Enantioselective Synthesis of Natural Dibenzybutyrolactone Lignans (-)-Enterolactone, (-)-Hinokinin, (-)-Pluvialotide, (-)-Enterodiol, and Furofuran Lignan (-)-Eudesmin via Tandem Conjugate Addition to γ-Alkoxybutenolides1,2

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A general and efficient method is described for the asymmetric synthesis of a variety of lignans. 5-(Methoxyloxy)-2(5H)-furanes 5 proved to be excellent chiral synthons in this respect and could be transformed with complete stereoselectivity into a number of lignans. The addition of lithiated dithianes 7 to enantiomerically pure butenolides 5 was followed by quenching of the resulting lactone enolate anions with a benzylbromide (9) or with an aldehyde (6). This tandem addition quenching procedure gave the diastereomerically pure adducts 11, 26, or 27 in 50–67% yield, with a carbon skeleton as found in most natural lignans. As examples of the wide applicability of this method, the syntheses of the enantiomerically pure natural lignans (-)-hinokinin (23b), (-)-enterolactone (24a), (-)-pluvialotide (24c), and (-)-enterodiol (25) in overall yields of 29–37% from 5a and (-)-eudesmin (30) in 16% overall yield from 5b are described.

Introduction

Lignans are a class of natural compounds that can be found in nearly any plant on the earth,3 and these compounds have shown a range of biological activities. An enormous variety of lignans are known today, but in general the following structural classes are defined: dibenzylbutanes such as dibenzybutyrolactones 1 and dioxabicyclo[3.3.0]octanes 2, 1-aryltetralin lignans 3, and dibenzocyclooctadienes 4 (Figure 1).4

Since the discovery that members of lignans of the structural type 1, like enterolactone and enterodiol, can be isolated from the urine of different mammals, which was in contrast with the opinion that they were plant metabolites only,2 interest in dibenzybutyrolactones has grown rapidly. These lignans have various biological activities such as antitumor activity,6 platelet-activating factor (PAF) antagonists,7 sodium selective diuretic properties,8 and inhibitory effects on microsomal monoxygenases in insects.9 Enterolactone production seems to be under endocrine control,10 and it depresses oestrogen-stimulated RNA synthesis.11 Natural enterolactone and enterodiol are racemic and they are unique in lacking para substitution in the benzylic groups.12 Furthermore they are known to have a dietary origin. (-)-Hinokinin and (-)-pluvialotide also belong to the structural type 1 lignans whereas (-)-eudesmin is a typical member of class 2 lignans. First discovered in 1896 eudesmin has been isolated from many plant species.13 It displays cAMP phosphodiesterase inhibitory activity.14 Podophyllotoxin and analogs, the most prominent members of type 3 lignans, have been used as antitumor and antiviral agents14 whereas anticancer activity has also been found for dibenzo-cyclooctadiene lignans 4.

A number of strategies, mainly based on alkylation or Michael addition to butenolides, to achieve stereocontrol synthesis of various structural classes of lignans have been developed.4,14–17 Methodology for the prepa-

ration of dibenzylbutane lignans include Stobbe condensation of aromatic aldehydes with succinic acid esters, oxidative coupling of propionic acid derivatives, nitrile oxide cycloaddition, 16 18 malonic ester substitution 19 and reductive cyclization of α-branched allylic esters. 21

Asymmetric syntheses of dibenzylbutyrolactone lignans by diastereoselective allylation or aldol reactions of monobenzyl-substituted butyro lactones have been particularly successful. 2 4,22 The required optically active butyro lactones are accessible from, for example, l-glutamic acid,22 via resolution of alkylic succinic esters,24 and from alkynyl sulfoxides, 26 whereas Posner et al. 25 used the conjugate addition of benzyl Grignard reagents to a chiral p-toluenesulfinyl butenolide as a key step. Recently routes to enantiomerically pure dibenzylbutyrolactone lignans were developed by Magnusson et al. 15 and Sibi et al. 18 These routes were based, respectively, on conjugate addition to chiral dihydrofuryl ketones and a nitrile oxide cycloaddition—lactone mediated resolution procedure.

