One-Pot Synthesis of Homoallylic Ketones from the Addition of Vinyl Grignard Reagent to Carboxylic Esters

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General Experimental Methods.

For reactions performed under anhydrous conditions, glassware was either oven- or flame-dried and the reaction was run under a positive pressure of argon. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Vinylmagnesium bromide reagent was either used as supplied (Aldrich) as a 1 *M* solution in THF, or freshly prepared[1] as a solution in THF from Mg (Aldrich; 99.98 % purity) and vinyl bromide (Aldrich; 98 %). The Grignard reagents were titrated against menthol and 2,2'-dipyridyl. CuCN was used as supplied (Aldrich; 99 % purity) and $Cu(OAc)_2\cdot H_2O$ (J.T. Baker; 99.7 % purity) was recrystallized from hot aqueous acetic acid solution (50% v/v) prior to use. Anhydrous $Cu(OAc)_2$ was prepared by heating freshly recrystallized $Cu(OAc)_2\cdot H_2O$ *in-vacuo* (150 °C) until a constant weight was achieved. Amino acids were obtained from Aldrich (threonine and alanine) or Avocado Research Chemicals (proline and serine), and were *N*-protected using standard procedures. (2*RS*)- and (2*S*)-1-benzenesulfonyl-pyrrolidine-2-carbonyl chloride was synthesized as previously described.[2] Flash chromatography was performed using silica gel (Silicycle; 230-400 mesh), neutral alumina (Aldrich; Brockmann I, 150 mesh), basic alumina (Acros; 50-200 mesh) and Florisil (Aldrich; 100-200 mesh). Analytical thin-layer chromatography was conducted with Silicycle silica gel F_{254} plates. NMR spectra were run at 400 MHz on a Bruker AV400. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. HRMS (EI and FAB) were obtained by the Université de Montréal Mass Spectroscopy facility. The reported yields are the actual isolated yields of purified material and are not optimized.

Procedure A: Preparation of compounds (2a, 2b, 2e, 2k, 2o)

Vinylmagnesium bromide reagent was added via syringe to a flame-dried two-neck flask. With rapid stirring, the reagent was cooled to −45 °C (dry ice/acetonitrile). On occasion, a little THF was added to the flask to facilitate stirring. While maintaining a positive pressure of argon, solid $Cu(OAc)_2$ was added as quickly as possible to the reaction flask, and the flask was re-sealed. After stirring for 10 min, a solution of the ester in THF (2 mL per 1 mmol ester) was added over 5 min, and the resultant mixture was stirred for 1 h. The cold bath was then removed and replaced with an ice bath, and stirring maintained at 0 °C for 1 h. With the ice bath in place, the reaction mixture was allowed to slowly warm to room temperature with overnight stirring. The reaction mixture was quenched by treatment with saturated NH_4Cl solution (200% v/v based on total reaction volume) at 0 °C. After vigorous shaking, the layers were separated, and the aqueous phase extracted with Et_2O or EtOAc. The combined extracts were washed with saturated NH_4Cl solution (x 1), saturated $NaHCO_3$ solution (x 1), pH 6.8 phosphate buffer (x 1), brine (x 1), dried ($MgSO_4$) and evaporated. The crude product was then purified as specified.

Note: The $Cu(OAc)_2$ could also be pre-dissolved with the ester in THF prior to reaction with the Grignard reagent at −45 °C with similar outcome.

Procedure B: Preparation of compound (2d)

Identical to general procedure A, with the exception that after stirring the reaction mixture at −45 °C for 1h, stirring was maintained at 0 °C for the specified time, and then worked up as in procedure A. The crude product was purified as specified.

Procedure C: Preparation of compounds (2f, 2g)

Identical to procedure A, with the following exceptions- 1: after completion of the reaction, NaH_2PO_4 solution (200% v/v based on total reaction volume; 2*M* aqueous) was substituted for saturated NH_4Cl solution as quenching reagent; 2: in the case of compound **2f**, stirring was maintained at 0 °C for 15 min before workup. The crude product was then purified as specified.

Procedure D: Preparation of compounds (2i, 2l, 2n)

Identical to procedure A, with the exception that the reaction was run in the absence of copper catalyst. The crude product was then purified as specified.

