Supporting Information

Effects of *N*-Substituents on the Functional Activities of Naltrindole Derivatives for the δ Opioid Receptor: Synthesis and Evaluation of Sulfonamide Derivatives

Chiharu Iwamatsu[1], Daichi Hayakawa[2], Tomomi Kono[1], Ayaka Honjo[1], Saki Ishizaki[1], Shigeto Hirayama[1,3], Hiroaki Gouda[2] and Hideaki Fujii[1,2,*]

[1] Laboratory of Medicinal Chemistry, School of Pharmacy, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan.

[2] School of Pharmacy, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan.

[3] Medicinal Research Laboratories, School of Pharmacy, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan.

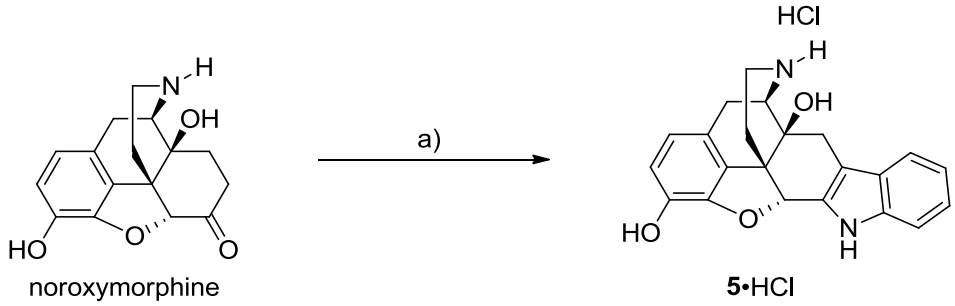
* Correspondence: fujiih@pharm.kitasato-u.ac.jp

Table of Contents

1. Synthesis of nor-NTI (**5**) hydrochloride S2
2. Previously reported synthetic method of the key intermediate **7** S2
3. Optimization of the reaction conditions for synthesis of nor-NTI (**5**) S4
4. Synthesis of NTI derivative (SYK-903) with *N*-(3-phenylpropyl) group S5
5. ^{1}H and ^{13}C NMR spectra S8
6. References S28

1. Synthesis of nor-NTI (5) hydrochloride

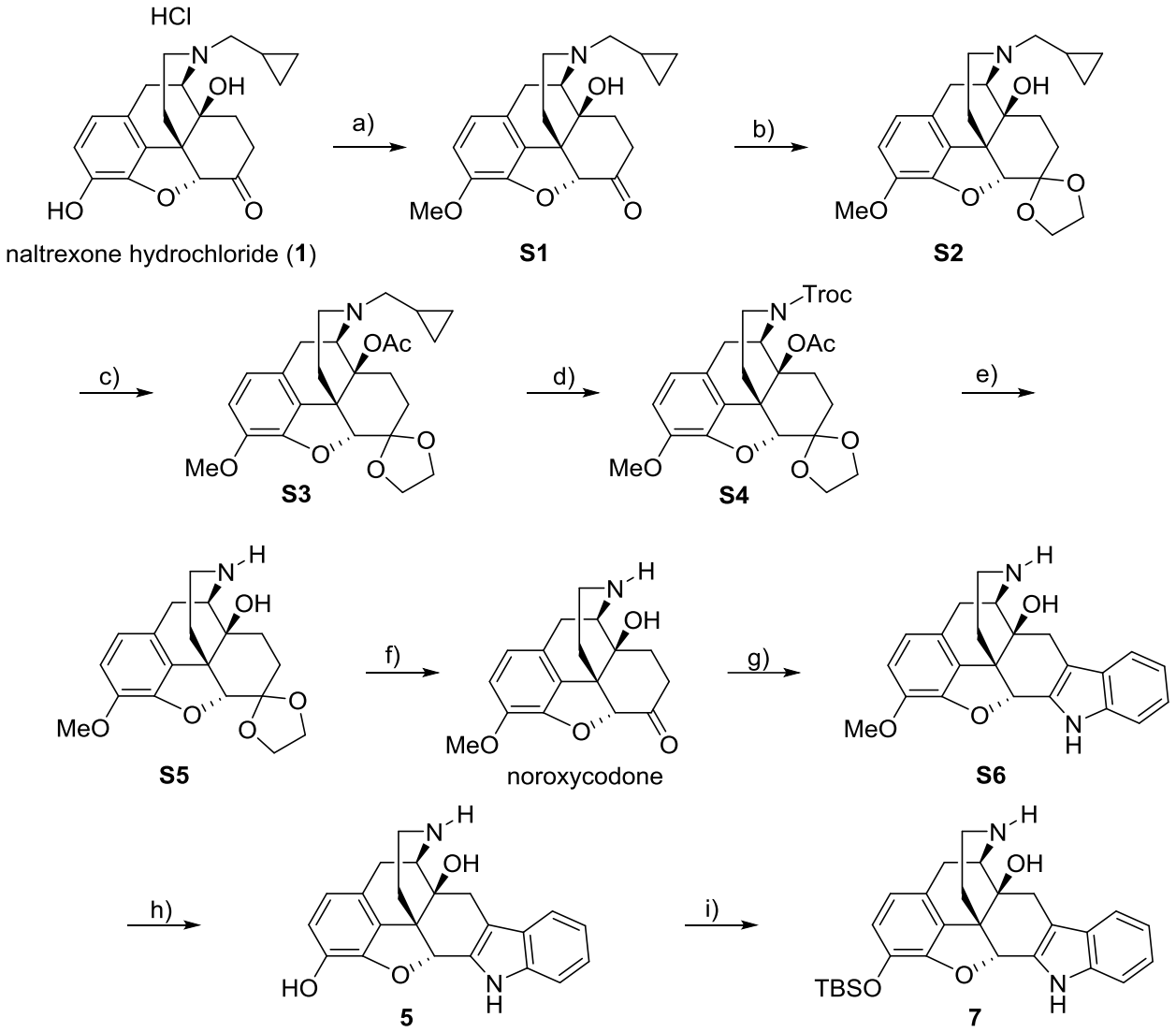
Portoghese *et al.* and Rice *et al.* independently reported the synthesis of nor-NTI (**5**) from noroxymorphone by the Fischer indole synthesis (Scheme S1) [1, 2]. This method is efficient from the viewpoints of both the yield and the number of reaction steps. However, noroxymorphone is difficult to obtain and very expensive compared with naltrexone hydrochloride (**1**).



Scheme S1. Synthesis of nor-NTI (**5**) hydrochloride. Reagents and conditions: a) $PhNHNH_2$·HCl, HCl/MeOH, MeOH, reflux, 98-99%.

2. Previously reported synthetic method of the key intermediate 7

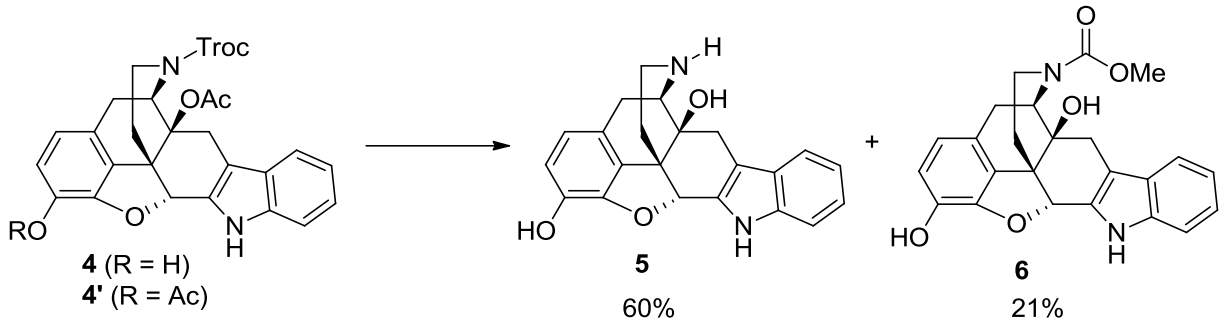
We previously reported the synthesis of the key intermediate **7** as shown in Scheme S2 [3]. The 3-*O*-methylation of naltrexone hydrochloride (**1**) and the subsequent acetalization provided compound **S2** [4-6]. After acetylation of the 14-hydroxy group in **S2**, the treatment of the obtained **S3** with Troc-Cl afforded compound **S4**. Both the carbamate and acetate were hydrolyzed under the basic conditions at the same time and the following deacetalyzation gave noroxycodone. The Fischer indolization of noroxycodone with phenylhydrazine hydrochloride yielded nor-NTI-3-*O*-methyl ether (**S6**). The exchange of the protective groups from methyl into TBS group provided the key intermediate **7** [3].



Scheme S2. Synthesis of the key intermediate **7**. Reagents and conditions: a) MeI, K_2CO_3, DMF, rt, 92%; b) ethylene glycol, *p*-TsOH·H_2O, toluene, reflux; c) Ac_2O, 85 °C, 92% (from **S1**); d) Troc-Cl, K_2CO_3, 1,1,2,2-tetrachloroethane, reflux, 92%; e) 12 M KOH aq, DMSO, 120 °C, 71%; f) 2 M HCl, MeOH, reflux; g) $PhNHNH_2$·HCl, $MeSO_3H$, EtOH, reflux, 84% (from **S5**); h) 1 M BBr_3, CH_2Cl_2, -10 °C, i) TBSCl, imidazole, DMF, rt, 87% (from **S6**).

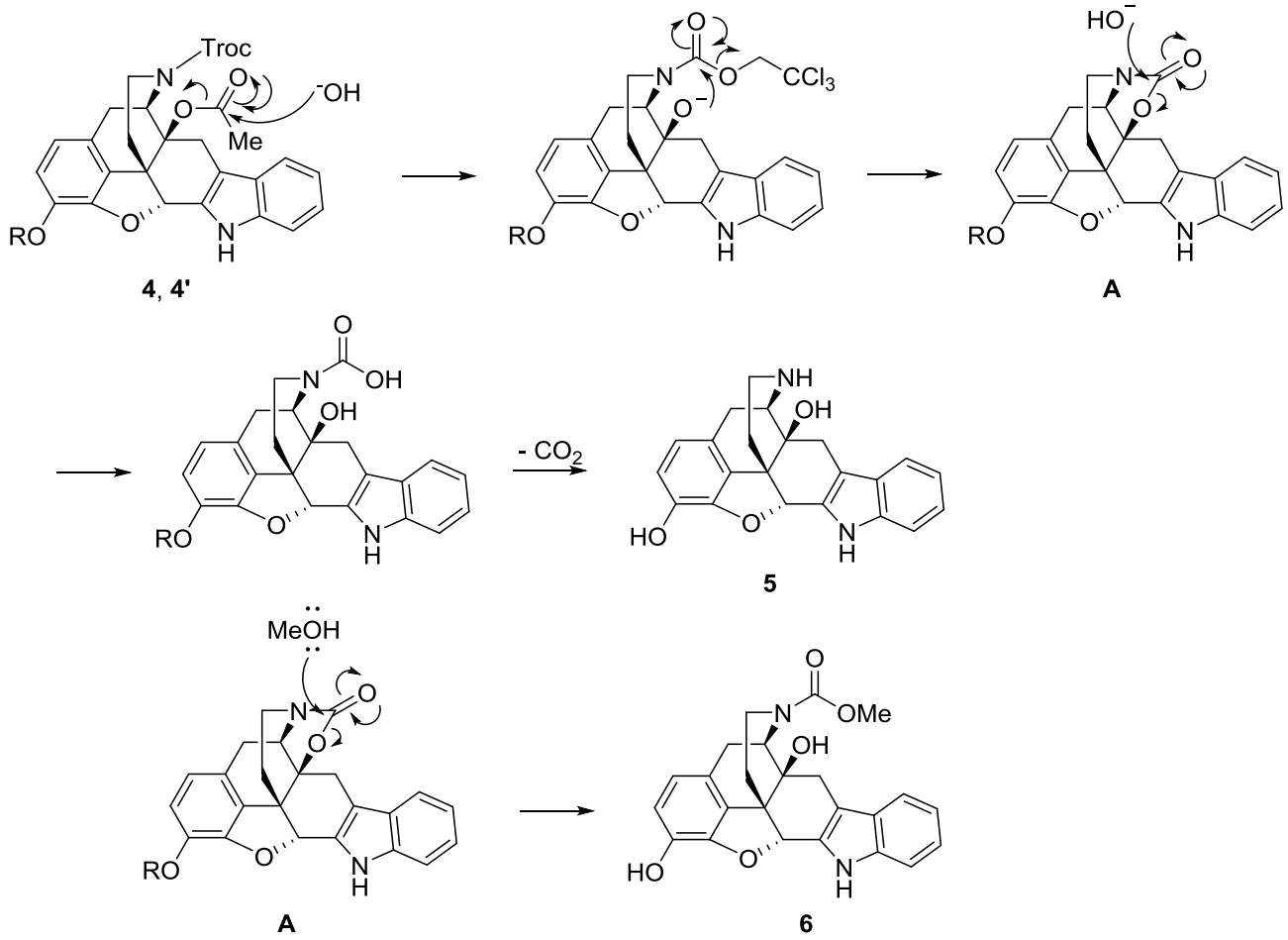
3. Optimization of the reaction conditions for synthesis of nor-NTI (5)

The treatment of a mixture of **4** and **4′** with 4 M NaOH aqueous solution using methanol as a solvent gave compounds **5** and **6** in 60% and 21% yields, respectively (Scheme S3).



Scheme S3. Hydrolysis of the mixture of compounds **4** and **4′** in methanol. Reagents and conditions: a) 4 M NaOH aq, MeOH, reflux.

We speculated that nor-NTI (**5**) was obtained by the mechanism as follows: at first, the hydrolysis of the acetate moiety provides the alkoxide anion, which intramolecularly attacks the carbonyl carbon of the carbamate to afford oxazolidinone **A**. In general, the hydrolysis of carbamates requires harsh reaction conditions. However, the

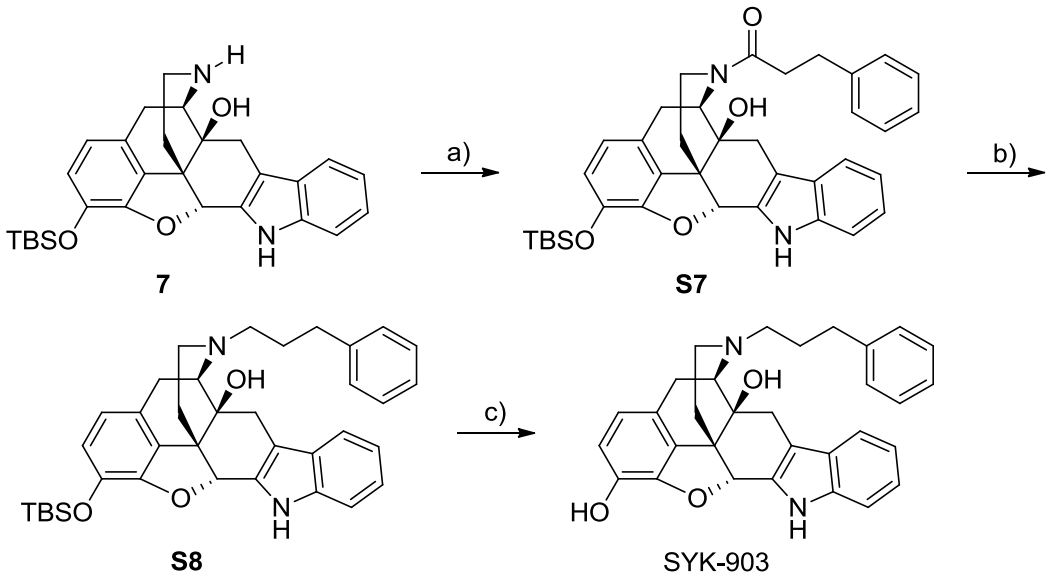


Scheme S4. Proposed reaction mechanism for providing compounds **5** and **6**.

oxazolidinone moiety in **A** would be prone to undergo hydrolysis due to its strained structure. As a result, the hydrolysis of oxazolidinone **A** proceeds under milder reaction conditions to provide nor-NTI (**5**). In the case that methanol was used as a solvent, the solvolysis of oxazolidinone **A** would concomitantly occur to give methyl carbamate **6** (Scheme S4). Based on the proposed reaction mechanism, the usage of a non-nucleophilic solvent would hamper the preparation of carbamates like **6**. Indeed, the usage of THF as a solvent instead of methanol successfully provided only the target compound **5**.

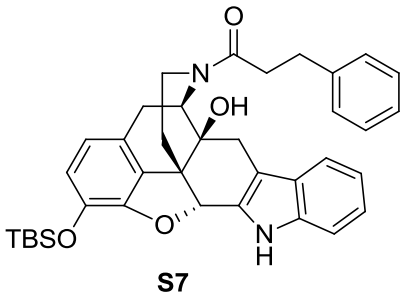
4. Synthesis of NTI derivative (SYK-903) with *N*-(3-phenylpropyl) group

SYK-903 was prepared from compound **7** (Scheme S5).



Scheme S5. Synthesis of SYK-903. Reagents and conditions: a) 3-phenylpropanoyl chloride, Et_3N, CH_2Cl_2, rt, 67%; b) BH_3·THF, THF, reflux, 90%; c) TBAF, THF, rt, 91%.

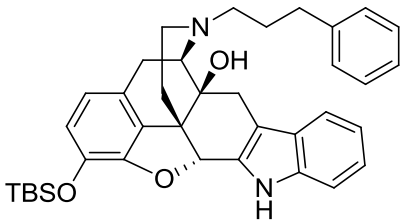
4.1. 1-(3-((*tert*-Butyldimethylsilyl)oxy)-6,7-didehydro-4,5α-epoxy-14β-hydroxyindolo[2′,3′:6,7]morphinan-17-yl)-3-phenylpropan-1-one (S7)



Under an Ar atmosphere, to a solution of compound **7** (132 mg, 0.28 mmol) in dichloromethane (1.3 mL) were added triethylamine (0.12 mL, 0.84 mmol) and 3-phenylpropanoyl chloride (80 μL, 0.56 mmol), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into saturated sodium bicarbonate aqueous solution and extracted with chloroform. Combined organic layers were washed with brine and dried over anhydrous

sodium sulfate. After removing the solvent *in vacuo*, the residue was purified by silica gel column chromatography to give compound **S7** (113 mg, 67%) as a light tan amorphous material; IR (film) cm^{-1}: 3415, 3026, 2928, 2857, 1713, 1614, 1496, 1444, 1328, 1273, 1214, 1162, 1112. ^1H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 2.1H), 0.02 (s, 0.9H), 0.03 (s, 2.1H), 0.04 (s, 0.9H), 0.88 (s, 9H), 1.67 (dd, *J* = 2.4, 12.5 Hz, 0.7H), 1.79 (dd, *J* = 2.8, 12.9 Hz, 0.3H), 2.28-2.43 (m, 1H), 2.62-3.08 (m, 7.3H), 3.13 (ddd, *J* = 3.6, 13.4, 13.4 Hz, 0.7H), 3.25-3.38 (m, 1H), 3.67 (dd, *J* = 4.6, 13.8 Hz, 0.7H), 4.28 (d, *J* = 6.5 Hz, 0.3H), 4.63 (dd, *J* = 4.7, 13.7 Hz, 0.3H), 5.28 (d, *J* = 6.7 Hz, 0.7H), 5.55 (s, 0.3H), 5.57 (s, 0.7H), 6.52 (d, *J* = 8.0 Hz, 0.3H), 6.53 (d, *J* = 8.1 Hz, 0.7H), 6.59 (br d, *J* = 8.1 Hz, 1H), 7.05 (br t, *J* = 7.4 Hz, 1H), 7.15-7.36 (m, 7H), 7.38 (d, *J* = 8.0 Hz, 0.3H), 7.41 (d, *J* = 7.9 Hz, 0.7H), 8.09 (br s, 0.7H), 8.17 (br s, 0.3H), a proton (OH) was not observed. ^{13}C NMR (100MHz, $CDCl_3$): δ -4.8, -4.7, 18.2, 25.5, 29.4, 29.7, 29.8, 29.9, 30.7, 31.49, 31.53, 32.5, 32.9, 34.6, 35.4, 39.1, 48.0, 48.2, 53.6, 58.3, 73.4, 73.6, 83.8, 84.0, 110.0, 110.6, 111.1, 111.3, 118.7, 118.9, 119.0, 119.4, 119.5, 122.3, 122.4, 122.9, 123.1, 124.8, 125.4, 126.1, 126.18, 126.20, 126.7, 128.27, 128.37, 128.45, 128.50, 128.7, 130.16, 130.21, 137.06, 137.11, 138.7, 138.8, 141.0, 141.4, 146.4, 146.5, 172.1, 172.4. HR-MS (ESI): Calcd for $C_{37}H_{43}N_2O_4Si$ $[M+H]^+$: 607.2992. Found: 607.3019.

