Enantioselective One Pot Construction of Bridged Tricyclic Lactones

So Hyun Jung, Ju Ha Baek, So Young Jang and Hyeung-geun Park*

[†]Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul 151-742, Korea.

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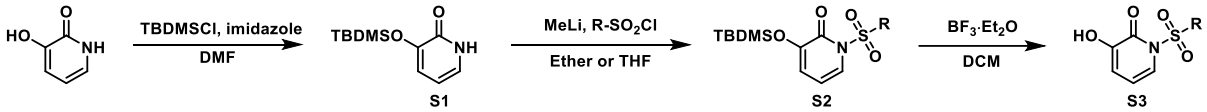
I. General Information

All reagents purchased from commercial sources were used without further purification. For the reactions that required heating, sand bath was used as heat source. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. Organocatalysts (A, B[1], C[2], D[3], E[4], F[4], G[4], H[4], I, J[5] and K[4]) were prepared according to the reported procedure. TLC analyses were performed using pre-coated TLC plate (silica gel 60 F254, 0.25 mm). Flash column chromatography was carried out using E. Merck Silica gel 60 (0.040-0.063 mm). Hitachi (UV detector L-2130, Pump L-2130 and software LaChrome 890-8800-12) and Waters (UV detector 2489, Pump 1525 and software Breeze 2 6.20.00.00) were used for HPLC. The values of enantiomeric excess (ee) of chiral products were determined by HPLC using 4.6 mm x 250 mm DAICEL Chiralpak AD-H, Chiralpak OD-H, Chiralpak AS-H, Chiralpak IG, Chiralpak ID and Chiralpak IC. Nuclear magnetic resonance (1H NMR, 13C NMR and 19F NMR) spectra were measured on JEOL JNM-ECZ400s [400 MHz (1H), 101 MHz (13C) and 376 MHz (19F)], Bruker AVANCE 500 [500 MHz (1H), 125 MHz (13C)], and 800-MHz Bruker Avance III HD spectrometer [800 MHz (1H), 200 MHz (13C)]. 1H-NMR spectra was recorded at 400 MHz with reference to $CDCl_3$ (δ 7.26), CD_3OD (δ 3.31) or DMSO–d6 (δ 2.50), 13C-NMR spectra was obtained by 101 MHz spectrometer relative to the central $CDCl_3$ (δ 77.16), CD_3OD (δ 49.0), or DMSO-d6 (δ 40.0) resonance. 19F-NMR spectra was obtained by 376 MHz spectrometer. Coupling constants (J) in 1H-NMR are in Hertz(Hz). Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were measured on JEOL JMS-700 spectrometers (double-focusing mass analyzer). Melting points were measured on a Büchi B-540 melting point apparatus and are not corrected. Infrared (IR) spectra were recorded on JASCO FT/IR-4200 spectrometers. Optical rotations were measured on a JASCO P-2000 digital polarimeter and calibrated with pure solvent as blank. X-ray crystallographic data was collected by Agilent SuperNova, Bruker D8-Venture and Bruker APEX-II CCD X-ray Diffractometer using graphite-monochromated Mo Kα radiation.

II. Synthetic Procedures

i. Preparation for 3-Hydroxy-2 Pyridones (1a-1g)[6]



Synthesis of **S1** (1st step) : To a solution of 2,3-dihydroxypyridine (1.0 equiv) and 1H-imidazole (2.5 equiv) in dry DMF (0.44 M) was treated dropwise over 1.5 h at r.t. with a solution of TBDMSCl (1.0 equiv) in dry DMF (0.44 M). The reaction mixture was stirred at room temperature under Ar atmosphere for 9 h. Upon completion, determined by TLC, the reaction was quenched with H_2O and diluted with Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, and the filtrate was concentrated until crystals started to appear. After standing overnight, the crystals were separated and washed with Et_2O. Further product was obtained by recrystallization of the mother liquor with Et_2O to yield **S1.**

Synthesis of **S2** (2nd step) : To a solution of **S1** (1.0 equiv) in dry Et_2O (0.2 M) (for **1b**, **1c**, **1d** THF was used) was treated dropwise at 0 °C over 45 min with a 1.6 M solution of MeLi in Et_2O (1.2 equiv) and stirred under Ar atmosphere for 2 h. A solution of RSO_2Cl (1.2 equiv) in dry Et_2O (0.2 M) (for **1b**, **1c**, **1d** THF was used) was then added dropwise over 50 min, and the reaction mixture was stirred at room temperature for 30 h. Upon completion, determined by TLC, the reaction was quenched with H_2O and diluted with Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography to give **S2**.

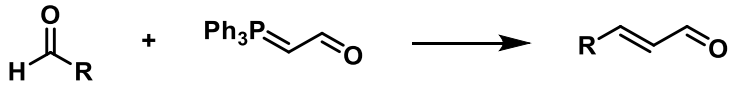
Synthesis of **S3** (3rd step) : To a solution of **S2** (1.0 equiv) in dry CH_2Cl_2 (0.64 M) was treated portionwise with $BF_3·Et_2O$ (22.1 mL, 0.17 mol, 1.1 equiv) over 45 min and stirred at room temperature under Ar atmosphere for 24 h. Since TLC indicated incomplete conversion, an additional portion of $BF_3·Et_2O$ (0.25 equiv) was added, and

stirring was continued for 12 h. Upon completion, determined by TLC, the reaction was quenched with H_2O and diluted with and the layers were separated The organic layer was separated and the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was diluted with $CHCl_3$/hexane (1:1) and recrystallized to afford **S3**.

ii. Preparation for α,β-Unsaturated Aldehydes

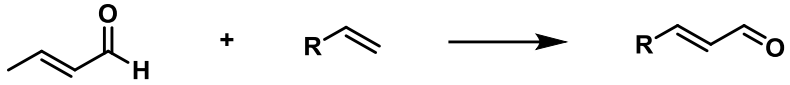
Compounds **2a, 2b, 2k, and 2m–2l** were purchased from commercial suppliers and used as received. Compounds **2c–2h** were prepared according to G*eneral Procedure B*, and compounds **2n–2x** according to *General Procedure A*. Compounds **2y**[7] **and 2z**[7] were synthesized following the literature procedure. Both *general procedure A* and *general procedure B* were adapted from reported methods.

General Procedure A[8-9]:



To a solution of (triphenylphosphoranylidene)acetaldehyde (1.0 equiv) and the aldehyde (1.0 equiv) in $CHCl_3$ (0.3 M) was refluxed overnight. Upon completion, determined by TLC, the reaction mixture was adsorbed onto silica gel and was purified by flash column chromatography to give desired compound.

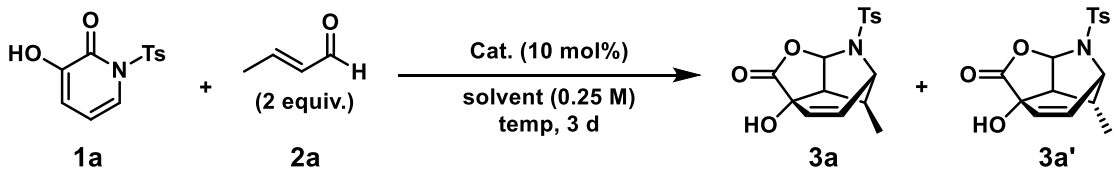
General Procedure B[10-13]:



To a solution of crotonaldehyde (3.0 equiv) and allylbenzene (1.0 equiv) in dry CH_2Cl_2 (0.20 M) was added Hoveyda–Grubbs II catalyst 10 (0.01 equiv). The reaction mixture was heated to 40 °C and stirred under Ar atmosphere for 5 h, after which an additional portion of catalyst 10 (0.01 equiv) was added and stirred overnight. Upon completion, determined by TLC, the solvent was evaporated to half under reduced pressure. The crude residue was purified directly by flash column chromatography to to give desired compound.

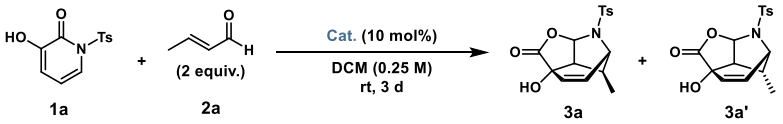
iii. Optimization for N-bridged tricycles

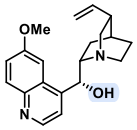
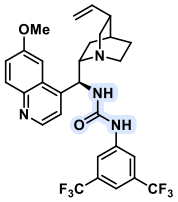
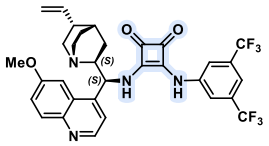
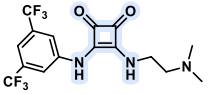
General Procedure C:

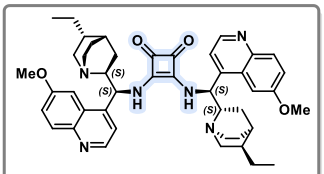
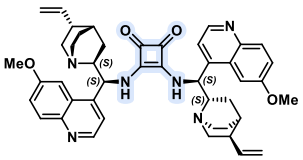
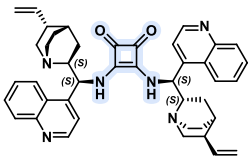
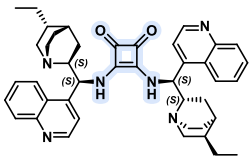


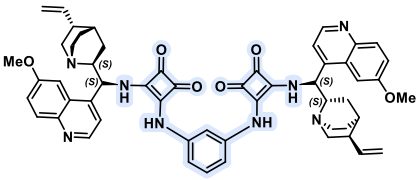
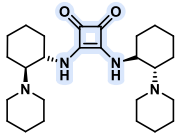
To a stirred solution of **1a** (1.0 equiv) and the organocatalyst (10 mol %) in the solvent (0.25 M) was added **2a** (2.0 equiv). The reaction mixture was stirred at the indicated temperature for 3 d in a sealed vial under air**.** Upon completion (TLC), the mixture was rapidly filtered through a short plug of silica gel (EtOAc) and concentrated under reduced pressure. The yield and diastereomeric ratio (dr) were determined by ^1H NMR of the crude using 1,2-dibromoethane as an internal standard. The enantiomeric excess (ee) was determined by chiral HPLC.

TableS1. Effect of Catalyst[a)]



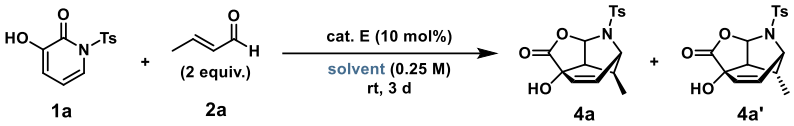
				
N.R.	cat. **A** **N.R.**	cat. **B** **79% yield, 4.9:1 dr** **8% ee**	cat. **C** **89% yield, 15:1 dr** **76% ee**	cat. **D**[b)] **86% yield, 6:1 dr** **racemate**

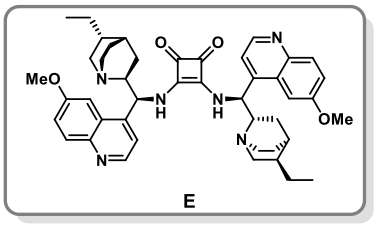
			
cat. E **83% yield, 6.6:1 dr** **83% ee**	**cat. F** **88% yield, 6.8:1 dr** **82% ee**	**cat. G** **85% yield, 4.9:1 dr** **69% ee**	**cat. H** **83% yield, 5.9:1 dr** **70% ee**

	
cat. **I** **77% yield, 7.9:1 dr** **70% ee**	cat. **J** **74% yield, 5.6:1 dr** **45% ee**

[a)]Reaction conditions: Reactions were performed with 1a (0.075 mmol), 2a (0.151 mmol), and catalyst (10 mol%) in DCM (0.30 mL, 0.25 M) at r.t for 3 d. Yields of 4a were determined by ^{1}H NMR spectroscopic analysis with 1,2-dibromoethane as an internal standard. Diastereomeric ratio (dr) was determined by spectroscopic analysis. Enantiomeric excess (ee) was determined by HPLC analysis. [b)]Reaction was performed at 55 °C for 24 h.

TableS2. Effect of Solvents[a)]

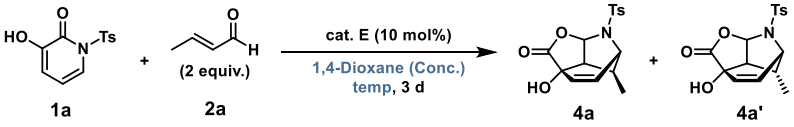


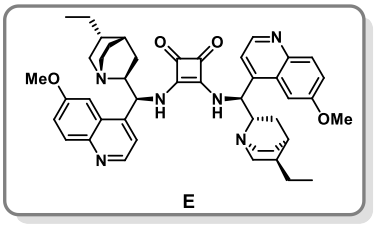


entry	solvent	conversion (%)[b)]	yield (%)[b)]	4a : 4a'[c)]	ee (%)[d)]
1	**1,4-Dioxane**	**97**	**85**	**14.4:1**	**89**
2	PhMe	>99	86	5.1:1	86
3	Diethyl ether	57	29	14.1:1	83
4	Chloroform	>99	84	6.7:1	84
5	THF	>99	92	7.4:1	87
6	DCM	>99	83	6.6:1	83
7	DCE	>99	90	6.2:1	81
8	MeCN	>99	83	12.1:1	82

[a)]Reaction conditions: Reactions were performed with 1a (0.075 mmol), 2a (0.151 mmol), and cat. E (10 mol%) in indicated solvent (0.30 mL, 0.25 M) at r.t for 3 d. [b)]Yields of 4a were determined by ^{1}H NMR spectroscopic analysis with 1,2-dibromoethane as an internal standard. [c)]Diastereomeric ratio (dr) was determined by spectroscopic analysis. [d)]Enantiomeric excess (ee) was determined by HPLC analysis.

TableS3. Effect of Reaction Concentrations and Temperatures[a)]

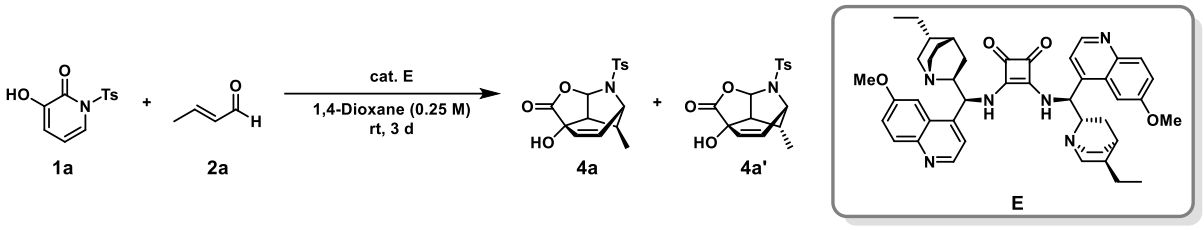




entry	conc. (M)	temp (°C)	conversion (%)[b)]	yield (%)[b)]	4a : 4a'[c)]	ee (%)[d)]
1	0.15	rt	79	62	13.3:1	90
2	**0.25**	**rt**	**97**	**85**	**14.4:1**	**89**
3	0.35	rt	>99	81	13:1	88
4	0.25	10	61	39	16.2:1	97
5	0.25	35	97	87	14.6:1	83

[a)]Reaction conditions: Reactions were performed with 1a (0.075 mmol), 2a (0.151 mmol), and cat. E (10 mol%) in the indicated concentration of 1,4-Dioxane at indicated temperture for 3 d. [b)]Yields of 4a were determined by ^{1}H NMR spectroscopic analysis with 1,2-dibromoethane as an internal standard. [c)]Diastereomeric ratio (dr) was determined by spectroscopic analysis. [d)]Enantiomeric excess (ee) was determined by HPLC analysis

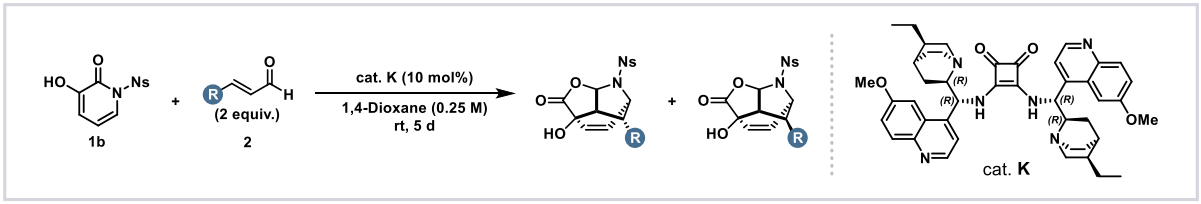
TableS4. Variation of Equivalents of Substrates and Catalyst Loadings[a)]

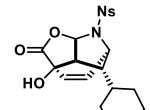


entry	**2a** (equiv)	catalyst loading (mol%)	conversion (%)[b)]	yield (%)[b)]	4a : 4a'[c)]	ee (%)[d)]
1	1.2	10	77	59	11:1	91
2	2	5	42	27	14.8:1	93
3	**2**	**10**	**97**	**85**	**14.4:1**	**89**
4	2	20	>99	83	11.4:1	90

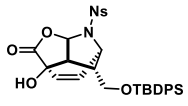
[a)]Reaction conditions: Reactions were performed with **1a** (0.075 mmol), indicated equivalent of **2a**, and cat. **E** (5, 10 or 20 mol%) in 1,4-Dioxane (0.30 mL, 0.25 M) at r.t for 3 d. [b)]Yields of **4a** were determined by ^{1}H NMR spectroscopic analysis with 1,2-dibromoethane as an internal standard. [c)]Diastereomeric ratio (dr) was determined by spectroscopic analysis. [d)]Enantiomeric excess (ee) was determined by HPLC analysis.

TableS5. Catalyst-Controlled Enantiodivergence Using a Pseudoenantiomeric Catalyst





ent-4v, 66%, - 98% ee
single dr

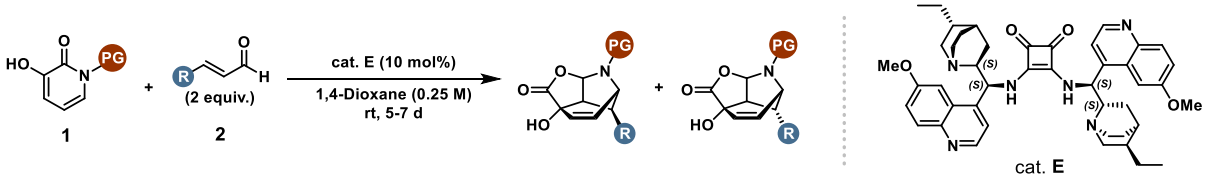


ent-4z, 84%, - 96% ee
single dr

[a)]Reaction conditions: Reactions were performed with **1a** (0.084 mmol), **2** (0.169 mmol), and cat. **K** (0.0084 mmol, 10 mol%) in 1,4-Dioxane (0.34 mL) at r.t for 5 d..Diastereomeric ratio (dr) was determined by spectroscopic analysis. Enantiomeric excess (ee) was determined by HPLC analysis.

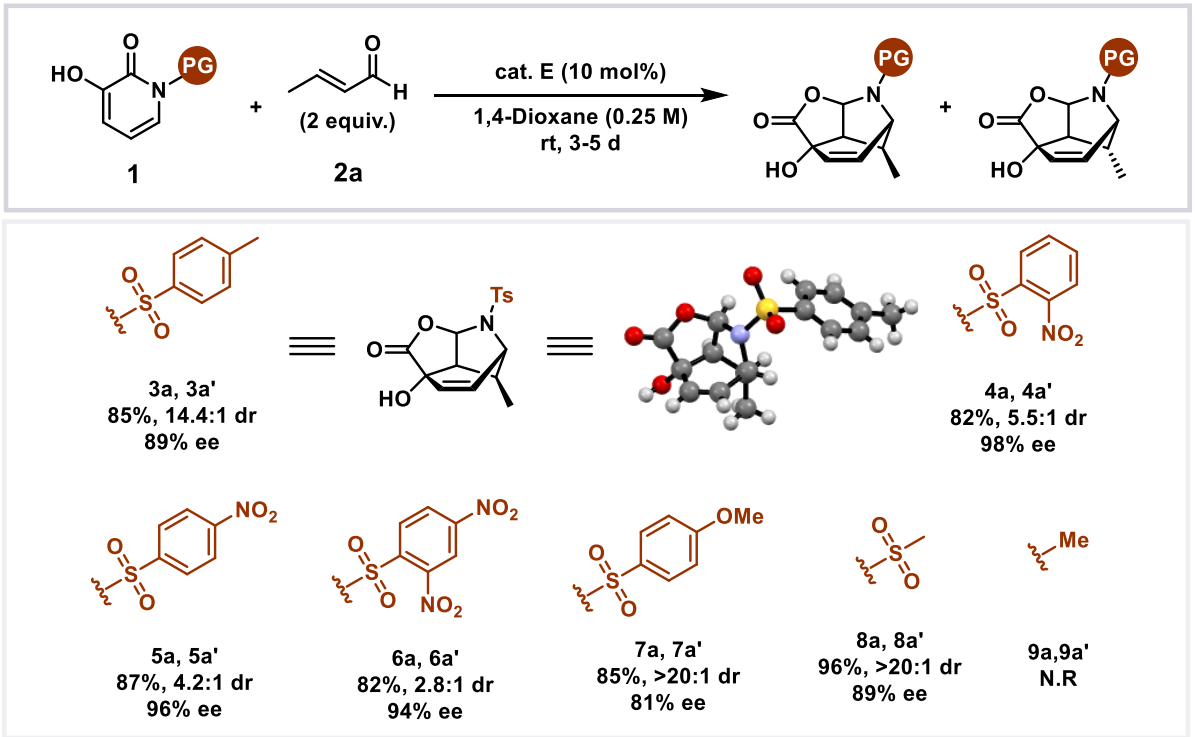
iv. General procedure for N-bridged tricycles

General Procedure D:



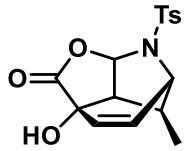
To a stirred solution of **1** (0.084 mmol, 1.0 equiv) and catalyst **E** (0.0084 mmol, 10 mol %) in solvent (0.34 mL) was added **2** (0.169 mmol, 2.0 equiv). The reaction mixture was stirred at the room temperature in a sealed vial under air. Upon completion, as determined by TLC, the mixture was passed through a short plug of silica gel (EtOAc), and the filtrate was concentrated under reduced pressure. The yield and diastereomeric ratio (dr) were determined by ^1H NMR analysis of the crude mixture using 1,2-dibromoethane as an internal standard. Purification by flash column chromatography on silica gel afforded the corresponding N-bridged tricyclic product. The enantiomeric excess (ee) was determined by chiral HPLC.

Scheme S1. Optimization of 3-hydroxy-2-pyridone substrates[a)]



[a)]Reaction conditions: Reactions were performed with **1** (0.084 mmol), **2a** (0.169 mmol), and catalyst **E**(10 mol%) in 1,4-dioxane (0.34 mL, 0.25 M) at r.t. for 3-5 days. Yields of products were determined by ^{1}H NMR spectroscopic analysis with 1,2-dibromoethane as an internal standard. Diastereomeric ratio (dr) was determined by spectroscopic analysis. Enantiomeric excess (ee) was determined by HPLC analysis.

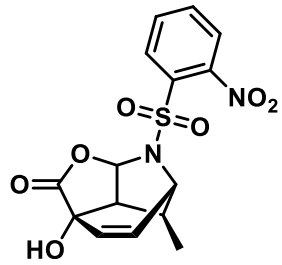
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-methyl-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3a)



Prepared from **1a** and **2a** according to General Procedure D. After 3 d, the reaction afforded **4a** (23.8 mg, **85%,** dr = **14.4:1, 89**% ee) as a white solid.

MP: 138.1-140.1 °C
IR (neat) : 3464, 3027, 2931, 1786, 1598, 1494, 1347, 1164, 832, 816
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 8.2 Hz, 2H), 7.28-7.25 (m, 2H), 6.10 (d, J = 5.5 Hz, 1H), 5.98 (dd, J = 9.1, 5.9 Hz, 1H), 5.73 (d, J = 9.1 Hz, 1H), 4.19 (t, J = 5.3 Hz, 1H), 3.19-3.16 (m, 2H), 2.40 (s, 3H), 2.25 (ddd, J = 10.9, 6.7, 2.6 Hz, 1H), 1.02 (q, J = 3.5 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.2, 144.3, 137.1, 130.8, 130.2, 130.0, 127.2, 88.8, 72.9, 58.1, 50.5, 35.2, 21.7, 11.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{16}H_{18}NO_5S]^+$ ($[M+H]^+$) 336.0906; found 336.0919
$[\alpha]^{20}_D$: -13.65 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark AD-H, hexane/isopropanol 70:30, 0.5 mL/min, λ=243nm) t_R = 33.9 min (major), 43.7 min (minor).

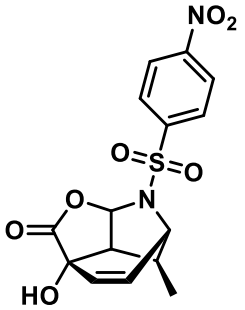
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-methyl-8-((2-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4a)



Prepared from **1b** and **2a** according to General Procedure D. After 5 d, the reaction afforded **5a** (25.4 mg, **82%,** dr = **5.5:1, 98**% ee) as a white solid.

MP: 156-159.5 °C
IR (neat) : 3503, 3100, 2935, 1782, 1542, 1489, 1372, 1170, 976, 785
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.08 (m, 1H), 7.73-7.65 (m, 3H), 6.40 (dd, J = 9.4, 6.2 Hz, 1H), 6.31 (d, J = 5.9 Hz, 1H), 5.77 (d, J = 9.6 Hz, 1H), 4.50 (t, J = 5.5 Hz, 1H), 3.28 (dd, J = 5.5, 4.1 Hz, 1H), 3.00 (br s, 1H), 2.47 (td, J = 7.2, 3.7 Hz, 1H), 1.12 (d, J = 6.9 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.8, 148.1, 134.3, 133.7, 132.6, 131.0, 130.7, 124.3, 89.2, 72.7, 59.1, 50.5, 35.8, 11.4
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{15}H_{15}N_2O_7S]^+$ ($[M+H]^+$) 367.0600; found 367.0604
$[\alpha]^{20}_D$: -204.89 (*c* 0.5, $CHCl_3$)
HPLC: (DAICEL Chiralpark AS-H, hexane/isopropanol 60:40, 1.0 mL/min, λ=243nm) t_R = 28.0 min (major), 48.6 min (minor).

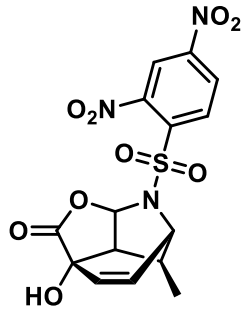
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-methyl-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (5a)



Prepared from **1c** and **2a** according to General Procedure D. After 5 d, the reaction afforded **6a** (27.0 mg, **87%,** dr = **4.2:1, 96**% ee) as a white solid.

MP: 213.7-216.2 °C
IR (neat): 3449, 2970, 1739, 1531, 1351, 1304, 1166, 976, 833
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.08 (m, 1H), 7.73-7.65 (m, 3H), 6.40 (dd, J = 9.4, 6.2 Hz, 1H), 6.31 (d, J = 5.9 Hz, 1H), 5.77 (d, J = 9.6 Hz, 1H), 4.50 (t, J = 5.5 Hz, 1H), 3.28 (dd, J = 5.5, 4.1 Hz, 1H), 3.00 (br s, 1H), 2.47 (td, J = 7.2, 3.7 Hz, 1H), 1.12 (d, J = 6.9 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.2, 150.5, 146.2, 131.7, 129.5, 128.6, 124.5, 88.5, 72.6, 58.4, 50.6, 35.5, 11.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{15}H_{15}N_2O_7S]^+$ ($[M+H]^+$) 367.0600; found 367.0591
$[\alpha]^{25}_D$: -16.28 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark ID, hexane/isopropanol 75:25, 1.0 mL/min, λ=243nm) t_R = 25.9 min (major), 34.4 min (minor).

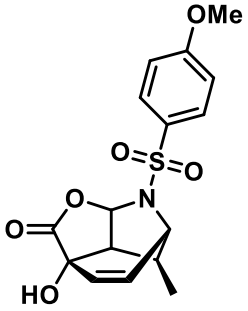
(1R,3aS,6S,7S,7aS)-8-((2,4-Dinitrophenyl)sulfonyl)-3a-hydroxy-7-methyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (6a)



Prepared from **1d** and **2a** according to General Procedure D. After 5 d, the reaction afforded **7a** (28.7 mg, **82%,** dr = **2.8:1, 94**% ee) as a white solid.

MP: 86.5-88.9 °C
IR (neat) : 3440, 2957, 1737, 1541, 1352, 1303, 1174, 975, 834
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52-8.48 (m, 2H), 8.32 (d, J = 8.2 Hz, 1H), 6.42 (dd, J = 9.4, 6.2 Hz, 1H), 6.32 (d, J = 5.9 Hz, 1H), 5.79 (d, J = 8.7 Hz, 1H), 4.55 (t, J = 5.3 Hz, 1H), 3.67 (br s, 1H), 3.31 (dd, J = 5.5, 4.1 Hz, 1H), 2.54-2.50 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.2, 150.1, 139.1, 132.8, 131.2, 130.5, 127.0, 119.8, 89.1, 72.5, 59.6, 50.4, 35.9, 29.9, 11.4
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{15}H_{14}N_3O_9S]^+$ ($[M+H]^+$) 412.0451; found 412.0459
$[\alpha]^{20}_D$: -237.24 (*c* 1.0, $CHCl_3$)
HPLC (DAICEL Chiralpark ID, hexane/isopropanol 80:20, 1.0 mL/min, λ=243nm) t_R = 48.1 min (major), 39.6 min (minor).

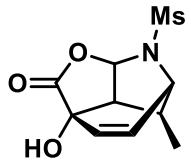
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-((4-methoxyphenyl)sulfonyl)-7-methyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (7a)



Prepared from **1e** and **2a** according to General Procedure D. After 4 d, the reaction afforded **8**a (28.7 mg, **81**%**,** dr = **>20:1, 81**% ee) as a white solid.

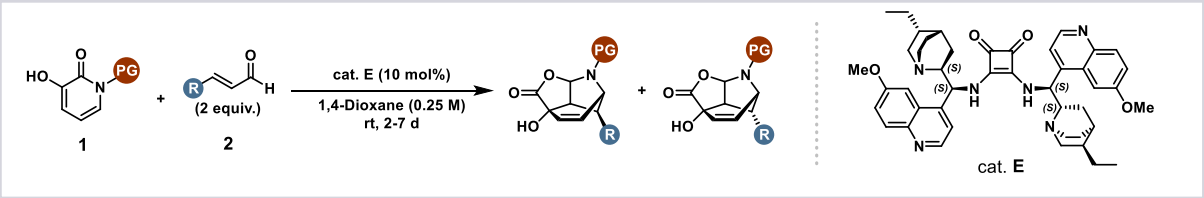
MP: 72.8-75.9 °C
IR (neat): 3461, 2972, 2843, 1787, 1578, 1459, 1346, 1160, 975, 771
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (dt, J = 9.6, 2.5 Hz, 2H), 6.95 (dt, J = 9.8, 2.5 Hz, 2H), 6.14 (d, J = 5.5 Hz, 1H), 6.00 (dd, J = 9.1, 6.4 Hz, 1H), 5.71 (d, J = 9.1 Hz, 1H), 4.20 (t, J = 5.3 Hz, 1H), 3.86 (s, 3H), 3.21-3.18 (m, 1H), 2.34-2.30 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.1, 163.4, 131.7, 130.8, 130.3, 129.5, 114.5, 88.8, 72.8, 57.9, 55.8, 50.6, 35.2, 11.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{16}H_{18}NO_6S]^+$ ($[M+H]^+$) 352.0855; found 352.0859
$[\alpha]^{25}_D$: -61.68 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark ID, hexane/isopropanol 75:25, 1.0 mL/min, λ=243nm) t_R = 51.1 min (major), 65.9 min (minor).

(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-methyl-8-(methylsulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (8a)

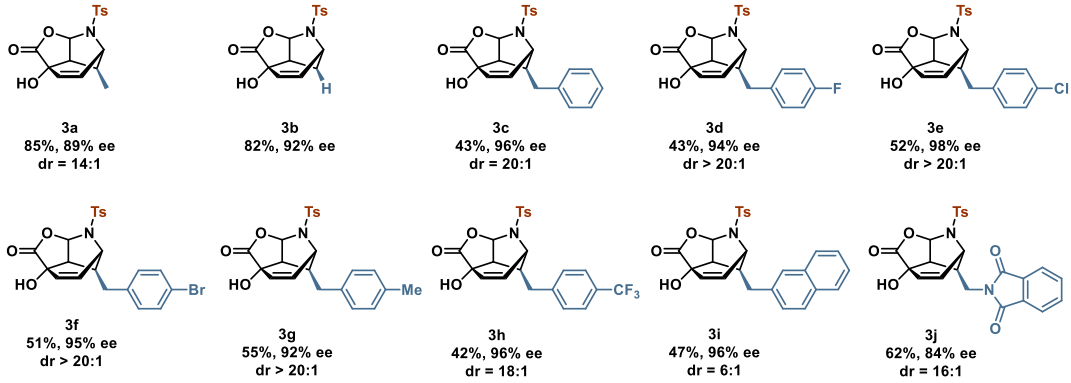


Prepared from **1f** and **2a** according to General Procedure D. After 5 d, the reaction afforded **9**a (21.1 mg, **96**%**,** dr = **>20:1, 89**% ee) as a white solid.
MP: 202.8-204.3 °C
IR (neat) : 3429, 2933, 1745, 1366, 1299, 1144, 1072, 980, 772
^{1}H NMR (400 MHz, MeOD) δ: 6.37 (dd, J = 9.4, 6.2 Hz, 1H), 6.01 (d, J = 5.5 Hz, 1H), 5.96 (dd, J = 8.7, 0.9 Hz, 1H), 4.24 (t, J = 5.3 Hz, 1H), 3.18 (td, J = 3.8, 1.8 Hz, 1H), 2.97 (s, 3H), 2.45 (ddd, J = 11.0, 6.9, 2.3 Hz, 1H), 1.10 (d, J = 6.9 Hz, 3H)
^{13}C NMR (101 MHz, MeOD) δ: 178.5, 132.4, 131.6, 89.8, 74.0, 59.4, 51.7, 41.5, 36.4, 11.6
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{10}H_{14}NO_5S]^+$ ($[M+H]^+$) 260.0593; found 260.0598
$[\alpha]^{25}_D$: -126.64 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark AD-H, hexane/isopropanol 60:40, 1.0 mL/min, λ=243nm) t_R = 9.7 min (major), 12.0 min (minor).

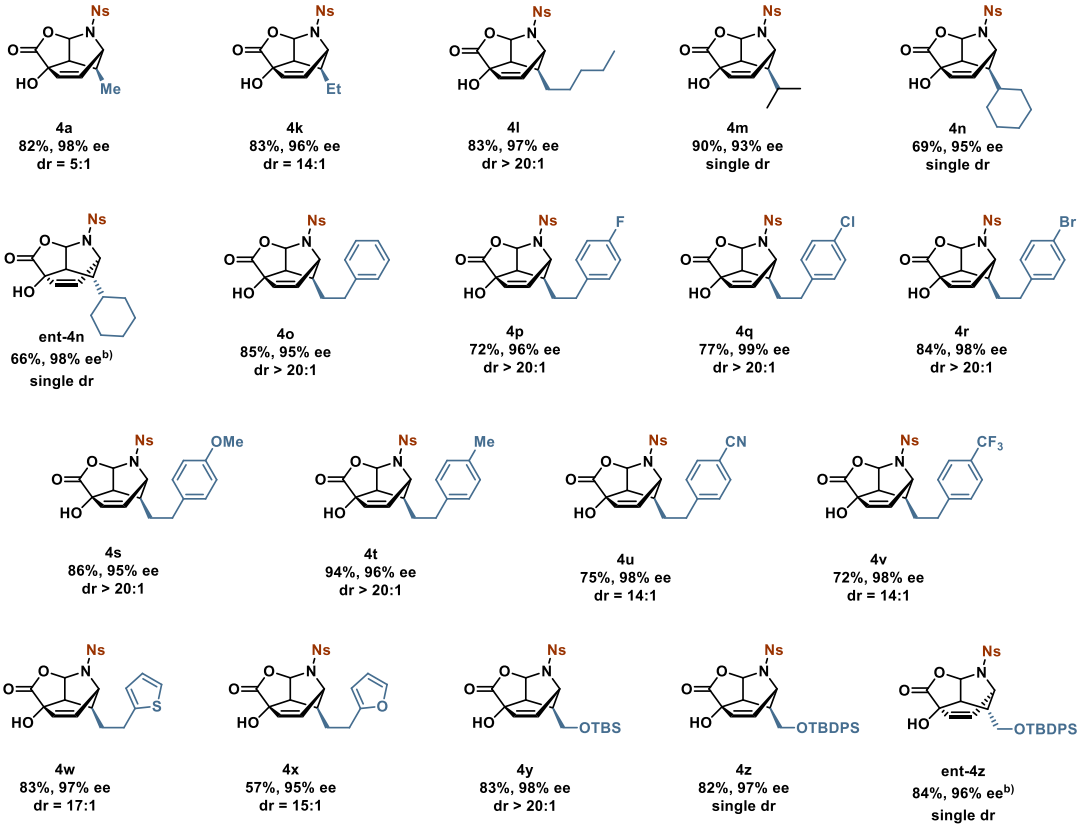
Scheme S2. Substrate scope[a)]



2-Tosyl (Ts) protected pyridones

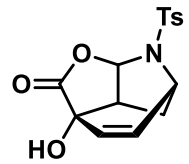


2-Nosyl (Ns) protected pyridones



[a)]Reaction conditions: Reactions were performed with **1** (0.084 mmol), **2a** (0.169 mmol), and catalyst **E**(10 mol%) in 1,4- dioxane (0.34 mL, 0.25 M) at r.t. for 5-7 days. Yields of products were determined by ^{1}H NMR spectroscopic analysis with 1,2-dibromoethane as an internal standard. Diastereomeric ratio (dr) was determined by spectroscopic analysis. Enantiomeric excess (ee) was determined by HPLC analysis. [b)]Reactions were perfomed with catalyst **K** (10 mol%) in same condition.

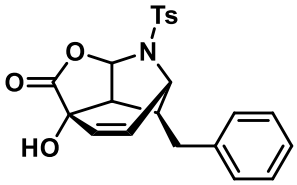
(1R,3aS,6R,7aS)-3a-Hydroxy-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3b)



Prepared from **1a** and **2b** according to General Procedure D. After 2 d, the reaction afforded 3**b** (22.1 mg, **82%, 92**% ee) as a white solid.

MP: 85.2-91.5°C
IR (neat): 3447, 2924, 2852, 1787, 1598, 1456, 1347, 1162, 986, 720
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 8.2 Hz, 2H), 7.29-7.26 (m, 2H), 6.24 (dd, J = 9.1, 6.4 Hz, 1H), 6.14 (d, J = 5.5 Hz, 1H), 5.59 (d, J = 9.1 Hz, 1H), 4.34 (t, J = 5.0 Hz, 1H), 3.51-3.39 (m, 2H), 2.40 (s, 3H), 1.86-1.79 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.0, 144.3, 136.9, 134.8, 130.0, 129.8, 127.2, 88.8, 73.8, 54.7, 46.7, 30.5, 21.7
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{15}H_{16}NO_5S]^+$ ($[M+H]^+$) 322.0749; found 322.0755
$[\alpha]^{20}_D$: -6.54 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark AD-H, hexane/isopropanol 70:30, 0.7 mL/min, λ=243nm) t_R = 29.7 min (major), 39.4 min (minor).

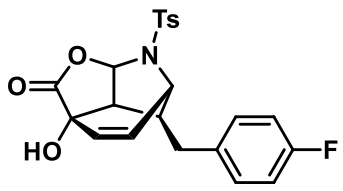
(1R,3aS,6S,7S,7aS)-7-Benzyl-3a-hydroxy-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3c)



Prepared from **1a** and **2c** according to General Procedure D. After 7 d, the reaction afforded **3c** (14.8 mg, **43%,** dr = **>20:1, 96**% ee) as a white solid.

MP: 200.3-205.1 °C
IR (neat): 3422, 2925, 2855, 1788, 1599, 1455, 1348, 1165, 970, 771
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J = 8.7 Hz, 2H), 7.31-7.21 (m, 5H), 7.10-7.08 (m, 2H), 6.09 (d, J = 5.5 Hz, 1H), 6.06 (dd, J = 9.1, 5.9 Hz, 1H), 5.82 (d, J = 9.1 Hz, 1H), 4.12 (t, J = 5.5 Hz, 1H), 3.32-3.26 (m, 2H), 2.71 (ddd, J = 39.6, 14.2, 8.0 Hz, 2H), 2.41 (d, J = 8.2 Hz, 3H), 2.35 (td, J = 8.0, 4.0 Hz, 1H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.0, 144.4, 138.7, 137.0, 131.4, 130.3, 130.0, 128.9, 128.7, 127.3, 126.9, 88.9, 72.9, 56.9, 49.1, 42.9, 32.6, 21.7
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{22}H_{22}NO_5S]^+$($[M+H]^+$) 412.1219; found 412.1225
$[\alpha]^{20}_D$: -75.10 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 35.8 min (major), 54.0 min (minor).

(1R,3aS,6S,7S,7aS)-7-(4-Fluorobenzyl)-3a-hydroxy-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3d)

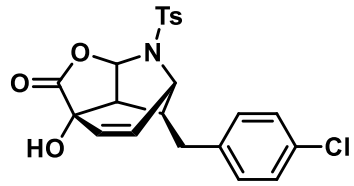


Prepared from **1a** and **2d** according to General Procedure D. After 7 d, the reaction afforded **3d** (15.5 mg, **43%,**

dr = **>20:1, 94**% ee) as a white solid.

MP: 79.5-85.3 °C
IR (neat): 3421, 2924, 1788, 1599, 1509, 1345, 1163, 971, 756
^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.10-6.95 (m, 4H), 6.11 (d, J = 5.9 Hz, 1H), 6.04 (dd, J = 9.1, 5.9 Hz, 1H), 5.80 (d, J = 9.1 Hz, 1H), 4.14 (t, J = 5.3 Hz, 1H), 3.25 (qd, J = 3.7, 1.6 Hz, 1H), 2.77-2.62 (m, 2H), 2.42 (s, 3H), 2.38-2.32 (m, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 144.4, 137.1, 134.3 (d, J = 3.9 Hz), 131.6, 130.3, 130.2 (d, J = 3.9 Hz), 130.0, 127.4, 127.3, 115.8 (d, J = 21.2 Hz), 88.8, 72.8, 56.8, 48.9, 43.1, 31.9, 21.7
^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.9
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{22}H_{21}FNO_5S]^+$ ($[M+H]^+$) 430.1124; found 430.1120
$[\alpha]^{25}_D$: -58.31 (*c* 0.5, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 35.7 min (major), 51.9 min (minor).

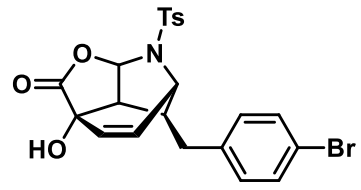
(1R,3aS,6S,7S,7aS)-7-(4-Chlorobenzyl)-3a-hydroxy-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3e)



Prepared from **1a** and **2e** according to General Procedure D. After 7 d, the reaction afforded **3e** (19.5 mg, **52**%**,** dr = **>20:1, 98**% ee) as a white solid.

MP: 87.6-91.1 °C
IR (neat): 3446, 2925, 1787, 1597, 1492, 1348, 1164, 969, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.68 (m, 2H), 7.33-7.24 (m, 4H), 7.05 (dd, J = 11.0, 2.3 Hz, 2H), 6.11 (d, J = 5.5 Hz, 1H), 6.04 (dd, J = 9.4, 6.2 Hz, 1H), 5.82-5.79 (m, 1H), 4.12 (t, J = 5.3 Hz, 1H), 3.27-3.24 (m, 2H), 2.69 (ddd, J = 38.3, 13.8, 7.9 Hz, 2H), 2.42 (s, 3H), 2.37-2.31 (m, 1H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 144.4, 137.0, 132.8, 131.6, 130.2, 130.0, 129.1, 127.3, 88.8, 72.9, 56.8, 48.9, 42.8, 32.1, 21.8
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{22}H_{21}ClNO_5S]^+$($[M+H]^+$) 446.0829; found 446.0824
$[\alpha]^{20}_D$: -96.41 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 37.4 min (major), 59.3 min (minor).

(1R,3aS,6S,7S,7aS)-7-(4-Bromobenzyl)-3a-hydroxy-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3f)

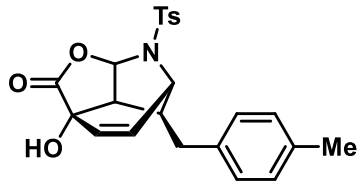


Prepared from **1a** and **2f** according to General Procedure D. After 7 d, the reaction afforded **3f** (21.1 mg, **51**%**,** dr = **>20:1, 95**% ee) as a white solid.

MP: 112.3-117.1 °C
IR (neat): 3460, 2960, 1787, 1597, 1489, 1349, 1164, 969, 757
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.2 Hz, 2H), 7.43-7.40 (m, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.2 Hz, 2H), 6.12 (d, J = 5.9 Hz, 1H), 6.03 (dd, J = 9.1, 6.4 Hz, 1H), 5.79 (d, J = 9.1 Hz, 1H), 4.14 (t, J = 5.3

Hz, 1H), 3.25 (td, J = 3.8, 1.8 Hz, 1H), 2.99 (br s, 1H), 2.68 (ddd, J = 37.7, 14.0, 7.8 Hz, 2H), 2.43 (s, 3H), 2.37 (td, J = 7.9, 3.8 Hz, 1H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 144.4, 137.5, 137.0, 132.0, 131.6, 130.6, 130.1, 130.0, 127.3, 120.8, 88.8, 72.8, 56.8, 48.9, 42.8, 32.2, 21.8
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{22}H_{21}BrNO_5S]^+$ ($[M+H]^+$) 490.0324; found 490.0319
$[\alpha]^{25}_D$: -11.70 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 41.1 min (major), 63.4 min (minor).

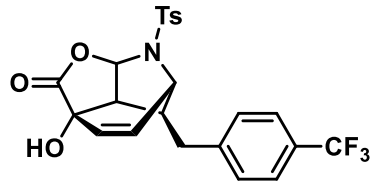
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-(4-methylbenzyl)-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3g)



Prepared from **1a** and **2g** according to General Procedure D. After 7 d, the reaction afforded **3g** (19.7 mg, **55%,** dr = **>20:1, 92**% ee) as a white solid.

MP: 85.2-90.5 °C
IR (neat): 3024, 2922, 1787, 1598, 1490, 1349, 1163, 969, 749
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 9.1 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 6.09 (d, J = 5.9 Hz, 1H), 6.04 (dd, J = 9.1, 6.4 Hz, 1H), 5.79 (d, J = 9.1 Hz, 1H), 4.13 (t, J = 5.3 Hz, 1H), 3.25 (td, J = 3.7, 2.0 Hz, 1H), 3.05 (br s, 1H), 2.72 (q, J = 7.2 Hz, 1H), 2.62 (dd, J = 14.0, 8.0 Hz, 1H), 2.42 (s, 3H), 2.39-2.35 (m, 1H), 2.33 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.9, 144.3, 137.1, 136.5, 135.5, 131.3, 130.4, 130.0, 129.6, 128.6, 127.3, 88.9, 72.9, 56.9, 49.1, 43.0, 32.2, 21.7, 21.2
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{23}H_{24}NO_5S]^+$ ($[M+H]^+$) 426.1375; found 426.1376
$[\alpha]^{25}_D$: -113.44 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 29.5 min (major), 44.2 min (minor).

(1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-tosyl-7-(4-(trifluoromethyl)benzyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3h)

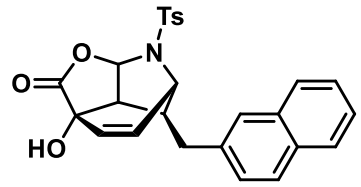


Prepared from **1a** and **2h** according to General Procedure D. After 7 d, the reaction afforded 3**h** (16.9 mg, **42%,** dr = **18:1, 96**% ee) as a white solid.

MP: 74.1-78.9 °C
IR (neat): 3447, 2925, 1788, 1598, 1449, 1326, 1164, 969, 758
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 7.8 Hz, 2H), 7.27 (t, J = 7.8 Hz, 4H), 6.13 (d, J = 5.5 Hz, 1H), 6.05 (dd, J = 9.2, 6.0 Hz, 1H), 5.81 (dt, J = 9.3, 1.4 Hz, 1H), 4.17 (dd, J = 5.7, 4.8 Hz, 1H), 3.26 (td, J = 3.7, 2.0 Hz, 1H), 3.08 (br s, 1H), 2.83 (dd, J = 14.0, 8.0 Hz, 1H), 2.74 (q, J = 7.2 Hz, 1H), 2.42 (qd, J = 7.9, 3.9 Hz, 4H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.6, 144.5, 142.7 (d, J = 6.7 Hz), 137.0, 131.7, 130.1 (d, J = 8.7 Hz), 129.2, 127.3, 125.9 (d, J = 3.9 Hz), 88.7, 72.8, 56.8, 48.9, 42.7, 32.6, 21.7

^{19}F NMR (378 MHz, $CDCl_3$) δ: -62.4
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{23}H_{21}F_3NO_5S]^+$ ($[M+H]^+$) 480.1093; found 480.1066
$[\alpha]^{25}_D$: -104.59 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 27.9 min (major), 38.4 min (minor).

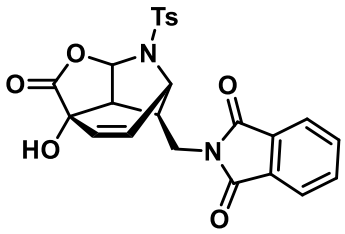
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-(naphthalen-2-ylmethyl)-8-tosyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (3i)



Prepared from **1a** and **2i** according to General Procedure D. After 7 d, the reaction afforded 3**i** (18.1 mg, **47%,** dr = **6:1, 96**% ee) as a white solid.

MP: 90.2-95.6 °C
IR (neat): 3446, 2925, 1786, 1599, 1449, 1349, 1164, 970, 783
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83-7.74 (m, 3H), 7.66-7.64 (m, 2H), 7.52 (s, 1H), 7.50-7.44 (m, 2H), 7.25-7.20 (m, 3H), 6.08-6.03 (m, 2H), 5.88 (d, J = 9.1 Hz, 1H), 4.08 (t, J = 5.0 Hz, 1H), 3.29 (td, J = 3.7, 2.1 Hz, 1H), 2.87 (ddd, J = 38.5, 14.1, 7.9 Hz, 2H), 2.74 (br s, 1H), 2.44-2.40 (m, 4H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.8, 144.3, 137.0, 136.1, 133.7, 132.4, 131.5, 130.3, 130.0, 128.7, 127.8, 127.6, 127.3, 126.9, 126.4, 125.9, 88.9, 72.9, 56.9, 49.2, 42.9, 32.8, 21.7
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{26}H_{24}NO_5S]^+$ ($[M+H]^+$) 462.1375; found 462.1384
$[\alpha]^{25}_D$: -22.43 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 85:15, 0.7 mL/min, λ=243nm) t_R = 54.2 min (major), 38.5 min (minor).

2-(((1R,3aS,6S,7R,7aS)-3a-Hydroxy-3-oxo-8-tosyl-1,3,3a,6,7,7a-hexahydro-1,6-epiminoisobenzofuran-7-yl)methyl)isoindoline-1,3-dione (3j)

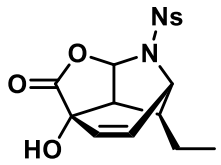


Prepared from **1a** and **2j** according to General Procedure D. After 7 d, the reaction afforded 3**j** (26.8 mg, **62%,** dr = **16:1, 84**% ee) as a white solid.

MP: 133.6-137.9 °C
IR (neat): 3422, 2924, 1791, 1597, 1489, 1350, 1166, 975, 756
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88-7.85 (m, 2H), 7.80-7.77 (m, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.30-7.24 (m, 2H), 6.16-6.12 (m, 2H), 5.86 (d, J = 9.7 Hz, 1H), 4.35 (t, J = 5.1 Hz, 1H), 4.13 (br s, 1H), 3.78 (dq, J = 24.4, 7.2 Hz, 2H), 3.34 (td, J = 3.8, 1.8 Hz, 1H), 2.54-2.49 (m, 1H), 2.41 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.4, 168.4, 144.5, 136.9, 134.7, 131.8, 131.3, 130.5, 130.0, 127.3, 123.9, 87.9, 72.3, 56.0, 48.6, 40.4, 35.2, 21.7
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{24}H_{21}N_2O_7S]^+$ ($[M+H]^+$) 481.1069; found 481.1058

[α]$^{20}_{D}$: -122.30 (*c* 1.0, CH_2Cl_2)
HPLC: (DAICEL Chiralpark OD-H, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 36.6 min (major), 24.9 min (minor).

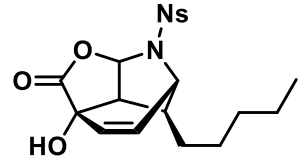
(1R,3aS,6S,7S,7aS)-7-ethyl-3a-Hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4k)



Prepared from **1b** and **2k** according to General Procedure D. After 6 d, the reaction afforded **4k** (26.5 mg, **83%,** dr = **14:1, 96**% ee) as a white solid.

MP: 117.3-121.2 °C
IR (neat): 3481, 2968, 1786, 1544, 1460, 1371, 1172, 982, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.06 (m, 1H), 7.73-7.64 (m, 3H), 6.39 (dd, J = 9.4, 6.2 Hz, 1H), 6.29 (d, J = 5.5 Hz, 1H), 5.78 (d, J = 9.1 Hz, 1H), 4.54 (t, J = 5.0 Hz, 1H), 3.36-3.31 (m, 2H), 2.28-2.23 (m, 1H), 1.53 (tt, J = 21.2, 7.0 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.8, 148.1, 134.3, 133.7, 132.6, 131.0, 130.8, 124.3, 89.2, 72.8, 57.9, 49.0, 43.3, 19.7, 12.1
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{16}H_{17}N_2O_7S]^+$ ($[M+H]^+$) 381.0756; found 381.0764
[α]$^{20}_{D}$: -105.12 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 20.8 min (major), 62.6 min (minor).

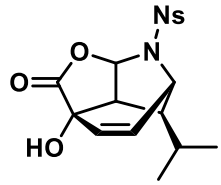
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-((4-nitrophenyl)sulfonyl)-7-pentyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4l)



Prepared from **1b** and **2m** according to General Procedure D. After 7 d, the reaction afforded **4l** (29.6 mg, **83%,** dr = **>20:1, 97**% ee) as a white solid.

MP: 55.8-59.7 °C
IR (neat): 3503, 2956, 1786, 1544, 1489, 1372, 1173, 972, 789
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.07 (m, 1H), 7.73-7.65 (m, 3H), 6.40 (dd, J = 9.4, 6.2 Hz, 1H), 6.29 (d, J = 5.5 Hz, 1H), 5.78-5.75 (m, 1H), 4.54 (t, J = 5.3 Hz, 1H), 3.33 (qd, J = 3.7, 1.7 Hz, 1H), 3.08 (br s, 1H), 2.34-2.28 (m, 1H), 1.53-1.21 (m, 8H), 0.89-0.86 (m, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.0, 148.1, 134.3, 133.7, 132.5, 131.0, 130.8, 124.3, 89.2, 72.8, 58.0, 49.3, 41.6, 31.8, 27.4, 26.3, 22.5, 14.1
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{19}H_{23}N_2O_7S]^+$ ($[M+H]^+$) 423.1226; found 423.1232
[α]$^{20}_{D}$: -111.99 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 14.7 min (major), 47.1 min (minor).

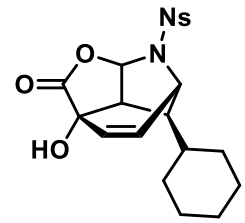
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-isopropyl-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4m)



Prepared from **1b** and **2l** according to General Procedure D. After 5 d, the reaction afforded **4m** (29.8 mg, **90%, single** dr**, 93**% ee) as a white solid.

MP: 108.1-113.4 °C
IR (neat): 3482, 2963, 1786, 1544, 1471, 1371, 1173, 961, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09-8.07 (m, 1H), 7.72-7.64 (m, 3H), 6.44 (dd, J = 9.4, 6.2 Hz, 1H), 6.28 (d, J = 5.9 Hz, 1H), 5.74 (d, J = 9.6 Hz, 1H), 4.57 (t, J = 5.3 Hz, 1H), 3.42 (qd, J = 3.8, 1.6 Hz, 1H), 2.97 (br s, 1H), 1.92 (dt, J = 10.4, 4.2 Hz, 1H), 1.80-1.75 (m, 1H), 0.95 (dd, J = 51.2, 6.4 Hz, 6H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.8, 148.1, 134.2, 133.8, 132.6, 131.1, 131.0, 131.0, 124.3, 89.4, 72.9, 57.7, 49.7, 48.2, 25.8, 21.1, 20.8
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{17}H_{19}N_2O_7S]^+$ ($[M+H]^+$) 395.0913; found 395.0904
$[\alpha]^{20}_D$: -255.84 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 15.8 min (major), 24.4 min (minor).

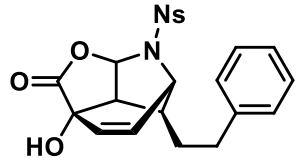
(1R,3aS,6S,7S,7aS)-7-Cyclohexyl-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4n)



Prepared from **1b** and **2v** according to General Procedure D. After 5 d, the reaction afforded **4n** (25.4 mg, **69%, single** dr, **95**% ee) as a white solid. (24.1 mg, **66**%, **single** dr, **-98**% ee with cat **K**)

MP: 205.2-207.9 °C
IR (neat): 3614, 2926, 1788, 1543, 1448, 1372, 1174, 962, 743
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.06 (m, 1H), 7.73-7.62 (m, 3H), 6.41 (dd, J = 9.4, 6.2 Hz, 1H), 6.25 (d, J = 5.9 Hz, 1H), 5.78 (d, J = 10.1 Hz, 1H), 4.56 (t, J = 5.3 Hz, 1H), 3.46-3.44 (m, 1H), 3.15 (br s, 1H), 1.97 (dt, J = 10.1, 4.1 Hz, 1H), 1.90 (d, J = 12.8 Hz, 1H), 1.71-1.65 (m, 3H), 1.53-1.44 (m, 2H), 1.28-1.10 (m, 3H), 1.02-0.90 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.9, 148.1, 134.2, 133.8, 132.5, 131.0, 124.3, 89.4, 72.8, 57.3, 48.3, 47.5, 34.7, 31.4, 31.1, 26.2, 25.8
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{20}H_{23}N_2O_7S]^+$ ($[M+H]^+$) 435.1226; found 435.1231
$[\alpha]^{20}_D$: -217.39 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IG, hexane/isopropanol 60:40, 1.0 mL/min, λ=243nm) t_R = 22.0 min (major), 14.1 min (minor).
ent-**4n** t_R = 13.5 min (major), 21.7 min (minor).

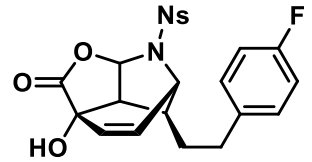
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-((4-nitrophenyl)sulfonyl)-7-phenethyl-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4o)



Prepared from **1b** and **2n** according to General Procedure D. After 5 d, the reaction afforded **4o** (32.6 mg, **85%,** dr = **>20:1, 95**% ee) as a white solid.

MP: 69.9-74.8 °C
IR (neat): 3503, 3026, 1785, 1543, 1456, 1370, 1172, 974, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08-8.06 (m, 1H), 7.73-7.64 (m, 3H), 7.30-7.14 (m, 5H), 6.36 (dd, J = 9.1, 6.4 Hz, 1H), 6.26 (d, J = 5.9 Hz, 1H), 5.79 (d, J = 9.1 Hz, 1H), 4.52 (t, J = 5.0 Hz, 1H), 3.32 (dd, J = 5.5, 4.1 Hz, 1H), 3.23 (br s, 1H), 2.71-2.56 (m, 2H), 2.36-2.30 (m, 1H), 1.90-1.79 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 148.1, 140.9, 134.3, 133.7, 132.6, 131.1, 131.0, 130.9, 128.7, 128.4, 126.5, 124.3, 89.0, 72.7, 57.9, 49.2, 41.0, 33.9, 28.2
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{22}H_{21}N_2O_7S]^+$ ($[M+H]^+$) 457.1069; found 457.1081
$[\alpha]^{20}_D$: -219.16 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 21.2 min (major), 43.4 min (minor).

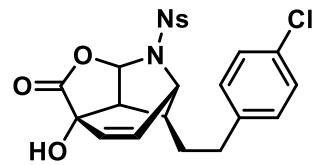
(1R,3aS,6S,7S,7aS)-7-(4-Fluorophenethyl)-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4p)



Prepared from **1a** and **2o** according to General Procedure D. After 3 d, the reaction afforded **4p** (29 mg, **72%,** dr = **>20:1, 96**% ee) as a white solid.

MP: 82.6-86.3 °C
IR (neat): 3481, 2928, 1785, 1601, 1509, 1306, 1173, 975, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08-8.06 (m, 1H), 7.73-7.65 (m, 3H), 7.10 (dd, J = 8.2, 5.5 Hz, 2H), 6.96 (t, J = 8.5 Hz, 2H), 6.37 (dd, J = 9.1, 5.9 Hz, 1H), 6.27 (d, J = 5.5 Hz, 1H), 5.79 (d, J = 9.6 Hz, 1H), 4.52 (t, J = 5.3 Hz, 1H), 3.33 (t, J = 4.8 Hz, 1H), 3.17 (br s, 1H), 2.67-2.55 (m, 2H), 2.33 (td, J = 7.5, 3.7 Hz, 1H), 1.85-1.78 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 148.1, 136.5, 134.3, 133.6, 132.6, 131.2, 131.0, 130.8, 129.8, 129.7, 124.3, 115.6, 115.4, 89.0, 72.7, 57.9, 49.2, 41.0, 33.1, 28.4
^{19}F NMR (378 MHz, $CDCl_3$) δ: -116.7
HRMS (ESI) m/z: $[M+NH_4]^+$ calcd for $[C_{22}H_{23}FN_3O_7S]^+$ ($[M+NH_4]^+$) 492.1235; found 492.1225
$[\alpha]^{20}_D$: -194.86 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 21.0 min (major), 48.6 min (minor).

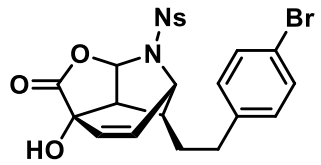
(1R,3aS,6S,7S,7aS)-7-(4-Chlorophenethyl)-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4q)



Prepared from **1b** and **2p** according to General Procedure D. After 3 d, the reaction afforded **4q** (32.1 mg, **77%,** dr = **>20:1, 99**% ee) as a white solid.

MP: 92.4-96.5 °C
IR (neat): 3481, 3026, 1787, 1544, 1441, 1370, 1172, 975, 771
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07-8.05 (m, 1H), 7.74-7.64 (m, 3H), 7.22 (dd, J = 8.9, 2.1 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.35 (dd, J = 9.1, 5.9 Hz, 1H), 6.25 (d, J = 5.9 Hz, 1H), 5.81 (d, J = 9.6 Hz, 1H), 4.49 (t, J = 5.3 Hz, 1H), 3.53 (br s, 1H), 3.34 (dd, J = 5.5, 4.1 Hz, 1H), 2.67-2.51 (m, 2H), 2.33-2.27 (m, 1H), 1.88-1.73 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.8, 148.0, 139.4, 134.3, 133.4, 132.6, 132.1, 131.2, 131.0, 130.6, 129.9, 129.8, 128.8, 124.3, 88.9, 72.8, 57.8, 49.0, 40.9, 33.2, 28.0
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{22}H_{20}N_2O_7SCl]^+$ ($[M+H]^+$) 491.0680; found 491.0674
$[\alpha]^{20}_D$: -181.18 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 22.9 min (major), 48.1 min (minor).

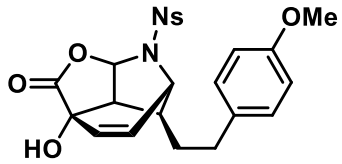
(1R,3aS,6S,7S,7aS)-7-(4-Bromophenethyl)-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4r)



Prepared from **1b** and **2q** according to General Procedure D. After 5 d, the reaction afforded **4r** (38.1 mg, **84%,** dr = **>20:1, 98**% ee) as a white solid.

MP: 101.8-105.9 °C
IR (neat): 3481, 3025, 1786, 1544, 1440, 1370, 1172, 975, 771
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.05 (m, 1H), 7.74-7.65 (m, 3H), 7.40-7.38 (m, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.38 (dd, J = 9.1, 5.9 Hz, 1H), 6.27 (d, J = 5.9 Hz, 1H), 5.79 (d, J = 9.1 Hz, 1H), 4.52 (t, J = 5.3 Hz, 1H), 3.34-3.32 (m, 1H), 3.17 (br s, 1H), 2.67-2.51 (m, 2H), 2.34-2.29 (m, 1H), 1.81 (tt, J = 22.9, 7.2 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 148.1, 139.9, 134.3, 133.6, 132.6, 131.8, 131.2, 131.0, 130.8, 130.2, 124.3, 120.2, 89.0, 72.7, 57.9, 49.1, 40.9, 33.3, 28.1
HRMS (ESI) m/z: $[M+NH_4]^+$ calcd for $[C_{22}H_{23}BrN_3O_7S]^+$ ($[M+NH_4]^+$) 552.0435; found 552.0421
$[\alpha]^{20}_D$: -195.18 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 22.6 min (major), 45.2 min (minor).

(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-(4-methoxyphenethyl)-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4s)

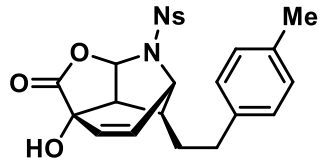


Prepared from **1b** and **2r** according to General Procedure D. After 5 d, the reaction afforded **4s** (35.3 mg, **86%,** dr = **>20:1, 95**% ee) as a white solid.

MP: 187.6-192.7 °C
IR (neat): 3471, 3026, 1787, 1544, 1441, 1370, 1174, 975, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (td, J = 3.5, 2.1 Hz, 1H), 7.71-7.64 (m, 3H), 7.07-7.05 (m, 2H), 6.84-6.81 (m, 2H), 6.35 (dd, J = 9.4, 6.2 Hz, 1H), 6.26 (d, J = 5.5 Hz, 1H), 5.77 (d, J = 9.1 Hz, 1H), 4.50 (t, J = 5.3 Hz, 1H), 3.79 (s, 3H), 3.30 (qd, J = 3.8, 1.6 Hz, 1H), 3.07 (br s, 1H), 2.66-2.51 (m, 2H), 2.34-2.28 (m, 1H), 1.88-1.73 (m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 158.2, 148.1, 134.3, 133.7, 132.9, 132.6, 131.1, 131.0, 131.0, 129.3, 124.3, 114.2, 89.0, 77.5, 77.2, 76.8, 72.7, 57.9, 55.4, 49.3, 41.0, 33.0, 28.4
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{23}H_{23}N_2O_8S]^+$ ($[M+H]^+$) 487.1175; found 487.1155
$[\alpha]^{20}_D$: -215.45 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 60:40, 1.0 mL/min, λ=243nm) t_R = 23.4 min (major), 37.9 min (minor).

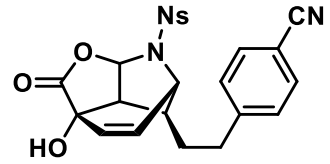
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-7-(4-methylphenethyl)-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4t)



Prepared from **1b** and **2s** according to General Procedure D. After 5 d, the reaction afforded **4t** (37.2 mg, **94%,** dr = **>20:1, 96**% ee) as a white solid.

MP: 95.7-99.6 °C
IR (neat): 3481, 3022, 1786, 1543, 1441, 1371, 1173, 974, 787
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (td, J = 3.7, 2.1 Hz, 1H), 7.71-7.64 (m, 3H), 7.10-7.03 (m, 4H), 6.36 (dd, J = 9.4, 6.2 Hz, 1H), 6.26 (d, J = 5.9 Hz, 1H), 5.78-5.76 (m, 1H), 4.51 (t, J = 5.5 Hz, 1H), 3.31 (qd, J = 3.7, 1.7 Hz, 1H), 2.98 (br s, 1H), 2.68-2.53 (m, 2H), 2.35-2.30 (m, 4H), 1.88-1.79 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.7, 148.1, 137.8, 136.0, 134.2, 133.7, 132.5, 131.1, 131.0, 131.0, 129.4, 128.3, 124.3, 89.0, 72.7, 58.0, 49.2, 41.0, 33.4, 28.3, 21.2
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{23}H_{23}N_2O_7S]^+$ ($[M+H]^+$) 471.1226; found 471.1218
$[\alpha]^{20}_D$: -209.07 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 20.8 min (major), 42.5 min (minor).

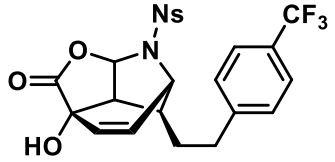
4-(2-((1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-((4-nitrophenyl)sulfonyl)-3-oxo-1,3,3a,6,7,7a-hexahydro-1,6-epiminoisobenzofuran-7-yl)ethyl)benzonitrile (4u)



Prepared from **1b** and **2t** according to General Procedure D. After 5 d, the reaction afforded **4u** (30.6 mg, **75%,** dr = **14:1, 98**% ee) as a white solid.

MP: 102-106.4 °C
IR (neat): 3421, 3022, 1788, 1543, 1441, 1371, 1173, 974, 743
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.06 (m, 1H), 7.75-7.65 (m, 3H), 7.58 (d, J = 8.2 Hz, 2H), 7.28-7.26 (m, 2H), 6.39 (dd, J = 9.1, 6.4 Hz, 1H), 6.30 (d, J = 5.5 Hz, 1H), 5.80 (d, J = 9.1 Hz, 1H), 4.56 (t, J = 5.3 Hz, 1H), 3.36 (dd, J = 5.5, 4.1 Hz, 1H), 3.12 (br s, 1H), 2.79-2.62 (m, 2H), 2.38-2.33 (m, 1H), 1.91-1.77 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.5, 148.1, 146.6, 134.4, 133.6, 132.6, 132.6, 131.3, 131.0, 130.7, 129.2, 124.4, 119.0, 110.4, 88.9, 72.7, 57.9, 49.1, 41.1, 34.0, 27.9
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{23}H_{20}N_3O_7S]^+$ ($[M+H]^+$) 482.1022; found 482.1020
$[\alpha]^{25}_D$: -229.94 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 50:50, 1.0 mL/min, λ=243nm) t_R = 38.9 min (major), 72.5 min (minor).

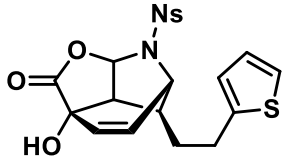
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-((4-nitrophenyl)sulfonyl)-7-(4-(trifluoromethyl)phenethyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4v)



Prepared from **1a** and **2u** according to General Procedure D. After 5 d, the reaction afforded **4v** (32 mg, **72%,** dr = 14**:1, 98**% ee) as a white solid.

MP: 86.7-90.3 °C
IR (neat): 3473, 2927, 1786, 1545, 1440, 1371, 1168, 975, 743
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.06 (m, 1H), 7.74-7.64 (m, 3H), 7.54 (d, J = 7.8 Hz, 2H), 7.34-7.28 (m, 2H), 6.39 (dd, J = 9.1, 6.4 Hz, 1H), 6.29 (d, J = 5.9 Hz, 1H), 5.80 (d, J = 9.1 Hz, 1H), 4.56 (t, J = 5.3 Hz, 1H), 3.36 (dd, J = 5.7, 4.3 Hz, 1H), 3.11 (br s, 1H), 2.78-2.62 (m, 2H), 2.39-2.32 (m, 1H), 1.86 (tt, J = 23.1, 7.1 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.6, 148.1, 145.0, 134.4, 133.6, 132.6, 131.3, 131.0, 130.8, 129.0, 128.7, 125.7, 125.7, 124.4, 89.0, 72.7, 57.9, 49.1, 41.0, 33.7, 28.1
^{19}F NMR (378 MHz, $CDCl_3$) δ: -62.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{23}H_{20}F_3N_2O_7S]^+$ ($[M+H]^+$) 525.0943; found 525.0947
$[\alpha]^{25}_D$: -215.70 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 60:40, 1.0 mL/min, λ=243nm) t_R = 10.7 min (major), 27.3 min (minor).

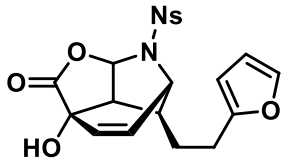
(1R,3aS,6S,7S,7aS)-3a-Hydroxy-8-((4-nitrophenyl)sulfonyl)-7-(2-(thiophen-2-yl)ethyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4w)



Prepared from **1b** and **2w** according to General Procedure D. After 5 d, the reaction afforded **4w** (32.2 mg, **83%,** dr = **17:1, 97**% ee) as a white solid.

MP: 77.7-83.4 °C
IR (neat): 3472, 2927, 1787, 1545, 1441, 1371, 1168, 975, 743
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (td, J = 3.5, 2.0 Hz, 1H), 7.72-7.65 (m, 3H), 7.14 (dd, J = 5.0, 0.9 Hz, 1H), 6.92 (q, J = 2.7 Hz, 1H), 6.79 (t, J = 1.6 Hz, 1H), 6.40 (dd, J = 9.1, 5.9 Hz, 1H), 6.28 (d, J = 5.5 Hz, 1H), 5.78 (d, J = 9.1 Hz, 1H), 4.54 (t, J = 5.3 Hz, 1H), 3.33 (dd, J = 5.9, 4.1 Hz, 1H), 2.96-2.84 (m, 3H), 2.39-2.35 (m, 1H), 1.94-1.87 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.6, 148.1, 143.4, 134.3, 133.7, 132.6, 131.2, 131.1, 131.0, 127.1, 124.9, 124.3, 123.7, 88.9, 72.7, 57.8, 49.2, 40.7, 28.5, 28.0
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{20}H_{19}N_2O_7S_2]^+$ ($[M+H]^+$) 463.0628; found 463.0604
$[\alpha]^{25}_D$: -211.67 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 70:30, 1.0 mL/min, λ=243nm) t_R = 18.9 min (major), 39.1 min (minor).

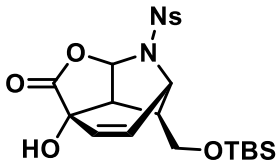
(1R,3aS,6S,7S,7aS)-7-(2-(Furan-2-yl)ethyl)-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4x)



Prepared from **1b** and **2x** according to General Procedure D. After 7 d, the reaction afforded **4x** (21.4 mg, **57%,** dr = **15:1, 95**% ee) as a white solid.

MP: 76.1-79.8 °C
IR (neat): 3566, 2916, 1789, 1543, 1489, 1373, 1172, 975, 731
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.06 (m, 1H), 7.73-7.64 (m, 3H), 7.30 (t, J = 0.9 Hz, 1H), 6.36 (dd, J = 9.4, 6.2 Hz, 1H), 6.29-6.27 (m, 2H), 6.02 (d, J = 3.2 Hz, 1H), 5.78 (d, J = 9.1 Hz, 1H), 4.51 (t, J = 5.3 Hz, 1H), 3.31 (td, J = 3.9, 2.0 Hz, 1H), 3.13 (br s, 1H), 2.76-2.61 (m, 2H), 2.35-2.29 (m, 1H), 1.86 (tt, J = 21.6, 7.2 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.6, 154.3, 148.1, 141.4, 134.3, 133.6, 132.6, 131.0, 130.9, 124.3, 110.5, 106.0, 88.9, 72.7, 57.8, 49.1, 40.8, 26.1, 25.0
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{20}H_{19}N_2O_8S]^+$ ($[M+H]^+$) 447.0857; found 447.0870
$[\alpha]^{20}_D$: -148.32 (*c* 0.65, $CHCl_3$)
HPLC: (DAICEL Chiralpark IC, hexane/isopropanol 60:40, 1.0 mL/min, λ=243nm) t_R = 16.0 min (major), 31.3 min (minor).

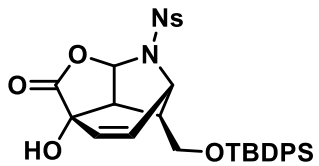
(1R,3aS,6S,7S,7aS)-7-(((tert-Butyldimethylsilyl)oxy)methyl)-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4y)



Prepared from **1b** and **2y** according to General Procedure D. After 5 d, the reaction afforded **4y** (34.9 mg, **83%,** dr = **>20:1, 98**% ee) as a white solid.

MP: 71.6-75.7 °C
IR (neat): 3631, 2928, 1785, 1545, 1372, 1174, 974, 773
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (dt, J = 5.3, 2.1 Hz, 1H), 7.74-7.65 (m, 3H), 6.41 (dd, J = 9.4, 6.2 Hz, 1H), 6.32 (d, J = 5.9 Hz, 1H), 5.79 (d, J = 9.1 Hz, 1H), 4.63 (t, J = 5.3 Hz, 1H), 3.77-3.68 (m, 2H), 3.37-3.35 (m, 1H), 2.62-2.56 (m, 1H), 1.69 (br s, 1H), 0.87 (s, 9H), 0.03 (s, 6H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.3, 148.1, 134.3, 133.6, 132.5, 131.1, 131.0, 124.4, 89.1, 77.5, 77.2, 76.8, 72.6, 59.7, 57.1, 47.5, 43.7, 25.9, 18.3, -5.3, -5.4
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{21}H_{29}N_2O_8SSi]^+$ ($[M+H]^+$) 497.1414; found 497.1425
$[\alpha]^{25}_D$: -153.95 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark ID, hexane/isopropanol 80:20, 1.0 mL/min, λ=243nm) t_R = 18.7 min (major), 17.8 min (minor).

(1R,3aS,6S,7S,7aS)-7-(((tert-Butyldiphenylsilyl)oxy)methyl)-3a-hydroxy-8-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3(1H)-one (4z)

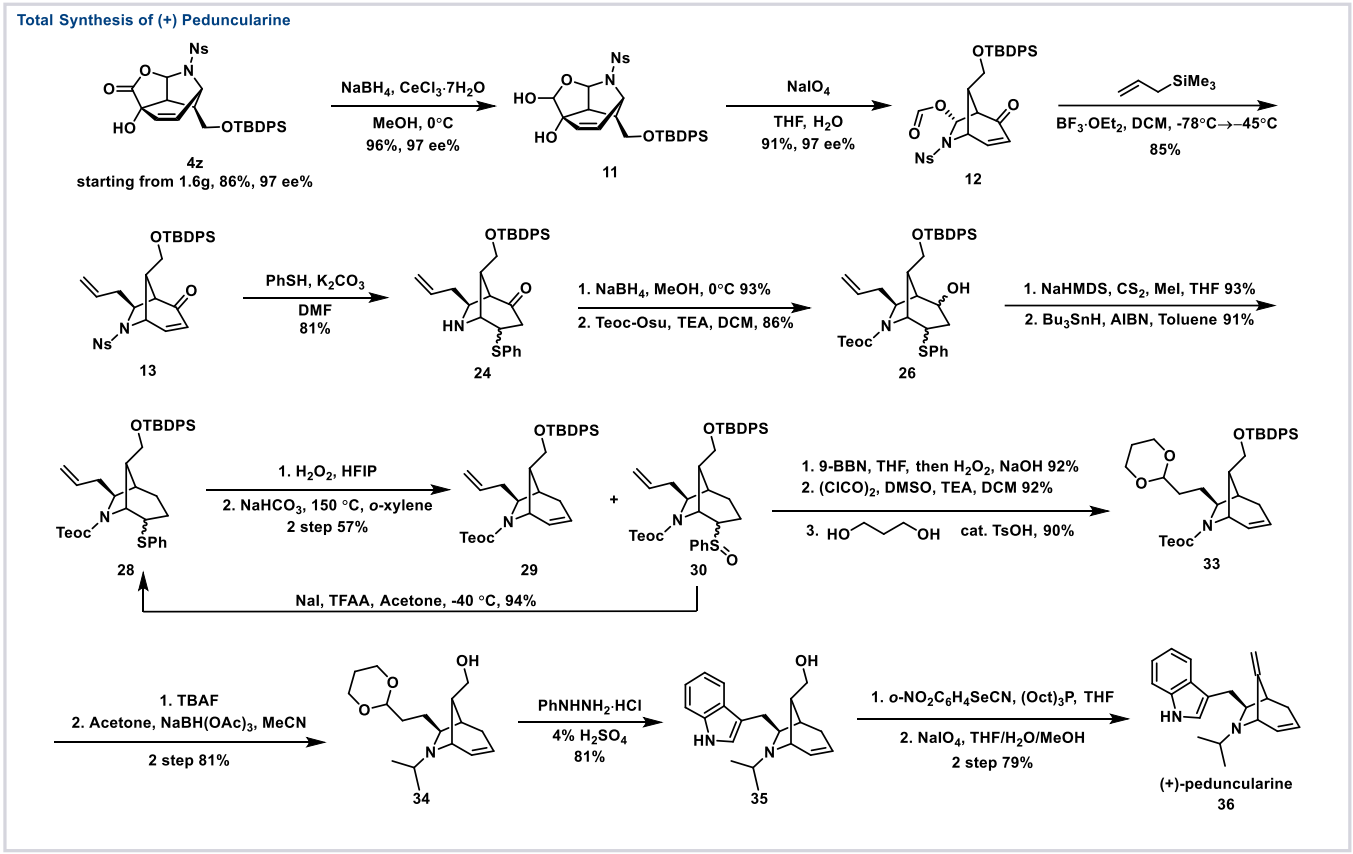


Prepared from **1b** and **2z** according to General Procedure D. After 5 d, the reaction afforded **4z** (43.1 mg, **82%, single** dr**, 97**% ee) as a white solid. (44.2 mg, **84**%, **-96**% ee with cat **K**)

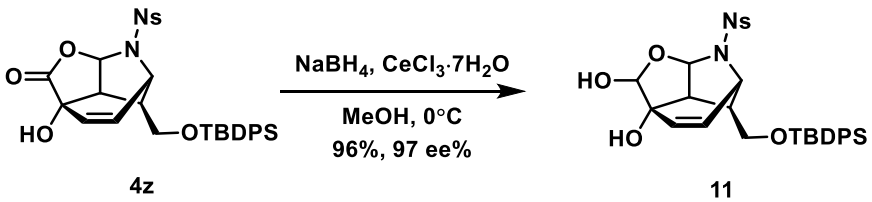
MP: 98.1-102.3 °C
IR (neat): 3649, 2931, 1789, 1546, 1373, 1175, 974, 743
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.08 (m, 1H), 7.74-7.59 (m, 7H), 7.46-7.36 (m, 6H), 6.30-6.25 (m, 2H), 5.65-5.63 (m, 1H), 4.67 (t, J = 5.5 Hz, 1H), 3.80-3.70 (m, 2H), 3.31-3.28 (m, 1H), 2.92 (br s, 1H), 2.64-2.58 (m, 1H), 1.04 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.3, 148.1, 135.7, 134.3, 133.5, 133.0, 133.0, 132.5, 131.1, 131.0, 130.7, 130.1, 128.0, 124.3, 89.1, 72.5, 60.4, 57.0, 47.4, 43.6, 26.9, 19.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{31}H_{33}N_2O_8SSi]^+$ ($[M+H]^+$) 621.1727; found 621.1737
$[\alpha]^{20}_D$: -180.31 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark ID, hexane/isopropanol 85:15, 1.0 mL/min, λ=243nm) t_R = 38.1 min (major), 28.6 min (minor).
ent-**4z** t_R = 27.2 min (major), 39.9 min (minor).

v. Synthesis of (+)-peduncularine

Scheme S3. Total synthesis of (+)-peduncularine



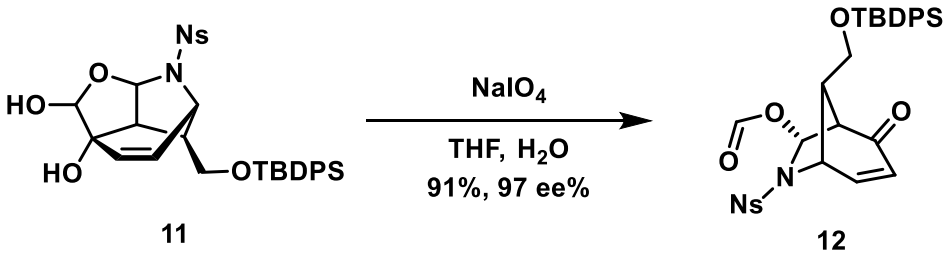
(1R,3aS,6S,7S,7aS)-7-(((tert-Butyldiphenylsilyl)oxy)methyl)-8-((4-nitrophenyl)sulfonyl)-1,6,7,7a-tetrahydro-1,6-epiminoisobenzofuran-3,3a(3H)-diol (11)



To a solution of **5q** (1614 mg, 2.6 mmol) and cerium(III) chloride heptahydrate (1162.5 mg, 3.12 mmol, 1.2 equiv) in MeOH (21.7 mL) was added sodium borohydride (147.5 mg, 3.9 mmol, 1.5 equiv) at 0 °C and the mixture was stirred for 10 min. Upon completion, determined by TLC, AcOH was added dropwise for quenching the extra sodium borohydride. The reaction mixture was concetrated in vacuo, diluted with EtOAc (30 mL) and H_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 10–40% EtOAc/hexanes) to give **11** (1549.7 mg, **96**%) as white solid.

MP: 88.1-94.6 °C
IR (neat): 3902, 3725, 2381, 1748, 1544, 1363, 1077, 1000, 773
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.09 (m, 1H), 7.68-7.57 (m, 7H), 7.44-7.34 (m, 6H), 6.09 (dd, J = 9.6, 5.9 Hz, 1H), 6.00 (d, J = 5.5 Hz, 1H), 5.76-5.74 (m, 1H), 4.91 (s, 1H), 4.41 (t, J = 5.3 Hz, 1H), 3.87-3.77 (m, 2H), 2.96 (td, J = 4.2, 1.4 Hz, 1H), 2.44 (dd, J = 9.1, 5.5 Hz, 1H), 1.02 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.3, 135.7, 133.9, 133.7, 133.4, 133.3, 131.9, 131.8, 131.3, 130.0, 129.6, 127.9, 124.1, 100.4, 92.6, 76.4, 60.8, 55.5, 47.2, 44.7, 27.0, 19.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{31}H_{35}N_2O_8SSi]^+$ ($[M+H]^+$) 623.1883; found 623.1900
$[\alpha]^{20}_D$: -10.99 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark AD-H, hexane/isopropanol 90:10, 0.7 mL/min, λ=243nm) t_R = 28.0 min (major), 26.9 min (minor).

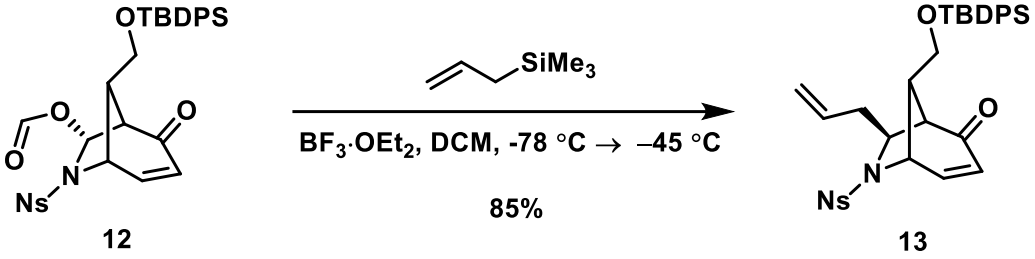
(1R,5S,7S,8S)-8-(((tert-Butyldiphenylsilyl)oxy)methyl)-6-((4-nitrophenyl)sulfonyl)-2-oxo-6-azabicyclo[3.2.1]oct-3-en-7-yl formate (12)



To a solution of **11** (5021 mg, 8.06 mmol) in THF (100.78 mL) was added $NaIO_4$ (4483.7 mg, 20.96 mmol, 2.6 equiv) in H_2O (6.05 mL) at room temperature under Ar atmosphere and the mixture was stirred for 3 h. Upon completion, determined by TLC, the reaction was quenched with H_2O (80 mL) and diluted with EtOAc (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 5–30% EtOAc/hexanes) to give **12** (4530.3 mg, **91**%) as a white solid.

MP: 157.3-161.1 °C
IR (neat): 3903, 3725, 2381, 1734, 1546, 1372, 1074, 988, 772
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.08 (m, 1H), 7.83 (d, J = 0.9 Hz, 1H), 7.79-7.70 (m, 3H), 7.58-7.55 (m, 4H), 7.47-7.36 (m, 6H), 7.18 (ddd, J = 9.6, 5.9, 1.4 Hz, 1H), 6.94 (dd, J = 5.9, 0.9 Hz, 1H), 6.09 (d, J = 10.1 Hz, 1H), 4.90 (t, J = 5.3 Hz, 1H), 3.70 (dd, J = 10.7, 6.2 Hz, 1H), 3.58 (dd, J = 10.7, 8.9 Hz, 1H), 3.47-3.44 (m, 1H), 2.85-2.80 (m, 1H), 1.03 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 193.9, 158.8, 148.1, 146.1, 135.6, 134.5, 133.2, 132.8, 132.7, 132.6, 132.5, 131.5, 130.2, 128.0, 124.8, 82.9, 60.7, 57.7, 56.2, 53.0, 26.9, 19.2
HRMS (ESI) m/z: $[M+Na]^+$ calcd for $[C_{31}H_{32}N_2NaO_8SSi]$+ ([M+Na]+) 643.1532; found 643.1541
$[\alpha]^{20}_D$: +29.39 (*c* 1.0, $CHCl_3$)
HPLC: (DAICEL Chiralpark ID, hexane/isopropanol 80:20, 1.0 mL/min, λ=243nm) t_R = 23.5 min (major), 22.3 min (minor).

(1R,5S,7S,8S)-7-allyl-8-(((tert-Butyldiphenylsilyl)oxy)methyl)-6-((4-nitrophenyl)sulfonyl)-6-azabicyclo[3.2.1]oct-3-en-2-one (13)

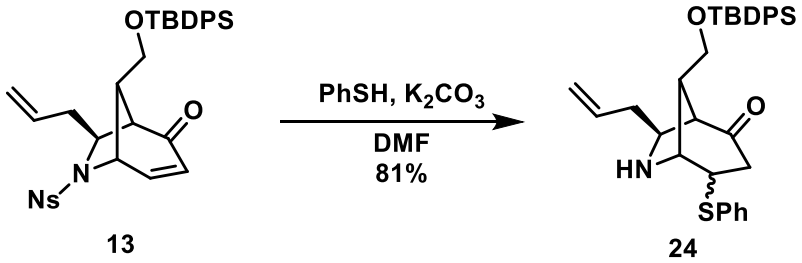


12 13

To a solution of **12** (1349 mg, 2.17 mmol) in dry CH_2Cl_2 (21.73 mL) were added sequentially allyltrimethylsilane (1.38 mL, 8.69 mmol, 4 equiv) and $BF_3{\cdot}Et_2O$ (0.54 mL, 4.35 mmol, 2 equiv), and the mixture was stirred at -78 °C under an Ar atmoshere[14]. Then the solution was warmed to -30 °C for 2 h. Upon completion, determined by TLC, the reaction was quenched with saturated solution of $NaHCO_3$ (10 mL) and then diluted with H_2O (40 mL). The heterogeneous solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 1:2:8 Et_2O/CH_2Cl_2/hexanes) to give **13** (1134.8 mg, **85**%) as a white solid.

MP: 65.2-71.1 °C
IR (neat): 3903, 3725, 2381, 1748, 1544, 1372, 1165, 998, 773
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.07 (m, 1H), 7.77-7.68 (m, 3H), 7.61 (tt, J = 6.4, 1.7 Hz, 4H), 7.47-7.36 (m, 6H), 7.00 (qd, J = 5.0, 1.4 Hz, 1H), 5.98 (dd, J = 9.6, 0.9 Hz, 1H), 5.63-5.52 (m, 1H), 5.05 (d, J = 9.1 Hz, 1H), 4.96 (dd, J = 17.4, 1.4 Hz, 1H), 4.65 (t, J = 4.8 Hz, 1H), 3.82 (dd, J = 9.6, 3.7 Hz, 1H), 3.70 (q, J = 5.6 Hz, 1H), 3.56 (dd, J = 10.7, 9.4 Hz, 1H), 2.86 (q, J = 4.4 Hz, 1H), 2.77 (d, J = 4.1 Hz, 1H), 2.41-2.35 (m, 1H), 2.19-2.11 (m, 1H), 1.06 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 197.4, 147.6, 135.7, 134.4, 134.2, 133.1, 133.0, 132.8, 132.1, 130.7, 130.5, 130.1, 130.0, 128.0, 128.0, 124.6, 119.3, 60.7, 60.5, 59.1, 55.4, 49.4, 37.7, 26.9, 19.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{37}N_2O_6SSi]+$ ([M+H]+) 617.2142; found 617.2165
$[\alpha]^{20}_D$: +31.82 (*c* 1.0, $CHCl_3$)

(1R,5R,7S,8S)-7-allyl-8-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-(phenylthio)-6-azabicyclo[3.2.1]octan-2-one (24)



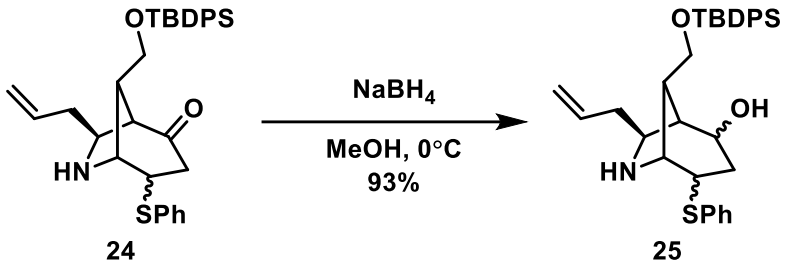
13 24

To a solution of **13** (1476 mg, 2.393 mmol) in dry DMF (11.97 mL) were added K_2CO_3 (727.6 mg, 5.265 mmol, 2.2 equiv) and thiophenol (0.73 mL, 7.179 mmol, 3 equiv), and the mixture was stirred at room temperature under an Ar atmosphere for 2 h. Upon completion, determined by TLC, the reaction was quenched with H_2O (30 mL) and diluted with EtOAc (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 1:2:8 Et_2O/CH_2Cl_2/hexanes) to give **24** (1049.8 mg, **81**%) as a clear oil.