Procedure E: Preparation of compound (2m)

Identical to procedure A, with the following exceptions- 1: the reaction was run in the absence of copper catalyst and, 2: after completion of the reaction, pH 6.8 phosphate buffer solution (200% v/v based on total reaction volume) was substituted for saturated NH_4Cl solution as quenching reagent. The crude product was then purified as specified.

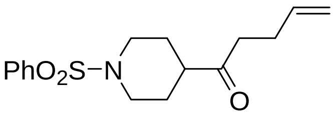
Procedure F: Preparation of compounds (2c, 2j)

A suspension of CuCN in THF (2 mL per 1 mmol CuCN) was cooled to –78 °C, and vinylmagnesium bromide reagent was added over 10 min, followed by a solution of the ester in THF (2 mL per 1 mmol ester). With the cold bath in place, the resultant mixture was allowed to slowly warm to room temperature with overnight stirring. The reaction mixture was quenched by treatment with HCl solution (1*M*, aqueous) (200% v/v based on total reaction volume) at 0 °C. After vigorous shaking, the layers were separated, and the aqueous phase extracted with Et_2O or EtOAc. The combined extracts were washed with saturated $NaHCO_3$ solution (x 1), pH 6.8 phosphate buffer (x 1), brine (x 1), dried ($MgSO_4$) and evaporated. The crude product was then purified as specified.

Procedure G: Preparation of compound (2h)

Identical to procedure F, with the following exception: after completion of the reaction, work up was achieved by pouring the crude reaction mixture onto a rapidly stirred mixture of NaH_2PO_4 solution (2*M*, aqueous; 100 mL) and Et_2O (100 mL) at 0 °C. After separation of the layers, the aqueous phase was extracted with Et_2O (x 2), and the combined organic phase was washed with saturated $NaHCO_3$ solution (x 1), brine (x 1), dried ($MgSO_4$) and evaporated. The crude product was then purified as specified.

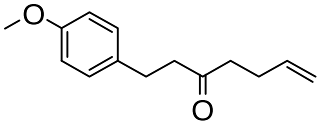
1-(1-Benzenesulfonyl-piperidin-4-yl)-pent-4-en-1-one (2a)



Prepared from methyl ester **1a** (281 mg, 1 mmol) and vinyl magnesium bromide (4 mmol) in the presence of $Cu(OAc)_2$ (0.5 mmol) according to procedure A (reaction time 12 h at room temperature) to yield crude product (264 mg). Purification by chromatography over silica gel (40:60 Et_2O/hexanes) gave **2a** as a cream colored solid (135 mg, 44 %). Recrystallization from EtOAc/hexanes gave pearly leaflets, mp 82-84 °C. TLC Rf 0.47 (20:80 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (dddd, J = 11.4, 11.4, 11.4, 4.0 Hz, 2H), 1.79-1.91 (m, 2H), 2.16-2.29 (m, 3H), 2.35 (dt, *J* = 11.7, 2.3 Hz, 2H), 2.45 (t, J = 7.4 Hz, 2H), 3.63-3.75 (m, 2H), 4.86-5.0 (m, 2H), 5.64-5.78 (m, 1H), 7.43-7.61 (m, 3H), 7.71 (d, J = 7.4

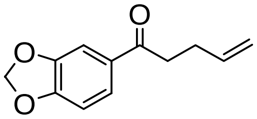
Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 136.8, 135.9, 132.8, 129.0, 127.5, 115.3, 47.2, 45.5, 39.5, 27.4, 26.8. HRMS (EI) m/z 307.1238 [M^+; calcd for $C_{16}H_{21}NO_3S$: 307.1242].

1-(4-Methoxy-phenyl)-hept-6-en-3-one (2b)



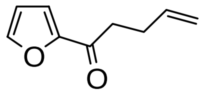
Prepared from methyl ester **1b** (408 mg, 2.1 mmol) and vinyl magnesium bromide (8.4 mmol) in the presence of $Cu(OAc)_2$ (0.63 mmol) according to procedure A (reaction time 12 h at room temperature) to yield crude product (475 mg). Purification by chromatography over basic alumina (activity grade I; 10:90 Et_2O/hexanes, increasing to 40:60 Et_2O/hexanes over 5 % increments) gave **2b** as a pale yellow oil (294 mg, 64 %). TLC R_f 0.33 (10:90 Et_2O/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25-2.34 (m, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.82 (t, *J* = 7.6 Hz, 2H), 3.75 (s, 3H), 4.90-5.04 (m, 2H), 5.70-5.83 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 157.8, 137.0, 133.0, 129.1, 115.1, 113.7, 55.1, 44.5, 41.9, 28.7, 27.6. HRMS (EI) m/z 218.1308 [M^+; calcd for $C_{14}H_{18}O_2$: 218.1307].

