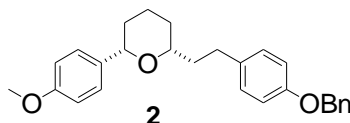


Electronic Supplementary Information

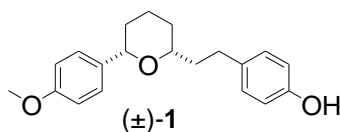
on

2-Arylcyclopropylmethanol as a substitute for homoallyl aryl alcohol in the construction of *cis*-2,6-disubstituted tetrahydropyran. Synthesis of (±)-centrolobine

Veejendra K. Yadav,* Ashish K. Verma, Piyush Kumar and Vijaykumar Hulikal



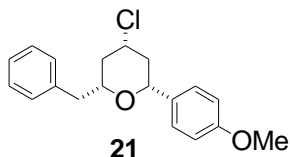
Reductive de-chlorination: A solution of **3**, *n*-Bu₃SnH (0.55 g, 510 μL) and azo-*bis*-isobutyronitrile (10 mg) were taken together in toluene (10 mL) and the resultant reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the residue filtered through a short silica gel column using mixtures of EtOAc and hexanes as the eluant to isolate the product **2**, 0.29 g, 95% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.43 (2H, d, *J* = 7.0 Hz), 7.40–7.36 (2H, m), 7.33–7.30 (3H, m), 7.11 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 5.03 (2H, s), 4.30 (1H, bd, *J* = 11.0 Hz), 3.80 (3H, s), 3.46–3.41 (1H, m), 2.77–2.64 (2H, m), 1.95–1.86 (2H, m), 1.82 (1H, d, *J* = 12.8 Hz), 1.76–1.69 (1H, m), 1.66–1.58 (2H, m), 1.54–1.46 (1H, m), 1.37–1.28 (1H, m). ¹³C NMR (125 MHz, CDCl₃): δ 158.7, 156.8, 137.2, 135.9, 134.9, 129.4, 128.5, 127.9, 127.5, 127.0, 114.6, 113.6, 79.0, 77.1, 70.0, 55.3, 38.3, 33.3, 31.2, 30.7, 24.0. IR: ν_{max} cm⁻¹ 1611, 1511, 1453, 1244, 1174, 1078, 1036, 827, 735. Calculated *m/z* for [M + H]⁺ = 403.2273, observed *m/z* = 403.2277.



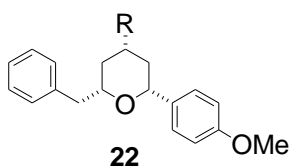
Hydrogenolysis: The product **2** above was taken in methanol (10 mL) and mixed with 5% Pd-C (10 mg). The resultant mixture was fitted with a hydrogen balloon and stirred at 30 °C for 2 h. It was filtered through a short silica gel column using mixtures of EtOAc and hexanes as the eluant to isolate (±)-centrolobine **1**, 0.22 g, 98% yield.

¹H NMR (500 MHz, CDCl₃): δ 7.30 (2H, d, *J* = 8.5 Hz), 7.05 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 6.73 (2H, d, *J* = 8.5 Hz), 4.69 (1H, bs), 4.29 (1H, dd, *J* = 9.8, 1.2 Hz), 3.80 (3H, s), 3.46–3.40 (1H, m), 2.74–2.63 (2H, m), 1.94–1.85 (2H, m), 1.82 (1H, bd, *J* = 12.5 Hz), 1.75–1.68 (1H, m), 1.67–1.58 (2H, m), 1.50 (1H, ddd, *J* = 15.3, 11.7, 4.0 Hz), 1.32 (1H, ddd, *J* = 15.3, 11.0, 4.0 Hz). ¹³C

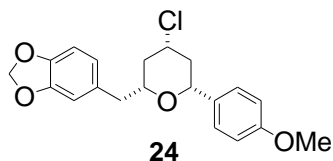
NMR (125 MHz, CDCl₃): δ 158.8, 153.5, 136.0, 134.8, 129.7, 127.2, 115.2, 113.7, 79.2, 77.2, 55.4, 38.4, 33.4, 31.3, 30.8, 24.1. IR: ν_{\max} cm⁻¹ 3380, 1613, 1514, 1454, 1247, 1175, 1076, 1035, 828. Calcd m/z for [M + H]⁺ = 313.1804, Observed m/z = 313.1807.



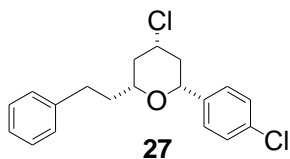
21: solid, mp 80 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.31–7.22 (7H, m), 6.88 (2H, d, J = 8.6 Hz), 4.33 (1H, dd, J = 11.3, 1.6 Hz), 4.11–4.05 (1H, m), 3.80 (3H, s), 3.72–3.66 (1H, m), 3.05 (1H, dd, J = 13.7, 5.5 Hz), 2.77 (1H, dd, J = 13.7, 7.0 Hz), 2.33 (1H, md, J = 15.0 Hz), 2.16 (1H, md, J = 15.0 Hz), 1.81 (1H, dd, J = 24.0, 11.6 Hz), 1.61 (1H, dd, J = 24.0, 11.6 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 159.2, 137.8, 133.7, 129.7, 128.4, 127.2, 126.5, 113.9, 78.3, 78.0, 56.0, 55.4, 44.2, 42.5, 41.4. IR: ν_{\max} cm⁻¹ 1612, 1514, 1248, 1175, 1154, 1077, 1034, 990, 827, 788, 750, 700. Calcd m/z for [M + H]⁺ = 317.1308, Observed m/z = 317.1306.



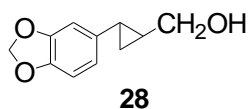
22: Colorless viscous liquid. ¹H NMR (500 MHz, CDCl₃): δ 7.30–7.18 (7H, m), 6.87 (2H, d, J = 8.9 Hz), 4.32 (1H, dd, J = 11.2, 2.0 Hz), 3.79 (3H, s), 3.01 (1H, dd, J = 13.7, 6.0 Hz), 2.72 (1H, dd, J = 13.7, 7.2 Hz), 1.92–1.86 (1H, md, J = 12.3 Hz), 1.79 (1H, bd, J = 12.3 Hz), 1.64–1.54 (2H, m), 1.49 (1H, ddd, J = 14.9, 11.2, 3.7 Hz), 1.29 (1H, ddd, J = 14.9, 10.9, 3.7 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 158.7, 138.9, 135.8, 129.6, 128.1, 127.0, 126.0, 113.6, 79.3, 79.2, 55.3, 43.2, 33.4, 30.5, 23.9. IR: ν_{\max} cm⁻¹ 1612, 1514, 1454, 1247, 1174, 1080, 1035, 827, 748, 700. Calcd m/z for [M + H]⁺ = 283.1698, Observed m/z = 283.1695.



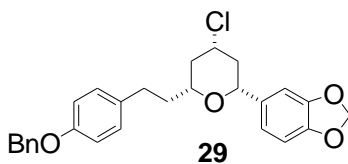
24: Solid, mp 82 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.27 (2H, d, J = 8.7 Hz), 6.89 (2H, d, J = 8.7 Hz), 6.75–6.72 (2H, m), 6.67 (1H, d, J = 7.8 Hz), 5.93 (2H, s), 4.33 (1H, bd, J = 11.5 Hz), 4.13–4.06 (1H, m), 3.80 (3H, s), 3.67–3.60 (1H, m), 2.96 (1H, dd, J = 13.7, 5.6 Hz), 2.70 (1H, dd, J = 13.7, 6.8 Hz), 2.37–2.31 (1H, m), 2.18–2.13 (1H, m), 1.80 (1H, dd, J = 24.0, 12.0 Hz), 1.59 (1H, dd, J = 24.0, 11.7 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 159.1, 147.5, 146.1, 133.6, 131.4, 127.1, 122.5, 113.8, 109.9, 108.1, 100.8, 78.3, 77.9, 55.9, 55.4, 44.1, 41.9, 41.2. Calcd m/z for [M + Na]⁺ = 383.1026, Observed m/z = 383.1021.



27: Colorless viscous liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.34–7.16 (5H, m), 4.32 (1H, dd, $J = 9.8, 1.2$ Hz), 4.15–4.08 (1H, m), 3.48–3.42 (1H, m), 2.83–2.70 (2H, m), 2.38–2.34 (1H, m), 2.22–2.18 (1H, m), 2.04–1.95 (1H, m), 1.86–1.81 (1H, m), 1.76 (1H, q, $J = 12.0$ Hz), 1.67 (1H, q, $J = 12.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ 141.7, 140.0, 133.3, 128.6, 128.5, 128.4, 127.1, 125.9, 77.6, 75.8, 55.5, 44.0, 42.0, 37.2, 31.5. IR: ν_{max} cm^{-1} 1600, 1493, 1454, 1351, 1322, 1158, 1125, 1087, 1014, 823, 763. Calcd m/z for $[\text{M}]^+ = 334.0891$, Observed $m/z = 334.0897$.

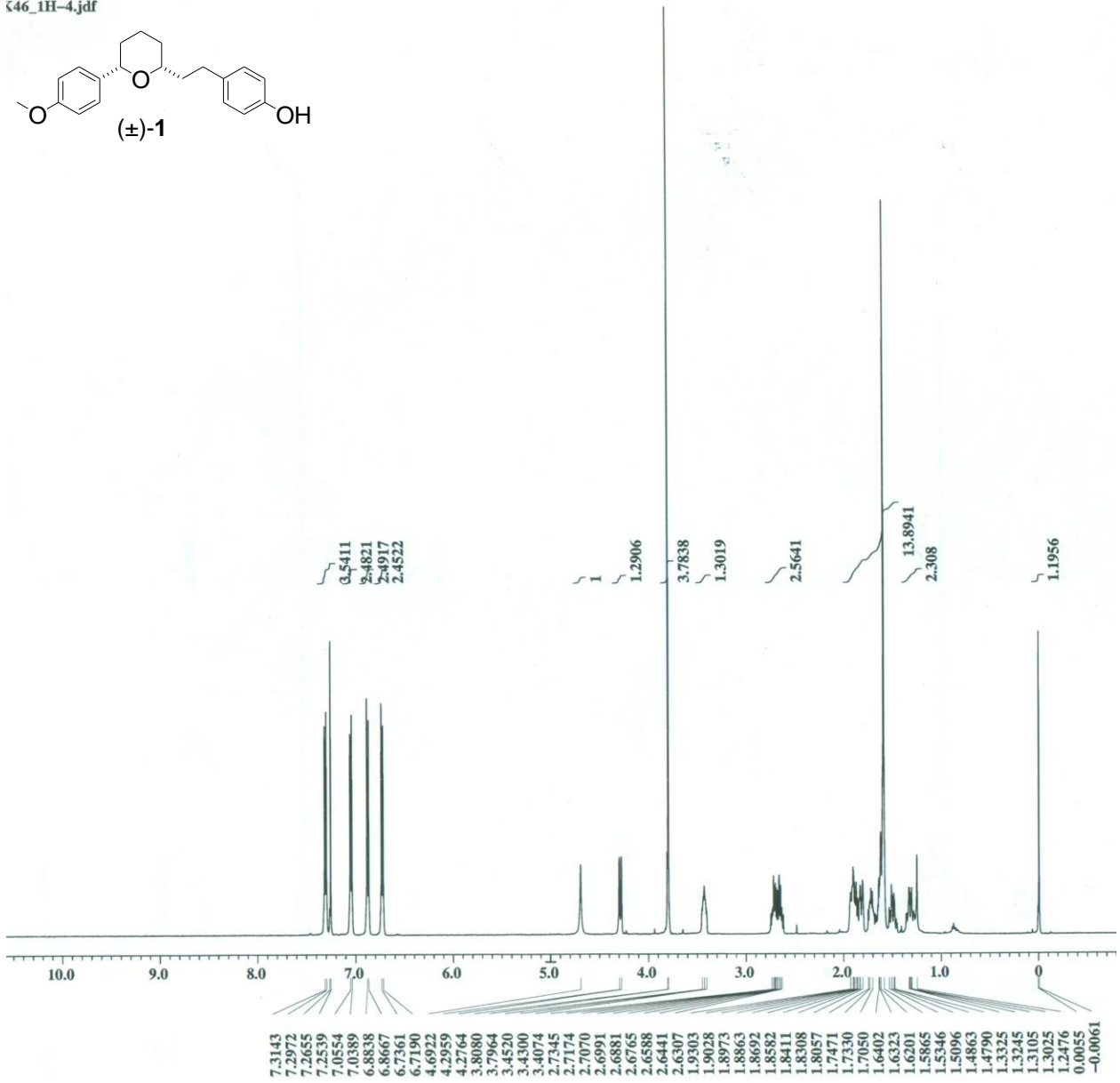
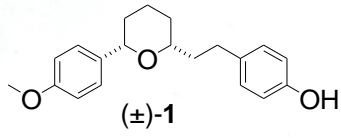