Elegant routes to aryltetralin and dibenzocyclooctadiene lignans using chiral oxazolines have been developed by Meyers and co-workers. 28 The chromium carbene complex might be formed in a one-pot procedure by conjugate addition of benzylic dithioacetal anions to an appropriate benzylic electrophile (Schemes 1 and 3). We envisaged that the basic lignan carbon framework, i.e., the dibenzylbutyrolactone structure, could be synthesized in a tandem conjugate addition–ketene formation. 29

Results and Discussion

The chiral butenolides (5R)-(5a) and (5S)-(menthylxylo)-2-(5H)-furanone (5b) (Figure 2) are the key synths in the methodology described here. Enantiomerically pure 5a and 5b might be readily available on a multigram scale from furural and 1- or d-menthol, respectively, involving a remarkable second-order asymmetric transformation. 25

Butenolides 5a and 5b have proven to be extremely valuable as chiral dienophile 30 and Michael acceptor, 31 generally providing products with enantiomeric excesses (ee) exceeding 99%, after removal of the auxiliary group d- or l-menthol.

An important feature is the easy removal, and in most cases recovery in high yield, of the chiral auxiliary alcohol d- or l-menthol by simple acetal hydrolysis after the asymmetric transformations of 5. Previously we have shown that several carbon nucleophiles enter trans-diastereoselective (with respect to the 5-methylxylo moiety) in conjugate addition reactions to butenolides 5a and 5b. 32 We envisaged that the basic lignan carbon framework, i.e., the dibenzylbutyrolactone structure, might be formed in a one-pot procedure by conjugate addition of benzyl dithioacetal anions to 5a followed by quenching of the resulting lactone enolate anion 10 with an appropriate benzyl electrophile (Schemes 1 and 3). The dithianes 7a–7c were prepared from the corresponding aldehydes following a literature procedure (Scheme 2). 34
Enantioselective Synthesis of Dibenzylbutyrolactone Lignans

The dithianes 7 were prepared in high yields from the corresponding aromatic aldehydes 6 in two steps, by modification of a reported procedure.35 In the first step the aldehydes were reduced to the alcohols 8 with NaBH4 in methanol and dichloromethane and subsequently converted to benzyl bromides 9 with PBr3 in Et2O. The results of the conversion of benzaldehydes 6 to the corresponding dithianes 7 or bromides 9 (Scheme 2) are summarized in Table 1.

The anions of dithioacetals were generated by treatment of a solution of the dithioacetal in THF with n-butyllithium at -20 °C. The conjugate addition (Scheme 3) of lithiated dithianes 7a,b,c,d to 5a at -80 °C was followed by quenching of the resulting lactone enolate anion 10 with benzyl bromides 9a,b,c,d at -80 to -30 °C to yield the dibenzylbutyrolactones 11 with a complete lignan skeleton.36 The results of this tandem conjugate addition-alkylation reaction to butenolide 5a are summarized in Scheme 3.

Single diastereoisomers are observed in all cases, indicating complete stereocorrelation in both the conjugate addition and enolate alkylation steps. According to 1H and 13C NMR, diastereoselectivities exceed 98%. As expected,32,33 the bulky menthylxoy moiety in 5 directs the dithioacetal anion to anti attack with respect to the γ-alkoxy substituent. Quenching of the resulting lactone enolate anion 10 with benzyl bromides 9 leads to the 3,4-trans dibenzylated product due to the steric effect of the aryl dithiane moiety at the 4-position. As a consequence, the lactones 11 have the (3R,4R)-configuration as is found in most natural dibenzylbutyln lignans.4 All the lactones 11 showed coupling constants 1JH.HH < 0.5 Hz. The small coupling constants for the acetal proton (H4) in the 1H NMR spectra are very distinctive for the trans relationship between the substituents at C3 and C4. For cis-4,5-disubstituted lactones, coupling constant 1JH.HH in the range of 3-6 Hz are observed.35,38 The trans relationship of the substituents at C3 and C4 could not unequivocally be determined by 1H NMR because of overlapping resonances of H3, H4, and benzyllic protons. The 3,4-trans geometry and the (3R,4R) absolute configuration in lactones 11 is evident from (i) related tandem additions of lithiotris(methylthio)methane to 5a and confirmation of the absolute configuration of the product via conversion to (2R,3R)-2,3-dimethylbutyranal,39 (ii) extensive NMR and X-ray stereochemical analyses of related conjugate addition and aldol products of 5a,35 and (iii) confirmation of the absolute configuration by comparison of specific rotations of the obtained lignans with optical rotations of natural lignans of known absolute configuration (vide infra).

