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TRIP-Catalyzed Asymmetric Synthesis of (+)-Yatein, (-)- α -Conidendrin, (+)-Iso- and (+)-Neoisostegane.

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Supporting Information Placeholder

ABSTRACT: The asymmetric allylation under the assistance of catalytic amounts of 3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (TRIP) allows the concise construction of the lignan scaffold from simple aldehydes and allylic bromides with full control of the two formed stereocenters. This young methodology has been employed to synthesize four naturally and pharmaceutically active lignans. Members of the dibenzylbutyrolactone-, the tetraline- and the dibenzocyclooctadiene-class have been synthesized in 40-47% overall yield along four steps synthetic routes.

Plant metabolites have been a key foundation of traditional folk medicine for thousands of years and deliver today a plethora of lead structures for medicinal chemistry.¹ One of these classes of metabolites is summarized as lignans, which describe a group consisting of dimeric phenylpropanes, linked at the C8 carbon (see Figure 1).²

Figure 1. Lignan subcore and examples for the diversity of lignan natural products.

The bioactivity of this compound class has reached an impressive range: antiviral,³⁻⁵ anticancer,⁵⁻⁷ cancer prevention,^{8, 9} anti-inflammatory,⁷ antimicrobial,⁷ antioxidant,^{6, 7, 10} immunosuppressive,⁷ hepatoprotective¹¹ and osteoporosis prevention¹² have been reported or suggested. This pharmacological attractiveness has triggered plenty of synthetic endeavours. Nevertheless, a short concise asymmetric synthesis of the substructure has remained troublesome until recently. We have been able to show that chiral phosphoric acids (CPAs), especially 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (TRIP, 1), provide catalytic stereoinduction on the allylation of benzaldehydes (see Scheme 1).¹³ We were able to demonstrate the applicability of the developed methodology on the natural product (-)-hydroxymatairesinol (9, see Figure 2). In order to further expand the portfolio of lignan natural products available within short synthetic procedures we envisaged the other classes of compounds herein.

Scheme 1. Asymmetric allylation of aldehydes yielding the butyrolactone core of lignans.

The first targets demonstrate the cyclooctadienes isostegane¹⁴⁻²¹ and neoisostegane²²⁻²⁴ (**5** and **6**, see Figure 2). Stegane natural products show a high potential as pharmacophores, as they provide strong inhibition of the tubulin assembly,²⁵ a process of high importance in the treatment of cancer. Isostegane (**5**) is a synthetic congener of the lignan steganacine, whereas neoisostegane (**6**) was isolated directly from the plant. Both compounds were found in the extracts of *steganotaenia araliacea*^{26, 27} but interestingly possess the opposite axial chirality.^{26, 28} Most probably the substitution in C5 position (see Figure 2, structures **3** and **4**) defines the different alignment for the cyclization step in case of steganacine's biosynthesis.

Figure 2. Representatives of lignan natural products and target molecules of this study.

Another lignan natural product is (-)-α-conidendrin (**8**).²⁹⁻³¹ This compound has been a template for studies onto the C4 configuration of pharmacophores like podophyllotoxin (**7**) and sikkimotxin.³² Especially interesting is the different orientation of the lactone carbonyl moiety in the aryltetralin structure when compared to other representatives of the natural product subclass (see structures **7** and **8** in Figure 2) and this compound class has been the most prominent studied as podophyllotoxin (**7**) is the precursor to frequently used chemotherapeutics.^{33, 34}

The third class of lignan natural products are dibenzylbutyrolactones. We were able to show the application of the developed allylation methodology to the synthesis of (-)-hydroxymatairesinol (**9**) previously.¹³ Nevertheless, we were also able to obtain (-)-yatein (**10**), another lignan natural product of this subclass, on the route to isostegane (**5**).

The retrosynthetic strategy is outlined in Scheme 2. Isostegane (**5**) and neoisostegane (**6**) can be accessed via an iron^{III} mediated aryl-aryl coupling.³⁵ Yatein (**10**) is simply obtained from the corresponding hydroxyl-dibenzylbutyrolactone precursor via hydrogenative dehydroxylation under acidic conditions.³¹ (-)-α-Conidendrin (**8**) can be easily prepared via a Friedel-Crafts alkylation under acidic conditions from the corresponding hydroxy-dibenzylbutyrolactone.^{31, 36} The latter key intermediate can be obtained via Rh^I-catalyzed 1,4-addition of the arylboronate^{37, 38} and the previously reported TRIP-catalyzed asymmetric allylation.¹³

Scheme 2. General retrosynthetic analysis and natural products en route.

