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A Novel Method to Access Chiral Nonnatural 2,4-Disubstituted Pyrrolidines from Aldehydes and Nitroolefins Only with *α*-Substituent

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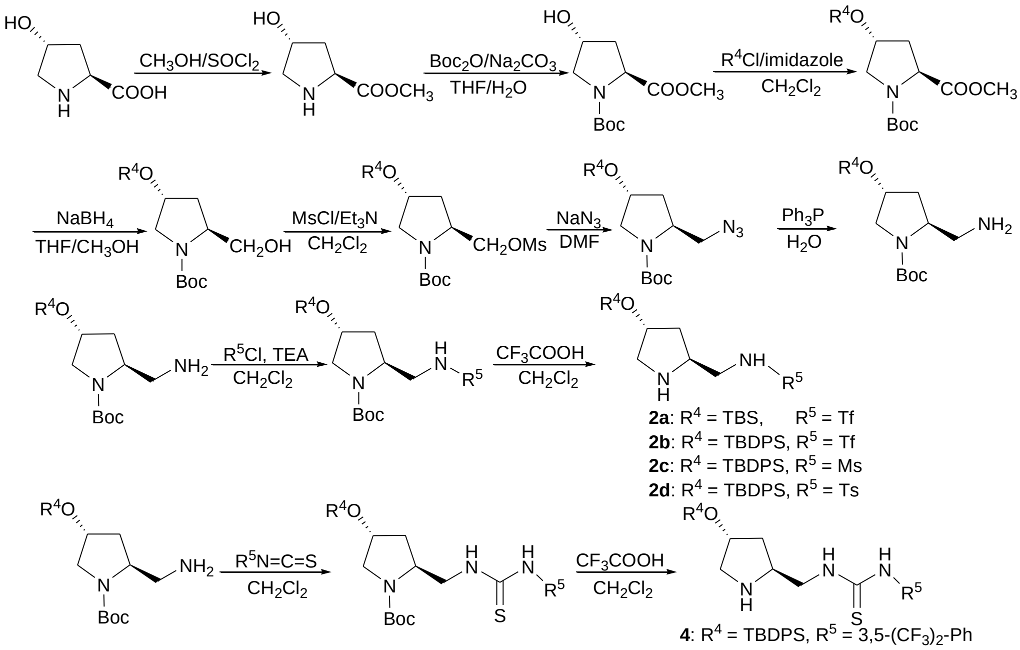
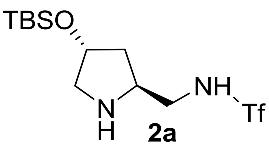
1. General Methods

All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial source were used without further purification. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was performed on silica gel H (10-40 μ). NMR spectra were recorded on 300 MHz and 500 MHz instruments. Chemical shifts (d) are given in ppm relative to TMS, coupling constants (*J*) in Hz. Optical rotations were measured on a Perkin Elmer 341 Polarimeter at λ = 589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column. ESI HRMS was recorded on a Bruker Apex-2.

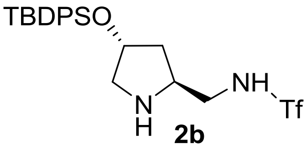
2. Synthesis of Chiral Catalysts

The synthesis of catalysts **1**, **3** from L-proline or (L)-4-hydroxy proline have been reported. [1, 2] The preparations of catalysts **2a-2d** and **4** were similar to catalyst **3**. Synthetic routine as follows:

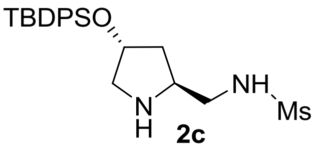




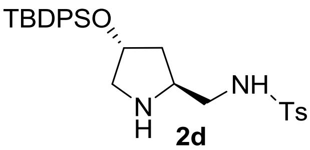
N-(((2*S*, 4*R*)-4-(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl)methyl)-1, 1, 1-trifluoro methanesulfonamide (2a): white solid, mp 144.3–146.5 °C; $[\alpha]_D^{20}$ = +20.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 2H), 4.52 (s, 1H), 4.13–3.78 (m, 1H), 3.47 (dd, *J* = 11.2, 6.8 Hz, 2H), 3.36–3.19 (m, 1H), 3.12 (d, *J* = 12.2 Hz, 1H), 1.95 (dd, *J* = 13.0, 5.8 Hz, 1H), 1.74 (dd, *J* = 16.9, 6.6 Hz, 1H), 0.87 (s, 9H), 0.03 (d, *J* = 20.8 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 123.4, 119.1, 77.4, 77.0, 76.6, 71.0, 60.7, 53.4, 46.6, 38.0, 25.5, 17.8, -5.0 ppm; HRMS (ESI-TOF) calcd. for $C_{12}H_{25}F_3N_2O_3SSi$ $[M+H]^+$ 363.1385, found 363.1384.


2b

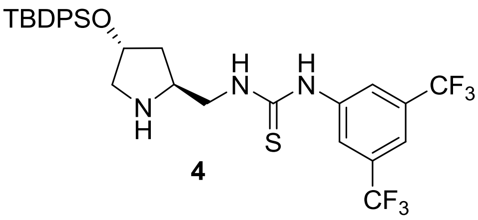
N-(((2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-yl)methyl)-1, 1, 1-trifluoro methanesulfonamide (2b): white solid, mp 148.8–150.3 °C; $[\alpha]_D^{20}$ = +16.2° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.30 (m, 1H), 6.98 (s, 1H), 4.59–4.39 (m, 1H), 4.02 (dd, J = 17.2, 11.3 Hz, 1H), 3.47–3.05 (m, 1H), 1.92 (dt, J = 16.1, 8.1 Hz, 1H), 1.51 (dt, J = 32.6, 11.4 Hz, 1H), 1.06 (s, 9H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.6, 132.9, 130.1, 127.9, 72.6, 60.3, 53.3, 47.0, 37.8, 26.8, 18.9 ppm; HRMS(ESI-TOF) calcd. for $C_{22}H_{29}F_3N_2O_3SSi$ $[M+H]^+$ 487.1698, found 487.1694.


2c

N-(((2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-yl)methyl)methanesulfonam ide (2c): white solid, mp 146.5–148.0 °C; $[\alpha]_D^{20}$ = +11.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.30 (m, 10H), 4.43 (s, 1H), 3.78 (ddd, J = 19.1, 10.3, 5.8 Hz, 2H), 3.28 (dd, J = 13.1, 3.6 Hz, 1H), 3.05–2.95 (m, 2H), 2.94 (s, 3H), 2.88 (dd, J = 12.2, 3.7 Hz, 1H), 1.99–1.78 (m, 2H), 1.53 (ddd, J = 13.7, 9.1, 4.8 Hz, 1H), 1.06 (s, 9H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.6, 133.4, 129.9, 127.8, 73.7, 68.0, 57.4, 54.3, 45.9, 40.0, 38.3, 26.8, 25.6, 19.0 ppm; HRMS(ESI-TOF) calcd. for $C_{22}H_{32}N_2O_3SSi$ $[M+H]^+$ 433.1981, found 433.1983.


2d

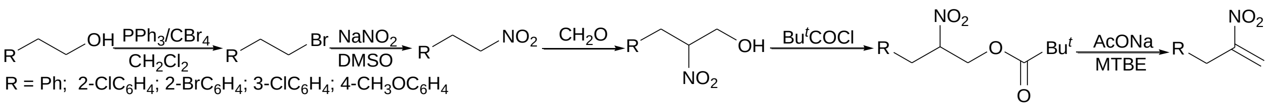
N-(((2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-yl)methyl)-4-methylbenzenes ulfonamide (2d): white solid, mp 92.0–93.5 °C; $[\alpha]_D^{20}$ = +5.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.63–7.30 (m, 10H), 7.23 (d, J = 5.9 Hz, 2H), 4.48 (s, 1H), 4.21 (s, 1H), 3.41–3.02 (m, 4H), 2.38 (d, J = 11.6 Hz, 3H), 2.05–1.69 (m, 4H), 1.03 (s, 9H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.5, 136.5, 135.6, 132.7, 132.5, 130.1, 129.7, 127.9, 127.0, 71.6, 59.0, 53.5, 43.2, 37.3, 26.7, 21.5, 18.9 ppm; HRMS (ESI-TOF) calcd. for $C_{28}H_{36}N_2O_3SSi$ $[M+H]^+$ 509.2294, found 509.2291.

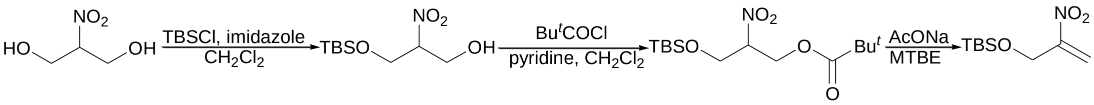

4

1-(3,5-bis(trifluoromethyl)phenyl)-3-(((2*S*,4*R*)-4-(*tert*-butyldiphenylsil yloxy)pyrrolidin-2-yl)methyl)thiourea 4: white solid, mp 85.7–84.8 °C; $[\alpha]_D^{20}$ = +11.6° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.84–7.28 (m, 11H), 4.47 (s, 1H), 4.04–3.70 (m, 1H), 3.43 (d, J = 11.0 Hz, 1H), 3.19 (dd, J = 48.7, 13.1 Hz, 1H), 2.96 (d, J = 11.8 Hz, 1H), 2.65 (d, J = 11.2 Hz, 1H), 1.93 (dd, J = 24.0, 11.4 Hz, 1H), 1.48 (tt, J = 15.3, 7.7 Hz, 1H), 1.07 (s, 9H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.9, 26.7, 26.8, 37.8, 47.0, 53.2, 60.3, 72.6, 77.2, 127.9, 130.0, 130.0, 132.8, 132.9, 135.5, 135.6 ppm; HRMS(ESI-TOF) calcd. for $C_{30}H_{33}F_6N_3OSSi$ $[M+H]^+$ 626.2096, found 626.2094.

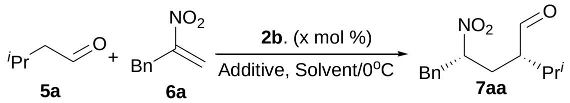
3. Synthesis of α-Substituent Nitroolefins

The details of the synthesis of 2-nitroprop-1-ene see the reference,[3] the synthetic routine of others α-substituent nitroolefins as follows:





4. Partial Results of Reaction Conditions Optimizations



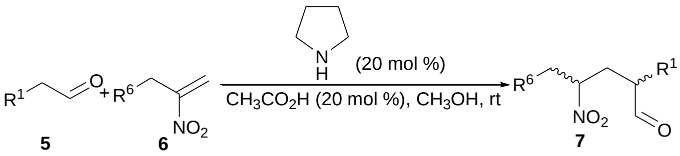
Entry	x	Solvent	Additive	Time (h)	Yield (%)[b]	Dr[c]	Ee (%)[c]
1	20	DMF	-	24	78	96:4	95
2	20	Hexane	-	24	56	93:7	96
3	20	Toluene	-	24	60	90:10	95
4	20	*t*-BuOCH$_3$	-	24	62	92:8	95
5	20	THF	-	24	70	96:4	94
6	20	CH_2Cl_2	-	24	64	88:12	75
7	20	$CHCl_3$	-	24	70	87:13	71
8	20	CH_3CN	-	24	82	88:12	74
9	20	*i*-PrOH	-	24	74	91:9	82
10	20	CH_3OH	-	24	96	80:20	52
11	5	DMF	*p*-$NO_2C_6H_4CO_2H$	26	84	96:4	95
12[d]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	26	92	96:4	93
13[e]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	26	94	95:5	92
14[f]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	26	94	94:6	92
15[g]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	15	84	90:10	93
16[h]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	41	74	97:3	96
17[i]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	28	80	96:4	95
18[j]	5	DMF	*p*-$NO_2C_6H_4CO_2H$	75	70	95:5	*95*

[a] Unless specified, reactions conducted on a 0.2 mmol scale of nitroolefin in solvent (1 mL) with isovaleraldehyde (2.0 mmol) in the presence of catalyst and equal equivalence of acid was added at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 10% acid was added. [e] 25% acid was added. [f] 50% acid was added. [g] Reaction at 10 °C. [h] Reaction at -10 °C. [i] Isovaleraldehyde (1.0 mmol) was added. [j] Isovaleraldehyde (0.4 mmol) was added.

A series of solvents, including nonpolar (hexane, toluene), polar aprotic (*t*-BuOCH$_3$, THF, CH_2Cl_2, $CHCl_3$, CH_3CN, DMF) and protic (*i*-PrOH, CH_3OH), were screened in the reaction. Moderate to good yields and enantiomeric excesses were obtained (Table, entries 1-10), with the best result being achieved in DMF (Table, entry 1). The ratios of additive *p*-nitrobenzoic acid to catalyst **2b** also influenced the reactive performance; when the ratio increased from 1:1 to 2:1, 5:1 and 10:1, the yields increased significantly with almost unchanging diastereoselectivities, but the enantioselectivities decreased slightly from 95% *ee* to 92% *ee* (Table, entries 11–14). The reaction temperature was also investigated and it was found that when the reaction ran at -10 °C better diastereoselectivity (97:3) and enantioselectivity (96% *ee*) were obtained, but 41 h was needed to furnish the reaction and it only gave 74% yield (Table, entries 11, 15 and 16). So, 0 °C was selected as the best reaction temperature. We also optimized the influence of the amount of aldehyde on the reaction. When the reaction ran with a 5-fold excess of aldehyde, good results were obtained, but the yield decreased slightly from 84% to 80% (Table, entries 11, 17 and 18).

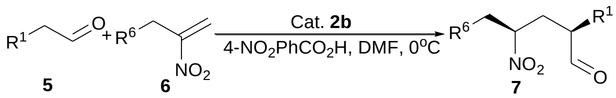
5. General Procedures for Michael Additions of Aldehydes to Nitroolefins

5.1 The Synthesis of the Racemic and Diastereomeric Product Mixtures:



The pyrrolidine (20 mmol %), CH_3CO_2H (20 mmol %) and aldehyde **5** (1.0 mmol) was mixed in CH_3OH (1 mL) at room temperature, after stirring for 15 min. and then the nitroolefin **6** (0.2 mmol) was added. The mixture was stirred at room temperature until the disappearance of the starting material monitored by TLC. The product was purified by silica gel column chromatography (petroleum ether and ethyl acetate as elution).

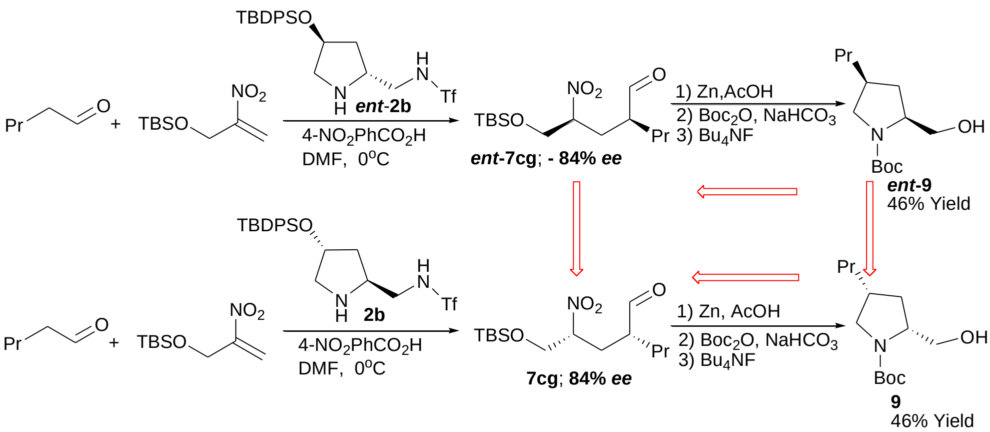
5.2 Catalytic Asymmetric Michael Additions of Aldehydes to Nitroolefins Only with α-Substituent:



The catalyst **2b** (5 mol %), 4-O_2NPhCO_2H (5 mol %) and aldehyde **5** (1.0 mmol) were mixed in 1 mL DMF at room temperature, after stirring for 15 minutes and then cooling to 0°C, the nitroolefin **6** (0.2 mmol) was added. The mixture was stirred at 0°C until the disappearance of the starting material monitored by TLC. The product was purified by silica gel column chromatography (petroleum ether and ethyl acetate as elution).

Diastereomeric ratios and enantiomeric purity of the products were determined by comparison with the HPLC analysis using chiral column.

6. Determination of the Absolute Configuration of the Major Diastereomer



The absolute configuration of the obtained asymmetric Michael compound ***ent*-7cg** was determined via conversion to the corresponding *N*-Boc protected pirrolidines ***ent*-9.** Compound ***ent*-9** has been reported previously by Goodman M. et al[4] and its NMR (^{1}H, ^{13}C) and specific rotation***** were consistent with those reported. The relative configurations of the remaining Michael adducts have been assigned by assumption of an identical reaction pathway. The absolute configurations of the remaining Michael adducts have been accordingly tentatively assigned.

(2*S*, 4*S*)-N-*tert*-Butyloxycarbonyl-2-hydroxymethyl-4-propylpyrrolidine (***ent*-9**)**:** (84% *ee*), colorless oil. $[\alpha]_D^{20}$ = -36.5^o (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.88 (dd, *J* = 15.4, 7.5 Hz, 1H), 3.58 (dt, *J* = 19.2, 10.6 Hz, 3H), 2.74 (t, *J* = 10.5 Hz, 1H), 2.10 (dt, *J* = 12.7, 6.2 Hz, 1H), 1.93 (d, *J* = 32.6 Hz, 1H), 1.43 (s, 9H), 1.26 (t, *J* = 10.4 Hz, 4H), 0.99 (dt, *J* = 20.7, 10.4 Hz, 1H), 0.87 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 80.3, 67.9, 61.3, 53.3, 37.2, 35.6, 35.1, 28.4, 21.3, 14.2 ppm; HRMS (ESI-TOF) calcd. for $C_{13}H_{25}NO_3$ $[M+Na]^+$ 266.1732, found 266.1649; $[M+H]^+$ 244.1913, found 244.1905.

***** A non-racemic mixture of two enantiomers will have a net optical rotation. It is possible to determine the specific rotation of the mixture and with knowledge of the specific rotation of the optical purity, the pure specific rotation can be determined.

$$\text{*specific rotation } [a]_D^{20} = \frac{[a]_{observed}}{\text{optical purity}} = -\frac{36.5^o}{84\%} = -43.45^o \quad \text{(literature: } -43.5^o)^{[4]}$$

7. Proposed Catalytic Cycle and Transition State Model

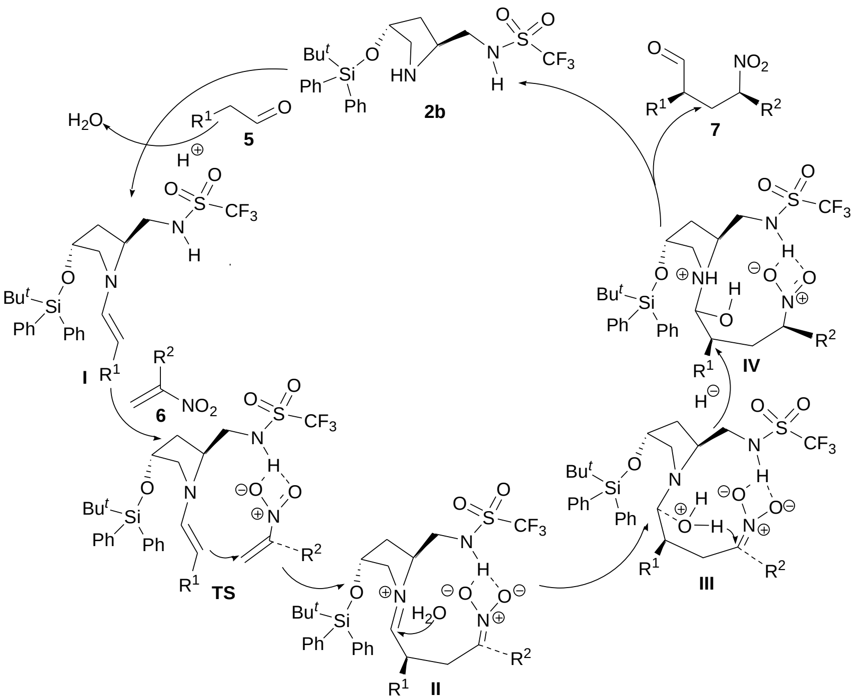
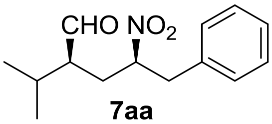


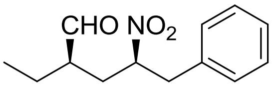
Fig. 1 Proposed catalytic cycle and transition state model.

We have proposed a catalytic cycle and transition state model (**Fig. 1**).[1c] Firstly, the catalyst **2b** and aldehyde **5** react to form the enamine **I**, this procedure could be accelerated greatly in the presence of additional Brønsted acids. Then, the enamine **I** reacts with the nitroolefins **6** *via* the transition state (**TS**), in which, the hydrogen bond between the sulfonamide proton and the nitro group could activate the nitroolefins; The bulky group (–OTBDPS) should effectively shield the *re*-face of an enamine double bond, which would make the nucleophilic attack occur from the nonshielded *si*-face to nitroolefin and afford the nitronate intermediate **II**. Here, the generated nitronate was thought to be stabilized by further coordination to the sulfonamide proton, thus slowing down any intermolecular protonation, especially from additional Brønsted acids, even slower than the rate of nucleophile attack of a water molecule to the iminium ion to give intermediate **III**. After the formation of intermediate **III**, protonation of the nitronate in an intramolecular manner in a six-member cycle transition state gives intermediate **IV**. Further hydrolysis to recycle the catalyst **2b** gives the observed major enantiomer of the products. This catalytic cycle and transition state model may explain the phenomenon that the presence of acid as additive only accelerated the reaction, while does not affects the diastereoselectivity of the process (Table 1, entries 3 and 10).

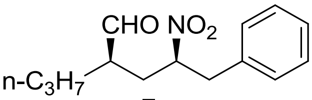
8. Characterization of the Michael Reaction Products



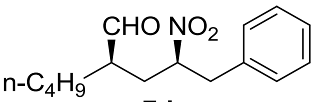
(2*S*, 4*R*)-2-isopropyl-4-nitro-5-phenylpentanal (7aa): oil, $[\alpha]_D^{20}$ = +23.8° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.5 Hz, 1H), 7.25 (dddd, *J* = 29.7, 17.7, 5.9, 4.3 Hz, 6H), 4.84–4.61 (m, 1H), 3.25 (dd, *J* = 14.2, 8.5 Hz, 1H), 3.06 (dt, *J* = 14.2, 6.9 Hz, 1H), 2.47 (dt, *J* = 15.0, 7.2 Hz, 1H), 2.34–2.22 (m, 1H), 2.20–2.03 (m, 1H), 1.84 (ddd, *J* = 18.9, 12.2, 6.0 Hz, 1H), 1.02–0.78 (m, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.8, 135.1, 128.8, 127.5, 87.7, 54.0, 39.576, 28.7, 28.2, 19.4 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{19}NO_3$ $[M+Na]^+$ 272.1263, found 272.1265; HPLC condition: Chiralpak AD-H, 221 nm, 1.0 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 36.09 min, t_{minor} = 23.61 min. *ee* = 95%, *dr* = 96:4.



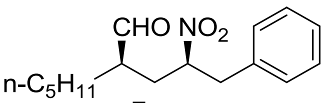
(2*R*, 4*R*)-2-ethyl-4-nitro-5-phenylpentanal (7ba): oil, $[\alpha]_D^{20}$ = +4.1° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75–9.47 (m, 1H), 7.54–6.80 (m, 5H), 5.00–4.60 (m, 1H), 3.39–2.88 (m, 2H), 2.39–2.20 (m, 1H), 2.20–1.87 (m, 2H), 1.85–1.62 (m, 1H), 1.62–1.38 (m, 1H), 1.07–0.70 (m, 4H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.9, 135.0, 128.8, 127.5, 88.1, 49.3, 40.5, 31.4, 22.3, 10.9 ppm; HRMS (ESI-TOF) calcd. for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106, found 258.1107; HPLC condition: Chiralpak AD-H, 221 nm, 1.0 mL/min, hexane/*i*-PrOH = 99/1, t_{major} = 30.11 min, t_{minor} = 27.53 min. *ee* = 93%, *dr* = 92:8.



(2*R*, 4*R*)-4-nitro-5-phenyl-2-propylpentanal (7ca): oil, $[\alpha]_D^{20}$ = +6.5° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, *J* = 9.4 Hz, 1H), 7.25 (dt, *J* = 37.2, 6.5 Hz, 5H), 4.97–4.66 (m, 1H), 3.26 (dt, *J* = 15.8, 7.9 Hz, 1H), 3.05 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.59–2.21 (m, 2H), 1.88–1.73 (m, 1H), 1.73–1.44 (m, 2H), 1.41–1.13 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5, 135.0, 128.8, 127.6, 87.2, 48.0, 40.1, 31.2, 30.2, 19.6, 14.0 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{19}NO_3$ $[M+Na]^+$ 272.1263, found 272.1267; HPLC condition: Chiralpak IA, 221nm, 1.0 mL/min, hexane/*i*-PrOH = 99/1, t_{major} = 23.30 min, t_{minor} = 17.50 min. *ee* = 95%, *dr* = 94:6.

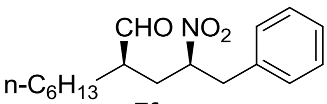


(*R*)-2-((*R*)-2-nitro-3-phenylpropyl)hexanal (7da): oil, $[\alpha]_D^{20}$ = +9.0° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (t, *J* = 5.4 Hz, 1H), 7.50–7.03 (m, 5H), 4.80 (dddt, *J* = 18.8, 13.9, 9.5, 4.6 Hz, 1H), 3.27 (dt, *J* = 17.2, 8.6 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.41 (ddt, *J* = 25.6, 18.7, 5.9 Hz, 2H), 1.81 (ddd, *J* = 14.4, 7.4, 4.5 Hz, 1H), 1.74–1.46 (m, 2H), 1.40–1.09 (m, 4H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) *δ* 202.5, 135.0, 128.9, 127.6, 87.2, 48.2, 40.1, 31.2, 28.4, 27.8, 22.6, 13.7 ppm; HRMS (ESI-TOF) calcd. for $[M+H]^+$ $C_{15}H_{21}NO_3$ 264.1600, found 264.1597; HPLC condition: Chiralpak AS-H, 221 nm, 0.5 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 32.43 min, t_{minor} = 43.36 min. *ee* = 90%, *dr* = 91:9.



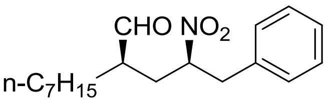
7ea

(*R*)-2-((*R*)-2-nitro-3-phenylpropyl)heptanal (7ea): oil, $[\alpha]_D^{20}$ = +14.0^o (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.74–9.51 (m, 1H), 7.48–7.03 (m, 5H), 4.90–4.66 (m, 1H), 3.27 (dt, *J* = 17.4, 8.7 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.40 (ddt, *J* = 25.6, 18.4, 5.9 Hz, 2H), 1.80 (ddd, *J* = 14.3, 7.3, 4.5 Hz, 1H), 1.74–1.46 (m, 2H), 1.41–1.09 (m, 6H), 0.86 (t, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 202.5, 135.0, 128.8, 127.6, 87.2, 48.2, 40.1, 31.7, 31.1, 28.0, 26.0, 22.3 13.9 ppm; HRMS (ESI-TOF) calcd. for $C_{16}H_{23}NO_3$ $[M+Na]^+$ 300.1576, found 300.1577; HPLC condition: Chiralpak AS-H, 221 nm, 0.5 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 122.18 min, t_{minor} = 26.22 min. *ee* = 90%, *dr* = 91:9.



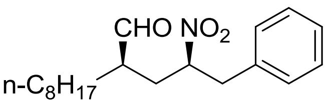
7fa

(*R*)-2-((*R*)-2-nitro-3-phenylpropyl)octanal (7fa): oil, $[\alpha]_D^{20}$ = +13.6^o (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.62 (dd, *J* = 18.0, 8.4 Hz, 1H), 7.48–7.01 (m, 5H), 4.95–4.65 (m, 1H), 3.27 (dt, *J* = 17.4, 8.7 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.55–2.26 (m, 2H), 1.80 (ddd, *J* = 14.3, 7.3, 4.5 Hz, 1H), 1.74–1.47 (m, 2H), 1.46–1.03 (m, 8H), 0.87 (t, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 202.5, 135.0, 128.8, 127.6, 87.2, 48.2, 40.1, 31.4, 31.1, 29.2, 28.0, 26.2, 22.5, 14.0 ppm; HRMS (ESI-TOF) calcd. for $C_{17}H_{25}NO_3$ $[M+Na]^+$ 314.1732, found 314.1732; HPLC condition: Chiralpak AS-H, 221 nm, 0.5 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 21.32 min, t_{minor} = 25.23 min. *ee* = 91%, *dr* = 93:7.



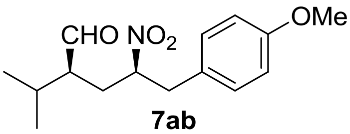
7ga

(*R*)-2-((*R*)-2-nitro-3-phenylpropyl)nonanal (7ga): oil, $[\alpha]_D^{20}$ = +14.0^o (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.70–9.53 (m, 1H), 7.47–7.04 (m, 5H), 4.80 (dtt, *J* = 18.1, 9.6, 4.7 Hz, 1H), 3.27 (dt, *J* = 17.3, 8.7 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.40 (ddt, *J* = 25.5, 18.6, 5.9 Hz, 2H), 1.80 (ddd, *J* = 14.4, 7.4, 4.5 Hz, 1H), 1.74–1.50 (m, 2H), 1.24 (s, 10H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 202.5, 135.0, 128.8, 127.5, 87.2, 48.2, 40.1, 31.6, 31.1, 29.5, 28.9, 28.1, 26.3, 22.6, 14.0 ppm; HRMS (ESI-TOF) calcd. for $C_{18}H_{27}NO_3$ $[M+Na]^+$ 328.1889, found 328.1889; HPLC condition: Chiralpak IC, 221 nm, 0.5 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 42.96 min, t_{minor} = 55.41 min. *ee* = 90%, *dr* = 91:9.



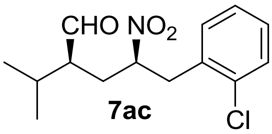
7ha

(*R*)-2-((*R*)-2-nitro-3-phenylpropyl)decanal (7ha): oil, $[\alpha]_D^{20}$ = +14.2^o (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.60 (d, *J* = 10.5 Hz, 1H), 7.44–7.06 (m, 5H), 4.91–4.64 (m, 1H), 3.27 (dt, *J* = 17.3, 8.7 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.40 (ddt, *J* = 29.4, 18.6, 6.0 Hz, 2H), 1.80 (ddd, *J* = 14.3, 7.3, 4.5 Hz, 1H), 1.62 (tdd, *J* = 22.2, 14.5, 8.1 Hz, 2H), 1.21 (d, *J* = 17.6 Hz, 10H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 202.5, 135.0, 128.9, 128.8, 128.77, 127.6, 87.28, 48.2, 40.1, 31.8, 31.1, 29.5, 29.2, 28.1, 26.3, 22.6, 14.1 ppm; HRMS (ESI-TOF) calcd. for $C_{19}H_{29}NO_3$ $[M+Na]^+$ 342.2045, found 342.2046; $[M-H]^-$ 318.2069, found 318.301; HPLC condition: Chiralpak IC, 221 nm, 0.5 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 43.15 min, t_{minor} = 56.91 min. *ee* = 90%, *dr* = 91:9.



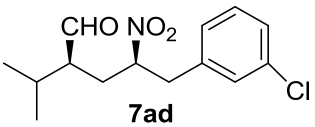
7ab

(2*S*, 4*R*)-2-isopropyl-5-(4-methoxyphenyl)-4-nitropentanal (7ab): oil, $[\alpha]_D^{20}$ = +10.7° (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.0 Hz, 1H), 7.15–6.71 (m, 4H), 4.80–4.58 (m, 1H), 3.77 (s, 3H), 3.26–2.93 (m, 2H), 2.53–2.36 (m, 1H), 2.36–2.19 (m, 1H), 2.20–2.00 (m, 1H), 1.85 (dt, *J* = 14.5, 5.3 Hz, 1H), 0.99–0.90 (m, 7H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 203.0, 158.9, 129.9, 127.0, 114.2, 88.0, 55.2, 54.0, 38.8, 28.6, 28.2, 22.3, 19.4 ppm; HRMS (ESI-TOF) calcd. for $C_{15}H_{21}NO_4$ $[M+Na]^+$ 302.1368, found 302.1370; $[M+H]^+$ 280.1549, found 280.1404; HPLC condition: Chiralpak AD-H, 221 nm, 1.0 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 34.48 min, t_{minor} = 23.69 min. *ee* = 96%, *dr* = 96:4.



