Synthesis of Saturated 1,4-Benzodiazepines via Pd-Catalyzed Carboamination Reactions.

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Supporting Information

Experimental procedures, characterization data for all new compounds, and description of stereochemical assignments (29 pages).

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General Considerations

All reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware using standard Schlenk techniques. All reagents were obtained from commercial sources and used without further purification. Toluene, THF, diethyl ether, and dichloromethane were purified using a GlassContour solvent purification system. Xylenes and diisopropylethylamine

were distilled over CaH_2 before use. Methyl 2-(phenylamino)benzoate,[1] methyl 2-(3,5-dichlorophenylamino)benzoate,[1] methyl 2-(4-methoxyphenylamino)benzoate,[2] *N*-benzylbut-3-enyl-2-amine,[3] *N*-allyloctan-1-amine,[4] *N*-benzylprop-2-en-1-amine,[4] and *tert*-butyl 4-bromobenzoate[5] were prepared according to literature procedures. (*E*)-but-2-enyl acetate was prepared by treatment of crotyl alcohol with acetic anhydride, triethylamine and DMAP at rt in dichloromethane. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The product yields reported in the experimental section are the result of a single experiment whereas the yields in the manuscript are an average of two experiments.

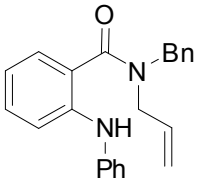
Substrate Synthesis

General Procedure 1: Saponifcation of benzoate substrates. A flask equipped with a magnetic stirbar was charged with the benzoate substrate (1.0 equiv) and a 1:1 mixture of water:EtOH (7.5 mL/mmol substrate). Finely ground KOH (2.5 equiv) was added, and the resulting mixture was heated to reflux for 3 h. The mixture was then cooled to rt and concentrated to remove all of the EtOH. Additional water (15 mL) was added, the mixture was acidified to pH ~ 2 with HCl (1 M), and a precipitate formed. The precipitate was collected by filtration and the crude product was purified by flash column chromatography on silica gel to furnish the pure carboxylic acid product.

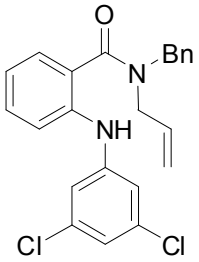
General Procedure 2: Peptide coupling of acid substrates with allylic amines. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate carboxylic acid substrate (1.0 equiv) and *N*-hydroxybenzotriazole, (1.2 equiv). The flask was purged with

nitrogen for 5 min, then the appropriate allylic amine substrate (1.0 equiv), diisopropylethylamine (3.0 equiv), and dichloromethane (3 mL/mmol substrate) were added. The resulting clear solution was stirred for ca. 2 min, then diisopropylcarbodiimide (1.05 equiv) was added. The reaction mixture was stirred for 12–24 h and then concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel to afford the pure benzamide product.

General Procedure 3: Reduction of amides to amine substrates. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate benzamide substrate (1.0 equiv) and purged with nitrogen for 5 min. THF (1 mL/mmol substrate) was added, the resulting solution was cooled to 0 °C, and a 1 M solution of $LiAlH_4$ in diethyl ether (1.0 equiv) was added slowly over 5 min. The reaction mixture was stirred at 0 °C for 15 min then warmed to rt and stirred until TLC analysis indicated complete consumption of starting material. The reaction mixture was cooled to 0 °C, then water (0.05 mL/mmol substrate), 6 M NaOH (0.05 mL/mmol substrate) and additional water (0.15 mL/mmol substrate) were sequentially added. The resulting white suspension was stirred vigorously for 30 min, then filtered and the white precipitate was washed with diethyl ether (3 × 30 mL). The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting product was purified by flash column chromatography on silica gel.



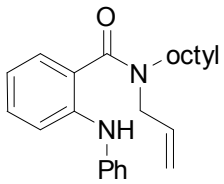
***N*-Allyl-*N*-benzyl-2-(phenylamino)benzamide (13b).** 2-(Phenylamino)benzoic acid (1.02 g, 4.8 mmol) was coupled with *N*-benzylprop-2-en-1-amine (680 mg, 4.6 mmol) for 24 h using General Procedure 2. Flash chromatography on silica gel (90:10 hexanes:ethyl acetate) afforded 1.40 g (89%) of the title compound as a white solid, m.p. 73–75 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.33 (d, *J* = 8.0 Hz, 1 H), 7.29–7.18 (m, 8 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.97–6.89 (m, 2 H), 6.83 (t, *J* = 8.0 Hz, 1 H), 5.81–5.69 (m, 1 H), 5.20–5.08 (m, 2 H), 4.67 (s, 2 H), 4.04–3.90 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60°C) δ 171.4, 142.6, 142.2, 136.9, 133.0, 130.2, 129.3, 128.7, 127.7, 127.49, 127.47, 124.7, 121.5, 119.8, 118.9, 117.9, 117.7, 49.4, one aliphatic carbon signal is incidentally equivalent; IR (film) 3332, 1627 cm^{-1}. MS (ESI) 343.1801 (343.1805 calcd for $C_{23}H_{22}N_2O$, $[M + H]^+$).



***N*-Allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (13d).** Methyl 2-(3,5-dichlorophenylamino)benzoate (2.50 g, 8.4 mmol) was saponified according to General Procedure 1. Purification via flash chromatography on silica gel using 50:50 hexanes:ethyl acetate → 100% ethyl acetate as the eluent to afforded 1.81 g (76%) of 2-(3,5-dichlorophenylamino)benzoic acid as a fluffy white solid, m.p. 245–246 °C. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 13.1 (s, br, 1 H), 9.54 (s, br, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.52–7.44 (m, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.22 (d, J = 2.0 Hz, 2 H), 7.11 (s, 1 H), 6.95 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.3, 144.3, 144.2, 134.7, 134.1, 131.9, 120.7, 120.0, 117.3, 116.6, 115.9.

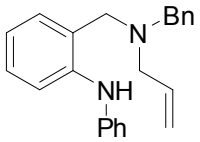
The above 2-(3,5-dichlorophenylamino)benzoic acid (998 mg, 3.5 mmol) was coupled with *N*-benzylprop-2-en-1-amine (556 mg, 3.8 mmol) for 15 h using General Procedure 2. Flash chromatography on silica gel (85:15 hexanes:ethyl acetate) afforded 1.24 g (85%) of the title compound as a white solid, m.p. 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 62 °C) δ 7.38–7.21 (m, 7 H), 7.17 (s, br, 1 H), 7.07–7.00 (m, 1 H), 6.97 (dt, J = 0.8, 7.6 Hz, 1 H), 6.88–6.83 (m, 3 H), 5.81–5.66 (m, 1 H), 5.22–5.07 (m, 2 H), 4.65 (s, 2 H), 4.04–3.83 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 62 °C) δ 170.8, 145.2, 139.9, 136.7, 135.7, 130.6, 128.9, 128.6, 127.7, 127.5, 121.9, 121.8, 120.5, 120.4, 118.1, 115.3, 115.2, 49.1, two aliphatic carbon signals are incidentally equivalent; IR (film) 3298, 1621 cm^{-1}. MS (ESI) 433.0850 (433.0845 calcd for $C_{23}H_{20}Cl_2N_2O$, $[M + Na]^+$).



