

Diastereoselective synthesis of carbapenams *via* Kinugasa reaction

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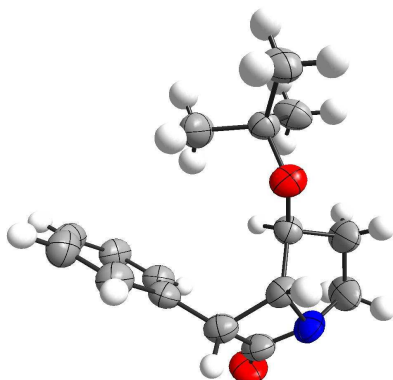
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Reaction of nitrones with acetylenes. General method: To a suspension of CuI (1 mmol) in dry, degassed acetonitrile (3 mL), triethylamine (1 mmol) and hydrazine monohydrate (0.2 mmol) were added under nitrogen. After cooling to 0°C acetylene **4** was added (1 mmol). The mixture was stirred for 10 min and then solution of nitrone (2 mmol) in acetonitrile was added slowly at 0°C. After next 30 min the mixture was warmed up and stirred at room temperature under nitrogen. The progress of the reaction was monitored by TLC. At the end buffer solution (pH 7) and ethyl acetate were added. Aqueous layer was washed with ethyl acetate and combined organic layers were dried over anhydrous sodium sulfate. After removal of solvent, residue was separated by column chromatography. The 5,6-*cis/trans* ratio was assigned by HPLC or ¹H NMR. In the case of **5a/5b**, chromatography on silica gel caused isomerization of **5a** into **5b** therefore silica gel was replaced by Florisil.

(4*S*,5*R*,6*R*)-4-*tert*-butoxy-6-phenyl-1-azabicyclo[3.2.0]heptan-7-one (5a): colourless needles, m.p. 109-111°C (*t*-butylmethyl ether); [α]_D = -163.8 (*c* 0.45, CH₂Cl₂); IR (film) ν : 1749 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ : 7.4-6.9 (5H, Ph), 4.42 (1H, d, *J*=5.8 Hz, H-6), 3.69 (1H, dd, *J*=5.8, 4.5 Hz, H-5), 3.54 (1H, ddd, *J*=11.5, 8.1, 6.2 Hz, H-2), 3.46 (1H, ddd, *J*=10.2, 5.5, 4.5 Hz, H-4), 2.82 (1H, ddd, *J*=11.5, 8.1, 6.3 Hz, H-2') 1.70 (1H, m, H-3), 1.56 (1H, m, H-3'), 0.76 (9H, s, *t*-Bu); ¹³C NMR (125 MHz, C₆D₆) δ : 177.3, 134.4, 128.72, 128.71, 127.4, 73.5, 71.1, 63.6, 55.7, 44.5, 38.5, 28.3; MS (HR, ESI) *m/z* [M+Na⁺] Calcd. for C₁₆H₂₁NO₂Na 282.1465. Found 282.1471; Anal. Calcd. for C₁₆H₂₁NO₂: C 74.10, H 8.16, N 5.40. Found: C 74.08, H 8.09, N 5.38; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: *t* = 6.5 min (hexane/*i*-propanol 95:5 v/v, 1 mL/min).



(4*S*,5*R*,6*S*)-4-*tert*-butoxy-6-(*tert*-butyldiphenylsilyloxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (5b): colourless oil; [α]_D = -28.2 (*c* 0.78, CH₂Cl₂); IR (film) ν : 1766 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ : 8.0-7.20 (10H, 2xPh), 4.41 (1H, m, H-4), 3.87-3.77 (2H, m, *J* 11.2, 6.4, 4.0 Hz, CH₂OSi), 3.65-3.55 (2H, ddd, *J* 11.6, 8.0, 3.5 Hz for H-2 and *J* 5.8, 2.5 Hz for H-5), 3.26 (1H, ddd, *J* 6.4, 5.8, 4.0 Hz, H-6), 2.79 (1H, ddd, *J* 11.6, 8.9, 6.9 Hz, H-2') 1.96 (1H, m, H-3), 1.67 (1H, m, H-3'), 1.15 (9H, s, *t*-Bu), 1.06 (9H, s, *t*-Bu); ¹³C NMR (125 MHz, C₆D₆) δ : 177.1, 136.2, 135.9, 133.1, 132.9, 130.19, 130.14, 128.3, 128.2, 73.7, 70.7, 63.6, 59.8, 54.2, 45.2, 39.6, 28.5, 27.0, 19.3; HR MS (ESI) *m/z* [M+Na⁺] Calcd. for C₂₇H₃₇NO₃SiNa 474.2435. Found 474.2432; Anal. Calcd. for C₂₇H₃₇NO₃Si: C 71.80, H 8.26, N 3.10. Found: C 71.87, H 8.30, N 3.04; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: *t* = 9.5 min (hexane/*i*-propanol 95:5 v/v, 1 mL/min).

