A Tandem Imine Addition/Ring-Closing Metathesis Approach to the Spirocyclic Core of Halichlorine and Pinnaic Acid

Supplementary Material

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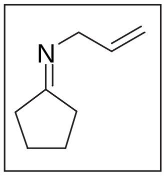
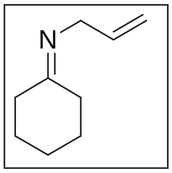
General Procedures: THF was distilled under a nitrogen atmosphere from sodium-benzophenone. CH_2Cl_2 and benzene were distilled from CaH_2. Glassware was dried by either flaming under vacuum or storing in a 140° C oven for at least 24 h. NMR spectra were obtained on a Varian GEMINI2000 spectrophotometer using TMS as an internal reference. IR spectra were obtained as thin films between KBr plates on a Perkin-Elmer 1600 series FTIR. The UFL Mass Spectroscopy Services performed HRMS.

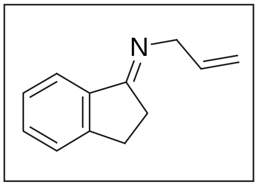
Imines from ketones (9a-e): The following procedure is representative: A sealable tube was charged with a 0.5 M solution of cyclohexanone **9b** (1.00 g, 10.2 mmol) in benzene (20 mL). Allylamine (1.5 mL, 20.4 mmol) and crushed molecular sieves (1g) were then added, the tube sealed and the reaction mixture heated to 40-45 °C. After stirring overnight, the ^{1}HNMR and ^{13}CNMR showed solely product. The solution was diluted with ether and filtered through a medium frit funnel. The ether was carefully removed by vacuum evaporation at low temperature. Benzene was removed by blowing N_2 over the solution to give the pure imine product as an orange-yellow oil (1.380 g, 99 % crude yield), that was used directly in the next reaction.



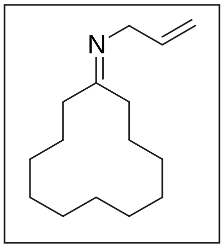
From 9a: ^{1}H NMR (300 MHz)δ: 1.65-1.94 (m, 4H), 2.10-2.47 (m, 4H), 3.89 (d, 2H, J=5.4 Hz), 5.02-5.28 (m, 2H), 5.94-6.14 (m, 1H); ^{13}C NMR (300 MHz)δ: 23.9, 24.6, 28.5, 36.1, 55.9, 114.7, 135.8, 180.9; IR (KBr) 680, 915, 994, 1678, 3342 (br) cm^{-1}.



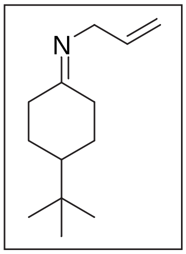
From 9b: ^{1}H NMR (300 MHz)δ: 1.40-1.80(m, 6H), 2.08-2.40 (m, 4H), 3.90 (m, 2H), 4.94-5.18 (m, 2H), 5.80-6.00 (m, 1H); ^{13}C NMR (300 MHz)δ: 25.7, 26.7, 27.5, 28.7, 39.6, 52.5, 114.8, 136.0, 174.3; IR (KBr) 680, 913, 993, 1448, 1659, 1713, 3306 cm^{-1}.



From 9c: ^{1}H NMR (300 MHz)δ: 2.55-2.67(m, 2H), 2.94-3.06 (m, 2H), 4.08 (d, 2H, J=5.6 Hz), 5.08-5.32 (m, 2H), 6.01-6.17 (m, 1H), 7.19-7.41 (m, 4H); ^{13}C NMR (300 MHz)δ: 27.6, 27.7, 55.8, 114.9, 122.0, 125.2, 126.5, 130.7, 135.6, 139.4, 149.2, 174.6; IR (KBr) 755, 914, 1325, 1466, 1607, 1654, 1713, 3072, 3375.8 (br) cm^{-1};

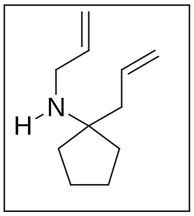


From 9d: ^{1}H NMR (300 MHz)δ: 1.10-1.32(m, 18H), 1.49-1.62 (m, 2H), 2.14 (t, 1H, J=6.6 Hz), 2.23 (t, 1H, J=6.6 Hz), 3.92 (d, 2H, J=5.4 Hz), 4.86-5.16 (qq, 2H, J=17.1, 1.8 Hz), 5.82-5.98 (m, 1H); ^{13}C NMR (300 MHz)δ: 21.9, 22.8, 22.9, 23.2, 23.9, 24.5, 25.2, 25.3, 29.4, 34.0, 40.1, 53.2, 114.4, 136.4, 173.1; IR (KBr) 732, 913, 993, 1469, 1660, 1709 cm^{-1}.

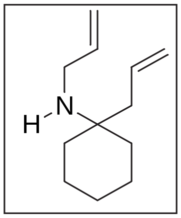


From 9e: ^{1}H NMR (300 MHz)δ: 0.77 (s, 9H), 0.92-1.44 (m, 3H), 1.57-2.42 (m, 5H), 2.68 (dq, 1H, J=14.0, 3.2 Hz), 3.86 (d, 2H, J=5.7 Hz), 4.90-5.10 (m, 2H), 5.76-5.96 (m, 1H); ^{13}C NMR (300 MHz)δ: 27.3, 28.0, 32.2, 39.3, 47.3, 52.7, 114.7, 136.1, 174.1; IR (KBr) 913, 993, 1220, 1365, 1478, 1662, 1718, 3077, 3305 (br) cm^{-1}.