As the first synthetic target we picked isostegane (**5**, see Scheme 3 for forward synthesis). By our previous study of this reaction¹³ we knew that the (*R*)-configured catalyst **1** should yield the right enantiomer. The asymmetric allylation of piperonal proved more difficult than expected and required further reaction optimization. Under the previously published standard conditions¹³ we observed diminished values for the enantiomeric excess (82%) and only moderate yields for **12** (see Table 1, entry 1). This fact may be attributed to the cyclic ether moiety, which can – due to its freely available lone pairs – act as a Lewis base itself and lower the activation energy of the uncatalyzed background reaction. The same phenomenon was observed for furyl substituents in our previous study.¹³ In order to prevent this unwanted side reaction, we studied the reaction again with regard to the reaction medium, as we observed a high influence of the latter. Dilution of the reaction and higher concentration of the allylating reagent increased the enantiomeric excess again into the nineties, whereas the yield was only improved slightly (see Table 1, entry 2). Therefore we omitted the polar component of the reaction medium – namely diisopropylether – and increased the concentration again. This gave a significant boost to the conversion with only a slightly

worse stereoutcome (see Table 1, entry 3). Having the solvent system set, the next step was to further improve the enantiomeric excess, which was achieved by diluting the reaction again (see Table 1, entries 4 and 5). In order to supply an appropriate amount of starting material the reaction was scaled up and the values from the analytical scale experiments could be reproduced almost perfectly (see Table 1, entry 6).

Table 1. Reaction optimization – asymmetric allylation of piperonal (**11**).

Entry	Solvent	Conc. [mM]	Conv. ^{a)} [%]	ee ^{b)} [%]
1 ^{c)}	Toluene /Pr ₂ O	54	52	82
2	Toluene /Pr ₂ O	14	68	91
3	Toluene	54	94	89
4	Toluene	34	85	92
5	Toluene	23	82	94
6 ^{d)}	Toluene	23	81 ^{d)}	92

Reaction conditions: piperonal (**11**, 27 μ mol), **2** (3.4 eq.), Zn⁰ (6.3 eq.), NH₄Cl (9.0 eq.), (*R*)-TRIP (**1**, 20 mol-%), for solvent and substrate concentration see table; a) the conversion was determined via HPLC-UV at 215 nm; b) determined via HPLC-UV on a chiral stationary phase; c) standard reaction conditions from initial study: **2** (1.5 eq.);¹³ d) preparative scale on 0.27 mmol substrate; isolated yield is reported for this entry.

Having product **12** in hand, the second benzylic group was easily attached using a rhodium(I) catalyzed 1,4-addition to the exocyclic double bond yielding dibenzylbutyrolactone (**14**).^{37,38} Simple hydrogenation under acidic conditions removed the benzylic hydroxyl function cleanly and provided (-)-yatein (**10**) in 3 steps from piperonal (**11**) with an overall yield of 51% {[α]_D²⁰ = -16.06 (c = 1.1, CHCl₃), lit.: [α]_D²² = -30.0 (c = 0.15, CHCl₃)³⁹}. Treating this natural product with iron(III) perchlorate in the presence of trifluoroacetic acid gave isostegane {**5**, [α]_D²⁰ = +165.4 (c = 0.41, CHCl₃), lit.: [α]_D²⁰ = +154.0 (c = 0.7, CHCl₃)¹⁹} and the dibenzocyclooctadiene core of the natural product class in 92% yield and 47% overall yield via a four steps synthetic route. This compound differs from stegane only by the axial chirality of the biaryl system and can be interconverted into the latter by simply heating it up (200°C, 39% yield, 61% recovered isostegane).¹⁹

Scheme 3. Forward synthesis of (-)-yatein (**10**) and (+)-isostegane (**5**).

The same reaction sequence was tested with aldehyde **15** in order to obtain the corresponding precursors for the neoisostegane natural product (**6**). The allylation sequence was tested under the same reaction conditions as for piperonal (**11**,