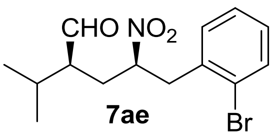
7ac

(2*S*, 4*R*)-5-(2-chlorophenyl)-2-isopropyl-4-nitropentanal (7ac): oil, $[\alpha]_D^{20}$ = -8.6° (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.24 (m, 4H), 4.97–4.74 (m, 1H), 3.26 (d, *J* = 9 Hz, 2H), 2.62–2.44 (m, 1H), 2.43–2.32 (m, 1H), 2.26–2.10 (m, 1H), 1.88 (m, 1H), 0.98 (dd, *J* =12, 6 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.6, 133.8, 133.0, 131.3, 129.8, 129.2, 127.3, 86.0, 53.8, 37.5, 29.0, 28.1, 19.3 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{18}ClNO_3$ $[M+Na]^+$ 306.0873, found 305.1768. HPLC condition: Chiralpak AS-H, 221 nm, 0.5 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 24.70 min, t_{minor} = 28.47 min. *ee* = 92%, *dr* = 94:6.



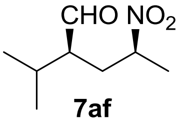
7ad

(2*S*, 4*R*)-5-(3-chlorophenyl)-2-isopropyl-4-nitropentanal (7ad): oil, $[\alpha]_D^{20}$ = +13.8° (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.4 Hz, 1H), 7.33–6.87 (m, 4H), 4.82–4.57 (m, 1H), 3.17 (dd, *J* = 14.4, 9.1 Hz, 1H), 3.06–2.94 (m, 1H), 2.51–2.35 (m, 1H), 2.35–2.22 (m, 1H), 2.20–2.00 (m, 1H), 1.97–1.72 (m, 1H), 1.00–0.83 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 137.2, 134.6, 130.2, 129.0, 127.8, 127.0, 87.5, 54.0, 39.0, 28.8, 28.2, 19.5 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{18}ClNO_3$ $[M+Na]^+$ 306.0873, found 306.0875; HPLC condition: Chiralpak AD-H, 254nm, 1.0 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 40.01 min, t_{minor} = 18.56 min. *ee* = 93%, *dr* = 99:1.



7ae

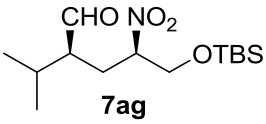
(2*S*, 4*R*)-5-(2-bromophenyl)-2-isopropyl-4-nitropentanal (7ae): oil, $[\alpha]_D^{20}$ = -14.3° (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.24 (dddd, *J* = 19.4, 17.9, 9.1, 2.1 Hz, 4H), 4.99–4.76 (m, 1H), 3.36–3.12 (m, 2H), 2.61–2.45 (m, 1H), 2.44–2.32 (m, 1H), 2.28 –2.09 (m, 1H), 1.88 (dt, *J* = 14.5, 5.4 Hz, 1H), 1.06–0.86 (m, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5, 134.7, 133.1, 131.3, 129.4, 127.9, 124.2, 86.2, 53.8, 39.8, 28.9, 28.1, 19.3 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{18}BrNO_3$ $[M+Na]^+$ 350.0368, found 350.0369; HPLC condition: Chiralpak IA, 221 nm, 1.0 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 23.04 min, t_{minor} = 32.70 min. *ee* = 91%, *dr* = 94:6.



7af

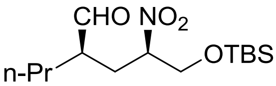
(2*S*, 4*S*)-2-isopropyl-4-nitropentanal (7af): oil, $[\alpha]_D^{20}$ = + 90.4° (c = 1.0, $CHCl_3$); ^1H NMR (300

MHz, $CDCl_3$) δ 9.69 (t, J = 5.8 Hz, 1H), 4.76–4.51 (m, 1H), 2.55–2.37 (m, 1H), 2.35–2.06 (m, 1H), 1.89–1.71 (m, 1H), 1.52 (d, J = 6.7 Hz, 3H), 1.00 (t, J = 6.4 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 202.9, 81.2, 53.9, 30.1, 28.3, 19.7, 19.3, 18.7 ppm; HRMS (ESI-TOF) calcd. for $C_8H_{15}NO_3$ $[M+Na]^+$ 196.0950, found 196.0950; $[M-H]^+$ 172.0974, found 172.1321; HPLC condition: Chiralpak IA, 221 nm, 1.0 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 31.83 min, t_{minor} = 29.83 min. *ee* = 98%, *dr* = 94:6.



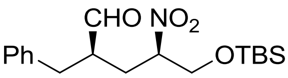
7ag

(2*S*, 4*R*)-5-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-nitropentanal (7ag): oil, $[\alpha]_D^{20}$ = + 14.6° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76–9.58 (m, 1H), 4.66–4.45 (m, 1H), 4.01–3.82 (m, 2H), 2.42–2.04 (m, 3H), 2.06–1.80 (m, 1H), 1.04–0.94 (m, 6H), 0.84 (d, J = 6.3 Hz, 9H), 0.03 (d, J = 11.8 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 86.9, 63.3, 53.9, 28.3, 25.6, 24.5, 19.7, 19.4, 18.1, -5.7 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{29}NO_4Si$ $[M+Na]^+$ 326.1764, found 326.1769; $[M-H]^-$ 302.1788, found 302.1392; HPLC condition: Chiralpak IC, 218 nm, 0.25 mL/min, hexane/*i*-PrOH = 96/4, t_{major} = 64.01 min, t_{minor} = 35.55 min. *ee* = 98%, *dr* = 89:11.



7cg

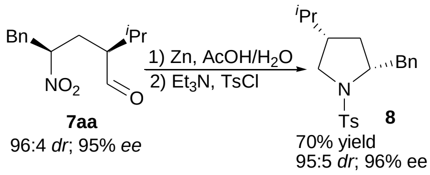
(2*R*, 4*R*)-5-(*tert*-butyldimethylsilyloxy)-4-nitro-2-propylpentanal (7cg): oil, $[\alpha]_D^{20}$ = +12.6 ° (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, J = 19.0 Hz, 1H), 4.62 (s, 1H), 4.17–3.77 (m, 2H), 2.61–2.26 (m, 2H), 1.91–1.77 (m, 1H), 1.59 (dd, J = 47.3, 38.9 Hz, 2H), 1.34 (dt, J = 52.0, 26.1 Hz, 2H), 0.94 (t, J = 6.5 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 86.9, 64.1, 48.0, 30.7, 27.6, 25.8, 20.0, 18.3, 14.2, -5.5 ppm; HRMS (ESI-TOF) calcd. for $C_{14}H_{29}NO_4Si$ $[M+Na]^+$ 326.1764, found 326.1765; HPLC condition: Chiralpak IC, 218 nm, 0.25mL/min, hexane/*i*-PrOH=96/4, t_{major} = 61.721 min, t_{minor} = 38.802 min, *ee* = 84%, *dr* = 80:20.



7ig

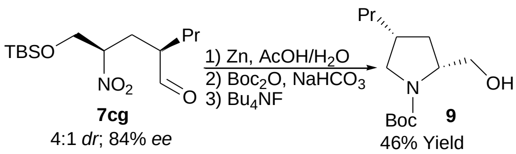
(2*R*, 4*R*)-2-benzyl-5-(*tert*-butyldimethylsilyloxy)-4-nitropentanal (7ig): oil, $[\alpha]_D^{20}$ = +7.57 ° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (d, J = 0.9 Hz, 1H), 7.35–7.24 (m, 3H), 7.16 (d, J = 6.9 Hz, 2H), 4.65–4.48 (m, 1H), 3.98–3.80 (m, 2H), 3.04 (dd, J = 14.0, 7.4 Hz, 1H), 2.92–2.81 (m, 1H), 2.79–2.66 (m, 1H), 2.46–2.26 (m, 1H), 1.87–1.69 (m, 1H), 0.84 (s, 9H), 0.01 (d, J = 1.3 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 137.1, 128.9, 127.0, 86.8, 63.8, 49.7, 35.0, 27.4, 25.6, -5.7 ppm; HRMS (ESI-TOF) calcd. for $C_{18}H_{29}NO_4Si$ $[M+Na]^+$ 374.1764, found 374.1744; HPLC condition: Chiralpak IC, 218 nm, 0.5mL/min, hexane/*i*-PrOH=96/4, t_{major} = 44.482 min, t_{minor} = 33.678 min, *ee* = 70%, *dr* = 86:14.

9. General Procedure for the Cascade Reduction/Cyclization Reaction: Synthesis of 2, 4-Disubstituted Pyrrolidines (8-10):

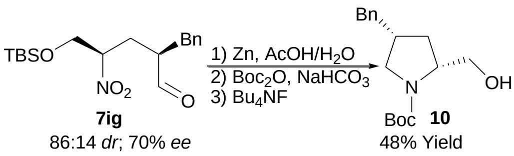


Zn (5.0 mmol) was added in small portions over a period of 2 min to a solution of the nitroaldehyde **7aa** (0.2 mmol) in H_2O/AcOH (1:1; 5 mL) at 0°C. The reaction mixture was stirred for 1.5 h at rt, then filtered, and the filtrate was adjusted to pH = 12 with 4 M NaOH. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was dissolved in CH_2Cl_2 (2 mL), cooled to 0°C and treated with triethylamine (2 equiv.) followed by *p*-toluenesulfonyl chloride (1.5 equiv.) for 6 h. After aqueous workup, the organic concentrate was purified by silica gel column chromatography to afford **8** (70 % yield from **7aa**).

Compound 8: white solid. mp 75.4–76.2 °C; $[\alpha]_D^{20}$ = + 85.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (m, 6H), 0.85–1.20 (m , 1H), 1.22–1.27 (m, 2H), 1.79–1.85 (s, 3H), 2.43–2.89 (m, 2H), 3.40–3.71 (m, 3H), 7.19–7.77 (m, 9H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0, 21.2, 21.5, 31.2, 36.9, 42.9, 45.4, 53.9, 62.3, 126.3, 127.4, 127.5, 128.3, 128.4, 129.5, 129.6, 129.6, 129.7, 135.2, 138.2, 141.3 ppm; HRMS (ESI-TOF) calcd. For $C_{21}H_{27}NO_2S$ $[M+Na]^+$ 380.1660, found 380.1673; HPLC condition: Chiralpak IC, 221 nm, 1.0 mL/min, hexane/*i*-PrOH = 98/2, t_{major} = 42.67 min, t_{minor} = 79.92 min. *ee* = 96%, *dr* = 96:4.



Compound 9: oil. $[\alpha]_D^{20}$ = + 32.89° (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.28 (s, 1H), 3.88 (s, 1H), 3.60–3.65 (m, 3H), 3.53 (d, *J* = 8.0 Hz, 1H), 2.76 (t, 1H), 2.12 (t, 1H), 2.01 (s, 1H), 1.44 (s, 9H), 1.40 (m, 4H), 1.01–1.07 (m, 1H), 0.87 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 21.3, 28.4, 35.1, 35.6, 53.3, 61.6, 67.3, 80.2, 156.9 ppm; HRMS (ESI-TOF) calcd. for $C_{13}H_{25}NO_3$ $[M+Na]^+$ 266.1732, found 266.1649; $[M+H]^+$ 244.1913, found 244.1905.



Compound 10: oil. $[\alpha]_D^{20}$ = +39.3 ° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.07 (m, 5H), 5.33 (d, *J* = 6.2 Hz, 1H), 3.91 (dd, *J* = 15.4, 7.3 Hz, 1H), 3.76–3.49 (m, 3H), 2.93 (t, *J* = 10.6 Hz, 1H), 2.77–2.51 (m, 2H), 2.40–2.22 (m, 1H), 2.08 (dt, *J* = 12.3, 6.2 Hz, 1H), 1.46 (d, *J* = 4.8 Hz, 9H), 1.28–1.07 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 140.0, 128.7, 128.6, 128.5, 126.3, 80.5, 67.8, 61.3, 53.0, 39.0, 35.3, 28.5 ppm; HRMS (ESI-TOF) calcd. for

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$C_{17}H_{25}NO_3$ $[M+Na]^+$ 314.1732, found 314.1728.

10. References

[1] (a) Wang,W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* 2005, **44**, 1369. (b) Zu, L. S.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* 2006, **8**, 3077. (c) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J*. 2006, **12**, 4321.

[2] Wang, C.; Yu, C.; Liu, C. L.; Peng, Y. G. *Tetrahedron Lett.* 2009, **50**, 2363.

[3] Miyashita, T.; Yanami, A.; Yoshikoshi, A. *Org. Syn.* 1990, Coll. **7**, 396; 1981, **60**, 101.

[4] Del Valle, J. R.; Goodman, M. *J. Org. Chem*. 2003, **68**, 3923.

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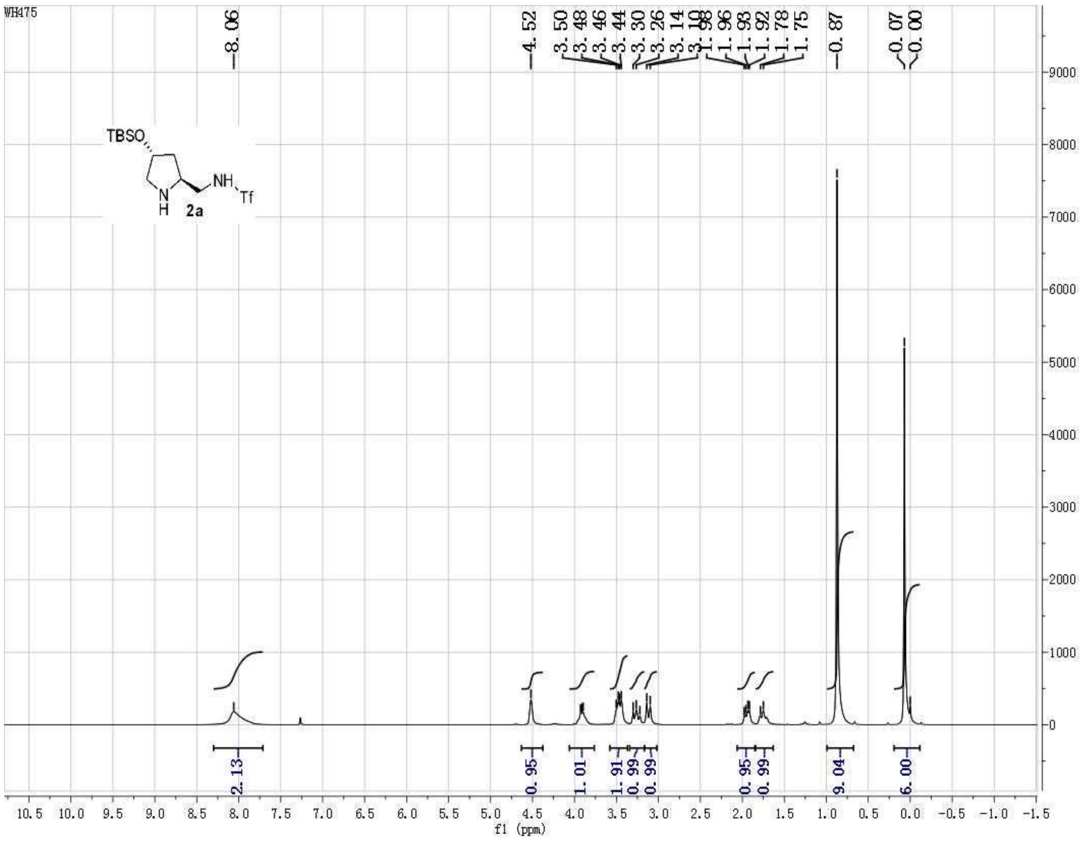
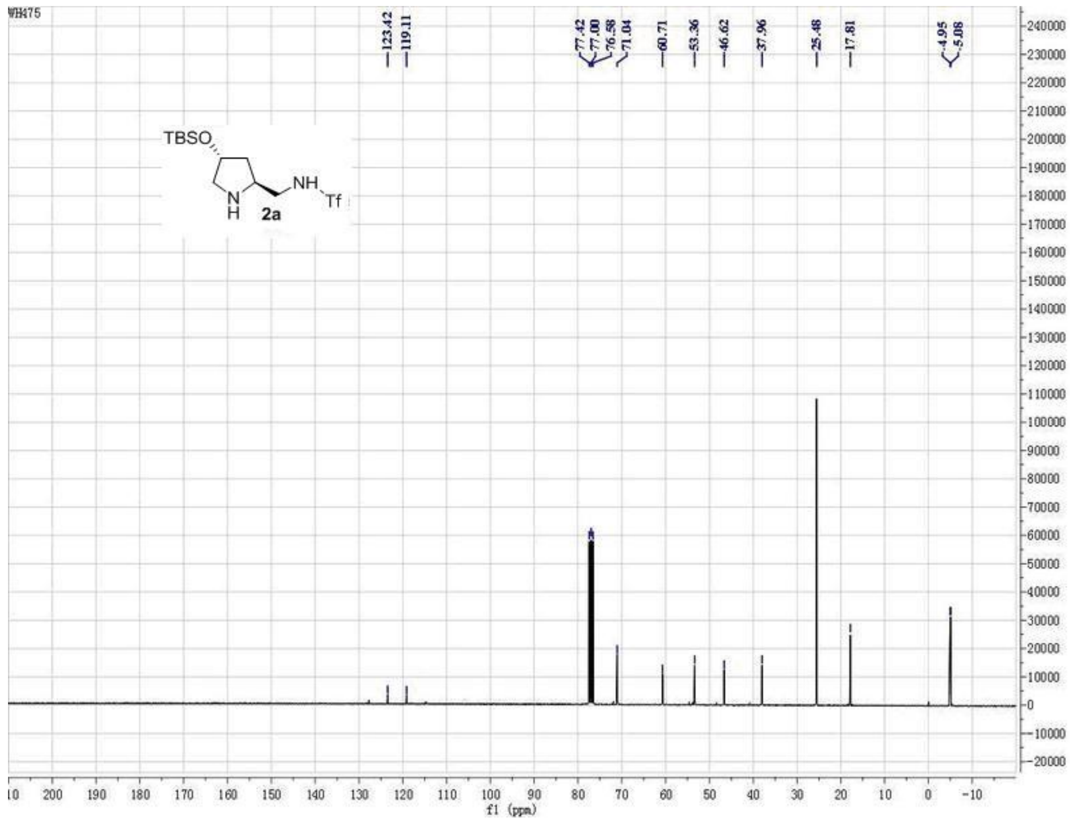
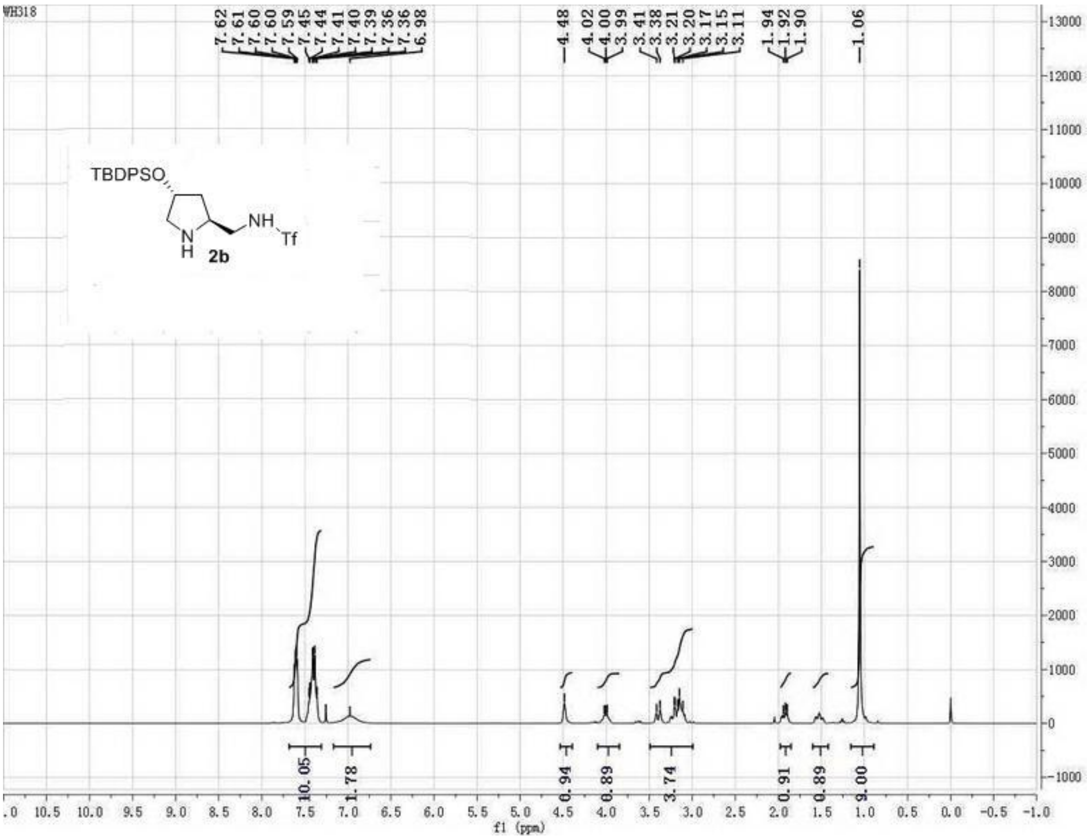
11. NMR Spectra for New Catalysts and Part of the Michael Addition Products