1-Benzo[1,3]dioxol-5-yl-pent-4-en-1-one (2c)



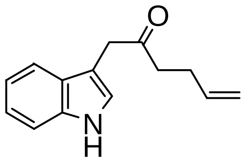
Prepared from methyl ester **1c** (360 mg, 2 mmol) and vinyl magnesium bromide (8.0 mmol) in the presence of CuCN (0.6 mmol) according to procedure F to yield crude product (340 mg). Purification by chromatography over silica gel (toluene) gave **2c** as a pale yellow oil (208 mg, 51 %). TLC R_f 0.37 (10:90 Et_2O/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40-2.47 (m, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 4.94-4.99 (m, 1H), 5.04 (dq, *J* = 16.0, 1.7 Hz, 1H), 5.79-5.92 (m, 1H), 6.0 (s, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.3, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 151.6, 148.1, 137.3, 131.7, 124.1, 115.2, 107.8, 101.8, 37.4, 28.3 (one line obscured). HRMS (EI) m/z 204.0792 [M^+; calcd for $C_{12}H_{12}O_3$: 204.0786].

1-Furan-2-yl-pent-4-en-1-one (2d)



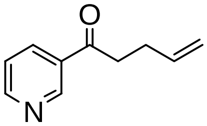
Prepared from methyl ester **1d** (126 mg, 1 mmol) and vinyl magnesium bromide (4.0 mmol) in the presence of Cu(OAc)$_2$ (0.5 mmol) according to procedure B (reaction time 1 h at 0 °C) to yield crude product (122 mg). Purification by chromatography over neutral alumina (activity grade I; 5:95 Et$_2$O/hexanes) gave **2d** as a yellow oil (72 mg, 48 %). R$_f$ 0.17 (5:95 Et$_2$O/hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.38-2.50 (m, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 4.93-5.00 (m, 1H), 5.00-5.10 (m, 1H), 5.75-5.92 (m, 1H), 6.49 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.15 (dd, *J* = 4.8, 0.9 Hz, 1H), 7.55 (dd, *J* = 1.6, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.7, 152.6, 146.2, 136.9, 116.9, 115.4, 112.1, 37.5, 28.0. HRMS (EI) m/z 150.0681 [M$^+$; calcd for $C_9H_{10}O_2$: 150.0681].

1-(1H-Indol-3-yl)-hex-5-en-2-one (2e)



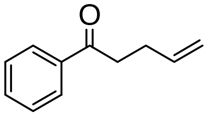
Prepared from methyl ester **1e** (190 mg, 1 mmol) and vinyl magnesium bromide (6 mmol) in the presence of Cu(OAc)$_2$ (0.5 mmol) according to procedure A (reaction time 12 h at room temperature) to yield crude product (261 mg). Purification by chromatography over silica gel (15:85 EtOAc/hexanes) gave **2e** as brown oil (79 mg, 37 %). TLC R$_f$ 0.47 (30:70 EtOAc/hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.23-2.34 (m, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 3.81 (s, 2H), 4.87-5.01 (m, 2H), 5.67-5.81 (m, 1H), 7.07-7.16 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 8.1-8.2 (br s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 208.6, 137.1, 136.1, 127.2, 123.1, 122.2, 119.8, 118.7, 115.1, 111.2, 108.6, 40.4, 40.0, 27.8. HRMS (EI) m/z 213.1156 [M$^+$; calcd for $C_{14}H_{15}NO$: 213.1154].

