Radical arylation of tyrosine and its application in the synthesis of a highly selective neurotensin receptor 2 ligand

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1. General remarks

Reagents, building blocks and dry solvents were obtained from commercial sources and were used as received. Unless otherwise noted, reactions were conducted without inert atmosphere. $^1$H-NMR were recorded on 360 and 600 MHz spectrometers using CDCl$_3$ and CD$_3$OD as solvents referenced to TMS (0 ppm), CHCl$_3$ (7.26 ppm) or CHD$_2$OD (3.31 ppm). Chemical shifts are reported in parts per million (ppm). Coupling constants are in Hertz (J Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). $^{13}$C-NMR were recorded at 91 and 151 MHz in CDCl$_3$ and CD$_3$OD using CDCl$_3$ (77.0 ppm) or CD$_3$OD (49.5 ppm) as standard. Chemical shifts are given in parts per million (ppm). Mass spectra were recorded using electron impact (EI). Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light to visualise components. Silica gel (Kieselgel 60, 40-63 μm, Merck) was used for flash column chromatography. The enantiomeric purity of compounds (S)- and (R)-12b was determined by chiral analytical HPLC (Varian 940-LC, column: Daicel Chiralpak® IC, 4.6 mm×250 mm, 5 μm, flow rate 0.8 mL/min, hexane / iso-propanol = 90:10, detection wavelength 254 nm and 280 nm).

2. Syntheses

2.1 General procedure for the radical arylation

Preparation of the arenediazonium tetrafluoroborate (method A): A mixture of the aniline (40.0 mmol), tetrafluoroboric acid (50%, 80.0 mmol, 14.0 mL) and water (15 mL) was cooled down to 0-5 °C. A pre-cooled solution of sodium nitrite (42.0 mmol, 2.90 g) in water (6.5 mL) was dropwise added keeping the temperature below 5 °C. After stirring for 30 minutes at this temperature the diazonium salt was filtered off and washed with cold diethyl ether. The solid was dried in vacuo and could be stored for a few weeks at −18 °C.

Preparation of the arenediazonium chloride (method B): To an ice-cooled degassed solution of the aniline (20.0 mmol) in hydrochloric acid (3 N, 20 mL) and water (20 mL) a degassed solution of sodium nitrite (1.38 g, 20.0 mmol) in water (10 mL) was dropwise added over a period of 10 minutes. After stirring for 20 more minutes at 0 °C, the clear solution was used for the biaryl coupling reactions (20 mmol / 50 mL = 0.4 M).

Biaryl coupling: A solution of the arenediazonium tetrafluoroborate (method A, 2.00 mmol) in water and acetonitrile (5 mL, ratio depends on the solubility of the
diazonium salt) or a 5 mL aliquot of the 0.4 M arenediazonium chloride solution (method B, 2.00 mmol) was added dropwise by a syringe pump to a vigorously stirred, degassed solution of methyl tyrosinate hydrochloride (6.00 mmol, 1.39 g) in water (6 mL), titanium(III)-chloride (4 mL, ca. 1 M solution in 3 N hydrochloric acid, 4.00 mmol) under nitrogen atmosphere within 10-15 minutes. After the addition was complete, the mixture was left to stir for 10 more minutes. Before threefold extraction with diethyl ether (3 x 75 mL), satd. aqueous sodium carbonate was used to adjust the pH of the crude mixture to a value of 8-9. The combined organic phases were washed with satd. aqueous sodium chloride and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH = 10:1) gave the desired arylated tyrosine derivatives.

2.2 General procedure for the Fmoc protection

To an ice-cooled solution of the arylated tyrosine derivative (1.00 mmol) in aqueous sodium carbonate (10%, 2 mL) and $p$-dioxane (1 mL) a solution of N-(9H-fluoren-2-ylmethoxy-carbonyloxy)succinimide (Fmoc-OSu) (1.18 mmol, 395 mg) in $p$-dioxane (2 mL) was added dropwise. After stirring for 24 hours with gradual warming to room temperature, the solution was poured in ice / water and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with satd. aqueous sodium chloride and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH/HCO$_2$H = 99:1:0.5) gave the desired Fmoc-protected tyrosine derivatives.

2.3 General procedure for the selective cleavage of the Fmoc-protected tyrosine methyl esters

A solution of the Fmoc-protected methyl tyrosinate derivative (1.00 mmol) in aqueous sodium carbonate (3%, 90 mL) and acetonitrile (60 mL) was stirred for 24 hours under nitrogen atmosphere. The reaction mixture was then washed with hexane (2 x 50 mL). Before threefold extraction with chloroform (3 x 100 mL), hydrochloric acid (2 N) was used to adjust the pH of the crude mixture to a value of 3-4. The combined organic phases were washed with satd. aqueous sodium chloride, dried over sodium sulfate and concentrated in vacuo.
2.4 Methyl (S)-2-amino-3-(6-hydroxybiphen-3-yl)propanoate [(S)-10a]

![Chemical Structure](structure.png)

Compound (S)-10a was prepared from methyl (S)-tyrosinate hydrochloride [(S)-9] and phenyldiazonium tetrafluoroborate (method A) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(6-hydroxy-biphen-3-yl)propanoate [(S)-10a] (0.43 mmol, 118 mg, 22%) was obtained as yellow oil.

$R_f = 0.4 \text{ (CH}_2\text{Cl}_2 / \text{MeOH}=10:1) \ [\text{UV}].$

$^1\text{H-NMR} \ (600 \text{ MHz, CDCl}_3): \delta \text{ (ppm) } = 2.82 \ (\text{dd, } J = 7.8 \text{ Hz, } J = 13.8 \text{ Hz, 1 H}), \ 3.05 \ (\text{dd, } J = 5.0 \text{ Hz, } J = 13.8 \text{ Hz, 1 H}), \ 3.69-3.72 \ (\text{m, 4 H}), \ 6.82 \ (\text{d, } J = 8.2 \text{ Hz, 1 H}), \ 7.01 \ (\text{dd, } J = 2.3 \text{ Hz, } J = 8.2 \text{ Hz, 1 H}), \ 7.03 \ (\text{d, } J = 2.2 \text{ Hz, 1 H}), \ 7.33-7.37 \ (\text{m, 1 H}), \ 7.41-7.45 \ (\text{m, 4 H}).$

$^{13}\text{C-NMR} \ (151 \text{ MHz, CDCl}_3): \delta = 39.9 \ (\text{CH}_2), \ 52.1 \ (\text{CH}_3), \ 55.6 \ (\text{CH}), \ 116.3 \ (\text{CH}), \ 127.7 \ (\text{C}q), \ 128.4 \ (\text{CH}), \ 128.7 \ (\text{CH}), \ 129.0 \ (2 \times \text{CH}), \ 129.1 \ (2 \times \text{CH}), \ 129.7 \ (\text{CH}), \ 131.0 \ (\text{C}q), \ 137.3 \ (\text{C}q), \ 151.8 \ (\text{C}q), \ 175.3 \ (\text{C}q).$

**MS (EI) m/z (%):** 271 (6) [M$^+$], 212 (7), 184 (26), 183 (100), 165 (5), 128 (3), 107 (7), 106 (4), 105 (4), 88 (6)

**HRMS (EI):** calcd. for C$_{16}$H$_{17}$NO$_3$ [M$^+$]: 271.1208, found: 271.1208.
2.5 Methyl (S)-2-amino-3-(4′-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-10b]

Compound (S)-10b was prepared from methyl (S)-tyrosinate hydro-chloride [(S)-9] and 4-fluorophenyl diazonium chloride (method B) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(4′-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-10b] (0.44 mmol, 127 mg, 22%) was obtained as colorless oil.

