

**Asymmetric Henry Reaction Catalyzed by C_2 -Symmetric Tridentate
Bis(oxazoline) and Bis(thiazoline) Complexes: Metal-controlled Reversal of
Enantioselectivity**

Da-Ming Du*, Shao-Feng Lu, Tao Fang, Jiayi Xu*

*Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education,
College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P. R. China
dudm@pku.edu.cn*

Supporting Information

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General Remarks

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures and were distilled prior to use. All reactions were carried out under an atmosphere of nitrogen in gas burner-dried glassware with magnetic stirring. Column chromatography was carried out using silica gel (200-300 mesh). For TLC, silica gel GF₂₅₄ was used. Melting points were uncorrected. The ¹H NMR spectra were recorded with 200, 300 and 400 MHz spectrometers, while the ¹³C NMR spectra were recorded at 50, 75 and 100 MHz respectively in CDCl₃ or DMSO-d₆ solution. Chemical shifts were reported in ppm using tetramethylsilane as internal standard. Infrared spectra and Mass spectra were obtained at Analytical Center of Peking University. Optical rotations were measured with polarimeter using a thermally jacketed 1 mL cell with 10 cm path length (concentration *c* given as g/100 mL). The enantiomeric excess (ee) of the Henry products were determined by chiral HPLC analysis on OB, OJ or AS columns (4.6 × 250 mm) with a mixture of hexane-isopropanol as an eluent at an rate of 1.0 mL/min, monitoring wave is 215 nm. The α-keto esters **3c–3h** were prepared according to the literature procedures.¹

General Procedure for the Catalytic Enantioselective Henry reaction. To a mixture of ligand **1d** (24.4 mg, 0.05 mmol) and hexane (2 mL) at 0 °C was added Et₂Zn (125 μL, 0.125 mmol, 1.0 M in hexane) under nitrogen. The mixture was allowed to stir for 0.5 h and α-keto ester **3** (0.25 mmol) was added followed by nitromethane (0.54 mL, 10 mmol). After being stirred for 24h at 0 °C, the mixture was quenched by diluted HCl (2 mL, 1 mol/L) and then extracted with ether (5 mL × 2). Purification by column chromatography afforded the desired Henry product **4**. The ee was determined by HPLC on OB, OJ, or AS column.

2-Hydroxy-2-methyl-3-nitro-propionic Acid Ethyl Ester (4a). Compound **4a** was prepared according to the general procedure using 29.1 mg (0.25 mmol) of α-keto ester **3a** and purified by column chromatography (25% AcOEt in petroleum ether) to yield 43.0 mg (97%) of **4a** as a pale yellow oil. The ee was determined by chiral HPLC on an OB column (hexane: 2-propanol 90:10, 1.0 mL/min, *t*_{minor}=12.0 min, *t*_{major}=13.6 min). [α]_D²⁰ = +15.5° (*c* = 0.26, CH₂Cl₂, 84% ee). [Lit.² [α]_D²³ = +10.2° (*c* 1.19, CH₂Cl₂, 92% ee)]. ¹H NMR (CDCl₃): δ = 4.86 (d, *J* = 13.8 Hz, 1H), 4.58 (d, *J* = 13.8 Hz, 1H), 4.34 (m, 2H), 3.85 (s, 1H), 1.46 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃): δ = 173.4, 80.9, 72.4, 63.0, 23.8, 13.9.

2-Hydroxy-2-trifluoromethyl-3-nitro-propionic Acid Ethyl Ester (4b). Compound **4b** was prepared according to the general procedure using 42.5 mg (0.25 mmol) of α-keto ester **3b** and purified by column chromatography (25% AcOEt in petroleum ether) to yield 20.8 mg (36%) of **4b** as a pale yellow oil. The ee was determined by chiral HPLC on an OJ column (hexane: 2-propane 90:10, 0.5 mL/min, *t*_{major} = 18.1 min, *t*_{minor} = 20.0 min). [α]_D²⁰ = +12.8° (*c* = 0.58, CH₂Cl₂, 13% ee). ¹H NMR (*d*₆-DMSO): δ = 8.00 (s, 1H), 5.47 (d, *J* = 13.8 Hz, 1H), 4.95 (dd, *J* = 13.8, 1.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ¹³C NMR

(*d*₆-DMSO): δ = 165.8, 122.7 (d, *J* = 287.3 Hz), 76.6, 75.8 (q, *J* = 28.5 Hz), 63.2, 13.7. HRMS (EI): calcd for C₆H₉NO₅F₃ [M + H]⁺ 232.04328, found 232.04317.

2-Hydroxy-3-nitro-2-phenyl-propionic Acid Ethyl Ester (4c). Compound **4c** was prepared according to the general procedure using 44.5 mg (0.25 mmol) of α -keto ester **3c** and purified by column chromatography (15% AcOEt in petroleum ether) to yield 57.4 mg (96%) of **4c** as a colorless oil. The ee was determined by chiral HPLC on an OJ column (hexane: 2-propanol 90:10, 1.0 mL/min, *t*_{major} = 24.9 min, *t*_{minor} = 32.2 min). $[\alpha]_D^{20} = -2.88^\circ$ (c = 1.11, CH₂Cl₂, 16% ee). [Lit.² $[\alpha]_D^{23} = -16.2^\circ$ (c 1.13, CH₂Cl₂, 86% ee)]. ¹H NMR (CDCl₃): δ = 7.62 (m, 2H), 7.41 (m, 3H), 5.27 (dd, *J* = 14.1, 1.2 Hz, 1H), 4.69 (d, *J* = 14.1 Hz, 1H), 4.35 (m, 2H), 4.26 (d, *J* = 1.2 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃): δ = 171.6, 136.4, 129.1, 128.9, 125.2, 80.7, 75.9, 63.6, 13.9.

2-Hydroxy-2-nitromethyl-4-phenyl-butyric Acid Ethyl Ester (4d). Compound **4d** was prepared according to the general procedure using 51.6 mg (0.25 mmol) of α -keto ester **3d** and purified by column chromatography (15% AcOEt in petroleum ether) to yield 63.5 mg (95%) of **4d** as a colorless oil. The ee was determined by chiral HPLC on an AS column (hexane: 2-propanol 90:10, 1.0 mL/min, *t*_{minor} = 11.6 min, *t*_{major} = 15.1 min). $[\alpha]_D^{20} = +15.2^\circ$ (c = 1.20, CH₂Cl₂, 71% ee). [Lit.² $[\alpha]_D^{23} = +16.5^\circ$ (c 1.27, CH₂Cl₂, 77% ee)]. ¹H NMR (CDCl₃): δ = 7.24 (m, 5H), 4.84 (d, *J* = 13.8 Hz, 1H), 4.58 (d, *J* = 13.4 Hz, 1H), 4.29 (m, 2H), 3.86 (br, 1H), 2.82 (m, 1H), 2.49 (m, 1H), 1.99 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (CDCl₃): δ = 172.6, 140.1, 128.5, 128.3, 126.3, 80.8, 75.0, 63.2, 38.2, 29.0, 14.0.

