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A Concise Atroposelective Formal Synthesis of (–)-Steganone

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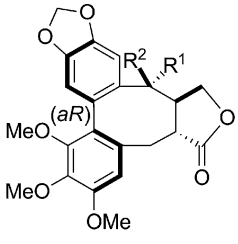
We describe herein the atroposelective formal synthesis of (–)-steganone, a parent member of *Steganotaenia araliacea* dibenzocyclooctadiene lignan lactones. Our synthesis features an atropodiastereoselective biaryl Suzuki–Miyaura cross-coupling reaction with *de* up to 99 % using as a chiral auxiliary an enantiopure and efficiently converted β-hydroxy sulfoxide derivative.

Introduction

(–)-Stegane (**1**) and its related compounds (–)-steganone (**2**) and (–)-steganacin (**3**) are dibenzocyclooctadiene lignan lactones isolated in 1973 from *Steganotaenia araliacea* (Figure 1).[1] Over the past two decades, these natural products have attracted considerable synthetic interest owing to their biological activities such as in vivo activity against P-388 leukemia in mice and in vitro activity against cells derived from a human nasopharynx (KB) carcinoma cell line.[1] (–)-Steganacin is known to inhibit the in vitro polymerization of microtubules and also binds to mammalian tubulin with an affinity comparable to that of colchicine.[2]



$R^1 = R^2 = H$: (–)-stegane (**1**)
$R^1, R^2 = O$: (–)-steganone (**2**)
$R^1 = OAc$, $R^2 = H$: (–)-steganacin (**3**)

Figure 1. Cyclooctadiene lignan lactones.

One of the most remarkable features of these structures is an unsymmetrical biaryl moiety with axial chirality. Many synthetic studies towards stegane, steganone and steganacin analogs have been described with various strategies to control the axial chirality of the biaryl system. These strategies have included oxidative biaryl coupling,[3] photocyclization,[4] S_NAr reactions,[5] Ullmann coupling[6] and Suzuki–Miyaura coupling chemistries.[7] The latter has been proven to be a valuable method for the atroposelective synthesis of the biaryl skeleton. Uemura et al.[7a,7b] reported the use of enantiopure bromoarene-chromium tricarbonyl complexes in the Suzuki–Miyaura coupling reaction with boronic acids to give, in high atroposelectivity, the biaryl skeleton of (–)-steganone.[7c] Baudoin et al. reported the ability to control biaryl configuration[7d] by exploiting a benzylic stereocenter through an atropodiastereoselective Suzuki–Miyaura coupling (*de* 74%). Harayama et al.[7e,7f] extended Bringmann's lactone strategy[8] to the enantioselective synthesis of the biphenyl moiety of stegane with an *ee* of 83%.

Recently, we reported on an atropodiastereoselective Suzuki–Miyaura coupling reaction, employing enantiopure β-hydroxy sulfoxide derivatives as chiral auxiliaries (Scheme 1).[9] The advantages of sulfoxides include i) the ability to introduce them readily in enantiomerically pure form, ii) their ability to serve as efficient stereocontrollers, and iii) their facile conversion into synthetically valuable functional groups suitable for further transformations.[10]

The excellent diastereoselectivities that we have already observed in the formation of the biaryl axis,[9] for example in the preparation of the biaryl subunit of vancomycin,[11] prompted us to investigate if the developed method would also be applicable to the synthesis of the biaryl part of (–)-steganone. Accordingly, we report in this paper a totally atropodiastereoselective synthesis of the known biaryl skeleton[7a,7f] of (–)-steganone.

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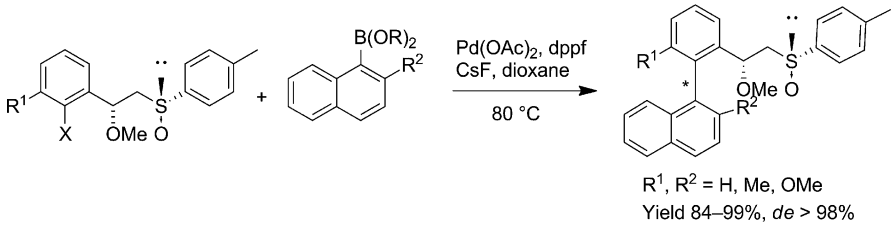


Scheme 1. Atropodiastereoselective Suzuki–Miyaura coupling reaction using enantiopure β-hydroxy sulfoxide derivatives as chiral auxiliaries.

Results and Discussion

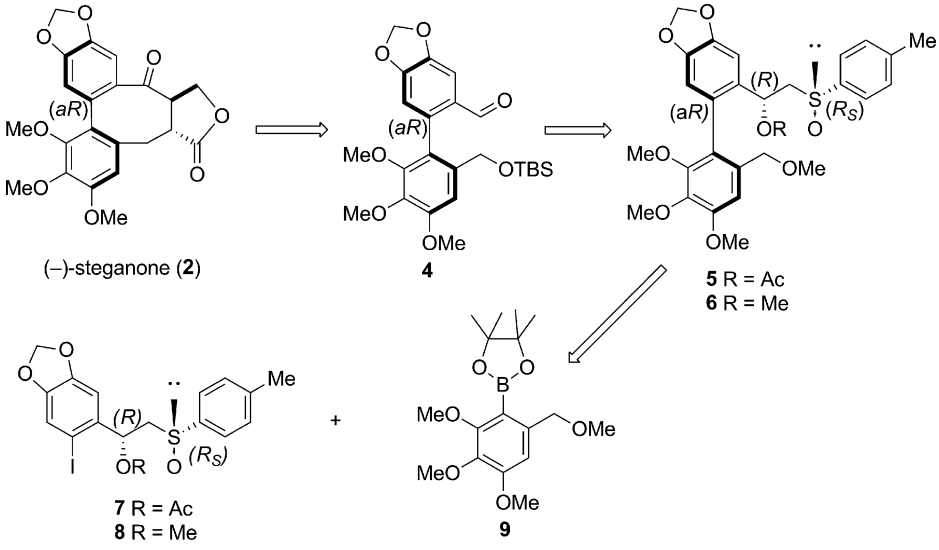
From a retrosynthetic point of view, boronic ester **9** and enantiopure aryl iodides **7** and **8** represent suitable building blocks for the envisaged atroposelective synthesis of the known biaryl skeleton **4** of (–)-steganone (Scheme 2).[12]

As outlined in Scheme 3, the synthesis of aryl iodides **7** and **8** commenced from commercially available piperonal (**10**).

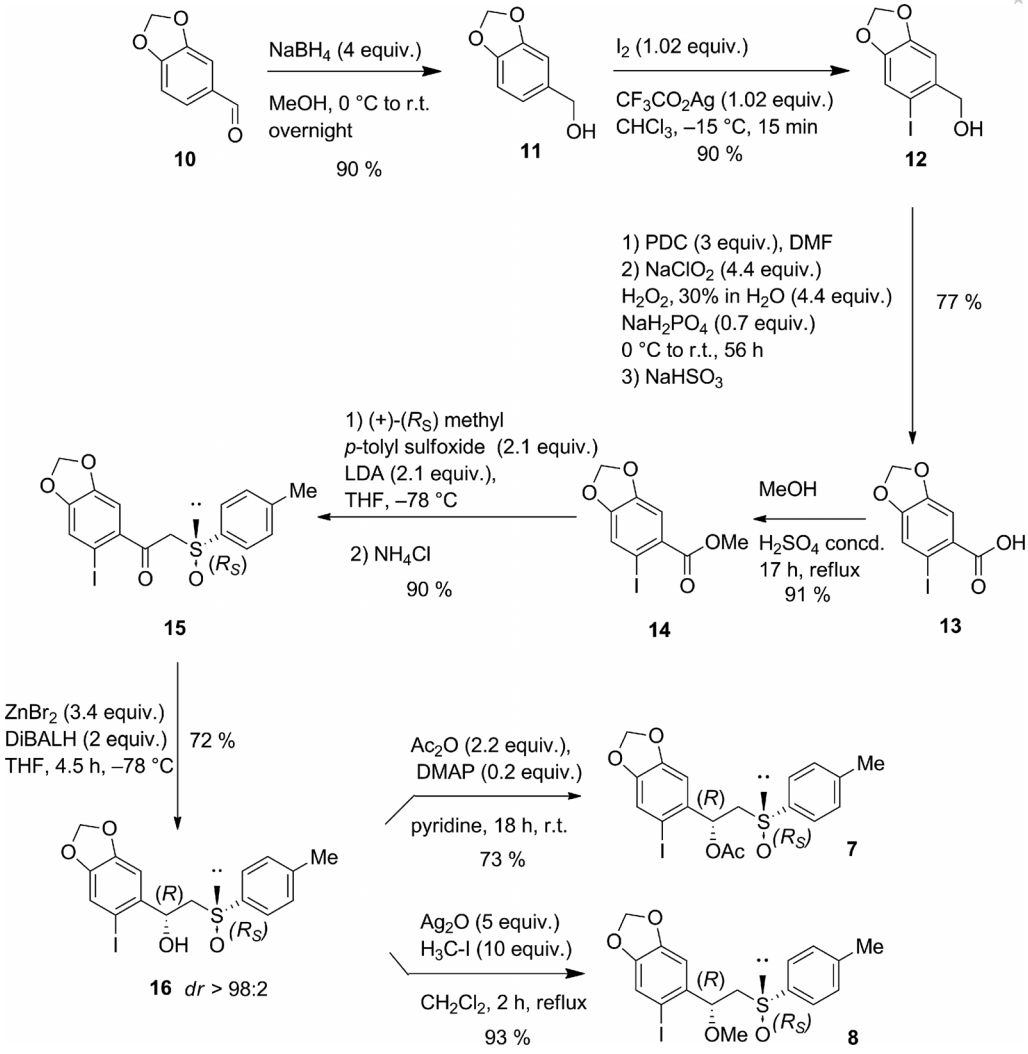
Reduction of the carbonyl function with $NaBH_4$ in MeOH followed by regioselective iodination in the presence of silver trifluoroacetate afforded corresponding iodide **12** in 81% yield over two steps. Corey and Schmidt[13] oxidation of the primary alcohol in **12** gave the aldehyde, which was directly transformed in 77% yield into carboxylic acid **13** using Pinnick conditions.[14] The corresponding methyl ester **14** was then subjected to addition of the lithiated anion of (+)-(R_S)-methyl *p*-tolyl sulfoxide (LDA, THF, –78 °C to 0 °C) to afford the β-keto sulfoxide **15** in 90% yield. Subsequent diastereoselective reduction of β-keto sulfoxide **15** with diisobutylaluminium hydride in the presence of zinc bromide provided (2*R*,R_S)-β-hydroxy sulfoxide **16** in which the OH group is *syn* to the bulky substituent of the sulfoxide as expected.[15] β-Hydroxy sulfoxide **16** was obtained in good yield (72%) and with excellent diastereoselectivity (*dr* > 98:2). In the last step to the aryl iodides, the stereogenic carbinol in **16** was converted into acetate **7** with acetic anhydride in pyridine (73% yield) and into methyl ether **8** with methyl iodide in the presence of silver oxide (93% yield).