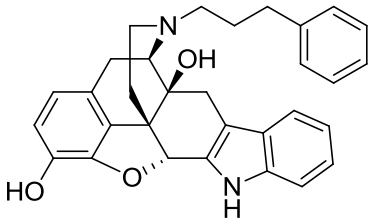
4.2. 3-((*tert*-Butyldimethylsilyl)oxy)-6,7-didehydro-4,5α-epoxy-17-(3-phenylpropyl)indolo[2′,3′:6,7]morphinan-14β-ol (S8)



S8

Under an Ar atmosphere, to a solution of compound **S7** (113 mg, 0.19 mmol) in THF (6 mL) was added 1.0 M solution of borane-THF complex in THF (1.1 mL, 1.1 mmol), and the mixture was refluxed with stirring for 24 hours. After cooling to room temperature, to the reaction mixture was added saturated sodium bicarbonate aqueous solution and extracted with chloroform. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removing the solvent *in vacuo*, the residue was purified by silica gel column chromatography to give compound **S8** (84 mg, 90%) as a white amorphous material; IR (film) cm^{-1}: 2928, 1496, 1444, 1328, 1270, 1161, 960, 854, 740, 425, 408. ^1H NMR (400 MHz, $CDCl_3$): δ -0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.73-1.94 (m, 3H), 2.26-2.40 (m, 2H), 2.48-2.64 (m, 3H), 2.62 (dd, *J* = 1.1, 15.7 Hz, 1H), 2.70 (d, *J* = 7.6 Hz, 2H), 2.81 (dd, *J* = 6.5, 18.8 Hz, 1H), 2.87 (d, *J* = 15.7 Hz, 1H), 3.12 (d, *J* = 6.5 Hz, 1H), 3.15 (d, *J* = 18.8 Hz, 1H), 4.84 (br s, 1H), 5.61 (s, 1H), 6.50 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 7.02 (ddd, *J* = 0.9, 7.1, 7.9 Hz, 1H), 7.14 (ddd, *J* = 1.1, 7.1, 8.1 Hz, 1H), 7.18-7.24 (m, 3H), 7.26-7.33 (m, 3H), 7.40 (d, *J* = 7.9 Hz, 1H), 8.01 (br s, 1H). ^{13}C NMR (100MHz, $CDCl_3$): δ -4.8, -4.7, 18.2, 23.6, 25.6, 28.8, 29.2, 31.4, 33.5, 43.5, 47.9, 53.9, 63.2, 72.6, 84.5, 111.0, 111.5, 118.5, 118.9, 119.2, 121.8, 122.7, 125.9, 126.3, 126.8, 128.36, 128.42, 129.0, 131.2, 137.1, 138.3, 141.8, 146.4. HR-MS (ESI): Calcd for $C_{37}H_{45}N_2O_3Si$ $[M+H]^+$: 593.3199. Found: 593.3855.

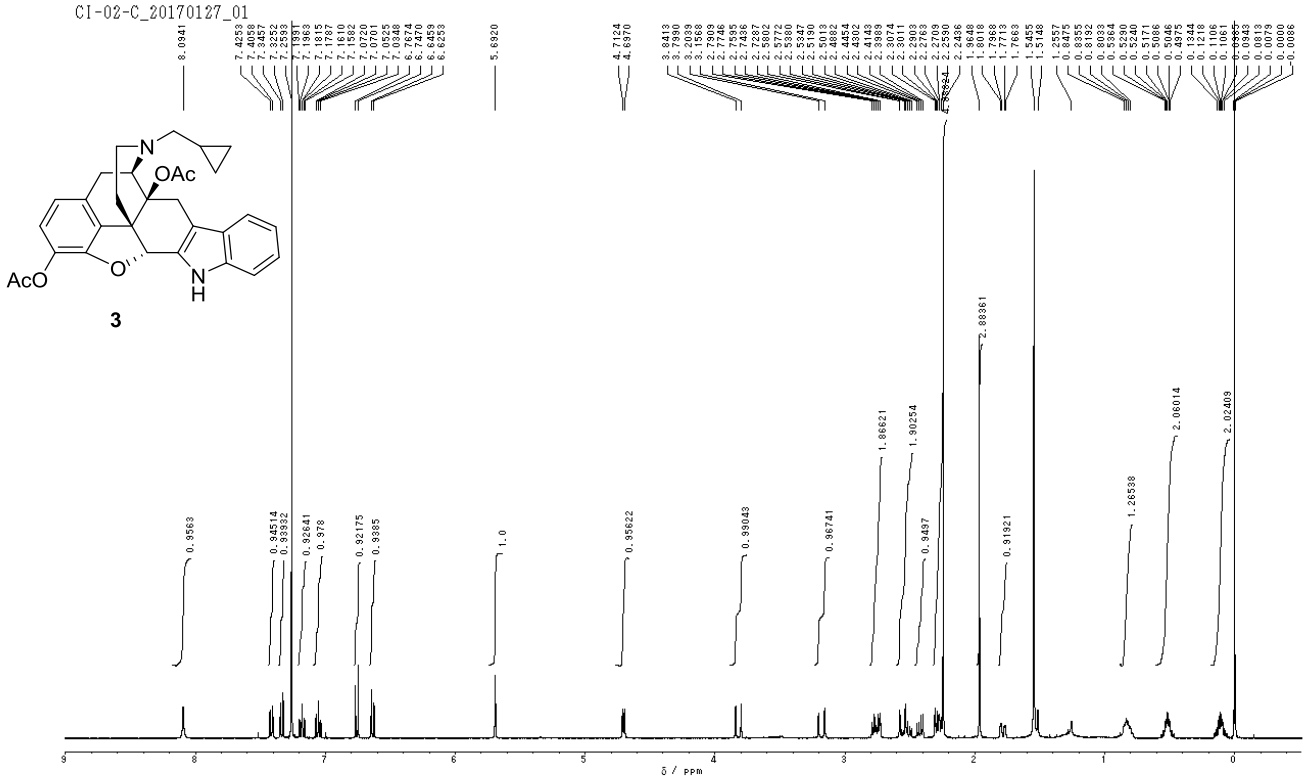
4.3. 6,7-Didehydro-4,5α-epoxy-17-(3-phenylpropyl)indolo[2′,3′:6,7]morphinan-3,14β-diol (SYK-903)

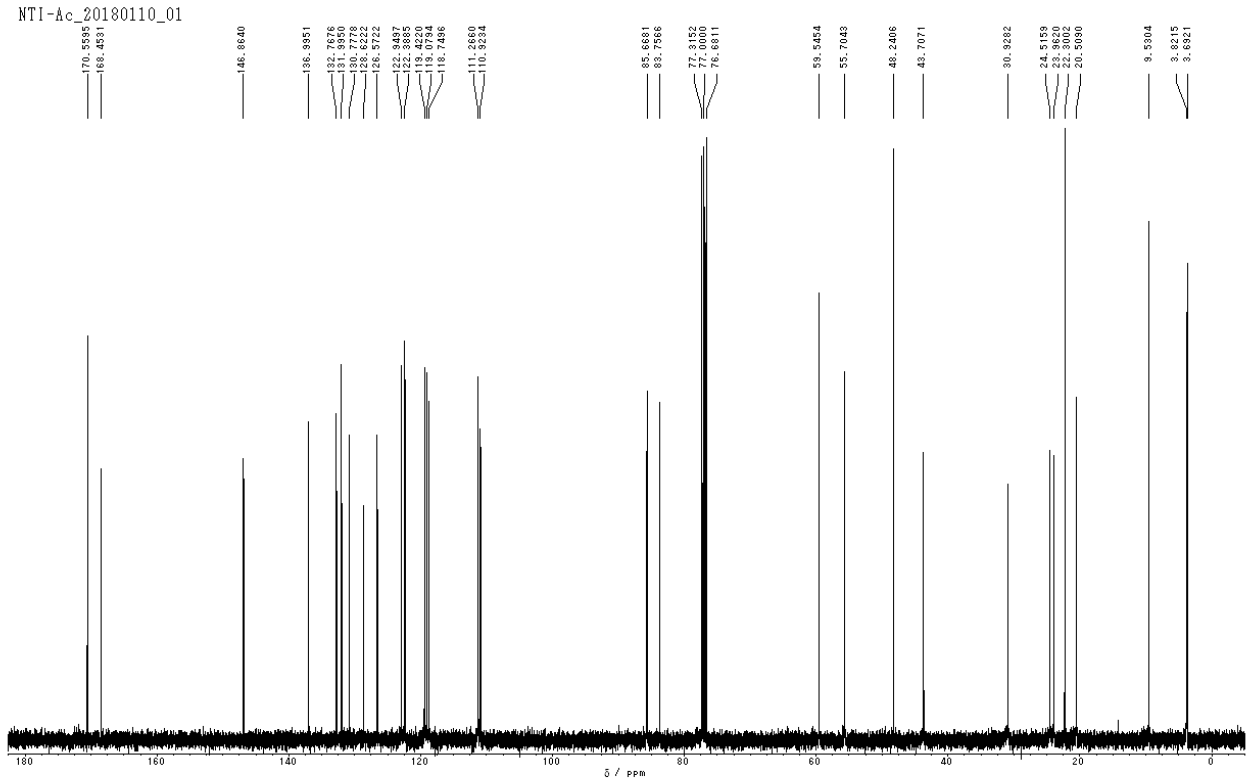


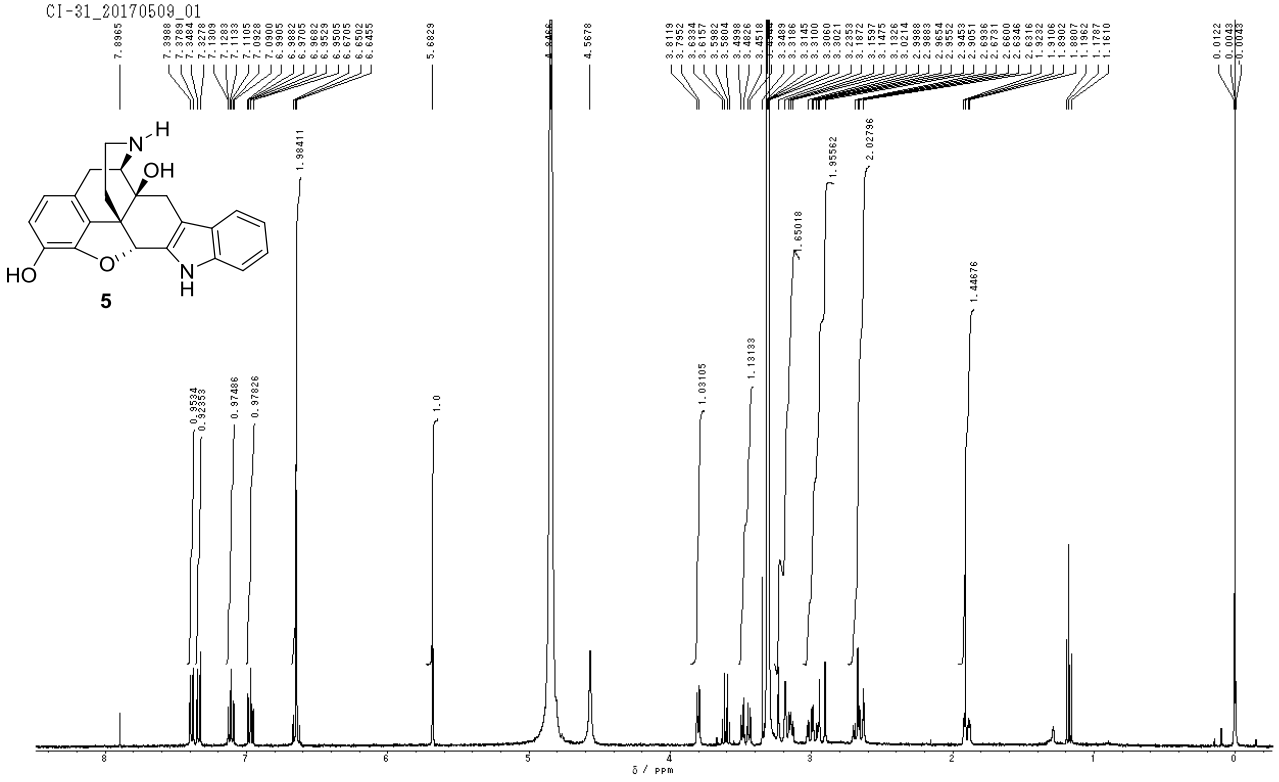
SYK-903

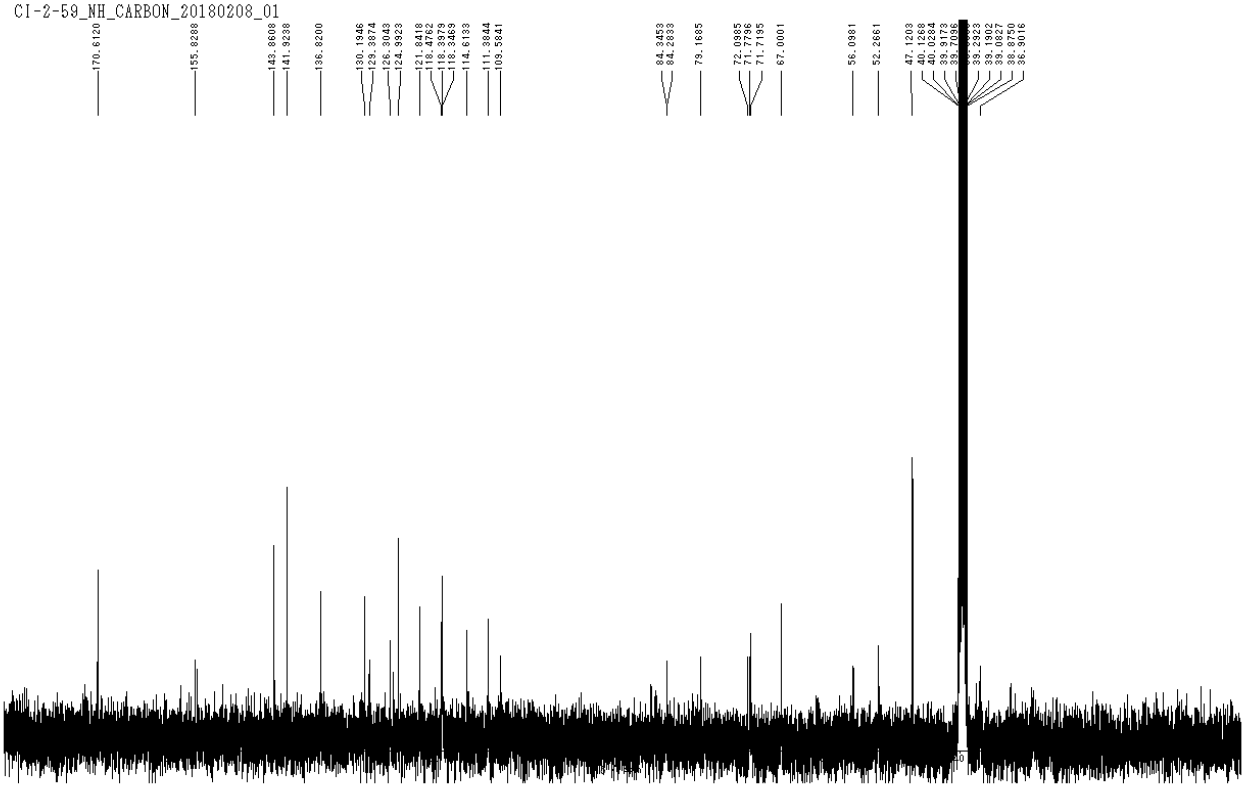
Under an Ar atmosphere, to a solution of compound **S8** (75 mg, 0.13 mmol) in THF (0.7 mL) was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.15 mL, 0.15 mmol), and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was poured into saturated sodium bicarbonate aqueous solution and extracted with chloroform. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removing the solvent *in vacuo*, the residue was purified by silica gel column chromatography to give SYK-903 (55 mg, 91%) as a light tan oil; IR (neat) cm^{-1}: 3398, 2928, 1455, 1326, 1159, 1116, 960, 742, 699. ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (br d, *J* = 12.6 Hz, 1H), 1.82-1.94 (m, 2H), 2.23-2.41 (m, 2H), 2.50-2.61 (m, 3H), 2.62 (dd, *J* = 0.9, 15.8 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.79 (dd, *J* = 6.5, 18.6 Hz, 1H), 2.88 (d, *J* = 15.8 Hz, 1H), 3.12 (d, *J* = 6.5 Hz, 1H), 3.13 (d, *J* = 18.6 Hz, 1H), 5.71 (s, 1H), 6.47 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 7.01 (ddd, *J* = 0.9, 7.0, 7.9 Hz, 1H), 7.12 (ddd, *J* = 1.1, 7.9, 8.1 Hz, 1H), 7.18-7.24 (m, 2H), 7.24-7.28 (m, 2H), 7.28-7.34 (m, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 8.20 (br s, 1H), two protons (OH) were not observed. ^{13}C NMR (100MHz, $CDCl_3$): δ 18.3, 23.4, 29.2, 33.4, 43.4, 48.0, 53.8, 58.4, 63.2, 72.9, 85.5, 111.3, 111.4, 117.2, 118.9, 119.1, 119.2, 122.7, 125.1, 125.9, 126.5, 128.3, 128.4, 128.7, 130.5, 137.2, 138.9, 141.7, 142.6. HR-MS (ESI): Calcd for $C_{31}H_{31}N_2O_3$ $[M+H]^+$: 479.2341. Found: 479.2334. *Anal.* Calcd for $C_{31}H_{30}N_2O_3 \cdot 1.3H_2O \cdot 0.1CHCl_3$: C, 72.68; H, 6.41; N, 5.45. Found: C, 72.57; H, 6.16; N, 5.28.

