Supplementary Information

An Efficient Enantioselective Method for Asymmetric Michael Addition of Nitroalkanes to α, β-Unsaturated Aldehydes

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A: General Information and Starting Materials

General. The ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruke DRX 400 (400 MHz) instrument. Chromatography was carried out with silica gel (350-400 mesh) using mixtures of petroleum ether and ethyl acetate as eluents. NMR data of known compounds are in agreement with literature values.

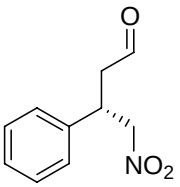
Materials. All solvent and inorganic reagents were of p.a. quality and used without purification. Nitroalkanes and α, β-unsaturated aldehydes were obtained from commercial sources. Cinnamyl-aldehyde and crotonaldehyde were purified by distillation before usage; other materials were used without purification. Lithium acetate was obtained from commercial sources; other lithium salts were prepared by the reaction of lithium hydroxide and corresponding acid. Catalyst **4** was prepared as described in the literature.[1]

B: General Procedure for the Michael Addition

To a mixed solution of CH_2Cl_2/MeOH=1/9(v/v, 2.0 mL) was added a,β-unsaturated aldehyde **1** (1.0 mmol), nitroalkane **2** (3.0 mmol), catalyst **4** (6.5 mg, 0.02 mmol) and lithium acetate (6.6 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for the time indicated in Table 2 and then the solvent was removed under vacuum. The residue was added water (5.0 mL) and extracted with CH_2Cl_2 three times. The combined organic phases were dried over unhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (350-400 mesh) to yield the desired addition product.

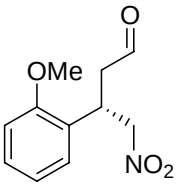
C: Characterization Data of Addition Products

4-Nitro-3-phenylbutanal



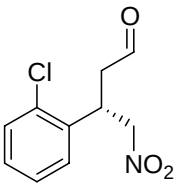
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.68 (s, 1H), 7.37-7.22 (m, 5H), 4.69-4.65 (m, 1H), 4.63-4.59 (m, 1H), 4.10-4.04 (m, 1H), 2.98-2.89 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.8, 138.2, 129.2, 128.1, 127.4, 79.4, 46.5, 38.0. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 23.8 min (major), 25.0 min (minor).

3-(2-Methoxyphenyl)-4-nitrobutanal



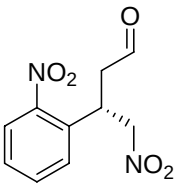
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.67 (s, 1H), 7.26-7.24 (m, 1H), 7.15-7.13 (m, 1H), 6.93-6.88 (m, 2H), 4.74-4.70 (m, 2H), 4.30-4.26 (m, 1H), 3.00-2.97 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 200.0, 157.2, 129.4, 121.1, 111.2, 78.0, 55.5, 45.1, 34.5. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 100:1, 0.8 mL/min]: 42.2 min (major), 44.0 min (minor).

3-(2-Chlorophenyl)-4-nitrobutanal



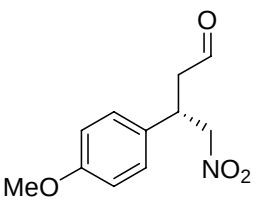
Light yellow solid. ^{1}H-NMR ($CDCl_3$): δ 9.72 (s, 1H), 7.42-7.41 (m, 1H), 7.25-7.24 (m, 3H), 4.77-4.70 (m, 2H), 4.57-4.54 (m, 1H), 3.07-3.04 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.9, 129.9, 129.1, 128.2, 127.5, 78.7, 45.3, 34.8. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 22.8 min (major), 24.3 min (minor).

4-Nitro-3-(2-nitrophenyl)butanal



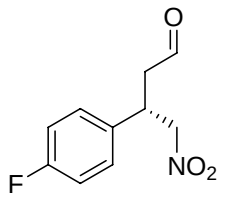
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.72 (s, 1H), 7.93-7.90 (m, 1H), 7.62-7.60 (m, 1H), 7.49-7.40 (m, 2H), 4.84-4.83 (m, 2H), 4.65-4.61 (m, 1H), 3.12-3.10 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.3, 133.7, 129.2, 128.7, 125.6, 78.1, 46.1, 29.7. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 9:1, 0.8 mL/min]: 52.1 min (major), 54.8 min (minor).

3-(4-Methoxyphenyl)-4-nitrobutanal



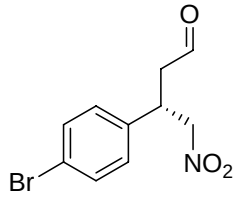
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.70 (s, 1H), 7.16-7.14 (d, *J*=8.8 Hz, 2H), 6.88-6.86 (d, *J*=8.8 Hz, 2H), 4.64-4.58 (m, 2H), 4.03 (m, 1H), 3.79 (s, 3H), 2.93-2.91 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 199.2, 130.1, 128.7, 114.8, 79.9, 55.5, 46.8, 37.6. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 23.8 min (major), 25.0 min (minor).

3-(4-Fluorophenyl)-4-nitrobutanal



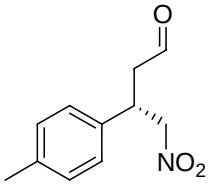
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.69 (s, 1H), 7.23-7.20 (m, 2H), 7.05-7.01 (m, 2H), 4.69-4.65 (m, 1H), 4.61-4.56 (m, 1H), 4.11-4.05 (m, 1H), 2.94-2.92 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.8, 163.7, 134.2, 129.3, 116.3, 79.6, 46.7, 37.4. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 31.4 min (major), 32.9 min (minor).

3-(4-Bromophenyl)-4-nitrobutanal



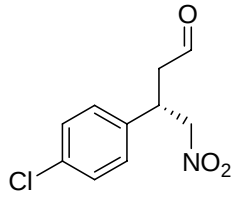
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.66 (s, 1H), 7.48-7.45 (m, 2H), 7.13-7.11 (m, 2H), 4.68-4.63 (m, 1H), 4.60-4.55 (m, 1H), 4.05-4.01 (m, 1H), 2.92-2.90 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.7, 132.6, 129.4, 122.1, 79.2, 46.4, 37.4. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 37.3 min (major), 38.9 min (minor).

4-Nitro-3-*p*-tolylbutanal



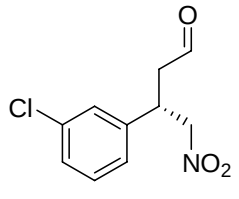
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.63 (s, 1H), 7.14-7.09 (m, 4H), 4.65-4.53 (m, 2H), 4.03-3.99 (m, 1H), 2.89-2.86 (m, 2H), 2.30 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 199.3, 137.9, 135.3, 130.1, 127.5, 79.7, 53.6, 46.5, 37.7. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 19.9 min (major), 20.8 min (minor).

3-(4-Chlorophenyl)-4-nitrobutanal



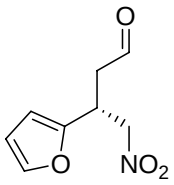
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.68 (s, 1H), 7.33-7.28 (m, 2H), 7.19-7.16 (m, 2H), 4.68-4.64 (m, 1H), 4.60-4.55 (m, 1H), 4.07-4.03 (m, 1H), 2.93-2.92 (d, *J*=6.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.6, 137.0, 134.2, 129.5, 128.2, 79.3, 46.5, 37.5. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 35.6 min (major), 37.2 min (minor).

3-(3-Chlorophenyl)-4-nitrobutanal



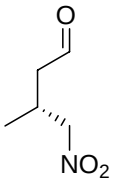
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.70 (s, 1H), 7.30-7.12 (m, 4H), 4.70-4.58 (m, 2H), 4.10-4.02 (m, 1H), 2.96-2.94 (d, *J*=6.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.5, 140.5, 135.2, 130.5, 128.6, 127.8, 126.0, 79.2, 46.5, 37.7. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 29.4 min (major), 31.0 min (minor).

3-(Furan-2-yl)-4-nitrobutanal



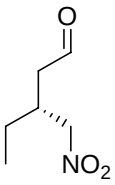
Light yellow oil. ^{1}H-NMR ($CDCl_3$): δ 9.75 (s, 1H), 7.35 (m, 1H), 6.31-6.28 (m, 1H), 6.18-6.17 (m, 1H), 4.73-4.60 (m, 2H), 4.21-4.14 (m, 1H), 3.04-2.89 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 198.7, 151.2, 142.8, 110.8, 107.7, 77.3, 44.2, 32.0. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 20:1, 0.8 mL/min]: 25.3 min (major), 26.5 min (minor).

