Supporting Information

TiCl₄ Promoted Multicomponent Reaction: a New Entry to the Functionalized α -Amino Acids

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General Information

All melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on Varian Mercury-Vx-300, Bruker Avance 400, Bruker AV-500, Bruker Avance DRX-500 spectrometers. IR spectra were recorded on a Mattson Genesis II FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 341 or an Autopol III autometric polarimeter. Anhydrous solvents were obtained as follow: THF and diethyl ether by distillation from sodium and benzophenone; pyridine, dichloromethane from CaH₂. All other solvents were reagent grade. All moisture sensitive reactions were carried out in a flame dried flask under nitrogen atmosphere. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 3-5 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. The title α -N-tosyl imino ester was made from ethyl glyoxylate and N-toluenesulfonylisocyanate (Aldrich) by Weinreb's procedure. Ref: Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

(±)**3**

(±)(R)-ethyl 2-((R)-tetrahydrofuran-3-yl)-2-(tosylamino)acetate (3). To a mixture of freshly distilled α -N-tosyl imino ester **1** (255 mg, 1.0 mmol) and 2,3-dihydrofuran (84.2 mg, 1.2 mmol) in dry CH₂Cl₂ (6.0 mL) at -78°C was added a solution of TiCl₄ (1.0 M in CH₂Cl₂, 1.2 mmol) and the resulting yellow solution containing some precipitate were stirred at -78°C for an hour. Triethylsilane (581.4 mg, 5.0 mmol) was added to the mixture at -78°C and the mixture was continuously stirred at -78°C for 2.0 hours. Saturated sodium bicarbonate solution (15 mL) was used to quench the reaction at -78°C. The mixture was allowed to warm to room temperature and the aqueous layer was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over

Na₂SO₄ and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford the α -*N*-tosylamino ester **3** (232.7 mg, 71% yield) as a white solid, Mp = 104-105°C; R_f = 0.29 (40% EtOAc in hexane). ¹H NMR(500MHz, CDCl₃): δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.84 (m, 1H), 1.97 (m, 1H), 2.41 (s, 3H), 2.49 (m, 1H), 3.64 (m, 1H), 3.72 (m, 2H), 3.78 (m 1H), 3.87 (m, 1H), 3.88 (q, *J* = 7.2 Hz, 2H), 5.22 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (125MHz, CDCl₃) δ 14.3, 21.9, 28.9, 42.9, 57.4, 62.2, 68.1, 69.7, 127.7, 130.1, 136.9, 144.2, 171.4. IR (film, NaCl), 559.1, 667.8, 816.1, 916.6, 1092.0, 1163.5, 1338.9, 1457.3, 1738.4, 2825.0 cm⁻¹; *m/z* (ESI) 328.1 (M+H)⁺.