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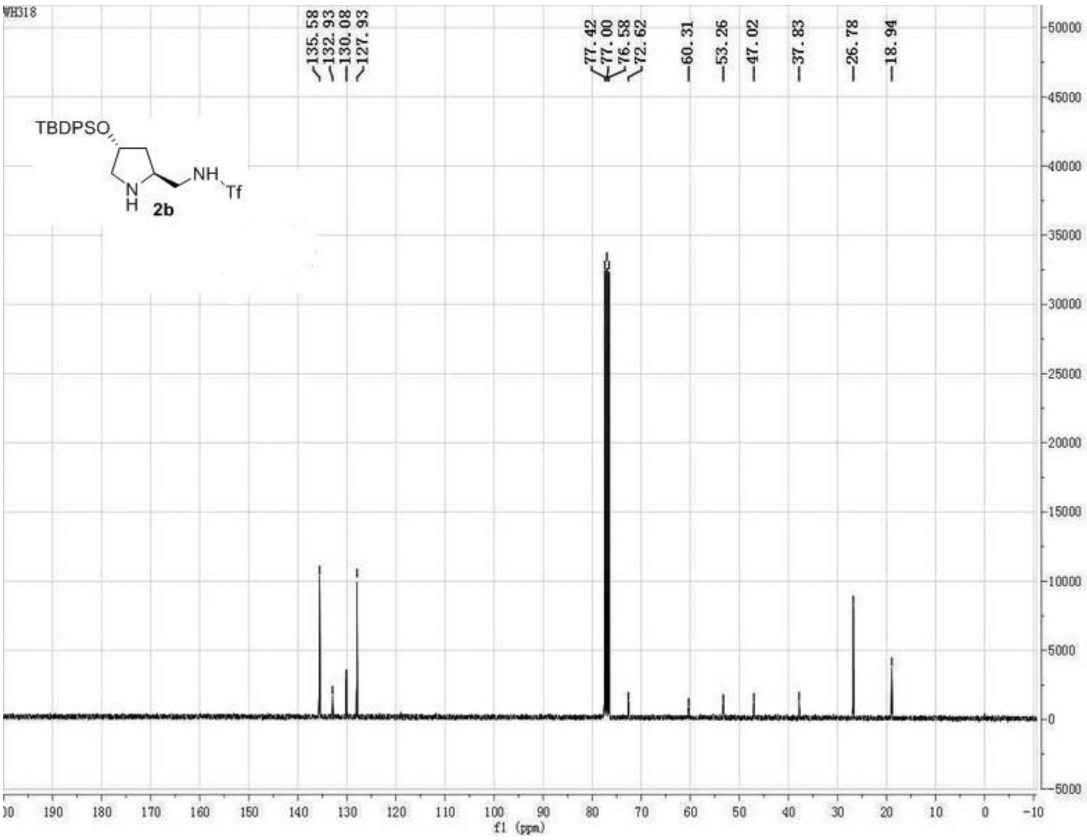
7.60
7.59
7.45
7.44
7.41
7.40
7.39
7.36
7.36
6.98
4.48
4.02
4.00
3.99
3.41
3.38
3.21
3.20
3.17
3.15
3.11
1.94
1.92
1.90
1.06
TBDPSO
NH
Tf
N
H
2b
10.05
1.78
0.94
0.89
3.74
0.91
0.89
9.00
f1 (ppm)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37.83
26.78
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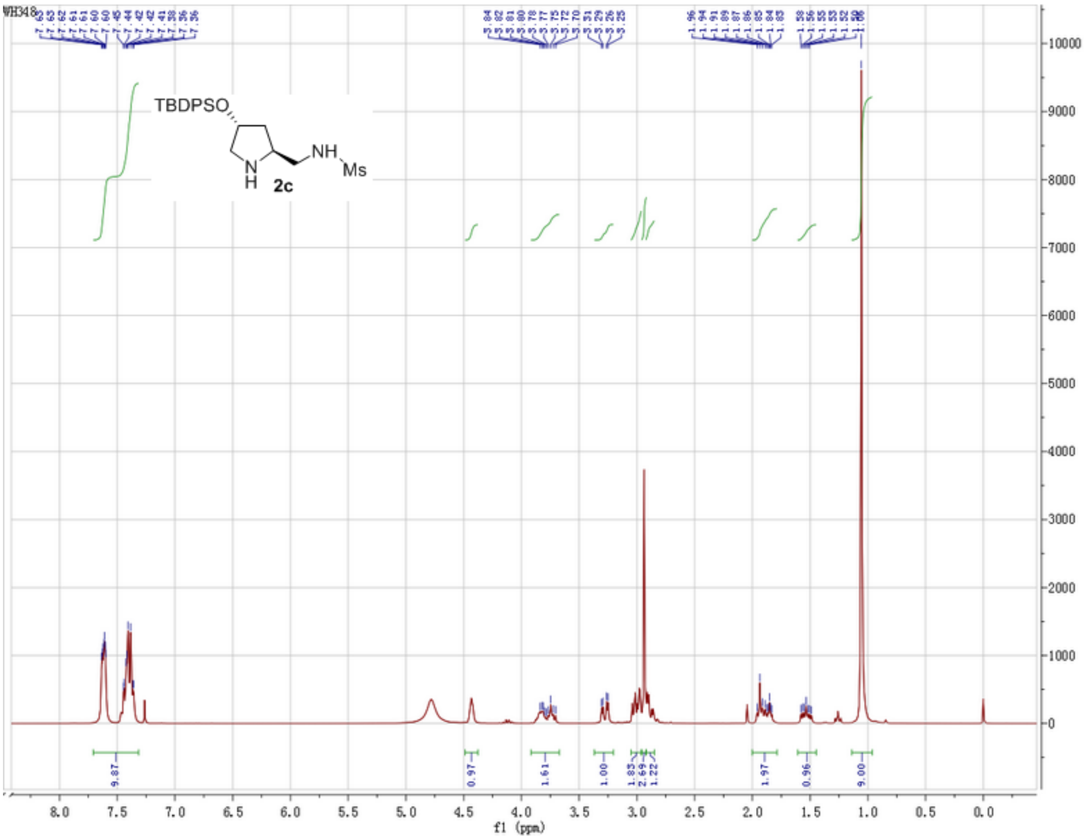
Tf
N
H
2b
f1 (ppm)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H
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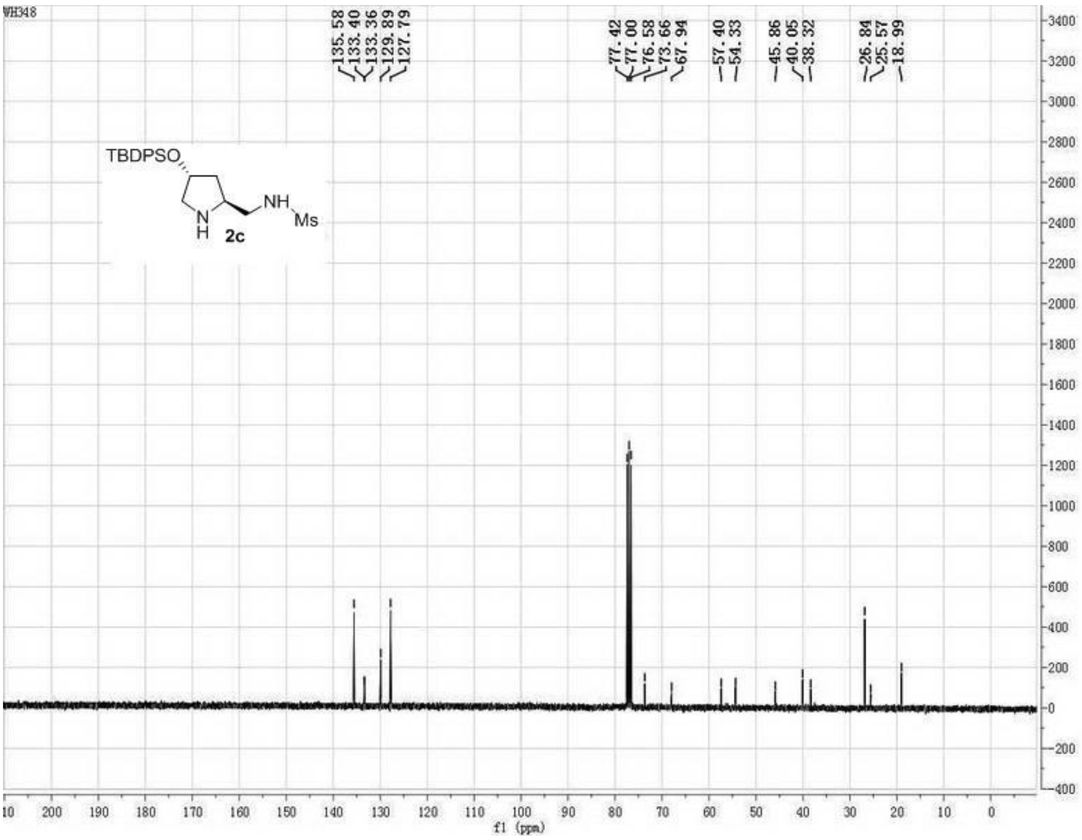
f1 (ppm)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54.33
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38.32
26.84
25.57
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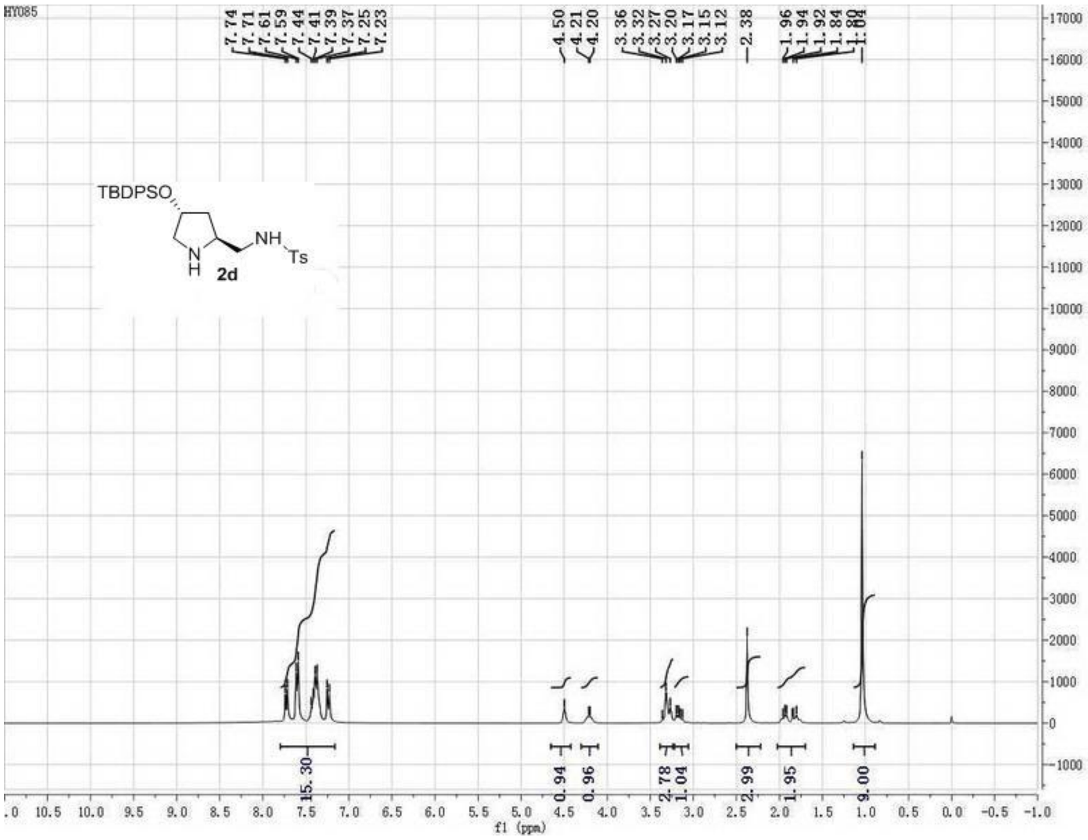
Ms
N
H
2c
f1 (ppm)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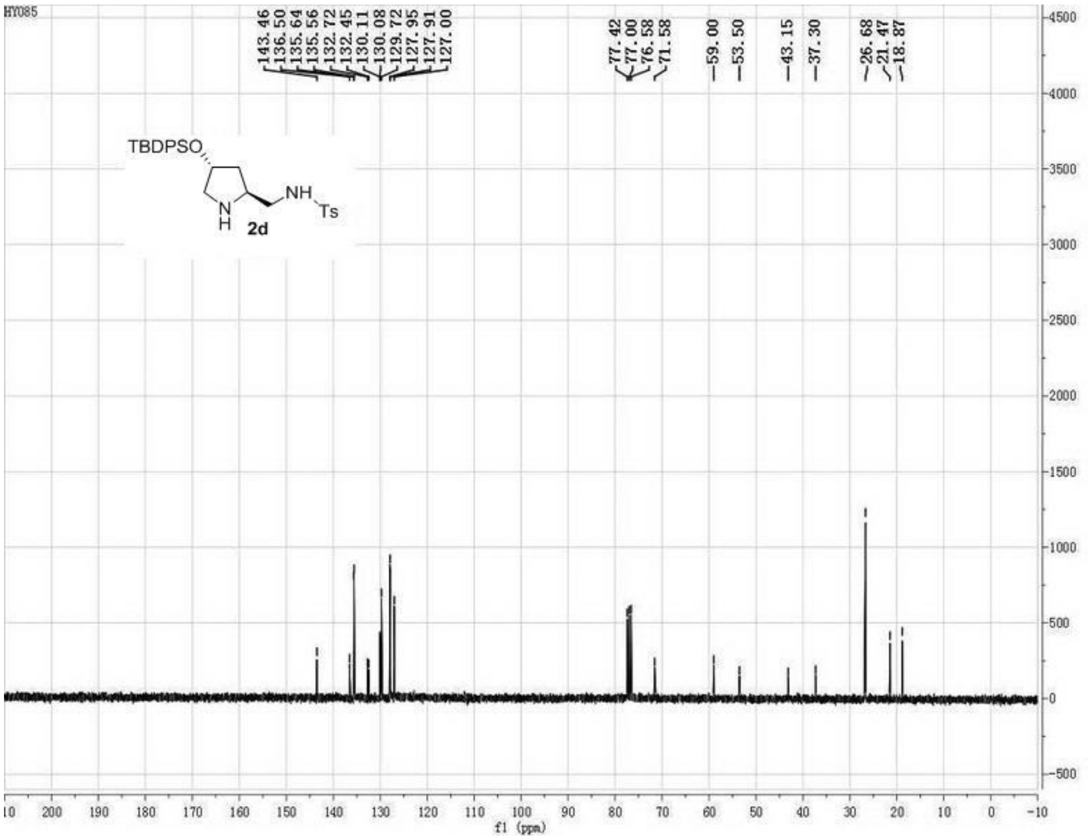
4.50 4.21 4.20
3.36 3.32 3.27 3.20 3.17 3.15 3.12
2.38
1.96 1.94 1.92 1.84 1.80 1.04
TBDPSO
NH
Ts
N
H
2d
15.30
0.94
0.96
2.78
1.04
2.99
1.95
9.00
f1 (ppm)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77.42 77.00 76.58 71.58
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53.50
43.15
37.30
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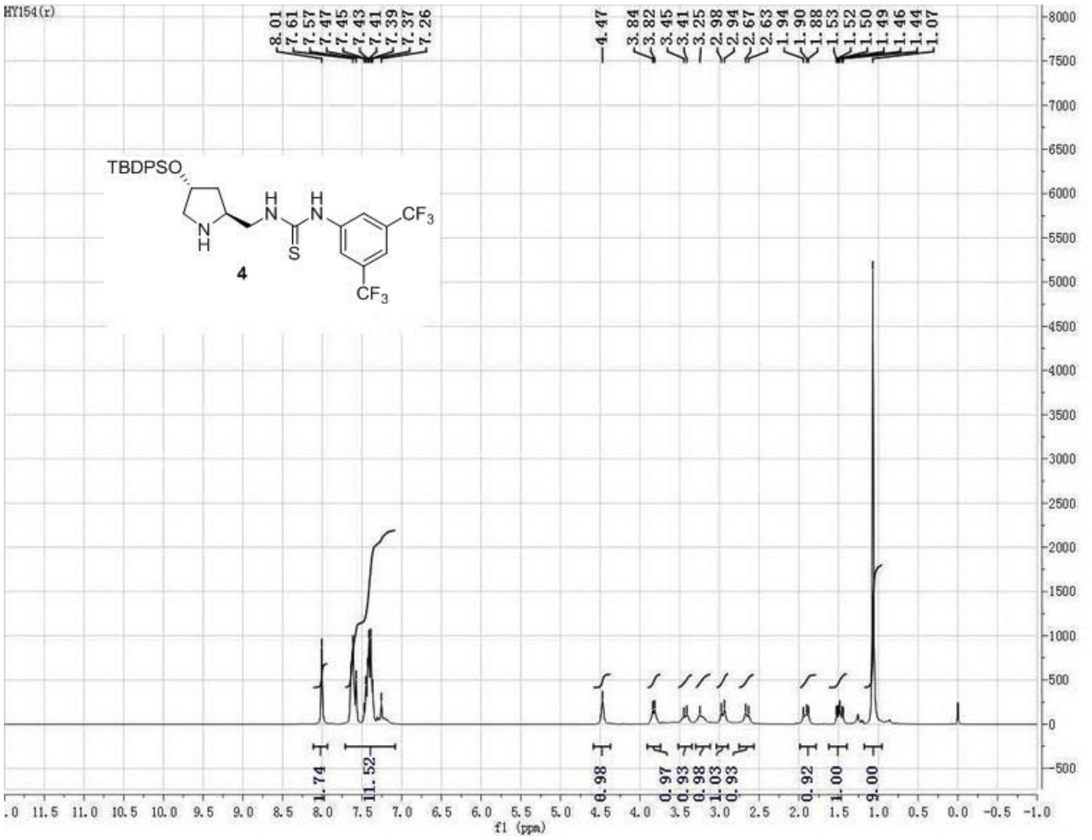
NH
Ts
N
H
2d
f1 (ppm)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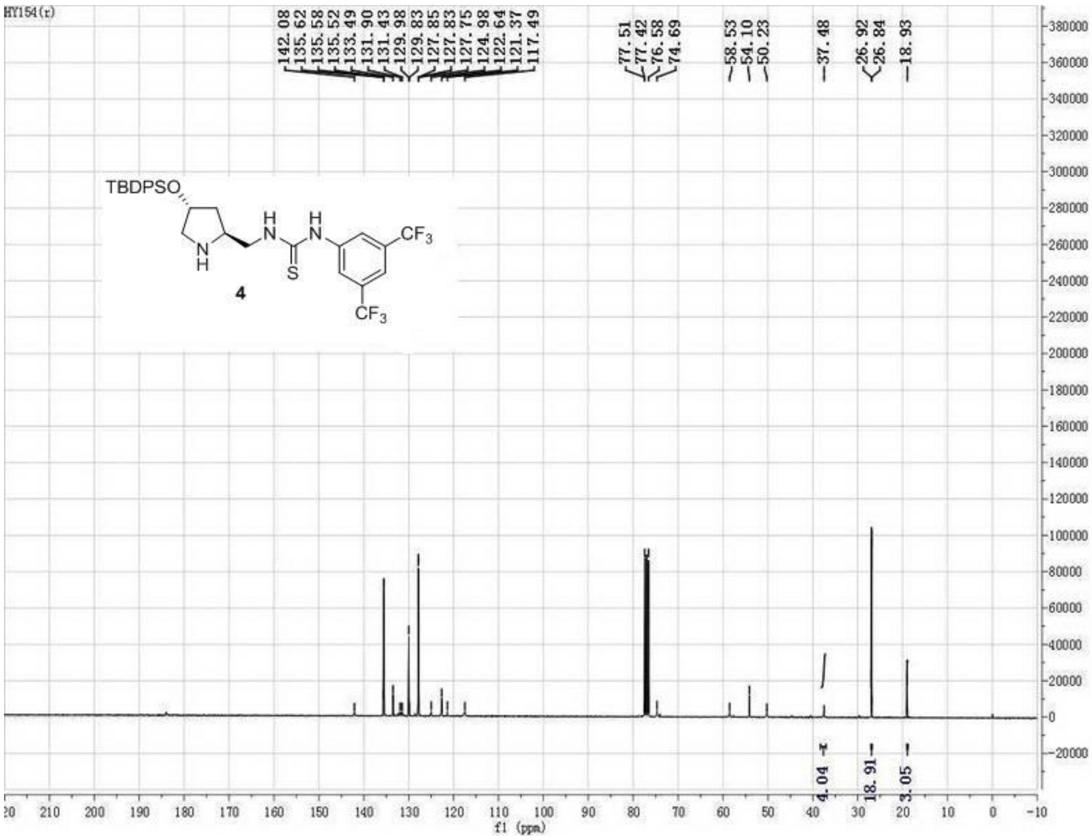
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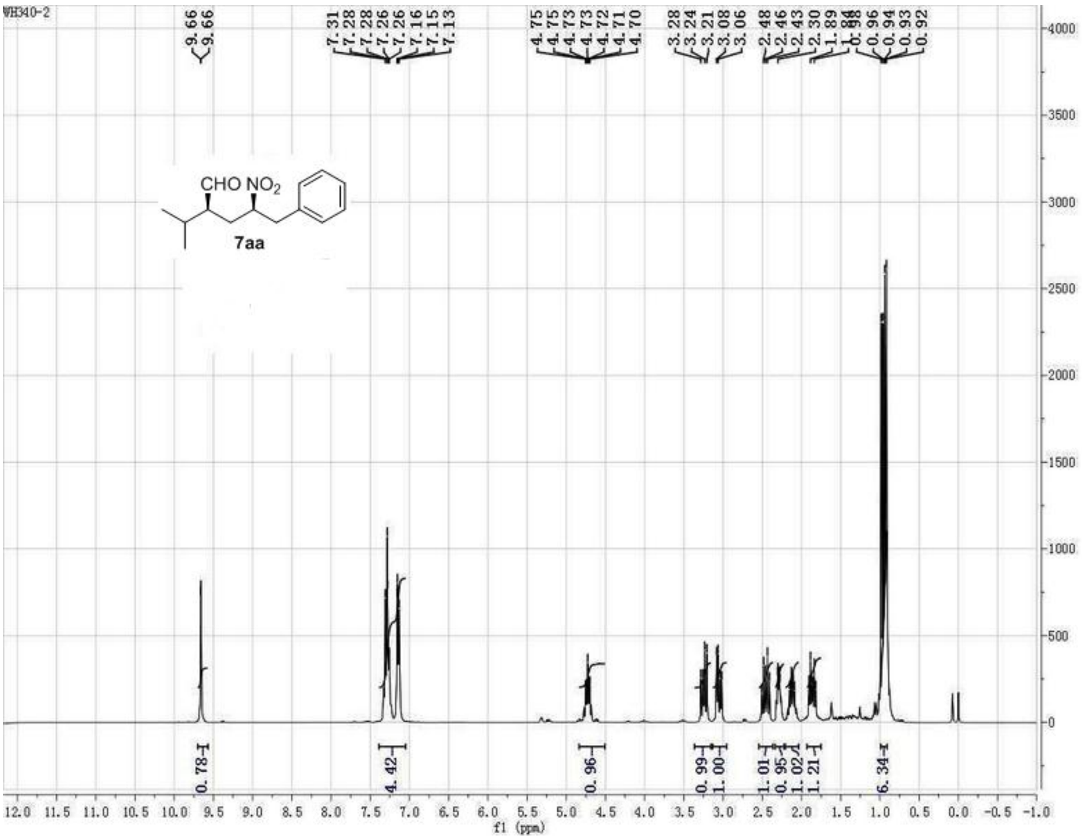
CF$_3$
CF$_3$
4
f1 (ppm)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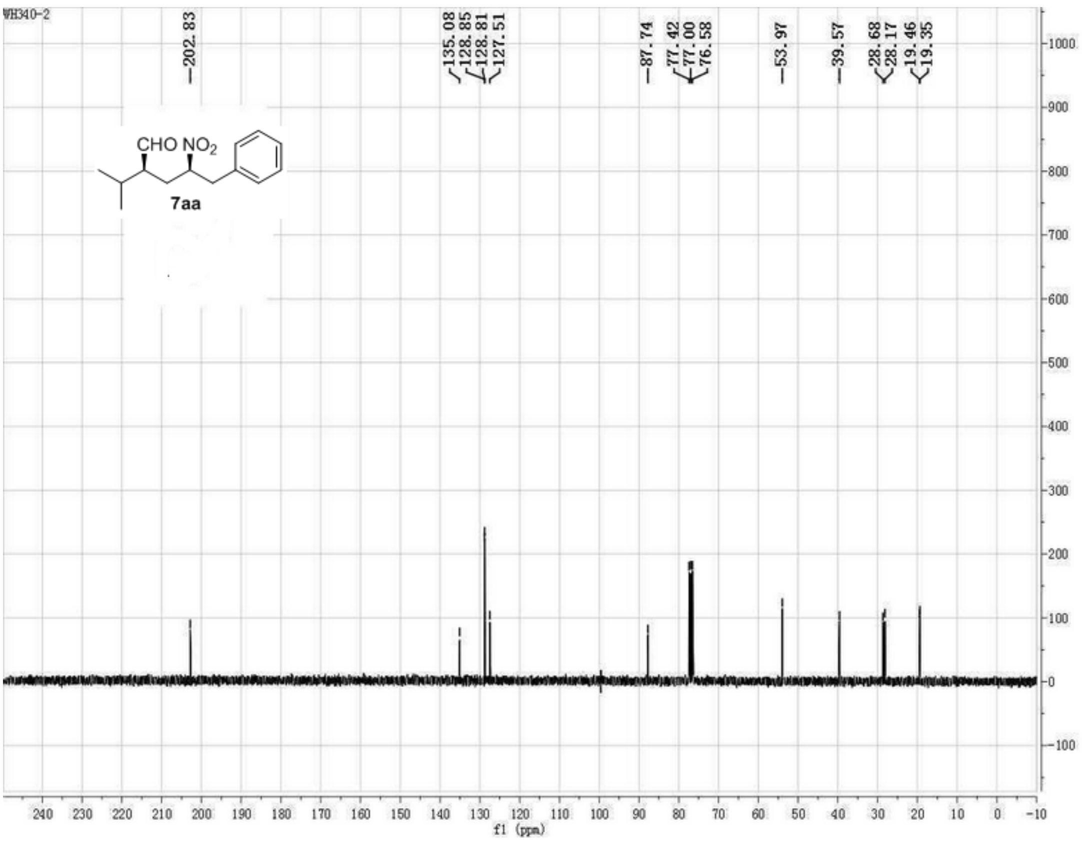
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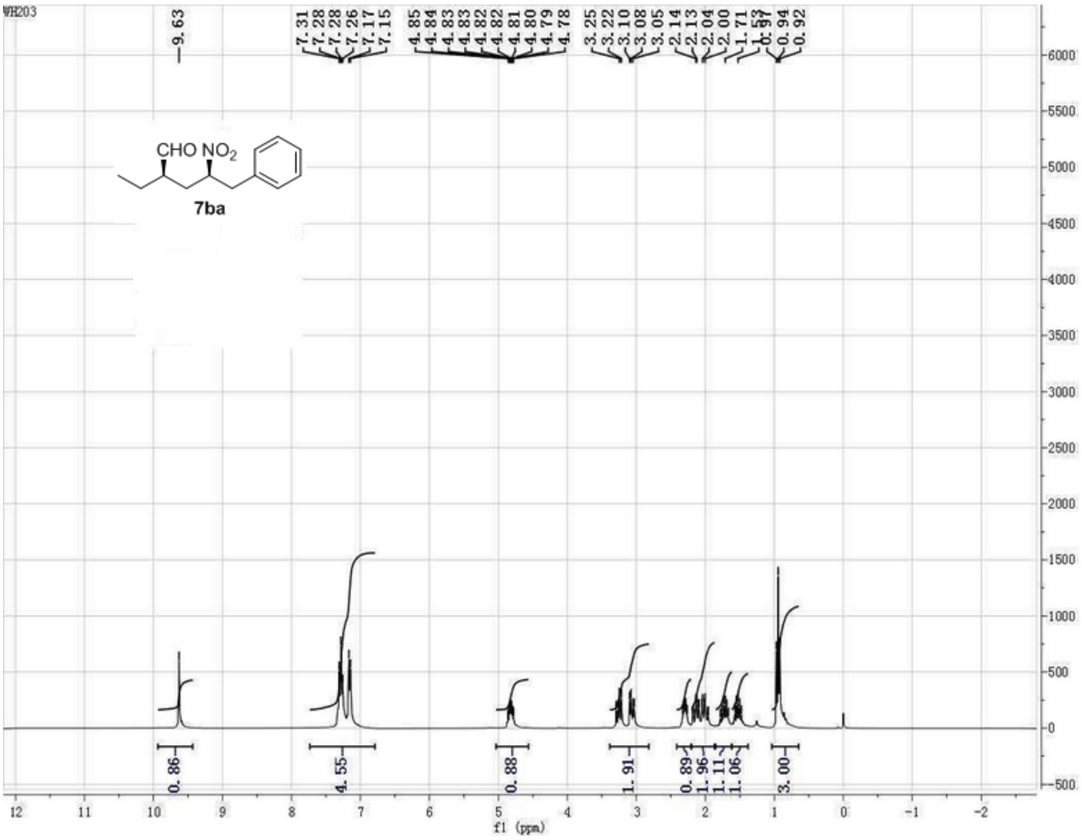
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3.25 3.22 3.10 3.08 3.05
2.14 2.13 2.04 2.00 1.71 1.53 0.97 0.94 0.92
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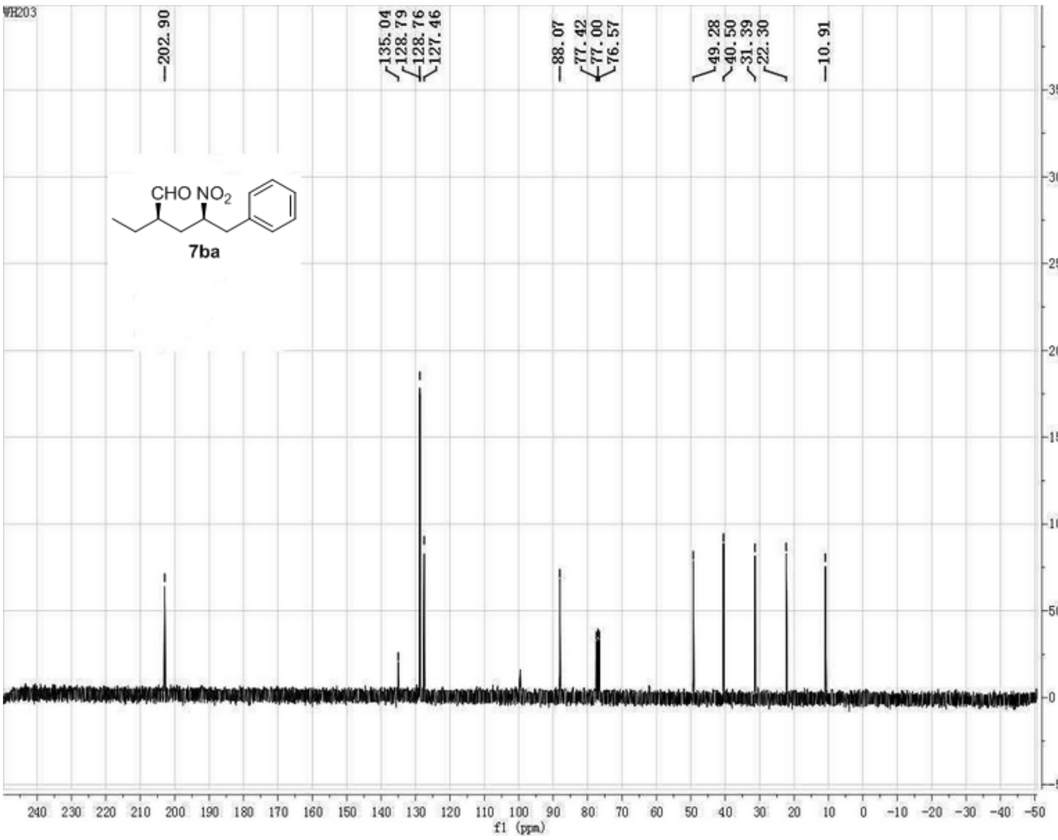
0.88
1.91
0.89 1.96 1.11 1.06
3.00
f1 (ppm)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f1 (ppm)

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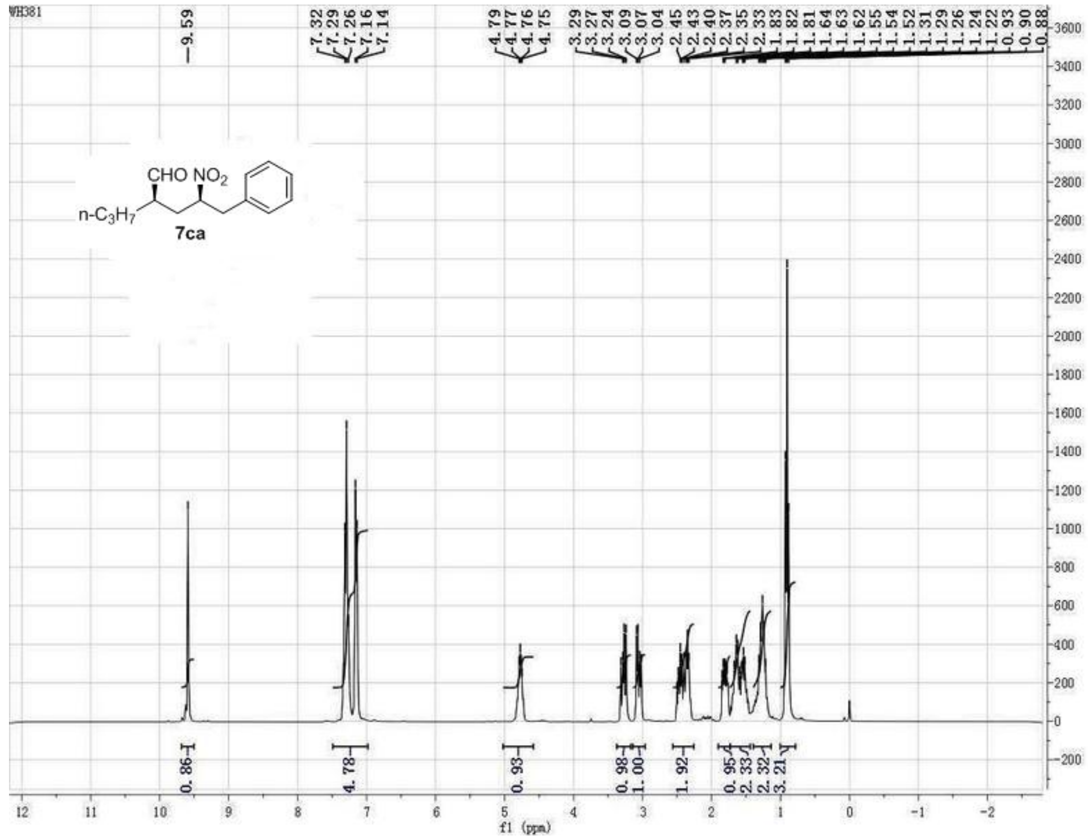

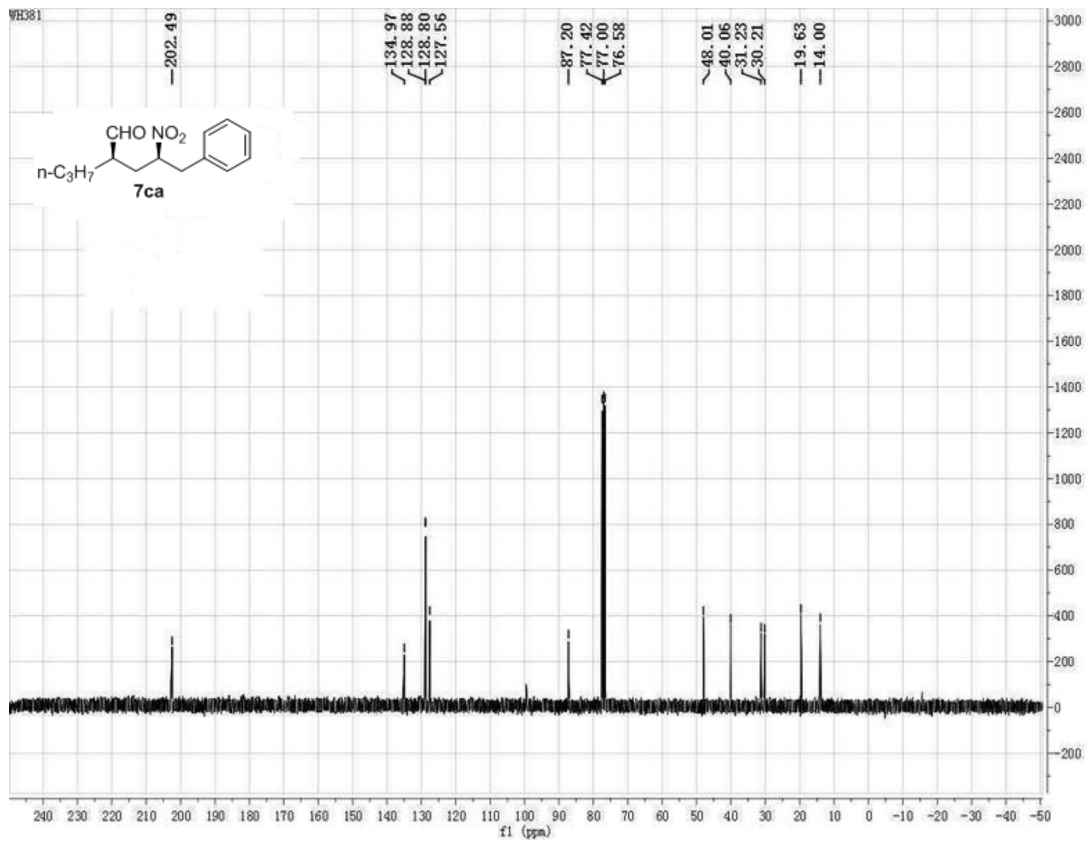

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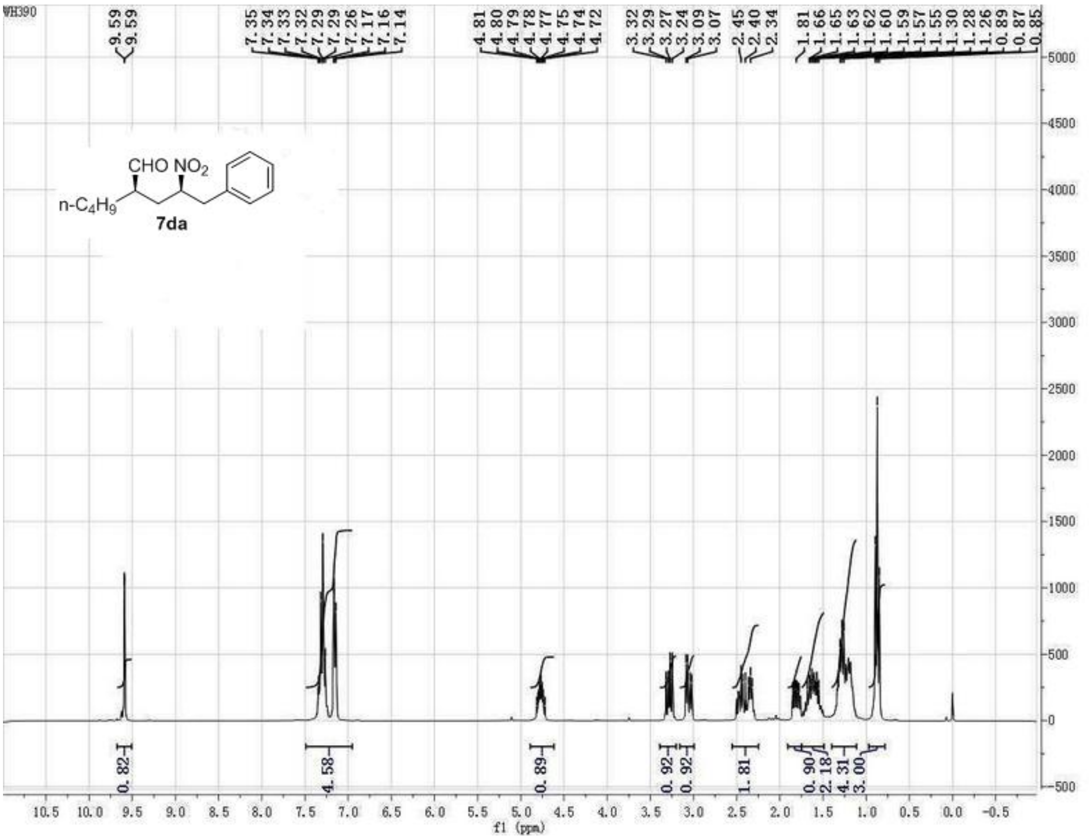

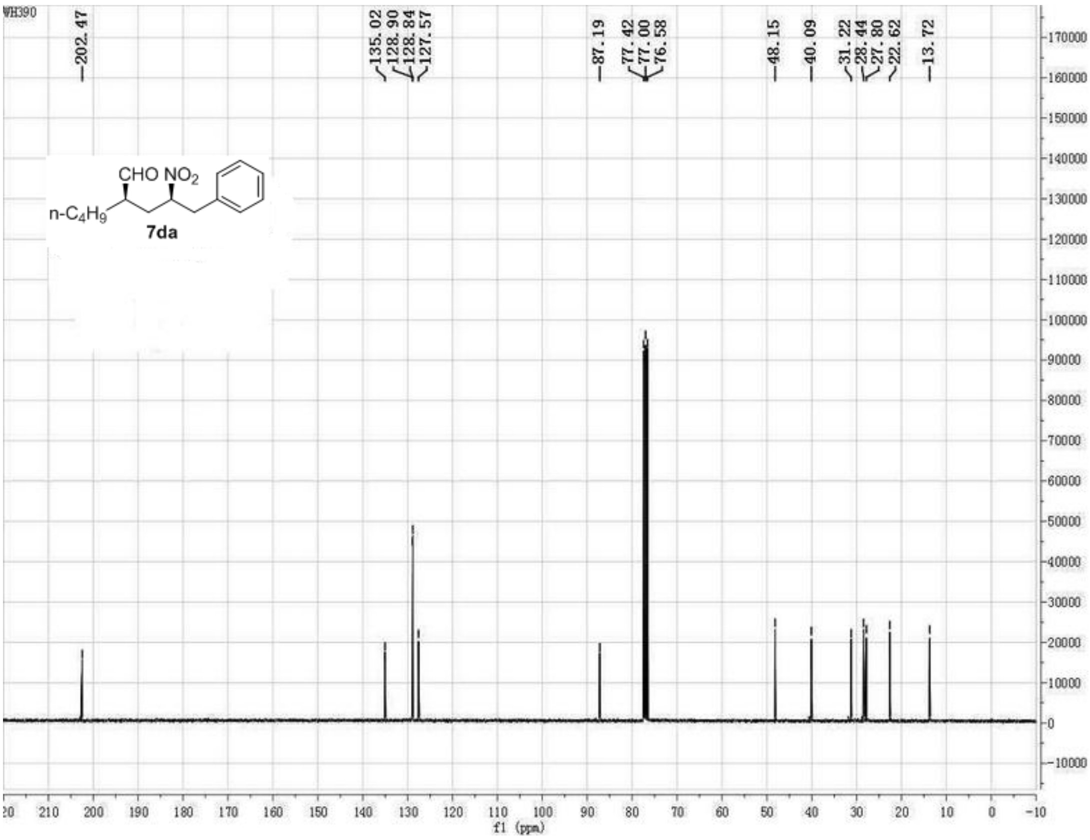

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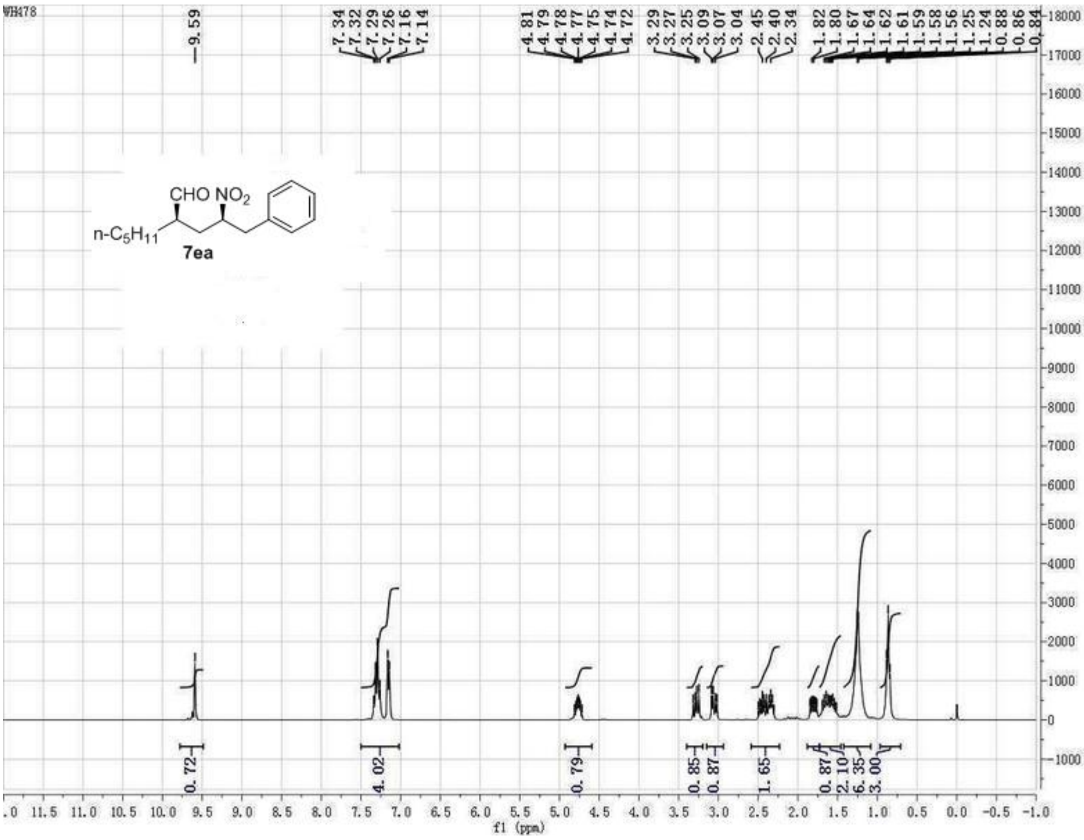