3-(Nitromethyl)butanal



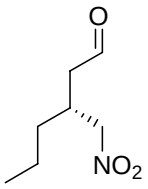
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.78 (s, 1H), 4.44-4.41 (m, 1H), 4.38-4.34 (m, 1H), 2.92-2.85 (m, 1H), 2.68-2.63 (m, 1H), 2.55-2.50 (m, 1H), 1.12-1.11 (d, *J*=5.5, 1H). ^{13}C-NMR ($CDCl_3$): δ 199.6, 80.2, 47.1, 27.3, 17.4. The enantiomeric excess was determined by HPLC. [AD-H column, 220 nm, hexane: IPA = 100:1, 0.8 mL/min]: 34.0 min (major), 35.3 min (minor).

3-(Nitromethyl)pentanal



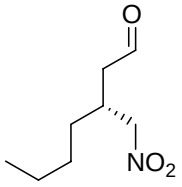
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.79 (s, 1H), 4.44-4.41 (m, 2H), 2.69-2.65 (m, 1H), 2.64-2.58 (m, 2H), 1.52-1.46 (m, 2H), 0.95-0.92 (t, *J*=6.0, 3H). ^{13}C-NMR ($CDCl_3$): δ 200.0, 78.2, 45.0, 33.5, 24.5, 10.9. The enantiomeric excess was determined by GC. [Chirasil-Dex CB column, 1.0 mL/min, 95°C isothermal.]: 53.2 min (minor), 53.7 min (major).

3-(Nitromethyl)hexanal



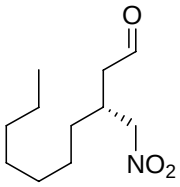
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.79 (s, 1H), 4.48-4.42 (m, 2H), 2.76-2.71 (m, 1H), 2.68-2.64 (m, 1H), 2.61-2.56 (m, 1H), 1.44-1.36 (m, 4H), 0.99-0.96 (t, *J*=5.6, 3H). ^{13}C-NMR ($CDCl_3$): δ 200.0, 78.5, 45.4, 33.7, 31.8, 19.7, 13.9. The enantiomeric excess was determined by GC. [Chirasil-Dex CB column, 1.0 mL/min, 95°C hold for 60 min, then 10°C/min to 200°C.]: 65.0 min (minor), 65.2 min (major).

3-(Nitromethyl)heptanal



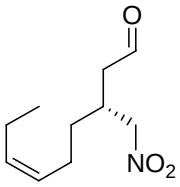
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.78 (s, 1H), 4.46-4.45 (m, 2H), 2.74-2.63 (m, 3H), 1.45-1.29 (m, 6H), 0.92-0.90 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 200.2, 78.6, 45.5, 32.1, 31.4, 28.8, 22.6, 14.0. The enantiomeric excess was determined by GC. [Chirasil-Dex CB column, 1.0 mL/min, 10°C/min from 70°C to 140°C then hold for 12 min.]: 17.3 min (minor), 17.5 min (major).

3-(Nitromethyl)decanal



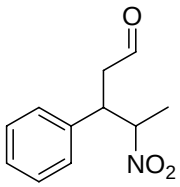
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.78 (s, 1H), 4.46-4.44 (d, *J*=6.0 Hz, 2H), 2.73-2.69 (m, 1H), 2.64-2.61 (m, 2H), 1.45-1.27 (m, 12H), 0.90-0.86 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 200.2, 78.6, 45.5, 32.1, 31.9, 31.7, 29.5, 29.2, 26.6, 22.7, 14.2. The enantiomeric excess was determined by GC. [Chirasil-Dex CB column, 1.0 mL/min, 10°C/min from 70°C to 150°C then hold for 30 min.]: 35.2 min (minor), 35.6 min (major).

(*Z*)-3-(Nitromethyl)non-6-enal



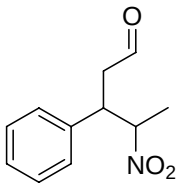
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.78 (s, 1H), 5.44-5.42 (m, 1H), 5.30-5.25 (m, 1H), 4.48-4.46 (m, 2H), 2.74-2.63 (m, 3H), 2.12-2.02 (m, 4H), 1.52-1.48 (m, 2H), 0.98-0.95 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 200.1, 133.5, 127.2, 79.4, 45.4, 31.8, 31.5, 24.2, 20.8, 14.4. The enantiomeric excess was determined by GC. [Chirasil-Dex CB column, 1.0 mL/min, 10°C/min from 70°C to 150°C then hold for 20 min.]: 24.2 min (minor), 24.4 min (major).

4-Nitro-3-phenylpentanal (Diastereomer 1)



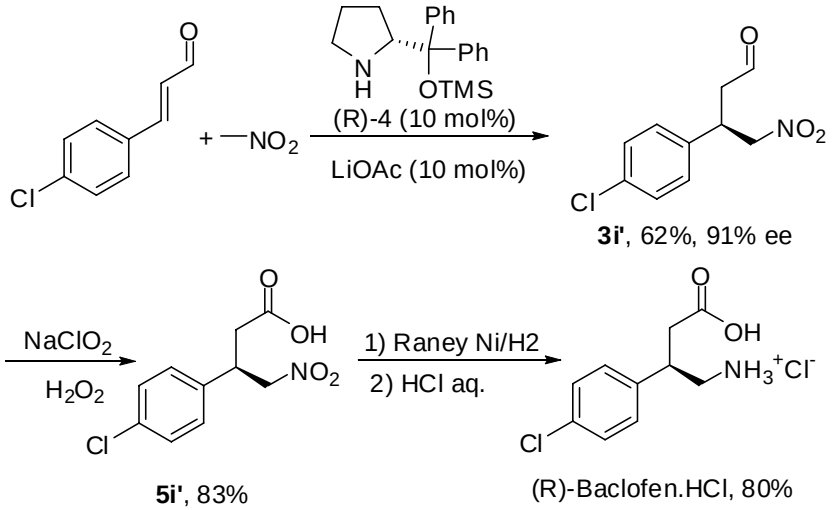
Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.56 (m, 1H), 7.38-7.19 (m, 5H), 4.81-4.75 (m, 1H), 3.78-3.73 (m, 1H), 2.99-2.93 (m, 1H), 2.78-2.73 (m, 1H), 1.35-1.34 (d, *J*=5.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 198.7, 137.6, 129.3, 128.3, 128.2, 87.1, 46.4, 44.3, 17.8. The enantiomeric excess was determined by GC. [Chirasil-Dex CB column, 1.0 mL/min, 10°C/min from 70 °C to 180°C then hold for 25 min.]: 26.9 min (major), 27.3 min (minor).

4-Nitro-3-phenylpentanal (Diastereomer 2)



Colorless oil. ^{1}H-NMR ($CDCl_3$): δ 9.67 (t, *J*=0.8 Hz, 1H), 7.34-7.16 (m, 5H), 4.89-4.83 (m, 1H), 3.84-3.79 (m, 1H), 3.03- 2.98 (m, 1H), 2.96-2.91 (m, 1H), 1.53-1.52 (d, *J*=5.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 199.2, 137.6, 129.0, 128.2, 128.1, 86.5, 44.8, 43.6, 16.7. The enantiomeric excess was determined by GC. [Chirasil- Dex CB column, 1.0 mL/min, 10°C/min from 70 °C to 180°C then hold for 25 min.]: 28.6 min (minor), 29.2 min (major).

