

Electronic Supplementary Information

Lewis acid-mediated radical cyclization: Stereocontrol in cascade radical addition-cyclization-trapping reactions

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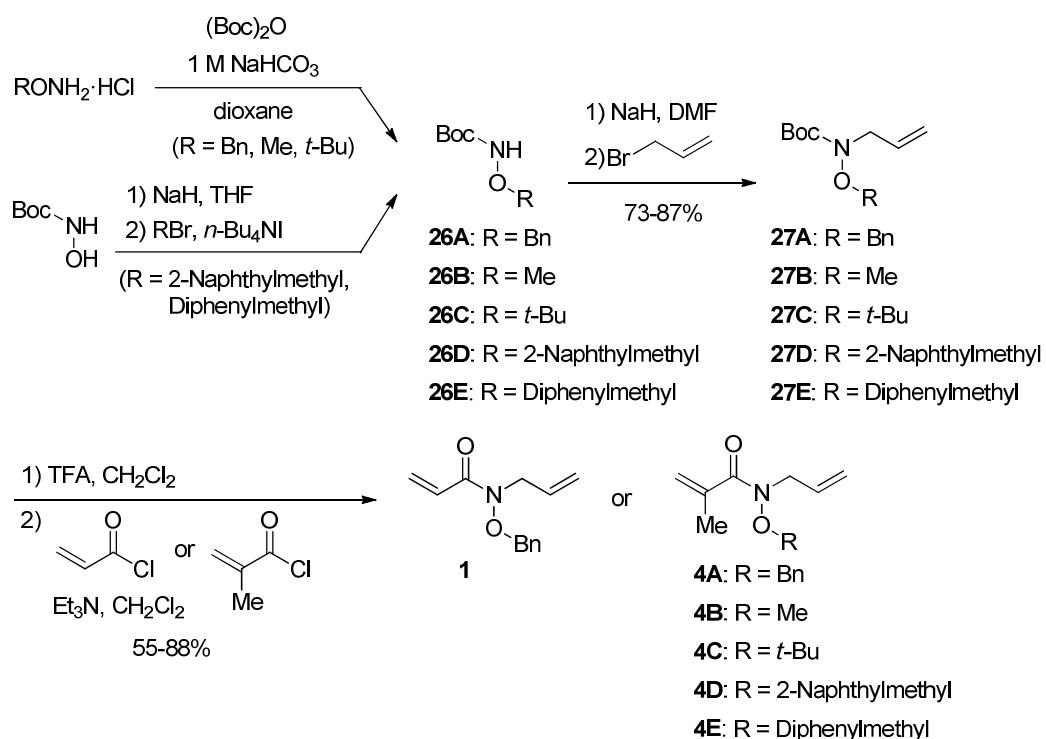
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1. The experimental procedure and the characterization data for substrates

1-1. Preparation of substrates 1 and 4A-E (Scheme 1)



Scheme 1

Preparation of 26A-E. Following the reported procedure,¹ 26A-C were obtained. Following the procedure modified from the reported method,² 26D and 26E were obtained.

26A. A colorless oil. IR (CHCl₃) 1743 cm⁻¹. ¹H NMR (CDCl₃) δ 7.40-7.30 (5H, m), 7.12 (1H, br s), 4.86 (2H, s), 1.48 (9H, s). ¹³C NMR (CDCl₃) δ 156.8, 135.8, 129.2, 128.5 (2C), 81.7, 78.4, 28.1. MS (EI⁺) *m/z* 223 (M⁺, 7), 92 (100). HRMS (EI⁺) calcd for C₁₂H₁₇NO₃ (M⁺) 223.1208, found 223.1214.

26B. A colorless oil. IR (CHCl₃) 1700 cm⁻¹. ¹H NMR (CDCl₃) δ 7.28 (1H, br s), 3.67 (3H, s), 1.45 (9H, s). ¹³C NMR (CDCl₃) δ 156.9, 81.6, 64.3, 28.1. MS (CI⁺) *m/z* 148 (M+H⁺, 11), 92 (100). HRMS (CI⁺) calcd for C₆H₁₄NO₃ (M+H⁺) 148.0974, found 148.0969.

26C. A colorless crystal. Mp 80-71 °C (AcOEt/hexane). IR (CHCl₃) 1748 cm⁻¹. ¹H NMR (CDCl₃) δ 6.75 (1H, br s), 1.45 (9H, s), 1.21 (9H, s). ¹³C NMR (CDCl₃) δ 157.6, 81.0, 80.2, 28.1, 26.1. MS (CI⁺) *m/z* 190 (M+H⁺, 10), 134 (100). HRMS (CI⁺) calcd for C₉H₂₀NO₃ (M+H⁺) 190.1443, found 190.1450.

26D. A colorless crystal. Mp 70-71 °C (AcOEt/hexane). IR (CHCl₃) 1742 cm⁻¹. ¹H NMR (CDCl₃) δ 7.90-7.81 (4H, m), 7.55-7.47 (3H, m), 7.10 (1H, br s), 5.02 (2H, s), 1.48 (9H, s). ¹³C NMR (CDCl₃) δ 156.7, 133.2, 132.7, 128.5, 128.1, 128.0, 127.7, 127.0, 126.2, 126.1, 118.1, 81.5, 53.0, 28.2. MS (EI⁺) *m/z* 273 (M⁺, 10), 128 (100). HRMS (EI⁺) calcd for C₁₆H₁₉NO₃ (M⁺) 273.1365, found 273.1363. Anal. calcd for C₁₆H₁₉NO₃: C, 70.31; H, 7.01; N, 5.12%. Found: C, 70.12; H, 6.83; N, 5.08%.

26E. A colorless oil. IR (CHCl₃) 1741 cm⁻¹. ¹H NMR (CDCl₃) δ 7.40-7.27 (10H, m), 7.07 (1H, br s), 5.90 (1H, s), 1.47 (9H, s). ¹³C NMR (CDCl₃) δ 156.5, 139.4, 128.5, 128.2, 127.9, 88.9, 81.8, 28.2. MS (FAB⁻) *m/z* 298 (M-H⁺,

40), 153 (100). HRMS (FAB⁻) calcd for C₁₈H₂₀NO₃ (M-H⁺) 298.1443, found 298.1436.

Preparation of 27A-E. After NaH (60% oil suspension, 440 mg 11 mmol) was washed with hexanes three times under argon atmosphere, DMF (40 mL) was added. To this stirred suspension was added a solution of **26A-E** (10 mmol) in DMF (10 mL) at 0 °C. After being stirred at same temperature for 20 min, allyl bromide (0.92 mL, 11 mmol) was added to the reaction mixture. After being stirred at the room temperature for 1 h, the reaction mixture was diluted with water and then extracted with AcOEt. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:10–1:5) afforded the products **27A-E**.

27A. A colorless oil. IR (CHCl₃) 1699 cm⁻¹. ¹H NMR (CDCl₃) δ 7.41–7.30 (5H, m), 5.87 (1H, m), 5.22 (1H, dd, J=17.1, 1.6 Hz), 5.17 (1H, dd, J=10.4, 1.6 Hz), 4.83 (2H, s), 4.00 (2H, br d, J=6.1 Hz), 1.49 (9H, s). ¹³C NMR (CDCl₃) δ 156.6, 135.6, 132.7, 129.3, 128.4, 128.3, 118.0, 81.3, 77.1, 52.7, 28.1. MS (EI⁺) *m/z* 263 (M⁺, 0.2), 91 (100). HRMS (EI⁺) calcd for C₁₅H₂₁NO₃ (M⁺) 263.1521, found 263.1519.

27B. A colorless oil. IR (CHCl₃) 1700 cm⁻¹. ¹H NMR (CDCl₃) δ 5.85 (1H, m), 5.21 (1H, dd, J=17.1, 1.6 Hz), 5.16 (1H, dd, J=10.4, 1.6 Hz), 4.00 (2H, br d, J=5.8 Hz), 3.65 (3H, s), 1.47 (9H, s). ¹³C NMR (CDCl₃) δ 156.4, 132.7, 117.9, 81.4, 62.5, 52.1, 28.2. MS (EI⁺) *m/z* 187 (M⁺, 0.4), 56 (100). HRMS (EI⁺) calcd for C₉H₁₇NO₃ (M⁺) 187.1208, found 187.1211.

27C. A colorless oil. IR (CHCl₃) 1726, 1692 cm⁻¹. ¹H NMR (CDCl₃) δ 5.88 (1H, m), 5.17 (1H, dd, J=17.1, 1.6 Hz), 5.14 (1H, dd, J=10.1, 1.6 Hz), 4.23 (1H, br m), 3.74 (1H, br m), 1.45 (9H, s), 1.23 (9H, s). ¹³C NMR (CDCl₃) δ 158.8, 132.8, 117.7, 81.5, 81.2, 56.2, 28.1, 27.1. MS (CI⁺) *m/z* 230 (M+H⁺, 8), 174 (100). HRMS (CI⁺) calcd for C₁₂H₂₄NO₃ (M+H⁺) 230.1757, found 230.1755.

27D. A colorless oil. IR (CHCl₃) 1697 cm⁻¹. ¹H NMR (CDCl₃) δ 7.86–7.81 (4H, m), 7.54 (1H, d, J=9.8 Hz), 7.51–7.46 (2H, m), 5.89 (1H, m), 5.24 (1H, dd, J=17.0, 1.6 Hz), 5.18 (1H, br d, J=9.7 Hz), 5.01 (2H, s), 4.00 (2H, br d, J=6.1 Hz), 1.51 (9H, s). ¹³C NMR (CDCl₃) δ 156.7, 133.3, 133.2 (2C), 132.8, 128.5, 128.1, 128.0, 127.7, 127.0, 126.2, 126.1, 118.1, 81.5, 77.4, 53.0, 28.2. MS (FAB⁺) *m/z* 314 (M+H⁺, 4), 141 (100). HRMS (FAB⁺) calcd for C₁₉H₂₄NO₃ (M+H⁺) 314.1756, found 314.1762.

27E. A colorless oil. IR (CHCl₃) 1698 cm⁻¹. ¹H NMR (CDCl₃) δ 7.42–7.27 (10H, m), 5.89 (1H, s), 5.71 (1H, m), 5.10 (1H, dd, J=17.4, 1.5 Hz), 5.08 (1H, dd, J=10.4, 1.5 Hz), 3.76 (2H, br d, J=5.5 Hz), 1.47 (9H, s). ¹³C NMR (CDCl₃) δ 157.1, 140.1, 132.6, 130.1, 128.3, 128.2, 117.6, 87.8, 81.7, 53.5, 28.2. MS (FAB⁺) *m/z* 340 (M+H⁺, 4), 167 (100). HRMS (FAB⁺) calcd for C₂₁H₂₆NO₃ (M+H⁺) 340.1912, found 340.1904.

Preparation of 1 and 4A-E. To a solution of **27A-E** (3.0 mmol) in CH₂Cl₂ (15 mL) was added TFA (2.3 mL, 30 mmol) under argon atmosphere at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was neutralized with saturated aqueous NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was dried over MgSO₄ and concentrated under reduced pressure to give crude amine. To a solution of crude amine and Et₃N (1.25 mL, 9.0 mmol) in CH₂Cl₂ (15 mL) was added acid chloride (3.3 mmol) under argon atmosphere at the room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with water and then extracted with AcOEt. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:6–1:3) afforded the products **1** and **4A-E**.

1. A colorless oil. IR (CHCl₃) 1653, 1618 cm⁻¹. ¹H NMR (CDCl₃) δ 7.42-7.32 (5H, m), 6.74 (1H, dd, *J*=17.1, 10.4 Hz), 6.42 (1H, dd, *J*=17.1, 1.8 Hz), 5.90 (1H, m), 5.73 (1H, dd, *J*=10.4, 1.8 Hz), 5.28 (1H, dd, *J*=17.1, 1.2 Hz), 5.23 (1H, dd, *J*=10.4, 1.2 Hz), 4.86 (2H, s), 4.31 (2H, d, *J*=6.1 Hz). ¹³C NMR (CDCl₃) δ 166.9, 134.3, 132.1, 129.4, 129.2, 129.0, 128.7, 126.3, 118.6, 77.5, 49.4. MS (EI⁺) *m/z* 217 (M⁺, 4), 91 (100). HRMS (EI⁺) calcd for C₁₃H₁₅NO₂ (M⁺) 217.1103, found 217.1098.

4A. A colorless oil. IR (CHCl₃) 1655, 1631 cm⁻¹. ¹H NMR (CDCl₃) δ 7.45-7.30 (5H, m), 5.88 (1H, m), 5.34 (1H, s), 5.29 (1H, dd, *J*=17.1, 1.3 Hz), 5.28 (1H, s), 5.23 (1H, br d, *J*=10.1 Hz), 4.84 (2H, s), 4.23 (2H, d, *J*=6.1 Hz), 1.98 (3H, s). ¹³C NMR (CDCl₃) δ 171.9, 140.6, 134.8, 132.3, 129.4, 128.9, 128.6, 118.5, 117.5, 77.4, 50.7, 19.9. MS (EI⁺) *m/z* 231 (M⁺, 45), 159 (100). HRMS (EI⁺) calcd for C₁₄H₁₇NO₂ (M⁺) 231.1259, found 231.1252.