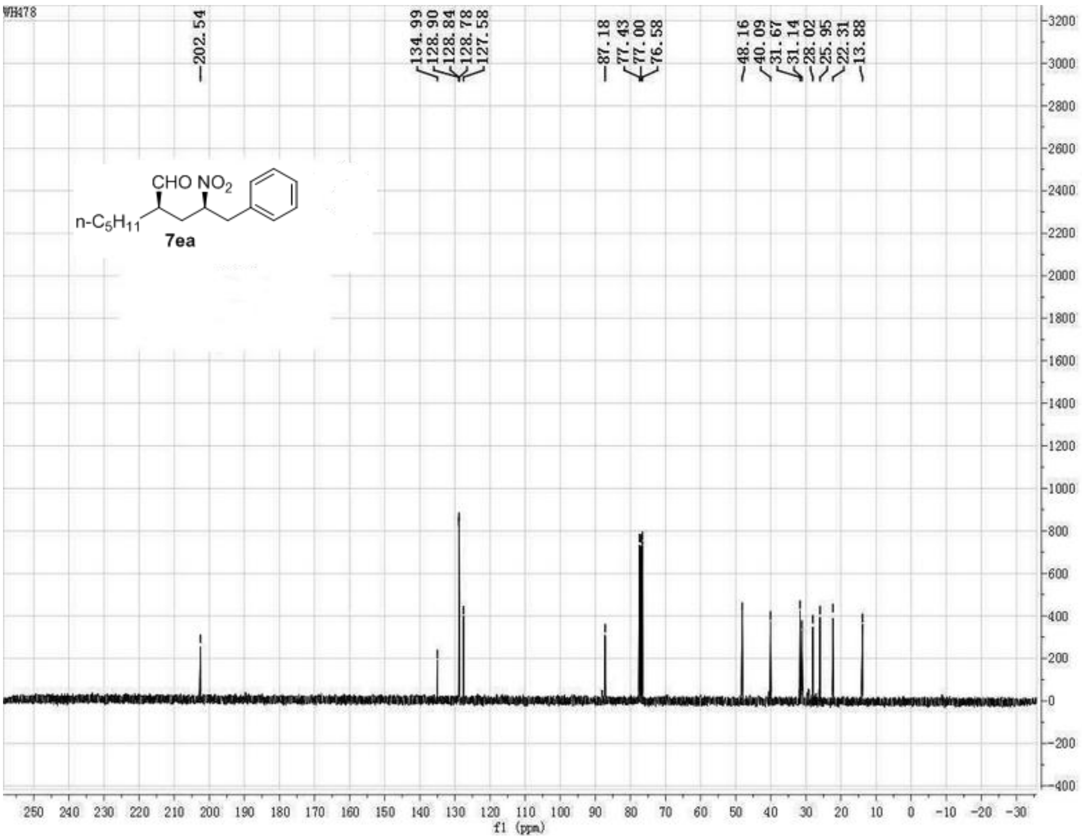

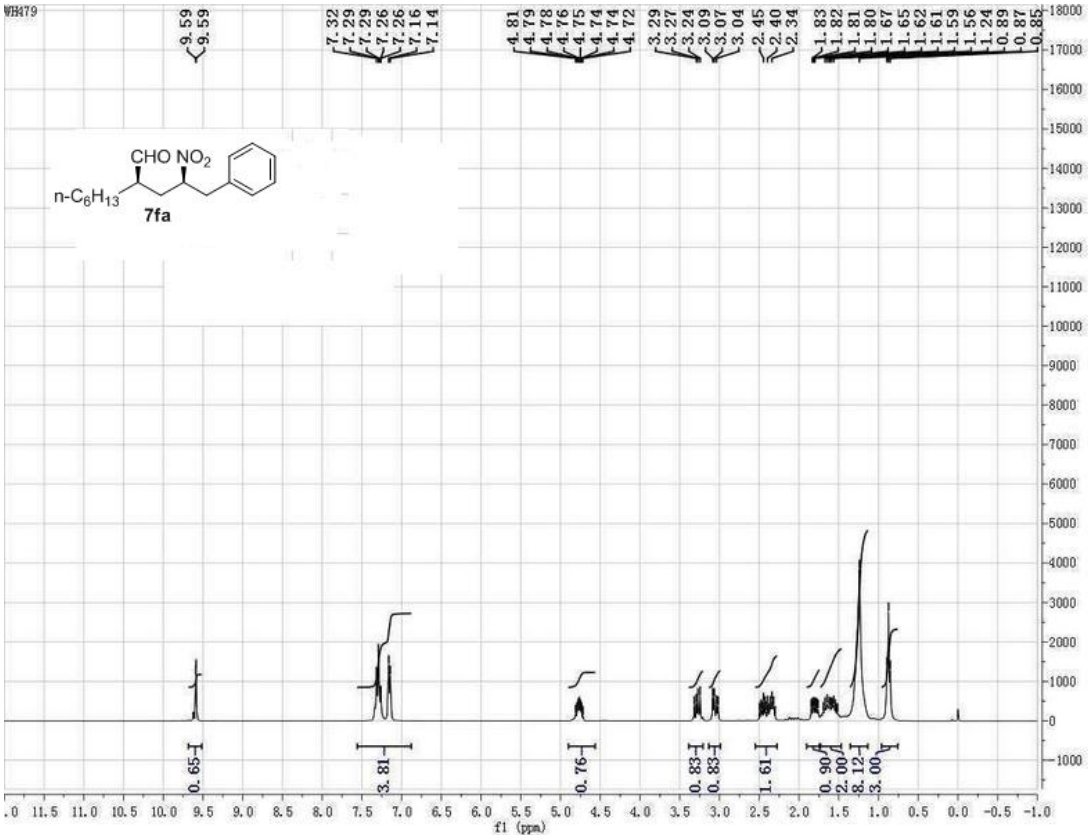

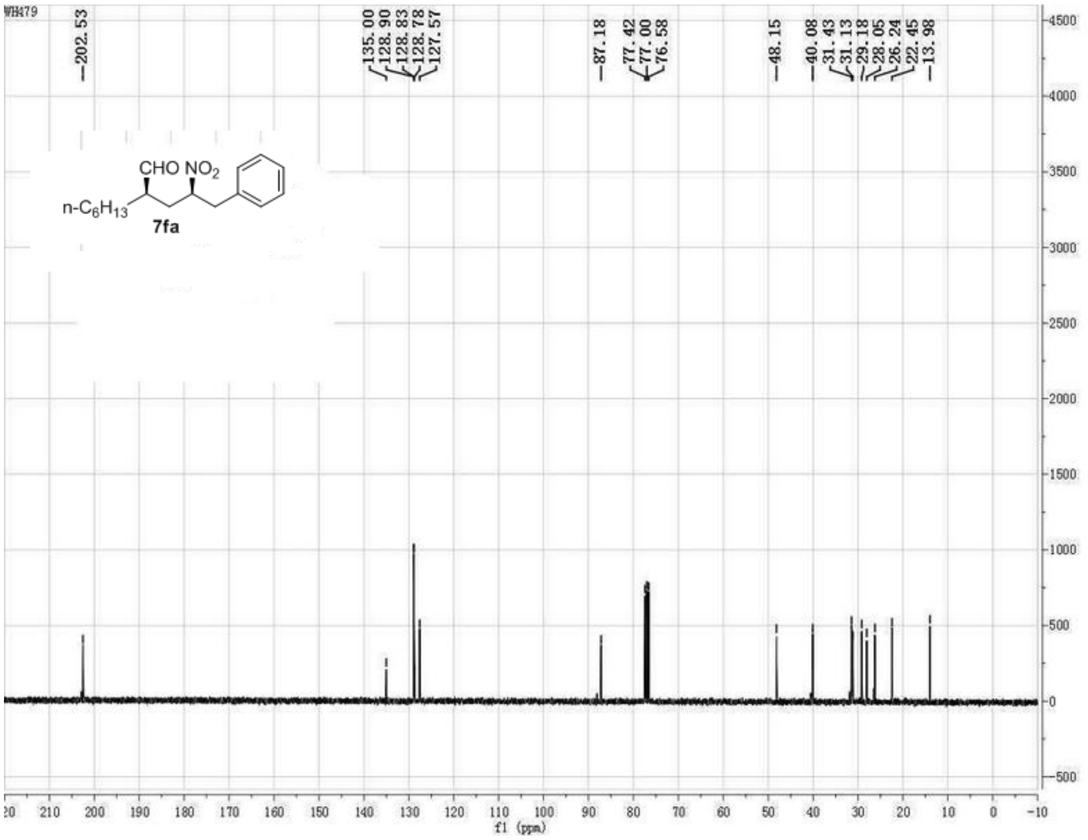

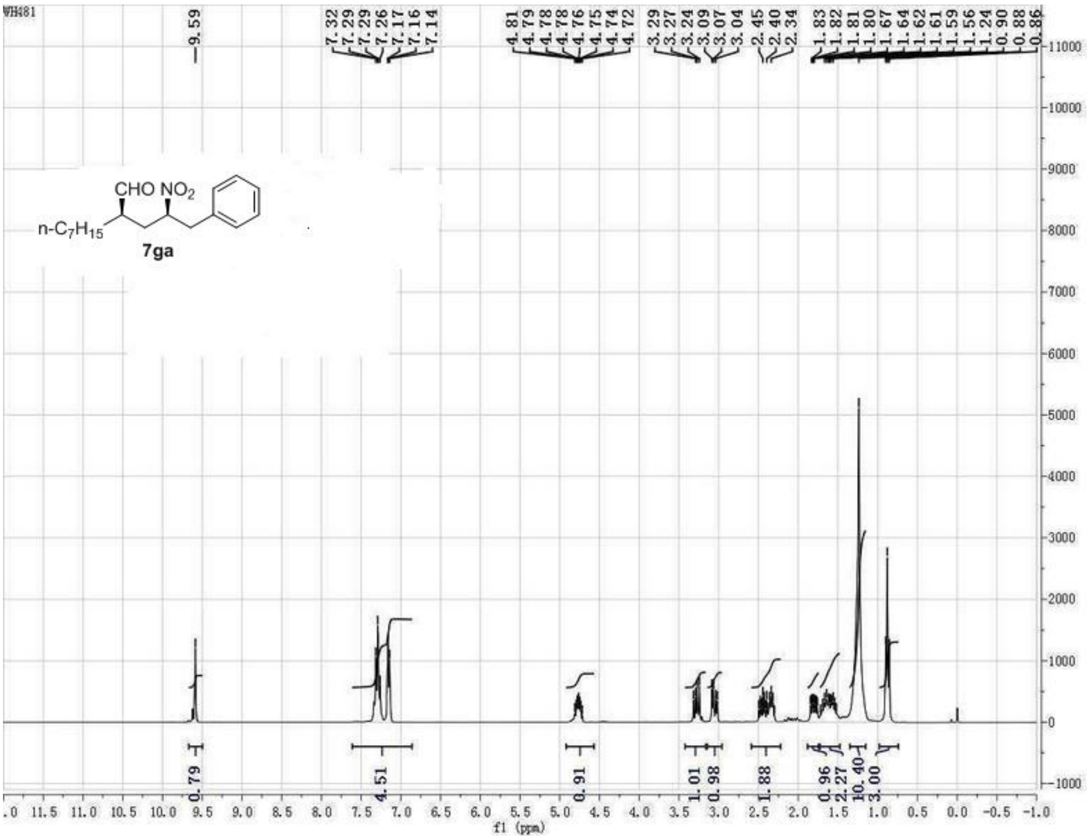
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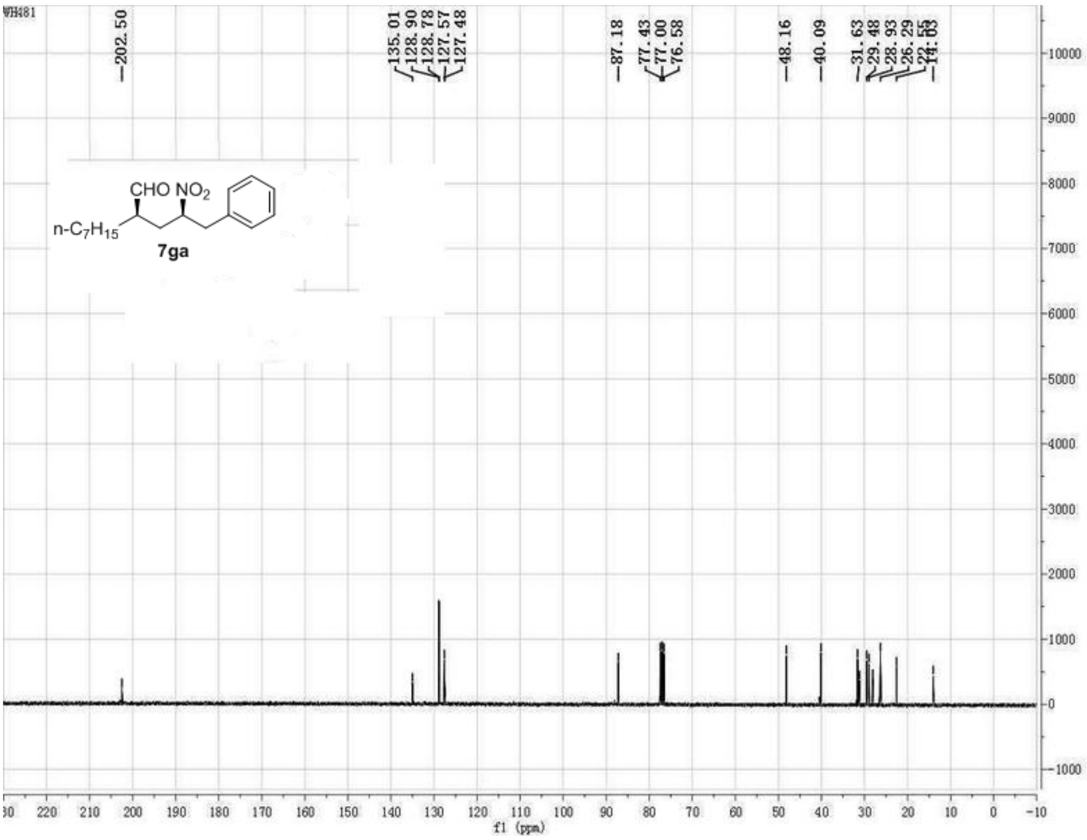
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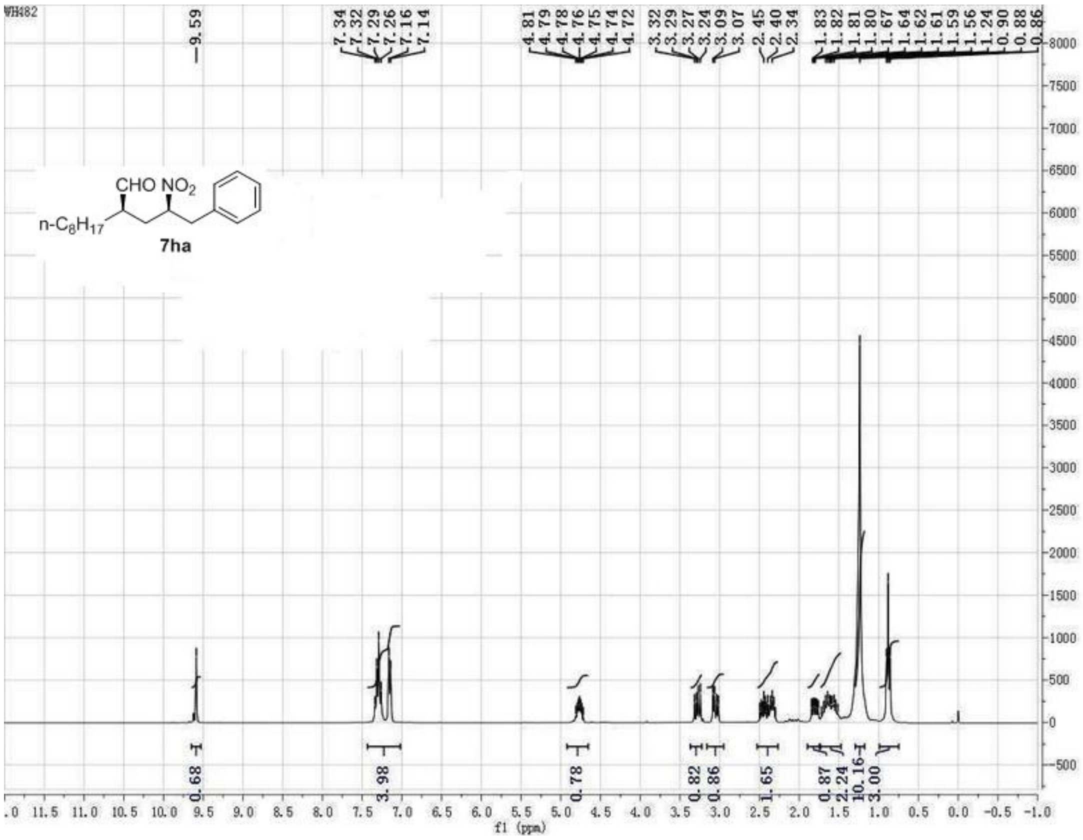

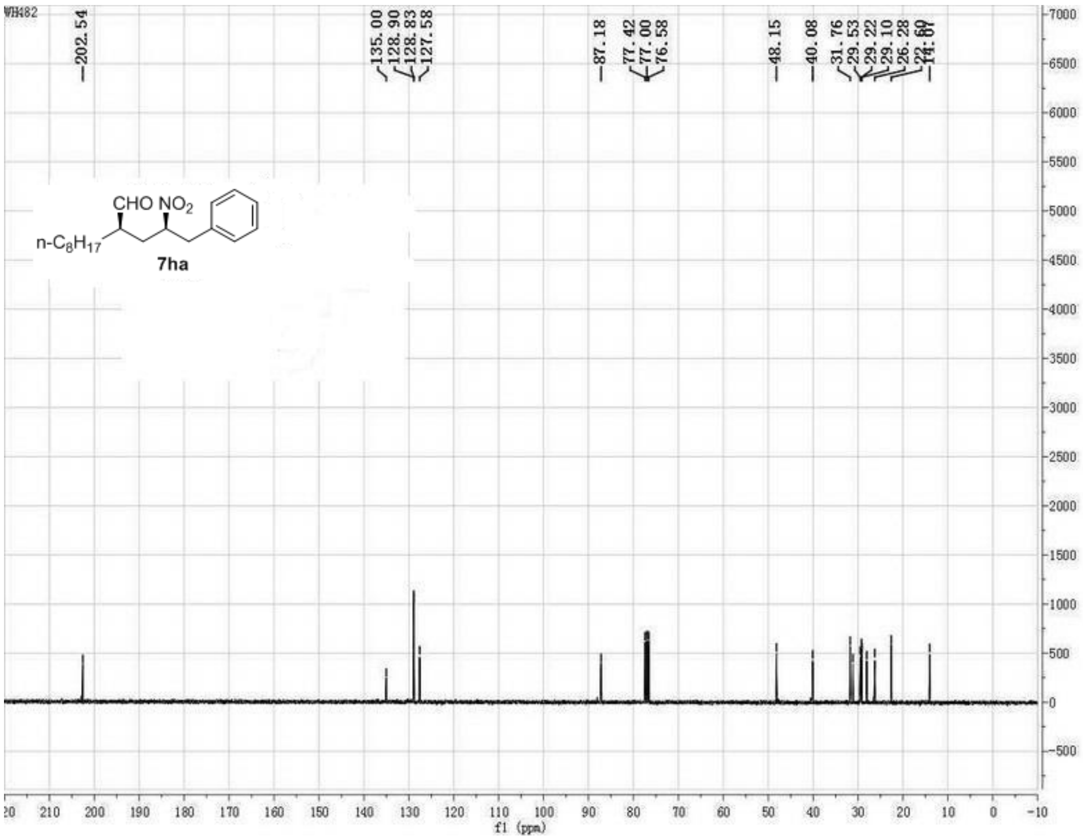

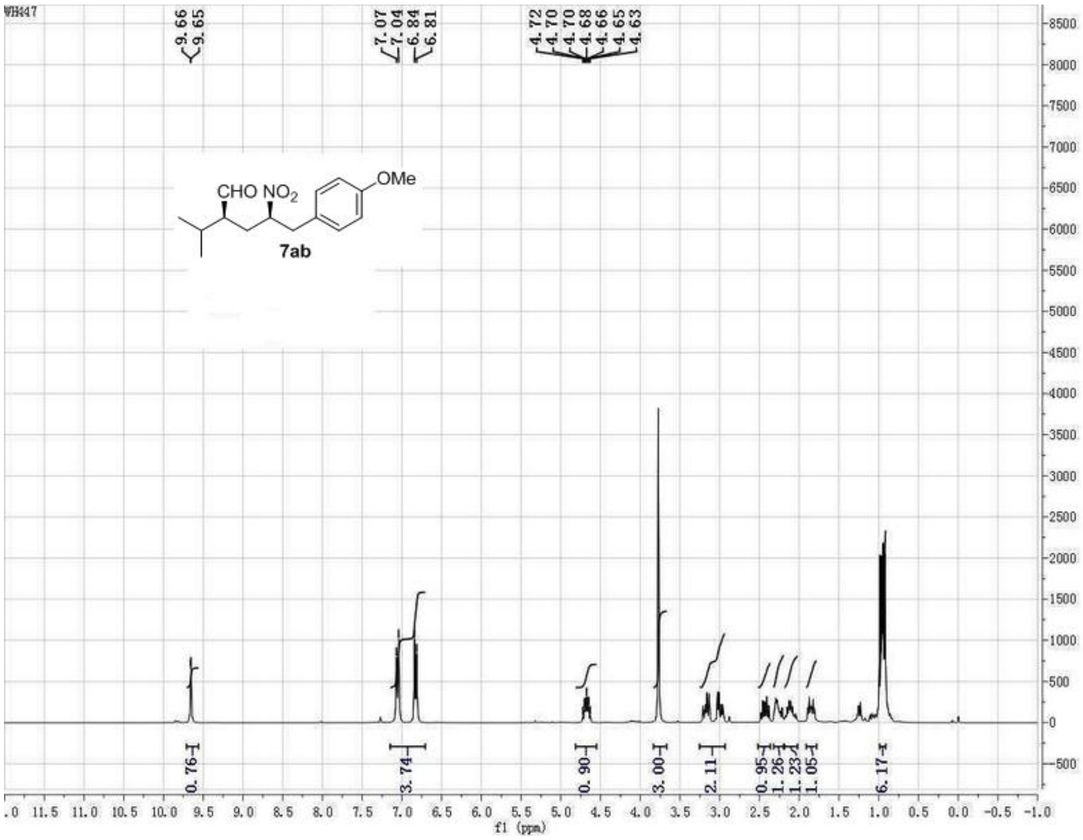
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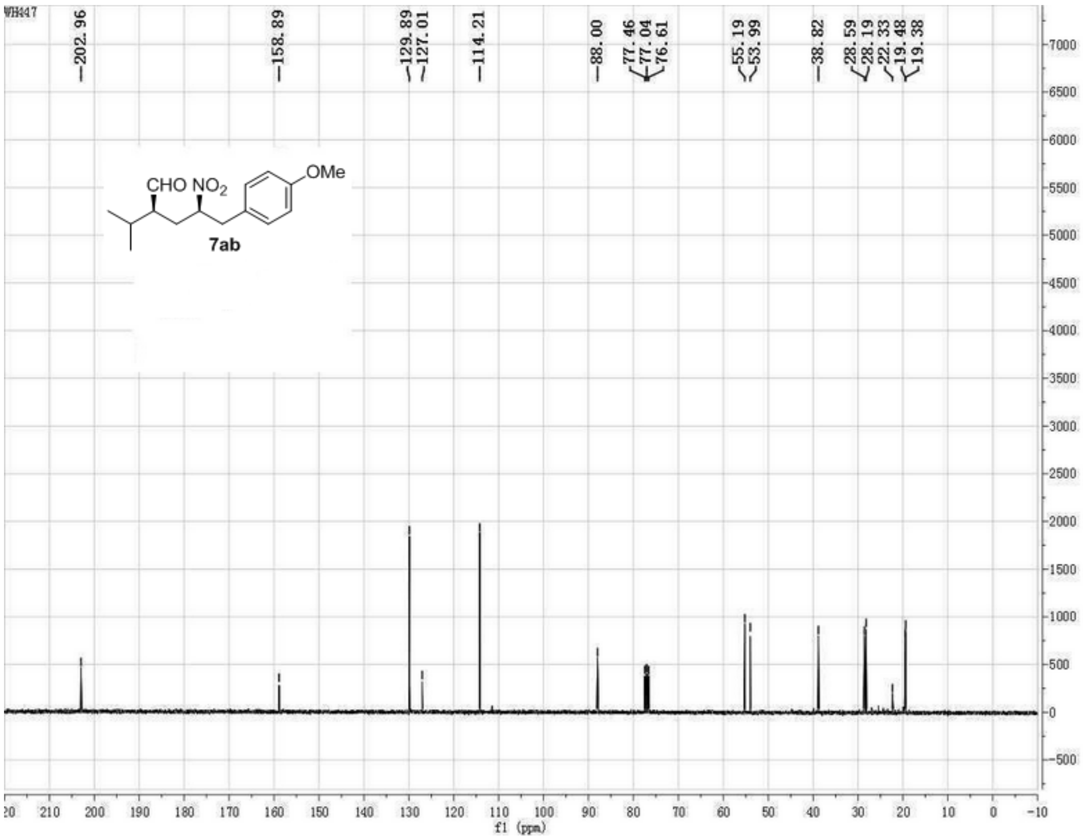
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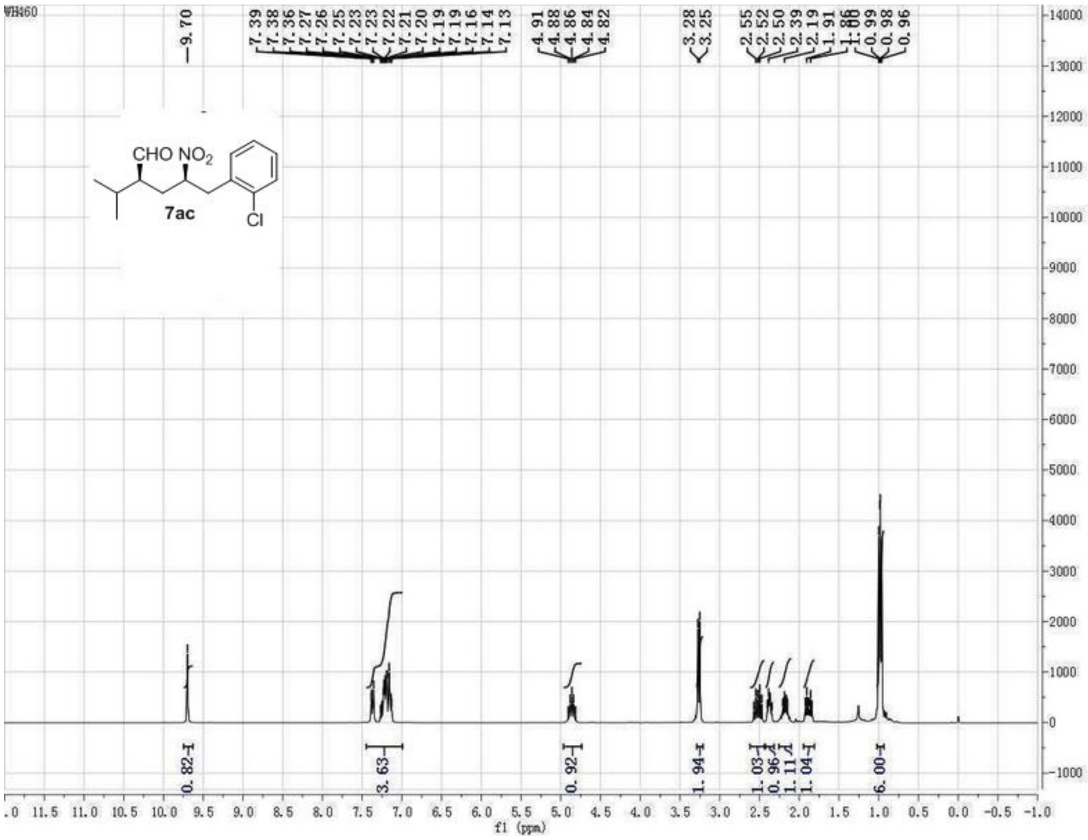
f1 (ppm)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7.20
7.19
7.19
7.16
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7.13
4.91
4.88
4.86
4.84
4.82
3.28
3.25
2.55
2.52
2.50
2.39
2.19
1.91
0.99
0.98
0.96
CHO NO2
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Cl
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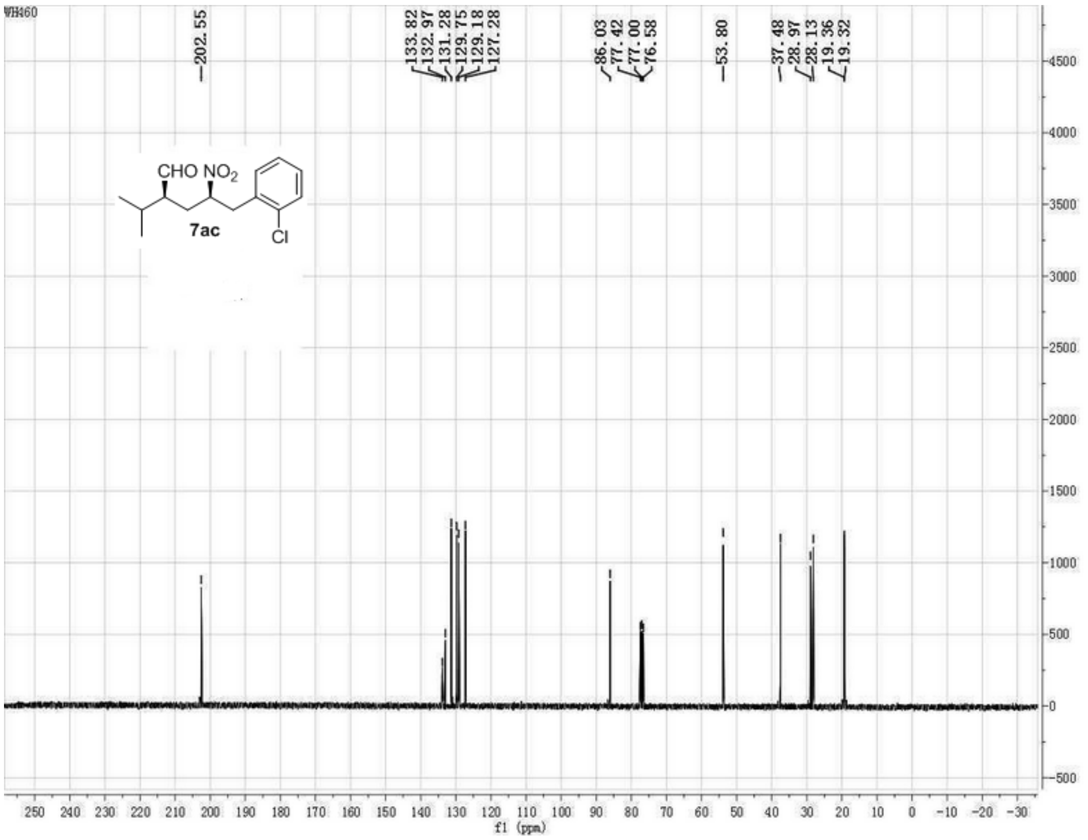
1.04
6.00
f1 (ppm)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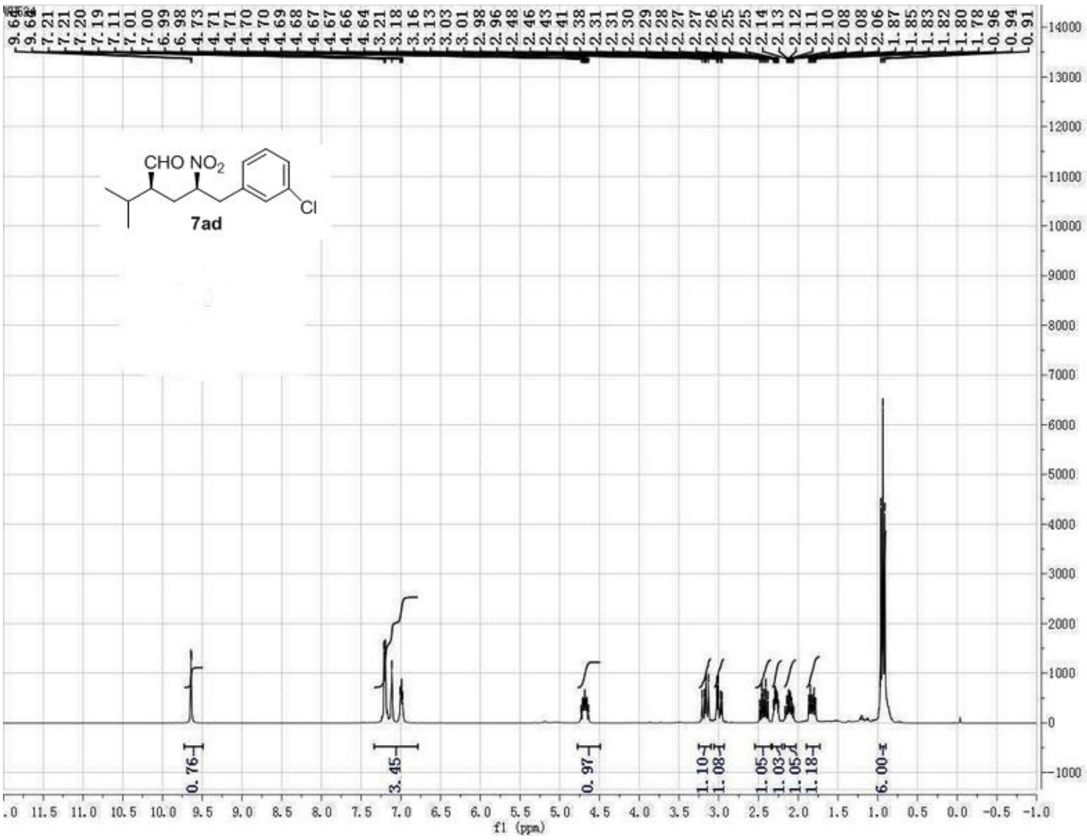
19.32
CHO NO2
7ac
Cl
f1 (ppm)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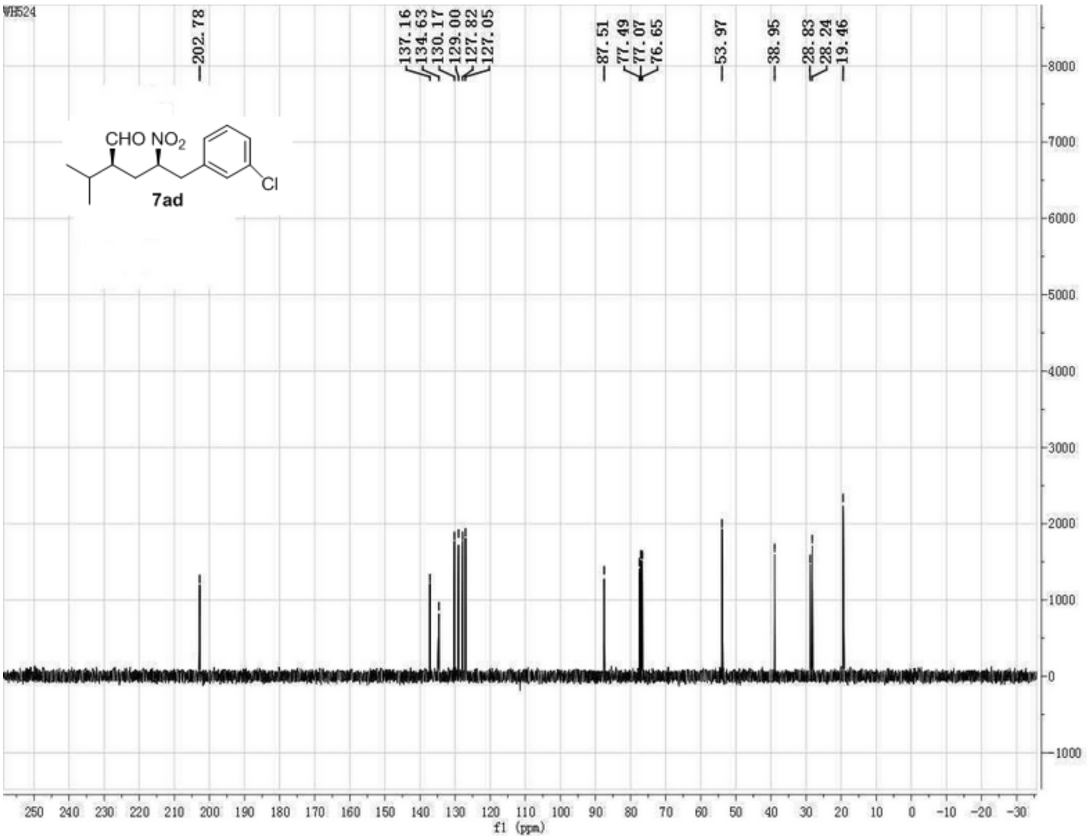
Cl
7ad
f1 (ppm)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28.83
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19.46
f1 (ppm)