Starting from the enantiomer 5(S)-(d-menthylxoy)-2(5H)-furanone 5b again the all-trans addition products are formed having the (3S,4S)-configuration. A typical example is the diastereoselective formation of (-)-eudesmin precursor 26, as shown in Scheme 7 (vide infra).

### Table 1. Yields of the Conversion of Benzaldehydes 6 to the Corresponding Dithianes 7 or Bromides 9 (Scheme 2)

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>R1</th>
<th>R2</th>
<th>dithiane</th>
<th>bromide</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>OBn</td>
<td>H</td>
<td>7a</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>OMe</td>
<td>OMe</td>
<td>7b</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>OMe</td>
<td>OMe</td>
<td>7c</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td>OMe</td>
<td>OMe</td>
<td>7d</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6a</td>
<td>OBn</td>
<td>H</td>
<td>8a</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>OMe</td>
<td>OMe</td>
<td>8b</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6c</td>
<td>OMe</td>
<td>OBn</td>
<td>8c</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6d</td>
<td>OMe</td>
<td>OMe</td>
<td>8d</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

* Yields are of isolated pure products after crystallization.

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36 It should be noted that after purification by chromatography, the addition products still contained a small amount of an impurity (<10%) which could be detected by 1H NMR. We were not able to remove this byproduct at this stage by chromatographic methods. The byproduct can however be effectively removed after the desulfurization and reduction steps as depicted in Scheme 6.
37 1H NMR of the crude product indicated single isomers, the main byproduct from the reaction is the monoalkylated furanone. In this case only the Michael addition took place and the resulting lactone enolate anion has not been quenched by the benzyl bromide.

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### Scheme 2

![Scheme 2](image)

### Scheme 3

![Scheme 3](image)

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Synthesis of (-)-Enterolactone, (-)-Hinokinin, (-)-Pluvialatide, and (-)-Enterodiol

Reducive desulfurizations of the addition products 11 to the 3,4-dibenzyalted lactones 20 were initially performed with Raney nickel,39 but its preparation is tedious.

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and a large excess of Raney nickel was often required to achieve complete reduction of the thioacetal group. For preparative purposes large quantities of Raney nickel are therefore required. Furthermore treatment of the benzyl-protected substrate 11a with Raney nickel led to a complex mixture of products 12–15, giving serious purification problems (Scheme 4).

It appears that the Raney nickel desulfurization reactions strongly depends on the dithiane used, as clean desulfurization was found in the case of some dibenzylated and monobenzylated lactones using this procedure. Illustrative is the isolation of lactones 18 and 19 in 71% and 66% overall yield, respectively, after tandem conjugate addition—alkylation or protonation and subsequent Raney nickel reduction of the conjugate addition products 16 and 17 (Scheme 5).

We preferred to use nickel boride for the desulfurization reactions of lactones 11. To complete the synthesis of 3,4-dibenzylactone lignan structures from 11, several steps, including thioacetal desulfurization, acetal hydrolysis with removal of the auxiliary menthol, reduction of an aldehyde group sensitive to epimerization at the a-position, and ring closure of the resulting alcohol to complete desulfurization. The reduction of the interme-

Scheme 4

11a → Raney nickel
THF, EtOH

12 R = R' = CH3Ph
13 R = R' = H
14 R = CH3Ph, R' = H
15 R = R' = H

Scheme 5

1) PhC(SPh)2Li
2) Mel or NH4Cl

5a

16 R = H
17 R = Me

18 R = H 71%
19 R = Me 66%

Scheme 6

1) NCl2/MeOH, THF
2) NaBH4
3) KOH (aq), NaBH4
4) HCl (aq)

20

21

22

23a R1 = R2 = OBn, R3 = R4 = H
23b R1 = OCH3, R2 = R3 = OCH2, R4 = H
23c R1 = OCH3, R2 = OMe, R3 = H

24a R1 = R2 = OH, R3 = R4 = H
24c R1 = OCH3, R2 = OMe, R3 = OH

25 Ar = 3-C6H3OH

24a Ar = 3-C6H3OH, R2 = R3 = H
24b Ar = 3-C6H3OH, R2 = R3 = H

5a

20

THF

LiAlH4

OH OH

82%
84%

87%
gave the enantiomerically pure lignan \((-\)-enterodiol\(^{(12,45)}\) (25) \((87\% \text{ yield, } [\alpha]_D^{20} = -13.2 \text{ (c 1.0, EtOH)})\). It should be emphasized that according to \(^1\)H NMR no trace of epimers of 23a-c and 24a,c was found. This means that for partial racemization, epimerization both at C3 and C4 in the dibenzylated lactones must have occurred which is highly unlikely. In addition optical rotations compared well with reported values of lignans obtained from natural sources or via different synthetic routes and indicate enantiomerically pure products. 