We next focused on the synthesis of boronic ester **9**, which is summarized in Scheme 4. Protection of the hydroxy groups of commercially available ethyl gallate (**17**) in the presence of K_2CO_3 and methyl iodide afforded **18** (96% yield), whose ester function was reduced with $LiAlH_4$ affording primary alcohol **19**. Subsequent protection of **19** furnished fully protected compound **20** in 92% yield. The following iodination in the presence of silver trifluoroacetate and I_2 gave aryl iodide **21** in an excellent yield of 92%. The palladium-catalyzed borylation[16] of aryl iodide **21** proceeded efficiently in 72% yield on treatment with pinacol borane in the presence of SPhos,[16b] palladium acetate and triethylamine at 80 °C affording pinacol boronic ester **9** in 4 h reaction time. The use of other types of ligands such as DPEPhos[16c] also led to **9** with the same yield but in a reaction time of 18 h. Alternatively, using (dicyclohexylphosphino)biphenyl[16d] enabled generation of **9** in a shorter reaction time (0.5 h) but with a lower yield of 60%.

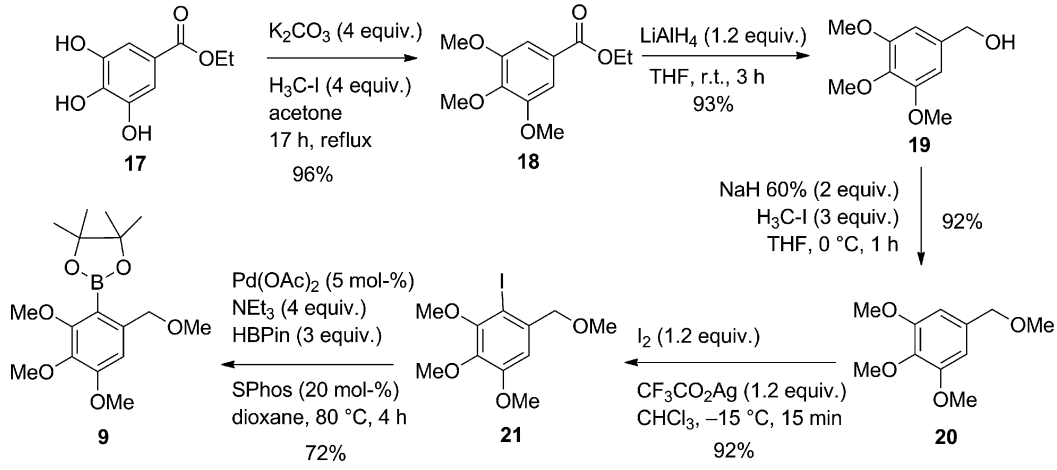
With the requisite substrates in hand, boronic ester **9** and iodides **7** and **8**, the crucial atroposterereoselective construction of the biaryl skeleton of (–)-steganone **2** by Suzuki–Miyaura coupling reaction was performed. We initially investigated the cross-coupling reaction between boronic ester **9** and aryl iodide **7** bearing an acetoxy substituent at the



Scheme 2. Retrosynthetic approach to the biaryl skeleton **4** of (–)-steganone.



Scheme 3. Synthesis of iodides **7** and **8** bearing an enantiopure sulfinyl moiety.

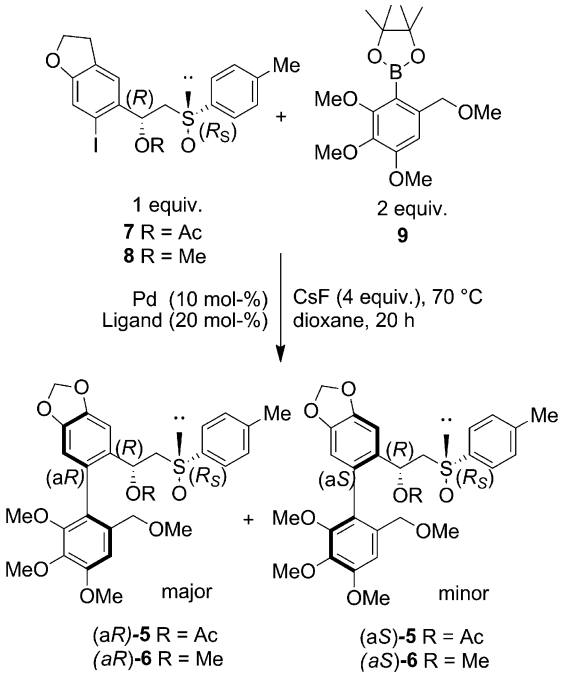


Scheme 4. Synthesis of boronic ester **9**.

side-chain using different palladium catalysts, various types of ligands, and CsF as base in 1,4-dioxane at 70 °C over the course of 20 h (Table 1). The first attempt with $Pd(OAc)_2$ and SPhos as the ligand afforded a 91:9 mixture of atropoisomers (a*R*)-**5** and (a*S*)-**5** in 61 % combined yield (Table 1, Entry 1). The use of the more bulky XPhos ligand[17] improved the atropodiastereoselectivity as only one atropodiastereomer was detected by ^{1}H NMR although the overall

reaction yield decreased to 32% (Table 1, Entry 2). Finally, the use of XPhos/palladium(II)/phenethylamine chloride as a precatalyst, known to be very efficient in sterically hindered Suzuki–Miyaura coupling reactions,[18] enabled us to obtain 68% of atropoisomer (a*R*)-**5** in enantiomerically pure form (Table 1, Entry 3). The use of (*S*)-BINAP or Pd-PEPPSI-*i*Pr[19] was not successful for the coupling reaction.

Table 1. Summary of reaction conditions and yields for Suzuki–Miyaura coupling reaction trials.



Entry	R	Pd/ligand	Yield[a] [%]	*dr* [a*R*/a*S*][b]
1	Ac	$Pd(OAc)_2$ /SPhos	61	91:9
2	Ac	$Pd(OAc)_2$ /XPhos	32	> 98:2
3	Ac	XPhos palladacycle	68	> 98:2
4	Me	$Pd(OAc)_2$ /SPhos	55	83:17
5	Me	$Pd(OAc)_2$ /XPhos	61	79:21
6	Me	$Pd(OAc)_2$ /DavePhos	36	83:17
7	Me	$Pd(PPh_3)_4$	53	> 98:2

[a] Combined yield (a*S* and a*R*). [b] Determined by ^{1}H NMR.

The absolute configuration of atropoisomer (a*R*)-**5**, identical to that of the natural product (–)-steganone, was confirmed by single-crystal X-ray analysis (Figure 2).

In our previous studies on the atropodiastereoselective Suzuki–Miyaura coupling we had noticed a strong influence of the protecting group at the C-2 side-chain. Therefore, we next employed methoxy compound **8**. A slight decrease in diastereoselectivity was observed with SPhos (83:17 with 55% yield, Table 1, Entries 1 and 4) and also with XPhos (79:21 with 61% yield, Table 1, Entry 5). The use of DavePhos[20] did not improve diastereoselectivity and actually was found to lower the yield (83:17, 36%, Table 1, Entry 6). Gratifyingly, changing the palladium source from $Pd(OAc)_2$ to $Pd(PPh_3)_4$ in the absence of added ligands afforded biaryl (a*R*)-**6** adduct in 53% yield and in diastereomerically pure form (Table 1, Entry 7). Once again, the absolute configuration of the major atropoisomer (a*R*)-**6** was undoubtedly confirmed by single-crystal X-ray analysis (Figure 3).

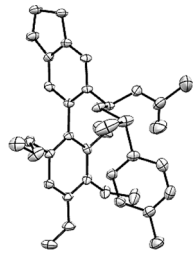


Figure 2. X-ray diffraction crystal structure of the biaryl (a*R*)-**5**.

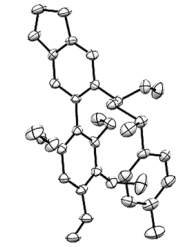
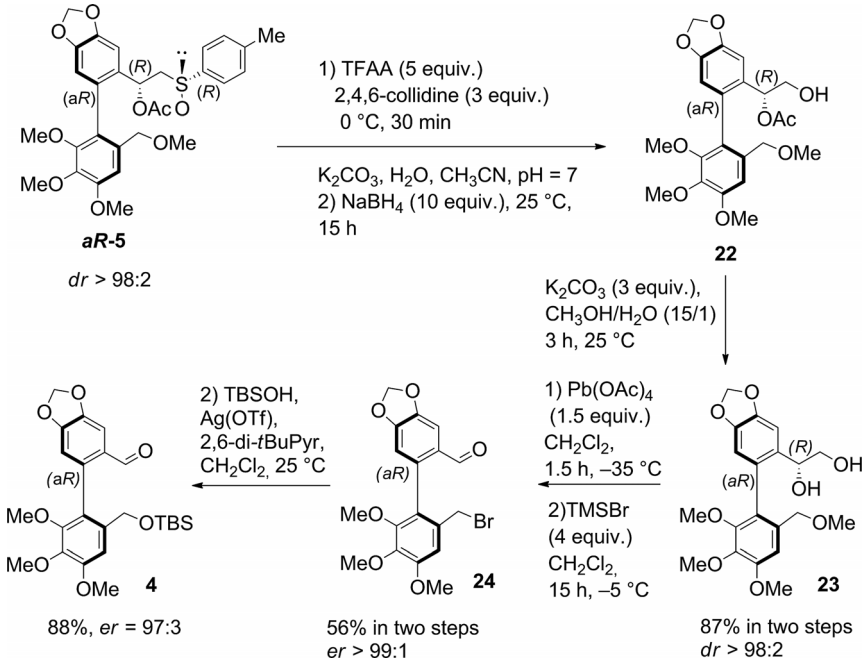


Figure 3. X-ray diffraction crystal structure of the biaryl (a*R*)-**6**.

