Supporting Information

Asymmetric Total Syntheses of Colchicine, β-Lumicolchicine and Allocolchicinoid NCME

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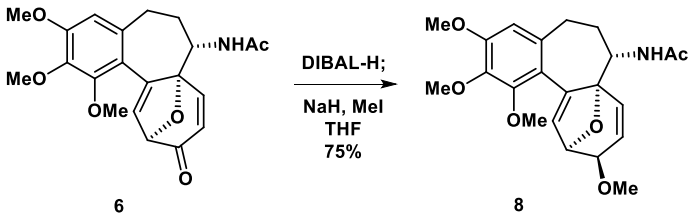
I. General Information

Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere under anhydrous conditions and all reagents were purchased from commercial suppliers without further purification. Solvent purification was conducted according to *Purification of Laboratory Chemicals* (Peerrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by Yantai Chemicals (China) using UV light as visualizing agent, an ethanolic solution of phosphomolybdic acid, or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200-300 mesh) supplied by Tsingtao Haiyang Chemicals (China). Preparative thin layer chromatography (PTLC) separations were carried out 0.50 mm Yantai (China) silica gel plates. NMR spectra were recorded on Bruker AV500, Bruker ARX400, and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ 7.26 ppm ^{1}H NMR, δ 77.00 ^{13}C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet.

High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Infrared spectra were recorded on a Shimadzu IR Prestige 21, using thin films of the sample on KBr plates. Optical rotations were measured with a Rudolph autopol I automatic polarimeter using 10 cm glass cells with a sodium 589 nm filter.

II. Experimental Procedures

Synthesis of 8



6 8

To the solution of **6**[1] (1.0 g, 2.6 mmol) in THF (30 mL) at -78 °C was added DIBAL-H (1M, 3.0 mL), and the reaction solution was stirred at this temperature for 1 h. H_2O (0.05 mL) was added and stirred at 0 °C for 30 minutes. NaH (60%, 150 mg, 3.9 mmol) was added, followed by MeI (0.74 g, 5.2 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction solution was poured into saturated aqueous NH_4Cl (50 mL) and diluted with ether (150 mL). After separation, the aqueous phase was re-extracted with ether (2 x 50 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography on silica gel (hexane/ethyl acetate = 1/2) afforded **8** (0.78 g, 75% yield) as a white solid.

R_f = 0.3 (hexane/ethyl acetate = 1/2);

$[\alpha]_D^{20}$ = 142.0 (c = 0.33, $CHCl_3$);

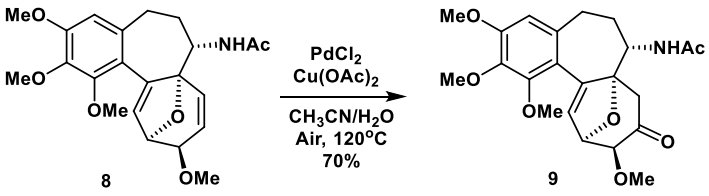
IR (film) λ_{max} 3248, 2940, 1630, 1558, 1472, 1099, 891, 729 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.08 (dd, *J* = 9.9, 1.2 Hz, 1H), 5.97 (d, *J* = 1.9 Hz, 1H), 5.86 (d, *J* = 8.5 Hz, 1H), 5.58 – 5.52 (m, 1H), 5.34 – 5.26 (m, 1H), 4.20 – 4.14 (m, 1H), 4.08 – 3.97 (m, 1H), 3.86 – 3.82 (m, 6H), 3.74 (s, 3H), 3.46 (s, 3H), 2.95 – 2.86 (m, 1H), 2.83 – 2.74 (m, 1H), 2.05 – 1.97 (m, 1H), 1.95 (s, 3H), 1.85 – 1.78 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 153.3, 151.2, 148.6, 141.0, 137.6, 134.4, 126.1, 125.8, 119.2, 109.4, 87.8, 80.9, 72.0, 62.3, 61.0, 57.2, 56.1, 50.2, 31.6, 26.4, 23.5;

HRMS (ESI) calcd for $C_{22}H_{28}O_6N$ $[M+H]^+$: 402.1911; found: 402.1906.

Synthesis 9



8 9

$PdCl_2$ (4.5 mg, 0.025 mmol) and $Cu(OAc)_2$ (10 mg, 0.05 mmol) were charged in a resealable 20-mL vial under air. A mixture of MeCN (2.7 mL) and water (0.3 mL) was added. After the addition of the corresponding substrate **8** (20 mg, 0.05 mmol), the homogenous reaction mixture was stirred for 16 h at 120 °C under O_2 atmosphere. The crude reaction mixture was then diluted with brine (10 mL) and ether (10 mL), the phases were separated and the aqueous phase was further extracted with ether (5 mL x 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified directly via column chromatography on silica gel (hexane/ethyl acetate = 1/3) to give **9** (15 mg, 70% yield) as a white solid.

R_f = 0.2 (hexane/ethyl acetate = 1/2);

[α]$_D^{26}$ = 86.7 (c = 0.5, $CHCl_3$);

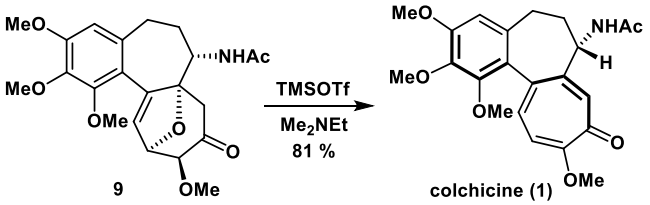
IR (film) λ_{max} 2932, 1651, 1504, 1198, 1308, 799 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.19 (d, *J* = 1.8 Hz, 1H), 5.91 (d, *J* = 9.2 Hz, 1H), 5.13 (dd, *J* = 4.9, 1.9 Hz, 1H), 4.02 – 3.96 (m, 1H), 3.96 (d, *J* = 4.9 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 3.02 – 2.96 (m, 1H), 2.89 – 2.82 (m, 1H), 2.64 (d, *J* = 16.0 Hz, 1H), 2.27 (d, *J* = 16.0 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.03 (s, 3H), 1.83 – 1.76 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.19, 169.54, 153.61, 151.23, 142.11, 140.43, 134.24, 128.85, 117.36, 108.62, 89.79, 84.78, 78.80, 61.29, 60.68, 59.89, 55.97, 49.99, 47.25, 31.70, 27.06, 23.47;

HRMS (ESI) calcd for $C_{22}H_{28}O_7N$ $[M+H]^+$: 418.1860; found: 418.1852.

Synthesis of colchicine (1)



Trimethylsilyl trifluoromethanesulfonate (0.06 mL) was added dropwise at 0 °C to a solution of **9** (20 mg, 0.048 mmol) and *N*,*N*-dimethylethylamine (0.1 mL) in DCM (5 mL). After the reaction mixture was stirred at room temperature for 12 h, saturated aqueous $NaHCO_3$ (5 mL) was added. After separation, the aqueous phase was further extracted with DCM (5 mL x 2). The combined organic phases were washed with saturated NH_4Cl (10 mL), brine (5 mL) and dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by chromatography (DCM/MeOH = 9/1) to afford **1** (16 mg, 81%) as a white solid.