(±)**5a**

(±)**6a**

(±) (*R*)-ethyl 2-((2*R*,3*R*)-2-allyl-tetrahydrofuran-3-yl)-2-(tosylamino)acetate (**5a**) and (±) (*R*)-ethyl 2-((2*S*,3*R*)-2-allyl-tetrahydrofuran-3-yl)-2-(tosylamino)acetate (**6a**). To a mixture of freshly distilled α -*N*-tosyl imino ester **1** (255 mg, 1.0 mmol) and 2,3-dihydrofuran (90.7 mg, 1.2 mmol) in dry CH₂Cl₂ (6.0 mL) at -78°C was added a solution of TiCl₄ (1.0 M in CH₂Cl₂, 1.2 mmol) and the resulting yellow solution containing some precipitate were stirred at -78°C for an hour. Allyltrimethylsilane (229 mg, 2.00 mmol) was added to the mixture at -78°C and mixture was continuously stirred at -78°C for 2 hours. Saturated sodium bicarbonate solution (15 mL) was used to quench the reaction at -78°C. The mixture was allowed to warm to room temperature and the aqueous layer was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford the α -*N*-tosylamino ester **5a** (219 mg, 59% yield) and **6a** (72.0mg, 20% yield). Major isomer (±) (*R*)-ethyl 2-((2*R*,3*R*)-2-allyl-tetrahydrofuran-3-yl)-2-(tosylamino)acetate (**5a**) : white crystals, Mp = 62-64°C; R_f = 0.24 (30% EtOAc in hexane). ¹H NMR(500MHz, CDCl₃): δ 1.06 (t, *J* = 7.2 Hz, 3H), 1.82 (m, 2H), 2.21 (m, 3H), 2.40 (s, 3H), 3.85-3.72 (m, 4H), 3.90 (q, *J* = 7.2 Hz, 2H), 5.08 (m, 2H), 5.39 (d, *J* = 10.2 Hz, 1H), 5.77 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 21.5, 27.7, 38.4, 46.1, 56.0, 61.9, 66.7, 79.0, 117.4, 127.4, 129.7, 134.3, 136.4, 143.9, 170.9; FT-IR (film, NaCl), 668.9, 916.8, 1091.4, 1162.8, 1265.0, 1445.3, 1738.3, 2923.2, 2974.2cm⁻¹; *m/z* (ESI) 390.2 (M⁺+Na); HRMS (ESI), Calcd for C₁₈H₂₅NO₅S : *m/z* 390.1351 (M + Na)⁺, found *m/z* 390.1343 (M + Na)⁺. Minor isomer (±) (*R*)-ethyl 2-((2*S*,3*R*)-2-allyl-tetrahydrofuran-3-yl)-2-(tosylamino)acetate (**6a**) : wax solid; R_f = 0.20 (30% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.12 (t, *J* = 7.2 Hz, 3H), 2.04 (m, 2H), 2.23 (m, 2H), 2.42 (s, 3H), 2.48 (m, 1H), 3.79 (m, 2H), 3.95 (m, 4H), 5.04 (m, 2H), 5.20 (d, *J* = 7.8 Hz, 1H), 5.78 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 21.5, 27.4, 33.7, 44.2, 55.7, 61.7, 66.0, 79.6, 117.0, 126.5, 127.4, 129.6, 134.8,

136.1, 143.8, 171.1; FT-IR (film, NaCl), 665.3, 814.7, 1091.2, 1162.5, 1338.3, 1446.2, 1738.3 cm^{-1} ; m/z (ESI) 366.5 (M-H) $^{-}$.

(±) (R)-ethyl 2-((2R,3R)-2-cyano-tetrahydrofuran-3-yl)-2-(tosylamino)acetate (5b).

To a mixture of freshly distilled α -N-tosyl imino ester **1** (153 mg, 0.60 mmol) and 2,3-dihydrofuran (50.5 mg, 0.72 mmol) in dry CH_2Cl_2 (4.0 mL) at -78°C was added a solution of TiCl_4 (1.0 M in CH_2Cl_2 , 0.60 mmol) and the resulting yellow solution containing some precipitate were stirred at -78°C for an hour. Trimethylsilyl cyanide (119 mg, 1.20 mmol) was added to the mixture at -78°C and mixture was continuously stirred at -78°C for 0.5 hour. The mixture was allowed to warm to 0°C and stirred at 0°C for 5.0 hours. Saturated sodium bicarbonate solution (10 mL) was used to quench the reaction at 0°C . The aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford **5b** (112.3 mg, 64% yield) as a yellow solid, $\text{Mp} = 105\text{-}107^\circ\text{C}$, $R_f = 0.34$ (45% EtOAc in hexane); ^1H NMR(400MHz, CDCl_3): δ 1.06 (t, $J = 7.1$ Hz, 3H), 1.89 (m, 1H), 2.06 (m, 1H), 2.40 (s, 3H), 2.88 (m, 1H), 4.81-3.81 (m, 5H), 4.70 (d, $J = 5.7$ Hz, 1H), 5.74 (d, $J = 9.4$ Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 13.8 (CH_3), 21.5 (CH_3), 27.6 (CH_2), 48.2 (CH), 55.5 (CH), 62.4 (CH_2), 67.9 (CH), 69.0 (CH_2), 118.4 (CN), 127.3 (CH), 129.8 (CH), 135.9 (C), 144.3 (C), 169.5 (CO); IR (film, NaCl), 578.2, 666.8, 815.4, 918.5, 1091.6, 1164.0, 1305.1, 1339.5, 1447.8, 1738.6, 2255.6, 2983.1 cm^{-1} ; m/z (ESI) 375.2 ($\text{M}^+ + \text{Na}$).