see Table 1). However, the dimethoxy motif showed significantly more background reaction, probably by chelating a Zn²⁺ ion in between the two lewis basic lone pairs of the methoxy groups. The only way to prevent this increased background activity was to add higher amounts of catalyst (40 mol-%), which lead to similar results as for piperonal. Neither lower temperatures nor less polar reaction medium (e.g. cyclohexane cosolvent) allowed to reduce the high catalyst loading. The Michael acceptor **16** was then subjected to the same synthetic route as outlined for the preparation of isostegane (**5**): 1,4-Addition of the trimethoxy aromat in the presence of Rh^I, dehydroxylation via palladium on charcoal and hydrogen under acidic conditions and the same iron mediated cyclization step of the dibenzocyclooctadiene provided **6** in 43% overall yield over four steps. The last step of the sequence proved to be less selective in terms of diastereoselectivity [d.r. of 4.2:1 in favor of the desired natural product **6** (see Scheme 4); the other diastereoisomer is referred to as compound **24** (see experimental section)]. This may be attributed to the *ortho*-substituent of the trimethoxy substituted aromatic fragment, which may show more steric interaction with the benzylic CH₂-group^{23,35} or exhibit electronic repulsion between the methoxy oxygen lone pair(s) and the lactone carbonyl group and hamper the proper alignment for the cyclization. Nonetheless, the diastereomers could be separated via preparative HPLC and full characterization of both compounds was achieved. The optical rotation values for **6** and **24** show significant differences {**6**: [α]_D²⁰ = +105.2 (c = 1.68, CHCl₃), lit.: [α]_D²⁰ = +107.7 (c = 0.51, CHCl₃)²⁴ and **24**: [α]_D²⁰ = -119.6 (c = 0.26, CHCl₃)}. The stereochemical assignment was obtained via the coupling constants in the ¹H-NMR spectra, which show doublets for the 5 α -proton and the 8 β -proton is case of the *iso*-configuration, whereas the natural configuration of stegane yields a doublet of a doublet, as the coupling towards protons 6 and 7 becomes >0 Hz (for proton numbering see Scheme 4, structure **6**).²⁷ The absence of the ¹H,¹H-NOESY cross peak in the spectra of compounds **6** and **24** of the two adjacent protons of the lactone ring confirms the trans substitution of the five-membered ring.

Scheme 4. Forward synthesis of (+)-neoisostegane (**6**).

Next, we aimed at the aryltetraline motif. For this matter, (-)-hydroxymatairesinol (**9**) was prepared as previously described¹³ and simply treated with trifluoroacetic acid (see Scheme 5). The reaction provided cleanly (-)- α -conidendrin {**8**, [α]_D²⁰ = -35.8 (c = 0.35, acetone), lit.: [α]_D²⁰ = -51.6 (c = 2.1, acetone)³¹} in 76% yield. This refers to 40% overall yield over the four step synthetic route (see Scheme 5).

Scheme 5. Forward synthesis of (-)-α-conidendrin (8).

In conclusion we have shown the applicability of our recently developed asymmetric allylation protocol via the preparation of four different lignan natural products. We were able to achieve high yielding and concise protocols (40 – 47% overall yield over four steps) for three additional subclasses of lignan natural products – namely dibenzylbutyrolactones (represented by hydroxymatairesinol and yatein), aryltetralins (represented by α-conidendrin) and dibenzocyclooctadienes (represented by neoistegane). After reoptimization the allylation key step provided the desired precursors in high yields (71 – >99%) and excellent stereoselectivities (92 – 98% ee, d.r. = >95:5), although on the expense of high catalyst loadings, in order to suppress the racemic background reaction.

EXPERIMENTAL SECTION

General.

All chemicals were purchased from Sigma Aldrich or Acros Organics and were used as received unless otherwise noted. All solvents were purchased from Roth. All moisture sensitive reactions were operated using standard Schlenk techniques with dry argon. Analytical thin layer chromatography (TLC) was carried out on Merck TLC silica gel aluminum sheets (silica gel 60, F₂₅₄, 20 x 20 cm) and spots were visualized by UV light (λ = 254 nm) and by staining with cerium ammonium molybdate solution [50 g (NH₄)₆Mo₇O₂₄ were dissolved in 400 mL H₂O and 50 mL conc. H₂SO₄ was added followed by 2.0 g Ce(SO₄)₂ or KMnO₄ solution (1 g KMnO₄ and 2 g Na₂CO₃ were dissolved in 100 mL H₂O) and developed by heating with a heat gun. Column chromatography was performed on silica gel 60 from Merck with particle sizes 40-63 μm. A 30- to 100-fold excess of silica gel was used with respect to the mass of dry crude product, depending on the separation problem. NMR spectra were recorded on a Bruker NMR unit at 300 (¹H) and 75 (¹³C) MHz, shifts are given in ppm and coupling constants (*J*) are given in Hz. Deuterated solvents for nuclear resonance spectroscopy were purchased from Roth. IR-spectra were recorded neat on a Bruker Alpha-P (ATR) instrument. Melting points were determined on a Gallenkamp MPD350.BM2.5 apparatus with an integrated microscopical support. They were measured in open capillary tubes with a mercury-in-glass thermometer and were not corrected. High resolution mass spectra were recorded on an Agilent 6230 TOF LC/MS using ESI (positive mode, capillary voltage 1.6 kV) or APCI (negative mode, 5.0 kV) methods. Chiral HPLC analysis was performed on a Shimadzu HPLC system with *n*-heptane/2-PrOH as eluent. Optical rotation values were measured on a Perkin Elmer

Polarimeter 341 or an Anton Paar MCP5100 unit. Compounds 2 and 9 were prepared as previously described.¹³

