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Highly Enantioselective Synthesis of Fused Bicyclic Dihydropyranones *via* Low-loading *N*-Heterocyclic Carbene Organocatalysis

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Supporting Information

Table of Contents

1. General Information

General Procedures. All reactions were performed in oven-dried or flame-dried reaction vessels, modified Schlenk flasks, or round-bottom flasks. The flasks were fitted with Teflon screw caps and reactions were conducted under an atmosphere of argon if needed. Gas-tight syringes with stainless steel needles were used to transfer air- and moisture-sensitive liquids. All moisture and/or air sensitive solid compounds were manipulated inside normal desiccators. Flash column chromatography was performed using silica gel (40–63 μm, 230–400 mesh).

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates (Merck) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and to a solution of $KMnO_4$ (1 g of $KMnO_4$, 6 g of K_2CO_3 and 0.1 g of KOH in 100 mL of H_2O) or vanillin (2 g of vanillin and 4 mL of concentrated H_2SO_4 in 100 mL of EtOH) followed by heating.

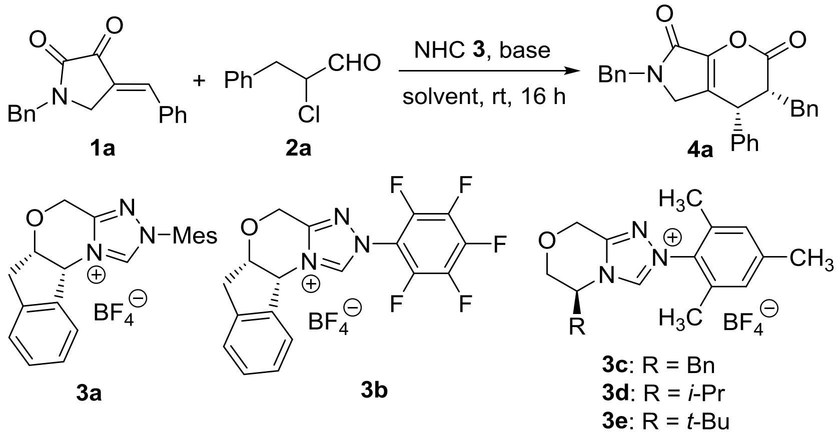
Organic solutions were concentrated at 30-50 ℃ on rotary evaporators at ~10 torr followed by drying on vacuum pump at ~1 torr. Reaction temperatures are reported as the temperature of the bath surrounding the vessel unless otherwise stated.

Materials. Commercial reagents and solvents were were obtained from Adamas-beta, Aldrich Chemical Co., Alfa Aesar, Macklin and Energy Chemical and used as received with the following exceptions: THF, 1,4-dioxane and toluene were purified by refluxing over Na-benzophenone under positive argon pressure followed by distillation. [1] The enone substrates were prepared according to literature procedure. [2]

Instrumentation.

- Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with Bruker AV 400 MHz and JEOL 600MHz spectrometers. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ($CHCl_3$)). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant(s) (Hz), integration].
- Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Bruker AV 400 MHz and JEOL 600MHz spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 77.0 ($CHCl_3$)). Data are reported as follows: chemical shift [multiplicity (if not singlet), assignment (C_q = fully substituted carbon)].
- High resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2 using an electrospray (ESI) ionization source.

2. **Optimization Study of the Asymmetric NHC-catalyzed [4+2] cycloaddition Reactions of the 4-benzylidene-pyrrolidine-2,3-dione 1a and 2-chloro-3-phenyl-propanal 2a**[a]

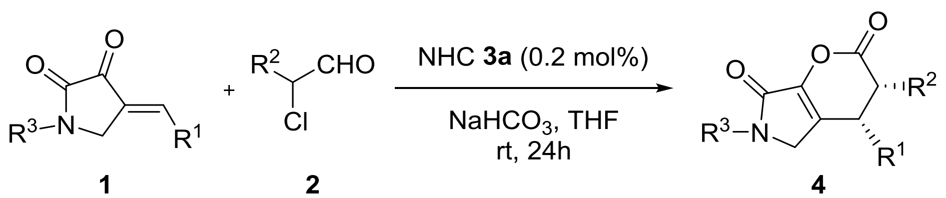


Entry	**3**	Solvent	Base [b]	Yield(%) [c]	ee(%) [d]
1	**3a**	THF	$NaHCO_3$	91	>99
2	**3b**	THF	$NaHCO_3$	17	90
3	**3c**	THF	$NaHCO_3$	16	-97
4	**3d**	THF	$NaHCO_3$	74	-98
5	**3e**	THF	$NaHCO_3$	60	-96
6	**3a**	THF	DBU	77	98
7	**3a**	THF	Et_3N	47	99
8	**3a**	THF	DIPEA	81	>99
9	**3a**	THF	K_3PO_4	83	>99
10	**3a**	THF	K_3CO_4	86	>99
11	**3a**	toluene	$NaHCO_3$	91	97
12	**3a**	CH_3CN	$NaHCO_3$	86	>99
13	**3a**	1,4-dioxane	$NaHCO_3$	89	95
14	**3a**	DCM	$NaHCO_3$	86	>99
15 [e]	**3a**	THF	$NaHCO_3$	91	>99
16 [f]	**3a**	THF	$NaHCO_3$	89	>99
17 [g]	**3a**	**THF**	**$NaHCO_3$**	**91**	**>99**

[a]Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), base (0.15 mmol), and catalyst **3** (0.01 mmol) in solvent (1.0 mL) at rt for 16 h; d.r. was determined to be >99:1 by ^{1}H-NMR analysis of the crude reaction mixture. [b]DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA: *N,N*-diisopropylethyl-amine; Mes: mesityl. [c]Yield of the isolated products **4a**. [d]Determined by HPLC using a chiral stationary phase. [e]5 mol % of **3a** was used. [f]1 mol % of **3a**, 0.2-mmol reaction scale, 24 h. [g]0.2 mol % of **3a**, 0.2-mmol reaction scale, 24 h.

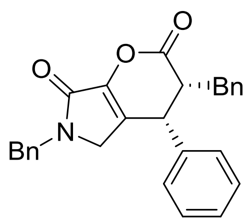
As showed in the above table, studies on NHC catalysts revealed that, in the presence of $NaHCO_3$, 10 mol% of indanol-derived catalyst **3a,** with an electron-rich *N*-mesityl substituent, afforded the desired product with excellent diastereoselectivity, enantioselectivity and yield (entry 1). Switching the *N*-substituent of NHC from mesityl to electron-deficient pentafluorobenzene led to inferior results (entry 2). The morpholine-based triazolium **3c** could deliver the desired bicyclic product **4a** with satisfying stereoselectivity, albeit quite poor conversion (entry 3). Triazoliums **3d** and **3e,** similar except for different chiral substituents, led to product **4a** in encouraging yields of 74% and 60%, without reducing *ee* values (entries 4 and 5). Using **3a** as the optimal catalyst, we further screened the effect of base additives (entries 6–10): neither organic bases (DBU, Et_3N, DIPEA) nor stronger inorganic bases (K_3PO_4, K_3CO_3) increased the isolated yield of the enantioenriched **4a**. Solvents had limited effect on reaction outcome: most of the solvents gave comparable yields and satisfying stereoselectivity, although 1,4-dioxane gave lower *ee* (entries 11–13). Perhaps most important for our goals, we found that the catalytic reaction remained highly efficient even as catalyst loading was gradually reduced from 10 mol% to 0.2 mol% (entries 4 and 15−17). In this way, we were able to obtain optimal yield and stereoselectivity using only 0.2 mol% of catalyst **3a** and inexpensive $NaHCO_3$ as base additive in THF at room temperature.

3. General Procedure for the Asymmetric Synthesis of Bicyclic Dihydropyrones 4a–4x by using α-Chloroaldehydes



The reaction was carried out with enones **1** (0.20 mmol), **2** (0.60 mmol), $NaHCO_3$ (0.30 mmol) in the presence of catalyst **3a** (0.0004 mmol) in anhydrous THF (2.0 mL) under argon atmosphere at room temperature for 24 hours. When the reaction was complete detected by TLC, the resulting reaction mixture was concentrated to dryness under reduced pressure at 35 ^{o}C. The residue was purified though column chromatograghy on silica gel (CH_2Cl_2/petroleum ether/ MeOH = 100 :100 :1) to afford the desired bicyclic dihydropyranones **4a – 4x**, which was dried under vacuum and further analyzed by ^{1}H-NMR, ^{13}C-HMR, HRMS, chiral HPLC analysis, *etc*.

***(3R,4R)-3,6-dibenzyl-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4a**



4a

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4a** as a white solid with 91% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.64 min, t_{major} = 6.59 min; $[\alpha]_D^{20}$ = –214.7 (*c* = 0.61 in $CHCl_3$).

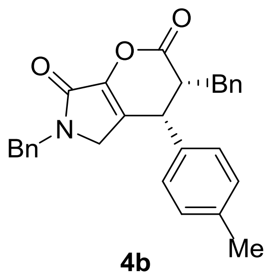
NMR and HRMS data for the product **4a**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.16 (m, 11H), 7.04 – 6.98 (m, 2H), 6.96 – 6.88 (m, 2H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 3.69 (d, *J* = 18.4 Hz, 1H), 3.59 (d, *J* = 7.2 Hz, 1H), 3.52 (d, *J* = 18.4 Hz, 1H), 3.45 – 3.37 (m, 1H), 3.33 (dd, *J* = 14.8, 4.4 Hz, 1H), 2.40 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.3, 162.8, 142.8, 137.8, 136.4, 136.1, 129.4, 129.0, 128.9, 128.6, 128.6, 128.3, 128.0, 126.8, 47.0, 46.7, 45.8, 40.9, 32.3.

HRMS (ESI): *m/z* calculated for $C_{27}H_{23}NO_3+Na^+$: 432.1570, found: 432.1580.

***(3R,4R)-3,6-dibenzyl-4-(p-tolyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4b**



4b

Prepared according to the general procedure using (*E*)-1-benzyl-4-(4-methylbenzylidene)pyrrolidine-2,3-dione **1b** (58.3 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4b** as a white solid with 87% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA

column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.51 min, t_{major} = 5.49 min; $[\alpha]_D^{20}$ = –188.9 (*c* = 0.54 in $CHCl_3$).

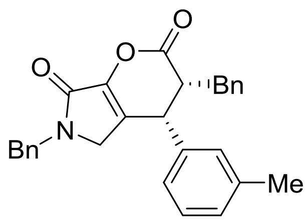
NMR and HRMS data for the product **4b**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.16 (m, 8H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.07 – 6.97 (m, 2H), 6.85 – 6.73 (m, 2H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 3.67 (d, *J* = 18.4 Hz, 1H), 3.58 – 3.46 (m, 2H), 3.42 – 3.27 (m, 2H), 2.40 (dd, *J* = 14.2, 10.0 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.4, 162.9, 142.7, 138.4, 137.9, 136.5, 132.9, 130.0, 129.0, 128.9, 128.6, 128.2, 127.9, 126.8, 47.0, 46.7, 45.9, 32.3, 21.1.

HRMS (ESI): *m/z* calculated for $C_{28}H_{25}NO_3$+MeOH+Na^+: 478.1989, found: 478.1992.

(3R,4R)-3,6-dibenzyl-4-(m-tolyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione **4c**



4c

Prepared according to the general procedure using (*E*)-1-benzyl-4-(3-methylbenzylidene)pyrrolidine-2,3-dione **1c** (58.3 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4c** as a white solid with 89% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.27 min, t_{major} = 4.99 min; $[\alpha]_D^{20}$ = –236.4 (*c* = 0.56 in $CHCl_3$).

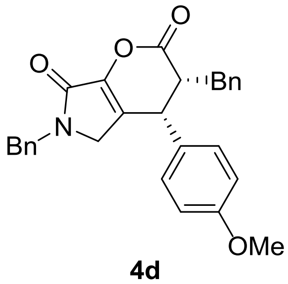
NMR and HRMS data for the product **4c**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.16 (m, 9H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.76 – 6.64 (m, 2H), 4.82 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 14.8 Hz, 1H), 3.67 (d, *J* = 18.4 Hz, 1H), 3.59 – 3.47 (m, 2H), 3.44 – 3.23 (m, 2H), 2.39 (dd, *J* = 14.6, 10.0 Hz, 1H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.4, 162.9, 142.8, 139.2, 137.9, 136.5, 135.9, 129.2, 129.0, 128.9, 128.6, 128.2, 127.9, 126.8, 125.2, 47.0, 46.7, 45.7, 40.9, 32.3, 21.4.

HRMS (ESI): *m/z* calculated for $C_{28}H_{25}NO_3$+Na^+: 446.1727, found: 446.1728.

***(3R,4R)-3,6-dibenzyl-4-(4-methoxyphenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4d**



4d

Prepared according to the general procedure using (*E*)-1-benzyl-4-(4-methoxybenzylidene)pyrrolidine-2,3-dione **1d** (61.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4d** as a white solid with 96% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.62 min, t_{major} = 5.59 min; $[\alpha]_D^{20}$ = –193.7 (*c* = 0.65 in $CHCl_3$).

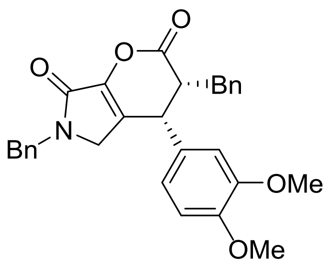
NMR and HRMS data for the product **4d**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.15 (m, 8H), 7.07 – 6.96 (m, 2H), 6.84 (s, 4H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.35 (d, *J* = 14.8 Hz, 1H), 3.80 (s, 3H), 3.67 (d, *J* = 18.4 Hz, 1H), 3.53 (dd, *J* = 12.8, 6.0 Hz, 2H), 3.45 – 3.26 (m, 2H), 2.40 (dd, *J* = 14.4, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 162.9, 159.6, 142.6, 137.9, 136.5, 129.1, 129.0, 128.9, 128.6, 128.2, 127.9, 127.8, 126.8, 114.7, 55.3, 46.9, 46.7, 46.0, 40.1, 32.3.

HRMS (ESI): *m/z* calculated for $C_{28}H_{25}NO_4$+MeOH+Na^+: 494.1938, found: 494.1940.

***(3R,4R)-3,6-dibenzyl-4-(3,4-dimethoxyphenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4e**



4e

Prepared according to the general procedure using (*E*)-1-benzyl-4-(3,4-dimethoxybenzylidene)pyrrolidine-2,3-dione **1e** (67.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4e** as a white solid with 93% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA

column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.37 min, t_{major} = 6.52 min; $[\alpha]_D^{20}$ = –88.4 (*c* = 0.63 in $CHCl_3$).

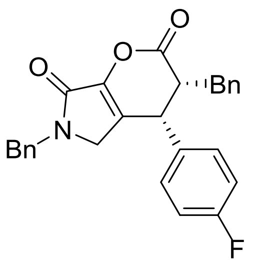
NMR and HRMS data for the product **4e**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.18 (m, 8H), 7.04 (d, *J* = 6.8 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.31 (d, *J* = 2.0 Hz, 1H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.69 (d, *J* = 18.8 Hz, 1H), 3.55 (d, *J* = 18.8 Hz, 1H), 3.51 (d, *J* = 6.8 Hz, 1H), 3.45 – 3.30 (m, 2H), 2.41 (dd, *J* = 14.4, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 162.9, 149.3, 149.0, 142.7, 137.8, 136.4, 129.0, 128.9, 128.8, 128.6, 128.3, 128.2, 127.9, 126.8, 120.2, 111.6, 110.9, 55.9, 55.8, 47.0, 46.7, 45.7, 40.5, 32.3.

HRMS (ESI): *m/z* calculated for $C_{29}H_{27}NO_5$+MeOH+Na^+: 524.2044, found: 524.2047.

<u>(3R,4R)-3,6-dibenzyl-4-(4-fluorophenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione</u> **<u>4f</u>**



4f

Prepared according to the general procedure using (*E*)-1-benzyl-4-(4-fluorobenzylidene)pyrrolidine-2,3-dione **1f** (59.1 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4f** as a white solid with 88% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 94% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.23 min, t_{major} = 5.01 min; $[\alpha]_D^{20}$ = –210.5 (*c* = 0.55 in $CHCl_3$).

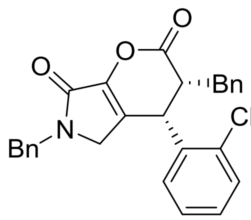
NMR and HRMS data for the product **4f**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.16 (m, 8H), 7.07 – 6.97 (m, 4H), 6.93 – 6.81 (m, 2H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 3.69 (d, *J* = 18.4 Hz, 1H), 3.58 (d, *J* = 7.2 Hz, 1H), 3.51 (d, *J* = 18.4 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.35 (dd, *J* = 14.8, 4.4 Hz, 1H), 2.36 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.2, 162.6, 142.9, 137.5, 136.4, 131.8, 129.7, 129.7, 128.9, 128.7, 128.3, 127.9, 126.9, 116.5, 116.3, 46.9, 46.7, 45.6, 40.1, 32.3.

HRMS (ESI): *m/z* calculated for $C_{27}H_{22}FNO_3$+MeOH+Na^+: 482.1738, found: 482.1742.

***(3R,4S)-3,6-dibenzyl-4-(2-chlorophenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4g**



4g

Prepared according to the general procedure using (*E*)-1-benzyl-4-(2-chlorobenzylidene)pyrrolidine-2,3-dione **1g** (62.3 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4g** as a syrup with 85% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 98% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.49 min, t_{major} = 6.48 min; $[\alpha]_D^{20}$ = –129.7 (*c* = 0.70 in $CHCl_3$).

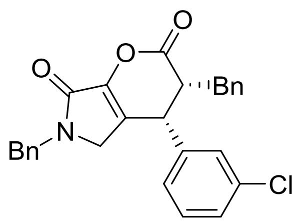
NMR and HRMS data for the product **4g**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.06 (m, 12H), 6.89 – 6.85 (m, 2H), 4.82 (d, *J* = 14.8 Hz, 1H), 4.33 – 4.21 (m, 2H), 3.76 (d, *J* = 18.8 Hz, 1H), 3.58 (d, *J* = 18.8 Hz, 1H), 3.45 – 3.34 (m, 2H), 2.60 (dd, *J* = 15.6, 11.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.6, 162.6, 142.7, 137.4, 136.5, 133.8, 131.5, 130.3, 129.5,, 129.2, 128.9, 128.8, 128.7, 128.3, 128.2, 127.9, 126.9, 47.2, 46.7, 46.2, 38.3, 32.5.

HRMS (ESI): *m/z* calculated for $C_{27}H_{22}ClNO_3$+MeOH+Na^+: 498.1443, found: 498.1449.

***(3R,4R)-3,6-dibenzyl-4-(3-chlorophenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4h**



4h

Prepared according to the general procedure using (*E*)-1-benzyl-4-(3-chlorobenzylidene)pyrrolidine-2,3-dione **1h** (62.3 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4h** as a white solid with 81% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.64 min, t_{major} = 6.64 min; $[\alpha]_D^{20}$ = –209.4 (*c* = 0.62 in $CHCl_3$).

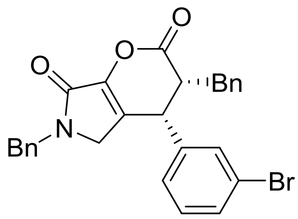
NMR and HRMS data for the product **4h**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.24 (m, 8H), 7.20 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.04 – 6.97 (m, 2H), 6.85 – 6.80 (m, 2H), 4.83 (d, *J* = 14.8 Hz, 1H), 4.35 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 18.4 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.48 – 3.31 (m, 2H), 2.37 (dd, *J* = 14.4, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.4, 162.9, 142.8, 139.2, 137.9, 136.5, 135.9, 129.2, 129.0, 128.9, 128.6, 128.6, 128.3, 127.9, 126.8, 125.2, 47.0, 46.7, 45.7, 40.9, 32.3.

HRMS (ESI): *m/z* calculated for $C_{27}H_{22}ClNO_3$+MeOH+Na^+: 498.1443, found: 498.1447.

***(3R,4R)-3,6-dibenzyl-4-(3-bromophenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4i**



4i

Prepared according to the general procedure using (*E*)-1-benzyl-4-(3-bromobenzylidene)pyrrolidine-2,3-dione **1i** (71.2 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4i** as a white solid with 87% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.67 min, t_{major} = 6.57 min; $[\alpha]_D^{20}$ = –242.7 (*c* = 0.52 in $CHCl_3$).

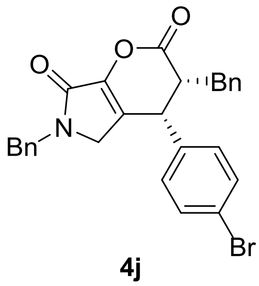
NMR and HRMS data for the product **4i**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.17 (m, 9H), 7.04 – 6.94 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.82 (d, *J* = 14.8 Hz, 1H), 4.35 (d, *J* = 14.8 Hz, 1H), 3.69 (d, *J* = 18.4 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.47 – 3.31 (m, 2H), 2.36 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.9, 162.6, 143.3, 138.2, 37.3, 136.3, 1331.7, 131.6, 131.0, 128.8, 128.3, 128.0, 127.5, 127.0, 126.2, 123.2, 46.9, 46.7, 45.4, 40.5, 32.4.

HRMS (ESI): *m/z* calculated for $C_{27}H_{22}BrNO_3$+MeOH+Na^+: 542.0937 (^{79}Br), 544.0917 (^{81}Br), found: 542.0947, 544.0931.

***(3R,4R)-3,6-dibenzyl-4-(4-bromophenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4j**



4j

Prepared according to the general procedure using (*E*)-1-benzyl-4-(4-bromobenzylidene)pyrrolidine-2,3-dione **1j** (71.2 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4j** as a white solid with 89% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.59 min, t_{major} = 6.48 min; $[\alpha]_D^{20}$ = –234.1 (*c* = 0.61 in $CHCl_3$).

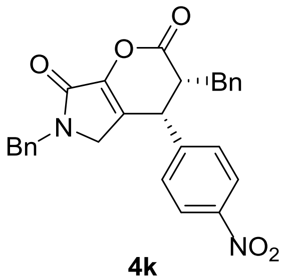
NMR and HRMS data for the product **4j**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 – 7.41 (m, 2H), 7.35 – 7.22 (m, 6H), 7.20 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.03 – 6.97 (m, 2H), 6.81 – 6.74 (m, 2H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 18.4 Hz, 1H), 3.58 – 3.46 (m, 2H), 3.46 – 3.31 (m, 2H), 2.37 (dd, *J* = 14.4, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.0, 162.6, 143.1, 137.4, 136.3, 135.1, 132.5, 129.7, 128.9, 128.7, 128.3, 128.0, 127.8, 127.0, 122.6, 46.9, 46.7, 45.4, 40.3, 32.3.

HRMS (ESI): *m/z* calculated for $C_{27}H_{22}BrNO_3$+MeOH+Na^+: 542.0937 (^{79}Br), 544.0917 (^{81}Br), found: 542.0925, 544.0944.

***(3R,4R)-3,6-dibenzyl-4-(4-nitrophenyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4k**



4k

Prepared according to the general procedure using (*E*)-1-benzyl-4-(4-nitrobenzylidene)pyrrolidine-2,3-dione **1k** (64.5 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4k** as a white solid with 94% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.55 min, t_{major} = 5.54 min; $[\alpha]_D^{20}$ = –276.4 (*c* = 0.59 in $CHCl_3$).

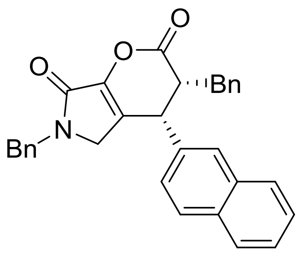
NMR and HRMS data for the product **4k**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (d, J = 8.8 Hz, 2H), 7.34 – 7.23 (m, 6H), 7.20 (dd, J = 7.6, 1.6 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 6.8 Hz, 2H), 4.78 (d, J = 14.8 Hz, 1H), 4.39 (d, J = 14.8 Hz, 1H), 3.72 (dd, J = 12.8, 5.6 Hz, 2H), 3.55 – 3.45 (m, 2H), 3.40 (dd, J = 14.8, 4.4 Hz, 1H), 2.33 (dd, J = 14.8, 10.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.6, 162.3, 148.0, 143.7, 143.4, 136.8, 136.2, 129.1, 128.9, 128.9, 128.8, 128.3, 128.0, 127.2, 126.6, 124.6, 46.8, 46.8, 45.1, 40.5, 32.4.

HRMS (ESI): *m/z* calculated for $C_{27}H_{22}N_2O_5$+MeOH+Na^+: 509.1683, found: 509.1691.

<u>(3R,4R)-3,6-dibenzyl-4-(naphthalen-2-yl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione</u> **<u>4l</u>**



4l

Prepared according to the general procedure using (*E*)-1-benzyl-4-(naphthalen-2-ylmethylene)pyrrolidine-2,3-dione **1l** (65.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4l** as a white solid with 82% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.47 min, t_{major} = 6.46 min; $[\alpha]_D^{20}$ = –306.6 (*c* = 0.51 in $CHCl_3$).

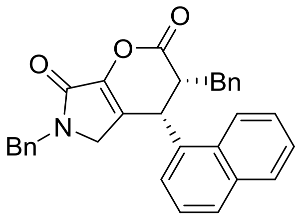
NMR and HRMS data for the product **4l**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 – 7.71 (m, 2H), 7.78 – 7.71 (m, 1H), 7.55 – 7.49 (m, 2H), 7.36 – 7.21 (m, 7H), 7.21 – 7.15 (m, 2H), 7.06 – 6.96 (m, 3H), 4.81 (d, J = 14.8 Hz, 1H), 4.32 (d, J = 14.8 Hz, 1H), 3.79 – 3.66 (m, 2H), 3.57 – 3.44 (m, 2H), 3.37 (dd, J = 14.8, 4.4 Hz, 1H), 2.41 (dd, J = 14.8, 10.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.3, 162.8, 142.9, 137.8, 136.4, 133.4, 133.3, 133.1, 129.5, 129.0, 128.9, 128.6, 128.4, 128.3, 127.9, 127.8, 127.6, 126.9, 126.7, 125.0, 47.0, 46.7, 45.7, 41.1, 32.4.

HRMS (ESI): *m/z* calculated for $C_{31}H_{25}NO_3$+MeOH+Na^+: 514.1989, found: 514.1993.

***(3R,4R)-3,6-dibenzyl-4-(naphthalen-1-yl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4m**



4m

Prepared according to the general procedure using (*E*)-1-benzyl-4-(naphthalen-1-ylmethylene)pyrrolidine-2,3-dione **1m** (65.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4m** as a white solid with 80% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.54 min, t_{major} = 5.33 min; $[\alpha]_D^{20}$ = –267.2 (*c* = 0.50 in $CHCl_3$).

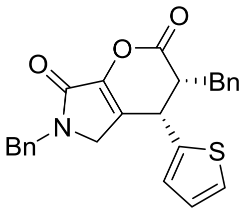
NMR and HRMS data for the product **4m**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.32 – 7.20 (m, 4H), 7.19 – 7.09 (m, 3H), 7.06 (t, *J* = 7.6 Hz, 2H), 6.70 (d, *J* = 7.2 Hz, 2H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.53 (d, *J* = 7.2 Hz, 1H), 4.17 (d, *J* = 14.8 Hz, 1H), 3.74 (d, *J* = 18.4 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.44 – 3.32 (m, 2H), 2.59 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.8, 162.8, 142.5, 137.7, 136.5, 134.1, 132.7, 131.8, 131.26, 129.3, 128.9, 128.8, 128.6, 128.1, 127.9, 126.7, 126.1, 126.0, 124.8, 121.9, 47.1, 46.6, 45.75, 34.5, 32.4.

HRMS (ESI): *m/z* calculated for $C_{31}H_{25}NO_3$+MeOH+Na^+: 514.1989, found: 514.1995.

***(3R,4S)-3,6-dibenzyl-4-(thiophen-2-yl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4n**



4n

Prepared according to the general procedure using (*E*)-1-benzyl-4-(thiophen-2-ylmethylene)pyrrolidine-2,3-dione **1n** (56.7 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4n** as a white solid with 87% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 5.05 min, t_{major} = 6.99 min; $[\alpha]_D^{20}$ = –200.3 (*c* = 0.77 in $CHCl_3$).

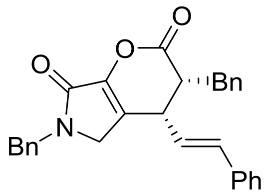
NMR and HRMS data for the product **4n**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.23 (m, 7H), 7.20 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.15 – 7.08 (m, 2H), 6.98 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.74 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.39 (d, *J* = 14.8 Hz, 1H), 3.91 (d, *J* = 6.0 Hz, 1H), 3.71 (d, *J* = 18.8 Hz, 1H), 3.65 (d, *J* = 18.8 Hz, 1H), 3.45 – 3.29 (m, 2H), 2.57 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.7, 162.6, 142.8, 138.2, 137.7, 136.4, 129.0, 128.9, 128.7, 128.2, 127.9, 127.6, 126.9, 126.6, 125.8, 46.8, 46.7, 46.7, 35.6, 32.3.

HRMS (ESI): *m/z* calculated for $C_{25}H_{21}NO_3S$+MeOH+Na^+: 470.1397, found: 470.1397.

***(3R,4S)-3,6-dibenzyl-4-((E)-styryl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4o**



4o

Prepared according to the general procedure using (*E*)-1-benzyl-4-((*E*)-3-phenylallylidene)pyrrolidine-2,3-dione **1o** (60.6 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4o** as a white solid with 93% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 94% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.19 min, t_{major} = 4.50 min; $[\alpha]_D^{20}$ = –238.2 (*c* = 0.66 in $CHCl_3$).

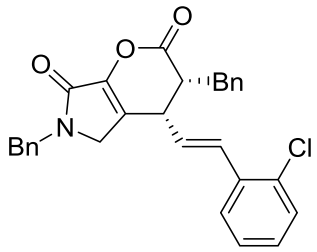
NMR and HRMS data for the product **4o**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.20 (m, 13H), 7.20 – 7.13 (m, 2H), 6.28 (d, *J* = 15.6 Hz, 1H), 5.88 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.45 (d, *J* = 14.8 Hz, 1H), 3.73 (d, *J* = 18.8 Hz, 1H), 3.66 (d, *J* = 18.8 Hz, 1H), 3.46 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.32 – 3.09 (m, 2H), 2.78 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.3, 162.7, 143.2, 137.7, 136.4, 135.5, 135.2, 129.0, 128.9, 128.8, 128.8, 128.6, 128.3, 127.9, 127.2, 126.9, 126.5, 122.7, 46.9, 46.7, 45.5, 38.1, 32.5.

HRMS (ESI): *m/z* calculated for $C_{29}H_{25}NO_3$+MeOH+Na^+: 490.1989, found: 490.1996.

***(3R,4S)-3,6-dibenzyl-4-((E)-2-chlorostyryl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4p**



4p

Prepared according to the general procedure using (*E*)-1-benzyl-4-((*E*)-3-(2-chlorophenyl)allylidene)pyrrolidine-2,3-dione **1p** (67.5 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4p** as a white solid with 82% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.87 min, t_{major} = 6.42 min; $[\alpha]_D^{20}$ = –194.2 (*c* = 0.52 in $CHCl_3$).

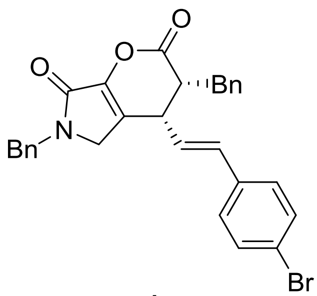
NMR and HRMS data for the product **4p**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.47 (dd, *J* = 7.2 Hz, *J* = 1.8 Hz, 1H), 7.36 – 7.19 (m, 13H), 6.72 (d, *J* = 15.6 Hz, 1H), 5.84 (dd, *J* = 15.6 Hz, *J* = 9.0 Hz, 1H), 4.73 (d, *J* = 15.0 Hz, 1H), 4.48 (d, *J* = 15.6 Hz**,** 1H), 3.73 (d, *J* = 19.2 Hz, 1H), 3.70 (d, *J* = 19.2 Hz, 1H), 3.47 (dd, *J* = 15.0 Hz, *J* = 4.2 Hz, 1H), 3.25 – 3.19 (m, 2H), 2.46 (dd, *J* = 15.0 Hz, *J* = 10.8 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 168.2, 162.5, 143.2, 137.5, 136.4, 133.1, 131.5, 129.8, 129.5, 129.0, 128.8, 128.8, 128.2, 127.9, 127.1, 127.0, 126.9, 126.8, 125.6, 46.8, 46.6, 45.4, 38.2, 32.4.

HRMS (ESI): *m/z* calculated for $C_{29}H_{24}ClNO_3+Na^+$: 492.1337, found: 492.1337.

***(3R,4S)-3,6-dibenzyl-4-((E)-4-bromostyryl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4q**



4q

Prepared according to the general procedure using (*E*)-1-benzyl-4-((*E*)-3-(4-bromophenyl)allylidene)pyrrolidine-2,3-dione **1q** (76.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4q** as a white solid with 92% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA

column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.84 min, t_{major} = 6.66 min; $[\alpha]_D^{20}$ = –184.1 (*c* = 0.70 in $CHCl_3$).

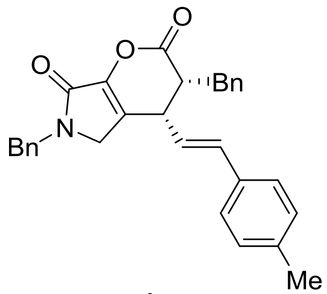
NMR and HRMS data for the product **4q**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.45 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.14 (m, 13H), 6.18 (d, *J* = 16.2 Hz, 1H), 5.86 (dd, *J* = 16.2 Hz, *J* = 9.0 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 4.43 (d, *J* = 15.6 Hz**,** 1H), 3.71 (d, *J* = 18.6 Hz, 1H), 3.66 (d, *J* = 18.6 Hz, 1H), 3.45 (dd, *J* = 15.0 Hz, *J* = 4.8 Hz, 1H), 3.22 – 3.16 (m, 2H), 2.73 (dd, *J* = 15.0 Hz, *J* = 10.8 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 168.2, 162.5, 143.2, 137.5, 136.4, 134.3, 134.0, 131.9, 128.9, 128.8, 128.3, 128.0, 127.9, 126.9, 126.8, 123.4, 122.4, 46.8, 46.7, 45.3, 38.0, 32.5.

HRMS (ESI): *m/z* calculated for $C_{29}H_{24}BrNO_3+Na^+$: 536.0832, found: 536.0838.

<u>(3R,4S)-3,6-dibenzyl-4-((E)-4-methylstyryl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione</u> **<u>4r</u>**



4r

Prepared according to the general procedure using (*E*)-1-benzyl-4-((*E*)-3-(*p*-tolyl)allylidene)pyrrolidine-2,3-dione **1r** (63.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4r** as a white solid with 85% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 97% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.76 min, t_{major} = 6.30 min; $[\alpha]_D^{20}$ = –171.1 (*c* = 0.45 in $CHCl_3$).

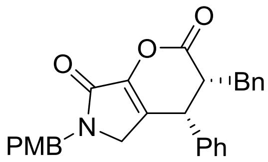
NMR and HRMS data for the product **4r**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.31 – 7.13 (m, 14H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.80 (dd, *J* = 15.6 Hz, *J* = 9.0 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 4.43 (d, *J* = 15.0 Hz**,** 1H), 3.71 (d, *J* = 19.2 Hz, 1H), 3.65 (d, *J* = 19.2 Hz, 1H), 3.44 (dd, *J* = 14.4 Hz, *J* = 4.2 Hz, 1H), 3.19 – 3.14 (m, 2H), 2.73 (dd, *J* = 14.4 Hz, *J* = 10.2 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 168.3, 162.7, 143.0, 138.6, 137.7, 136.4, 135.1, 132.7, 129.5, 129.0, 128.9, 128.7, 128.2, 127.9, 127.3, 126.8, 126.4, 121.546.8, 46.7, 45.5, 38.1, 32.5, 21.2.

HRMS (ESI): *m/z* calculated for $C_{30}H_{27}NO_3+MeOH+Na^+$: 504.2145, found: 504.2146.

***(3R,4R)-3-benzyl-6-(4-methoxybenzyl)-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4s**



4s

Prepared according to the general procedure using (*E*)-4-benzylidene-1-(4-methoxybenzyl)pyrrolidine-2,3-dione **1s** (61.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4s** as a white solid with 93% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 98% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.88 min, t_{major} = 6.95 min; $[\alpha]_D^{20}$ = –206.4 (*c* = 0.66 in $CHCl_3$).

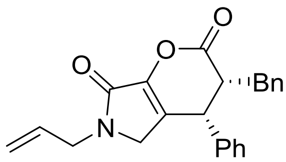
NMR and HRMS data for the product **4s**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.19 (m, 6H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.96 – 6.88 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.74 (d, *J* = 14.8 Hz, 1H), 4.28 (d, *J* = 14.8 Hz, 1H), 3.77 (s, 3H), 3.66 (d, *J* = 18.4 Hz, 1H), 3.57 (d, *J* = 6.8 Hz, 1H), 3.50 (d, *J* = 18.4 Hz, 1H), 3.44 – 3.28 (m, 2H), 2.39 (dd, *J* = 14.4, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.4, 162.7, 159.3, 142.8, 142.1, 137.8, 136.1, 129.6, 129.4, 129.0, 128.6, 128.5, 128.4, 128.0, 126.8, 114.2, 55.3, 46.8, 46.1, 45.8, 40.9, 32.3.

HRMS (ESI): *m/z* calculated for $C_{28}H_{25}NO_4$+MeOH+Na^+: 494.1938, found: 494.1936.

***(3R,4R)-6-allyl-3-benzyl-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4t**



4t

Prepared according to the general procedure using (*E*)-1-allyl-4-benzylidenepyrrolidine-2,3-dione **1t** (55.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloro-3-phenylpropanal (101.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4t** as a white solid with 96% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.41 min, t_{major} = 5.92 min; $[\alpha]_D^{20}$ = –255.8 (*c* = 0.43 in $CHCl_3$).

NMR and HRMS data for the product **4t**:

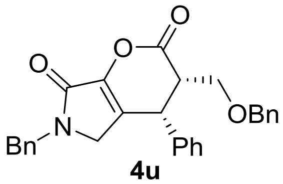
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31 – 7.15 (m, 6H), 6.97 (d, *J* = 6.8 Hz, 2H), 6.91 – 6.84 (m, 2H), 5.70 – 5.59 (m, 1H), 5.12 – 5.01 (m, 2H), 4.04 (dd, *J* = 15.2, 6.0 Hz, 1H), 3.87 (dd, *J* = 15.2, 6.0 Hz, 1H), 3.74 (d, *J* = 18.8 Hz, 1H), 3.57 (d, *J* = 7.2 Hz, 1H), 3.52 (d, *J* =

18.8 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.29 (dd, J = 14.4, 4.4 Hz, 1H), 2.35 (dd, J = 14.4, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.3, 162.6, 142.9, 137.8, 136.1, 132.6, 129.4, 129.0, 128.7, 128.5, 128.4, 128.0, 126.8, 118.5, 47.0, 45.8, 45.3, 41.0, 32.3.

HRMS (ESI): *m/z* calculated for $C_{23}H_{21}NO_3$+Na^+: 382.1414, found: 382.1418.

***(3S,4R)-6-benzyl-3-((benzyloxy)methyl)-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4u**



4u

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and 4-(benzyloxy)-2-chlorobutanal (127.6 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4u** as a white solid with 92% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.29 min, t_{major} = 5.91 min; $[\alpha]_D^{20}$ = –238.7 (c = 0.71 in $CHCl_3$).

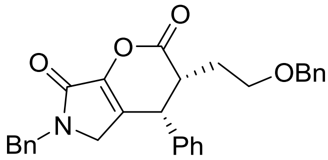
NMR and HRMS data for the product **4u**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.25 (m, 11H), 7.24 – 7.18 (m, 2H), 7.11 – 6.99 (m, 2H), 4.78 (d, J = 14.8 Hz, 1H), 4.47 (d, J = 14.8 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 4.33 (d, J = 11.6 Hz, 1H), 4.09 (d, J = 7.2 Hz, 1H), 3.91 (dd, J = 9.6, 4.4 Hz, 1H), 3.76 (d, J = 18.8 Hz, 1H), 3.64 (d, J = 18.8 Hz, 1H), 3.44 – 3.36 (m, 1H), 3.07 (t, J = 11.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.1, 162.8, 143.6, 137.5, 136.4, 135.2, 129.3, 128.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 73.5, 65.6, 47.2, 46.7, 44.7, 39.5.

HRMS (ESI): *m/z* calculated for $C_{28}H_{25}NO_4$+MeOH+Na^+: 494.1938, found: 494.1939.

***(3R,4R)-6-benzyl-3-(2-(benzyloxy)ethyl)-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4v**



4v

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and 3-(benzyloxy)-2-chloropropanal (119.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4v** as a white solid with 91% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.31 min, t_{major} = 6.03 min; $[\alpha]_D^{20}$ = –251.9 (*c* = 0.54 in $CHCl_3$).

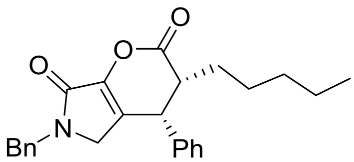
NMR and HRMS data for the product **4v**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.17 (m, 13H), 7.02 – 6.87 (m, 2H), 4.82 (d, *J* = 14.8 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.42 – 4.35 (m, 2H), 3.71 (d, *J* = 18.8 Hz, 1H), 3.65 (d, *J* = 7.2 Hz, 1H), 3.61 – 3.46 (m, 3H), 3.34 (q, *J* = 6.8 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.53 – 1.42 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.7, 162.9, 143.0, 138.1, 136.5, 136.3, 129.4, 128.9, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 126.9, 73.1, 66.9, 47.0, 46.7, 42.1, 40.7, 27.5.

HRMS (ESI): *m/z* calculated for $C_{29}H_{27}NO_4$+MeOH+Na^+: 508.2094, found: 508.2098.

***(3R,4R)-6-benzyl-3-pentyl-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4w**



4w

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and 2-chloroheptanal (89.2 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4w** as a white solid with 90% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 4.03 min, t_{major} = 4.80 min; $[\alpha]_D^{20}$ = –93.5 (*c* = 0.51 in $CHCl_3$).

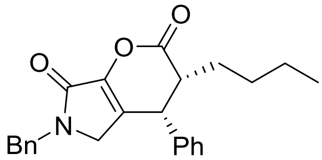
NMR and HRMS data for the product **4w**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29 – 7.18 (m, 6H), 7.17 – 7.12 (m, 2H), 6.94 (dd, *J* = 7.6, 1.6 Hz, 2H), 4.76 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 14.8 Hz, 1H), 3.74 – 3.64 (m, 2H), 3.54 (d, *J* = 18.4 Hz, 1H), 2.90 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.36 – 1.23 (m, 2H), 1.22 – 0.99 (m, 5H), 0.76 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.5, 167.1, 161.9, 157.4, 142.1, 135.5, 135.2, 128.3, 127.9, 127.3, 127.2, 127.1, 126.9, 126.6, 46.1, 45.7, 43.4, 41.0, 30.4, 25.7, 25.6, 21.3, 12.9.

