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

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Enantioselective Synthesis of Natural Dibenzylbutyrolactone Lignans (-)-Enterolactone, (-)-Hinokinin, (-)-Pluviatolide, (-)-Enterodiol, and Furofuran Lignan (-)-Eudesmin via Tandem Conjugate Addition to γ-Alkoxybutenolides

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A general and efficient method is described for the asymmetric synthesis of a variety of lignans. 5-(Methyloxy)-2(5H)-furanones proved to be excellent chiral synths in this respect and could be transformed with complete stereoselectivity into a number of lignans. The addition of lithiated dithianes to enantiomerically pure butenolides was followed by quenching of the resulting lactone enolate anions with a benzylbromide or with an aldehyde. This tandem addition quenching procedure gave diastereomerically pure adducts 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, (-)-enterolactone, (-)-pluviatolide, and (-)-enterodiol in overall yields of 29–37% from 5a and (-)-eudesmin 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, and these compounds have shown a range of biological activities. An enormous variety of lignans is known today, but in general the following structural classes are defined: dibenzylbutanes such as dibenzylbutylactones and dioxacyclobutanes, 1-aryltetralin lignans, and dibenzocyclooctadienes.

Since the discovery that members of lignans of the structural type 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, interest in dibenzylbutyrolactones has grown rapidly. These lignans have various biological activities such as antitumor activity, platelet-activating factor (PAF) antagonists, sodium selective diuretic properties, and inhibitory effects on microsomal monoxygenases in insects. Enterolactone production seems to be under endocrine control, and it depresses oestrogen-stimulated RNA synthesis. Natural enterolactone and enterodiol are racemic and they are unique in lacking para substitution in the benzylic groups. Furthermore they are known to have a dietary origin.

(-)-Hinokinin and (-)-pluviatolide 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. It displays cAMP phosphodiesterase inhibitory activity. Podophyllotoxin and analogs, the most prominent members of type 3 lignans, have been used as anticancer and antiviral agents whereas anticancer activity has also been found for dibenzocyclooctadienes.

A number of strategies, mainly based on alkylation or Michael addition to butenolides, to achieve stereocontrolled synthesis of various structural classes of lignans have been developed. Methodology for the preparation of 1


Figure 1.
Asymmetric syntheses of dibenzybutyro lactone lignans by diastereoselective alkylation or aldol reactions of monobenzyl-substituted butyrolactones have been particularly successful.4,22 The required optically active butyrolactones are accessible from, for example, l-glutamic acid,22 via resolution of alkylated succinic esters,22 and from alkenyl sulfoxides,24 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 dibenzybutylene lignans were developed by Magnusson et al.15 and Sibi et al.14 These routes were based, respectively, on conjugate addition to chiral dihydrofurfuryl ketones and a nitrile oxide cyclodaddition—lipase mediated resolution procedure.

Elegant routes to aryltetralin and dibenzo[cyclooctadiene] lignans using chiral oxazolines have been developed by Meyers and co-workers.26 The chromium carbene route, recently reported by Miller and Hegedus,27 offers a valuable alternative.

Improvement of current methodology for the total synthesis of enantiomerically pure lignans is however highly warranted,13 as several routes are rather lengthy or multistep syntheses of chiral starting materials are required whereas modest stereoselectivities are found in several cases. Our goal was to develop a short and flexible route based on readily available chiral synths, with absolute stereocontrol, to various structural classes of lignans.

This paper presents full details of our new approach to dibenzybutyrolactone lignans and dioxabicyclo[3.3.0]-

(29) Tomioka, K.; Koga, K. Heterocycles 1979, 12, 1523.

Results and Discussion

The chiral butenolides (5R)-5a and (5S)-menthoxy-2(5H)-furanone (5b) (Figure 2) are the key synthons in the methodology described here. Enantiomerically pure 5a and 5b are readily available on a multigram scale from furfural and l- or d-menthol, respectively, involving a remarkable second-order asymmetric transformation.22

Butenolides 5a and 5b have proven to be extremely valuable as chiral dienophile31 and Michael acceptor,22 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-menthoxy moiety) in conjugate addition reactions to butenolides 5a and 5b.23 We envisaged that the basic lignan carbon framework, i.e., the dibenzybutyrolactone structure, might be formed in a one-pot procedure by conjugate addition of benzylidichjioacetal anions to 5a followed by quenching of the resulting lactone enolate anion 10 with an appropriate benzyl electrophile (Schemes 1 and 3). The dihanses 7a–7c were prepared from the corresponding aldehydes following a literature procedure (Scheme 2).24 Stirring a solution of the benzaldehydes 6 with 2 equiv of thiophenol and a catalytic amount of AlCl3 gave