(R)-4-[(S)-benzo[d][1,3]dioxol-5-yl(hydroxy)methyl]-3-methylenedihydrofuran-2(3H)-one (12). (R)-TRIP (40 mg, 0.053 mmol, 20 mol-%), zinc dust (< 10 μm, 110 mg, 1.7 mmol), ammonium chloride (130 mg, 2.4 mmol) and piperonal (11, 40 mg, 0.27 mmol) were combined in a round bottom flask. Toluene (8 mL) was added, followed by allylic bromide 2 (71.7 mg, 0.41 mmol) and the mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of NH₄Cl_{sat.}, aq. solution (10 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phase was dried over Na₂SO₄, filtered and concentrated. The obtained crude product was purified via flash chromatography (SiO₂, hexanes/EtOAc 3/1 to 2/1) to give the title compound 12 as a white solid (54 mg, 0.22 mmol, 81%). Mp: 107-109 °C (from CDCl₃); [α]_D²⁰ = +8.9 (c = 0.91, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): 6.84 (s, 1H), 6.78 (s, 2H), 6.35 (d, *J* = 2.1, 1H), 5.97 (s, 2H), 5.86 (d, *J* = 2.1, 1H), 4.59 (d, *J* = 8.0, 1H), 4.15 (dd, *J*₁ = 9.6, *J*₂ = 8.3, 1H), 4.01 (dd, *J*₁ = 9.6, *J*₂ = 4.5, 1H), 3.39-3.30 (m, 1H), 2.25 (br s, 1H); ¹³C{¹H}-NMR (75 MHz, CDCl₃): 170.8, 148.3, 147.9, 135.2, 134.8, 125.6, 120.4, 108.4, 106.8, 101.4, 75.6, 67.6, 45.6; IR (film) $\tilde{\nu}$ = 3408, 1733, 1488, 1443, 1396, 1379, 1248, 1144, 1039, 1005, 958, 930, 821; HRMS(ESI): *m/z*: calc. for C₁₃H₁₃O₅⁺: 249.0758 [M+H]⁺, found: 249.0756; HPLC analysis on a chiral stationary phase: Daicel Chiralpak IA (4.6 x 250 mm, 5 μm particle size), *n*-heptane/2-propanol 75/25, 1.0 mL/min, 30 °C, UV 230 nm, *t*_{ret}(enantiomer 1) = 8.0 min, *t*_{ret}(enantiomer 2) = 10.2 min; *t*_{ret}(major isomer) = 10.2 min, ee = 92%.

(3R,4R)-4-[(S)-benzo[d][1,3]dioxol-5-yl(hydroxy)methyl]-3-(3,4,5-trimethoxybenzyl)dihydrofuran-2(3H)-one (14). [Rh(cod)Cl]₂ (3 mg, 0.007 mmol), the boronic acid pinacol ester 13 (97 mg, 0.33 mmol) and 12 (54 mg, 0.22 mmol) were dissolved in dioxane (600 μL). Water (150 μL) and Et₃N (30 μL, 22 mg, 0.22 mmol) were added and the mixture was stirred at 70°C for 3 h. The obtained orange solution was diluted with EtOAc (10 mL), washed with NaHCO₃ sat., aq. solution and the aqueous solution was reextracted with EtOAc (2 x 10 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified via flash chromatography (SiO₂, toluene/EtOAc 3/1) to give the desired compound 14 as a colorless oil (80 mg, 0.19 mmol, 87%). [α]_D²⁰ = -10.6 (c = 1.45, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): 6.74-6.66 (m, 3H), 6.35 (s, 2H), 5.95 (dd, *J*₁ = 3.8, *J*₂ = 1.2, 2H), 4.62 (d, *J* = 6.5, 1H), 3.94 (d, *J* = 7.6, 2H), 3.80 (s, 9H), 3.04-2.85 (m, 3H), 2.60 (p, *J* = 7.2, 1H), 2.36 (br s, 1H); ¹³C{¹H}-NMR (75 MHz, CDCl₃): 179.1, 153.0, 148.1, 147.5, 136.6, 135.5, 133.3, 119.2, 108.2, 106.6, 106.1, 101.3, 75.2, 68.4, 60.8, 56.1, 45.0, 43.6, 35.5; IR (film) $\tilde{\nu}$ = 3487 (br), 2939, 2839, 1757, 1591, 1505, 1488, 1459, 1443, 1422, 1384, 1348, 1322, 1237, 1185, 1123, 1033, 1005, 909, 813, 782, 726; HRMS(ESI): *m/z*: calc. for C₂₂H₂₄O₈NH₄⁺: 434.1809 [M+NH₄]⁺, found: 434.1809.

