Electronic Supplementary Material (ESI) for ChemComm.
This journal is © The Royal Society of Chemistry 2020

Asymmetric Organocatalytic Multicomponent Reactions for Efficient Construction of Bicyclic Compounds Bearing Bisacetal and Isoxazolidine Moieties

Jun-Ping Pei,[a] Xue-Jiao Lv,[a] Chen-Jun Peng[a] and Yan-Kai Liu*[ab]

[a]Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China

[b]Laboratory for Marine Drugs and Bioproducts of Qingdao National Laboratory for Marine Science and Technology, Qingdao 266003, China

E-mail: liuyankai@ouc.edu.cn

Supporting Information

Contents

A. General information 1

B. The synthesis of the start materials 3

C. Optimization of the reaction conditions 5

C1. Optimization of the Michael Addition 5
C2. Optimization of the second step 6

D. One-pot synthesis of 5a 7

E. Scope of the reaction 8

F. Synthesis of Bicyclic 1,2-Oxazinane Derivatives 17

G. Synthetic transformation 19

H. 1 mmol Scale synthesis of 5a 21

I. Control experiments 22

I1. Control experiment 1: 22
I2. Control experiment 2: 23
I3. Control experiment 3: 24
I4. Control experiment 4: 25
I5. Control experiment 5: 26
I6. Control experiment 6: 31

J. Other reactions: 31

J1. The reaction of **1a** with (*E*)-4-oxo-4-phenylbut-2-enoic acid **15** : 31
J2. The reaction of crotonaldehyde with benzyl hydroxyl carbamate and **2a**: 32

K. NMR spectra and HPLC traces 33

L. Single crystal X-Ray diffraction data 76

A. General information

The ^{1}H and ^{13}C NMR spectra were recorded at 400/500 MHz for ^{1}H and at 100/125 MHz for ^{13}C. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CDCl_3$ at 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) were obtained from the Waters Q-Tof Ultima Global. LC-MS was performed using an Acquity UPLC H-Class coupled to a SQ Detector 2 mass spectrometer (Waters) using a BEH C18 column (1.7 μm, 2.1 × 50 mm). X-ray data were obtained from Zhongke chemical technology service center. Optical rotations are reported as follows: $[\alpha]_D^{20}$ (c in g per 100 mL, solvent: $CHCl_3$).

Note: NMR signals containing common solvent contaminants were list. H_2O in $CDCl_3$ at 1.56 ppm ^{1}H NMR; Ethyl acetate in $CDCl_3$ at 2.05 (s), 4.12 (q), 1.26 (t) ppm ^{1}H NMR; Dichloromethane in $CDCl_3$ at 5.30 (s) ppm ^{1}H NMR; Acetone in $CDCl_3$ at 2.17 (s) ppm ^{1}H NMR.

All the reactions were set up under air and using freshly distilled solvents, without any precautions to exclude moisture, unless otherwise noted open air chemistry on the bench-top. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (300-400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF254, 0.25 mm) were used, using UV light as the visualizing agent and an phosphomolybdic acid or basic aqueous potassium permanganate ($KMnO_4$) as stain developing solutions. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

HPLC analyses on chiral stationary phase were performed on an Hitachi Chromaste. Daicel Chiralpak IA or IB columns with *n*-hexane/*i*-PrOH as the eluent were used. HPLC traces were compared to racemic samples which prepared by mixture of two enantiomeric final products obtained using (*S*) and (*R*) catalyst.

Commercial reagents and solvents were purchased from Sigma Aldrich, Fluka, and Alfa Aesar used as received, without further purification. All Michael acceptors **2** were prepared according to literature procedures.[1] The lactols **1** was prepared according to literature procedures.[2] The 1,2-oxazinan-3-one **6** was prepared according to literature procedures.[3]

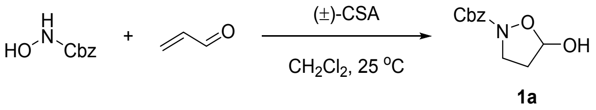
---

[1] Zhao, Y.-M.; Cheung, M. S.; Lin, Z.; Sun, J. Enantioselective synthesis of β,γ-unsaturated α-fluoroesters catalyzed by N-heterocyclic carbenes. *Angew. Chem., Int. Ed.* **2012**, *51* (41), 10359-10363.

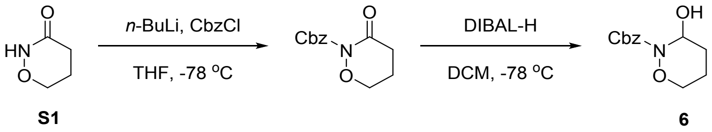
[2] Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters. *Angew. Chem., Int. Ed.* **2013**, *52* (42), 11114-11118.

[3] Wolfe, S.; Wilson, M.-C.; Cheng, M.-H.; Shustov, G. V.; Akuche, C. I. Cyclic hydroxamates, especially multiply substituted [1,2]oxazinan-3-ones. *Can. J. Chem.* **2003**, *81* (8), 937-960.

B. The synthesis of the start materials



Acrolein (1.80 mL, 30.0 mmol) was added dropwise to a mixture of benzyl hydroxycarbamate (5.00 g, 29.9 mmol) and 10-camphorsulfonic acid (1.40 g, 6.03 mmol) in dichloromethane (150 mL), and the mixture was stirred at room temperature for 20 min. The reaction mixture was then diluted with $CHCl_3$ (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (100mL x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by recrystallization (from petroleum ether/ethyl acetate) to afford benzyl 5-hydroxyisoxazolidine- 2-carboxylate **1a** as white solid (4.79 g, 72%).



To a stirred solution of 1,2-oxazinan-3-one (120 mg, 1.19 mmol) in THF (2.5 mL)was added *n*-BuLi (2.5 M solution in hexane, 0.48 mL) at −78 °C. After being stirred at the same temperature for 30 min, benzyl carbonochloridate (243 mg, 1.42 mmol) was added. The reaction mixture was stirred for 1 h and gradually warmed to rt, after which it was quenched with satd aq. NH_4Cl (10 mL) at 0 °C and warmed to rt. The water layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The product was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 3/1) to afford the product a colorless oil (135 mg, 49%).

To a stirred solution of benzyl 3-oxo-1,2-oxazinane-2-carboxylate (70.5 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL)was added DIBAL-H (1.5 M solution in toluene, 0.36 mL) at −78 °C. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with MeOH and a saturated potassium sodium tartrate solution, and the reaction mixture was warmed up to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic extracts were washed with brine and dried over Na_2SO_4 and the solvent was evaporated. The product was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 3/1) to afford the product **6** a colorless oil (46 mg, 65%)

C. Optimization of the reaction conditions

C1. Optimization of the Michael Addition

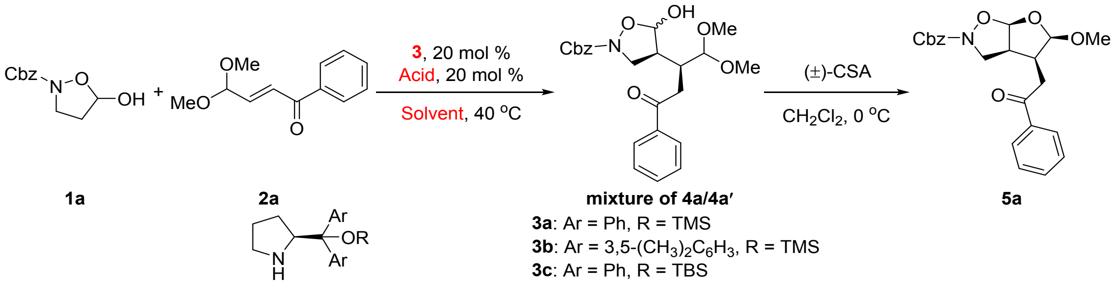


Table S1. Optimization of the Michael Addition[a]

Entry	Cat.	Solvent	Acid	Yield (%)[b]	ee (%)[c]
1	**3a**	toluene	C_6H_5COOH	42	91
2	**3b**	toluene	C_6H_5COOH	45	93
3	**3c**	toluene	C_6H_5COOH	53	97
4	**3c**	tetrahydrofuran	C_6H_5COOH	43	96
5	**3c**	$CHCl_3$	C_6H_5COOH	45	96
6	**3c**	MTBE	C_6H_5COOH	61	>99
7	**3c**	ethyl acetate	C_6H_5COOH	25	97
8	**3c**	MeCN	C_6H_5COOH	50	96
9	**3c**	acetone	C_6H_5COOH	53	97
10	**3c**	MTBE	4-$NO_2C_6H_4COOH$	58	>99
11	**3c**	MTBE	CH_3COOH	58	99
12	**3c**	MTBE	4-$MeOC_6H_4COOH$	56	99

[*a*] Unless otherwise specified, all reactions were carried out using 1**a** (0.10 mmol, 1.0 equiv), **2a** (0.13 mmol, 1.3 equiv) in solvent (0.3 mL) with **3** (20 mol %) and **acid** (20 mol %) at 40 °C. After workup, the mixture was purified by flash chromatography on silica gel to afford **4a/4a'**. Compound **4a/4a'** was dissolved in redistilled CH_2Cl_2 (0.1 mmol in 1 mL) at 0 °C, and CSA (20 mol %) was added. After full conversion of the second step, the residue was purified by flash chromatography on gel to give product **5a**.[*b*] Isolated yield of **5a** over two steps. [*c*] Determined by HPLC analyses of isolated compound **5a** on chiral stationary phases. TMS = Trimethylsilyl. TBS = *tert*-Butyldimethylsilyl. MTBE = *tert*-Butyl methyl

ether. CSA = Camphorsulfonic acid.

C2. Optimization of the second step

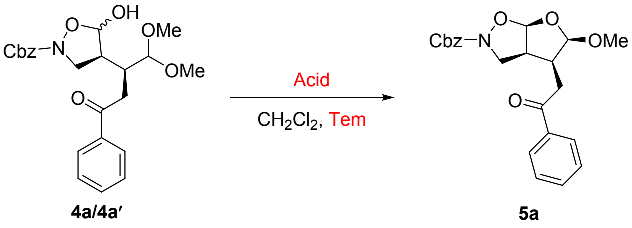
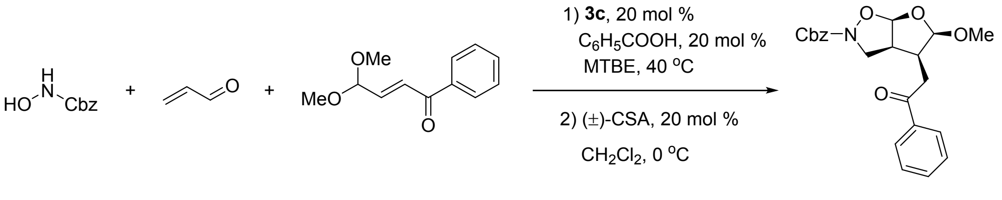


Table S2. Optimization of the second step[a]

Entry	Acid	Tem (°C)	Yield (%)[b]	ee (%)[c]
1	$BF_3·Et_2O$ (20 mol %)	0	51	97
2	Trifluoroacetic acid (20 mol %)	0	25	97
3	Diphenylphosphate (20 mol %)	0	-	-
4	Diphenylphosphate (20 mol %)	25	46	97
5	CSA (20 mol %)	0	80	97
6	*p*-TsOH (20 mol %)	0	46	97
7	CSA (20 mol %)	25	77	97
8	CSA (20 mol %)	40	66	97
9	CSA (20 mol %) + 4Å MS	0	-	-

[*a*] Unless otherwise specified, all reactions were carried out using **4a/4a'** (0.05 mmol, 1.0 equiv) in redistilled CH_2Cl_2 (0.3 mL) with acid. After workup, the mixture was purified by flash chromatography on silica gel to afford **5a**. [*b*] Isolated yield of **5a**. [*c*] Determined by HPLC analyses of isolated compound **5a** on chiral stationary phases. *p*-TsOH = *p*-Toluenesulfonic acid. CSA = Camphorsulfonic acid.

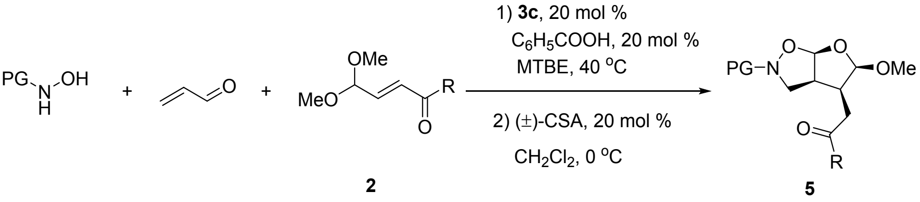
D. One-pot synthesis of 5a



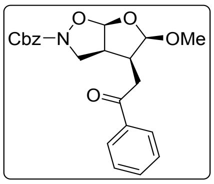
2a **5a**

A glass vial equipped with a magnetic stirring bar was charged with benzyl hydroxycarbamate (16.7 mg, 0.10 mmol, 1.0 equiv), acrylaldehyde (8.4 mg, 0.18 mmol, 1.8 equiv), **2a** (26.8 mg, 0.13 mmol, 1.3 equiv), **3c** (7.4 mg, 0.02 mmol, 0.2 equiv) and C_6H_5COOH (2.5 mg, 0.02 mmol, 0.2 equiv) in MTBE (0.3 mL) at 40 °C. The reaction was stirred at 40 °C for 72 h until the consumption of benzyl hydroxycarbamate (monitored by TLC analysis). After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to afford **4a/4a’** colorless oil (36 mg). Then, compound **4a/4a’** (36 mg, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C. CSA (3.89 mg, 0.2 equiv) was added to the reaction mixtures. The reaction was stirred at 0 °C for 12 h until the consumption of **4a/4a’**, then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:2) to give product **5a** (25 mg, 63% over two steps, >99% ee, dr >20:1).

E. Scope of the reaction

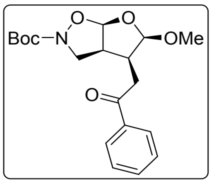


General procedure: A glass vial equipped with a magnetic stirring bar was charged with N-protected hydroxylamine (0.10 mmol, 1.0 equiv) , acrylaldehyde (0.18 mmol, 1.8 equiv), **2** (0.13 mmol, 1.3 equiv), **3c** (0.02 mmol, 0.2 equiv) and C_6H_5COOH (0.02 mmol, 0.2 equiv) in MTBE (0.3 mL) at 40 °C. The resulting reaction mixture was kept under vigorous stirring until the consumption of N-protected hydroxylamine (monitored by TLC analysis). After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1 to 2:1) to afford **4/4'**. Then, compound **4/4'** (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.10 mmol in 0.6 mL) at 0 °C. CSA (0.2 equiv) was added to the reaction mixtures. After full conversion of the second step, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 11:2 to 5:2) to give product **5** for NMR and HPLC analysis.



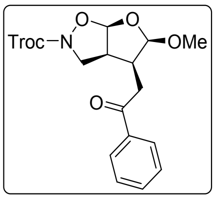
benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-oxo-2-phenylethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5a)

5a was obtained as a colorless oil 24 mg in 61% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 7/2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 10.1 Hz, 2H), 7.37 – 7.28 (m, 3H), 5.98 (d, *J* = 5.2 Hz, 1H), 5.32 – 5.24 (m, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.01 (d, *J* = 5.1 Hz, 1H), 4.13 (d, *J* = 10.8 Hz, 1H), 3.46 – 3.33 (m, 3H), 3.28 – 3.17 (m, 4H), 2.88 (dt, *J* = 14.8, 7.4 Hz, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.1, 156.8, 136.6, 136.1, 133.6, 128.9, 128.7, 128.4, 128.3, 128.2, 109.2, 105.9, 67.9, 56.3, 48.1, 46.7, 40.2, 35.6 ppm. **HRMS**: $[M+H]^+$ *calcd*. For $C_{22}H_{24}NO_6^+$ 398.1598, found 398.1595. **$[\alpha]_D^{20}$** 45.21 (*c* = 0.49 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 22.59 min, t_{minor} = 18.13 min, **ee >99%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



***tert*-butyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-oxo-2-phenylethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5b)**

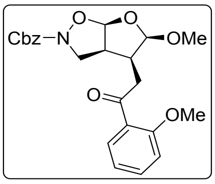
5b was obtained as a white solid 19 mg in 52% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 9/2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 5.94 (d, *J* = 4.7 Hz, 1H), 5.03 (d, *J* = 5.0 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.44 – 3.36 (m, 3H), 3.32 (s, 3H), 3.21 (dd, *J* = 18.3, 7.2 Hz, 1H), 2.87 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.50 (s, 9H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.1, 155.3, 136.5, 133.4, 128.7, 128.0, 108.7, 105.8, 81.4, 56.2, 47.8, 46.5, 40.0, 35.3, 28.4 ppm. **HRMS**: $[M+Na]^+$ *calcd*. For $C_{19}H_{25}NNaO_6^+$ 386.1574, found 386.1578. **$[\alpha]_D^{20}$** 12.75 (*c* = 1.08 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 8.17 min, t_{minor} = 7.05 min, **ee = 97%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



2,2,2-trichloroethyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-oxo-2-phenylethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5c)

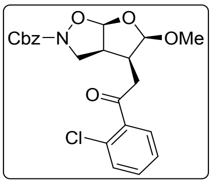
5c was obtained as a yellow oil 22 mg in 50% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 11/2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.02 (d, *J* = 4.9 Hz, 1H), 5.03 (d, *J* = 5.1 Hz, 1H), 4.89 – 4.78 (m, 1H), 4.66 (s, 1H), 4.14 (d, *J* = 9.1 Hz, 1H), 3.47 (ddd, *J* = 8.6, 6.0, 2.5 Hz, 2H), 3.40 (dd, *J* = 18.4, 7.3 Hz, 1H), 3.31 – 3.21 (m, 4H), 2.93

– 2.83 (m, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.0, 136.5, 133.7, 128.9, 128.1, 110.1, 109.3, 105.9, 75.7, 47.9, 46.8, 40.1, 35.5, 29.8 ppm. **HRMS**: $[M+Na]^+$ *calcd.* For $C_{17}H_{18}Cl_3NNaO_6^+$ 460.0092, found 460.0095. **$[\alpha]_D^{20}$** 22.42 (*c* = 0.97 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 10.90 min, t_{minor} = 9.55 min, **ee = 98%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



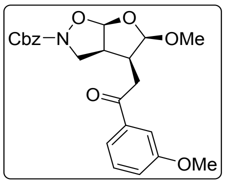
benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-(2-methoxyphenyl)-2-oxoethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5d)

5d was obtained as a colorless oil 20 mg in 47% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.39 (d, *J* = 6.3 Hz, 2H), 7.34 – 7.28 (m, 3H), 7.04 – 6.93 (m, 2H), 5.95 (d, *J* = 4.7 Hz, 1H), 5.26 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.98 (d, *J* = 5.0 Hz, 1H), 4.22 – 4.12 (m, 1H), 3.86 (s, 3H), 3.40 – 3.35 (m, 2H), 3.32 (d, *J* = 7.3 Hz, 2H), 3.22 (s, 3H), 2.88 – 2.79 (m, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 158.7, 136.1, 133.9, 130.2, 128.6, 128.3, 128.2, 127.8, 120.8, 111.7, 109.0, 106.1, 67.8, 56.2, 55.7, 48.1, 46.7, 40.6, 40.5 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{23}H_{26}NO_7^+$ 428.1704, found 428.1709. **$[\alpha]_D^{20}$** 49.22 (*c* = 1.28 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 24.46 min, t_{minor} = 21.18 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



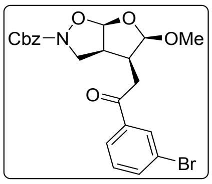
benzyl (3a*S*,4*S*,5*R*,6a*R*)-4-(2-(2-chlorophenyl)-2-oxoethyl)-5-methoxytetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5e)

5e was obtained as a colorless oil 18 mg in 42% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 7/2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 9H), 5.97 (d, J = 4.8 Hz, 1H), 5.26 (d, J = 12.3 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 4.99 (d, J = 5.0 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.42 – 3.28 (m, 3H), 3.27 – 3.14 (m, 4H), 2.93 – 2.78 (m, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.2, 138.9, 136.1, 132.2, 130.9, 128.8, 128.6, 128.3, 128.3, 127.2, 109.1, 105.7, 67.9, 56.3, 48.0, 46.7, 40.3, 40.0 ppm. **HRMS**: $[M+Na]^+$ *calcd*. For $C_{22}H_{22}ClNNaO_6^+$ 454.1028, found 454.1029. **$[\alpha]_D^{20}$** 17.97 (c = 0.63 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 25.61 min, t_{minor} = 20.93 min, **ee = 90%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



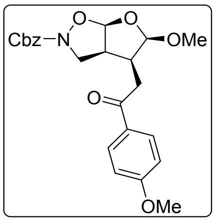
benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-(3-methoxyphenyl)-2-oxoethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5f)

5f was obtained as a colorless oil 24 mg in 56% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 7/2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 2.6, 1.6 Hz, 1H), 7.44 – 7.27 (m, 6H), 7.14 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 5.98 (d, J = 5.1 Hz, 1H), 5.27 (d, J = 12.3 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 5.01 (d, J = 5.1 Hz, 1H), 4.16 – 4.09 (m, 1H), 3.86 (s, 3H), 3.46 – 3.32 (m, 3H), 3.28 – 3.16 (m, 4H), 2.86 (qd, J = 7.4, 5.1 Hz, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.9, 160.0, 137.9, 136.1, 129.9, 128.6, 128.3, 128.3, 120.9, 120.0, 112.4, 109.1, 105.9, 67.9, 56.3, 55.6, 48.1, 46.7, 40.2, 35.7 ppm. **HRMS**: $[M+H]^+$ *calcd*. For $C_{23}H_{26}NO_7^+$ 428.1704, found 428.1706. **$[\alpha]_D^{20}$** 52.70 (c = 1.17 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 26.62 min, t_{minor} = 23.52 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



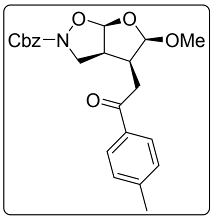
benzyl (3a*S*,4*S*,5*R*,6a*R*)-4-(2-(3-bromophenyl)-2-oxoethyl)-5-methoxytetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5g)

5g was obtained as a colorless oil 28 mg in 59% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 7/2). ^{1}**H NMR** (500 MHz, CDCl$_3$) δ 8.10 (t, *J* = 1.8 Hz, 1H), 7.89 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.73 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.45 – 7.29 (m, 6H), 5.99 (d, *J* = 5.2 Hz, 1H), 5.29 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.01 (d, *J* = 5.0 Hz, 1H), 4.15 – 4.09 (m, 1H), 3.45 – 3.34 (m, 3H), 3.24 (s, 3H), 3.19 (dd, *J* = 18.4, 7.0 Hz, 1H), 2.90 – 2.81 (m, 1H) ppm. ^{13}**C NMR** (125 MHz, CDCl$_3$) δ 196.7, 138.2, 136.5, 136.0, 131.2, 130.5, 128.7, 128.4, 128.3, 126.7, 123.2, 109.2, 105.8, 67.9, 56.3, 48.0, 46.6, 40.0, 35.8 ppm. **HRMS**: [M+H]$^+$ *calcd.* For $C_{22}H_{23}BrNO_6^+$ 476.0703, found 476.0700. $[\alpha]_D^{20}$ 29.86 (*c* = 1.22 in CHCl$_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 23.64 min, t_{minor} = 18.79 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



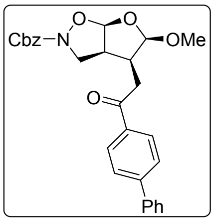
benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-(4-methoxyphenyl)-2-oxoethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5h)

5h was obtained as a colorless oil 26 mg in 61% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1). ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.98 – 7.90 (m, 2H), 7.44 – 7.38 (m, 2H), 7.38 – 7.29 (m, 3H), 6.96 – 6.90 (m, 2H), 5.97 (d, *J* = 5.1 Hz, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.99 (d, *J* = 5.0 Hz, 1H), 4.12 (dd, *J* = 10.8, 2.1 Hz, 1H), 3.88 (s, 3H), 3.45 – 3.26 (m, 3H), 3.26 – 3.12 (m, 4H), 2.86 (qd, *J* = 7.3, 4.9 Hz, 1H) ppm. ^{13}**C NMR** (125 MHz, CDCl$_3$) δ 196.6, 163.9, 136.1, 130.5, 129.6, 128.6, 128.3, 128.3, 113.9, 109.2, 106.0, 67.8, 56.2, 55.6, 48.1, 46.6, 40.2, 35.1 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{23}H_{26}NO_7^+$ 428.1704, found 428.1702. **$[\alpha]_D^{20}$** 61.86 (c = 1.45 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 260 nm, t_{major} = 22.66 min, t_{minor} = 17.93 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



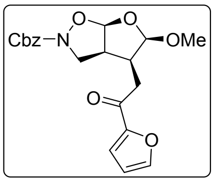
benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-oxo-2-(*p*-tolyl)ethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5i)

5i was obtained as a colorless oil 24 mg in 58% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.30 (m, 3H), 7.27 (d, J = 8.2 Hz, 2H), 5.97 (d, J = 5.1 Hz, 1H), 5.33 – 5.23 (m, 1H), 5.12 (d, J = 12.3 Hz, 1H), 5.00 (d, J = 5.0 Hz, 1H), 4.13 (dd, J = 10.7, 2.2 Hz, 1H), 3.47 – 3.30 (m, 3H), 3.23 (s, 4H), 2.87 (qd, J = 7.3, 4.8 Hz, 1H), 2.43 (s, 3H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.7, 156.8, 144.5, 136.1, 134.1, 129.5, 128.6, 128.3, 128.3, 109.2, 106.0, 67.8, 56.2, 48.1, 46.6, 40.2, 35.4, 21.8 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{23}H_{26}NO_6^+$ 412.1755, found 412.1756. **$[\alpha]_D^{20}$** 50.72 (c = 1.35 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 20.11 min, t_{minor} = 18.58 min, **ee >99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



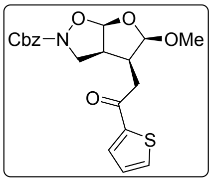
benzyl (3a*S*,4*S*,5*R*,6a*R*)-4-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-5-methoxytetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5j)

5j was obtained as a colorless oil 24 mg in 51% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 7/2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 8.00 (m, 2H), 7.73 – 7.67 (m, 2H), 7.67 – 7.61 (m, 2H), 7.53 – 7.46 (m, 2H), 7.42 (ddd, *J* = 8.0, 4.2, 1.5 Hz, 3H), 7.38 – 7.28 (m, 3H), 5.99 (d, *J* = 5.1 Hz, 1H), 5.29 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.03 (d, *J* = 5.0 Hz, 1H), 4.15 (dd, *J* = 10.7, 2.1 Hz, 1H), 3.51 – 3.32 (m, 3H), 3.32 – 3.13 (m, 4H), 2.90 (qd, *J* = 7.3, 4.9 Hz, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.6, 156.8, 146.3, 139.8, 136.1, 135.2, 129.1, 128.8, 128.6, 128.5, 128.3, 128.3, 127.4, 127.4, 109.2, 105.9, 67.9, 56.3, 48.1, 46.7, 40.2, 35.6 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{28}H_{28}NO_6^+$ 474.1911, found 474.1915. **$[\alpha]_D^{20}$** 54.98 (*c* = 1.63 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 30.46 min, t_{minor} = 33.91 min, **ee >99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



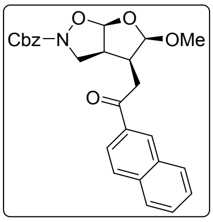
benzyl (3a*S*,4*S*,5*R*,6a*R*)-4-(2-(furan-2-yl)-2-oxoethyl)-5-methoxytetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5k)

5k was obtained as a colorless oil 24 mg in 62% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 5/2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.7 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.28 (m, 3H), 7.19 (d, *J* = 3.6 Hz, 1H), 6.55 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.95 (d, *J* = 4.4 Hz, 1H), 5.27 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.97 (d, *J* = 5.0 Hz, 1H), 4.20 – 4.09 (m, 1H), 3.44 – 3.31 (m, 2H), 3.23 (s, 4H), 3.10 (dd, *J* = 18.1, 7.3 Hz, 1H), 2.88 – 2.73 (m, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 187.1, 156.7, 152.4, 146.7, 136.1, 128.6, 128.3, 117.5, 112.5, 109.1, 105.8, 67.8, 56.3, 48.0, 46.6, 39.8, 35.3 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{20}H_{22}NO_7^+$ 388.1391, found 388.1390. **$[\alpha]_D^{20}$** 57.32 (*c* = 1.58 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 27.61 min, t_{minor} = 25.12 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-oxo-2-(thiophen-2-yl)ethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5l)

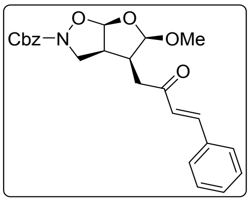
5l was obtained as a colorless oil 17 mg in 42% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.66 (d, *J* = 4.9 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.28 (m, 3H), 7.13 (t, *J* = 4.3 Hz, 1H), 5.96 (d, *J* = 4.3 Hz, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.97 (d, *J* = 5.0 Hz, 1H), 4.13 (d, *J* = 8.3 Hz, 1H), 3.40 – 3.28 (m, 3H), 3.24 (s, 3H), 3.16 (dd, *J* = 17.8, 7.4 Hz, 1H), 2.90 – 2.82 (m, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.0, 156.7, 143.7, 136.1, 134.2, 132.5, 128.7, 128.4, 128.4, 128.3, 109.2, 105.8, 67.9, 56.3, 48.0, 46.6, 40.2, 36.0 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{20}H_{22}NO_6S^+$ 404.1162, found 404.1162. **$[\alpha]_D^{20}$** 50.59 (*c* = 0.92 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 260 nm, t_{major} = 27.37 min, t_{minor} = 24.43 min, **ee >99%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-(2-(naphthalen-2-yl)-2-oxoethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5m)

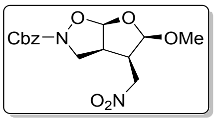
5m was obtained as a colorless oil 27 mg in 60% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 7/2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.02 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.94 – 7.85 (m, 2H), 7.61 (dddd, *J* = 23.9, 8.2, 6.9, 1.3 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.35 – 7.26 (m, 3H), 6.00 (d, *J* = 5.2 Hz, 1H), 5.29 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.05 (d, *J* = 5.1 Hz, 1H), 4.20 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.54 (dd, *J* = 18.2, 7.3 Hz, 1H), 3.50 – 3.32 (m, 3H), 3.26 (s, 3H), 2.94 (qd, *J* = 7.4, 5.0 Hz, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.9, 136.1, 135.8, 133.8, 132.6, 130.0, 129.7, 128.8, 128.7, 128.6, 128.3, 128.3, 127.9, 127.1, 123.7, 109.2, 105.9, 67.9, 56.3, 48.1, 46.7, 40.2, 35.6 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{26}H_{26}NO_6^+$

448.1755, found 448.1754. **[α]$_D$^{20}** 65.93 (*c* = 1.68 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], *λ* = 260 nm, t_{major} = 28.01 min, t_{minor} = 16.74 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.



benzyl (3a*S*,4*S*,5*R*,6a*R*)-5-methoxy-4-((*E*)-2-oxo-4-phenylbut-3-en-1-yl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5n)

5n was obtained as a colorless oil 23 mg in 54% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1). **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.61 – 7.51 (m, 3H), 7.47 – 7.38 (m, 5H), 7.38 – 7.27 (m, 3H), 6.73 (d, *J* = 16.2 Hz, 1H), 5.95 (d, *J* = 4.2 Hz, 1H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 4.96 (d, *J* = 5.0 Hz, 1H), 4.12 (q, *J* = 8.5 Hz, 1H), 3.37 (d, *J* = 6.5 Hz, 2H), 3.24 (s, 3H), 3.09 (dd, *J* = 18.0, 7.4 Hz, 1H), 2.93 (dd, *J* = 18.0, 7.1 Hz, 1H), 2.85 – 2.76 (m, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 197.9, 156.8, 143.4, 136.1, 134.3, 130.9, 129.1, 128.6, 128.5, 128.3, 128.3, 125.9, 109.1, 105.9, 67.9, 56.2, 48.1, 46.6, 40.1, 37.5 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{24}H_{26}NO_6^+$ 424.1755, found 424.1757. **[α]$_D$^{20}** 47.50 (*c* = 0.90 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], *λ* = 210 nm, t_{major} = 26.10 min, t_{minor} = 18.63 min, **ee = 95%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.

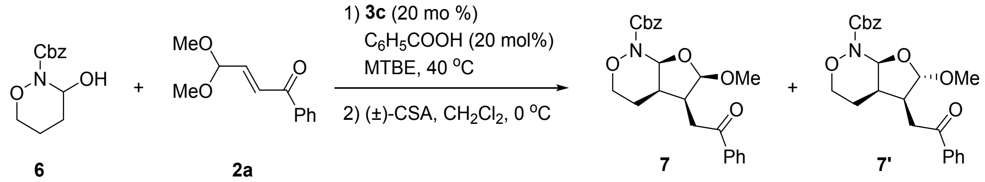


benzyl (3a*S*,4*R*,5*R*,6a*R*)-5-methoxy-4-(nitromethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (5o)

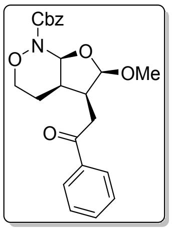
5o was obtained as a colorless oil 13 mg in 40% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1).**^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.43 – 7.29 (m, 5H), 5.99 (d, *J* = 5.4 Hz, 1H), 5.25 (d, *J* = 12.3 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.00 (d, *J* = 5.0 Hz, 1H), 4.70 (dd, *J* = 14.3, 7.0 Hz, 1H), 4.58 (dd, *J* = 14.3, 8.1 Hz, 1H), 4.13 (dd, *J* = 11.8, 2.9 Hz, 1H), 3.46 (dd, *J* = 11.8, 9.8 Hz, 1H), 3.34 (dddd, *J* = 9.8, 8.4, 5.5, 2.9 Hz, 1H), 3.24 (s, 3H), 3.04 (tdd, *J* = 8.3, 7.0, 5.0 Hz, 1H) ppm. **^{13}C NMR** (125

MHz, $CDCl_3$) δ 156.4, 135.7, 128.6, 128.4, 128.2, 109.2, 104.2, 72.0, 68.0, 56.3, 46.9, 46.1, 42.5 ppm. **HRMS**: $[M+H]^+$ *calcd.* For $C_{15}H_{19}N_2O_7^+$ 339.3235, found 339.3233. **$[\alpha]_D^{20}$** 20.69 (c = 0.83 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 205 nm, t_{major} = 15.10 min, t_{minor} = 17.17 min, **ee >99%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.

F. Synthesis of Bicyclic 1,2-Oxazinane Derivatives

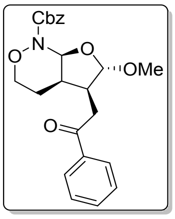


A glass vial equipped with a magnetic stirring bar was charged with lactols **6** (23.7 mg, 0.10 mmol, 1.0 equiv), **2** (26.7 mg, 0.13 mmol, 1.3 equiv), **3c** (7.4 mg, 0.02 mmol, 0.2 equiv) and C_6H_5COOH (2.4 mg, 0.02 mmol, 0.2 equiv) in MTBE (0.3 mL) at 40 °C. The reaction was stirred at 40 °C for 4 d. After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:2) to afford **S7** and **S7'**. Then, compound **S7** and **S7'** (1.0 equiv) was respectively dissolved in anhydrous CH_2Cl_2 (0.10 mmol in 0.6 mL) at 0 °C. CSA (0.2 equiv) was added to the reaction mixtures. The reaction was stirred at 0 °C for 12 h until the consumption of **S7** and **S7'**, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give product **7** and **7'** for NMR and HPLC analysis.



benzyl (4a*R*,5*S*,6*R*,7a*S*)-6-methoxy-5-(2-oxo-2-phenylethyl)hexahydro-1*H*-furo[2,3-*c*][1,2]oxazine-1-carboxylate (7)

7 was obtained as a colorless oil 12 mg in 29% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.36 (ddd, *J* = 13.4, 12.1, 5.0 Hz, 5H), 5.92 (d, *J* = 4.6 Hz, 1H), 5.26 (q, *J* = 12.3 Hz, 2H), 5.03 (d, *J* = 5.4 Hz, 1H), 4.16 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.74 (dd, *J* = 17.4, 6.6 Hz, 1H), 3.38 – 3.27 (m, 4H), 3.16 (dd, *J* = 18.3, 7.4 Hz, 1H), 3.01 – 2.92 (m, 1H), 2.49 – 2.33 (m, 2H), 1.43 (dd, *J* = 12.4, 6.1 Hz, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.6, 136.8, 135.9, 133.4, 128.8, 128.7, 128.4, 128.4, 128.1, 104.6, 70.1, 68.1, 55.9, 41.5, 33.6, 33.5, 22.6 ppm. **HRMS**: $[M+Na]^+$ *calcd*. For $C_{23}H_{25}NNaO_6^+$ 434.1574, found 434.1577. **$[\alpha]_D^{20}$** 15.57 (*c* = 0.68 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 17.95 min, t_{minor} = 14.69 min, **ee = 98%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.



