

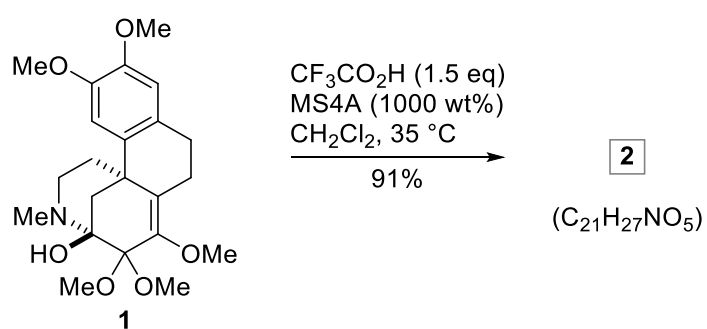
Problem Session

July 11, 2020

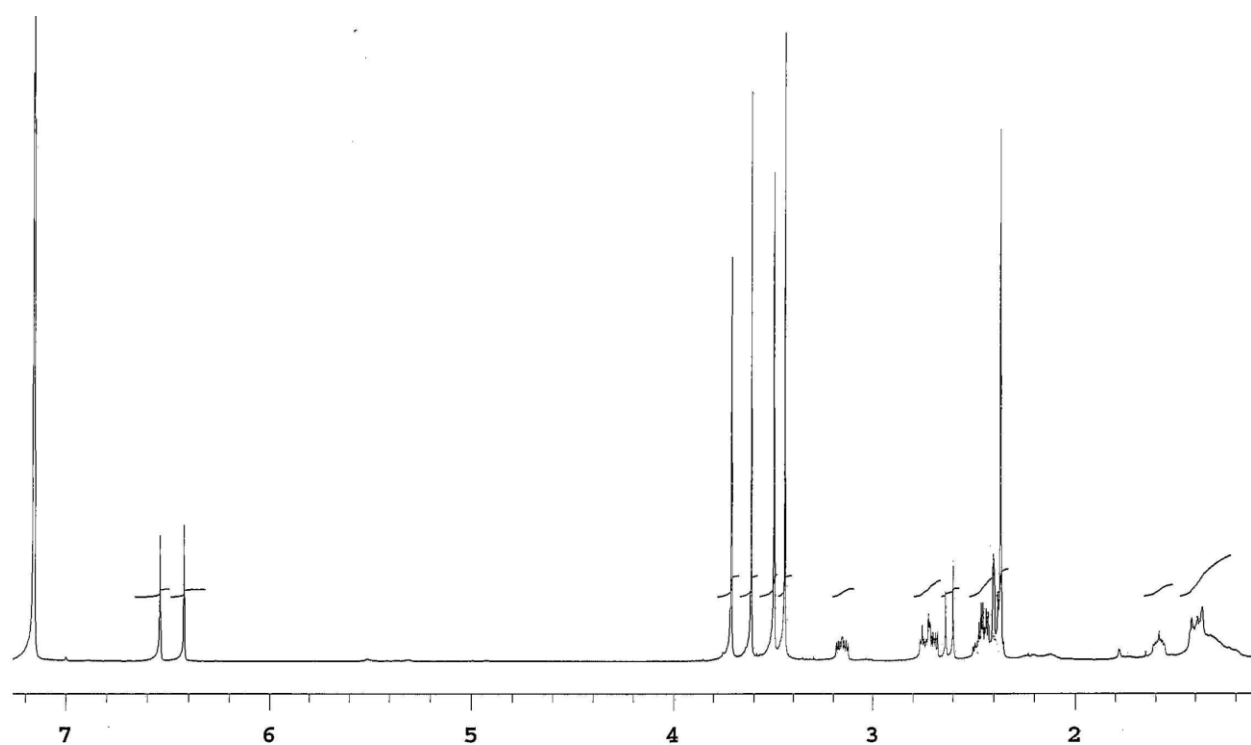
Hiroaki Itoh

Please provide the structure of **2** and assign the ^1H and ^{13}C NMR signals shown in page 2.

For assignment of the signals, please use the 2D NMR data and difference NOE shown in page 3.