(±) (S)-ethyl 2-((S)-tetrahydro-2H-pyran-3-yl)-2-(tosylamino)acetate (8) : The procedure described for **3** was used for **8**. α -N-tosyl imino ester **1** (255 mg, 1.0 mmol), 3,4-dihydro-2H-pyran (101 mg, 1.20 mmol), TiCl_4 (1M in CH_2Cl_2 , 1.20 mmol) and triethylsilane (581.4 mg, 5.00 mmol) to afford **8** (334 mg, 98% yield) as a white solid, $\text{Mp} = 102.2\text{-}103.8^\circ\text{C}$, $R_f = 0.41$ (50% EtOAc in hexane); ^1H NMR(400MHz, CDCl_3): δ 1.06 (3H, t, $J = 7.1$ Hz), 1.41 (ddd, $J = 23.4, 11.2, 4.1$ Hz, 1H), 1.72-1.51 (m, 4H), 1.93 (m, 1H), 2.04 (s, 3H), 3.38-3.32 (m, 2H), 3.92-3.74 (m, 3H), 3.88 (q, $J = 7.1$ Hz, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.69 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 13.9, 21.5, 24.6, 25.0, 38.8, 57.1, 61.8, 68.2, 69.8, 127.4, 129.6, 136.3, 143.8, 170.7; IR (film, NaCl) 559.3, 666.8, 1090.0, 1162.9, 1340.1, 1738.5, 2720.9, 2748.1, 2787.0 cm^{-1} ; m/z (ESI) 342.1 ($\text{M} + \text{H}$) $^{+}$.

(±)9a

(±)10a

(±)(S)-ethyl 2-((2S,3S)-2-allyl-tetrahydro-2H-pyran-3-yl)-2-(tosylamino)acetate (9a) and (±)(S)-ethyl 2-((2R,3S)-2-allyl-tetrahydro-2H-pyran-3-yl)-2-(tosylamino)acetate (10a): The procedure described for **5a** and **6a** was used for **9a** and **10a**. α -N-tosyl imino ester **1** (128 mg, 0.50 mmol), 3,4-dihydro-2H-pyran (168 mg, 1.0 mmol), TiCl_4 (1M in CH_2Cl_2 , 0.60 mmol) and allyltrimethylsilane (115 mg, 1.00 mmol) to afford unseparable mixture of **9a** and **10a** (178.5 mg, 94% yield) as a white solid, $\text{Mp} = 88\text{--}91^\circ\text{C}$, $R_f = 0.43$ (50% EtOAc in hexane); ^1H NMR(400MHz, CDCl_3): δ 1.00 (t, $J = 7.1$ Hz, 3H, major), 1.07 (t, $J = 7.1$ Hz, 3H, minor), 1.34 (m, 2H), 1.76 (m, 2H), 1.97 (m, 1H), 2.29 (m, 1H), 2.37 (s, 3H), 2.55 (s, 1H), 3.28 (m, 1H, major), 3.43 (m, 1H, major), 3.48 (m, 1H, minor), 3.54 (m, 1H, minor), 3.88 (m, 3H), 4.03 (d, $J = 8.8$ Hz, 1H), 4.97 (m, 2H, minor), 5.08 (m, 2H, major), 5.24 (s, 1H), 5.68 (m, 1H, minor), 5.86 (m, 1H, major), 7.27 (d, $J = 7.9$ Hz, 2H), 7.69 (d, $J = 7.9$ Hz, 2H, major), 7.73 (d, $J = 7.9$ Hz, 2H, minor); ^{13}C NMR (100MHz, CDCl_3) δ 13.8, 21.5, 23.3, 25.7, 33.2 (minor), 36.7 (major), 39.2 (minor), 41.6 (major), 55.9 (major), 56.7 (minor), 61.5 (minor), 61.8 (major), 65.2 (minor), 67.8 (major), 76.8, 117.0, 127.4, 129.6, 134.5, 136.1 (major), 136.8 (minor), 143.7 (minor), 143.8 (major), 170.5 (major), 171.3 (minor); IR (film, NaCl), 668.0, 815.4, 1089.22, 1163.24, 1340.1, 1738.1, 2931.1 cm^{-1} , m/z (ESI) 382.1 ($\text{M}^+ + \text{H}$), 404.2 ($\text{M}^+ + \text{Na}$).