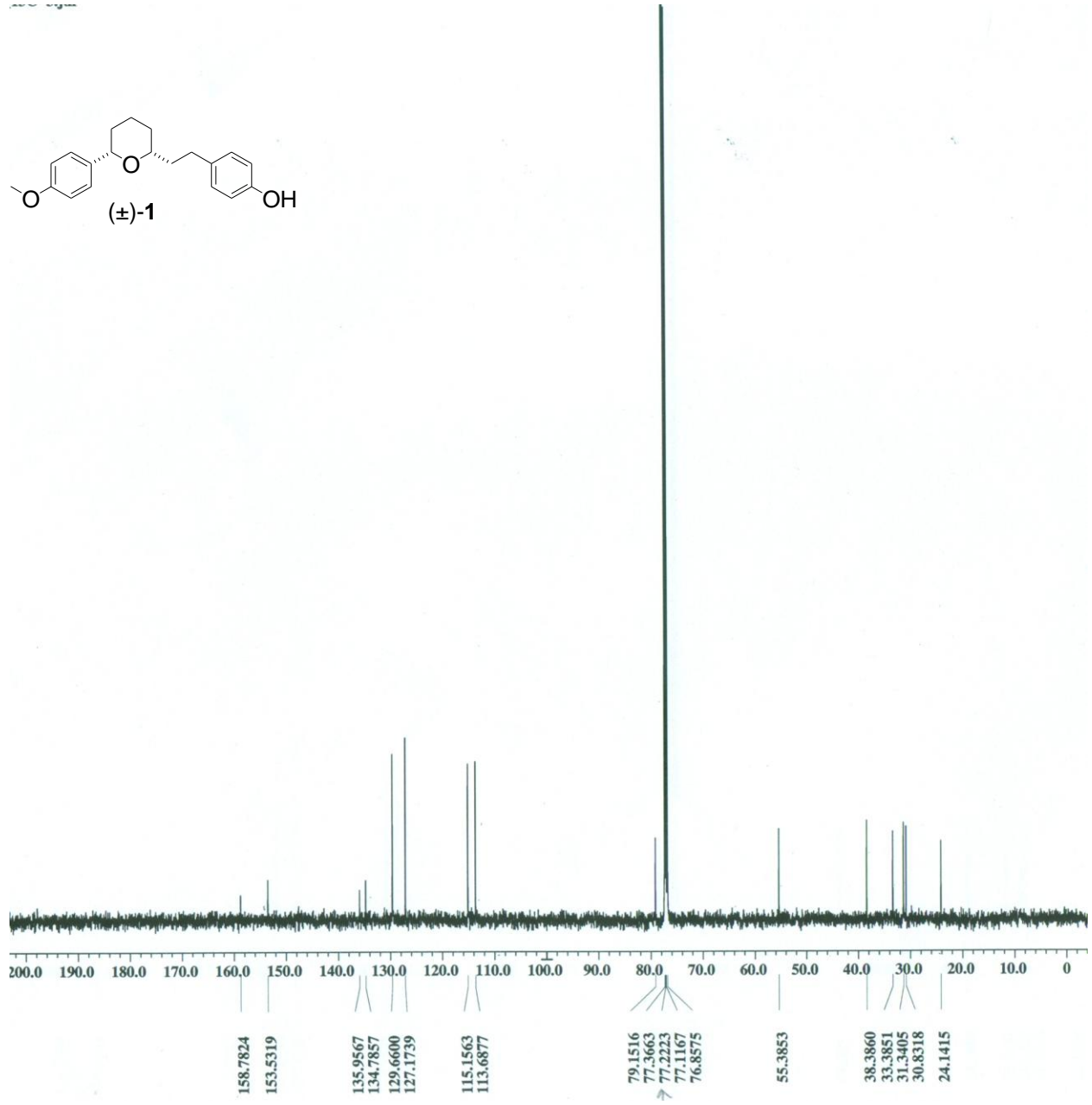
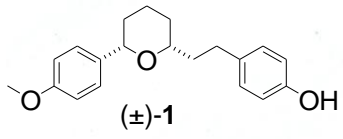
28. Colorless liquid. ^1H NMR (400 MHz, CDCl_3): δ 6.69 (1H, d, $J = 7.8$ Hz), 6.56 (1H, dd, $J = 7.8, 1.8$ Hz), 6.53 (1H, d, $J = 1.8$ Hz), 3.57 (2H, d, $J = 6.9$ Hz), 1.79–1.73 (1H, m), 1.39–1.31 (1H, m), 0.88–0.83 (2H, m). ^{13}C NMR (100 MHz, CDCl_3): δ 147.7, 145.6, 136.3, 119.1, 108.0, 106.4, 100.8, 66.5, 24.8, 21.1, 13.3. IR: ν_{max} cm^{-1} 3360, 2882, 1609, 1505, 1494, 1464, 1440, 1254, 1235, 1208, 1182, 1077, 1039, 934, 886, 853, 810. Calcd m/z for $[\text{M}]^+ = 192.0786$, Observed $m/z = 192.0778$.

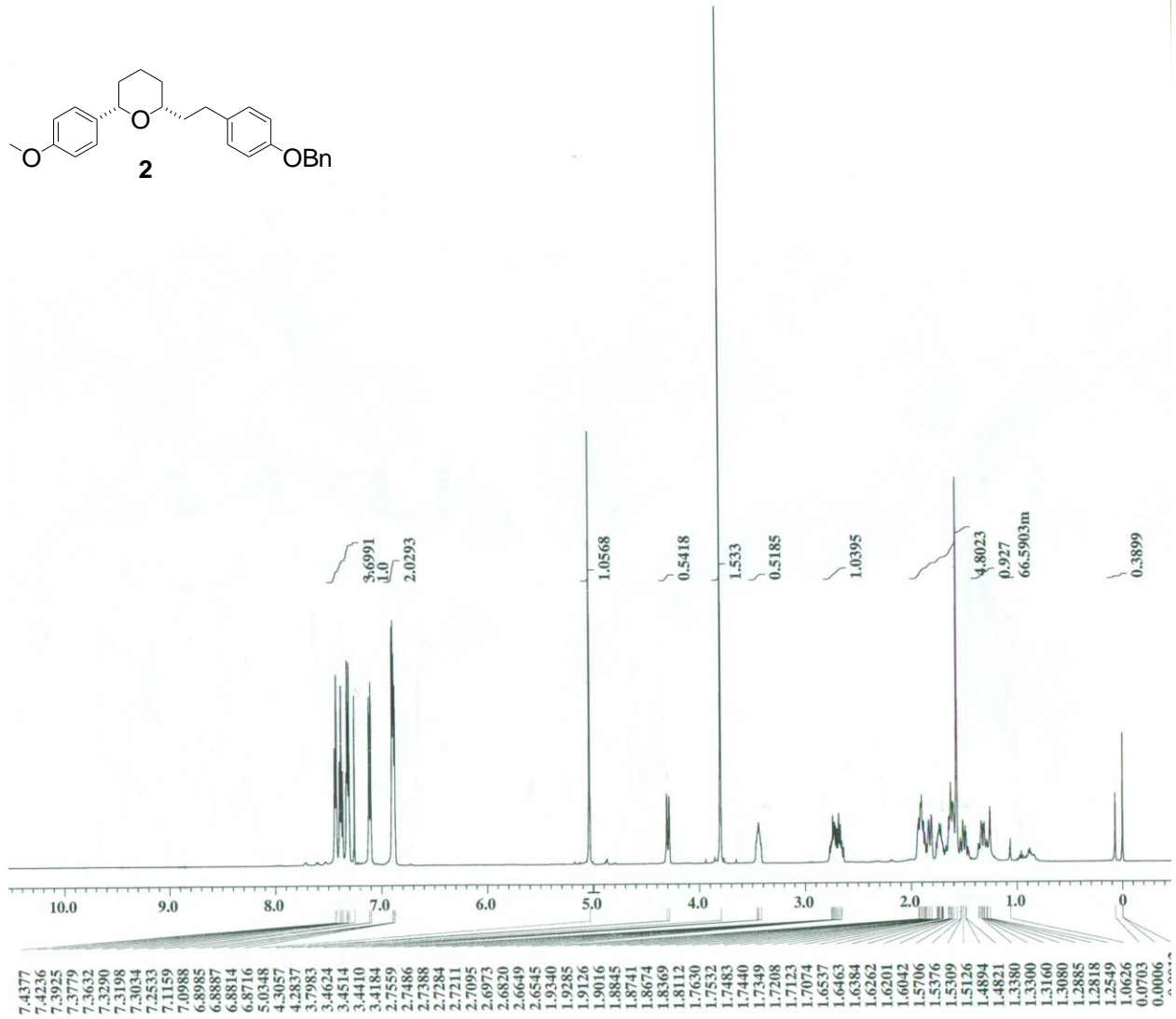
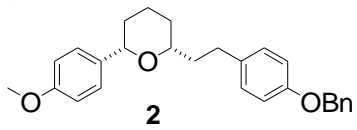


29: White solid, mp 48 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.43–7.29 (5H, m), 7.08 (2H, d, $J = 8.6$ Hz), 6.89 (2H, d, $J = 8.6$ Hz), 6.87 (1H, s), 6.79–6.78 (2H, m), 5.94 (2H, s), 5.03 (2H, s), 4.25 (1H, dd, $J = 11.4, 1.2$ Hz), 4.14–4.06 (1H, m), 3.44–3.38 (1H, m), 2.76–2.62 (2H, m), 2.36–2.30 (1H, m), 2.18–2.14 (1H, m), 1.98–1.90 (1H, m), 1.80–1.72 (1H, m), 1.78 (1H, q, $J = 12.3$ Hz), 1.64 (1H, q, $J = 12.3$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 157.0, 147.7, 147.0, 137.2, 135.5, 134.1, 129.4, 128.6, 127.9, 127.5, 119.2, 114.7, 108.0, 106.6, 101.0, 78.0, 75.8, 70.0, 55.7, 44.2, 42.1, 37.5, 30.5. IR: ν_{max} cm^{-1} 1610, 1509, 1489, 1443, 1240, 1069, 1038, 934, 741. Calcd m/z for $[\text{M} + \text{Na}]^+ = 473.1496$, Observed $m/z = 473.1493$.