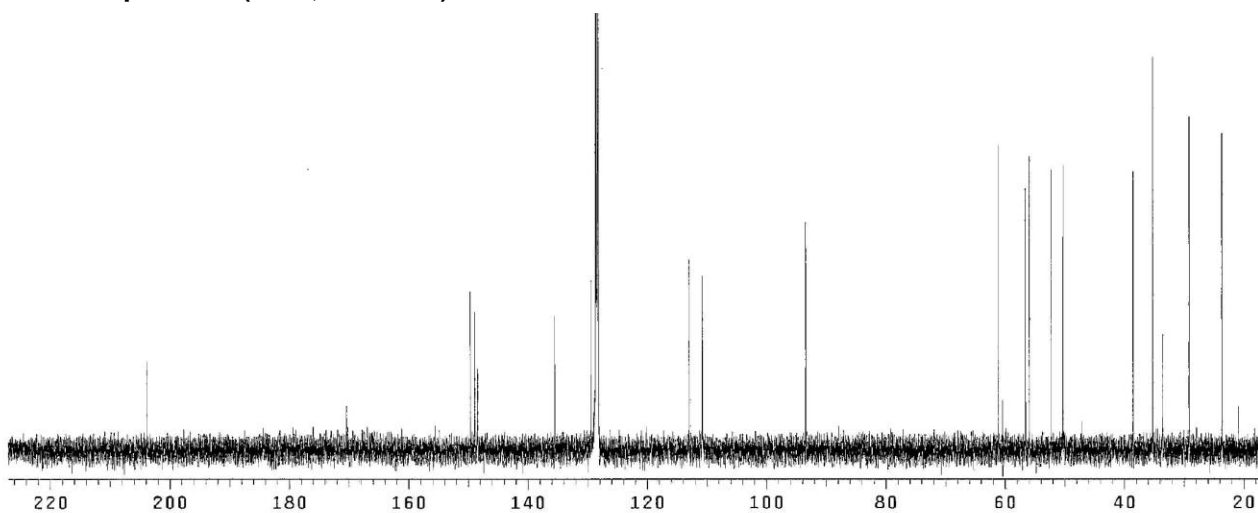


¹H NMR spectrum (C₆D₆, 500 MHz)



¹H NMR (C₆D₆, 500 MHz) δ 6.54 (s, 1H), 6.42 (s, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.50 (s, 3H), 3.44 (s, 3H), 3.17–3.13 (m, 1H), 2.76–2.68 (m, 2H), 2.62 (d, $J = 18.1$ Hz, 1H), 2.49–2.35 (m, 3H), 2.39 (d, $J = 18.1$ Hz, 1H), 2.37 (s, 3H), 1.61–1.56 (m, 1H), 1.42–1.37 (m, 1H)

¹³C NMR spectrum (C₆D₆, 125 MHz)



¹³C NMR (C₆D₆, 125 MHz) δ 203.8, 149.7, 148.9, 148.4, 135.5, 129.45, 129.41, 113.0, 110.8, 93.5, 61.1, 56.6, 56.0, 52.3, 50.4, 50.2, 38.6, 35.3, 33.6, 29.1, 23.7

2D NMR data

**a/b* indicates that a cross peak was observed at *a/b* ppm

¹H–¹H COSY (C₆D₆, 500 MHz)

3.17–3.13/2.76–2.68, 3.17–3.13/1.61–1.56, 2.76–2.68/2.49–2.35, 2.62/2.39, 1.61–1.56/1.42–1.37

¹H–¹³C HMQC (C₆D₆, 500 MHz)

6.54/110.8, 6.42/113.0, 3.71/52.3, 3.61/61.1, 3.50/56.6, 3.44/56.0, 3.17–3.13/50.2, 2.76–2.68/50.2, 2.76–2.68/23.7, 2.62/50.4, 2.49–2.35/29.1, 2.39/50.4, 2.37/35.3, 1.61–1.56/33.6, 1.42–1.37/33.6

¹H–¹³C HMBC (C₆D₆, 500 MHz)

