Supplementary Material (ESI) for Chemical Communications


# Bronsted acid catalyzed regioselective aza-Ferrier reaction: A novel synthetic method of α-(*N*-Boc-2-pyrrolidinyl)aldehydes

*Eiji Tayama,* Seijun Otoyama, and Wataru Isaka*

Graduate School of Science and Technology, Niigata University, Niigata 950-2181, Japan

E-mail: tayama@gs.niigata-u.ac.jp

## Electronic Supplementary Information

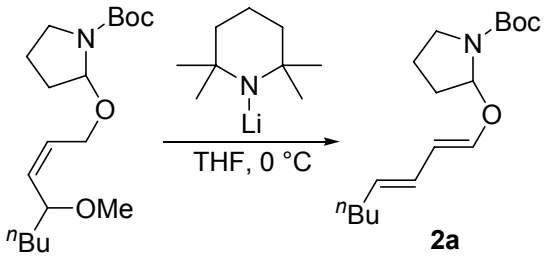
**Contents:**

**Experimental details and products characterization**

**General**: Infrared (IR) spectra were recorded on a HITACHI Infrared Spectrometer 270–30. $^{1}H$ and $^{13}C$ NMR spectra were measured on a JEOL JMN–Excalibur ($^{1}H$: 270 MHz, $^{13}C$: 68 MHz) and a Varian UNITY plus–500SW ($^{1}H$: 500 MHz, $^{13}C$: 125 MHz) spectrometers. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel $60F_{254}$) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan). The elemental analyses were recorded on a Yanaco CHN Corder, MT–3. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flask with a magnetic stirring bar under an atmosphere of dry argon. Tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc., Japan as anhydrous solvent. Dichloromethane was distilled from calcium hydride prior to use.

*The $^{13}C$ NMR analysis of (N-tert-butoxycarbonyl)pyrrolidines could not be performed because of low sensitivities of the rotamers.*

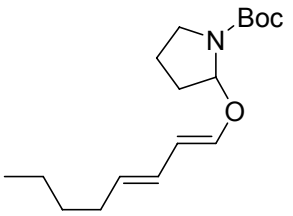
**Representative procedure of 1,4-Elimination Reaction:**




A solution of 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.6 mmol) in THF (3.5 mL) was treated with a 1.6 M hexane solution of *n*-butyllithium (0.94 mL, 1.5 mmol) at 0 °C and stirred for 30 min at room temperature. A solution of **1** (325 mg, 0.992 mmol) in THF (1.5 mL) was added to the solution at 0 °C and the reactant was stirred for 15 h at 0 °C. The resulting mixture was quenched with water and extracted with diethyl ether. The combined extracts were washed with brine, dried over sodium sulfate

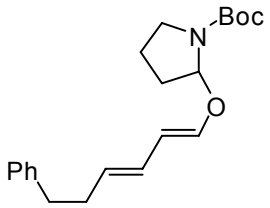
and concentrated. The residue was purified by chromatography on silica gel (hexane/diethyl ether = 5/1 as eluent) to obtain **2a** (239 mg, 82% yield) as a colorless oil.

**(1'*E*, 3'*E*)-*N*-*tert*-Butoxycarbonyl-2-(octa-1',3'-dien-1'-yloxy)pyrrolidine (2a):** colorless oil; 6:4



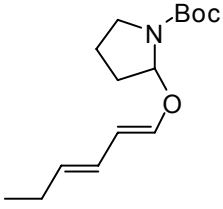

mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 6.70 (0.4H, d, *J* = 11.6 Hz, OC<u>H</u>=CHCH=CH), 6.52 (0.6H, d, *J* = 11.6 Hz, OC<u>H</u>=CHCH=CH), 5.98-5.76 (1H, br, OCH=CHC<u>H</u>=CH), 5.65-5.30 (2H, m, 2-H and OCH=CHCH=C<u>H</u>), 5.58 (1H, dd, *J* = 11.6, 10.9 Hz, OCH=C<u>H</u>CH=CH), 3.62-3.40 (1H, m, 5-H), 3.40-3.17 (1H, m, 5-H), 2.18-1.75 (6H, m, 3-H, 4-H, and OCH=CHCH=CHC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 1.48 (9H, s, *t*-Bu), 1.40-1.20 (4H, m, OCH=CHCH=CHCH$_2$(C<u>H</u>$_2$)$_2$CH$_3$), 0.88 (3H, t, *J* = 6.2 Hz, OCH=CHCH=CH(CH$_2$)$_3$C<u>H</u>$_3$); IR (film) 2956, 2924, 1710, 1660, 1624, 1478, 1454, 1390, 1324, 1286, 1254, 1148, 1118, 1086, 1030, 970, 942, 914, 882, 852, 770 cm$^{-1}$; Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12; H, 9.89; N, 4.74. Found: C, 69.42; H, 10.00; N, 4.65.

**(1'*E*, 3'*E*)-*N*-*tert*-Butoxycarbonyl-2-(6'-phenylhexa-1',3'-dien-1'-yloxy)pyrrolidine (2b):** colorless




oil; 5:5 mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 7.33-7.11 (5H, m, Ph), 6.72 (0.5H, d, *J* = 12.3 Hz, OC<u>H</u>=CHCH=CH), 6.53 (0.5H, d, *J* = 12.3 Hz, OC<u>H</u>=CHCH=CH), 6.02-5.80 (1H, m, OCH=CHC<u>H</u>=CH), 5.64-5.32 (2H, m, 2-H and OCH=CHCH=C<u>H</u>), 5.58 (1H, dd, *J* = 12.3, 10.9 Hz, OCH=C<u>H</u>CH=CH), 3.58-3.40 (1H, m, 5-H), 3.40-3.19 (1H, m, 5-H), 2.67 (2H, t, *J* = 7.6 Hz, OCH=CHCH=CHCH$_2$C<u>H</u>$_2$Ph), 2.47-2.27 (2H, m, OCH=CHCH=CHC<u>H</u>$_2$CH$_2$Ph), 2.18-1.69 (4H, m, 3-H and 4-H), 1.47 (9H, s, *t*-Bu); IR (film) 3020, 2972, 2924, 1704, 1658, 1624, 1478, 1452, 1384, 1324, 1286, 1254, 1146, 1092, 1030, 972, 940, 914, 882, 852, 770, 744, 698 cm$^{-1}$; Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.68; H, 8.65; N, 4.01.

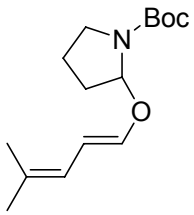
**(1'*E*, 3'*E*)-*N*-*tert*-Butoxycarbonyl-2-(hexa-1',3'-dien-1'-yloxy)pyrrolidine (2c):** colorless oil; 5:5




mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 6.72 (0.5H, d, *J* = 12.2 Hz, OC<u>H</u>=CHCH=CH), 6.53 (0.5H, d, *J* = 12.2 Hz, OC<u>H</u>=CHCH=CH), 5.98-5.75 (1H,

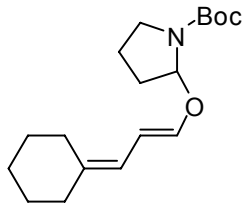
m, OCH=CHC<u>H</u>=CH), 5.65-5.32 (2H, m, 2-H and OCH=CHCH=C<u>H</u>), 5.59 (1H, dd, *J* = 12.2, 11.1 Hz, OCH=C<u>H</u>CH=CH), 3.60-3.40 (1H, m, 5-H), 3.40-3.17 (1H, m, 5-H), 2.19-1.73 (6H, m, 3-H, 4-H, and OCH=CHCH=CHC<u>H</u>$_2$CH$_3$), 1.48 (9H, s, *t*-Bu), 0.98 (3H, t, *J* = 7.3 Hz, OCH=CHCH=CHC<u>H</u>$_3$); IR (film) 2960, 2928, 2880, 1704, 1658, 1624, 1478, 1454, 1390, 1342, 1324, 1286, 1254, 1170, 1148, 1118, 1088, 1030, 972, 942, 914, 882, 852, 772 cm$^{-1}$; Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.18; H, 9.55; N, 5.12.

**(1'*E*)-*N*-*tert*-Butoxycarbonyl-2-(4'-methylpenta-1',3'-dien-1'-yloxy)pyrrolidine (2d):** colorless oil;



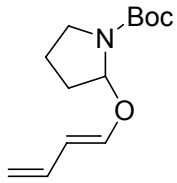

6:4 mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 6.71 (0.4H, d, *J* = 11.5 Hz, OC<u>H</u>=CHCH=C), 6.52 (0.6H, d, *J* = 11.5 Hz, OC<u>H</u>=CHCH=C), 5.79 (1H, dd, *J* = 11.5, 11.5 Hz, OCH=C<u>H</u>CH=C), 5.67 (0.6H, d, *J* = 11.5 Hz, OCH=CHC<u>H</u>=C), 5.63 (0.4H, d, *J* = 11.5 Hz, OCH=CHC<u>H</u>=C), 5.56 (0.4H, d, *J* = 3.5 Hz, 2-H), 5.38 (0.6H, d, *J* = 3.5 Hz, 2-H), 3.59-3.40 (1H, m, 5-H), 3.40-3.20 (1H, m, 5-H), 2.19-1.80 (4H, m, 3-H and 4-H), 1.74 (3H, s, OCH=CHCH=C(C<u>H</u>$_3$)$_2$), 1.67 (3H, s, OCH=CHCH=C(C<u>H</u>$_3$)$_2$), 1.48 (9H, s, *t*-Bu); IR (film) 2968, 2916, 1704, 1662, 1624, 1478, 1454, 1392, 1326, 1286, 1256, 1160, 1128, 1090, 1042, 980, 944, 916, 882, 854, 772 cm$^{-1}$; Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.08; H, 9.47; N, 5.15.