***N*-Allyl-*N*-octyl-2-(phenylamino)benzamide (13f).** Methyl 2-(phenylamino)benzoate (2.76 g, 12.1 mmol) was saponified according to General Procedure 1. Purification via flash chromatography on silica gel using 70:30 hexanes:ethyl acetate as the eluent to afforded 1.96 g (76%) of 2-(phenylamino)benzoic acid as a white solid, m.p. 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 10.8 (s, br, 1 H), 9.32 (s, br, 1 H), 8.04 (dd, J = 0.8, 6.4 Hz, 1 H), 7.40–7.32 (m,

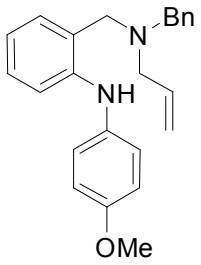
3 H), 7.30–7.20 (m, 3 H), 7.13 (t, J = 5.6 Hz, 1 H), 6.76 (t, J = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 173.7, 148.9, 140.3, 135.2, 132.6, 129.4, 124.1, 123.2, 117.2, 114.0, 110.4; IR (film) 3339, 1658 cm^{-1}.

The above 2-(phenylamino)benzoic acid (1.0 g, 4.7 mmol) was coupled with *N*-allyloctan-1-amine (790 mg, 4.7 mmol) for 24 h using General Procedure 2. Flash chromatography on silica gel (90:10 hexanes:ethyl acetate) afforded 1.55 g (91%) of the title compound as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 60°C) δ 7.33 (d, J = 8 Hz, 1 H), 7.29–7.15 (m, 4 H), 7.05 (d, J = 7.6 Hz, 2 H), 6.92 (t, J = 7.2 Hz, 1 H), 6.88–6.81 (m, 2 H), 5.87–5.71 (m, 1 H), 5.23–5.12 (m, 2 H), 4.10–3.96 (m, 2 H), 3.46–3.31 (m, 2 H), 1.61–1.48 (m, 2 H), 1.31–1.15 (m, 10 H), 0.86 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60°C) δ 171.0, 142.6, 141.9, 129.4, 129.2, 127.6, 127.4, 125.1, 121.4, 119.6, 119.0, 118.8, 117.4, 46.8, 31.8, 29.2, 29.1, 27.9, 26.9, 22.6, 13.9, one aliphatic carbon signal is incidentally equivalent; IR (film) 3311, 1622 cm^{-1}. MS (ESI) 365.2589 (365.2587 calcd for $C_{24}H_{32}N_2O$, $[M + H]^+$).



2-{[Allyl(benzyl)amino]methyl}-*N*-phenylaniline (14b). *N*-Allyl-*N*-benzyl-2-(phenylamino)benzamide (4.95 g, 14.5 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (98:2 hexanes:ethyl acetate) afforded 3.19 g (67%) of the title compound as a white solid, m.p. 70–71 °C . ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, br, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.32–7.15 (m, 11 H), 6.89 (t, J = 7.2 Hz, 1 H), 6.78 (t, J = 7.2 Hz, 1 H), 5.96–5.84 (m, 1 H), 5.18 (dd, J = 2.4, 14.4 Hz, 2 H), 3.66 (s, 2 H), 3.54 (s, 2 H), 3.06 (d, J = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.0, 138.6, 134.4, 131.1, 129.3, 129.2, 128.4,

128.1, 127.1, 125.2, 120.2, 119.2, 118.8, 117.7, 114.9, 57.9, 57.7, 55.8; IR (film) 3255, 1593 cm^{-1}. MS (ESI) 329.2017 (329.2018 calcd for $C_{23}H_{24}N_2$, $[M + H]^+$).

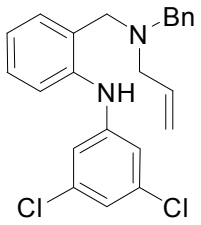


2-{[Allyl(benzyl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (14c). Methyl 2-(4-methoxyphenylamino)benzoate (6.12 g, 23.8 mmol) was saponified according to General Procedure 1. Purification via flash chromatography on silica gel using 50:50 hexanes:ethyl acetate → 100% ethyl acetate as the eluent to afforded 5.20 g (89%) of 2-(4-methoxyphenylamino)benzoic acid as a light yellow solid, m.p. 185–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.7 (s, br, 1 H), 9.14 (s, br, 1 H), 8.02 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.33–7.27 (m, 1 H), 7.24–7.16 (m, 2 H), 6.97–6.90 (m, 3 H), 6.69 (dt, *J* = 1, 7.5 Hz, 1 H) 3.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 157.0, 150.5, 135.2, 132.9, 132.5, 126.4, 116.3, 114.7, 113.4, 109.4, 55.5; IR (film) 3323, 1664 cm^{-1}.

The above 2-(4-methoxyphenylamino)benzoic acid (2.0 g, 8.2 mmol) was coupled with *N*-benzylprop-2-en-1-amine (1.2 g, 8.2 mmol) for 18 h using General Procedure 2. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) afforded 2.96 g (97%) of *N*-allyl-*N*-benzyl-2-(4-methoxyphenylamino)benzamide as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.40–7.02 (m, 10 H), 6.89–6.83 (m, 2 H), 6.79–6.71 (m, 1 H), 5.84–5.75 (m, 1 H), 5.22–5.11 (m, 2 H), 4.69 (s, 2 H), 3.98 (d, *J* = 4.4 Hz, 2 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 171.7, 155.8, 144.2, 137.1, 135.4, 133.1, 130.4, 128.8, 127.8, 127.52,

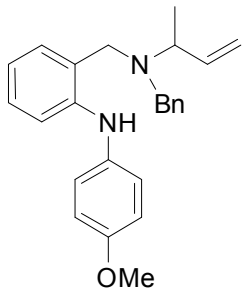
127.51, 123.0, 122.6, 118.4, 117.9, 115.6, 115.0, 55.7, 49.6, 2 aliphatic carbon signals are incidentally equivalent; IR (film) 3351, 1626 cm^{-1}. MS (ESI) 373.1911 (373.1911 calcd for $C_{24}H_{24}N_2O_2$, $[M + H]^+$).

N-Allyl-*N*-benzyl-2-(4-methoxyphenylamino)benzamide (2.96 g, 8.0 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) afforded 1.68 g (59%) of the title compound as an off-white, solid, m.p. 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, br, 1 H), 7.29 (d, *J* = 4.4 Hz, 4 H), 7.26–7.19 (m, 1 H), 7.16–7.02 (m, 5 H), 6.89–6.83 (m, 2 H), 6.72 (dt, *J* = 1.6, 6.8 Hz, 1 H), 5.97–5.85 (m, 1 H), 5.22–5.15 (m, 2 H), 3.80 (s, 3 H), 3.66 (s, 2 H), 3.55 (s, 2 H), 3.06 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 145.1, 138.7, 136.1, 134.5, 131.0, 129.2, 128.3, 128.2, 127.1, 123.8, 121.3, 118.7, 118.1, 114.6, 113.0, 58.0, 57.6, 55.8, 55.6; IR (film) 3240, 1599 cm^{-1}. MS (ESI) 359.2120 (359.2133 calcd for $C_{24}H_{26}N_2O$, $[M + H]^+$).