6.54/149.7, 6.54/148.9, 6.54/135.5, 6.54/129.4, 6.54/38.6,
6.42/149.7, 6.42/148.9, 6.42/135.5, 6.42/129.4, 6.42/29.1,
3.71/93.5,
3.61/148.4,
3.50/149.7,
3.44/148.9,
2.76–2.68/148.4, 2.76–2.68/129.4, 2.76–2.68/29.1,
2.62/203.8, 2.62/129.4, 2.62/38.6,
2.49–2.35/129.4, 2.49–2.35/50.4,
2.39/203.8, 2.39/129.4, 2.39/38.6,
2.37/93.5, 2.37/50.2

Difference NOE experiments (C₆D₆, 500 MHz)

Irradiation of the signal at 6.54 led to enhancements in the signals at 3.50, 2.62, 2.39, 1.61–1.56, and 1.42–1.37.

Irradiation of the signal at 6.42 led to enhancements in the signals at 3.44 and 2.49–2.35.

Irradiation of the signal at 3.71 led to an enhancement in the signal at 2.37.

Irradiation of the signal at 3.50 led to an enhancement in the signal at 6.54.

Irradiation of the signal at 3.44 led to an enhancement in the signal at 6.42.

Irradiation of the signal at 2.62 led to enhancements in the signals at 6.54, 2.39, and 1.61–1.56.

Structure determination by NMR experiments —case study

1. Introduction

■ Hasubanan alkaloids

Structural feature: aza[4.4.3]propellane core

Firstly discovered hasubanan alkaloid: (-)-hasubanonine isolated from *Stephania japonica* (Figure 1)



Figure 1. *Stephania japonica* and structure of hasubanonine.

■ Total synthesis of hasubanan alkaloids

(see also PS by Y. Imamura 20181208)

Racemic syntheses: hasubanonine,^{1,2} metaphanine,^{3,4} cephamine,^{5,6} cepharatine A⁷,

Enantioselective syntheses: (+)-cepharamine⁸, [(-)-8-demethoxyrunanine, (-)-cepharatines A, C, and D]⁹, [(-)-hasubanonine, (-)-runanine, (-)-delavayine, (+)-periglaucine B, (-)-stephabenine, (+)-*N,O*-demethylstephine, (+)-*N,O*-dimethyloxostephine, (+)-oxostephabenine, (-)-prosthephanaberrine, (-)-stephanaberrine]^{10,11}

Partial and formal syntheses were also reported^{12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32}

Reference 31 is featured in this PS: Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187-1199.

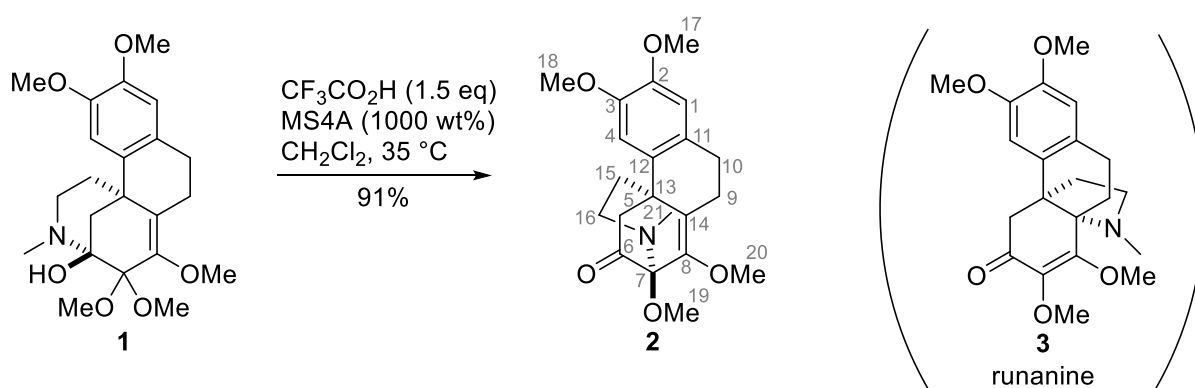


Figure 2. Generation of 2 from 1 in the attempted synthesis of 3.

Note: In the reference 31, GIAO ¹³C NMR calculation method was also used for supporting the structure.

