Enantioselective Synthesis of Natural Dibenzyldutyrolactone 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-Alkoxybutenolides1,2

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A general and efficient method is described for the asymmetric synthesis of a variety of lignans. 5-(Menthylxyloxy)-2(5H)-furanones 5 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 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), (--)-pluviatolide (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 is known today, but in general the following structural classes are defined: dibenzylbutanones such as dibenzylbutyrolactones 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,5 interest in dibenzylbutyrolactones 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 (--)-pluviatolide also belong to the structural type 1 lignans whereas (--)-eudesmin is a typical member of class 2 lignans. First discovered in 1596 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 anticancer and antiviral agents14 whereas anticancer activity has also been found for dibenzocyclooctadiene lignans 4.

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.2,14–17 Methodology for the prepa-
oration of dibenzylbutane lignans include Stobbe condensation of aromatic aldehydes with succinic acid esters,\(^\text{18}\) oxidative coupling of propionic acid derivatives,\(^\text{19}\) nitrile oxide cycloaddition,\(^\text{16}\) malonic ester substitution\(^\text{20}\) and reductive cyclization of \(\alpha\)-bruno allylic esters.\(^\text{21}\)

Asymmetric syntheses of dibenzylbutyro lactone lignans by diastereoselective alkylation or aldol reactions of monobenzyl-substituted butyro lactones have been particularly successful.\(^\text{4,22}\) The required optically active butyro lactones are accessible from, for example, \(\beta\)-glutamic acid,\(^\text{22}\) via resolution of alkylated succinic and alkyl sulfoxides,\(^\text{24}\) whereas Posner et al.\(^\text{25}\) used the conjugate addition of benzyl Grignard reagents to a chiral \(p\)-tolenesulfinyl butenolide as a key step. Recently routes to enantiomerically pure dibenzylbutane lignans were developed by Magnusson et al.\(^\text{15}\) and Sibi et al.\(^\text{14}\) These routes were based, respectively, on conjugate addition to chiral dihydrofuryl ketones and a nitrile oxide cycloaddition–lipase mediated resolution procedure.

Elegant routes to aryltetralin and dibenzocyclooctadiene lignans using chiral oxazolines have been developed by Meyers and co-workers.\(^\text{26}\) The chromium carbene might be formed in a one-pot procedure by conjugate addition of benzylic dithioacetal anions to an appropriate benzylic electrophile (Schemes 1 and 3). quenching of the resulting lactone enolate anion followed by Meyers and coworkers.\(^\text{26}\) The chromium carbene route, recently reported by Miller and Hagedus,\(^\text{27}\) offers a valuable alternative.

Improvement of current methodology for the total synthesis of enantiomerically pure lignans is however highly warranted,\(^\text{14,28}\) as several routes are rather lengthy or multistep synthesis 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 synthons, with absolute stereoccontrol, to various structural classes of lignans.

This paper presents full details\(^\text{13}\) of our new approach to dibenzylbutyro lactone lignans and dioxabicyclo[3.3.0]-

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Enantioselective Synthesis of Dibenzylbutyrolactone Lignans

were prepared in high yields from the corresponding conversion of benzaldehydes. Dichloromethane and subsequently converted to benzyl n-butyllithium at -20 °C. The conjugate addition (Scheme 1) of a solution of the dithioacetal in THF with the corresponded aldehyde 9 was quenched by the benzyl bromide. In this case only the Michael addition took place and the resulting lactone enolate anion has not been quenched by the benzyl bromide.

The anions of dithioacetals 7 were generated by treatment of 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 are summarized in Table 1.

The diastereoselectivities exceed 98%. As expected, the bulky menthylxy moiety in directs the dithiaoacetal 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 arylidithiane moiety at the 4-position. As a consequence, the lactones 11 have the (3R,4R)-configuration as is found in most natural dibenzylbutan lignans. All the lactones 11 showed coupling constants J_H4_H5 < 0.5 Hz. The small coupling constants for the acetol proton (H₅) 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 J_H4_H5 in the range of 3-6 Hz are observed.

The results of the tandem conjugate addition-alkylation reaction to butenolide 5a are summarized in Scheme 3.

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>H</td>
<td>7b</td>
<td>80</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>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>9a</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>OCH₂O</td>
<td>7b</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6c</td>
<td>OMe</td>
<td>OBn</td>
<td>9c</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6d</td>
<td>OMe</td>
<td>OMe</td>
<td>9d</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

* Yields are of isolated pure products after crystallization.