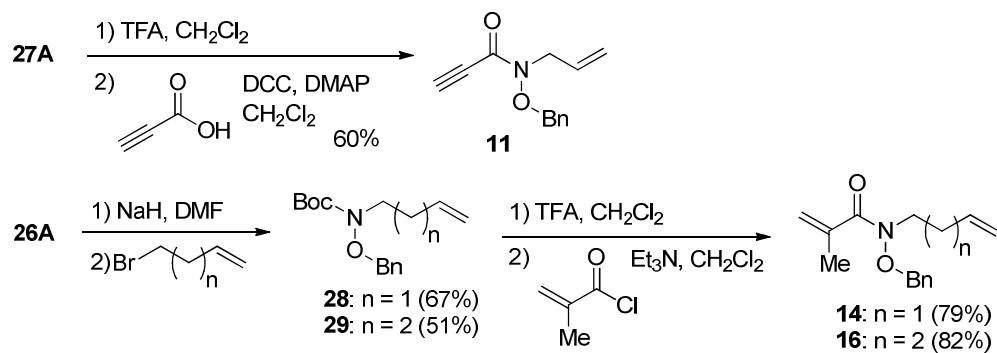
4B. A colorless oil. IR (CHCl₃) 1656, 1631 cm⁻¹. ¹H NMR (CDCl₃) δ 5.88 (1H, m), 5.33 (1H, s), 5.29 (1H, dd, *J*=18.6, 1.5 Hz), 5.25 (1H, s), 5.24 (1H, dd, *J*=13.2, 1.5 Hz), 4.25 (2H, d, *J*=5.8 Hz), 3.68 (3H, s), 2.00 (3H, s). ¹³C NMR (CDCl₃) δ 171.5, 140.3, 132.2, 118.3, 117.4, 62.1, 49.5, 19.8. MS (EI⁺) *m/z* 155 (M⁺, 23), 69 (100). HRMS (EI⁺) calcd for C₈H₁₃NO₂ (M⁺) 155.0946, found 155.0939.

4C. A colorless oil. IR (CHCl₃) 1668, 1631 cm⁻¹. ¹H NMR (CDCl₃) δ 5.80 (1H, m), 5.31 (1H, s), 5.28 (1H, s), 5.18-5.13 (2H, m), 3.30 (2H, br s), 1.84 (3H, s), 1.19 (9H, s). ¹³C NMR (CDCl₃) δ 174.9, 140.6, 132.8, 118.9, 118.0, 82.9, 55.4, 27.3, 19.7. MS (EI⁺) *m/z* 197 (M⁺, 8), 71 (100). HRMS (EI⁺) calcd for C₁₁H₁₉NO₂ (M⁺) 197.1416, found 197.1412.

4D. A colorless oil. IR (CHCl₃) 1657, 1630 cm⁻¹. ¹H NMR (CDCl₃) δ 7.86-7.78 (4H, m), 7.52-7.43 (3H, m), 5.88 (1H, m), 5.36 (1H, s), 5.29 (1H, dd, *J*=17.1, 1.6 Hz), 5.29 (1H, s), 5.23 (1H, dd, *J*=10.0, 1.6 Hz), 5.00 (2H, s), 4.24 (2H, d, *J*=5.8 Hz), 1.99 (3H, s). ¹³C NMR (CDCl₃) δ 171.8, 140.4, 133.3, 133.1, 132.2, 132.1, 128.6, 128.3, 128.0, 127.7, 126.6, 126.5, 126.3, 118.4, 117.5, 77.0, 50.8, 19.8. MS (EI⁺) *m/z* 281 (M⁺, 0.1), 141 (100). HRMS (EI⁺) calcd for C₁₈H₁₉NO₂ (M⁺) 281.1416, found 281.1425.

4E. A colorless oil. IR (CHCl₃) 1657, 1631 cm⁻¹. ¹H NMR (CDCl₃) δ 7.42-7.29 (10H, m), 5.94 (1H, s), 5.73 (1H, m), 5.17 (1H, s), 5.17-5.14 (2H, m), 5.12 (1H, dd, *J*=8.9, 1.6 Hz), 3.90 (2H, d, *J*=5.8 Hz), 1.87 (3H, s). ¹³C NMR (CDCl₃) δ 172.2, 140.2, 139.5, 132.3, 128.3, 128.2, 128.1, 118.0, 117.7, 87.4, 52.3, 19.7. MS (CI⁺) *m/z* 308 (M+H⁺, 1.6), 167 (100). HRMS (CI⁺) calcd for C₂₀H₂₂NO₂ (M+H⁺) 308.1650, found 308.1652.

1-2. Preparation of substrates 11, 14 and 16 (Scheme 2)



Scheme 2

Preparation of substrate 11. To a solution of **27A** (789 mg, 3.0 mmol) in CH₂Cl₂ (15 mL) was added TFA (2.3 mL, 30 mmol) under argon atmosphere at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was neutralized with saturated aqueous NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was dried over MgSO₄ and concentrated under reduced pressure to give crude amine. To a solution of crude amine, DCC (744 mg, 3.6 mmol) and DMAP (44 mg, 0.36 mmol) in CH₂Cl₂ (15 mL) was added acid (0.20 mL, 3.3 mmol) under argon atmosphere at the room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:5–1:3) afforded **11** (387 mg, 60%).

11. A colorless oil. IR (CHCl₃) 1641 cm⁻¹. ¹H NMR (CDCl₃) δ 7.42–7.30 (5H, m), 5.82 (1H, m), 5.26 (1H, dd, *J*=17.1, 1.5 Hz), 5.23 (1H, dd, *J*=11.0, 1.5 Hz), 4.96 (2H, s), 4.21 (2H, d, *J*=5.8 Hz), 1.31 (1H, s). ¹³C NMR (CDCl₃) δ 153.8, 134.1, 131.0, 129.4, 129.0, 128.6, 119.3, 79.1, 78.1, 75.4, 49.5. MS (EI⁺) *m/z* 215 (M⁺, 29), 129 (100). HRMS (EI⁺) calcd for C₁₃H₁₃NO₂ (M⁺) 215.0946, found 215.0939.

Preparation of substrates 14 and 16. Following the same procedure as for **1** or **4A-E**, the synthetic intermediates **28** and **29** and the substrates **14** and **16** were obtained.

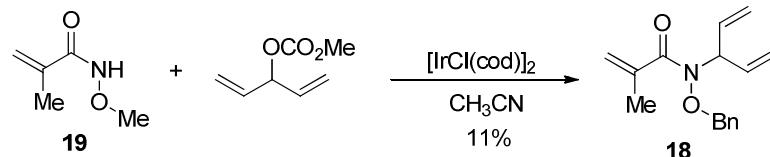
28. A colorless oil. IR (CHCl₃) 1699 cm⁻¹. ¹H NMR (CDCl₃) δ 7.42–7.31 (5H, m), 5.77 (1H, m), 5.09 (1H, dd, *J*=17.1, 1.5 Hz), 5.03 (1H, dd, *J*=10.4, 1.5 Hz), 4.84 (2H, s), 3.47 (2H, t, *J*=7.0 Hz), 2.36 (2H, m), 1.50 (9H, s). ¹³C NMR (CDCl₃) δ 156.6, 135.7, 135.3, 129.4, 128.5, 128.4, 116.7, 81.2, 76.9, 49.2, 31.4, 28.2. MS (FAB⁺) *m/z* 278 (M+H⁺, 16), 91 (100). HRMS (FAB⁺) calcd for C₁₆H₂₄NO₃ (M+H⁺) 278.1756, found 278.1762.

29. A colorless oil. IR (CHCl₃) 1699 cm⁻¹. ¹H NMR (CDCl₃) δ 7.43–7.30 (5H, m), 5.79 (1H, m), 5.01 (1H, br d, *J*=17.0 Hz), 4.96 (1H, dd, *J*=10.0, 1.2 Hz), 4.83 (2H, s), 3.42 (2H, t, *J*=7.3 Hz), 2.08 (2H, m), 1.70 (2H, m), 1.50 (9H, s). ¹³C NMR (CDCl₃) δ 156.6, 137.9, 135.7, 129.4, 128.5, 128.4, 115.0, 81.2, 76.9, 49.1, 30.8, 28.3, 26.1. MS (FAB⁺) *m/z* 292 (M+H⁺, 15), 91 (100). HRMS (FAB⁺) calcd for C₁₇H₂₆NO₃ (M+H⁺) 292.1913, found 292.1907.

14. A colorless oil. IR (CHCl₃) 1650 cm⁻¹. ¹H NMR (CDCl₃) δ 7.40–7.31 (5H, m), 5.76 (1H, m), 5.29 (1H, s), 5.24 (1H, s), 5.09 (1H, dd, *J*=17.1, 1.8 Hz), 5.05 (1H, dd, *J*=10.1, 1.8 Hz), 4.81 (2H, s), 3.67 (2H, t, *J*=7.0 Hz), 2.40 (2H, m), 1.96 (3H, s). ¹³C NMR (CDCl₃) δ 171.7, 140.6, 134.6, 134.5, 129.1, 128.7, 128.4, 117.1, 117.0, 76.4, 46.4, 31.3, 19.8. MS (EI⁺) *m/z* 245 (M⁺, 1.3), 91 (100). HRMS (EI⁺) calcd for C₁₅H₁₉NO₂ (M⁺) 245.1416, found 245.1405.

16. A colorless oil. IR (CHCl₃) 1631 cm⁻¹. ¹H NMR (CDCl₃) δ 7.38–7.30 (5H, m), 5.77 (1H, m), 5.29 (1H, s), 5.23 (1H, s), 5.01 (1H, dd, *J*=17.1, 1.8 Hz), 4.97 (1H, dd, *J*=10.1, 1.8 Hz), 4.79 (2H, s), 3.61 (2H, t, *J*=7.3 Hz), 2.05 (2H, m), 1.99 (3H, s), 1.74 (2H, m). ¹³C NMR (CDCl₃) δ 171.2, 140.4, 137.1, 134.4, 128.9, 128.4, 128.2, 116.7, 114.9, 76.1, 46.1, 30.3, 25.8, 19.5. MS (EI⁺) *m/z* 259 (M⁺, 0.5), 91 (100). HRMS (EI⁺) calcd for C₁₆H₂₁NO₂ (M⁺) 259.1572, found 259.1581.

1-3. Preparation of substrate 18 (Scheme 3)



Scheme 3

Preparation of substrate 18. To a solution of amide **19** (1.15 g, 10 mmol) in CH₃CN (40 mL) was added a solution of carbonate (1.42 g, 12 mmol) and [IrCl(cod)]₂ (536 mg, 0.80 mmol) in CH₃CN (20 mL) under argon atmosphere at the room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with H₂O and then extracted with AcOEt. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:10–1:5) afforded the product **18** (283 mg, 11%).

18. A colorless oil. IR (CHCl₃) 1656 cm⁻¹. ¹H NMR (CDCl₃) δ 7.40–7.32 (5H, m), 6.05 (2H, m), 5.37–5.26 (7H, m), 4.88 (2H, s), 1.99 (3H, s). ¹³C NMR (CDCl₃) δ 172.5, 140.9, 134.8, 134.5, 129.2, 128.7, 128.5, 118.5, 117.3, 78.6, 63.7, 19.7. MS (FAB⁺) *m/z* 258 (M+H⁺, 100). HRMS (FAB⁺) calcd for C₁₆H₂₀NO₂ (M+H⁺) 258.1494, found 258.1492.

2. NOESY of chiral products

The NOESY studies of *trans*-**2a**, *cis*-**2a**, *cis*-**21** and *trans*-**22** are shown in Figures 1 and 2.

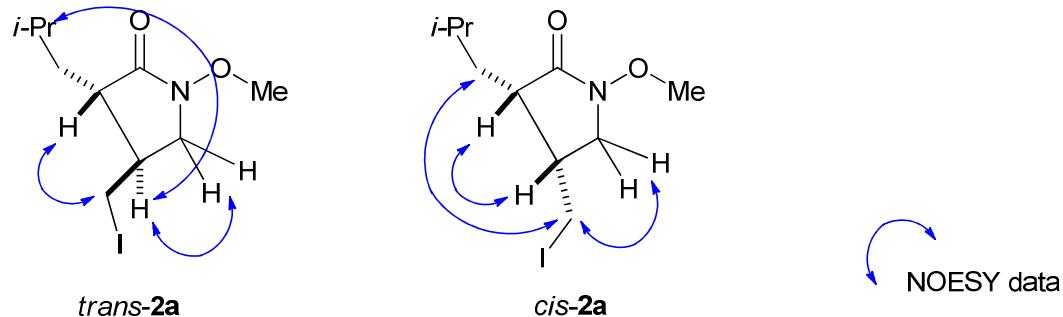


Fig. 1 NOESY study of *trans*-**2a** and *cis*-**2a**.

