Intramolecular aminyl and iminyl radical additions to α,β-unsaturated esters. Diastereoselective tandem cyclofunctionalization and hydrogen transfer reactions.

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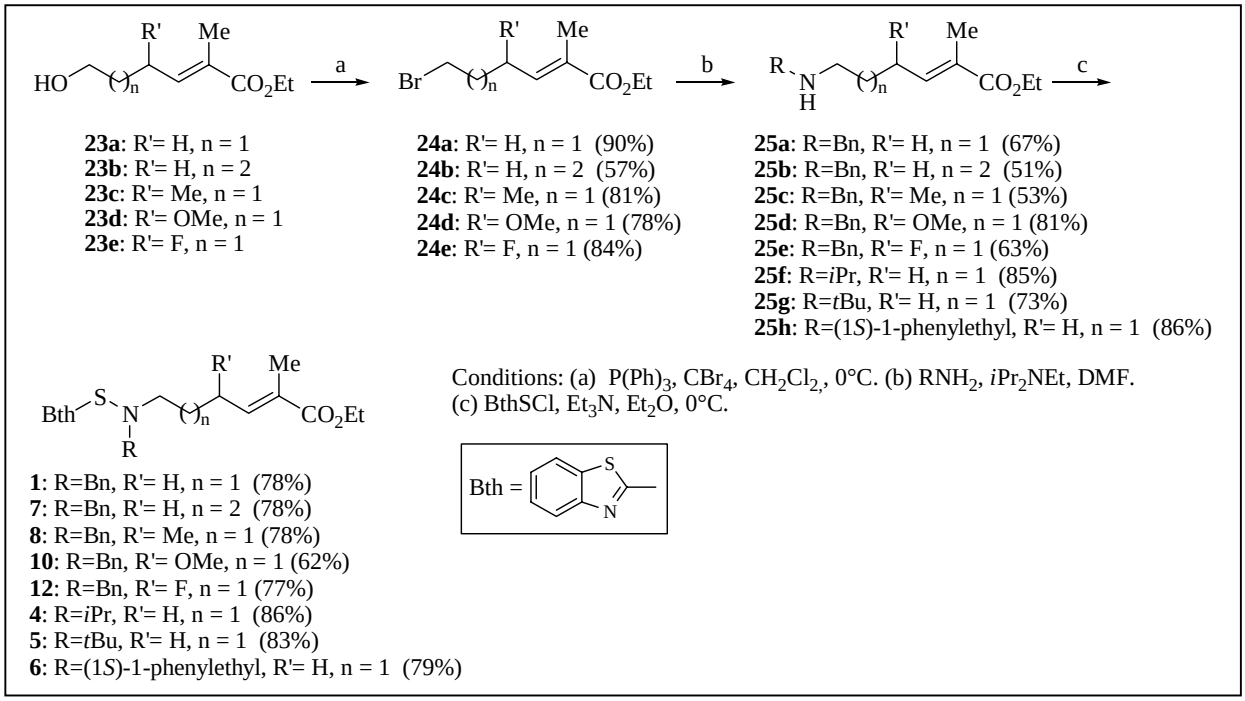


Scheme1

The preparation and characterization of alcohols **23a-c**,[1] **23d**,[2] and **23e**[3] have been reported previously.

General procedures were used for the preparation of compounds 24a, 24c-e from corresponding alcohols 23a, 23c-e.

To a solution of the appropriate alcohol (1 equiv) in CH_2Cl_2 (0.2 M) at 0° C were added successively CBr_4 (1.1 equiv) and triphenylphosphine (1.1 equiv). The reaction mixture was brought to room temperature and stirred until the transformation of the alcohol was complete (2-3 hours), as indicated by thin-layer chromotography. The CH_2Cl_2 was then evaporated, and a hexane:Et_2O solution (1:1, 0.1 M) was added. The mixture was filtered through Celite® and concentrated under reduced pressure.

6-Bromo-2-methyl-hex-2-ethyl enoate (24a). After purification by flash chromotography on silica gel (hexane:EtOAc, 19:1), bromide **24a** was obtained as a colorless oil (90% from alcohol **23a**). R_f 0.44 (hexane:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J*

= 7.1 Hz, 3H), 1.85 (d, *J* = 1.5 Hz, 3H), 2.00 (quint, *J* = 7.0 Hz, 2H), 2.34 (q, *J* = 7.0 Hz, 2H), 3.41 (t, *J* = 7.0 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 6.68 (tq, *J* = 1.5, 7.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 14.2, 27.0, 31.4, 33.0, 60.5, 129.2, 139.6, 167.9 ppm; IR (neat) $\nu_{max.}$ 3000, 1720, 1655, 1270, 1200, 1180, 1115 cm^{-1}; MS (FAB) 237 (97%, MH, ^{81}Br), 235 (100%, MH, ^{79}Br); HRMS Calcd for $C_9H_{16}{}^{79}BrO_2$ (MH) 235.0334, found 235.0329 (+2.0 ppm). Anal. Calcd for $C_9H_{15}BrO_2$: C, 45.98; H, 6.43. Found: C, 45.51; H, 6.59.

(±)-6-Bromo-2,4-dimethyl-hex-2-ethyl enoate (24c). After purification by flash chromatography on silica gel (hexane:EtOAc, 19:1), bromide **24c** was obtained as a colorless oil (81% from alcohol **23c**). R_f 0.18 (hexane:EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.6 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.85 – 1.95 (m, 2H), 1.89 (d, *J* = 1.5 Hz, 3H), 2.72 – 2.84 (m, 2H), 3.25 – 3.42 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.46 (dq, *J* = 1.5, 10.3 Hz, 1H) ppm; IR (neat) $\nu_{max.}$ 2980, 2940, 2780, 2750, 1715, 1655, 1460, 1210, 1180, 755 cm^{-1}; MS (FAB) 251 (96%, MH, ^{81}Br), 249 (100%, MH, ^{79}Br); HRMS calculed for $C_{10}H_{18}{}^{79}BrO_2$ (MH) 249.0490, found 249.0493 (-1.2 ppm). Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88. Found: C, 47.68; H, 7.03.

(±)-6-Bromo-4-methoxy-2-methyl-hex-2-ethyl enoate (24d). After purification by flash chromatography on silica gel (hexane:EtOAc, 19:1), bromide **24d** was obtained as a colorless oil (78% from alcohol **23d**). R_f 0.33 (EtOAc: MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.87 – 2.19 (m, 2H), 1.92 (d, *J* = 1.5 Hz, 3H), 3.29 (s, 3H), 3.39 – 3.58 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.24 (dt, *J* = 4.0, 8.8 Hz, 1H), 6.55 (dq, *J* = 1.5, 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.2, 29.6, 37.5, 56.9, 60.9, 75.2, 131.2, 140.5, 167.4 ppm; IR (neat) $\nu_{max.}$ 3000, 2950, 2920, 2830, 1720, 1660, 1450, 1220, 1190, 1130, 755 cm^{-1}; MS (FAB) 267 (81%, MH, ^{81}Br), 265 (88%, MH, ^{79}Br), 235 (34%, M - 31), 233 (33%, M - 31), 97 (100%),

79 (92%); HRMS Calcd for $C_{10}H_{18}{}^{79}BrO_3$ (MH) 265.0440, found 265.0451 (-4.4 ppm). Anal. Calcd for $C_{10}H_{17}BrO_3$: C, 45.30; H, 6.46. Found: C, 45.51; H, 6.81.

(±)-6-Bromo-4-fluoro-2-methyl-hex-2-ethyl enoate (24e). After purification by flash chromotography on silica gel (pentane:EtOAc, 19:1), bromide **24e** was obtained as a colorless oil (84% from alcohol **23e**). R_f 0.21 (Hexane:EtOAc, 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.90 (dd, *J* = 1.5, 3.0 Hz, 3H), 1.98 – 2.14 (m, 1H), 2.29 – 2.42 (m, 1H), 3.42 – 3.56 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 5.48 (dddd, *J* = 4.0, 8.0, 49.0 Hz, 1H), 6.70 (ddq, *J* = 1.5, 8.0, 14.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.1, 27.9, 37.5, 37.7, 61.0, 86.6, 88.2, 131.6, 131.7, 136.2, 136.5, 167.0 ppm; IR (neat) $\nu_{max.}$ 3000, 2950, 2920, 2890, 1725, 1665, 1175, 1020, 750 cm^{-1}; MS (FAB) 255 (96%, MH, ^{81}Br), 253 (100%, MH, ^{79}Br), 154 (92%), 137 (87%), 136 (85%), 55 (82%); HRMS Calcd for $C_9H_{15}{}^{79}BrFO_2$ (MH) 253.0239, found 253.0232 (+2.9 ppm). Anal. Calcd for $C_9H_{14}BrFO_2$: C, 42.71; H, 5.58. Found: C, 42.62; H, 5.88.