***N*-{2-[(Allyl<benzyl>amino)methyl]phenyl}-3,5-dichloroaniline (14d).** *N*-Allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (950 mg, 2.3 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (98:2 hexanes:ethyl acetate) afforded 712 mg (78%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, br, 1 H), 7.35–7.17 (m, 7 H), 7.15 (dd, *J* = 1.0, 7.5 Hz, 1 H), 6.89 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.86–6.76 (m, 3 H), 5.93–5.82 (m, 1 H), 5.24–5.15 (m, 2 H), 3.61 (s, 2 H), 3.52 (s, 2 H), 3.04 (d, *J* = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 141.6, 138.3, 135.3, 134.2, 131.3, 129.3,

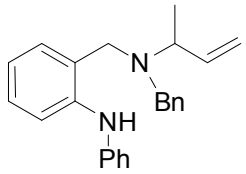
128.5, 128.3, 127.4, 126.7, 121.2, 119.23, 119.17, 117.1, 114.4, 57.9, 57.5, 56.0; IR (film) 3238, 1594 cm^{-1}. MS (ESI) 397.1234 (397.1233 calcd for $C_{23}H_{22}Cl_2N_2$, $[M + H]^+$).



2-{[Benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (14a). 2-(4-Methoxyphenylamino)benzoic acid (494 mg, 1.8 mmol) was coupled with *N*-benzylbut-3-enyl-2-amine (314 mg, 1.9 mmol) for 22 h using General Procedure 2. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) afforded 499 mg (66%) of *N*-benzyl-*N*-(but-3-en-2-yl)-2-(4-methoxyphenylamino)benzamide as a viscous, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.37–7.10 (m, 6 H), 7.07–6.97 (m, 3 H), 6.88–6.83 (m, 2 H), 6.76 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.69–6.63 (m, 1 H), 5.95–5.84 (m, 1 H), 5.19–5.08 (m, 2 H), 4.88–4.80 (m, 1 H), 4.77 (d, *J* = 15.5 Hz, 1 H), 4.44 (d, *J* = 16.0 Hz, 1 H), 3.79 (s, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 172.1, 155.8, 144.0, 138.6, 135.4, 130.2, 128.4, 127.30, 127.26, 126.9, 123.6, 122.4, 118.6, 116.3, 115.8, 115.0, 114.9, 55.7, 49.7, 18.0, one aliphatic carbon signal is incidentally equivalent; IR (film) 3354, 1626 cm^{-1}. MS (ESI) 387.2067 (387.2067 calcd for $C_{25}H_{26}N_2O_2$, $[M + H]^+$).

The above *N*-benzyl-*N*-(but-3-en-2-yl)-2-(4-methoxyphenylamino)benzamide (1.49 g, 2.0 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) afforded 701 mg (49%) of the title compound as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, br, 1 H), 7.35–7.05 (m, 8 H), 7.01 (d, *J* = 8.8 Hz, 2 H),

6.85 (d, *J* = 8.8 Hz, 2 H), 6.69 (dt, *J* = 2.0, 7.2 Hz, 1 H), 6.03–5.91 (m, 1 H), 5.23 (d, *J* = 10.4 Hz, 1 H), 5.11 (d, *J* = 17.2 Hz, 1 H), 3.80 (s, 3 H), 3.74 (d, *J* = 12.8 Hz, 1 H), 3.65–3.55 (m, 2 H), 3.53–3.46 (m, 1 H), 3.38 (quint, *J* = 6.4 Hz, 1 H), 1.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 145.2, 139.6, 138.4, 136.0, 131.1, 129.1, 128.3, 128.1, 127.0, 123.7, 121.3, 118.0, 116.9, 114.5, 112.9, 55.6, 55.1, 53.61, 53.57, 14.5; IR (film) 3240, 1599 cm^{-1}. MS (ESI) 373.2276 (373.2274 calcd for $C_{25}H_{28}N_2O$, $[M + H]^+$).

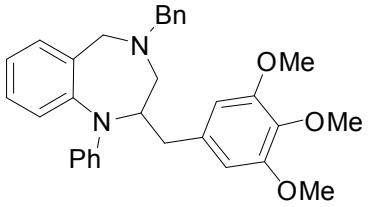


2-{[Benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (14e). 2-(Phenylamino)benzoic acid (995 mg, 4.7 mmol) was coupled with *N*-benzylbut-3-enyl-2-amine (748 mg, 4.6 mmol) for 22 h using General Procedure 2. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) afforded 1.52 g (92%) of *N*-benzyl-*N*-(but-3-en-2-yl)-2-(phenylamino)benzamide as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.31 (d, *J* = 8.0 Hz, 1 H), 7.28–7.13 (m, 8 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.93 (t, *J* = 7.6 Hz, 1 H), 6.88–6.79 (m, 2 H), 5.91–5.78 (m, 1 H), 5.15–5.04 (m, 2 H), 4.85–4.72 (m, 2 H), 4.41 (d, *J* = 15.6 Hz, 1 H), 1.20 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 171.7, 142.6, 141.8, 138.8, 138.4, 130.0, 129.3, 128.4, 127.2, 126.9, 126.6, 125.6, 121.4, 120.0, 118.8, 117.8, 116.3, 55.6, 46.7, 17.9; IR (film) 3377, 1624 cm^{-1}. MS (ESI) 357.1962 (357.1961 calcd for $C_{24}H_{24}N_2O$, $[M + H]^+$).

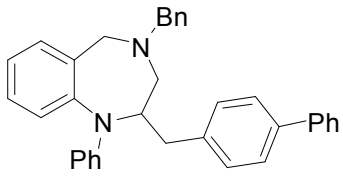
The above *N*-benzyl-*N*-(but-3-en-2-yl)-2-(phenylamino)benzamide (5.34 g, 15 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (98:2 hexanes:ethyl acetate) afforded 3.17 g (62%) of the title compound as a viscous, light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, br, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.33–7.01 (m, 9 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.88 (dt, *J* = 0.8, 7.6 Hz, 1 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.03–5.91 (m, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 5.11 (d, *J* = 17.2 Hz, 1 H), 3.76 (d, *J* = 13.2 Hz, 1 H), 3.65–3.54 (m, 2 H), 3.49 (d, *J* = 13.2 Hz, 1 H), 3.37 (quint, *J* = 6.8 Hz, 1 H), 1.22 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.9, 139.5, 138.3, 131.2, 129.2, 129.1, 128.4, 128.0, 127.0, 125.0, 120.2, 119.2, 117.8, 117.0, 114.6, 55.2, 53.7, 53.5, 14.5; IR (film) 3253, 1593 cm^{-1}. MS (ESI) 343.2171 (343.2169 calcd for $C_{24}H_{26}N_2$, $[M + H]^+$).

General Procedure 4: Pd-Catalyzed Synthesis of 1,4-Benzodiazepines. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $PdCl_2(MeCN)_2$ (2 mol %), cyclohexyldiphenylphosphine (4 mol %), NaO*t*Bu (2.0 equiv), and aryl bromide (2.0 equiv). The tube was purged with nitrogen and a solution of the amine substrate (1.0 equiv) in xylenes (5 mL/mmol amine) was added. The mixture was heated to 135 °C with stirring until the starting material had been consumed as judged by TLC analysis (18–24 h; the reaction times were not minimized). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

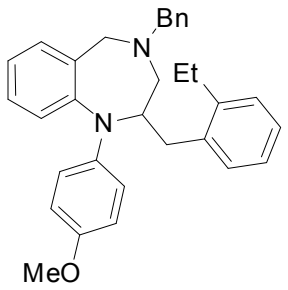


4-Benzyl-1-phenyl-2-(3,4,5-trimethoxybenzyl)methyl]-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (17). General Procedure 4 was used for the coupling of 2-{[allyl(benzyl)amino]methyl}-*N*-phenylaniline (50 mg, 0.15 mmol) with 5-bromo-1,2,3-trimethoxybenzene (75 mg, 0.30 mmol) to afford 60 mg (79%) of the title compound as a foamy, white solid with a wide m.p. range 51–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.29–7.21 (m, 2 H), 7.18–7.12 (m, 4 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.77–6.71 (m, 3 H), 6.40 (s, 2 H), 4.49 (m, 1 H), 3.81 (s, 3 H), 3.73 (s, 6 H), 3.72–3.63 (m, 2 H), 3.60 (d, *J* = 14.0 Hz, 1 H), 3.41 (d, *J* = 13.0 Hz, 1 H), 2.81–2.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 148.5, 143.7, 139.3, 137.1, 136.3, 135.5, 130.4, 129.7, 129.1, 128.4, 128.3, 127.8, 127.0, 125.6, 118.2, 115.4, 106.1, 62.6, 60.8, 58.9, 57.9, 57.7, 56.0, 39.0; IR (film) 1591 cm^{-1}. MS (ESI) 495.2637 (495.2648 calcd for $C_{32}H_{34}N_2O_3$, $[M + H]^+$).

