0)	6.50s	6.93dd (1.8, 8.1)	6.84dd (1.2, 7.9)	6.64s
	6.65d (8.1) (2 H)	6.67d (1.7)	6.44s (2 H)	6.87d (7.9)	6.79d (8.0)	6.62s
	6.36dd (1.9, 8.1)	6.60d (8.0)	6.30dd (1.7, 7.8)	6.71d (8.1)	6.74d (8.2)	6.35dd (1.6, 3.3)
		6.57d (1.0)		6.45dd (1.8, 8.1)	6.47dd (1.7, 8.0)	6.33dd (1.4, 1.7)
		6.47dd (1.7, 8.10)		6.36d (1.8)	6.36d (1.7)	

* All spectra recorded in $CDCl_3$ solution. † H-A is H-1 of menthyloxy group.

fluorescent plates. Flash chromatography was performed with silica gel (Merck 9385, Kieselgel 60, 230–400 mesh). Small-scale purifications were conducted on a Chromatotron 7924 using 1, 2 or 4 mm plates prepared from silica gel (Merck 7749, Kieselgel, 50 F_{254} gipshaltig).

The reactions carried out under an inert atmosphere refer to the use of argon and 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran was dried by being stirred overnight over calcium hydride, passed down a dry alumina column and then distilled from sodium wire and benzophenone. Diethyl ether and dichloromethane were dried by passage down a dry alumina column and then distillation from calcium hydride. Dimethylformamide was distilled from calcium hydride, whilst dry toluene and benzene were prepared by distillation from calcium hydride and stored over sodium wire. Solutions of butyllithium in hexane were obtained from Aldrich and were regularly estimated.[26,27] Lithium aluminium hydride was used as a solid, or a solution in dry tetrahydrofuran, estimated as described by Brown.[28]

Preparation of (−)-5-(1-*Menthyloxy*)*furan*-2(5H)-*one* **2a**.—5-Methoxyfuran-2(5*H*)-one (131.8 g, 1.16 mol) and (−)-menthol (216.5 g, 1.39 mol, 1.20 mol equiv.) were stirred at 120–130 °C for 3 days, in a reaction vessel equipped with a reflux condenser. The reaction mixture was then distilled *in vacuo* (106–108 °C, 0.007 mmHg) to afford both isomers of **2** (148.6 g, 54%). HPLC showed that the green semi-solid product consisted of 60.4 and 39.6% of the respective isomers.

The isomers of **2** were twice recrystallised from light petroleum (b.p. 40–60 °C), at a temperature of −25 to −30 °C, to afford diastereomerically pure **2a** as white needles (36.8 g), m.p. 70.4–71.2 °C (lit.,[15] 70.5–70.7 °C). The green mother liquors were combined, and gave a second crop of pure **2a** (total: 61.98 g, 23%).

The remaining green liquor (86.59 g, 0.364 mol) was re-epimerised by dissolution in dry benzene (500 cm^3) and refluxing with a catalytic amount of PTSA (0.21 g, 1.10 mmol, 3.03×10^{-3} mol equiv.) for 1 h. After this time, the reaction mixture was allowed to cool to room temperature before being washed with water (3×100 cm^3). The organic layer was then dried ($MgSO_4$), filtered and evaporated to afford a green semi-solid material. This was then recrystallised as above.

2a: *m*/*z* (CI) 256, ($M + NH_4^+$, 100%); $[\alpha]_D^{20}$ −137 (EtOH, *c* 1.00); δ_H 7.15 (d, *J* 5.77), 6.19 (d, *J* 5.78), 6.07(s), 3.64(dt) (J_1 4.30, J_2 10.69), 0.93 (d, *J* 6.45), 0.86 (d, *J* 7.05), 0.78 (d, *J* 6.90), 2.06–2.16 (m, 2 H), 1.58–1.69 (3 H) and 0.98–1.38 (4 H).