R_f = 0.3 (DCM/MeOH = 9/1);

$[\alpha]_D^{20}$ = -150 (c = 0.33, $CHCl_3$);

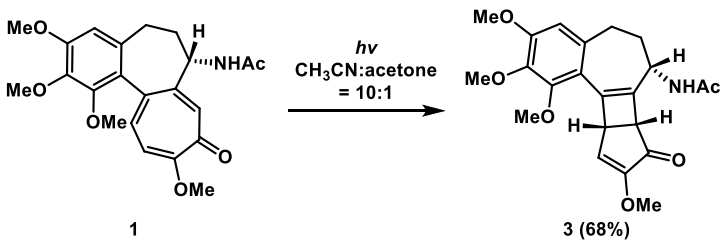
IR (film) 3315, 3240, 2935, 1732, 1614, 1487, 1249, 1138, 1020 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.4 Hz, 1H), 7.68 (s, 1H), 7.37 (d, *J* = 10.7 Hz, 1H), 6.92 (d, *J* = 10.9 Hz, 1H), 6.53 (s, 1H), 4.74 – 4.57 (m, 1H), 4.02 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.65 (s, 3H), 2.52 (m, 1H), 2.41 – 2.32 (m, 2H), 2.02 – 1.97 (m, 1H), 1.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 170.2, 164.0, 153.5, 153.0, 151.1, 141.5, 137.2, 135.8, 134.3, 130.3, 125.5, 113.2, 107.2, 61.6, 61.3, 56.4, 56.1, 52.8, 36.3, 29.8, 22.7;

HRMS-ESI calcd for $C_{22}H_{26}O_6N$ $[M+H]^+$: 400.1755, found 400.1747.

Synthesis of β-lumicolchicine (3)



1 **3 (68%)**

Colchicine **1** (10 mg, 0.025 mmol) were dissolved in a mixture solution of acetonitrile and acetone (10:1, 8 mL) and irradiated for 25 minutes with a 125-W high-pressure mercury arc lamp surrounded by a Pyrex water jacket. The solvent was evaporated under reduced pressure, and the crude product was purified by a flash column chromatography on silica gel (DCM/MeOH = 16/1) to give β-Lumicolchicine **3** (6.8 mg, 68%) as white solids.

R_f = 0.51 (DCM/MeOH = 8/1).

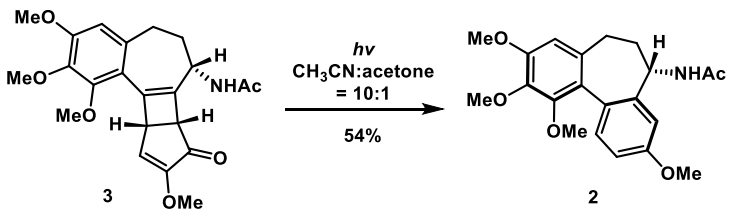
$[\alpha]_D^{26}$ = + 249 (c = 1.0, $CHCl_3$) {lit. [α] + 304 (c = 0.5, $CHCl_3$)};[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, *J* = 2.9 Hz, 1H), 6.46 (s, 1H), 6.00 (d, *J* = 6.9 Hz, 1H), 4.80 (d, *J* = 4.6 Hz, 1H), 4.09 (d, *J* = 2.5 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.68 (s, 3H), 3.60 (s, 1H), 2.74 (dd, *J* = 15.3, 9.1 Hz, 1H), 2.56 (dd, *J* = 15.3, 9.5 Hz, 1H), 2.04 (s, 3H), 1.98 – 1.83 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.81, 170.27, 157.77, 153.09, 151.72, 145.10, 140.29, 138.81, 137.37, 128.80, 117.73, 109.17, 61.38, 60.83, 56.83, 55.93, 51.44, 51.35, 43.17, 32.54, 31.31, 23.50;

HRMS (ESI) Calcd for $C_{22}H_{25}NO_6Na$ [M+Na]$^+$: 422.1574; Found: 422.1573.

Synthesis of NCME (2)



β-Lumicolchicine **3** (10 mg, 0.024 mmol) were dissolved in a mixture solution of acetonitrile and acetone (10:1, 8 mL) and irradiated for 20 minutes with a 125-W high-pressure mercury arc lamp surrounded by a Pyrex water jacket. The solvent was evaporated under reduced pressure, and the crude product was purified by a flash column chromatography on silica gel (DCM/MeOH = 16/1) to give **2** (4.8 mg) in 54% yield as a white solid. Anal. data are consistent with those described in reference.[3]

R_f = 0.53 (DCM/MeOH = 8/1);

$[\alpha]_D^{26}$ = - 30 (c = 1.0, $CHCl_3$) {lit. [α] - 65 (c = 0.0056, $CHCl_3$)};[3]

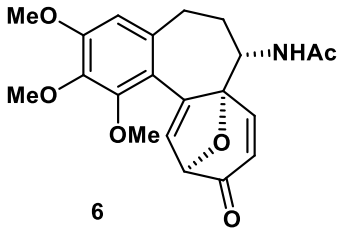
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.95 – 6.84 (m, 2H), 6.78 (s, 1H), 4.53 (dt, *J* = 12.0, 7.9 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.47 (s, 3H), 2.48 (d, *J* = 5.3 Hz, 1H), 2.15 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.89 (s, 3H), 1.85 (d, *J* = 5.4 Hz, 1H);

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.84, 158.83, 152.56, 150.79, 142.28, 141.04, 135.21, 131.04, 126.62, 124.77, 111.21, 109.91, 108.57, 61.00, 60.95, 56.30, 55.44, 48.57, 38.97, 30.60, 23.13;

HRMS (ESI) Calcd for $C_{21}H_{26}NO_5$ [M+H]$^+$: 372.1805; Found: 372.1824.

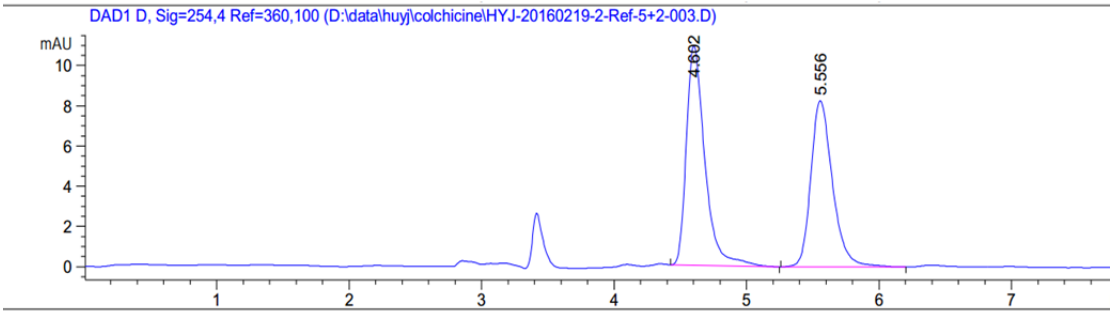
III. HPLC Analysis of *ee* Value

(a)

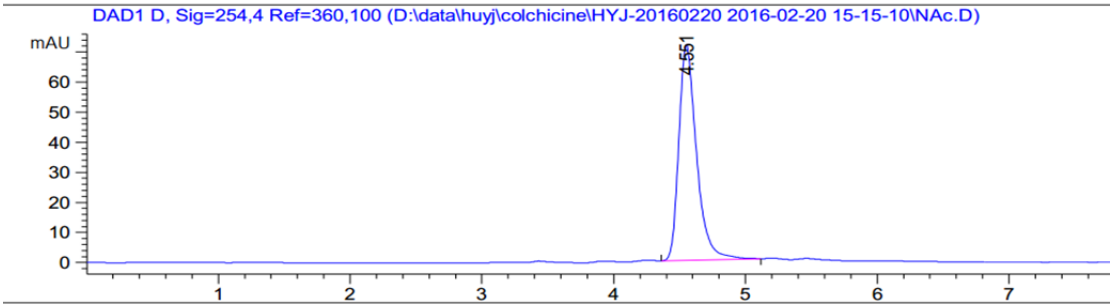


6

HPLC analysis: Daicel Chiralpak AD-H column; hexane/*i*-propanol = 75:25, 1 mL/min, λ = 254 nm; t_R(major) = 4.6 min, t_R(minor) = 5.6 min. > 99% *ee*.