D: Procedure for the Preparation of (R)-Baclofen

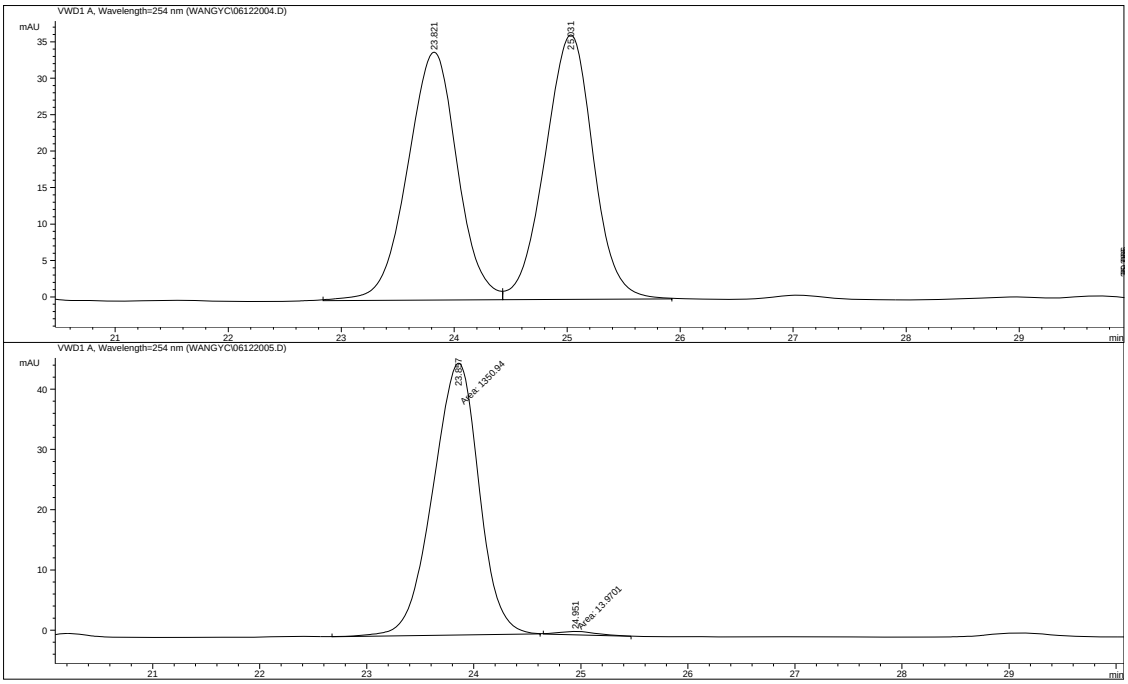


The preparation of **3i'** was according to the general procedure for the Michael addition described above using (R)-**4** as catalyst with 62% of isolation yield and 91% *ee*.

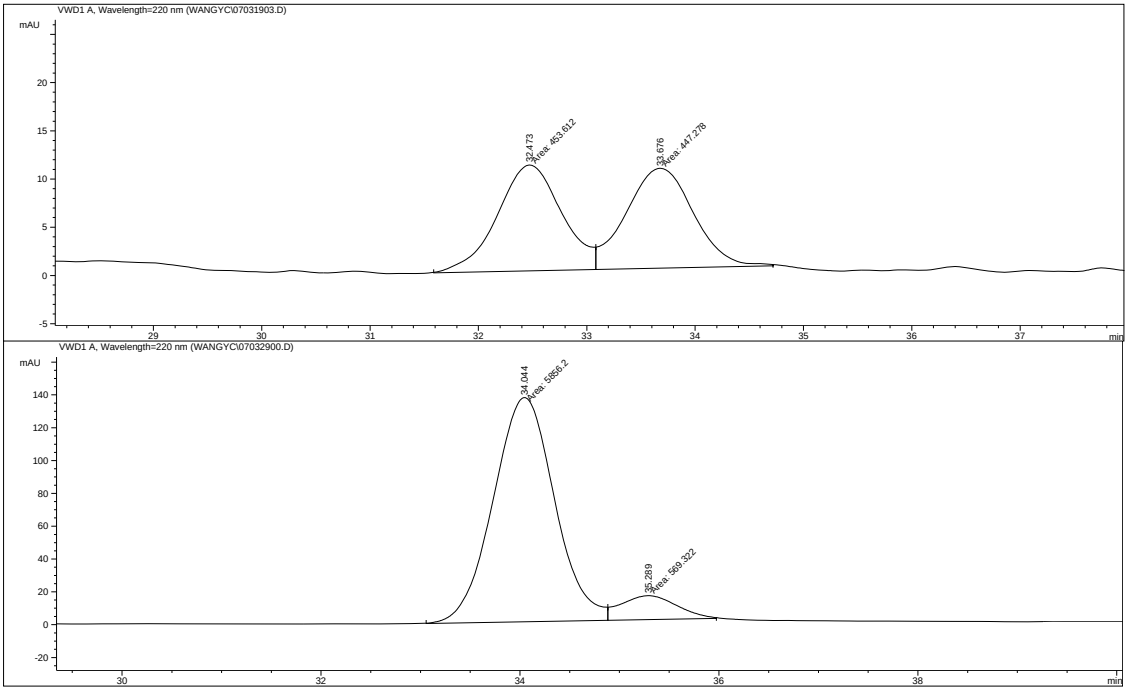
The oxidation step was taken up according to similar literature procedure. [2] **3i'** (227.6 mg, 1.0 mmol) was dissolved in 6.0 mL of MeCN, and 6.0 mL of water. The solution was cooled down to 0 ^{o}C, KH_2PO_4 (370.6 mg, 2.7 mmol) and $NaClO_2$ (270.6 mg, 2.5 mmol) were added. After the injection of 1 mL H_2O_2 (35%), the mixture was warmed up to room temperature and stirred for 2 hours. The pH was adjusted to 3 with 1M HCl and 10 mL saturated Na_2SO_3 solution were added. The resulting mixture was extracted 3 times with 10 mL of CH_2Cl_2, the combined organic layers were washed with 10 mL of water, dried over Na_2SO_4, and concentrated under vacuum. The residual acid was directly hydrogenation according to literature procedure [3] afforded the (R)-baclofen hydrochloride salt as a white solid in 66% yield (total yield of the above two steps). ^{1}H-NMR (d^6-DMSO): δ 8.19 (m, 3H), 7.27-7.29 (m, 4H), 3.32 (m, 1H), 2.99 (m, 1H), 2.78-2.83 (m, 2H), 2.51 (m, 1H). ^{13}C-NMR (d^6-DMSO): δ 170.9, 138.1, 130.4, 128.6, 127.2, 41.9, 37.7, 36.5. $[\alpha]_D^{20}$= -2.0 (c=0.6 in H_2O). These results are in agreement with the reported data. [3-4]