Table 4 ^{13}C NMR spectra of dibenzylbutyrolactone derivatives*

Carbon atom	6a	6b	6c	7a	7b	8a	8b	9a	9b	9c	13a	13b	13c
C-2	177.26s	177.08s	177.32s	177.41s	177.32s	178.06s	177.88s	177.97s	178.27s	177.96s	178.94s	179.08s	178.82s
C-3	51.55d	51.46d	51.40d	52.08d	51.76d	52.21d	51.93d	52.35d	51.84d	52.05d	51.68d	51.38d	51.43d
C-4	48.14d	48.02d	48.26d	47.67d	47.69d	47.89d	47.73d	47.76d	47.66d	47.75d	39.76d	39.85d	39.73d
C-5	100.81d	100.72d	100.78d	102.10d	102.08d	102.91d	102.75d	104.07d	104.04d	103.71d	72.02t	72.03t	71.96t
C-6	75.04d	74.90d	75.37d	74.62d	74.64d	74.53d	74.40d	74.60d	74.57d	74.81d	74.31d	74.37d	74.55d
C-7	70.78d	70.90s	70.40s	49.28d	49.55d	50.50d	50.64d	37.26t	37.23t	37.18t	38.14t	38.06t	38.11t
C-1′1″	132.76s	133.53s	134.68s	132.95s	133.80s	133.69s	133.68s	132.63s	133.77s	135.53s	132.77s	134.04s	135.74s
	132.03s	130.39s	130.89s	132.30s	133.27s	132.46s	133.51s	129.38s	129.15s	130.33s	130.42s	130.24s	131.42
C-2′2″	110.34d	107.66d	107.63d	110.01d	107.90d	110.65d	107.33d	110.74d	107.36d	107.80d	110.98d	108.04d	108.28d
	110.13d	107.54d	106.69d	110.01d	107.39d	109.50d	106.75d	109.72d	106.57d	104.12d	109.70d	106.89d	103.48d
C-3′3″4′4″	149.23s	148.94s	153.62s	149.12s	148.97s	149.34s	149.06s	149.21s	148.94s	153.29s	149.45s	148.98s	138.00s
	149.12s	148.53s	153.47s	148.82s	148.71s	149.08s	148.59s	149.06s	148.03s	153.18s	149.33s	148.22s	153.50s
	148.90s	147.77s	152.97s	148.82s	147.98s	148.69s	148.06s	148.95s	147.89s	147.83s	149.14s	147.82s	147.86s
	148.47s	147.41s	148.03s	148.56s	147.65s	148.31s	148.56s	147.91s	147.53s	147.83s	140.06s	147.82s	146.36s
C-5′5″	112.75d	112.59d	152.97s	111.19d	111.34d	111.27d	110.30d	112.24d	111.42d	153.18s	111.89d	111.48d	153.50s
	110.57d	110.29d	109.98s	110.74d	111.00d	110.73d	110.25d	111.12d	110.72d	108.86d	111.48d	111.22d	108.57d
C-6′6″	120.69d	120.95d	122.48d	120.62d	120.94d	120.38d	120.83d	121.07d	121.24d	121.98d	120.45d	120.45d	121.33d
	120.04d	120.71d	104.47d	119.71d	120.62d	119.73d	120.83d	119.45d	120.74d	107.80d	119.13d	120.30d	108.28d
OMe	55.89q	55.78q	60.87q	55.86q	55.83q	55.98q	55.79q	55.95q	55.76q	55.99q	55.98q	55.87q	60.90q
OMe	55.84q	55.73q	56.25q	55.86q	55.83q	55.80q	55.40q	55.85q	55.47q	55.99q	55.94q	55.75q	56.17q
OMe	55.78q	—	55.90q	55.81q	—	55.69q	—	55.85q	—	55.99q	55.85q	—	56.12q
OMe	55.73q	—	—	55.79q	—	55.59q	—	55.74q	—	—	55.78q	—	—
OCH_2O	—	100.99t	101.60t	—	101.21t	—	101.37t	—	101.34t	101.19t	—	101.31t	101.04t

* All spectra recorded in $CDCl_3$ solution. OMenth and SPh carbons not included.

Preparation of (−)-(4R,5R)-4-[3′,4′-*Dimethoxy-α,α-bis(phenylthio)benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **4a**.—3,4-Dimethoxybenzaldehyde diphenyl thioacetal (2.57 g, 6.98 mmol) was dissolved in dry THF (20 cm^3), under argon, and the solution cooled to −78 °C. To the stirred solution was added, *via* a syringe, BuLi (2.30 mol dm^{-3}; 3.10 cm^3, 7.13 mmol, 1.02 equiv.), and stirring was continued at −78 °C for 2 h. Pre-cooled (−78 °C) (−)-5-menthyloxyfuranone **2a** (2.16 g, 9.08 mmol, 1.30 mol equiv.), dissolved in dry THF (10 cm^3), was then added *via* a double-ended needle to the orange solution and stirring was continued at −78 °C for 2 h before quenching of the reaction by addition of brine (10 cm^3). The mixture was allowed to warm to room temperature and then extracted with diethyl ether (2 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a yellow gum. Purification of this by flash chromatography on silica (CH_2Cl_2) afforded **4a** as a light-sensitive colourless foam (3.73 g, 88%); $[\alpha]_D^{23}$ −79.6 (*c* 0.250, $CHCl_3$) (Found: C, 69.4; H, 7.1. $C_{35}H_{42}O_5S_2$ requires C, 69.31; H, 6.93%); ν_{max}(neat)/cm^{-1} 1790 (γ-lactone); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* 497 (M − SPh^+, 5%), 389 (2%), 341 (75) and 285 (100).

Preparation of (−)-(4R,5R)-4-[3′,4′-*Methylenedioxy-α,α-bis*-(*phenylthio*)*benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **4b**.—3,4-Methylenedioxybenzaldehyde diphenyl thioacetal (1.77 g, 5.03 mmol) was dissolved in dry THF (50 cm^3) under an argon atmosphere and the solution was cooled to −78 °C. To the stirred solution was added, *via* a syringe, BuLi (2.30 mol dm^{-3}; 2.40 cm^3, 5.52 mmol, 1.10 mol equiv.), and the solution stirred at −78 °C for 2 h. Pre-cooled (−78 °C) (−)-5-menthyloxybutenolide **2a** (1.49 g, 6.26 mmol, 1.25 mol equiv.), dissolved in dry THF (25 cm^3), was then added *via* a double-ended needle to the orange solution, and stirring was continued at −78 °C for 2 h before quenching of the reaction by addition of brine (10 cm^3). The mixture was allowed to warm to room temperature and then extracted with diethyl ether (2 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a yellow gum, purification of which by flash chromatography on silica (light petroleum–CH_2Cl_2) afforded **4b** as a light-sensitive colourless foam (2.37 g, 80%); $[\alpha]_D^{21}$ −66.6 (*c* 0.980, $CHCl_3$) (Found: C, 69.2; H, 6.4. $C_{34}H_{38}O_5S_2$ requires C, 69.15; H, 6.44%); ν_{max}(neat)/cm^{-1} 1795 (γ-lactone); λ_{max}(MeOH)/nm 289.6 (ε 12 040); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* 481 (M − SPh^+, 5%), 373 (10%), 325 (5), 297 (100) and 269 (87).