IR (neat): 3728, 2384, 1714, 1586, 1472, 1285, 1113, 999, 803
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (dq, J = 6.7, 1.3 Hz, 4H), 7.46-7.34 (m, 8H), 7.29-7.24 (m, 3H), 5.80-5.70 (m, 1H), 5.09-5.04 (m, 2H), 3.79-3.73 (m, 2H), 3.62-3.53 (m, 2H), 3.32 (t, J = 6.9 Hz, 1H), 2.73 (td, J = 9.8, 4.9 Hz, 1H), 2.64 (dd, J = 16.8, 7.1 Hz, 1H), 2.46 (d, J = 4.1 Hz, 1H), 2.32 (dd, J = 16.8, 11.3 Hz, 1H), 2.24-2.10 (m, 2H), 0.96 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.9, 135.7, 135.6, 135.0, 133.1, 133.0, 132.9, 132.8, 130.0, 129.3, 128.0,

127.9, 117.8, 61.2, 59.6, 57.3, 55.4, 48.6, 45.7, 42.7, 41.5, 26.9, 19.2
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{40}NO_2SSi]^+$ ($[M+H]^+$) 542.2549; found 542.2566
$[\alpha]^{20}_D$: +9.82 (*c* 1.0, $CHCl_3$)

(1R,5R,7S,8S)-7-allyl-8-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-(phenylthio)-6-azabicyclo[3.2.1]octan-2-ol (25)

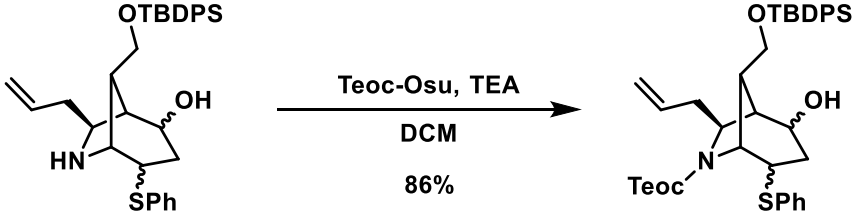


24 25

To a stirred solution of **24** (738 mg, 1.36 mmol) in MeOH (11.35 mL) at 0 °C was added sodium borohydride (77.3 mg, 2.04 mmol, 1.5 equiv) and the mixture was stirred for 10 min at same temperature. Upon completion, determined by TLC, the reaction mixture was quenched with H_2O (30 mL) and concentrated in vacuo. The crude reaction mixture was diluted with EtOAc (30 mL) and H_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 10–40% EtOAc/hexanes) to give **25** (685.4 mg, **93**%) as a white solid.

MP: 64.3-68.8 °C
IR (neat): 3445, 2953, 2858, 2320, 1679, 1427, 1348, 1250, 1186, 1113, 998, 742
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (tt, J = 4.8, 1.5 Hz, 4H), 7.45-7.35 (m, 8H), 7.25-7.17 (m, 3H), 5.80-5.70 (m, 1H), 5.06 (d, J = 1.4 Hz, 1H), 5.03 (d, J = 2.7 Hz, 1H), 4.17-4.02 (m, 2H), 3.86 (t, J = 4.3 Hz, 1H), 3.68 (q, J = 6.1 Hz, 1H), 3.38 (d, J = 4.6 Hz, 1H), 2.95 (t, J = 7.1 Hz, 1H), 2.72 (s, 1H), 2.35-2.29 (m, 1H), 2.21-1.97 (m, 4H), 1.77-1.69 (m, 1H), 1.01 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.0, 135.7, 133.9, 133.4, 133.3, 132.4, 130.0, 129.9, 129.1, 127.9, 127.9, 127.3, 117.0, 70.6, 62.4, 58.8, 57.3, 45.1, 44.3, 44.2, 42.9, 33.6, 27.0, 19.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{33}H_{42}NO_2SSi]^+$ ($[M+H]^+$) 544.2700; found 544.2692
$[\alpha]^{20}_D$: -46.61 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5R,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-2-hydroxy-4-(phenylthio)-6-azabicyclo[3.2.1]octane-6-carboxylate (26)



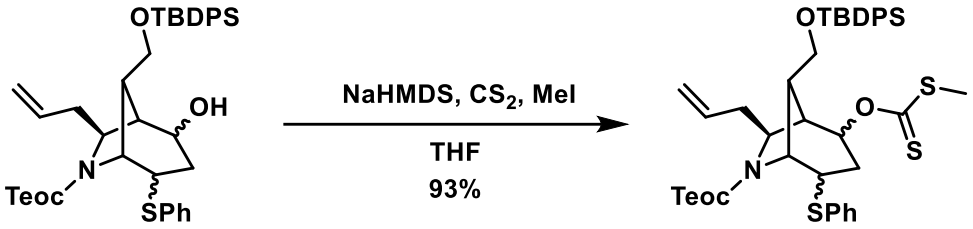
25 26

To a solution of **25** (1050 mg, 1.93 mmol) in dry CH_2Cl_2 (38.61 mL) were added Teoc-OSu (1001.4 mg, 3.86 mmol, 2 equiv) and Et_3N (0.54 mL, 3.86 mmol, 2 equiv), and the mixture was stirred at reflux under Ar atmosphere for 1 day. Upon completion, determined by TLC, the reaction was quenched with H_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–20% EtOAc/hexanes) to give **26** (1148.5 mg, **86**%) as a white solid.

MP: 51.2-55.3 °C

IR (neat): 3424, 2953, 2857, 1666, 1586, 1428, 1350, 1250, 1112, 998, 739
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.61 (m, 4H, HCAr), 7.48-7.31 (m, 8H, HCAr), 7.26-7.16 (m, 3H, HCAr), 5.76-5.66 (m, 1H, HC=), 5.08-5.01 (m, 2H, H_2C=), 4.52 (d, J = 5.0 Hz, 0.3H, CHN rotamer), 4.48 (d, J = 5.0 Hz, 0.7H, CHN rotamer), 4.35-4.19 (m, 2H, CHH', CHH'), 4.17-4.05 (m, 1H, CHH'), 3.99 (q, J = 5.6 Hz, 1H, CHH'), 3.85 (s, 1H, CH(OH)), 3.77 (q, J = 5.8 Hz, 0.7H, CH(SPh) rotamer), 3.70 (dd, J = 12.1, 5.3 Hz, 0.3H, CH(SPh) rotamer), 3.45 (dd, J = 10.3, 3.0 Hz, 0.7H, CHN rotamer), 3.38 (dd, J = 10.1, 2.7 Hz, 0.3H, CHN rotamer), 2.98-2.93 (m, 0.7H, CHH' rotamer), 2.81 (dd, J = 14.2, 2.7 Hz, 0.3H, CHH' rotamer), 2.43 (td, J = 9.1, 5.0 Hz, 0.7H, CH rotamer), 2.35 (q, J = 2.7 Hz, 0.3H, CH rotamer), 2.26-2.19 (m, 1H, CH, 0.3H, CHH' rotamer), 2.02-1.75 (m, 0.7H, CHH' rotamer, 1H, CHH', 2H, CH_2), 1.08-0.96 (s and s, 9H, tBu rotamer, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.2, 135.8, 135.7, 135.2, 133.5, 132.0, 130.5, 130.0, 129.1, 129.0, 128.0, 127.9, 127.0, 126.5, 117.7, 70.3, 70.2, 63.6, 63.2, 62.3, 62.2, 60.3, 60.1, 58.6, 58.1, 45.2, 44.9, 44.3, 43.9, 43.8, 42.2, 37.9, 36.4, 35.7, 35.1, 27.1, 27.0, 19.3, 18.0, 17.6, -1.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{39}H_{54}NO_4SSi_2]^+$ ($[M+H]^+$) 688.3307; found 688.3317
$[\alpha]^{20}_D$: -5.57 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5R,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(((methylthio)carbonothioyl)oxy)-4-(phenylthio)-6-azabicyclo[3.2.1]octane-6-carboxylate (27)

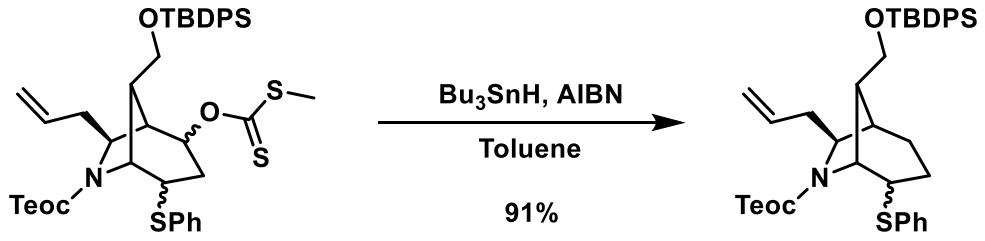


26 **27**

To a solution of **26** (848 mg, 1.23 mmol) in dry THF (12.3 mL) was added a 2.00 M solution of sodium bis(trimethylsilyl)amide in THF (1.2 mL, 2.46 mmol, 2 equiv), and the reaction mixture was stirred at –78 °C under Ar atmosphere for 30 min. Carbon disulfide (0.22 mL, 3.69 mmol, 3 equiv) was then added, and the mixture was stirred for 1 h at –78 °C. Subsequently, iodomethane (0.38 mL, 6.15 mmol, 5 equiv) was added, and the mixture was stirred for an additional 1.5 h at –78 °C. Upon completion, determined by TLC, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–20% Et_2O/hexanes) to give **27** (892.1 mg, **93**%) as a clear oil.

IR (neat): 3725, 3071, 2954, 2857, 2371, 1696, 1586, 1426, 1349, 1250, 1112, 999, 740
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.60 (m, 4H, HCAr), 7.50-7.18 (m, 11H, HCAr), 5.76-5.64 (m, 1H, HC=), 5.53 (d, J = 2.7 Hz, 1H, CH(O)), 5.08-5.01 (m, 2H, H_2C=), 4.69 (d, J = 5.0 Hz, 0.3H, CHN rotamer), 4.64 (d, J = 5.0 Hz, 0.7H, CHN rotamer), 4.37-4.04 (m, 2H, CH_2, 1H, CHH'), 3.79 (td, J = 11.5, 4.4 Hz, 1H, CHH'), 3.72 (q, J = 5.8 Hz, 0.7H, CH(SPh) rotamer), 3.62 (q, J = 5.9 Hz, 0.3H, CH(SPh) rotamer), 3.56 (dd, J = 10.3, 3.0 Hz, 0.7H, CHN rotamer), 3.48 (dd, J = 10.1, 2.7 Hz, 0.3H, CHN rotamer), 3.01-2.96 (m, 0.7H, CHH' rotamer), 2.83 (dd, J = 13.5, 4.8 Hz, 0.3H, CHH' rotamer), 2.54-2.44 (m, 1H, CH, 1H, CH), 2.36 (s and s, 3H, OCH_3), 2.17 (dd, J = 15.6, 5.5 Hz, 0.3H, CHH' rotamer), 2.08 (dd, J = 15.8, 5.3 Hz, 0.7H, CHH' rotamer), 1.99-1.84 (m, 1H, CHH', 1H, CHH'), 1.17-0.94 (s and s, 9H, tBu rotamer, 2H, CH_2), 0.05 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.6, 155.1, 135.7, 135.5, 134.6, 133.6, 133.5, 132.1, 130.3, 129.9, 129.2, 129.1, 128.0, 127.9, 127.2, 126.6, 118.0, 80.7, 80.5, 63.7, 63.3, 62.1, 60.2, 60.0, 58.1, 57.5, 45.3, 44.5, 42.0, 41.7, 40.7, 37.8, 36.2, 32.3, 31.7, 27.1, 27.0, 19.4, 19.3, 19.1, 18.0, 17.6, -1.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{41}H_{56}NO_4S_3Si_2]^+$ ($[M+H]^+$) 778.2905; found 778.2914
$[\alpha]^{20}_D$: -13.49 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5R,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(phenylthio)-6-azabicyclo[3.2.1]octane-6-carboxylate (28)

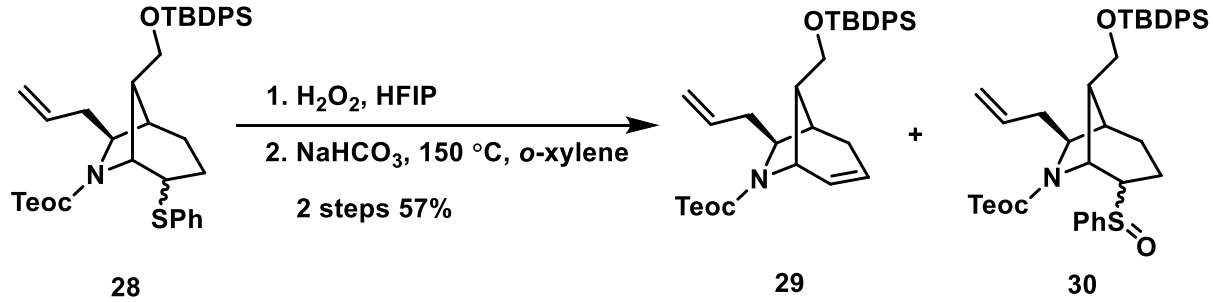


27 28

To a stirred solution of **27** (952 mg, 1.22 mmol) in dry PhMe (12.23 mL) were added a 0.20 M solution of 2,2′-azobis(2-methylpropionitrile) in THF (AIBN, 1.22 mL, 0.25 mmol, 0.2 equiv) and n-Bu_3SnH (0.66 mL, 2.45 mmol, 2 equiv) at room temperature under Ar atmosphere. The resulting mixture was degassed under an Ar atmosphere for 15 min and then heated to 90 °C for 1 h. Upon completion, determined by TLC, the solvent was removed in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–10% Et_2O/hexanes) to give **28** (750.1 mg, **91**%) as a clear oil.

IR (neat): 3735, 3071, 2953, 2858, 2310, 1692, 1586, 1427, 1344, 1250, 1113, 997, 740
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68-7.61 (m, 4H, HCAr), 7.48-7.29 (m, 8H, HCAr), 7.25-7.15 (m, 3H, HCAr), 5.79-5.67 (m, 1H, HC=), 5.05-5.00 (m, 2H, H_2C=), 4.52 (d, J = 5.5 Hz, 0.3H, CHN rotamer), 4.47 (d, J = 5.5 Hz, 0.7H, CHN rotamer), 4.36-4.03 (m, 2H, CH_2), 3.97-3.75 (m, 2H, CH_2), 3.64 (dd, J = 10.1, 2.7 Hz, 0.7H, CHN rotamer), 3.55 (dd, J = 10.3, 2.5 Hz, 0.3H, CHN rotamer), 3.45 (q, J = 5.6 Hz, 0.7H, CH(SPh) rotamer), 3.35 (q, J = 5.8 Hz, 0.3H, CH(SPh) r otamer), 2.97-2.93 (m, 0.7H, CHH' rotamer), 2.80 (dd, J = 12.8, 5.5 Hz, 0.3H, CHH' rotamer), 2.51-2.42 (m, 1H, CH), 2.08 (dd, J = 13.3, 2.7 Hz, 1H, CH), 2.00-1.73 (m, 1H, CHH', 1H, CHH'), 1.68-1.54 (m, 1H, CHH'), 1.48-1.33 (m, 2H, CH_2), 1.08-0.92 (s and s, 9H, tBu rotamer, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.0, 136.2, 135.7, 133.5, 132.2, 130.6, 130.0, 129.0, 128.9, 128.0, 127.9, 126.9, 126.4, 117.2, 63.4, 63.0, 62.3, 62.2, 61.1, 60.9, 59.1, 58.5, 46.9, 45.3, 45.1, 44.6, 38.1, 38.0, 37.1, 36.4, 27.0, 26.3, 25.1, 19.3, 17.6, -1.2, -1.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{39}H_{54}NO_3SSi_2]^+$ ($[M+H]^+$) 672.3357; found 672.3347
$[\alpha]^{20}_D$: -2.30 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (29)



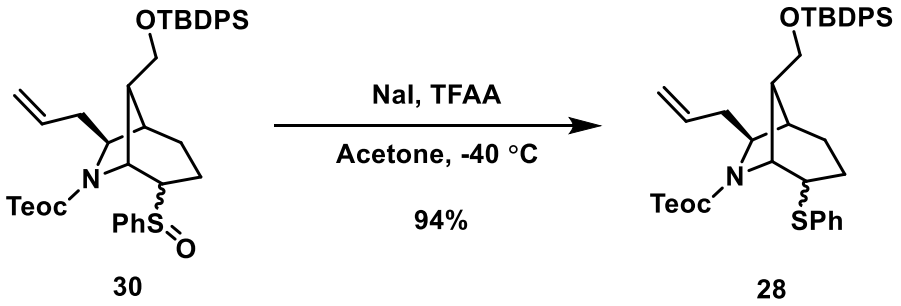
28 29 30

To a solution of **28** (551 mg, 0.82 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (17.82 mL) was added aqueous H_2O_2 (0.15 mL, 1.48 mmol, 30% w/w, 1.8 equiv) dropwise, and the mixture was stirred at room temperature for 30 min. Upon completion, determined by TLC, the reaction mixture was treated with saturated aqueous sodium sulfite (5 mL) and extracted with CH_2Cl_2 (36 mL). After drying the combined organic layers over Na_2SO_4, the solvent was removed under reduced pressure to give a mixture of two sulfoxide epimers, which was used directly in the next reaction without further purification. This crude sulfoxide mixture was dissolved in o-xylene (2.05 mL), treated with sodium bicarbonate (344.4 mg, 4.1 mmol, 5 equiv), and then stirred for 6 h at 150 °C in sealed tube. Upon completion, determined by TLC, the reaction was quenched with H_2O (20 mL) and diluted with Et_2O (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting

crude product was purified by flash column chromatography (silica gel, 0–15% Et_2O/hexanes) to give **29** (260.3 mg, **57**%) as a clear oil.

IR (neat): 3071, 2954, 2857, 1698, 1589, 1427, 1324, 1249, 1184, 1113, 998, 741
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (dd, J = 10.1, 8.3 Hz, 4H, HCAr), 7.45-7.36 (m, 6H, HCAr), 6.07-6.04 (m, 0.4H, HC=rotamer), 5.91-5.87 (m, 0.6H, HC=rotamer), 5.85-5.73 (m, 1H, HC=), 5.52 (d, J = 9.7 Hz, 1H, HC=), 5.07-5.02 (m, 2H, H_2C=), 4.20-4.12 (m, 2H, CHH', CHH', 0.4H, CHN rotamer), 4.07 (t, J = 5.1 Hz, 0.6H, CHN rotamer), 3.81-3.70 (m, 2H, CH_2), 3.56 (dd, J = 9.9, 3.0 Hz, 0.6H, CHN rotamer), 3.47 (dd, J = 10.1, 2.8 Hz, 0.4H, CHN rotamer), 2.71 (d, J = 13.3 Hz, 0.6H, CHH' rotamer), 2.64-2.60 (m, 0.4H, CHH' rotamer), 2.50-2.42 (m, 1H, CH), 2.17-2.04 (m, 1H, CHH' rotamer, 1H, CHH' rotamer, 1H, CH), 1.89 (t, J = 9.4 Hz, 1H, CHH' rotamer), 1.05 (s and s, 9H, tBu rotamer), 1.00 (dd, J = 9.4, 7.1 Hz, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.8, 135.9, 135.8, 135.7, 133.8, 129.8, 129.1, 128.5, 128.2, 127.8, 127.8, 117.0, 66.1, 65.5, 63.2, 63.1, 61.9, 53.6, 42.3, 41.6, 39.0, 38.4, 37.7, 36.8, 31.9, 29.9, 27.0, 19.4, 18.0, -1.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{33}H_{48}NO_3Si_2]^+$ ($[M+H]^+$) 562.3167; found 562.3146
$[\alpha]^{20}_D$: +125.21 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5R,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(phenylsulfinyl)-6-azabicyclo[3.2.1]octane-6-carboxylate (30)

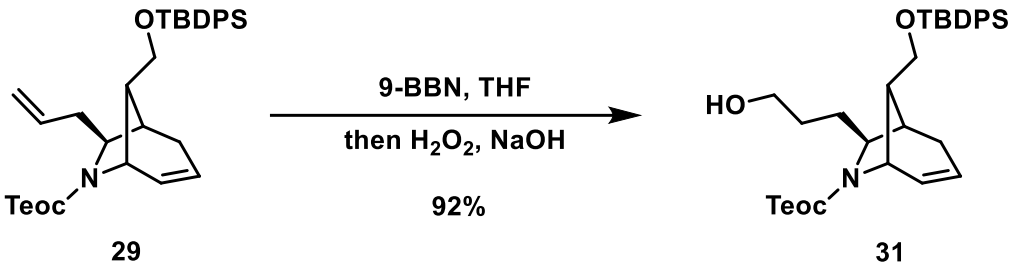


30 **28**

To a stirred suspension of **30** (85 mg, 0.12 mmol) and NaI (37 mg, 0.25 mmol, 2.0 equiv) in dry acetone (1.48 mL) at −40 °C under an Ar atmosphere was added dropwise trifluoroacetic anhydride (0.05 mL, 0.37 mmol, 3.0 equiv). The reaction mixture was stirred at −40 °C for 10 min. Upon completion, determined by TLC, the reaction was quenched by sequential addition of saturated Na_2SO_3 (10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–10% Et_2O/hexanes) to give **28** (77.7 mg, **94**%).

IR (neat): 3071, 2953, 2858, 1693, 1589, 1427, 1330, 1251, 1182, 1113, 998, 745
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.56 (m, 6H, HCAr), 7.52-7.36 (m, 9H, HCAr), 5.81-5.68 (m, 1H, HC=), 5.09-5.02 (m, 2H, H2C=), 4.91 (d, J = 5.5 Hz, 0.2H, CHN rotamer), 4.84 (d, J = 5.5 Hz, 0.8H, CHN rotamer), 4.41-4.20 (m, 2H, CH2), 3.88-3.67 (m, 2H, CH2), 3.61 (dd, J = 10.1, 2.7 Hz, 0.8H, CHN rotamer), 3.51 (dd, J = 10.1, 2.7 Hz, 0.2H, CHN rotamer), 3.03-2.98 (m, 0.8H, CH(SPh) rotamer), 2.84 (d, J = 10.1 Hz, 0.2H, CH(SPh) rotamer), 2.61-2.46 (m, 1H, CHH', 1H, CHH'), 2.27 (t, J = 24.7 Hz, 1H, CH), 2.05-1.92 (m, 1H, CH), 1.38-1.28 (m, 2H, CH2), 1.24-1.19 (m, 1H, CHH'), 1.06 (s and s, 9H, tBu rotamer), 1.02-0.80 (m, 2H, CH2), 0.05 (s and s, 9H, SiMe3 rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.8, 143.1, 135.7, 135.4, 133.5, 133.3, 131.6, 130.0, 130.0, 129.2, 128.0, 127.9, 125.7, 117.5, 66.1, 63.8, 62.3, 60.2, 54.1, 44.4, 36.5, 27.0, 23.8, 19.3, 18.6, 17.5, -1.2, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{39}H_{54}NO_4SSi_2]^+$ ($[M+H]^+$) 688.3312; found 688.3317
$[\alpha]^{20}_D$: -40.09 (*c* 1.0, $CHCl_3$)

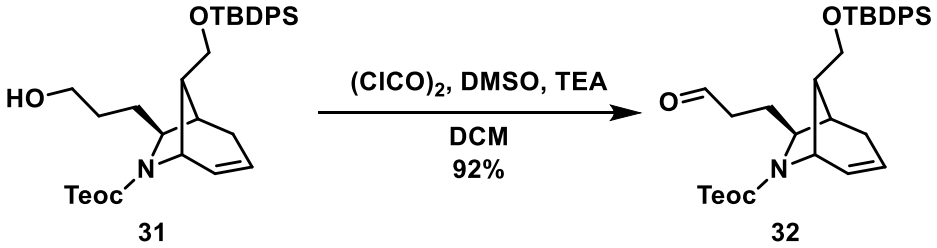
2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-7-(3-hydroxypropyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (31)



To a solution of **29** (385 mg, 0.68 mmol) in dry THF (4.57 mL) was added 9-BBN dimer (334.4 mg, 1.37 mmol, 2 equiv) and the mixture was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was cooled to 0 °C and treated with EtOH (1.46 mL)[7]. After stirring for 10 min, aq. NaOH (6 M, 0.47 mL) and aqueous H_2O_2 (30% w/w, 0.98 mL) were added, and the resulting mixture was heated to 50 °C for 1 h. Upon completion, determined by TLC, the reaction mixture was cooled to room temperature, the reaction was quenched with H_2O (20 mL), diluted with Et_2O (30 mL), and the aqueous phase was saturated with Na_2CO_3. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 10–30% EtOAc/hexanes) to give **31** (365.6 mg, **92**%) as a clear oil.

IR (neat): 3445, 2953, 2858, 1697, 1679, 1427, 1348, 1250, 1186, 1113, 998, 742
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.63 (m, 4H, HCAr), 7.45-7.36 (m, 6H, HCAr), 6.08-6.04 (m, 0.3H, HC= rotamer), 5.91-5.88 (m, 0.7H, HC= rotamer), 5.54-5.51 (m, 1H, HC=), 4.18-4.11 (m, 2H, CHH', CHH', 0.3H, CHN rotamer), 4.07 (t, J = 4.8 Hz, 0.7H, CHN rotamer), 3.81-3.65 (m, 2H, CH_2(OH), 2H, CH_2), 3.56 (dd, J = 9.1, 2.7 Hz, 0.7H, CHN rotamer), 3.41 (d, J = 7.8 Hz, 0.3H, CHN rotamer), 2.52-2.45 (m, 1H, CH), 2.19-1.81 (m, 2H, CH2, 1H, CH, 1H, CHH' rotamer), 1.69-1.44 (m, 1H, CHH' rotamer, 2H, CH_2), 1.05 (s and s, 9H, tBu rotamer), 1.00 (dd, J = 8.9, 7.5 Hz, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.1, 135.8, 135.7, 133.9, 133.8, 129.8, 129.2, 128.5, 128.2, 127.8, 127.8, 77.5, 77.2, 76.8, 66.0, 63.3, 62.9, 62.4, 61.9, 53.4, 42.6, 41.8, 38.6, 38.4, 32.0, 31.0, 30.5, 29.8, 27.0, 19.3, 18.0, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{50}NO_4Si_2]^+$ ($[M+H]^+$) 580.3278; found 580.3268
$[\alpha]^{20}_D$: +103.74 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-7-(3-oxopropyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (32)

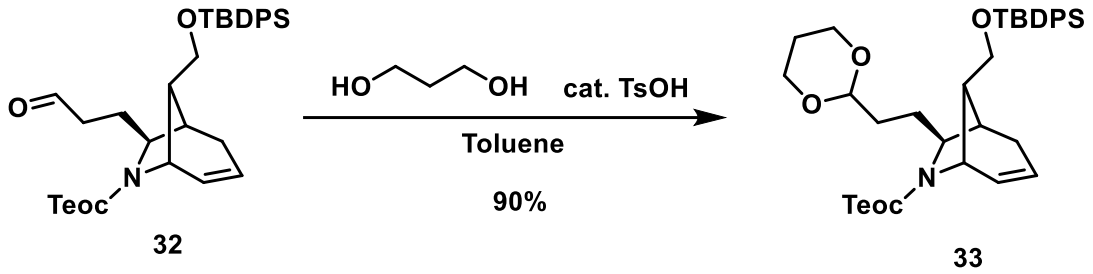


To a solution of DMSO (0.15 mL, 2.08 mmol, 3.4 equiv) in dry CH_2Cl_2 (2.37 mL) was added oxalyl chloride (0.13 mL, 1.53 mmol, 2.5 equiv), and the mixture was stirred at 0 °C under Ar atmosphere for 1 h. A solution of **31** (355 mg, 0.61 mmol) in CH_2Cl_2 (5.95 mL) was then added, and after an additional 1 h at –78 °C, Et_3N (0.64 mL, 4.59 mmol, 7.5 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h[7]. Upon completion, determined by TLC, the reaction was quenched with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 5–25% EtOAc/hexanes) to give **32** (327.1 mg, **92**%) as a clear oil.

IR (neat): 3567, 2954, 2857, 1697, 1648, 1427, 1339, 1250, 1184, 1113, 998, 742
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.77 (t, J = 1.6 Hz, 1H, CHO), 7.67-7.62 (m, 4H, HCAr), 7.45-7.36 (m, 6H, HCAr), 6.06 (t, J = 7.6 Hz, 0.3H, HC=rotamer), 5.92-5.88 (m, 0.7H, HC= rotamer), 5.51 (d, J = 9.7 Hz, 1H, HC=), 4.21-4.11 (m, 2H, CHH', CHH', 0.3H, CHN rotamer), 4.07 (t, J = 4.8 Hz, 0.7H, CHN rotamer), 3.81-3.69 (m, 2H,

CH_2), 3.52 (dd, J = 8.3, 5.1 Hz, 0.7H, CHN rotamer), 3.41 (dd, J = 9.2, 3.7 Hz, 0.3H, CHN rotamer), 2.51-2.47 (m, 2H, CH2, 0.3H, CH rotamer), 2.44-2.39 (m, 0.7H, CH rotamer), 2.19-1.67 (m, 5H, 2 x CH_2, CH), 1.05 (s and s, 9H, tBu rotamer), 1.02-0.93 (m, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.3, 156.4, 135.7, 133.8, 133.7, 129.8, 128.6, 128.0, 127.8, 66.1, 65.4, 63.4, 63.3, 61.8, 53.7, 42.6, 41.8, 41.7, 38.8, 38.3, 31.8, 27.4, 27.0, 19.3, 18.0, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{48}NO_4Si_2]^+$ ($[M+H]^+$) 578.3122; found 578.3145
$[\alpha]^{20}_D$: +109.44 (*c* 0.8, $CHCl_3$)

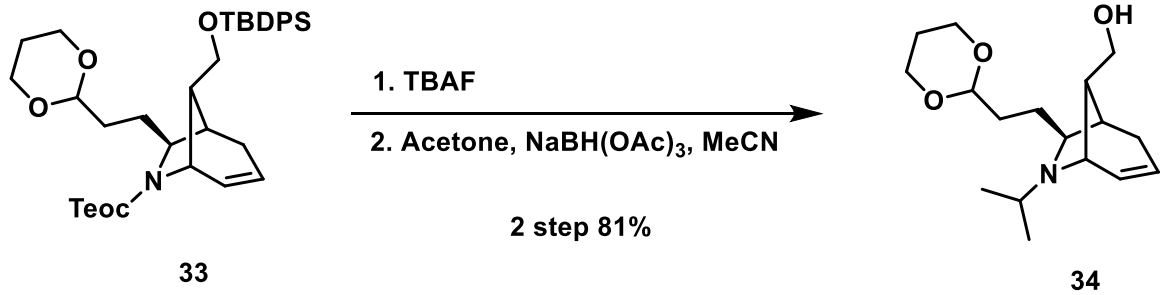
2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-7-(2-(1,3-dioxan-2-yl)ethyl)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (33)



To a solution of **32** (323 mg, 0.56 mmol) and p-toluenesulfonic acid (TsOH, 10.6 mg, 0.06 mmol, 0.1 equiv) in dry toluene (4.22 mL) was added propane-1,3-diol (0.12 mL, 1.68 mmol, 3 equiv), and the mixture was stirred at 50 °C under Ar atmosphere for 2 h. Upon completion, determined by TLC, the reaction mixture was cooled to room temperature, the reaction was quenched with H_2O (20 mL), diluted with Et_2O (30 mL), and the aqueous phase was saturated with $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 5–25% EtOAc/hexanes) to give **33** (319 mg, **90**%) as clear oil.

IR (neat): 3567, 2954, 2856, 1697, 1648, 1543, 1428, 1347, 1249, 1113, 999, 742
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.62 (m, 4H, HCAr), 7.44-7.36 (m, 6H, HCAr), 6.04 (d, J = 5.9 Hz, 0.4H, HC=rotamer), 5.90-5.87 (m, 0.6H, HC=rotamer), 5.50 (d, J = 9.1 Hz, 1H, HC=), 4.55-4.51 (m, 1H, -O_2CH), 4.20-4.06 (m, 2H, CH_2, 2H, CH_2, 1H, CHN), 3.78-3.69 (m, 2H, CH_2, 2H, CH_2), 3.48 (dd, J = 9.6, 3.2 Hz, 0.6H, CHN rotamer), 3.38 (d, J = 7.3 Hz, 0.4H, CHN rotamer), 2.49 (dd, J = 12.1, 7.5 Hz, 1H, CH), 2.17-1.87 (m, 1H, CHH', 2H, CH_2, 2H, CH_2), 1.63 (td, J = 10.5, 5.3 Hz, 2H, CH_2), 1.53-1.44 (m, 1H, CHH'), 1.36-1.29 (m, 1H, CH), 1.04 (s and s, 9H, tBu rotamer), 1.02-0.97 (m, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.9, 135.7, 133.8, 129.8, 128.5, 128.1, 127.8, 127.7, 123.8, 102.5, 102.2, 95.1, 87.9, 67.0, 66.8, 66.2, 63.1, 63.0, 61.9, 53.5, 42.4, 38.5, 37.5, 33.2, 33.0, 32.0, 29.2, 28.7, 27.0, 26.0, 19.3, 18.0, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{36}H_{54}NO_5Si_2]^+$ ($[M+H]^+$) 636.3541; found 636.3559
$[\alpha]^{20}_D$: +100.78 (*c* 0.8, $CHCl_3$)

((1R,5S,7S,8S)-7-(2-(1,3-Dioxan-2-yl)ethyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-3-en-8-yl)methanol (34)

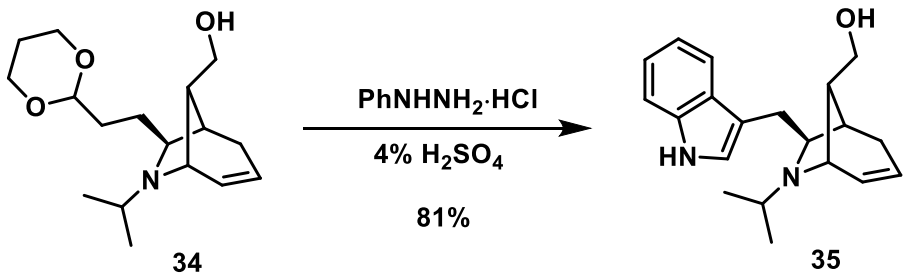


To a solution of **33** (105 mg, 0.22 mmol) in dry CH_3CN (2.73 mL) was added a 1.0 M solution of n-Bu_4NF in

THF (0.77 mL, 0.77 mmol, 3.5 equiv) at 65 °C under Ar atmosphere, and the mixture was stirred for 6 h. Upon completion, determined by TLC, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 0–20% MeOH/EtOAc) to give the crude amine, which was used in the next step without further purification. To a mixture of the crude amine (0.22 mmol) and acetone (80.4 µL, 1.09 mmol, 5 equiv) in dry CH_3CN (2.41 mL) was added sodium triacetoxyborohydride (92 mg, 0.43 mmol, 2 equiv), and the mixture was stirred at room temperature under Ar atmosphere for 14 h[8]. Upon completion, determined by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and diluted with 10% i-PrOH in $CHCl_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with 10% i-PrOH in $CHCl_3$ (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 1:5:95 Et_3N/MeOH/CH_2Cl_2) to give **34** (38.5 mg, **81**% over two steps) as a clear oil.

IR (neat): 3337, 2929, 2364, 1680, 1647, 1543, 1397, 1247, 1142, 1003, 770
^{1}H NMR (399 MHz, $CDCl_3$) δ: 6.11 (d, J = 9.1 Hz, 1H), 5.86-5.83 (m, 1H), 4.57 (t, J = 4.3 Hz, 1H), 4.38 (s, 1H), 4.06 (t, J = 5.5 Hz, 2H), 3.75 (q, J = 11.9 Hz, 4H), 3.35 (q, J = 6.4 Hz, 1H), 3.19 (d, J = 11.0 Hz, 1H), 2.94 (s, 1H), 2.48-2.33 (m, 2H), 2.16-1.95 (m, 5H), 1.78-1.51 (m, 8H), 1.34 (d, J = 13.7 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.0, 120.8, 101.4, 74.8, 66.9, 66.9, 58.8, 55.4, 41.3, 38.4, 32.7, 31.9, 29.8, 28.3, 25.8, 19.9, 19.5
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{17}H_{30}NO_3]^+$ ($[M+H]^+$) 296.2226; found 296.2235
$[\alpha]^{20}_D$: +30.29 (*c* 0.6, $CHCl_3$)

((1R,5S,7S,8S)-7-((1H-indol-3-yl)methyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-3-en-8-yl)methanol (35)

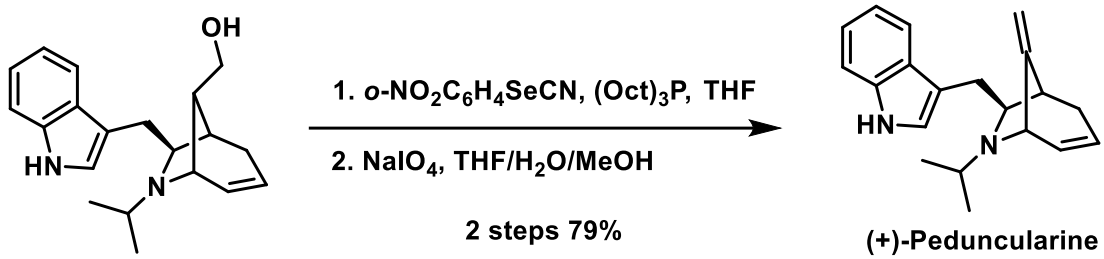


34 **35**

To a deoxygenated solution of H_2SO_4 (1.29 mL, 4% in H_2O) was added $PhNHNH_2$·HCl (20.5 mg, 0.141 mmol, 1.1 equiv), and the mixture was stirred at 50 °C for 10 min until complete dissolution. **34** (38 mg, 0.129 mmol) was added to the preheated hydrazine–sulfuric acid solution, and the resulting mixture was heated to reflux under Ar atmosphere for 2 h[8]. Upon completion, as determined by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and diluted with 10% i-PrOH in $CHCl_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with 10% i-PrOH in $CHCl_3$ (3 × 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–15% MeOH/CH_2Cl_2) to give **35** (32.5 mg, **81**%) as a white solid.

MP: 86.4-91.1 °C
IR (neat): 3257, 2928, 2372, 1671, 1648, 1542, 1386, 1250, 1154, 981, 741
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.19 (td, J = 7.5, 1.2 Hz, 1H), 7.13-7.09 (m, 1H), 6.97 (d, J = 1.8 Hz, 1H), 5.84-5.76 (m, 2H), 3.77 (ddd, J = 24.5, 11.0, 7.5 Hz, 2H), 3.65 (t, J = 4.1 Hz, 1H), 3.06-2.96 (m, 2H), 2.86 (q, J = 11.1 Hz, 2H), 2.63 (sept, J = 7.7, 4.1 Hz, 1H), 2.21-2.15 (m, 2H), 1.74 (dq, J = 16.6, 1.5 Hz, 1H), 1.25 (dd, J = 53.5, 6.4 Hz, 6H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.3, 129.3, 127.8, 127.4, 122.1, 121.7, 119.4, 119.2, 115.0, 111.2, 71.1, 61.1, 57.0, 51.4, 42.7, 39.4, 34.3, 33.2, 23.8, 22.7
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{20}H_{27}N_2O]^+$ ($[M+H]^+$) 311.2123; found 311.2127
$[\alpha]^{25}_D$: +93.36 (*c* 1.0, $CHCl_3$)

3-(((1R,5S,7S)-6-Isopropyl-8-methylene-6-azabicyclo[3.2.1]oct-3-en-7-yl)methyl)-1H-indole ((+)-peduncularine 36)



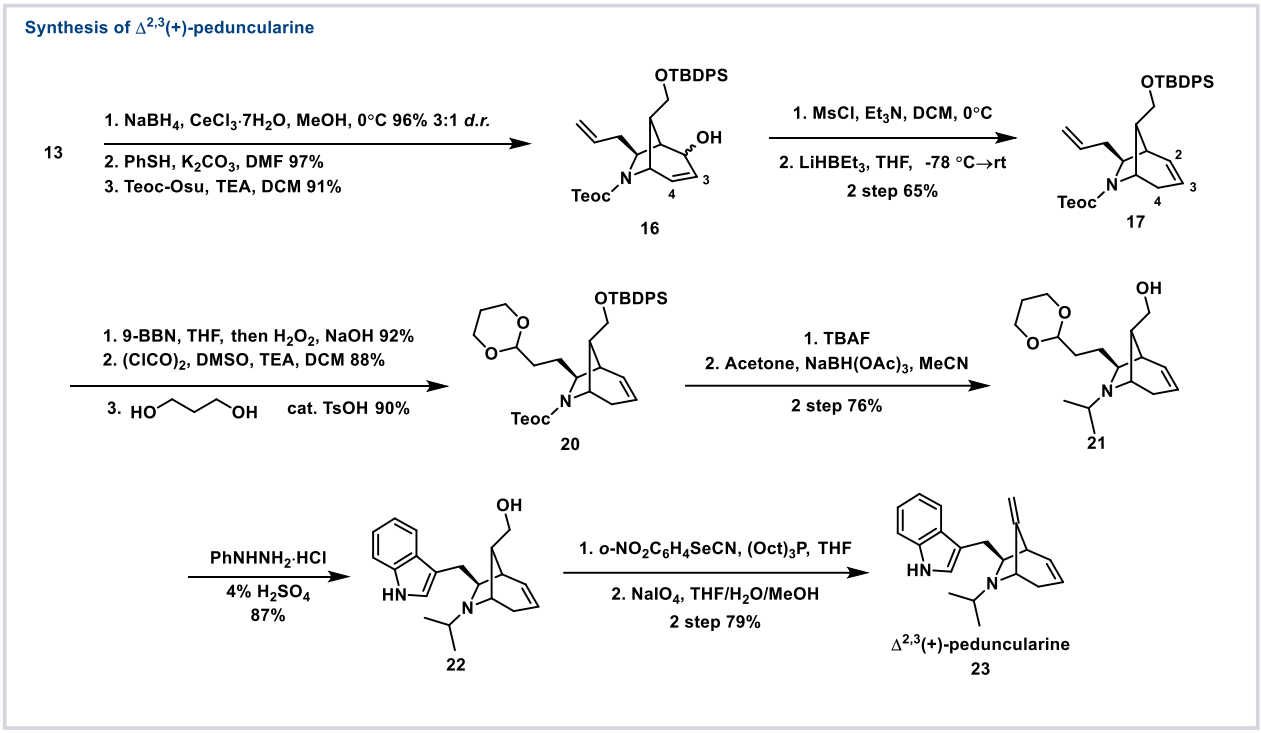
35 **36**

To a stirred solution of **35** (30 mg, 0.097 mmol) in dry THF (0.97 mL) was added o-$NO_2C_6H_4SeCN$ (54.9 mg, 0.242 mmol, 2.5 equiv). Then, the mixture was cooled to 0 °C and $(Oct)_3P$ (>85%, 0.12 mL, 0.22 mmol, 2.3 equiv) was added dropwise, and the resulting mixture was stirred at rt under Ar atmosphere for 2 h. Upon completion, as determined by TLC, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 0–5% MeOH/CH_2Cl_2) to give the crude selenide, which was used in the next step without further purification. To a mixture of the crude selenide(0.097 mmol) in wet MeOH (1.73 mL), THF (1.73 mL) and H_2O (0.35 mL) was added $NaIO_4$ (27 mg, 0.126 mmol, 1.3 equiv), and the mixture was sonicated to ensure homogeneity. The resulting reaction mixture was stirred at room temperature for 2 h. Upon completion, as determined by TLC, the presence of the selenoxide was confirmed. To suppress undesired N-oxide formation, the reaction mixture was promptly quenched with H_2O (10 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. To a mixture of the crude selenoxide was added toluene (4.22 mL) followed by Et_3N (19.6 mg, 0.194 mmol, 2 equiv), and the mixture was heated at 90 °C for 1 h. Upon completion, as determined by TLC, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Amine silica gel, 0–10% EtOAc/hexanes) to give (+)-peduncularine **36** (22.4 mg, **79**% over two steps) as a white solid.

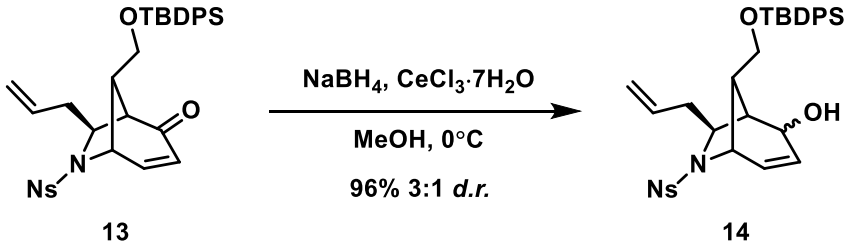
MP: 147.5-150.2 °C
IR (neat): 3872, 3027, 2926, 2373, 1688, 1648, 1542, 1374, 1247, 1147, 800, 741
^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.98 (br s, 1H), 7.61 (dq, J = 7.9, 0.9 Hz, 1H), 7.36 (dt, J = 8.1, 1.0 Hz, 1H), 7.20 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.12 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 6.99 (s, 1H), 5.96 (ddt, J = 9.3, 5.2, 2.0 Hz, 1H), 5.69 (dt, J = 8.7, 2.5 Hz, 1H), 4.96 (s, 1H), 4.82 (s, 1H), 3.85 (d, J = 5.2 Hz, 1H), 3.01 (sept, J = 5.8 Hz, 1H), 2.95 (d, J = 15.2 Hz, 1H), 2.89 (d, J = 11.3 Hz, 1H), 2.71 (dd, J = 14.9, 11.3 Hz, 1H), 2.51 (br d, J = 4.7 Hz, 1H), 2.46 (ddt, J = 17.7, 5.0, 2.6 Hz, 1H), 2.08 (ddt, J = 17.7, 3.7, 1.8 Hz, 1H), 1.31 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ: 150.3, 136.4, 130.8, 128.6, 128.0, 122.2, 121.5, 119.5, 119.3, 115.3, 111.2, 101.5, 70.0, 60.6, 51.0, 46.0, 40.3, 34.4, 23.8, 22.9
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{20}H_{25}N_2]^+$ ($[M+H]^+$) 293.2012; found 293.2004
$[\alpha]^{20}_D$: +67.12 (*c* 0.315, $CHCl_3$) literature values **- $[\alpha]^{20}_D$:** -68 (*c* 0.315, $CHCl_3$)[15]

vi.Synthesis of $\Delta^{2,3}$-(+)- peduncularine

Scheme S4. Total synthesis of $\Delta^{2,3}$-(+)- peduncularine



(1R,5S,7S,8S)-7-Allyl-8-(((tert-Butyldiphenylsilyl)oxy)methyl)-6-((4-nitrophenyl)sulfonyl)-6-azabicyclo[3.2.1]oct-3-en-2-ol (14)

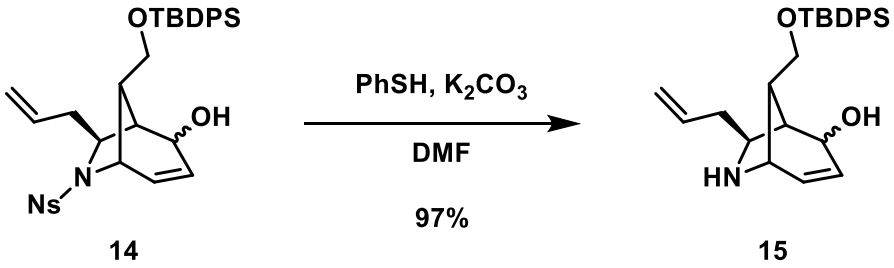


To a solution of **13** (716 mg, 1.16 mmol) and cerium(III) chloride heptahydrate (519 mg, 1.39 mmol, 1.2 equiv) in MeOH (9.67 mL) was added sodium borohydride (65.9 mg, 1.74 mmol, 1.5 equiv) at 0 °C and the mixture was stirred for 10 min. Upon completion, determined by TLC, AcOH was added dropwise for quenching the extra sodium borohydride. The reaction mixture was concetrated in vacuo, diluted with EtOAc (30 mL) and H_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 1:3:8 CH_2Cl_2/Et_2O/hexanes) to give **14** as a mixture of diastereomers (683.6 mg, **95**%, 3:1 dr) as a white solid.

MP: 62.3-66.8°C
IR (neat): 3546, 3071, 2931, 2858, 1641, 1543, 1428, 1345, 1217, 1163, 999, 743
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-8.06 (m, 1H), 7.71-7.61 (m, 7H), 7.46-7.37 (m, 6H), 5.89 (q, J = 4.9 Hz, 1H), 5.69-5.59 (m, 1H), 5.51-5.48 (m, 1H), 5.03-4.96 (m, 2H), 4.29 (dd, J = 10.1, 3.2 Hz, 1H), 4.25-4.21 (m, 2H), 3.75-3.67 (m, 2H), 2.72-2.66 (m, 1H), 2.38-2.30 (m, 2H), 2.15-2.07 (m, 1H), 1.06 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.2, 135.7, 135.1, 134.2, 133.6, 133.4, 131.8, 130.7, 130.3, 130.0, 129.6, 127.9, 124.2, 118.2, 68.3, 60.9, 58.3, 57.5, 47.2, 46.1, 38.4, 27.0, 19.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{39}N_2O_6SSi]^+$ ($[M+H]^+$) 619.2298; found 619.2289

$[\alpha]^{20}_D$: +46.59 (*c* 1.0, $CHCl_3$)

(1R,5S,7S,8S)-7-Allyl-8-(((tert-Butyldiphenylsilyl)oxy)methyl)-6-azabicyclo[3.2.1]oct-3-en-2-ol (15)

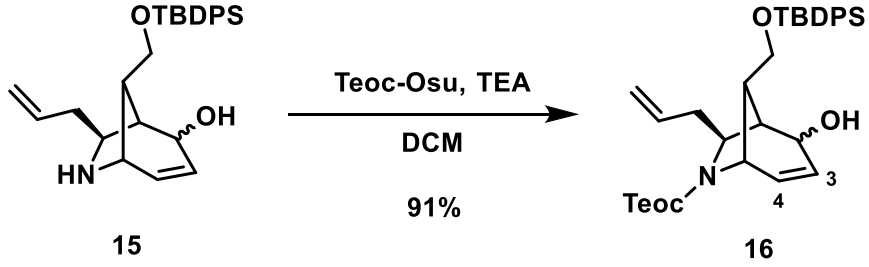


14 15

To a solution of **14** (500 mg, 0.81 mmol) in dry DMF (4.04 mL) were added K_2CO_3 (335 mg, 2.42 mmol, 3 equiv) and thiophenol (0.17 mL, 1.62 mmol, 2 equiv), and the mixture was stirred at room temperature under Ar atmosphere for 2 h. Upon completion, determined by TLC, the reaction was quenched with H_2O (30 mL) and diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–20% MeOH/EtOAc) to give **15** (343.1 mg, 97%) as a yellow oil.

IR (neat): 3341, 2932, 2858, 1647, 1428, 1315, 1113, 1072, 998, 742
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.13 (br s, 1H), 7.61 (qd, J = 7.3, 1.4 Hz, 4H), 7.45-7.35 (m, 6H), 5.84-5.66 (m, 3H), 5.23-5.10 (m, 2H), 4.29-4.26 (m, 2H), 3.98-3.94 (m, 2H), 3.80-3.71 (m, 2H), 2.83 (s, 1H), 2.60-2.37 (m, 3H), 0.95-1.10 (9H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.6, 133.1, 132.7, 130.0, 127.9, 123.2, 119.3, 67.5, 60.2, 56.9, 53.7, 46.9, 45.6, 37.0, 26.9, 19.2
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{27}H_{36}NO_2Si]^+$ ($[M+H]^+$) 434.2515; found 434.2517
$[\alpha]^{20}_D$: +4.79 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-2-hydroxy-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (16)



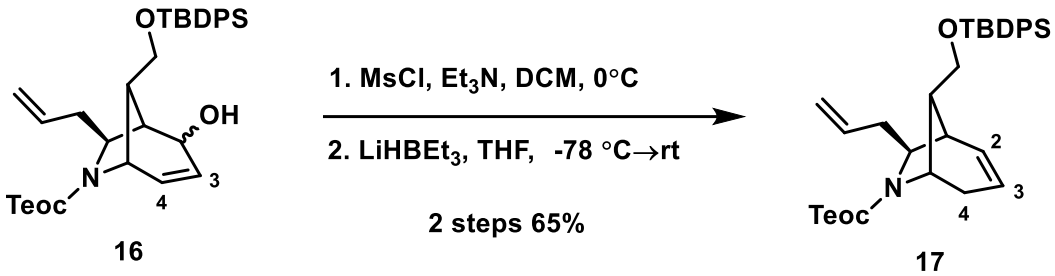
15 16

To a solution of **15** (226 mg, 0.52 mmol) in dry CH_2Cl_2 (10.42 mL) was treated with Teoc-OSu (270.3 mg, 1.04 mmol, 2 equiv) and Et_3N (0.15 mL, 1.04 mmol, 2 equiv), and the mixture was stirred at room temperature under Ar atmosphere overnight. Upon completion, determined by TLC, the reaction was quenched with H_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–20% EtOAc/hexanes) to give **16** (272.2 mg, **91**%) as a clear oil.

IR (neat): 3421, 2954, 2858, 1672, 1427, 1326, 1114, 1065, 997, 740
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.61 (m, 4H, HCAr), 7.46-7.36 (m, 6H, HCAr), 6.14-6.10 (m, 0.4H, HC=rotamer), 5.95 (dd, J = 9.1, 5.5 Hz, 0.6H, HC=rotamer), 5.85-5.73 (m, 1H, HC=), 5.53-5.49 (m, 1H, HC=), 5.12-5.05 (m, 2H, H_2C=), 4.23-4.07 (m, 2H, CH_2, 1H, CHN, 1H, CH(OH)), 3.96 (dd, J = 9.8, 3.4 Hz, 1H, CH), 3.74-3.69 (m, 2H, CH_2), 2.80-2.63 (m, 1H, CH, 1H, CHH'), 2.28 (d, J = 3.7 Hz, 1H, CH), 2.19-2.11 (m, 1H,

CHH'), 1.51-1.43 (m, 1H, -OH), 1.04 (s and s, 9H, tBu rotamer), 1.02-0.97 (m, 2H, CH2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.6, 135.7, 135.5, 133.6, 133.5, 131.0, 130.2, 130.1, 129.9, 129.7, 127.9, 117.3, 68.6, 63.4, 63.2, 61.4, 56.5, 55.7, 53.2, 46.9, 46.2, 45.9, 45.0, 38.7, 38.1, 27.0, 19.3, 18.0, -1.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{33}H_{48}NO_4Si_2]^+$ ($[M+H]^+$) 578.3116; found 578.3099
$[\alpha]^{20}_D$: +48.47 (*c* 1.0, $CHCl_3$)

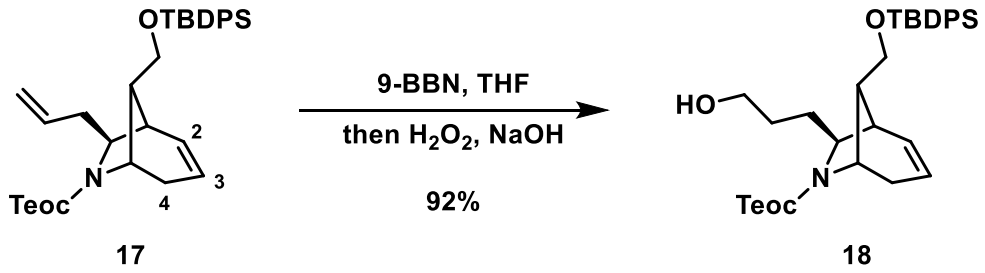
2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-7-allyl-8-(((tert-butyldiphenylsilyl)oxy)methyl)-6-azabicyclo[3.2.1]oct-2-ene-6-carboxylate (17)



To a stirred solution of **16** (271 mg, 0.47 mmol) in dry CH_2Cl_2 (4.69 mL) was added Et_3N (0.23 mL, 1.64 mmol, 3.5 equiv) at room temperature under Ar atmosphere and the resulting mixture was cooled to –78 °C. Methanesulfonyl chloride (0.11 mL, 1.41 mmol, 3 equiv) was then added dropwise, and the reaction mixture was allowed to warm to –15 °C. Upon completion, determined by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). After drying the combined organic layers over Na_2SO_4, the solvent was removed under reduced pressure to give mesylated product, which was used directly in the next reaction without further purification. This crude mixture was dissolved in dry THF (2.34 mL), treated with 1.00 M solution of $LiHBEt_3$ in THF (14.04 mL, 14.04 mmol, 30 equiv) at -78 °C and the mixture was stirred at room temperature under Ar atmosphere for 2 h. Upon completion, determined by TLC, the reaction was quenched with H_2O (40 mL) dropwise and diluted with Et_2O (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–10% Et_2O/hexanes) to give **17** (171.2 mg, **65**%) as a clear oil.

IR (neat): 3071, 2954, 2858, 1697, 1415, 1350, 1113, 999, 740
^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.65 (dq, J = 8.0, 1.4 Hz, 4H, HCAr), 7.46-7.37 (m, 6H, HCAr), 5.82-5.64 (m, 1H, HC=, 1H, HC=), 5.46-5.40 (m, 1H, HC=), 5.04 (dt, J = 13.7, 3.3 Hz, 2H, H_2C=), 4.24-4.01 (m, 2H, CH_2, 1H, CHN), 3.82-3.62 (m, 2H, CH_2, 1H, CH), 2.75-2.56 (m, 1H, CH), 2.54-2.18 (m, 1H, CHH', 1H, CHH', 1H, CH), 2.07-1.88 (m, 1H, CHH', 1H, CHH'), 1.05 (s and s, 9H, tBu rotamer), 1.03-0.98 (m, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 155.2, 135.8, 135.7, 135.6, 133.9, 129.8, 128.9, 128.6, 127.8, 126.4, 125.8, 117.2, 117.1, 67.3, 66.6, 63.0, 61.8, 54.8, 54.7, 42.1, 41.2, 38.3, 38.2, 37.5, 37.4, 29.6, 28.6, 27.0, 19.4, 18.1, 18.0, -1.3
HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{33}H_{48}NO_3Si_2]^+$ ($[M+H]^+$) 562.3167; found 562.3150
$[\alpha]^{20}_D$: +29.65 (*c* 1.0, $CHCl_3$)

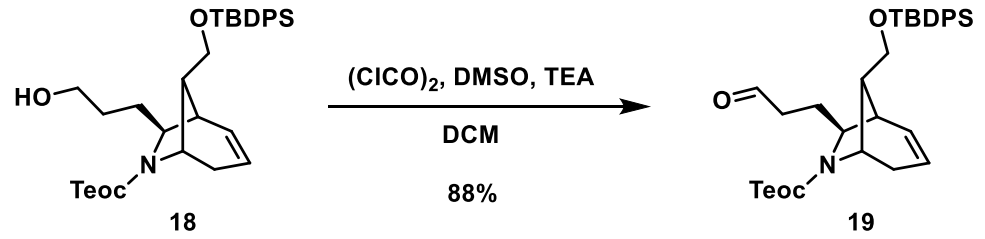
2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-7-(3-hydroxypropyl)-6-azabicyclo[3.2.1]oct-2-ene-6-carboxylate (18)



To a solution of **17** (159 mg, 0.28 mmol) in dry THF (1.89 mL) was added 9-BBN dimer (138.1 mg, 0.57 mmol, 2 equiv) and the mixture was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was cooled to 0 °C and treated with EtOH (0.6 mL). After stirring for 10 min, aq. NaOH (6 M, 0.19 mL) and aqueous H_2O_2 (30% w/w, 0.40 mL) were added, and the resulting mixture was heated to 50 °C for 1 h. Upon completion, determined by TLC, the reaction mixture was cooled to room temperature, the reaction was quenched with H_2O (20 mL), diluted with Et_2O (30 mL), and the aqueous phase was saturated with Na_2CO_3. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 10–30% EtOAc/hexanes) to give **18** (150.6 mg, **92**%) as a clear oil.

IR (neat): 3447, 3070, 2954, 2858, 1692, 1427, 1352, 1113, 999, 741
^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.66-7.61 (m, 4H, HCAr), 7.46-7.36 (m, 6H, HCAr), 5.70-5.65 (m, 1H, HC=), 5.46-5.40 (m, 1H, HC=), 4.20-4.01 (m, 2H, CH_2, 1H, CHN), 3.81-3.55 (m, 2H, CH_2(OH), 1H, CH_2, 1H CHN), 2.61-2.36 (m, 1H, CH, 1H, CHH'), 2.23-2.12 (m, 1H, CH, 0.6H, CHH'), 1.98-1.75 (m, 2H, CH_2), 1.66-1.32 (m, 2H, CH_2, 1H, CHH', 0.4H, CHH'), 1.05 (s and s, 9H, tBu rotamer), 1.03-0.97 (m, 2H, CH_2), 0.04 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7, 155.2, 135.7, 133.8, 129.8, 128.9, 128.5, 127.8, 126.4, 125.8, 67.2, 63.3, 63.1, 62.8, 62.2, 61.9, 54.6, 54.4, 42.4, 41.5, 39.1, 39.0, 30.3, 30.1, 29.9, 29.6, 29.5, 28.4, 27.0, 19.4, 18.0, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{50}NO_4Si_2]^+$ ($[M+H]^+$) 580.3278; found 580.3260
$[\alpha]^{20}_D$: +24.44 (*c* 1.0, $CHCl_3$)

2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-7-(3-oxopropyl)-6-azabicyclo[3.2.1]oct-2-ene-6-carboxylate (19)

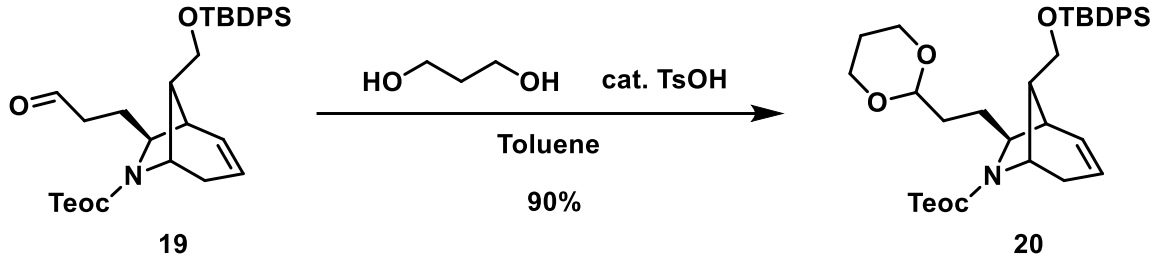


To a solution of DMSO (0.25 mL, 3.53 mmol, 3.4 equiv) in dry CH_2Cl_2 (4.02 mL) was added oxalyl chloride (0.22 mL, 2.60 mmol, 2.5 equiv), and the mixture was stirred at 0 °C under Ar atmosphere for 1 h. A solution of **18** (602 mg, 1.04 mmol) in CH_2Cl_2 (10.08 mL) was then added, and after an additional 1 h at –78 °C, Et_3N (1.09 mL, 7.79 mmol, 7.5 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Upon completion, determined by TLC, the reaction was quenched with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 5–25% EtOAc/hexanes) to give **19** (530.6 mg, **88**%) as a clear oil.

IR (neat): 3071, 2954, 2858, 1693, 1427, 1350, 1112, 937, 741
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (s, 1H, CHO), 7.66-7.60 (m, 4H, HCAr), 7.45-7.36 (m, 6H, HCAr), 5.68-5.63 (m, 1H, HC=), 5.46-5.40 (m, 1H, HC=), 4.23-3.48 (m, 2H, CH_2, 2H, CH_2, 1H CHN, 1H, CHN), 2.56-1.88 (m, 2H, CH_2, 2H, CH_2, 1H CHH', 1H, CH, 1H, CH), 1.71-1.63 (m, 1H, CHH'), 1.05 (s and s, 9H, tBu rotamer), 1.03-0.97 (m, 2H, CH_2), 0.04 s and s, 9H, $SiMe_3$ rotamer)

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.1, 201.7, 155.8, 139.1, 135.7, 133.8, 129.9, 128.4, 128.0, 127.8, 126.6, 126.0, 67.3, 66.5, 63.2, 61.8, 61.7, 54.8, 54.7, 42.4, 41.8, 41.6, 41.5, 39.3, 38.9, 29.4, 28.3, 27.0, 26.6, 26.4, 19.3, 18.1, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{33}H_{48}NO_4Si_2]^+$ ($[M+H]^+$) 578.3122; found 578.3153
$[\alpha]^{20}_D$: +22.21 (*c* 1.0, $CHCl_3$)

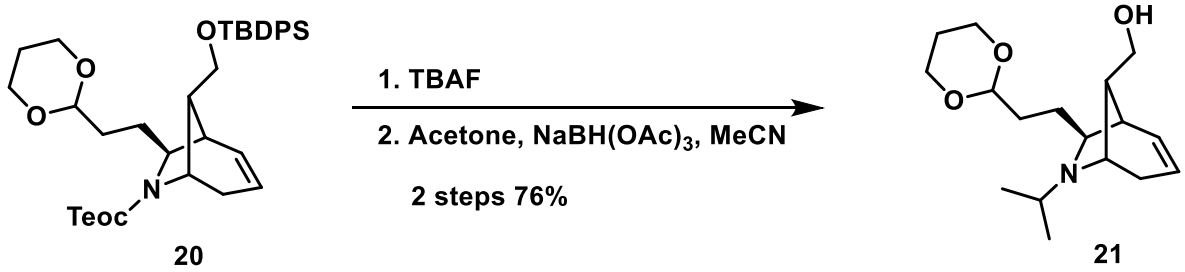
2-(Trimethylsilyl)ethyl (1R,5S,7S,8S)-7-(2-(1,3-dioxan-2-yl)ethyl)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-6-azabicyclo[3.2.1]oct-2-ene-6-carboxylate (20)



To a solution of **19** (100 mg, 0.17 mmol) and p-toluenesulfonic acid (TsOH, 3.3 mg, 0.02 mmol, 0.1 equiv) in dry toluene (1.31 mL) was added propane-1,3-diol (0.04 mL, 0.52 mmol, 3 equiv), and the mixture was stirred at 50 °C under Ar atmosphere for 2 h. Upon completion, determined by TLC, the reaction mixture was cooled to room temperature, the reaction was quenched with H_2O (20 mL), diluted with Et_2O (30 mL), and the aqueous phase was saturated with $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 5–25% EtOAc/hexanes) to give **20** (99.1 mg, **90**%) as a clear oil.

IR (neat): 3070, 2955, 2856, 1695, 1427, 1349, 1112, 998, 741
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.62 (m, 4H, HCAr), 7.45-7.35 (m, 6H, HCAr), 5.65 (t, J = 7.8 Hz, 1H, HC=), 5.43-5.38 (m, 1H, HC=), 4.55-4.50 (m, 1H, $-O_2CH$), 4.21-4.01 (m, 2H, CH_2, 2H, CH_2, 1H, CHN), 3.79-3.54 (m, 2H, CH_2, 2H, CH_2, 1H, CHN), 2.54-1.83 (m, 2H, CH_2, 2H, CH_2, 1H, CHH', 1H, CH), 1.63-1.25 (m, 2H, CH_2, 1H, CHH', 1H, CH), 1.05 (s and s, 9H, tBu rotamer), 1.02-0.96 (m, 2H, CH_2), 0.03 (s and s, 9H, $SiMe_3$ rotamer)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.4, 135.7, 133.8, 133.7, 129.8, 128.9, 128.6, 127.8, 126.3, 125.7, 102.4, 102.1, 68.1, 67.3, 67.0, 63.0, 62.0, 61.9, 54.6, 54.5, 42.2, 41.4, 39.0, 38.1, 33.0, 32.9, 29.5, 28.4, 28.3, 27.6, 27.0, 25.9, 19.3, 18.0, -1.3
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{36}H_{54}NO_5Si_2]^+$ ($[M+H]^+$) 636.3541; found 636.3526
$[\alpha]^{20}_D$: +27.88 (*c* 1.0, $CHCl_3$)

((1R,5S,7S,8S)-7-(2-(1,3-Dioxan-2-yl)ethyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-2-en-8-yl)methanol (21)

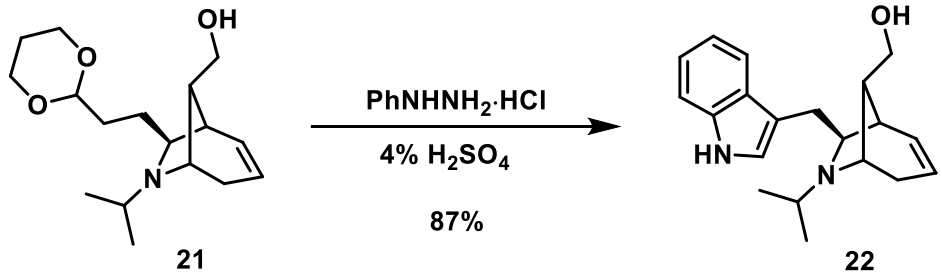


To a solution of **20** (185 mg, 0.29 mmol) in dry CH_3CN (3.64 mL) was added a 1.0 M solution of n-Bu_4NF in THF (0.64 mL, 0.64 mmol, 2.2 equiv) at 65 °C under Ar atmosphere, and the mixture was stirred for 6 h. Upon completion, determined by TLC, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 0–20% MeOH/EtOAc) to give the crude amine, which was used in the next step without further purification. To a mixture

of the crude amine (0.29 mmol) and acetone (106.7 μL, 1.44 mmol, 5 equiv) in dry CH_3CN (3.2 mL) was added sodium triacetoxyborohydride (122.1 mg, 0.58 mmol, 2 equiv), and the mixture was stirred at room temperature under Ar atmosphere for 14 h. Upon completion, determined by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and diluted with 10% i-PrOH in $CHCl_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with 10% i-PrOH in $CHCl_3$ (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 1:5:95 Et_3N/MeOH/CH_2Cl_2) to give **21** (64.3 mg, **76**% over two steps) as a clear oil.

IR (neat): 3384, 3025, 2964, 2849, 1647, 1431, 1397, 1088, 997, 874
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.83 (t, J = 8.0 Hz, 1H), 5.52 (d, J = 9.7 Hz, 1H), 4.48 (t, J = 4.8 Hz, 1H), 4.08 (q, J = 5.2 Hz, 2H), 3.81 (d, J = 7.4 Hz, 2H), 3.77-3.70 (m, 2H), 3.54 (s, 1H), 2.93-2.87 (m, 1H), 2.74 (q, J = 4.1 Hz, 1H), 2.55-2.50 (m, 1H), 2.37 (dt, J = 19.0, 1.7 Hz, 1H), 2.14-1.89 (m, 4H), 1.61-1.46 (m, 4H), 1.32 (dd, J = 12.2, 1.1 Hz, 1H), 1.10 (dd, J = 8.3, 6.4 Hz, 6H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 131.4, 125.7, 102.4, 71.8, 67.0, 61.3, 56.5, 50.1, 43.5, 39.5, 33.4, 33.3, 25.9, 25.1, 23.7
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{17}H_{30}NO_3]^+$ ($[M+H]^+$) 296.2226; found 296.2227
$[\alpha]^{20}_D$: -3.82 (*c* 1.0, $CHCl_3$)

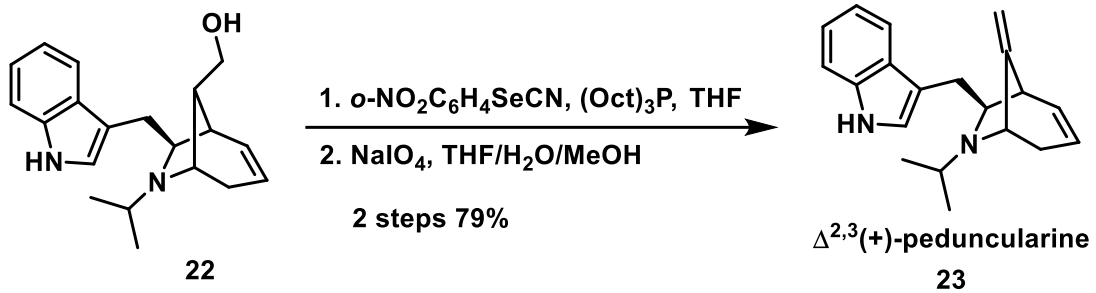
((1R,5S,7S,8S)-7-((1H-Indol-3-yl)methyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-2-en-8-yl)methanol (22)



To a deoxygenated solution of H_2SO_4 (1.39 mL, 4% in H_2O) was added $PhNHNH_2$·HCl (22.1 mg, 0.153 mmol, 1.1 equiv), and the mixture was stirred at 50 °C for 10 min until complete dissolution. **21** (41 mg, 0.139 mmol) was added to the preheated hydrazine–sulfuric acid solution, and the resulting mixture was heated to reflux under Ar atmosphere for 2 h. Upon completion, as determined by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and diluted with 10% i-PrOH in $CHCl_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with 10% i-PrOH in $CHCl_3$ (3 × 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, 0–15% MeOH/CH_2Cl_2) to give **22** (37.6 mg, **87**%) as a white solid.

MP: 82.6-87.9 °C
IR (neat): 3413, 2976, 2927, 1829, 1457, 1316, 1098, 939, 742
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.21-7.09 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 5.68 (t, J = 8.0 Hz, 1H), 5.50 (d, J = 9.6 Hz, 1H), 3.87-3.79 (m, 2H), 3.63 (s, 1H), 3.22 (dd, J = 11.0, 3.7 Hz, 1H), 3.06-3.00 (m, 1H), 2.92-2.79 (m, 2H), 2.74-2.69 (m, 1H), 2.45-2.27 (m, 2H), 1.93 (dq, J = 19.2, 2.6 Hz, 1H), 1.26 (dd, J = 63.8, 6.2 Hz, 6H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.2, 131.4, 127.8, 125.7, 122.0, 121.7, 119.3, 119.2, 115.0, 111.2, 71.7, 61.3, 57.0, 50.0, 43.4, 39.4, 34.7, 25.2, 24.1, 23.9
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{20}H_{27}N_2O]^+$ ($[M+H]^+$) 311.2123; found 311.2116
$[\alpha]^{20}_D$: +13.29 (*c* 0.535, $CHCl_3$)

3-(((1R,5S,7S)-6-Isopropyl-8-methylene-6-azabicyclo[3.2.1]oct-2-en-7-yl)methyl)-1H-indole ($\Delta^{2,3}$-(+)-Peduncularine 23)

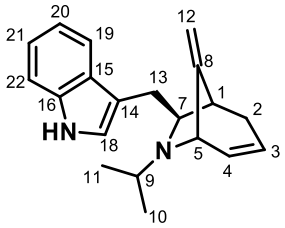


22 23

To a stirred solution of **22** (25 mg, 0.081 mmol) in dry THF (0.81 mL) was added o-$NO_2C_6H_4SeCN$ (45.7 mg, 0.201 mmol, 2.5 equiv). Then, the mixture was cooled to 0 °C and $(Oct)_3P$ (>85%, 0.10 mL, 0.19 mmol, 2.3 equiv) was added dropwise, and the resulting mixture was stirred at rt under Ar atmosphere for 2 h. Upon completion, as determined by TLC, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 0–5% MeOH/CH_2Cl_2) to give the crude selenide, which was used in the next step without further purification. To a mixture of the crude selenide(0.081 mmol) in wet MeOH (0.67 mL), THF (1.44 mL) and H_2O (0.29 mL) was added $NaIO_4$ (22.4 mg, 0.105 mmol, 1.3 equiv), and the mixture was sonicated to ensure homogeneity. The resulting reaction mixture was stirred at room temperature for 2 h. Upon completion, as determined by TLC, the presence of the selenoxide was confirmed. To suppress undesired N-oxide formation, the reaction mixture was promptly quenched with H_2O (10 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. To a mixture of the crude selenoxide was added toluene (3.50 mL) followed by Et_3N (16.3 mg, 0.161 mmol, 2 equiv), and the mixture was heated at 90 °C for 1 h. Upon completion, as determined by TLC, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Amine silica gel, 0–10% EtOAc/hexanes) to give △2,3(+)-peduncularine **23** (18.5 mg, **79**% over two steps) as a white solid.

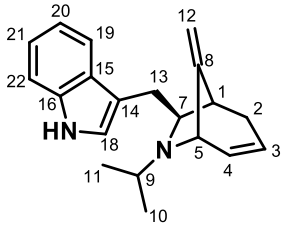
MP: 59.6-63.2 °C
IR (neat): 3416, 2967, 2924, 1686, 1456, 1309, 1227, 1175, 1153, 1097, 741, 667
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.38-7.36 (m, 1H), 7.22-7.11 (m, 2H), 6.98 (t, J = 1.1 Hz, 1H), 5.81-5.77 (m, 1H), 5.48-5.45 (m, 1H), 5.03 (s, 1H), 4.86 (s, 1H), 3.94 (s, 1H), 3.31 (d, J = 9.5 Hz, 1H), 3.10-3.05 (m, 1H), 2.83 (d, J = 13.5 Hz, 1H), 2.70 (dt, J = 18.3, 1.9 Hz, 2H), 2.61 (d, J = 6.4 Hz, 1H), 2.26 (d, J = 17.9 Hz, 1H), 1.36 (d, J = 5.3 Hz, 3H), 1.19 (d, J = 3.7 Hz, 3H)
^{13}C NMR (126 MHz, $CDCl_3$) δ: 151.0, 136.4, 134.2, 128.0, 125.1, 122.2, 121.8, 119.5, 119.3, 115.0, 111.3, 101.6, 71.3, 61.5, 50.3, 45.4, 34.6, 32.5, 24.0, 23.8
HRMS (FAB) m/z: $[M+H]^+$ calcd for $[C_{20}H_{25}N_2]^+$ ($[M+H]^+$) 293.2018; found 293.2008
$[\alpha]^{20}_D$: -18.23 (*c* 1,0 $CHCl_3$) literature values **-$[\alpha]^{25}_D$:** -4.6 (*c* 0.13, MeOH)[18]

-Tabulated 1H and 13C NMR Spectral Data Comparison for Peduncularine (36)



(+)-Peduncularine

No.	Current Synthesis In ppm, 800 MHz, $CDCl_3$	Dekhane Synthesis In ppm, 500 MHz, $CDCl_3$[16]	Woerpel Synthesis In ppm, 500 MHz, $CDCl_3$[14]	Natural Peducularine In ppm, 300 MHz, $CDCl_3$[17]
NH	7.98 (1H, br s)	8.10 (1H, br s)	7.98 (1H, br s)	8.93 (1H, br s)
H19	7.61 (1H, dq, *J* 7.9, 0.9)	7.63 (1H, d, *J* 7.9)	7.61 (1H, d, *J* 7.9)	7.61 (1H, d, *J* 7.7)
H22	7.36 (1H, dt, *J* 8.1, 1.0)	7.38 (1H, d, *J* 7.9)	7.36 (1H, d, *J* 8.1)	7.36 (1H, d, *J* 8.0)
H21	7.20 (1H, ddd, *J* 8.1, 7.0, 1.2)	7.22 (1H, t, *J* 7.3)	7.20 (1H, t, *J* 7.5)	7.18 (1H, t, *J* 7.9)
H20	7.12 (1H, ddd, *J* 7.9, 7.0, 1.0)	7.14 (1H, t, *J* 7.6)	7.12 (1H, t, *J* 7.5)	7.10 (1H, t, *J* 8.0)
H18	6.99 (1H, s)	7.00 (1H, s)	6.99 (1H, s)	6.99 (1H, s)
H4	5.96 (1H, ddt, *J* 9.3, 5.2, 2.0)	5.98 (1H, ddt, *J* 9.8, 5.4, 1.9)	5.95 (1H, ddt, *J* 9.3, 5.2, 2.0)	5.93 (1H, ddt, *J* 9.3, 5.3, 2.0)
H3	5.69 (1H,dt, *J* 8.7, 2.5)	5.72 (1H, dt, *J* 9.5, 2.8)	5.69 (1H, dt, *J* 9.3, 2.8)	5.70 (1H, dt, *J* 9.4, 3.1)
H12	4.96 (1H, s)	4.98 (1H, s)	4.95 (1H, s)	4.97 (1H, s)
H12’	4.82 (1H, s)	4.84 (1H, s)	4.82 (1H, s)	4.85 (1H, s)
H5	3.85 (1H, d, *J* 5.2)	3.89 (1H, d, *J* 5.4)	3.84 (1H, d, *J* 5.0)	3.83 (1H, d, *J* 5.3)
H9	3.01 (1H, sept, *J* 5.8)	3.04 (1H, sept, *J* 6.0)	3.00 (1H, sept, *J* 6.2)	3.03 (1H, sept, *J* 6.3)
H13	2.95 (1H, d, *J* 15.2)	2.99 (1H, d, *J* 14.8)	2.95 (1H, d, *J* 15.4)	2.97 (1H, dd, *J* 16.5, 2.5)
H7	2.89 (1H, d, *J* 11.3)	2.92 (1H, dd, *J* 11.4, 2.5)	2.89 (1H, d, *J* 11.3)	2.92 (1H, dd, *J* 13.3, 2.6)
H13’	2.71 (1H, dd, *J* 14.9, 11.3)	2.74 (1H, dd, *J* 14.8, 11.4)	2.71 (1H, dd, *J* 14.7, 11.4)	2.70 (1H, dd, *J* 13.8, 10.6)
H1	2.51 (1H, br d, *J* 4.7)	2.54 (1H, br d, *J* 4.4)	2.50 (1H, br d, *J* 4.1)	2.53 (1H, br d, *J* 4.8)
H2	2.46 (1H, ddt, *J* 17.7, 5.0, 2.6)	2.48 (1H, ddt, *J* 17.7, 4.7, 2.5)	2.46 (1H, ddt, *J* 17.6, 4.6, 2.4)	2.44 (1H, ddt, *J* 17.8, 4.9, 2.5)
H2’	2.08 (1H, ddt, *J* 17.7, 3.7, 1.8)	2.09 (1H, dt, *J* 17.7, 1.9)	2.07 (1H, ddt, *J* 17.6, 3.3, 1.7)	2.04 (1H, ddt, *J* 17.8, 3.6, 1.9)
H10	1.31 (3H, d, *J* 6.4)	1.34 (3H, d, *J* 6.3)	1.31 (3H, d, *J* 6.3)	1.33 (3H, d, *J* 6.4)
H11	1.17 (3H, d, *J* 6.2)	1.20 (3H, d, *J* 6.3)	1.17 (3H, d, *J* 6.1)	1.17 (3H, d, *J* 6.2)



(+)-Peduncularine

No.	Current Synthesis In ppm, 151 MHz, $CDCl_3$	Dekhane Synthesis In ppm, 125 MHz, $CDCl_3$[16]	Woerpel Synthesis In ppm, 125 MHz, $CDCl_3$[14]	Natural Peducularine In ppm, 75 MHz, $CDCl_3$[17]
C8	150.3	150.0	150.1	149.9
C16	136.4	136.2	136.1	136.0
C4	130.8	130.6	130.6	130.3
C3	128.6	128.5	128.4	128.6
C15	128.0	127.8	127.8	127.6
C21	122.2	122.0	122.0	121.9
C18	121.5	121.4	121.3	121.3
C20	119.5	119.3	119.3	119.1
C19	119.3	119.1	119.0	119.0
C14	115.3	115.0	115.0	114.7
C22	111.2	111.1	111.0	111.0
C12	101.5	101.5	101.4	101.4
C7	70.0	69.9	69.8	69.8
C5	60.6	60.4	60.4	60.5
C9	51.0	50.9	50.9	50.9
C1	46.0	45.9	45.9	45.7
C2	40.3	40.1	40.1	40.1
C13	34.4	34.2	34.2	34.0
C10	23.8	23.7	23.6	23.5
C11	22.9	22.7	22.7	22.5

III. Mechanistic Investigations

-NMR Studies

<Interaction between cat **C** and **1a** at room temperature>

To probe the interaction between catalyst **C** and substrate **1a**, we performed ^{1}H NMR titrations in two modes: (i) catalyst **C** (1.0 equiv) with increasing amounts of **1a** (0.1–2.0 equiv) and (ii) **1a** (1.0 equiv) with increasing amounts of catalyst **C** (0.1–0.4 equiv). Under condition (i), the squaramide NH resonances of catalyst **C** shifted differentially: one moved upfield from δ 10.26 to 10.02 ppm (Δδ = −0.24 ppm), whereas the other shifted downfield from δ 8.37 to 8.42 ppm (Δδ = +0.05 ppm), indicating distinct changes in the local environments of the two NH sites upon addition of **1a**. Therefore, catalyst **C** interacts with substrate **1a**.

<condition (i)>

[cat **C** (1 equiv.) + **1a** (0.1~2 equiv.)]

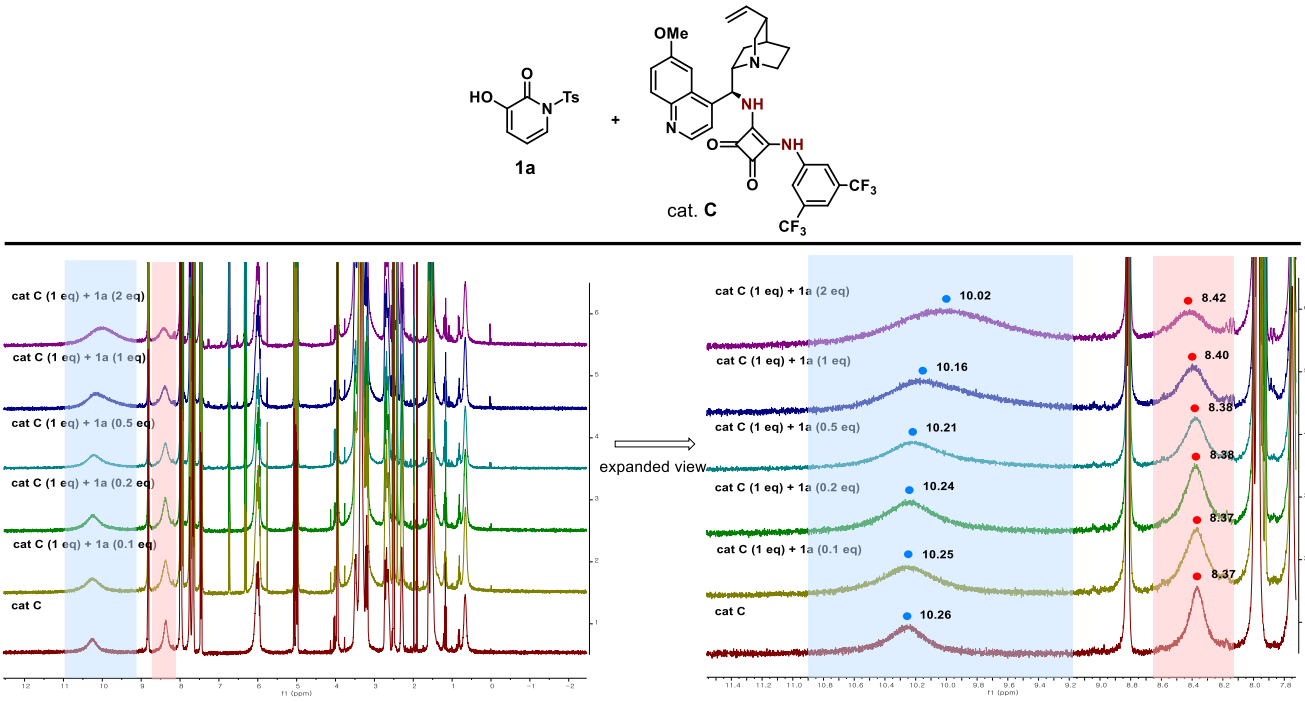


Figure S1. The chemical shifts of the squaramide NH resonances in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 750 μL, room temperature) observed during titration of **1a** with catalyst **C**: a) **1a** (30.0 μmol, 1.00 equiv); b) **1a** (1.00 equiv) with cat. **C** (0.10 equiv); c) **1a** (1.00 equiv) with cat. **C** (0.20 equiv); d) **1a** (1.00 equiv) with cat. **C** (0.50 equiv); e) **1a** (1.00 equiv) with cat. **C** (1.00 equiv); f) **1a** (1.00 equiv) with cat. **C** (2.00 equiv).

<condition (ii)>

[**1a** (1 equiv.) + cat **C** (0.1~0.4 equiv.)]

To probe the binding site of catalyst **C** on substrate **1a**, we observed ^{1}H and ^{13}C NMR spectra under mode (ii): **1a** (30.0 μmol, 1.00 equiv) with increasing amounts of catalyst **C** (0.10–0.40 equiv). In the ^{1}H NMR spectra, the OH resonance of **1a** shifted downfield from δ 9.77 to 9.95 ppm (Δδ = +0.18 ppm), while other signals of **1a** showed negligible changes. The downfield movement of the OH signal is consistent with proton transfer/hydrogen bonding to the tertiary amine of cat **C** (i.e., partial formation of an $[H–NR_3]^{+}\cdots O^{-}$/H-bonded complex).

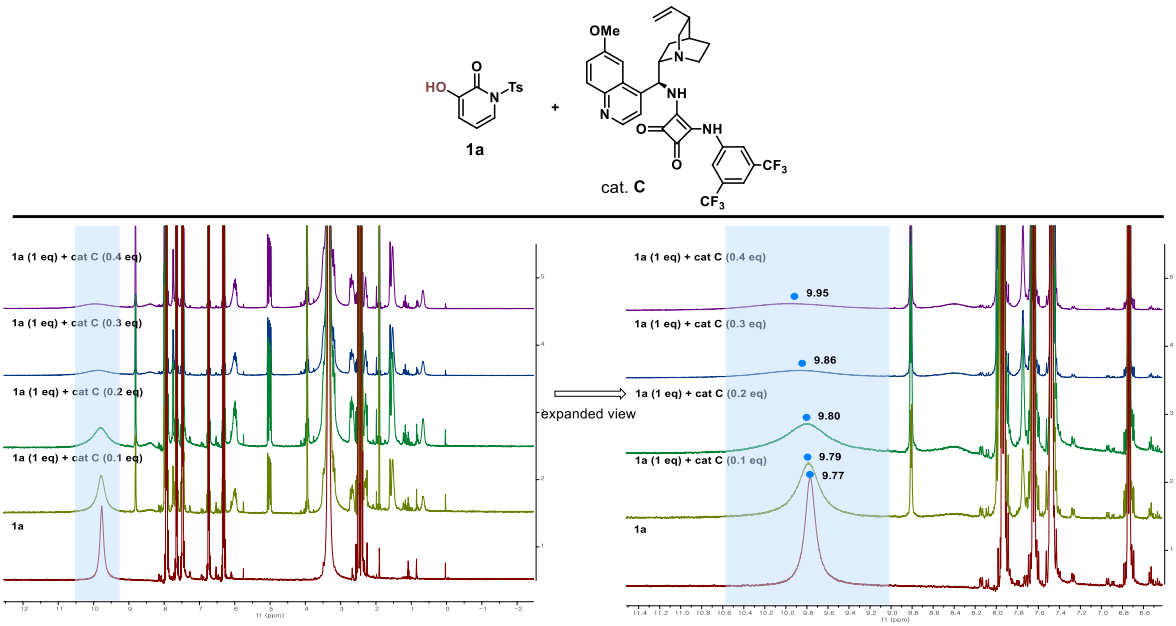


Figure S2. The chemical shifts of the OH resonance of 1a in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 750 µL, room temperature) observed during titration of **1a** with catalyst **C**: a) **1a** (30.0 µmol, 1.00 equiv); b) **1a** (1.00 equiv) with cat. **C** (0.10 equiv); c) **1a** (1.00 equiv) with cat. **C** (0.20 equiv); d) **1a** (1.00 equiv) with cat. **C** (0.30 equiv); e) **1a** (1.00 equiv) with cat. **C** (0.40 equiv).

[**1a** (1 equiv) + quinuclidine(QC) (0.1~0.4 equiv)]

To verify that the OH signal of **1a** responds specifically to a tertiary amine, we repeated the titration using quinuclidine (the tertiary-amine fragment of catalyst C). Under otherwise identical conditions (^{1}H NMR, 400 MHz, $CDCl_3$, 750 µL, rt), **1a** (1.00 equiv) was treated with increasing amounts of quinuclidine (0.10–0.40 equiv). The OH resonance of **1a** broadened and disappeared into the baseline across the titration, consistent with rapid acid–base exchange/proton transfer between **1a** and quinuclidine on the NMR timescale. These observations support that the tertiary amine site of catalyst C engages the OH group of **1a** via an acid–base interaction under the measurement conditions.

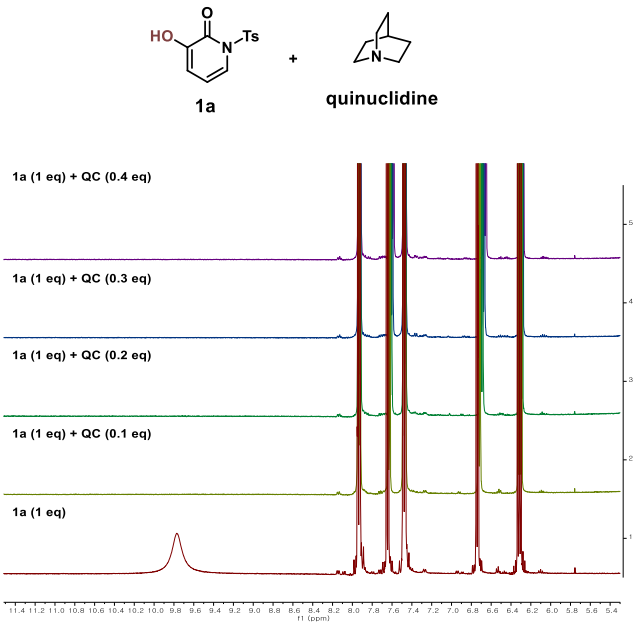


Figure S3. The chemical shift/behavior of the OH resonance of **1a** in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 750 µL, room temperature) observed during titration of **1a** with quinuclidine: a) **1a** (30.0 µmol, 1.00 equiv); b) **1a** (1.00 equiv) +

quinuclidine (0.10 equiv); c) **1a** (1.00 equiv) + quinuclidine (0.20 equiv); d) **1a** (1.00 equiv) + quinuclidine (0.30 equiv); e) **1a** (1.00 equiv) + quinuclidine (0.40 equiv). *(Note: the OH signal progressively broadens and disappears due to rapid acid–base exchange with quinuclidine.)*

[**1a** (1 equiv) + cat **L**(QC) (0.1~0.4 equiv)]

To assess whether the squaramide domain engages the OH group of **1a**, we performed a control titration using a squaramide-only analogue (catalyst **L**). Under otherwise identical conditions (^{1}H NMR, 400 MHz, $CDCl_3$, 750 µL, rt), **1a** (30.0 µmol, 1.00 equiv) was treated with increasing amounts of cat. **L** (0.10–0.40 equiv). The OH resonance of **1a** showed no measurable change in chemical shift across the series. These results indicate that the squaramide NH donors do not interact detectably with the OH under these conditions.

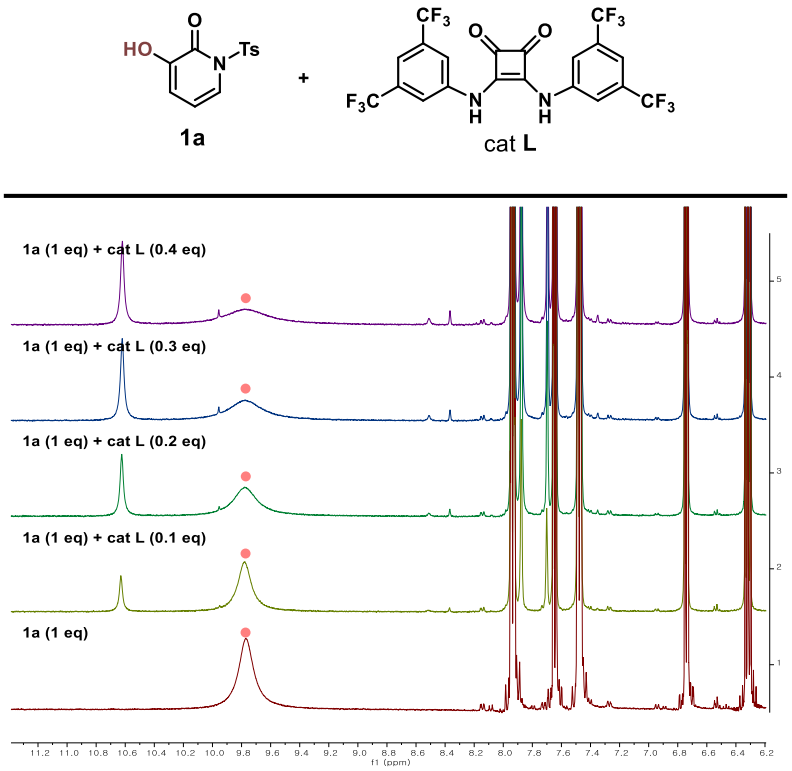


Figure S4. The chemical shift of the OH resonance of **1a** in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 750 µL, room temperature) observed during titration of **1a** with squaramide catalyst **L**: a) **1a** (30.0 µmol, 1.00 equiv); b) **1a** (1.00 equiv) with cat. **L** (0.10 equiv); c) **1a** (1.00 equiv) with cat. **L** (0.20 equiv); d) **1a** (1.00 equiv) with cat. **L** (0.30 equiv); e) **1a** (1.00 equiv) with cat. **L** (0.40 equiv).