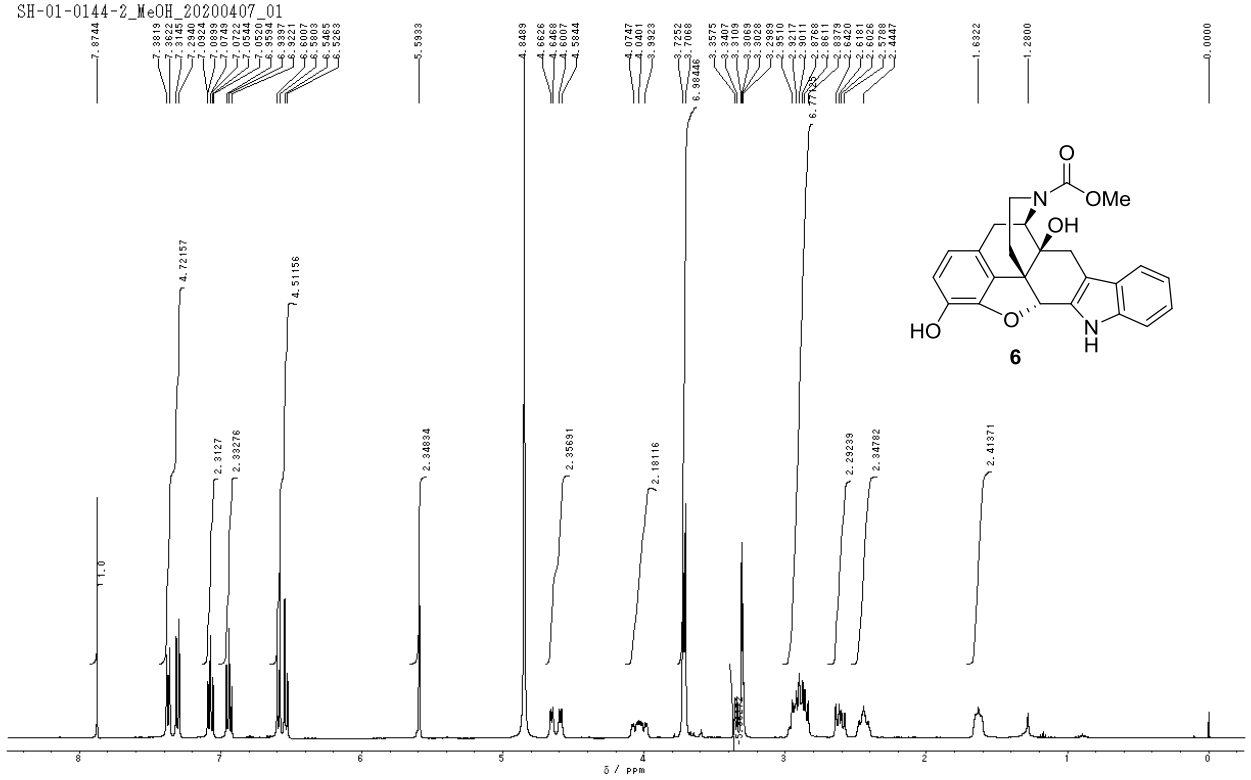
5. ^{1}H and ^{13}C NMR spectra

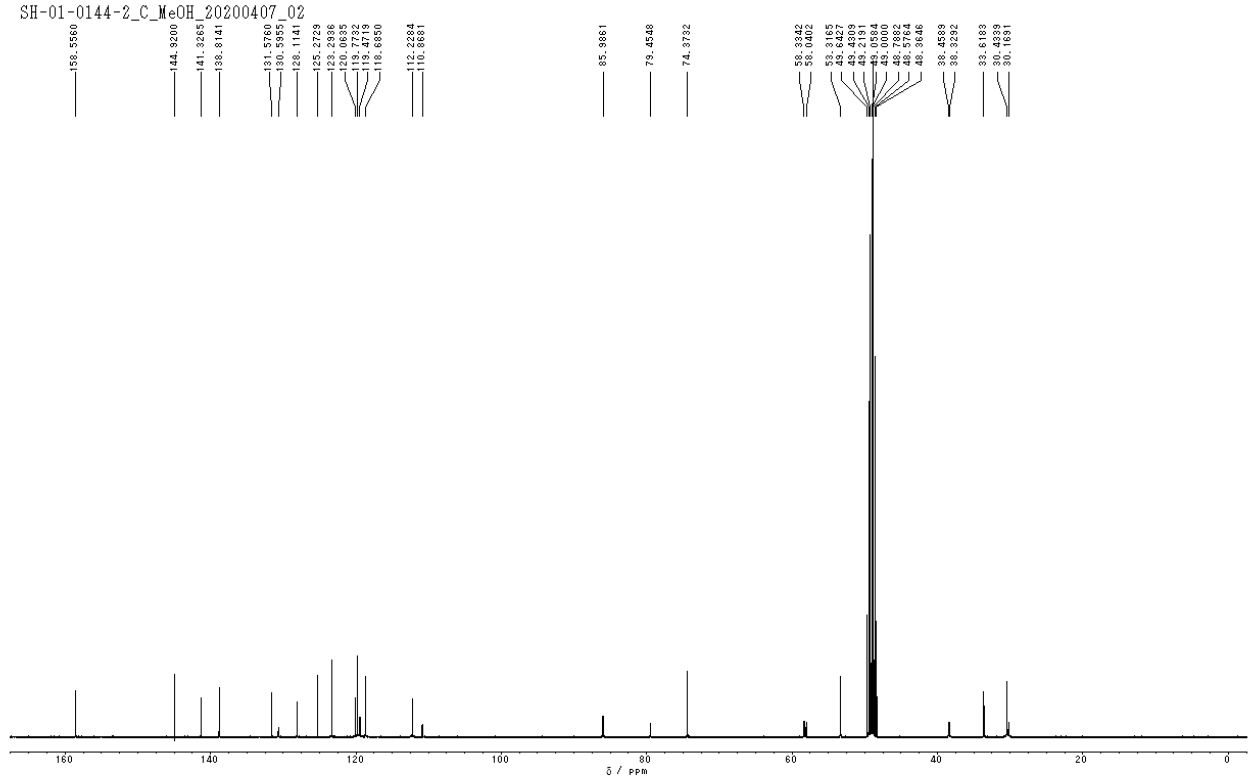


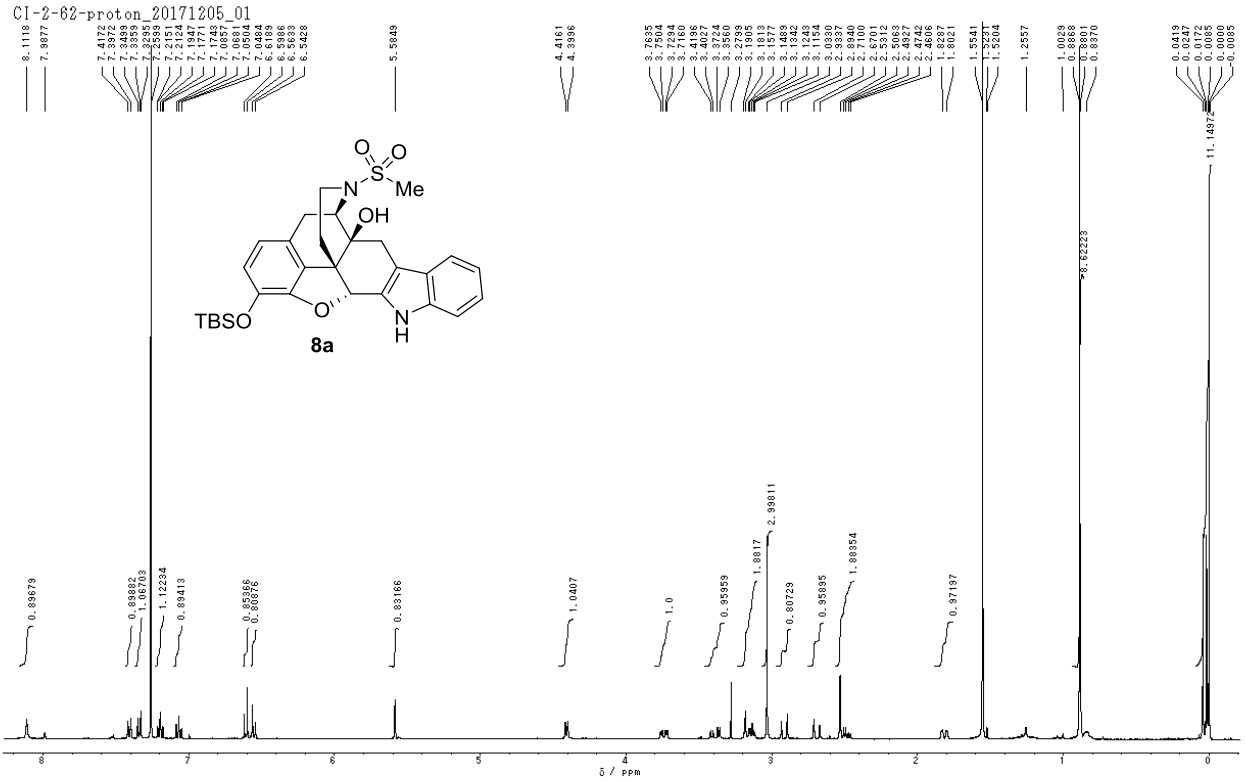


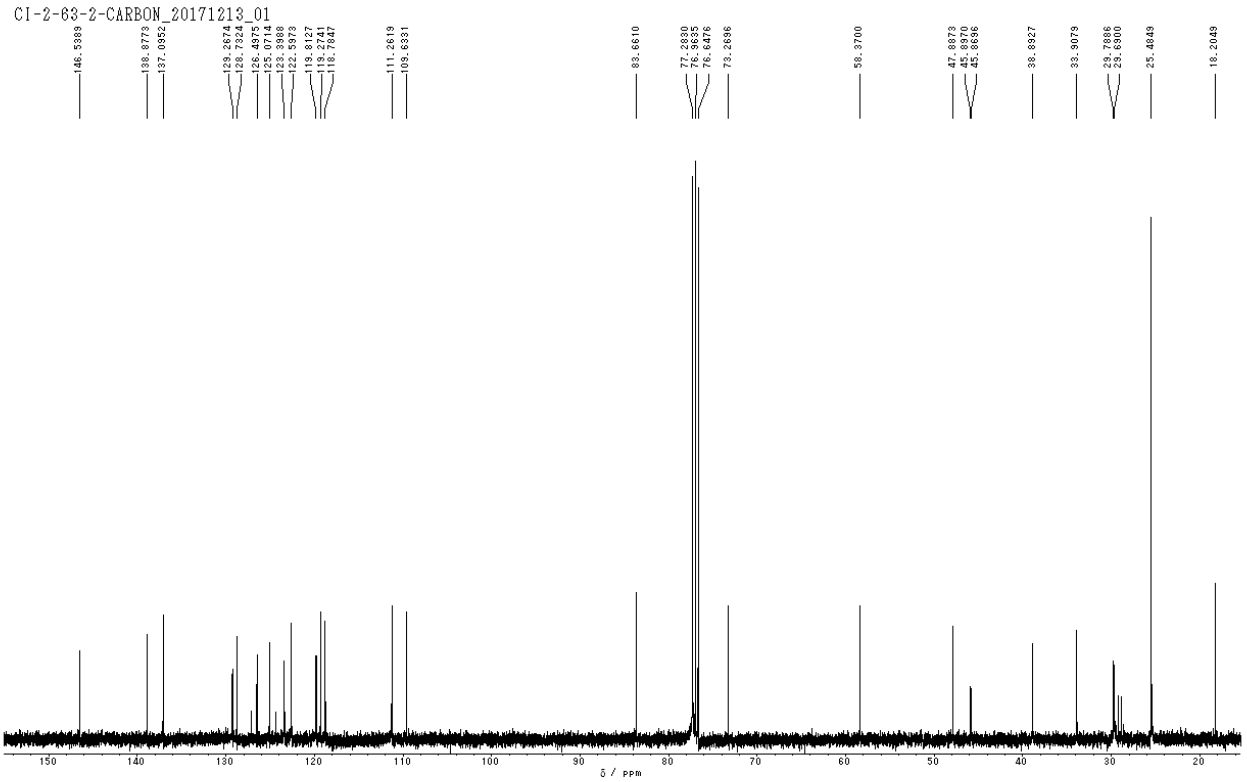

CI-31_20170509_01
5
δ / ppm


CI-2-59_NH_CARBON_20180208_01

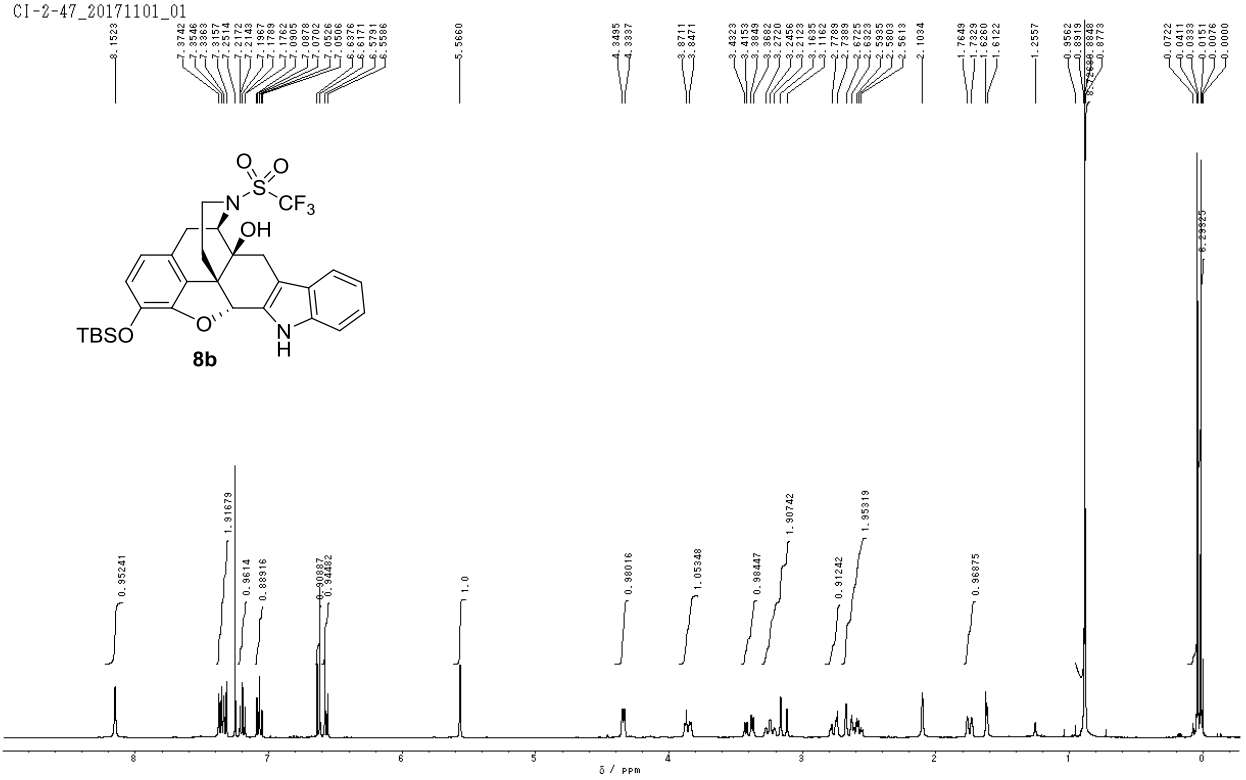

SH-01-0144-2_MeOH_20200407_01
7.8744
7.3819
7.3622
7.3445
7.2940
7.0924
7.0839
7.0749
7.0722
7.0544
7.0520
6.9594
6.9337
6.9221
6.6007
6.5803
6.5465
6.5263
5.5933
4.8489
4.6626
4.6468
4.6007
4.5844
4.0747
4.0401
3.9923
3.7252
3.7068
6.38446
3.3575
3.3407
3.3109
3.3089
3.3028
3.2909
3.2510
3.2217
3.2011
6.77122
2.8758
2.8661
2.8379
2.8420
2.6181
2.6026
2.4749
2.4447
1.6322
1.2800
0.0000
4.72157
4.51156
2.3127
2.33276
2.34834
2.35681
2.18116
2.29239
2.34782
2.41371
11.0
O
N
OMe
OH
HO
O
N
H
6
8
7
6
5
4
3
2
1
0
δ / ppm


SH-01-0144-2_C_MeOH_20200407_02
158.5580
144.9200
141.3265
138.8141
131.5760
130.5955
128.1141
125.2729
123.2936
120.0635
119.7732
119.4715
116.6850
112.2284
110.8681
85.9861
79.4548
74.9732
58.3342
58.0402
53.8185
53.4427
49.4309
49.2191
49.0584
49.0000
48.9282
48.7923
48.5764
48.3646
38.4589
38.3292
33.6183
30.4833
30.1691
160
140
120
100
80
60
40
20
0
δ / ppm