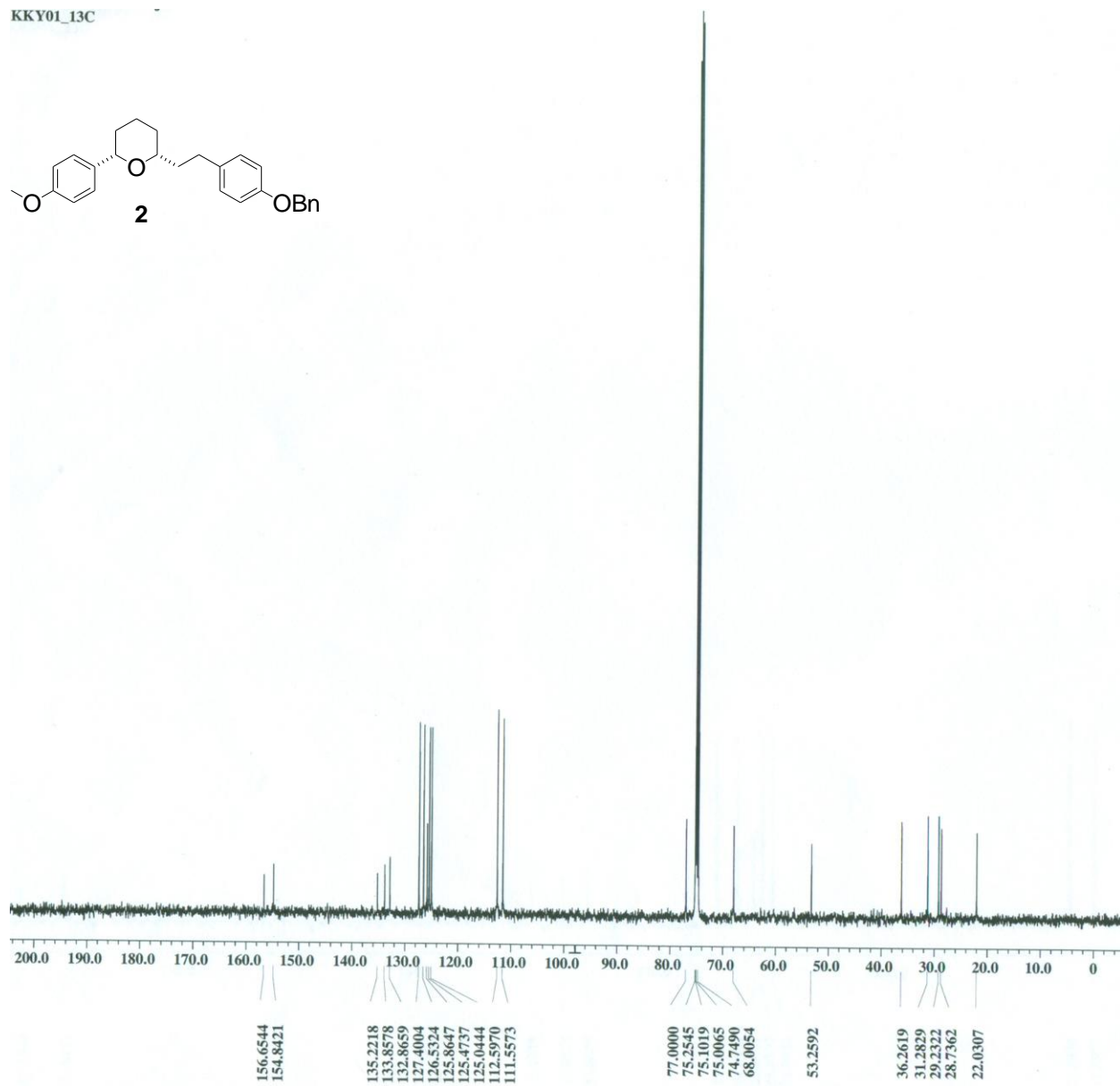
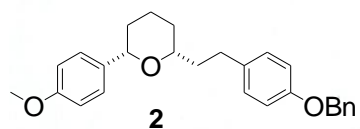
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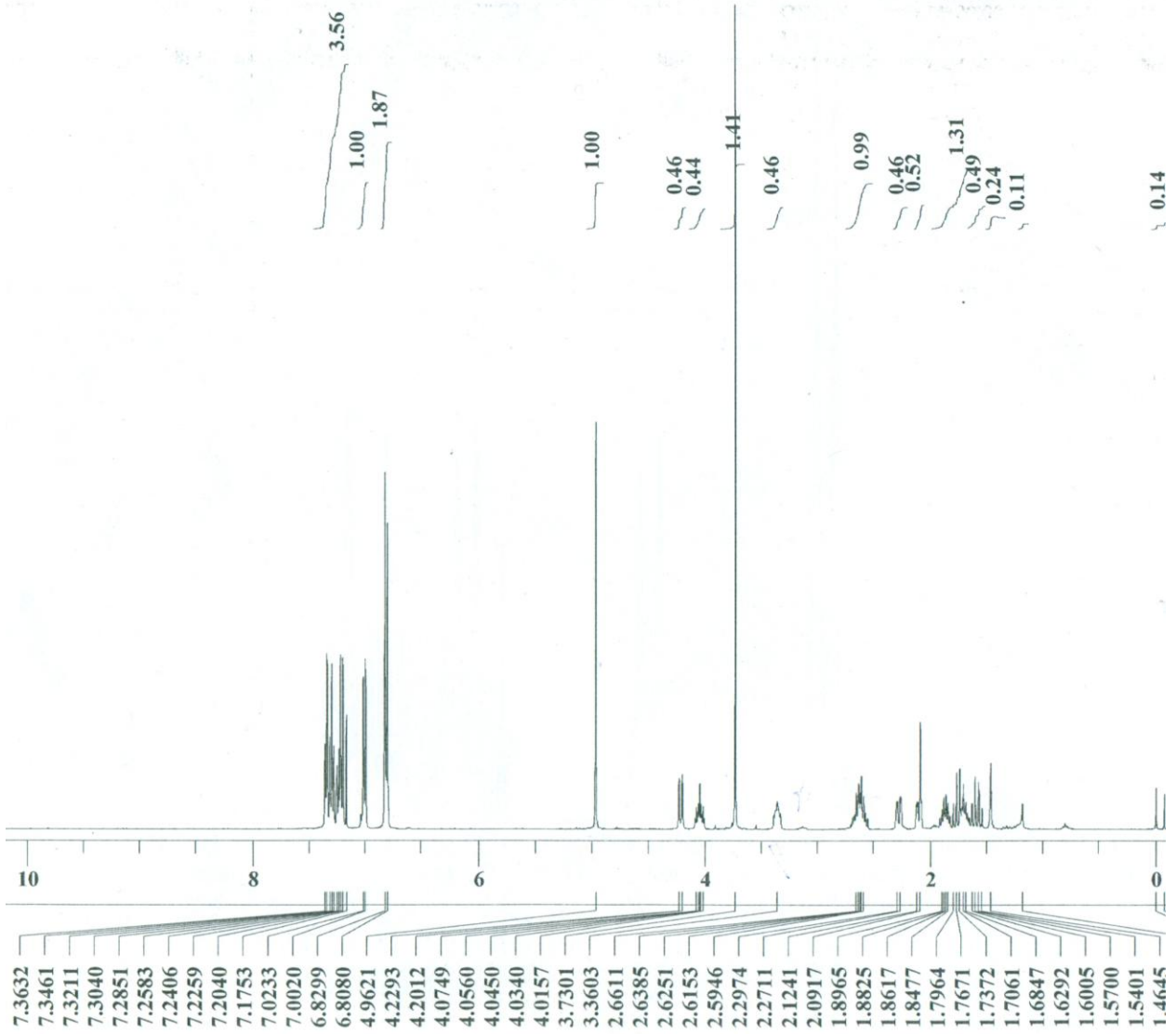
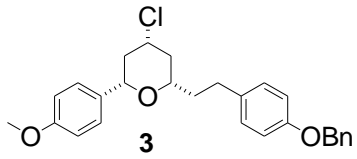


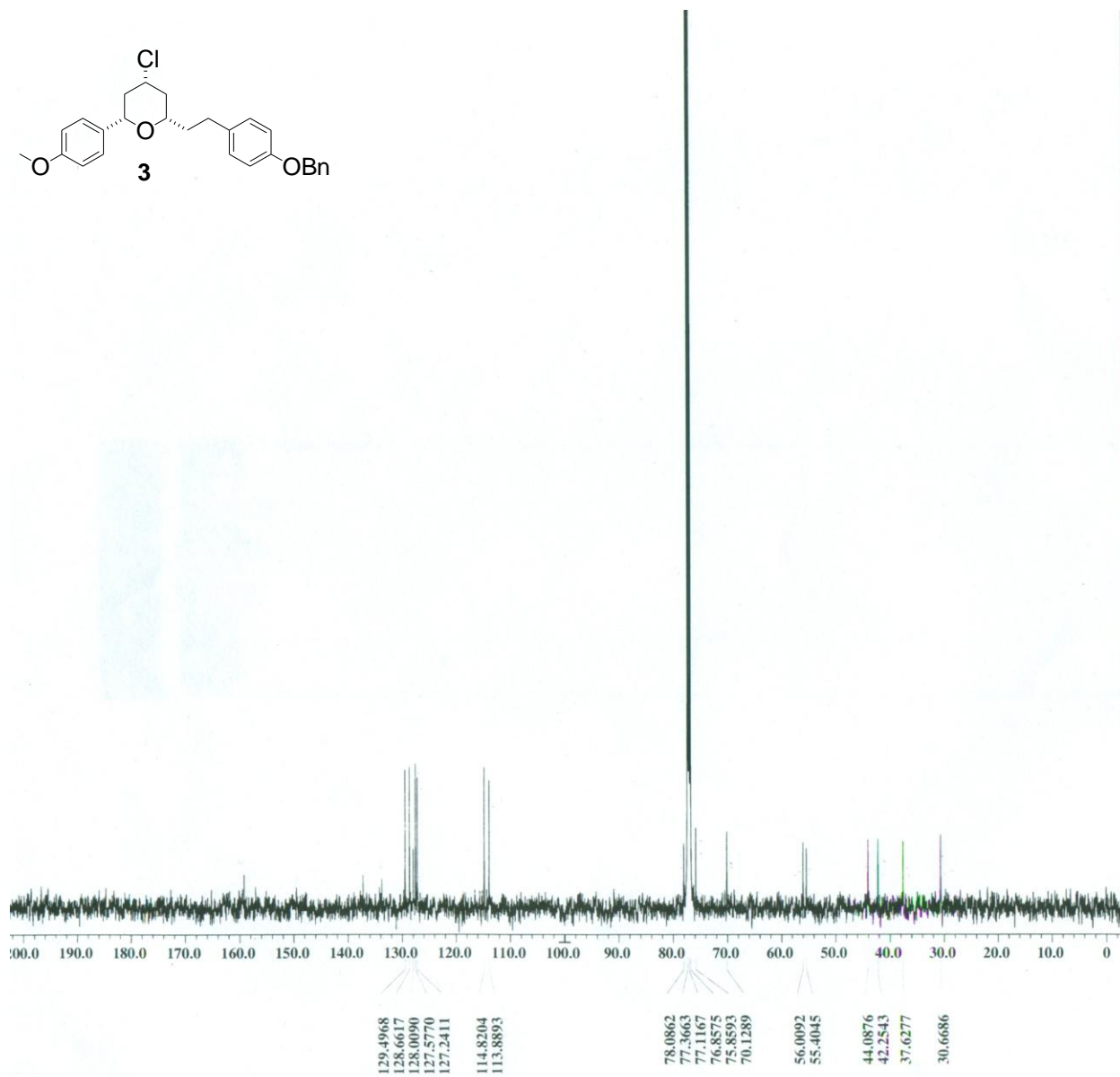
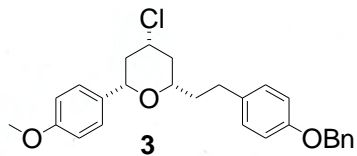