(-)-Yatein (10). Compound 14 (68 mg, 0.16 mmol) was dissolved in EtOH (5.5 mL). Pd/C (10 wt-%, 20.4 mg, 2.0 mg Pd, 0.019 mmol, 0.07 eq.) and HClO₄ (70 wt-%, 15 μL) were added and the reaction mixture was placed under an atmosphere of hydrogen and stirred for 16 h. The mixture was passed through a pad of celite, the pad was washed with EtOAc (20

mL) and the combined filtrate was washed with NaHCO_3 sat. aq. solution (10 mL). The phases were separated and the aqueous phase was reextracted with EtOAc (2 x 20 mL) and the combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The obtained crude product was purified via flash chromatography (SiO_2 , hexanes/EtOAc 1/1) to give product **10** as yellow oil (46 mg, 0.11 mmol, 72%). $[\alpha]_{\text{D}}^{20} = -16.06$ ($c = 1.1$, CHCl_3), lit.: $[\alpha]_{\text{D}}^{22} = -30.0$ ($c = 0.15$, CHCl_3).³⁹ $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.72 – 6.66 (m, 1H), 6.50 – 6.43 (m, 2H), 6.35 (s, 2H), 5.93 (dd, $J_1 = 2.9$, $J_2 = 1.4$ Hz, 2H), 4.17 (dd, $J_1 = 9.2$, $J_2 = 7.1$ Hz, 1H), 3.90–3.85 (m, 1H), 3.83 (s, 6H), 3.82 (s, 3H), 2.90 (dd, $J_1 = 5.8$, $J_2 = 3.2$ Hz, 2H), 2.66 – 2.41 (m, 4H); $^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (75 MHz, CDCl_3): 178.7, 153.4, 148.1, 146.5, 137.0, 133.5, 131.7, 121.7, 108.9, 108.4, 106.3, 101.2, 71.3, 61.0, 56.2, 46.6, 41.2, 38.5, 35.4; IR (film) $\tilde{\nu} = 2937$, 2840, 1764, 1590, 1504, 1489, 1459, 1444, 1422, 1345, 1320, 1239, 1186, 1124, 1035, 1011, 909, 810, 726; HRMS(ESI): m/z : calc. for $\text{C}_{22}\text{H}_{25}\text{O}_7^+$: 401.1595 $[\text{M}+\text{H}]^+$, found: 401.1594.

(+)-Isostegane (5). (–)-Yatein (**10**, 24.0 mg, 0.06 mmol) was dissolved in CH_2Cl_2 (1.0 mL). $\text{Fe}(\text{ClO}_4)_3$ (50.0 mg, 0.14 mmol, 2.4 eq.) was added, followed by trifluoroacetic acid (100 μL , 149 mg, 1.3 mmol, 22 eq.). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by the addition of NaHCO_3 sat. aq. solution and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified via flash chromatography (SiO_2 , hexanes/EtOAc 1/1) to give **5** as a yellow oil (21.8 mg, 0.055 mmol, 92% yield). $[\alpha]_{\text{D}}^{20} = +165.4$ ($c = 0.41$, CHCl_3), lit.: $[\alpha]_{\text{D}}^{20} = +154.0$ ($c = 0.7$, CHCl_3).¹⁹ $^1\text{H-NMR}$ (300 MHz, CDCl_3): 6.70 (s, 1H), 6.62 (s, 1H), 6.62 (s, 1H), 6.00 (d, $J = 1.4$, 1H), 5.97 (d, $J = 1.4$ Hz, 2H), 4.37 (dd, $J_1 = 8.4$, $J_2 = 6.3$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 4H), 3.77 (dd, $J_1 = 11.1$, $J_2 = 8.7$ Hz, 1H), 3.57 (s, 3H), 3.12 (d, $J = 13.3$ Hz, 1H), 2.64 (d, $J = 13.1$ Hz, 1H), 2.39 (dd, $J_1 = 13.1$, $J_2 = 9.3$ Hz, 1H), 2.29 (dd, $J_1 = 13.3$, $J_2 = 9.1$ Hz, 1H), 2.14 – 2.04 (m, 1H); $^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (75 MHz, CDCl_3): 176.7, 153.5, 152.0, 147.8, 146.1, 141.0, 136.2, 132.5, 128.5, 126.6, 111.9, 108.9, 107.6, 101.4, 70.2, 61.1, 61.0, 56.2, 50.2, 47.2, 34.3, 32.5; IR (film) $\tilde{\nu} = 2922$, 2852, 1772, 1595, 1482, 1454, 1403, 1339, 1223, 1142, 1119, 1102, 1081, 1034, 994, 921; HRMS(ESI): m/z : calc. for $\text{C}_{22}\text{H}_{23}\text{O}_7^+$: 399.1438 $[\text{M}+\text{H}]^+$, found: 399.1437.