2-Hydroxy-2-nitromethyl-butyric Acid Ethyl Ester (4e). Compound **4e** was prepared according to the general procedure using 32.5 mg (0.25 mmol) of α -keto ester **3e** and purified by column chromatography (25% AcOEt in petroleum ether) to yield 33.2 mg (70%) of **4e** as a colorless oil. The ee was determined by chiral HPLC on an AS column (hexane: 2-propanol 95:5, 1.0 mL/min, *t*_{minor} = 12.1 min, *t*_{major} = 14.3 min). $[\alpha]_D^{20} = +23.1^\circ$ (c = 1.24, CH₂Cl₂, 85% ee). [Lit.² $[\alpha]_D^{23} = +20.2^\circ$ (c 1.0, CHCl₃, 90% ee)]. ¹H NMR (CDCl₃): δ = 4.84 (d, *J* = 13.6 Hz, 1H), 4.57 (d, *J* = 13.6 Hz, 1H), 4.34 (m, 2H), 3.72 (s, 1H), 1.73 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (CDCl₃): δ = 172.8, 80.7, 75.5, 62.9, 30.0, 14.0, 6.9.

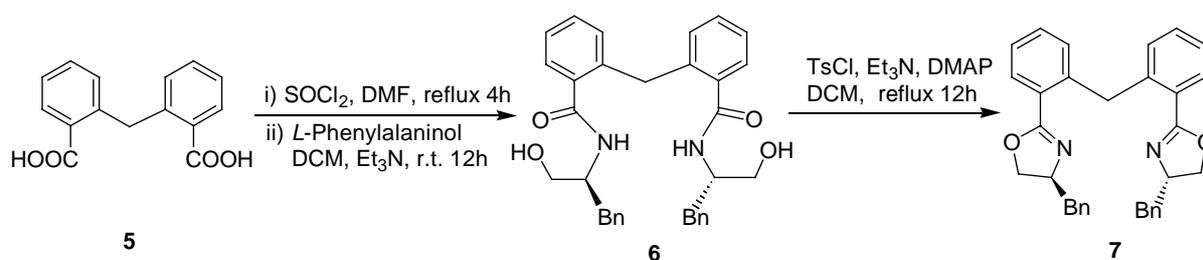
2-Hydroxy-2-nitromethyl-hexanoic Acid Ethyl Ester (4f). Compound **4f** was prepared according to the general procedure using 39.6 mg (0.25 mmol) of α -keto ester **3f** and purified by column chromatography (15% AcOEt in petroleum ether) to yield 54.8 mg (92%) of **4f** as a colorless oil. The ee was determined by chiral HPLC on an AS column (hexane: 2-propanol 90:10, 1.0 mL/min, *t*_{minor} = 7.0 min, *t*_{major} = 8.0 min). $[\alpha]_D^{20} = +17.2^\circ$ (c = 0.91, CH₂Cl₂, 82% ee). ¹H NMR (CDCl₃): δ = 4.83 (d, *J* = 13.8 Hz, 1H), 4.57 (d, *J* = 13.4 Hz, 1H), 4.35 (m, 2H), 3.73 (s, 1H), 1.65 (m, 2H), 1.34 (m, 7H), 0.90 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (CDCl₃): δ

=172.9, 80.9, 75.2, 63.0, 36.2, 24.7, 22.5, 14.0, 13.8. HRMS (EI): calcd for C₉H₁₈NO₅ [M + H]⁺ 220.11850, found 220.11825.

2-Hydroxy-4-methyl-2-nitromethyl-pentanoic Acid Ethyl Ester (4g). Compound **4g** was prepared according to the general procedure using 39.6 mg (0.25 mmol) of α -keto ester **3g** and purified by column chromatography (15% AcOEt in petroleum ether) to yield 48.2mg (88%) of **4g** as a pale yellow oil. The ee was determined by chiral HPLC on an AS column (hexane: 2-propanol 90:10, 1.0 mL/min, t_{minor} =6.6 min, t_{major} =7.5 min). $[\alpha]_{\text{D}}^{20}$ = +19.1° (c = 1.16, CH₂Cl₂, 65% ee). [Lit.² $[\alpha]_{\text{D}}^{23}$ = +21.1° (c 1.02, CH₂Cl₂, 92% ee)]. ¹H NMR (CDCl₃): δ = 4.80 (d, J = 13.6 Hz, 1H), 4.54 (d, J = 13.4 Hz, 1H), 4.34 (m, 2H), 3.73 (s, 1H), 1.71 (m, 2H), 1.60 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H). ¹³C NMR (CDCl₃): δ = 173.2, 81.5, 75.3, 63.0, 44.5, 24.1, 23.8, 23.4, 14.0.

2-Hydroxy-2-nitromethyl-decanoic Acid Ethyl Ester (4h). Compound **4h** was prepared according to the general procedure using 53.6 mg (0.25 mmol) of α -keto ester **3h** and purified by column chromatography (9% AcOEt in petroleum ether) to yield 58.5mg (88%) of **4h** as a colorless solid. The ee was determined by chiral HPLC on an AS column (hexane: 2-propanol 98:2, 1.0 mL/min, t_{minor} =8.3 min, t_{major} =9.1 min). $[\alpha]_{\text{D}}^{20}$ = +10.8° (c = 1.77, CH₂Cl₂, 80% ee). ¹H NMR (*d*₆-DMSO): δ = 5.89 (s, 1H), 5.00 (d, J = 13.2 Hz, 1H), 4.59 (d, J = 13.2 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 1.58 (m, 2H), 1.21 (m, 15H), 0.84 (t, J = 6.9 Hz, 3H). ¹³C NMR (*d*₆-DMSO): δ = 172.2, 81.9, 75.5, 61.0, 36.7, 31.3, 28.9, 28.7, 28.5, 22.3, 22.1, 14.0, 13.9. HRMS (EI): calcd for C₁₃H₂₆NO₅ [M + H]⁺ 276.18110, found 276.18058.