HRMS (ESI): *m/z* calculated for $C_{25}H_{27}NO_3$+MeOH+Na^+: 444.2145, found: 444.2145.

***(3R,4R)-6-benzyl-3-butyl-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4x**



4x

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and 2-chlorohexanal (80.8 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4x** as a white solid with 94% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.38 min, t_{major} = 6.41 min; $[\alpha]_D^{20}$ = –162.2 (*c* = 0.72 in $CHCl_3$).

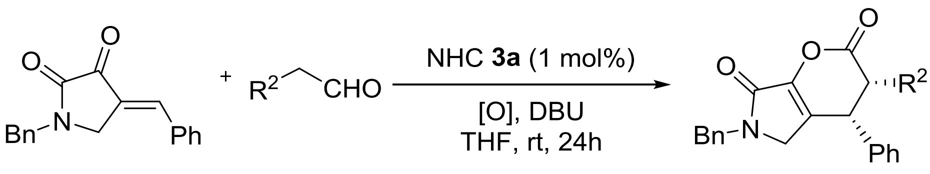
NMR and HRMS data for the product **4x**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.25 (m, 6H), 7.22 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.06 – 6.95 (m, 2H), 4.83 (d, *J* = 14.8 Hz, 1H), 4.40 (d, *J* = 14.8 Hz, 1H), 3.83 – 3.69 (m, 2H), 3.61 (d, *J* = 18.4 Hz, 1H), 2.96 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.83 – 1.67 (m, 1H), 1.43 – 1.06 (m, 5H), 0.84 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 163.0, 143.2, 136.5, 136.2, 129.3, 128.9, 128.3, 128.2, 128.1, 127.9, 127.7, 47.1, 46.7, 44.4, 42.0, 29.3, 26.4, 22.4, 13.8.

HRMS (ESI): *m/z* calculated for $C_{24}H_{25}NO_3$+MeOH+Na^+: 430.1989, found: 430.1988.

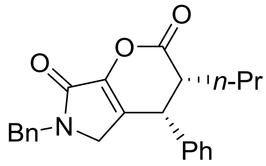
4. General Procedure for the Asymmetric Synthesis of Bicyclic Dihydropyrones 4y–4z via oxidatative NHC catalysis



1 **4y-4z**

The reaction was carried out with enones **1** (0.20 mmol), aldehydes (0.60 mmol), 3,3',5,5'-tetra-*tert*-butyldiphenoquinone (0.24 mmol), DBU (0.004 mmol) in the presence of catalyst **3a** (0.002 mmol) in anhydrous THF (2.0 mL) under argon atmosphere at room temperature for 24 hours. When the reaction was complete detected by TLC, the resulting reaction mixture was concentrated to dryness under reduced pressure at 35 ^{o}C. The residue was purified though column chromatograghy on silica gel (CH_2Cl_2/petroleum ether/ MeOH = 100 :100 :1) to afford the desired bicyclic dihydropyranones **4y** – **4z**, which was dried under vacuum and further analyzed by ^{1}H-NMR, ^{13}C-HMR, HRMS, chiral HPLC analysis, *etc*.

***(3R,4R)-6-benzyl-4-phenyl-3-propyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4y**



4y

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and pentanal (51.7 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4y** as a white solid with 80% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 5.61 min, t_{major} = 6.60 min; $[\alpha]_D^{20}$ = –173.5 (*c* = 0.72 in $CHCl_3$).

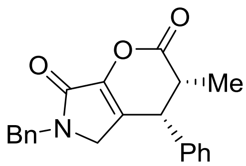
NMR and HRMS data for the product **4y**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.19 (m, 8H), 7.05 – 6.99 (m, 2H), 4.83 (d, *J* = 14.8 Hz, 1H), 4.39 (d, *J* = 14.8 Hz, 1H), 3.83 – 3.71 (m, 2H), 3.60 (d, *J* = 18.8 Hz, 1H), 2.99 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.46 – 1.33 (m, 2H), 1.21 – 1.08 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 162.9, 143.2, 136.5, 136.2, 129.4, 128.9, 128.3, 128.2, 128.1, 127.9, 127.7, 47.1, 46.7, 44.2, 42.0, 28.8, 20.4, 13.8.

HRMS (ESI): *m/z* calculated for $C_{23}H_{23}NO_3$+MeOH+Na^+: 416.1832, found: 416.1828.

***(3R,4R)-6-benzyl-3-methyl-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrole-2,7-dione* 4z**



4z

Prepared according to the general procedure using (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.20 mmol, 1.0 equiv) and propionaldehyde (34.8 mg, 0.60 mmol, 3.0 equiv). Purification of the crude product via column chromatography delivered **4z** as a white solid with 85% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IA column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 0.7 mL/min), UV 254 nm, t_{minor} = 6.09 min, t_{major} = 7.64 min; $[\alpha]_D^{20}$ = –30.8 (*c* = 0.49 in $CHCl_3$).

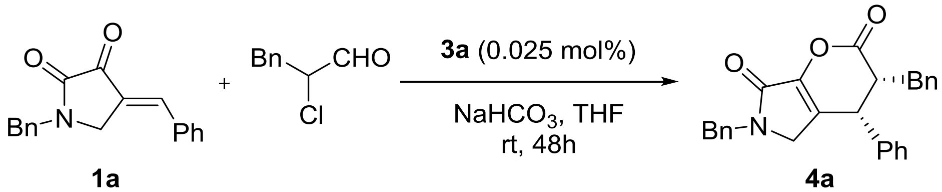
NMR and HRMS data for the product **4z**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.20 (m, 8H), 7.04 – 6.97 (m, 2H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.44 (d, *J* = 14.8 Hz, 1H), 3.77 (d, *J* = 18.4 Hz, 1H), 3.72 (d, *J* = 7.2 Hz, 1H), 3.63 (d, *J* = 18.4 Hz, 1H), 3.25 – 3.15 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.9, 162.9, 143.5, 141.6, 136.5, 135.9, 129.4, 128.9, 128.4, 128.2, 127.9, 127.8, 47.1, 46.7, 43.8, 39.3, 12.8.

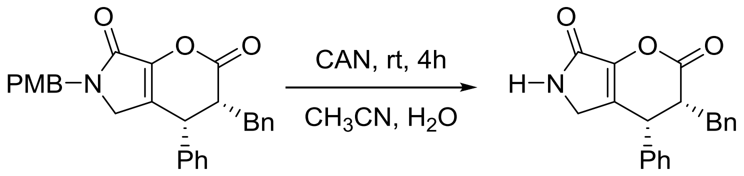
HRMS (ESI): *m/z* calculated for $C_{21}H_{19}NO_3$+MeOH+Na^+: 388.1519, found: 388.1521.

5. Gram-scale Synthesis of 4a *via* 250 ppm-level Catalysis



The reaction was carried out with enones **1a** (1.00 g, 3.61 mmol), **2** (1.82 g, 10.82 mmol), $NaHCO_3$ (0.45 g, 5.41 mmol) in the presence of catalyst **3a** (0.38 mg, 0.00090 mmol) in anhydrous THF (8.0 mL) under argon atmosphere at room temperature for 48 hours. When the reaction was complete detected by TLC, the resulting reaction mixture was concentrated to dryness under reduced pressure at 35 ^{o}C. The residue was purified though column chromatograghy on silica gel (CH_2Cl_2/petroleum ether/ MeOH = 100 :100 :1) to afford the desired bicyclic dihydropyranones **4a** (1.21 g) as a white solid with 82% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess was determined to be 99% by previous method.

6. Procedure for Synthetic Transformations 4s



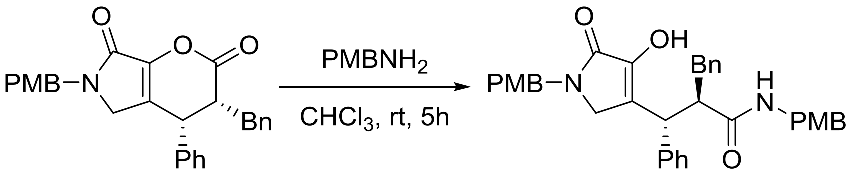
To a solution of bicyclic dihydropyranone **4s** (44.0 mg, 0.10 mmol) in 1 mL of CH_3CN/H_2O (v/v = 5:1) was added CAN (109.6 mg, 0.20 mmol), and the reaction was stirred at room temperature for 4 hours. When the reaction was complete detected by TLC, H_2O (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (10 mL X 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure at 30 ^{o}C. The residue was purified though column chromatograghy on silica gel (CH_2Cl_2/petroleum ether/ MeOH = 100 :100 :1) to afford the desired product **5** as a white solid with 85% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IG column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 15.23 min, t_{major} = 16.38 min; $[\alpha]_D^{20}$ = –190.5 (*c* = 0.40 in $CHCl_3$).

NMR and HRMS data for the product **5**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.21 (m, 6H), 7.04 (d, *J* = 6.8 Hz, 2H), 7.00 – 6.93 (m, 2H), 6.86 (s, 1H), 3.91 (d, *J* = 18.4 Hz, 1H), 3.71 (d, *J* = 18.4 Hz, 1H), 3.67 (d, *J* = 7.2 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.35 (dd, *J* = 14.8, 4.4 Hz, 1H), 2.43 (dd, *J* = 14.8, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.3, 165.7, 142.7, 137.8, 136.0, 131.5, 129.4, 129.0, 128.7, 128.6, 128.0, 126.9, 118.5, 45.6, 43.4, 41.1, 32.4.

HRMS (ESI): *m/z* calculated for $C_{20}H_{17}NO_3+Na^+$: 342.1101, found: 342.1103.



4s, 98% *ee* **6**, 90% yield, 99% *ee*

To a solution of bicyclic dihydropyranone **4s** (44.0 mg, 0.10 mmol) in $CHCl_3$ (1 mL) was added $PMBNH_2$ (20.6 mg, 0.15 mmol), and the reaction was stirred at room temperature for 5 hours. When the reaction was complete detected by TLC, the resulting reaction mixture was concentrated to dryness under reduced pressure at 30 °C. The residue was purified though column chromatograghy on silica gel (CH_2Cl_2 / MeOH = 80 :1) to afford the desired product **6** as a white solid with 90% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak IG column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :1, 1.0 mL/min), UV 254 nm, t_{minor} = 15.77 min, t_{major} = 16.68 min; $[\alpha]_D^{20}$ = –37.5 (*c* = 0.53 in $CHCl_3$).

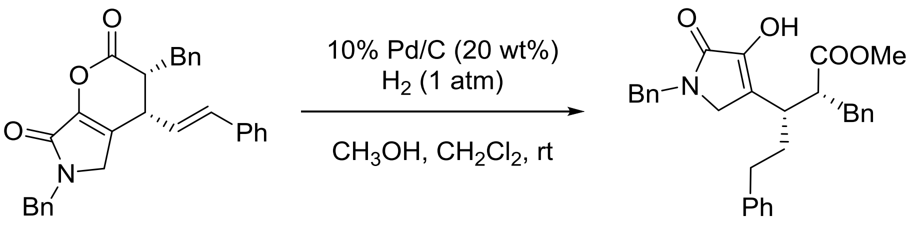
NMR and HRMS data for the product **6**:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.10 (m, 13H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 8.4 Hz, 2H), 4.96 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 14.8 Hz, 1H), 4.45 (d, *J* = 14.8 Hz, 1H), 3.87 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.82 – 3.67 (m, 8H), 3.63 (d, *J* = 18.0 Hz, 1H), 3.54 (d, *J* = 18.0 Hz, 1H), 3.38 (td, *J* = 11.2, 3.2 Hz, 1H), 3.03 (dd, *J* = 12.8, 2.8 Hz, 1H), 2.93 – 2.86 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.5, 167.7, 159.3, 158.6, 141.8, 141.0, 139.9, 129.7, 129.5, 129.2, 128.7, 128.4, 128.3, 127.0, 126.2, 121.6, 114.3, 113.6, 55.3, 55.2, 54.9, 49.6, 47.9, 46.4, 42.2, 38.1.

HRMS (ESI): *m/z* calculated for $C_{36}H_{36}N_2O_5+Na^+$: 599.2516, found: 599.2514.

7. Hydrogenation of the chiral product 4o



4o, 94% *ee* **7**, 74% yield, 94% *ee*

To a solution of of bicyclic dihydropyranone **4o** (43.5 mg, 94% *ee*, 0.10 mmol) in CH_2Cl_2 / MeOH (*v*/*v* = 2:1, 1 mL) was added 10% Pd/C (8.7 mg, 20 wt %). The reaction was stirred under a hydrogen atmosphere (1 atm) at room temperature for 5 hours. When the reaction was complete detected by TLC, the resulting reaction mixture was filtered through silica gel and the filtrate was concentrated to dryness under reduced pressure at 30 °C. The residue was purified though column chromatograghy on silica gel (petroleum ether / ethyl acetate = 6 :1) to afford the desired product **7** as a white solid with 74% yield. The diastereomeric ratio was determined to be >99:1 by crude ^{1}H-NMR analysis, and the enantiomeric excess of the major product was determined to be 94% by chiral HPLC analysis on Chiralpak IG column (CH_2Cl_2/*n*-hexane/CH_3OH = 75 :25 :0.5, 0.7 mL/min), UV 254 nm, t_{minor} = 9.63 min, t_{major} = 10.30 min; $[\alpha]_D^{20}$ = –21.4 (*c* = 0.41 in $CHCl_3$).

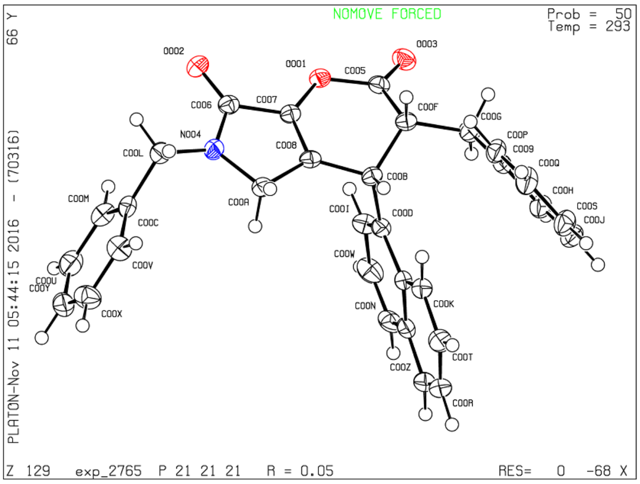
NMR and HRMS data for the product **7**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.72 – 7.55 (m, 1H), 7.37 – 7.27 (m, 3H), 7.26 – 7.12 (m, 8H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 4.70 (d, *J* = 15.0 Hz, 1H), 4.61 (d, *J* = 15.0 Hz, 1H), 3.58 (d, *J* = 18.0 Hz, 1H), 3.50 (d, *J* = 18.0 Hz, 1H), 3.45 (s, 3H), 2.98 – 2.95 (m, 1H), 2.84 – 2.80 (m, 1H), 2.77 (d, *J* = 10.2 Hz, 1H), 2.73 (dd, *J* = 13.2 Hz, *J* = 3.6 Hz, 1H), 2.57 – 2.46 (m, 2H), 1.83 – 1.73 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 174.8, 167.5, 143.6, 141.4, 138.9, 136.5, 128.9, 128.6, 128.3, 128.3, 127.9, 127.8, 126.3, 125.9, 120.4, 52.0, 51.5, 47.8, 46.8, 39.2, 37.3, 33.6, 33.4.

HRMS (ESI): *m/z* calculated for $C_{30}H_{31}NO_4+Na^{+}$: 492.2145, found: 492.2147.

8. Crystal Data and Structure Refinement for the Enantiopure 4m



Identification code	**4m**
Empirical formula	$C_{31}H_{25}NO_3$
Formula weight	459.52
Temperature/K	293.10(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.15832(19)
b/Å	17.7083(6)
c/Å	21.1704(6)
α/°	90
β/ °	90

γ/°	90
Volume/Å^3	2308.70(13)
Z	4
ρ_{calc}g/cm^3	1.322
μ/mm^{-1}	0.674
F(000)	968.0
Crystal size/mm^3	0.65 × 0.3 × 0.2
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.354 to 145.594
Index ranges	$-4 \leq h \leq 7$, $-21 \leq k \leq 18$, $-20 \leq l \leq 26$
Reflections collected	12883
Independent reflections	4502 [R_{int} = 0.0392, R_{sigma} = 0.0363]
Data/restraints/parameters	4502/0/316
Goodness-of-fit on F^2	1.023
Final R indexes [I>=2σ (I)]	R_1 = 0.0476, wR_2 = 0.1249
Final R indexes [all data]	R_1 = 0.0497, wR_2 = 0.1276
Largest diff. peak/hole / e Å^{-3}	0.21/-0.30
Flack parameter	0.04(14)

9. NMR Studies & Discussion of the *cis*-Configuration of the Bicyclic Dihydropyrones

In order to provide more details on how to determine the *cis*-configuration, we performed a set of NMR experiments as follows:

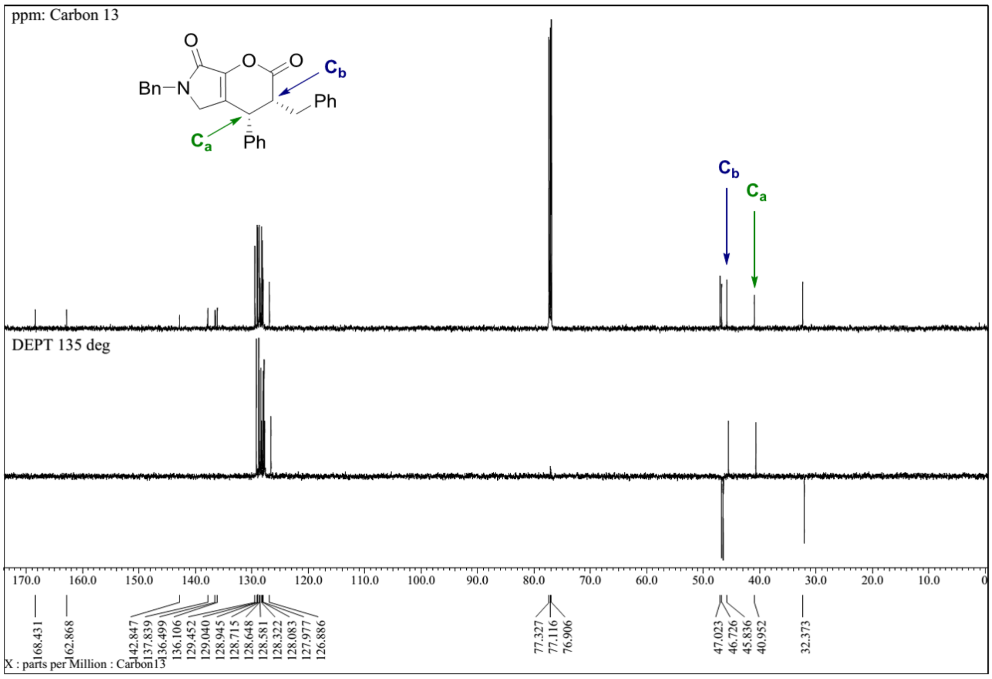


Figure a. DEPT 135 degree analysis of the product **4a**

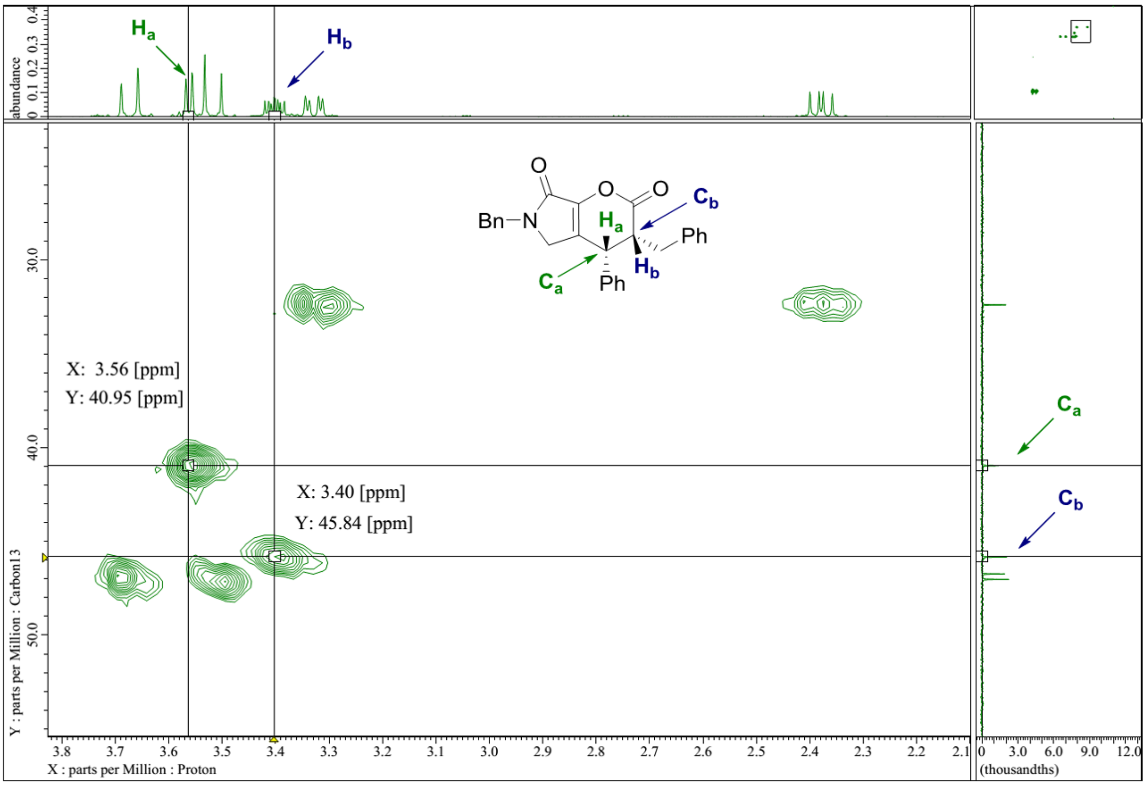


Figure b. HMQC analysis of the product **4a**

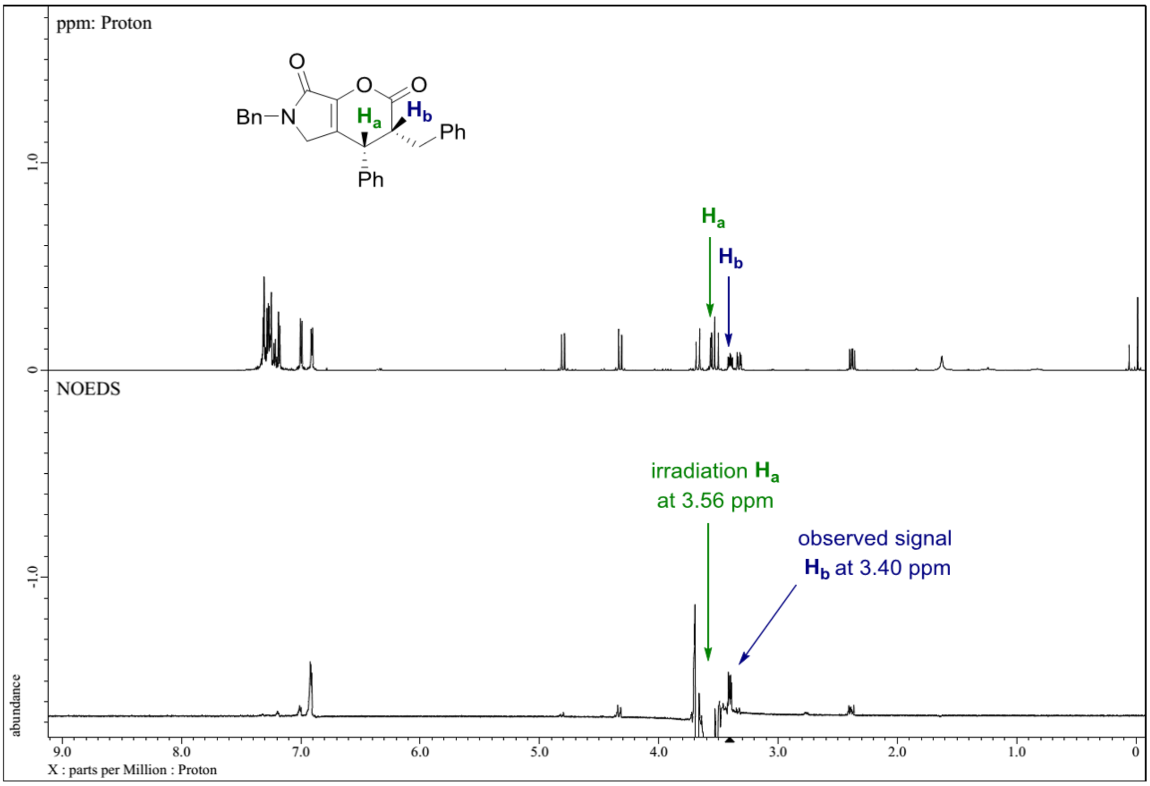


Figure c. NOEDS analysis of the product **4a**

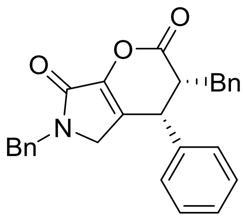
As shown in the above figures, we chose compound **4a** as a representative example, and a set of NMR analysis, including DEPT 135 deg. (Fig. a) and HMQC (Fig. b) has been performed. Then, we successfully determined the chemical shift of the crucial chiral H_a is at 3.56 ppm, and the coupling constant of H_a (with H_b) is 7.2 Hz which indicates the *cis*-configuration of the adjacent two chiral centers. Determination of the relative configuration of other products **4** could also refer to this method, and we found that the tendency of the coupling constant of the two chiral protons "H_a with H_b" is usually < 8.0 Hz. Furthermore, the NOEDS experiment was also carried out based on the representative **4a**, and obvious NOE signal was observed, which also can determine the *cis*-configuration of the products (Fig. c).

10. References and notes

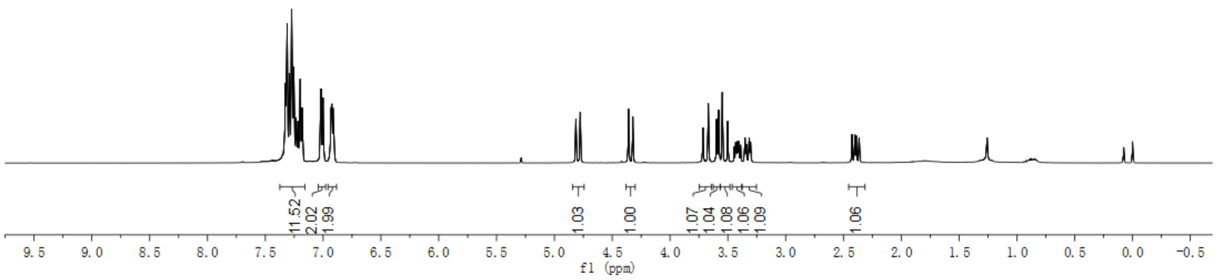
[1] (a) E. Krell, *Handbook of Laboratory Distillation*, Elseriver Publishing Company,Amsterdam-London-New York, **1963**; b) M. J. Rosengart, *The Technique of Distillation and Rectification in the Laboratory*, VEB Verlag Technik, Berlin, 1954; c) H. Stage *Columns for laboratory distillation*, *Angew. Chem.* **1947**, *19*, 175.

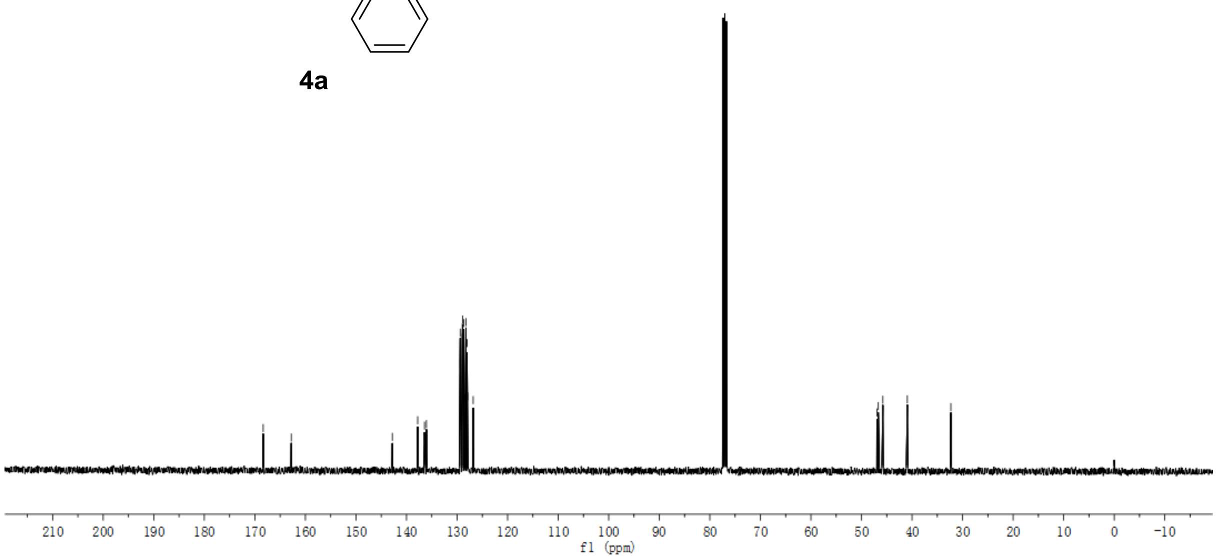
[2] P. L. Southwick, E. F. Barnas, *J. Org. Chem.* **1962**, *27*, 98.

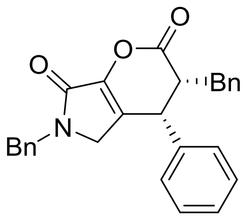
11. NMR and HPLC Spectra of the Chiral Products



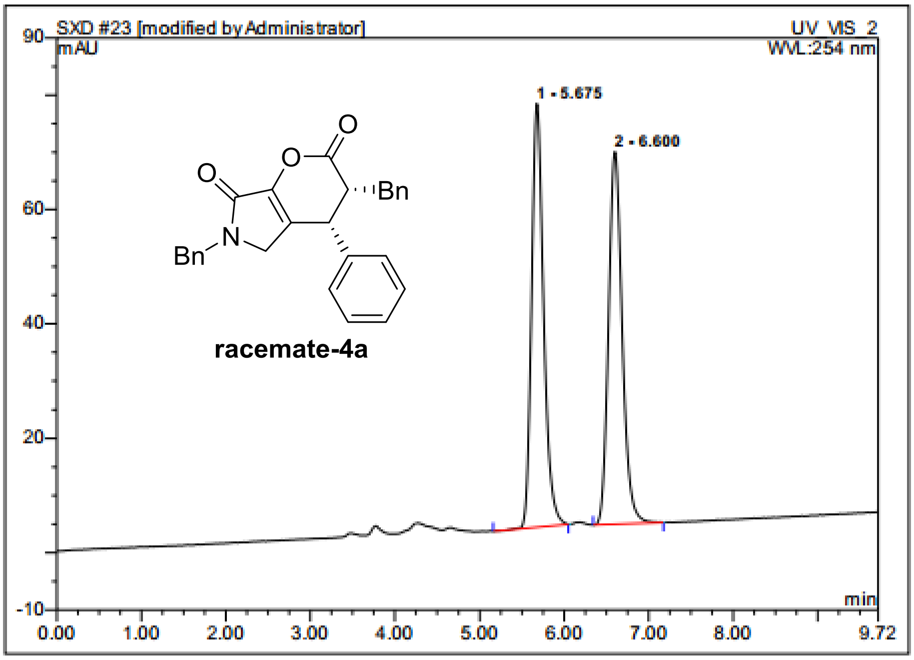
4a



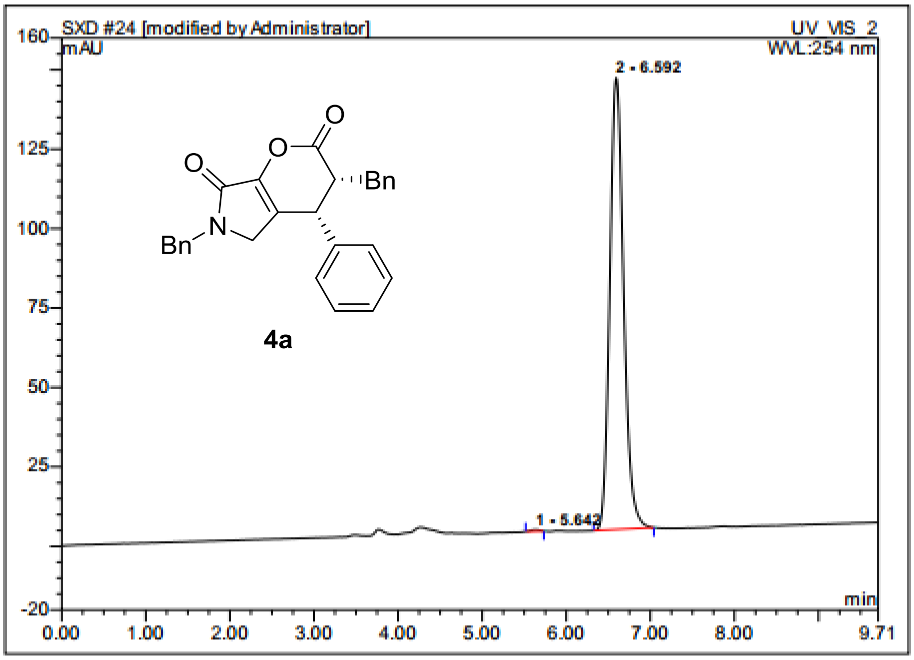




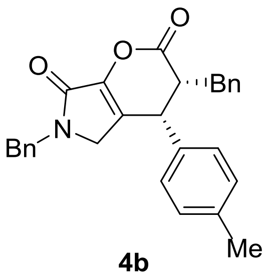
4a



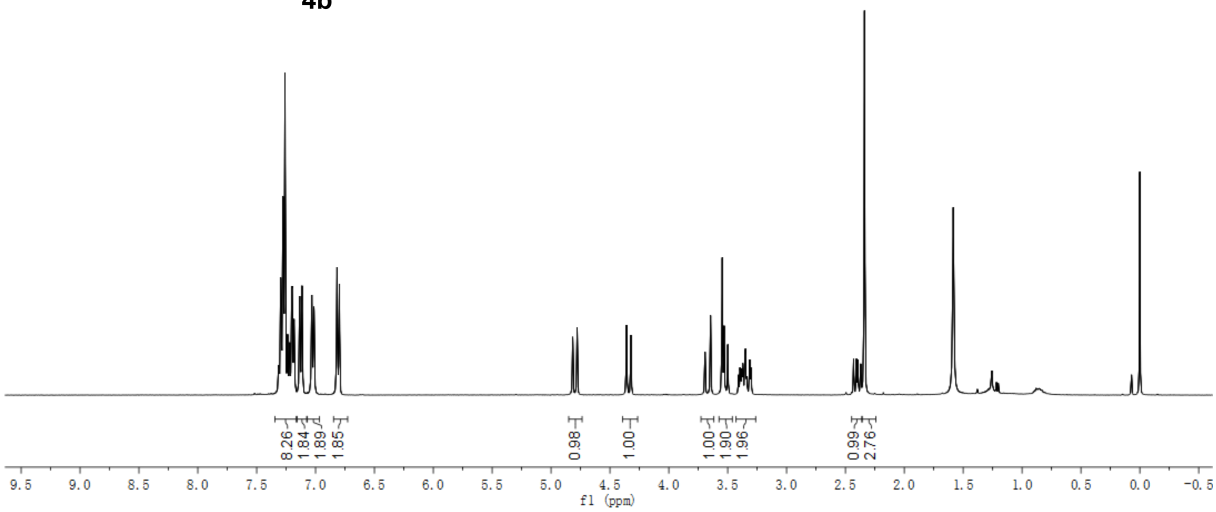
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.68	n.a.	74.044	12.196	50.04	n.a.	BMB*
2	6.60	n.a.	65.085	12.177	49.96	n.a.	BMB*
Total:			139.129	24.373	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.64	n.a.	0.473	0.060	0.22	n.a.	BMB*
2	6.59	n.a.	142.057	27.073	99.78	n.a.	BMB*
Total:			142.530	27.134	100.00	0.000	


O
O
O
Bn
N
Bn
Me

4b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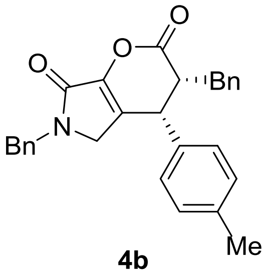
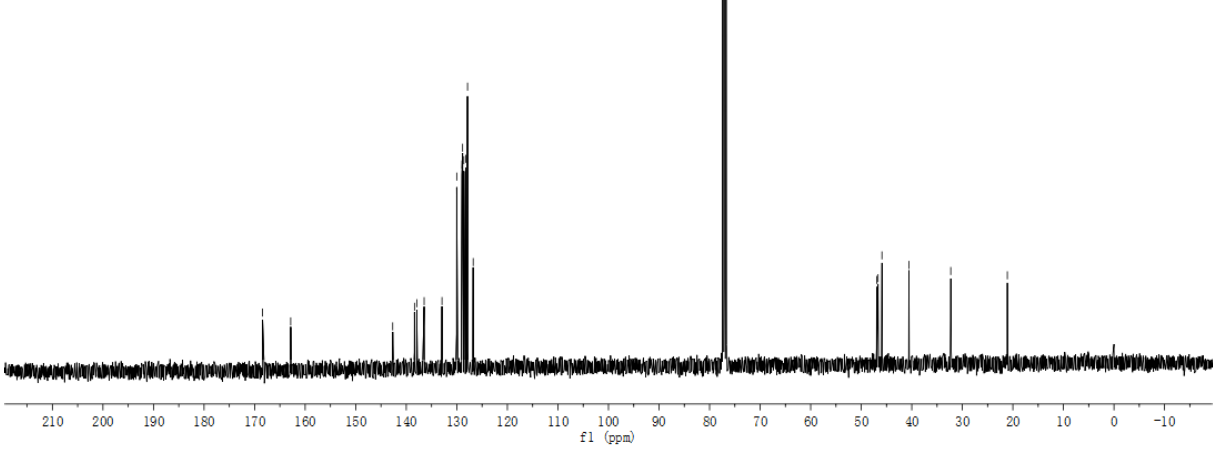
1.84
1.89
1.85
0.98
1.00
1.00
1.90
1.96
0.99
2.76
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


O
O
O
Bn
N
Bn
Me

4b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132.930
130.016
128.983
128.854
128.608
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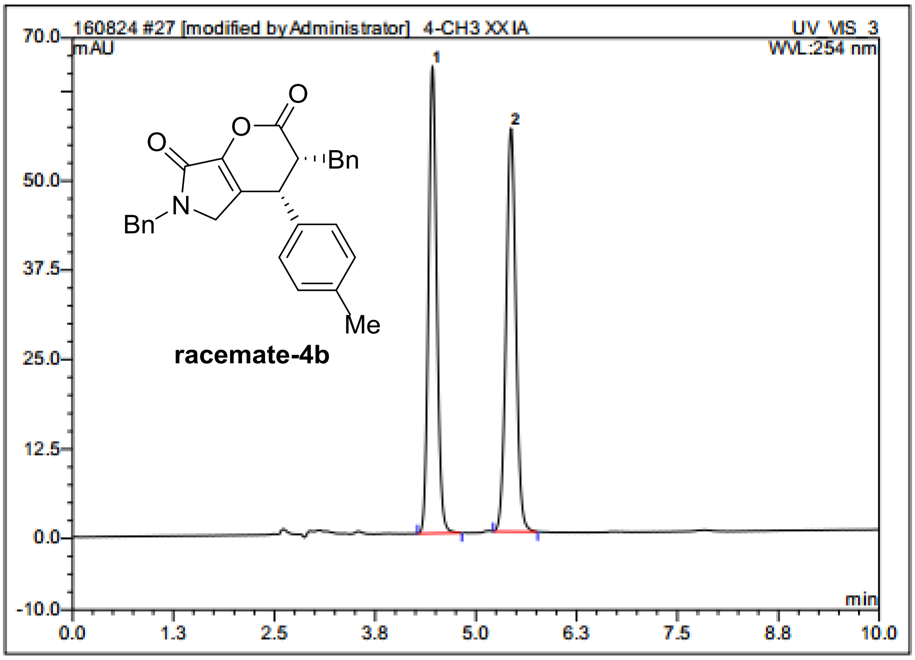
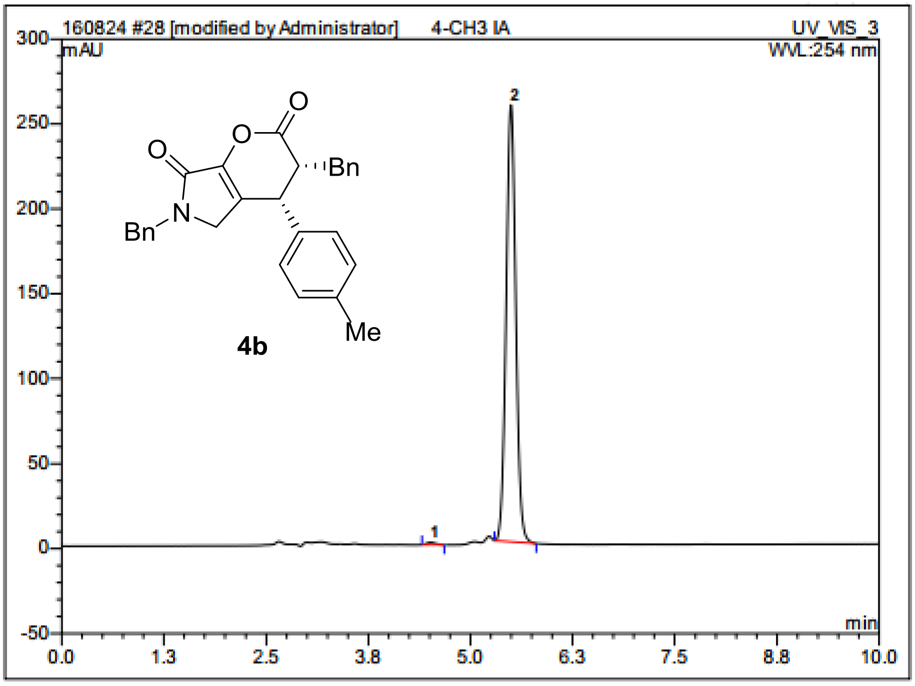
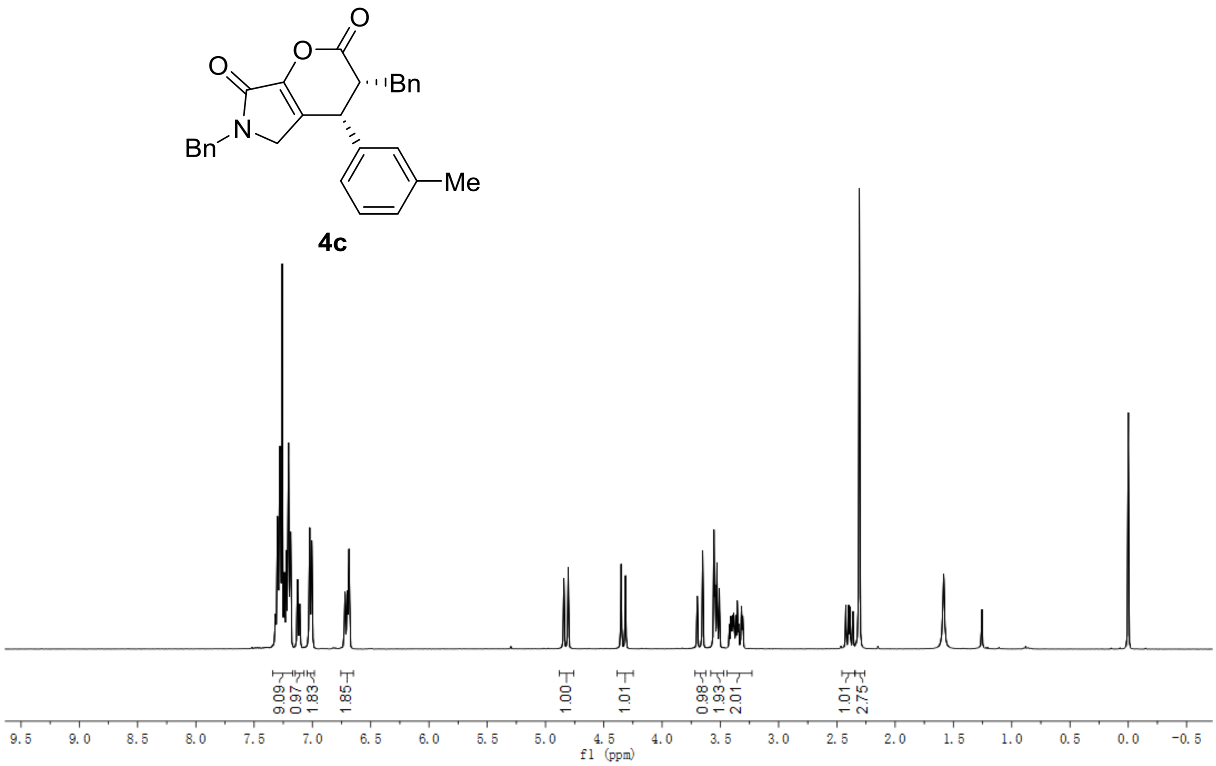
127.876
126.758
46.946
46.671
45.903
40.568
32.290
21.098
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.46	n.a.	65.334	7.794	49.48	n.a.	BMB
2	5.43	n.a.	56.398	7.956	50.52	n.a.	BMB*
Total:			121.732	15.750	100.00		