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 menthylxy moiety in directs the dithiaoacetal 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 arylidithiane moiety at the 4-position. As a consequence, the lactones 11 have the (3R,4R)-configuration as is found in most natural dibenzylbutan lignans. All the lactones 11 showed coupling constants J_H4_H5 < 0.5 Hz. The small coupling constants for the acetol proton (H₅) 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 J_H4_H5 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 H₃, H₄, 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-dimethylbutan-2-one, (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-menthylxy)-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.


(36) It should be noted that after purification by chromatography, the addition products 11 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.


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 enantioerratically pure lignan (-)-enterodiol\textsuperscript{12,45} (25) (87% yield, \([a]^{23}_{D} = -13.2 (c = 1.0, \text{EtOH})).

It should be emphasized that according to \(\text{H} \text{NMR} \) no trace of epimers of 23a–c and 24a,c was found. This means that for partial racemization, epimerization both at C\textsubscript{3} and C\textsubscript{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 enantioerratically pure products.

It should be emphasized that besides the easy access to butyrolactones bearing identical C\textsubscript{3} and C\textsubscript{4} benzyl substituents, the method presented here allows facile routes and indicate enantioerratically pure products.

For the synthesis of (-)-eudesmin (30) we started with 5(S)(d-menthyl)-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 \(-90^\circ\text{C}\) provided lactone 26 in 62\% yield. Much to our surprise two diastereoisomers of 26 were obtained in a 60:40 ratio. Extensive NMR studies \((\text{H} \text{NMR}, \text{COSY, and NOESY})\) and conversion of 26 into (-)-eudesmin (30) unambiguously showed that the lithiated dithiane added trans with respect to the menthoxyl 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\textsubscript{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.\textsuperscript{28,33} The stereochemical result of the aldol step is in contrast with our previous findings\textsuperscript{46} (see also ref 33). Similar observations of low diastereoselectivity in the quenching of lactone enolates witharyl aldehydes have been made by Fujimoto and co-workers\textsuperscript{47} in the synthesis of racemic pinoresinol and in aldol reactions of lactone enolates lacking a C\textsubscript{4} substituent.\textsuperscript{33} In a related reaction, only one distinct product formation 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 \(\text{H} \text{NMR}\) or \(^{13}\text{C} \text{NMR}\). 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 \((-\)-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 C\textsubscript{3},C\textsubscript{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\textsubscript{3}OEt\textsubscript{2}. Subsequent multistep reduction of 28 with 4 equiv of LiAIH\textsubscript{4} afforded tetrol 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.
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-menthylxylo)-2(5H)-furanone (5b). 1H and 13C NMR data were in agreement with those reported for racemic eudesmin49 whereas an identical rotation (δH 6.42 (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,9R) of synthetic (−)-eudesmin (30) is based upon the absolute configuration50 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-(menthylxylo)-2(5H)-furanones 5a and 5b are excellent chiral syntheses 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 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 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,14,22 whereas Vandewalle and co-workers53 used the 5-(menthylxylo)butenolide approach in an elegant route to podophytoxins 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 data were recorded at 200 or 300 MHz. 13C NMR data were recorded at 50 or 75.5 MHz. CDC13 was used as solvent unless stated otherwise. Chemical shifts are reported in ppm relative to TMS. Coupling constants 4 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 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-(Menthylxylo)-2(5H)-furanones 5 were synthesized according to the procedure previously described.30 Bis(phenylthio)phenylmethane was prepared according to the procedure of Ager.54 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 Thiocetal Formation:33 3-(benzxylo)-1-(bis(phenylthio)methyl)benzenes (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 thiophenol 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 (15.7 g, 81%) was obtained after one crystallization from EtO/EtOH hexane as a yellow-white solid: mp 95.8–96.4 °C; 1H NMR δ 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, 128.58, 128.00, 127.81, 127.57, 120.52, 119.54, 114.03, 69.63, 60.32.

4-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); 1H NMR δ 7.38–7.18 (m, 10H), 6.98 (d, 1H, J = 1), 6.78 (d, 1H, J = J = 1), 6.62 (d, 1H, J = 7), 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, 127.30, 108.04, 107.66, 101.01, 59.96.