It should be emphasized that besides the easy access to butyrolactones bearing identical C3 and C4 benzyl substituents, the method presented here allows facile preparation of \((-\)-eudesmin \((30)\) unambiguously showed that the lithiated dithiane added trans with respect to the menthyloxy substituent in 5b and that the addition of the enolate to 6d occurred exclusively trans with respect to the dithiane substituent. It appeared that the diastereoisomers 26a and 26b are epimeric at the secondary carbinol stereocenter C4, indicating low selectivity in the aldol step.

The stereochemical assignment of 26a and 26b is based on NOESY NMR data and molecular modeling; the NOE effects of the proton at the carbinol stereogenic center are very distinctive in this respect.\(^{(2b,33)}\) The stereochemical result of the aldol step is in contrast with our previous findings\(^{(46)}\) (see also ref 33). Similar observations of low diastereoselectivity in the quenching of lactone enolates with aryl aldehydes have been made by Fujimoto and co-workers\(^{(47)}\) in the synthesis of racemic pinoresinol and in aldol reactions of lactone enolates lacking a C4 substituent.\(^{(33)}\) In a related reaction, only different in the substitution pattern of the aromatic groups, we found complete selectivity in the aldol step. Thus addition of the lithiated dithiane 7e to 5a was followed by an aldol reaction with aldehyde 6e. The tandem addition quenching product 27 was isolated in 50% yield (Scheme 7). No epimer could be detected by means of \(^1\)H or \(^13\)C NMR. The origin of the large difference in selectivity due to an apparently small substituent effect in the aromatic aldehyde remains obscure at present. The dioxabicyclo[3.3.0]octane lignan \((-\)-eudesmin \((30)\) was synthesized from adduct 26 in three steps as outlined in Scheme 8. The low diastereoselectivity at the exocyclic benzylic stereogenic center in the synthesis of 26 (Scheme 7) causes no problems in the preparation of \((-\)-30) since both diastereomers are converted to \((-\)-eudesmin). The integrity of the C3,C4 stereocenters in 26 is retained throughout the synthetic route toward 30 and the absolute configuration at these centers is decisive for the absolute configuration at the benzyl positions of 30. Dithiane 26 was first converted into ketone 28 in 89% yield using HgO in combination with BF\(_3\)-OEt\(_2\). Subsequent multistep reduction of 28 with 4 equiv of LiAlH\(_4\) afforded tetrox 29 in 67% yield. The formation of 29 from 28 involves a ketone and an ester reduction, ring opening and formation of a hemiacetal, which is supposed to be in equilibrium with the aldehyde and d-menthol, and finally reduction of the aldehyde moiety to the alcohol.

\[ ^{1}H \text{ and } ^{13}C \text{ NMR spectra of 29 indicated the presence of three different stereoisomers of the tetrol 29 due to low selectivity in the reduction steps resulting in epimers at the benzylic stereocenters. As the stereochemical integrity at the crucial C3 and C6 stereogenic centers (lactone numbering) is not affected, this mixture of stereoisomers could be used in the final ring closure step. The formation of the dioxabicyclo[3.3.0]octane structure was completed by dehydration of 29 using BF₃·OEt₂, according to a method described by Fujimoto and co-workers.}\]

Enantiomerically pure (−)-eudesmin (30) (mp 106–108 °C, lit.\(^{48}\) mp 107–109 °C) was obtained in 16% overall yield in four steps from 5(S)-(d-methylxlylo)-2(5H)-furanone (5b). \(^{1}H \text{ and } ^{13}C \text{ NMR data were in agreement with those reported for racemic eudesmin}\(^{69}\) whereas an identical rotation \(\{a\}_D^{20} = -64.2 \text{ (c 1.1, CHCl₃)}\) and mass spectrum were obtained for the synthetic optically pure (−)-30 and the natural product. The absolute configuration \((1S,2R,S,6R)\) of synthetic \((-\)-eudesmin \((-30)\) is based upon the absolute configuration\(^{(5b)}\) of butenolide 5b and the all-trans stereoselectivity in the tandem conjugate addition aldol reaction giving Michael adduct 26.

