Asymmetric Synthesis of Antimicrotubule Biaryl Hybrids of Allocolchicine and Steganacin


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A) Synthesis of Suzuki coupling precursors

1. General iodination procedure (GP1)

To a solution of the aromatic compound (1 equiv) in chloroform at 0°C were added silver trifluoroacetate (1.2 equiv) and iodine (1.05 equiv) in one portion. After stirring for 15 min at 0°C, the mixture was filtered through Celite and washed with a saturated aq. Na₂SO₃ solution. The organic layer was dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel.

2. Synthesis of (S)-10a and (R)-10a

(S)-(−)-α-Methyl-2-iodo-4,5-methylenedioxybenzyl alcohol (10a)

![Chemical structure of 10a]

To a solution of dichloromethane (5 mL) under argon at room temperature were added (R)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 323 µL, 0.32 mmol, 0.1 equiv) and BH₃•Me₂S (10 M in Me₂S, 323 µL, 3.23 mmol, 1 equiv). After stirring for 30 min at room temperature, a solution of methylenedioxyacetophenone (530 g, 3.23 mmol, 1 equiv) in dichloromethane (5 mL) was added dropwise over 2 h. The solution was stirred for another 3 h, methanol was then added dropwise and the solvents evaporated in vacuo. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give the expected product as an oil (532 mg, 3.20 mmol, 99%), [α]D²² -46 (c 0.99, CHCl₃). The general procedure GP1 using this alcohol (517 mg, 3.11 mmol) in chloroform (17 mL) gave, after purification by flash chromatography (silica gel, dichloromethane), (S)-10a as a white powder in 97% ee (669 mg, 2.29 mmol, 74%), [α]D²² -44 (c 0.99, CHCl₃); HPLC (Chiracel OD, hexane/ethanol 95/5, 1.0 mL/min) tR 10.2 min (major enantiomer), 13.6 min (minor enantiomer).

(R)-(−)-α-Methyl-2-iodo-4,5-methylenedioxybenzyl alcohol (10a)

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Compound (R)-10a was obtained in the same manner as above for (S)-10a, from 3,4-methylenedioxyacetophenone (170 mg, 1.04 mmol) and using (S)-2-methyl-CBS-oxazaborolidine for the reduction, to afford iodo alcohol (R)-10a as an oil in 96% ee (227 mg, 0.78 mmol, 75% from methylenedioxyacetophenone), \([\alpha]_{D}^{23} +46 \text{ (c 1.00, CHCl}_3\text{); HPLC (Chiracel OD, hexane/ethanol 95/5, 1.0 mL/min) } t_R \text{ 10.2 min (minor enantiomer), 13.6 min (major enantiomer).}

3. Synthesis of (S)-10d

a) \(\alpha\)-Ethyl-3,4-methylenedioxybenzyl alcohol (14)

To a solution of 3,4-methylenedioxybenzaldehyde (2.5 g, 16.65 mmol) in THF (50mL) at -78°C was added ethylmagnesium bromide (1 M in THF, 25 mL, 24.98 mmol, 1.5 equiv) dropwise over 2 h. The mixture was stirred for 30 min at -78°C and was then allowed to warm up to room temperature. A solution of acetic acid 10% was added and the aqueous layer was
extracted with diethylether. The combined organic layers were washed with water and a saturated aq NaHCO₃ solution until the aqueous phase reached pH 7, were dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give alcohol 14 as an oil (2.84 g, 15.75 mmol, 95%). The physical data were identical to those previously described in the literature.²

b) 1-(3,4-methylenedioxyphenyl)propan-1-one (15)

To a solution of alcohol 14 (2.41 g, 13.35 mmol) in dichloromethane (50 mL) was added PCC (3.74 g, 17.36 mmol, 1.3 equiv) portionwise and the suspension was stirred at room temperature for 16 h before being filtered on Celite and MgSO₄. The filtrate was evaporated under vacuum and the residue purified by flash chromatography (silica gel, heptanes/ethyl acetate 9/1) to give the ketone as a white powder (2.11 g, 11.80 mmol, 89%). The ¹H NMR and IR spectra were identical to those previously described in literature.³ ¹³C NMR (75 MHz, CDCl₃) δ = 159.1 (C7), 151.7 (C3 or C4), 148.3 (C3 or C4), 132.0 (C1), 124.2 (C6), 108.0 (C2 and C5), 101.9 (C11), 31.7 (C8), 8.6 (C9) ppm.

c) (S)-(−)-α-Ethyl-3,4-methylenedioxybenzyl alcohol (14)

To a solution of dichloromethane (12 mL) under argon at room temperature were added (R)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 670 µL, 0.67 mmol, 0.1 equiv) and BH₃•Me₂S (10 M in Me₂S, 670 µL, 6.70 mmol, 1 equiv). After stirring for 30 min at room temperature, a solution of ketone 15 (1.19 g, 6.70 mmol, 1 equiv) in dichloromethane (12 mL) was added dropwise over 2 h. The solution was stirred for another 2 h, methanol was then

added dropwise and the solvents evaporated in vacuo. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give (S)-14 as an oil (1.18 g, 6.52 mmol, 97%), $[\alpha]_D^{25} -30$ (c 1.05, CHCl$_3$).