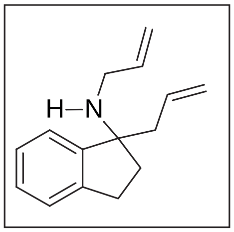
Dienes (10a-f): The following procedure for **10b** is representative: In a 100 mL round-bottom flask, fitted with a condenser, was added imine **7b** (1.347 g, 9.832 mmol) followed by THF (20 mL, 0.5 M) under N_2 at room temperature. Allyl magnesium bromide (1M in ether; 19.7 mL, 19.7 mmol) was added all at once to the reaction mixture. The reaction was allowed to stir overnight, then quenched with water. After diluting with EtOAc, the reaction was extracted thrice with 1M HCl. The aqueous layers were combined and made basic (pH=14) with 2M NaOH. The basic solution was then extracted (5X) with EtOAc. After combining the organic layers and drying over Na_2SO_4, the solvent was removed with low heat and chromatography of the resultant oil (Hex:EtOAc) gave the product **10b** as a yellow oil (1.324 g, 74% yield).



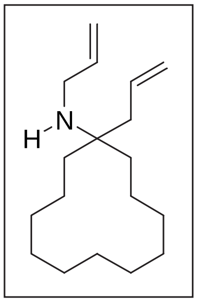
10a: ^{1}H NMR (300 MHz)δ: 1.13 (s, br, 1H), 1.40-1.80 (m, 8H), 2.23 (d, 2H, J=7.2 Hz), 3.14 (d, 2H, J=6 Hz), 4.98-5.20 (m, 4H), 5.72-5.98 (m, 2H); ^{13}C NMR (300 MHz)δ: 24.1, 37.1, 41.9, 45.7, 64.3, 115.2, 117.4, 135.0, 137.6; IR (KBr) 725, 914, 993, 1461, 1640, 3329 (br) cm^{-1}; HRMS (POS CI, M+1) calc for $C_{11}H_{20}N$ 166.1596, found 166.1683. (69% yield)



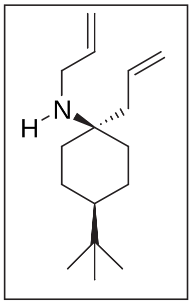
10b: ^{1}H NMR (300 MHz)δ: 1.10 (s, br, 1H), 1.22-1.70 (m, 10H), 2.17 (d, 2H, J=7.5 Hz), 3.13 (d, 2H, J=6.3 Hz), 5.00-5.21 (m, 4H), 5.74-5.97 (m, 2H); ^{13}C NMR (300 MHz)δ: 21.6, 26.0, 35.3, 41.2, 43.8, 53.7, 115.1, 117.3, 134.3, 137.7; IR (KBr) 707, 913, 996, 1449, 1639, 3330 (br) cm^{-1}; HRMS (POS CI, M+1) calc for $C_{12}H_{22}N$ 180.1752, found 180.1769. (74% yield)



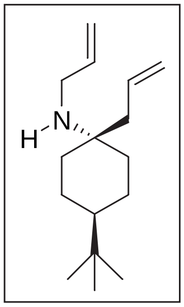
10c: ^{1}H NMR (300 MHz)δ: 1.65 (s, br, 1H), 1.98-2.23 (m, 2H), 2.35-2.58 (m, 2H), 2.74-3.14 (m, 4H), 4.94-5.20 (m, 4H), 5.62-5.98 (m, 2H), 7.06-7.28 (m, 4H); ^{13}C NMR (300 MHz)δ: 29.7, 35.1, 44.7, 45.8, 68.3, 115.4, 118.3, 123.5, 124.8, 126.1, 127.3, 134.1, 137.1, 143.6, 146.0; IR (KBr) 761, 915, 994, 1456, 1640, 2359 (weak), 3072, 3324 (weak) cm^{-1}; HRMS (POS CI, M+1) calc for $C_{15}H_{20}N$ 214.1596, found 214.1602. (91% yield)



10d: ^{1}H NMR (300 MHz)δ: 1.10-1.44 (m, 22H), 2.06 (dd, 2H, J=7.5, 1.0 Hz), 3.10 (dd, 2H, J=6.3, 1.2 Hz), 4.93-5.19 (m, 4H), 5.66-5.98 (m, 2H); ^{13}C NMR (300 MHz)δ: 18.9, 21.9, 22.5, 26.1, 26.5, 32.3, 39.2, 44.3, 57.3, 115.5, 117.4, 134.1, 137.1; IR (KBr) 909, 992, 1441,1467, 1639, 3072, 3416 (br) cm^{-1}; HRMS (POS CI, M+1) calc for $C_{18}H_{33}N$ 264.2691, found 264.2704. (80% yield)



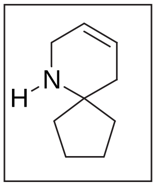
10e (minor isomer): ^{1}H NMR (500 MHz)δ: 0.84 (s, 9H), 0.92 (tt, 1H, J = 13.4 Hz, 2.9 Hz), 1.17 (td, 2H, J = 12.8 Hz, 3.8 Hz), 1.25 (qd, 2H, J = 1.6 Hz, 1.6 Hz), 1.49 (dq, 2H, J = 12.9 Hz, 3.9 Hz), 1.69 (dt, 2H, J = 11.6 Hz, 3.7 Hz), 2.08 (dt, 2H, J = 7.4 Hz, 1.1 Hz), 3.08 (dt, 2H, J = 5.9 Hz, 1.5 Hz), 5.01 (ddt, 1H, J = 17.0 Hz, 2.4 Hz, 1.5 Hz), 5.02 (d, 1H, J = 11.1 Hz), 5.06 (ddt, 1H, J = 10.0 Hz, 2.4 Hz, 1.5 Hz), 5.18 (dq, 1H, J = 17.4 Hz, 1.7 Hz), 5.83 (ddt, 1H, J = 17.0 Hz, 10.0 Hz, 7.4 Hz), 5.93 (ddt, 1H, J = 16.9 Hz, 10.5 Hz, 5.9 Hz); NOE couplings: 3.08-1.69, 2.08-1.69, 2.08-1.17, 5.83-1.17; ^{13}C NMR (300 MHz)δ: 22.0, 27.5, 32.3, 35.3, 43.8, 44.4, 48.0, 53.0, 114.8, 117.1, 134.7, 138.0; IR (KBr) 707, 913, 995, 1090, 1365, 1449, 1468, 1640, 3075, 3332 (weak) cm^{-1}; HRMS (POS CI, M+1) calc for $C_{16}H_{29}N$ 236.2378, found 236.2342. (24% yield)



