
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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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 dibenzylbutan(diol) 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) 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 enantio pure 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 enantio metrically pure secondary amine 6 as starting materials followed by a Michael reaction of lithiated 7 to SH-furan-2-one to give the 1,4-adducts 8 in good
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: ZnBr₂, ZnI₂, MgBr₂, ClTi(O₂CMe)₂, and BrTi(NEt₃)₂, for example, did not improve stereocontrol, whereas ZnCl₂ 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 co-solvent was found to be ≥ 98%.

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)⁹ [α]D = −73.0 (c = 0.60, CHCl₃), lit.¹¹ [α]D = +73.6 (c = 0.35, CHCl₃)], (−)-sesamin (13)¹² [α]D = −71.0 (c = 0.30, CHCl₃), lit.¹³ [α]D = +68.7 (c = 0.40, CHCl₃) and (−)-aschantin (14) [α]D = −64.0 (c = 0.55, CHCl₃), lit.¹⁵ [α]D = +65.0 (c = 0.40, CHCl₃)] 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-butyro lactone 15. 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 of 16 gave (±)-yatein (17) in very good yield (88%) and optical purity [α]D = +30.6 (c = 1.10, CHCl₃), lit.¹⁶ [α]D = −30.0 (c = 0.15, CHCl₃)]. 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 Ti₃O₅ in the presence of BF₃·OEt₂ in neat TFA gave (−)-isostegane (18)¹⁸ [α]D = −156.9 (c = 2.8, CHCl₃), lit.¹⁸ [α]D = +154.0 (c = 0.7, CHCl₃)] in very good yield (77%). This also constitutes a formal total synthesis of the known anti-tumor lignan ste-
ganecin (3), as Koga and co-workers\textsuperscript{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),\textsuperscript{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)\textsuperscript{21} \([\alpha]_D^{22} +27.0 \text{ (c = 1.15, CHCl}_3 \text{)}, \text{lit.} \text{22b} \ [\alpha]_D^{22} +37.8 \text{ (c = 2.0, CHCl}_3 \text{)}\) in excellent yield (91%). Refluxing 19 in a methanolic solution containing HCl analogous to Ward and co-workers\textsuperscript{23} afforded the anti-tumor lignan (+)-burseran (4)\textsuperscript{24} \([\alpha]_D^{22} +37.8 \text{ (c = 2.0, CHCl}_3 \text{)}\); \text{lit.} \text{25,18a} \ [\alpha]_D^{22} -34.8 \text{ (c = 0.93, CHCl}_3 \text{)}\) 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 \(\gamma\)-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\(_2\)Cl\(_2\) 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 \(^1\)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 \(\gamma\)-Butyrolactones 9a–c; General Procedure 1 (GP1)

Anhyd LiCl (2.2 equiv) was put in a dried Schlenk-flask after which disisopropyl amine (1.2 equiv) and anhyd THF (3 mL per mmol disisopropyl amine) were added. The flask was cooled to \(-78\) \(^\circ\)C and \(n\)-BuLi (1.2 equiv, 1.6 M) was added dropwise. The soln was stirred at \(0\) \(^\circ\)C for 30 min. This mixture was added via a syringe pump to another flask cooled to \(-78\) \(^\circ\)C containing the Michael adduct. After 20 min at \(-100\) \(^\circ\)C the cooling bath was removed and the reaction was quenched by adding quickly sat. NH\(_4\)Cl soln under vigorous stirring. The mixture was allowed to warm to r.t., H\(_2\)O was added and the organic phase was separated. The aq phase was extracted with Et\(_2\)O, HClO\(_4\), EtOH, 4 atm, rt. The mixture was added via a syringe pump to another flask cooled to \(-78\) \(^\circ\)C containing the Michael adduct (1 equiv) in anhyd THF (10 mL per mmol Michael adduct). After 90 min, the soln was cooled to \(-100\) \(^\circ\)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 \(-100\) \(^\circ\)C the cooling bath was removed and the reaction was quenched by adding quickly sat. NH\(_4\)Cl soln under vigorous stirring. The mixture was allowed to warm to r.t., H\(_2\)O was added and the organic phase was separated. The aq phase was extracted with Et\(_2\)O (3 \(\times\) 5 mL) and the combined organic layers were washed with 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\(_2\)O (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 Et₂O and H₂O. After partitioning, the aq phase was extracted with Et₂O (3 × 5 mL). The combined org. layers were washed with sat. NaCl soln (3 × 5 mL), dried with MgSO₄ 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 hydrolysed with H₂O and immediately partitioned between H₂O and EtOAc. After removal of the aq phase, the organic layer was washed with sat. NaCl soln (2 × 5 mL), dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography.