d) (S)-(-)-$\alpha$-Ethyl-2-iodo-4,5-methylenedioxybenzyl alcohol (10d)

The slightly modified general procedure GP1 using alcohol (631 mg; 3.49 mmol), silver trifluoroacetate (925 mg, 4.19 mmol, 1.2 equiv), iodine (974 mg, 3.84 mmol, 1.1 equiv) in chloroform (35 mL) gave, after purification by flash chromatography (silica gel, dichloromethane), (S)-10d as a white solid in 98% ee (610 mg, 1.99 mmol, 57%), $[\alpha]_D^{25} -29$ (c 1.05, CHCl$_3$); HPLC (Chiracel OD, hexane/ethanol 95/5, 1.0 mL/min) $t_R$ 10.4 min (major enantiomer), 13.5 min (minor enantiomer); M.p. 117 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.19 (s, 1H, $H_3$), 7.01 (s, 1H, $H_6$), 5.96 (d, $J$ = 1.5Hz, 2H, $H_{11a}$), 5.95 (d, $J$ = 1.5Hz, 2H, $H_{11b}$), 5.76 (dd, $J$ = 7.5, 5.1Hz, 1H, $H_7$), 1.97 (br s, 1H, $H_{10}$), 1.79-1.56 (m, 2H, $H_8$), 0.98 (t, $J$ = 7.5Hz, 3H, $H_9$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 148.9 (C$_4$ or C$_5$), 147.9 (C$_4$ or C$_5$), 140.3 (C$_7$), 118.4 (C$_2$), 107.3 (C$_6$), 101.8 (C$_{11}$), 85.5 (C$_2$), 78.8 (C$_7$), 31.0 (C$_8$), 10.3 (C$_9$) ppm; IR (neat) $\nu$ = 3307, 1470 cm$^{-1}$. 

4. Synthesis of boronate 8b

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\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{OH} \\
\text{MeO} & \quad \text{MeO} \\
\text{OMe} & \quad \text{OTES} \\
\text{I} & \quad \text{I}
\end{align*}
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a) 1-Iodo-6-triethylsilyloxyethyl-2,3,4-trimethoxybenzene (17).

To a solution of alcohol 16\(^4\) (200 mg, 0.62 mmol) and 2,6-lutidine (108 µL, 0.93 mmol) in dichloromethane (2 mL) under argon at 0 °C was added dropwise triethylsilyl trifluoromethane sulfonate (169 µL, 0.74 mmol). After stirring for 5 min at 0 °C and 25 min at 25 °C, a saturated aq. NaHCO\(_3\) solution was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO\(_4\) and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 85/15), to give 12 as an oil (266 mg, 98%); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta = 0.69\) (q, \(J = 7.8\) Hz, 6 H), 1.02 (t, \(J = 7.7\) Hz, 9 H), 3.87 (s, 3 H), 3.88 (s, 6 H), 4.61 (s, 2 H), 7.04 (s, 1 H) ppm; \(^1^3\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta = 4.6, 6.9, 56.0, 60.8, 61.1, 69.1, 82.6, 107.0, 138.8, 140.9, 152.6, 154.0\) ppm; HRMS (ESI) calcd for C\(_{16}\)H\(_{27}\)INaO\(_4\)Si \([M+Na]^+\): 461.0621; found: 461.0610.

b) Boronate 8b.

To a solution of iodide 17 (265 mg, 0.60 mmol), Pd(OAc)\(_2\) (7 mg, 0.030 mmol), 2-(dicyclohexylphosphino)biphenyl (21 mg, 0.060 mmol) in dioxane (3 mL) under argon at room temperature were added dropwise triethylamine (253 µL, 1.81 mmol) and pinacolborane (175 µL, 1.21 mmol). The mixture was heated to 80°C for 30 min, cooled to room temperature, and a saturated aq. NH\(_4\)Cl solution was added dropwise. The aqueous layer was extracted with dichloromethane, the combined organic layers were dried over MgSO\(_4\), filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 9/1), to give 8b as an oil (209 mg, 79%); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta = 0.63\) (q, \(J = 7.9\) Hz, 6 H), 0.98 (t, \(J = 7.6\) Hz, 9 H), 1.37 (s, 12 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.76 (s, 2 H), 6.93 (s, 1 H) ppm; \(^1^3\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta = 4.6, 6.9, 24.9, 55.9, 60.9, 61.6, 64.2, 83.6, 105.8, 140.2, 142.3, 154.9, 157.3\) ppm; HRMS (ESI) calcd for C\(_{22}\)H\(_{39}\)BNaO\(_6\)Si \([M+Na]^+\): 461.2507; found: 461.2499.