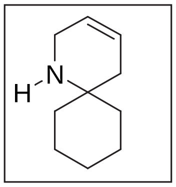
10f (major isomer; equatorial N): ^{1}H NMR (500 MHz)δ: 0.86 (s, 9H), 1.00 (tt, 2H, J = 12.1 Hz, 3.4 Hz), 1.13 (qd, 2H, J = 13.1 Hz, 3.1 Hz), 1.28 (td, 2H, J = 13.1 Hz, 3.6 Hz), 1.63 (d, 2H, J = 13.2 Hz), 1.71 (d, 1H, J = 13.0 Hz), 2.26 (dt, 2H, J = 7.4 Hz, 1.1 Hz), 2.41 (s, br, 1H), 3.20 (dt, 2H, J = 6.1 Hz, 1.4 Hz), 5.03 (ddt, 1H, J = 10.0 Hz, 2.0 Hz, 1.4 Hz), 5.08 (ddt, 1H, J = 17.2 Hz, 2.0 Hz, 1.1 Hz), 5.11 (ddt, 1H, J = 9.6 Hz, 2.0 Hz, 1.1 Hz), 5.15 (ddt, 1H, J = 16.7 Hz, 2.0 Hz, 1.4 Hz), 5.78 (ddt, 1H, J = 17.2 Hz, 10.3 Hz, 7.3 Hz), 5.91 (ddt, 1H, J = 16.8 Hz, 10.0 Hz, 6.1 Hz); NOE couplings: 2.26-1.13, 2.26-1.71, 3.20-1.28, 3.20-1.71; ^{13}C NMR (300 MHz)δ: 23.1, 27.5, 32.3, 35.9, 36.0, 44.0, 47.7, 54.5, 115.8, 118.0, 133.9, 137.1; IR (KBr) 733, 913, 996, 1365, 1467, 1640, 3075, 3318 (br, weak) cm^{-1}; HRMS (POS CI, M+1) calc for $C_{16}H_{29}N$ 236.2378, found 236.2342. (46% yield)

Spirobicyclics (11a-e): The following procedure for **11c** is representative for ring-closing metathesis of unprotected dienes: In a 50 mL round-bottom flask, a solution was prepared of diene **10c** (54 mg, 0.25 mmol) in CH_2Cl_2 (25 mL, 0.01M). After flushing with argon, p-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol) was added and the solution was stirred for 30-60 min at room temperature. Next, bis-tricyclohexylphosphine benzylidine ruthenium (IV) dichloride (Grubbs catalyst) (21 mg, 25 μmol) was added, flushing with argon. The reaction was stirred at rt for 15 hrs, after which TLC analysis showed about 70% conversion. More Grubbs catalyst (11 mg) was added and the reaction continued to stir for another 8 hrs, until all starting material was consumed by TLC (0.15 equiv Grubbs catalyst added total). The reaction solvent was evaporated, then redissolved in EtOAc. The organic layer was extracted thrice with 1M

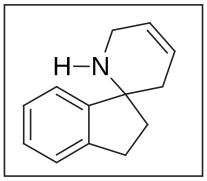
HCl (100 mL total), discarding the organic layer. The aqueous layers were combined, then made basic (pH =14) with NaOH (s). The base solution was extracted 5X with EtOAc. After drying the organic layer with Na_2SO_4 and evaporation of the solvent, the product **9d** (44 mg, 93 % yield) was isolated as a pure substance**.**



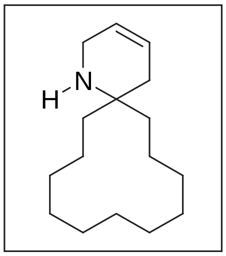
11a: ^{1}H NMR (300 MHz)δ: 1.60-2.30 (m, 8H), 2.39 (m, 2H), 3.67 (m, 2H), 5.80 (m, 1H), 5.87 (m, 1H), 9.60 (s, br, 1H); ^{13}C NMR (300 MHz)δ: 23.9, 36.6, 38.0, 42.4, 59.8, 125.2, 125.8; IR (KBr) 762, 787, 1448, 3391(br) cm^{-1}; HRMS (EI POS) calc for $C_9H_{15}N$ 137.1204, found 137.1201. (92% yield)



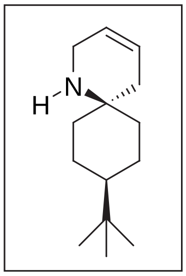
11b: ^{1}H NMR (300 MHz)δ: 1.30-2.05 (m, 10H), 2.41 (m, 2H), 3.61 (m, 2H), 5.60-5.90 (m, 2H), 9.57 (s, br, 1H); ^{13}C NMR (300 MHz)δ: 21.2, 24.9, 30.8, 32.9, 38.3, 55.3, 119.0, 124.7; IR (KBr) 649, 1097, 1148, 1448, 3024, 3288 (br) cm^{-1}; HRMS (POS EI) calc for $C_{10}H_{17}N$ 151.1361, found 151.1382. (76% yield)