**(1'*E*)-*N*-*tert*-Butoxycarbonyl-2-(3'-cyclohexylideneprop-1'-en-1'-yloxy)pyrrolidine (2e):** colorless



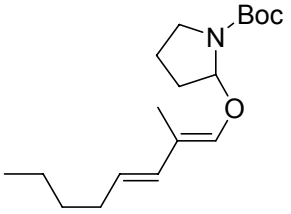

oil; 6:4 mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 6.73 (0.4H, d, *J* = 11.6 Hz, OC<u>H</u>=CHCH=C), 6.54 (0.6H, d, *J* = 11.6 Hz, OC<u>H</u>=CHCH=C), 5.83 (1H, dd, *J* = 11.6, 11.6 Hz, OCH=C<u>H</u>CH=C), 5.70-5.48 (1.4H, m, 2-H and OCH=CHC<u>H</u>=C), 5.38 (0.6H, d, *J* = 2.2 Hz, 2-H), 3.61-3.40 (1H, m, 5-H), 3.40-3.18 (1H, m, 5-H), 2.23-1.70 (8H, m, 3-H, 4-H, and *c*-Hex), 1.60-1.40 (6H, m, *c*-Hex), 1.48 (9H, s, *t*-Bu); IR (film) 3036, 2920, 2848, 1706, 1660, 1622, 1478, 1446, 1390, 1342, 1324, 1286, 1256, 1152, 1116, 1092, 1030, 984, 942, 916, 882, 854, 772 cm$^{-1}$; Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.11; H, 9.65; N, 4.51.

**(1'*E*)-*N-tert*-Butoxycarbonyl-2-(buta-1',3'-dien-1'-yloxy)pyrrolidine (2f):** colorless oil; 6:4 mixture



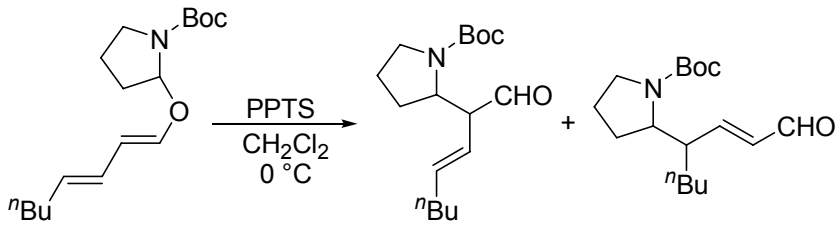
of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 6.83 (0.4H, d, *J* = 12.2 Hz, OC<u>H</u>=CHCH=$CH_2$), 6.64 (0.6H, d, *J* = 12.2 Hz, OC<u>H</u>=CHCH=$CH_2$), 6.33-6.10 (1H, m, OCH=CHC<u>H</u>=$CH_2$), 5.68-5.52 (0.4H, br, 2-H), 5.62 (1H, dd, *J* = 12.2, 11.3 Hz, OCH=C<u>H</u>CH=$CH_2$), 5.40 (0.6H, br, 2-H), 4.97 (1H, dd, *J* = 17.7, 7.2 Hz, OCH=CHCH=C<u>H</u>$_2$), 4.87-4.75 (1H, m, OCH=CHCH=C<u>H</u>$_2$), 3.59-3.41 (1H, m, 5-H), 3.40-3.20 (1H, m, 5-H), 2.18-1.76 (4H, m, 3-H and 4-H), 1.48 (9H, s, *t*-Bu); IR (film) 3084, 2972, 2888, 1710, 1650, 1600, 1478, 1454, 1398, 1344, 1326, 1286, 1254, 1146, 1118, 1092, 1060, 1030, 994, 958, 932, 914, 882, 852, 772 cm$^{-1}$; Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 64.96; H, 8.94; N, 5.81.

**(1'*E*, 3'*E*)-*N-tert*-Butoxycarbonyl-2-(2'-methylocta-1',3'-dien-1'-yloxy)pyrrolidine (2g):** colorless



oil; 6:4 mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 6.56 (0.4H, s, OC<u>H</u>=C($CH_3$)CH=CH), 6.36 (0.6H, s, OC<u>H</u>=C($CH_3$)CH=CH), 5.97 (0.4H, d, *J* = 16.7 Hz, OCH=C($CH_3$)C<u>H</u>=CH), 5.91 (0.6H, d, *J* = 15.1 Hz, OCH=C($CH_3$)C<u>H</u>=CH), 5.58-5.30 (2H, m, 2-H and OCH=C($CH_3$)CH=C<u>H</u>), 3.60-3.41 (1H, m, 5-H), 3.41-3.17 (1H, m, 5-H), 2.19-1.55 (6H, m, 3-H, 4-H, and OCH=C($CH_3$)CH=CHC<u>H</u>$_2$($CH_2$)$_2$$CH_3$), 1.67 (3H, d, *J* = 1.1 Hz, OCH=C(C<u>H</u>$_3$)CH=CH), 1.47 (9H, s, *t*-Bu), 1.43-1.21 (4H, m, OCH=C($CH_3$)CH=CHC$H_2$(C<u>H</u>$_2$)$_2$$CH_3$), 0.89 (3H, t, *J* = 7.0 Hz, OCH=C($CH_3$)CH=CH($CH_2$)$_3$C<u>H</u>$_3$); IR (film) 2952, 2924, 1704, 1650, 1630, 1454, 1390, 1324, 1284, 1254, 1170, 1148, 1116, 1092, 1032, 952, 918, 882, 860, 836, 772 cm$^{-1}$; Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10; N, 4.53. Found: C, 69.92; H, 10.20; N, 4.48.

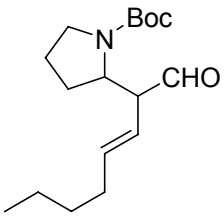
**Representative procedure of aza-Ferrier Reaction:**



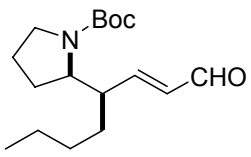

**2a** **3a** **4a**

A solution of **2a** (60 mg, 0.20 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in dichloromethane (1.0 mL) was stirred for 3 h at 0 °C. The resulting mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with diethyl ether. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to obtain **3a** (57 mg, 96% yield, 7:3 mixture of stereoisomers) as a colorless oil.

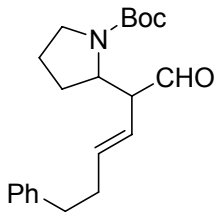
**(2'*E*)-*N*-*tert*-Butoxycarbonyl-2-(1'-formylhept-2'-en-1'-yl)pyrrolidine (3a):** colorless oil; (2*R**, 2'*S**)/(2*R**, 2'*R**) = 7:3 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.68 (0.7H, d, *J* = 1.4 Hz, CHO), 9.60 (0.3H, d, *J* = 3.0 Hz, CHO), 5.61 (1H, dt, *J* = 15.7, 6.5 Hz, CH=C<u>H</u>$(CH_2)_3CH_3$), 5.50-5.33 (1H, m, C<u>H</u>=CH$(CH_2)_3CH_3$), 4.30-4.10 (1H, m, 2-H), 3.65-3.04 (3H, br, 5-H and C<u>H</u>CHO), 2.08 (2H, td, *J* = 7.0, 6.5 Hz, CH=CHC<u>H</u>$_2(CH_2)_2CH_3$), 1.95-1.65 (4H, m, 3-H and 4-H), 1.52-1.18 (4H, m, CH=CHC$H_2(C$<u>H</u>$_2)_2CH_3$), 1.46 (9H, s, *t*-Bu), 0.89 (3H, t, *J* = 7.0 Hz, CH=CH$(CH_2)_3C$<u>H</u>$_3$); IR (film) 2952, 2924, 2870, 2724, 1724, 1690, 1454, 1392, 1252, 1168, 1108, 970, 915, 870, 768 cm$^{-1}$; Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12; H, 9.89; N, 4.74. Found: C, 69.41; H, 10.04; N, 4.64.