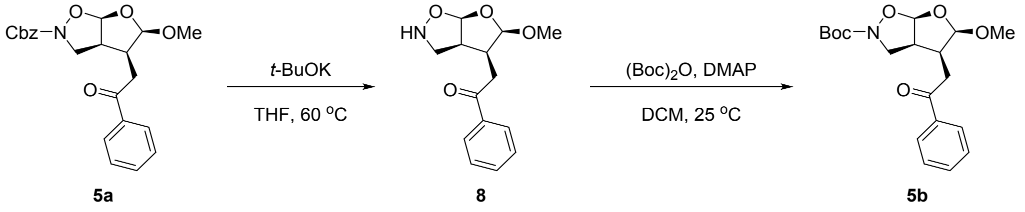
benzyl (4a*R*,5*S*,6*S*,7a*S*)-6-methoxy-5-(2-oxo-2-phenylethyl)hexahydro-1*H*-furo[2,3-*c*][1,2]oxazine-1-carboxylate (7')

7' was obtained as a colorless oil 14 mg in 34% yield for two steps after column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.36 (ddd, *J* = 20.1, 13.0, 7.1 Hz, 5H), 6.05 (d, *J* = 3.6 Hz, 1H), 5.25 (q, *J* = 12.3 Hz, 2H), 4.96 (d, *J* = 6.2 Hz, 1H), 4.12 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.77 (t, *J* = 11.6 Hz, 1H), 3.45 (s, 3H), 3.30 (dd, *J* = 17.4, 4.0 Hz, 1H), 3.12 (dd, *J* = 17.4, 11.0 Hz, 1H), 2.79 (td, *J* = 10.6, 6.1 Hz, 1H), 2.67 (td, *J*

= 11.0, 6.1 Hz, 1H), 1.70 (ddd, *J* = 24.8, 12.4, 4.8 Hz, 1H), 1.51 (dd, *J* = 13.4, 6.4 Hz, 1H) ppm. ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 198.2, 136.4, 135.8, 133.6, 128.9, 128.7, 128.4, 128.3, 128.1, 107.5, 69.7, 68.1, 56.9, 44.3, 35.5, 35.3, 22.4 ppm. **HRMS**: $[M+Na]^+$ *calcd*. For $C_{23}H_{25}NNaO_6^+$ 434.1574, found 434.1576. $[\alpha]_D^{20}$ 58.98 (*c* = 0.61 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 27.45 min, t_{minor} = 11.99 min, **ee = 99%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.

G. Synthetic transformation

2-((3a*S*,4*S*,5*R*,6a*R*)-5-methoxyhexahydrofuro[3,2-*d*]isoxazol-4-yl)-1-phenylethan-1-one (8)

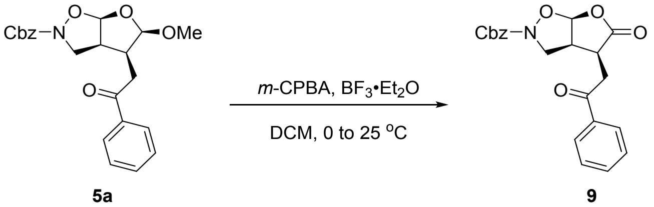


To a solution of **5a** (20 mg, 0.05 mmol) in anhydrous THF (0.4 mL) was added *t*-BuOK (28 mg, 0.25 mmol) at room temperature. The reaction was stirred at 60 °C for 48 h. The mixture was extracted with ethyl acetate. The combine organic layers were dried over Na_2SO_4 and the solvent evaporated. The product was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 3/2) to afford the desired product **8** colorless oil (12 mg, 91%). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 6.47 (s, 1H), 6.00 (d, *J* = 5.1 Hz, 1H), 4.99 (d, *J* = 4.9 Hz, 1H), 3.38 (s, 3H), 3.36 – 3.24 (m, 2H), 3.17 (dd, *J* = 18.2, 6.7 Hz, 1H), 3.06 (d, *J* = 12.2 Hz, 1H), 2.87 (dt, *J* = 15.4, 8.2 Hz, 2H) ppm. ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 198.0, 136.6, 133.6, 128.9, 128.1, 109.7, 104.4, 55.6, 49.2, 48.7, 40.2, 35.5 ppm. **HRMS**: $[M+Na]^+$ *calcd*. For $C_{14}H_{17}NNaO_4^+$ 286.1050, found 286.1052. $[\alpha]_D^{20}$ -46.43 (*c* = 0.54 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 240 nm, t_{major} = 10.31

min, t_{minor} = 9.63 min, **ee = 93%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.

To a solution of **8** (8 mg, 0.03 mmol) and di-*tert*-butyl dicarbonate (17 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (0.2 mL) was added DMAP (0.75 mg, 0.006 mmol) at 0 °C. The reaction was stirred at 25 °C for 2 h before the solvent was removed under vacuum. The product was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 3/2) to afford the desired product **5b** colorless oil (10.7 mg, 97%). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 8.69 min, t_{minor} = 7.58 min, **ee = 91%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.

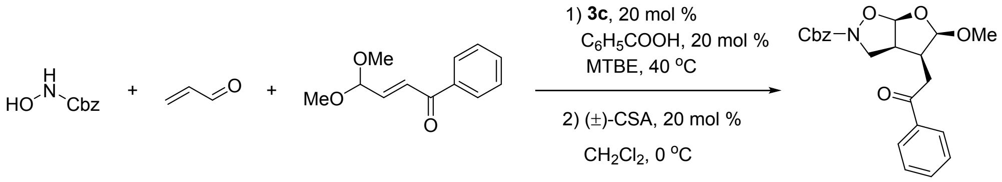
benzyl (3a*S*,4*S*,6a*R*)-5-oxo-4-(2-oxo-2-phenylethyl)tetrahydrofuro[3,2-*d*]isoxazole-2(3*H*)-carboxylate (9)



To a solution of **5a** (30 mg, 0.07 mmol) and *m*-CPBA (25 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (19 mg, 0.14 mmol) at 0 °C. The reaction was stirred at 25 °C for 4 h before the solvent was removed under vacuum. The product was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 7/2) to afford the desired product **7** colorless oil (20 mg, 70%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.92 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.38 (dt, *J* = 9.9, 7.3 Hz, 5H), 6.24 (d, *J* = 5.4 Hz, 1H), 5.25 (d, *J* = 12.1 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 3.89 (dt, *J* = 6.0, 5.1 Hz, 2H), 3.74 (dd, *J* = 18.7, 3.0 Hz, 1H), 3.49 – 3.41 (m, 1H), 3.41 – 3.29 (m, 2H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.0, 174.7, 158.4, 135.7, 135.1, 134.2, 129.0, 128.8, 128.7, 128.6, 128.3, 105.0, 69.2, 46.9, 46.0, 37.7, 37.1 ppm. **HRMS**: $[M+Na]^+$ *calcd*. For

$C_{21}H_{19}NNaO_6^+$ 404.1105, found 404.1106. **$[\alpha]_D^{20}$** 113.33 (*c* = 1.00 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], *λ* = 210 nm, t_{major} = 17.79 min, t_{minor} = 19.19 min, **ee = 94%**. The diastereomeric ratio was determined by NMR ***dr*** **>20:1**.

H. 1 mmol Scale synthesis of 5a

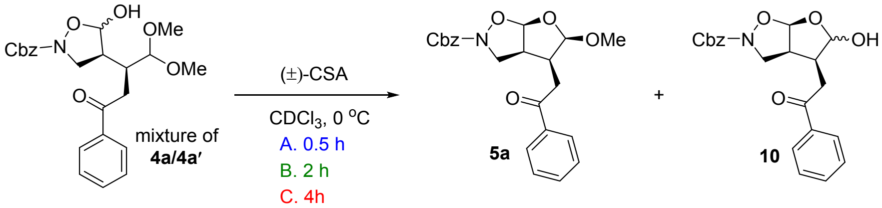


2a **5a**

A glass vial equipped with a magnetic stirring bar was charged with benzyl hydroxycarbamate (167 mg, 1.0 mmol, 1.0 equiv), acrylaldehyde (84 mg, 1.8 mmol, 1.8 equiv), **2a** (268 mg, 1.3 mmol, 1.3 equiv), **3c** (74 mg, 0.2 mmol, 0.2 equiv) and C_6H_5COOH (25 mg, 0.2 mmol, 0.2 equiv) in MTBE (3 mL) at 40 °C. The reaction was stirred at 40 °C for 4.5 d until the consumption of benzyl hydroxycarbamate (monitored by TLC analysis). After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to afford **4a/4a'** colorless oil (372 mg). Then, compound **4a/4a'** (372 mg, 0.85 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (5 mL) at 0 °C. CSA (39.3 mg, 0.17 mmol, 0.2 equiv) was added to the reaction mixtures. The reaction was stirred at 0 °C for 12 h until the consumption of **4a/4a'**, then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:2) to give product **5a** (179 mg, 63% over two steps, >99% ee, dr >20:1).

I. Control experiments

I1. Control experiment 1:



A glass vial equipped with a magnetic stirring bar was charged with mixture of **4a/4a'** (11 mg, 0.025 mmol, 1.0 equiv), CSA (1.2 mg, 0.005 mmol, 0.2 equiv) in $CDCl_3$ (0.5 mL) at 0 °C. After 0.5 h/ 2 h/ 4 h, the reaction mixture was transferred directly to the NMR tube for crude ^1H NMR experiments. It is found that compound **10** is gradually consumed, while the amount of **5a** is increased.

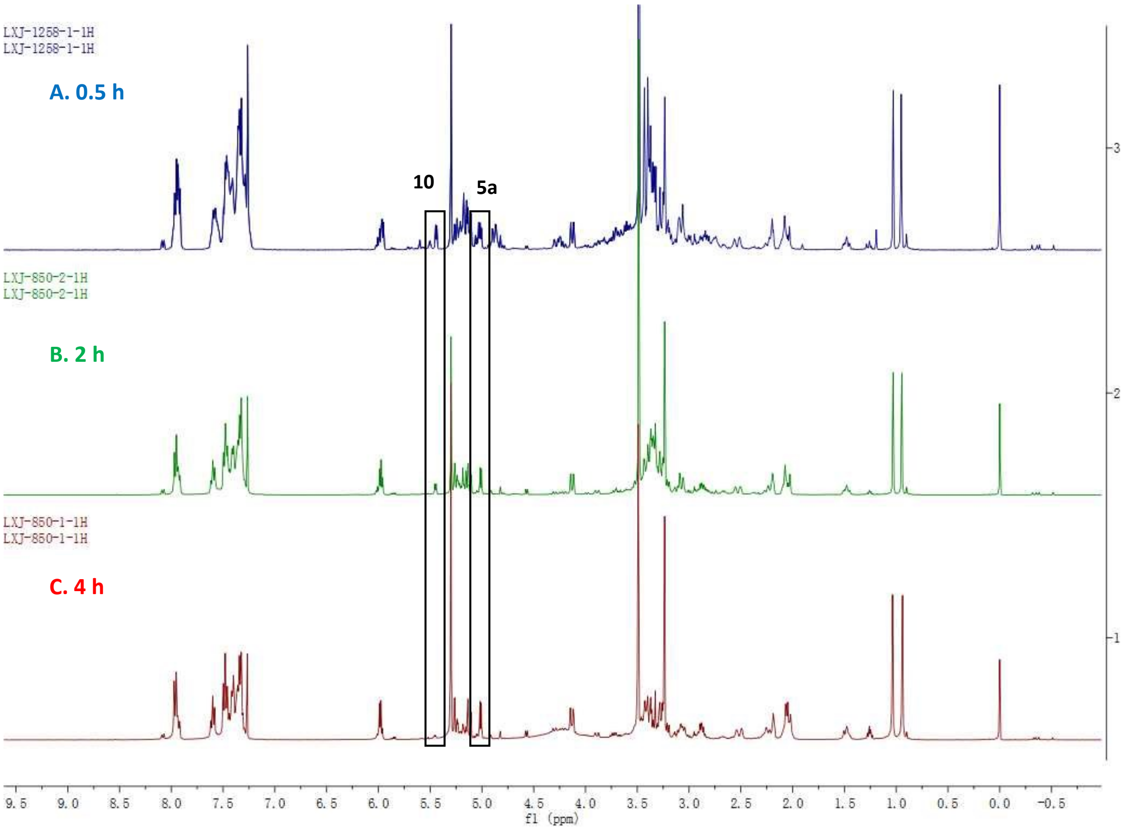
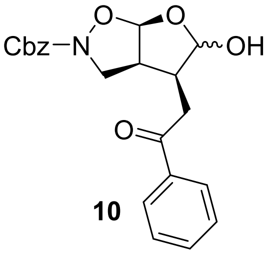


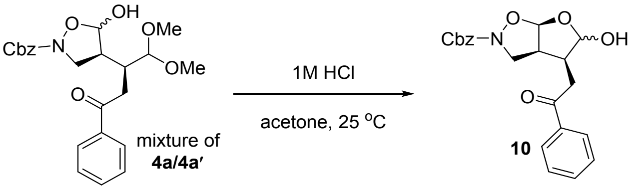
Figure 1. The ^1H NMR spectrum of control experiment 1 (400 MHz, $CDCl_3$)



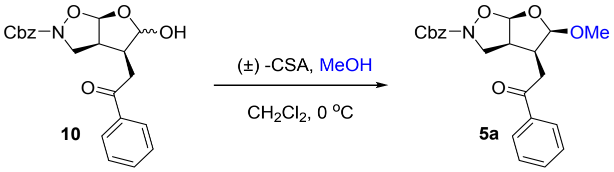
10

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.49 – 7.42 (m, 4H), 7.33 (q, *J* = 5.3 Hz, 3H), 5.96 (d, *J* = 5.3 Hz, 1H), 5.47 – 5.41 (m, 1H), 5.18 (dd, *J* = 29.1, 12.1 Hz, 2H), 4.13 (d, *J* = 11.2 Hz, 1H), 3.41 (ddd, *J* = 25.7, 12.5, 7.5 Hz, 3H), 3.22 (dd, *J* = 18.4, 7.5 Hz, 1H), 2.91 – 2.78 (m, 2H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.0, 157.9, 136.4, 136.0, 133.5, 128.7, 128.6, 128.6, 128.1, 109.2, 98.7, 67.9, 48.1, 47.2, 40.5, 35.5 ppm. **MS**: [M+Na]$^+$ *calcd*. For $C_{21}H_{21}NNaO_6^+$ 406.13, found 406.11.

I2. Control experiment 2:

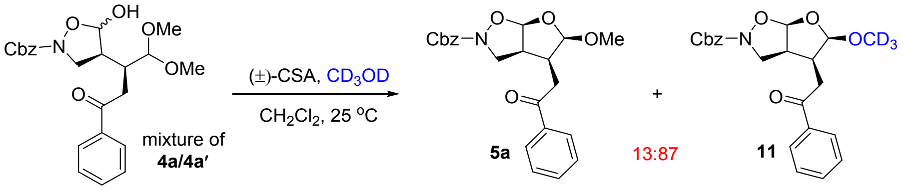


Synthesis of compound 10: A glass vial equipped with a magnetic stirring bar was charged with mixture of **4a/4a’** (22 mg, 0.05 mmol, 1.0 equiv), 1 M HCl (0.2 mL) and acetone (0.2 mL). The reaction was stirred at 25 °C for 4 h until the consumptions of **4a** and **4a’**, then the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give product **10** as a colorless oil (15 mg, 77%).



Transformation between 10 and 5a: Compound **10** (15 mg, 1.0 equiv) was dissolved in anhydrous CH$_2$Cl$_2$ (0.4 mL) at 0 °C. Then MeOH (3 μL, 2.0 equiv) and CSA (2.0 mg, 0.2 equiv) was added to the reaction mixture. The reaction was stirred at 0 °C for 15 h until the consumption of **10**, then the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:2) to give product **5a** (11 mg, 71%).

I3. Control experiment 3:



The mixture of **4a/4a’** (22 mg, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C. Then CD_3OD (41 μL, 20.0 equiv) and CSA (5.0 mg, 0.4 equiv) was added to the reaction mixture. The reaction was stirred at 25 °C for 2 h until the consumption of **4a/4a’**, then the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:2) to give mixture of **5a** and **11** (7 mg, 35%).

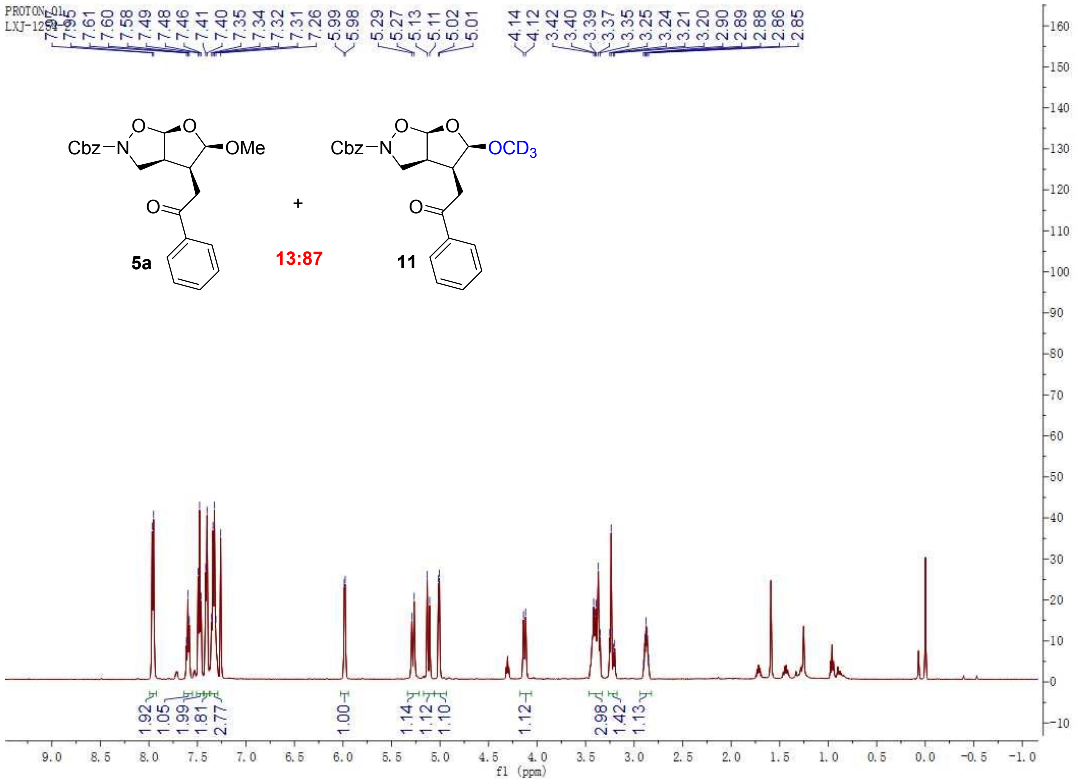
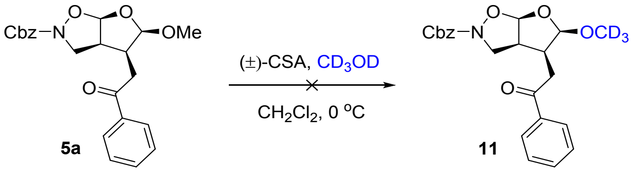


Figure 2. The ^{1}H NMR spectrum of **5a+11** (500 MHz, $CDCl_3$)

I4. Control experiment 4:



Compound **5a** (20 mg, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.3 mL) at 0 °C. Then CD_3OD (20 µL, 10.0 equiv) and CSA (2.3 mg, 0.2 equiv) was added to the reaction mixture. The reaction was stirred at 0 °C for 11 h, then the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:2) for NMR analysis.

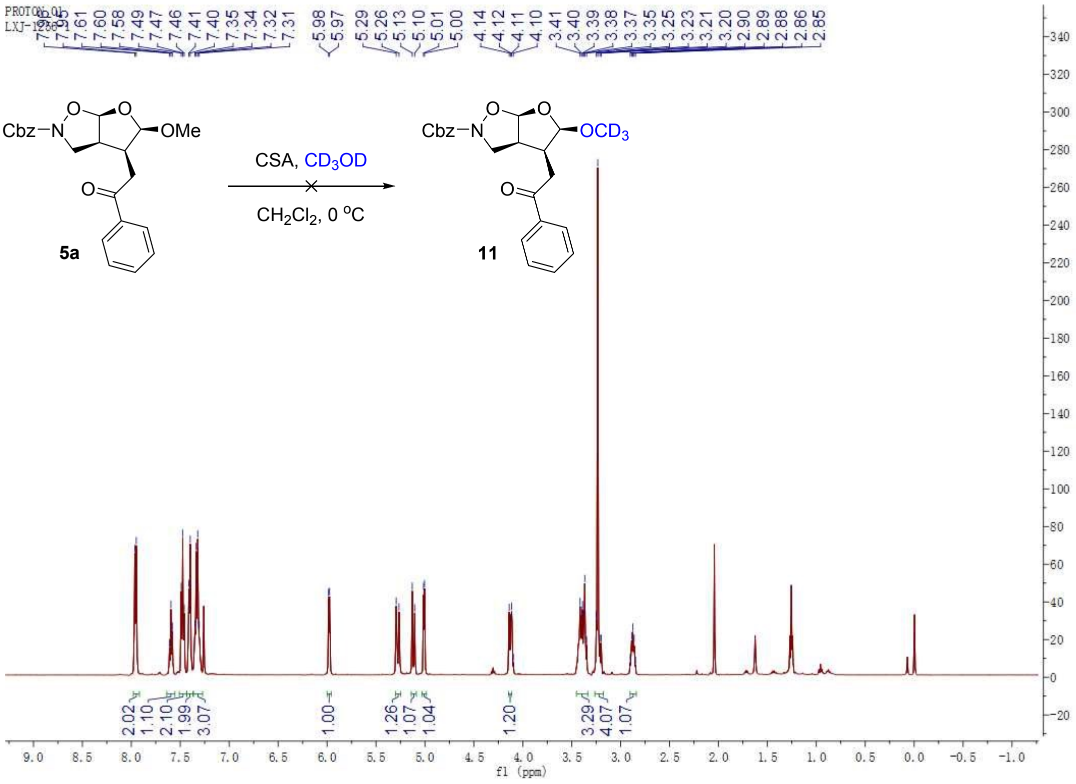
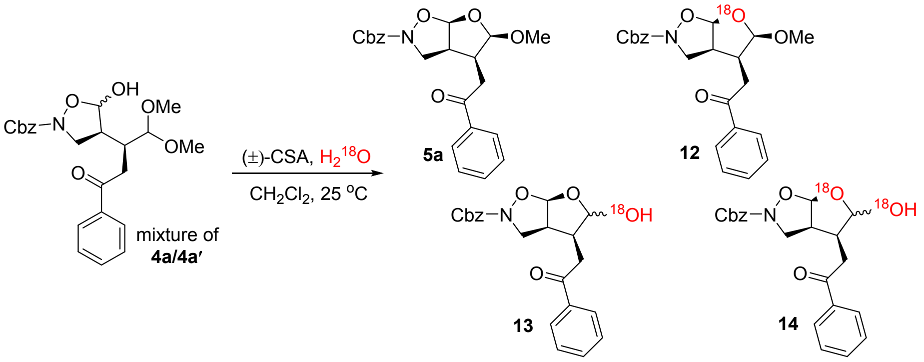
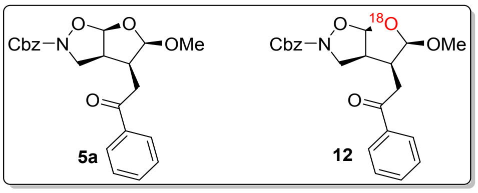


Figure 3. The ^1H NMR spectrum of control experiment 4 (500 MHz, $CDCl_3$)

I5. Control experiment 5:



The mixture of **4a/4a'** (22 mg, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) at 25 °C. Then $H_2{}^{18}O$ (10 μL, 10.0 equiv) and CSA (5.8 mg, 0.5 equiv) was added to the reaction mixture. The reaction was stirred at 25 °C for 5 h until the consumption of **4a/4a'**, then the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give compounds **5a**, **12**, **13** and **14** (11% yield for **5a** and **12**, 37% yield for **13** and **14**).



5a+12 was obtained as a colorless oil 2 mg in 11% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 6.9 Hz, 2H), 7.38 – 7.29 (m, 3H), 5.98 (d, *J* = 5.2 Hz, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.01 (d, *J* = 5.0 Hz, 1H), 4.13 (d, *J* = 10.6 Hz, 1H), 3.47 – 3.33 (m, 3H), 3.29 – 3.19 (m, 4H), 2.88 (dd, *J* = 13.4, 6.9 Hz, 1H) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197. 9, 156.6, 136.4, 135.9, 133.5, 128.7, 128.5, 128.2, 128.2, 128.0, 109.0, 109.0, 105.8, 105.8, 67.7, 56.1, 47.9, 46.5, 40.0, 35.4 ppm. **5a: MS**: $[M+Na]^+$ *calcd*. For $C_{22}H_{23}NNaO_6{}^+$ 420.14, found 420.17. **12: MS**: $[M+Na]^+$ *calcd*. For $C_{22}H_{23}NNaO_5{}^{18}O^+$ 422.15 found 422.11.

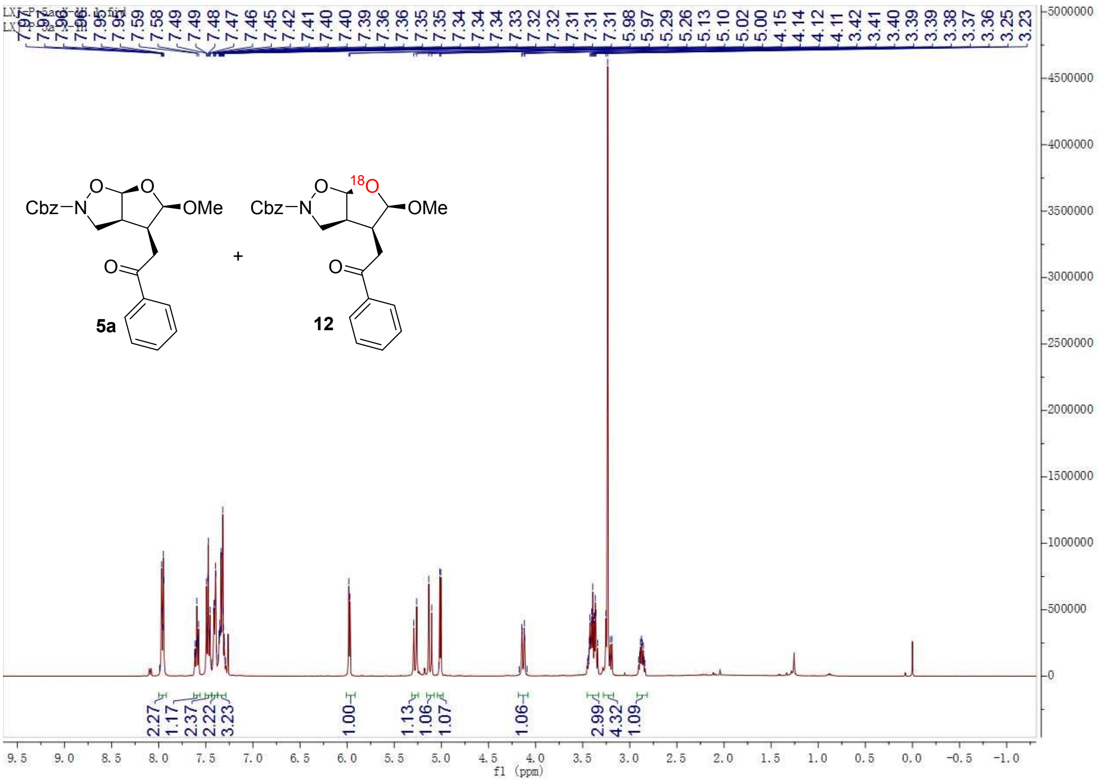


Figure 4. The ^{1}H NMR spectrum of **5a+12** (500 MHz, $CDCl_3$)

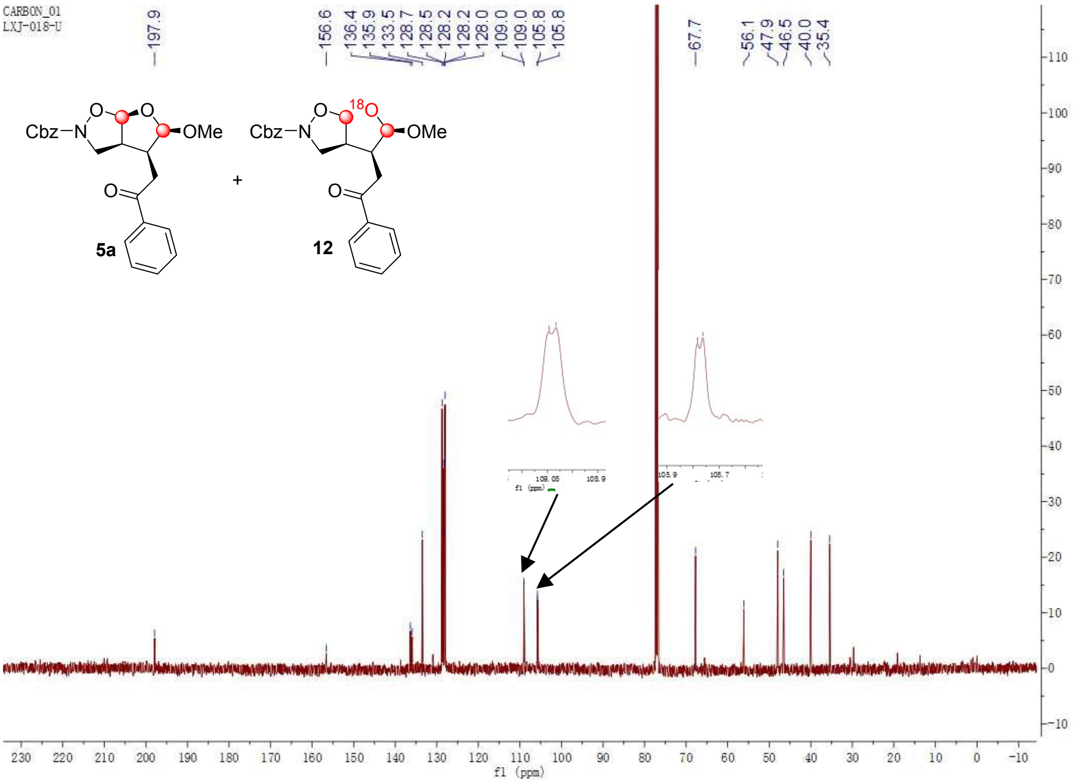


Figure 5. The ^{13}C NMR spectrum of **5a+12** (125 MHz, $CDCl_3$)

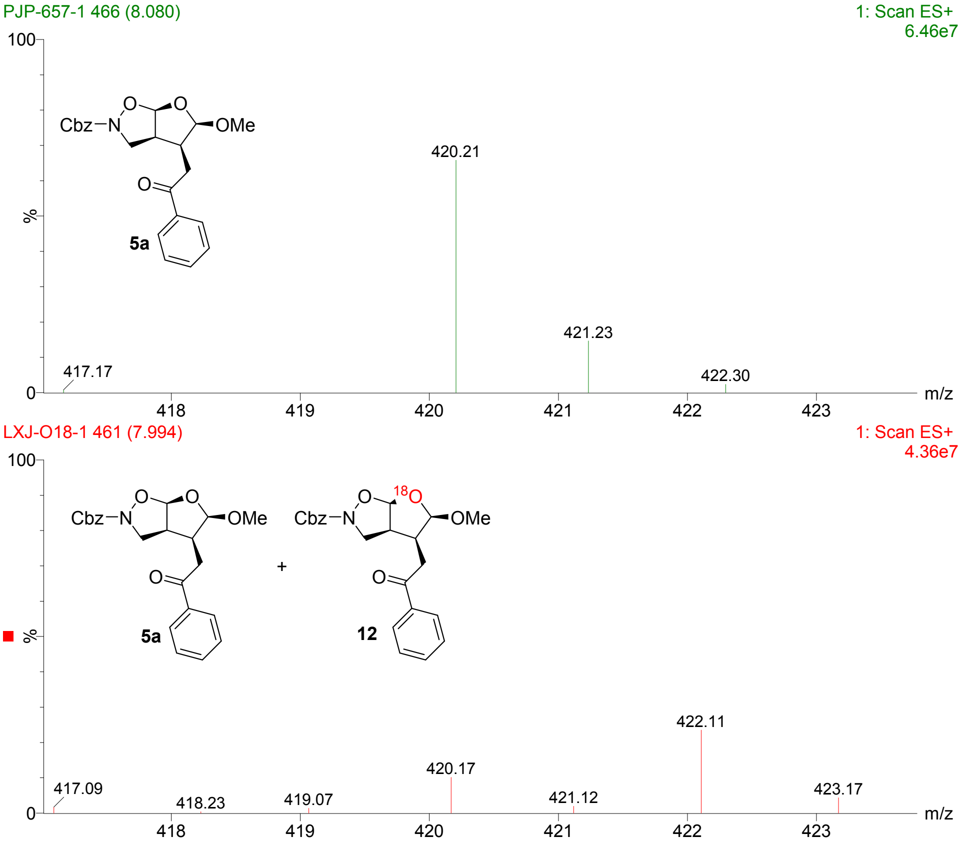
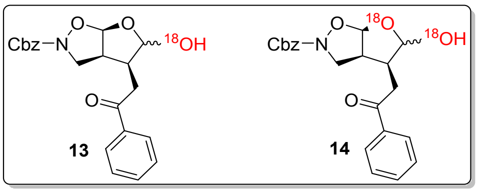


Figure 6. The MS of **5a** and **5a+12**



13+14 was obtained as a colorless oil 7 mg in 37% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 3H), 7.42 (d, *J* = 6.0 Hz, 2H), 7.33 (d, *J* = 6.6 Hz, 3H), 5.96 (d, *J* = 5.3 Hz, 1H), 5.45 (d, *J* = 4.8 Hz, 1H), 5.18 (q, *J* = 12.0 Hz, 2H), 4.13 (d, *J* = 11.3 Hz, 1H), 3.47 – 3.34 (m, 3H), 3.22 (dd, *J* = 18.5, 7.5 Hz, 1H), 2.83 (dt, *J* = 14.8, 7.4 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.0, 157.9, 136.4, 136.0, 133.5, 128.7, 128.6, 128.6, 128.4, 128.1, 109.2, 109.2, 98.7, 98.6, 67.9, 48.1, 47.2, 40.5, 35.5 ppm. **13: MS**: $[M+Na]^+$ *calcd.* For $C_{21}H_{21}NNaO_5{}^{18}O^+$ 408.13, found 408.08. **14: MS**: $[M+Na]^+$ *calcd.* For $C_{21}H_{21}NNaO_4{}^{18}O_2{}^+$ 410.13 found 410.14.