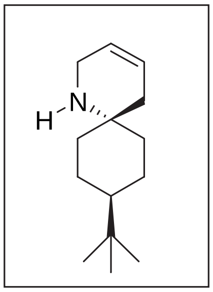
11c: ^{1}H NMR (300 MHz)δ: 1.96-2.40 (m, 4H), 2.58 (s, br, 1H), 2.76-3.08 (m, 2H), 3.32-3.60 (m, 2H), 5.75-5.94 (m, 2H), 7.10-7.42 (m, 4H); ^{13}C NMR (300 MHz)δ: 29.4, 35.7, 38.2, 42.3, 63.2, 123.1, 124.7, 125.1, 125.7, 126.5, 127.6, 142.9, 148.1; IR (KBr) 704, 738, 1265, 3051, 3286 (br, weak) cm^{-1}; HRMS (EI POS) calc for $C_{13}H_{15}N$ 185.1204, found 185.1234. (75% yield)



11d: ^{1}H NMR (300 MHz)δ: 1.16-2.00 (m, 22H), 2.16 (m, 2H), 2.93 (s, br, 1H), 3.49 (m, 2H), 5.60-5.85 (m, 2H); ^{13}C NMR (300 MHz)δ: 18.7, 21.9, 22.4, 26.1, 26.5, 31.9, 35.5, 41.1, 53.0, 124.2, 125.5; IR (KBr) 728, 1445, 1470, 3286 (weak) cm^{-1}; HRMS (LSIMS POS, M+1) calc for $C_{16}H_{29}N$ 236.2378, found 236.2359. (75% yield)

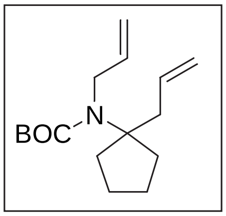


11e: ^{1}H NMR (300 MHz)δ: 0.89 (s, 9H), 0.90-1.15 (m, 1H), 1.17-1.35 (m, 6H), 1.45-1.65 (m, 2H), 1.81-1.95 (m, 2H), 3.23 (s, br, 1H), 3.31-3.40 (t, 2H, J = 2.3 Hz), 5.55-5.74 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.3, 27.5, 32.7, 34.8, 38.6, 40.3, 48.7, 49.1, 124.8, 125; IR (KBr) 656, 732, 905, 1098, 1363, 1435, 1655, 3444 (br) cm^{-1}; HRMS (LSIMS POS, M+1) calc for $C_{14}H_{25}N$ 208.2065, found 208.2066. (72% yield)

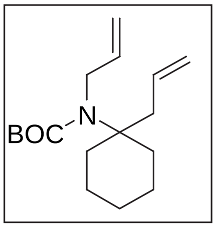


11f: ^{1}H NMR (300 MHz)δ: 0.87 (s, 9H), 0.90-1.06 (m, 1H), 1.10-1.40 (m, 6H), 1.48-1.67 (m, 2H), 1.84-1.98 (m, 2H), 2.66 (s, br, 1H), 3.28-3.40 (t, 2H, J = 2.3 Hz), 5.58-5.78 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.0, 27.7, 32.4, 35.1, 38.8, 40.4, 48.4, 49.4, 124.2, 124.5; IR (KBr) 650, 734, 908, 1098, 1363, 1435, 1651, 3440 (br) cm^{-1}; HRMS (LSIMS POS, M+1) calc for $C_{14}H_{25}N$ 208.2065, found 208.2066. (70% yield)

N-Boc Protected Dienes: The following procedure for **13a** is representative: To a solution of **10a** (100 mg, 0.606 mmol) in CH_3CN (2.4 mL, 0.25 M) under argon, was added Et_3N (404 μL, 2.90 mmol). The reaction was stirred for 5 min, then Boc_2O was added (595 mg, 2.73 mmol). After stirring the reaction at 50 ºC for 24 hrs (or until TLC shows rxn compete), the solution was diluted with EtOAc and washed with 1M HCl, and then brine. Upon drying with Na_2SO_4 and evaporation of the solvent, the crude product was purified by column chromatography (Hex/EtOAc). The pure product (**13a**) was isolated as a colorless oil (123 mg, 77% yield).

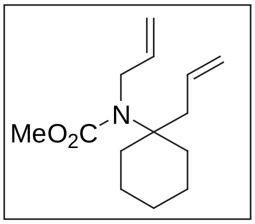


13a: ^{1}H NMR (300 MHz)δ: 1.40 (s, 9H), 1.42-1.68 (m, 4H), 1.73-1.88 (m, 2H), 1.93-2.06 (m, 2H), 2.39 (d, 2H, J=7.5 Hz), 3.73 (d, 2H, J=4.5 Hz), 4.92-5.10 (m, 4H), 5.62-5.88 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.8, 28.4, 37.5, 40.8, 50.1, 68.7, 79.1, 113.8, 117.6, 134.9, 137.1, 155.6; IR (KBr) 912, 981, 1170, 1248, 1380, 1697, 3076 cm^{-1}; HRMS (EI POS, M+) calc for $C_{16}H_{27}NO_2$ 265.2042, found 265.1973, (77% yield).

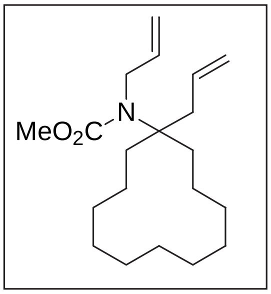


13b: ^{1}H NMR (300 MHz)δ: 1.20-1.60 (m, 15H), 1.62-2.00 (m, 4H), 2.56 (d, 2H, J=8.6 Hz), 3.80 (d, 2H, J=7.5 Hz), 4.86-5.10 (m, 4H), 5.57-5.88 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.6, 25.6, 28.4, 29.6, 34.7, 38.8, 47.0, 61.2, 79.0, 114.3, 117.2, 134.7, 137.8, 155.4; IR (KBr) 911, 994, 1166, 1241, 1375, 1453, 1695, 3076 cm^{-1}; HRMS (POS CI, M+1) calc for $C_{17}H_{29}NO_2$ 280.2277, found 280.2328. (70% yield).