<Interaction between cat **C** and **2a** at room temperature>

To probe the interaction between catalyst **C** and **2a**, we performed ^{1}H NMR titrations in two modes (400 MHz, $CDCl_3$, 750 µL, rt). In mode (i), cat. **C** (1.0 equiv) was titrated with **2a** at 1, 2, 5, 10, and 20 equiv. At these higher loadings, both squaramide NH resonances shifted progressively downfield. We chose higher **2a** equivalents because hydrogen-bonding to an aldehyde carbonyl is weak, and at low concentrations (0.10–0.40 equiv) the NH shifts were not apparent. In mode (ii), **2a** (1.0 equiv) was titrated with low loadings of cat. **C** (0.10–0.40 equiv); under these conditions the aldehydic ^{1}H signal of **2a** showed no meaningful perturbation, likewise indicating that low catalyst amounts do not produce a detectable effect. Taken together, results from (i) and (ii) are consistent with a weak but real interaction in which the squaramide NH donors of cat. **C** engage the carbonyl of **2a**.

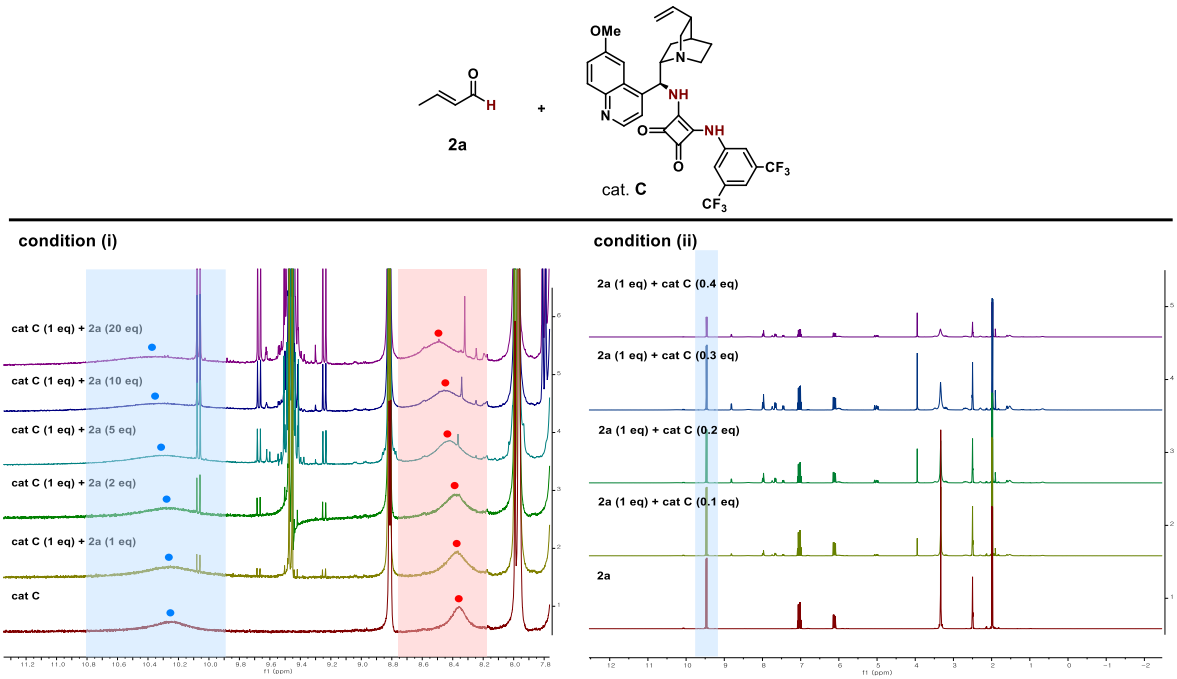
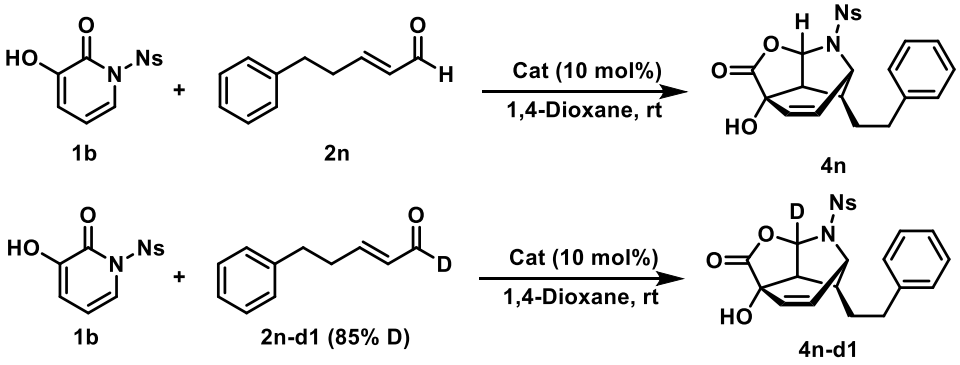


Figure S5. **(condition i)** The chemical shifts of the squaramide NH resonances of catalyst **C** in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 750 μL, room temperature) observed during titration of catalyst **C** with **2a**: a) cat. **C** (1.00 equiv); b) cat. **C** (1.00 equiv) with **2a** (1.0 equiv); **c)** cat. **C** (1.00 equiv) with **2a** (2.0 equiv); d) cat. **C** (1.00 equiv) with **2a** (5.0 equiv); e) cat. **C** (1.00 equiv) with **2a** (10.0 equiv); f) cat. **C** (1.00 equiv) with **2a** (20.0 equiv). **(condition ii)** The chemical shift of the aldehydic proton of **2a** in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 750 μL, room temperature) observed during titration of **2a** with catalyst **C**: a) **2a** (30.0 μmol, 1.00 equiv); b) **2a** (1.00 equiv) with cat. **C** (0.10 equiv); c) **2a** (1.00 equiv) with cat. **C** (0.20 equiv); d) **2a** (1.00 equiv) with cat. **C** (0.30 equiv); e) **2a** (1.00 equiv) with cat. **C** (0.40 equiv).

- KIE Experiments

< Kinetic Isotope Effect (k_H/k_D) for **1b** + **2n** (using **2n-d1**) >



To a stirred solution of **1b** (0.084 mmol, 1.0 equiv) and catalyst **E** (0.0084 mmol, 10 mol %) in solvent (0.34 mL) was added **2n or 2n-d1** (0.169 mmol, 2.0 equiv) and 1,3,5-trimethoxybenzene (0.084 mmol, 1.0 equiv) as an internal standard. The reaction mixture was stirred at the room temperature in a sealed vial under air. An aliquot (5.0 μL) of the mixture was removed on time, and diluted with MeCN (200 μL) under air. The yield of the product was determined by LC analysis.

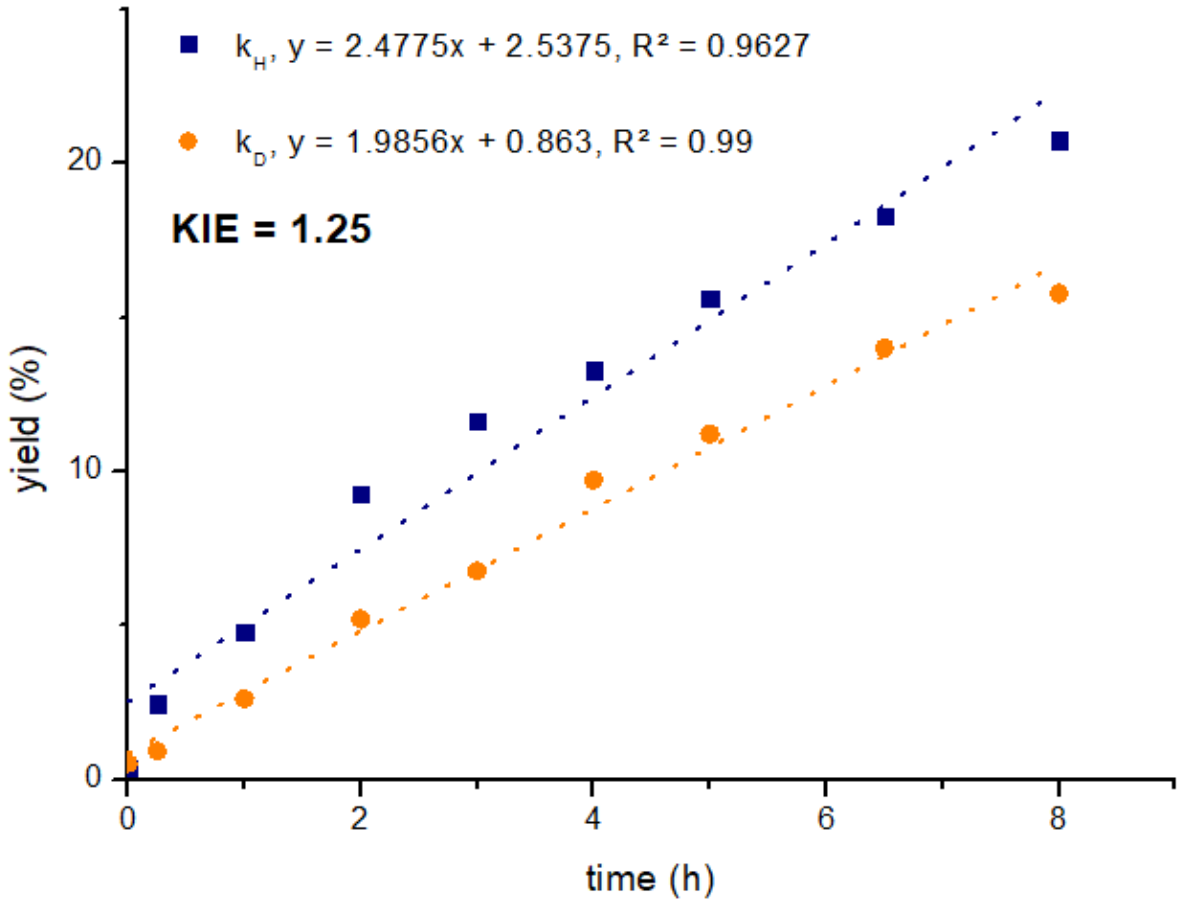


Figure S6. Kinetic isotope effect (KIE) for **1b** + **2n** vs **2n-d1** (85% D) measured by the parallel initial-rate method.

<2n ^{1}H NMR>

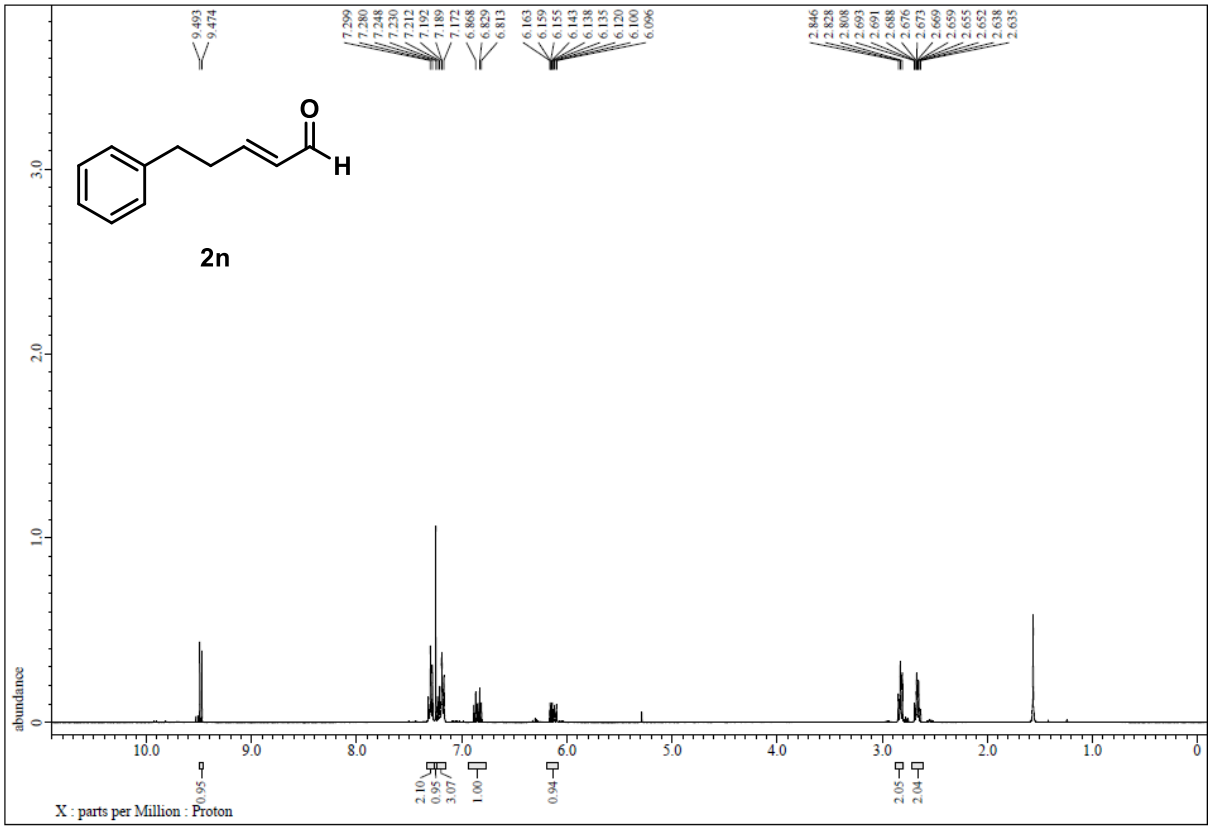


Figure S7. ^{1}H NMR for **2n**

<2n-d1 ^{1}H NMR>

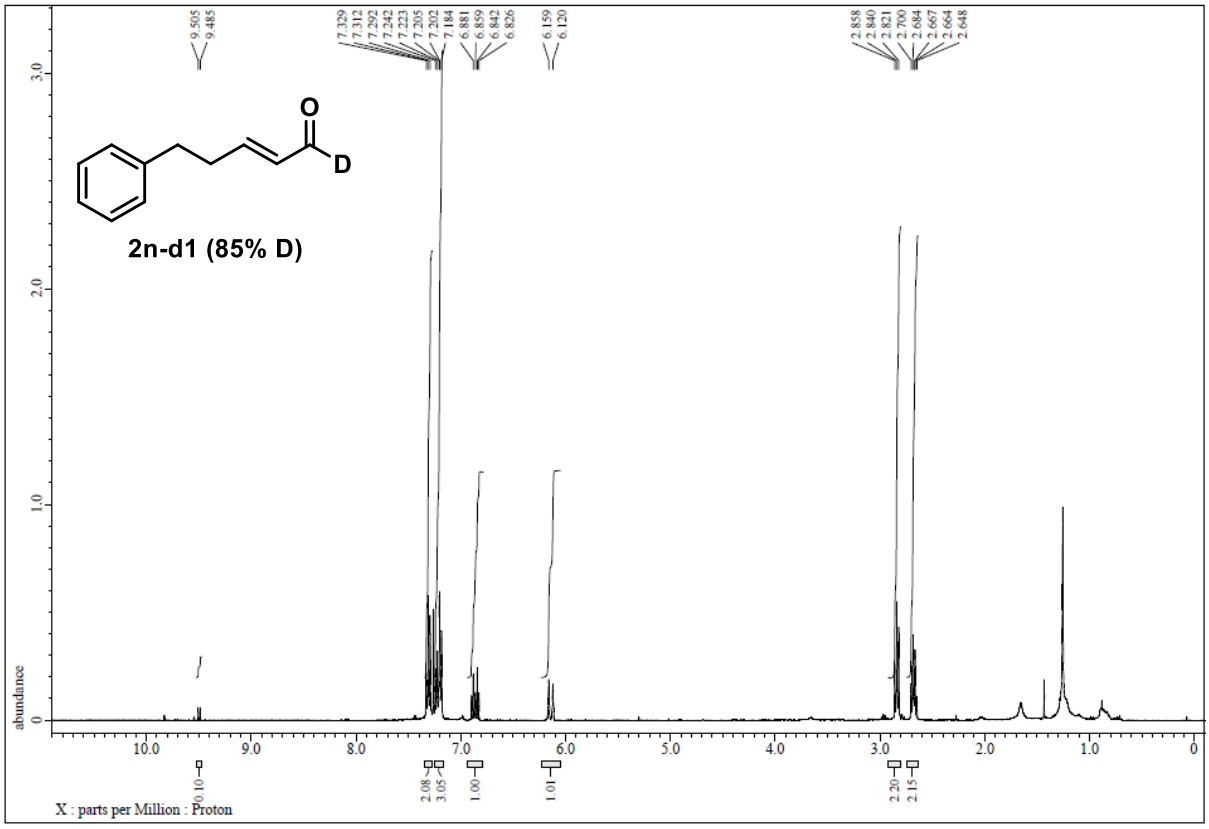
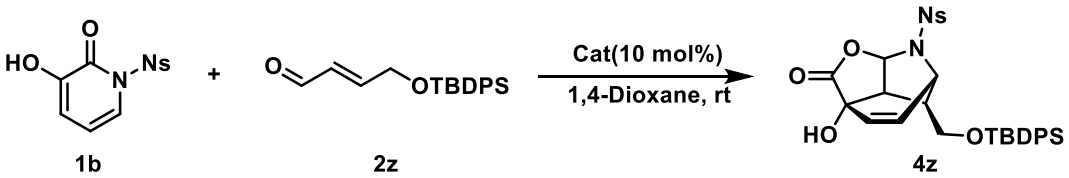


Figure S8. ^{1}H NMR for **2n-d1**

- Recyclability of Catalyst C in the Reaction of **1b** + **2z** (Five Cycles)

After completion of the preparative-scale reaction of **1b** with **2z** in the presence of catalyst **E**, the mixture was diluted with EtOAc and H_2O to form a biphasic system. The layers were separated, and the organic phase was washed with 1 N HCl (15 mL). Under these acidic conditions, catalyst **E** became protonated and transferred to the aqueous layer, while the organic layer retained the product and any residual **2z**. The acidic aqueous fractions were combined, basified with aqueous NH_4OH (15 mL) to basic pH, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was recrystallized from a minimal amount of MeOH to afford clean catalyst **E**, which was used directly in subsequent recycling experiments.



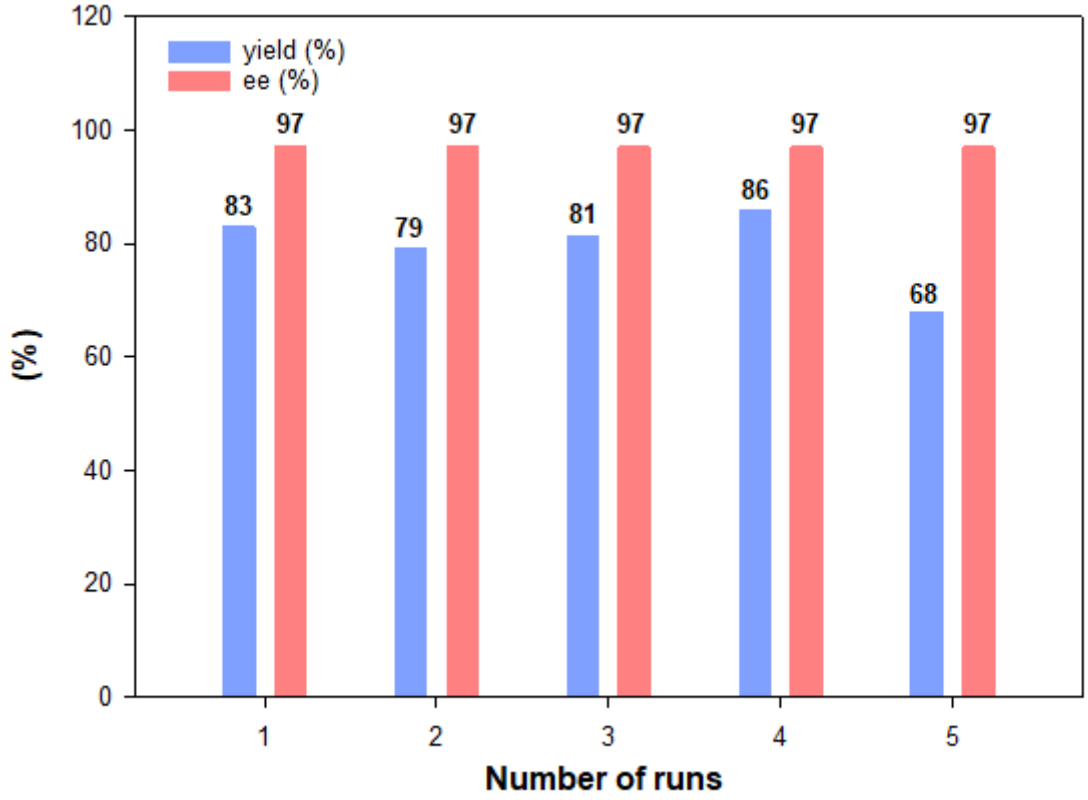
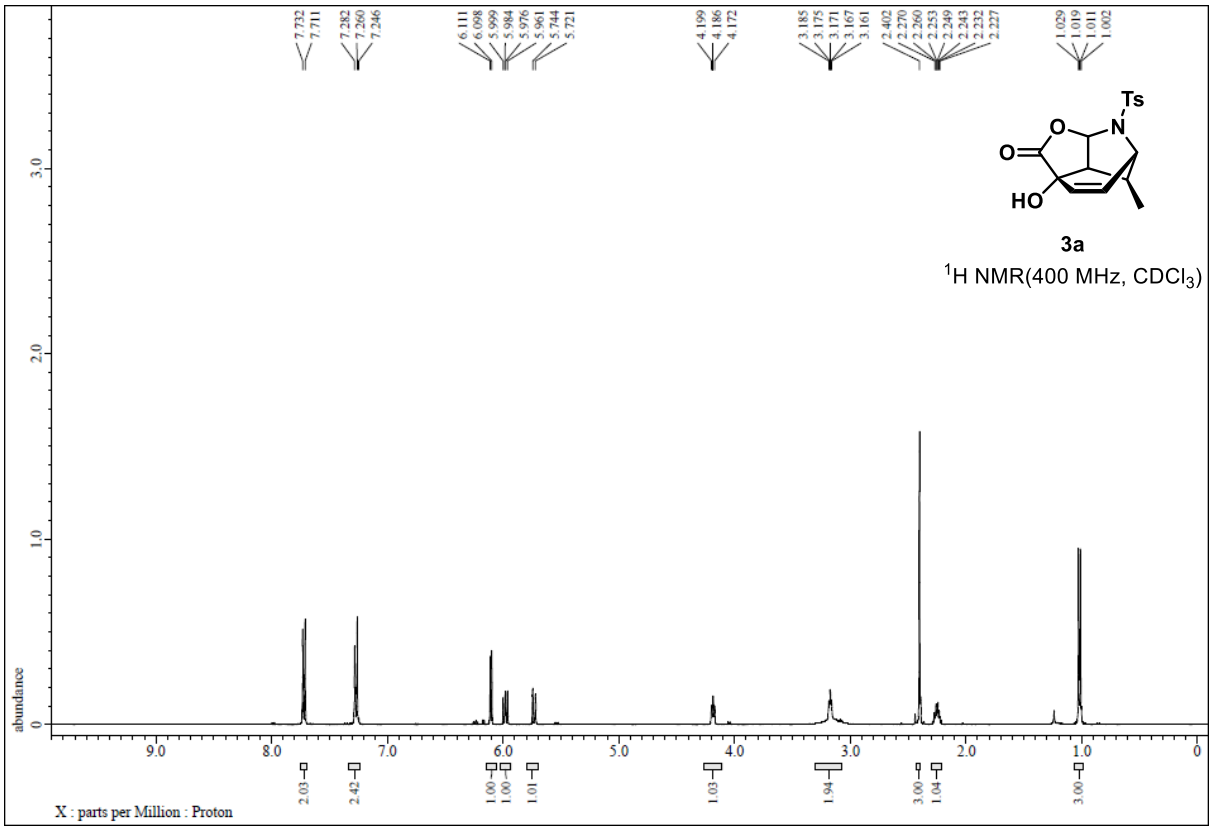
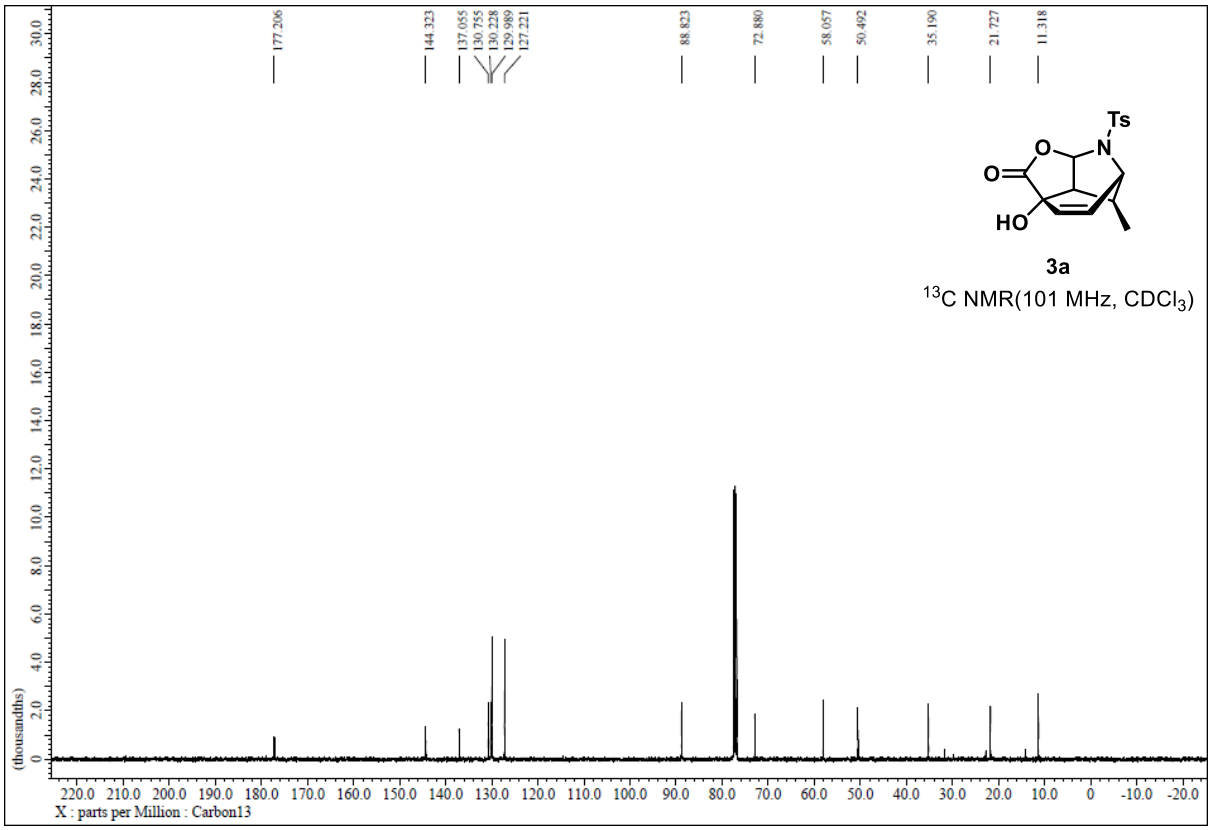


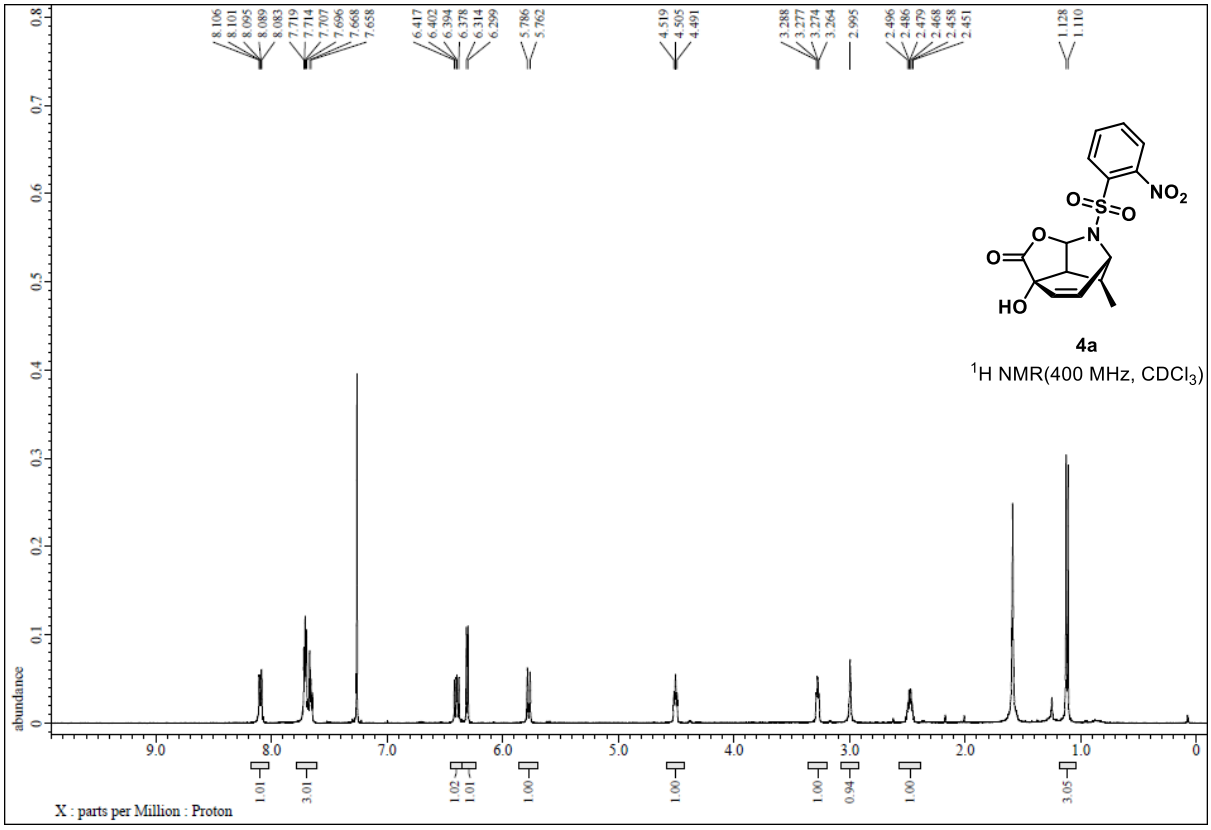
Figure S9. The reaction was conducted according to General Procedure D; product yields were determined by ^1H NMR spectroscopy using 1,2-dibromoethane as the internal standard, and enantiomeric excess (ee) values were determined by HPLC analysis.

IV. NMR Spectra

-^{1}H and ^{13}C, and ^{19}F NMR Spectra of Isolated Compounds

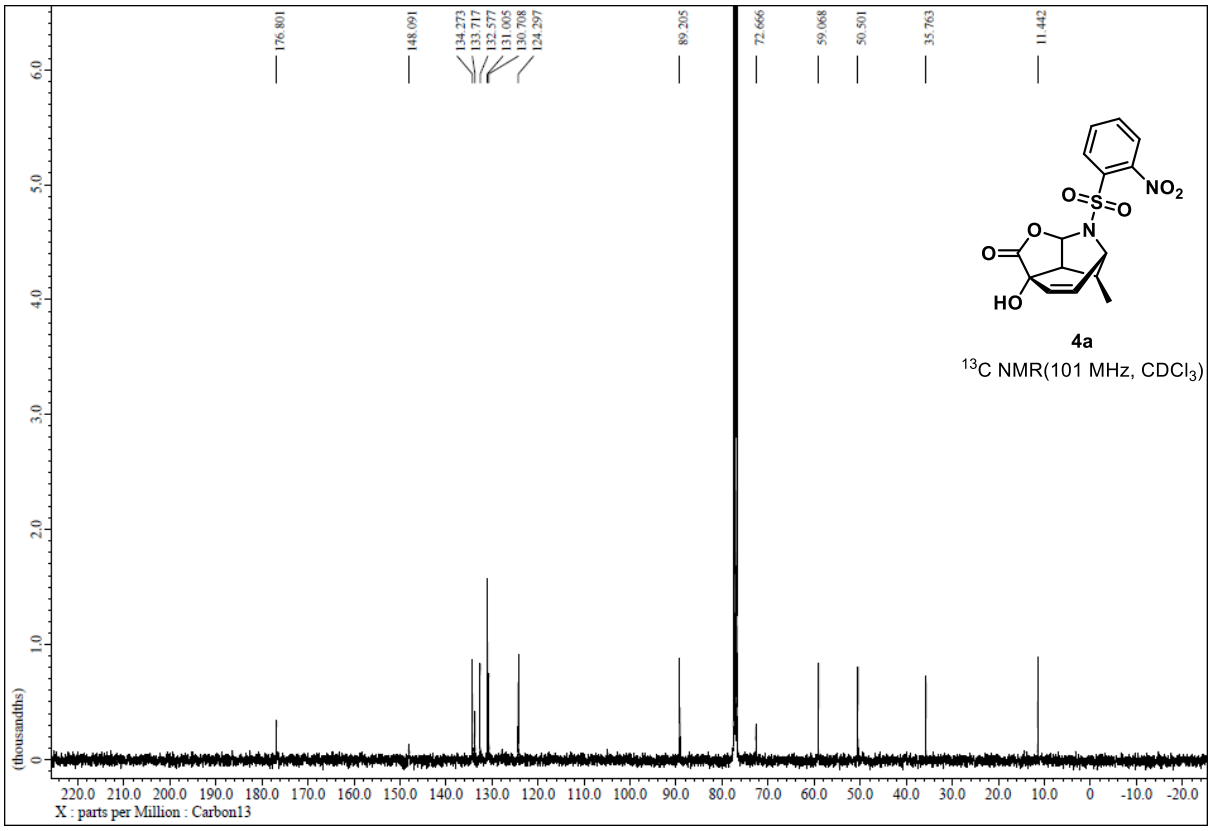






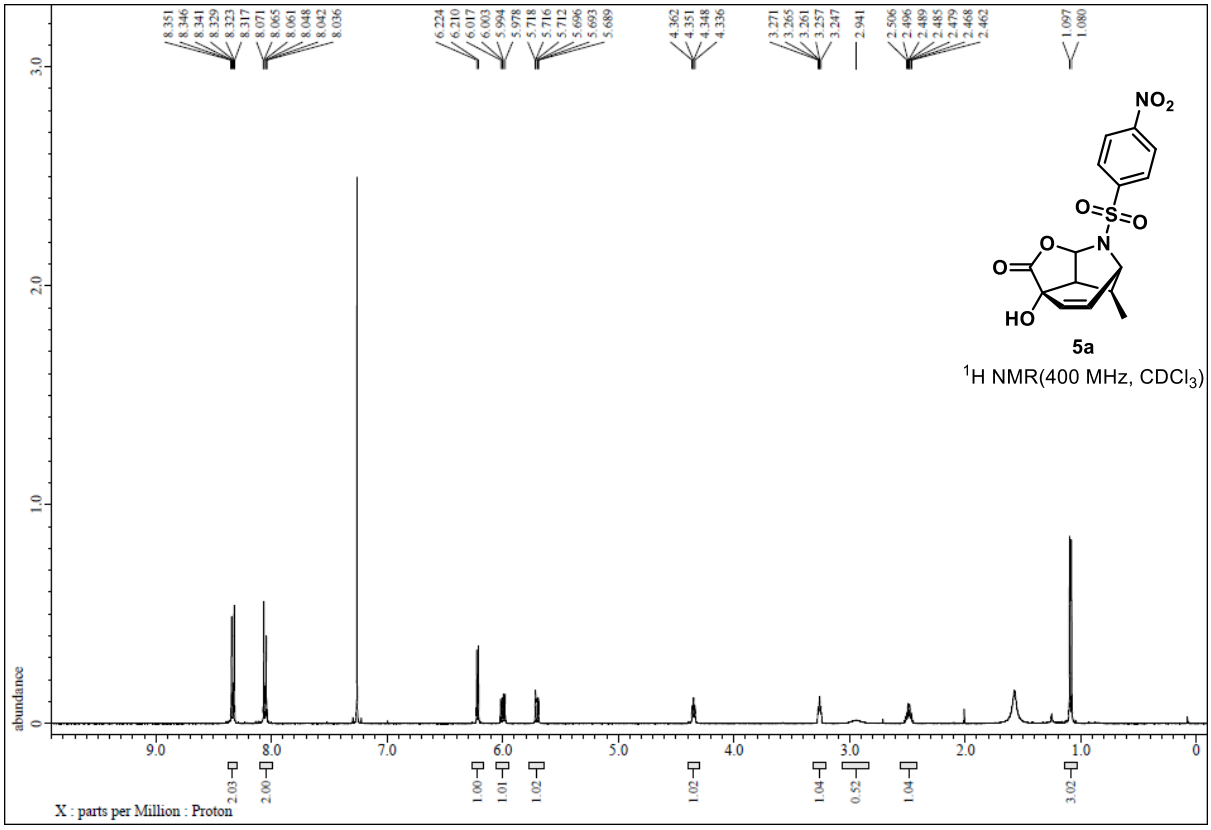
4a

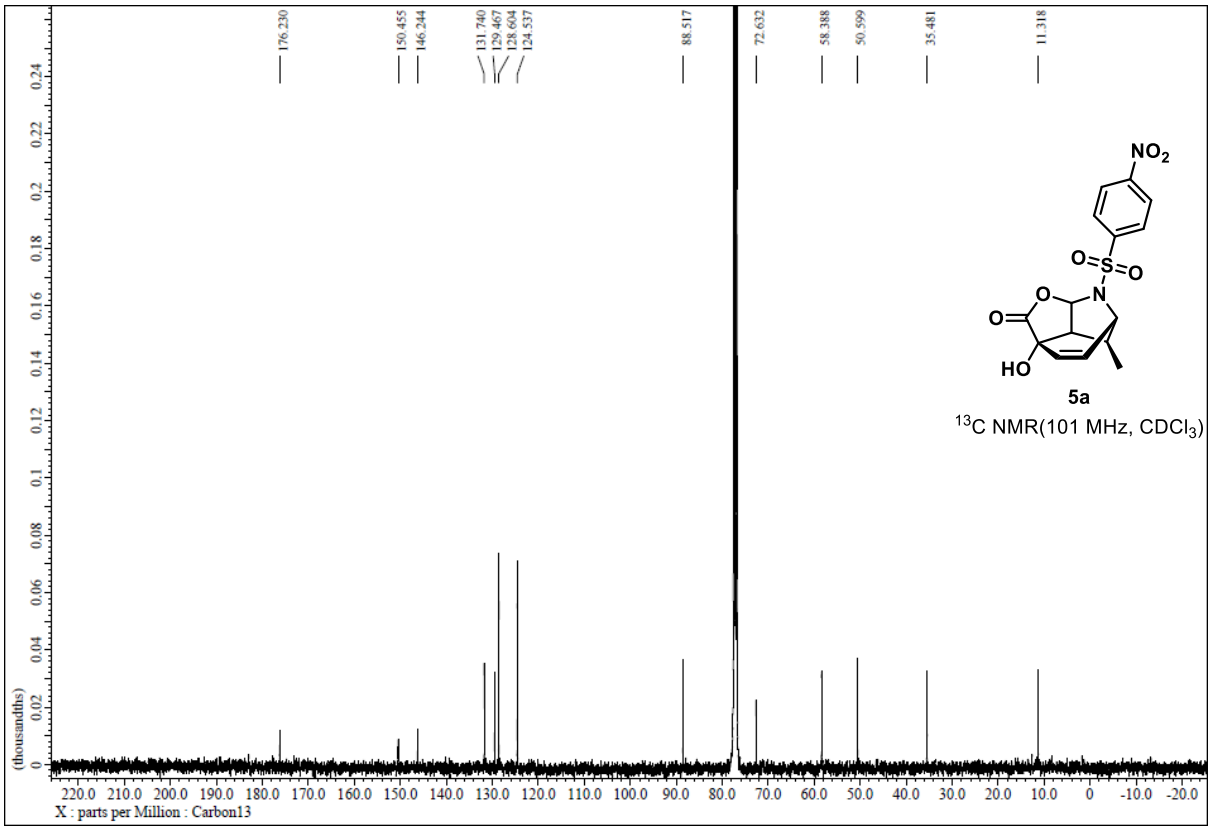
^{1}H NMR(400 MHz, $CDCl_3$)

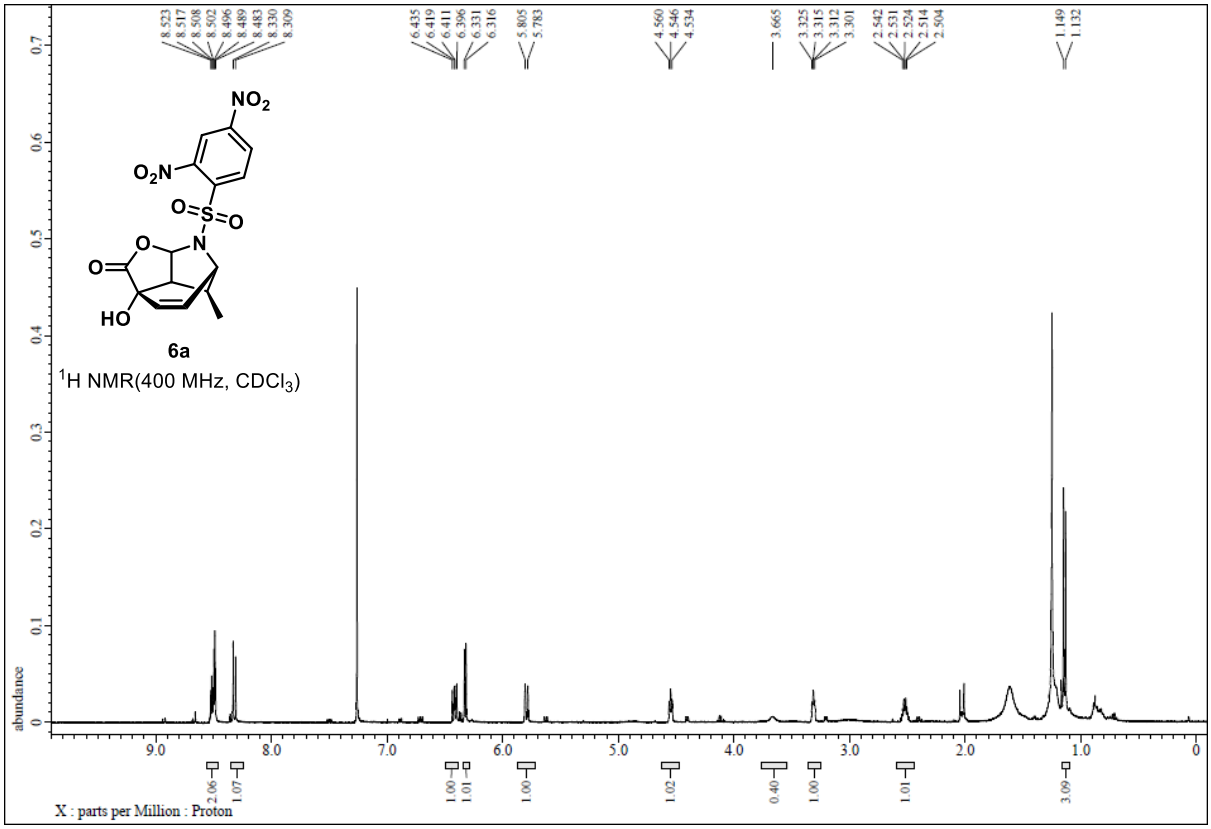


4a

^{13}C NMR(101 MHz, $CDCl_3$)

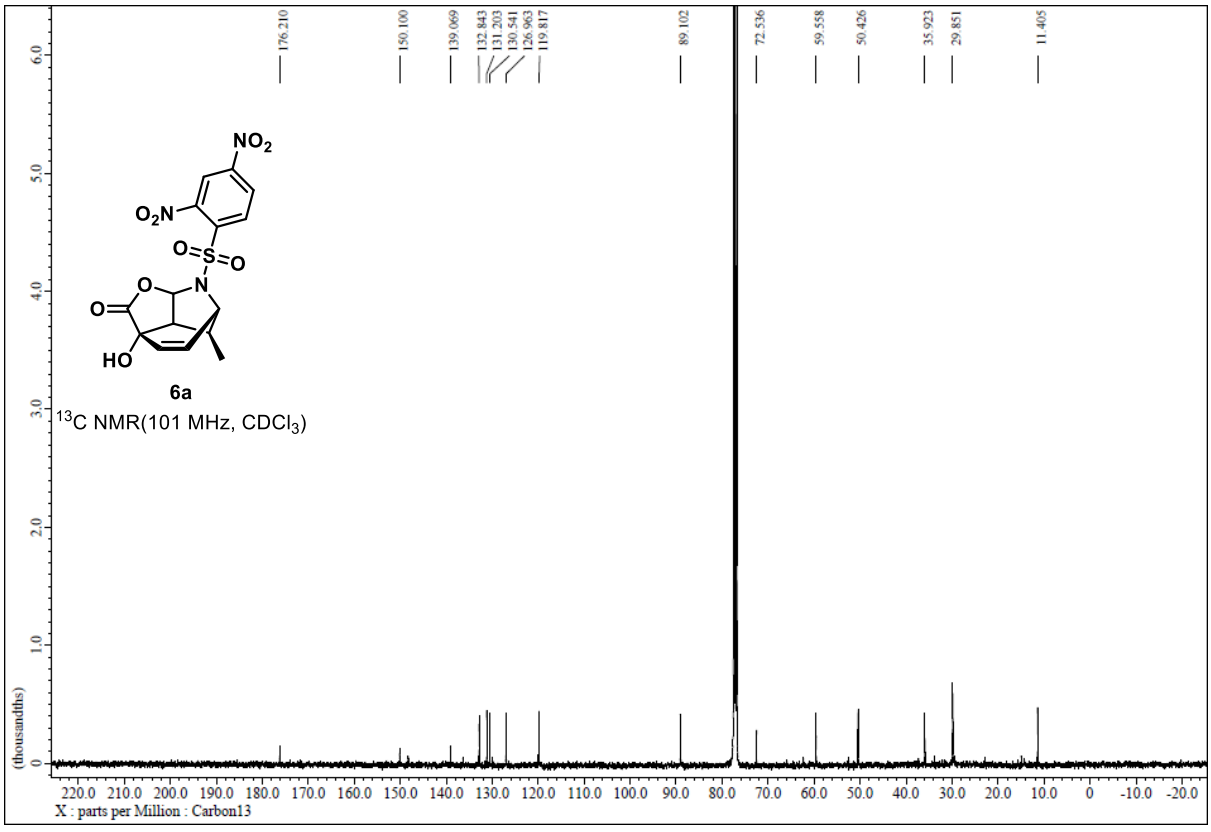

8.351
8.346
8.341
8.329
8.323
8.317
8.071
8.065
8.061
8.048
8.042
8.036
6.224
6.210
6.017
6.003
5.994
5.978
5.718
5.716
5.712
5.696
5.693
5.689
4.362
4.351
4.348
4.336
3.271
3.265
3.261
3.257
3.247
2.941
2.506
2.496
2.489
2.485
2.479
2.468
2.462
1.097
1.080
abundance
X : parts per Million : Proton
NO2
O=S=O
N
O
O
HO
5a
1H NMR(400 MHz, CDCl3)


176.230
150.455
146.244
131.740
129.467
128.604
124.537
88.517
72.632
58.388
50.599
35.481
11.318
(thousandths)
X : parts per Million : Carbon13
NO2
O=S=O
N
O
O
HO
5a
13C NMR(101 MHz, CDCl3)



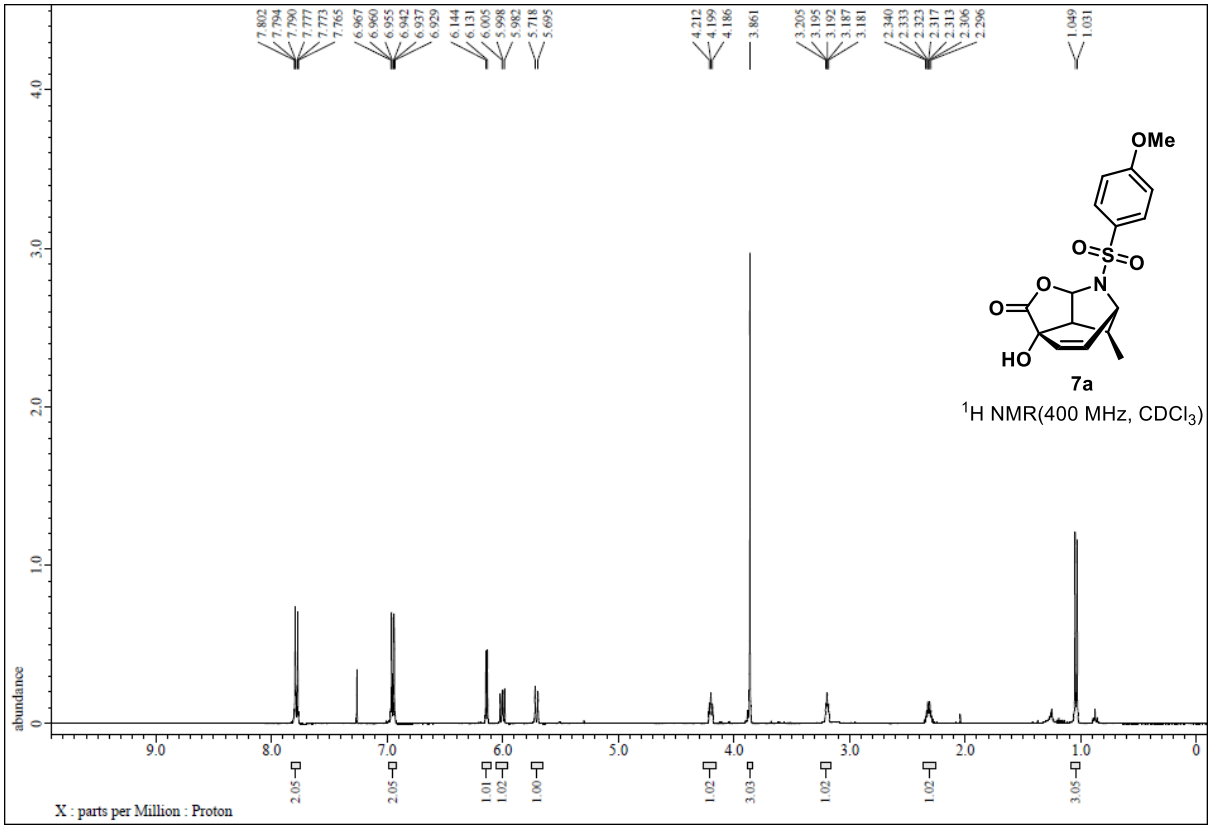
6a

^{1}H NMR(400 MHz, $CDCl_3$)



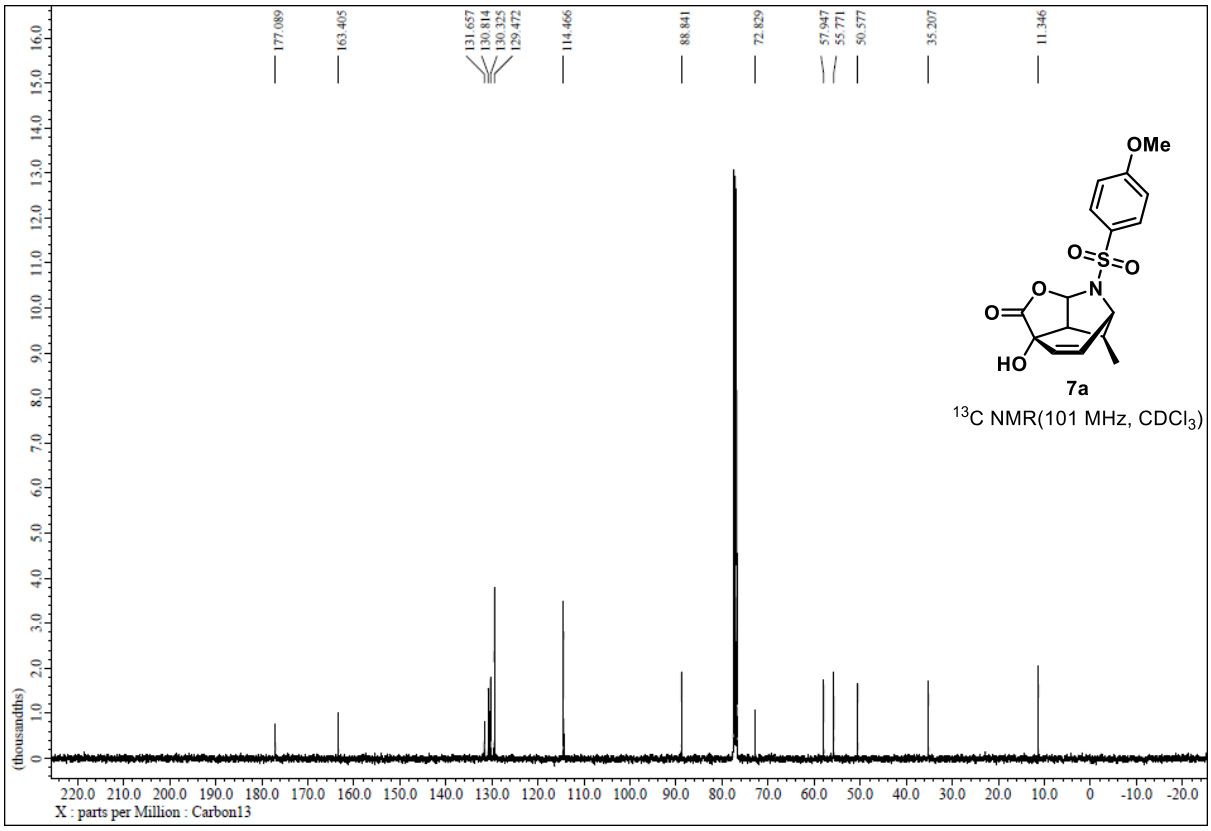
6a

^{13}C NMR(101 MHz, $CDCl_3$)



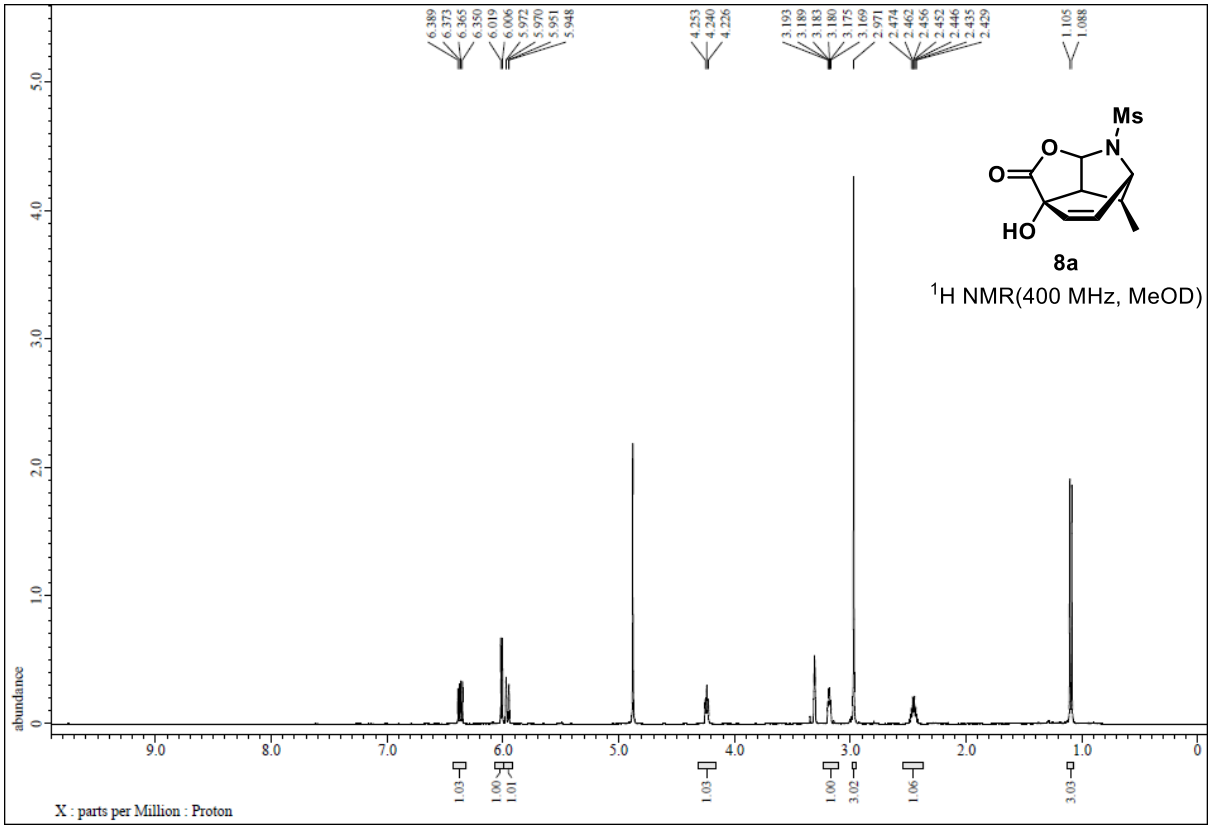
7a

^{1}H NMR(400 MHz, $CDCl_3$)



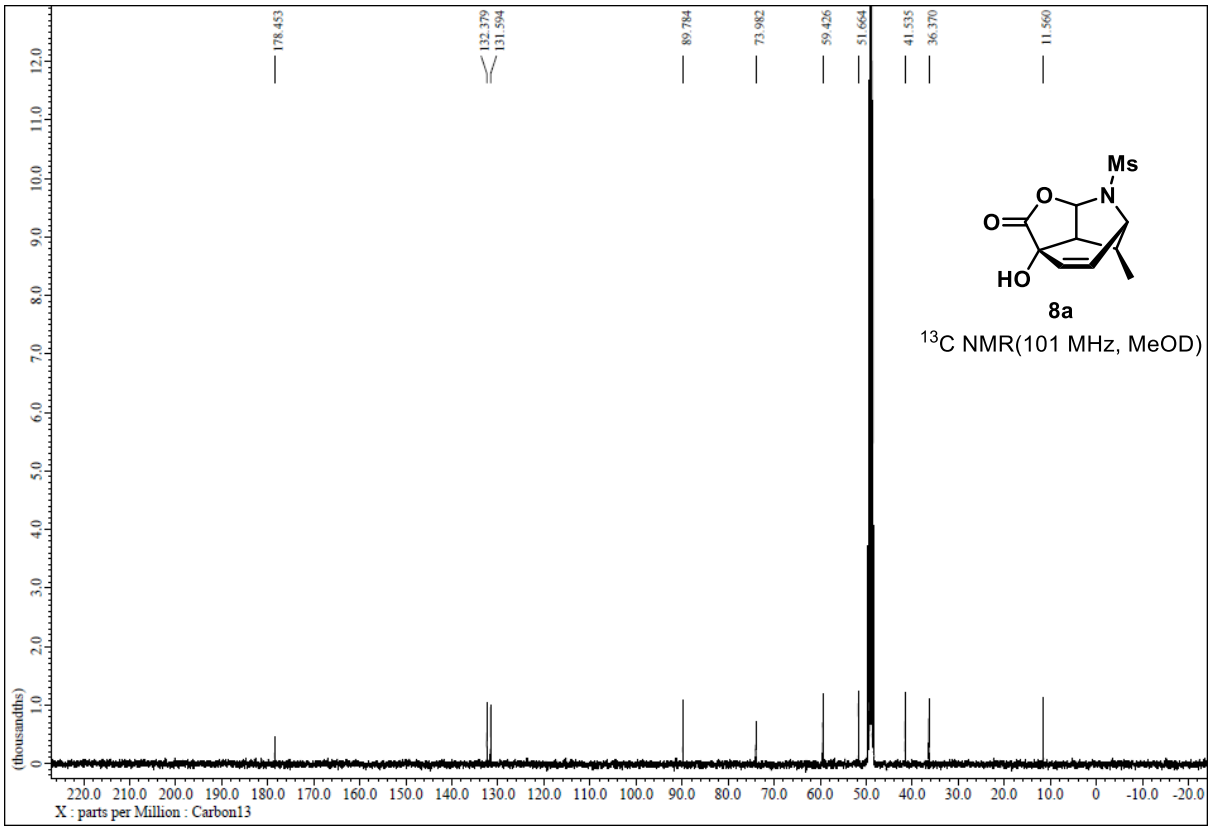
7a

^{13}C NMR(101 MHz, $CDCl_3$)



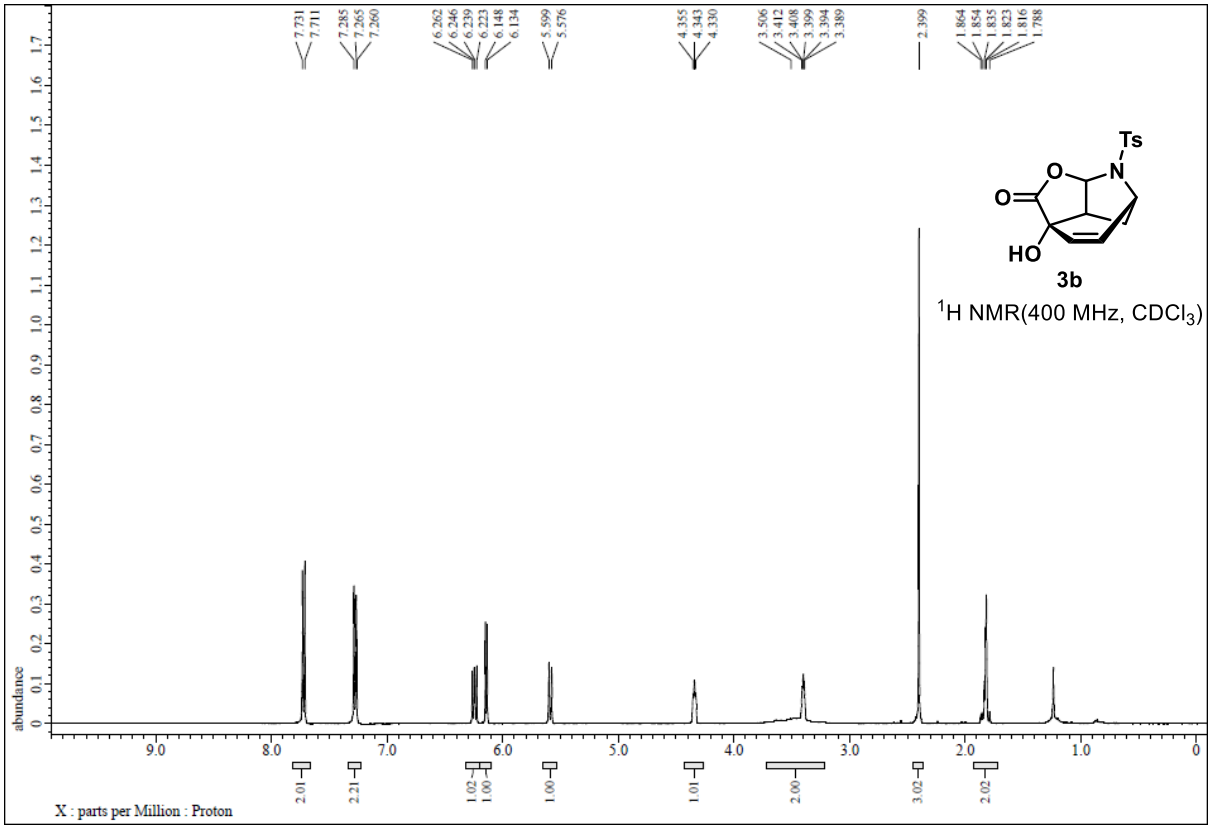
8a

^{1}H NMR(400 MHz, MeOD)



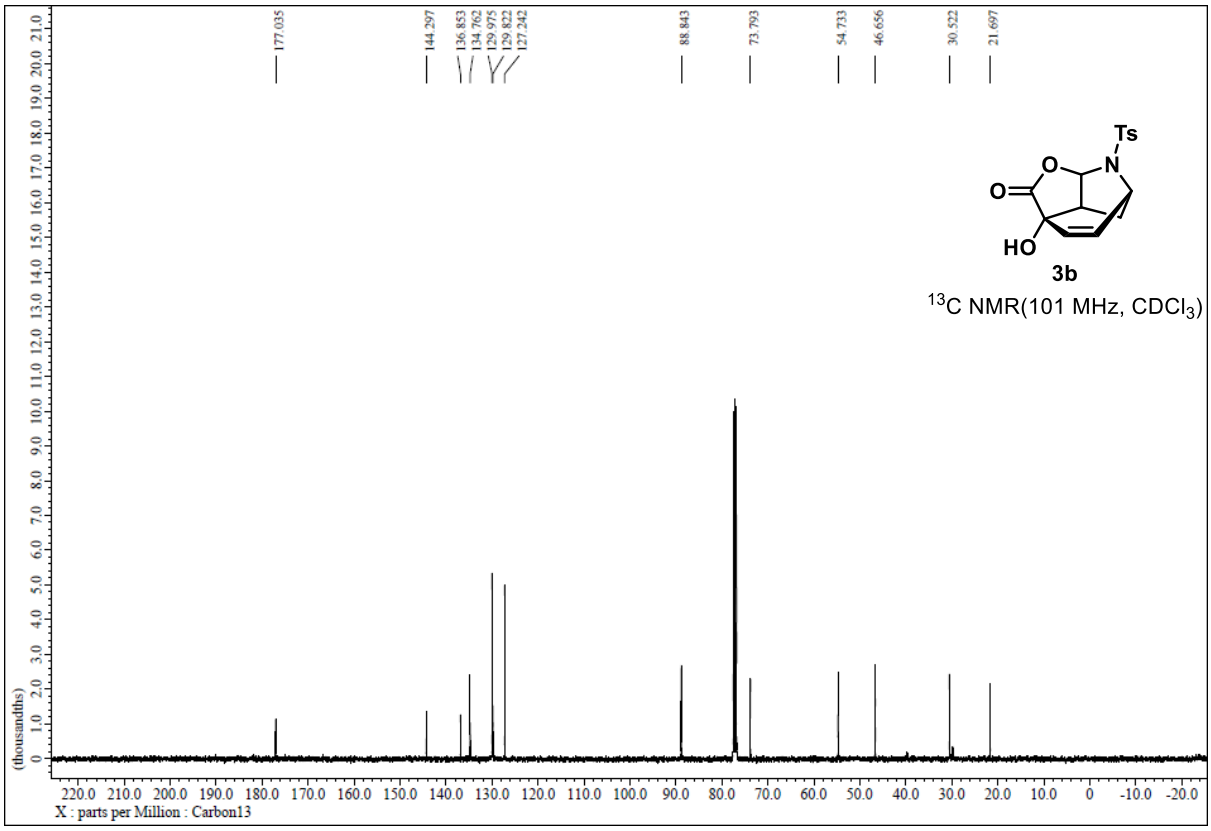
8a

^{13}C NMR(101 MHz, MeOD)



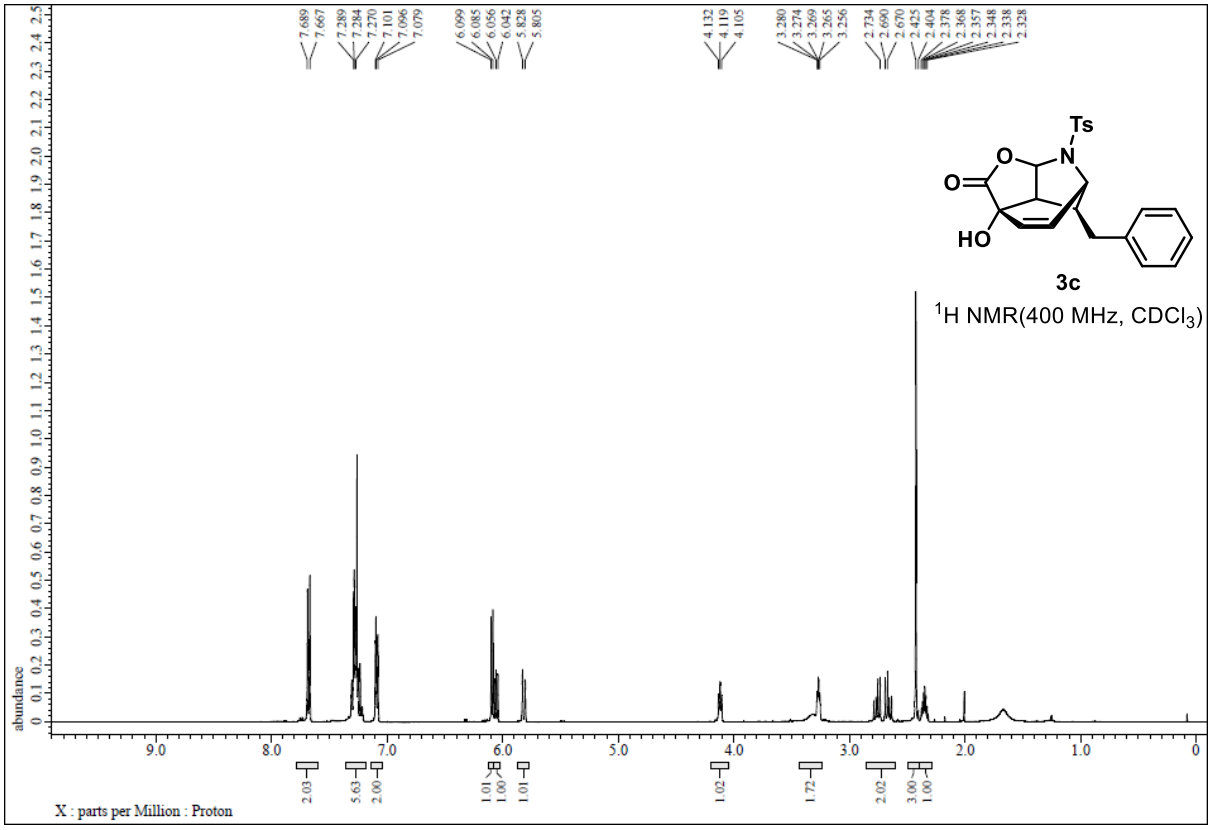
3b

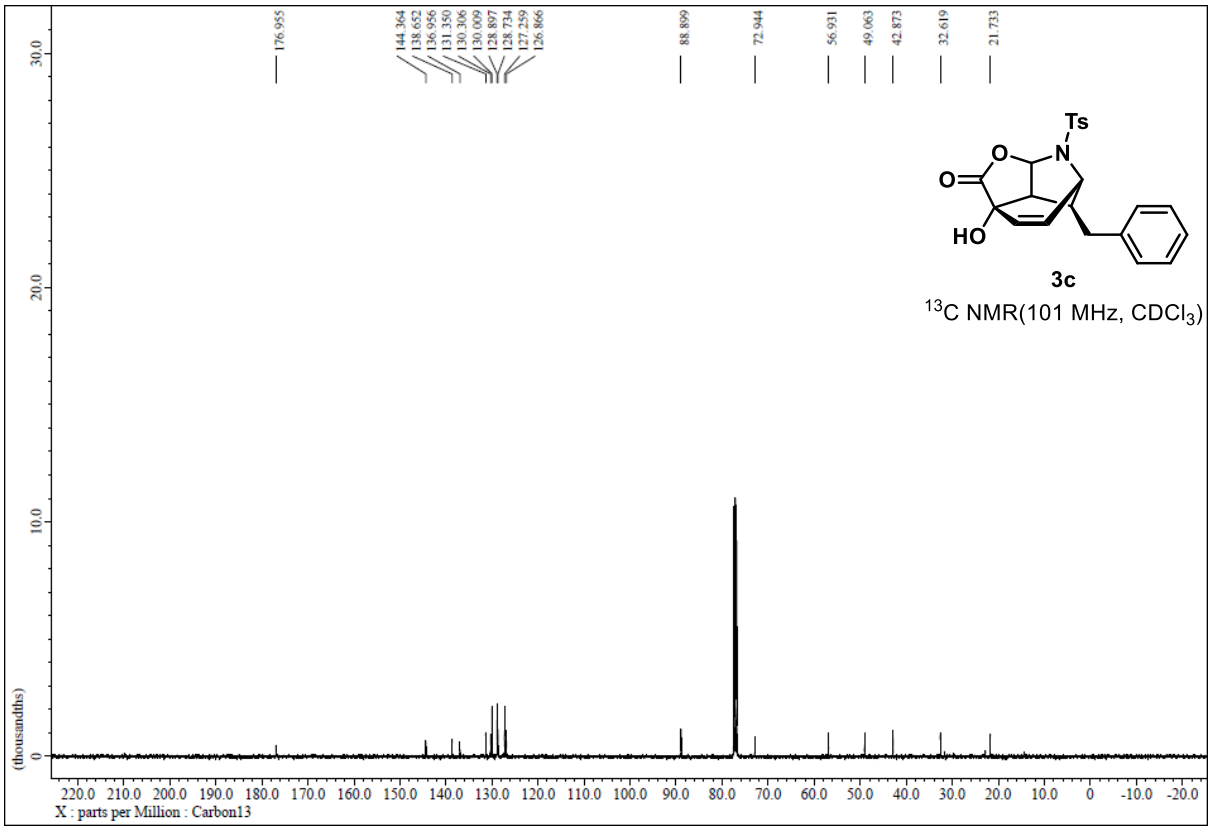
^{1}H NMR(400 MHz, $CDCl_3$)



3b

^{13}C NMR(101 MHz, $CDCl_3$)


7.689
7.667
7.289
7.284
7.270
7.101
7.096
7.079
6.099
6.085
6.056
6.042
5.828
5.805
4.132
4.119
4.105
3.280
3.274
3.269
3.265
3.256
2.734
2.690
2.670
2.425
2.404
2.378
2.368
2.357
2.348
2.338
2.328
Ts
O
N
O
HO
3c
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


176.955
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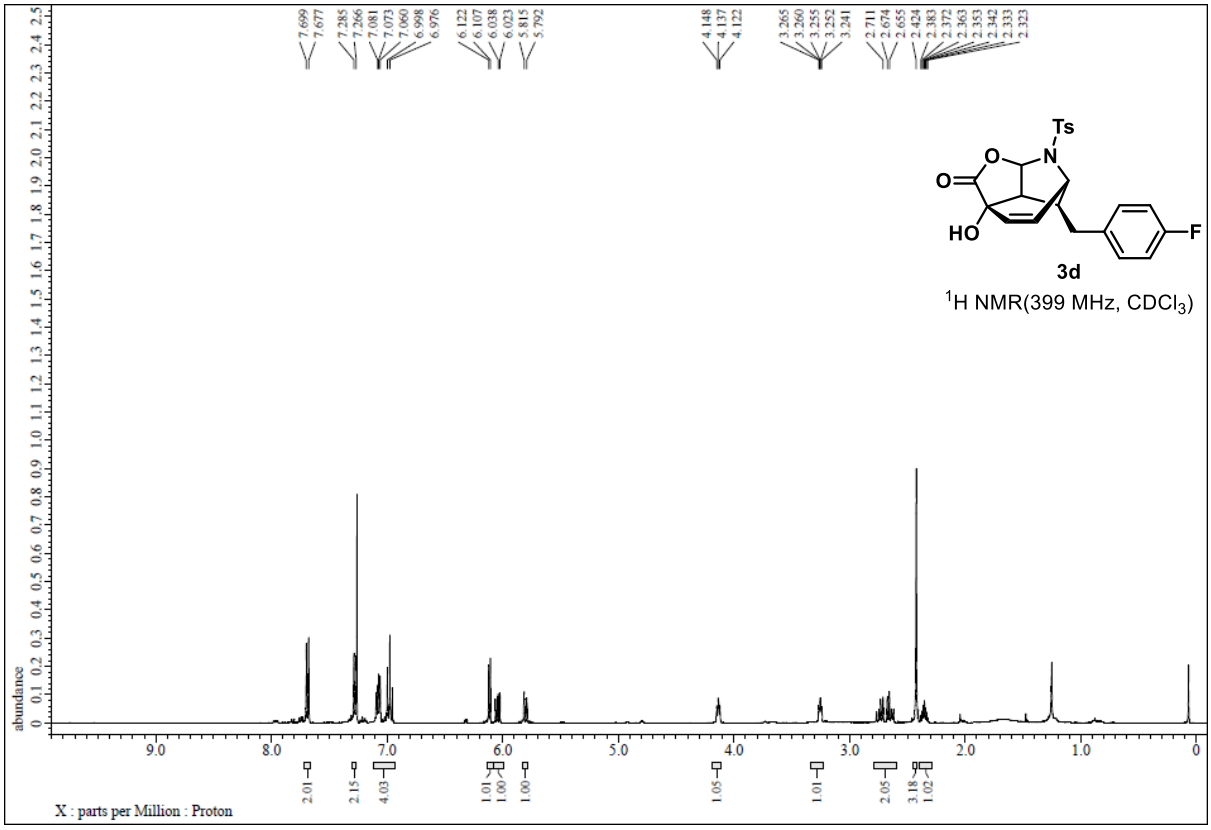
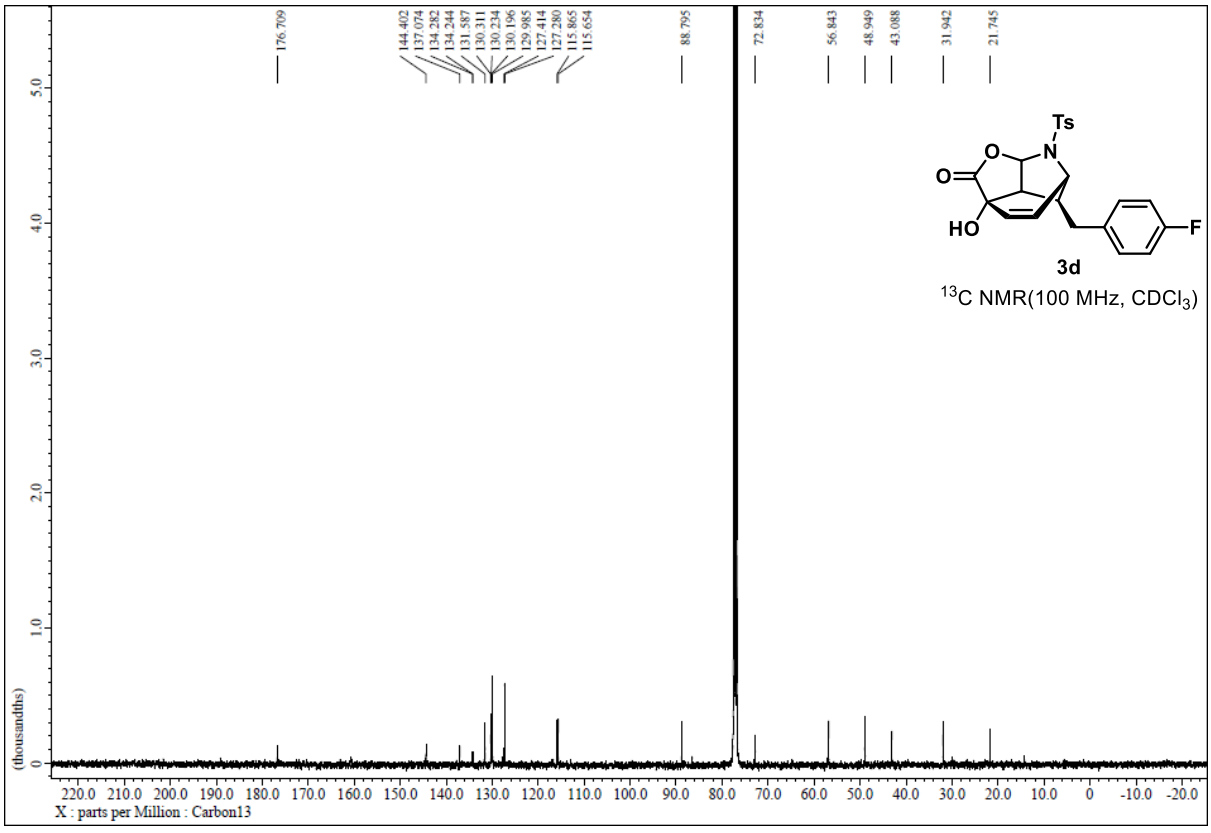
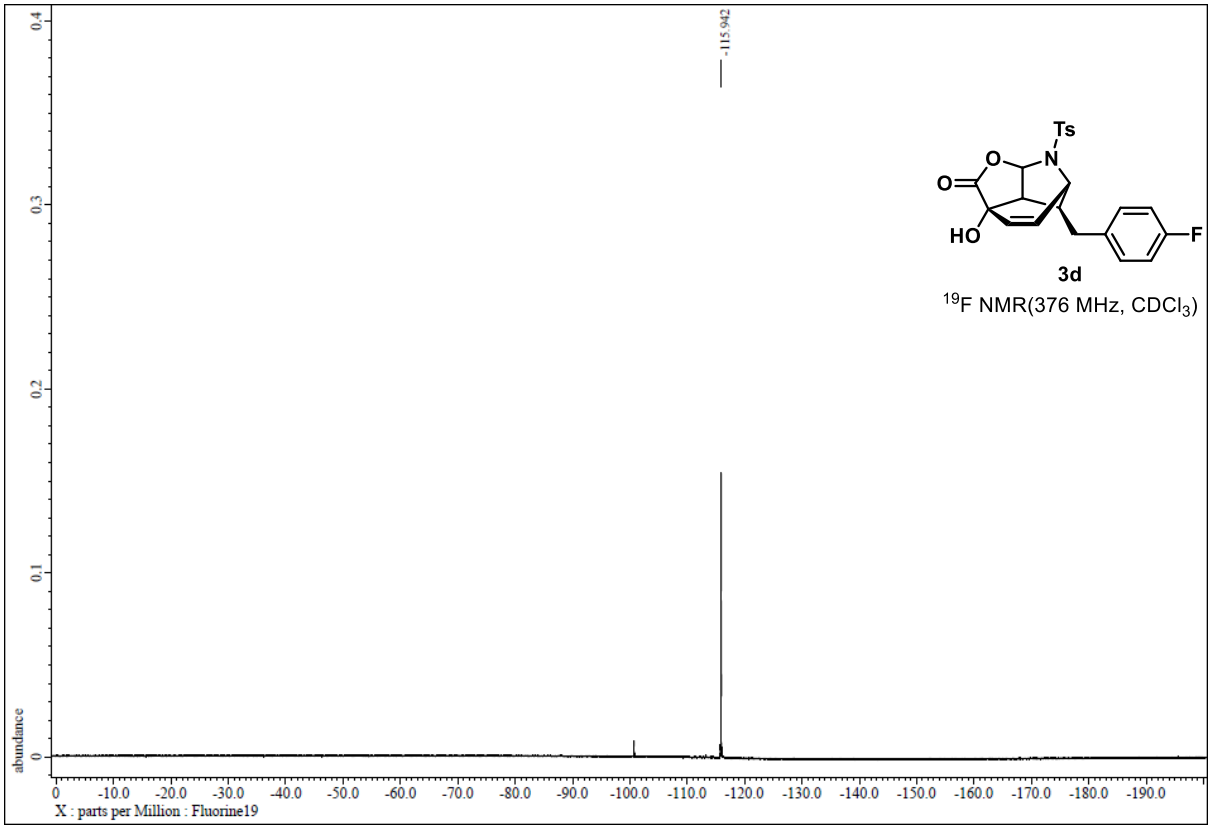
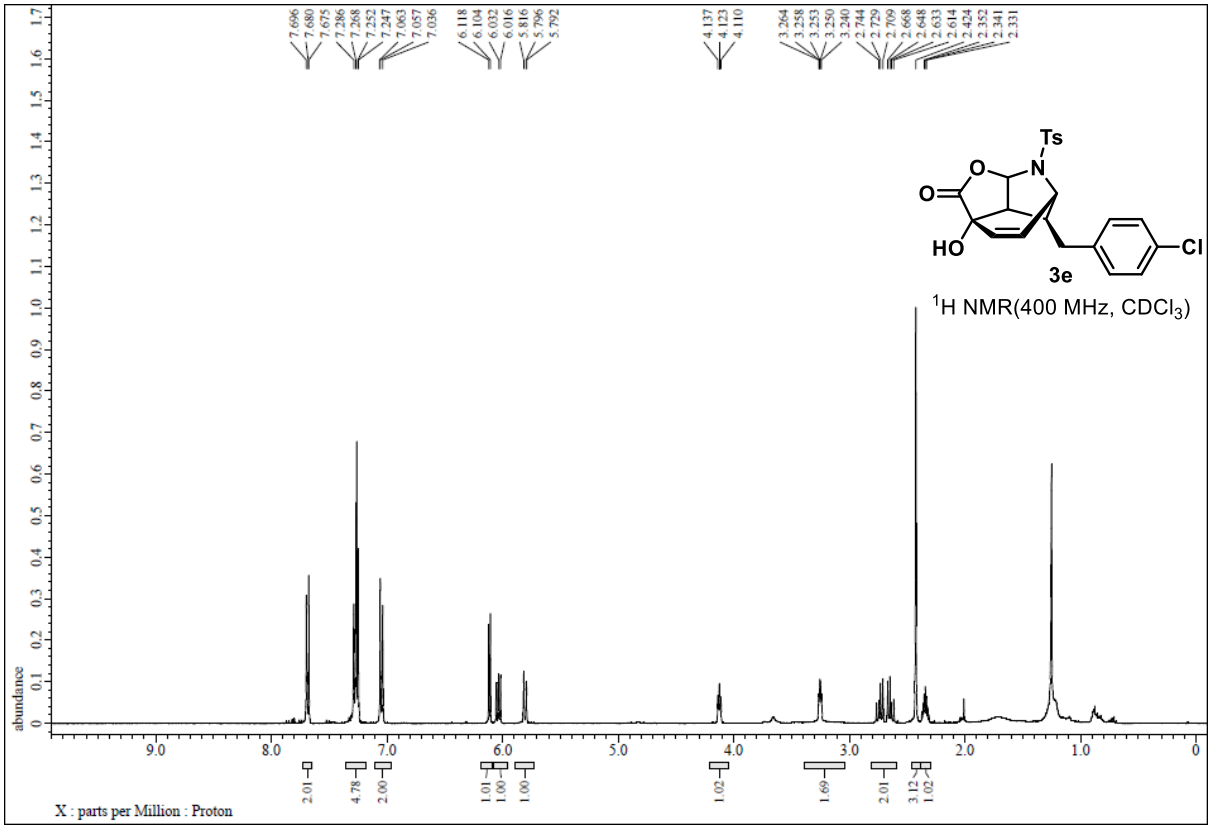
138.652
136.956
131.350
130.306
130.009
128.897
128.734
127.259
126.866
88.899
72.944
56.931
49.063
42.873
32.619
21.733
Ts
O
N
O
HO
3c
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

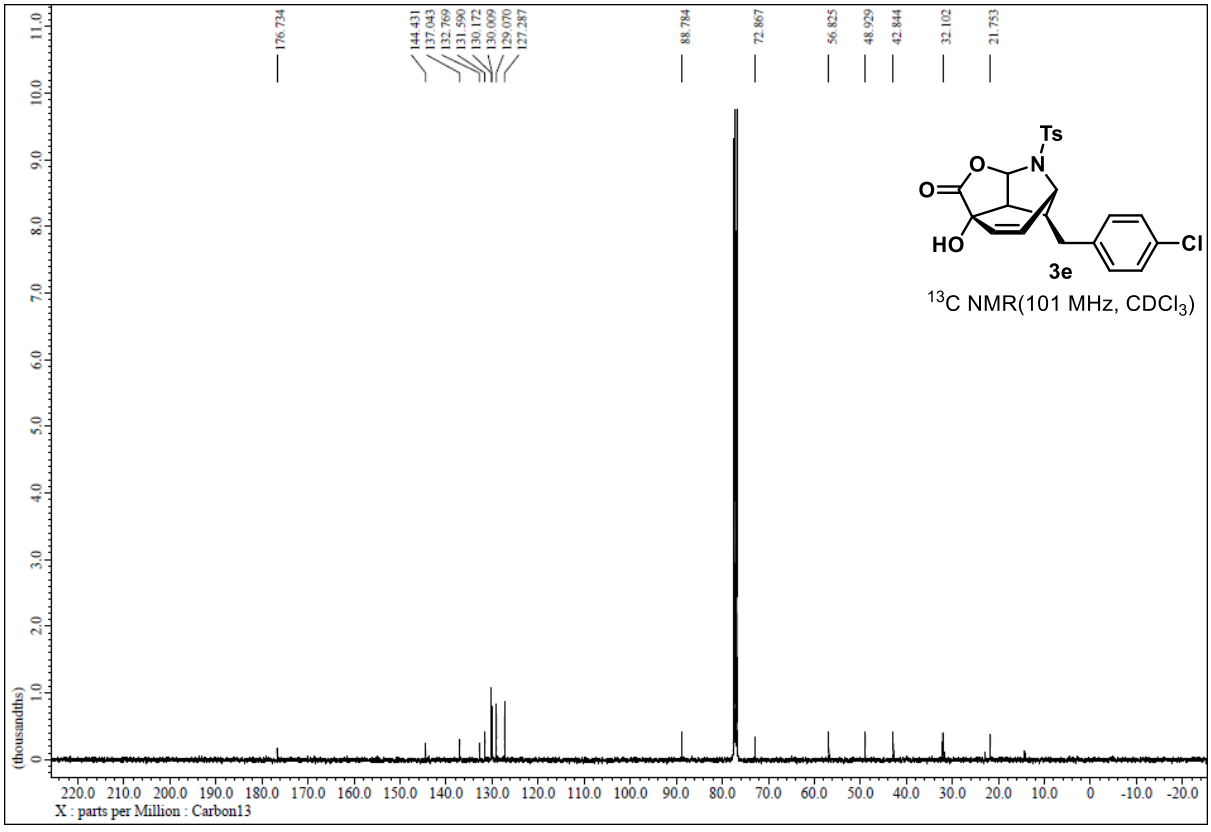

7.699
7.677
7.285
7.266
7.081
7.073
7.060
6.998
6.976
6.122
6.107
6.038
6.023
5.815
5.792
4.148
4.137
4.122
3.265
3.260
3.255
3.252
3.241
2.711
2.674
2.655
2.424
2.383
2.372
2.363
2.353
2.342
2.333
2.323
Ts
N
O
O
HO
F
3d
^{1}H NMR(399 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


176.709
144.402
137.074
134.282
134.244
131.587
130.311
130.234
130.196
129.985
127.414
127.280
115.865
115.654
88.795
72.834
56.843
48.949
43.088
31.942
21.745
Ts
N
O
O
HO
F
3d
^{13}C NMR(100 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

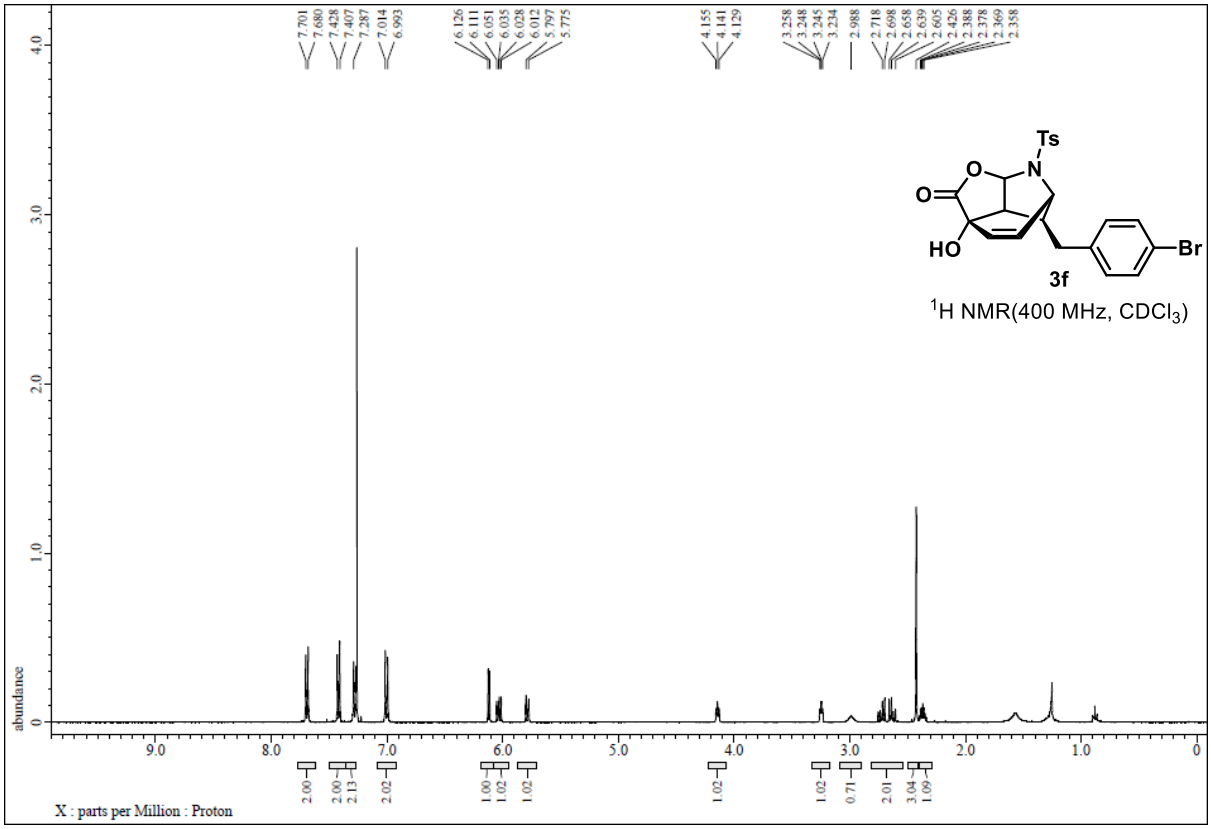

-115.942
Ts
N
O
O
HO
F
3d
19F NMR(376 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0 -10.0 -20.0 -30.0 -40.0 -50.0 -60.0 -70.0 -80.0 -90.0 -100.0 -110.0 -120.0 -130.0 -140.0 -150.0 -160.0 -170.0 -180.0 -190.0
X : parts per Million : Fluorine19