(R)-4-[(S)-(3,4-dimethoxyphenyl)(hydroxy)methyl]-3-methylenedihydrofuran-2(3H)-one (16). (R)-TRIP (84 mg, 0.112 mmol, 40 mol-%), zinc dust (< 10 μm , 112 mg, 1.7 mmol), ammonium chloride (128 mg, 2.4 mmol) and 3,4-dimethoxybenzaldehyde (**15**, 46 mg, 0.28 mmol) were combined in a round bottom flask. Toluene (11.4 mL) was added, followed by allylic bromide **2** (168 mg, 0.95 mmol) and the mixture was stirred for 16 h at 4°C. The reaction was quenched by the addition of NH_4Cl sat. aq. solution (10 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The obtained crude product was purified via flash chromatography (SiO_2 , toluene/EtOAc 3/2) to give the title compound **16** as a white solid (74 mg, 0.28 mmol, >99%). Mp: 70–74 °C (from CDCl_3); $[\alpha]_{\text{D}}^{20} = +14.4$ ($c = 1.7$, acetone); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.88 – 6.85 (m, 3H), 6.36 (d, $J = 1.9$, 1H), 5.85 (dd, $J_1 = 2.1$, $J_2 = 0.7$ Hz, 1H), 4.62 (d, $J = 8.0$ Hz, 1H), 4.15 (dd, $J_1 = 9.6$, $J_2 = 8.3$ Hz, 1H), 4.02 (dd, $J_1 = 9.6$, $J_2 = 4.4$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.43 – 3.33 (m, 1H),

2.34 (br s, 1H); $^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (75 MHz, CDCl_3): 170.8, 149.4, 149.3, 135.3, 133.4, 125.5, 119.1, 111.1, 109.4, 75.7, 67.7, 56.1, 45.7; IR (film) $\tilde{\nu} = 3249$ (br), 1760, 1751, 1516, 1507, 1461, 1260, 1237, 1143, 1123, 1022, 1003, 988, 950, 912, 856, 818, 725, 649; HPLC analysis on a chiral stationary phase: Daicel Chiralpak IE (4.6 x 250 mm, 5 μm particle size), *n*-heptane/2-propanol 70/30, 0.9 mL/min, 30 °C, UV 215 nm, t_{ret} (enantiomer 1) = 11.8 min, t_{ret} (enantiomer 2) = 13.2 min; t_{ret} (major isomer) = 13.3 min, ee = 95%; HRMS(ESI): m/z : calc. for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{NH}_4^+$: 282.1336 $[\text{M}+\text{NH}_4]^+$, found: 282.1338.

(3R,4R)-4-[(S)-(3,4-dimethoxyphenyl)(hydroxy)methyl]-3-(2,3,4-trimethoxybenzyl)dihydrofuran-2(3H)-one (18). $[\text{Rh}(\text{cod})\text{Cl}]_2$ (3 mg, 0.007 mmol), the (2,3,4-trimethoxyphenyl)boronic acid (**17**, 64 mg, 0.30 mmol), Et_3N (28 μL , 20 mg, 0.2 mmol) and lactone **16** (52 mg, 0.20 mmol) were dissolved in dioxane/water 4/1 (600 μL) in a 10 mL Biotage vial. The vial was capped and crimped and placed in a preheated oil bath (55°C oil bath temperature) and stirred for 20 h. The reaction mixture was cooled to room temperature, quenched in NaHCO_3 aq. sat. solution (10 mL) and the obtained slurry was extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified via flash chromatography (SiO_2 , toluene/EtOAc 1/1) to give the desired compound **18** as a yellow oil (62 mg, 0.14 mmol, 72%). $[\alpha]_{\text{D}}^{20} = -23.8$ ($c = 0.41$, CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3): 6.88 (d, $J = 8.6$ Hz, 1H), 6.82 – 6.70 (m, 3H), 6.60 (d, $J = 8.6$ Hz, 1H), 4.50 (d, $J = 8.0$ Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 – 3.82 (m, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.10 (qd, $J_1 = 13.9$, $J_2 = 5.7$ Hz, 2H), 2.93 (dt, $J_1 = 7.9$, $J_2 = 5.7$ Hz, 1H), 2.55 (p, $J = 7.8$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (75 MHz, CDCl_3): 178.9, 153.0, 151.5, 149.4, 149.1, 142.1, 134.4, 125.6, 123.3, 118.3, 111.3, 109.3, 108.1, 76.4, 68.6, 61.3, 61.0, 56.1, 56.0, 45.9, 44.5, 29.5; IR (film) $\tilde{\nu} = 3496$ (br), 3008, 2937, 2837, 1754, 1603, 1514, 1494, 1465, 1417, 1257, 1234, 1184, 1153, 1139, 1095, 1023, 808, 748; HRMS(ESI): m/z : calc. for $\text{C}_{23}\text{H}_{28}\text{O}_8\text{NH}_4^+$: 450.2122 $[\text{M}+\text{NH}_4]^+$, found: 450.2130.

