General Conjugate-Addition Method for the Synthesis of Enantiomerically Pure Lignans. Total Synthesis of (-)- and (+)-Burseran, (-)-Dehydroxycubebin, (-)-Trichostin, (-)-Cubebin, (-)-5''-Methoxyhinokinin, and (-)-Hinokinin

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Conjugate addition of benzylic diphenyldithioacetal anions to enantiomerically pure (-)-(2*R*)- and (+)-(2*S*)-2-(benzyloxy)-2,5-dihydro-4-[3,4-(methylenedioxy)benzoyl]furan (**2r** and **2s**) gave complete lignan skeletons of the dibenzylbutane class. Desulfurization followed by hydrogenolysis and, when appropriate, oxidation gave the title enantiomerically pure (>99% ee) lignans **45-50** in 24-35% overall yields from **2r** and **2s**.

The name lignan was introduced in 1936 by Haworth[1] for a class of natural products[2,3] that consists of two phenylpropane moieties joined at the central carbon atoms of the propyl chains. The carbon skeleton defines the three classes of lignans, namely dibenzylbutanes, phenyltetralines,[4] and dibenzocyclooctanes. Lignans are variously oxygenated and carry functionalities such as five-membered ring lactones and tetrahydrofurans as well as hydroxy, methoxy, and methylenedioxy substituents on the aromatic rings. The biosynthesis of lignans proceeds by a radical oxidative dimerization of 1-phenyl-1-propene derivatives.[5] Lignans were long thought to be plant metabolites only. However, the dibenzylbutanes enterolactone and enterodiol were isolated from the urine of different mammals[6] and were later suggested to be secreted by the normal flora of intestinal bacteria.[7]

Lignans have interesting biological properties, and useful drugs have been developed from the well-known lignans podophyllotoxin and steganacin (of the phenyltetraline and dibenzocyclooctane classes, respectively) for the treatment of cancer and other ailments.[8] Lignans of the dibenzylbutane class have antitumor activity,[9] function as platelet-activating-factor (PAF) antagonists,[10] show sodium ion selective diuretic properties,[11] and inhibit microsomal monooxygenases in insects.[12] Enterolactone production seems to be under endocrine control,[13] and it depresses oestrogen-stimulated RNA synthesis.[14] Crude plant materials containing lignans have long been used in folk medicine.[4]

Synthetic routes exist for the preparation of both racemic and optically active lignans.[15] Recent syntheses include podophyllum and dibenzocyclooctane lignans.[16]

Chart I

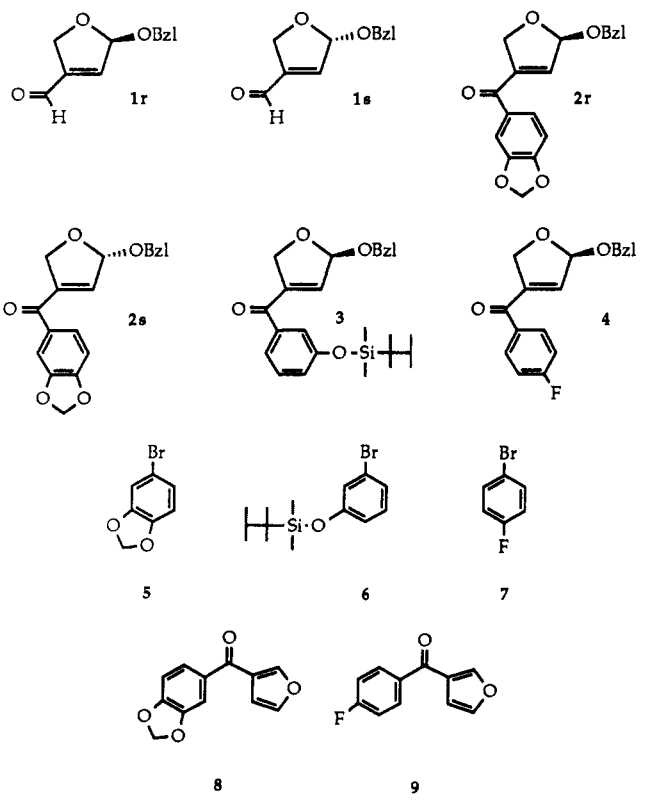

Table I. Product Yields in the Grignard Addition/Allylic Alcohol Oxidation Sequence Leading to α/β-Unsaturated Ketones (cf. Chart I)

starting mtrl	product	yield,[a] %	$[\alpha]^{25}_D$, deg
1r	**2r**	90	-48.6
1s	**2s**		+46.9
1r	**3**	69	-20.4
1r	**4**	60	-24.0

[a] Isolated yield of chromatographed product.

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(6) (a) Stitch, S. R.; Toumba, J. K.; Groen, M. B.; Funke, C. W.; Leemhuis, J.; Vink, J.; Woods, G. F. *Nature* **1980**, *287*, 738. (b) Setchell, K. D. R.; Lawson, A. M.; Mitchell, F. L.; Adlercreutz, H.; Kirk, D. N.; Axelson, M. *Nature* **1980**, *287*, 740.
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(13) Setchell, K. D. R.; Lawson, A. M.; Axelson, M.; Adlercreutz, H. *Res. Steroids* **1981**, *9*, 207.
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(15) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75.
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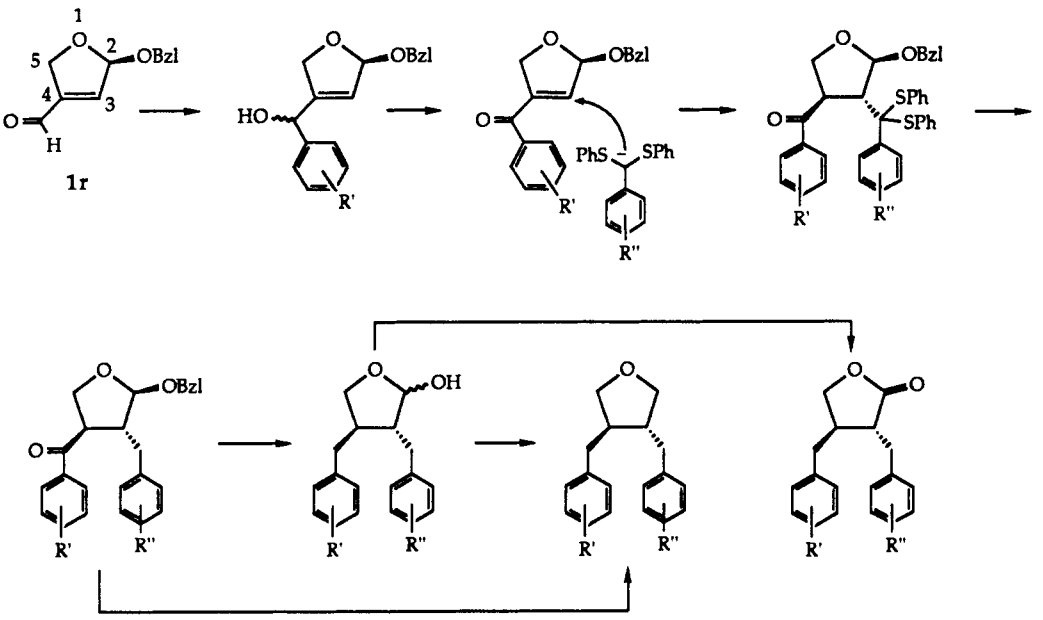
0022-3263/90/1955-4340$02.50/0

Scheme I



Several research groups have prepared compounds of the dibenzylbutane class by a combination of Michael addition, alkylation, or aldol condensation of succinic acid derivatives or benzylbutanolides,[17] by oxidative dimerization of 3-phenylpropionic acid dianions,[18] and recently by tin hydride-induced reductive cyclization of α-bromo allylic esters.[19] Some of the title lignans have been synthesized previously: (±)-cubebin,[17a] (±)-, (+)-, and (−)-burseran,[20] (±)- and (−)-hinokinin.[21] The present paper represents a new approach to the synthesis of dibenzylbutane lignans, employing conjugate addition of benzylic dithioacetals to chiral dihydrofuran ketones as the key reaction step followed by various reduction and oxidation steps (Scheme I). A preliminary report has been published.[22]

Dibenzylbutane lignans have been transformed into numerous cyclic lignans of the phenyltetralin and dibenzocyclooctane classes.[23] Therefore, synthetic routes leading to dibenzylbutane lignans may also constitute viable routes to the cyclic lignans.

The diastereospecific conjugate addition of dithioacetal anions (Chart II) to the enantiomerically pure ketones **2–4** (Chart I) is the key step in our synthetic sequence (Scheme I). The benzyloxy group in **2–4** forces the nucleophile to an anti attack. The steric bulk of the aryldithiane moiety in turn forces the aryl ketone moiety into a trans relationship. The diastereomeric excess (de) was consistently high (virtually 100%) for compounds **28–38** (Chart III), and as a matter of fact the 2,3-trans products (see Scheme I for numbering) seem to be formed exclusively (see below).

The enantiomerically pure aldehydes **1r** and **1s** (Chart I) were conveniently prepared in 15–20% overall yield over six reaction steps, starting with D- and L-arabinose, respectively.[24] The Grignard reagents made from the bromobenzene derivatives **5–7** (Chart I) were added to **1r** and **1s**, and oxidation of the intermediate alcohols with chromium trioxide in pyridine gave the ketones **2r**, **2s**, **3**, and

Table II. Yields and Optical Rotation of Products from Conjugate Addition of Dithioacetal Anions to α/β-Unsaturated Ketones and Aldehydes (cf. Chart III)

starting mtrl	product	yield,[a] %	$[\alpha]^{25}_D$, deg	^{1}H NMR,[b] δ ppm/J, Hz
2r, 10	**28r**	60	+96.9	5.61/d, 0.5
2s, 10	**28s**		−90.7	5.61/d, 0.5
2r, 11	**29**	67	+55.2	5.47/s
2r, 12	**30**	74	+62.2	5.50/s
2r, 14	**31**	80	+44.7	5.38/d, 1.0
2r, 18	**32**	40 (56)	+40.2	5.35/s
2r, 24	**33**	31 (43)	+42.8	5.30/d, 0.7
2r, 25	**34r**		+21.2	5.49/s
2s, 25	**34s**	61	−22.0	5.49/s
3, 13	**35**	69	+36.1	5.47/s
4, 15	**36**	22	+32.6	5.48/s
2s, 16	**37**	33 (64)	−40.6	5.46/s
2s, 20	**38**	32 (70)	−35.3	5.31/s
1r, *c*	**39**	46	−69.1	4.98/s

[a] Isolated yield of chromatographed product. Figures in parentheses are based on the amount of **2** that was consumed; remaining **2** was isolated in the chromatography of the product mixtures. [b] H-2 signal. [c] Methyl 3,4-(methylenedioxy)benzyl ether/lithium.