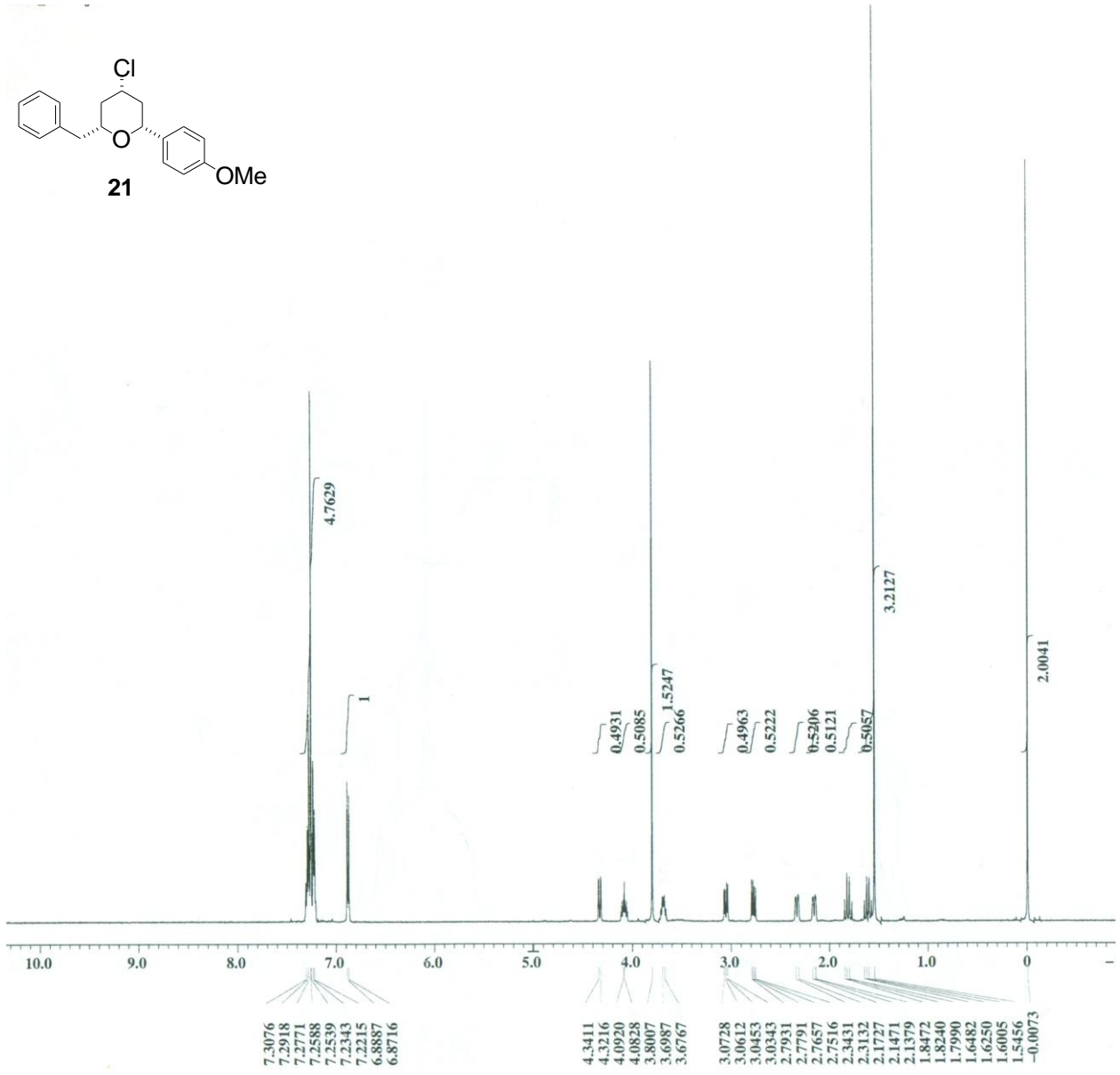
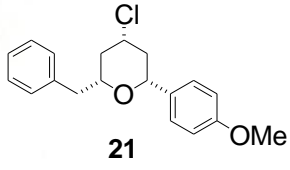
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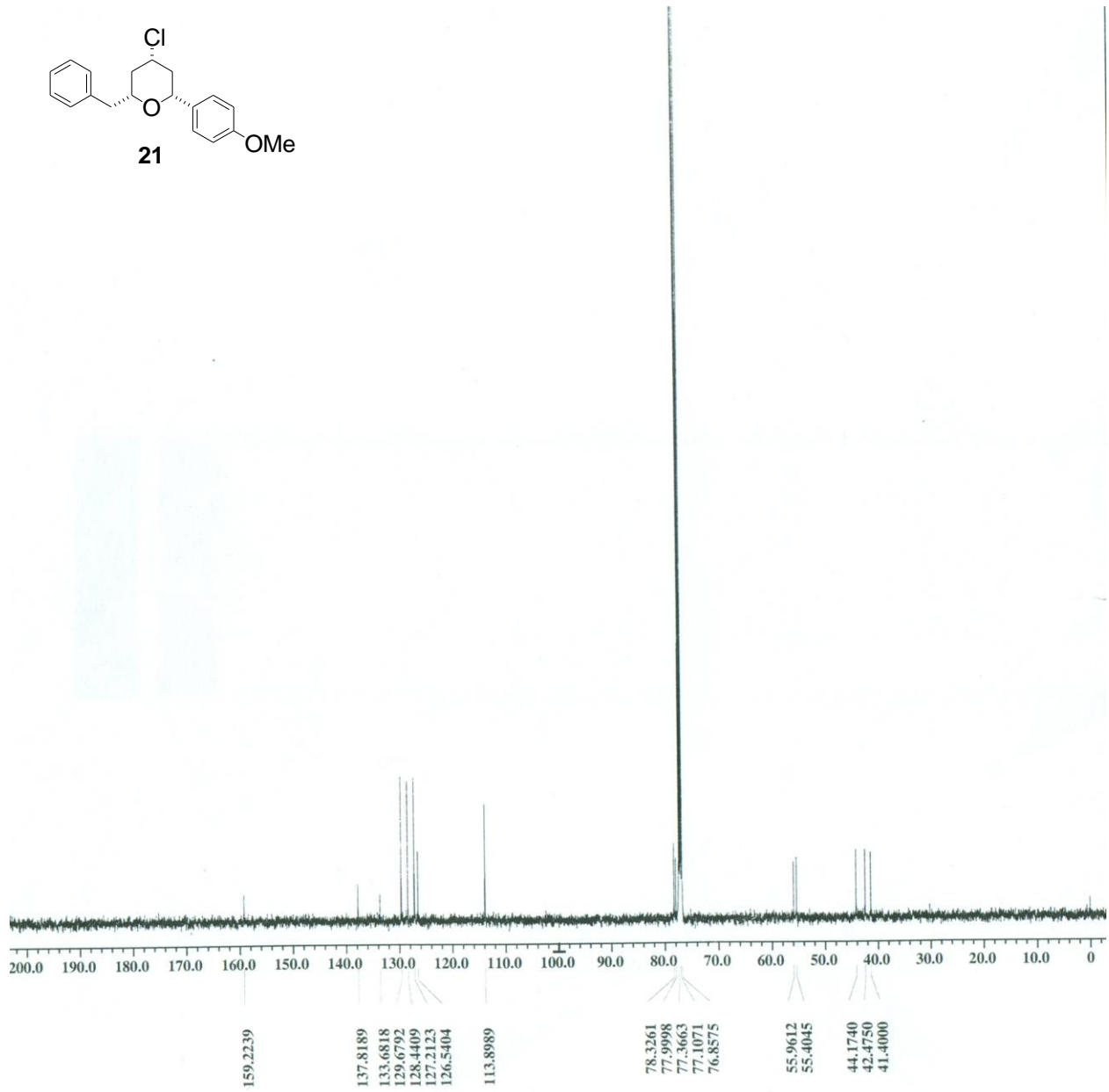
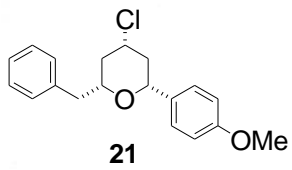