(±)9b

(±)10b

(±)(S)-ethyl 2-((2R,3S)-2-cyano-tetrahydro-2H-pyran-3-yl)-2-(tosylamino)acetate (9b) and (±)(S)-ethyl 2-((2S,3S)-2-cyano-tetrahydro-2H-pyran-3-yl)-2-(tosylamino)acetate (10b): The procedure described for **5b** was used for **9b** and **10b**. α -N-tosyl imino ester **1** (153 mg, 0.600 mmol), 3,4-dihydro-2H-pyran (60.6 mg, 0.720 mmol), TiCl_4 (1M in CH_2Cl_2 , 0.720 mmol) and trimethylsilyl cyanide (119 mg, 1.20 mmol) to afford unseparable mixture of **9b** and **10b** (180.9 mg, 99% yield) as a yellow solid, $\text{Mp} = 107\text{--}110^\circ\text{C}$, $R_f = 0.42$ (45% EtOAc in hexane); ^1H NMR(400MHz, CDCl_3): δ 1.048 (t, $J = 7.1$ Hz, 3H, major), 1.054 (t, $J = 7.1$ Hz, minor), 1.63-1.54 (br, 4H), 2.04 (br, 1H, minor), 2.19 (br, 1H, major), 2.38 (s, 3H), 3.43 (m, 1H, major), 3.70 (m, 1H, minor), 3.99-3.96 (m, 3H), 4.04 (dd, $J = 9.1, 3.8$ Hz, 1H), 4.36 (d, $J = 9.3$ Hz, major), 4.64 (d, $J = 4.3$ Hz), 7.27 (d, $J = 8.2$ Hz, 2H), 7.69 (d, $J = 8.2$ Hz, 2H, minor), 7.72 (d, $J = 8.2$ Hz, 2H, major); ^{13}C NMR (100MHz, CDCl_3) δ 13.7 (CH_3 , minor), 13.8 (CH_3 , minor), 21.5 (CH_3), 21.7 (CH_2 , major), 23.0 (CH_2 , minor), 23.5 (CH_2 , major), 24.7 (CH_2 , minor), 41.4 (CH , minor), 41.6 (CH , major), 55.5 (CH , major), 57.1 (minor), 62.3 (CH_2 , minor), 62.6 (CH_2 ,

major), 64.6 (CH₂, minor), 66.7 (CH, minor), 67.5 (CH, major), 67.6 (CH₂, major), 115.3 (CN, minor), 117.1 (CN, major), 127.3 (CH, minor), 127.5 (CH, major), 129.7 (CH, minor), 129.8 (CH, major), 135.4 (C, major), 136.3 (C, minor), 169.6 (CO, major), 169.7 (CO, minor); IR (film, NaCl), 548.2, 668.3, 815.3, 919.6, 1021.0, 1089.0, 1164.17, 1341.10, 1447.3, 1735.2, 2255.0, 2339.7, 2360.8, 2866.5, 2935.6 cm⁻¹; *m/z* (ESI) 367.3 (M⁺+H), 389.2 (M⁺+Na).