General procedure for the preparation of compounds 25a, 25c-h from corresponding bromides 24a, 24c-e.

To a solution of the appropriate bromide (1.0 equiv) in DMF (0.8 M) were added successively *i*Pr$_2$NEt (1.5 M) and the corresponding amine (3.0 equiv). The reaction mixture was stirred at room temperature until the transformation of the bromide was complete (16–24 hours), as indicated by thin-layer chromotography. After being diluted with EtOAc, the mixture was then washed with H_2O (3x) and a saturated aqueous solution of NaCl. The organic layer was dried on $MgSO_4$, filtered, and concentrated under reduced pressure.

6-Benzylamino-2-methyl-hex-2-ethyl enoate (25a). After purification by flash chromatography on silica gel (EtOAc), amine **25a** was obtained as a colorless oil (67% from bromide **24a**). R_f 0.32 (EtOAc:MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.64 (quin, *J* = 7.5 Hz, 2H), 1.82 (s, 3H), 2.22 (q, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H),

3.76 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 6.75 (t, J = 7.5 Hz, 1H), 7.22 – 7.31 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 14.2, 26.3, 28.9, 48.8, 53.9, 60.3, 126.8, 127.9, 128.2, 140.3, 141.5, 160.9, 168.0 ppm; IR (neat) $\nu_{max.}$ 3340, 3090, 3070, 3030, 2940, 1710, 1650, 1495, 1270, 740, 700 cm^{-1}; MS (FAB) 262 (75%, MH), 91 (100%); HRMS Calcd for $C_{16}H_{24}NO_2$ (MH) 262.1807, found 262.1799 (+3.0 ppm). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.60; H, 9.33; N, 5.85.

(±)-6-Benzylamino-2,4-dimethyl-hex-2-ethyl enoate (25c). After purification by flash chromatography on silica gel (EtOAc), amine **25c** was obtained as a colorless oil (53% from bromide **24c**). R_f 0.18 (hexane:EtOAc, 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3H), 1.19 (bs, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.48 – 1.66 (m, 2H), 1.84 (d, J = 1.5 Hz, 3H), 2.54 – 2.66 (m, 3H), 3.76 (d, J = 1.5 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 6.54 (dq, J = 1.5, 10.3 Hz, 1H) ppm, 7.23 - 7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 14.2, 20.1, 31.2, 37.1, 47.4, 54.1, 60.4, 126.6, 126.8, 128.0, 128.3, 140.4, 147.2, 168.3 ppm; IR (neat) $\nu_{max.}$ 3340, 3030, 2970, 2940, 1710, 1650, 1270, 750, 700 cm^{-1}; MS (FAB) 276 (72%, MH), 91 (100%); HRMS Calcd for $C_{17}H_{26}NO_2$ (MH) 276.1964, found 276.1957 (+2.4 ppm). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.93; H, 9.40; N, 5.12.

(±)-6-Benzylamino-4-methoxy-2-methyl-hex-2-ethyl enoate (25d). After purification by flash chromatography on silica gel (EtOAc), amine **25d** was obtained as a colorless oil (81% from bromide **24d**). R_f 0.43 (EtOAc: MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 1.45 (bs, 1H), 1.62 – 1.88 (m, 2H), 1.88 (d, J = 1.5 Hz, 3H), 2.66 – 2.76 (m, 2H), 3.26 (s, 3H), 3.77 (s, 2H), 4.11 – 4.18 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 6.59 (dq, J = 1.5, 9.0 Hz, 1H), 7.22 – 7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.2, 35.0, 45.5, 54.1, 56.7, 60.8, 76.2, 126.9, 128.1, 128.4, 130.3, 140.4, 141.7, 167.6 ppm; IR (neat) $\nu_{max.}$ 3340, 3070, 3040,

2990, 2940, 2830, 1715, 1655, 1495, 1260, 1140, 750, 705 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.15; H, 8.62; N, 4.88.

(±)-6-Benzylamino-4-fluoro-2-methyl-hex-2-ethyl enoate (25e). After purification by flash chromatography on silica gel (EtOAc), amine **25e** was obtained as a colorless oil (63% from bromide **24e**). R_f 0.65 (EtOAc: MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.42 (bs, 1H), 1.72 – 2.08 (m, 2H), 1.88 (dd, *J* = 1.5, 3.0 Hz, 3H), 2.73 – 2.85 (m, 2H), 3.79 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 5.43 (dddd, *J* = 4.0, 8.0, 49.0 Hz, 1H), 6.73 (ddq, *J* = 1.5, 8.0, 14.0 Hz, 1H), 7.23 – 7.36 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.2, 35.2, 35.4, 44.7, 44.8, 53.9, 54.0, 61.0, 84.5, 87.6, 89.2, 127.0, 128.1, 128.4, 137.7, 137.9, 140.2, 167.3 ppm; IR (neat) $\nu_{max.}$ 3340, 3090, 3070, 3040, 2990, 2840, 1720, 1660, 1500, 1260, 1035, 750, 705 cm^{-1}; MS (FAB) 280 (40%, MH), 91 (100%); HRMS Calcd for $C_{16}H_{23}FNO_2$ (MH) 280.1713, found 280.1704 (+3.2 ppm). Anal. Calcd for $C_{16}H_{22}FNO_2$: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.24; H, 8.13; N, 5.00.

6-*Iso*-propylamino-2-methyl-hex-2-ethyl enoate (25f). After purification by flash chromatography on silica gel (EtOAc), amine **25f** was obtained as a colorless oil (73% from bromide **24a**). R_f 0.35 (EtOAc:MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.2 Hz, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.62 (quin, *J* = 7.3 Hz, 2H), 1.83 (s, 3H), 2.19 – 2.24 (m, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.78 (sep, *J* = 6.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H) ppm; IR (neat) $\nu_{max.}$ 3360, 2970, 1710, 1650, 1260, 750 cm^{-1}; MS (FAB) *m/z* 214 (100%, MH^+), 198 (9%, M^+-15); HRMS Calcd for $C_{12}H_{24}NO_2$ (MH) 214.1807, found 214.1814 (-3.2 ppm). Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 64.81; H, 10.76; N, 6.27.

6-*tert*-Butylamino-2-methyl-hex-2-ethyl enoate (25g). After purification by flash chromatography on silica gel (EtOAc), amine **25g** was obtained as a colorless oil (85% from

bromide **24a**). R_f 0.35 (EtOAc:MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.60 (quin, *J* = 7.5 Hz, 2H), 1.83 (d, *J* = 1.1 Hz, 3H), 2.22 (q, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 6.75 (tq, *J* = 1.1, 7.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.3, 26.7, 29.0, 29.9, 42.2, 50.4, 60.4, 128.0, 141.7, 168.2 ppm; IR (neat) $\nu_{max.}$ 3360, 2970, 1710, 1650, 1270 cm^{-1}; MS (FAB) *m/z* 228 (100%, MH^+), 212 (32%, MH^+-15); HRMS Calcd for $C_{13}H_{26}NO_2$ (MH) 228.1964, found 228.1973 (- 4.2 ppm). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 67.06; H, 11.27; N, 6.17.

6-((1*S*)-1-Phenyl-ethyl)-amino-2-methyl-hex-2-ethyl enoate (25h). After purification by flash chromatography on silica gel (EtOAc), amine **25h** was obtained as a colorless oil (86% from bromide **24a**). R_f 0.43 (EtOAc:MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (bs, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.59 (quin, *J* = 7.5 Hz, 2H), 1.81 (d, *J* = 1.5 Hz, 3H), 2.18 (sep, *J* = 7.5 Hz, 2H), 2.40 - 2.56 (m, 2H), 3.75 (q, *J* = 6.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.72 (tq, *J* = 1.5, 7.5 Hz, 1H), 7.20 – 7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.2, 24.3, 26.4, 29.1, 47.3, 58.2, 60.3, 126.4, 126.8, 127.9, 128.3, 141.6, 145.7, 168.1 ppm; IR (neat) $\nu_{max.}$ 3340, 3070, 3040, 2940, 2870, 1710, 1650, 1495, 1270, 740, 700 cm^{-1}; MS (FAB) *m/z* 276 (100%, MH^+), 260 (14%, M^+-15), 105 (100%). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.13; H, 9.59; N, 5.24.

General procedure for the preparation of compounds 1, 4-8, 10, and 12 from corresponding amines 25a-h.

