A General Approach to the Asymmetric Synthesis of Lignans: (−)-Methyl Piperitol, (−)-Sesamin, (−)-Aschantin, (+)-Yatein, (+)-Dihydroclusin, (+)-Burseran, and (−)-Isostegane

Dieter Enders,* Vivien Lausberg, Giuseppe Del Signore, Otto Mathias Berner

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Str. 1, 52074 Aachen, Germany
Fax +49(241)8092127; E-mail: enders@rwth-aachen.de

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Dedicated to Professor Hans-Joachim Gais on the occasion of his 60th birthday

Abstract: A highly efficient, diastereo- and enantioselective route was developed to access a great variety of lignans. The asymmetric synthesis of the 2,3-disubstituted γ-butyrolactones **9a**−**c** could be improved in the case of aldol reactions by employing 2.2 equivalents of LiCl as an additive to provide, after purification, highly diastereo- and enantioenriched starting materials for the synthesis of the furofuran lignans (−)-methyl piperitol, (−)-sesamin, and (−)-aschantin. Furthermore, the γ-butyrolactone **15** was converted into dibenzylbutyrolactone lignan (+)-yatein, the dibenzylbutandiol type (+)-dihydroclusin, the tetrahydrofuran type (+)-burseran, and the dibenzocyclooctadiene type (−)-isostegane.

Key words: α-amino nitriles, asymmetric synthesis, chiral auxiliary, lignans, aldol reaction

Lignans constitute a class of natural products with a great diversity in structure as can be exemplified with a possible classification according to their carbon skeleton (Figure 1).[1]

These compounds possess significant pharmacological activities, especially antiviral and antitumor properties, and have therefore been the target of extensive synthetic research.[2,3]

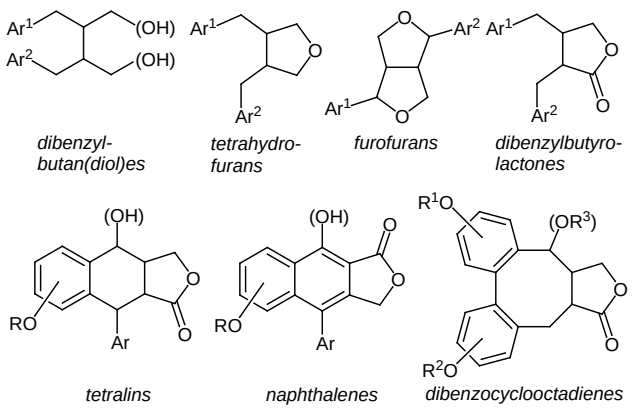

Figure 1 Classification of lignans.

Podophyllotoxin (**1**), for example, has been under continuous investigation owing to its significant anti-tumor activity. However, it is unsuitable for medicinal use due to side-effects and therefore several analogs of **1** have been prepared in order to enhance its pharmacological profile. Among the analogs of (**1**), some have found clinical use.[1,2,4] Moreover, the derivative isodeoxypodophyllotoxin (**2**) shows some biological activity. Furthermore, certain other compounds belonging to different subgroups of lignans such as steganacin (**3**) and burseran (**4**)[5] exhibit anti-tumor activity. On the other hand, some furofuran lignans such as methyl piperitol (**5**) possess platelet activating factor (PAF) antagonist activity (Figure 2).[6] Thus, lignans possess a pharmacological array of properties which evoked our interest in developing a general route to access this valuable class of compounds.

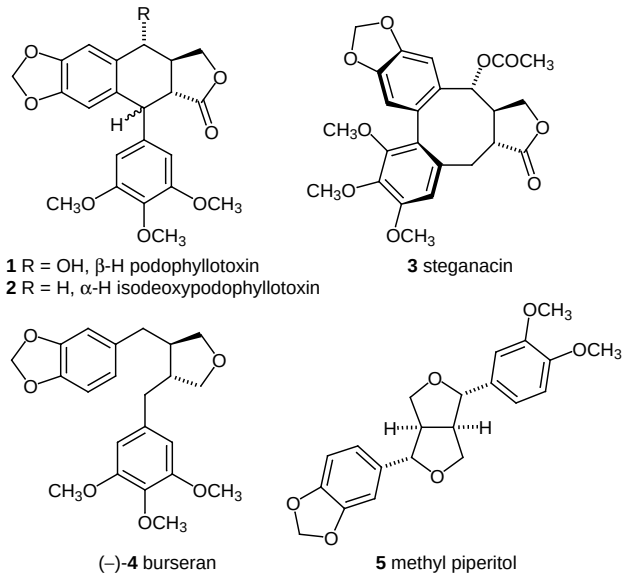

Figure 2 Some pharmacologically active lignans.

We have recently developed a highly efficient diastereo- and enantioselective route via enantiopure α-amino nitriles to 2,3-dibenzylated γ-butyrolactones **9**, which are very important building blocks in the synthesis of lignans (Scheme 1).[7] The synthesis commenced with an asymmetric Strecker reaction using different aromatic aldehydes and the enantiomerically pure secondary amine **6** as starting materials followed by a Michael reaction of lithiated **7** to 5*H*-furan-2-one to give the 1,4-adducts **8** in good

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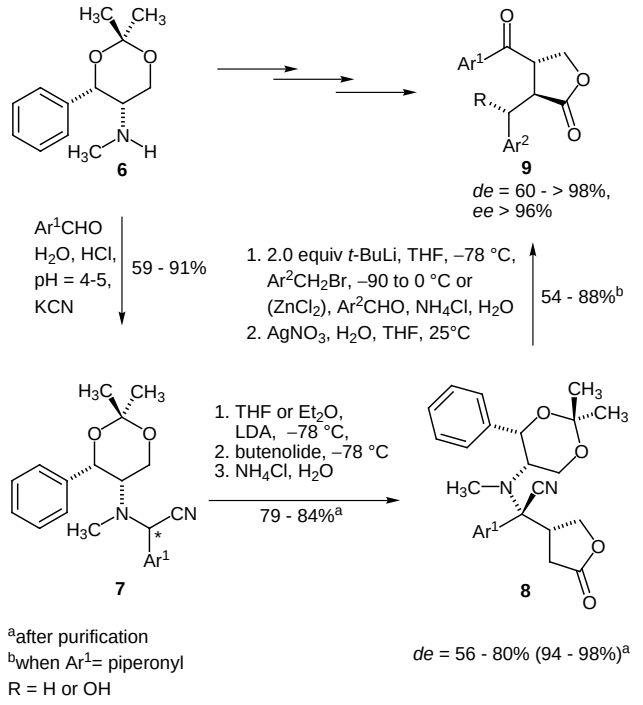
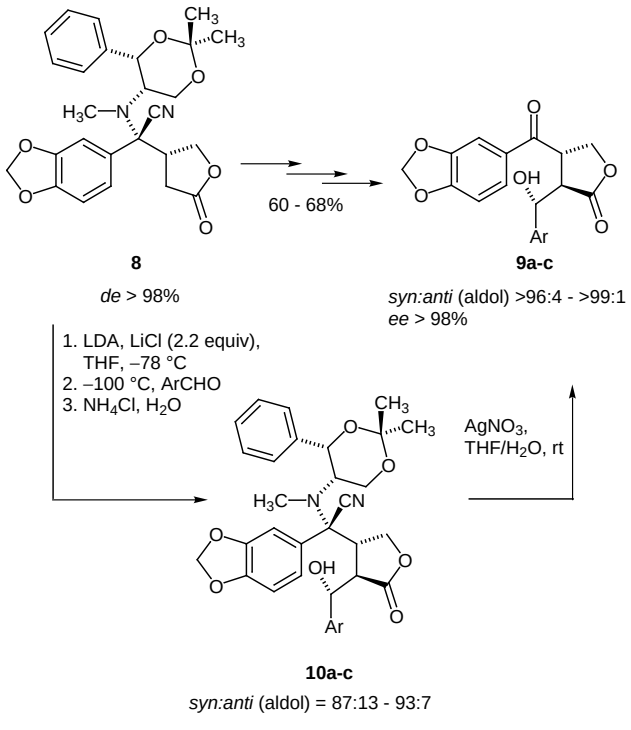


Scheme 1



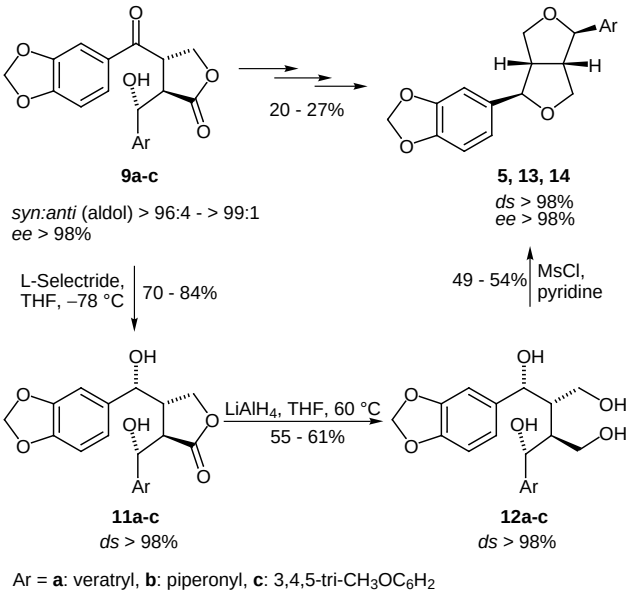
Scheme 2

yields and diastereoselectivities. Alkylation of **8** provided the products **9** after cleavage of the auxiliary with excellent induction (de ≥ 98%, ee = 96–97%), whereas the *syn*/*anti* selectivity of the aldol addition (de = 60–75%) still required some improvement.