![Figure 2](https://example.com/figure2.png)
Enantioselective Synthesis of Dibenzylbutyrolactone Lignans

Scheme 2

\[
\begin{array}{c}
\text{R}^1 \text{R}^2 \text{R}^3 \\
\end{array}
\]

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>( \text{R}^1 )</th>
<th>( \text{R}^2 )</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>80</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>OBn</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>80</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6e</td>
<td>OBn</td>
<td>OMe</td>
<td>7e</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6a</td>
<td>OBn</td>
<td>OMe</td>
<td>7a</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>OMe</td>
<td>OMe</td>
<td>7b</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6c</td>
<td>OMe</td>
<td>OBn</td>
<td>7c</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6d</td>
<td>OMe</td>
<td>OMe</td>
<td>7d</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

*Yields are of isolated pure products after crystallization.*

The dithianes 7 in high yields. The benzyl bromides 9 were prepared in high yields from the corresponding aromatic aldehydes 6 in two steps, by modification of a reported procedure. In the first step the aldehydes were reduced to the alcohols 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 benzyl bromides 9 are summarized in Table 1.

The anions of dibuthioacetals 7 were generated by treatment of a solution of the dibuthioacetal in THF with n-butyllithium at -20 °C. The conjugate addition (Scheme 3) of lithiated dithianes 7a,b,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. 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 stereocontrol in both the conjugate addition and enolate alkylation steps. According to ¹H and ¹³C NMR, diastereoselectivities exceed 98%. As expected, the bulky menthoxy moiety in 5 directs the dibuthioacetal anion to anti attack with respect to the \( \gamma \)-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 aryldithiane moiety at the 4-position. As a consequence, the lactones 11 have the (3R,4R)-configuration as is found in most natural dibenzylbutane lignans. All the lactones 11 showed coupling constants \( J_{H1,H2} < 0.5 \) Hz. The small coupling constants for the acetal proton (H₅) in the ¹H NMR spectra are very distinctive for the trans relationship between the substituents at C₄ and C₅. For cis-4,5-disubstituted lactones, coupling constant \( J_{H1,H2} \) in the range of 3–6 Hz are observed. The trans relationship of the substituents at C₃ and C₄ could not unequivocally be determined by ¹H NMR because of overlapping resonances of H₅, H₆, and benzylic 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-dimethylbutanediol, (ii) extensive NMR and X-ray stereochemical analyses of related conjugate addition and aldol products of 5a, 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-menthoxy)-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).

**Synthesis of (-)-Enterolactone, (-)-Hinokinin, (-)-Pluviatolide, and (-)-Enterodiol**

Reductive desulfurizations of the addition products 11 to the 3,4-dibenzylated lactones 20 were initially performed with Raney nickel, but its preparation is tedious.
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 O-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 yield of 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 α-position, and ring closure of the resulting alcohol to the γ-lactone without affecting the stereocenters at C3 and C4, are necessary (Scheme 6). We devised a one-pot procedure for the conversion of lactones 11 to lactones 23, which proved to be highly efficient.

Small scale (1 mmol) desulfurizations of the addition products 11 are best performed using nickel boride generated in situ from 5 equiv of NiCl₂·6H₂O and 20 equiv of NaBH₄ in MeOH in the presence of the substrate (in the case of 11a and 11c some THF is added to improve solubility). The excess of NiCl₂ is necessary to achieve complete desulfurization. The reduction of the interme-


gave the enantiomerically pure lignan (-)-enterodiol\(^{12,45}\) (25) (87% yield, [a]\(_D\) -13.2 (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 C\(_3\) and C\(_4\) 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 C\(_3\) and C\(_4\) benzyl substituents, the method presented here allows facile introduction of two distinctly substituted benzyl moieties as is illustrated in the synthesis of (-)-pluvialidov (24e).

**Synthesis of (-)-Eudesmin (30)**

For the synthesis of (-)-eudesmin (30) we started with 5(S)-(d-menthyloxy)-2(5H)-furanone (5b) as shown in Scheme 7. Conjugate addition of lithiated dithioacetal 7d to 5b followed by an aldol condensation of the resulting lactone enolate anion with 3,4-dimethoxybenzaldehyde (6d) at -90 °C provided lactone 26 in 62% yield. Much to our surprise two diastereoisomers of 26 were obtained in a 60:40 ratio. Extensive NMR studies (\(^1\)H NMR, COSY, and NOESY) and conversion of 26 into (-)-eudesmin (30) (Scheme 8) unambiguously showed that the lithiated dithiane added trans with respect to the methyloxy 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 C\(_4\), 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.\(^ {28,33}\) 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 C\(_4\) 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 (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 C\(_3\),C\(_4\) 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 benzylic 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 tetro 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.


