Supporting Information

Total Synthesis of (±)-Rhazinal Using Novel Palladium-Catalyzed Cyclizations

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General Information. Tetrahydrofuran (THF) was distilled from Na/benzophenone. Triethylamine (Et₃N) was distilled from calcium hydride. Dichloromethane (CH₂Cl₂) and ether (Et₂O) were dried by passing through a column of activated alumina prior to use. n-Butyllithium (n-BuLi) and t-butyllithium (t-BuLi) were titrated periodically with diphenylacetic acid. All other starting materials and solvents are commercially available and were used without further purification. Chromatography was carried out with silica gel. All mixed solvent systems were reported as v/v solutions. Extracts were dried over MgSO₄, and solvents were removed with a rotary evaporator under reduced pressure. ¹H and ¹³C NMR spectra were recorded in CDCl₃ (7.27 ppm, 77.23 ppm) on a 400 MHz spectrometer.

General Procedure for Oxidative Heck Reaction of 9 (Table 1, entry 7)

To pyrrole **9** (60 mg, 0.338 mmol) was added first Dioxane:AcOH:DMSO (9:3:1, 0.1M), then Pd(OAc)₂ (7.6 mg, 0.034 mmol), then t-BuOOH (1.0 eq, 0.338 mmol). The solution was heated to 45 °C for 3 h, cooled to room temperature, filtered over a plug of silica gel (30% EtOAc in hexanes) and concentrated under vacuum. The product was purified by flash chromatography (10% EtOAc in hexanes) to afford 39.6 mg (62%) of 8-Ethyl-8-vinyl-5,6,7,8-tetrahydro-indolizine **10** as a pale yellow oil.

(*E*)-ethyl 4-ethylhex-4-enoate 7. To the neat known allylic alcohol 6 (1.00 g, 9.88 mmol) was added ethyl orthoacetate (12.7 mL, 69.2 mmol) and propionic acid (44 mg, 0.6 mmol). The solution was heated at 120 °C for 1 h under conditions for distillative removal of ethanol. The product was purified via flash chromatography (10% EtOAc in hexanes) to afford 1.45 g (94%) of the desired ester 7 as a colorless oil: IR (film): 2961, 1726, 1453, 1265 cm⁻¹; ¹H NMR: δ 5.14 (q, J = 7.0 Hz, 1H), 4.08 (m, 2H), 2.34 (m, 2H), 2.26 (m, 2H), 1.98 (m, 2H), 1.54 (d, J = 7.0 Hz, 3H), 1.20 (m, 3H), 0.96 (m, 3H); ¹³C NMR: δ 173.4, 139.9, 118.5, 60.2, 32.9, 31.5, 22.7, 14.1, 12.8, 12.6; HRMS (EI+): m/z (M+) calcd for C₁₀H₁₈O₂ 170.1308; found 170.1307.

(*E*)-ethyl 4-ethylhex-4-en-1-ol . A solution of ester **7** (700 mg, 4.5 mmol) in Et₂O was added over 5 min. to a mixture of lithium aluminum hydride (170 mg, 4.5 mmol) in Et₂O (15mL) at 0 °C. After addition of the ester, the solution was allowed to warm to room temperature and stirred for 2 h. The resulting mixture was then cooled back down to 0°C and sodium sulfate decahydrate was added in excess until there was no visible sign of bubbling. The reaction was then filtered through a plug of Celite and concentrated under vacuum to yield a yellow oil. The product was purified by column chromatography (35% EtOAc in hexanes) to afford 460 mg (80%) of (*E*)-ethyl 4-ethylhex-4-en-1-ol as a colorless oil: IR (film): 3415, 2966, 1457, 1265 cm⁻¹; ¹H NMR: δ 5.20 (q, J = 7.0 Hz, 1H), 3.62 (m, 2H), 2.09 (m, 4H), 1.67 (m, 2H), 1.58 (d, J = 7.0 Hz, 3H), 1.57 (br s, 1H), 0.97 (d, J = 7.0 Hz, 3H); ¹³C NMR: δ 141.3, 118.2, 62.9, 32.8, 30.9, 22.6, 12.9, 12.7; HRMS (EI+): m/z (M+) calcd for C₈H₁₆O 128.1201; found 128.1203.

(*E*)-4-ethylhex-4-enyl 4-methylbenzenesulfonate 8. To a solution of (*E*)-ethyl 4-ethylhex-4-en-1-ol (400 mg, 3.1 mmol) in CH₂Cl₂ (5 mL) at 0 °C was added *p*-toluene sulfonyl chloride (0.91 g, 4.7 mmol) was added, followed by pyridine (0.54 mL, 6.7 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was dilute with ether (20 mL) and washed with H₂O (20 mL), 1M HCl (20 mL), sat'd soln. NaHCO₃ (20 mL), and brine. The organic extracts were combined and dried, filtered and concentrated under vacuum to afford a yellow oil. The product was purified by column chromatography (15% EtOAc in hexanes) to afford 808 mg (92%) of the desired tosylate 8 as a colorless oil: IR (film): 1290, 715 cm⁻¹; ¹H NMR: δ 7.80 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.04 (q, J = 7.0 Hz, 1H), 4.01 (m, 2H), 2.46 (s, 3H), 1.98 (m, 4H), 1.74 (m, 2H), 1.53 (d, J = 7.0 Hz, 3H), 0.97 (m, 3H); ¹³C NMR: δ 144.6, 139.6, 133.1, 129.8, 127.9, 119.0, 70.4, 32.0, 27.3, 22.4, 21.6, 12.9, 12.7; HRMS (EI+): m/z (M+H+) calcd for C₁₅H₂₂O₃S 283.1368; found 283.1373.

1-((*E***)-4-ethylhex-4-enyl)-1***H***-pyrrole 9.** Pyrrole (568 mg, 8.4 mmol) was added to a stirred suspension of KH (1.10 g, 8.4 mmol) in dry N,Ndimethylformamide (DMF, 42 mL) and the resulting solution was stirred at room temperature for 5 min. Then a solution of tosylate 8 (1.20 g, 4.2mmol) in DMF (10mL) was added and the flask containing the tosylate was rinsed with an additional 2 mL DMF. The resulting mixture was stirred at room temperature for 2 h, then quenched with H₂O (20mL) and partitioned between ethyl acetate (100mL) and 1 M HCl (20mL). The separated aqueous phase was extracted with ethyl acetate (2x 40mL) and then combined organic phases washed with H₂O (3x40mL) and brine (50 mL), dried, filtered, and concentrated under vacuum to yield a brown oil. The product was purified by column chromatography (10% EtOAc in hexanes) to afford 476 mg (64%) of **9** as a colorless oil: IR (film): 1226, 715 cm⁻¹; ¹H NMR: δ 6.65 (m, 2H), 6.13 (m, 2H), 5.20 (q, J = 10.0 Hz, 1H), 3.84 (m, 2H), 2.05 (m, 2H), 1.98 (m, 2H), 1.87 (m, 2H), 1.59 (d, I = 10.0 Hz, 3H), 0.97 (m, 3H); ¹³C NMR: δ 141.2, 120.4, 118.7, 107.7, 49.1, 33.5, 29.7, 22.6, 13.0, 12.7; HRMS (EI+): m/z (M+) calcd for $C_{12}H_{19}N$ 177.1517; found 177.1517.

8-Ethyl-8-vinyl-5,6,7,8-tetrahydro-indolizine 10. IR (film): 1276, 715 cm⁻¹; 1 H NMR: δ 6.52 (d, J = 2.0 Hz, 1H), 6.14 (t, J = 3.0 Hz, 1H), 5.93 (d, J = 2.0 Hz, 1H), 5.82 (q, J = 7.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 4.81, (d, J = 18.5 Hz, 1H), 4.14 (q, J = 7.5 Hz, 2H), 3.86 (t, J = 7.0 Hz, 2H), 3.93 (m, 1H), 3.84 (m, 1H), 2.36 (m, 2H), 2.05 (m, 2H), 1.88 (m, 2H), 1.79 (m, 1H), 1.70 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H); 13 C NMR: δ 173.9, 145.2, 132.5, 118.9, 113.8, 107.4, 105.1, 60.3, 45.3, 41.8, 35.6, 31.0, 30.0, 19.8,14.2; HRMS (EI+): m/z (M+) calcd for $C_{15}H_{23}NO_2$ 249.1728; found 249.1720.