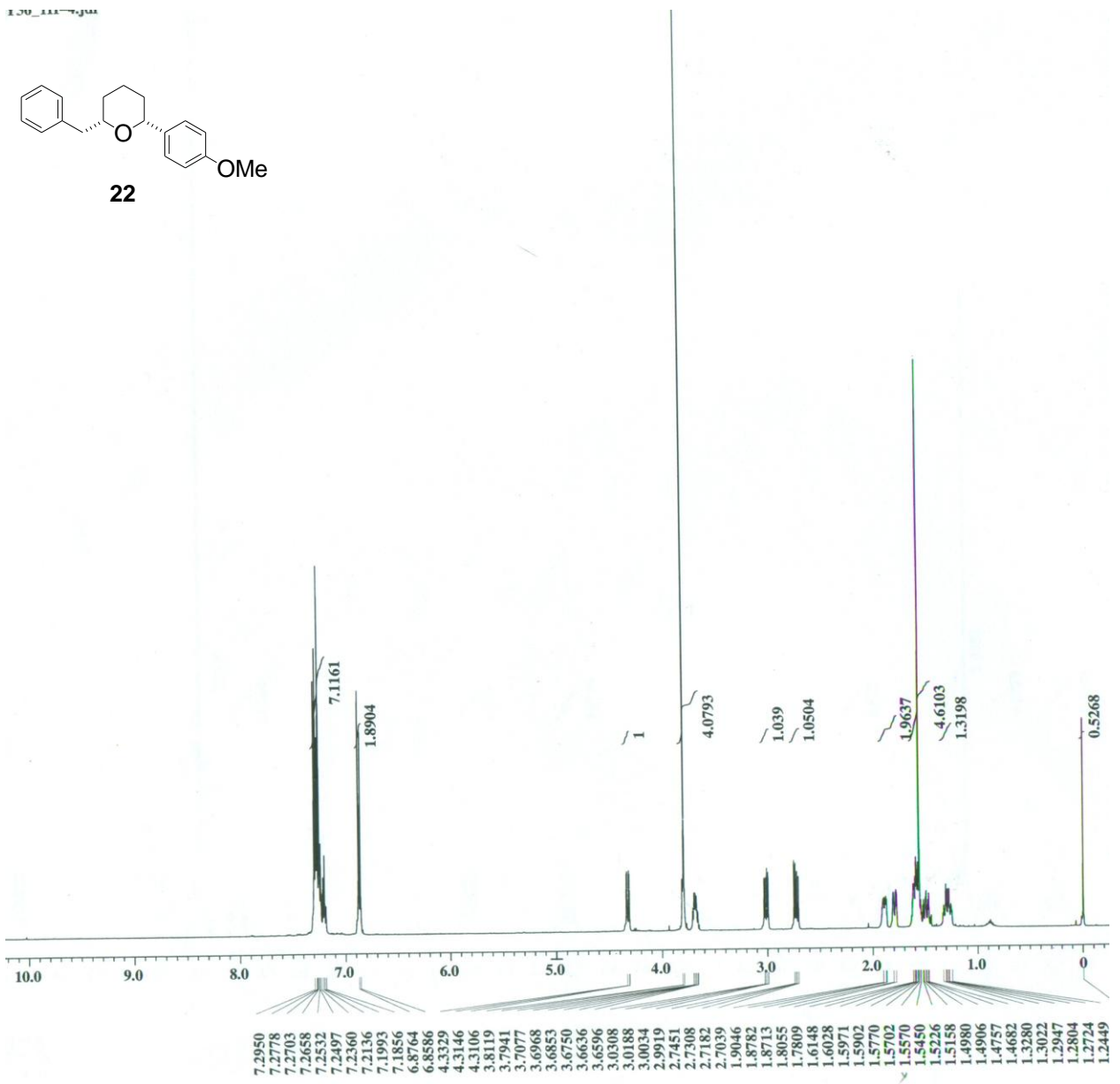
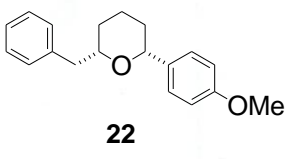


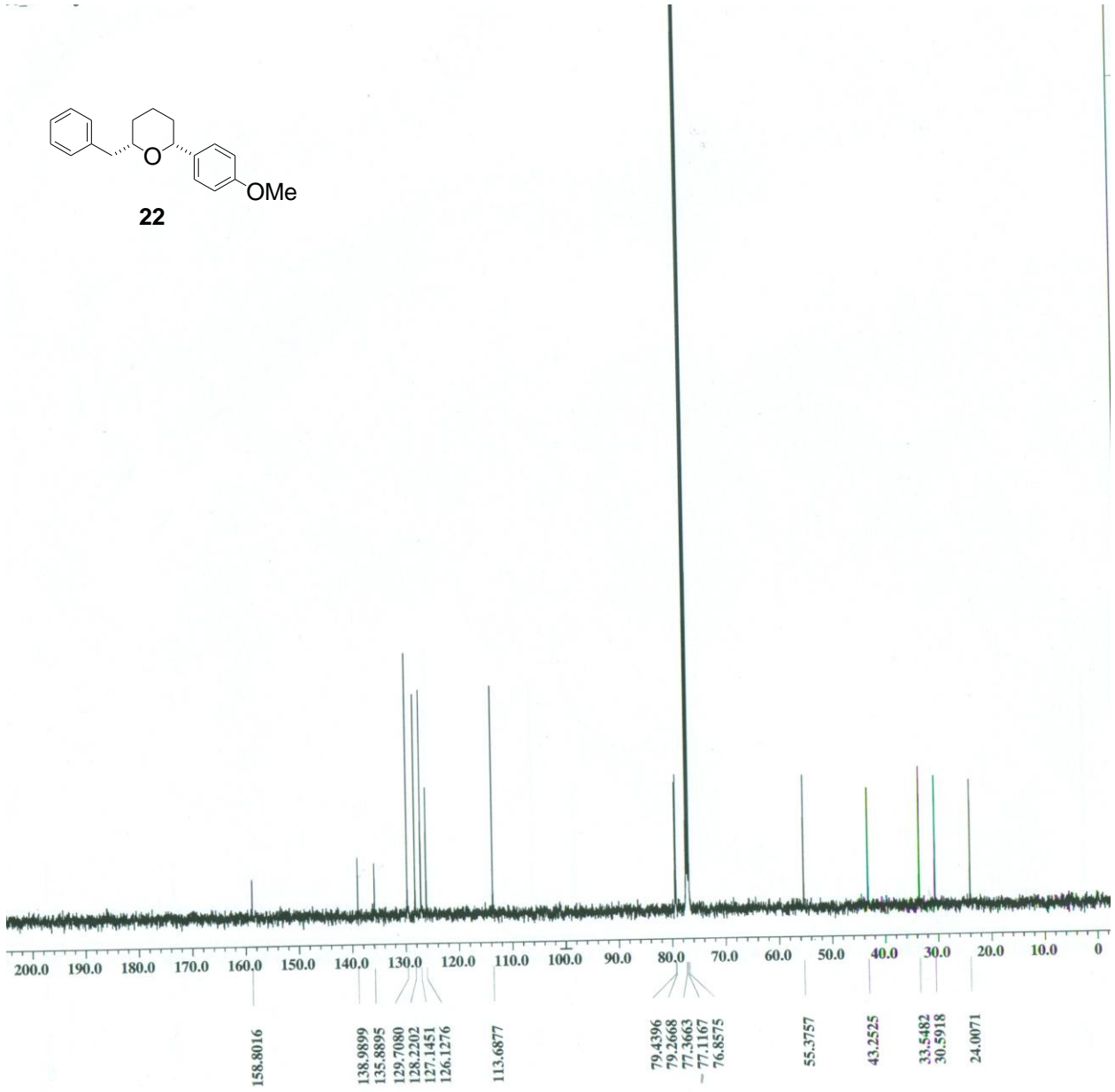
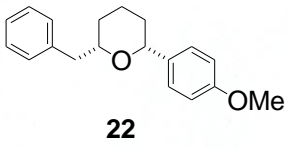
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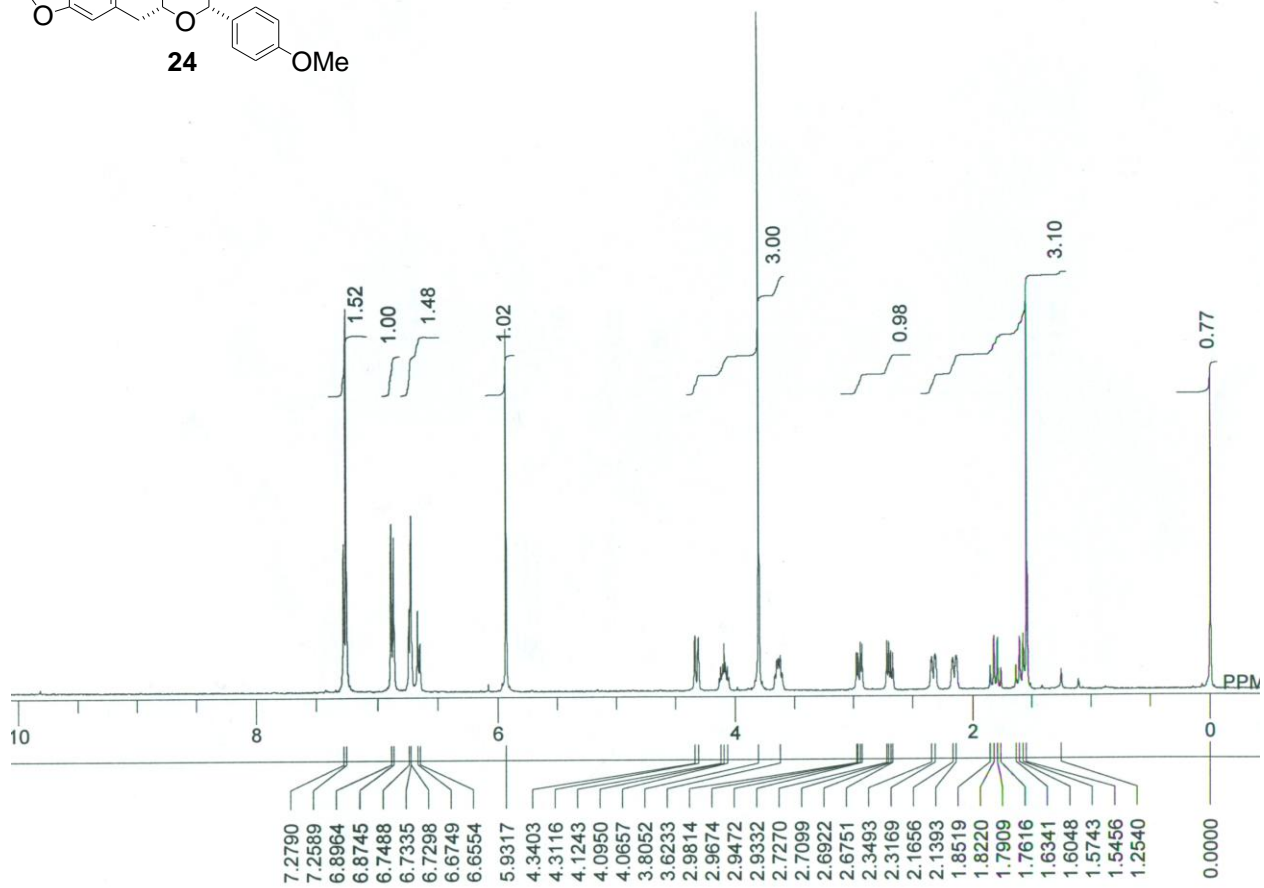
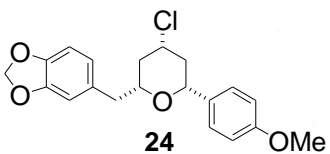