5. Synthesis of boronate 8c

![Chemical Structure]

a) \( \text{N-tert-butoxycarbonyl-3,4,5-trimethoxybenzylamine} \)

To a solution of 3,4,5-trimethoxybenzylamine 18 (3.00 g, 15.21 mmol) and triethylamine (3.18 mL, 22.82 mmol, 1.5 equiv) in dichloromethane (40 mL) was added Boc\(_2\O\) (3.98 g, 18.25 mmol, 1.2 equiv) portionwise and the mixture was stirred at room temperature for 2 h. 5N HCl was then added dropwise and the organic layer was washed with brine, dried over MgSO\(_4\), filtered and evaporated under vacuum. The oily residue was crystallized in an ethyl acetate/heptanes mixture to give the expected product as a white solid (3.99 g, 13.43 mmol, 88%). The \(^1H\) NMR and IR spectra were identical to those previously described in literature.\(^5\) M.p. 96 °C; \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta = 156.0\) (C\(_9\)), 153.5 (2C, C-OCH\(_3\)), 137.3 (C-OCH\(_3\)), 134.9 (C\(_1\)), 104.6 (2C, C\(_2\) and C\(_6\)), 79.7 (C\(_9\)), 61.0 (OCH\(_3\)), 56.2 (2C, OCH\(_3\)), 45.1 (C\(_7\)), 28.6 (3C, C\(_{11}\)) ppm; HRMS (ESI) calcd for C\(_{15}\)H\(_{23}\)NO\(_5\)Na [M+Na\(^+\)]: 320.1474; found: 320.1472.

b) \( \text{N-tert-butoxycarbonyl-2-iodo-3,4,5-trimethoxybenzylamine} \)

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The general procedure GP1 using the N-Boc protected amine (1.50 g, 5.05 mmol) in chloroform (50 mL) gave, after purification by flash chromatography (silica gel, heptanes/ethyl acetate 8/2), boronate 19 as an oil (2.09 g, 4.93 mmol, 98%): M.p. 76 °C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta = 6.81\) (s, 1H, \(H_6\)), 5.05 (br s, 1H, \(H_8\)), 4.10 (d, \(J = 5.7\)Hz, 2H, \(H_7\)), 3.87 (s, 3H, OCH\textsubscript{3}), 3.86 (s, 6H, OCH\textsubscript{3}), 1.46 (s, 9H, \(H_{11}\)) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta = 155.8\) (\(C_9\)), 154.0 (\(C_3\) or \(C_5\)), 153.2 (\(C_3\) or \(C_5\)), 141.5 (\(C\)-OCH\textsubscript{3}), 136.9 (\(C_1\)), 108.9 (\(C_6\)), 86.5 (\(C_2\)), 79.8 (\(C_{10}\)), 61.1 (OCH\textsubscript{3}), 60.9 (OCH\textsubscript{3}), 56.3 (OCH\textsubscript{3}), 49.6 (\(C_7\)), 28.5 (3C, \(C_{11}\)) ppm; IR (neat) \(\nu = 3364, 1682, 1277, 1162, 1096, 1007\) cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{15}H\textsubscript{22}NIO\textsubscript{5}Na [\(M+Na^+\)]: 446.0440; found: 446.0423.

c) Boronate 8c

To a solution of iodide 19 (2.09 g, 4.93 mmol), Pd(OAc)\textsubscript{2} (55 mg, 0.25 mmol, 0.05 equiv) and 2-(dicyclohexylphosphino)biphenyl (173 mg, 0.49 mmol, 0.1 equiv) in dioxane (20 mL) under argon at room temperature were added dropwise triethylamine (2.10 mL, 14.79 mmol, 3 equiv) and pinacolborane (1.43 mL, 9.86 mmol, 2 equiv). The mixture was heated to 80°C for 30 min, cooled to room temperature, and a saturated aq. NH\textsubscript{4}Cl solution was added dropwise. The aqueous layer was extracted with dichloromethane, the combined organic layers were dried over MgSO\textsubscript{4}, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 9/1, 8/2, 75/25 and then 7/3) to give boronate 8c as a brown solid (1.93 g, 4.56 mmol, 92%): M.p. 95-98 °C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta = 6.11\) (s, 1H, \(H_6\)), 5.13 (br s, 1H, \(H_8\)), 4.22 (d, \(J = 6.0\)Hz, 2H, \(H_7\)), 3.86 (s, 3H, OCH\textsubscript{3}), 3.85 (s, 3H, OCH\textsubscript{3}), 3.83 (s, 3H, OCH\textsubscript{3}), 1.45 (s, 9H, \(H_{11}\)), 1.38 (s, 12H, \(H_{16}\)) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta = 157.8\) (\(C_9\)), 155.8 (\(C_3\) or \(C_5\)), 155.1 (\(C_3\) or \(C_5\)), 141.1 (\(C_4\)), 139.4 (\(C_7\)), 109.2 (\(C_6\)), 84.0 (2C, \(C_{15}\)), 79.3 (\(C_{10}\)), 61.7 (OCH\textsubscript{3}), 60.9 (OCH\textsubscript{3}), 56.1 (OCH\textsubscript{3}), 45.3 (\(C_7\)), 28.6 (3C, \(C_{11}\)), 25.0 (4C, \(C_{16}\)) ppm; IR (neat) \(\nu = 3367, 1704, 1360\) cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{15}H\textsubscript{22}NIO\textsubscript{5}Na [\(M+Na^+\)]: 446.0440; found: 446.0423.