2. Assignment of NMR signals

2-1. A set of data for the assignment

1. grouping signals based on their chemical shifts (^1H and ^{13}C), integrals, and coupling constants (^1H)
2. determine the ^1H - ^{13}C correlation using ^1H - ^{13}C **HMQC** (or HSQC, $^1J_{\text{CH}}$)
3. determine the connectivity using
 - through-bond correlation: coupling constants, ^1H - ^1H **COSY** ($^3J_{\text{HH}}$), ^1H - ^{13}C **HMBC** ($^2J_{\text{CH}}$ and $^3J_{\text{CH}}$)
 - through-space correlation: NOE (**1D NOE**, ^1H - ^1H ROESY or NOESY)

2-2. Grouping ^1H signals based on the chemical shifts

For rough estimation of chemical shifts of methyl and methylene, Table 1 and equation 1 are useful (for detailed list, see references 33 and 34)

$$\delta_{\text{XCH}_2\text{Y}} (\text{ppm}) = 0.2 + X + Y \quad (1)$$

X and Y are substituent chemical shifts

Table 1. Brief list of substituent chemical shifts for methyl and methylene in ^1H NMR³⁴

atom for substituent (X, Y)	substituent chemical shifts (ppm)
H	0.5
C (sp ³)	0.9
C (sp ² or sp)	1.6
O	2.8
N (except for -N ₂ O = 3.5)	1.9
S (except for -SO ₂ - = 2.6)	1.8
F	3.4
Cl, Br, I	2.5

e.g. NMe: $0.2 + 0.5 + 1.9 = 2.6$ ppm, OMe: $0.2 + 0.5 + 2.8 = 3.5$ ppm

For rough estimation of chemical shifts of methine, Table 2 and equation 2 are useful (for detailed list, see reference 35)

$$\delta_{\text{CHXYZ}} (\text{ppm}) = 0.25 + X + Y + Z \quad (2)$$

Table 2. Selected substituent chemical shifts for methine in ^1H NMR

substituent (X, Y, Z)	substituent chemical shifts (ppm)
R	0.00
-OH, -OR	1.14
-COR, -CO ₂ R, -CO ₂ H	0.47

2-3. Grouping ^{13}C signals based on the chemical shifts

- Alkane (no heteroatom): 0–60 ppm

For estimation of chemical shifts of alkanes, Table 3 and Table 4 are useful.³³

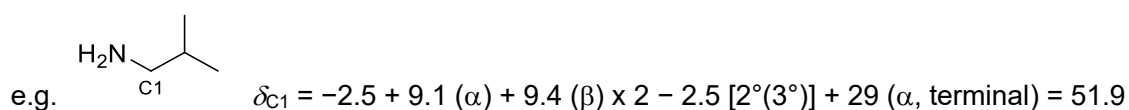
Table 3. ^{13}C NMR chemical shift parameters for linear and branched alkanes

^{13}C	shift parameter (ppm)
–	-2.5
α	9.1
β	9.4
γ	-2.5
δ	0.3
ε	0.1
$1^\circ(3^\circ)^a$	-1.1
$1^\circ(4^\circ)^a$	-3.4
$2^\circ(3^\circ)^a$	-2.5
$2^\circ(4^\circ)^a$	-7.2
$3^\circ(2^\circ)^a$	-3.7
$3^\circ(3^\circ)^a$	-9.5
$4^\circ(1^\circ)^a$	-1.5
$4^\circ(2^\circ)^a$	-8.4

^aFor example, $1^\circ(3^\circ)$ indicates the methyl group possessing R_2CH . $4^\circ(2^\circ)$ indicates the R_3C group possessing RCH_2 group.

Table 4. Selected substituent chemical shifts for alkanes

substituent (X)	substituent chemical shifts (ppm)				
	α		β		γ
	terminal	internal	terminal	internal	
CH_3	9	6	10	8	-2
OR	58	51	8	5	-4
NH_2	29	24	11	10	-5
NHR	37	31	8	6	-4
NR_2	42		6		-3

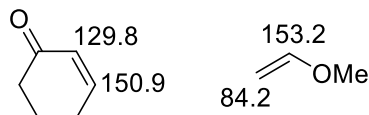


For other typical effects of substituents, see reference 33.