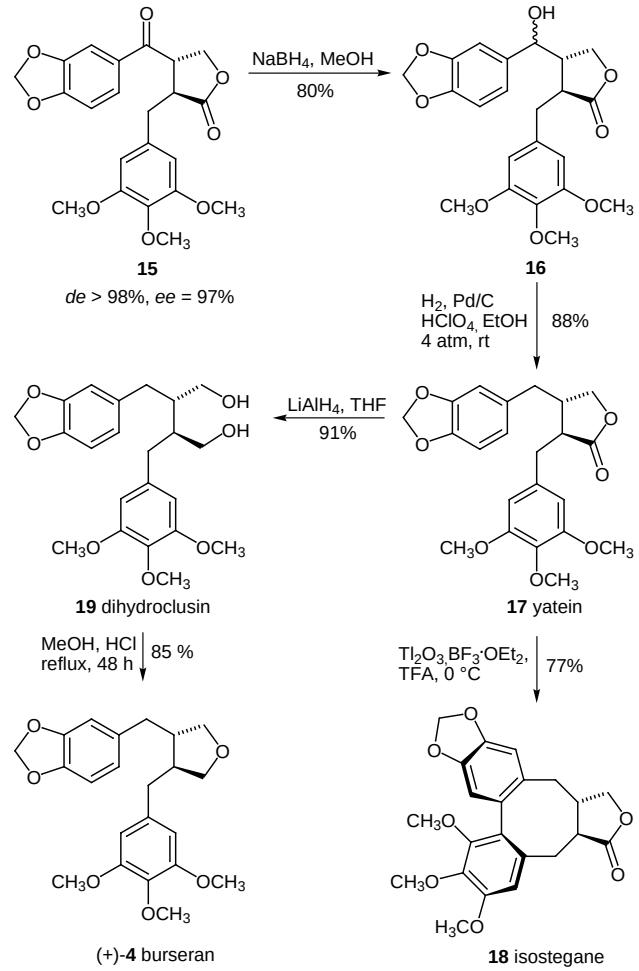
Initial experiments to increase the selectivity of the aldol reaction via transmetalation of the intermediate lithium lactone enolate were met with moderate success: $ZnBr_2$, ZnI_2, $MgBr_2$, $ClTi(OiPr)_3$ and $BrTi(NEt_2)_3$, for example, did not improve stereocontrol, whereas $ZnCl_2$ had a slightly favorable effect. However, by using LiCl as additive the stereocontrol could now be increased. Best results were obtained by using 2.2 equivalents of LiCl and by adding the aldehyde at –100 °C. This resulted in a *syn*/*anti* ratio of 87:13–93:7 where the *syn/anti* nomenclature refers to the stereochemistry between the alcohol group and the adjacent stereocenter (Scheme 2). Due to the instability of the obtained alcohols **10a**–**c**, a purification of the products was only possible after the cleavage of the auxiliary resulting in even higher ratios *syn*/*anti* (aldol) of 96:4–99:1. The enantiomeric excesses determined via ^1H NMR shift experiments using Pirkle-alcohol as chiral cosolvent was found to be ≥ 98%.[7,8]

The aldol compounds **9a**–**c** were converted into natural products following the procedure of Ogiku et al.[9] Reduction of **9a**–**c** was performed with L-selectride at –78 °C to give the diol lactones **11a**–**c** in good yield and high diastereomeric purity. Performing the lithium aluminium hydride reduction at 60 °C for 1 hour gave the tetraols **12a**–**c** in moderate yield. Finally, mesylation of the primary hydroxyl groups with methanesulfonyl chloride in pyridine followed by spontaneous intramolecular double cyclization provided (–)-methyl piperitol (**5**)[10] {$[\alpha]_D^{22}$ –73.0 (c = 0.60, $CHCl_3$), lit.[11] $[\alpha]_D^{22}$ +73.6 (c = 0.35, $CHCl_3$)}, (–)-sesamin (**13**)[12] {$[\alpha]_D^{22}$ –71.0 (c = 0.30, $CHCl_3$), lit.[13] $[\alpha]_D^{22}$ +68.7 (c = 0.40, $CHCl_3$)} and (–)-aschantin (**14**) {$[\alpha]_D^{22}$ –64.0 (c = 0.55, $CHCl_3$), lit.[13] $[\alpha]_D^{22}$ +65.0 (c = 0.40, $CHCl_3$)} in high optical purity (Scheme 3). To the best of our knowledge, this constitutes the first synthesis of aschantin and the first asymmetric synthesis of methyl piperitol.

We were interested in extending this methodology to other lignans. The most plausible way to reach this goal is to synthesize yatein (**17**), which is a springboard to other classes of lignans, in an efficient way. A suitable starting material for this is our previously synthesized virtually diastereo- and enantiopure *trans*-2,3-disubstituted γ-butyrolactone **15**.[7] Reduction of the ketone was accomplished with sodium borohydride in methanol to give the alcohol **16** as a pair of epimers (83:17) in 80% yield. Catalytic hydrogenolysis[14] of **16** gave (+)-yatein (**17**)[15] in very good yield (88%) and optical purity {$[\alpha]_D^{22}$ +30.6 (c = 1.10, $CHCl_3$), lit.[16b] $[\alpha]_D^{22}$ –30.0 (c = 0.15, $CHCl_3$)}. Having opened a very efficient access to the tetrahydrofuran lignan yatein (**17**), we decided to continue by synthesis of the dibenzocyclooctadiene type compound, (–)-isostegane (**18**). Modification of the oxidative coupling by Planchenault et al.[17] of **17** with Tl_2O_3 in the presence of $BF_3{\cdot}OEt_2$ in neat TFA gave (–)-isostegane (**18**)[18] {$[\alpha]_D^{22}$ –156.9 (c = 2.8, $CHCl_3$), lit. [18a] $[\alpha]_D^{22}$ +154.0 (c = 0.7, $CHCl_3$)} in very good yield (77%). This also constitutes a formal total synthesis of the known anti-tumor lignan ste-



Scheme 3



Scheme 4

ganacin (**3**), as Koga and co-workers[19] elegantly made this transformation earlier. Furthermore, by changing conditions of the oxidative coupling, access to tetralin lignans can be obtained by the transformation of yatein to isodeoxypodophyllotoxin (**2**).[17,20] We were also interested in accessing the dibenzylbutandiole and tetrahydrofuran lignans and thus subjected yatein to reductive conditions with lithium aluminium hydride to give (+)-dihydroclusin (**19**)[21] {$[\alpha]_D^{22}$ +27.0 (c = 1.15, $CHCl_3$), lit.[22b] $[\alpha]_D^{22}$ −27.13 (c = 0.24, $CHCl_3$)} in excellent yield (91%). Refluxing **19** in a methanolic solution containing HCl analogous to Ward and co-workers[23] afforded the anti-tumor lignan (+)-burseran (+)-(**4**)[24] {$[\alpha]_D^{22}$ +37.8 (c = 2.0, $CHCl_3$); lit.[25,18a] $[\alpha]_D^{22}$ −34.8 (c = 0.93, $CHCl_3$)} in 85% yield.