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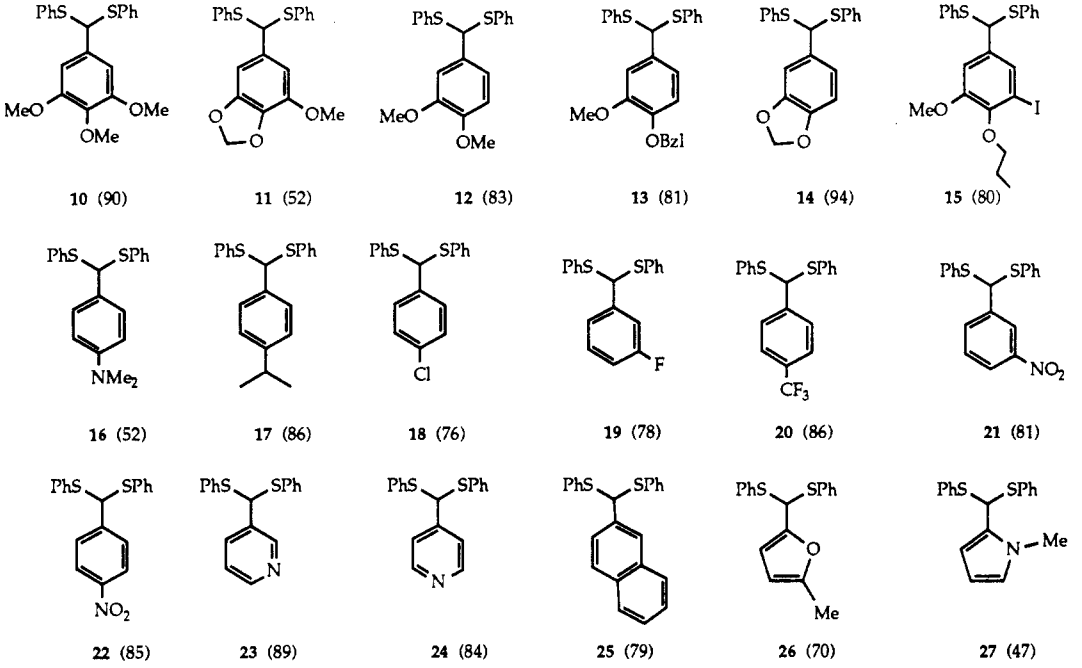
(24) Sundin, A.; Frejd, T.; Magnusson, G. *J. Org. Chem.* **1986**, *51*, 3927. Aldehydes **1r** and **1s** were used as starting materials in the synthesis of the four possible stereoisomers of the mycotoxin botryodiplodin.[28] Being chiral isoprene units, **1r** and **1s** are useful in terpene synthesis as exemplified by the Diels–Alder reaction with cyclopentadiene (Magnusson, G. *J. Org. Chem.* **1985**, *50*, 1998) to give complete norbornane skeletons (Sundin, A.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1985**, *26*, 5605).

Chart II. Bis(phenylthio) Acetals Prepared from the Corresponding Aldehydes in the Yields Shown (%)



4 (Chart I; Table I). The aldehydes **1r** and **1s** were earlier shown to be sensitive toward acids, which caused 1,4-elimination of benzyl alcohol and the formation of 3-carboxaldehyde.[24] The ketones are also sensitive, and **2** and **4** gave small amounts of the benzoylfurans **8** and **9**, respectively, after prolonged contact with deuteriochloroform or silica gel, which both may be slightly acidic.

The dithioacetals **10–27** were prepared in 47–94% yield by the tributylphosphine-promoted reaction of substituted benzaldehydes and diphenyldisulfide[25] (Chart II). The method is generally applicable and gives normally high yields of product. Furthermore, transformation of a phenyl dithioacetal moiety into a methylene group is readily performed with Raney nickel,[26] as exemplified by the reduction of **31** and **34r** to give **41** and **43**, respectively.

The anions of the dithioacetals **10–16**, **18**, **20**, **24**, and **25** (Chart II) were generated by treatment with butyllithium at −78 °C. Conjugate addition of these anions to the appropriate ketones (**2–4**) gave the complete lignan skeletons **28–38**. Several of these compounds carried "unnatural" substituents; thus *chiral lignan analogues* are accessible by the present route (Chart III, Table II).

The aldehyde **1r** was used as acceptor in a conjugate addition of the benzylic anion generated by treatment of methyl 3,4-(methylenedioxy)benzyl ether with lithium metal. The enolate formed in the addition was trapped as the silyl enol ether **39**. Enolate trapping has been shown to increase the yield significantly in conjugate additions to aldehydes and ketones.[27,28] The benzyloxy group of **1r** seems to direct the attacking nucleophile as efficiently as it does in the ketones **2–4**. The ^{1}H NMR spectrum of **39** clearly showed that the 2-(benzyloxy)- and 3-(methylenedioxy)benzyl groups were trans related (singlet at 4.98 ppm) and that no 2,3-cis byproduct was present (see below). Treatment of **39** with tetrabutylammonium fluoride gave the aldehyde **40** as a 15:1 epimeric (C-4) mixture, the major component probably being the one with a 3,4-trans relationship.

Table III. Yields and Optical Rotation of Products from Various Reduction and Oxidation Reactions (cf. Chart IV)

starting mtrl	product	yield,[a] %	$[\alpha]^{25}_D$, deg	^{1}H NMR,[b] δ ppm/*J*, Hz
31	**41**	49	−86.5	4.95/d, 2.0
41	**42**	[c]		4.90/d, 1.8
34r	**43**	50	−59.6	5.03/d, 2.0
41	**44**	[c]		4.88/d, 4.5
28r	**45r**		−45.1 (lit.[20b] −34.8)	
28s	**45s**	52	+44.1 (lit.[20b] +37.5)	
31	**46**	43	−54.9 (lit. −45,[43] −37[44])	
29	**47**	36	−52.1 (lit.[30b] −62.25)	
31	**48**	36	−69.2 (lit. −68[45])	
47	**49**	59	−31.0 (lit. −37,[30a] 10.2,[30b] −14.2[30b])	
48	**50**	83	−34.7 (lit.[21b] −34.0)	

[a] Isolated yield of chromatographed product. [b] H-2 signal. [c] Obtained in low yield by hydrogenation of **41** in 2-propanol/ethyl acetate.

The conjugate-addition products **28r**, **28s**, **29**, **31**, and **34r** (Chart III) were desulfurized by Raney nickel, which was added in portions in response to TLC analysis of the progression of the reaction. It is somewhat difficult to add exactly the required amount of Raney nickel, but when this was accomplished, a clean desulfurized product was obtained. With excess Raney nickel, some overreduction occurred, which was revealed as the appearance of polar byproducts on the TLC plate.

The desulfurized products were either purified (**41**, **43**) or submitted to hydrogenolysis over palladium-on-carbon, to yield variously oxygenated tetrahydrofurans depending on the reaction conditions used (Chart IV and Table III). The phenyl ketone moiety was reduced to a benzylic group in both acidic and basic media. When reductions were performed in acidic media, the fully reduced tetrahydrofurans (−)-burseran[29] (**45r**), (+)-burseran (**45s**), and (−)-

(25) Tazaki, M.; Takagi, M. *Chem. Lett.* **1979**, 767.
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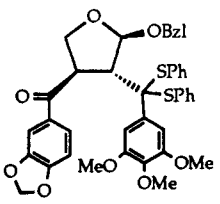
(28) Rehnberg, N.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 3589. Rehnberg, N.; Magnusson, G. *Acta Chem. Scand.*, in press.

(29) (a) Cole, J. R.; Bianchi, E.; Trumbull, E. R. *J. Pharm. Sci.* **1969**, *58*, 175. (b) Trumbull, E. R.; Cole, J. R. *Ibid.* **1969**, *58*, 176. The optical rotation for natural burseran was not given; the absolute configuration of burseran is not known.

Chart III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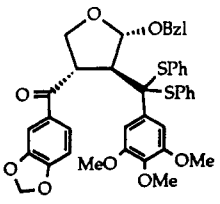
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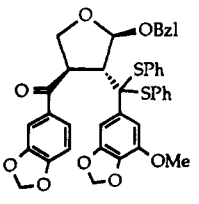
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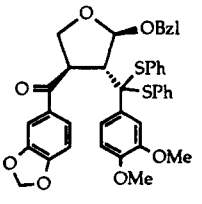
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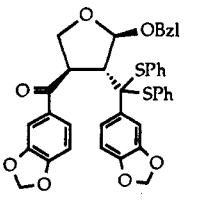
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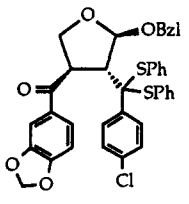
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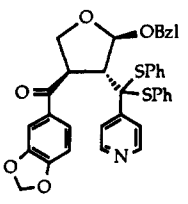
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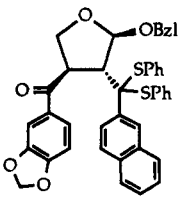
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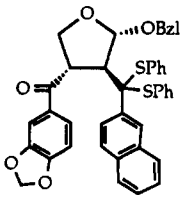
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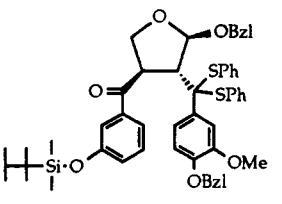
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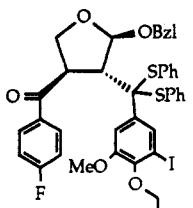
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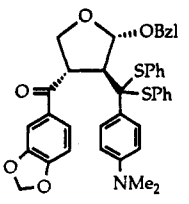
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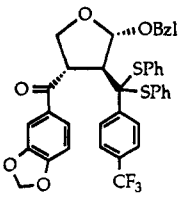
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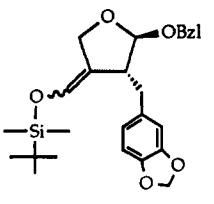
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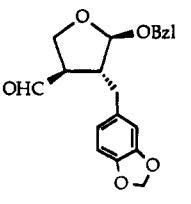
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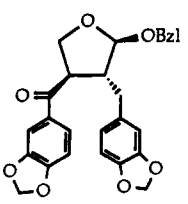
Chart IV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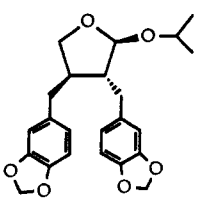
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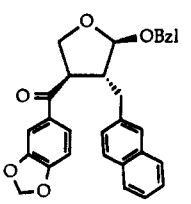
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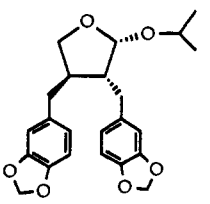
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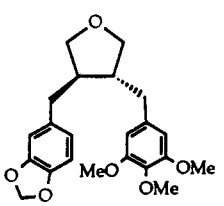
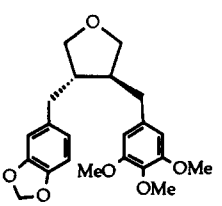
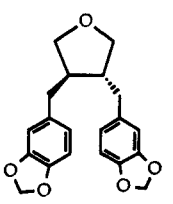
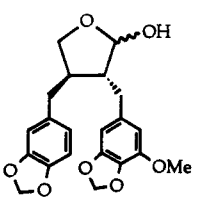
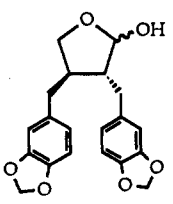
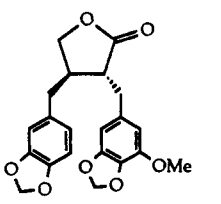

45r (-)-Burseran

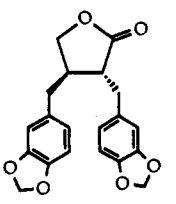

45s (+)-Burseran

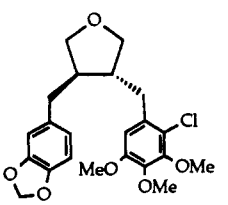

46 (-)-Dehydroxycubebin


47 (-)-Trichostin


48 (-)-Cubebin


49 (-)-5"-Methoxyhinokinin


50 (-)-Hinokinin


51 2"-chloroburseran

dehydroxycubebin (**46**) were obtained, whereas in neutral or basic media the hemiacetals (-)-trichostin[30] (**47**) and (-)-cubebin[31] (**48**) were the products. Compound **46** was also obtained by hydrogenolysis of the hemiacetal **48**. There is some precedence for this type of hydrogenolytic cleavage of acetals to produce ethers.[32] However, ex-

(30) (a) Badheka, L. P.; Prabhu, B. R.; Mulchandani, N. B. *Phytochemistry* **1987**, *26*, 2033; the name 5"-methoxyhinokinin was used for compound **49**. (b) Koul, S. K.; Taneja, S. C.; Pushpangadan, P.; Dhar, K. L. *Ibid.* **1988**, *27*, 1479; the name dehydrotrichostin was used for compound **49**.

(31) Haworth, R. D.; Kelly, W. *J. Chem. Soc.* **1937**, 384.

perimental evidence for hydrogenolytic cleavage of hemiacetals to produce the corresponding ether seems to be lacking in the literature, although it was suggested that hemiacetals might be intermediates when ketones and aldehydes were hydrogenated to ethers in alcohol solvents.[32b] It should be noticed that several reduction steps could be performed simultaneously as exemplified by the preparation of (+)-burseran (**45s**) from **28s**. Cleavage of the dithioacetal moiety by Raney nickel, followed by hydrogenolysis of both the ketone and the benzyloxy groups gave **45s** in an overall yield of 52%.