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.51	n.a.	1.333	0.167	0.47	n.a.	BMB*
2	5.49	n.a.	257.046	35.127	99.53	n.a.	BMB*
Total:			258.379	35.294	100.00		


Bn
Me
4c
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1.00
1.01
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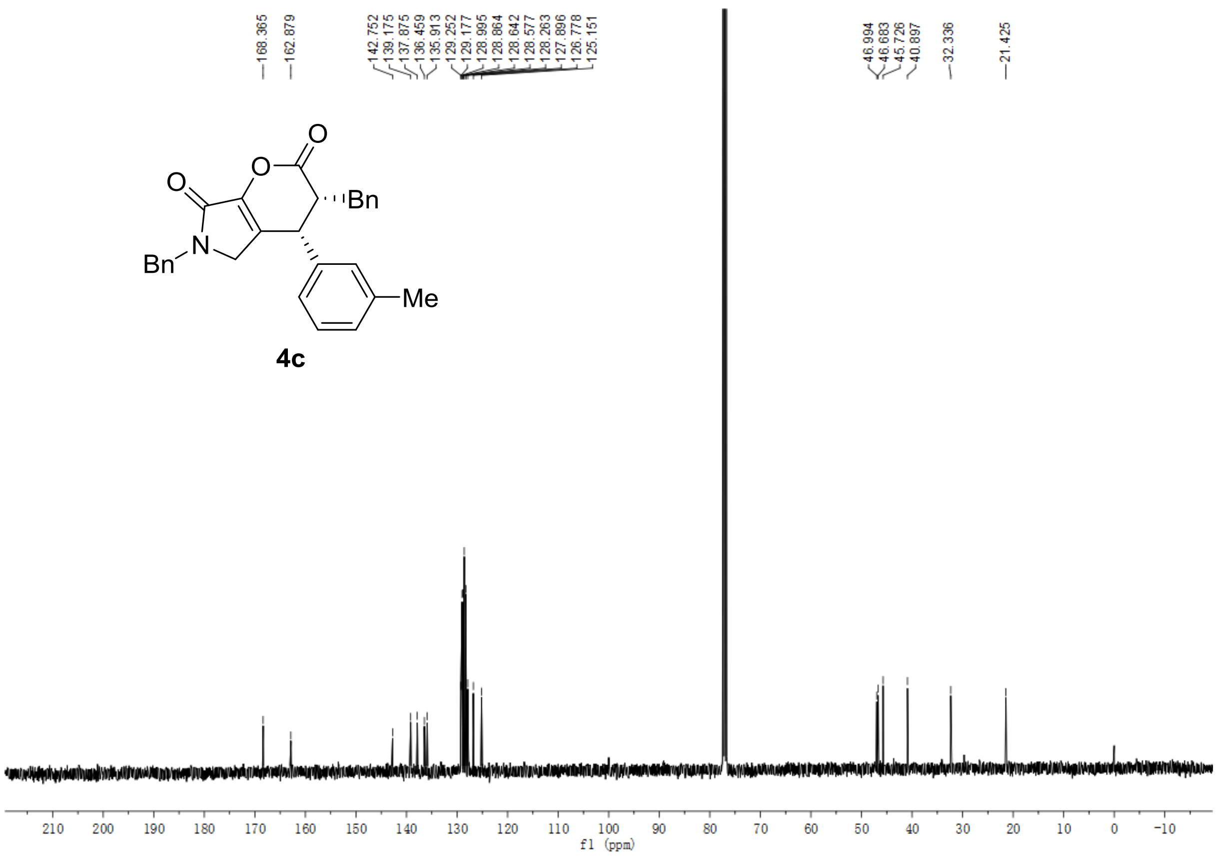
2.01
1.01
2.75
f1 (ppm)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136.459
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129.252
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128.577
128.263
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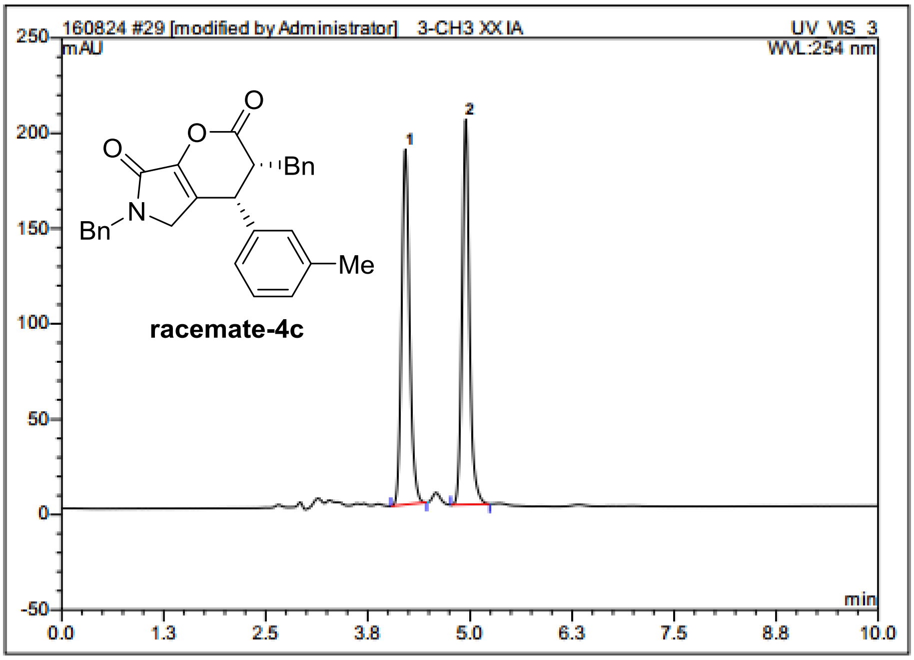
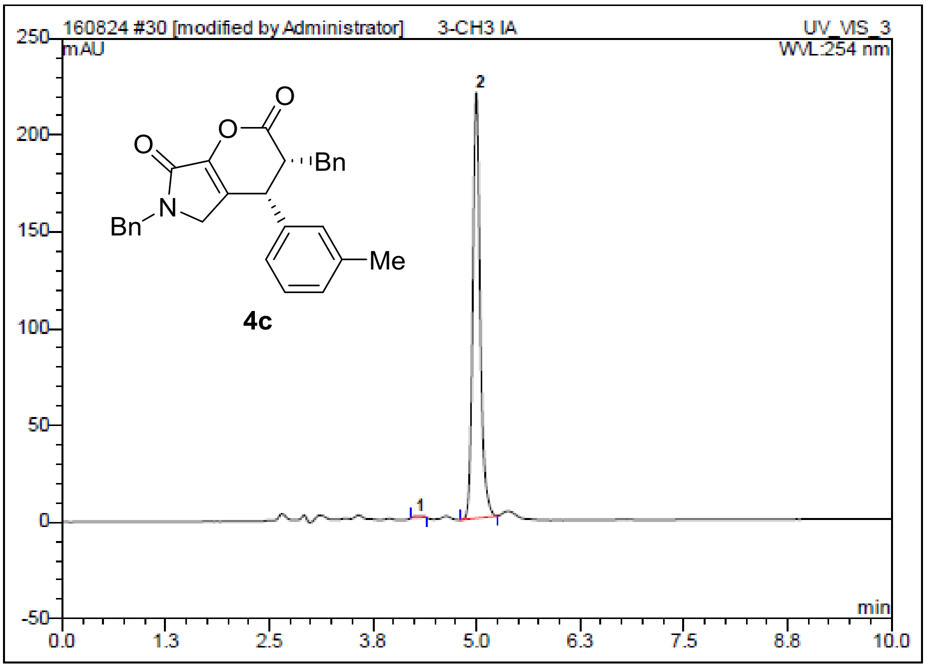
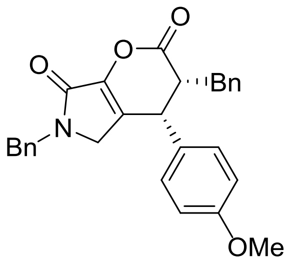
45.726
40.897
32.336
21.425
Bn
Me
4c
f1 (ppm)



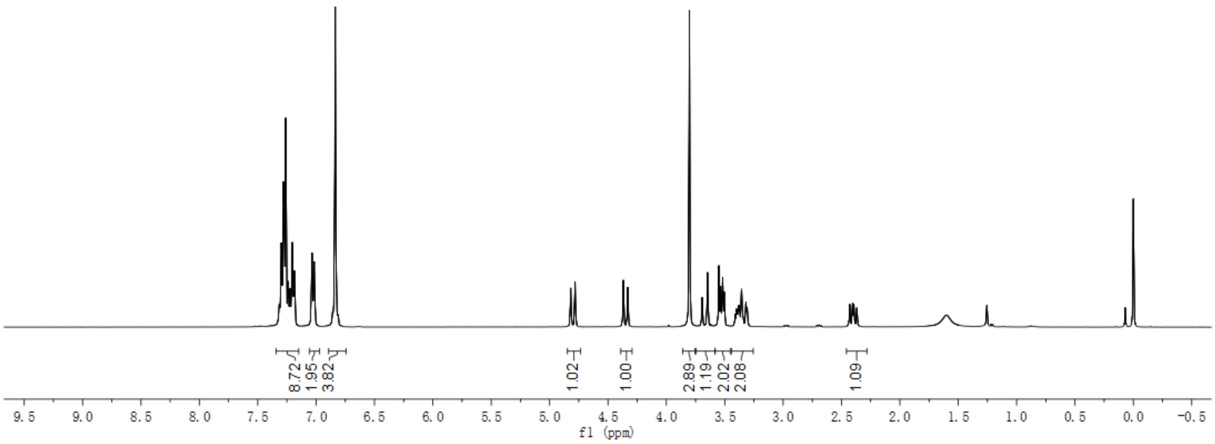
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.21	n.a.	186.099	21.059	50.80	n.a.	BMB*
2	4.95	n.a.	201.792	20.395	49.20	n.a.	BMB*
Total:			387.891	41.455	100.00		



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.27	n.a.	0.704	0.092	0.40	n.a.	BMB*
2	4.99	n.a.	220.037	23.015	99.60	n.a.	BMB*
Total:			220.741	23.107	100.00		


O
O
O
Bn
N
Bn
OMe

4d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1.95
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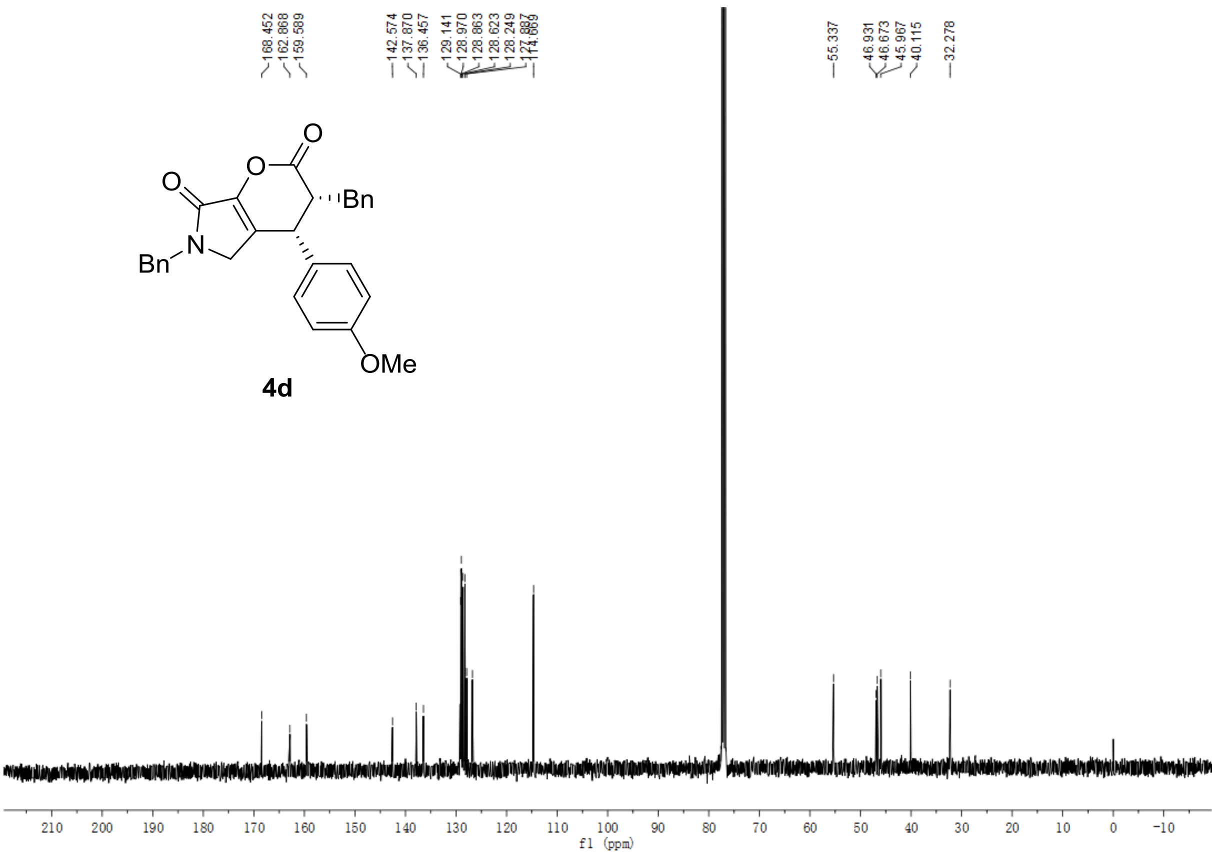
1.02
1.00
2.89
1.19
2.02
2.08
1.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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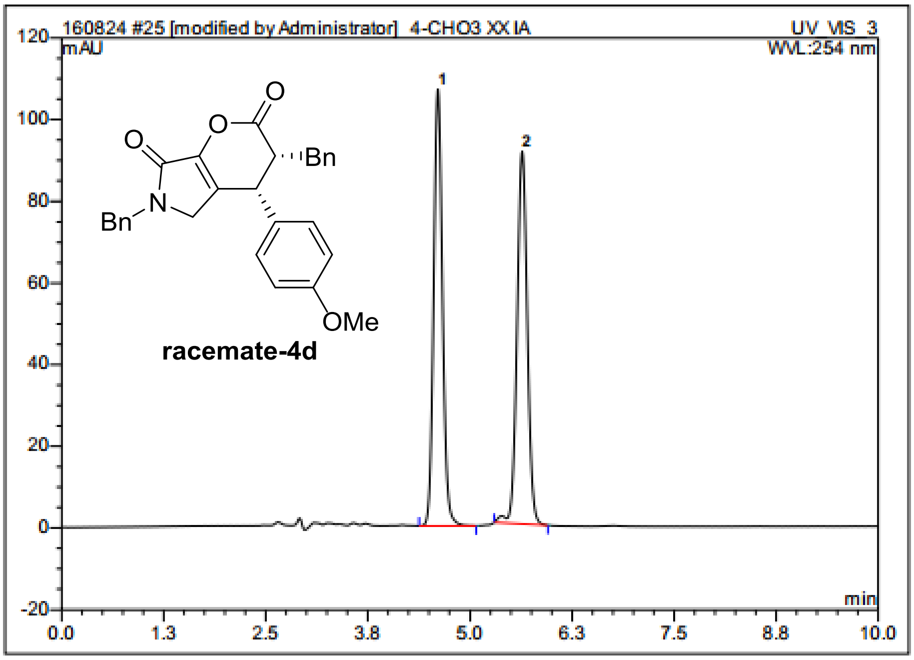
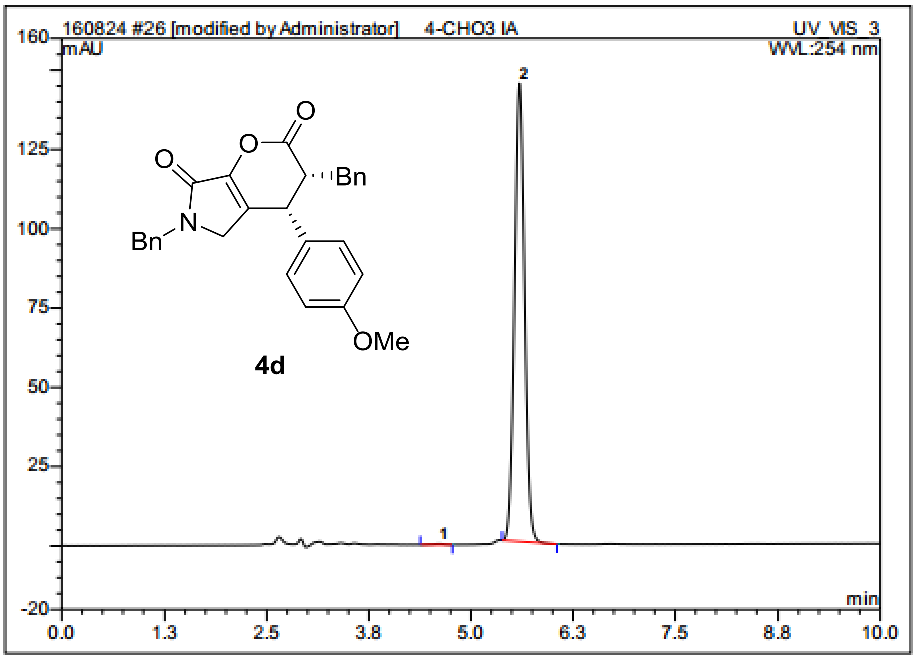
55.337
46.931
46.673
45.967
40.115
32.278
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

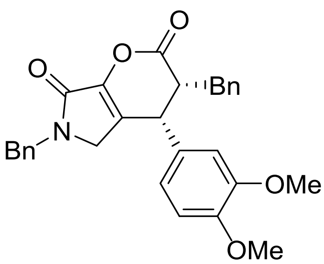
4d



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.61	n.a.	106.947	13.431	50.21	n.a.	BMB*
2	5.64	n.a.	91.138	13.318	49.79	n.a.	BMB*
Total:			198.084	26.750	100.00		



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.62	n.a.	0.278	0.052	0.25	n.a.	BMB
2	5.59	n.a.	144.402	20.680	99.75	n.a.	BMB*
Total:			144.680	20.733	100.00		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O
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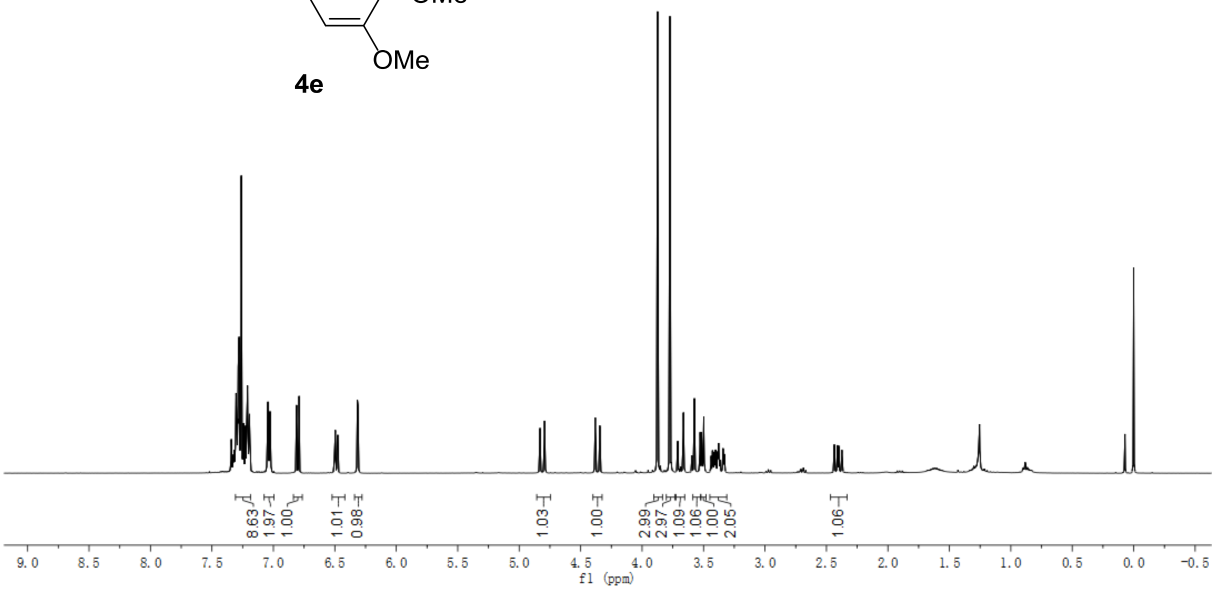
N
Bn
OMe
OMe

4e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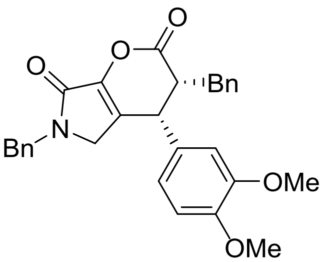
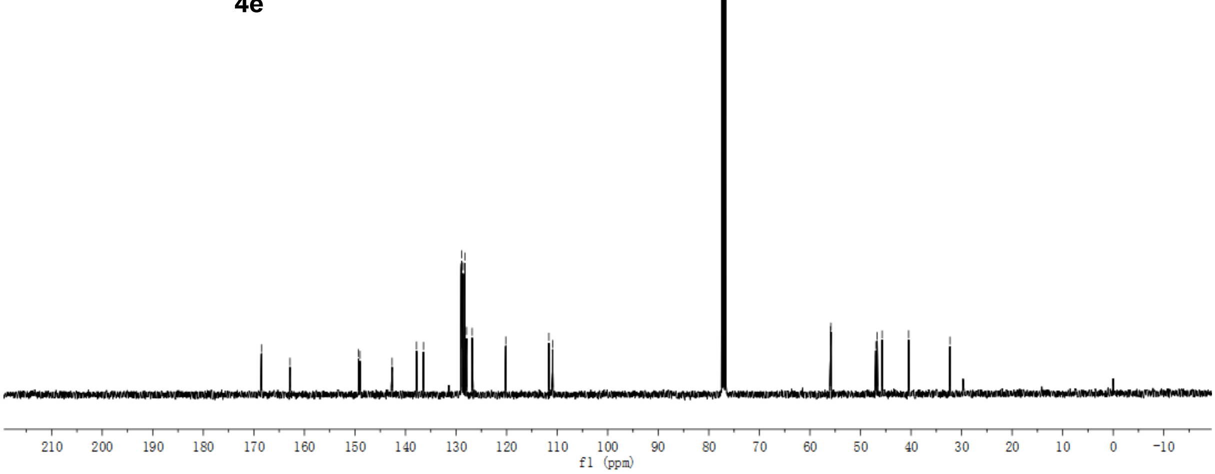
0.98
1.03
1.00
2.99
2.97
1.09
1.06
1.00
2.05
1.06
f1 (ppm)


O
O
O
Bn
N
Bn
OMe
OMe

4e


168.490
162.853
149.298
149.008
142.653
137.819
136.442
129.016
128.879
128.583
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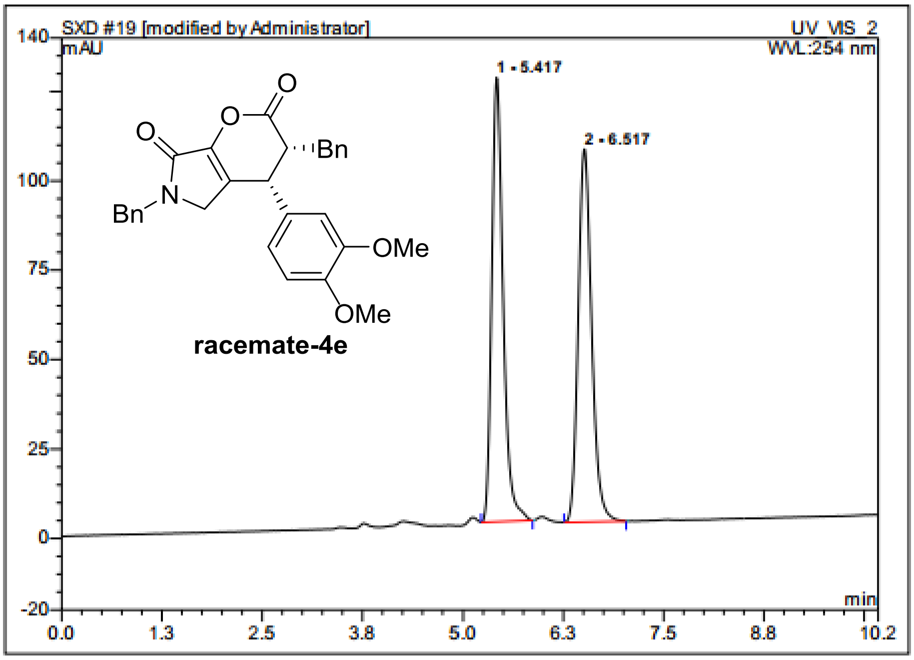
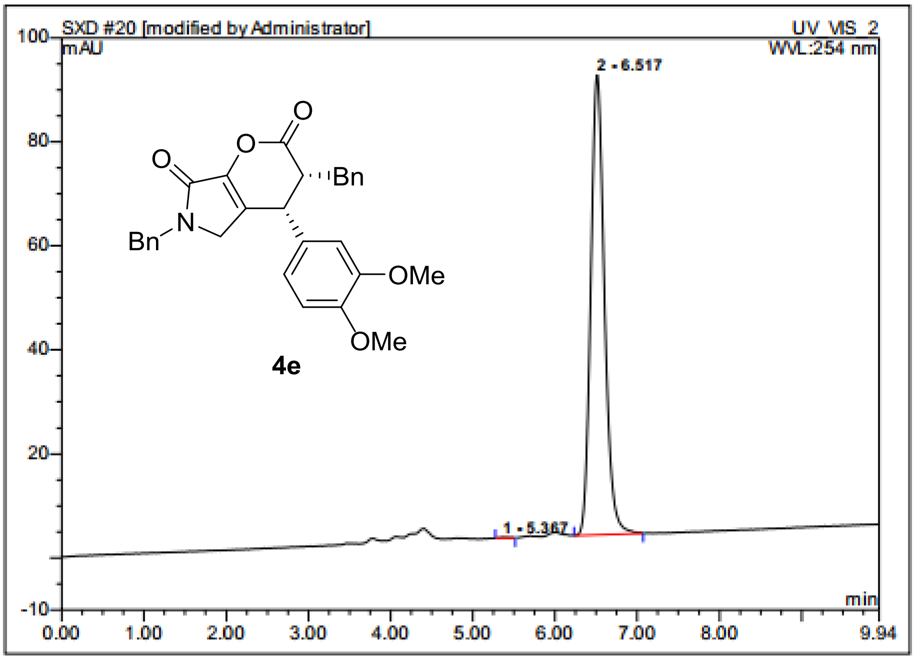
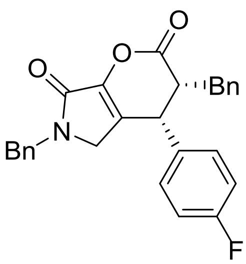
110.902
55.938
55.846
46.977
46.692
45.708
40.472
32.297
f1 (ppm)



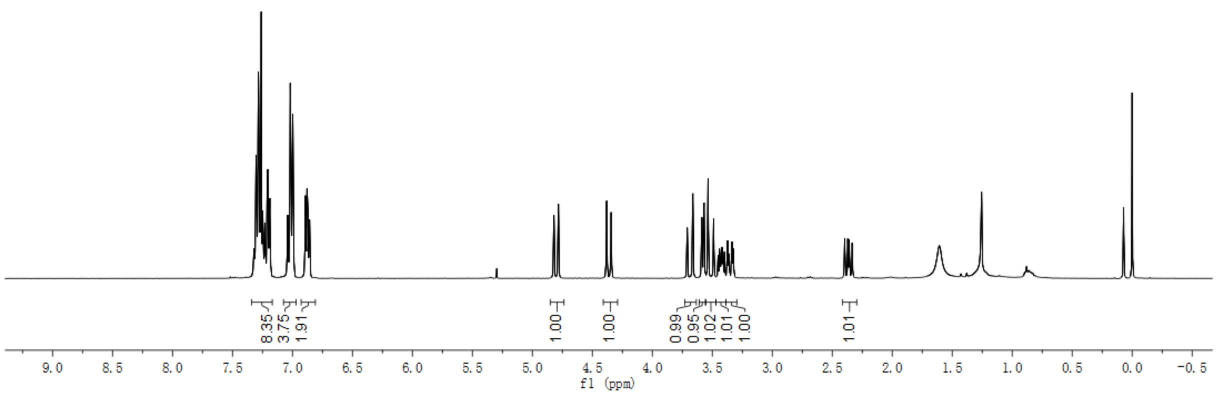
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.42	n.a.	124.170	20.401	50.16	n.a.	BMB*
2	6.52	n.a.	104.264	20.273	49.84	n.a.	BMB*
Total:			228.434	40.674	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.37	n.a.	0.165	0.022	0.13	n.a.	BMB*
2	6.52	n.a.	88.421	17.064	99.87	n.a.	BMB*
Total:			88.586	17.085	100.00	0.000	



4f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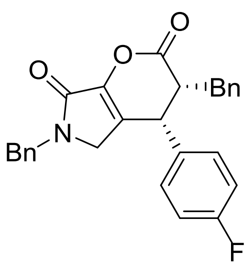
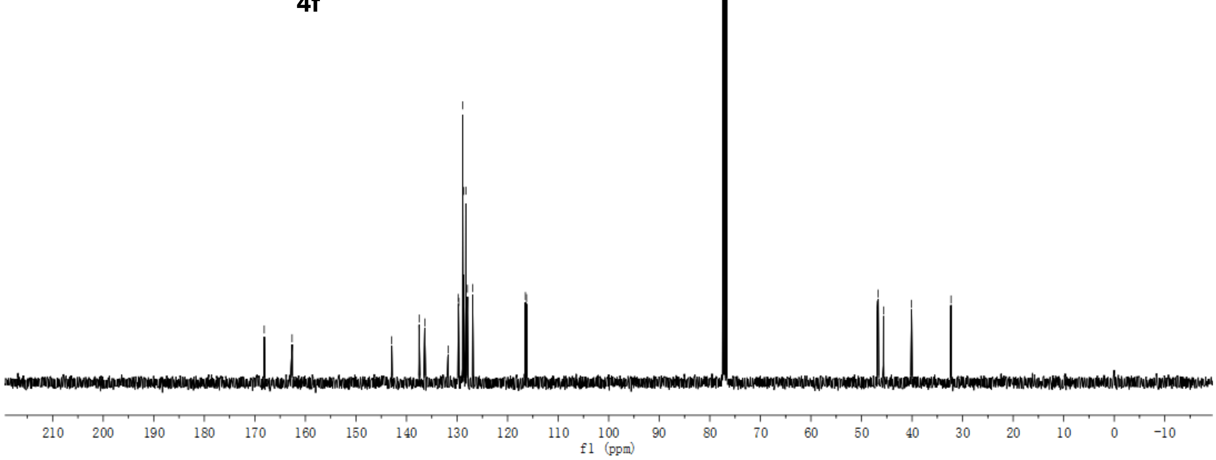
3.75
1.91
1.00
1.00
0.99
0.95
1.02
1.01
1.00
1.01
f1 (ppm)



4f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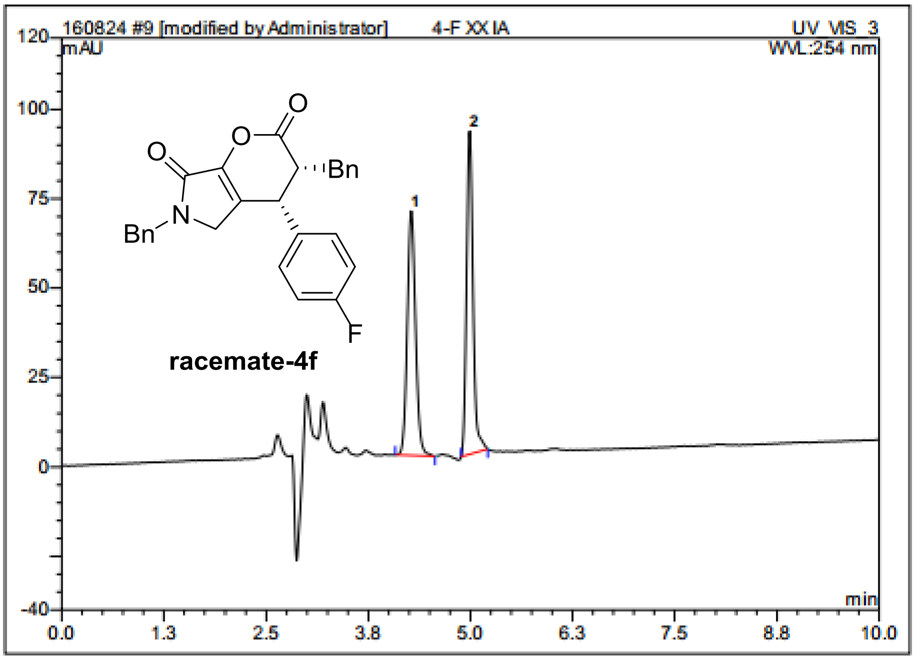
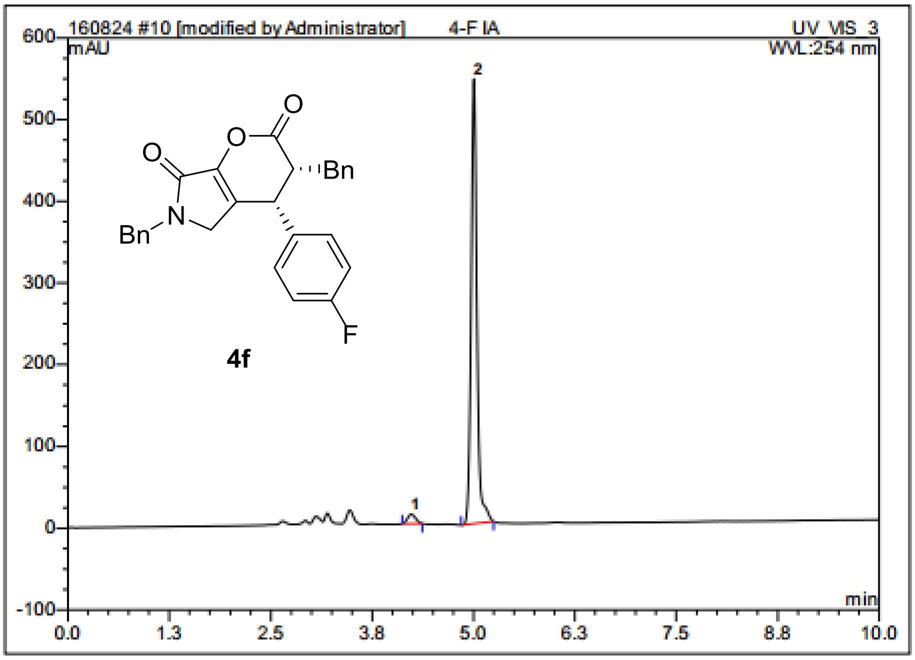
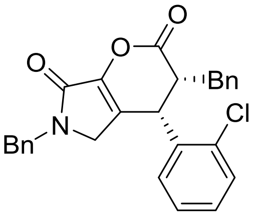
116.261
46.869
46.689
45.637
40.104
32.289
f1 (ppm)



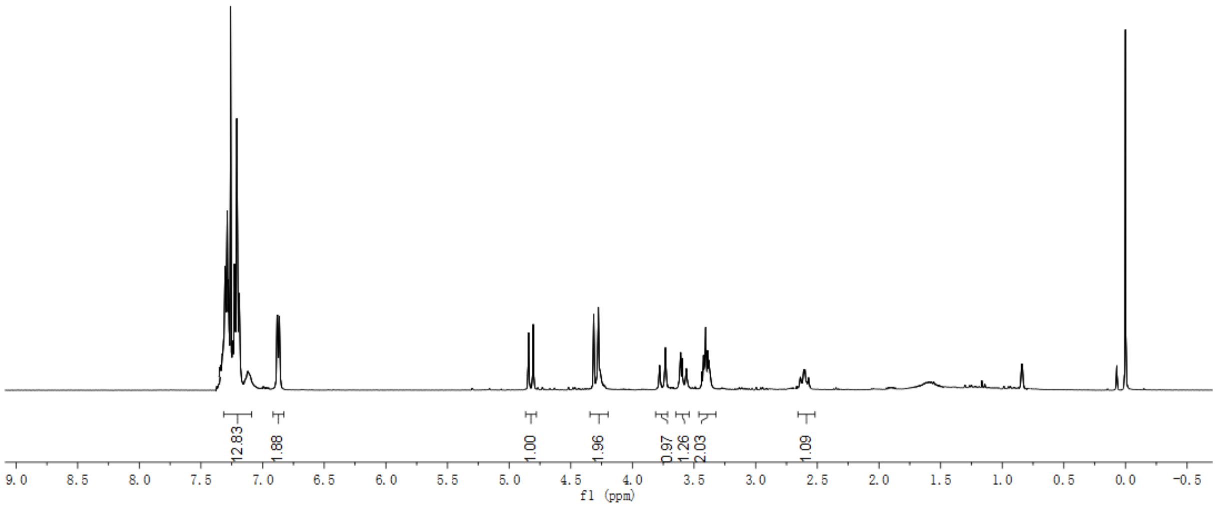
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.27	n.a.	68.300	7.982	49.02	n.a.	BMB*
2	4.99	n.a.	90.309	8.301	50.98	n.a.	BMB*
Total:			158.610	16.283	100.00		



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.23	n.a.	11.387	1.321	2.86	n.a.	BMB*
2	5.01	n.a.	544.266	44.883	97.14	n.a.	BMB*
Total:			555.653	46.204	100.00		


O
O
O
Bn
Cl
Bn
N

4g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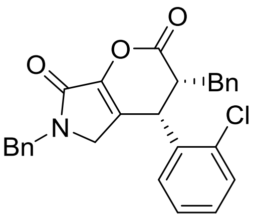
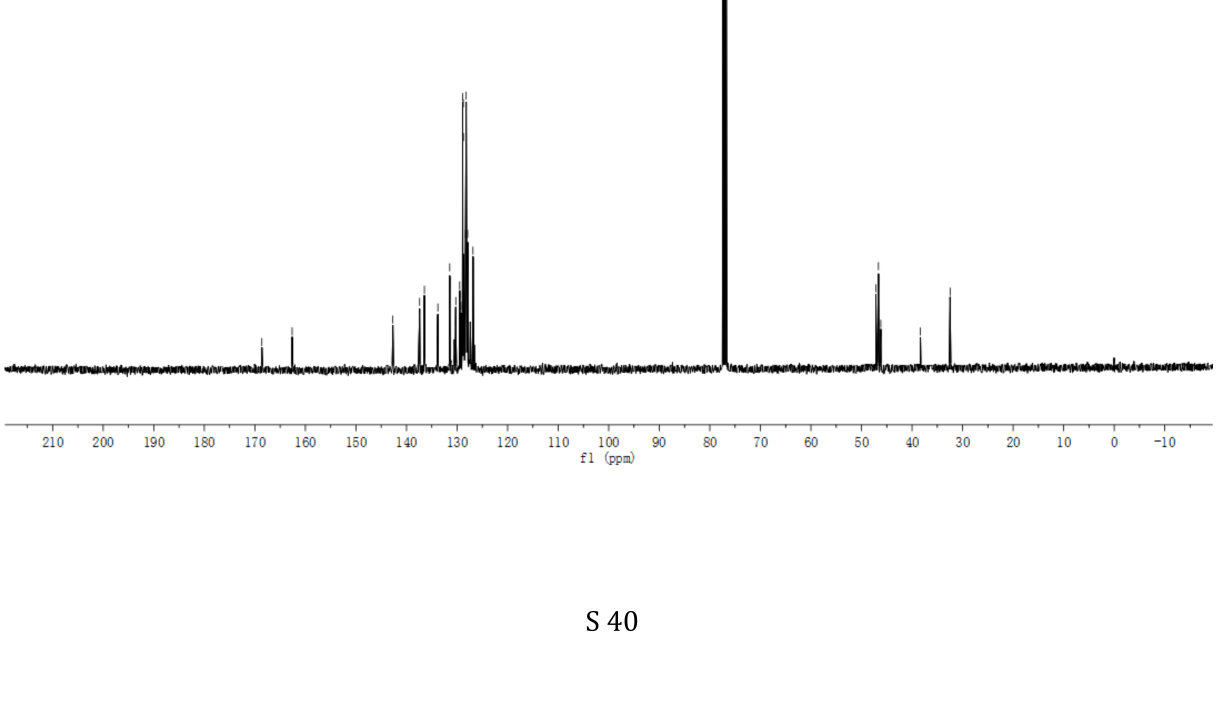
1.00
1.96
0.97
1.26
2.03
1.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