**(2*R**, 4'*R**, 1'*E**)-*N*-*tert*-Butoxycarbonyl-2-(1'-formylhept-1'-en-3'-yl)pyrrolidine (4a):** colorless oil; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.52 (1H, d, *J* = 7.8 Hz, CHO), 6.69 (1H, dd, *J* = 15.7, 8.5 Hz, C<u>H</u>=CHCHO), 6.11 (1H, ddd, *J* = 15.7, 7.8, 0.8 Hz, CH=C<u>H</u>CHO), 4.05-2.76 (4H, br, 2-H, 5-H, and C<u>H</u>CH=CHCHO), 2.00-1.63 (4H, m, 3-H and 4-H), 1.55-1.16 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2CH_3$), 1.48 (9H, s, *t*-Bu), 0.88 (3H, t, *J* = 6.6 Hz, $CH_2CH_2CH_2C$<u>H</u>$_3$); IR (film) 2956, 2924, 2868, 2728, 1692, 1632, 1476, 1454, 1392, 1366, 1252, 1166, 1112, 1010, 978, 912, 870, 770 cm$^{-1}$; Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12; H, 9.89; N, 4.74. Found: C, 69.38; H, 10.04; N, 4.62.

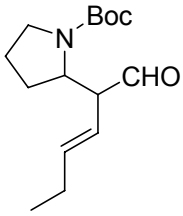


**(2'*E*)-*N-tert*-Butoxycarbonyl-2-(1'-formyl-5'-phenylpent-2'-en-1'-yl)pyrrolidine (3b):** colorless oil;



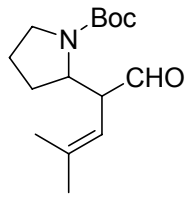

(2*R**, 2'*S**)/(2*R**, 2'*R**) = 6:4 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.64 (0.6H, s, CHO), 9.56 (0.4H, s, CHO), 7.34-7.10 (5H, m, Ph), 5.72-5.52 (1H, m, CH=C<u>H</u>$CH_2CH_2Ph$), 5.52-5.31 (0.4H, m, C<u>H</u>=$CHCH_2CH_2Ph$), 5.43 (0.6H, dd, *J* = 15.4, 9.2 Hz, C<u>H</u>=$CHCH_2CH_2Ph$), 4.26-4.05 (1H, m, 2-H), 3.64-3.01 (3H, br, 5-H and C<u>H</u>CHO), 2.71 (2H, t, *J* = 6.8 Hz, $CH=CHCH_2C\underline{H}_2Ph$), 2.41 (2H, dt, *J* = 7.3, 6.8 Hz, $CH=CHC\underline{H}_2CH_2Ph$), 2.11-1.56 (4H, m, 3-H and 4-H), 1.45 (9H, s, *t*-Bu); IR (film) 3056, 2968, 2928, 2720, 1720, 1688, 1602, 1494, 1478, 1452, 1398, 1366, 1284, 1252, 1168, 1108, 1028, 970, 912, 864, 768, 746, 698 $cm^{-1}$; Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.27; H, 8.53; N, 4.08.

**(2'*E*)-*N-tert*-Butoxycarbonyl-2-(1'-formylpent-2'-en-1'-yl)pyrrolidine (3c):** colorless oil; (2*R**,




2'*S**)/(2*R**, 2'*R**) = 7:3 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.68 (0.7H, d, *J* = 1.4 Hz, CHO), 9.61 (0.3H, d, *J* = 3.0 Hz, CHO), 5.83-5.56 (0.3H, m, CH=C<u>H</u>$CH_2CH_3$), 5.65 (0.7H, dt, *J* = 15.4, 6.5 Hz, CH=C<u>H</u>$CH_2CH_3$), 5.52-5.32 (1H, m, C<u>H</u>=$CHCH_2CH_3$), 4.32-4.10 (1H, m, 2-H), 3.70-3.05 (3H, br, 5-H and C<u>H</u>CHO), 2.09 (2H, td, *J* = 7.3, 6.5 Hz, $CH=CHC\underline{H}_2CH_3$), 1.96-1.66 (4H, m, 3-H and 4-H), 1.46 (9H, s, *t*-Bu), 1.00 (3H, t, *J* = 7.3 Hz, $CH=CHCH_2C\underline{H}_3$); IR (film) 2964, 2928, 2872, 2716, 1720, 1692, 1478, 1454, 1392, 1366, 1284, 1254, 1170, 1108, 970, 912, 864, 770 $cm^{-1}$; Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.60; H, 9.50; N, 5.21.

***N-tert*-Butoxycarbonyl-2-(1'-formyl-3'-methylbut-2'-en-1'-yl)pyrrolidine (3d):** colorless oil; (2*R**,

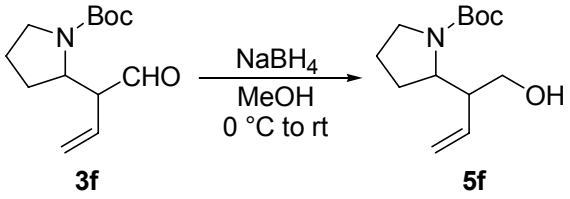



2'*S**)/(2*R**, 2'*R**) = 8:2 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.64 (0.8H, d, *J* = 1.9 Hz, CHO), 9.51 (0.2H, br, CHO), 5.19 (0.8H, d, *J* = 9.7 Hz, C<u>H</u>=$C(CH_3)_2$), 5.11 (0.2H, d, *J* = 10.0 Hz, C<u>H</u>=$C(CH_3)_2$), 4.30-4.11 (1H, m, 2-H), 3.65-3.16 (3H, m, 5-H and C<u>H</u>CHO), 2.15-1.96 (1H, br, 3-H or 4-H), 1.92-1.54 (3H, m, 3-H and 4-H), 1.79 (3H, s, $CH=C(C\underline{H}_3)_2$), 1.66 (3H, s, $CH=C(C\underline{H}_3)_2$), 1.47 (9H, s, *t*-Bu); IR (film) 2968, 2924, 2876, 2712, 1720, 1692, 1478, 1452, 1392, 1366, 1252, 1168, 1110, 912, 854, 770 $cm^{-1}$; Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.13; H, 9.63; N, 5.15.

***N-tert*-Butoxycarbonyl-2-(1'-formyl-2'-cyclohexylideneethyl)pyrrolidine (3e):** colorless oil; (2*R**, 2'*S**)/(2*R**, 2'*R**) = 7:3 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.64 (0.7H, d, *J* = 1.6 Hz, CHO), 9.59-9.49 (0.3H, br, CHO), 5.14 (0.7H, d, *J* = 9.5 Hz, C=CH), 5.07 (0.3H, d, *J* = 10.3 Hz, C=CH), 4.32-4.10 (1H, m, 2-H), 3.67-3.15 (3H, br, 5-H and C<u>H</u>CHO), 2.22-1.38 (14H, m, 3-H, 4-H, and *c*-Hex), 1.47 (9H, s, *t*-Bu); IR (film) 2924, 2852, 2712, 1684, 1476, 1448, 1388, 1254, 1164, 1112, 1028, 986, 934, 912, 850, 768 cm$^{-1}$; Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.51; H, 9.72; N, 4.58.

***N-tert*-Butoxycarbonyl-2-(1'-formylprop-2'-en-1'-yl)pyrrolidine (3f):** colorless oil; (2*R**, 2'*S**)/(2*R**, 2'*R**) = 6:4 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.72 (0.6H, d, *J* = 0.8 Hz, CHO), 9.65 (0.4H, d, *J* = 2.7 Hz, CHO), 5.94-5.75 (1H, m, C<u>H</u>=CH$_2$), 5.34 (1H, dd, *J* = 10.5, 1.4 Hz, CH=C<u>H</u>$_2$), 5.22 (1H, d, *J* = 17.3 Hz, CH=C<u>H</u>$_2$), 4.33-4.15 (1H, m, 2-H), 3.65-3.12 (3H, m, 5-H and C<u>H</u>CHO), 2.20-1.67 (4H, m, 3-H and 4-H), 1.46 (9H, s, *t*-Bu); IR (film) 3076, 2968, 2876, 2720, 1722, 1692, 1640, 1478, 1452, 1394, 1366, 1286, 1254, 1170, 1108, 992, 922, 860, 770 cm$^{-1}$; The elemental analysis of **3f** was unsuccessful because of its instability. The analysis was performed after reduction to **5f** with sodium borohydride.

***N-tert*-Butoxycarbonyl-2-(1'-hydroxybut-3'-en-2'-yl)pyrrolidine (5f):**

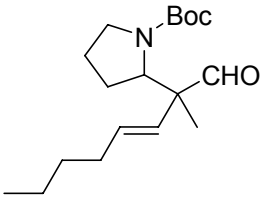



**3f** **5f**

To a solution of **3f** (65 mg, 0.27 mmol) in methanol (1.4 mL) was added sodium borohydride (12 mg, 0.32 mmol) at 0 °C and the mixture was stirred for 2 h at the same temperature. The resulting mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2:1 as eluent) to give **5f** (64 mg, 98% yield) as a colorless oil.

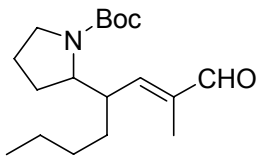
**5f:** colorless oil; (2*R**, 2'*S**)/(2*R**, 2'*R**) = 6:4 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 500 MHz) δ 5.94 (0.4H, br, C<u>H</u>=$CH_2$), 5.53 (0.6H, br, C<u>H</u>=$CH_2$), 5.19-5.05 (2H, m, CH=C<u>H</u>$_2$), 4.29 (0.6H, br, 2-H), 4.01 (0.4H, br, 2-H), 3.75-3.66 (0.4H, m, 5-H or C<u>H</u>$_2$OH), 3.55-3.16 (3.6H, m, 5-H and C<u>H</u>$_2$OH), 2.37 (0.6H, br, C<u>H</u>CH=$CH_2$), 2.08-1.67 (4.4H, m, 3-H, 4-H, and C<u>H</u>CH=$CH_2$), 1.47 (9H, s, *t*-Bu); IR (film) 3440, 3072, 2968, 2880, 1670, 1478, 1454, 1398, 1366, 1254, 1168, 1114, 1048, 1000, 914, 866, 772, 704 cm$^{-1}$; Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.76; H, 9.70; N, 5.66.