\[ R_f = 0.4 \ (\text{CH}_2\text{Cl}_2 / \text{MeOH} = 10:1) \ [\text{UV}] \]

\[ ^1\text{H-NMR} \ (360 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}) = 2.80 \ (\text{dd, } J = 7.7 \text{ Hz, } J = 13.7 \text{ Hz, 1 H}), \ 3.05 \ (\text{dd, } J = 3.9 \text{ Hz, } J = 13.6 \text{ Hz, 1 H}), \ 3.72 \ (\text{s, 4 H}), \ 6.74 \ (\text{d, } J = 8.1 \text{ Hz, 1 H}), \ 6.95-7.01 \ (\text{m, 2 H}), \ 7.09 \ (\text{t, } J = 8.8 \text{ Hz, } J_{\text{HF}} = 8.8 \text{ Hz, 2 H}), \ 7.42 \ (\text{dd, } J_{\text{HF}} = 5.4 \text{ Hz, } J = 8.9 \text{ Hz, 2 H}) \]

\[ ^{13}\text{C-NMR} \ (91 \text{ MHz, CDCl}_3): \delta = 39.7 \ (\text{CH}_2), \ 52.1 \ (\text{CH}_3), \ 55.5 \ (\text{CH}), \ 115.5 \ (d, J_{\text{CF}} = 21.0 \text{ Hz, } 2 \times \text{CH}), \ 116.4 \ (\text{CH}), \ 127.7 \ (C_q), \ 128.5 \ (C_q), \ 129.6 \ (\text{CH}), \ 130.8 \ (d, J_{\text{CF}} = 8.1 \text{ Hz, } 2 \times \text{CH}), \ 131.1 \ (\text{CH}), \ 133.6 \ (d, J_{\text{CF}} = 2.9 \text{ Hz, C}_q), \ 152.1 \ (C_q), \ 162.1 \ (d, J_{\text{CF}} = 245.8 \text{ Hz, C}_q), \ 175.2 \ (C_q) \]

\[ \text{MS (EI) } m/z \ (%): 290 \ (29) \ [M^+\text{+H}], \ 289 \ (92) \ [M^+], \ 231 \ (25), \ 230 \ (100), \ 229 \ (30), \ 228 \ (14), \ 213 \ (15), \ 203 \ (49), \ 202 \ (100), \ 201 \ (100), \ 200 \ (32), \ 199 \ (45), \ 195 \ (32), 187 \ (12), \ 186 \ (17), \ 185 \ (22), \ 184 \ (17), \ 183 \ (70), \ 182 \ (15), \ 181 \ (60), \ 173 \ (11), \ 172 \ (15), \ 171 \ (33), \ 170 \ (40), \ 165 \ (15), \ 159 \ (25), \ 157 \ (19), \ 153 \ (21), \ 152 \ (45), \ 151 \ (12), \ 147 \ (11), \ 146 \ (27), \ 133 \ (42), \ 127 \ (11), \ 120 \ (12), \ 115 \ (74), \ 114 \ (38), \ 107 \ (22), \ 89 \ (52), \ 88 \ (94), \ 77 \ (15), \ 74 \ (19) \]

\[ \text{HRMS (EI)}: \text{calcd. for } \text{C}_{16}\text{H}_{16}\text{FNO}_3 \ [M^+] : 289.1114, \text{ found: 289.1114.} \]
2.6 Methyl (R)-2-amino-3-(4'-fluoro-6-hydroxybiphen-3-yl)propanoate [(R)-10b]

![Chemical structure of (R)-10b](image)

Compound (R)-10b was prepared from methyl (R)-tyrosinate hydrochloride [(R)-9] and 4-fluorophenyl diazonium chloride (method B) according to the general procedure for the radical arylation described above. Methyl (R)-2-amino-3-(4'-fluoro-6-hydroxybiphen-3-yl)propanoate [(R)-10b] (0.46 mmol, 133 mg, 23%) was obtained as colorless oil. The analytical data is in agreement with those of the (S)-enantiomer.
2.7 Methyl (S)-2-amino-3-(4’-chloro-6-hydroxybiphen-3-yl)propanoate [(S)-10c]

![Chemical Structure](attachment:structure.png)

Compound (S)-10c was prepared from methyl (S)-tyrosinate hydrochloride [(S)-9] and 4-chlorophenyl diazonium chloride (method B) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(4’-chloro-6-hydroxybiphen-3-yl)propanoate [(S)-10c] (0.81 mmol, 249 mg, 41%) was obtained as white solid.

$R_f = 0.5 \ (CH_2Cl_2 / MeOH = 10:1) \ [UV]$.

$^1H$-NMR (360 MHz, CD$_3$OD): $\delta$ (ppm) = 2.94 (dd, $J = 6.0$ Hz, $J = 13.9$ Hz, 1 H), 3.02 (dd, $J = 7.0$ Hz, $J = 13.9$ Hz, 1 H), 3.71 (s, 3 H), 3.83 (dd, $J = 6.0$ Hz, $J = 7.0$ Hz, 1 H), 6.85 (d, $J = 8.3$ Hz, 1 H), 7.01 (dd, $J = 8.6$ Hz, 1 H), 7.09 (d, $J = 2.2$ Hz, 1 H), 7.37 (d, $J = 8.6$ Hz, 2 H), 7.54 (d, $J = 8.6$ Hz, 2 H).

$^{13}C$-NMR (91 MHz, CD$_3$OD): $\delta$ = 39.9 (CH$_2$), 49.9 (CH$_3$), 56.4 (CH), 117.3 (CH), 128.6 (C$q$), 128.7 (C$q$), 129.0 (2 × CH), 130.7 (CH), 131.9 (2 × CH), 132.4 (CH), 133.6 (C$q$), 138.7 (C$q$), 154.6 (C$q$), 175.3 (C$q$).

**MS (EI) m/z (%)**: 307 (3) [37Cl-M$^-$], 305 (8) [35Cl-M$^-$], 248 (4), 246 (10), 219 (42), 217 (100), 181 (15), 152 (10), 136 (10), 107 (58), 88 (58), 70 (9), 57 (21), 43 (60).

**HRMS (EI)**: calcd. for C$_{16}$H$_{16}$ClO$_3$ [M$^+$]: 305.0819, found: 305.0821.
2.8 Methyl (S)-2-amino-3-(4’-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-10d]

![Chemical Structure](image)

Compound (S)-10d was prepared from methyl (S)-tyrosinate hydrochloride [(S)-9] and 4-bromophenyl diazonium chloride (method B) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(4’-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-10d] (0.63 mmol, 219 mg, 32%) was obtained as yellow oil.

\[ R_t = 0.4 \text{ (CH}_2\text{Cl}_2 / \text{MeOH = 10:1}) \text{ [UV].} \]

\[ ^1\text{H-NMR (360 MHz, CDCl}_3\text{): } \delta (\text{ppm}) = 2.80 \text{ (dd, } J = 7.7 \text{ Hz, } J = 13.7 \text{ Hz, 1 H), 3.03 \text{ (dd, } J = 4.2 \text{ Hz, } J = 13.8 \text{ Hz, 1 H), 3.70 \text{ (s, 4 H), 6.73 \text{ (d, } J = 8.2 \text{ Hz, 1 H), 6.93 \text{ (dd, 2.2 Hz, } J = 8.2 \text{ Hz, 1 H), 7.00 \text{ (d, } J = 2.3 \text{ Hz, 1 H), 7.36 \text{ (d, } J = 8.7 \text{ Hz, 2 H), 7.48 \text{ (d, } J = 8.6 \text{ Hz, 2 H).} \]

\[ ^{13}\text{C-NMR (91 MHz, CDCl}_3\text{): } \delta = 39.9 \text{ (CH}_2\text{), 51.2 \text{ (CH}_3\text{), 55.4 \text{ (CH), 116.5 \text{ (CH), 121.0 \text{ (C}_q\text{), 127.4 \text{ (C}_q\text{), 128.1 \text{ (C}_q\text{), 129.6 \text{ (CH), 130.8 \text{ (2 } \times \text{ CH), 131.0 \text{ (CH), 131.3 \text{ (2 } \times \text{ CH), 152.4 \text{ (C}_q\text{), 162.7 \text{ (C}_q\text{) 175.0 \text{ (C}_q\text{).} \]

\[ \text{MS (EI) } m/z \%: 349 (9) [^{79}\text{Br-M}^+\text{], 292 (10), 290 (11), 264 (31), 263 (100), 262 (32), 261 (100), 194 (12), 183 (10), 182 (49), 181 (37), 152 (11), 89 (10), 88 (34).} \]

\[ \text{HRMS (EI): calcd. for C}_{16}\text{H}_{16}\text{BrNO}_3 [M^+]: 349.0314, found: 349.0312.} \]
2.9 Methyl (S)-2-amino-3-(4’-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-10e]