**Tetraols 12a-c; General Procedure 3 (GP3)**

LiAlH₄ (10 equiv) was suspended with anhyd THF (2 mL per mmol LiAlH₄) 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 stir with an additional 10 min. The precipitate was removed via filtration and was extracted twice by reflushing 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 CH₂Cl₂ (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 H₂O, 10% soln of citric acid (2 × 5 mL), and finally with sat. NaCl soln. The organic layer was dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography.

**Thioesters 13a,b; General Procedure 5 (GP5)**

To the thioester 12a-b dissolved in anhyd THF (10 mL per mmol thioester) was added at 0°C, pyridine (0.8 mL per mmol thioester) and MeSO₄Cl (3 equiv). The reaction mixture was allowed to warm to r.t. overnight. The mixture was washed with H₂O, 10% soln of citric acid (2 × 5 mL), and finally with sat. NaCl soln. The organic layer was dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography.

**4-Nitrobenzaldehydes 14a,b; General Procedure 6 (GP6)**

To the ketone 13a,b dissolved in anhyd CH₂Cl₂ (10 mL per mmol ketone) was added at 0°C, pyridine (0.8 mL per mmol ketone) and NCS (3 equiv). The reaction mixture was allowed to warm to r.t. overnight. The mixture was washed with H₂O, 10% soln of citric acid (2 × 5 mL), and finally with sat. NaCl soln. The organic layer was dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography.

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MS (EL 70 eV): m/z (%) = 402 (0.3) [M^+], 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).


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

Ketone 9b (480 mg, 1.25 mmol) was reduced with 1-L-Selenic acid according to GP2. Work-up and column chromatography (CH_{2}Cl_{2}-MeOH, 30:1) gave 11b (340 mg, 70%) as a colorless solid; mp 186^\circ C.

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


(1R,2S,3S,4R)-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_{2}Cl_{2}-MeOH, 10:1) gave 12a (135 mg, 55%) as a colorless solid; mp 181^\circ C.

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

Anal. Calcd for C_{25}H_{26}O_{8} (406.43): C, 62.18; H, 4.70. Found: C, 62.67; H, 5.07.

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

Ketone 9c (486 mg, 1.13 mmol) was reduced with 1-L-Selenic acid according to GP2. Work-up and column chromatography (CH_{2}Cl_{2}-MeOH, 30:1) gave 11c (410 mg, 64%) as a colorless solid; mp 174^\circ C.

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


(1R,2S,3S,4R)-1-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_{2}Cl_{2}-MeOH, 10:1) gave 12b (100 mg, 58%) as a colorless solid; mp 208^\circ C.

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


IR (KBr): 3282 (vs, br, OH), 2991 (m), 2911 (s), 2888 (s), 1502 (vs), 1469 (m), 1448 (m), 1438 (m), 1343 (m), 1235 (m), 1136 (s), 1110 (s), 1066 (s), 1026 (s), 991 (m), 97 (m), 927 (m), 874 (m), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.

IR (KBr): 3228 (vs, br, OH), 2991 (m), 2982 (m), 2909 (s), 2854 (s), 1502 (vs), 1469 (m), 1448 (m), 1438 (m), 1343 (m), 1235 (m), 1136 (s), 1110 (s), 1066 (s), 1026 (s), 991 (m), 97 (m), 927 (m), 874 (m), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.