(4*S*,5*R*,6*R*)-4-*tert*-butoxy-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1-azabicyclo[3.2.0]heptan-7-one (5c): colourless oil; [α]_D = -22.0 (*c* 0.65, CH₂Cl₂); IR (film) ν : 1762 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.70-7.20 (10H, 2xPh), 3.91 (1H, m, H-4), 3.87-3.72 (2H, m, CH₂CH₂OSi), 3.62 (1H, m, H-6), 3.57-3.51 (2H, dd, *J* 5.4, 4.1 Hz for H-5 and *J* 11.6, 7.9, 5.4 Hz for H-2), 2.95 (1H, m, H-2') 2.05 (1H, m, H-3), 1.95-1.83 (2H, m, H-3', CHHCH₂OSi), 1.73 (1H, m, CHHCH₂OSi), 1.13 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu); ¹³C NMR (125 MHz, CDCl₃) δ : 180.9, 135.5, 133.6, 129.7, 127.7, 74.1, 70.4, 62.1, 61.5, 47.0, 44.2,

38.8, 28.5, 26.8, 19.2; HR MS (ESI) m/z $[M+Na^+]$ Calcd. for $C_{28}H_{39}NO_3NaSi$ 488.2591. Found 488.2574; Anal. Calcd. for $C_{28}H_{39}NO_3Si$: C 72.21, H 8.44, N 3.01. Found: C 72.19, H 8.48, N 2.96; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: $t = 13.5$ min (hexane/*i*-propanol 90:10 v/v , 1 mL/min).

Benzyl ((4*S*,5*R*,6*R*)-4-*tert*-butoxy-7-oxo-1-azabicyclo[3.2.0]heptan-6-yl)methylcarbamate (5e).

colourless oil; $[\alpha]_D^{20} = +20.5$ (c 1.8, CH_2Cl_2); IR (film) ν : 1761, 1721 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ : 7.40-6.90 (5H, Ph), 5.13-4.97 (2H, OCH_2Ph), 4.87 (1H, br s, NH), 3.90 (1H, br m, H-4), 3.47-3.35 (3H, H-2, H-5, $CHHNHCbz$), 3.15-3.00 (2H, H-6, $CHHNHCbz$), 2.65 (1H, m, H-2'), 1.65-1.45 (2H, H-3), 0.99 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) δ : 176.9, 154.9, 135.9, 127.3, 127.1, 126.9, 72.6, 68.8, 65.5, 61.3, 49.6, 43.7, 37.8, 36.0, 26.9; HR MS (ESI) m/z $[M+Na^+]$ Calcd. for $C_{19}H_{26}N_2O_4Na$ 369.1790. Found 369.1782; Anal. Calcd. for $C_{19}H_{26}N_2O_4$: C 65.87, H 7.56, N 8.09. Found: C 65.79, H 7.61, N 8.08; CC: florisil, hexane-ethyl acetate (5:1 v/v); HPLC: $t = 9.2$ min (hexane/*i*-propanol 90:10 v/v , 1 mL/min);