Preparation of Ligand 7.³



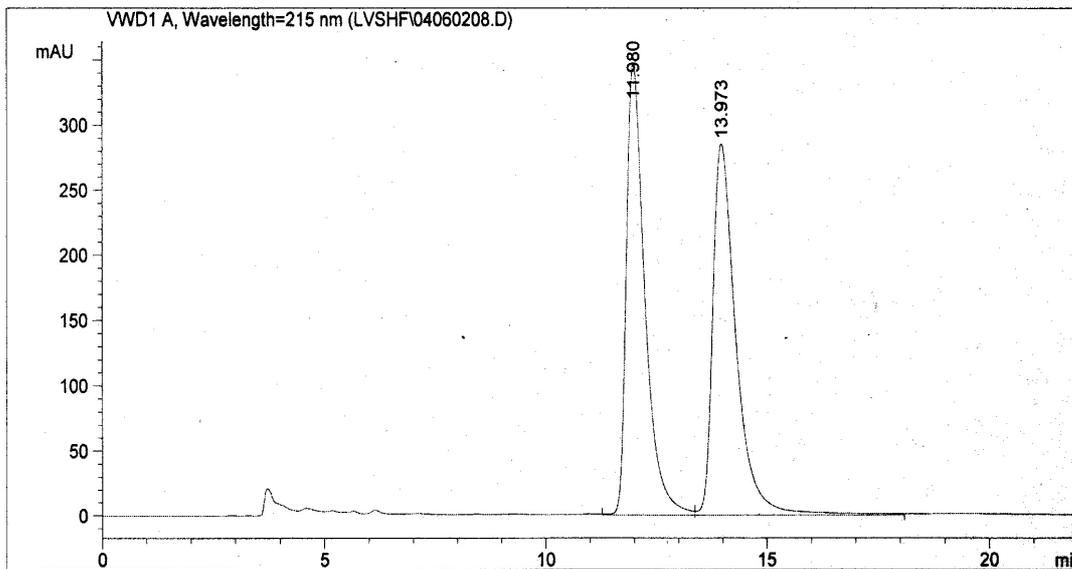
The starting material diphenylmethane-2,2'-dicarboxylic acid **5** was prepared according to the literature.⁴ The dicarboxylic acid **5** (300 mg, 1.17 mmol), SOCl₂ (3 mL, 41.7 mmol) and 2 drops of DMF were refluxed for 4 h. The solution was evaporated to dryness and the residue was extracted with benzene. Evaporation of the solvent gave the dicarboxylic acid dichloride. The above dicarboxylic acid dichloride in CH₂Cl₂ (5 mL) was added dropwise to a solution of L-phenylalaninol (389 mg, 2.57 mmol) and Et₃N (1.6 mL, 11.4 mmol) in CH₂Cl₂ (5 mL) at 0 °C and stirred at room temperature for 12 h to afford crude bisamide **6** intermediate. Then DMAP (15 mg, 0.12 mmol), Et₃N (1.5 ml, 10.7 mmol) and TsCl (451 mg, 2.34 mmol) were added in sequence and refluxed for 12 h. The reaction mixture was quenched by saturated NH₄Cl solution (10 mL) and extracted by CH₂Cl₂ (10 mL × 2). The organic layer was

combined and washed by saturated NaHCO₃ solution (10 mL). The water layer was extracted with CH₂Cl₂ (10 mL). The organic extracts were dried over anhydrous Na₂SO₄, concentrated and purified by silica gel column chromatography (25% AcOEt in petroleum ether) to afford the product as a yellow oil in 46% overall yield. $[\alpha]_D^{20} = -41.3^\circ$ (c = 1.36, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.78 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.26 (m, 14H), 7.06 (d, *J* = 7.4 Hz, 2H), 4.75 (s, 2H), 4.49 (m, 2H), 4.19 (t, *J* = 9.0 Hz, 2H), 3.98 (dd, *J* = 7.3, 8.3 Hz, 2H), 3.10 (dd, *J* = 13.7, 5.2 Hz, 2H), 2.51 (dd, *J* = 13.7, 8.8 Hz, 2H). ¹³C NMR (CDCl₃): δ = 164.2, 141.2, 138.0, 130.6, 130.5, 129.8, 129.2, 128.4, 127.6, 126.3, 125.8, 71.1, 68.0, 41.6, 38.2. IR (neat): 1642, 1493, 1353, 1049, 1030, 968, 777, 725, 700 cm⁻¹. MS (70eV, EI): *m/z* (%) 486 (M⁺, 94), 395 (100), 351 (22), 261 (59), 117 (45), 91 (83). HRMS (EI): calcd for C₃₃H₃₀N₂O₂: 486.23073, found 486.23004.

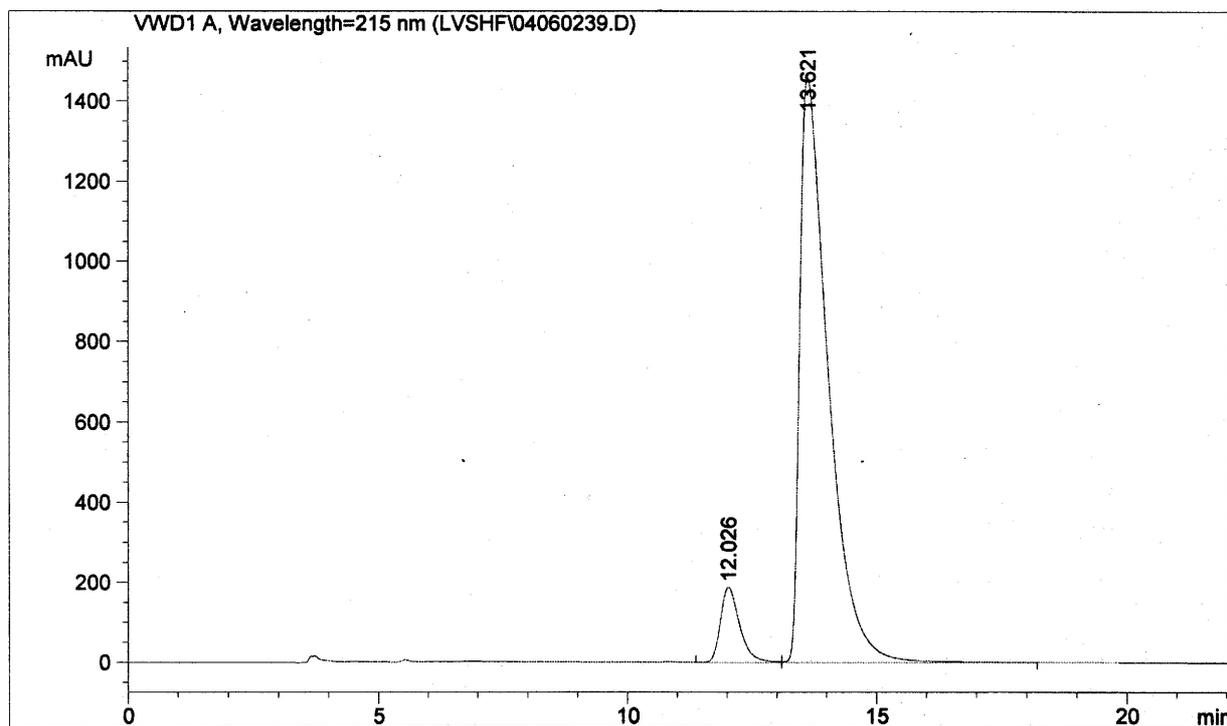
Reference:

- (1) Macritchie, J. A.; Sicoock, A.; Willis, C. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3895-3902.
- (2) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875-4881.
- (3) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541-4544.
- (4) Renaud, R. N.; Layton, R. B.; Fraser, R. R. *Can. J. Chem.* **1973**, *51*, 3380-3385.