To complete the synthesis of the key skeleton **4** of (–)-steganone,[12] biaryl (a*R*)-**5** was submitted to a modified Pummerer reaction[21] (TFAA, 2,4,6-collidine, CH_3CN, 0 °C) followed by addition of K_2CO_3 and $NaBH_4$ to afford corresponding primary alcohol **22** whose acetate was hydrolysed with K_2CO_3 in $MeOH/H_2O$ to afford the resulting 1,2-diol **23** in excellent yield (87% over 2 steps). No epimerization of the benzylic stereogenic carbinol was detected (Scheme 5). Oxidative cleavage of **23** gave the aldehyde, which was used in the following step without further purification due to its configurational instability. Selective bromination[22] of the primary methoxy group with TMSBr in CH_2Cl_2 gave enantiopure functionalized biaryl **24** (56% over 2 steps), whose enantiomeric purity was confirmed by chiral HPLC.[23] Finally, conversion to the enantioenriched (*er* = 97:3)[24] silylated known biaryl **4** was accomplished in 88% yield by treatment of **24** with *tert*-butyldimethylsilanol in the presence of silver triflate and 2,6-di-*tert*-butylpyridine.[25]

Conclusions

In the present work we have accomplished the formal synthesis of (–)-steganone by a completely atropodiastereoselective construction of the biaryl unit. Readily available enantiopure β-hydroxy sulfoxide derivatives served as chiral auxiliaries in the Suzuki–Miyaura cross-coupling reaction. Transformation of the biaryl coupling adduct (a*R*)-**5** gave, without loss of the axial chirality, in five steps, known biaryl precursor **4**, an established precursor to (–)-steganone.



Scheme 5. Synthesis of biaryl scaffold **4**.

Experimental Section

General: Starting materials, if commercially available, were purchased and used as received after checking their purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air and moisture-sensitive materials were stored in Schlenk tubes under argon. Et_2O, 1,4-dioxane and THF were dried by distillation over sodium/benzophenone after the characteristic blue color of sodium diphenyl ketyl (benzophenone sodium radical-anion) had been found to persist.[26] CH_2Cl_2 was dried with CaH_2 under argon. Diisopropylamine and triethylamine were dried with KOH under argon. Melting ranges (M.p.) given were found to be reproducible after recrystallization, unless stated otherwise ("decomp."), and are uncorrected. Thin-Layer chromatography (TLC) was carried out with 0.25 mm Merck silica-gel (60-F254). Column chromatography was carried out using MERCK silica gel (40–63 μm). *n*-Butyllithium (1.6 M in hexanes, Aldrich), was used as solution and its concentration was determined following the Wittig–Harborth Double titration method [(total base) – (residual base after reaction with 1,2-dibromoethane)].[27] *NMR*-spectra were recorded with Bruker Avance300 (^{1}H NMR = 300 MHz, ^{13}C NMR = 75.5 MHz) and Bruker Avance400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 100.6 MHz) machines. Chemical shifts were referenced relative to partially deuterated chloroform (δ[^{1}H] = 7.26 and accordingly δ[^{13}C] = 77.16 ppm) and given in ppm on the δ-scale. Multiplicities were abbreviated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants were given in Hz. The spectra were processed with the program Bruker TOPSIN 2.1. *IR*-spectra of neat products were recorded on Perkin–Elmer's *Spectrum One*^{TM}. Mass spectra and elementary analysis were carried out by the Analytical Service of the University of Strasbourg. The angles of rotation were measured with a Perkin–Elmer Polarimeter 341 and denoted as specific rotations: $[a]_D^{20}$. Crystal X-ray diffraction analysis were carried out by the Radiocrystallography Service of the University of Strasbourg.

Benzo[*d*][1,3]dioxol-5-ylmethanol[28] **(11):** To a suspension of piperonal (**10**) (20.00 g, 133.20 mmol) in methanol (400 mL) was added portionwise $NaBH_4$ (20.16 g, 532.90 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h, then quenched with water (100 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **11** as a colorless solid, yield 18.83 g (119.88 mmol, 90%). The product was used without further purification in the next step; m.p. 52–53 °C (ref.[25] 53–54 °C); R_f = 0.43 (cyclohexane/Et_2O = 1:1). IR (ATR): $\tilde{\nu}$ = 3304.1 (O–H), 2904.4, 1437.4, 1244.6 (C–O), 1033.0 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (s, br. d, 1 H, O*H*), 4.56 (s, 2 H, Ar-CH_2O), 5.94 (s, 2 H, OCH_2O), 6.75 (d, *J* = 7.8 Hz, 1 H, Ar-*H*), 6.82 (d, *J* = 7.8 Hz, 1 H, Ar-*H*), 6.85 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 65.3 (Ar-CH_2O), 101.0 (OCH_2O), 107.9 (*C*H^{Ar}), 108.2 (*C*H^{Ar}), 120.5 (*C*H^{Ar}), 134.9 (C), 147.1 (C), 147.8 (C) ppm.

(6-Iodobenzo[*d*][1,3]dioxol-5-yl)methanol[29] **(12):** To a solution of benzyl alcohol derivative **11** (5.00 g, 32.86 mmol) in chloroform (100 mL) at –15 °C, silver trifluoroacetate (7.77 g, 34.51 mmol) and iodine (8.76 g, 34.51 mmol) were added portionwise at –15 °C. The reaction mixture was stirred for 15 min at –15 °C, then quenched with a saturated aqueous solution of sodium thiosulfate (100 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **12** as a slightly brown solid, yield 8.15 g (29.57 mmol, 90%). The product was used without purification in the next step; m.p. 111–114 °C (ref.[26] 109–109 °C); R_f = 0.63 (cyclohexane/Et_2O = 1:1). IR (ATR): $\tilde{\nu}$ = 3243.0 (O–H), 2909.1, 1479.7, 1225.8 (C–O), 1033.0 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, br. d, 1 H, O*H*), 4.59 (s, 2 H, Ar-CH_2O), 5.97 (s, 2 H, OCH_2O), 6.99 (s, 1 H, Ar-*H*), 7.25 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 69.3 (Ar-CH_2O), 85.4 (C-I), 101.7 (OCH_2O), 109.4 (*C*H^{Ar}), 118.5 (*C*H^{Ar}), 136.3 (C), 147.9 (C), 148.6 (C) ppm.

6-Iodobenzo[*d*][1,3]dioxole-5-carboxylic Acid[30] **(13):** Benzyl alcohol derivative **12** (5.00 g, 17.98 mmol) was dissolved in *N*,*N* dimethylformamide (150 mL). Pyridinium dichromate (20.30 g, 53.95 mmol) was added portionwise at 25 °C. The reaction mixture was stirred

for 2 h at 25 °C, then diluted with water (200 mL). The mixture was extracted with diethyl ether (4× 100 mL). The organic layer was treated with a saturated aqueous solution of $NaHSO_3$ (100 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the benzaldehyde derivative as a slightly yellow solid. IR (ATR): $\tilde{\nu}$ = 2904.4, 2857.4 (C–H), 1663.1 (C=O), 1381.0, 1249.3 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.08 (s, 2 H, OCH_2O), 7.30 (s, 1 H, Ar-*H*), 7.33 (s, 1 H, Ar-*H*), 9.88 (s, 1 H, Ar-CO-*H*) ppm. To a solution of benzaldehyde derivative (4.93 g) in acetonitrile (180 mL) was added a solution of NaH_2PO_4 (1.29 g, 10.79 mmol) in water (12 mL) and H_2O_2 (6.30 mL, 61.14 mmol, 30% in water) at 25 °C. To the previous solution, was added dropwise a solution of sodium chlorite (6.91 g, 61.14 mmol) in water (60 mL) during 15 min at 0 °C. The reaction mixture was warmed up to 25 °C. After 3 h, the reaction was not completed (Checked by TLC: CH_2Cl_2/cyclohexane = 1:1). H_2O_2 (1.85 mL, 17.98 mmol, 30% in water) and a solution of NaH_2PO_4 (0.37 g, 3.06 mmol) in water (4 mL) were added successively to the reaction mixture at 25 °C. A solution of sodium chlorite (2.03 g, 17.98 mmol) in water (20 mL) was added dropwise at 0 °C. The mixture was left stirring for 38 h at 25 °C, then quenched with a saturated aqueous solution of $NaHSO_3$ (100 mL) for 15 min at 0 °C. The mixture was acidified with an aqueous solution of 2 M HCl up to pH = 1. The aqueous layer was extracted with diethyl ether (4× 100 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **13** as a yellow solid, yield 4.32 g (13.84 mmol, 77%). The product was used without purification in the next step; m.p. 220–223 °C (ref.[30] 221–223 °C); R_f = 0.33 (EtOAc). IR (ATR): $\tilde{\nu}$ = 3200.0–2500.0 (O–H), 1672.5 (C=O), 1272.8 (C–O), 1244.6 (C–O), 1145.9 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ = 6.22 (s, 2 H, OCH_2O), 7.43 (s, 1 H, Ar-*H*), 7.60 (s, 1 H, Ar-*H*), 13.06 (s, 1 H, Ar-CO_2H) ppm. ^{13}C NMR (75.5 MHz, DMSO): δ = 84.9 (C-I), 102.5 (OCH_2O), 110.1 (CH^{Ar}), 119.8 (CH^{Ar}), 129.1 (C), 147.8 (C), 150.5 (C), 166.9 (CO_2H) ppm.

Methyl 6-Iodobenzo[*d*][1,3]dioxole-5-carboxylate[27] (14): To a solution of carboxylic acid **13** (2.00 g, 6.85 mmol) in methanol (80 mL), was added dropwise concd. sulfuric acid (5.50 mL, 99.06 mmol) at 25 °C. The reaction mixture was stirred at reflux for 17 h. Methanol was evaporated then the residue was taken up in water (80 mL). The aqueous layer was extracted with EtOAc (3× 30 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2× 50 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **14** as a slightly colorless solid, yield 1.9 g (6.23 mmol, 91%). The product was used without purification in the next step; m.p. 86–88 °C (ref.[27] 78–80 °C); R_f = 0.28 (cyclohexane/Et_2O = 8:2). IR (ATR): $\tilde{\nu}$ = 2956.2, 2913.8, 1719.5 (C=O), 1489.1, 1235.2 (C–O), 1127 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 6.05 (s, 2 H, OCH_2O), 7.31 (s, 1 H, Ar-*H*), 7.46 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 84.9 (C-I), 101.8 (OCH_2O), 111.0 (CH^{Ar}), 125.3 (CH^{Ar}), 127.5 (C), 148.1 (C), 151.1 (C), 165.9 (CO_2Me) ppm.