![Chemical Structure](image)

Compound (S)-10e was prepared from methyl (S)-tyrosinate hydrochloride [(S)-9] and 4-iodophenyl diazonium chloride (method B) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(4’-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-10e] (0.43 mmol, 169 mg, 21%) was obtained as yellow oil.

\[ R_f = 0.3 \ (\text{CH}_2\text{Cl}_2 / \text{MeOH} = 10:1) \ [\text{UV}] \]

\[ ^1\text{H-NMR} \ (360 \text{ MHz, CDCl}_3): \delta (\text{ppm}) = 2.80 \ (\text{dd, } J = 7.6 \text{ Hz, } J = 13.7 \text{ Hz, } 1 \text{ H}), 3.04 \ (\text{dd, } J = 3.8 \text{ Hz, } J = 13.7 \text{ Hz, } 1 \text{ H}), 3.70-3.74 \ (\text{m, } 4 \text{ H}), 6.68 \ (\text{d, } J = 8.2 \text{ Hz, } 1 \text{ H}), 6.95 \ (\text{dd, } J = 2.2 \text{ Hz, } J = 3.7 \text{ Hz, } 1 \text{ H}), 6.98 \ (\text{d, } J = 2.1 \text{ Hz, } 1 \text{ H}), 7.19-7.22 \ (\text{m, } 2 \text{ H}), 7.68-7.71 \ (\text{m, } 2 \text{ H}). \]

\[ ^{13}\text{C-NMR} \ (91 \text{ MHz, CDCl}_3): \delta = 39.5 \ (\text{CH}_2), 52.1 \ (\text{CH}_3), 55.2 \ (\text{CH}), 92.8 \ (\text{C}_q), 116.5 \ (\text{CH}), 127.6 \ (\text{C}_q), 128.6 \ (\text{C}_q), 129.6 \ (\text{CH}), 130.9 \ (\text{CH}), 131.0 \ (2 \times \text{CH}), 137.3 \ (2 \times \text{CH}), 137.5 \ (\text{C}_q), 152.3 \ (\text{C}_q), 174.9 \ (\text{C}_q). \]

\[ \text{MS (EI)} \ m/z \ (%): 397 (4) [M⁺], 330 (30), 310 (11), 309 (30), 184 (25), 183 (100), 182 (16), 181 (13), 136 (17), 108 (27), 181 (37), 107 (80), 91 (11), 88 (36), 77 (12), 34 (19), 33 (23). \]

\[ \text{HRMS (EI): calcd. for C}_{16}\text{H}_{16}\text{INO}_3 [M⁺]: 397.0175, \text{ found: 397.0176.} \]
2.10 Methyl (S)-2-amino-3-(4′-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-10f]

Compound (S)-10f was prepared from methyl (S)-tyrosinate hydrochloride [(S)-9] and 4-nitrilophenyldiazonium tetrafluoro-borate (method A) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(4′-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-10f] (0.57 mmol, 168 mg, 28%) was obtained as yellow oil.

$R_f = 0.5$ (CH$_2$Cl$_2$ / MeOH = 10:1) [UV].

$^1$H-NMR (360 MHz, CDCl$_3$): $\delta$ (ppm) = 2.81 (dd, $J = 8.0$ Hz, $J = 13.9$ Hz, 1 H), 3.08 (dd, $J = 4.8$ Hz, $J = 13.9$ Hz, 1 H), 3.72 (t, $J = 3.7$ Hz, 1 H), 3.74 (s, 3 H), 6.67 (d, $J = 8.2$ Hz, 1 H), 6.98 (dd, $J = 2.3$ Hz, $J = 8.2$ Hz, 1 H), 7.04 (d, $J = 2.2$ Hz, 1 H), 7.57-7.64 (m, 4 H).

$^{13}$C-NMR (151 MHz, CDCl$_3$): $\delta$ = 39.5 (CH$_2$), 52.2 (CH$_3$), 55.4 (CH), 110.3 (C$q$), 116.7 (CH), 118.9 (C$q$), 126.8 (C$q$), 128.4 (C$q$), 129.9 (2 $\times$ CH), 130.4 (CH), 131.1 (CH), 131.9 (2 $\times$ CH), 143.1 (C$q$), 152.5 (C$q$), 175.1 (C$q$).

MS (EI) m/z (%): 296 (11) [M$^+$], 237 (26), 210 (7), 209 (49), 208 (100), 206 (5), 190 (7), 119 (7), 89 (20), 88 (63).

HRMS (EI): calcd. for C$_{17}$H$_{16}$N$_2$O$_3$ [M$^+$]: 296.1161, found: 296.1160.
2.11 Methyl (S)-2-amino-3-(4’-methoxy-6-hydroxybiphen-3-yl)propanoate [(S)-10g]

Compound (S)-10g was prepared from methyl (S)-tyrosinate hydrochloride [(S)-9] and 4-methoxyphenyldiazonium tetra-fluoroborate (method A) according to the general procedure for the radical arylation described above. Methyl (S)-2-amino-3-(4’-methoxy-6-hydroxybiphen-3-yl)propanoate [(S)-10g] (0.38 mmol, 116 mg, 19%) was obtained as yellow oil.

\[ R_f = 0.4 \ (\text{CH}_2\text{Cl}_2 / \text{MeOH} = 10:1) \] [UV].

\[ ^1\text{H-NMR} \ (360 \text{ MHz, CDCl}_3): \delta (\text{ppm}) = 2.73-2.91 \ (\text{m, 1 H}), 2.96-3.06 \ (\text{m, 1 H}), 3.70-3.72 \ (\text{m, 4 H}), 3.82 \ (\text{s, 3 H}), 6.70 \ (\text{dd, } J = 2.1 \text{ Hz, } J = 8.3 \text{ Hz, 1 H}), 6.80 \ (\text{d, } J = 8.2 \text{ Hz, 1 H}), 6.95 \ (\text{d, } J = 8.6 \text{ Hz, 2 H}), 7.01 \ (\text{d, } J = 2.2 \text{ Hz, 1 H}), 7.41 \ (\text{d, } J = 8.6 \text{ Hz, 2 H}). \]

\[ ^{13}\text{C-NMR} \ (151 \text{ MHz, CDCl}_3): \delta = 39.6 \ (\text{CH}_2), 52.0 \ (\text{CH}_3), 55.2 \ (\text{CH}_3), 55.3 \ (\text{CH}), 114.0 \ (2 \times \text{CH}), 115.6 \ (\text{CH}), 127.3 \ (\text{C}_q), 128.0 \ (\text{C}_q), 129.0 \ (\text{CH}), 130.2 \ (2 \times \text{CH}), 130.4 \ (\text{C}_q), 131.0 \ (\text{CH}), 155.6 \ (\text{C}_q), 158.8 \ (\text{C}_q), 175.0 \ (\text{C}_q). \]

\[ \text{MS (EI) } m/z \ (%): 301 (3) \ [\text{M}^+], 213 (27), 195 (8), 136 (19), 108 (33), 107 (100), 91 (10), 88 (27), 77 (9), 33 (9). \]

\[ \text{HRMS (EI)}: \text{calcd. for C}_{17}\text{H}_{19}\text{NO}_4 \ [\text{M}^+]: 301.1314, \text{found: 301.1314.} \]
2.12 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(6-hydroxybiphen-3-yl)propanoate [(S)-11a]

Compound (S)-11a was prepared from methyl (S)-2-amino-3-(6-hydroxybiphen-3-yl)propanoate [(S)-10a] (0.43 mmol, 118 mg) and Fmoc-OSu (0.57 mmol, 191 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(6-hydroxybiphen-3-yl)propanoate [(S)-11a] (0.18 mmol, 90 mg, 42%) was obtained as yellow oil.

R<sub>f</sub> = 0.1 (CH<sub>2</sub>Cl<sub>2</sub> / MeOH / HCO<sub>2</sub>H = 99:1:0.5) [UV].