Table 5 ^1H NMR spectra of lirionol derivatives*

	10	12a[22]	12b[22]
1-H	4.11d (2.6)	4.17m (2.1, 2.2)	4.17m (2.7)
4-H	4.15d (1.9)	4.85d (6.4)	4.96d (5.8)
5-H	3.12dd (1.5, 8.5)	2.69m (2.1, 3.0, 6.7, 7.9)	2.63m
6a-H	3.21dd (8.5, 18.2)	2.84dd (7.9, 18.6)	2.76dd (8.1, 18.9)
6b-H	2.38d (18.2)	3.17d (18.6)	2.90d (18.9)
9-H	3.46t (2.6)	2.40m (2.2, 3.0, 7.6)	2.26m (1.7, 2.7, 7.4)
	6.72s		
Arom.	6.68s		
	6.66s		
	6.43s		

* All spectra recorded in $CDCl_3$ solution.

Preparation of (−)-(4R,5R)-4-(3′,4′-*Dimethoxybenzyl*)-5-(1-*menthyloxy*)*butyrolactone* **5a**.—Compound **4a** (0.29 g, 0.479 mmol) was dissolved in MeOH (100 cm^3), and $NiCl_2 \cdot 6H_2O$ (2.29 g, 9.6 mmol, 20.1 mol equiv.) added to the solution. The stirred green solution was then cooled to 0 °C and $NaBH_4$ (1.13 g, 29.7 mmol, 62.1 mol equiv.) was added to it carefully to minimise the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 1 h at room temperature. After this time, water (20 cm^3) was added to the mixture which was then passed through a short Celite/silica column to remove the nickel salts. The filtrate was diluted with water (80 cm^3) and the resulting solution extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to afford **5a** as a colourless foam (0.19 g, 100%); $[\alpha]_D^{24}$ −84.9 (*c* 0.929, $CHCl_3$) (Found: 70.8; H, 8.9. $C_{23}H_{34}O_5$ requires C, 70.77; H, 8.72%);

Table 6 ^{1}H NMR spectra of aryltetralins*

	14a	14b	14c
1-H	4.10d (10)	4.08br d (11.0)	3.93br d (11.2)
2-H	2.54dd (11, 14)	2.47dd (11.0, 13.6)	2.13dd (11.2, 13.7)
3-H	2.64br m	2.59br m	1.84m
4a-H	2.94m	2.92dd (10.7, 14.0)	2.07d (8.0) (2 H)
4b-H	2.97m	2.95dd (5.1, 14.0)	
5-H	6.62s	6.60s	6.67s
8-H	6.33s	6.33s	6.42s
CH_2	4.53dd (6, 8)	4.51dd (6.6, 8.6)	3.75dd (6.6, 8.4)
	3.96m	3.97dd (8.6, 10.6)	3.13dd (8.4, 10.7)
OMe	3.87s	3.86s	3.91s
OMe	3.87s	3.62s	3.51s
OMe	3.82s	—	3.51s
OMe	3.60s	—	—
OCH_2O	—	5.93d (1.4)	5.31d (1.2)
	—	3.92d (1.4)	5.27d (1.2)
2'-H	6.82s	6.76s	6.60s
5'-H	6.82s	6.76s	—
6'-H	6.71s	6.60s	6.60s

* All spectra recorded in $CDCl_3$ solution.

Table 7 ^{13}C NMR spectra of aryltetralins*

Carbon atom	14a	14b	14c
C-1	48.81d	48.90d	48.61d
C-2	45.73d	45.75d	46.70d
C-2a	175.71s	175.64s	175.41s
C-3	40.08d	39.99d	40.08d
C-3a	71.04t	75.05t	70.96t
C-4	32.55t	32.55t	32.91t
C-4a	126.80s	126.83s	127.77s
C-5	110.86d	108.07d	108.42d
C-6	147.68s	146.42s	146.41s
C-7	147.60s	147.66s	146.62s
C-8	112.87d	111.33d	109.92d
C-8a	131.33s	131.27s	132.24s
C-1'	135.54s	136.95s	136.83s
C-2'	112.81d	112.82d	106.43d
C-3'	147.82s	147.71s	153.09s
C-4'	148.71s	147.76s	138.74s
C-5'	111.30d	109.21d	153.09s
C-6'	121.86d	123.01d	106.43d
OMe	55.90q	55.87q	60.84q
OMe	55.90q	55.82q	56.14q
OMe	55.85q	—	56.14q
OMe	55.76q	—	—
OCH_2O	—	100.98t	101.10t

* All spectra recorded in $CDCl_3$ solution.

ν_{max}(neat)/cm^{-1} 1790 (γ-lactone); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 390 ($M^{\cdot+}$, 31%), 251 (14), 235 (100) and 151 ($ArCH_2^+$, 35) (Found: M^+, 390.2406. $C_{23}H_{34}O_5$ requires M^+, 390.2406).