To a mixture of 2,2'–dithiobisbenzothiazole (0.55 equiv) in CH_2Cl_2 (0.4 M) were added successively pyridine (0.1 equiv) and oxalyl chloride (0.55 equiv). The mixture was stirred at reflux for 20 minutes. This solution was then added dropwise via cannula to a solution of the appropriate amine (1.0 equiv) and Et_3N (5.0 equiv) in Et_2O (0.3 M) recooled to 0° C. The

reaction mixture was stirred at room temperature for 20 minutes and then diluted with Et_2O (0.01 M). The organic layer was washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

6-[(Benzothiazol-2-ylsulfanyl)-benzyl-amino]-2-methyl-hex-2-ethyl enoate (1). After purification by flash chromatography on silica gel (hexane:EtOAc, 8:2), benzothiazolyle **1** was obtained as a yellowish resin (78% from amine **25a**). R_f 0.44 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.79 (s, 3H), 1.84 (quin, *J* = 7.5 Hz, 2H), 2.16 (q, *J* = 7.5 Hz, 2H), 3.09 (t, *J* = 7.5 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.37 (s, 2H), 6.67 (t, *J* = 7.5 Hz, 1H), 7.27 – 7.44 (m, 7H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.2, 25.9, 26.9, 56.0, 60.3, 63.5, 120.9, 121.6, 123.7, 125.9, 127.8, 128.4, 129.0, 134.9, 137.2, 140.8, 154.6, 167.9, 175.7 ppm; IR (neat) $\nu_{max.}$ 3070, 3020, 2990, 2950, 2860, 1715, 1655, 1565, 1475, 1030, 1015, 735, 675 cm^{-1}; MS (FAB) 427 (34%, MH), 260 (45%, M - 166), 167 (23%, $C_7H_5NS_2$), 91 (100%); HRMS Calcd for $C_{23}H_{27}N_2O_2S_2$ (MH) 427.1514, found 427.1522 (-1.9 ppm).

6-[(Benzothiazol-2-ylsulfanyl)-isopropyl-amino]-2-methyl-hex-2-ethyl enoate (4). After purification by flash chromatography on silica gel (hexane:EtOAc, 8:2), benzothiazolyle **4** was obtained as a yellowish resin (86% from amine **25f**). R_f 0.54 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.2 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.83 (s, 3H), 1.88 (quin, *J* = 7.5 Hz, 2H), 2.24 (q, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 3.39 (sep, *J* = 6.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.72 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.2, 26.3, 27.8, 55.9, 58.1, 60.4, 120.8, 121.4, 123.5, 125.8, 128.3, 134.7, 141.0, 155.0, 168.0, 179.8 ppm; IR (neat) $\nu_{max.}$ 3070, 2980, 2940, 2870, 1715, 1655, 1570, 1475, 1030, 1015,735, 675

cm^{-1}; MS (FAB) 379 (53%, MH), 212 (100%, M - 166), 167 (45%, $C_7H_5NS_2$); HRMS Calcd for $C_{19}H_{27}N_2O_2S_2$ (MH) 379.1514, found 379.1493 (+5.5 ppm). Anal. Calcd for $C_{19}H_{26}N_2O_2S_2$: C, 60.28; H, 6.92; N, 7.40; S, 16.94. Found: C, 60.04; H, 6.88; N, 7.50; S, 16.86.

6-[(Benzothiazol-2-ylsulfanyl)-*tert*-butyl-amino]-2-methyl-hex-2-ethyl enoate (5). After purification by flash chromatography on silica gel (hexane: EtOAc, 19:1), benzothiazolyle **5** was obtained as a yellowish resin (83% from amine **25g**). R_f 0.61 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 9H), 1.82 (s, 3H), 1.88 (bs, 2H), 2.21 (bs, 2H), 2.98 (bs, 1H), 3.20 (bs, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.2, 26.4, 27.9, 28.5, 52.8, 60.4, 60.5, 120.8, 121.3, 123.4, 125.8, 128.2, 134.7, 141.1, 154.9, 168.0, 180.7 ppm; IR (neat) $\nu_{max.}$ 3070, 2990, 2870, 1715, 1655, 1570, 1475, 1030, 1015, 735, 670 cm^{-1}; MS (FAB) 393 (65%, MH), 226 (100%, M - 166), 167 (53%, $C_7H_5NS_2$); HRMS Calcd for $C_{20}H_{29}N_2O_2S_2$ (MH) 393.1671, found 393.1663 (+1.9 ppm). Anal. Calcd for $C_{20}H_{28}N_2O_2S_2$: C, 61.19; H, 7.19; N, 7.14; S, 16.33. Found: C, 61.02; H, 7.24; N, 7.13; S, 16.33.

6-[(Benzothiazol-2-ylsulfanyl)-((1*S*)-1-phenyl-ethyl-amino]-2-methyl-hex-2-ethyl enoate (6). After purification by flash chromatography on silica gel (hexane:EtOAc, 8:2), benzothiazolyle **6** was obtained as a yellowish resin (79% from amine **25h**). R_f 0.51 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.65 (d, *J* = 7.0 Hz, 3H), 1.76 (s, 3H), 1.81 (quin, *J* = 7.5 Hz, 2H), 2.02 – 2.16 (m, 2H), 2.95 (bs, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.37 (bs, 1H), 6.62 (t, *J* = 7.5 Hz, 1H), 7.24 – 7.46 (m, 7H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.2, 19.8, 26.1, 27.2, 55.8, 60.3, 65.5, 120.9, 121.5, 123.6, 125.9, 127.3, 127.7, 128.2, 128.4, 134.7, 140.9, 154.7,

167.9, 178.7 ppm; IR (neat) $\nu_{max.}$ 3060, 3020, 2980, 2940, 2870, 1715, 1650, 1565, 1470, 1030, 1015, 730, 670 cm^{-1}; MS (FAB) 441 (11%, MH), 274 (38%, M - 166), 167 (13%, $C_7H_5NS_2$), 105 (100%); HRMS Calcd for $C_{24}H_{29}N_2O_2S_2$ (MH) 441.1671, found 441.1690 (-4.4 ppm). Anal. Calcd for $C_{24}H_{28}N_2O_2S_2$: C, 65.42; H, 6.41; N, 6.36; S, 14.55. Found: C, 65.57; H, 6.61; N, 6.46; S, 14.34.

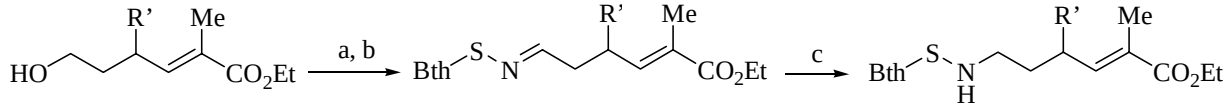
7-[(Benzothiazol-2-ylsulfanyl)-benzyl-amino]-2-methyl-hept-2-ethyl enoate (7). After purification by flash chromatography on silica gel (Hexane:EtOAc, 20:1), benzothiazolyle **7** was obtained as a yellowish resin (74% from amine **25b**). R_f 0.57 (Hexane: EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.43 (quin, *J* = 7.5 Hz, 2H), 1.72 (quin, *J* = 7.5 Hz, 2H), 1.76 (d, *J* = 1.5 Hz, 3H), 2.11 (q, *J* = 7.5 Hz, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.35 (s, 2H), 6.69 (tq, *J* = 1.5, 7.5 Hz, 1H), 7.27 – 7.43 (m, 8H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.3, 25.8, 27.7, 28.3, 56.1, 60.4, 63.5, 84.5, 121.0, 121.7, 123.7, 125.9, 127.9, 128.1, 128.5, 129.0, 134.9, 137.4, 141.6, 154.7, 168.2, 176.3 ppm; IR (neat) $\nu_{max.}$ 3070, 3040, 2990, 2950, 2860, 1715, 1655, 1565, 1470, 1030, 1015, 730, 675 cm^{-1}; MS (FAB) 441 (47%, MH), 274 (74%, M-166), 167 (39%, $C_7H_5NS_2$), 91 (100%); HRMS Calcd for $C_{24}H_{29}N_2O_2S_2$ (MH) 441.1671, found 441.1686 (-3.5 ppm).

(±)-6-[(Benzothiazol-2-ylsulfanyl)-benzyl-amino]-2,4-dimethyl-hex-2-ethyl enoate (8). After purification by flash chromatography on silica gel (hexane:EtOAc, 20:1), benzothiazolyle **8** was obtained as a yellowish resin (71% from amine **25c**). R_f 0.64 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.6 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.66 – 1.87 (m, 2H), 1.78 (s, 3H), 2.46 – 2.56 (m, 1H), 3.01 (t, *J* = 7.3 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.33 (s, 2H), 6.48 (d, *J* = 10.0 Hz, 1H), 7.24 – 7.44 (m, 7H), 7.82 (d, *J* = 8.0 Hz,

1H), 7.85 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 14.2, 19.8, 30.8, 34.7, 54.4, 60.4, 63.4, 120.9, 121.6, 123.6, 125.8, 126.9, 127.8, 128.3, 129.0, 134.8, 137.1, 146.5, 154.6, 168.0, 176.0 ppm; IR (neat) $\nu_{max.}$ 3070, 3040, 2970, 2940, 2870, 1710, 1655, 1565, 1475, 1030, 1015, 730, 675 cm^{-1}; MS (FAB) 441 (35%, MH), 274 (46%, M - 166), 167 (20%, $C_7H_5NS_2$), 91 (100%); HRMS Calcd for $C_{24}H_{29}N_2O_2S_2$ (MH) 441.1671, found 441.1659 (+2.6 ppm). Anal. Calcd for $C_{24}H_{28}N_2O_2S_2$: C, 65.42; H, 6.41; N, 6.36. Found: C, 65.22; H, 6.65; N, 6.46.