■ Alkene (no heteroatom): 110–150 ppm

If the alkene has no heteroatom, chemical shifts can be estimated by simple additivity (for details, see reference 33).

Please also consider the effects of polar substituents (electronegativity, resonance effect) though many cases cannot be explained by simple additivity.

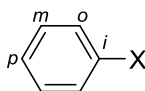


■ Aryl: 95–165 ppm

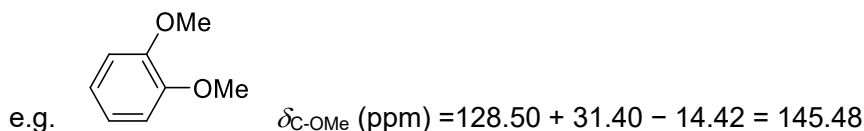
Chemical shifts of ^{13}C of the substituted aryl can be well explained by simple additivity. For rough estimation of chemical shifts of substituted benzene rings, Table 5 and equation 3 are useful (for detailed list, see reference 36)

$$\delta_{\text{C (aryl)}} (\text{ppm}) = 128.50 + i + o + m + p \quad (3)$$

Table 5. Selected substituent chemical shifts for monosubstituted benzene (CDCl_3)³⁶



substituent (X)	substituent chemical shifts (ppm)			
	<i>i</i>	<i>o</i>	<i>m</i>	<i>p</i>
CH ₃	9.22	0.66	-0.11	-3.04
Et	15.59	-0.48	0.0	-2.65
OMe	31.40	-14.42	1.04	-7.71



■ Ketone, aldehyde: 190–220 ppm, carboxylic acid, ester, amide: 150–185 ppm

2-4. Coupling constant

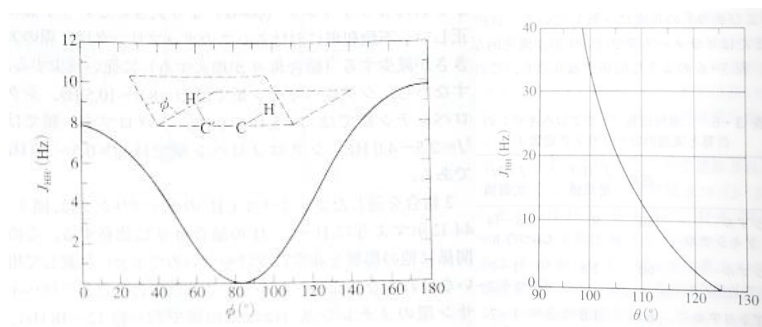
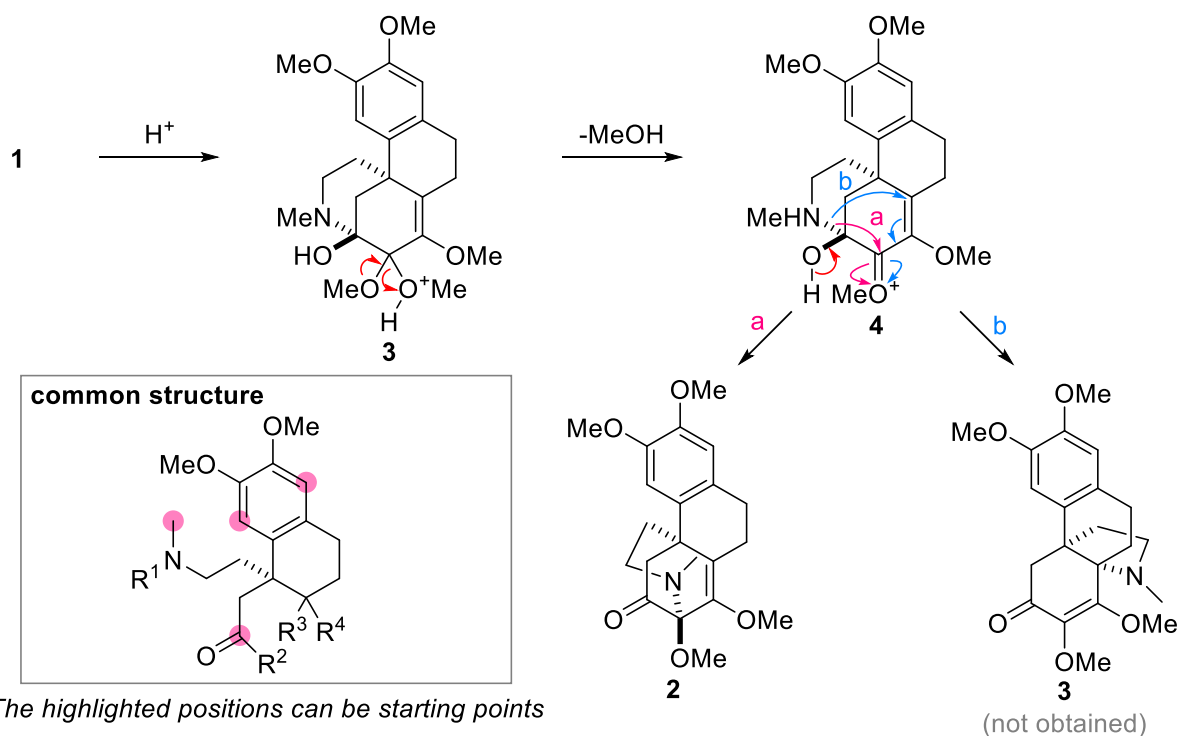