In conclusion, we have increased the diastereoselectivity of our previously reported aldol reaction by using LiCl as additive. The obtained 2,3-disubstituted γ-butyrolactones were successfully converted into a broad range of different lignans. By using the other enantiomer of amine **6**, one can easily access both enantiomers of the lignans demonstrating the high diversity and utility of this methodology.

All moisture-sensitive reactions were carried out by using standard Schlenk techniques unless stated otherwise. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from Na-Pb alloy, CH_2Cl_2 from CaH_2 under argon. Reagents of commercial quality were used from freshly opened containers or purified by common methods. *n*-BuLi (1.6 M in hexane) was purchased from Merck, Darmstadt. Preparative column chromatography: Merck silica gel 60, particle size 0.040−0.063 mm (230−240 mesh, flash). Analytical TLC: silica gel 60 F_{254} plates from Merck, Darmstadt. Optical rotation values were measured on a Perkin−Elmer P241 polarimeter; solvents used were of Merck UVASOL-quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 (CI 100 eV; EI 70 eV) spectrometer. High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer. IR spectra were taken on a Perkin−Elmer FT/IR 1760. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded on Gemini 300 or Varian Inova 400 ($CDCl_3$ as solvent, TMS as internal standard) spectrometers.

2,3-Disubstituted γ-Butyrolactones 9a−c; General Procedure 1 (GP1)

Anhyd LiCl (2.2 equiv) was put in a dried Schlenk-flask after which diisopropyl amine (1.2 equiv) and anhyd THF (3 mL per mmol diisopropyl amine) were added. The flask was cooled to –78 °C and *n*-BuLi (1.2 equiv, 1.6 M) was added dropwise. The soln was stirred at 0 °C for 30 min. This mixture was added via a syringe pump to another flask cooled to −78 °C containing the Michael adduct **8** (1 equiv) in anhyd THF (10 mL per mmol Michael adduct). After 90 min, the soln was cooled to −100 °C and the corresponding aromatic aldehyde (1.2 equiv) dissolved in anhyd THF (2 mL per mmol aldehyde) was added very slowly via a syringe pump. After 20 min at −100 °C the cooling bath was removed and the reaction was quenched by adding quickly sat. NH_4Cl soln under vigorous stirring. The mixture was allowed to warm to r.t., H_2O was added and the organic phase was separated. The aq phase was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with sat. NaCl soln, dried with $MgSO_4$ and evaporated in vacuo. The crude product was dissolved in THF (10 mL per mmol aldol product) and the flask was covered with aluminium foil. $AgNO_3$ (2 N, 4 equiv) was added and the mixture was stirred 15 min (TLC control) after which Et_2O (20 mL per mmol aldol product) was added and

stirring was continued for an additional 30 min. The Ag-residues were removed via filtration and washed with Et_2O and H_2O. After partitioning, the aq phase was extracted with Et_2O (3 × 5 mL). The combined org. layers were washed with sat. NaCl soln (3 × 5 mL), dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography or recrystallization.

Lactone Diols 11a–c; General Procedure 2 (GP2)

Alcohol **9a–c** (1 equiv) was dissolved in anhyd THF (16 mL per mmol alcohol) and cooled to −78 °C. L-Selectride (1.3 equiv) was added dropwise and after 30 min the cooling bath was removed. The mixture was hydolysed with H_2O and immediately partitioned between H_2O and EtOAc. After removal of the aq phase, the organic layer was washed with sat. NaCl soln (2 × 5 mL), dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography.

Tetraols 12a–c; General Procedure 3 (GP3)

$LiAlH_4$ (10 equiv) was suspended with anhyd THF (2 mL per mmol $LiAlH_4$) in a Schlenk-flask equipped with a condenser. The suspension was heated to 60 °C and diol **11a–c** (1 equiv) dissolved in anhyd THF (10 mL per mmol diol) was slowly injected via a syringe pump. After 1 h at 60 °C the soln was allowed to cool to r.t., hydrolyzed with 10% NaOH soln and stirred for an additional 10 min. The precipitate was removed via filtration and was extracted twice by refluxing in THF. The combined filtrates were evaporated in vacuo. The crude product was purified via column chromatography.

Furofuran Lignans 5,13,14; General Procedure 4 (GP4)

To the tetraol **12a–c** dissolved in anhyd CH_2Cl_2 (10 mL per mmol tetraol) was added at 0°C, pyridine (0.8 mL per mmol tetraol) and MsCl (3 equiv). The reaction mixture was allowed to warm to r.t. overnight. The mixture was washed with H_2O, 10% soln of citric acid (2 × 5 mL), and finally with sat. NaCl soln. The organic layer was dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography.

(3*R*,4*S*)-4-(1,3-Benzodioxol-5-ylcarbonyl)-3-[(*R*)-1-(3,4-dimethoxyphenyl)-1-hydroxymethyl]tetrahydro-2-furanone (9a)

Compound **8**[7] (1.020 g, 2.20 mmol) was subjected to the aldol reaction conditions followed by the cleavage of the auxiliary according to GP1. Work-up and column chromatography (Et_2O–pentane, 10:1) gave **9a** (600 mg, 68% over two steps) as a colorless solid; mp 133 °C.

$[\alpha]_D^{22}$ +62.0 (c = 0.99, $CHCl_3$).

syn:*anti* (aldol) = 93:7 (^{1}H NMR); ≥ 99:1 (after column chromatography, ^{1}H NMR); ee ≥ 98% (determined with ^{1}H NMR shift reagent: Pirkle-alcohol).

The analytical data are identical to those reported earlier.[7]

(3*R*,4*S*)-4-(1,3-Benzodioxol-5-ylcarbonyl)-3-[(*R*)-1-(1,3-benzodioxol-5-yl)-1-hydroxymethyl]tetrahydro-2-furanone (9b)

Compound **8**[7] (1.020 g, 2.20 mmol) was subjected to the aldol reaction conditions followed by the cleavage of the auxiliary according to GP1. Work-up and recrystallization from CH_2Cl_2 gave **9b** (550 mg, 65% over two steps) as a colorless solid; mp 146 °C.

$[\alpha]_D^{22}$ +74.0 (c = 1.00, acetone).

syn:*anti* (aldol) = 88:12 (^{1}H NMR); ≥ 96:4 (after recrystallization, ^{1}H NMR); ee ≥ 98% (determined with ^{1}H NMR shift reagent: Pirkle-alcohol).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.22 (dd, 1 H, *J* = 2.7, 6.0 Hz, C*H*CO_2), 4.10 (dd, 1 H, *J* = 5.7, 8.4 Hz, C*H*HOC=O), 4.38 (ddd, 1 H, *J* = 5.7, 6.0, 8.4 Hz, C*H*CH_2OC=O), 4.57 (t, 1 H, *J* = 8.4 Hz, CH*H*OC=O), 5.13 (m, br, 1 H, C*H*OH), 5.89 (s, 1 H, OC*H*HO), 5.93 (s, 1 H, OCH*H*O), 6.03 (d, br, 1 H, *J* = 3.7 Hz, O*H*), 6.11 (s, 2 H, OCH_2O), 6.72 (d, 1 H, *J* = 8.1 Hz, arom. C*H*), 6.83 (d, 1 H, *J* = 8.4 Hz, arom. C*H*), 6.86 (s, 1 H, arom. C*H*), 6.89 (d, 1 H, *J* = 8.4 Hz, arom. C*H*), 7.02 (d, 1 H, *J* = 1.7 Hz, arom. C*H*), 7.24 (dd, 1 H, *J* = 1.7, 8.4 Hz, arom. C*H*).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.44 (*C*HCH_2OC=O), 51.63 (*C*HCO_2), 68.70 (*C*H_2OC=O), 69.84 (*C*HOH), 100.70, 102.03 (O*C*H_2O), 106.15, 107.43, 107.60, 107.81, 118.56, 124.76 (arom. *C*H), 129.56, 136.40, 146.08, 147.01, 147.65, 151.69 (arom. *C*), 176.02 (O*C*=O), 196.26 (*C*=O).

IR (KBr): 3469 (s, br, OH), 3072 (vw), 2984 (vw), 2902 (w), 2881 (m), 1754 (vs, C=$O_{lactone}$), 1673 (vs, C=$O_{arylketone}$), 1605 (s), 1500 (vs), 1446 (vs), 1414 (m), 1386 (m), 1362 (m), 1255 (vs), 1194 (s), 1176 (s), 1134 (m), 1112 (m), 1094 (m), 1079 (m), 1038 (vs), 937 (s), 926 (s), 875 (m), 820 (m), 807 (m), 788 (m), 744 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 384 (0.3) [$M^{+\cdot}$], 234 (12), 151 (5), 150 (40), 149 (100), 121 (23), 91 (6), 65 (14), 63 (14), 62 (5).