1-Pyridin-3-yl-pent-4-en-1-one (2f)



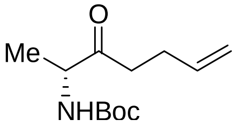
Prepared from methyl ester **1f** (306 mg, 2.2 mmol) and vinyl magnesium bromide (6.6 mmol) according to procedure C (reaction time 4 h at -45 °C) to yield crude product (338 mg). Purification by chromatography over basic alumina (activity grade I; 40:60 EtOAc/hexanes) gave **2f** as a yellow oil (147 mg, 42 %). R_f 0.24 (40:60 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42-2.52 (m, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 4.99 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.04 (dq, *J* = 17.0, 1.7 Hz, 1H), 5.79-5.92 (m, 1H), 7.38 (ddd, *J* = 8.0, 2.0, 1.9 Hz, 1H), 8.19 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.71-8.77 (m, 1H), 9.14 (d, *J* = 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 153.4, 149.6, 136.7, 135.3, 132.0, 123.6, 115.6, 38.0, 27.7. HRMS (EI) m/z 161.0842 [M^+; calcd for $C_{10}H_{11}NO$: 161.0841].

1-Phenyl-pent-4-en-1-one (2g)



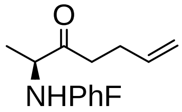
Prepared from methyl ester **1g** (1.36 g, 10 mmol) and vinyl magnesium bromide (30 mmol) according to procedure C to yield crude product (1.65 g). Short-path distillation gave the title compound as a pale yellow oil that was contaminated with ca. 5 % tertiary alcohol **3g** (1.11 g, 69 %). The contaminant could be removed by chromatography over basic alumina; thus a portion (210 mg) was chromatographed (10:90 Et_2O/hexanes elution) to yield pure product (181 mg) as a colourless oil. TLC Rf 0.49 (10:90 Et2O/hexanes). 1H NMR (400 MHz, $CDCl_3$) δ 2.43-2.57 (m, 2H), 3.08 (t, *J* = 7.4 Hz, 2H), 4.97-5.15 (m, 2H), 5.84-5.98 (m, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 137.2, 136.8, 132.9, 128.5, 127.9, 115.2, 37.6, 28.0. HRMS (EI) m/z 160.0895 [M^+; calcd for $C_{11}H_{12}$: 160.0888].

tert-Butyl-(1*R*)-1-methyl-2-oxo-hex-5-enylcarbamate (2h)



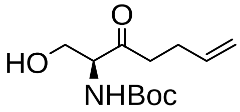
Prepared from methyl ester **1h** (1.0 mg, 4.92 mmol) and vinyl magnesium bromide (29.5 mmol) in the presence of CuCN (2.1 mmol) according to procedure G to yield crude product (1.32 g). Purification by chromatography over basic alumina (activity grade III; 2.5:97.5 Et_2O/toluene) gave **2h** as a pale yellow oil (862 mg, 77 %). TLC R_f 0.24 (20:80 Et_2O/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.0 Hz, 3H), 1.41 (s, 9H), 2.26-2.38 (m, 2H), 2.48-2.68 (m, 2H), 4.22-4.34 (m, 1H), 4.92-5.07 (m, 2H), 5.24-5.34 (m, 1H), 5.70-5.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 155.1, 136.7, 115.4, 79.6, 55.0, 38.1, 28.2, 27.4, 17.7. HRMS (EI) m/z 227.1523 [M^+; calcd for $C_{12}H_{21}NO_3$: 227.1521]. $[\alpha]_D^{20}$ = –28 ° (c 0.01, $CHCl_3$).

(2*S*)-2-(9-Phenyl-9H-fluoren-9-ylamino)-hept-6-en-3-one (2i)



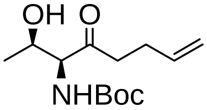
Prepared from methyl ester **1i** (343 mg, 1 mmol) and vinyl magnesium bromide (6 mmol) according to procedure D (reaction time 48 h at room temperature) to yield crude product (324 mg). Purification by chromatography over silica gel gave (in order of elution) **2i** as a pale yellow solid (96 mg, 26 %) followed by recovered starting material (102 mg). Recrystallization of **2i** from $(^iPr)_2O$ gave colorless blocks, mp 104-107 °C. TLC R_f 0.40 (10:90 Et_2O/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, *J* = 7.1 Hz, 3H), 1.52-1.61 (m, 1H), 1.81-2.03 (m, 2H), 2.12-2.21 (m, 1H), 2.68 (q, *J* = 7.1 Hz, 1H), 3.44 (br s, 1H), 4.81-4.84 (m, 1H), 4.86 (t, *J* = 1.3 Hz, 1H), 5.49-5.60 (m, 1H), 7.05-7.42 (m, 11H), 7.65-7.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 149.9, 149.5, 144.5, 141.0, 139.9, 137.0, 128.2, 128.0, 127.7, 127.1, 126.4, 126.1, 125.3, 119.8, 119.7, 114.9, 73.1, 56.7, 39.0, 27.3, 20.8. HRMS (FAB) m/z 368.2022 [M+H$^+$; calcd for [$C_{26}H_{26}NO$]$^+$: 368.2009]. [α]$_D^{20}$ = +242 ° (c 0.01, CHCl$_3$).