2-Hydroxy-2-methyl-3-nitro-propionic Acid Ethyl Ester (4a)

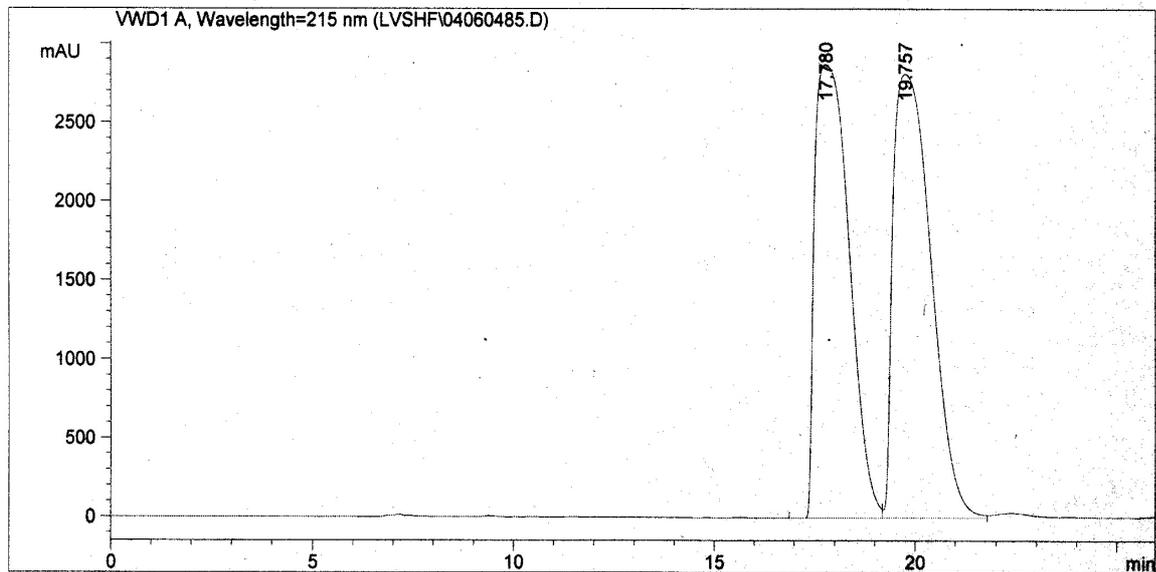


rac-4a

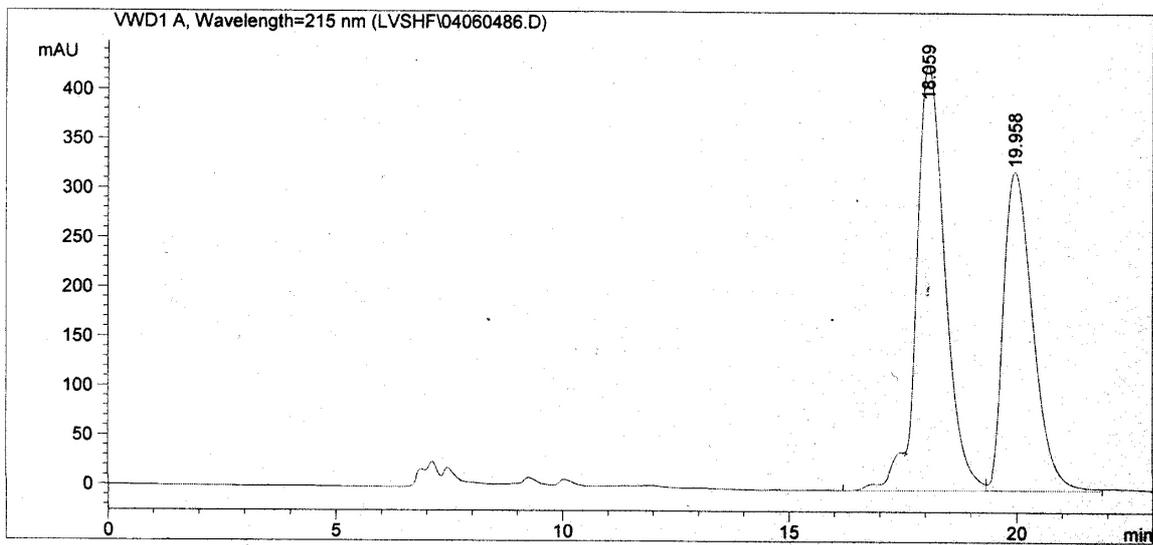


(R)-4a

2-Hydroxy-2-trifluoromethyl-3-nitro-propionic Acid Ethyl Ester (4b)