6. Synthesis of boronate 8d
According to a modified literature procedure, reduction of 3,4,5-trimethoxyphenylacetic acid (1.50 g, 6.63 mmol) with LiAlH$_4$ (5.52 g, 66.3 mmol, 10 equiv) in diethylether (130 mL) gave, after flash chromatography (silica gel, heptanes/ethyl acetate 4/6), the expected product as a white solid (1.05 g, 4.95 mmol, 75%): M.p. 41 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ = 6.43 (s, 2H, H$_2$ and H$_6$), 3.85-3.80 (m, 11H, OCH$_3$ and H$_8$), 2.78 (t, $J = 6.6$Hz, 2H, H$_7$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ = 153.3 (2C, C$_{-}$OCH$_3$), 136.7 (C$_{-}$OCH$_3$), 134.4 (C$_1$), 106.0 (2C, C$_2$ and C$_6$), 63.6 (C$_8$), 60.9 (OCH$_3$), 56.2 (2C, OCH$_3$), 39.6 (C$_7$) ppm; IR (neat) ν = 3393, 3331, 2940, 1588, 1421 cm$^{-1}$; HRMS (ESI) calcd for C$_{11}$H$_{16}$O$_4$Na [M+Na$^+$]: 235.0946; found: 235.0934.

b) 2-(2-iodo-3,4,5-trimethoxyphenyl)ethanol (21).

The general procedure GPI using the above alcohol (1.01 g, 4.77 mmol) in chloroform (40 mL) gave, after purification by flash chromatography (silica gel, heptanes/ethyl acetate 1/1), alcohol 21 as a white solid (1.47 g, 4.33 mmol, 91%): M.p. 68-69°C ; $^1$H NMR (300 MHz,

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CDCl$_3$ $\delta$ = 6.70 (s, 1H, $H_6$), 3.88 (s, 3H, OCH$_3$), 3.86-3.83 (m, 8H, 2 OCH$_3$ and $H_8$), 3.03 (t, $J$ = 6.6Hz, 2H, $H_7$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 153.7 (C$_3$ or C$_5$), 153.4 (C$_3$ or C$_5$), 140.9 (C$_4$), 136.9 (C$_7$), 109.9 (C$_6$), 88.5 (C$_2$), 62.4 (C$_8$), 61.1 (OCH$_3$), 60.9 (OCH$_3$), 56.3 (OCH$_3$), 44.0 (C$_7$) ppm; IR (neat) $\nu$ = 3338, 3251, 2931, 1385 cm$^{-1}$; HRMS (ESI) calcd for C$_{11}$H$_{15}$IO$_4$Na $[M+Na]^+$: 360.9913; found: 360.9943.

c) 2-Iodo-1-(2-triethylsilyloxy)ethyl-3,4,5-trimethoxybenzene.

![Chemical Structure](image)

To a solution of the alcohol 21 (120.7 mg, 0.357 mmol) and 2,6-lutidine (62 $\mu$L, 0.54 mmol, 1.5 equiv) in dichloromethane (2 mL) under argon at 0°C was added dropwise triethylsilyltrifluoromethane sulfonate (97 $\mu$L, 0.43 mmol, 1.2 equiv). After stirring for 20 min at 0°C and 40 min at room temperature, a saturated aq. NaHCO$_3$ solution was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8/2) to give the title compound as a yellow oil (132.8 mg, 0.29 mmol, 82%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 6.70 (s, 1H, $H_6$), 3.88 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.79 (t, $J$ = 7.2Hz, 2H, $H_8$), 2.98 (t, $J$ = 7.2Hz, 2H, $H_7$), 0.92 (t, $J$ = 8.1Hz, 9H, $H_{10}$), 0.56 (q, $J$ = 8.1Hz, 6H, $H_9$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 153.4 (C$_3$ or C$_5$), 153.2 (C$_3$ or C$_5$), 140.8 (C$_4$), 137.5 (C$_7$), 110.3 (C$_6$), 88.4 (C$_2$), 62.5 (C$_8$), 61.1 (OCH$_3$), 60.8 (OCH$_3$), 56.2 (OCH$_3$), 44.3 (C$_7$), 6.9 (3C, C$_{10}$), 4.5 (3C, C$_9$) ppm; IR (neat) $\nu$ = 2952, 2874, 1479, 1385 cm$^{-1}$; HRMS (ESI) calcd for C$_{17}$H$_{29}$INaO$_4$Si $[M+Na]^+$: 475.0778; found: 475.0774.
d) Boronate 8d