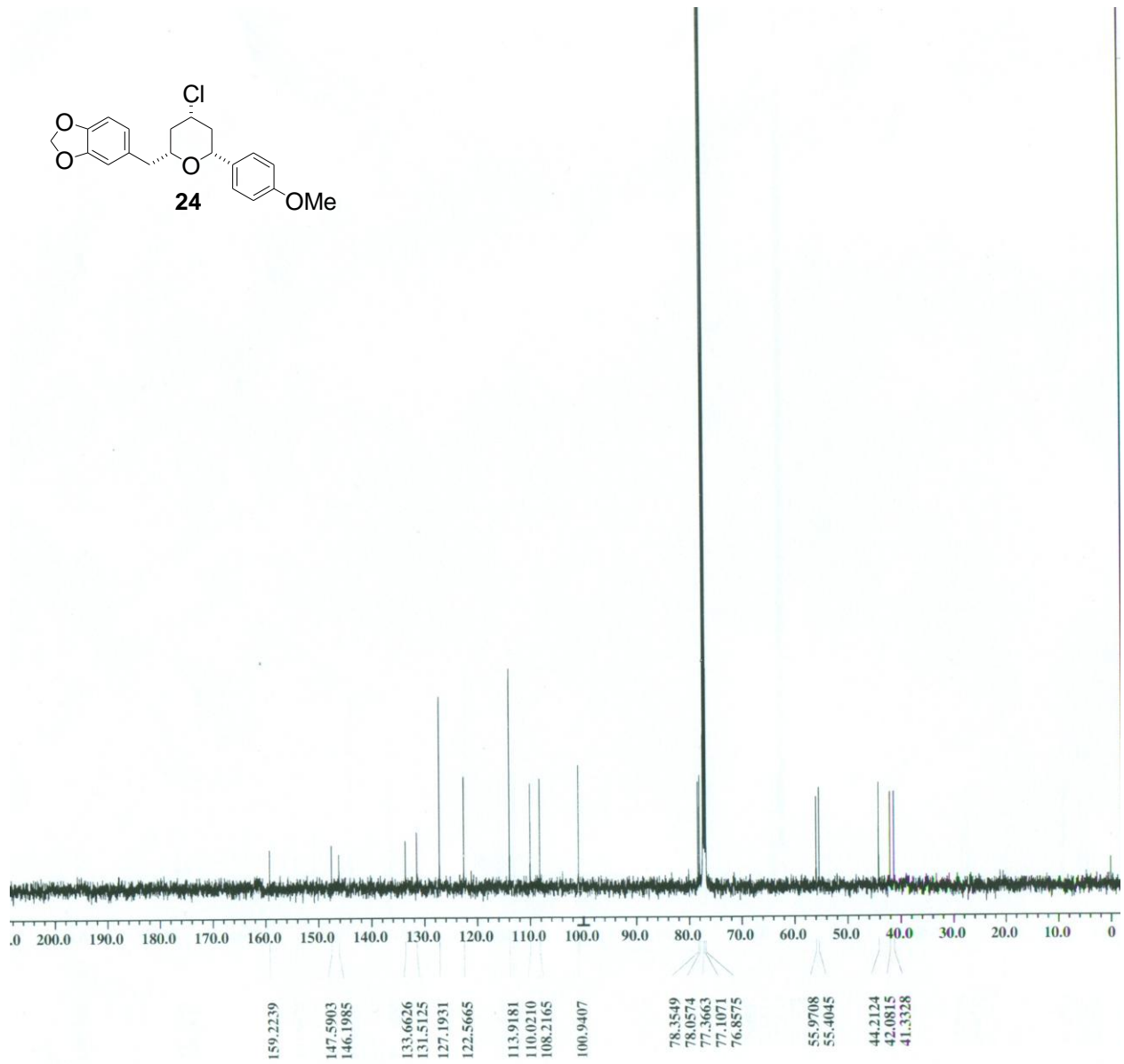
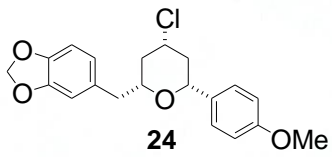
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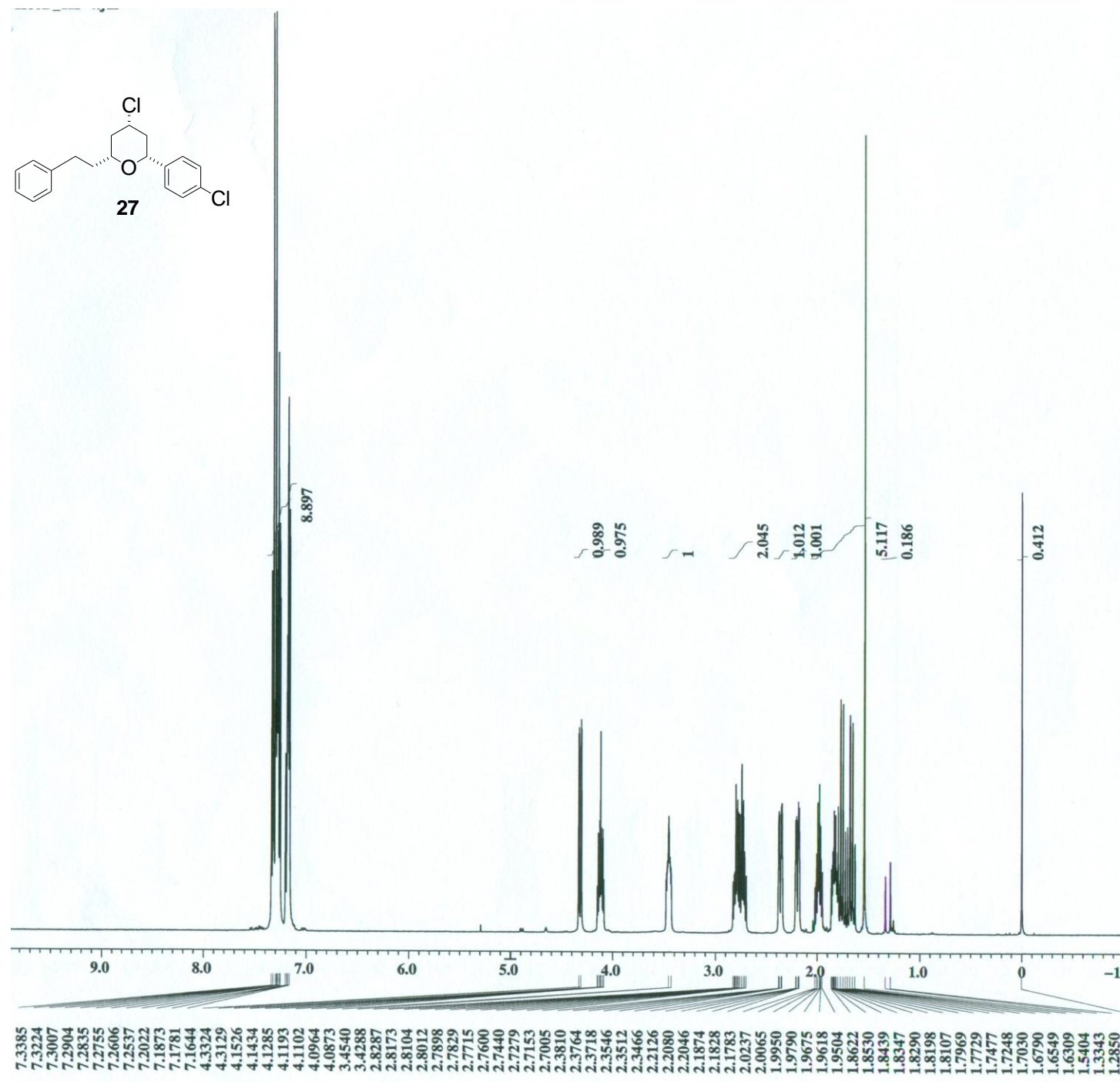
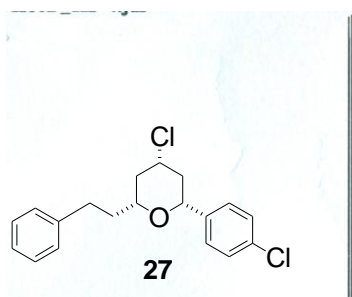


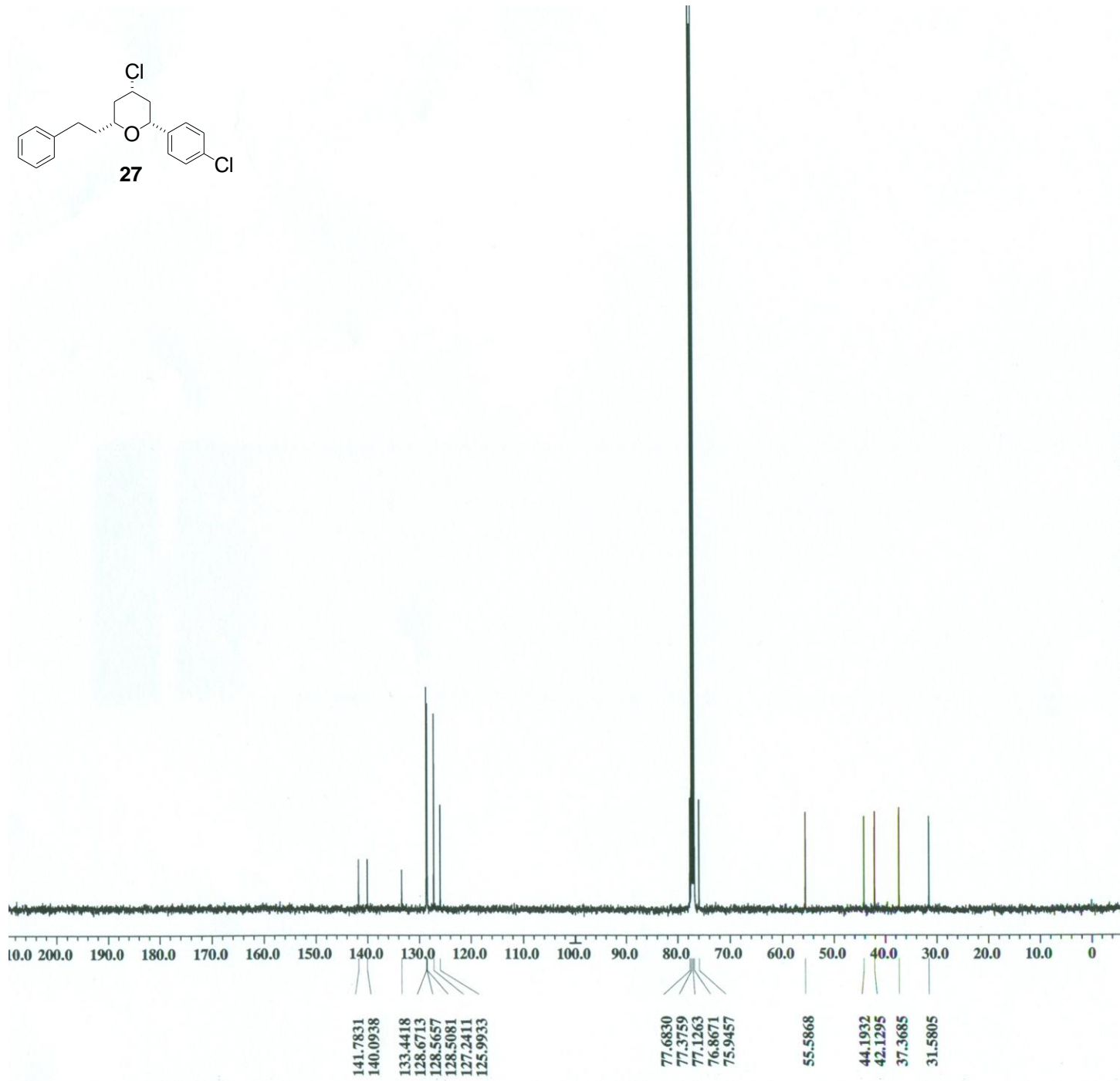
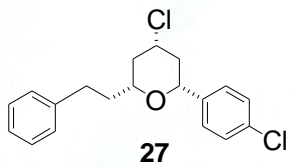