Finally, oxidation of (-)-trichostin (**47**) and (-)-cubebin (**48**) with chromium trioxide gave (-)-5''-methoxyhinokinin[30] (**49**) and (-)-hinokinin[31] (**50**), respectively (Table III).

An unexpected reaction occurred when (-)-burseran (**45r**) was left in $CDCl_3$ for several days, resulting in the formation of a small amount of 2''-chloroburseran (**51**). The structure of **51** was determined from the mass and NMR spectra (see the Experimental Section).

The conjugate addition of the various nucleophiles to compounds **1-4** produced compounds **28-39** with high diastereoselectivity (de >99%, see below) and the final lignans (**45-50**) were of high enantiomeric purity (ee >99%). The high diastereomeric excess is probably due to efficient steric hindrance by the benzyloxy moiety in **1-4**, thereby directing the dithioacetal anion to the less hindered side of the dihydrofuran ring. All the conjugate-addition products **28-39** showed coupling constants ($J_{2,3}$) of <1 Hz (Table II). The desulfurized 2,3-trans acetals **41-43** had $J_{2,3}$ in the range 1.8-2.0 Hz, whereas the 2,3-cis acetal **44** had $J_{2,3}$ = 4.5 Hz (Table III). It has been demonstrated[33] that $J_{2,3}$ for tetrahydrofuran acetals is within 4.3-6.8 Hz for 2,3-cis hydrogens. We therefore conclude that compounds **28-43** have a 2,3-trans stereostructure. Using similar (benzyloxy)tetrahydrofurans, we have earlier determined the ^1H NMR detection limit[28] of a small amount of 2,3-cis compound in the 2,3-trans analogue to be approximately 0.3%. Since no ^1H NMR signals with $J_{2,3}$ > 2 Hz were detected between 4.9 and 5.8 ppm with the present lignan derivatives **28-43**, we conclude that the conjugate additions proceeded with a de of >99%.

The lignans **45-50** should be enantiomerically pure (ee >99%) for the following reasons: (i) The basic conditions used in the synthesis of **2-4** (from enantiomerically pure **1**[24]) and in the conjugate additions should racemize neither the ketones **2-4** nor the addition products **28-38**. (ii) Compounds **45-50** were pure according to the ^1H NMR spectra. If **45-50** were racemic mixtures, racemization must have occurred on both C-3 and C-4, which we consider to be highly improbable. (iii) Optical rotations (absolute values) for **45-50** were consistently high (cf. Table III) and compared well with the values reported for the natural compounds. (iv) The presence of a small amount (ca. 1%) of added (+)-burseran (**45s**) in (-)-burseran (**45r**) can be detected by ^1H NMR using additions of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium; with synthetic **45r** and shift reagent, no ^1H NMR signals for **45s** were detected.

In summary, compounds **1-4** are suitable starting materials for the synthesis of enantiomerically pure lignans and are valuable complements to chiral butenolides[34] and lactone sulfoxides.[17d]

Experimental Section

Liquid chromatography purifications were performed in the gravity mode. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Melting points are uncorrected. Mass spectra were recorded on a Finnigan 4021 spectrometer. NMR spectra were recorded using a Varian XL-300 spectrometer. Chemical shifts are given in ppm downfield from Me_4Si. Atoms are numbered as indicated in Scheme I; hydrogens of the aromatic rings in the 3- and 4-position of the tetrahydrofuran skeleton are marked with a double prime ('') and a single prime (') respectively. The heptane used is a mixture of isomers with boiling range 94-100 °C.

(2*R*)-2-(Benzyloxy)-2,5-dihydrofuran-4-carbaldehyde (**1r**) and (2*S*)-2-(benzyloxy)-2,5-dihydrofuran-4-carbaldehyde (**1s**) were prepared as reported.[24] 4-Bromo-1,2-dimethoxybenzene (**5**) and 1-bromo-4-fluorobenzene (**7**) are commercially available.

(-)-(2*R*)-2-(Benzyloxy)-2,5-dihydro-4-[3,4-(methylenedioxy)benzoyl]furan (2r). Magnesium turnings (0.238 g, 9.79 mmol) in tetrahydrofuran (1 mL) were activated by addition of 1,2-dibromoethane (five drops). A solution of 4-bromo-1,2-(methylenedioxy)benzene (**5**, 0.641 g, 3.19 mmol) in tetrahydrofuran (2.5 mL) was added dropwise. After 0.5 h, the solution was separated from residual magnesium and transferred to a clean reaction flask and cooled with an ice bath. Compound **1r**[24] (0.500 g, 2.45 mmol) in tetrahydofuran (5 mL) was added dropwise to the cooled solution with stirring. After 25 min, aqueous ammonium sulfate (10 mL, 10%) and diethyl ether (20 mL) were added. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Toluene was added to the resulting syrup and removed in vacuo (≤30 °C) three times. The crude allylic alcohol was oxidized without further purification.

A solution of the crude allylic alcohol in dichloromethane (5 mL) was added to a solution of chromium trioxide (1.72 g, 17.2 mmol) in dry pyridine[35] (2.71 g, 34.3 mmol) and dry dichloromethane (43 mL). After 20 min, the solution was decanted. The reaction flask was washed with diethyl ether (75 mL). The combined solutions were washed with aqueous sodium hydroxide (25 mL, 1 M), aqueous hydrochloric acid (25 mL, 5%), and aqueous sodium hydrogencarbonate (2 × 25 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, EtOAc/heptane, 1:7) to give **2r** (0.715 g, 90%): mp 49-52 °C (MeOH/$CHCl_3$); $[\alpha]^{25}_D$ -48.6° (*c* 0.69, $CHCl_3$); IR (CCl_4) 1655 (C=O), 1610 (C=C), 1450 (CH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (dd, 1 H, *J* = 8.2, 1.7 Hz, H-6'), 7.38-7.26 (m, 6 H, ArH), 6.85 (dd, 1 H, *J* = 8.1, 0.5, Hz, H-5'), 6.32 (dt, 1 H, *J* = 2.3, 1.2 Hz, H-3), 6.12 (dt, 1 H, *J* = 4.4, 1.1 Hz, H-2), 6.06 (s, 2 H, OCH_2O), 5.11 (ddd, 1 H, *J* = 14.0, 4.5, 2.4 Hz, H-5), 4.94 (ddd, 1 H, *J* = 13.9, 2.0, 1.1 Hz, H-5), 4.82, 4.64 (AB q, 1 H each, *J* = 11.7 Hz, PhCH_2); ^{13}C NMR (CD_3COCD_3) δ 195.3 (C=O), 159.0, 155.2, 149.9, 145.5, 140.7, 138.6, 135.0, 134.5, 134.2, 132.5, 115.7, 114.9, 114.7, 109.1 (C=C, OCH_2O, C-2), 80.9, 75.3 (C-5, PhCH_2). Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.4; H, 5.0. Found: C, 70.2; H, 4.9.

(+)-(2*S*)-2-(Benzyloxy)-2,5-dihydro-4-[3,4-(methylenedioxy)benzoyl]furan (2s). Compound **1s**[24] was treated essentially as above (**2r**) to give **2s**: $[\alpha]^{25}_D$ +46.9° (*c* 0.60, $CHCl_3$). **2r** and **2s** had identical ^1H NMR spectra.

(-)-(2*R*)-2-(Benzyloxy)-2,5-dihydro-4-[3-[[dimethyl(2,3-dimethyl-2-butyl)silyl]oxy]benzoyl]furan (3). Compound **1r** (2.00 g, 9.80 mmol) was treated with the Grignard reagent prepared from **6** (4.01 g, 12.7 mmol), following the procedure for the preparation of **2r**. Chromatography (CH_2Cl_2/heptane, 2:1) of the crude product gave **3** (2.95 g, 69%): $[\alpha]^{25}_D$ -20.4° (*c* 0.9, MeOH); ^1H NMR (CD_3OD) δ 7.46-7.24 (m, 8 H, ArH), 7.11 (ddd, 1 H, *J* = 7.5, 2.5, 1.6 Hz, ArH), 6.42 (dt, 1 H, *J* = 2.3, 1.3 Hz, H-3), 6.14 (dt, 1 H, *J* = 4.3, 1.2 Hz, H-2), 5.02 (ddd, 1 H, *J* = 13.8, 4.3, 2.4 Hz, H-5), 4.89 (ddd, 1 H, *J* = 13.8, 2.1, 1.2 Hz, H-5), 4.78, 4.64

(32) (a) von Rudloff, E.; Tulloch, A. P. *Can. J. Chem.* **1957**, *35*, 1504. (b) Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* **1963**, 5598. (c) van Rijsbergen, R.; Anteunis, M. J. O.; de Bruyn, A. *Carbohydr. Res.* **1982**, *105*, 269.

(33) Stevens, J. D.; Fletcher, Jr., H. G. *J. Org. Chem.* **1968**, *33*, 1799.

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(AB q, 1 H each, J = 11.7 Hz, PhCH_2O), 1.75 (heptet, 1 H, J = 6.9 Hz, Me_2CH), 0.97 (s, 6 H, $(Me)_2CSi$), 0.97 (d, 6 H, J = 6.9 Hz, Me_2CH), 0.25 (s, 6 H, Me_2Si). Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.2; H, 7.8. Found: C, 71.1; H, 8.0.

(-)-(2*R*)-2-(Benzyloxy)-4-(4-fluorobenzoyl)-2,5-dihydrofuran (4). Compound **1r** (3.00 g, 14.7 mmol) was treated with the Grignard reagent prepared from **7** (3.34 g, 19.0 mmol) following the procedure for the preparation of **2r**. Chromatography (EtOAc/heptane, 1:13) of the crude product gave **4** (2.62 g, 60%) and 3-(4-fluorobenzoyl)furan (**9**). Compound **4** had: $[\alpha]^{25}_D$ -24.0° (c 2.2, $CHCl_3$); MS m/e (rel int) 191 (M^+ - $PhCH_2O$, 17), 123 ($FC_6H_4CO^+$, 100); ^1H NMR ($CDCl_3$) δ 7.86–7.82 (m, 2 H, ArH), 7.38–7.31 (m, 5 H, PhH), 7.17–7.11 (m, 2 H, ArH), 6.35 (dt, 1 H, J = 2.3, 1.3 Hz, H-3), 6.13 (dt, 1 H, J = 4.4, 1.2 Hz, H-2), 5.13 (ddd, 1 H, J = 14.0, 4.4, 2.4 Hz, H-5), 4.95 (ddd, 1 H, J = 14.0, 2.2, 1.1 Hz, H-5), 4.83, 4.65 (AB q, 1 H each, J = 11.6 Hz, $PhCH_2$). Anal. Calcd for $C_{18}H_{15}FO_3$: C, 72.5; H, 5.1. Found: C, 72.6; H, 5.1.

1-Bromo-3-[[dimethyl(2,3-dimethyl-2-butyl)silyl]oxy]benzene (6). Dimethyl(2,3-dimethyl-2-butyl)chlorosilane (6.70 g, 37.5 mmol) was added to a stirred solution of *m*-bromophenol (6.00 g, 34.7 mmol) and imidazole (3.48 g, 51.1 mmol) in dry *N,N*-dimethylformamide (15 mL). The mixture was stirred for 50 min, diethyl ether (100 mL) and water (40 mL) were added, and the organic layer was washed with water (2 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated, and the residue was chromatographed (SiO_2, heptane) to give **6** (11.23 g, 95%): ^1H NMR ($CDCl_3$) δ 7.12–7.07 (m, 2 H, ArH), 7.01–6.98 (m, 1 H, ArH), 6.79–6.72 (m, 1 H, ArH), 1.72 (heptet, 1 H, J = 6.9 Hz, Me_2CH), 0.95 (s, 6 H, $(Me)_2CSi$), 0.94 (d, 6 H, J = 6.9 Hz, Me_2CH), 0.23 (s, 6 H, $(Me)_2Si$). Anal. Calcd for $C_{14}H_{23}BrOSi$: C, 53.3; H, 7.4. Found: C, 53.2; H, 7.3.