<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ (ppm) = 3.03 (dd, J = 6.0 Hz, J = 14.0 Hz, 1 H), 3.09 (dd, J = 5.6 Hz, J = 14.3 Hz, 1 H), 3.70 (s, 3 H), 4.16 (t, J = 6.9 Hz, 1 H), 4.31-4.34 (m, 1 H), 4.37-4.41 (m, 1 H), 4.65 (dd, J = 5.9 Hz, J = 13.8 Hz, 1 H), 5.46 (d, J = 8.2 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 7.00 (s, 1 H), 7.26-7.30 (m, 2 H), 7.34-7.38 (m, 4 H), 7.40-7.44 (m, 3 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.71-7.77 (m, 2 H).

<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ = 37.3 (CH<sub>2</sub>), 47.0 (CH), 52.3 (CH<sub>3</sub>) 54.9 (CH<sub>2</sub>), 65.0 (CH), 116.1 (CH), 119.8 (2 × CH), 119.9 (2 × CH), 124.7 (CH), 125.0 (CH), 127.0 (2 × CH), 127.5 (CH), 127.6 (2 × CH), 128.9 (C<sub>q</sub>), 129.0 (4 × CH), 131.1 (C<sub>q</sub>), 137.1 (C<sub>q</sub>), 141.2 (2 × C<sub>q</sub>), 143.6 (2 × C<sub>q</sub>), 151.8 (C<sub>q</sub>), 155.7 (C<sub>q</sub>), 172.4 (C<sub>q</sub>).

MS (EI) m/z (%): 196 (16), 183 (21), 179 (20), 178 (100), 177 (9), 176 (13), 166 (38), 165 (53), 152 (8), 93 (13).

HRMS (EI): calcd. for C<sub>31</sub>H<sub>27</sub>NO<sub>5</sub> [M<sup>+</sup>]: 493.1889, found: 493.1889.
2.13 Methyl (S)-2-N-(fluorenlymethoxycarbonyl)-3-(4’-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-11b]

![Chemical Structure](image)

Compound (S)-11b was prepared from methyl (S)-2-amino-3-(4’-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-10b] (0.74 mmol, 213 mg) and Fmoc-OSu (0.87 mmol, 291 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl (S)-2-N-(fluorenlymethoxycarbonyl)-3-(4’-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-11b] (0.33 mmol, 169 mg, 45%) was obtained as white solid.

$$R_f = 0.1 \text{ (CH}_2\text{Cl}_2 / \text{MeOH} / \text{HCO}_2\text{H} = 99:1:0.5) [\text{UV}].$$

$^1$H-NMR (360 MHz, CDCl$_3$): $\delta$ (ppm) = 3.01 (dd, $J = 6.2$ Hz, $J = 14.0$ Hz, 1 H), 3.10 (dd, $J = 5.2$ Hz, $J = 14.0$ Hz, 1 H), 3.70 (s, 3 H), 4.14 (t, $J = 6.9$ Hz, 1 H), 4.29-4.41 (m, 2 H), 4.65 (dd, $J = 5.9$ Hz, $J = 13.9$ Hz, 1 H), 5.40 (d, $J = 8.3$ Hz, 1 H), 5.82 (s, 1 H), 6.82 (d, $J = 8.2$ Hz, 1 H), 6.90-6.98 (m, 2 H), 7.05 (t, $J = 8.7$ Hz, $J_{HF} = 8.7$ Hz, 2 H), 7.20-7.26 (m, 2 H), 7.32-7.41 (m, 4 H), 7.51 (t, $J = 8.1$ Hz, 2 H), 7.72 (d, $J = 7.6$ Hz, 2 H).

$^{13}$C-NMR (91 MHz, CDCl$_3$): $\delta$ = 37.5 (CH$_2$), 47.1 (CH), 52.3 (CH$_3$), 54.9 (CH$_2$), 67.0 (CH), 115.7 (d, $J_{CF} = 21.2$ Hz, 2 × CH), 116.2 (CH), 119.9 (2 × CH), 120.0 (2 × CH), 125.0 (CH), 127.0 (2 × CH), 127.4 (CH), 127.7 (2 × CH), 129.8 (C$_q$), 130.7 (d, $J_{CF} = 8.2$ Hz, 2 × CH), 131.2 (C$_q$), 133.1 (d, $J_{CF} = 3.0$ Hz, C$_q$), 141.2 (2 × C$_q$), 143.6 (2 × C$_q$), 151.8 (C$_q$), 155.7 (C$_q$), 162.3 (d, $J_{CF} = 246.9$ Hz, C$_q$), 172.1 (C$_q$).

MS (EI) m/z (%): 230 (12), 202 (42), 201 (100), 179 (49), 178 (100), 177 (17), 176 (28), 165 (11), 152 (15), 151 (11), 89 (17), 88 (24), 76 (13).

HRMS (EI): calcd. for C$_{31}$H$_{26}$FNO$_5$ [M$^+$]: 511.1795, found: 511.1796.
2.14 Methyl \((R)-2-N-(\text{fluorenylmethoxycarbonyl})-3-(4'-\text{fluoro}-6\text{-hydroxybiphen-3-yl})\text{propanoate }[(R)-11b]\)

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\begin{center}
\includegraphics[width=0.2\textwidth]{structure.png}
\end{center}
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Compound \((R)-11b\) was prepared from methyl \((R)-2\text{-amino-3-(4'-\text{fluoro}-6\text{-hydroxybiphen-3-yl})propanoate }[(R)-10b]\) (0.70 mmol, 203 mg) and Fmoc-OSu (0.83 mmol, 277 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl \((R)-2-N-(\text{fluorenylmethoxy-carbonyl})-3-(4'-\text{fluoro}-6\text{-hydroxybiphen-3-yl})\text{propanoate }[(R)-11b]\) (0.29 mmol, 150 mg, 42%) was obtained as white solid. The analytical data is in agreement with those of the \((S)\)-enantiomer.
2.15 Methyl \((S)\)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-chloro-6-hydroxybiphen-3-yl)propanoate \([((S)-11c]\)

![Chemical Structure](image)

Compound \((S)-11c\) was prepared from methyl \((S)\)-2-amino-3-(4'-chloro-6-hydroxybiphen-3-yl)propanoate \([((S)-10c]\) (0.80 mmol, 245 mg) and Fmoc-OSu (0.94 mmol, 317 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl \((S)\)-2-N-(fluorenylmethoxy-carbonyl)-3-(4'-chloro-6-hydroxybiphen-3-yl)propanoate \([((S)-11c]\) (0.42 mmol, 220 mg, 52%) was obtained as white solid.

\(R_f = 0.1\) (CH\(_2\)Cl\(_2\) / MeOH / HCO\(_2\)H = 99:1:0.5) [UV].

\(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 3.01 (dd, \(J = 6.2\) Hz, \(J = 14.0\) Hz, 1 H), 3.10 (dd, \(J = 5.5\) Hz, \(J = 14.0\) Hz, 1 H), 3.67 (s, 3 H), 4.14 (t, \(J = 7.0\) Hz, 1 H), 4.31 (dd, \(J = 7.1\) Hz, \(J = 10.6\) Hz, 1 H), 4.38 (dd, \(J = 7.4\) Hz, \(J = 10.5\) Hz, 1 H), 4.65 (dd, \(J = 5.9\) Hz, \(J = 13.9\) Hz, 1 H), 5.40 (d, \(J = 8.3\) Hz, 1 H), 5.88 (s, 1 H), 6.81 (d, \(J = 8.2\) Hz, 1 H), 6.93 (d, \(J = 8.2\) Hz, 1 H), 6.96 (s, 1 H), 7.23 (t, \(J = 7.5\) Hz, 2 H), 7.32-7.38 (m, 6 H), 7.50 (dd, \(J = 7.5\) Hz, \(J = 15.8\) Hz, 2 H), 7.73 (dd, \(J = 2.6\) Hz, \(J = 7.5\) Hz, 2 H).