CI-2-62-proton_20171205_01
TBSO
OH
N
S
O
Me
H
8a
δ / ppm

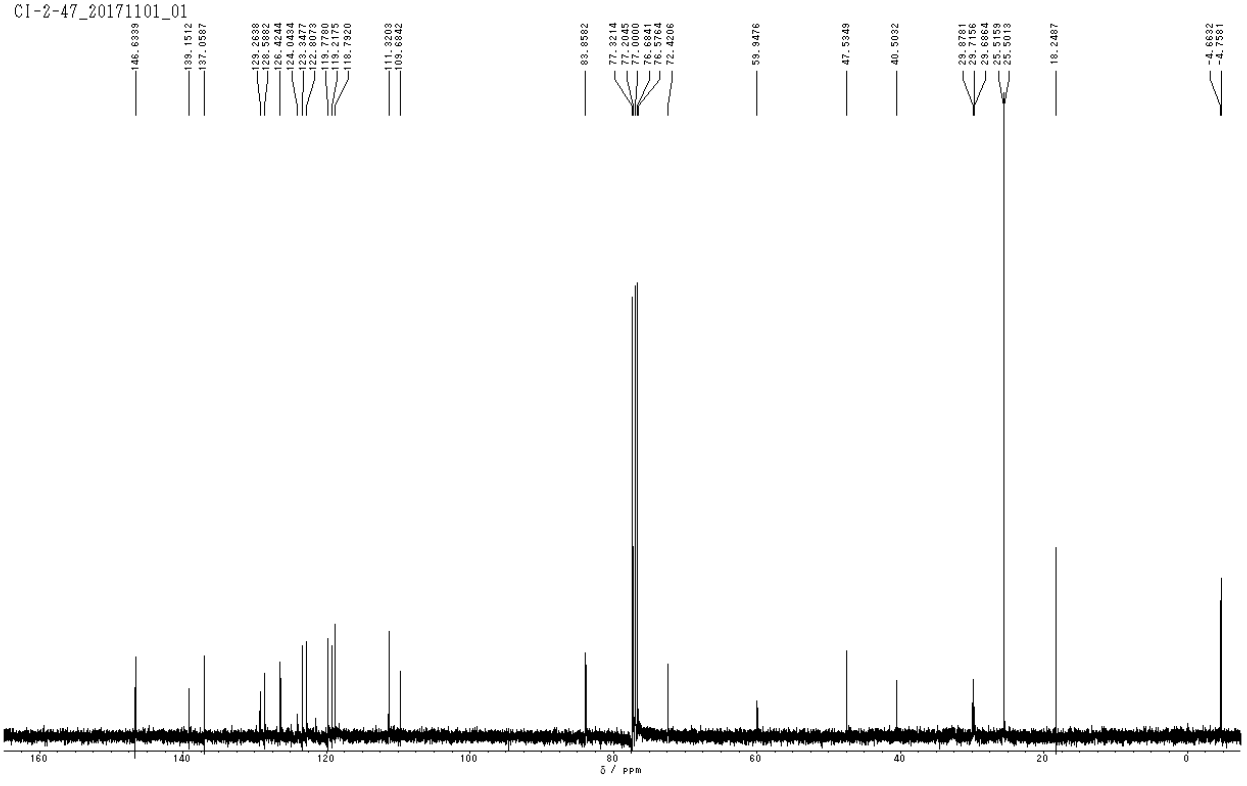

CI-2-63-2-CARBON_20171213_01
δ / ppm

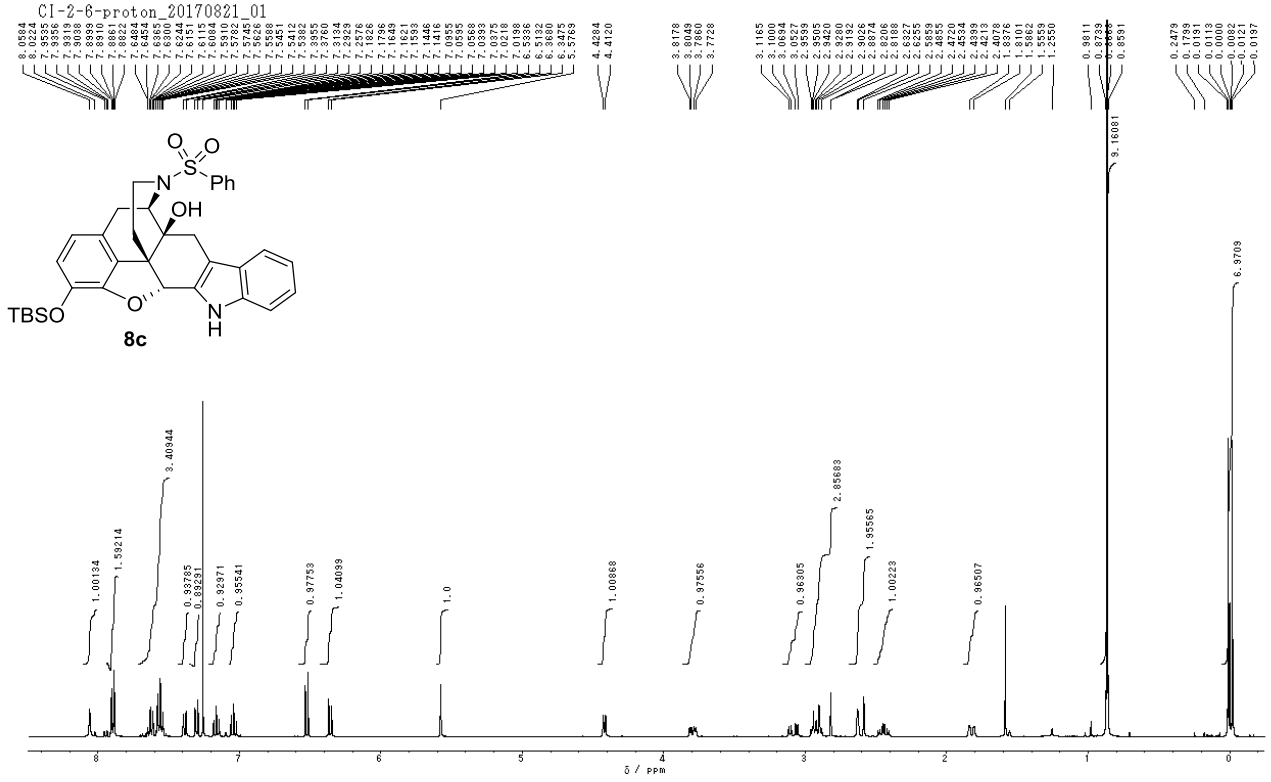
CI-2-47_20171101_01

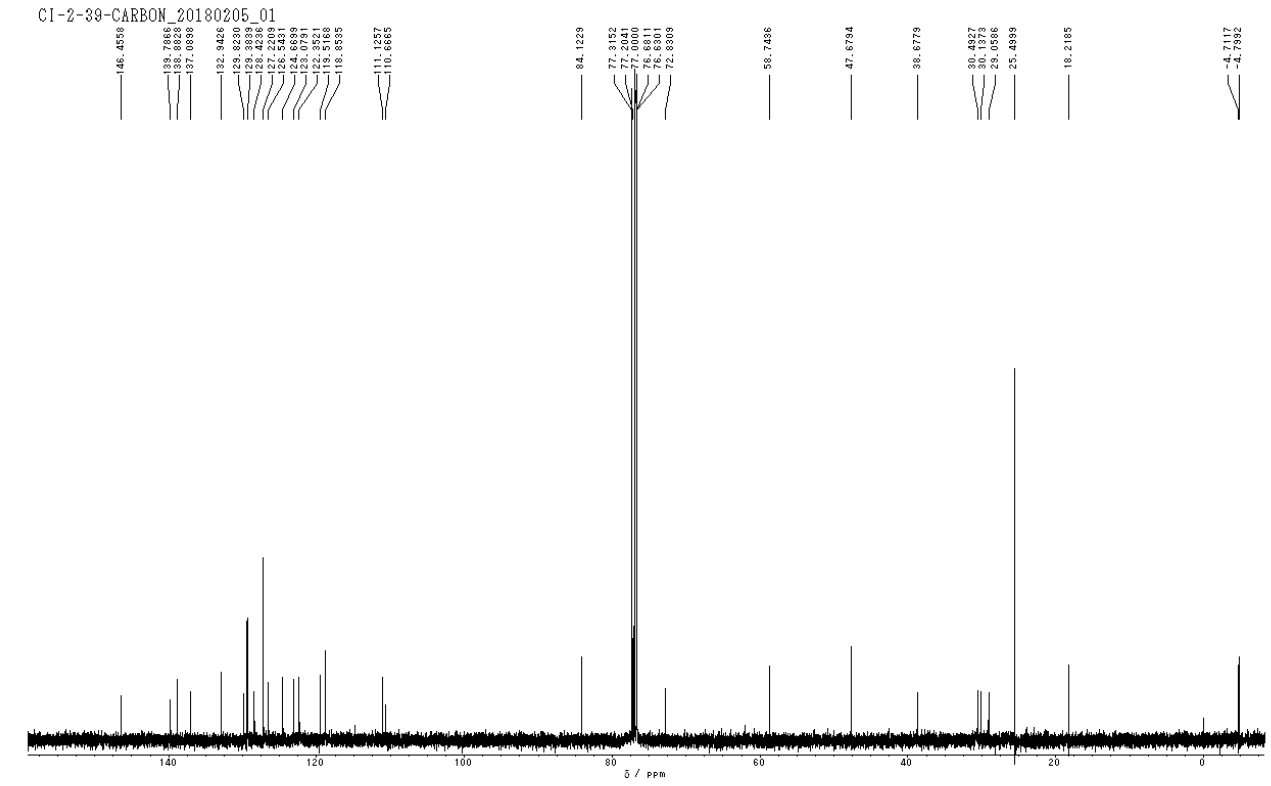


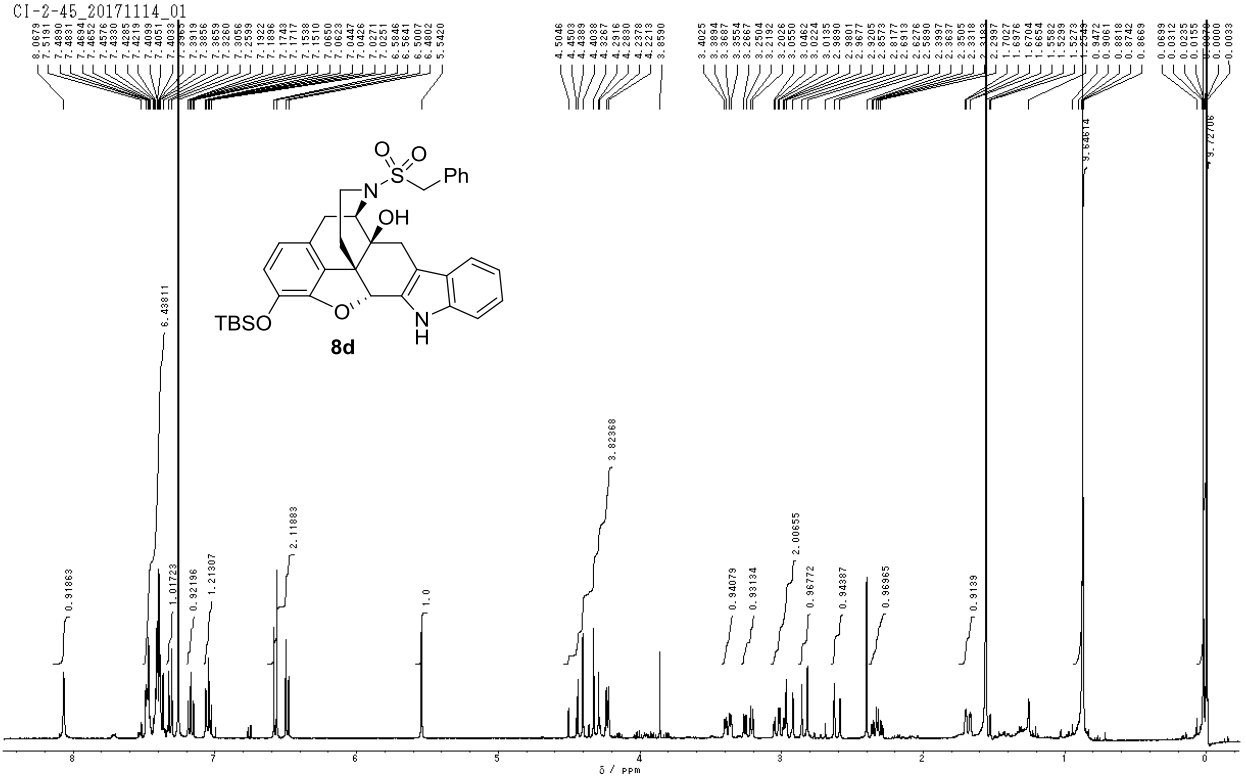
8b

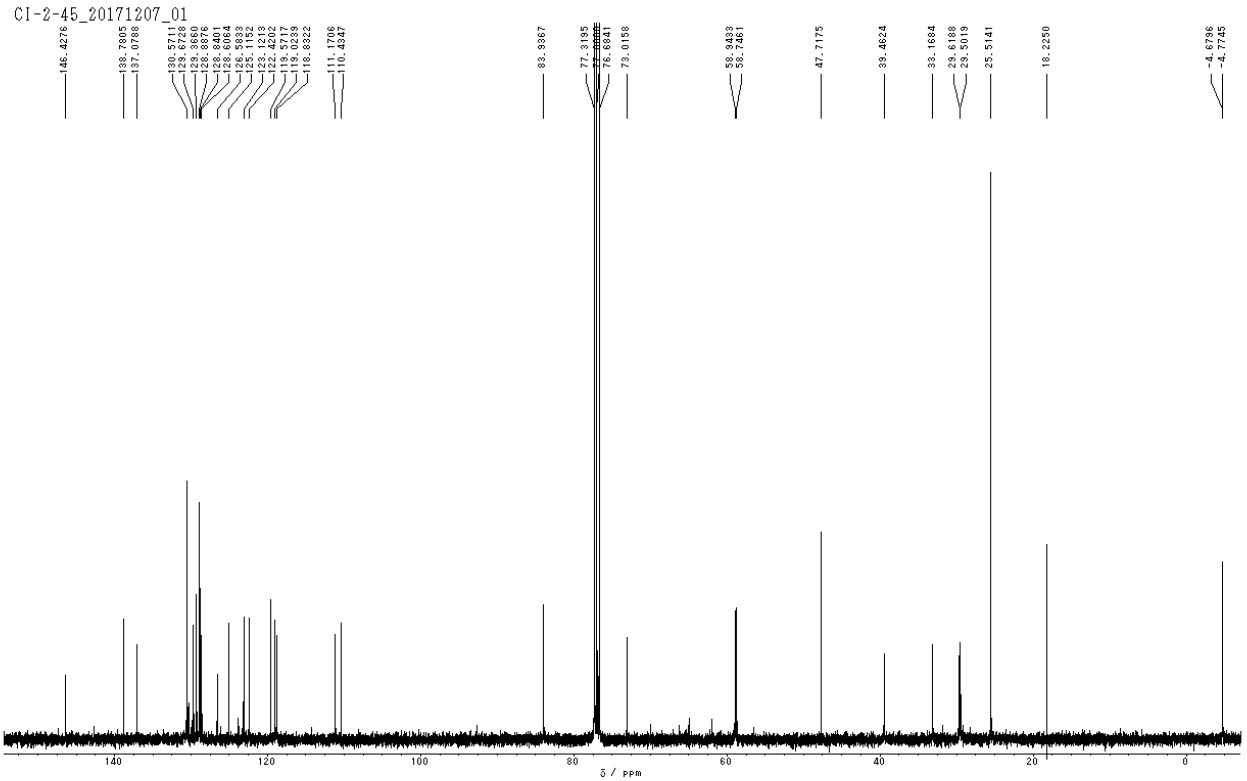
CI-2-47_20171101_01

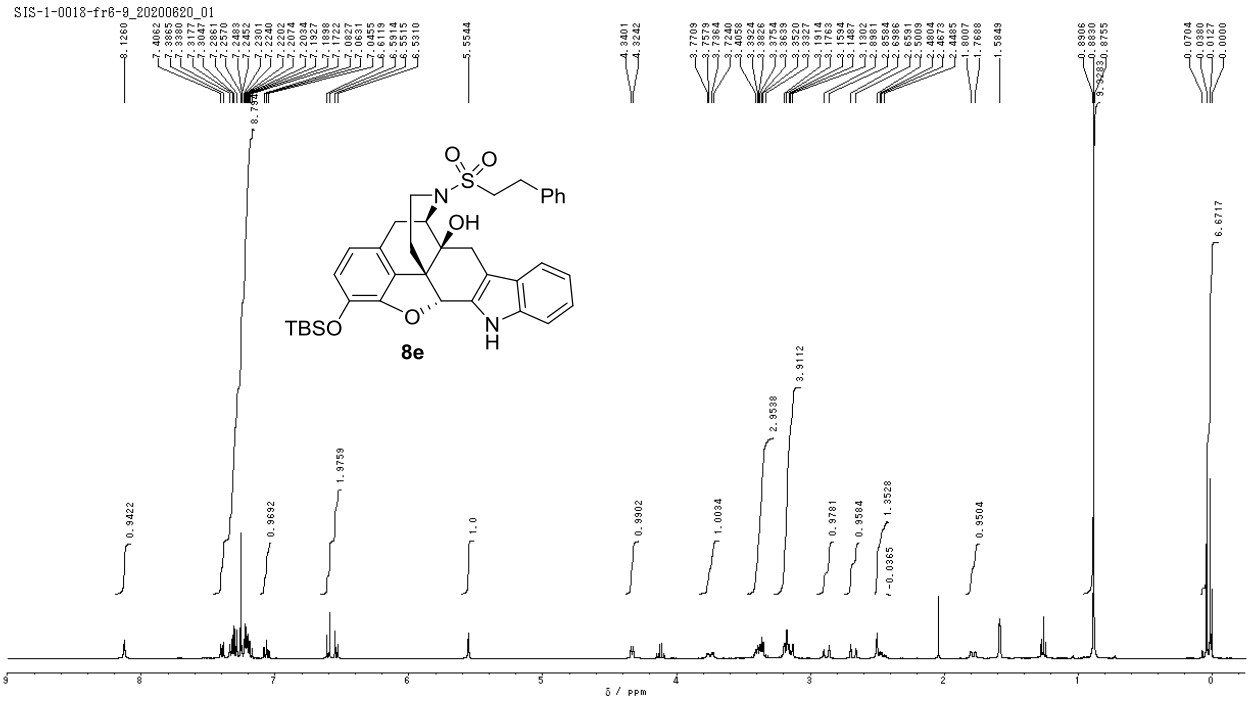


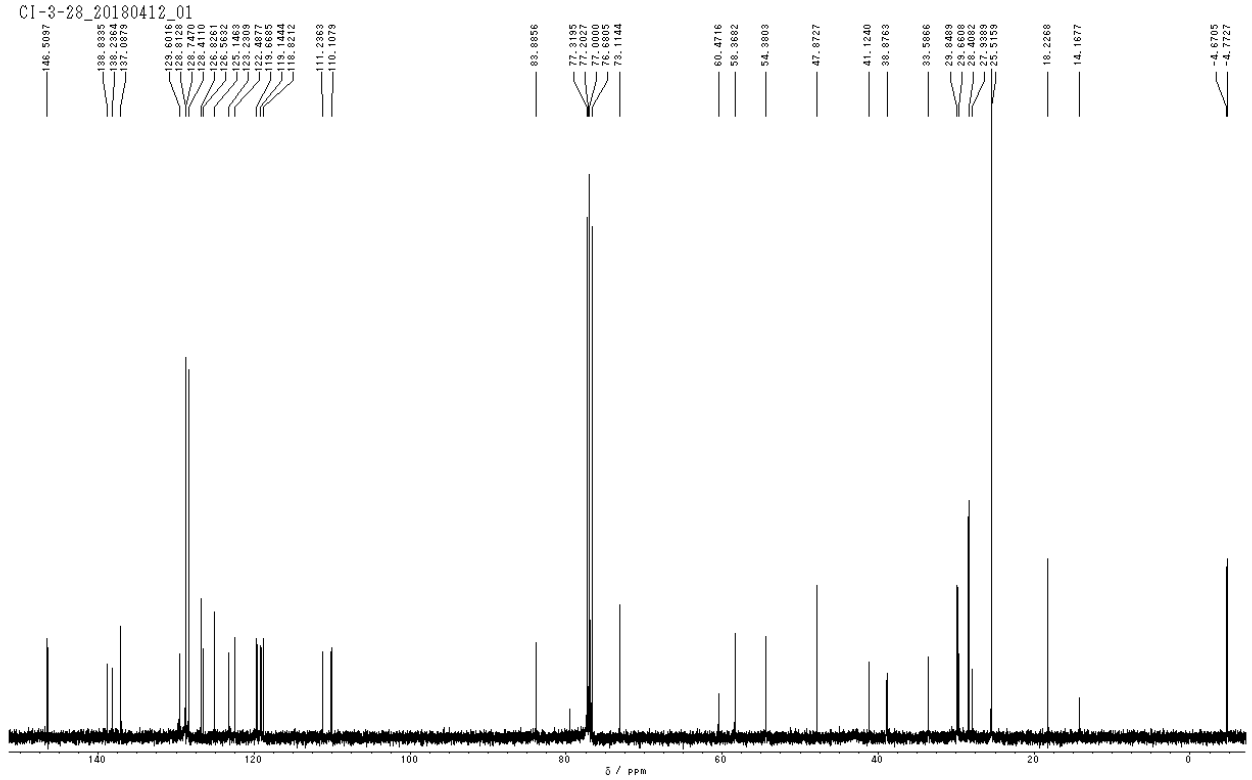

CI-2-6-proton_20170821_01
TBSO
OH
Ph
8c
δ / ppm

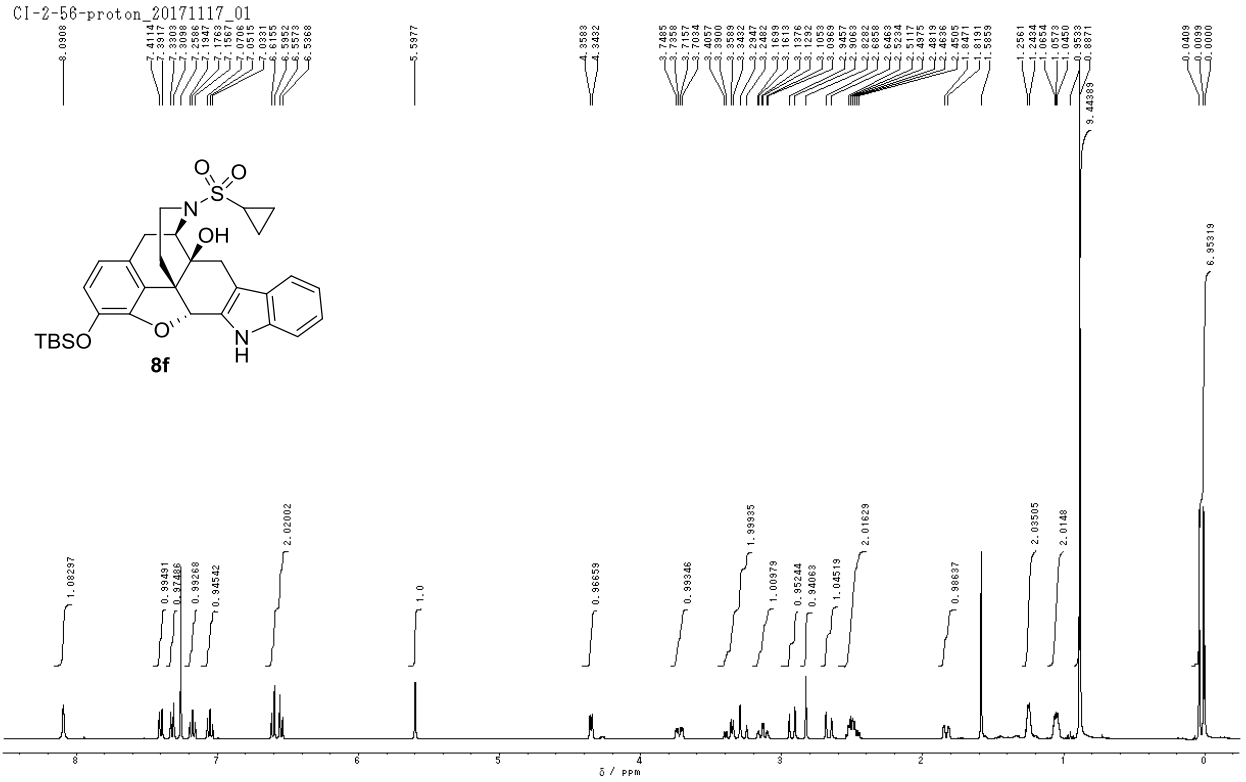

CI-2-39-CARBON_20180205_01
δ / ppm

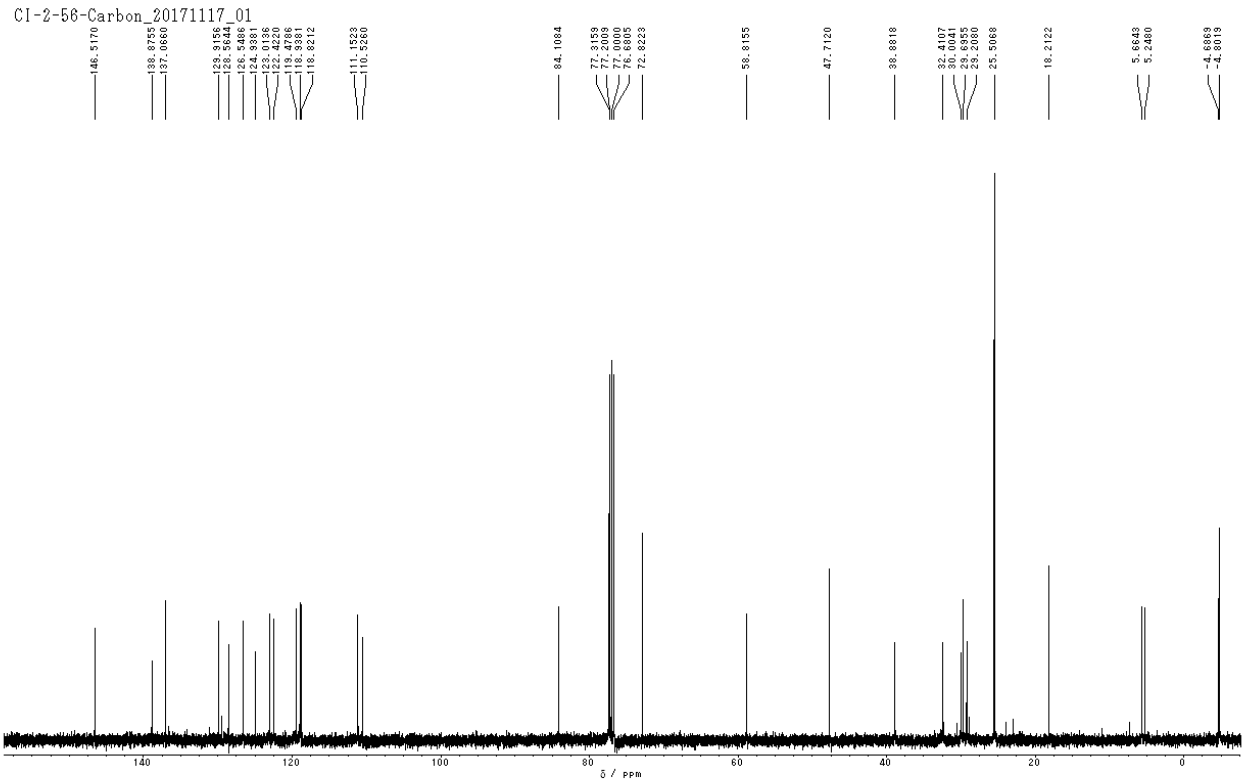

CI-2-45_20171114_01
8d
δ / ppm

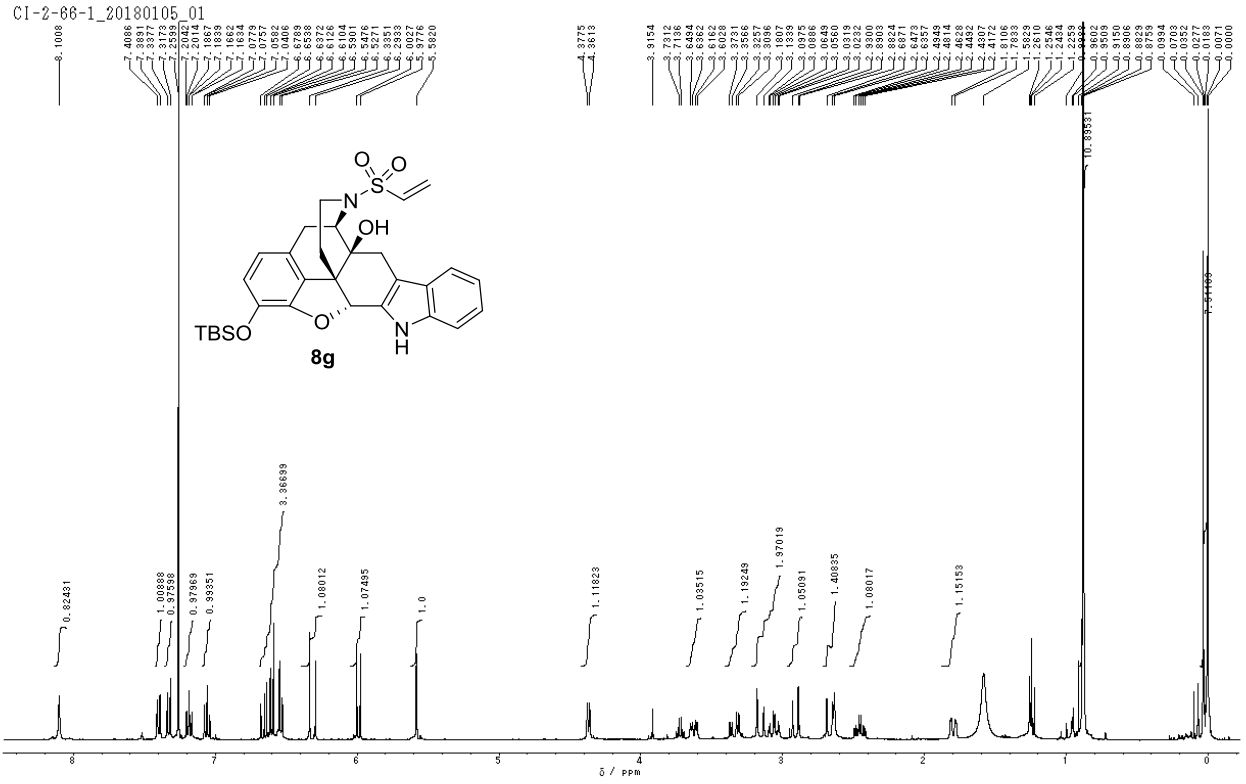

CI-2-45_20171207_01
δ / ppm

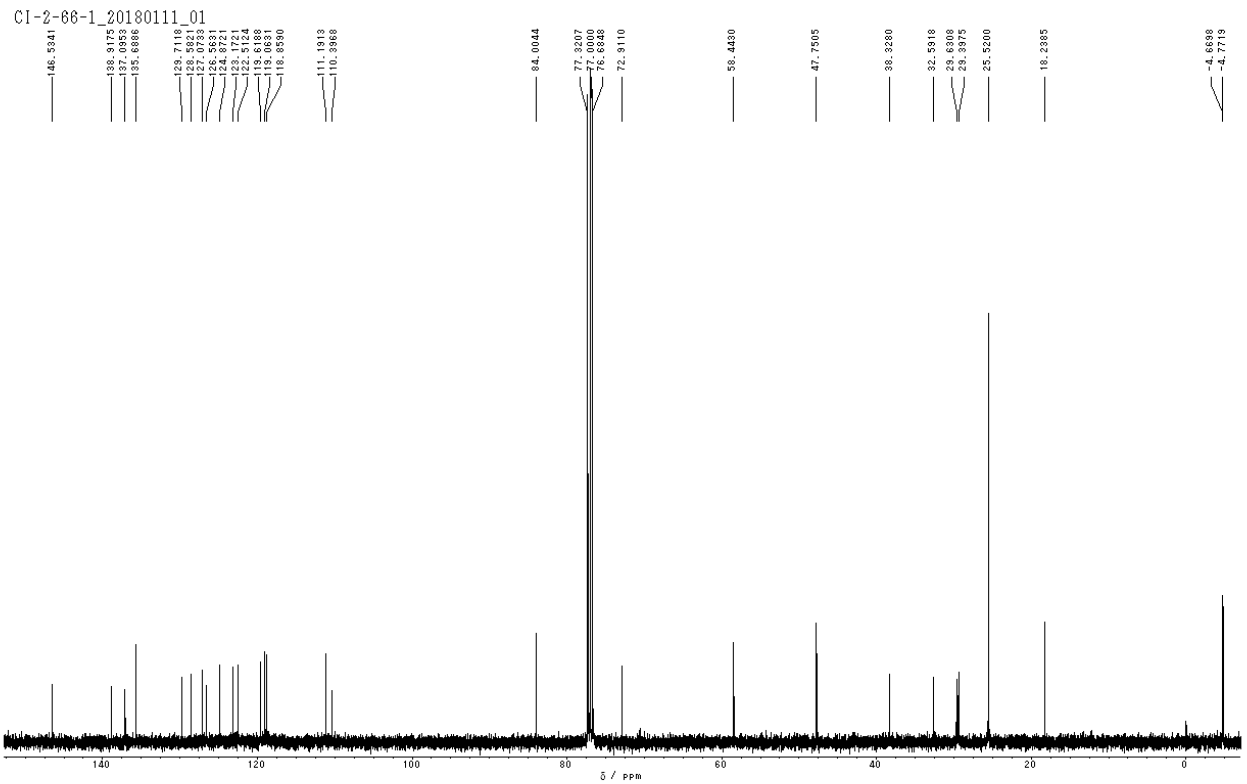

SIS-1-0018-fr6-9_20200620_01
8.1260
7.4062
7.3865
7.3689
7.3177
7.3047
7.2861
7.2670
7.2480
7.2452
7.2301
7.2240
7.2072
7.2074