Anal. Calcd for $C_{20}H_{16}O_8$ (384.34): C, 62.50; H, 4.20. Found: C, 62.25; H, 4.17.

(3*R*,4*S*)-4-(1,3-Benzodioxol-5-ylcarbonyl)-3-[(*R*)-1-hydroxy-1-(3,4,5-trimethoxyphenyl)methyl]tetrahydro-2-furanone (9c)

Compound **8**[7] (1.020 g, 2.20 mmol) was subjected to the aldol reaction conditions followed by the cleavage of the auxiliary according to GP1. Work-up and column chromatography (Et_2O–pentane, 30:1) gave **9c** (570 mg, 60% over two steps) as a colorless solid; mp 143 °C.

$[\alpha]_D^{22}$ +58.0 (c = 1.01, $CHCl_3$).

syn:anti (aldol) = 87:13 (^{1}H NMR); ≥ 98:2 (after column chromatography, ^{1}H NMR); ee ≥ 98% (determined with ^{1}H NMR shift reagent: Pirkle-alcohol).

The analytical data are identical to those reported earlier.[7]

(3*R*,4*S*)-4-[(*R*)-1-(1,3-Benzodioxol-5-yl)-1-hydroxymethyl]-3-[(*R*)-1-(3,4-dimethoxyphenyl)-1-hydroxymethyl]tetrahydro-2-furanone (11a)

Ketone **9a** (550 mg, 1.37 mmol) was reduced with L-selectride according to GP2. Work-up and column chromatography (CH_2C1_2–MeOH, 30:1) gave **11a** (410 mg, 75%) as a colorless solid; mp 165 °C.

$[\alpha]_D^{22}$ +20.7 (c = 0.95, acetone).

ds ≥ 98% (^{1}H NMR).

IR (KBr): 3500 (vs, br, OH), 3055 (w), 3005 (m), 2962 (m), 2941 (m), 2910 (m), 2836 (m), 1742 (vs, C=$O_{lactone}$), 1640 (w), 1609 (w), 1595 (m), 1517 (vs), 1505 (vs), 1487 (s), 1469 (s), 1439 (s), 1414 (m), 1398 (m), 1307 (s), 1256 (vs), 1236 (vs), 1217 (vs), 1199 (vs), 1153 (m), 1135 (s), 1081 (s), 1028 (vs), 989 (m), 940 (m), 916 (m), 864 (m), 818 (m), 790 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDC1_3$): δ = 2.10 (d, 1 H, *J* = 2.7 Hz, OH), 2.76 (dddd, 1 H, *J* = 4.0, 4.0, 4.4, 8.4 Hz, C*H*CH_2C = O), 2.77 (d, 1 H, *J* = 4.7 Hz, OH), 2.94 (dd, 1 H, *J* = 3.7, 4.4 Hz, $CHCO_2$), 3.80 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.17 (dd, 1 H, *J* = 4.4, 9.0 Hz, C*H*HOC=O), 4.29 (dd, 1 H, *J* = 8.4, 8.7 Hz, CH*H*OC=O), 4.62 (dd, 1 H, *J* = 4.0, 4.7 Hz, C*H*OH), 5.21 (dd, 1 H, *J* = 3.0, 5.0 Hz, C*H*OH), 5.93 (d, 1 H, *J* = 1.7 Hz, OC*H*HO), 5.96 (d, 1 H, *J* = 1.7 Hz, OCH*H*O), 6.39 (d, 1 H, *J* = 1.4 Hz, ArH), 6.58 (dd, 1 H, *J* = 1.7, 8.4 Hz, ArH), 6.60 (d, 1 H, *J* = 1.7 Hz, ArH), 6.63 (d, 1 H, *J* = 8.1 Hz, ArH), 6.76 (d, 1 H, *J* = 8.4 Hz, ArH), 6.83 (dd, 1 H, *J* = 1.4, 8.4 Hz, ArH).

^{13}C NMR (75 MHz, $CDC1_3$): δ = 42.59 (*C*HCH_2C=O), 48.94 (*C*HCO_2), 55.67, 55.76 (OCH_3), 70.62 (*C*H_2C=O), 73.16, 75.09 (CHOH), 101.37 (OCH_2O), 105.80, 107.82, 108.53, 110.73, 117.61, 118.73 (ArH), 133.39, 134.74, 147.30, 147.91, 148.47, 148.85 (Ar), 178.61 (OC=O).

MS (EI, 70 eV): *m/z* (%) = 402 (0.3) [$M^{+\cdot}$], 167 (14), 166 (100), 165 (52), 151 (27), 149 (10), 137 (7), 123 (8), 122 (5), 121 (5), 119 (6), 109 (6), 107 (5), 105 (6), 95 (30), 93 (8), 85 (5), 83 (6), 80 (5), 79 (15), 77 (24), 71 (6), 69 (7), 67 (9), 65 (12), 63 (7).

Anal. Calcd for $C_{21}H_{22}O_8$ (402.40): C, 62.68; H, 5.51. Found: C, 62.30; H, 5.63.

(3*R*,4*S*)-3,4-Di[(*R*)-1-(1,3-benzodioxol-5-yl)-1-hydroxymethyl]tetrahydro-2-furanone (11b)

Ketone **9b** (480 mg, 1.25 mmol) was reduced with L-Selectride according to GP2. Work-up and column chromatography (CH_2C1_2–MeOH, 30:1) gave **11b** (340 mg, 70%) as a colorless solid; mp 186 °C.

$[\alpha]_D^{22}$ +26.6 (c = 1.01, acetone).

ds ≥ 98% (^{1}H NMR).

IR (KBr): 3559 (vs, OH), 3414 (vs, br, OH), 3067 (w), 2969 (m), 2903 (s), 1753 (vs, $C{=}O_{lactone}$), 1501 (vs), 1443 (s), 1395 (m), 1318 (w), 1257 (vs), 1234 (s), 1192 (m), 1109 (w), 1093 (w), 1076 (m), 1068 (m), 1035 (s), 993 (w), 938 (m), 906 (w), 866 (vw), 810 (w), 785 (w), 661 (vw) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.50 (m, br, 1 H, C*H*CO_2), 2.54 (m, br, 1 H, C*H*CH_2C=O), 4.23 (dd, 1 H, *J* = 1.9, 8.3 Hz, C*H*HOC=O), 4.35 (dd, 1 H, *J* = 8.2, 8.3 Hz, CH*H*OC=O), 4.56 (m, br, 1 H, C*H*OH), 4.91 (m, br., 1 H, C*H*OH), 5.49 (d, 1 H, *J* = 4.1 Hz, OH), 5.67 (d, 1 H, *J* = 3.8 Hz, OH), 5.90 (d, 1 H, *J* = 1.1 Hz, OC*H*HO), 5.91 (d, 1 H, *J* = 1.1 Hz, OCH*H*O), 5.93 (d, 1 H, *J* = 1. 1 Hz, OC*H*HO), 5.95 (d, 1 H, *J* = 1. 1 Hz, OCH*H*O), 6.36 (d, 1 H, *J* = 1.1 Hz, ArH), 6.43 (s, 1 H, ArH), 6.44 (d, 1 H, *J* = 8.2 Hz, ArH), 6.49 (dd, 1 H, *J* = 1.1, 8.0 Hz, ArH), 6.57 (d, 1 H, *J* = 8.0 Hz, ArH), 6.59 (d, 1 H, *J* = 8.0 Hz, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.19 (*C*HCH_2C=O), 47.65 (*C*HCO_2), 71.36 (*C*HOH), 71.72 (*C*H_2OC=O), 72.62 (*C*HOH), 100.57, 100.64 (O*C*H_2O), 105.40, 105.48, 106.94, 107.03, 117.90, 117.98 (Ar), 136.17, 136.26, 145.40, 145.55, 146.43, 146.50 (Ar), 178.53 (OC=O).

MS (EI, 70 eV): *m/z* (%) = 386 (1) [$M^{+\cdot}$], 236 (23), 152 (9), 151 (84), 150 (77), 149 (100), 132 (6), 131 (6), 123 (18), 122(6), 121 (35), 119 (7), 103 (9), 93 (47), 91 (14), 77 (11), 66 (6), 65(47), 64 (9), 63 (42), 62 (17), 61 (10), 58 (5), 57 (13), 55 (6), 53 (10), 51 (11), 50 (9).