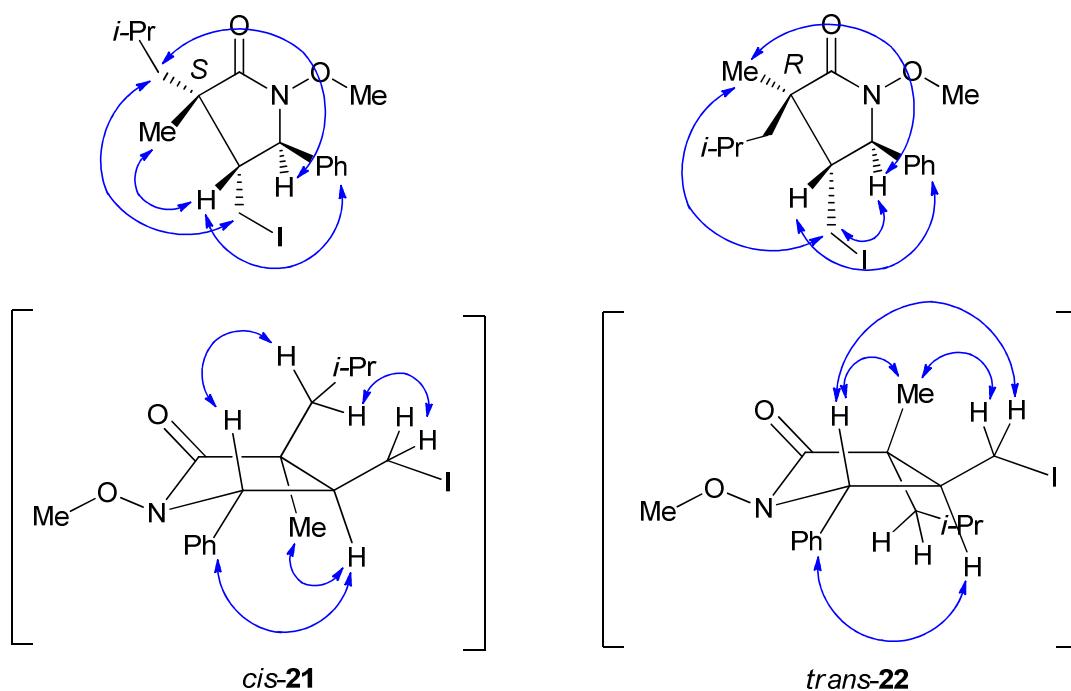
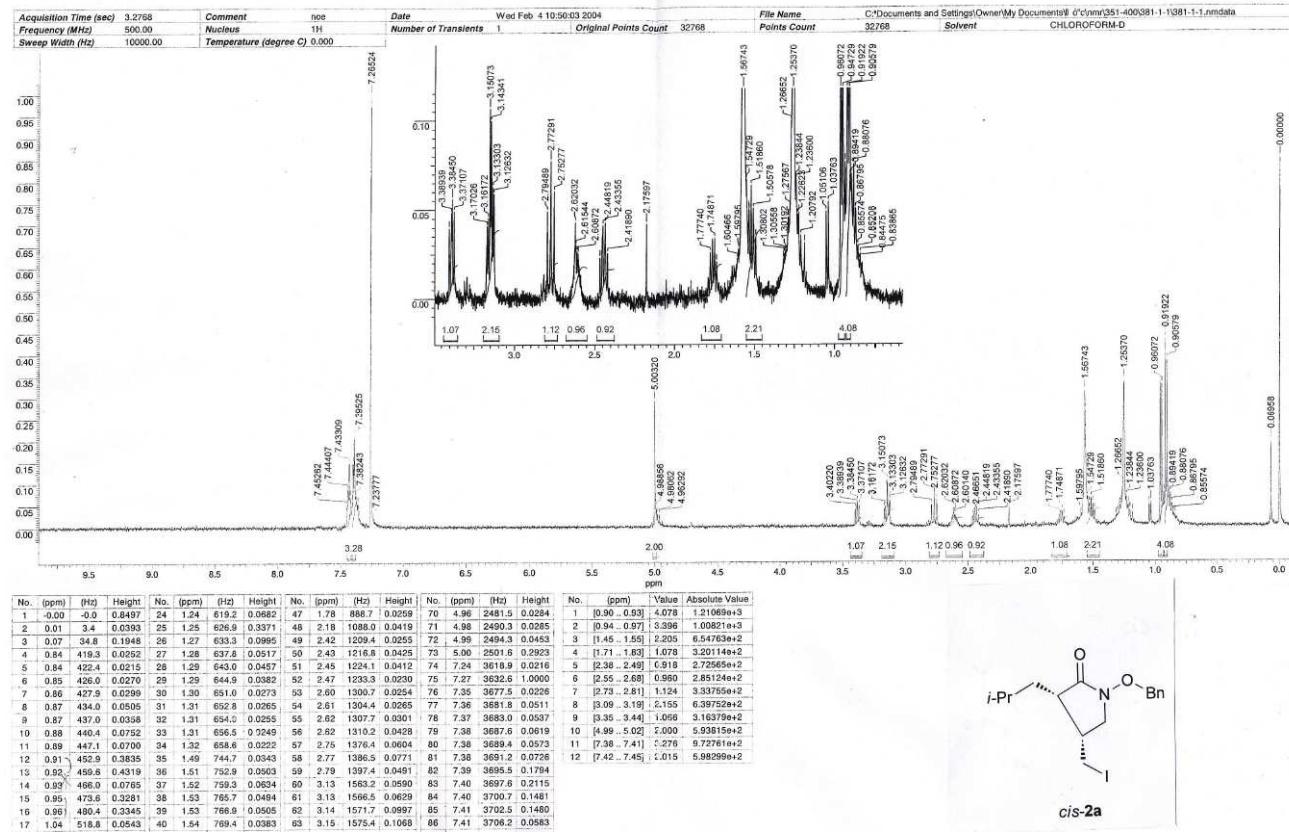


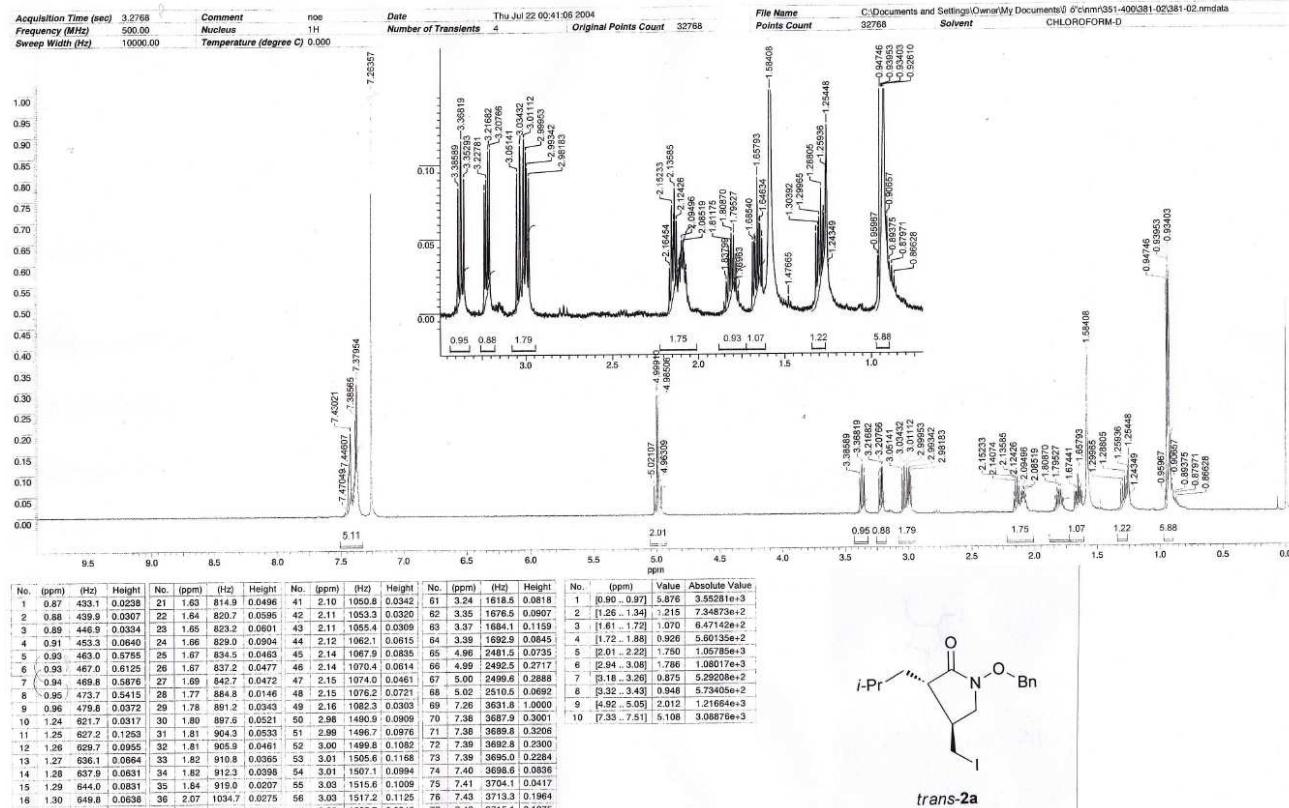
Fig. 2 NOESY study of *cis*-**21** and *trans*-**22**.