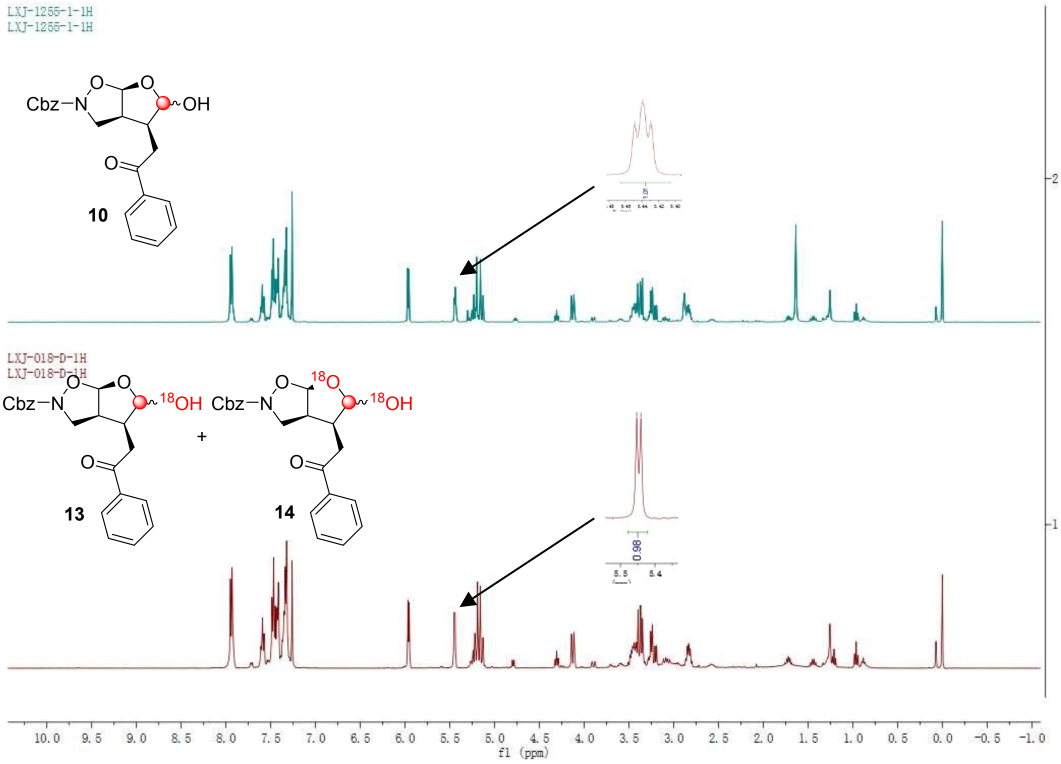


Figure 7. The ^{1}H NMR spectrum of **10** and **13+14** (400 MHz, CDCl$_3$)

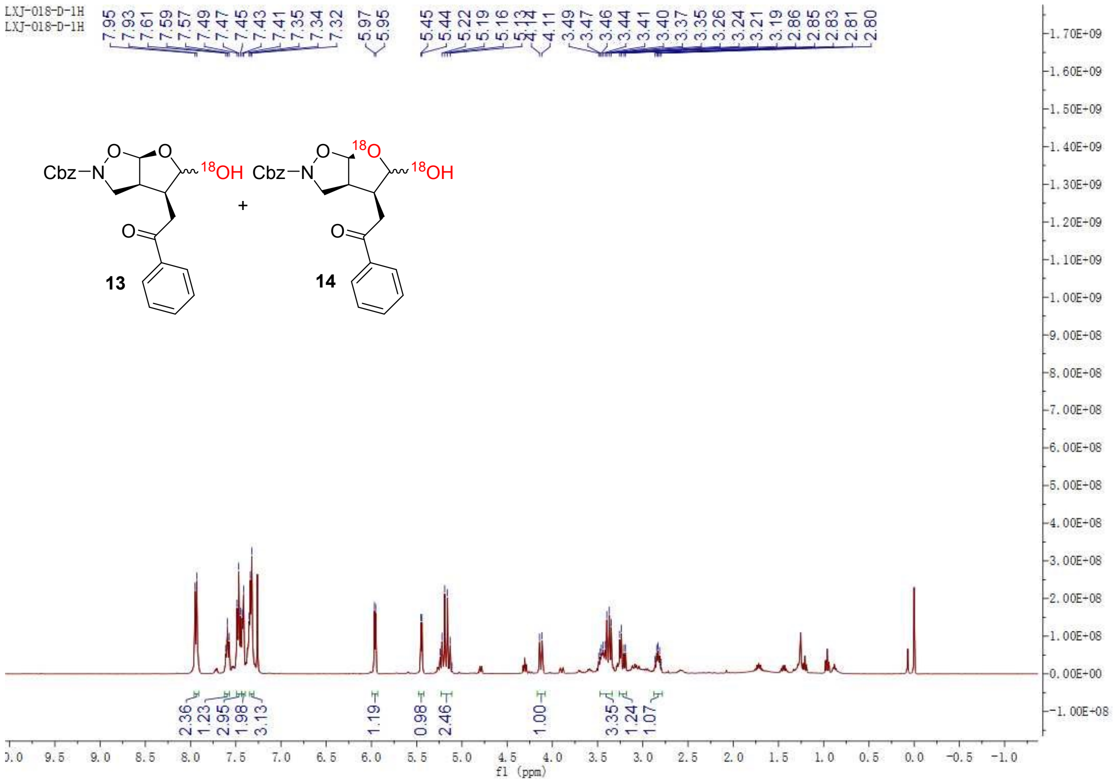


Figure 8. The ^{1}H NMR spectrum of **13+14** (400 MHz, CDCl$_3$)

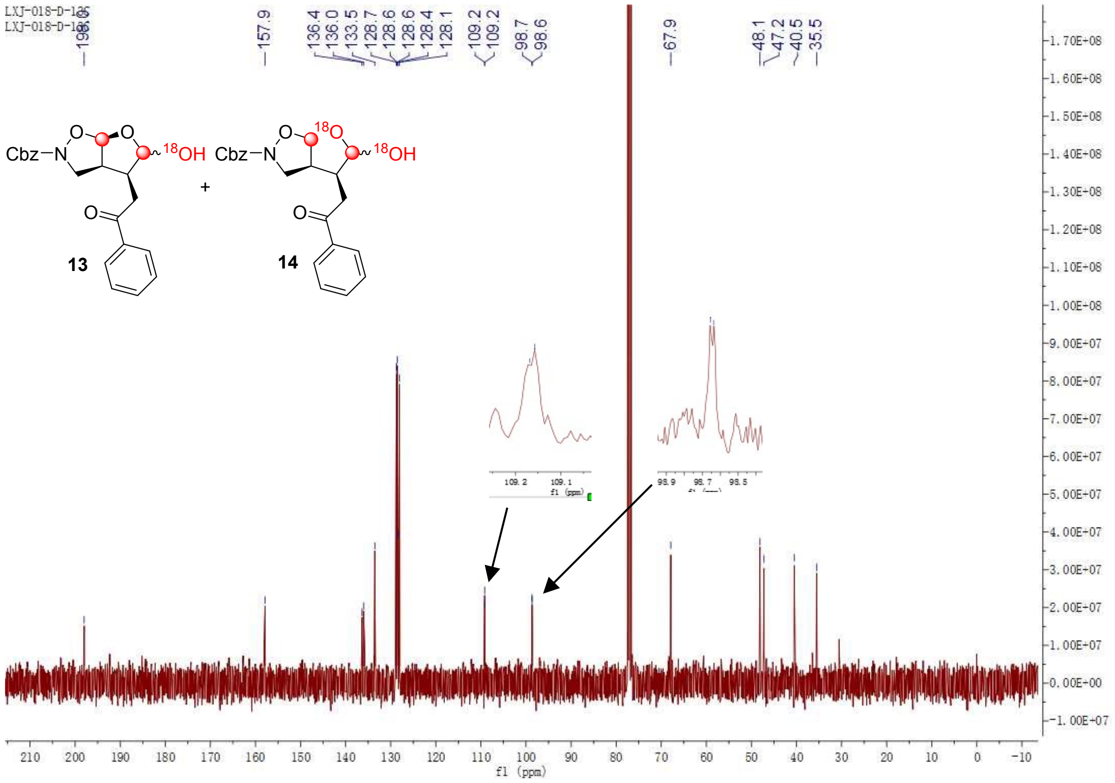


Figure 9. The ^{13}C NMR spectrum of **13+14** (100 MHz, $CDCl_3$)

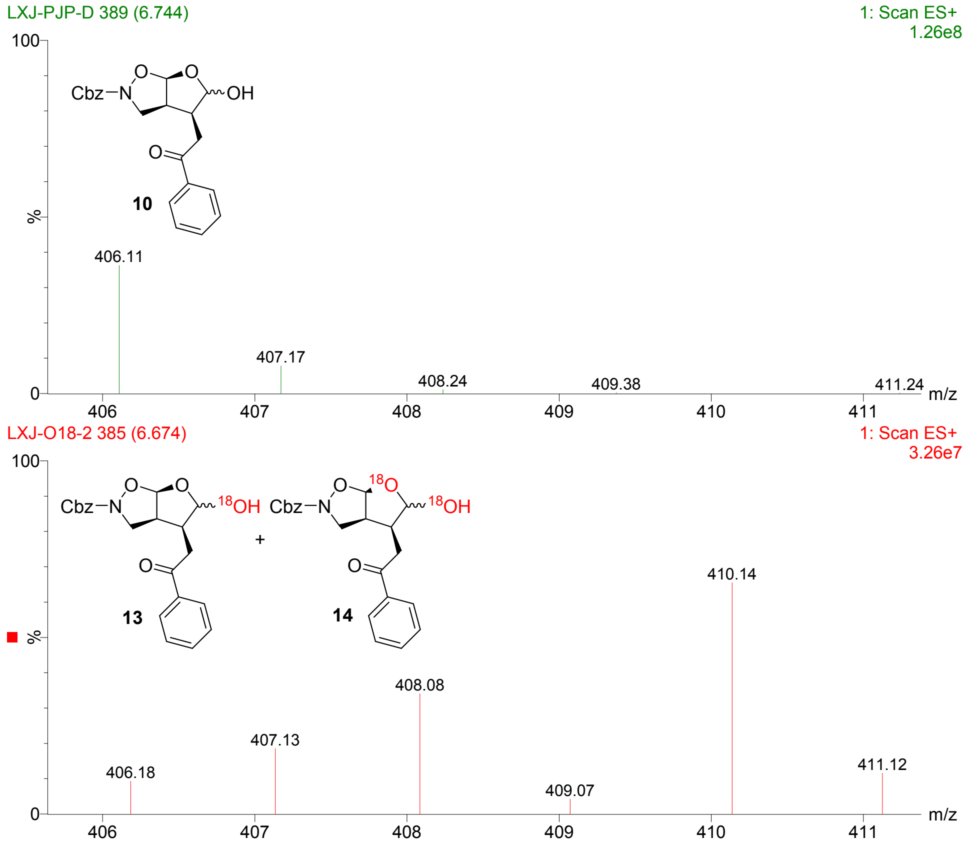
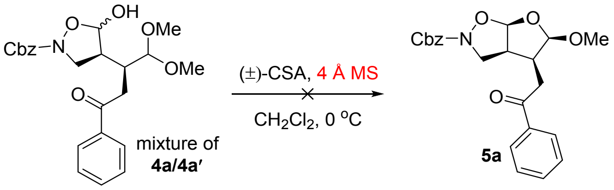


Figure 10. The MS of **10** and **13+14**

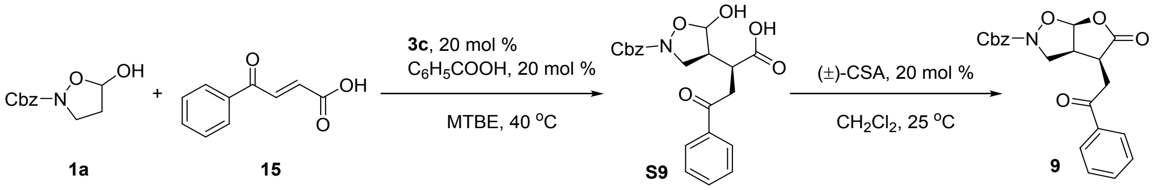
I6. Control experiment 6:



The mixture of **4a/4a'** (11 mg, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.3 mL) at 0 °C. Then CSA (1.1 mg, 0.2 equiv) and 4 Å MS (5 mg) was added to the reaction mixtures at 0 °C for 3 d. The reaction was detected by TLC.

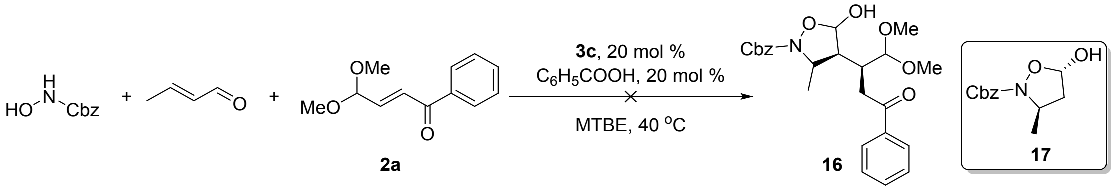
J. Other reactions:

J1. The reaction of **1a** with (*E*)-4-oxo-4-phenylbut-2-enoic acid **15** :



A glass vial equipped with a magnetic stirring bar was charged with lactols **1a** (22.3 mg, 0.10 mmol, 1.0 equiv), **15** (22.9 mg, 0.13 mmol, 1.3 equiv), **3c** (7.4 mg, 0.02 mmol, 0.2 equiv) and C_6H_5COOH (2.4 mg, 0.02 mmol, 0.2 equiv) in MTBE (0.3 mL) at 40 °C. After completion of the reaction, the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to afford **S9** white solid (30 mg). Then, compound **S9** (1.0 equiv) was respectively dissolved in anhydrous CH_2Cl_2 (0.10 mmol in 0.5 mL) at 25 °C. CSA (0.4 equiv) was added to the reaction mixture. The reaction was stirred at 25 °C for 12 h until the consumption of **S9**, the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give product **9** colorless oil (12 mg, 32%). $[\alpha]_D^{20}$ 115.62 (*c* = 0.31 in $CHCl_3$). The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], λ = 210 nm, t_{major} = 17.75 min, t_{minor} = 19.15 min, **ee = 96%**. The diastereomeric ratio was determined by NMR ***dr* >20:1**.

J2. The reaction of crotonaldehyde with benzyl hydroxyl carbamate and **2a**:



A glass vial equipped with a magnetic stirring bar was charged with benzyl hydroxyl carbamate (16.7 mg, 0.10 mmol, 1.0 equiv), crotonaldehyde (13 mg, 0.18 mmol, 1.8 equiv), **2a** (27 mg, 0.13 mmol, 1.3 equiv), **3c** (7.4 mg, 0.02 mmol, 0.2 equiv) and C_6H_5COOH (2.4 mg, 0.02 mmol, 0.2 equiv) in MTBE (0.3 mL) at 40 °C. The resulting reaction mixture was kept under vigorous stirring until the consumption of benzyl hydroxyl carbamate (monitored by TLC analysis). Instead of the compound **16**, the product **17** was obtained as colorless oil (20 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.69 (dd, J = 4.7, 2.7 Hz, 1H), 5.19 (q, J = 12.3 Hz, 2H), 4.40 (h, J = 6.8 Hz, 1H), 2.43 (dd, J = 12.5, 7.9 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.31 (d, J = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 135.9, 128.6, 128.3, 128.0, 98.6, 68.0, 54.1, 43.2, 21.5 ppm. **HRMS**: $[M+Na]^+$ *calcd.* For $C_{12}H_{15}NO_4Na^+$ 260.0893, found 260.0889. The absolute configuration of lactol **19** was confirmed according to the literature.[4,5]

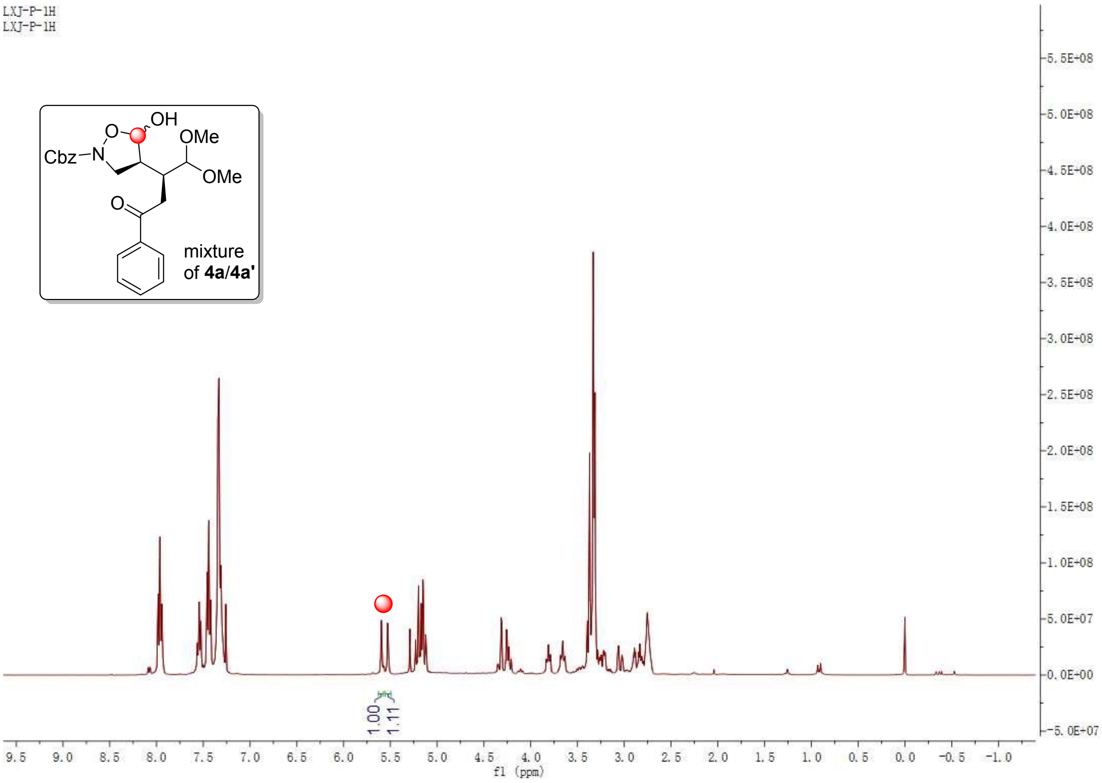
---

[4] Ibrahem I., Rios R., Vesely J., Zhao G.-L. and Córdova A., Organocatalytic asymmetric 5-hydroxyisoxazolidine synthesis: A highly enantioselective route to b-amino acids. *Chem. Commun.*, **2007**, 849–851.

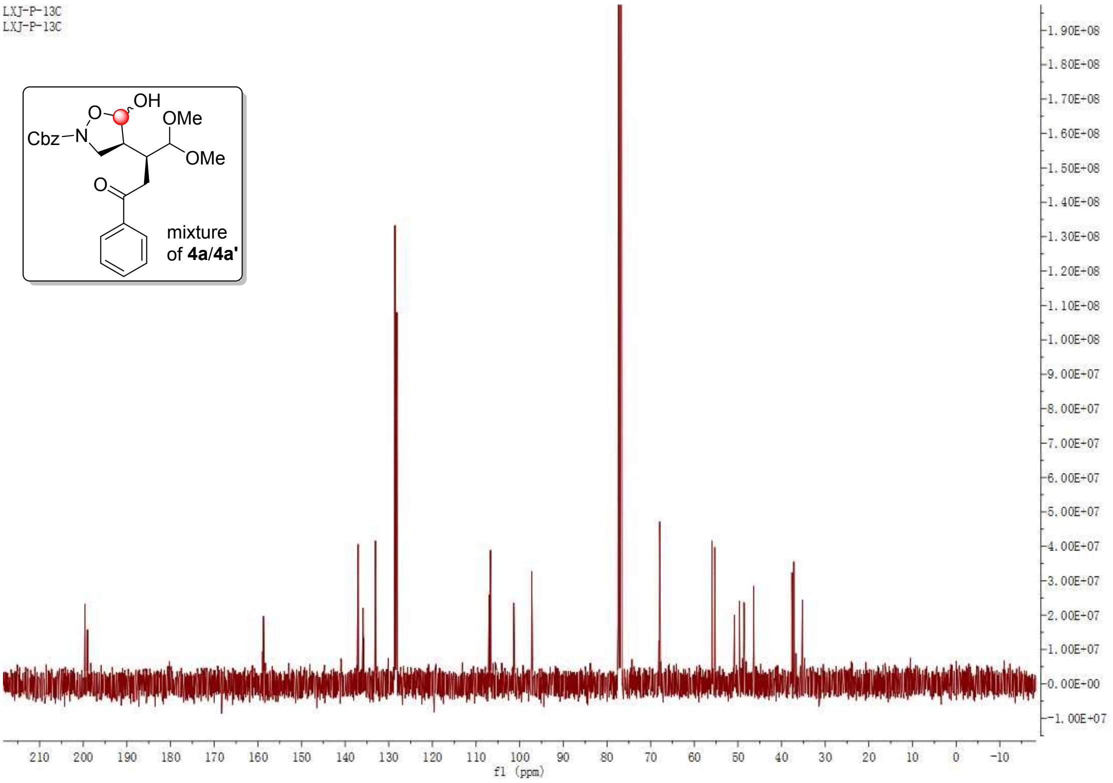
[5] Dou Q.-Y., Y.-Q. Zhang Tu, Y., Tian J.-M., Zhang F.-M. Wang and S.-H., Spiro-Pyrrolidine-Catalyzed Asymmetric Conjugate Addition of Hydroxylamine to Enals and 2,4-Dienals. *Adv. Synth. Catal.* **2016**, *358*, 874 –879

K. NMR spectra and HPLC traces

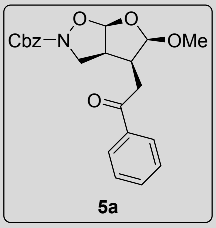
The ^{1}H NMR spectrum of 4a/4a' (400 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 4a/4a' (100 MHz, CDCl$_3$)

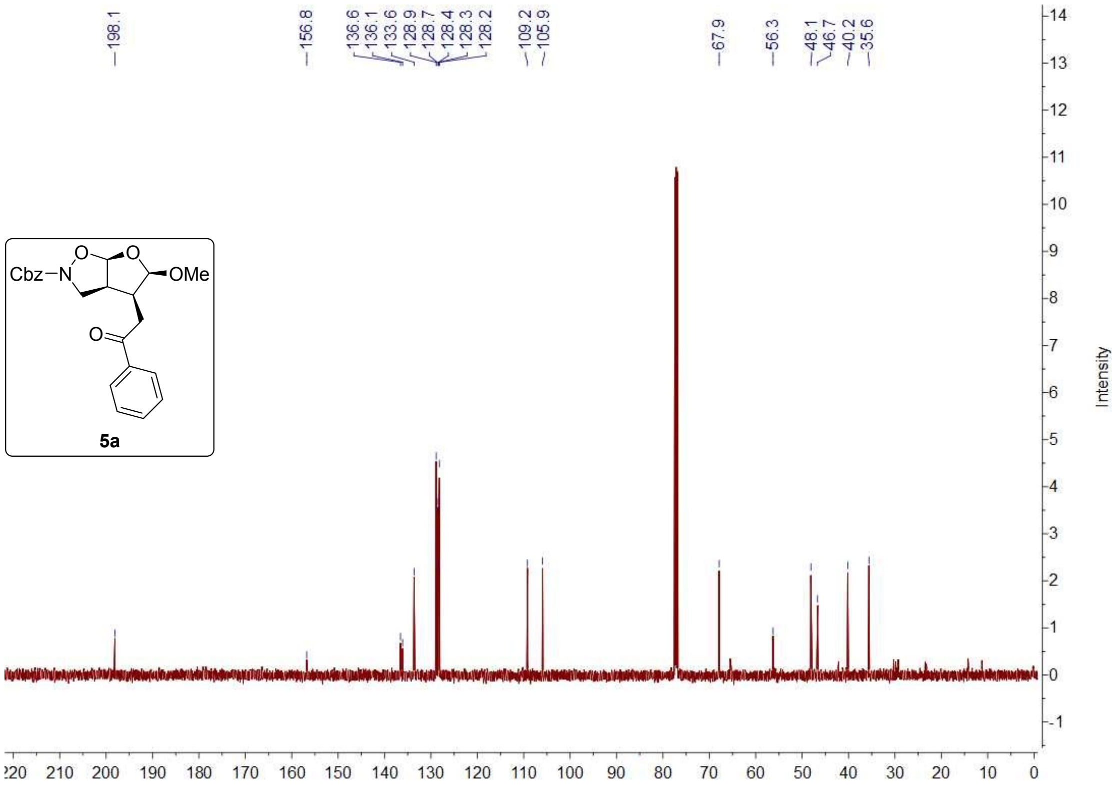


The ^{1}H NMR spectrum of 5a (400 MHz, $CDCl_3$)



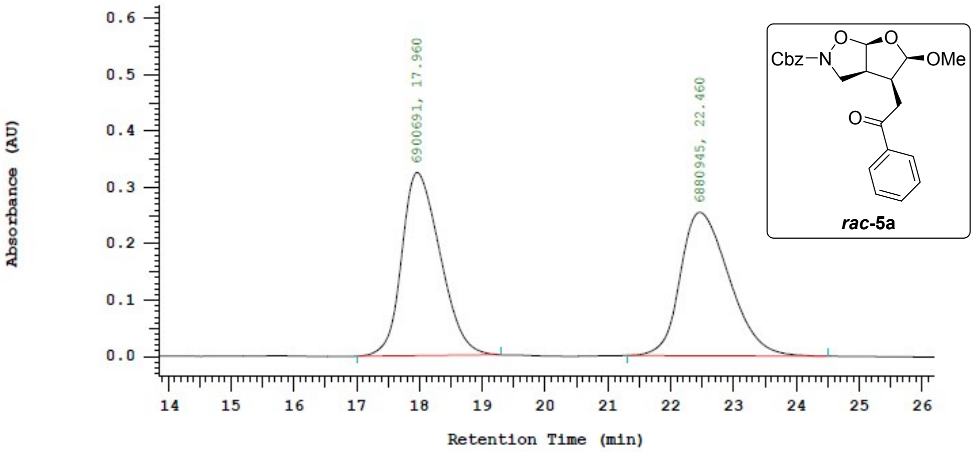
5a

The ^{13}C NMR spectrum of 5a (125 MHz, $CDCl_3$)



The HPLC of racemic 5a

Chrom Type: Fixed WL Chromatogram, 210 nm

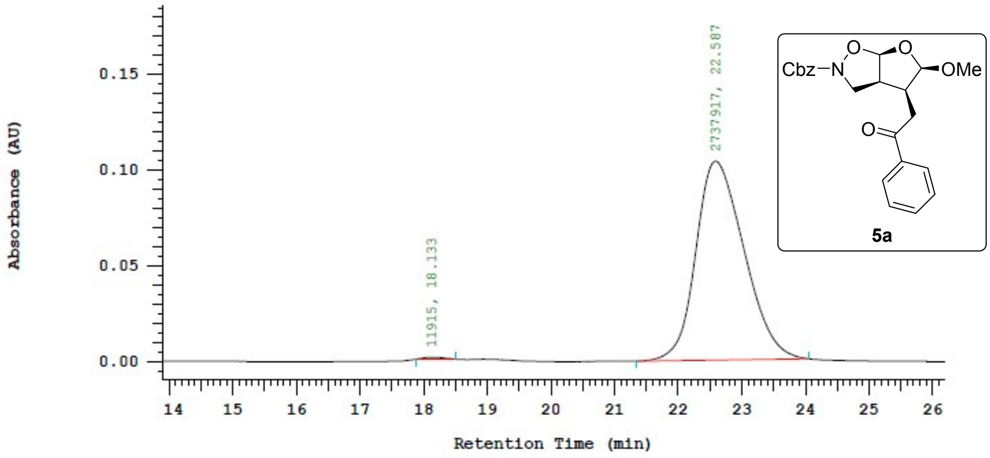


Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	17.960	6900691	50.072	BB
2	22.460	6880945	49.928	BB
		13781636	100.000	

The HPLC of chiral 5a

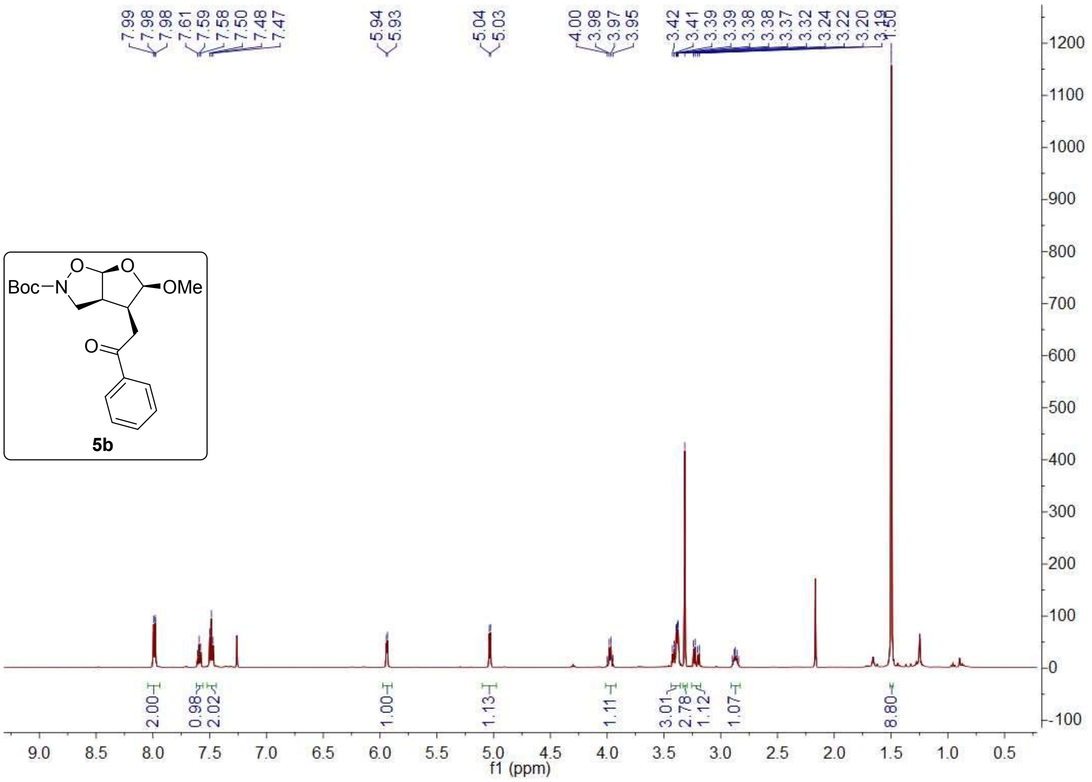
Chrom Type: Fixed WL Chromatogram, 210 nm



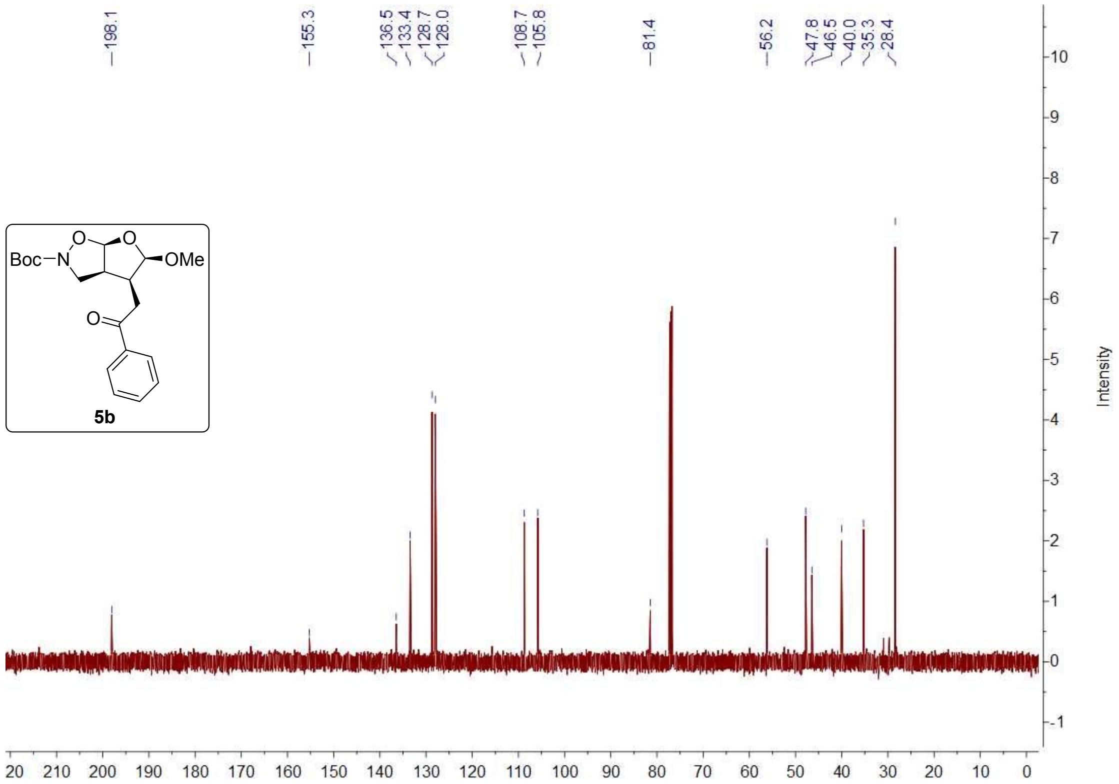
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	18.133	11915	0.433	BB
2	22.587	2737917	99.567	BB
		2749832	100.000	

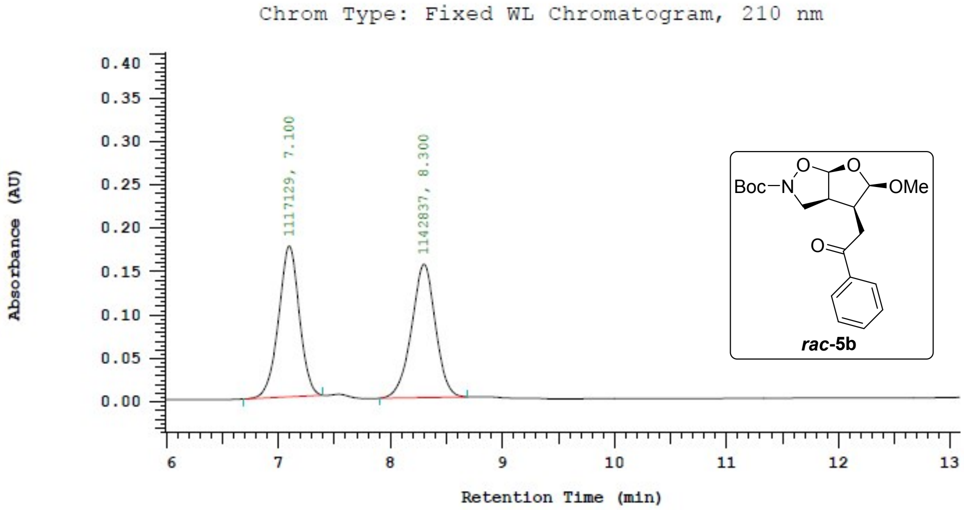
The ^{1}H NMR spectrum of 5b (500 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5b (125 MHz, CDCl$_3$)



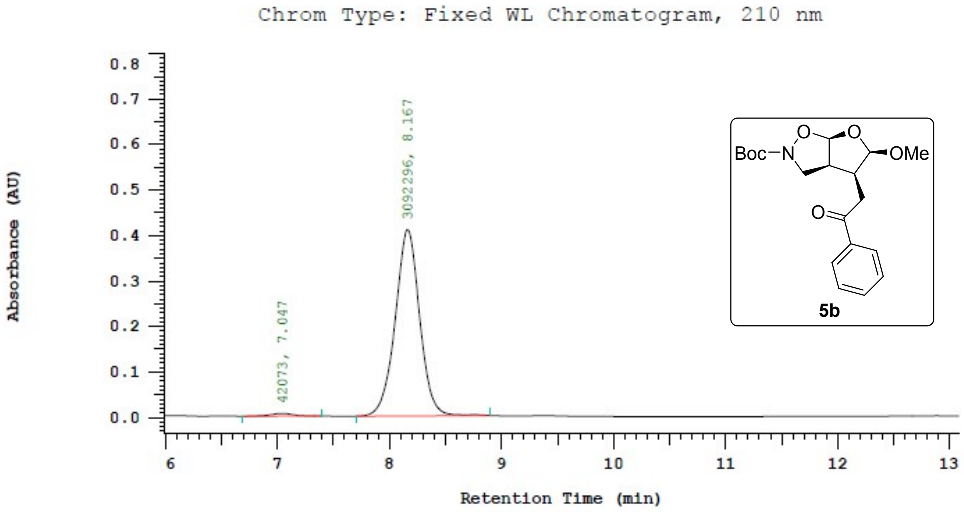
The HPLC of racemic 5b


Chrom Type: Fixed WL Chromatogram, 210 nm

```
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%
```