(4*S*,5*R*,6*S*)-4-*tert*-butoxy-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (5f) colourless oil; $[\alpha]_D^{20} = 72.2$ (c 1.87, CH_2Cl_2); IR (film) ν : 1768 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ : 4.54 (1H, dt, H-4), 4.49 (1H, d, J 5.3 Hz, $CH(OEt)_2$), 3.71 (1H, ddd, J 11.7, 8.1, 1.8 Hz, H-2), 3.63 (1H, dd, J 6.2, 1.6 Hz, H-5), 3.54 (1H, dd, J 6.2, 5.3 Hz, H-6), 3.51-3.38 (3H, OCH_2CH_3), 3.24 (1H, m, $OCHHCH_3$), 2.84 (1H, m, H-2), 2.04 (1H, m, H-3), 1.66 (1H, m, H-3'), 1.14 (9H, s, *t*-Bu), 1.08-1.02 (6H, 2xt, OCH_2CH_3); ^{13}C NMR (125 MHz, C_6D_6) δ : 176.0, 100.1, 73.8, 71.3, 63.5, 63.4, 63.1, 56.3, 46.1, 39.3, 28.5, 15.4; HR MS (ESI) m/z $[M+Na^+]$ Calcd. for $C_{15}H_{27}NO_4Na$ 308.1832. Found 308.1842; Anal. Calcd. for $C_{15}H_{27}NO_4$: C 63.13, H 9.54, N 4.91. Found: C 63.19, H 9.65, N 5.02; CC: florisil, hexane-ethyl acetate (9:1 v/v).

(4*S*,5*R*,6*S*)-4-*tert*-butoxy-6-phenyl-1-azabicyclo[3.2.0]heptan-7-one (6a): colourless crystals, m.p. 107-109°C (benzene); $[\alpha]_D^{20} = -27.4$ (c 0.25, CH_2Cl_2); IR (film) ν : 1758 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ : 7.4-6.9 (5H, Ph), 3.84 (1H, d, J 2.2 Hz, H-6), 3.60 (1H, m, H-2), 3.45 (1H, m, H-2'), 3.40 (1H, dd, J 5.0, 2.2 Hz, H-5), 2.72 (1H, ddd, J 13.4, 8.4, 5.0 Hz, H-4), 1.84-1.65 (2H, H-3), 0.94 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) δ : 174.9, 136.4, 129.1, 128.3, 127.6, 74.9, 73.6, 65.9, 60.6, 43.8, 37.8, 28.3; HR MS (ESI) m/z $[M+Na^+]$ Calcd. for $C_{16}H_{21}NO_2Na$ 282.1465. Found 282.1466; Anal. Calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40. Found: C 74.14, H 8.22, N 5.55; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: $t = 9.5$ min (hexane/*i*-propanol 95:5 v/v , 1 mL/min).

(4*S*,5*R*,6*R*)-4-*tert*-butoxy-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (6f) colourless oil; $[\alpha]_D^{20} = -74.8.0$ (c 0.53, CH_2Cl_2); IR (film) ν : 1765 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ : 4.54 (1H, dt, H-4), 4.49 (1H, d, J 5.3 Hz, $CH(OEt)_2$), 3.71 (4H, H-2, $OCHHCH_3$, OCH_2CH_3), 3.47-3.35 (3H, H-2', H-4, $OCHHCH_3$), 3.11 (1H, dd, J 5.1, 2.5 Hz, H-6), 2.71 (1H, m, H-3), 1.67 (1H, m, H-3'), 1.15-1.05 (6H, 2xt, OCH_2CH_3), 1.07 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) δ : 174.5, 100.5, 74.4, 63.1, 62.3, 60.6, 60.1, 44.6, 38.2, 28.4, 28.0, 15.4; Anal. Calcd. for $C_{15}H_{27}NO_4$: C 63.13, H 9.54, N 4.91. Found: C 63.22, H 9.60, N 4.93; HR MS (ESI) m/z $[M+Na^+]$ Calcd. for $C_{15}H_{27}NO_4Na$ 308.1832. Found 308.1825; CC: florisil, hexane-ethyl acetate (9:1 v/v).