3. ^1H NMR of all obtained products

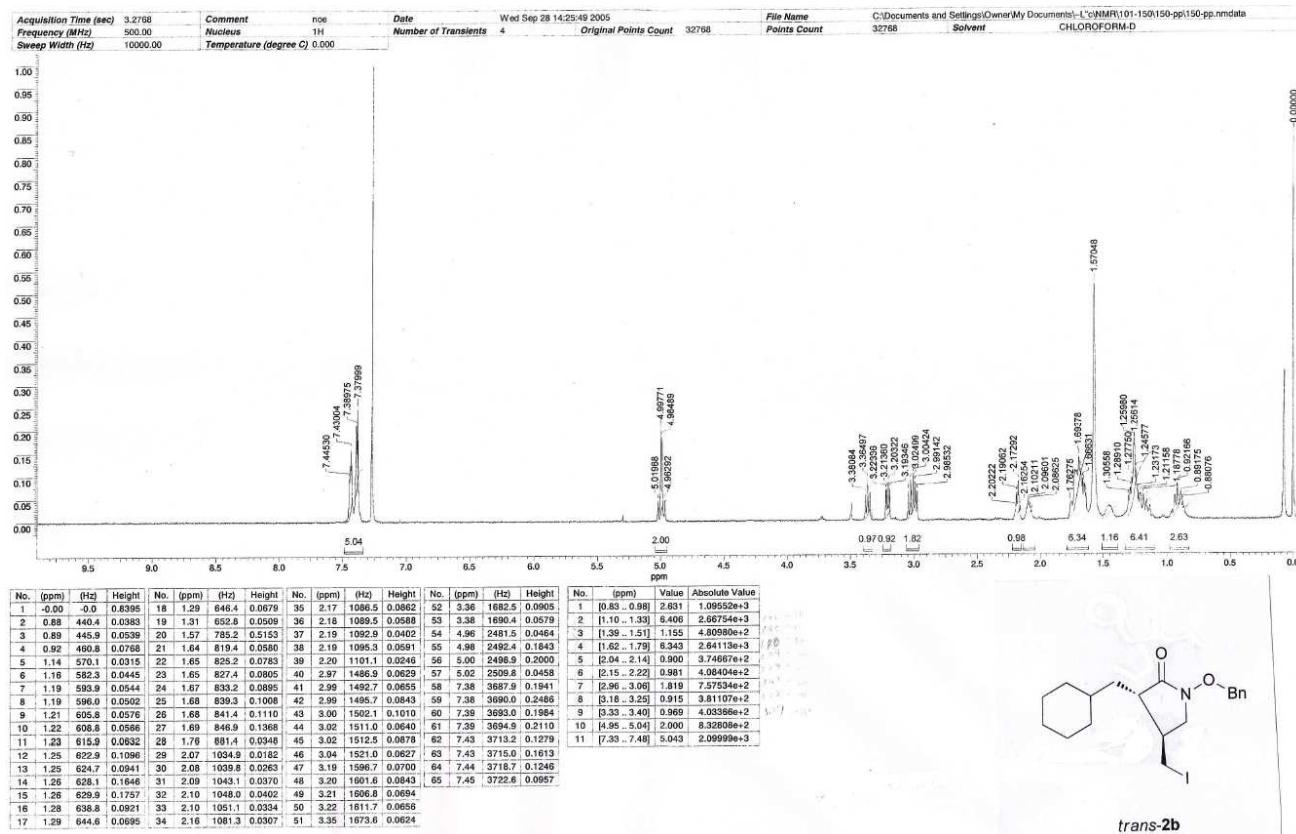
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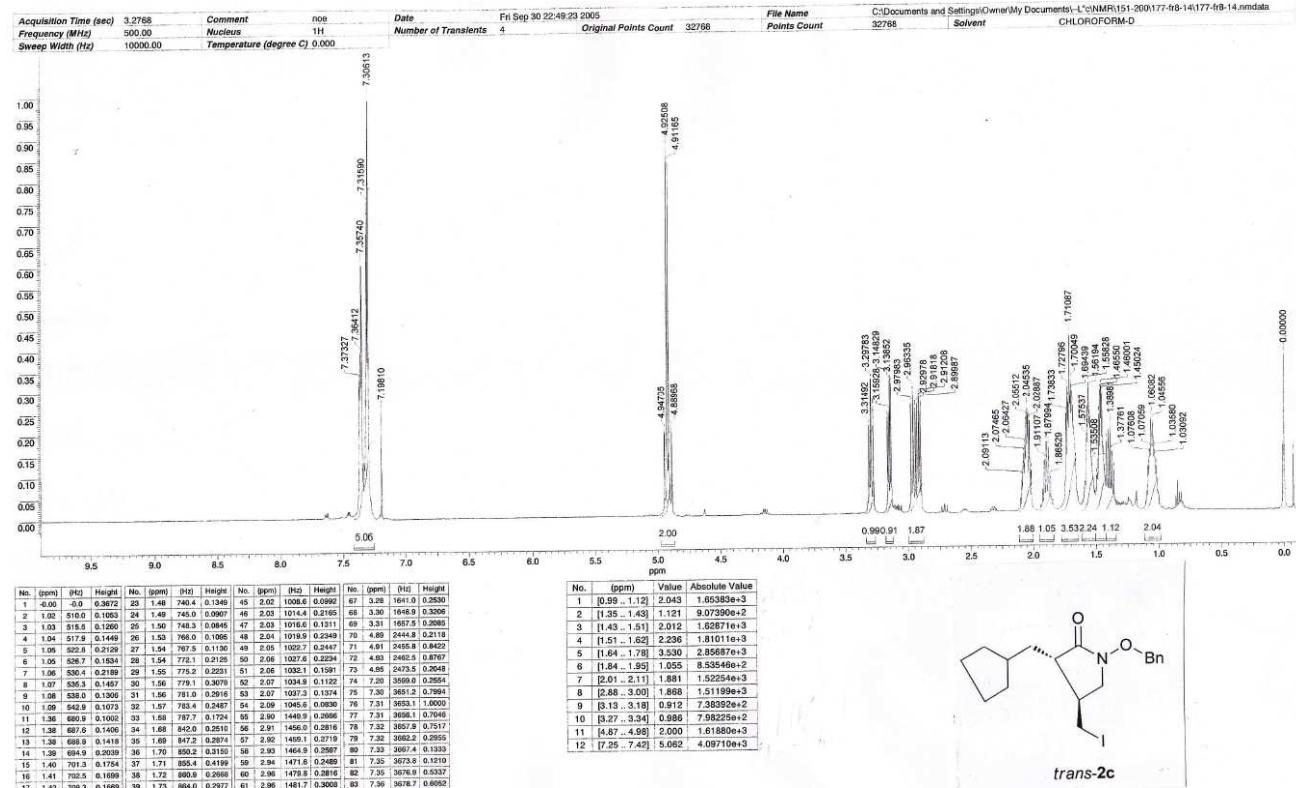
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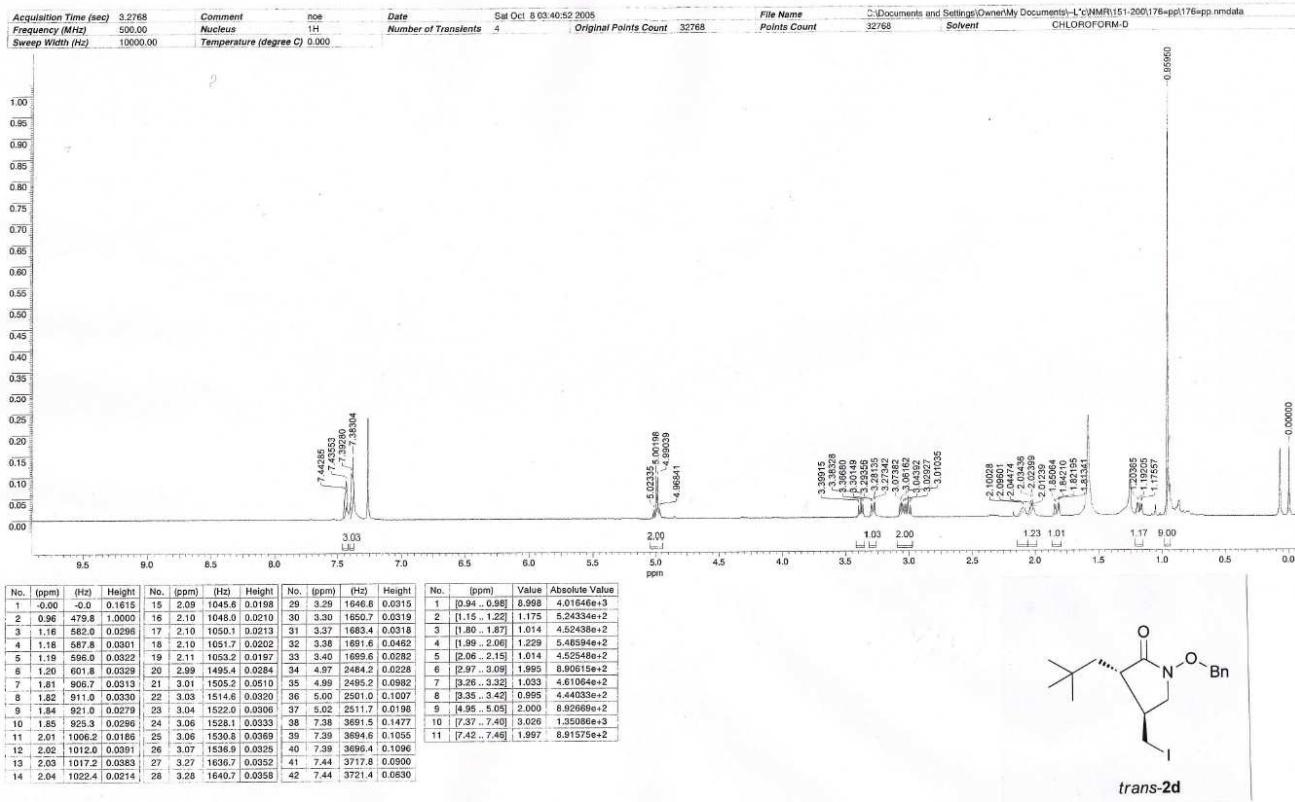
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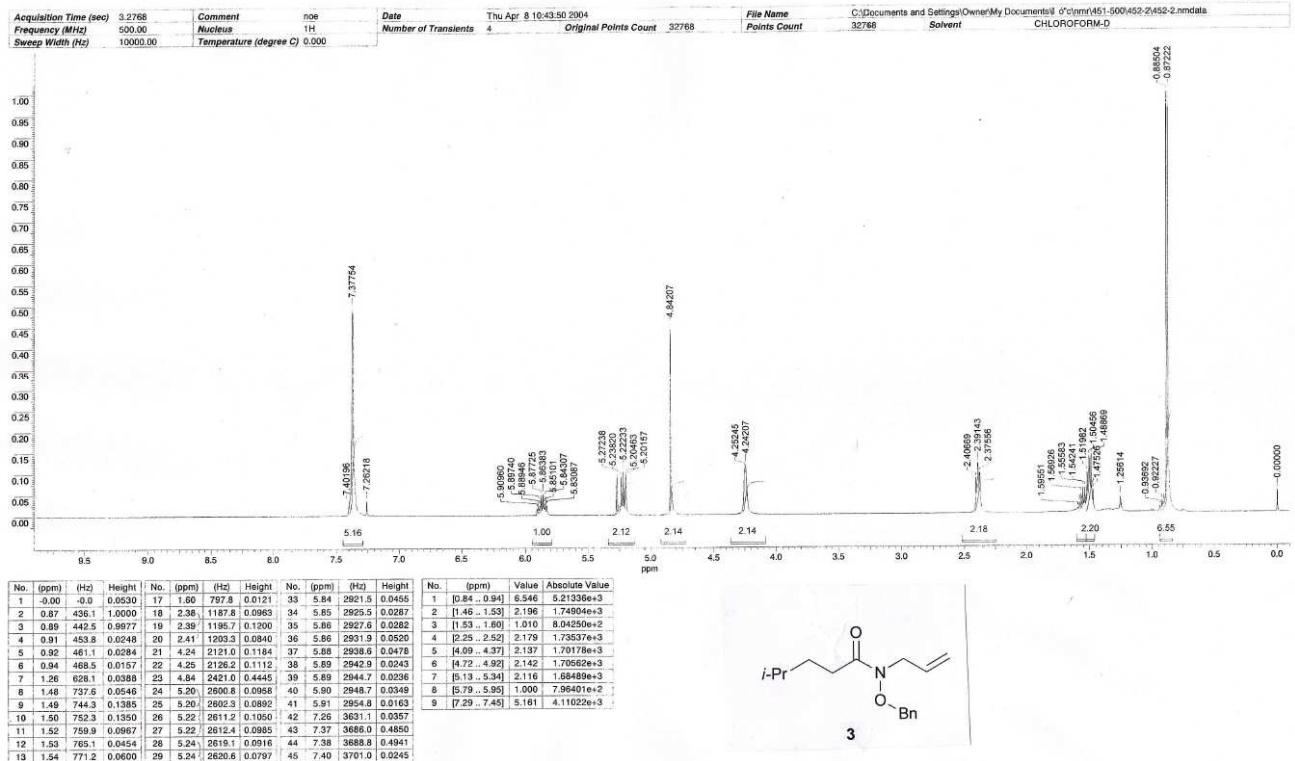