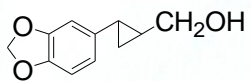
N_1H



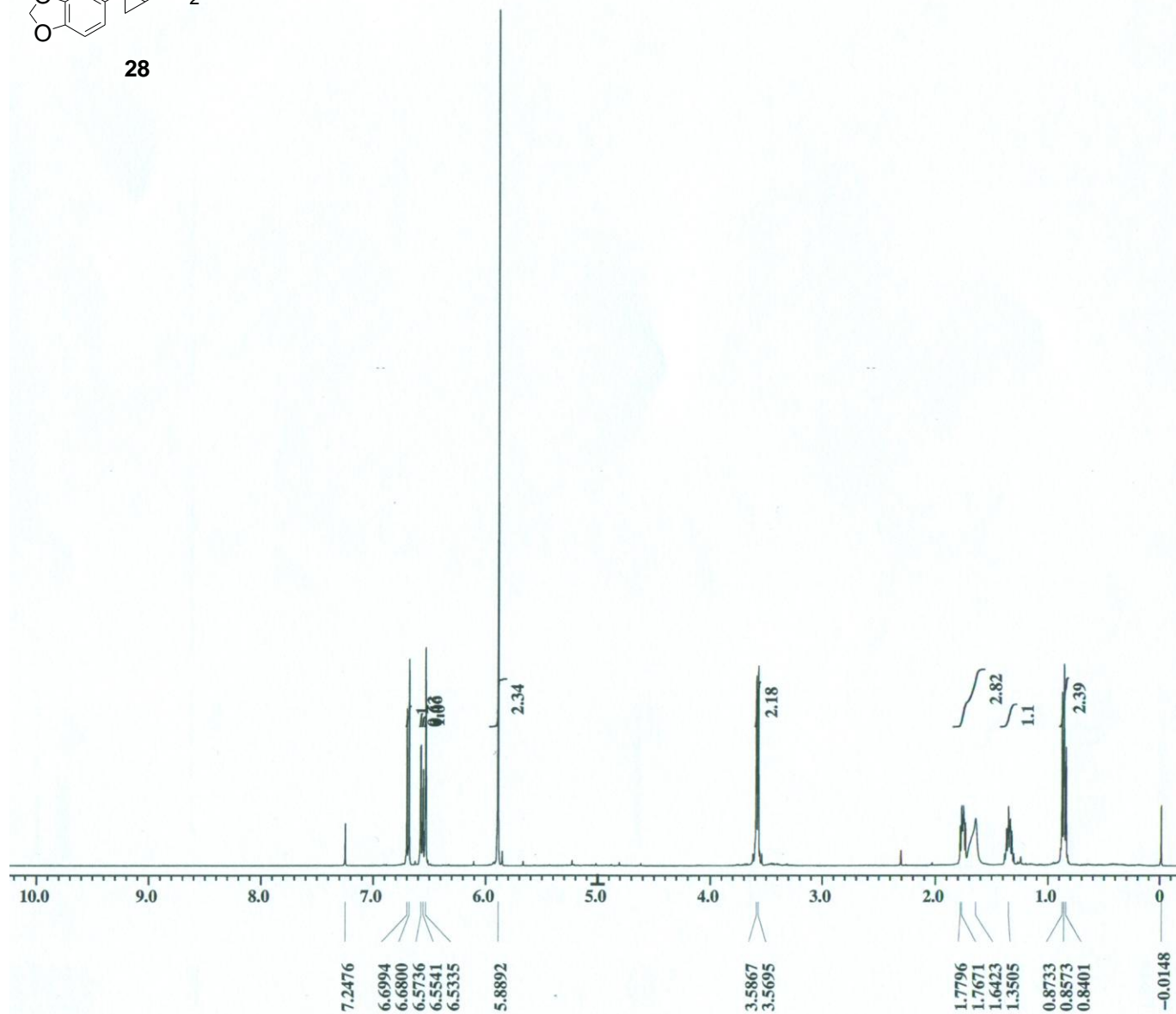


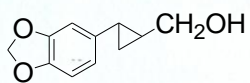




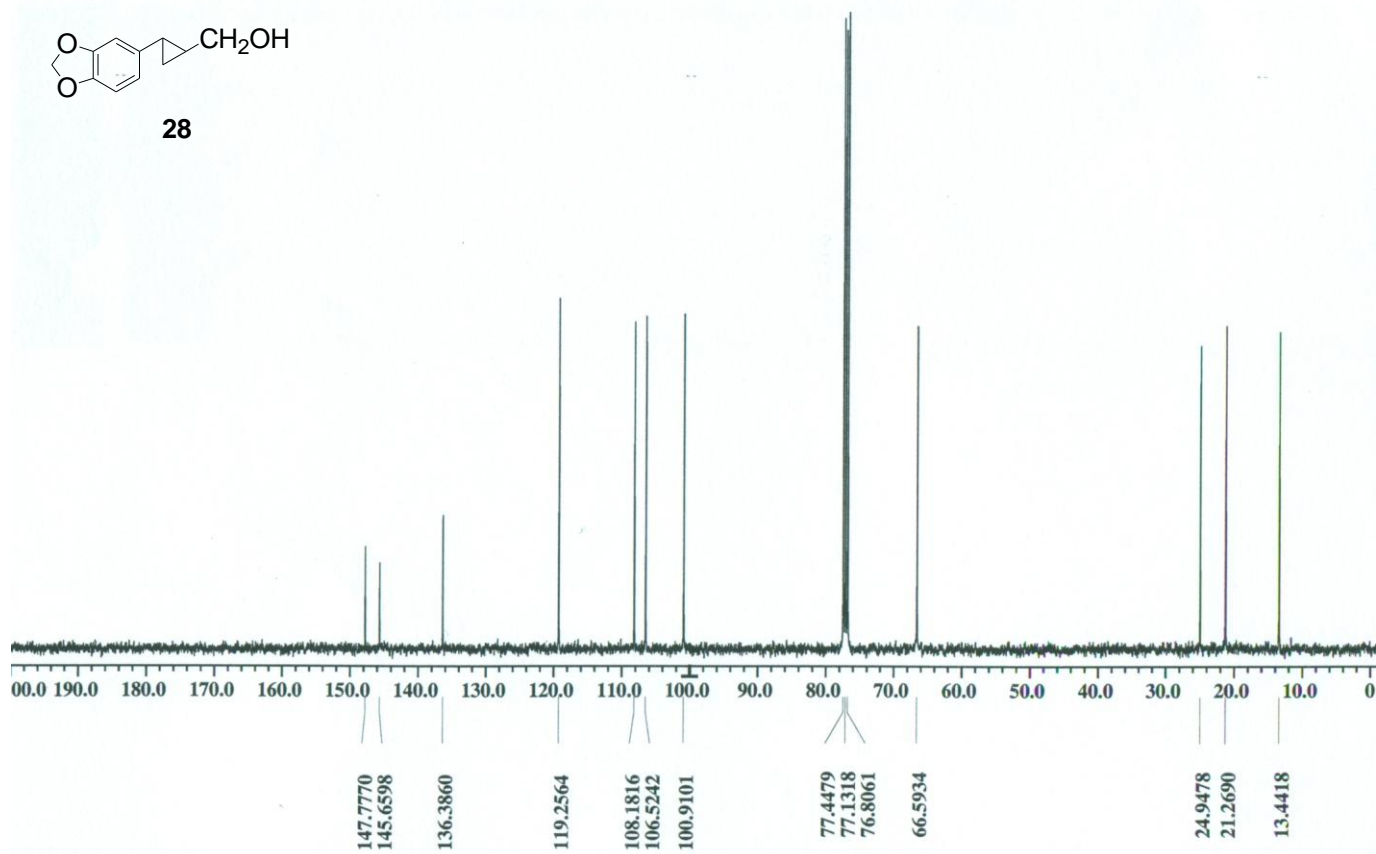


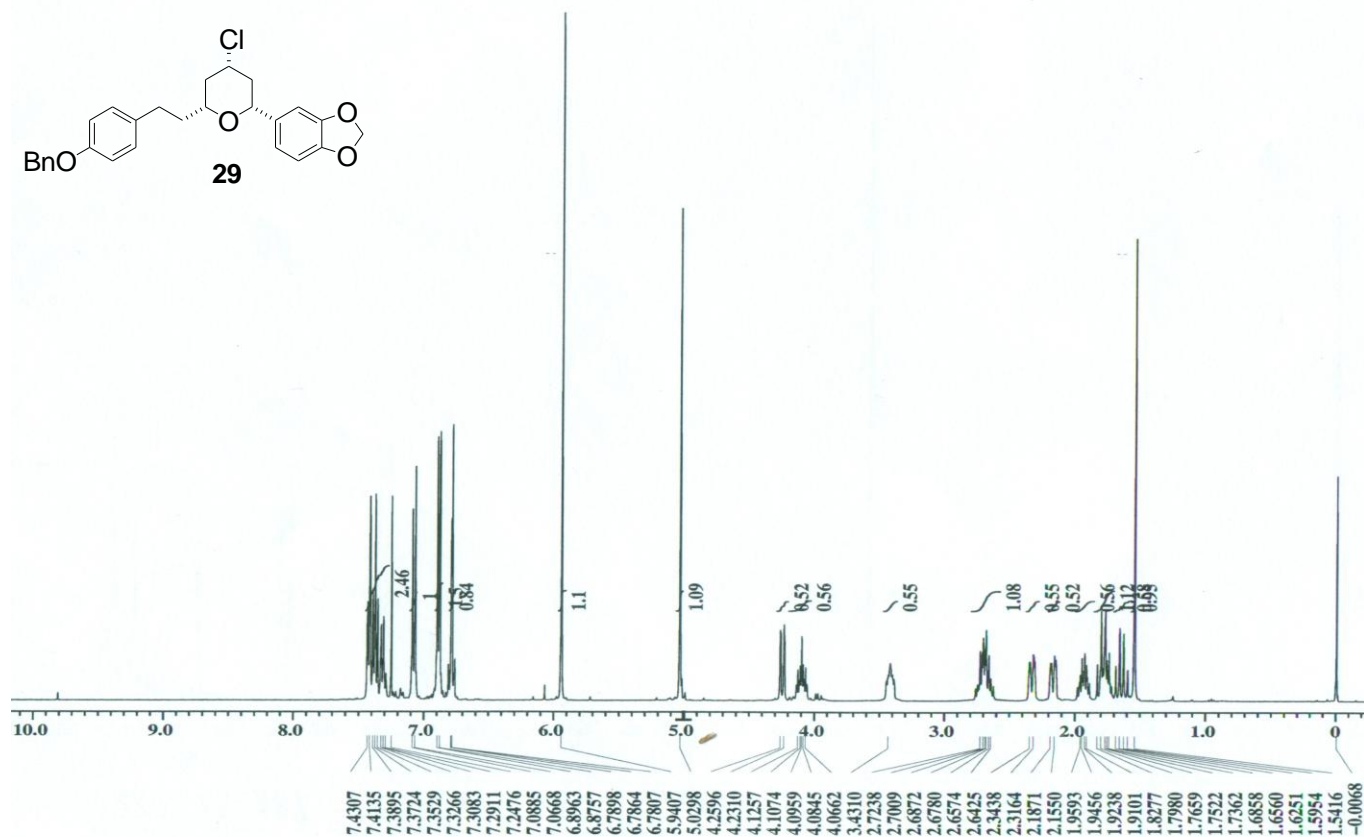
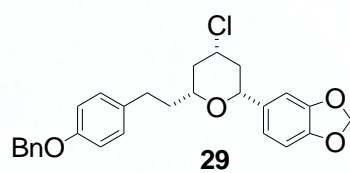
28