7.2034
7.1927
7.1898
7.1722
7.1627
7.0631
7.0455
6.6119
6.5914
6.5815
6.5310
5.5544
4.3401
4.3242
3.7709
3.7579
3.7364
3.7240
3.4058
3.3824
3.3826
3.3754
3.3658
3.3520
3.3327
3.1914
3.1763
3.1554
3.1487
3.1302
2.8881
2.8586
2.8586
2.6591
2.5009
2.4804
2.4673
2.4405
2.4007
1.7688
1.5849
0.8806
0.8630
0.8755
0.0704
0.0380
0.0127
0.0000
TBSO
O
O
S
N
Ph
OH
O
N
H
8e
0.9422
0.9682
1.9759
1.0
0.9902
1.0034
2.9538
3.9112
0.9781
0.9584
1.3528
-0.0365
0.9504
6.6717
δ / ppm

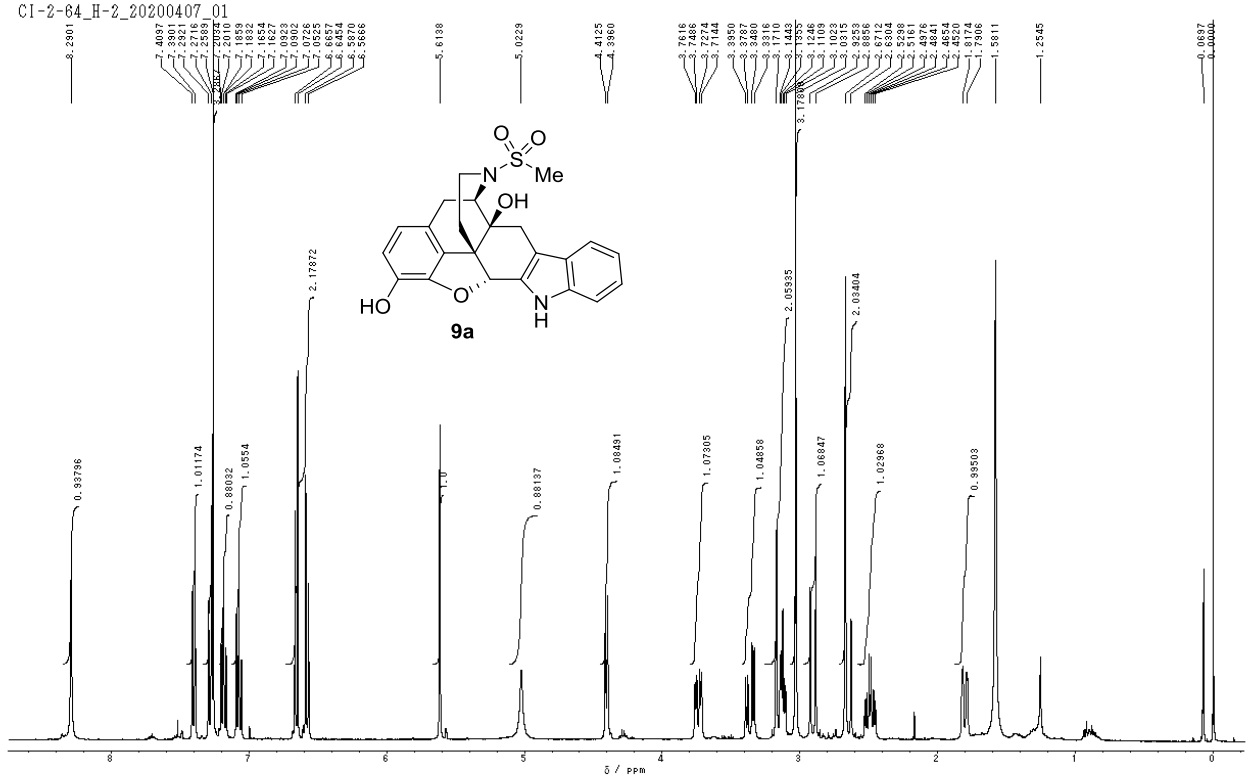

CI-3-28_20180412_01
146.5097
138.8335
138.2854
137.0879
129.6016
128.8128
128.7470
128.4110
126.8281
126.5522
125.1463
123.2309
122.4877
119.6685
119.1444
118.8212
111.2363
110.1079
83.8856
77.3195
77.2027
77.0000
76.6805
73.1144
60.4716
58.3882
54.3803
47.8727
41.1240
38.8763
33.5866
29.8489
29.6608
28.4082
27.9389
25.5153
18.2268
14.1677
-4.6705
-4.7727
δ / ppm