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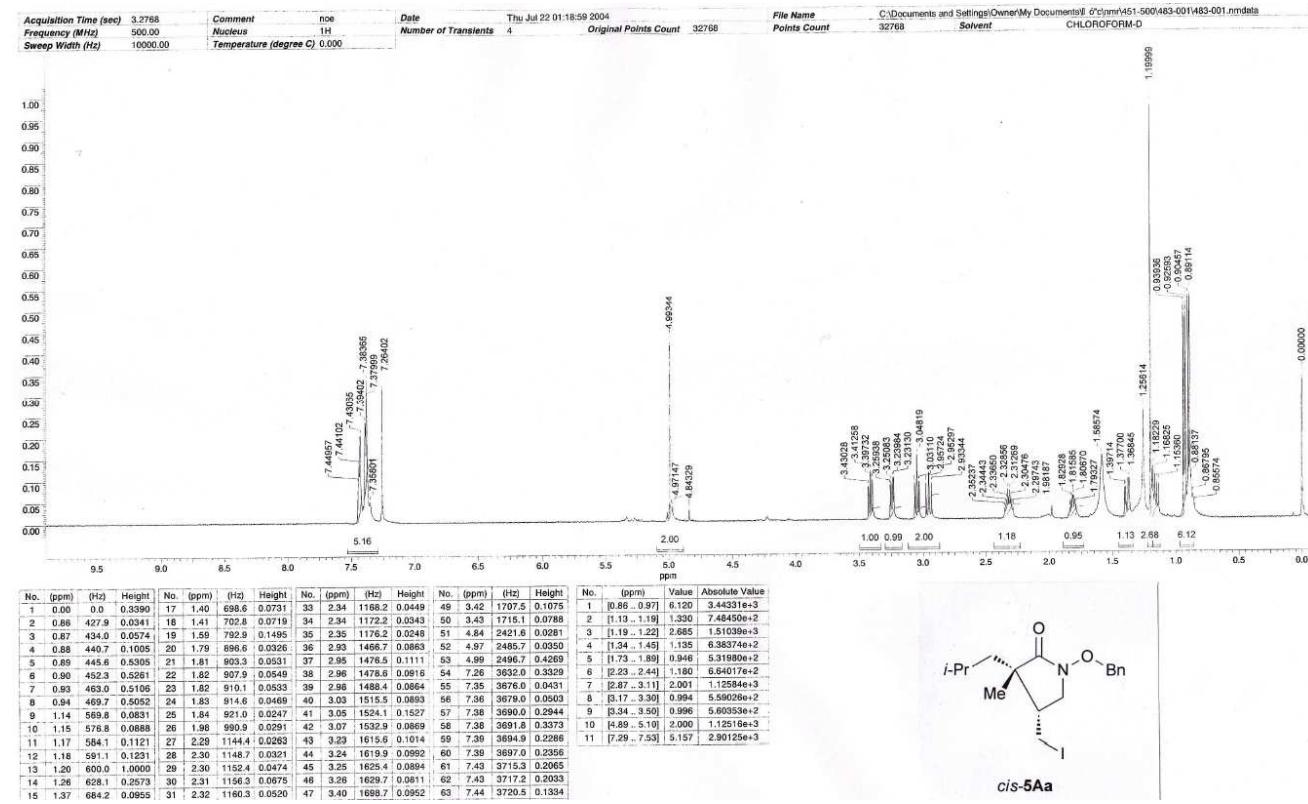
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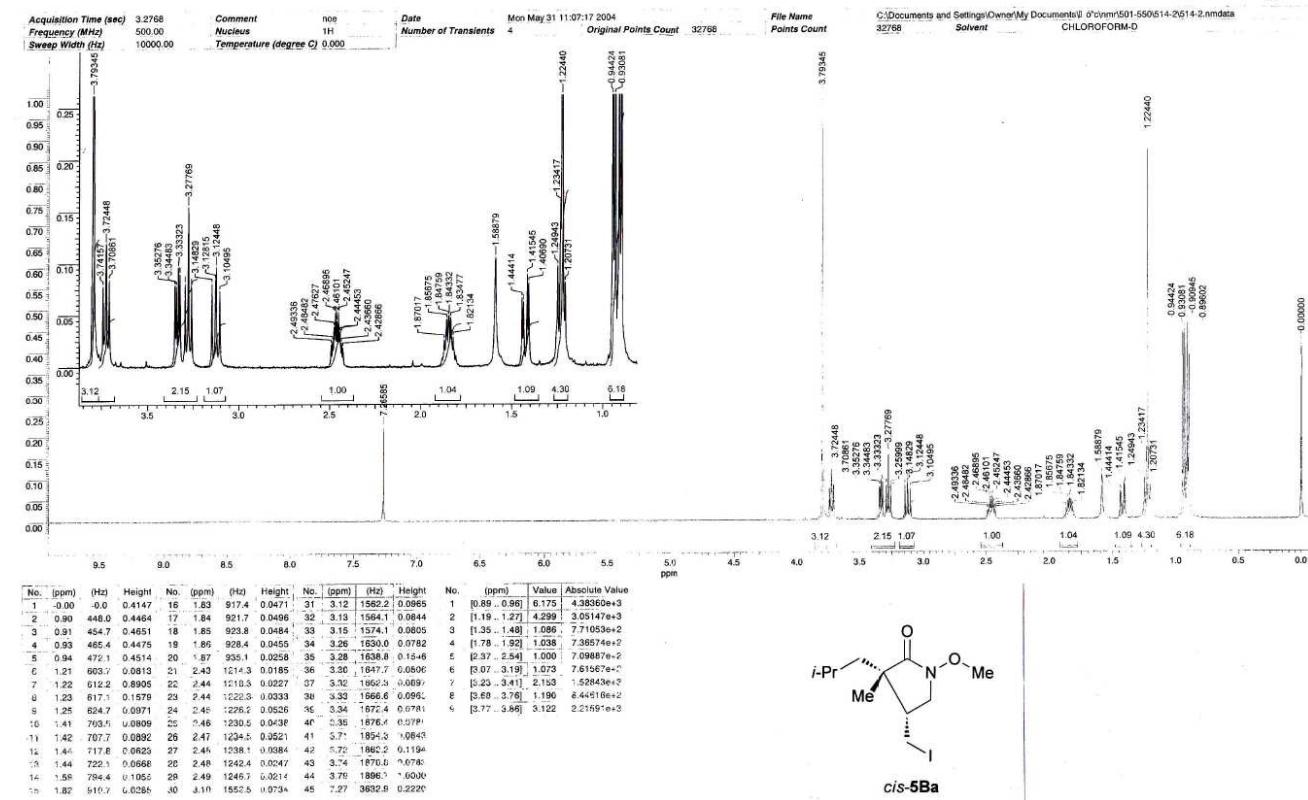
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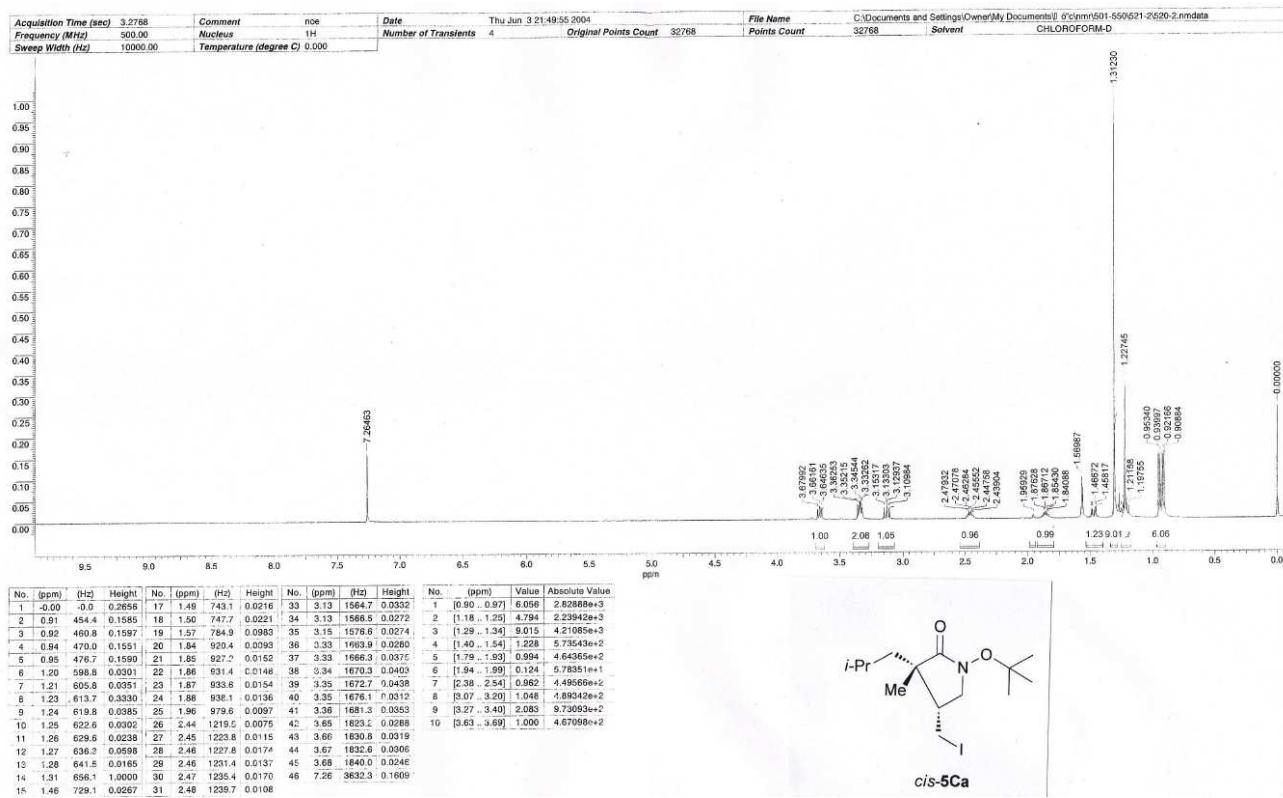
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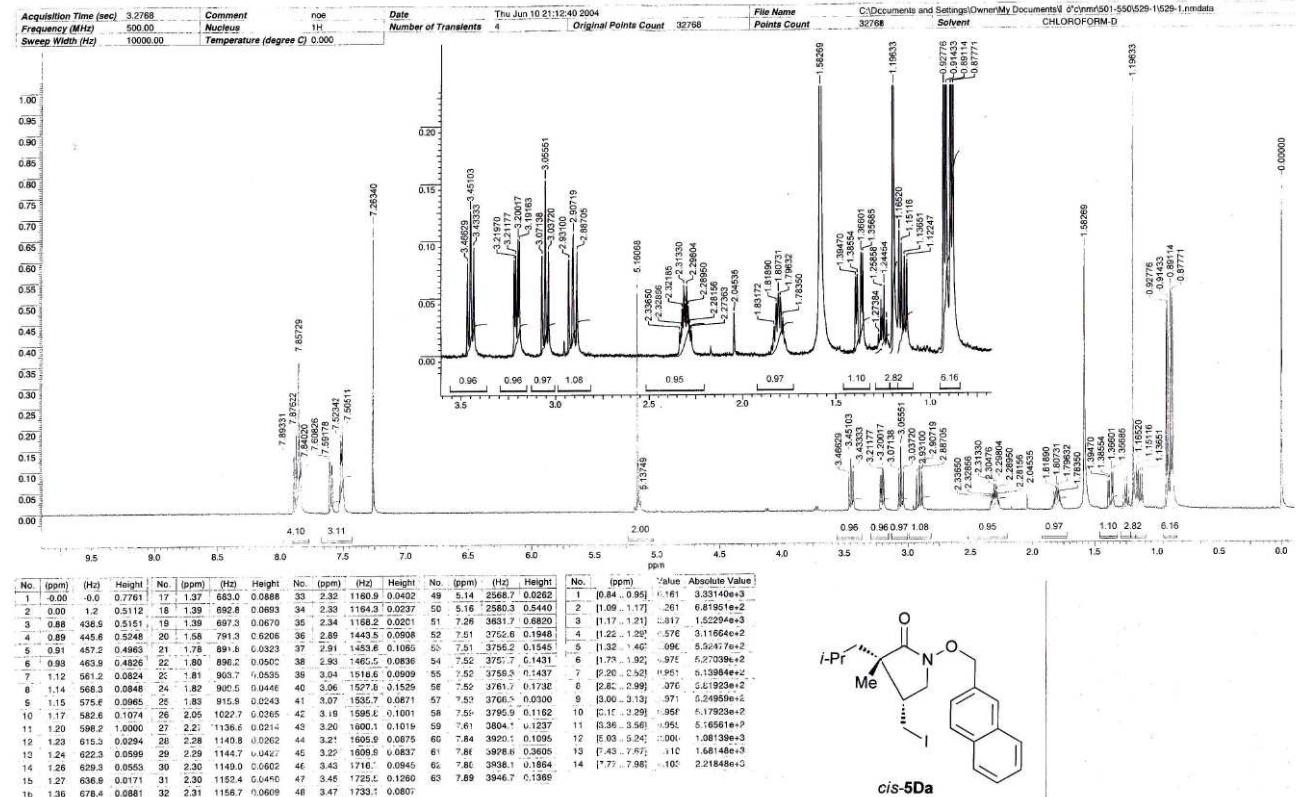
5Ba