(±)-6-[(Benzothiazol-2-ylsulfanyl)-benzyl-amino]-4-methoxy-2-methyl-hex-2-ethyl enoate (10). After purification by flash chromatography on silica gel (hexane:EtOAc, 20:1), benzothiazolyle **10** was obtained as a yellowish resin (62% from amine **25d**). R_f 0.31 (EtOAc:Hexane, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.83 (d, *J* = 1.5 Hz, 3H), 1.84 – 2.01 (m, 2H), 3.17 (s, 3H), 3.17 – 3.24 (m, 2H), 4.04 (dt, *J* = 4.0, 8.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.37 (d, *J* = 2.4 Hz, 2H), 6.52 (dq, *J* = 1.5, 8.8 Hz, 1H), 7.28 – 7.44 (m, 7H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.2, 33.2, 52.6, 56.6, 60.8, 63.8, 75.1, 84.5, 121.0, 121.7, 123.8, 125.9, 127.9, 128.5, 129.2, 130.4, 134.9, 137.3, 141.2, 154.7, 158.3, 167.5 ppm; IR (neat) $\nu_{max.}$ 3070, 3030, 2980, 2940, 2870, 2820, 1715, 1655, 1565, 1475, 1120, 1030, 1015, 730, 670 cm^{-1}; MS (FAB) 457 (29%, MH), 425 (2%, M - 31), 290 (47%, M - 166), 167 (28%, $C_7H_5NS_2$), 91 (100%); HRMS Calcd for $C_{24}H_{29}N_2O_3S_2$ (MH) 457.1620, found 457.1641 (-4.7 ppm). Anal. Calcd for $C_{24}H_{28}N_2O_3S_2$: C, 63.13; H, 6.18; N, 6.13; S, 14.04. Found: C, 62.82; H, 6.06; N, 6.09; S, 13.84.

(±)-6-[(Benzothiazol-2-ylsulfanyl)-benzyl-amino]-4-fluoro-2-methyl-hex-2-ethyl enoate (12). After purification by flash chromatography on silica gel (hexane:EtOAc, 20:1), benzothiazolyle **12** was obtained as a yellowish resin (77% from amine **25e**). R_f 0.56 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.83 (s, 3H), 1.98 – 2.22 (m, 2H), 3.19 – 3.37 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.40 (d, *J* = 2.0 Hz, 2H), 5.33 (dddd, *J* = 4.0, 8.0, 49.0 Hz, 1H), 6.68 (ddq, *J* = 1.5, 8.0, 14.0 Hz, 1H), 7.28 – 7.48 (m, 7H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.1, 33.3, 33.5, 51.8, 60.9, 63.9, 86.7, 88.3, 121.0, 121.7, 123.9, 126.0, 128.0, 128.5, 129.0, 130.9, 131.0, 134.8, 137.0, 137.3, 154.5, 167.1 ppm; IR (neat) $\nu_{max.}$ 3070, 3020, 2990, 2960, 2940, 2860, 1720, 1660, 1470, 1030, 1015, 730, 675 cm^{-1}; MS (FAB) 445 (10%, MH), 425 (2%, M - 19), 278 (22%, M - 166), 167 (24%, $C_7H_5NS_2$), 91 (100%, MH-354); HRMS Calcd for $C_{23}H_{26}FN_2O_2S_2$ (MH) 445.1420, found 445.1427 (-1.6 ppm). Anal. Calcd for $C_{23}H_{25}FN_2O_2S_2$: C, 62.14; H, 5.67; N, 6.30. Found: C, 62.22; H, 5.63; N, 6.34.



23a: R'= H
23c: R'= Me
23d: R'= OMe

17: R'= H (84%)
19: R'= Me (51%)
21: R'= OMe (50%)

15: R'= H (87%)
16: R'= Me (94%)

Conditions: (a) 1) PCC, CH_2Cl_2, molecular sieves 4A. (b) $BthSNH_2$, CH_2Cl_2, molecular sieves 4A. (c) $NaBH_4$, $CHCl_3$, CH_3OH.

Scheme 2.

General procedure for the preparation of imines 17, 19, and 21 from alcohols 23a, 23c-d.

To a solution of the appropriate alcohol (1.0 equiv) in CH_2Cl_2 (0.2 M) at 0° C were added successively the 4Å molecular sieve (50% p/p) and the PCC (2.0 equiv). The reaction mixture was brought to room temperature and stirred until the transformation of the alcohol was judged complete by TLC (1-3 hours). The mixture was then filtered on Florisil® and rinced with Et_2O. The filtrate was concentrated under reduced pressure and the resultant crude aldehyde was quickly purified by flash chromatography on silica gel. The corresponding aldehyde (1.0 equiv) was solubilized in CH_2Cl_2 (0.2 M). 4Å molecular sieve (50% p/p) and the *S*-Benzothiazol-2-yl-thiohydroxylamine (1.1 equiv) were added to the solution, and the mixture was stirred until the transformation of the aldehyde was judged complete by TLC (2–7 days). The reaction mixture was then filtered on Celite® and concentrated under reduced pressure.

6-(Benzothiazol-2-ylsulfanylimino)-2-methyl-hex-2-ethyl enoate (17). Purification of the crude product by flash chromatography on silica gel (hexane:EtOAc, 8:2) was performed to arrive at an inseparable isomer mixture (ratio of 1.3:1.0) of imine **17** (84% from alcohol **23a**) as a yellowish resin. R_f 0.21 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) (maj.) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.89 (s, 3H), 2.48 – 2.68 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.81 (tq, *J* = 1.5, 7.0 Hz, 1H), 7.26 – 7.46 (m, 2H), 7.80 – 7.90 (m, 2H), 8.16 (t, *J* = 4.0 Hz, 1H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) (min.) δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.89 (s, 3H), 2.48 – 2.68 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.74 (tq, *J* = 1.5, 7.0 Hz, 1H), 7.26 – 7.46 (m, 2H), 7.80 – 7.90 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (maj. + min.) δ 12.5, 12.6, 14.2, 24.0, 24.3, 34.1, 36.5, 60.5, 60.7, 120.9, 121.0, 121.7, 121.9, 123.8, 124.0, 126.0, 129.1, 130.0, 134.8, 134.9, 138.2, 139.6, 153.9, 164.6, 165.4, 167.6, 167.9, 171.7 ppm; IR (10 mg/1 mL $CDCl_3$) $\nu_{max.}$ 3060, 2980, 2960, 2930, 2900,

2240, 1700, 1650, 1620, 1190, 1010 cm^{-1}; MS (FAB) *m/z* 335 (100%, MH^+), 168 (17%, M^+-166), 167 (18%, $C_7H_5NS_2$); HRMS Calcd for $C_{16}H_{19}N_2O_2S_2$ (MH) 335.0888, found 335.0900 (-3.6 ppm). Anal. Calcd for $C_{16}H_{18}N_2O_2S_2$: C, 57.46; H, 5.42; N, 8.38; S, 19.17. Found: C, 57.43; H, 5.45; N, 8.40; S, 19.40.

(±)-6-(Benzothiazol-2-ylsulfanylimino)-2,4-dimethyl-hex-2-ethyl enoate (19). Purification of the crude product by flash chromatography on silica gel (hexane:EtOAc, 8:2) was performed to arrive at an inseparable isomer mixture (ratio of 1.2:1.0) of imine **19** (51% from alcohol **23c**) as a yellowish resin. R_f 0.33 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) (maj.) δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.88 (s, 3H), 2.34 – 2.62 (m, 2H), 2.92 – 3.04 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.58 (d, *J* = 11.0 Hz, 1H), 7.24 – 7.46 (m, 2H), 7.78 (t, *J* = 5.0 Hz, 1H), 7.80 – 7.90 (m, 2H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) (min.) δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.90 (s, 3H), 2.34 – 2.62 (m, 2H), 2.92 – 3.04 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.62 (d, *J* = 11.0 Hz, 1H), 7.24 – 7.46 (m, 2H), 7.80 – 7.90 (m, 2H), 8.05 (t, *J* = 5.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (maj. + min.) δ 12.7, 14.2, 19.9, 30.5, 30.7, 41.8, 44.2, 60.6, 60.7, 120.9, 121.0, 121.7, 121.9, 123.8, 124.0, 126.0, 127.6, 128.3, 134.8, 134.9, 144.0, 144.9, 153.8, 153.9, 164.0, 165.3, 167.8, 168.0, 171.5, 171.8 ppm; IR (10 mg/1 mL $CDCl_3$) $\nu_{max.}$ 3070, 2970, 2940, 2910, 2880, 2240, 1715, 1650, 1620, 1280, 1010 cm^{-1}; MS (FAB) *m/z* 349 (100%, MH^+), 182 (9%, M^+-166), 167 (18%, $C_7H_5NS_2$); HRMS Calcd for $C_{17}H_{21}N_2O_2S_2$ (MH) 349.1045, found 349.1057 (-3.5 ppm). Anal. Calcd for $C_{17}H_{20}N_2O_2S_2$: C, 58.59; H, 5.78; N, 8.04. Found: C, 58.71; H, 5.86; N, 7.76.