3-[3,4-(Methylenedioxy)benzoyl]furan (8). On prolonged heating during crystallization of **2r** or when a solution of **2r** in deuteriochloroform was allowed to stand for some hours, benzyl alcohol was eliminated and **8** was formed: mp 88–88.5 °C ($MeOH/CHCl_3$); MS m/e (rel int) 216 (M^+, 48), 149 ($CH_2O_2C_6H_3CO^+$, 30), 95 ($C_4H_3OCO^+$, 100); ^1H NMR ($CDCl_3$) δ 7.91 (dd, 1 H, J = 1.4, 0.8 Hz, ArH), 7.50 (t, 1 H, J = 1.7 Hz, ArH), 7.48 (dd, 1 H, J = 8.2, 1.7 Hz, H-6), 7.38 (d, 1 H, J = 1.7 Hz, H-2), 6.88 (d, 1 H, J = 8.1 Hz, H-5), 6.87 (dd, 1 H, J = 1.9, 0.8 Hz, ArH), 6.07 (s, 2 H, OCH_2O). Anal. Calcd for $C_{12}H_8O_4$: C, 66.7; H, 3.7. Found: C, 66.5; H, 3.7.

3-(4-Fluorobenzoyl)furan (9) was obtained by chromatography of the reaction mixture from the preparation of **4**. Compound **9**: mp 80–81 °C ($MeOH/H_2O$); MS m/e (rel int) 190 (M^+, 25), 123 ($FC_6H_4CO^+$, 15), 95 ($C_4H_3OCO^+$, 100); ^1H NMR ($CDCl_3$) δ 7.93–7.88 (m, 3 H, ArH), 7.52 (dd, 1 H, J = 1.9, 1.5 Hz, ArH), 7.26–7.15 (m, 2 H, ArH), 6.89 (dd, 1 H, J = 1.9, 0.8 Hz, β'). Anal. Calcd for $C_{11}H_7FO_2$: C, 69.5; H, 3.7. Found: C, 69.1; H, 3.5.

5-[Bis(phenylthio)methyl]-1,2,3-trimethoxybenzene (10). Tributylphosphine (11.3 g, 56.0 mmol) in benzene (14 mL) was added dropwise to a stirred solution of diphenyl disulfide (11.67 g, 53.4 mmol) and 3,4,5-trimethoxybenzaldehyde (10.0 g, 51.0 mmol) in benzene (19 mL).[25] The mixture was stirred for 2.5 h. Diethyl ether (100 mL) was added, and the solution was washed with aqueous hydrochloric acid (3 × 25 mL, 10%), aqueous sodium hydroxide (2 × 25 mL, 2 M), and water (2 × 25 mL). The organic phase was dried (Na_2SO_4) and concentrated, and the residue was chromatographed (SiO_2, EtOAc/heptane, 1:10) to give **10** (18.15 g, 90%): mp 100–101 °C (EtOH); ^1H NMR ($CDCl_3$) δ 7.39–7.26 (m, 10 H, PhS), 6.54 (s, 2 H, H-4, H-6), 5.35 [s, 1 H, $(PhS)_2CH$], 3.83 (s, 3 H, MeO), 3.73 (s, 6 H, MeO). Anal. Calcd for $C_{22}H_{22}O_3S_2$: C, 66.3; H, 5.6. Found: C, 66.2; H, 5.6.

5-[Bis(phenylthio)methyl]-1-methoxy-2,3-(methylenedioxy)benzene (11). 3-Methoxy-4,5-(methylenedioxy)benzaldehyde[36] (7.80 g, 43.3 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 20:1 → 1:15), **11** (9.38 g, 52%): ^1H NMR ($CDCl_3$) δ 7.38–7.25 (m, 10 H, PhS), 6.64 (d, 1 H, J = 1.6 Hz, ArH), 6.60 (d, 1 H, J = 1.5 Hz, ArH), 5.96 (s, 2 H, OCH_2O), 5.3 [s, 1 H, $(PhS)_2CH$], 3.80 (s, 3 H, MeO). Anal. Calcd for $C_{21}H_{18}O_3S_2$: C, 65.9; H, 4.7. Found: C, 66.2; H, 4.7.

4-[Bis(phenylthio)methyl]-1,2-dimethoxybenzene (12). 3,4-Dimethoxybenzaldehyde (2.50 g, 15.0 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:10), **12** (4.60 g, 83%): mp 68–69 °C (EtOH/EtOAc) [lit.[37] mp 63–64 °C ($CHCl_3$/MeOH)]; ^1H NMR ($CDCl_3$) δ 7.37–7.34 (m, 4 H, PhH), 7.27–7.24 (m, 6 H, PhH), 6.90 (d, 1 H, J = 2.0 Hz, H-3), 6.87 (ddd, 1 H, J = 8.0, 2.1, 0.4 Hz, H-5), 6.73 (d, 1 H, J = 8.2 Hz, H-6), 5.41 [s, 1 H, $(PhS)_2CH$], 3.86 (s, 3 H, MeO), 3.81 (s, 3 H, MeO).

1-(Benzyloxy)-4-[bis(phenylthio)methyl]-2-methoxybenzene (13). 4-(Benzyloxy)-3-methoxybenzaldehyde (2.00 g, 8.26 mmol) was treated as above (**10**) to give, after crystallization (EtOH) and chromatography (SiO_2, EtOAc/heptane, 1:3), **13** (2.98 g, 81%): mp 102–103 °C (EtOH); ^1H NMR ($CDCl_3$) δ 7.44–7.23 (m, 15 H, PhH), 6.92 (d, 1 H, J = 2.0 Hz, H-3), 6.80 (dd, 1 H, J = 8.3, 2.0 Hz, H-5), 6.74 (d, 1 H, J = 8.3 Hz, H-6), 5.38 [s, 1 H, $(PhS)_2CH$], 5.13 (s, 2 H, $PhCH_2$), 3.82 (s, 3 H, Me). Anal. Calcd for $C_{27}H_{24}O_2S_2$: C, 72.9; H, 5.4. Found: C, 72.8; H, 5.4.

4-[Bis(phenylthio)methyl]-1,2-(methylenedioxy)benzene (14). 3,4-(Methylenedioxy)benzaldehyde (10.0 g, 66.6 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:20), **14** (21.90 g, 94%): mp 45–47.5 °C (EtOH) [lit.[38] mp 48 °C (acetone)]; ^1H NMR ($CDCl_3$) δ 7.38–7.24 (m, 10 H, PhH), 6.99 (d, 1 H, J = 1.8 Hz, H-3), 6.78 (ddd, 1 H, J = 8.0, 1.8, 0.4 Hz, H-5), 6.66 (d, 1 H, J = 8.1 Hz, H-6), 5.95 (s, 2 H, OCH_2O), 5.36 [s, 1 H, $(PhS)_2CH$].

5-[Bis(phenylthio)methyl]-1-iodo-3-methoxy-2-propoxybenzene (15). 3-Iodo-5-methoxy-4-propoxybenzaldehyde[39] (3.00 g, 9.37 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:50), **5** (3.90 g, 80%): ^1H NMR ($CDCl_3$) δ 7.36–7.25 (m, 11 H, ArH), 6.83 (d, 1 H, J = 2.0 Hz, ArH), 5.29 [s, 1 H, $(PhS)_2CH$], 3.90 (t, 2 H, J = 6.7 Hz, CH_2O), 3.88 (s, 3 H, MeO), 1.83 (sextet, 2 H, J = 7.0 Hz, $MeCH_2$), 1.06 (t, 3 H, J = 7.4 Hz, $MeCH_2$). Anal. Calcd for $C_{23}H_{23}IO_2S_2$: C, 52.9; H, 4.4. Found: C, 53.0; H, 4.5.

1-[Bis(phenylthio)methyl]-4-(dimethylamino)benzene (16). 4-(Dimethylamino)benzaldehyde (0.857 g, 5.74 mmol) was treated as in the preparation of **10**, except that washing with aqueous hydrochloric acid was omitted, to give, after chromatography (SiO_2, EtOAc/heptane, 1:30), **16** (1.05 g, 52%): mp 137–138 °C (heptane/toluene) (lit.[40] mp 138 °C); ^1H NMR ($CDCl_3$) δ 7.37–7.21 (m, 12 H, ArH), 6.68 (bs, 2 H, ArH), 5.43 [s, 1 H, $(PhS)_2CH$], 2.95 (s, 6 H, $(Me)_2N$).

1-[Bis(phenylthio)methyl]-4-prop-2-ylbenzene (17). 4-Prop-2-ylbenzaldehyde (1.19 g, 8.06 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:250), **17** (2.42 g, 86%): mp 60–64 °C (heptane); ^1H NMR ($CDCl_3$) δ 7.37–7.23 (m, 12 H, ArH), 7.14 (d, 2 H, J = 8.1 Hz, ArH), 5.43 [s, 1 H, $(PhS)_2CH$], 2.88 (heptet, 1 H, J = 6.8 Hz, Me_2CH), 1.23 (d, 6 H, J = 6.9 Hz, Me_2CH). Anal. Calcd for $C_{22}H_{22}S_2$: C, 75.4; H, 6.3. Found: C, 75.4; H, 6.5.

1-[Bis(phenylthio)methyl]-4-chlorobenzene (18). 4-Chlorobenzaldehyde (2.50 g, 17.8 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:200), **18** (4.63 g, 76%): mp 89–90 °C (EtOH/EtOac) (lit.[40] mp 91 °C); ^1H NMR ($CDCl_3$) δ 7.37–7.21 (m, 14 H, ArH), 5.38 [s, 1 H, $(PhS)_2CH$].

1-[Bis(phenylthio)methyl]-3-fluorobenzene (19). 3-Fluorobenzaldehyde (1.00 g, 8.06 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, heptane), **19** (2.04 g, 78%): ^1H NMR ($CDCl_3$) δ 7.38–7.18 (m, 11 H, ArH), 7.12–7.07 (m, 2 H, ArH), 6.96–6.90 (m, 1 H, ArH), 5.38 [s, 1 H, $(PhS)_2CH$]. Anal. Calcd for $C_{19}H_{15}FS_2$: C, 69.9; H, 4.6. Found: C, 70.0; H, 4.7.

1-[Bis(phenylthio)methyl]-4-(trifluoromethyl)benzene (20). 4-(Trifluoromethyl)benzaldehyde (1.00 g, 5.74 mmol) was treated as in the preparation of **10** to give, after chromatography

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(SiO_2, heptane), **20** (1.84 g, 86%): mp 79–81 °C (EtOH); ^1H NMR ($CDCl_3$) δ 7.52 (d, 2 H, J = 8.2 Hz, ArH), 7.44 (d, 2 H, J = 8.4 Hz, ArH), 7.36–7.24 (m, 10 H, ArH), 5.42 [s, 1 H, $(PhS)_2CH$]. Anal. Calcd for $C_{20}H_{15}F_3S_2$: C, 63.8; H, 4.0. Found: C, 63.7; H, 4.1.

1-[Bis(phenylthio)methyl]-3-nitrobenzene (21). 3-Nitrobenzaldehyde (10.0 g, 66.2 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:10) and crystallization (EtOH/EtOAc), **21** (18.9 g, 81%): mp 64–65 °C (EtOH/EtOAc) [lit.[41] mp 65.5 °C (95% EtOH)]; ^1H NMR ($CDCl_3$) δ 8.13 (t, 1 H, J = 2.0 Hz, H-2), 8.08 (ddd, 1 H, J = 8.2, 2.3, 1.1 Hz, H-4), 7.66 (dt, 1 H, J = 7.7, 1.3 Hz, H-6), 7.42 (t, 1 H, J = 7.9 Hz, H-5), 7.36–7.24 (m, 10 H, PhH), 5.48 [s, 1 H, $(PhS)_2CH$].

1-[Bis(phenylthio)methyl]-4-nitrobenzene (22). 4-Nitrobenzaldehyde (2.50 g, 16.6 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 1:40), **22** (4.96 g, 85%): mp 98–99 °C (EtOH) (lit.[42] mp 98–99.5 °C); ^1H NMR ($CDCl_3$) δ 8.10 (d with further coupling, 2 H, J = 8.8 Hz, H-3, H-5), 7.45 (d with further coupling, 2 H, J = 8.5 Hz, H-2, H-6), 7.36–7.26 (m, 10 H, PhH), 5.43 [s, 1 H, $(PhS)_2CH$].