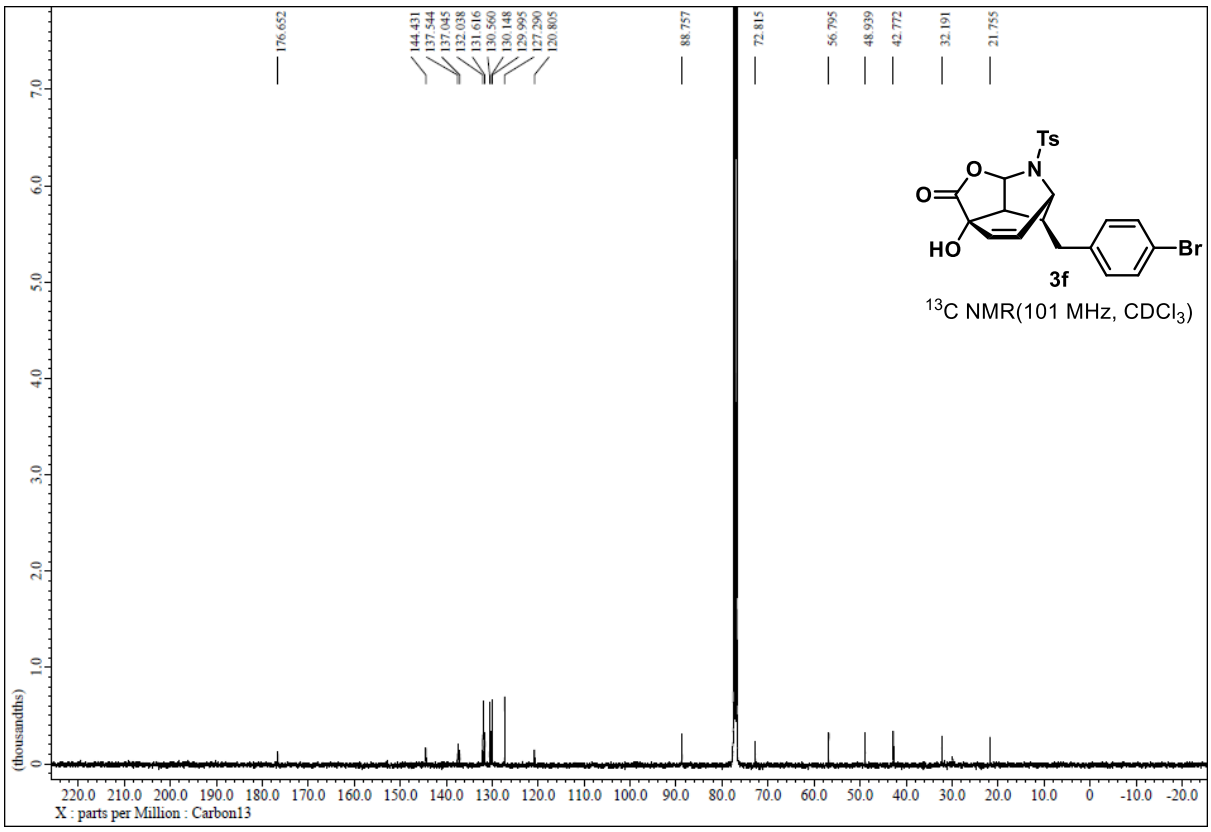
^{1}H NMR(400 MHz, $CDCl_3$)



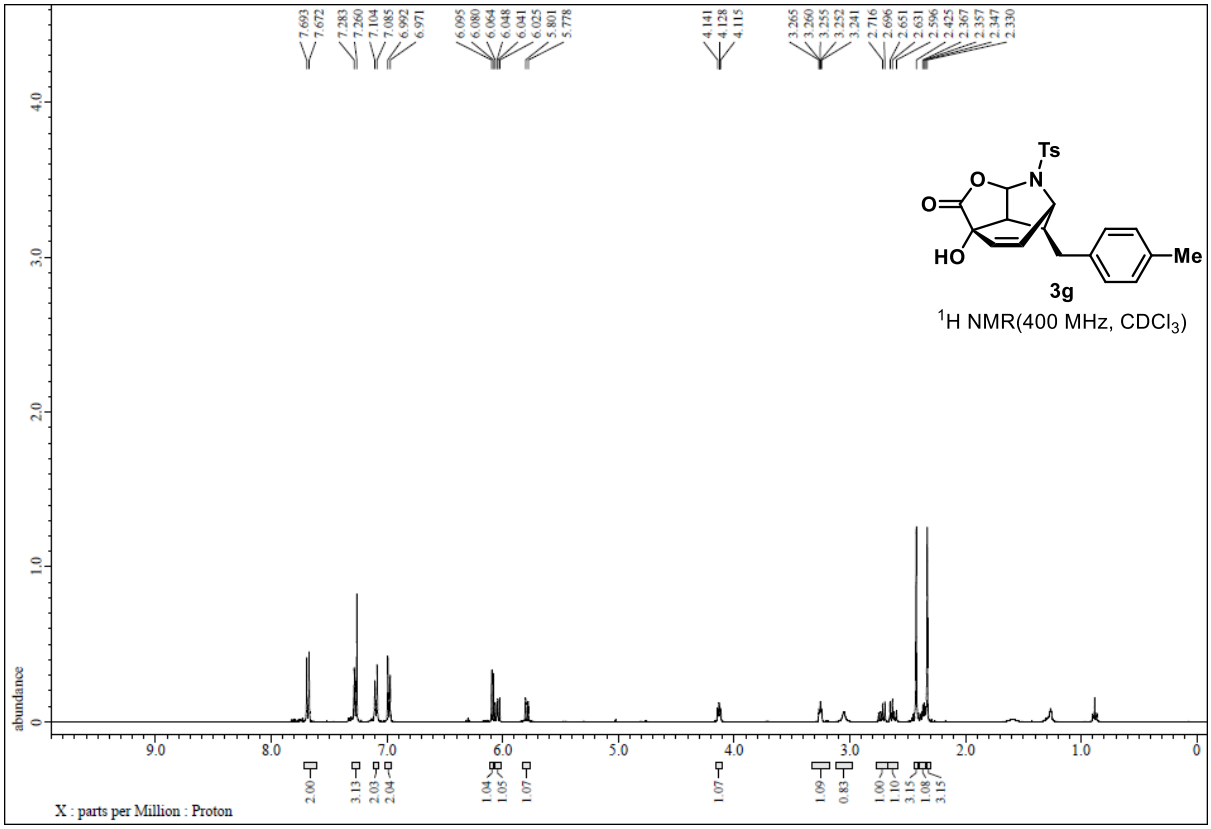
^{13}C NMR(101 MHz, $CDCl_3$)



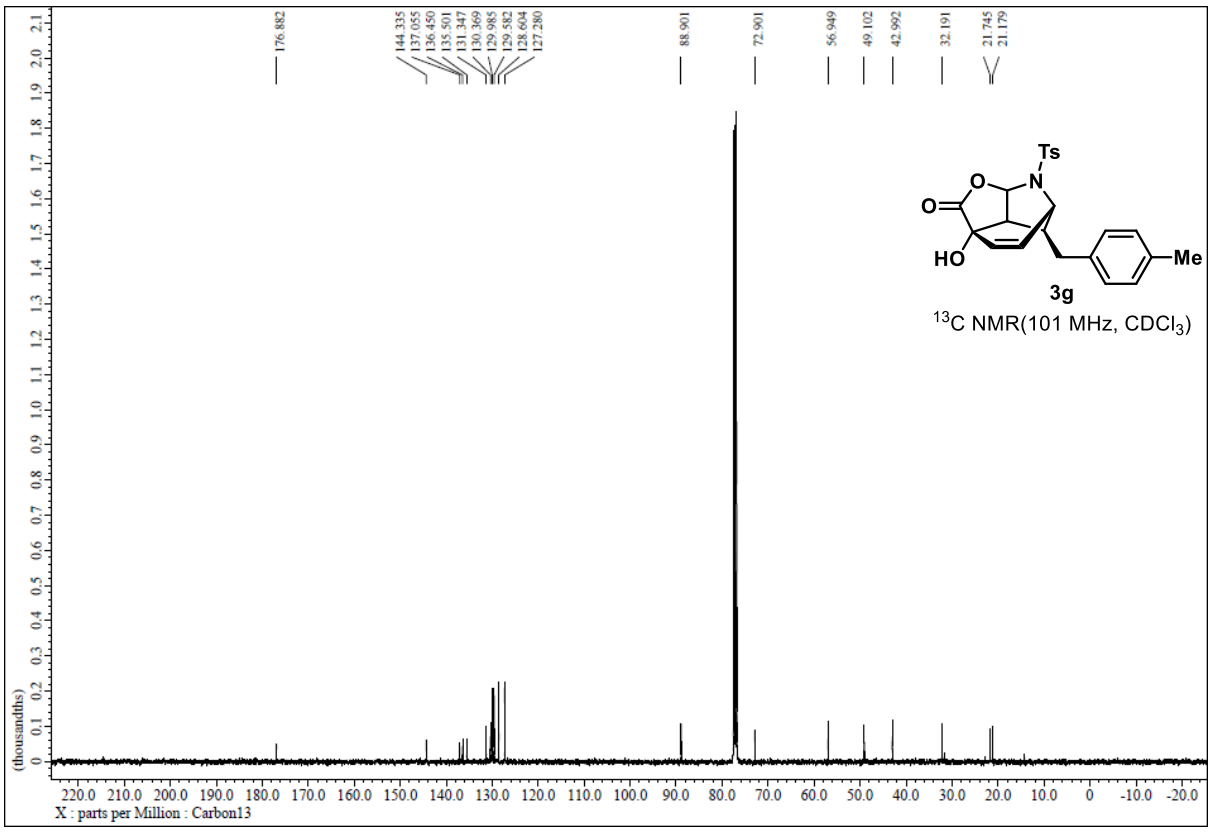
^{1}H NMR(400 MHz, $CDCl_3$)



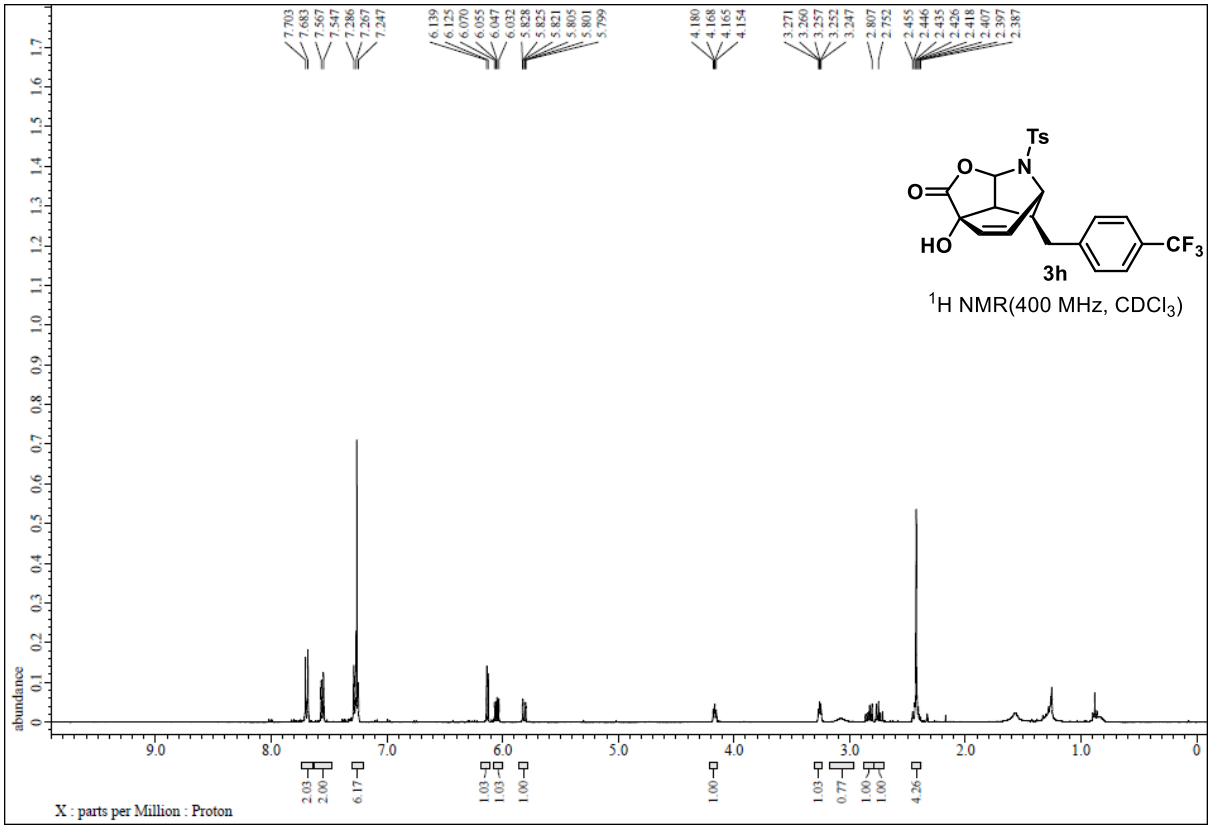
^{13}C NMR(101 MHz, $CDCl_3$)

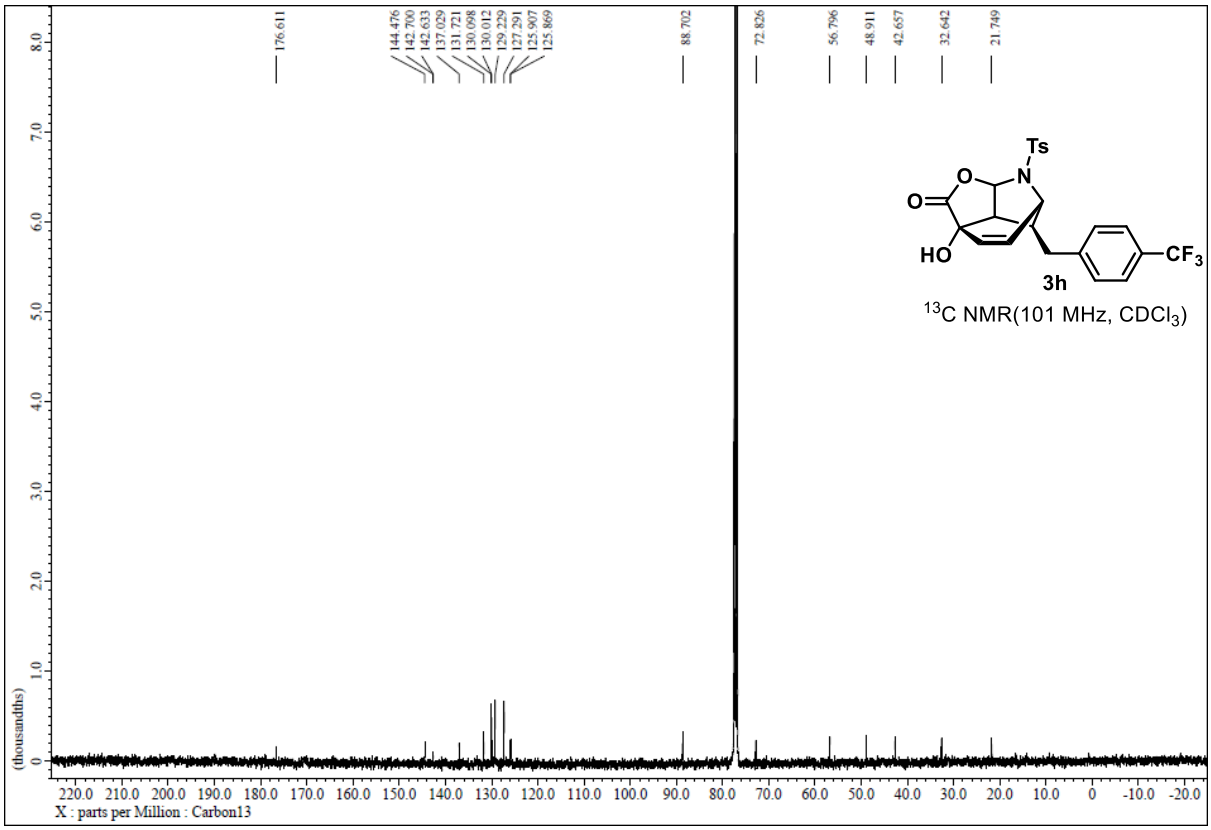


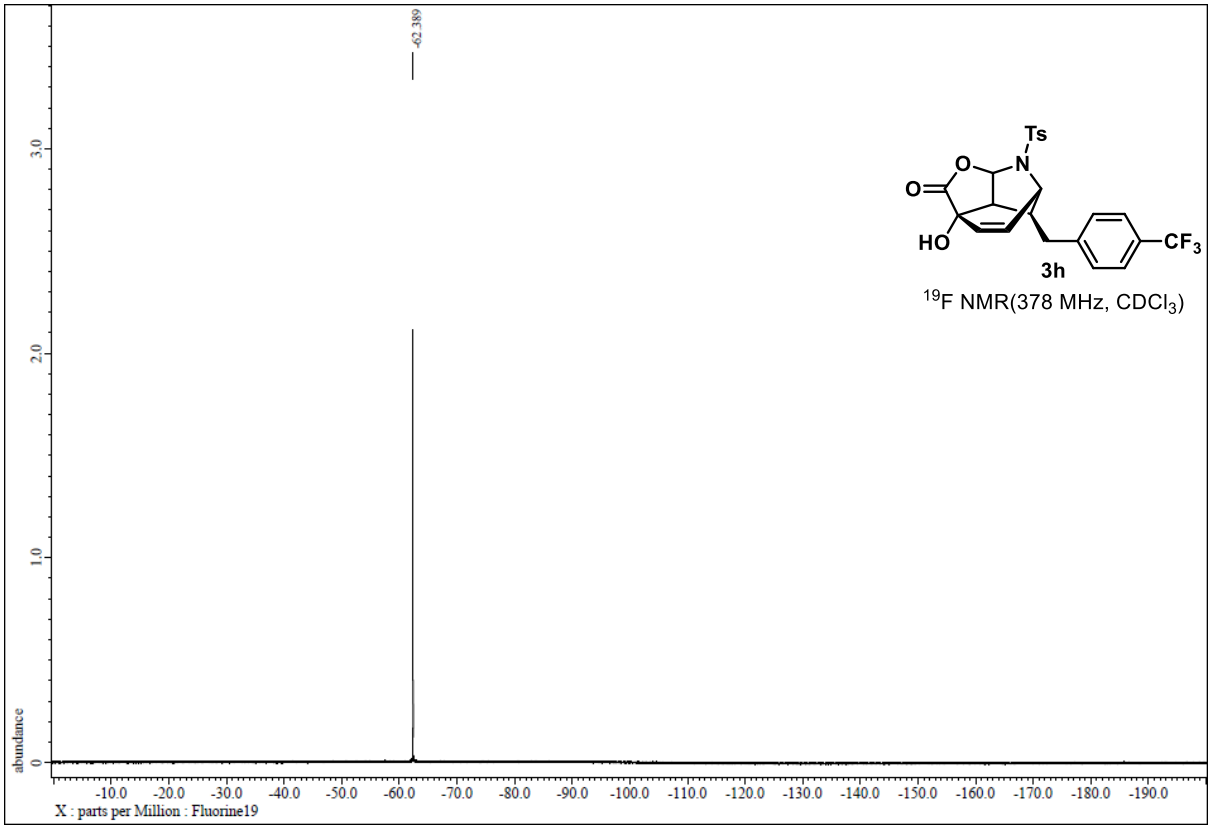
^{1}H NMR(400 MHz, $CDCl_3$)



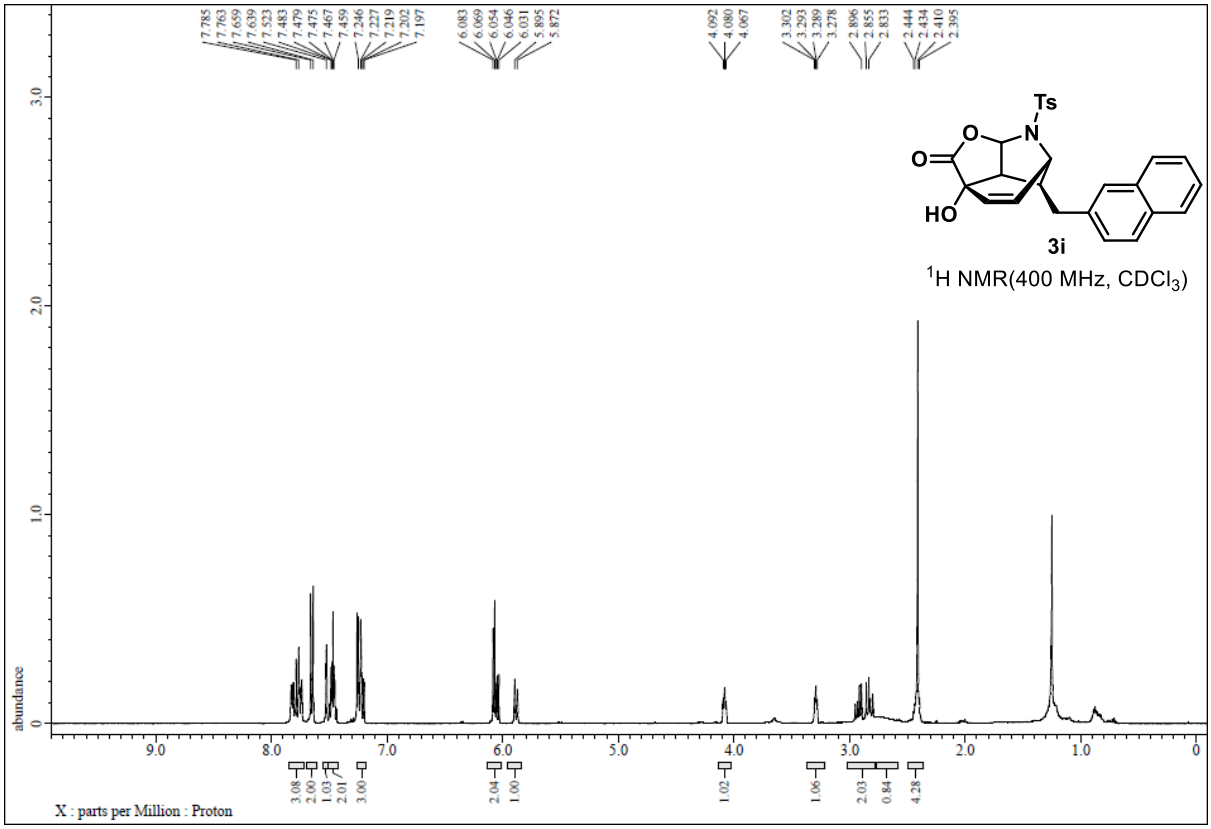
^{13}C NMR(101 MHz, $CDCl_3$)

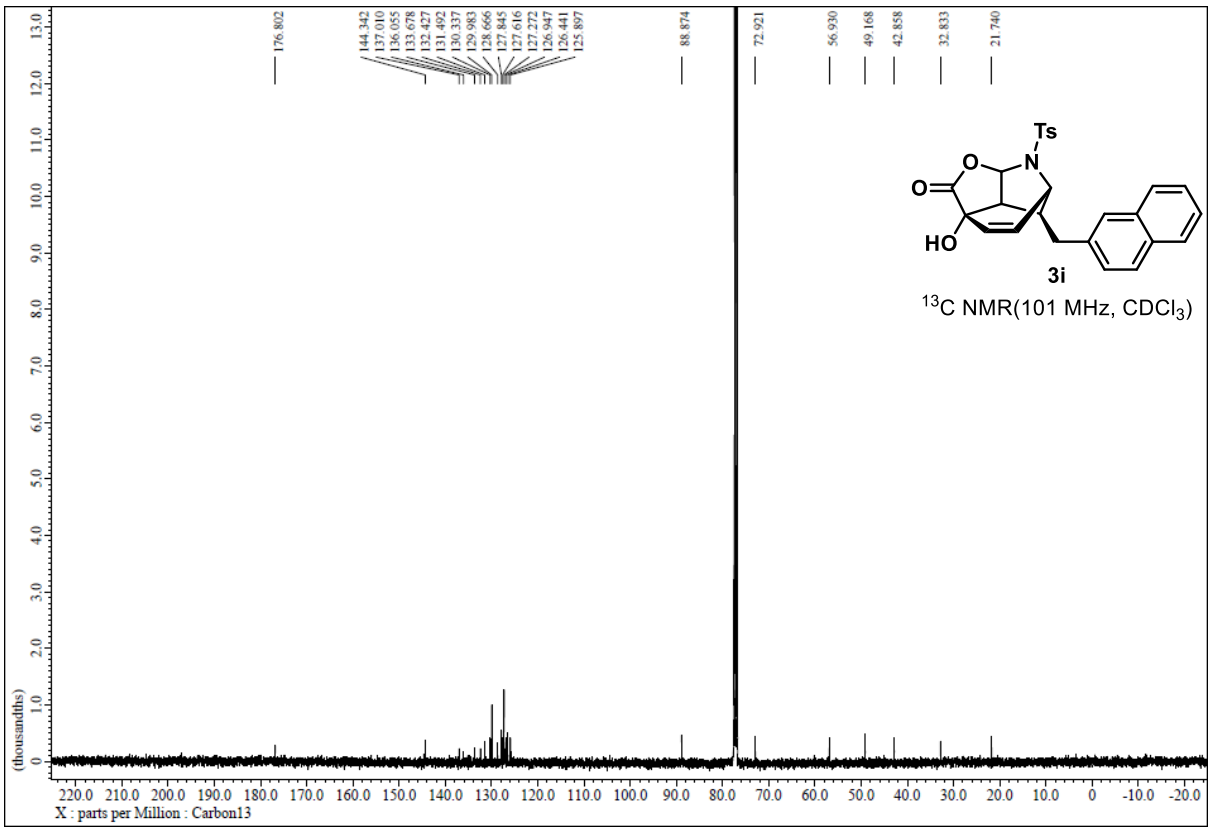

7.703
7.683
7.567
7.547
7.286
7.267
7.247
6.139
6.125
6.070
6.055
6.047
6.032
5.828
5.825
5.821
5.805
5.801
5.799
4.180
4.168
4.165
4.154
3.271
3.260
3.257
3.252
3.247
2.807
2.752
2.455
2.446
2.435
2.426
2.418
2.407
2.397
2.387
abundance
X : parts per Million : Proton
Ts
N
O
O
HO
CF3
3h
1H NMR(400 MHz, CDCl3)

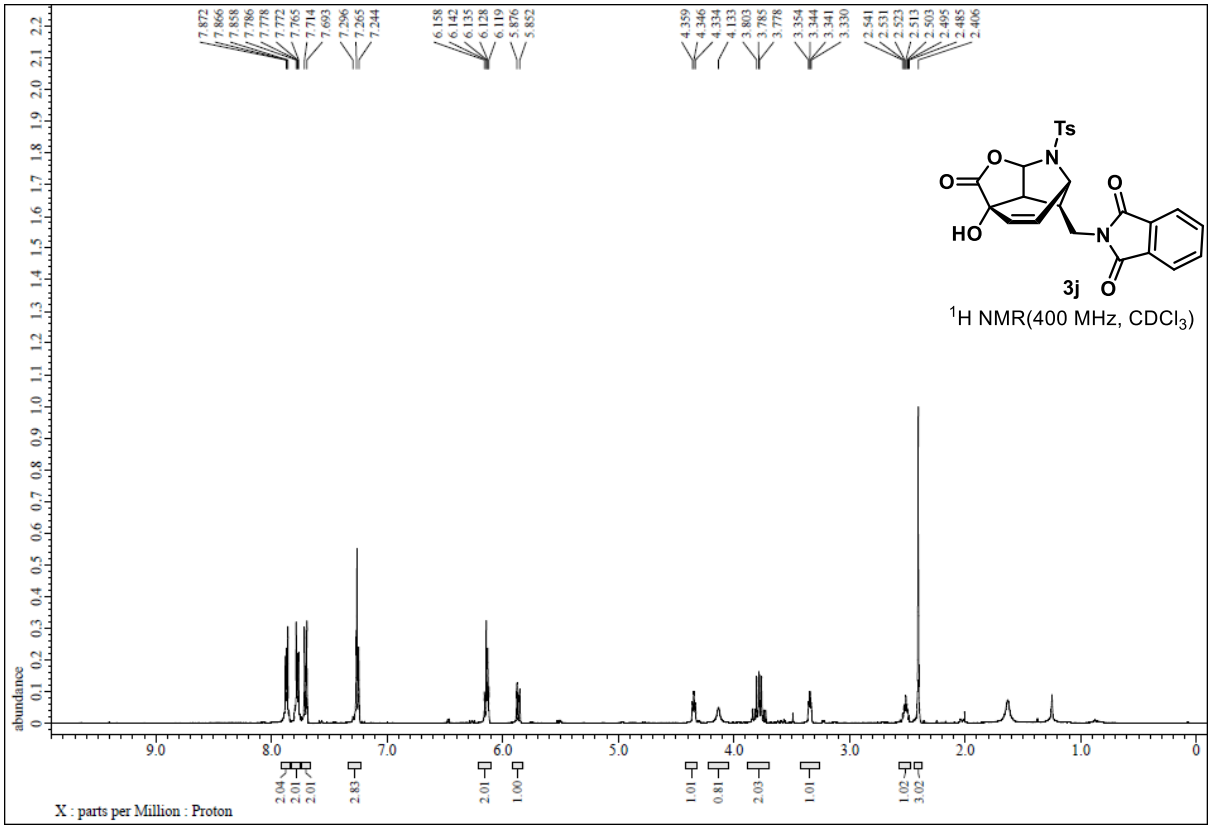

176.611
144.476
142.700
142.633
137.029
131.721
130.098
130.012
129.229
127.291
125.907
125.869
88.702
72.826
56.796
48.911
42.657
32.642
21.749
(thousandths)
X : parts per Million : Carbon13
Ts
N
O
O
HO
CF3
3h
13C NMR(101 MHz, CDCl3)

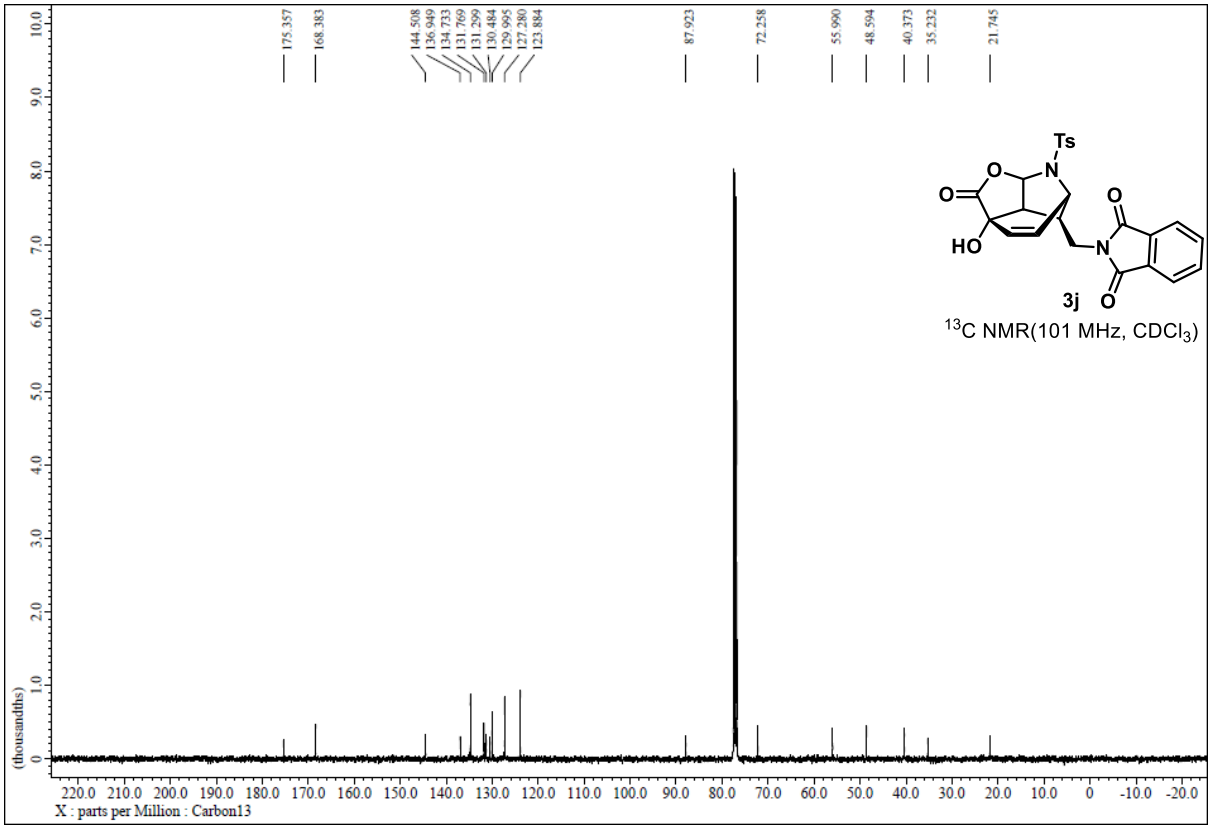


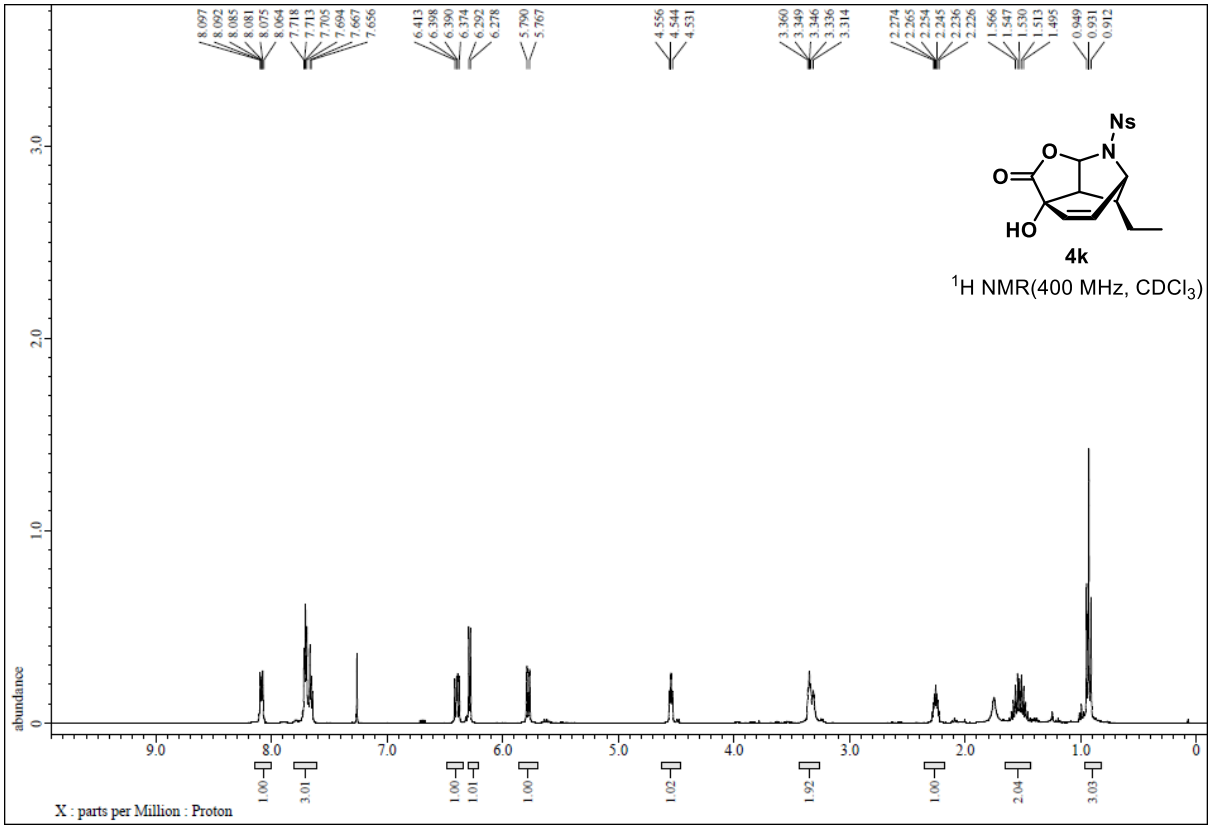
^{19}F NMR(378 MHz, $CDCl_3$)


7.785
7.763
7.659
7.639
7.523
7.483
7.479
7.475
7.467
7.459
7.246
7.227
7.219
7.202
7.197
6.083
6.069
6.054
6.046
6.031
5.895
5.872
4.092
4.080
4.067
3.302
3.293
3.289
3.278
2.896
2.855
2.833
2.444
2.434
2.410
2.395
Ts
O
N
O
HO
3i
^{1}H NMR(400 MHz, CDCl$_3$)
abundance
X : parts per Million : Proton

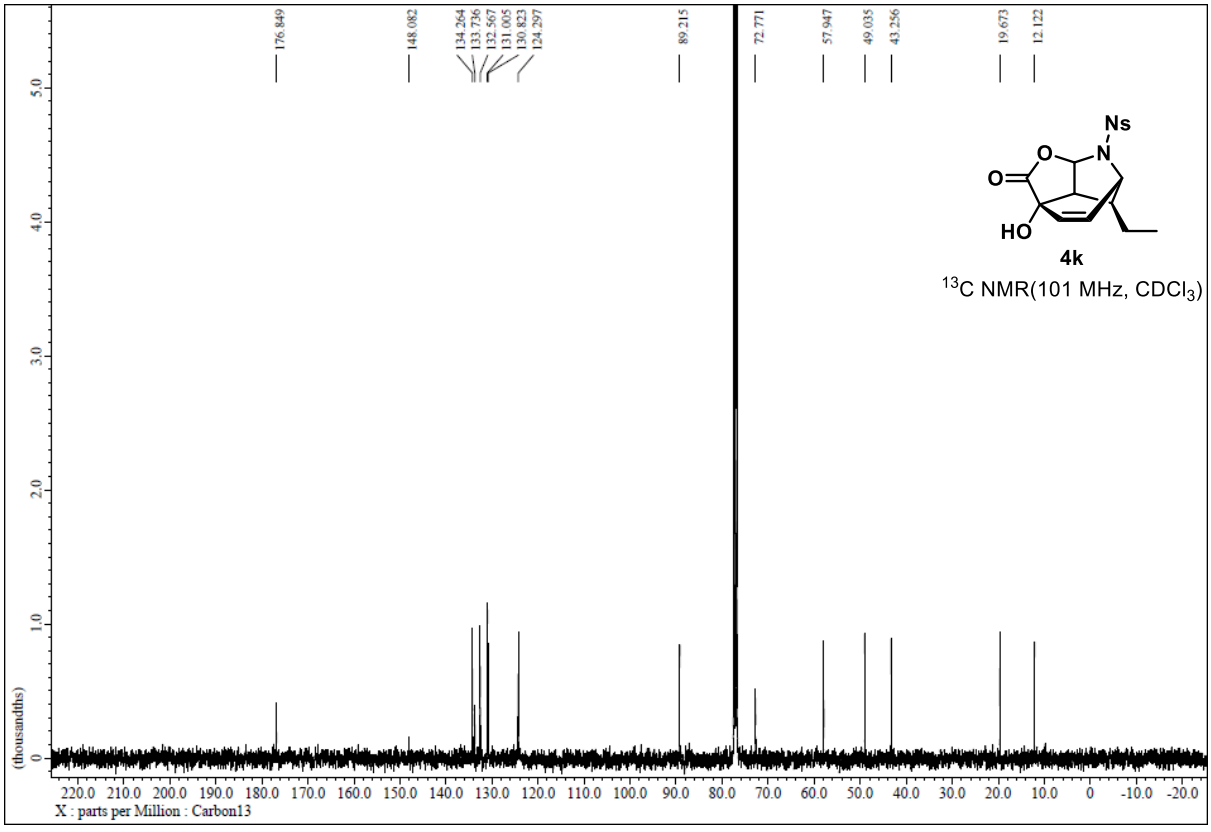

176.802
144.342
137.010
136.055
133.678
132.427
131.492
130.337
129.983
128.666
127.845
127.616
127.272
126.947
126.441
125.897
88.874
72.921
56.930
49.168
42.858
32.833
21.740
Ts
O
N
O
HO
3i
^{13}C NMR(101 MHz, CDCl$_3$)
(thousandths)
X : parts per Million : Carbon13


7.872
7.866
7.858
7.786
7.778
7.772
7.765
7.714
7.693
7.296
7.265
7.244
6.158
6.142
6.135
6.128
6.119
5.876
5.852
4.359
4.346
4.334
4.133
3.803
3.785
3.778
3.354
3.344
3.341
3.330
2.541
2.531
2.523
2.513
2.503
2.495
2.485
2.406
abundance
X : parts per Million : Proton
Ts
O
N
O
HO
O
N
O
3j
^{1}H NMR(400 MHz, CDCl$_3$)

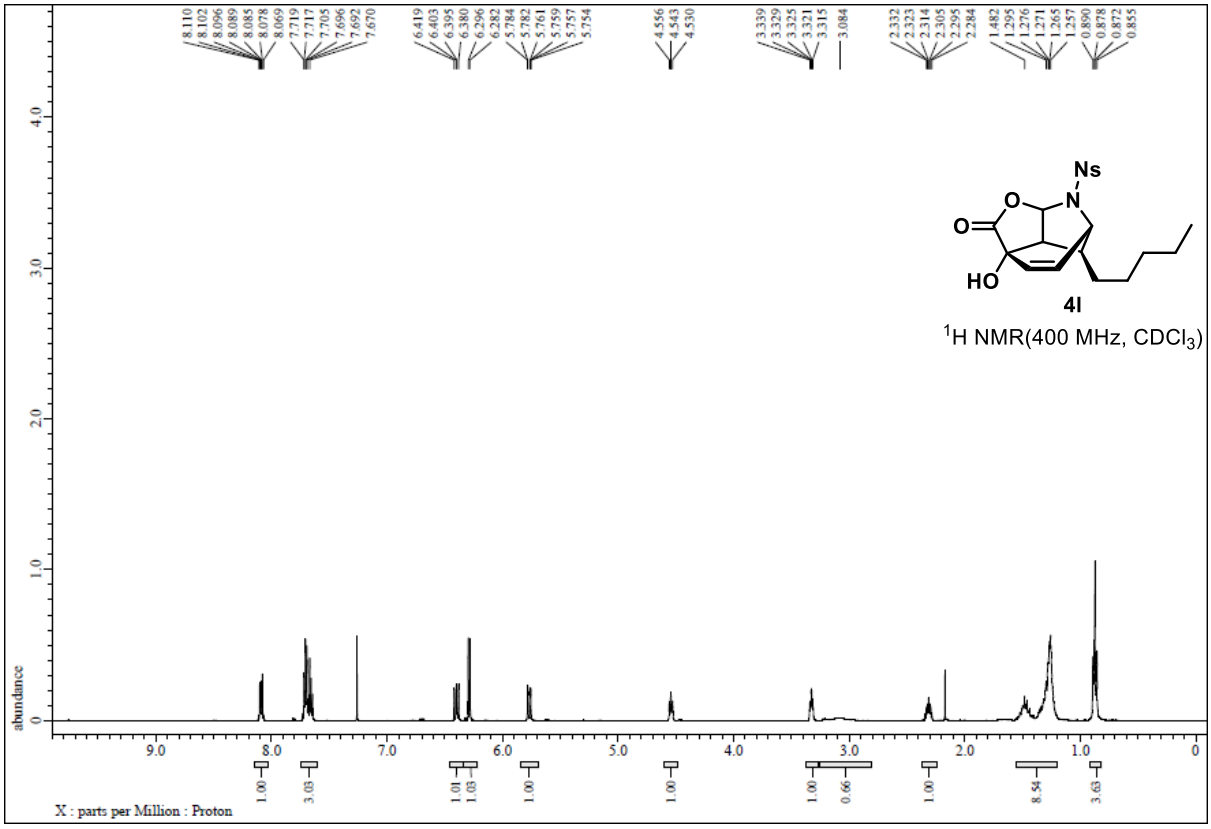

175.357
168.383
144.508
136.949
134.733
131.769
131.299
130.484
129.995
127.280
123.884
87.923
72.258
55.990
48.594
40.373
35.232
21.745
(thousandths)
X : parts per Million : Carbon13
Ts
O
N
O
HO
O
N
O
3j
^{13}C NMR(101 MHz, CDCl$_3$)



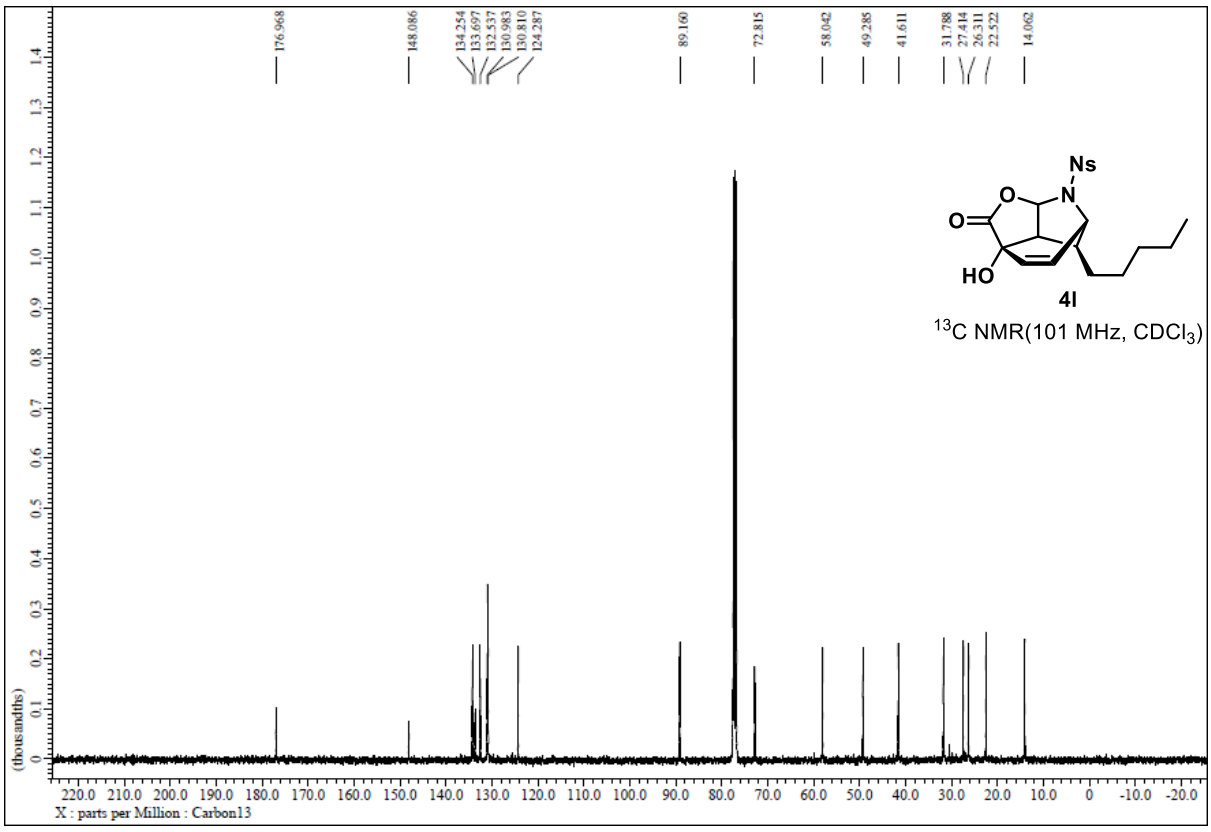
^{1}H NMR(400 MHz, $CDCl_3$)



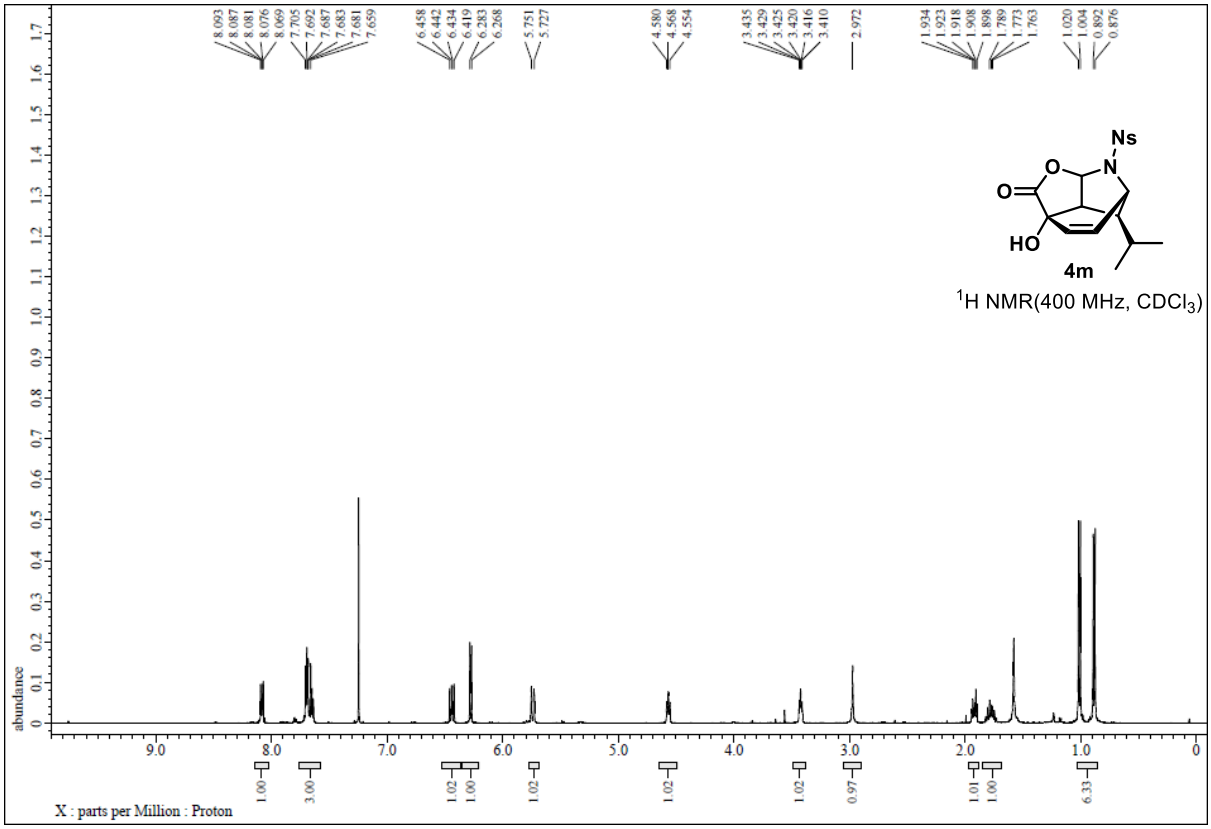
^{13}C NMR(101 MHz, $CDCl_3$)

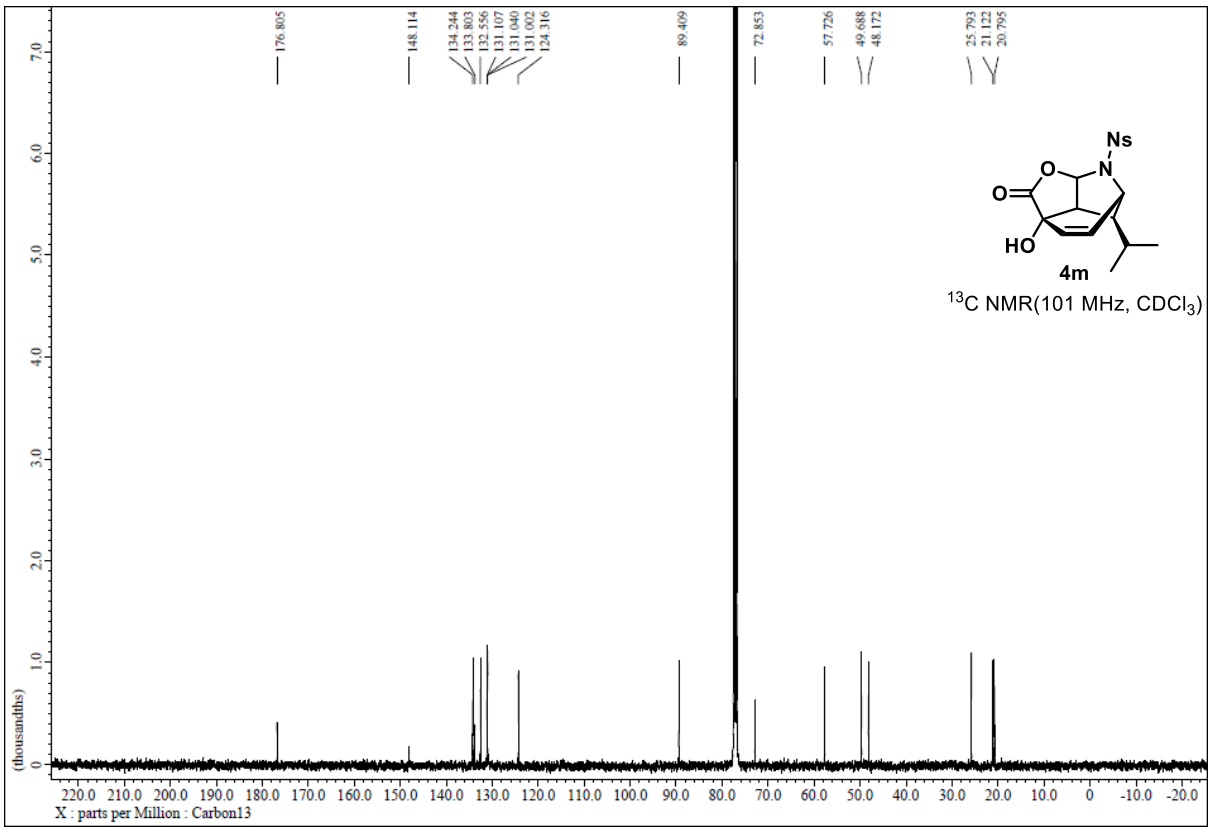


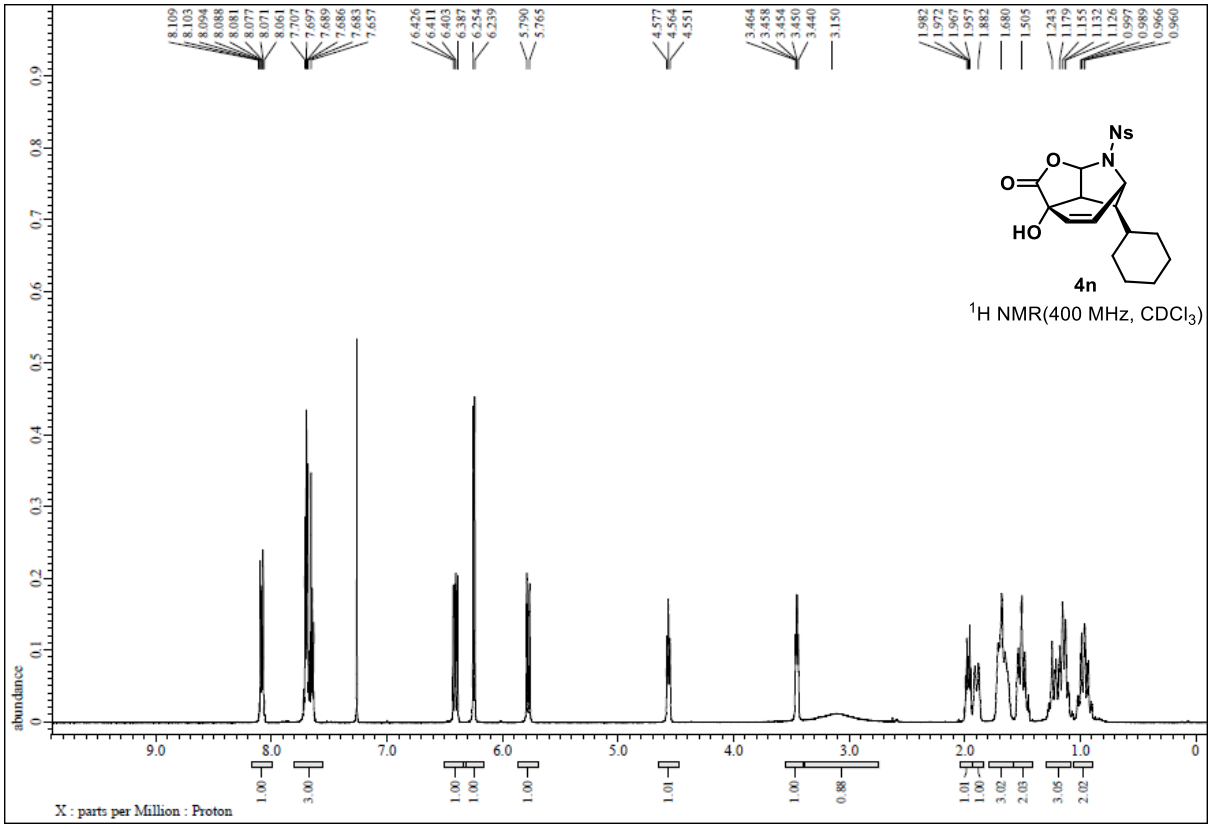
^{1}H NMR(400 MHz, $CDCl_3$)



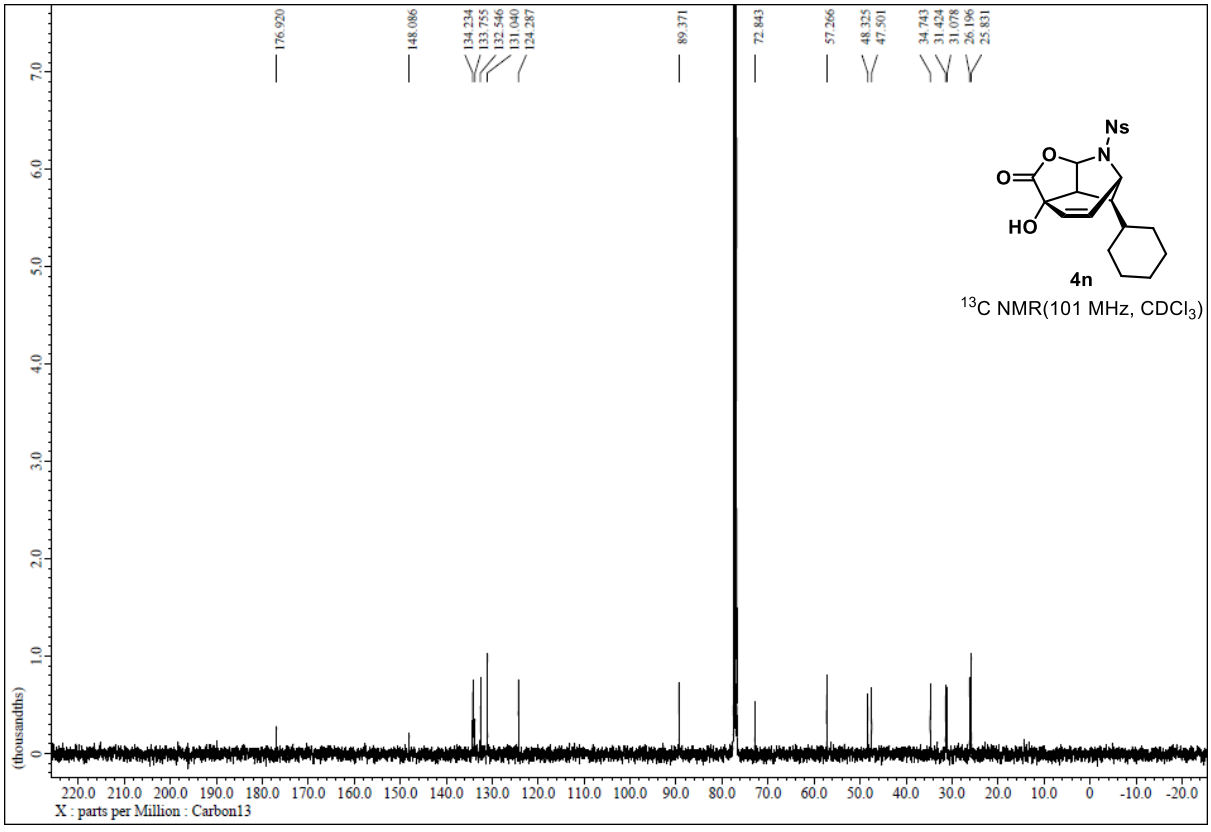
^{13}C NMR(101 MHz, $CDCl_3$)


8.093
8.087
8.081
8.076
8.069
7.705
7.692
7.687
7.683
7.681
7.659
6.458
6.442
6.434
6.419
6.283
6.268
5.751
5.727
4.580
4.568
4.554
3.435
3.429
3.425
3.420
3.416
3.410
2.972
1.934
1.923
1.918
1.908
1.898
1.789
1.773
1.763
1.020
1.004
0.892
0.876
Ns
N
O
O
HO
4m
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

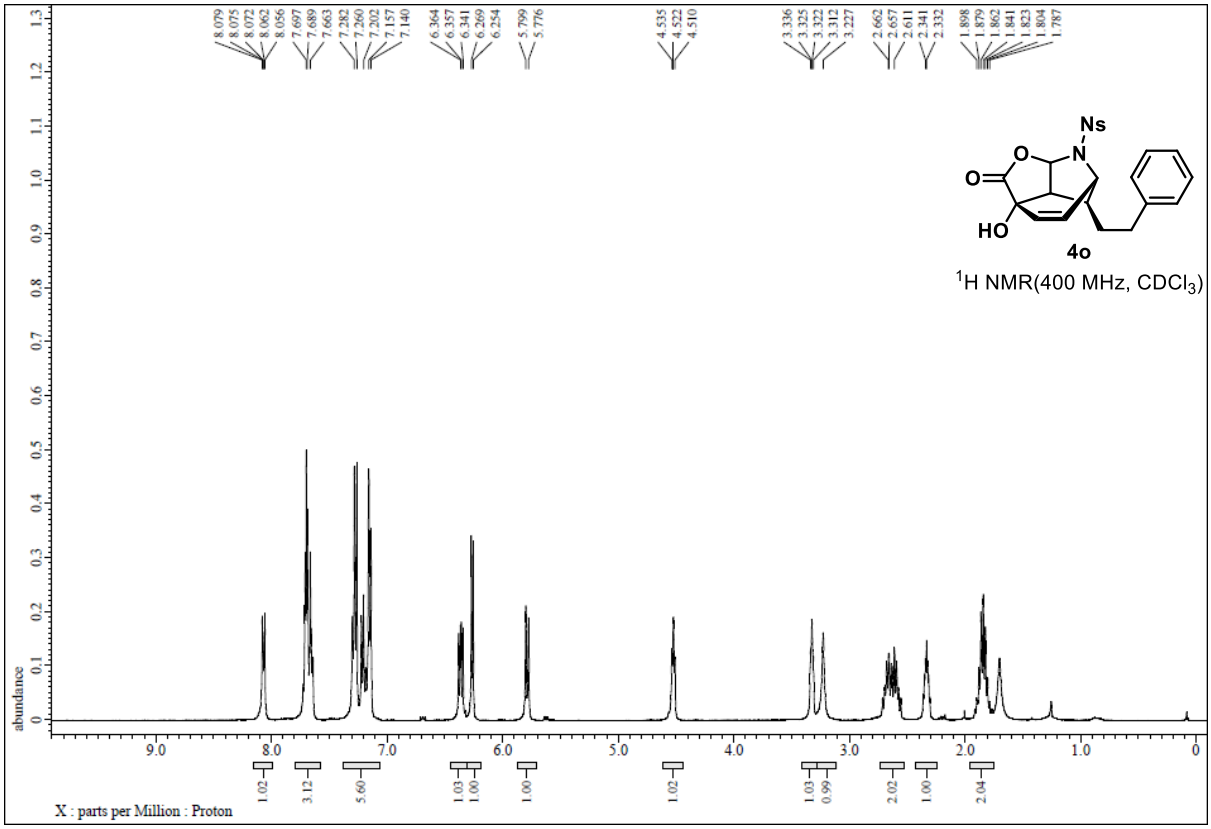

176.805
148.114
134.244
133.803
132.556
131.107
131.040
131.002
124.316
89.409
72.853
57.726
49.688
48.172
25.793
21.122
20.795
Ns
N
O
O
HO
4m
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13



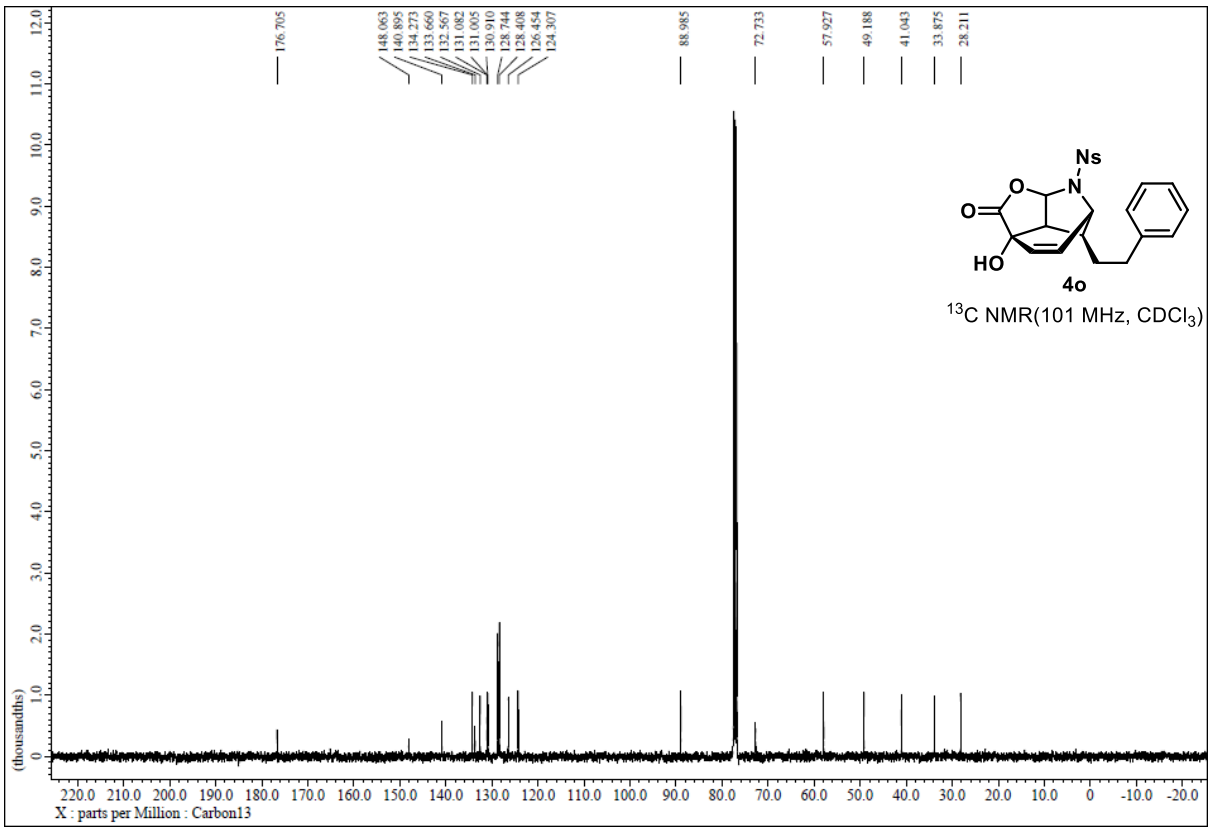
^{1}H NMR(400 MHz, $CDCl_3$)



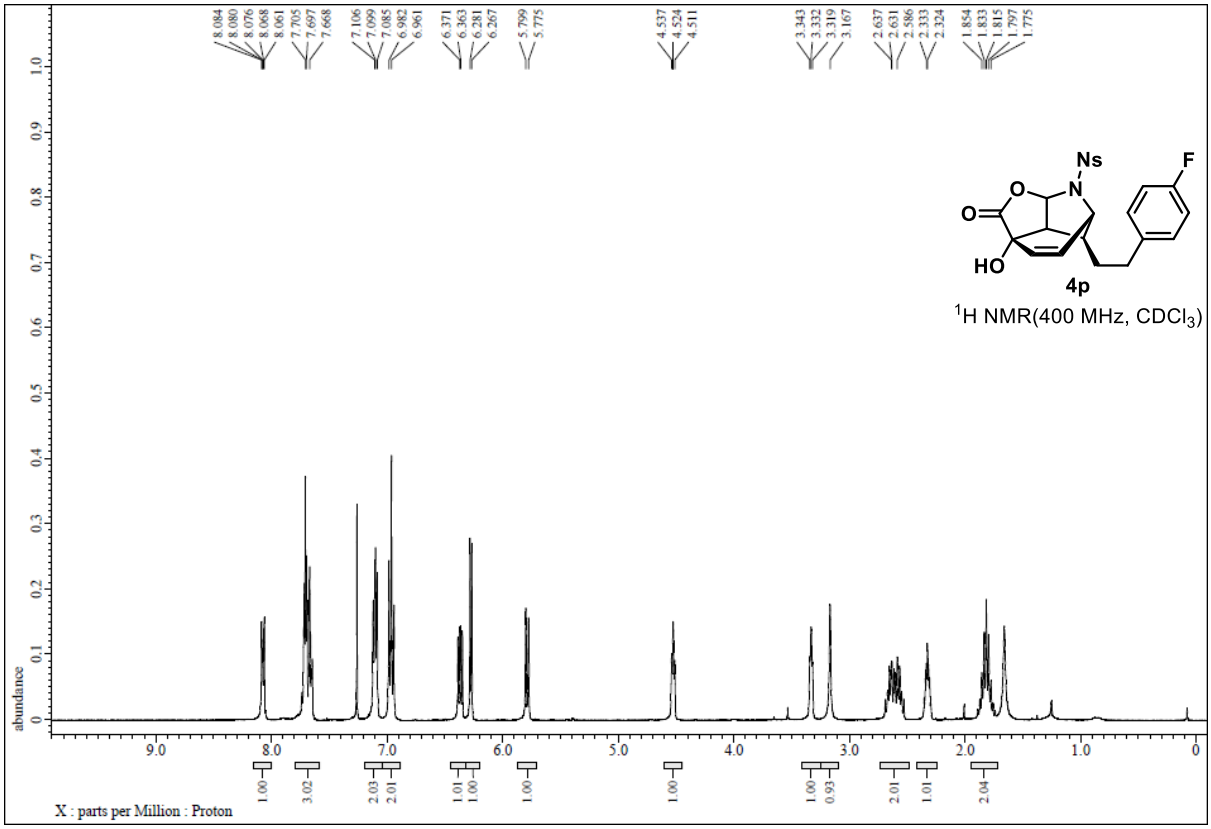
^{13}C NMR(101 MHz, $CDCl_3$)

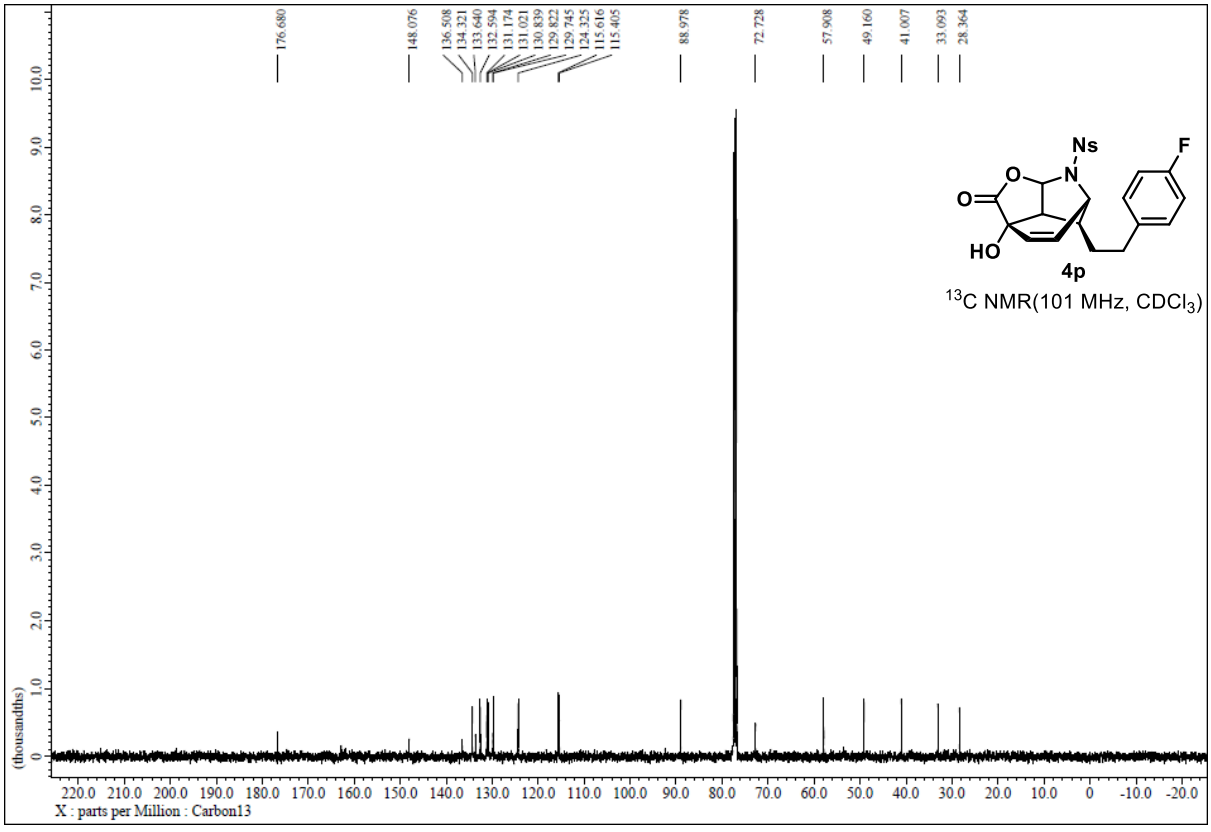


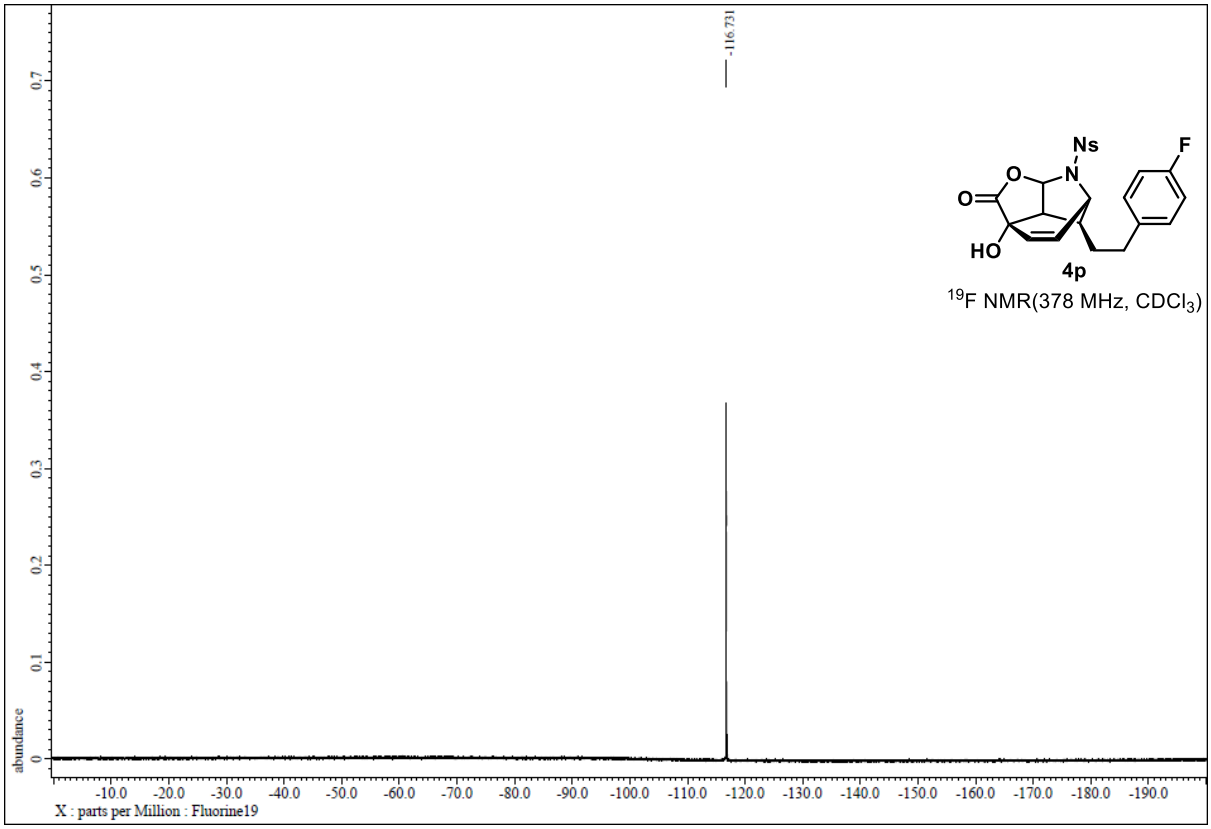
^{1}H NMR(400 MHz, $CDCl_3$)



^{13}C NMR(101 MHz, $CDCl_3$)

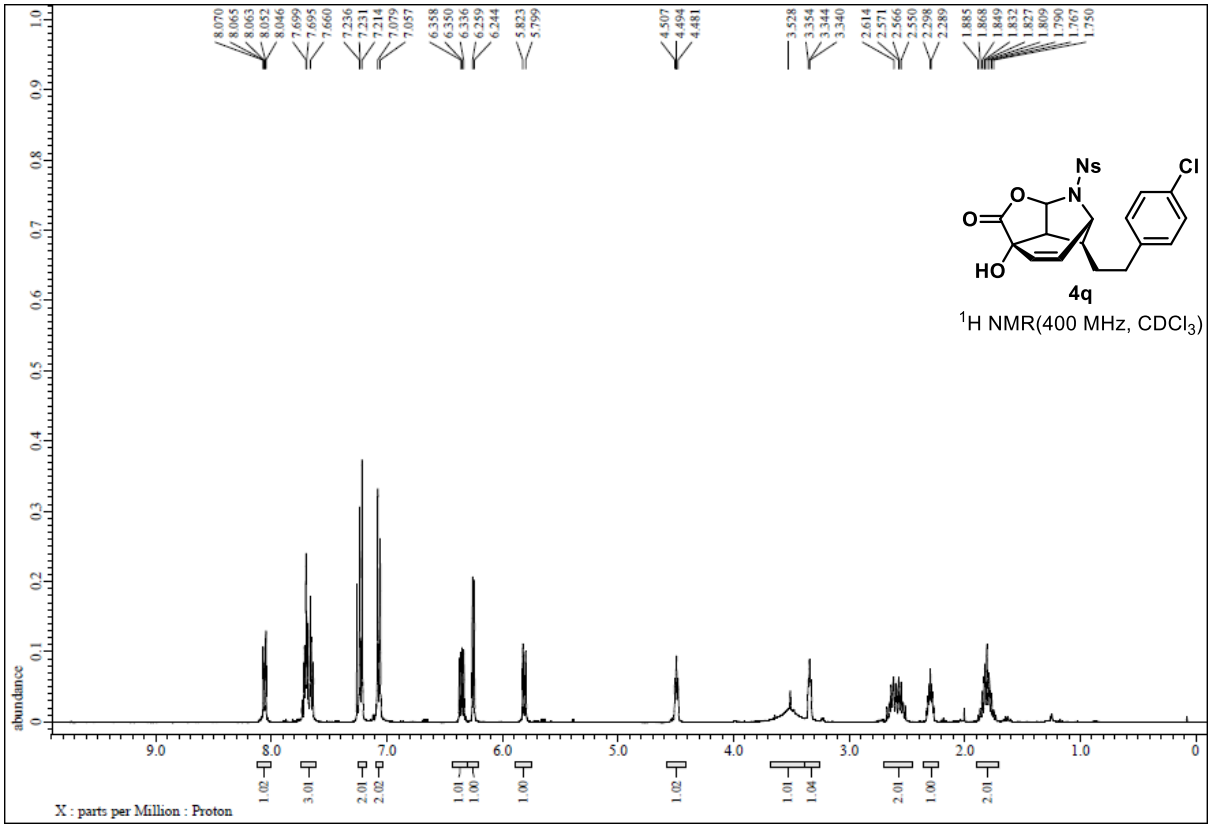

8.084
8.080
8.076
8.068
8.061
7.705
7.697
7.668
7.106
7.099
7.085
6.982
6.961
6.371
6.363
6.281
6.267
5.799
5.775
4.537
4.524
4.511
3.343
3.332
3.319
3.167
2.637
2.631
2.586
2.333
2.324
1.854
1.833
1.815
1.797
1.775
abundance
X : parts per Million : Proton
Ns
F
O
N
O
HO
4p
1H NMR(400 MHz, CDCl3)

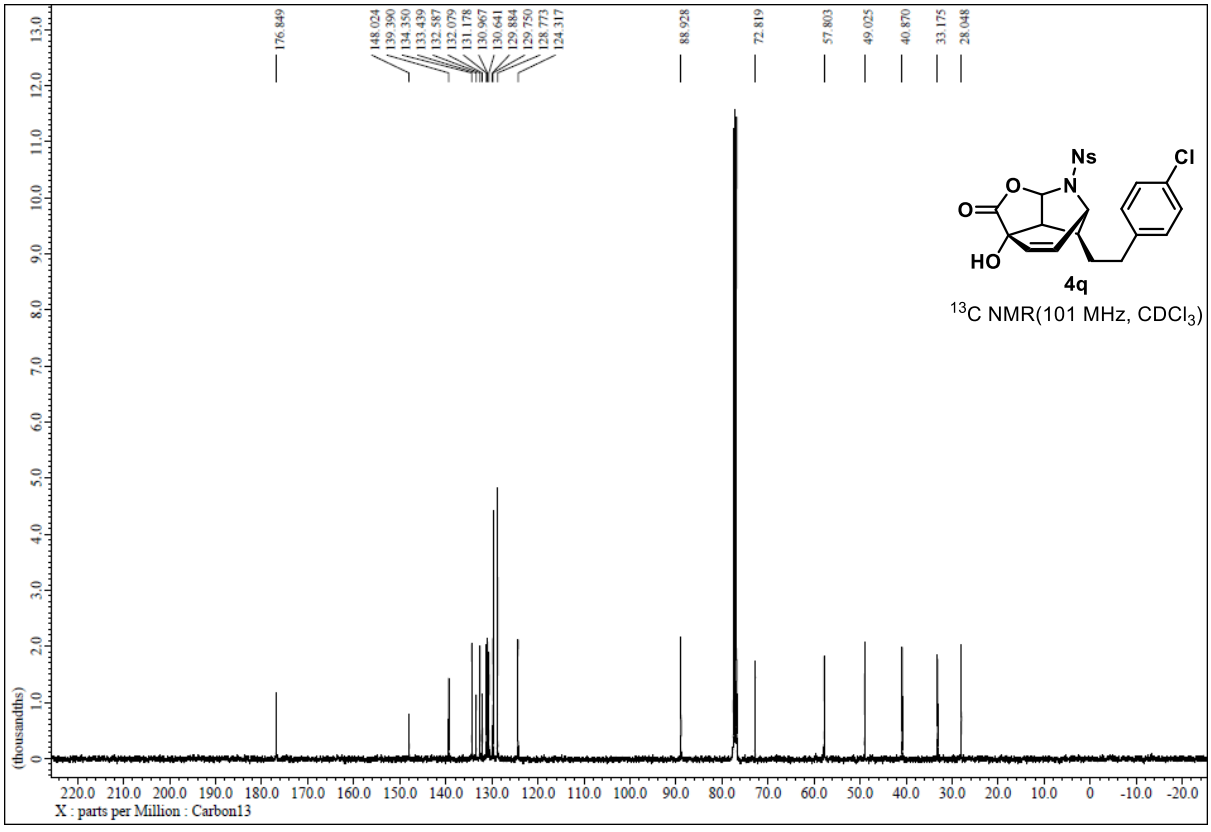

176.680
148.076
136.508
134.321
133.640
132.594
131.174
131.021
130.839
129.822
129.745
124.325
115.616
115.405
88.978
72.728
57.908
49.160
41.007
33.093
28.364
(thousandths)
X : parts per Million : Carbon13
Ns
F
O
N
O
HO
4p
13C NMR(101 MHz, CDCl3)

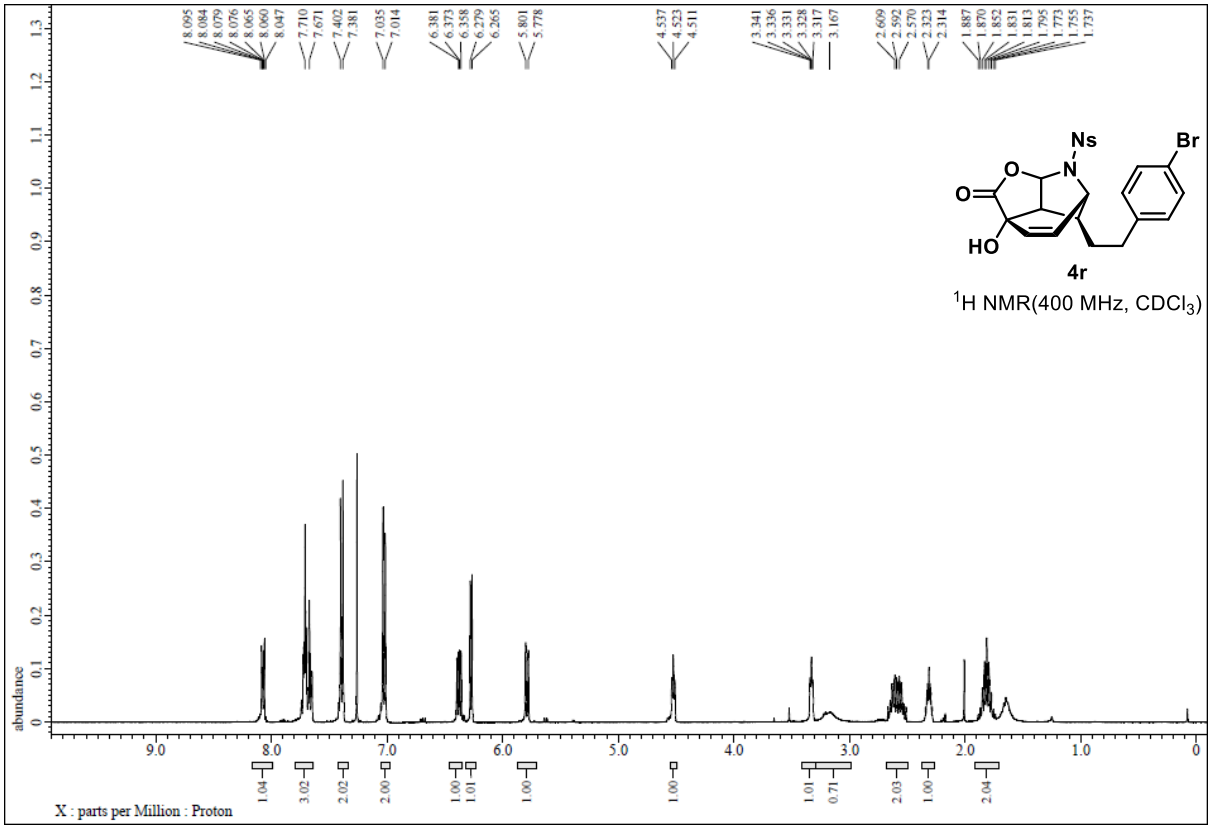


4p

^{19}F NMR(378 MHz, $CDCl_3$)


8.070
8.065
8.063
8.052
8.046
7.699
7.695
7.660
7.236
7.231
7.214
7.079
7.057
6.358
6.350
6.336
6.259
6.244
5.823
5.799
4.507
4.494
4.481
3.528
3.354
3.344
3.340
2.614
2.571
2.566
2.550
2.298
2.289
1.885
1.868
1.849
1.832
1.827
1.809
1.790
1.767
1.750
abundance
X : parts per Million : Proton
Ns
Cl
O
N
O
HO
4q
1H NMR(400 MHz, CDCl3)


176.849
148.024
139.390
134.350
133.439
132.587
132.079
131.178
130.967
130.641
129.884
129.750
128.773
124.317
88.928
72.819
57.803
49.025
40.870
33.175
28.048
(thousandths)
X : parts per Million : Carbon13
Ns
Cl
O
N
O
HO
4q
13C NMR(101 MHz, CDCl3)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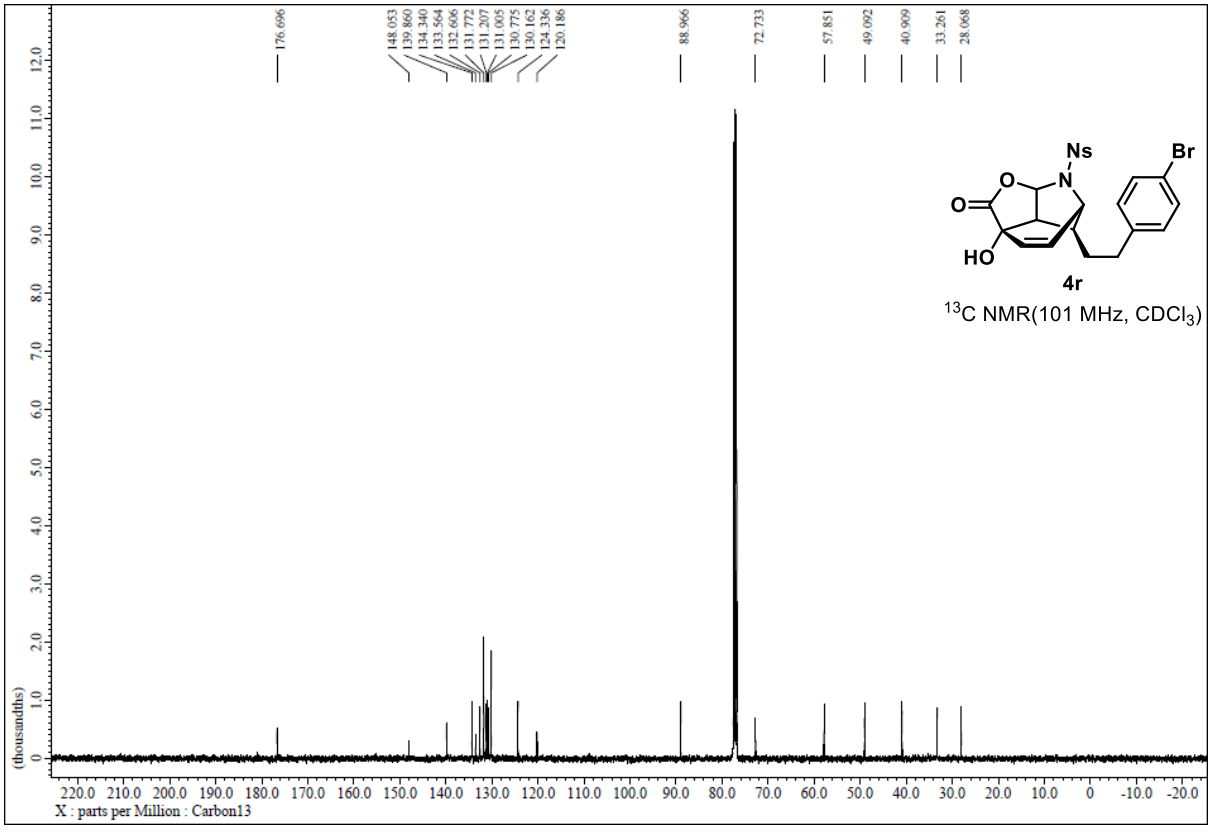
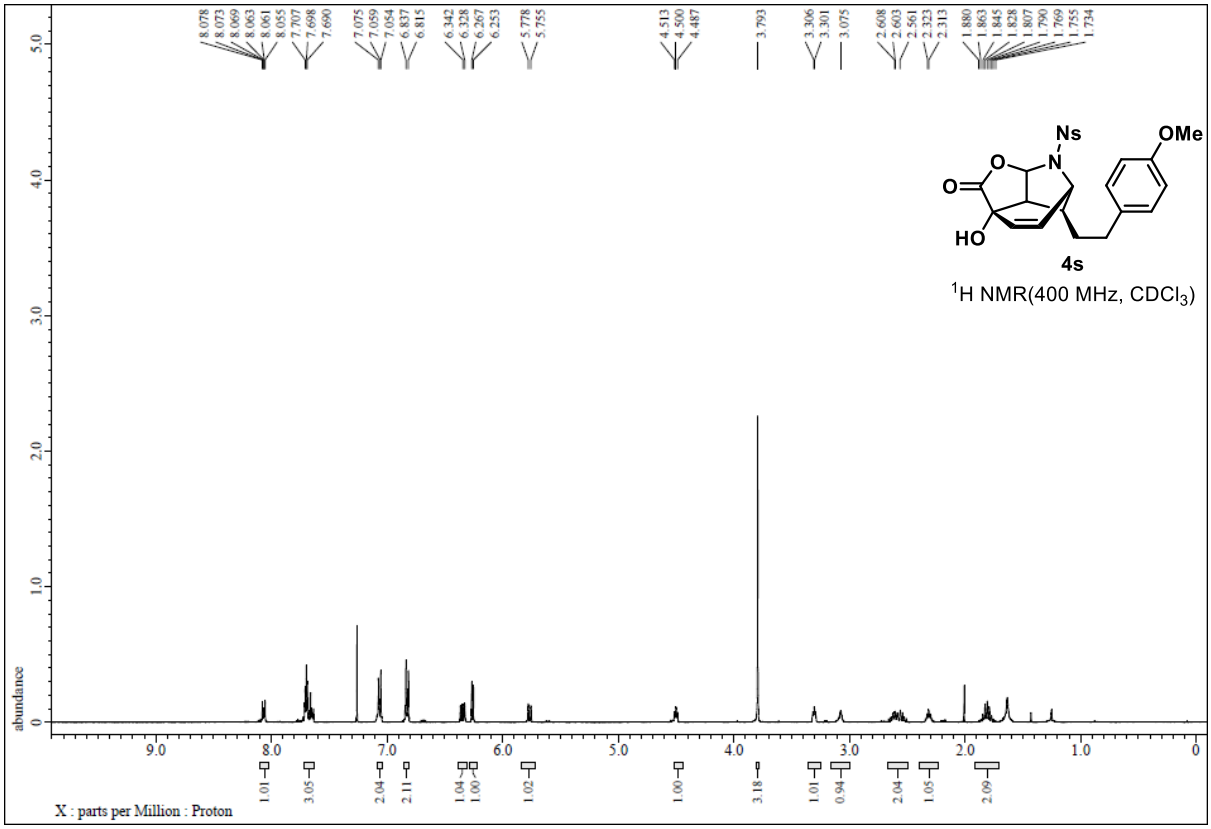
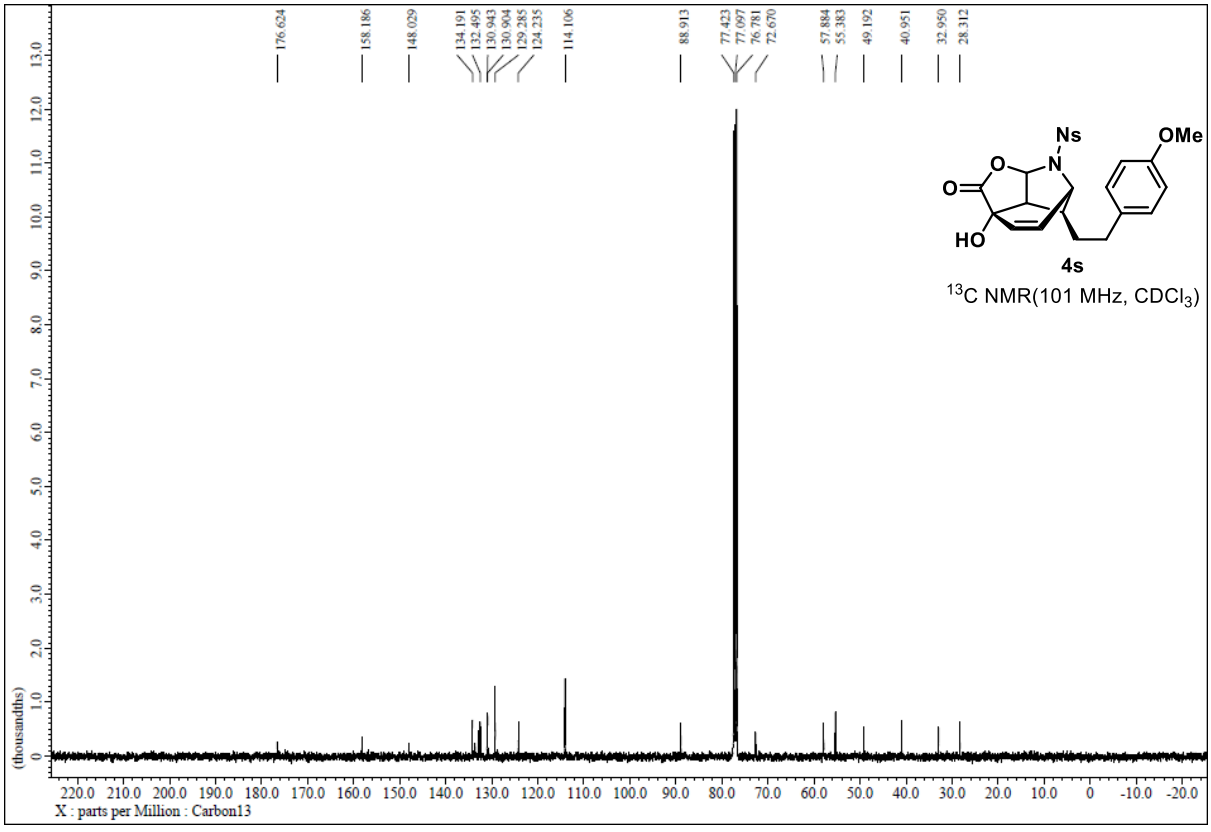
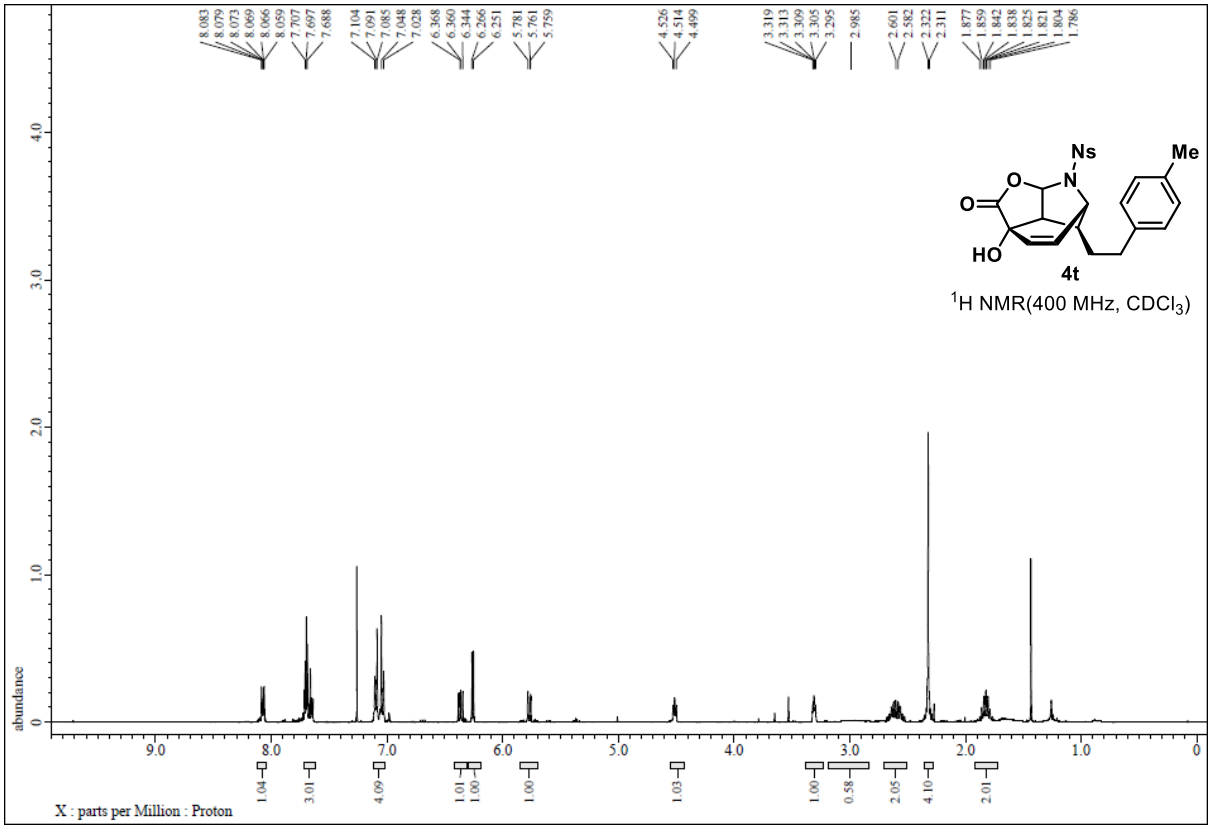
8.084
8.079
8.076
8.065
8.060
8.047
7.710
7.671
7.402
7.381
7.035
7.014
6.381
6.373
6.358
6.279
6.265
5.801
5.778
4.537
4.523
4.511
3.341
3.336
3.331
3.328
3.317
3.167
2.609
2.592
2.570
2.323
2.314
1.887
1.870
1.852
1.831
1.813
1.795
1.773
1.755
1.737
Ns
Br
O
N
O
HO
4r
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton
1.04
3.02
2.02
2.00
1.00
1.01
1.00
1.00
1.01
0.71
2.03
1.00
2.04


