Supporting Information for:

Synthesis of pyrazole containing α-amino acids via a highly regioselective condensation/aza-Michael reaction of β-aryl α,β-unsaturated ketones

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Table of Contents

1. Experimental Procedures and Data of All Known Compounds S2–S5

2. References S5

3. NMR Spectra of All New Compounds S6–S44
1. Experimental Procedures and Data of All Known Compounds

**Dimethyl (2S)-2-aminobutandioate hydrochloride.**\(^1\) To a suspension of L-aspartic acid (4) (5.00 g, 37.6 mmol) in methanol (30 mL) at 0 °C under argon was added dropwise thionyl chloride (4.00 mL, 52.6 mmol). The reaction mixture was warmed to room temperature and then heated under reflux for 3 h. The solution was concentrated in vacuo to give a colourless oil and triturated with diethyl ether to give dimethyl (2S)-2-aminobutandioate hydrochloride as a colourless solid (7.55 g, 100%). Mp 115–116 °C (lit.\(^1\) 114–115 °C); \([\alpha]_D^{24} +22.0 \ (c \ 1.0, \ MeOH); \delta_H (400 MHz, DMSO-d\_6) 2.99 (1H, dd, J 18.0, 5.5 Hz, 3-HH), 3.05 (1H, dd, J 18.0, 5.5 Hz, 3-HH), 3.66 (3H, s, OMe), 3.74 (3H, s, OMe), 4.35 (1H, t, J 5.5 Hz, 2-H), 8.72 (3H, s, CHN\_3\^+); \delta_C (101 MHz, DMSO-d\_6) 34.0 (CH\_2), 48.4 (CH), 52.2 (CH\_3), 168.7 (C), 169.6 (C); m/z (CI) 162 (MH\^+ 100%), 148 (5), 102 (20).

**Dimethyl (2S)-2-(tritylamino)butandioate (5).**\(^2\) To a solution of dimethyl (2S)-2-aminobutandioate hydrochloride (7.46 g, 37.7 mmol) in dichloromethane (150 mL) at 0 °C was added dropwise triethylamine (11.0 mL, 75.4 mmol) and triphenylmethyl chloride (10.5 g, 37.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was washed with 2 M citric acid (100 mL), water (100 mL), brine (100 mL), then dried (MgSO\_4) and concentrated in vacuo to give a colourless oil. The crude product was purified by column chromatography (elution with 50% diethyl ether in petroleum ether) to give 5 as a colourless solid (15.2 g, 100%). Mp 71–72 °C (lit.\(^2\) 70–71 °C); \([\alpha]_D^{24} +36.6 \ (c \ 1.0, \ CHCl\_3); \delta_H (400 MHz, CDCl\_3) 2.51 (1H, dd, J 14.7, 7.0 Hz, 3-HH), 2.66 (1H, dd, J 14.7, 5.4 Hz, 3-HH), 2.93 (1H, d, J 10.1 Hz, NH), 3.25 (3H, s, OMe), 3.67 (3H, s, OMe), 3.68–3.73 (1H, m, 2-H), 7.15–7.20 (3H, m, ArH), 7.23–7.28 (6H, m, ArH), 7.46–7.51 (6H, m, ArH); \delta_C (101 MHz, CDCl\_3) 39.0 (CH\_2), 50.5 (CH), 50.7 (CH\_3), 52.4 (CH\_3), 69.9 (C), 125.2 (3 × CH), 126.6 (6 × CH), 127.5 (6 × CH), 144.4 (3 × C), 169.7 (C), 172.6 (C); m/z (El) 403 (M\^+ 1%), 326 (35), 243 (100), 165 (30), 83 (70).

**Methyl (2S)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate (6).**\(^2\) A solution of dimethyl methylphosphonate (3.00 mL, 27.3 mmol) in THF (50 mL) was cooled to –78 °C under an argon atmosphere. n-Butyl lithium (2.5 M in hexane, 11.0 mL, 28.6 mmol) was added dropwise and the reaction mixture stirred for 1 h. In a separate reaction vessel, a solution of dimethyl (2S)-2-(tritylamino)butandioate (5) (5.00 g, 12.4 mmol) in THF (100 mL) was cooled to –78 °C and then the dimethyl methylphosphonate/n-butyl lithium solution was cannulated into the flask and the reaction mixture stirred at –78 °C for 2 h to give a yellow solution. The reaction was quenched with a saturated solution of ammonium chloride (3 mL) and allowed to warm to room temperature. The mixture was concentrated in
The resulting residue was diluted with ethyl acetate (100 mL), washed with water (2 × 100 mL), brine (100 mL) then dried (MgSO₄) and concentrated in vacuo. The crude product was purified by column chromatography (elution with 75% ethyl acetate in petroleum ether) to give 6 as a colourless solid (5.65 g, 92%). Mp 117–118 °C (lit.² 117–118.5 °C); [α]D²⁴ +31.1 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 2.78 (1H, dd, J 16.7, 6.9 Hz, 3-HH), 2.85–2.95 (2H, m, 3-HH and NH), 3.06 (2H, d, J₄₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋أشياء ונתגש מוחלט (4 mL) ב-argon. Anhydrous potassium carbonate (0.06 g, 0.42 mmol) was added to the solution and stirred for 0.5 h. An aldehyde (0.80 mmol) was added to the suspension and heated at 50 °C until the reaction was complete by TLC. The reaction mixture was allowed to cool to room temperature and then concentrated in vacuo. The resultant residue was dissolved in ethyl acetate (30 mL) and washed with water (20 mL), brine (30 mL) then dried (MgSO₄) and concentrated in vacuo. The products were purified by column chromatography on eluting with 20–40% diethyl ether in petroleum ether.

