Electronic Supplementary Information

Acid-catalyzed synthesis of methylene bridged (*S*)-tyrosine-phenol dimers

Sean P. Bew, David L. Hughes and Sunil V. Sharma*

School of Chemical Sciences & Pharmacy, University of East Anglia, Norwich, NR4 7T

s.bew@uea.ac.uk

Experimental Section $[\alpha]_D^{22}$ were measured on a Perkin-Elmer 241 and are given in 10^{-1} deg cm^2 g^{-1} using a 1 mL cell with 1 dm path length. FT-IR were recorded on a PE Paragon 1000FT. ^{1}H- and ^{13}C-NMR were recorded on a Bruker AC-400 or a Varian Gemini 300 and unless otherwise stated $CDCl_3$ was used as solvent. Low and high resolution MS were run on a either a Micromass Quattro II, Finnigan MAT95 or MAT 900 spectrometer. Microwave syntheses were performed on a Biotage Emrys Creator.

***N*-(Benzyloxycarbonyl)-3-(hydroxymethyl)-(*S*)-tyrosine 15**. A 1M sodium hydroxide (32 mmol, 32 mL) solution of *N*-Cbz-(*S*)-tyrosine (5.0 g, 15.8 mmol) was added to a solution of borax (13 g) in water (90 mL) and the solution stirred for 30 min at room temperature. Aqueous formaldehyde (5.7 mL 35% solution, 66.4 mmol) was added in one portion and the flask flushed with nitrogen and sealed with a glass stopper. The reaction was stirred at 40 °C for 5 days, after which it was allowed to cool and acidified with 3M hydrochloric acid to pH 2. The suspension was extracted with ethyl acetate (3 x 50 mL), washed with brine, dried over magnesium sulphate and the solvent evaporated *in vacuo* affording **15** as a clear oil (5.4 g, 88%) which was used 'as is' without further purification.

***N*-(Benzyloxycarbonyl)-3-(methoxymethyl)-(*S*)-tyrosine methyl ester 16**. *Conventional procedure.* To anhydrous methanol (50 mL) was added **15** (5.2 g, 15 mmol) and PTSA (100 mg). The resulting solution was heated at reflux for 5 h under an atmosphere of argon. The solvent was removed *in vacuo* and residue treated with aqueous sodium bicarbonate (10%, 20 mL), extracted with ethyl acetate (3 x 20 mL) and the organic layer washed with brine, dried and evaporated *in vacuo*. Column chromatography using petrol–ethyl acetate (3 : 1) afforded **16** as a colorless oil (5.8 g, 90%).

Microwave procedure An anhydrous methanolic solution (5 mL) of **15** (0.52 g, 1.5 mmol) and PTSA (10 mg) was placed in a Smith reaction tube equipped with a PTFE coated rubber septa and sealed with an aluminum crimp cap. The solution was heated in a Personal Chemistry microwave synthesizer at 110 °C for 30 min. **16** was afforded (100% yield) after purification as outlined above. $[\alpha]^{24}_D$ +25.7 (*c* = 1, $CHCl_3$); IR (neat): 3343, 2952, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (br, 1 H), 7.36–7.28 (m, 5 H), 6.91 (dd, *J* = 8.2, 1.9 Hz, 1 H), 6.77 (d, *J* = 8.2 Hz, 1 H), 6.74 (d, *J* = 1.9 Hz, 1 H), 5.22 (d, *J* =

7.9 Hz, 1 H), 5.10 (d, *J* = 12.3 Hz, 1 H), 5.05 (d, *J* = 12.3 Hz, 1 H), 4.48 (dd, *J* = 7.9, 5.9 Hz, 1 H), 4.55 (s, 2 H), 3.69 (s, 3 H), 3.39 (s, 3 H), 3.03 (dd, *J* = 14.1, 5.7 Hz, 1 H), 2.96 (dd, *J* = 14.1, 5.7 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 155.8, 155.3, 136.3, 130.2, 129.1, 128.6, 128.3, 128.2, 126.9, 122.4, 116.6, 73.5, 66.9, 58.2, 54.9, 52.2, 37.2 ppm; MS (EI) *m*/*z* 373.2 $(M)^+$; HRMS (ES) *m*/*z* 391.1864 $(M + NH_4)^+$ (calcd for $C_{20}H_{27}N_2O_6$ 391.1864).