176.696
148.053
139.860
134.340
133.564
132.606
131.772
131.207
131.005
130.775
130.162
124.336
120.186
88.966
72.733
57.851
49.092
40.909
33.261
28.068
Ns
Br
O
N
O
HO
4r
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13


8.078
8.073
8.069
8.063
8.061
8.055
7.707
7.698
7.690
7.075
7.059
7.054
6.837
6.815
6.342
6.328
6.267
6.253
5.778
5.755
4.513
4.500
4.487
3.793
3.306
3.301
3.075
2.608
2.603
2.561
2.323
2.313
1.880
1.863
1.845
1.828
1.807
1.790
1.769
1.755
1.734
Ns
OMe
O
N
O
HO
4s
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


176.624
158.186
148.029
134.191
132.495
130.943
130.904
129.285
124.235
114.106
88.913
77.423
77.097
76.781
72.670
57.884
55.383
49.192
40.951
32.950
28.312
Ns
OMe
O
N
O
HO
4s
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13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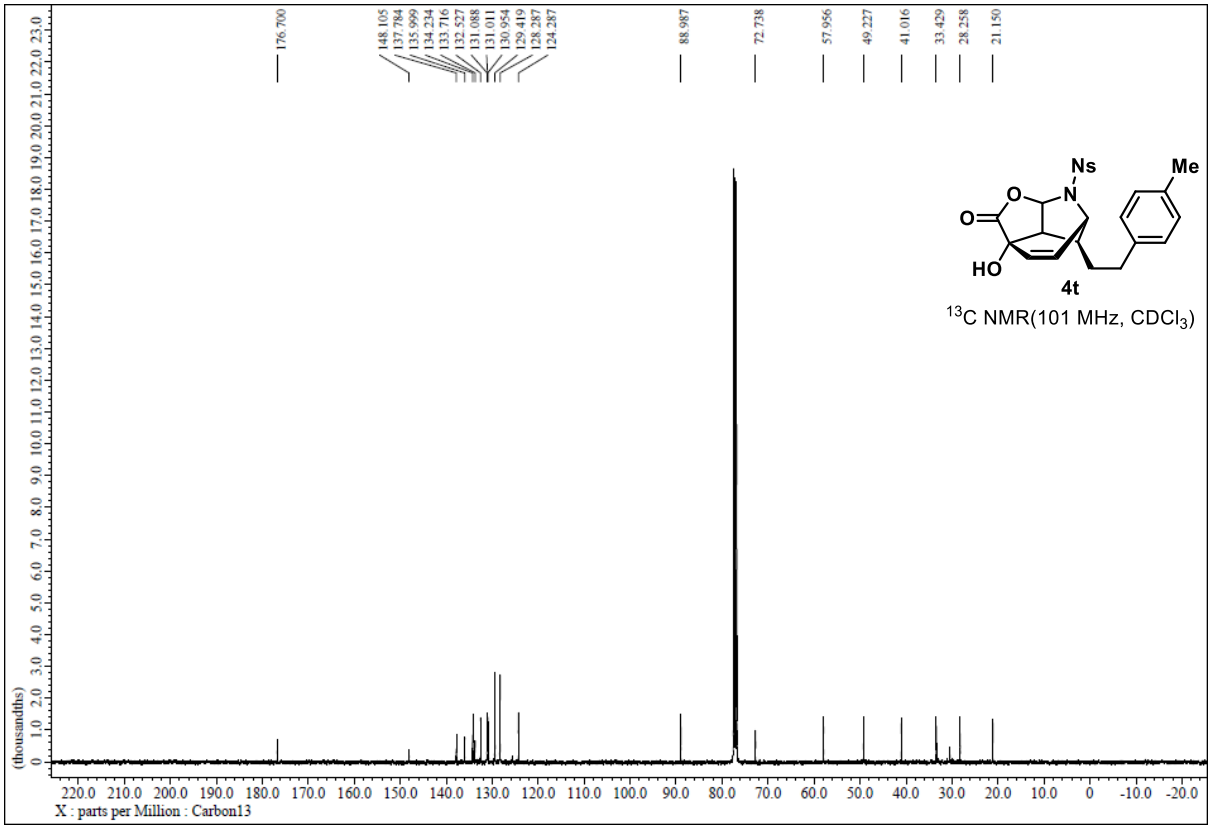
8.079
8.073
8.069
8.066
8.059
7.707
7.697
7.688
7.104
7.091
7.085
7.048
7.028
6.368
6.360
6.344
6.266
6.251
5.781
5.761
5.759
4.526
4.514
4.499
3.319
3.313
3.309
3.305
3.295
2.985
2.601
2.582
2.322
2.311
1.877
1.859
1.842
1.838
1.825
1.821
1.804
1.786
Ns
Me
O
N
O
HO
4t
1H NMR(400 MHz, CDCl3)
abundance
X : parts per Million : Proton
1.04
3.01
4.09
1.01
1.00
1.00
1.03
1.00
0.58
2.05
4.10
2.01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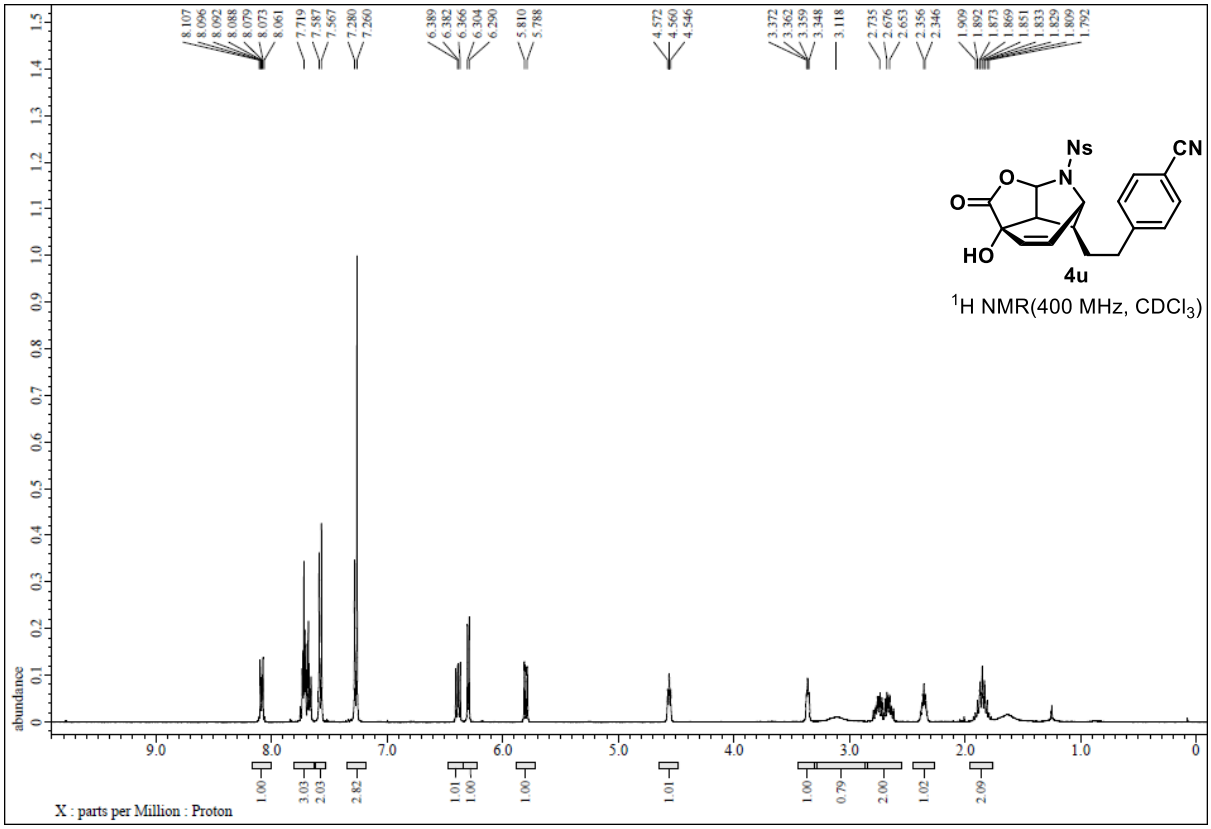
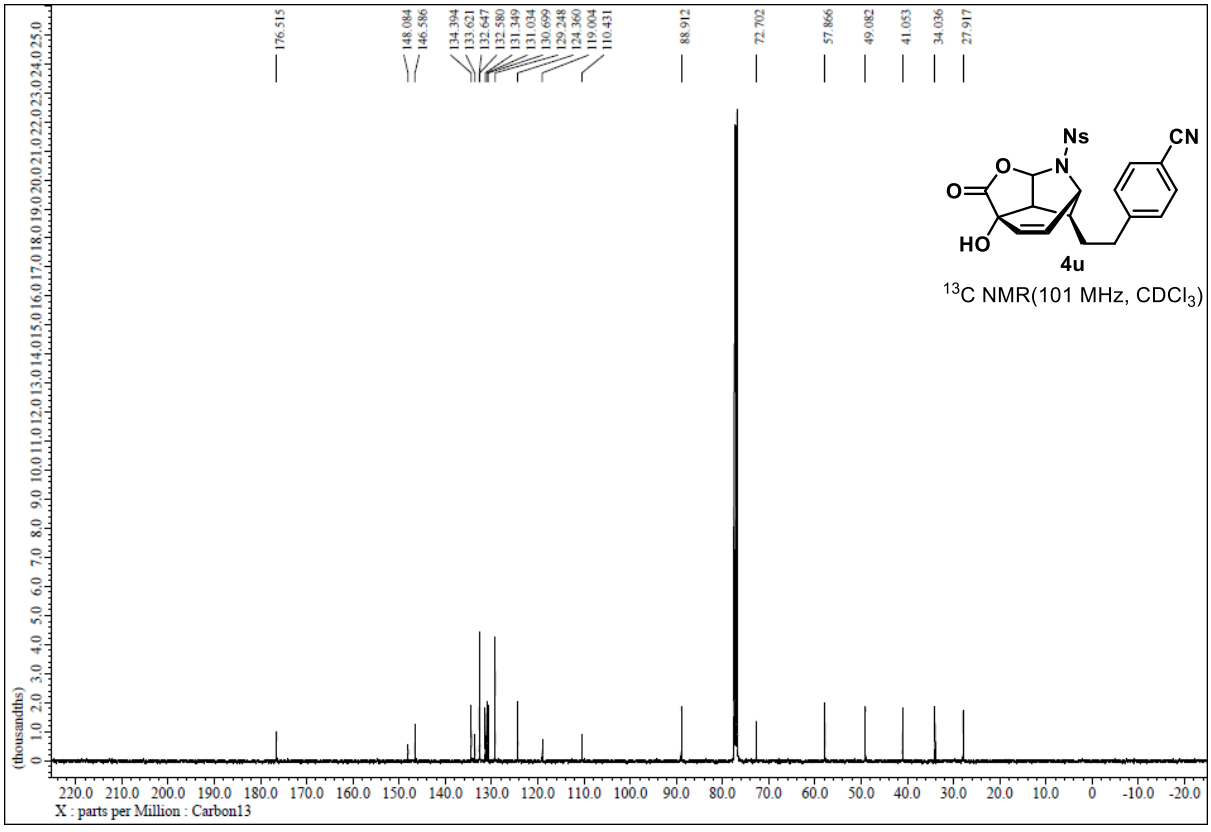
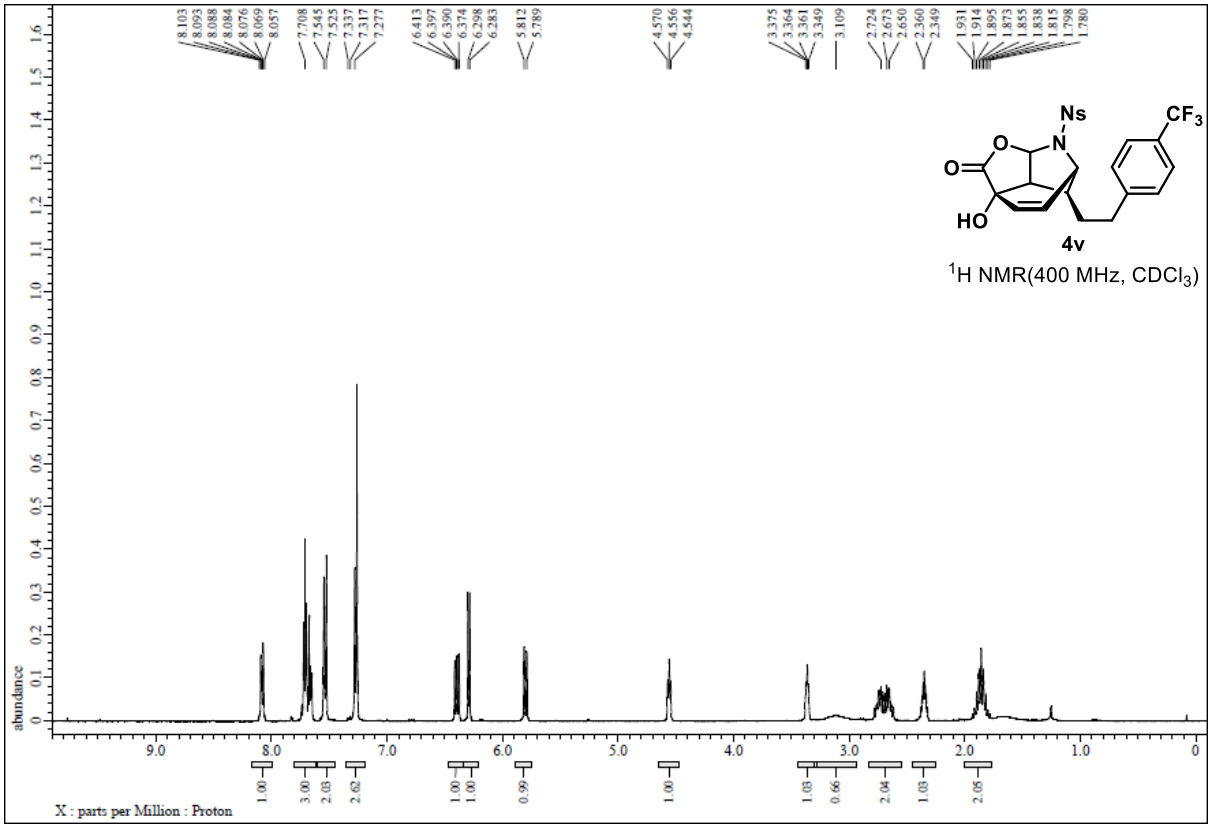
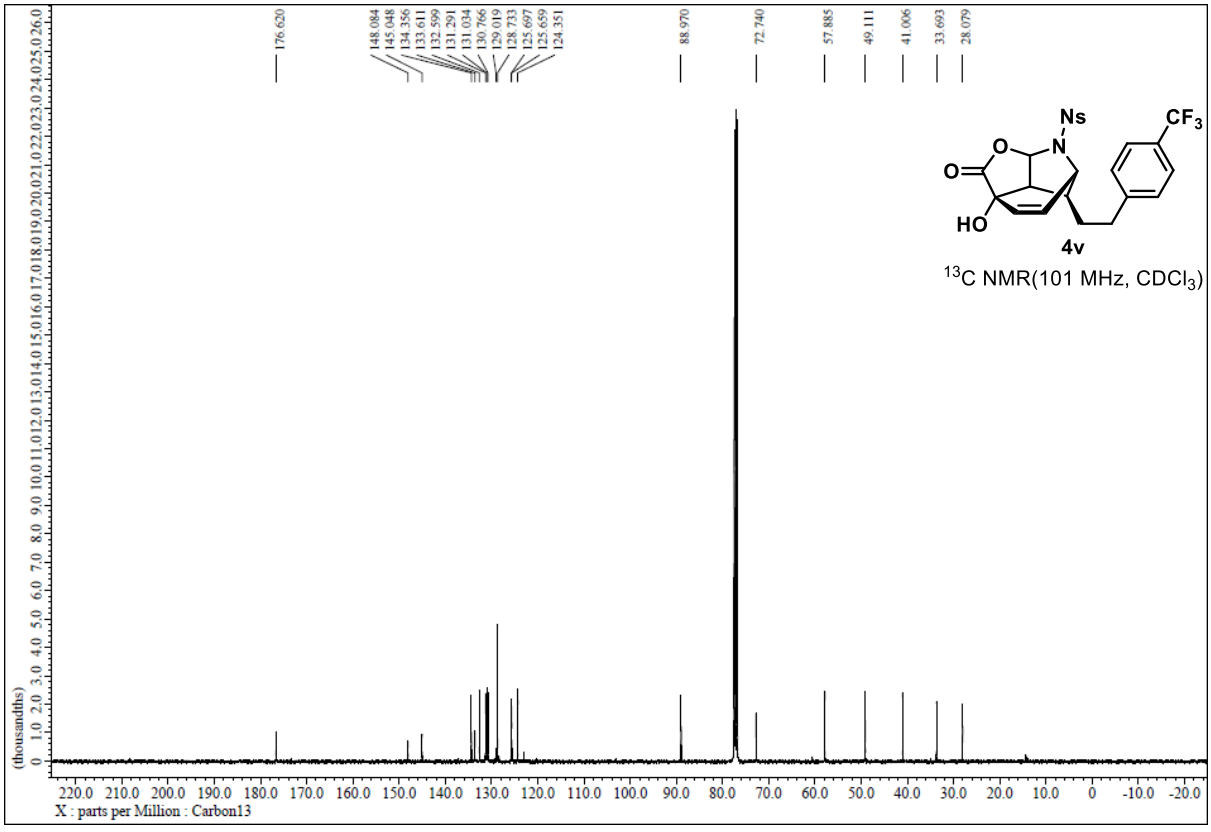
137.784
135.999
134.234
133.716
132.527
131.088
131.011
130.954
129.419
128.287
124.287
88.987
72.738
57.956
49.227
41.016
33.429
28.258
21.150
Ns
Me
O
N
O
HO
4t
13C NMR(101 MHz, CDCl3)
(thousandths)
X : parts per Million : Carbon13


8.107
8.096
8.092
8.088
8.079
8.073
8.061
7.719
7.587
7.567
7.280
7.260
6.389
6.382
6.366
6.304
6.290
5.810
5.788
4.572
4.560
4.546
3.372
3.362
3.359
3.348
3.118
2.735
2.676
2.653
2.356
2.346
1.909
1.892
1.873
1.869
1.851
1.833
1.829
1.809
1.792
abundance
X : parts per Million : Proton
Ns
CN
O
N
HO
4u
^{1}H NMR(400 MHz, $CDCl_3$)


176.515
148.084
146.586
134.394
133.621
132.647
132.580
131.349
131.034
130.699
129.248
124.360
119.004
110.431
88.912
72.702
57.866
49.082
41.053
34.036
27.917
(thousandths)
X : parts per Million : Carbon13
Ns
CN
O
N
HO
4u
^{13}C NMR(101 MHz, $CDCl_3$)


8.103
8.093
8.088
8.084
8.076
8.069
8.057
7.708
7.545
7.525
7.337
7.317
7.277
6.413
6.397
6.390
6.374
6.298
6.283
5.812
5.789
4.570
4.556
4.544
3.375
3.364
3.361
3.349
3.109
2.724
2.673
2.650
2.360
2.349
1.931
1.914
1.895
1.873
1.855
1.838
1.815
1.798
1.780
abundance
X : parts per Million : Proton
Ns
CF3
O
N
O
HO
4v
1H NMR(400 MHz, CDCl3)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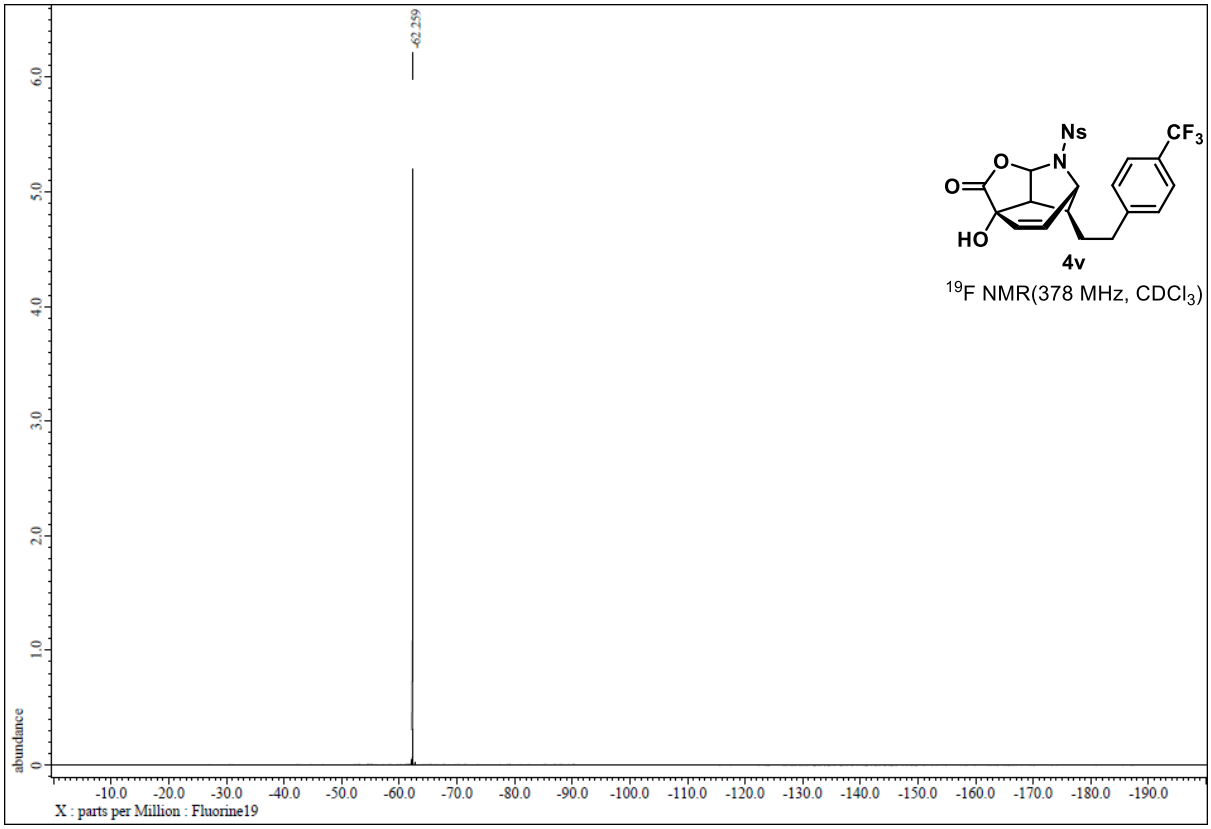
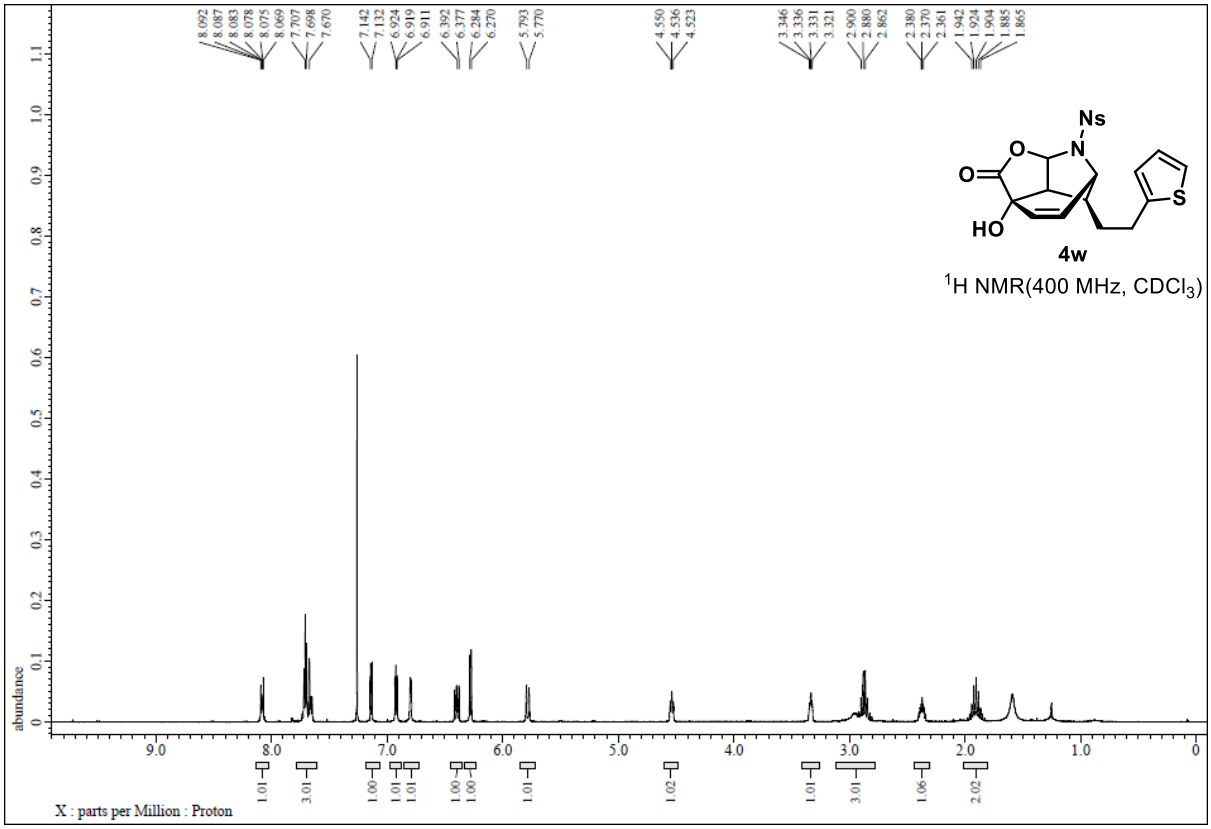
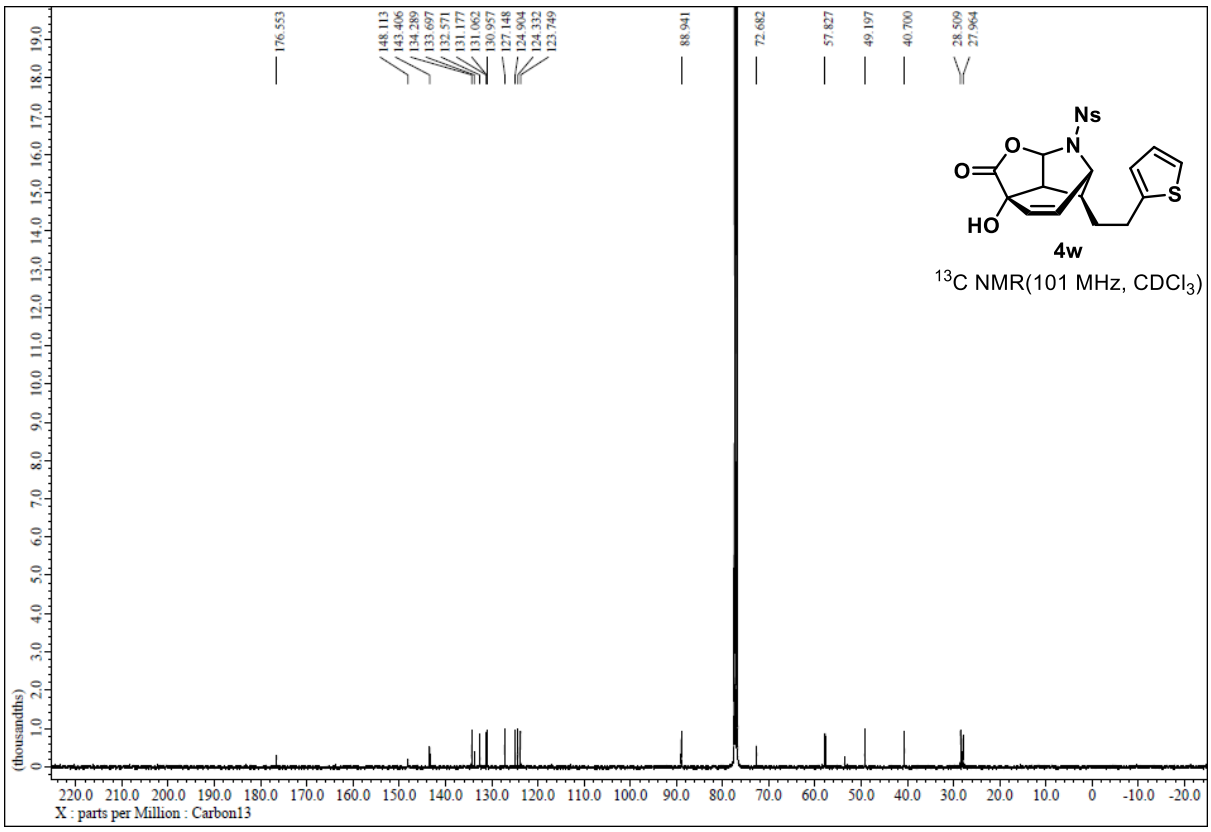
145.048
134.356
133.611
132.599
131.291
131.034
130.766
129.019
128.733
125.697
125.659
124.351
88.970
72.740
57.885
49.111
41.006
33.693
28.079
(thousandths)
X : parts per Million : Carbon13
Ns
CF3
O
N
O
HO
4v
13C NMR(101 MHz, CDCl3)



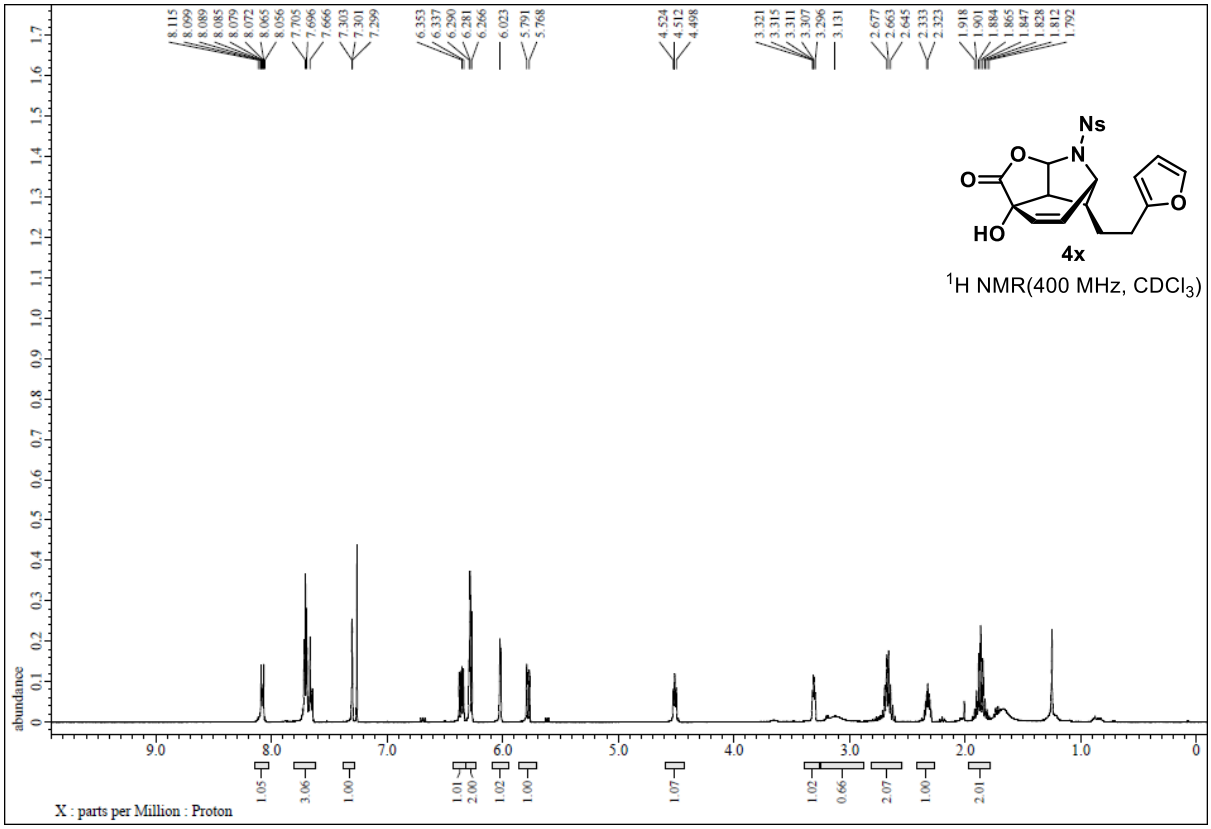
^{19}F NMR(378 MHz, $CDCl_3$)



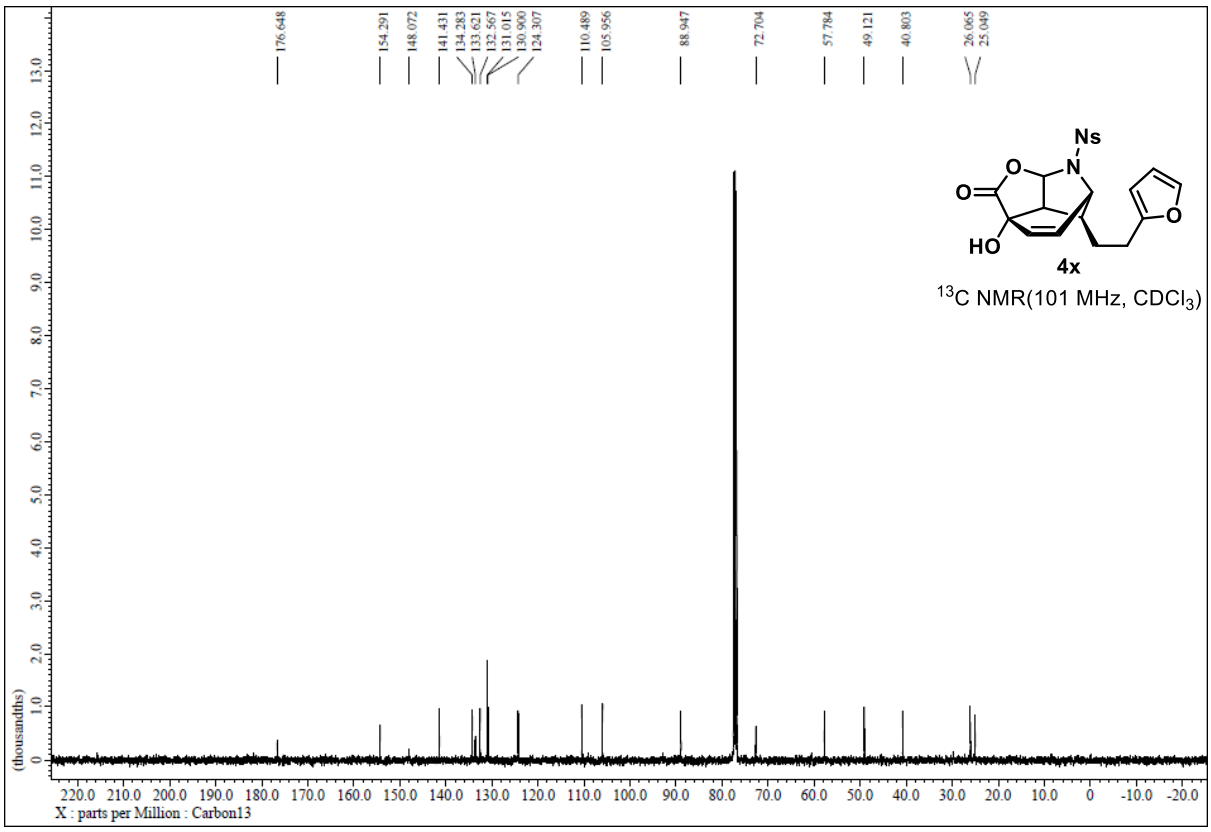
^{1}H NMR(400 MHz, $CDCl_3$)



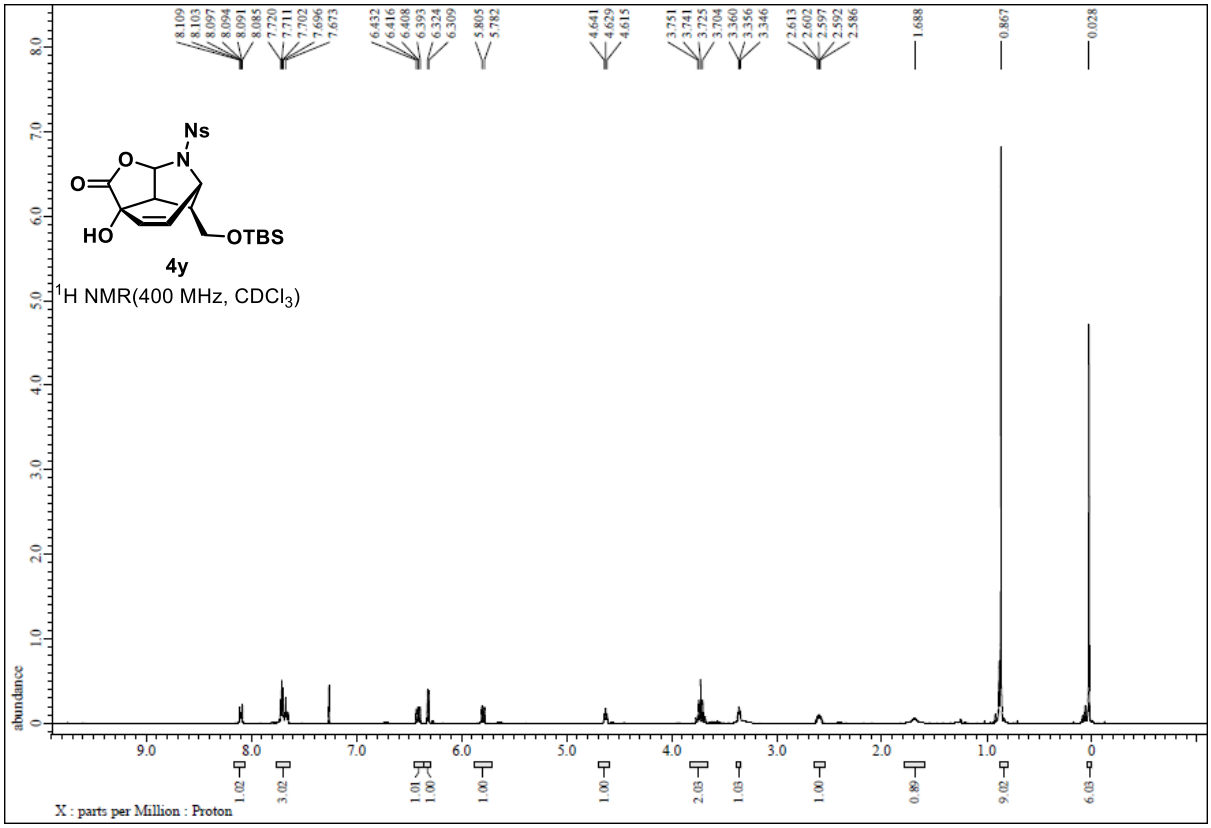
^{13}C NMR(101 MHz, $CDCl_3$)

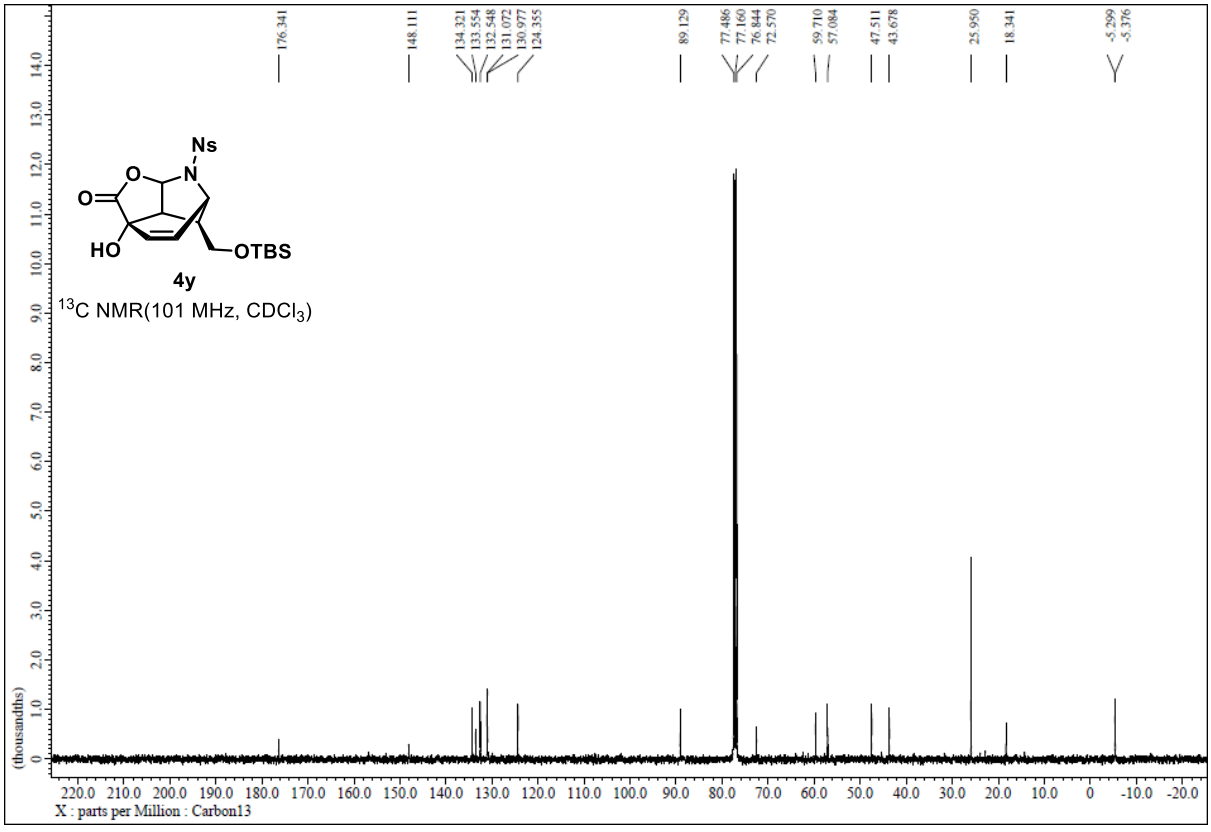


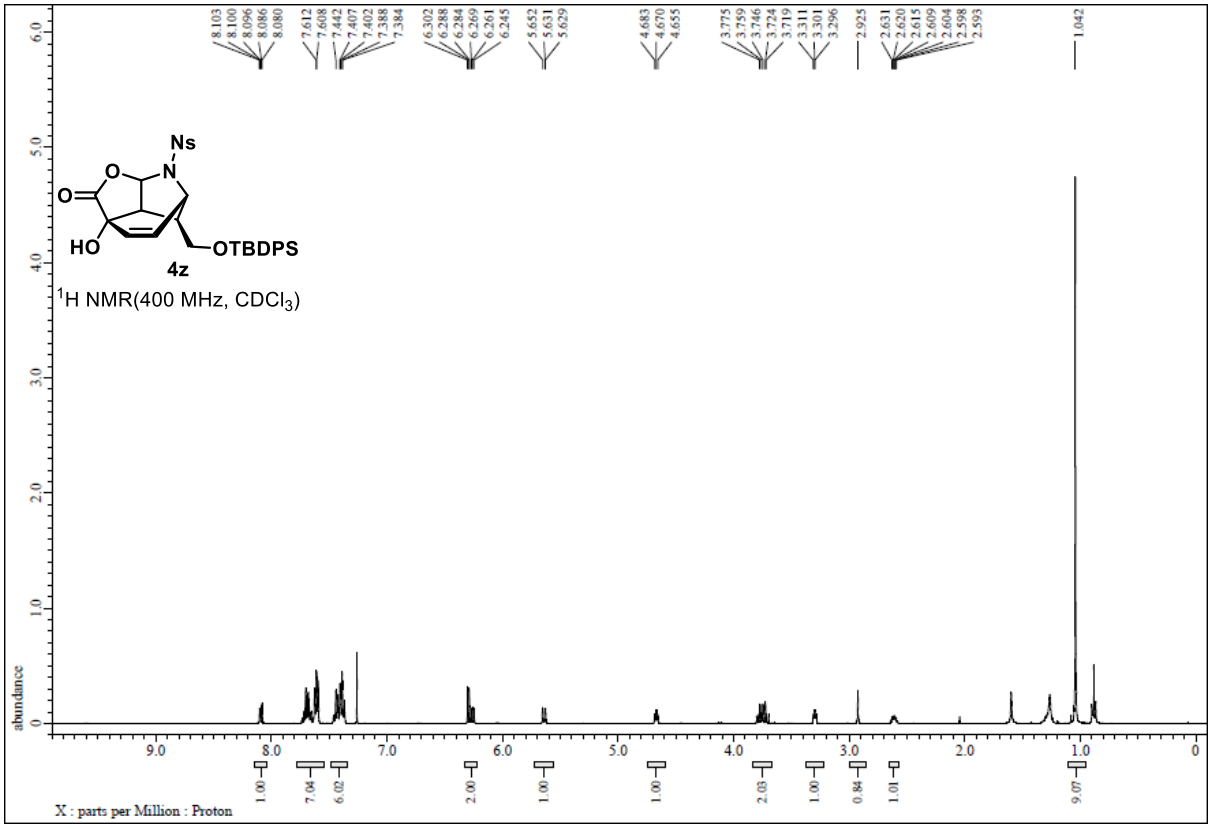
^{1}H NMR(400 MHz, $CDCl_3$)

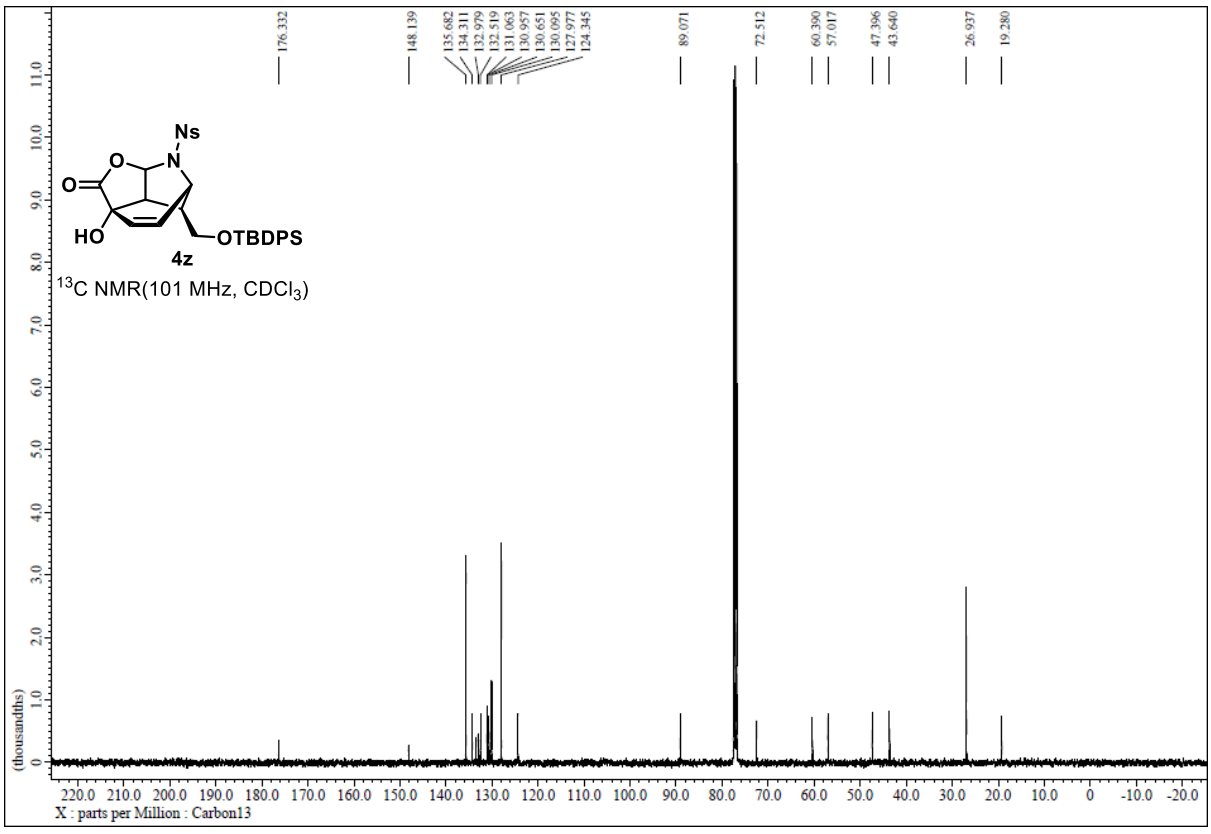


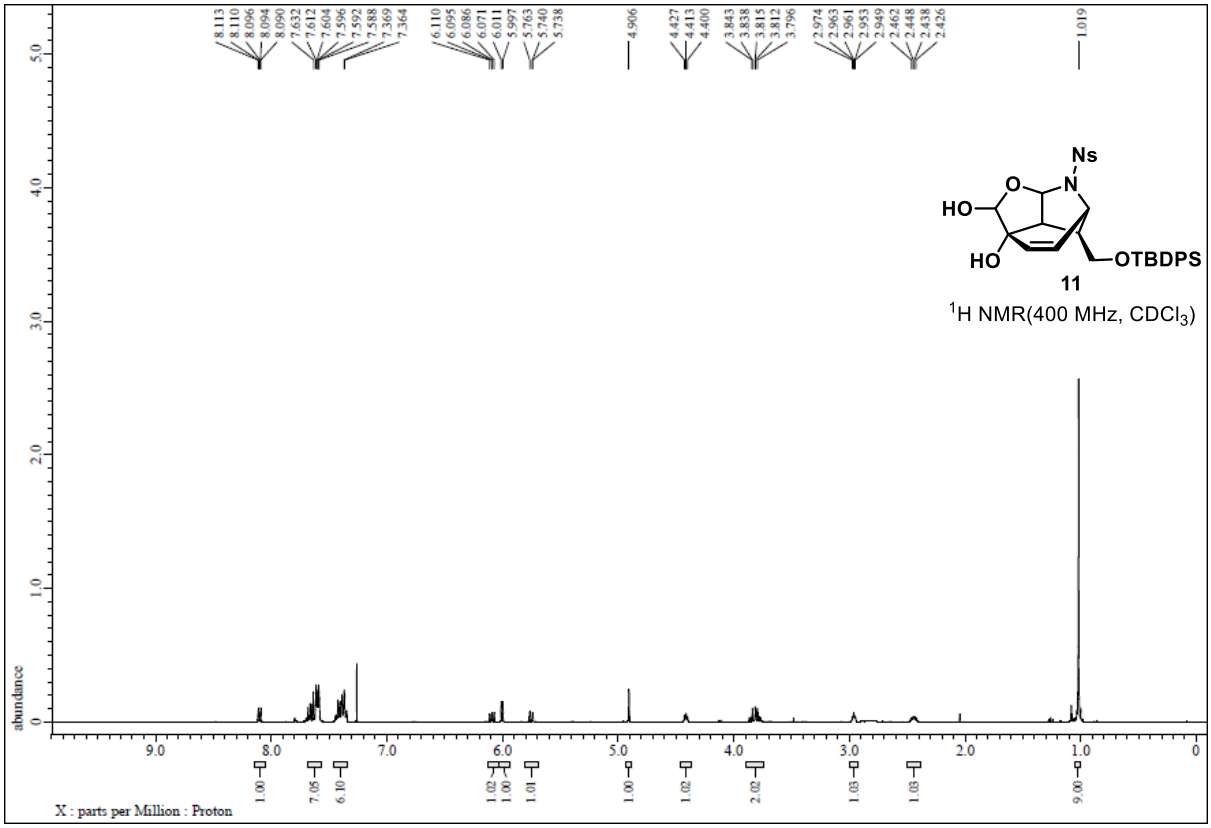
^{13}C NMR(101 MHz, $CDCl_3$)

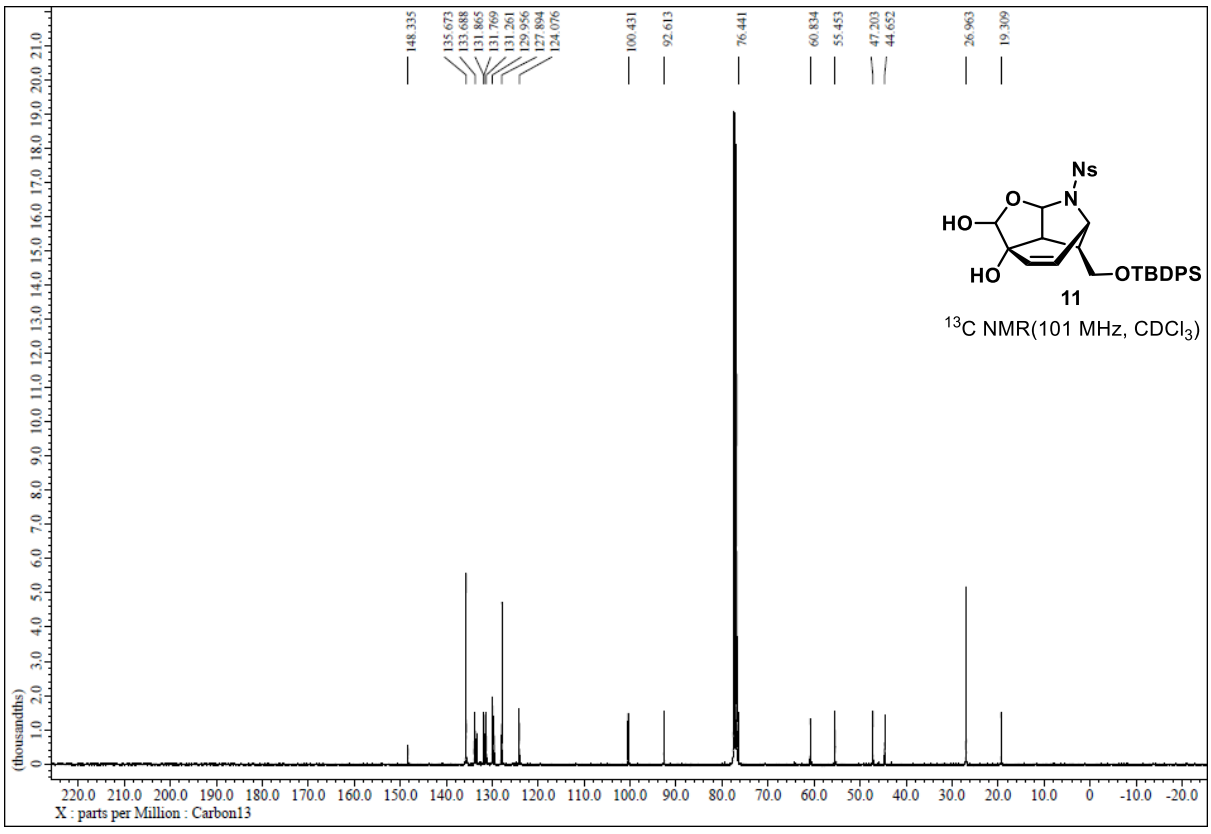

Ns
O
N
O
HO
OTBS
4y
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

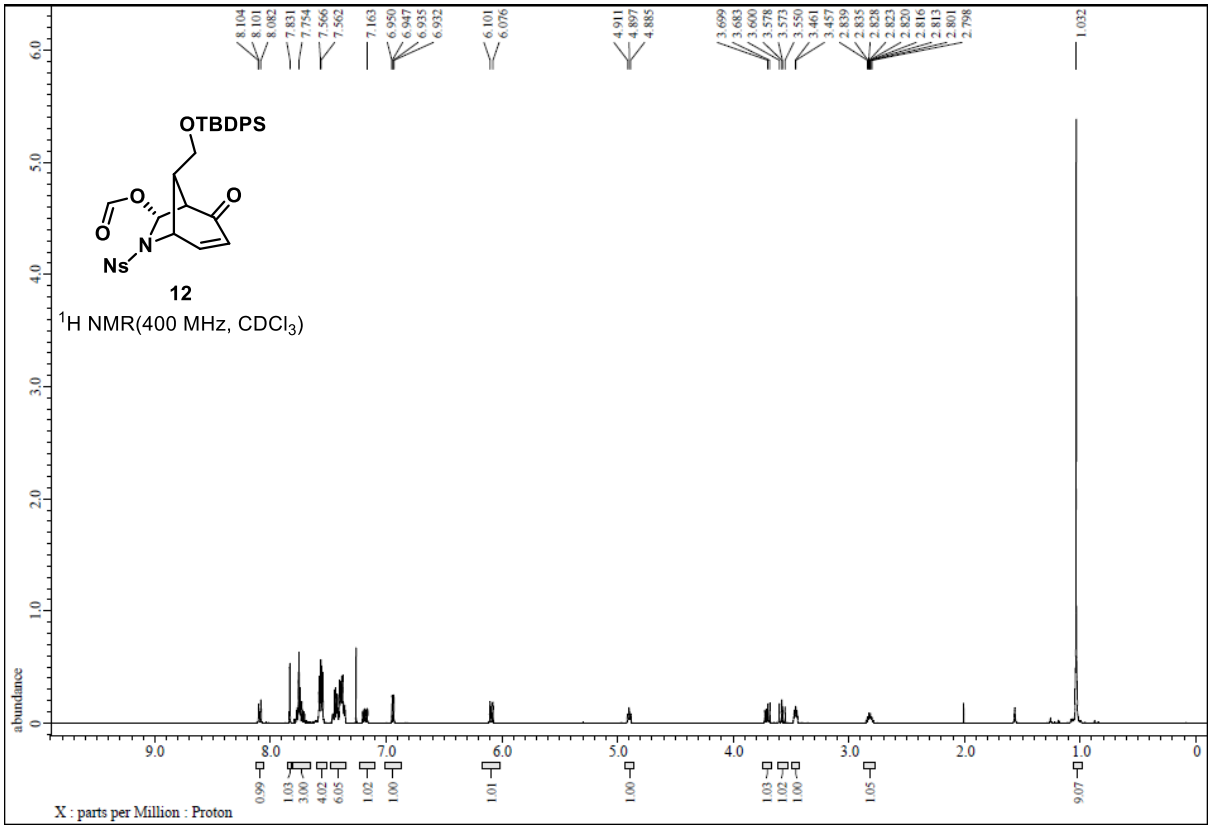

Ns
O
N
O
HO
OTBS
4y
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

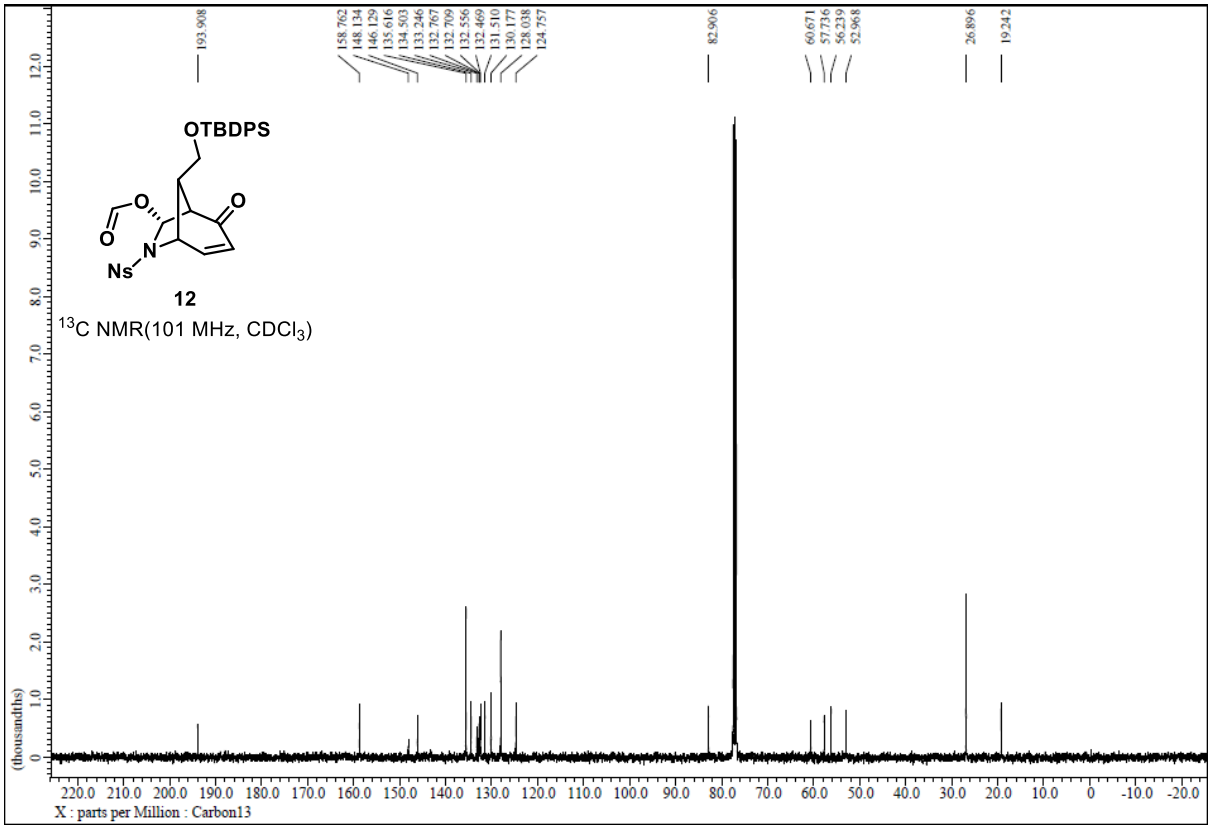

Ns
O
N
O
HO
OTBDPS
4z
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

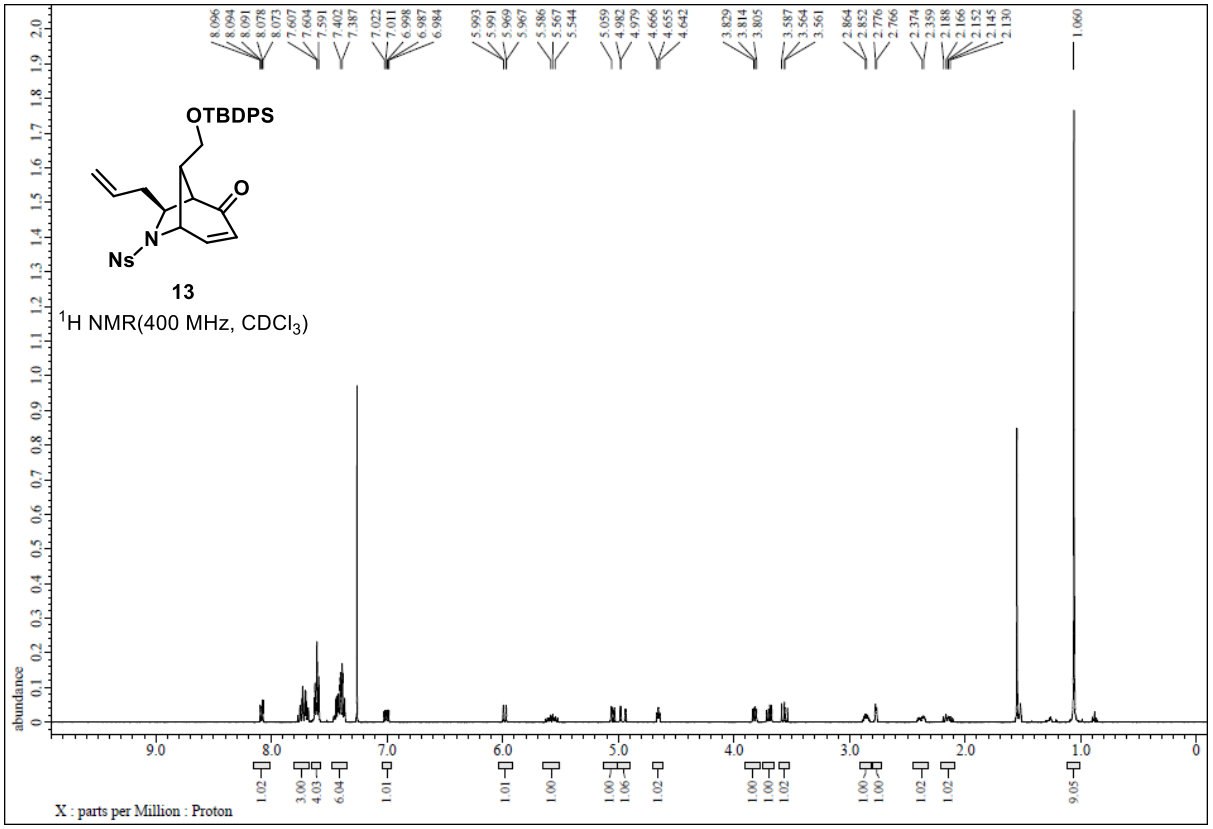

Ns
O
N
O
HO
OTBDPS
4z
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

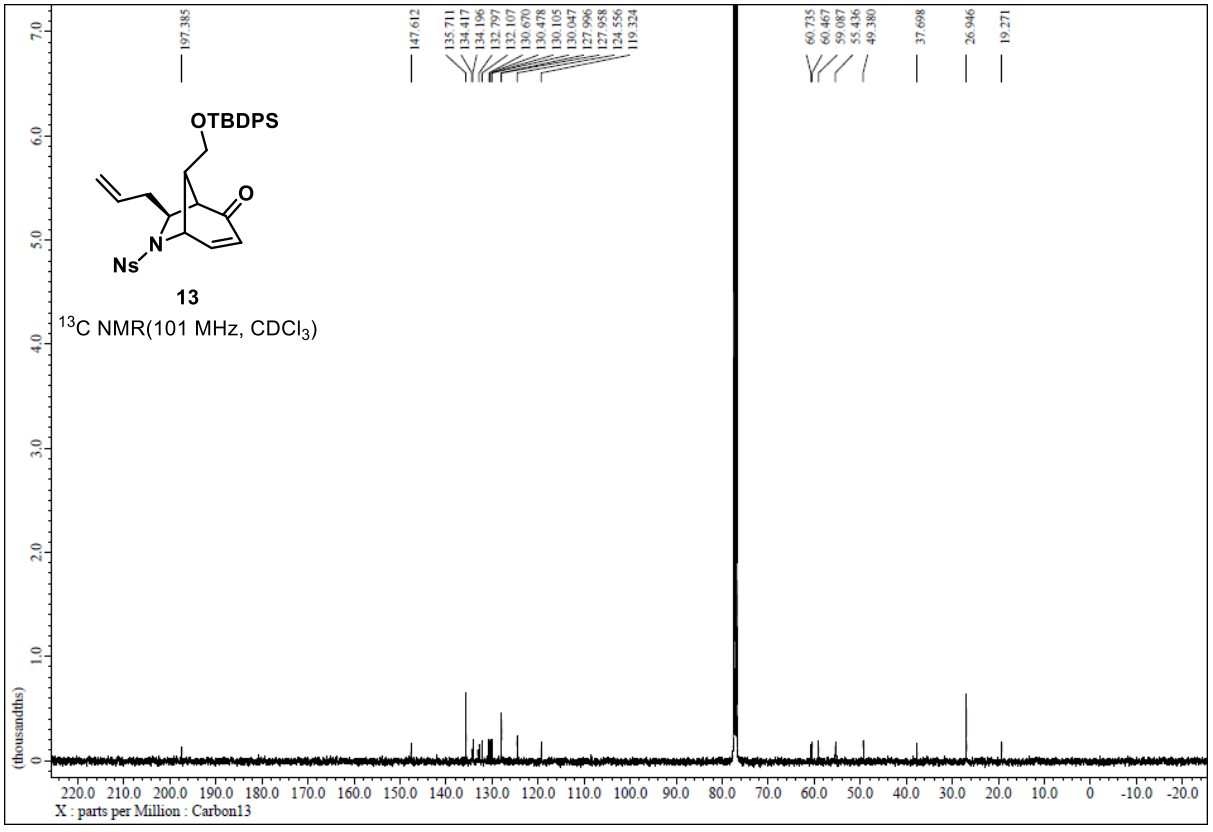

8.113
8.110
8.096
8.094
8.090
7.632
7.612
7.604
7.596
7.592
7.588
7.369
7.364
6.110
6.095
6.086
6.071
6.011
5.997
5.763
5.740
5.738
4.906
4.427
4.413
4.400
3.843
3.838
3.815
3.812
3.796
2.974
2.963
2.961
2.953
2.949
2.462
2.448
2.438
2.426
1.019
abundance
X : parts per Million : Proton
Ns
N
O
HO
HO
OTBDPS
11
1H NMR(400 MHz, CDCl3)

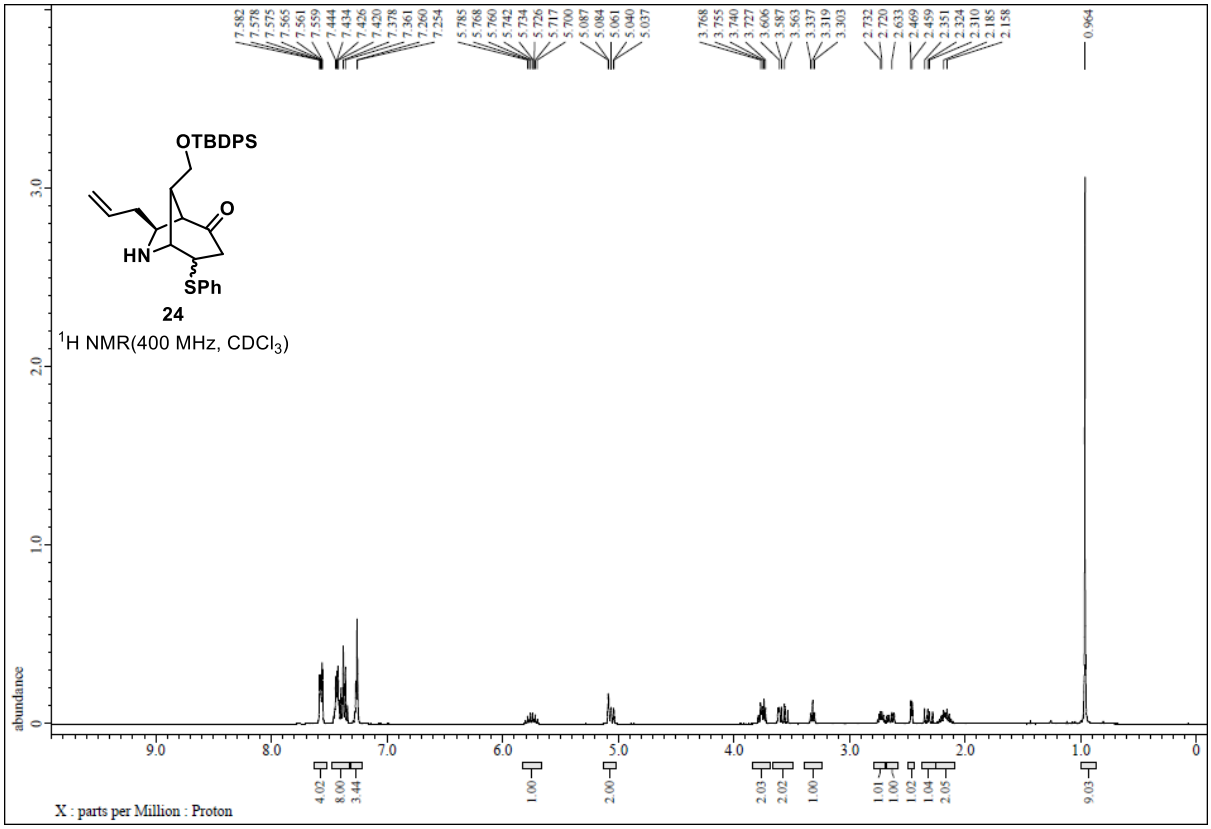

148.335
135.673
133.688
131.865
131.769
131.261
129.956
127.894
124.076
100.431
92.613
76.441
60.834
55.453
47.203
44.652
26.963
19.309
(thousandths)
X : parts per Million : Carbon13
Ns
N
O
HO
HO
OTBDPS
11
13C NMR(101 MHz, CDCl3)

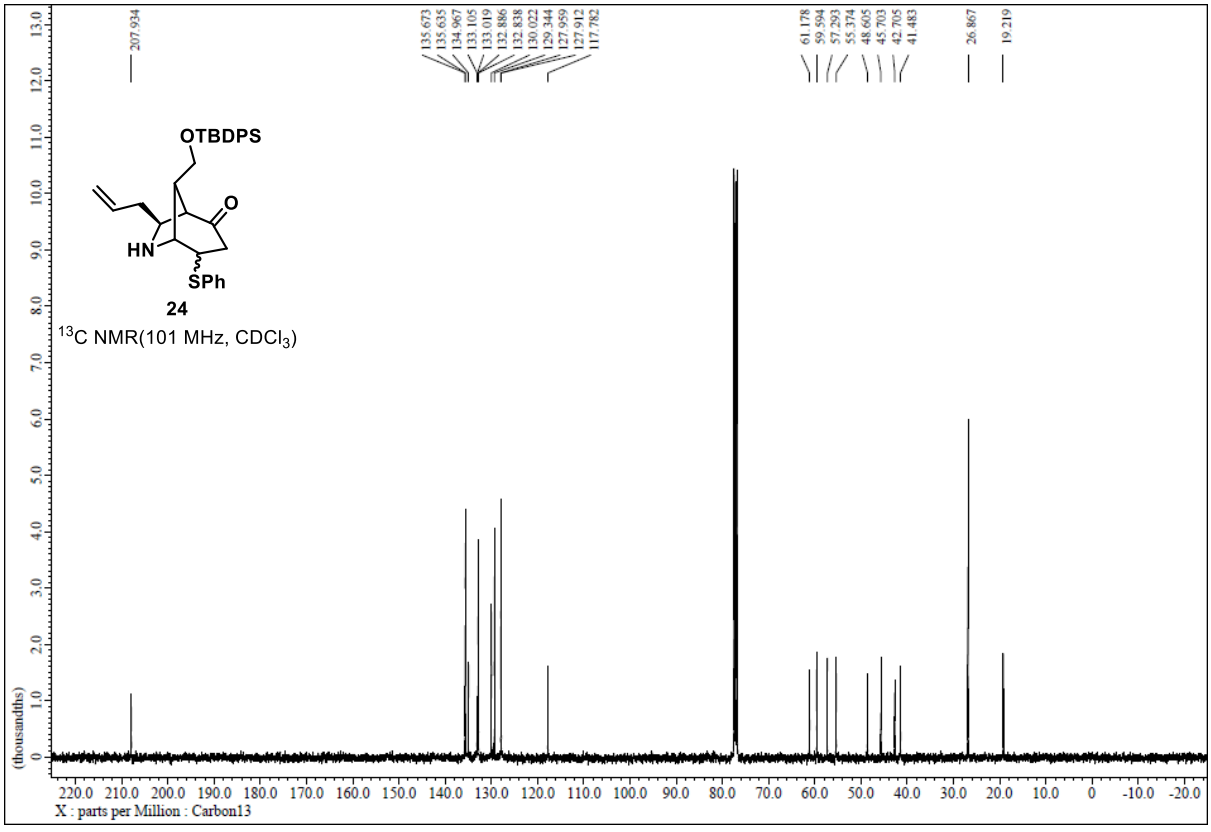

OTBDPS
O
O
O
N
Ns
12
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

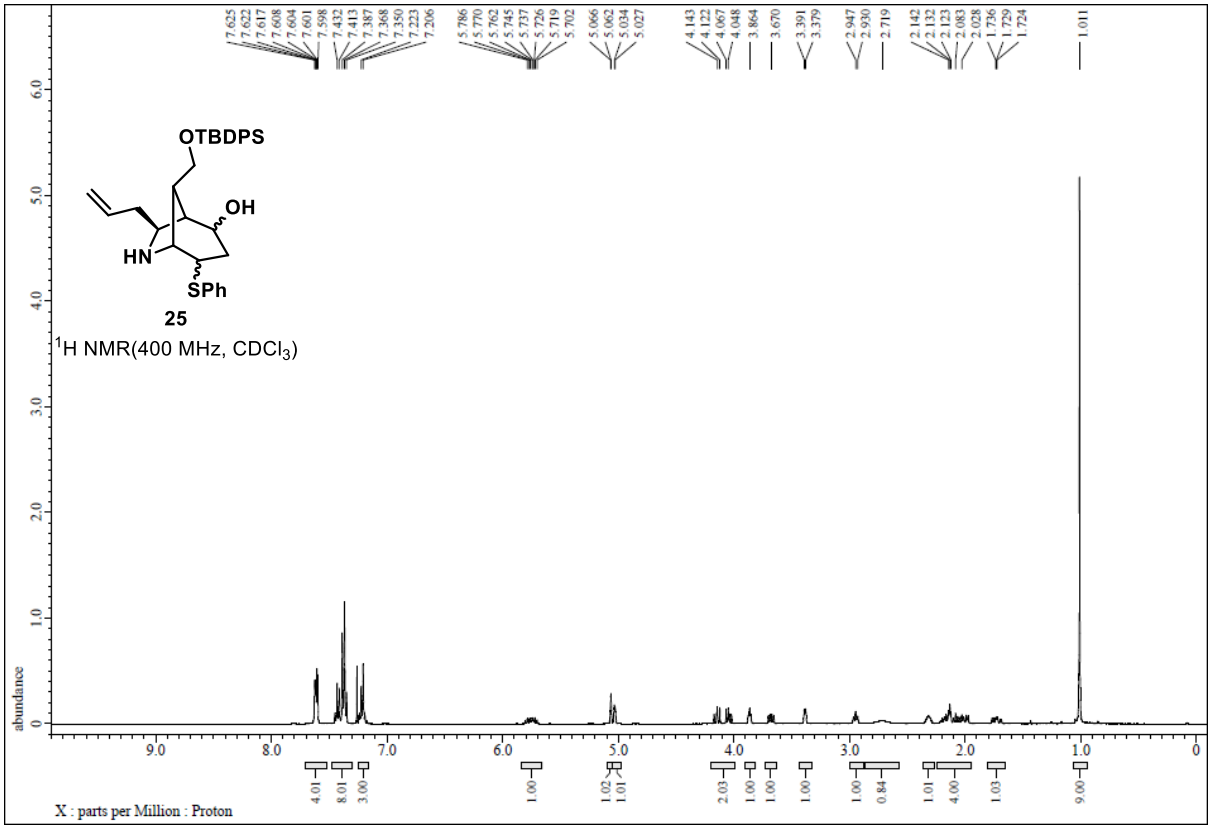

OTBDPS
O
O
O
N
Ns
12
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

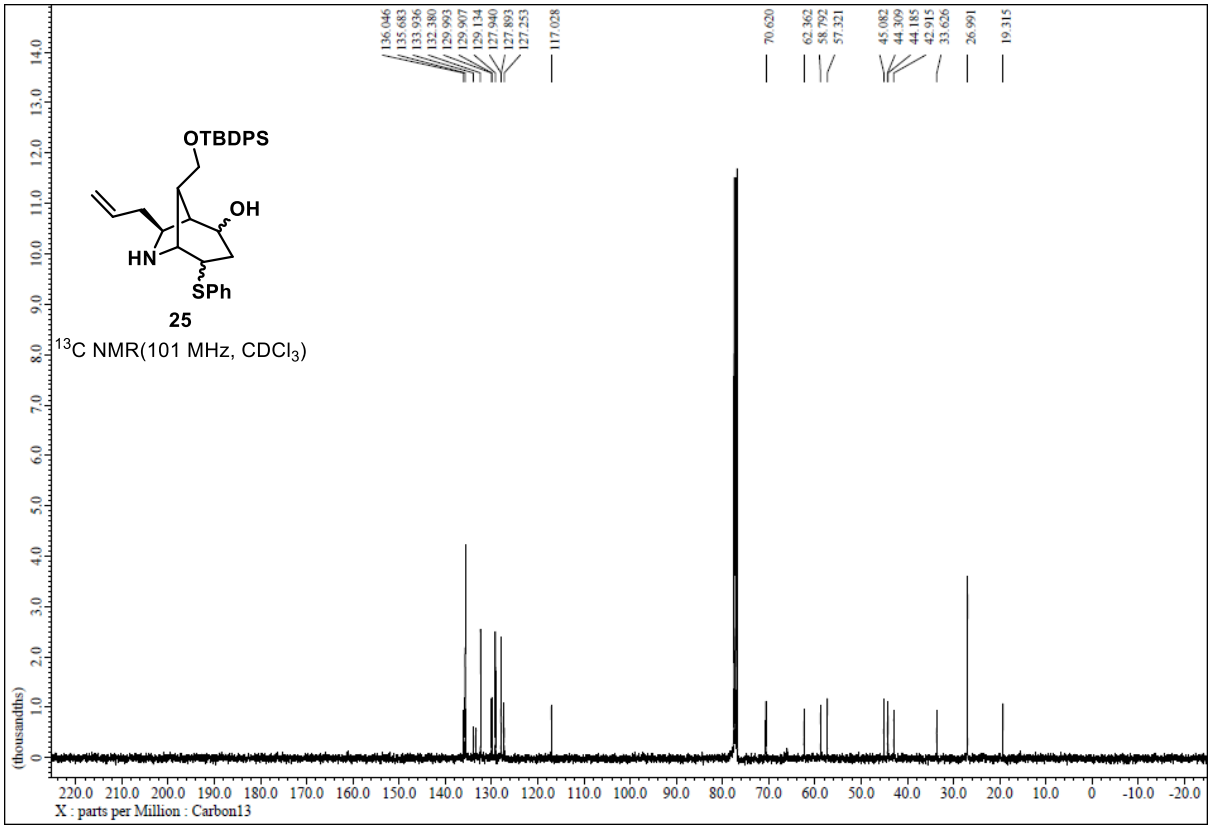

OTBDPS
O
N
Ns
13
1H NMR(400 MHz, CDCl3)
abundance
X : parts per Million : Proton

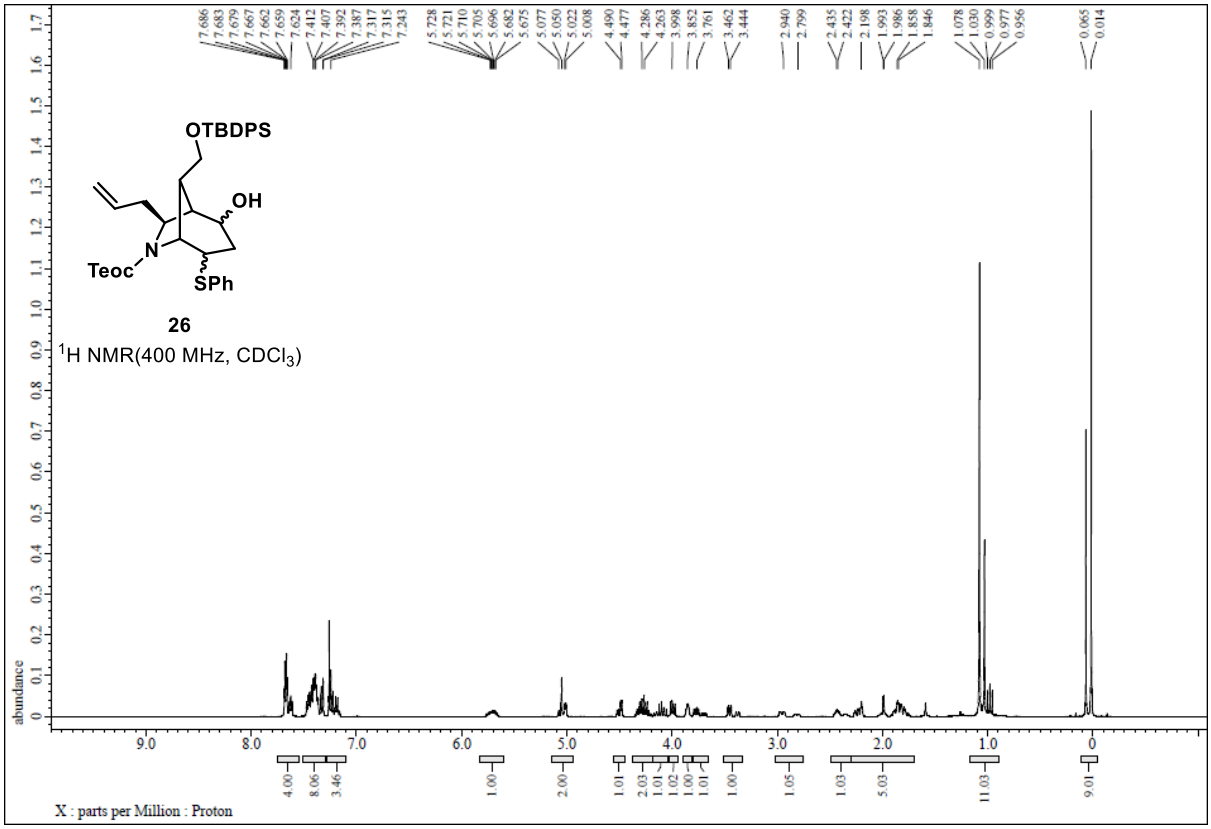

OTBDPS
O
N
Ns
13
13C NMR(101 MHz, CDCl3)
(thousandths)
X : parts per Million : Carbon13


OTBDPS
O
HN
SPh
24
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


OTBDPS
O
HN
SPh
24
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

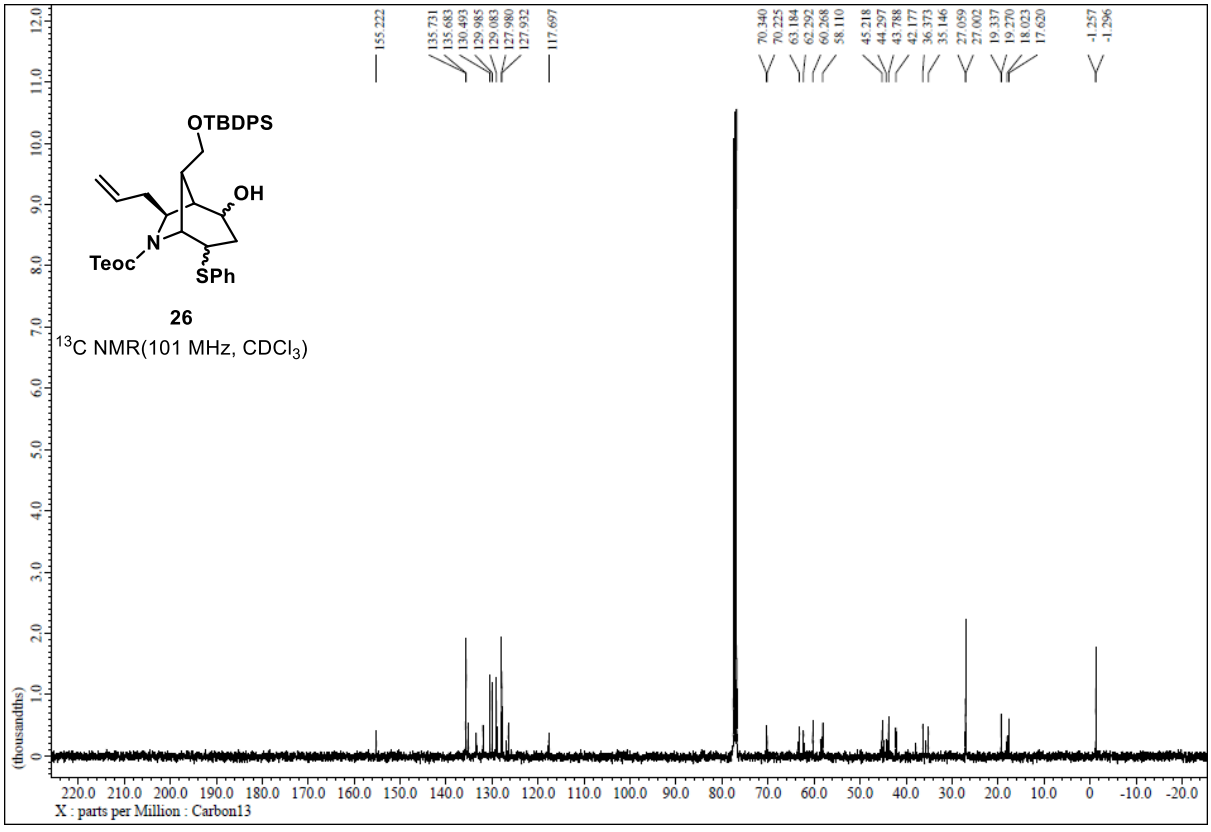

OTBDPS
OH
HN
SPh
25
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


OTBDPS
OH
HN
SPh
25
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13



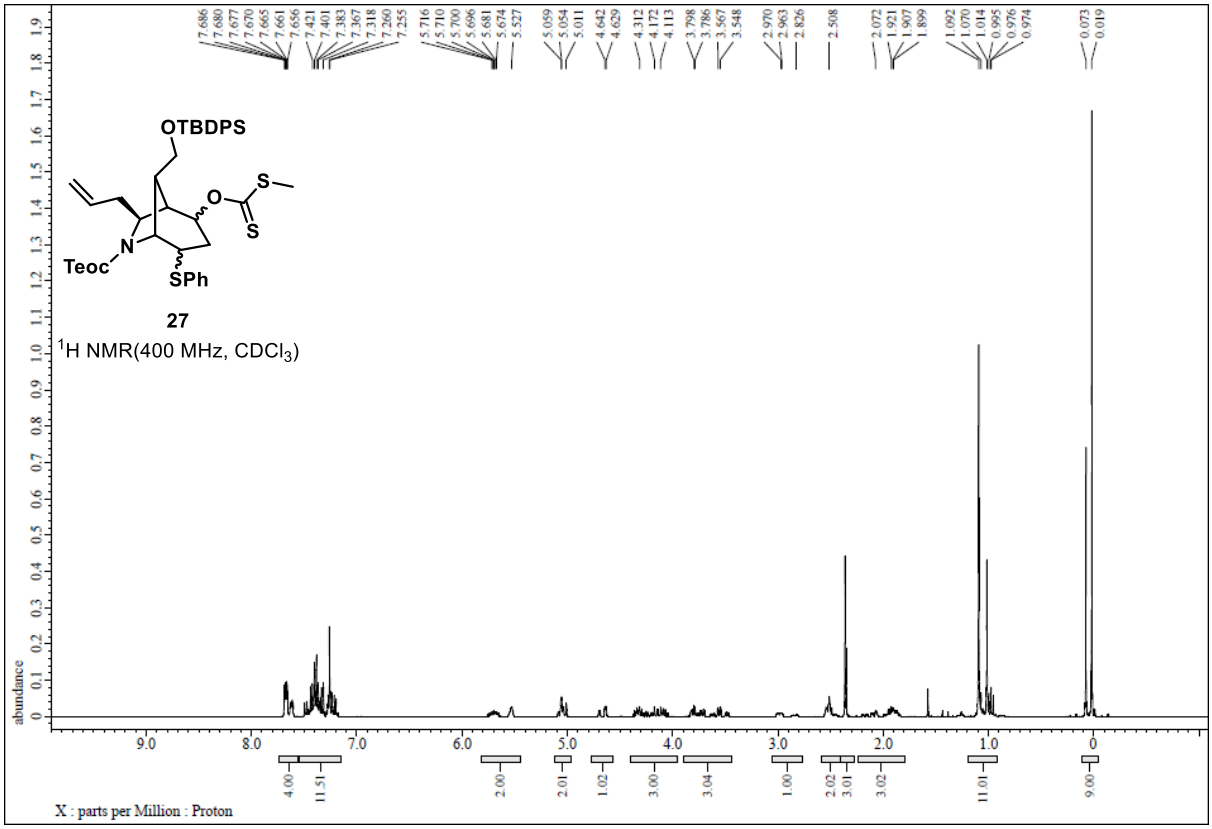
26

^{1}H NMR(400 MHz, $CDCl_3$)