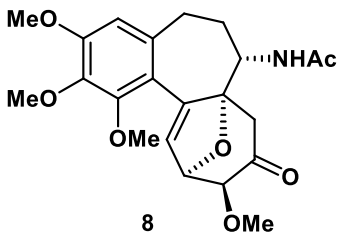


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.602	BB	0.1456	106.28229	10.91946	53.0118
2	5.556	BB	0.1726	94.20567	8.28594	46.9882



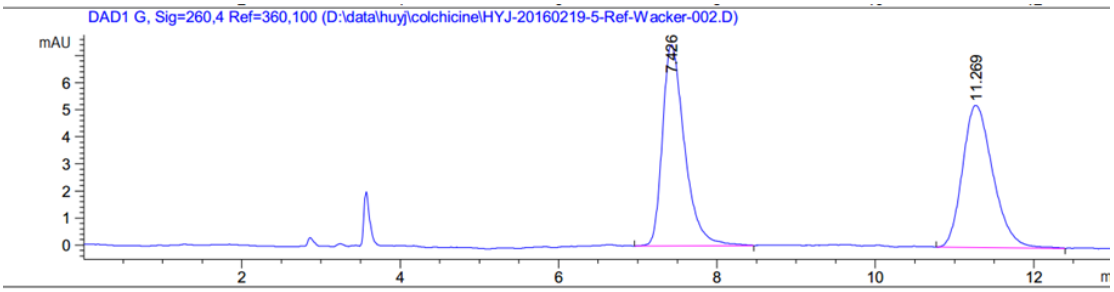
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.551	BB	0.1406	667.80676	71.76360	100.0000

(b)

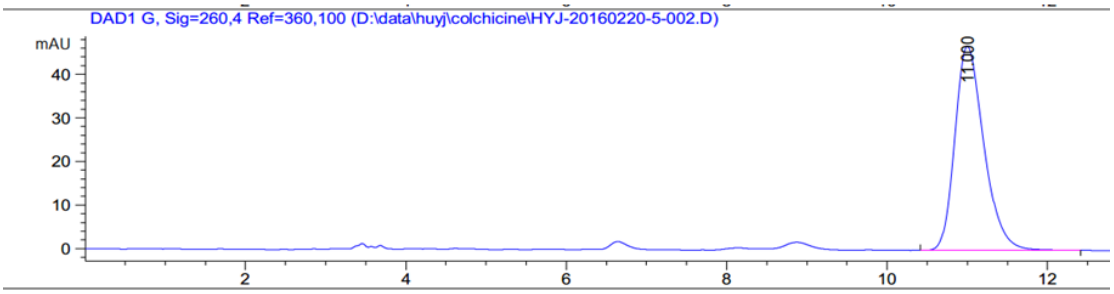


8

HPLC analysis: Daicel Chiralpak AD-H column; hexane/*i*-propanol = 80:20, 1 mL/min, λ = 260 nm; t_R(minor) = 7.4 min, t_R(major) = 11.3 min. > 99% *ee*.

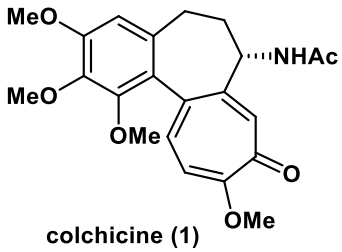


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.426	BB	0.2945	144.26382	7.42947	50.7805
2	11.269	BB	0.4066	139.82912	5.25265	49.2195



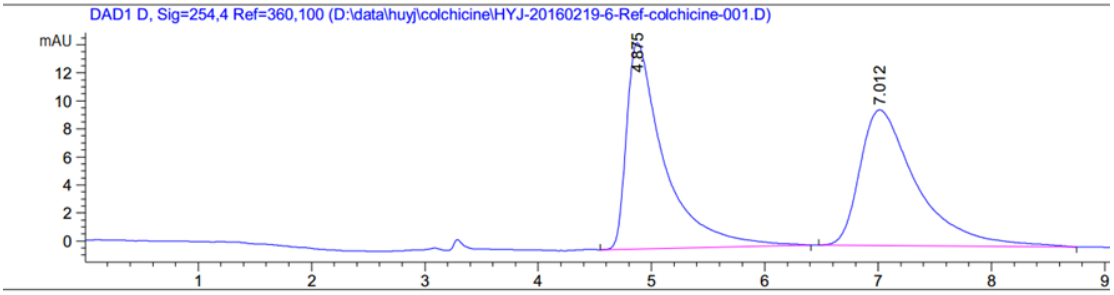
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.000	BB	0.3891	1185.07092	46.84715	100.0000

(c)

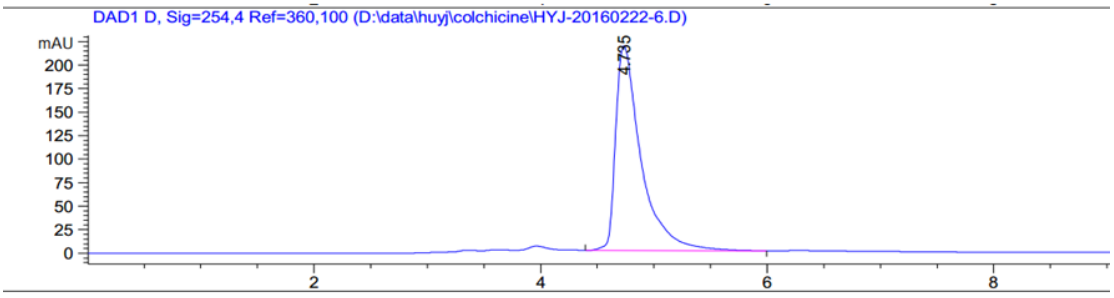


colchicine (1)

HPLC analysis: Daicel Chiralpak AD-H column; hexane/*i*-propanol = 70:30, 1 mL/min, λ = 254 nm; t_R(major) = 4.9 min, t_R(major) = 7.0 min. > 99% *ee*.



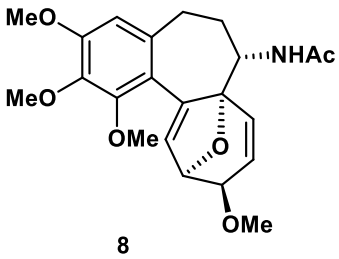
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.875	BB	0.3311	339.20428	14.70766	50.2097
2	7.012	BB	0.5098	336.37128	9.66964	49.7903



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.735	BB	0.2301	3401.63550	217.92906	100.0000

IV. X-ray Crystallographic DataX-Ray data for 8:

Crystal data and structure refinement for **8** (CCDC 1563364).