2-(Menthylxylo)-4-bis(phenylthio)methyl)1-methoxybenzene (7d) was synthesized according to the procedure for the preparation of 7a. Starting from 6d (8.3 g, 50 mmol), pure 7d (14.2 g, 80%) was obtained after one crystallization from EtOH/EtOAc: mp 68–69 °C (lit.15 mp 68–69 °C); 1H NMR δ 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, 134.41, 132.43, 131.88, 128.67, 127.51, 120.10, 110.76, 110.51, 59.97, 55.76.

Enantioselective Synthesis of Dibenzylbutyrolactone Lignans

CHCl3/hexane: mp 82.6-82.9 °C; 1H NMR δ 7.45-7.18 (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), 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, 55.82.

General Procedure for the Synthesis of Benzyl bromides:3-3-(Benzyloxy)-1-bromomethyl/benzene (9a). To a stirred solution of 9a (10.5 g, 50 mmol) in 50 mL of CHCl3 was added 2.2 g of NaBH4 (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 15.5 g of PBr5 (57 mmol) in 35 mL of ether. After stirring for 3 h at room temperature, the reaction mixture was poured into 100 mL of water, followed by extraction 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 (lit.39 mp 55 °C); 1H 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, 138.22, 136.80, 129.93, 126.99, 126.12, 126.85, 115.83, 115.02, 70.07, 33.56.

5-(Bromomethyl)-1-benzaldehyde (9b) was synthesized according to the procedure for the 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 (lit.35 mp 55 °C); 1H NMR δ 6.78 (s, 1H), 6.73 (d, 2H, J = 7), 6.48 (d, 1H, J = 7), 5.92 (s, 2H), 4.46 (s, 2H); 13C NMR δ 147.47, 147.61, 122.55, 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/EtOAc: mp 69.3-72.4 °C (lit.36 mp 70-72 °C, lit.35 mp 73 °C); 1H NMR δ 7.46-7.27 (m, 5H), 6.96-6.81 (m, 3H), 5.17 (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: 1H NMR δ 6.97-6.68 (m, 2H), 6.79 (m, 1H), 4.48 (s, 2H), 3.90 (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,5R)-5-(3-Benzyl Schlögl phenyl) methyl)-4-(13-benzodiox-3-yl)benzyl)phenyl)methyl)-5-(1-methoxy)-dihydro-2(3H)-furanone (11a). To a stirred solution of 7a (4.1 g, 10 mmol) in 50 mL of THF was added at -20 °C 8.7 mL of BuLi (1.6 N, 50 mmol), resulting in a dark red solution. This 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 stirred at -80 °C for 2 h and 1.29 mL of TMEDA was added, immediately followed by 9a (3.1 g, 11 mmol). The mixture was allowed to warm slowly to -20 °C, and stirred at this temperature for 16 h, poured into 300 mL of water, and extracted with 3 x 100 mL of CH2Cl2. The combined organic layers were washed with saturated NH4Cl (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) after which 11a (0.71 g, 67%) was obtained as a very viscous yellow oil. The solidified (52% remaining) sample of 11a (5.7 g, 1.1 g) was synthesized according to the procedure for the preparation of 9a. To a stirred solution of 8a in 100 mL of ether was added dropwise 15.5 g of PBr5 (57 mmol) in 35 mL of ether. After stirring for 3 h at room temperature, the reaction mixture was poured into 100 mL of water, followed by extraction 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 (lit.39 mp 55 °C); 1H 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 147.47, 147.61, 122.55, 109.28, 108.12, 101.16, 24.09.

(3R,4R,5R)-5-(3-Benzyl phenyl) methyl)-4-(13-benzodiox-3-yl)benzyl)phenyl)methyl)-5-(1-methoxy)-dihydro-2(3H)-furanone (11b). To a solution of 11a in 25 mL of THF was added at -90 °C 13.8 mL of n-BuLi in hexanes (1.6 N, 50 mmol). The mixture was stirred at -90 °C for 1 h and subsequently a solution of 5a (1.19 g, 5 mmol) in 40 mL of THF was added dropwise during 30 min and stirring at -90 °C was continued.