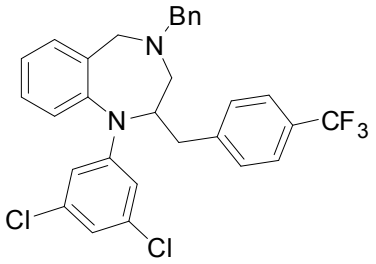


4-Benzyl-2-(biphenyl-4-ylmethyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (18). General Procedure 4 was used for the coupling of 2-{[allyl(benzyl)amino]methyl}-*N*-phenylaniline (51 mg, 0.15 mmol) with 4-bromobiphenyl (71 mg, 0.30 mmol) to afford 65 mg (88%) of the title compound as a foamy, white solid with a wide m.p. range 50–66 °C. ^{1}H NMR

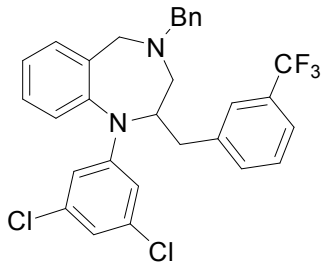
(400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.47–7.13 (m, 17 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.79–6.72 (m, 3 H), 4.55–4.47 (m, 1 H), 3.67–3.59 (m, 3 H), 3.44 (d, *J* = 12.8 Hz, 1 H), 2.90–2.71 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 143.8, 141.0, 139.3, 139.0, 138.9, 137.0, 130.4, 129.6, 129.5, 129.2, 128.9, 128.7, 128.3, 128.0, 127.04, 127.03, 126.9, 125.6, 118.2, 115.5, 62.7, 59.0, 58.0, 56.8, 37.3, one aromatic carbon signal is incidentally equivalent; IR (film) 1593 cm^{-1}. MS (ESI) 481.2645 (481.2638 calcd for $C_{35}H_{32}N_2$, $[M + H]^+$).



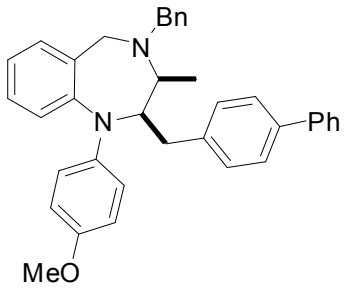
4-Benzyl-2-(2-ethylbenzyl)-1-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (19). General Procedure 4 was used for the coupling of 2-{[allyl(benzyl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (49 mg, 0.14 mmol) with 1-bromo-2-ethylbenzene (39 μL, 0.28 mmol) to afford 60 mg (94%) of the title compound as a viscous, colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.31–7.26 (m, 1 H), 7.20–7.01 (m, 7 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.77–6.73 (m, 2 H), 6.72–6.67 (m, 2 H), 4.36–4.30 (m, 1 H), 3.75 (s, 3 H), 3.68 (d, *J* = 14.0 Hz, 2 H), 3.59 (d, *J* = 13.5 Hz, 1 H), 3.40 (d, *J* = 13.0 Hz, 1 H), 2.83 (d, *J* = 7.0 H, 2 H), 2.77–2.55 (m, 4 H), 1.15 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 145.4, 143.0, 142.3, 139.3, 137.6, 136.0, 130.2, 130.1, 128.8, 128.30, 128.27, 127.8, 127.0, 126.3, 125.7, 124.3, 118.8, 114.6, 62.7, 59.2, 59.1, 57.6, 55.6, 34.5, 25.4, 15.3, one aromatic carbon signal is incidentally equivalent; IR (film) 1507 cm^{-1}. MS (ESI) 463.2735 (463.2749 calcd for $C_{32}H_{34}N_2O$, $[M + H]^+$).



4-Benzyl-1-(3,5-dichlorophenyl)-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (20). General Procedure 4 was used for the coupling of *N*-{2-[(allyl<benzyl>amino)methyl]phenyl}-3,5-dichloroaniline (53 mg, 0.13 mmol) with 1-bromo-4-(trifluoromethyl)benzene (38 μL, 0.27 mmol) to afford 53 mg (74%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.38–7.24 (m, 7 H), 7.21 (d, *J* = 6.5 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 7.0 Hz, 1 H), 6.69 (t, *J* = 2.0 Hz, 1 H), 6.48 (d, *J* = 1.0 Hz, 2 H), 4.45–4.35 (m, 1 H), 3.67 (d, *J* = 13.0 Hz, 1 H), 3.60 (d, *J* = 13.0 Hz, 2 H), 3.38 (d, *J* = 13 Hz, 1 H), 2.85–2.65 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 143.1, 141.2, 138.8, 135.6, 130.8, 130.0, 129.4, 128.9, 128.5, 128.43, 128.40, 127.4, 127.3, 125.33, 125.29, 124.2 (q, *J* = 272 Hz), 117.5, 112.2, 62.9, 59.2, 57.2, 37.6, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.4 (m); IR (film) 1580 cm^{-1}. MS (ESI) 541.1432 (541.1425 calcd for $C_{30}H_{25}Cl_2F_3N_2$, $[M + H]^+$).

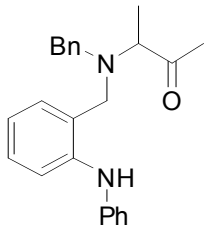


4-Benzyl-1-(3,5-dichlorophenyl)-2-[3-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (21). General Procedure 4 was used for the coupling of *N*-{2-[(allyl<benzyl>amino)methyl]phenyl}-3,5-dichloroaniline (53 mg, 0.13 mmol) with 1-bromo-3-(trifluoromethyl)benzene (38 μL, 0.27 mmol) to afford 56 mg (78%) of the title compound as a viscous, colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.2 Hz, 1 H), 7.38–7.22 (m, 10 H), 7.19 (d, *J* = 6.8 Hz, 1 H), 6.92 (d, *J* = 6.8 Hz, 1 H), 6.63 (t, *J* = 1.6 Hz, 1 H), 6.47 (d, *J* = 1.2 Hz, 2 H), 4.41 (m, 1 H), 3.64 (s, 2 H), 3.60 (d, *J* = 13.2 Hz, 1 H), 3.36 (d, *J* = 13.2 Hz, 1 H), 2.85–2.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 141.2, 139.8, 138.7, 137.5, 135.6, 132.3, 130.8, 130.5, 130.1, 128.8, 128.4, 127.33, 127.26, 126.20, 126.16, 124.1 (q, *J* = 272 Hz), 123.3, 123.2, 117.5, 112.3, 62.9, 58.9, 57.4, 37.5, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6 (m); IR (film) 1580 cm^{-1}. MS (ESI) 541.1429 (541.1425 calcd for $C_{30}H_{25}Cl_2F_3N_2$, $[M + H]^+$).