\(^{[44]}\) Especially the phenolic lignans show a large concentration, and solvent dependency for the specific rotation.


...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.[56]

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-menthyl)-2(5H)-furanone (5b). [1H and 13C NMR data were in agreement with those reported for racemic eudesmin[49] whereas an identical rotation ([α]D₉⁰ = −64.2 (c 1.1, CHCl₃)) and mass spectrum were obtained for the synthetic optically pure (−)-30 and the natural product. The absolute configuration (1S,2R,5S,6R) of synthetic (−)-eudesmin (30) is based upon the absolute configuration[50] of butenolide 5b and the all-trans stereosequence in the tandem conjugate addition aldol reaction giving Michael adduct 26.

Conclusions

We have shown that 5-(menthyl)-2(5H)-furanones 5a and 5b are excellent chiral synths for the preparation of dibenzylbutyrolactone and dioxabicyclo[3.3.0]octane lignans via short and completely diastereoselective routes. The tandem Michael addition−alkylation (or aldol) procedures allow easy variation in benzyl substituents, give complete stereoccontrol 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 dibenzylbutyrolactones 11, 26, and 27 are also excellent precursors for the synthesis of dibenzocyclooctadiene-type lignans 4 and aryltetralin lignans 3 (Scheme 9).

Oxidative coupling of dibenzyltetrahydrofurans to type 4 lignans is well documented,[12,45] whereas Vandewalle and co-workers[52] used the 5-(menthyl)butenolide approach in an elegant route to podophyllotoxin 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. 1H NMR spectra were recorded at 200 or 300 MHz. 13C NMR spectra were recorded at 50 or 75.5 MHz. CDC63 was used as solvent unless stated otherwise. Chemical shifts are reported in ppm relative to TMS. Coupling constants J are denoted in hertz. IR spectra were recorded neat or as KBr pellet. Microanalyses were performed by the analytical department of the University of Groningen. HRMS mass spectra were recorded on an AEI MS-902 spectrometer. The thioacetilation, 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-(Menthyl)-2(5H)-furanones 5 were synthesized according to the procedure previously described.[30] Bis(phenylthio)phenylmethane was prepared according to the procedure of Ager.[34] 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 Thioacetilation: 3-(Benzyl)-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 thionephene 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 × 10 mL saturated Na₂CO₃ solution, dried over Na₂SO₄, and concentrated. Pure thioacetal 7a (15.7 g, 81%) was obtained after one crystallization from EtO/ hexane as a white-yellow solid: mp 95.8-96.4 °C; [α]D₈⁰ = 7.42-7.15 (m, 16H), 7.04-6.85 (m, 3H), 5.40 (s, 1H), 5.01 (s, 2H); 13C NMR δ 158.77, 141.15, 136.83, 134.47, 132.55, 129.49, 128.85, 128.58, 128.00, 127.81, 127.57, 120.52, 114.94, 114.03, 69.65, 60.32.

Bis(phenylthio)phenylmethane was prepared according to the procedure of Ager.[34] 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 Thioacetilation: 3-(Benzyl)-1-(bis(phenylthio)methyl)benzene (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 EtO/H₂O mp 45-47.5 °C (lit.[13] mp 45-47.5 °C); [α]D₈⁰ = 7.38-7.18 (m, 10H), 6.98 (d, 1H, J = 1), 6.97 (s, 1H, J = 1), 6.62 (d, 1H, J = 1), 5.87 (s, 2H), 5.36 (s, 1H); 13C NMR δ 147.59, 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)-1,3-benzodioxole (7d) was synthesized according to the procedure for the preparation of 7a. Starting from 6d (6.3 g, 50 mmol), pure thioacetal 7d (14.2 g, 80%) was obtained after one crystallization from EtO/CH₂Cl₂ mp 68-69 °C (lit.[13] mp 68-69 °C); [α]D₈⁰ = 7.40-7.21 (m, 10H), 6.95-6.75 (m, 3H), 5.44 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H); 13C NMR δ 148.67, 148.54, 143.41, 132.43, 131.88, 128.67, 127.51, 120.10, 110.67, 110.51, 59.97, 55.76.

1H and 13C 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 C₄ stereogenic centers (lactone numbering) is not affected, this mixture of stereoisomers could be used in the final ring closure step.