***tert*-Butyl-(1*S*)-1-Hydroxymethyl-2-oxo-hex-5-enylcarbamate (2j)**



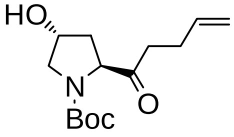
Prepared from methyl ester **1j** (877 mg, 4 mmol) and vinyl magnesium bromide (24 mmol) in the presence of CuCN (1.2 mmol) according to procedure F to yield crude product (1.01 g). Purification by chromatography over florisil (5:95 EtOAc/hexanes increasing to 100% EtOAc in 5 % increments) gave **2j** as an oil (576 mg, 59%). TLC R$_f$ 0.56 (60:40 EtOAc/hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.43 (s, 9H), 2.30-2.38 (m, 2H), 2.57-2.75 (m, 2H), 3.87 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.95 (dd, *J* = 11.5, 3.8 Hz, 1H), 4.26-4.34 (br s, 1H), 4.94-5.06 (m, 2H), 5.57-5.65 (br s, 1H), 5.71-5.84 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 207.6, 155.9, 136.7, 115.4, 80.1, 62.6, 61.5, 39.0, 28.2, 27.2. HRMS (EI) m/z 243.1471 [M$^+$; calcd for $C_{12}H_{21}NO_4$: 243.1471]. [α]$_D^{20}$ = +10 ° (c 0.01, CHCl$_3$).

***tert*-Butyl-(1*S*)-1-[(1*R*)-hydroxyethyl]-2-oxo-hex-5-enylcarbamate (2k)**



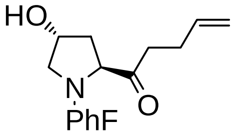
Prepared from methyl ester **1k** (489 mg, 2.1 mmol) and vinyl magnesium bromide (12.6 mmol) in the presence of Cu(OAc)$_2$ (0.63 mmol) according to procedure A (reaction time 12 h at room temperature) to yield crude product (512 mg). Purification by chromatography over basic alumina (activity grade I; 40:60 EtOAc/hexanes increasing to 90:10 EtOAc/hexanes in 10% increments) gave **2k** as pale yellow oil (265 mg, 49%). TLC R$_f$ 0.46 (40:60 EtOAc/hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.15 (d, *J* = 6.3 Hz, 3H), 1.40 (s, 9H), 2.25-2.34 (m, 2H), 2.56-2.78 (m, 2H), 4.16 (br d, *J* = 8.2 Hz, 1H), 4.22-4.33 (m, 1H), 4.88-5.04 (m, 2H), 5.45-5.54 (m, 1H), 5.68-5.82 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 208.8, 156.2, 136.8, 115.4, 80.0, 67.0, 63.9, 39.5, 28.2, 27.2, 19.4. HRMS (EI) m/z 257.1626 [M$^+$; calcd for $C_{13}H_{23}NO_4$: 257.1627]. $[\alpha]_D^{20}$ = –19 ° (c 0.01, $CHCl_3$).

***tert*-Butyl-(2*R*,4*S*)-4-Hydroxy-2-pent-4-enoyl-pyrrolidine-1-carbamate (2l)**



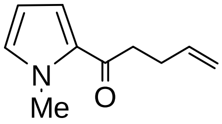
Prepared from methyl ester **1l** (PG = Boc) (270 mg, 1.1 mmol) and vinyl magnesium bromide (4.4 mmol) according to procedure D (reaction time 24 h at room temperature) to yield crude product (347 mg). Purification by chromatography over florisil (20:80 EtOAc) gave **2l** (PG = Boc) as a viscous oil which slowly crystallized on standing, (207 mg, 70 %). Recrystallisation from Et_2O/hexanes gave colorless needles, mp 104-106 °C. TLC R_f 0.21 (40:60 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.74-1.83 (br m, 1H), 1.83-2.02 (br m, 1H), 2.39-2.59 (br m, 1H), 3.13-3.26 (m, 1H), 3.52-3.71 (m, 1H), 4.11 (t, *J* = 8.2 Hz, 1H), 4.19-4.35 (br m, 1H), 5.08-5.25 (m, 2H), 5.29-5.52 (m, 2H), 5.78-5.99 (m, 2H), 6.49-6.72 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 139.4, 136.8, 116.2, 115.3, 81.0, 78.6, 68.9, 65.1, 56.3, 37.6, 28.2. HRMS (FAB) m/z 270.1719 [M+H$^+$; calcd for $[C_{14}H_{24}NO_4]^+$: 270.1700]. $[\alpha]_D^{20}$ = –60 ° (c 0.01, $CHCl_3$).