(R)-ethyl 2-((3R,5R)-tetrahydro-5-phenylfuran-3-yl)-2-(tosylamino)acetate (13) : To a mixture of freshly distilled α -*N*-tosyl imino ester **1** (76.6 mg, 0.300 mmol) and (*R*)-2,3-dihydro-2-phenylfuran **11** (52.6 mg, 0.360 mmol) in dry CH₂Cl₂ (3.0 mL) at -78°C was added a solution of TiCl₄ (1.0 M in CH₂Cl₂, 0.36 mmol) and the resulting orange solution were stirred at -78°C for 50 mins. Dry acetonitrile (61.6 mg, 1.50 mmol) was added at -78°C and the mixture was stirred at -78°C for 10 mins. Triethylsilane (174.4 mg, 1.50 mmol) was added and the mixture was stirred at -78°C for an hour. Then the mixture was warmed to -20 °C and stirred at -20 °C for two hours. Then the mixture was recooled to -30 °C and quenched carefully with 10 mL ice-chilled saturated sodium bicarbonate solution. After the mixture was warmed to room temperature, the aqueous layer was extracted with dichloromethane (3 X 15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford the α -*N*-tosylamino ester **13** (84.7 mg, 70% yield) as clear crystals, Mp = 97 -99°C, *R_f* = 0.41 (hex : EtOAc = 1 : 1), [α]_D²³ = -17.9° (*c* 1.03, CHCl₃); ¹H NMR(400MHz, CDCl₃): δ 1.06 (t, *J* = 7.3 Hz, 3H), 1.96 (m, 1H), 2.33 (m, 1H), 2.42 (s, 3H), 2.59 (m, 1H), 3.94-3.76 (m, 4H), 4.09 (dd, *J* = 9.1, 7.3 Hz, 1H), 4.99 (t, *J* = 7.0 Hz, 1H), 5.28 (d, *J* = 9.9 Hz, 1H), 7.31 (m, 7H), 7.72 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (100MHz, CDCl₃) δ 13.9 (CH₃), 21.5 (CH₃), 36.7 (CH₂), 42.3 (CH), 56.7 (CH), 62.0 (CH₂), 69.8 (CH₂), 79.8 (CH), 125.4 (CH), 127.4 (CH), 128.4 (CH), 129.7 (CH), 136.3 (C), 142.6 (C), 143.9 (C), 170.9 (CO); FT-IR (film, NaCl), 562.1, 666.6, 701.4, 1026.3, 1163.3, 1339.2, 1494.6, 1599.1, 1736.2, 2872.4, 2981.7 cm⁻¹; *m/z* (ESI) 404.1 (M + H)⁺.

(R)-Ethyl 2-((2R,3R,5R)-2-cyano-tetrahydro-5-phenylfuran-3-yl)-2-(tosylamino)acetate (14): To a mixture of freshly distilled α -*N*-tosyl imino ester **1** (76.6 mg, 0.300 mmol) and (*R*)-2,3-dihydro-2-phenylfuran **11** (52.6 mg, 0.360 mmol) in dry CH₂Cl₂ (3.0 mL) at -78°C was added a solution of TiCl₄ (1.0 M in CH₂Cl₂, 0.36 mmol) and the resulting orange solution were stirred at -78°C for an hour. Trimethylsilyl cyanide (59.5 mg, 0.60 mmol) was added to the mixture quickly at -78°C and the mixture was

continuously stirred at -78°C for 0.5 hour. Then the mixture was allowed to warm to -20°C and stirred at -20°C for 5.0 hours. Ice-cooled saturated sodium bicarbonate solution (10 mL) was used to quench the reaction carefully at -20°C . The aqueous layer was extracted with dichloromethane (3 X 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford **14** (80.4 mg, 65% yield) as a yellow oil, $R_f = 0.28$ (hex : EtOAc = 1 : 1), $[\alpha]^{23}_{\text{D}} = -17.2^{\circ}$ (c 1.0, CHCl_3); ^1H NMR(400MHz, CDCl_3): δ 1.06 (t, $J = 7.2$ Hz, 3H), 2.09 (m, 1H), 2.43 (s, 3H), 2.45 (m, 1H), 2.92 (m, 1H), 3.95 (m, 3H), 4.82 (d, $J = 6.4$ Hz, 1H), 5.18 (t, $J = 6.9$ Hz, 1H), 5.54 (d, $J = 9.4$ Hz, 1H), 7.30 (m, 7H), 7.74 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 13.8 (CH_3), 21.6 (CH_3), 35.7 (CH_2), 47.6 (CH), 55.0 (CH), 62.8 (CH_2), 68.3 (CH), 81.8 (CH), 118.1 (CN), 125.4 (CH), 127.4 (CH), 128.0 (CH), 129.9 (CH), 135.6 (C), 140.3 (C), 144.4 (C), 169.6 (CO); FT-IR (film, NaCl), 553.7, 668.4, 815.2, 914.5, 1092.2, 1164.0, 1340.1, 1449.7, 1494.9, 1598.6, 1738.5, 2249.5 cm^{-1} ; m/z (ESI) 427.4 ($\text{M} - \text{H}$) $^-$.