5-(*tert*-**Butyl-diphenyl-silanyloxy)-2-methylene-pentanal 12.** To a mixture of an aqueous formaldehyde solution (37% formaldehyde in water, 15.5 mmol, 1.0 eq) and aldehyde **11** (15.5 mmol) in *i*-PrOH (1.55 mL) was added propionic acid (1.55 mmol, 10 mol%) followed by pyrrolidine (1.55 mmol, 10 mol%). The reaction was stirred at 45 °C for 25 h. A sat'd solution of NaHCO₃ (45 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried, and concentrated under vacuum. The product was purified by column chromatography (10% EtOAc in hexanes) to afford 5.35 g (98%) of **12** as a colorless oil: IR (film): 3070, 1960, 1471 cm⁻¹; ¹H NMR: δ 9.51 (s, 1H), 7.69 (m, 4H), 7.45 (m, 6H), 6.22 (s, 1H), 5.98 (s, 1H), 3.68 (m, 2H), 2.39 (m, 2H), 1.73 (m, 2H), 1.09 (s, 9H); ¹³C NMR: δ 194.6, 149.8, 135.5, 134.2, 133.8, 129.6, 127.7, 63.6, 30.4, 26.8, 24.3, 19.2; HRMS (EI+): m/z (M+Li+) calcd for $C_{22}H_{28}O_2Si$ 359.2019; found 359.2021.

6-(tert-Butyl-diphenyl-silanyloxy)-3-methylene-hexan-2-ol 13. To a cooled (0 °C) solution of acrolein 12 (4.81 g, 13.36 mmol) in Et₂O (50 mL), was added MeLi (0.8 M in Et₂O, 19 mL, 15.2 mmol) over 2 h via cannula. The flask containing the MeLi was rinsed with an additional 5 mL Et₂O. After addition of MeLi, the solution was allowed to warm to room temperature over 6 h. The resulting solution was then cooled back down to 0 °C and a saturated solution of NH₄Cl was slowly added. The solution was allowed to warm to room temperature and extracted with Et₂O (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered, and concentrated under vacuum to yield a yellow

oil. The product was purified by column chromatography (20% EtOAc in hexanes) to afford 2.52 g (50%) of **13** as a colorless oil: IR (film): 3376, 2933 cm⁻¹; ¹H NMR: δ 7.59 (m, 4H), 7.34 (m, 6H), 4.95 (s, 1H), 4.70 (s, 1H), 4.15 (m, 1H), 3.62 (m, 2H), 2.13 (m, 1H), 2.06 (m, 1H), 1.67 (m, 2H), 1.49 (br s, 1H), 1.2 (d, J = 2.0 Hz, 3H), 0.97 (m, 1H); ¹³C NMR: δ 152.9, 135.5, 133.9, 129.5, 127.6, 108.3, 71.0, 63.5, 31.0, 27.9, 26.8, 22.2, 19.2; HRMS (EI+): m/z (M+H+) calcd for $C_{23}H_{32}O_2Si$ 369.2250; found 369.2251.

7-(*tert*-Butyl-diphenyl-silanyloxy)-4-eth-(E)-ylidene-heptanoic acid ethyl ester 14. To a solution of allylic alcohol 13 (5.09 g, 13.8 mmol) neat was added ethyl orthoacetate (17.8 mL, 69.2 mmol) and propionic acid (61 mg, 0.8 mmol). The solution was heated at 120 °C for 1 h under conditions for distillative removal of ethanol and excess ethyl orthoacetate. The product was subsequently purified by column chromatography (15% EtOAc in hexanes) to afford 5.70 g (94%) of 14 as a colorless oil: IR (film): 3048, 1654 cm⁻¹; ¹H NMR: δ 7.71 (m, 4H), 7.43 (m, 6H), 5.25 (q, J = 7.5 Hz, 1H), 4.25 (m, 2H), 3.68 (m, 2H), 2.41 (m, 2H), 2.30 (m, 2H), 2.13 (m, 2H), 1.67 (m, 2H), 1.63 (d, J = 7.5 Hz, 3H), 1.28 (m, 3H), 1.08(s, 9H); ¹³C NMR: δ 173.5, 138.0, 135.5, 134.0, 129.5, 127.6, 119.5, 63.6, 60.2, 33.2, 31.9, 31.1, 26.8, 26.0, 22.2, 19.2, 14.2, 13.2; HRMS (EI+): m/z (M+Li+) calcd for C₂₇H₃₈O₃Si 445.2742; found 445.2740.

7-(*tert*-Butyl-diphenyl-silanyloxy)-4-eth-(**Z**)-ylidene-heptan-1-ol. To a cooled (0 °C) solution a solution of TBDMS-ether **14** (20.0 g, 45.6 mmol) in Et₂O (230 mL) was added TBAF (1.0 M in THF, 59.2 mmol). The reaction was allowed to warm to room temperature and after 1 h the reaction was quenched with a sat'd solution of brine and extracted with Et₂O (3 x 200 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered, and concentrated under vacuum to yield a yellow oil. The product was subsequently purified by column chromatography (20% EtOAc in hexanes) to afford 7.30 g (80%) of 7-(*tert*-Butyl-diphenyl-silanyloxy)-4-eth-(**Z**)-ylidene-heptan-1-ol as a colorless oil: IR (film): 3508, 2940, 1728 cm⁻¹; ¹H NMR: δ 5.20 (q, J = 6.8 Hz, 1H), 4.07 (q, J q, J = 6.8 Hz, 2H), 3.56 (t, J = 6.8 Hz, 2H), 2.90 (br s, 1H), 2.35 (m, 2H), 2.25 (m, 2H), 2.05 (m, 2H), 1.67 (m, 2H), 1.63 (d, J = 7.5 Hz, 3H), 1.27 (t, J = 6.8 Hz, 3H); ¹³C NMR: δ 173.6, 137.8,

119.7, 62.3, 60.1, 33.2, 31.7, 30.9, 26.5, 14.1, 13.1; HRMS (EI+): m/z (M+) calcd for $C_{11}H_{21}O_3$ 201.1491; found 201.1492.

Toluene-4-sulfonic acid 7-(*tert*-butyl-diphenyl-silanyloxy)-4-eth-(E)-ylidene-heptyl ester 15. Following the same procedure as described for compound 8, reaction of 7-(*tert*-Butyl-diphenyl-silanyloxy)-4-eth-(Z)-ylidene-heptan-1-ol (1.06 g, 5.27 mmol) in CH₂Cl₂ (17.6 mL) with p-toluene sulfonyl chloride (1.3 g, 6.9 mmol) and pyridine (0.9 mL, 11.3 mmol) afforded 1.40g (75%) of **15** as a colorless oil: IR (film): 3043, 1742, 1375 cm⁻¹; ¹H NMR: δ 7.74 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.20 (q, J = 7.0 Hz, 1H), 4.06 (q, J = 6.5 Hz, 2H), 3.96 (t, J = 6.5 Hz, 2H), 2.38 (s, 1H), 2.28 (m, 2H), 2.18 (m, 2H), 2.01 (m, 2H), 1.66 (m, 2H), 1.48 (d, J = 7.0 Hz, 3H), 1.22 (t, J = 6.5 Hz, 3H); ¹³C NMR: δ 173.1, 144.7, 136.2, 133.0, 129.8, 127.8, 120.7, 70.1, 60.3, 33.0, 31.4, 27.1, 25.4, 21.5, 14.1 13.1; HRMS (EI+): m/z (M+) calcd for C₁₈H₂₇O₅ Si 355.1579; found 355.1583.

4-Eth-(Z)-ylidene-7-pyrrol-1-yl-heptanoic acid ethyl ester 5. Following the same procedure as described for compound **9**, treatment of the potassium salt of pyrrole (568 mg, 8.4 mmol in dry *N*,*N*-dimethylformamide (DMF, 42 mL) with a solution of tosylate **15** (1.20 g, 4.2mmol) in DMF (10mL) afforded 476 mg (67%) of **5** as a colorless oil: IR (film): 3047, 1747 cm⁻¹; ¹H NMR: δ 6.66 (m, 2H), 6.14 (m, 2H), 5.29 (q, J = 6.5 Hz, 1H), 4.14 (q, J = 7.5 Hz, 2H), 3.86 (t, J = 7.5 Hz, 2H), 2.39 (m, 2H), 2.31 (m, 2H), 2.10 (m, 2H), 1.88 (m, 2H), 1.57 (d, J = 7.5 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H); ¹³C NMR: δ 173.4, 137.0, 120.5, 120.31, 109.0, 60.3, 49.3, 33.1, 31.7, 29.8, 26.9,14.2 13.2; HRMS (EI+): m/z (M+) calcd for C₁₅H₂₃NO₂ 249.1728; found 249.1720.