(3R,4R)-4-(3,4-dimethoxybenzyl)-3-(3,4,5-trimethoxybenzyl)dihydrofuran-2(3H)-one (19). Compound **18** (60 mg, 0.14 mmol) was dissolved in MeOH (3 mL). Pd/C (10 wt-%, 30.0 mg, 3.0mg Pd, 0.03 mmol, 0.2 eq.) and HClO_4 (70 wt-%, 30 μL) were added and the reaction mixture was placed under an atmosphere of hydrogen and stirred for 16 h. The mixture was passed through a pad of celite, the pad was washed with CH_2Cl_2 (10 mL) and the combined filtrate was washed with NaHCO_3 aq. sat. solution (10 mL). The aqueous phase was reextracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The obtained crude product was purified via flash chromatography (SiO_2 , cyclohexane/EtOAc 2/1) to give product **19** as yellow oil (46 mg, 0.11 mmol, 79%). $[\alpha]_{\text{D}}^{20} = -44.0$ ($c = 2.3$, CHCl_3), lit.: $[\alpha]_{\text{D}}^{22} = -48.6$ ($c = 1.23$, CHCl_3).²⁴ $^1\text{H-NMR}$ (300 MHz, CDCl_3): 6.88 (d, $J = 8.5$ Hz, 1H), 6.72 (d, $J = 8.7$ Hz, 1H), 6.60 (d, $J = 8.5$ Hz, 1H), 6.58 – 6.49 (m, 2H), 4.10 (dd, $J_1 = 9.1$, $J_2 = 7.2$ Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.89 – 3.80 (m, 1H), 3.83 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.15 (dd, $J_1 = 13.8$, $J_2 = 5.0$ Hz, 1H), 2.83 (dd, $J_1 = 13.8$, $J_2 = 7.6$ Hz, 1H), 2.73 – 2.44 (m, 3H), 2.34 (dd, $J_1 = 13.2$, $J_2 = 9.1$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (75 MHz, CDCl_3): 178.9, 153.0, 152.2, 149.1, 147.9, 142.3, 131.1, 125.1, 123.9, 120.6, 111.9, 111.4, 107.5, 71.5, 61.0, 60.9, 56.1, 56.0,

55.9, 45.8, 42.1, 38.3, 29.6; IR (film) $\tilde{\nu}$ = 3000, 2936, 2836, 1765, 1601, 1514, 1494, 1464, 1417, 1381, 1261, 1235, 1198, 1154, 1095, 1065, 1012, 804, 749; HRMS(ESI): m/z : calc. for $C_{23}H_{28}O_7NH_4^+$: 434.2173 $[M+NH_4]^+$, found: 434.2173.

(+)-Neoisostegane (6). Compound **19** (36 mg, 86 μ mol) was dissolved in CH_2Cl_2 (1.4 mL). $Fe(ClO_4)_3 \cdot 7H_2O$ (73 mg, 210 μ mol) and trifluoroacetic acid (140 μ L) were added and the reaction mixture was stirred at room temperature for 21 h. The reaction was quenched by the addition of $NaHCO_3$ aq. sat. solution (5 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The obtained crude product was purified via flash chromatography (SiO_2 , cyclohexane/EtOAc 3/2) to give a mixture of compound **6** and diastereoisomer **24** (32 mg, 77 μ mol, 90%, d.r. = 4.2 : 1 in favour of compound **6**). This mixture was further purified via preparative HPLC [Phenomenex LUNA AXIATM pack (5 μ m, C18(2), 100 Å, 250 x 21.2 mm), 30 mL/min flow, isocratic eluent: $H_2O/MeCN$ 60/40] to give neoistegane (**6**, 27 mg, 65 μ mol, 76%) as a pale yellow oil (from $CHCl_3$) and compound **24** (4.2 mg, 10 μ mol, 12%) as a pale yellow oil (from $CHCl_3$).

(+)-Neoisostegane (6): $[\alpha]_D^{20}$ = +105.2 (c = 1.68, $CHCl_3$), lit.: $[\alpha]_D^{20}$ = +107.7 (c = 0.51, $CHCl_3$);²⁴ 1H -NMR (300 MHz, $CDCl_3$): 6.71 (s, 1H), 6.68 (s, 1H), 6.51 (s, 1H), 4.38 (dd, J_1 = 8.4, J_2 = 6.7 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 6H), 3.87 (s, 3H), 3.85 (s, 3H), 3.77 (dd, J_1 = 11.3, J_2 = 8.4 Hz, 1H), 3.67 (d, J = 13.0 Hz, 1H), 2.66 (d, J = 13.1 Hz, 1H), 2.41 (dd, J_1 = 13.2, J_2 = 9.9 Hz, 1H), 2.28–2.15 (m, 1H), 2.02 (dd, J_1 = 13.0, J_2 = 9.1 Hz, 1H), 1.91 (dd, J_1 = 13.1, J_2 = 9.2 Hz, 1H); $^{13}C\{^1H\}$ -NMR (75 MHz, $CDCl_3$): 176.4, 151.6, 150.7, 149.0, 147.5, 142.1, 136.3, 132.6, 131.0, 126.8, 114.1, 112.3, 109.8, 70.1, 61.2, 60.9, 56.24, 56.22, 56.20, 49.9, 46.9, 34.4, 24.2; IR (film) $\tilde{\nu}$ = 3013, 2936, 2847, 1774, 1603, 1570, 1517, 1490, 1464, 1445, 1398, 1341, 1326, 1280, 1253, 1224, 1209, 1172, 1117, 1098, 1081, 1066, 1035, 994, 958, 938, 914, 845, 701, 747; HRMS(ESI): m/z : calc. for $C_{23}H_{26}O_7NH_4^+$: 432.2017 $[M+NH_4]^+$, found: 432.2023