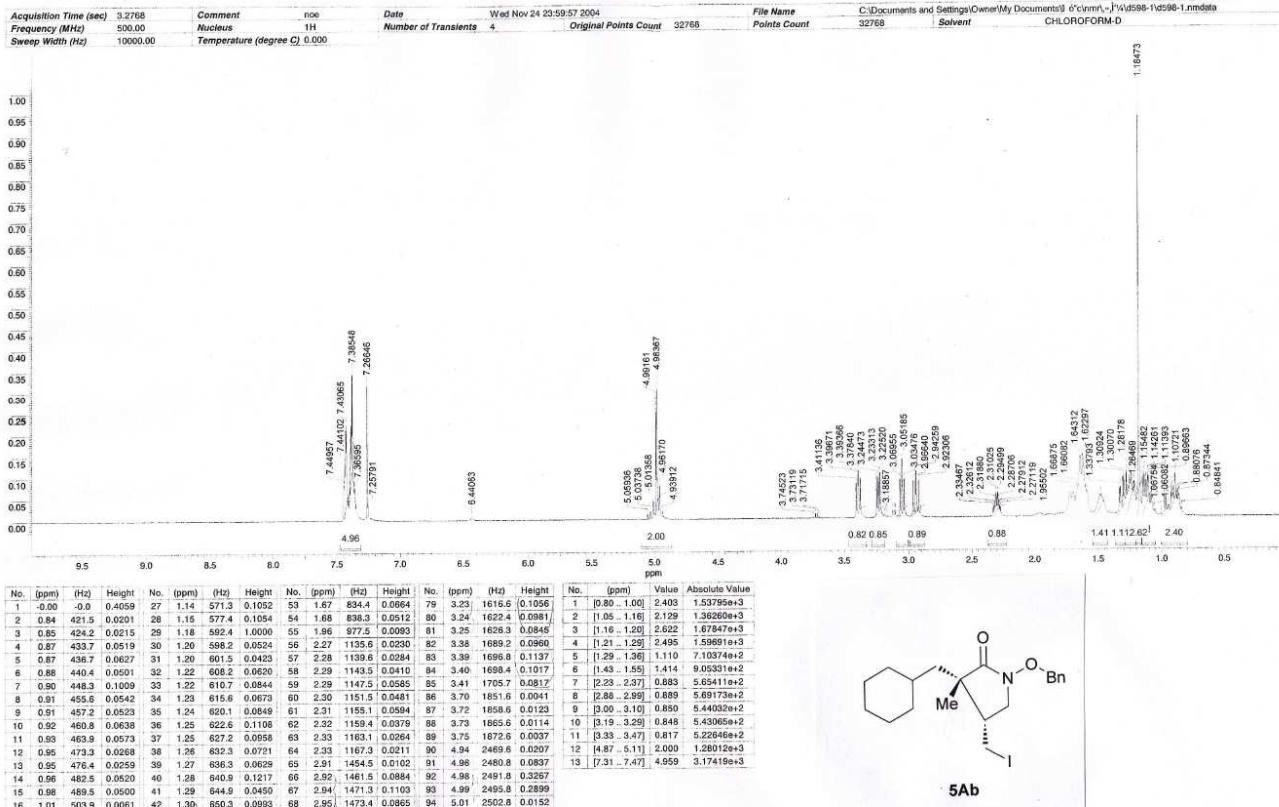
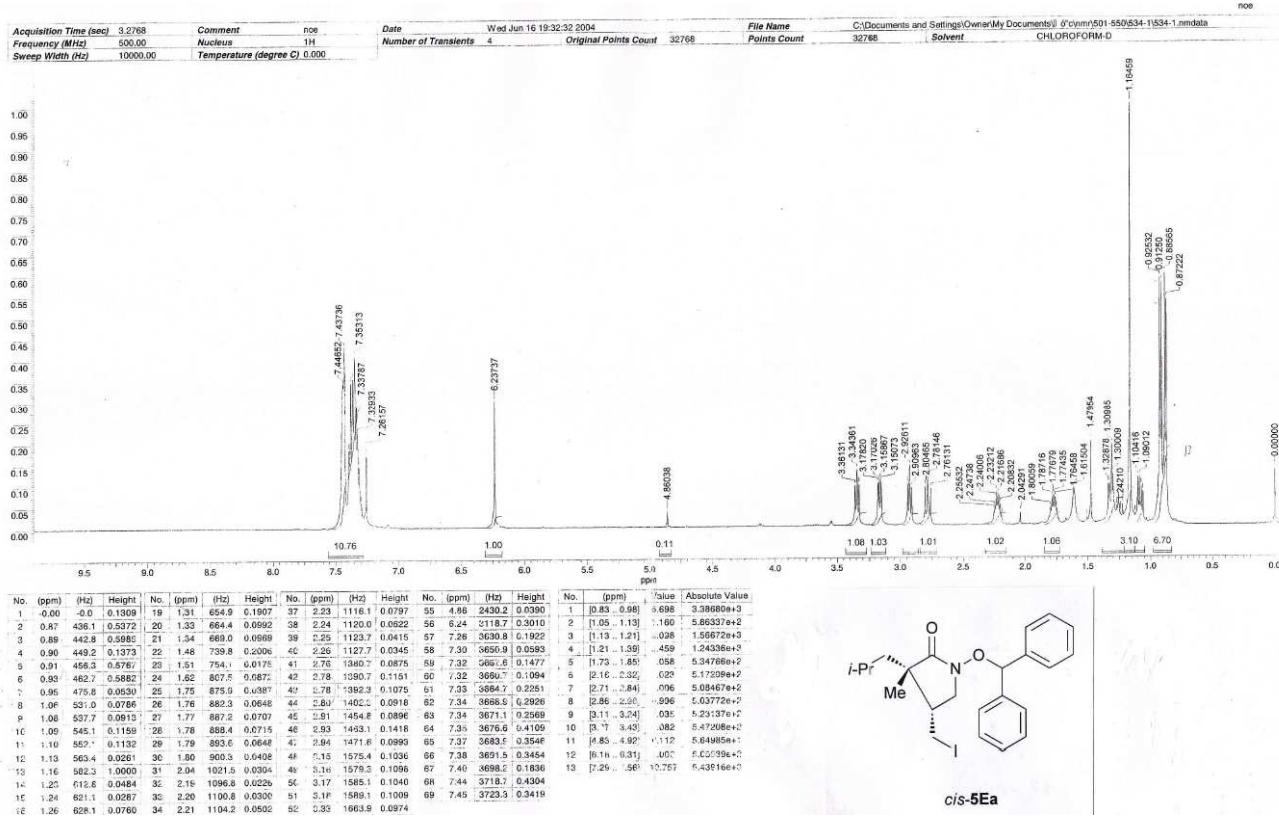
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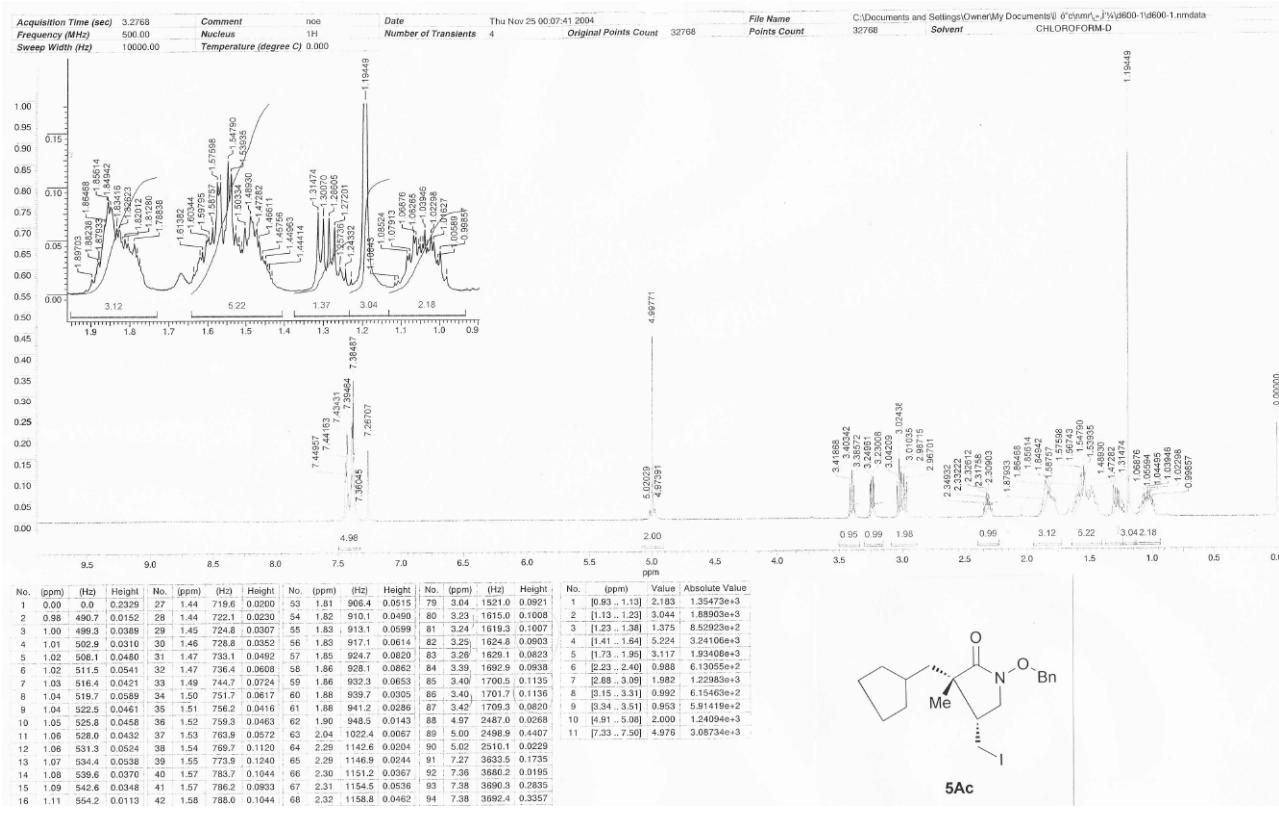
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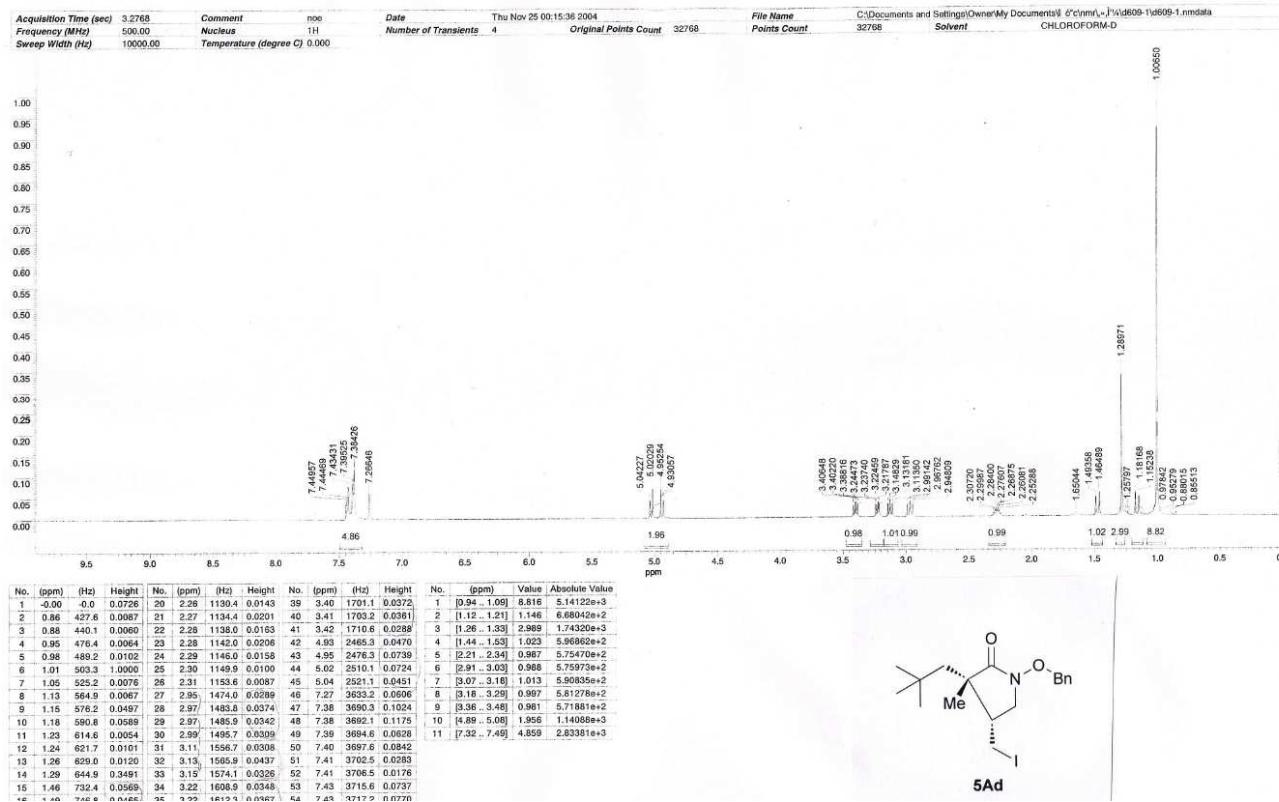
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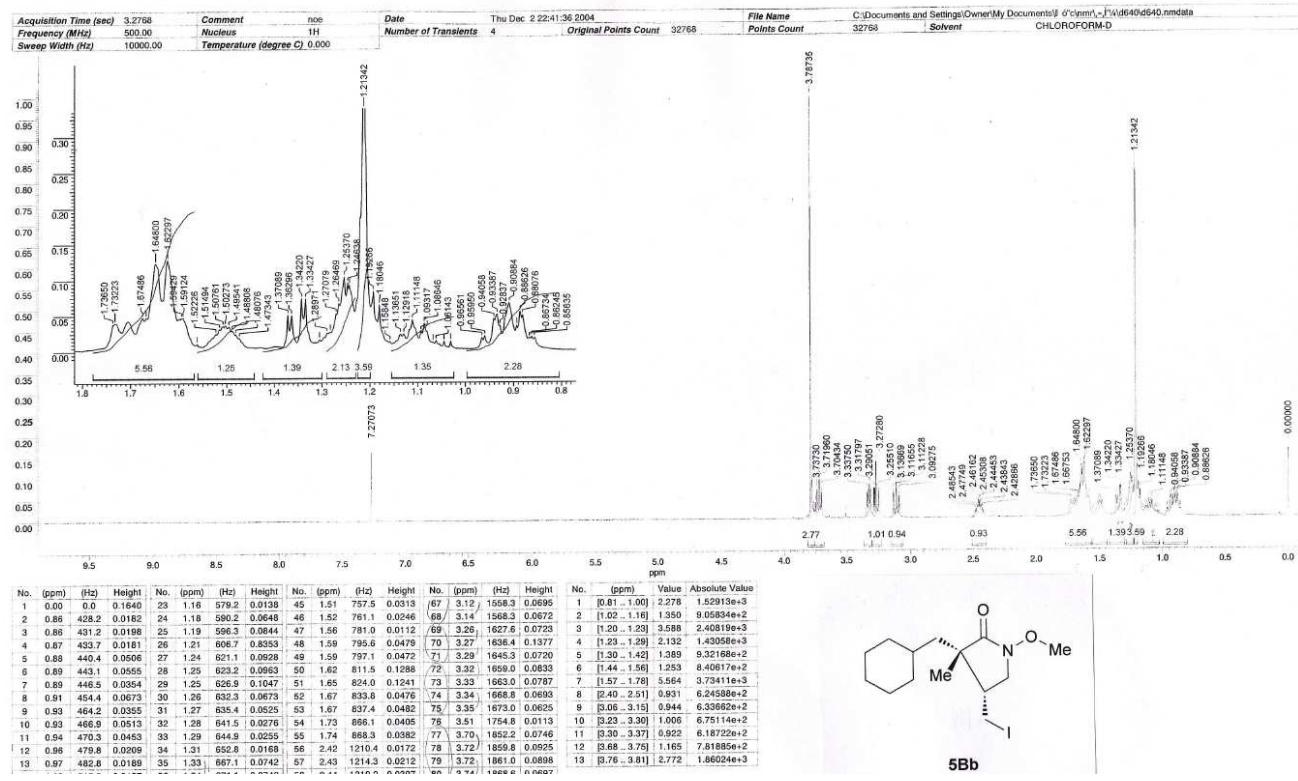
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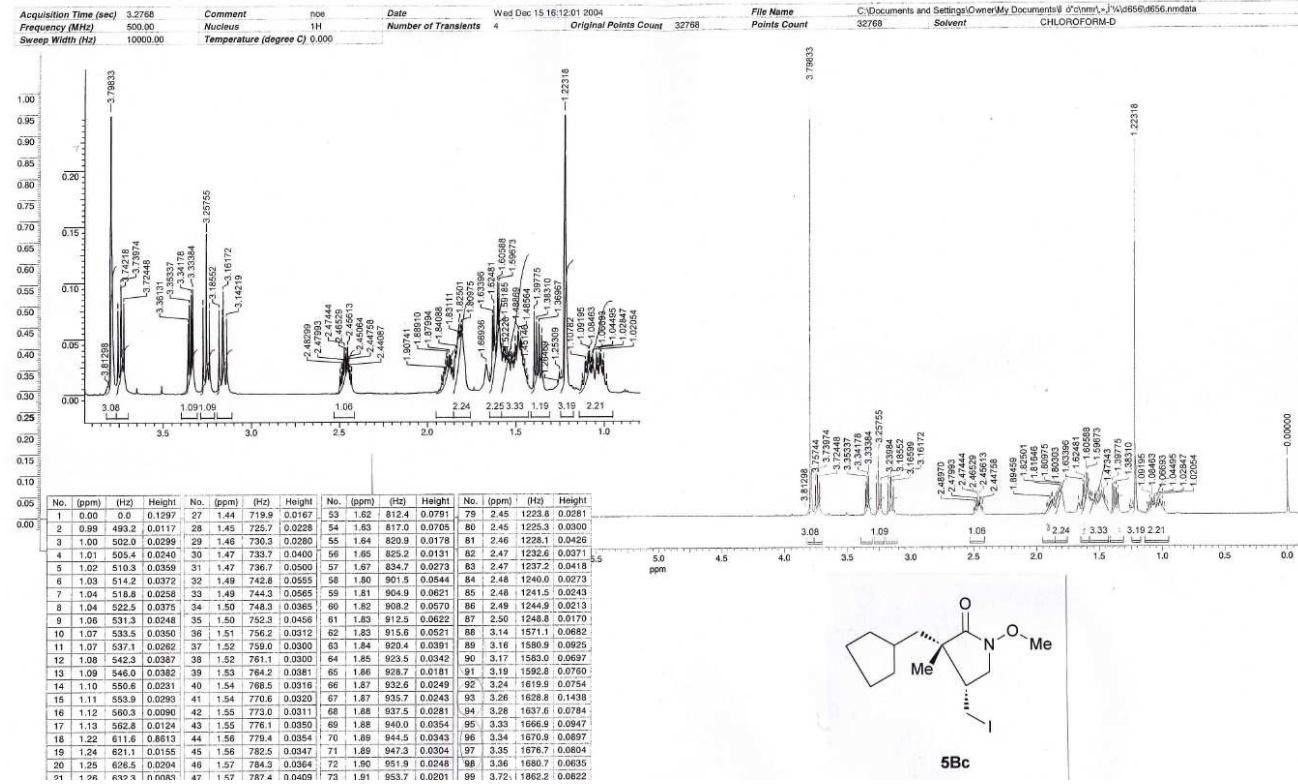