Preparation of (−)-(4R,5R)-4-(3',4'-*Methylenedioxybenzyl*)-5-(1-*menthyloxy*)*butyrolactone* **5b**.—Compound **4b** (2.05 g, 3.47 mmol) was dissolved in MeOH (100 cm^3) and $NiCl_2 \cdot 6H_2O$ (16.71 g, 70.2 mmol, 20.02 mol equiv.) was added to the solution. The stirred green solution was then cooled to 0 °C and $NaBH_4$ (7.95 g, 209 mmol, 60.2 mol equiv.) was added to it carefully, to minimise the effervescence products. The black suspension was then removed from the ice-bath and thoroughly stirred for 1 h at room temperature. After this time, water (20 cm^3) was added to the mixture which was then passed through a short Celite/silica column to remove the nickel salts. The filtrate was diluted with water (100 cm^3) and the resulting solution extracted with diethyl ether (4 × 80 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to afford **5b** as a colourless foam (1.20 g, 92%); $[\alpha]_D^{21}$ −74.4 (*c* 2.350, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1795 (γ-lactone); λ_{max}(MeOH)/nm 279.8 (ε 17 363); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 374 $M^{\cdot+}$, 20%), 235 (32), 219 (90) and 135 ($ArCH_2^+$, 100%) (Found: M^+, 374.2090. $C_{22}H_{30}O_5$ requires M^+, 374.2093).

Preparation of (−)-(3S,4R,5R,6R)-3-(3',4'-*Dimethoxy*-α-*hydroxybenzyl*)-4-[3'',4''-*dimethoxy*-α,α-*bis*(*phenylthio*)*benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **6a**.—3,4-Dimethoxybenzaldehyde diphenyl thioacetal (1.11 g, 3.00 mmol) was dissolved in dry THF (15 cm^3), under an argon atmosphere, and the solution then cooled to −78 °C. To the stirred solution was added, *via* a syringe, BuLi (2.29 mol dm^{-3}; 1.45 cm^3, 3.32 mmol, 1.11 mol equiv.), and stirring was continued at −78 °C for 3 h. After this time, pre-cooled (−78 °C) **2a** (0.89 g, 3.75 mmol, 1.25 mol equiv.), dissolved in dry THF (10 cm^3), was added *via* a cooled double-ended needle to the orange solution. Stirring was continued at −78 °C for 2 h before pre-cooled (−78 °C) solution of veratraldehyde (0.76 g, 4.57 mmol, 1.52 equiv.) in dry THF (10 cm^3), was added to it *via* a double-ended needle. After being stirred at −78 °C for a further 2 h, the solution was quenched by the addition of brine (5 cm^3) and allowed to warm to room temperature before being extracted with diethyl ether (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to give a yellow foam which was purified by flash chromatography on silica (CH_2Cl_2/EtOAc). This gave **6a** as a colourless foam (1.87 g, 81%); $[\alpha]_D^{23}$ −144.1 (*c* 0.476, $CHCl_3$) (Found: C, 68.2; H, 6.95. $C_{44}H_{52}O_8S_2$ requires C, 68.39; H, 6.74%); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone) and 3550 (OH); see Tables 3 and 4 for ^{1}H and ^{13}C NMR data; *m/z* 259 (Ar^1CHSPh^+, 6%), 166 ($Ar^2CHO^{\cdot+}$, 6%) and 166 ($Ar^2CHO^{\cdot+}$, 100%).

Preparation of (−)-(3S,4R,5R,6R)-3-(3',4'-*Methylenedioxy*-α-*hydroxybenzyl*)-4-[3'',4''-*dimethoxy*-α,α-*bis*(*phenylthio*)-*benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **6b**.—3,4-Dimethoxybenzaldehyde diphenyl thioacetal (0.45 g, 1.22 mmol) was dissolved in dry THF (10 cm^3), under a nitrogen atmosphere, and the solution then cooled to −78 °C and stirred. To the stirred solution was added, *via* a syringe, BuLi (2.38 mol dm^{-3}; 0.70 cm^3, 1.66 mmol, 1.36 equiv.) and stirring continued at −78 °C for 3 h. After this time, a pre-cooled (−78 °C) solution of **2a** (0.50 g, 2.09 mmol, 1.7 mol equiv.) in dry THF (5 cm^3), was added *via* a double-ended needle to the orange solution and stirring was continued at −78 °C for 1.75 h. A pre-cooled (−78 °C) solution of piperonal (0.30 g, 2.00 mmol, 1.63 mol equiv.), in dry THF (5 cm^3) was added to it *via* a cooled double-ended needle. After being stirred at −78 °C for a further 2 h, the solution was quenched by the addition of a solution of TFA (1 mol equiv.) in THF at −78 °C. The reaction mixture was then allowed to warm to room temperature before saturated aqueous $NaHCO_3$ (5 cm^3) was added to it, and the whole extracted with diethyl ether (2 × 40 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a yellow foam, which was purified by flash chromatography on silica (CH_2Cl_2) to give **6b** as a colourless foam (0.92 g, 99%); $[\alpha]_D^{23}$ −145.2 (*c* 0.984, $CHCl_3$) (Found: C, 68.3; H, 6.4. $C_{43}H_{48}O_8S_2$ requires C, 68.25; H, 6.35%); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone) and 3500 (OH); see Tables 3 and 4 for ^{1}H and ^{13}C NMR data; *m/z* 259 (Ar^1CHSPh^+, 26%) and 151 (Ar^2CHOH^+, 100%).