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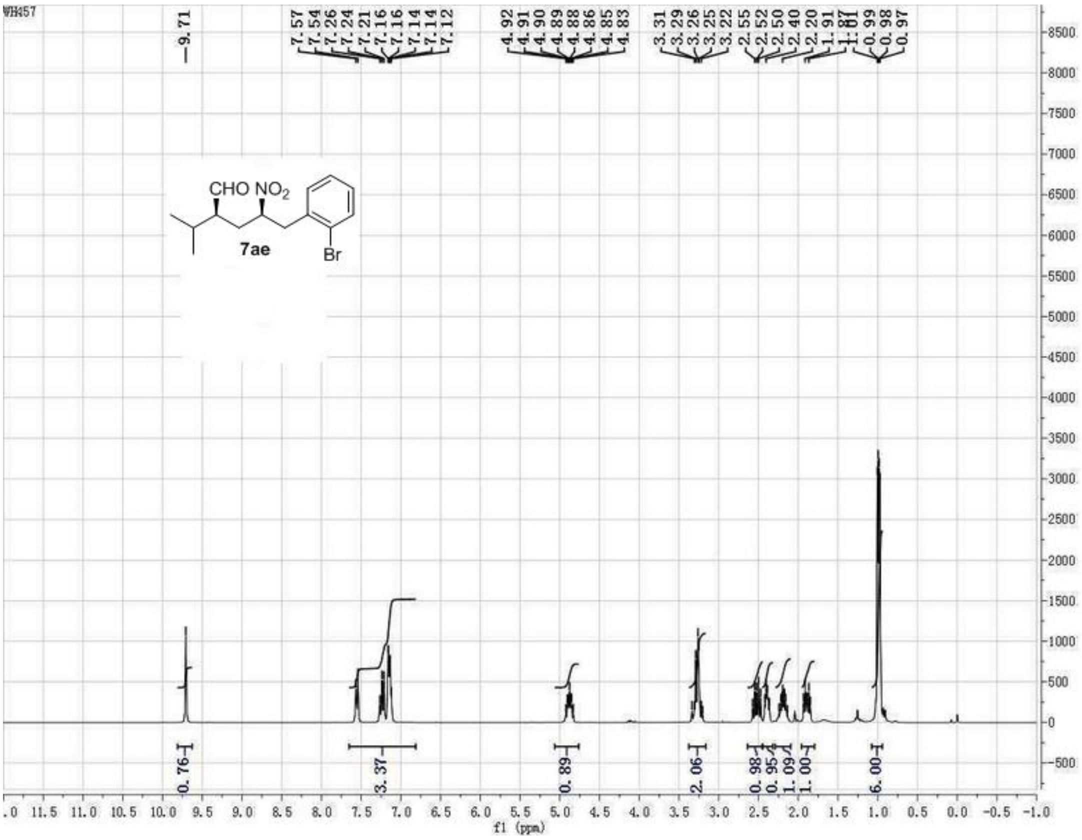

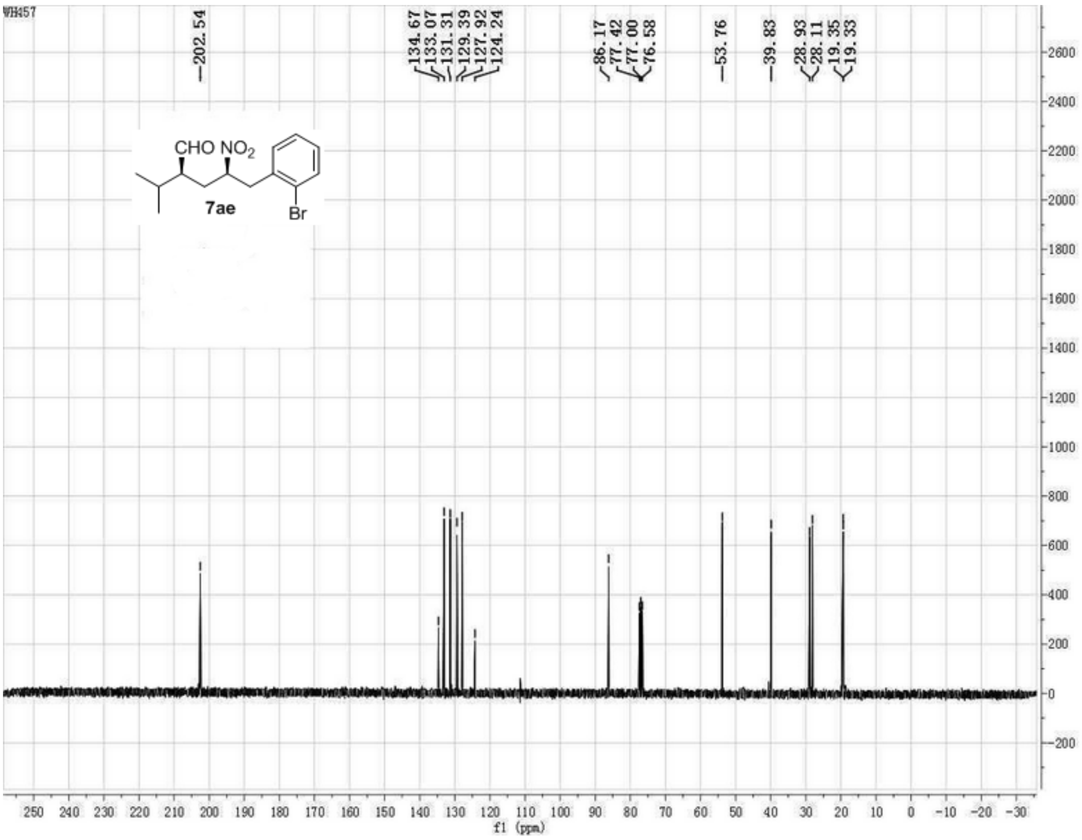

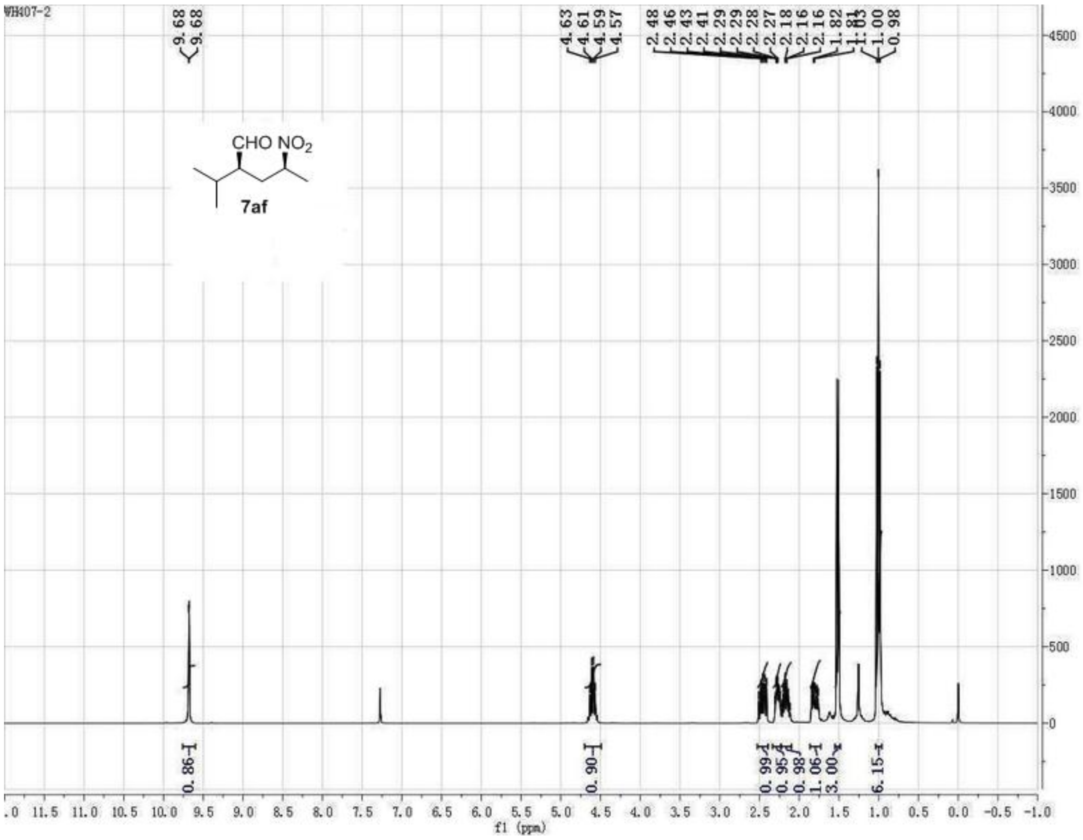
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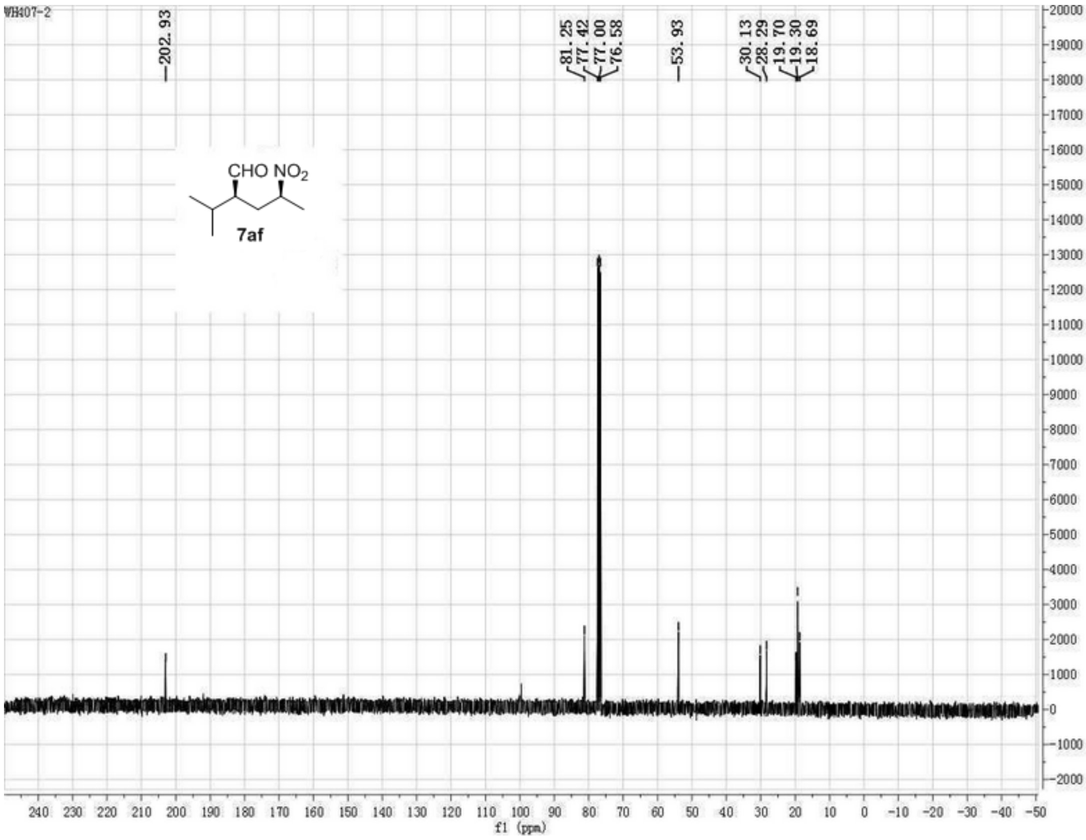
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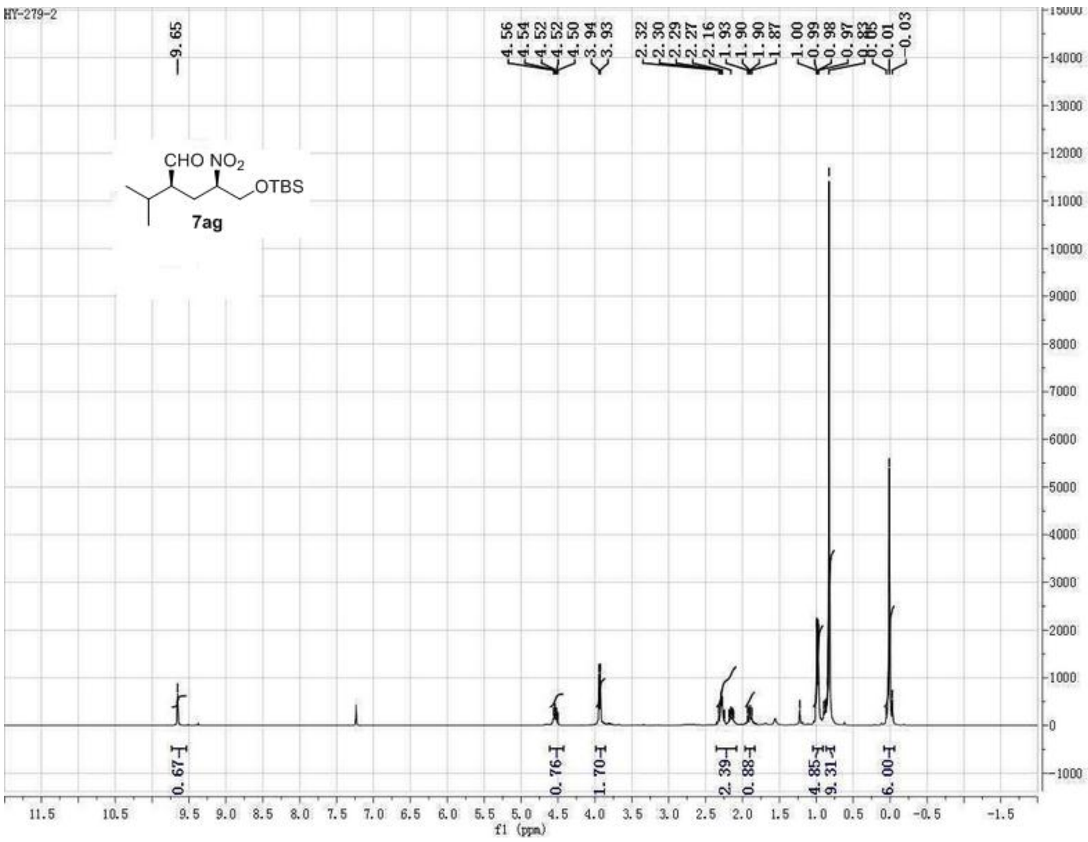
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1.00 0.99 0.98 0.97 0.85 0.83 0.01 0.03
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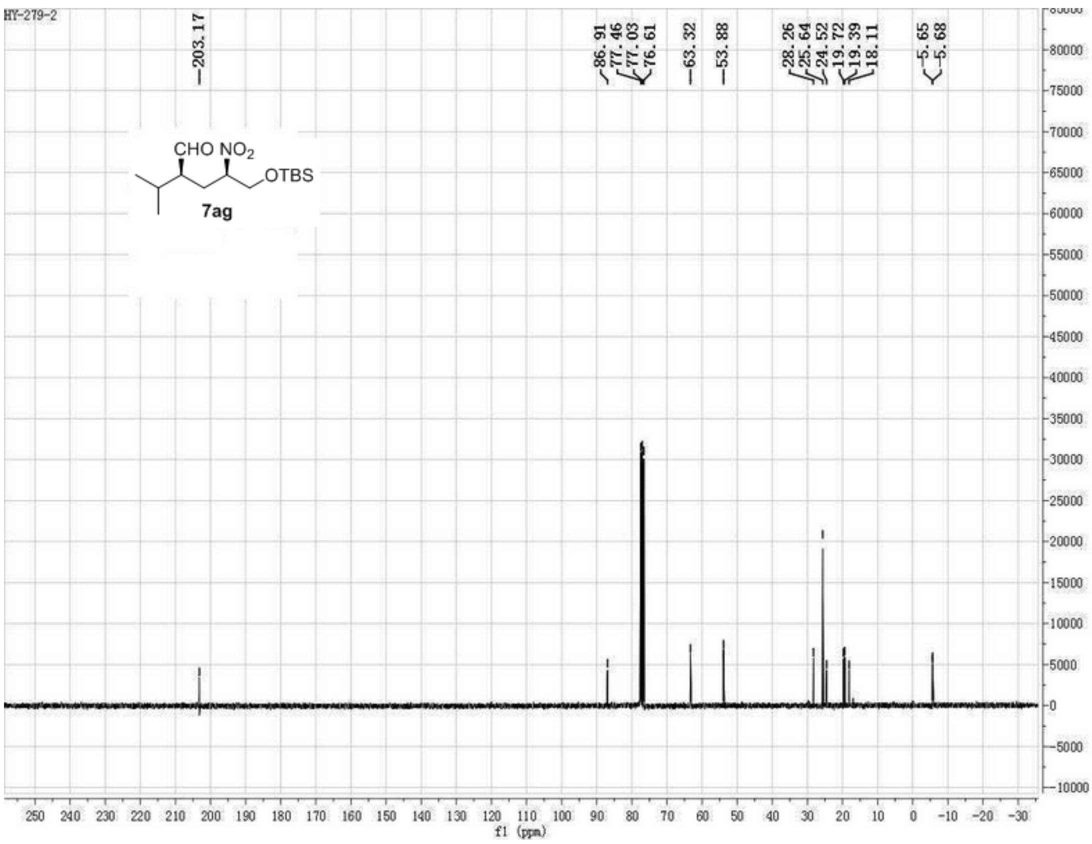
f1 (ppm)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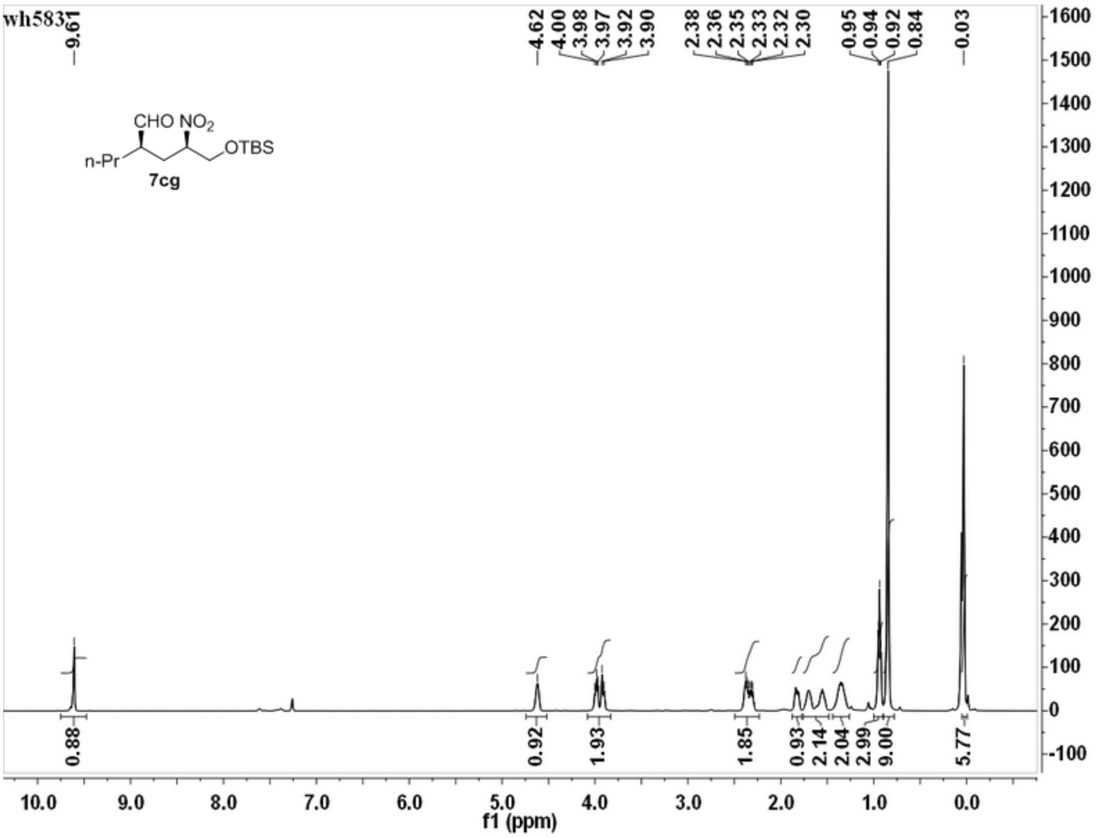
f1 (ppm)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2.33
2.32
2.30
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0.92
0.84
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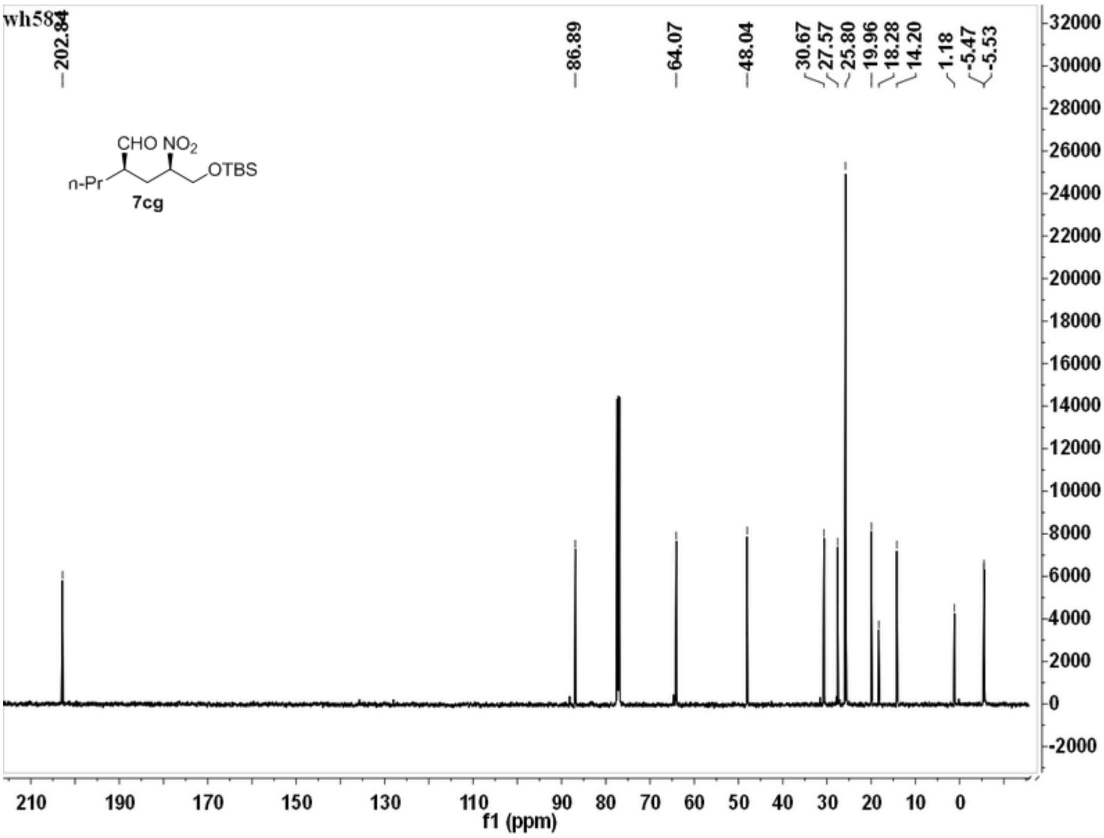
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14.20
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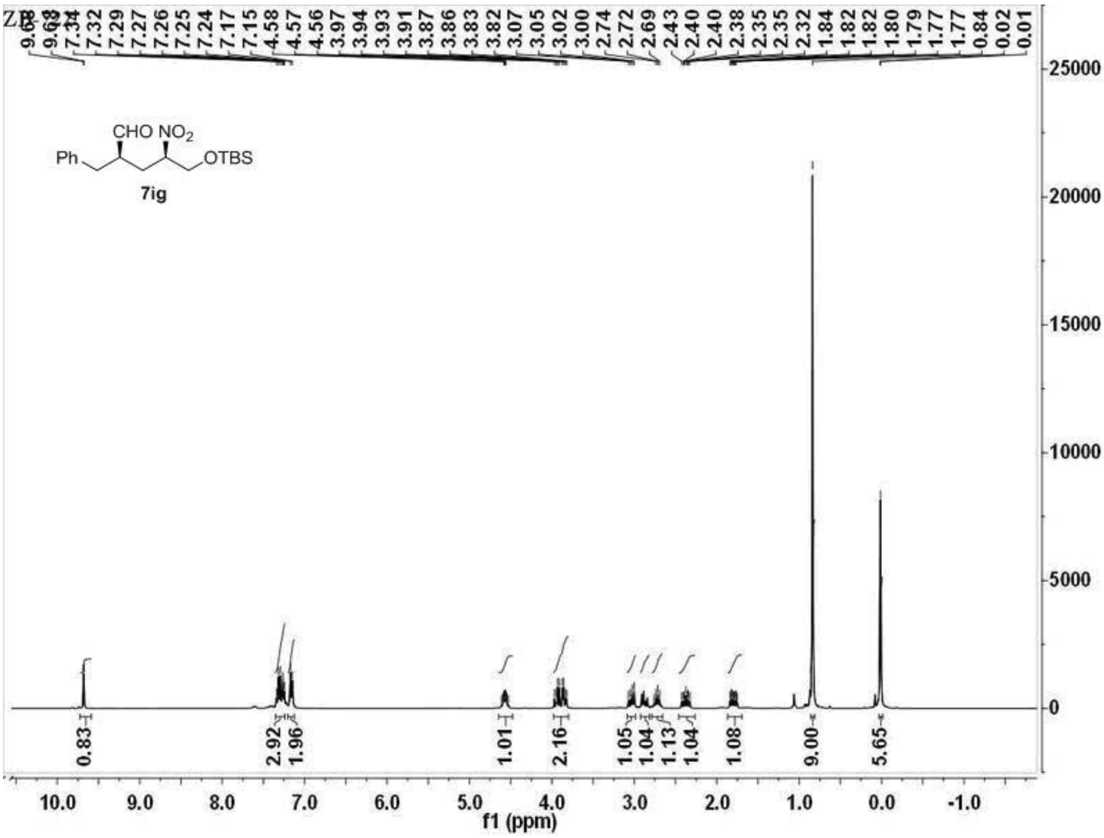
f1 (ppm)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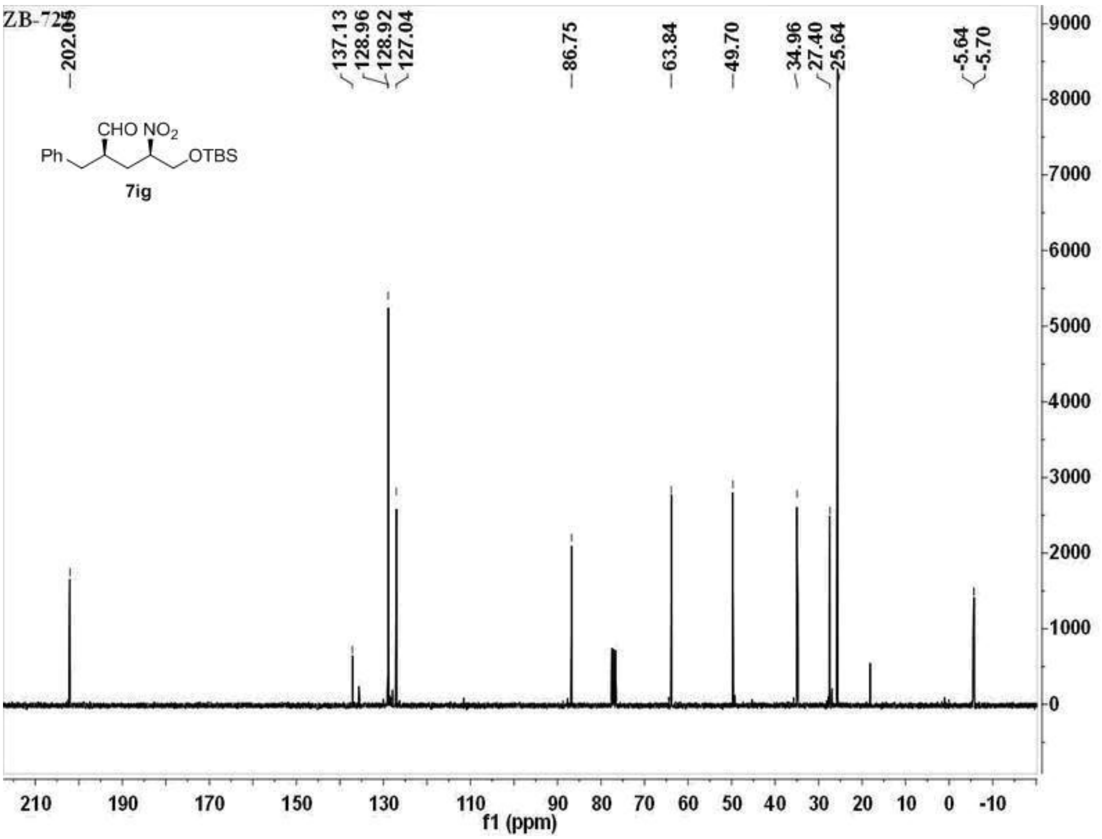
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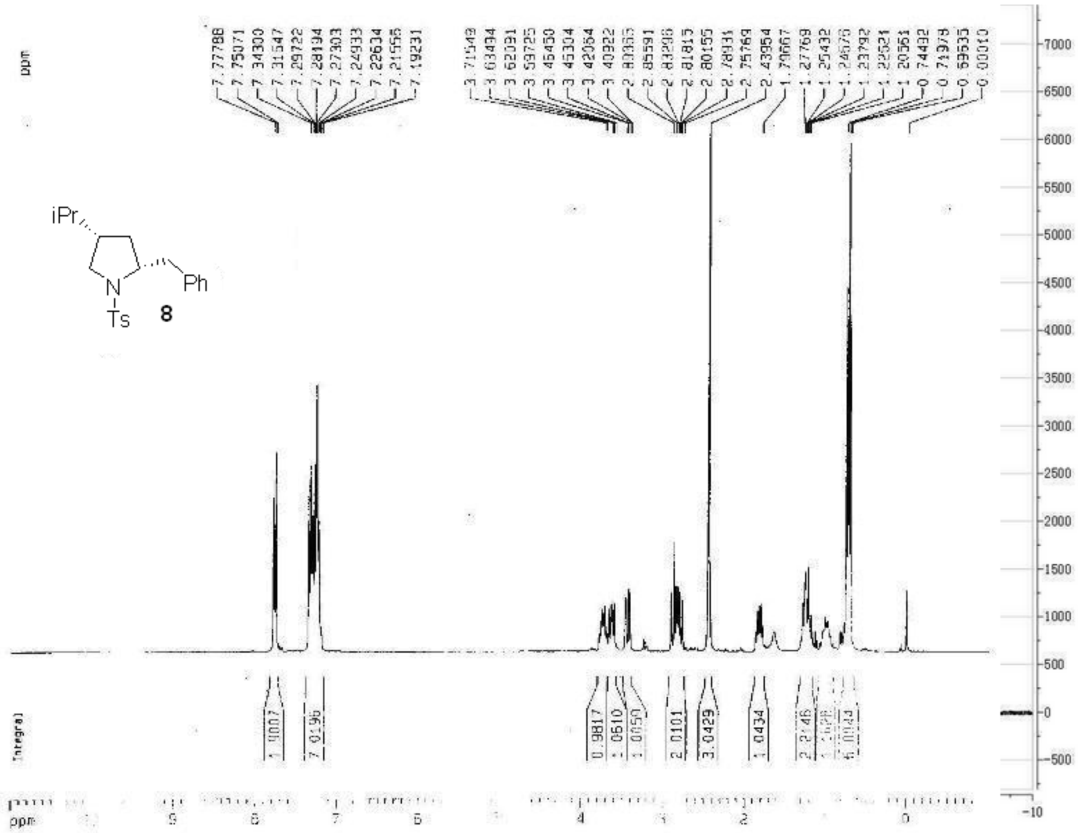