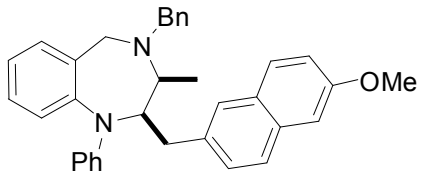
(±)-(2*R*,3*S*)-4-Benzyl-2-(biphenyl-4-methyl)-1-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (15). General Procedure 4 was used for the coupling of

2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 4-bromobiphenyl (64 mg, 0.28 mmol) to afford 48 mg (65%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 2 H), 7.52 (d, *J* = 7.5 Hz, 2 H), 7.48–7.18 (m, 11 H), 7.12–7.04 (m, 2 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 9.0 Hz, 2 H), 6.47 (d, *J* = 9.0 Hz, 2 H), 4.41 (td, *J* = 2.3, 11.0 Hz, 1 H), 3.85–3.65 (m, 7 H), 3.48 (dq, *J* = 2.0, 6.8 Hz, 1 H), 2.97 (d, *J* = 13.5 Hz, 1 H), 2.50 (dd, *J* = 10.5, 14.0 Hz, 1 H), 1.42 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.0, 143.4, 141.0, 140.8, 140.0, 138.8, 137.0, 130.8, 129.7, 129.5, 128.7, 128.5, 128.3, 127.9, 127.0, 126.98, 126.95, 126.8, 124.3, 119.0, 114.4, 67.5, 61.2, 57.1, 55.6, 52.4, 33.8, 19.2; IR (film) 1504 cm^{-1}. MS (ESI) 525.2909 (525.2900 calcd for $C_{37}H_{36}N_2O$, $[M + H]^+$).

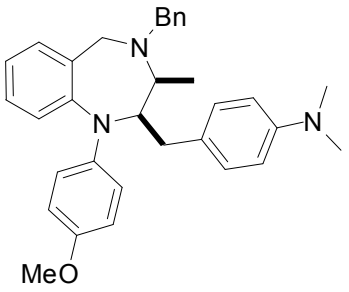


(±)-3-{benzyl[2-(phenylamino)benzyl]amino}butan-2-one (16). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (49 mg, 0.14 mmol) with 1-bromo-3,5-dichlorobenzene (66 mg, 0.29 mmol) to afford 8.7 mg (12%) of the title compound as a viscous, colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, br, 1 H), 7.37–7.31 (m, 3 H), 7.30–7.11 (m, 7 H), 7.09–7.04 (m, 2 H), 6.90 (tt, *J* = 1.0, 7.5 Hz, 1 H), 6.77 (td, *J* = 7.5, 1.5 Hz, 1 H), 3.89 (d, *J* = 13.0 Hz, 1 H), 3.72 (d, *J* = 13.0 Hz, 1 H), 3.53 (d, *J* = 13.0 Hz, 1 H), 3.44 (q, *J* = 7.0 Hz, 1 H), 3.42 (d, *J* = 13.5 Hz, 1 H), 2.15 (s, 3 H), 1.28 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 143.3, 142.6, 138.7, 131.5, 129.13, 129.11, 128.6,

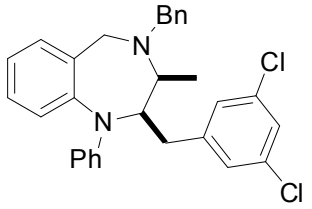
128.5, 127.5, 124.3, 120.7, 119.2, 118.3, 115.0, 62.8, 54.6, 53.9, 27.9, 8.1; IR (film) 1714, 1593 cm^{-1}. MS (ESI) 359.2117 (359.2118 calcd for $C_{24}H_{26}N_2O$, $[M + H]^+$).



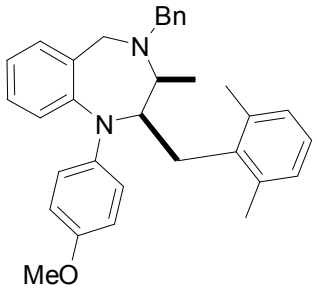
(±)-(2*R*,3*S*)-4-Benzyl-2-[(6-methoxynaphthalen-2-yl)methyl]-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (22). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (50 mg, 0.15 mmol) with 2-bromo-6-methoxynaphthalene (70 mg, 0.28 mmol) to afford 59 mg (81%) of the title compound as a foamy, light yellow solid with a wide m.p. range 51–69 °C. This material contained ca. 8% of ketone **16**, which could not be separated by chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 9.6 Hz, 1 H), 7.43–7.15 (m, 9 H), 7.12–7.07 (m, 3 H), 7.06–7.00 (m, 2 H), 6.86 (dd, *J* = 2.0, 7.2 Hz, 1 H), 6.63 (t, *J* = 7.2 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 2 H), 4.68 (dt, *J* = 2.0, 10.8 Hz, 1 H), 3.90 (s, 3 H), 3.80 (d, *J* = 14.0 Hz, 1 H), 3.73–3.63 (m, 3 H), 3.58 (dd, *J* = 2.4, 6.8 Hz, 1 H), 3.07 (dd, *J* = 2.0, 15.2 Hz, 1 H), 2.54 (dd, *J* = 10.8, 15.2 Hz, 1 H), 1.46 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.8, 143.4, 140.8, 138.4, 135.2, 133.1, 131.1, 130.9, 129.0, 128.9, 128.4, 128.3, 127.8, 127.7, 127.3, 126.8, 126.7, 125.6, 118.6, 117.7, 115.3, 110.0, 105.6, 64.6, 60.8, 56.8, 55.3, 52.1, 33.6, 19.1; IR (film) 1605, 1592 cm^{-1}. MS (ESI) 499.2741 (499.2749 calcd for $C_{35}H_{34}N_2O$, $[M + H]^+$).



(±)-4-[(2*R*,3*S*)-4-Benzyl-1-(4-methoxyphenyl)-3-methyl(-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)methyl]-*N*,*N*-dimethylaniline (23). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 4-bromo-*N*,*N*-dimethylaniline (56 mg, 0.28 mmol) to afford 55 mg (81%) of the title compound as a viscous, colorless film. This material contained ca. 8% of ketone **16**, which could not be separated by chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.16 (m, 6 H), 7.11–6.99 (m, 4 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 6.63 (d, *J* = 9.2 Hz, 2 H), 6.47 (d, *J* = 9.2 Hz, 2 H), 4.32 (td, *J* = 2.0, 10.4 Hz, 1 H), 3.81–3.67 (m, 6 H), 3.64 (d, *J* = 14.0 Hz, 1 H), 3.51–3.41 (m, 1 H), 2.91 (s, 6 H), 2.83 (dd, *J* = 2.0, 14.8 Hz, 1 H), 2.33 (dd, *J* = 10.8, 14.8 Hz, 1 H), 1.38 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 149.1, 145.3, 143.6, 140.9, 136.9, 130.8, 129.7, 129.6, 128.8, 128.5, 128.2, 127.8, 126.7, 124.0, 119.1, 114.4, 113.0, 67.7, 61.2, 57.0, 55.6, 52.1, 40.9, 33.1, 19.1; IR (film) 1506 cm^{-1}. MS (ESI) 492.3014 (492.3009 calcd for $C_{33}H_{37}N_3O$, $[M + H]^+$).