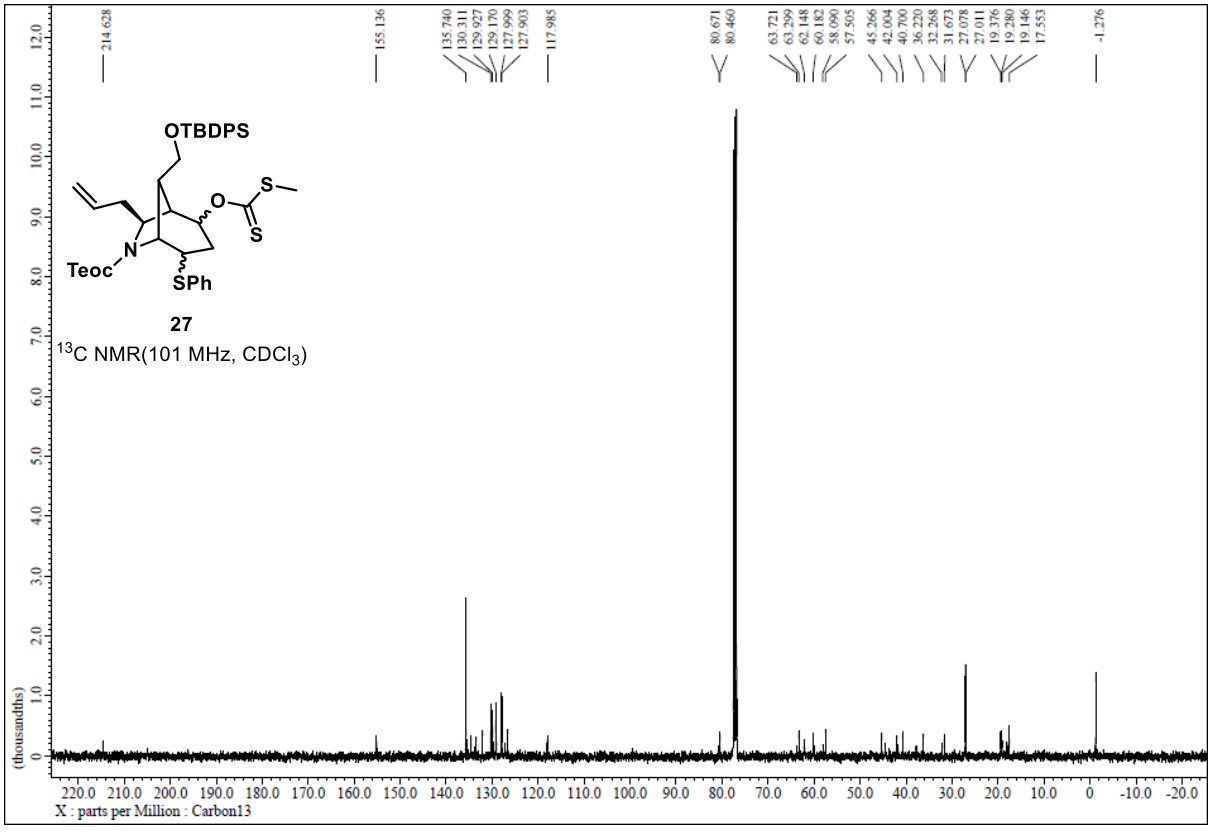
26

^{13}C NMR(101 MHz, $CDCl_3$)



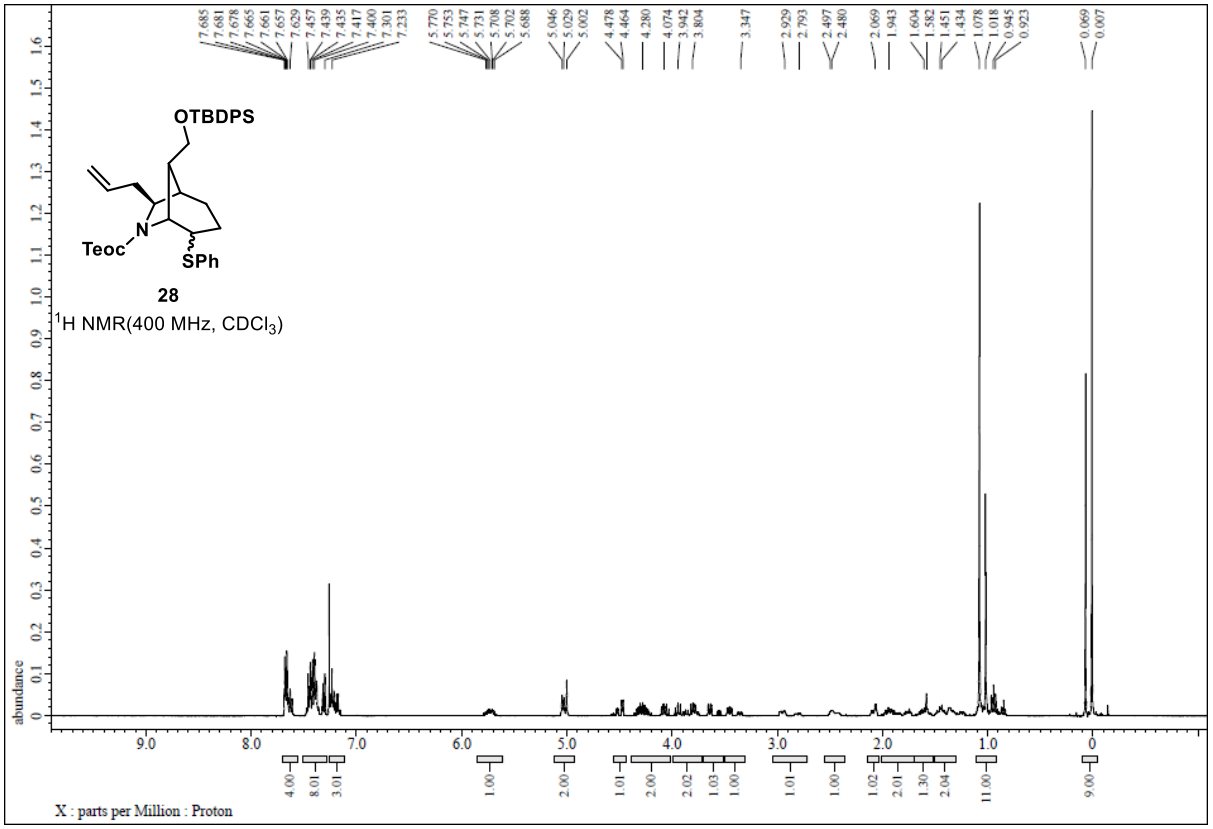
27

^{1}H NMR(400 MHz, $CDCl_3$)



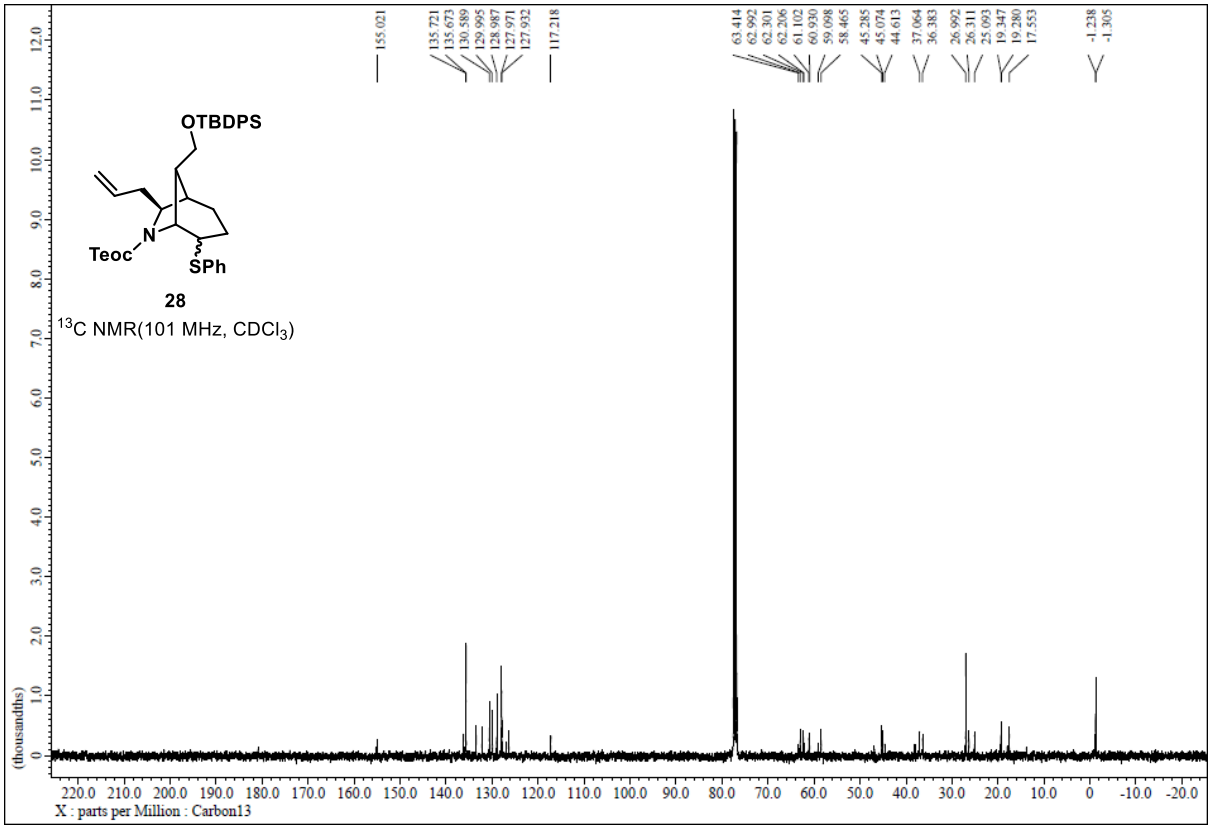
27

^{13}C NMR(101 MHz, $CDCl_3$)



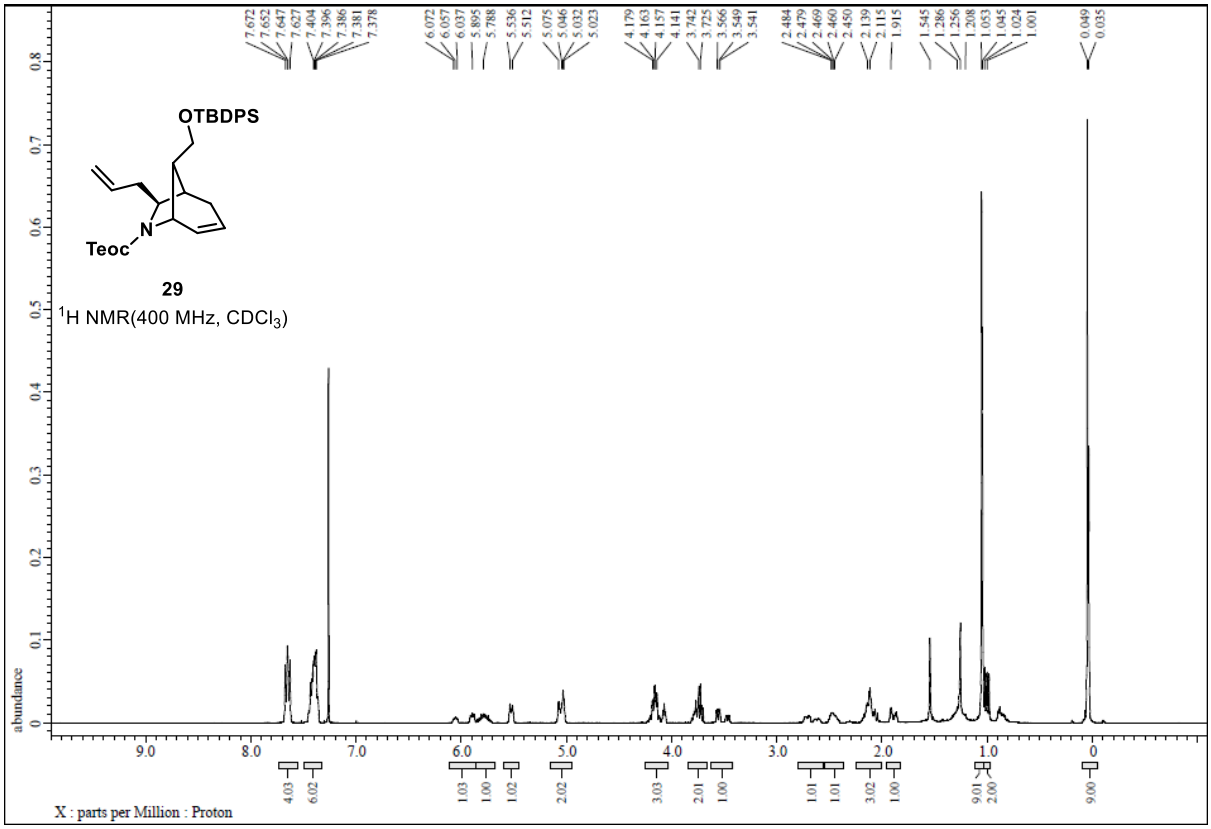
28

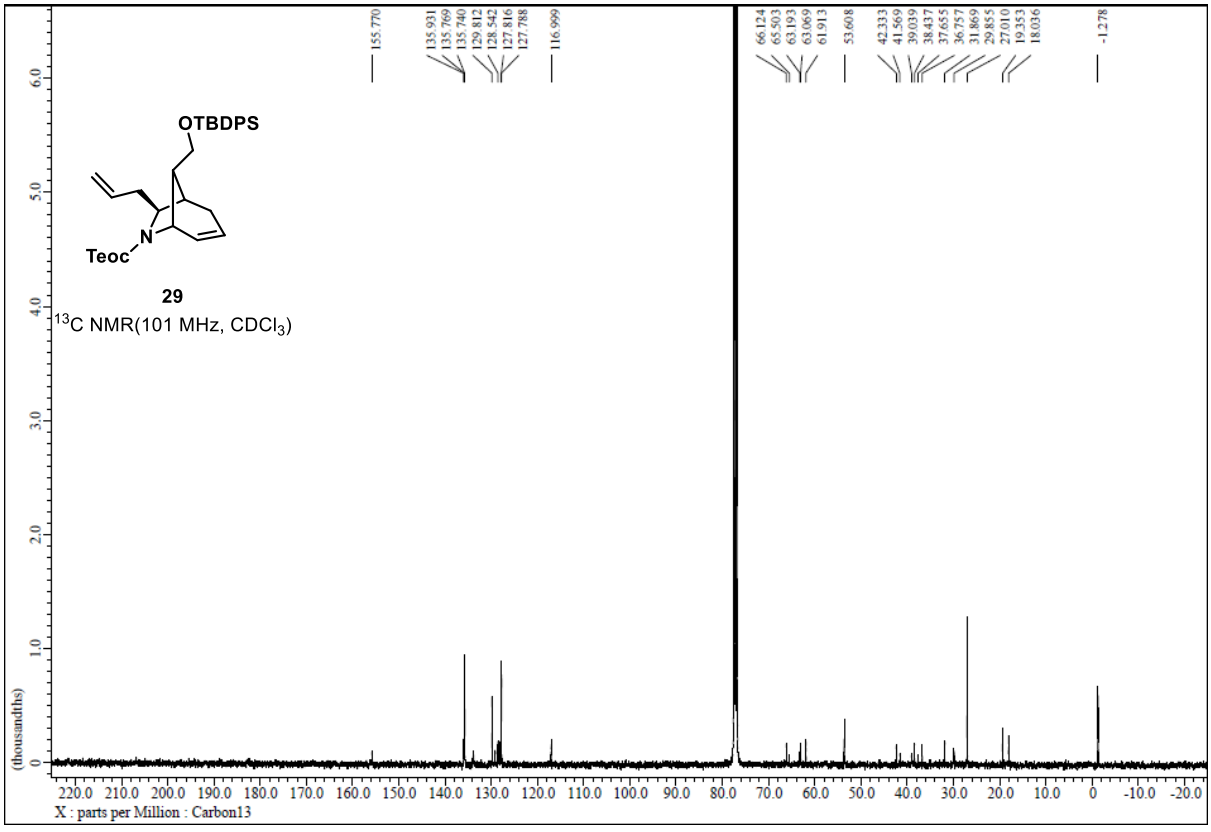
^{1}H NMR(400 MHz, $CDCl_3$)

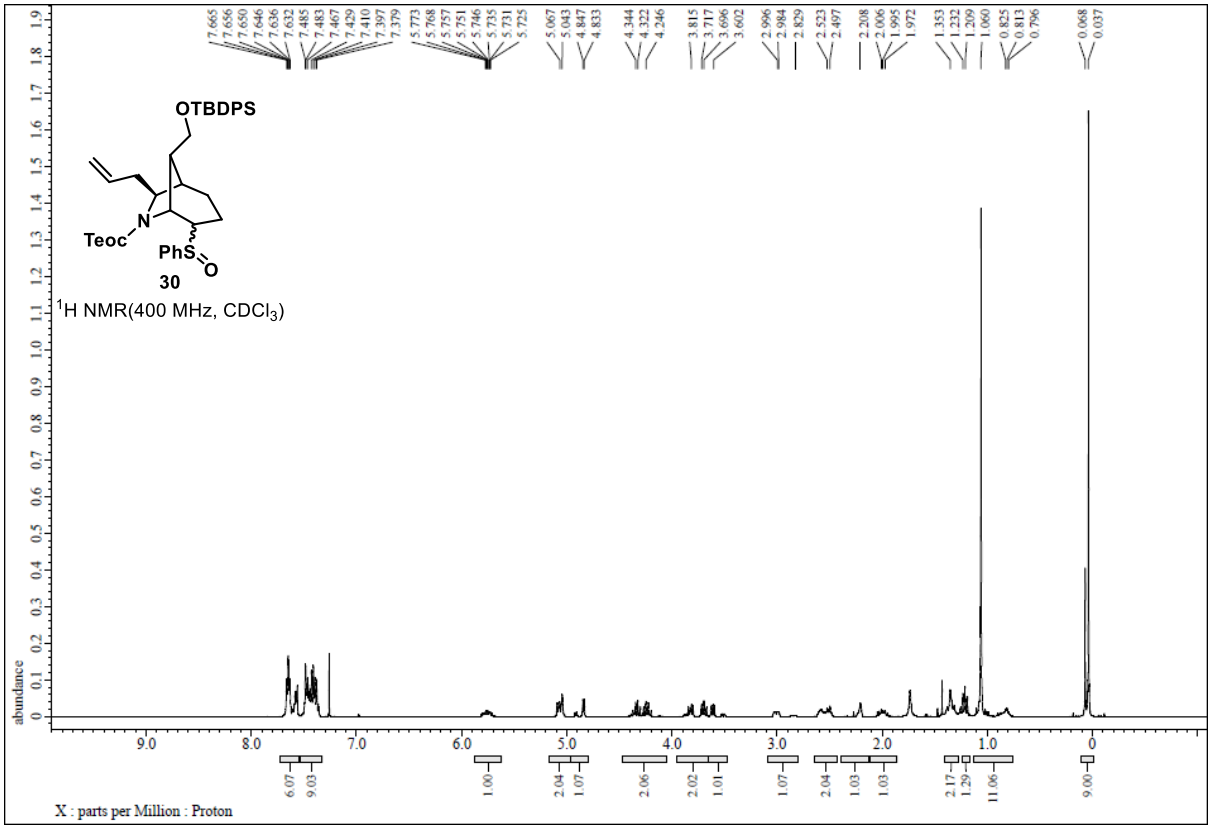


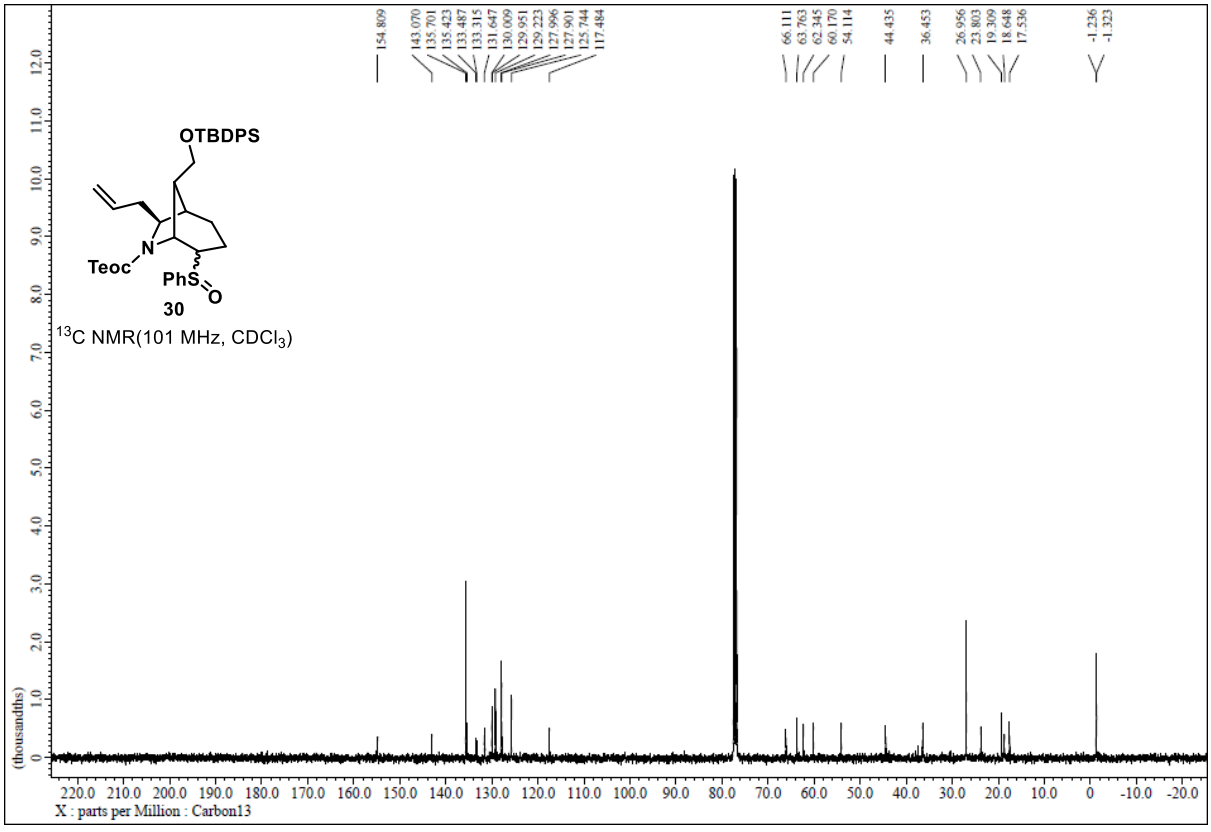
28

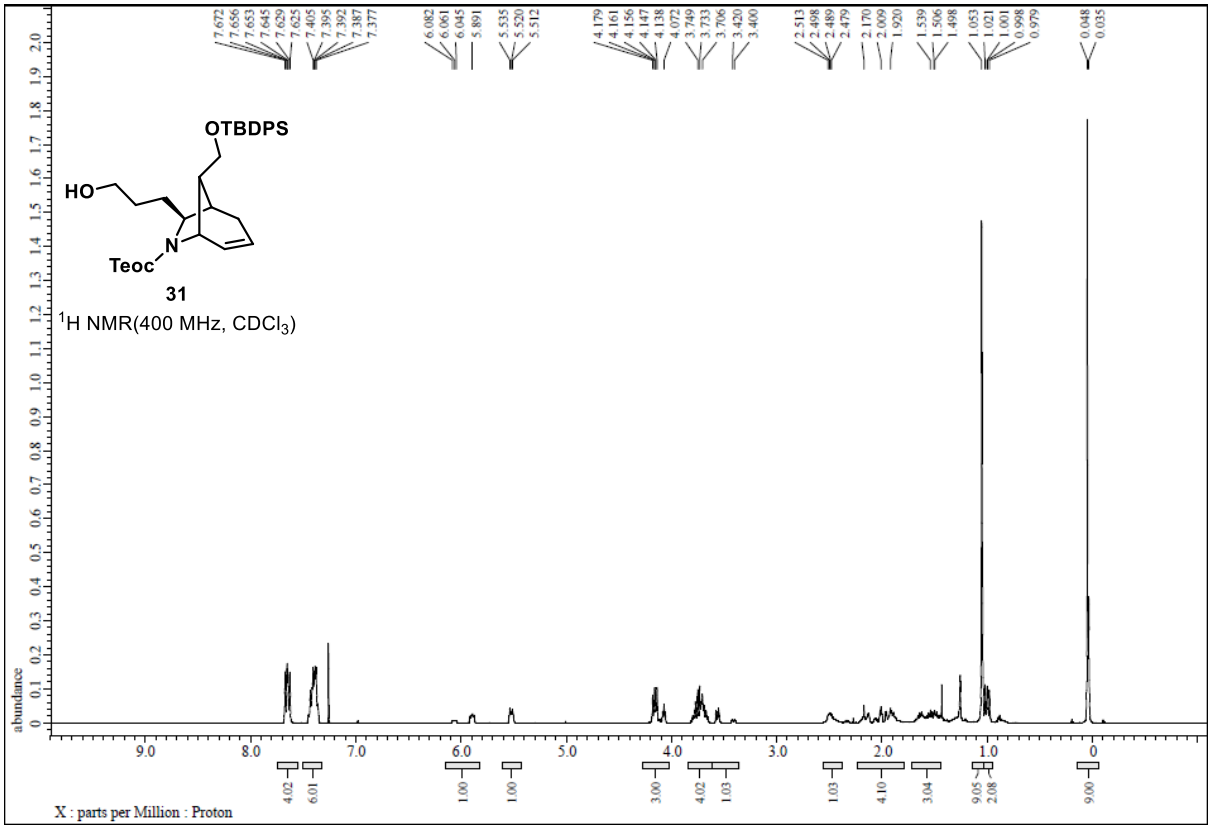
^{13}C NMR(101 MHz, $CDCl_3$)

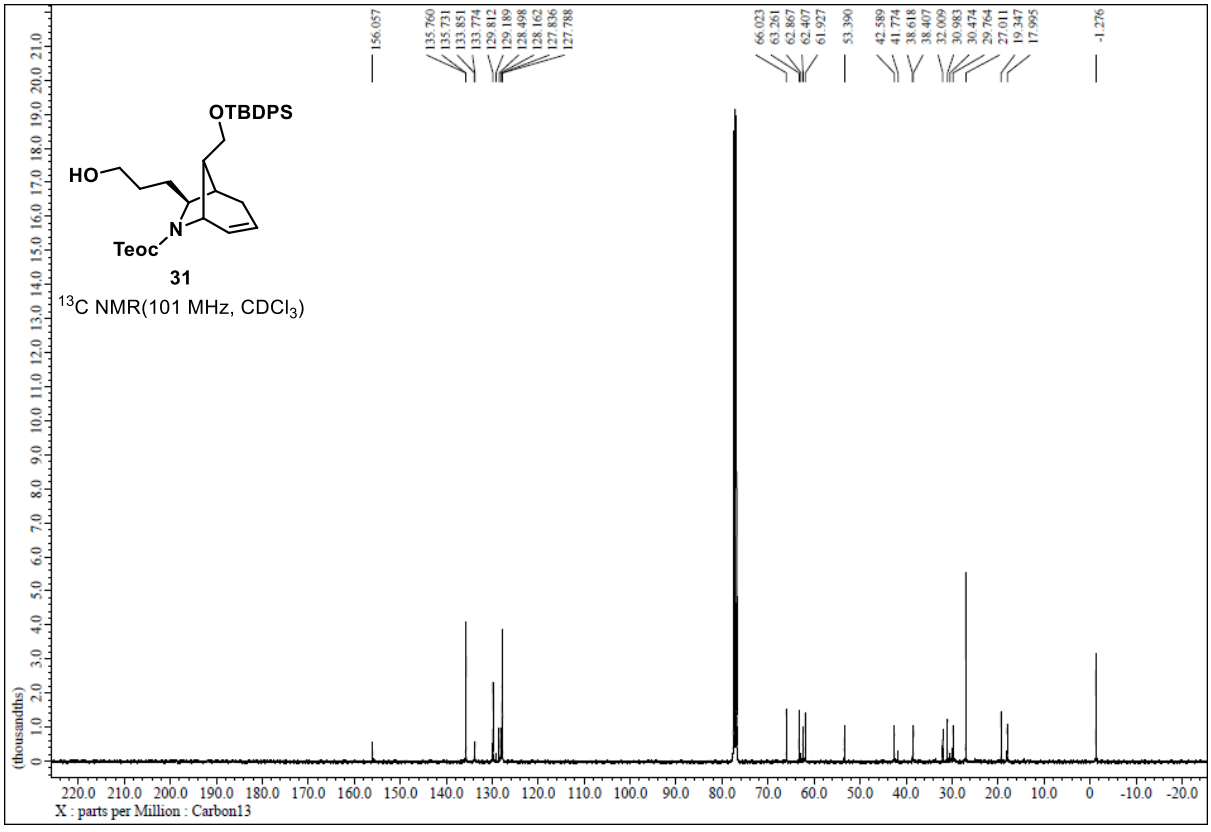

OTBDPS
N
Teoc
29
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

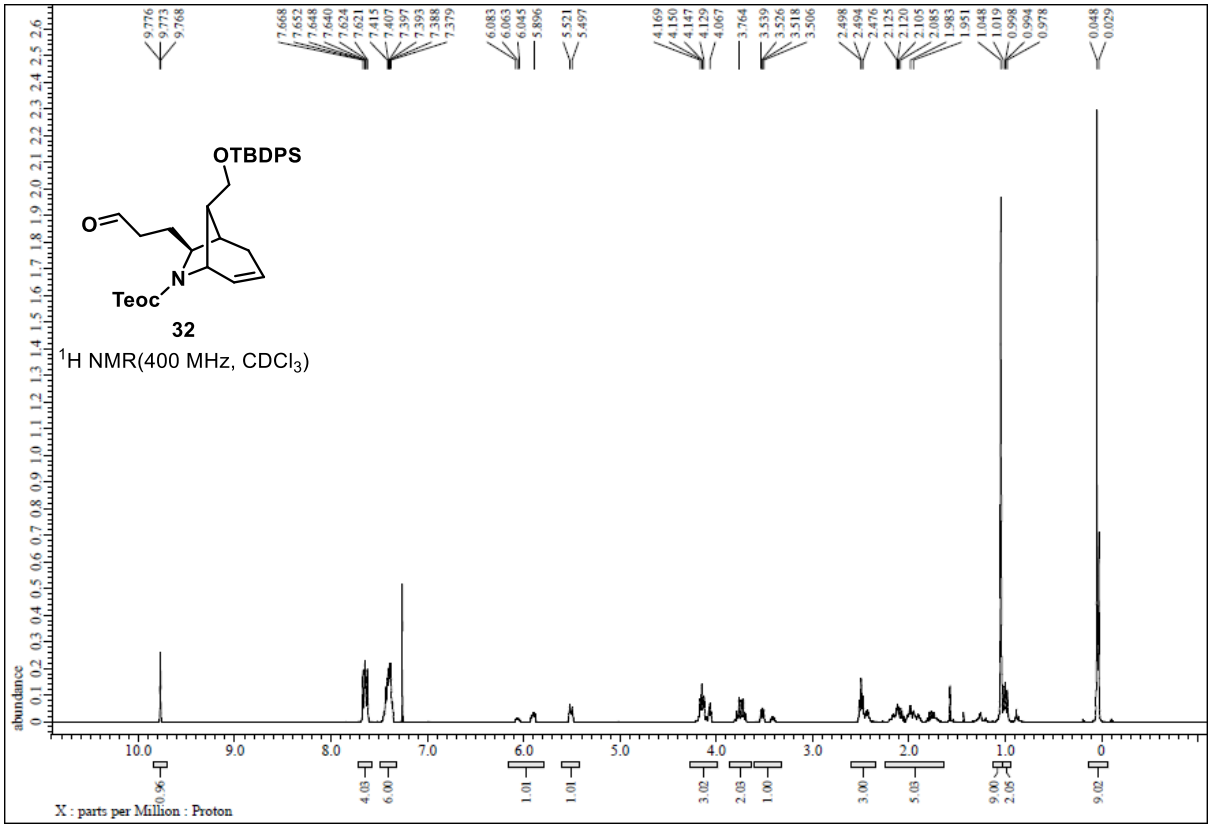

OTBDPS
N
Teoc
29
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

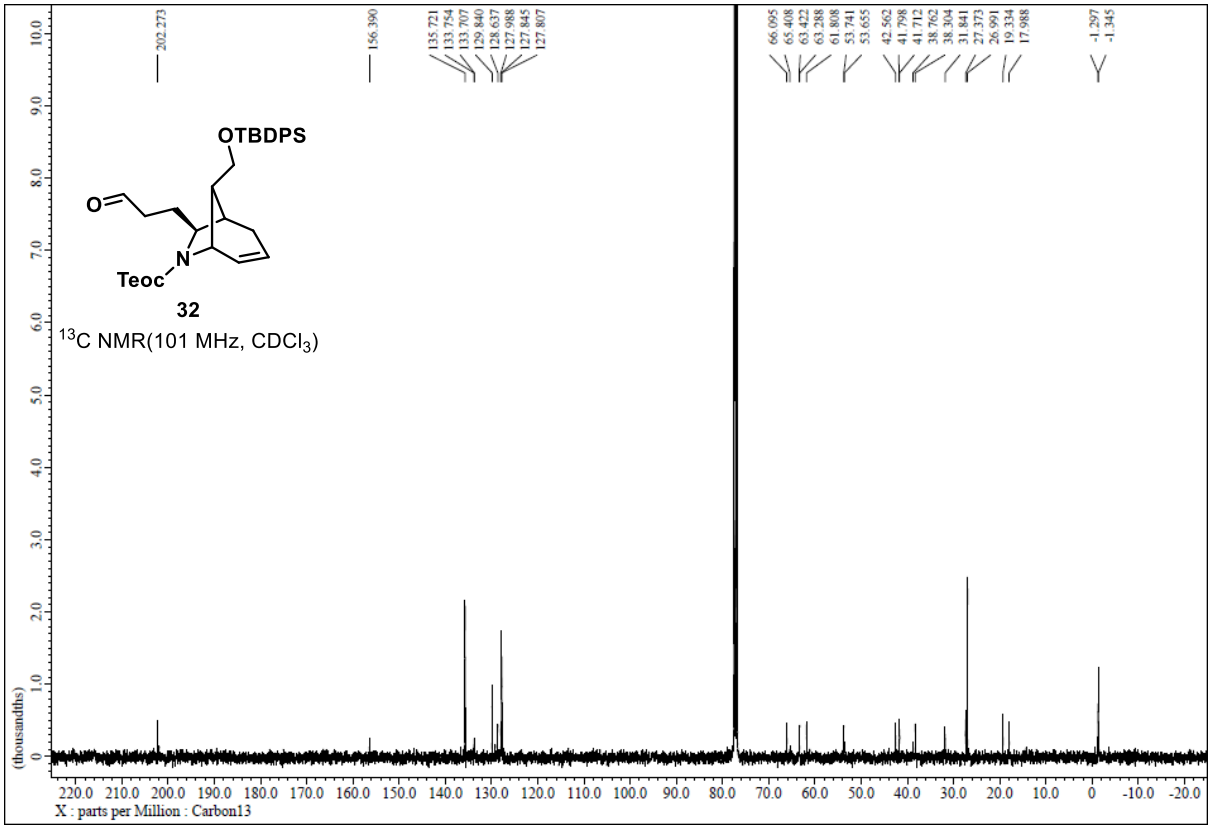

OTBDPS
Teoc
N
PhS
O
30
1H NMR(400 MHz, CDCl3)
abundance
X : parts per Million : Proton

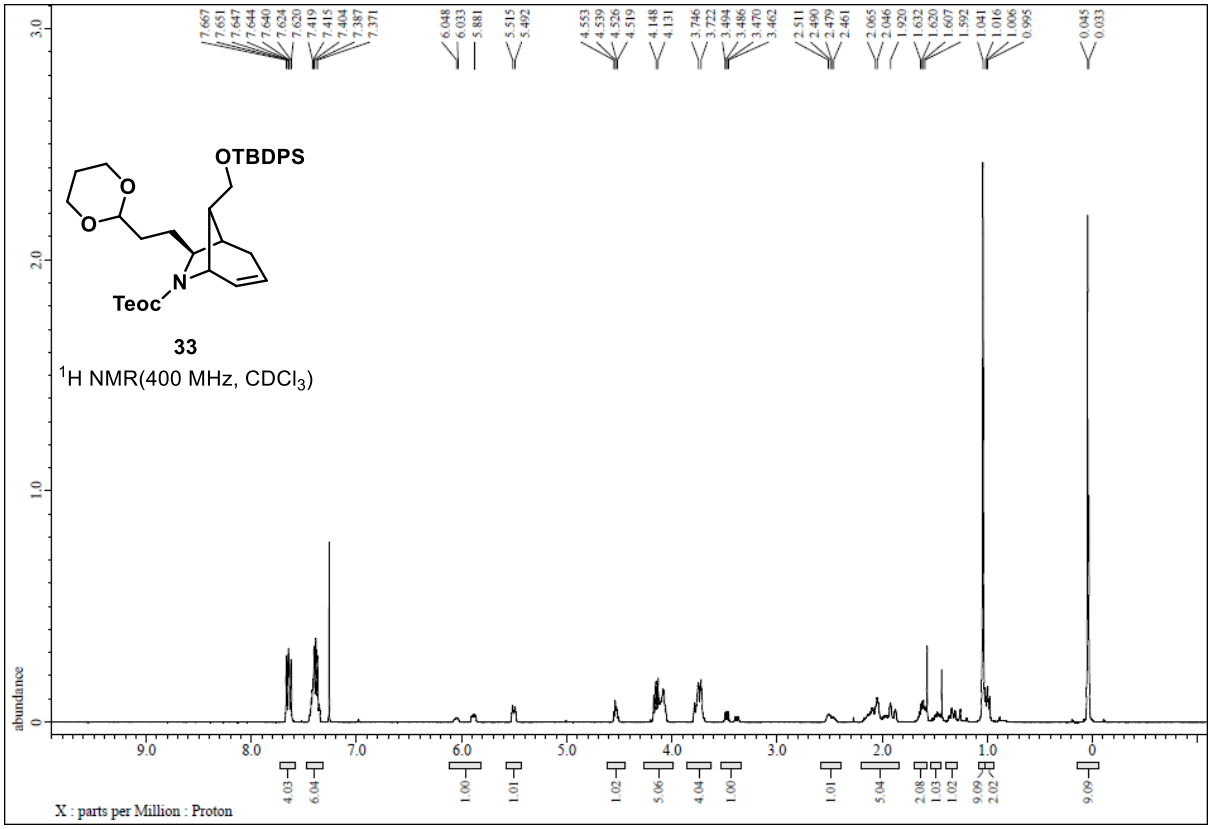

OTBDPS
Teoc
N
PhS
O
30
13C NMR(101 MHz, CDCl3)
(thousandths)
X : parts per Million : Carbon13

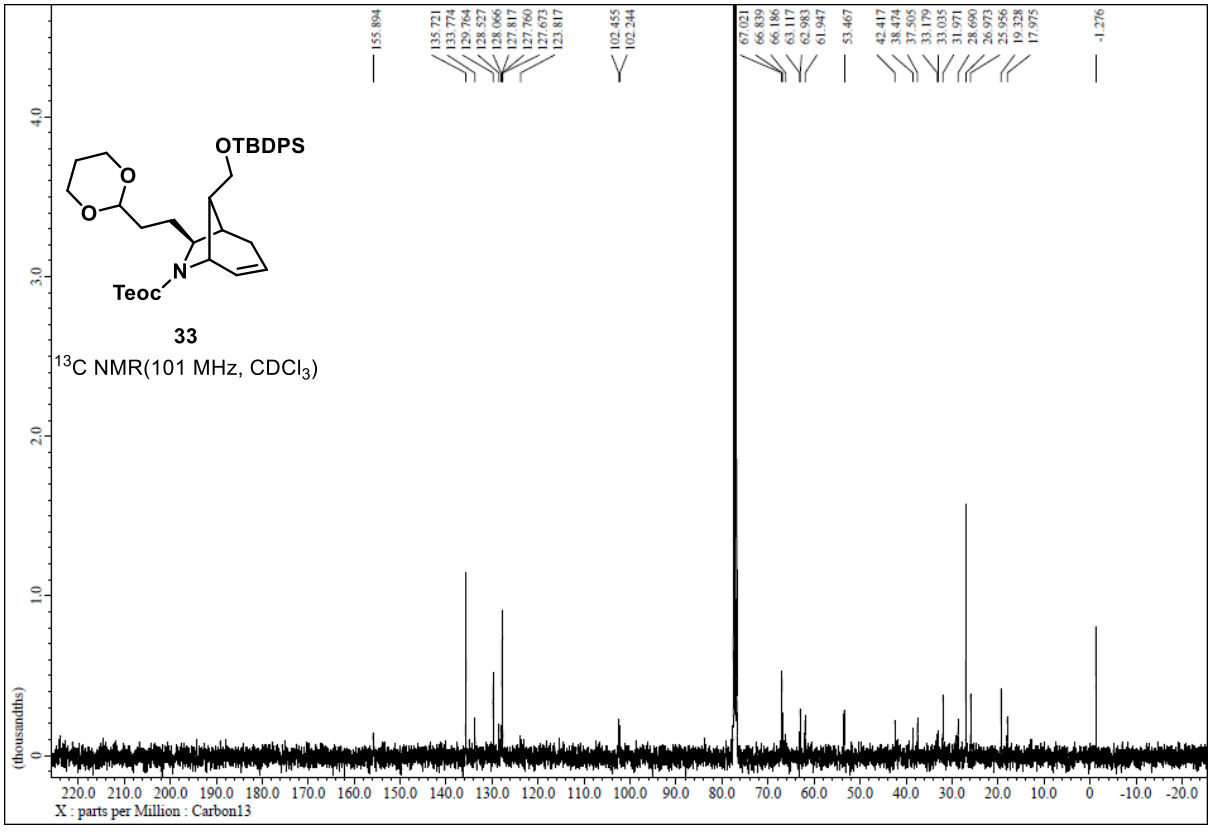

OTBDPS
HO
N
Teoc
31
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

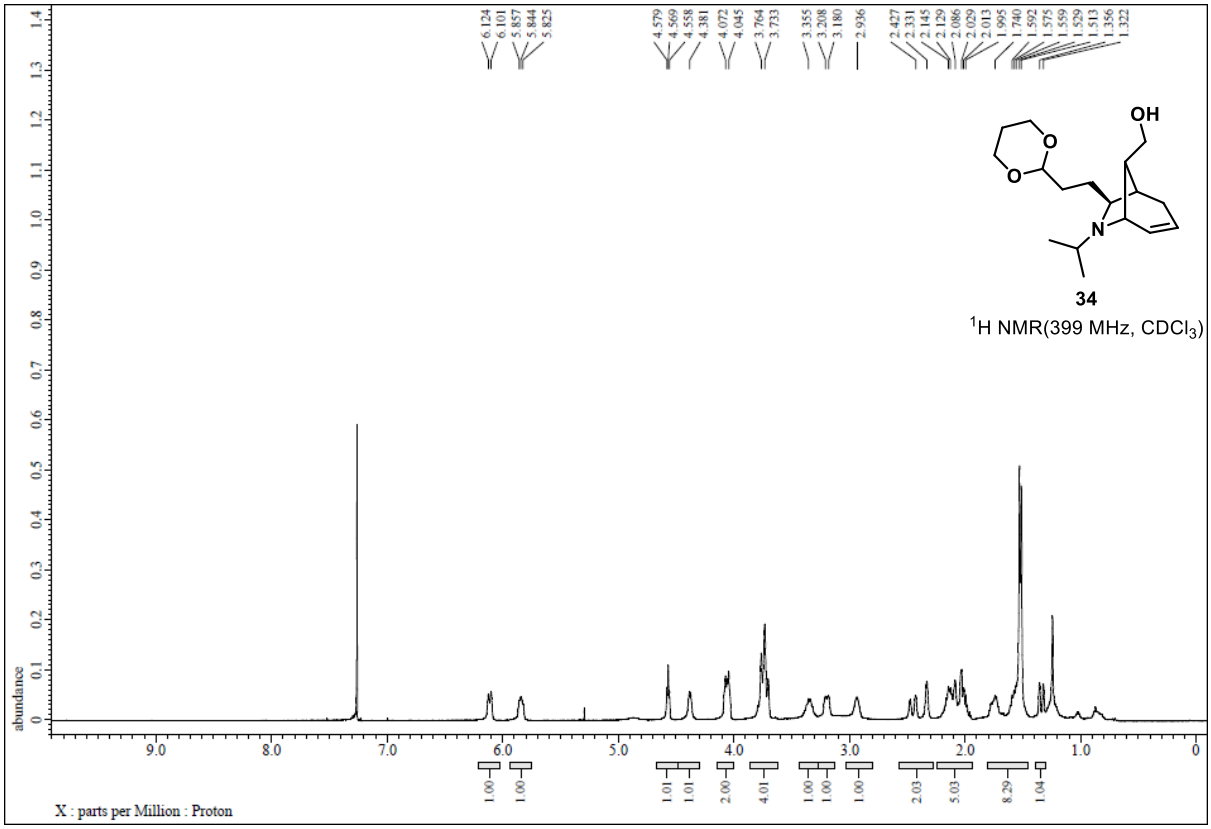

OTBDPS
HO
N
Teoc
31
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13


OTBDPS
O
N
Teoc
32
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


OTBDPS
O
N
Teoc
32
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

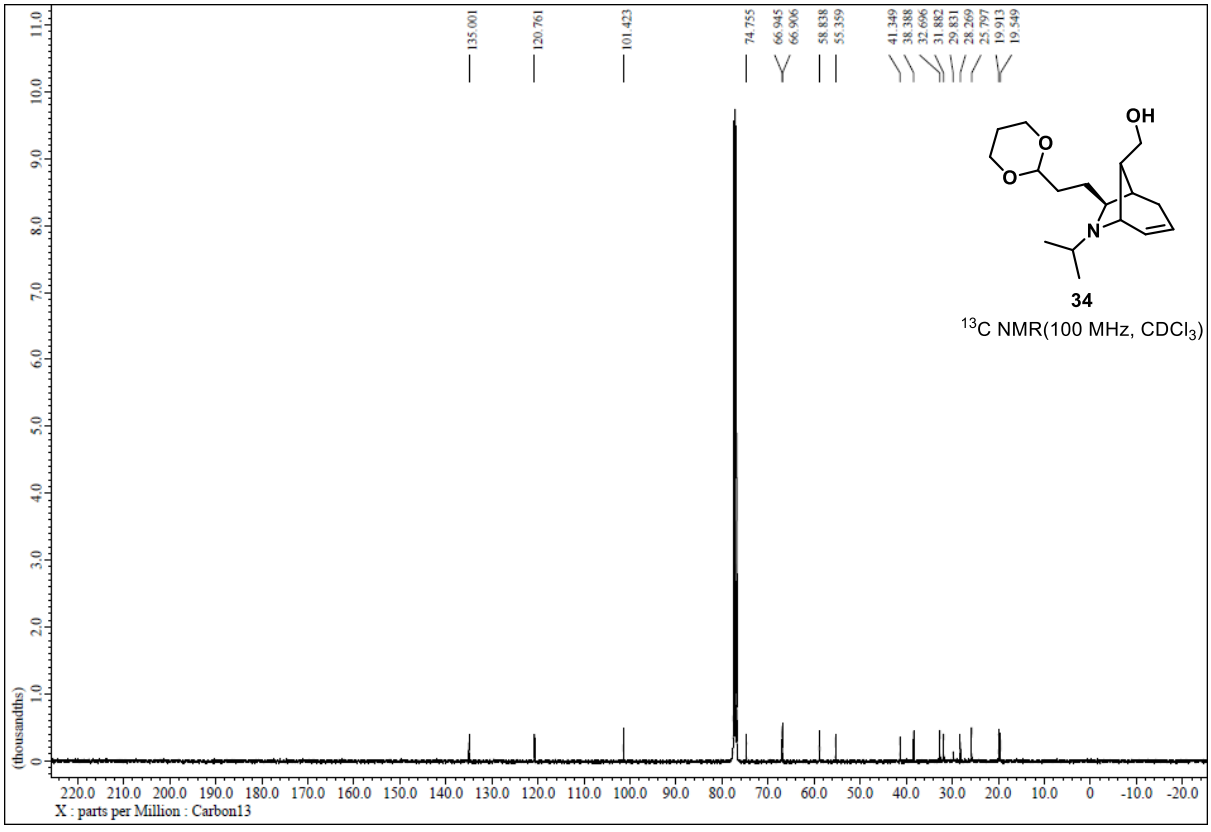

OTBDPS
O
O
N
Teoc
33
1H NMR(400 MHz, CDCl3)
abundance
X : parts per Million : Proton


OTBDPS
O
O
N
Teoc
33
13C NMR(101 MHz, CDCl3)
(thousandths)
X : parts per Million : Carbon13



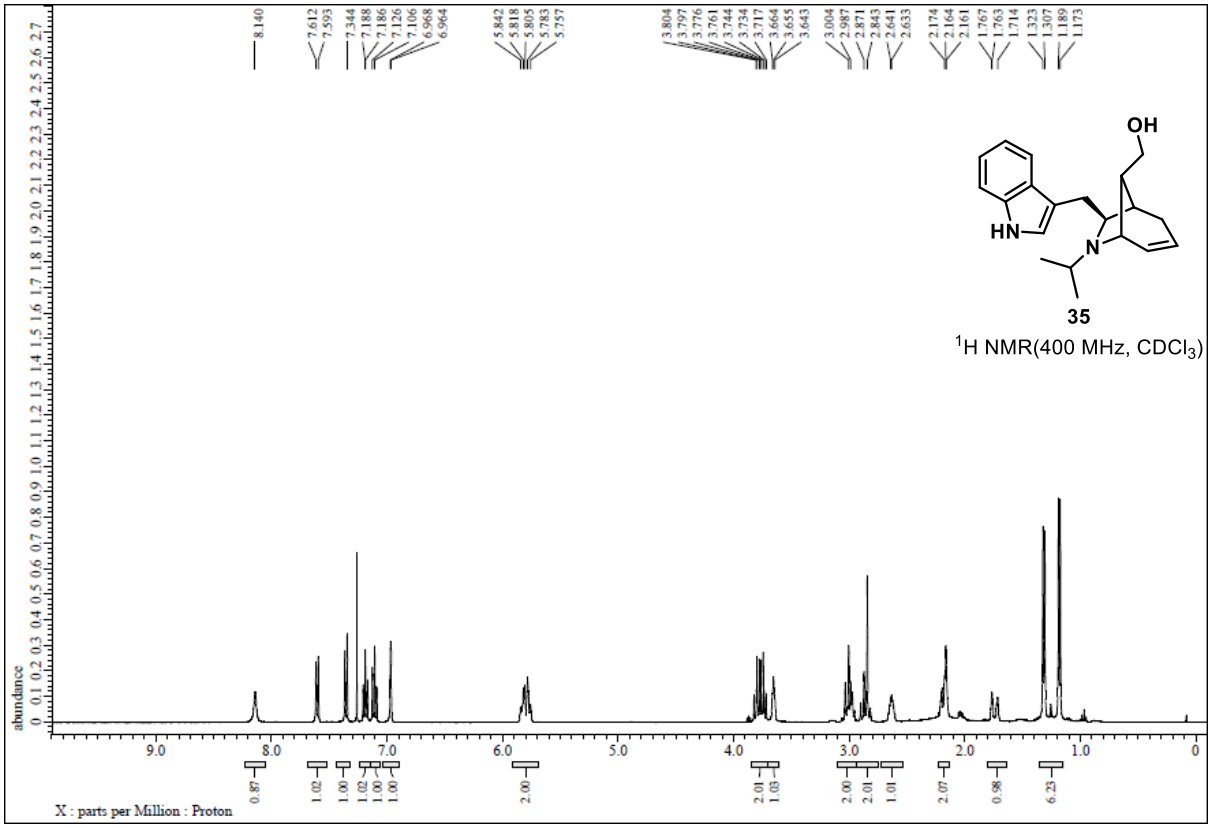
34

^{1}H NMR(399 MHz, $CDCl_3$)

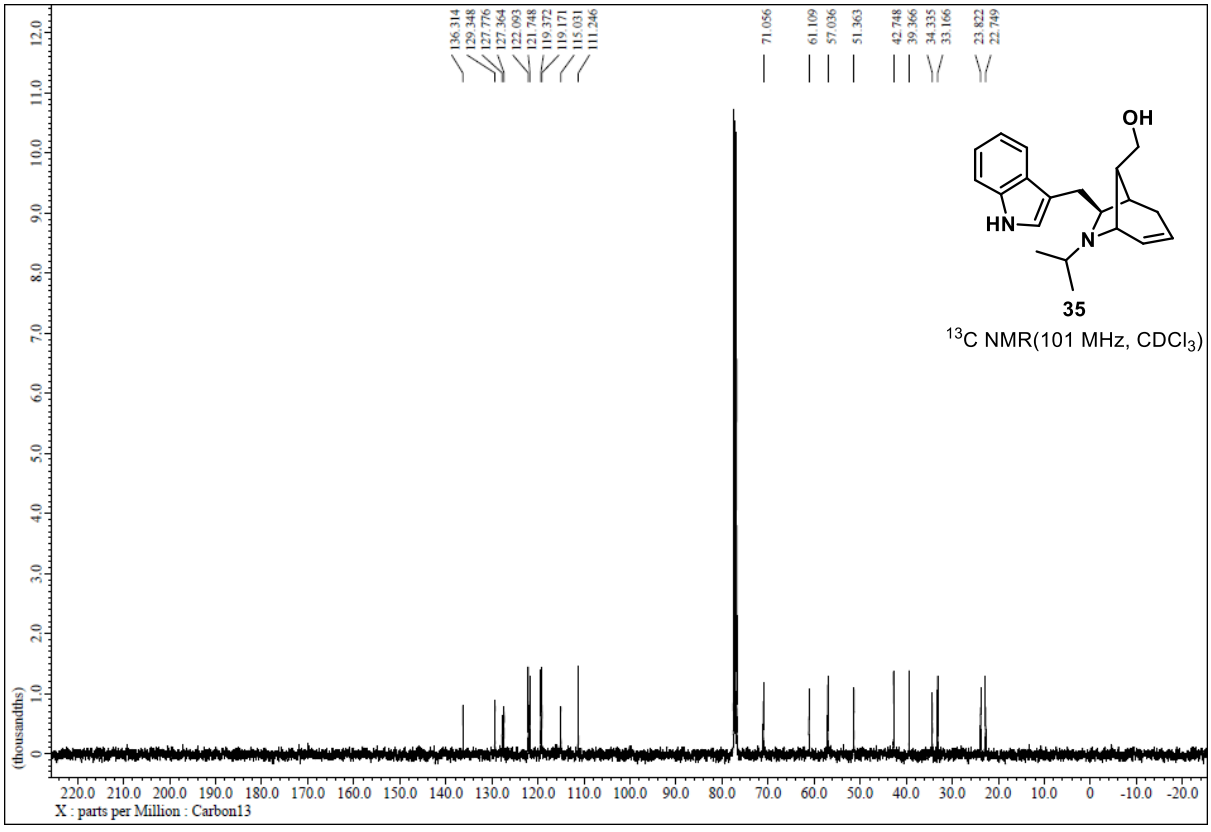


34

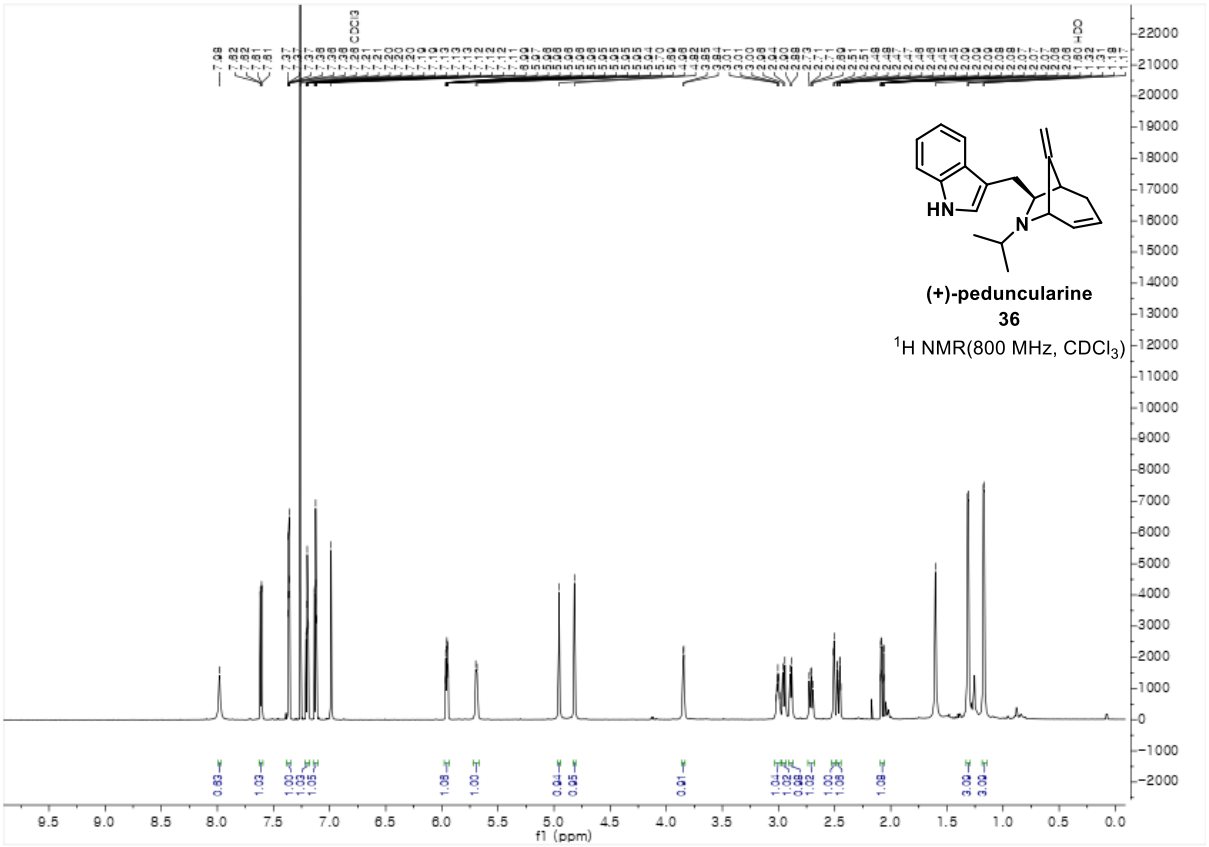
^{13}C NMR(100 MHz, $CDCl_3$)

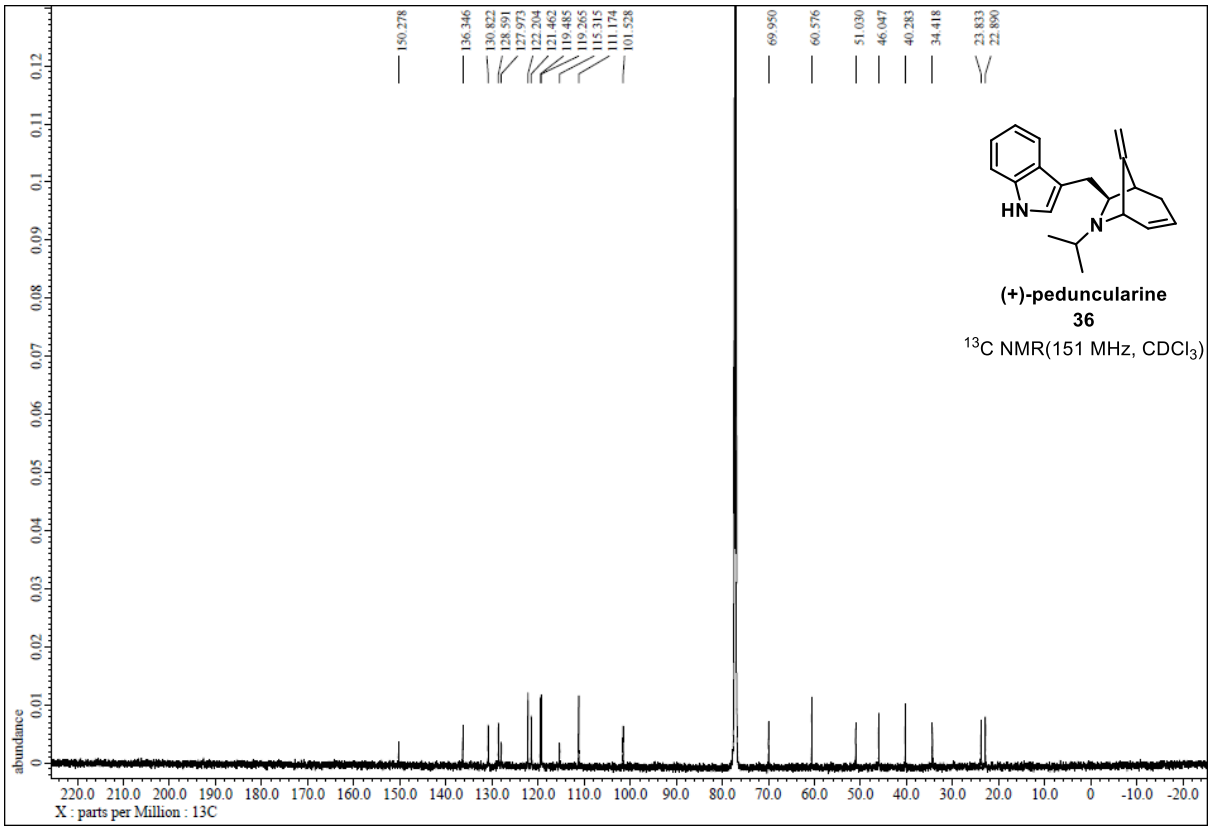


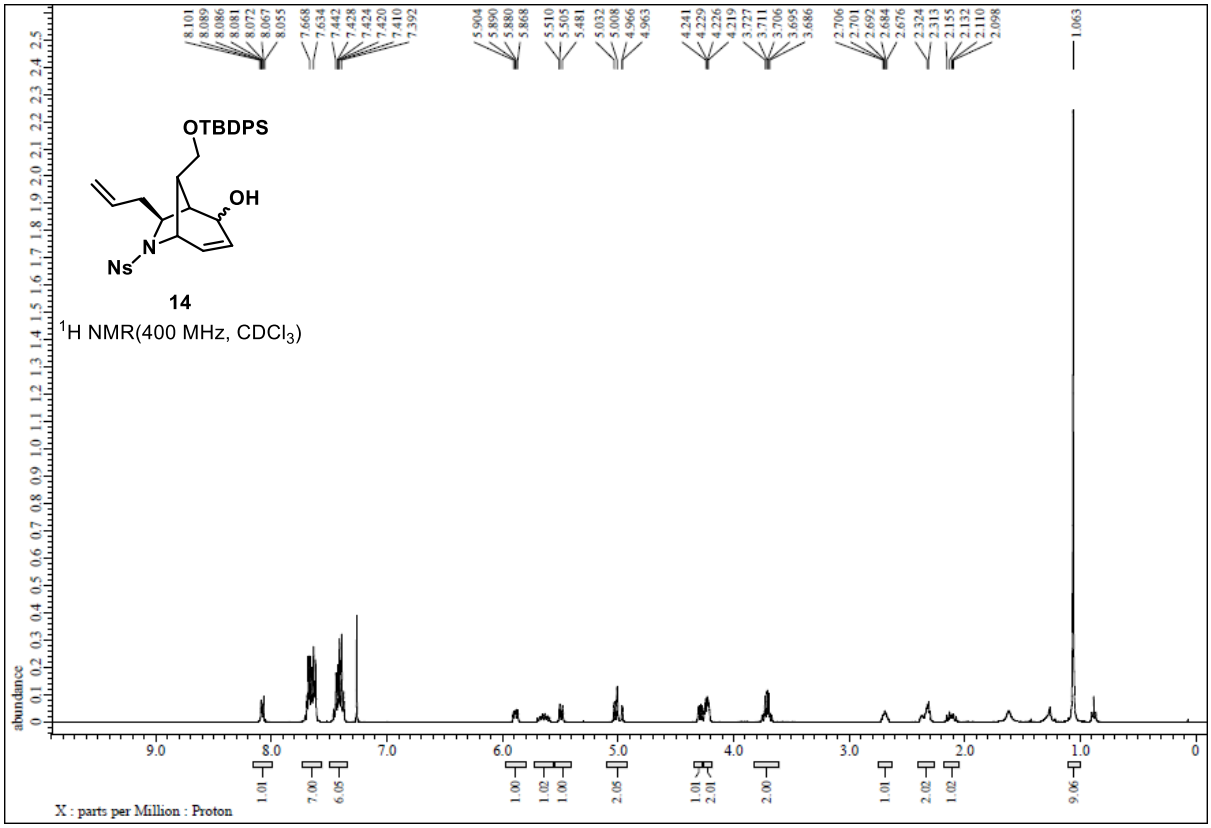
^{1}H NMR(400 MHz, $CDCl_3$)

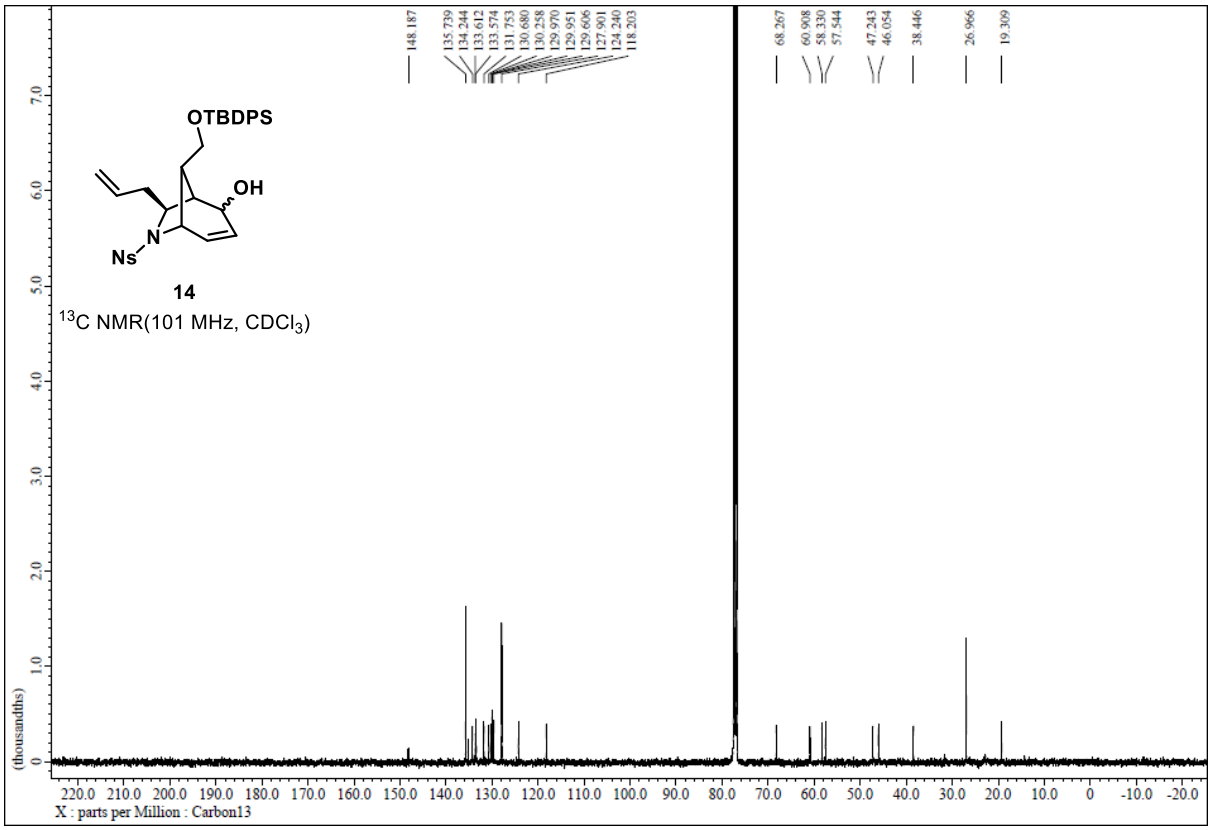


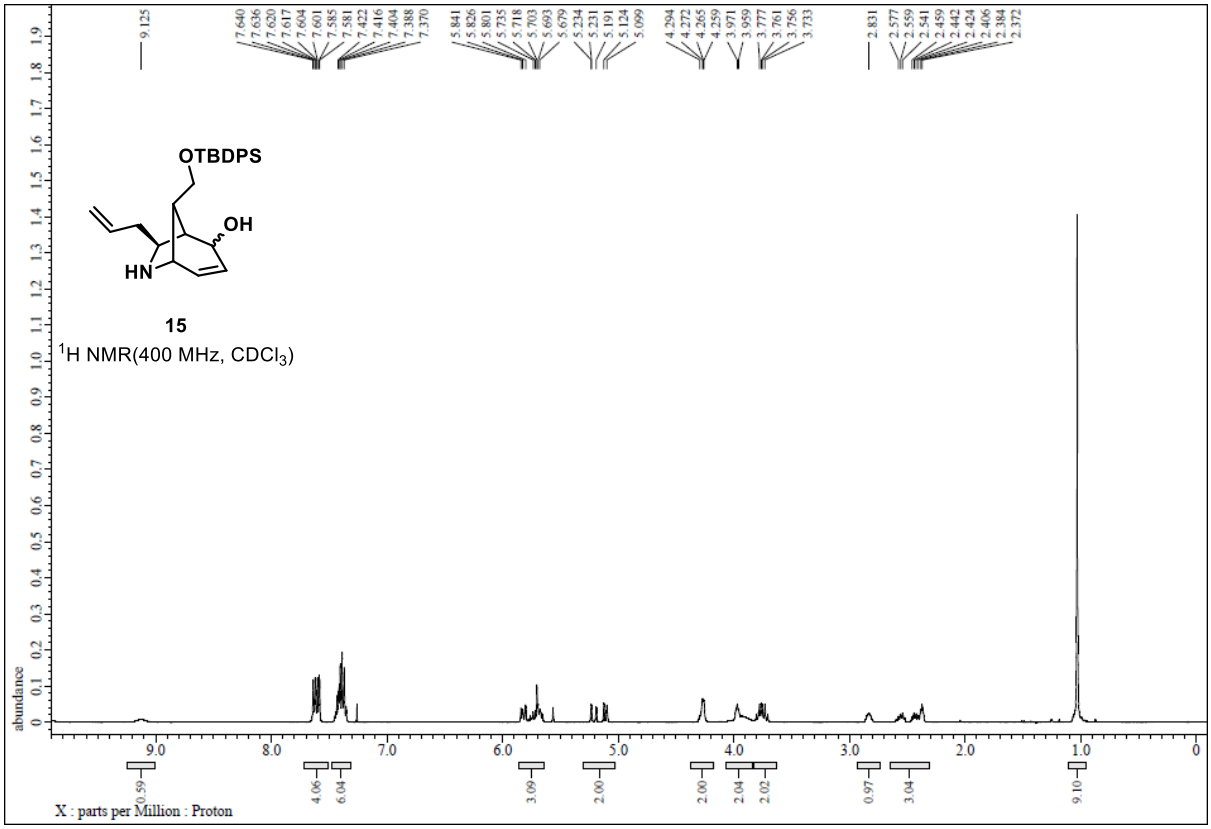
^{13}C NMR(101 MHz, $CDCl_3$)

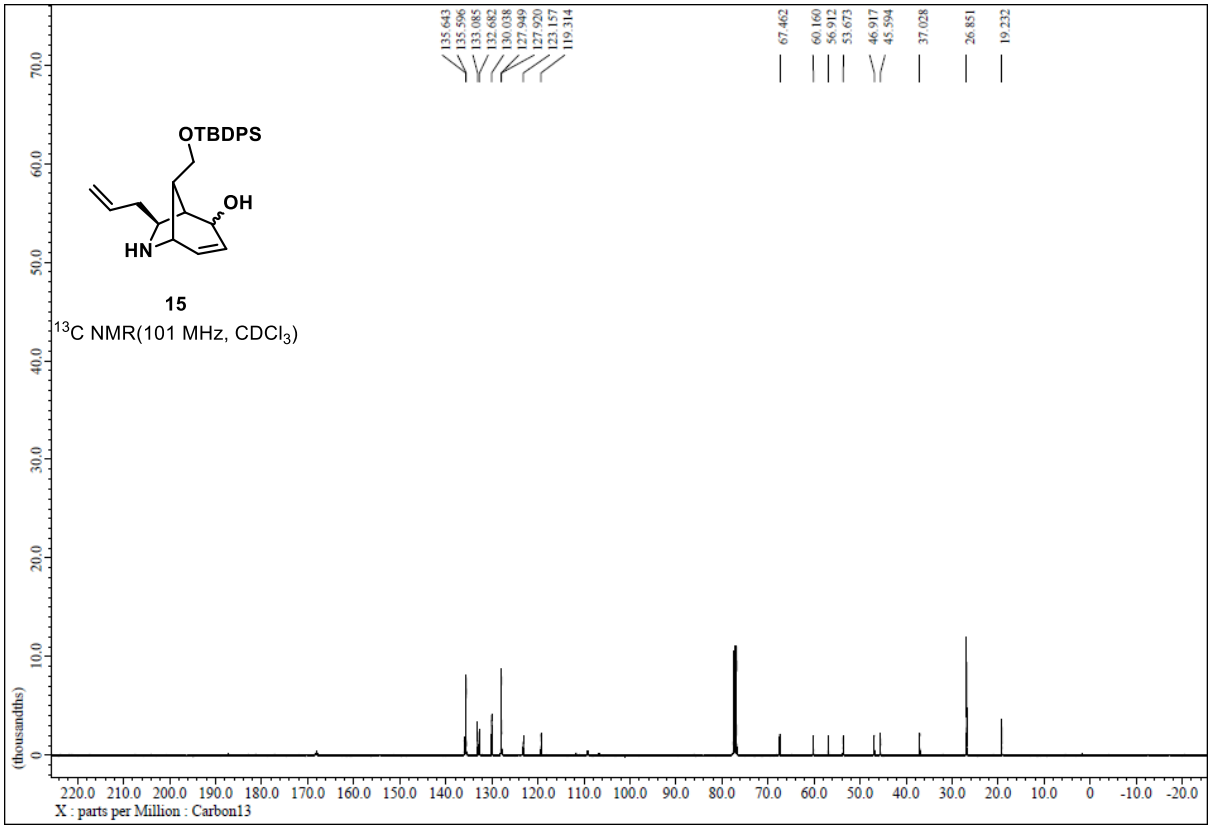

HN
N
(+)-peduncularine
36
^{1}H NMR(800 MHz, $CDCl_3$)
f1 (ppm)

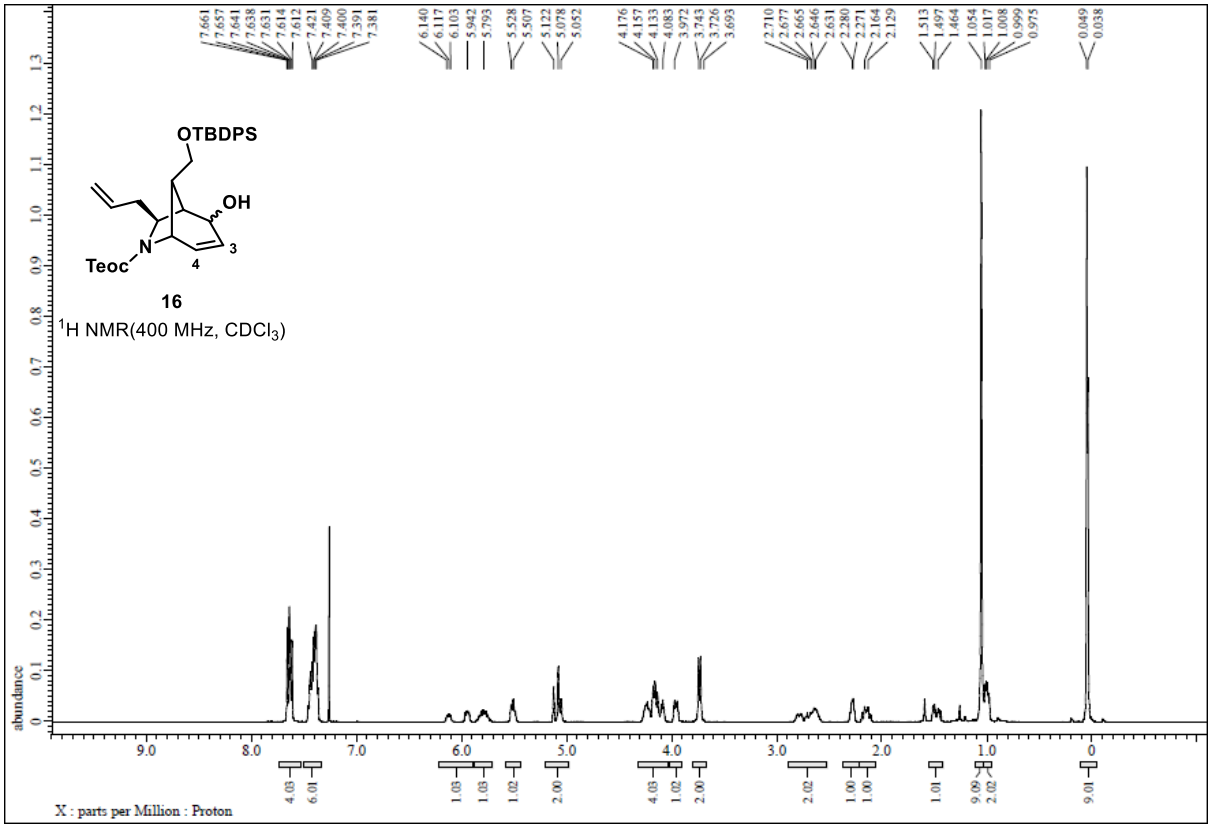

150.278
136.346
130.822
128.591
127.973
122.204
121.462
119.485
119.265
115.315
111.174
101.528
69.950
60.576
51.030
46.047
40.283
34.418
23.833
22.890
HN
N
(+)-peduncularine
36
^{13}C NMR(151 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C

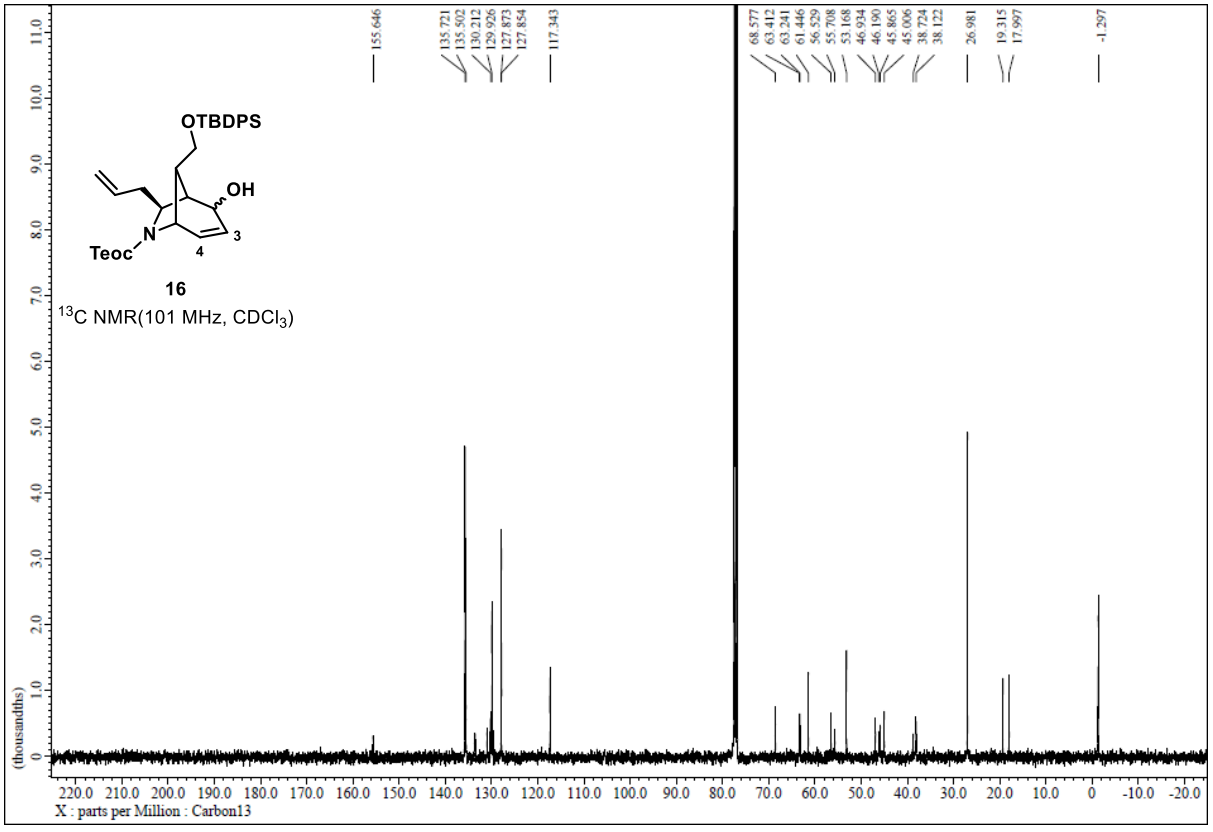

OTBDPS
OH
N
Ns
14
1H NMR(400 MHz, CDCl3)
X : parts per Million : Proton

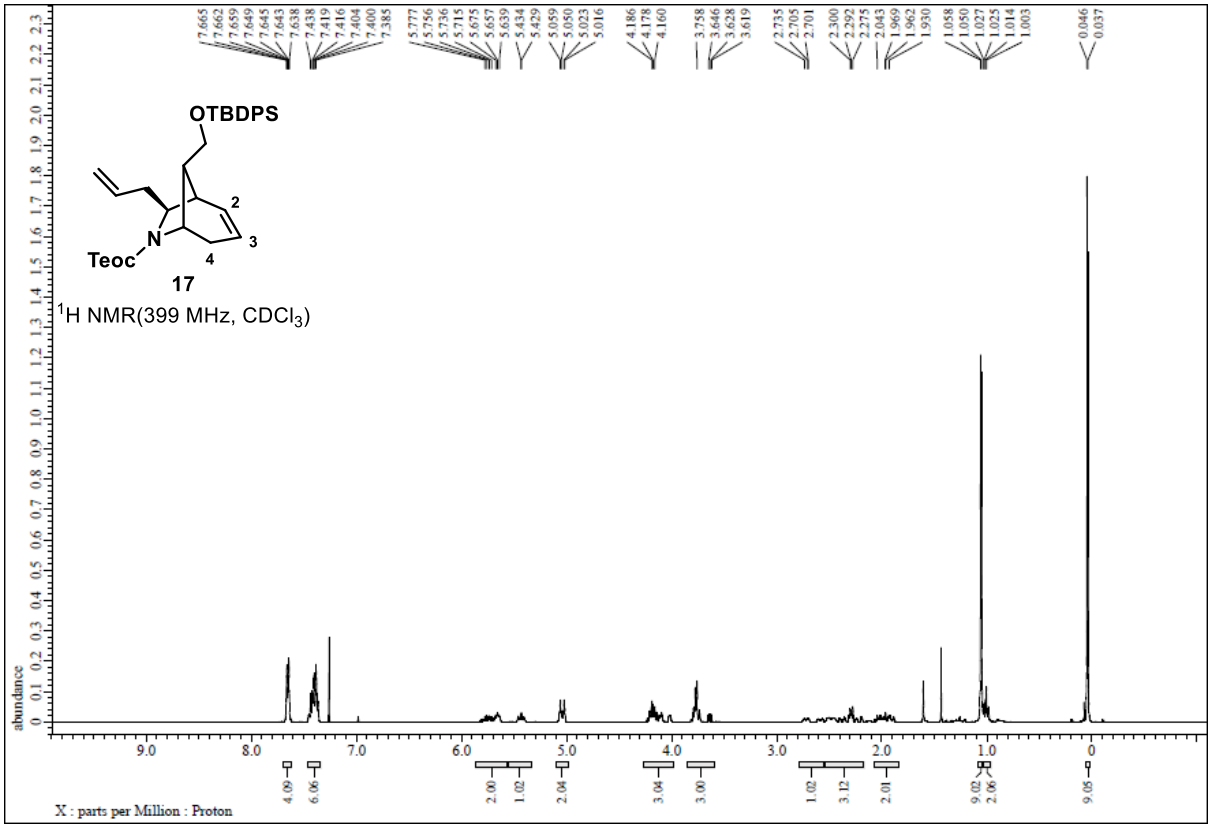

OTBDPS
OH
N
Ns
14
13C NMR(101 MHz, CDCl3)
X : parts per Million : Carbon13

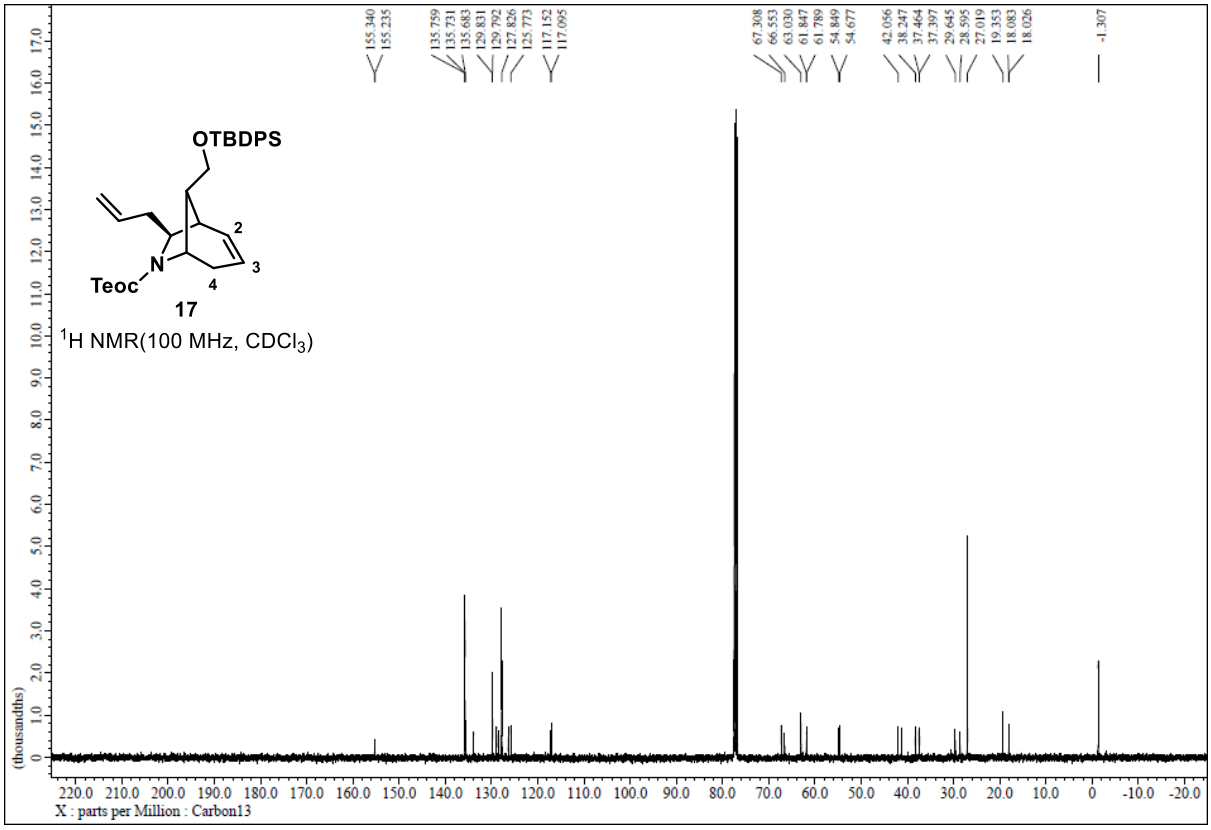

OTBDPS
OH
HN
15
1H NMR(400 MHz, CDCl3)
abundance
X : parts per Million : Proton

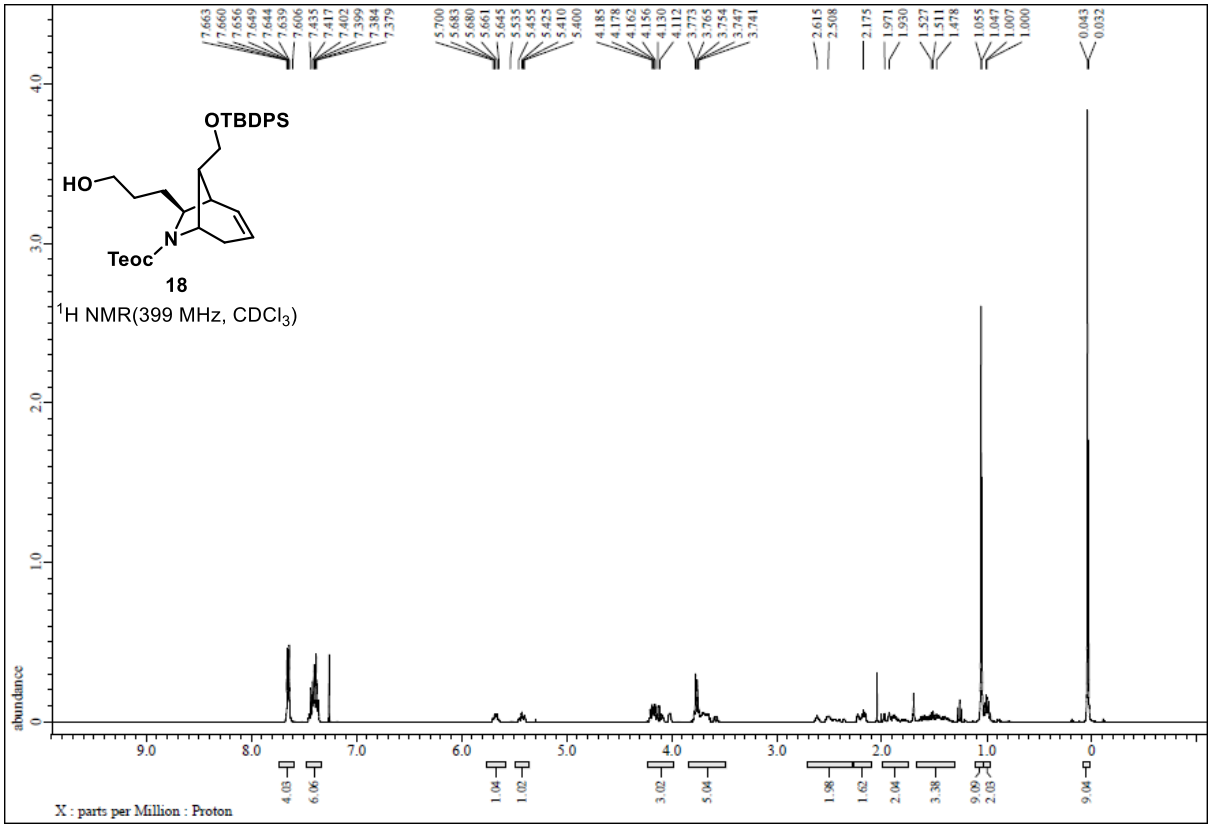

OTBDPS
OH
HN
15
13C NMR(101 MHz, CDCl3)
(thousandths)
X : parts per Million : Carbon13