3-[Bis(phenylthio)methyl]pyridine (23). Pyridine-3-carboxaldehyde (0.863 g, 8.06 mmol) was treated as in the preparation of **16** to give, after chromatography (SiO_2, EtOAc/heptane, 1:4), **23** (2.22 g, 89%): mp 45.5–46.5 °C ($EtOH/H_2O$); ^1H NMR ($CDCl_3$) δ 8.47–8.43 (m, 2 H, ArH), 7.70 (d with further coupling, 1 H, J = 8.0 Hz, ArH), 7.37–7.18 (m, 10 H, PhH), 7.20 (ddd, 1 H, J = 8.0, 4.9, 0.5 Hz, ArH), 5.42 [s, 1 H, $(PhS)_2CH$]. Anal. Calcd for $C_{18}H_{15}NS_2$: C, 69.9; H, 4.9. Found: C, 69.9; H, 4.8.

4-[Bis(phenylthio)methyl]pyridine (24). Pyridine-4-carboxaldehyde (2.00 g, 18.7 mmol) was treated as in the preparation of **16** to give, after chromatography (SiO_2, EtOAc/heptane, 1:3), **24** (4.82 g, 84%): mp 55–57 °C (heptane/toluene); ^1H NMR ($CDCl_3$) δ 8.48 (d, 2 H, J = 6.0 Hz, ArH), 7.35–7.21 (m, 12 H, ArH), 5.31 [s, 1 H, $(PhS)_2CH$]. Anal. Calcd for $C_{18}H_{15}NS_2$: C, 69.9; H, 4.9. Found: C, 69.8; H, 5.1.

2-[Bis(phenylthio)methyl]naphthalene (25). 2-Naphthaldehyde (1.26 g, 8.07 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, EtOAc/heptane, 0:1 → 1:50) and crystallization (EtOH/EtOAc), **25** (2.29 g, 79%): mp 108–109.5 °C; ^1H NMR ($CDCl_3$) δ 7.83–7.80 (m, 2 H, ArH) 7.74–7.70 (m, 2 H, ArH), 7.61 (dd, 1 H, J = 8.6, 1.9 Hz, NaphtH), 7.50-7.43 (m, 2 H, ArH), 7.39–7.34 (m, 4 H, PhH), 7.26–7.20 (m, 6 H, PhH), 5.59 [s, 1 H, $(PhS)_2CH$]. Anal. Calcd for $C_{23}H_{18}S_2$: C, 77.0; H, 5.1. Found: C, 77.4; H, 5.3.

2-[Bis(phenylthio)methyl]-5-methylfuran (26). 5-Methyl-2-furaldehyde (0.887 g, 8.06 mmol) was treated as in the preparation of **10** to give, after chromatography (SiO_2, CH_2Cl_2/heptane, 1:10), **26** (1.77 g, 70%): ^1H NMR ($CDCl_3$) δ 7.41–7.25 (m, 10 H, PhH), 6.05 (d with further coupling, 1 H, J = 3.2 Hz, ArH), 5.84–5.82 (m, 1 H, ArH), 5.43 [s, 1 H, $(PhS)_2CH$], 2.29 (d, 3 H, J = 1.0 Hz, Me). Anal. Calcd for $C_{18}H_{16}OS_2$: C, 69.2; H, 5.2. Found: C, 69.4; H, 5.2.

2-[Bis(phenylthio)methyl]-1-methylpyrrole (27). 1-Methylpyrrole-2-carboxaldehyde (0.880 g, 8.06 mmol) was treated as in the preparation of **16** to give, after chromatography (SiO_2, EtOAc/heptane, 1:100), **27** (1.18 g, 47%): ^1H NMR ($CDCl_3$) δ 7.35–7.23 (m, 10 H, PhH), 6.60 (ddd, 1 H, J = 2.7, 1.9, 0.3 Hz, ArH), 6.04 (ddd, 1 H, J = 3.7, 1.9, 0.6 Hz, ArH), 5.88 (ddd, 1 H, J = 3.7, 2.7, 0.4 Hz, ArH), 5.66 [s, 1 H, $(PhS)_2CH$], 3.68 (s, 3 H, MeN). Anal. Calcd for $C_{18}H_{17}NS_2$: C, 64.6; H, 4.3. Found: C, 64.4; H, 4.3.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-3-[(3,4,5-trimethoxyphenyl)bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)benzoyl]tetrahydrofuran (28r). To a stirred solution of **10** (0.676 g, 1.70 mmol) in dry tetrahydrofuran (10 mL) at −78 °C and under a nitrogen atmosphere was added a solution of BuLi (1.70 mmol, 1.48 M) in hexane (1.15 mL). After 20 min, **2r** (0.500 g, 1.54 mmol) in tetrahydrofuran (5 mL) was added dropwise. After 5 min, the cooling bath was removed. When the reaction mixture had reached room temperature, saturated aqueous sodium hydrogen carbonate (15 mL) and diethyl ether (30 mL) were added. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, EtOAc/heptane, 1:4) to give **28r** (0.675 g, 60%): mp 60.5–64 °C (2-propanol); $[\alpha]^{25}_D$ +96.9° (*c* 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.47 (d, 2 H, J = 7.4 Hz, ArH), 7.37–7.10 (m, 15 H, ArH), 6.80 (s, 2 H, H-2″ and H-6″), 6.73 (d, 1 H, J = 8.4 Hz, H-5′), 6.01 (q, 2 H, J = 1.3 Hz, OCH_2O), 5.61 (d, 1 H, J = 0.5 Hz, H-2), 4.75, 4.48 (AB q, 1 H each, J = 12.2 Hz, $PhCH_2$), 4.38 (dd, 1 H, J = 6.4, 1.1 Hz, H-3), 4.31 (q with further coupling, 1 H, J = 8.1 Hz, H-4), 4.04 (t, 1 H, J = 8.4 Hz, H-5), 3.74 (t, 1 H, J = 8.9 Hz, H-5), 3.74 (s, 3 H, MeO), 3.53 (s, 6 H, MeO). Anal. Calcd for $C_{41}H_{38}O_8S_2$: C, 68.1; H, 5.3. Found: C, 68.3; H, 5.3.

(−)-(2*R*,3*R*,4*S*)-2-(Benzyloxy)-3-[(3,4,5-trimethoxyphenyl)bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)benzoyl]tetrahydrofuran (28s). Compound **2s** was treated essentially as in the preparation of **28r** to give **28s**: $[\alpha]^{25}_D$ −90.7° (*c* 0.75, $CHCl_3$). **28r** and **28s** had identical ^1H NMR spectra.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-3-[[3-methoxy-4,5-(methylenedioxy)phenyl]bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)benzoyl]tetrahydrofuran (29). Compound **2r** (3.82 g, 11.8 mmol) was treated with the benzyllithium from **11** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, EtOAc/heptane 1:5), **29** (5.60 g, 67%): $[\alpha]^{25}_D$ +55.2° (*c* 0.6, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 7.51 (d, 2 H, J = 7.0 Hz, ArH), 7.39–7.07 (m, 16 H, ArH), 6.76 (d, 1 H, J = 8.6 Hz, H-5′), 6.63 (d, 1 H, J = 1.8 Hz, ArH), 6.02, 5.91 (s, 2 H each, OCH_2O), 5.47 (s, 1 H, H-2), 4.72, 4.50 (AB q, 1 H each, J = 12.1 Hz, $PhCH_2$), 4.43–4.36 (q with further coupling, 1 H, J = 6.0 Hz, H-4), 4.26 (dd, 1 H, J = 6.4, 1.0 Hz, H-3), 4.09 (t, 1 H, J = 8.5 Hz, H-5), 3.74 (dd, 1 H, J = 9.6, 8.4 Hz, H-5), 3.50 (s, 3 H, MeO). Anal. Calcd for $C_{40}H_{34}O_8S_2$: C, 68.0; H, 4.8. Found: C, 68.0; H, 4.9.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-3-[(3,4-dimethoxyphenyl)bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)benzoyl]tetrahydrofuran (30). Compound **2r** (0.500 g, 1.54 mmol) was treated with the benzyllithium from **12** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, EtOAc/heptane, 1:4 → 1:3), **30** (0.793 g, 74%): mp 65–69 °C (heptane/toluene); $[\alpha]^{25}_D$ +62.2° (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.49 (d, 2 H, J = 7.0 Hz, ArH), 7.35–7.01 (m, 17 H, ArH), 6.75 (d, 1 H, J = 8.5 Hz, H-5′), 6.54 (d, 1 H, J = 8.8 Hz, H-5″), 6.02 (q, 2 H, J = 1.0 Hz, OCH_2O), 5.50 (s, 1 H, H-2), 4.72, 4.46 (AB q, 1 H each, J = 12.1 Hz, $PhCH_2$), 4.40 (q with further coupling, 1 H, J = 7.1 Hz, H-4), 4.31 (dd, 1 H, J = 6.4, 1.1 Hz, H-3), 4.09 (dd, 1 H, J = 8.7, 8.1 Hz, H-5), 3.80 (s, 3 H, MeO), 3.74 (dd, 1 H, J = 9.6, 8.4 Hz, H-5), 3.53 (s, 3 H, MeO). Anal. Calcd for $C_{40}H_{36}O_7S_2$: C, 69.2; H, 5.2. Found: C, 69.3; H, 5.2.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-4-[3,4-(methylenedioxy)benzoyl]-3-[[3,4-(methylenedioxy)phenyl]bis(phenylthio)methyl]tetrahydrofuran (31). Compound **2r** (3.43 g, 10.5 mmol) was treated with the benzyllithium from **14** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, EtOAc/heptane, 1:7), **31** (5.74 g, 80%): mp 65–68 °C (2-propanol); $[\alpha]^{25}_D$ +44.7° (*c* 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.56 (d, 2 H, J = 7.1 Hz, ArH), 7.37–7.06 (m, 17 H, ArH), 6.77 (d, 1 H, J = 8.7 Hz, H-5′), 6.47 (d, 1 H, J = 8.2 Hz, H-5″), 6.03 (q, 2 H, J = 1.1 Hz, OCH_2O), 5.90 (s, 2 H, OCH_2O), 5.38 (d, 1 H, J = 1.0 Hz, H-2), 4.69, 4.43 (AB q, 1 H each, J = 12.0 Hz, $PhCH_2$), 4.43 (q with further coupling, 1 H, J = 7.8 Hz, H-4), 4.22 (dd, 1 H, J = 6.4, 1.1 Hz, H-3), 4.10 (t, 1 H, J = 8.4 Hz, H-5), 3.74 (dd, 1 H, J = 9.8, 8.3 Hz, H-5). Anal. Calcd for $C_{39}H_{32}O_7S_2$: C, 69.2; H, 4.8. Found: C, 69.1; H, 4.8.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-3-[(4-chlorophenyl)bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)benzoyl]tetrahydrofuran (32). Compound **2r** (0.500 g, 1.54 mmol) was treated with the benzyllithium from **18** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, EtOAc/heptane, 1:8), **32** (0.412 g, 40%): mp 60–63 °C (2-propanol); $[\alpha]^{25}_D$ +40.2° (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.53 (d, 4 H, J = 8.9 Hz, ArH), 7.38–7.01 (m, 17 H, ArH), 6.77 (d, 1 H, J = 8.6 Hz, H-5′), 6.04 (q, 2 H, J = 1.3 Hz, OCH_2O), 5.35 (s, 1 H, H-2), 4.68, 4.42 (AB q, 1 H each, J = 12.1 Hz, $PhCH_2$), 4.44 (bq, 1 H, H-4), 4.27 (dd, 1 H, J = 6.4, 1.3 Hz, H-3), 4.13 (t, 1 H, J = 8.5 Hz, H-5), 3.75 (dd, 1 H, J = 9.8, 8.4 Hz, H-5). Anal. Calcd for $C_{38}H_{31}ClO_5S_2$: C, 68.4; H, 4.7. Found: C, 68.5; H, 4.8.