E: CSP-HPLC or CSP-GC Analysis of Addition Products

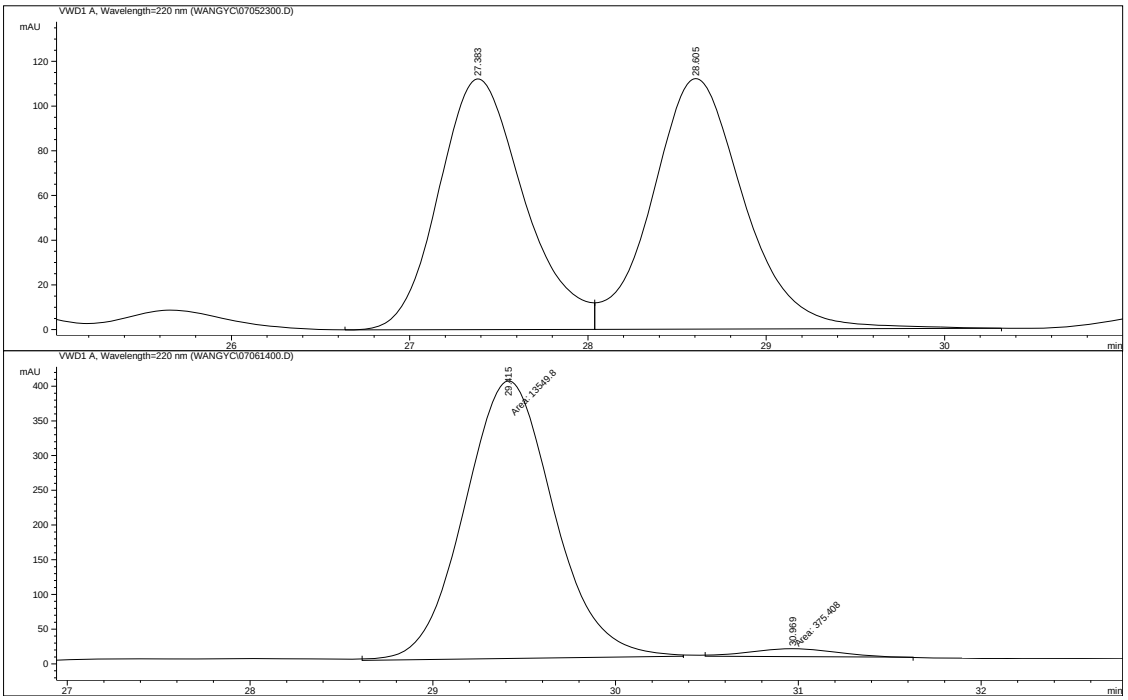
4-Nitro-3-phenylbutanal



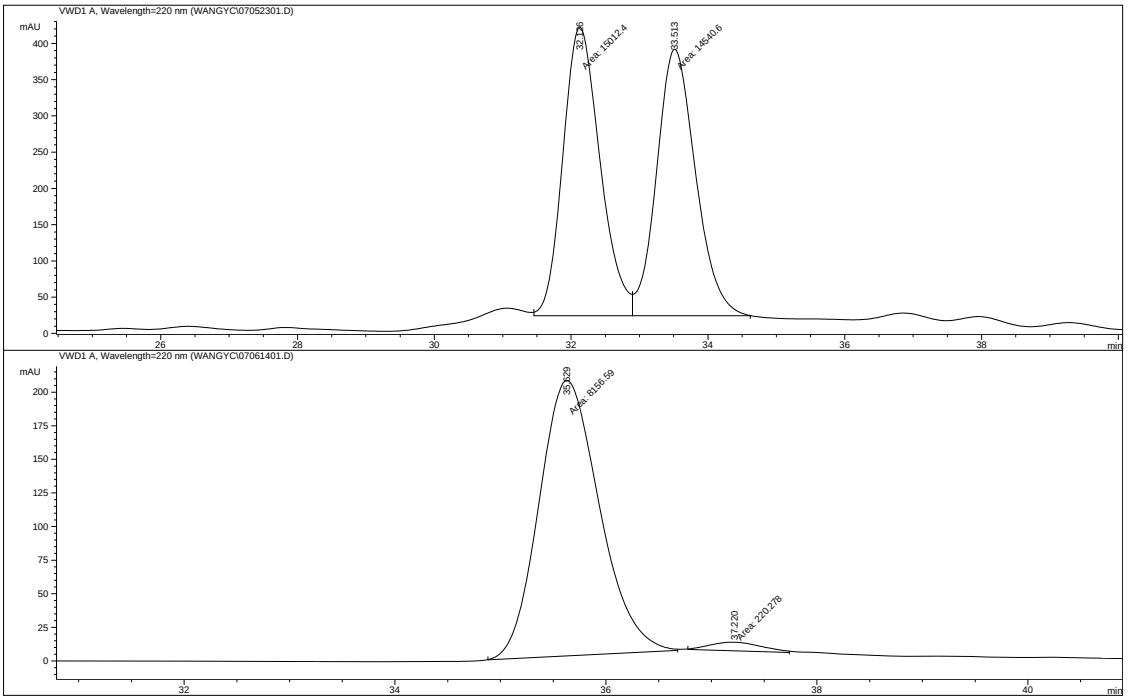
3-(Nitromethyl)butanal



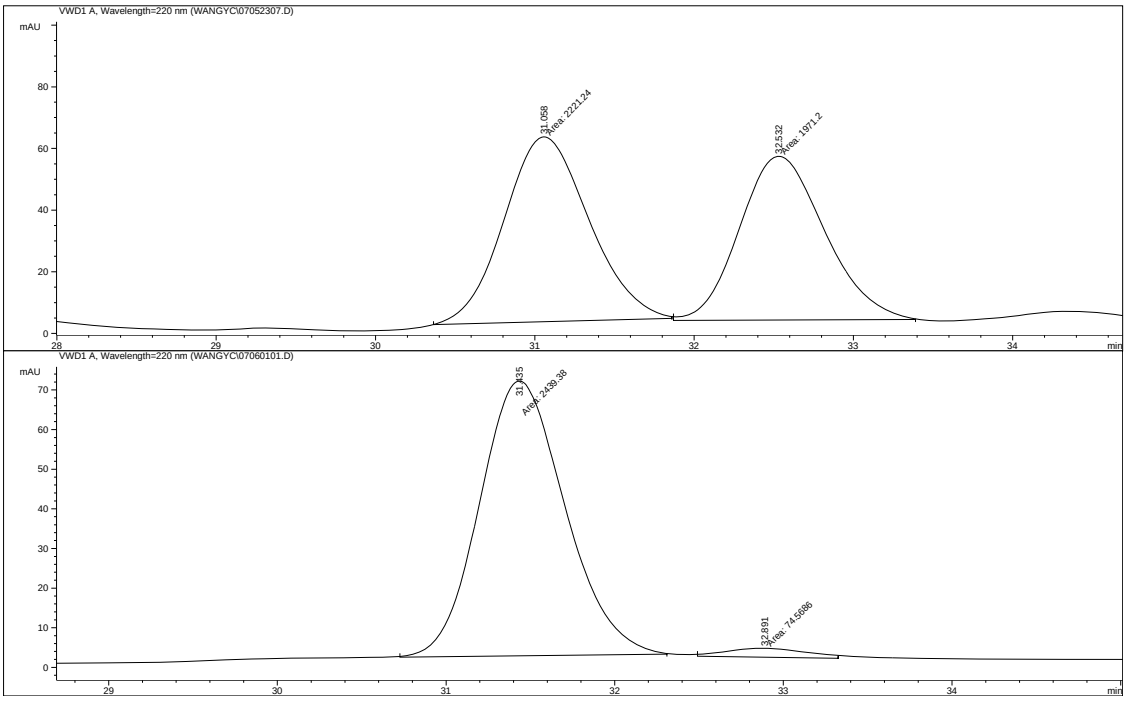
3-(3-Chlorophenyl)-4-nitrobutanal



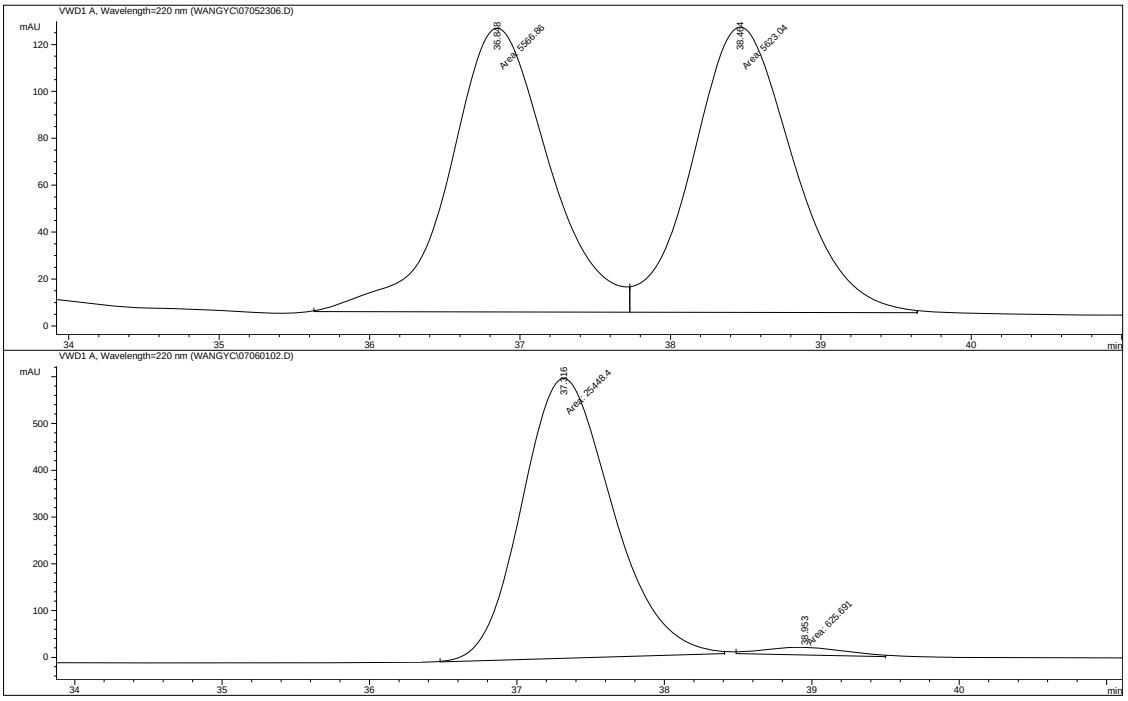