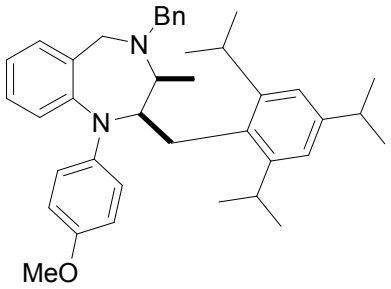


(±)-(2*R*,3*S*)-4-benzyl-2-(3,5-dichlorobenzyl)-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (24). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (49 mg, 0.14 mmol) with 1-bromo-3,5-dichlorobenzene (66 mg, 0.29 mmol) to afford 44 mg (63%) of the title compound as a viscous, colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 4 H), 7.32–7.22 (m, 2 H), 7.21–7.03 (m, 5 H), 7.01–6.97 (m, 2 H), 6.85 (dd, *J* = 1.2, 7.6 Hz, 1 H), 6.70 (t, *J* = 7.2 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 2 H), 4.52 (td, *J* = 2.4, 11.6 Hz, 1 H), 3.69 (s, 2 H), 3.63–3.57 (m, 2 H), 3.50 (dq, *J* = 2.4, 6.8 Hz, 1 H), 2.90 (dd, *J* = 2.4, 15.2 Hz, 1 H), 2.41 (dd, *J* = 11.2, 15.2 Hz, 1 H), 1.41 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 143.7, 142.9, 140.5, 138.3, 134.5, 131.0, 130.8, 129.2, 128.33, 128.30, 127.5, 126.9, 126.3, 125.9, 118.2, 115.4, 64.5, 60.6, 57.0, 52.7, 33.2, 19.1; IR (film) 1592 cm^{-1}. MS (ESI) 487.1698 (487.1708 calcd for $C_{30}H_{28}Cl_2N_2$, [M + H]$^+$).



(±)-(2*R*,3*S*)-4-Benzyl-2-(2,6-dimethylbenzyl)-1-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (25). General Procedure 4 was used for the coupling of

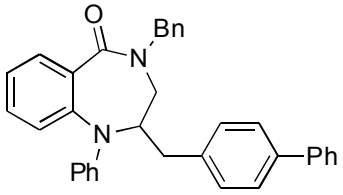
2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 2-bromo-*meta*-xylene (37 μL, 0.28 mmol) to afford 58 mg (87%) of the title compound as a viscous, colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 4 H), 7.29–7.25 (m, 1 H), 7.08–7.03 (m, 1 H), 7.02–6.89 (m, 5 H), 6.69–6.65 (m, 2 H), 6.63–6.56 (m, 3 H), 4.48–4.42 (m, 1 H), 3.99 (d, *J* = 14.5 Hz, 1 H), 3.88 (d, *J* = 14.0 Hz, 1 H), 3.72 (s, 3 H), 3.57 (d, *J* = 14.0 Hz, 1 H), 3.53 (d, *J* = 14.5 Hz, 1 H), 3.24 (dq, *J* = 2.5, 7.0 Hz, 1 H), 3.02 (dq, *J* = 8.0, 14.5 Hz, 2 H), 2.16 (s, 6 H), 1.23 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 146.7, 146.0, 142.9, 140.7, 137.2, 137.1, 132.8, 130.6, 128.6, 128.3, 127.8, 126.7, 126.5, 125.8, 122.5, 122.0, 114.4, 65.3, 60.9, 56.1, 55.5, 55.3, 29.9, 20.7, 19.2; IR (film) 1506 cm^{-1}. MS (ESI) 477.2905 (477.2900 calcd for $C_{33}H_{36}N_2O$, $[M + H]^+$).



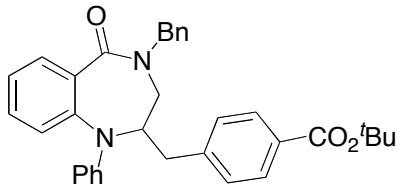
(±)-(2*R*,3*S*)-4-Benzyl-1-(4-methoxyphenyl)-3-methyl-2-(2,4,6-triisopropylbenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (26). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 2-bromo-1,3,5-triisopropylbenzene (71 μL, 0.28 mmol) to afford 51 mg (64%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5 H), 7.12 (td, *J* = 1.5, 8.0 Hz, 1 H), 7.05–7.01 (dd, *J* = 1.5, 7.5 Hz, 1 H), 6.95 (td, *J* = 1.0, 7.0 Hz, 1 H), 6.90 (s, 2 H), 6.78 (d, *J* = 7.5 Hz, 1 H), 6.73–6.68 (m, 2 H), 6.67–6.61 (m, 2 H), 4.16 (t, *J* = 5.0 Hz, 1 H), 4.03 (d, *J* = 14.0 Hz, 1 H), 3.78–3.70 (m, 4 H), 3.54 (dd, *J* = 10.5, 14.0 Hz, 2 H), 3.22–

3.10 (m, 4 H), 2.90 (dd, *J* = 5.5, 15.0 Hz, 1 H), 2.89–2.81 (m, 1 H), 1.24 (d, *J* = 7.0 Hz, 6 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.11 (d, *J* = 6.5 Hz, 6 H), 1.03 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 147.4, 147.2, 146.5, 142.9, 140.5, 132.7, 132.2, 130.6, 128.6, 128.2, 127.8, 126.7, 126.1, 122.6, 122.4, 120.8, 114.4, 67.5, 60.1, 56.0, 55.9, 55.5, 34.1, 29.2, 29.0, 24.6, 24.1, 23.8, 18.8; IR (film) 1507 cm^{-1}. MS (ESI) 575.4002 (575.3996 calcd for $C_{40}H_{50}N_2O$, $[M + H]^+$).

General Procedure 5: Pd-Catalyzed Synthesis of 1,4-Benzodiazepin-5-ones. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd) or $Pd(dba)_2$ (2 mol %), tris(4-fluorophenyl)phosphine (4 mol %), NaO*t*Bu (2.0 equiv), and aryl bromide (2.0 equiv). The tube was purged with nitrogen and a solution of the amine substrate (1.0 equiv) in xylenes (5 mL/mmol amine) was added. The mixture was heated to 135 °C with stirring until the starting material had been consumed as judged by TLC analysis (18–24 h; the reaction times were not minimized). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

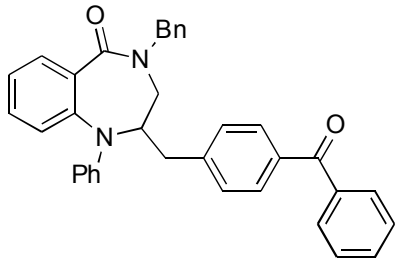


2-([1,1'-Biphenyl]-4-ylmethyl)-4-benzyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (30). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (40 mg, 0.12 mmol) with 4-bromobiphenyl (52 mg, 0.22 mmol) to afford 44 mg (76%) of the title compound as a white solid with a wide m.p. range 67–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.62–7.58 (m, 2 H), 7.55–7.40 (m, 6 H), 7.39–7.34 (m, 1 H), 7.32–7.20 (m, 3 H), 7.19–7.01 (m, 7 H), 6.77 (t, *J* = 7.5 Hz, 1 H), 6.52 (d, *J* = 8 Hz, 2 H), 5.10 (d, *J* = 14.5 Hz, 1 H), 4.15 (d, *J* = 14.5 Hz, 1 H), 3.99–3.89 (m, 1 H), 3.27 (dd, *J* = 11.5, 15.5 Hz, 1 H), 3.22–3.09 (m, 2 H), 2.44 (dd, *J* = 10.0, 14.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 148.3, 140.6, 139.8, 139.6, 137.0, 136.4, 136.2, 132.3, 130.4, 130.3, 129.03, 129.02, 128.8, 128.6, 128.4, 127.5, 127.4, 127.3, 127.1, 127.0, 118.3, 113.7, 62.9, 51.3, 50.1, 36.4; IR (film) 1648 cm^{-1}. MS (ESI) 495.2423 (495.2431 calcd for $C_{35}H_{30}N_2O$, $[M + H]^+$).