(R_S)-1-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)-2-(*p*-tolylsulfinyl)ethanone (15): To a solution of diisopropylamine (7.76 mL, 54.89 mmol) in dry tetrahydrofuran (40 mL), was added dropwise at –78 °C a solution of *n*-butyllithium (34.31 mL, 54.89 mmol, 1.6 M in hexanes) under argon. The reaction mixture was stirred at 0 °C for 30 min under argon. The solution of lithium diisopropylamide was cannulated onto a solution of methyl *p*-tolyl (+)-(R_S)-sulfoxide[31] (8.46 g, 54.89 mmol) in dry tetrahydrofuran (40 mL) at –78 °C. The mixture was stirred for 1 h at 0 °C. Into a solution of aryl methyl ester **14** (8.00 g, 26.14 mmol) in dry tetrahydrofuran (40 mL), was cannulated the solution of lithiated (+)-(R_S)-methyl *p*-tolylsulfoxide at –78 °C. The mixture was stirred at –78 °C for 2 h, then quenched with a saturated aqueous solution of NH_4Cl (60 mL) at –78 °C. The mixture was acidified with an aqueous solution of 2 M HCl up to pH = 3. The aqueous layer was extracted with EtOAc (3× 100 mL). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with EtOAc to yield **15** as a yellow solid, yield 10.23 g (49.40 mmol, 90%); m.p. 127–129 °C; R_f = 0.84 (cyclohexane/EtOAc = 8:2). $[\alpha]_D^{20}$ = +168.5 (c = 1, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2970.5, 2909.6, 1686.0 (C=O), 1469.3, 1252.6 (C–O), 1232.3 (C=O), 1012.2 (S=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3^{pTol}), 4.41 (AB, J_{AB} = 13.8 Hz, 2 H, $\Delta\nu$ = 84.4 Hz, CH_2SO), 6.05 (s, 2 H, OCH_2O), 6.98 (s, 1 H, Ar-*H*), 7.33 (s, 1 H, Ar-*H*), 7.47 (A_2B_2, 4 H, J_{AB} = 8.1 Hz, $\Delta\nu$ = 99.0 Hz, CH^{pTol}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.5 (CH_3^{pTol}), 67.9 (CH_2SO), 82.8 (C-I), 102.6 (OCH_2O), 110.2 (CH^{Ar}), 120.7 (CH^{Ar}), 124.4 (CH^{pTol}), 130.1 (CH^{pTol}), 135.3 (C), 139.9 (C), 142.3 (C), 148.4 (C); 151.1 (C), 192.7 (CO^{ketone}) ppm. $C_{16}H_{13}IO_4S$ (428.24): calcd. C 44.87, H 3.06; found C 44.85, H 3.26.

(1*R*)-1-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)-2-[(R_S)-*p*-tolylsulfinyl]ethanol (16): A solution of β-ketosulfoxide **15** (10.00 g, 23.35 mmol) in dry THF (200 mL) was cannulated into a flask containing freshly dried zinc bromide (17.88 g, 79.39 mmol) under argon at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. A solution of DiBALH (70.05 mL, 70.05 mmol, in 1 M toluene) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 4 h. EtOAc (200 mL) and a saturated aqueous solution of (potassium/sodium) tartrate (200 mL) were added at 25 °C. The mixture was stirred for 15 h at 25 °C until formation of two layers. The aqueous layer was extracted with EtOAc (3× 100 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2/EtOAc = 8:2 to yield **16** as a colorless solid, yield 7.53 g (16.79 mmol, 72%); m.p. 70–73 °C; R_f = 0.20 (CH_2Cl_2/EtOAc = 8:2), $[\alpha]_D^{20}$ = –13.8 (c = 1, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3248.2 (O–H), 2902.8, 1469.3, 1239.0 (C–O), 1032.5 (S=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3^{pTol}), 2.93 (AB of ABX, J_{AB} = 13.2, J_{AX} = 9.9 Hz, 2 H, $\Delta\nu$ = 149.0 Hz, CH_2SO), 4.58 (s, br. d, 1 H, O*H*), 5.48 (d, HX of ABX, 1 H, J_{AX} = 9.9 Hz, C*H*OCH_2), 5.90 (AB, J_{AB} = 1.2 Hz, 2 H, $\Delta\nu$ = 19.9 Hz, OCH_2O), 7.18 (s, 1 H, Ar-*H*), 7.24 (s, 1 H, Ar-*H*), 7.46 (A_2B_2, J_{AB} = 8.1 Hz, $\Delta\nu$ = 74.0 Hz, 4 H, H^{pTol}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.47 (CH_3^{pTol}), 62.4 (CH_2SO), 74.9 [*C*H(OH)CH_2], 84.1 (C-I), 101.8 (OCH_2O), 107.8 (CH^{Ar}), 118.3 (CH^{Ar}), 123.9 (CH^{pTol}), 130.2 (CH^{pTol}), 137.4 (C), 140.3 (C), 142.2 (C), 148.2 (C), 148.9 (C) ppm. $C_{16}H_{15}IO_4S$ (430.26): calcd. C 44.66, H 3.5; found C 44.24, H 3.79.

(1*R*)-1-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)-2-[(R_S)-*p*-tolylsulfinyl]ethyl Acetate (7): To a solution of β-hydrooxy sulfoxide **16** (500 mg, 1.16 mmol) and DMAP (280 mg, 0.23 mmol) in pyridine (30 mL) was added dropwise acetic anhydride (0.24 mL, 2.58 mmol) under argon at 25 °C. The reaction mixture was stirred for 15 h at 25 °C under argon. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL) then extracted with EtOAc (3× 15 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2/EtOAc = 8:2 to yield **7** as a colorless solid, yield 0.40 g (0.85 mmol, 73%); m.p. 61–65 °C; R_f = 0.3 (Et_2O). $[\alpha]_D^{20}$ = +72.3 (c = 1.05, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2920.4, 1741.8 (C=O), 1468.3, 1223.2 (C–O), 1025.0 (S=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3CO), 2.44 (s, 3 H, CH_3^{pTol}), 3.23 (AB

of ABX, J_{AB} = 13.5, J_{AX} = 10.2, J_{BX} = 3.0 Hz, 2 H, $\Delta\nu$ = 127.0 Hz, CH_2SO), 5.98 (s, 2 H, OCH_2O), 6.02 (dd, X of ABX, 1 H, J_{AX} = 10.2, J_{BX} = 2.7 Hz, C*H*OAc), 6.88 (s, 1 H, Ar-*H*), 7.16 (s, 1 H, Ar-*H*), 7.50 (A_2B_2, 4 H, J_{AB} = 8.1 Hz, $\Delta\nu$ = 169.0 Hz, H$^{p\text{Tol}}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (*C*H$_3$CO), 21.5 (*C*H$_3^{p\text{Tol}}$), 62.6 (*C*H$_2$SO), 74.1 (*C*HOAc), 84.5 (C-I), 101.9 (O*C*H$_2$O), 106.9 (*C*H$^{\text{Ar}}$), 118.7 (*C*H$^{\text{Ar}}$), 124.6 (*C*H$^{p\text{Tol}}$), 130.2 (*C*H$^{p\text{Tol}}$), 134.0 (C), 140.1 (C), 142.1 (C), 148.6 (C), 149.0 (C), 169.3 (*C*O$_2$CH$_3$) ppm. HRMS ES *m*/*z* [M + Na]$^+$ calcd. for $C_{18}H_{17}NaIO_5S$: 494.9739, found 494.973.

5-Iodo-6-{(1*R*)-1-methoxy-2-[(*R*$_S$)-*p*-tolylsulfinyl]ethyl}benzo[*d*]-[1,3]dioxole (8): To a solution of β-hydrooxy sulfoxide **16** (3.00 g, 6.97 mmol) and iodomethane (4.38 mL, 69.73 mmol) in CH_2Cl_2 (60 mL) under argon at 25 °C, was added portionwise freshly prepared silver oxide[32] (8.08 g, 34.86 mmol). The reaction mixture was heated at reflux for 2 h. After being cooled to 25 °C, the mixture was filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with cyclohexane/EtOAc = 9:1 to yield **8** as a colorless solid, yield 2.50 g (6.48 mmol, 93%); m.p. 92–93 °C; R_f = 0.23 (cyclohexane/EtOAc = 8:2). $[\alpha]_D^{20}$ = +8.4 (*c* = 1.24, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2916.3, 1476.0, 1093.4 (C–O), 1029.0 (S=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, C*H*$_3^{p\text{Tol}}$), 2.97 (AB of ABX, J_{AB} = 12.9, J_{AX} = 10.2, J_{BX} = 3.3 Hz, 2 H, $\Delta\nu$ = 196.0 Hz, CH_2SO), 3.00 (s, 3 H, OCH_3), 4.13 (dd, X of ABX, 1 H, J_{AX} = 10.2, J_{BX} = 3.3 Hz, C*H*OMe), 5.84 (s, 1 H, OCH_2O), 5.86 (s, 1 H, OCH_2O), 6.78 (s, 1 H, Ar-*H*), 6.99 (s, 1 H, Ar-*H*), 7.28 (A_2B_2, 4 H, J_{AB} = 8.1 Hz, $\Delta\nu$ = 167.0 Hz, *H*$^{p\text{Tol}}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.5 (*C*H$_3^{p\text{Tol}}$), 56.7 (O*C*H$_3$), 63.6 (*C*H$_2$SO), 82.2 (*C*HOMe), 85.5 (C-I), 101.9 (O*C*H$_2$O), 107.1 (*C*H$^{\text{Ar}}$), 118.6 (CH$^{\text{Ar}}$), 125.0 (*C*H$^{p\text{Tol}}$), 129.9 (*C*H$^{p\text{Tol}}$); 134.3 (C), 140.1 (C), 142.0 (C), 148.6 (C), 149.3 (C) ppm. $C_{17}H_{17}IO_4S$ (444.28): calcd. C 45.96, H 3.86; found C 45.87, H 4.02.