3-(8-Vinyl-5,6,7,8-tetrahydro-indolizin-8-yl)-propionic acid ethyl ester 16. Following the same procedure as described for compound **10**. IR (film): 2948, 1767, 1712 cm⁻¹; ¹H NMR: δ 6.52 (d, J = 2.0 Hz, 1H), 6.14 (t, J = 3.0 Hz, 1H), 5.93 (d, J = 2.0 Hz, 1H), 5.82 (q, J = 7.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 4.81, (d, J = 18.5 Hz, 1H), 4.14 (q, J = 7.5 Hz, 2H), 3.86 (t, J = 7.0 Hz, 2H), 3.93 (m, 1H), 3.84 (m, 1H), 2.36 (m, 2H), 2.05 (m, 2H), 1.88 (m, 2H), 1.79 (m, 1H), 1.70 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H);

¹³C NMR: δ 173.9, 145.2, 132.5, 118.9, 113.8, 107.4, 105.1, 60.3, 45.3, 41.8, 35.6, 31.0, 30.0, 19.8,14.2; HRMS (EI+): m/z (M+) calcd for C₁₅H₂₃NO₂ 249.1728; found 249.1720.

3-(8-Ethyl-3-formyl-5,6,7,8-tetrahydro-indolizin-8-yl)-N-(phenyl)-

propionamide 3a. Following a procedure analogous to the one described for compound **3b**, **21** and aniline afforded 150 mg (63%) of **3a** as a foamy solid. IR (film): 3300, 1721, 1656 cm⁻¹; ¹H NMR: δ 9.42 (s, 1 H), 7.49 (d, J = 9.0 Hz, 2 H), 7.35 (d, J = 9.0 Hz, 2 H) 7.20 (br s, 1 H), 7.11 (t, J = 5 Hz, 1 H), 6.92 (d, J = 5.0 Hz, 1 H), 6.01 (t, J = 5 Hz, 1 H), 4.41 (m, 1H), 4.33 (m, 1H), 2.34 (m, 1 H), 2.27 (m, 1 H), 2.05 (m, 2 H), 1.97 (m, 2 H), 1.70 (m, 4 H), 0.86 (m, 3H); ¹³C NMR: δ 178.5, 170.8, 146.2, 137.8, 130.8, 129.0, 124.3, 124.2, 119.6, 107.5, 45.4, 38.2, 35.2, 33.7, 33.0, 28.8, 19.6, 8.6; HRMS (EI+): m/z (M+) calcd for $C_{20}H_{25}N_2O_2$ 325.1916; found 325.1909.

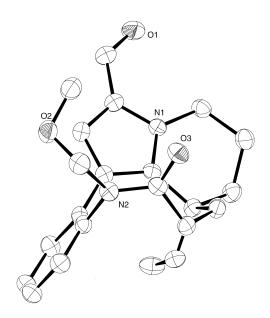
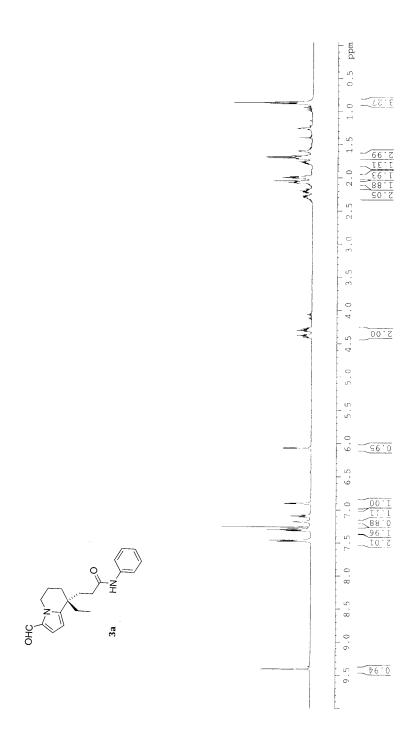
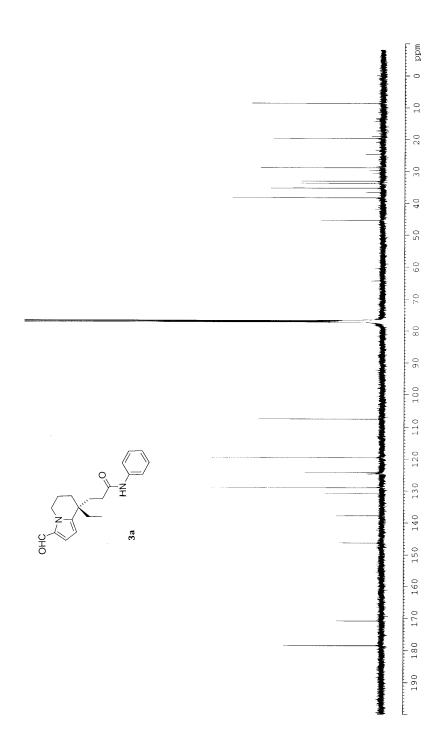
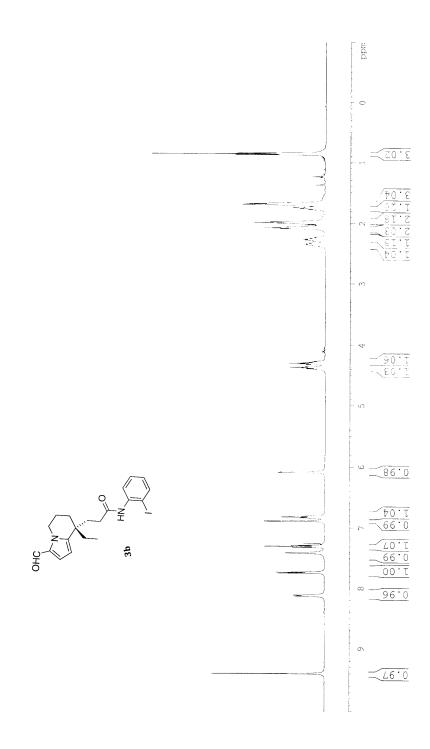
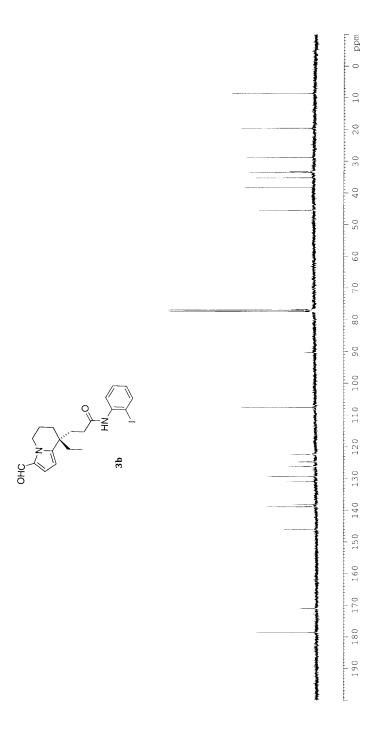


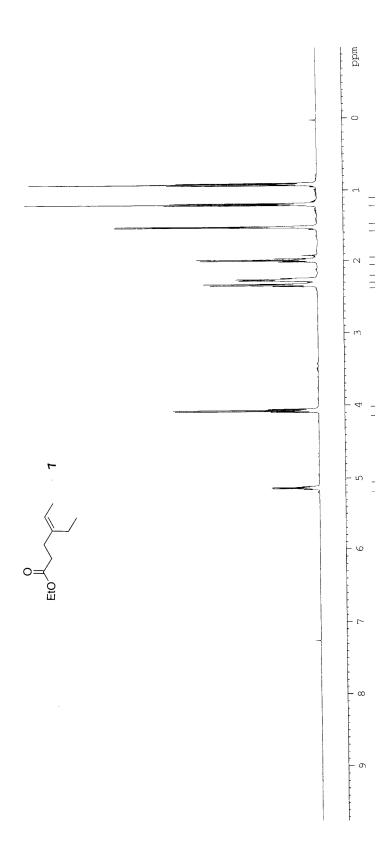
Figure 2. X-ray structure of *N*-MOM-rhazinal **26**. For clarity, the unnatural enantiomeric series is shown and hydrogen atoms are omitted.