To a solution of the above iodide (1.30 g, 2.88 mmol), Pd(OAc)$_2$ (32 mg, 0.14 mmol, 0.05 equiv) and 2-(dicyclohexylphosphino)biphenyl (101 mg, 0.29 mmol, 0.1 equiv) in dioxane (13 mL) under argon at room temperature were added dropwise triethylamine (1.20 mL, 8.64 mmol, 3 equiv) and pinacolborane (836 µL, 5.76 mmol, 2 equiv). The mixture was heated to 80°C for 30 min, cooled to room temperature, and a saturated aq. NH$_4$Cl solution was added dropwise. The aqueous layer was extracted with dichloromethane, the combined organic layers were dried over MgSO$_4$, filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 9:1) to give a 95:5 inseparable mixture of boronate 8d and the proto-deiodination product as a brown oil (1.15 g, 2.45 mmol of 8d, 85%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 6.55$ (s, 1H, $H_6$), 3.85 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 3.76 (t, $J = 7.2$Hz, 2H, $H_8$), 2.83 (t, $J = 7.2$Hz, 2H, $H_7$), 1.37 (s, 12H, $H_{15}$), 0.92 (t, $J = 7.8$Hz, 9H, $H_{10}$), 0.55 (q, $J = 7.8$Hz, 6H, $H_9$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta = 157.1$ (C-OCH$_3$), 154.5 (C-OCH$_3$), 139.2 (2C, C-OCH$_3$ and C$_7$), 110.0 (C$_6$), 83.8 (2C, C$_{14}$), 64.8 (C$_8$), 61.6 (OCH$_3$), 60.9 (OCH$_3$), 56.1 (OCH$_3$), 39.9 (C$_7$), 25.0 (4C, C$_{13}$), 6.9 (3C, C$_{10}$), 4.5 (3C, C$_9$) ppm; IR (neat) $\nu = 2953, 2936, 1338$ cm$^{-1}$; HRMS (ESI) calcd for C$_{23}$H$_{41}$BNaO$_6$Si [M+Na$^+$]: 475.2663; found: 475.2681.

B) Synthesis of non-racemic biaryls 9c-g

1. Synthesis of ($R$, aS)-9c (Scheme 7)
The general Suzuki coupling procedure from iodide (R)-10a (212 mg, 0.72 mmol), boronate 8b (474 mg, 1.08 mmol), ligand L¹ (32.3 mg, 0.07 mmol) in dioxane (0.64 mL) and water (0.07 mL) gave, after flash chromatography (heptanes/ethyl acetate 9:1, then 7:3), a mixture of the TES-protected biaryl and the proto-deiodination product of (R)-10a (122 mg). Treatment of this mixture (122 mg) with TBAF in THF (2.5 mL) gave, after flash chromatography (heptanes/ethyl acetate 1:1, then 1:2), biphenyl (R, aS)-9c as a yellow solid (89.4 mg, 34 % from (R)-10a), [α]D²5 -51 (c 1.22, CHCl₃).
2. Synthesis of (S, aR)-9e (Table 2, entry 3)

The general Suzuki coupling procedure from iodide (S)-10d (250 mg, 0.82 mmol), boronate 8b (538 mg, 1.23 mmol), ligand L1 (32 mg, 0.08 mmol) in dioxane (0.74 mL) and water (0.08 mL) gave, after flash chromatography (heptanes/ethyl acetate 9/1, 85/15, 8/2 and then 7/3), a mixture of the TES-protected coupling product and the proto-deiodination product of (S)-10d (178 mg). Treatment of this mixture (139 mg) with TBAF in THF (3 mL) gave, after flash chromatography (heptanes/ethyl acetate 1/1), biphenyl (S, aR)-9e as a white solid (101 mg, 0.27 mmol, 42% from (S)-10d); [α]D22 +67 (c 0.97, CHCl3): M.p. 155 °C; 1H NMR (300 MHz, CDCl3) δ = 7.04 (s, 1H, H3), 6.95 (s, 1H, H11), 6.61 (s, 1H, H6), 6.01 (d, J = 0.6Hz, 2H, H17), 4.39 (d, J = 12.6Hz, 1H, H21a), 4.31 (d, J = 12.6Hz, 1H, H21b), 4.13 (t, J = 7.2Hz, 1H, H13), 3.94 (s, 3H, H18 or H20), 3.92 (s, 3H, H19), 3.55 (s, 3H, H18 or H20), 3.07 (br s, 1H, H16 or H22), 1.84-1.61 (m, 2H, H14), 0.70 (t, J = 7.2Hz, 3H, H15) ppm; 13C NMR (75 MHz, CDCl3) δ = 153.2 (C8 or C10), 150.8 (C8 or C10), 148.0 (C4 or C5), 146.8 (C4 or C5), 141.6 (C9), 136.9 (C2), 135.0 (C12), 127.9 (C1), 126.1 (C7), 110.0 (C9), 107.6 (C3), 106.3 (C11), 101.4 (C17), 72.4 (C13), 62.9 (C21), 61.4 (OCH3), 61.3 (OCH3), 56.2 (OCH3), 28.4 (C14), 10.5 (C15) ppm; IR (neat) 3368, 2932, 1479, 1228, 1094, 1037, 992 cm⁻¹; HRMS (ESI) calcd for C20H24O7Na [M+Na⁺]: 399.1420; found: 399.1412.