Figure 3. Coupling constant plotted against dihedral angle based on Karplus equation.³³ (left) Vicinal coupling, (right) geminal coupling. Please note that other factors also affect the coupling constant.

3. Answer

3-1. Estimation of candidate structures based on the reaction conditions



3-2. Grouping the characteristic ^1H signals based on the chemical shifts and integrals

6.54, 6.42 (s, 1H): **aryl**

3.71, 3.61, 3.50, 3.44 (s, 3H): **OMe**

2.37 (s, 3H): **NMe (H21)**

3-3. Grouping the characteristic ^{13}C signals based on the chemical shifts

203.8: **ketone (C6)**

149.7, 148.9, 148.4: **C(sp²)-OMe**

135.5, 129.45, 129.41, 113.0, 110.8: **C(sp²)**

93.5: **acetal?**

3-4. *N,O*-acetal and the adjacent structure

The ^{13}C signal at 93.5 ppm:

^1H - ^{13}C **HMQC correlation**: no cross peak

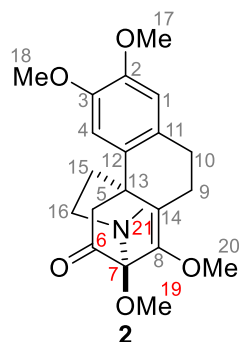
^1H - ^{13}C **HMBC correlations**: 3.71/93.5, 2.37/93.5

→The correlations are consistent with *N,O*-acetal: 93.5 (**C7**), 3.71 (**H19**), 2.37 (**H21**)

*These ^{13}C chemical shifts of **C19** and **C21** were determined from ^1H - ^{13}C **HMQC**: 52.3 (**C19**), 35.3 (**C21**)

Supporting data: **NOE** [3.71(**H19**)/2.37(**H21**)]

The above data were consistent with the structure of **2**.



3-5. Ketone and the adjacent structure

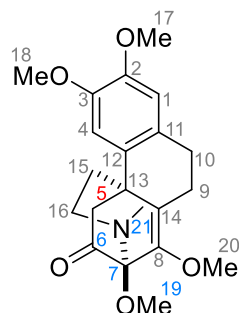
^1H - ^{13}C HMBC correlations: 2.62/203.8 (**C6**), 2.39/203.8 (**C6**)

→The ^1H signals 2.62 and 2.39 were determined to be **H5** (**H5a** and **H5b**)