IR (KBr): 3173 (vs, br, OH), 2991 (m), 2909 (s), 2854 (s), 1502 (vs), 1469 (m), 1448 (m), 1438 (m), 1343 (m), 1235 (m), 1136 (s), 1110 (s), 1066 (s), 1026 (s), 991 (m), 97 (m), 927 (m), 874 (m), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.

IR (KBr): 3067 (w), 2969 (m), 2911 (s), 2888 (s), 1502 (vs), 1469 (m), 1448 (m), 1438 (m), 1343 (m), 1235 (m), 1136 (s), 1110 (s), 1066 (s), 1026 (s), 991 (m), 97 (m), 927 (m), 874 (m), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.

IR (KBr): 3228 (vs, br, OH), 2991 (m), 2982 (m), 2909 (s), 2854 (s), 1502 (vs), 1469 (m), 1448 (m), 1438 (m), 1343 (m), 1235 (m), 1136 (s), 1110 (s), 1066 (s), 1026 (s), 991 (m), 97 (m), 927 (m), 874 (m), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.

IR (KBr): 3228 (vs, br, OH), 2991 (m), 2982 (m), 2909 (s), 2854 (s), 1502 (vs), 1469 (m), 1448 (m), 1438 (m), 1343 (m), 1235 (m), 1136 (s), 1110 (s), 1066 (s), 1026 (s), 991 (m), 97 (m), 927 (m), 874 (m), 857 (w), 819 (m), 786 (w), 764 (w), 676 (m), 591 (w) cm^{-1}.
1H NMR (400 MHz, DMSO-d$_6$): $\delta = 1.94$ (m, 2 H, CH$_2$OH), 3.51 (m, 4 H, CH$_2$O), 4.65 (dd, 2 H, $J = 3.9, 4.7$ Hz, CHO$_2$H), 5.04 (m, 2 H, CH$_2$OH), 5.40 (d, 2 H, $J = 4.7$ Hz, CHO$_2$H), 5.93 (s, 2 H, OCH$_3$O) 5.94 (s, 2 H, OCH$_3$O), 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).

13C NMR (100 MHz, DMSO-d$_6$): $\delta = 44.25$ (CH$_2$OH), 59.30 (CH$_2$O), 71.03 (CH$_3$O), 100.42 (OCH$_3$O), 106.01, 106.95, 118.56 (arom. CH), 138.90, 145.14, 146.44 (arom. C).

MS (EI, 70 eV): m/z (%) = 390 (36), 372 (13), 354 (32), 294 (11), 255 (22), 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), 147 (9), 135 (24), 131 (11), 123 (12), 122 (7), 121 (13), 116 (6), 115 (10), 93 (36), 91 (6), 77 (65), 67 (22), 63 (6).


(1R,2S,3S,4R)-1-(1,3-Benzodioxol-5-yl)-2,3-di(hydroxymethyl)-4-(3,4,5-trimethoxy)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$_2$Cl$_2$:MeOH = 10:1) gave 12c (145 mg, 61% as a colorless solid; mp 174 °C).

MS (EI, 70 eV): [M]$^+$ = 371 (0.6), 274 (19), 262 (13), 207 (53), 191 (31), 182 (16), 164 (14), 153 (13), 119 (12), 104 (11), 77 (20), 67 (22), 55 (10).

Anal. Calcd for C$_{22}$H$_{22}$O$_7$ (436.46): C, 60.54; H, 6.47. Found: C, 60.95; H, 6.48.

(−)-Methyl Piperitol (5)

Tetraol 22a (130 mg, 0.32 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$_2$O-pentane, 9:1) gave 5 (65 mg, 54%) as a colorless solid; mp 74°C.

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), 1127 (vs), 1038 (vs), 1008 (m), 931 (m), 838 (w), 788 (m), 731 (m), 716 (m) cm$^{-1}$.

IR (KBr): 2938 (m), 2882 (m), 1593 (s), 1502 (m), 1488 (vs), 1382 (vs), 1315 (m), 1252 (vs), 1186 (m), 1101 (m), 1038 (vs), 925 (s), 861 (w), 788 (m), 731 (m), 716 (m) cm$^{-1}$.