(±)-6-(Benzothiazol-2-ylsulfanylimino)-4-methoxy-2-methyl-hex-2-ethyl enoate (21). Purification of the crude product by flash chromatography on silica gel (hexane:EtOAc, 9:1) was performed to arrive at an inseparable isomer mixture (ratio of 1.1:1.0) of imine **21** (50% from

alcohol **23d**) as a yellowish resin. R_f 0.34 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) (maj.) δ 1.32 (t, *J* = 7.0 Hz, 3H), 1.96 (s, 3H), 2.50 – 2.86 (m, 2H), 3.33 (s, 3H), 4.18 – 4.26 (m, 2H), 4.37 – 4.45 (m, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 7.28 – 7.46 (m, 2H), 7.81 – 7.91 (m, 2H), 7.94 (t, *J* = 4.6 Hz, 1H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) (min.) δ 1.30 (t, *J* = 7.0 Hz, 3H), 1.95 (s, 3H), 2.50 – 2.86 (m, 2H), 3.33 (s, 3H), 4.18 – 4.26 (m, 2H), 4.37 – 4.45 (m, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 7.28 – 7.46 (m, 2H), 7.81 – 7.91 (m, 2H), 8.15 (t, *J* = 5.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (maj. + min.) δ 13.1, 14.2, 40.2, 42.7, 56.8, 56.9, 61.0, 61.1, 73.9, 74.7, 120.9, 121.0, 121.8, 121.9, 123.9, 124.0, 126.0, 131.4, 131.9, 134.9, 139.1, 139.7, 153.9, 154.0, 162.1, 163.7, 167.1, 167.3, 171.7 ppm; IR (10 mg/1 mL $CDCl_3$) $\nu_{max.}$ 3070, 2990, 2940, 2910, 2830, 2240, 1710, 1655, 1615, 1270, 1030 cm^{-1}; MS (FAB) 365 (46%, MH), 157 (100%); HRMS Calcd for $C_{17}H_{21}N_2O_3S_2$ (MH) 365.0994, found 365.0983 (+2.9 ppm). Anal. Calcd for $C_{17}H_{20}N_2O_3S_2$: C, 56.02; H, 5.53; N, 7.69; S, 17.59. Found: C, 55.89; H, 5.11; N, 7.71; S, 17.46.

General procedure for the preparation of amines 15 and 16 from imines 17 and 19.

The appropriate imine (1.0 equiv) was solubilized in a mixture of MeOH and $CHCl_3$ (1:1, 0.15 M) at 0° C. Sodium borohydride (0.7 equiv) was added, and the solution was stirred for 15 min at room temperature. The reaction mixture was then diluted with $CHCl_3$, and the organic layer was washed with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

6-(Benzothiazol-2-ylsulfanylamino)-2-methyl-hex-2-ethyl enoate (15). After purification by flash chromatography on silica gel (Hexane:EtOAc, 8:2), amine **15** was obtained as a colorless oil (87% from imine **17**). R_f 0.53 (Hexane:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.78 (quin, *J* = 7.1 Hz, 2H), 1.84 (s, 3H), 2.28 (q, *J* = 7.0 Hz,

2H), 3.16 (q, *J* = 7.0 Hz, 2H), 3.38 (t, *J* = 5.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 6.74 (t, *J* = 7.5 Hz, 1H), 7.24 – 7.43 (m, 2H), 7.76 – 7.84 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.2, 25.8, 29.2, 52.3, 60.5, 121.0, 121.5, 123.7, 125.9, 128.6, 134.9, 140.7, 154.7, 168.0, 177.8 ppm; IR (neat) $\nu_{max.}$ 3060, 2980, 2930, 2860, 1705, 1650, 1265, 1090, 760 cm^{-1}; MS (FAB) *m/z* 337 (100%, MH^+), 170 (16%, M^+-166), 167 (27%, $C_7H_5NS_2$); HRMS Calcd for $C_{16}H_{21}N_2O_2S_2$ (MH) 337.1045, found 337.1052 (-2.2 ppm).

(±)-6-(Benzothiazol-2-ylsulfanylamino)-2,4-dimethyl-hex-2-ethyl enoate (16). After purification by flash chromatography on silica gel (Hexane:EtOAc, 19:1), amine **16** was obtained as a colorless oil (94% from imine **19**). R_f 0.51 (Hexane:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.6 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.57 – 1.82 (m, 2H), 1.85 (s, 3H), 2.58 – 2.71 (m, 1H), 3.02 – 3.16 (m, 2H), 3.32 (t, *J* = 5.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.53 (d, *J* = 10.0 Hz, 1H), 7.23 – 7.43 (m, 2H), 7.76 – 7.84 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 14.2, 20.0, 30.8, 37.2, 50.9, 60.5, 121.0, 121.5, 123.7, 125.9, 127.2, 134.9, 146.4, 154.8, 168.2, 177.9 ppm; IR (neat) $\nu_{max.}$ 3050, 2950, 2920, 2860, 1700, 1645, 1270, 1090, 750 cm^{-1}; MS (FAB) *m/z* 351 (100%, MH^+), 167 (32%, $C_7H_5NS_2$); HRMS Calcd for $C_{17}H_{23}N_2O_2S_2$ (MH) 351.1201, found 351.1208 (-2.0 ppm).

General procedure for the preparation of compounds 2a, 2b, 9a, 9b, 11a, 11b, 13a, 13b, 14a, and 14b by tandem cyclization/radical reductions of benzothiazolyles 1, 8, 10, and 12.

The appropriate benzothiazolyle (1.0 equiv) and AIBN (0.15 equiv) were solubilized in anhydrous THF (99.9%, Aldrich) (0.03 M). Tributyltin hydride (2.0 equiv) in solution with anhydrous THF (0.3 M) was added dropwise to the reaction mixture via syringe pump over a 3 hour period. AIBN (0.15 equiv) was added at 30 min intervals, and the reaction mixture was

irradiated for 10 min (solar lamp; 275 W). After the addition of Bu_3SnH, the reaction mixture was stirred for 1 h (for the reactions performed at below room temperatures, 1,3-dinitrobenzene was added 15 minutes before the reaction mixtures were allowed to warm). The mixture was then concentrated under reduced pressure.

(±)-(2*R*)-2-[(2*S*)-1-Benzyl-pyrrolidin-2-yl]-ethyl propionate (2a) and (±)-(2*S*)-2-[(2*S*)-1-Benzyl-pyrrolidin-2-yl]-ethyl propionate (2b). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of compounds **2a** and **2b** in a ratio of 2:1. After purification by flash chromatography on silica gel (hexane:EtOAc, 24:1), pyrrolidines **2a** and **2b** were isolated as an inseparable mixture of isomers (colorless oil) (73% from **1**). R_f 0. 46 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) (**2a**) δ 1.22 (d, *J* = 6.6 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.60 – 1.98 (m, 4H), 2.08 – 2.18 (m, 1H), 2.68 – 2.96 (m, 3H), 3.20 (d, *J* = 13.0 Hz, 1H), 4.11 – 4.18 (m, 3H), 7.20 – 7.35 (m, 5H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) (**2b**) δ 1.17 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.60 – 1.98 (m, 4H), 2.08 – 2.18 (m, 1H), 2.68 – 2.96 (m, 3H), 3.26 (d, *J* = 13.0 Hz, 1H), 4.0 (d, *J* = 13.0 Hz, 1H), 4.11 – 4.18 (m, 2H), 7.20 – 7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (**2a**) δ 13.9, 14.1, 22.6, 27.1, 42.2, 54.2, 59.3, 59.9, 66.4, 126.5, 127.9, 128.4, 140.0, 175.2 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (**2b**) δ 10.7, 23.0, 26.2, 41.9, 54.0, 58.8, 60.0, 65.0, 126.6, 128.0, 128.4, 139.9, 175.5 ppm; IR (neat) $\nu_{max.}$ 3090, 3060, 3030, 2980, 2880, 2800, 1730, 1610, 1500, 1455, 1250, 1180, 1120, 740, 700 cm^{-1}; MS (FAB) *m/z* 262 (34%, MH^+), 260 (70%), 160 (100%), 91 (76%); HRMS Calcd for $C_{16}H_{22}NO_2$ (M - H) 260.1650, found 260.1659 (-3.3 ppm).