Ethyl 3,4,5-Trimethoxybenzoate[33] (18): Ethyl gallate (**17**) (30.00 g, 149.87 mmol) was dissolved in acetone (500 mL) then potassium carbonate (84.54 g, 599.49 mmol) was added portionwise at 25 °C under argon. The reaction mixture was heated at reflux. At reflux, iodomethane (56.54 mL, 899.23 mmol) was added dropwise during 30 min via syringe. Stirring was continued at reflux for 24 h. After being cooled to 25 °C, the solution was diluted with acetone (300 mL), filtered through silica and the filtrate was treated with water (400 mL). The resulting solution was treated with a saturated aqueous solution of sodium thiosulfate (100 mL). The aqueous layer was extracted with EtOAc (3× 300 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **18** as a slightly yellow solid, yield 34.5 g (6.69 mmol, 96%). The product was used without purification in the next step; m.p. 48–49 °C (ref.[30] 52 °C); R_f = 0.55 (cyclohexane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, ^3J = 7.08 Hz, 3 H, CH_3CH$_2$), 3.90 (s, 3 H, Ar-OCH_3), 3.91 (s, 6 H, Ar-OCH_3), 4.36 (q, ^3J = 7.1 Hz, 2 H, OCH_2-CH$_3$), 7.30 (s, 2 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4 (*C*H$_3$CH$_2$), 56.2 (Ar-O*C*H$_3$), 60.9 (Ar-O*C*H$_3$), 61.1 (O*C*H$_2$CH$_3$), 106.8 (*C*H$^{\text{Ar}}$), 125.5 (C), 142.2 (C), 152.9 (C), 166.2 (*C*O$_2$Et) ppm.

(3,4,5-Trimethoxyphenyl)methanol[34] (19): 100 mL of dry tetrahydrofuran were added in a flask containing $LiAlH_4$ (3.36 g, 88.50 mmol) under argon. The solution of aryl ethyl ester **18** (15.00 g, 62.43 mmol) in dry tetrahydrofuran (50 mL) was cannulated at 0 °C under argon. Release of hydrogen gas was observed. The reaction mixture was stirred at 25 °C for 2 h. Water (4 mL) was added very slowly at 0 °C, then an aqueous solution of 2 M sodium hydroxide (4 mL) and water (12 mL) were added at 25 °C. The mixture was allowed to stir at 25 °C for 15 h. The resulting solution was filtered through Celite® 545. The filtrate was washed with brine (200 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **19** as a colorless liquid, yield 12 g (58.03 mmol, 93%). The product was used without purification in the next step. R_f = 0.33 (EtOAc). IR (ATR): $\tilde{\nu}$ = 3445.2 (O–H), 2932.6, 2838.6, 1592.6, 1230.5 (C–O), 1122.5 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, br. d, 1 H, O*H*), 3.82 (s, 3 H, Ar-OCH_3), 3.84 (s, 6 H, Ar-OCH_3), 4.60 (s, 2 H, Ar-CH_2O), 6.58 (s, 2 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 56.0 (Ar-O*C*H$_3$), 60.8 (Ar-O*C*H$_3$), 67.9 (Ar-*C*H$_2$O), 104.2 (*C*H$^{\text{Ar}}$), 136.8 (C), 137.2 (C), 153.3 (C) ppm.

1,2,3-Trimethoxy-5-(methoxymethyl)benzene[35] (20): Sodium hydride (0.20 g, 5.04 mmol) (60% in mineral oil) was added in a dry Schlenk flask, then washed with dry hexane (2× 15 mL) under argon. A solution of benzyl alcohol derivative **19** (0.50 g, 2.52 mmol) in dry tetrahydrofuran (10 mL) was cannulated onto the sodium hydride suspension under argon at 0 °C. The reaction mixture was stirred for 30 min at 0 °C then iodomethane (0.48 mL, 7.57 mmol) was added. The reaction was stirred for further 30 min at 0 °C, then quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with diethyl ether (4× 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield **20** as a yellow liquid, yield 0.51 g (2.44 mmol, 92%). The product was used without purification in the next step. R_f = 0.48 (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40 (s, 3 H, OCH_3), 3.62 (s, 3 H, Ar-OCH_3), 3.84 (s, 6 H, Ar-OCH_3), 4.39 (s, 2 H, Ar-CH_2O), 6.57 (s, 2 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 56.0 (O*C*H$_3$), 58.1 (Ar-O*C*H$_3$), 60.8 (Ar-O*C*H$_3$) 74.9 (Ar-*C*H$_2$O), 104.6 (*C*H$^{\text{Ar}}$), 133.9 (C), 137.4 (C), 153.3 (C) ppm.

2-Iodo-3,4,5-trimethoxy-1-(methoxymethyl)benzene (21): Iodine (0.57 g, 2.26 mmol) and silver trifluoroacetate (0.5 g, 2.26 mmol) were added portionwise to a solution of benzyl methyl ether derivative **20** (0.40 g, 1.88 mmol) in chloroform (25 mL). The mixture was stirred at –15 °C for 15 min. The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (25 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with cyclohexane/EtOAc = 9:1 to yield **21** as a yellow solid, yield 0.59 g (1.73 mmol, 92%); m.p. 42–46 °C; R_f = 0.4 (cyclohexane/EtOAc = 9:1). IR (ATR): $\tilde{\nu}$ = 2981.7, 2934.5, 2812.0, 1562.6, 1100.6 (C–O), 1006.0 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, OCH_3), 3.77 (s, 3 H, Ar-OCH_3), 3.78 (s, 6 H, Ar-OCH_3), 4.32 (s, 2 H, Ar-CH_2O), 6.80 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 56.1 (O*C*H$_3$), 58.6 (Ar-O*C*H$_3$), 60.7 (Ar-O*C*H$_3$), 60.9 (Ar-O*C*H$_3$), 78.7 (C-I), 84.9 (Ar-*C*H$_2$-O), 108.1 (*C*H$^{\text{Ar}}$), 136.2 (C), 141.3 (C), 151.0 (C), 152.9 (C) ppm. $C_{11}H_{15}IO_4$ (338.14): calcd. C 39.07, H 4.47; found C 39.09, H 4.26.

4,4,5,5-Tetramethyl-2-[2,3,4-trimethoxy-6-(methoxymethyl)phenyl]-1,3,2-dioxaborolane (9): To a solution of aryl iodide **21** (1.00 g, 2.96 mmol) and SPhos (242 mg, 0.59 mmol) in dry 1,4-dioxane (20 mL) were added $Pd(OAc)_2$ (33.8 mg, 5 mol-%) and dry triethylamine (1.64 mL, 11.83 mmol) under argon. The resulting solution was degassed by bubling argon during 15 min and pinacolborane (1.33 mL, 8.87 mmol) was added dropwise by syringe. The reaction mixture was heated at 85 °C for 4 h, then quenched with a saturated aqueous solution of NH_4Cl (50 mL). The mixture was extracted with diethyl ether (4× 50 mL). The organic layer was treated with charcoal, filtered, dried with Na_2SO_4 and concentrated under re-

duced pressure. The crude product was purified by column chromatography on silica gel, eluting with EtOAc/cyclohexane = 1:9 to 3:7 to yield **9** as slightly orange oil, yield 0.72 g (2.13 mmol, 72%). R_f = 0.25 (cyclohexane/EtOAc = 8:2). IR (ATR): $\tilde{\nu}$ = 2977.3, 2936.7, 1598.0, 1144.2 (C–O), 1096.8 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 12 H, $H^{pinacol}$), 3.31 (s, 3 H, OCH_3), 3.86 (s, 3 H, Ar-OCH_3), 3.85 (s, 3 H, Ar-OCH_3), 3.88 (s, 3 H, Ar-OCH_3), 4.45 (s, 2 H, Ar-CH_2O), 6.66 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.9 ($CH_3^{pinacol}$), 56.1 (OCH_3), 57.9 (Ar-OCH_3), 60.8 (Ar-OCH_3), 61.5 (Ar-OCH_3), 74.3 (Ar-CH_2O), 83.6 ($C^{pinacol}$), 104.5 (C-B), 107.4 (Ar-CH_2O), 138.3 (C), 140.8 (C), 154.4 (C), 157.2 (C) ppm. ^{11}B NMR (128.4 MHz, $CDCl_3$): δ = 31.30 ppm. $C_{17}H_{27}BO_6$ (338.21): calcd. C 60.37, H 8.05; found C 60.19, H 8.1.

(a*R*)-2-[(*R*$_S$)-*p*-Tolylsulfinyl]-1-{(1*R*)-6-[2,3,4-trimethoxy-6-(methoxymethyl)phenyl]benzo[*d*][1,3]dioxol-5-yl}ethyl acetate [(a*R*)-5]: A solution of aryl iodide **7** (200 mg, 0.42 mmol), Pd source (10 mol-%) and ligand (20 mol-%) in 1,4-dioxane (6 mL) was stirred for 1 h at 25 °C under argon. Another solution was prepared from aryl boronic ester **7** (290 mg, 0.85 mmol) and CsF (260 mg, 1.80 mmol) in 1,4-dioxane (6 mL) and was stirred for 30 min at 25 °C under argon. The first solution was cannulated onto the second solution at 25 °C. The reaction mixture was heated at 70 °C for 20 h under argon, then quenched with water (10 mL) and extracted with CH_2Cl_2 (3× 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvents evaporated. The crude product was purified by column chromatography on silica gel, eluting from cyclohexane/EtOAc = 6:4 to EtOAc to yield the mixture of both atropodiastereoisomers (a*R*)-**5** and (a*S*)-**5**. The major atropodiastereoisomer (a*R*)-**5** was obtained after recrystallization from diethyl ether/pentane mixture as a slightly yellow solid. The yield and the diastereoisomer ratio depend on source of palladium and the nature of the ligands (see Table 1); m.p. 124–126 °C. $[\alpha]_D^{20}$ = +5.39 (*c* = 1.13, $CHCl_3$); R_f = 0.34 (cyclohexane/EtOAc = 6:4). IR (ATR): $\tilde{\nu}$ = 2916.3, 1747.0 (C=O), 1479.5, 1222.1 (C–O), 1022.2 (C–O), 1015.5 (S=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3 H, CH_3CO), 2.40 (s, 3 H, CH_3^{pTol}), 3.11 (AB of ABX, J_{AB} = 13.2, J_{AX} = 9.9, J_{BX} = 3.33 Hz, 2 H, $\Delta\nu$ = 279.7 Hz, CH_2SO), 3.15 (s, 3 H, OCH_3), 3.54 (s, 3 H, Ar-OCH_3), 3.84 (s, 3 H, Ar-OCH_3), 3.79 (AB, J_{AB} = 11.7 Hz, 2 H, $\Delta\nu$ = 118.3 Hz, Ar-CH_2O), 3.94 (s, 3 H, Ar-OCH_3), 5.73 (dd, X of ABX, 1 H, J_{AX} = 9.9, J_{BX} = 3.3 Hz, $CHOAc$), 6.01 (AB, 2 H, J_{AB} = 1.2 Hz, $\Delta\nu$ = 19.9 Hz, OCH_2O), 6.56 (s, 1 H, Ar-*H*), 6.72 (s, 1 H, Ar-*H*), 7.04 (s, 1 H, Ar-*H*), 7.29 (A_2B_2, 4 H, J_{AB} = 8.4 Hz, $\Delta\nu$ = 199.7 Hz, H^{pTol}) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.0 (CH_3CO), 21.5 (CH_3^{pTol}), 55.9 (OCH_3), 58.4 (Ar-OCH_3), 60.8 (Ar-OCH_3), 60.9 (Ar-OCH_3), 63.9 (CH_2SO), 68.1 ($CHOAc$), 72.1 (Ar-CH_2O), 101.5 (OCH_2O), 106.7 (CH^{Ar}), 107.4 (CH^{Ar}), 110.6 (CH^{Ar}), 124.3 (CH^{pTol}), 124.6 (C), 128.2 (C), 129.9 (CH^{pTol}), 130.8 (C), 132.2 (C), 140.4 (C), 141.4 (C), 141.5 (C), 147.4 (C), 147.6 (C), 150.7 (C), 153.3 (C), 169.4 (C^{Ac}) ppm. HRMS ES *m*/*z* $[M + Na]^+$ calcd. for $C_{29}H_{32}NaO_9S$: 579.1665, found 579.166.