No.	RT	Area	Area %	BC
1	7.100	1117129	49.431	BB
2	8.300	1142837	50.569	BB
		2259966	100.000	

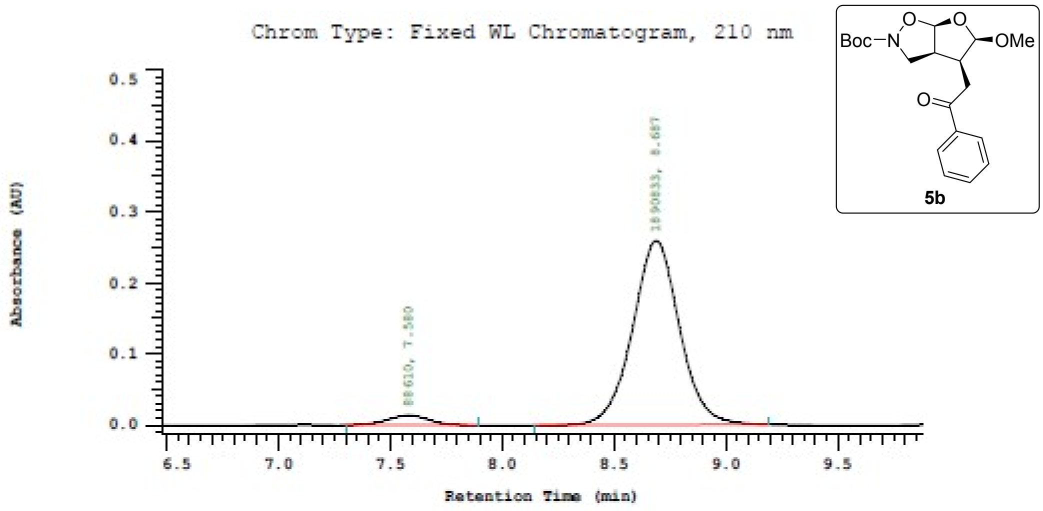
The HPLC of chiral 5b


Chrom Type: Fixed WL Chromatogram, 210 nm

```
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%
```

No.	RT	Area	Area %	BC
1	7.047	42073	1.342	BB
2	8.167	3092296	98.658	BB
		3134369	100.000	

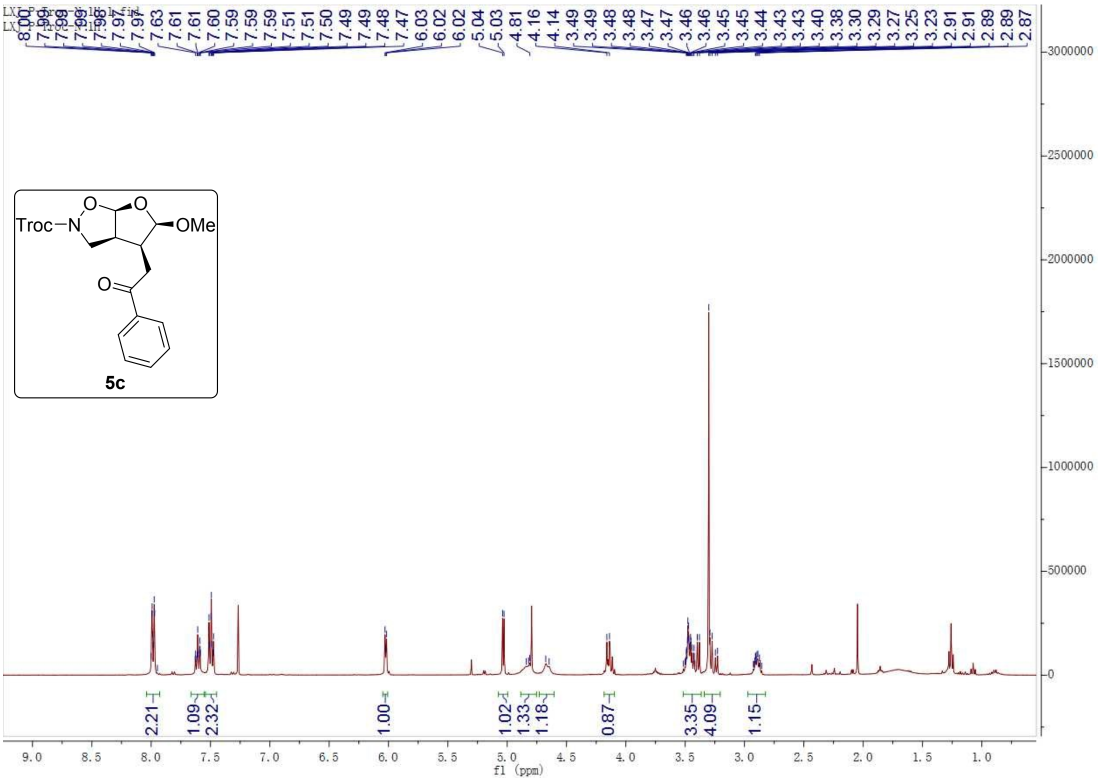
The HPLC of chiral 5b in transformation



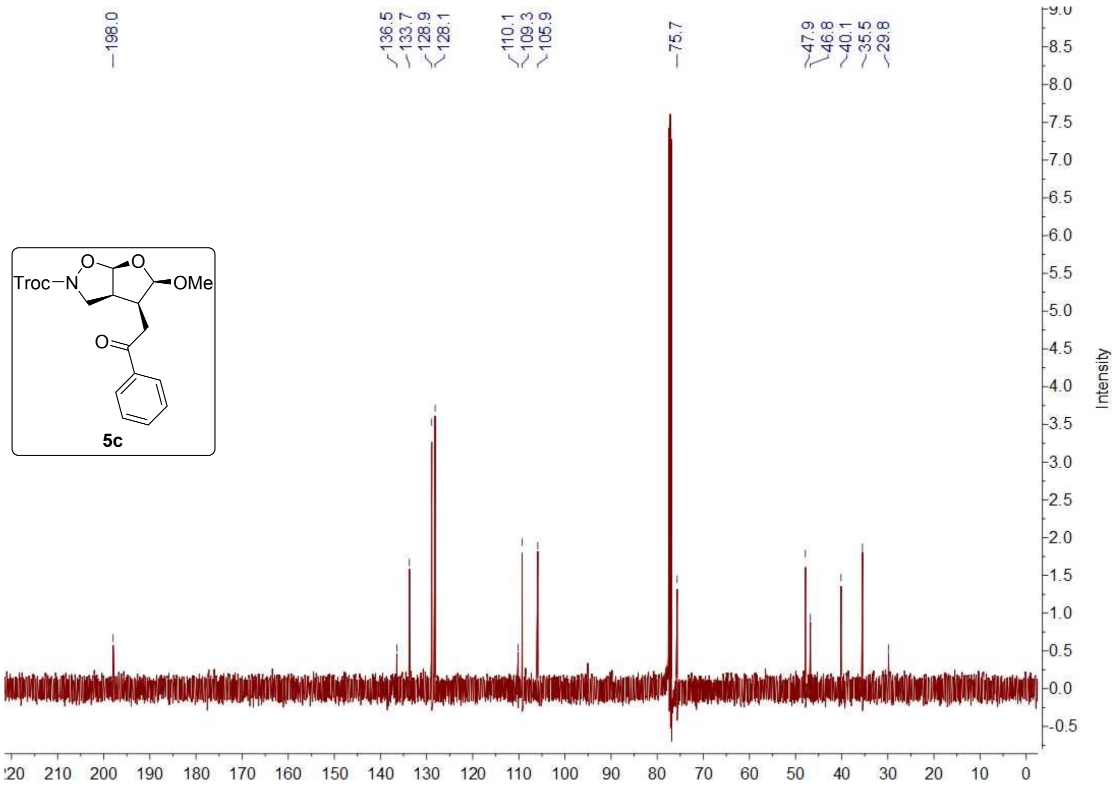
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	7.580	88610	4.477	BB
2	8.687	1890833	95.523	BB
		1979443	100.000	

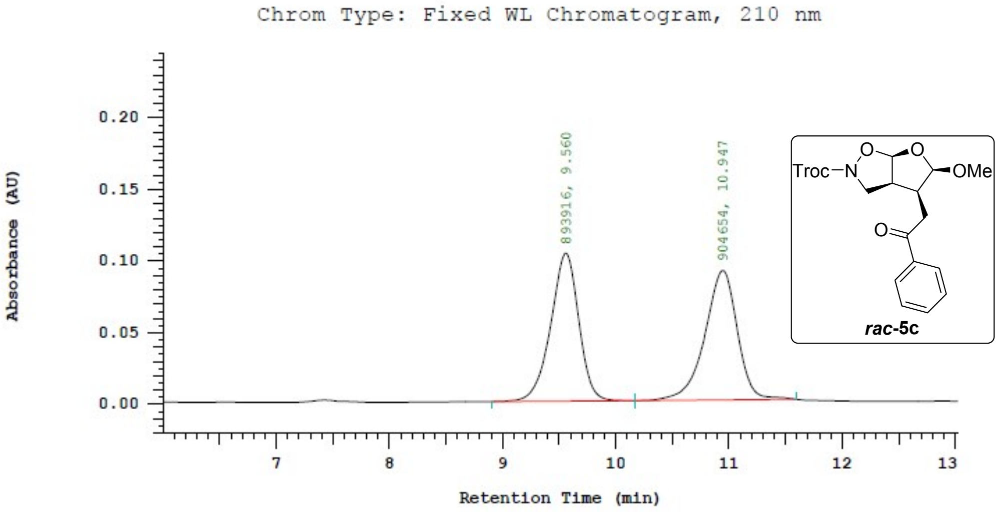
The ^{1}H NMR spectrum of 5c (400 MHz, $CDCl_3$)



The ^{13}C NMR spectrum of 5c (125 MHz, $CDCl_3$)



The HPLC of racemic 5c



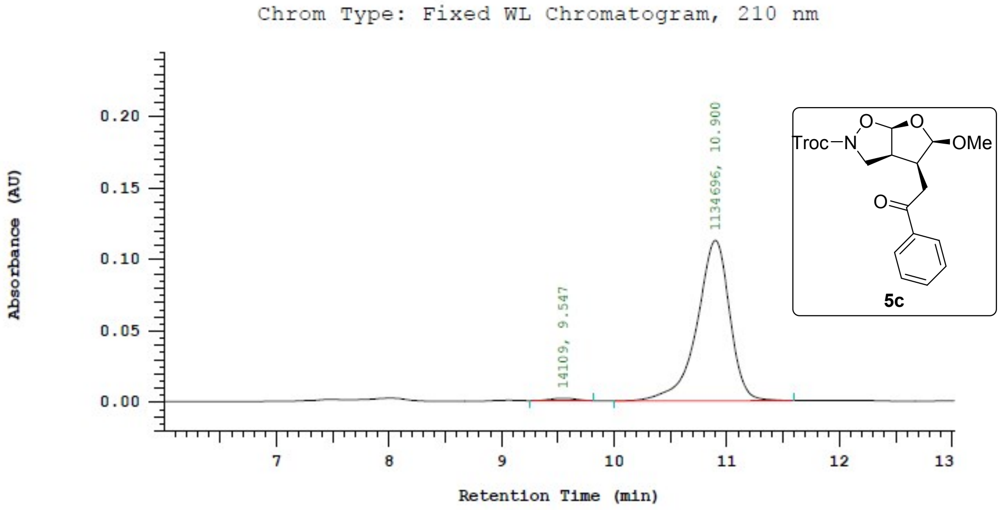
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	9.560	893916	49.701	BB
2	10.947	904654	50.299	BB
		1798570	100.000	

The HPLC of chiral 5c



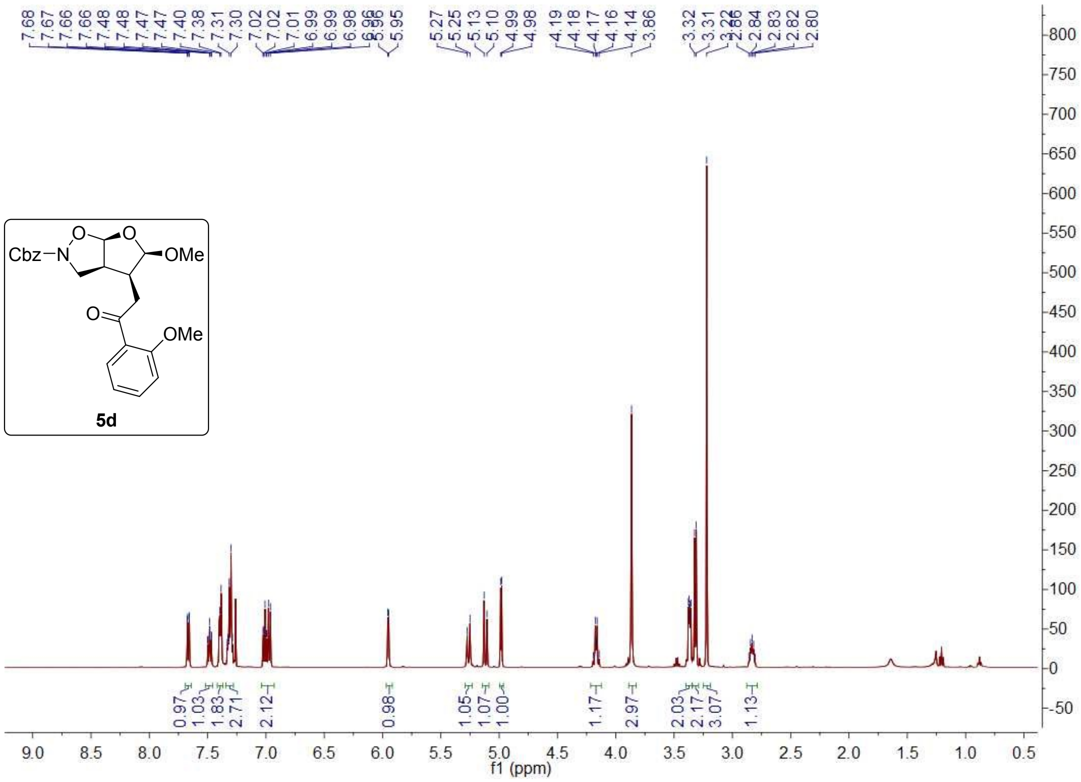
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

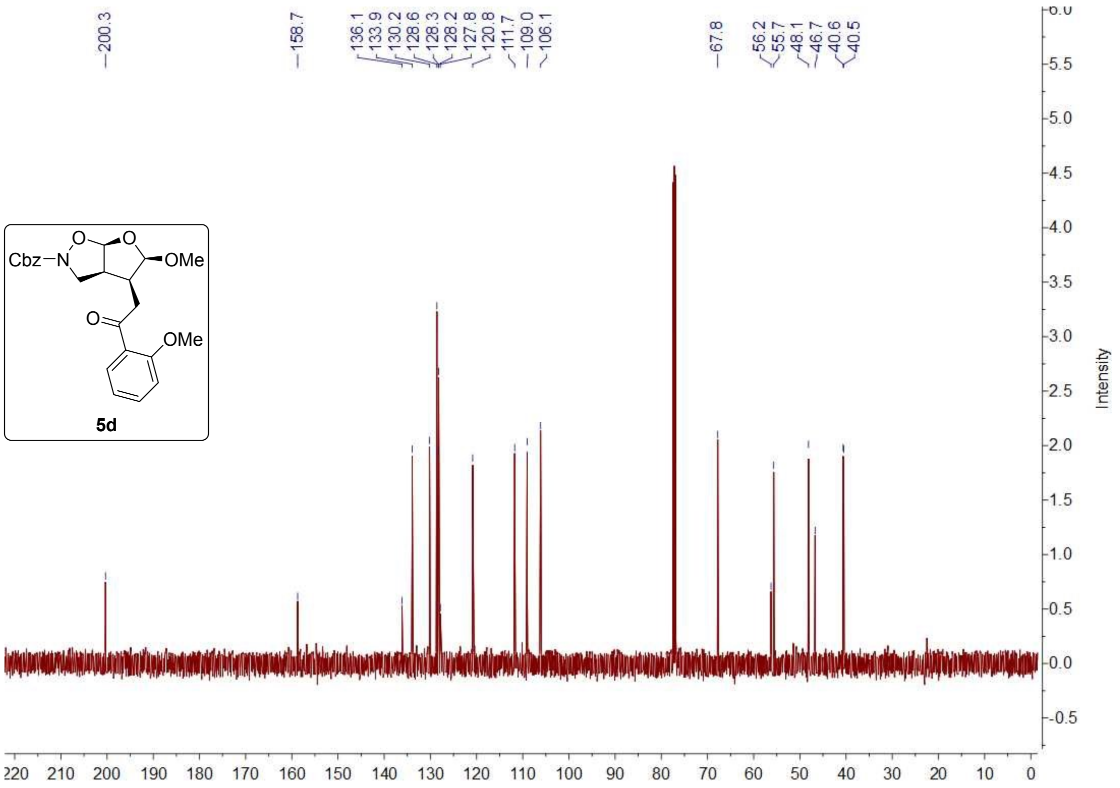
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	9.547	14109	1.228	BB
2	10.900	1134696	98.772	BB
		1148805	100.000	

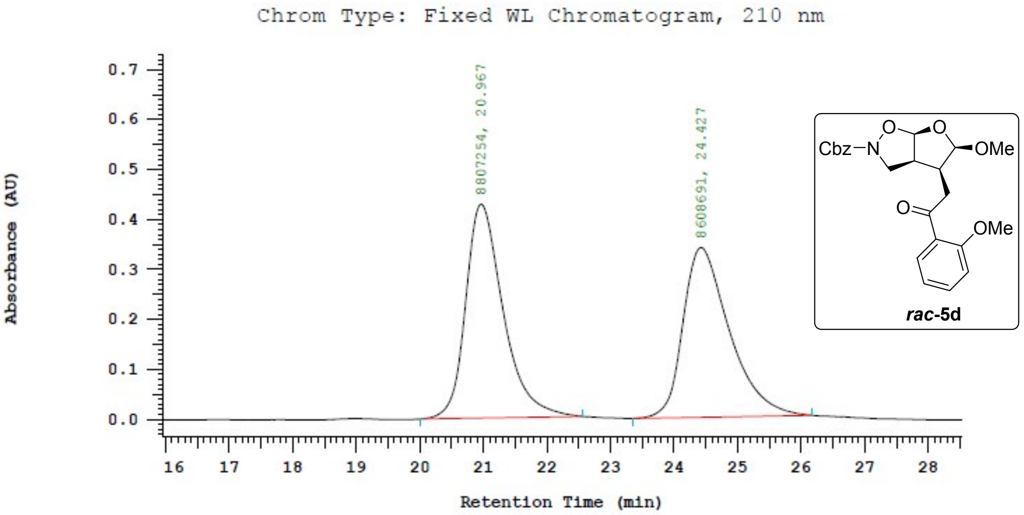
The ^{1}H NMR spectrum of 5d (500 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5d (125 MHz, $CDCl_3$)

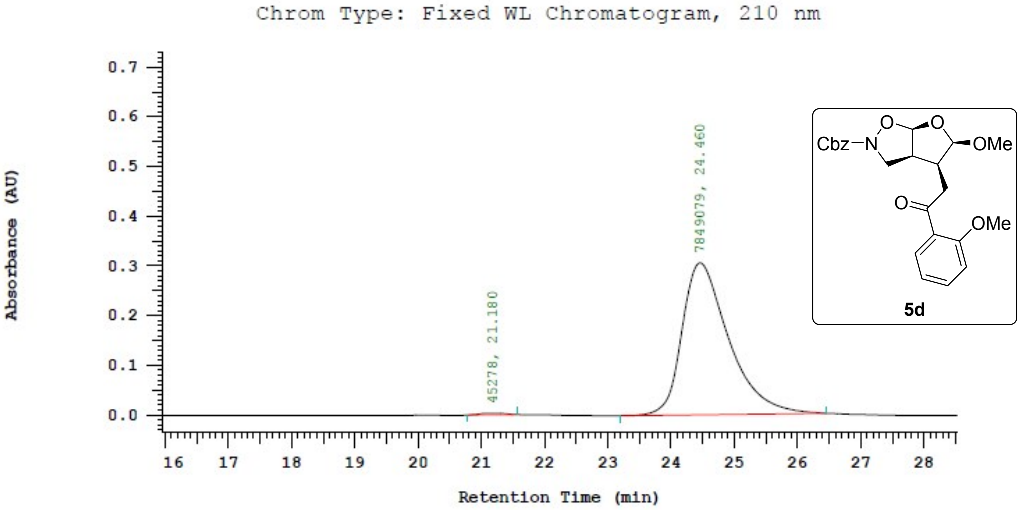


The HPLC of racemic 5d



```
                    Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.             RT                 Area                Area %              BC
   1           20.967            8807254               50.570              BB
   2           24.427            8608691               49.430              BB

                                17415945              100.000
```

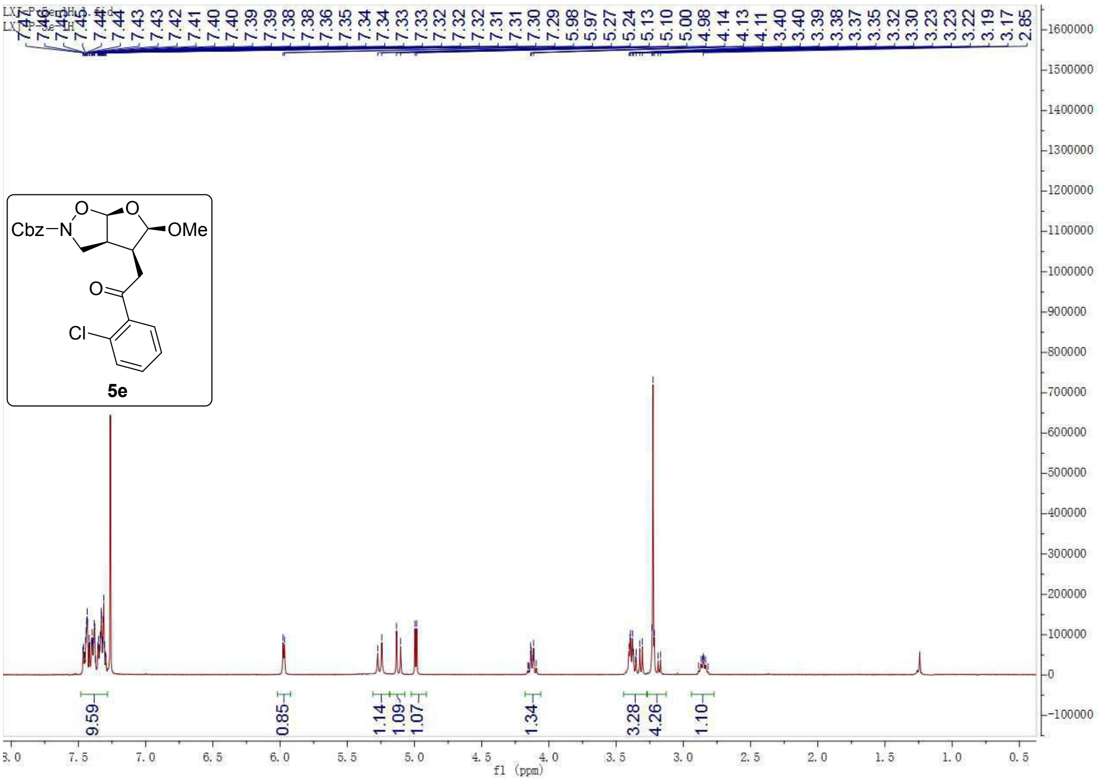
The HPLC of chiral 5d



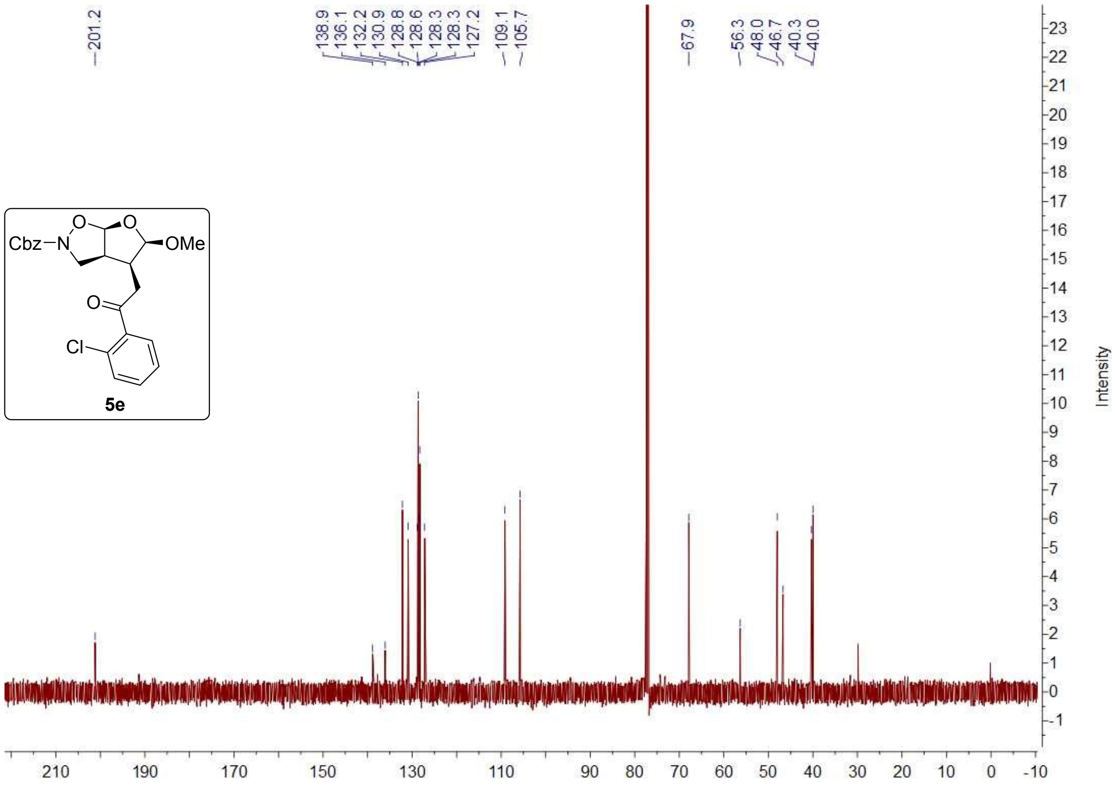
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	21.180	45278	0.574	BB
2	24.460	7849079	99.426	BB
		7894357	100.000	

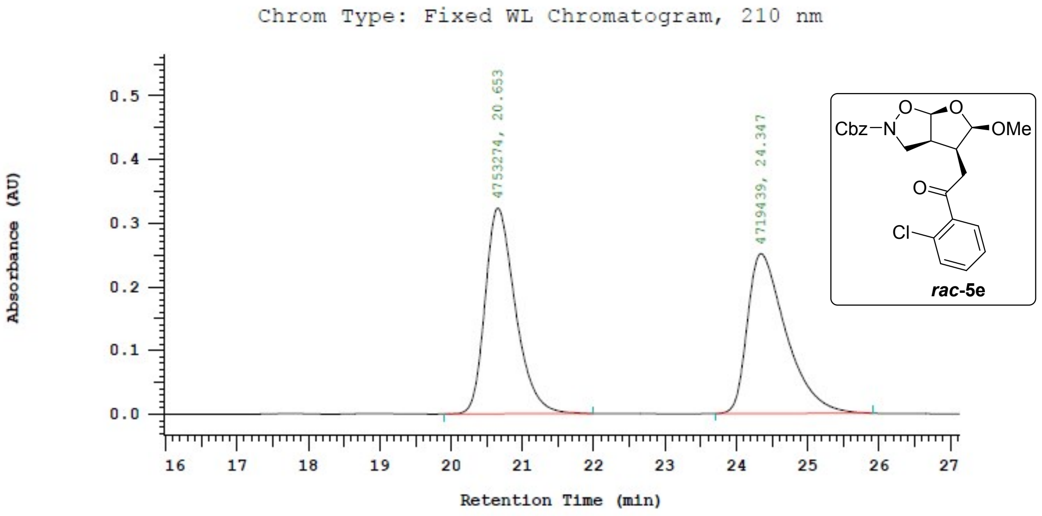
The ^{1}H NMR spectrum of 5e (400 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5e (125 MHz, $CDCl_3$)

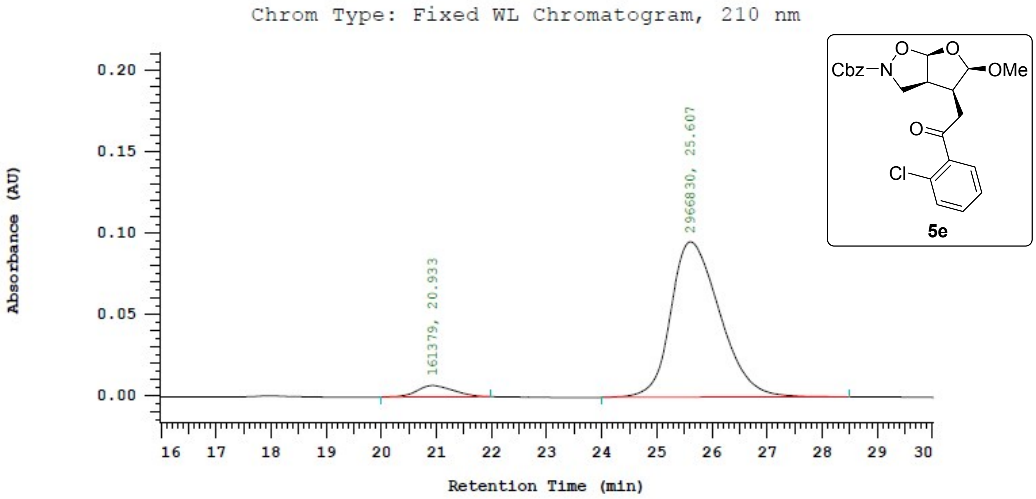


The HPLC of racemic 5e



```
                 Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.            RT              Area              Area %           BC

 1           20.653          4753274            50.179          BB
 2           24.347          4719439            49.821          BB

                             9472713           100.000
```

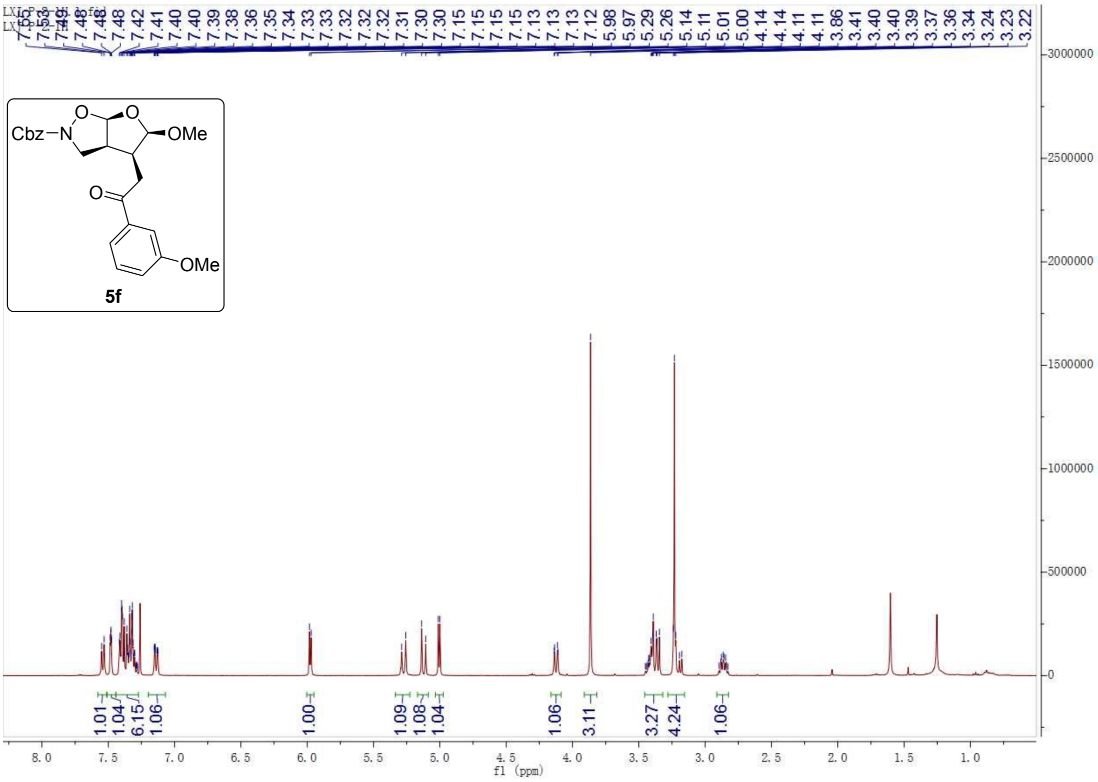
The HPLC of chiral 5e



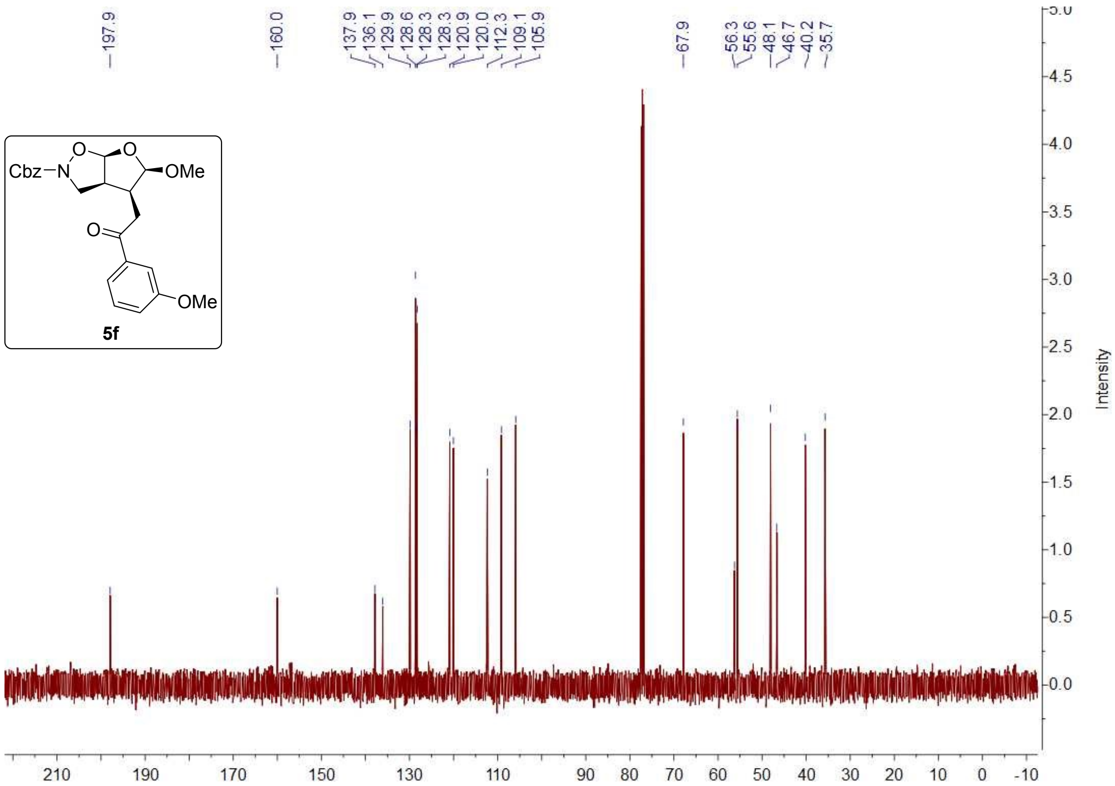
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	20.933	161379	5.159	BB
2	25.607	2966830	94.841	BB
		3128209	100.000	