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(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-3-[bis(phenylthio)-4-pyridylmethyl]-4-[3,4-(methylenedioxy)benzoyl]tetrahydrofuran (33). Compound **2r** (0.500 g, 1.54 mmol) was treated with the benzyllithium from **24** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, EtOAc/heptane, 1:5 → 1:2), **33** (0.303 g, 31%) and **2r** (0.136 g, 27%). Compound **33**: $[\alpha]^{25}_D$ +42.8° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.28 (dd, 2 H, *J* = 4.9, 1.6 Hz, ArH), 7.52–7.09 (m, 19 H, ArH), 6.80 (dd, 1 H, *J* = 8.2, 0.4 Hz, H-5′), 6.05 (q, 2 H, *J* = 1.3 Hz, OCH_2O), 5.30 (d, 1 H, *J* = 0.7 Hz, H-2), 4.70, 4.43 (AB q, 1 H each, *J* = 12.1 Hz, $PhCH_2$), 4.56 (q with further coupling, 1 H, *J* = 6.3 Hz, H-4), 4.32 (dd, 1 H, *J* = 6.3, 1.4 Hz, H-3), 4.22 (t, 1 H, *J* = 8.7 Hz, H-5), 3.80 (dd, 1 H, *J* = 9.8, 8.4 Hz, H-5). Anal. Cacld for $C_{37}H_{31}NO_5S_2$: C, 70.1; H, 4.9. Found: C, 70.2; H, 5.2.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-4-[3,4-(methylenedioxy)-benzoyl]-3-[2-naphthylbis(phenylthio)methyl]tetrahydrofuran (34r). Compound **2r** was treated essentially as in the preparation of **34s** to give **34r**: $[\alpha]^{25}_D$ +21.2° (*c* 1.0, $CHCl_3$). Compounds **34r** and **34s** had identical ^1H NMR spectra.

(−)-(2*R*,3*R*,4*S*)-2-(Benzyloxy)-4-[3,4-(methylenedioxy)-benzoyl]-3-[2-naphthylbis(phenylthio)methyl]tetrahydrofuran (34s). Compound **2s** (0.600 g, 1.85 mmol) was treated with the benzyllithium from **25** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, CH_2Cl_2/heptane, 2:1), **34s** (0.773 g, 61%): $[\alpha]^{25}_D$ −22.0° (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.98–7.91 (m, 2 H, ArH), 7.75–7.61 (m, 2 H, ArH), 7.58–6.92 (m, 20 H, ArH), 6.70 (d, 1 H, *J* = 8.4 Hz, H-5′), 6.00 (q, 2 H, *J* = 1.5 Hz, OCH_2O), 5.49 (s, 1 H, H-2), 4.70, 4.44 (d, 1 H, *J* = 12.1 Hz, $PhCH_2$), 4.49 (q with further coupling, 1 H, H-4), 4.41 (dd, 1 H, *J* = 6.0, 0.9 Hz, H-3), 4.12 (t, 1 H, *J* = 8.4 Hz, H-5), 3.78 (dd, 1 H, *J* = 9.6, 8.4 Hz, H-5). Anal. Calcd for $C_{42}H_{34}O_5S_2$: C, 73.9; H, 5.0. Found: C, 73.9; H, 5.4.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-3-[[4-(benzyloxy)-3-methoxyphenyl]bis(phenylthio)methyl]-4-[3-[[dimethyl(2,3-dimethyl-2-butyl)silyl]oxy]benzoyl]tetrahydrofuran (35). Compound **3** (0.700 g, 1.60 mmol) was treated with the benzyllithium from **13** via the procedure for the preparation of **28r** to give, after chromatography (CH_2Cl_2/heptane, 2:3 → 2:1), **35** (0.975 g, 69%): $[\alpha]^{25}_D$ +36.1° (*c* 0.9, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 7.45–6.97 (m, 26 H, ArH), 6.58 (d, 1 H, *J* = 8.6 Hz, H-5″), 5.47 (s, 1 H, H-2), 5.06 (s, 2 H, $PhCH_2OAr$), 4.70, 4.44 (AB q, 1 H each, *J* = 12.2 Hz, $PhCH_2OCH$), 4.49 (q with further coupling, 1 H, H-4), 4.32 (dd, 1 H, *J* = 6.1, 1.0 Hz, H-3), 4.11 (t, 1 H, *J* = 8.7 Hz, H-5), 3.74 (t, 1 H, *J* = 9.0 Hz, H-5), 3.53 (s, 3 H, MeO), 1.73 (heptet, 1 H, *J* = 6.9 Hz, Me_2CH), 0.96 (s, 6 H, Me_2CSi), 0.95 (d, 6 H, *J* = 6.5 Hz, Me_2CH), 0.24 (s, 3 H, MeSi), 0.23 (s, 3 H, MeSi). Anal. Calcd for $C_{53}H_{58}O_5S_2Si$: C, 72.1; H, 6.6. Found: C, 72.4; H, 6.7.

(+)-(2*S*,3*S*,4*R*)-2-(Benzyloxy)-4-(4-fluorobenzoyl)-3-[(3-iodo-5-methoxy-4-propoxyphenyl)bis(phenylthio)methyl]-tetrahydrofuran (36). Compound **4** (1.80 g, 6.04 mmol) was treated with the benzyllithium from **15** via the procedure for the preparation of **28r** to give, after chromatography (CH_2Cl_2/heptane, 1:1 → 2:1), **36** (1.11 g, 22%): $[\alpha]^{25}_D$ +32.6° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.69–6.91 (m, 11 H, ArH), 5.48 (s, 1 H, H-2), 4.73, 4.48 (AB q, 1 H each, *J* = 11.8 Hz, $PhCH_2$) 4.48 (m, 1 H, H-4), 4.32 (dd, 1 H, *J* = 6.5, 1.2 Hz, H-3), 4.14 (t, 1 H, *J* = 8.4 Hz, H-5), 3.78 (1 H, H-5), 3.76 (t, 2 H, *J* = 6.8 Hz, CH_2CH_2O), 3.43 (s, 3 H, MeO), 1.77 (sextet, 2 H, *J* = 7.0 Hz, $MeCH_2$), 1.03 (t, 3 H, *J* = 7.4 Hz, $MeCH_2$). Anal. Calcd for $C_{41}H_{38}FIO_5S_2$: C, 60.0; H, 4.7. Found: C, 60.2; H, 4.8.

(−)-(2*R*,3*R*,4*S*)-2-(Benzyloxy)-3-[[4-(dimethylamino)-phenyl]bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)-benzoyl]tetrahydrofuran (37). Compound **2s** (0.600 g, 1.85 mmol) was treated with the benzyllithium from **16** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, EtOAc/heptane, 1:8), **37** (0.414 g, 33%) and **2s** (0.287 g, 48%). Compound **37**: $[\alpha]^{25}_D$ −40.6° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.60–7.48 (m, 4 H, ArH), 7.38–7.04 (m, 15 H, ArH), 6.75 (d, 1 H, *J* = 8.6 Hz, H-5′), 6.44 (d, 2 H, *J* = 9.1 Hz, H-3′ and H-5″), 6.02 (s, 2 H, OCH_2O), 5.46 (s, 1 H, H-2), 4.69, 4.45 (AB q, 1 H each, *J* = 12.2 Hz, $PhCH_2O$), 4.37 (q with further coupling, 1 H, *J* = 6.1 Hz, H-4), 4.20 (dd, 1 H, *J* = 6.3, 1.2 Hz, H-3), 4.05 (t, 1 H, *J* = 8.4 Hz, H-5), 3.71 (dd, 1 H, *J* = 9.8, 8.3 Hz, H-5), 2.90 (s, 6 H, Me_2N). Anal. Calcd for $C_{40}H_{37}NO_5S_2$: C, 71.1; H, 5.5. Found: C, 71.0; H, 5.4.

(−)-(2*R*,3*R*,4*S*)-2-(Benzyloxy)-3-[[4-(trifluoromethyl)-phenyl]bis(phenylthio)methyl]-4-[3,4-(methylenedioxy)-benzoyl]tetrahydrofuran (38). Compound **2s** (0.600 g, 1.85 mmol) was treated with the benzyllithium from **20** via the procedure for the preparation of **28r** to give, after chromatography (SiO_2, CH_2Cl_2/heptane, 1:1 → EtOAc/heptane, 1:5), **38** (0.418 g, 32%) and **2s** (0.322 g, 54%). Compound **38**: $[\alpha]^{25}_D$ −35.3° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.68 (d, 2 H, *J* = 8.2 Hz, ArH), 7.53 (d, 2 H, *J* = 7.6 Hz, ArH), 7.43–7.03 (m, 17 H, ArH), 6.77 (dd, 1 H, *J* = 7.6, 1.0 Hz, H-5′), 6.04 (q, 2 H, *J* = 1.5 Hz, OCH_2O), 5.31 (s, 1 H, H-2), 4.68, 4.41 (AB q, 1 H each, *J* = 12.1 Hz, $PhCH_2O$), 4.50 (q with further coupling, 1 H, *J* = 6.5 Hz, H-4), 4.33 (dd, 1 H, *J* = 6.4, 1.6 Hz, H-3), 4.16 (t, 1 H, *J* = 8.6 Hz, H-5), 3.78 (dd, 1 H, *J* = 9.8, 8.2 Hz, H-5). Anal. Calcd for $C_{39}H_{31}F_3O_5S_2$: C, 66.8; H, 4.5. Found: C, 66.9; H, 4.4.

(−)-(2*R*,3*R*)-2-(Benzyloxy)-3-[3,4-(methylenedioxy)-benzyl]-4-[[(*tert*-butyldimethylsilyl)oxy]methylene]tetrahydrofuran (39). [3,4-(Methylenedioxy)benzyl]lithium was prepared by adding a solution of methyl 3,4-(methylenedioxy)-benzyl ether (1.63 g, 9.80 mmol) in tetrahydrofuran (33 mL) to finely divided lithium (0.272 g, 39.2 mmol) under argon. When the reaction had started, the mixture was cooled to −30 to −20 °C. When the reaction was completed, the resulting organolithium solution was filtered and transferred to an ice-cooled reaction flask containing CuCN (0.878 g, 9.80 mmol). After 10 min, the mixture was cooled to −78 °C. *tert*-Butyldimethylsilyl chloride (2.96 g, 19.6 mmol) in tetrahydrofuran (5 mL) was added followed by dropwise addition of **1r** (1.00 g, 4.90 mmol) in tetrahydrofuran (15 mL). After 5 min, the cooling bath was removed. When the reaction mixture had reached room temperature, aqueous ammonium sulfate (10%, 12 mL) and diethyl ether (25 mL) were added. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, EtOAc/heptane, 0:1 → 1:20) to give **39** (1.02 g, 46%): $[\alpha]^{25}_D$ −69.1° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 5 H, PhH), 6.71 (d, 1 H, *J* = 7.8 Hz, H-5″), 6.64 (d, 1 H, *J* = 1.6 Hz, H-2″), 6.58 (dd, 1 H, *J* = 8.0, 1.7 Hz, H-6″), 5.92 (q, 2 H, *J* = 1.4 Hz, OCH_2O), 5.84 (dt, 1 H, *J* = 2.5, 1.2 Hz, SiOCH), 4.98 (s, 1 H, H-2), 4.70, 4.46 (AB q, 1 H each, *J* = 12.0 Hz, $PhCH_2$), 4.57 (q, 2 H, *J* = 1.2 Hz, H-5), 2.85 (t with further coupling, 1 H, *J* = 8.1 Hz, H-3), 2.72 (dd, 1 H, *J* = 13.5, 7.7 Hz, $ArCH_2$), 2.45 (dd, 1 H, *J* = 13.5, 8.3 Hz, $ArCH_2$), 0.88 (s, 9 H, MeC), 0.05 (s, 6 H, MeSi). Anal. Calcd for $C_{26}H_{34}O_5Si$: C, 68.7; H, 7.5. Found: C, 68.6; H, 7.5.