(a*S*)-2-[(*R*$_S$)-*p*-Tolylsulfinyl]-1-{(1*R*)-6-[2,3,4-trimethoxy-6-(methoxymethyl)phenyl]benzo[*d*][1,3]dioxol-5-yl}ethyl acetate [(a*S*)-5]: R_f = 0.31 (cyclohexane/EtOAc = 6:4). ^1H NMR (300 MHz, $CDCl_3$): δ = 1. 97 (s, 3 H, CH_3CO), 2.35 (s, 3 H, CH_3^{pTol}), 3.10 (AB of ABX, J_{AB} = 12.9, J_{AX} = 10.5, J_{BX} = 3.3 Hz, 2 H, $\Delta\nu$ = 216.4 Hz, CH_2SO), 3.13 (s, 3 H, OCH_3), 3.26 (s, 3 H, Ar-OCH_3), 3.68 (AB, J_{AB} = 11.1 Hz, 2 H, $\Delta\nu$ = 43.5 Hz, Ar-CH_2O), 3.82 (s, 3 H, Ar-OCH_3), 3.85 (s, 3 H, Ar-OCH_3), 5.50 (dd, X of ABX, 1 H, J_{AX} = 9.9, J_{BX} = 3.0 Hz, $CHOAc$), 5.97 (s, 2 H, OCH_2O), 6.53 (s, 1 H, Ar-*H*), 6.62 (s, 1 H, Ar-*H*), 6.84 (s, 1 H, Ar-*H*), 7.29 (A_2B_2, 4 H, J_{AB} = 5.4 Hz, $\Delta\nu$ = 104.8 Hz, H^{pTol}) ppm.

(a*R*)-5-{(1*R*)-1-Methoxy-2-[(*R*$_S$)-*p*-tolylsulfinyl]ethyl}-6-[2,3,4-trimethoxy-6-(methoxymethyl)phenyl]benzo[*d*][1,3]dioxole: [(a*R*)-6]. A solution of aryl iodide **8** (200 mg, 0.45 mmol), Pd source (10 mol-%) and ligand (20 mol-%) in 1,4-dioxane (6 mL) was stirred for 1 h at 25 °C under argon. Another solution was prepared from arylboronic ester **9** (330 mg, 0.90 mmol) and CsF (280 mg, 1.80 mmol) in 1,4-dioxane (6 mL) was stirred for 30 min at 25 °C under argon. The first solution was cannulated at 25 °C onto the second solution. The reaction mixture was heated at 70 °C for 20 h under argon. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3× 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvents evaporated. The crude product was purified by column chromatography on silica gel, eluting from cyclohexane/EtOAc = 6:4 to EtOAc to yield the mixture of both atropodiastereoisomers (a*R*)-**6** and (a*S*)-**6**. The major atropodiastereoisomer (a*R*)-**6** was obtained after recrystallization from 2-propanol as a colorless solid. The yield and the diastereoisomer ratio depend on source of palladium and the nature of the ligands (see Table 1); m.p. 203–204 °C. $[\alpha]_D^{20}$ = +24 (*c* = 0.25, $CHCl_3$); R_f = 0.4 (cyclohexane/EtOAc = 6:4). IR (ATR): $\tilde{\nu}$ = 2925.0, 2826.0, 1600.0, 1477.8, 1095.9 (C–O), 1039.3 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3^{pTol}), 2.60 (dd, X of ABX, 1 H, J_{AX} = 10.6, J_{BX} = 2.7 Hz, $CHOMe$), 3.06 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3), 3.34 (AB of ABX, J_{AB} = 12.4, J_{AX} = 10.8, J_{BX} = 2.8 Hz, 2 H, $\Delta\nu$ = 178.2 Hz, CH_2SO), 3.34 (s, 3 H, Ar-OCH_3), 3.74 (s, 3 H, Ar-OCH_3), 3.88–3.95 (m, 2 H, Ar-CH_2-OCH_3), 3.96 (s, 3 H, Ar-OCH_3), 6.01 (s, 2 H, OCH_2O), 6.51 (s, 1 H, Ar-*H*), 6.76 (s, 1 H, Ar-*H*), 7.05 (s, 1 H, Ar-*H*), 7.19 (A_2B_2, 4 H, J_{AB} = 7.8 Hz, $\Delta\nu$ = 110 Hz, Ar-H^{pTol}) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.4 (CH_3^{pTol}), 55.9 (OCH_3), 56.5 (Ar-OCH_3), 58.7 (Ar-OCH_3), 60.7 (Ar-OCH_3), 63.9 (CH_2SO), 72.1 (Ar-CH_2O), 75.9 ($CHOMe$), 101.3 (OCH_2O), 105.6 (CH^{Ar}), 107.7 (CH^{Ar}), 110.1 (CH^{Ar}), 124.9 (C), 125.0 (CH^{pTol}), 128.0 (C), 129.7 (CH^{pTol}), 132.2 (C), 132.5 (C), 139.5 (C), 141.4 (C), 142.0 (C), 146.9 (C), 147.9 (C), 149.6 (C), 153.1 (C) ppm. HRMS ES *m*/*z* $[M + Na]^+$ calcd. for $C_{28}H_{32}NaO_8S$: 551.1716, found 551.171.

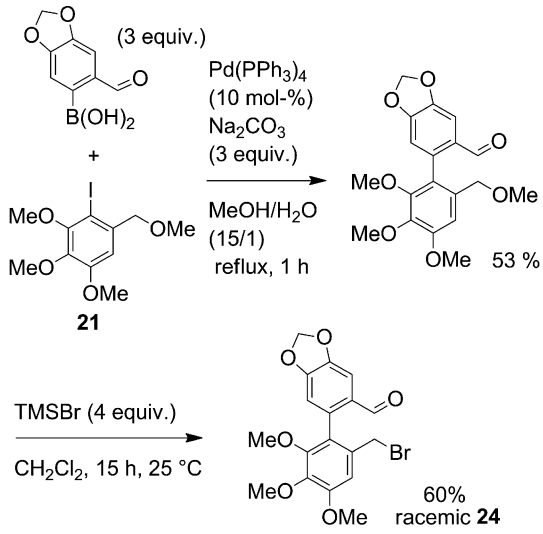
(a*S*)-5-{(1*R*)-1-Methoxy-2-[(*R*$_S$)-*p*-tolylsulfinyl]ethyl}-6-[2,3,4-trimethoxy-6-(methoxymethyl)phenyl]benzo[*d*][1,3]dioxole [(a*S*)-6]: R_f = 0.38 (cyclohexane/EtOAc = 6:4). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3^{pTol}), 2.65 (dd, X of ABX, 1 H, J_{AX} = 7.4, J_{BX} = 2.7 Hz, $CHOMe$), 3.08 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3), 3.20 (AB of ABX, J_{AB} = 10.8, J_{AX} = 7.8, J_{BX} = 3.3 Hz, 2 H, CH_2SO), 3.34 (s, 3 H, Ar-OCH_3), 3.74 (s, 3 H, Ar-OCH_3), 3.94–3.96 (m, 2 H, Ar-CH_2-OCH_3), 3.96 (s, 3 H, Ar-OCH_3), 5.99 (s, 2 H, OCH_2O), 6.20 (s, 1 H, Ar-*H*), 6.28 (s, 1 H, Ar-*H*), 6.40 (s, 1 H, Ar-*H*), 6.99 (A_2B_2, 4 H, J_{AB} = 9.0 Hz, $\Delta\nu$ = 217 Hz, Ar-H^{pTol}) ppm.