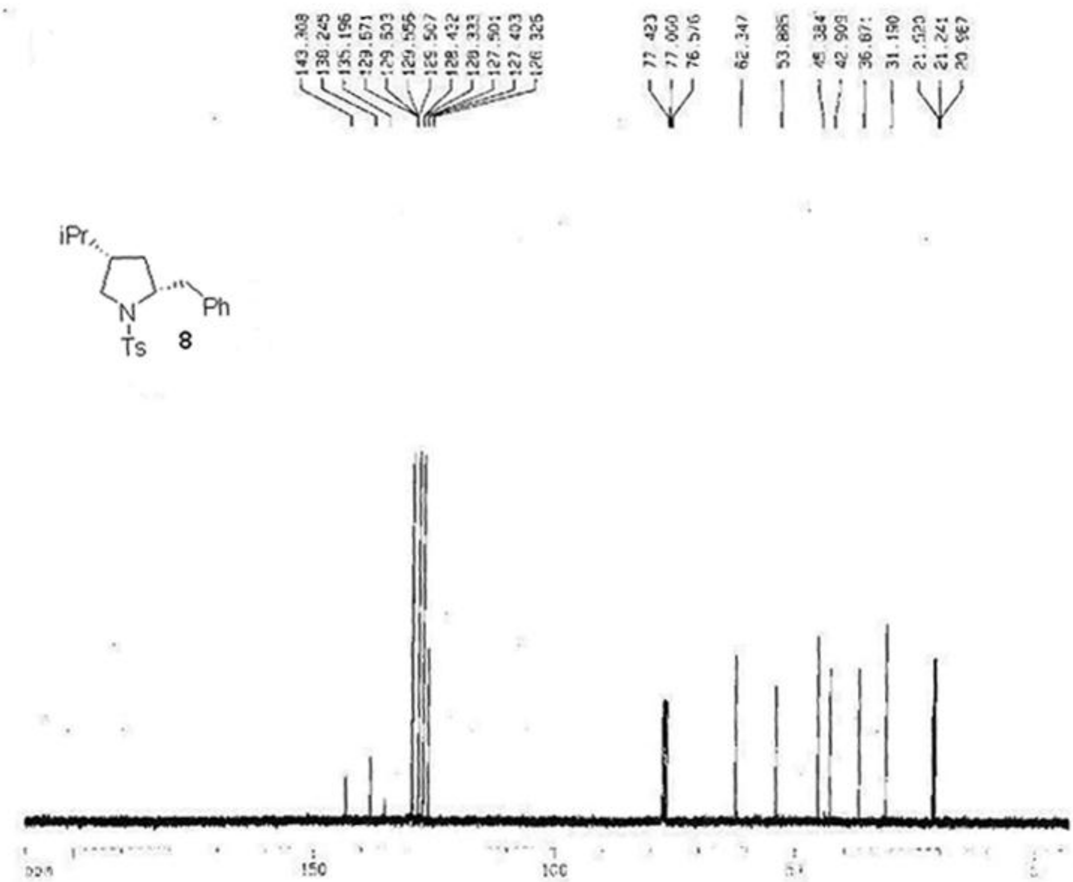

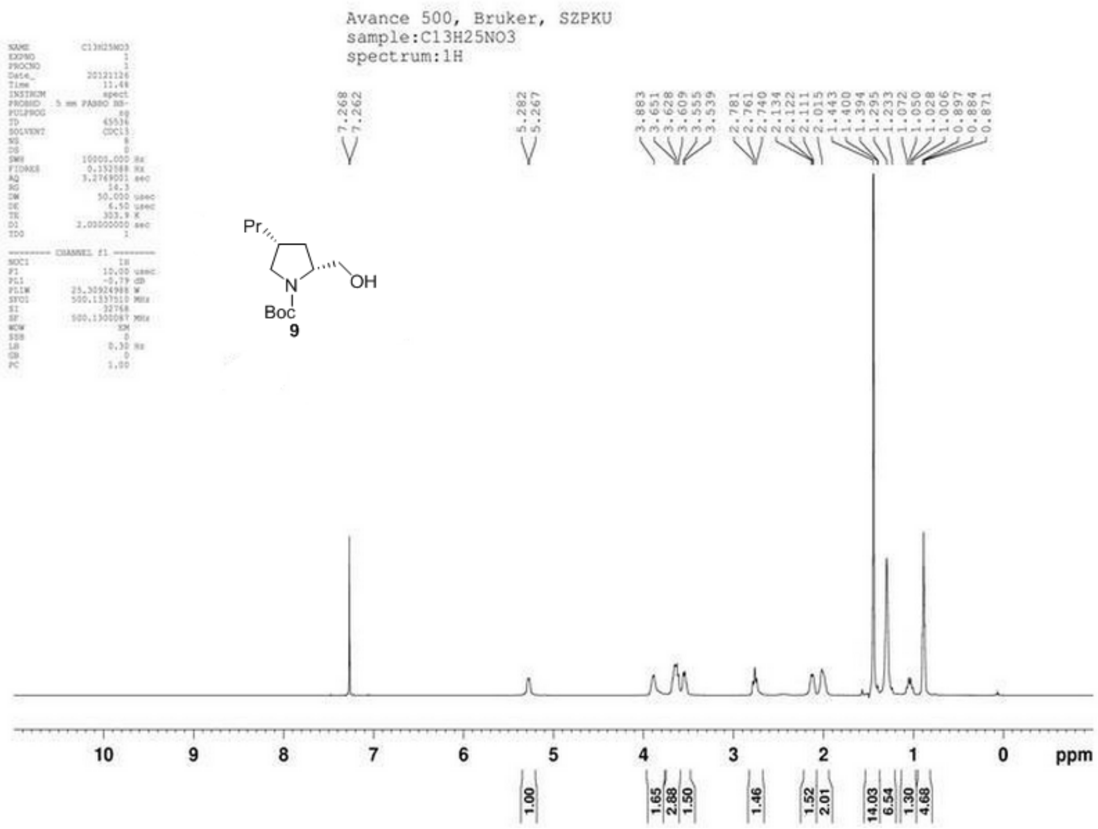
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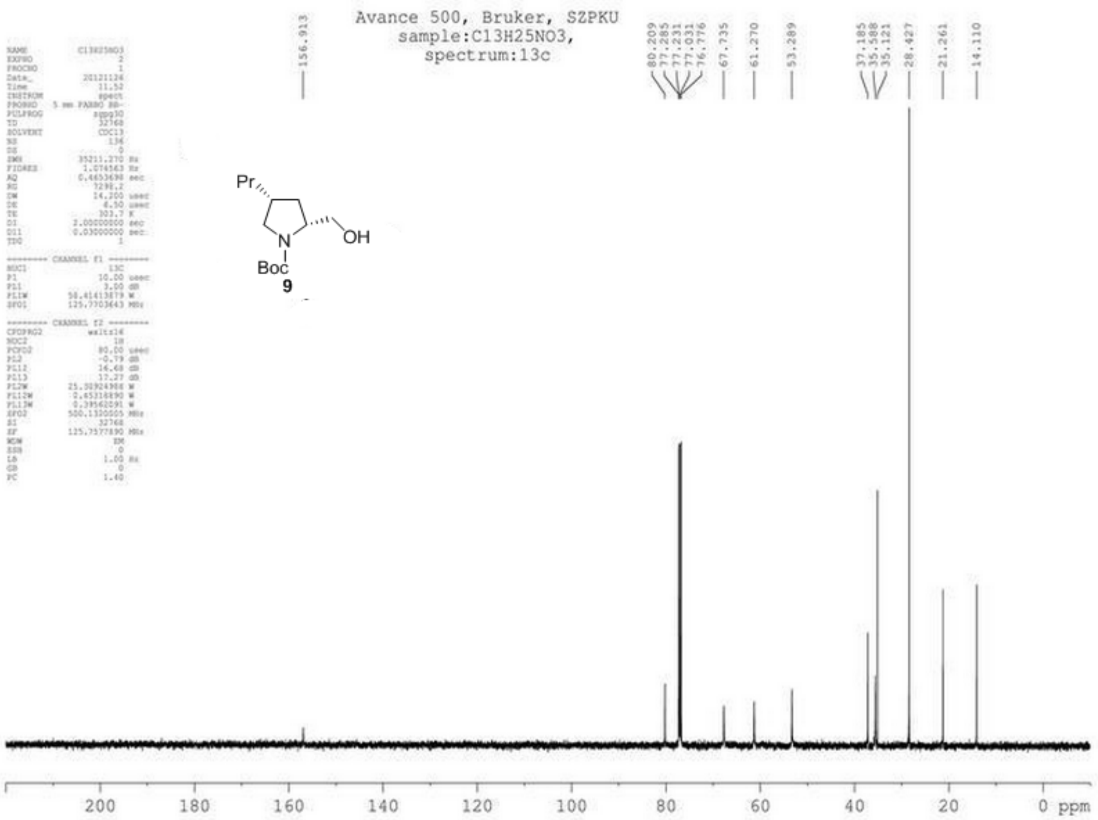
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OH
Boc
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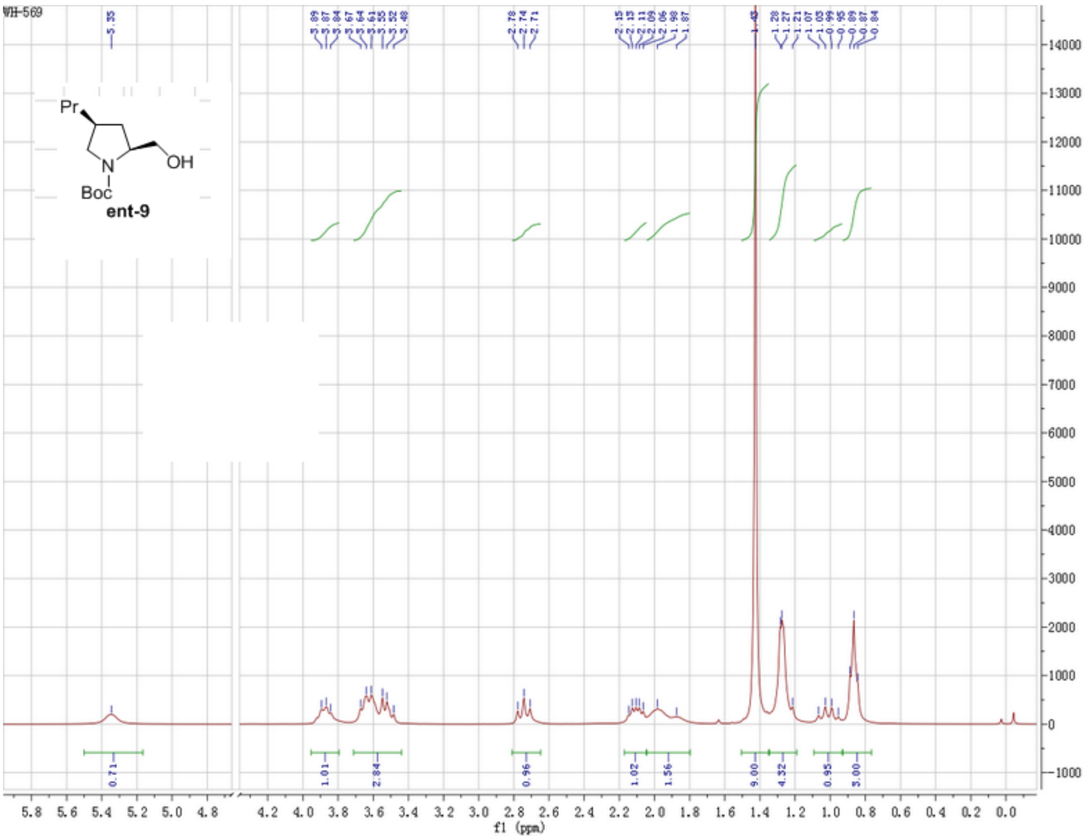
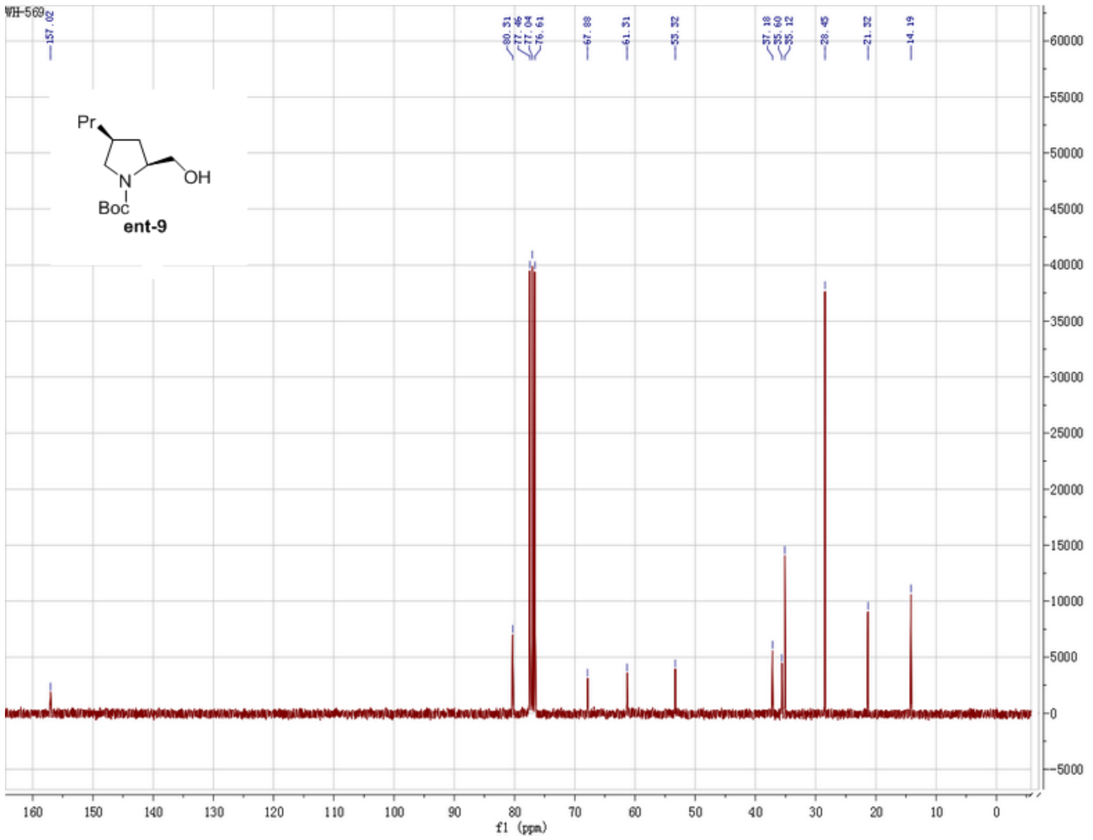
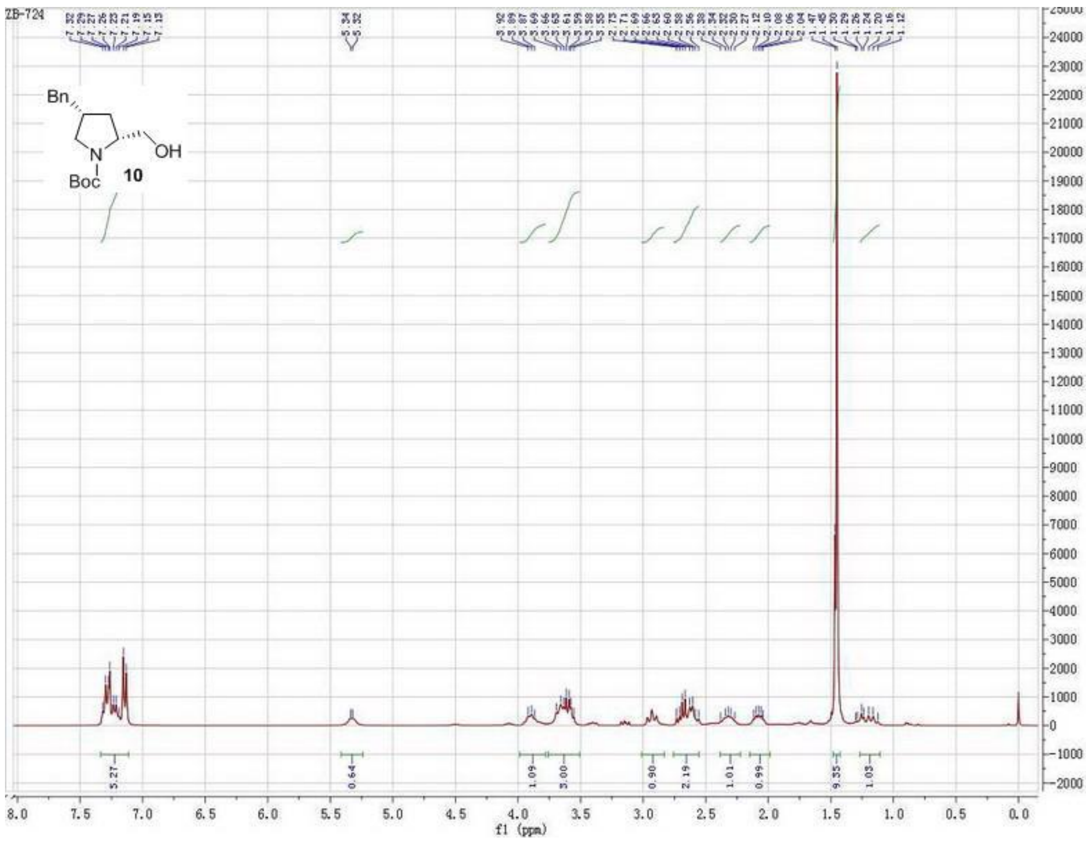
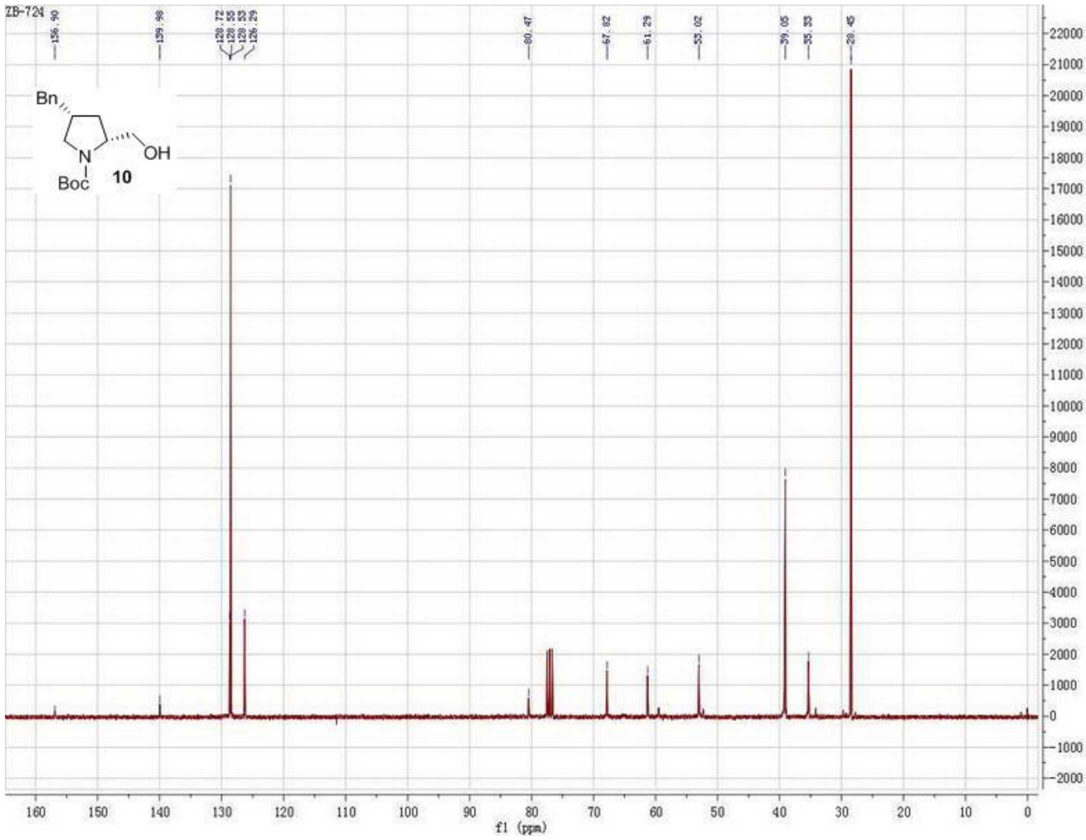
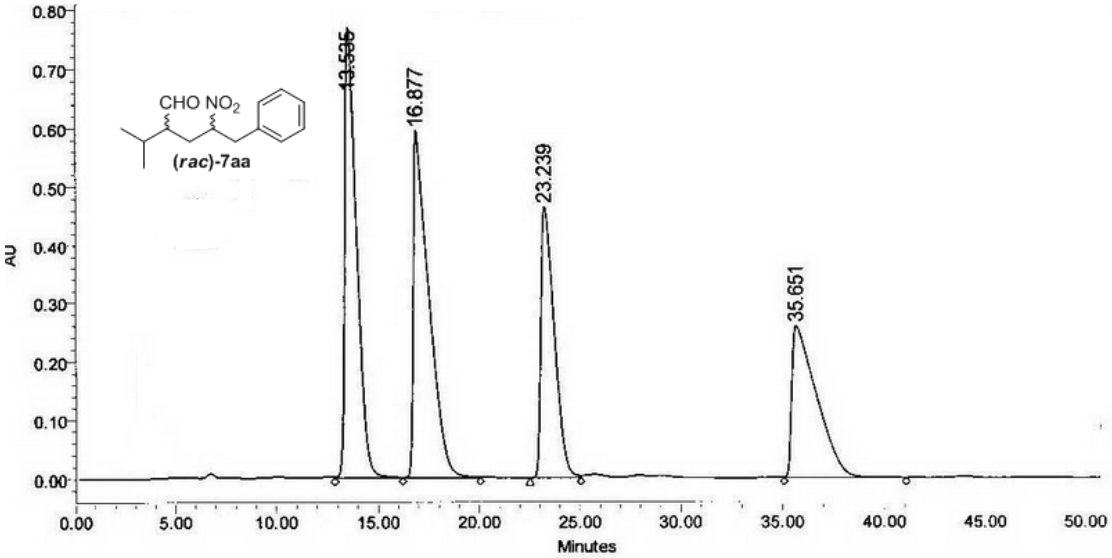




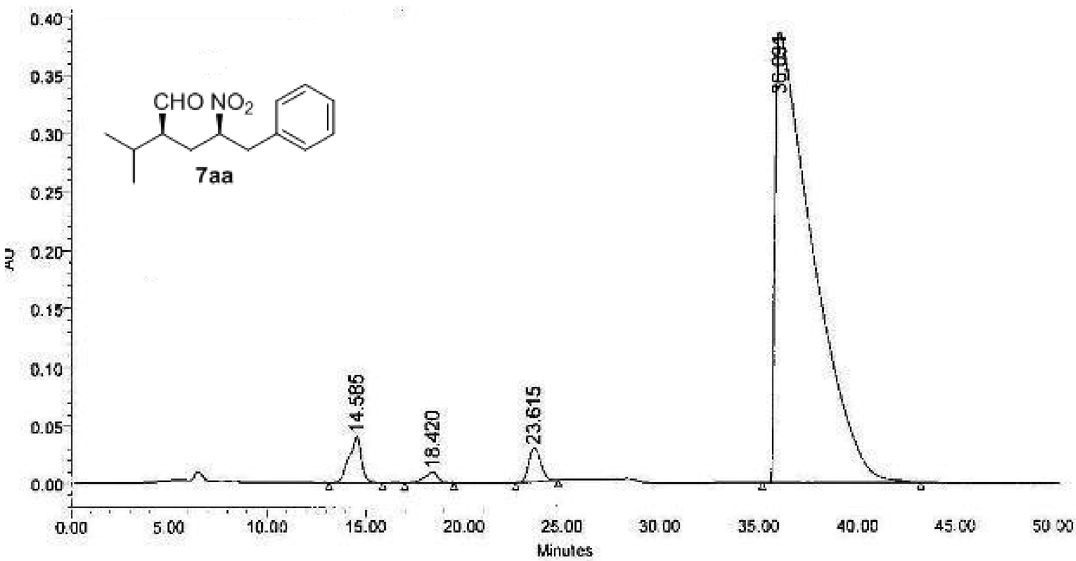




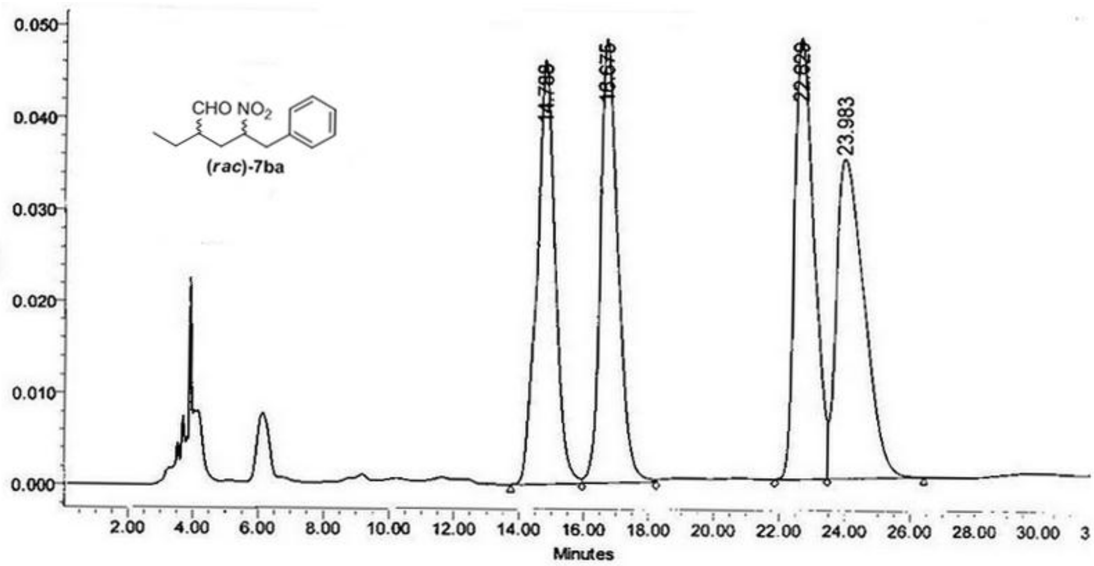
12. Part of the HPLC Analysis Data



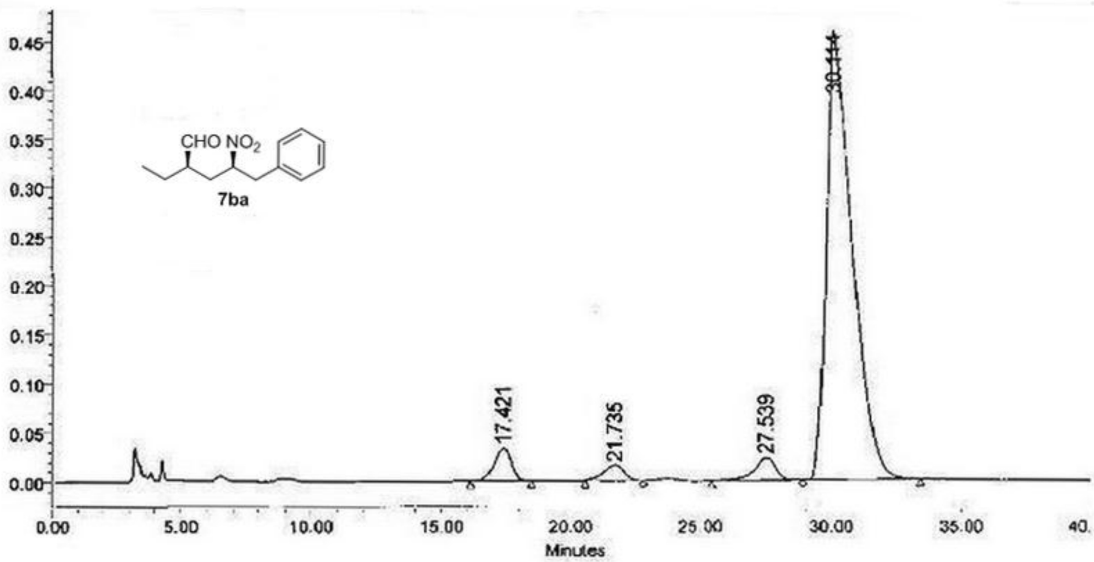
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.535	30739489	29.26	770201	36.83
2	16.877	31324500	29.82	597153	28.55
3	23.239	21290111	20.27	465821	22.27
4	35.651	21704284	20.66	258225	12.35



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.585	1719211	3.17	40462	8.67
2	18.420	434492	0.80	9249	1.98
3	23.615	1235359	2.28	29238	6.26
4	36.091	50843135	93.75	387880	83.09



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.788	1806194	23.61	46197	26.01
2	16.675	1818613	23.77	48362	27.23
3	22.629	1970697	25.76	48098	27.08
4	23.983	2054797	26.86	34948	19.68



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.421	1483209	4.25	32999	6.20
2	21.735	826097	2.37	15355	2.88
3	27.539	1260629	3.61	23031	4.33
4	30.114	31321611	89.77	460919	86.59