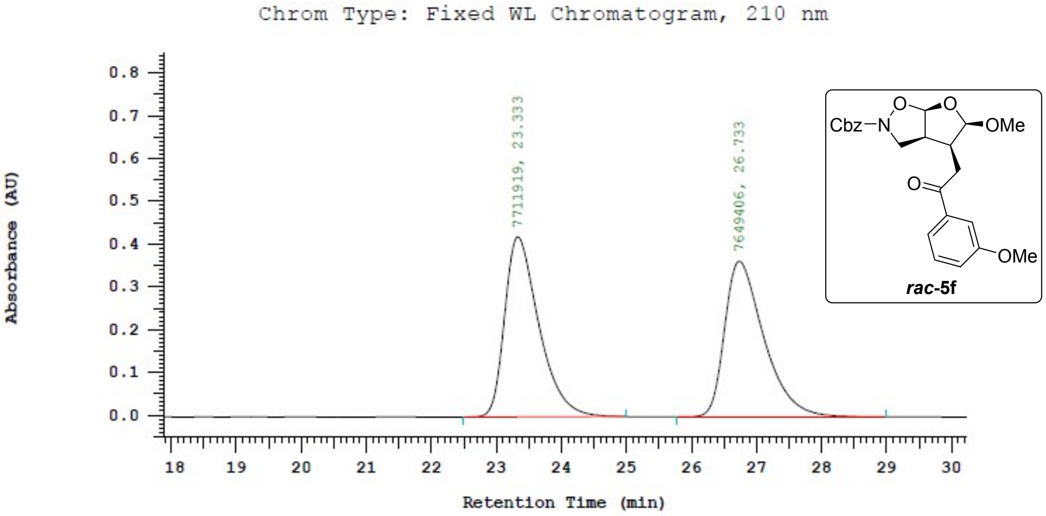
The ^{1}H NMR spectrum of 5f (400 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5f (125 MHz, CDCl$_3$)



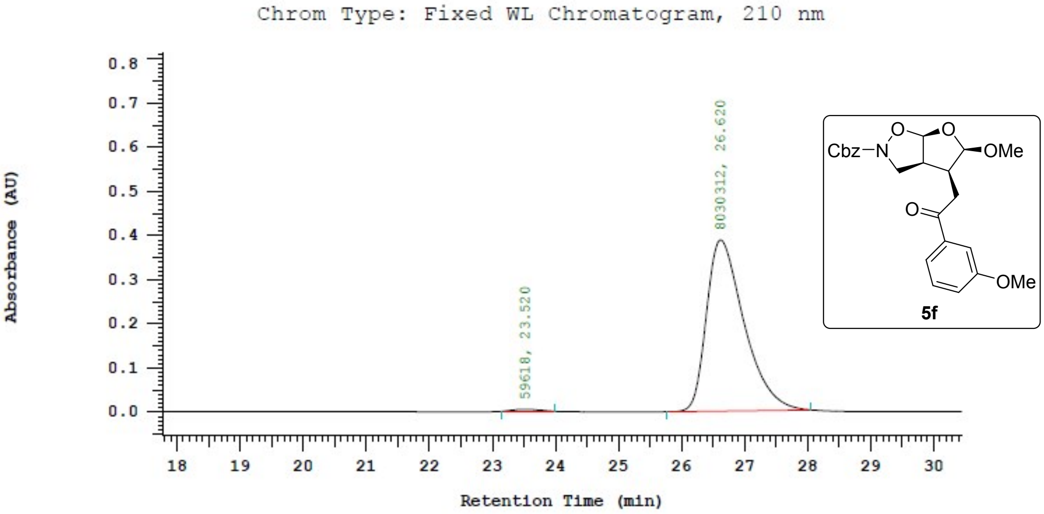
The HPLC of racemic 5f



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	23.333	7711919	50.203	BB
2	26.733	7649406	49.797	BB
		15361325	100.000	

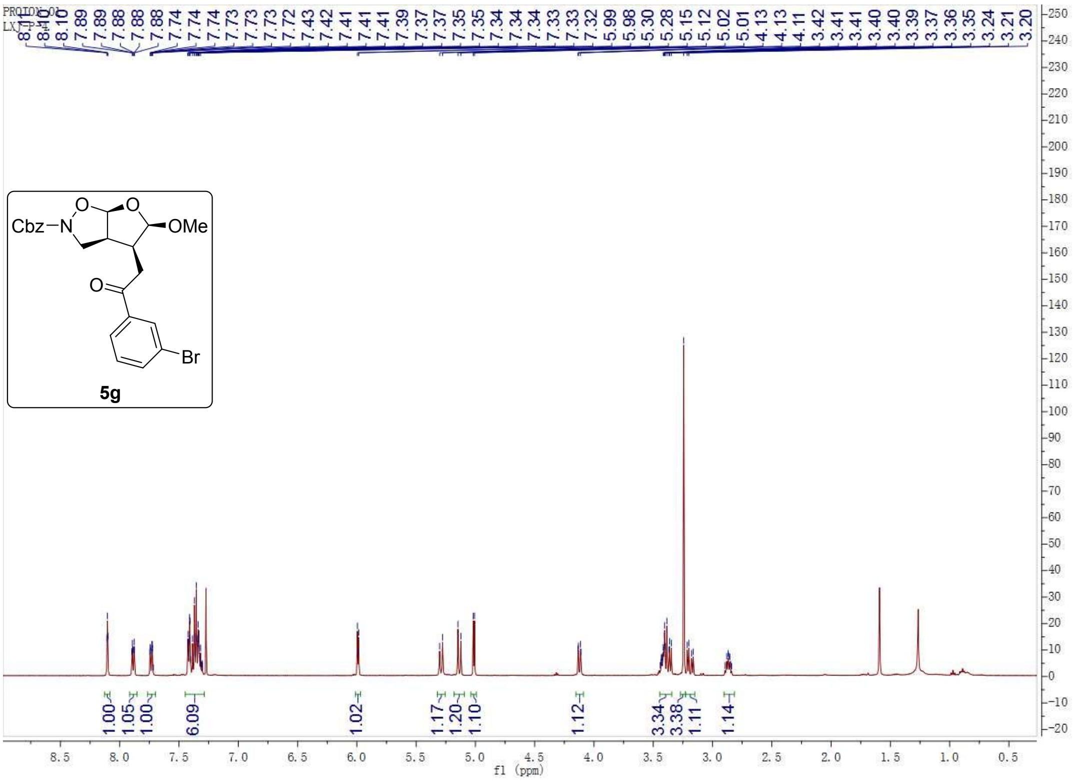
The HPLC of chiral 5f



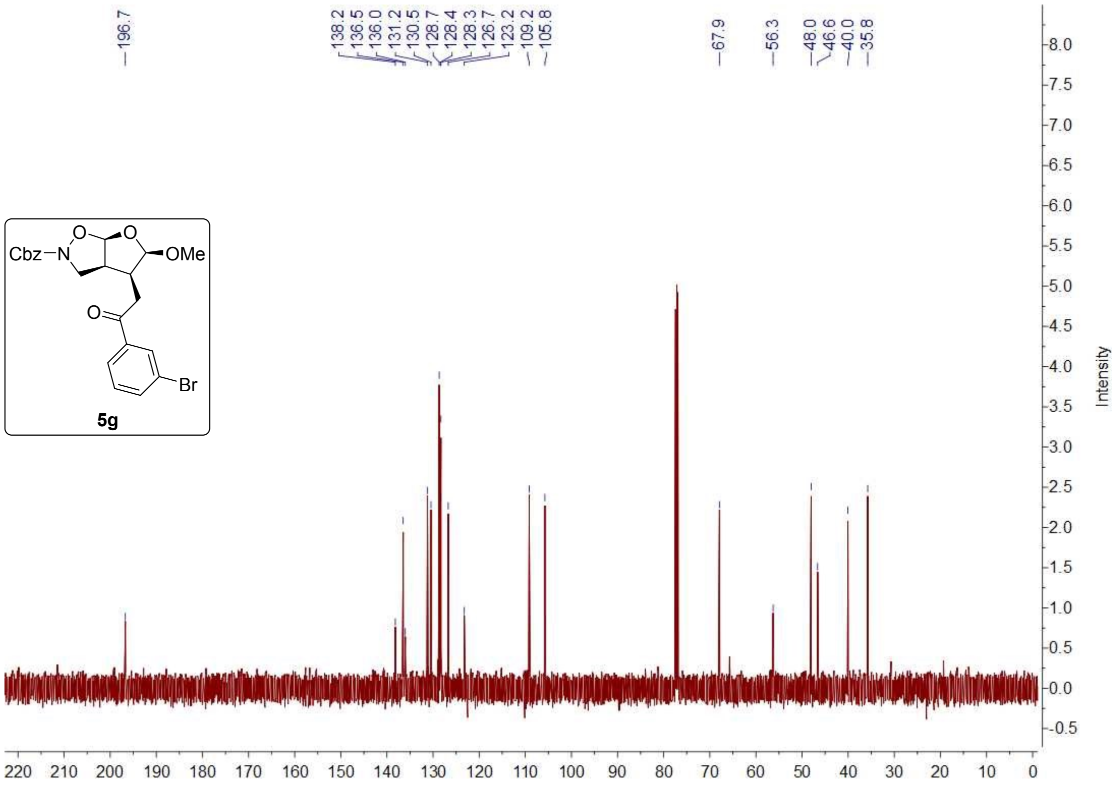
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	23.520	59618	0.737	BB
2	26.620	8030312	99.263	BB
		8089930	100.000	

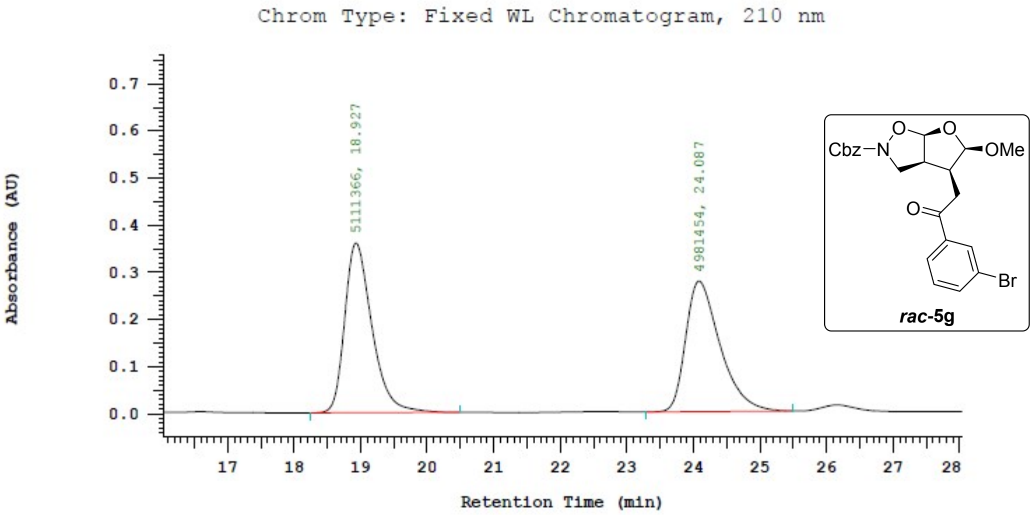
The ^{1}H NMR spectrum of 5g (500 MHz, $CDCl_3$)



The ^{13}C NMR spectrum of 5g (125 MHz, $CDCl_3$)

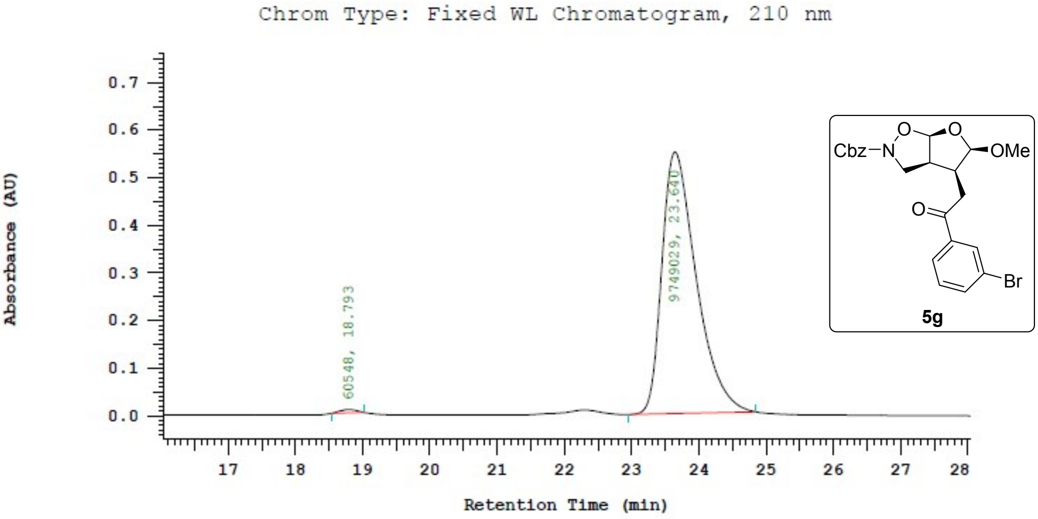


The HPLC of racemic 5g



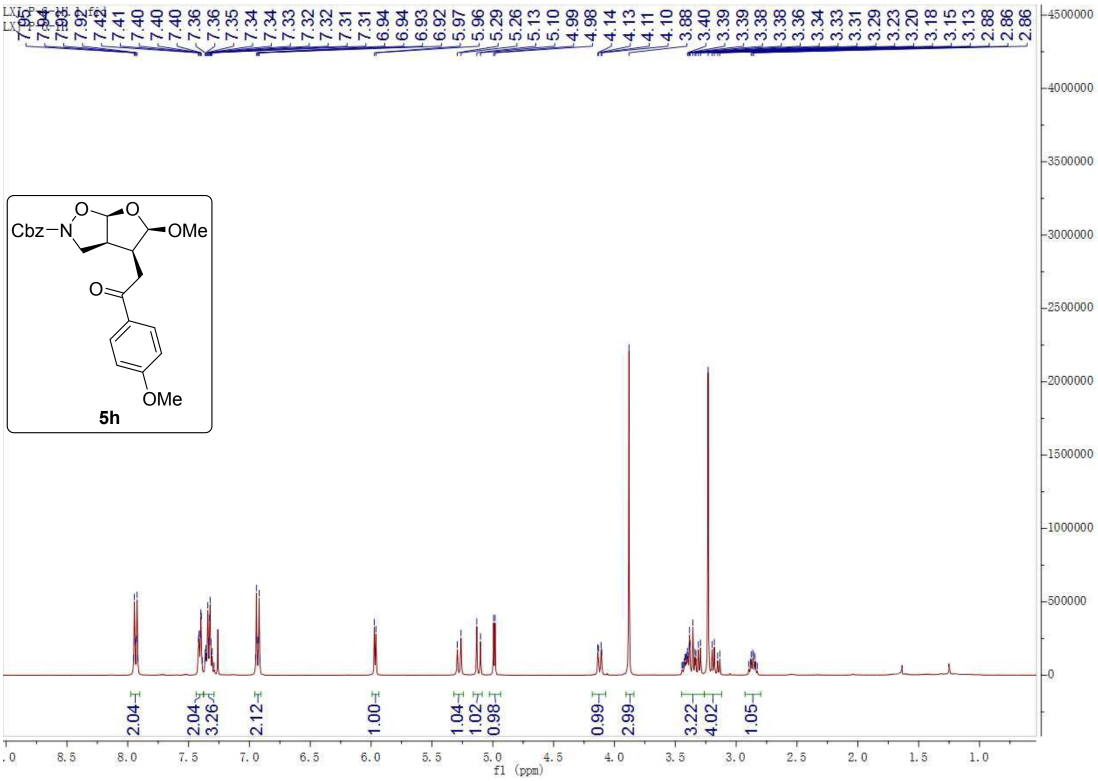
```
                    Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.            RT              Area              Area %            BC

  1          18.927           5111366            50.644            BB
  2          24.087           4981454            49.356            BB

                             10092820           100.000
```

The HPLC of chiral 5g

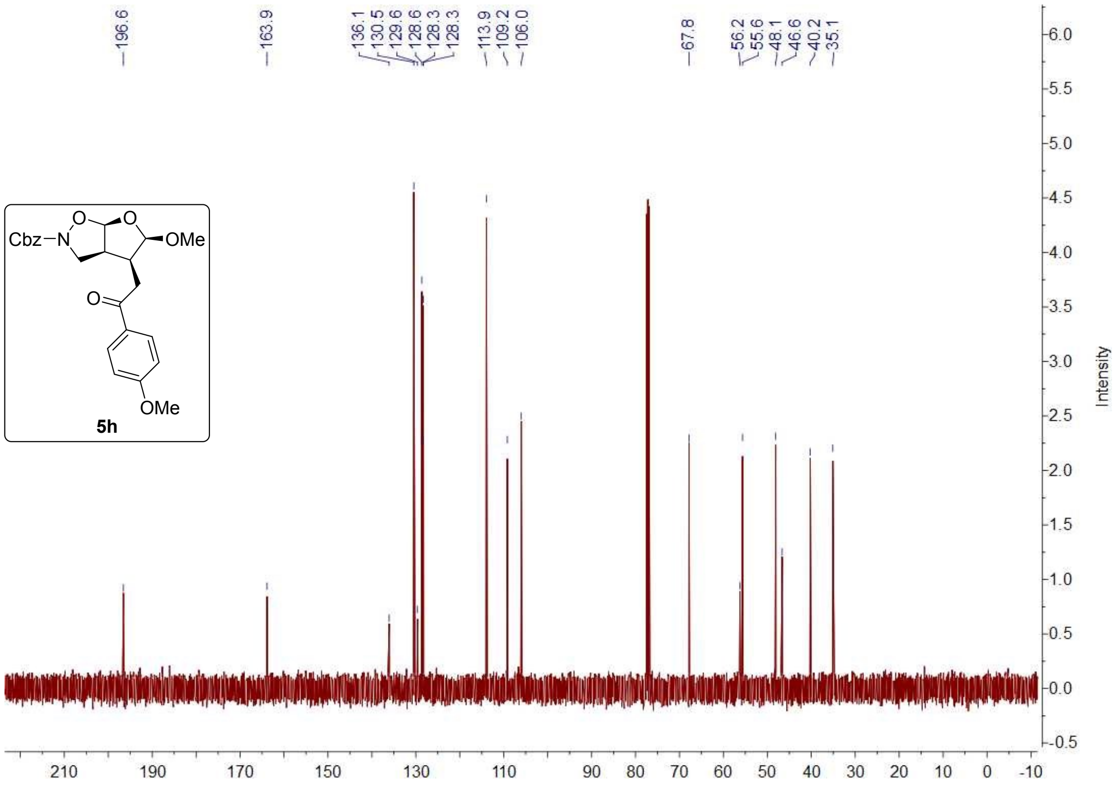


```
                    Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.            RT                 Area               Area %             BC

 1            18.793              60548               0.617             BB
 2            23.640            9749029              99.383             BB

                                9809577             100.000
```

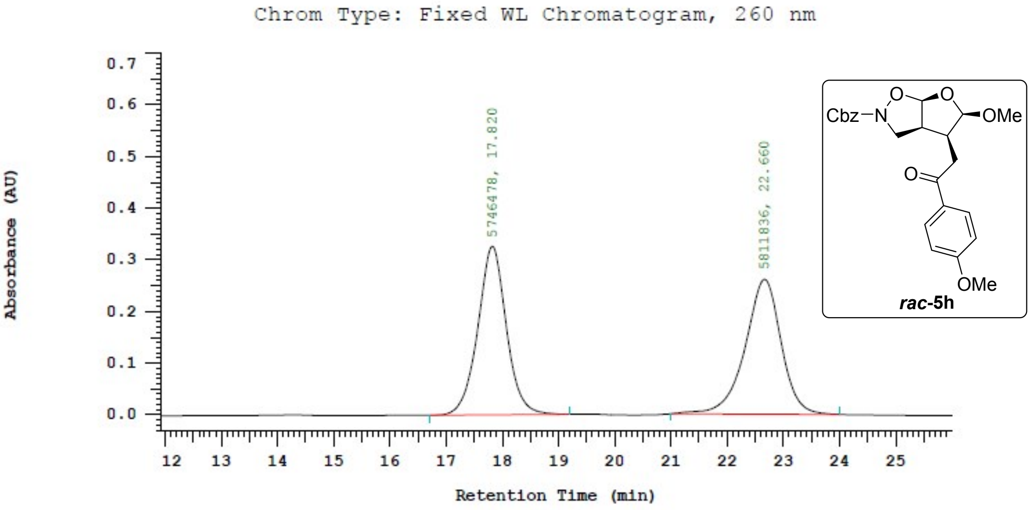
The ^{1}H NMR spectrum of 5h (400 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5h (125 MHz, CDCl$_3$)



The HPLC of racemic 5h



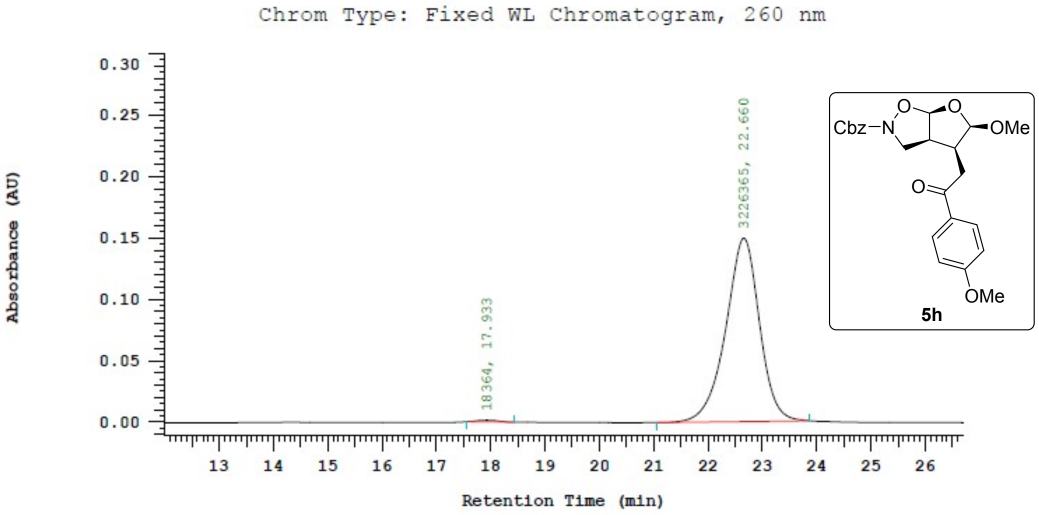
Chrom Type: Fixed WL Chromatogram, 260 nm

Peak Quantitation: AREA

Calculation Method: AREA%

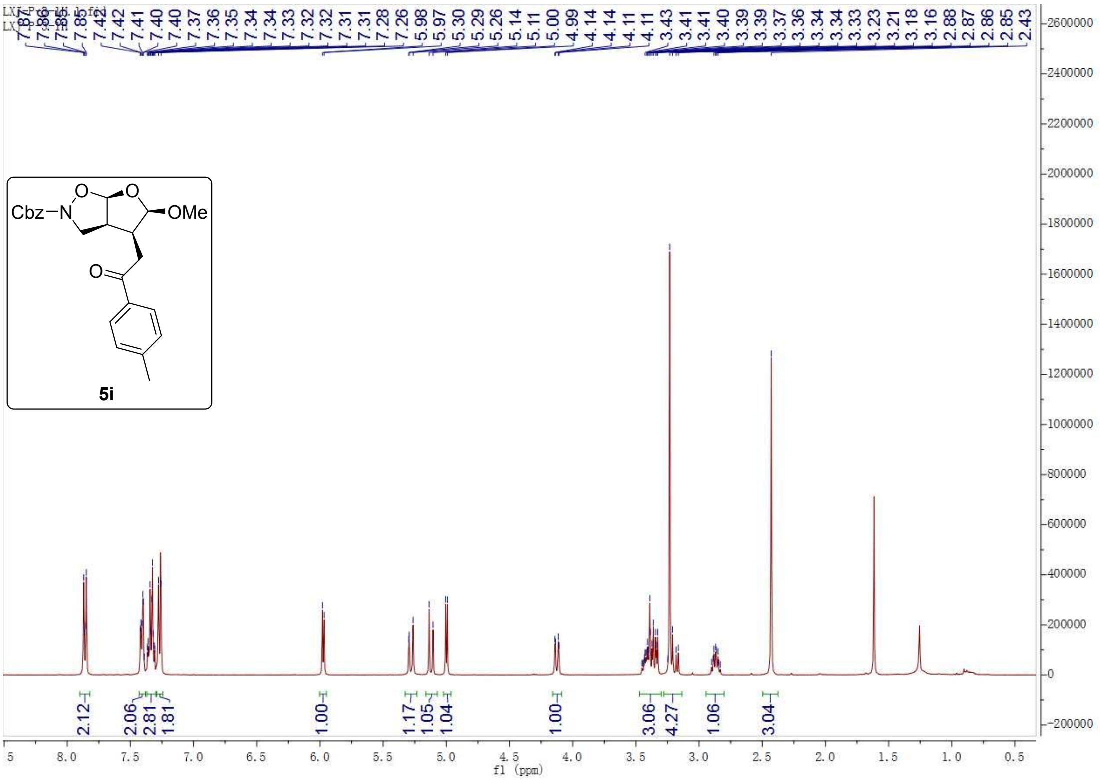
No.	RT	Area	Area %	BC
1	17.820	5746478	49.717	BB
2	22.660	5811836	50.283	BB
		11558314	100.000	

The HPLC of chiral 5h

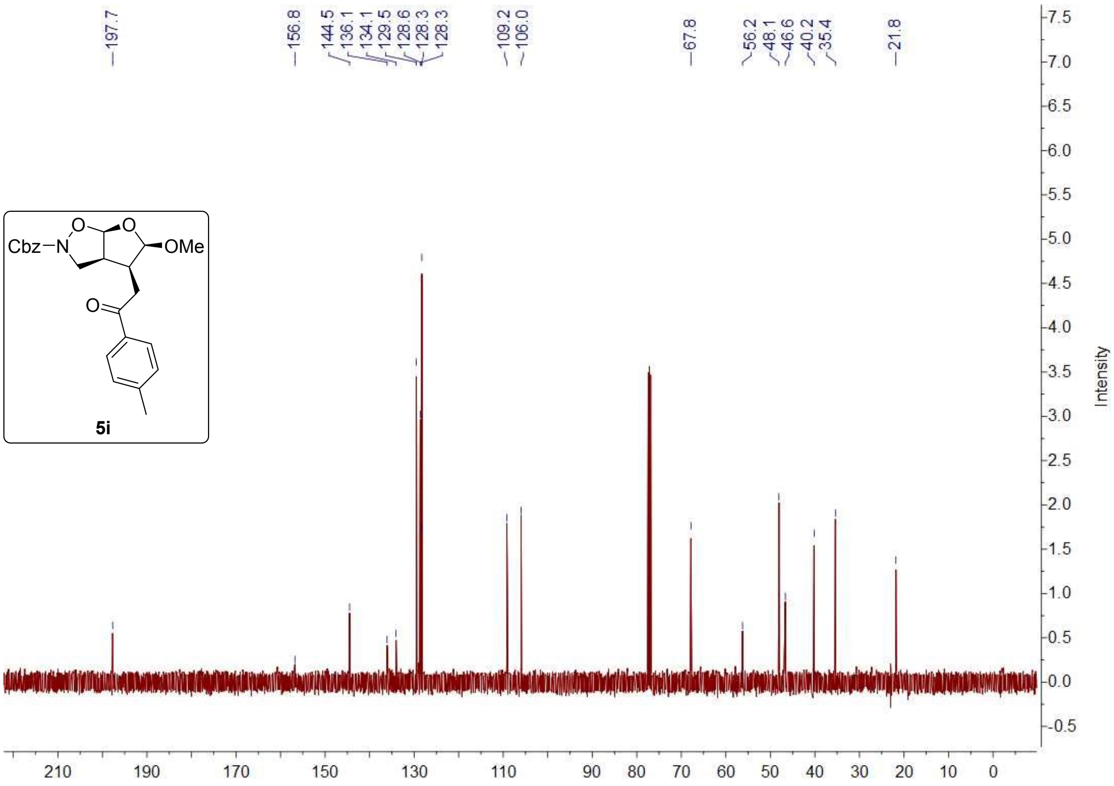


```
                    Chrom Type: Fixed WL Chromatogram, 260 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.            RT              Area             Area %          BC

  1          17.933            18364              0.566          BB
  2          22.660          3226365             99.434          BB

                               3244729            100.000
```

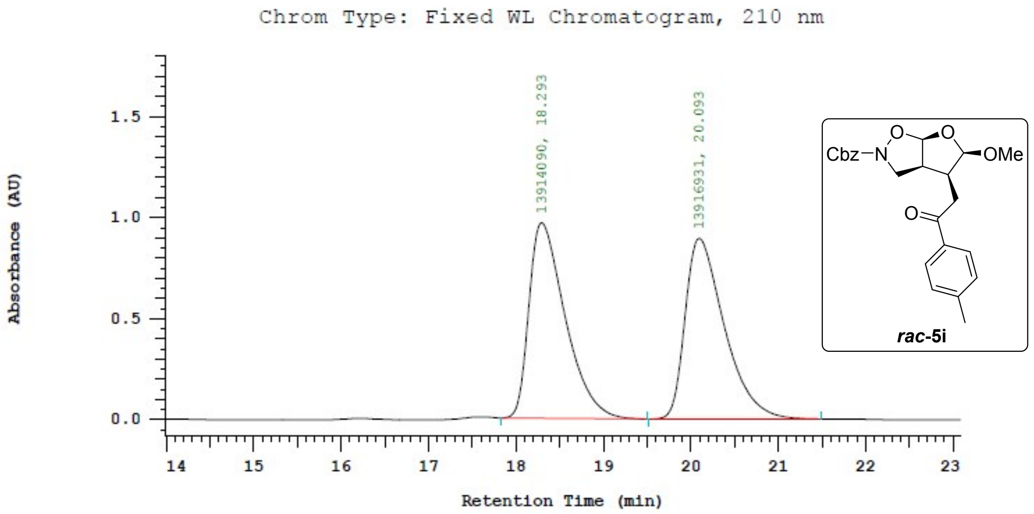
The ^{1}H NMR spectrum of 5i (400 MHz, $CDCl_3$)



The ^{13}C NMR spectrum of 5i (125 MHz, $CDCl_3$)



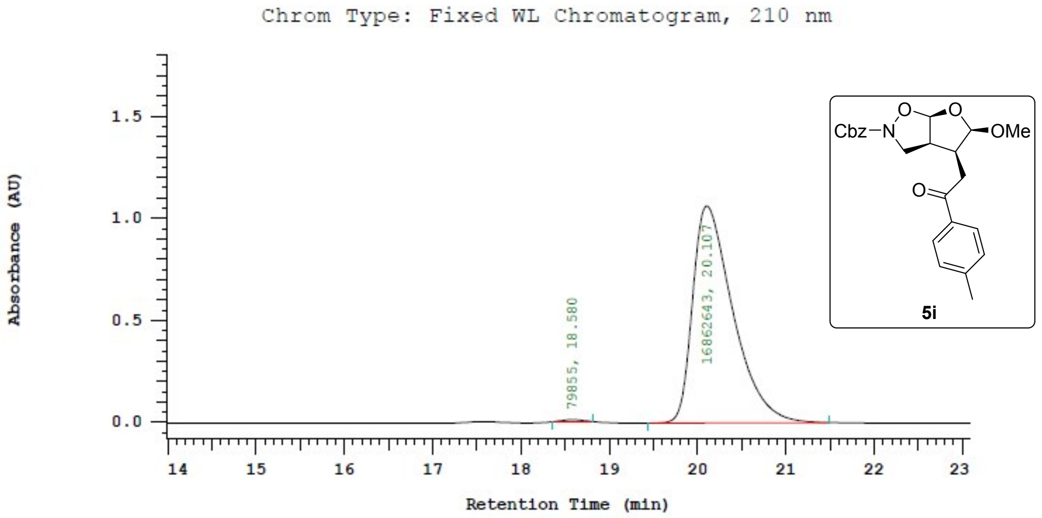
The HPLC of racemic 5i



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

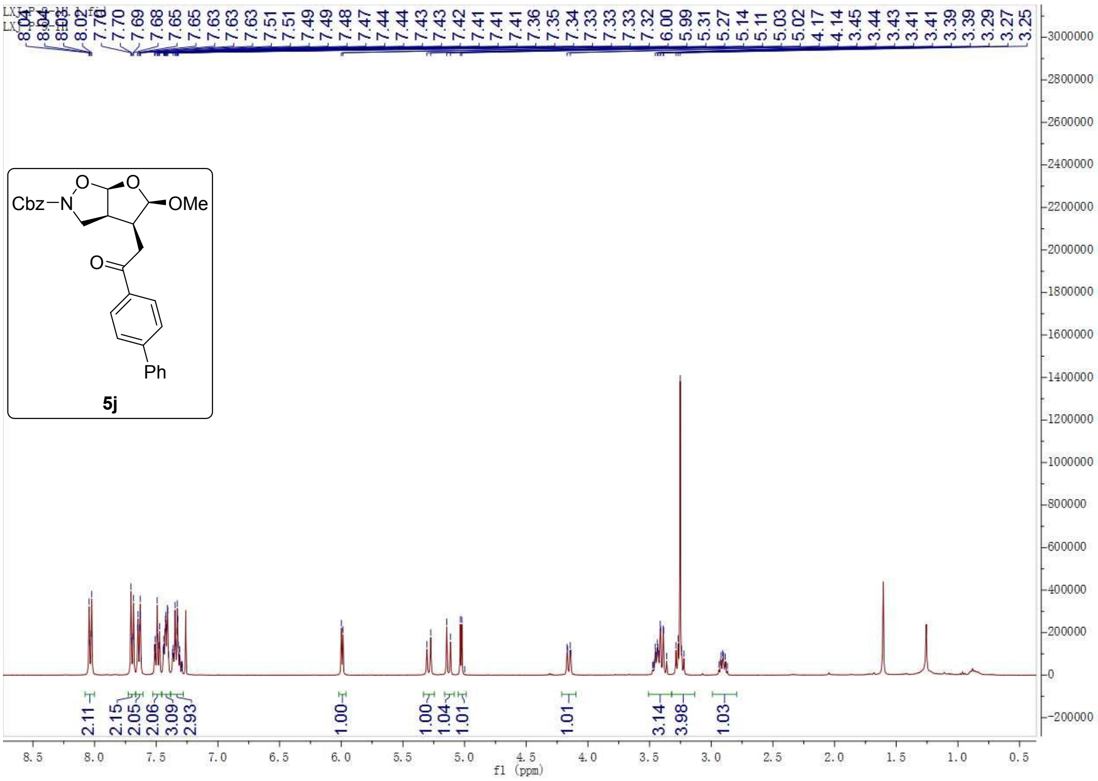
No.	RT	Area	Area %	BC
1	18.293	13914090	49.995	BB
2	20.093	13916931	50.005	BB
		27831021	100.000	

The HPLC of chiral 5i

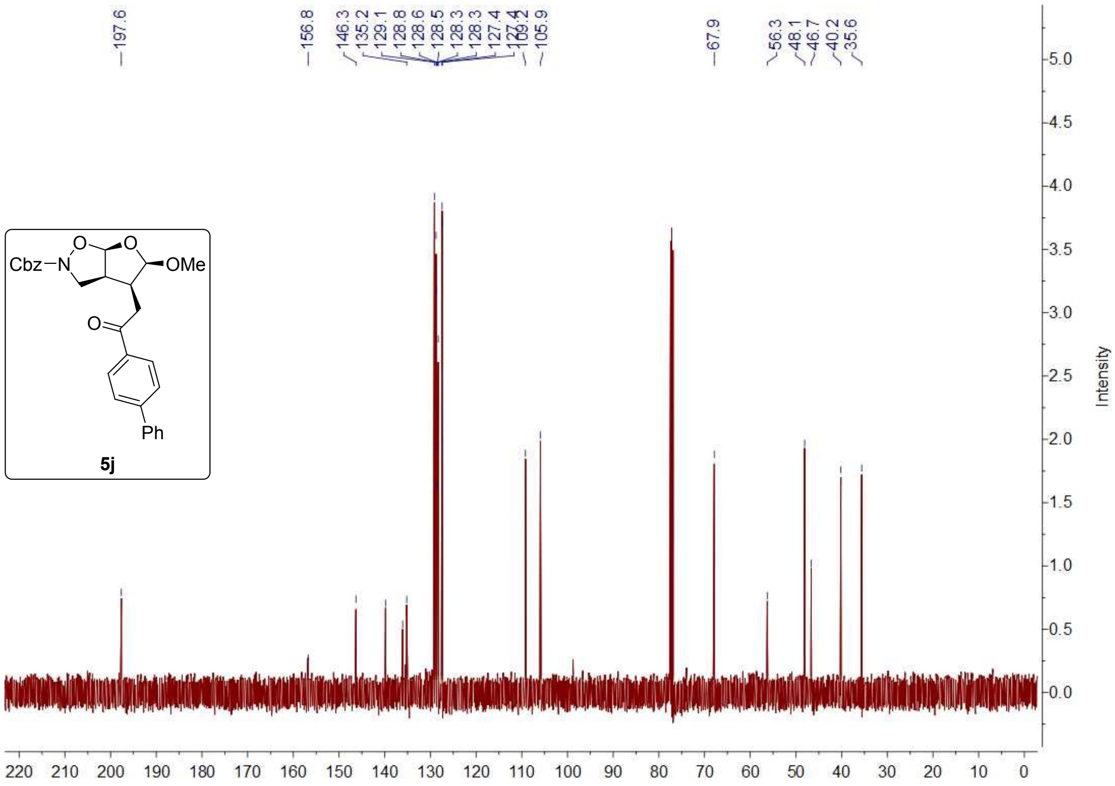


```
                        Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.              RT                 Area                 Area %            BC
-------------------------------------------------------------------------------
  1            18.580                79855                0.471            BB
  2            20.107             16862643               99.529            BB
-------------------------------------------------------------------------------
                                  16942498              100.000
-------------------------------------------------------------------------------
```