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(R)-Ethyl 2-((2R,3R,5R)-2-allyl-tetrahydro-5-phenylfuran-3-yl)-2-(tosylamino)acetate (15) : To a mixture of freshly distilled α -N-tosyl imino ester **1** (72.2 mg, 0.283 mmol) and (R)-2,3-dihydro-2-phenylfuran **11** (50.0 mg, 0.340 mmol) in dry CH_2Cl_2 (3.0 mL) at -78°C was added a solution of TiCl_4 (1.0 M in CH_2Cl_2 , 0.36 mmol) and the resulting orange solution were stirred at -78°C for 50 mins. Dry acetonitrile (58.1 mg, 1.42 mmol) was added at -78°C and the mixture was stirred at -78°C for 10 mins. Allyltrimethylsilane (65.2 mg, 0.570 mmol) was added and the mixture was stirred at -78°C for an hour. Then the mixture was warmed to -20°C and stirred at -20°C for two hours. Then the mixture was recooled to -30°C and the reaction was quenched carefully with 10 mL ice-cooled saturated sodium bicarbonate solution. After the mixture was warmed to room temperature, the aqueous layer was extracted with dichloromethane (3 X 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford the α -N-tosylamino ester **15** (89.1 mg, 71% yield) as a yellow oil, $R_f = 0.38$ (40% EtOAc in hexane), $[\alpha]^{23}_{\text{D}} = -9.6^{\circ}$ (c 1.0, CHCl_3); ^1H NMR(400MHz, CDCl_3) : δ 1.05 (t, $J = 7.1$ Hz, 3H), 1.80 (m, 1H), 2.21 (m, 1H), 2.31 (m, 1H), 2.38 (m, 2H), 2.42 (s, 3H), 3.90 (m, 3H), 4.05 (m, 1H), 4.89 (t, $J = 7.7$ Hz, 1H), 5.12 (m, 2H), 5.40 (d, $J = 9.9$ Hz, 1H), 5.89 (m, 1H), 7.33-7.23 (m, 7H), 7.73 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 13.8 (CH_3), 21.5 (CH_3), 36.1 (CH_2), 38.6 (CH_2), 45.9 (CH), 55.9 (CH), 62.0 (CH_2), 79.5 (CH), 79.6 (CH), 117.7 (CH_2), 125.7 (CH), 127.4 (CH), 128.3 (CH), 129.7 (CH), 134.1 (C), 136.3 (C), 142.1 (C), 144.0 (C), 171.0 (CO); FT-IR (film, NaCl), 545.1, 667.9, 816.2, 1025.4, 1093.9, 1163.2, 1349.2, 1746.9, 2980.6 cm^{-1} ; m/z (ESI) 444.1 ($\text{M} + \text{H}$) $^+$, 466.3 ($\text{M} + \text{Na}$) $^+$.

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(R)-ethyl 2-((3R,5R)-tetrahydro-5-(naphthalen-2-yl)furan-3-yl)-2-(tosylamino)acetate (16) : The procedure described for **13** was used for **16**. α -N-tosyl imino ester **1** (76.6 mg, 0.300 mmol), (R)-2,3-dihydro-2-(naphthalen-2-yl)furan **12** (70.3 mg, 0.360 mmol), TiCl_4 (1M in CH_2Cl_2 , 0.360 mmol), acetonitrile (61.6 mg, 1.50 mmol) and triethylsilane (174 mg, 1.50 mmol) to afford **16** (89.0 mg, 65% yield) as a yellow oil, $R_f = 0.40$ (hex : EtOAc = 1 : 1), $[\alpha]_D^{23} = -25.2^\circ$ (c 1.00, CHCl_3); ^1H NMR(500MHz, CDCl_3): δ 1.07 (t, $J = 7.2$ Hz, 3H), 2.04 (m, 1H), 2.40 (m, 1H), 2.41 (s, 3H), 2.64 (m, 1H), 3.87-3.93 (m, 4H), 4.17 (dd, $J = 9.0, 7.0$ Hz, 2H), 5.17 (t, $J = 7.0$ Hz, 1H), 5.31 (d, $J = 9.5$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.36 (dd, $J = 8.5, 1.5$ Hz, 1H), 7.46 (m, 2H), 7.74 (d, $J = 8.0$ Hz, 3H), 7.81 (d, $J = 8.5$ Hz, 3H); ^{13}C NMR (125MHz, CDCl_3) δ 13.9 (CH_3), 21.6 (CH_3), 36.7 (CH_2), 42.4 (CH), 56.8 (CH), 62.0 (CH_2), 70.0 (CH_2), 80.0 (CH), 123.7 (CH), 123.9 (CH), 125.8 (CH), 126.2 (CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 129.8 (CH), 132.8 (C), 133.2 (C), 136.4 (C), 140.0 (C), 144.0 (C), 171.0 (CO); FT-IR (film, NaCl) 550.9, 593.0, 675.2, 737.1, 817.5, 1029.7, 1091.7, 1161.9, 1349.3, 1599.0, 1743.8 cm^{-1} ; m/z (ESI) 454.1 ($\text{M} + \text{H}$) $^+$.