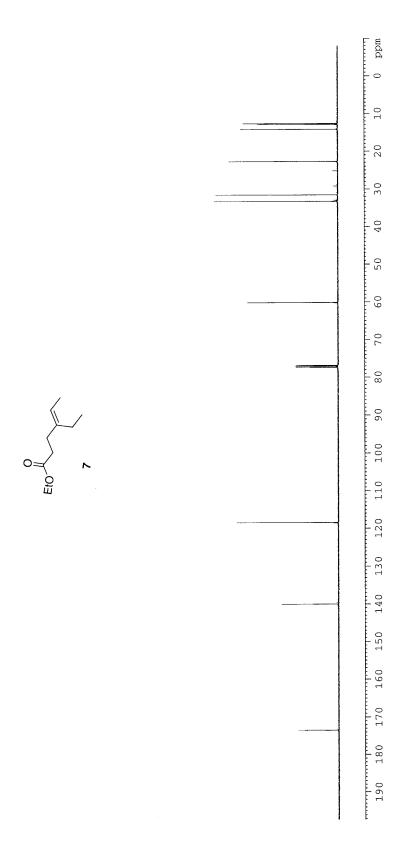


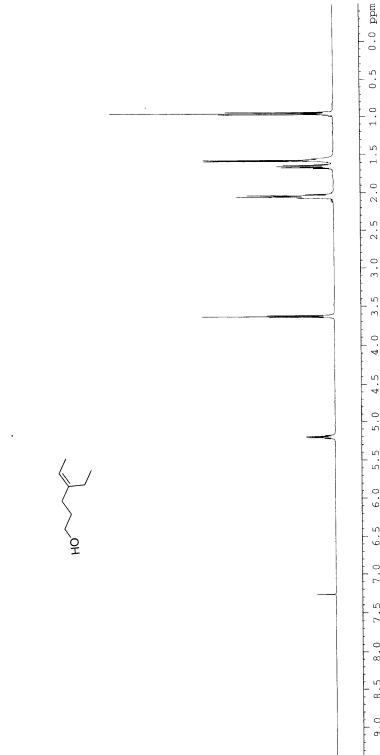


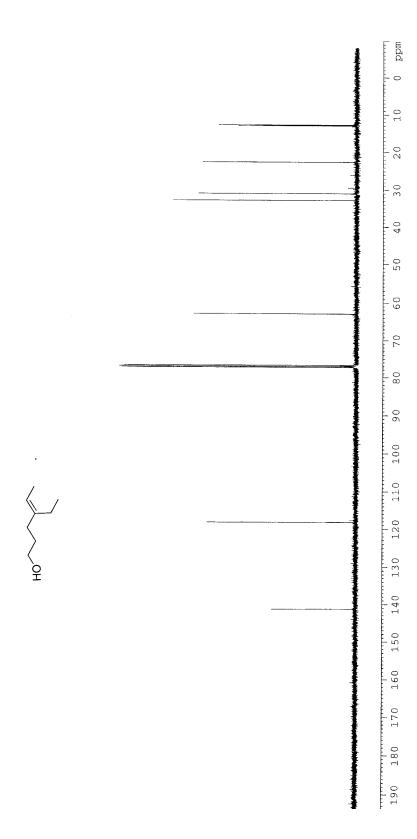


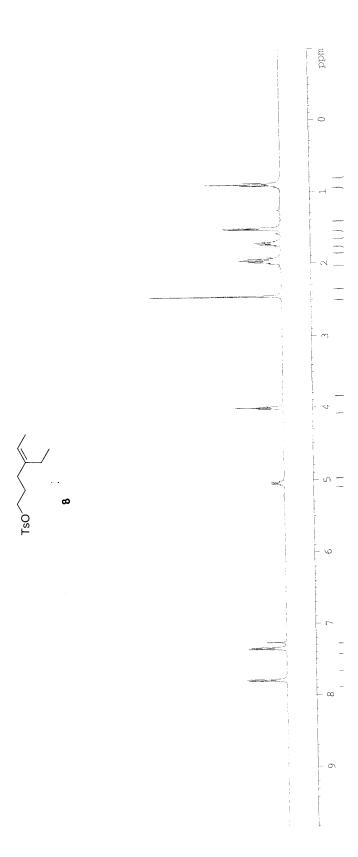


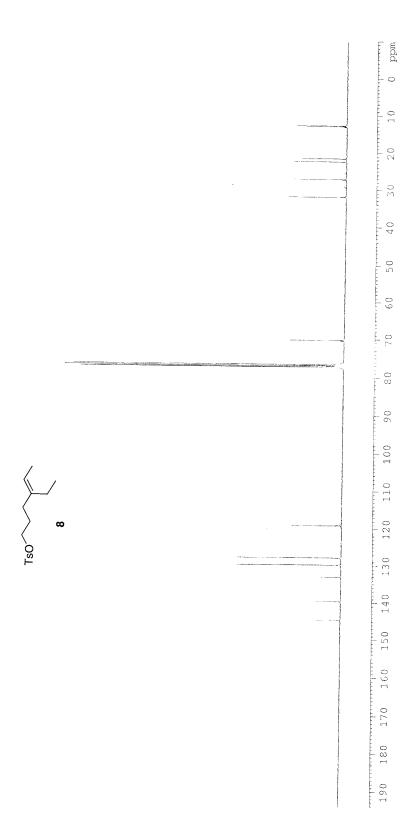


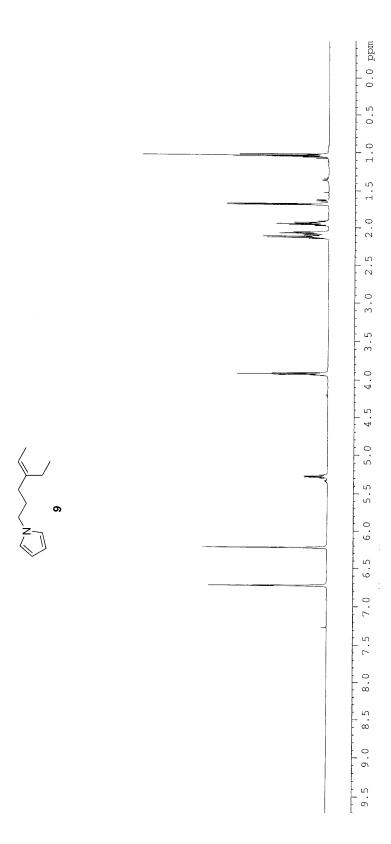


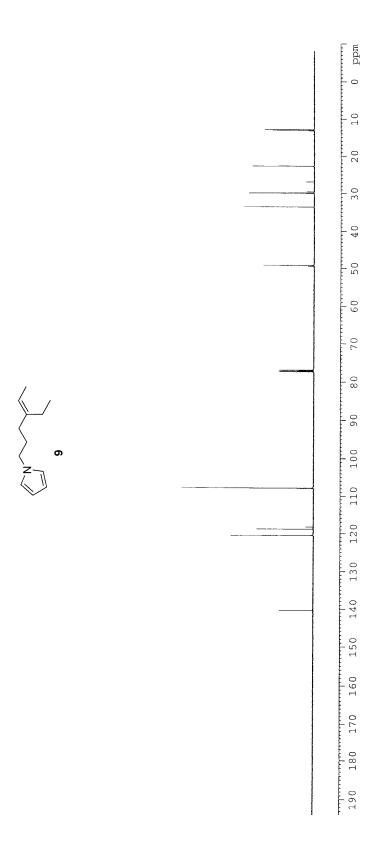


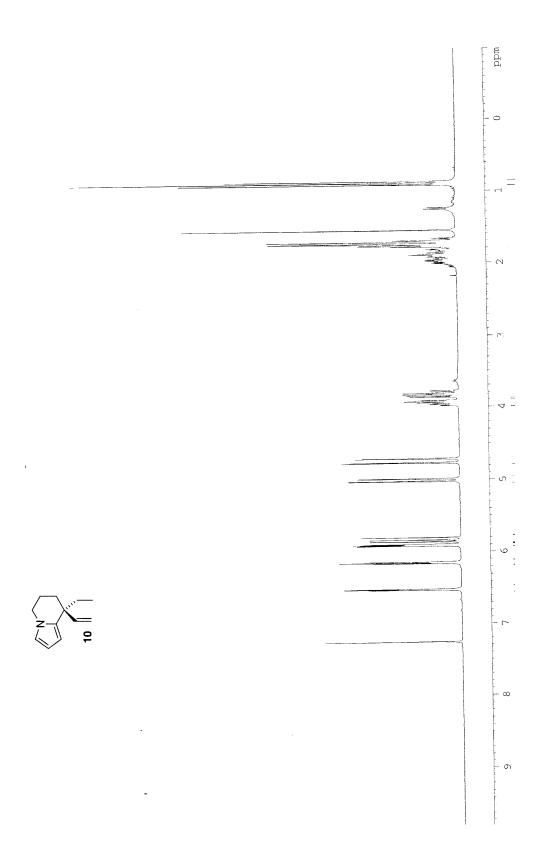