Preparation of (−)-(3S,4R,5R,6R)-3-(3',4',5'-*Trimethoxy*-α-*hydroxybenzyl*)-4-[3'',4''-*methylenedioxy*-α,α-*bis*(*phenylthio*)-*benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **6c**.—3,4-Methylenedioxybenzaldehyde diphenyl thioacetal (1.85 g, 5.26 mmol) was

dissolved in dry THF (50 cm^3), under an argon atmosphere and the solution then cooled to −78 °C. To the stirred solution was added, *via* a syringe, BuLi (2.30 mol dm^{-3}; 2.51 cm^3, 5.77 mmol, 1.10 mol equiv.). Stirring was continued at −78 °C for 1.83 h, after which time, a pre-cooled (−78 °C) solution of **2a** (1.49 g, 6.26 mmol, 1.19 mol equiv.) in dry THF (30 cm^3) was added, *via* a double-ended needle, to the orange solution. Stirring was continued at −78 °C for 2 h before pre-cooled (−78 °C) 3,4,5-trimethoxybenzaldehyde (1.31 g, 6.68 mmol, 1.27 mol equiv.), dissolved in dry THF (30 cm^3), was added *via* a double-ended needle. After being stirred at −78 °C for a further 1.67 h, the solution was quenched by the addition of brine (10 cm^3). The reaction mixture was allowed to warm to room temperature, when it was extracted with diethyl ether (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a yellow foam, purification of which by flash chromatography on silica (CH_2Cl_2/EtOAc) afforded **6c** as a white solid, m.p. 149–151 °C (3.29 g, 80%); $[\alpha]_D^{25}$ −159.1 (*c* 2.628, $CHCl_3$) (Found: C, 67.3; H, 6.6. $C_{44}H_{50}O_9S_2$ requires C, 67.18; H, 6.36%); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone) and 3500 (OH); λ_{max}(MeOH)/nm 281.3 (ε 11 445); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 243 (Ar^1CHSPh^+, 6%) and 196 ($Ar^2CHO^{\bullet+}$, 100%).

Preparation of (−)-(3S,4R,5R,6R,7S)- *and* (+)-(3S,4R,5R,6R,7R)-3-(3′,4′-*Dimethoxy-α-hydroxybenzyl*)-4-[3″,4″-*dimethoxy-α-(phenylthio)benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **7a** *and* **8a**.—3,4-Dimethoxybenzyl phenyl sulfide (1.01 g, 3.88 mmol) was dissolved in dry THF (30 cm^3), under an argon atmosphere, and the solution then cooled to −78 °C. To the stirred solution was added, *via* a syringe, BuLi (2.29 mol dm^{-3}; 2.04 cm^3, 4.67 mmol, 1.20 mol equiv.), and stirring was continued at −78 °C for 2 h. After this time, a pre-cooled (−78 °C) solution at **2a** (1.27 g, 5.34 mmol, 1.37 mol equiv.) in dry THF (10 cm^3) was added, *via* a double-ended needle, to the well stirred deep-red solution and the mixture was stirred at −78 °C for 2 h. A pre-cooled solution of veratraldehyde (0.86 g, 5.18 mmol, 1.33 mol equiv.) in dry THF (10 cm^3) was then added to it, *via* a double-ended needle. The mixture was stirred at −78 °C for a further 1.25 h and then quenched by the addition of brine (10 cm^3). The mixture was allowed to warm to room temperature and then extracted with EtOAc (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to yield a yellow foam, purification of which by flash chromatography on silica (CH_2Cl_2/EtOAc) afforded a mixture of **7a** and **8a** as a colourless gum (2.03 g, 81%). HPLC analysis showed a 1:1 ratio of the two isomers, which were subsequently separated on silica (light petroleum–CH_2Cl_2) using a chromatotron. Compound **7a** had $[\alpha]_D^{18}$ −179.1 (*c* 0.732, $CHCl_3$) (Found: C, 68.7; H, 7.3. $C_{38}H_{48}O_8S$ requires C, 68.67; H, 7.23%); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone) and 3560 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 664 ($M^{\bullet+}$, 1%), 343 (12), 259 (Ar^1CHSPh^+, 12%) and 167 (Ar^2CHOH^+, 100%) (Found: M^+, 664.3070. $C_{38}H_{48}O_8S$ requires M^+, 664.3070). **8a**: $[\alpha]_D^{18}$ +27.5 (*c* 1.008, $CHCl_3$) (Found: C, 68.6; H, 7.4. $C_{38}H_{48}O_8S$ requires C, 68.67; H, 7.23%); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone) and 3560 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 664 ($M^{\bullet+}$, 1%), 343 (8), 259 (Ar^1CHSPh^+, 15%) and 167 (Ar^2CHOH^+, 100%) (Found: M^+, 664.3070. $C_{38}H_{48}O_8S$ requires M^+, 664.3070).