(±)-(2*R*)-2-[(2*S*,3*S*)-1-Benzyl-3-methyl-pyrrolidin-2-yl]-ethyl propionate (9a) and (±)-(2*S*)-2-[(2*S*,3*S*)-1-Benzyl-3-methyl-pyrrolidin-2-yl]-ethyl propionate (9b). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of compounds **9a** and **9b** in a ratio of 1:1.

After purification by flash chromatography on silica gel (hexane:EtOAc, 15:1), pyrrolidines **9a** and **9b** were isolated as an inseparable mixture of isomers (colorless oil) (74% from benzothiazolyle **8**). R_f 0.61 (Hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) (**9b**) δ 0.94 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.23 – 1.34 (m, 1H), 1.79 – 1.92 (m, 1H), 2.05 – 2.15 (m, 1H), 2.19 – 2.31 (m, 1H), 2.56 (t, *J* = 4.6 Hz, 1H), 2.70 (quin, *J* = 6.6 Hz, 1H), 2.83 (t, *J* = 7.7 Hz, 1H), 3.33 (d, *J* = 13.2 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 7.19 – 7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (**9a**) δ 13.1, 14.3, 21.4, 31.5, 35.4, 42.5, 52.3, 60.0, 60.1, 74.2, 126.6, 128.1, 128.5, 140.2, 175.9 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (**9b**) δ 11.2, 14.3, 21.3, 32.1, 33.8, 42.0, 51.9, 59.4, 60.1, 73.4, 126.6, 128.1, 128.4, 140.1, 175.6 ppm; IR (neat) $\nu_{max.}$ 3090, 3060, 3030, 2960, 2870, 2790, 1730, 1610, 1500, 1455, 1250, 1190, 1120, 745, 705 cm^{-1}; MS (FAB) *m/z* 276 (42%, MH^+), 174 (100%), 91 (51%); HRMS Calcd for $C_{17}H_{26}NO_2$ (MH) 276.1964, found 276.1968 (-1.6 ppm). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.95; H, 9.43; N, 5.13.

(±)-(2*R*)-2-[(2*R*,3*S*)-1-Benzyl-3-methoxy-pyrrolidin-2-yl]-ethyl propionate (11a) and (±)-(2*S*)-2-[(2*R*,3*S*)-1-Benzyl-3-methoxy-pyrrolidin-2-yl]-ethyl propionate (11b). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of compounds **11a** and **11b** in a ratio of 2:1. Purification by flash chromatography on silica gel (hexane:EtOAc, 19:1) allowed the separation of pyrrolidines **11a** and **11b** (56% from benzothiazolyle **10**) as a colorless oil.

(**11a**): R_f 0.49 (Hexane:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.61 – 1.75 (m, 2H), 2.23 – 2.32 (m, 1H), 2.64 – 2.77 (m, 3H), 3.26 (s, 3H), 3.27 (d, *J* = 13.0 Hz, 1H), 3.91 - 3.93 (m, 1H), 4.02 (d, *J* = 13.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.14 – 7.28 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.2, 29.5, 41.5, 51.9, 56.1, 59.6, 60.1, 73.0, 83.2, 126.7, 128.0, 128.5, 139.8, 175.4 ppm; IR (neat) $\nu_{max.}$ 3080, 3060,

3020, 2970, 2930, 2800, 1730, 1495, 1455, 1100, 750, 700 cm^{-1}; HRMS Calcd for $C_{17}H_{24}NO_3$ (M - H) 290.1756, found 290.1759 (-0.9 ppm). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.73; H, 8.91; N, 4.85.

(**11b**): R_f 0.46 (Hexane:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.63 – 1.79 (m, 2H), 2.29 – 2.36 (m, 1H), 2.61 (quin, *J* = 6.3 Hz, 1H), 2.80 – 2.88 (m, 2H), 3.21 (s, 3H), 3.35 (d, *J* = 13.0 Hz, 1H), 3.65 - 3.67 (m, 1H), 3.99 (d, *J* = 13.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.17 – 7.27 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 14.2, 30.2, 41.5, 51.8, 56.2, 59.4, 60.4, 72.1, 82.7, 126.8, 128.2, 128.4, 139.9, 175.2 ppm; IR (neat) $\nu_{max.}$ 3080, 3060, 3020, 2980, 2930, 2810, 1730, 1490, 1450, 1110, 745, 700 cm^{-1}; MS (FAB) *m/z* 292 (34%, MH^+), 190 (100%), 91 (95%); HRMS Calcd for $C_{17}H_{24}NO_3$ (M - H) 290.1756, found 290.1741 (+5.3 ppm). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.13; H, 9.04; N, 4.82.

(±)-(2*R*)-2-[(2*R*,3*S*)-1-Benzyl-3-fluoro-pyrrolidin-2-yl]-ethyl propionate (13a), (±)-(2*S*)-2-[(2*R*,3*S*)-1-Benzyl-3-fluoro-pyrrolidin-2-yl]-ethyl propionate (13b), (±)-(2*R*)-2-[(2*R*,3*R*)-1-Benzyl-3-fluoro-pyrrolidin-2-yl]- ethyl propionate (14a) and (±)-(2*S*)-2-[(2*R*,3*R*)-1-Benzyl-3-fluoro-pyrrolidin-2-yl]- ethyl propionate (14b). GC analysis of the crude reaction mixture indicated the presence of compounds **13a**, **13b**, **14a**, **14b** in a ratio of 9:4:2:1, respectively. Purification by flash chromatography on silica gel (hexane: EtOAc, 24: 1) allowed the separation of pyrrolidines **13a**, **13b**, and **14a** (67% from benzothiazolyle **12**) as a colorless oil.

(**13a**): R_f 0.81 (Hexane:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.77 – 1.98 (m, 2H), 2.36 – 2.44 (m, 1H), 2.77 – 2.89 (m, 2H), 3.36 (d, *J* = 13.0 Hz, 1H), 4.09 (d, *J* = 13.0 Hz, 1H), 4.15 (d, *J* = 7.1 Hz, 2H), 5.29 – 5.46 (m, 1H), 7.22 – 7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 31.3, 31.6, 40.5, 51.5, 58.9,

60.3, 73.7, 73.9, 94.8, 96.6, 126.9, 128.1, 128.5, 139.3, 175.0 ppm; IR (neat) $\nu_{max.}$ 3080, 3060, 3020, 2970, 2930, 2880, 2800, 1730, 1605, 1495, 1450, 1185, 750, 700 cm^{-1}; MS (FAB) *m/z* 280 (35%, MH^+), 178 (91%), 91 (100%); HRMS Calcd for $C_{16}H_{21}FNO_2$ (M - H) 278.1556, found 278.1568 (-4.2 ppm).

(**13b**): R_f 0.81 (Hexane:EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.72 – 2.06 (m, 2H), 2.43 – 2.52 (m, 1H), 2.57 – 2.66 (m, 1H), 2.92 (t, *J* = 8.0 Hz, 1H), 6.29 (dd, *J* = 5.5, 35.0 Hz, 1H), 3.47 (d, *J* = 13.2 Hz, 1H), 4.05 (d, *J* = 13.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.01 (dd, *J* = 4.5, 53.5 Hz, 1H), 7.21 – 7.34 (m, 5H) ppm; IR (neat) $\nu_{max.}$ 3080, 3060, 3030, 2980, 2940, 2880, 2800, 1735, 1495, 1450, 1185, 745, 700 cm^{-1}; MS (FAB) *m/z* 280 (46%, MH^+), 178 (100%), 91 (89%); HRMS Calcd for $C_{16}H_{23}FNO_2$ (MH) 280.1713, found 280.1710 (+1.1 ppm). Anal. Calcd for $C_{16}H_{22}FNO_2$: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.74; H, 8.19; N, 5.11.

(**14a**): R_f 0.51 (Hexane:EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.85 – 2.14 (m, 2H), 2.16 – 2.26 (m, 1H), 2.85 – 3.08 (m, 3H), 3.21 (d, *J* = 13.0 Hz, 1H), 3.91 (d, *J* = 13.2 Hz, 1H), 4.09 – 4.21 (m, 2H), 5.14 - 5.31 (m, 1H), 7.21 – 7.36 (m, 5H) ppm; IR (neat) $\nu_{max.}$ 3080, 3060, 3030, 2980, 2880, 2800, 1730, 1495, 1455, 1180, 735, 700 cm^{-1}; MS (FAB) *m/z* 280 (33%, MH^+), 178 (79%), 91 (100%); HRMS Calcd for $C_{16}H_{23}FNO_2$ (MH) 280.1713, found 280.1718 (-1.8 ppm). Anal. Calcd for $C_{16}H_{22}FNO_2$: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.93; H, 8.32; N, 5.19.