Scheme 9

General Procedure for Thioacetilation: 3-(Benzyl)-1-(bis(phenylthio)methyl)benzene (7c) was synthesized according to the procedure for the preparation of 7a. Starting from 6c (10 g, 50 mmol), pure 7c (16 g, 88%) was obtained after one crystallization from...
**General Procedure for the Synthesis of Benzylbromides**

A solution of 10.5 g of 55% NaH in 50 mL of THF was added to a mixture of 1.54 g of dimethoxybenzene and 1.29 mL of DMF in 50 mL of THF. The mixture was stirred for 3 h at room temperature, and then cooled to -78 °C. A solution of 1.54 g of 3-bromopyridine in 25 mL of THF was added dropwise over 1 h. The reaction mixture was then cooled to -80 °C for 2 h, and then quenched with 10% aq. HCl. The mixture was then filtered and the filtrate was evaporated to dryness. The resulting crude product was purified by column chromatography (silica gel, hexane/CHCl₃ 6:1), IR (KBr) 1776 cm⁻¹ (C=O); 'H NMR δ 7.43-7.03 (m, 24H), 2.80 (m, 3H), 2.10-1.92 (m, 3H), 3.43 (dt, 1H, J=4.3, J=10.6), 3.24-3.19 (m, 1H), 3.02-2.80 (m, 3H), 2.10-1.92 (m, 2H), 1.71-1.54 (m, 2H), 1.40-1.19 (m, 2H), 0.95-0.74 (m, 3H), 0.95 (d, 3H, J=6.6), 0.89 (d, 3H, J=7.3), 0.72 (d, 3H, J=7.0); 13C NMR δ 177.14, 174.71, 147.14, 147.16, 122.59, 109.28, 108.12, 101.16, 24.09.

**Enantioselective Synthesis of Dibenzylbutyrolactone Lignans**

6.71 (d, 1H, J=1.8), 6.98 (d, 1H, J=1.8, J=8.1), 6.71 (d, 1H, J=8.1), 5.35 (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, 120.65, 113.41, 111.06, 70.71, 59.76, 58.82.

for 90 min. The reaction mixture was poured into 200 mL of saturated aqueous NH₄Cl and extracted with Et₂O (3 × 100 mL). The organic layers were dried over Na₂SO₄ and concentrated. The intermediate was dissolved in 40 mL of THF and 5 teaspoons of Raney nickel were added. The mixture was stirred at room temperature for 16 h and the supernatant liquid was decanted from the solid material. The solids were saturated aqueous NH₄Cl and extracted with Et₂O (3 mL). The organic layers were dried over Na₂SO₄ and concentrated. The crude product extracts were dried over Na₂SO₄ and concentrated. The crude adduct was purified by chromatography (silica gel, CH₂Cl₂) to give pure 18 (1.17 g, 71%) as a white solid: mp 94.5~95°C; [α]D 175.6, 141.6, 128.9, 128.5, 127.6, 103.8, 76.8, 47.5, 42.6, 39.4, 37.5, 34.1, 33.1, 31.0, 22.9, 21.5, 20.7, 15.4; HRMS calcd 330.218, found 330.218.

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Starting from **23a** (120 mg, 0.25 mmol) in 30 mL of THF was added at -90°C a solution of n-BuLi in hexanes (1.6 N, 5.9 mmol) to give pure **23b** (69 mg, 0.23 mmol), pure **23c** (24a) was synthesized following the same procedure as for compound **23a**. Starting from **11b** (0.24 g, 0.3 mmol) pure **23b** (65 mg, 56%) was obtained as a colorless viscous oil: [α]D 175.6; [α]D 175.6 (c 1.08, CHCl₃) (lit.16 [α]D 175.6 (c 0.7, CHCl₃)). Spectral data were identical to those reported in the literature.

To a solution of **23a** (1.54 g, 6.0 mmol) CH₂Cl₂, was added at -90°C a solution of n-BuLi in hexanes (1.6 N, 5.9 mmol) to give pure **23b** (69 mg, 0.23 mmol), pure **23c** (24a) was synthesized following the same procedure as for compound **23a**. Starting from **11c** (0.816 g, 1 mmol), **23b** (0.276 g, 62%) was obtained after purification by chromatography (silica gel, CH₂Cl₂) as a colorless oil: [α]D 175.6; [α]D 175.6 (c 1.08, CHCl₃) (lit.16 [α]D 175.6 (c 0.7, CHCl₃)). Spectral data were identical to those reported in the literature.
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Starting from 26,5 g (30 mmol), pure 26 as a mixture of isomers: 1H NMR (mixture of isomers) δ 7.0–6.75 (m, 6H), 4.75 (m, 1H), 4.26 (m, 1H), 3.90–3.60 (m, 8H), 3.89 (s, 6H), 3.87 (s, 6H), 3.15–3.10 (m, 2H); 13C NMR δ 155.07, 152.37, 149.03, 158.91, 133.36, 132.82, 131.62, 130.16, 129.34, 129.06, 128.79, 128.29, 127.51, 127.37, 127.20, 127.05, 126.93, 125.82, 125.31, 115.42, 112.52, 110.91, 110.54, 109.85, 76.97, 74.59, 70.92, 70.71, 70.38, 55.78, 55.57, 54.07, 51.11, 47.85, 39.33, 34.08, 31.28, 25.48, 22.52, 22.12, 20.09, 15.01; HRMS M+ − 2 × CH3S = 772 = 218 = 554, calcd 554.288, found 554.287.