Compound 24: $[\alpha]_D^{20}$ = -119.6 (c = 0.26, $CHCl_3$); 1H -NMR (300 MHz, $CDCl_3$): 6.74 (s, 1H), 6.59 (s, 1H), 6.44 (s, 1H), 4.32 (dd, J_1 = 8.5, J_2 = 7.5 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 3.76 (dd, J_1 = 11.0, J_2 = 8.5 Hz, 1H), 3.38 (dd, J_1 = 15.9, J_2 = 7.7 Hz, 1H), 2.96 (dd, J_1 = 14.6, J_2 = 7.9 Hz, 1H), 2.73 (dd, J_1 = 15.9, J_2 = 7.9 Hz, 1H), 2.62 – 2.47 (m, 1H), 2.43 – 2.33 (m, 2H); $^{13}C\{^1H\}$ -NMR (75 MHz, $CDCl_3$): 178.8, 152.0, 151.6, 148.3, 147.7, 141.7, 137.1, 134.4, 128.6, 123.8, 114.0, 113.1, 110.1, 70.5, 61.2, 61.0, 56.28, 56.24, 56.17, 42.2, 40.8, 33.3, 29.9, 25.1; IR (film) $\tilde{\nu}$ = 2933, 2851, 1768, 1603, 1569, 1517, 1488, 1463, 1448, 1420, 1399, 1346, 1318, 1261, 1247, 1213, 1169, 1144, 1116, 1095, 1071, 1049, 1010, 991, 955, 935, 911; HRMS(ESI): m/z : calc. for $C_{23}H_{26}O_7NH_4^+$: 432.2017 $[M+NH_4]^+$, found: 432.2022.

(-)- α -Conidendrin (8). Hydroxymatairesinol (**9**, 37 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (200 μ L). Trifluoroacetic acid (25 μ L, 37 mg, 0.33, 3.3 eq.) was added and the reaction mixture was stirred for 24 h at room temperature. The obtained solution was directly applied to flash chromatography (silica gel, hexanes/EtOAc 1/2) to give (-)- α -conidendrin (**8**, 27 mg,

0.076 mmol, 76%). Mp: 224–226 °C (from acetone), lit.: 222–224 °C;³¹ $[\alpha]_D^{20}$ = -35.8 (c = 0.35, acetone), lit.: $[\alpha]_D^{20}$ = -51.6 (c = 2.1, acetone);³¹ 1H -NMR (300 MHz, methanol- d_4): 6.78–6.75 (m, 2H), 6.69 – 6.63 (m, 2H), 6.26 (s, 1H), 4.22 – 4.03 (m, 2H), 3.90 (d, J = 10.6 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.12 (dd, J_1 = 15.5, J_2 = 4.8 Hz, 1H), 3.00 – 2.83 (m, 1H), 2.74–2.52 (m, 2H); $^{13}C\{^1H\}$ -NMR (75 MHz, methanol- d_4): 180.0, 149.4, 147.9, 146.7, 145.9, 135.8, 133.3, 127.5, 122.4, 117.0, 116.3, 113.3, 112.7, 73.4, 56.4, 50.7, 43.0, 30.2; IR (film) $\tilde{\nu}$ = 3402 (br), 2956, 2929, 2522, 1757, 1613, 1598, 1583, 1509, 1468, 1440, 1426, 1365, 1351, 1323, 1242, 1196, 1153, 1109, 1086, 1027, 995, 927, 913, 890, 873, 779, 748, 733; HRMS(ESI): m/z : calc. for $C_{20}H_{21}O_6^+$: 357.1333 $[M+H]^+$, found: 357.1332.

ASSOCIATED CONTENT

Supporting Information

For 1H - and ^{13}C -NMR data and HPLC chromatograms see the electronic supporting information.

The Supporting Information is available free of charge on the ACS Publications website.

NMR and HPLC data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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