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$_2$O-pentane, 9:1) gave 13 (35 mg, 49%) as a colorless solid; mp 122 °C.

IR (KBr): 2973 (w), 2882 (m), 1610 (w), 1503 (vs), 1488 (vs), 1444 (vs), 1382 (vs), 1315 (m), 1252 (vs), 1186 (m), 1101 (m), 1038 (vs), 925 (s), 861 (w), 788 (m), 731 (m), 716 (m) cm$^{-1}$.

The rest of the analytical data are in agreement with those previously reported.$^{26}$

(−)-Achantic (14)

Tetraol 12e (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$_2$O) gave 14 (70 mg, 53%) as a colorless solid; mp 122 °C.

IR (KBr): 2978 (m), 2882 (m), 1503 (m), 1488 (s), 1462 (s), 1422 (m), 1329 (m), 1242 (vs), 1127 (vs), 1038 (s), 1008 (m), 929 (s), 815 (m), 788 (m), 683 (m) cm$^{-1}$.

The rest of the analytical data are in agreement with those previously reported.$^{26}$

(−)-Mandelic Acid (15)

Tetraol 12c (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 Synthesis 2002, No. 4, 515–522 ISSN 0039-7881 © Thieme Stuttgart · New York
control), the reaction mixture was partitioned with CH₂Cl₂ and H₂O. The aq phase was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography (Et₂O-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.

\[ \text{[\text{Et}_{2}O]}_{22} +1.1 \text{ (c = 0.93, acetone).} \]

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.

1H NMR (400 MHz, CDCl₃): \( \delta = 2.00 \) (d, 1 H, \( J = 2.4 \text{ Hz}, \text{ ArH} \)), 2.71 (t, 1 H, \( J = 8.0 \text{ Hz}, \text{ CH} \)), 3.16 (m, 1 H, OCH₃), 3.75 (s, 6 H, OCH₃), 3.76 (s, 3 H, OCH₃), 4.18 (dd, 1 H, \( J = 1.3, 6.9 \text{ Hz}, \text{ OCH} \)), 4.29 (dd, 1 H, \( J = 1.3, 1.7 \text{ Hz}, \text{ OCH} \)), 4.33 (dd, 1 H, \( J = 1.3, 1.7 \text{ Hz}, \text{ OCH} \)), 6.53 (d, 1 H, \( J = 6.6, 8.2 \text{ Hz}, \text{ CH(OH)} \)), 5.90 (d, 1 H, \( J = 1.3, 1.7 \text{ Hz}, \text{ CH(OH)} \)), 5.93 (d, 1 H, \( J = 1.3, 1.7 \text{ Hz}, \text{ OCH(OH)} \)), 6.55 (s, 1 H, \( \text{ ArH} \)), 6.56 (s, 1 H, \( \text{ ArH} \)), 6.63 (s, 1 H, \( \text{ ArH} \)).

HRMS: \( m/z \) calcd for C₂₂H₂₄O₇ (M⁺), 398.13663; found, 398.13663.

(+)-Dihydroclusin (19)

To a suspension of LiAlH₄ (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. NH₄Cl (10 mL) and H₂O (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 MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography (Et₂O-pentane, 1:1) to give 19 (96 mg, 91%) as a colorless solid; mp 180–181 °C.

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.

1H NMR (400 MHz, CDCl₃): \( \delta = 1.77–1.85 \) (m, 2 H, CH₂), 2.58 (dd, 2 H, \( J = 1.3, 6.9 \text{ Hz}, \text{ ArCH} \)), 2.68 (t, 1 H, \( J = 8.5 \text{ Hz}, \text{ ArCH} \)), 2.71 (t, 1 H, \( J = 7.7 \text{ Hz}, \text{ ArCH} \)), 2.98 (br s, 2 H, OH), 2.98 (dd, 2 H, \( J = 3.9, 11.3 \text{ Hz}, \text{ CH(OH)} \)), 3.75 (s, 6 H, OCH₃), 3.76 (s, 3 H, OCH₃), 3.74–3.77 (m, 2 H, \( \text{CH(OH)} \)), 5.85 (s, 2 H, OCH₂), 6.29 (s, 2 H, ArH), 6.53 (dd, 1 H, \( J = 1.6, 8.0 \text{ Hz}, \text{ ArH} \)), 6.57 (d, 1 H, \( J = 1.4 \text{ Hz}, \text{ ArH} \)), 6.64 (d, 1 H, \( J = 8.0 \text{ Hz}, \text{ ArH} \)).