**(3'*E*)-*N*-*tert*-Butoxycarbonyl-2-(1'-formyloct-3'-en-2'-yl)pyrrolidine (3g):** colorless oil; 8:2 mixture



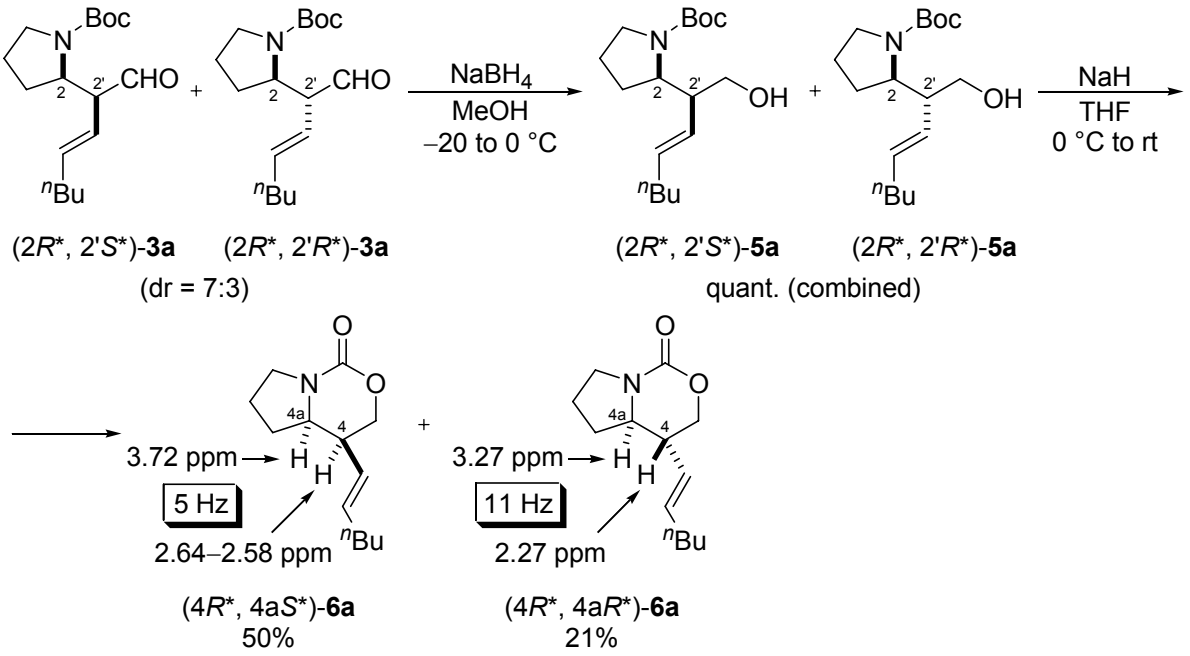

of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.54 (1H, s, CHO), 5.64 (0.8H, d, *J* = 15.8, C<u>H</u>=CH$(CH_2)_3CH_3$), 5.53 (1H, dt, *J* = 15.8, 6.5 Hz, CH=C<u>H</u>$(CH_2)_3CH_3$), 5.37 (0.2H, d, *J* = 15.8 Hz, C<u>H</u>=CH$(CH_2)_3CH_3$), 4.31 (0.2H, br, 2-H), 4.08 (0.8H, br, 2-H), 3.90-3.45 (1H, br, 5-H), 3.27-3.06 (1H, m, 5-H), 2.10 (2H, td, *J* = 6.8, 6.5 Hz, CH=CHC<u>H</u>$_2(CH_2)_2CH_3$), 2.05-1.63 (4H, m, 3-H and 4-H), 1.55-1.20 (4H, m, CH=CHC$H_2$(C<u>H</u>$_2)_2CH_3$), 1.45 (9H, s, *t*-Bu), 1.09 (2.4H, s, C<u>H</u>$_3$CCHO), 1.06 (0.6H, s, C<u>H</u>$_3$CCHO), 0.89 (3H, t, *J* = 7.0 Hz, CH=CH$(CH_2)_3$C<u>H</u>$_3$); IR (film) 2960, 2924, 2868, 2716, 1724, 1690, 1454, 1388, 1318, 1282, 1250, 1168, 1110, 978, 912, 870, 770, 730 cm$^{-1}$; Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10; N, 4.53. Found: C, 69.89; H, 10.16; N, 4.42.

**(2'*E*)-*N*-*tert*-Butoxycarbonyl-2-(2'-formyloct-2'-en-4'-yl)pyrrolidine (4g):** colorless oil; 7:3 mixture




of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.44 (1H, s, CHO), 6.47 (0.3H, d, *J* = 10.0 Hz, C<u>H</u>=C$(CH_3)$CHO), 6.31 (0.7H, d, *J* = 10.8 Hz, C<u>H</u>=C$(CH_3)$CHO), 4.12-3.73 (1H, br, 2-H), 3.70-2.72 (3H, br, 5-H and C<u>H</u>CH=C$(CH_3)$CHO), 2.00-1.66 (4H, m, 3-H and 4-H), 1.75 (3H, s, CH=C(C<u>H</u>$_3$)CHO), 1.63-1.04 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.45 (6.3H, s, *t*-Bu), 1.40 (2.7H, s, *t*-Bu), 0.87 (3H, t, *J* = 7.0 Hz, $CH_2CH_2CH_2$C<u>H</u>$_3$); IR (film) 2956, 2924, 2868, 2704, 1690, 1640, 1454, 1392, 1250, 1168, 1106, 1006, 912, 870, 832, 770 cm$^{-1}$; Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10; N, 4.53. Found: C, 69.85; H, 10.25; N, 4.36.

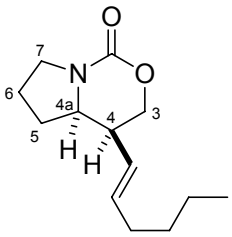
**Determination of the relative stereochemistry of 3a:** The relative stereochemistry of **3a** was determined by $^1$H NMR analysis after conversion to the corresponding cyclic carbamate **6a**. The relative stereochemistry of **6a** was determined by $^1$H NMR (500 MHz) assay. The major isomer (50% yield) showed a *syn*-coupling constant (5 Hz) between 4-H and 4a-H, which assigned as (4*R**, 4a*S**)-**6a**. The minor isomer (21% yield) showed a *anti*-coupling constant (11 Hz) between 4-H and 4a-H, which assigned as (4*R**, 4a*R**)-**6a**.




(Step 1) A solution of diastereomixture of **3a** (84 mg, 0.28 mmol) in methanol (1.4 mL) was treated with sodium borohydride (13 mg, 0.34 mmol) at –20 °C. The mixture was stirred for 2.5 h at the same temperature and for 2 h at 0 °C. The resulting mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3/1 as eluent) to give **5a** (84 mg, quant.) as a colorless oil.

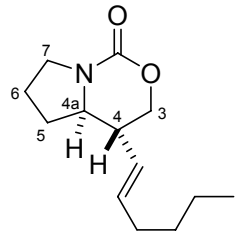
(Step 2) Sodium hydride (55 wt% in oil, 13 mg, 0.30 mmol) in THF (1.2 mL) was added to a solution of **5a** (72 mg, 0.24 mmol) at 0 °C. After stirring for 2 h at 0 °C and for 15 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (ethyl acetate as eluent) to give (4*R**, 4a*S**)-**6a** (27 mg, 50% yield) as a colorless oil and (4*R**, 4a*R**)-**6a** (11 mg, 21% yield) as a colorless oil.

**(4*R**, 4a*S**, 1'*E*)-4-(Hex-1'-enyl)hexahydro-1*H*-pyrrolo[1,2-c][1,3]oxazin-1-one [(4*R**, 4a*S**)-6a]:**



colorless oil; $^1$H NMR ($CDCl_3$, 500 MHz) δ 5.67 (1H, dt, *J* = 15.6, 7.0 Hz, 4-CH=C<u>H</u>$(CH_2)_3CH_3$), 5.38 (1H, ddt, *J* = 15.6, 9.3, 1.5 Hz, 4-C<u>H</u>=CH$(CH_2)_3CH_3$), 4.32 (1H, dd, *J* = 10.8, 3.0 Hz, 3-H), 4.22 (1H, dd, *J* = 10.8, 2.0 Hz, 3-H), 3.72 (1H, ddd, *J* = 10.5, 4.5, 4.5 Hz, 4a-H), 3.53-3.47 (2H, m, 7-H), 2.64-2.58 (1H, m, 4-H), 2.05 (2H, dt, *J* = 7.0, 7.0 Hz, 4-CH=CHC<u>H</u>$_2(CH_2)_2CH_3$), 1.97-1.88 (2H, m, 5-H and 6-H), 1.84-1.72 (1H, m, 6-H), 1.69-1.58 (1H, m, 5-H), 1.39-1.25 (4H, m, 4-CH=CHC$H_2$(C<u>H</u>$_2)_2CH_3$), 0.89 (3H, t, *J* = 7.0 Hz, 4-CH=CH$(CH_2)_3$C<u>H</u>$_3$); $^{13}$C NMR ($CDCl_3$, 68 MHz) δ 152.6, 136.2, 123.0, 71.7, 59.3, 46.9, 37.8, 32.3, 31.3, 29.6, 22.6, 22.1, 13.9; IR (film) 2952, 2924, 1684, 1472, 1426, 1384, 1342, 1292, 1238, 1206, 1170, 1132, 1090, 1066, 1006, 974, 920, 754, 728 cm$^{-1}$; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.83; H, 9.53; N, 6.31.