3. Synthesis of (S, aR)-9f (Table 2, entry 5).
The general Suzuki coupling procedure from iodide (S)-10a (93 mg, 0.32 mmol), boronate 8c (203 mg, 0.48 mmol), ligand L1 (12 mg, 0.03 mmol) in dioxane (0.29 mL) and water (0.03 mL) gave, after flash chromatography (heptanes/ethyl acetate 85/15, 75/25, 7/3, and then 1/1), a mixture of biaryl (S, aR)-9f and pinacol (67.5 mg). Further purification by preparative TLC (heptanes/ethyl acetate 1/1) afforded pure (S, aR)-9f as an oil (58 mg, 39%); [α]D24 +30 (c 1.04, CHCl3); 1H NMR (300 MHz, CDCl3) δ = 7.12 (s, 1H, H3), 6.80 (s, 1H, H11), 6.57 (s, 1H, H6), 6.00 (s, 2H, H16), 4.49 (br s, 1H, H21), 4.42 (q, J = 6.6 Hz, 1H, H13), 3.99 (s, 1H, H20), 3.91 (s, 3H, H17 or H19), 3.90 (s, 3H, H18), 3.56 (s, 3H, H17 or H19), 3.03 (br s, 1H, H15), 1.41 (s, 9H, H24), 0.70 (t, J = 6.6 Hz, 3H, H14) ppm; 13C NMR (75 MHz, CDCl3) δ = 155.7 (C22), 153.1 (C8 or C10), 151.0 (C8 or C10), 148.0 (C4 or C5), 147.0 (C4 or C5), 141.3 (C9), 138.1 (C2), 133.2 (C12 or C1 or C7), 127.3 (C12 or C1 or C7), 126.6 (C12 or C1 or C7), 109.7 (C6), 108.5 (C11), 106.2 (C3), 101.4 (C16), 79.7 (C23), 66.6 (C13), 61.5 (OCH3), 61.3 (OCH3), 56.2 (OCH3), 42.8 (C20), 28.5 (3C, C24), 21.8 (C14) ppm; IR (neat) ν = 3369, 2928, 1482 cm⁻¹; HRMS (ESI) calculated for C24H31NO8Na [(M+Na)+]: 484.1947; found: 484.1954.

4. Synthesis of (S, aR)-9g (Table 2, entry 9).

The general Suzuki coupling procedure from iodide (S)-10a (93 mg, 0.32 mmol), boronate 8d (275 mg of a 95/5 mixture with deboronated product, 0.48 mmol), ligand L5 (13 mg, 0.03 mmol) in dioxane (0.29 mL) and water (0.03 mL) gave, after flash chromatography (heptanes/ethyl acetate 9/1, then 7/3), a mixture of the expected TES-protected biaryl and the proto-deiodination product of (S)-10a (91 mg). Treatment of this mixture (66 mg) with TBAF in THF (1.5 mL) gave, after flash chromatography (heptanes/ethyl acetate 1/1), biphenyl (S, aR)-9g as a white solid (50 mg, 0.132 mmol, 57% from (S)-10a); [α]D22 +46 (c 1.00, CHCl3); M.p. 153 °C; 1H NMR (300 MHz, CDCl3) δ = 7.09 (s, 1H, H3), 6.69 (s, 1H, H11), 6.57 (s, 1H, H6), 6.00 (s, 2H, H17), 4.41 (q, J = 6.3 Hz, 1H, H13), 3.90 (s, 3H, H17 or H19), 3.88 (s, 3H, H18), 3.58 (t, J = 6.9 Hz, 2H, H21), 3.54 (s, 3H, H17 or H19), 3.11 (br s, 1H, H15 or H22), 2.70 (quint, J
= 13.5, 6.9Hz, 1H, H\textsubscript{20a}), 2.52 (quint, J = 13.5, 6.9Hz, 1H, H\textsubscript{20a}), 1.32 (d, J = 6.3Hz, 3H, H\textsubscript{14}) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ = 152.9 (C\textsubscript{8} or C\textsubscript{10}), 151.0 (C\textsubscript{8} or C\textsubscript{10}), 147.8 (C\textsubscript{4} or C\textsubscript{5}), 146.8 (C\textsubscript{4} or C\textsubscript{5}), 140.9 (C\textsubscript{9}), 138.1 (C\textsubscript{2}), 132.8 (C\textsubscript{12}), 128.1 (C\textsubscript{7} or C\textsubscript{7}), 127.5 (C\textsubscript{7} or C\textsubscript{7}), 110.1 (C\textsubscript{6}), 109.7 (C\textsubscript{11}), 106.0 (C\textsubscript{3}), 101.3 (C\textsubscript{16}), 66.6 (C\textsubscript{13}), 62.0 (C\textsubscript{21}), 61.4 (OCH\textsubscript{3}), 61.2 (OCH\textsubscript{3}), 56.2 (OCH\textsubscript{3}), 36.6 (C\textsubscript{20}), 21.7 (C\textsubscript{14}) ppm; IR (neat) ν = 3369, 2928, 1482 cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{20}H\textsubscript{24}O\textsubscript{7}Na [M+Na\textsuperscript{+}]: 399.1420; found 399.1428.