HRMS: \( m/z \) calcd for C₂₅H₃₁O₁₆ (M⁺), 436.18350; found, 436.18354.

(-)-Isostegane (18)

(+)-Yatein (17) (90 mg, 0.22 mmol) dissolved in trifluoroacetic acid (TFA; 1 mL) was added at 0 °C rapidly to a soln containing Ti(O₂)(283 mg, 0.62 mmol) and BF₃·OEt₂ (0.06 mL, 0.5 mmol) in TFA (1.5 mL). The reaction was quenched after 10 s by adding sat. aq NaHCO₃. The aq layer was extracted with CH₂Cl₂ (3 × 10 mL) after which the combined organic layers were dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography (Et₂O-pentane, 1:1) to give 18 (69 mg, 77%) as a colorless solid; mp 171–2 °C.

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.

1H NMR (400 MHz, CDCl₃): \( \delta = 2.00–2.17 \) (m, 2 H, CH₂), 2.22 (dd, 1 H, \( J = 9.3, 13.6 \text{ Hz}, \text{ CH(H)CH(O)} \)), 2.32 (dd, 1 H, \( J = 9.6, 13.2 \text{ Hz}, \text{ CH(OH)CO} \)), 2.57 (d, 1 H, \( J = 12.9 \text{ Hz}, \text{ CH(CH)CO} \)), 3.06 (d, 1 H, \( J = 13.2 \text{ Hz}, \text{ CH(CH)CO} \)), 3.50 (s, 1 H, \( \text{ OCH} \)), 3.70 (dd, 1 H, \( J = 8.5, 11.0 \text{ Hz}, \text{ CH(OH)CO} \)), 3.81 (s, 3 H, \( \text{ OCH} \)), 3.82 (s, 3 H, \( \text{ OCH} \)), 4.29 (dd, 1 H, \( J = 6.6, 8.2 \text{ Hz}, \text{ CH(OH)CO} \)), 5.90 (d, 1 H, \( J = 1.3 \text{ Hz}, \text{ OCH(OH)} \)), 5.93 (d, 1 H, \( J = 1.3 \text{ Hz}, \text{ OCH(OH)} \)), 6.55 (s, 1 H, \( \text{ ArH} \)), 6.56 (s, 1 H, \( \text{ ArH} \)), 6.63 (s, 1 H, \( \text{ ArH} \)).

HRMS: \( m/z \) calcd for C₂₂H₂₄O₆ (M⁺), 398.13656; found, 398.13663.

(-)-Bursearan (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 soln was evaporated. The residue was neutralized with sat. NaHCO₃ and the aq phase was extracted with
CH₂Cl₂ (3 × 10 mL). The combined org. layers were dried with MgSO₄ and evaporated in vacuo. The crude product was purified via column chromatography (Et₂O–pentane, 3:1) to give (+)-4 (42 mg, 85%) as an colorless oil.

$$[\alpha]_D^{23} +37.8 (c = 2.0, \text{CHCl}_3)$$ & [lit. 22 $$[\alpha]_D^{23} = 34.8 (c = 0.93, \text{CHCl}_3)$$]

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.

HRMS: m/z calcd for C₂₂H₂₆O₆ (M⁺): 386.1729; found, 386.17294.

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**References**


11. (9) For previous syntheses of the racemate see: (a) ref. 5.


25. (23) For previous asymmetric syntheses see: (a) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. Tetrahydrobenz 1994, 40, 1303. (b) ref. 12c.