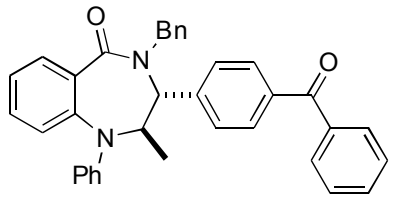
***tert*-Butyl-4-[(4-benzyl-5-oxo-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)methyl]benzoate (32).** General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (36 mg, 0.10 mmol) with *tert*-butyl 4-bromobenzoate (40 μL, 0.20 mmol) to afford 39 mg (72%) of the title compound as a foamy white solid with a wide m.p.

range 68–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.86 (m, 3 H), 7.52 (dt, *J* = 2.0, 7.6 Hz, 1 H), 7.42 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.29–7.20 (m, 2 H), 7.17–7.08 (m, 4 H), 7.07–6.98 (m, 4 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.47 (d, *J* = 8.0 Hz, 2 H), 5.14 (d, *J* = 14.4 Hz, 1 H), 4.06 (d, *J* = 14.4 Hz, 1 H), 3.94–3.82 (m, 1 H), 3.30–3.10 (m, 2 H), 3.04 (dd, *J* = 5.2, 15.2 Hz, 1 H), 2.44 (dd, *J* = 6.0, 14.0 Hz, 1 H), 1.61 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.5, 148.2, 142.1, 139.6, 136.9, 136.2, 132.3, 130.5, 130.4, 130.3, 129.9, 129.1, 128.7, 128.5, 128.4, 127.5, 127.2, 118.4, 113.6, 81.1, 62.7, 51.3, 50.2, 36.8, 28.2; IR (film) 1711, 1649 cm^{-1}. MS (ESI) 541.2465 (541.2462 calcd for $C_{34}H_{34}N_2O_3$, $[M + Na]^+$).

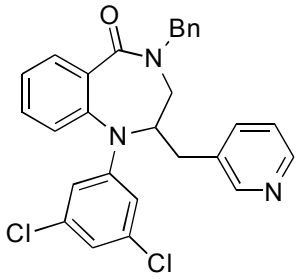


2-(4-Benzoylbenzyl)-4-benzyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (33). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (34 mg, 0.10 mmol) with 4-bromobenzophenone (52 mg, 0.20 mmol) to afford 33 mg (64%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.81–7.76 (m, 2 H), 7.72 (d, *J* = 8 Hz, 2 H), 7.64–7.59 (m, 1 H), 7.56–7.48 (m, 3 H), 7.47–7.41 (m, 2 H), 7.28–7.21 (m, 1 H), 7.16–7.10 (m, 6 H), 7.04 (d, *J* = 7.5 Hz, 2 H), 6.78 (t, *J* = 7.5 Hz, 1 H), 6.48 (d, *J* = 7.5 Hz, 2 H), 5.15 (d, *J* = 14.5 Hz, 1 H), 4.13 (d, *J* = 14.5 Hz, 1 H), 3.98–3.90 (m, 1 H), 3.27 (dd, *J* = 11.5, 15.5 Hz, 1 H), 3.19 (dd, *J* = 4.5, 14.0 Hz, 1 H), 3.09 (dd, *J* = 5.0, 15.0 Hz, 1 H), 2.50 (dd, *J* = 9.5, 14.0 Hz, 1 H); ^{13}C NMR

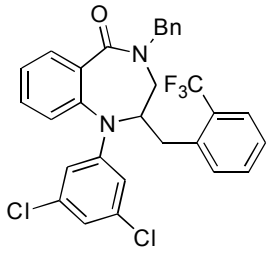
(100 MHz, $CDCl_3$) δ 196.2, 169.5, 148.2, 142.3, 139.5, 137.5, 136.8, 136.2, 136.1, 132.5, 132.4, 130.6, 130.4, 130.3, 130.0, 129.1, 128.7, 128.6, 128.4, 128.3, 127.6, 127.2, 118.4, 113.6, 62.7, 51.3, 50.2, 36.9; IR (film) 1649, 1603 cm^{-1}. MS (ESI) 523.2377 (523.2380 calcd for $C_{36}H_{30}N_2O_2$, $[M + H]^+$).



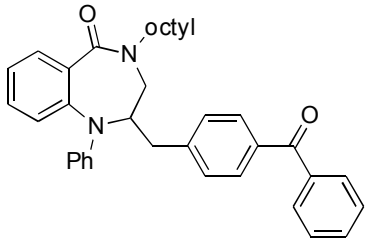
(±)-(2*R*,3*R*)-3-(4-benzoylphenyl)-4-benzyl-2-methyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (S1). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (34 mg, 0.10 mmol) with 4-bromobenzophenone (52 mg, 0.20 mmol) to afford 5 mg (9%) of the title compound as an off-white film in ca. 80% purity. The structure and relative stereochemistry of **31** was assigned based on analogy to **S1**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 7.84–7.79 (m, 2 H), 7.64–7.58 (m, 1 H), 7.54–7.43 (m, 3 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29–7.21 (m, 1 H), 7.16–7.09 (m, 3 H), 7.00–6.94 (m, 2 H), 6.85 (t, *J* = 7.6 Hz, 2 H), 6.79 (d, *J* = 7.6 Hz, 2 H), 6.63 (d, *J* = 7.2 Hz, 2 H), 5.21 (d, *J* = 15.2 Hz, 1 H), 4.79 (d, *J* = 10.4 Hz, 1 H), 3.40–3.31 (m, 1 H), 2.45 (d, *J* = 14.8 Hz, 1 H), 1.46 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 161.7, 147.8, 146.7, 142.4, 137.5, 136.6, 135.6, 132.9, 132.5, 130.7, 130.0, 129.2, 128.7, 128.4, 128.3, 128.1, 127.8, 127.1, 124.1, 123.4, 123.3, 122.9, 121.3, 79.8, 48.9, 43.8, 18.2; IR (film) 1653, 1603 cm^{-1}. MS (ESI) 523.2371 (523.2380 calcd for $C_{36}H_{30}N_2O_2$, $[M + H]^+$).



4-Benzyl-1-(3,5-dichlorophenyl)-2-(pyridine-3-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (34). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (35 mg, 0.09 mmol) with 3-bromopyridine (17 μL, 0.17 mmol) to afford 32 mg (78%) of the title compound as a white solid, m.p. 153–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 1.5, 4.5 Hz, 1 H), 8.30 (d, *J* = 2.0 Hz, 1 H), 7.90 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.58 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.51 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.34–7.27 (m, 2 H), 7.26–7.21 (m, 1 H), 7.20–7.15 (m, 3 H), 7.05–7.01 (m, 2 H), 6.72 (t, *J* = 1.5 Hz, 1 H), 6.10 (s, 2 H), 5.33 (d, *J* = 14.5 Hz, 1 H), 3.93 (d, *J* = 14.5 Hz, 1 H), 3.62–3.54 (m, 1 H), 3.25 (dd, *J* = 11.5, 15.0 Hz, 1 H), 3.09 (dd, *J* = 5.5, 15.5 Hz, 1 H), 2.89 (dd, *J* = 5.0, 14.0 Hz, 1 H), 2.42 (dd, *J* = 9.0, 14.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 150.0, 149.8, 148.6, 137.4, 136.9, 136.0, 135.4, 132.8, 132.2, 130.8, 130.1, 128.9, 128.5, 128.4, 128.0, 123.6, 118.1, 111.4, 62.9, 51.0, 50.1, 34.1; IR (film) 1643 cm^{-1}. MS (ESI) 488.1292 (488.1291 calcd for $C_{28}H_{23}Cl_2N_3O$, $[M + H]^+$).