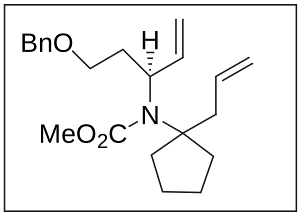
Methyl Carbamate Protected Dienes: The following procedure for **13c** is representative: To a 25 mL round bottom flask charged with NaH (58 mg, 2.4 mmol, 60% dispersion) was added THF (0.1 mL) under argon. The solution was cooled to 0 ºC, then a solution of diene **8b** (43 mg, 0.24 mmol) in THF (0.38 mL) was added via syringe. The solution was allowed to stir for 15 mins, then $ClCO_2Me$ (0.22 mL, 2.9 mmol) was slowly added. The reaction was stirred overnight (or until TLC shows rxn to be complete), then diluted with CH_2Cl_2 and extracted with 1M HCl, then brine. After drying with Na_2SO_4, and evaporation of the solvent, the crude product was chromatographed on silica gel (Hex/EtOAc) to give (**13c**) was as an orange oil (52 mg, 91% yield).



13c: ^{1}H NMR (300 MHz)δ: 1.32-1.60 (m, 6H), 1.78 (m, 2H), 1.97 (m, 2H), 2.62 (d, 2H, J=7.5 Hz), 3.61 (s, 3H), 3.87 (d, 2H, J=5.1 Hz), 4.92-5.14 (m, 4H), 5.56-5.90 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.6, 25.5, 34.4, 38.5, 46.9, 51.9, 61.6, 114.8, 117.4, 134.5, 137.4, 156.6; IR (KBr) 914, 997, 1239, 1372, 1446, 1701, 2360 (weak), 3075.7 cm^{-1}; HRMS (POS CI, M+1) calc for $C_{14}H_{23}NO_2$ 238.1807, found 238.1810, (91% yield).

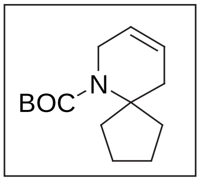


13d: ^{1}H NMR (300 MHz)δ: 1.30-1.80 (m, 20H), 2.00-2.22 (m, 2H), 2.68-2.88 (m, 2H), 3.85 (s, 3H), 4.08 (d, 2H, J=6.0 Hz), 5.12-5.33 (m, 4H), 5.80-6.10 (m, 2H); ^{13}C NMR (300 MHz)δ: 19.7, 21.9, 22.1, 26.1, 26.3, 30.3, 47.1, 52.0, 56.2, 64.6, 115.1, 117.1, 134.8, 137.8, 149.0; IR (KBr) 914, 995, 1161, 1237, 1370, 1446, 1469, 1703, 3075 cm^{-1}; HRMS (POS LSIMS, M+1) calc for $C_{20}H_{35}NO_2$ 322.2746, found 322.2742, (95% yield).

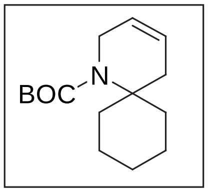


18b: ^{1}H NMR (300 MHz)δ: 1.48-1.76 (m, 4H), 1.76-1.94 (m, 2H), 1.98-2.33 (m, 4H), 2.34-2.56 (m, 2H), 3.35-3.56 (m, 2H), 3.64 (s, 3H), 3.86-3.99 (m, 1H), 4.49 (q, 2H, J = 12 Hz), 4.92-5.12 (m, 4H), 5.76-5.93 (m, 1H), 6.07-6.24 (m, 1H), 7.23-7.41 (m, 5H); ^{13}C NMR (300 MHz)δ: 22.3, 35.1, 37.4, 37.5, 40.7, 51.3, 57.8, 67.5, 70.8, 72.8, 115.8, 117.1, 127.5, 128.3, 135.5, 138.5, 138.7, 156.6; IR (KBr) 697, 735, 914, 998, 1100, 1260, 1449, 1698, 3072 cm^{-1}; HRMS (LS IMS, M+1) calc for $C_{22}H_{31}NO_3$ 358.2382, found 358.2366, (61% yield).

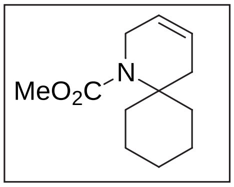
Spirobicyclics (14a-d): The following procedure for **14a** is representative: To a solution of **13a** (38 mg, 0.14 mmol) in CH_2Cl_2 (14 mL, 0.01 M) under argon was added bis-tricyclohexylphosphine benzylidine ruthenium (IV) dichloride (Grubb's catalyst) (6 mg, 0.05 equiv) and the reaction stirred for 24 hrs at rt. The reaction was diluted with CH_2Cl_2, and extracted with H_2O, then brine. After drying with Na_2SO_4, evaporation of solvent and chromatographic purification (Hex/EtOAc), the pure product **14a** was isolated as a colorless oil (28 mg, 81%).



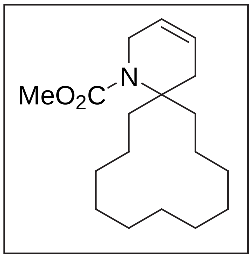
14a: ^{1}H NMR (300 MHz)δ: 1.40 (s, 9H), 1.46-1.76 (m, 4H), 1.78-2.04 (m, 4H), 2.09 (d, 2H, J=1.5 Hz), 3.98 (m, 2H), 5.66 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.7, 28.5, 33.7, 37.7, 45.6, 64.2, 79.5, 125.6, 125.9, 156.1; IR (KBr) 773, 1171, 1364, 1458, 1686, 1701 cm^{-1}; HRMS (EI POS) calc for $C_{14}H_{23}NO_2$ 237.1729, found 237.1668, (81% yield).