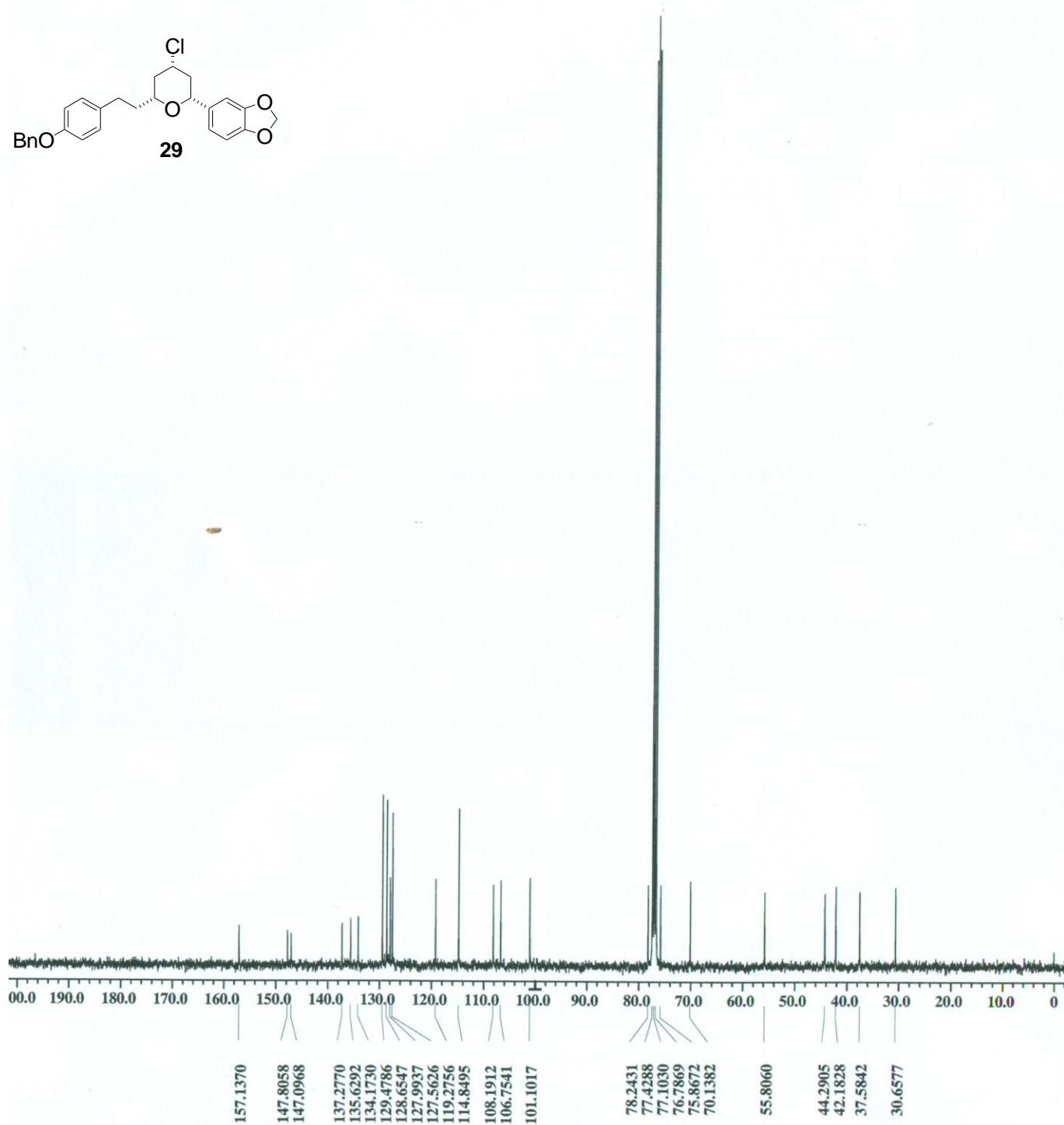
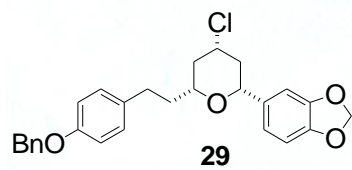


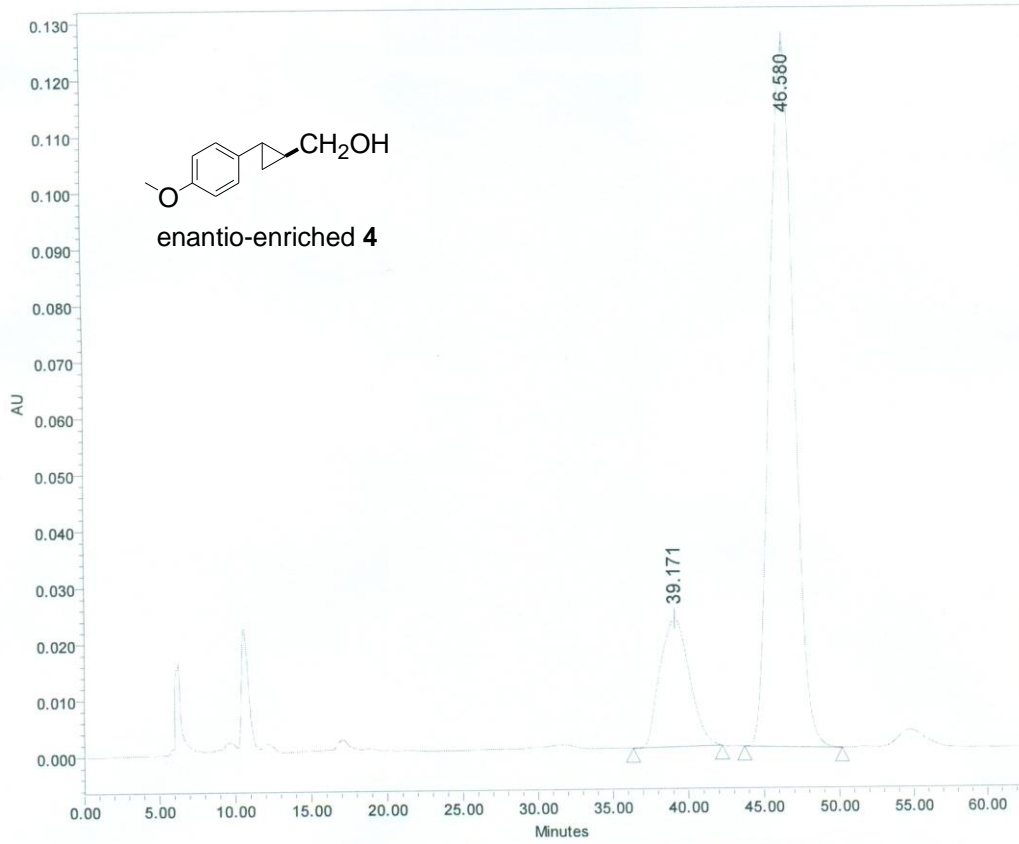


28







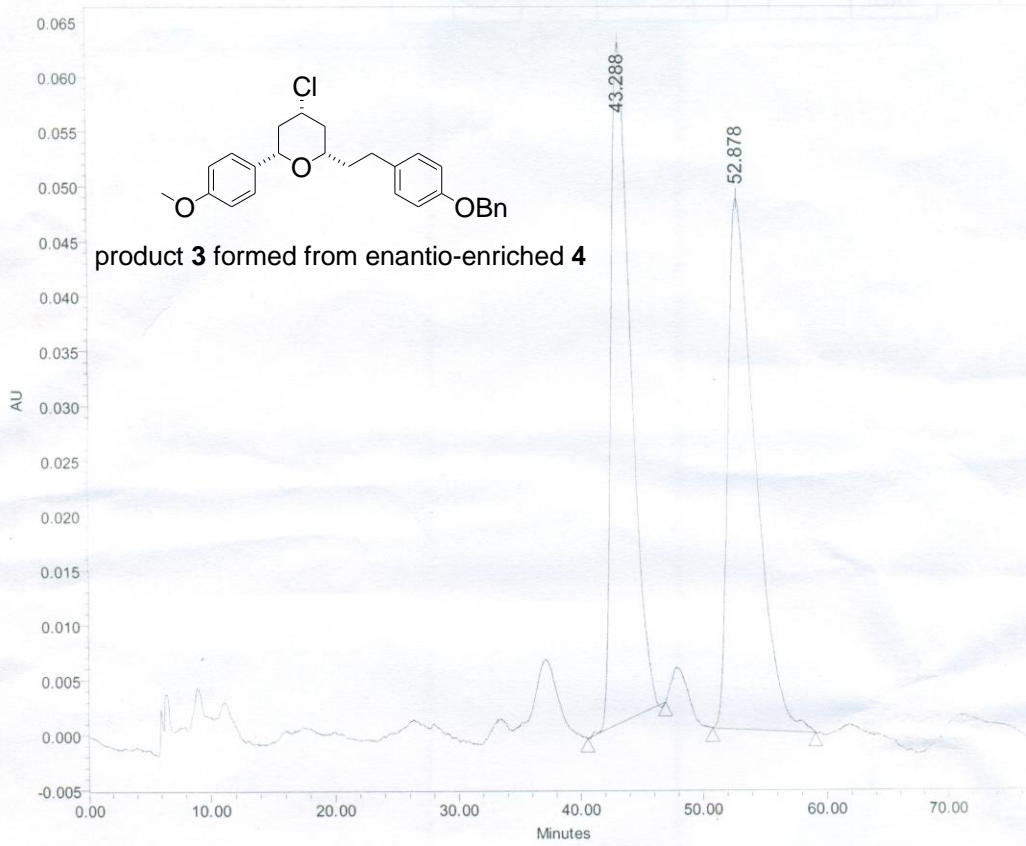


Sample Name: VKYD OD(0.5 mL); Date Acquired: 7/8/2014 3:03:35 PM IST; Vial: 1; Injection: 1

Peak Summary with Statistics

Name :

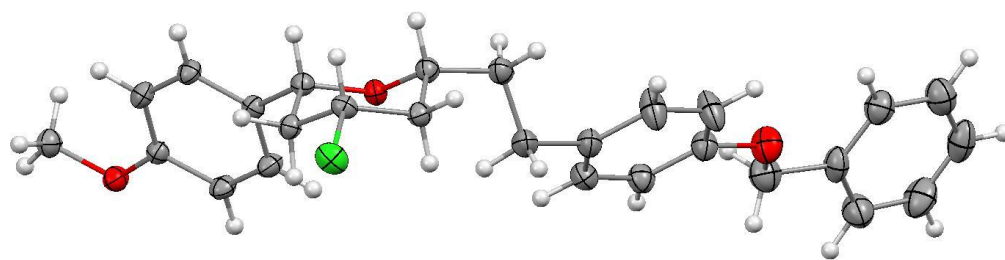
	Sample Name	Vial	Inj	Retention Time (min)	Area	% Area	Height
1	VKYD OD(0.5 mL)	1	1	46.580	13981246	81.89	124999
2	VKYD OD(0.5 mL)	1	1	39.171	3092391	18.11	22828
Mean				42.876			
Std. Dev.				5.239			



Peak Summary with Statistics

Name:

	Sample Name	Vial	Inj	Retention Time (min)	Area	% Area	Height
1	VKYD46	1	1	52.878	7417285	51.65	48406
2	VKYD46	1	1	43.288	6942741	48.35	62063
Mean				48.083			
Std. Dev.				6.781			



The ORTEP plot of the X-ray structure of (±)-3