\(^{13}\)C-NMR (91 MHz, CDCl\(_3\)): \(\delta\) = 37.4 (CH\(_2\)), 47.0 (CH), 52.3 (CH\(_3\)), 54.9 (CH\(_2\)), 67.0 (CH), 116.3 (CH), 119.8 (2 \(\times\) CH), 119.9 (2 \(\times\) CH), 124.9 (CH), 126.9 (2 \(\times\) CH), 127.6 (2 \(\times\) CH), 128.8 (2 \(\times\) CH), 129.8 (C\(_q\)), 130.3 (2 \(\times\) CH), 131.1 (C\(_q\)), 133.4 (C\(_q\)), 135.7 (CH), 141.2 (2 \(\times\) C\(_q\)), 143.5 (2 \(\times\) C\(_q\)), 143.6 (C\(_q\)), 151.9 (C\(_q\)), 155.7 (C\(_q\)), 172.1 (C\(_q\)).

MS (EI) \(m/z\) (%): 220 (8), 219 (32), 218 (25), 217 (88), 181 (9), 179 (28), 178 (100), 177 (11), 176 (18), 152 (12), 91 (8), 89 (8), 88 (8).

HRMS (EI): calcd. for C\(_{31}\)H\(_{26}\)\(^{35}\)ClNO\(_5\) [M\(^+\)]: 527.1499, found: 527.1499.
2.16 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-11d]

![Chemical Structure](image)

Compound (S)-11d was prepared from methyl (S)-2-amino-3-(4'-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-10d] (0.32 mmol, 112 mg) and Fmoc-OSu (0.41 mmol, 139 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl (S)-2-N-(fluorenylmethoxy-carbonyl)-3-(4'-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-11d] (0.20 mmol, 117 mg, 64%) was obtained as white-beige solid.

\[ R_f = 0.2 \text{ (CH}_2\text{Cl}_2 / \text{MeOH / HCO}_2\text{H = 99:1:0.5) [UV].} \]

**1H-NMR** (360 MHz, CDCl₃): \( \delta \text{ (ppm) = 3.01 (dd, } J = 6.1 \text{ Hz, } J = 13.9 \text{ Hz, 1 H), 3.10 (dd, } J = 5.4 \text{ Hz, } J = 13.9 \text{ Hz, 1 H), 3.61 (s, 3 H), 4.14 (t, } J = 7.0 \text{ Hz, 1 H), 4.26-4.34 (m, 1 H), 4.36 – 4.41 (m, 1 H), 4.65 (dd, } J = 5.9 \text{ Hz, } J = 13.9 \text{ Hz, 1 H), 5.43 (d, } J = 8.3 \text{ Hz, 1 H), 6.80 (d, } J = 8.2 \text{ Hz, 1 H), 6.94 (d, } J = 8.4 \text{ Hz, 1 H), 6.96 (s, 1 H), 7.23 (d, } J = 7.5 \text{ Hz, 2 H), 7.30 (d, } J = 8.4 \text{ Hz, 2 H), 7.33-7.39 (m, 2 H), 7.46-7.53 (m, 4 H), 7.72 (d, } J = 7.6 \text{ Hz, 2 H).} \]

**13C-NMR** (91 MHz, CDCl₃): \( \delta = 37.4 \text{ (CH}_2\text{), 47.0 \text{ (CH), 52.4 \text{ (CH}_3\text{), 55.0 \text{ (CH}_2\text{), 67.0 \text{ (CH), 116.3 \text{ (CH), 119.9 \text{ (4 \times CH), 121.6 (C}_q\text{), 124.9 (CH), 127.0 (2 \times CH), 127.2 (CH), 127.7 (2 \times CH), 127.8 (C}_q\text{), 129.9 (C}_q\text{), 130.7 (2 \times CH), 131.0 (C}_q\text{), 131.7 (2 \times CH), 141.2 (2 \times C}_q\text{), 143.6 (2 \times C}_q\text{), 151.8 (C}_q\text{), 155.7 (C}_q\text{), 172.1 (C}_q\text{).} \)

**MS (EI) m/z (%):** 264 (11), 263 (48), 262 (11), 261 (49), 182 (23), 181 (16), 179 (43), 178 (100), 176 (13), 165 (12).

**HRMS (EI):** calcd. for C₃₁H₂₆⁷⁹BrNO₅ \([\text{M}^+]\): 571.0994, found: 571.0994.
2.17 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-11e]

Compound (S)-11e was prepared from methyl (S)-2-amino-3-(4'-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-10e] (0.16 mmol, 65 mg) and Fmoc-OSu (0.21 mmol, 71 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-11e] (0.09 mmol, 54 mg, 53%) was obtained as yellow solid.

\[ R_f = 0.1 \text{ (CH}_2\text{Cl}_2 / \text{MeOH / HCO}_2\text{H = 99:1:0.5)} \text{ [UV].} \]

\[ ^1\text{H-NMR (360 MHz, CDCl}_3\text{): } \delta \text{ (ppm) = 3.02 (dd, } J = 5.6 \text{ Hz, } J = 14.4 \text{ Hz, 1 H), 3.11 (dd, } J = 5.7 \text{ Hz, } J = 14.0 \text{ Hz, 1 H), 3.72 (s, 3 H), 4.15 (t, } J = 7.0 \text{ Hz, 1 H), 4.31-4.37 (m, 1 H), 4.40-4.45 (m, 1 H), 4.59-4.68 (m, 1 H), 5.40 (d, } J = 8.3 \text{ Hz, 1 H), 6.70 (d, } J = 8.3 \text{ Hz, 1 H), 6.90-6.95 (m, 1 H), 6.96 (s, 1 H), 7.23 (t, } J = 7.5 \text{ Hz, 2 H), 7.34-7.43 (m, 4 H), 7.50-7.55 (m, 2 H), 7.71-7.75 (m, 4 H).} \]

\[ ^{13}\text{C-NMR (151 MHz, CDCl}_3\text{): } \delta = 37.5 \text{ (CH}_2\text{), 47.1 \text{ (CH), 52.4 (CH}_3\text{), 54.9 (CH}_2\text{), 67.0 (CH), 93.4 (C}_q\text{), 116.3 (CH), 119.9 (2 \times \text{CH}), 120.0 (2 \times \text{CH}), 125.0 (\text{CH}), 127.0 (2 \times \text{CH}), 127.3 (\text{CH}), 127.7 (2 \times \text{CH}), 129.0 (C}_q\text{), 130.1 (C}_q\text{), 130.9 (2 \times \text{CH}), 137.4 (C}_q\text{), 138.0 (2 \times \text{CH), 141.3 (2 \times C}_q\text{), 143.6 (2 \times C}_q\text{), 151.7 (C}_q\text{), 155.6 (C}_q\text{), 172.1 (C}_q\text{).} \]

\[ \text{MS (EI) m/z (%): 310 (14), 309 (52), 183 (24), 182 (28), 181 (16), 179 (35), 178 (100), 177 (10), 176 (14), 165 (12), 152 (10).} \]

\[ \text{HRMS (EI): calcd. for C}_{35}\text{H}_{26}\text{INO}_5 [M^+] : 619.0856, \text{ found: 619.0855.} \]
2.18 Methyl (S)-2-\(N\)-(fluorenylmethoxycarbonyl)-3-(4'-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-11e]

\[
\text{C}_{32}\text{H}_{26}\text{N}_{2}\text{O}_{5} \\
518.56 \text{ g/mol}
\]

Compound (S)-11f was prepared from methyl (S)-2-amino-3-(4'-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-10f] (0.57 mmol, 168 mg) and Fmoc-OSu (0.62 mmol, 246 mg) according to the general procedure for the introduction of the Fmoc protecting group described above. Methyl (S)-2-\(N\)-(fluorenylmethoxycarbonyl)-3-(4'-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-11f] (0.37 mmol, 191 mg, 65%) was obtained as white solid.

\[
R_f = 0.1 \text{ (CH}_2\text{Cl}_2 / \text{MeOH / HCO}_2\text{H = 99:1:0.5)} \text{ [UV].}
\]