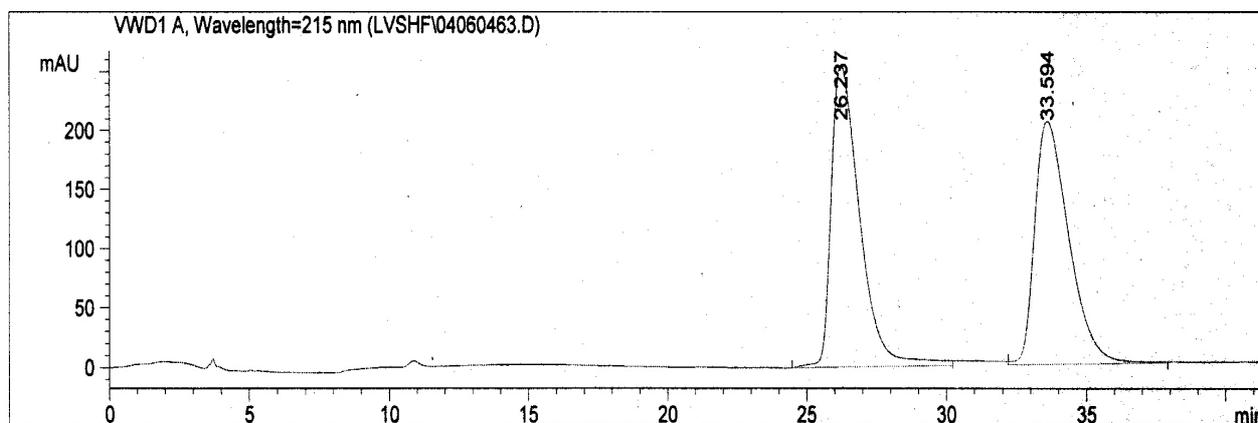


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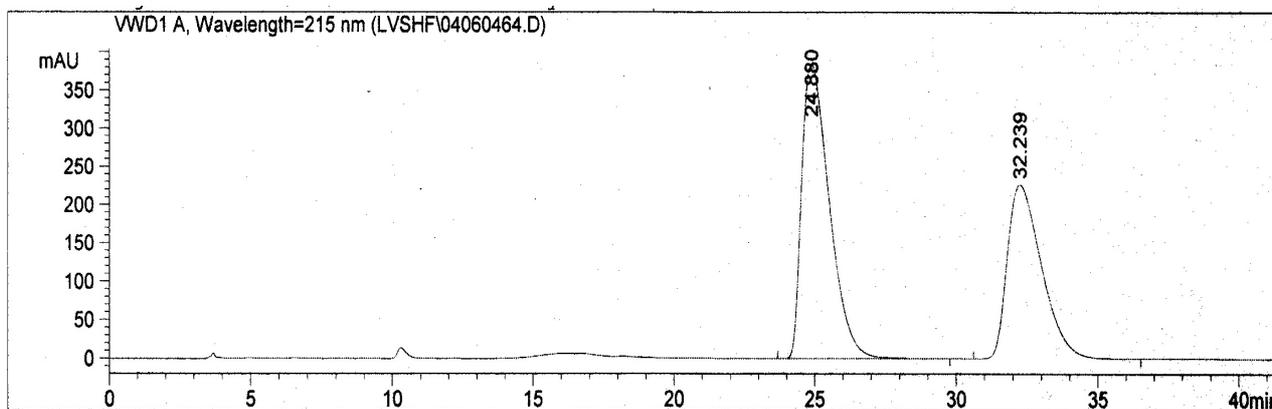


(*R*)-4b

2-Hydroxy-3-nitro-2-phenyl-propionic Acid Ethyl Ester (4c)

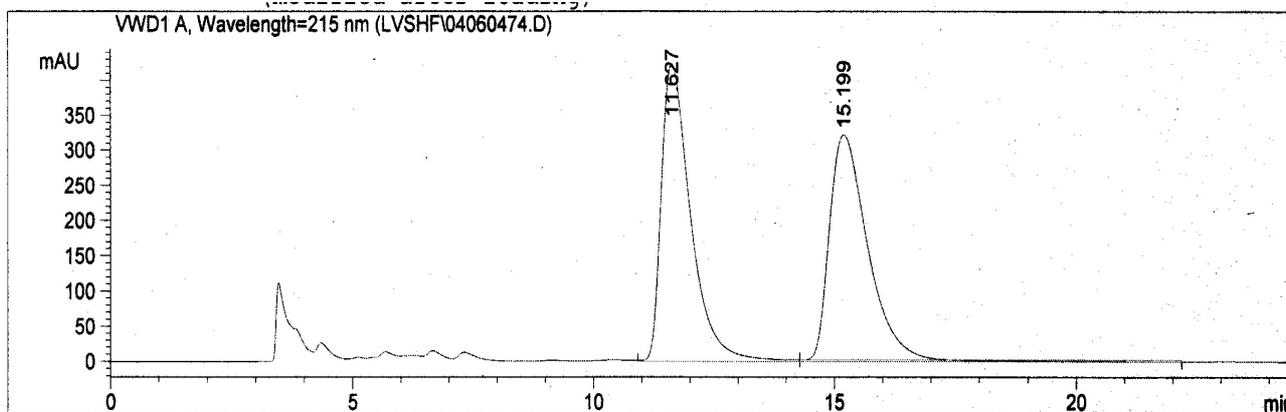


rac-4c

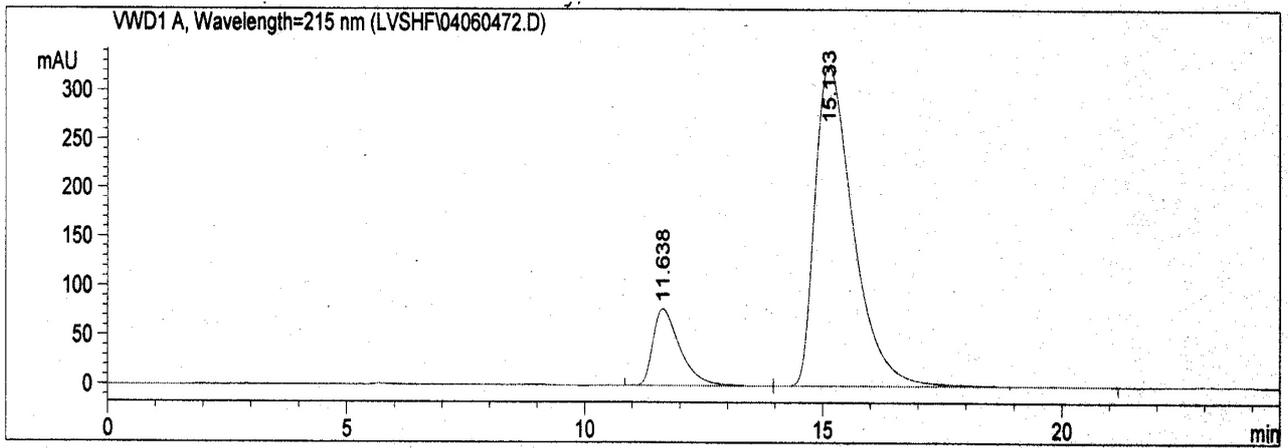


(*R*)-4c

2-Hydroxy-2-nitromethyl-4-phenyl-butyric Acid Ethyl Ester (4d)