17

(R)-ethyl 2-((2S,3R,5R)-2-cyano-tetrahydro-5-(naphthalen-2-yl)furan-3-yl)-2-(tosylamino)acetate (17) : The procedure described for **5b** was used for **17**. α -N-tosyl imino ester **1** (76.6 mg, 0.300 mmol), (R)-2,3-dihydro-2-(naphthalen-2-yl)furan **12** (70.3 mg, 0.360 mmol), TiCl_4 (1M in CH_2Cl_2 , 0.36 mmol) and trimethylsilyl cyanide (89.3 mg, 0.900 mmol) to afford **17** (84.7 mg, 59% yield) as a yellow oil, $R_f = 0.40$ (hex : EtOAc = 1 : 1), $[\alpha]_D^{23} = -55.2^\circ$ (c 1.05, CHCl_3); ^1H NMR(400MHz, CDCl_3): δ 1.05 (t, $J = 7.1$ Hz, 3H), 2.19 (m, 1H), 2.41 (s, 3H), 2.52 (m, 1H), 2.97 (m, 1H), 3.97 (m, 3H), 4.90 (d, $J = 6.5$ Hz, 1H), 5.35 (t, $J = 6.9$ Hz, 1H), 5.70 (d, $J = 5.3$ Hz, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.39 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.48 (m, 2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.82 (m, 4H); ^{13}C NMR (100MHz, CDCl_3) δ 13.8 (CH_3), 21.6 (CH_3), 35.6 (CH_2), 47.5 (CH), 55.0 (CH), 62.8 (CH_2), 68.4 (CH), 82.0 (CH), 118.2 (CN), 123.2 (CH), 124.4 (CH), 126.2 (CH), 126.4 (CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.6 (CH), 129.9 (CH), 133.0 (C), 135.7 (C), 137.6 (C), 144.4 (C), 169.6 (CO); FT-IR (film, NaCl), 667.6, 817.2, 1092.0, 1163.7, 1446.5, 1738.2, 2820.8, 2922.3 cm^{-1} ; m/z (ESI) 477.5 ($\text{M} - \text{H}$) $^-$.

18

(R)-ethyl 2-((2R,3R,5R)-2-allyl-tetrahydro-5-(naphthalen-2-yl)furan-3-yl)-2-(tosylamino)acetate (18) : The procedure described for **15** was used for **18**. α -N-tosyl imino ester **1** (76.6 mg, 0.300 mmol), (R)-2,3-dihydro-2-(naphthalen-2-yl)furan **12** (70.6 mg, 0.360 mmol), TiCl_4 (1M in CH_2Cl_2 , 0.36 mmol), acetonitrile (61.6 mg, 1.50 mmol) and allyltrimethylsilane (68.6 mg, 0.600 mmol) to afford **18** (104.8 mg, 71% yield) colorless oil, $R_f = 0.48$ (Hex : EtOAc = 3 : 2), $[\alpha]_D^{23} = -17.0^\circ$ (c 0.73, CHCl_3); ^1H NMR (500MHz, CDCl_3): δ 1.06 (t, $J = 7.0$ Hz, 3H), 1.87 (m, 1H), 2.29-2.39 (m, 2H), 2.42 (s, 3H), 2.48 (m, 2H), 3.87-3.97 (m, 3H), 4.13 (q, $J = 6.0$ Hz, 1H), 5.07 (t, $J = 7.5$ Hz, 1H), 5.14-5.21 (m, 2H), 5.41 (d, $J = 10.0$ Hz, 1H), 5.92-5.98 (m, 1H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.40 (dd, $J = 8.5, 1.5$ Hz, 1H), 7.46 (m, 2H), 7.74-7.82 (m, 6H); ^{13}C NMR (125MHz, CDCl_3) δ 13.9 (CH_3), 21.6 (CH_3), 36.0 (CH_2), 38.7 (CH_2), 46.0 (CH), 56.0 (CH), 62.0 (CH_2), 79.6 (CH), 79.9 (CH), 117.8 (CH_2), 123.9 (CH), 124.4 (CH), 125.8 (CH), 126.1 (CH), 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 129.8 (CH), 132.9 (C), 133.2 (C), 134.2 (CH), 136.3 (C), 139.6 (C), 144.0 (C), 171.0 (CO); FT-IR (film, NaCl) 499.4, 666.2, 815.7, 1024.4, 1161.81, 1348.4, 1744.2 cm^{-1} ; m/z (ESI) 494.1 ($\text{M} + \text{H}$) $^+$, 516.2 ($\text{M} + \text{Na}$) $^+$.