Anal. Calcd for $C_{20}H_{18}O_8$ (386.36): C, 62.18; H, 4.70. Found: C, 62.67; H, 5.07.

(3*R*,4*S*)-4-[(R)-1-(1,3-Benzodioxol-5-yl)-1-hydroxymethyl]-3-[(*R*)-1-hydroxy-1-(3,4,5-trimethoxyphenyl)methyl]tetrahydro-2-furanone (11c)

Ketone **9c** (486 mg, 1.13 mmol) was reduced with L-Selectride according to GP2. Work-up and column chromatography (CH_2C1_2–MeOH, 30:1) gave **11c** (410 mg, 84%) as a colorless solid; mp 174 °C.

$[\alpha]_D^{22}$ +18.4 (c = 1.00, acetone).

ds ≥ 98% (^{1}H NMR).

IR (KBr): 3478 (s, br, OH), 2971 (m), 2941 (m), 2907 (w), 2840 (w,), 1758 (vs, $C{=}O_{lactone}$), 1595 (s), 1506 (vs), 1492 (s), 1461 (s), 1420 (s), 1389 (m), 1334 (m), 1238 (vs), 1191 (s), 1127 (vs), 1080 (s), 1035 (vs), 926 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDC1_3$): δ = 2.72 (dddd, 1 H, *J* = 3.6, 3.8, 4.1, 8.2 Hz, C*H*CH_2C=O), 2.84 (dd, 1 H, *J* = 3.6, 3.8 Hz, CHCO_2), 3.16 (d, 1 H, *J* = 3.3 Hz, OH), 3.65 (d, 1 H, *J* = 5.2 Hz, OH), 3.76 (s, 9 H, OCH_3), 4.22 (dd, 1 H, *J* = 3.8, 8.8 Hz, C*H*HOC=O), 4.36 (dd, 1 H, *J* = 8.2, 8.8 Hz, CH*H*OC=O), 4.61 (dd, 1 H, *J* = 3.6, 3.8 Hz, C*H*OH), 5.11 (dd, 1 H, *J* = 3.8, 4.1 Hz, C*H*OH), 5.89 (d, 1 H, *J* = 1.4 Hz, OC*H*HO), 5.94 (d, 1 H, *J* = 1.6 Hz, OCH*H*O), 6.34 (s, 2 H, ArH), 6.35 (d, 1 H, *J* = 1.4 Hz, ArH), 6.50 (dd, 1 H, *J* = 1.4, 8.0 Hz, ArH), 6.54 (d, 1 H, *J* = 8.0 Hz, ArH).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 42.56 (*C*HCH_2C=O), 48.82 (*C*HCO_2), 56.00 (*m*-OCH_3), 60.78 (*p*-OCH_3), 71.26 (*C*H_2C=O), 73.04, 74.73 (CHOH), 101.40 (OCH_2O), 102.45, 105.68, 107.65, 118.50 (Ar), 134.85, 136.83, 136.92, 147.07, 147.78, 152.98 (Ar), 179.31 (OC=O).

MS (EI, 70 eV): *m/z* (%) = 432 (4) [$M^{+\cdot}$], 236 (10), 219 (7), 198 (5), 197 (29), 196 (100), 195 (6), 182 (6), 181 (53), 169 (8), 153 (9), 152 (6), 151 (33), 150 (10), 149 (17), 138 (7), 135 (6), 125 (26), 123 (11), 121 (7), 111 (5), 110 (18), 97 (6), 95 (12), 93 (31), 91 (5), 85 (6), 83 (6), 82 (5), 81 (6), 79 (6), 77 (10), 71 (6), 70 (6), 69 (8), 67 (7), 66 (5), 65 (14), 63 (5), 57 (14), 56 (5), 55 (13), 53 (7), 51 (7), 45 (5).

Anal. Calcd for $C_{22}H_{24}O_9$ (432.43): C, 61.11; H, 5.59. Found: C, 61.15; H, 5.97.

(1*R*,2*S*,3*S*,4*R*)-1-(1,3-Benzodioxol-5-yl)-4-(3,4-dimethoxyphenyl)-2,3-di(hydroxymethyl)butan-1,4-diol (12a)

Diol **11a** (241 mg, 0.60 mmol) was reduced with $LiAlH_4$ (228 mg, 6.00 mmol) according to GP3. Purification via column chromatography (CH_2Cl_2–MeOH,10:1) gave **12a** (135 mg, 55%) as a colorless solid; mp 181 °C.

$[\alpha]_D^{22}$ +37.0 (c = 1.00, acetone).

IR (KBr): 3414 (s, br, OH), 3071 (w), 3007 (m), 2959 (m), 2941 (m), 2892 (m), 2860 (s), 1518 (vs), 1491 (s), 1465 (s), 1438 (m), 1413 (m), 1381 (w), 1365 (w), 1323 (m), 1257 (vs), 1236 (vs), 1208 (m), 1157 (m), 1138 (s), 1105 (w), 1066 (s), 1026 (vs), 991 (w), 927 (m), 892 (m), 874 (w), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.94 (m, 1 H, C*H*CH_2OH), 1.99 (m, 1 H, C*H*CH_2OH), 3.52 (m, 4 H, C*H*$_2$OH), 3.60 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.64 (dd, 1 H, *J* = 4.7, 5.2 Hz, C*H*OH), 4.66 (dd, 1 H, *J* = 4.4, 5.0 Hz, C*H*OH), 5.05 (t, 1 H, *J* = 4.4 Hz, CH_2OH), 5.08 (t, 1 H, *J* = 4.4 Hz, CH_2OH), 5.38 (d, 1 H, *J* = 5.0 Hz, CHO*H*), 5.42 (d, 1 H, *J* = 5.2 Hz, CHO*H*), 5.91 (d, 1 H, *J* = 1.1 Hz, OC*H*HO), 5.95 (d, 1 H, *J* = 1.4 Hz, OCH*H*O), 6.33 (d, 1 H, *J* = 1.4 Hz, ArH), 6.43 (d, 1 H, *J* = 1.7 Hz, ArH), 6.51 (dd, 1 H, *J* = 1.1, 8.2 Hz, ArH), 6.53 (dd, 1 H, *J* = 1.7, 8.5 Hz, ArH), 6.54 (d, 1 H, *J* = 8.2 Hz, ArH), 6.75 (d, *J* = 8.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.19, 44.33 (*C*HCH_2OH), 54.77, 55.24 (OCH_3), 59.32, 59.39 (CH_2OH), 71.10, 71.18 (CHOH), 100.46 (OCH_2O), 105.91, 106.81, 109.07, 110.57, 117.61, 118.47 (Ar), 137.21, 138.81, 145.10, 146.46, 146.94, 147.88 (Ar).

MS (EI, 70 eV): *m/z* (%) = 406 (8) [$M^{+\cdot}$], 238 (16), 222 (38), 210 (7), 207 (8), 194 (7), 192 (6), 191 (11), 189 (17), 177 (6), 174 (17), 168 (9), 167 (50), 165 (5), 151 (100), 150 (27), 139 (31), 135 (7), 131 (5), 123 (16), 121 (6), 108 (9), 97 (6), 95 (5), 93 (23), 91 (6), 85 (5), 81 (5), 79 (5), 77 (6), 69 (5), 65 (10).

Anal. Calcd for $C_{21}H_{26}O_8$ (406.43): C, 62.06; H, 6.45. Found: C, 62.18; H, 6.58.

(1*R*,2*S*,3*S*,4*R*)-1,4-Di(1,3-benzodioxol-5-yl)-2,3-di(hydroxymethyl)butan-1,4-diol (12b)

Diol **11b** (170 mg, 0.44 mmol) was reduced with $LiAlH_4$ (167 mg, 4.40 mmol) according to GP3. Purification via column chromatography (CH_2Cl_2–MeOH, 10:1) gave **12b** (100 mg, 58%) as a colorless solid; mp 208 °C.

$[\alpha]_D^{22}$ +26.0 (c = 0.98, MeOH).