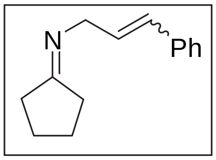
14b: ^{1}H NMR (300 MHz)δ: 1.37-2.00 (m, 17H), 2.09 (d, 2H, J=2.7Hz), 2.48 (d, 2H, J=12.9), 3.94 (m, 2H), 5.66 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.5, 26.3, 28.5, 35.5, 36.0, 43.6, 56.8, 79.3, 124.9, 125.7, 156.0; IR (KBr) 1365, 1458, 1686, 1706 cm^{-1}; HRMS (POS CI, M+1) calc for $C_{15}H_{25}NO_2$ 252.1964, found 252.1932, (64% yield).



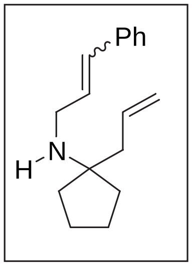
14c: ^{1}H NMR (300 MHz)δ: 1.20-1.61 (m, 8H), 2.10 (d, 2H, J=2.1 Hz), 2.49 (m, 2H), 3.61 (s, 3H), 3.97 (m, 2H), 5.58-5.73 (m, 2H); ^{13}C NMR (300 MHz)δ: 22.4, 26.2, 35.3, 36.0, 43.3, 52.0, 57.1, 125.0, 125.2, 156.6; IR (KBr) 654, 769, 828, 1092, 1219, 1347, 1445, 1713, 3032 cm^{-1}; HRMS (POS CI, M+1) calc for $C_{12}H_{19}NO_2$ 210.1494, found 210.1518, (78% yield).



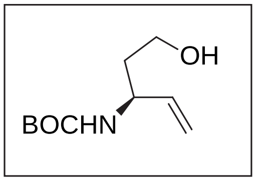
14d: ^{1}H NMR (300 MHz)δ: 1.10-1.62 (m, 20H), 2.12 (m, 2H), 2.26 (m, 2H), 3.81 (s, 3H), 3.95 (m, 2H), 5.64 (m, 2H); ^{13}C NMR (300 MHz)δ: 19.7, 21.8, 22.1, 26.2, 26.4, 31.5, 36.5, 43.9, 51.9, 60.6, 122.8, 123.5, 157.1; IR (KBr) 1235, 1326, 1435, 1712 cm^{-1}; HRMS (POS CI, M+1) calc for $C_{18}H_{31}NO_2$ 294.3300, found 294.2404, (76% yield).



Cinnamyl Imine: To a solution of cinnamyl amine (**26**) (2.49 g, 18.7 mmol) in benzene (37 mL, 0.5 M), was added cyclopentanone (1.98 mL, 22.4 mmol) and crushed molecular sieves (1.5 g). The reaction solution was heated to reflux with a condenser for 21 hrs. After cooling the solution, the sieves were filtered off and the benzene was evaporated to give the product as a crude orange oil (3.30 g, 89 % crude), that was used directly in the next reaction. ^{1}H NMR (300 MHz)δ: 1.66-1.90 (m, 4H), 2.21 (t, 2H, J = 7.2 Hz), 2.38 (t, 2H, 7.1 Hz), 4.02 (d, 2H, J = 4.8 Hz), 6.20-6.62 (m, 2H), 7.14-7.43 (m, 5H); ^{13}C NMR (300 MHz)δ: 24.1, 24.8, 28.9, 36.4, 55.5, 126.1, 127.0, 127.8, 128.3, 130.2, 137.1, 181.4 ; IR (KBr) 680, 736, 966, 1676, 3031, 3390 (br)cm^{-1}; HRMS (LSIMS POS, M+1) calc for $C_{14}H_{17}N$ 200.1439, found 200.1435.

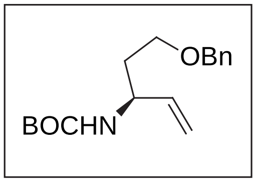


Phenyl-Substituted Diene (15): The same procedure for dienes **10a-f** was used. The product (**15**) was isolated as a tan solid (54% yield, 2-steps). ^{1}H NMR (300 MHz)δ: 1.40 (m, 2H), 1.75 (m, 4H), 2.05 (m, 2H), 2.46 (d, 2H, J = 6.9 Hz), 3.66 (d, 2H, J = 6.6 Hz), 5.012-5.35 (m, 2H), 5.82-6.05 (m, 1H), 6.48-6.75 (m, 2H), 7.05-7.55 (m, 5H), 9.12 (s, br, 2H); ^{13}C NMR (300 MHz)δ: 23.6, 34.8, 39.7, 45.0, 68.3, 119.5, 120.0, 126.4, 127.8, 128.0, 131.1, 135.2, 136.1; HRMS (LSIMS POS, M+1) calc for $C_{17}H_{23}N$ 242.1909, found 242.1921.