Preparation of (−)-(3S,4R,5R,6R,7S)- *and* (+)-(3S,4R,5R,6R,7R)-3-(3′,4′-*Methylenedioxy-α-hydroxybenzyl*)-4-[3″,4″-*dimethoxy-α-(phenylthio)benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **7b** *and* **8b**.—3,4-Dimethoxybenzyl phenyl sulfide (0.99 g, 3.80 mmol) was dissolved in dry THF (25 cm^3), under an argon atmosphere, and the solution then cooled to −78 °C. To the stirred solution was added, *via* a syringe, BuLi (1.25 mol dm^{-3}; 3.34 cm^3, 4.18 mmol, 1.10 mol equiv.), and the mixture stirred at −78 °C for 3.33 h. A pre-cooled (−78 °C) solution of **2a** (141 g, 5.94 mmol, 1.56 mol equiv.) in dry THF (10 cm^3) was then added, *via* a double-ended needle, to the deep red solution. Stirring was continued at −78 °C for 2 h, before a pre-cooled solution of piperonal (1.06 g, 7.08 mmol, 1.86 mol equiv.) in dry THF (10 cm^3) was added, *via* a double-ended needle, to the mixture. This was stirred at −78 °C for a further 2 h and then quenched by the addition of brine (5 cm^3). The mixture was allowed to warm to room temperature before extraction with diethyl ether (5 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to give a yellow foam which, on purification by flash chromatography on silica (CH_2Cl_2/EtOAc), afforded a mixture of **7b** and **8b** as a colourless gum (2.13 g, 86%). HPLC analysis showed a 1:1 ratio of the two isomers, which were subsequently separated by preparative HPLC. Compound **7b** had $[\alpha]_D^{22}$ −160.5 (*c* 1.440, $CHCl_3$) (Found: C, 68.1; H, 7.0. $C_{37}H_{44}O_8S$ requires C, 68.52; H, 6.79%); ν_{max}(neat)/cm^{-1} 1770 (γ-lactone) and 3540 (OH); λ_{max}(MeOH)/nm 283.3; see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (CI) 389 (M − Ar^1CHSPh^+, 2%), 343 (12), 259 (Ar^1CHSPh^+, 63%) and 151 (Ar^2CHOH^+, 100%). Compound **8b**: $[\alpha]_D^{22}$ +17.5 (*c* 1.612, $CHCl_3$) (Found: C, 68.3; H, 6.8. $C_{37}H_{44}O_8S$ requires C, 68.52; H, 6.79%); ν_{max}(neat)/cm^{-1} 1770 (γ-lactone) and 3550 (OH); λ_{max}(MeOH)/nm 283.2 (ε 15 050); see Tables 3 and 4 for ^1H and ^{13}C NMR data; see Fig. 1 for X-ray; *m/z* (EI/CI), 539 (M − SPh^+, 2%), 343 (36), 259 (Ar^1CHSPh^+, 100%) and 151 (Ar^2CHOH^+, 59%).

Preparation of (−)-(3S,4R,5R,6R)-3-(3′,4′-*Dimethoxy-α-hydroxybenzyl*)-4-(3″,4″-*dimethoxybenzyl*)-5-(1-*menthyloxy*)-*butyrolactone* **9a**.—Compound **6a** (0.67 g, 0.868 mmol) was dissolved in MeOH (150 cm^3) and $NiCl_2 \cdot 6H_2O$ (4.22 g, 17.7 mmol, 20.4 mol equiv.) was added to the solution. The stirred green solution was cooled to 0 °C and $NaBH_4$ (2.02 g, 53.2 mmol, 61.2 mol equiv.) was added to it carefully, to minimise the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 1 h at room temperature. After this time, the mixture was diluted with water (20 cm^3) and passed through a short Celite/silica column, in order to remove the nickel salts. Water (50 cm^3) was added to the resulting solution which was extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to afford essentially pure **9a** as a colourless foam (0.49 g, 100%); $[\alpha]_D^{23}$ −131.2 (*c* 0.224, $CHCl_3$) (Found: C, 68.9; H, 8.1. $C_{32}H_{44}O_7$ requires C, 69.06; H, 7.91%); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone) and 3500 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 556 ($M^{\bullet+}$, 1%), 390 (M − $Ar^2CHO^{\bullet+}$, 8%), 251 (21), 235 (6), 166 ($Ar^2CHO^{\bullet+}$, 80%) and 151 ($Ar^1CH_2^+$, 100%) (Found: M^+, 556.3040. $C_{32}H_{44}O_7$ requires M^+, 556.3036).

Preparation of (−)-(3S,4R,5R,6R)-3-(3′,4′-*Methylenedioxy-α-hydroxybenzyl*)-4-(3″,4″-*dimethoxybenzyl*)-5-(1-*menthyloxy*)-*butyrolactone* **9b**.—$NiCl_2 \cdot 6H_2O$ (6.92 g, 29.1 mmol, 20.0 mol equiv.) was added to a solution of compound **6b** (1.10 g, 1.45 mmol) dissolved in MeOH (60 cm^3). The stirred green solution was cooled to 0 °C and $NaBH_4$ (3.31 g, 87.1 mmol, 59.9 mol equiv.) was added to it carefully, to minimise the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 1 h at room temperature. After this time, the reaction mixture was diluted with water (10 cm^3) and passed through a short Celite/silica column, in order to remove the nickel salts. Water (30 cm^3) was added to the resulting solution, which was then extracted with diethyl ether (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to afford essentially pure **9b**

as a colourless foam (0.78 g, 100%); $[\alpha]_D^{20}$ −112.3 (*c* 0.680, $CHCl_3$) (Found: C, 68.9; H, 7.5. $C_{31}H_{40}O_8$ requires C, 68.89; H, 7.41%); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone) and 3480 (OH); λ_{max}(MeOH)/nm 282.5 (ε 9450); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 540 ($M^{\bullet+}$, 2%), 390 (M − $Ar^2CHO^{\bullet+}$, 4%, 251 (5), 235 (4) and 151 (Ar^2CHOH^+ or $Ar^1CH_2^+$, 100%) (Found: M^+, 540.2723. $C_{31}H_{40}O_8$ requires M^+, 540.2723).