IR (KBr): 3228 (vs, br, OH), 2991 (m), 2911 (s), 2888 (s), 1502 (vs), 1492 (vs), 1440 (vs), 1372 (m), 1334 (m), 1314 (m), 1078 (s), 1038

(vs), 992 (m), 936 (vs), 860 (w), 814 (s), 787 (m), 770 (m), 734 (w), 721 (w), 677 (w), 612 (m), 565 (w), 531 (vw) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.94 (m, 2 H, C*H*CH_2OH), 3.51 (m, 4 H, C*H*$_2$OH), 4.65 (dd, 2 H, *J* = 3.9, 4.7 Hz, C*H*OH), 5.04 (m, 2 H, CH_2O*H*), 5.40 (d, 2 H, *J* = 4.7 Hz, CHO*H*), 5.93 (s, 2 H, OCH_2O) 5.94 (s, 2 H, OCH_2O), 6.43 (s, 2 H, ArH), 6.49 (d, 2 H, *J* = 8.0 Hz, ArH) 6.66 (d, 2 H, *J* = 8.0 Hz, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.25 (*C*HCH_2OH), 59.30 (*C*H_2OH), 71.03 (*C*HOH), 100.42 (O*C*H_2O), 106.01, 106.95, 118.56 (arom. *C*H), 138.90, 145.14, 146.44 (arom. *C*).

MS (EI, 70 eV): *m/z* (%) = 390 (6), 372 (13), 354 (11), 324 (5), 294 (11), 255 (10), 222 (28), 204 (20), 194 (11), 191 (14), 178 (9), 176 (8), 175 (7), 174 (36), 173 (21), 161 (12), 152 (12), 151 (100), 150 (41), 149 (50), 148 (8), 144 (7), 143 (9), 135 (24), 131 (11), 123 (13), 122 (7), 121 (13), 116 (6), 115 (10), 103 (7), 93 (36), 91 (6), 77 (7), 65 (22), 63 (6).

Anal. Calcd for $C_{20}H_{22}O_8$ (390.39): C, 61.53; H, 5.68. Found: C, 61.28; H, 5.90.

(1*R*,2*S*,3*S*,4*R*)-1-(1,3-Benzodioxol-5-yl)-2,3-di(hydroxymethyl)-4-(3,4,5-trimethoxyphenyl)butan-1,4-diol (12c)

Diol **11c** (240 mg, 0.55 mmol) was reduced with $LiAlH_4$ (209 mg, 5.50 mmol) according to GP3. Purification via column chromatography (CH_2Cl_2–MeOH, 10:1) gave **12c** (145 mg, 61%) as a colorless solid; mp 174 °C.

$[\alpha]_D^{22}$ +45.0 (c = 1.01, MeOH).

IR (KBr): 3221 (vs, br, OH), 2943 (s), 2895 (s), 2834 (m), 1596 (s), 1506 (vs), 1491 (s), 1452 (vs), 1417 (m), 1331 (m), 1256 (s), 1233 (s), 1130 (vs), 1086 (m), 1071 (m), 1038 (vs), 1006 (s), 931 (m), 838 (vw), 822 (w), 812 (m), 782 (w), 716 (m), 666 (w), 644 (w), 552 (vw) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.96 (m, 2 H, C*H*CH_2OH), 3.51 (m, 2 H, C*H*$_2$OH), 3.58 (m, 2 H, C*H*$_2$OH), 3.63 (s, 3 H, *p*-OCH_3), 3.67 (s, 6 H, *m*-OCH_3), 4.67 (m, 2 H, C*H*OH), 5.06 (t, 1 H, *J* = 4.7 Hz, CH_2O*H*), 5.07 (t, 1 H, *J* = 4.4 Hz, CH_2O*H*), 5.42 (d, 1 H, *J* = 5.2 Hz, CHO*H*), 5.44 (d, 1 H, *J* = 5.0 Hz, CHO*H*), 5.91 (s, 1 H, OC*H*HO), 5.94 (s, 1 H, OCH*H*O), 6.28 (s, 2 H, ArH), 6.42 (s, 1 H, ArH), 6.46 (d, 1 H, *J* = 8.0 Hz, ArH), 6.62 (d, 1 H, *J* = 8.0 Hz, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.31, 44.36 (*C*HCH_2OH), 55.39 (*m*-OCH_3), 59.32, 59.37 (CH_2OH), 59.76 (*p*-OCH_3), 71.10, 71.42 (CHOH), 100.46 (OCH_2O), 102.83, 105.95, 106.90, 118.47 (Ar), 135.48, 138.91, 140.56, 145.03, 146.42, 151.97 (Ar).

MS (EI, 70 eV): *m/z* (%) = 436 (14) [$M^{+\cdot}$], 418 (36), 400 (26), 370 (12), 340 (10), 339 (14), 308 (10), 301 (13), 268 (12), 250 (10), 237 (10), 224 (32), 222 (32), 220 (13), 219 (18), 207 (15), 204 (23), 198 (27), 197 (100), 196 (31), 195 (16), 191 (22), 189 (18), 188 (10), 182 (11), 181 (27), 174 (49), 173 (21), 169 (65), 161 (11), 154 (25), 153 (10), 152 (14), 151 (81), 150 (28), 149 (29), 139 (12), 138 (26), 135 (23), 131 (10), 123 (12), 121 (10), 93 (27), 91 (7), 77 (10), 65 (17), 55 (10).

Anal. Calcd for $C_{22}H_{28}O_9$ (436.46): C, 60.54; H, 6.47. Found: C, 60.95; H, 6.48.

(–)-Methyl Piperitol (5)

Tetraol **12a** (130 mg, 0.32 mmol) was treated according to GP4 with methanesulfonyl chloride (110 mg, 0.96 mmol) and pyridine (0.26 mL). Work-up and column chromatography (Et_2O–MeOH, 70:1) gave **5** (65 mg, 54%) as a colorless solid; mp 74°C.

$[\alpha]_D^{22}$ –73.0 (c = 0.60, $CHCl_3$), lit. [11] $[\alpha]_D^{22}$ +73.6° (c = 0.35, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (m, 2 H, C*H*CH_2O), 3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.31 (m, 2 H, C*H*$_2$CH), 4.41 (m, 2 H, C*H*$_2$CH), 5.00 (d, 1 H, *J* = 7.7 Hz, C*H*OCH_2), 5.02 (d, 1 H, *J* = 8.0 Hz, C*H*OCH_2), 5.97 (s, 2 H, OCH_2O), 6.78–6.98 (m, 6 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.74, 49.89 (*C*HCH_2O), 55.99, 56.03 (OCH_3), 67.24, 67.33 (*C*H_2CH), 81.92, 82.04 (*C*HOCH_2), 101.24 (OCH_2O), 106.40, 108.36, 109.17, 111.17, 118.55, 119.82 (Ar), 132.54, 134.29, 147.65, 148.24, 149.09, 149.42 (Ar).

HRMS: *m/z* calcd for $C_{21}H_{22}O_6$ (M^+), 370.1416; found, 370.1417.

The rest of the analytical data are in agreement with those previously reported.[9,11,26]

(–)-Sesamin (13)

Tetraol **12b** (80 mg, 0.20 mmol) was treated according to GP4 with methanesulfonyl chloride (69 mg, 0.60 mmol) and pyridine (0.16 mL). Work-up and column chromatography (Et_2O–pentane, 9:1) gave **13** (35 mg, 49%) as a colorless solid; mp 122 °C.

$[\alpha]_D^{22}$ –71.0 (c = 0.30, $CHCl_3$), lit. [13] $[\alpha]_D^{22}$ = +68.7 (c = 0.40, $CHCl_3$).

IR (KBr): 2973 (w), 2882 (m), 1610 (w), 1503 (vs), 1488 (vs), 1444 (vs), 1382 (m), 1315 (m), 1245 (vs), 1190 (m), 1101 (m), 1038 (vs), 925 (s), 861 (w), 809 (m), 788 (m), 731 (m), 716 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (m, 2 H, C*H*CH_2O), 3.31 (dd, 2 H, *J* = 7.1, 9.3 Hz, C*H*$_2$CH), 3.49 (dd, 2 H, *J* = 7.1, 9.1 Hz, C*H*$_2$CH), 4.33 (d, 2 H, *J* = 9.3 Hz, C*H*OCH_2), 5.97 (s, 4 H, OCH_2O), 6.75 (s, 2 H, ArH), 6.76 (s, 2 H, ArH), 6.87 (s, 2 H, ArH).

^{13}C NMR (75 MHz, $CDC1_3$): δ = 52.47 (*C*HCH_2O), 71.73 (*C*H_2°CH), 76.74 (*C*HOCH_2), 101.14 (OCH_2O), 106.80, 108.09, 120.29 (Ar), 136.85, 147.44, 147.99 (Ar).

HRMS: *m/z* calcd for $C_{20}H_{18}O_6$ (M^+), 354.1103; found, 354.1101.