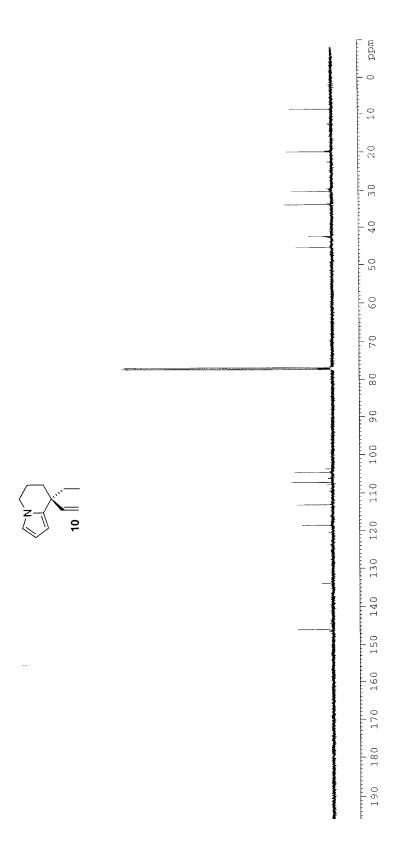


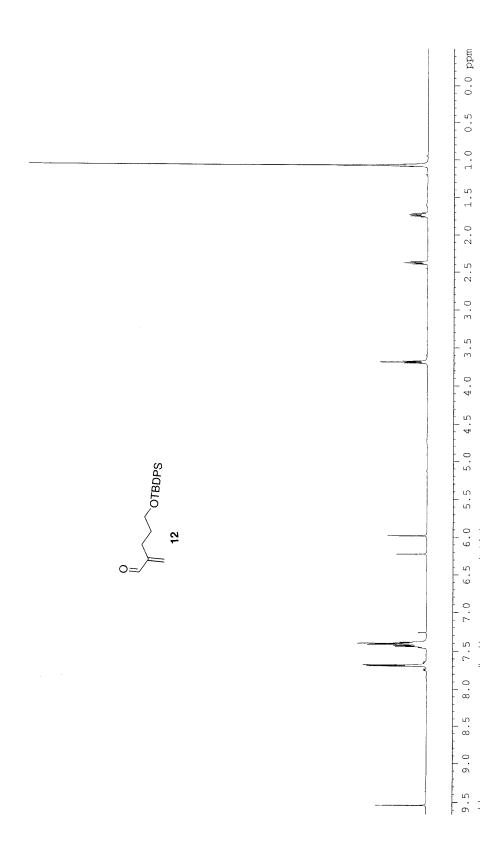


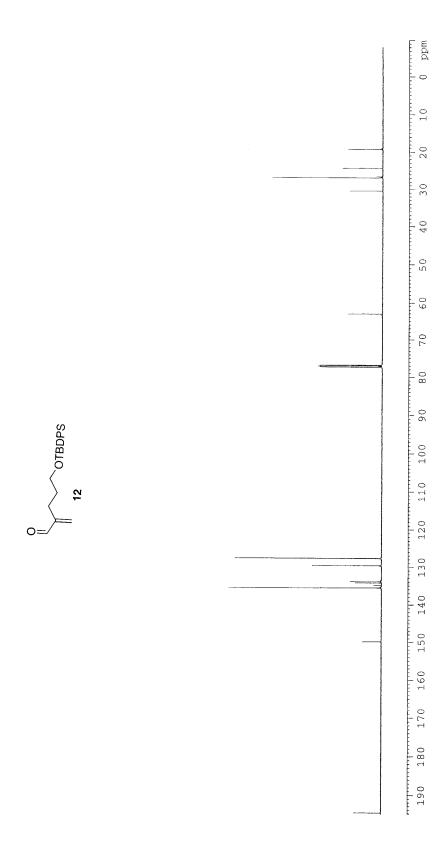


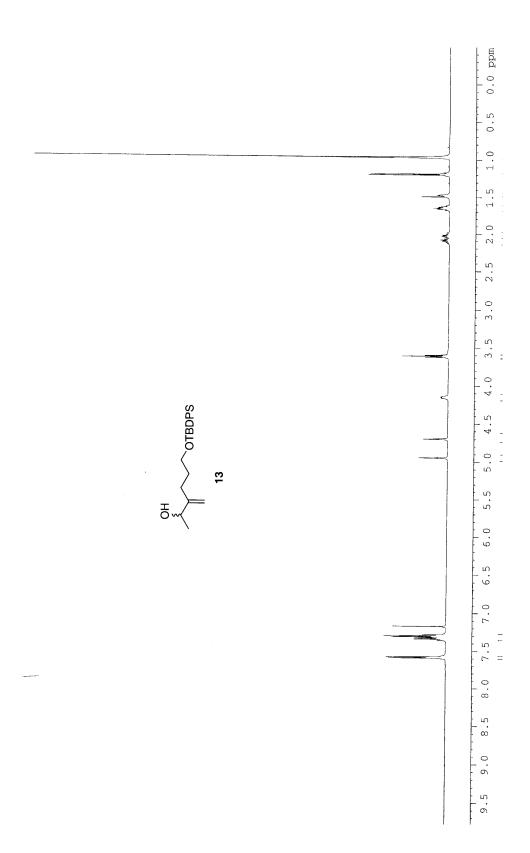


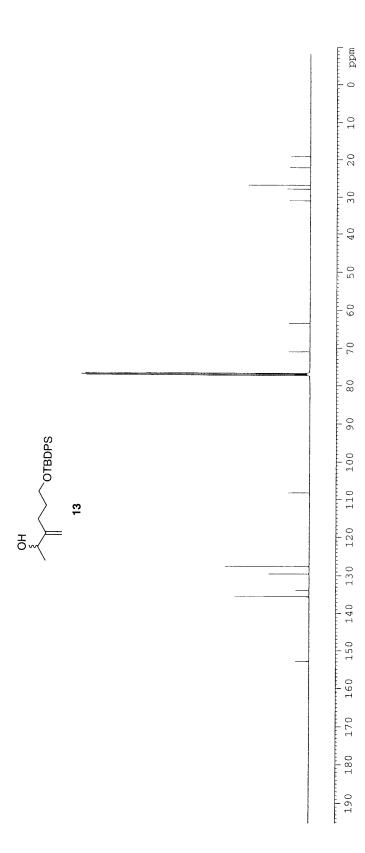


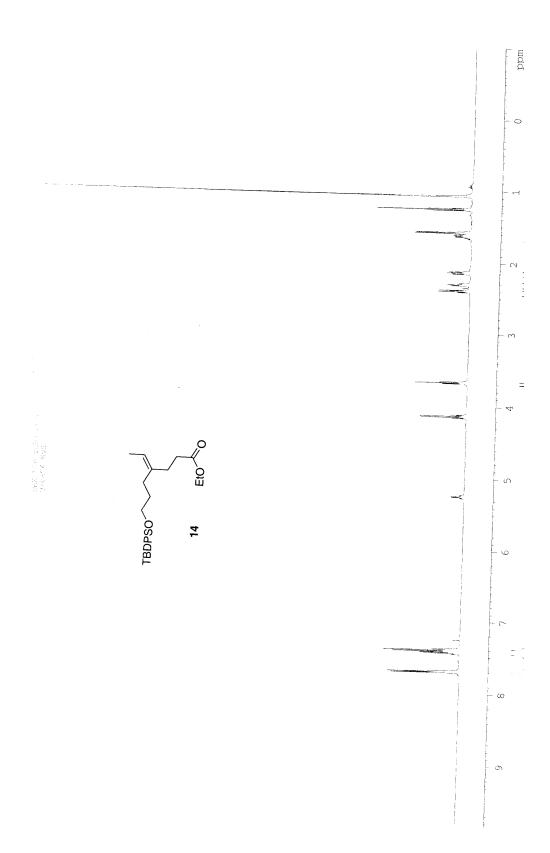


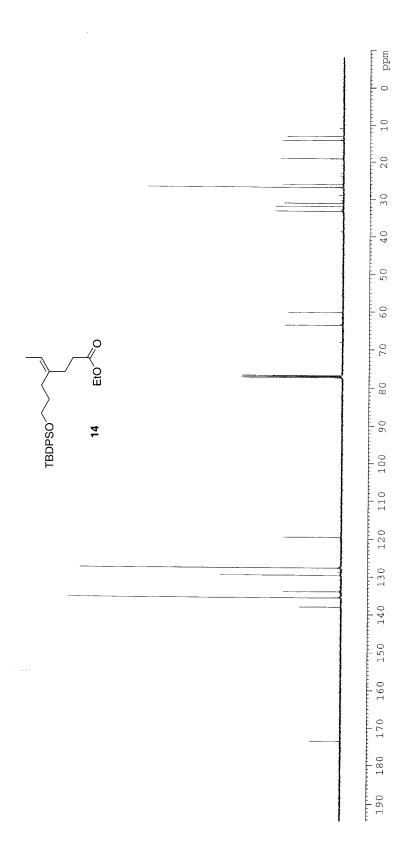