\(^1\text{H-NMR (360 MHz, CDCl}_3\): } \delta (ppm) = 3.03 (dd, \(J = 6.5 \text{ Hz, } J = 13.9 \text{ Hz, 1 H}), 3.16 (dd, \(J = 5.4 \text{ Hz, } J = 14.1 \text{ Hz, 1 H}), 3.75 (s, 3 H), 4.13 (t, \(J = 6.9 \text{ Hz, 1 H}), 4.31 (dd, \(J = 7.2 \text{ Hz, } J = 10.4 \text{ Hz, 1 H}), 4.41 (dd, \(J = 7.3 \text{ Hz, } J = 10.3 \text{ Hz, 1 H}), 4.67 (dd, \(J = 6.1 \text{ Hz, } J = 13.8 \text{ Hz, 1 H}), 5.33 (d, \(J = 8.1 \text{ Hz, 1 H}), 6.81 (d, \(J = 8.0 \text{ Hz, 1 H}), 7.01 (d, \(J = 7.8 \text{ Hz, 2 H}), 7.26 (t, \(J = 7.4 \text{ Hz, 2 H}), 7.39 (t, \(J = 7.3 \text{ Hz, 2 H}), 7.47-7.52 (m, 2 H), 7.54-7.57 (m, 2 H), 7.62 (d, \(J = 8.2 \text{ Hz, 2 H}), 7.75 (d, \(J = 7.5 \text{ Hz, 2 H}).
\]

\(^13\text{C-NMR (151 MHz, CDCl}_3\): } \delta = 37.6 (\text{CH}_2), 47.1 (\text{CH}), 52.5 (\text{CH}_3), 54.9 (\text{CH}), 67.1 (\text{CH}_2), 111.1 (\text{C}_q), 116.7 (\text{CH}), 118.7 (\text{C}_q), 120.0 (4 \times \text{CH}), 125.0 (\text{CH}), 127.0 (2 \times \text{CH}), 127.7 (2 \times \text{CH}), 128.6 (\text{C}_q), 129.8 (2 \times \text{CH}), 130.8 (\text{CH}), 131.2 (\text{C}_q), 132.3 (2 \times \text{CH}), 142.2 (2 \times \text{C}_q), 143.6 (3 \times \text{C}_q), 151.6 (\text{C}_q), 155.6 (\text{C}_q), 171.9 (\text{C}_q).

\text{MS (EI) } m/z (\%): 296 (18), 237 (38), 209 (70), 208 (98), 179 (61), 178 (100), 177 (36), 176 (56), 152 (25), 151 (22), 150 (12), 119 (11), 89 (58) 88 (79), 76 (28), 46 (16).

\text{HRMS (EI): calcd. for C}_{32}\text{H}_{26}\text{N}_{2}\text{O}_{5} [M^+]: 518.1842, found: 518.1843.
2.19  \((S)-2-N-(\text{Fluorenylmethoxycarbonyl})-3-(6-hydroxybiphen-3-yl)pro-\)
\(\text{pionic acid } [(S)-12a]\)

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}}
\]

Compound \((S)-12a\) was prepared from methyl \((S)-2-N-(\text{fluorenylmethoxycarbonyl})-3-(6-\)
\(\text{hydroxybiphen-3-yl})propanoate \([(S)-11a]\) (0.16 mmol, 79 mg) according to the general
\text{procedure for the selective saponification described above.} \((S)-2-N-(\text{Fluorenylmethoxycarbonyl})-3-(6-\)
\(\text{hydroxybiphen-3-yl})\text{propionic acid } [(S)-12a]\) (0.11 mmol, 51 mg, 66\%) was obtained as yellow oil.

\[R_f = 0.1 \ (\text{CH}_2\text{Cl}_2 \ / \ \text{MeOH = 10:1}) \ [\text{UV}].\]

\[1^H\text{-NMR} \ (600 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}) = 3.06 \ (\text{dd, } J = 5.4 \text{ Hz, } J = 13.7 \text{ Hz, 1 H}), 3.15 \ (\text{dd, } J = 5.1 \text{ Hz, } J = 13.8 \text{ Hz, 1 H}), 4.17 \ (\text{t, } J = 7.0 \text{ Hz, 1 H}), 4.30-4.34 \ (\text{m, 1 H}), 4.38-4.43 \ (\text{m, 1 H}), 4.64-4.70 \ (\text{m, 1 H}), 5.41 \ (\text{t, } J = 7.9 \text{ Hz, 1 H}), 6.86 \ (\text{d, } J = 8.0 \text{ Hz, 1 H}), 6.99 \ (\text{d, } J = 8.3 \text{ Hz, 1 H}), 7.05 \ (\text{s, 1 H}), 7.22-7.25 \ (\text{m, 2 H}), 7.29-7.34 \ (\text{m, 4 H}), 7.41-7.45 \ (\text{m, 3 H}), 7.56 \ (\text{d, } J = 7.3 \text{ Hz, 2 H}), 7.72-7.76 \ (\text{m, 2 H}).\]

\[13C\text{-NMR} \ (151 \text{ MHz, CDCl}_3): \delta = 37.0 \ (\text{CH}_2), 47.0 \ (\text{CH}), 54.7 \ (\text{CH}_2), 65.1 \ (\text{CH}), 116.2 \ (\text{CH}), 119.9 \ (2 \times \text{CH}), 120.0 \ (2 \times \text{CH}), 124.7 \ (\text{CH}), 125.1 \ (\text{CH}), 127.0 \ (2 \times \text{CH}), 127.6 \ (\text{CH}), 127.7 \ (2 \times \text{CH}), 128.9 \ (\text{C}_q), 129.0 \ (4 \times \text{CH}), 131.2 \ (\text{C}_q), 137.0 \ (\text{C}_q), 141.5 \ (2 \times \text{C}_q), 144.2 \ (2 \times \text{C}_q), 151.8 \ (\text{C}_q), 155.9 \ (\text{C}_q), 175.2 \ (\text{C}_q).\]

\text{MS (EI) \ m/z (%): 196 (8), 184 (13), 183 (84), 179 (26), 178 (100), 177 (7), 176 (10), 166 (19), 165 (30), 152 (7).}

\text{HRMS (EI): calcd. for C}_{30}H_{25}NO_5 \ [M^+]: 479.1733, \text{ found: 479.1731.}
Compound (S)-12b was prepared from methyl (S)-2-N-(fluorenyl-methoxycarbonyl)-3-(4′-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-11b] (0.33 mmol, 169 mg) according to the general procedure for the selective saponification described above. (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4′-fluoro-6-hydroxybiphen-3-yl)propionic acid [(S)-12b] (0.22 mmol, 110 mg, 67%) was obtained as yellow oil.

\[ R_f = 0.1 \ (\text{CH}_2\text{Cl}_2 \ / \text{MeOH} = 10:1) \ [\text{UV}].\]

\[^1^H\text{-NMR}\ (360 \text{ MHz}, \text{CDCl}_3): \delta \ (\text{ppm}) = 3.00-3.15 \ (m, 2 \text{ H}), 4.10-4.18 \ (m, 1 \text{ H}), 4.24-4.42 \ (m, 2 \text{ H}), 4.60-4.68 \ (m, 1 \text{ H}), 5.36 \ (d, J = 8.2 \text{ Hz}, 1 \text{ H}), 6.79-6.86 \ (m, 1 \text{ H}), 6.94-7.11 \ (m, 4 \text{ H}), 7.20-7.27 \ (m, 2 \text{ H}), 7.32-7.41 \ (m, 4 \text{ H}), 7.46-7.55 \ (m, 3 \text{ H}), 7.73 \ (t, J = 7.4 \text{ Hz}, 2 \text{ H}).\]