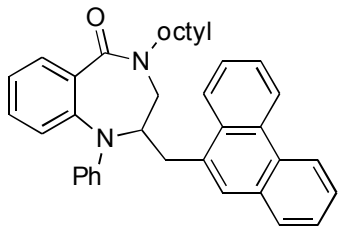


4-Benzyl-1-(3,5-dichlorophenyl)-2-[2-(trifluoromethyl)benzyl]-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (35). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (36 mg, 0.09 mmol) with 1-bromo-2-(trifluoromethyl)benzene (23 μL, 0.17 mmol) to afford 25 mg (50%) of the title compound as a white solid, m.p. 235–237 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.69–7.60 (m, 2 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.38 (quint, *J* = 7.6 Hz, 2 H), 7.32–7.23 (m, 2 H), 7.19–7.09 (m, 3 H), 7.08–7.02 (m, 2 H), 6.62 (t, *J* = 1.6 Hz, 1 H), 5.81 (d, *J* = 2.0 Hz, 2 H), 5.39 (d, *J* = 14.4 Hz, 1 H), 3.90 (d, *J* = 14.0 Hz, 1 H), 3.83–3.73 (m, 1 H), 3.28 (dd, *J* = 11.6, 15.2 Hz, 1 H), 3.09 (dd, *J* = 4.8, 14.8 Hz, 1 H), 2.85 (dd, *J* = 7.2, 14.4 Hz, 1 H), 2.75–2.64 (m, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.0 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 150.5, 137.3, 136.9, 136.5, 135.6, 135.1, 132.9, 132.1, 131.6, 130.9, 130.5, 128.8, 128.6, 128.5, 127.9, 127.2, 126.6, 126.5, 124.3 (q, *J* = 275 Hz), 117.8, 111.4, 63.4, 51.5, 50.3, 33.6; IR (film) 1646 cm^{-1}. MS (ESI) 577.1023 (577.1032 calcd for $C_{30}H_{23}Cl_2F_3N_2O$, $[M + Na]^+$).



2-(4-Benzoylbenzyl)-4-octyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (36). General Procedure 5 was used for the coupling of *N*-allyl-*N*-octyl-2-(phenylamino)benzamide

(35 mg, 0.10 mmol) with 4-bromobenzophenone (52 mg, 0.20 mmol) to afford 36 mg (69%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.78 (m, 4 H), 7.61 (dt, *J* = 1.5, 7 Hz, 1 H), 7.55–7.47 (m, 3 H), 7.44–7.38 (m, 3 H), 7.28–7.24 (m, 2 H), 7.19–7.12 (m, 2 H), 6.77 (t, *J* = 7.0 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 2 H), 4.54–4.40 (m, 1 H), 3.62–3.53 (m, 1 H), 3.43–3.20 (m, 3 H), 3.15 (dd, *J* = 5.5, 15.5 Hz, 1 H), 2.66 (dd, *J* = 9.0, 13.5 Hz, 1 H), 1.50–1.00 (m, 12 H), 0.83 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 169.3, 148.3, 142.5, 139.5, 137.5, 136.6, 136.3, 132.5, 132.1, 130.8, 130.4, 130.01, 129.98, 129.1, 128.9, 128.3, 127.1, 118.6, 113.7, 63.5, 52.1, 47.1, 37.2, 31.7, 29.4, 29.1, 28.7, 26.6, 22.6, 14.1; IR (film) 1649, 1602 cm^{-1}. MS (ESI) 545.3166 (545.3163 calcd for $C_{37}H_{40}N_2O_2$, $[M + H]^+$).

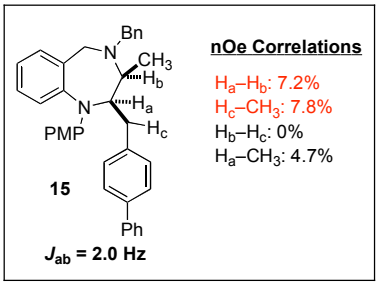


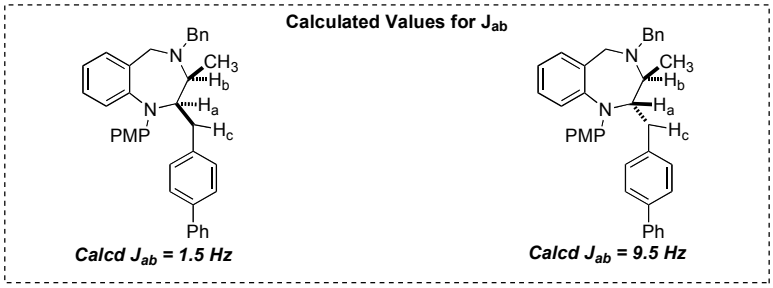
4-Octyl-2-(phenanthren-9-ylmethyl)-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (37). General Procedure 5 was used for the coupling of *N*-allyl-*N*-octyl-2-(phenylamino)benzamide (38 mg, 0.10 mmol) with 9-bromophenanthrene (50 mg, 0.19 mmol) to afford 41 mg (74%) of the title compound as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85–8.76 (m, 1 H), 8.69 (d, *J* = 8.4 Hz, 1 H), 8.22–8.16 (m, 1 H), 7.87–7.80 (m, 3 H), 7.77–7.79 (m, 2 H), 7.69–7.55 (m, 4 H), 7.46 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.37 (dd, *J* = 0.8, 8 Hz, 1 H), 7.15–7.07 (m, 2 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 4.87–4.77 (m, 1 H), 3.72 (dd, *J* = 5.2, 14.8 Hz, 1 H), 3.58–3.46 (m, 1 H), 3.40 (dd, *J* = 11.6, 14.8 Hz, 1 H), 3.20–2.97 (m, 3 H), 1.42–0.95 (m, 12 H), 0.82 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 148.8, 139.6, 137.1, 132.2, 131.8, 131.5, 131.1, 130.9, 130.6, 130.4, 129.9, 129.2, 128.2, 127.8,

127.3, 127.0, 126.9, 126.7, 126.6, 123.9, 123.6, 122.5, 118.3, 113.6, 62.4, 52.6, 47.0, 34.5, 31.7, 29.3, 29.0, 28.6, 26.5, 22.6, 14.1; IR (film) 1646 cm^{-1}. MS (ESI) 541.3217 (541.3213 calcd for $C_{38}H_{40}N_2O$, $[M + H]^+$).

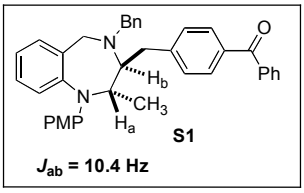
Assignment of Stereochemistry

The stereochemistry of **15** was assigned on the basis of nOe correlations as shown below. In addition, the measured value of J_{ab} = 2.0 Hz correlates well with the calculated value of 1.5 Hz for a *cis*-arrangement of these protons. The stereochemistry of other disubstituted products was assigned based on analogy to **15**.





The *trans*-stereochemistry of **S1** was assigned on the basis of the measured value of J_{ab} = 10.4 Hz. The stereochemistry of **31** was assigned based on analogy to **S1**.



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