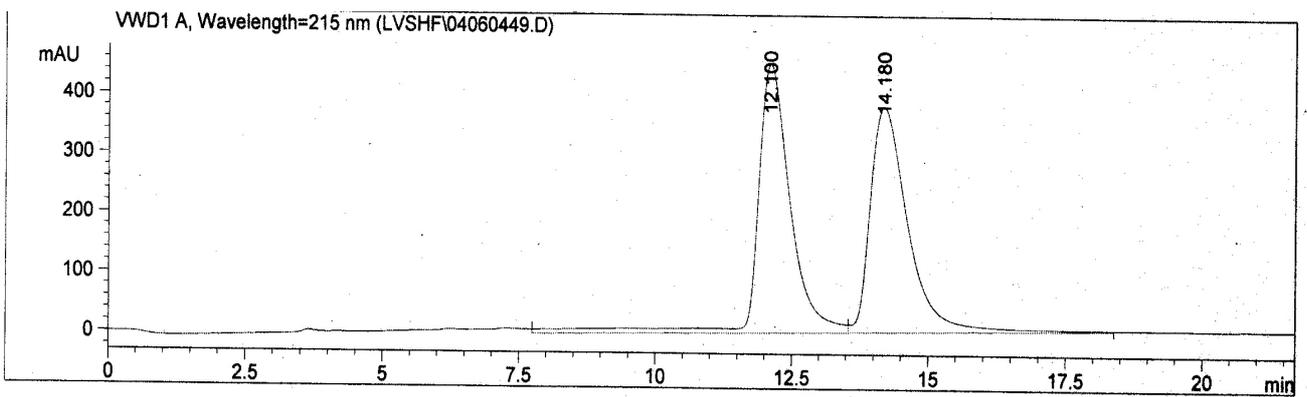


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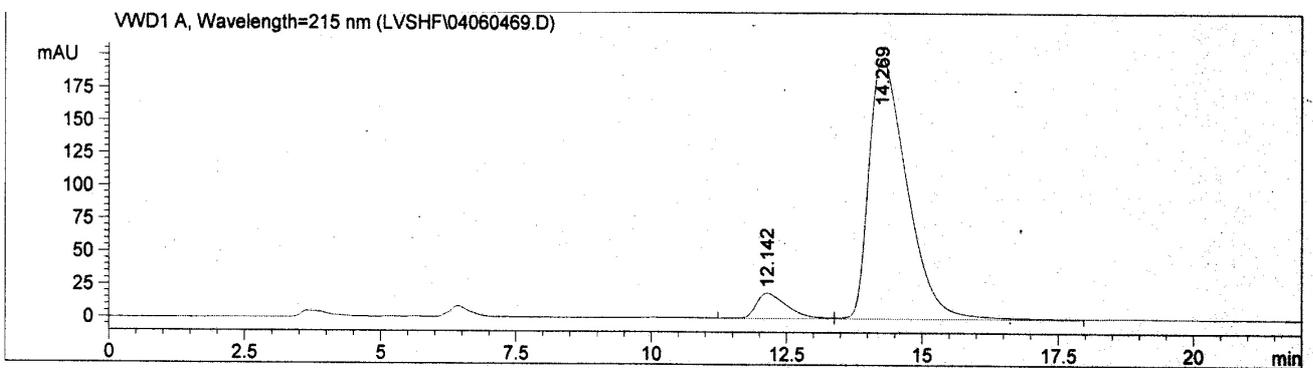


(R)-4d

2-Hydroxy-2-nitromethyl-butyrlic Acid Ethyl Ester (4e)

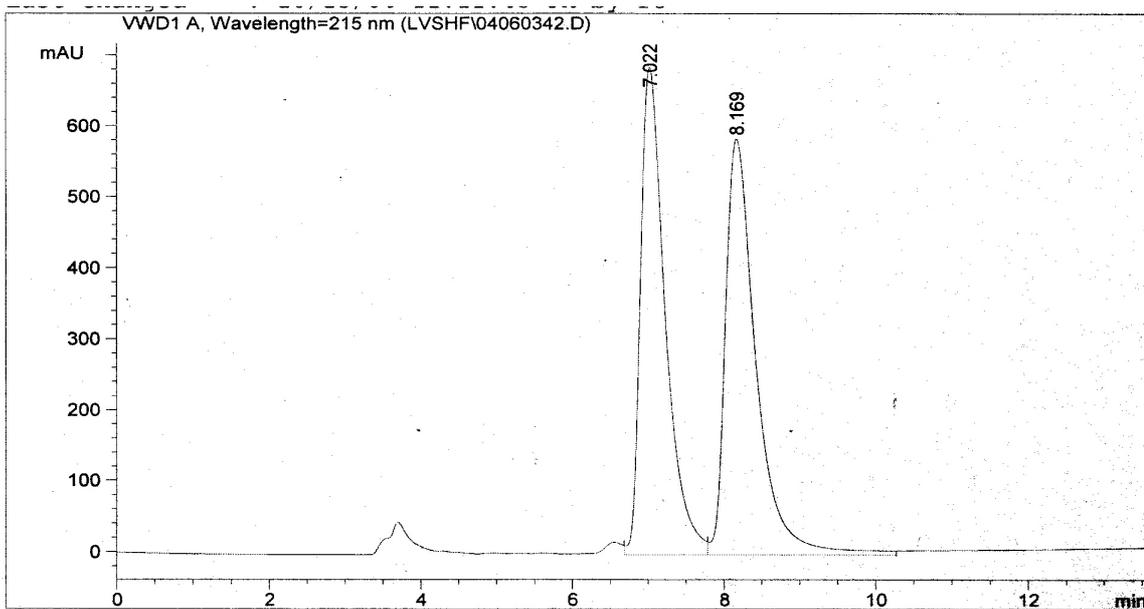


rac-4e

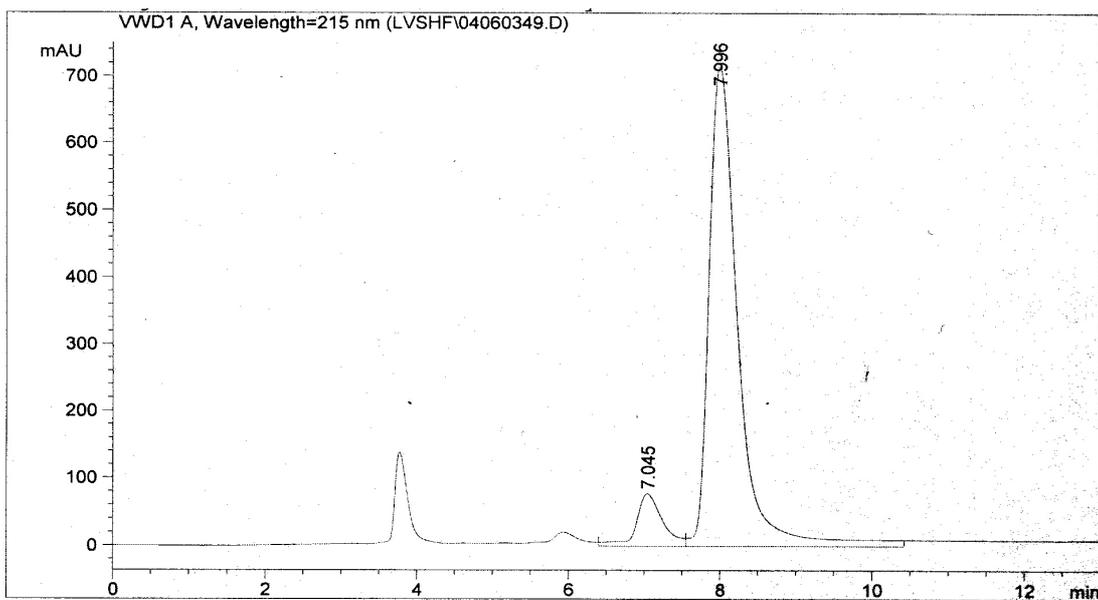


(R)-4e

2-Hydroxy-2-nitromethyl-hexanoic Acid Ethyl Ester (4f)