3-(4-Chlorophenyl)-4-nitrobutanal



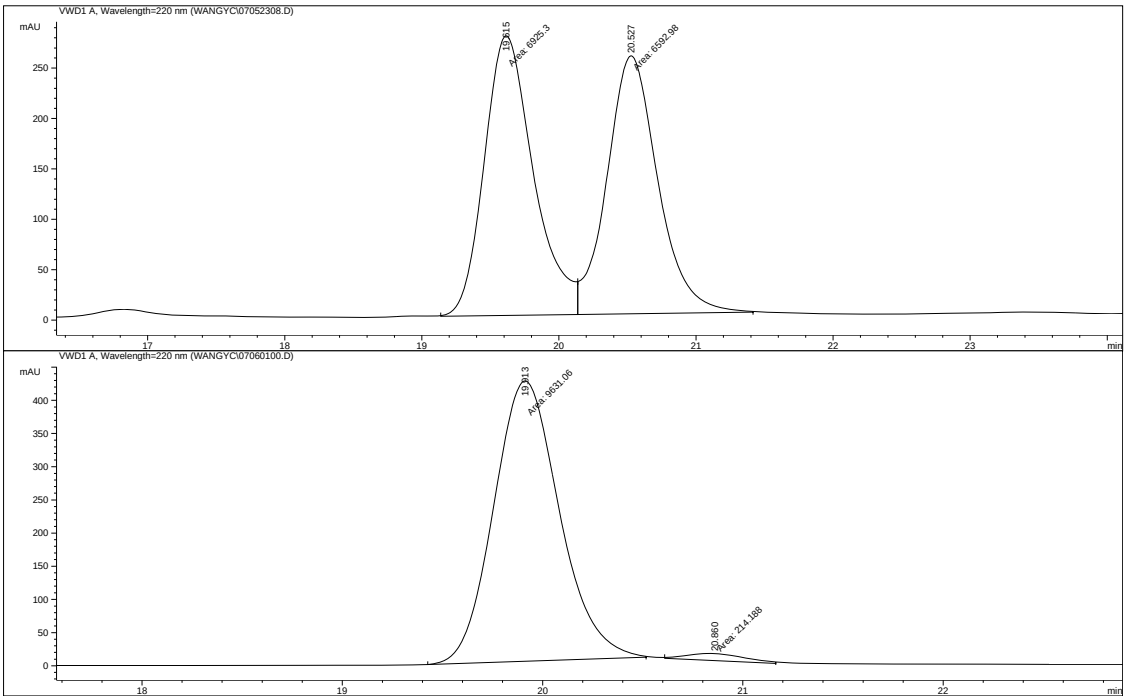
3-(4-Fluorophenyl)-4-nitrobutanal



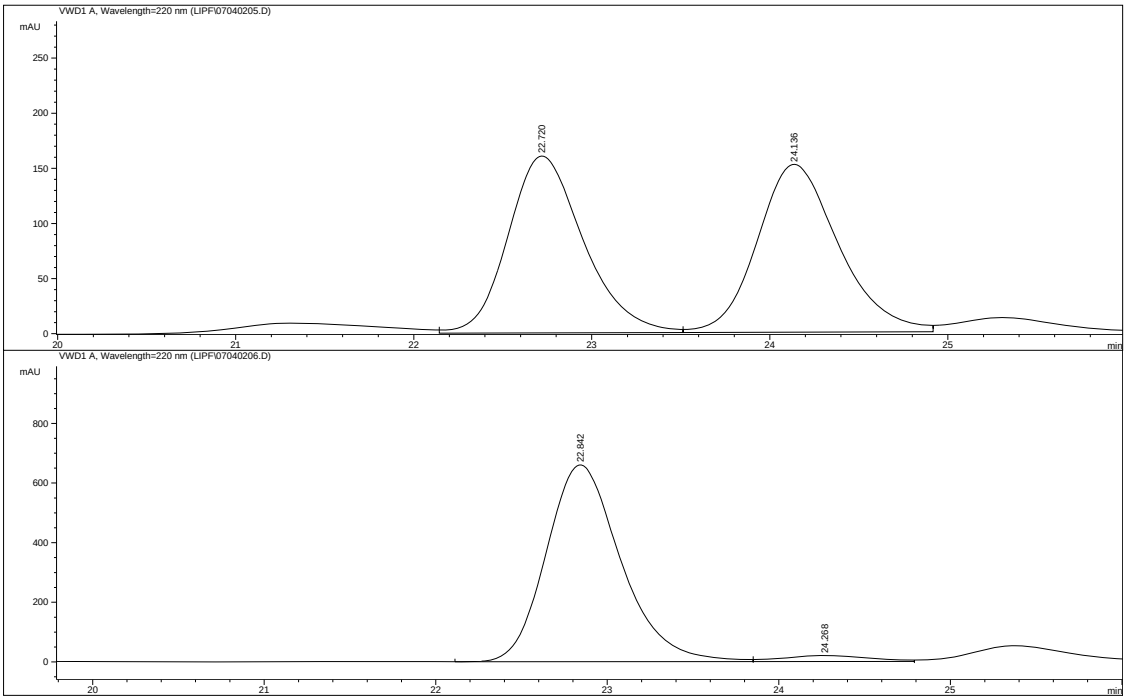
3-(4-Bromophenyl)-4-nitrobutanal



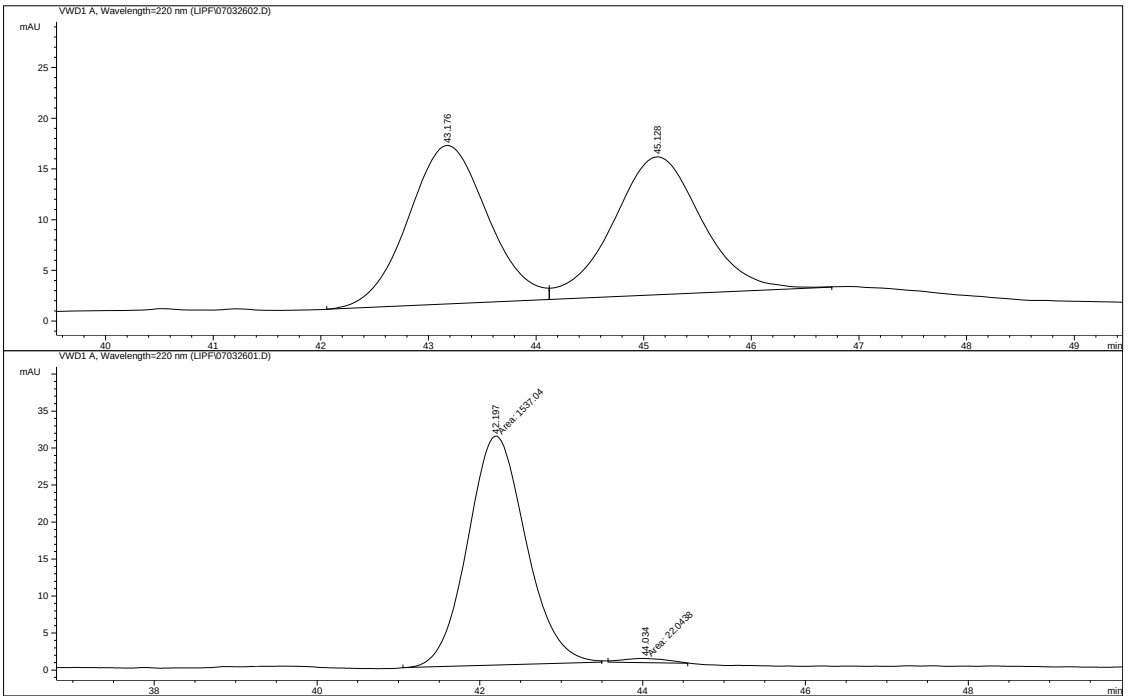
4-Nitro-3-p-tolylbutanal



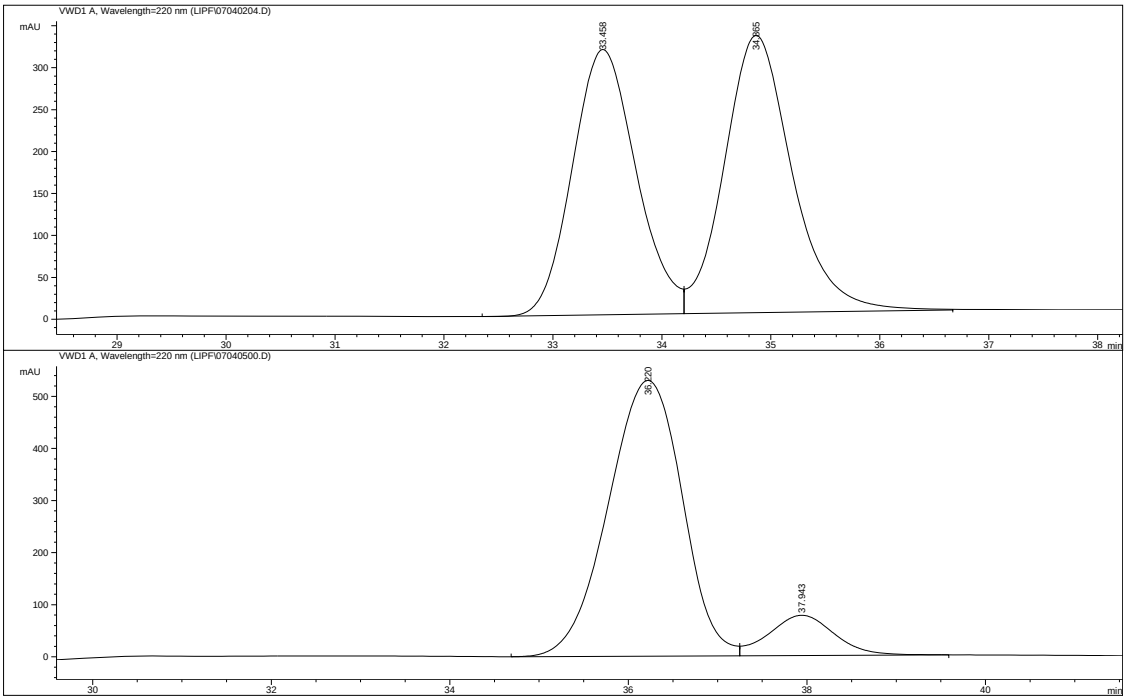