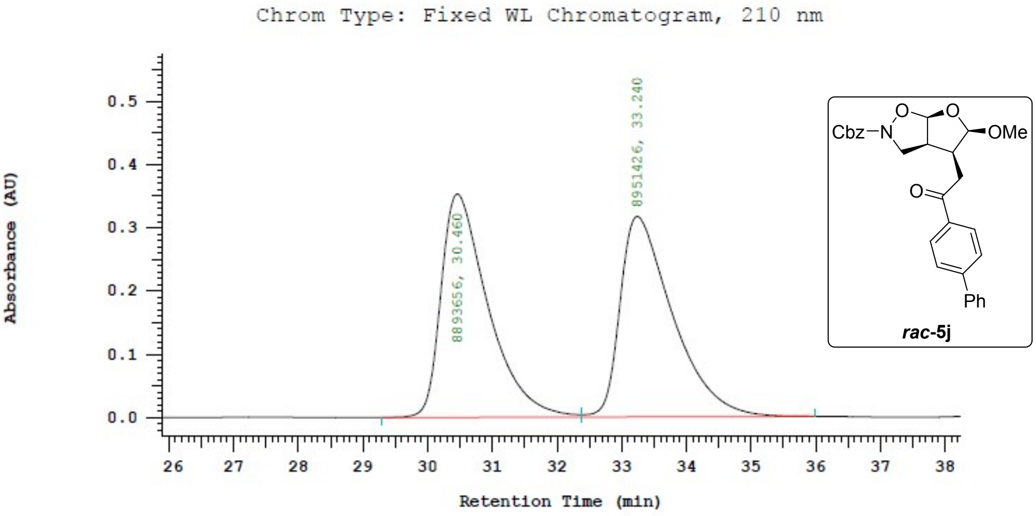
The ^{1}H NMR spectrum of 5j (400 MHz, $CDCl_3$)



The ^{13}C NMR spectrum of 5j (125 MHz, CDCl$_3$)



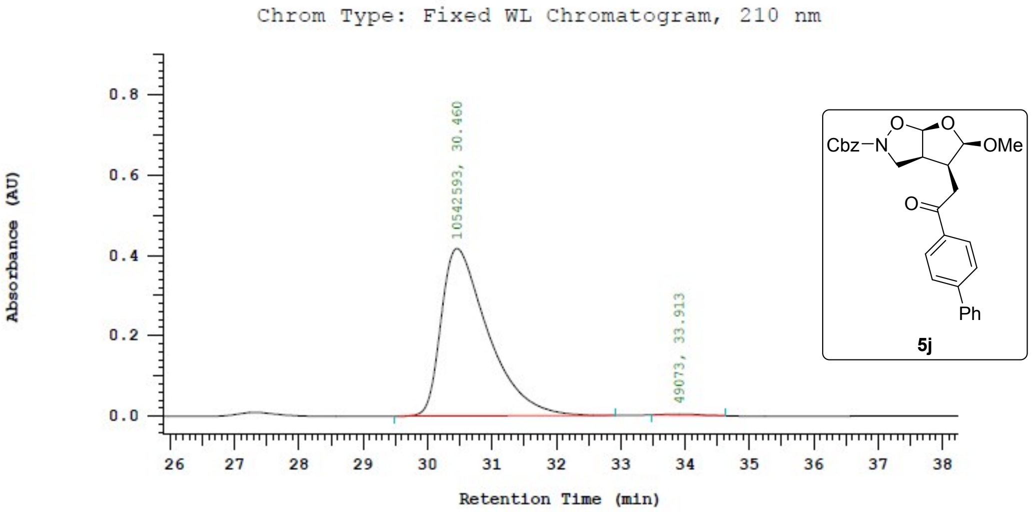
The HPLC of racemic 5j



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	30.460	8893656	49.838	BV
2	33.240	8951426	50.162	VB
		17845082	100.000	

The HPLC of chiral 5j



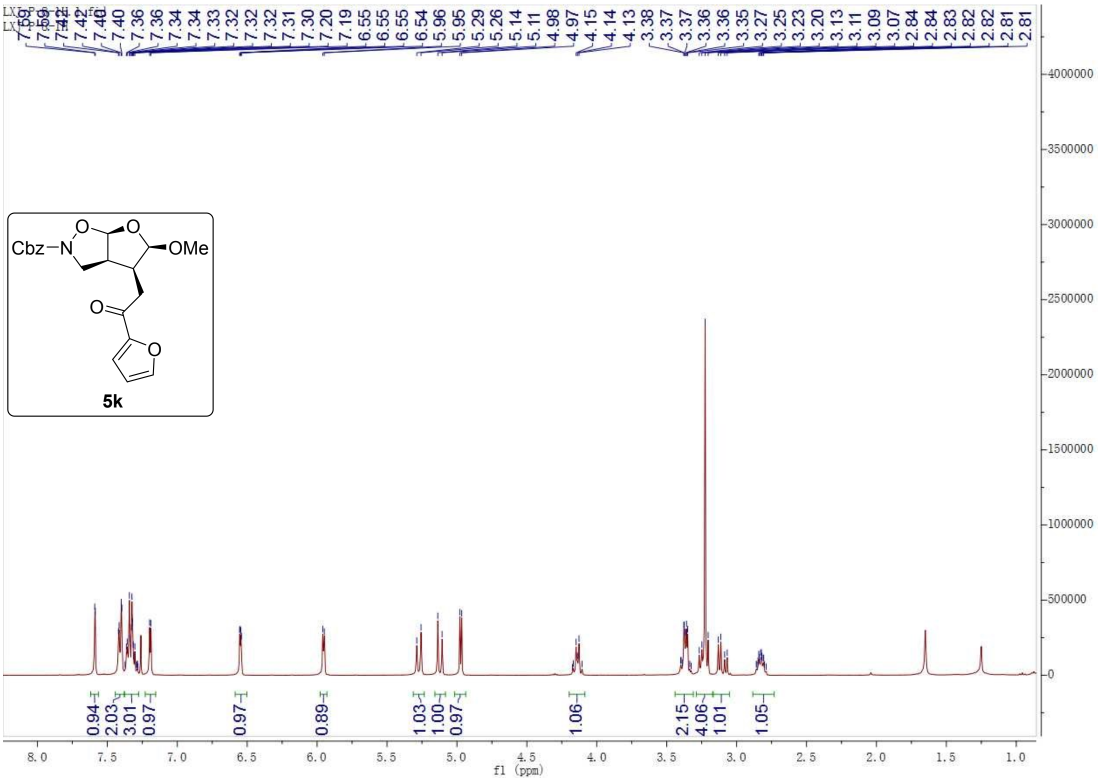
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

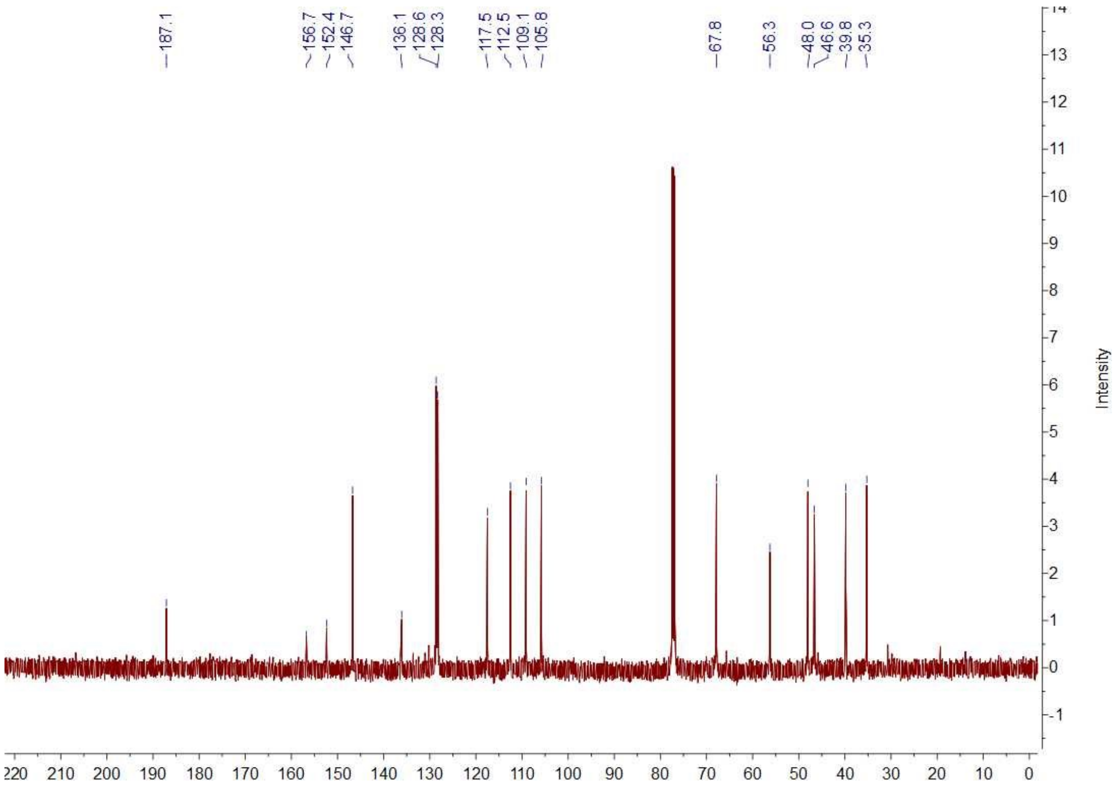
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	30.460	10542593	99.537	BB
2	33.913	49073	0.463	BB
		10591666	100.000	

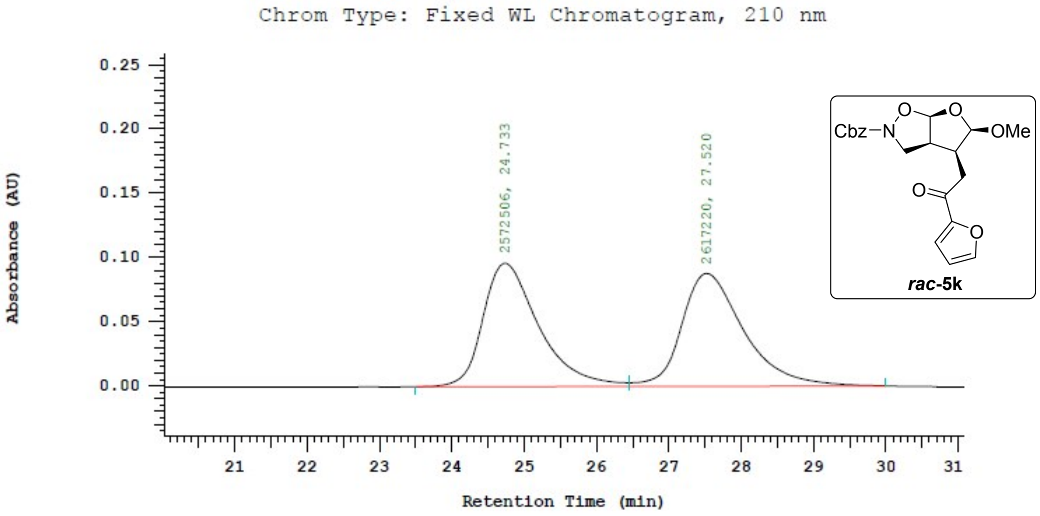
The ^{1}H NMR spectrum of 5k (400 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5k (125 MHz, CDCl$_3$)



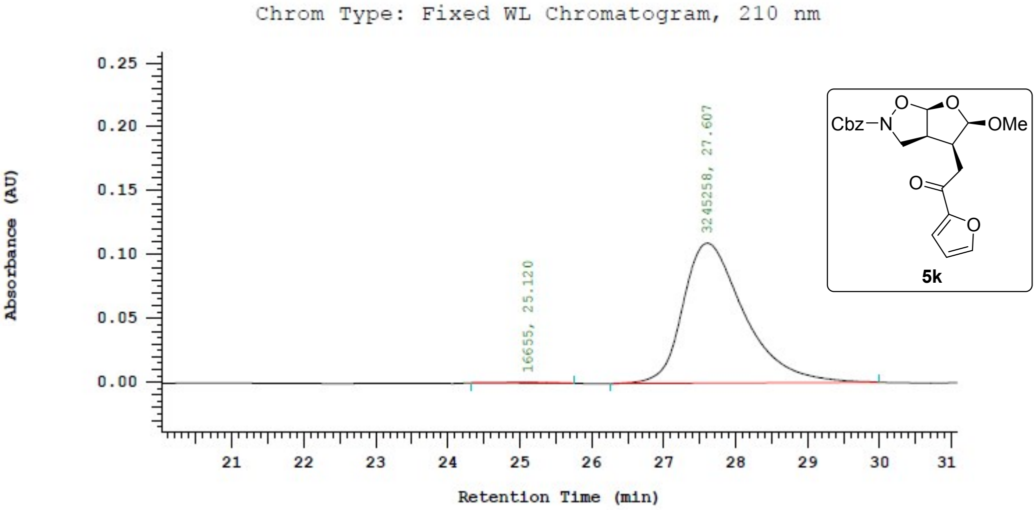
The HPLC of racemic 5k



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	24.733	2572506	49.569	BV
2	27.520	2617220	50.431	VB
		5189726	100.000	

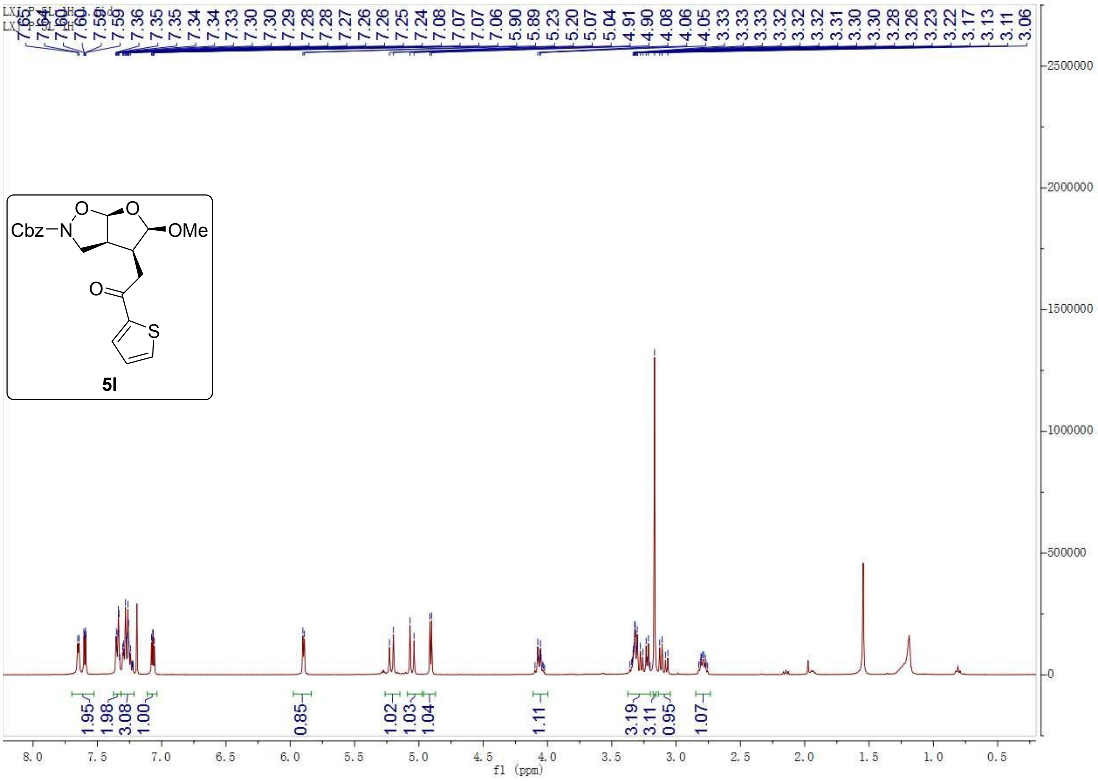
The HPLC of chiral 5k



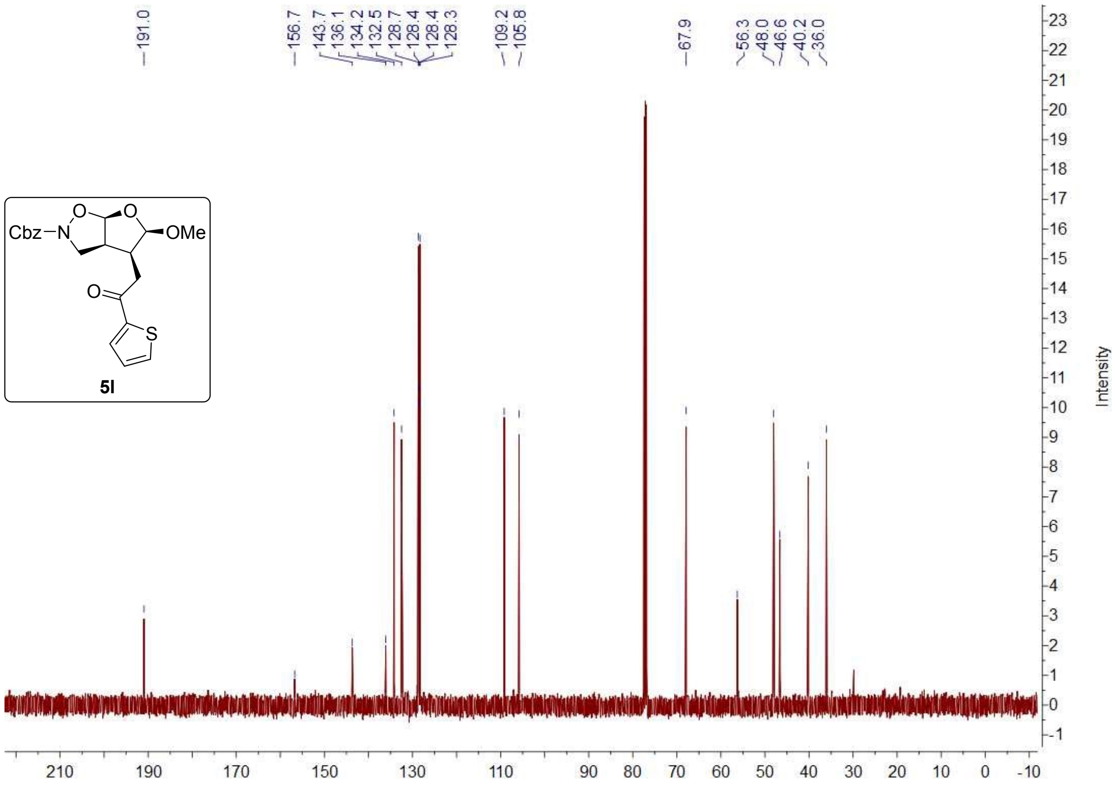
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	25.120	16655	0.511	BB
2	27.607	3245258	99.489	BB
		3261913	100.000	

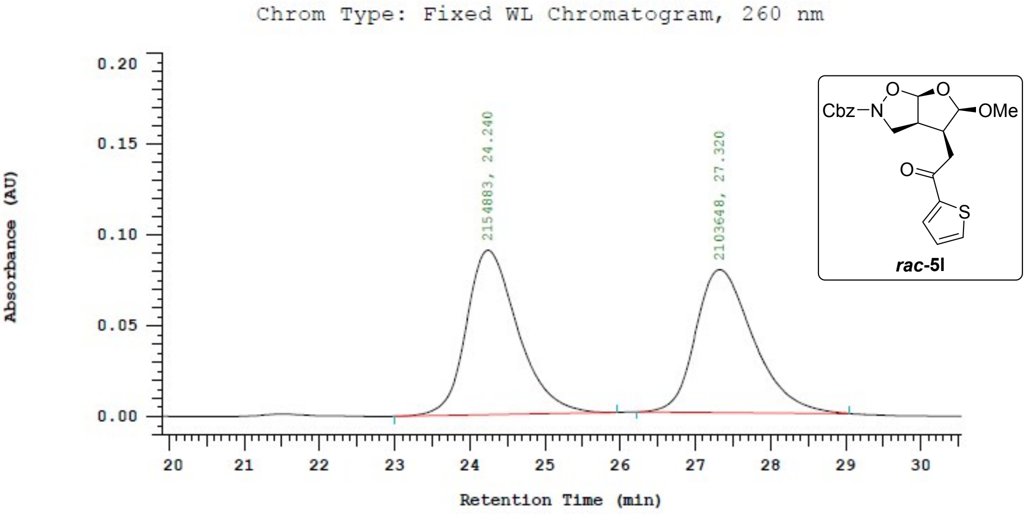
The ^{1}H NMR spectrum of 5l (400 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5l (125 MHz, CDCl$_3$)



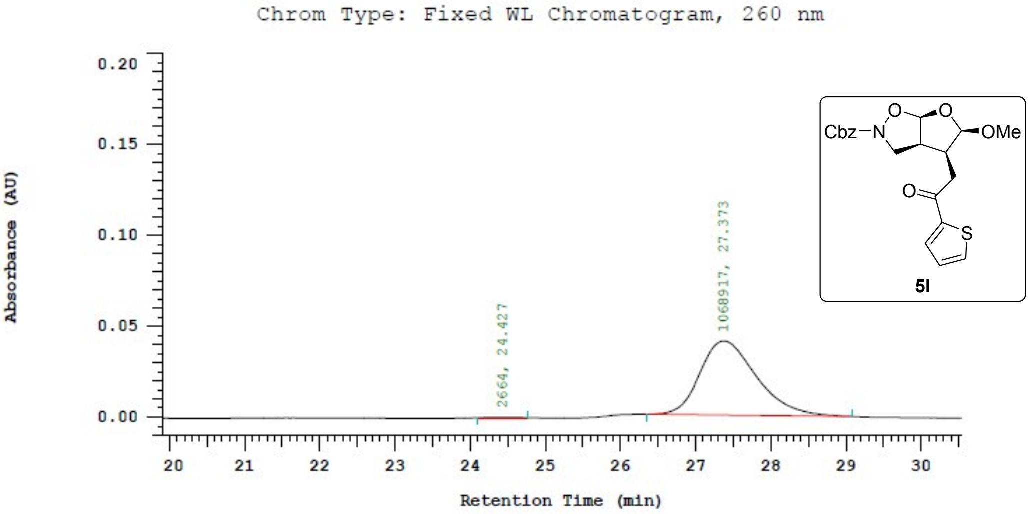
The HPLC of racemic 5l



Chrom Type: Fixed WL Chromatogram, 260 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	24.240	2154883	50.602	BB
2	27.320	2103648	49.398	BB
		4258531	100.000	

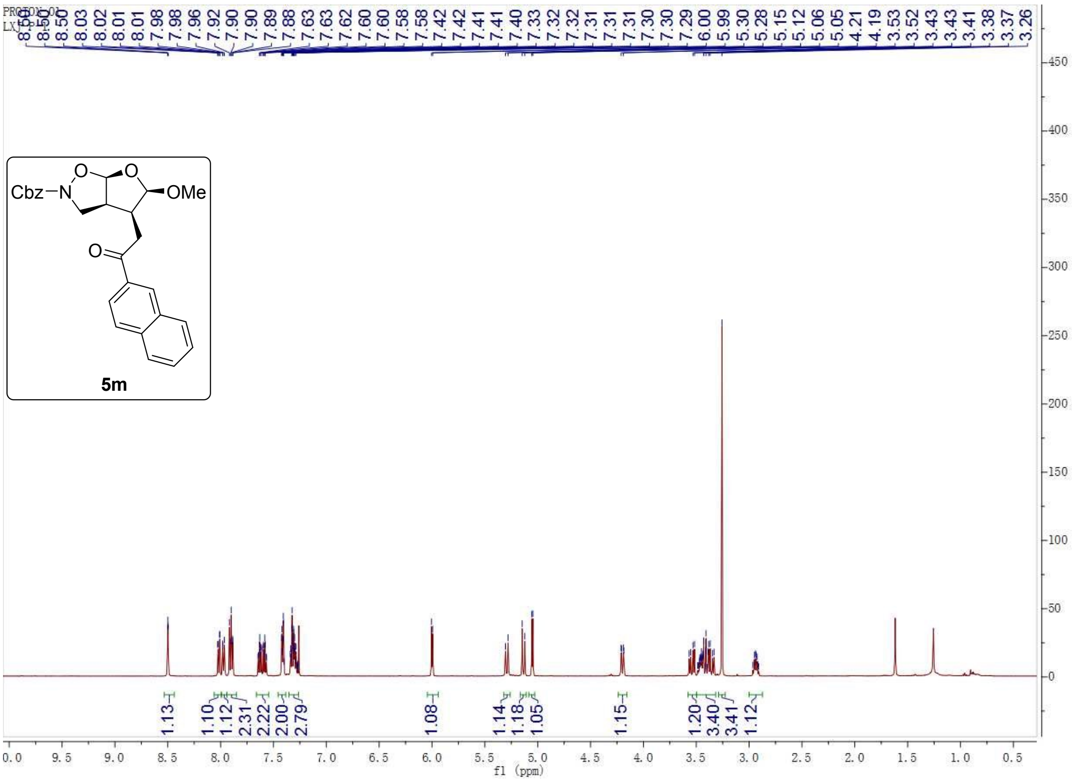
The HPLC of chiral 5l



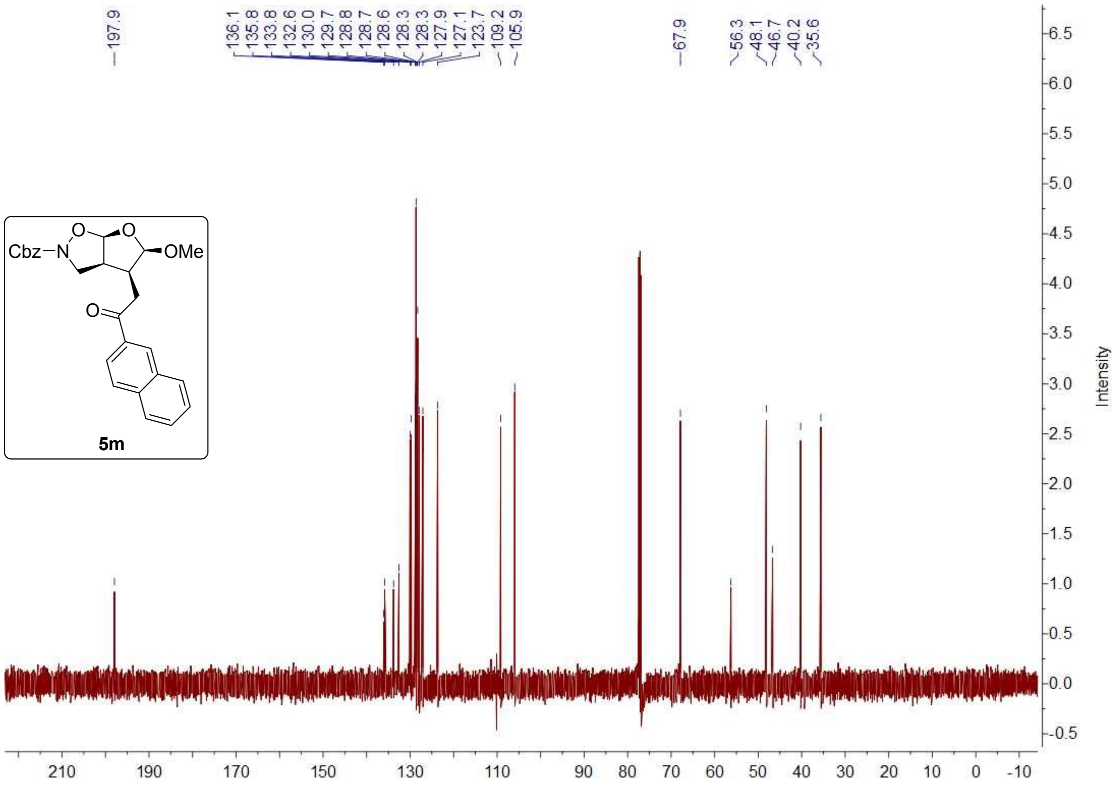
Chrom Type: Fixed WL Chromatogram, 260 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	24.427	2664	0.249	BB
2	27.373	1068917	99.751	BB
		1071581	100.000	

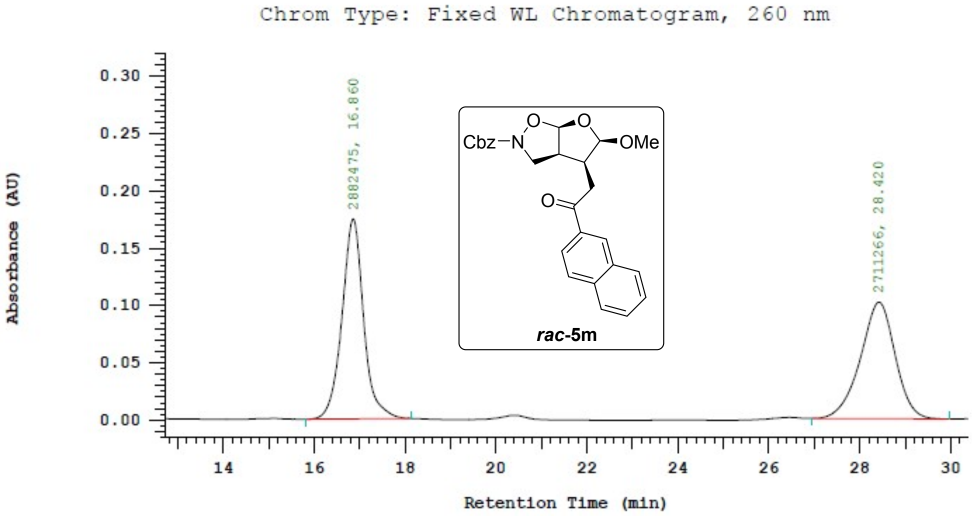
The ^{1}H NMR spectrum of 5m (500 MHz, $CDCl_3$)



The ^{13}C NMR spectrum of 5m (125 MHz, CDCl$_3$)



The HPLC of racemic 5m

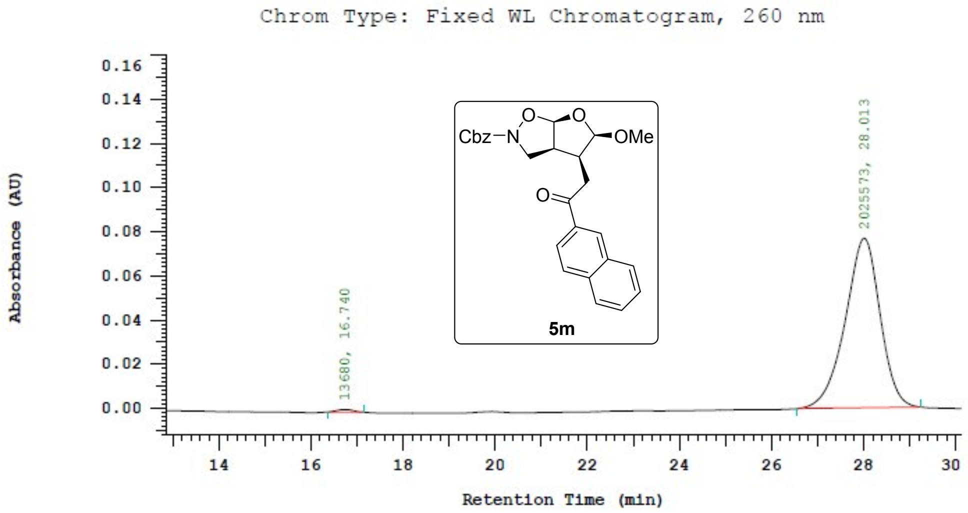


Chrom Type: Fixed WL Chromatogram, 260 nm

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	16.860	2882475	51.530	BB
2	28.420	2711266	48.470	BB
		5593741	100.000	

The HPLC of chiral 5m



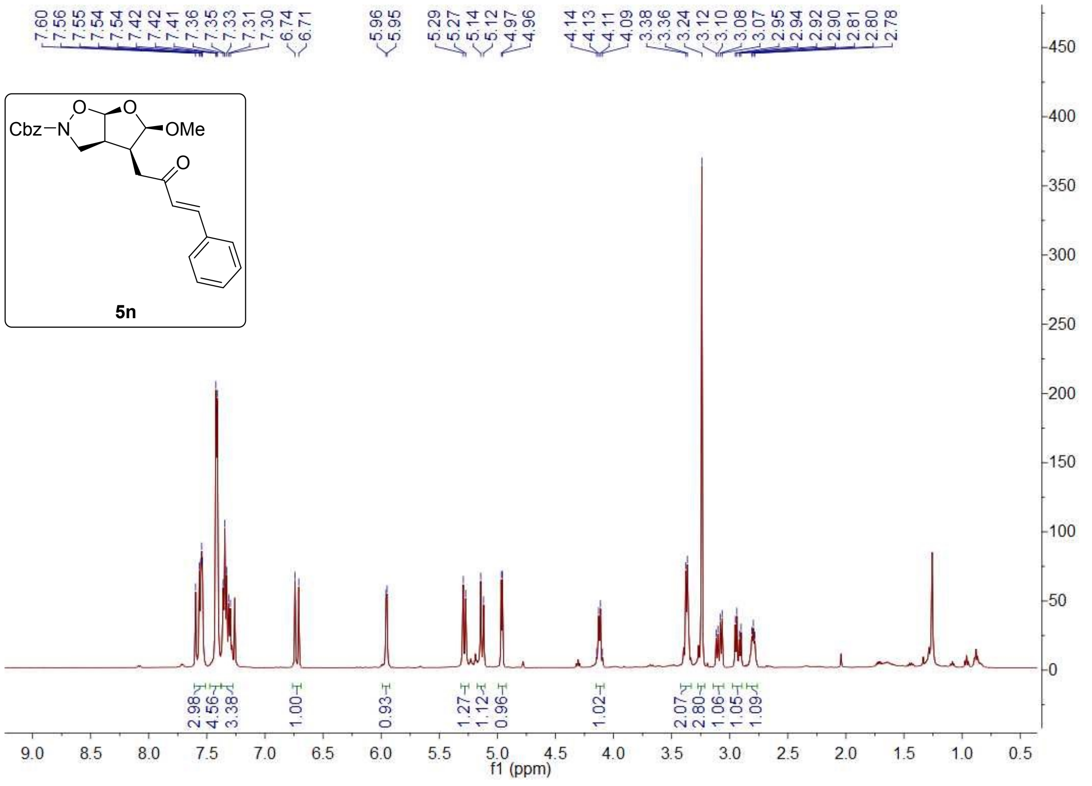
Chrom Type: Fixed WL Chromatogram, 260 nm