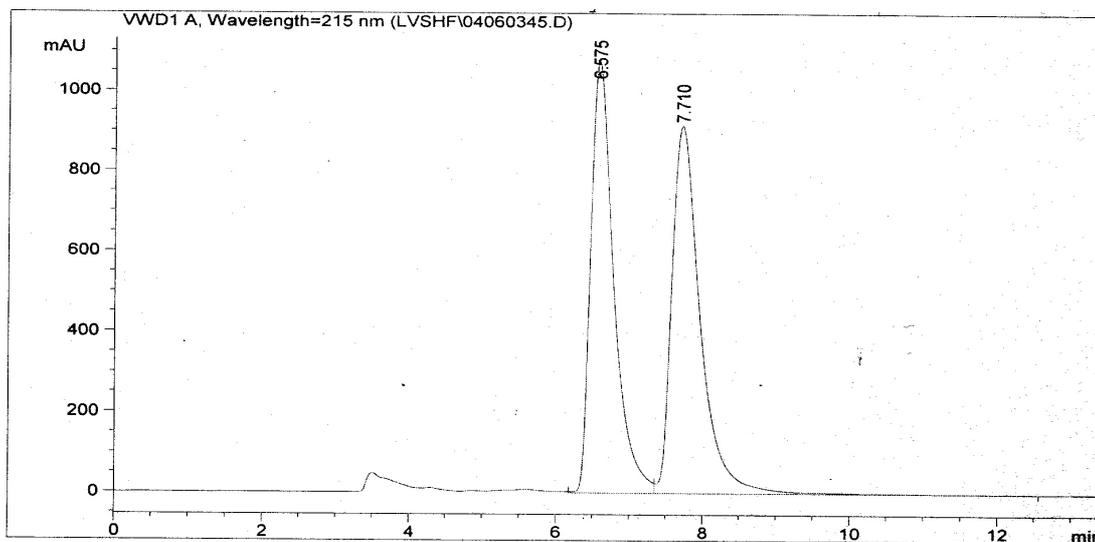


rac-4f

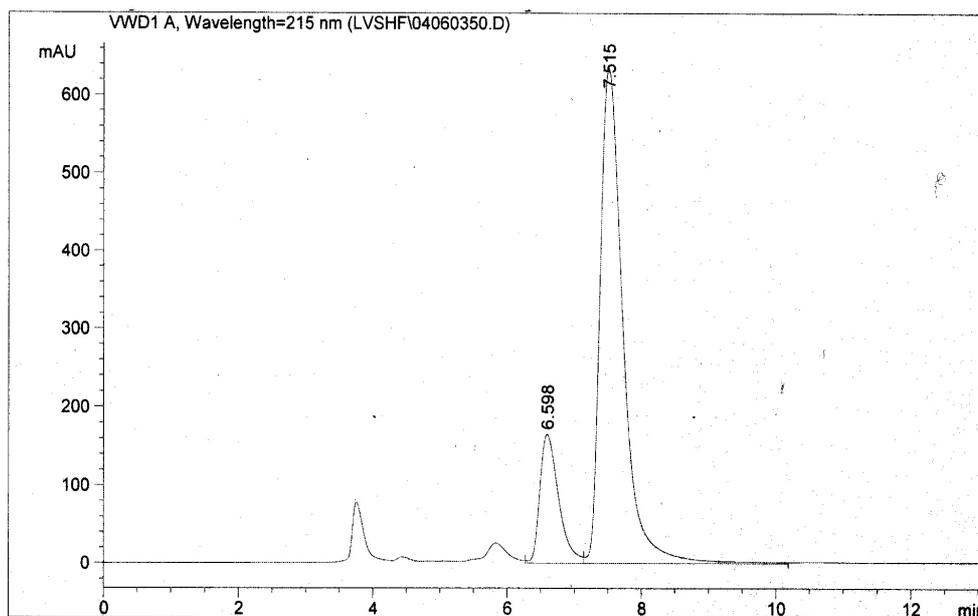


(*R*)-4f

2-Hydroxy-4-methyl-2-nitromethyl-pentanoic Acid Ethyl Ester (4g)