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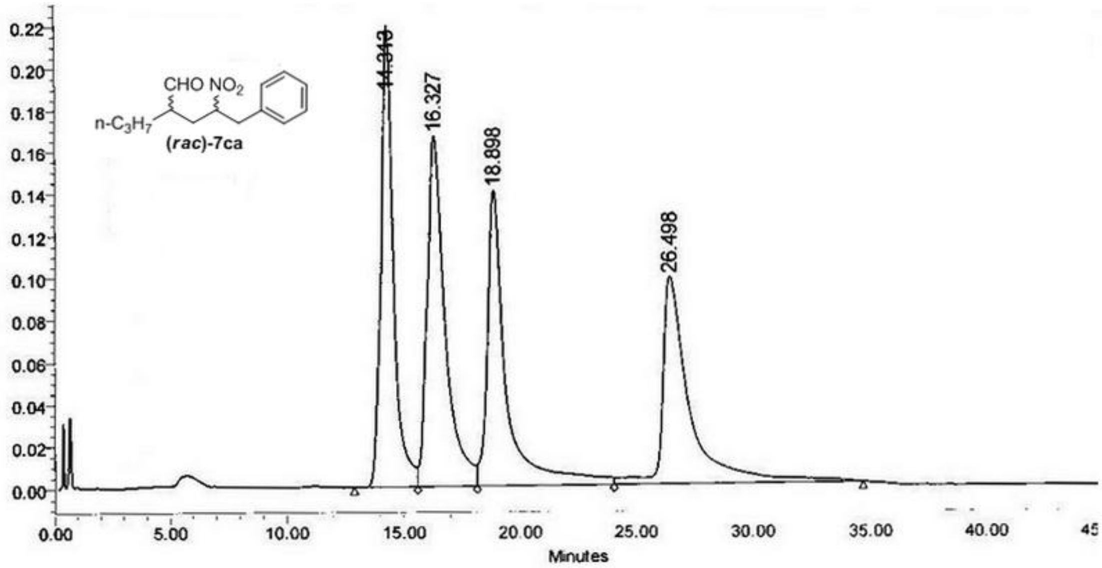
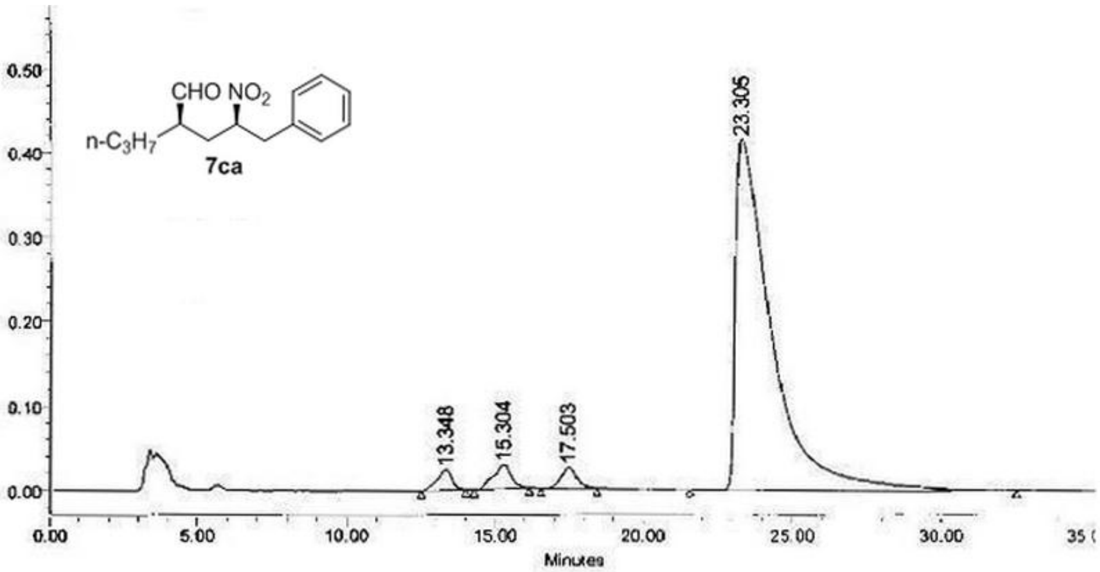
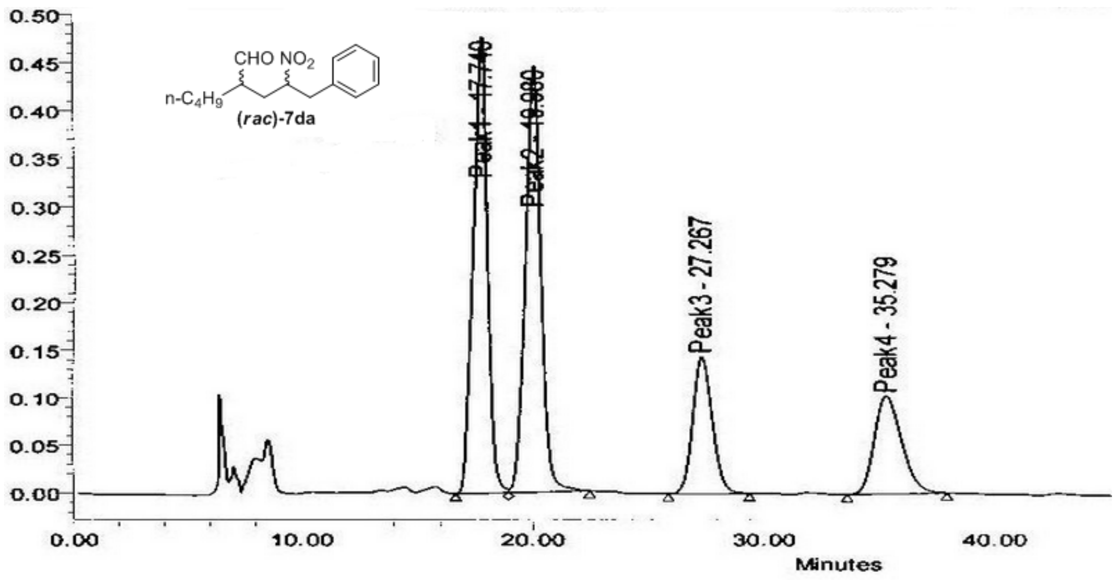


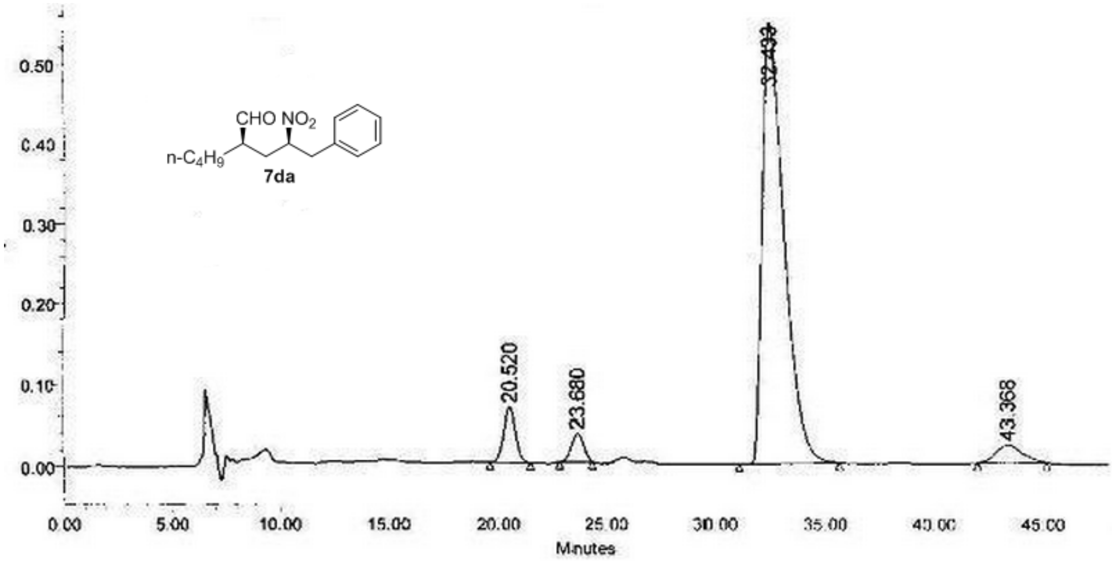
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	14.313	8083949	24.66	219311	35.16
2	16.327	8942405	27.28	166620	26.71
3	18.898	7875459	24.03	139753	22.40
4	26.498	7876243	24.03	98123	15.73



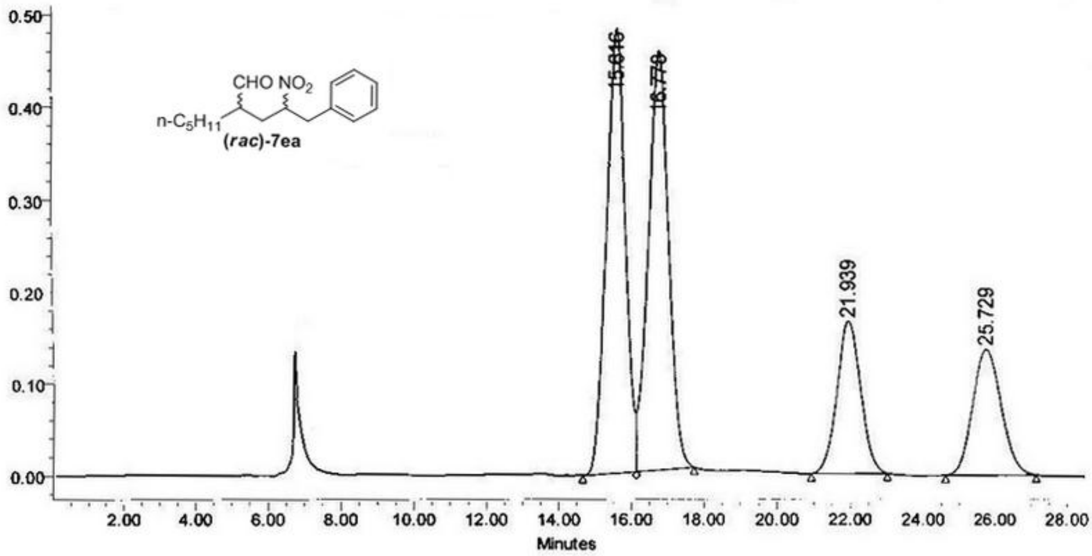
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	13.348	799348	2.12	23675	4.80
2	15.304	1178250	3.13	28167	5.71
3	17.503	904265	2.40	24742	5.01
4	23.305	34762802	92.34	416797	84.48



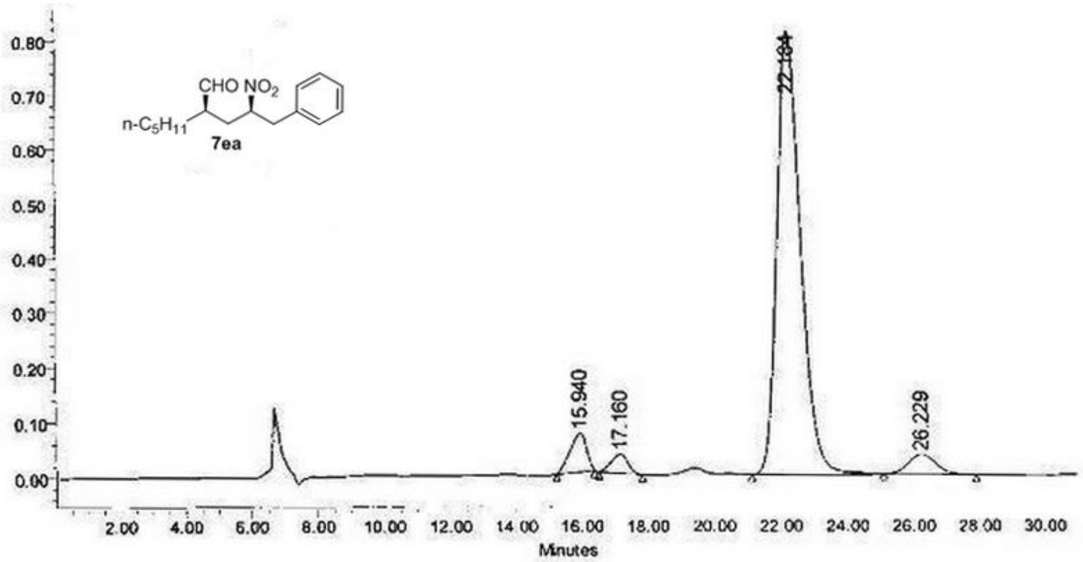
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	17.740	20296022	35.02	477987	40.80
2	Peak2	19.980	20787648	35.87	446629	38.12
3	Peak3	27.267	8425383	14.54	144159	12.31
4	Peak4	35.279	8445874	14.57	102728	8.77



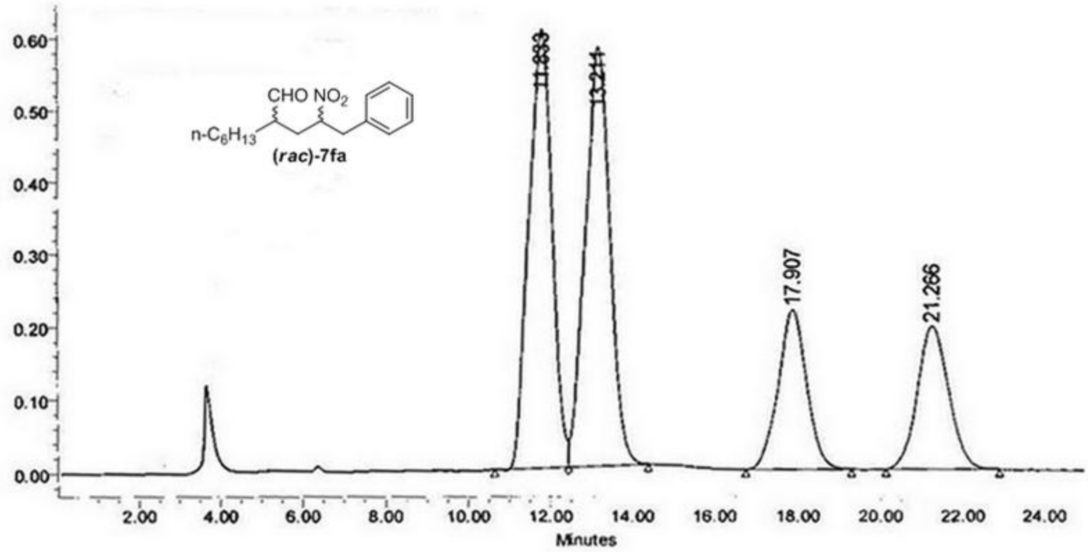
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	20.520	2516260	5.79	66772	9.93
2	23.680	1328798	3.06	34246	5.09
3	32.433	37751410	86.83	549108	81.69
4	43.368	1881218	4.33	22081	3.28



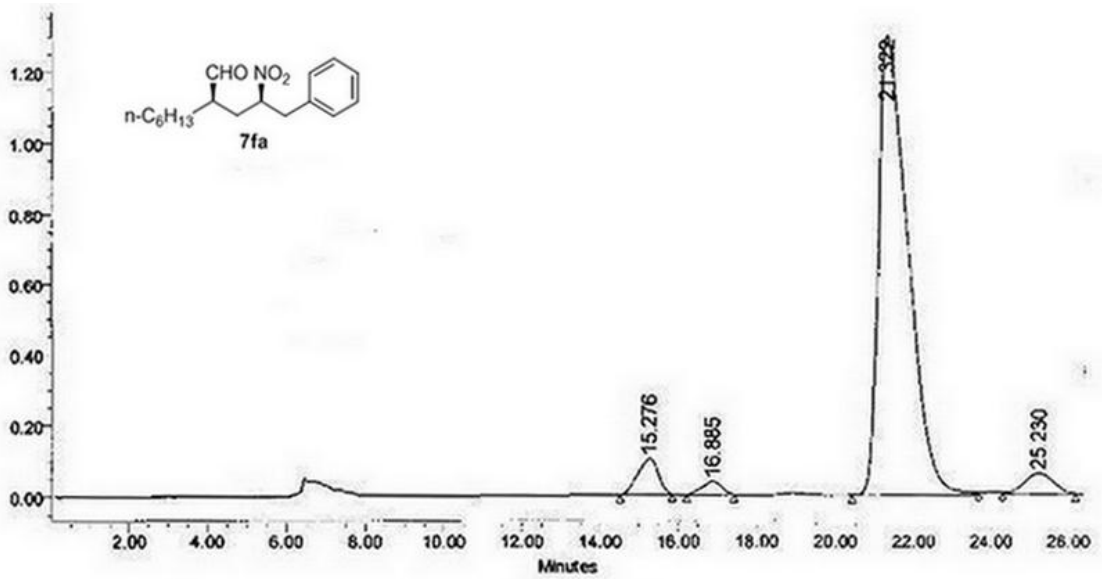
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.616	17472439	34.89	482461	38.85
2	16.778	17629500	35.20	455708	36.70
3	21.939	7470671	14.92	166150	13.38
4	25.729	7506835	14.99	137413	11.07



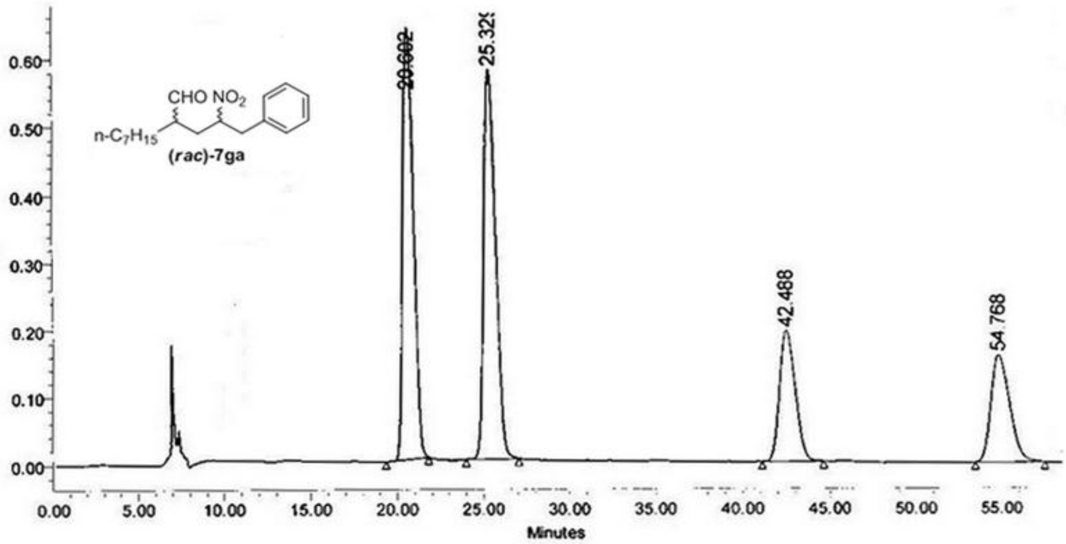
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.940	2382455	5.25	70225	7.35
2	17.160	1184917	2.61	34604	3.62
3	22.184	39727192	87.47	813813	85.21
4	26.229	2123673	4.68	36419	3.81



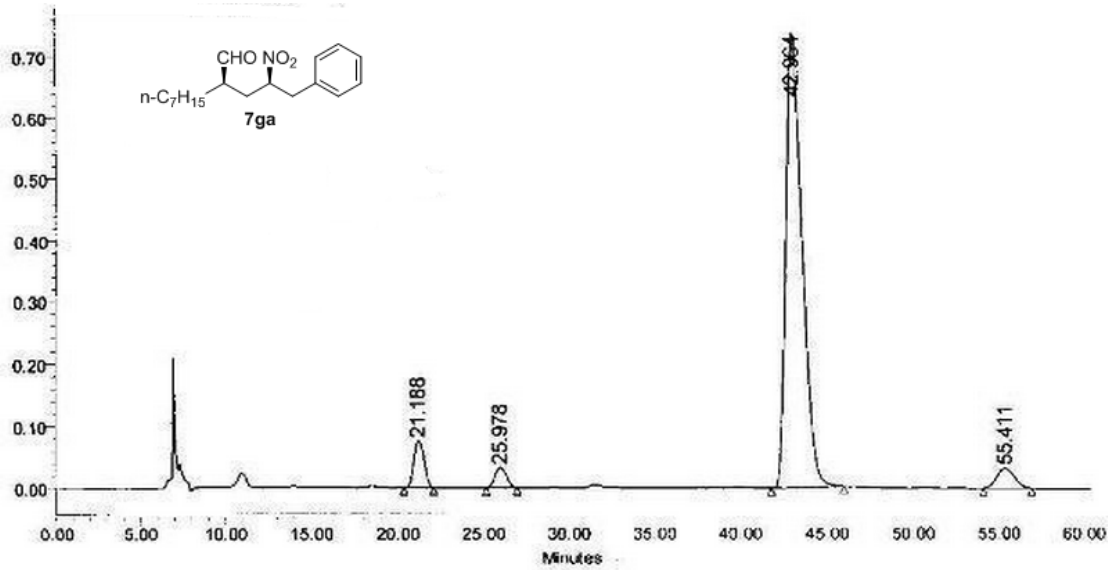
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.833	23697327	34.58	606142	37.88
2	13.211	24140914	35.23	579896	36.24
3	17.907	10322704	15.06	218190	13.63
4	21.266	10370309	15.13	196075	12.25



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.276	3566918	4.74	99496	6.67
2	16.885	1223977	1.63	35783	2.40
3	21.322	67429802	89.59	1299174	87.09
4	25.230	3048345	4.05	57287	3.84



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	20.602	27316967	34.57	637574	40.67
2	25.329	27601153	34.93	576149	36.75
3	42.488	12099995	15.31	194748	12.42
4	54.768	11998433	15.18	159178	10.15



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.188	3087177	5.65	75004	8.52
2	25.978	1508290	2.76	32045	3.64
3	42.964	47725533	87.29	740850	84.18
4	55.411	2351853	4.30	32199	3.66

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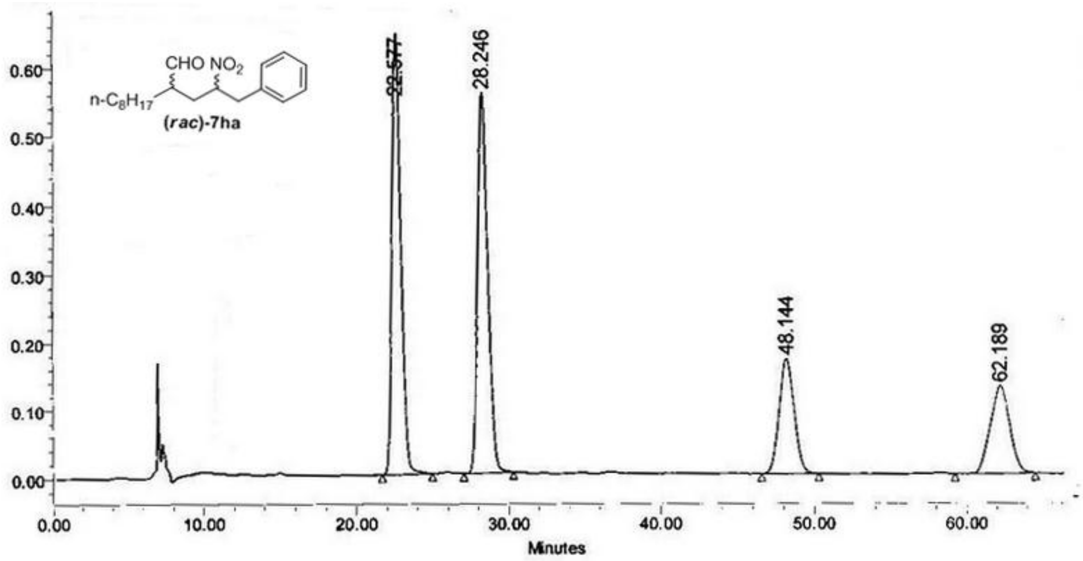
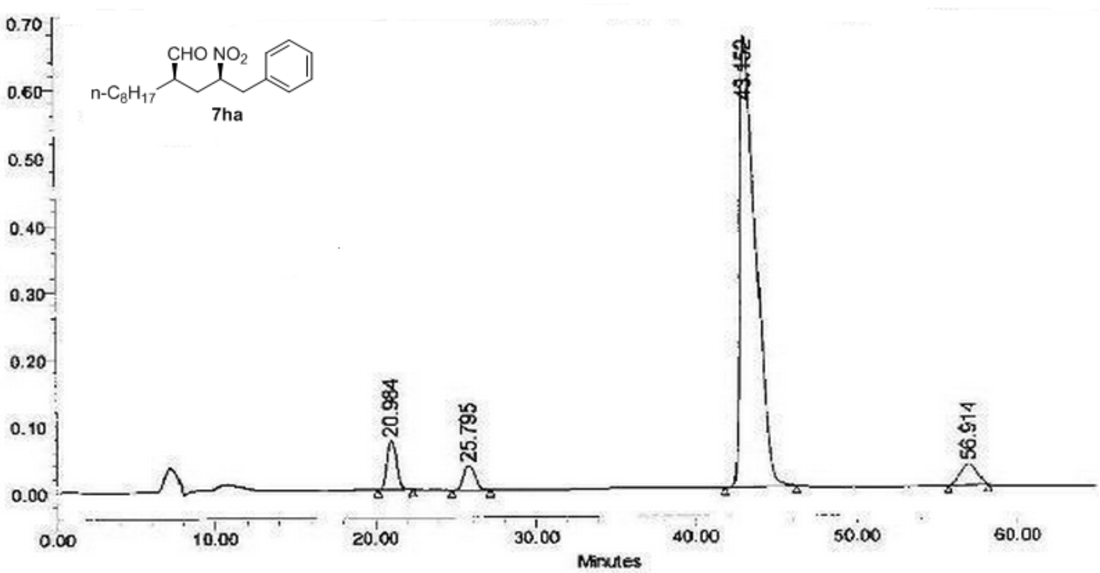


	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	22.577	26434087	34.98	645365	42.88
2	28.246	26238069	34.72	557500	37.05
3	48.144	11488728	15.20	171376	11.39
4	62.189	11400056	15.09	130676	8.68



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	20.984	3058457	5.69	72212	8.90
2	25.795	1723492	3.21	35519	4.38
3	43.152	46741784	86.97	672313	82.89
4	56.914	2222280	4.13	31084	3.83

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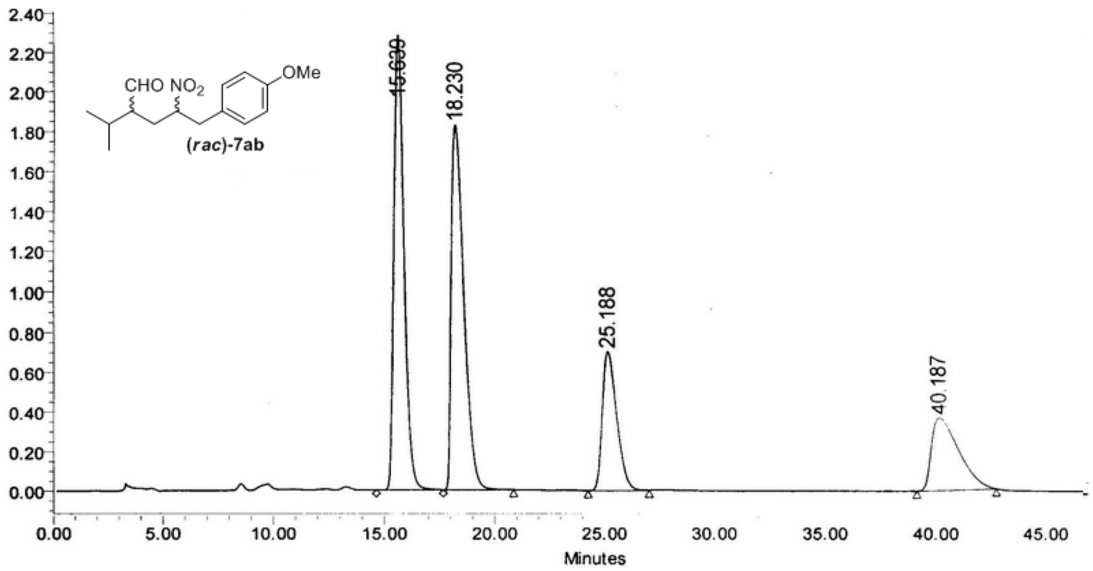
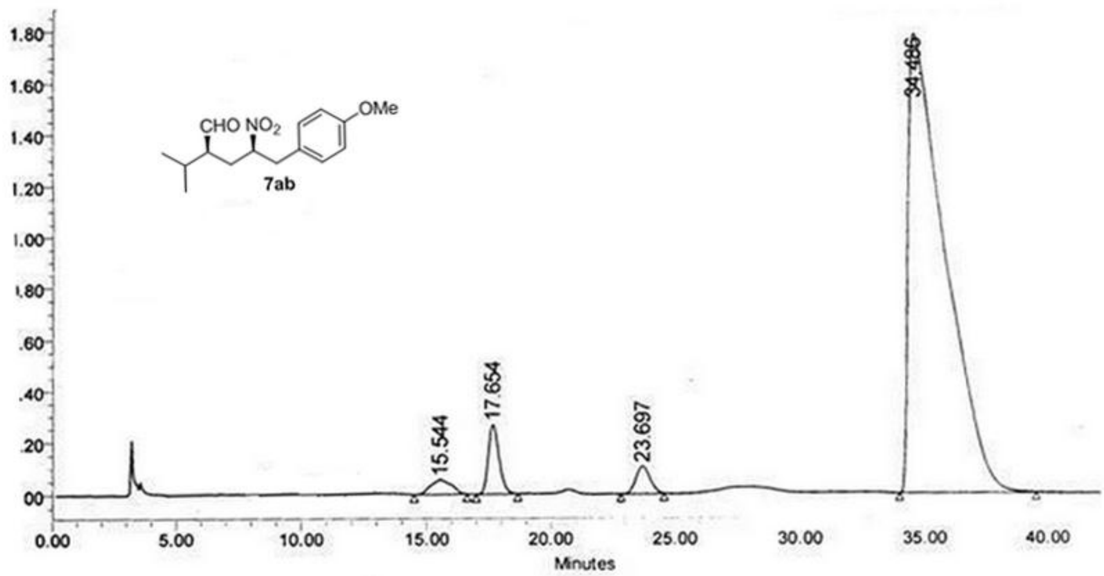


	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.639	72224872	34.60	2286659	44.10
2	18.230	72770187	34.86	1827097	35.24
3	25.188	32013005	15.34	703821	13.57
4	40.187	31717953	15.20	367493	7.09



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.544	3222958	1.63	55522	2.51
2	17.654	7943792	4.03	264779	11.95
3	23.697	4135651	2.10	105086	4.74
4	34.486	181933239	92.24	1790014	80.80