O
O
O
Bn
Cl
Bn
N

4g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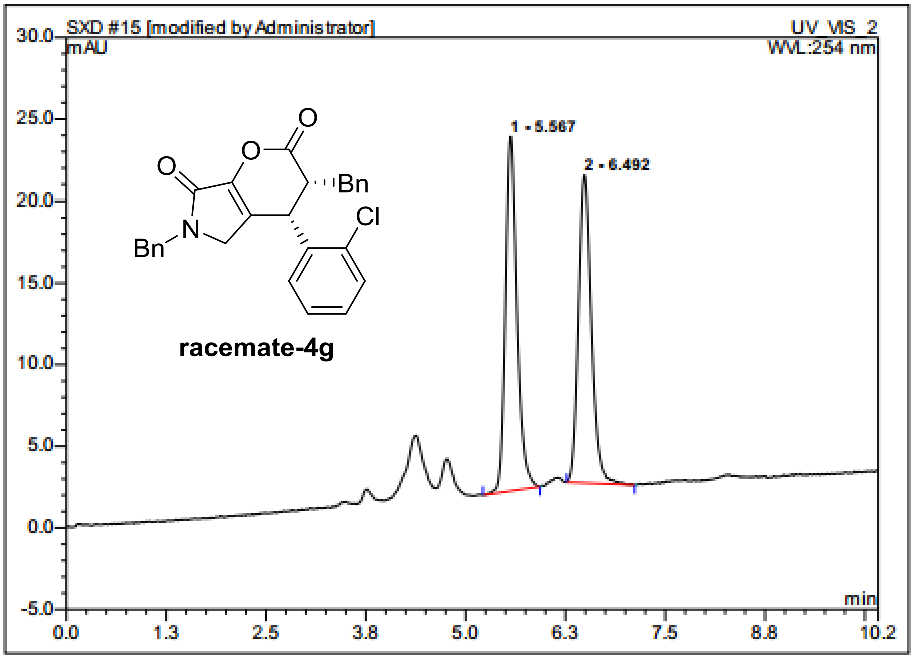
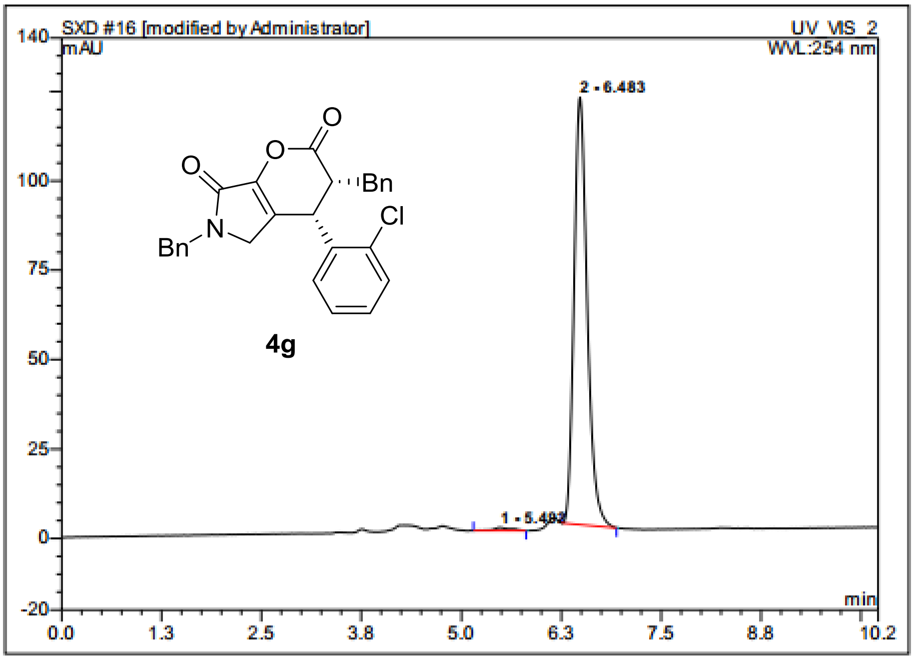
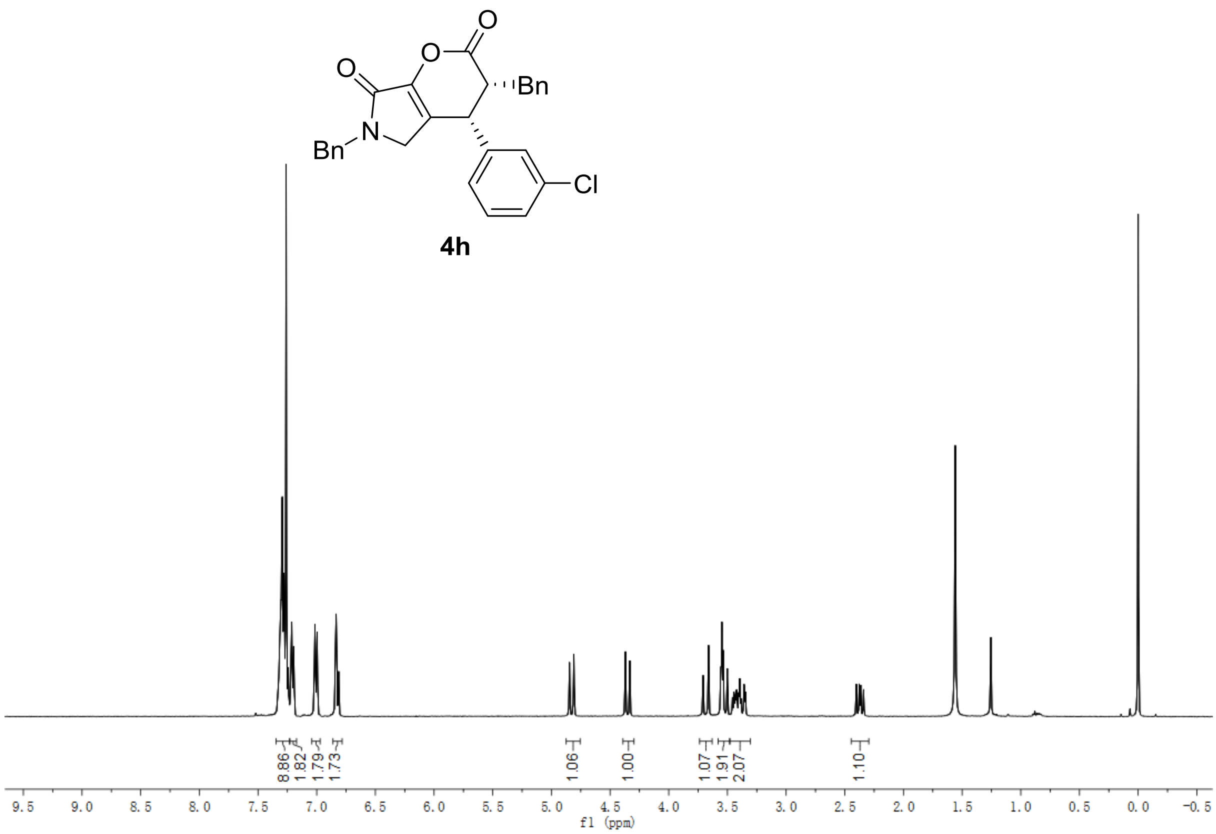
136.458
133.796
131.455
130.256
129.489
129.458
129.232
128.883
128.770
128.738
128.315
128.197
127.905
126.850
47.151
46.647
46.182
38.342
32.470
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



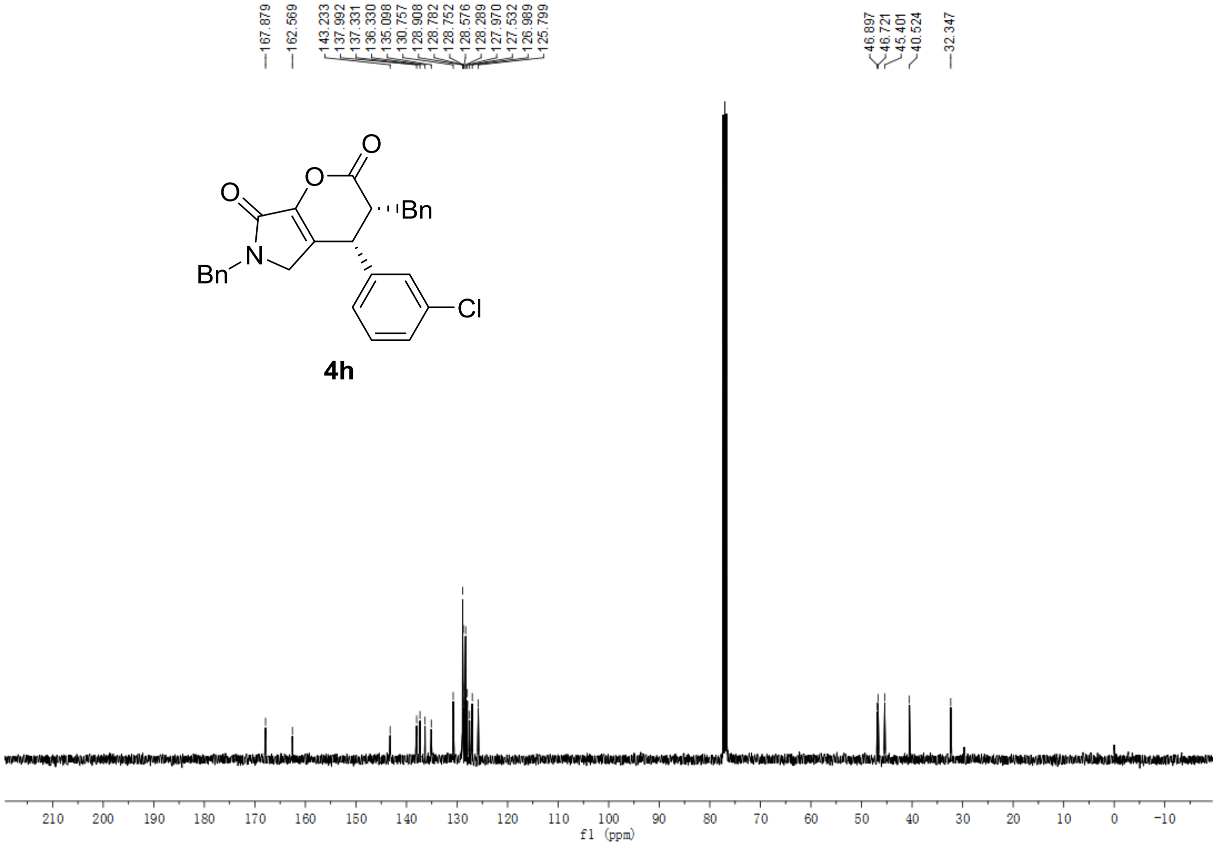
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.57	n.a.	21.677	3.657	50.79	n.a.	BMB*
2	6.49	n.a.	18.811	3.544	49.21	n.a.	BMB*
Total:			40.487	7.201	100.00	0.000	



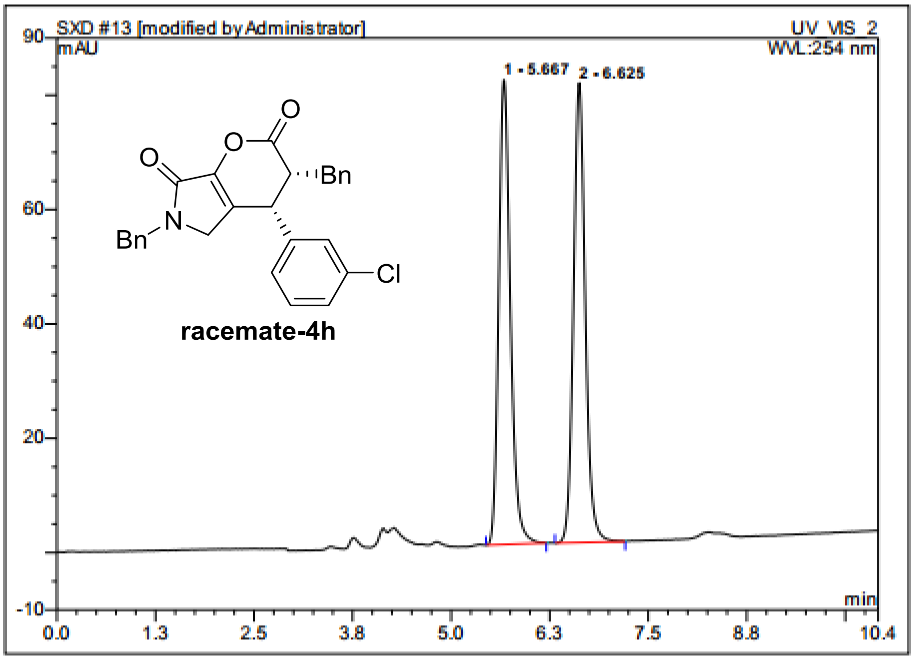
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.49	n.a.	0.844	0.217	0.94	n.a.	BMB*
2	6.48	n.a.	119.520	22.850	99.06	n.a.	BMB*
Total:			120.364	23.067	100.00	0.000	



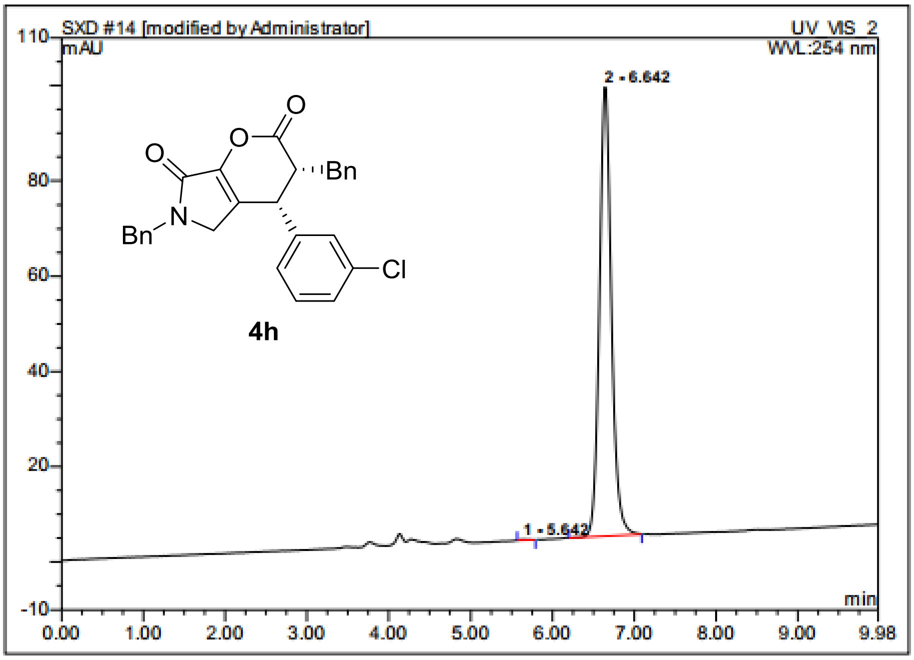
4h



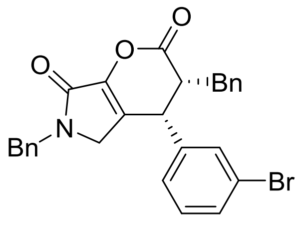
4h



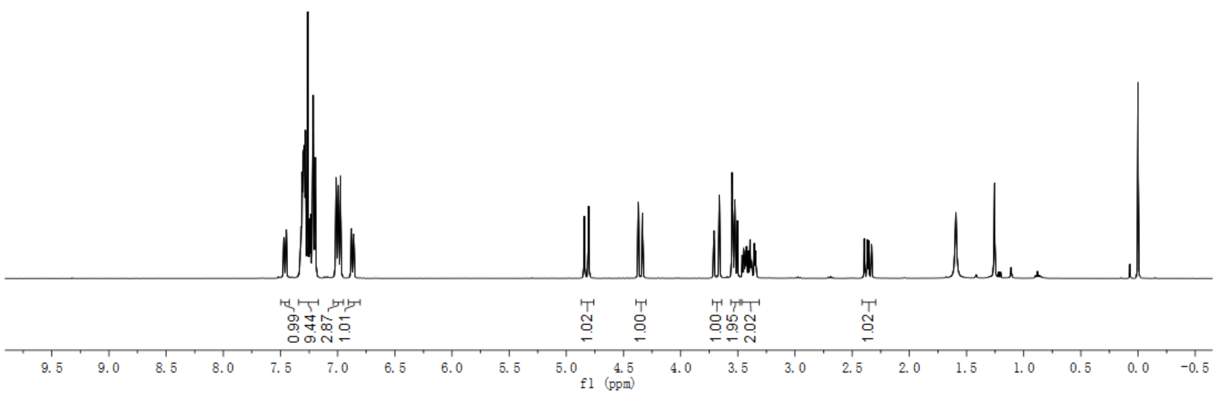
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.67	n.a.	81.230	13.962	50.08	n.a.	BMB*
2	6.63	n.a.	80.373	13.916	49.92	n.a.	BMB*
Total:			161.603	27.877	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.64	n.a.	0.179	0.023	0.14	n.a.	BMB*
2	6.64	n.a.	94.275	15.969	99.86	n.a.	BMB*
Total:			94.453	15.992	100.00	0.000	


O
O
O
Bn
N
Bn
Br

4i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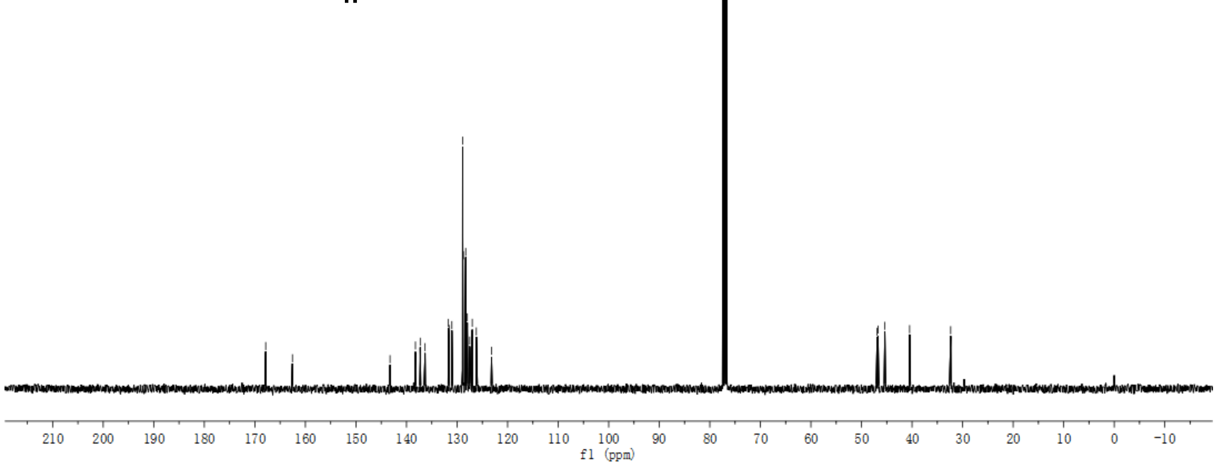
9.44
2.87
1.01
1.02
1.00
1.00
1.95
2.02
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


167.852
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128.909
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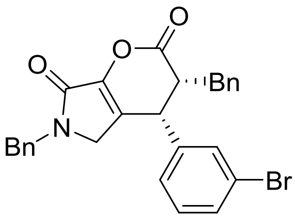
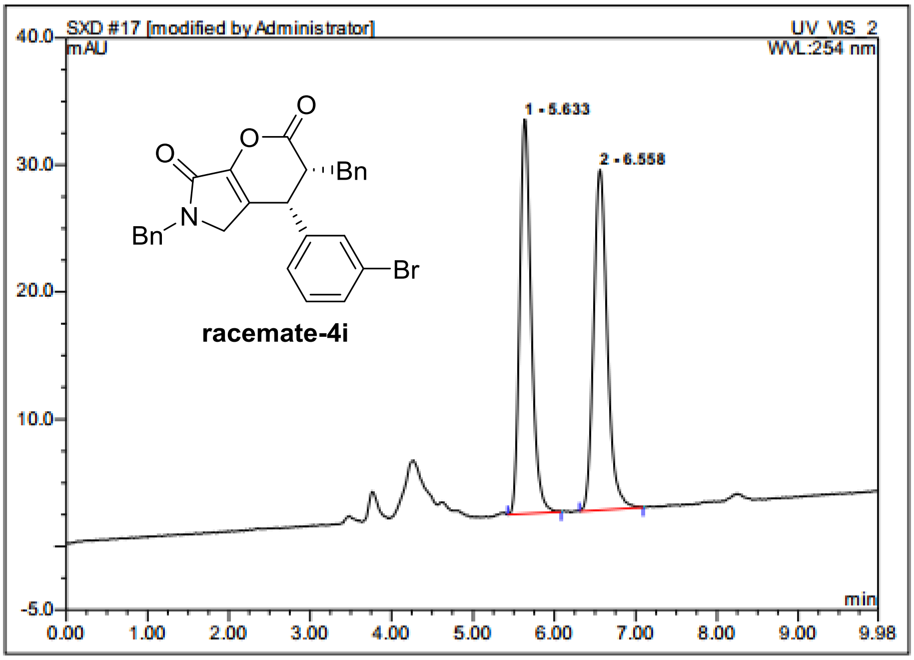
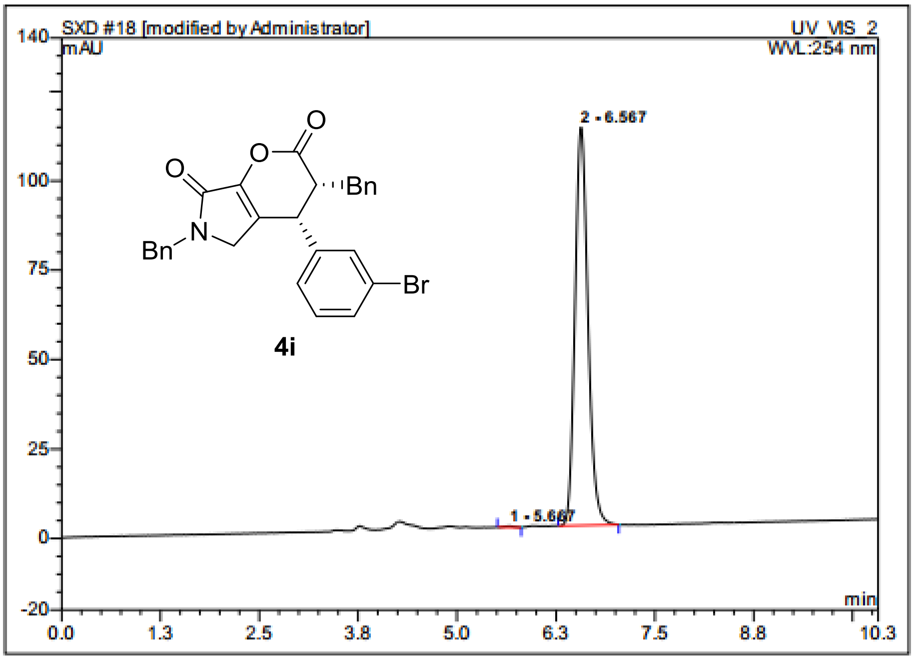
128.289
127.972
127.501
126.996
126.186
123.177
46.907
46.724
45.372
40.476
32.355
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
O
Bn
N
Bn
Br

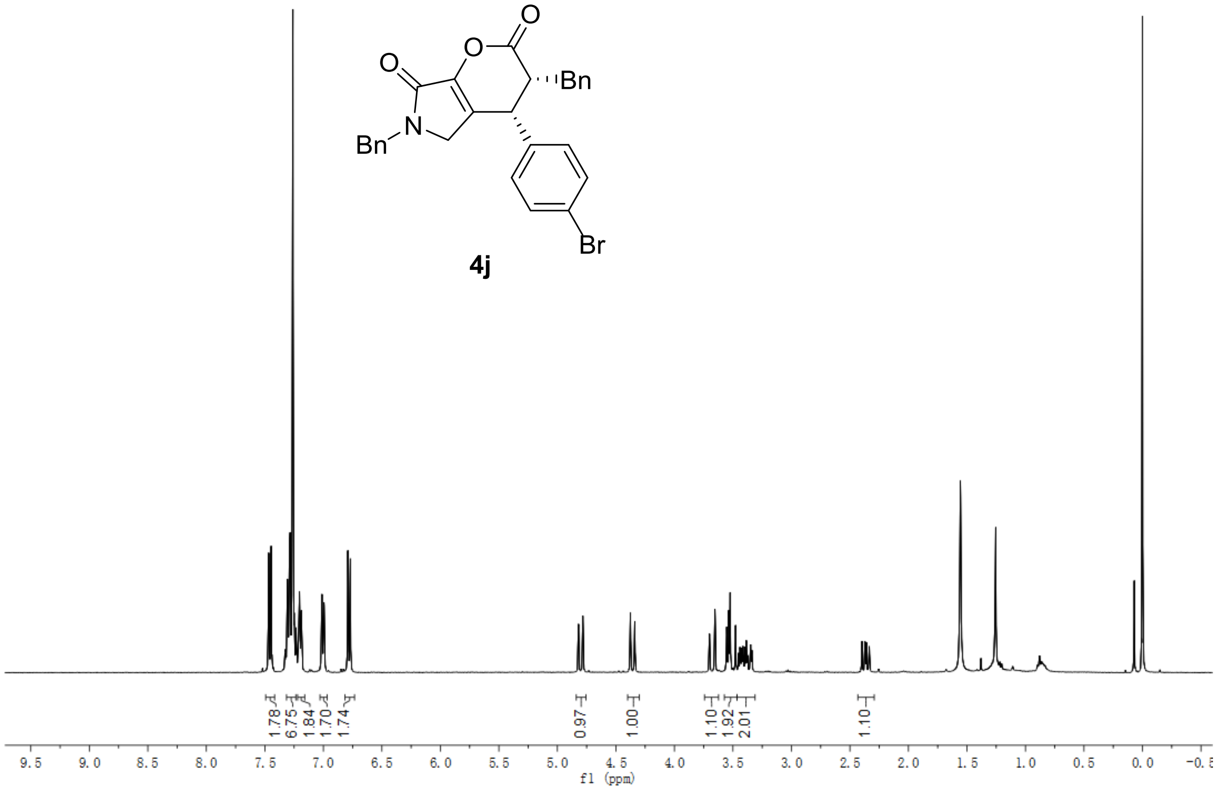
4i



No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.63	n.a.		31.023	5.100	49.54	n.a.	BMB*
2	6.56	n.a.		26.754	5.194	50.46	n.a.	BMB*
Total:				57.776	10.293	100.00	0.000	



No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.67	n.a.		0.368	0.051	0.24	n.a.	BMB*
2	6.57	n.a.		111.287	21.180	99.76	n.a.	BMB*
Total:				111.654	21.232	100.00	0.000	


O
O
O
Bn
Bn
N
Br
4j
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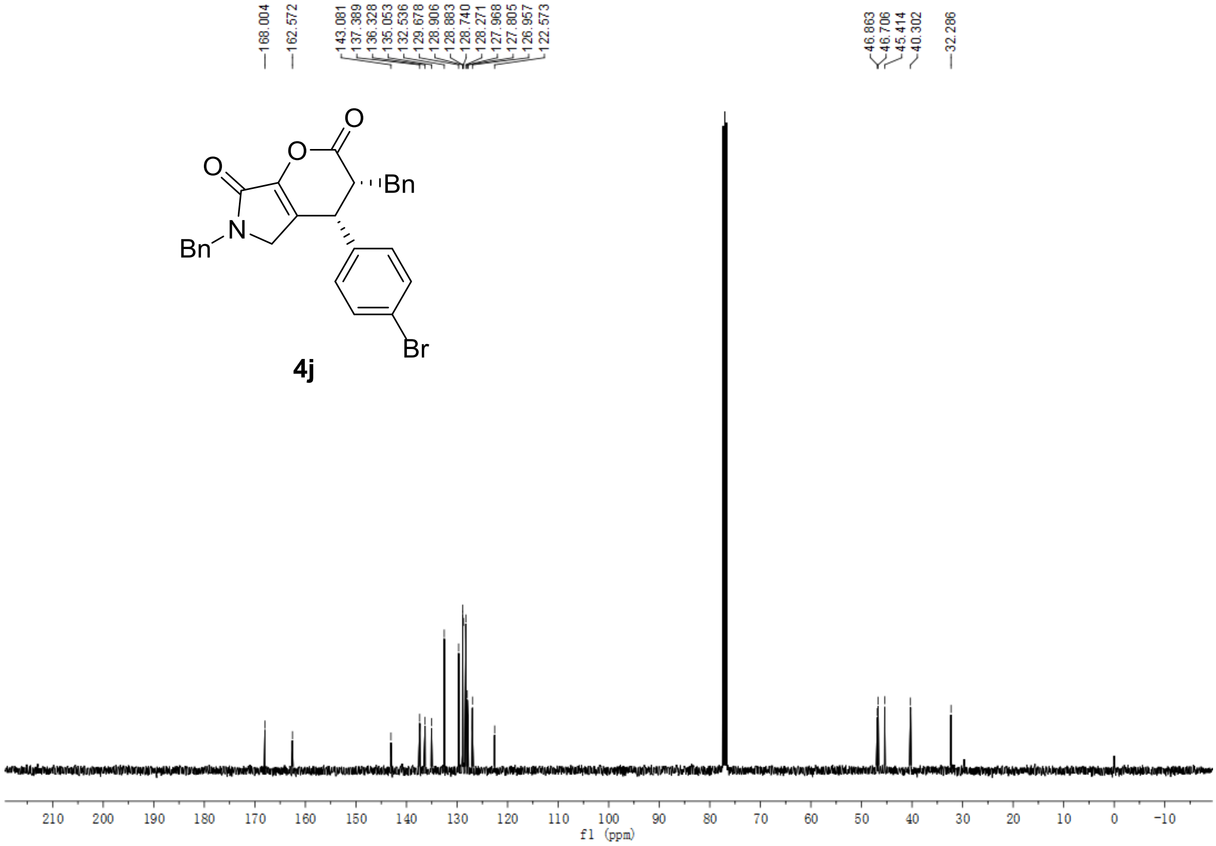
1.84
1.70
1.74
0.97
1.00
1.10
1.92
2.01
1.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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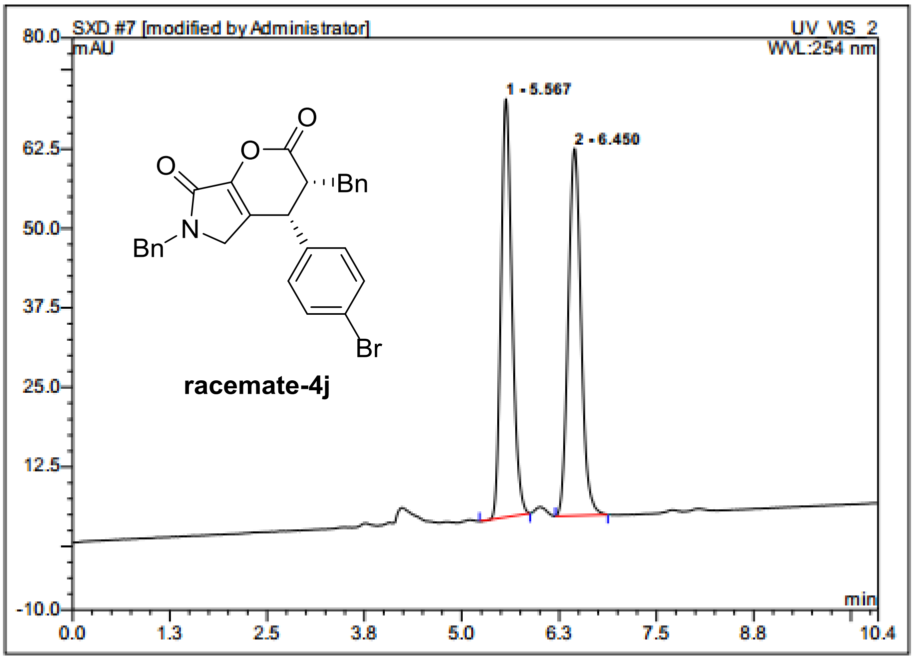
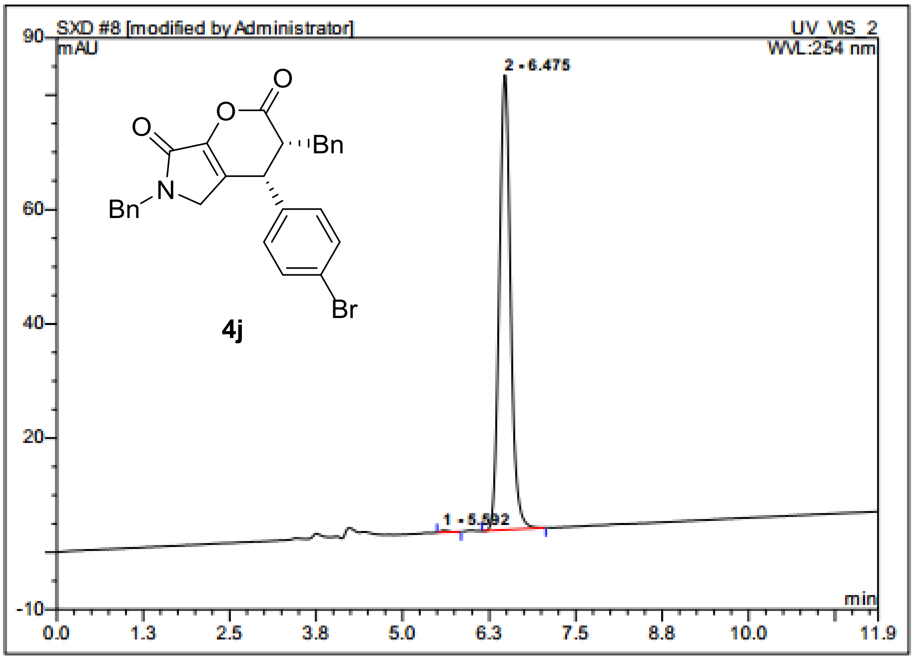
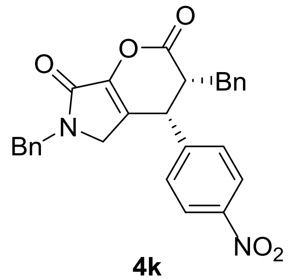
127.805
126.957
122.573
46.863
46.706
45.414
40.302
32.286
O
O
O
Bn
Bn
N
Br
4j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



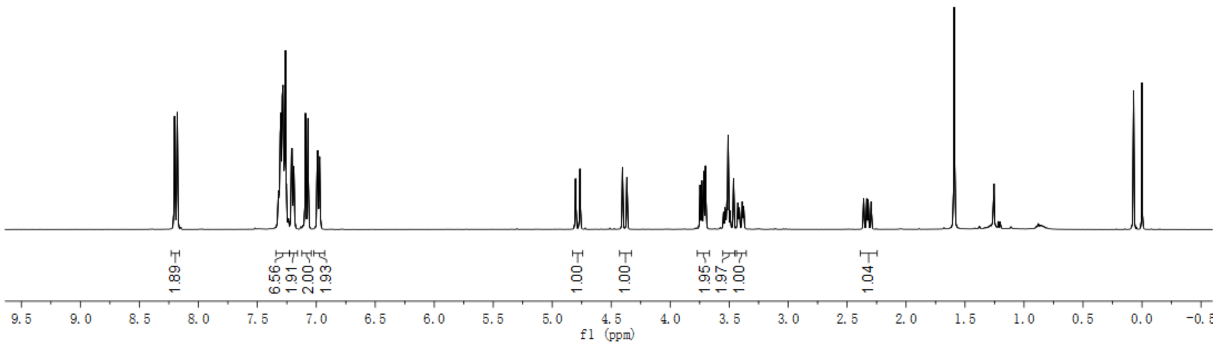
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.57	n.a.	65.799	10.754	49.45	n.a.	BMB*
2	6.45	n.a.	57.769	10.994	50.55	n.a.	BMB*
Total:			123.569	21.748	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.59	n.a.	0.326	0.036	0.24	n.a.	BMB*
2	6.48	n.a.	79.535	15.086	99.76	n.a.	BMB*
Total:			79.862	15.122	100.00	0.000	


O
O
O
Bn
N
Bn
NO2

4k


1.89
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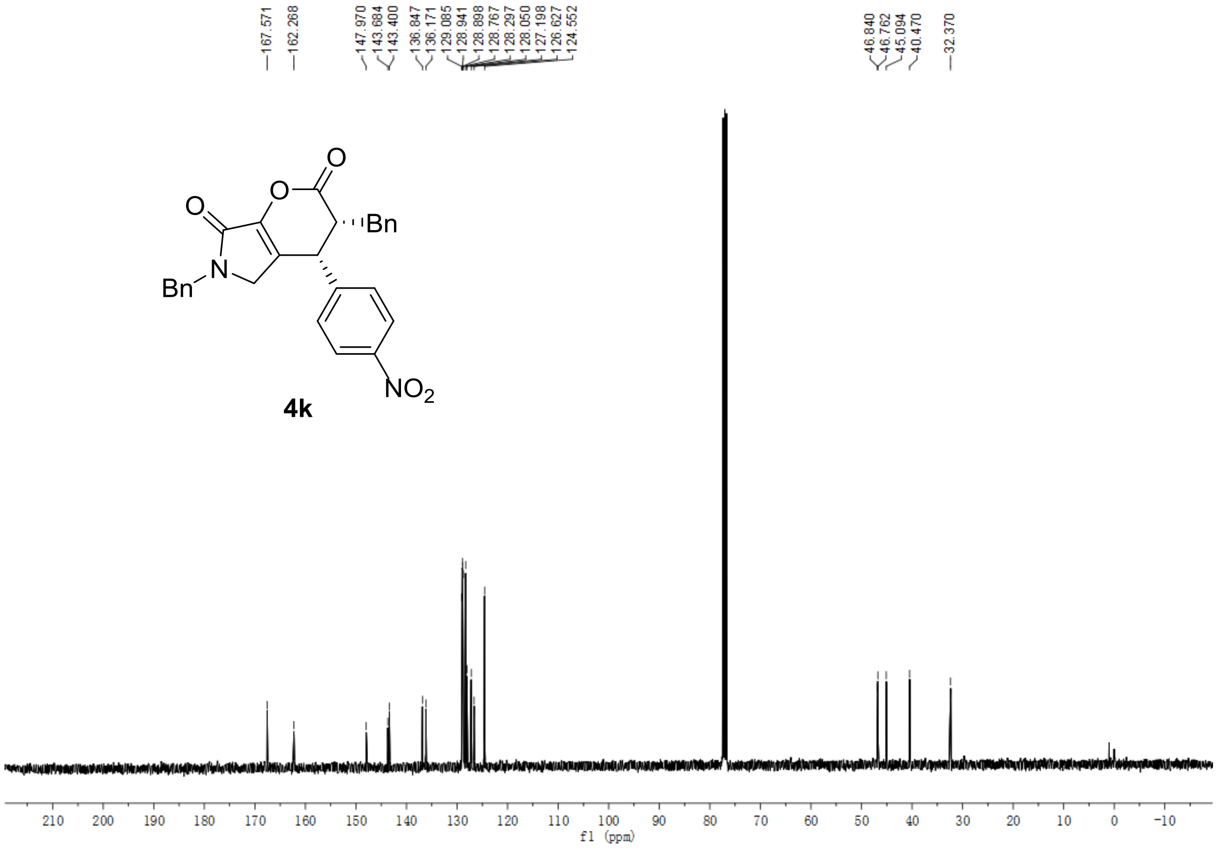
1.00
1.00
1.95
1.97
1.00
1.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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126.627
124.552
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46.762
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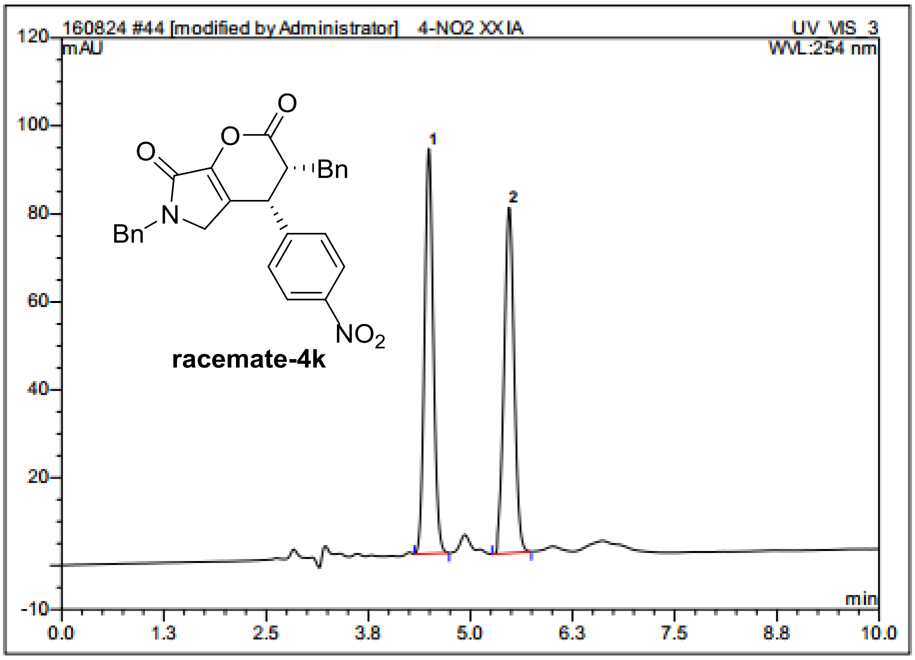
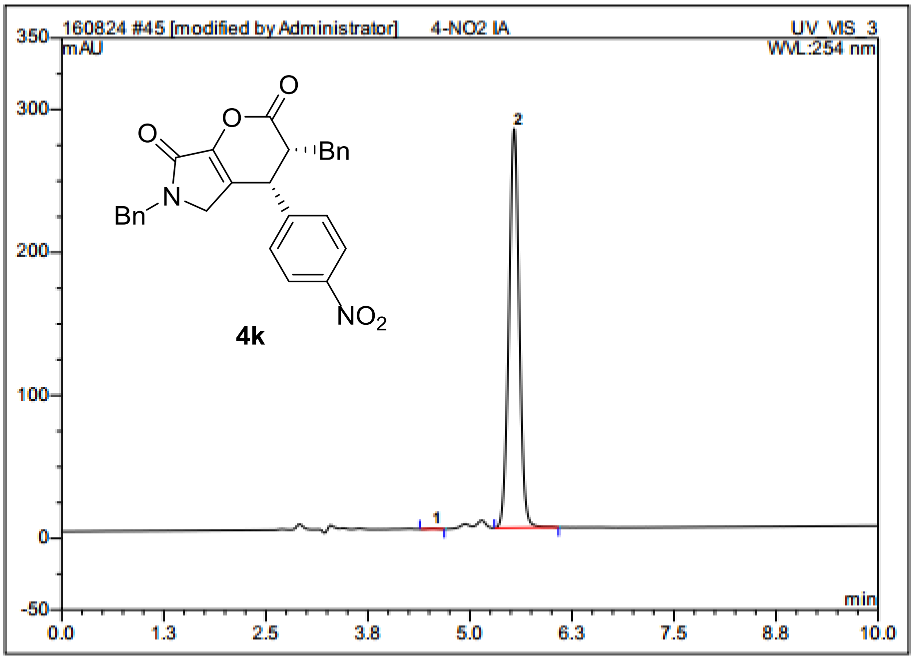
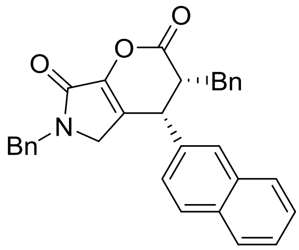
40.470
32.370
4k
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