3-(2-Chlorophenyl)-4-nitrobutanal



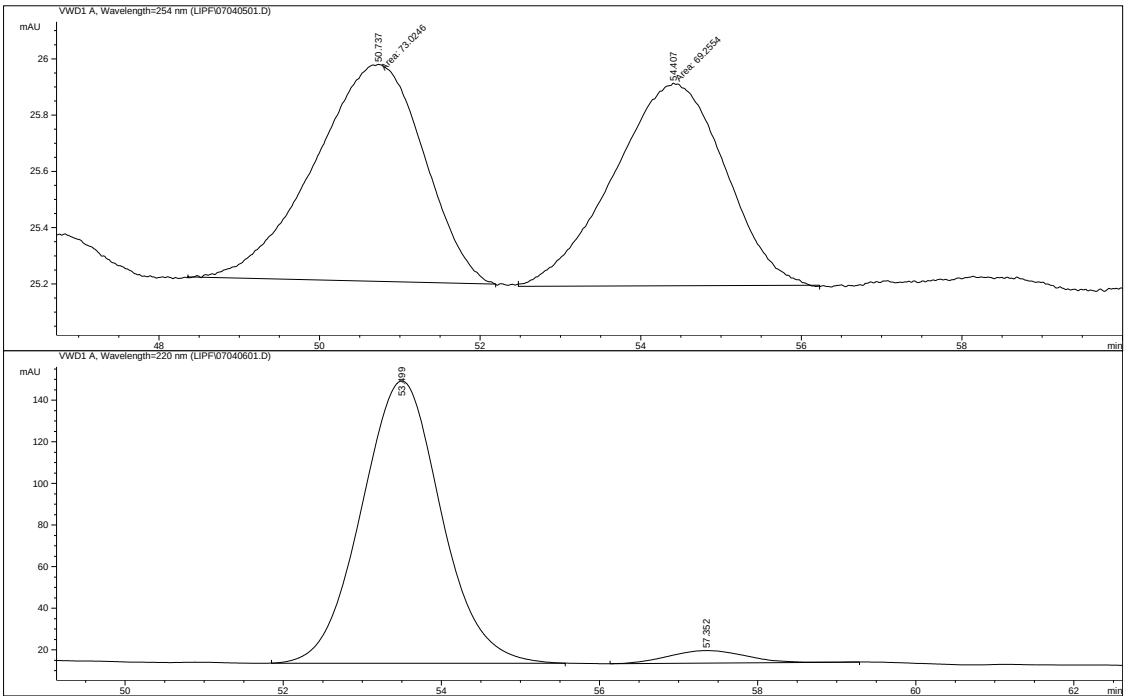
3-(2-Methoxyphenyl)-4-nitrobutanal



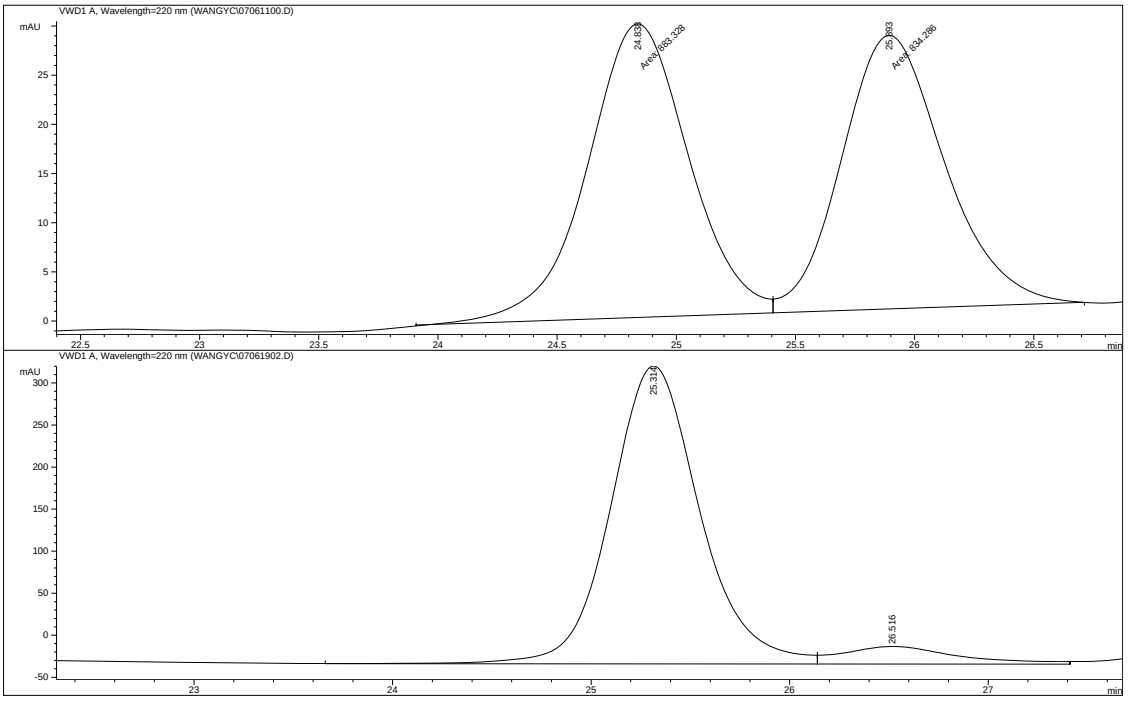
3-(4-Methoxyphenyl)-4-nitrobutanal



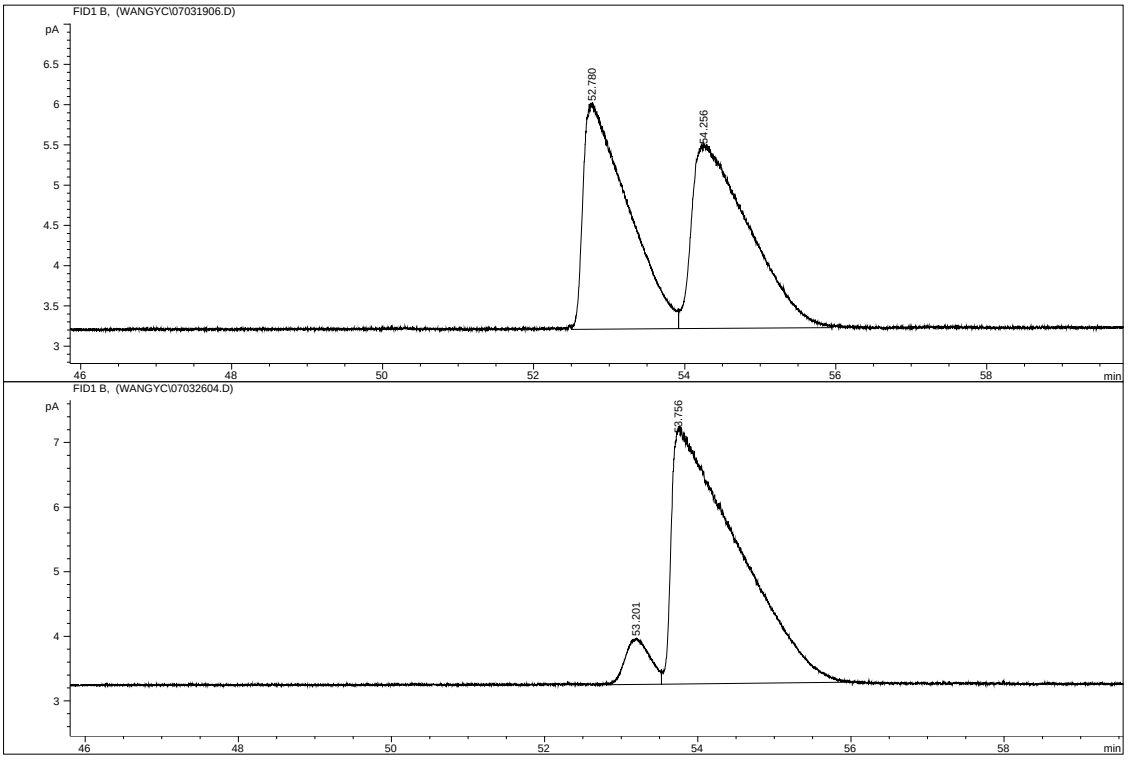
4-Nitro-3-(2-nitrophenyl)butanal



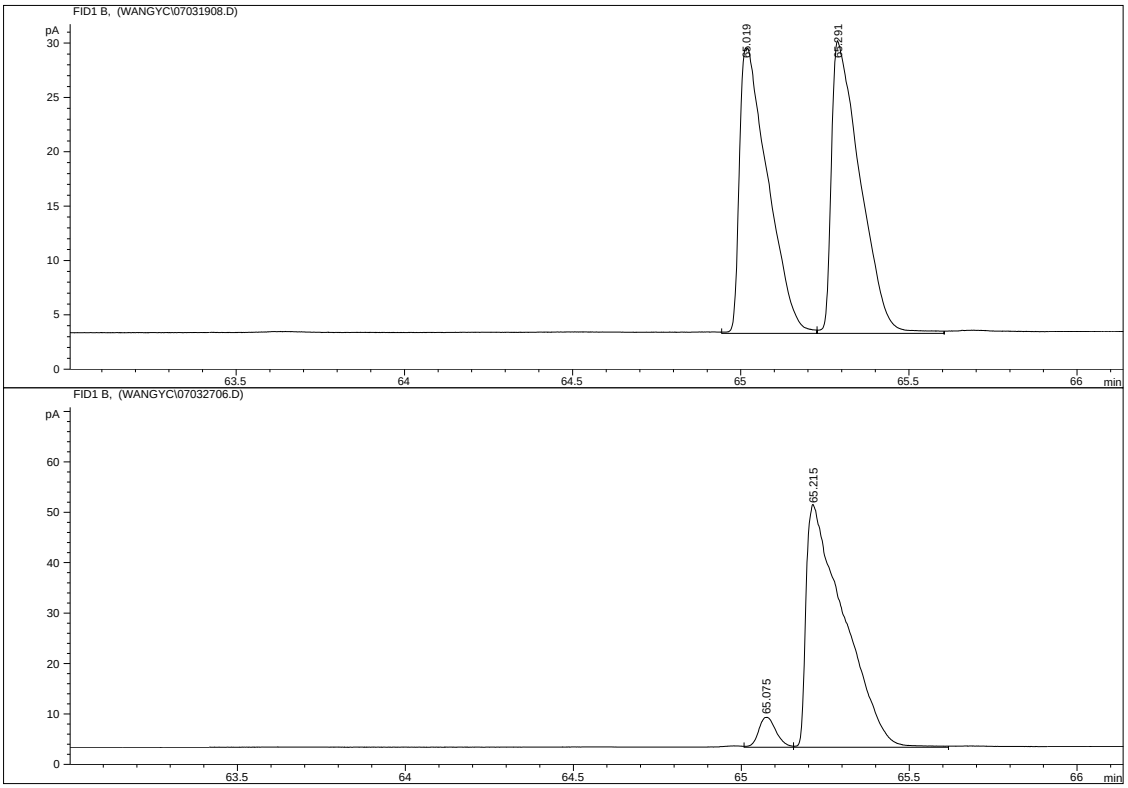