Deprotection of tosyl group from **5a**

5a (84.8 mg, 0.231 mmol) was mixed with 1N LiOH (3.23 mL, 3.23 mmol) and THF (1.15 mL) and was stirred at room temperature for an hour. Then the solution was adjusted to pH = 2 with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuum. The crude product was used for the next reaction without purification. Thus, to a flask equipped with a condenser were added the crude product from last step, sodium phosphate dibasic (179.4 mg, 1.26 mmol), methanol (5.0 mL) and 3% Na/Hg (2.95 g, 3.83 mmol). The mixture was refluxed for one day. Then sodium phosphate dibasic (179.4 mg, 1.26 mmol) and 3% Na/Hg (2.95 g, 3.83 mmol) were added. The mixture was refluxed for another day. Water (2.0 mL) was used to quench the reaction. Mercury was removed and washed with methanol. The solution was concentrated. The resulting solid was dissolved in 10 mL methanol and sodium phosphate dibasic was removed by filtration. After removing the solvent from the filtrate, the crude product was further purified by column chromatography on silica gel (eluent: CHCl_3 : CH_3OH : aqueous ammonia = 5 : 3 : 1) to afford the desired product **7a** (41.8 mg, 98% yield, two steps) as a white solid, $R_f = 0.36$ (CHCl_3 : CH_3OH : aqueous ammonia =

5 : 3 : 1). ^1H NMR(500MHz, CD_3OD): δ 1.86 (ddd, $J = 15.0, 12.5, 7.5$ Hz, 1H), 2.08 (m, 1H), 2.25 (dt, $J = 14.5, 7.5$ Hz, 1H), 2.40 (m, 1H), 2.45 (m, 1H), 3.54 (d, $J = 6.0$ Hz), 3.81 (m, 2H), 3.97 (dt, $J = 11.0, 3.5$ Hz, 1H), 5.06 (dt, $J = 10.5, 1.0$ Hz, 1H), 5.13 (dd, $J = 15.5, 2.0$ Hz, 1H), 5.86 (m, 1H) ; ^{13}C NMR (125 MHz, CD_3OD), δ 28.0 (CH_2), 38.2 (CH_2), 44.6 (CH), 56.5 (CH), 66.0 (CH_2), 79.7 (CH), 116.5 (CH_2), 134.4 (CH), 171.9 (CO); FT-IR (film, NaCl), 575.4, 687.1, 1365.1, 1404.1, 1512.8, 1639.3 cm^{-1} ; HRMS (ESI), Calcd for $\text{C}_9\text{H}_{15}\text{NO}_3$: m/z 186.1130 ($\text{M} + \text{H}$) $^+$, found m/z 186.1127 ($\text{M} + \text{H}$) $^+$.

Determination of Diastereomeric Ratios:

The chiral products **13** – **18** was reduced to primary alcohol with LiAlH_4 in ethyl ether at 0°C , then the crude product was subject to coupling reaction with (*R*)-Mosher acid with the aid of EDCI and DMAP. The coupling product was purified by flash chromatography and the desired Mosher ester was taken ^{19}F NMR to determine the de% with integration.

Ref : Lee, J.; Kobayashi, Y.; Tezuka, K.; and Kishi Y. *Org. Lett.*, **1999**, *1*, 2181-84.