\[^{13}^C\text{-NMR}\ (91 \text{ MHz}, \text{CDCl}_3): \delta = 37.5 \ (\text{CH}_2), 47.1 \ (\text{CH}), 54.9 \ (\text{CH}_2), 67.1 \ (\text{CH}), 115.9 \ (d, J_{CF} = 21.0 \text{ Hz}, 2 \times \text{CH}), 116.2 \ (\text{CH}), 120.0 \ (4 \times \text{CH}), 125.0 \ (\text{CH}), 127.0 \ (2 \times \text{CH}), 127.4 \ (\text{CH}), 127.7 \ (2 \times \text{CH}), 129.9 \ (C_q), 130.7 \ (d, J_{CF} = 7.9 \text{ Hz}, 2 \times \text{CH}), 131.2 \ (C_q), 133.1 \ (d, J_{CF} = 3.1 \text{ Hz}, C_q), 141.2 \ (2 \times C_q), 143.6 \ (2 \times C_q), 151.8 \ (C_q), 156.0 \ (C_q), 162.3 \ (d, J_{CF} = 246.8 \text{ Hz}, C_q), 175.3 \ (C_q).\]

\[ \text{MS (EI) } m/z \ (%): 208 \ (19), 196 \ (8), 179 \ (23), 178 \ (100), 177 \ (7), 176 \ (11), 166 \ (18), 165 \ (26), 88 \ (6), 76 \ (6).\]

\[ \text{HRMS (EI): caled. for } C_{30}H_{24}FNO_5 \ [M^+]: 497.1638, \text{ found: } 497.1638.\]

\[ \text{Chiral analytical HPLC: } t_R = 15.3 \text{ min; ee} > 99%.\]
2.21  \((R)-2-N-(Fluorenylmethoxycarbonyl)-3-(4'-fluoro-6-hydroxybiphen-3-yl)propionic\) acid \([(R)-12b]\)

\[
\begin{align*}
\text{F} & \quad \text{OH} \\
\text{C} & \quad \text{O} \\
\text{NH} & \quad \text{CO}_{2}H
\end{align*}
\]

\((R)-12b\)  
\(C_{20}H_{24}FNO_{5}\)  
497.51 g/mol

Compound \((R)-12b\) was prepared from methyl \((R)-2-N-(fluorenyl-methoxycarbonyl)-3-(4'-fluoro-6-hydroxybiphen-3-yl)propanoate\ (\((R)-11b\)) (0.29 mmol, 150 mg) according to the general procedure for the selective saponification described above. \((R)-2-N-(Fluorenylmethoxycarbonyl)-3-(4'-fluoro-6-hydroxybiphen-3-yl)propionic\) acid \([(R)-12b]\) (0.16 mmol, 80 mg, 55%) was obtained as yellow oil. Chiral analytical HPLC: \(t_R = 17.9\) min; ee > 98%. All other analytical data is in agreement with those of the \((S)\)-enantiomer reported above.
2.22 (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4’-chloro-6-hydroxybiphen-3-yl)propionic acid [(S)-12c]

Compound (S)-12c was prepared from methyl (S)-2-N-(fluorenyl-methoxycarbonyl)-3-(4’-chloro-6-hydroxybiphen-3-yl)propan-oate [(S)-11c] (0.14 mmol, 76 mg) according to the general procedure for the selective saponification described above. (S)-2-N-(Fluorenylmethoxycarbonyl) -3- (4’-chloro-6-hydroxybiphen-3-yl)propionic acid [(S)-12c] (0.08 mmol, 41 mg, 57%) was obtained as white solid.

$$R_f = 0.1 \ (\text{CH}_2\text{Cl}_2 / \text{MeOH} = 10:1) \ [\text{UV}].$$

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ (ppm) = 3.05 (dd, $J = 5.3$ Hz, $J = 13.8$ Hz, 1 H), 3.16 (dd, $J = 4.8$ Hz, $J = 13.5$ Hz, 1 H), 4.17 (t, $J = 6.9$ Hz, 1 H), 4.30 (dd, $J = 7.2$ Hz, $J = 10.4$ Hz, 1 H), 4.40 (dd, $J = 7.1$ Hz, $J = 10.5$ Hz, 1 H), 4.53-4.60 (m, 1 H), 6.83 (d, $J = 8.1$ Hz, 1 H), 7.00 (d, $J = 7.7$ Hz, 1 H), 7.07 (s, 1 H), 7.26 (t, $J = 7.5$ Hz, 2 H), 7.37-7.41 (m, 4 H), 7.46 (d, $J = 8.5$ Hz, 2 H), 7.52-7.57 (m, 2 H), 7.75 (d, $J = 7.4$ Hz, 2 H).

$^{13}$C-NMR (91 MHz, CDCl$_3$): $\delta = 36.9$ (CH$_2$), 46.9 (CH), 54.9 (CH$_2$), 66.7 (CH), 115.9 (CH), 119.7 (4 $\times$ CH), 124.8 (CH), 126.8 (2 $\times$ CH), 127.5 (2 $\times$ CH), 128.2 (2 $\times$ CH), 129.6 (C$_q$), 130.3 (2 $\times$ CH), 131.2 (C$_q$), 132.7 (C$_q$), 136.5 (CH), 141.0 (2 $\times$ C$_q$), 143.5 (2 $\times$ C$_q$), 143.6 (C$_q$), 152.3 (C$_q$), 155.8 (C$_q$), 175.1 (C$_q$).

MS (EI) $m$/%: 179 (15), 178 (100), 177 (11), 176 (19), 152 (10), 151 (8), 89 (7), 88 (7), 76 (9), 46 (7).

HRMS (EI): calcd. for C$_{30}$H$_{24}$ClNO$_5$ [M$^+$]: 513.1343, found: 513.1341.
2.23 (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4’-bromo-6-hydroxybiphen-3-yl)propionic acid [(S)-12d]

Compound (S)-12d was prepared from methyl (S)-2-N-(fluorenyl-methoxycarbonyl)-3-(4’-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-11d] (0.09 mmol, 51 mg) according to the general procedure for the selective saponification described above. (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4’-bromo-6-hydroxybiphen-3-yl)propionic acid [(S)-12d] (0.09 mmol, 26 mg, 52%) was obtained as colorless oil.

R$_f$ = 0.1 (CH$_2$Cl$_2$ / MeOH = 10:1) [UV].

$^1$H-NMR (600 MHz, CDCl$_3$): δ (ppm) = 3.04 (dd, J = 5.5 Hz, J = 13.6 Hz, 1 H), 3.12 (dd, J = 5.5 Hz, J = 14.0 Hz, 1 H), 4.14 (t, J = 6.9 Hz, 1 H), 4.29-4.33 (m, 1 H), 4.36-4.40 (m, 1 H), 4.63-4.68 (m, 1 H), 5.33-5.36 (m, 1 H), 6.81 (d, J = 7.7 Hz, 1 H), 6.95-6.99 (m, 1 H), 7.00 (s, 1 H), 7.22 (t, J = 7.2 Hz, 2 H), 7.26-7.30 (m, 2 H), 7.35-7.41 (m, 2 H), 7.48-7.55 (m, 4 H), 7.73 (d, J = 7.9 Hz, 2 H).

$^{13}$C-NMR (151 MHz, CDCl$_3$): δ = 37.5 (CH$_2$), 47.1 (CH), 54.9 (CH$_2$), 67.2 (CH), 116.5 (CH), 120.0 (4 × CH), 121.9 (C$_q$), 125.0 (CH), 127.0 (2 × CH), 127.2 (CH), 127.8 (C$_q$), 127.9 (2 × CH), 130.1 (C$_q$), 130.7 (2 × CH), 131.1 (C$_q$), 132.0 (2 × CH), 141.3 (2 × C$_q$), 143.5 (2 × C$_q$), 151.7 (C$_q$), 156.0 (C$_q$), 175.3 (C$_q$).