**Conclusions**

We have shown that 5-(methylxlylo)-2(5H)-furanones 5a and 5b are excellent chiral synths for the preparation of dibenzyhtyrolactone and dioxabicyclo[3.3.0]octane ligands via short and completely diastereoselective routes. The tandem Michael addition–alkylation (or aldol) procedures allow easy variation in benzyl substituents, give complete stereocontrol at the essential stereogenic centers, and allow assembly of the lignan structural framework in enantiomerically pure form in a single step.\(^{51}\) The enantiomerically pure dibenzyhtyrolactones 11, 26, and 27 are also excellent precursors for the synthesis of dibenzycollooctadiene-type ligands 4 and aryltetrailn ligands 3 (Scheme 9).

Oxidative coupling of dibenzyltetrahydrofurans to type 4 lignans is well documented,\(^{14,52}\) whereas Vandewalle and co-workers\(^{53}\) used the 5-(methylxlylo)butenolide approach in an elegant route to podophylloctin and analogues 3. The flexibility with respect to hydroxy (and keto groups) at the benzylic positions in 11, 26, and 27, as described above, is essential to the synthesis of the various structural classes of lignans as depicted in Figure 1.

**Experimental Section**

**General Remarks.** Melting points are uncorrected. \(^{1}H \text{ NMR data were recorded at 200 or 300 MHz.} \(^{13}C \text{ NMR data were recorded at 50 or 75.5 MHz.} \text{ CDCCl₃ was used as solvent unless stated otherwise. Chemical shifts are reported in ppm relative to TMS. Coupling constants } \(J \text{ are denoted in hertz. IR spectra were recorded near or as KBr pellet. Microanalyses were performed by the analytical department of the University of Groningen. HRMS mass spectra were recorded on a AEI MS-902 spectrometer. The thioacetalization, bromination, and the tandem addition reactions were performed under an inert nitrogen atmosphere in flame-dried glassware. Flash chromatography was performed using Merck silica gel 60. Solvents were purified using standard procedures. 5-(Methylxlylo)-2(5H)-furanones 5 were synthesized according to the procedure previously described.}^{30} \text{ Bis(phenylthio)phenylmethane was prepared according to the procedure of Ager.}^{54} \text{ Benzaldehydes 6 were purchased from Janssen Chimica and used without purification. All other reagents are commercially available and were used without purification unless stated otherwise.}

**General Procedure for Thioacetal Formation:**\(^{44} \text{ 3-benzylxlylo)-1-(bis(phenylthio)methyl)benzene (7a). To a stirred solution of 6a (10.6 g, 50 mmol) in 100 mL of CH₂Cl₂ was added 12.0 g (109 mmol, 2.2 equiv) of triphenylmethylated phenol followed by 1.3 g of AlCl₃ in portions. After stirring for 2 h, the reaction mixture was quenched with 100 mL of water. The resulting mixture was extracted with 3 × 100 mL of CH₂Cl₂. The combined CH₂Cl₂ layers were washed with 3 × 100 mL saturated Na₂CO₃ solution, dried over Na₂SO₄, and concentrated. Pure thioacetal 7a (16.7g, 81%) was obtained after one crystallization from EtOH/hexane as a white-yellow solid: mp 95.8–96.4 °C; \(^{1}H \text{ NMR } \delta = 7.42–7.15 \text{ (m, 16H), 7.04–6.85} \text{ (m, 3H), 5.40 \text{ (s, 1H), 5.01} \text{ (s, 2H);}^{13}C \text{ NMR } \delta = 158.77, 141.15, 136.83, 134.47, 132.55, 129.49, 128.58, 128.00, 127.81, 127.57, 120.52, 114.94, 114.03, 69.66, 60.32.}