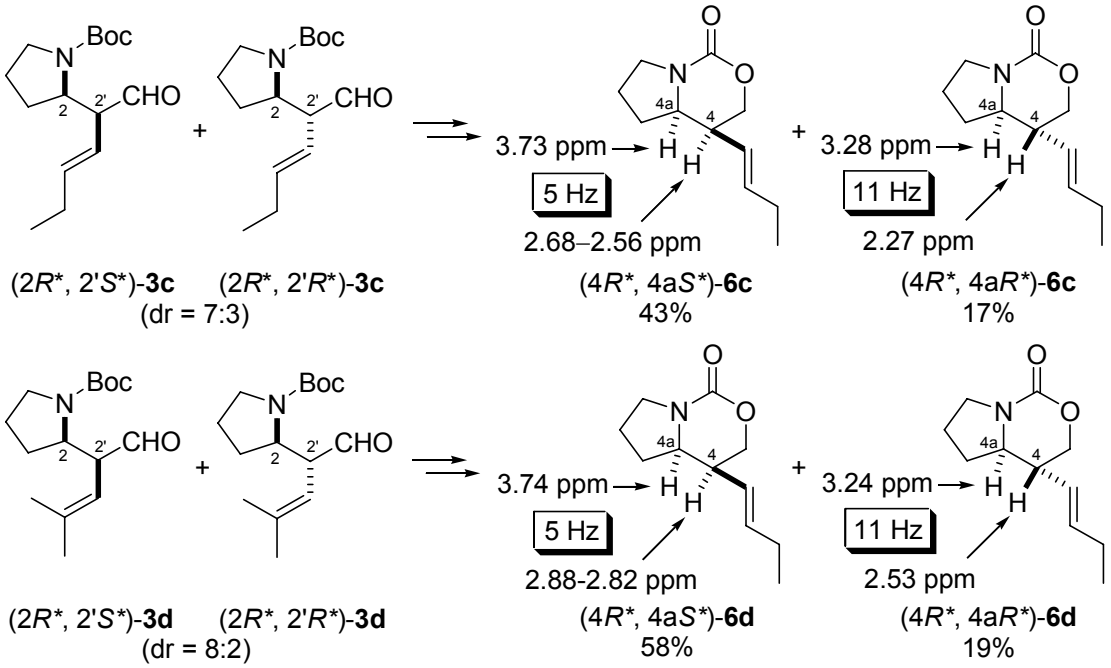
**(4*R**, 4a*R**, 1'*E*)-4-(Hex-1'-enyl)hexahydro-1*H*-pyrrolo[1,2-c][1,3]oxazin-1-one [(4*R**, 4a*R**)-6a]:**



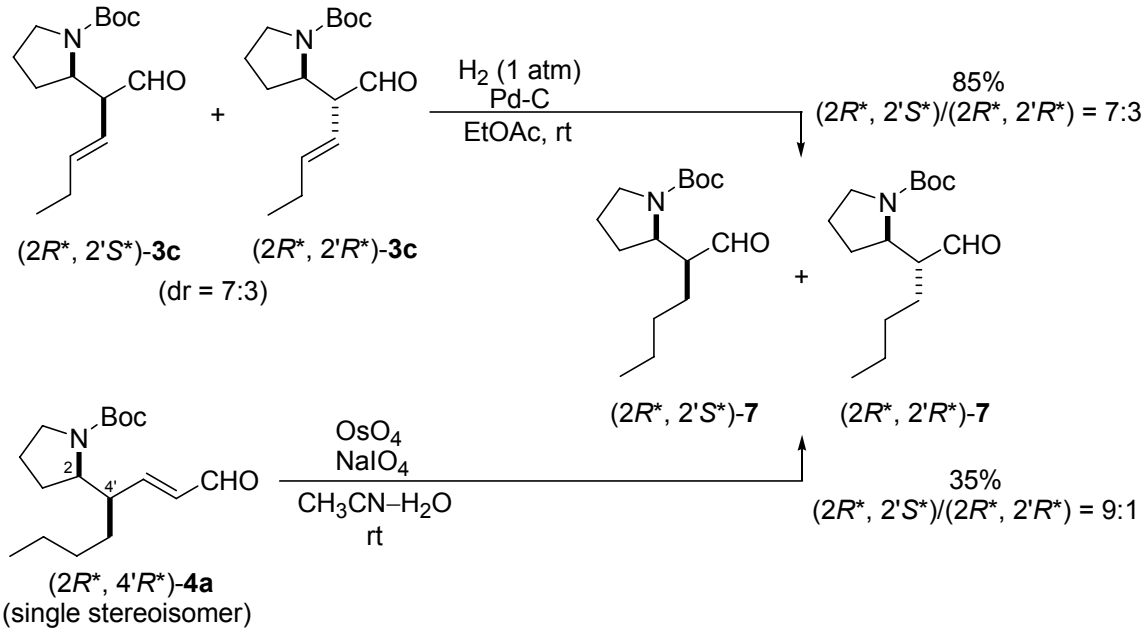
colorless oil; $^1$H NMR ($CDCl_3$, 500 MHz) δ 5.67 (1H, dt, *J* = 15.5, 7.0 Hz, 4-CH=C<u>H</u>$(CH_2)_3CH_3$), 5.15 (1H, dd, *J* = 15.5, 8.0 Hz, 4-C<u>H</u>=CH$(CH_2)_3CH_3$), 4.17 (1H, dd, *J* = 11.0, 4.0 Hz, 3-H), 3.94 (1H, dd, *J* = 11.0, 11.0 Hz, 3-H), 3.58 (1H, ddd, *J* = 10.5, 10.5, 7.5 Hz, 7-H), 3.50 (1H, ddd, *J* = 10.5, 10.5, 2.0 Hz, 7-H), 3.27 (1H, ddd, *J* = 11.0, 10.5, 5.0 Hz, 4a-H), 2.27 (1H, dddd, *J* = 11.0, 11.0, 8.0, 4.0 Hz, 4-H), 2.17-2.08 (1H, m, 5-H), 2.03 (2H, dt, *J* = 7.0, 7.0 Hz, 4-CH=CHC<u>H</u>$_2(CH_2)_2CH_3$), 2.00-1.94 (1H, m, 6-H), 1.83-1.71 (1H, m, 6-H), 1.43 (1H, dddd, *J* = 12.3, 12.3, 10.5, 7.5 Hz, 5-H), 1.37-1.24 (4H, m, 4-CH=CHC$H_2$(C<u>H</u>$_2)_2CH_3$), 0.90 (3H, t, *J* = 7.0 Hz, 4-CH=CH$(CH_2)_3$C<u>H</u>$_3$); $^{13}$C NMR ($CDCl_3$, 68 MHz) δ 152.7, 136.0, 123.8, 70.3, 61.1, 47.0, 42.3, 32.3, 32.2, 31.2, 22.6, 22.0, 13.8; IR (film) 2952, 2924, 1704, 1472, 1428, 1340, 1284, 1242, 1206, 1184, 1168, 1140, 1088, 1062, 1020, 972, 920, 904, 754, 728 cm$^{-1}$; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.06; H, 9.56; N, 6.26.

**Determination of the relative stereochemistries of 3b–3g:** The relative stereochemistries of **3c** and **3d** were also determined by the same procedures described above. Other compounds (**3b**, **3e**, **3f**, **3g**) were

determined by the analogy to the diastereomer ratios of **3a**, **3c**, and **3d**. The selected $^{1}$H NMR assignments were shown below.

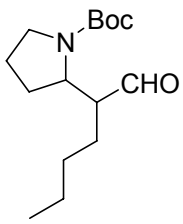


**Determination of the relative stereochemistry of 4a:** The relative stereochemistry of α,β-unsaturated aldehyde **4a** was determined by $^1$H NMR comparison of the authentic sample **7**. The authentic sample **7** [(2*R**, 2'*S**)/(2*R**, 2'*R**) = 7:3] was prepared from **3c** by hydrogenation. Osmium oxidation of **4a** afforded **7** in 36% yield as a mixture of (2*R**, 2'*S**)/(2*R**, 2'*R**) = 9:1. Thus, the relative stereochemistry of **4a** was determined as (2**R*, 4'*R**).