Peak Quantitation: AREA

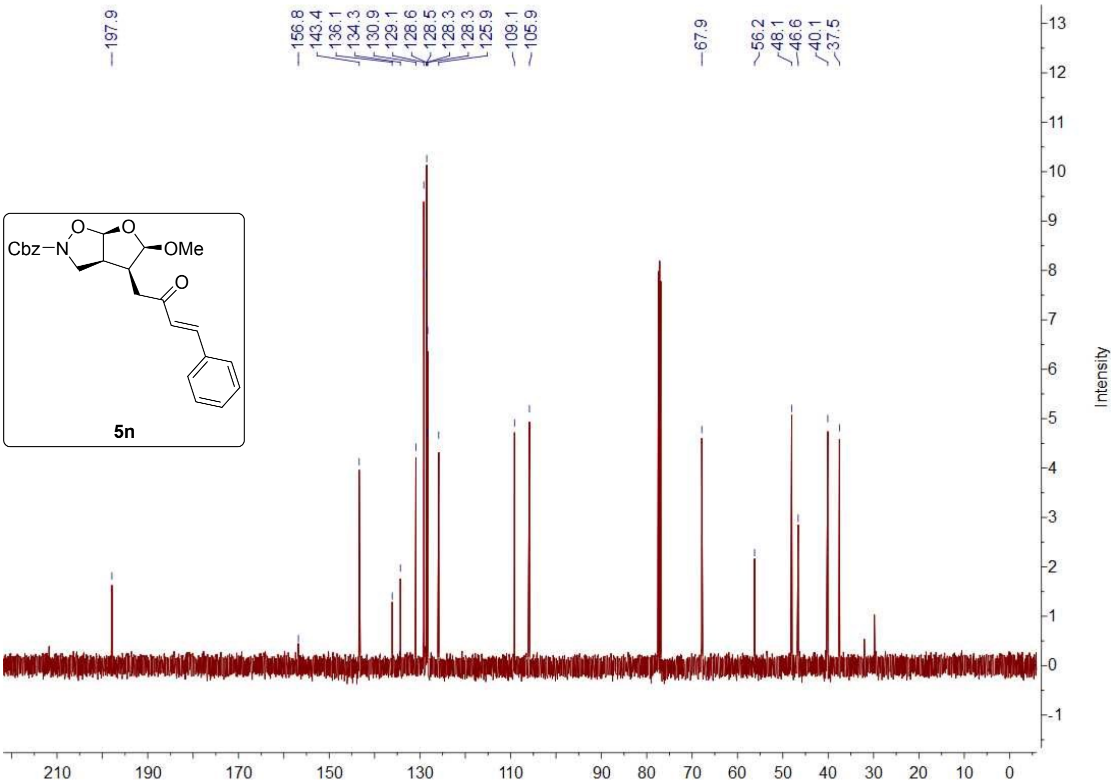
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	16.740	13680	0.671	BB
2	28.013	2025573	99.329	BB
		2039253	100.000	

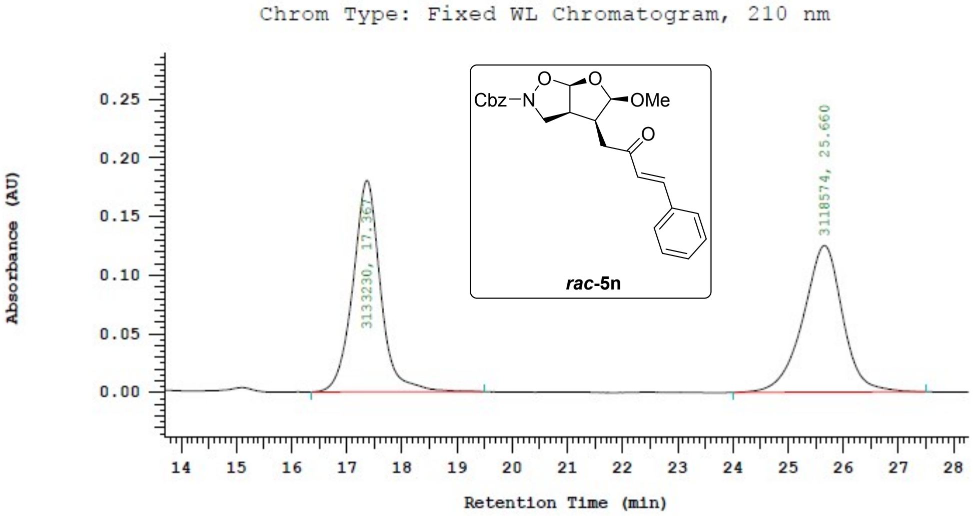
The ^{1}H NMR spectrum of 5n (500 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5n (125 MHz, $CDCl_3$)



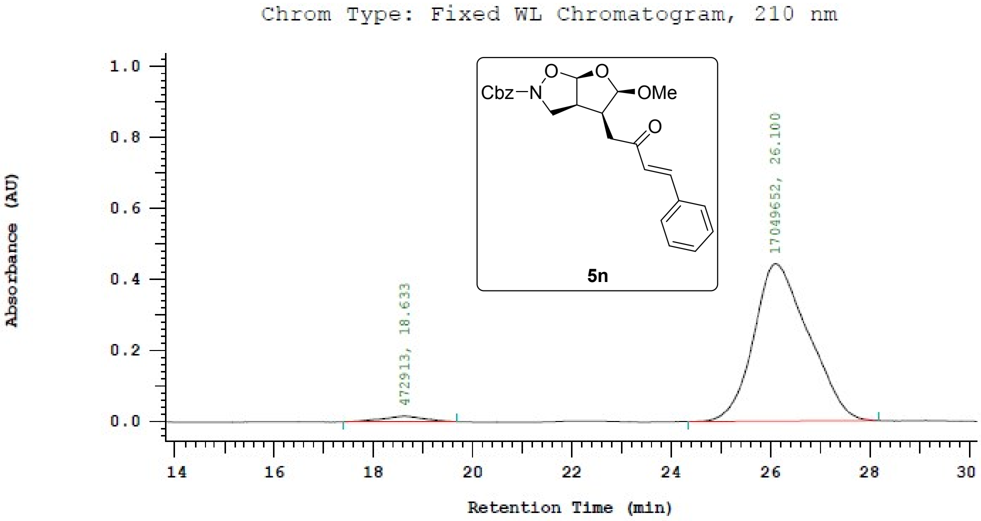
The HPLC of racemic 5n



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	17.367	3133230	50.117	BB
2	25.660	3118574	49.883	BB
		6251804	100.000	

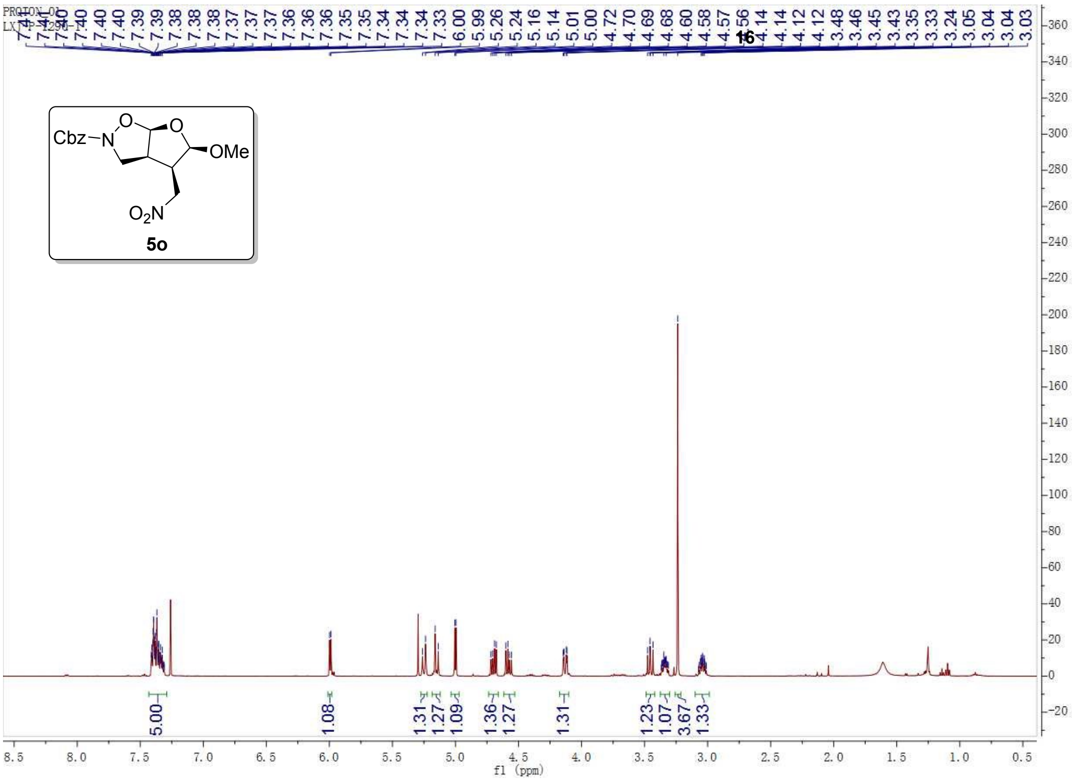
The HPLC of chiral 5n



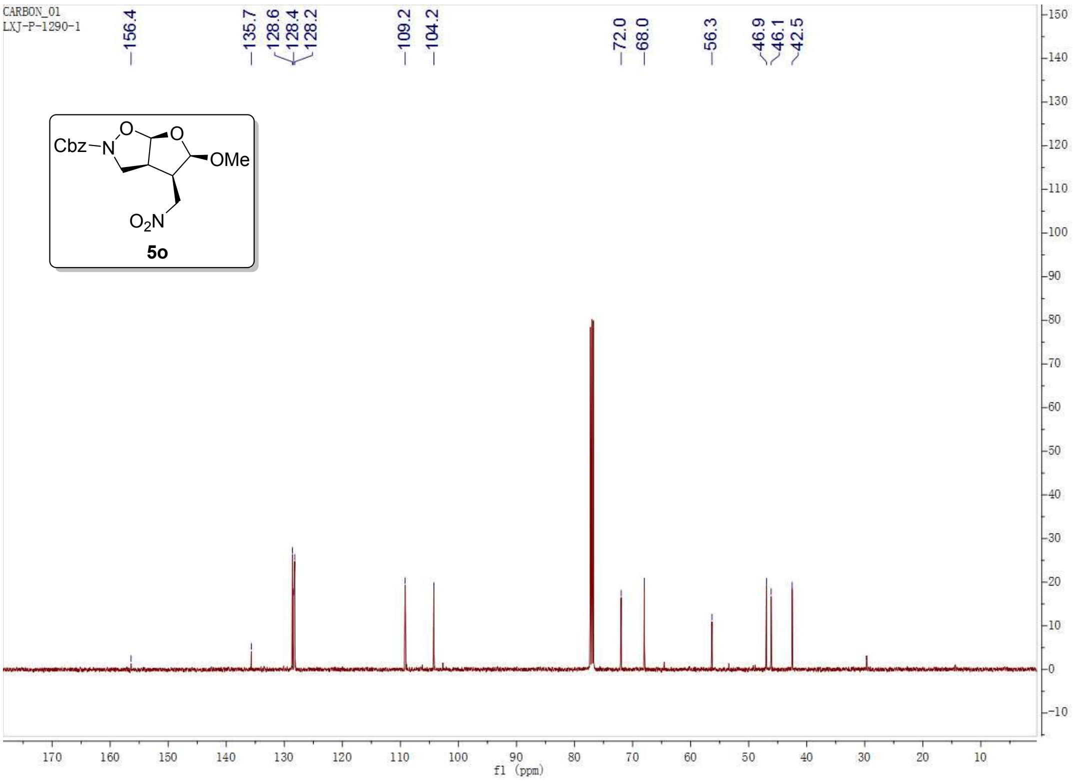
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	18.633	472913	2.699	BB
2	26.100	17049652	97.301	BB
		17522565	100.000	

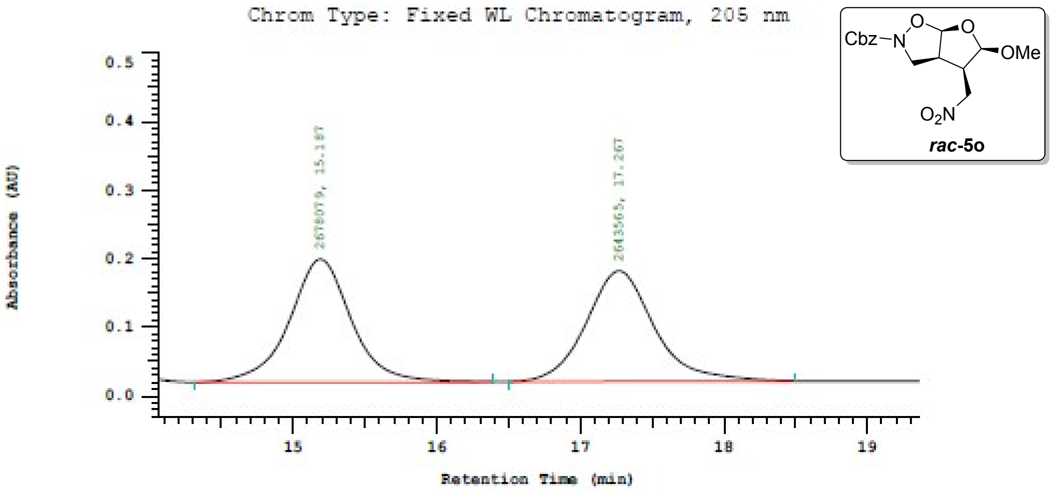
The ^{1}H NMR spectrum of 5o (500 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 5o (125 MHz, CDCl$_3$)

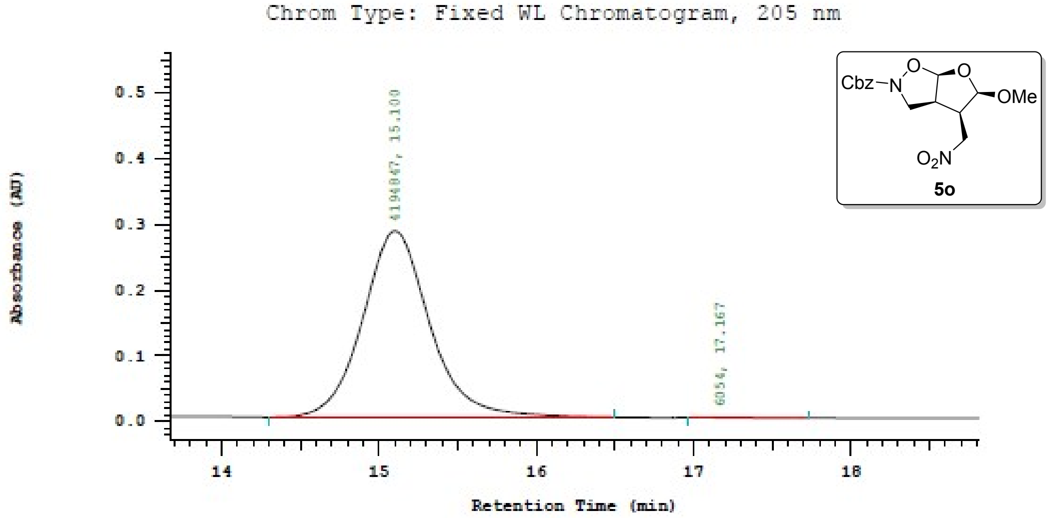


The HPLC of racemic 5o



```
                    Chrom Type: Fixed WL Chromatogram, 205 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.              RT               Area              Area %            BC

 1             15.187            2678079            50.324            BB
 2             17.267            2643565            49.676            BB

                                 5321644           100.000
```

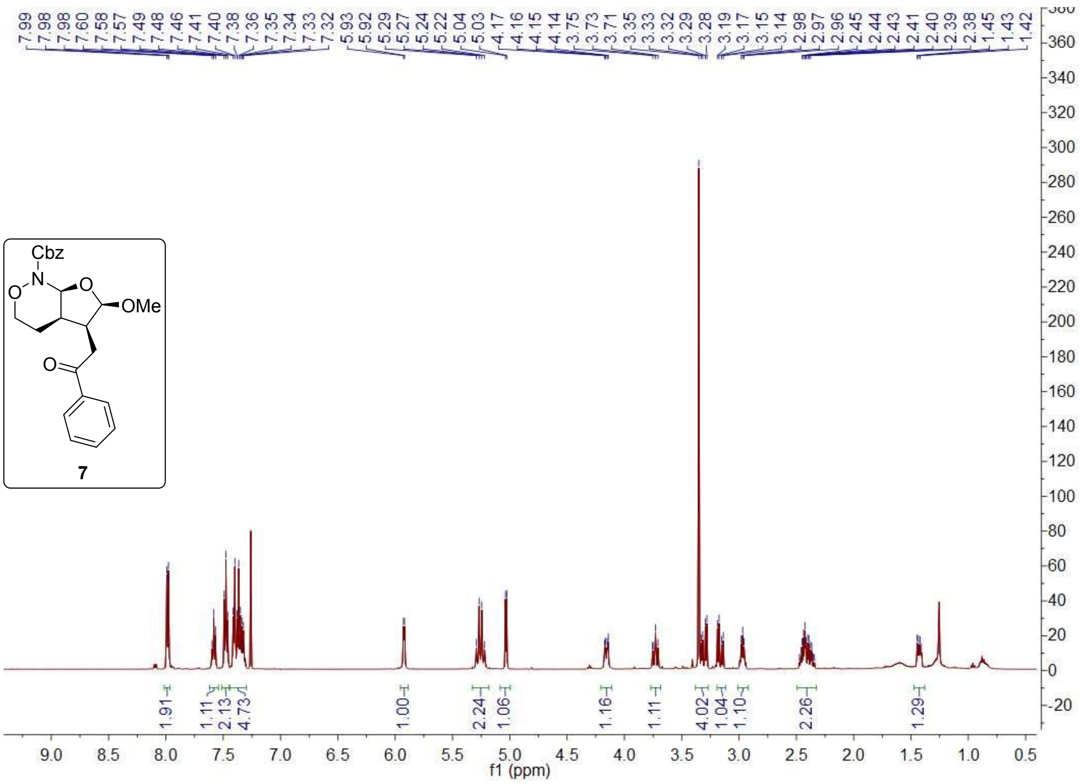
The HPLC of chiral 5o



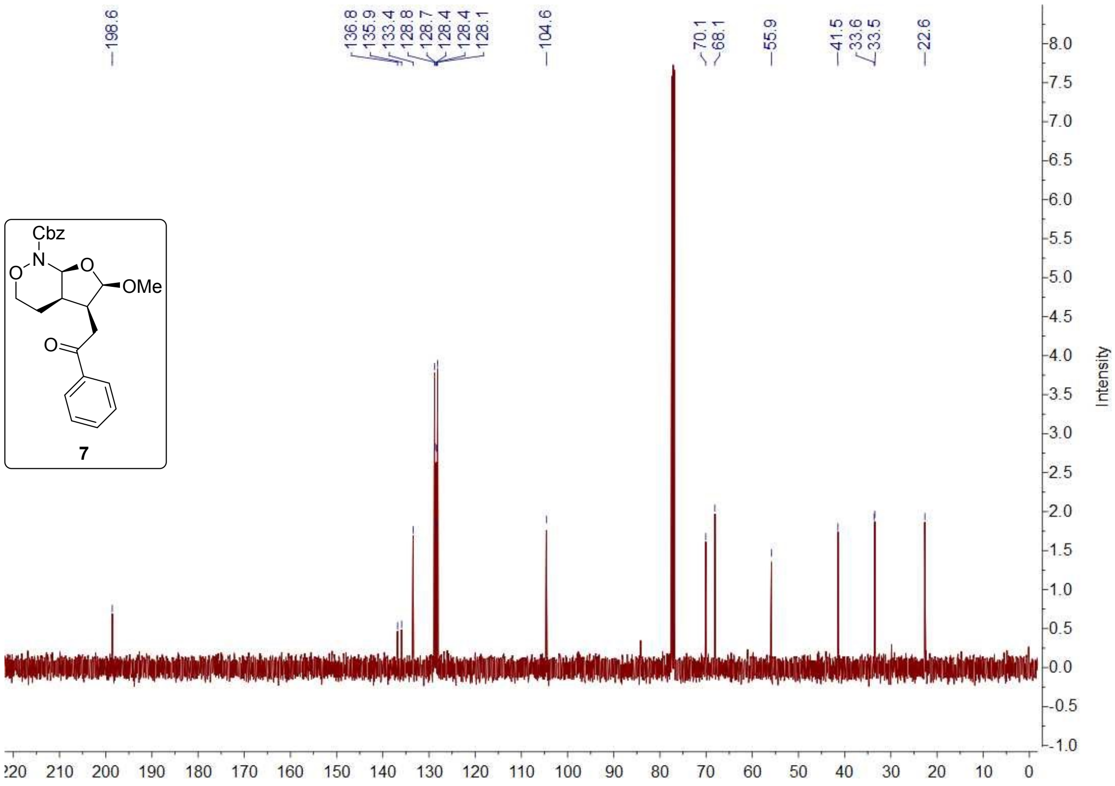
```
                    Chrom Type: Fixed WL Chromatogram, 205 nm
Peak Quantitation: AREA
Calculation Method: AREA%
```

No.	RT	Area	Area %	BC
1	15.100	4194847	99.856	BB
2	17.167	6054	0.144	BB
		4200901	100.000	

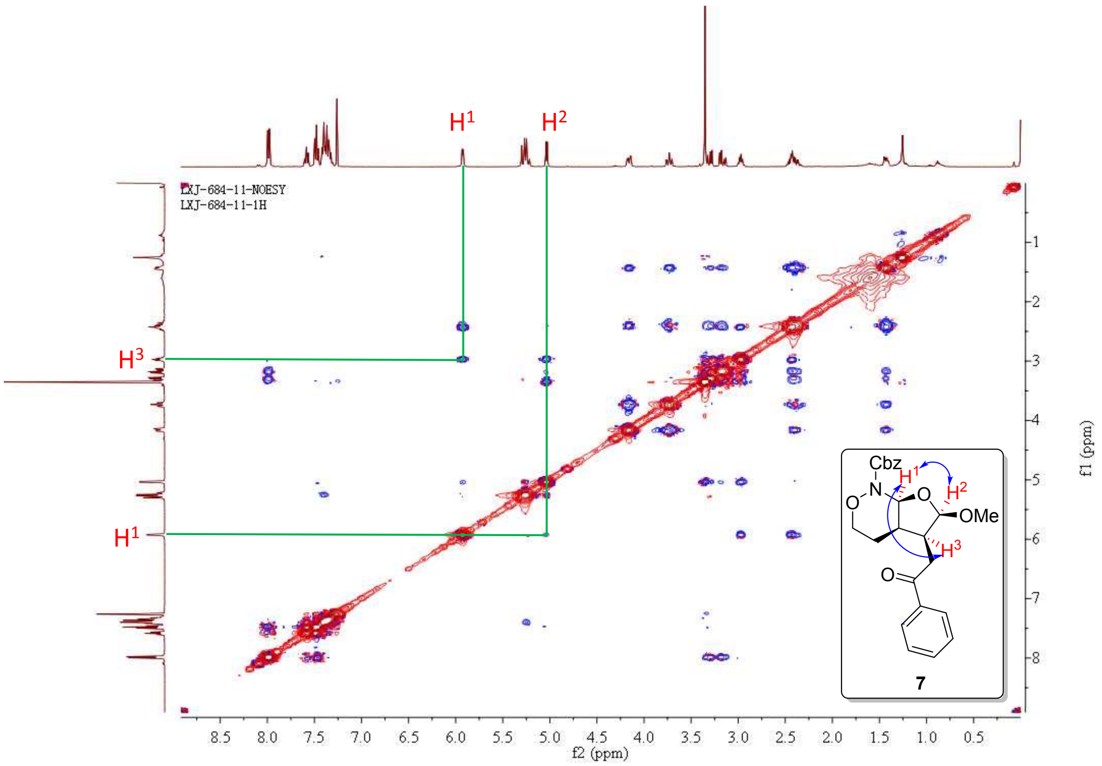
The ^{1}H NMR spectrum of 7 (500 MHz, $CDCl_3$)



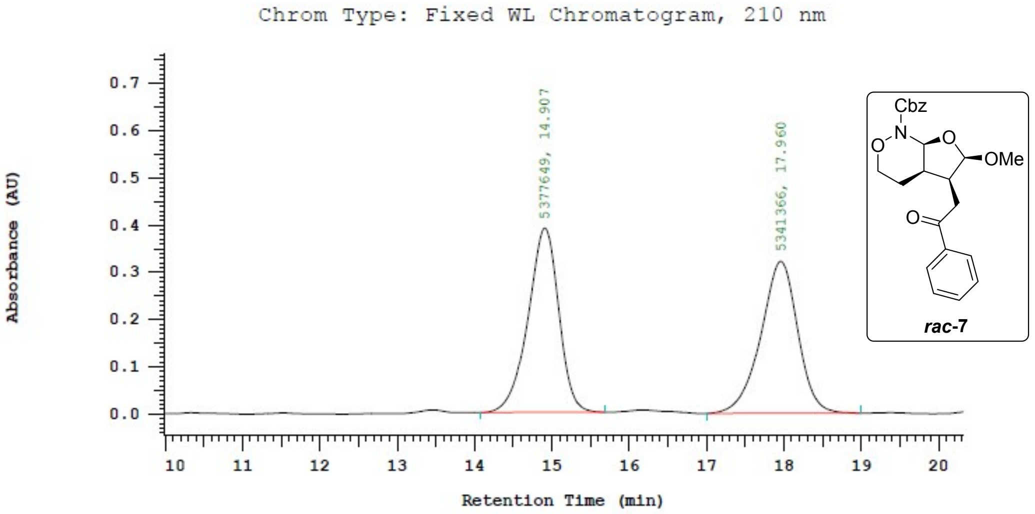
The ^{13}C NMR spectrum of 7 (125 MHz, CDCl$_3$)



The NOESY spectrum of 7 (400 MHz, CDCl$_3$)



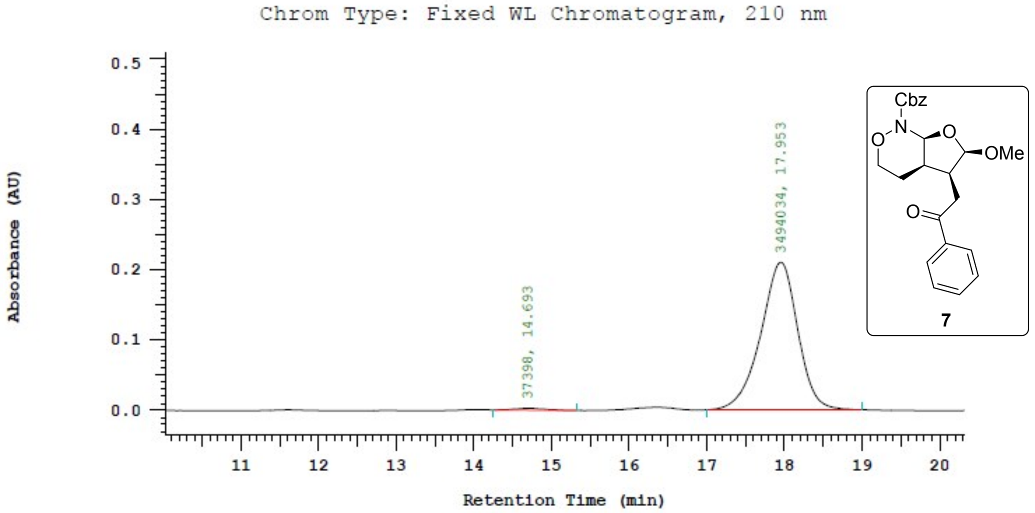
The HPLC of racemic 7



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	14.907	5377649	50.169	BB
2	17.960	5341366	49.831	BB
		10719015	100.000	

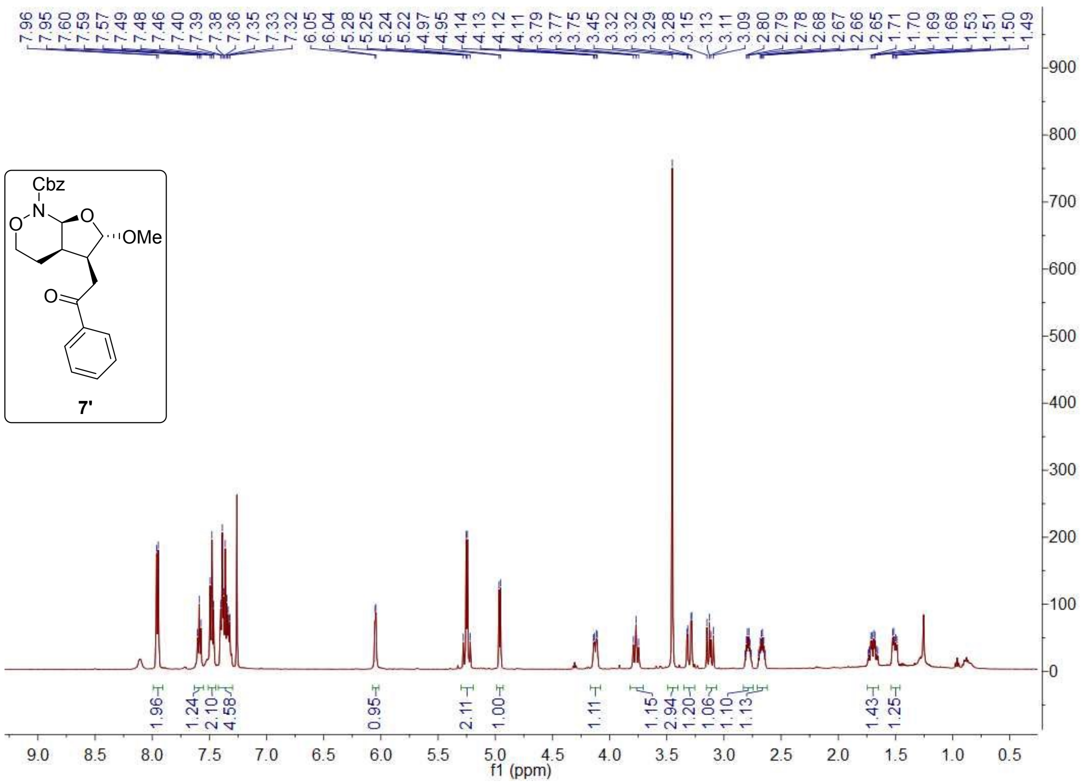
The HPLC of chiral 7



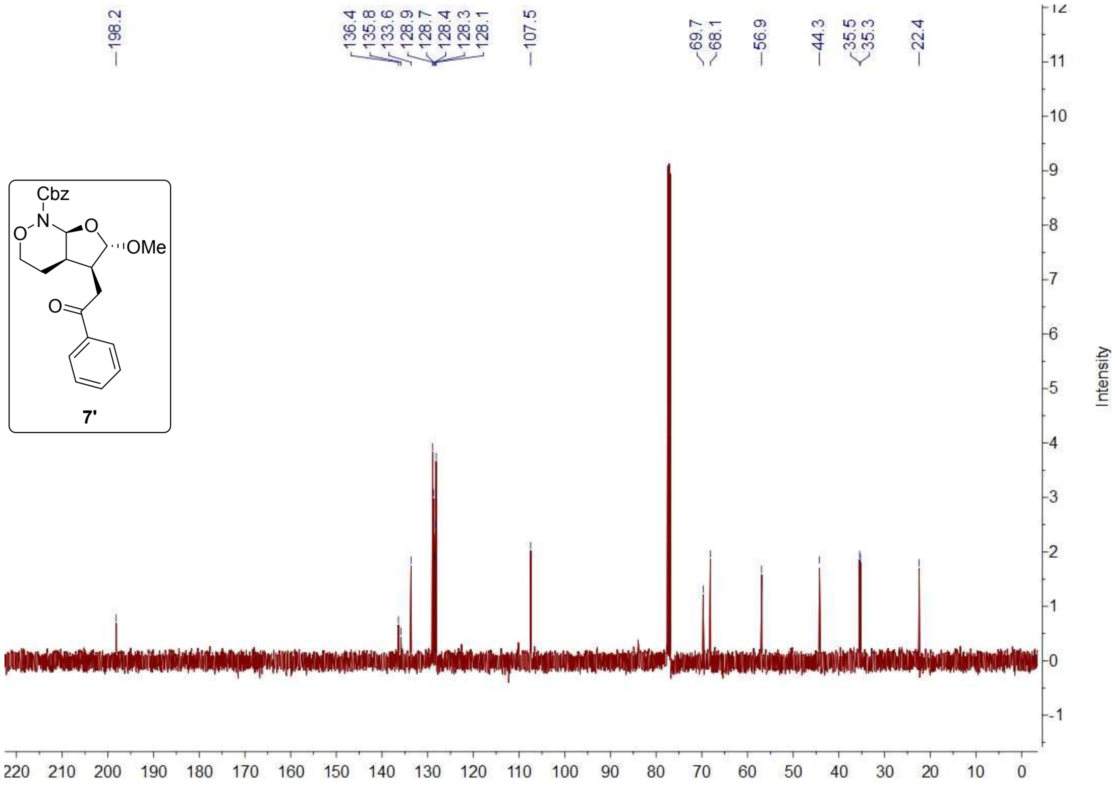
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	14.693	37398	1.059	BB
2	17.953	3494034	98.941	BB
		3531432	100.000	

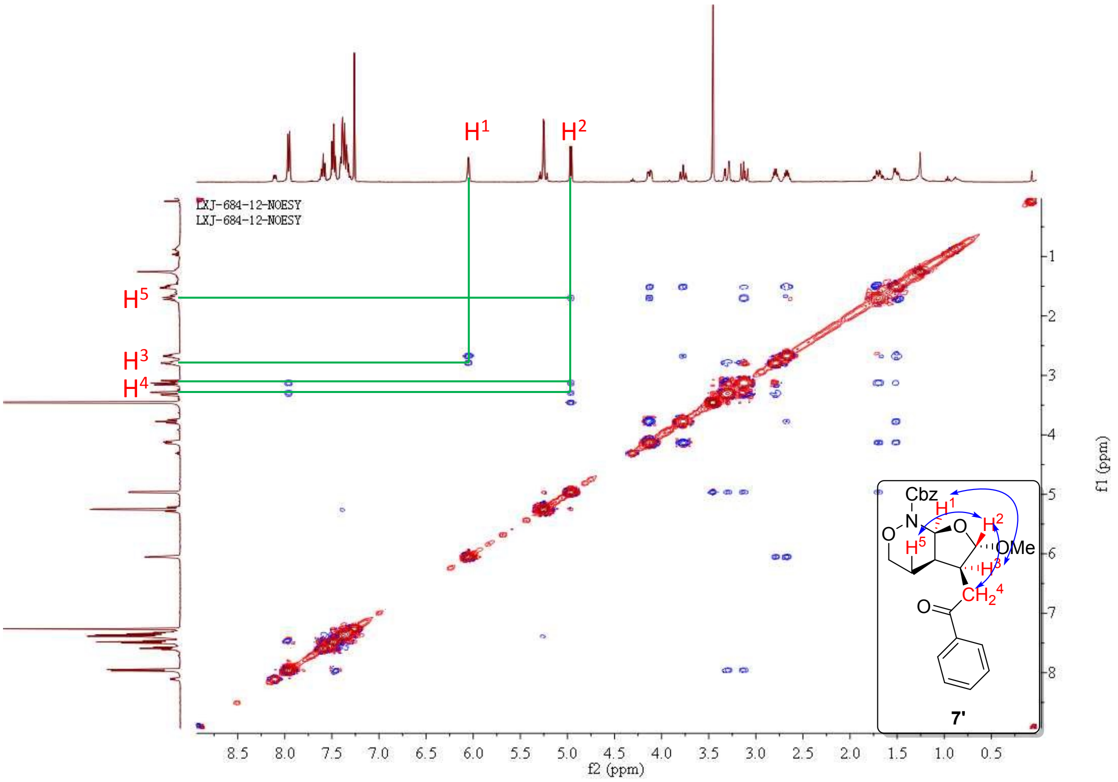
The ^{1}H NMR spectrum of 7' (500 MHz, $CDCl_3$)



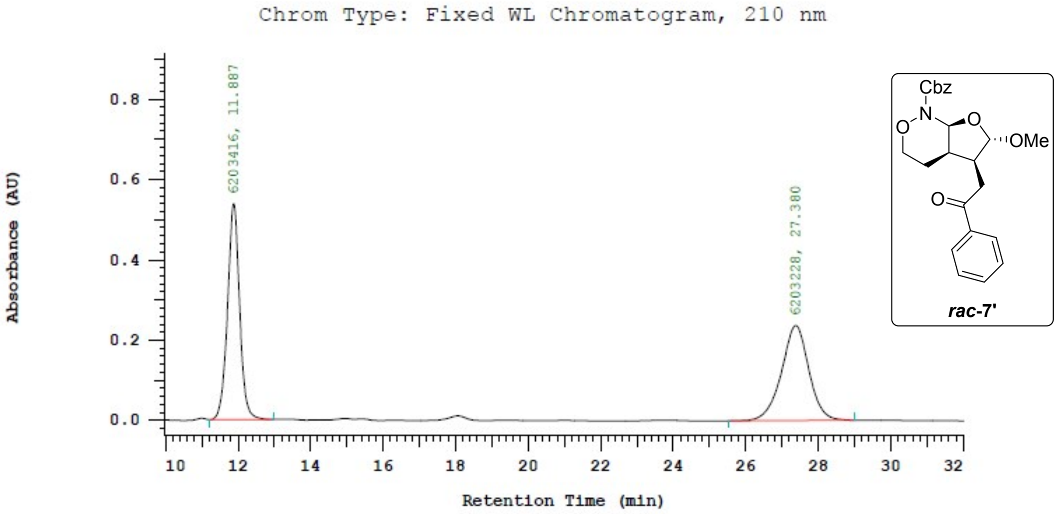
The ^{13}C NMR spectrum of 7' (125 MHz, $CDCl_3$)