8

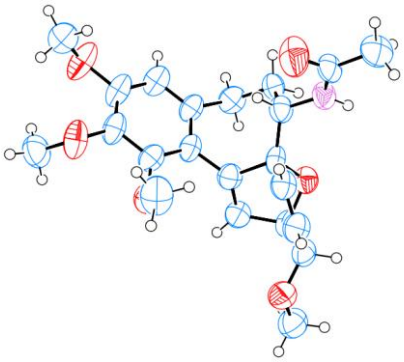
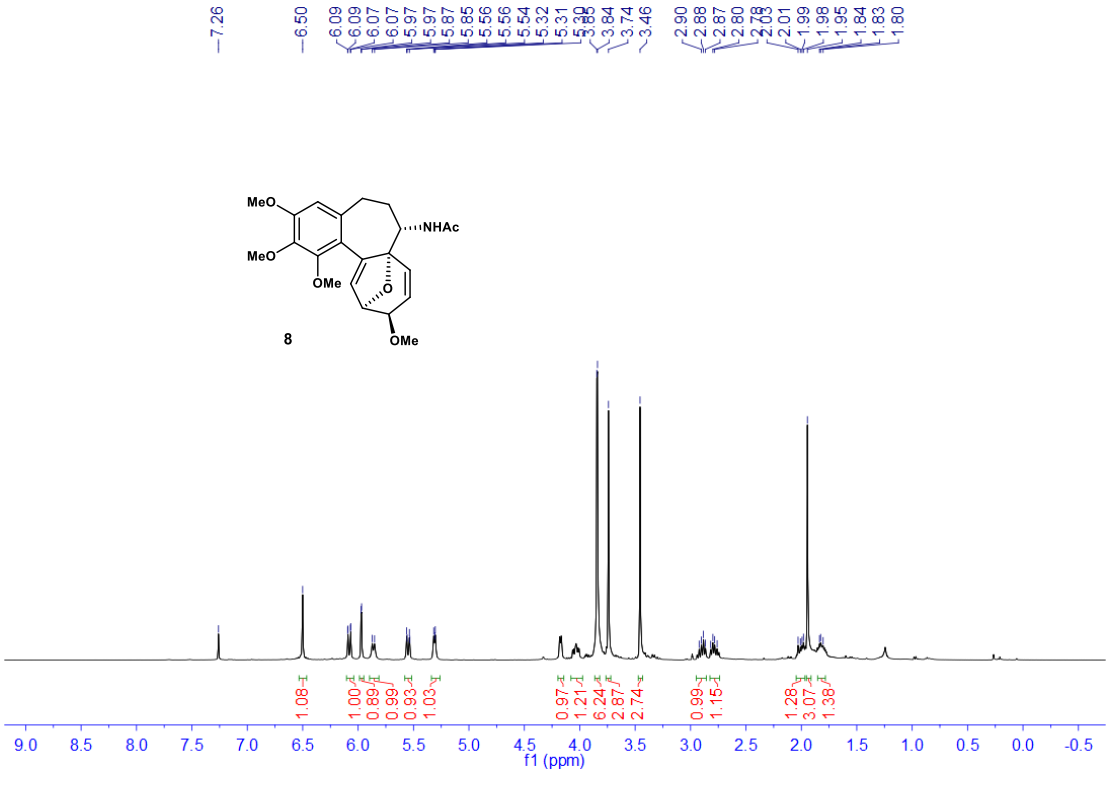
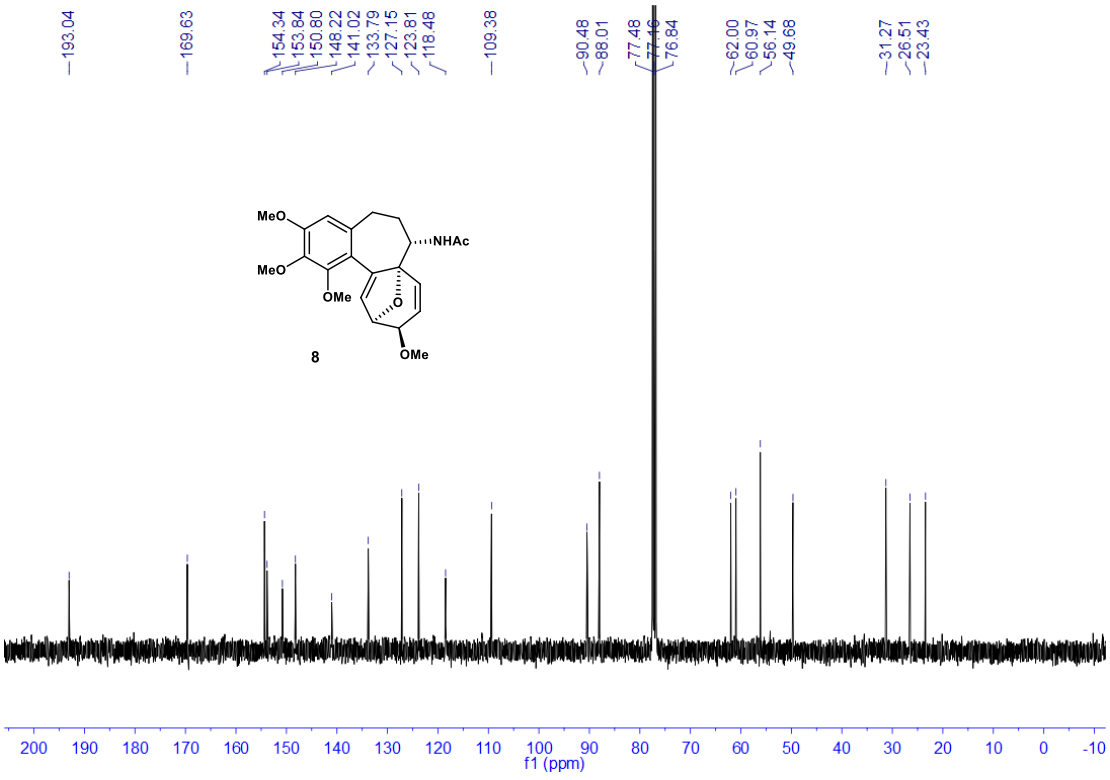


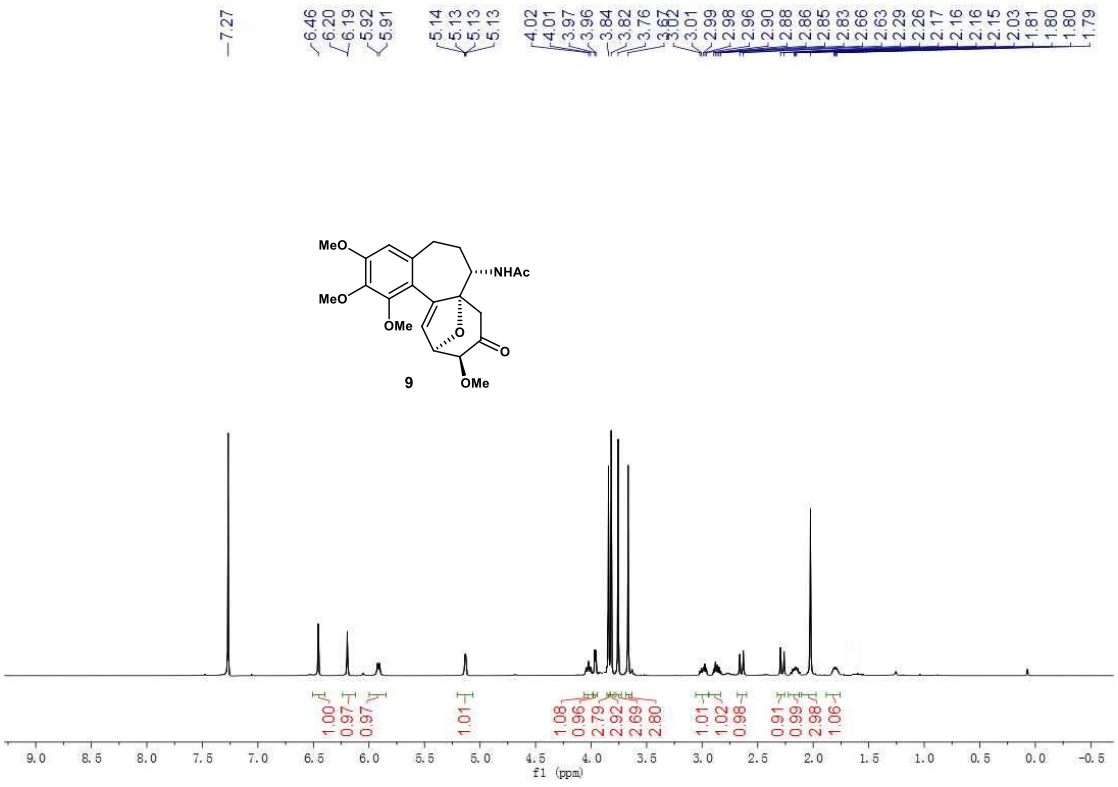
Table 1 Crystal data and structure refinement for **8**.