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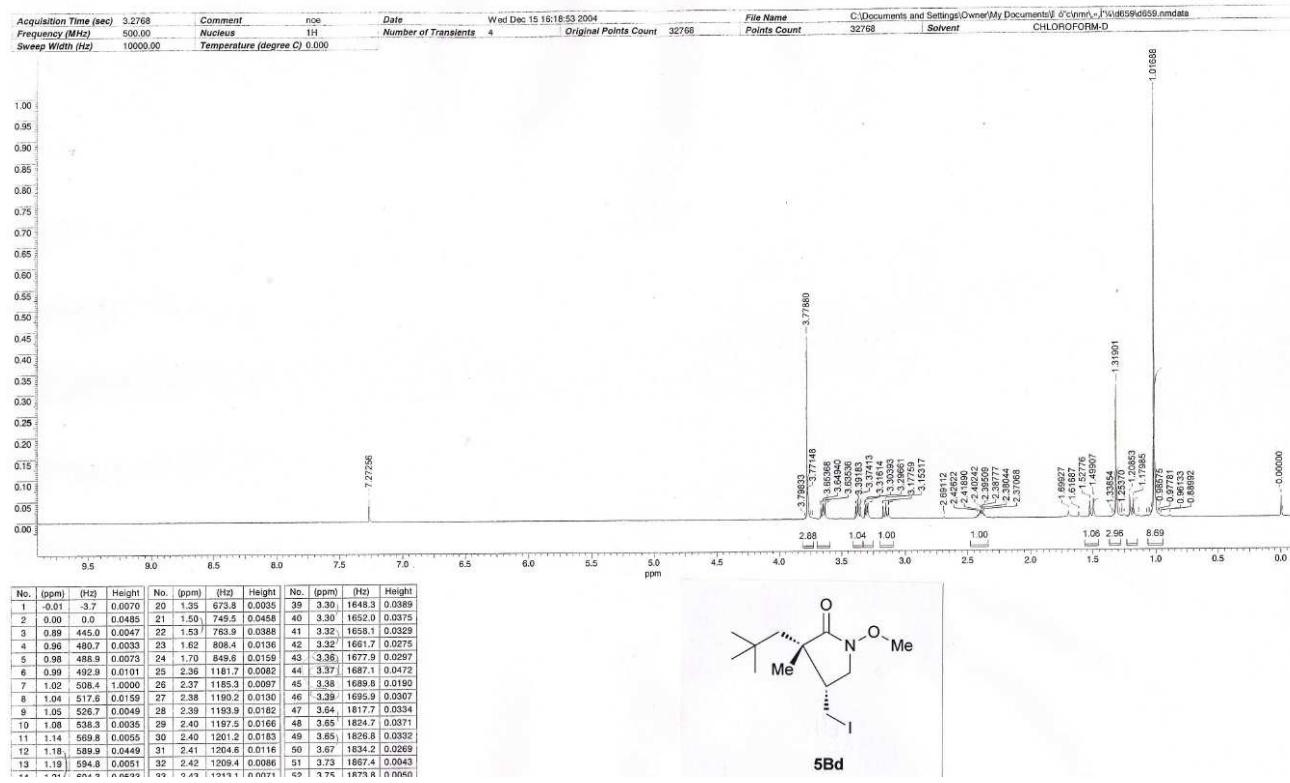
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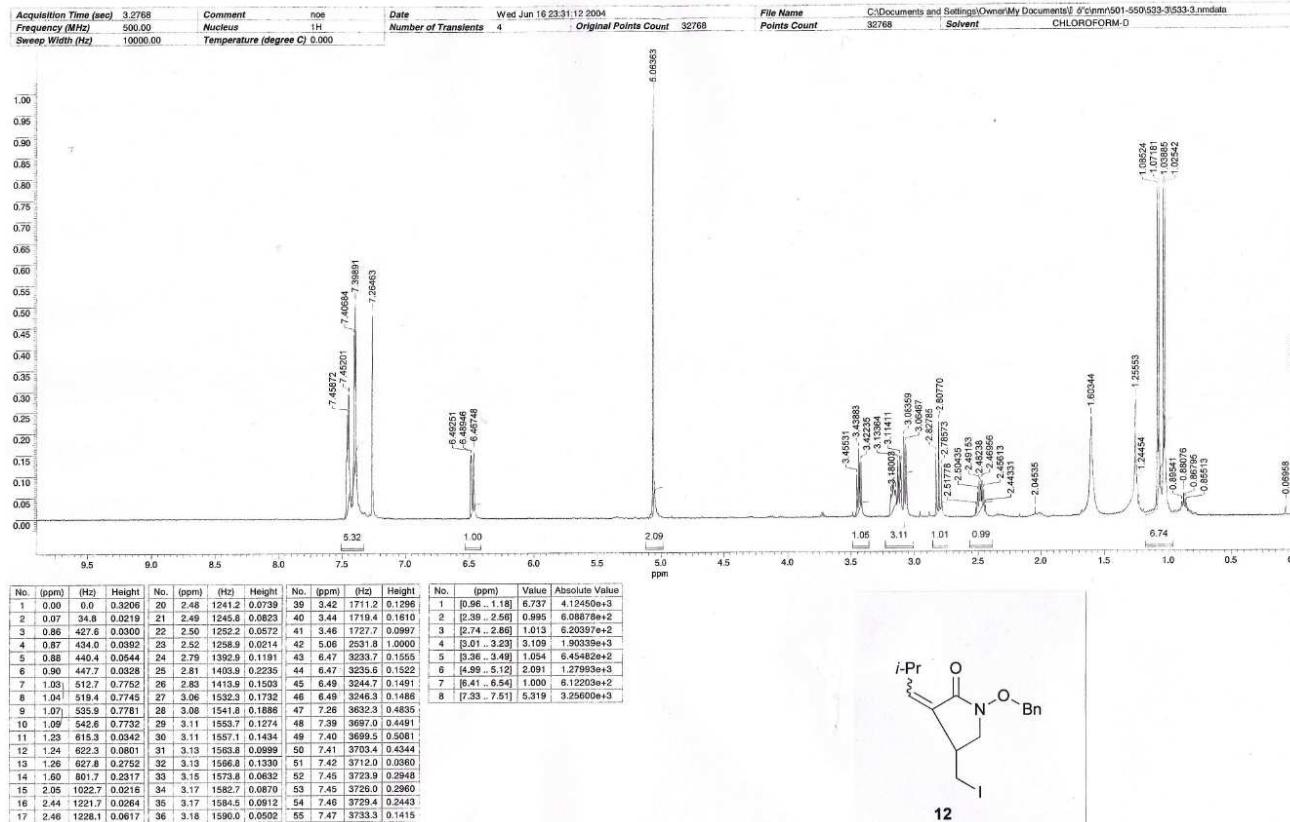
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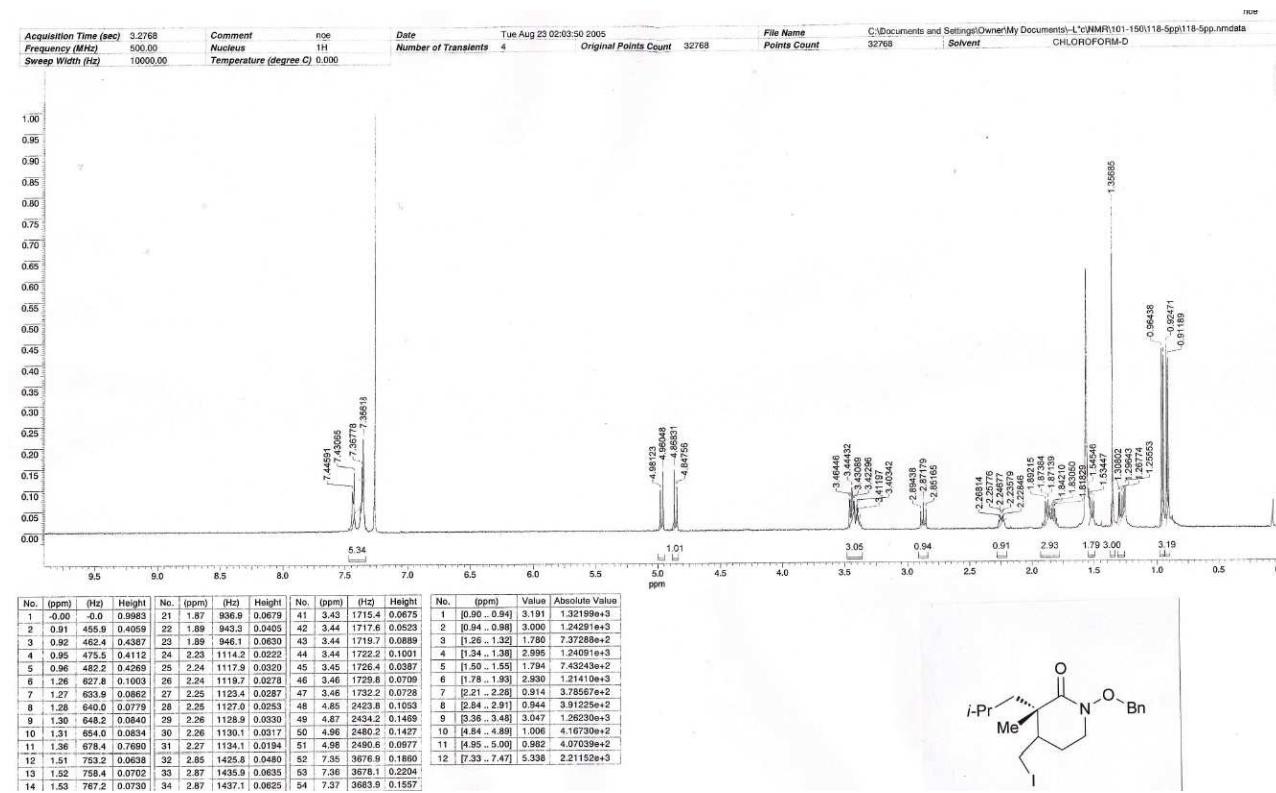
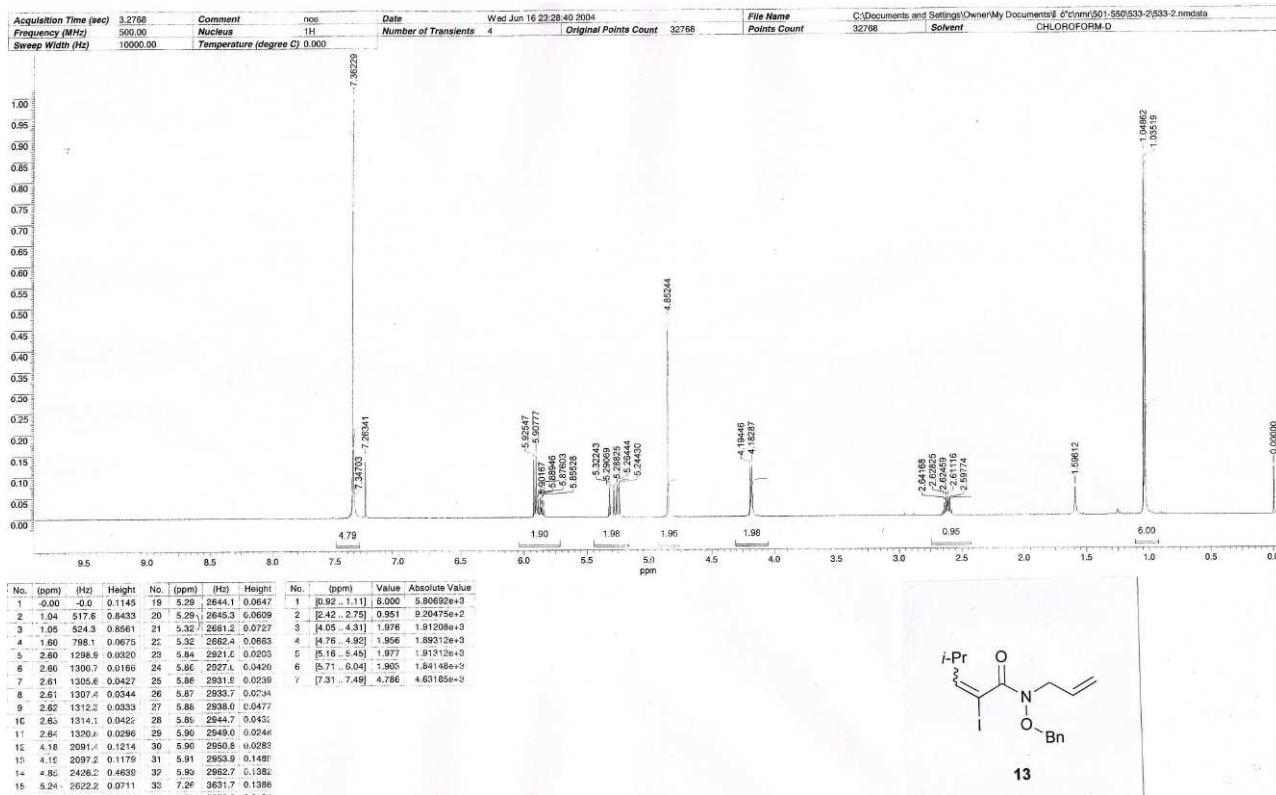
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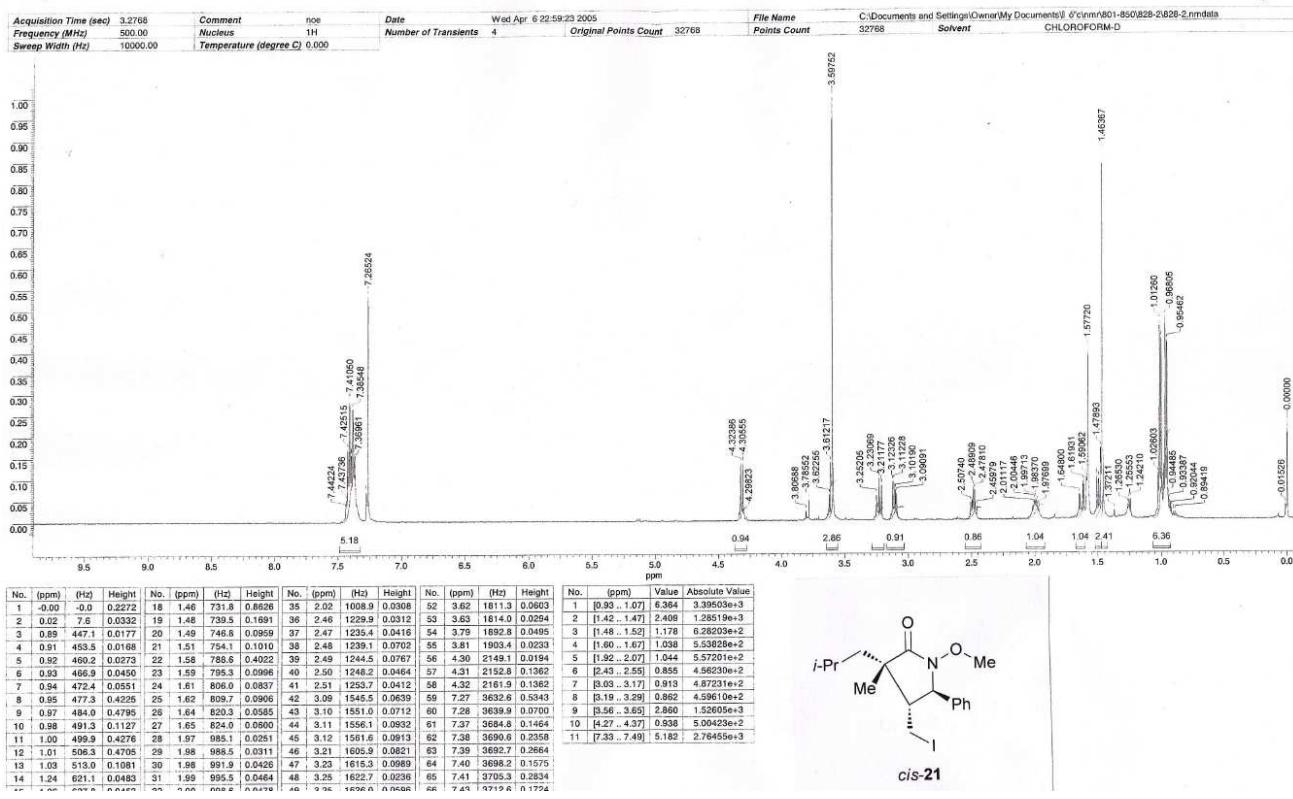