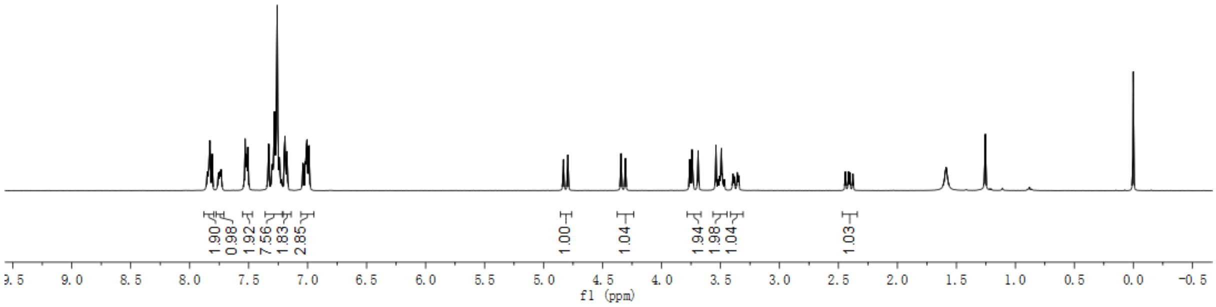
No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.49	n.a.		92.130	11.484	50.40	n.a.	BMB*
2	5.47	n.a.		78.623	11.304	49.60	n.a.	BMB*
Total:				170.753	22.789	100.00		



No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.55	n.a.		0.390	0.055	0.14	n.a.	BMB*
2	5.54	n.a.		279.216	40.924	99.86	n.a.	BMB*
Total:				279.605	40.980	100.00		


O
O
O
Bn
N
Bn

4l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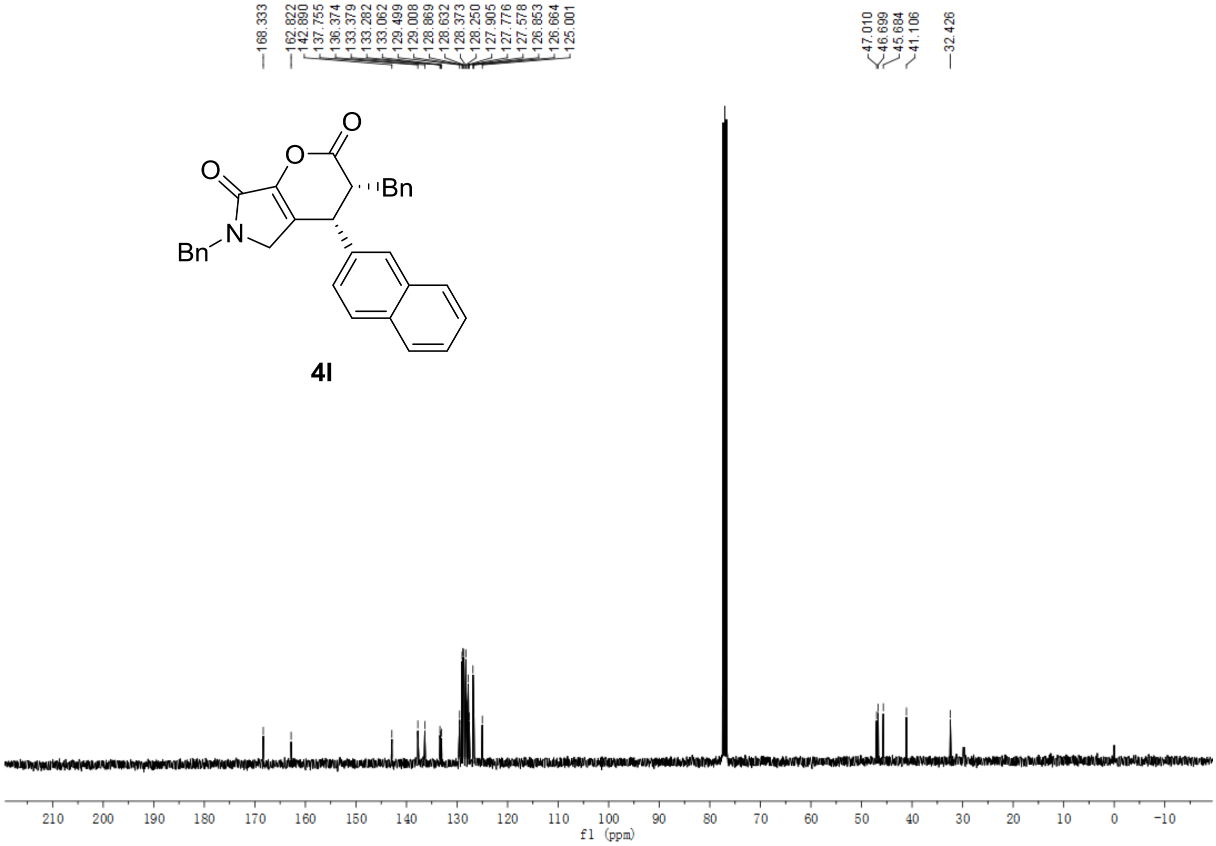
1.92
7.56
1.83
2.85
1.00
1.04
1.94
1.98
1.04
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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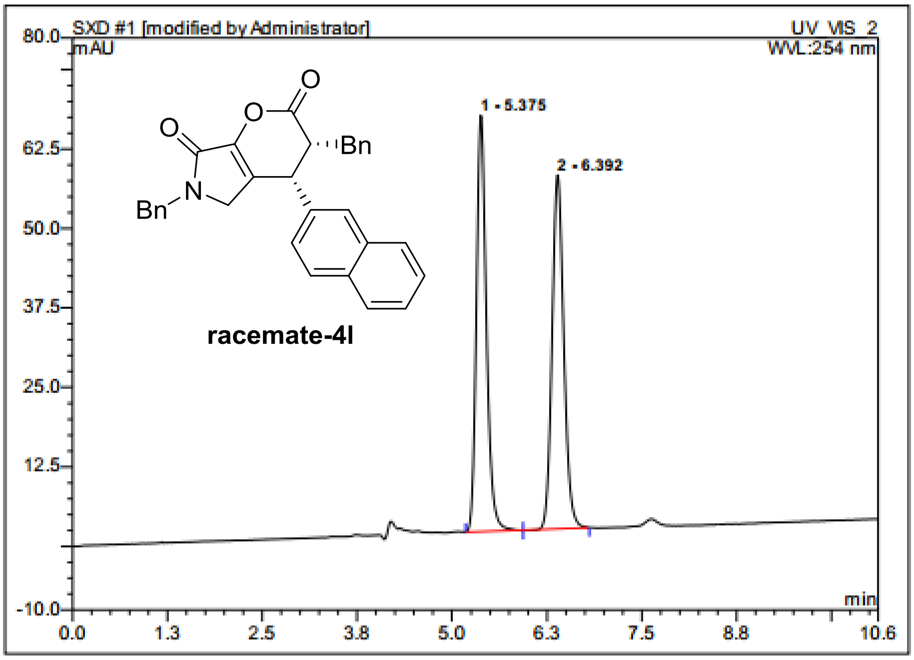
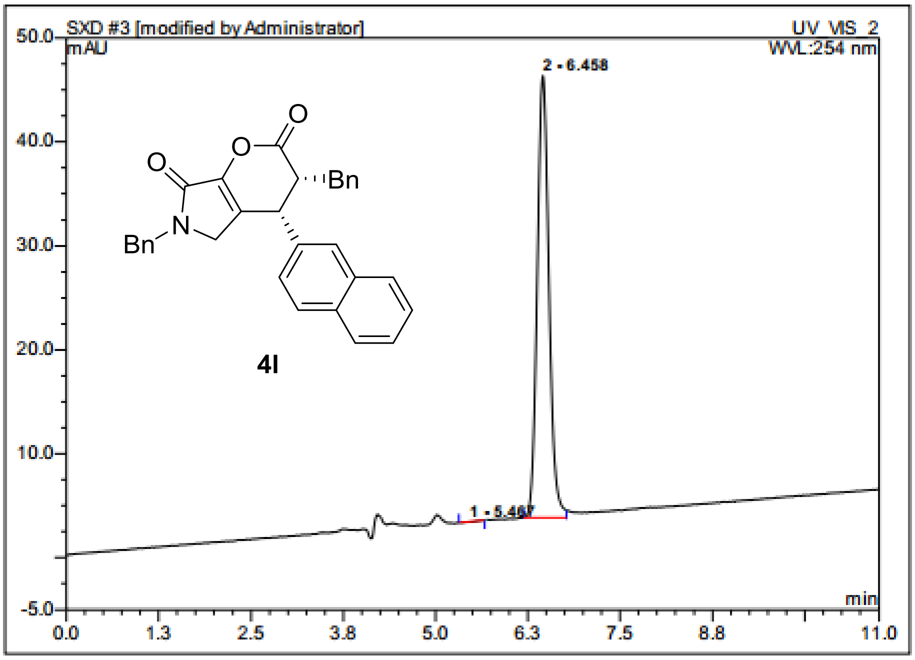
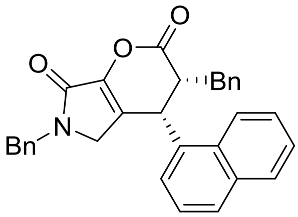
127.776
127.578
126.853
126.664
125.001
47.010
46.699
45.684
41.106
32.426
O
O
O
Bn
N
Bn
4l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



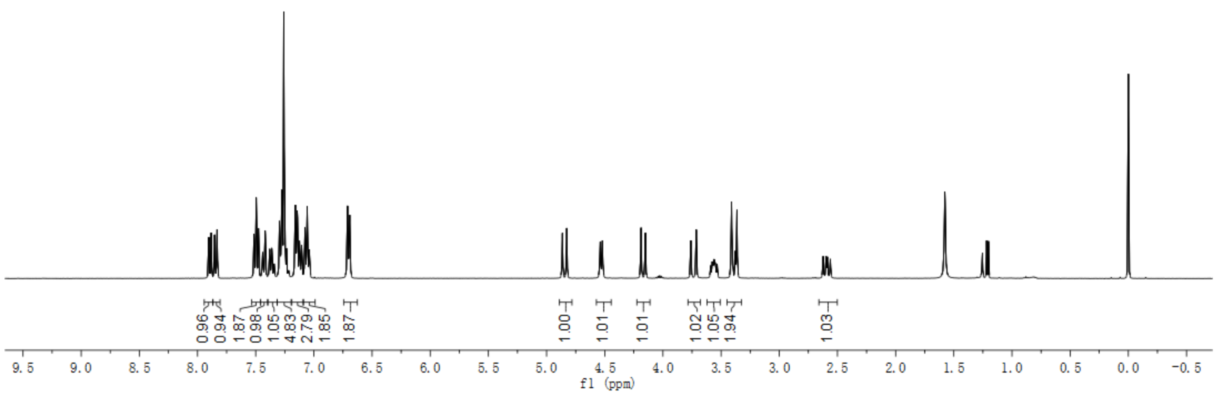
No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.38	n.a.		65.458	9.985	50.06	n.a.	BM *
2	6.39	n.a.		55.652	9.960	49.94	n.a.	MB*
Total:				121.110	19.945	100.00	0.000	

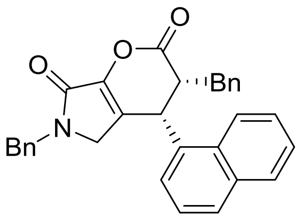


No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.47	n.a.		0.017	0.007	0.09	n.a.	BMB*
2	6.46	n.a.		42.499	7.819	99.91	n.a.	BM *
Total:				42.517	7.826	100.00	0.000	

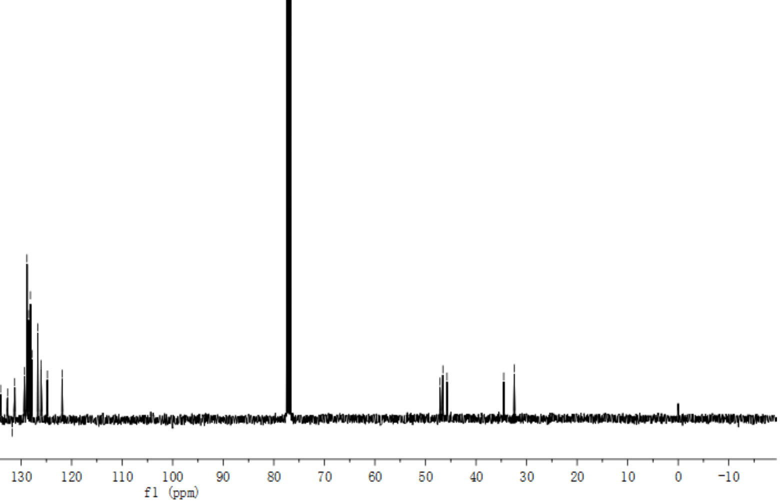

O
O
O
Bn
N
Bn

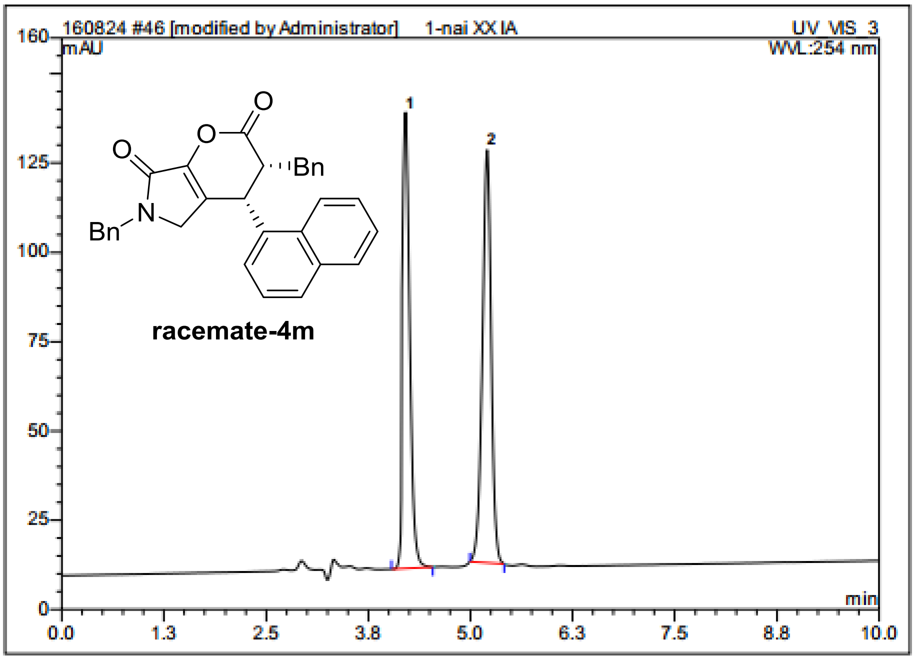
4m


0.96
0.94
1.87
0.98
1.05
4.83
2.79
1.85
1.87
1.00
1.01
1.01
1.02
1.05
1.94
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

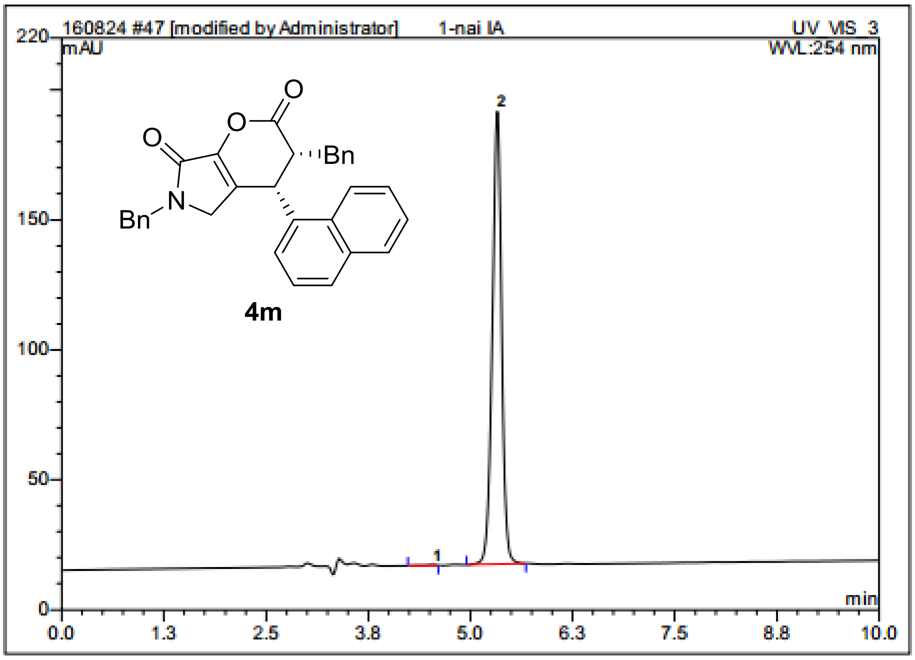

O
O
O
Bn
N
Bn

4m

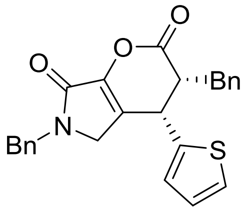

168.824
162.752
142.500
137.742
136.491
134.050
132.668
131.774
131.264
129.321
128.860
128.836
128.545
128.141
127.848
126.688
126.056
126.014
124.800
121.877
47.128
46.549
45.752
34.516
32.436
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



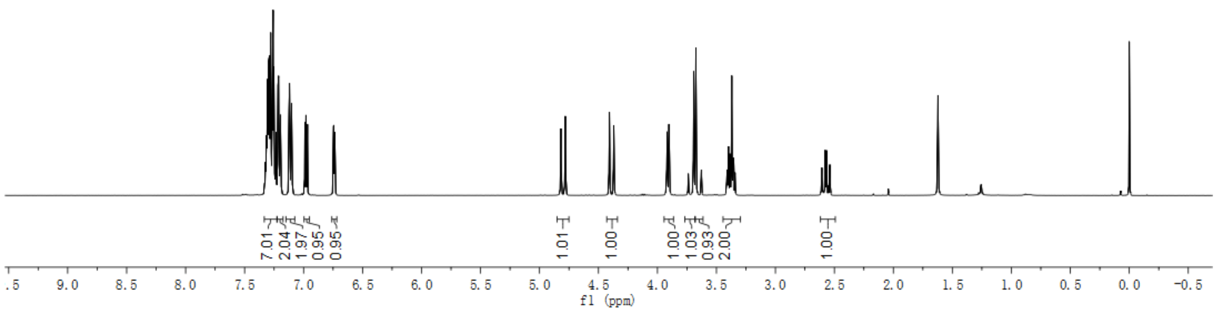
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.21	n.a.	127.669	13.393	48.11	n.a.	BMB*
2	5.21	n.a.	115.554	14.446	51.89	n.a.	BMB*
Total:			243.223	27.840	100.00		

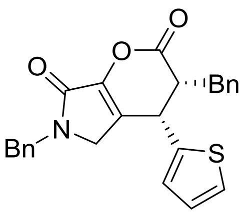


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.54	n.a.	0.236	0.037	0.16	n.a.	BMB*
2	5.33	n.a.	174.166	23.086	99.84	n.a.	BMB
Total:			174.403	23.122	100.00		

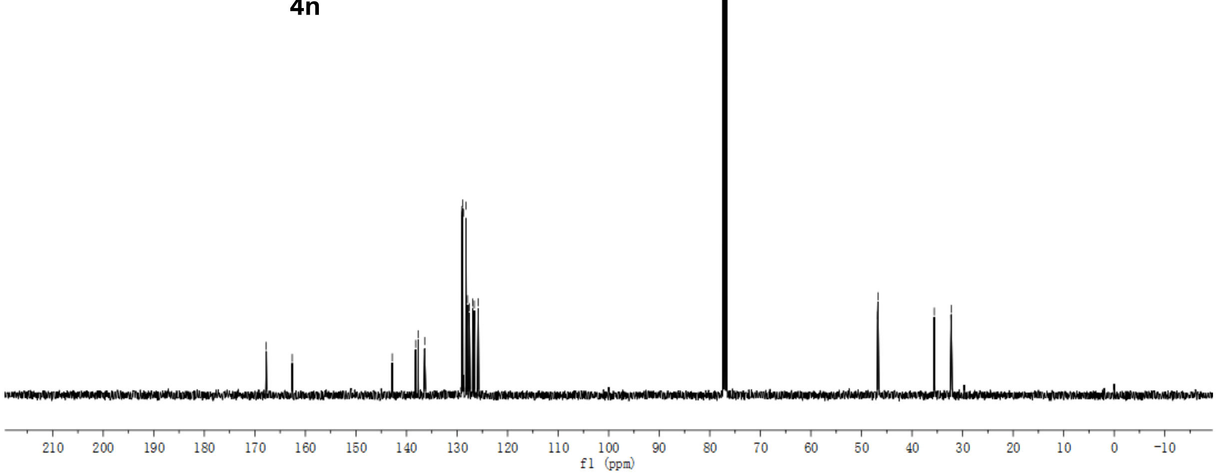


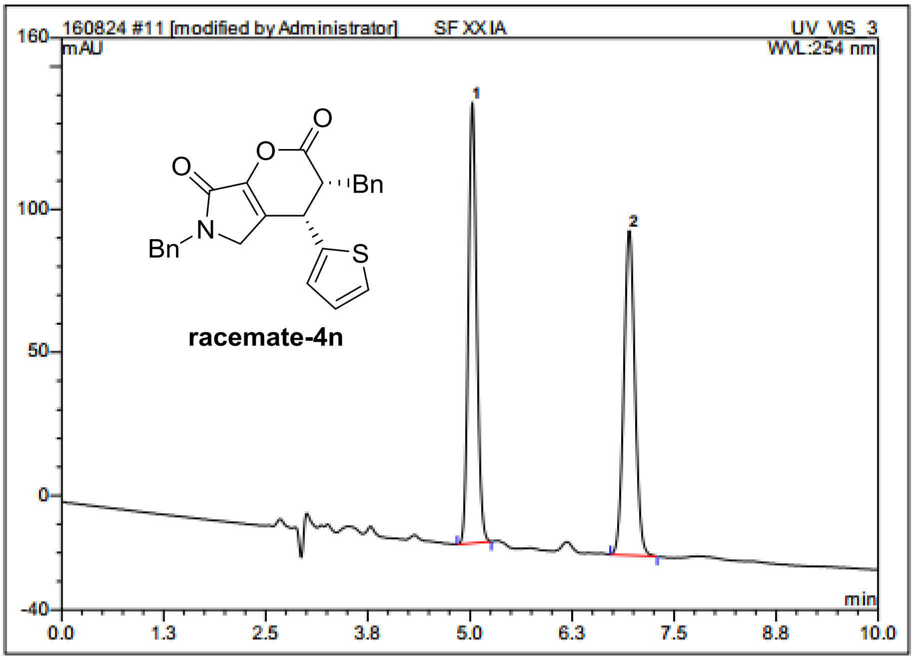
4n



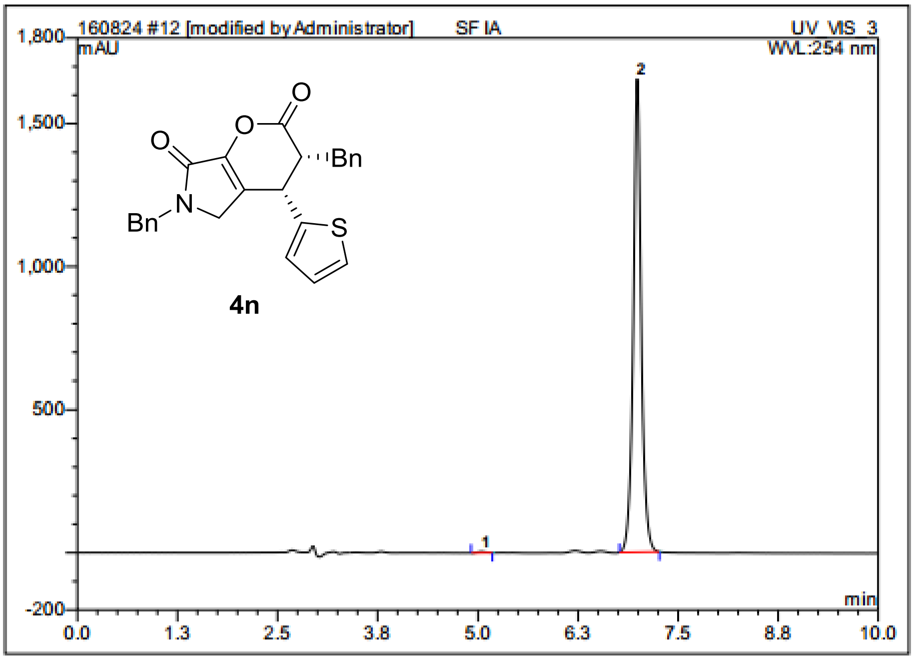


4n

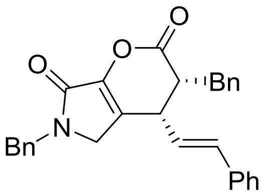




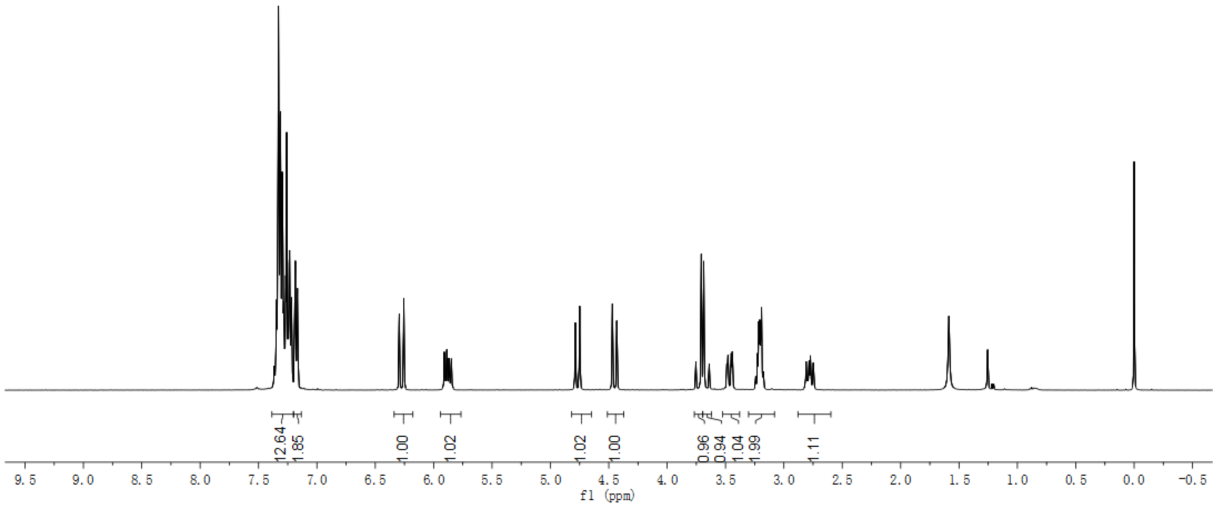
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.03	n.a.	154.114	18.189	50.46	n.a.	BMB*
2	6.95	n.a.	113.463	17.858	49.54	n.a.	BMB
Total:			267.577	36.048	100.00		

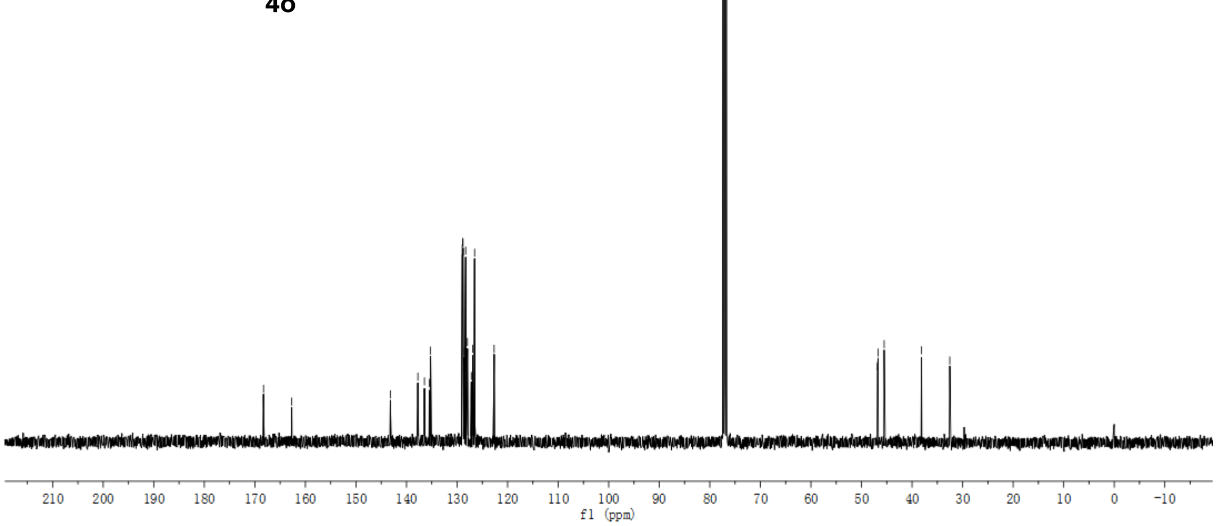


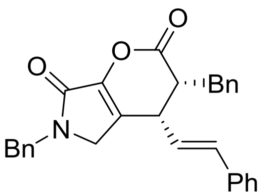
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.05	n.a.	4.151	0.457	0.24	n.a.	BMB*
2	6.99	n.a.	1654.401	190.470	99.76	n.a.	BMB*
Total:			1658.552	190.927	100.00		


O
O
O
Bn
N
Bn
Ph

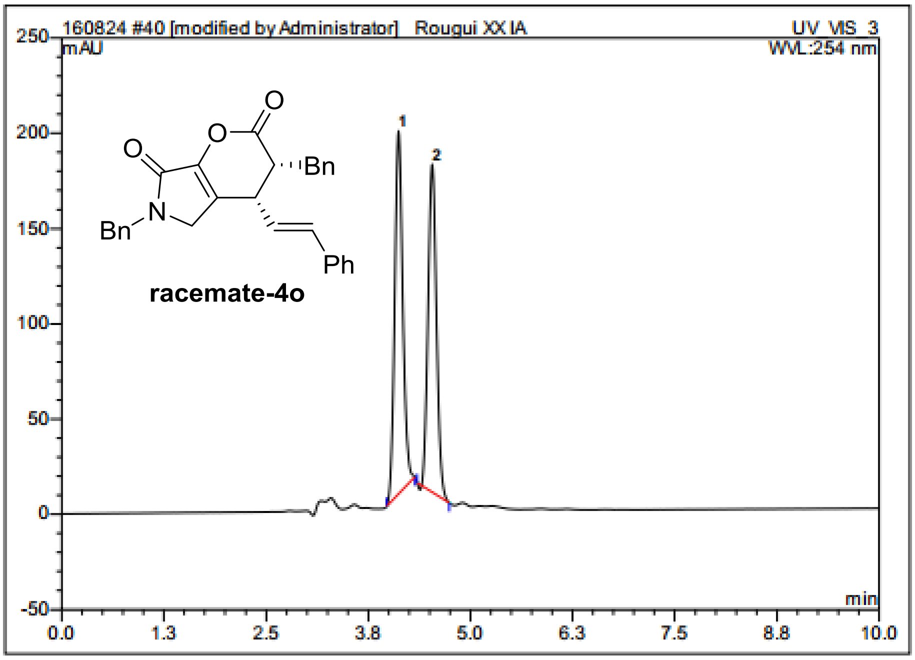
4o


12.64
1.85
1.00
1.02
1.02
1.00
0.96
0.94
1.04
1.99
1.11
f1 (ppm)

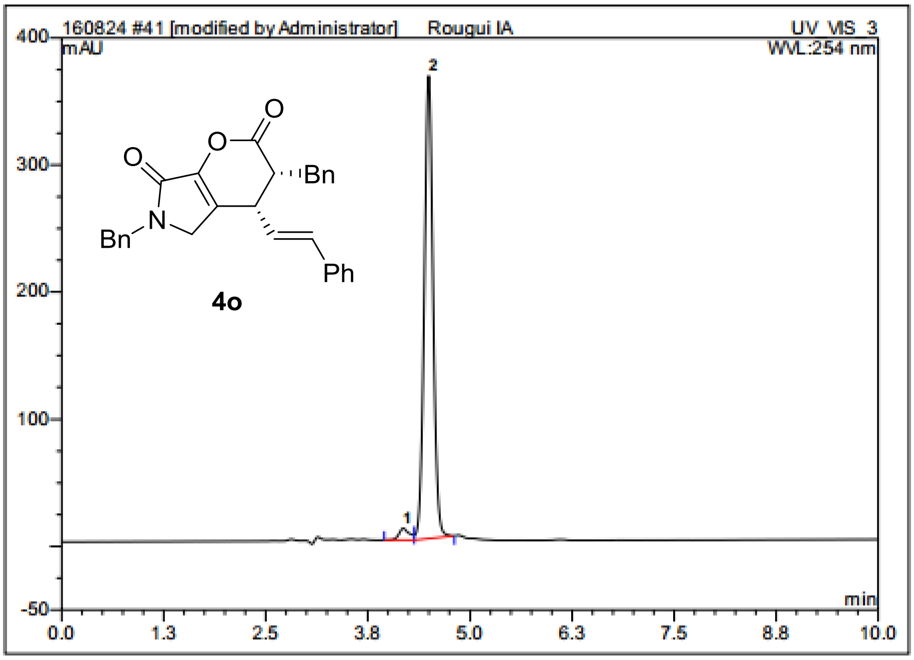

168.285
162.695
143.188
137.749
136.450
135.495
135.234
128.975
128.906
128.825
128.771
128.555
128.285
127.945
127.174
126.899
126.528
122.668
46.855
46.729
45.514
38.135
32.533
f1 (ppm)


O
O
O
Bn
N
Bn
Ph

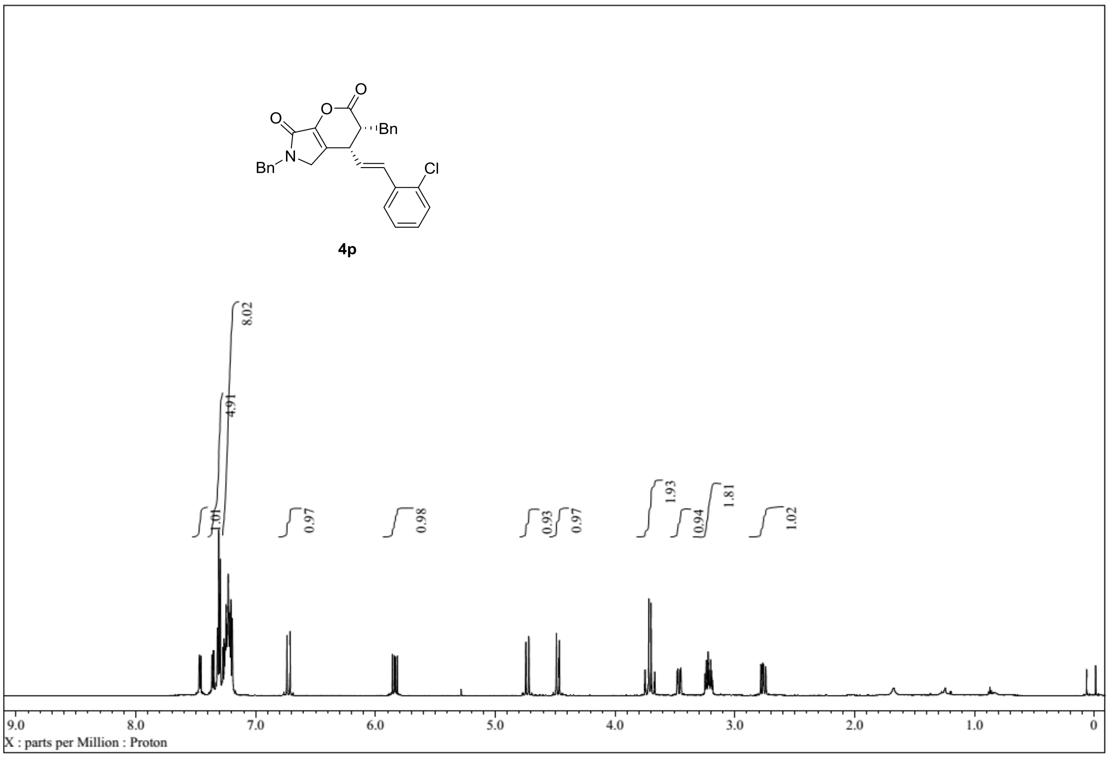
4o



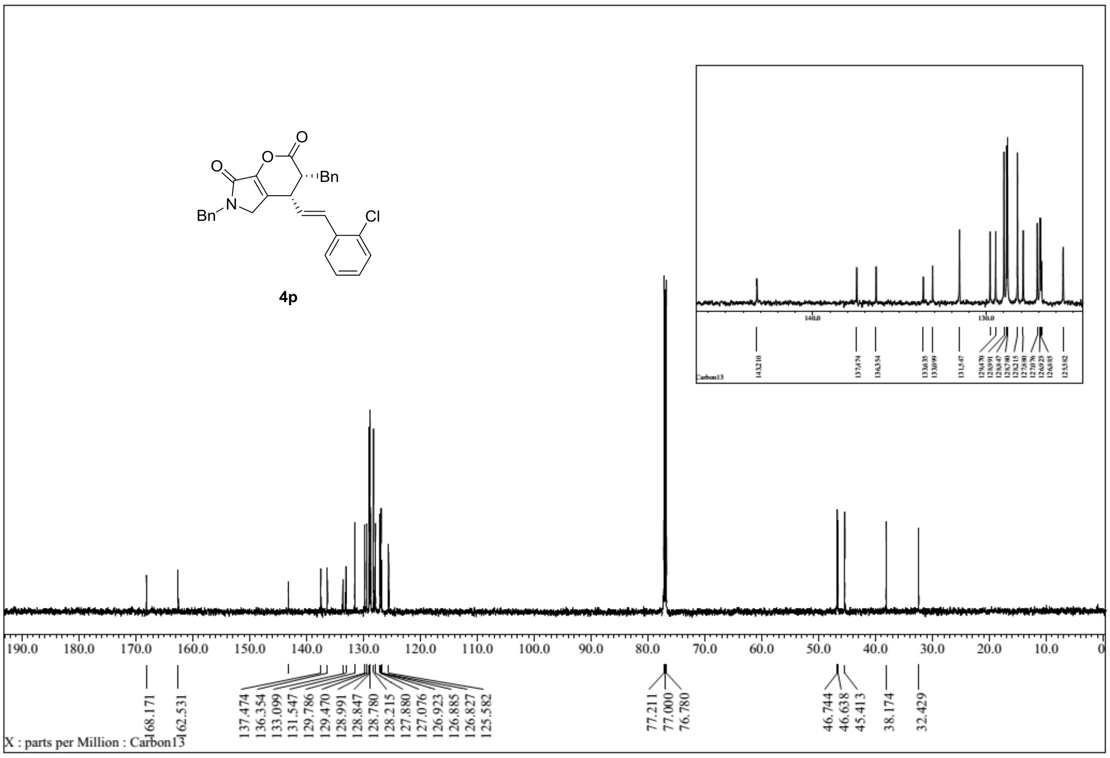
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.12	n.a.	190.526	21.855	51.62	n.a.	BMB*
2	4.53	n.a.	172.036	20.485	48.38	n.a.	BMB*
Total:			362.562	42.339	100.00		



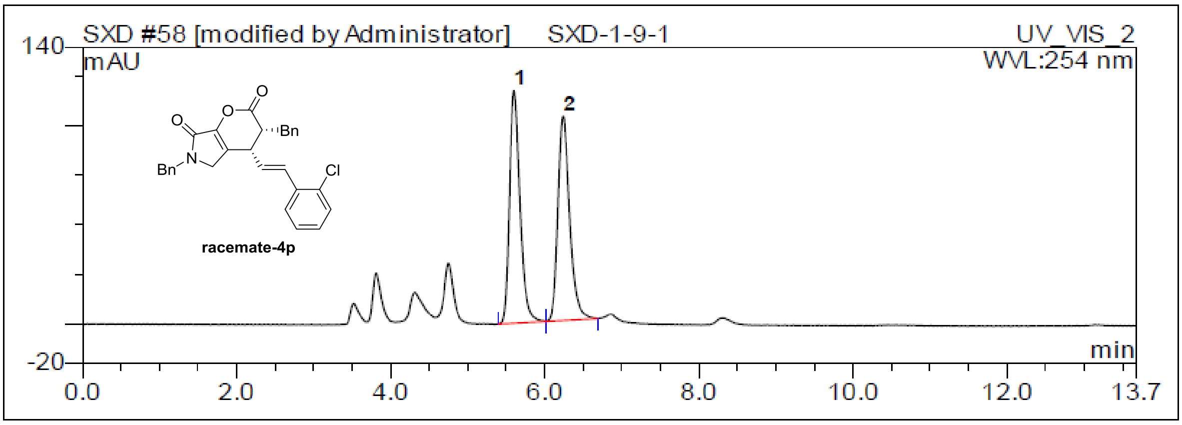
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.19	n.a.	9.215	1.370	2.93	n.a.	BM *
2	4.50	n.a.	363.978	45.414	97.07	n.a.	MB*
Total:			373.192	46.784	100.00		