1-[(2*R*,4*S*)-4-Hydroxy-1-(9-phenyl-9H-fluoren-9-yl)-pyrrolidin-2-yl]-pent-4-en-1-one (2m)



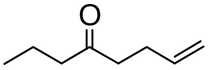
Prepared from methyl ester **1m** (5.0 g, 13 mmol) and vinyl magnesium bromide (65 mmol) according to procedure E (total reaction time ca. 7 days at room temperature) to yield crude product (5.26 g). Purification by chromatography over florisil (20:80 EtOAc/hexanes) gave **2m** as a semi-solid product (3.74 g, 70 %). Trituration of the product with Et_2O/hexanes (1:1) produced a white solid which could be collected by filtration. Recrystallization from Et_2O gave colorless needles, mp 101-103 °C. TLC R_f 0.35 (50:50 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 1.35-1.44 (m, 1H), 1.50 (d, *J* = 6.0 Hz, 1H), 1.61-1.75 (m, 2H), 1.85-2.06 (m, 2H), 2.11-2.21 (m, 1H), 2.99 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.23 (dd, *J* = 9.1, 5.6 Hz, 1H), 3.61 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.45 (sextet, *J* = 5.9 Hz, 1H), 4.89 (t, *J* = 1.4 Hz, 1H), 4.90-4.94 (m, 1H), 5.58-5.69 (m, 1H), 7.05-7.81 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 148.4, 145.5, 142.4, 141.8, 139.4, 137.4, 128.8, 128.4, 128.3, 127.7, 127.6, 127.4, 127.3, 126.8, 120.0, 119.7, 114.8, 77.2, 76.4, 70.2, 64.3, 57.1, 38.9, 38.7, 27.1. HRMS (FAB) m/z 410.2139 [M+H$^+$; calcd for $[C_{28}H_{28}NO_2]^+$: 410.2109]. $[\alpha]_D^{20}$ = +226 ° (c 0.01, $CHCl_3$).

1-(1-Methyl-1H-pyrrol-2-yl)-pent-4-en-1-one (2n)



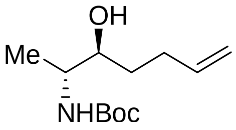
Prepared from methyl ester **1n** (306 mg, 2.2 mmol) and vinyl magnesium bromide (6.6 mmol) according to procedure D (reaction time 12 h at room temperature) to yield crude product (354 mg). Purification by chromatography over basic alumina (activity grade I; 5:95 Et_2O/hexanes) gave **2n** as pale yellow oil (128 mg, 36 %). TLC R_f 0.46 (10:90 Et_2O/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 2.37-2.46 (m, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 3.91 (s, 3H), 4.93-4.99 (m, 1H), 5.01-5.09 (m, 1H), 5.79-5.92 (m, 1H), 6.09 (dd, *J* = 4.0, 2.7 Hz, 1H), 6.75-6.79 (m, 1H), 6.93 (dd, *J* = 4.0, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 137.5, 130.8, 130.5, 118.8, 114.8, 107.7, 37.9, 37.5, 28.8. HRMS (EI) m/z 163.1007 [M$^+$; calcd for $C_{10}H_{13}NO$: 163.0997].