General procedure for the preparation of compounds 2a, 2b, 9a, and 9b by tandem cyclization/radical reduction of amines 15 and 16.

The appropriate amine (1.0 equiv) as well as the AIBN (0.15 equiv) were solubilized in anhydrous THF (99.9%, Aldrich) (0.03 M). The tributylitin hydride (2.5 equiv) in solution with

the anhydrous THF (0.3 M) was added dropwise to the reaction mixture via syringe pump over a period of 3 hours. AIBN (0.15 equiv) was added at 30 min intervals, and the reaction mixture was irradiated for 10 min (solar lamp; 275 W). After the addition of Bu_3SnH, the reaction mixture was stirred for 1 h (for the reactions performed at below room temperatures, 1,3-dinitrobenzene was added 15 minutes before the reaction mixtures were allowed to warm). The mixture was then concentrated under reduced pressure and diluted in acetonitrile (0.2 M). Et_3N (1.5 equiv) and benzyl bromide (1.5 equiv) were added successively. After being stirred until the transformation of the corresponding amine was complete (15 hours), the reaction mixture was concentrated under reduced pressure.

^{1}H NMR analysis of the crude reaction mixture indicated the presence of compounds **2a** and **2b** in a ratio of 1:1. After purification by flash chromatography on silica gel (hexane:Et_2O, 9:1), pyrrolidines **2a** and **2b** were isolated as a mixture of isomers (colorless oil) (78% from amine **15**).

^{1}H NMR analysis of the reaction mixture indicated the presence of compounds **9a** and **9b** in a ratio of 1:2, respectively. After purification by flash chromatography on silica gel (hexane:Et_2O, 9:1), pyrrolidines **9a** and **9b** were isolated as a mixture of isomers (colorless oil) (77% from amine **16**).

General procedure for the preparation of compounds 18b, 18a, 20b, 20a, 22b, and 22a by tandem cyclization/radical reduction of imines 17, 19, and 21.

The appropriate imine (1.0 equiv) and AIBN (0.15 equiv) were solubilized in anhydrous THF (99.9%, Aldrich) (0.03 M). Tributyltin hydride (2.5 equiv), in solution with anhydrous THF (0.3 M), was added dropwise to the reaction mixture via syringe pump over a period of 3 hours. AIBN (0.15 equiv) was added at 30 min intervals, and the reaction mixture was irradiated for 10 min (solar lamp; 275 W). After the addition of Bu_3SnH, the reaction mixture was stirred for 1 h

(for the reactions performed at below room temperatures, 1,3-dinitrobenzene was added 15 minutes before the reaction mixtures were allowed to warm). The mixture was then concentrated under reduced pressure.

(±)-(2*S*)-2-[(2*S*)-3,4-Dihydro-2*H*-pyrrol-2-yl]-ethyl propionate (18b) and (±)-(2*R*)-2-[(2*S*)-3,4-Dihydro-2*H*-pyrrol-2-yl]-ethyl propionate (18a). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of compounds **18b** and **18a** in a ratio of 6:1, respectively. After purification by flash chromatography on silica gel (EtOAc:MeOH, 49:1), pyrrolenines **18b** and **18a** were isolated as an inseparable mixture of isomers (colorless resin) (90% from imine **17**). R_f 0.53 (EtOAc:MeOH, 20:1); ^{1}H NMR (400 MHz, C_6D_6) (**18b**) δ 0.96 (t, *J* = 7.1 Hz, 3H), 1.00 – 1.12 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.36 – 1.50 (m, 1H), 1.72 – 1.98 (m, 2H), 2.65 (quin, *J* = 7.1 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 4.23 – 4.32 (m, 1H), 7.13 (t, *J* = 1.3 Hz, 1H) ppm; ^{1}H NMR (400 MHz, C_6D_6) (**18a**) δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.00 – 1.12 (m, 1H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.18 – 1.28 (m, 1H), 1.56 – 1.68 (m, 2H), 2.44 (quin, *J* = 7.1 Hz, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 4.15 – 4.23 (m, 1H), 7.14 (t, *J* = 1.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, C_6D_6) (**18b**) δ 13.6, 14.9, 24.3, 37.7, 45.7, 60.7, 76.1, 166.0, 175.3 ppm; ^{13}C NMR (100 MHz, C_6D_6) (**18a**) δ 13.6, 15.6, 25.9, 37.6, 46.7, 60.7, 76.3, 166.3, 175.2 ppm; IR (neat) $\nu_{max.}$ 2970, 2940, 2900, 2880, 1740, 1625, 1260 cm^{-1}; MS (FAB) *m/z* 170 (100%, MH^+); HRMS Calcd for $C_9H_{16}NO_2$ (MH) 170.1181, found 170.1187 (-3.5 ppm).

(±)-(2*S*)-2-[(2*S*,3*S*)-3-Methyl-3,4-dihydro-2*H*-pyrrol-2-yl]-ethyl propionate (20b) and (±)-(2*R*)-2-[(2*S*,3*S*)-3-Methyl-3,4-dihydro-2*H*-pyrrol-2-yl]-ethyl propionate (20a). GC analysis of the crude reaction mixture indicated the presence of compounds **20b** and **20a** in a ratio of 10:1, respectively. After purification by flash chromatography on silica gel (CH_2Cl_2:MeOH, 49:1), pyrrolenines **20b** and **20a** were isolated as an inseparable mixture of isomers (colorless resin) (81% from imine **19**). R_f 0.51 (CH_2Cl_2: MeOH, 20:1); brute formula:

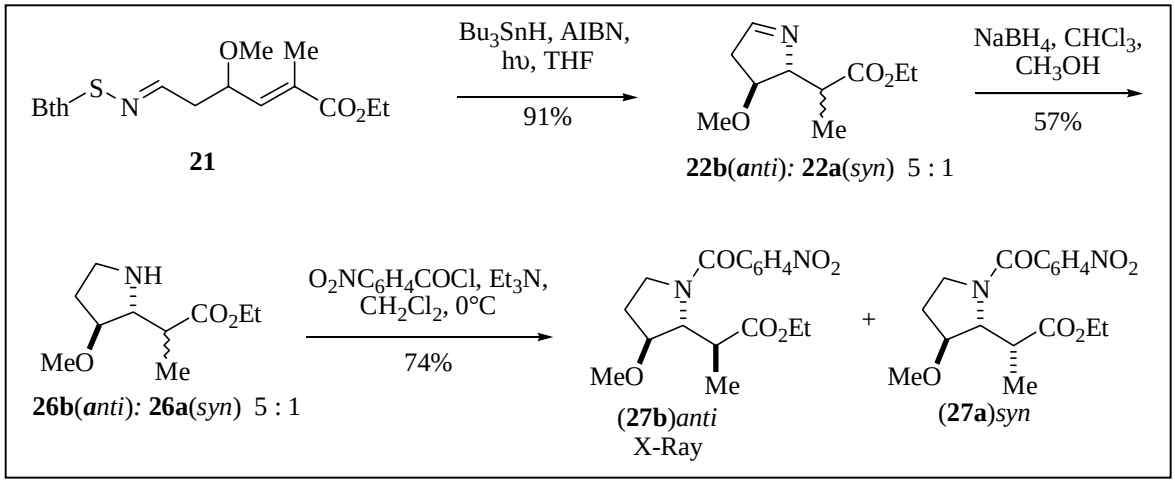
$C_{10}H_{17}NO_2$; MM: 183.25 g/mol; ^{1}H NMR (400 MHz, C_6D_6) (**20b**) δ 0.73 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.48 – 1.57 (m, 1H), 1.69 – 1.78 (m, 1H), 2.06 – 2.16 (m, 1H), 2.72 (quin, *J* = 7.0 Hz, 1H), 3.93 – 4.04 (m, 3H), 7.10 (s, 1H) ppm; ^{1}H NMR (400 MHz, C_6D_6) (**20a**) δ 0.78 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.48 – 1.57 (m, 1H), 1.69 – 1.78 (m, 1H), 2.06 – 2.16 (m, 1H), 2.42 (quin, *J* = 7.0 Hz, 1H), 3.93 – 4.04 (m, 3H), 7.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, C_6D_6) (**20b**) δ 13.2, 14.9, 21.7, 32.1, 44.9, 46.7, 60.7, 83.4, 165.4, 175.0 ppm; ^{13}C NMR (100 MHz, C_6D_6) (**20a**) δ 15.1, 21.3, 22.5, 30.8, 34.0, 45.9, 46.2, 67.9, 165.8, 175.1 ppm; IR (neat) $\nu_{max.}$ 2985, 2940, 2910, 2880, 1730, 1630, 1260, 1125 cm^{-1}; MS (FAB) *m/z* 184 (100%, MH^+); HRMS Calcd for $C_{10}H_{18}NO_2$ (MH) 184.1338, found 184.1341 (-1.9 ppm).