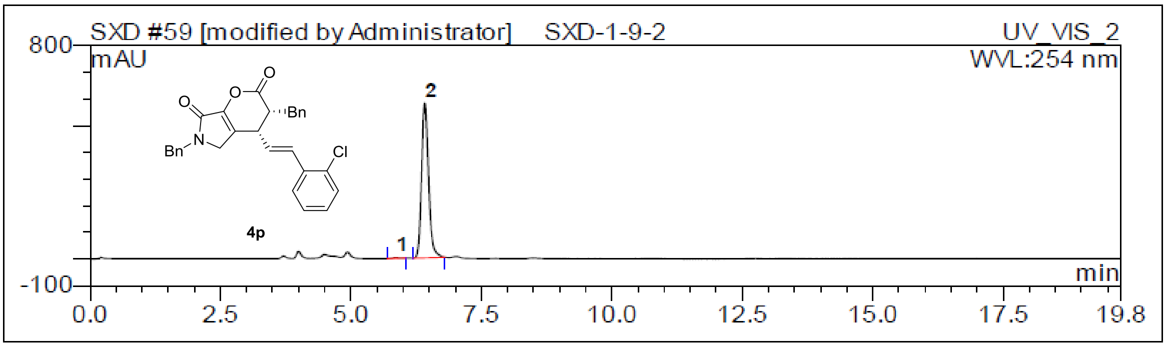
Bn
Cl
4p
8.02
4.91
1.01
0.97
0.98
0.93
0.97
1.93
0.94
1.81
1.02
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
X : parts per Million : Proton



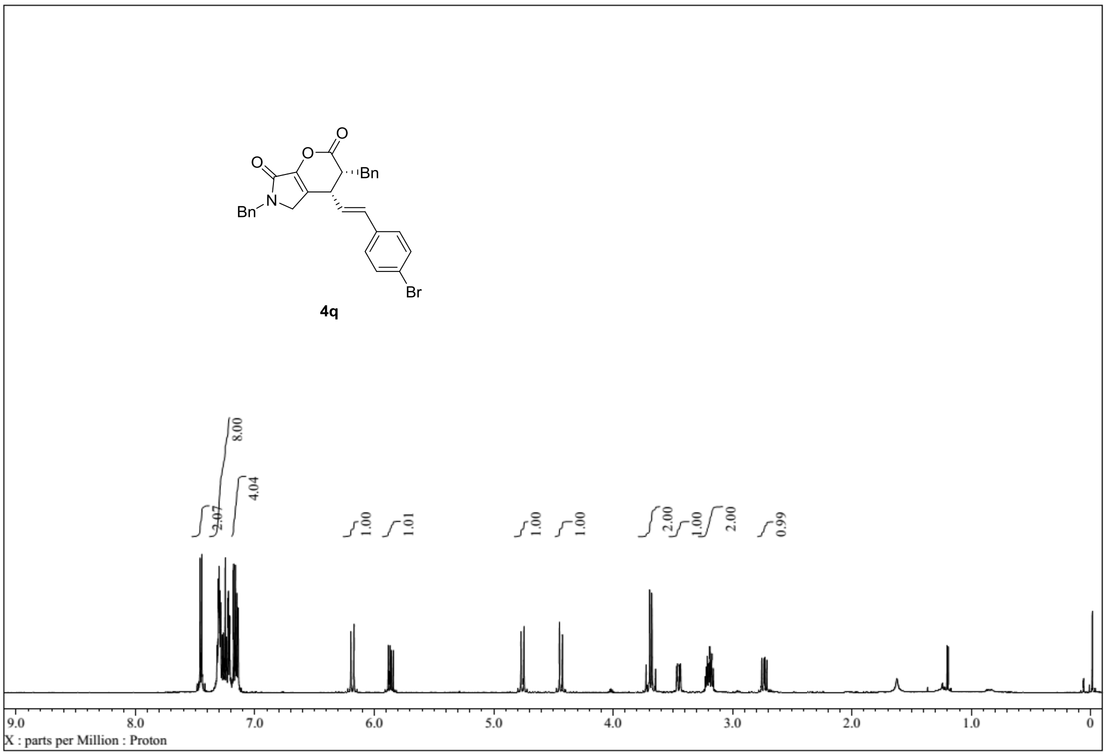
Bn
Cl
4p
140.0
130.0
Carbon13
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
168.171
162.531
137.474
136.354
133.099
131.547
129.786
129.470
128.991
128.847
128.780
128.215
127.880
127.076
126.923
126.885
126.827
125.582
77.211
77.000
76.780
46.744
46.638
45.413
38.174
32.429
X : parts per Million : Carbon13



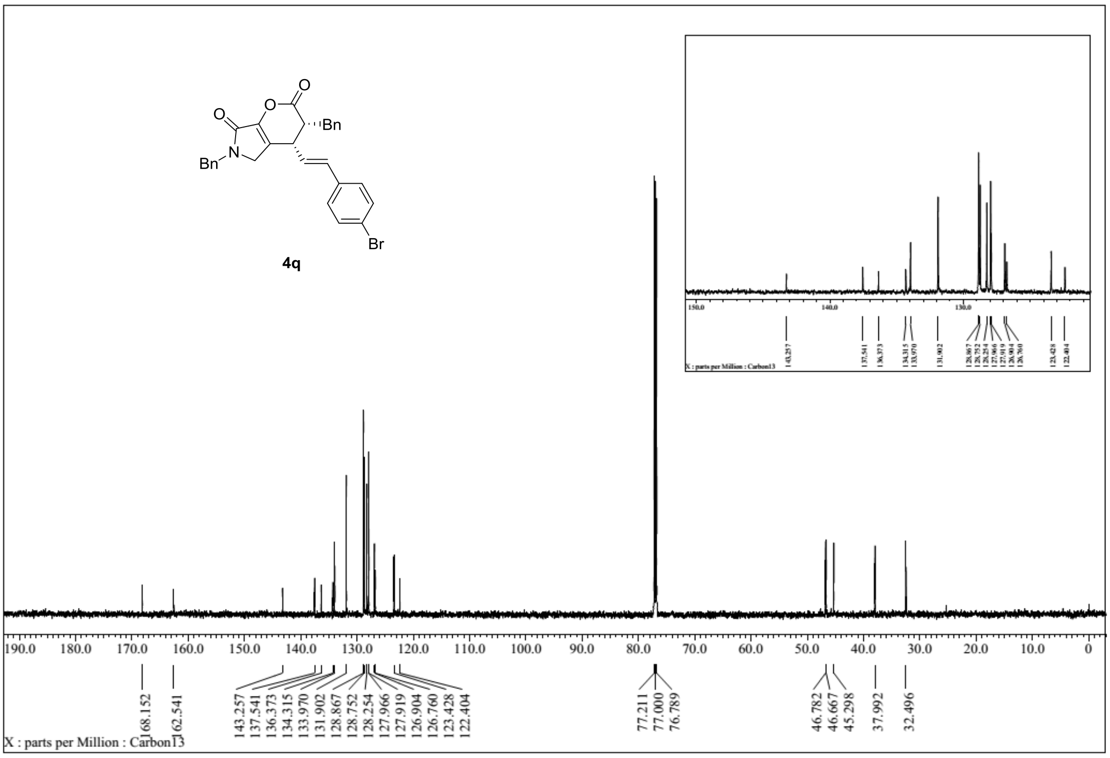
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.60	117.697	18.540	50.29
2	6.24	103.443	18.322	49.71
Total:		221.140	36.862	100.00



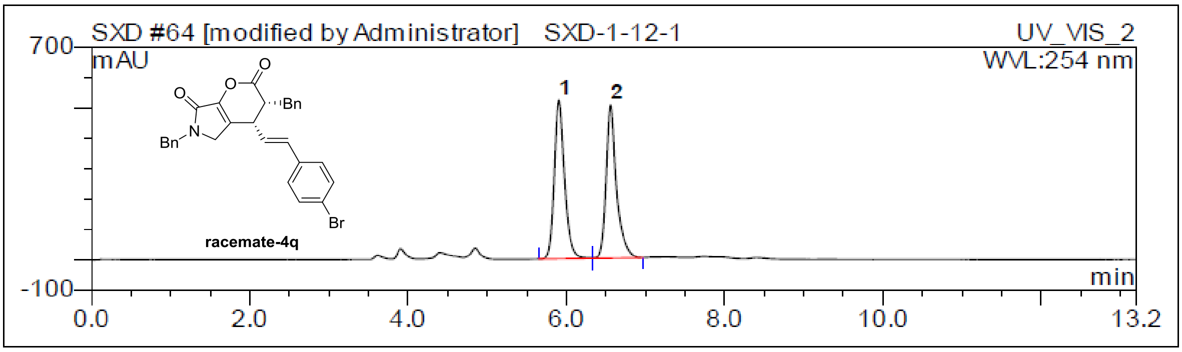
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.87	3.410	0.438	0.49
2	6.42	581.299	89.900	99.51
Total:		584.709	90.339	100.00



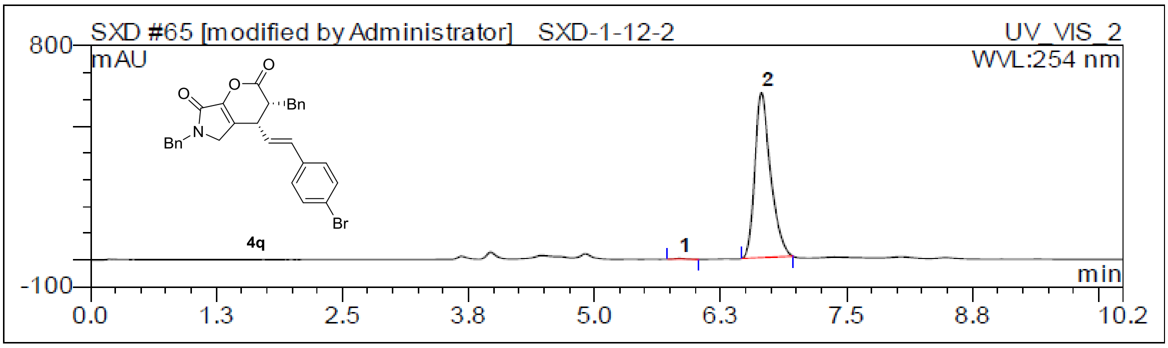
O
O
O
N
Bn
Bn
Br
4q
8.00
4.04
2.07
1.00
1.01
1.00
1.00
2.00
1.00
2.00
0.99
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : Proton



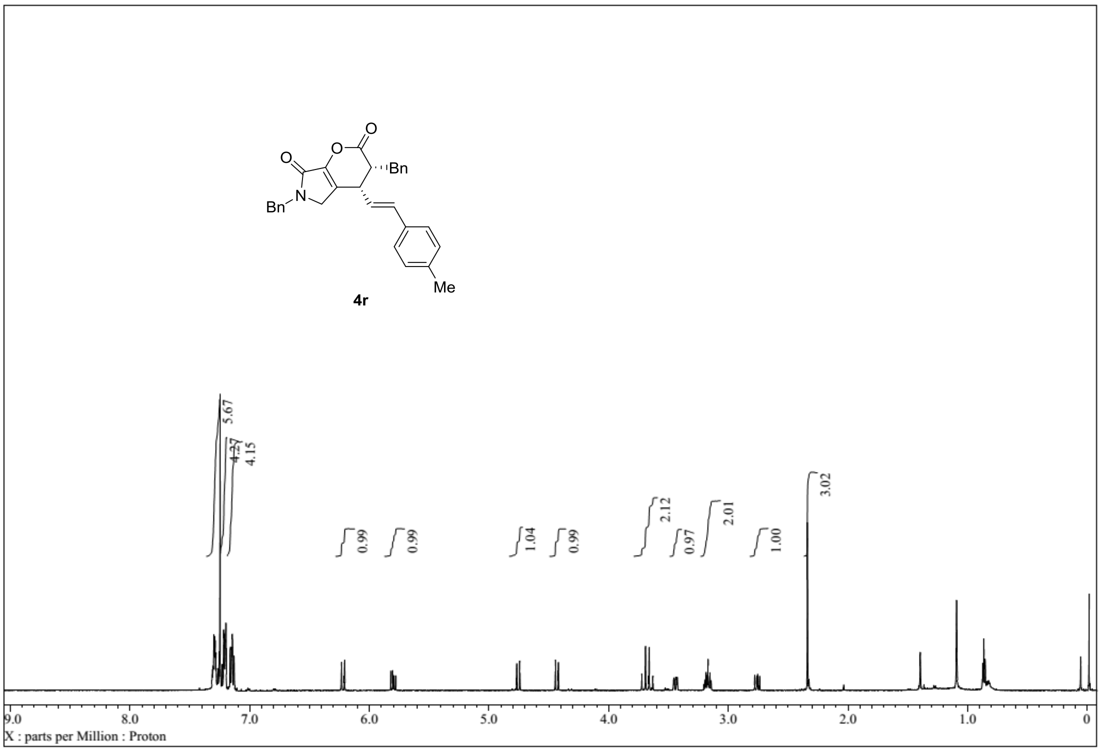
O
O
O
N
Bn
Bn
Br
4q
168.152
162.541
143.257
137.541
136.373
134.315
133.970
131.902
128.867
128.752
128.254
127.966
127.919
126.904
126.760
123.428
122.404
77.211
77.000
76.789
46.782
46.667
45.298
37.992
32.496
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : Carbon13



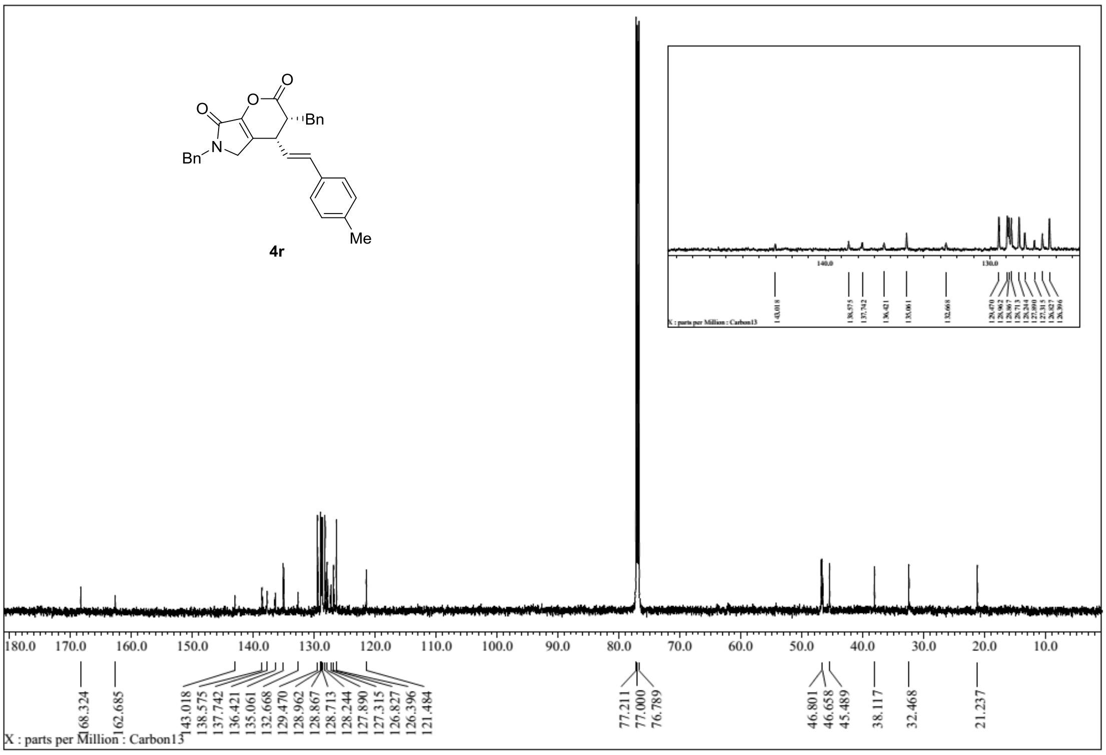
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.91	522.073	78.661	50.50
2	6.56	504.355	77.101	49.50
Total:		1026.427	155.762	100.00



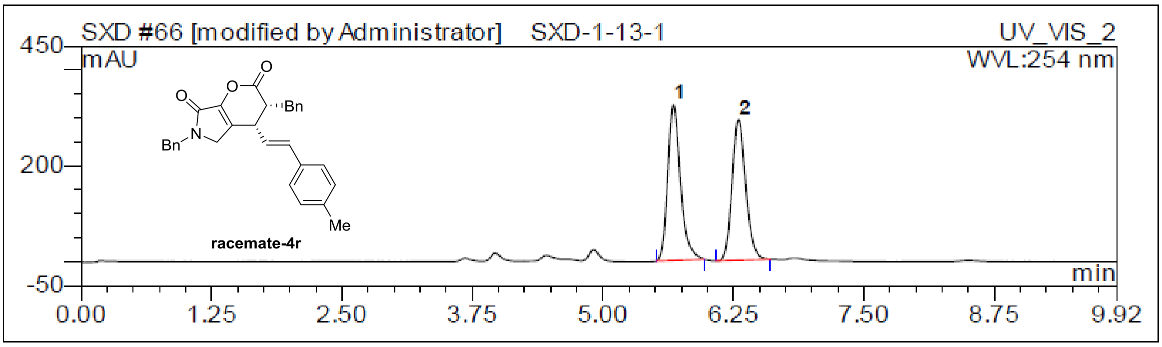
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.84	3.088	0.380	0.34
2	6.66	617.403	111.453	99.66
Total:		620.491	111.833	100.00



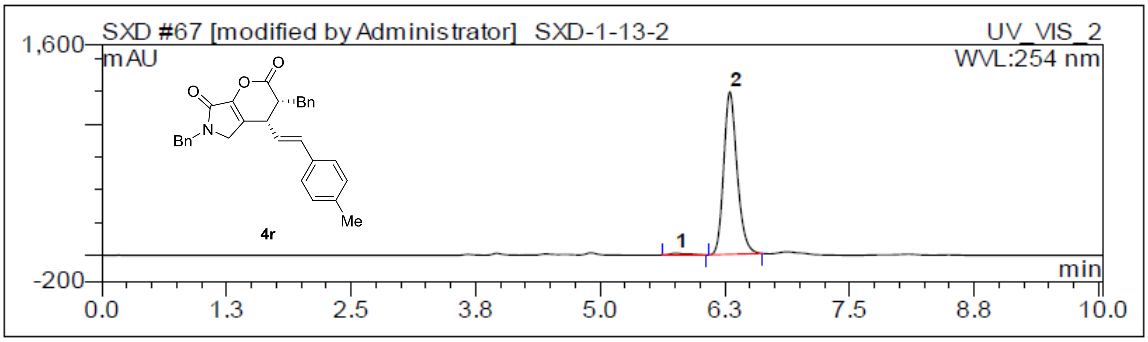
O
O
O
Bn
N
Bn
Me
4r
5.67
4.27
4.15
0.99
0.99
1.04
0.99
2.12
0.97
2.01
1.00
3.02
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : Proton



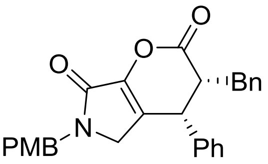
O
O
O
Bn
N
Bn
Me
4r
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
168.324
162.685
143.018
138.575
137.742
136.421
135.061
132.668
129.470
128.962
128.867
128.713
128.244
127.890
127.315
126.827
126.396
121.484
77.211
77.000
76.789
46.801
46.658
45.489
38.117
32.468
21.237
X : parts per Million : Carbon13



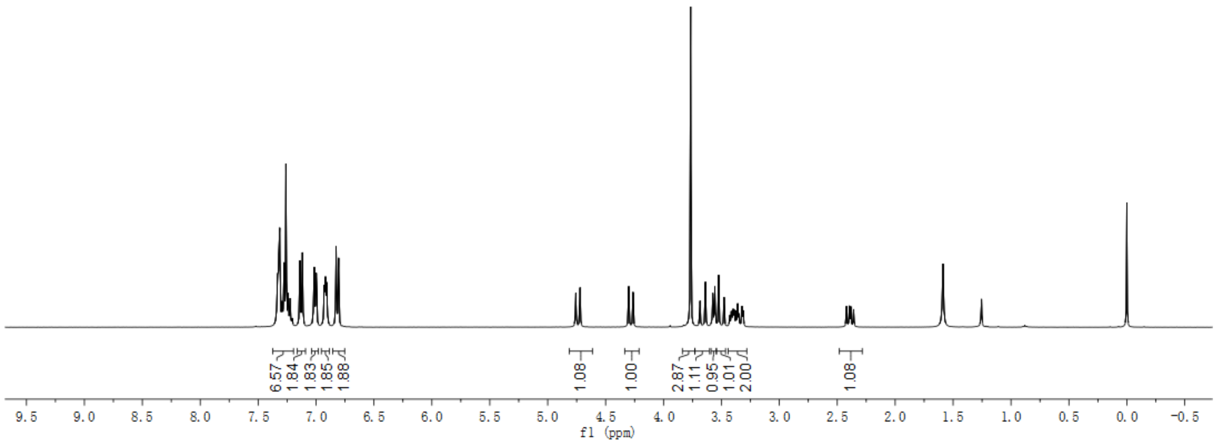
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.68	324.599	46.100	50.91
2	6.30	293.355	44.449	49.09
Total:		617.954	90.549	100.00



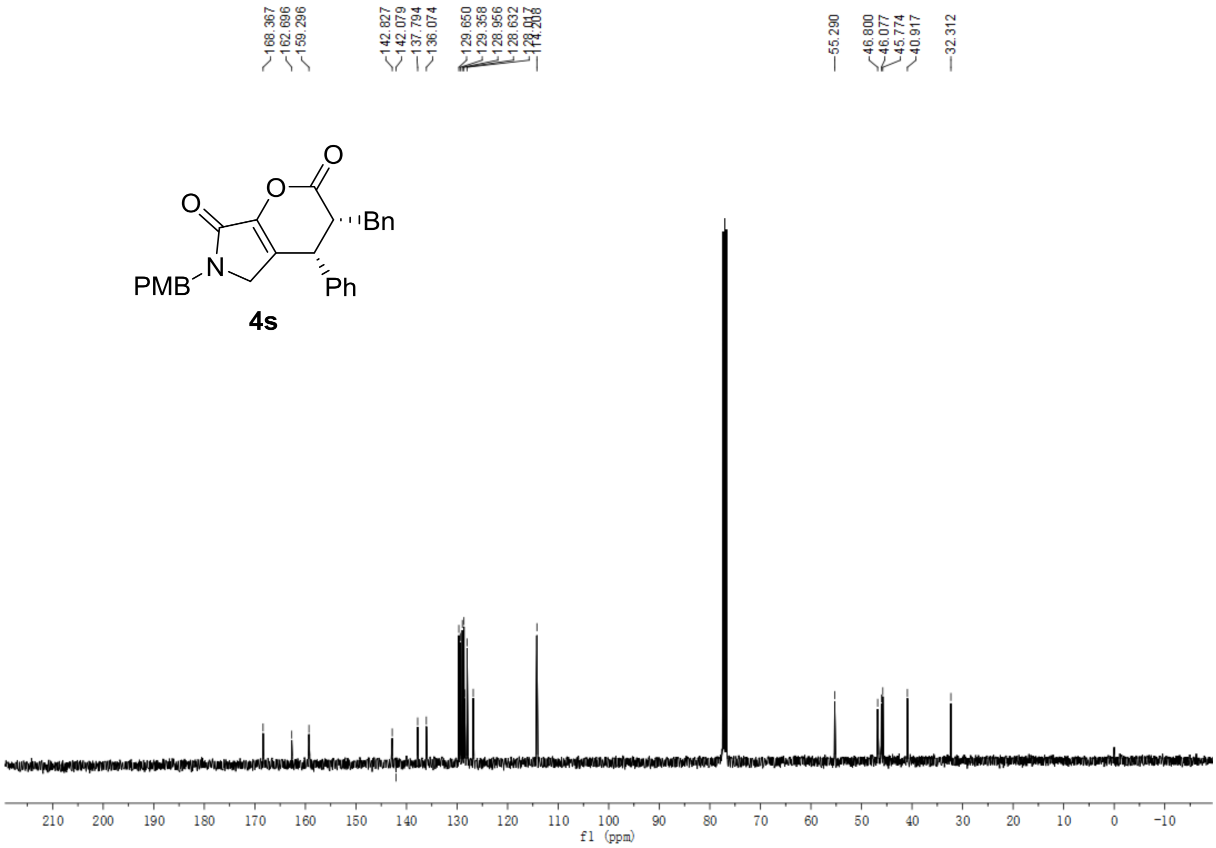
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.76	14.205	2.895	1.48
2	6.30	1239.586	193.115	98.52
Total:		1253.791	196.010	100.00

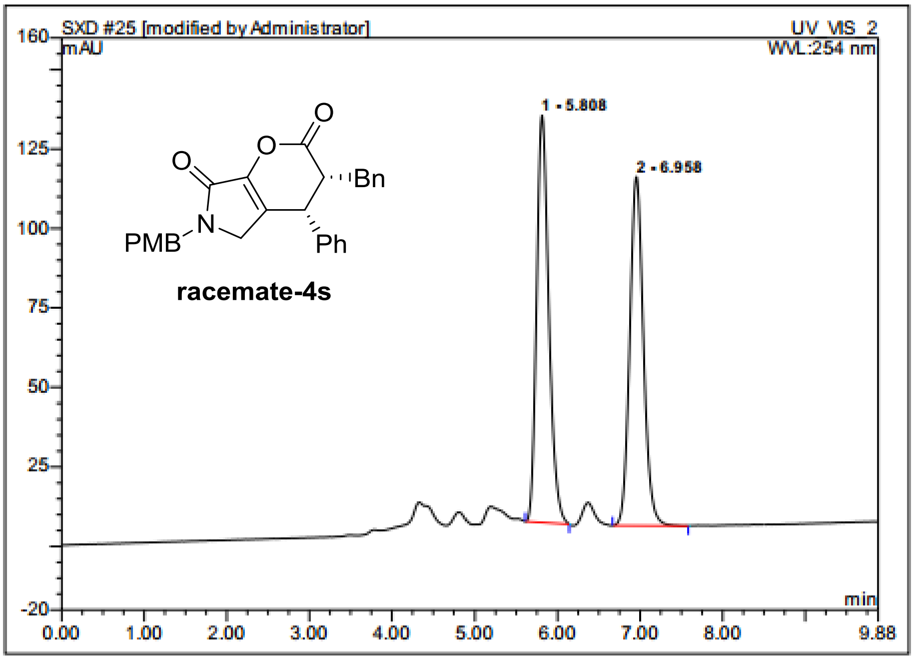

O
O
O
Bn
N
PMB
Ph

4s

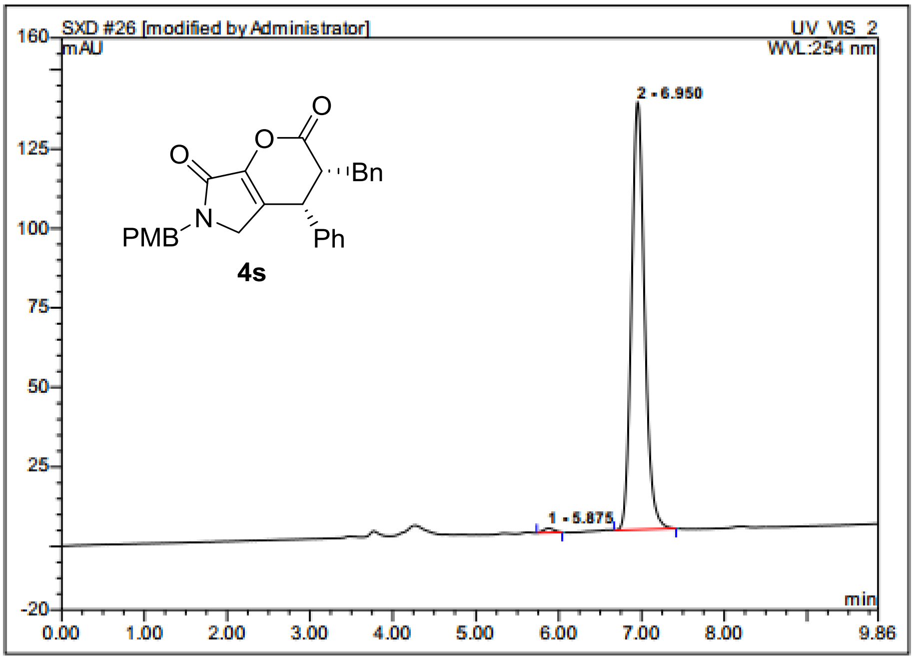

6.57
1.84
1.83
1.85
1.88
1.08
1.00
2.87
1.11
0.95
1.01
2.00
1.08
f1 (ppm)

4s

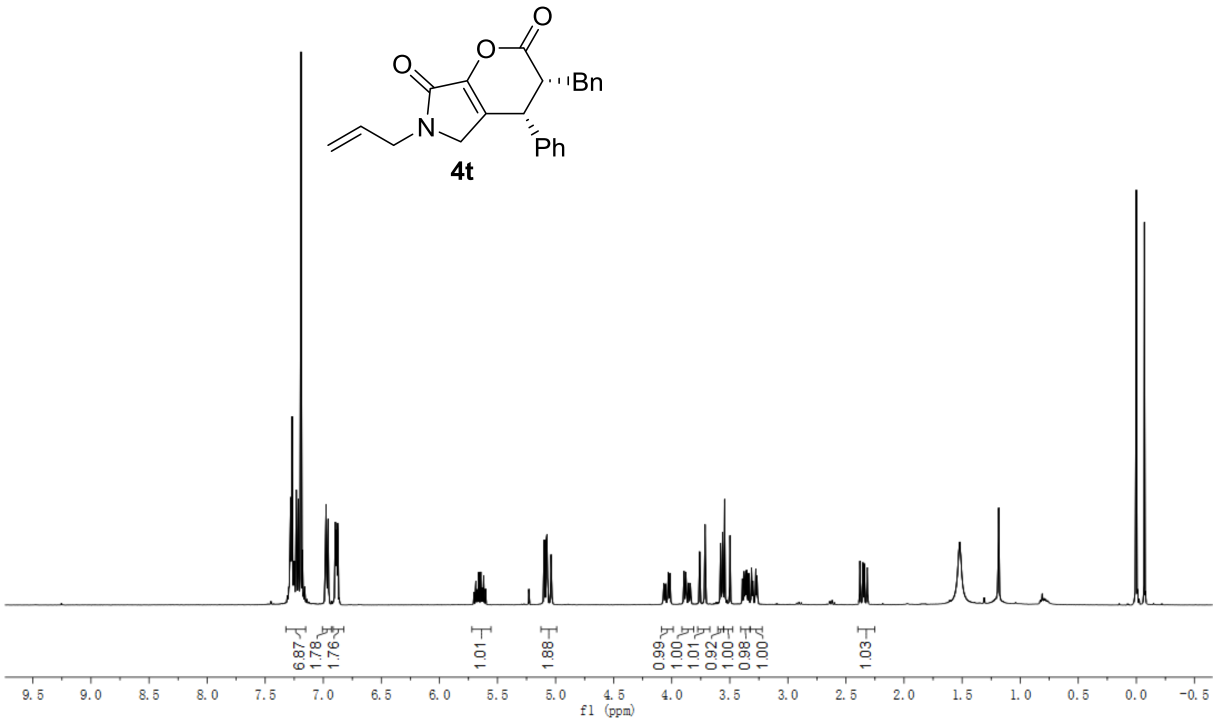

O
O
O
Bn
N
PMB
Ph
168.367
162.696
159.296
142.827
142.079
137.794
136.074
129.650
129.358
128.956
128.632
55.290
46.800
46.077
45.774
40.917
32.312
f1 (ppm)

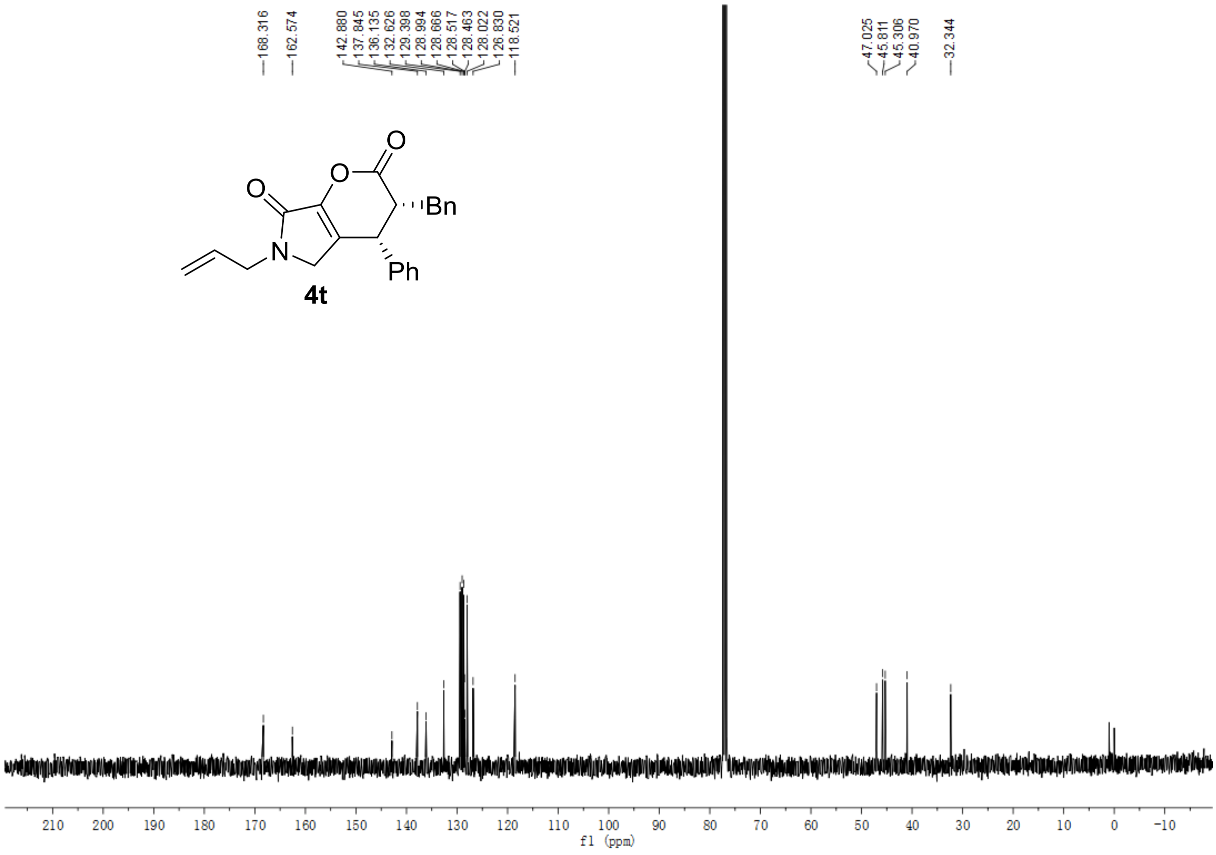


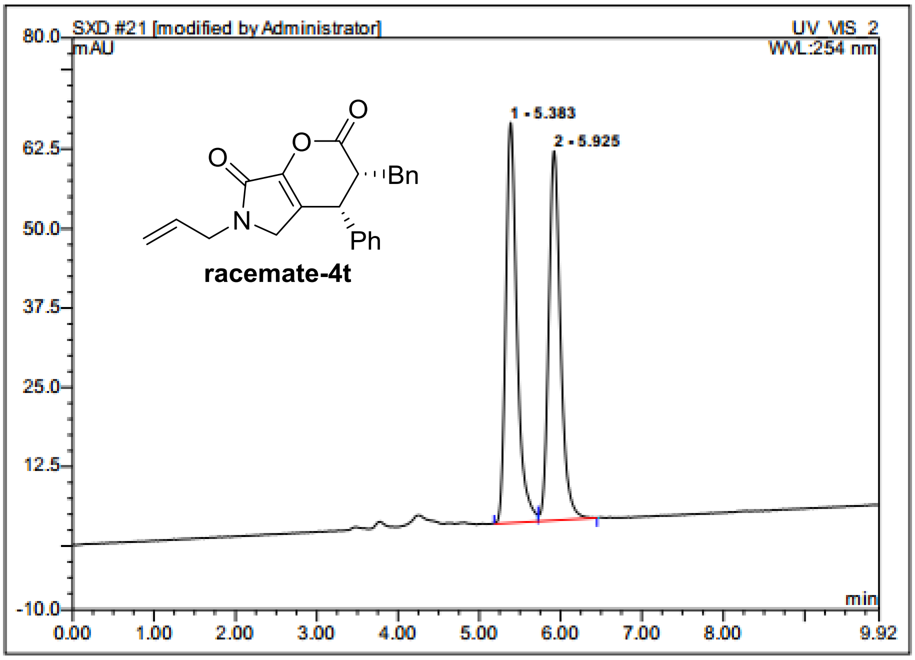
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.81	n.a.	127.957	21.895	50.95	n.a.	BMB*
2	6.96	n.a.	109.790	21.081	49.05	n.a.	BMB*
Total:			237.747	42.976	100.00	0.000	



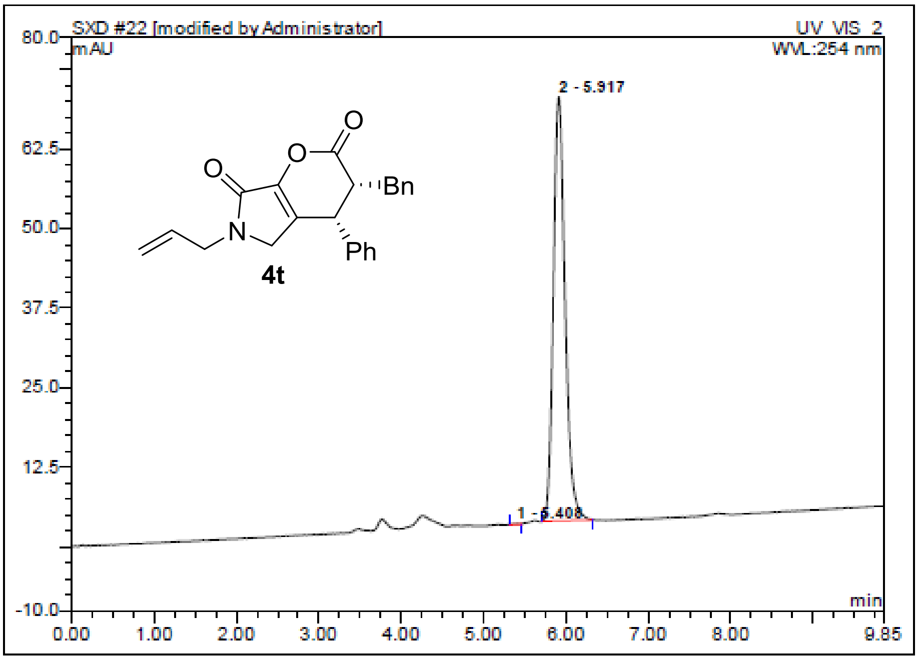
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.88	n.a.	1.329	0.205	0.83	n.a.	BMB*
2	6.95	n.a.	134.517	24.559	99.17	n.a.	BMB*
Total:			135.845	24.763	100.00	0.000	


4t
Bn
Ph
6.87
1.78
1.76
1.01
1.88
0.99
1.00
1.01
0.92
1.00
0.98
1.00
1.03
f1 (ppm)

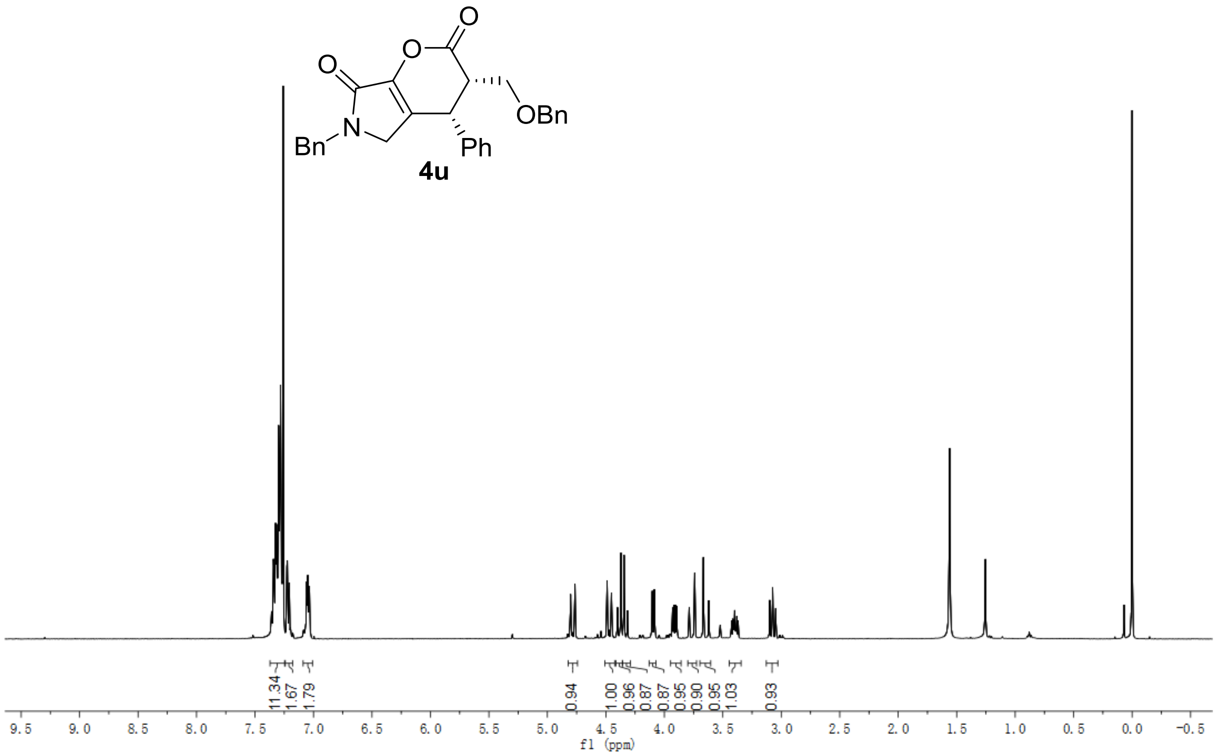

168.316
162.574
142.880
137.845
136.135
132.626
129.398
128.994
128.666
128.517
128.463
128.022
126.830
118.521
47.025
45.811
45.306
40.970
32.344
4t
Bn
Ph
f1 (ppm)