Oct-7-en-4-one (2o)



Prepared from methyl ester **1o** (1.02 g, 10 mmol) and vinyl magnesium bromide (40 mmol) in the presence of $Cu(OAc)_2$ (3 mmol) according to procedure A (reaction time 12 h at room temperature) to yield crude product (1.22 g). Purification by chromatography over florisil (hexane) gave **2o** as a pale yellow oil (353 mg, 29 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.84 (t, *J* = 8.0 Hz, 3H), 1.48-1.61 (m, 2H), 2.25 (q, *J* = 8.0 Hz, 2H), 2.32 (t, *J* = 8.0 Hz, 2H), 2.44 (t, *J* = 8.0 Hz, 2H), 4.87-5.02 (m, 2H), 5.66-5.79 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.1, 137.0, 114.9, 44.6, 41.6, 27.6, 17.1, 13.6.

***tert*-Butyl-(2*R*,3*S*)-3-hydroxy-hept-6-enyl-carbamate (4)**



A solution of **2h** (200 mg, 0.88 mmol) in EtOH (2 mL) was slowly added to a suspension of lithium tri-*tert*-butoxyaluminohydride (895 mg, 3.5 mmol) in EtOH (15 mL) at −78 °C. After 2 h, the reaction was poured onto a mixture of citric acid solution (10% aqueous, 100 ml)/ice (100 g)/EtOAc (50ml) with vigorous stirring. The layers were separated and the aqueous layer was extracted twice with EtOAc/CH$_2$Cl$_2$ (3:1). The combined extracts were washed with HCl solution (1 *M* aqueous) (x1), NaHCO$_3$ solution (saturated, aqueous) (x1), brine, dried and evaporated to afford crude alcohol **4** (169 mg). TLC R$_f$ 0.32 (25:75 EtOAc/hexanes). The ^{1}H NMR spectrum of the crude product (400 MHz) revealed a pair of well resolved methyl doublets (97:3 ratio): (2*R*,3*S*)-diastereomer (major): δ 1.05, *J* = 6.8 Hz; (2*R*,3*R*)-diastereomer (minor): δ 1.13, *J* = 6.8 Hz. Recrystallization of the crude product (hexane) gave a diastereomerically enriched sample (d.r. ≥ 99:1), mp 90-91 °C.

In an alternative procedure, reduction of compound **2h** with NaBH$_4$ in MeOH at 0 °C gave alcohol **4** with d.r. (2*R*,3*S*)-**4**:(2*R*,3*R*)-**4** = 75:25.

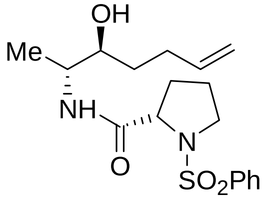
Peaks for major diastereomer (2*R*,3*S*)-**4**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.05 (d, *J* = 6.8 Hz, 3H), 1.40 (s, 9H) partially overlapped with 1.41-1.49 (m, 2H), 2.02-2.14 (m, 1H), 2.18-2.29 (m, 1H), 2.52 (br s, 1H), 3.58-3.71 (m, 2H), 4.81 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J*

= 10.1 Hz, 1H), 5.01 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.73-5.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 138.4, 115.2, 79.7, 74.1, 50.9, 32.6, 30.5, 28.6, 14.7. HRMS (EI) m/z 229.1682 [M^+; calcd for $C_{12}H_{23}NO_3$: 229.1678]. $[\alpha]_D^{20}$ = +16 ° (c 0.01, $CHCl_3$).

Peaks for minor diastereomer (2*R*,3*R*)-**4** (abstracted from 75:25 mixture obtained above): ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.5, 115.1, 79.5, 74.5, 50.5, 33.4, 30.1, 28.6, 18.4.

<u>Determination of enantiomeric purity</u>:

Example: Synthesis of (2'*S*)-*N*-[(2*R*,3*S*)-3-hydroxy-hept-6-enyl]-1-methylpyrrolidine-2-carboxamide (5)



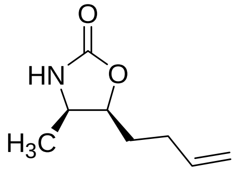
Alcohol **4** (as a 97:3 mixture of diastereomers, 9.9 mg, 0.043 mmol) was treated with a solution of TFA in CH_2Cl_2 (1:1, 1 mL) at 0 °C . After 1 h, the volatiles were removed under reduced pressure, and the resultant residue co-evaporated twice (1 mL each) from HCl saturated dioxane solution. The crude product was dissolved in CH_2Cl_2 (1 mL) containing DIPEA (30 μL, 0.17 mmol), and then treated with (2*RS*)- or (2*S*)-1-benzenesulfonyl-pyrrolidine-2-carbonyl chloride (1.16 mL of a 0.037*M* solution in CH_2Cl_2, equivalent to 11.8 mg, 0.043 mmol). After 3 h, the volatiles were removed under reduced pressure and the resultant residue taken up into EtOAc. The organic phase was washed with HCl solution (1*M* aqueous), $NaHCO_3$ solution (saturated, aqueous), brine, dried ($MgSO_4$) and evaporated to give the title compound (14.1 mg, 90%).