The NOESY spectrum of 7' (400 MHz, $CDCl_3$)

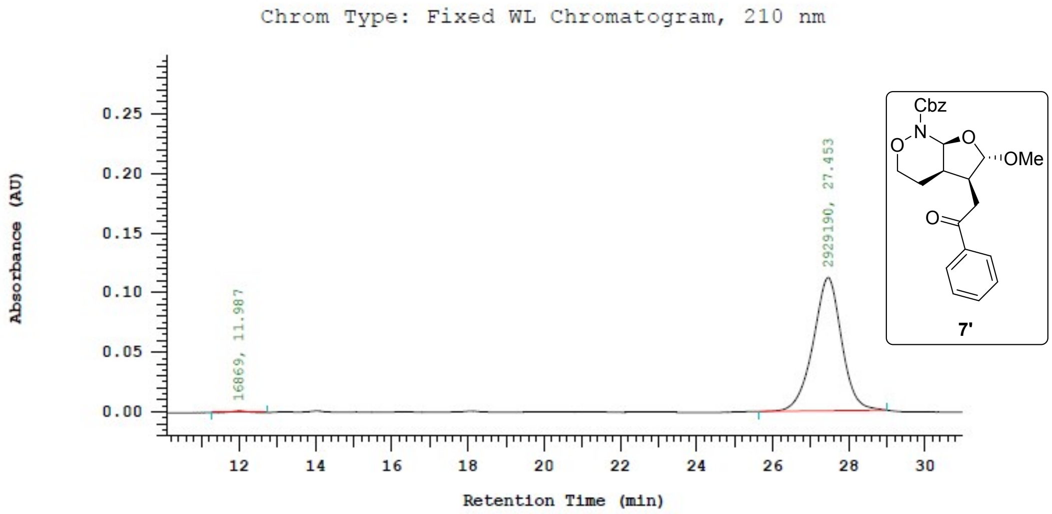


The HPLC of racemic 7'



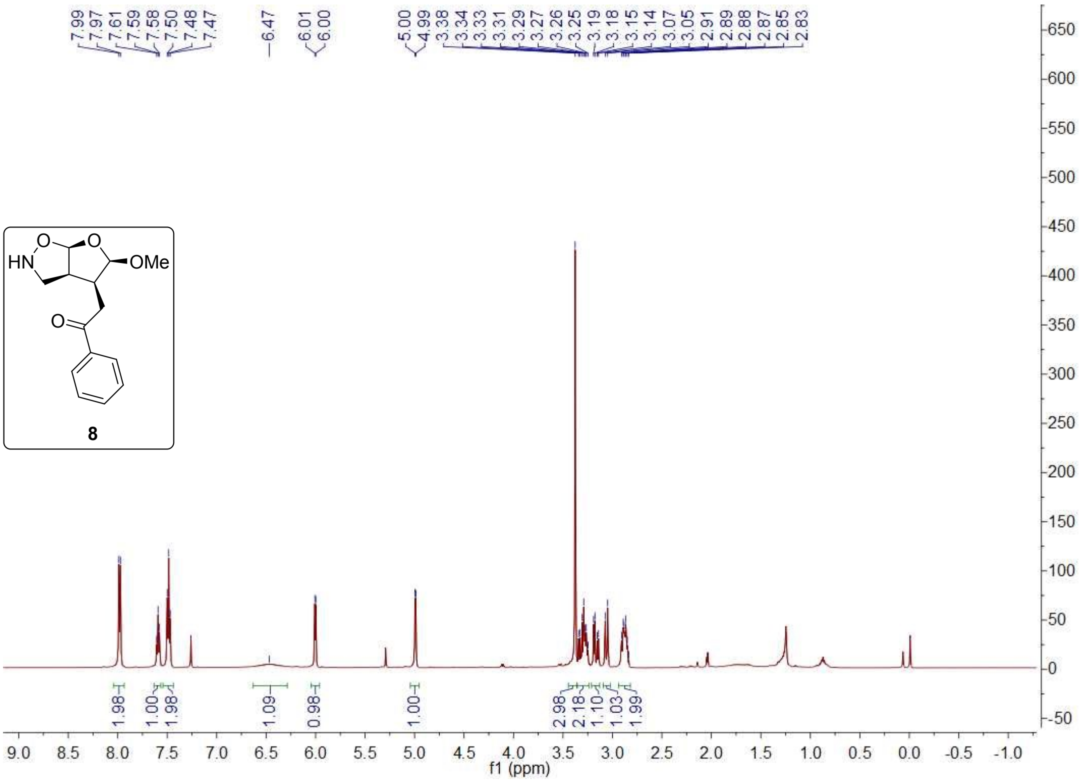
```
                Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.          RT              Area             Area %           BC

  1        11.887          6203416           50.001           BB
  2        27.380          6203228           49.999           BB

                          12406644          100.000
```

The HPLC of chiral 7'

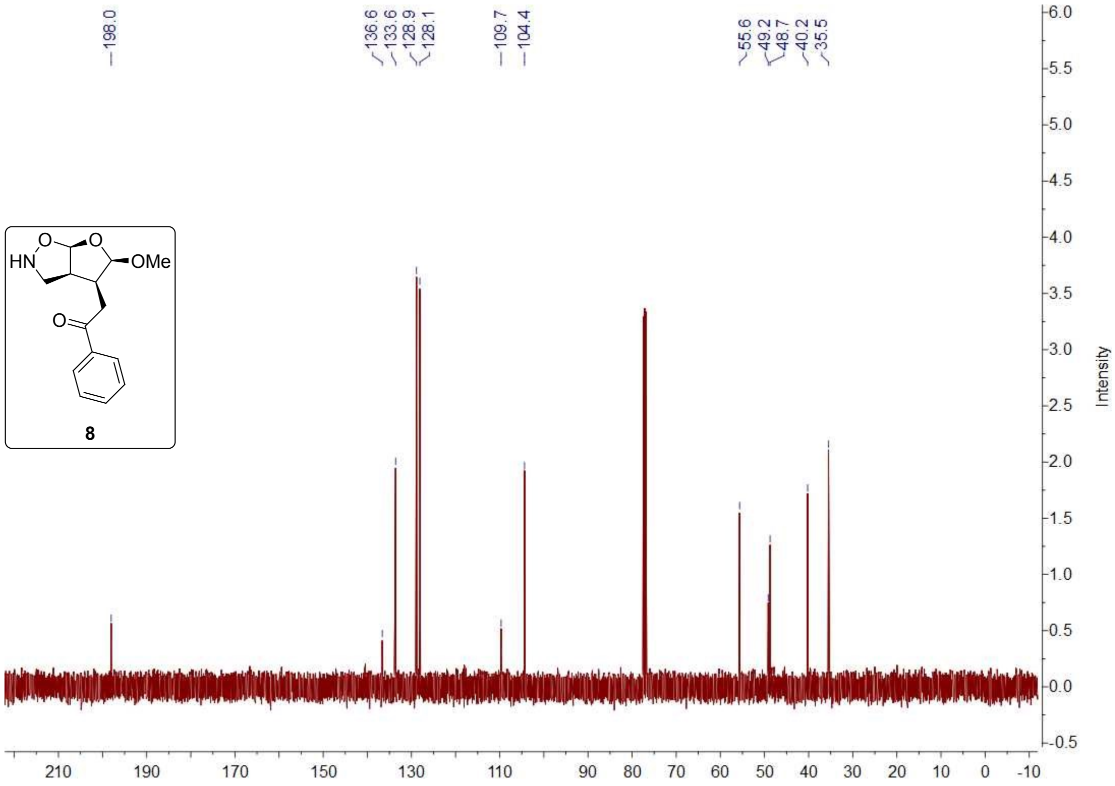


```
                 Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.              RT               Area               Area %            BC

 1             11.987             16869               0.573            BB
 2             27.453           2929190              99.427            BB

                                2946059             100.000
```

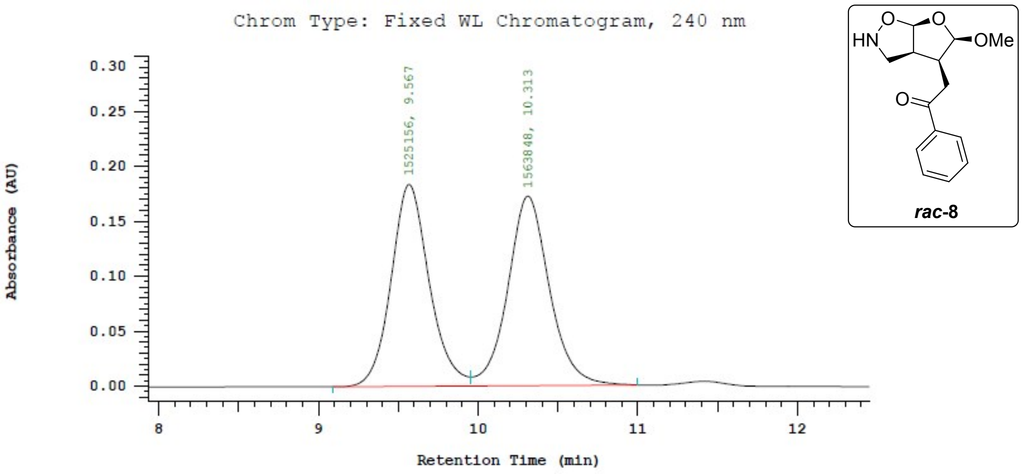
The ^{1}H NMR spectrum of 8 (500 MHz, CDCl$_3$)



The ^{13}C NMR spectrum of 8 (125 MHz, CDCl$_3$)

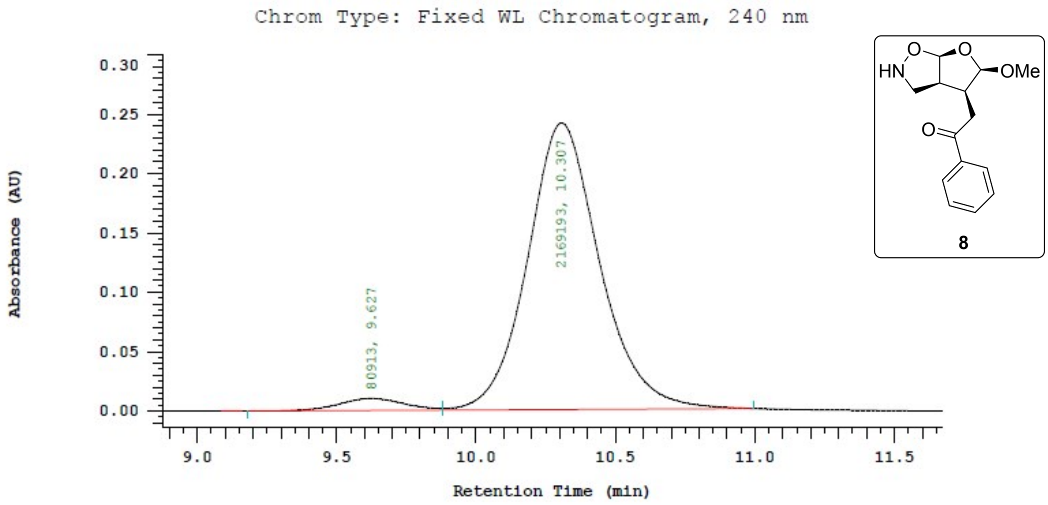


The HPLC of racemic 8



```
                 Chrom Type: Fixed WL Chromatogram, 240 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.              RT               Area               Area %            BC

  1            9.567           1525156              49.374            BV
  2           10.313           1563848              50.626            VB

                                3089004             100.000
```

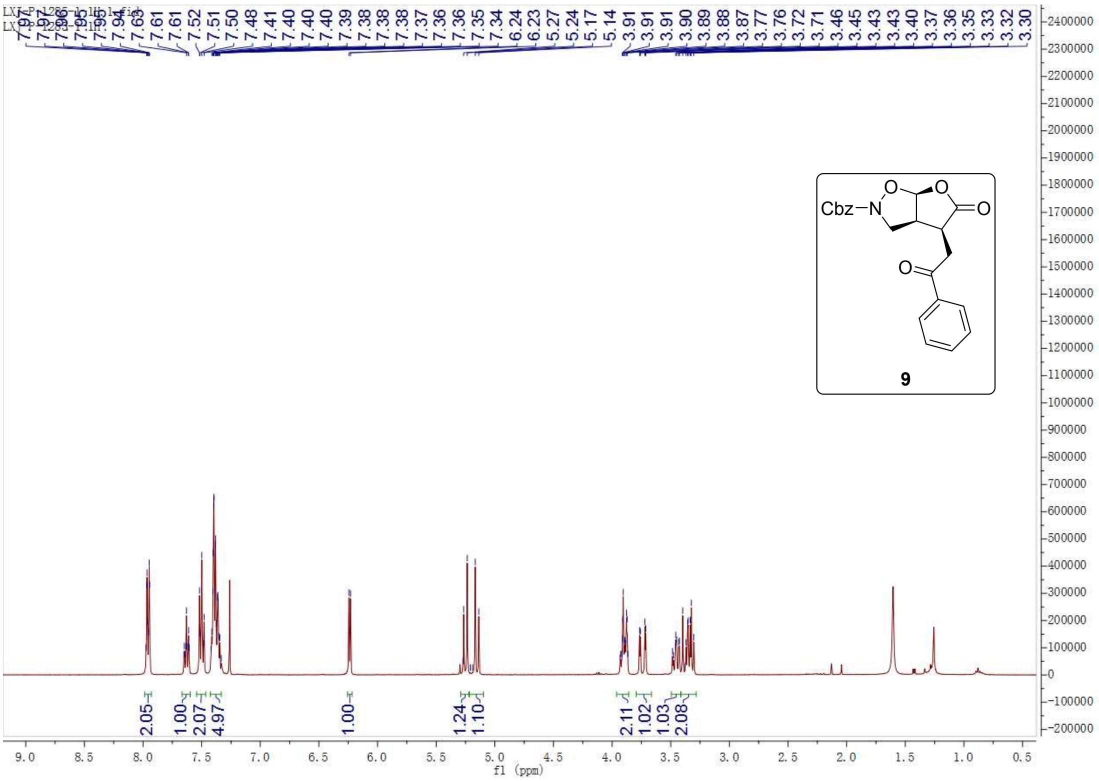
The HPLC of chiral 8



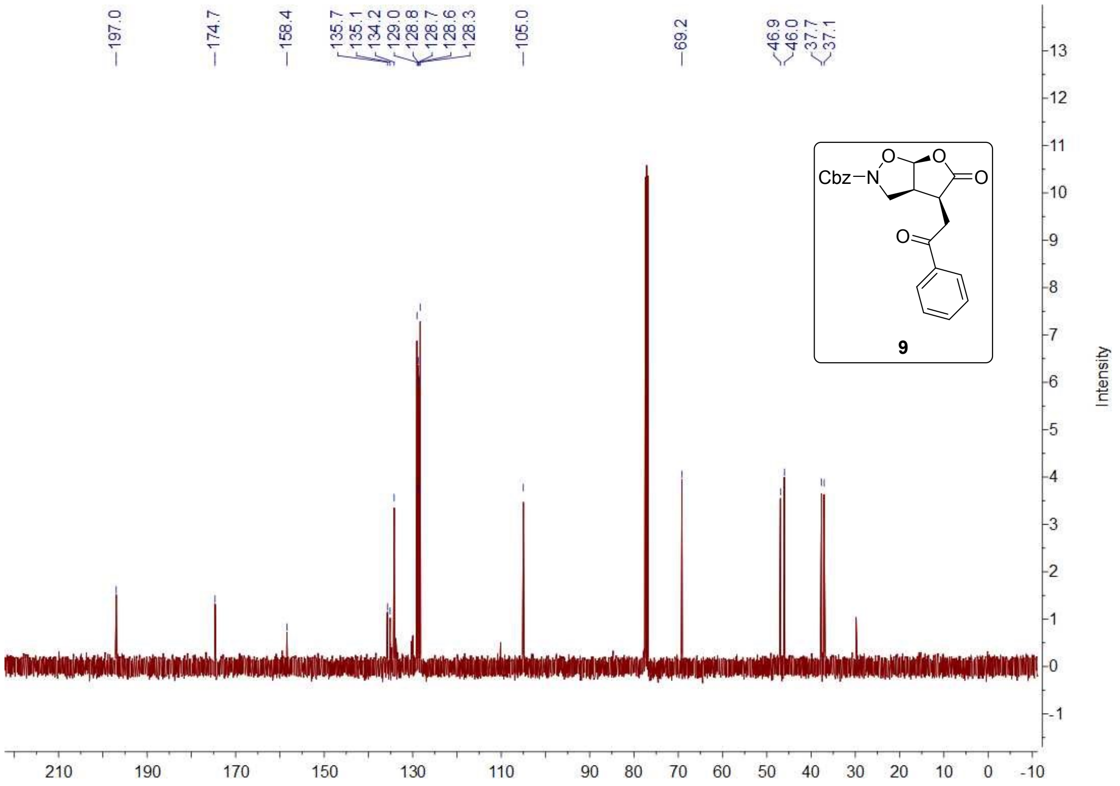
Chrom Type: Fixed WL Chromatogram, 240 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	9.627	80913	3.596	BV
2	10.307	2169193	96.404	VB
		2250106	100.000	

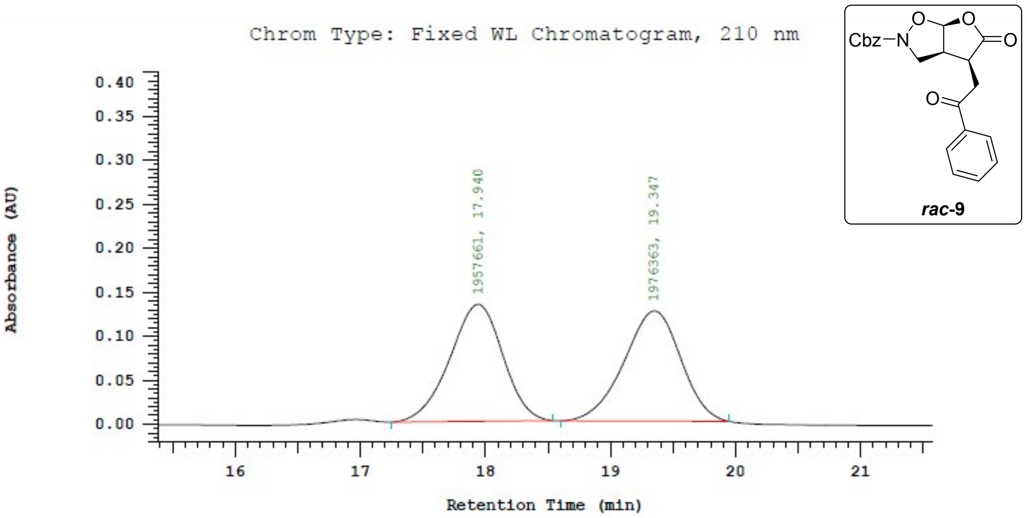
The ^{1}H NMR spectrum of 9 (500 MHz, $CDCl_3$)



The ^{13}C NMR spectrum of 9 (125 MHz, CDCl$_3$)



The HPLC of racemic 9

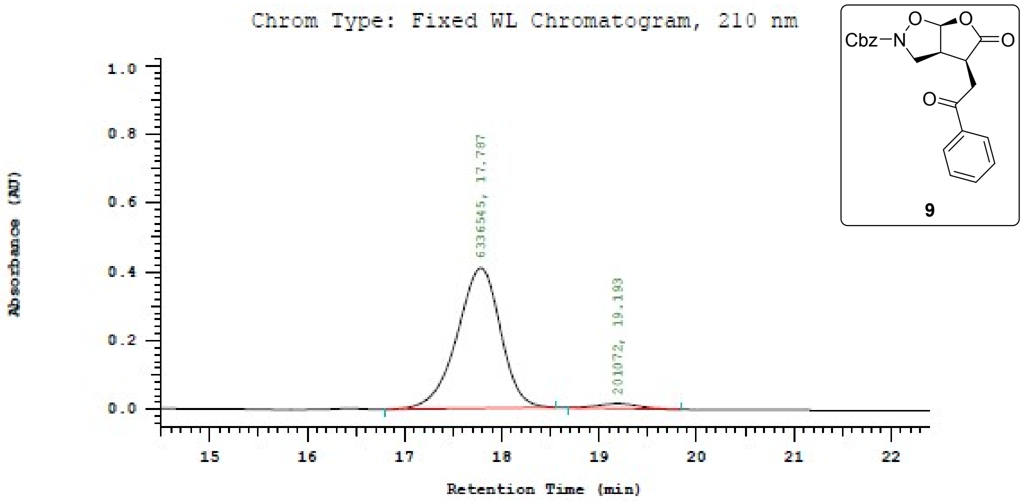


Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	17.940	1957661	49.762	BB
2	19.347	1976363	50.238	BB
		3934024	100.000	

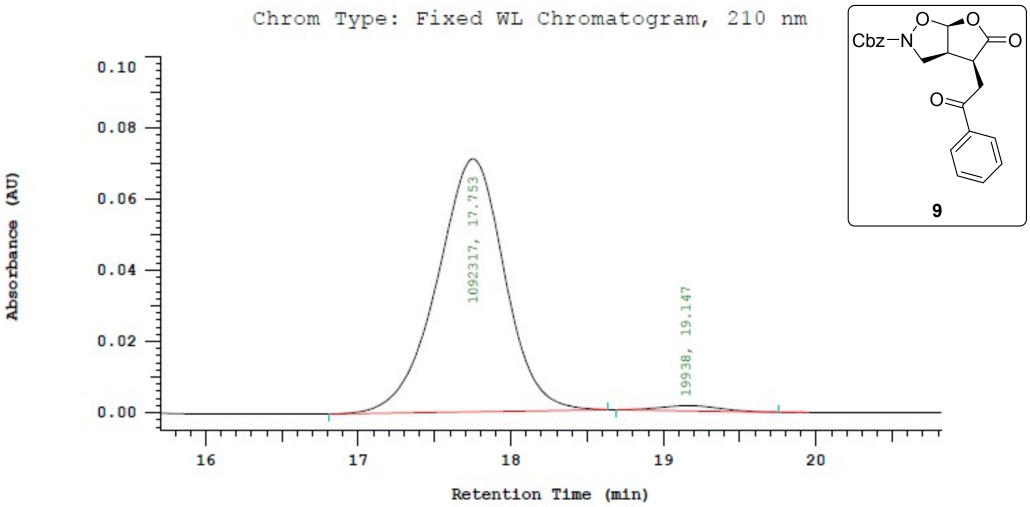
The HPLC of chiral 9 in transformation



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	17.787	6336545	96.924	BB
2	19.193	201072	3.076	BB
		6537617	100.000	

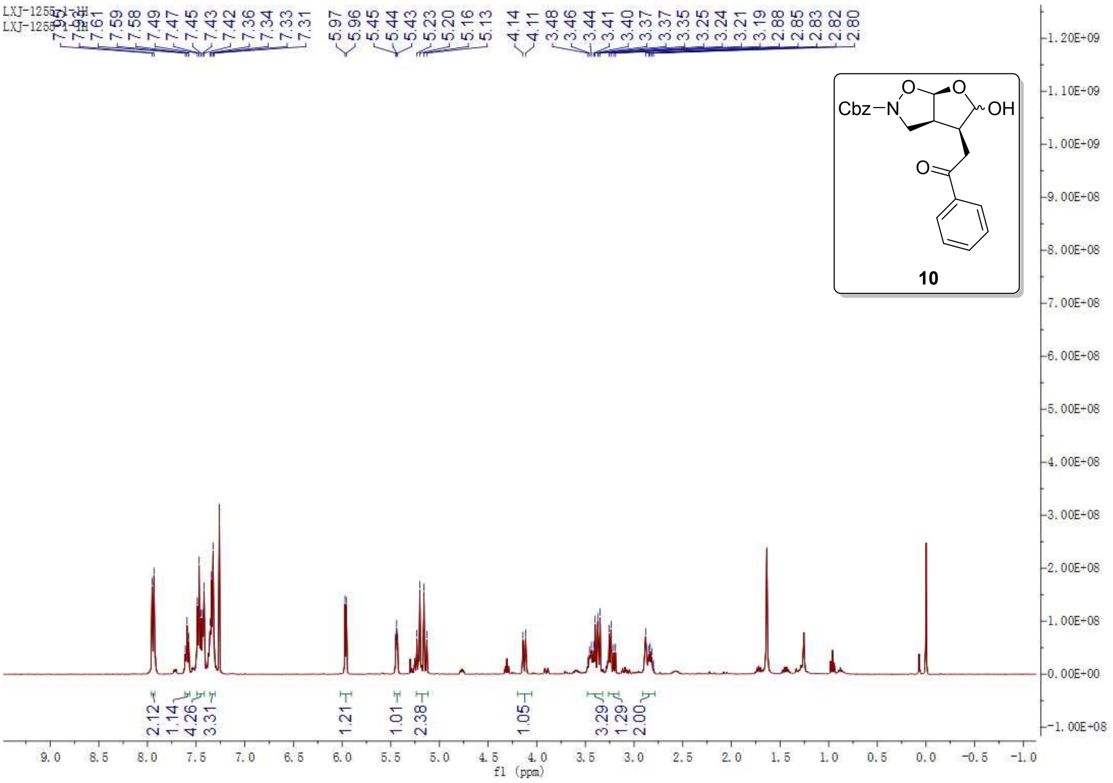
The HPLC of chiral 9 in other reactions



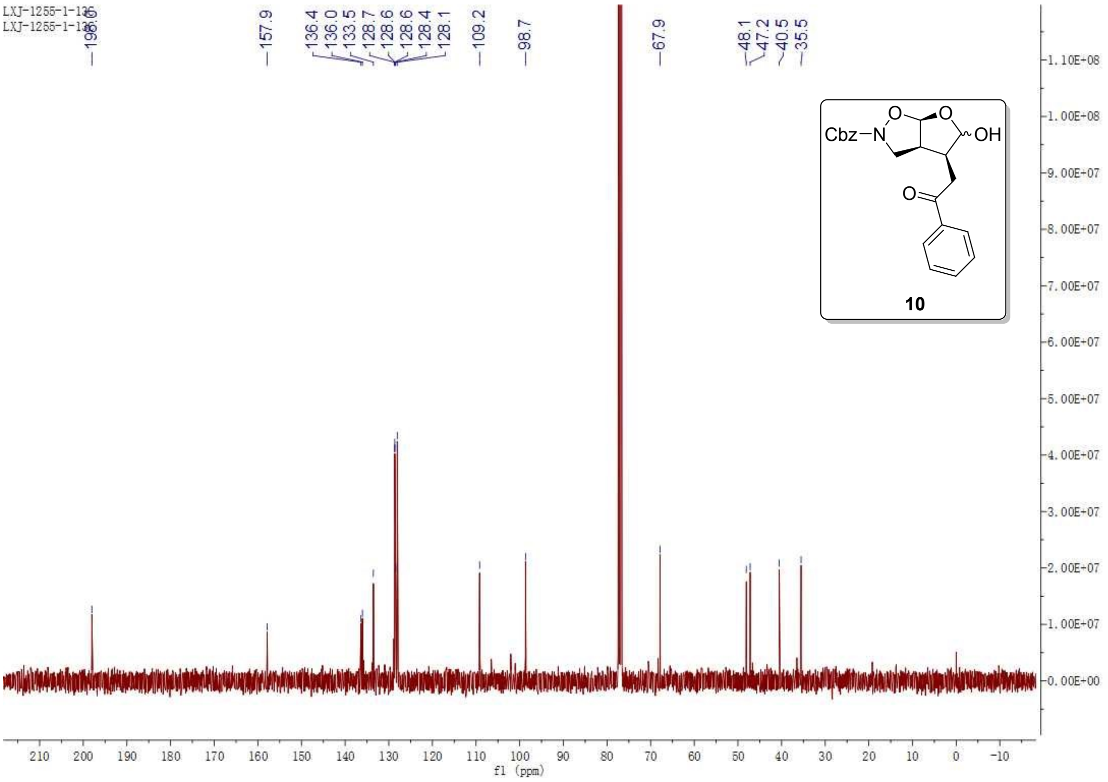
Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	17.753	1092317	98.207	BB
2	19.147	19938	1.793	BB
		1112255	100.000	

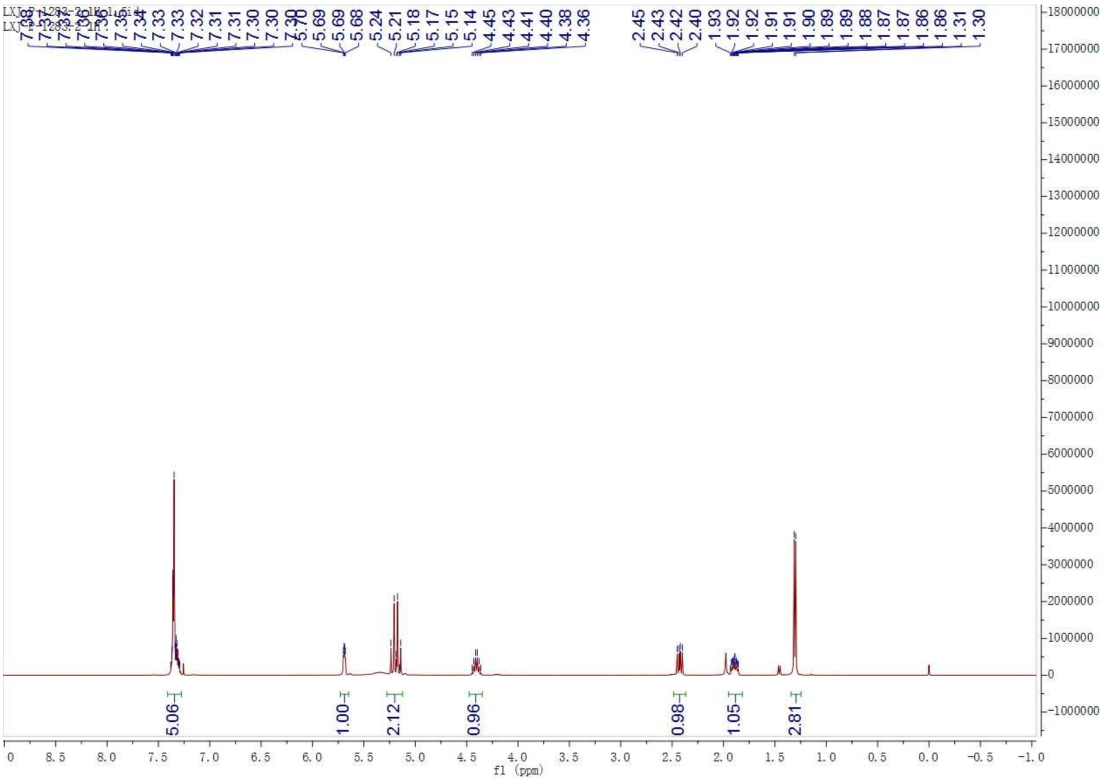
The ^{1}H NMR spectrum of 10 (400 MHz, CDCl$_3$)



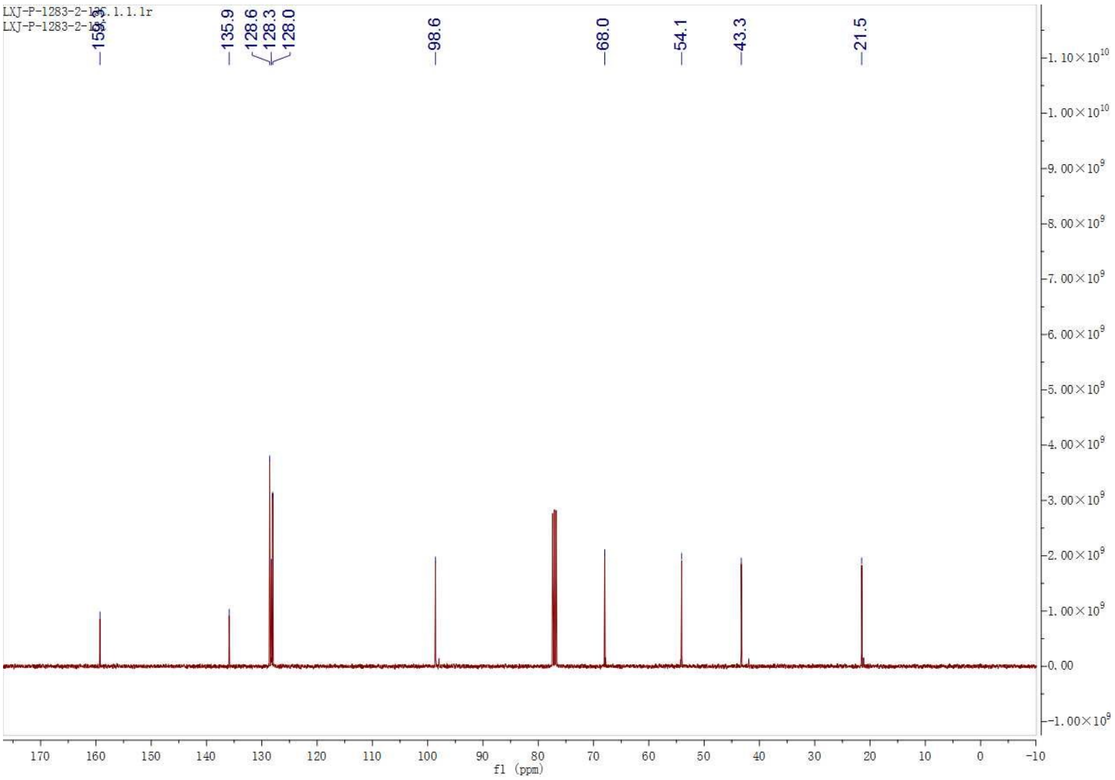
The ^{13}C NMR spectrum of 10 (100 MHz, CDCl$_3$)



The ^1H NMR spectrum of 17 (400 MHz, $CDCl_3$)



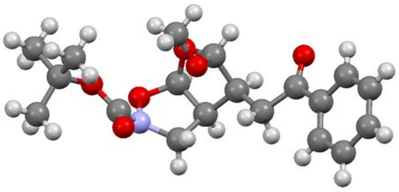
The ^{13}C NMR spectrum of 17 (100 MHz, $CDCl_3$)

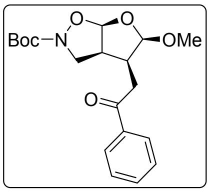


L. Single crystal X-Ray diffraction data

[CCDC 1968770 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.].

Absolute configuration of **5b** - CCDC 1968770





```
Bond precision:   C-C = 0.0044 A          Wavelength=0.71073

Cell:             a=10.9242(19)     b=7.1718(13)        c=12.651(2)
                  alpha=90          beta=105.167(3)     gamma=90
Temperature:      296 K

                  Calculated                  Reported
Volume            956.6(3)                    956.6(3)
Space group       P 21                        P 1 21 1
Hall group        P 2yb                       P 2yb
Moiety formula    C19 H25 N O6                C19 H25 N O6
Sum formula       C19 H25 N O6                C19 H25 N O6
Mr                363.40                      363.40
Dx,g cm-3         1.262                       1.262
Z                 2                           2
Mu (mm-1)         0.094                       0.094
F000              388.0                       388.0
F000'             388.21
h,k,lmax          14,9,16                     14,9,16
Nref              4406[ 2381]                 3910
Tmin,Tmax                                     0.694,0.746
Tmin'

Correction method= # Reported T Limits: Tmin=0.694 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 1.64/0.89       Theta(max)= 27.521

R(reflections)= 0.0406( 3117)      wR2(reflections)= 0.0893( 3910)

S = 1.034                  Npar= 240
```