Identification code	20170719
Empirical formula	$C_{22}H_{27}NO_6$
Formula weight	401.44
Temperature/K	293
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.467(3)
b/Å	9.477(5)
c/Å	14.485(5)
α 4.	90
β 0.	97.593(8)
γ 7.	90
Volume/Å^3	1016.1(8)
Z	2
ρ $_{calc}$g/cm^3	1.312
μ .31^{-1}	0.786
F(000)	428.0
Crystal size/mm^3	0.2 tal size/mm
Radiation	CuK α uKiationize/mm
2uKiationize/mmladeructure ref	6.156 to 135.818
Index ranges	-8 ex ranges.818aderucture refinement
Reflections collected	5523
Independent reflections	2732 [R_{int} = 0.0916, R_{sigma} = 0.0753]
Data/restraints/parameters	2732/1/268
Goodness-of-fit on F^2	1.120
Final R indexes [I>=2eters	R_1 = 0.0654, wR_2 = 0.1660
Final R indexes [all data]	R_1 = 0.0873, wR_2 = 0.2212
Largest diff. peak/hole / e Å^{-3}	0.25/-0.29
Flack parameter	1.2(4)

V. ^{1}H and ^{13}C NMR Spectra






7.27
6.46
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6.19
5.92
5.91
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5.13
5.13
5.13
4.02
4.01
3.97
3.96
3.84
3.82
3.76
3.62
3.01
2.99
2.98
2.96
2.90
2.88
2.86
2.85
2.83
2.66
2.63
2.29
2.26
2.17
2.16
2.16
2.15
2.03
1.81
1.80
1.80
1.79
MeO
MeO
OMe
NHAc
O
O
OMe
9
1.00
0.97
0.97
1.01
1.08
0.96
2.79
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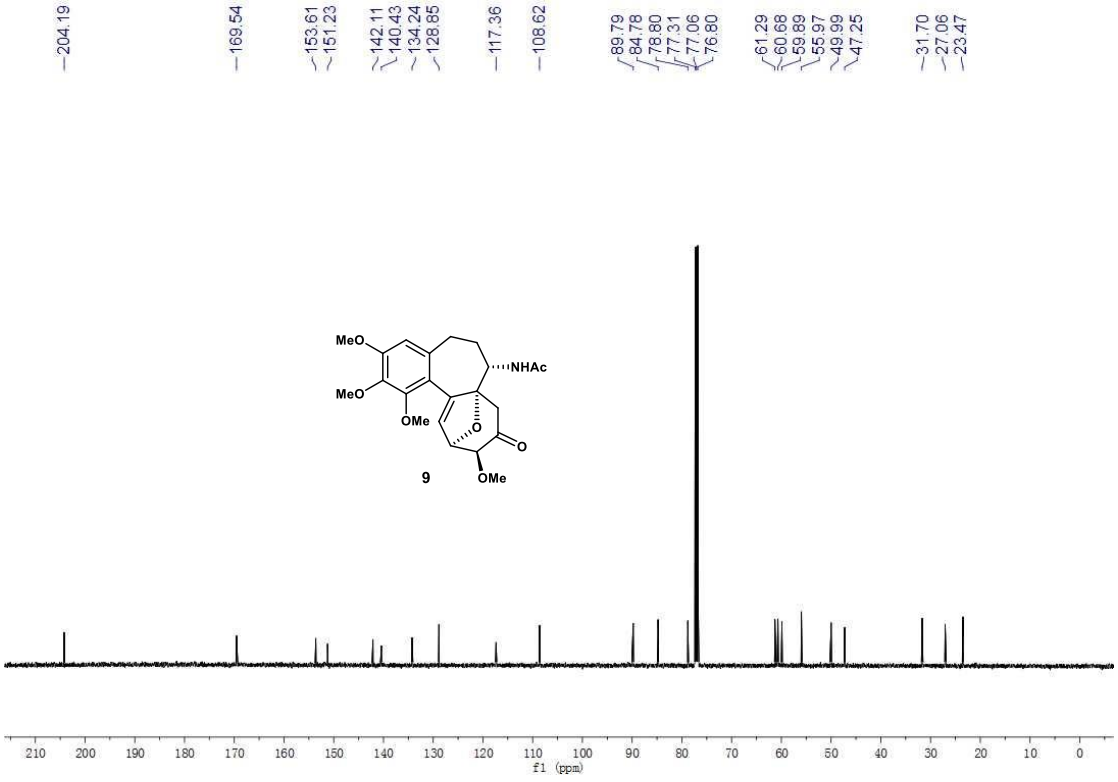
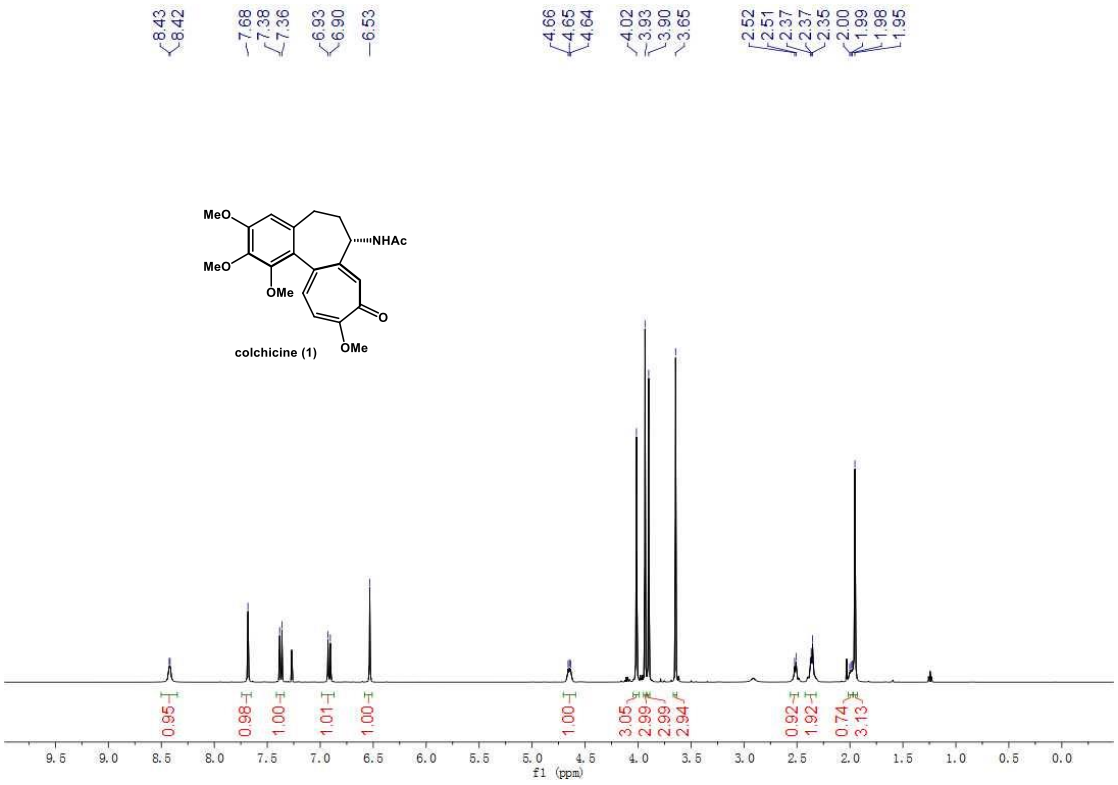
2.80
1.01
1.02
0.98
0.91
0.99
2.98
1.06
f1 (ppm)