(−)-(2*S*,3*R*,4*R*/4*S*)-2-(Benzyloxy)-3-[3,4-(methylenedioxy)benzyl]-4-formyltetrahydrofuran (40). A solution of tetramethylammonium fluoride trihydrate (83 mg, 0.26 mmol) in tetrahydrofuran/acetic acid (1.64 mL, 19:1) was added to **39** (0.100 g, 0.220 mmol). The solution was stirred for 2.5 h, and the solvent was removed at reduced pressure. The residue was diluted with diethyl ether (15 mL) and washed with water (2 × 5 mL). Drying (Na_2SO_4), concentration, and chromatography (SiO_2, EtOAc/heptane, 1:5) gave **40** (58 mg, 78%, epimeric ratio 15:1): $[\alpha]^{25}_D$ −64.2° (*c* 0.2, $CHCl_3$). Major epimer: ^1H NMR ($CDCl_3$) δ 9.56 (d, 1 H, *J* = 1.8 Hz, CHO), 7.34–7.21 (m, 5 H, Ph), 6.74 (d, 1 H, *J* = 7.8 Hz, H-5″), 6.67 (d, 1 H, *J* = 1.6 Hz, H-2″), 6.62 (dd, 1 H, *J* = 7.8, 1.7 Hz, H-6″), 5.95 (s, 2 H, OCH_2O), 4.96 (d, 1 H, *J* = 0.7 Hz, H-2), 4.66, 4.38 (AB q, 1 H each, *J* = 11.8 Hz, $PhCH_2$), 4.31 (dd, 1 H, *J* = 9.1, 5.1 Hz, H-5), 4.16 (dd, 1 H, *J* = 9.0, 8.1 Hz, H-5), 2.85 (dt, 1 H, *J* = 7.9, 2.4 Hz, H-3), 2.77 (dd, 1 H, *J* = 13.5, 7.8 Hz, $ArCH_2$), 2.68 (dddd, 1 H, *J* = 7.9, 5.0, 2.7, 1.8 Hz, H-4), 2.54 (dd, 1 H, *J* = 13.3, 8.2 Hz, $ArCH_2$). Minor epimer: ^1H NMR ($CDCl_3$) δ 9.77 (d, 1 H, *J* = 2.2 Hz, CHO). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.6; H, 5.9. Found: C, 70.6; H, 6.0.

(−)-(2*S*,3*R*,4*R*)-2-(Benzyloxy)-4-[3,4-(methylenedioxy)-benzoyl]-3-[3,4-(methylenedioxy)benzyl]tetrahydrofuran (41). (a) To a solution of **31** (1.00 g, 1.48 mmol) in ethanol/ethyl acetate (30 mL, 2:1) was added Raney nickel in portions (the reaction was monitored by TLC: SiO_2, EtOAc/heptane, 1:5). When the starting material had been consumed the solution was separated from the Raney nickel and filtered (Celite), and the residue was washed with ethyl acetate (30 mL). Concentration and chromatography (SiO_2, EtOAc/heptane, 1:10 → 5:1) gave **41** (0.336 g, 49%): $[\alpha]^{25}_D$ −86.5° (*c* 6.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35–7.17 (m, 7 H, ArH), 6.76 (dd, 1 H, *J* = 8.2, 0.4 Hz, ArH),

6.65 (dd, 1 H, J = 7.4, 0.5 Hz, H-6″), 6.61 (d, 1 H, J = 1.4 Hz, H-3″), 6.58 (dd, 1 H, J = 7.9, 1.8 Hz, H-7″), 6.02 (s, 2 H, OCH_2O), 5.90 (s, 2 H, OCH_2O), 4.95 (d, 1 H, J = 2.0 Hz, H-2), 4.72, 4.41 (AB q, 1 H each, J = 12.2 Hz, $PhCH_2$), 4.26 (t, 1 H, J = 8.2 Hz, H-5), 4.22 (t, 1 H, J = 7.9 Hz, H-5), 3.61 (dt, 1 H, J = 7.9, 5.5 Hz, H-4), 3.07 (q with further coupling, 1 H, J = 7.3 Hz, H-3), 2.80 (dd, 1 H, J = 13.8, 7.8 Hz, $ArCH_2$), 2.62 (dd, 1 H, J = 13.8, 8.7 Hz, $ArCH_2$). Anal. Calcd for $C_{27}H_{24}O_7$: C, 70.4; H, 5.2. Found: C, 70.4; H, 5.4.

(b) [3,4-(Methylenedioxy)benzyl]lithium was prepared by addition of methyl 3,4-(methylenedioxy)benzyl ether (0.383 g, 2.30 mmol) in tetrahydrofuran (7.8 mL) to finely divided lithium (64 mg, 9.23 mmol) under argon. When the reaction had started, the mixture was cooled to −30 to −20 °C. When the reaction was completed, the resulting organolithium solution was filtered and transferred to an ice-cooled reaction flask containing CuCN (0.207 g, 2.30 mmol). After 10 min the mixture was cooled to −78 °C. Compound **2r** (0.360 g, 1.15 mmol) in tetrahydrofuran (3.5 mL) was added. After 5 min the cooling bath was removed. When the reaction mixture had reached room temperature it was extracted and dried as in the preparation of **39**. Removal of solvents gave a residue which was chromatographed (SiO_2, EtOAc/heptane, 1:7 → 1:5) to give **41** (89 mg, 17%).

2,3-*trans*-Isopropylcubebin (42) and 2,3-*cis*-Isopropylcubebin (44). See preparation of **46** (b).

(−)-(2*S*,3*R*,4*R*)-2-(Benzyloxy)-4-[3,4-(methylenedioxy)benzoyl]-3-(2-naphthylmethyl)tetrahydrofuran (43). Compound **34r** (0.700 g, 1.03 mmol) was treated essentially as in the preparation of **41**, but with dimethoxyethane as solvent, to give, after chromatography (SiO_2, EtOAc/heptane, 4:1), **43** (0.324 g, 68%): $[\alpha]^{25}_D$ −59.6° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.79–7.10 (m, 14 H, ArH), 6.56 (d, 1 H, J = 8.0 Hz, H-3′), 5.96 (q, 1 H, J = 1.4 Hz, OCH_2O), 5.03 (d, 1 H, J = 2.0 Hz, H-2), 4.70, 4.40 (AB q, 1 H each, J = 12.2 Hz, $PhCH_2$), 4.26 (d, 2 H, J = 8.0 Hz, H-5), 3.68 (dt, 1 H, J = 8.0, 5.7 Hz, H-4), 3.25 (ddt, 1 H, J = 8.0, 5.7, 1.9 Hz, H-3), 3.05 (dd, 1 H, J = 13.6, 7.9 Hz, $ArCH_2$), 2.88 (dd, J = 13.9, 8.3 Hz, $ArCH_2$).

(−)-(3*R*,4*R*)-3-(3,4,5-Trimethoxybenzyl)-4-[3,4-(methylenedioxy)benzyl]tetrahydrofuran [(−)-Burseran, 45r]. Compound **28r** was treated essentially as in the preparation of **45s** to give **45r**: $[\alpha]^{25}_D$ −45.1° (*c* 1.1, $CHCl_3$) [lit.[20b] $[\alpha]^{25}_D$ −34.8° (*c* 0.926, $CHCl_3$)]; IR (CCl_4) 1250, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (dd, 1 H, J = 7.5, 0.8 Hz, ArH), 6.56 (s, 1 H, ArH) 6.54 (dd, 1 H, J = 8.4, 1.7 Hz, ArH), 6.28 (s, 2 H, H-2″, H-6″), 5.93 (q, 2 H, J = 1.5 Hz, OCH_2O), 3.96–3.89 (m, 2 H, H-2, H-5), 3.83 (s, 6 H, MeO), 3.82 (s, 3 H, MeO), 3.56–3.49 (m, 2 H, H-2 and H-5), 2.59–2.51 (m, 4 H, $ArCH_2$), 2.20–2.16 (m, 2 H, H-3, H-4); ^{13}C NMR signals are in agreement with reported data (inter alia) δ 73.27 (C-2 and C-5), 39.92, 39.18 (2 $ArCH_2$) (lit.[20b] δ 73.2, 39.9, 39.2).

(+)-(3*S*,4*S*)-3-(3,4,5-Trimethoxybenzyl)-4-[3,4-(methylenedioxy)benzyl]tetrahydrofuran [(+)-Burseran, 45s]. To an ice-cooled solution of **28s** (0.800 g, 1.11 mmol) in 1,2-dimethoxyethane (35 mL) was added Raney nickel in portions (the reaction was monitored by TLC: SiO_2, EtOAc/heptane, 2:3). When the starting material had been consumed the solution was separated from the Raney nickel and filtered (Celite), and the residue was washed with 1,2-dimethoxyethane (40 mL), ethanol (40 mL), and toluene (40 mL). Concentration of the solution gave an oil (0.512 g). A portion (0.422 g) was dissolved in acetic acid/water (17 mL, 9:1), and palladium-on-carbon (0.422 g, 10%) was added. Hydrogenation (1 atm, 6.5 h), coconcentration with toluene (2 × 10 mL), and chromatography (SiO_2, EtOAc/heptane, 1:4) gave **45s** (0.184 g, 52%): $[\alpha]^{25}_D$ +44.1° (*c* 1.1, $CHCl_3$) [lit.[20b] $[\alpha]^{25}_D$ +37.5° (*c* 0.982, $CHCl_3$)]. **45r** and **45s** had identical ^1H NMR spectra.

(−)-(3*R*,4*R*)-3,4-Bis[3,4-(methylenedioxy)benzyl]tetrahydrofuran [(−)-Dehydroxycubebin, 46]. (a) To an ice-cooled solution of **31** (0.603 g, 0.89 mmol) in 1,2-dimethoxyethane (28 mL) was added Raney nickel in portions (the reaction was monitored by TLC: SiO_2, EtOAc/heptane, 2:3). When the starting material had been consumed the solution was separated from the Raney nickel and filtered (Celite), and the filtrum was washed with 1,2-dimethoxyethane (32 mL), EtOH (32 mL), and toluene (32 mL). Concentration of the solution gave an oil that was dissolved in acetic acid/1,2-dimethoxyethane/water (16.5 mL, 5:4:1), and palladium-on-carbon (0.420 g, 10%) was added. Hydrogenation (1 atm, 24 h), coconcentration with toluene (2 × 10 mL), and chromatography (SiO_2, EtOAc/heptane, 1:10) gave **46** (0.132 g, 43%): $[\alpha]^{25}_D$ −54.9° (*c* 7.9, $CHCl_3$) [lit.[43] $[\alpha]_D$ −45°, lit.[44] $[\alpha]_D$ −37° (*c* 1.0, $CHCl_3$)]; IR (CCl_4) 1254, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (dd, 2 H, J = 7.6, 0.6 Hz, ArH), 6.55 (s, 2 H, ArH), 6.54 (dd, 2 H, J = 8.6, 1.7 Hz, ArH), 5.93 (q, 4 H, OCH_2O), 3.90 (dd, 2 H, J = 8.7, 6.8 Hz, H-2, H-5), 3.50 (dd, 2 H, J = 8.7, 6.1 Hz, H-2, H-5), 2.58 (dd, 2 H, J = 13.7, 6.7 Hz, $ArCH_2$), 2.49 (dd, 2 H, J = 13.7, 7.9 Hz, $ArCH_2$), 2.14 (heptet, 2 H, H-3, H-4); ^{13}C NMR signals are in agreement with reported data (inter alia) δ 73.29 (C-2, C-5), 39.21 (2 $ArCH_2$) (lit.[44] δ 73.16, 39.17).