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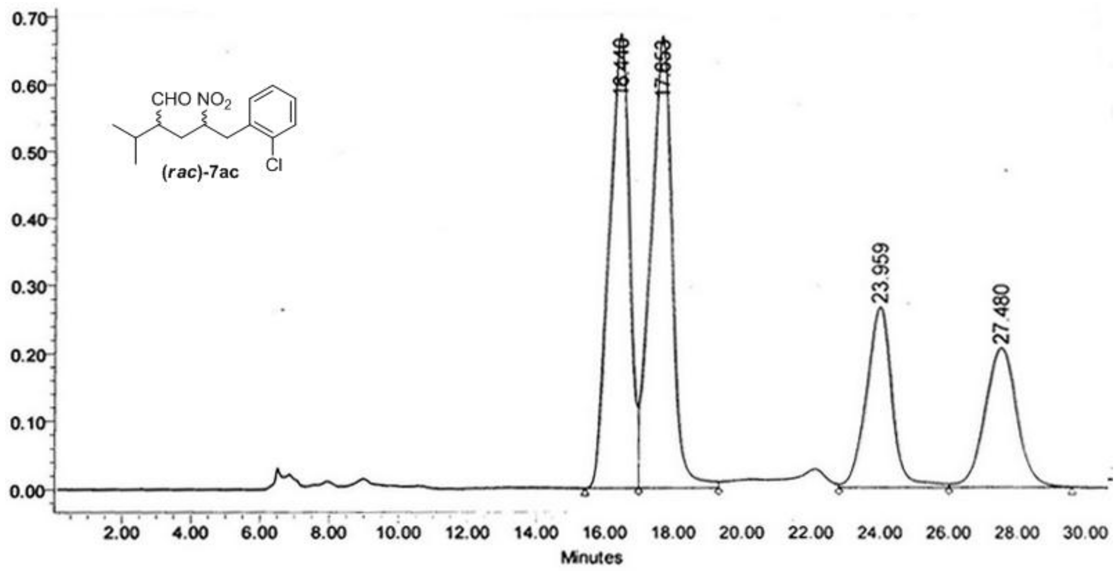
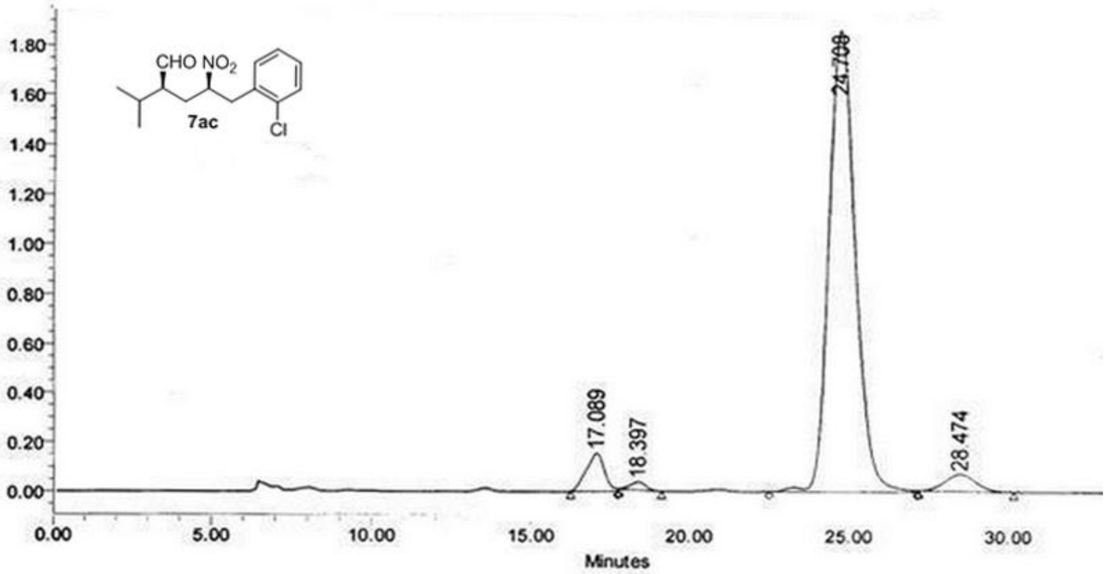
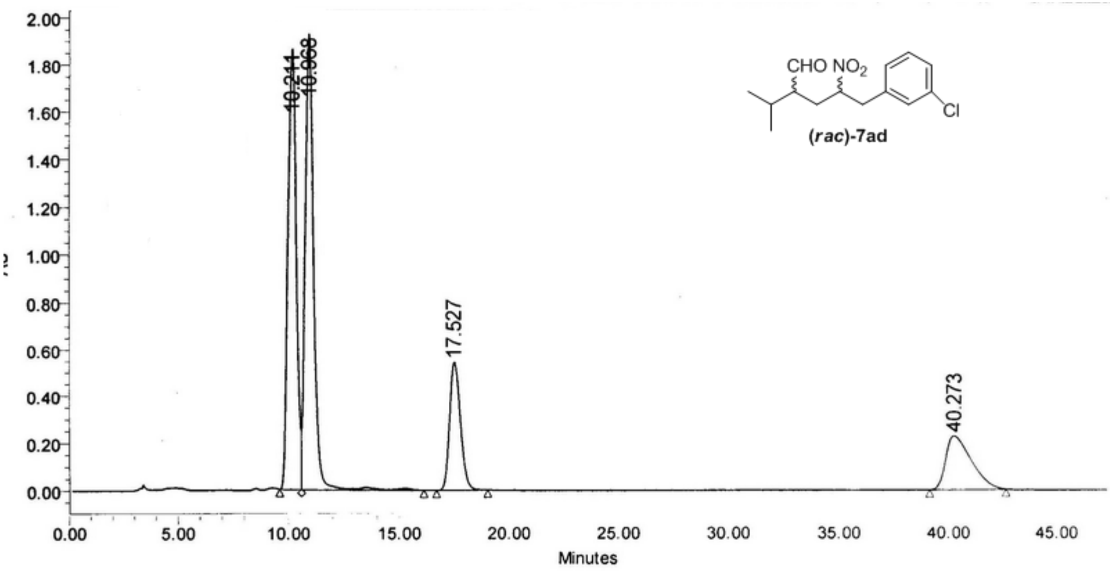


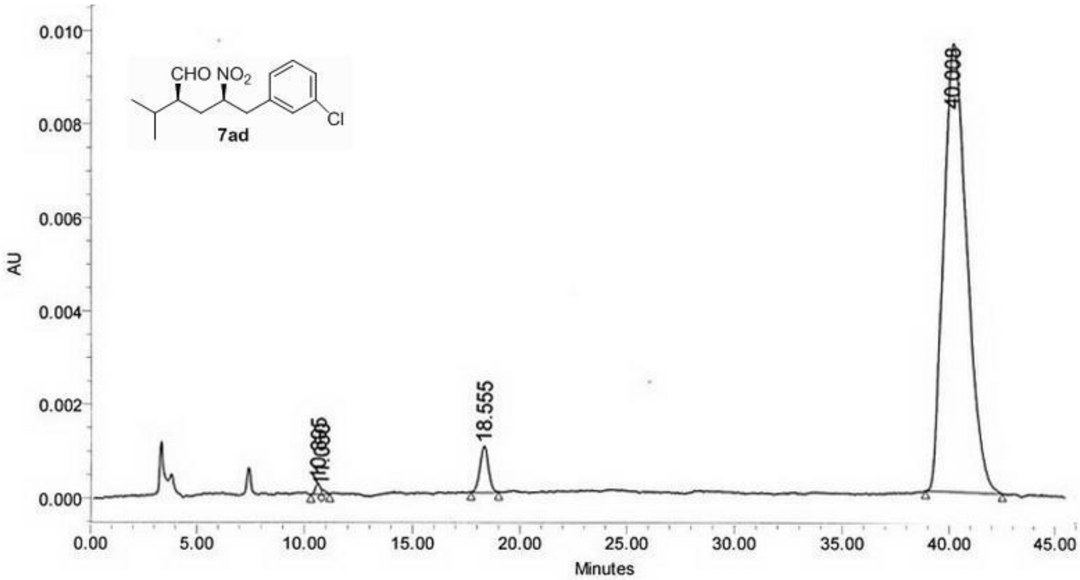
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.440	27585794	32.90	676098	37.11
2	17.653	29011686	34.60	673128	36.94
3	23.959	13796391	16.46	266734	14.64
4	27.480	13445099	16.04	206024	11.31



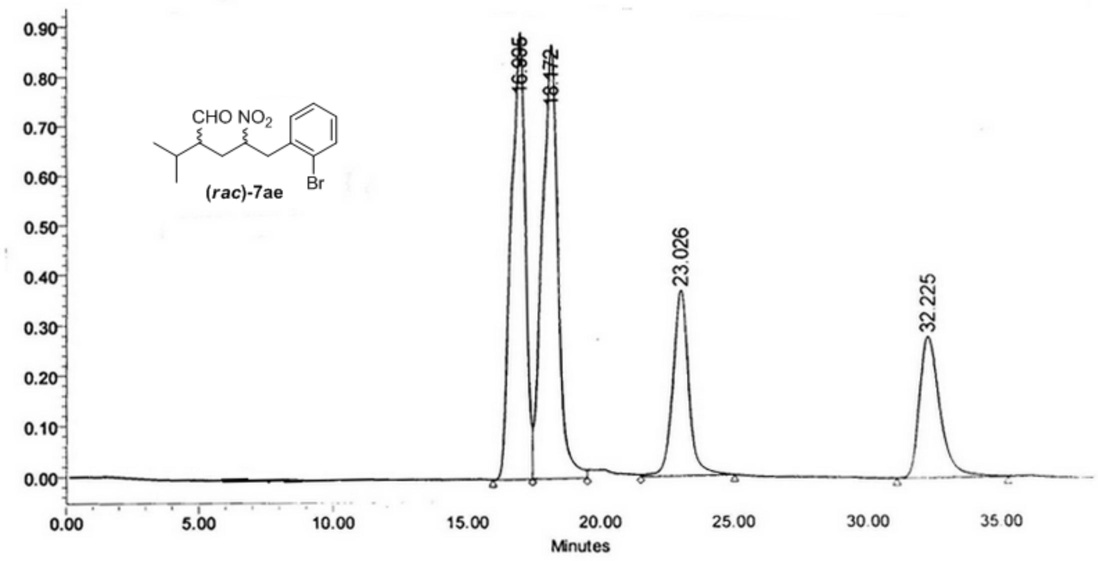
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.089	6204820	5.24	154495	7.27
2	18.397	1070017	0.90	32255	1.52
3	24.708	106498839	89.95	1868027	87.96
4	28.474	4620205	3.90	69057	3.25



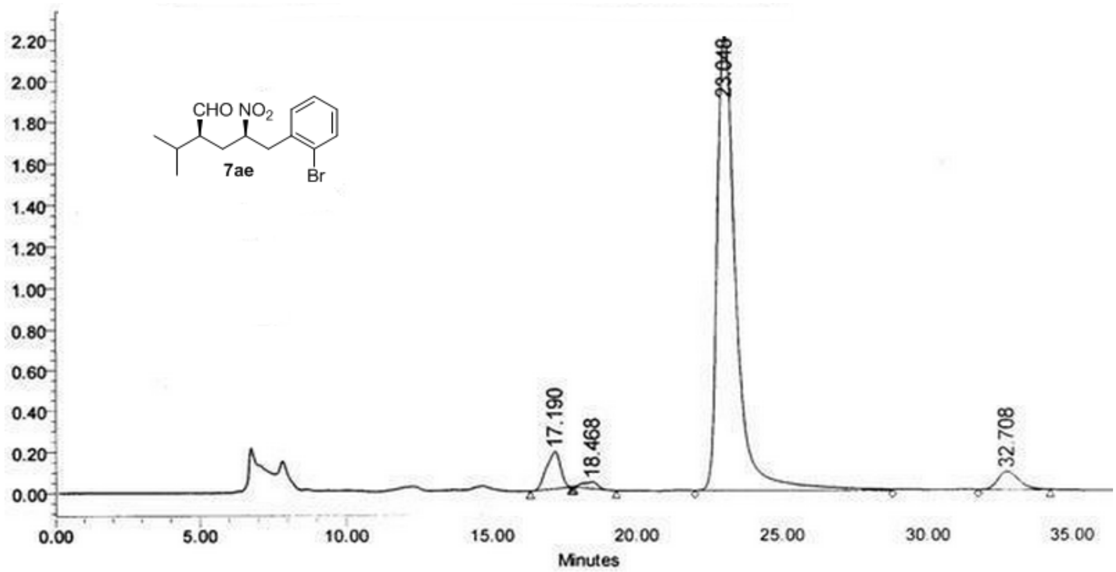
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	10.211	48488270	35.28	1863207	40.81
2	10.968	51801958	37.69	1928009	42.23
3	17.527	18653462	13.57	546549	11.97
4	40.273	18484505	13.45	227758	4.99



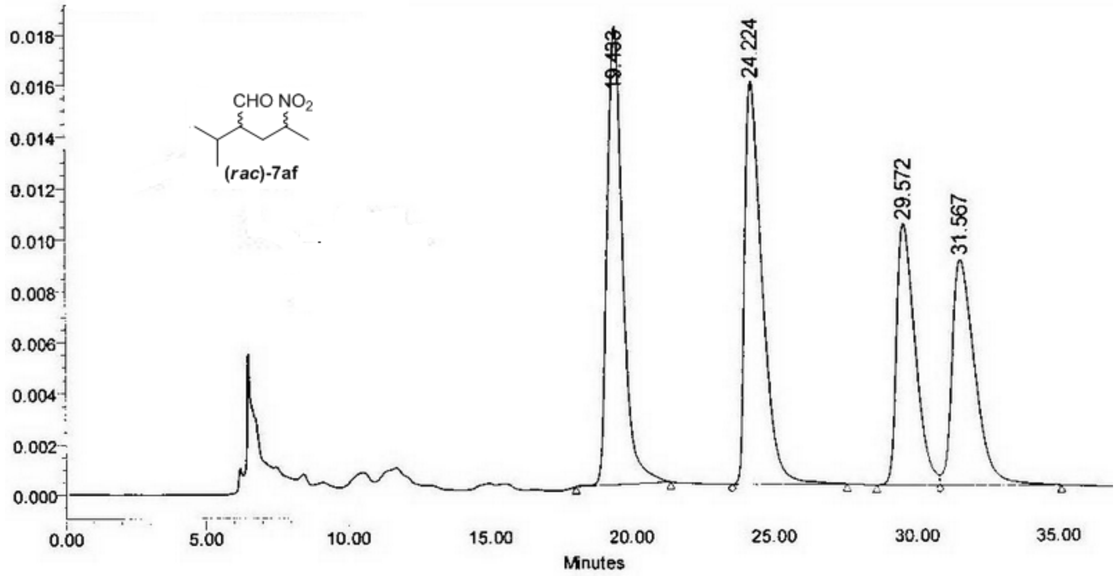
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	10.895	3297	0.44	224	2.06
2	11.050	1100	0.15	97	0.89
3	18.555	26766	3.55	972	8.94
4	40.008	722621	95.87	9584	88.11



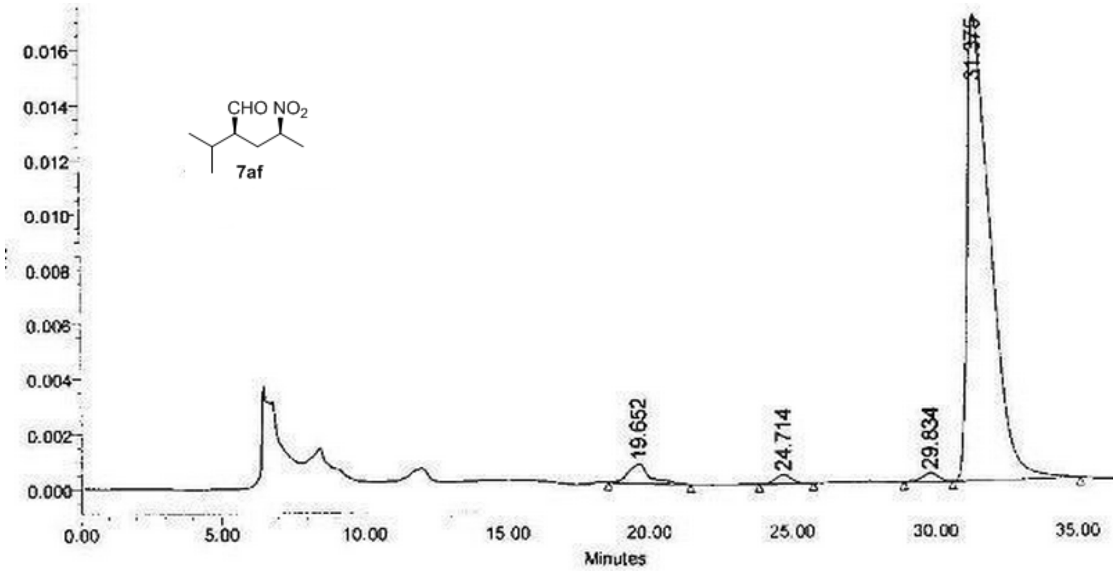
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	16.995	33011400	33.39	895796	37.09
2	18.172	35782050	36.19	869749	36.01
3	23.026	15128536	15.30	368809	15.27
4	32.225	14954218	15.12	280774	11.63



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	17.190	6041886	5.43	179979	7.14
2	18.468	1141860	1.03	32408	1.28
3	23.048	99540290	89.47	2220178	88.03
4	32.708	4536146	4.08	89490	3.55



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	19.433	686303	29.61	17967	33.93
2	24.224	667728	28.80	15782	29.80
3	29.572	467031	20.15	10294	19.44
4	31.567	497082	21.44	8911	16.83



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	19.652	36419	3.57	703	3.83
2	24.714	12589	1.23	332	1.81
3	29.834	11961	1.17	311	1.69
4	31.375	959150	94.02	17004	92.66

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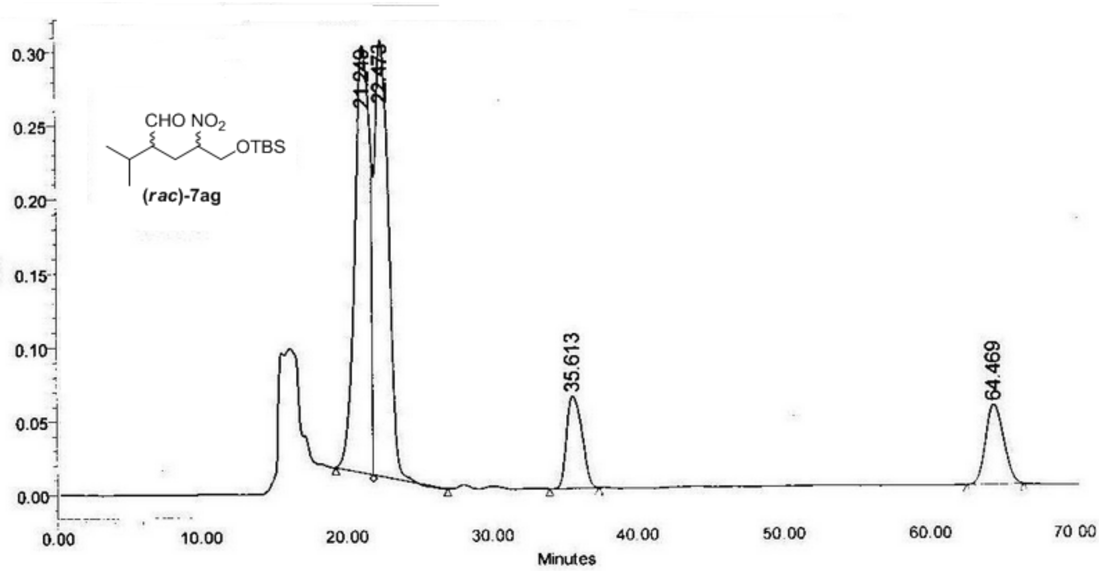
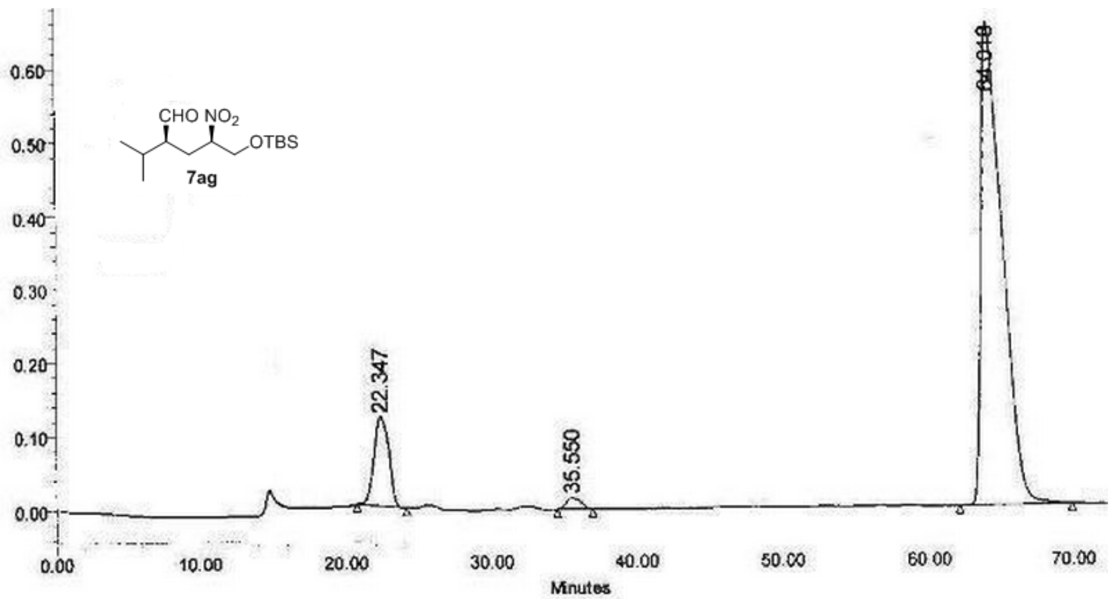
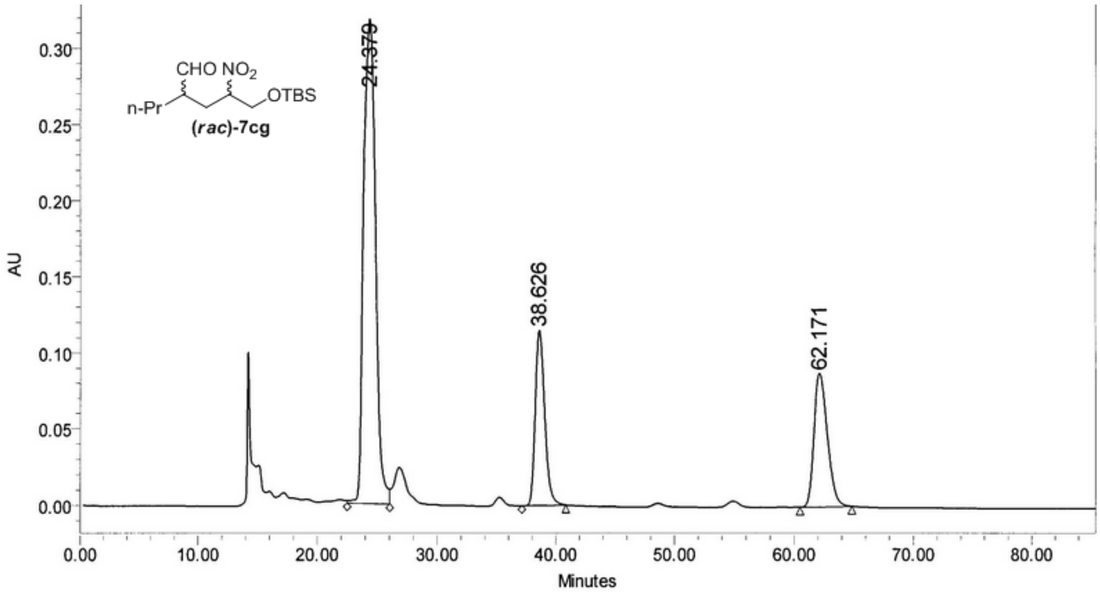


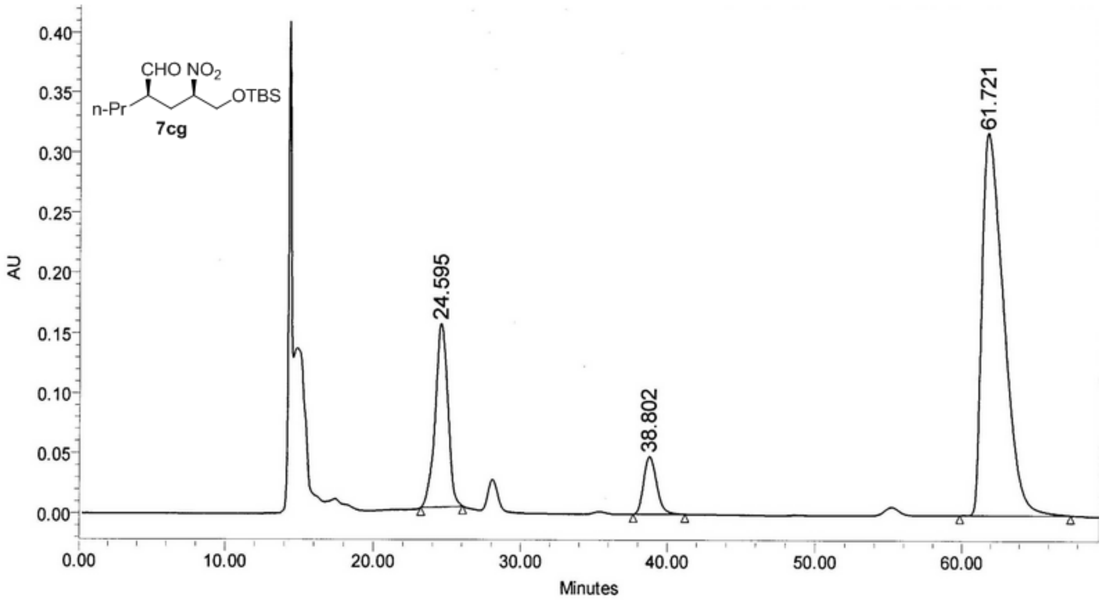
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.249	20332764	40.60	290006	41.24
2	22.473	20430966	40.79	295879	42.07
3	35.613	4616772	9.22	62811	8.93
4	64.469	4703187	9.39	54551	7.76



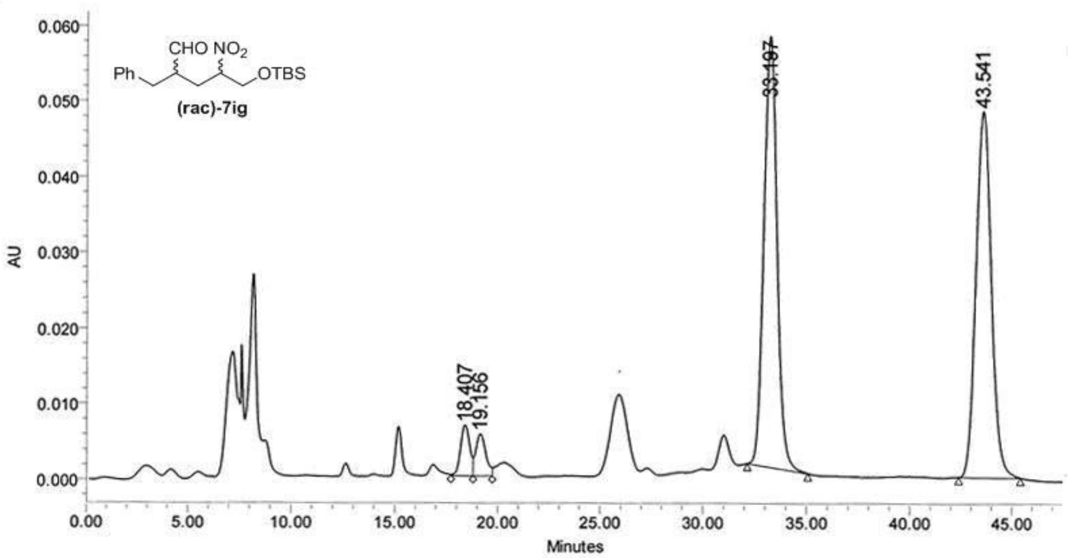
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	22.347	8342000	10.92	119796	15.12
2	35.550	1077897	1.41	15123	1.91
3	64.018	67005261	87.67	657529	82.97



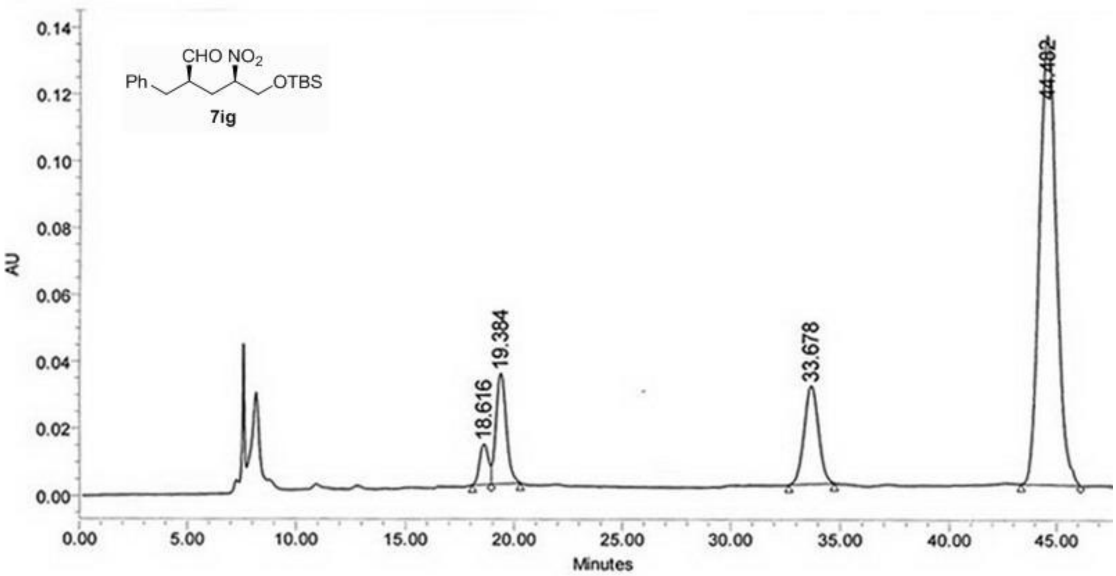
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	24.379	21850814	62.60	317932	61.19
2	38.626	6325633	18.12	114516	22.04
3	62.171	6730707	19.28	87161	16.77



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	24.595	9035082	20.19	152597	29.47
2	38.802	2966019	6.63	47617	9.19
3	61.721	32738839	73.18	317667	61.34



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.407	207760	3.82	6656	5.66
2	19.156	186381	3.43	5490	4.67
3	33.197	2500736	45.96	57027	48.50
4	43.541	2545895	46.79	48417	41.17



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.616	338112	3.33	11810	5.68
2	19.384	1078921	10.64	32713	15.73
3	33.678	1311746	12.94	29089	13.99
4	44.482	7411369	73.09	134291	64.59

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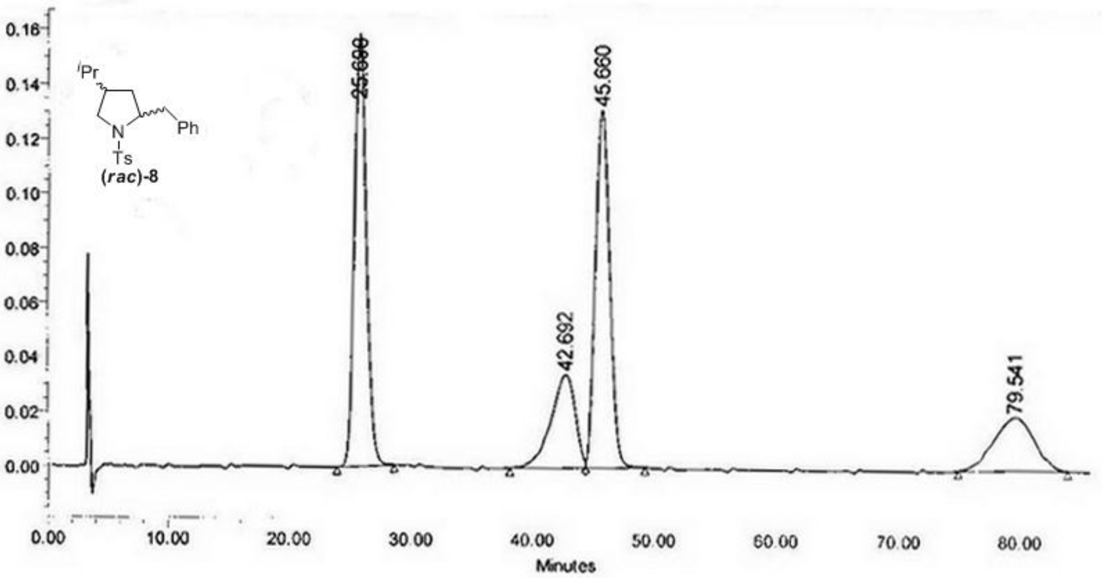
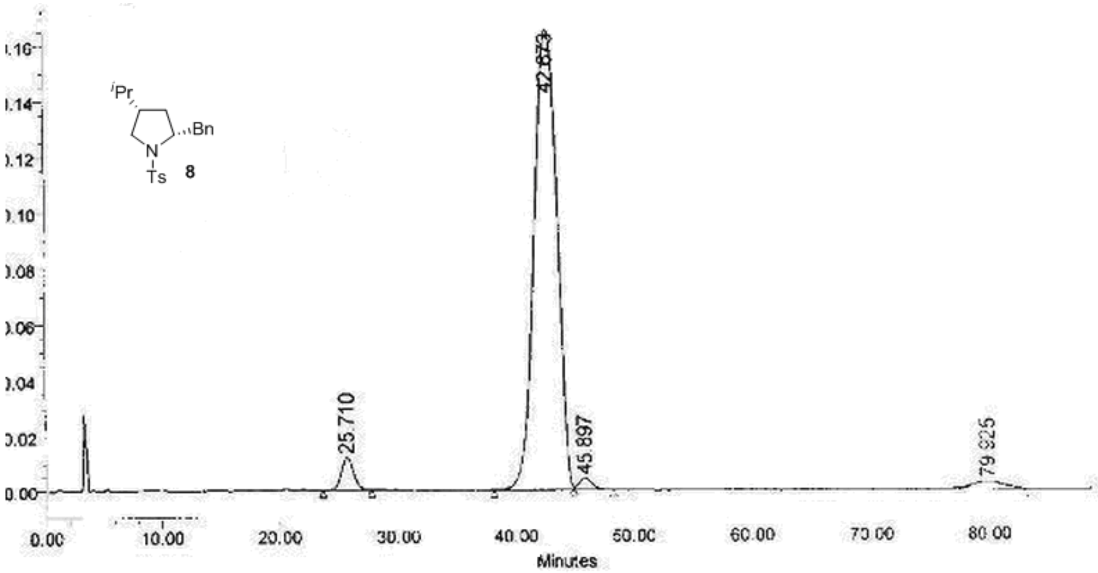


	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	25.690	10730614	34.79	158388	46.11
2	42.692	4743096	15.38	33899	9.87
3	45.660	10777369	34.94	131573	38.30
4	79.541	4590745	14.88	19637	5.72



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	25.710	845499	3.51	12084	6.55
2	42.673	22503321	93.31	165833	89.82
3	45.897	317559	1.32	4164	2.26
4	79.925	449807	1.87	2537	1.37