**General Procedure for the Horner-Wadsworth-Emmons Reaction:**³ Methyl (2S,5E)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate (6) (0.20 g, 0.40 mmol) was dissolved in acetonitrile (4 mL) at room temperature under argon. Anhydrous potassium carbonate (0.06 g, 0.42 mmol) was added to the solution and stirred for 0.5 h. An aldehyde (0.80 mmol) was added to the suspension and heated at 50 °C until the reaction was complete by TLC. The reaction mixture was allowed to cool to room temperature and then concentrated in vacuo. The resultant residue was dissolved in ethyl acetate (30 mL) and washed with water (20 mL), brine (30 mL) then dried (MgSO₄) and concentrated in vacuo. The products were purified by column chromatography on eluting with 20–40% diethyl ether in petroleum ether.

**Methyl (2S,5E)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate (7).³** Using the general procedure above gave 7 after 36 h as a yellow oil (0.18 g, 95%). Spectroscopic data was consistent with the literature.³ νmax/cm⁻¹ (NaCl) 3023 (NH), 2950 (CH), 1737 (C=O), 1657 (C=C), 1608, 1205; [α]D²⁵ +111.0 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 2.80 (1H, dd, J 15.2, 7.0 Hz, 3-HH), 2.88–2.97 (2H, m, 3-HH and NH), 3.28 (3H, s, OMe), 3.79–3.89 (1H, m, 2-H), 6.69 (1H, d, J 16.2 Hz, 5-H), 7.14–7.29 (10H, m, ArH and 6-H), 7.37–7.41 (3H, m, ArH), 7.44–7.53 (8H, m, ArH); δC (101 MHz, CDCl₃) 45.7 (CH₂), 52.0 (CH₃), 53.7 (CH), 71.3 (C), 126.4 (3 × CH), 127.9 (6 × CH), 128.1 (2 × CH), 128.4 (6 × CH), 128.8 (2 × CH), 129.0 (CH), 130.6 (CH), 134.4 (C), 143.3 (CH), 145.8 (3 × C), 174.5 (C), 197.5 (C); m/z (FAB) 476.2231 (MH⁺, 1%), 301 (5), 254 (90), 243 (100), 237 (55), 167 (45).

**Methyl (2S,5E)-6-(4-nitrophenyl)-4-oxo-2-(tritylamino)hex-5-enoate (8).⁴** Using the general procedure above gave 8 after 24 h as an off-white solid (0.15 g, 72%). Spectroscopic data was consistent with the literature.⁴ Mp 139–141 °C; νmax/cm⁻¹ (neat) 2951 (CH), 1742
(C=O), 1712 (C=O), 1490, 1509, 1341; [α]_D^{25} +43.3 (c 0.2, CHCl_3); δ_H (400 MHz, CDCl_3) 2.80 (1H, dd, J 15.5, 6.9 Hz, 3-HH), 2.91 (1H, dd, J 15.5, 5.1 Hz, 3-HH), 2.95 (1H, br s, NH), 3.31 (3H, s, OMe), 3.55–3.76 (1H, m, 2-H), 6.77 (1H, d, J 16.2 Hz, 5-H), 7.17–7.32 (10H, m, 2 × Ph), 7.41–7.53 (6H, m, 6-H and Ph), 7.66 (2H, d, J 8.8 Hz, 2’-H and 6’-H), 8.25 (2H, d, J 8.8 Hz, 3’-H and 5’-H); δ_C (101 MHz, CDCl_3) 46.2 (CH_2), 52.1 (CH_3), 53.7 (CH), 71.3 (C), 124.3 (CH), 126.6 (3 × CH), 128.0 (6 × CH), 128.8 (6 × CH), 128.9 (2 × CH), 129.6 (2 × CH), 139.9 (CH), 140.6 (C), 145.7 (3 × C), 148.6 (C), 174.3 (C), 197.0 (C); m/z (FAB) 543.1903 (MNa^+). C_{32}H_{38}N_3O_4Na requires 543.1896, 443 (9%), 413 (9), 351 (19), 329 (58), 243 (100), 176 (78), 154 (32).