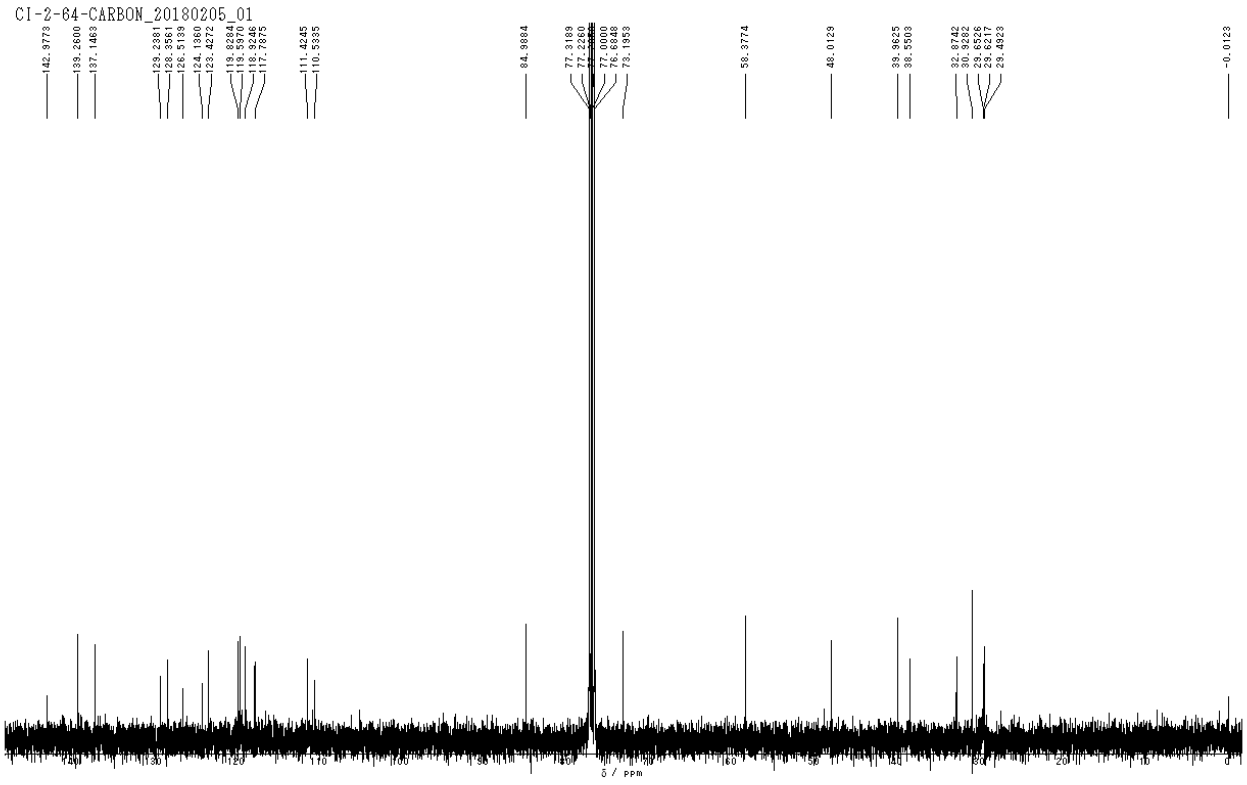

CI-2-56-proton_20171117_01
TBSO
OH
8f
δ / ppm

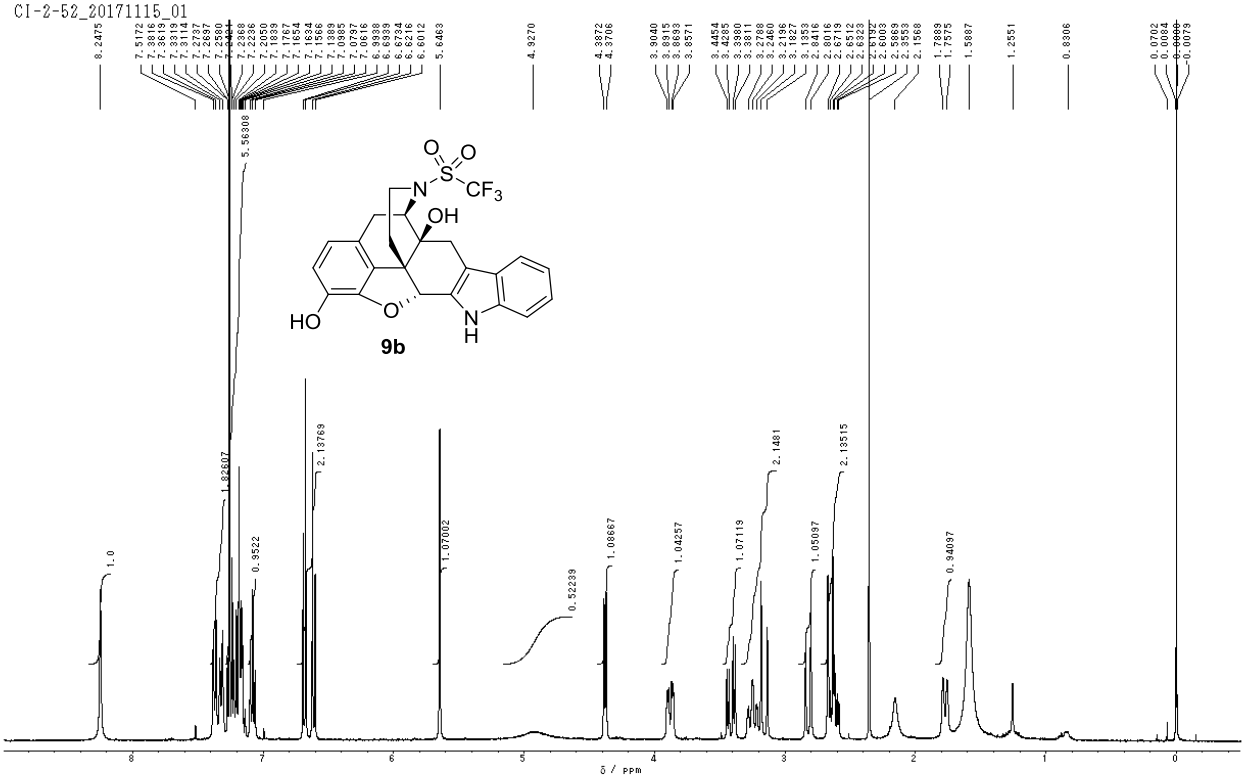

CI-2-56-Carbon_20171117_01
δ / ppm

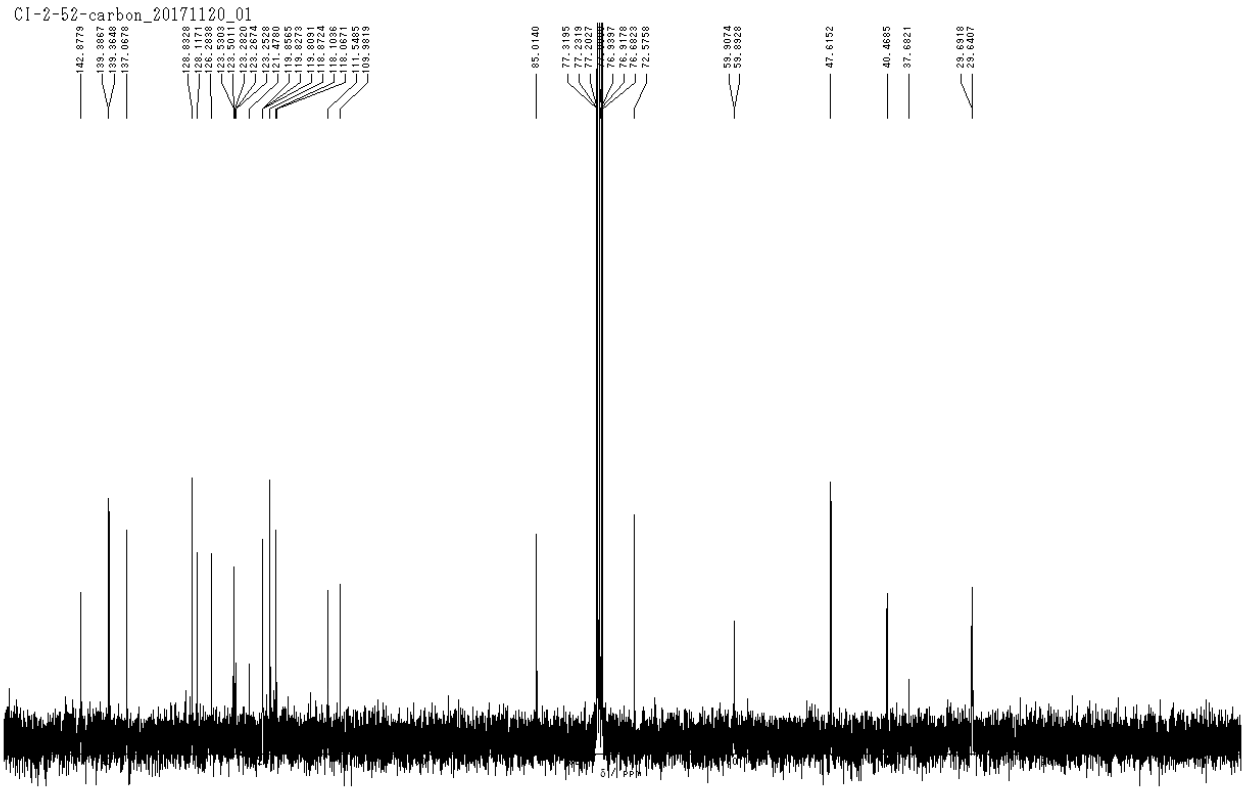

CI-2-66-1_20180105_01
TBSO
OH
8g
δ / ppm

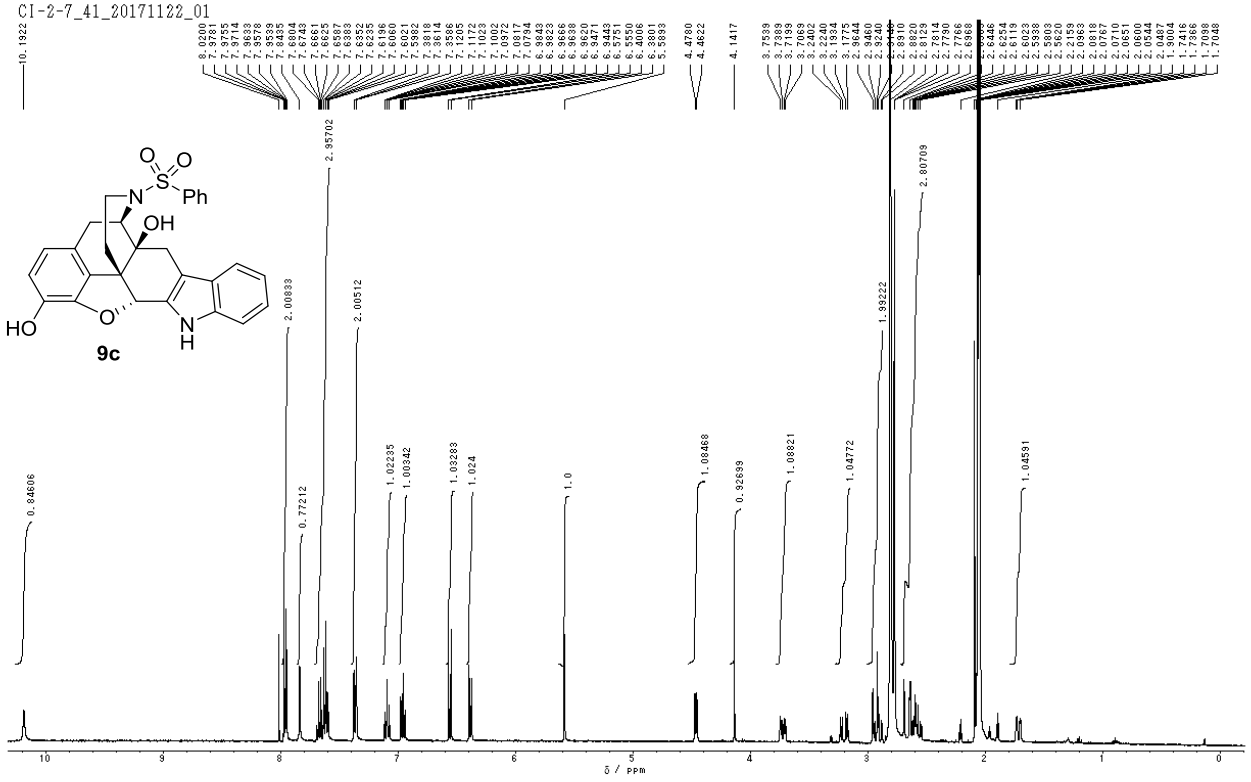

CI-2-66-1_20180111_01
δ / ppm

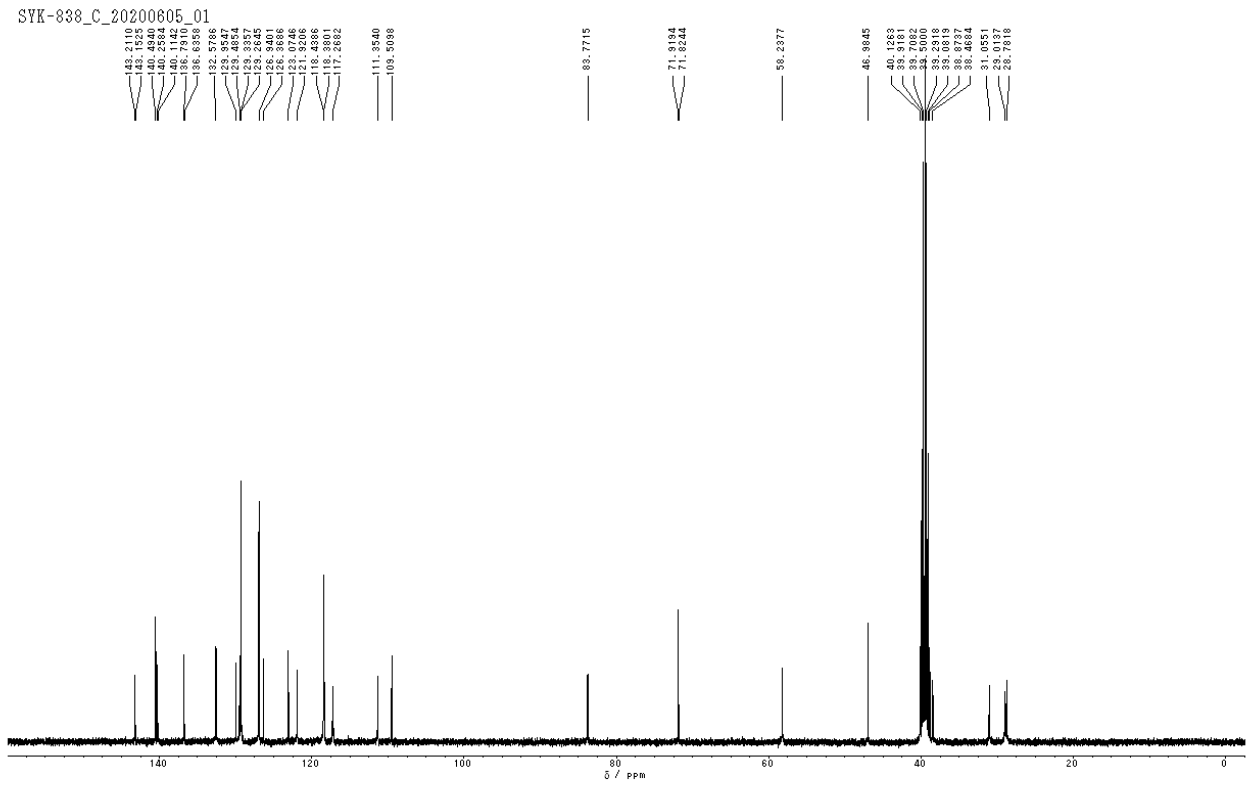

CI-2-64_H-2_20200407_01
9a
δ / ppm

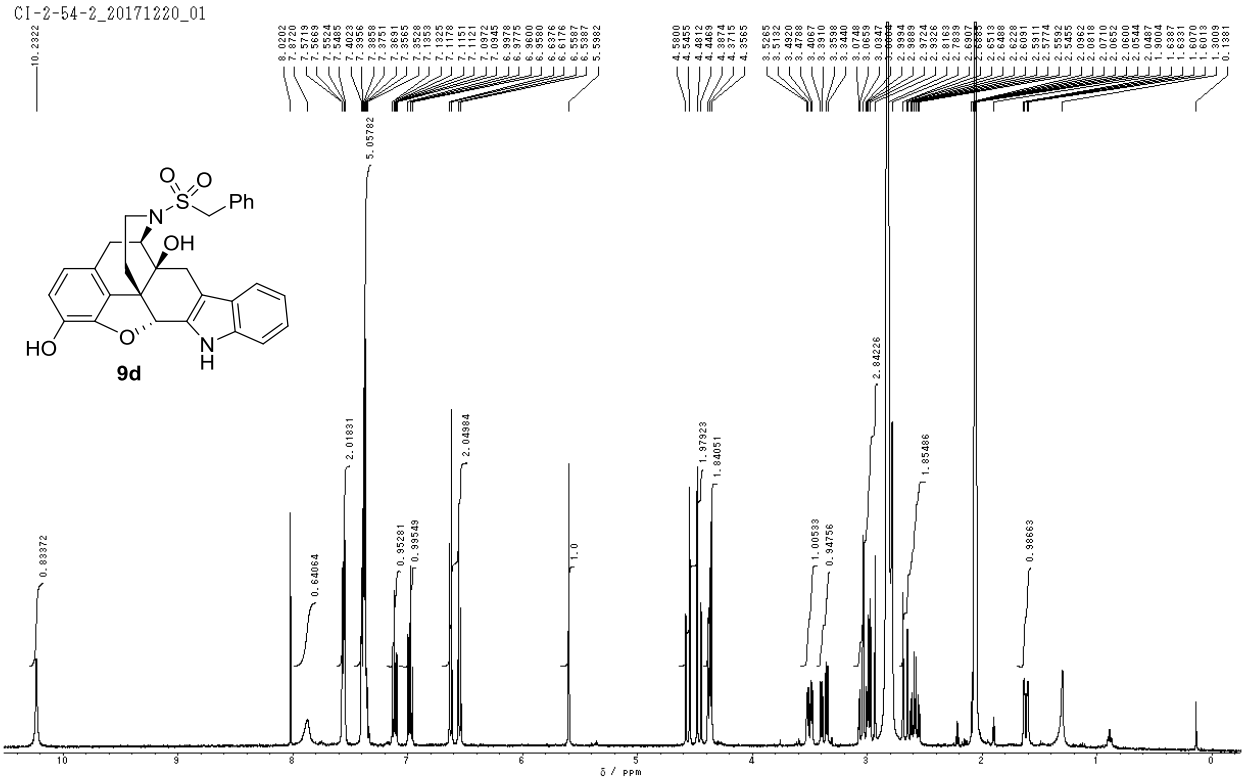

CI-2-64-CARBON_20180205_01
δ / ppm

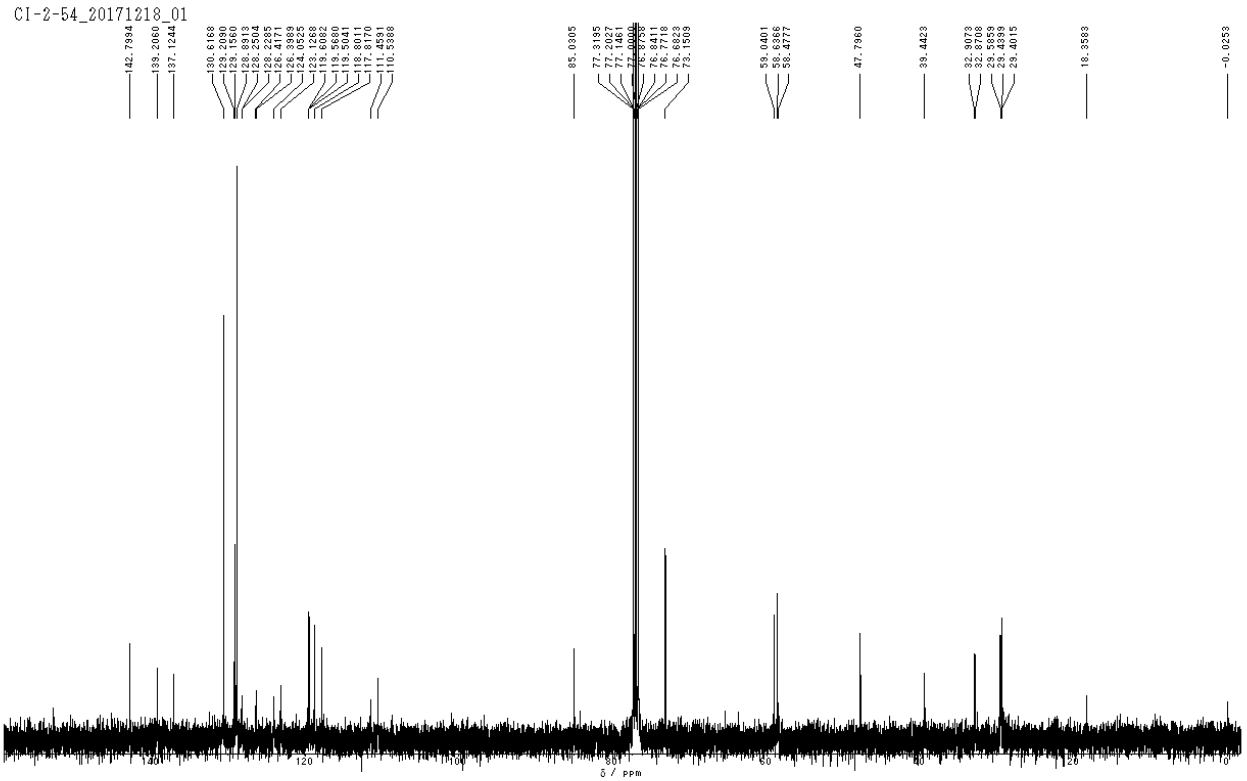

CI-2-52_20171115_01
9b
δ / ppm