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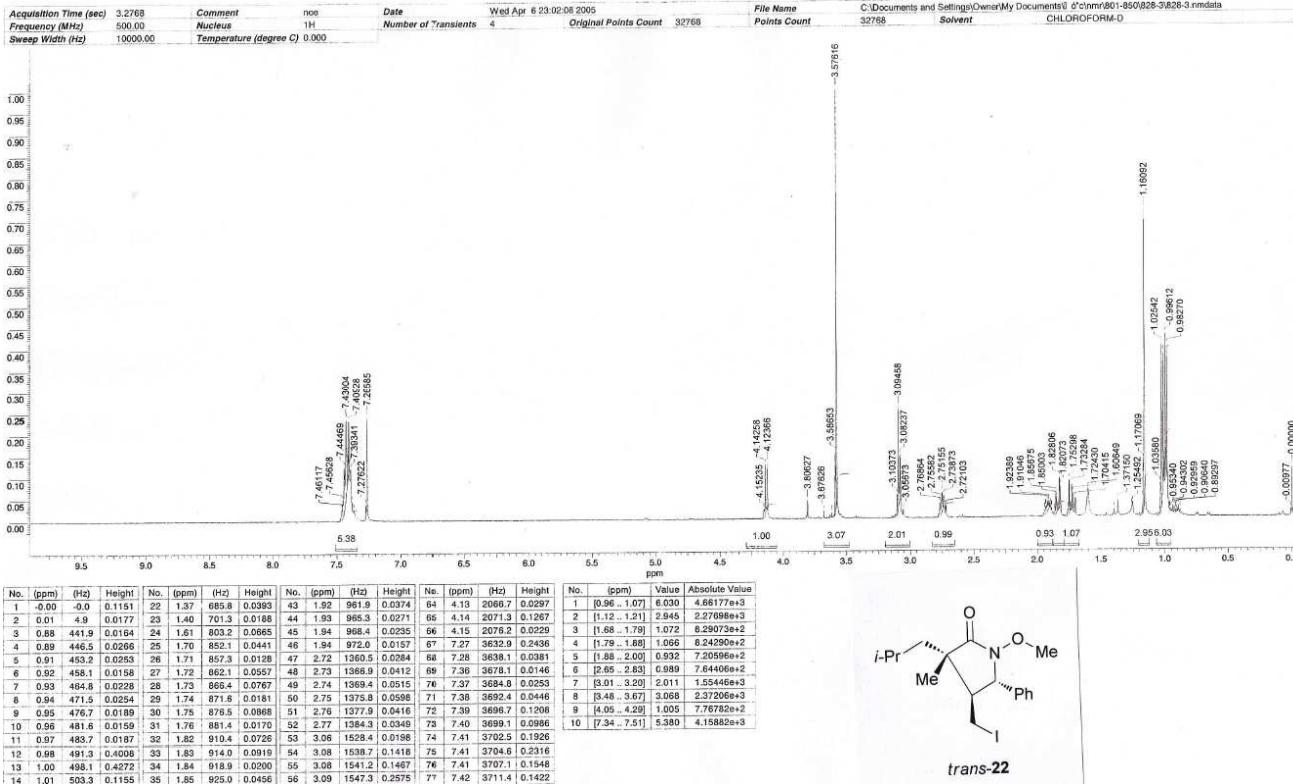
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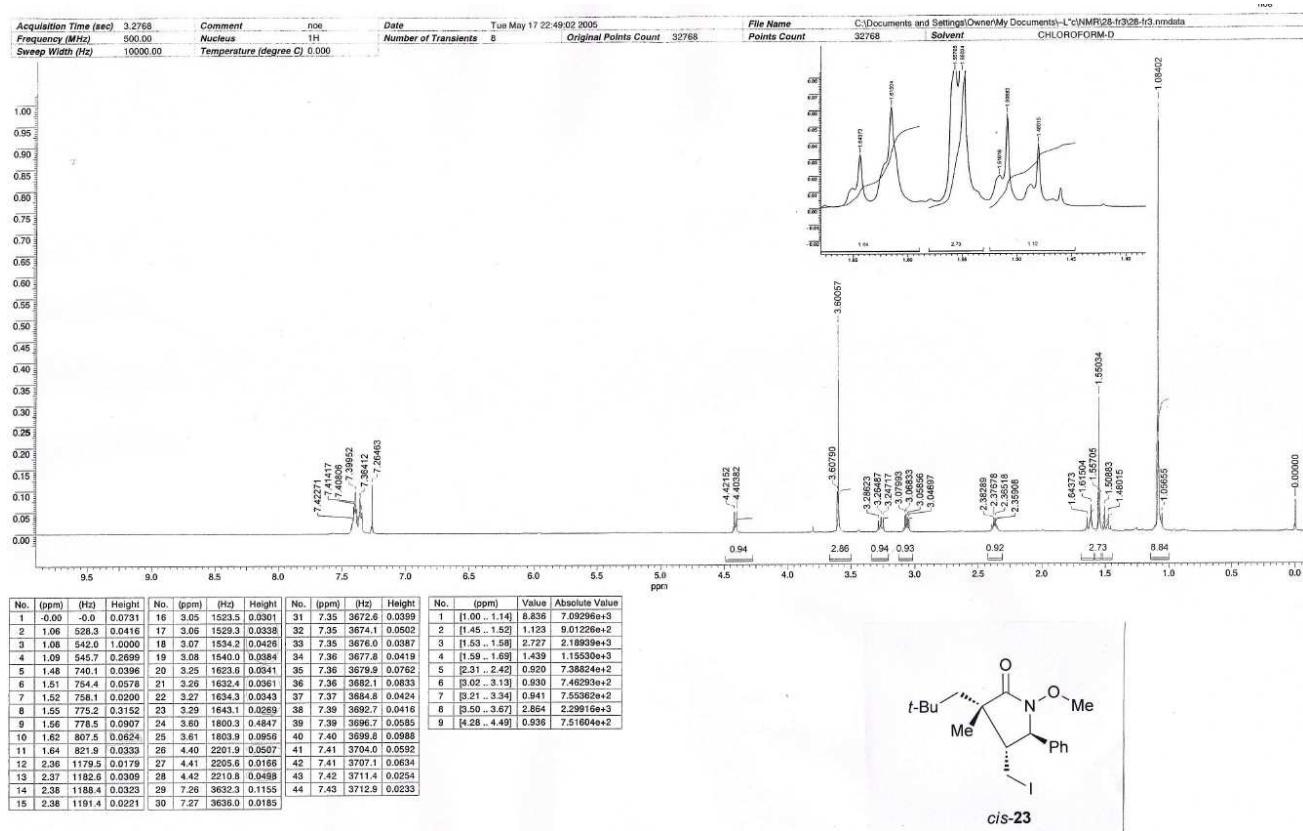
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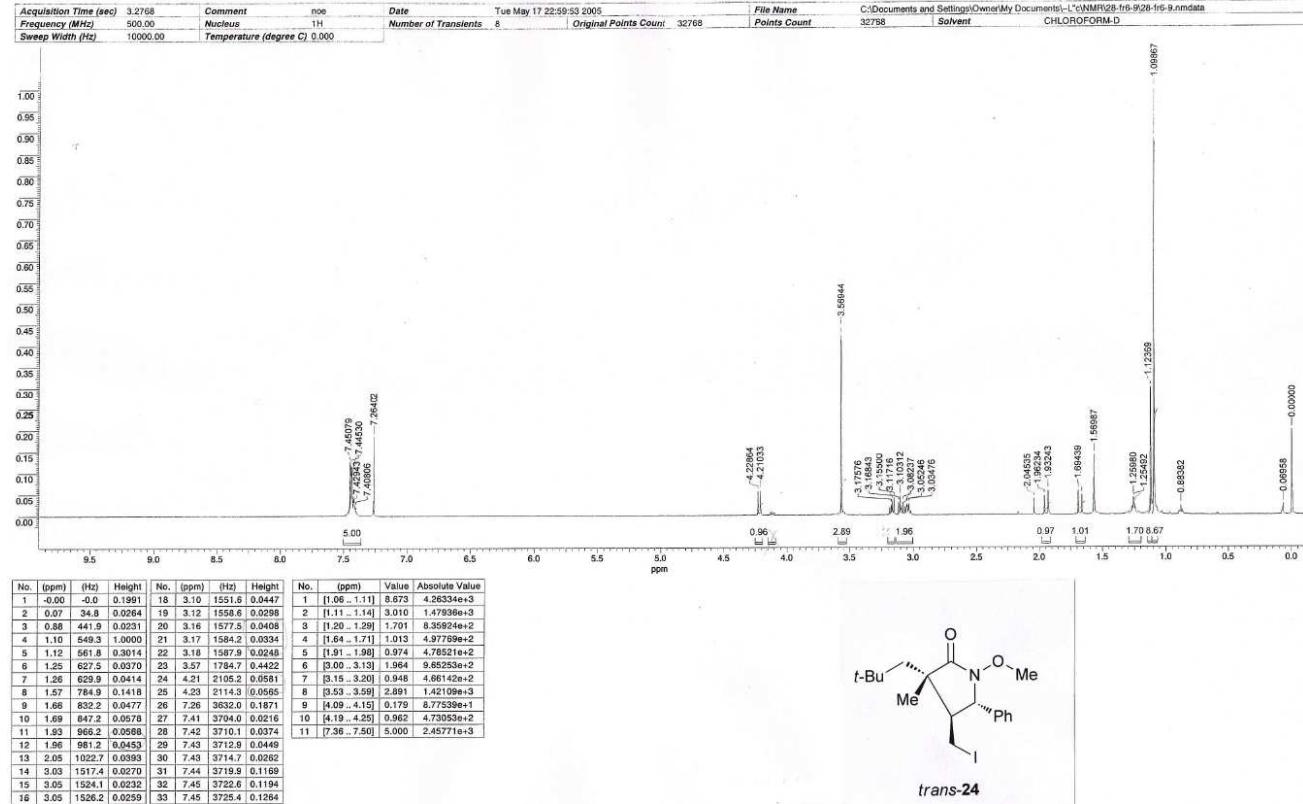
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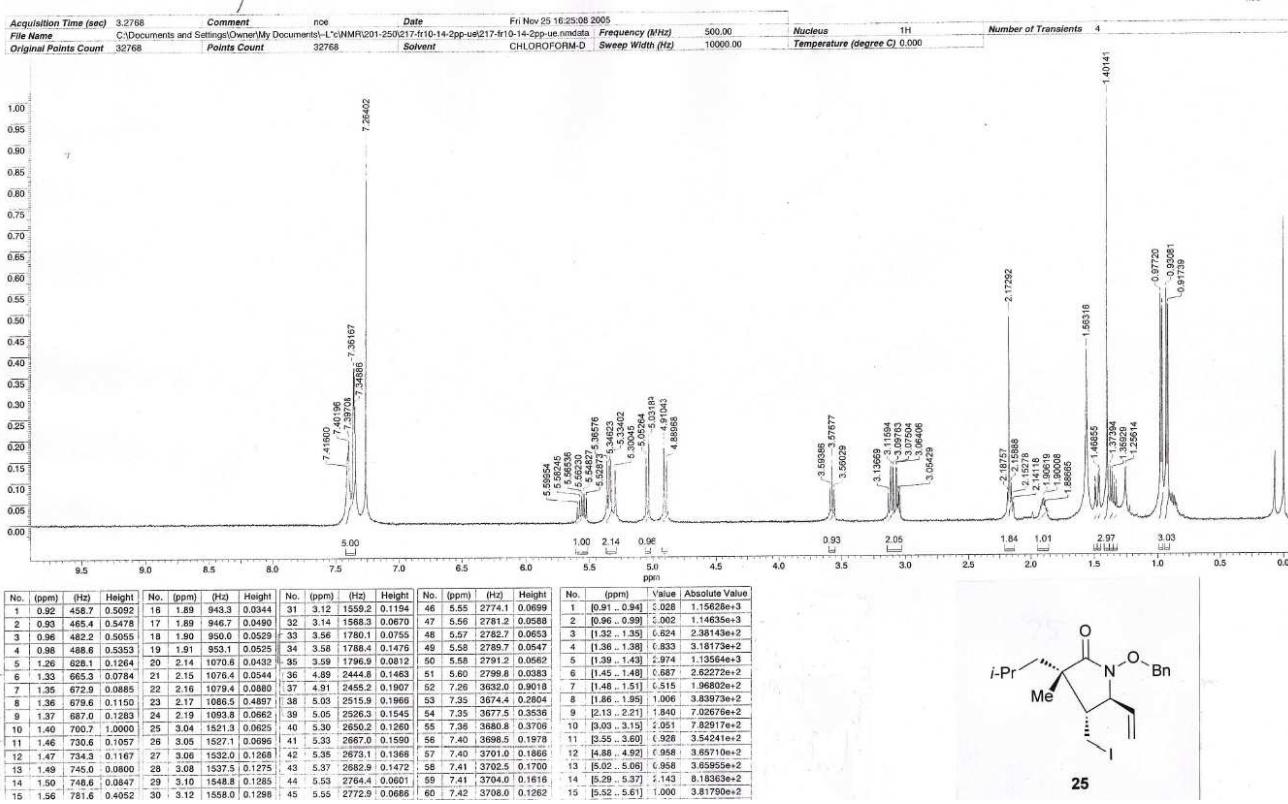


cis-23



trans-24





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