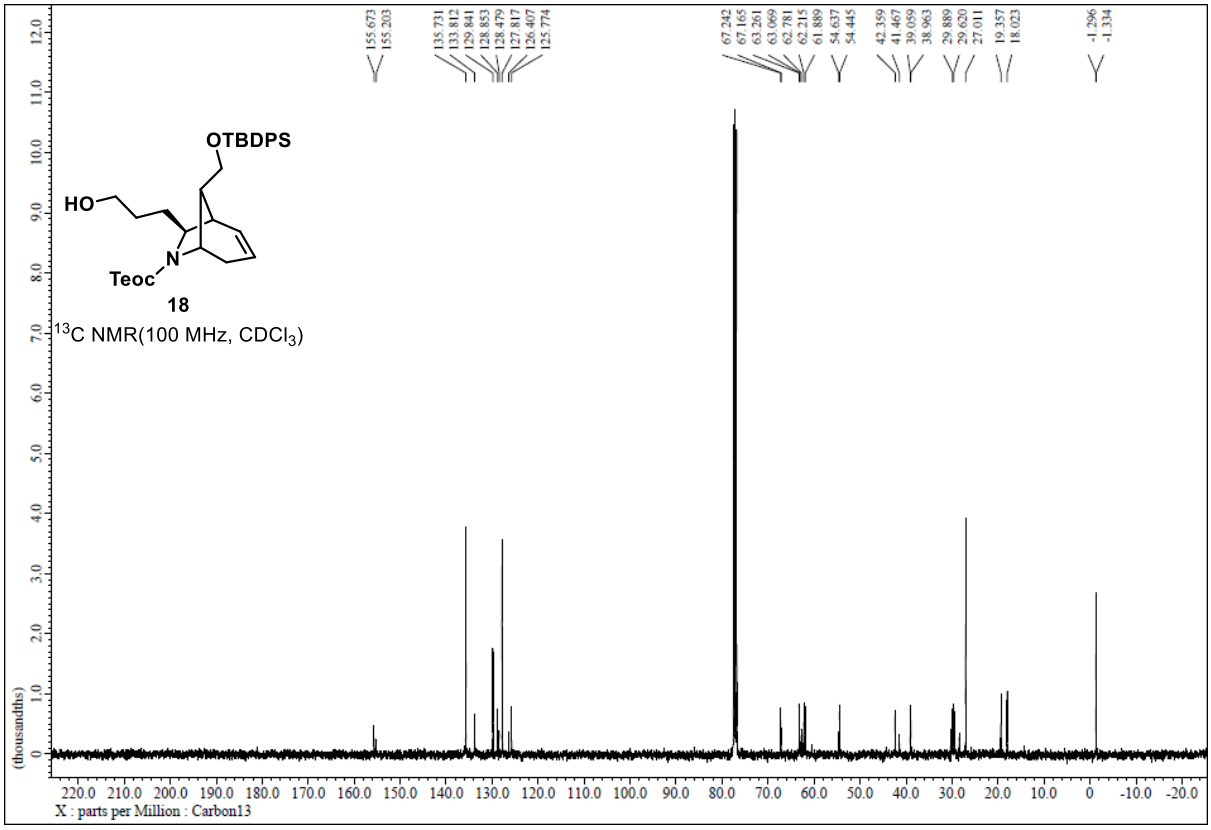

OTBDPS
OH
N
Teoc
3
4
16
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

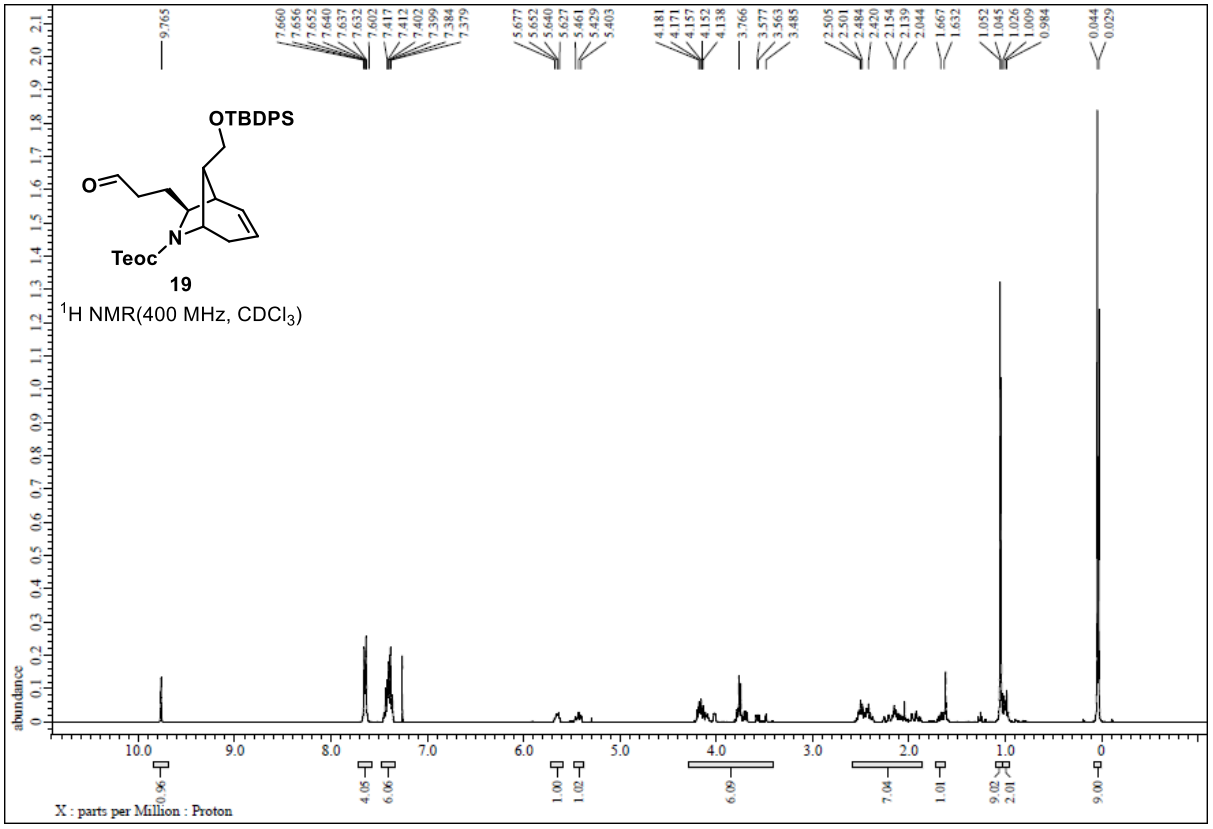

OTBDPS
OH
N
Teoc
3
4
16
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

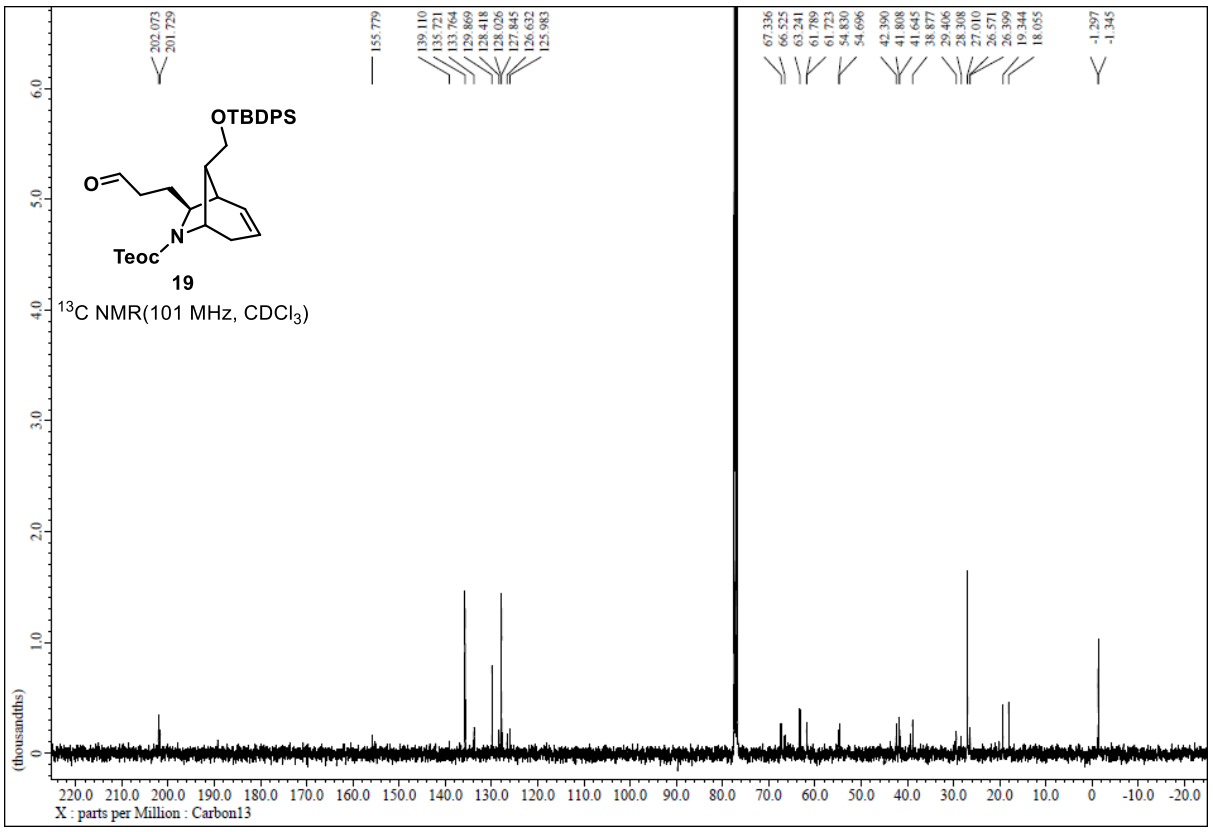

OTBDPS
Teoc
N
2
3
4
17
^{1}H NMR(399 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

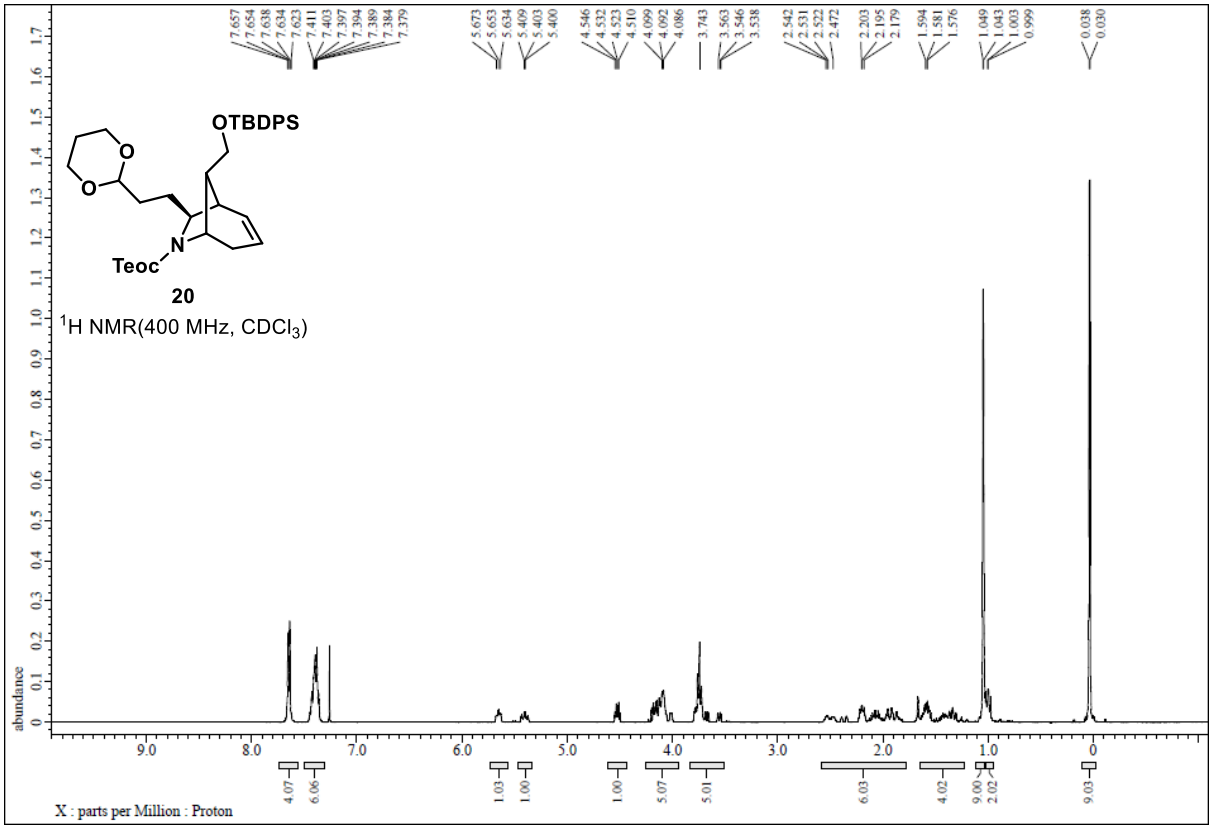

OTBDPS
Teoc
N
2
3
4
17
^{1}H NMR(100 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

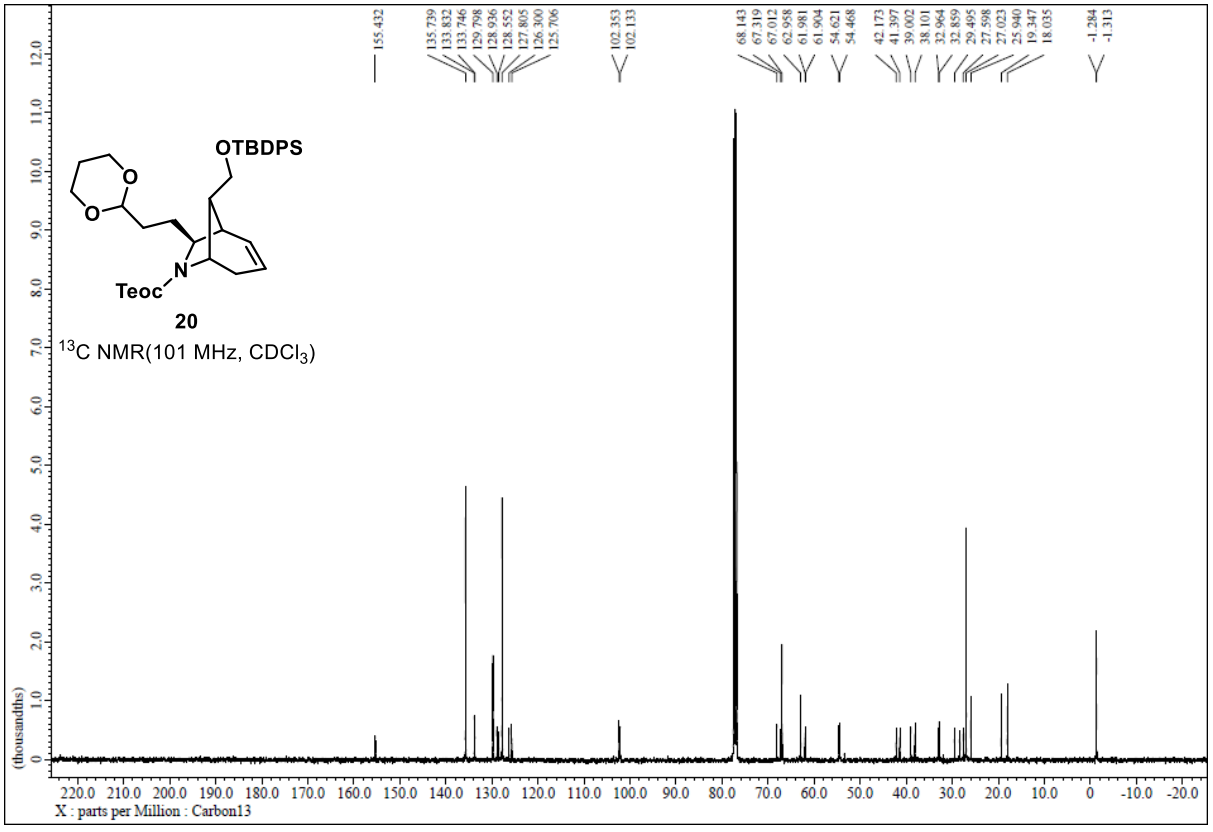

OTBDPS
HO
N
Teoc
18
^{1}H NMR(399 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

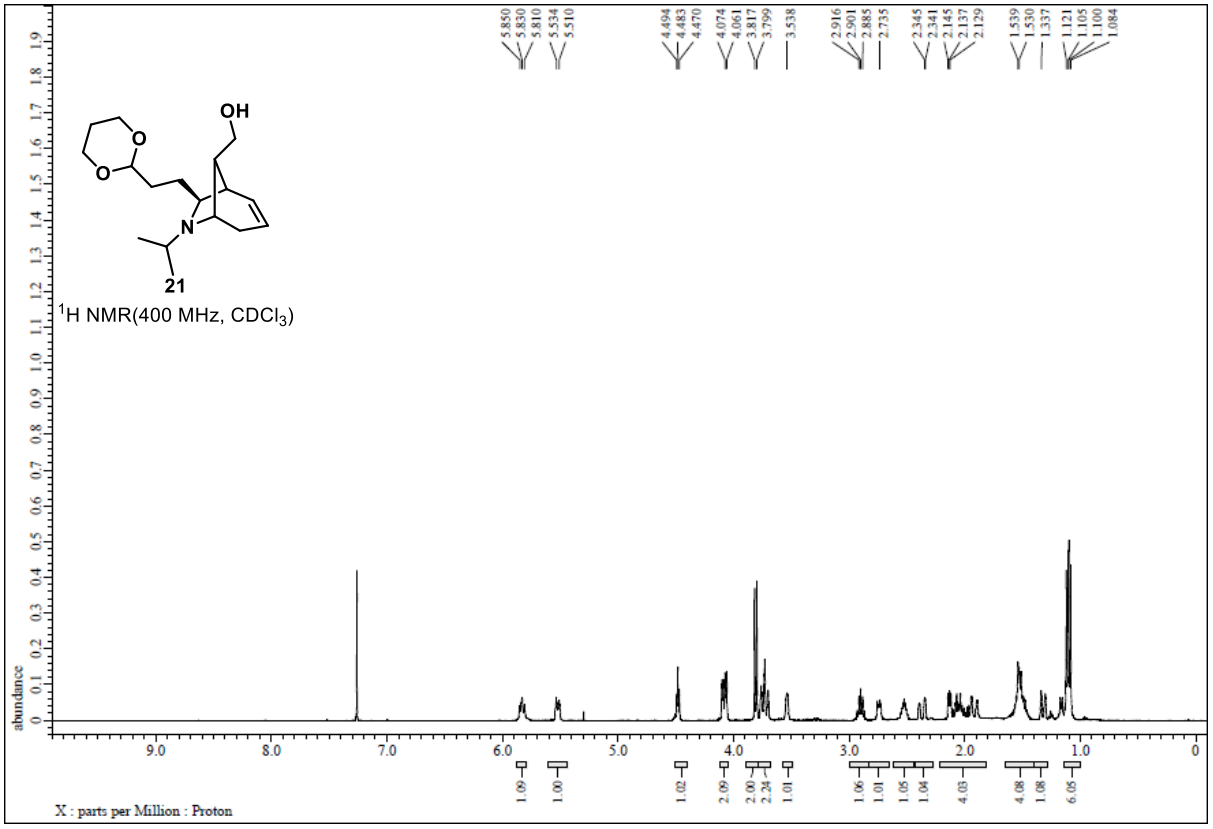

OTBDPS
HO
N
Teoc
18
^{13}C NMR(100 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

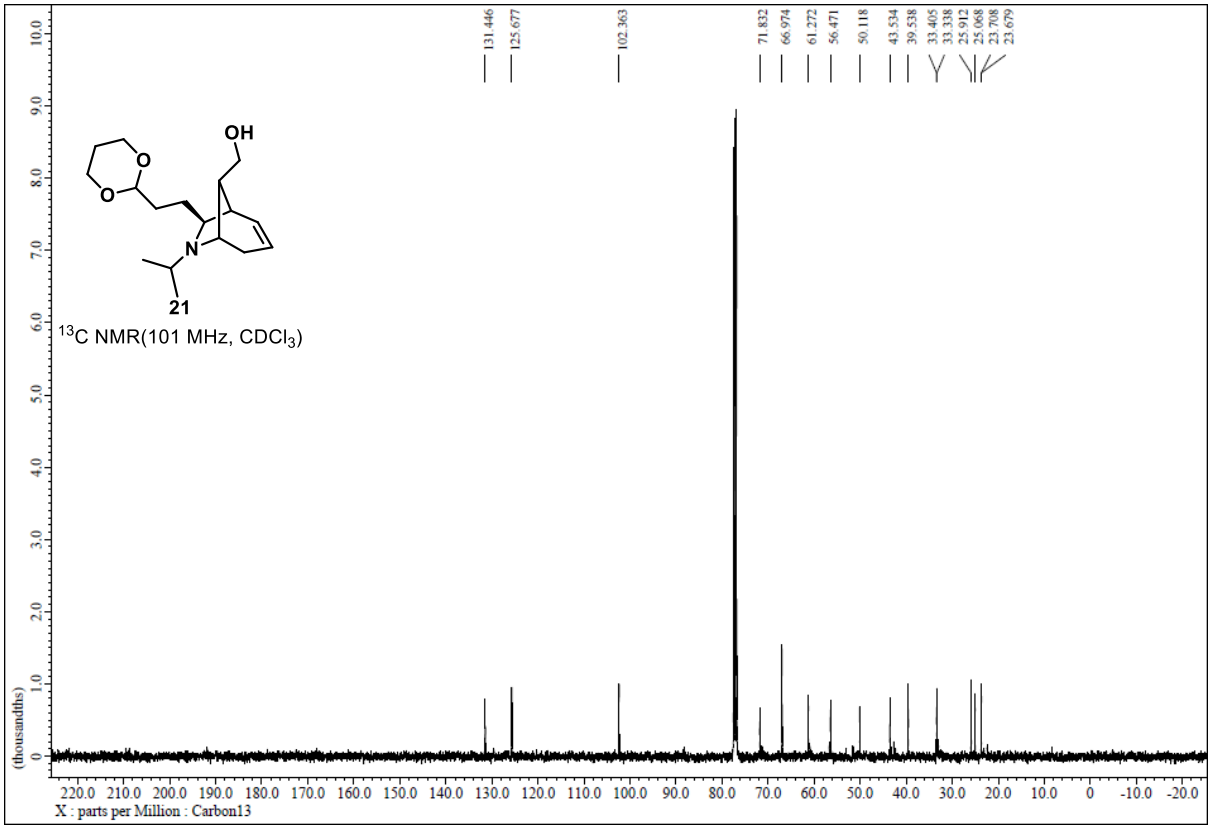

OTBDPS
O
N
Teoc
19
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

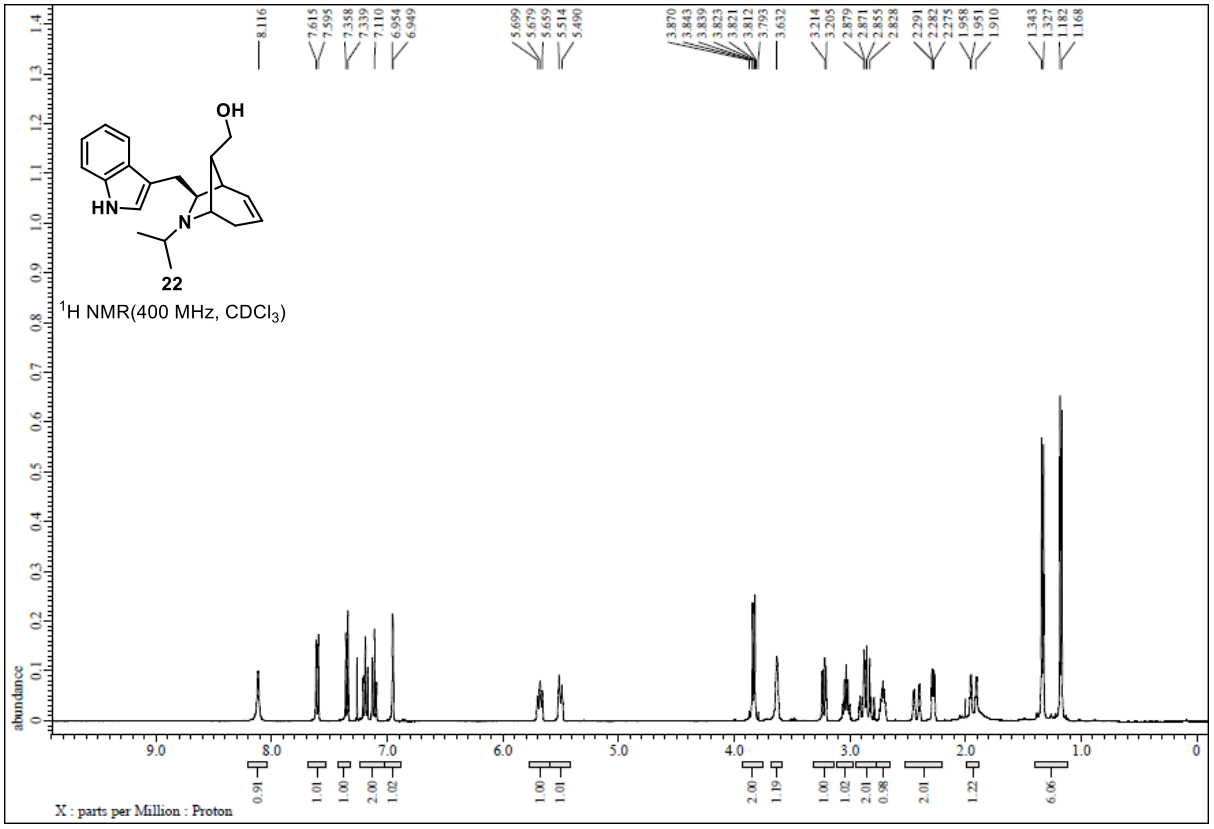

OTBDPS
O
N
Teoc
19
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13

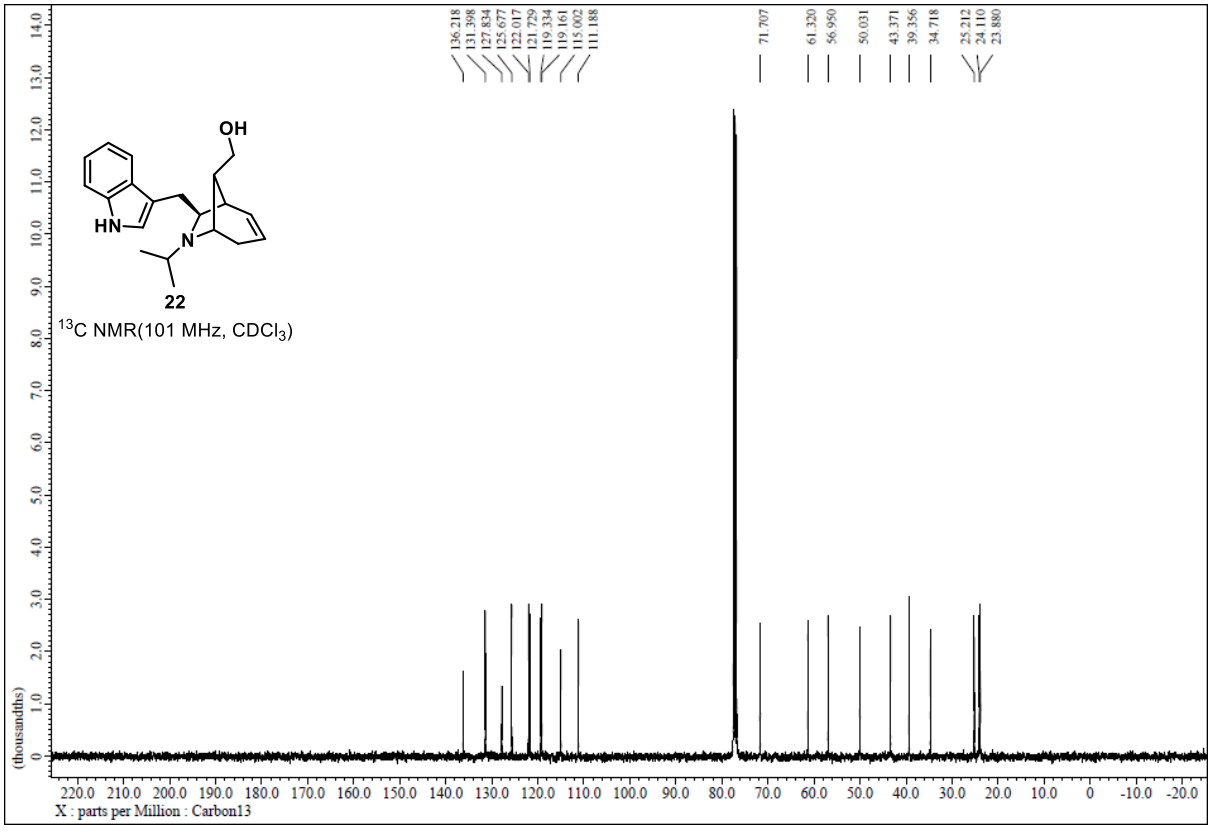

OTBDPS
O
O
N
Teoc
20
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton

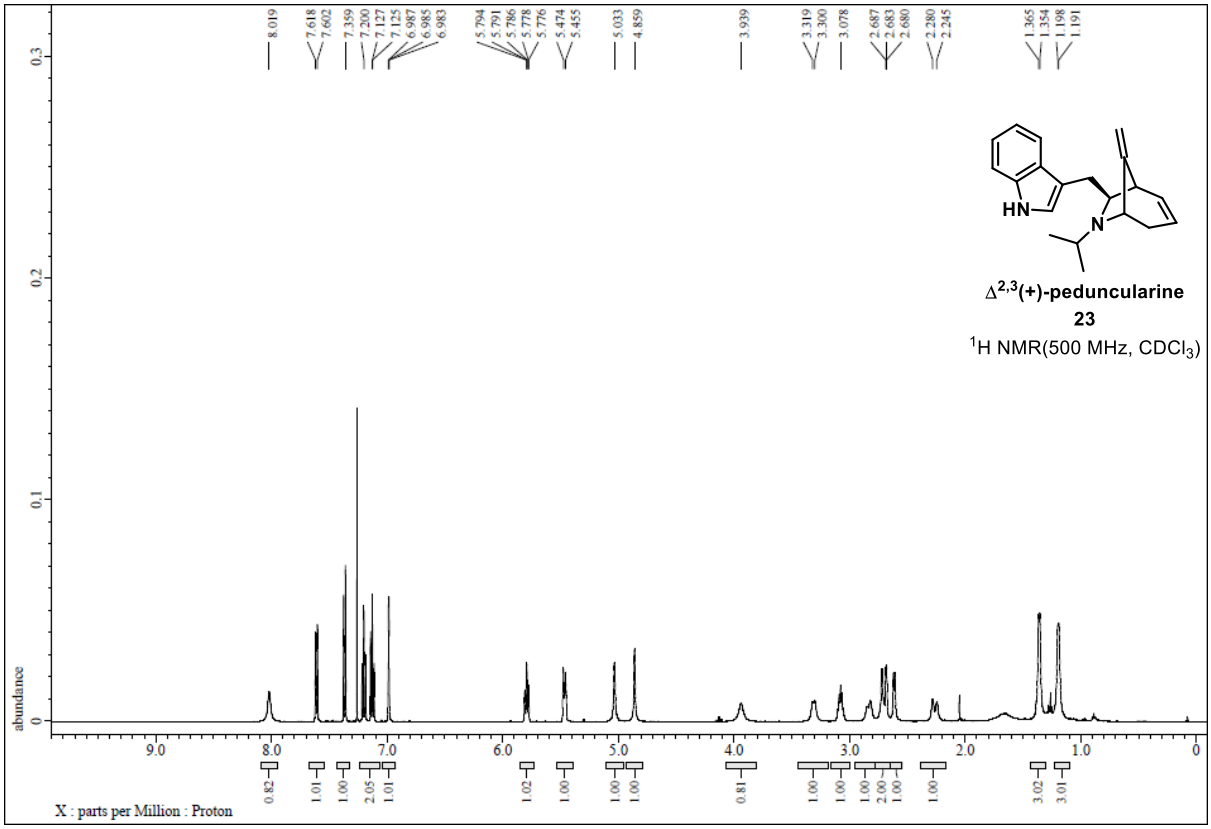

OTBDPS
O
O
N
Teoc
20
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13


OH
O
O
N
21
^{1}H NMR(400 MHz, $CDCl_3$)
abundance
X : parts per Million : Proton


OH
O
O
N
21
^{13}C NMR(101 MHz, $CDCl_3$)
(thousandths)
X : parts per Million : Carbon13


OH
HN
N
22
^{1}H NMR(400 MHz, CDCl$_3$)
abundance
X : parts per Million : Proton

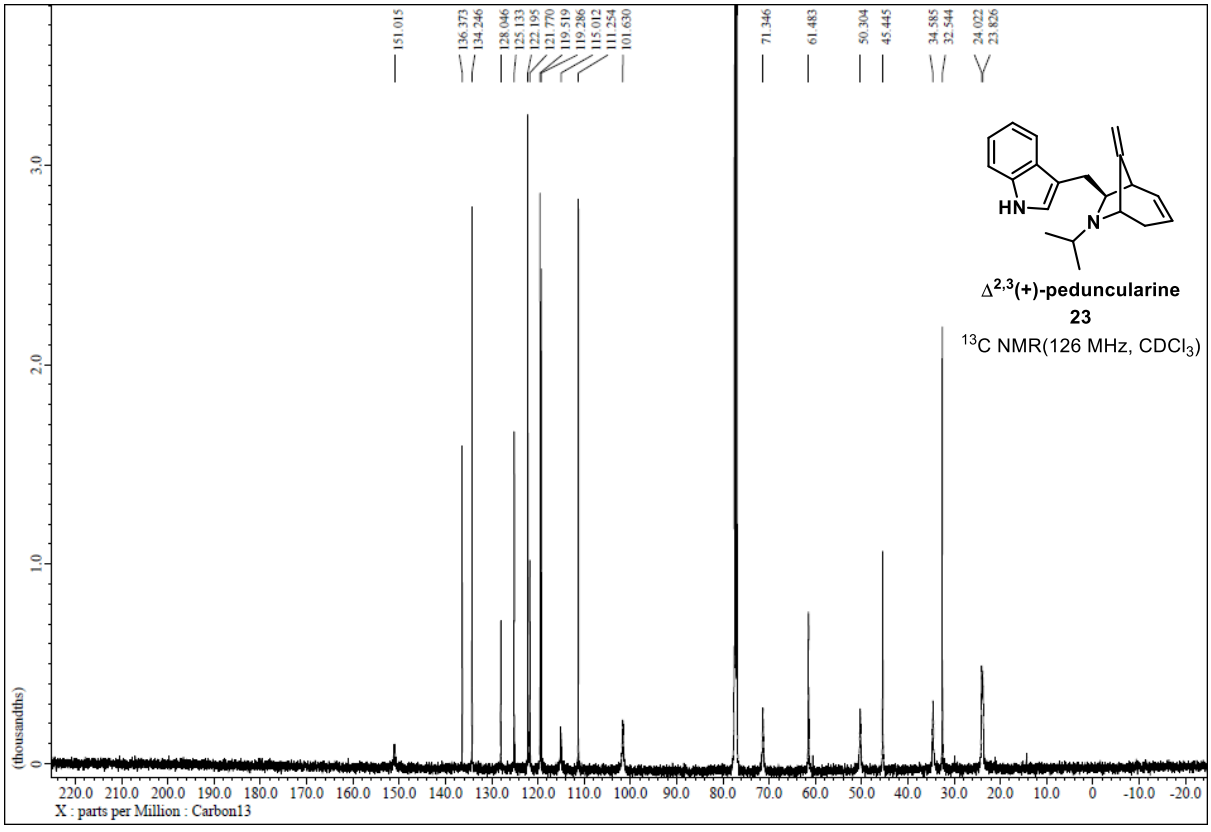

OH
HN
N
22
^{13}C NMR(101 MHz, CDCl$_3$)
(thousandths)
X : parts per Million : Carbon13



$\Delta^{2,3}$(+)-peduncularine

23

^{1}H NMR(500 MHz, $CDCl_3$)



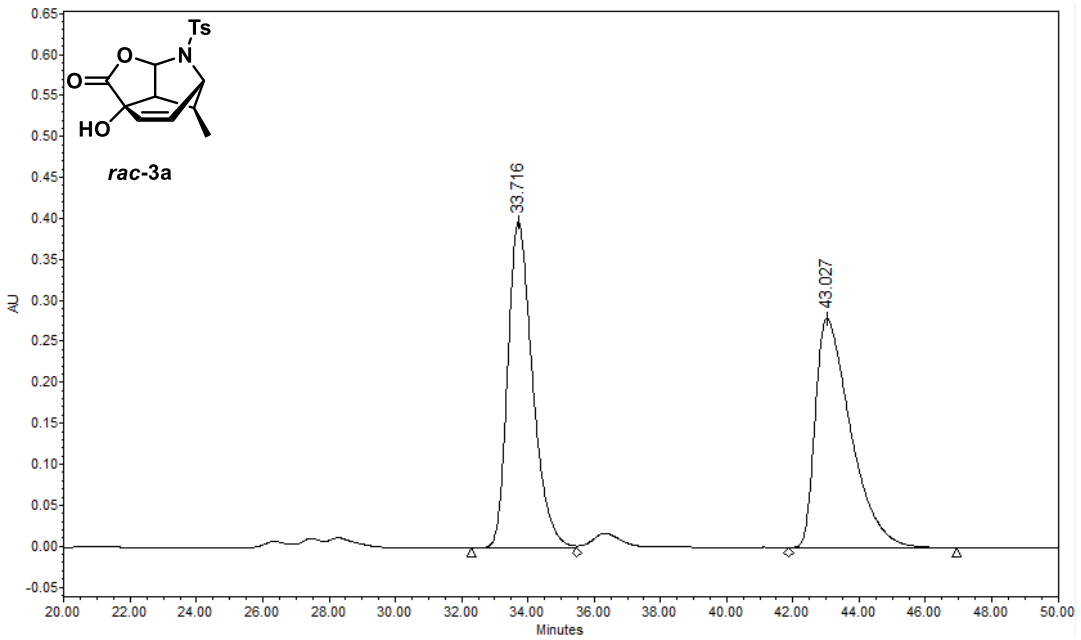
$\Delta^{2,3}$(+)-peduncularine

23

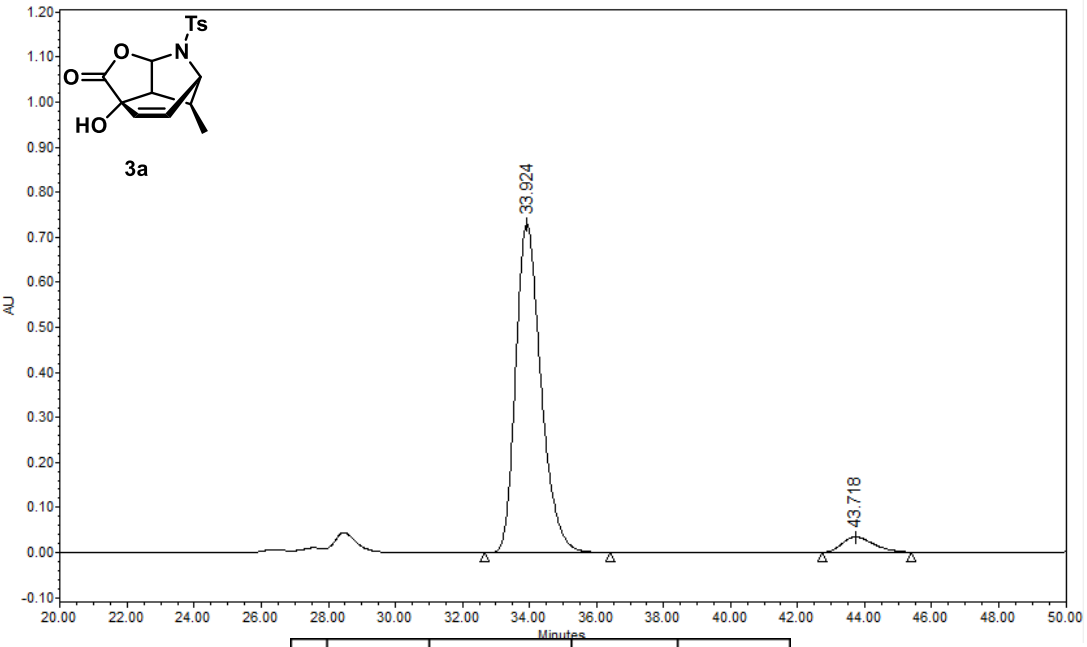
^{13}C NMR(126 MHz, $CDCl_3$)

V. HPLC Traces

AD-H, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 0.5 mL/min (**3a**)

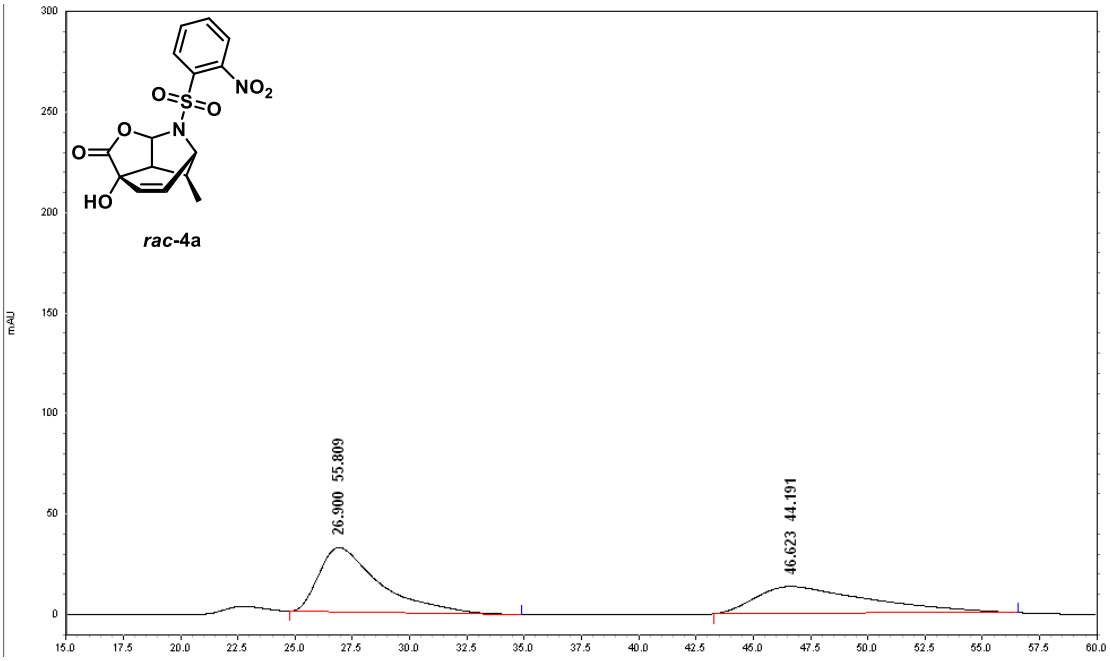


	RT	Area	% Area	Height
1	33.716	20730731	49.82	397240
2	43.027	20878592	50.18	280230

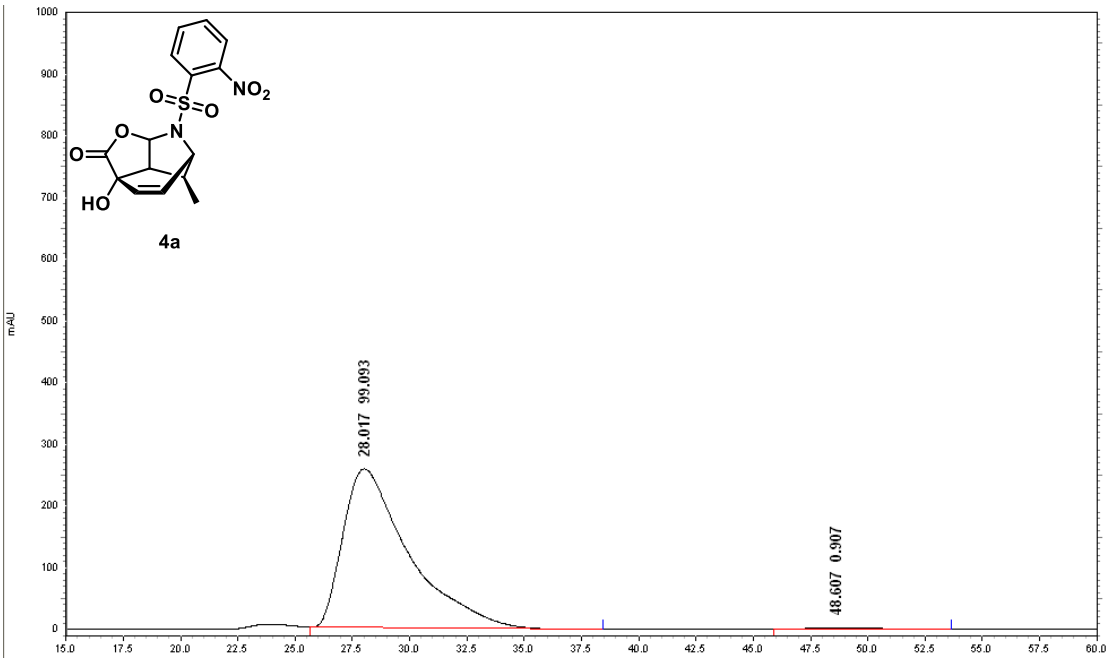


	RT	Area	% Area	Height
1	33.924	38292808	94.55	730308
2	43.718	2207051	5.45	34131

AS-H, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (**4a**)

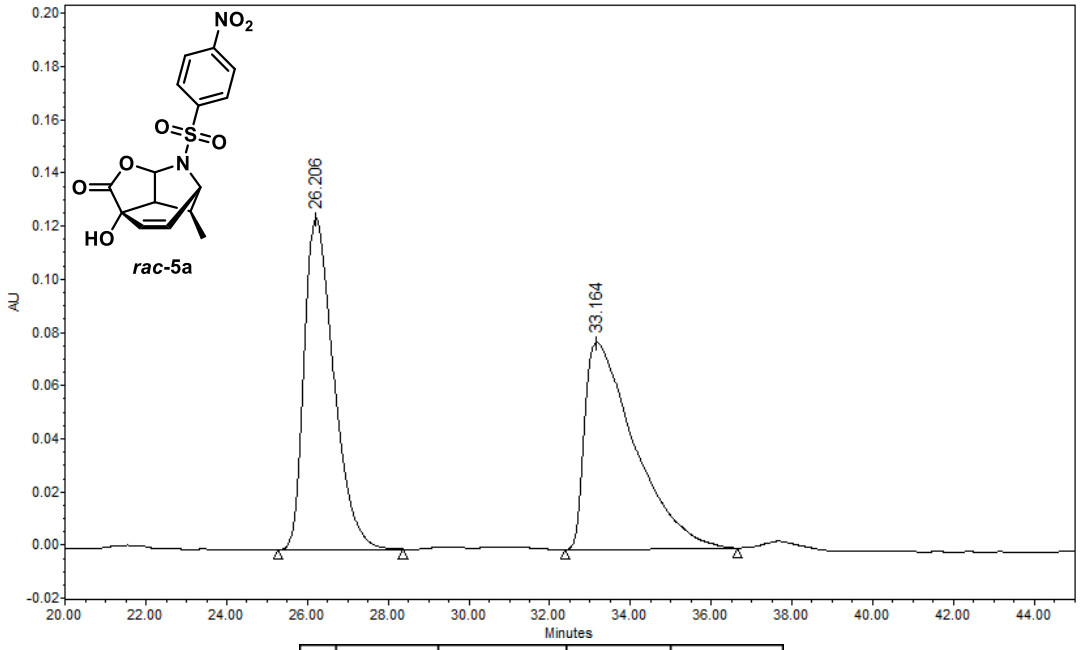


Retention Time	Area	Area Percent
26.900	23476264	55.809
46.623	18589381	44.191

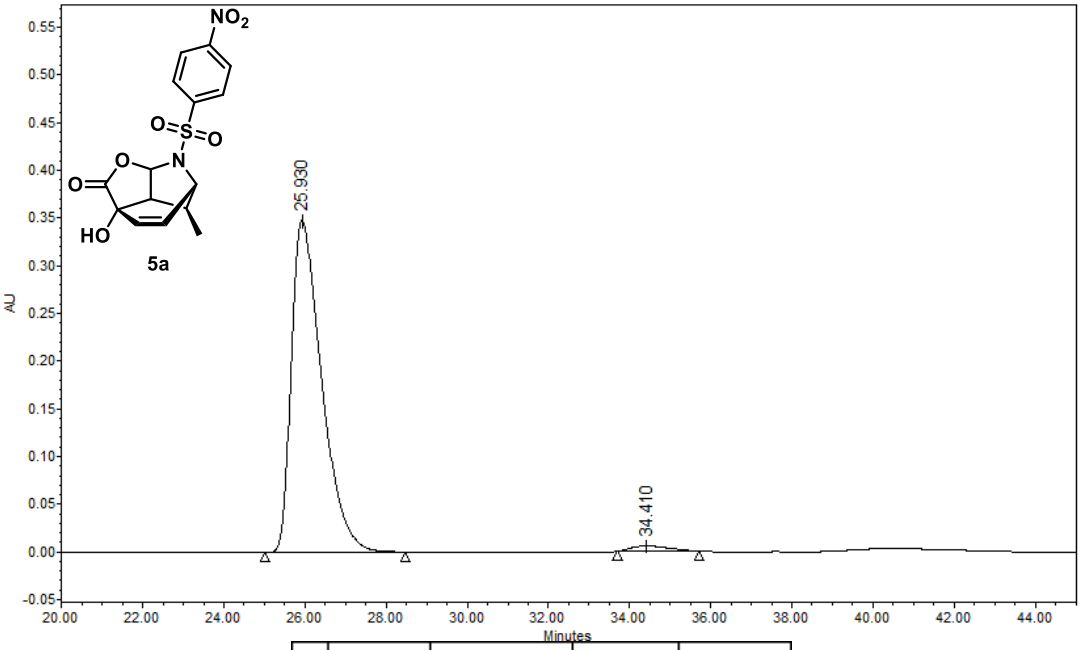


Retention Time	Area	Area Percent
28.017	204956594	99.093
48.607	1875351	0.907

ID, Hexane : 2-Propanol = 75:25, λ = 243 nm, flow rate = 1.0 mL/min (**5a**)

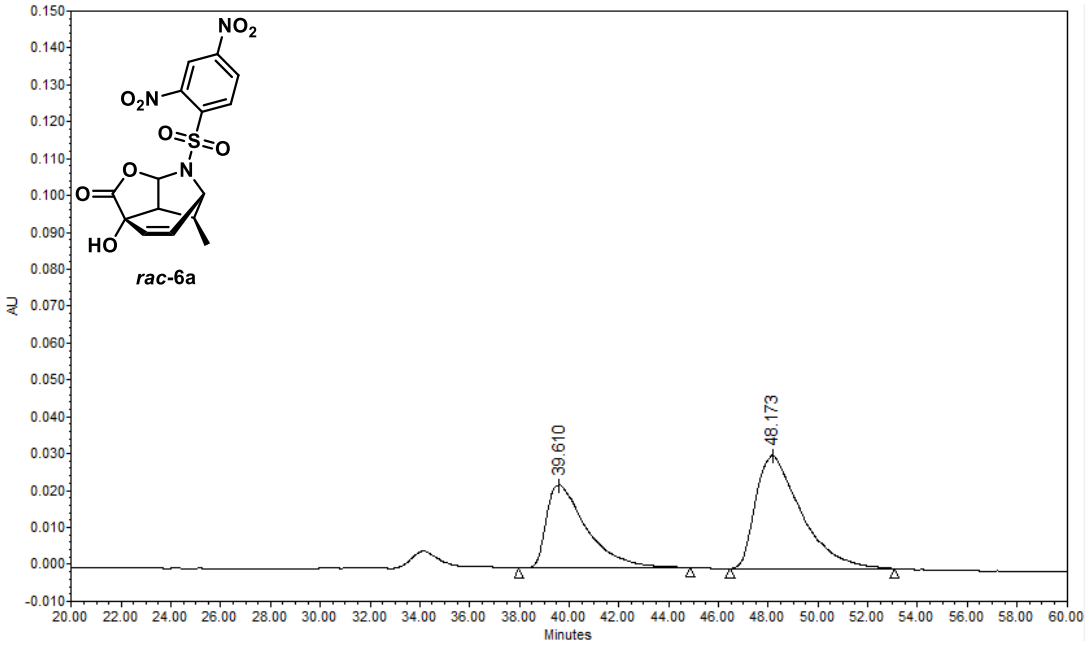


	RT	Area	% Area	Height
1	26.206	6368209	48.67	124690
2	33.164	6715684	51.33	77940

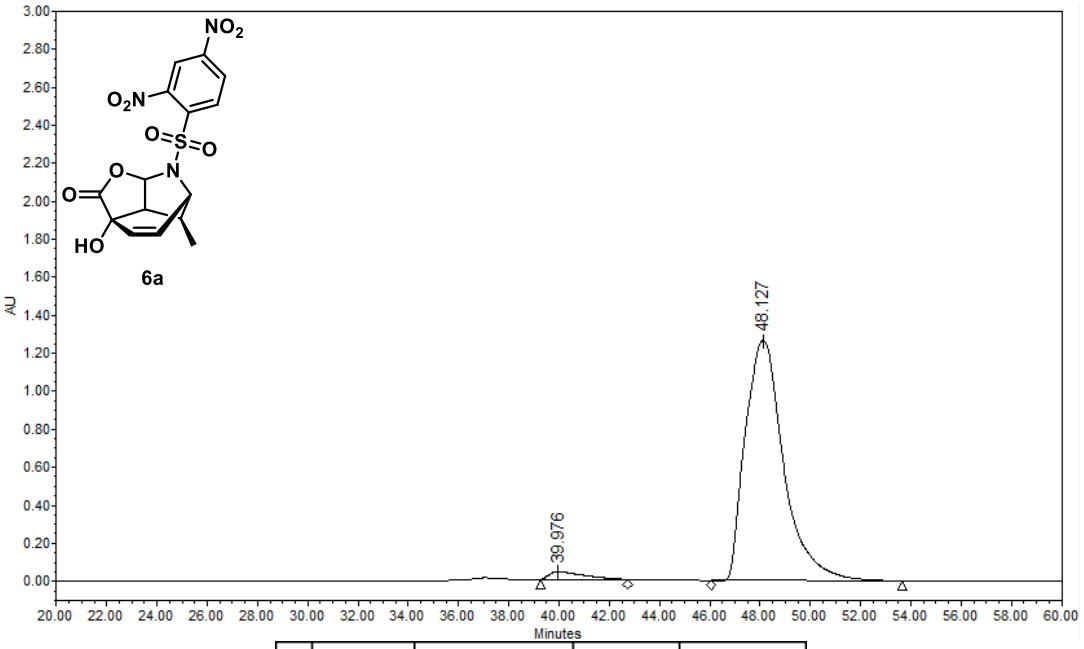


	RT	Area	% Area	Height
1	25.930	18025161	98.03	347895
2	34.410	361814	1.97	5705

ID, Hexane : 2-Propanol = 80:20, λ = 243 nm, flow rate = 1.0 mL/min (6**a**)

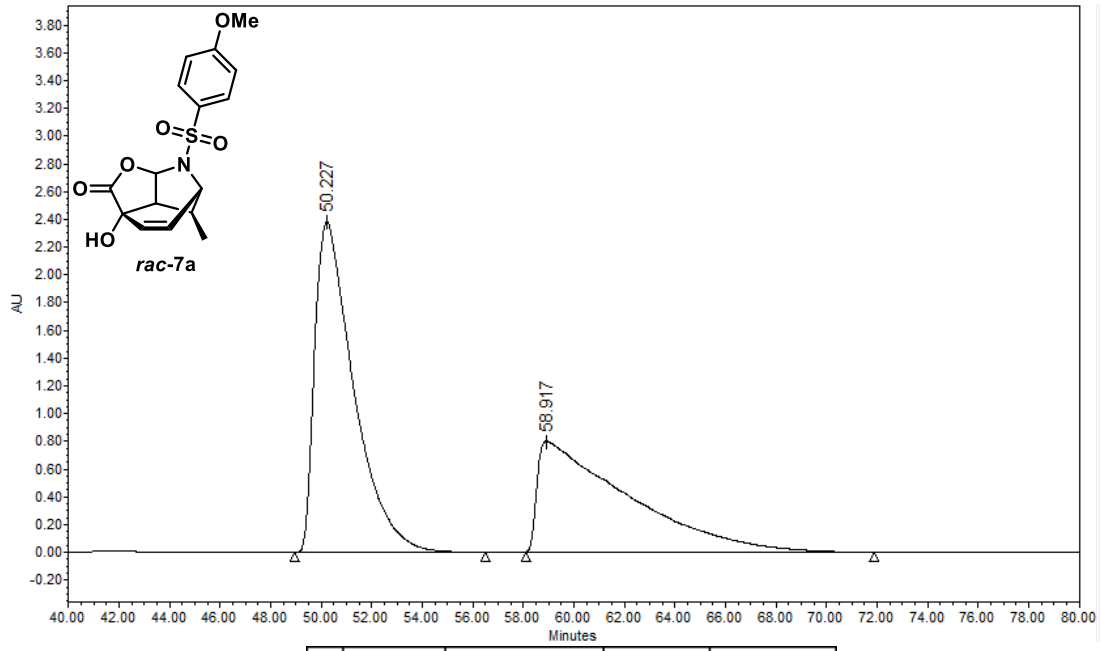


	RT	Area	% Area	Height
1	39.610	2532203	39.78	22536
2	48.173	3832835	60.22	30617

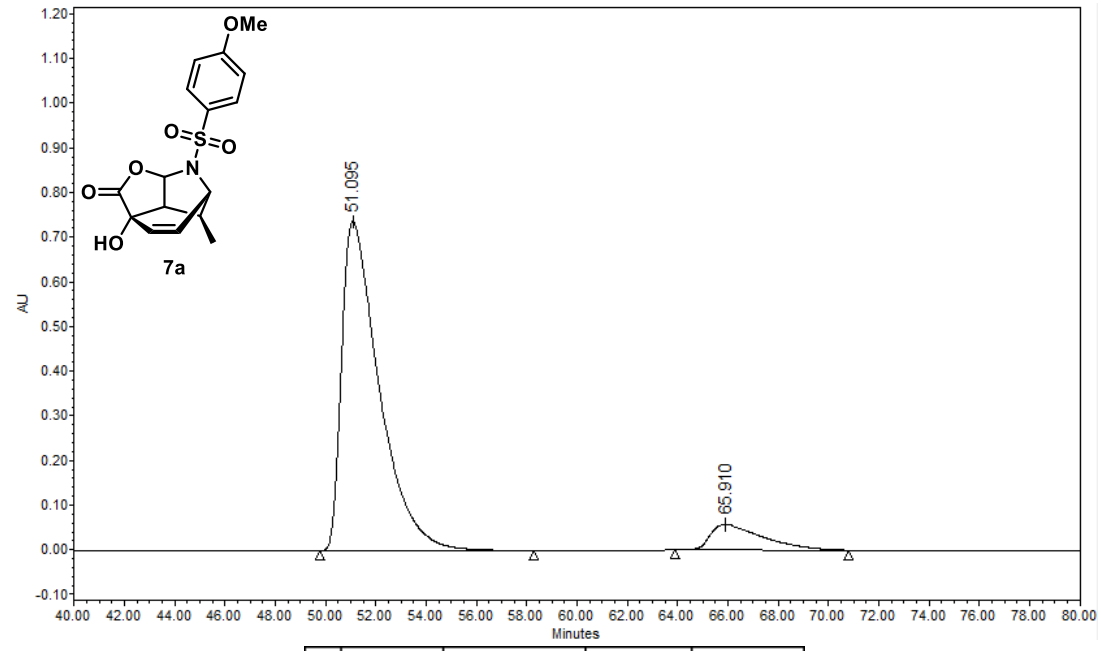


	RT	Area	% Area	Height
1	39.976	4141339	2.99	41449
2	48.127	134227160	97.01	1262415

ID, Hexane : 2-Propanol = 75:25, λ = 243 nm, flow rate = 1.0 mL/min (**7a**)

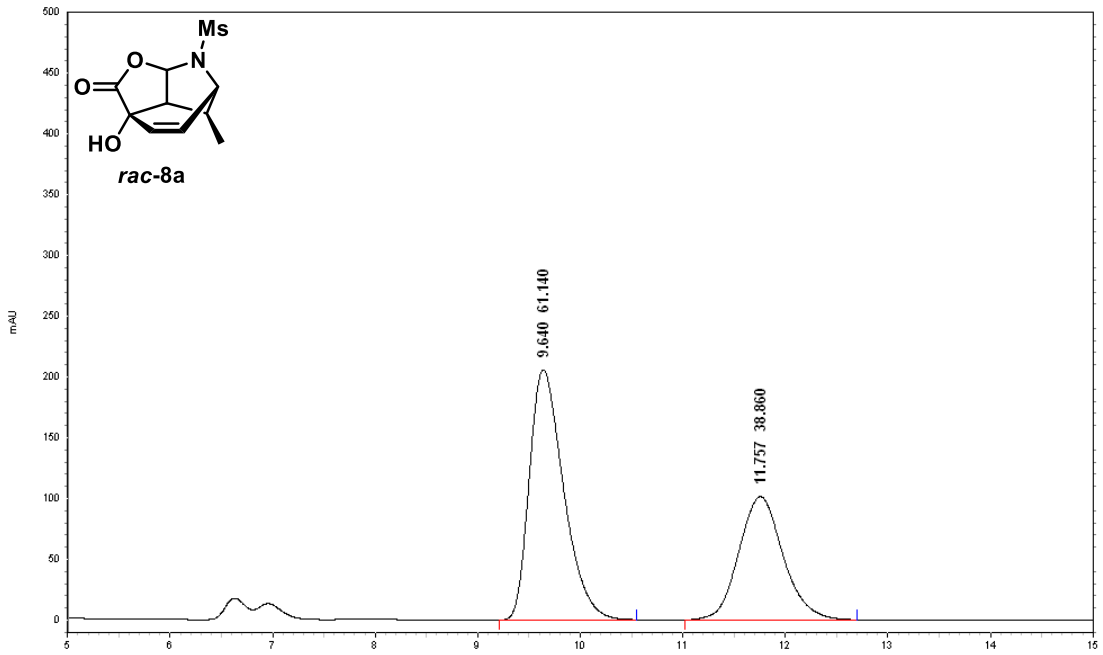


	RT	Area	% Area	Height
1	50.227	254954093	56.18	2385033
2	58.917	198866677	43.82	799401

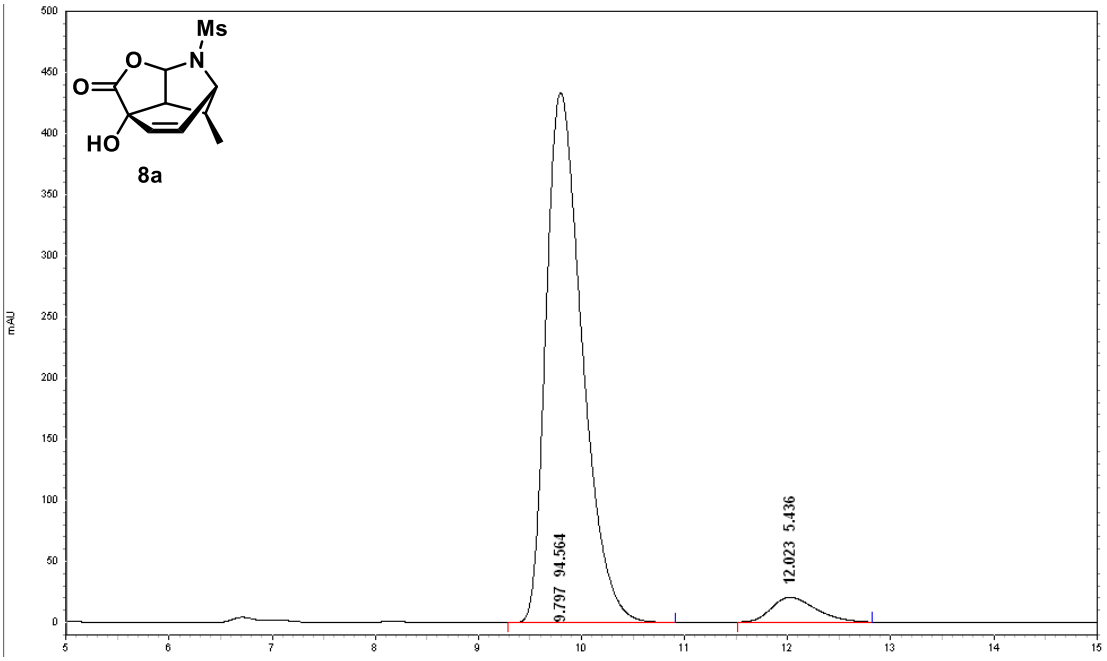


	RT	Area	% Area	Height
1	51.095	76541125	90.44	737828
2	65.910	8091268	9.56	57360

AD-H, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (8**a**)

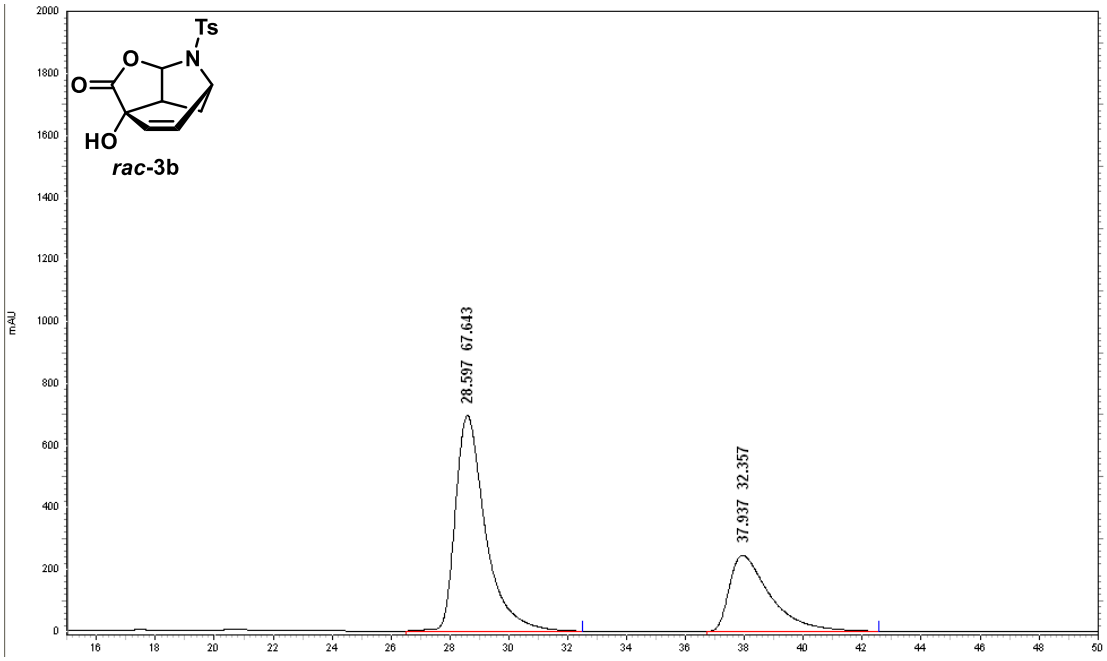


Retention Time	Area	Area Percent
9.640	19132679	61.140
11.757	12160658	38.860

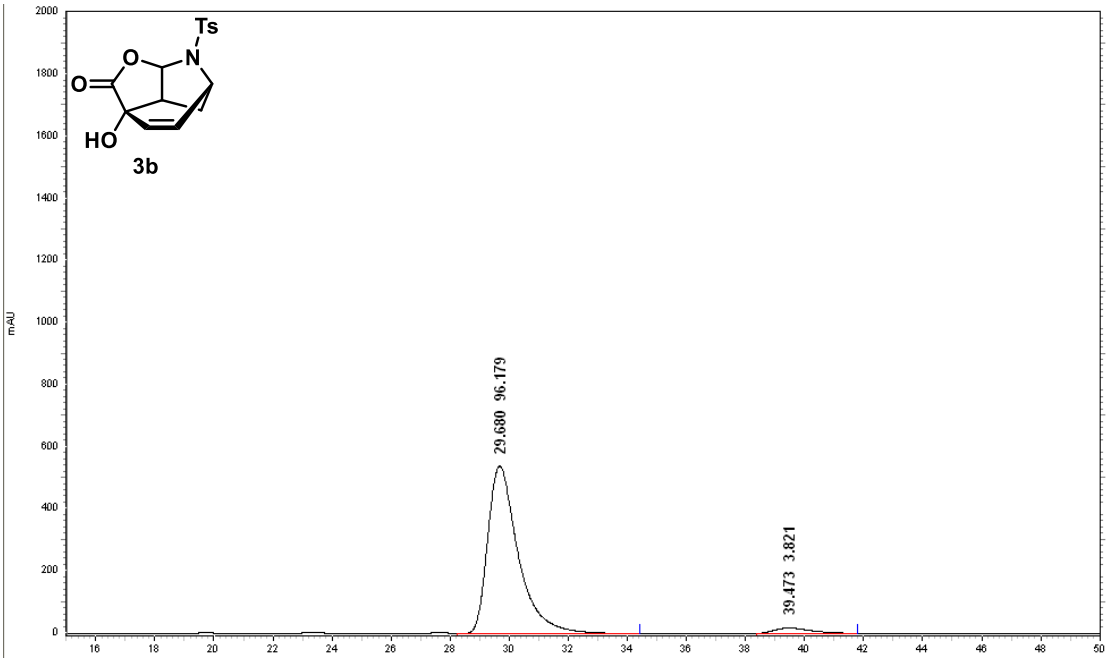


Retention Time	Area	Area Percent
9.797	42245621	94.564
12.023	2428384	5.436

AD-H, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 0.7 mL/min (**3b**)

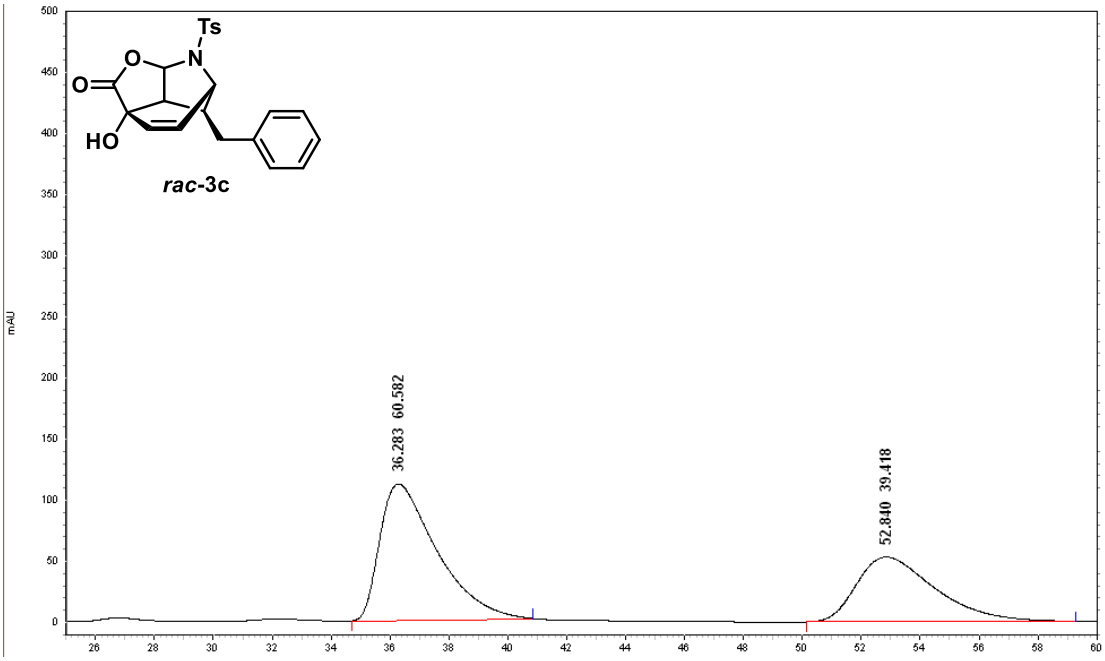


Retention Time	Area	Area Percent
28.597	196703696	67.643
37.937	94091922	32.357

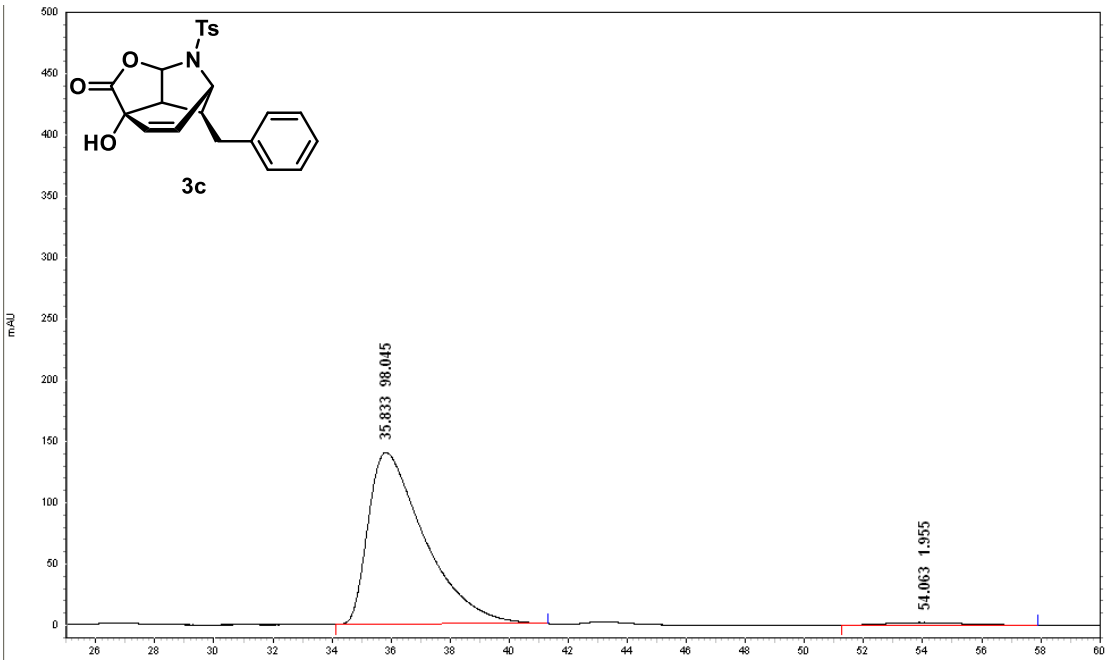


Retention Time	Area	Area Percent
29.680	154433118	96.179
39.473	6135042	3.821

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3c**)

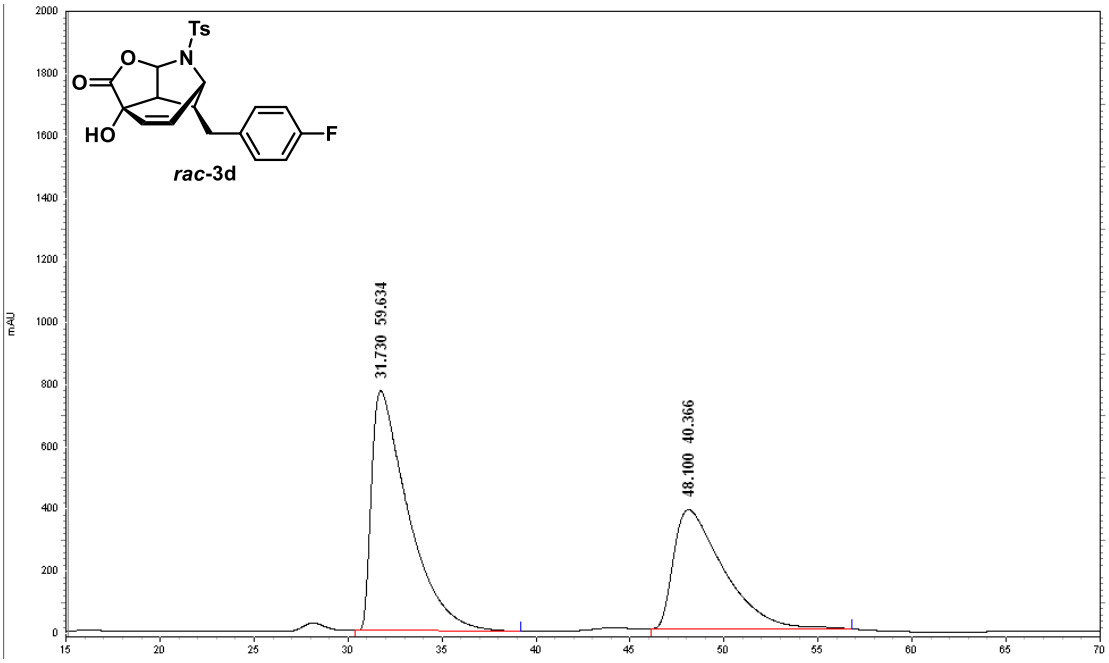


Retention Time	Area	Area Percent
28.597	196703696	67.643
37.937	94091922	32.357

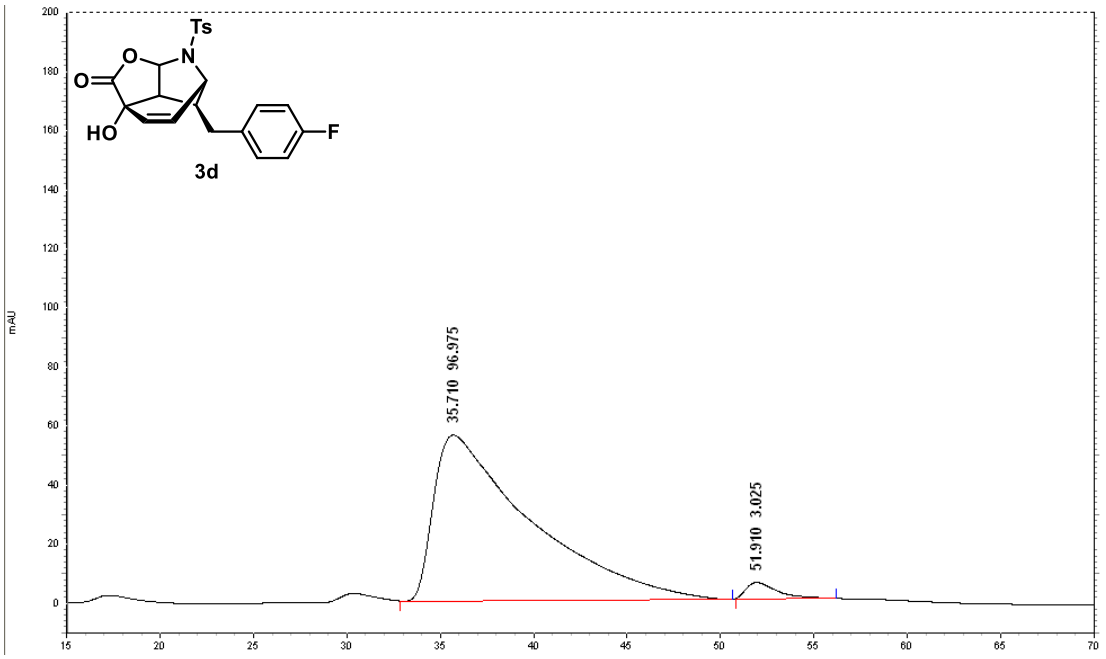


Retention Time	Area	Area Percent
35.833	74643592	98.045
54.063	1488462	1.955

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3d**)

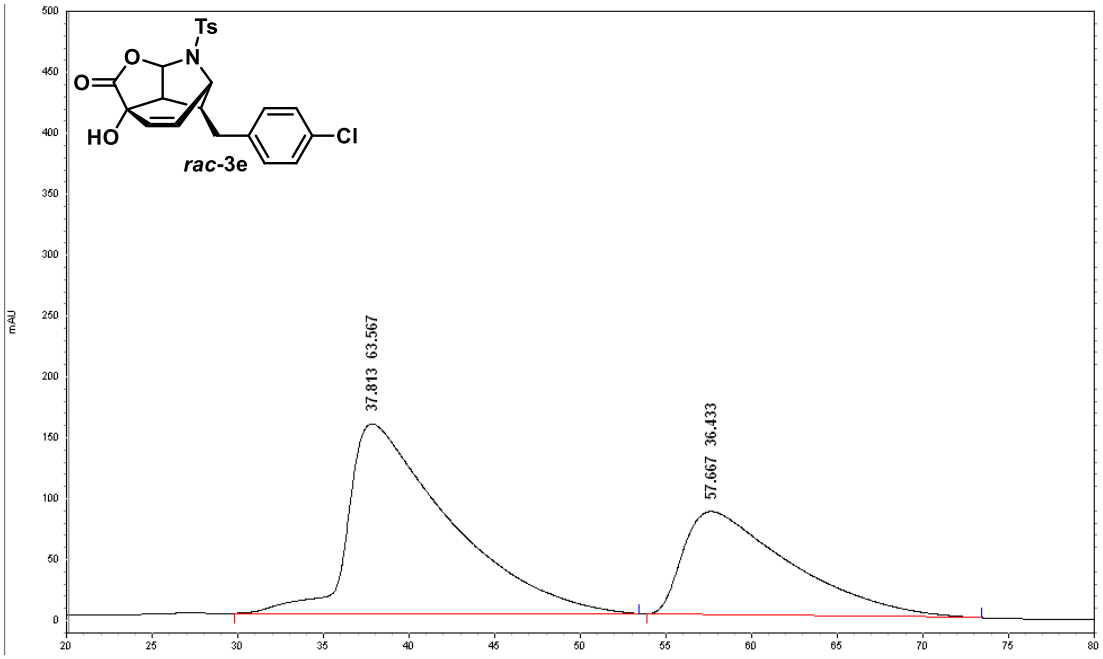


Retention Time	Area	Area Percent
31.730	420131707	59.634
48.100	284385525	40.366

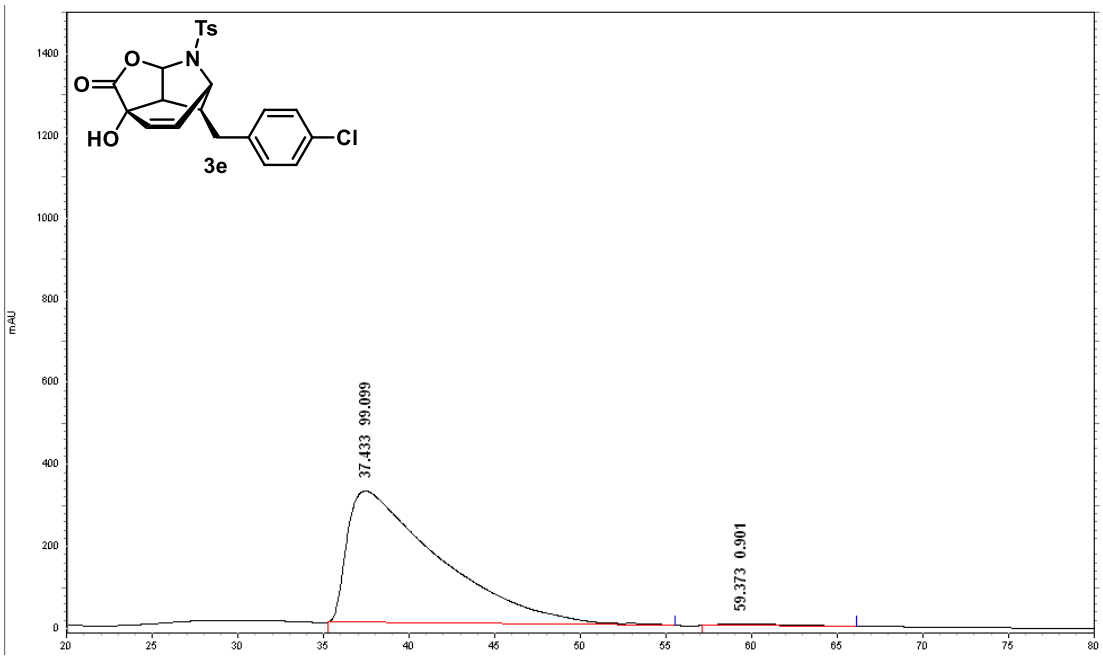


Retention Time	Area	Area Percent
35.710	80859187	96.975
51.910	2521946	3.025

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3e**)

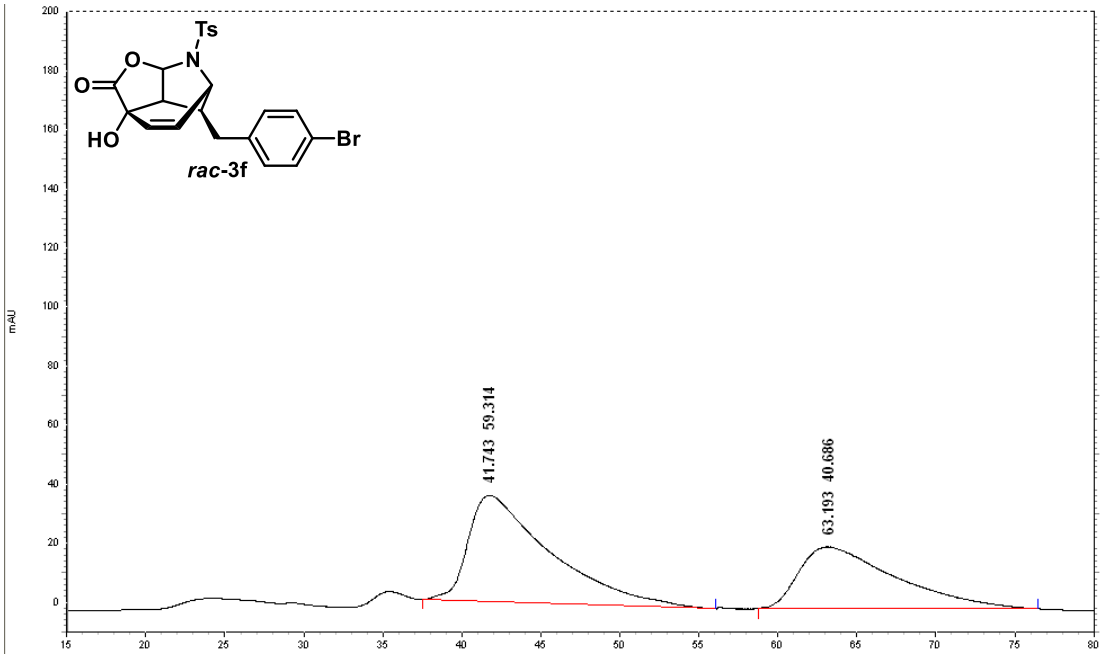


Retention Time	Area	Area Percent
37.813	256618416	63.567
57.667	147078726	36.433

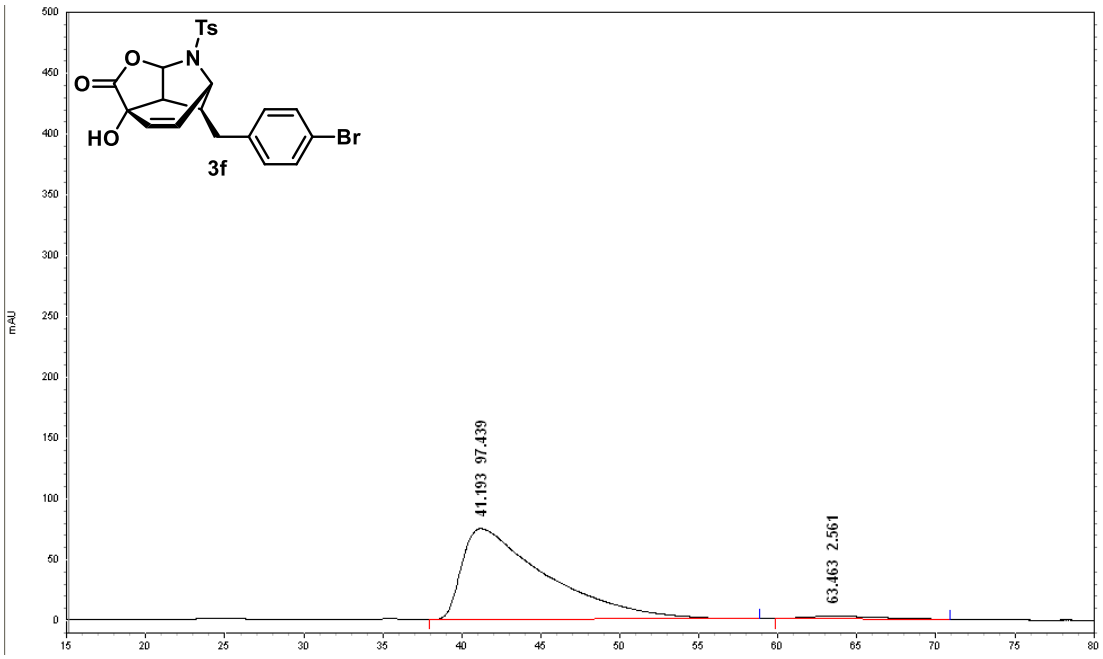


Retention Time	Area	Area Percent
37.433	479274176	99.099
59.373	4359666	0.901

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3f**)

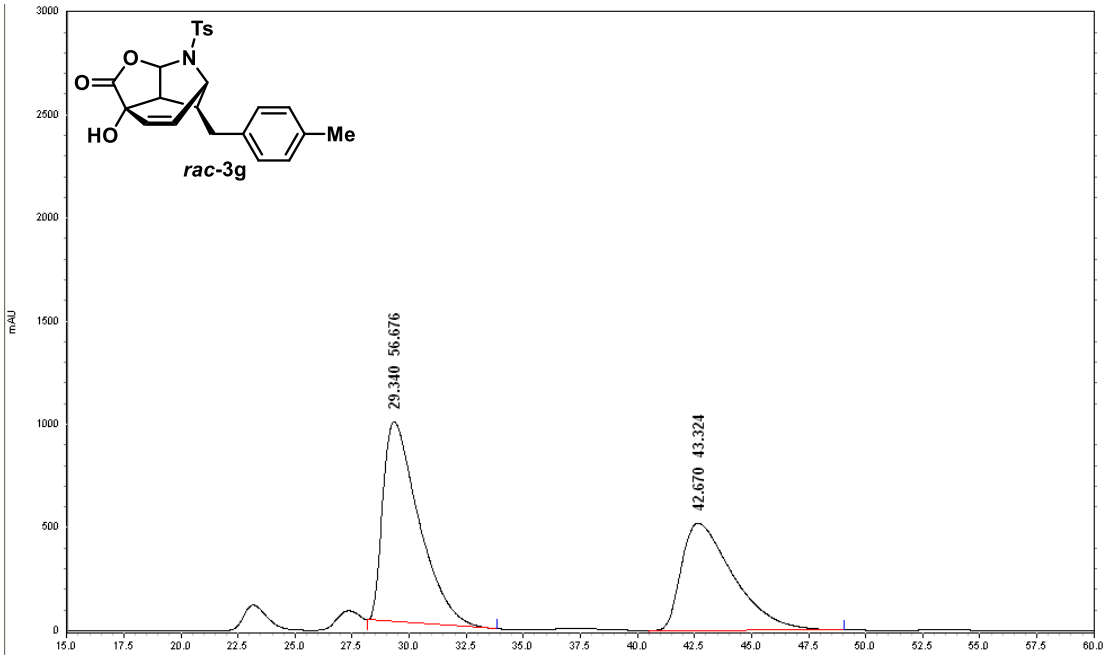


Retention Time	Area	Area Percent
41.743	51957644	59.314
63.193	35640294	40.686

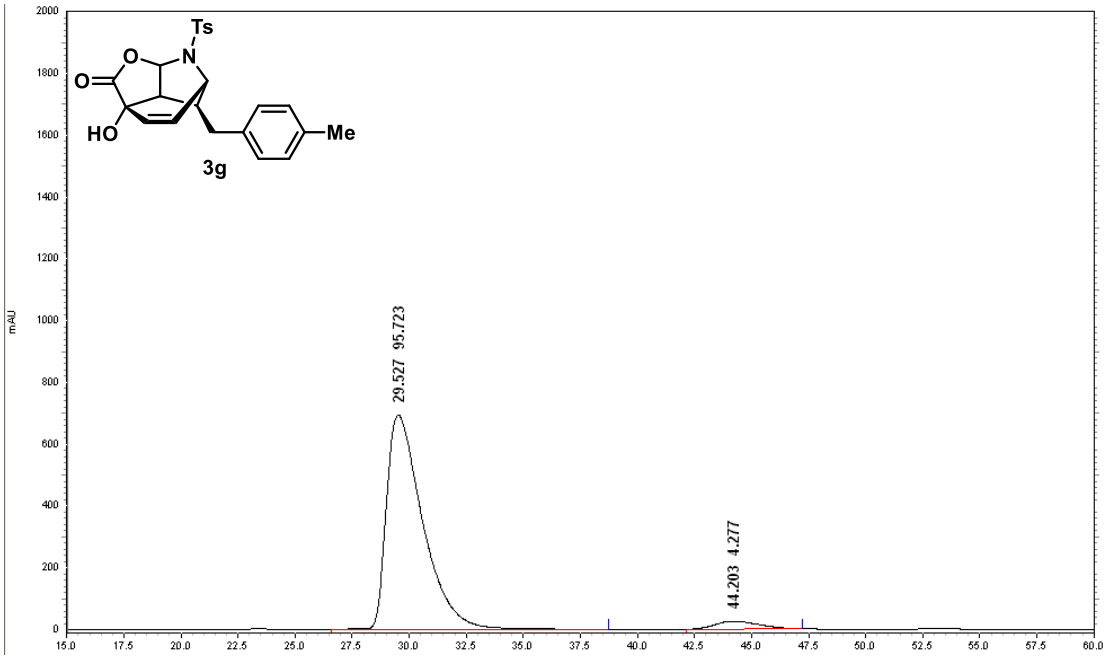


Retention Time	Area	Area Percent
41.193	110899835	97.439
63.463	2914551	2.561

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3g**)

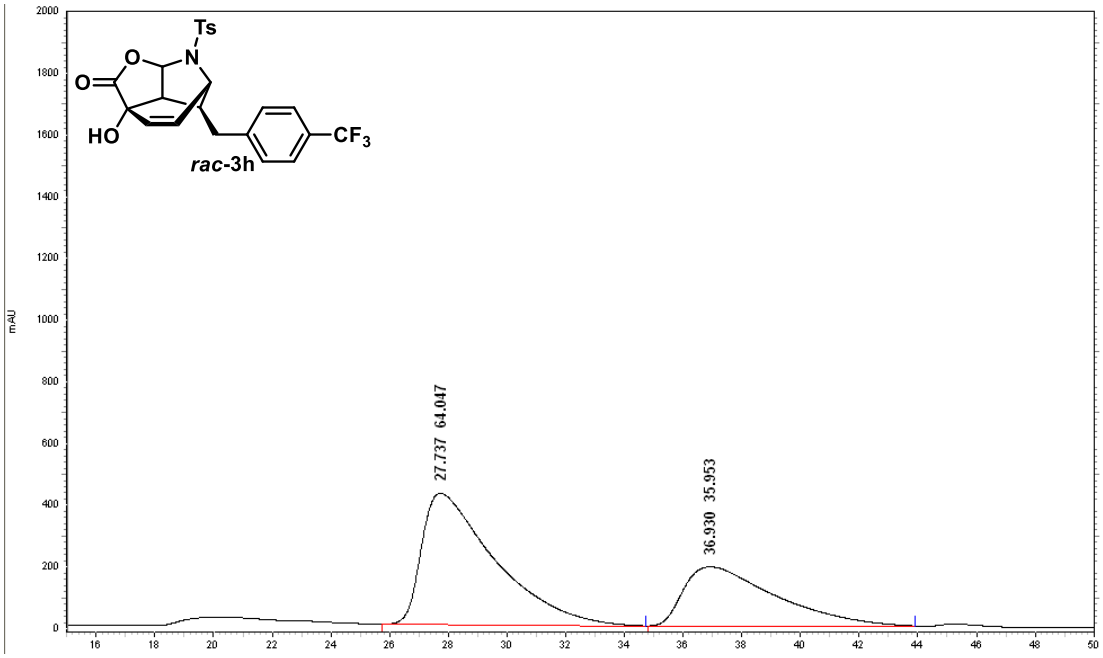


Retention Time	Area	Area Percent
29.340	426576508	56.676
42.670	326087480	43.324

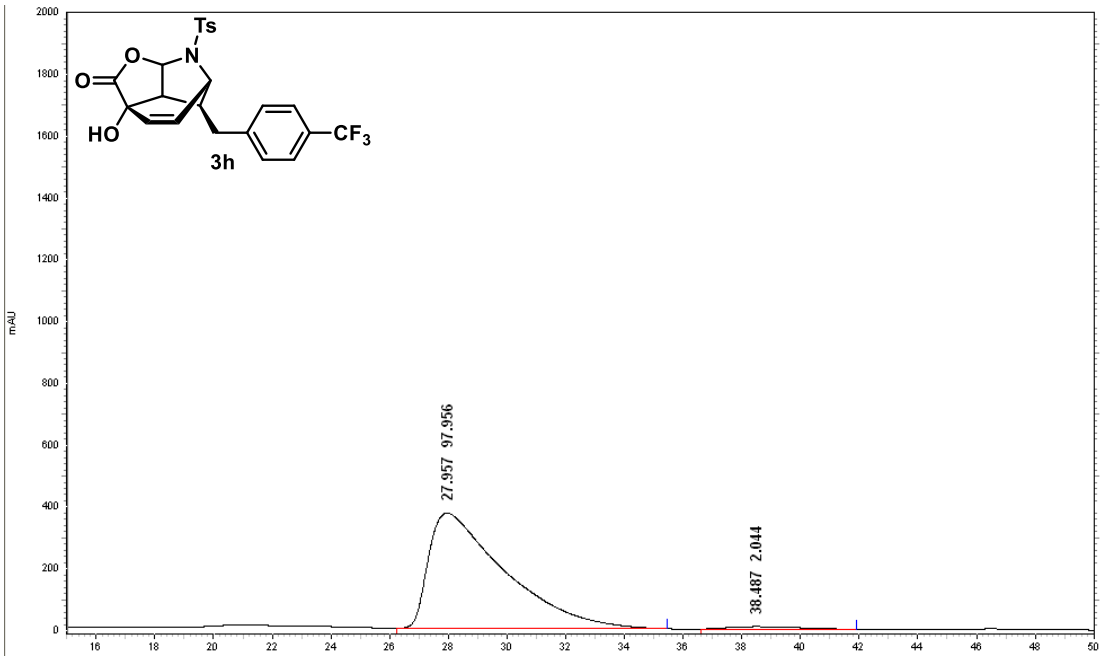


Retention Time	Area	Area Percent
29.527	306172837	95.723
44.203	13679035	4.277

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3h**)