***N*-(Benzyloxycarbonyl)-3-bromo-5-(hydroxymethyl)-*(S)*-tyrosine methyl ester 11**. To a solution of **15** (1.0 g, 2.7 mmol) in methanol (25 mL) was added, under argon, with stirring thionyl chloride drop wise (0.23 mL, 3.2 mmol). The reaction was heated at reflux for 3 h. The solvent was removed *in vacuo*, the residue redissolved in ethyl acetate (50 mL), washed with water, dilute aqueous sodium bicarbonate, brine, dried over magnesium sulphate, filtered and the solvent evaporated. The product was added to acetonitrile (20 mL), NBS (530 mg, 3.0 mmol) added and stirred at room temperature under argon for 18 h. The solvent was evaporated, the residue taken up in ethyl acetate, washed with brine, dried over magnesium sulphate, filtered and the solvent evaporated *in vacuo*. Chromatography (hexane–ethyl acetate 80 : 20) afforded **11** as an oil (550 mg, 48%). $[\alpha]^{24}_D$ +49.4 (*c* = 2.1, $CHCl_3$); IR (neat): 3469, 3296, 1719, 1691 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.41 (s, 1 H), 7.32–7.24 (m, 5 H), 7.07 (s, 1 H), 5.02 (d, *J* = 12.7 Hz, 1 H), 4.90 (d, *J* = 12.7 Hz, 1 H), 4.64 (s, 2 H), 4.38 (m, 1 H), 3.67 (s, 3 H), 3.03 (dd, *J* = 14.0, 5.1 Hz, 1 H), 2.81 (dd, *J* = 14.0, 5.1 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 172.6, 157.2, 150.5, 136.9, 132.9, 132.0, 129.7, 129.4, 128.3, 127.8, 127.4, 109.9, 63.4, 60.5, 55.9, 51.6, 36.4 ppm. HRMS (ES, nanospray) *m*/*z* 455.0811 $(M + NH_4)^+$ (calcd for $C_{19}H_{24}BrN_2O_6$ 455.0812).

***N*-(Benzyloxycarbonyl)-3-bromo-5-(methoxymethyl)-(*S*)-tyrosine methyl ester 17**. NBS (250 mg, 1.42 mmol) and **16** (525 mg, 1.40 mmol) in acetonitrile (5.5 mL) was stirred at room temperature under argon for 15 h. Incorporating the same work up procedure as for **11**, **17** was afforded as a pale yellow oil (480 mg, 78%). $[\alpha]^{24}_D$ +33.5 (*c* = 2, $CHCl_3$); IR (neat): 3327, 1702, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.18 (m, 5 H), 7.06 (d, *J* = 1.6 Hz, 1 H), 6.69 (d, *J* = 1.6 Hz, 1 H), 5.22 (d, *J* = 7.9 Hz, 1 H), 4.99 (d, *J* = 12.2 Hz, 1 H), 4.94 (d, *J* = 12.2 Hz, 1 H), 4.45 (m, 1 H), 4.40 (s, 2 H), 3.59 (s, 3 H),

3.27 (s, 3 H), 2.91 (dd, J = 13.8, 5.7 Hz, 1 H), 2.82 (dd, J = 13.8, 5.7 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 155.9, 151.1, 136.5, 132.9, 128.9, 128.7, 128.5, 128.4, 128.2, 124.6, 110.6, 72.4, 67.1, 58.6, 55.1, 52.7, 37.2 ppm; MS (EI) *m/z* 452.2 $(M)^+$; HRMS (ES) 469.0969 $(M + NH_4)^+$ (calcd for $C_{20}H_{26}N_2O_6Br$ 469.0969).