**5-Bis(phenylthio)methyl)-1,3-benzodioxole (7b) was synthesized according to the procedure for the preparation of 7a. Starting from 6b (7.5 g, 50 mmol), pure thioacetal 7b (15.2 g, 90%) was obtained after one crystallization from EtOH: mp 45–47.5 °C (lit.\(^{15}\) mp 45–47.5 °C); \(^{1}H \text{ NMR } \delta = 7.38–7.18 \text{ (m, 10H), 6.98} \text{ (d, 1H, } J = 1), 6.78 \text{ (d, 1H, } J = 1, J = 7), 6.62 \text{ (d, 1H, } J = 7), 5.87 \text{ (s, 2H), 5.36} \text{ (s, 1H);}^{13}C \text{ NMR } \delta = 149.59, 147.14, 134.38, 133.29, 132.12, 128.64, 127.54, 121.30, 108.04, 107.66, 101.01, 59.96.}

**4-(Bis(phenylthio)methyl)-1,2-dimethoxybenzene (7d) was synthesized according to the procedure for the preparation of 7a. Starting from 6d (6.3 g, 50 mmol), pure 7d (14.2 g, 80%) was obtained after one crystallization from EtOH/MeOH: mp 68–69 °C (lit.\(^{15}\) mp 68–69 °C); \(^{1}H \text{ NMR } \delta = 7.40–7.21 \text{ (m, 10H), 7.30–6.75} \text{ (m, 3H), 5.44} \text{ (s, 1H), 3.84} \text{ (s, 3H), 3.30} \text{ (s, 3H);}^{13}C \text{ NMR } \delta = 148.67, 148.54, 134.41, 132.43, 131.88, 128.67, 127.51, 120.10, 110.67, 110.51, 59.97, 55.76.**

\(^{(50)}\) For the assignment of the absolute configuration of a 1,4-addition product to (+)-5(S)-(methylxlylo)-2(5H)-furanone (5b), see ref. 33.  
\(^{(53)}\) van Oeveren et al.  
Enantioselective Synthesis of Dibenzylobutyrilactone Lignans

CH₂Cl₂/hexane: mp 82.6–82.9°C; [α] NMR δ 7.45–7.78 (m, 15H), 6.98 (d, 1H, J = 1.8), 6.90 (dd, 1H, J = 1.8, J = 8.1), 6.71 (d, 1H, J = 8.1), 6.53 (s, 1H), 6.05 (s, 2H), 3.82 (s, 3H); 13C NMR δ 149.21, 147.72, 136.73, 134.32, 132.40, 131.67, 128.61, 128.37, 127.73, 127.53, 127.33, 126.65, 113.41, 111.06, 70.71, 59.76, 55.82.

**General Procedure for the Synthesis of Benzylbromides**. 3-({Benzyloxy)-1-(bromomethyl)benzene (9a). To a stirred solution of 8a (10.5 g, 50 mmol) in 50 mL of CH₂Cl₂ was added 2.5 mL of NaOH (62 mmol) in 25 mL of MeOH. After stirring for 1 h, the reaction mixture was poured into 100 mL of water, followed by extraction with CH₂Cl₂ (3 x 50 mL), drying (Na₂SO₄), and evaporation of the solvent. The alcohol 8a obtained in this way was used in the next step without purification.

To a stirred solution of 8a in 100 mL of ether was added dropwise a 55.5 mL/m of PBr₃ (57 mmol) in 35 mL of ether. After stirring for 3 h at room temperature, the reaction mixture was removed from water, followed by crystallization with CH₂Cl₂ (3 x 50 mL), drying of the organic layer (Na₂SO₄), and evaporation of the solvent. After crystallization of the residue from n-hexane, pure 9a (11.2 g, 80%) was obtained: mp 51–53°C ([α] NMR δ 7.47–7.26 (m, 5H), 7.06–6.93 (m, 4H), 5.10 (s, 2H), 4.50 (s, 2H)); 13C NMR δ 159.02, 139.26, 136.80, 129.93, 128.69, 128.12, 127.60, 121.65, 115.53, 110.72, 70.07, 33.86.

5-(Bromomethyl)-1,3-benzenediol (9b) was synthesized according to the procedure of preparation of 9a. Starting from 6b (7.5 g, 50 mmol), pure 9b (7.8 g, 73%) was obtained after crystallization from n-hexane: mp 45.6–47.2°C ([α] NMR δ 7.46–7.27 (m, 5H), 7.06–6.93 (m, 4H), 5.10 (s, 2H), 4.46 (s, 2H)); 13C NMR δ 147.74, 147.61, 122.25, 109.28, 108.12, 101.16, 24.09.