**Preparation of authentic sample 7 from 3c by hydrogenation:** A mixture of **3c** [(2*R**, 2'*S**)/(2*R**, 2'*R**) = 7:3] (82 mg, 0.31 mmol) and palladium on activated carbon (loading: 10 wt. %, 3 mg) in ethyl acetate (1.5 mL) was stirred for 6 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3/1 as eluent) to give **7** [(2*R**, 2'*S**)/(2*R**, 2'*R**) = 7:3] (71 mg, 85% yield) as a colorless oil.

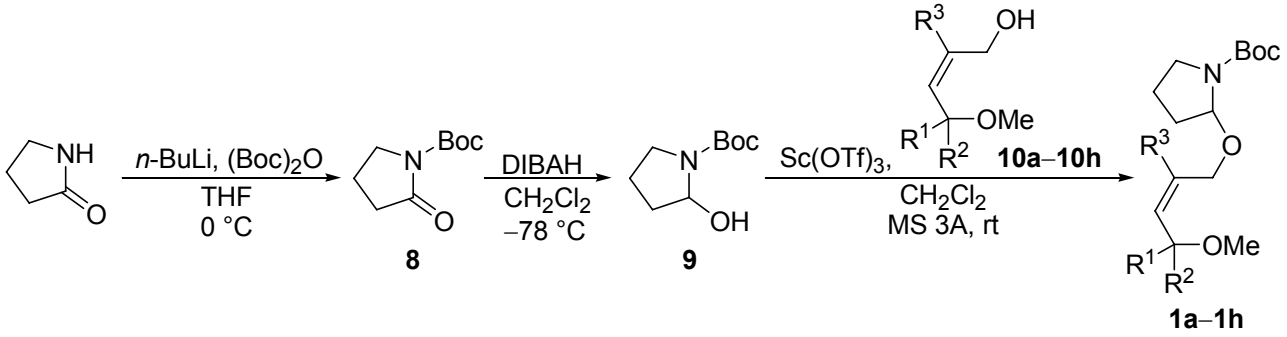
***N-tert*-Butoxycarbonyl-2-(1'-formylpent-1'-yl)pyrrolidine (7):** colorless oil; (2*R**, 2'*S**)/(2*R**, 2'*R**) = 7:3 mixture of stereoisomers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 9.74 (0.7H, d, *J* = 1.9 Hz, CHO), 9.62 (0.3H, d, *J* = 3.5 Hz, CHO), 4.08 (1H, br, 2-H), 3.69-3.11 (2H, m, 5-H and/or C<u>H</u>CHO), 2.97-2.31 (1H, m, 5-H and/or C<u>H</u>CHO), 2.10-1.58 (5H, m, 3-H, 4-H, and C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.48 (6.3H, s, *t*-Bu), 1.45 (2.7H, s, *t*-Bu), 1.39-1.17 (5H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.89 (3H, t, *J* = 5.9 Hz, CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); IR (film) 2956, 2928, 2868, 2720, 1720, 1692, 1478, 1454,



1392, 1366, 1254, 1168, 1110, 912, 870, 772 $cm^{-1}$; Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 67.08; H, 10.23; N, 5.09.

**Preparation of 7 from 4a by osmium oxidation:** A mixture of **4a** (61 mg, 0.21 mmol), osmium tetroxide (4 wt.% in water, 20 μL, 0.003 mmol), and sodium periodate (97 mg, 0.45 mmol) in acetonitrile (0.4 mL) and water (1.8 mL) was stirred for 4 days at room temperature. The resulting mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to give **7** [(2*R**, 2'*S**)/(2*R**, 2'*R**) = 9:1] (20 mg, 35% yield) as a colorless oil.

**Preparation of substrates 1a–1h:**



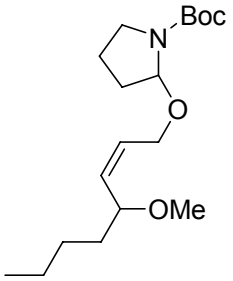

(Step 1) A solution of 2-pyrrolidinone (851 mg, 10.0 mmol) in THF (25 mL) was treated with a 1.6 M hexane solution of *n*-butyllithium (6.3 mL, 10 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. The mixture was treated with di-*tert*-butyl dicarbonate (2.5 mL, 11 mmol) at 0 °C and stirred for 2 h. The mixture was quenched with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The crude product of **8** (2.22 g) was obtained as a colorless oil and used without purification in step 2.

(Step 2) To a solution of **8** (2.22 g) in dichloromethane (40 mL) was added a 1 M solution of diisobutylaluminium hydride (DIBAH) (20 mL, 20 mmol) at –78 °C. After stirring for 1.5 h at –78 °C, methanol (2.8 mL) and a saturated aqueous solution of potassium sodium tartrate (40 mL) were added in succession. The mixture was allowed to warm to room temperature and stirred for 3 h. The resulting mixture was diluted with water and extracted with dichloromethane. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:1 as eluent) to give **9** (1.64 g, 88% yield) as a colorless viscous oil.

(Step 3) A mixture of **9** (661 mg, 3.53 mmol), allylic alcohol **10a** (685 mg, 4.33 mmol), scandium trifluoromethanesulfonate (35 mg, 0.071 mmol), and molecular sieves 3Å (1.8 g) in dichloromethane (18 mL) was stirred for 23 h at room temperature and the resulting mixture was quenched with saturated aqueous sodium hydrogen carbonate. The molecular sieves 3Å was removed by filtration and the filtrate was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 4:1 as eluent) afforded **1a** (936 mg, 81% yield) as a colorless oil.

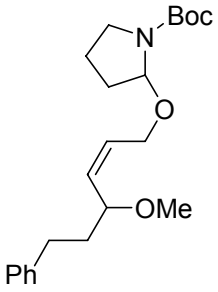
**1b**–**1g** were prepared by the same procedures described above using allylic alcohols **10b**–**10h** instead of **10a**.

**(*E*)-*N*-*tert*-Butoxycarbonyl-2-(4'-methoxyoct-2'-en-1'-yloxy)pyrrolidine (1a):** colorless oil; mixture



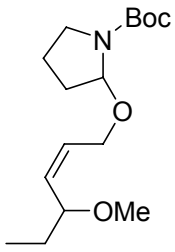

of stereoisomers and rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 5.89-5.68 (1H, m, 2'-H), 5.54-5.13 (2H, m, 2-H and 3'-H), 4.35-3.81 (3H, m, 5-H and 4'-H), 3.60-3.21 (5H, m, 1'-H and $OCH_3$), 2.20-1.18 (10H, m, 3-H, 4-H, 5'-H, 6'-H, and 7'-H), 1.48 (9H, s, *t*-Bu), 0.89 (3H, t, *J* = 6.6 Hz, 8'-H); IR (film) 2952, 2928, 2812, 1702, 1456, 1384, 1324, 1286, 1254, 1166, 1102, 1066, 976, 946, 916, 878, 852, 772 cm$^{-1}$; Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16; N, 4.28. Found: C, 66.12; H, 10.18; N, 4.24.

**(*E*)-*N*-*tert*-Butoxycarbonyl-2-(4'-methoxy-6'-phenylhex-2'-en-1'-yloxy)pyrrolidine (1b):** colorless



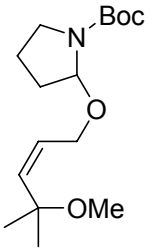

oil; mixture of stereoisomers and rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 7.32-7.13 (5H, m, Ph), 5.78 (1H, br, 2'-H), 5.43 (1H, dd, *J* = 10.2, 10.2 Hz, 3'-H), 5.28 (0.5H, br, 2-H), 5.14 (0.5H, br, 2-H), 4.30-3.81 (3H, m, 5-H and 4'-H), 3.49-3.18 (2H, m, 1'-H), 3.28 (1.5H, s, $OCH_3$), 3.26 (1.5H, s, $OCH_3$), 2.77-2.54 (2H, m, 6'-H), 2.15-1.65 (6H, m, 3-H, 4-H, and 5'-H), 1.47 (9H, s, *t*-Bu); IR (film) 3056, 3016, 2972, 2928, 2812, 1702, 1604, 1476, 1452, 1388, 1286, 1254, 1168, 1102, 1062, 946, 916, 878, 852, 770, 746, 698 cm$^{-1}$; Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.18; H, 8.84; N, 3.68.

**(*E*)-*N*-*tert*-Butoxycarbonyl-2-(4'-methoxyhex-2'-en-1'-yloxy)pyrrolidine (1c):** colorless oil; mixture



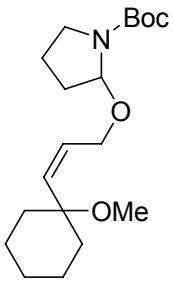

of stereoisomers and rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 5.91-5.66 (1H, m, 2'-H), 5.52-5.09 (2H, m, 2-H and 3'-H), 4.36-3.74 (3H, m, 5-H and 4'-H), 3.58-3.17 (5H, m, 1'-H and $OCH_3$), 2.18-1.33 (6H, m, 3-H, 4-H, and 5'-H), 1.48 (9H, s, *t*-Bu), 0.88 (3H, t, *J* = 7.2 Hz, 6'-H); IR (film) 2968, 2928, 2876, 2812, 1700, 1454, 1386, 1324, 1286, 1254, 1168, 1102, 1068, 946, 916, 878, 852, 772 cm$^{-1}$; Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18 H, 9.76; N, 4.68. Found: C, 64.23; H, 9.81; N, 4.61.