204.19
169.54
153.61
151.23
142.11
140.43
134.24
128.85
117.36
108.62
89.79
84.78
78.80
77.31
77.06
76.80
61.29
60.68
59.89
55.97
49.99
47.25
31.70
27.06
23.47
MeO
MeO
OMe
NHAc
O
O
OMe
9
f1 (ppm)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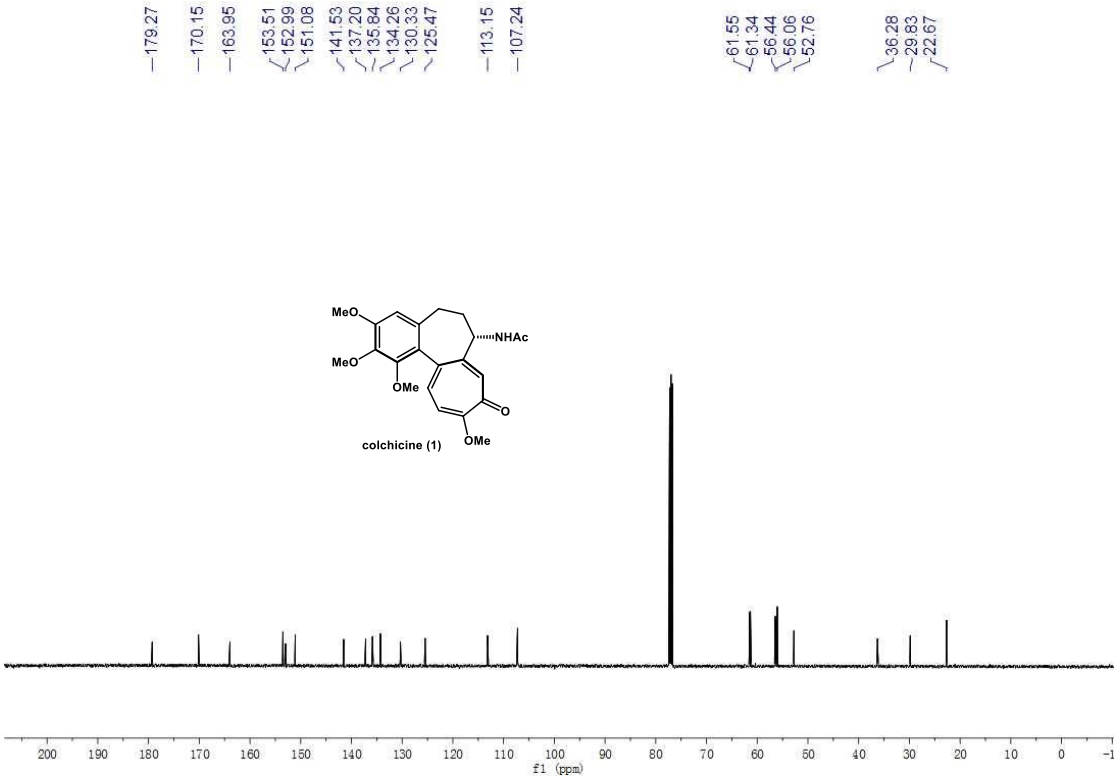
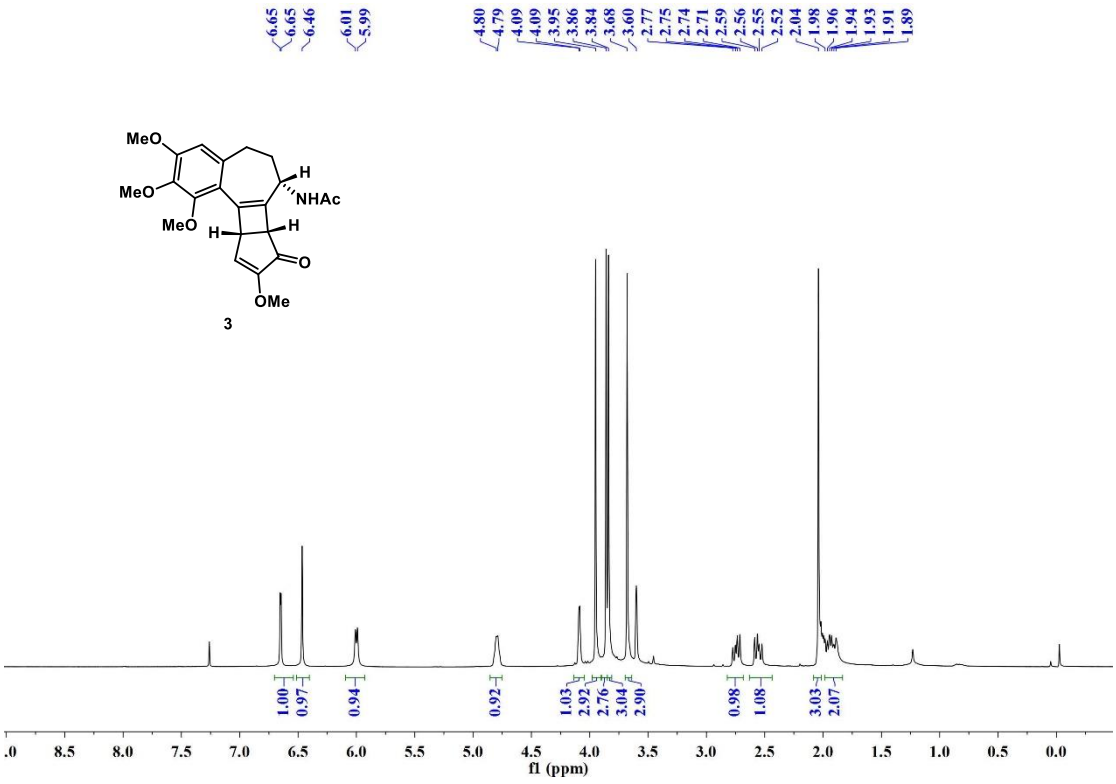
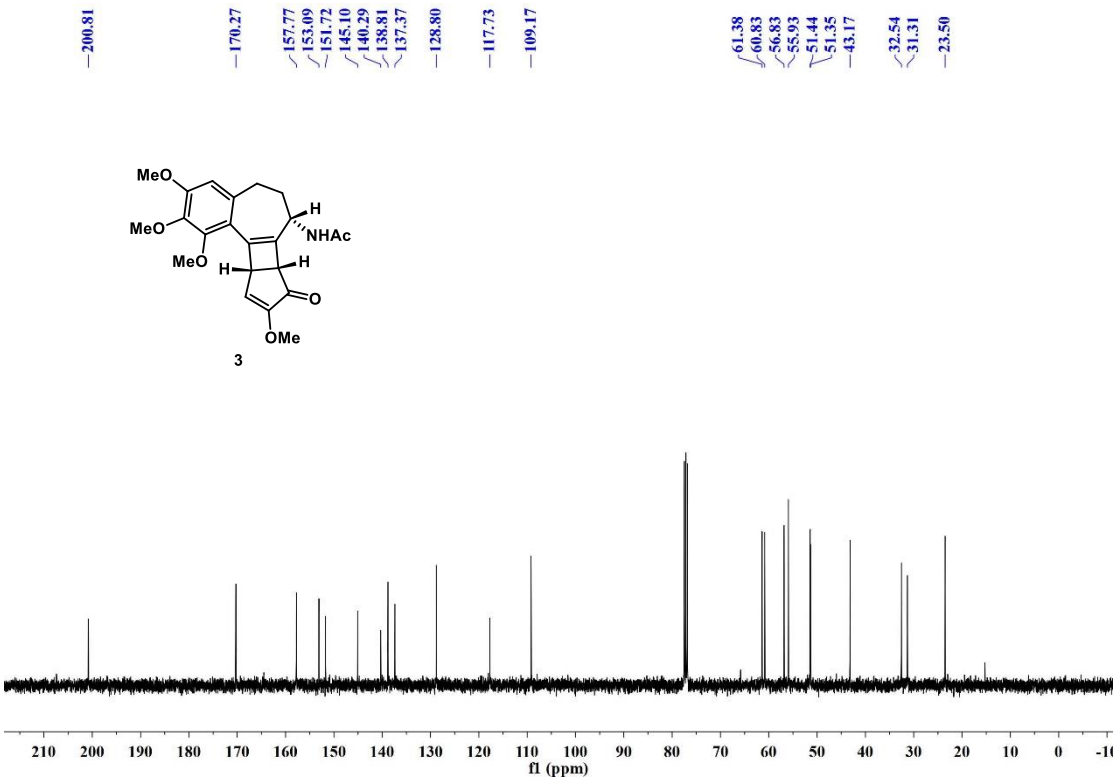
8.42
7.68
7.38
7.36
6.93
6.90
6.53
4.66
4.65
4.64
4.02
3.93
3.90
3.65
2.52
2.51
2.37
2.35
2.00
1.99
1.98
1.95
MeO
MeO
OMe
NHAc
O
OMe
colchicine (1)
0.95
0.98
1.00
1.01
1.00
1.00
3.05
2.99
2.99
2.94
0.92
1.92
0.74
3.13
f1 (ppm)