A portion was chromatographed (60:40 EtOAc/hexanes) for characterization. Peaks for major diastereomer (2*R*,3*S*,2'*S*)-**5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.9 Hz, 3H), 1.38-1.82 (m, 5H), 2.04-2.34 (m, 3H), 3.13-3.23 (m, 1H), 3.52-3.60 (m, 1H), 3.61-3.67 (m, 1H), 3.95-4.06 (m, 2H), 4.93-4.99 (m, 1H), 5.00-5.08 (m, 1H), 5.75-5.88 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 7.51-7.58 (m, 2H), 7.61-7.67 (m, 1H), 7.80-7.86 (m, 2H).

Analagous signals for (2*R*,3*S*,2'*R*)-**5**, if present in the *crude* product, were partially obscured by a small impurity peak which appeared in the vicinity of the methyl doublet for (2*R*,3*S*,2'*R*)-**5**, as shown by chemical shift comparison. Thus, diastereomeric alcohol mixture (2*R*,3*S*)-**4**:(2*R*,3*R*)-**4** = 75:25 (obtained from $NaBH_4$ reduction of **2h** as described above) was deprotected and coupled to (2*RS*)-1-benzenesulfonyl-pyrrolidine-2-carbonyl chloride in a manner analogous to that described above, to give a 3:3:1:1 ratio of (2*R*,3*S*,2'*R*)-**5**:(2*R*,3*S*,2'*S*)-**5**:(2*R*,3*R*,2'*S*)-**5**:(2*R*,3*R*,2'*R*)-**5**. Each diastereomer gave a well resolved methyl doublet in the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) at δ 1.13, 1.15, 1.19 and 1.22.

To confirm that the impurity peak did not arise from diastereomer (2*R*,3*S*,2'*R*)-**5**, the 3:3:1:1 diastereomeric mixture (2*R*,3*S*,2'*R*)-**5**:(2*R*,3*S*,2'*S*)-**5**:(2*R*,3*R*,2'*S*)-**5**:(2*R*,3*R*,2'*R*)-**5** was incrementally added to (2*R*,3*S*,2'*S*)-**5**. At levels approaching 1-2 %, diastereomeric signals for (2*R*,3*S*,2'*R*)-**5** were clearly visible, as shown by the appearance of the upfield methyl doublet at δ 1.13.

(4*R*,5*S*)-5-But-3-enyl-4-methyl-oxazolidin-2-one (6)



A solution of alcohol **4** (as 99:1 mixture of diastereomers, 30 mg, 0.031 mmol) in DMF (1 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil; 27 mg) in DMF (0.5 mL) at 0 °C, and the resultant mixture was stirred for 3h at room temperature. The reaction mixture was cooled to 0 °C, treated with NH_4Cl solution (saturated aqueous, 2 mL), diluted with water (5 mL), and extracted with a mixture of Et_2O/CH_2Cl_2 (2:1). The organic phase was washed with water (x 2), brine (x 1), dried ($MgSO_4$) and evaporated to give crude product (30 mg). Purification by chromatography over silica (50:50 EtOAc/hexanes) gave pure title compound (14.4 mg, 71%) as a colorless solid. TLC R_f 0.35 (60:40 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.5 Hz, 3H), 1.52-1.62 (m, 1H), 1.77-1.88 (m, 1H), 2.07-2.19 (m, 1H), 2.23-2.34 (m, 1H), 3.89 (q, *J* = 6.7 Hz, 1H), 4.52-4.60 (m, 1H), 4.97-5.02 (m, 1H), 5.02-5.09 (m, 1H), 5.72-5.84

(m, 1H), 5.91 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 136.9, 115.8, 79.2, 51.0, 29.9, 28.4, 15.9.

References

(1) Vogel, A. I. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., Rev.; Longman: London, 1989; p 539.
(2) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Amer. Chem. Soc.* **1984**, *106*, 1095-1098.