N-(Benzyloxycarbonyl)-3-bromo-5-[(5-tert-butyl-2-hydroxyphenyl)methylene]-(S)-tyrosine methyl ester 1. a) *Conventional procedure* A mixture of **17** (120 mg, 0.26 mmol), *para-tert*-butyl phenol (60 mg, 0.4 mmol) was refluxed in toluene in the presence of PTSA (10 mg). The title product was isolated as detailed for **1** (synthesised from **11**) and purified via flash column-chromatography affording **1** as a clear oil (68 mg, 46%). Analysis of the physical data for the title compound with that reported earlier for the same product confirmed its identity.

b) Microwave procedure A mixture of **17** (200 mg, 0.43 mmol), *para-tert*-butylphenol (100 mg, 0.66 mmol) and PTSA (15 mg) in anhydrous dichloromethane (5 mL) was heated at 120 °C (sealed tube fitted with an aluminum crimp cap lined with a PTFE rubber seal) in the microwave synthesizer for 30 min.. Purification as detailed earlier afforded **1** as a clear oil (165 mg, 70%). Analysis of the physical data for the title compound with that reported earlier for the same product confirmed its identity.

***N*-(Benzyloxycarbonyl)-3-bromo-5-[(5-allyloxy-2-hydroxyphenyl)methylene]-(*S*)-tyrosine methyl ester 2**

A mixture of **17** (100 mg, 0.22 mmol), *O*-allylhydroquinone (75 mg, 0.5 mmol) and PTSA (5 mg) in anhydrous dichloromethane (4 mL) was heated at 120 °C (sealed tube fitted with an aluminum crimp cap lined with a PTFE rubber seal) in the microwave synthesizer for 60 min. After which the solvent was removed in vacuo and the product purified via flash column gradient chromatography using a hexane–ethyl acetate (5 to 30 %) mobile phase. The product (**2**) was afforded as a clear oil (70 mg, 56%). Analysis of the title compound with that reported earlier confirmed its identity.

***N*-(Benzyloxycarbonyl)-3-bromo-5-[(5-phenyl-2-hydroxyphenyl)methylene]-*(S)*-tyrosine methyl ester 3**

A mixture of **17** (100 mg, 0.22 mmol), *para*-hydroxybiphenyl (85 mg, 0.5 mmol) and PTSA (5 mg) in anhydrous dichloromethane (4 mL) was heated at 120 °C (sealed tube fitted with an aluminum crimp cap lined with a PTFE rubber seal) in the microwave synthesizer for 45 min. After which the product was purified via gradient flash chromatography using hexane–ethyl acetate (5 to 30 %) as the mobile phase affording **3** as a clear oil (85 mg, 66%). Analysis and comparison of the physical data for the title compound with that reported earlier for the same product confirmed its identity.

***N*-(Benzyloxycarbonyl)-3-iodo-5-(methoxymethyl)-(*S*)-tyrosine methyl ester 13**

A solution of **16** (350 mg, 0.9 mmol) and *N*-iodosuccinimide (250 mg, 1.1 mmol) in acetonitrile (5 mL) was stirred at room temperature under argon for 20 h. The acetonitrile was evaporated *in vacuo* and the residue suspended in dichloromethane (20 mL), and washed successively with water (5 mL), saturated aqueous sodium thiosulphate (5 mL) and brine (5 mL). The organic layer was separated, dried over magnesium sulphate and the solvent evaporated under reduced pressure. Flash chromatography using hexane–dichloromethane (30%) afforded the title product as a clear oil (165 mg, 39%). $[\alpha]^{23}_{D}$ +21.5 (*c* = 2, $CHCl_3$); IR (neat): 3316, 2947, 2821, 1736, 1711, 1423, 1216, 738, 697 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.50 (s, 1 H), 7.31–7.22 (m, 5 H), 7.03 (s, 1 H), 5.03 (d, *J* = 12.5 Hz, 1 H), 4.97 (d, *J* = 12.5 Hz, 1 H), 4.45 (s, 2 H), 4.37 (m, 1 H), 3.66 (s, 3 H), 3.31 (s, 3 H), 3.01 (dd, *J* = 13.9, 5.0 Hz, 1 H), 2.78 (dd, *J* = 13.9, 5.0 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 173.4, 157.9, 154.4, 139.9, 137.7, 131.4, 130.8, 129.1, 128.6. 128.2, 125.7, 86.0, 71.9, 67.1, 58.0, 56.4, 52.3, 36.8 ppm.