1-(Benzyloxy)-4-(bromomethyl)-2-methoxybenzene (9c) was synthesized according to the procedure for the preparation of 9a. Starting from 6c (12.1 g, 50 mmol), pure 9c (13.0 g, 84%) was obtained after crystallization from hexane/CH₂Cl₂: mp 69.8–73.4°C ([α] NMR δ 7.46–7.27 (m, 5H), 6.96–6.81 (m, 3H), 5.10 (s, 2H), 4.50 (s, 2H), 3.92 (s, 3H)); 13C NMR δ 149.68, 148.38, 136.86, 130.68, 128.58, 127.91, 127.22, 121.49, 113.71, 112.59, 70.93, 56.03, 34.38.

4-(Bromomethyl)-1,2-dimethoxybenzene (9d) was synthesized according to the procedure for the preparation of 9a. Starting from 6d (9.9 g, 50 mmol), pure 9d (11.2 g, 81%) was obtained after crystallization from n-hexane: [α] NMR δ 6.97–6.88 (m, 2H), 6.79 (m, 1H), 4.48 (s, 2H), 3.96 (s, 3H), 3.86 (s, 3H); 13C NMR δ 148.00, 148.85, 130.02, 121.35, 111.86, 110.82, 55.73, 34.24.

(3R,4R,SR)-3-({1,3-Benzodioxol-5-ylmethyl)-4-((1,3-benzo-dioxol-5-yl)-dihydro-2(3H)-furanone (11a) was synthesized by the following procedure. To a stirred solution of 7a (4.14 g, 10 mmol) in 50 mL of THF was added at –20°C 8.7 mmol of BuLi (1.19 g, 5.5 mmol). The solution was stirred at –20°C for 90 min and subsequently cooled to –85°C. A solution of 5a (2.38 g, 10 mmol) in 30 mL of THF was added dropwise, keeping the temperature below –80°C. The reaction mixture was warmed to –20°C and stirred at this temperature for 2 h, poured into 200 mL of water, and extracted with 3 x 100 mL of CH₂Cl₂. The combined organic layers were washed with saturated Na₂CO₃ (2 x 50 mL) and water (50 mL) and dried (Na₂SO₄). The solvent was evaporated, and the resulting crude product (9.82 g) was purified by flash chromatography (silica gel, CH₂Cl₂/n-hexane 1:1) for which 11a (6.71 g, 67%) was obtained as a very viscous yellow oil and was used as such for the next step.

(3R,4R,SR)-3-((Benzylthio)methyl)phenylmethyl)-4-((1,3-benzo-dioxol-5-yl)-dihydro-2(3H)-furanone (11b) was synthesized according to the procedure for the preparation of 11a. A solution of 5a (1.19 g, 5 mmol) in 50 mL of THF was added dropwise during 30 min and stirring at –90°C was continued


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for 90 min. The reaction mixture was poured into 200 mL of saturated aqueous NH₄Cl and extracted with EtO₂ (3 × 100 mL). The organic layers were dried over Na₂SO₄ and concentrated. The intermediate 16 was dissolved in 40 mL of THF and 5 teaspoons of Raney nickel were added. The mixture was stirred at -60° C for 15 min and the mixture was warmed to -30° C and stirred for 3 h. Then the reaction mixture was cooled to 0° C. A solution of 11a (0.85 g, 1.0 mmol) and NiCl₂·6H₂O (1.15 g, 5 mmol) in 5 mL of THF and 50 mL of CH₃OH was cooled to 0°C. NaBH₄ (0.76 g, 20 mmol) was added in small portions in about 20 min at such a rate that the temperature was kept below 10°C. Immediately after the last portion of NaBH₄ was added, 10 mL of a 2 N aqueous solution of KOH (20 mmol) was added at once, followed by additional NaBH₄ (0.19 g, 5 mmol), and the mixture was allowed to warm to room temperature while being stirred for 2 h. The black precipitate was filtered off over Celite and the filtrate was acidified with 2 N HCl to pH = 1. Subsequently methanol and THF were removed in vacuo. The remaining suspension was added 20 mL of water, and the water layer was extracted with 3 × 30 mL of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to give 0.71 g of a viscous yellow oil. Methanol was removed by bulb-to-bulb distillation (0.1 mmHg/100°C) and the remaining oil was purified by chromatography (silica gel, CH₂Cl₂) to give pure 23a (0.263 g, 62%) as a colorless viscous oil: [α]D₂⁰ = -22 (c 0.90, CHCl₃); IR (neat) δ 1740, 1670, 1580, 1530, 1470, 1460, 1430, 1350, 1330, 1280, 1265, 1240, 1220, 1190, 1170, 1150, 1130, 1090, 1080, 940, 430, 380, 350; 1H NMR δ 7.5 2.93, 2.82 (m, 4H), 2.65-2.56 (m, 8H), 2.05-1.95 (m, 4H), 1.8-1.6 (m, 4H); 13C NMR δ 178.5, 136.2, 128.6, 128.0, 127.9, 127.5, 121.9, 121.2, 115.7, 115.4, 113.4, 112.9, 71.1, 69.9, 46.3, 41.2, 38.5, 35.1; HRMS calc 478.2143, found 478.2148. Anal. Calc for C₂₅H₂₄O₄C: H, 5.90; Found: C, 76.30; H, 9.20.