**MS (EI) m/z (%):** 263 (10), 261 (10), 179 (21), 178 (100), 177 (11), 176 (19), 166 (13), 165 (18), 152 (11), 76 (11).

**HRMS (EI):** calcd. for C$_{30}$H$_{24}$BrNO$_5$ [M$^+$]: 557.0838, found: 557.0835.
2.24 (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4′-iodo-6-hydroxybiphen-3-yl)propionic acid [(S)-12e]

Compound (S)-12e was prepared from methyl (S)-2-N-(fluorenyl-methoxycarbonyl)-3-(4′-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-11e] (0.03 mmol, 18 mg) according to the general procedure for the selective saponification described above. (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4′-iodo-6-hydroxybiphen-3-yl)propionic acid [(S)-12e] (0.01 mmol, 8 mg, 46%) was obtained as yellow solid.

\[ R_f = 0.1 \text{ (CH}_2\text{Cl}_2 / \text{MeOH = 10:1)} \] [UV].

\[^1\text{H-NMR}\] (600 MHz, CDCl\textsubscript{3}): \( \delta \text{ (ppm)} = 3.04-3.12 \text{ (m, 2 H), 4.08-4.17 (m, 1 H), 4.25-4.31 (m, 1 H), 4.33-4.39 (m, 1 H), 4.59-4.67 (m, 1 H), 6.73 (d, } J = 8.2 \text{ Hz, 1 H), 6.93-6.97 (m, 1 H), 6.99 (s, 1 H), 7.31 (t, } J = 7.4 \text{ Hz, 2 H), 7.36-7.42 (m, 4 H), 7.50-7.58 (m, 2 H), 7.70-7.78 (m, 4 H).}

\[^{13}\text{C-NMR}\] (91 MHz, CDCl\textsubscript{3}): \( \delta = 37.5 \text{ (CH}_2\text{), 47.2 \text{ (CH), 54.8 \text{ (CH}_2\text{), 67.0 \text{ (CH), 93.3 \text{ (C}_q\text{), 115.4 \text{ (CH), 119.9 \text{ (4 \times CH), 125.0 \text{ (CH), 127.0 \text{ (2 \times CH), 127.6 \text{ (CH), 127.7 \text{ (2 \times CH), 129.1 \text{ (C}_q\text{), 130.0 \text{ (C}_q\text{), 131.2 \text{ (2 \times CH), 137.1 \text{ (C}_q\text{), 138.3 \text{ (2 \times CH), 141.3 \text{ (2 \times C}_q\text{), 143.8 \text{ (2 \times C}_q\text{), 152.8 \text{ (C}_q\text{), 155.9 \text{ (C}_q\text{), 175.6 \text{ (C}_q).}}}

\text{MS (EI) \text{ m/z (%): 183 (15), 179 (29), 178 (100), 177 (17), 176 (27), 166 (10), 165 (15), 152 (13), 151 (11), 89 (11), 76 (11).}

\text{HRMS (EI): calcd. for C}_{30}\text{H}_{24}\text{INO}_5 \text{ [M\textsuperscript{+}]: 605.0699, found: 605.0696.}
2.25 (S)-2-N-(Fluorenylmethoxycarbonyl)-3-(4’-nitrilo-6-hydroxybiphen-3-yl)propionic acid [(S)-12f]

Compound (S)-12f was prepared from methyl (S)-2-N-(fluorenyl-methoxycarbonyl)-3-(4’-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-11f] (0.10 mmol, 52 mg) according to the general procedure for the selective saponification described above. (S)-2-N-(Fluorenyl-methoxycarbonyl)-3-(4’-nitrilo-6-hydroxybiphen-3-yl)propionic acid [(S)-12f] (0.07 mmol, 35 mg, 69%) was obtained as white solid.

\[ R_f = 0.1 \text{ (CH}_2\text{Cl}_2 / \text{MeOH = 10:1) [UV].} \]

\[ ^1\text{H-NMR (360 MHz, CDCl}_3\text{): } \delta \text{ (ppm) = 3.01 (dd, } J = 6.1 \text{ Hz, } J = 13.8 \text{ Hz, 1 H), 3.14 (dd, } J = 4.5 \text{ Hz, } J = 13.7 \text{ Hz, 1 H), 4.06-4.16 (m, 1 H), 4.28 (dd, } J = 8.0 \text{ Hz, } J = 13.9 \text{ Hz, 1 H), 4.38 (dd, } J = 7.8 \text{ Hz, } J = 13.1 \text{ Hz, 1 H), 4.61-4.69 (m, 1 H), 5.44 (t, } J = 7.7 \text{ Hz, 1 H), 6.74-6.85 (m, 1 H), 6.97-7.03 (m, 2 H), 7.20 (dd, } J = 6.9 \text{ Hz, } J = 13.9 \text{ Hz, 2 H), 7.32-7.39 (m, 2 H), 7.46-7.50 (m, 4 H), 7.52-7.59 (m, 2 H), 7.70-7.75 (m, 2 H).} \]

\[ ^{13}\text{C-NMR (91 MHz, CDCl}_3\text{): } \delta = 37.1 (\text{CH}_2), 47.1 (\text{CH}), 54.9 (\text{CH}), 67.4 (\text{CH}_2), 110.5 (\text{C}_q), 116.8 (\text{CH}), 118.8 (\text{C}_q), 120.1 (4 \times \text{CH}), 124.9 (\text{CH}), 127.0 (2 \times \text{CH}), 127.8 (2 \times \text{CH}), 128.2 (\text{C}_q), 129.8 (2 \times \text{CH}), 130.7 (\text{CH}), 131.2 (\text{C}_q), 132.1 (2 \times \text{CH}), 142.5 (2 \times \text{C}_q), 143.4 (3 \times \text{C}_q), 152.0 (\text{C}_q), 159.1 (\text{C}_q), 175.1 (\text{C}_q). \]

**MS (EI) m/z (%):** 208 (19), 196 (8), 179 (22), 178 (100), 177 (7), 176 (11), 166 (18), 165 (26), 88 (6), 76 (6).

**HRMS (EI):** calcd. for C\text{\textsubscript{31}}H\text{\textsubscript{24}}N\text{\textsubscript{2}}O\text{\textsubscript{5}} [M\textsuperscript{+}]: 504.1685, found: 504.1683.
3. $^1$H- and $^{13}$C-NMR spectra of compounds

3.1 Methyl (S)-2-amino-3-(6-hydroxybiphen-3-yl)propanoate [(S)-10a]
3.2 Methyl (S)-2-amino-3-(4'-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-10b]
3.3 Methyl (S)-2-amino-3-(4’-chloro-6-hydroxybiphen-3-yl)propanoate [(S)-10c]
3.4 Methyl (S)-2-amino-3-(4’'-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-10d]
3.5 Methyl (S)-2-amino-3-(4'-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-10e]
3.6 Methyl (S)-2-amino-3-(4'-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-10f]
3.7 Methyl (S)-2-amino-3-(4'-methoxy-6-hydroxybiphen-3-yl)propanoate [(S)-10g]
3.8 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(6-hydroxybiphen-3-yl)propanoate [(S)-11a]
3.9 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-fluoro-6-hydroxybiphen-3-yl)propanoate [(S)-11b]
3.10 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4’-chloro-6-hydroxybiphen-3-yl)propanoate [(S)-11c]
3.11 Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-bromo-6-hydroxybiphen-3-yl)propanoate [(S)-11d]
3.12  Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4'-iodo-6-hydroxybiphen-3-yl)propanoate [(S)-11e]
3.13  Methyl (S)-2-N-(fluorenylmethoxycarbonyl)-3-(4’-nitrilo-6-hydroxybiphen-3-yl)propanoate [(S)-11e]
3.14 \((S)-2-N-(\text{Fluorenylmethoxycarbonyl})-3-(6\text{-hydroxybiphen-3-yl})\text{propionic acid}\ [(S)-12a]\)
3.15 (S)-2-N-(Fluorenlymethoxycarbonyl)-3-(4'-fluoro-6-hydroxybiphen-3-yl)propionic acid [(S)-12b]
3.16 \((S)-2-N-(\text{Fluorenylmethoxycarbonyl})-3-(4'-\text{chloro-6-hydroxybiphen-3-yl})\text{propionic acid} \) [(S)-12c]

![NMR Spectrum Image]
3.17 (S)-2-\(N\)-(Fluorenylmethoxycarbonyl)-3-(4’-bromo-6-hydroxybiphen-3-yl)propionic acid [(S)-12d]
3.18  \((S)-2-N-(\text{Fluorenlymethoxycarbonyl})-3-(4'-\text{iodo-6-hydroxybiphen-3-yl})\text{propionic acid} \ [(S)-12e]\)
3.19 (S)-2-N-(Fluorenlymethoxycarbonyl)-3-(4’-nitrilo-6-hydroxybiphen-3-yl)propionic acid [(S)-12f]
4. References