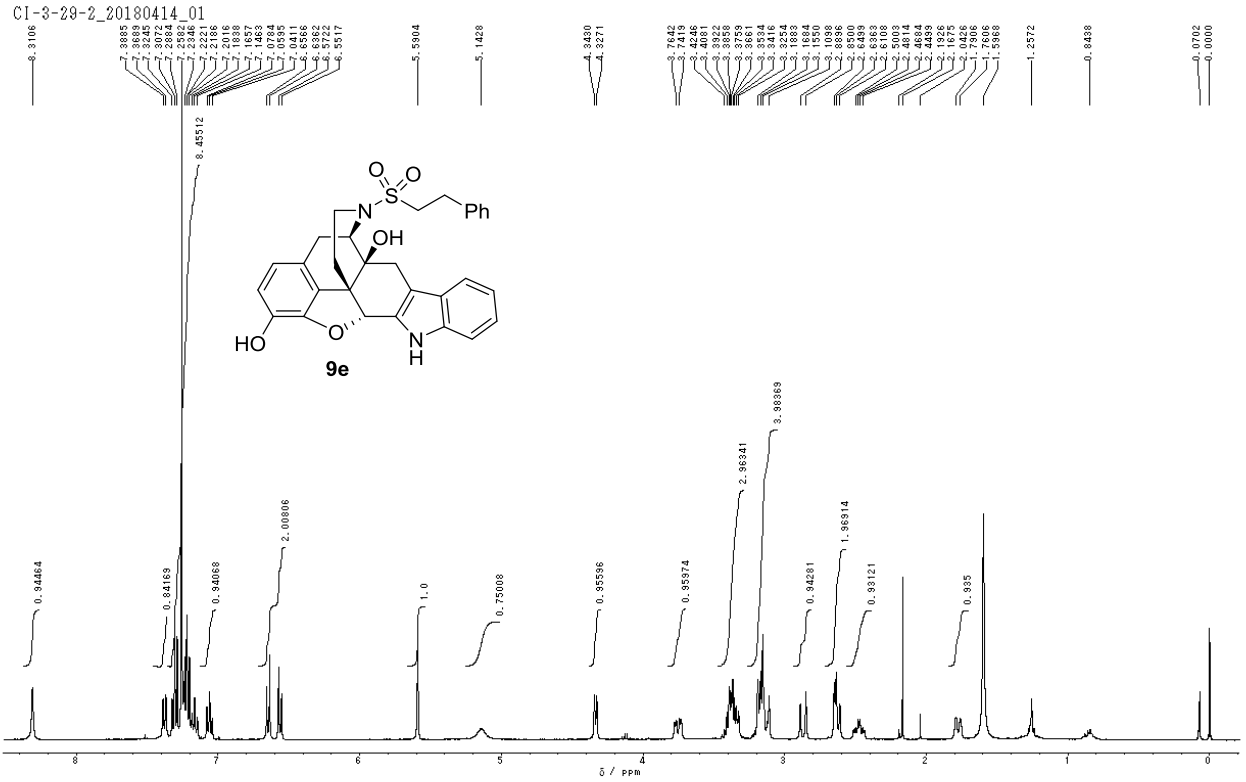

CI-2-52-carbon_20171120_01
δ / ppm

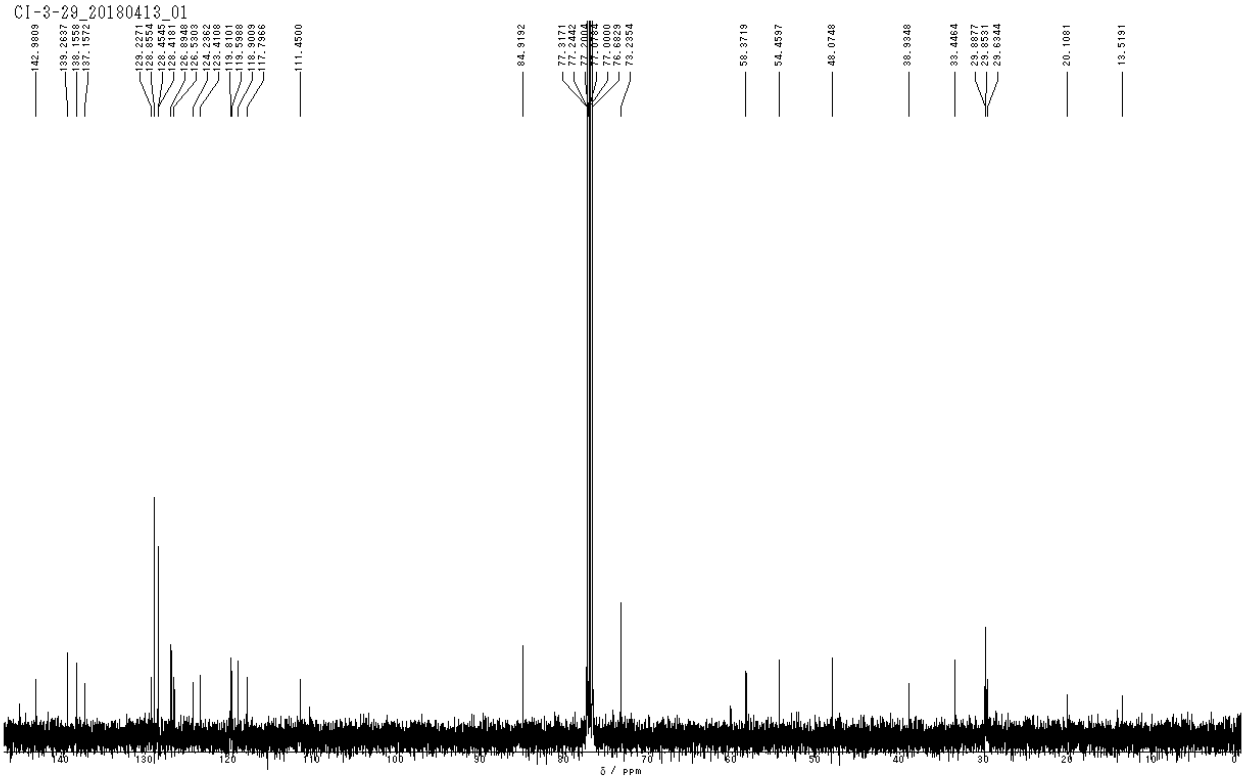

CI-2-7_41_20171122_01
9c
δ / ppm

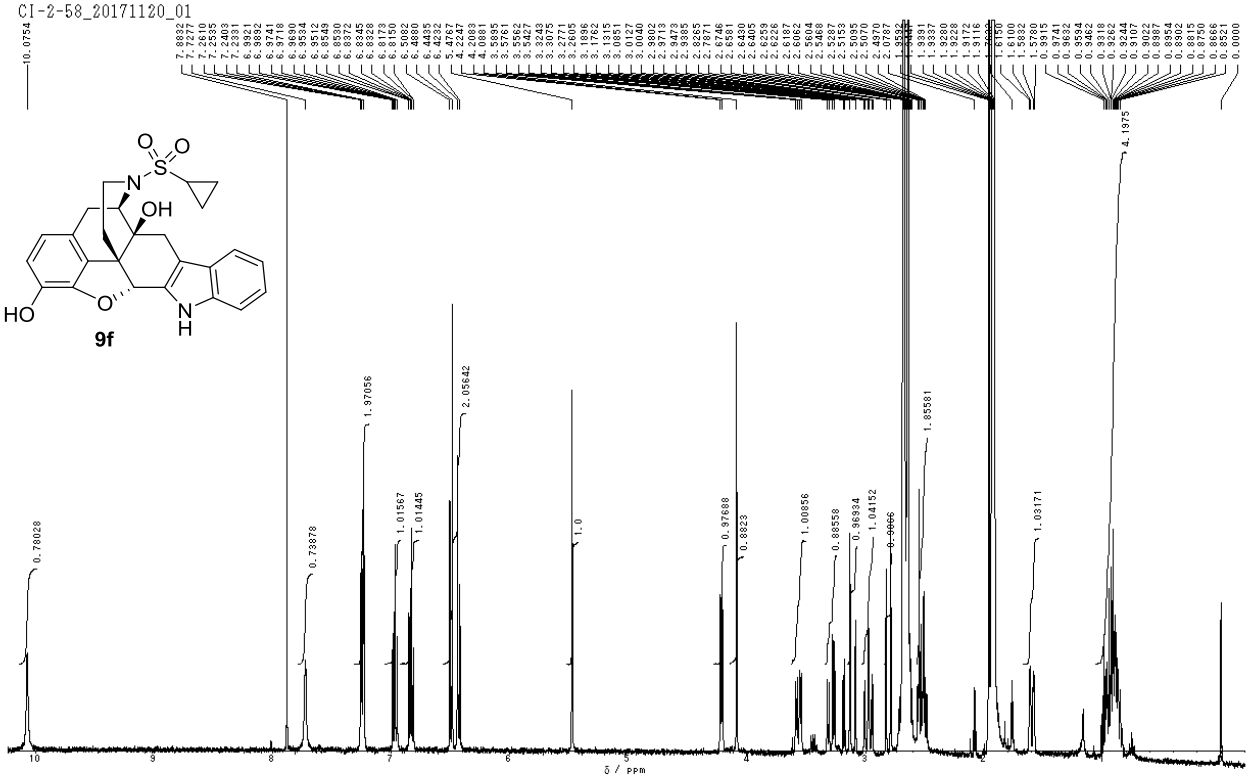

SYK-838_C_20200605_01
δ / ppm

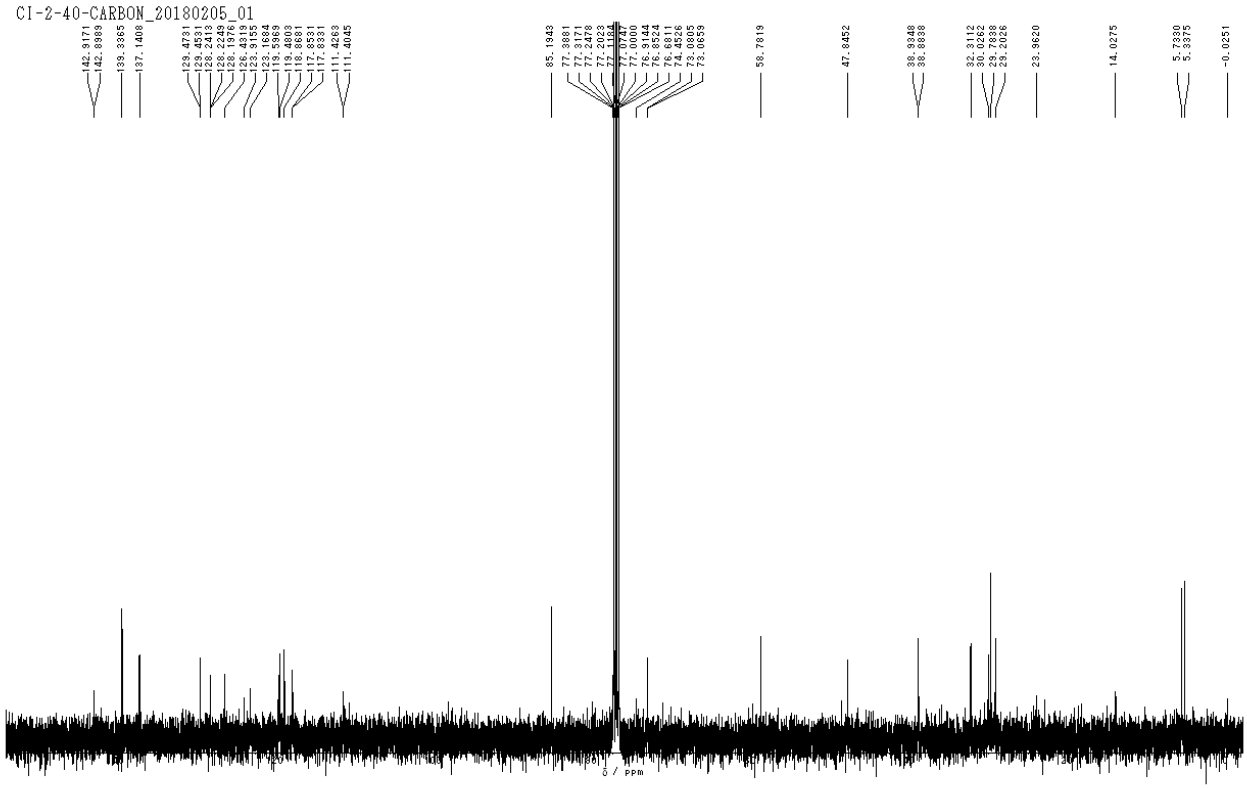

CI-2-54-2_20171220_01
9d
δ / ppm

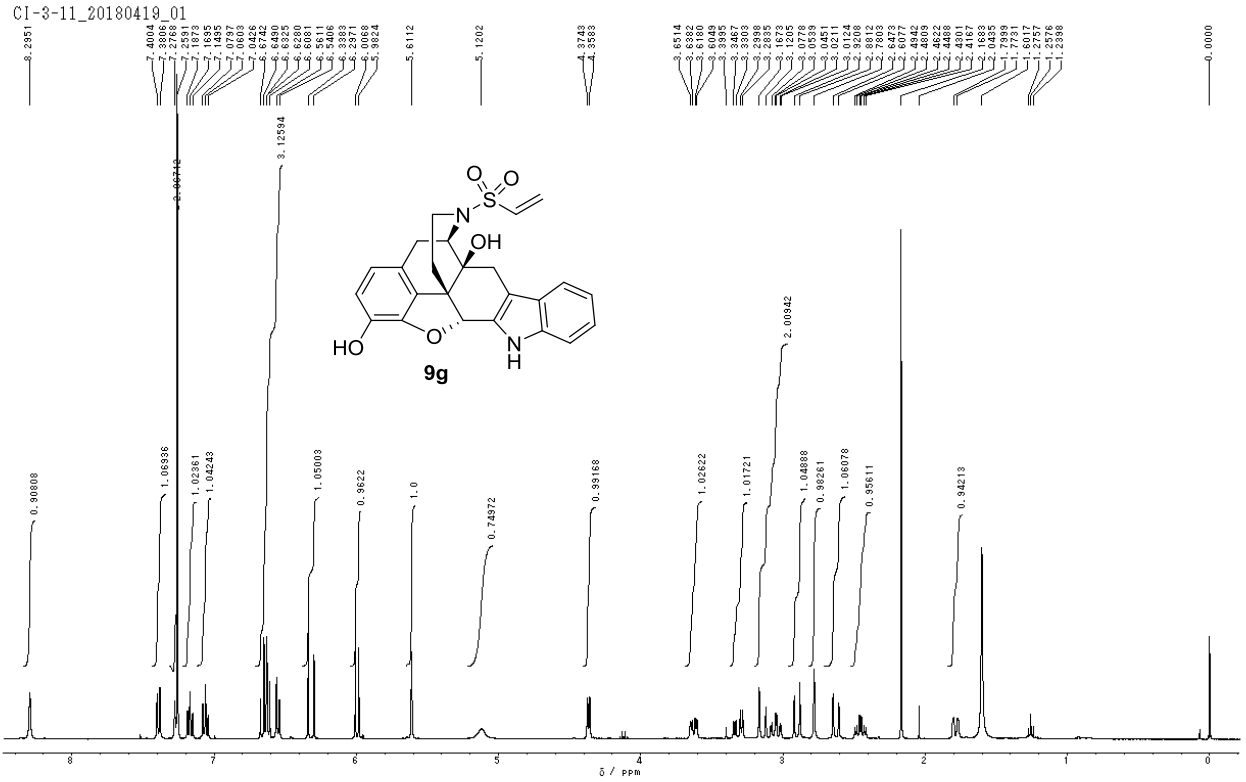

CI-2-54_20171218_01
δ / ppm

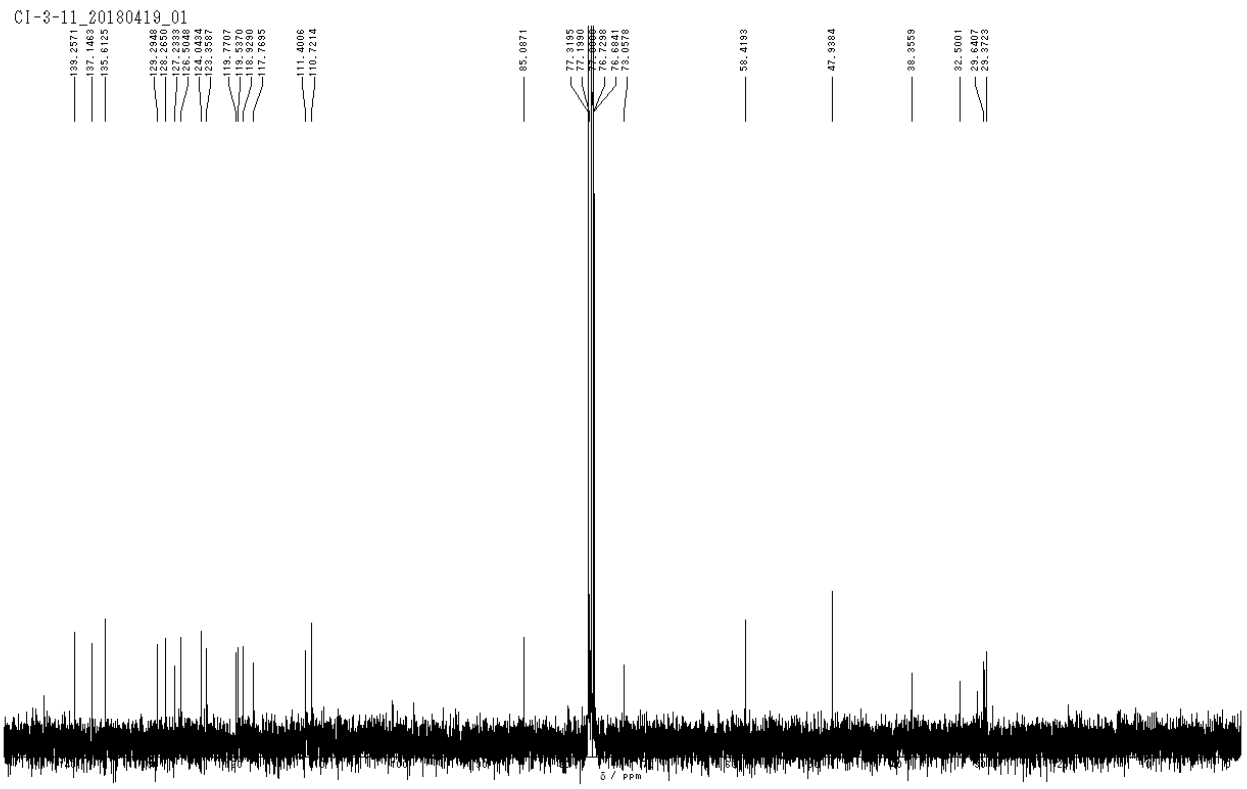

CI-3-29-2_20180414_01
8.45512
0.94464
0.84169
0.84068
2.00806
1.0
0.75008
0.95596
0.95974
2.96341
3.98369
0.94281
1.36914
0.93121
0.935
δ / ppm
9e