**Methyl (2S,5E)-6-(4′-methoxyphenyl)-4-oxo-2-(tritylamino)hex-5-enoate (9).** Using the general procedure above gave 9 after 36 h as a colourless oil (0.16 g, 76%). Spectroscopic data was consistent with the literature.ν_max/cm⁻¹ (neat) 3320 (NH), 3057, 3021, 2951 (CH), 1736 (C=O), 1653 (C=O), 1595 (C=C), 1510, 1447, 1252, 1171, 1028; [α]_D^{23} +54.1 (c 1.0, CHCl_3); δ_H (400 MHz, CDCl_3) 2.78 (1H, dd, J 15.0, 7.0 Hz, 3-HH), 2.84–2.99 (2H, m, 3-HH and NH), 3.27 (3H, s, OMe), 3.71–3.93 (4H, m, 2-H and OMe), 6.59 (1H, d, J 16.1 Hz, 5-H), 6.92 (2H, d, J 8.7 Hz, ArH), 7.11–7.35 (9H, m, ArH), 7.39–7.59 (9H, m, 6-H and ArH); δ_C (101 MHz, CDCl_3) 45.7 (CH_2), 52.0 (CH_3), 54.0 (CH), 55.4 (CH_3), 71.3 (C), 114.5 (2 × CH), 124.3 (CH), 126.6 (3 × CH), 127.1 (C), 128.0 (6 × CH), 128.9 (6 × CH), 130.2 (2 × CH), 143.2 (CH), 145.9 (3 × C), 161.8 (C), 174.6 (C), 197.5 (C); m/z (FAB) 506.2329 (MH^+). C_{33}H_{32}N_4O requires 506.2331, 428 (5%), 262 (11), 243 (100), 162 (18), 86 (5).

**Methyl (2S,5E)-6-(naphthalen-2-yl)-4-oxo-2-(tritylamino)hex-5-enoate (10).** Using the general procedure above gave 10 after 48 h as a yellow solid (0.19 g, 89%). Spectroscopic data was consistent with the literature. Mp 62–63 °C; ν_max/cm⁻¹ (NaCl) 3055 (NH), 2982 (CH), 1734 (C=O), 1655 (C=C), 1604, 1593, 1489, 1172; [α]_D^{24} +64.1 (c 1.0, CHCl_3); δ_H (400 MHz, CDCl_3) 2.84 (1H, dd, J 15.1, 7.0 Hz, 3-HH), 2.92–3.00 (2H, m, 3-HH and NH), 3.29 (3H, s, OMe), 3.79–3.86 (1H, m, 2-H), 6.80 (1H, d, J 16.2 Hz, 5-H), 7.15–7.30 (9H, m, ArH), 7.50–7.55 (8H, m, ArH), 7.62–7.69 (2H, m, 6-H and ArH), 7.84–7.89 (3H, m, ArH), 7.94 (1H, br s, ArH); δ_C (101 MHz, CDCl_3) 45.8 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 123.5 (CH), 126.5 (CH), 126.6 (3 × CH), 126.8 (CH), 127.4 (CH), 127.8 (CH), 127.9 (6 × CH), 128.1 (CH), 128.6 (CH), 130.6 (CH), 131.9 (C), 133.3 (C), 134.4 (C), 143.4 (CH), 145.8 (3 × C), 174.5 (C), 197.5 (C); m/z (FAB) 526.2388 (MH^+). C_{36}H_{32}N_4O requires 526.2382, 448 (7%), 273 (8), 243 (100), 181 (19), 165 (24).

**Methyl (2S,5E)-6-(3′-nitrobenzene-4-yl)-4-oxo-2-(tritylamino)hex-5-enoate (11).** Using the general procedure above gave 11 after 72 h as a yellow foam (0.20 g, 84%). Spectroscopic data was consistent with the literature. ν_max/cm⁻¹ (neat) 3030 (NH), 1736 (C=O), 1657 (C=C), 1603, 1530,
1514, 1348; [α]$^D_{23}$ +61.7 (c 1.0, CHCl$_3$); δ$_H$ (400 MHz, CDCl$_3$) 2.82 (1H, dd, $J$ 15.2, 6.9 Hz, 3-HH), 2.90–3.02 (2H, m, 3-HH and NH), 3.30 (3H, s, OMe), 3.77–3.88 (1H, m, 2-H), 6.75 (1H, d, $J$ 16.2 Hz, 5-H), 7.12–7.32 (9H, m, ArH), 7.45–7.73 (12H, m, ArH and 6-H), 7.93 (1H, d, $J$ 7.9 Hz, ArH), 8.23 (1H, d, $J$ 7.9 Hz, ArH), 8.48 (1H, s, ArH); δ$_C$ (101 MHz, CDCl$_3$) 45.8 (CH$_2$), 52.0 (CH$_3$), 53.8 (CH), 71.3 (C), 121.9 (CH), 122.6 (CH), 126.5 (3 × CH), 126.9 (CH), 127.7 (2 × CH), 127.9 (6 × CH), 128.8 (6 × CH), 129.1 (2 × CH), 129.9 (CH), 132.9 (CH), 134.6 (C), 140.6 (C), 141.7 (C), 142.1 (CH), 145.7 (3 × C), 148.8 (C), 174.4 (C), 197.4 (C); m/z (FAB) 597.2384 (MH$^+$. C$_{38}$H$_{33}$N$_2$O$_5$ requires 597.2389), 519 (23%), 419 (5), 353 (32), 243 (100), 194 (9), 166 (54).

2. References