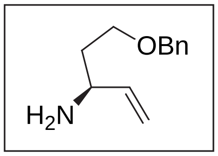


1-(1,1-dimethylethoxy)-N-(1-(2-hydroxyethyl)-2-propenyl) methanamide: To a 500 mL 3-neck round bottom flask fitted with a condenser and addition funnel under argon was added a solution of methyltriphenyl phosphonium bromide (16.53 g, 46.31 mmol) in CH_2Cl_2 (93 mL, 0.5 M) followed by sodium amide (1.81 g, 46.3 mmol). To the resultant ylide was added a solution of lactol **(16)** (2.00 g, 9.85 mmol) in CH_2Cl_2 (62 mL, 0.16 M) dropwise. Toluene (232 mL) was then added and the solution was refluxed for 4 hrs, and then stirred at room temperature for 3 days. The solvent was concentrated to remove CH_2Cl_2, followed by filtration of the

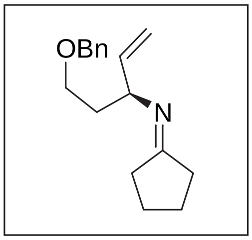
$Ph_3P{=}O$ precipitate. The concentrated reaction mixture was then cooled in a freezer for 2 hrs, and more $Ph_3P{=}O$ solid was removed by vacuum filtration. Toluene was next removed from the crude reaction mixture and then purified by column chromatography on silica gel (EtOAc/Hex) to give the desired **(17)** as a light yellow oil (1.63 g, 82 %). ^{1}H NMR (300 MHz)δ: 1.45 (s, 10H), 1.89 (m, 1H), 3.41 (s, br, 1H), 3.66 (m, 2H), 4.35 (m, 1H), 4.85 (m, 1H), 5.15 (dd, 2H, J=17.4, 10.2 Hz), 5.83 (m, 1H); ^{13}C NMR (300 MHz)δ: 28.2, 37.6, 49.2, 58.5, 79.6, 114.5, 138.2, 156.3; IR (KBr) 919, 990, 1056, 1171, 1508, 1686, 3083, 3336 (br) cm^{-1}; HRMS (CI POS, M+1) calc for $C_{10}H_{20}NO_3$ 202.1443, found 202.1470.



Benzylether: NaH (174 mg, 7.25 mmol) was placed in a round bottom flask under argon and a solution of the alcohol (1.325 g, 6.592 mmol) in THF (13 mL, 0.5 M) was added and the reaction stirred at room temperature for 15 min. Next, benzyl bromide (1.57 mL, 13.2 mmol) was added followed by Bu_4NI (486 mg, 1.32 mmol). After stirring the reaction overnight, TLC analysis confirmed that all starting material had been consumed. The solid was filtered off and rinsed well with EtOAc. The filtrate was then diluted with EtOAc and washed with H_2O and brine. The organic layers were dried over Na_2SO_4, the solvent removed under reduced pressure, and the resultant oil purified by chromatography (Hex/EtOAc) to give the protected alcohol as a colorless oil **(**1.73g, 92% yield**)**. ^{1}H NMR (300 MHz)δ: 1.43 (s, 9H), 1.62-1.81 (m, 1H), 1.84-2.02 (m, 1H), 3.45-3.67 (m, 2H), 4.28 (s, br, 1H), 4.48 (s, 2H), 5.02-5.24 (m, 2H), 5.67-5.84 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (300 MHz)δ: 28.3, 34.2, 51.0, 67.2, 73.1, 78.9, 114.4, 127.6, 128.3, 138.0, 138.3, 155.3; IR (KBr) 698, 737, 919, 1101, 1171, 1248, 1365, 1498, 1702, 2360 (weak), 3030, 3345 cm^{-1}; HRMS (LSIMS POS, M+1) calc for $C_{17}H_{25}NO_3$ 292.1913, found 292.1960.

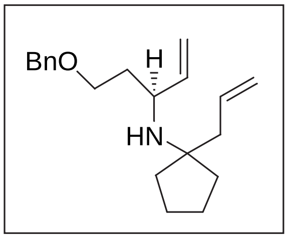


Amine 17 To a solution of the carbamate (100 mg, 0.344 mmol) in CH_2Cl_2 (1.7 mL, 0.2 M) under argon was added freshly distilled TFA (530 μL, 6.88 mmol) and the solution was stirred for 75 min at room temperature. After diluting the reaction with 5 mL of CH_2Cl_2, 2M NaOH (ca. 2 mL) was added and the solution was stirred vigorously for 1 hr to convert the TFA salt to free amine. The solution was further diluted with more CH_2Cl_2 and extracted three times with 1M NaOH, followed by brine. The organic layer was dried over Na_2SO_4, and the solvent removed under vacuum. The product **19b** was chromatographed (Hex/EtOAc/Et_3N) to give a yellow oil (64 mg, 97 % yield). ^{1}H NMR (300 MHz)δ: 1.31 (s, br, 2H), 1.62-1.82 (m, 2H), 3.42-3.62 (m, 3H), 4.48 (s, 2H), 4.96-5.15 (qt, 2H, J = 17.4, 10.5, 1.4 Hz), 5.71-5.86 (m, 1H), 7.20-7.38 (m, 5H); ^{13}C NMR (300 MHz)δ: 37.2, 51.9, 67.6, 72.9, 113.4, 127.5, 127.5, 128.3, 138.3, 143.0; IR (KBr) 698, 734, 915, 1102, 1364, 1454, 2359 (weak), 3030, 3302 (weak), 3374 (weak) cm^{-1}; HRMS (POS LSIMS, M+1) calc for $C_{12}H_{17}NO$ 192.1388, found 192.1392.

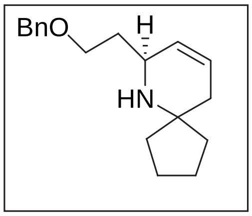


Imine: In a 10 mL round-bottom flask, a solution was prepared of free amine **17** (20 mg, 0.059 mmol) and cyclopentanone (7.8 μL, 0.089 mmol) in benzene (3 mL). The reaction mixture was heated to 60 °C on a rotory-evaporator to azeotropically remove water.