(a*R*)-1-{(*R*)-6-[2,3,4-Trimethoxy-6-(methoxymethyl)phenyl]benzo[*d*][1,3]dioxole-5-yl}ethane-1,2-diol (23): To a suspension solution of aryl sulfoxide (a*R*)-**5** (500 mg, 0.89 mmol) and 2,4,6-collidine (0.36 mL, 2.69 mmol) in dry acetonitrile (30 mL) was added dropwise trifluoroacetic anhydride (0.64 mL, 4.5 mmol) at 0 °C under argon. The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with water (4.75 mL) then basified with K_2CO_3 until pH = 7. Stirring was continued for another 30 min at 25 °C. Sodium borohydride (0.35 g, 8.98 mmol) was added portionwise at 25 °C. The mixture was stirred for 15 h at 25 °C, then quenched with a saturated aqueous solution of NH_4Cl (80 mL). The aqueous layer was extracted with EtOAc (3× 40 mL). The combined organic layers were washed successively with an aqueous solution of 1 M HCl (2× 40 mL), $NaHCO_3$ (40 mL), brine (40 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure affording a colorless oil. The crude product was

characterized by ^{1}H NMR spectroscopy. The residue was taken up in methanol (3 mL) then K_2CO_3 (0.38 g, 2.69 mmol), water (0.48 mL) were added successively. The mixture was stirred for 3 h at 25 °C, then quenched with water (10 mL) and extracted with EtOAc (3× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure affording a yellow liquid. The crude product was purified by column chromatography on silica gel, eluting from cyclohexane/EtOAc = 6:4 to EtOAc to yield **23** as a colorless foam, yield 0.31 g (0.78 mmol, 87% over two steps). R_f = 0.56 (EtOAc). $[\alpha]_D^{20}$ = +54.44 (c = 0.36, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3453.6 (O–H), 2936.0, 2885.4, 1474.1, 1376.4, 1235.3 (C–O), 1072.4, 1029.0, 989.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, br. d, 1 H, O*H*), 3.20 (s, br. d, 1 H, O*H*), 3.23 (s, 3 H, OCH_3), 3.54 (s, 3 H, Ar-OCH_3), 3.56 (AB of ABX, J_{AB} = 11.1, J_{AX} = 8.1, J_{BX} = 3.9 Hz, 2 H, $\Delta\nu$ = 190.7 Hz, CHOHCH_2OH), 3.88 (s, 3 H, Ar-OCH_3), 3.89 (s, 3 H, Ar-OCH_3), 4.04 (AB, J_{AB} = 11.7 Hz, 2 H, $\Delta\nu$ = 37.2 Hz, Ar-CH_2OCH$_3$), 4.37 (dd, X of ABX, 1 H, J_{AX} = 8.1, J_{BX} = 3.9 Hz, C*H*OHCH$_2$OH), 5.98 (s, 2 H, OCH_2O), 6.59 (s, 1 H, Ar-*H*), 6.85 (s, 1 H, Ar-*H*), 7.05 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 56.3 (O*C*H$_3$), 58.4 (Ar-O*C*H$_3$), 61.1 (Ar-O*C*H$_3$), 61.2 (Ar-O*C*H$_3$), 65.9 (CHOH*C*H$_2$OH),71.3 (*C*HOHCH$_2$OH), 72.3 (Ar-*C*H$_2$OCH$_3$), 101.2 (O*C*H$_2$O), 106.6 (*C*H^{Ar}), 108.3 (*C*H^{Ar}), 110.2 (*C*H^{Ar}), 126.2 (C), 128.0 (C),132.5 (C), 134.1 (C), 141.6 (C),146.9 (C), 147.6 (C),150.5 (C), 153.1 (C) ppm. HRMS ES m/z [M + Na]$^+$ calcd. for $C_{20}H_{24}NaO_8$: 415.1369, found 415.1363.

(a*R*)-6-[6-(Bromomethyl)-2,3,4-trimethoxyphenyl]benzo[*d*][1,3]dioxole-5-carbaldehyde (24): The diol **23** (110 mg, 0.29 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL) and added dropwise to a suspension of $Pb(OAc)_4$ (120 mg, 0.27 mmol) in dry CH_2Cl_2 (4 mL) under argon at –35 °C. The reaction mixture was stirred for 1.5 h at –35 °C under argon, then filtered through Celite® 545 and concentrated under reduced pressure. The residue was taken up in dry CH_2Cl_2 (4.8 mL) and TMSBr (0.15 mL, 1.16 mmol) was added at –5 °C under argon. The mixture was stirred at –5 °C for 15 h, then diluted with CH_2Cl_2 (20 mL) and quenched with a saturated solution of $NaHCO_3$ (10 mL). The organic layer was washed with $NaHCO_3$ (2× 15 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with cyclohexane/CH_2Cl_2 = 1:1 to yield the desired product **24** as a yellow foam, yield 0.07 g (0.16 mmol, 56% over two steps); R_f = 0.45 (CH_2Cl_2). $[\alpha]_D^{20}$ = –4.2 (c = 0.92, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2956.7, 2931.4, 2869.8 (C–H, aldehyde), 1721.5 (C=O), 1279.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (s, 3 H, Ar-OCH_3), 3.89 (s, 3 H, Ar-OCH_3), 3.93 (s, 3 H, Ar-OCH_3), 4.20 (AB, J_{AB} = 10.4 Hz, 2 H, $\Delta\nu$ = 79.4 Hz, Ar-CH_2Br), 6.03–6.06 (m, 2 H, OCH_2O), 6.78 (s, 1 H, Ar-*H*), 6.82 (s, 1 H, Ar-*H*), 7.49 (s, 1 H, Ar-*H*), 9.49 (s, 1 H, *H*^{aldehyde}) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 31.8 (Ar-*C*H$_2$-Br), 56.1 (Ar-O*C*H$_3$), 60.9 (Ar-O*C*H$_3$), 61.0 (Ar-O*C*H$_3$), 102.2 (O*C*H$_2$O), 106.3 (*C*H^{Ar}), 109.2 (*C*H^{Ar}), 110.7 (*C*H^{Ar}), 124.5 (C), 129.8 (C), 131.7 (C), 136.1 (C), 142.3 (C), 148.3 (C), 151.7 (C), 152.3 (C), 153.9 (C), 190.0 (*C*OH^{aldehyde}) ppm. HRMS ESI m/z [M + Na]$^+$ calcd. for $C_{18}H_{17}BrNaO_6$: 431.0106, found 431.010. The enantiomeric ratio (> 99:1) of the desired product was determined by chiral HPLC [Daicel Chiralcel OD-H 250 mm × 4.6 mm, 5 µm; flow rate 0.5 mL/min, 80% hexane, 20% 2-propanol, T_r (a*S*)16.03, (a*R*)19.59 min].

Racemic 6-[6-(Bromomethyl)-2,3,4-trimethoxyphenyl]benzo[*d*][1,3]-dioxole-5-carbaldehyde (24): Racemic compound **24** has been synthesized by Suzuki coupling reaction[7c] between **21** and the boronic acid bearing already the aldehyde[36] followed by the bromination step.



(a*R*)-6-(6-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2,3,4-trimethoxyphenyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (4): Silver triflate (13.2 mg, 0.05 mmol) and *tert*-butyldimethylsilanol (0.01 mL, 0.06 mmol) were added to a solution of aryl bromide **24** (8.00 mg, 0.02 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.01 mL, 0.04 mmol) in CH_2Cl_2 (0.3 mL) under argon at 0 °C. The mixture was stirred for 15 min, then the cooling bath was removed and stirring was continued for 1 h at 25 °C. The mixture was filtered through Celite® 545 and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (cyclohexane/CH_2Cl_2 = 1:1 to CH_2Cl_2) to yield the desired product **4**, yield 7.9 mg (0.02 mmol, 88%). R_f = 0.5 (CH_2Cl_2). $[\alpha]_{20}^{D}$ = –2.4 (c = 0.208 , $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2954.9, 2918.1, 2847.4 (C–H^{aldehyde}), 1725.5 (C=O), 1599.5, 1479.6, 1464.3, 1396.7, 1322.9, 1261.4 (C–O), 1242.9 (C–O), 1144.6 (C–O), 1104.9 (C–O), 1040.1 (C–O), 843.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.06 (s, 3 H, CH_3^{TBS}), –0.05 (s, 3 H, CH_3^{TBS}), 0.85 [s, 9 H, C(CH_3)$_3$], 3.60 (s, 3 H, Ar-OCH_3), 3.85 (s, 3 H, Ar-OCH_3), 3.90 (s, 3 H, Ar-OCH_3), 4.27 (AB, J_{AB} = 13.2 Hz, 2 H, $\Delta\nu$ = 34.9 Hz, Ar-CH_2OTBS), 6.07–6.09 (m, 2 H, OCH_2O), 6.65 (s, 1 H, Ar-*H*), 6.94 (s, 1 H, Ar-*H*), 7.43 (s, 1 H, Ar-*H*), 9.47 (s, 1 H, *H*^{aldehyde}) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.3 (*C*H$_3^{TBS}$), –5.2 (*C*H$_3^{TBS}$), 26.0 [C(*C*H$_3$)$_3$], 29.9 [*C*(CH$_3$)$_3$], 56.1 (Ar-O*C*H$_3$), 61.0 (Ar-O*C*H$_3$), 61.1 (Ar-O*C*H$_3$), 63.0 (Ar-*C*H$_2$-OTBS), 102.2 (O*C*H$_2$O), 106.1 (*C*H^{Ar}), 106.4 (*C*H^{Ar}), 111.0 (*C*H^{Ar}), 121.8 (C), 129.7 (C), 135.6 (C), 137.2 (C), 141.0 (C), 148.1 (C), 151.4 (C), 152.4 (C), 153.8 (C), 190.5 (*C*OH^{aldehyde}) ppm. HRMS ESI m/z [M + Na]$^+$ calcd. for $C_{24}H_{32}NaO_7Si$: 483.1815, found 483.1810. The enantiomeric ratio (*er* 97:3) of the desired product was estimated by ^{1}H NMR of crude product with Eu(hfc)$_3$. The determination of enantiomeric excess of compound **4** with several chiral HPLC columns (Daicel Chiralcel OD-H, Chiralpak AD-H, Chiralpak IA) was unsuccessful.

Supporting Information (see footnote on the first page of this article): ^{1}H- and ^{13}C-NMR spectra of compounds **14**–**16**, **7**, **8**, **21**, **9**, (a*R*)-**5**, (a*R*)-**6**, **23**, **24** and **4**, enantiomeric excess determination of **24** and **4** and crystallographic data of compounds (a*R*)-**5** and (a*R*)-**6**.

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[1] a) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, R. F. Bryan, *J. Am. Chem. Soc.* **1973**, *95*, 1335–1336; b) R. W.-J. Wang, L. I. Rebhun, S. M. Kupchan, *Cancer Res.* **1977**, *37*, 3071–3079; c) F. Zavala, D. Guenard, J.-P. Robin, E. Brown, *J. Med. Chem.* **1980**, *23*, 546–549; d) R. Dhal, E. Brown, J.-P. Robin, *Tetrahedron* **1983**, *39*, 2787–2794.