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 room temperature for 16 h and the supernatant was extracted four times with EtO₂ and the combined organic layers were dried over Na₂SO₄ and concentrated. The crude product 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 -96.9 (c 0.30, CHCl₃); IR (neat) 3058, 1752, 1412, 1286, 1225, 1037, 7659, 4750, 4266, 3944, 3750, 3410, 3307, 2526, 2290, 2195, 20.73, 15.48; HRMS calcd 330.219, found 330.218.

(3R,4R)-3-Methyl-4-(phenylmethyl)-5-(1-methoxy)-dihydro-2(3H)-furanone (19). To a solution of [bis(phenylmethyl)benzene] (1.54 g, 5 mmol) in 30 mL of THF was added at -90 °C a solution of n-BuLi in hexanes (1.6 N, 5.9 mmol). The mixture was stirred at room temperature for 16 h and the supematant was extracted with 3× EtO₂ and the combined organic layers were washed with water, dried over Na₂SO₄, and concentrated. The crude product 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 25° = -24.5 (c 1.08, CHCl₃); IR (neat) 3076, 1768, 1657, 1501, 1470, 1463, 1371, 1317, 1308, 1285, 1278, 1273, 1215, 1213, 1141, 112.7, 108.8, 108.2, 101.0, 71.1, 71.0, 65.9, 46.4, 41.1, 38.2, 34.7; HRMS calcd 446.173, found 446.173.

(3R,4R)-3,4-Bis[(3-hydroxyphenyl)methyl]dihydro-2(3H)-furanone (24a). To a solution of 23a (120 mg, 0.25 mmol) in 20 mL of EtOAc was added 50 mg of 5% Pd on carbon. The flask was charged with 10 mL of 10% H₂ in a balloon filled with H₂ gas and stirred at room temperature for 16 h. The Pd/C was filtered off over Celite and the filtrate was concentrated to give 67 mg of a colorless gum. This was crystallized from CHCl₃ to give 24a (61 mg, 82%) as slightly brown crystals: mp 132-134 °C; [α]D 25° = -38.4 (c 0.5, CHCl₃); lit.44b [α]D 25° = -40.5 (c 0.535, CHCl₃). Spectral data were identical to those reported in the literature.

(3R,4R)-4-(1,3-Benzodioxol-5-ylmethyl)-3-(4-hydroxy-3-methoxyphenyl)methyl)dihydro-2(3H)-furanone (25). To a stirred solution of 25a (0.816 g, 1 mmol) in 30 mL of THF was added at -90 °C a solution of n-BuLi in hexanes (1.6 N, 5.9 mmol). The mixture was stirred at room temperature for 3 h at -90 °C. During this period the color became yellow-orange. After 3 h at -90 °C, the reaction mixture with 200 mL of saturated aqueous NH₄Cl was extracted with EtO₂ (3 × 100 mL). The organic layers were dried over Na₂SO₄ and concentrated. The solids were extracted four times with EtO₂ and the combined organic extracts were dried over Na₂SO₄ and concentrated. The crude product was purified by chromatography (silica gel, CH₂Cl₂) to give pure 26a (0.263 g, 62%) as a colorless viscous oil: [α]D 25° = -22 (c 0.90, CHCl₃); IR (neat) 3030, 2953, 2893, 1752, 1412, 1368, 1297, 1286, 128.5, 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 calcd 478.214, found 478.214. Anal. Calcd for C₂₂H₂₂O₃: C, 76.70; H, 9.36. Found: C, 76.30; H, 9.05.
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175.90, 148.70, 148.36, 148.21, 1147.81, 1368.58, 1329.39, 1324.43, 1328.12, 1329.14, 1285.06, 1274.94, 1148.45, 1124.44, 110.21, 109.90, 109.14, 109.04, 106.06, 77.31, 73.34, 70.87, 55.36, 51.06, 47.70, 47.40, 38.94, 33.81, 30.98, 25.12, 22.28, 21.91, 20.69, 14.80; H NMR δ 28(40%) 7.4–6.5 (m, 16H), 5.83 (s, 1H), 4.77 (dd, 1H, J = 1.9, J = 8.0), 3.79 (s, 3H), 3.63 (s, 3H), 3.32 (dt, 1H, J = 10.4, J = 4.2), 3.08 (s, 1H), 2.54 (d, 1H, J = 1.9), 2.05–1.80 (m, 2H), 1.70–1.50 (m, 3H), 1.40–1.25 (m, 2H), 0.98–0.55 (m, 3H), 0.87 (d, 3H, J = 6.6), 0.79 (d, 3H, J = 7.3); 13C NMR δ 175.05, 148.77, 148.48, 148.21, 147.44, 136.46, 132.89, 132.43, 132.15, 132.77, 128.34, 128.06, 127.45, 126.10, 122.11, 119.24, 109.54, 109.32, 108.38, 77.49, 73.74, 70.74, 55.36, 52.65, 47.42, 43.01, 39.86, 34.06, 31.10, 28.68, 22.55, 21.79, 20.75, 15.07; HRMS M+ = 2 × C14H26O5S = 772 ± 218 = 554, calculated 554.288, found 554.287.