(3S,4R,5R,7aS)-3-[[(3-Benzoyloxy)-4-methoxyphenyl]hydroxy[4-(3-Benzoyloxy)-4-methoxyphenyl]bis[(phenylthio)methyl]-5-(l-menthyl)methylidihydro-2(3H)-furanone (27) was synthesized according to the procedure for the preparation of 26. Starting from 7e (4.44 g, 10 mmol), 5a (2.58 g, 10 mmol), and 6e (7.5 g, 30 mmol), pure 27 (4.6 g, 50%) was obtained after triple chromatography (Al2O3, CH2Cl2) as a viscous oil: [α]D26 +98 (c 0.60, CHCl3); 1H NMR δ 7.4–6.6 (m, 24H), 6.60–6.50 (m, 2H), 5.1–4.95 (m, 2H), 5.05–4.90 (m, 2H), 4.93 (bs, 1H), 4.67 (d, 1H, J = 8.4), 3.74 (s, 6H), 3.40 (dt, 1H, J = 14.7, J = 6.6); 13C NMR δ 176.98, 149.21, 148.23, 147.38, 137.96, 136.73, 132.00, 131.16, 132.48, 131.81, 130.07, 128.97, 128.36, 128.27, 128.21, 128.12, 127.66, 127.57, 127.20, 127.05, 126.93, 126.82, 126.31, 115.24, 112.52, 110.91, 110.54, 109.65, 76.97, 74.59, 70.92, 70.71, 70.38, 55.78, 55.57, 54.07, 51.11, 47.85, 39.33, 34.08, 31.28, 25.48, 22.52, 22.12, 20.09, 15.01; HRMS M+ − C12H14S = 924 = 352 = 572 (C49H44O12S) found 924 = 352 = 572 (C49H44O12S), calcd 924 = 352 = 572 (C49H44O12S), found 572 = 256, 572 = 256.

(3R,4S,5S)-6aR)-3-[(3,4-Dimethoxyphenyl)hydroxy]methylidihydro-3H-furo[3,4-c]furan ((-)-Eudesmin, 30). To a stirred solution of 29 (200 mg, 0.47 mmol) in 40 mL of CH2Cl2 was added an N2 atmosphere at 0 °C and 20 pL of BF3OEt2 (48% BF3). The clear solution became brown immediately. After stirring for 4 days. Subsequent washing of the organic layers with 30 mL of brine, drying (Na2SO4), and evaporation of the solvent was followed by chromatography (silica gel, CH2Cl2 followed by ether) to afford after one crystallization from MeOH pure 30. To a stirred solution of 29 (200 mg, 0.47 mmol) in 40 mL of CH2Cl2 was added an N2 atmosphere at 0 °C and 2 mL of BF3OEt2 (48% BF3). The solution became brown immediately. After stirring for 16 h at 4 °C, 30 mL of saturated NaHCO3 was added and the mixture was extracted with CH2Cl2 (3 × 20 mL). Subsequent washing of the organic layers with 30 mL of brine, drying (Na2SO4), and evaporation of the solvent was followed by chromatography (silica gel, CH2Cl2 followed by ether) to afford after one crystallization from MeOH pure 30 (80 mg, 44%). mp 106–108 °C; [α]D26 +64.2 (c 1.1, CHCl3); 1H NMR δ 6.95–6.80 (m, 6H), 4.76 (d, 2H, J = 4.2), 4.26 (dd, 2H, J = 5.8, J = 9.0), 3.90–3.87 (m, 2H), 3.86 (s, 3H), 3.86 (s, 3H), 3.15–3.05 (m, 2H); 13C NMR δ 145.99, 148.26, 133.55, 118.29, 110.86, 109.94, 85.60, 71.55, 55.78, 55.76, 54.00; HRMS calcd 368.173, found 368.173.

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