**(*E*)-*N-tert*-Butoxycarbonyl-2-(4'-methoxy-4'-methylpent-2'-en-1'-yloxy)pyrrolidine (1d):** colorless



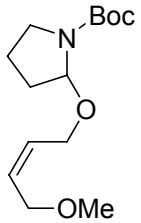

oil; 6:4 mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 5.58 (1H, br, 2'-H), 5.36 (1H, d, *J* = 12.2 Hz, 3'-H), 5.31 (0.4H, br, 2-H), 5.17 (0.6H, br, 2-H), 4.43-4.17 (2H, m, 5-H), 3.50-3.21 (2H, m, 1-H), 3.17 (3H, s, $OCH_3$), 2.20-1.65 (4H, m, 3-H and 4-H), 1.49 (9H, s, *t*-Bu), 1.29 (6H, s, 5'-H and 4'-$CH_3$); IR (film) 2968, 2932, 2820, 1698, 1454, 1390, 1322, 1286, 1254, 1170, 1104, 1070, 998, 976, 950, 916, 878, 855, 770 cm$^{-1}$; Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18 H, 9.76; N, 4.68. Found: C, 64.14; H, 9.80; N, 4.65.

**(*E*)-*N-tert*-Butoxycarbonyl-2-(3'-cyclohexyl-4'-methoxyprop-2'-en-1'-yloxy)pyrrolidine (1e):**



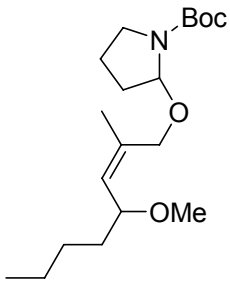

colorless oil; 6:4 mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 5.72-5.54 (1H, m, 2'-H), 5.48 (0.4H, br, 2-H), 5.37-5.23 (1H, m, 3'-H), 5.17 (0.6H, br, 2-H), 4.45-4.18 (2H, m, 5-H), 3.61-3.05 (3H, m, 1'-H and 4'-H), 3.20 (1.2H, s, $OCH_3$), 3.11 (1.8H, s, $OCH_3$), 2.19-1.21 (14H, m, 3-H, 4-H, and *c*-Hex), 1.50 (3.6H, s, *t*-Bu), 1.48 (5.4H, s, *t*-Bu); IR (film) 2920, 2852, 2820, 1702, 1478, 1452, 1392, 1322, 1286, 1256, 1166, 1110, 950, 916, 878, 850, 770 cm$^{-1}$; Anal. Calcd for $C_{19}H_{33}NO_4$: 67.22; H, 9.80; N, 4.13. Found: C, 67.22; H, 10.01; N, 4.04.

**(*E*)-*N-tert*-Butoxycarbonyl-2-(4'-methoxybut-2'-en-1'-yloxy)pyrrolidine (1f):** colorless oil; 5:5




mixture of rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 5.82-5.59 (2H, m, 2'-H and 3'-H), 5.29 (0.5H, br, 2-H), 5.18 (0.5H, br, 2-H), 4.29-3.90 (2H, m, 5-H), 4.01 (2H, s, 4'-H), 3.51-3.21 (2H, m, 1'-H), 3.33 (3H, s, $OCH_3$), 2.19-1.68 (4H, m, 3-H and 4-H), 1.49 (9H, s, *t*-Bu); IR (film) 2972, 2928, 2888, 2812, 1704, 1478, 1454, 1392, 1342, 1286, 1254, 1166, 1106, 1064, 954, 914, 878, 852, 770 cm$^{-1}$; Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97 H, 9.29; N, 5.16. Found: C, 62.20; H, 9.37; N, 5.13.

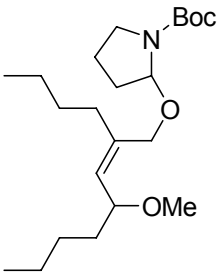
**(*E*)-*N-tert*-Butoxycarbonyl-2-(4'-methoxy-2'-methyloct-2'-en-1'-yloxy)pyrrolidine (1g):** colorless




oil; mixture of stereoisomers and rotamers; $^1$H NMR ($CDCl_3$, 270 MHz) δ 5.35-5.01 (2H, m, 2-H and 3'-H), 4.26-3.78 (3H, m, 5-H and 4'-H), 3.55-3.12 (5H, m, 1'-H and $OCH_3$), 2.20-1.16 (10H, m, 3-H, 4-H, 5'-H, 6'-H, and 7'-H), 1.81 (3H, s, 2'-

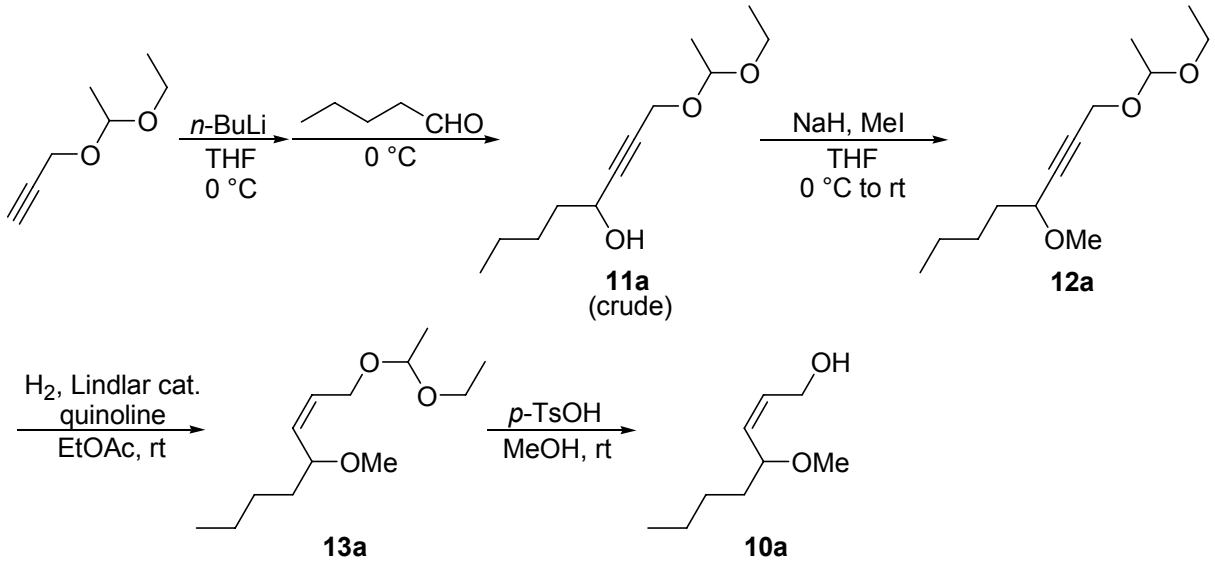
$CH_3$), 1.49 (9H, s, *t*-Bu), 0.88 (3H, t, $J$ = 6.5 Hz, 8'-H); IR (film) 2928, 2812, 1700, 1454, 1386, 1324, 1286, 1254, 1168, 1104, 1056, 948, 916, 878, 770 $cm^{-1}$; Anal. Calcd for $C_{19}H_{35}NO_4$: C, 66.83; H, 10.33; N, 4.10. Found: C, 67.10; H, 10.28; N, 4.23.

**(*E*)-*N*-*tert*-Butoxycarbonyl-2-[(2'-but-1'-yl)-4'-methoxyoct-2'-en-1'-yloxy]pyrrolidine (1h):**




colorless oil; mixture of stereoisomers and rotamers; $^1H$ NMR ($CDCl_3$, 270 MHz) δ 5.51-5.08 (2H, m, 2-H and 3'-H), 4.26-3.84 (3H, m, 5-H and 4'-H), 3.60-3.15 (5H, m, 1'-H and $OCH_3$), 2.22-1.20 (16H, m, 3-H, 4-H, 5'-H, 6'-H, 7'-H, and 2'-$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (9H, s, *t*-Bu), 0.97-0.82 (6H, m, 8'-H and 2'-$CH_2CH_2CH_2C\underline{H}_3$); IR (film) 2950, 2928, 2868, 2812, 1704, 1454, 1388, 1324, 1286, 1254, 1168, 1102, 1056, 952, 916, 878, 854, 772 $cm^{-1}$; Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 69.10; H, 10.90; N, 3.74.