(3R,4R,5R,7aS)-3-[(3-(Benzyloxy)-4-methoxyphenyl)hydroyxymethyl]-4-(3-benzylxy)-4-methoxyphenyl)bisis(phenylthio)methyl)-5-(l-menthyloxy)dihydro-2(3H)-furanone (27) was synthesized according to the procedure for the preparation of 26. Starting from 7e (4.44 g, 10 mmol), 5a (2.38 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]25D = −98 (c 0.60, CHCl3); H 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 = 3.7, J = 10.6), 3.03 (d, 1H, J = 8.4), 2.75 (s, 1H), 2.14–1.90 (m, 2H), 1.92–1.80 (m, 2H), 1.36–1.12 (m, 2H), 0.98–0.58 (m, 3H), 0.86 (d, 3H, J = 6.6), 0.80 (d, 3H, J = 7.3), 0.69 (d, 3H, J = 6.6); 13C NMR δ 176.98, 148.49, 142.51, 142.23, 147.38, 136.79, 136.73, 132.00, 133.16, 132.48, 131.81, 130.07, 128.79, 128.26, 128.21, 128.12, 127.66, 127.57, 127.20, 127.05, 126.93, 120.82, 120.31, 115.24, 112.22, 110.91, 110.54, 100.65, 76.97, 74.59, 70.92, 70.71, 70.35, 57.58, 57.57, 54.07, 51.11, 47.85, 39.33, 34.06, 31.38, 28.48, 22.52, 22.12, 20.99, 15.01; HRMS M+ = C28H32S = C28H32O5 + 108 = 572 (C13H14O5S3), calculated 572.260, found 572.258.

(3R,4S,5S)-6aR)-3-(3,4-Dimethoxyphenyl)dihydro-methyl)-4-(3,4-dimethoxyphenyl)oxomethyl-5-(d-methylthoxy)-dihydro-3(2H)-furanone (28). To a stirred solution of 28 (200 mg, 0.47 mmol) in 40 mL of CH2Cl2 was added under an N2 atmosphere at 0 °C 20 μL of BF3·OEt2 (48% BF3). The clear 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 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 (is silica gel, CH2Cl2 followed by ether) to afford after one crystallization from MeOH pure 29 (30 mg, 44%); mp 106–108 °C; [α]25D = −64.2 (c 1.1, CHCl3); 1H NMR δ 6.85–6.70 (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), 1H NMR δ 142.99, 148.26, 133.35, 118.29, 110.86, 109.94, 85.80, 71.60, 55.81, 55.65, 55.64; HRMS (due to H2O elimination, MS identical to MS of eudesmin) M+ − H2O = 404 – 15 = 386, calculated 386.173, found 386.173.

1,4-Bis(3,4-dimethoxyphenyl)tetrahydro-[1S-(1α,3αq,4α-6αq)-1H,3H-furo[1,3-c]furan-3(3H)-yl]-oct-4-en-3-one (−)-Eudesmin, 30. To a stirred solution of 29 (200 mg, 0.47 mmol) in 40 mL of CH2Cl2 was added under an N2 atmosphere at 0 °C 20 μL of BF3·OEt2 (48% BF3). The clear 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 (is silica gel, CH2Cl2 followed by ether) to afford after one crystallization from MeOH pure 30 (30 mg, 44%); mp 106–108 °C; [α]25D = −64.2 (c 1.1, CHCl3); 1H NMR δ 6.85–6.70 (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), 1H NMR δ 142.99, 148.26, 133.35, 118.29, 110.86, 109.94, 85.80, 71.60, 55.81, 55.65, 55.64; HRMS calculated 386.173, found 386.173.

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