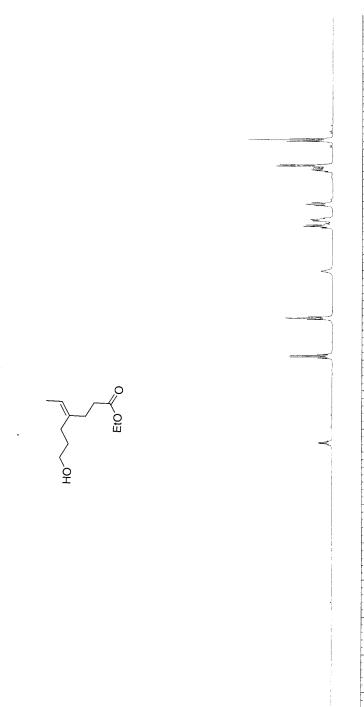




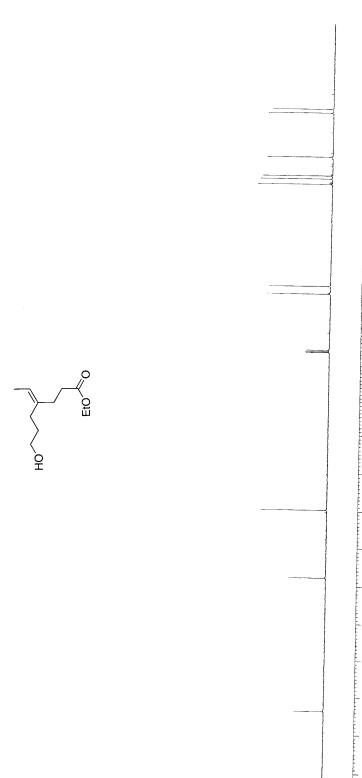


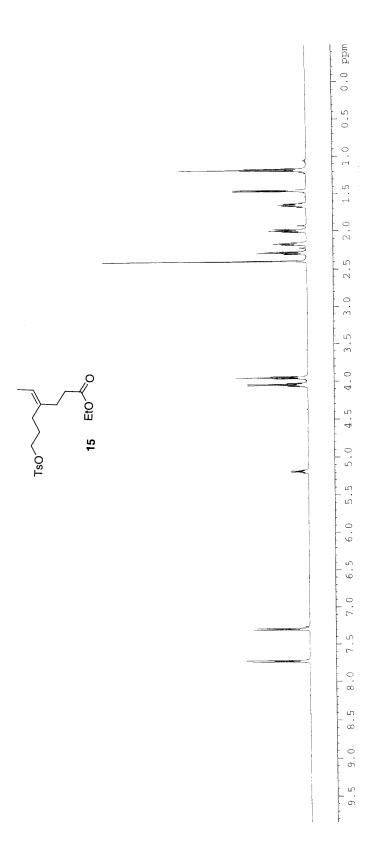


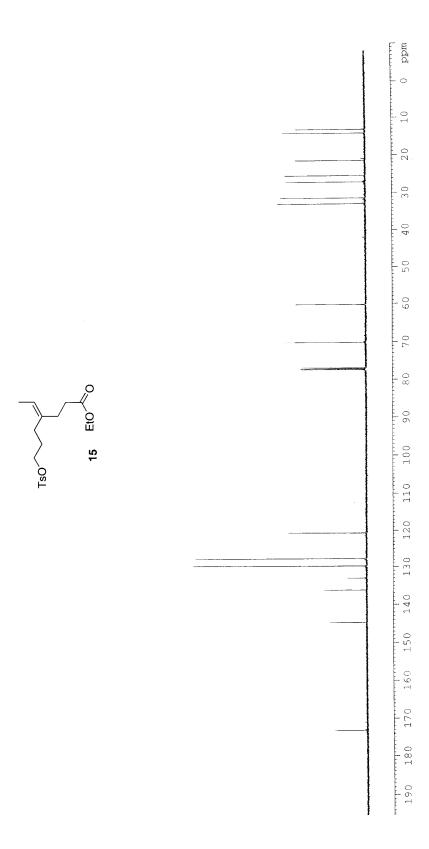


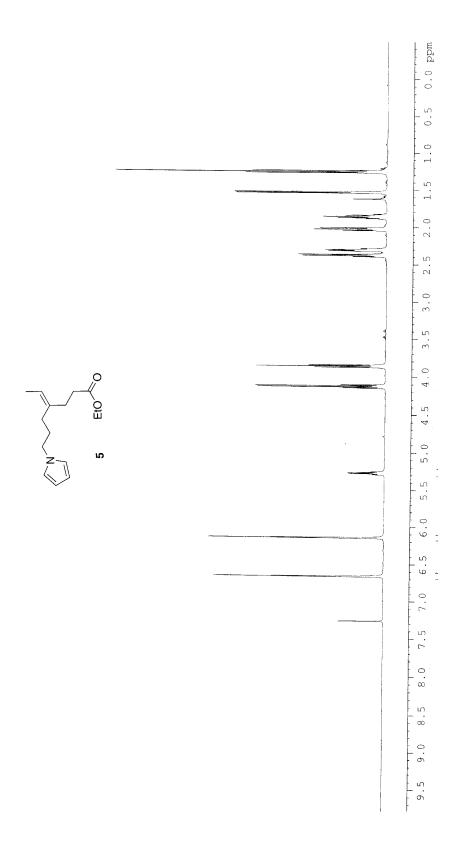


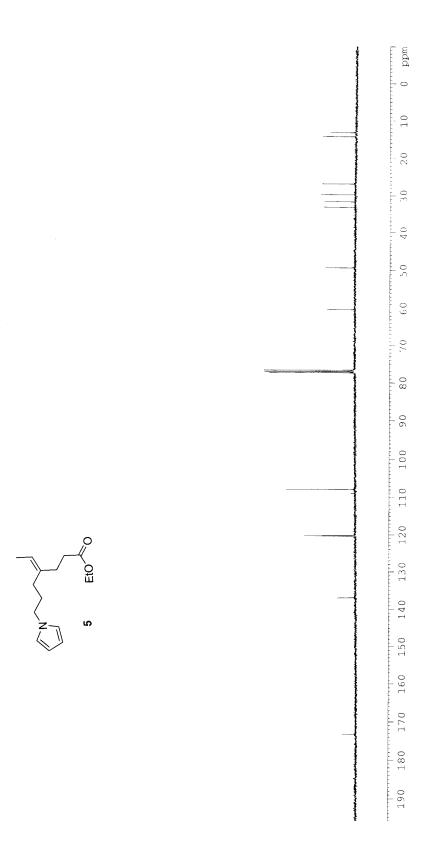
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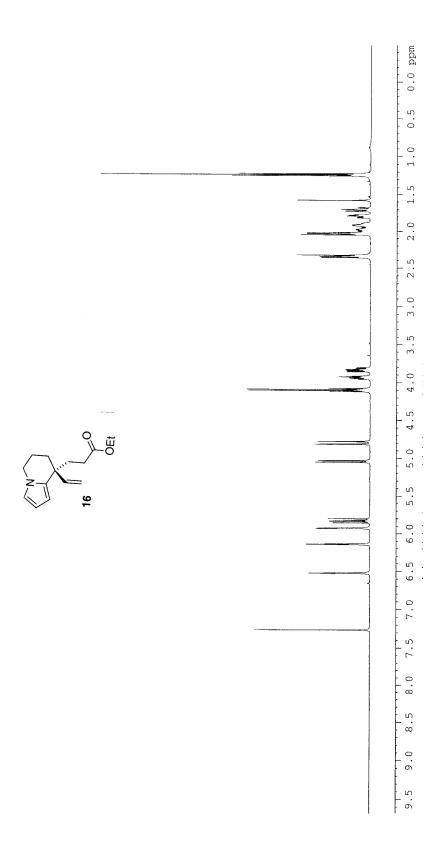