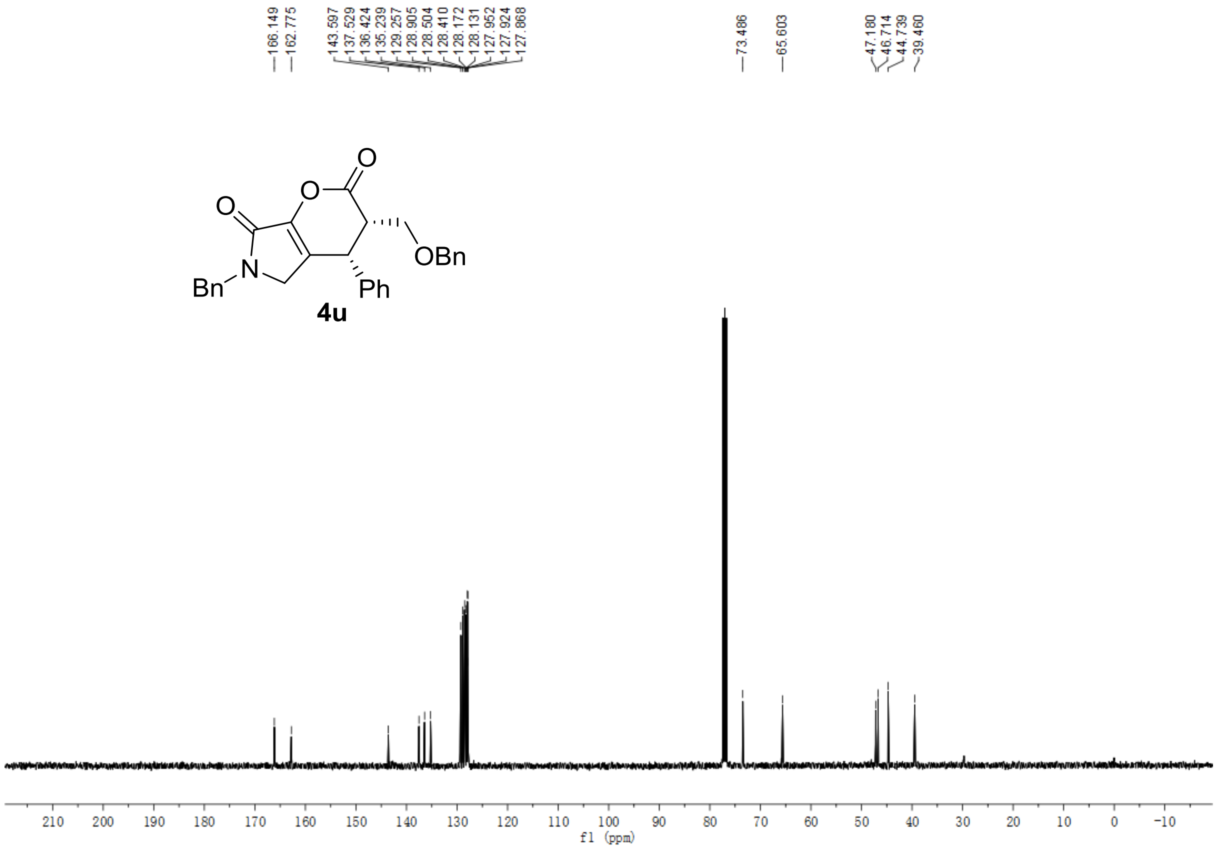


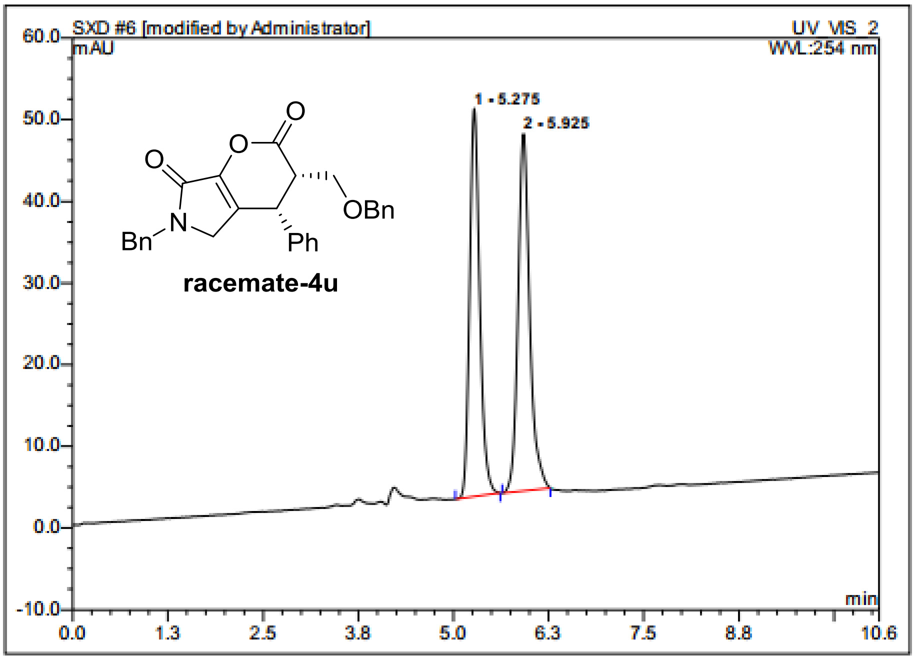
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.38	n.a.	63.035	10.051	50.64	n.a.	BM *
2	5.93	n.a.	58.138	9.798	49.36	n.a.	MB*
Total:			121.174	19.849	100.00	0.000	



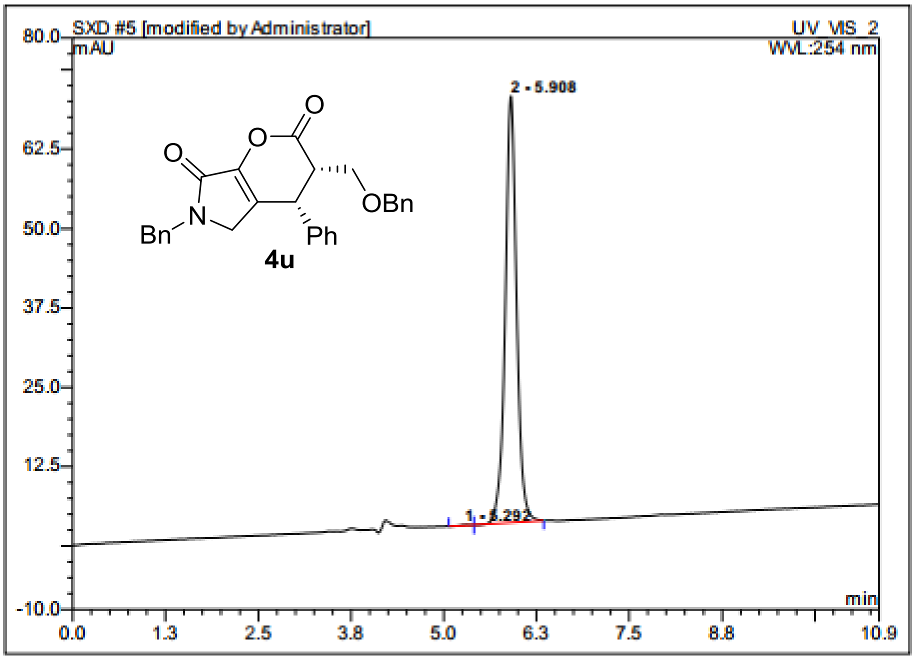
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.41	n.a.	0.098	0.009	0.08	n.a.	BMB*
2	5.92	n.a.	66.492	10.910	99.92	n.a.	BMB*
Total:			66.591	10.918	100.00	0.000	


O
O
O
N
Bn
OBn
Ph
4u
11.34
1.67
1.79
0.94
1.00
0.96
0.87
0.87
0.95
0.90
0.95
1.03
0.93
f1 (ppm)

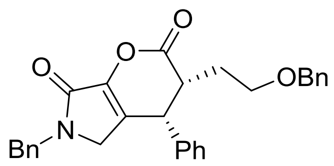

166.149
162.775
143.597
137.529
136.424
135.239
129.257
128.905
128.504
128.410
128.172
128.131
127.952
127.924
127.868
73.486
65.603
47.180
46.714
44.739
39.460
O
O
O
N
Bn
OBn
Ph
4u
f1 (ppm)



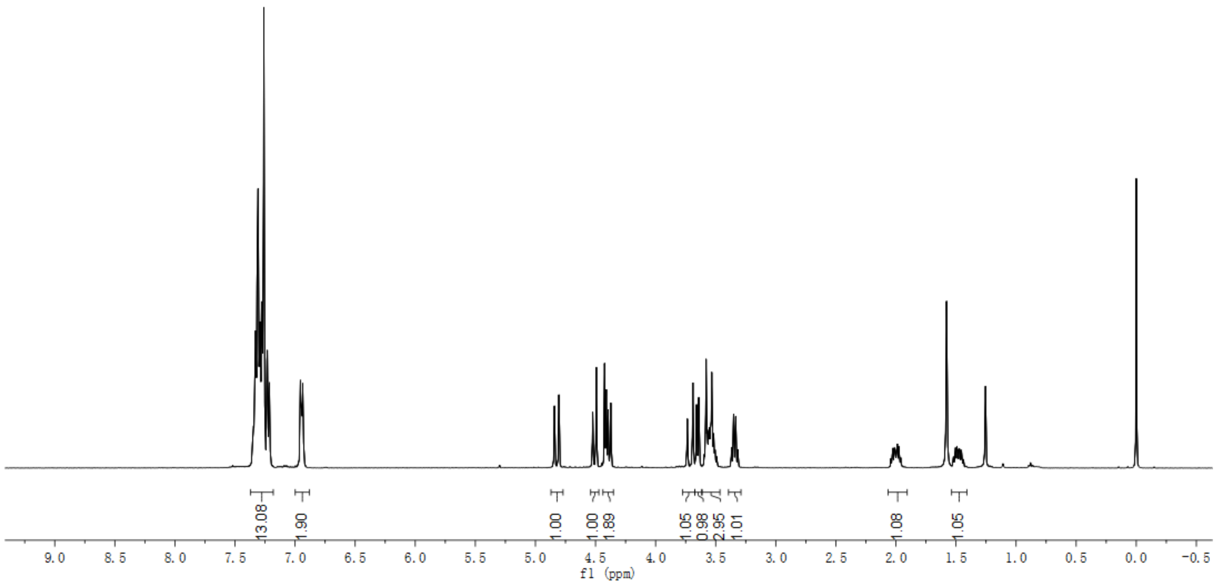
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.28	n.a.	47.517	7.295	48.38	n.a.	BMB*
2	5.93	n.a.	43.702	7.785	51.62	n.a.	BMB*
Total:			91.219	15.081	100.00	0.000	



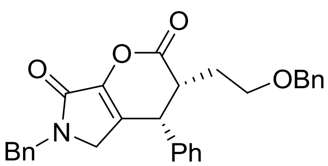
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.29	n.a.	0.129	0.011	0.09	n.a.	BM *
2	5.91	n.a.	67.150	11.959	99.91	n.a.	MB*
Total:			67.280	11.970	100.00	0.000	



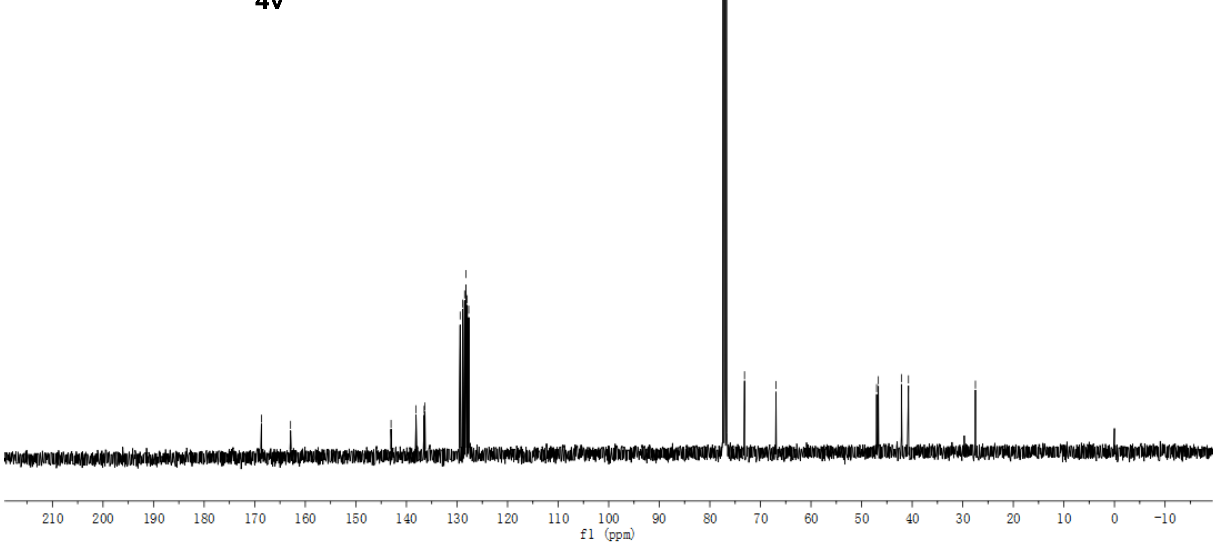
4v



13.08
1.90
1.00
1.00
1.89
1.05
0.98
2.95
1.01
1.08
1.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



4v



168.676
162.907
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138.103
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128.894
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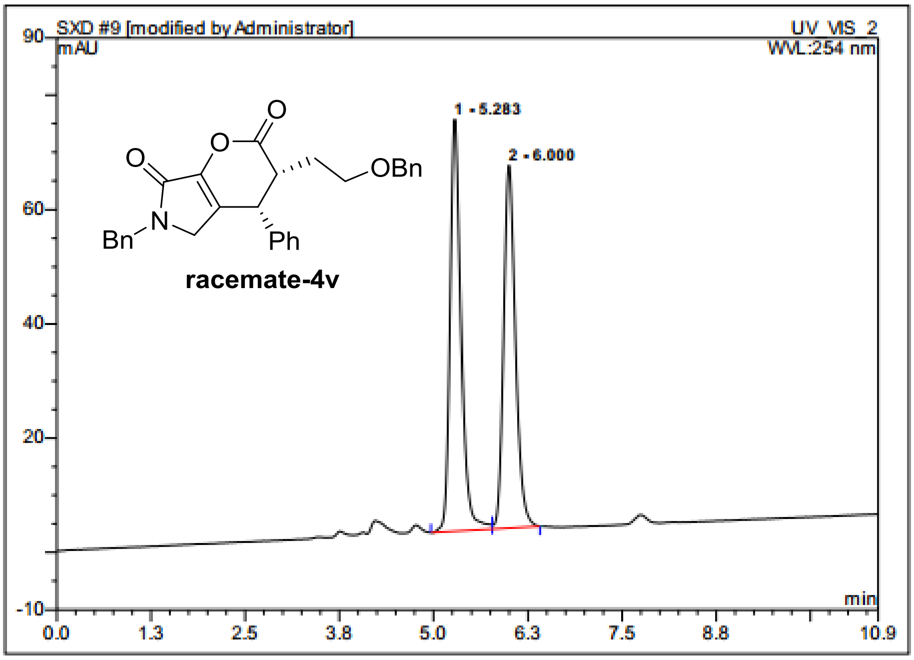
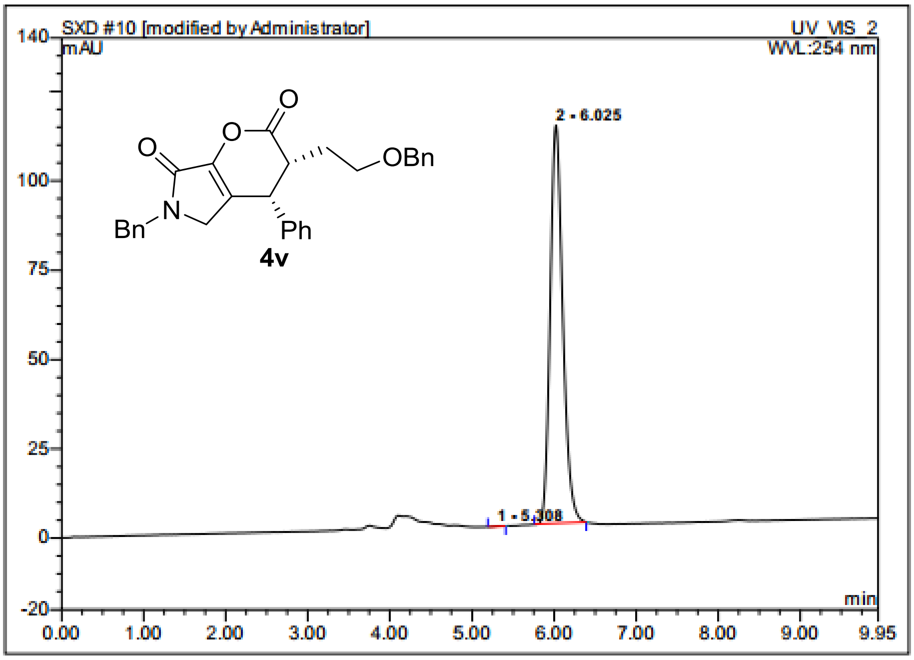
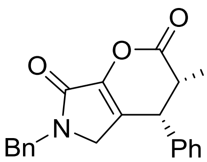
128.319
128.214
127.980
127.914
127.875
127.674
73.149
66.924
47.023
46.682
42.127
40.726
27.491
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



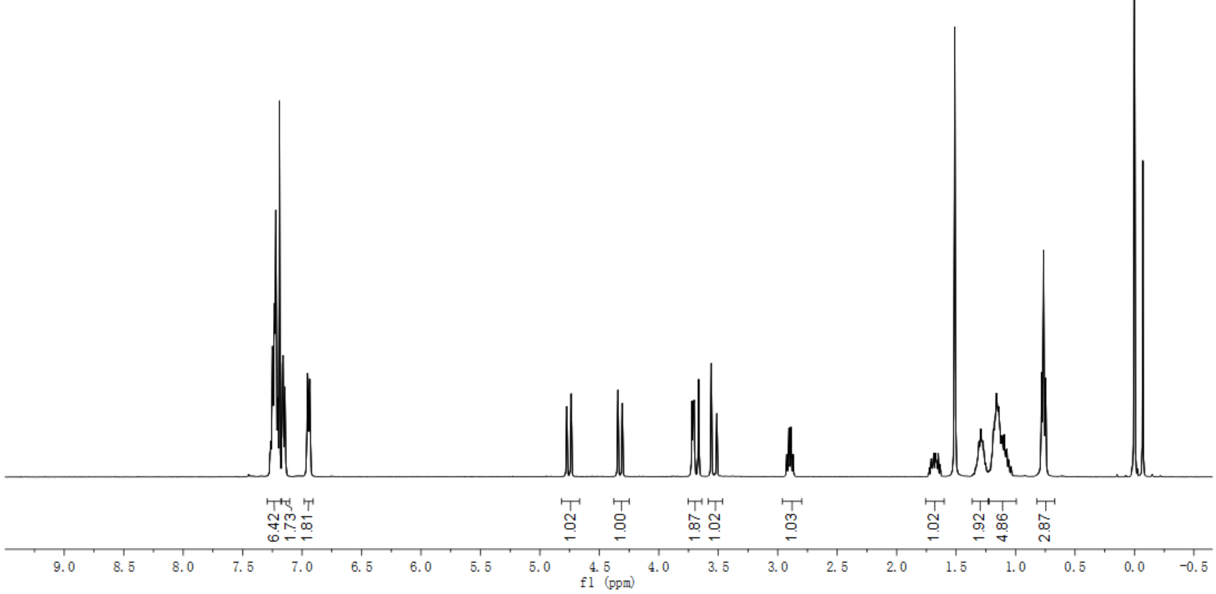
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.28	n.a.	72.036	12.025	51.00	n.a.	BM *
2	6.00	n.a.	63.405	11.555	49.00	n.a.	MB*
Total:			135.441	23.580	100.00	0.000	

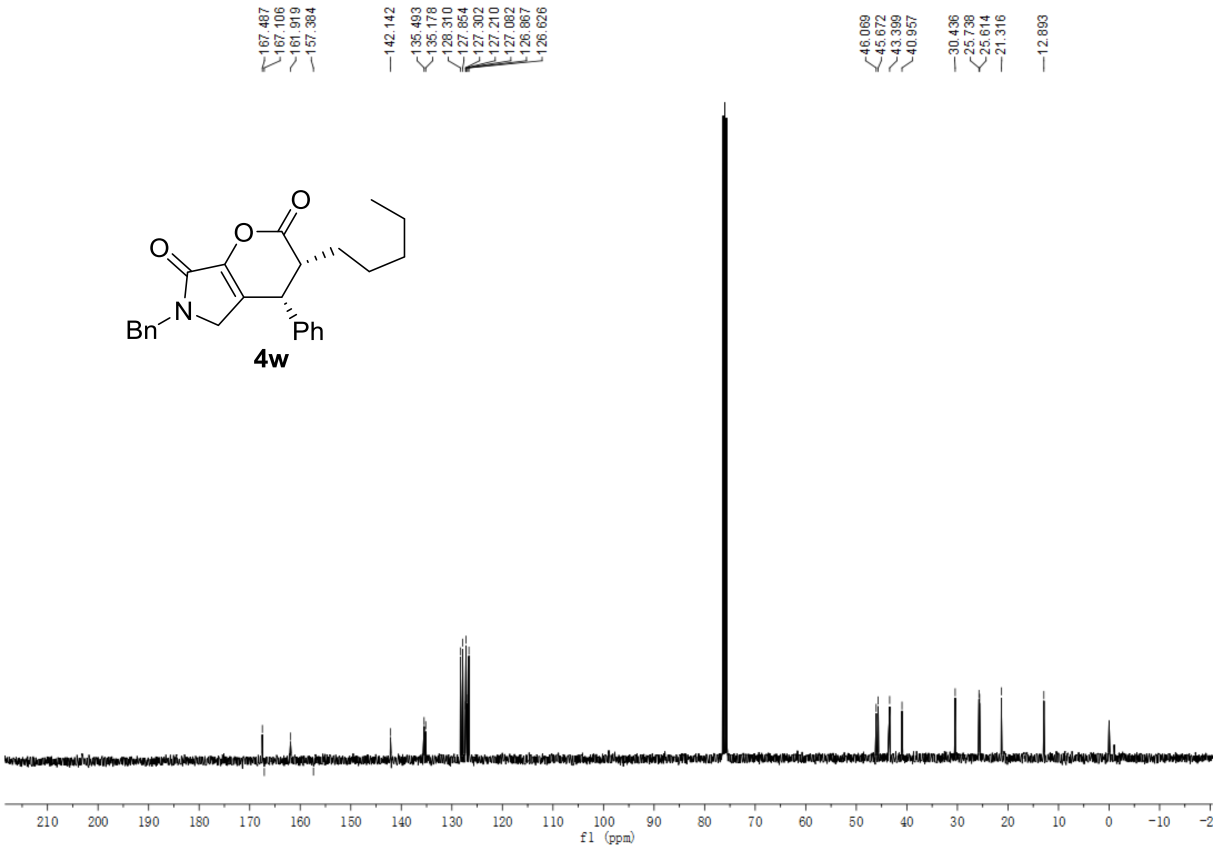


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.31	n.a.	0.121	0.017	0.08	n.a.	BMB*
2	6.03	n.a.	111.274	19.827	99.92	n.a.	MB*
Total:			111.396	19.843	100.00	0.000	

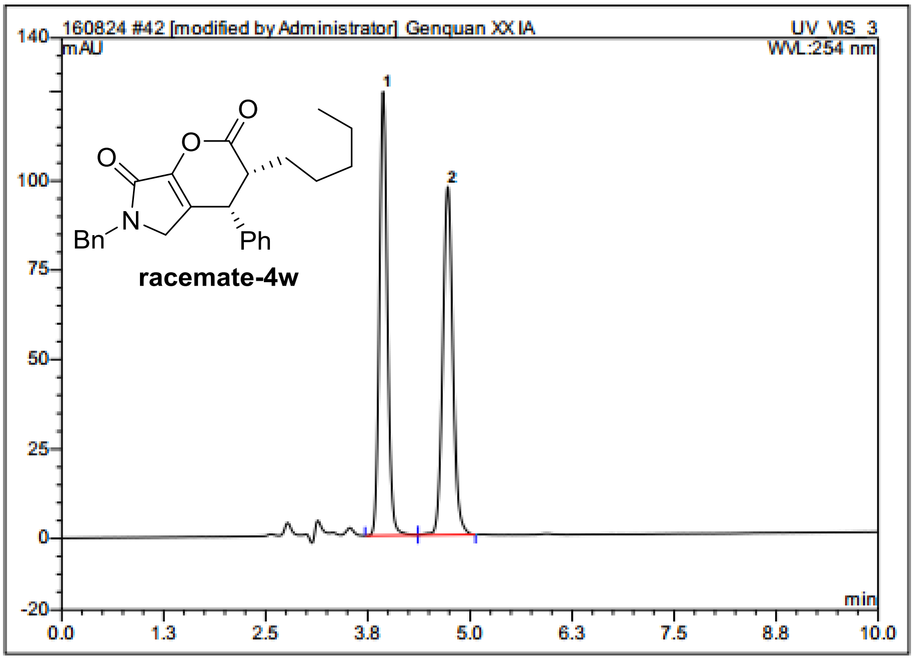

O
O
O
Bn
N
Ph

4w

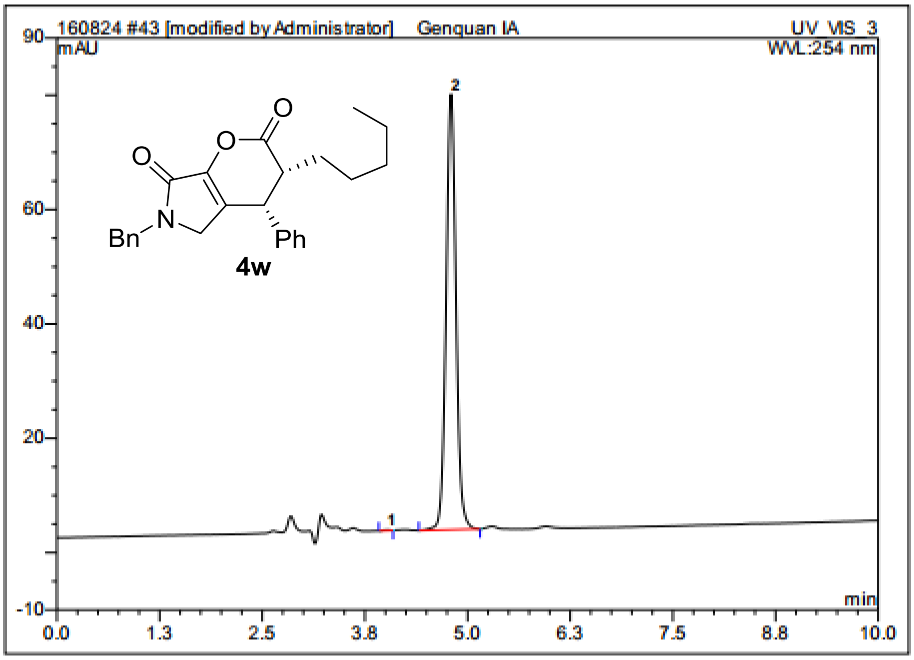

6.42
1.73
1.81
1.02
1.00
1.87
1.02
1.03
1.02
1.92
4.86
2.87
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


167.487
167.106
161.919
157.384
142.142
135.493
135.178
128.310
127.854
127.302
127.210
127.082
126.867
126.626
46.069
45.672
43.399
40.957
30.436
25.738
25.614
21.316
12.893
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)

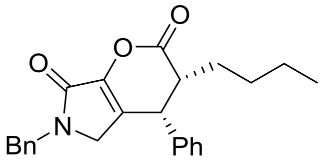
4w



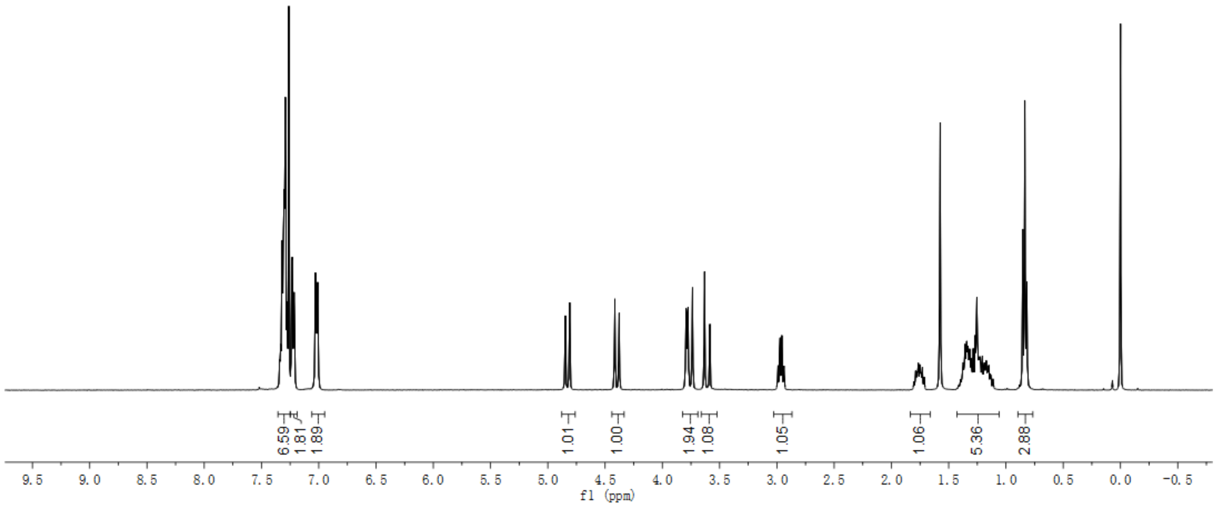
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.94	n.a.	124.089	14.007	50.35	n.a.	BM *
2	4.73	n.a.	97.356	13.814	49.65	n.a.	MB*
Total:			221.446	27.821	100.00		

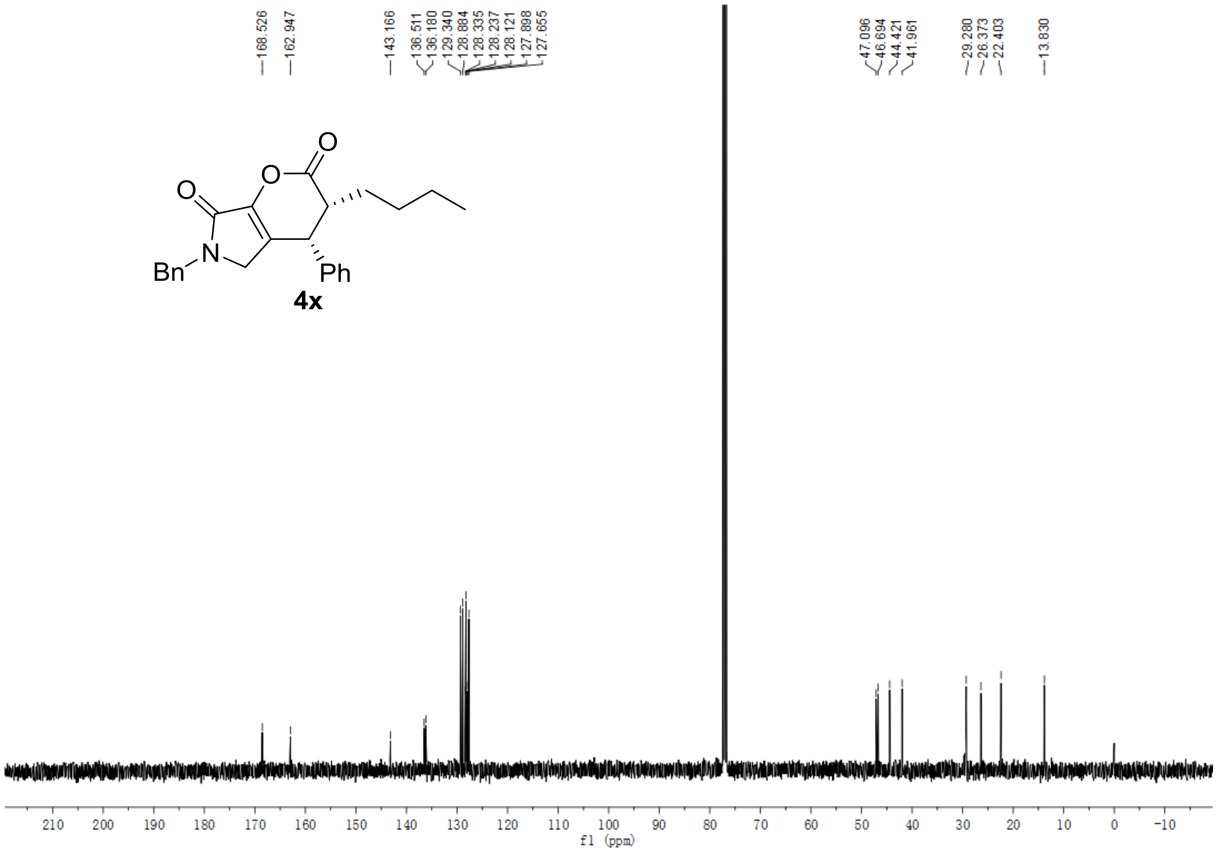


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.03	n.a.	0.118	0.011	0.11	n.a.	BMB*
2	4.80	n.a.	76.146	10.632	99.89	n.a.	BMB*
Total:			76.264	10.643	100.00		


O
O
O
N
Bn
Ph

4x


6.59
1.81
1.89
1.01
1.00
1.94
1.08
1.05
1.06
5.36
2.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


168.526
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136.511
136.180
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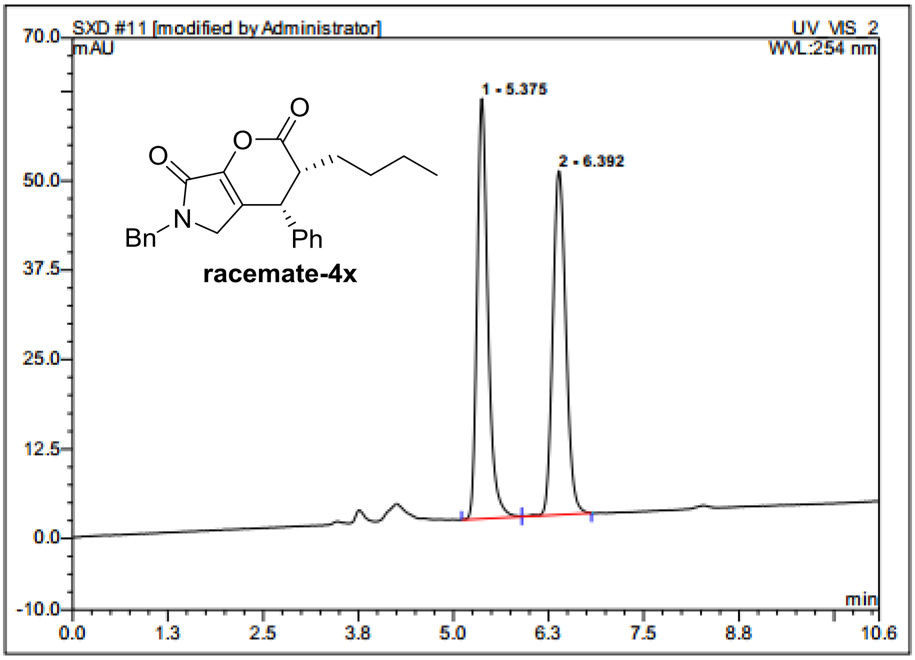
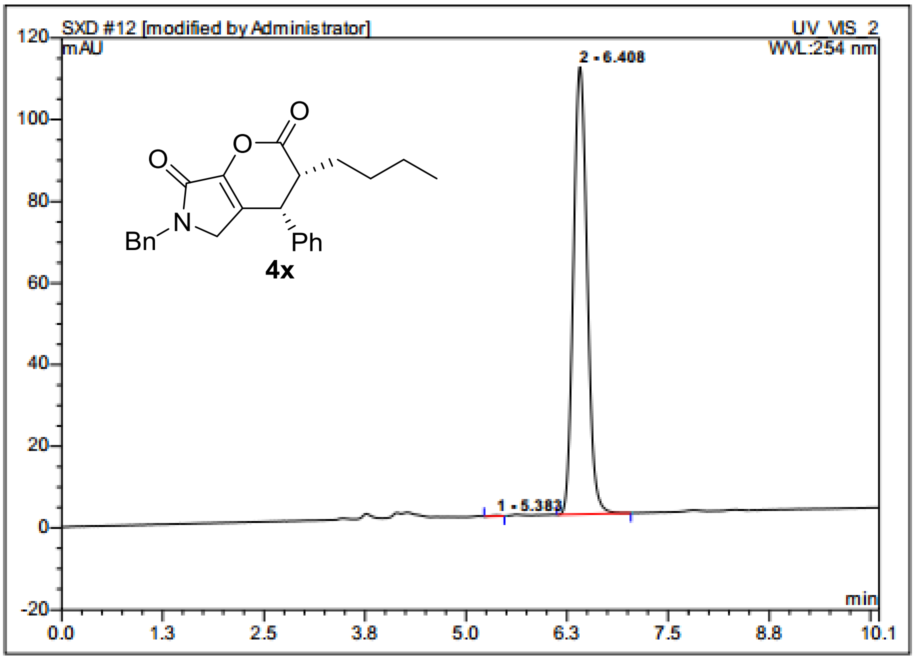
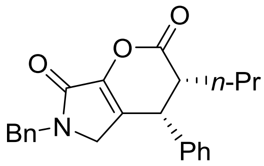
128.884
128.335
128.237
128.121
127.898
127.655
47.096
46.694
44.421
41.961
29.280
26.373
22.403
13.830
O
O
O
N
Bn
Ph
4x
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



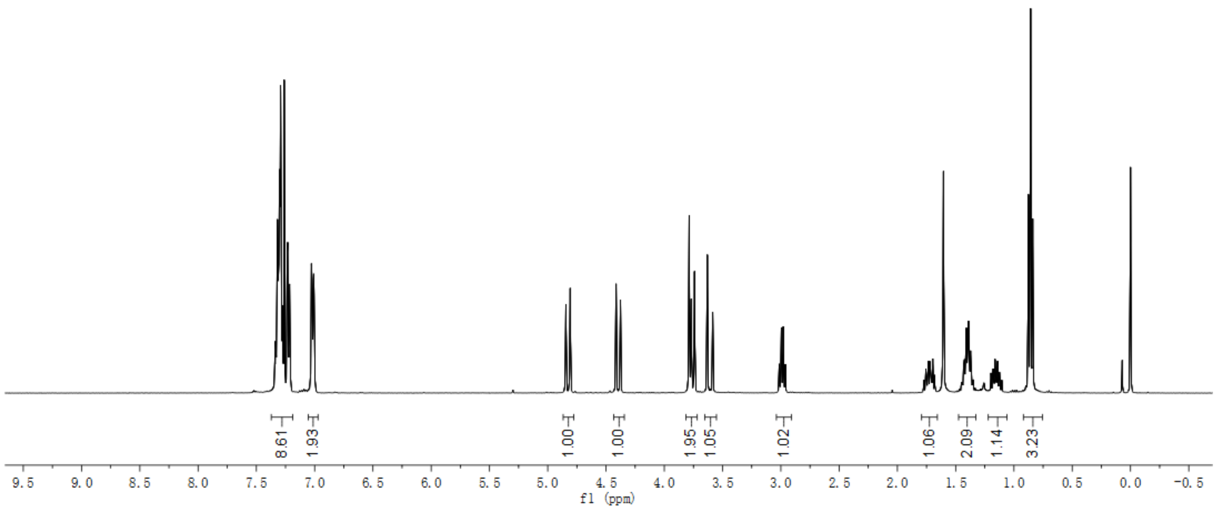
No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.38	n.a.		58.784	9.719	50.32	n.a.	BM
2	6.39	n.a.		48.084	9.595	49.68	n.a.	MB
Total:				106.868	19.314	100.00	0.000	

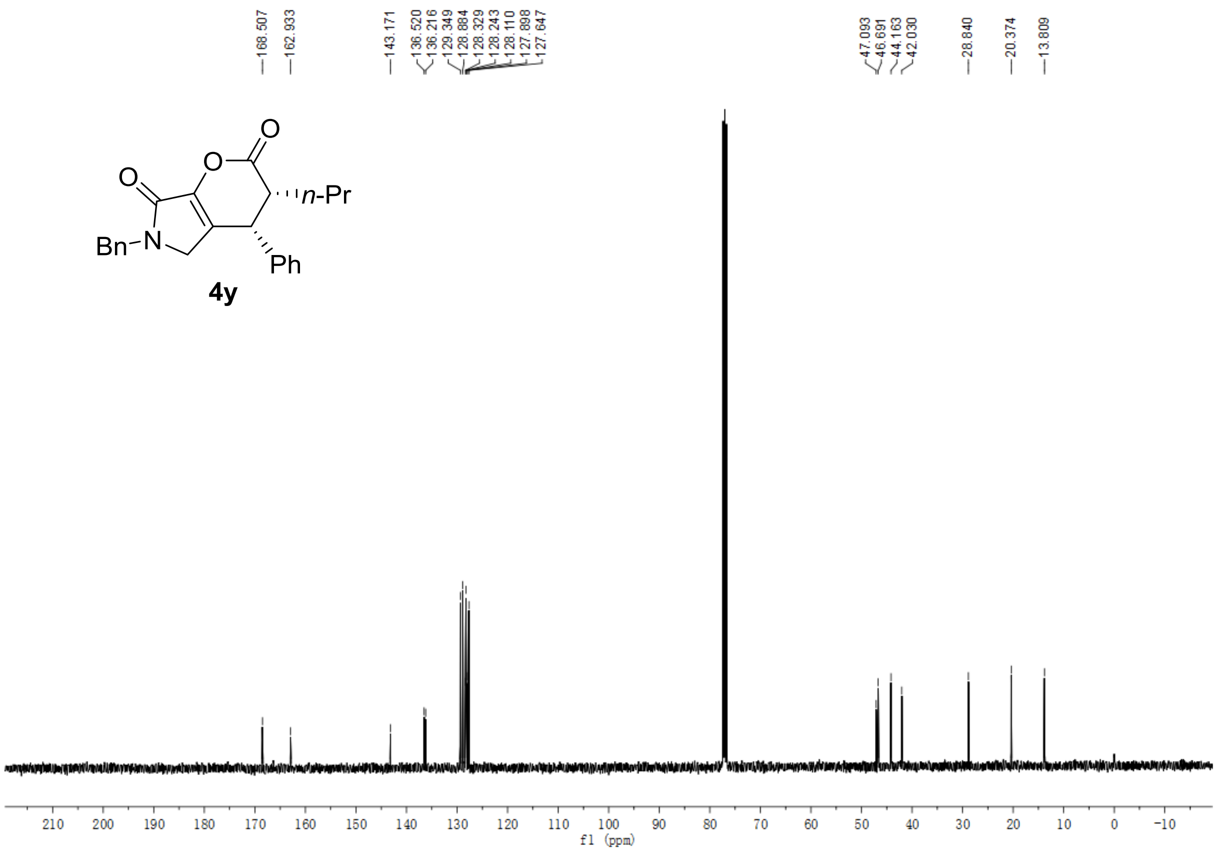


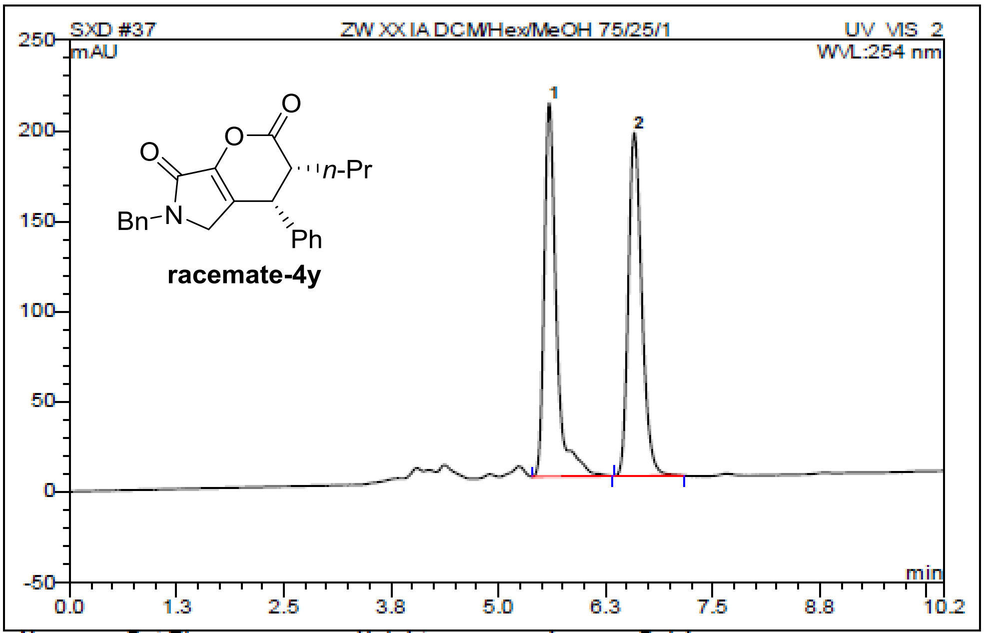
No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.38	n.a.		0.179	0.023	0.11	n.a.	BMB*
2	6.41	n.a.		109.537	21.605	99.89	n.a.	BMB*
Total:				109.716	21.628	100.00	0.000	