***N*-(Benzyloxycarbonyl)-3,5-*bis*(*N*-morpholinomethyl)-(*S*)-tyrosine methyl ester 18**

To a solution of *N*-Cbz-(*S*)-tyrosine methyl ester (1.0 g, 3.04 mmol) in glacial acetic acid (2 mL), *N*-morpholine (0.58 mL, 6.68 mmol) and formaldehyde (0.6 mL, 35% solution, 6.7 mmol) were added. The resulting mixture was stirred at 50 °C for 18 h. All the volatiles were removed by vacuum distillation. Residual water was azeotropically removed using toluene affording a pale brown waxy solid

(**18**), which was used directly in next reaction without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 6.76 (s, 2 H), 5.25 (d, *J* = 6.0 Hz, 1 H), 5.03 (d, *J* = 12.1 Hz, 1 H), 4.99 (d, *J* = 12.1 Hz, 1 H), 4.55 (m, 1 H), 3.68–3.63 (m, 11 H), 3.60–3.47 (m, 4 H), 2.96 (dd, *J* = 13.2, 5.2 Hz, 1 H), 2.90 (dd, *J* = 13.2, 5.2 Hz, 1 H), 2.44 (m, 8 H) ppm.

***N*-(Benzyloxycarbonyl)-*O*-acetyl-3,5-*bis*(acetoxymethyl)-(*S*)-tyrosine methyl ester 19**

A mixture of **18** (380 mg, 0.7 mmol), acetic anhydride (3 mL) and glacial acetic acid (1 mL) was heated at reflux for 24 h under argon. All of the volatile components of the reaction were removed by vacuum distillation. The resultant residue was redissolved in ethyl acetate (10 mL) and washed successively with aqueous sodium bicarbonate (10%, 10 mL), water (5 mL) and brine (5 mL). The organic layer was dried over magnesium sulphate and the solvents removed in vacuo affording a pale yellow oil. Purification of this oil *via* flash column chromatography using hexane–ethyl acetate as the eluent (gradient 10 to 30%) afforded **19** as a clear colorless waxy solid (330 mg, 80%). Recrystallization from hexane–dichloromethane afforded **19** as white needle shaped crystals. M.p. 58–60 °C; $[\alpha]^{21.5}_D$ +46.5 (*c* = 1, $CHCl_3$); IR (neat): 3303, 2950, 2919, 1735, 1686, 1536, 1376, 1012, 903 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 7.15 (s, 2 H), 5.30 (d, *J* = 8.0 Hz, 1 H), 5.08 (m, 2 H), 4.96 (s, 4 H), 4.65 (m, 1 H), 3.70 (s, 3 H), 3.15–3.04 (m, 2 H), 2.30 (s, 3 H), 2.02 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 170.7, 169.3, 155.8, 146.8, 136.3, 134.5, 131.5, 129.4, 128.7, 128.4, 128.3, 67.2, 61.3, 54.9, 52.6, 37.6, 20.9, 20.7 ppm; MS (CI) *m*/*z* 533.2 $(M + NH_4)^+$; HRMS (EI) *m*/*z* 515.1791 $(M)^+$ (calcd for $C_{26}H_{29}NO_{10}$ 515.1786).

***N*-(Benzyloxycarbonyl)-3,5-*bis*(methoxymethyl)-*(S)*-tyrosine methyl ester 20**

A solution of **19** (120 mg, 0.2 mmol) and PTSA (7 mg) in anhydrous methanol (3 mL) was heated at 110 °C (sealed tube fitted with an aluminum crimp cap lined with a PTFE rubber seal) in the microwave synthesizer for 30 min. The methanol was removed *in vacuo* and the residue was dissolved in dichloromethane (5 mL). This solution was passed through a small plug of solid sodium bicarbonate and the solvent evaporated affording **20** (75 mg, 85%) as clear colorless oil. $[\alpha]^{22}_D$ +36.0 (*c* = 1, $CHCl_3$); IR