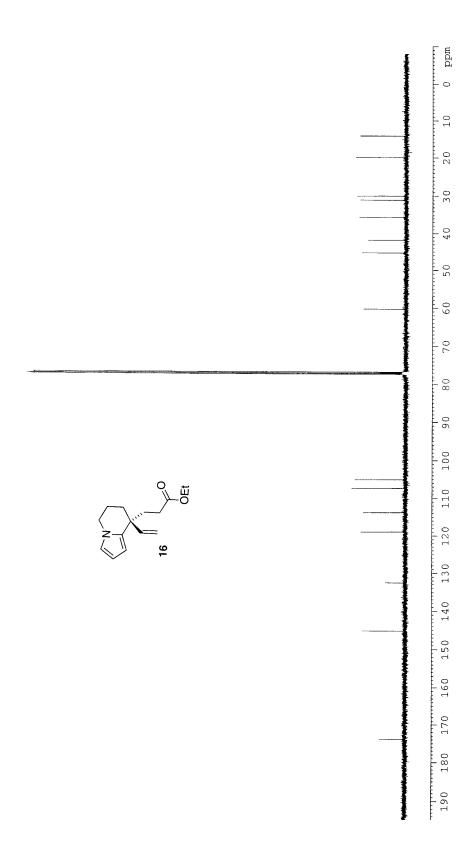


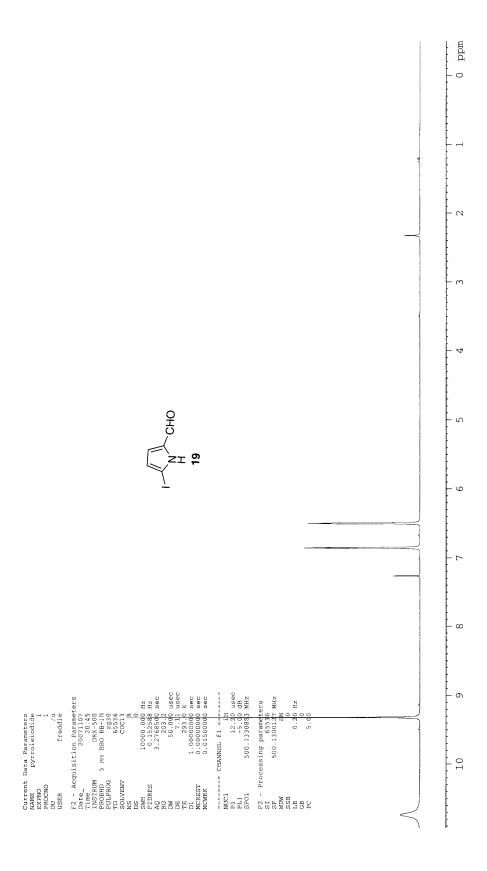


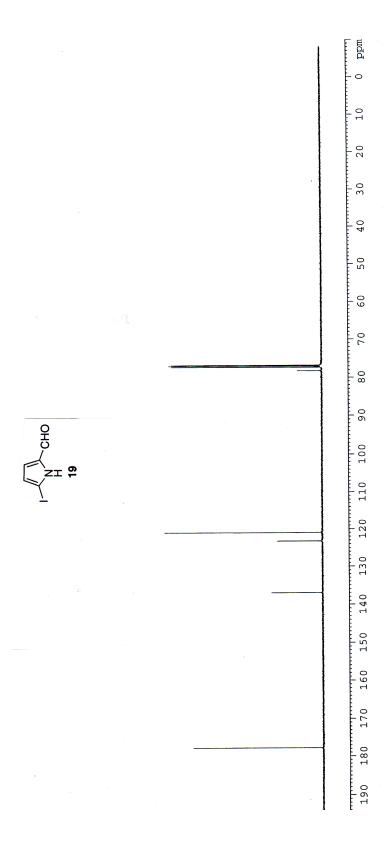


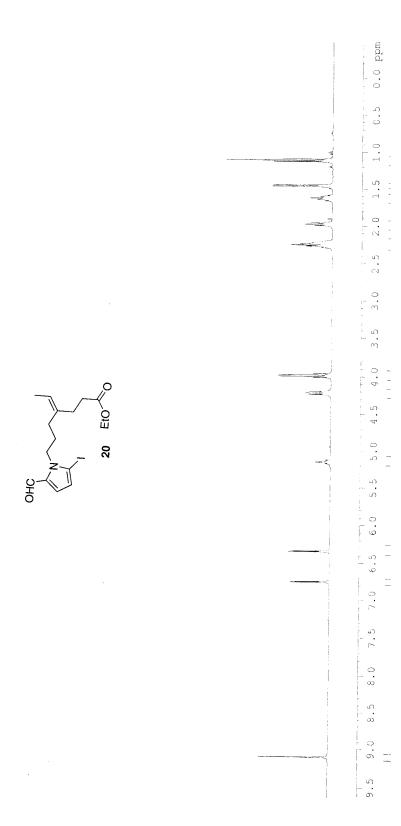


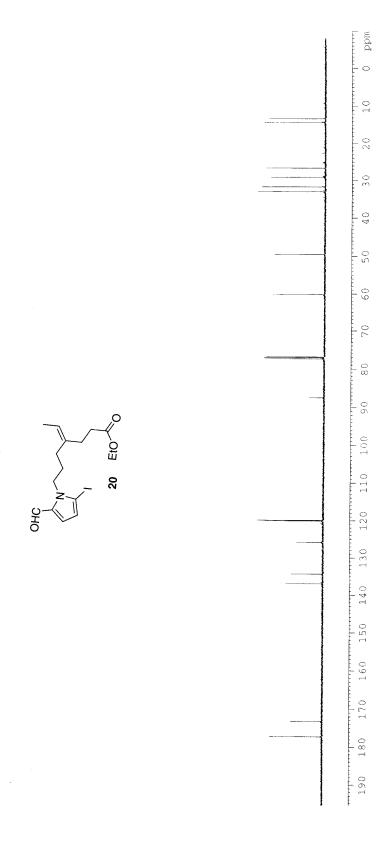


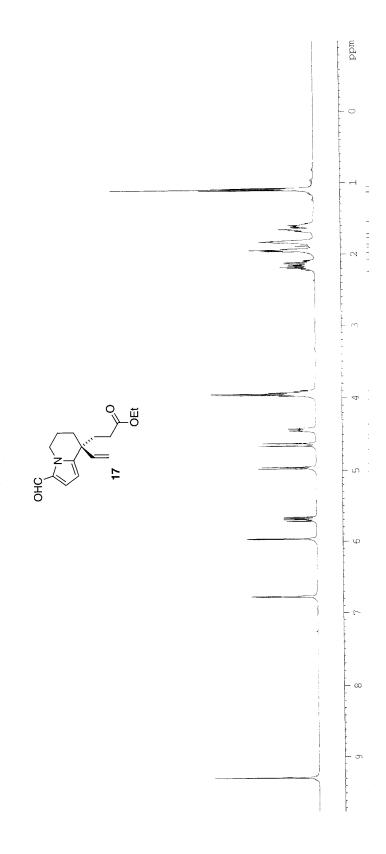


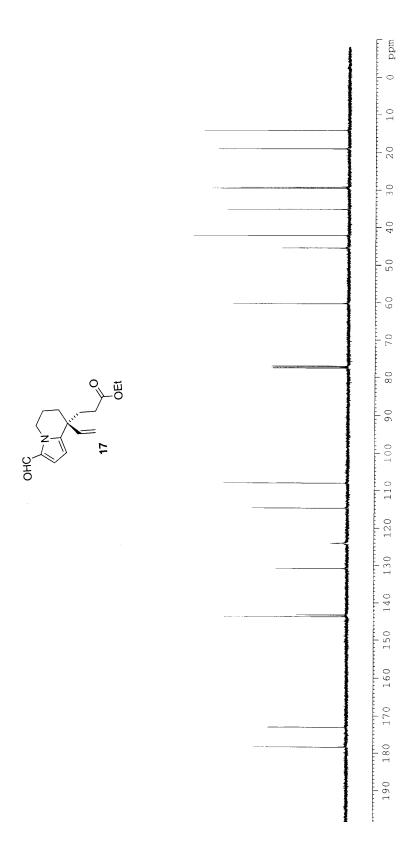