[2] a) K. Tomioka, T. Ishiguro, H. Mizuguchi, N. Komeshima, K. Koga, S. Tsukagoshi, T. Tsuruo, T. Tashiro, S. Tanida, T. Kishi, *J. Med. Chem.* **1991**, *34*, 54–57; b) D. B. M. Wickramaratne, T. Pengsuparp, W. Mar, H.-B. Chai, T. E. Chagwedera, C. W. W. Beecher, N. R. Farnsworth, A. D. Kinghorn, J. M. Pezzuto, G. A. Cordell, *J. Nat. Prod.* **1993**, *56*, 2083–2090; c) D. L. Sackett, *Pharmacol. Ther.* **1993**, *59*, 163–228.

[3] a) A. S. Kende, L. S. Liebeskind, *J. Am. Chem. Soc.* **1976**, *98*, 267–268; b) F. E. Ziegler, J. A. Schwartz, *J. Org. Chem.* **1978**, *43*, 985–991; c) K. Tomioka, T. Ishiguro, K. Koga, *Tetrahedron Lett.* **1980**, *21*, 2973–2976; d) K. Tomioka, T. Ishiguro, Y. Itaka, K. Koga, *Tetrahedron* **1984**, *40*, 1303–1312; e) P. Magnus, J. Schultz, T. Gallagher, *J. Am. Chem. Soc.* **1985**, *107*, 4984–4988; f) P. Magnus, J. Schultz, T. Gallagher, *J. Chem. Soc., Chem. Commun.* **1984**, 1179–1180; g) R. Dhal, Y. Landais, A. Lebrun, V. Lenain, J.-P. Robin, *Tetrahedron* **1994**, *50*, 1153–1164; h) D. Planchenault, R. Dhal, J.-P. Robin, *Tetrahedron* **1995**, *51*, 1395–1404; i) R. S. Ward, D. D. Hughes, *Tetrahedron* **2001**, *57*, 2057–2064; j) R. S. Ward, D. D. Hughes, *Tetrahedron* **2001**, *57*, 4015–4022.

[4] a) L. R. Hughes, R. A. Raphael, *Tetrahedron Lett.* **1976**, *17*, 1543–1546; b) D. Becker, L. R. Hughes, R. A. Raphael, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1674–1681; c) G. R. Krow, K. M. Damodaran, E. Michener, R. Wolf, J. Guare, *J. Org. Chem.* **1978**, *43*, 3950–3953; d) N. S. Narasimhan, I. S. Aidhen, *Tetrahedron Lett.* **1988**, *29*, 2987–2988.

[5] a) E. R. Larson, R. A. Raphael, *J. Chem. Soc. Perkin Trans. 1* **1982**, 521–525; b) A. I. Meyers, J. R. Flisak, R. A. Aitken, *J. Am. Chem. Soc.* **1987**, *109*, 5446–5452.

[6] a) F. E. Ziegler, K. W. Fowler, N. D. Sinha, *Tetrahedron Lett.* **1978**, *19*, 2767–2770; b) E. Brown, R. Dhal, J.-P. Robin, *Tetrahedron Lett.* **1979**, *20*, 733–736; c) E. R. Larson, R. A. Raphael, *Tetrahedron Lett.* **1979**, *20*, 5041–5042; d) F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, N. D. Sinha, *J. Am. Chem. Soc.* **1980**, *102*, 790–798; e) J.-P. Robin, O. Gringore, E. Brown, *Tetrahedron Lett.* **1980**, *21*, 2709–2712.

[7] a) M. Uemura, A. Daimon, Y. Hayashi, *J. Chem. Soc., Chem. Commun.* **1995**, 1943–1944; b) K. Kamikawa, T. Watanabe, A. Daimon, M. Uemura, *Tetrahedron* **2000**, *56*, 2325–2337; c) L. G. Monovich, Y. Le Huérou, M. Rönn, G. A. Molander, *J. Am. Chem. Soc.* **2000**, *122*, 52–57; d) A. Joncour, A. Décor, S. Thoret, A. Chiaroni, O. Baudoin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4149–4152; *Angew. Chem.* **2006**, *118*, 4255; e) H. Abe, S. Takeda, T. Fujita, K. Nishioka, Y. Takeuchi, T. Harayama, *Tetrahedron Lett.* **2004**, *45*, 2327–2329; f) S. Takeda, H. Abe, Y. Takeuchi, T. Harayama, *Tetrahedron* **2007**, *63*, 396–408.

[8] a) G. Bringmann, D. Menche, *Acc. Chem. Res.* **2001**, *34*, 615–624; b) G. Bringmann, M. Breuning, S. Tasler, *Synthesis* **1999**, 525–558, and references cited therein.

[9] a) P.-E. Broutin, F. Colobert, *Org. Lett.* **2003**, *5*, 3281–3284; b) P.-E. Broutin, F. Colobert, *Eur. J. Org. Chem.* **2005**, 1113–1128; c) P.-E. Broutin, F. Colobert, *Org. Lett.* **2005**, *7*, 3737–3740.

[10] For selected recent reviews on the preparation, the use in synthesis and the transformation of chiral sulfoxides, see: a) E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303–4356; b) L. H. S. Smith, S. C. Coote, H. F. Sneddon, D. J. Procter, *Angew. Chem. Int. Ed.* **2010**, *49*, 5832–5844; *Angew. Chem.* **2010**, *122*, 5968; c) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129–6144; d) T. Toru, C. Bolm (Eds.), *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH, Weinheim, Germany, **2008**; e) J. L. García Ruano, A. M. Martín Castro, *Heteroat. Chem.* **2007**, *18*, 537–548; f) B. Ferber, H. B. Kagan, *Adv. Synth. Catal.* **2007**, *349*, 493–507; g) C. Cardellicchio, F. Naso, M. A. M. Capozzi, *Phosphorus Sulfur Silicon Relat. Elem.* **2005**, *180*, 1161–1170.

[11] T. Leermann, P.-E. Broutin, F. R. Leroux, F. Colobert, *Org. Biomol. Chem.* **2012**, *10*, 4095–4102.

[12] Compound **4** is an advanced intermediate in previous syntheses of (–)-steganone, see ref.[7a,7f]

[13] E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, *20*, 399–402.

[14] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.

[15] A. Solladié-Cavallo, J. Suffert, A. Adib, G. Solladié, *Tetrahedron Lett.* **1990**, *31*, 6649–6652.

[16] a) T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510; b) K. L. Billingsley, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363; *Angew. Chem.* **2007**, *119*, 5455; c) P.-E. Broutin, I. Čerňa, M. Campaniello, F. Leroux, F. Colobert, *Org. Lett.* **2004**, *6*, 4419–4422; d) O. Baudoin, D. Guénard, F. Guéritte, *J. Org. Chem.* **2000**, *65*, 9268–9271.

[17] R. A. Altman, B. P. Fors, S. L. Buchwald, *Nature Protocols* **2007**, *2*, 2881–2887.

[18] a) M. R. Biscoe, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687; b) T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

[19] M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749–4755.

[20] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.

[21] H. Sugihara, R. Tanikaga, A. Kaji, *Synthesis* **1978**, 881–882.

[22] Chemoselective deprotection of the primary methoxy group failed no matter what conditions were used.

[23] Chiral HPLC [Daicel Chiralcel OD-H 250 mm × 4.6 mm, 5 μm; flow rate 0.5 mL/min, *n*-hexane/2-propanol 80:20, t_r = 16.03 min (for a*S*)-**24**, 19.59 min (for a*R*)-**24**].

[24] The enantiomeric purity of **4** was determined by ^{1}H NMR experiment with Eu(hfc)$_3$ as a chiral chemical shift reagent.

[25] P. Pasetto, X. Chen, C. M. Drain, R. W. Franck, *Chem. Commun.* **2001**, 81–82.

[26] W. Schlenk, E. Bergmann, *Justus Liebigs Ann. Chem.* **1928**, *464*, 1–42.

[27] M. Schlosser, *Organoalkali Chemistry*, in: *Organometallics in Synthesis: A Manual*, 2nd edition (Ed.: M. Schlosser), Wiley-VCH, Weinheim, Germany, **2002**, p. 295.

[28] T. Kametani, M. Aizawa, H. Kurobe, T. Matsuura, H. Nemoto, K. Fukumoto, *Chem. Pharm. Bull.* **1982**, *30*, 1493–1495.

[29] M. Matveenko, O. J. Kokas, M. G. Banwell, A. C. Willis, *Org. Lett.* **2007**, *9*, 3683–3685.

[30] P. Lv, K. Huang, L. Xie, X. Xu, *Org. Biomol. Chem.* **2011**, *9*, 3133–3135.

[31] G. Solladié, J. Hutt, A. Girardin, *Synthesis* **1987**, *2*, 173–177.

[32] M. Tanabe, R. H. Peters, *Org. Synth.* **1981**, *60*, 92–101.

[33] T. Yoshino, S. Imori, H. Togo, *Tetrahedron* **2006**, *62*, 1309–1317.

[34] A. P. Prakasham, A. K. Saxena, S. Luqman, D. Chanda, T. Kaur, A. Gupta, D. K. Yadav, C. S. Chanotiya, K. Shanker, F. Khan, A. S. Negi, *Bioorg. Med. Chem.* **2012**, *20*, 3049–3057.

[35] X. Z. Zhao, K. Maddali, S. J. Smith, M. Métifiot, B. C. Johnson, C. Marchand, S. H. Hughes, Y. Pommier, T. R. Burke, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7309–7313.

[36] G. R. Geen, I. S. Mann, M. V. Mullane, *Tetrahedron* **1998**, *54*, 9875–9894.

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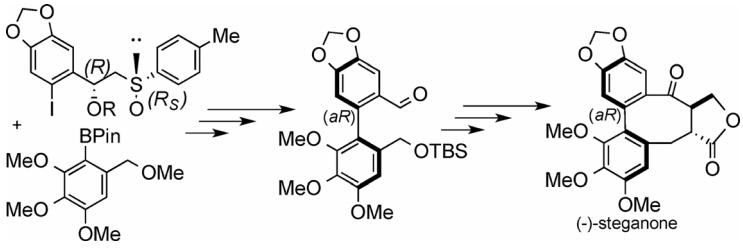
Atroposelectivity



A highly atroposelective formal synthesis of (–)-steganone is described highlighting the use of an enantiopure sulfoxide as a chiral auxiliary in the Suzuki–Miyaura cross-coupling reaction.

Keywords: Natural products / Cross-coupling / Biaryls / Atropoisomerism / Atroposelectivity / Diastereoselectivity / Chiral auxiliaries / Sulfoxides