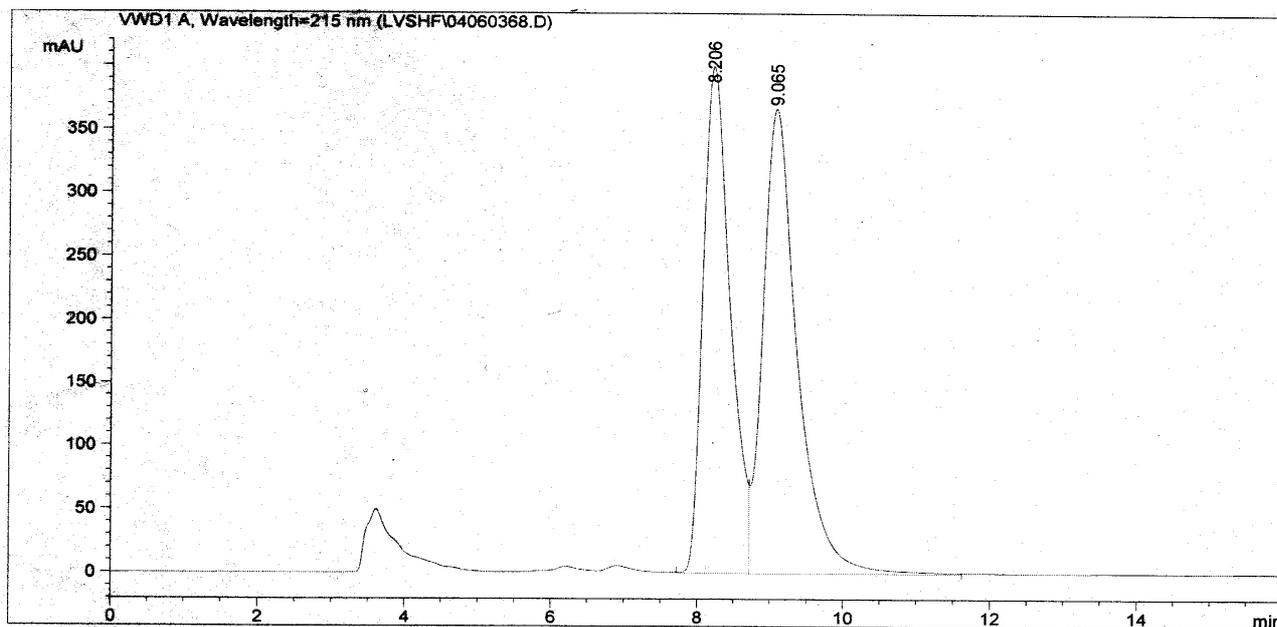


rac-4g

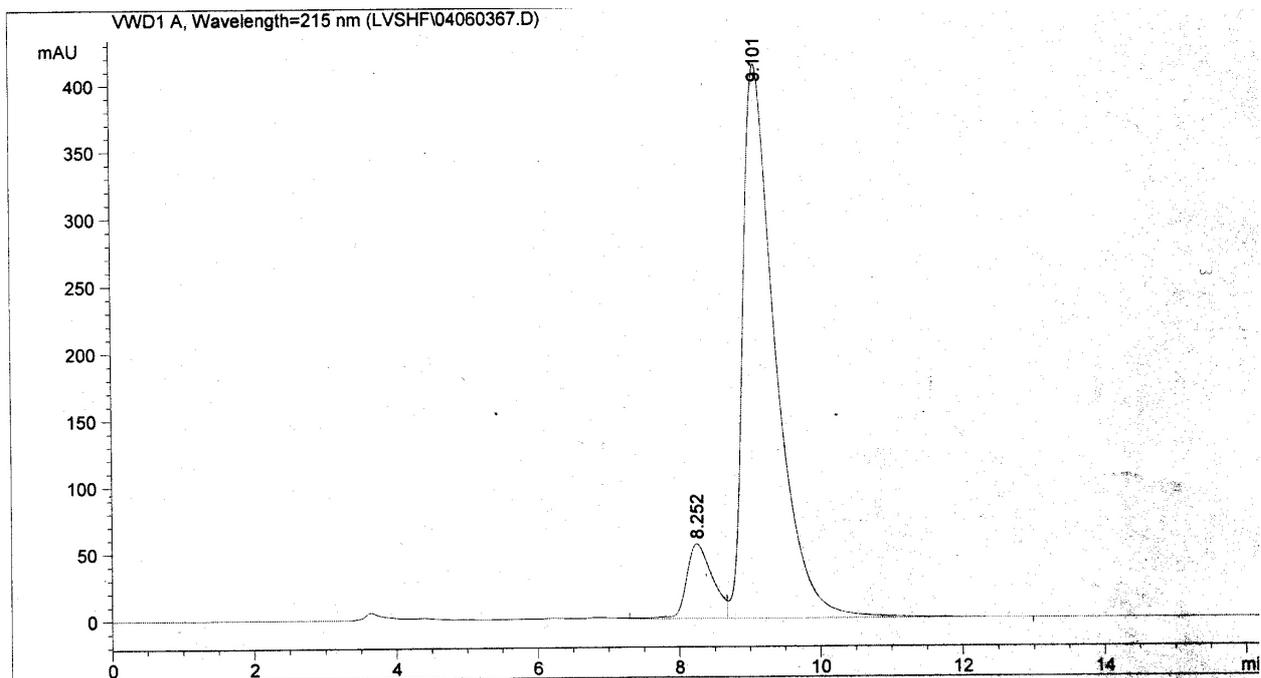


(*R*)-4g

2-Hydroxy-2-nitromethyl-decanoic Acid Ethyl Ester (4h)

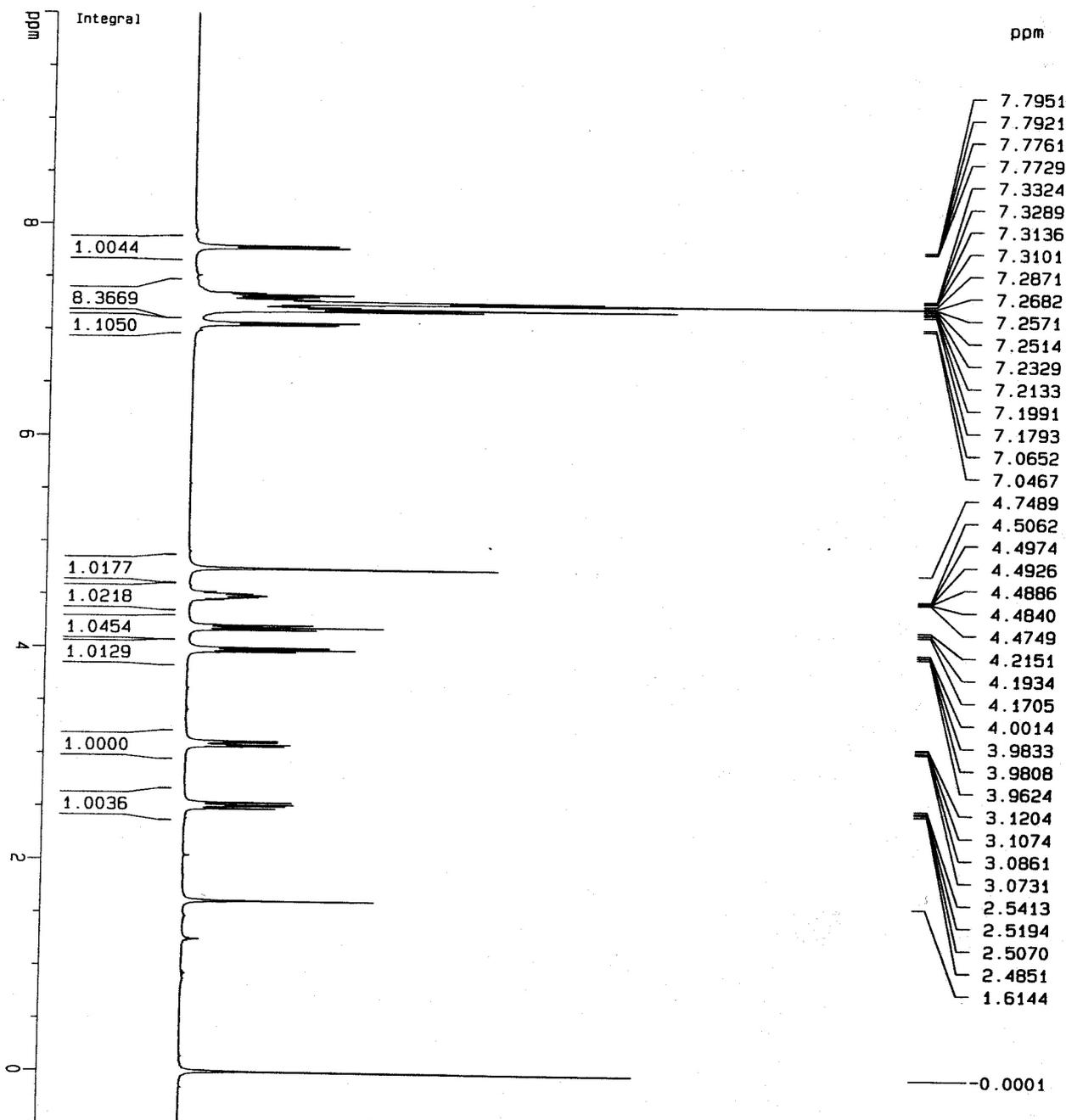


rac-4h



(R)-4h

¹H NMR of 7



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¹³C NMR of 7