(3*S*,4*S*,3*S*,6*S*)-3,4-di-*tert*-butoxy-6-phenyl-1-azabicyclo[3.2.0]heptan-7-one (7) colourless oil; $[\alpha]_D^{20} = +163.1$ (c 0.85, CH_2Cl_2); IR (film) ν : 1767 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ : 7.40-6.98 (5H, Ph), 4.52 (1H, d, J 5.4 Hz, H-6), 3.86 (1H, m, H-3), 3.69-3.62 (3H, H-2, H-4, H-5), 2.98 (1H, dd, J 12.25, 4.9 Hz, H-2'), 0.93 (9H, s, *t*-Bu), 0.85 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) δ : 176.7, 134.6, 129.1, 128.3, 127.3, 83.3, 77.3, 74.0, 73.9, 64.2, 57.6, 53.1, 28.5; Anal. Calcd. for $C_{20}H_{29}NO_3$: C 72.47, H 8.82, N 4.23. Found: C 72.37, H 8.91, N 4.41; HR MS (ESI) m/z $[M+Na^+]$ Calcd. for $C_{20}H_{29}NO_3Na$ 354.2040. Found 354.2052; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: $t = 5.5$ min (hexane/*i*-propanol 95:5 v/v , 1 mL/min).

(3*R*,5*R*,6*S*)-3-*tert*-butoxy-6-phenyl-1-azabicyclo[3.2.0]heptan-7-one (9) colourless crystals; m.p. 70-73°C (benzene); $[\alpha]_D -221.0$ (c 0.2, CH₂Cl₂); IR (film) ν : 1757cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ : 7.40-6.98 (5H, Ph), 4.46 (1H, d, *J* 5.7 Hz, H-6), 3.91 (1H, m, H-3), 3.48 (1H, *J* 11.2, 5.6 Hz, H-2), 3.41 (1H, m, H-5), 2.80 (1H, dd, *J* 11.2, 6.7 Hz, H-2'), 1.49 (1H, m, H-4), 1.28 (1H, m, H-4'), 0.86 (9H, s, *t*-Bu); ¹³C NMR (125 MHz, C₆D₆) δ : 176.6, 134.9, 128.7, 128.6, 127.1, 76.4, 73.3, 56.9, 55.9, 53.0, 35.9, 28.1; Anal. Calcd. for C₁₆H₂₁NO₂: C 74.10, H 8.16, N 5.40. Found: C 74.21, H 8.24, N 5.47; HR MS (ESI) *m/z* [M+Na⁺] Calcd. for C₁₆H₂₁NO₂Na 282.1465. Found 282.1476; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: *t* = 7.5 min (hexane/*i*-propanol 95:5 v/v, 1 mL/min).

(3*S*,5*S*,6*S*)-3-*tert*-butoxy-6-phenyl-1-azabicyclo[3.2.0]heptan-7-one (10) colourless crystals; m.p. 61-63°C (benzene); $[\alpha]_D +174.7$ (c 0.6, CH₂Cl₂); IR (film) ν : 1760cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ : 7.40-6.90 (5H, Ph), 4.38 (1H, d, *J* 5.6 Hz, H-6), 3.91 (1H, *J* 8.2, 6.2, 5.6 Hz, H-5), 3.80 (1H, m, H-3), 3.69 (1H, dd, *J* 11.8, 5.6 Hz, H-2), 2.71 (1H, dd, *J* 11.8, 2.5 Hz, H-2'), 1.42 (1H, ddd, *J* 13.5, 6.2, 2.5 Hz, H-4), 1.03 (1H, ddd, *J* 13.5, 8.2, 6.1 Hz, H-4'), 0.87 (9H, s, *t*-Bu); ¹³C NMR (125 MHz, C₆D₆) δ : 177.2, 135.0, 128.7, 128.3, 127.1, 75.9, 73.5, 56.9, 55.4, 54.5, 36.7, 28.1; Anal. Calcd. for C₁₆H₂₁NO₂: C 74.10, H 8.16, N 5.40. Found: C 74.28, H 8.20, N 5.49; HR MS (ESI) *m/z* [M+Na⁺] Calcd. for C₁₆H₂₁NO₂Na 282.1465. Found 282.1455; CC: florisil, hexane-diethyl ether (85:15 v/v); HPLC: *t* = 4.6 min (hexane/*i*-propanol 95:5 v/v, 1 mL/min).