The rest of the analytical data are in agreement with those previously reported.[26]

(–)-Aschantin (14)

Tetraol **12c** (144 mg, 0.33 mmol) was treated according to GP4 with methanesulfonyl chloride (113 mg, 0.99 mmol) and pyridine (0.27 mL). Work-up and column chromatography (Et_2O) gave **14** (70 mg, 53%) as a colorless solid; mp 122 °C.

$[\alpha]_D^{22}$ –64.0 (c = 0.55, $CHCl_3$), lit. [13] $[\alpha]_D^{22}$ +65.0 (c = 0.40, $CHCl_3$).

IR (KBr): 2938 (m), 2882 (m), 1593 (m), 1505 (s), 1488 (s), 1462 (s), 1422 (m), 1329 (m), 1242 (vs), 1127 (vs), 1038 (vs), 1008 (m), 929 (m), 815 (m), 788 (m), 683 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.58 (m, 2 H, C*H*CH_2O), 3.35 (dd, 1 H, *J* = 7.1, 9.3 Hz, C*H*HOCH), 3.40 (dd, 1 H, *J* = 7.1, 9.4 Hz, CH*H*OCH), 3.55 (dd, 1 H, *J* = 7.7, 9.3 Hz, C*H*HOCH), 3.56 (dd, 1 H, *J* = 7.7, 9.3 Hz, CH*H*OCH), 3.84 (s, 3 H, *p*-OCH_3), 3.87 (s, 6 H, *m*-OCH_3), 4.40 (d, 1 H, *J* = 7.4 Hz, C*H*OCH_2), 4.43 (d, 1 H, *J* = 7.1 Hz, C*H*OCH_2), 5.97 (s, 2 H, OCH_2O), 6.57 (s, 2 H, ArH), 6.76 (d, 1 H, *J* = 7.7 Hz, ArH), 6.80 (dd, 1 H, *J* = 1.4, 8.0 Hz, ArH), 6.90 (d, 1 H, *J* = 1.0 Hz, ArH).

^{13}C NMR (75 MHz, $CDC1_3$): δ = 52.44, 52.56 (*C*HCH_2O), 56.15 (*m*-OCH_3), 60.85 (*p*-OCH_3), 71.73 (*C*H_2CH), 76.86, 77.35 (*C*HOCH_2), 101.19 (OCH_2O), 103.46, 106.76, 108.15, 120.29 (Ar), 136.76, 137.68, 138.51, 147.54, 148.07, 153.35 (Ar).

HRMS: *m/z* calcd for $C_{22}H_{24}O_7$ (M^+), 400.1522; found, 400.1523.

The rest of the analytical data are in agreement with those previously reported.[26]

(3*S*,4*S*)-4-[(*R*)-1-(1,3-Benzodioxol-5-yl)-1-hydroxymethyl]-3-(3,4,5-trimethoxybenzyl)tetrahydro-2-furanone (16)

Ketone **15**[7] (307.2 mg, 0.74 mmol) was dissolved in MeOH (30 mL) after which $NaBH_4$ (90 mg, 2.34 mmol) was added. After 2 h (TLC

control), the reaction mixture was partitioned with CH_2Cl_2 and H_2O. The aq phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography (Et_2O–pentane, 1:1 to 3:1) to give **16** (248.4 mg, 80%) as a mixture of diastereomers (83:17). For analytical purposes a small sample was purified via preparative HPLC to give the major diastereomer (α-alcohol) in pure form; mp 141 °C.

$[\alpha]_D^{22}$ +1.1 (c = 0.93, acetone).

IR (KBr): 3471 (m, br, OH), 2939 (m), 2839 (w), 1763 (vs, $C{=}O_{lactone}$), 1592 (s), 1507 (s), 1490 (s), 1460 (s), 1423 (s), 1385 (w), 1325 (m), 1242 (vs), 1187 (s), 1127 (vs), 1036 (s), 1008 (s), 928 (m), 815 (w), 783 (w), 738 (m), 672 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (d, 1 H, *J* = 2.8 Hz, OH), 2.63 (ddd, 1 H, *J* = 7.1, 7.2, 7.4 Hz, $CHCO_2$), 2.95 (m, 2 H, C*H*HCHCO$_2$, C*H*CH$_2$C = O), 3.06 (m, 1 H, CH*H*CHCO$_2$), 3.83 (s, 9 H, OCH_3), 3.95 (d, 2 H, *J* = 7.7 Hz, C*H*$_2$C = O), 4.63 (dd, 1 H, *J* = 2.5, 6.9 Hz, C*H*OH), 5.97 (d, 1 H, *J* = 1.4 Hz, OC*H*HO), 5.98 (d, 1 H, *J* = 1.4 Hz, OCH*H*O), 6.39 (s, 2 H, ArH), 6.73 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.59 (*C*H$_2$CHCO$_2$), 43.69 (*C*HCO$_2$), 45.02 (*C*HCH$_2$C=O), 56.09 (*m*-OCH_3), 60.85 (*p*-OCH_3), 68.36 (*C*H$_2$C=O), 75.34 (*C*HOH), 101.38 (OCH_2O), 106.17, 106.74, 108.23, 119.29 (Ar), 133.28, 135.46, 147.65, 148.19, 153.11 (Ar), 179.04 (OC=O).

MS (EI, 70 eV): *m/z* (%) = 417 (26) [$M^{+\cdot}$+1], 416 (100) [$M^{+\cdot}$], 238 (5), 221 (7), 183 (5), 182 (40), 181 (80), 177 (6), 169 (6), 168 (6), 167 (10), 161 (5), 152 (5), 151 (38), 149 (9), 148 (8), 135 (6), 131 (8), 123 (5), 93 (17), 65 (12).

Anal. Calcd for $C_{22}H_{28}O_9$ (416.43): C, 63.45; H, 5.81. Found: C, 63.09; H, 5.84.

(+)-Yatein (17)

The epimeric mixture of alcohol **16** (200 mg, 0.48 mmol) was dissolved in anhyd EtOH (30 mL) and two drops of aq $HClO_4$ was added. The mixture was hydrogenated using 10% Pd/C (60 mg) as catalyst at 4 atm. After 16 h, the soln was neutralized with solid Na_2CO_3 and the catalyst was filtered off. The solvent was evaporated in vacuo and the crude product was purified via column chromatography (Et_2O–pentane, 1:1) to give **17** (170 mg, 88%) as a colorless oil.

$[\alpha]_D^{22}$ +30.6 (c = 1.10, $CHCl_3$); lit. [16b] $[\alpha]_D^{22}$ –30.0 (c = 0.15, $CHCl_3$).

IR (KBr): 3015 (m), 2938 (m), 2840 (m), 1767 (vs, $C{=}O_{lactone}$), 1591 (s), 1504 (s), 1490 (s), 1244 (vs), 1188 (vs), 755 (vs) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46–2.64 (m, 4 H, CH_2), 2.88–2.94 (m, 2 H, CH), 3.06 (m, 1 H, CH*H*CHCO$_2$), 3.83 (s, 9 H, OCH_3), 3.88 (dd, 1 H, *J* = 7.4, 9.0 Hz, C*H*HOC=O), 4.18 (dd, 1 H, *J* = 7.2, 9.3 Hz, C*H*HOC=O), 5.94 (dd, 2 H, *J* = 1.4, 3 Hz, OCH_2O), 6.36 (s, 2 H, ArH), 6.46–6.49 (m, 2 H, ArH), 6.69 (dd, 1 H, *J* = 1.0, 6.9 Hz, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.23 (*C*H$_2$CHCO$_2$), 38.33 (*C*H$_2$CHCH$_2$C=O), 41.01 (*C*HCH$_2$C=O), 46.44 (*C*HCO$_2$), 56.09 (*m*-OCH_3), 60.88 (*p*-OCH_3), 71.20 (*C*H$_2$C=O), 101.10 (OCH_2O), 106.16, 108.31, 108.77, 121.54 (Ar), 131.53, 133.34, 136.80, 146.40, 147.92, 153.24 (Ar), 178.56 (OC=O).

MS (EI, 70 eV): *m/z* (%) = 401 (22) [$M^{+\cdot}$ + 1], 400 (100) [$M^{+\cdot}$], 182 (23), 181 (49), 151 (5), 136 (5), 135 (19), 77 (5).

HRMS: *m/z* calcd for $C_{22}H_{24}O_7$ (M^+), 400.15220; found, 400.15223.