Preparation of (−)-(3S,4R,5R,6R)-3-(3′,4′,5′-*Trimethoxy*-α-*hydroxybenzyl*)-4-(3″,4″-*methylenedioxybenzyl*)-5-(1-*menthyloxy*)*butyrolactone* **9c**.—$NiCl_2 \cdot 6H_2O$ (6.65 g, 27.9 mmol, 20.0 mol equiv.) was added to a solution of compound **6c** (1.10 g, 1.40 mmol) dissolved in MeOH (150 cm^3). The stirred green solution was cooled to 0 °C and $NaBH_4$ (3.16 g, 83.2 mmol, 59.4 mol equiv.) was added to it carefully, to minimise the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 1.33 h at room temperature. After this time, the reaction mixture was diluted with water (10 cm^3) and passed through a short Celite/silica column, in order to remove the nickel salts. Water (50 cm^3) was added to the resulting solution, which was then extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to afford essentially pure **9c** as a colourless foam (0.73 g, 92%); $[\alpha]_D^{23}$ −125.6 (*c* 0.479, $CHCl_3$) (Found: C, 67.4; H, 7.45. $C_{32}H_{42}O_9$ requires C, 67.37; H, 7.37%); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone) and 3500 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 570 ($M^{\bullet+}$, 9%), 374 (M − $Ar^2CHO^{\bullet+}$, 5%), 235 (4), 219 (15), 197 (Ar^2CHOH^+, 196 ($Ar^2CHO^{\bullet+}$, 33%), 196 ($Ar^2CHO^{\bullet+}$, 33%) and 135 (Ar^1CH_2, 100%) (Found: M^+, 570.2830. $C_{32}H_{42}O_9$ requires M^+, 570.2829).

Attempted Cyclisation of **9b**.—Compound **9b** (70 mg, 1.30 × 10^{-4} mol) was dissolved in dry CH_2Cl_2 (15 cm^3) and the solution stirred whilst TFA (0.3 cm^3, 3.89 mmol, 30.0 mol equiv.) dissolved in dry CH_2Cl_2 (15 cm^3) was added to it; stirring was continued for 20 h with regular HPLC monitoring. On completion of the reaction, the organic layer was washed with water, until the pH was neutral, then dried ($MgSO_4$), filtered and evaporated to give a red gum. Purification was carried out on silica (CH_2Cl_2/EtOAc) using a Chromatotron to afford **10** as the main fraction (13 mg); ν_{max}(neat)/cm^{-1} 1725 (C=O) and 3300–3500 (OH); see Table 5 for ^1H NMR data.

Preparation of (−)-(3S,4R,6R)-3-(3′,4′-*Dimethoxy*-α-*hydroxybenzyl*)-4-(3″,4″-*dimethoxybenzyl*)*butyrolactone* **13a**.—To the alcohol **9a** (311 mg, 0.559 mmol), under an argon atmosphere, was added, *via* a syringe, a solution of KOH in EtOH (0.40 mol dm^{-3}; 5.60 cm^3, 2.24 mmol, 4.01 mol equiv.). $NaBH_4$ (85 mg, 2.24 mmol, 4.01 mol equiv.) was then added to the well stirred pale yellow solution *via* a solid addition side-arm, and the stirring was continued for 30 min. The reaction was then quenched by the addition to the mixture of aqueous HCl until pH 3.0. An equal volume of water (5.60 cm^3) was then added to the mixture which was then extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were set aside overnight with traces of acid still present, and then thoroughly washed with water (3 × 30 cm^3), dried ($MgSO_4$) and filtered. Purification on silica (light petroleum–CH_2Cl_2) using a Chromatotron afforded **13a** as a colourless foam (113 mg, 5%); $[\alpha]_D^{23}$ −39.3 (*c* 1.172, $CHCl_3$) (Found: C, 65.7; H, 6.6. $C_{22}H_{26}O_7$ requires C, 65.67; H, 6.47%); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone) and 3550 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 402 ($M^{\bullet+}$, 15%), 385 (41), 236 (6), 191 (4), 167 (Ar^2CHOH^+, 61%), 151 ($Ar^1CH_2^+$, 78%) and 137 (Ar^{1+}, 11%) (Found: M^+, 402.1680. $C_{22}H_{26}O_7$ requires M^+, 402.1679).

Preparation of (−)-(3S,4R,6R)-3-(3′,4′-*Methylenedioxy*-α-*hydroxybenzyl*)-4-(3″,4″-*dimethoxybenzyl*)*butyrolactone* **13b**.—The alcohol **9b** (201 mg, 0.372 mmol) was dissolved in EtOH (1 cm^3) under an argon atmosphere and to the stirred solution was added, *via* a syringe, a solution of KOH in EtOH (0.74 mol dm^{-3}; 2.00 cm^3, 1.48 mmol, 3.99 mol equiv.). Solid $NaBH_4$ (56.4 mg, 1.48 mmol, 3.99 mol equiv.) was then added to the well stirred pale yellow solution, *via* a solid addition side-arm, and the stirring was continued for 1.15 h. The reaction was quenched by the addition to the mixture of aqueous HCl until pH 3.0. An equal volume of water (3.0 cm^3) was then added to the mixture which was then extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were stored overnight with traces of acid still present and then thoroughly washed with water (3 × 20 cm^3), dried ($MgSO_4$) and filtered. Purification by Chromatotron on silica (light petroleum–CH_2Cl_2) afforded **13b** as a colourless foam (53.8 mg, 38%); $[\alpha]_D^{23}$ −35.2 (*c* 1.076, $CHCl_3$) (Found: C, 65.3; H, 5.85. $C_{21}H_{21}O_7$ requires C, 65.28; H, 5.70%); ν_{max}(neat)/cm^{-1} 1770 (γ-lactone) and 3600 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 386 ($M^{\bullet+}$, 6), 369 (32), 236 (12), 191 (2) and 151 ($Ar^1CH_2^+$ or Ar^2CHOH^+, 100%) (Found: M^+, 386.1366. $C_{21}H_{22}O_7$ requires M^+, 386.1366).