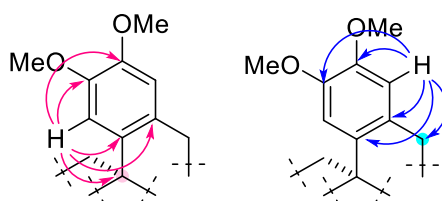
*The ^{13}C chemical shift of **C5** was determined from ^1H - ^{13}C HMQC: 50.4 (**C5**)

Supporting data: coupling constant ($J = 18.1$ Hz, geminal)

two cross peaks in ^1H - ^{13}C HMQC: 2.62 (**H5a**)/50.4 (**C5**), 2.39 (**H5b**)/50.4 (**C5**)



3-6. Aryl and the adjacent structure



^1H - ^{13}C HMBC correlations: (series A) 6.54/149.7, 6.54/148.9, 6.54/135.5, 6.54/129.4, 6.54/**38.6**

^1H - ^{13}C HMBC correlations: (series B) 6.42/149.7, 6.42/148.9, 6.42/135.5, 6.42/129.4, 6.42/**29.1**

→The ^{13}C signal 38.6 in series A was consistent with the quaternary carbon (**C13**, no cross peak in ^1H - ^{13}C HMQC)

→The ^1H signal at 6.54 was determined to be **H4**

*The ^{13}C chemical shift of **C4** was determined from ^1H - ^{13}C HMQC: 110.8 (**C4**)

→The ^{13}C signal at 29.1 in the series B was consistent with the methylene (**C10**)

*The ^1H chemical shift of **H10** was determined from ^1H - ^{13}C HMQC: 2.49–2.35 (2H, **H10**)

→The ^1H signal at 6.42 was determined to be **H1**

*The ^{13}C chemical shift of **C1** was determined from ^1H - ^{13}C HMQC: 113.0 (**C1**)

The ^{13}C signal at 135.5 was determined to be either **C11** or **C12**

The ^{13}C signal at 129.45 or 129.41 was determined to be either **C11** or **C12**

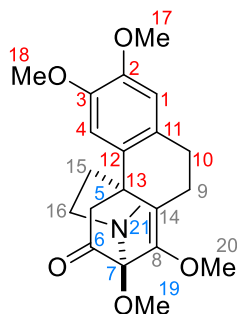
NOE: 6.54 (**H4**)/3.50, 6.42 (**H1**)/3.44

→The ^1H signals at 3.50 and 3.44 were determined to be **H18** and **H17**, respectively

*corresponding ^{13}C signal was determined from ^1H - ^{13}C **HMQC**: 56.6 (**C18**), 56.0 (**C17**)

^1H - ^{13}C HMBC: 3.50 (**H18**)/149.7, 3.44 (**H17**)/148.9

→The ^{13}C signals at 149.7 and 148.9 were determined to be **C3** and **C2**, respectively

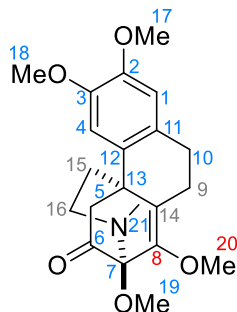


3-7. Remaining OMe groups and the adjacent structure

The remaining signal of **C(sp²)-OMe** (148.4) was determined to be **C8**

→The remaining ^1H and ^{13}C signals of **OMe** were determined to be **H20** (3.61) and **C20** (61.1), respectively

Supporting data: ^1H - ^{13}C **HMBC** correlation (3.61/148.4)



3-8. Other moieties

^1H - ^{13}C HMBC: 2.76–2.68/29.1 (**C10**)

The ^1H signal of 2.76–2.68 (2H) was determined to be **H9a**

In ^1H - ^{13}C **HMQC**, two cross peaks were observed from **H9a** because of the overlapped ^1H signals: 50.2 and 23.7

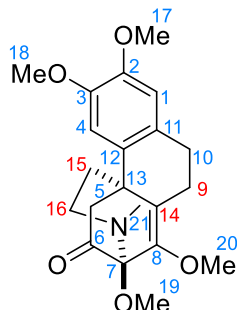
Based on the chemical shift, the ^{13}C signal at 23.7 was determined to be **C9**