3-(Furan-2-yl)-4-nitrobutanal



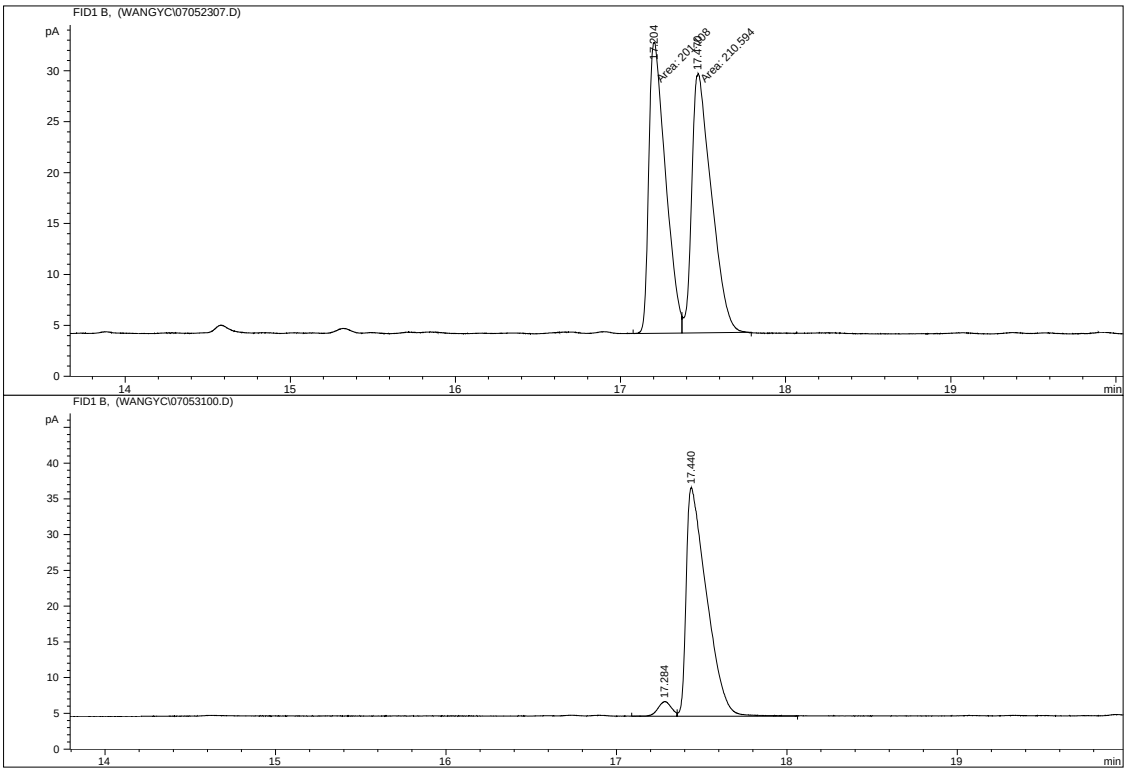
3-(Nitromethyl)pentanal



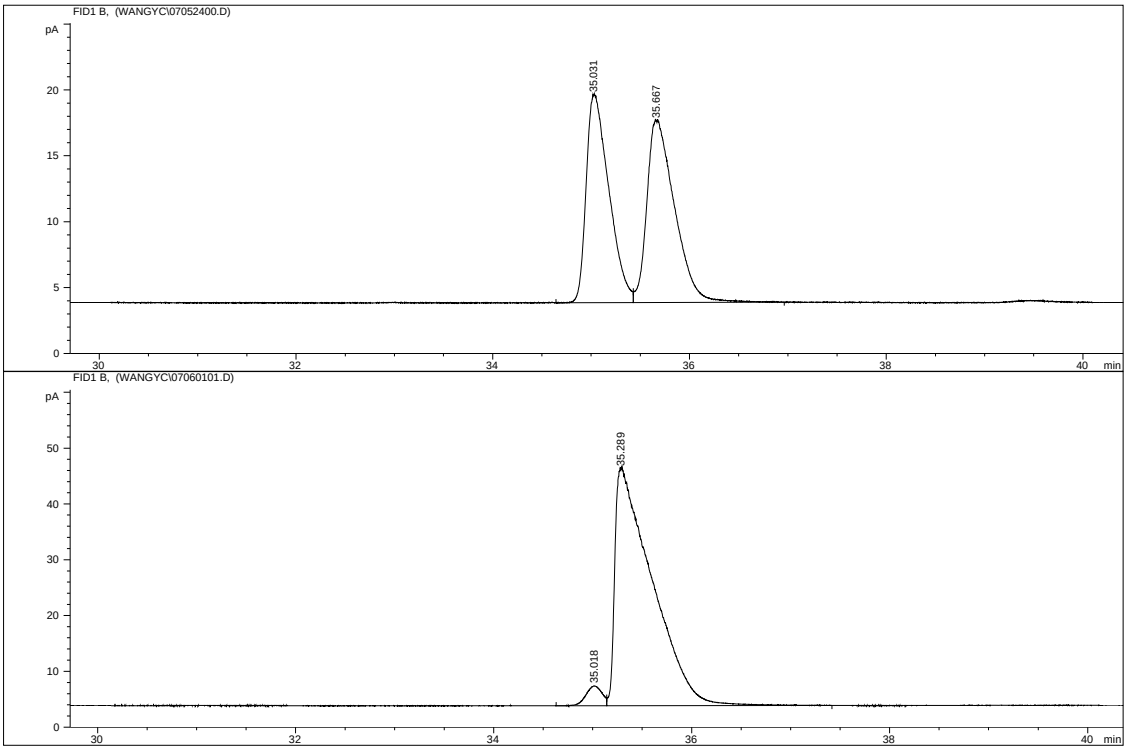
3-(Nitromethyl)hexanal



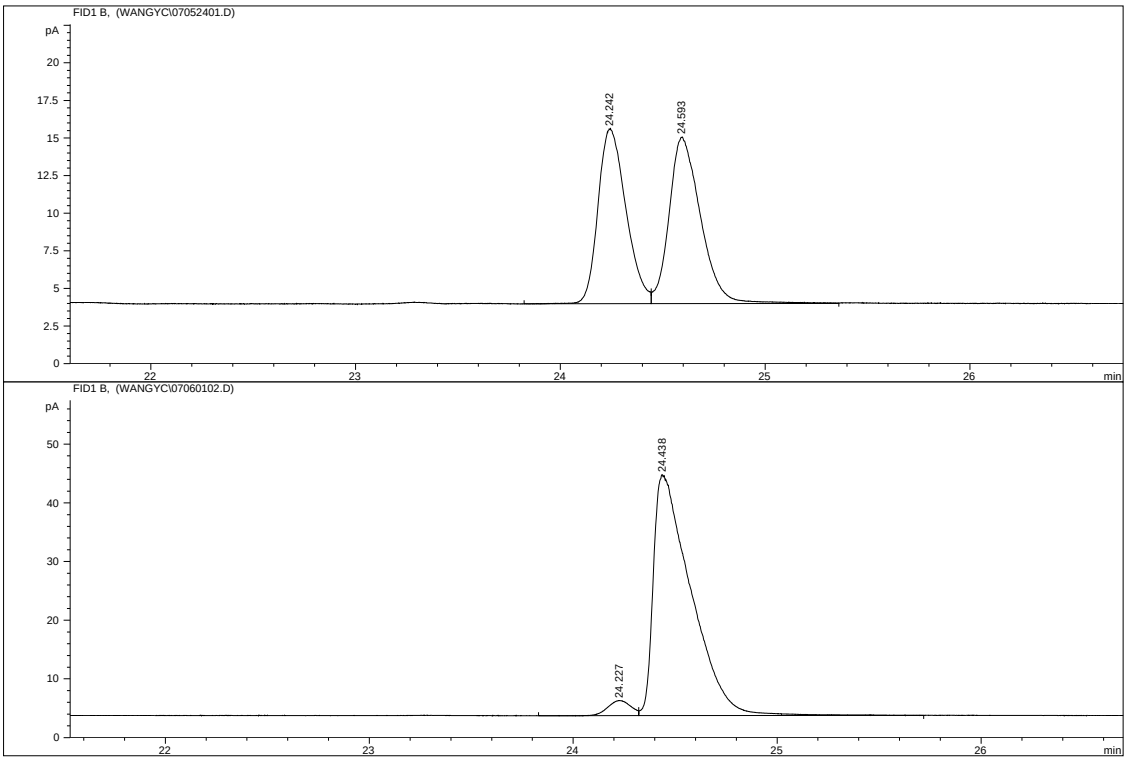
3-(Nitromethyl)heptanal



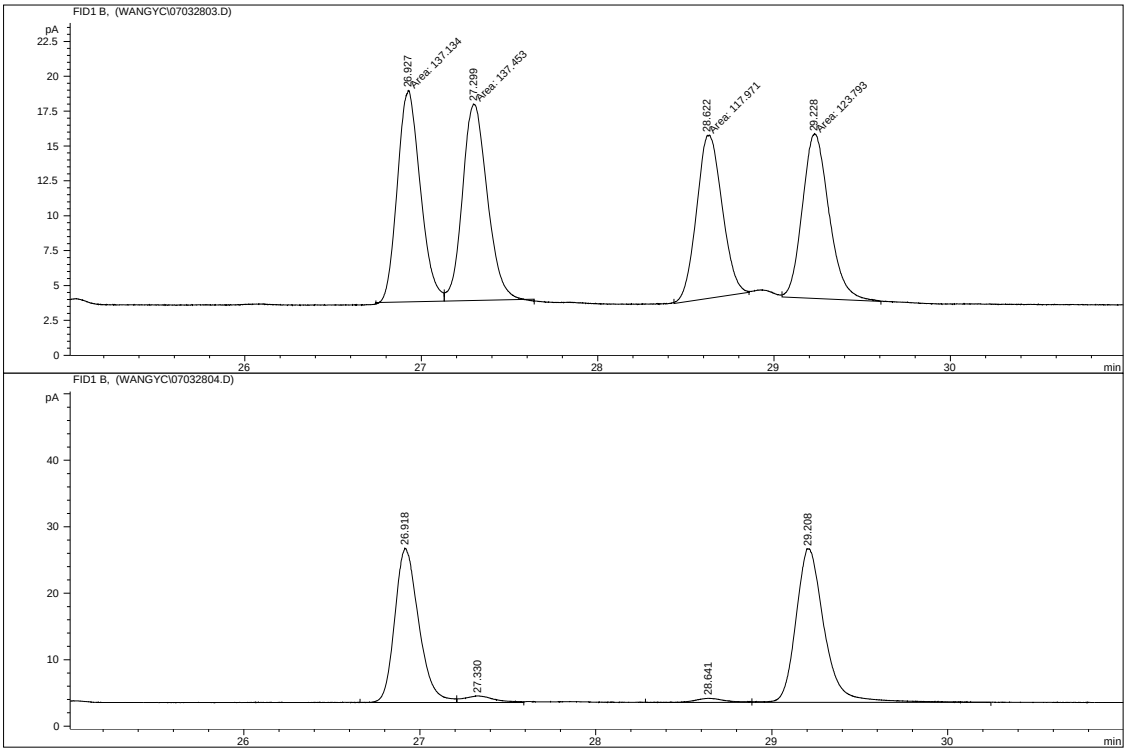
3-(Nitromethyl)decanal



(*Z*)-3-(Nitromethyl)non-6-enal



4-Nitro-3-phenylpentanal



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2. S. Brandau, A. Landa, J. Franzén, M. Marigo and K. A. Jørgensen, A*ngew. Chem. Int. Ed.*, 2006, **45**, 4305.
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