**Preparation of (*Z*)-4-methoxyoct-2-en-1-ol (10a):**




(Step 1) A solution of 3-(1-ethoxyethoxy)prop-1-yne[1] (1.28 g, 10.0 mmol) in THF (30 mL) was treated with a 1.61 M hexane solution of *n*-butyllithium (6.6 mL, 10.6 mmol) at 0 °C. The mixture was stirred for 20 min at the same temperature and 1-butanal (1.17 mL, 11.0 mmol) was added to the resulting mixture at 0 °C. After stirring for 1 h at the same temperature, the resulting mixture was quenched with

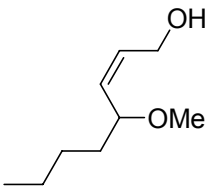
(1) K. Takeda, A. Nakajima, M. Takeda, E. Yoshii, *Org. Syn.,* 1999, **76**, 199.

saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The crude product of **11a** was dissolved in THF (50 mL) and sodium hydride (55% in oil, 655 mg, 15 mmol) was added to the solution at 0 °C. The mixture was stirred for 20 min at room temperature and treated with iodomethane (0.93 mL, 15 mmol) at 0 °C. After stirring for 4 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 20:1 to 10:1 as eluent) gave **12a** (1.85 g, 81% yield) as a colorless oil.

(Step 2) Lindlar catalyst (loading: 5 wt. %, poisoned with lead, 0.34 g) was added to a solution of **12a** (1.85 g, 8.10 mmol) and quinoline (0.38 mL, 3.2 mmol) in ethyl acetate (41 mL) and the mixture was stirred for 4 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1 as eluent) to afford **13a** (1.80 g, 96% yield) as a colorless oil.

(Step 3) To a solution of **13a** (1.80 g, 7.81 mmol) in methanol (16 mL) was added *p*-toluenesulfonic acid monohydrate (74 mg, 0.39 mmol) and the mixture was stirred for 14 h at room temperature. The resulting mixture was evaporated to remove methanol and the residue was diluted with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3:1 to 1:1 as eluent) to afford **10a** (1.03 g, 83% yield) as a colorless oil.

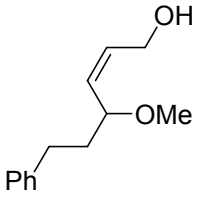
**10a:** colorless oil; $^1$H NMR (270 MHz, $CDCl_3$) δ 5.82 (1H, dddd, *J* = 11.3, 6.9, 6.2, 1.1 Hz, 2-H), 5.40



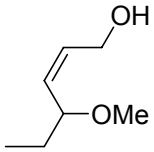

(1H, ddt, *J* = 11.3, 8.6, 1.4 Hz, 3-H), 4.29 (1H, ddd, *J* = 13.1, 6.9, 1.4 Hz, 1-H), 4.18 (1H, ddd, *J* = 13.1, 6.2, 1.4 Hz, 1-H), 3.91 (1H, dtd, *J* = 8.6, 6.4, 1.1 Hz, 4-H), 3.28 (3H, s, $OCH_3$), 1.72-1.56 (2H, m, 5-H), 1.50-1.19 (5H, m, 6-H, 7-H, and OH), 0.90

(3H, t, $J$ = 6.8 Hz, 8-H); $^{13}$C NMR (68 MHz, $CDCl_3$) δ 133.1, 131.6, 76.8, 58.9, 56.0, 35.0, 27.4, 22.7, 14.0; IR (film) 3360, 2924, 2860, 2816, 1464, 1406, 1380, 1312, 1250, 1188, 1124, 1094, 1020, 980, 946, 892, 865, 730 cm$^{-1}$; Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.31; H, 11.66.

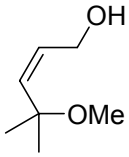
**Preparation of allylic alcohols (10b–e):** Prepared by the same procedure described for **10a** using the corresponding aldehydes or ketones (2-phenylpropionaldehyde for **10b**, propionaldehyde for **10c**, acetone for **10d**, cyclohexanone for **10e**) instead of 1-butanal in step 1.



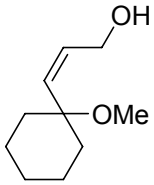

**10b**




**10c**

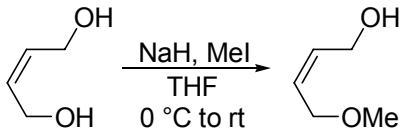



**10d**




**10e**

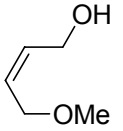
**Preparation of (*Z*)-4-methoxybut-2-en-1-ol (10f):**




**10f**

Sodium hydride (55% in oil, 0.57 g, 13 mmol) was added to a solution of (*Z*)-2-buten-1,4-diol (3.3 mL, 40 mmol) in THF (40 mL) at 0 °C and the mixture was stirred for 20 min at room temperature. The resulting mixture was treated with iodomethane (0.62 mL, 10 mmol) and stirred for 10 min at 0 °C, for 4 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C and extracted with ethyl acetate. The combined extracts was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:1 to 1:2 as eluent) to give **10f** (822 mg, 81% yield) as a pale yellow oil.

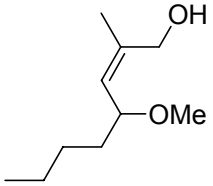
**10f**[2]**:** colorless oil; $^1$H NMR (270 MHz, $CDCl_3$) δ 5.84 (1H, dtt, $J$ = 11.3, 6.2, 1.1 Hz, 2-H), 5.70 (1H, dtt, $J$ = 11.3, 6.2, 1.1 Hz, 3-H), 4.22 (2H, dd, $J$ = 6.2, 1.1 Hz, 1-H), 4.02 (2H, dd, $J$ = 6.2, 1.1 Hz, 4-H), 3.36 (3H, s, $OCH_3$), 1.92 (1H, s, OH); $^{13}$C NMR (68 MHz, $CDCl_3$) δ 132.3, 128.2,




(2) J. R. Peterson, J. K. Zjawiony, S. Liu, C. D. Hufford, A. M. Clark, R. D. Rogers, *J. Med. Chem.,* 1992, **35**, 4069; I. Ichikizaki, C.-C. Yao, Y. Fujita, Y. Hasebe, *Bull. Chem. Soc. Jpn.,* 1955, **28**, 80.

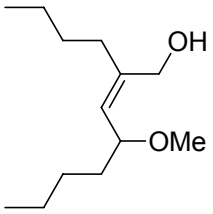
68.1, 58.7, 58.2; IR (film) 3400, 3016, 2924, 2876, 2820, 1452, 1412, 1330, 1285, 1188, 1112, 1028, 986, 948, 904 $cm^{-1}$.

**(*Z*)-4-Methoxy-2-methyloct-2-en-1-ol (10g):** Prepared by the same procedure described for **10a** using




(*Z*)-1-(1-ethoxyethoxy)-4-methoxy-2-methyloct-2-ene[3] in step 3; colorless oil; $^1$H NMR (270 MHz, $CDCl_3$) δ 5.19 (1H, d, *J* = 8.8 Hz, 3-H), 4.22 (1H, d, *J* = 12.2 Hz, 1-H), 4.10 (1H, d, *J* = 12.2 Hz, 1-H), 3.92 (1H, dt, *J* = 8.8, 6.3 Hz, 4-H), 3.25 (3H, s, $OCH_3$), 1.86 (3H, d, *J* = 1.1 Hz, 2-$CH_3$), 1.74-1.54 (2H, m, 5-H and OH), 1.48-1.18 (5H, m, 5-H, 6-H, and 7-H), 0.89 (3H, t, *J* = 6.8 Hz, 8-H); $^{13}$C NMR (68 MHz, $CDCl_3$) δ 138.7, 129.3, 76.7, 61.9, 55.6, 35.1, 27.5, 22.7, 21.4, 14.0; IR (film) 3420, 2928, 2864, 2816, 1450, 1378, 1240, 1186, 1116, 1088, 1006, 946, 864, 774, 730 $cm^{-1}$; Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.89; H, 11.88.

**(*Z*)-2-(But-1-yl)-4-methoxyoct-2-en-1-ol (10h):** Prepared by the same procedure described for **10a**




using (*Z*)-2-(but-1-yl)-1-(1-ethoxyethoxy)-4-methoxyoct-2-ene[3] in step 3; colorless oil; $^1$H NMR (270 MHz, $CDCl_3$) δ 5.19 (1H, d, *J* = 8.9 Hz, 3-H), 4.21 (1H, d, *J* = 12.0 Hz, 1-H), 4.10 (1H, d, *J* = 12.0 Hz, 1-H), 3.96 (1H, dt, *J* = 8.9, 6.5 Hz, 4-H), 3.26 (3H, s, $OCH_3$), 2.21-2.11 (2H, m, 5-H), 1.72-1.19 (11H, m, 6-H, 7-H, 2-$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$, and OH), 0.92 (3H, t, *J* = 7.0 Hz, 8-H or 2-$CH_2CH_2CH_2C\underline{H}_3$), 0.89 (3H, t, *J* = 7.0 Hz, 8-H or 2-$CH_2CH_2CH_2C\underline{H}_3$); $^{13}$C NMR (68 MHz, $CDCl_3$) δ 143.1, 129.1, 76.8, 60.7, 55.6, 35.03, 34.96, 30.3, 27.5, 22.7, 22.4, 14.0, 13.9; IR (film) 3432, 2952, 2924, 2864, 1464, 1378, 1242, 1188, 1116, 1088, 1020, 966, 864, 776, 730 $cm^{-1}$; Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 72.58; H, 12.39.

(3) E. Tayama, R. Hashimoto, *Tetrahedron Lett.,* 2007, **48**, 7950.