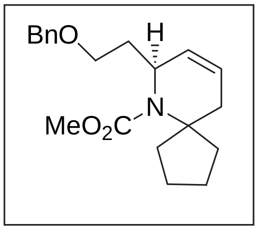
More benzene (3 mL) was added and evaporated as before. This process was repeated four more times, adding cyclopentanone (39 µL, 0.45 mmol total) and benzene (45 mL total) as necessary to complete the reaction. The remaining solvent was pumped off and the imine product was found to be a yellow oil (23 mg, 96 % yield), which was used crude in the next reaction. ^{1}H NMR (300 MHz)δ: 1.64-2.02 (m, 6H), 2.70-2.90 (m, 2H), 2.34 (t, 2H, J = 7.2 Hz), 3.38-3.57 (m, 2H), 3.94 (q, 1H, J = 6.9 Hz), 4.40-4.54 (m, 2H), 4.96-5.10 (m, 2H), 5.74-5.90 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (300 MHz)δ: 23.9, 24.8, 28.7, 36.2, 36.3, 62.3, 66.9, 72.8, 114.0, 127.3, 127.5, 128.1, 138.3, 139.4, 180.2.



18a In a 25 mL round-bottom flask fitted with a condenser, the imine (226 mg, 0.879 mmol) was dissolved in THF (1.8 mL, 0.5 M) and the solution was stirred under argon. All at once, a soln of allylmagnesium bromide in ether (8.8 mL, 1M) was added to the reaction flask and the reaction was allowed to stir at rt for 3 hrs. The reaction solution was then cooled in an ice bath and quenched with H_2O, then the THF was removed by vacuum. The crude reaction mixture was then diluted with EtOAc and extracted well with 1M HCl, discarding the organic layer. The aqueous layer was made basic (pH = 14) with NaOH (s) and the product was extracted into EtOAc with several washings. After drying the organic layer with Na_2SO_4 and removal of the solvent, the pure diene **18a** was collected as an orange oil (199 mg, 76% yield). ^{1}H NMR (300 MHz)δ: 1.37-1.84 (m, 10H), 2.14-2.32 (m, 2H), 3.30-3.60 (m, 3H), 4.47 (d, 2H, J = 4.8 Hz), 4.90-5.16 (m, 4H), 5.62-5.94 (m, 2H), 7.20-7.40 (m, 5H); ^{13}C NMR (300 MHz)δ: 23.5, 23.8, 37.4, 37.5, 37.9, 42.3, 54.0, 65.1, 67.5, 72.8, 113.7, 117.3, 127.4, 127.5, 128.2, 135.5, 138.4, 144.2; IR (KBr) 697, 734, 913, 996, 1102, 1363, 1454, 1638, 2360, 3071, 3355 (br, weak) cm^{-1}; HRMS (EI POS, M+1) calc for $C_{20}H_{29}NO$ 300.2327, found 300.2330.



Spirobicyclic (19a): In a 10 mL round-bottom flask fitted with a condenser, was added a solution of diene **21b** (20 mg, 0.067 mmol) in CH_2Cl_2 (6.7 mL, 0.01 M). After flushing with argon, p-toluenesulfonic acid monohydrate (13 mg, 0.067 mmol) was added and the reaction was stirred for 30 mins. Grubbs' monoimidazolinylidenemonophosphine carbene complex (2.8 mg, 3.3 µmol) was added. The solution was stirred at rt. overnight. After 24 hrs, the reaction was 50 % done. More of the catalyst (2.8 mg, 3.3 µmol) was added and the reaction stirred for another 24 hrs, (56 hrs. total). After removal of the solvent, the reaction was diluted with ethyl acetate and extracted thrice with 1M HCl. The organic layer was discarded and the aqueous layer was made basic (pH = 14) with NaOH (s), and the product was extracted into three washings of EtOAc. The organic layer was extracted once with brine, then dried with Na_2SO_4. After evaporation of the solvent, the product was purified by column chromatography with $CHCl_3$/MeOH to give the pure spirobicyclic **19a** (20.6 mg, 83 % yield). ^{1}H NMR (300 MHz)δ: 1.46-2.26 (m, 12H), 3.56-3.79 (m, 3H), 3.92 (s, br, 1H), 4.50 (q, 2H, J = 12 Hz), 5.54-5.64 (m, 1H), 5.70-5.81 (m, 1H), 7.22-7.40 (m, 5H); ^{13}C NMR (300 MHz)δ: 23.3, 24.1, 35.0, 35.2, 36.5, 41.1, 49.5, 60.9, 67.5, 73.0, 125.2, 127.6, 127.7, 128.4, 129.1, 138.3; IR (KBr) 697, 733, 1102, 1454, 3027, 3323 (weak) cm^{-1}; HRMS (LSIMS, M+1) calc for $C_{19}H_{25}NO$ 272.2014, found 272.2028.



Spirobicyclic (19b): A solution of **18b** (20 mg, 0.056 mmol) in CH_2Cl_2 (5.6 mL, 0.01 M) was prepared and stirred under argon. Bis-tricyclohexylphosphine benzylidine ruthenium (IV) dichloride (Grubb's catalyst) (2.3 mg, 0.05 equiv) was added and the reaction was stirred for 2.5 hrs at rt. The solvent was evaporated and the product was chromatographically purified to give **19b** as a colorless oil (17 mg, 92%). ^{1}H NMR (300 MHz)δ: 1.40-2.30 (m, 12H), 3.53 (t, 2H, J = 6.9 Hz), 3.65 (s, 3H), 4.42-4.63 (m, 3H), 5.82-5.92 (m, 1H), 5.93-6.02 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (300 MHz)δ: 24.5, 25.0, 35.6, 36.8, 37.7, 39.8, 51.9, 52.3, 65.5, 68.1, 72.7, 125.7, 127.4, 127.5, 128.3, 130.8, 138.4, 155.9; IR (KBr) 697, 735, 773, 1099, 1310, 1440, 1697, 3030 cm^{-1}; HRMS (LSIMS POS, M+1) calc for $C_{20}H_{27}NO_3$ 330.2069, found 330.2091.