(3R,4R)-2,3-Bis[(3-hydroxyphenyl)methyl]-1,4-butane- diol (23b) was synthesized from 23a according to a literature procedure for racemic 24c. Starting from racemic 23c (103 mg, 0.23 mmol), pure 24c (69 mg, 84%) was obtained as a gum, which was dissolved in 40 mL of THF and added to a solution of 1.6 g of 3% KOH in 50 mL of water at -10°C. The mixture was allowed to warm to 20°C and stirred for 2 h. Subsequently the reaction mixture was cooled to 0°C and stirred for 1 h at -10°C. The color of the reaction mixture was then allowed to warm to 20°C and the mixture was warmed to 60°C. The reaction mixture was then cooled to 5°C and stirred for 1 h at 5°C. The reaction mixture was then allowed to warm to 20°C and the mixture was cooled to 0°C and stirred for 1 h at -30°C. The reaction mixture was then allowed to warm to 20°C and the mixture was cooled to 0°C and stirred for 1 h at -30°C. Quenching of the reaction mixture with 200 mL of saturated aqueous NH₄Cl allowed by extraction with EtO₂ (3 × 100 mL), drying of the organic layers (Na₂SO₄), and evaporation of the solvent. The crude adduct was purified by chromatography (silica gel, CH₂Cl₂ followed by ether) to afford pure 26 (4.6 g, 62%) as a colorless viscous oil (40% mixture (6R/5S), 40% mixture (6S/5R), 40% mixture (6S/5R)). Starting from racemic 23a (0.816 g, 1 mmol), pure 26 (0.24 g, 58%) was obtained as a colorless viscous oil: [α]D₂⁰ = -3.9 (c 1.00, CHCl₃). Spectral data were identical to those reported for compound 23a.
Enantioselective Synthesis of Dibenzylbutyrelactone Lignans

In this work, a synthetic route to the enantiomerically pure dibenzylbutyrelactone lignans is described. The key steps involve the enantioselective addition of a metal reagent to a chiral salt, followed by chromatographic purification. The resulting compounds were characterized by spectroscopic techniques, including NMR and mass spectrometry.

For example, the NMR spectrum of a representative lignan showed the following signals:

- 5.44 (s, 1H), 4.85 (d, 1H, J = 8.0), 3.91 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 3.40–3.15 (m, 2H), 2.24–2.18 (m, 2H), 1.89–1.86 (m, 1H), 1.73–1.62 (m, 1H, 1.61–1.49 (m, 2H), 1.24–1.08 (m, 2H), 0.98–0.56 (m, 3H), 0.82 (d, 3H, J = 6.6), 0.76 (d, 3H, J = 6.6), 0.71 (d, 3H, J = 6.6).

13C NMR δ 192.98, 173.20, 154.15, 149.01, 148.63, 148.29, 137.11, 132.38, 126.00, 123.51, 118.60, 110.13, 109.61, 108.83, 100.49, 78.80, 78.51, 55.88, 55.73, 55.49, 55.36, 50.13, 47.37, 42.91, 39.55, 34.00, 31.02, 25.07, 22.65, 21.98, 20.65, 15.28; HRMS calcd 570.283, found 570.283.

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