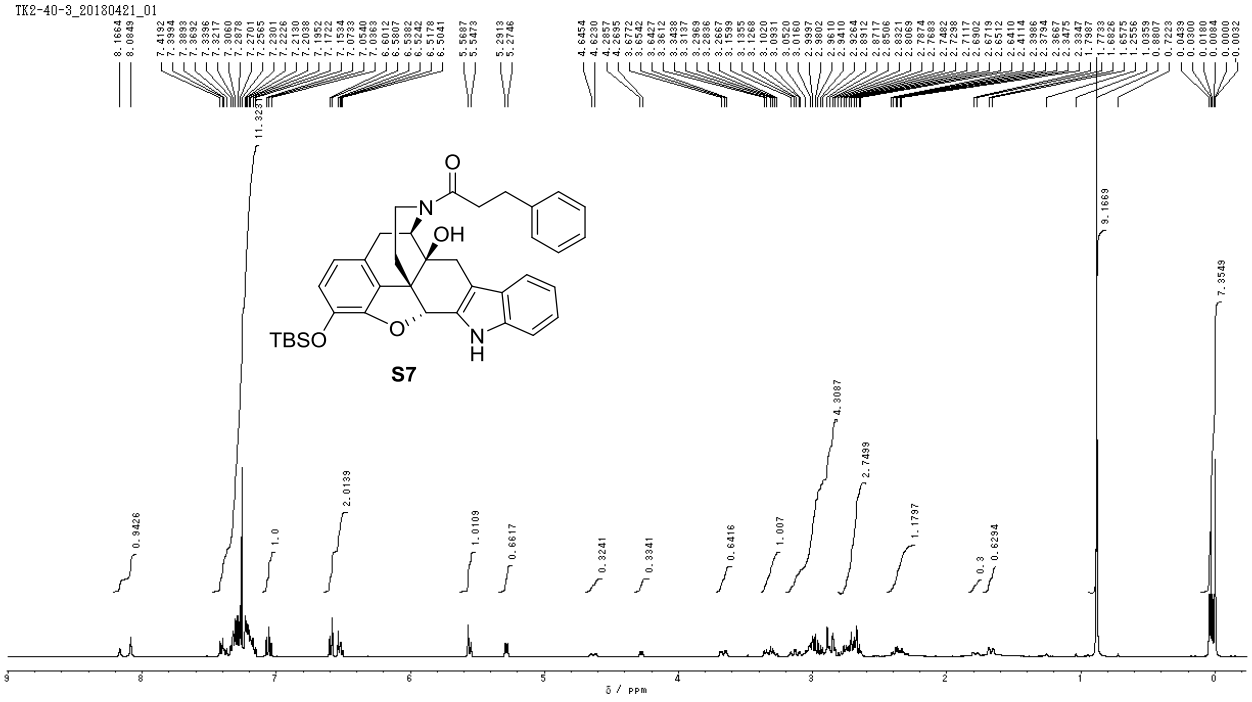

CI-3-29_20180413_01
δ / ppm

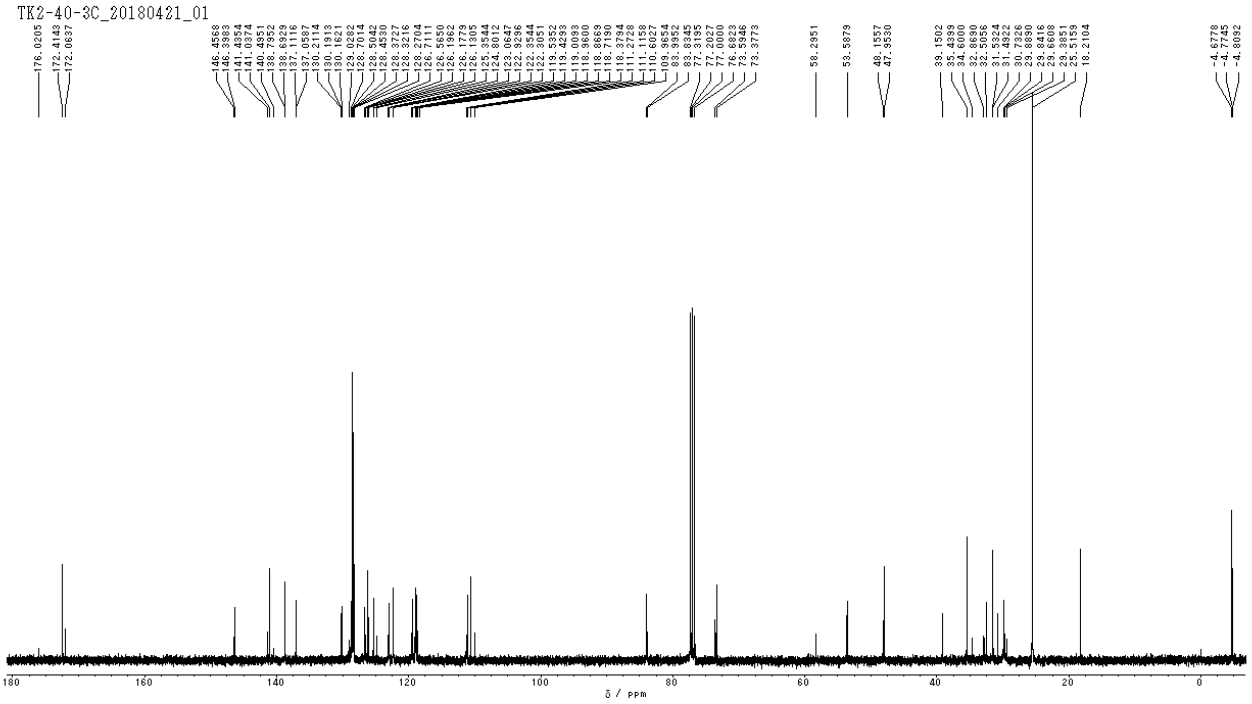

CI-2-58_20171120_01
9f
δ / ppm

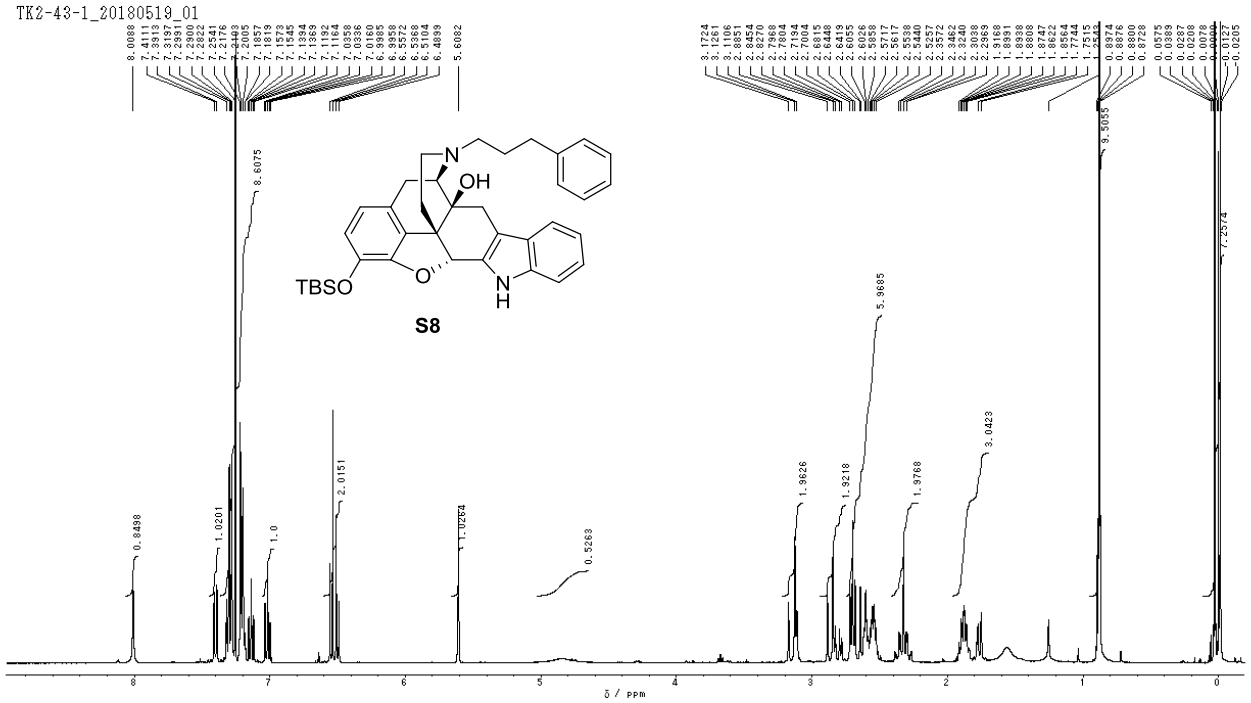

CI-2-40-CARBON_20180205_01
δ / ppm

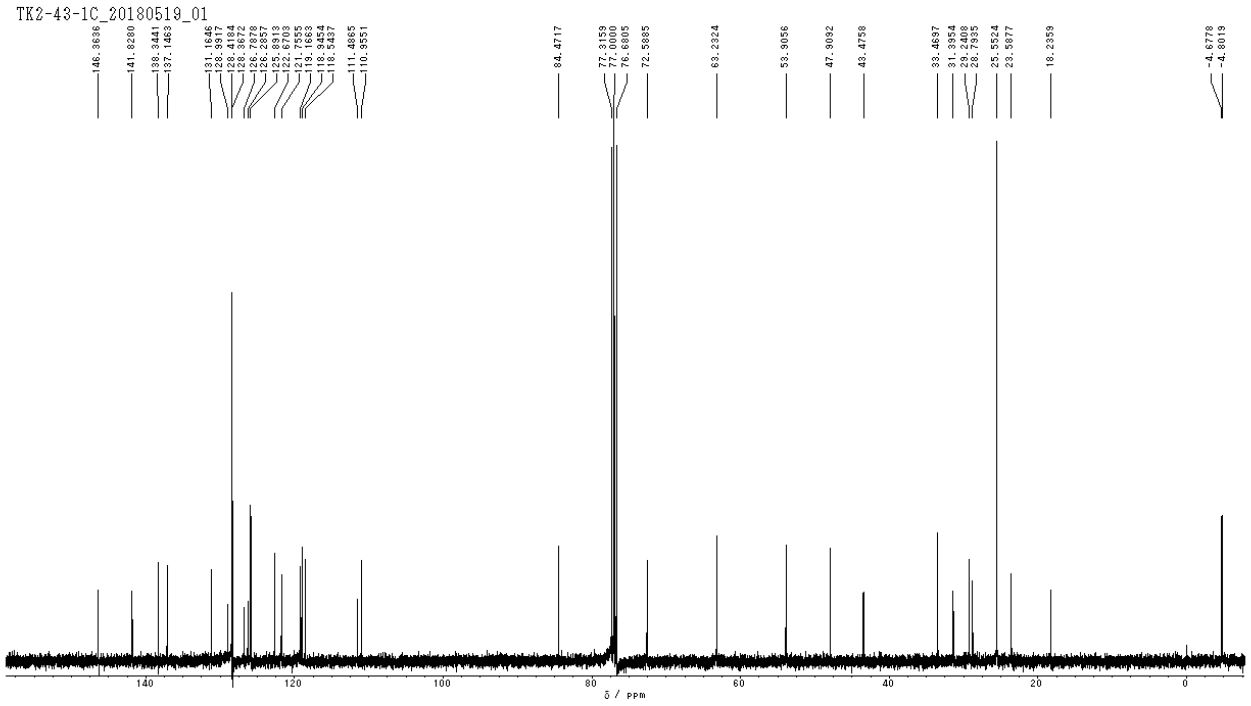

CI-3-11_20180419_01
9g
δ / ppm

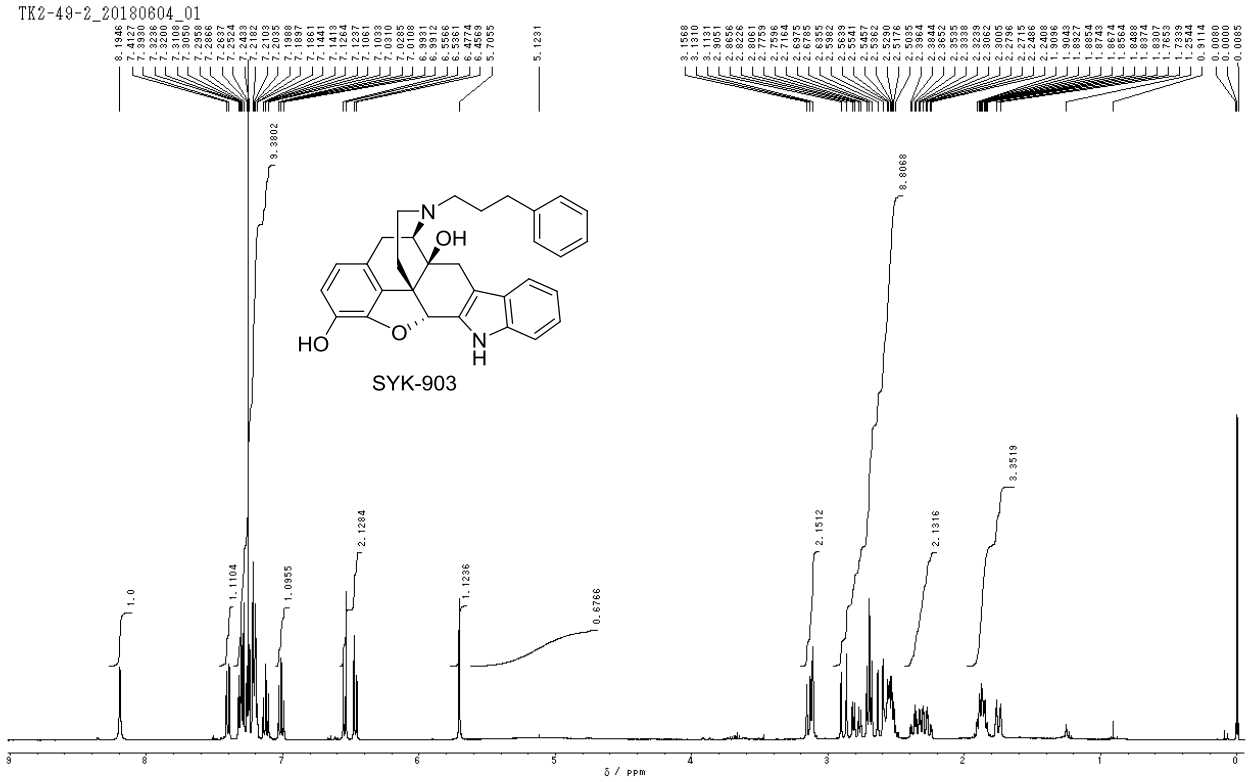

CI-3-11_20180419_01
δ / ppm

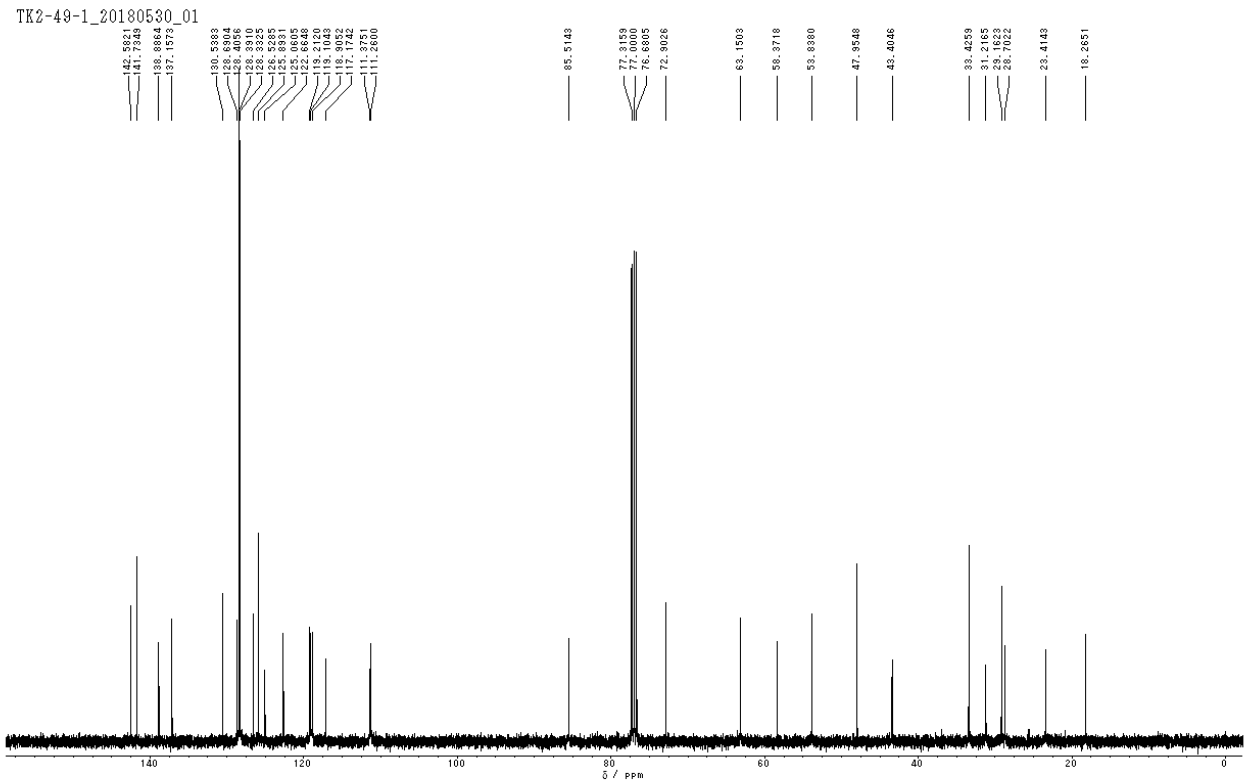

TK2-40-3_20180421_01
TBSO
OH
N
O
H
S7
δ / ppm


TK2-40-3C_20180421_01
δ / ppm


TK2-43-1_20180519_01
TBSO
OH
N
O
N
H
S8
δ / ppm


TK2-43-1C_20180519_01
δ / ppm


TK2-49-2_20180604_01
SYK-903
δ / ppm


TK2-49-1_20180530_01
δ / ppm

6. References

1. Portoghese, P. S.; Larson, D. L.; Sultana, M.; Takemori, A. E. Opioid Agonist and Antagonist Activities of Morphindoles Related to Naltrindole. *J. Med. Chem.* **1992**, *35*, 4325−4329.
2. McLamore, S.; Ullrich, T.; Rothman, R. B.; Xu, H.; Dersch, C.; Coop, A.; Davis, P.; Porreca, F.; Jacobson, A. E.; Rice, K. C. Effect of *N*-Alkyl and *N*-Alkenyl Substituents in Noroxymorphindole, 17-Substituted-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinans, on Opioid Receptor Affinity, Selectivity, and Efficacy. *J. Med. Chem.* **2001**, *44*, 1471−1474.
3. Hirayama, S.; Iwai, T.; Higashi, E.; Nakamura, M.; Iwamatsu, C.; Itoh, K.; Nemoto, T.; Tanabe, M.; Fujii, H. Discovery of δ opioid receptor full inverse agonists and their effects on restraint stress induced cognitive impairment in mice. *ACS Chem. Neurosci.* **2019**, *10*, 2237−2242.
4. Cheng, C.-Y.; Hsin, L.-W.; Lin, Y.-P.; Tao, P.-L.; Jong, T.-T. *N*-Cubylmethyl Substituted Morphinoids as Novel Narcotic Antagonists. *Bioorg. Med. Chem.* **1996**, *4*, 73−80.
5. Nagase, H.; Imaide, S.; Tomatsu, M.; Nemoto, T.; Nakajima, M.; Nakao, K.; Mochizuki, H.; Fujii, H. Investigation of Beckett-Casy model 2: Synthesis of novel 15−16 nornaltrexone derivatives and their pharmacology. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3726−3729.
6. Nagase, H.; Yamamoto, N.; Yata, M.; Ohrui, S.; Okada, T.; Saitoh, T.; Kutsumura, N.; Nagumo, Y.; Irukayama-Tomobe, Y.; Ishikawa, Y.; et al. Design and Synthesis of Potent and Highly Selective Orexin 1 Receptor Antagonists with a Morphinan Skeleton and Their Pharmacologies. *J. Med. Chem.* **2017**, *60*, 1018−1040.