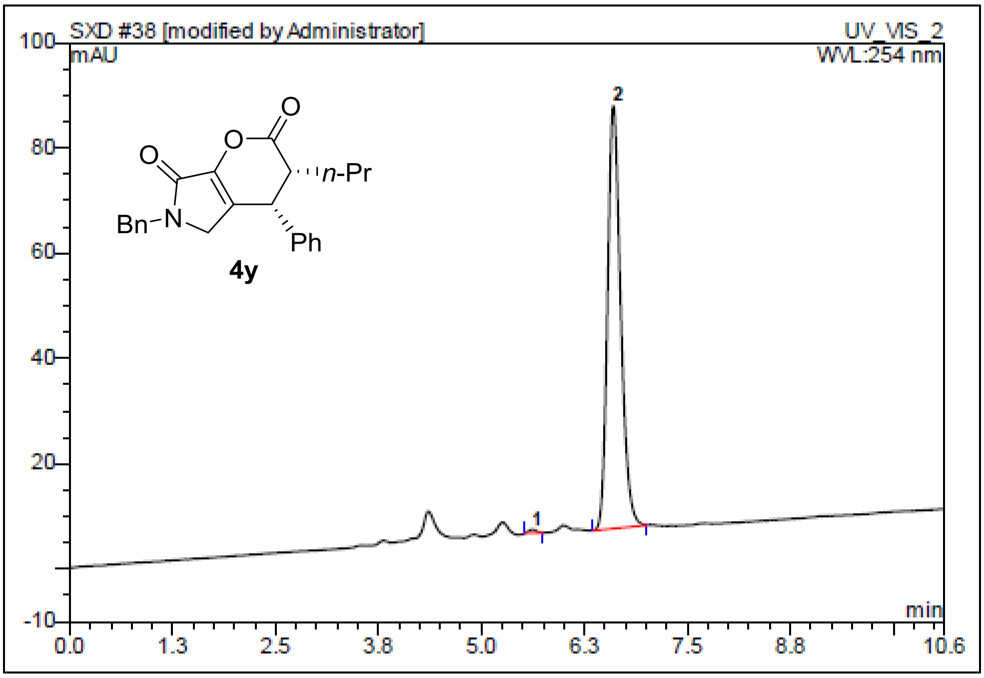
4y



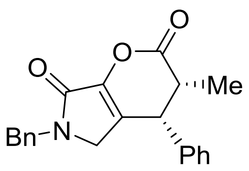




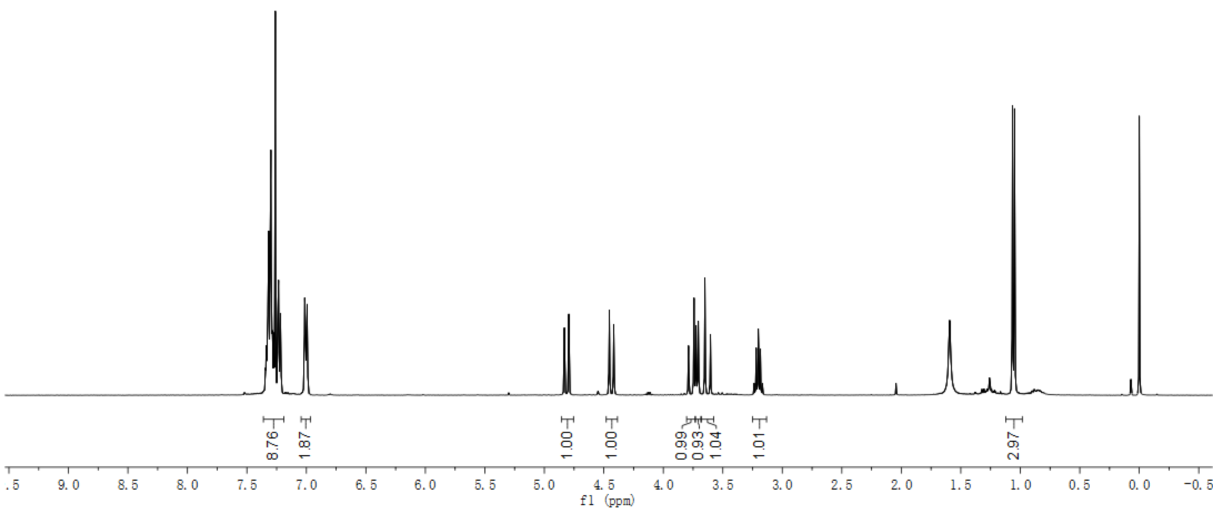
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.59	206.573	34.042	49.55
2	6.58	189.824	34.658	50.45
Total:		396.397	68.699	100.00

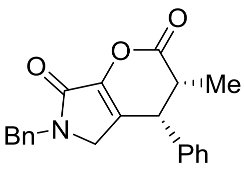


No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.61	0.660	0.075	0.50
2	6.60	80.369	14.845	99.50
Total:		81.029	14.920	100.00

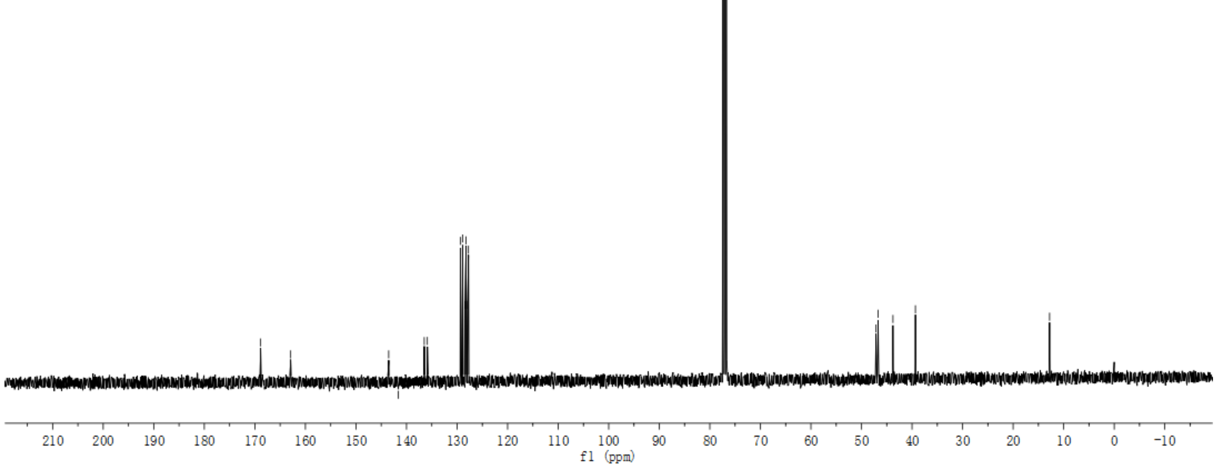


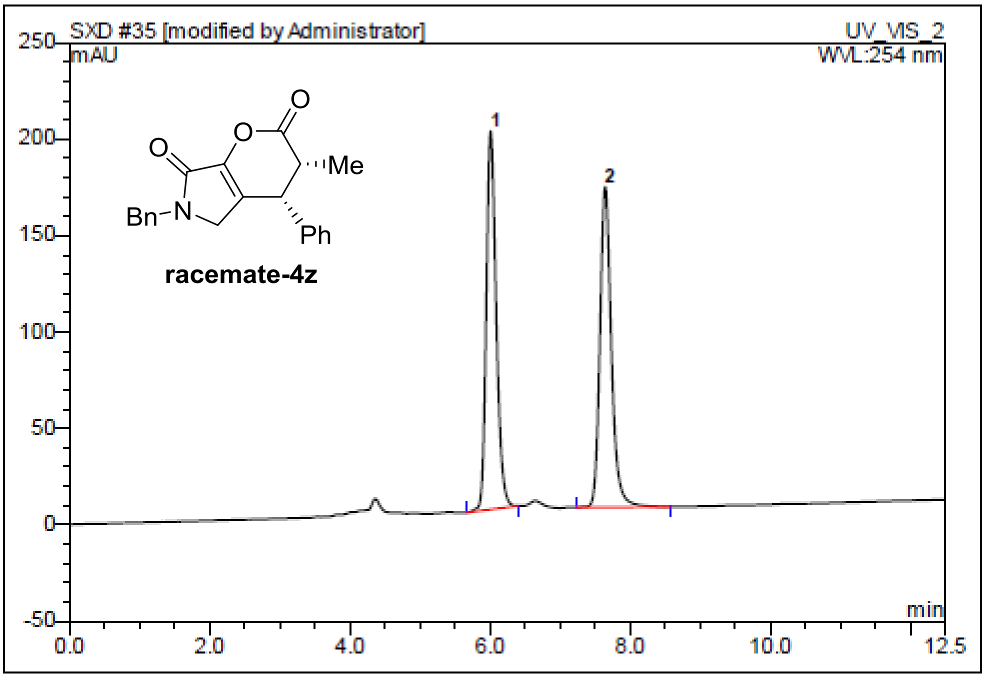
4z



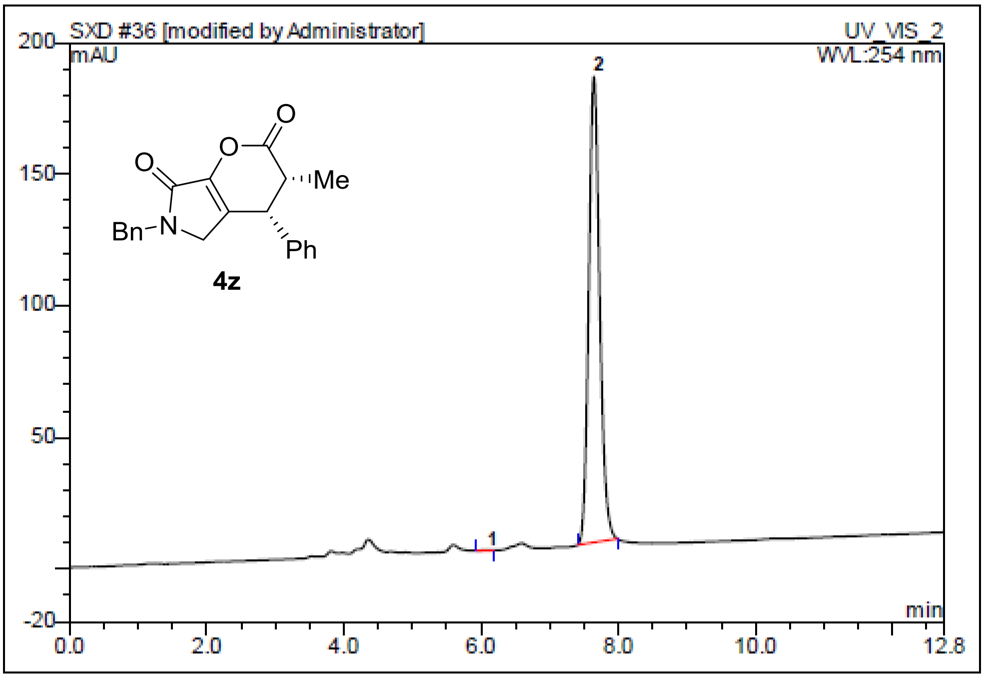


4z

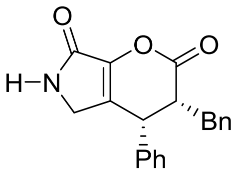




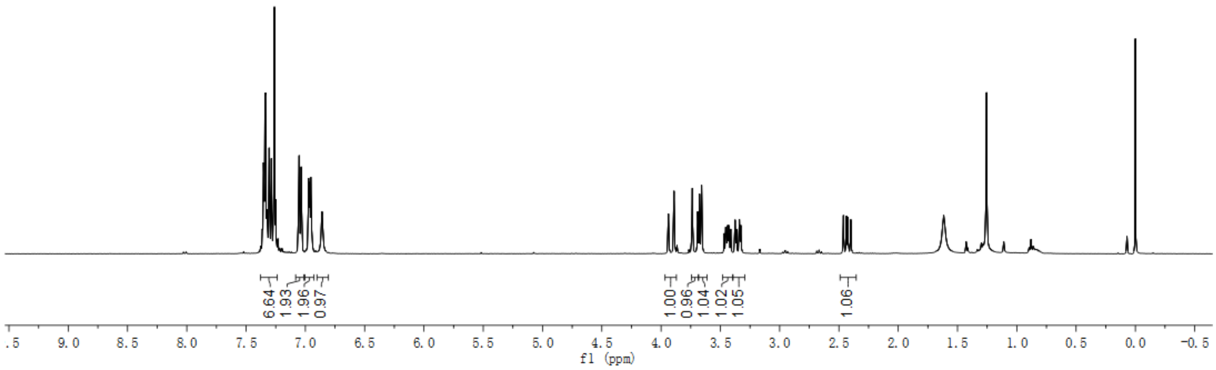
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	6.01	196.069	32.180	50.50
2	7.64	165.919	31.546	49.50
Total:		361.988	63.727	100.00

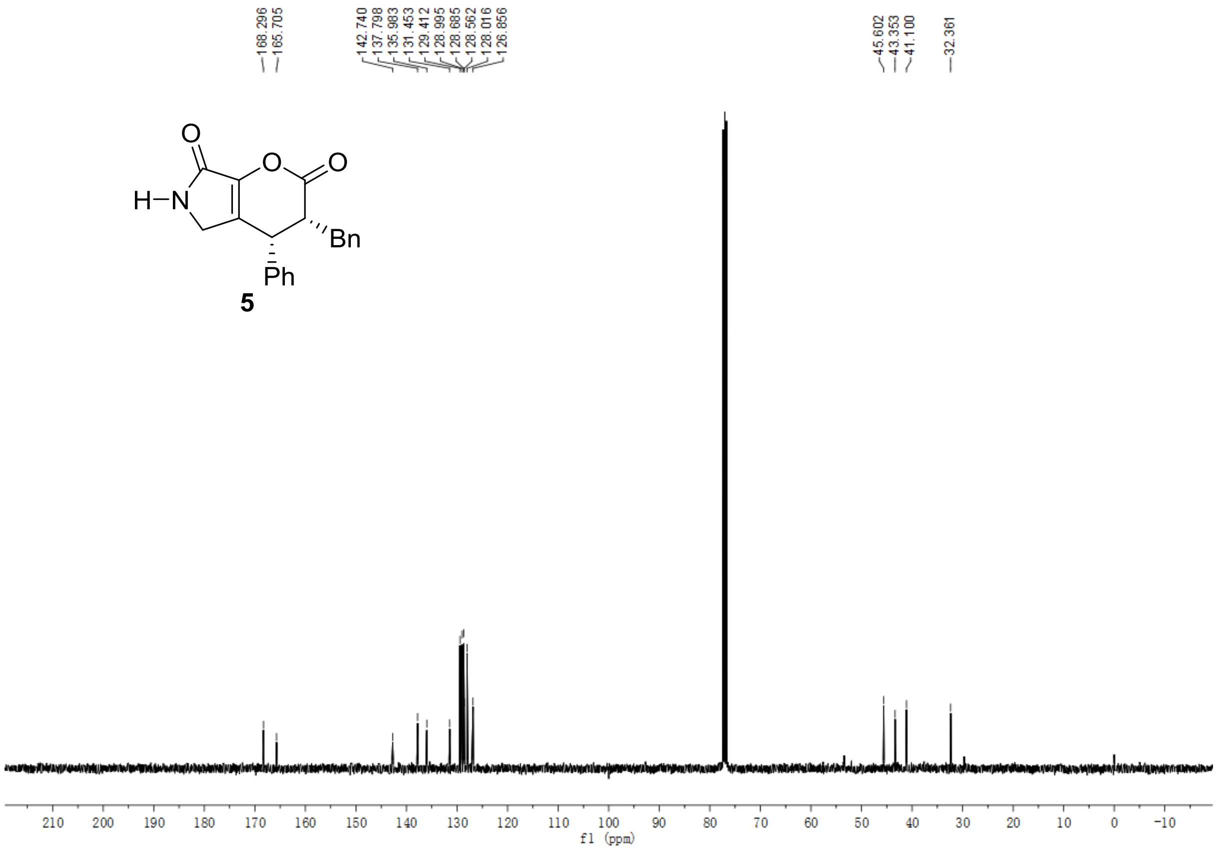


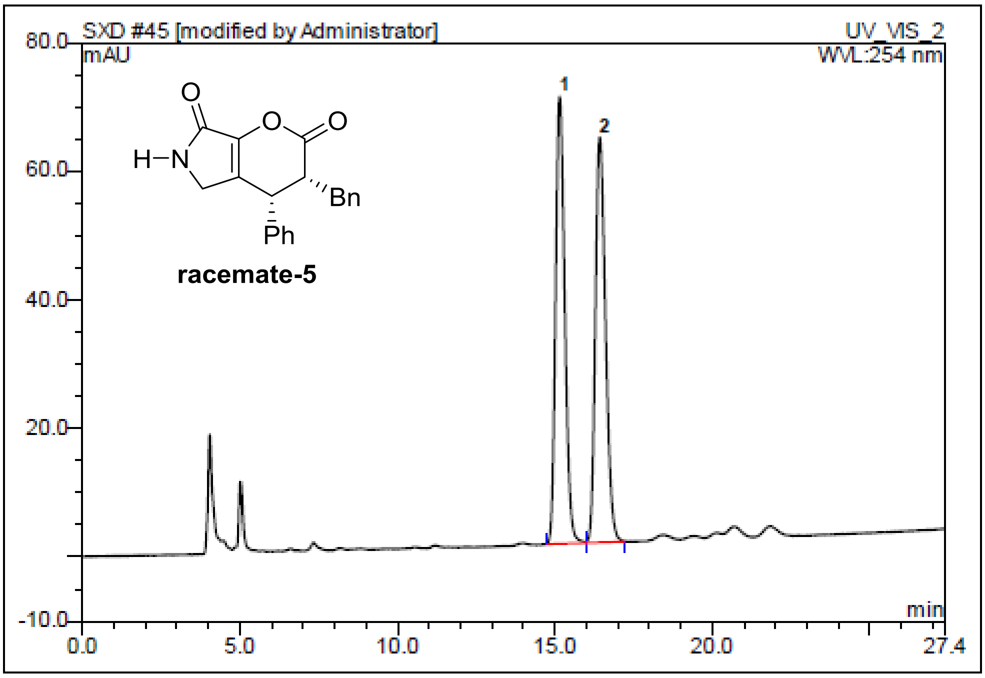
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	6.09	0.125	0.017	0.05
2	7.64	176.994	32.688	99.95
Total:		177.119	32.705	100.00


O
O
O
H–N
Bn
Ph

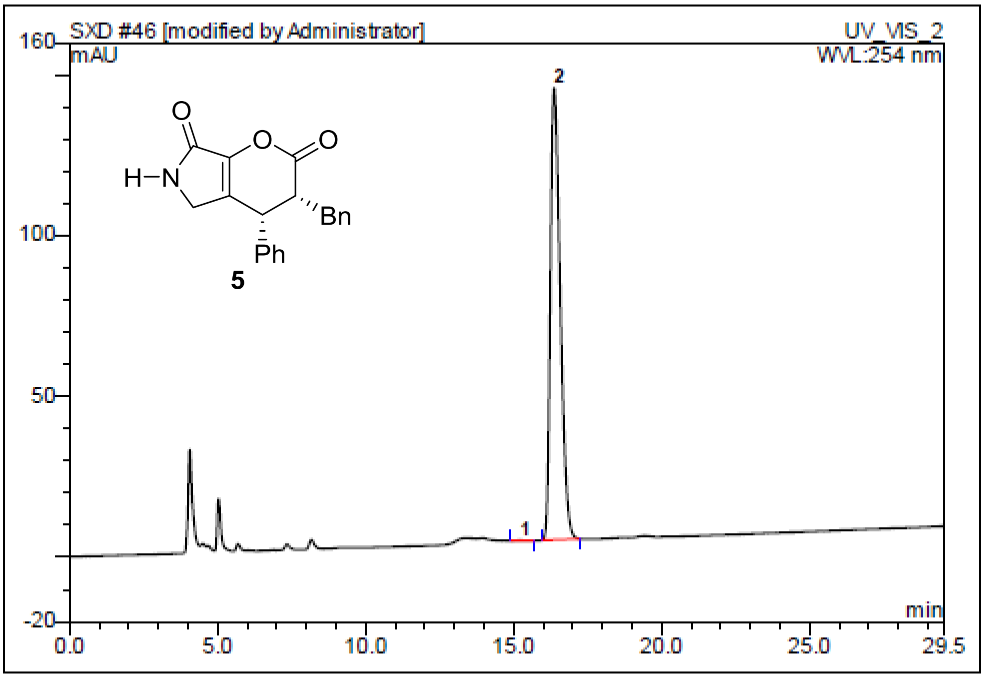
5


6.64
1.93
1.96
0.97
1.00
0.96
1.04
1.02
1.05
1.06
f1 (ppm)

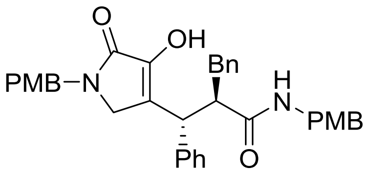

168.296
165.705
142.740
137.798
135.983
131.453
129.412
128.995
128.685
128.562
128.016
126.856
45.602
43.353
41.100
32.361
5
f1 (ppm)



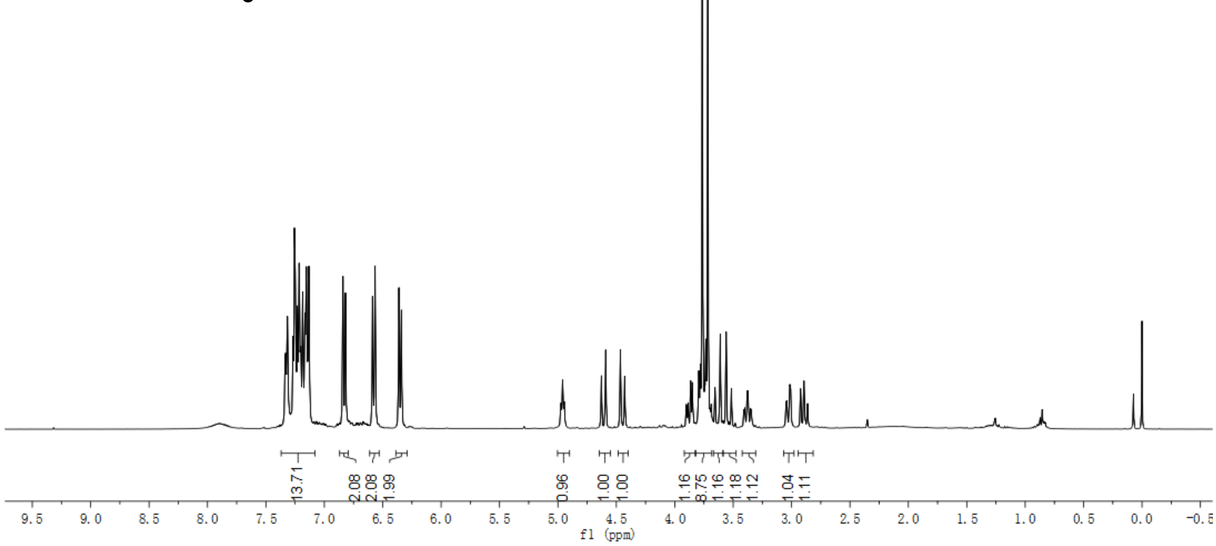
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	15.16	69.550	23.530	49.95
2	16.43	63.013	23.573	50.05
Total:		132.562	47.103	100.00

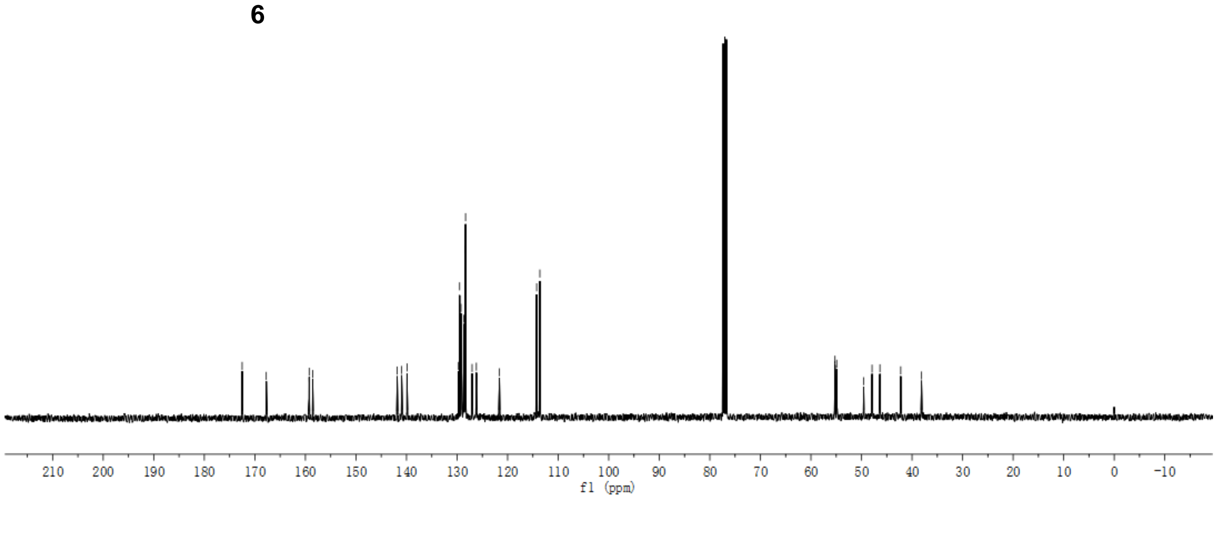


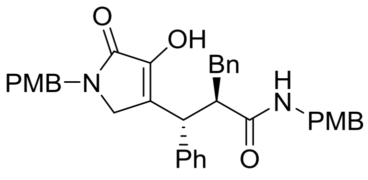
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	15.23	0.168	0.037	0.07
2	16.38	140.463	54.311	99.93
Total:		140.631	54.349	100.00


O
OH
Bn
PMB−N
H
N
PMB
Ph
O

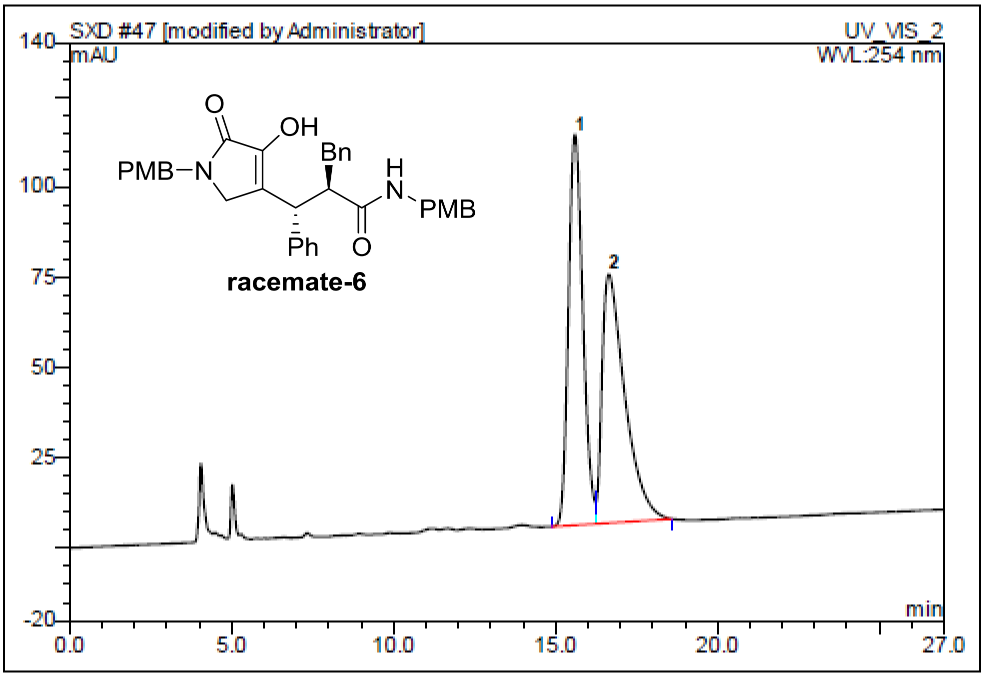
6


13.71
2.08
2.08
1.99
0.96
1.00
1.00
1.16
8.75
1.16
1.18
1.12
1.04
1.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

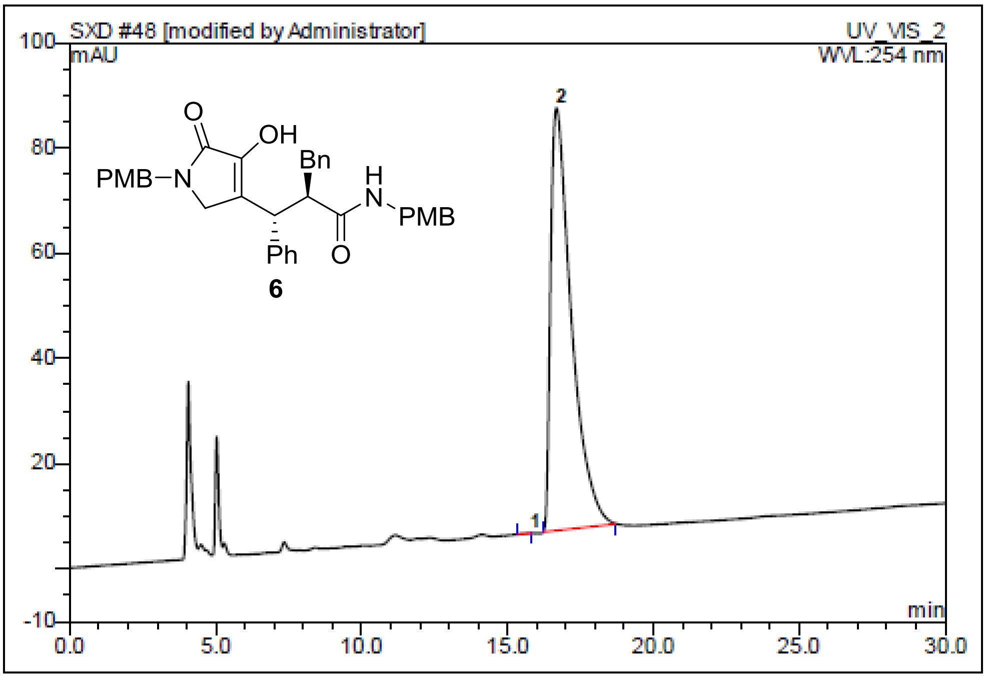

172.515
167.739
159.248
158.552
141.837
140.955
139.902
129.718
129.498
129.225
128.687
128.445
128.317
114.252
113.620
55.283
55.238
54.899
49.557
47.910
46.351
42.236
38.129
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OH
Bn
PMB−N
H
N
PMB
Ph
O

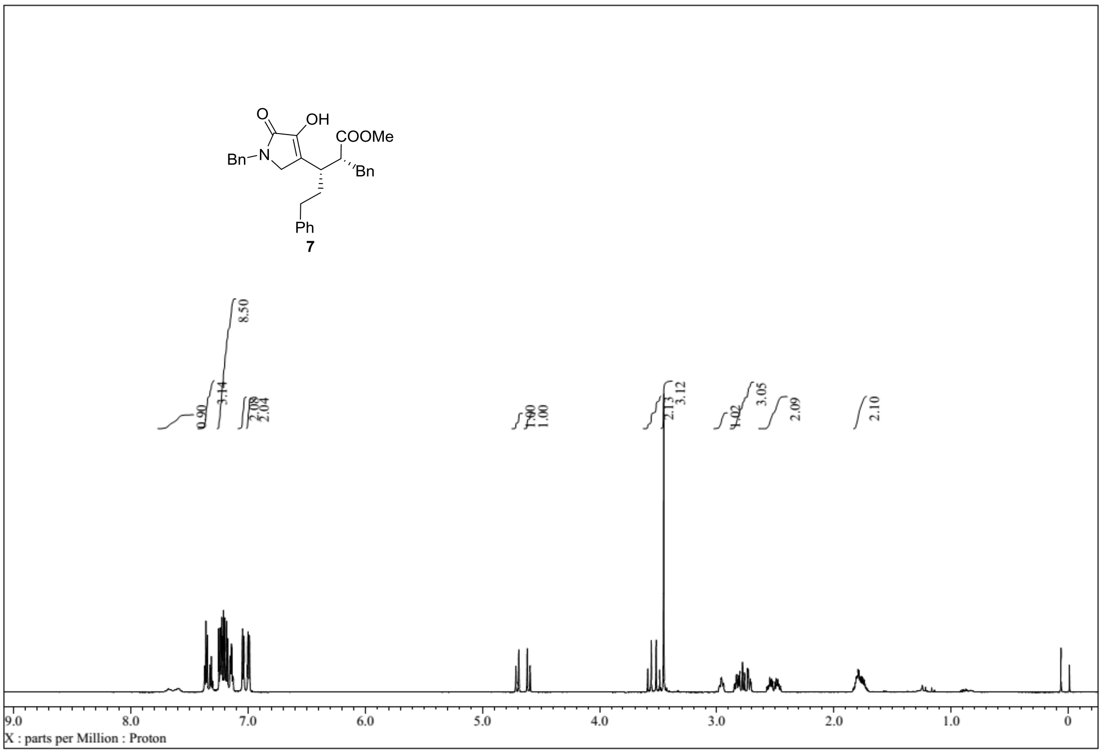
6

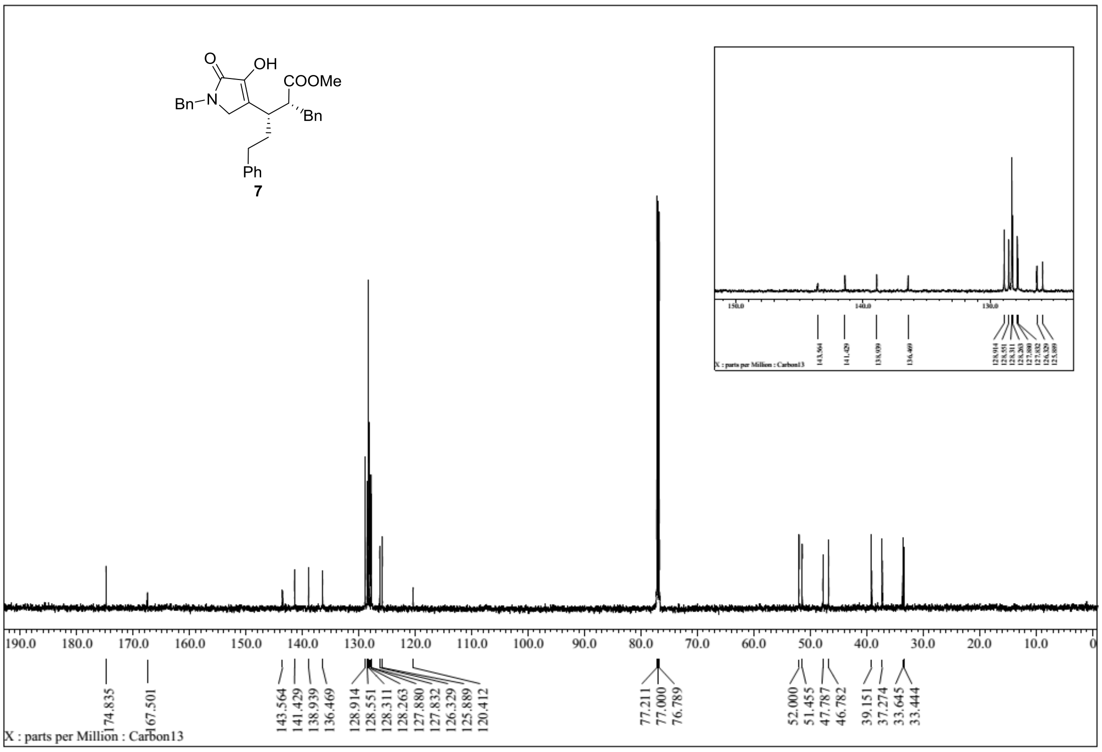


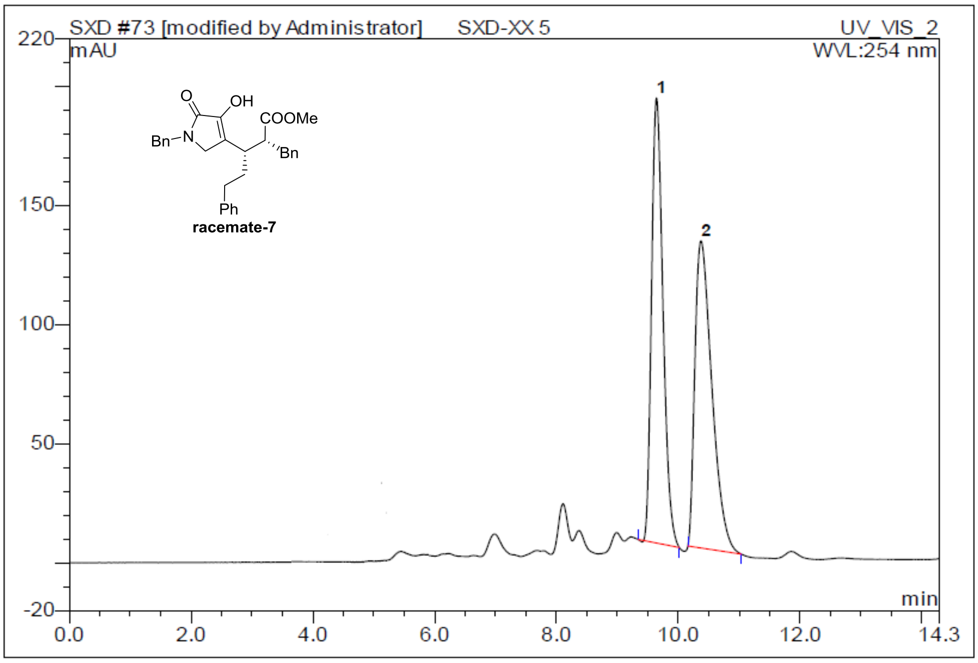
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	15.60	108.117	55.702	49.66
2	16.65	68.826	56.454	50.34
Total:		176.943	112.155	100.00



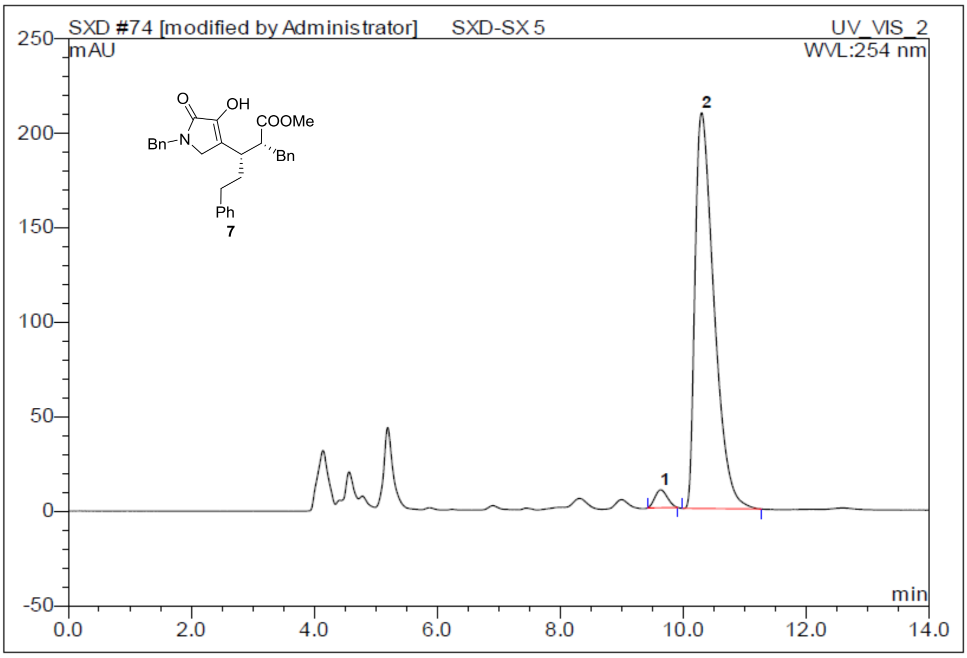
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	15.77	0.062	0.023	0.03
2	16.68	80.293	66.368	99.97
Total:		80.356	66.391	100.00


O
OH
COOMe
Bn
N
Bn
Ph
7
0.90
3.14
8.50
2.08
2.04
1.00
1.00
2.13
3.12
1.02
3.05
2.09
2.10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : Proton


O
OH
COOMe
Bn
N
Bn
Ph
7
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
174.835
167.501
143.564
141.429
138.939
136.469
128.914
128.551
128.311
128.263
127.880
127.832
126.329
125.889
120.412
77.211
77.000
76.789
52.000
51.455
47.787
46.782
39.151
37.274
33.645
33.444
X : parts per Million : Carbon13



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	9.64	187.067	40.512	49.27
2	10.38	129.087	41.704	50.73
Total:		316.154	82.216	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	9.63	9.467	2.232	2.90
2	10.30	209.520	74.881	97.10
Total:		218.987	77.114	100.00