(±)-(2*S*)-2-[(2*R*,3*S*)-3-Methoxy-3,4-dihydro-2*H*-pyrrol-2-yl]-ethyl propionate (22b) and (±)-(2*R*)-2-[(2*R*,3*S*)-3-Methoxy-3,4-dihydro-2*H*-pyrrol-2-yl]-ethyl propionate (22a). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of compounds **22b** and **22a** in a ratio of 5:1, respectively. After purification by flash chromatography on silica gel (CH_2Cl_2:MeOH, 49:1), pyrrolenines **22b** and **22a** were isolated as an inseparable mixture of isomers (colorless resin) (91% from imine **21**). R_f 0.47 (CH_2Cl_2:MeOH, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) (**22b**) δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.99 – 2.20 (m, 2H), 2.64 (quin, *J* = 7.1 Hz, 1H), 2.91 (s, 3H), 3.53 (td, *J* = 2.6, 6.6 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 4.50 – 4.55 (m, 1H), 7.12 – 7.16 (m, 1H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) (**22a**) δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.99 – 2.20 (m, 2H), 2.54 (quin, *J* = 7.1 Hz, 1H), 2.96 (s, 3H), 3.70 (td, *J* = 2.4, 6.6 Hz, 1H), 3.90 (q, *J* = 7.1 Hz, 2H), 4.43 – 4.47 (m, 1H), 7.12 – 7.16 (m, 1H) ppm; ^{13}C NMR (100 MHz, C_6D_6) (**22b**) 13.6, 14.8, 43.5, 44.6, 56.7, 60.9, 80.8, 81.9, 165.2, 174.6 ppm; ^{13}C NMR (100 MHz, C_6D_6) (**22a**) 13.6, 15.0, 43.8, 44.3, 56.7, 60.9, 81.1, 81.9,

165.5, 174.8 ppm; IR (neat) $\nu_{max.}$ 2990, 2940, 2910, 2815, 1730, 1630, 1260, 1105 cm^{-1}; MS (FAB) 200 (100%, MH), 168 (9%, M - 31); HRMS Calcd for $C_{10}H_{18}NO_3$ (MH) 200.1287, found 200.1276 (-1.4 ppm).

The relative configurations of cyclic products as determined by X-ray diffraction and as confirmed by ^{1}H NMR spectra.

Imines **22a** and **22b**, obtained from the cyclization-reduction reaction of compound **21**, were reduced via $NaBH_4$ into the corresponding amines **26a** and **26b** (Scheme 3). The latter were then transformed into crystalline products **27a** and **27b** by the treatment of *p*-nitrobenzoyle chloride. Separation of major isomer **27b** followed by X-ray analysis confirmed the *trans*, *anti* outcome that had been expected. A *trans*, *anti* result was also obtained in the same manner for pyrrolenine **22b**.

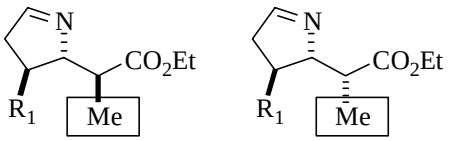


Scheme 3.

(±)-(2*S*)-2-[(2*R*,3*S*)-1-(4-nitrobenzoyl)-3-methoxy-pyrrolidin-2-yl]-ethyl propionate (27b). To a mixture of imines **22b** and **22a** (ratio of 5:1) (0.236 g, 1.184 mmol) in a MeOH:$CHCl_3$ (1:1) solution (8 mL) was added sodium borohydride (31.4 mg, 0.829 mmol). The reaction mixture was stirred for 15 min before the addition of a $NaHCO_3$ saturated aqueous solution (5 mL). The aqueous layer was extracted with $CHCl_3$ (3 X 10 mL), and the combined

organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2:MeOH, 19:1) to arrive at amines **26b** and **26a** (ratio of 5:1) (0.137 g, 0.681 mmol) (57%). To a solution of theses amines (**26b**:**26a** in a 5:1 ratio; 83.8 mg, 0.416 mmol) in CH_2Cl_2 (2 mL) at 0° C were added successively Et_3N (75 μL, 0.541 mmol) and *p*-nitrobenzoyl chloride. The reaction mixture was stirred at room temperature for 1 hour before being concentrated under reduced pressure. Isomers **27b** and **27a** were separated by flash chromatography on silica gel (hexane:EtOAc, 7:3) (0.108 g, 74%). The structure of major isomer **27b** was confirmed by X-ray analysis. R_f 0.61 (CH_2Cl_2:MeOH, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.92 – 2.02 (m, 1H), 2.06 – 2.18 (m, 1H), 3.16 (quin, *J* = 7.0 Hz, 1H), 3.28 – 3.52 (m, 2H), 3.33 (s, 3H), 3.84 (t, *J* = 2.4 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.65 (d, *J* = 6.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 14.1, 30.9, 39.9, 47.9, 56.6, 60.9, 63.5, 81.2, 123.7, 127.9, 142.9, 148.4, 168.4, 173.5 ppm; IR (neat) $\nu_{max.}$ 3080, 2990, 2940, 2910, 2880, 2840, 1720, 1600, 1530, 1430, 1110, 750, 720 cm^{-1}; MS (FAB) *m/z* 351 (100%, MH^+), 305 (42%), 249 (62%), 150 (100%). Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.38; H, 6.62; N, 8.01.

As observed previously, the ^{1}H NMR chemical shift of the hydrogen belonging to the methyl group α to the ester of *anti* compound **22b** was upfield to those of *syn* compound **22a**.



anti *syn*

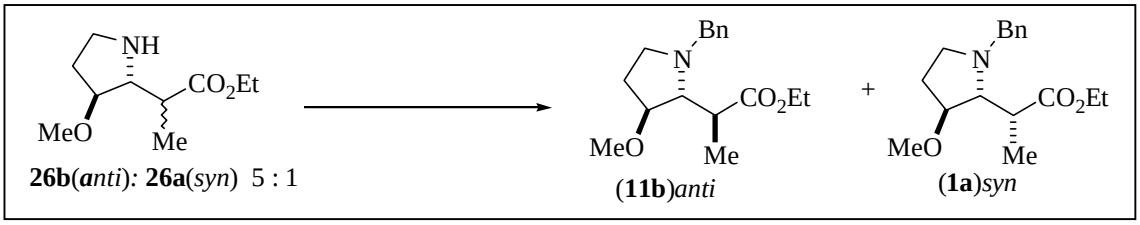
(1.01 ppm vs 1.21 ppm). The relative configurations of pyrrolenines **18a**, **18b**, **20a**, and **20b**, were also deduced by comparing the ^{1}H NMR spectra with that of compounds **22a** and **22b**. The

results obtained are presented in Table 1. For each pair of isomers, the *anti* configuration was assigned to the product bearing the methyl hydrogens with the highest resonance.

Table 1: Proofs of structure for pyrrolenines 18a, 18b, 20a, and 20b as confirmed by ^{1}H NMR spectra.

Entry	Substrate	δCH$_3$ (ppm)	
	R_1	*anti*	*syn*
1	OMe	1.01 (**22b**)	1.21 (**22a**)
2	H	1.01 (**18b**)	1.39 (**18a**)
3	Me	1.02 (**20b**)	1.35 (**20a**)

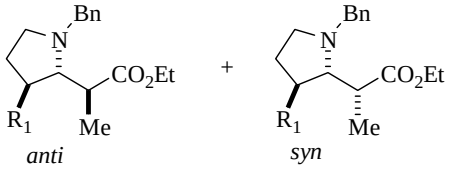
From the determination of the relative configuration of amines **26a** and **26b** in Scheme 3, it was possible to establish the proofs of structure for pyrrolidines **11a** and **11b**. Treating the mixture of amines **26a** and **26b** with benzyl bromide in a mildly basic medium gave pyrrolidines **11a** and **11b,** for which the major isomer **11b** had to have been *trans, anti* (Scheme 4).



Scheme 4

As was the case with the pyrrolenines, the methyl hydrogens of *anti* isomer **11b** resonated higher than those of *syn* isomer **11a** (1.14 ppm vs 1.22 ppm). Again by ^{1}H NMR spectra, the relative configurations of pyrrolidines **2a**, **2b**, **9a**, **9b**, **13a**, and **13b** were determined as *trans, anti* to the isomers bearing the methyl hydrogens with the highest resonance. The relative configurations of the pyrrolidines were also determined and are presented in Table 2.

Table 2: Proofs of structure for pyrrolidines 2a, **2b**, **9a**, **9b**, **13a**, **and 13b as confirmed by ^{1}H NMR spectra.**



Entry	Substrate	δCH3 (ppm)	
	R_1	*anti*	*syn*
1	OMe	1.14 (**11b**)	1.22 (**11a**)
2	H	1.17 (**2b**)	1.22 (**2a**)
3	Me	1.19 (**9b**)	1.26 (**9a**)
4	F	1.18 (**13b**)	1.31 (**13a**)

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