Preparation of (−)-6-epi-*Podorhizol* **13c**.[24]—The alcohol **9c** (348 mg, 0.611 mmol) was dissolved in EtOH (2 cm^3) under an argon atmosphere and to the stirred solution was added, *via* a syringe, a stirred solution of KOH in EtOH (0.53 mol dm^{-3}; 4.60 cm^3, 2.43 mmol, 3.98 mol equiv.). Solid $NaBH_4$ (92.9 mg, 2.44 mmol, 4.00 mol equiv.) was then added to the well stirred pale yellow solution, *via* a solid addition side-arm, and the stirring was continued for 45 min. The reaction was quenched by the addition to the mixture of aqueous HCl until pH 3.0. An equal volume of water (6.6 cm^3) was added to the mixture which was then extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were set aside overnight with traces of acid still present and then thoroughly washed with water (3 × 30 cm^3), dried ($MgSO_4$), and filtered. Purification by Chromatotron on silica (light petroleum–CH_2Cl_2) afforded **13c** as a colourless foam (108 mg, 43%); $[\alpha]_D^{25}$ −36.3° (*c* 2.160, $CHCl_3$) (Found: C, 63.3; H, 5.9. $C_{22}H_{24}O_8$ requires C, 63.46; H, 5.77%); ν_{max}(neat)/cm^{-1} 1770 (OH); λ_{max}(MeOH)/nm 285.1 (ε 13 020); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 416 ($M^{\bullet+}$, 14%), 399 (60), 263 (2), 238 (32), 220 (13), 197 (Ar^2CHOH^+, 59%), 196 (Ar^2CHO^+, 70%) and 135 ($Ar^1CH_2^+$, 100%) (Found: M^+, 416.1470. $C_{22}H_{24}O_8$ requires M^+, 416.1471.

Preparation of (−)-(1S,2R,3R)-1-(3′,4′-*Dimethoxyphenyl*)-3-(*hydroxymethyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydronaphthalene*-2-*carboxylic Acid Lactone* **14a**.—Compound **13a** (48.3 mg, 0.125 mmol) was dissolved in dry CH_2Cl_2 (5 cm^3) under an argon atmosphere and to the stirred solution was added freshly distilled TFA (0.50 cm^3, 6.49 mmol, 51.9 mol equiv.), *via* a syringe. The resulting well mixed solution was allowed to stand at room temperature for 1 h, after which HPLC analysis revealed a single peak. CH_2Cl_2 (50 cm^3) was added to the reaction mixture and the organic layer separated, washed with water (5 × 20 cm^3), dried ($MgSO_4$), filtered and evaporated to afford **14a** as a white foam (43.6 mg, 91%); $[\alpha]_D^{22}$ −58.7 (*c* 0.872, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1795 (γ-lactone); see Tables 6 and 7 for ^1H and ^{13}C NMR data; *m/z* (EI) 384 (M^+, 100%), 325 (6) and 269 (19) (Found: M^+, 384.1570. $C_{22}H_{24}O_6$ requires M^+, 384.1567).

Preparation of (−)-(1S,2R,3R)-1-(3′,4′-*Methylenedioxyphenyl*)-3-(*hydroxymethyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydronaphthalene*-2-*carboxylic Acid Lactone* **14b**.—Compound **13b** (54.0 mg, 0.14 mmol) was dissolved in dry CH_2Cl_2 (5 cm^3) under an argon atmosphere and to the stirred solution was added freshly distilled TFA (0.50 cm^3, 6.49 mmol, 46.4 mol equiv.), *via* a

syringe. The resulting solution was stirred at room temperature for 3 h, after which HPLC analysis revealed a single product. CH_2Cl_2 (50 cm^3) was added to the mixture and the organic layer was washed with water (5 × 20 cm^3), dried ($MgSO_4$), filtered and evaporated, to afford **14b** as a white foam (49.5 mg, 96%); $[\alpha]_D^{20}$ −64.4 (*c* 0.990, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1795 (γ-lactone); λ_{max}(MeOH)/nm 281.7; see Tables 6 and 7 for ^1H and ^{13}C NMR data; *m/z* (EI) 368 (M^+, 100%) (Found: M^+, 368.1260. $C_{21}H_{20}$ requires M^+, 368.1260).

Preparation of (−)-*Deoxyisopodophyllotoxin* **14c**.—Compound **13c** (43.0 mg, 0.103 mmol) was dissolved, with stirring, in neat, freshly distilled TFA (5 cm^3), under an argon atmosphere. The solution was then allowed to stand at room temperature for 2.33 h after which time, HPLC indicated that **13c** had completely disappeared. CH_2Cl_2 (50 cm^3) was added to the mixture and the organic layer was washed with water (5 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated, to yield a white foam. This was recrystallised twice from CH_2Cl_2–light petroleum to afford **14c** (38.0 mg, 92%) as a white solid, m.p. 258–259 °C (lit., 256–258 °C); $[\alpha]_D^{21}$ −53.3 (*c* 0.976, $CHCl_3$) (Found: C, 66.2; H, 5.5%. $C_{22}H_{22}O_7$ requires C, 66.33; H, 5.53%); ν_{max}(neat)/cm^{-1} 1790 (γ-lactone); see Tables 6 and 7 for ^1H and ^{13}C NMR data; *m/z* (EI) 398 (M^+, 25%) (Found: M^+, 398.1370. $C_{22}H_{22}O_7$ requires M^+, 398.1374).

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