^1H - ^{13}C HMBC: 2.37 (**H21**)/50.2

→The ^{13}C signal at 50.2 was determined to be **C16**

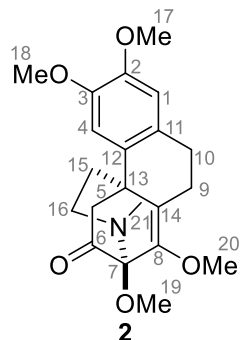
*The ^1H chemical shifts of **H16a** and **H16b** were determined from ^1H - ^{13}C **HMQC**: 3.17-3.13 (**H16a**), 2.76–2.68 (**H16b**)

Based on the sp^2 -type chemical shifts, either of ^{13}C signal at 129.45 or 129.41 correspond to **C14** 2.62 (**H5a**)/129.4, no cross peak at 2.62/135.5 \rightarrow The ^{13}C signal at 135.5 was determined to be **C11** Unassigned signals were determined to be **C15** (33.6) and **H15** (1.61–1.56, 1.42–1.37) using 1H - ^{13}C **HMQC**, **H9b** (1H of 2.49–2.35) using the chemical shift and the integral



(The observed 1H - 1H COSY, 1H - ^{13}C HMBC, and NOE correlations were not contradictory to the above assignments)

4. Summary

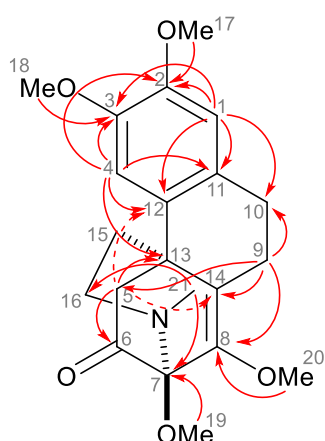


1H NMR (C_6D_6 , 500 MHz) δ 6.54 (s, 1H, **H4**), 6.42 (s, 1H, **H1**), 3.71 (s, 3H, **H19**), 3.61 (s, 3H, **H20**), 3.50 (s, 3H, **H18**), 3.44 (s, 3H, **H17**), 3.17–3.13 (m, 1H, **H16a**), 2.76–2.68 (m, 2H, **H16b** and **H9a**), 2.62 (d, $J = 18.1$ Hz, 1H, **H5a**), 2.49–2.35 (m, 3H, **H9b** and **H10**), 2.39 (d, $J = 18.1$ Hz, 1H, **H5b**), 2.37 (s, 3H, **H21**), 1.61–1.56 (m, 1H, **H15**), 1.42–1.37 (m, 1H, **H15**)

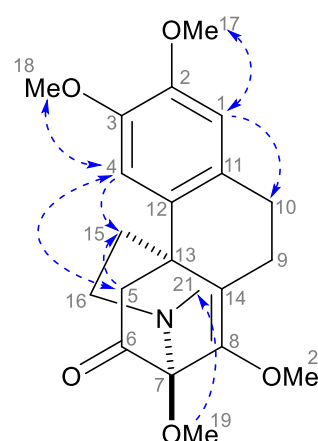
^{13}C NMR (C_6D_6 , 125 MHz) δ 203.8 (**C6**), 149.7 (**C3**), 148.9 (**C2**), 148.4 (**C8**), 135.5 (**C11**), 129.45 (**C12** or **C14**), 129.41 (**C12** or **C14**), 113.0 (**C1**), 110.8 (**C4**), 93.5 (**C7**), 61.1 (**C20**), 56.6 (**C18**), 56.0 (**C17**), 52.3 (**C19**), 50.4 (**C5**), 50.2 (**C16**), 38.6 (**C13**), 35.3 (**C21**), 33.6 (**C15**), 29.1 (**C10**), 23.7 (**C9**)

35.3 (**C21**), 33.6 (**C15**), 29.1 (**C10**), 23.7 (**C9**)

1H - ^{13}C HMBC



NOE



Note

1. $^4J_{CH}$ (H9/C5) was observed

2. Dotted arrows: 2.62/129.4 in HMBC is derived from H5/C12 and/or H5/C14

Figure 4. 1H - ^{13}C HMBC and NOE correlations.

5. References

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