179.27
170.15
163.95
153.51
152.99
151.08
141.53
137.20
135.84
134.26
130.33
125.47
113.15
107.24
61.55
61.34
56.44
56.06
52.76
36.28
29.83
22.67
MeO
MeO
OMe
NHAc
O
OMe
colchicine (1)
f1 (ppm)


6.65
6.65
6.46
6.01
5.99
4.80
4.79
4.09
4.09
3.95
3.86
3.84
3.68
3.60
2.77
2.75
2.74
2.71
2.59
2.56
2.55
2.52
2.04
1.98
1.96
1.94
1.93
1.91
1.89
MeO
MeO
MeO
H
NHAc
H
H
O
OMe
3
1.00
0.97
0.94
0.92
1.03
2.92
2.76
3.04
2.90
0.98
1.08
3.03
2.07
f1 (ppm)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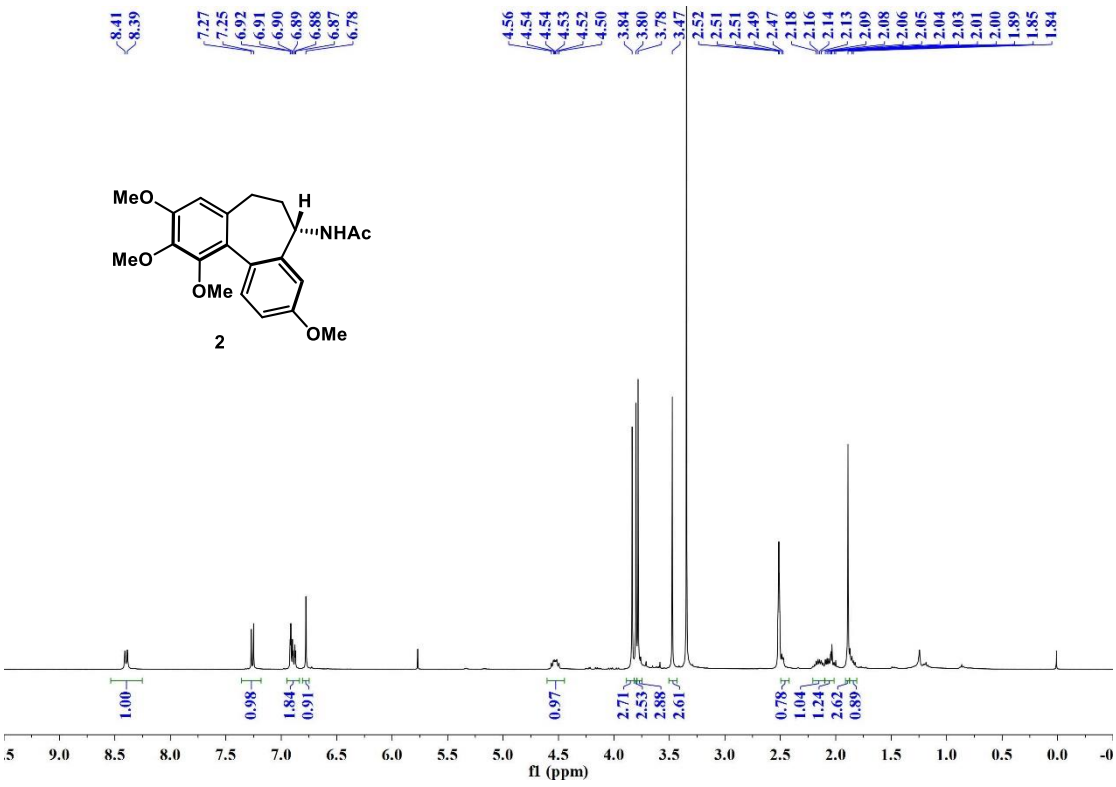
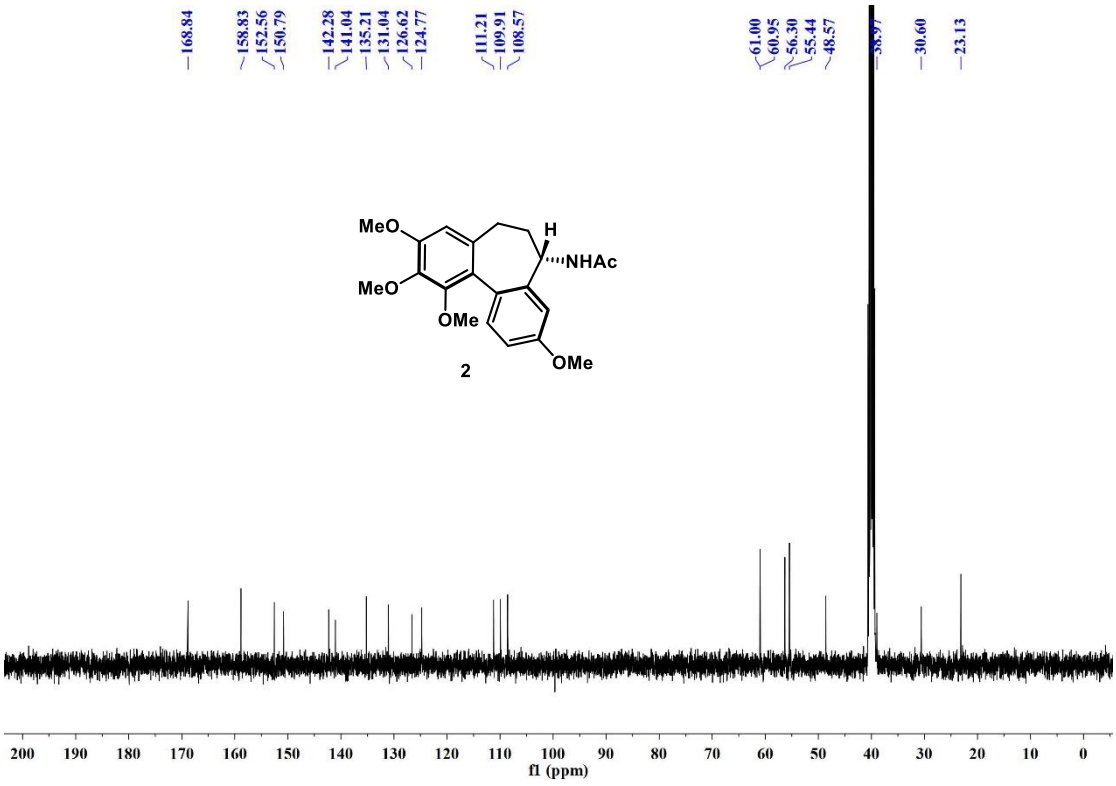
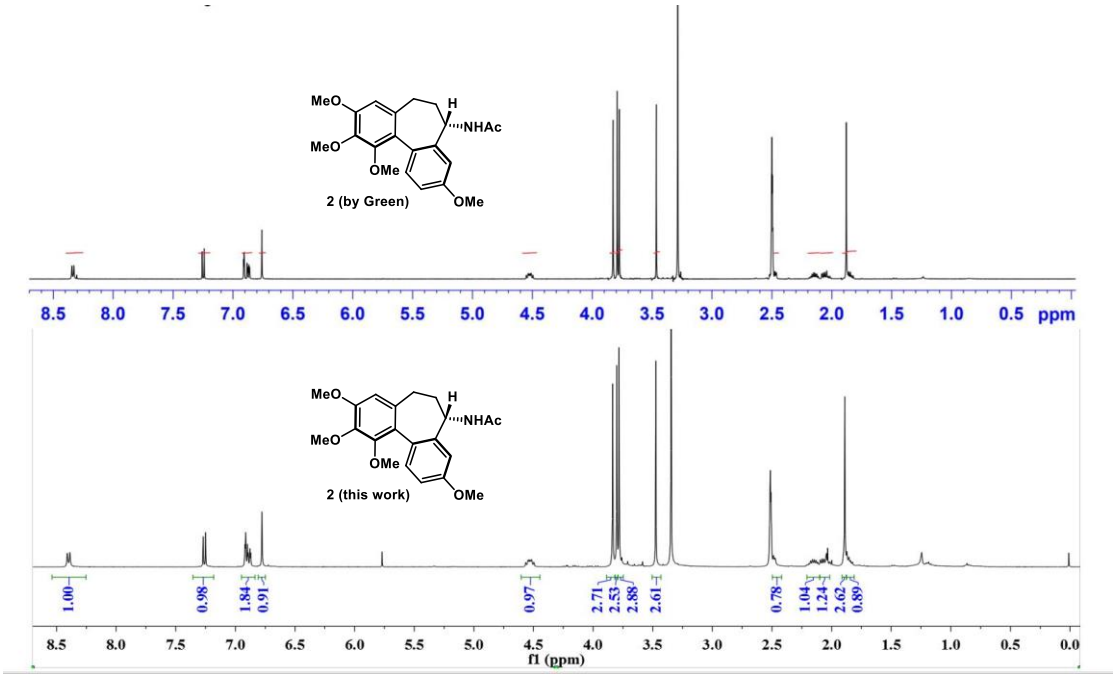
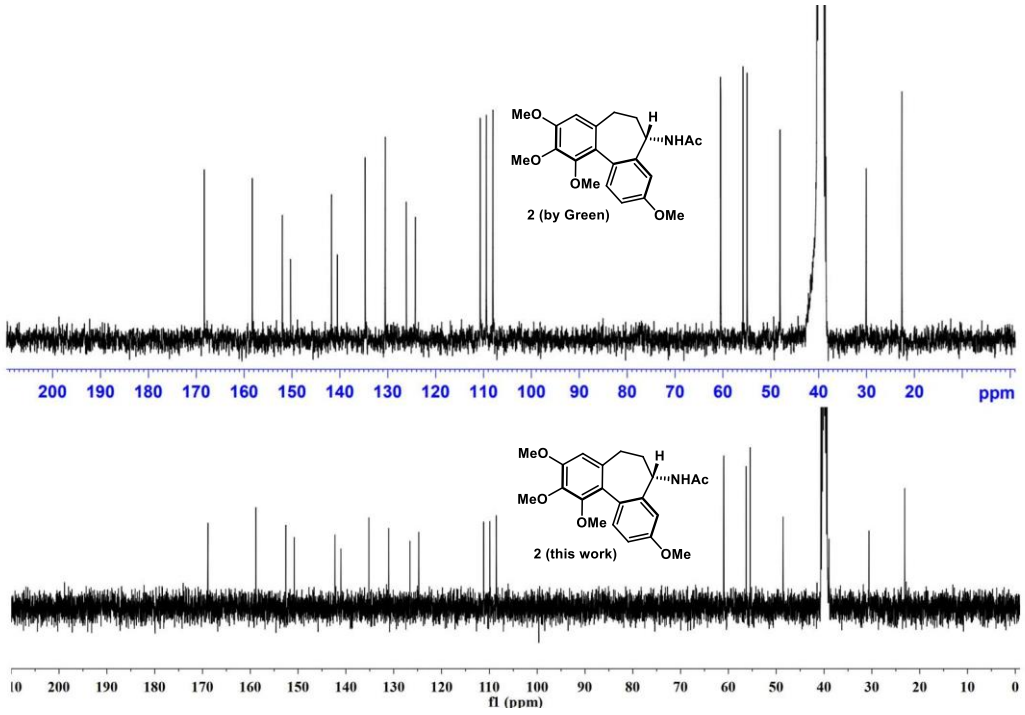
170.27
157.77
153.09
151.72
145.10
140.29
138.81
137.37
128.80
117.73
109.17
61.38
60.83
56.83
55.93
51.44
51.35
43.17
32.54
31.31
23.50
MeO
MeO
MeO
H
NHAc
H
H
O
OMe
3
f1 (ppm)


8.41
8.39
7.27
7.25
6.92
6.91
6.90
6.89
6.88
6.87
6.78
4.56
4.54
4.54
4.53
4.52
4.50
3.84
3.80
3.78
3.47
2.52
2.51
2.51
2.49
2.47
2.18
2.16
2.14
2.13
2.09
2.08
2.06
2.05
2.04
2.03
2.01
2.00
1.89
1.85
1.84
MeO
MeO
OMe
H
NHAc
OMe
2
1.00
0.98
1.84
0.91
0.97
2.71
2.53
2.88
2.61
0.78
1.04
1.24
2.62
0.89
fl (ppm)


168.84
158.83
152.56
150.79
142.28
141.04
135.21
131.04
126.62
124.77
111.21
109.91
108.57
61.00
60.95
56.30
55.44
48.57
30.60
23.13
MeO
MeO
OMe
H
NHAc
OMe
2
fl (ppm)

Comparison of ^{1}H-NMR and ^{13}C-NMR spectra of NCME (2)





VI References

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