Racemic biaryls (±)-9c, (±)-9e, (±)-9f and (±)-9g were obtained in the same manner as for their S,aR enantiomers from racemic iodides (±)-10a or (±)-10d, as described in Figure 1 and Table 2.

C) Synthesis of target compounds 5a-f

1. Dibenzoxepine (S, aS)-5a (Scheme 7).

From (R, aS)-9c: the general cyclodehydration procedure from diol (R, aS)-9c (76.8 mg, 0.21 mmol) in 11 mL of dichloromethane at -50°C gave, after preparative TLC (heptanes/ethyl acetate 6/4), dibenzoxepine (S, aS)-5a as an oil in 94% ee (62 mg, 86%); [α]D\textsuperscript{23} +119 (c 1.00, CHCl\textsubscript{3}); HPLC (Chiralpak AD, hexane/ethanol 99/1, 1.0 mL/min) t\textsubscript{R} 14.7 min (minor enantiomer), 22.5 min (major enantiomer).

From (S, aS)-9d: the general cyclodehydration procedure from diol (S, aS)-9d (10 mg, 0.03 mmol) in 2 mL of dichloromethane at -50°C gave, after preparative TLC (heptanes/ethyl acetate 1/1), dibenzoxepine (S, aS)-5a as an oil in 96% ee (7.4 mg, 80%).

2. Dibenzoxepine (R, aR)-5b (Scheme 10).
The general cyclodehydration procedure from diol \((S, aR)-9e\) (23.3 mg, 0.06 mmol) in 1.5 mL of dichloromethane at -78°C gave, after preparative TLC (heptanes/ethyl acetate 6/4), dibenzoxepine \((R, aR)-5b\) as an oil in 95% ee (18 mg, 77%, 91/9 mixture of interconverting atropisomers); \([\alpha]_D^{25} -80\) (c 0.90, CHCl3); HPLC (Chiracel OD, hexane/ethanol 99.5/0.5, 1.0 mL/min) \(t_R\) 27.6 min (major enantiomer), 55.4 min (minor enantiomer); \(^1\)H NMR (300 MHz, CDCl3) \(\delta = 7.06\) (s, 1H, \(H_6\)), 6.88 (s, 1H, \(H_3\)), 6.64 (s, 1H, \(H_{11}\)), 5.96 (d, \(J = 1.5\)Hz, 1H, \(H_{17a}\)), 5.94 (d, \(J = 1.5\)Hz, 1H, \(H_{17b}\)), 4.29 (d, \(J = 11.1\)Hz, 1H, \(H_{16a}\)), 3.88-3.77 (m, 8H, 2 OCH3, \(H_{13}\) and \(H_{16b}\)), 3.64 (s, 3H, \(H_{18}\) or \(H_{20}\)), 1.89 (m, 2H, \(H_{14}\)), 0.70 (t, \(J = 7.5\)Hz, 3H, \(H_{15}\)) ppm; \(^{13}\)C NMR (75 MHz, CDCl3) \(\delta = 153.1\) (C8 or C10), 150.5 (C8 or C10), 147.3 (C4 or C5), 146.8 (C4 or C3), 142.7 (C9), 131.5 (2C) and 130.9 (C2, C12 and C1), 126.5 (C7), 109.9 (C6), 108.4 (C11), 105.7 (C3), 101.3 (C17), 74.5 (C13), 67.9 (C16), 61.3 (OCH3), 61.0 (OCH3), 56.2 (OCH3), 25.2 (C14), 11.1 (C15) ppm; IR (neat) \(\nu = 2933, 1482\ \text{cm}^{-1}\); HRMS (ESI) calcd for C20H22O6Na \([M+Na^+]: 381.1314\); found: 381.1302.