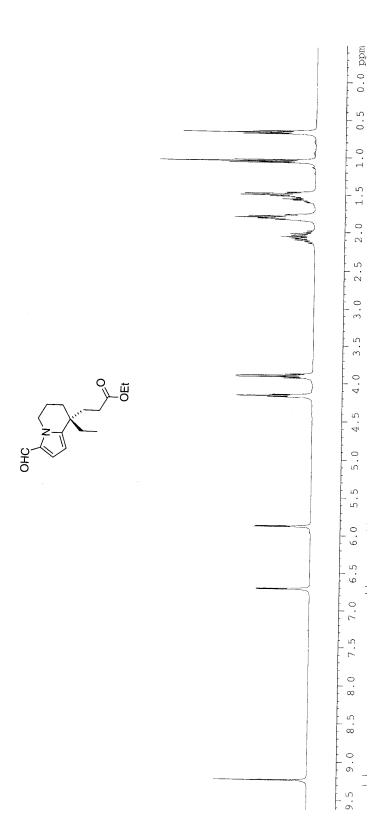


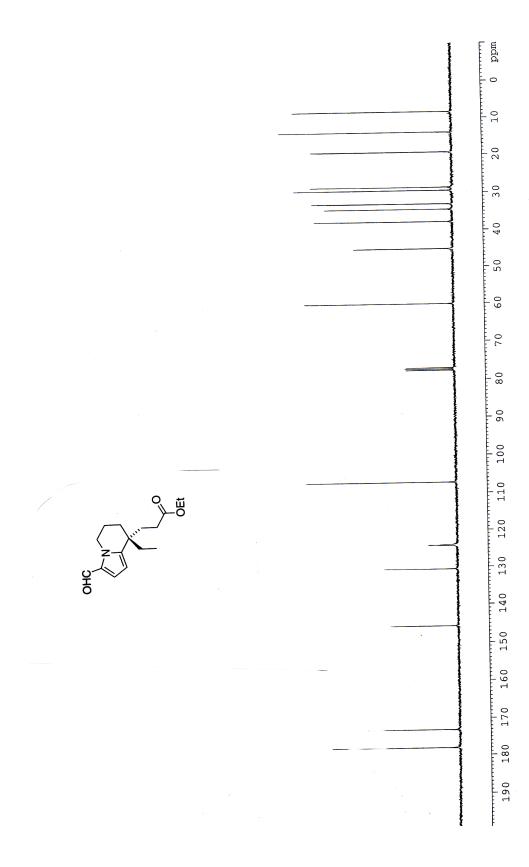


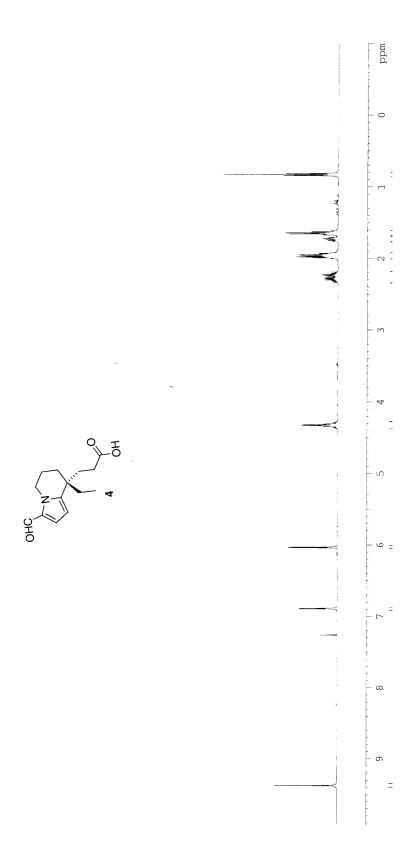


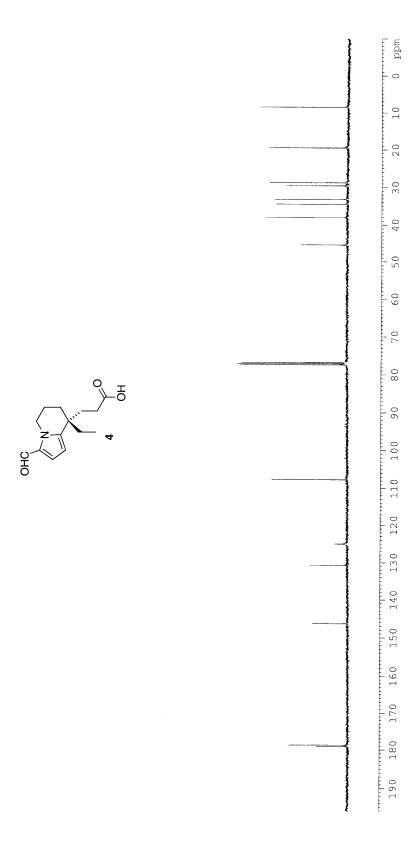


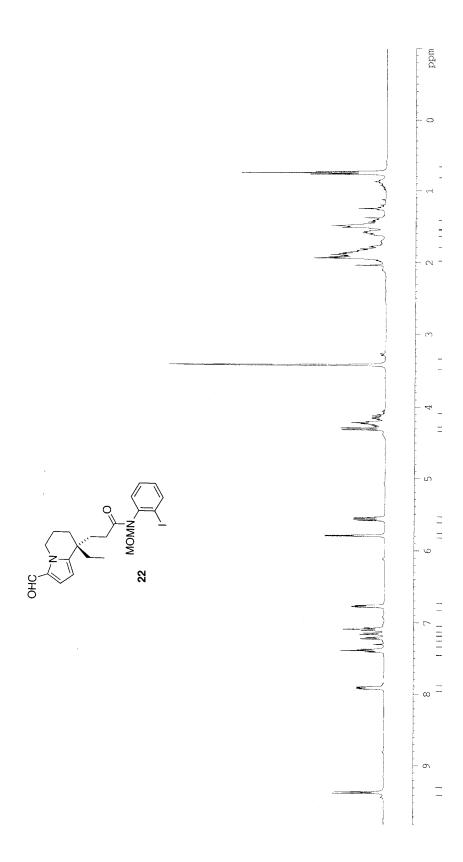


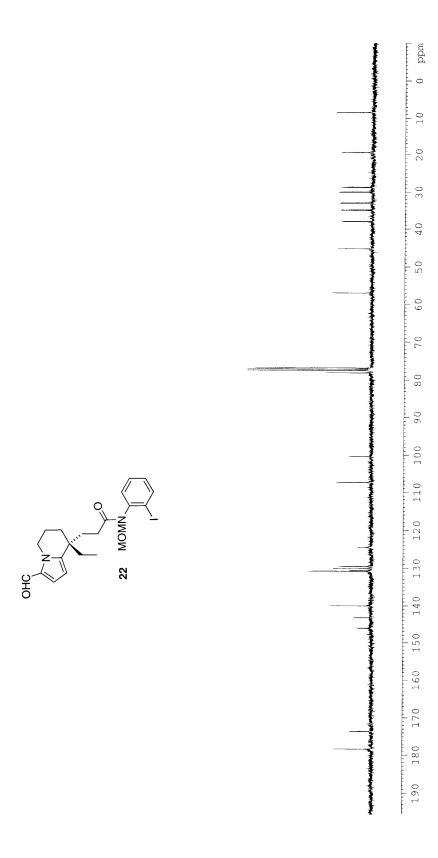












8.0 8.5 9.5

48