(–)-Isostegane (18)

(+)-Yatein **(17)** (90 mg, 0.22 mmol) dissolved in trifluoroacteic acid (TFA; 1 mL) was added at 0 °C rapidly to a soln containing Tl_2O_3 (283 mg, 0.62 mmol) and $BF_3{\cdot}OEt_2$ (0.06 mL, 0.5 mmol) in TFA (1.5 mL). The reaction was quenched after 10 s by adding sat. aq $NaHCO_3$. The aq layer was extracted with CH_2Cl_2 (3 × 10 mL) after which the combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography (Et_2O–pentane, 1:1) to give **18** (69 mg, 77%) as a colorless solid; mp 171–2 °C.

$[\alpha]_D^{22}$ –156.9 (c = 2.8, $CHCl_3$); lit. [18a] $[\alpha]_D^{22}$ +154.0 (c = 0.7, $CHCl_3$).

IR (KBr): 2931 (m), 1778 (vs, $C{=}O_{lactone}$), 1595 (m), 1484 (vs), 1455 (s), 1403 (s), 1224 (vs), 1105 (vs), 1038 (vs), 997 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00–2.17 (m, 2 H, CH), 2.22 (dd, 1 H, *J* = 9.3, 13.6 Hz, C*H*HCHCO$_2$), 2.32 (dd, 1 H, *J* = 9.6, 13.2 Hz, CH*H*CHCO$_2$), 2.57 (d, 1 H, *J* = 12.9 Hz, C*H*HCH$_2$CO$_2$), 3.06 (d, 1 H, *J* = 13.2 Hz, CH*H*CH$_2$CO$_2$), 3.50 (s, 1 H, OCH_3), 3.70 (dd, 1 H, *J* = 8.5, 11.0 Hz, C*H*HOC=O), 3.81 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.29 (dd, 1 H, *J* = 6.6, 8.2 Hz, C*H*HOC=O), 5.90 (d, 1 H, *J* = 1.3 Hz, OC*H*HO), 5.93 (d, 1 H, *J* = 1.3 Hz, OCH*H*O), 6.55 (s, 1 H, ArH), 6.56 (s, 1 H, ArH), 6.63 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.55 (*C*H$_2$CHCO$_2$), 34.39 (*C*H$_2$CHCH$_2$C=O), 47.27 (*C*HCO$_2$), 50.33 (*C*HCH$_2$C=O), 56.30 (OCH_3), 61.07 (OCH_3), 61.23 (OCH_3), 70.31 (*C*H$_2$C=O), 101.46 (OCH_2O), 107.74, 109.05, 112.02 (Ar), 126.70, 128.58, 132.74, 136.33, 146.16, 147.93, 152.14, 153.60 (Ar), 176.83 (OC=O).

MS (EI, 70 eV): *m/z* (%) = 399 (24) [$M^{+\cdot}$ + 1], 398 (100) [$M^{+\cdot}$].

HRMS: *m/z* calcd for $C_{22}H_{22}O_7$ (M^+), 398.13655; found, 398.13663.

(+)-Dihydroclusin (19)

To a suspension of $LiAlH_4$ (80 mg, 2.1 mmol) in anhyd THF was added at 0 °C (+)-yatein (**17**) (105 mg, 0.26 mmol) dissolved in anhyd THF (3 mL). The ice-bath was removed and the mixture stirred for 3 h at r.t. EtOAc was added dropwise after which sat. NH_4Cl (10 mL) and H_2O (5 mL) were added. The mixture was filtered and the filtrate was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography (Et_2O) to give **19** (96 mg, 91%) as a colorless solid; mp. 98–100 °C.

$[\alpha]_D^{22}$ +27.0 (c = 1.15, $CHCl_3$); lit. [22b] $[\alpha]_D^{22}$ –27.13 (c = 0.24, $CHCl_3$).

IR (KBr): 3248 (m), 2938 (m), 2892 (m), 1591 (s), 1512 (s), 1486 (vs), 1458 (s), 1433 (s), 1241 (vs), 1130 (vs), 1034 (s), 1005 (vs), 925 (m), 908 (m), 815 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77–1.85 (m, 2 H, C*H*), 2.58 (ddd, 2 H, *J* = 1.9, 6.3, 8.5 Hz, ArC*H*$_2$), 2.68 (t, 1 H, *J* = 8 Hz, ArC*H*$_2$), 2.71 (t, 1 H, *J* = 7.7 Hz, ArC*H*$_2$), 2.98 (br s, 2 H, OH), 3.48 (dd, 2 H, *J* = 3.9, 11.3 Hz, C*H*$_2$OH), 3.75 (s, 6 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.74–3.77 (m, 2 H, C*H*$_2$OH), 5.85 (s, 2 H, OC*H*$_2$O), 6.29 (s, 2 H, ArH), 6.53 (dd, 1 H, *J* = 1.6, 8.0 Hz, ArH), 6.57 (d, 1 H, *J* = 1.4 Hz, ArH), 6.64 (d, 1 H, *J* = 8.0 Hz, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.16 (Ar*C*H$_2$), 36.86 (Ar*C*H$_2$), 43.96 (ArCH$_2$*C*H), 44.33 (ArCH$_2$*C*H), 56.31 (*m*-OCH_3), 60.56 (CH_2OH), 61.15 (*p*-OCH_3), 101.08 (OCH_2O), 103.49, 106.11, 108.34, 109.56, 122.13 (Ar), 134.58, 136.36, 136.66, 145.98, 147.84, 153.30 (Ar).

MS (EI, 70 eV): *m/z* (%) = 405 (20) [$M^{+\cdot}$+ 1], 404 (100) [$M^{+\cdot}$], 209 (6), 183 (8), 182 (75), 181 (80), 167 (10), 151 (12), 136 (10), 135 (47), 77 (7).

HRMS: *m/z* calcd for $C_{22}H_{28}O_7$ (M^+), 404.18350; found, 404.18354.

(+)-Burseran (4)

(+)-Dihydroclusin (**19**) (52 mg, 0.13 mmol) was dissolved in MeOH (30 mL) and 32% HCl (1 mL) was added. The soln was refluxed for 48 h after which the solvent was evaporated. The residue was neutralized with sat. $NaHCO_3$ and the aq phase was extracted with

CH_2Cl_2 (3 × 10 mL). The combined org. layers were dried with $MgSO_4$ and evaporated in vacuo. The crude product was purified via column chromatography (Et_2O–pentane, 3:1) to give (+)-**4** (42 mg, 85%) as an colorless oil.

$[\alpha]_D^{22}$ +37.8 (c = 2.0, $CHCl_3$); lit.[21a] $[\alpha]_D^{22}$ –34.8 (c = 0.93, $CHCl_3$).

IR (KBr): 3010 (m), 2935 (s), 1590 (vs), 1504 (vs), 1489 (vs), 1462 (s), 1445 (s), 1421 (s), 1243 (vs), 1128 (vs), 1039 (s), 755 (vs) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.07–2.16 (m, 2 H, CH), 2.40–2.56 (m, 4 H, ArCH_2), 3.44 (t, 1 H, *J* = 6.0 Hz, CH_2O), 3.47 (t, 1 H, *J* = 6.0 Hz, CH_2O), 3.75 (s, 3 H, OCH_3), 3.76 (s, 6 H, OCH_3), 3.84 (t, 1 H, *J* = 6.6 Hz, CH_2O), 3.86 (t, 1 H, *J* = 6.6 Hz, CH_2O), 5.86 (dd, 2 H, *J* = 1.4, 4.1 Hz, OCH_2O), 6.21 (s, 2 H, ArH), 6.46–6.49 (m, 2 H, ArH), 6.63 (d, 1 H, *J* = 8.0 Hz, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.52 (ArCH_2), 40.26 (ArCH_2), 46.72 (CH), 46.96 (CH), 56.36 (*m*-OCH_3), 61.18 (*p*-OCH_3), 73.55 (CH_2O), 101.14 (OCH_2O), 105.78, 108.28, 109.20, 121.69 (Ar), 134.28, 136.32, 136.57, 146.05, 147.84, 153.27, (Ar).

MS (EI, 70 eV): *m/z* (%) = 387 (20) [$M^{+\cdot}$ + 1], 386 (85) [$M^{+\cdot}$], 183 (11), 182 (100), 181 (25), 167 (13), 151 (17), 136 (7), 135 (20), 77 (6).

HRMS: *m/z* calcd for $C_{22}H_{26}O_6$ (M^+): 386.1729; found, 386.17294.

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