(b) **41** (56 mg, 0.12 mmol) in 2-propanol/ethyl acetate (2:1, 3 mL) was hydrogenated over palladium-on-carbon (50 mg, 10%). After 1.5 h the catalyst was filtered off, and the solvent was removed. The residue was chromatographed (SiO_2, EtOAc/heptane, 1:30 → 1:10) to give **46** (14 mg, 34%), 2,3-*cis*-isopropylcubebin (**44**, 10.9 mg, 22%), and 2,3-*trans*-isopropylcubebin (**42**, 7.5 mg, 15%). **42**: ^1H NMR δ 6.71–6.48 (m, 6 H, ArH), 5.92 (s, 4 H, OCH_2O), 4.90 (d, 1 H, J = 1.8 Hz, H-2), 3.93 (dd, 1 H, J = 8.6, 7.0 Hz, H-5), 3.78 (heptet, 1 H, J = 6.2 Hz, Me_2CH), 3.64 (t, 1 H, J = 8.1 Hz, H-5), 2.64 (dd, 1 H, J = 14.0, 7.6 Hz, $ArCH_2$), 2.58–2.54 (m, 2 H, $ArCH_2$), 2.42 (dd, 1 H, J = 14.4, 7.4 Hz, $ArCH_2$), 2.11–2.07 (m, 2 H, H-3, H-4), 1.18 (d, 3 H, J = 6.3 Hz, *Me*CH), 1.02 (d, 3 H, J = 6.1 Hz, *Me*CH). **44**: ^1H NMR δ 6.74–6.58 (m, 6 H, ArH), 5.924, 5.918 (s, 2 H each, OCH_2O), 4.88 (d, 1 H, J = 4.5 Hz, H-2), 3.98 (t, 1 H, J = 8.2 Hz, H-5), 3.77 (heptet, 1 H, J = 6.2 Hz, Me_2CH), 3.54 (dd, 1 H, J = 8.5, 6.6 Hz, H-5), 2.75–2.67, 2.55–2.31, 2.03–1.92 (m, 2 H, 3 H, 1 H, $ArCH_2$, H-3, H-4), 1.17 (d, 3 H, J = 6.2 Hz, *Me*CH), 1.07 (d, 3 H, J = 6.1 Hz, *Me*CH).

(c) **48** (6 mg) and palladium-on-carbon (25 mg, 10%) were stirred in acetic acid (1 mL) under hydrogen for 2 h. TLC and ^1H NMR on the crude reaction mixture showed the formation of **46**.

(−)-(2*R*/2*S*,3*R*,4*R*)-3-[3-Methoxy-4,5-(methylenedioxy)benzyl]-4-[3,4-(methylenedioxy)benzyl]tetrahydrofuran-2-ol [(−)-Trichostin, 47]. Compound **29** (591 mg, 0.84 mmol) was treated with Raney nickel as in the preparation of **45**. The desulfurized product was dissolved in tetrahydrofuran (15 mL). Hydrogenation (1 atm, 3 h) over palladium-on-carbon (0.615 g, 10%) and chromatography (SiO_2, EtOAc/heptane, 1:2) gave **47** (0.116 g, 36%, 2,3-trans/2,3-cis ≈ 3:2): $[\alpha]^{25}_D$ −52.1° (*c* 1.1, MeOH) [lit.[30b] $[\alpha]^{20}_D$ −62.25° (*c* 0.8, MeOH)]; MS *m/e* (rel int) 386 (M^+, 4), 368 ($M^+ - H_2O$, 2), 165 (30), 135 (45); ^1H NMR (CD_3COCD_3/D_2O) δ 6.76–6.56 (m, 3 H, ArH), 6.52, 6.45, 6.39, 6.33 (d, 2 H, J = 1.5 Hz, ArH), 5.93–5.90 (m, 4 H, OCH_2O), 5.17, 5.13 (d, 1 H, J = 4.6, 2.1 Hz, H-2), 3.97, 3.87, 3.68, 3.49 (t, 2 H, J = 9.3, 8.7, 8.1, 7.1 Hz, H-5), 3.84, 3.83 (s, 3 H, MeO), 2.80–1.90 (m, 6 H, H-3, H-4, $ArCH_2$).

(−)-(2*R*/2*S*,3*R*,4*R*)-3,4-Bis[3,4-(methylenedioxy)benzyl]tetrahydrofuran-2-ol [(−)-Cubebin, 48]. To an ice-cooled solution of **31** (2.60 g, 3.84 mmol) in 1,2-dimethoxyethane (104 mL) Raney nickel was added in portions (the reaction was monitored by TLC: SiO_2, EtOAc/heptane, 2:3). When the starting material was consumed, the solution was separated from the Raney nickel and filtered (Celite), and the filtrum was washed with 1,2-dimethoxyethane/water (50 mL, 10:1) and toluene (30 mL). Concentration of the solution gave an oil that was dissolved in 1,2-dimethoxyethane/water/ethyldiisopropylamine (91 mL, 85:15:0.05), and palladium-on-carbon (2.60 g, 10%) was added. Hydrogenation (4 atm, 20 h), coconcentration with toluene (2 × 10 mL), chromatography (SiO_2, EtOAc/heptane 1:3 → 1:2), and crystallization (MeOH) gave **48** (0.487 g, 36%): mp 125–128 °C [lit.[31] mp 132 °C (MeOH)]; $[\alpha]^{25}_D$ −69.2° (*c* 0.5, CD_3OD) [lit.[45] $[\alpha]$ −68.0° (*c* 1.11, MeOH); ^1H NMR signals are in agreement with reported data (inter alia) δ 5.13, 5.11 (d, 1 H, J = 4.6, 2.4 Hz, H-2) [lit.[45] δ 5.12, 5.10 (J = 5.4, 2.5 Hz)].

(−)-(3*R*,4*R*)-3-[3-Methoxy-4,5-(methylenedioxy)benzyl]-4-[3,4-(methylenedioxy)benzyl]butyrolactone [(−)-5″-Methoxyhinokinin, (−)-Dehydrotrichostin, 49]. Compound **47** (36

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mg, 0.09 mmol) was treated with chromium trioxide as in the preparation of **50** to yield, after chromatography (SiO_2, EtOAc/heptane, 1:2), **49** (21 mg, 59%): $[\alpha]^{25}_D$ −31.0° (*c* 1.3, MeOH) [lit.[30a] $[\alpha]^{25}_D$ −37° (*c* 0.15, $CHCl_3$), lit.[30b] $[\alpha]^{20}_D$ 10.2° (*c* 0.5, MeOH) and $[\alpha]^{20}_D$ −14.2° (*c* 1.3, MeOH)]; MS *m/e* (rel int) 384 (M^+, 8), 165 ($C_9H_9O_3$, 100), 135 ($C_8H_7O_2$, 63); ^1H NMR ($CDCl_3$) δ 6.70 (dd, 1 H, *J* = 7.0, 1.3 Hz, ArH), 6.47 (dd, 1 H, *J* = 7.0, 1.6 Hz, ArH), 6.46 (s, 1 H, ArH), 6.32 (d, 1 H, *J* = 1.5 Hz, ArH), 6.30 (d, 1 H, *J* = 1.5 Hz, ArH) 5.96–5.93 (m, 4 H, OCH_2O), 4.16 (dd, 1 H, *J* = 9.3, 6.8 Hz, H-5), 3.90–3.85 (1 H, H-5), 3.86 (s, 3 H, MeO), 2.95 (dd, 1 H, *J* = 14.0, 4.8 Hz, $ArCH_2$), 2.82 (dd, 1 H, *J* = 13.9, 6.8 Hz, $ArCH_2$), 2.62–2.46 (m, 4 H, H-3, H-4, $ArCH_2$); ^{13}C NMR ($CDCl_3$) δ 178.4 (CO), 149.0, 147.9, 146.4, 143.6, 134.1, 132.1, 131.6, 121.6, 108.8, 108.4, 108.3, 103.3 (Ar), 101.4, 101.1 (OCH_2O), 71.2 (C-5), 56.6 (MeO), 46.6, 41.2 (C-3 and C-4), 38.4, 35.2 ($ArCH_2$).

(−)-(3*R*,4*R*)-3,4-Bis[3,4-(methylenedioxy)benzyl]butyrolactone [(−)-Hinokinin, 50]. To a solution of chromium trioxide (0.291 g, 2.91 mmol) in dry pyridine[35] (0.459 g, 5.81 mmol) and dry dichloromethane (7.3 mL) was added a solution of **48** (0.148 g, 0.415 mmol) in dichloromethane (3 mL). After 10 min, the solution was decanted. The reaction flask was washed with dichloromethane (20 mL). The combined solutions were washed with aqueous sodium hydroxide (5 mL, 1 M), aqueous hydrochloric acid (5 mL, 5%), and saturated aqueous sodium hydrogen carbonate (2 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, dichloromethane) to give **50** (0.122 g, 83%) as an oil: $[\alpha]^{25}_D$ −34.7° (*c* 0.7, $CHCl_3$) [lit.[21b] $[\alpha]^{17}_D$ −34.0° (*c* 0.981); mp 64–65 °C (MeOH)]; ^1H NMR ($CDCl_3$) δ 6.75–6.69 (m, 2 H, ArH), 6.63–6.58 (m, 2 H, ArH), 6.48–6.45 (m, 2 H, ArH), 5.95–5.93 (m, 4 H, OCH_2O), 4.13 (dd, 1 H, *J* = 9.2, 6.9 Hz, H-5), 3.86 (dd, 1 H, *J* = 9.1, 7.0 Hz, H-5), 2.99 (dd, 1 H, *J* = 14.1, 4.9 Hz, $ArCH_2$), 2.84 (dd, 1 H, *J* = 14.1, 7.1 Hz, $ArCH_2$), 2.64–2.42 (m, 4 H, $ArCH_2$, H-3, H-4); ^{13}C NMR signals are in agreement with reported data (inter alia) δ 178.41 (CO), 34.87 ($ArCH_2$) (lit.[21h] δ 178.39, 34.78).

3-(2-Chloro-3,4,5-trimethoxybenzyl)-4-[3,4-(Methylenedioxy)benzyl]tetrahydrofuran (2″-Chloroburseran, 51). Treatment of **45** with $CDCl_3$ at room temperature for several days gave, after chromatography, a small amount of **51**: MS *m/e* (rel int) 422 (M^+, 3), 420 (M^+, 10), 216 (20), 215 (18), 182 (25), 181 (43), 136 (54), 135 (100); ^1H NMR ($CDCl_3$) δ 6.68 (d with further coupling, 1 H, *J* = 8.4 Hz, ArH), 6.54 (s, 1 H, ArH), 6.53 (dd, 1 H, *J* = 6.7, 1.7 Hz, ArH), 6.41 (s, 1 *H*, H-6″), 5.92 (q, 2 H, *J* = 1.3 Hz, OCH_2O), 3.96 (dd, 1 H, *J* = 8.8, 7.1 Hz, H-2 or H-5), 3.9 (1 H, H-2 or H-5), 3.90, 3.87, 3.81 (s, 3 H each, MeO), 3.57 (dd, 1 H, *J* = 8.7, 5.9 Hz, H-2 or H-5), 3.52 (dd, 1 H, *J* = 8.7, 6.0 Hz, H-2 or H-5), 2.83 (dd, 1 H, *J* = 13.6, 2.8 Hz, $ArCH_2$), 2.65–2.48 (m, 3 H, $ArCH_2$), 2.32–2.18 (m, 2 H, H-3, H-4).

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Synthesis of Highly Functionalized Flavones and Chromones Using Cycloacylation Reactions and C-3 Functionalization. A Total Synthesis of Hormothamnione

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The cycloacylations of hydroxy- and methoxy-substituted phenols with aryl- and alkylpropiolic acids using Eaton's reagent (10% phosphorus pentoxide in methanesulfonic acid) gives highly substituted flavones and chromones in up to 63% yield. Styrylchromones were prepared from 2-methylchromones by condensation reactions of the 2-methyl group with various substituted benzaldehydes in sodium ethoxide and ethanol in almost quantitative yield. Methylation or hydroxylation at C-3 of these highly substituted flavones and styrylchromones was accomplished in a highly regioselective manner employing lithium diisopropylamide followed by quenching with an electrophile. Quenching of the initial anion with methyl triflate gave 3-methyl products while quenching of the initial anion with trimethylborate followed by oxidation gave 3-hydroxy products. A total synthesis of the naturally occurring styrylchromone hormothamnione, containing a 3-methyl substituent, is reported by use of these synthetic techniques.

The chromones, flavones, and related compounds are widely distributed in nature and have been found to play an important role in a number of biological processes.[1-4] In humans, naturally occurring chromones and flavones have shown biological effects as well. These are typified by the furochromone khellin (1), which has exhibited lipid-altering capabilities,[5] or by 3,4′,7-trihydroxyflavone (2), 5-hydroxy-4′,7-dimethoxyflavone (3), and 3,3′,4′,7-tetrahydroxyflavone (4), which have been shown to possess antiinflammatory activity.[6]

Other naturally occurring compounds that either are flavone-based or are flavones have been shown to be capable of mediating DNA strand cleavage in the presence of copper(II) and oxygen, presumably involving intercalation of the flavone.[7-9] These compounds, such as (−)-

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