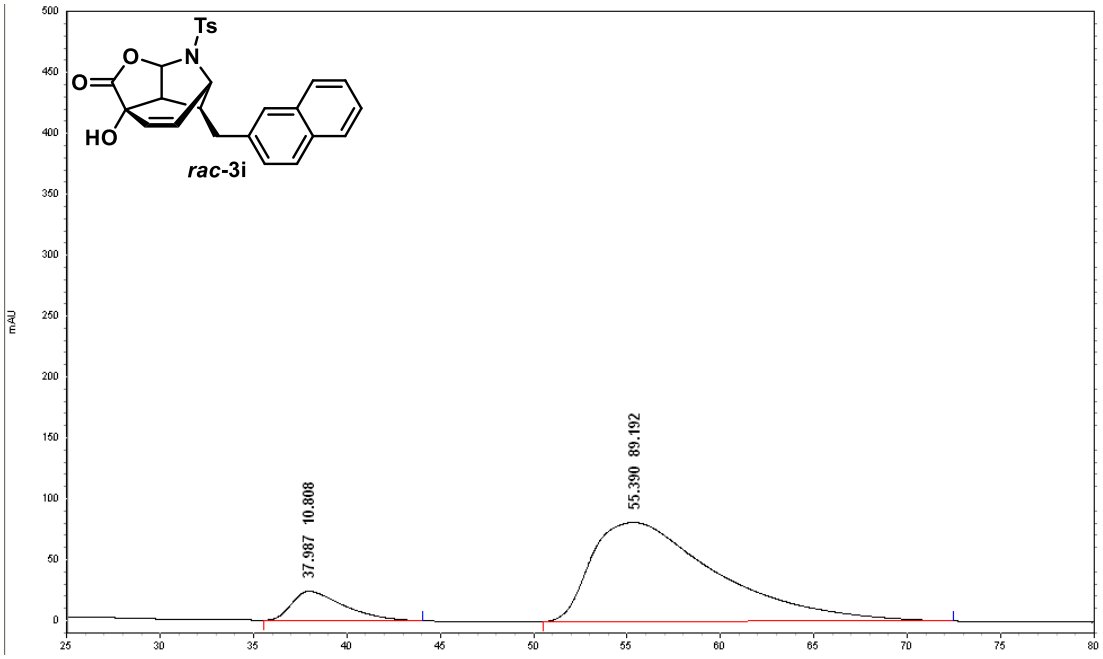


Retention Time	Area	Area Percent
27.737	294942940	64.047
36.930	165569270	35.953

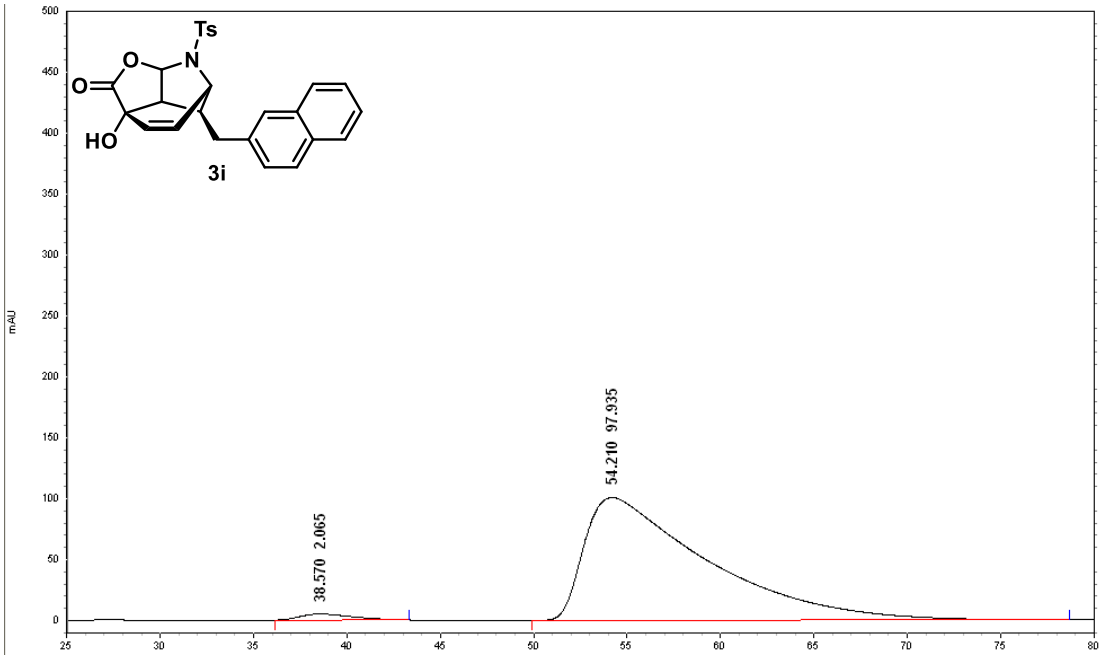


Retention Time	Area	Area Percent
27.957	267852543	97.956
38.487	5589287	2.044

OD-H, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 0.7 mL/min (**3i**)

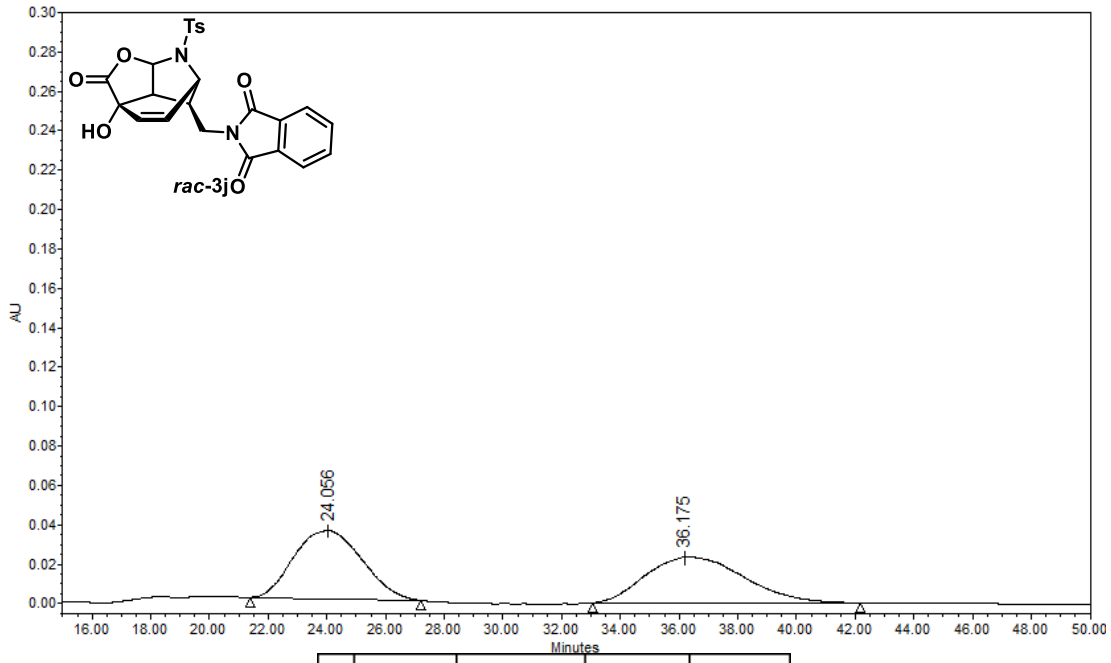


Retention Time	Area	Area Percent
37.987	18446767	10.808
55.390	152230796	89.192

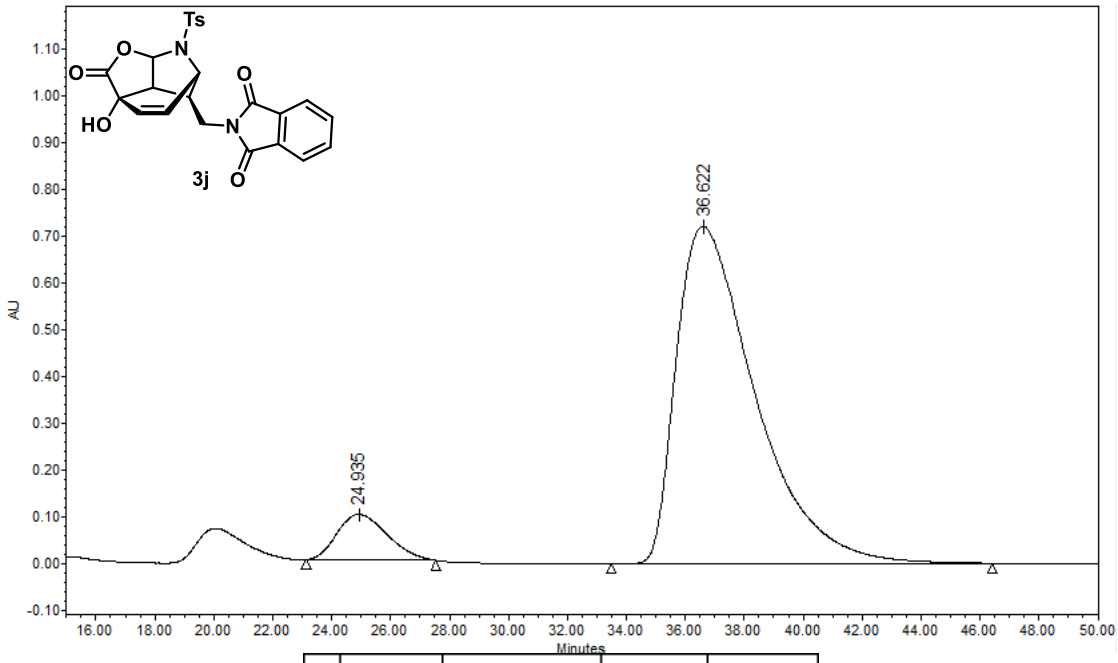


Retention Time	Area	Area Percent
38.570	3887456	2.065
54.210	184340338	97.935

OD-H, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**3j**)

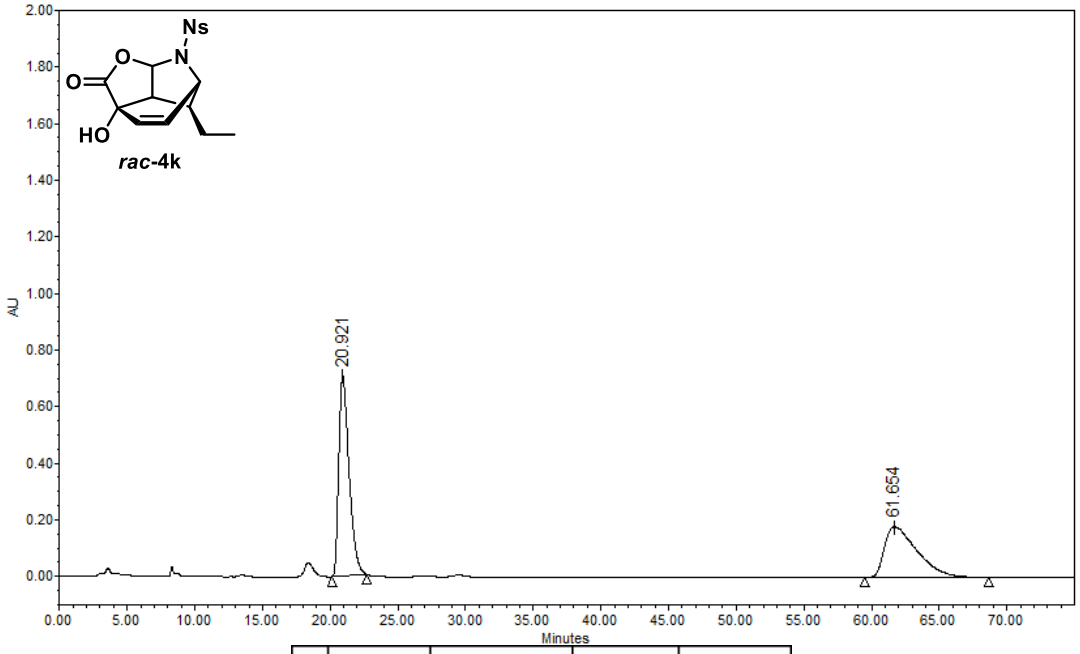


	RT	Area	% Area	Height
1	24.056	5576101	50.92	34736
2	36.175	5375175	49.08	23215

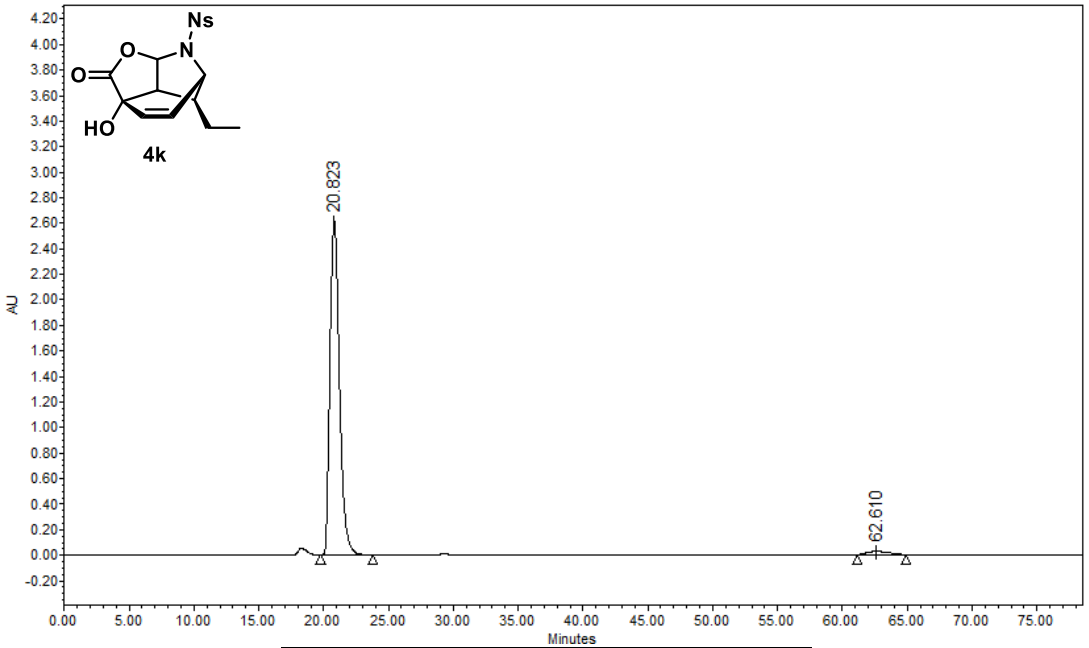


	RT	Area	% Area	Height
1	24.935	11206545	7.79	96375
2	36.622	132679022	92.21	719549

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4k**)

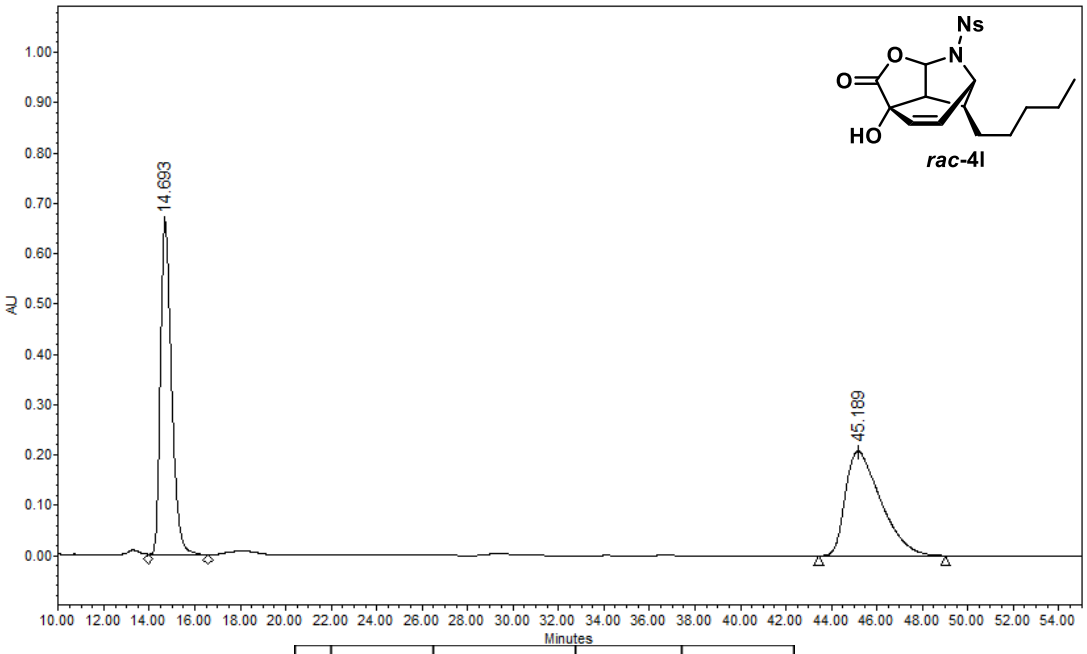


	RT	Area	% Area	Height
1	20.921	33312122	52.72	670820
2	61.654	29873951	47.28	178703

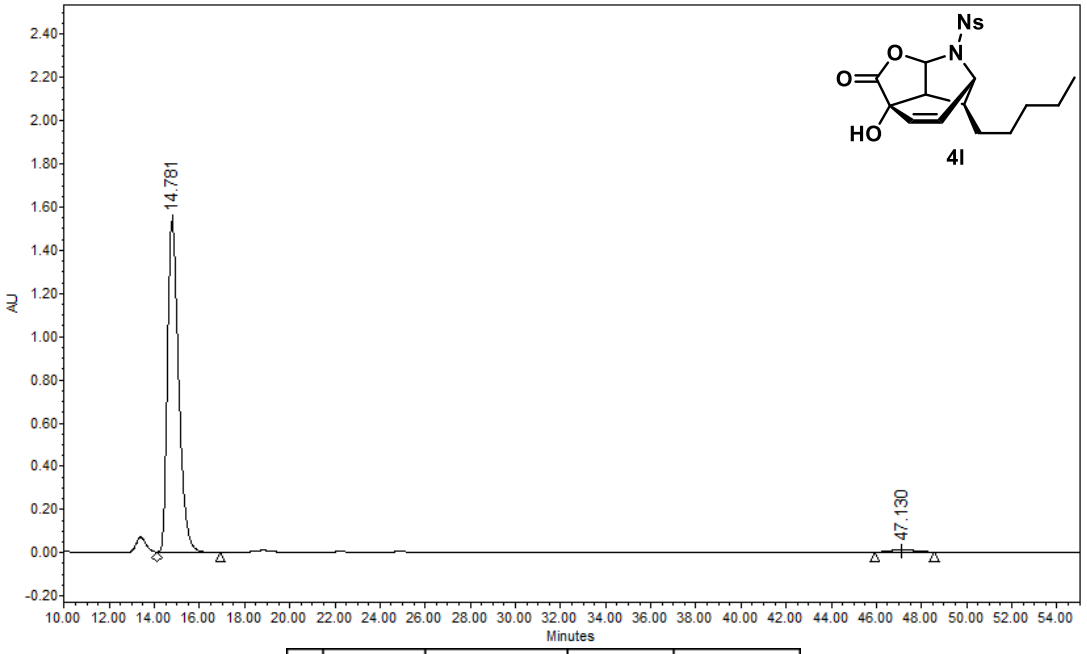


	RT	Area	% Area	Height
1	20.823	132502206	97.77	2607802
2	62.610	3023077	2.23	24896

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4l**)

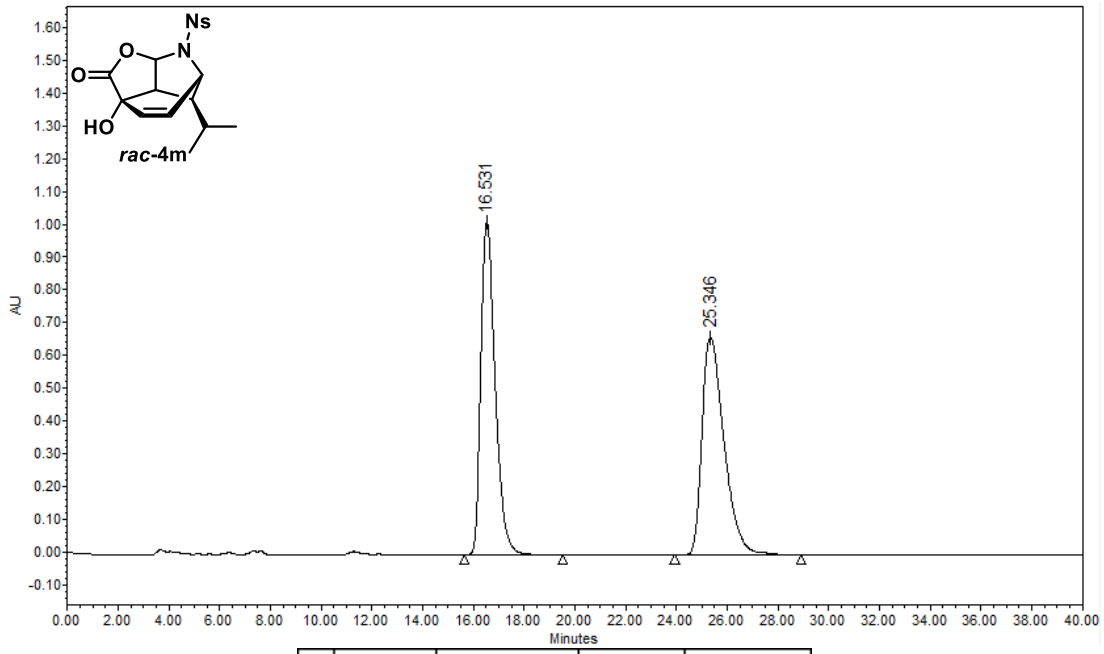


	RT	Area	% Area	Height
1	14.693	22501429	50.18	660532
2	45.189	22337459	49.82	207320

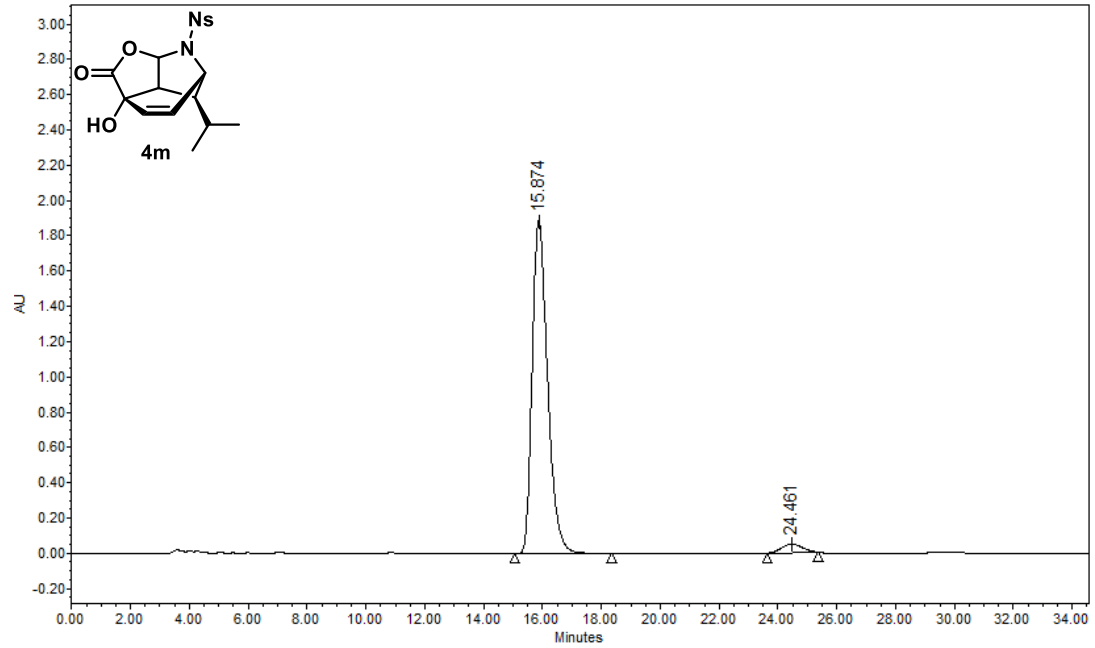


	RT	Area	% Area	Height
1	14.781	53240366	98.34	1535478
2	47.130	897382	1.66	10422

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4m**)

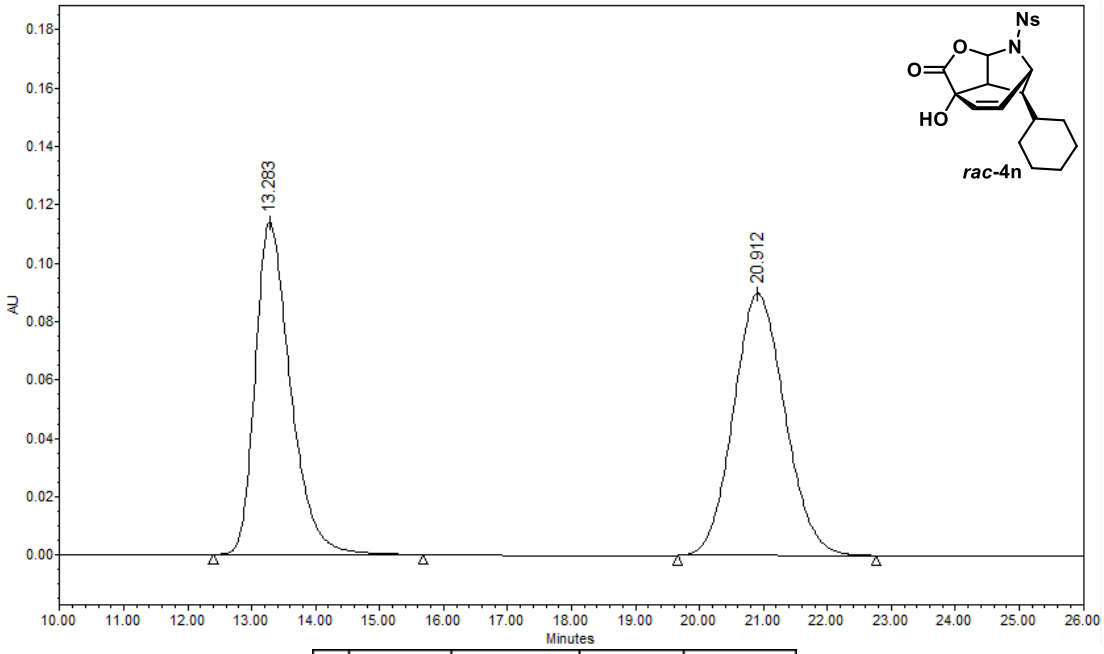


	RT	Area	% Area	Height
1	16.531	39695037	49.82	1013411
2	25.346	39989612	50.18	662750

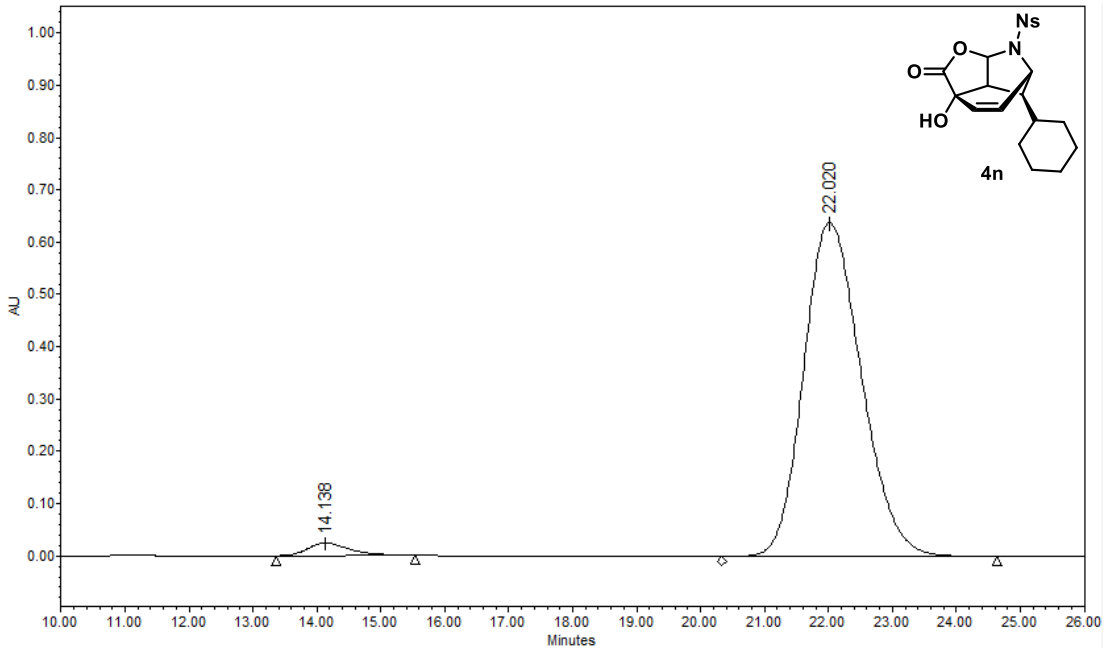


	RT	Area	% Area	Height
1	15.874	68560194	96.61	1885522
2	24.461	2402282	3.39	49361

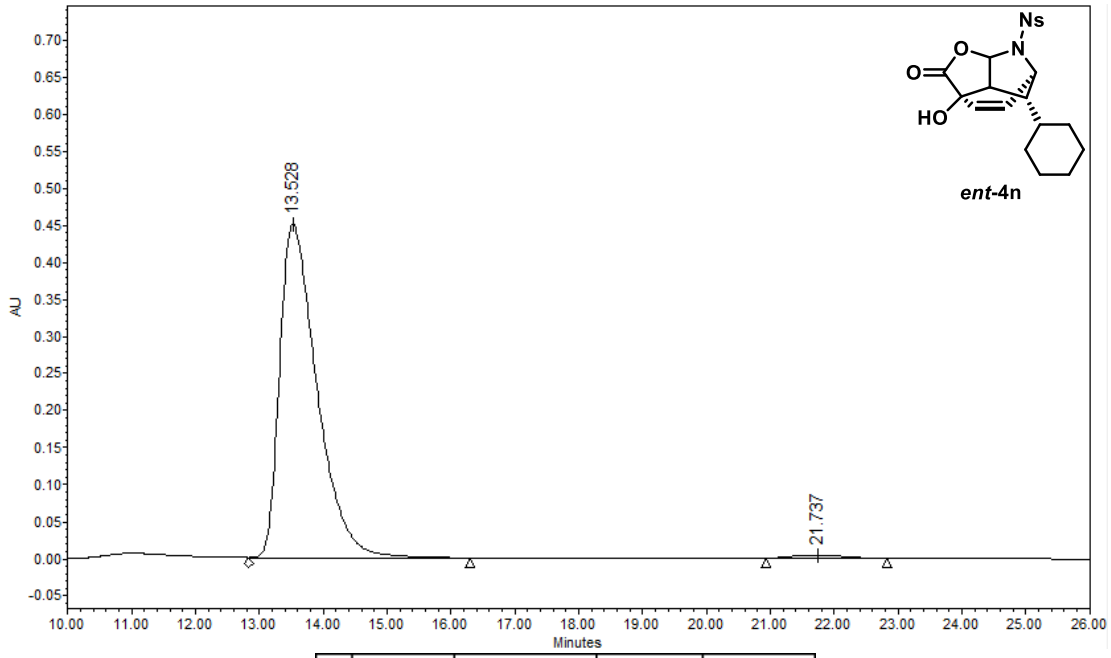
IG, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (**4n**)



	RT	Area	% Area	Height
1	13.283	4349829	46.46	113802
2	20.912	5013155	53.54	89870

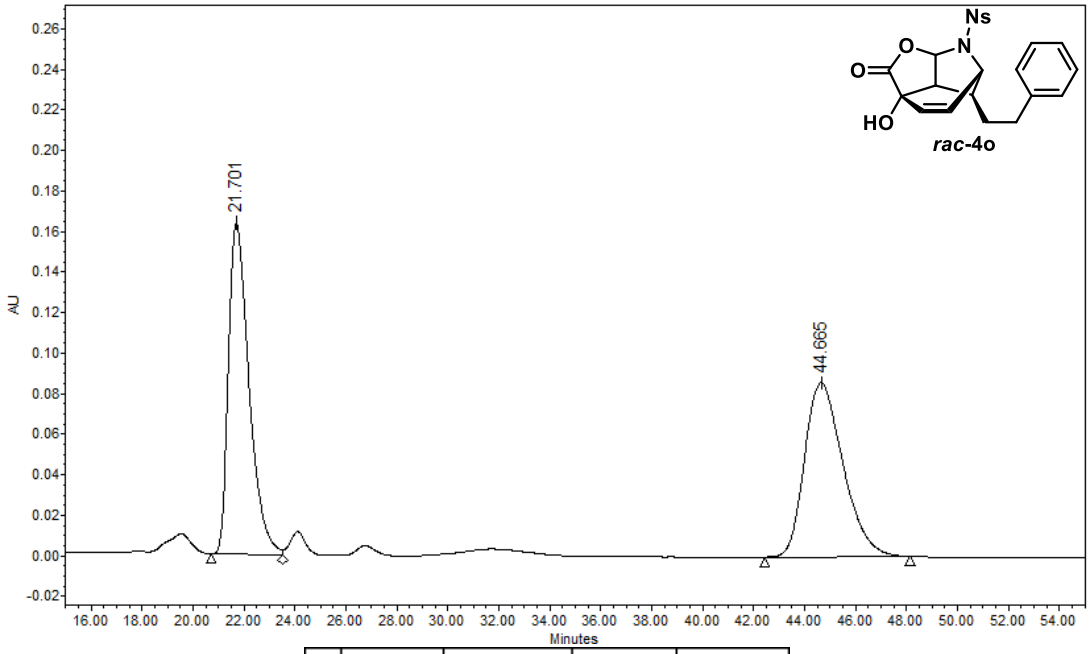


	RT	Area	% Area	Height
1	14.138	1094087	2.66	24122
2	22.020	40046006	97.34	637615

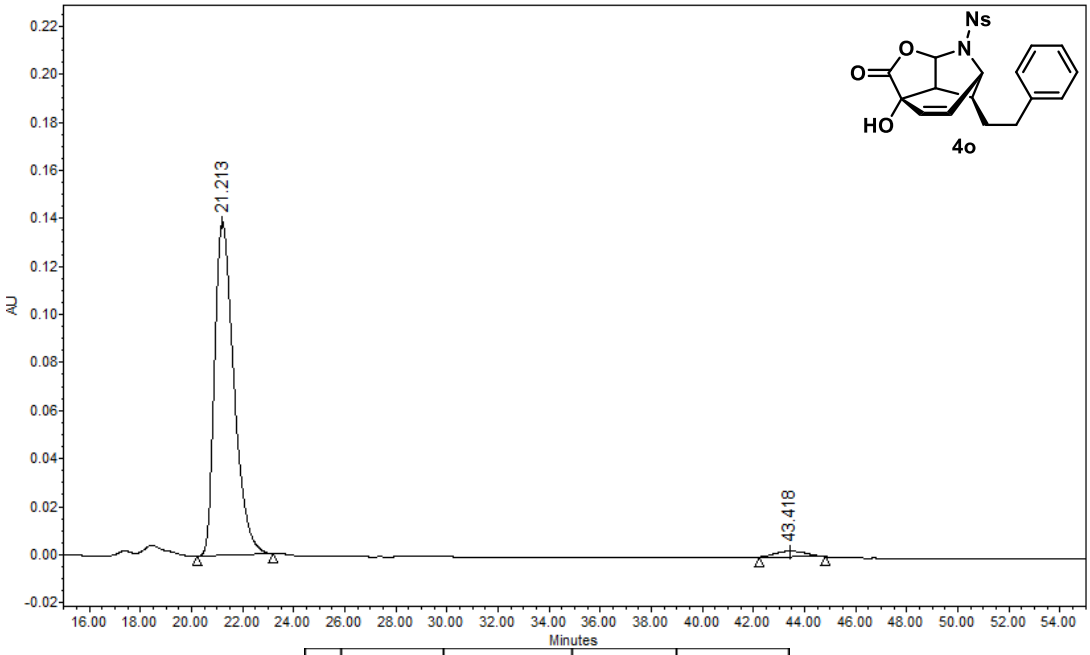


	RT	Area	% Area	Height
1	13.528	18343485	98.80	451021
2	21.737	221859	1.20	4212

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4o**)

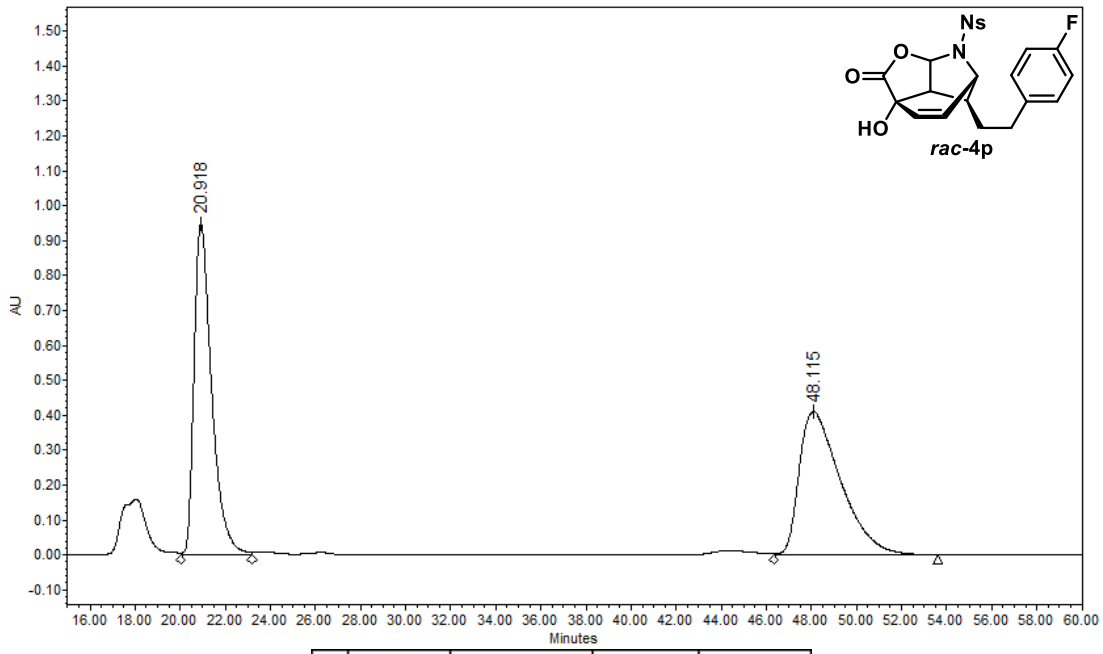


	RT	Area	% Area	Height
1	21.701	9209671	50.58	163922
2	44.665	8999951	49.42	86111

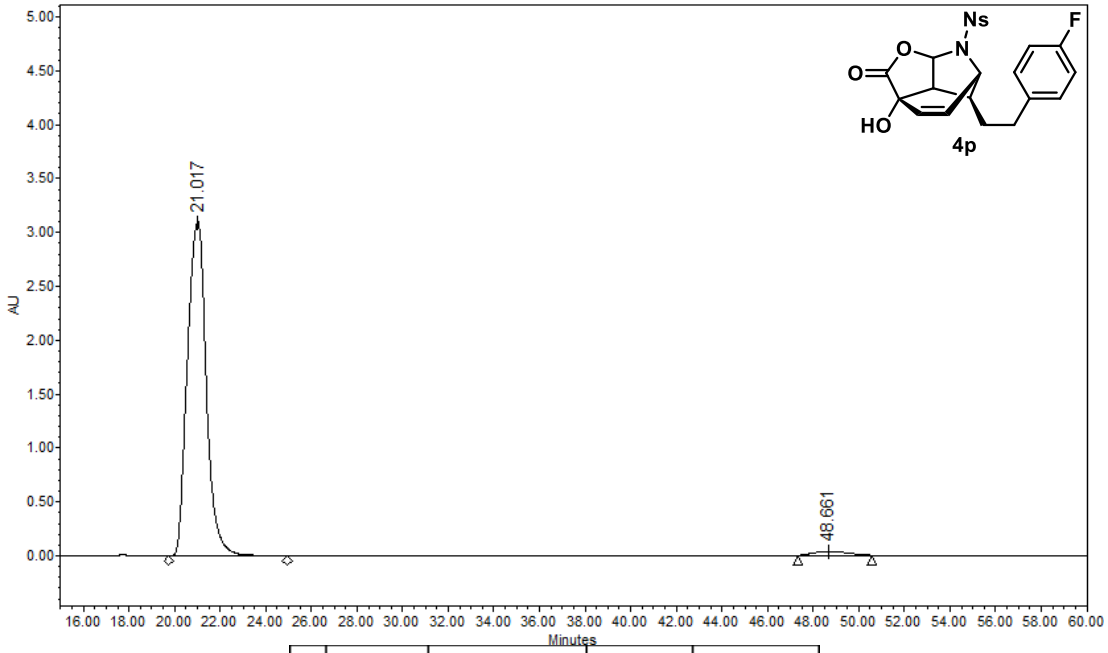


	RT	Area	% Area	Height
1	21.213	7275941	97.41	138788
2	43.418	193775	2.59	2391

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4p**)

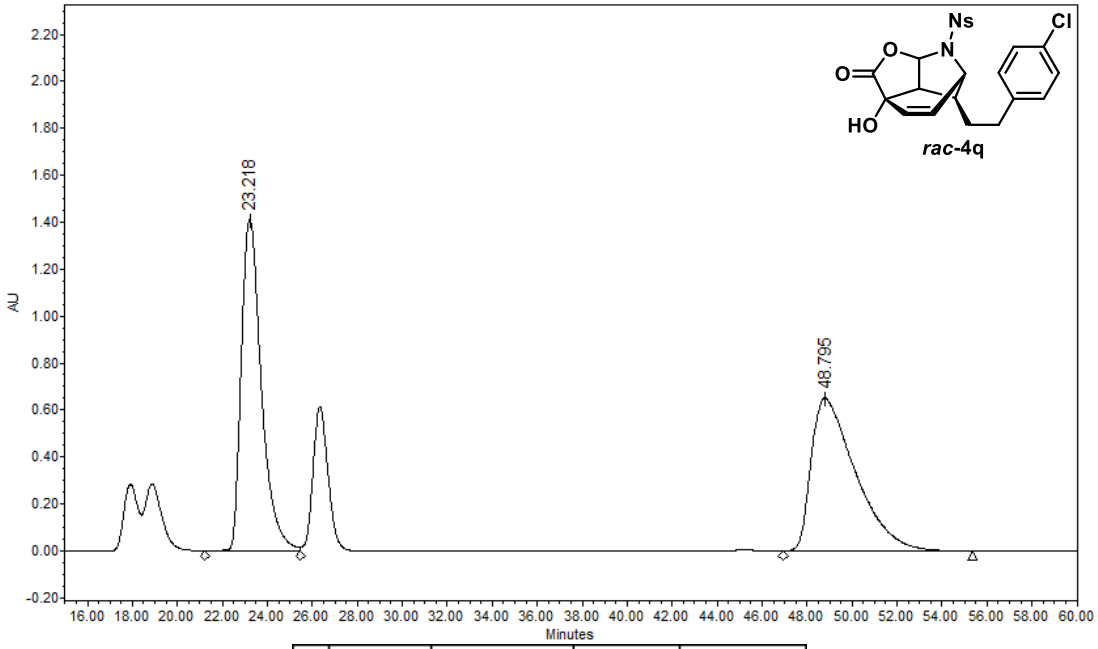


	RT	Area	% Area	Height
1	20.918	51456604	49.59	949457
2	48.115	52311988	50.41	411155

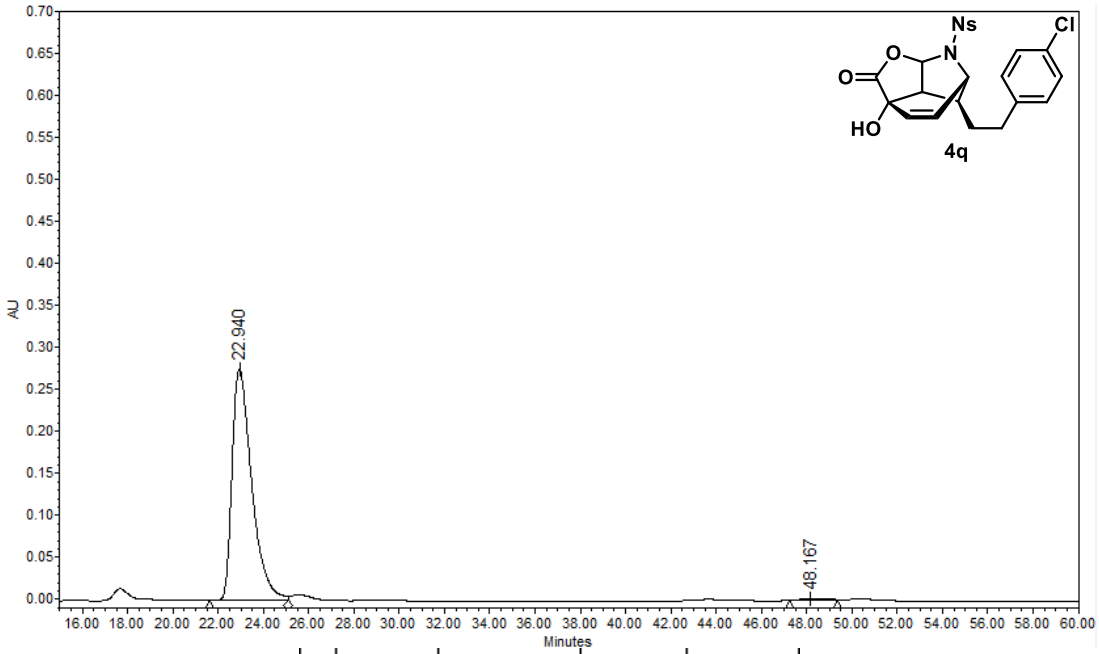


	RT	Area	% Area	Height
1	21.017	178651753	97.96	3096680
2	48.661	3726025	2.04	36880

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4q**)

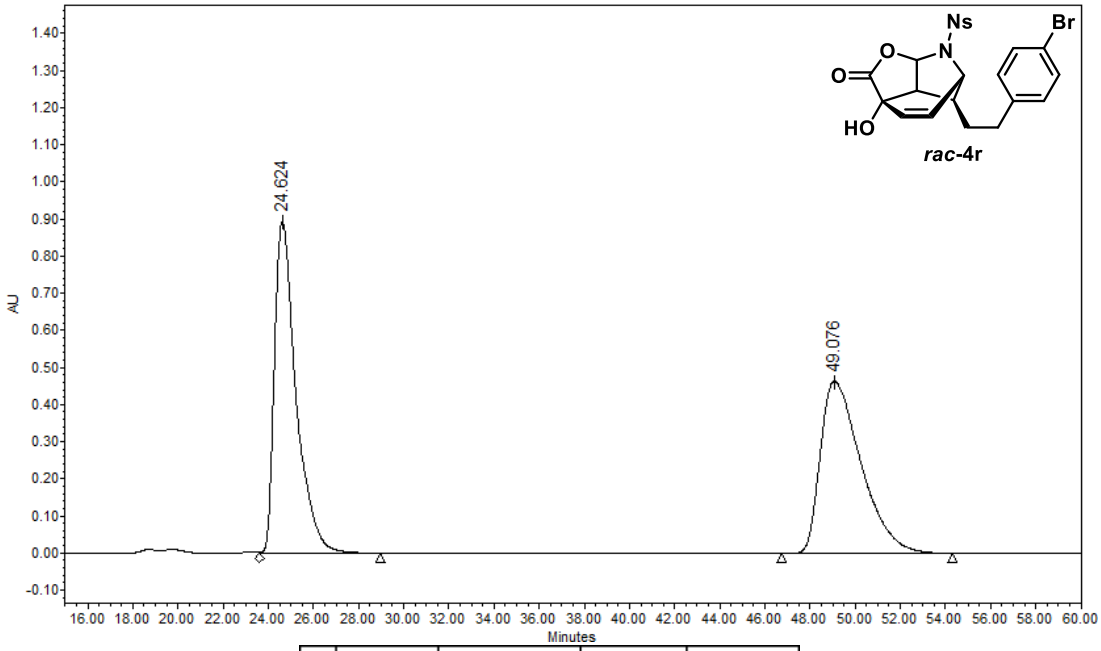


	RT	Area	% Area	Height
1	23.218	87680879	49.64	1410072
2	48.795	88969889	50.36	651576

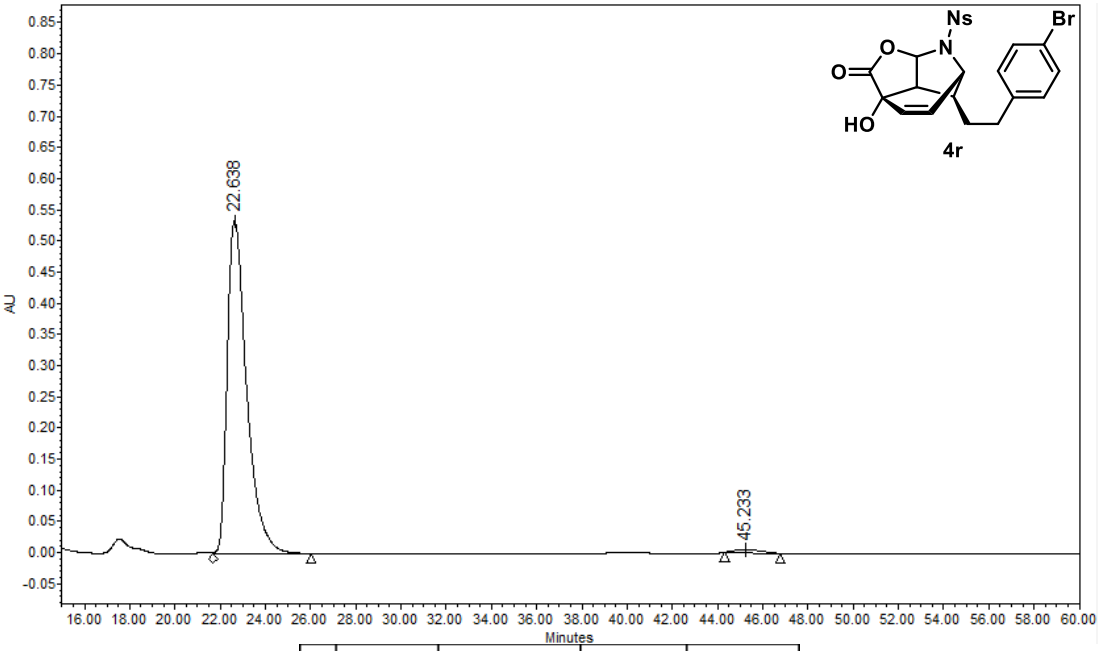


	RT	Area	% Area	Height
1	22.940	16660643	99.32	275707
2	48.167	113498	0.68	1603

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4r**)

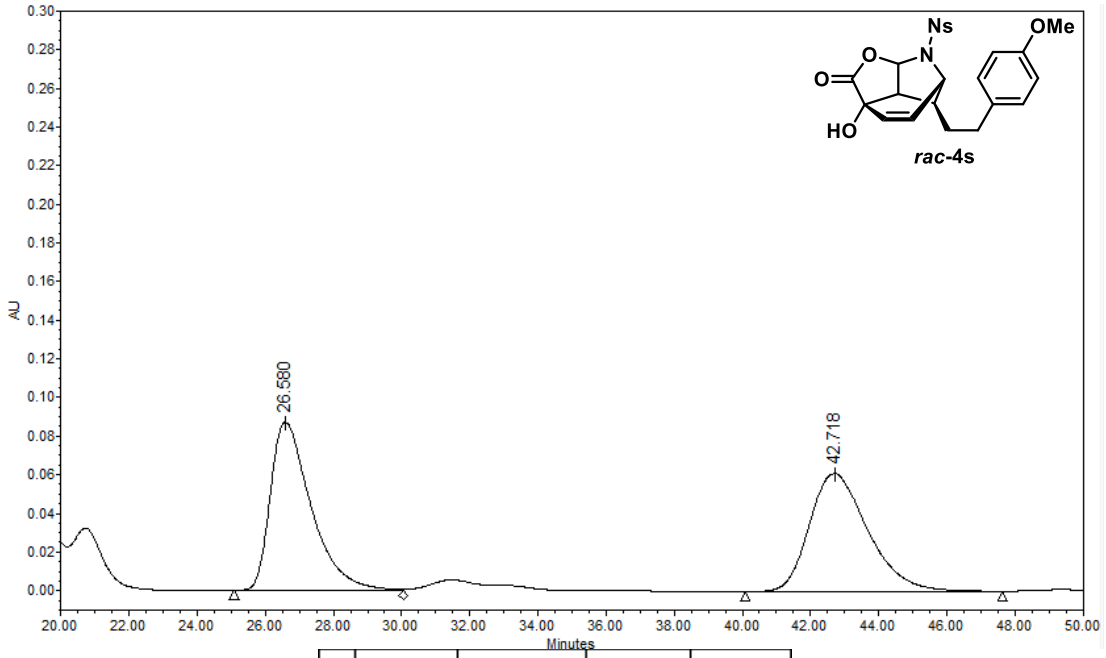


	RT	Area	% Area	Height
1	24.624	59381351	50.53	894777
2	49.076	58146375	49.47	463045

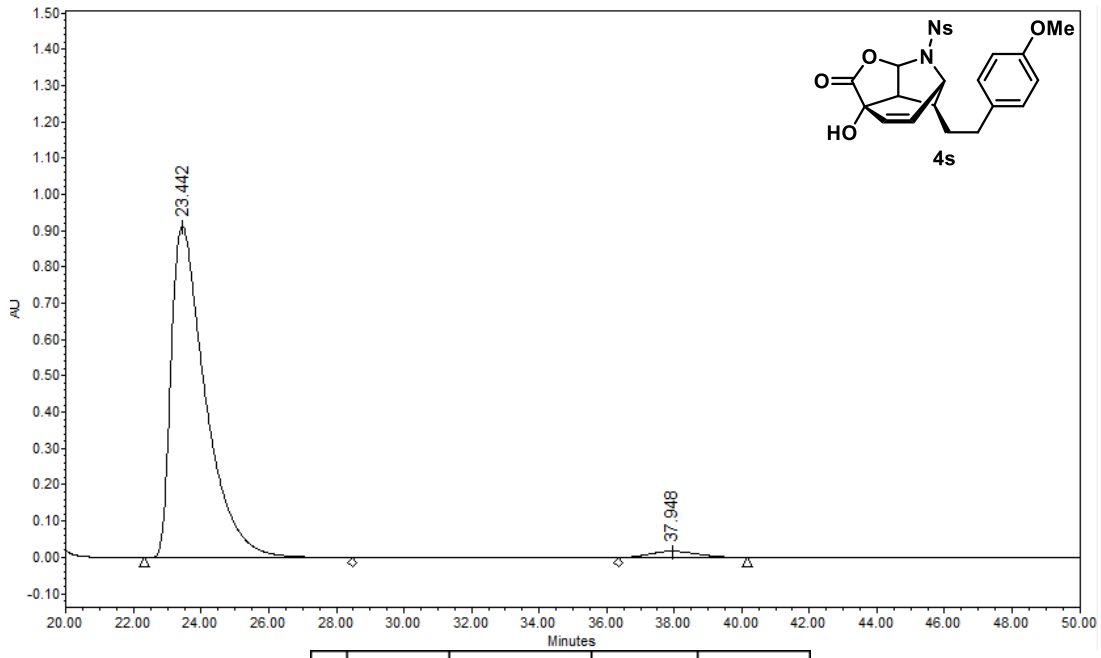


	RT	Area	% Area	Height
1	22.638	31788220	98.73	533880
2	45.233	410300	1.27	4987

IC, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (**4s**)

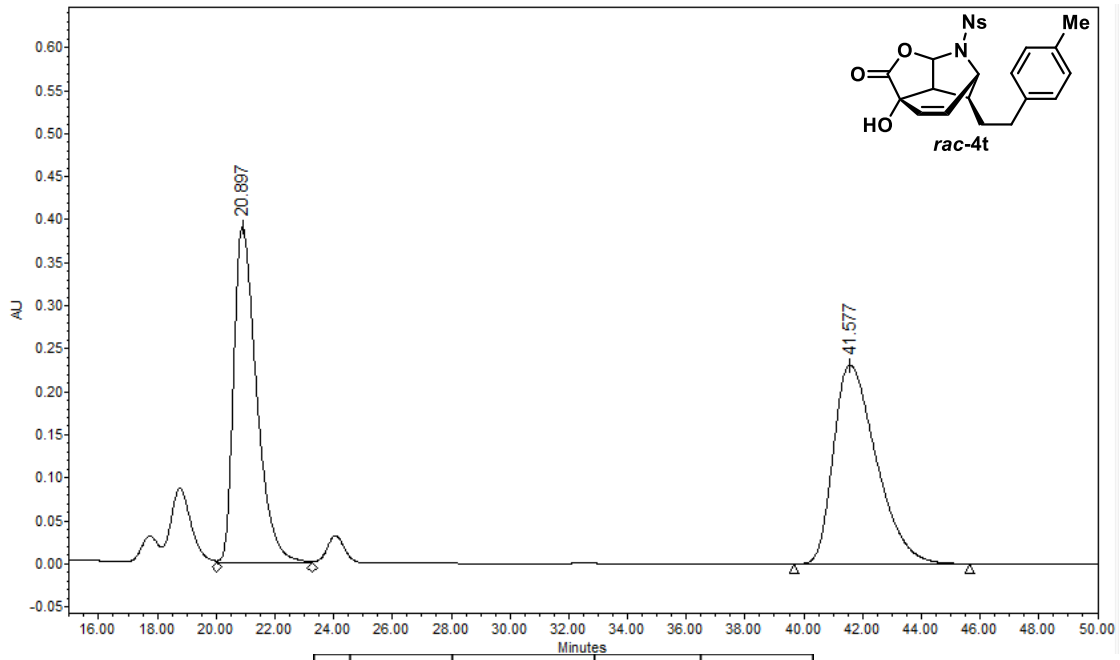


	RT	Area	% Area	Height
1	26.580	7269438	50.06	87071
2	42.718	7252301	49.94	61001

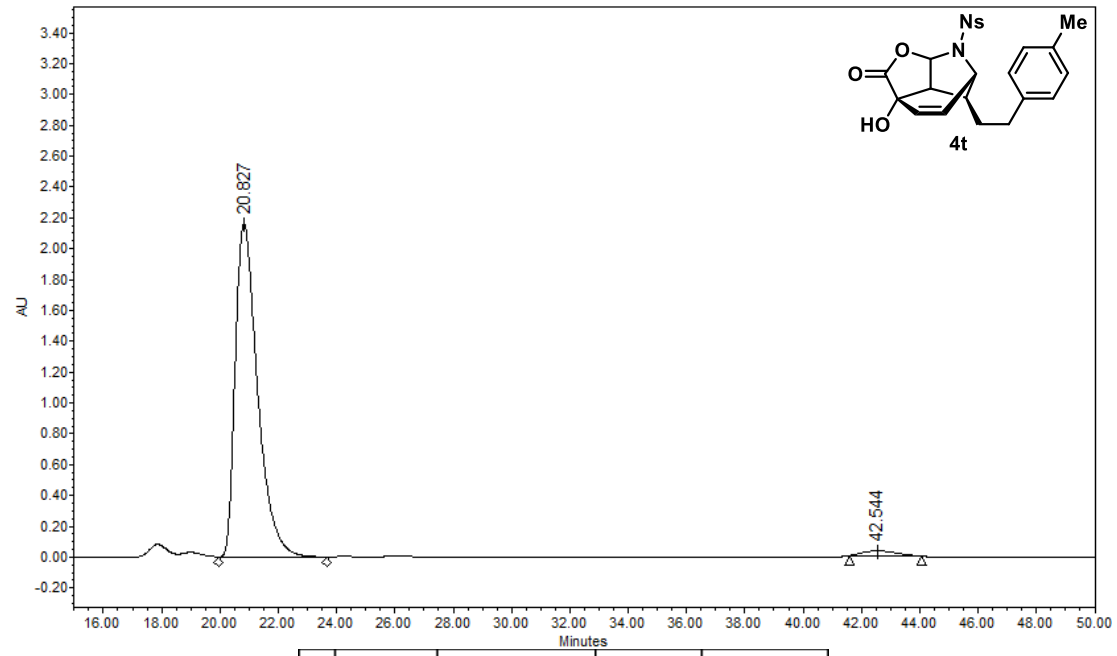


	RT	Area	% Area	Height
1	23.442	64146800	97.45	913117
2	37.948	1679365	2.55	17301

IC, Hexane : 2-Propanol = 70:30, λ = 243 nm, flow rate = 1.0 mL/min (**4t**)

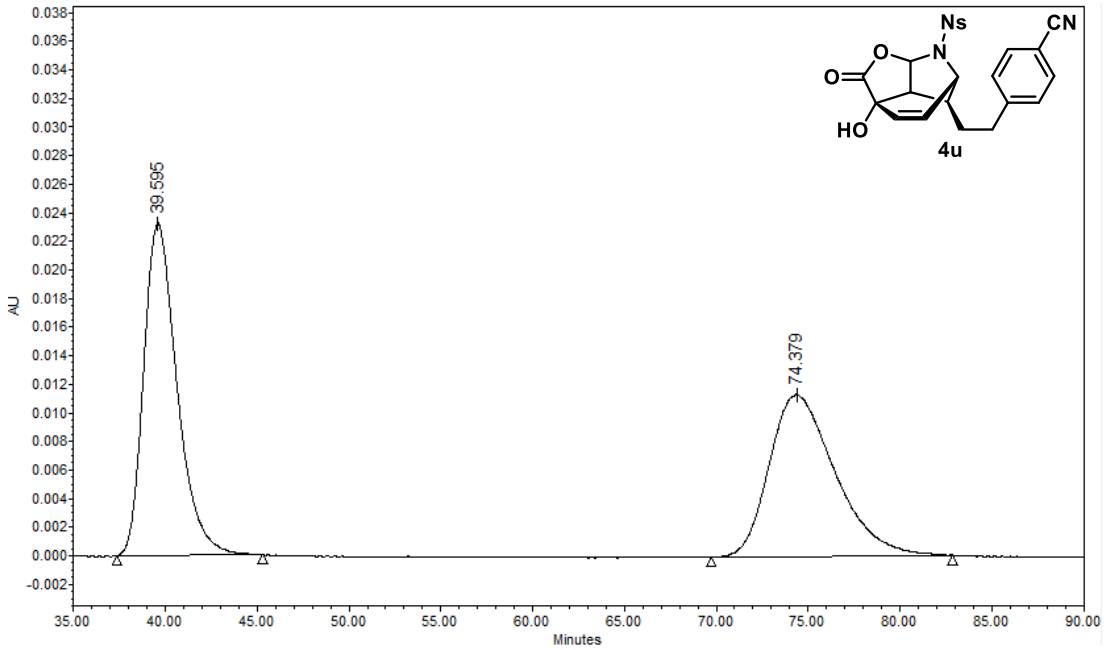


	RT	Area	% Area	Height
1	20.897	21082965	47.31	390278
2	41.577	23484039	52.69	231242

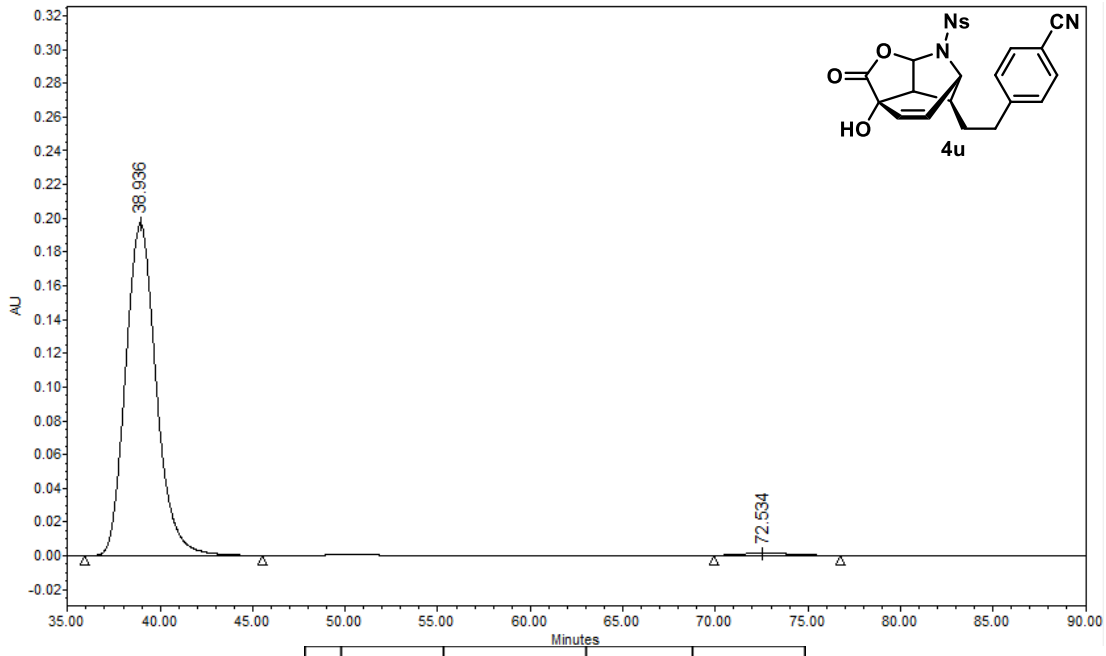


	RT	Area	% Area	Height
1	20.827	115500019	97.77	2162396
2	42.544	2628459	2.23	32875

IC, Hexane : 2-Propanol = 50:50, λ = 243 nm, flow rate = 1.0 mL/min (**4u**)

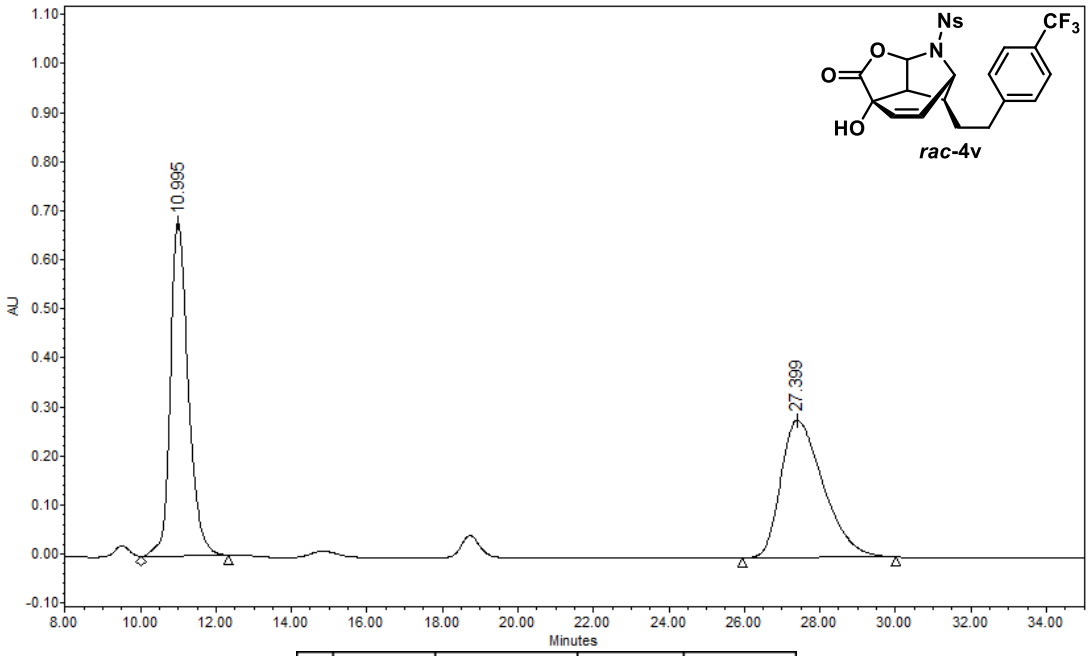


	RT	Area	% Area	Height
1	39.595	2904094	50.78	23233
2	74.379	2814908	49.22	11352

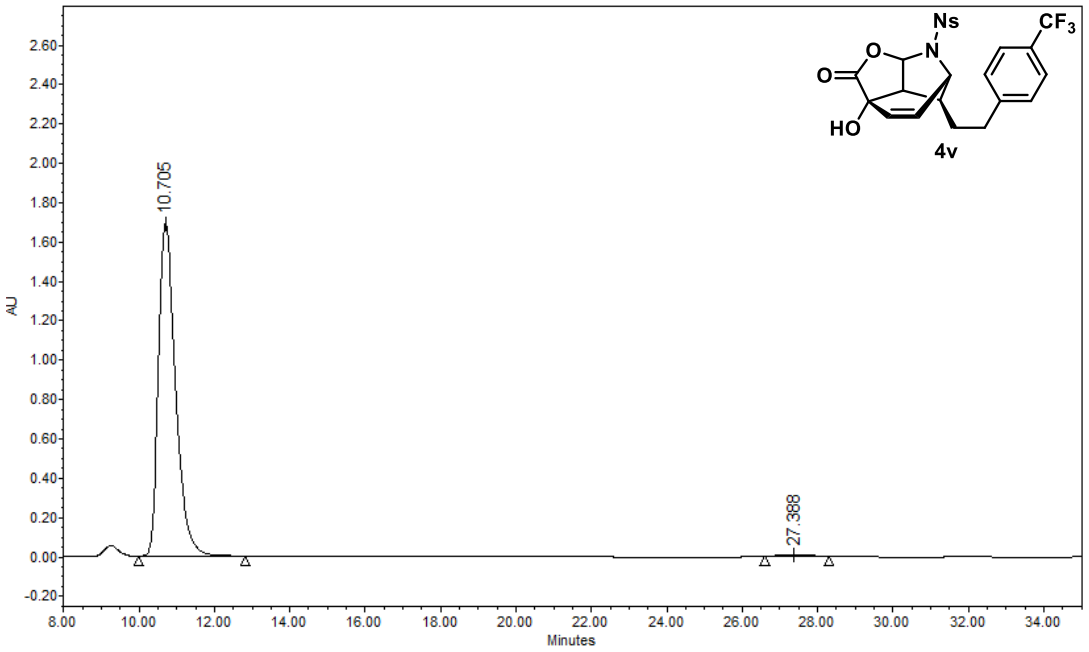


	RT	Area	% Area	Height
1	38.936	22672270	98.75	197091
2	72.534	286832	1.25	1379

IC, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (**4v**)

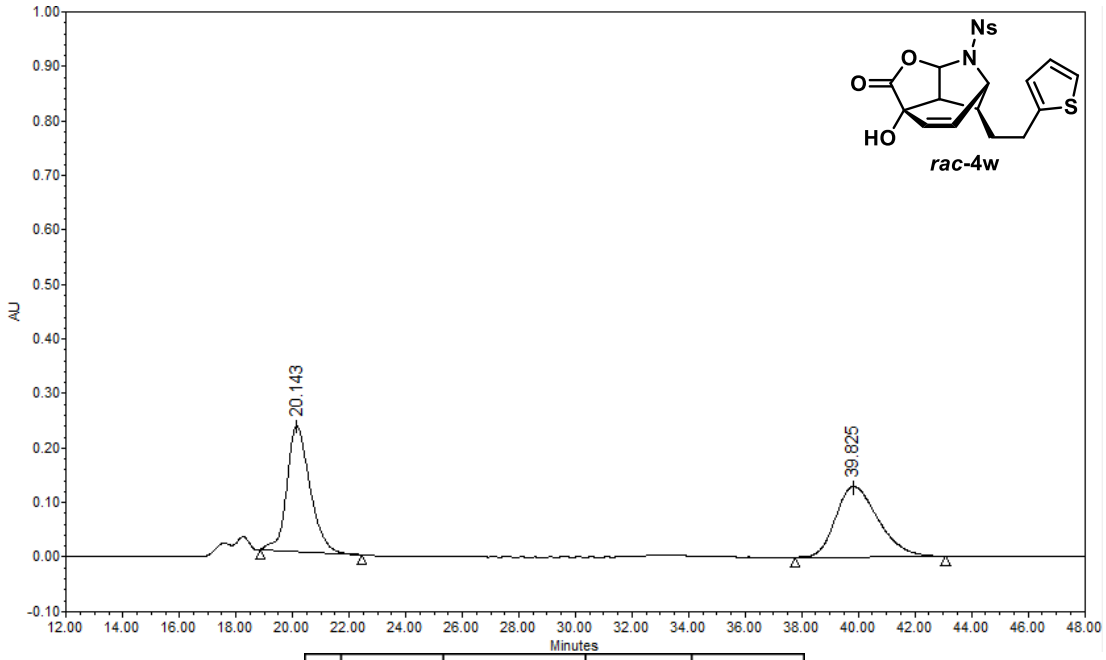


	RT	Area	% Area	Height
1	10.995	22416263	50.61	680455
2	27.399	21876082	49.39	279686

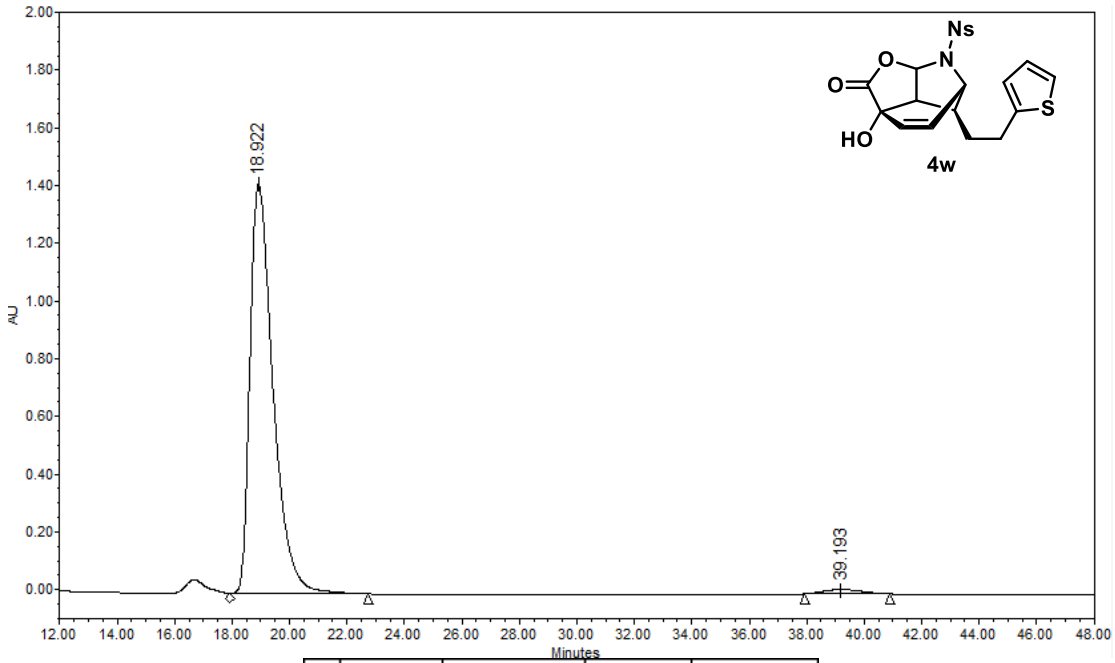


	RT	Area	% Area	Height
1	10.705	53439923	99.08	1691833
2	27.388	494655	0.92	8477

IC, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (**4w**)

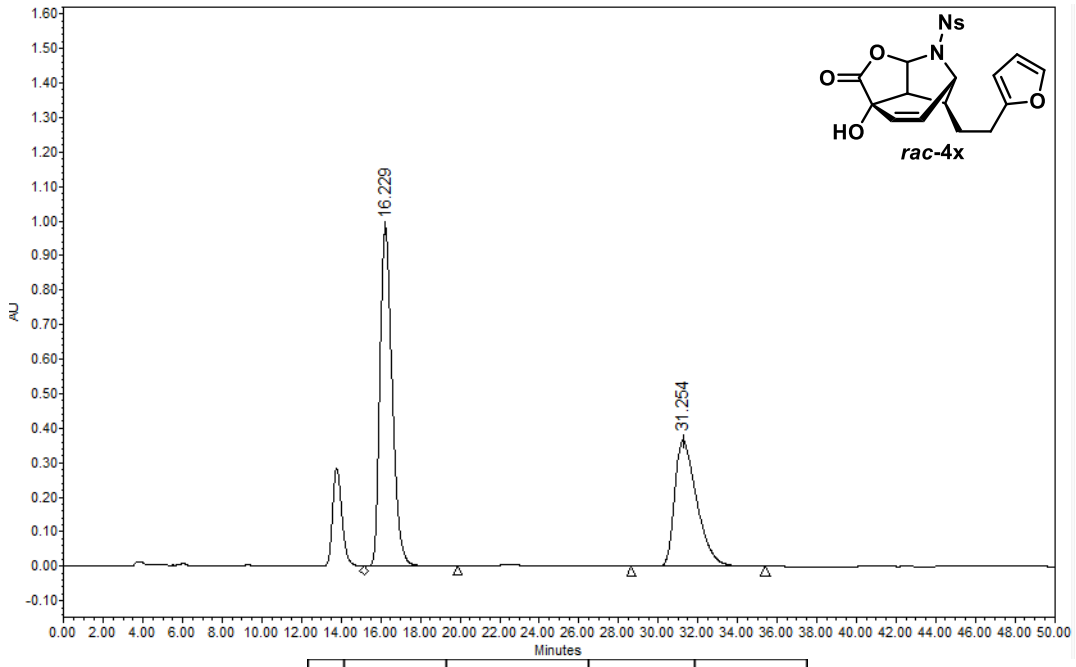


	RT	Area	% Area	Height
1	20.143	13084803	49.33	230338
2	39.825	13439657	50.67	128677

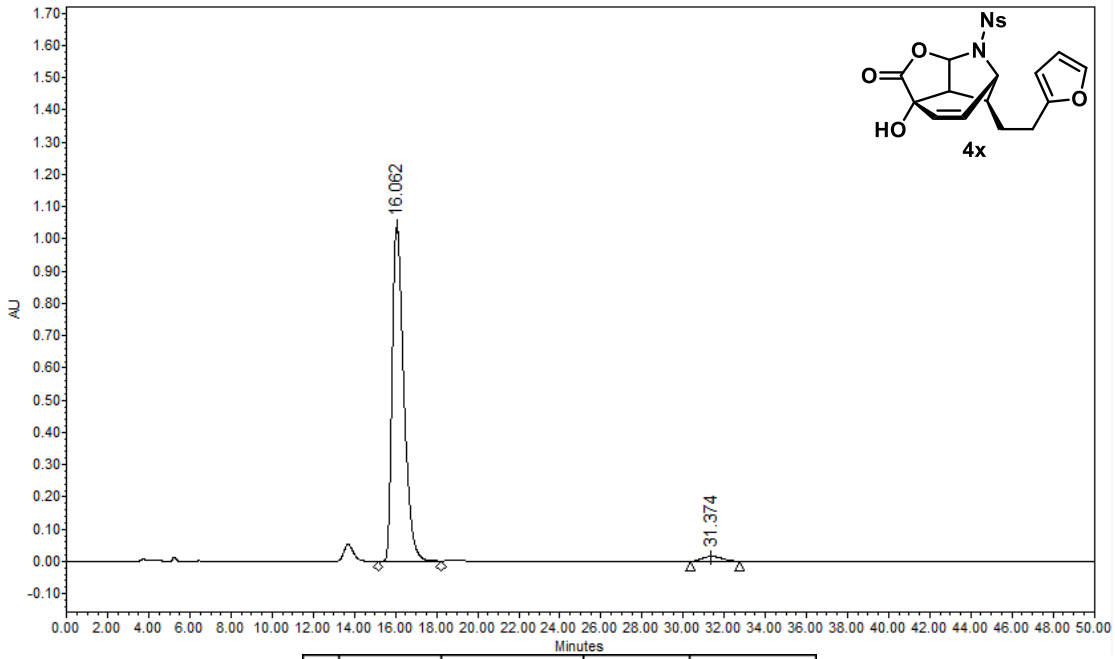


	RT	Area	% Area	Height
1	18.922	79198613	98.29	1419915
2	39.193	1380976	1.71	14921

IC, Hexane : 2-Propanol = 60:40, λ = 243 nm, flow rate = 1.0 mL/min (**4x**)

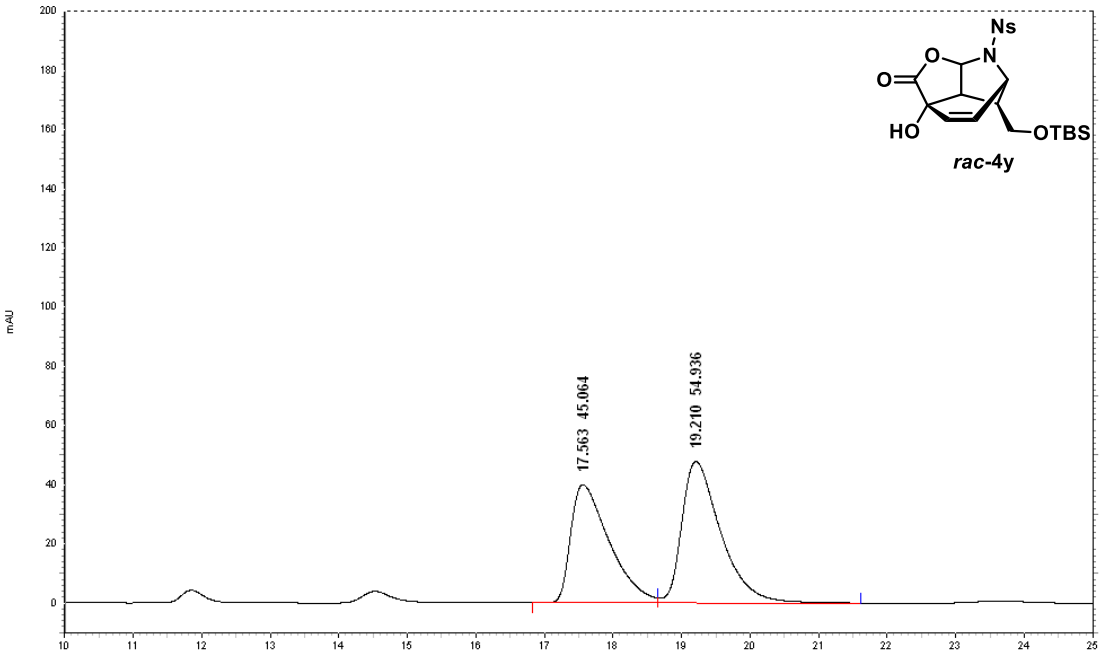


	RT	Area	% Area	Height
1	16.229	42188618	59.80	981333
2	31.254	28362183	40.20	365309

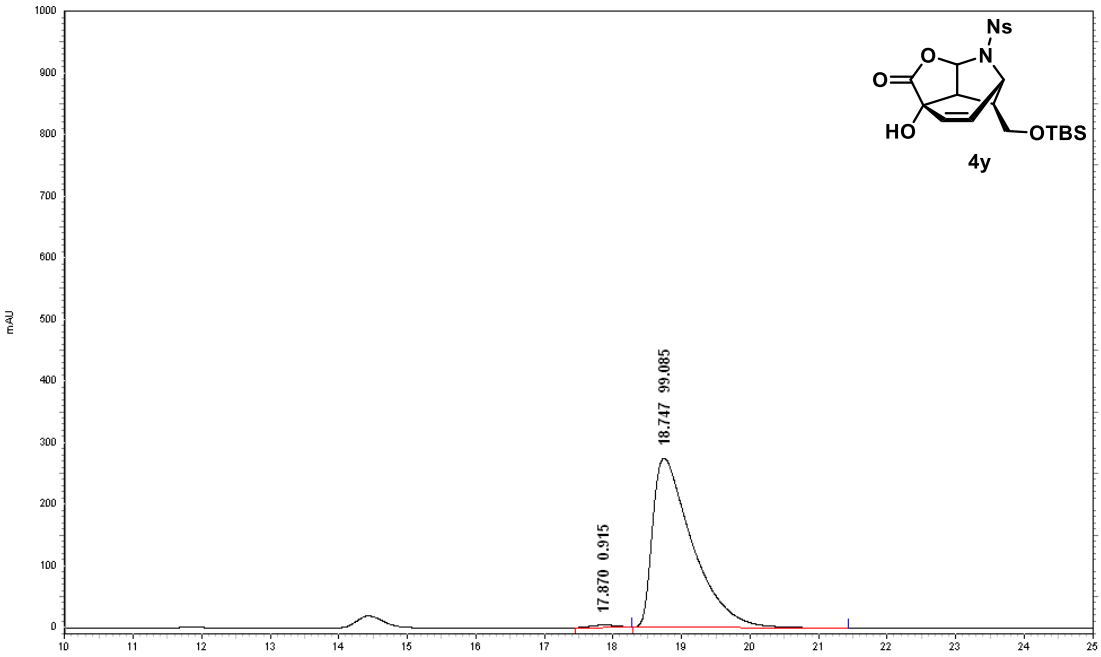


	RT	Area	% Area	Height
1	16.062	40988202	97.59	1041640
2	31.374	1014287	2.41	15009

ID, Hexane : 2-Propanol = 80:20, λ = 243 nm, flow rate = 1.0 mL/min (**4y**)

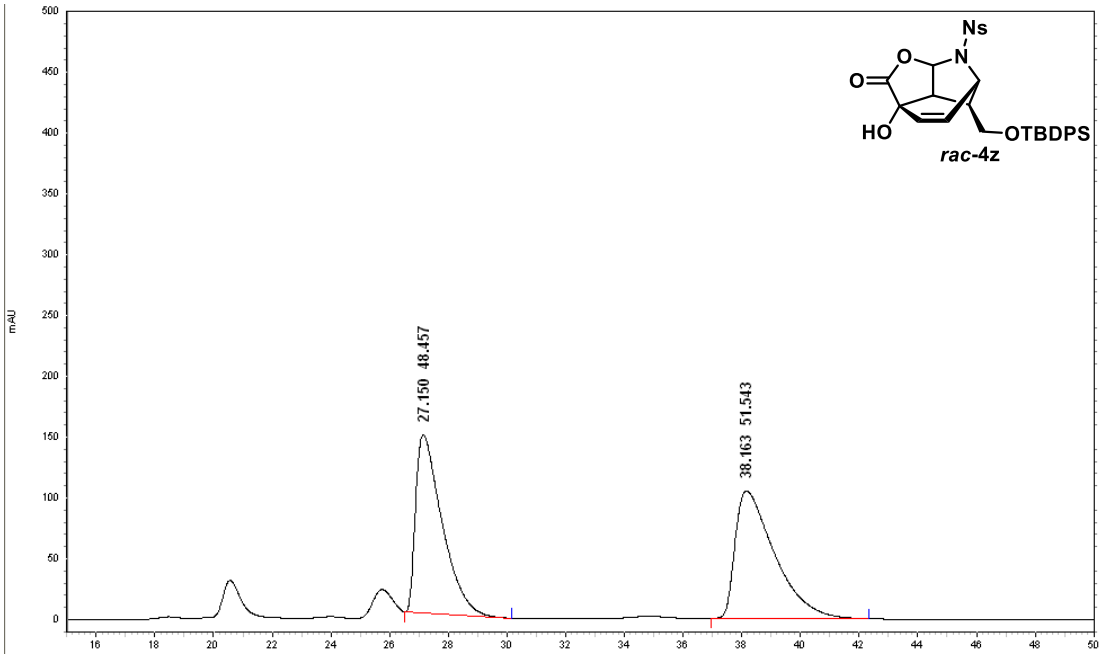


Retention Time	Area	Area Percent
17.563	6205638	45.064
19.210	7565072	54.936

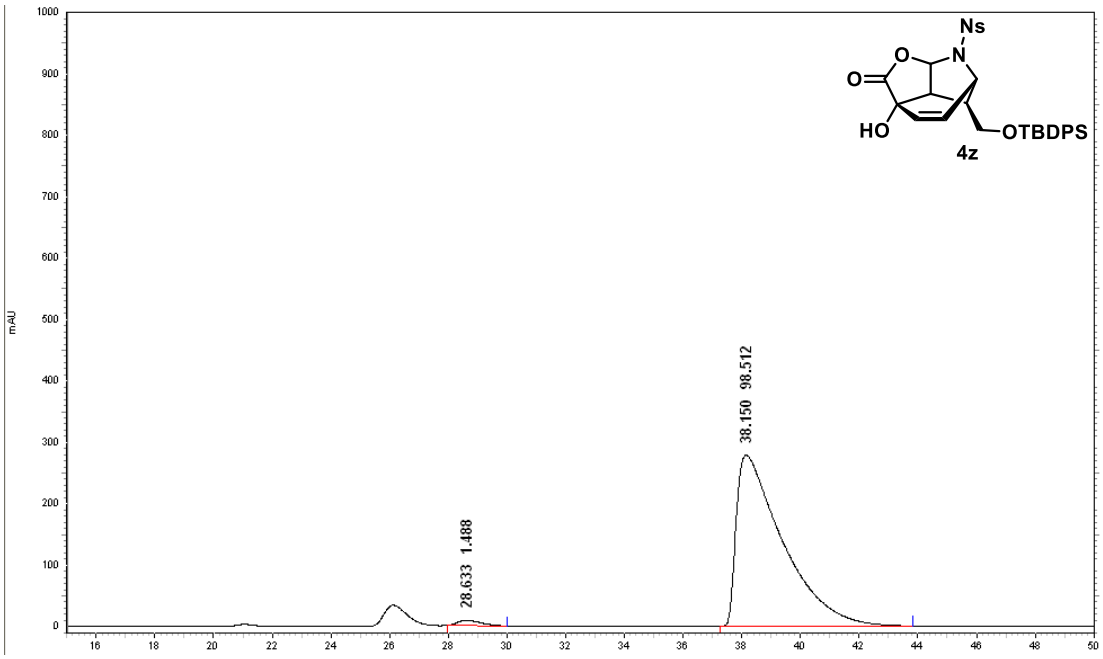


Retention Time	Area	Area Percent
17.870	408167	0.915
18.747	44201501	99.085

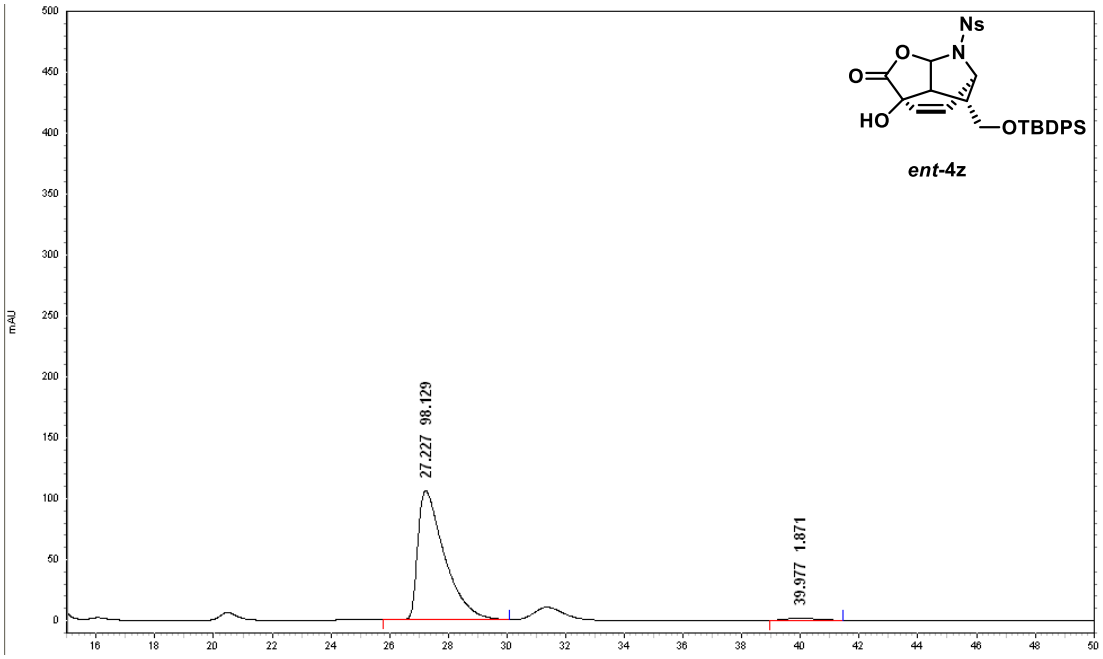
ID, Hexane : 2-Propanol = 85:15, λ = 243 nm, flow rate = 1.0 mL/min (**4z**)



Retention Time	Area	Area Percent
27.150	36799141	48.457
38.163	39142214	51.543



Retention Time	Area	Area Percent
28.633	1851411	1.488
38.150	122538935	98.512



Retention Time	Area	Area Percent
27.227	26615936	98.129
39.977	507597	1.871

VI. Crystallographic Data

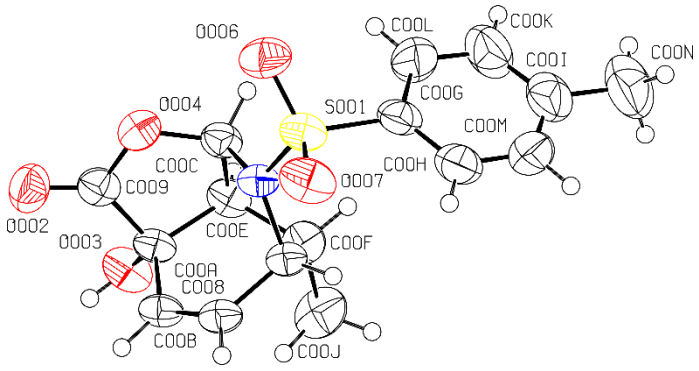


Figure S10. Molecular structure of compound **3a** (50% probability elliposoids) CCDC No : 2495584
-The crystal was prepared by vapor diffusion using Ethyl Acetate-Pentane

Empirical formula	$C_{16}H_{17}NO_5S$
Formula weight	335.36
Temperature/K	295.1(4)
Crystal system	monoclinic
Space group	C2
a/Å	12.6434(15)
b/Å	6.5202(6)
c/Å	19.975(3)
α/°	90
β/°	99.998(12)
γ/°	90
Volume/Å^3	1621.7(3)
Z	4
ρ_{calc}g/cm^3	1.374
μ/mm^{-1}	0.224
F(000)	704.0
Crystal size/mm^3	0.3 × 0.1 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.214 to 59.184
Index ranges	-16 ≤ h ≤ 14, -8 ≤ k ≤ 6, -16 ≤ l ≤ 26
Reflections collected	3819
Independent reflections	2850 [R_{int} = 0.0244, R_{sigma} = 0.0547]
Data/restraints/parameters	2850/1/211
Goodness-of-fit on F^2	1.117
Final R indexes [I>=2σ (I)]	R_1 = 0.0625, wR_2 = 0.1604
Final R indexes [all data]	R_1 = 0.0906, wR_2 = 0.1731
Largest diff. peak/hole / e Å^{-3}	0.31/-0.24
Flack parameter	0.08(7)

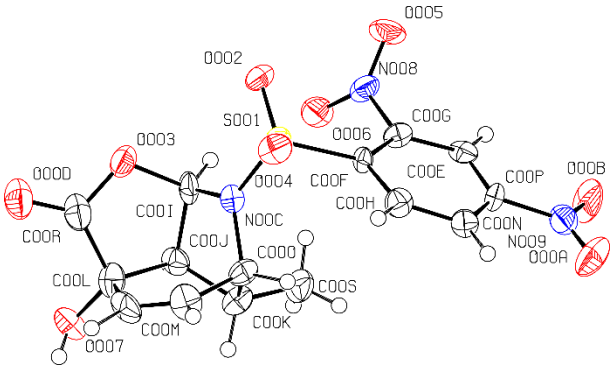


Figure S11. Molecular structure of compound **6a'** (50% probability elliposoids) CCDC No : 2495586
-The crystal was prepared by vapor diffusion using Ethyl Acetate-Pentane

Empirical formula	$C_{15}H_{13}N_3O_9S$
Formula weight	411.34
Temperature/K	160.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.4004(14)
b/Å	7.845(2)
c/Å	32.682(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1641.1(7)
Z	4
ρ_{calc}g/cm^3	1.665
μ/mm^{-1}	0.259
F(000)	848.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.986 to 58.928
Index ranges	-8 ≤ h ≤ 8, -10 ≤ k ≤ 10, -44 ≤ l ≤ 39
Reflections collected	10351
Independent reflections	3890 [R_{int} = 0.1708, R_{sigma} = 0.2798]
Data/restraints/parameters	3890/0/255
Goodness-of-fit on F^2	0.985
Final R indexes [I>=2σ (I)]	R_1 = 0.0895, wR_2 = 0.1270
Final R indexes [all data]	R_1 = 0.2186, wR_2 = 0.1753
Largest diff. peak/hole / e Å^{-3}	0.36/-0.40
Flack parameter	0.0(3)

VII. Reference

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