(neat): 3337, 2928, 2824, 2287, 1704, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 6.84 (s, 2 H), 5.23 (d, *J* = 7.9 Hz, 1 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.02 (d, *J* = 12.2 Hz, 1 H), 4.58 (ddd, *J* = 7.9, 6.2, 5.3 Hz, 1 H), 4.51 (s, 4 H), 3.70 (s, 3 H), 3.39 (s, 6 H), 3.03 (dd, *J* = 13.9, 5.5 Hz, 1 H), 2.96 (dd, *J* = 13.9, 5.5 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 172.4, 155.9, 153.4, 136.5, 129.2, 128.7, 128.4, 128.3, 126.9, 123.9, 71.8, 67.1, 58.5, 55.2, 52.5, 37.5 ppm; MS (EI) *m*/*z* 417.3 $(M)^+$; HRMS (ES) *m*/*z* 435.2125 $(M + NH_4)^+$ (calcd for $C_{22}H_{31}N_2O_7$ 435.2126).

One pot protocol for synthesis of *N*-(benzyloxycarbonyl)-3,5-*bis*(methoxymethyl)-(*S*)-tyrosine methyl ester 20

N-Cbz-*(S)*-tyrosine (630 mg, 2.0 mmol) was dissolved in aqueous sodium hydroxide (1M, 4 mL) and diluted with water (5 mL). Formaldehyde (0.9 mL, 35%, 10 mmol) was added and the flask was thoroughly flushed with nitrogen and subsequently closed with a glass stopper. The reaction mixture was stirred at 40 °C for 5 days. After acidifying the reaction to pH 2 (10% hydrochloric acid) the solution was extracted with ethyl acetate (3 x 20 mL). Combined organic extracts was washed with brine (20 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was esterified with methanol using PTSA as the catalyst and microwave irradiation (120 °C for 45 min.). Subsequent removal of the methanol and purification via flash gradient chromatography using hexane–ethyl acetate (5 to 30 %) mobile phase afforded the title product (**20**) as an oil (367 mg, 44 %). An alternative more efficient protocol for the synthesis of **20** employs a very similar procedure but however, instead of heating to 40 °C for 5 days, the reaction is heated at reflux (100 °C) for 3.5 h. Employing an identical work-up procedure and subsequent microwave-assisted acid-catalyzed esterification and purification procedure **20** was afforded in an overall 50 % yield.

***N*-(Benzyloxycarbonyl)-3,5-*bis*(hydroxymethyl)-*(S)*-tyrosine methyl ester 21**

To a solution of **10** (400 mg, 1.07 mmol) in anhydrous methanol (20 mL) was added, with stirring, (caution) thionyl chloride drop wise (0.1 mL, 1.4 mmol) under an atmosphere of argon. The resulting mixture was heated at reflux for 3 h. The solvent was removed *in vacuo* and the residue was dissolved in

ethyl acetate (20 mL), which was successively washed with water (10 mL), dilute aqueous sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulphate, filtered and the ethyl acetate removed under vacuum. Purification *via* flash gradient chromatography using hexane–ethyl acetate (5 to 30 %) mobile phase afforded the title product (**21**) as an oil (210 mg, 54%). $[\alpha]^{22}_{D}$ +41.1 (*c* = 1.2, $CHCl_3$); IR (neat): 3347, 2932, 2821, 1694, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.33–7.25 (m, 5 H), 6.74 (s, 2 H), 5.48 (d, *J* = 8.2 Hz, 1 H), 5.02 (d, *J* = 12.5 Hz, 1 H), 4.98 (d, *J* = 12.5 Hz, 1 H), 4.59 (s, 4 H), 4.51 (m, 1 H), 3.67 (s, 3 H), 2.97 (dd, *J* = 13.8, 6.2 Hz, 1 H), 2.86 (dd, *J* = 13.8, 6.2 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 172.7, 156.3, 153.6, 136.4, 128.7, 128.5, 128.4, 128.2, 127.0, 126.6, 67.2, 62.6, 55.4, 52.6, 37.5 ppm; MS (ES) *m/z* 407.2 $(M)^+$; HRMS (ES) 407.1812 $(M + NH_4)^+$ (calcd for $C_{20}H_{27}N_2O_7$ 407.1813).

References

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