3. Dibenzoxocine \((R, aR)-5f\) (Scheme 10).

The general cyclodehydration procedure from diol \((S, aR)-9g\) (28.1 mg, 0.08 mmol) in 2.5 mL of dichloromethane at -45°C gave, after preparative TLC (heptanes/ethyl acetate 1/1), dibenzoxocine \((R, aR)-5f\) as a white solid in 96% ee (22.5 mg, 84%); \([\alpha]_D^{24} -39\) (c 1.00, CHCl3); HPLC (Chiralpak AD, hexane/ethanol 95/5, 1.0 mL/min) \(t_R\) 7.5 min (major
enantiomer), 20.3 min (minor enantiomer); M.p. 161-162°C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta = 7.07\) (s, 1H, \(H_3\)), 6.79 (s, 1H, \(H_6\)), 6.52 (s, 1H, \(H_{11}\)), 6.01 (d, \(J = 1.5\) Hz, 1H, \(H_{17a}\)), 5.98 (d, \(J = 1.5\) Hz, 1H, \(H_{17b}\)), 4.08 (q, \(J = 6.6\) Hz, 1H, \(H_{13}\)), 4.12 (m, 1H, \(H_{16a}\)), 3.92 (s, 3H, \(H_{19}\)), 3.90 (s, 3H, \(H_{18}\) or \(H_{20}\)), 3.59 (s, 3H, \(H_{18}\) or \(H_{20}\)), 3.59 (t, \(J = 10.8\) Hz, 1H, \(H_{16b}\)), 2.59 (dd, \(J = 14.4, 5.7\) Hz, 1H, \(H_{15a}\)), 2.52 (ddd, \(J = 14.4, 10.8, 1.5\) Hz, 1H, \(H_{15b}\)), 1.40 (d, \(J = 6.6\) Hz, 3H, \(H_{14}\)) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta = 153.2\) (C\(_8\) or C\(_{10}\)), 151.4 (C\(_8\) or C\(_{10}\)), 147.8 (C\(_4\) or C\(_5\)), 146.2 (C\(_4\) or C\(_5\)), 140.8 (C\(_9\)), 137.4 (C\(_{12}\)), 135.7 (C\(_2\)), 128.9 (C\(_{17}\)), 126.2 (C\(_7\)), 110.3 (C\(_6\)), 108.0 (C\(_{11}\)), 105.2 (C\(_3\)), 101.3 (C\(_{17}\)), 72.0 (C\(_{13}\)), 37.2 (C\(_{15}\)), 21.4 (C\(_{14}\)) ppm; IR (neat) \(\nu = 2921, 2842, 1454\) cm\textsuperscript{-1}; HRMS (ESI) calcd for C\(_{20}\)H\(_{22}\)O\(_6\)Na [\(M+Na^+\)]: 381.1314; found: 381.1322.

Racemic target compounds (±)-5a-d and (±)-5f were obtained in a similar manner as for their \(R_aR\) enantiomers from racemic biaryls (±)-9c and (±)-9e-g, as described in Schemes 6 and 10.

4. Dibenzazepine (±)-5e (Scheme 10).

\[
\text{O} \quad \text{MeO} \quad \text{MeO} \\
\text{MeO} \quad \text{NMe} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe} \\
\text{(±)-5e}
\]

To a solution of (±)-5c (27 mg, 0.078 mmol) in acetonitrile (2 mL) were added formaldehyde (37% aq., 70 \(\mu\)L, 0.94 mmol) and sodium cyanoborohydride (25 mg, 0.39 mmol) and the resulting mixture was stirred at 20°C for 1 h. A 15% aq. solution of NaOH was then added and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over MgSO\(_4\), filtered and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, dichloromethane/methanol 97:3, then 95:5, then 92:8), to give dibenzazepine (±)-5e as a yellow film (27 mg, 97%); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta = 7.08\) (s, 1H), 6.92 (s, 1H), 6.71 (s, 1H), 6.01 (d, \(J = 1.5\) Hz, 1H), 5.99 (d, \(J = 1.8\) Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.70 (s, 3H), 3.51 (d, \(J = 12.0\) Hz, 1H), 3.40 (q, \(J = 6.9\) Hz, 1H), 3.01 (d, \(J = 12.0\) Hz, 1H), 2.32 (s, 3H), 1.46 (d, \(J = 6.9\) Hz, 3H) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta = 152.8, 150.6, 146.9, 146.5, 142.3, 130.6, 130.5, 129.6, 126.0, 110.0, 109.0,\)
106.2, 101.3, 61.2, 61.0, 59.1, 56.2, 55.4, 37.6, 16.2 ppm; IR (film) ν = 2935, 1481 cm$^{-1}$; HRMS (ESI) calcd for C$_{20}$H$_{24}$NO$_5$ [M+H$^+$]: 358.1654; found: 358.1617.
D) $^1$H, $^{13}$C NMR and NOESY or ROESY spectra for 9c, 9e-g and 5a-f
(S, aR)-9f
INTERCONVERTING ATROPISOMERS.
Monte-Carlo calculations:
The more stable conformation for the median ring is twist-boat-chair (TBC)
E) Copies of HPLC traces for (S)-10a, (R)-10a, (S)-10d and final compounds

(±)-10a:

(S)-10a:

(R)-10a:
(±)-10d:

(5)-10d:

Sample Name: AJA084A; Date Acquired: 17/03/2003 10:23:53; Processed Channel Descr. PDA 240.0 nm

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(R,aR)-5a:

(S,aS)-5a from (S,aS)-9d (using TFA):
(±)-5a:

(S, aS)-5a from (R,aS)-9c (using TFA):

(S, aS)-5a from (S, aR)-9c (using Deoxofluor):
(±)-5b:

(R,aR)-5b:
(±)-5c:

(R,aR)-5c:
(±)-5f:

(R,aR)-5f: