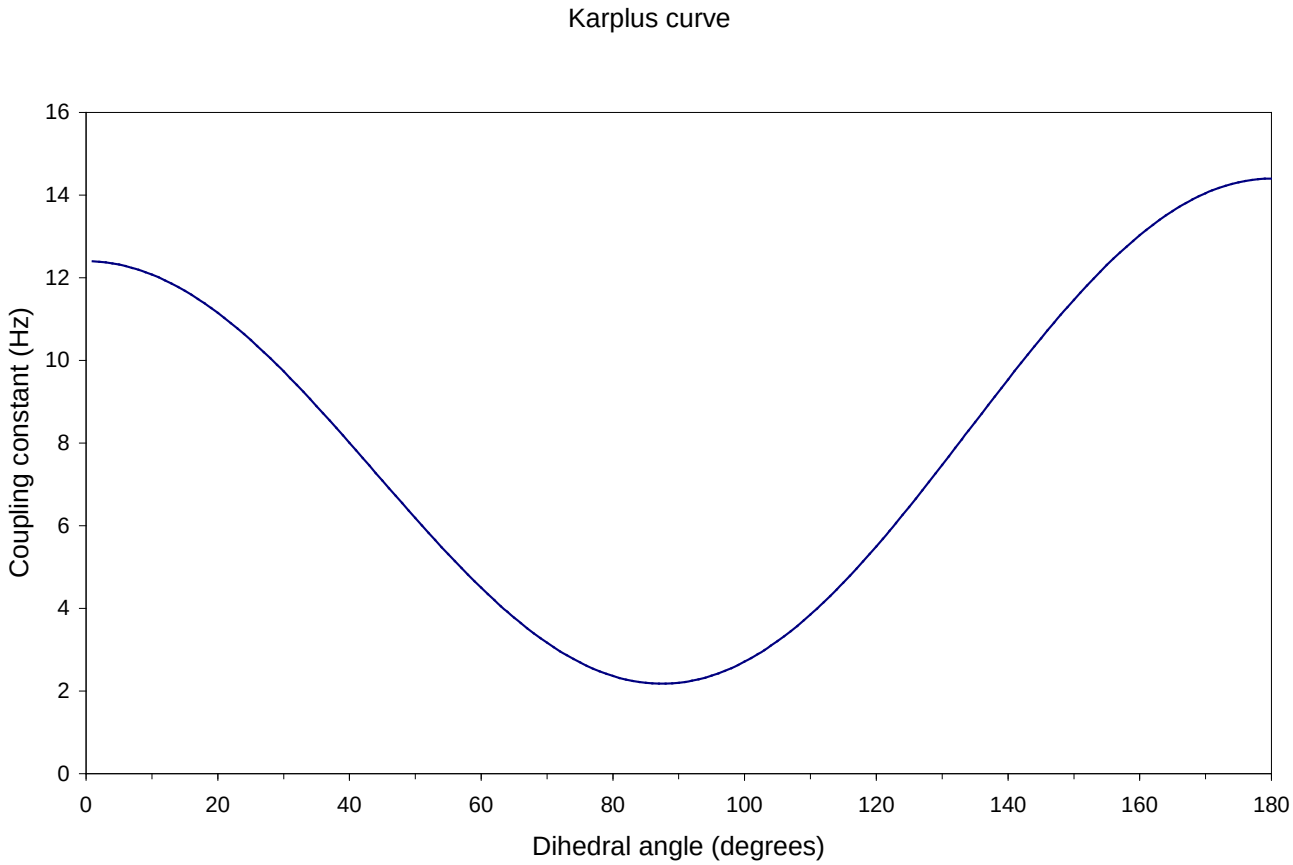
Solutions to:

Problems
for
Organic Structure Analysis

Professor Marcel Jaspars

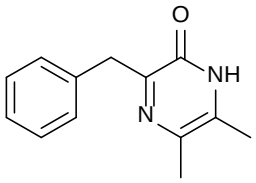
Throughout these problems use the following:



Dec 2014
EAQ 1

a.) Describe the strategy used to determine the structure of an unknown compound using high resolution MS, $^{1}H/^{13}C$/DEPT-135 1D NMR and 2D NMR experiments (HSQC, COSY, HMBC). Use structures and diagrams to illustrate your answer. (8)

b.) Butrepyrazinone is a small molecule produced by a bacterium isolated from a mangrove swamp in Ghana. Its structure is given below together with a comprehensive 1D and 2D NMR dataset. Fully assign all the ^{1}H and ^{13}C NMR shifts to the structure of butrepyrazinone, explaining your reasoning. (12)



Butrepyrazinone

Table: ^{1}H , ^{13}C, HMBC and NOE NMR data of butrepyrazinone in $CDCl_3$ at 600 MHz.

Atom	**δ_H/ppm, mult (*J*/Hz)**	**δ_C/ppm**		**HMBC C → H**	**NOE data**
A		157.5	C	i	
B		154.6	C	i	
C		138.3	C	i, g	
D		132.2	C	j, k	
E		129.9	C	j, k	
F	7.40, d (8)	129.9	2 x CH	i, g, h	f-g, f-i
G	7.25, t (8)	128.8	2 x CH	f	g-f, g-h
H	7.18, t (8)	126.9	CH	f	h-g
I	4.10, s	39.6	CH_2	f	i-f
J	2.21, s	16.7	CH_3		j-k
K	2.28, s	18.9	CH_3		k-j, k-NH
	12.23, bs		NH		NH-k

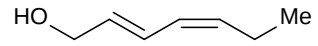
EAQ2

a.) Briefly explain how the size of a ^{1}H-^{1}H NOE is related to the interproton distance and the molecular size. (4)

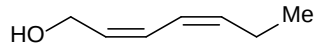
b.) Explain, using structural diagrams how you can determine whether a double bond is E or Z using NOE data. (4)

c.) A synthetic chemist has separated a mixture of three dienols (A-C) and is uncertain of their stereochemistry. She acquires three ^{1}H NMR and NOE datasets as given below. Determine which dataset belongs with which stereoisomer explaining your reasoning. (12)

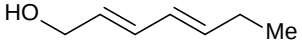
A



B



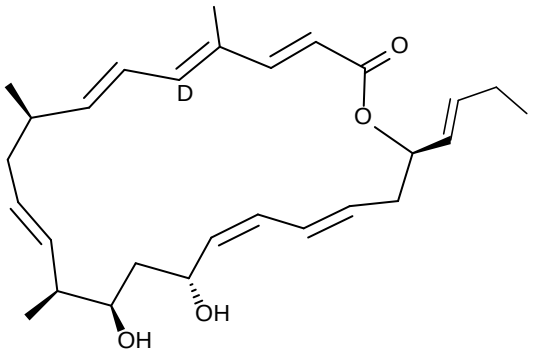
C



^{1}H NMR and NOE data acquired for compounds A, B and C.

#	*Dataset 1*		*Dataset 2*		*Dataset 3*	
	δ_H/ppm	**NOE**	**δ_H/ppm**	**NOE**	**δ_H/ppm**	**NOE**
1	4.18	5.80, 6.24	4.18	5.80, 6.24	4.18	5.66, 5.97
2	5.80	4.18, 6.03	5.80	4.18, 5.97	5.66	4.18, 6.23
3	6.24	4.18, 5.61	6.24	2.02, 4.18	6.23	2.02, 5.66
4	6.03	2.02, 5.80	5.97	5.47, 5.80	5.97	4.18, 5.47
5	5.61	0.78, 2.02, 6.24	5.47	0.78, 2.02, 5.97	5.47	0.78, 2.02, 5.97
6	2.02	0.78, 5.61, 6.03	2.02	0.78, 5.47, 6.24	2.02	0.78, 5.47, 6.23
7	0.78	2.02, 5.61	0.78	2.02, 5.47	0.78	2.02, 5.57

Jan 2014
EAQ1



Atom	δ_C	mult	δ_H, mult. (*J* in Hz)	COSY (H to H)	HMBC (H to C)
A	166.6	C			
B	148.5	CH	7.14, d (15.7)	o	A, D, O, G, Me4
C	145.5	CH	5.68, dd (14.7, 8.1)	n, w	D, W, Me1
D	138.2	CH	6.19, d (11.2)	n	B, C, Me4
E	135.4	CH	5.79, dt (15.3, 6.3)	m, x	P, X, Me3
F	133.1	CH	5.27, m	j, s	U
G	132.3	C			
H	131.9	CH	5.64, m	l, v	I
I	131.6	CH	6.04, t (10.6)	k, l	H, L, R
J	131.1	CH	5.27, m	f, u	S
K	130.8	CH	5.42, dd (10.5, 7.6)	i, r	L, R
L	129.2	CH	6.61, dd (14.6, 11.7)	h, i	I, V
M	127.3	CH	5.49, ddt (6.4, 1.4, 15.4)	e, p	X
N	125.7	CH	6.28, dd (14.7, 11.2)	c, d	G, W
O	117.5	CH	5.73, d (15.7)	b	A ,G
P	73	CH	5.32, m	m, v	A
Q	71.8	CH	3.74, dd (10.3, 4.4)	s, t	F, R
R	65.8	CH	4.80, t (7.5)	t, k	
S	44	CH	2.03, m	f, q, Me2	
T	41.4	CH2	1.59, m; 1.47 dd (14.1, 6.1)	q, r	R
U	40.9	CH2	2.32, dt (3.7, 12.9); 1.89, m	j, w	C, F, W
V	39.2	CH2	2.46, m	h, p	H, L, P
W	37.5	CH	2.40, m	c, u, Me1	
X	25.4	CH2	2.05, m	e, Me3	E, M, Me3
Me1	20.5	CH3	1.08, d (6.7)	w	C, W, U
Me2	17.3	CH3	1.02, d (6.8)	s	F, Q, S
Me3	13.4	CH3	0.97, t (7.4)	x	E, X
Me4	12.5	CH3	1.81, s		B, D, G

The 1D and 2D NMR data is given for the compound shown. In this case the ^{1}H-^{1}H COSY data allows you to assign most of the shifts to the atoms in the molecule, once you find a suitable starting point. To simplify matters, one assignment has already been made for you on the structure.

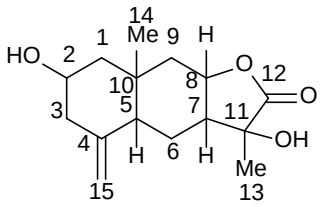
(a) Use the ^{1}H-^{1}H COSY data to assign the majority of shifts to atoms in the structure. Draw the structure indicating the correlations showing atom letters and arrows. 8

(b) Use the HMBC data to complete the assignments, Draw the structure indicating the correlations showing atom letters and arrows. 6

(c) Using coupling constants, confirm that the double bond stereochemistry of each disubstituted double bond is as shown. 4

(d) How would you determine the stereochemistry of the trisubstituted double bond? 2

EAQ2



Racemosalactone D

Atom	δ_H/ppm	mult *J*/Hz
1	1.81	d, 12.0
1'	1.90	dd, 12.0, 4.0
2	3.84	ddd, 12.0, 4.0, 4.0
3	1.99	dd, 12.0, 12.0
3'	2.68	dd, 12.0. 4.0
4	-	-
5	1.81	d, 12.4
6	1.05	ddd, 13.6, 12.4, 12.4
6'	1.63	ddd, 13.6, 6.0
7	2.29	m
8	4.96	m
9	1.50	dd, 13.2, 4.4
9'	2.25	m
10	-	-
11	-	-
12	-	-
13	1.46	s
14	0.79	s
15	4.57	s
15'	4.90	s

The ^{1}H NMR data for racemosalactone D is given in the table above.

(a) Using diagrams explain what the Karplus relationship is, and which dihedral angles give rise to large, medium and zero coupling constants. 4

(b) For racemosalactone D, draw all the coupling constants on the structure. 5

(c) Using the information from parts a.) and b.) determine the relative stereochemistry of the separate systems C1/C2/C3, C5/C6/C7 and C8/C9. 6

(d) Strong NOEs are observed between H7-H5, H7-H8, Me13-H6, Me13-H9', Me14-H1', Me14-H2, Me14-H3', Me14-H6, Me14-H9'. Using this information determine the relative stereochemistry of the whole molecule (ie of the separate systems in part c.) in relation to each other). Draw a clear conformational diagram showing the NOEs. 5

Jan 2013

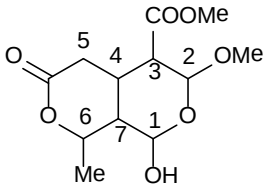
EAQ1

a.) Briefly explain how coupling constants can be used to make assignments of relative stereochemistry in rigid cyclic molecules. Use stereochemical diagrams to illustrate you answer (6)

b.) The ^{1}H NMR data is given for the compound below.

i. Indicate all the coupling constants between adjacent protons using this data. (4)

ii. Use the information from b.) part i.) to determine the relative stereochemistry for all substituents and protons in this molecule. Draw an stereochemical diagram to explain your answer. (10)



H	*δ/ppm*	*mult*	*J/Hz*
1	5.88	d	3
2	5.48	d	8
3	2.59	dd	10, 8
4	3.00	dddd	12, 10, 10, 5
5a	2.49	dd	17, 5
5b	2.54	dd	17, 12
6	4.52	dq	10, 7
7	1.75	ddd	10, 10, 3

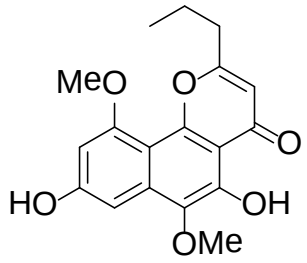
EAQ2

1D and 2D NMR data is given for compound **1** below.

a.) Use the COSY data to assign aliphatic part of the structure. (3)

b.) Use the1D, COSY and HMBC NMR data to assign all $^{1}H/^{13}C$ NMR shifts to the structure explaining your reasoning. (12)

c.) The hydroxyl ^{1}H NMR signal at 12.90 ppm shows an NOE to the singlet at 3.95 ppm. Use this to assign the position of the OH. Suggest a reason why this OH is observed whereas the other OH is not. (5)



1

Table 1. 1D and 2D NMR spectroscopic data (400 MHz, $CDCl_3$) compound **1**
All COSY are 3 bonds unless otherwise stated.
HMBC are C to H and are 2 or 3 bonds.

	δC	**δH (*J* in Hz)**	**HMBC**	**COSY**
A	183.4, C	-	A-i	
B	170.1, C	-	B-i, B-p, B-q	
C	160.2, C	-	C-o	
D	158.3, C	-	D-l, D-m	
E	152.4, C	-		
F	147.1, C	-		
G	136.1, C	-		
H	134.7, C	-	H-f, H-m, H-n	
I	109.5, CH	6.23, s	I-p	
J	109.3, C	-	J-f, J-i	
K	104.9, C	-	K-l, K-m	
L	96.7, CH	6.43, d (1.6)	L-m	l-m (4 bond)
M	96.3, CH	7.01, d (1.6)	M-l	m-l (4 bond)
N	60.4, CH_3	3.95, s		
O	56.2, CH_3	3.94, s		
P	36.5, CH_2	2.68, t (7.7)	P-i, P-q, P-r	p-q
Q	20.0, CH_2	1.84, m	Q-p, Q-r	q-p, q-r
R	13.7, CH_3	1.01, t (7.7)	R-p, R-q	r-q
OH		12.90 s		

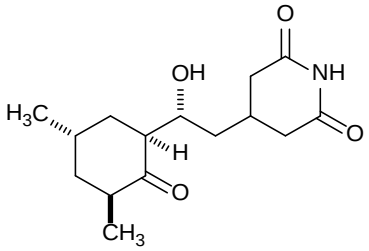
Jan 2012

EAQ1. The 1D and 2D NMR data is given below for the antibacterial agent cycloheximide. Use this data to:

(a) Assign all the ^{1}H and ^{13}C data to the structure of cycloheximide. Explain all your reasoning. Draw structures indicating your COSY and HMBC correlations. [12]

(b) Explain how you would determine the relative stereochemistry in the left hand ring system. Use structural diagrams to explain your answer and indicate draw the expected conformation. [6]

(c) Explain why the ^{13}C chemical shifts of the amide carbonyls are different. [2]



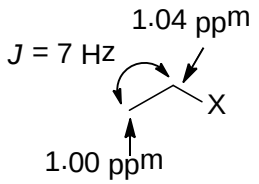
Cycloheximide

1D and 2D NMR data for cycloheximide (CD_3OD, 400 MHz)

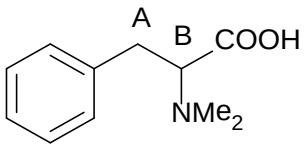
Atom	δ ^{13}C/ppm, mult	δ ^{1}H/ppm, mult	COSY H→H	HMBC C→H
A	215.04, C	-		d, e, f/f', g, k/k', o
B	174.45, C	-		i, l
C	174.34, C	-		j, l
D	66.37, CH	3.98, q	h, e	e, h, k'
E	51.00, CH	2.53, ddd	d, k/k'	d, h', k'
F	42.89, CH_2	1.88, ddd; 1.55 td	g, m	g, n, o
G	40.46, CH	2.64, m	f/f', o	f', o
H	39.93, CH_2	1.42, t	l	d, e, l
I	38.19, CH_2	2.60, m; 2.30 m	l	h, j/j'
J	36.71, CH_2	2.70, m; 2.30 m	l	h, i/i'
K	35.19, CH_2	2.03, ddd; 1.73, td	e, m	d, e, n
L	27.79, CH	2.30, m	h, i, j	d, h, i/i', j/j'
M	27.17, CH	2.12, m	f', k', n	f', k/k'
N	17.38, CH_3	1.23, d	m	f', k'
O	13.55, CH_3	0.90, d	g	f', g

EAQ2.

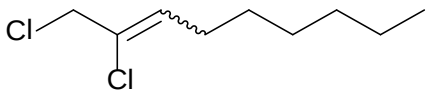
(a) The ^{1}H NMR spectrum at 500 MHz of the spin system below shows 20 peaks. Draw the normal splitting pattern expected for this spin system and explain why in this case a greater number of peaks appear. [5]



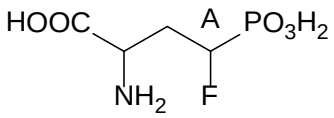
(b) Draw the expected coupling patterns for the protons at carbons A and B in the molecule below and explain their appearance. [5]



(c) Describe a strategy using NMR techniques to determine the stereochemistry of the double bond shown below. Explain the expected results for your experiment for the *E* and *Z* isomer. [5]



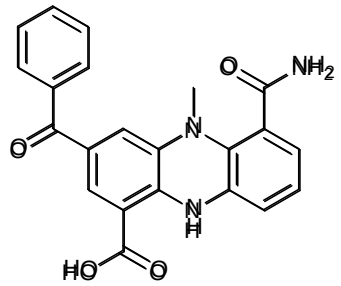
(d) For the molecule below sketch and explain the appearance of the ^{19}F and ^{31}P NMR spectra. Draw and explain the expected appearance of carbon A in the 13C NMR spectrum. [5]



Jan 2011

EAQ1 Dermacozine C was isolated from the deep sea bacterium *Dermacoccus abyssi*. The 1D and 2D NMR data have been provided below.

a.) Use the COSY data to construct 2 spin systems and indicate where they must be placed on dermacozine C (5)
b.) Use the data to assign all ^{1}H and ^{13}C NMR shifts, explaining your reasoning. (10)
c.) Which additional NMR experiment would you perform to confirm all four OH and NH ^{1}H chemical shifts, including a stereospecific assignment for the NH_2 shifts. (5)



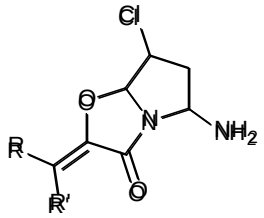
Dermacozine C

1D and 2D NMR data for dermacozine C at 400 MHz in DMSO-d_6

	δ_C (mult)	δ_H	COSY H→H	HMBC H→C
A	193.6 (C)			
B	170.6 (C)			
C	169.1 (C)			
D	145.7 (C)			
E	138.8 (C)			
F	138.3 (C)			
G	134.5 (C)			
H	133.3 (C)			
I	132.2 (CH)	7.61	m, n	K, L
J	129.2 (CH)	7.43		A, C, D, T
K	129.2 (CH)	7.63	m	A, I, L
L	129.2 (CH)	7.63	n	A, I, K
M	128.9 (CH)	7.54	i, k	F, N
N	128.9 (CH)	7.54	i, l	F, M
O	127.9 (C)			
P	124.6 (C)			
Q	124.3 (CH)	6.73	r	B, H, S
R	121.6 (CH)	6.58	q, s	G, P
S	115.3 (CH)	6.60	r	H, Q
T	114.3 (CH)	6.66		A, D, E, J, O
U	107.4 (C)			
V	40.0 (CH_3)	2.98		E, H
W		14.71		
X		9.76		E, G, H, S, U
Y		a. 7.84 b. 7.46		B

EAQ 2 The substructure of a molecule derived from a Norwegian seasquirt is shown below.

a.) Assign the ^{1}H chemical shifts for the protons attached to carbons (4)
b.) Assign all the coupling constants (4)
c.) Use the coupling constant information together with the NOESY data to determine the relative stereochemistry of the 3 stereocentres in the substructure. (6)
d.) One of the expected couplings is missing. Explain why this might be the case. (2)
e.) If the absolute stereochemistry at the carbon bearing the chlorine is *S*, give the absolute stereochemistry at the other two stereocentres. (4)



no	δ_H/ppm (mult, *J*/Hz)	NOESY (ppm)
12’	2.76 (ddd, 15.0, 8.0, 3.0)	5.08, 6.32
12	2.81 (dd, 15.0, 7.0)	5.08, 5.46
11	5.08 (t, 3.0)	2.76, 2.81, 6.32
13	5.46 (dd, 8.0, 7.0)	2.81
10	6.32 (d, 3.0)	2.76, 5.08

Jan 2010 EAQ1

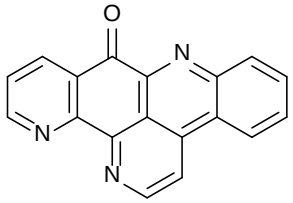
The 1D (^{1}H, ^{13}C) and 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC) data for the marine invertebrate compound ascididemin are given below.

a.) Use the ^{1}H-^{1}H COSY data to construct three spin systems. Indicate on the structure of ascididemin where these belong. (4)

b.) Explain the multiplicities (coupling patterns) observed for each proton in the three spin systems. (4)

c.) Assign all the ^{1}H and ^{13}C NMR chemical shifts to the structure of ascididemin using the data provided. Explain your reasoning. Are there any chemical shifts that cannot be assigned using the data given? (10)

d.) Give an additional 2D NMR experiment that could provide additional data to confirm you assignment and explain how it would help. (2)



Ascididemin

1D and 2D NMR data of ascididemin in $CDCl_3$ at 400 MHz

Atom No	δ ^{13}C/ppm		δ ^{1}H/ppm	mult *J*/Hz	^{1}H-^{1}H COSY H→H	HMBC C→H
1	181.9	C				C1-H9
2	155.7	CH	9.11	*dd*, 4.8, 1.8	H2-H9, H2-H14	C2-H9, C2-H14
3	152.5	C				C3-H2, C3-H9
4	149.9	CH	9.22	*d*, 5.6	H4-H18	C4-H18
5	149.8	C				C5-H4, C5-H18
6	146.1	C				C6-H11, C6-H16
7	145.9	C				
8	138.2	C				C8-H4, C8-H16
9	136.8	CH	8.70	*dd*, 8.0, 1.8	H9-H14	C9-H2
10	133.2	CH	8.52	*dd*, 7.7, 1.3	H10-H11	C10-H12
11	132.1	CH	7.94	*ddd*, 8.2, 7.7, 1.3	H11-H10, H11-H12	C11-H16
12	131.1	CH	7.89	*ddd*, 8.2, 7.7, 1.3	H12-H11, H12-H16	C12-H10
13	129.2	C				C13-H14
14	125.8	CH	7.60	*dd*, 8.0, 4.8	H14-H7, H14-H9	C14-H2
15	123.7	C				C15-H18
16	123.2	CH	8.63	*dd*, 7.7, 1.3	H16-H12	C16-H10
17	118.2	C				C17-H18
18	117.1	CH	8.48	*d*, 5.6	H18-H4	C18-H4

Jan 2010 EAQ2

A marine invertebrate derived compound contains C, H, O, N and I. The MS, 1D and 2D NMR data is given below.

a.) Use the data to calculate the molecular formula. (4)
b.) Use the COSY data to construct 2 spin systems. (6)
c.) Using the remaining atoms construct a final spin system, taking account of the symmetry and crucial HMBC correlations. (5)
d.) Using the remaining HMBC correlations, propose a structure that is consistent with all the data. (5)

MS (M^+) 506.9192 *m/z*
IR 1660, 1630 cm^{-1}

Atom label	δ_C (ppm)	δ_H (ppm) mult, int	^1H-^1H COSY correlations	^1H-^{13}C HMBC correlations
A	167.7 C	-		A-h, A-k
B	157.7 C	-		B-c, B-j
C	140.2 2CH	7.76 s, 2H		C-c, C-l
D	138.9 C	-		D-k
E	134.6 C	-		E-g
F	131.8 CH	7.52 t, 1H	f-g	F-h
G	128.7 2CH	7.46 t. 2H	g-f, g-h	G-g
H	126.9 2CH	7.73 d, 2H	h-g	H-f, H-h
I	90.6 2C	-		I-c
J	60.7 CH_3	3.86 s, 3H		
K	41.0 CH_2	3.67 q, 2H	k-l, k-NH	K-l
L	34.0 CH_2	2.84 t, 2H	l-k	L-c
NH	-	6.14 bs	NH-k	

H = 1.0078; C = 12.0000; N = 14.0031; O = 15.9949; I = 126.9045

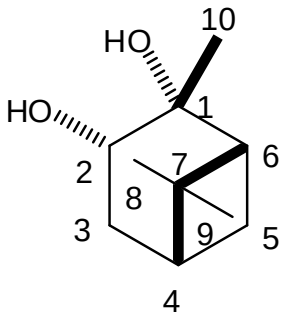
Jan 2009 EAQ1

The structure of pinanediol is given below together with 1D and 2D NMR data.

Use this data to:

a.) Assign all the ^{1}H and ^{13}C chemical shifts. Show how you have used the data to derive your conclusions. (12)

b.) Draw a clear conformational drawing of pinanediol and indicate how you can use the NOESY data to confirm your assignments in part a.) and use this data to determine the orientation of MeI and MeJ. Also determine the relative stereochemistry of protons f/f' and h/h'. (8)



Pinanediol

Atom label	δ_C (ppm), mult	δ_H (ppm) mult, *J*/Hz	^{1}H-^{1}H COSY correlations	^{1}H-^{13}C long range correlations	^{1}H-^{1}H NOESY correlations
A	73.9 s	-		A-f, A-h', A-g	
B	69.2 d	3.96 dd 5.1, 9.4	b-f/f'	B-f', B-g	b-f/f', b-g, b-j
C	54.0 d	1.99 t 5.7	c-d, c-h	C-i, C-j	
D	40.6 d	1.90 m	d-c, d-h	D-i, D-j	d-f/f'
E	39.0 d	-		E-f', E-h', E-i, E-j	
F	38.1 t	2.43 m	f-b, f-f'	F-h'	f-b, f-d, f-j
F'		1.62 m	f'-b, f'-f		f'-b, f'-d
G	29.7 q	1.28 s			g-b
H	28.2 t	2.17 m	h-c, h-d, h-h'	H-f/f'	h-h', h-i
H'		1.35 d 5.0	h'-h		h'-h
I	27.9 q	1.25 s	i-j		i-h
J	24.2 q	0.91 s	j-i	J-i	j-b, j-f

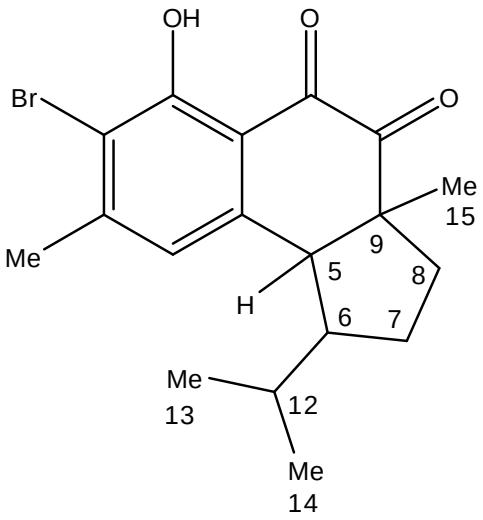
Jan 2009 EAQ2

a.) Describe how proton-proton coupling constants and NOE data can be used to determine the relative stereochemistry of cyclic molecules. Use a specific example to illustrate your answer and give details of the process that needs to be carried out. (8)

b.) Hamigeran B, isolated from a sponge has the plane structure given below. The ^{1}H NMR data with coupling constants as well as selected NOE data has been given in the table below.

i. Use the NOE data to determine the relative stereochemistry around the five membered ring. Draw a clear conformational drawing and explain your reasoning. (7)

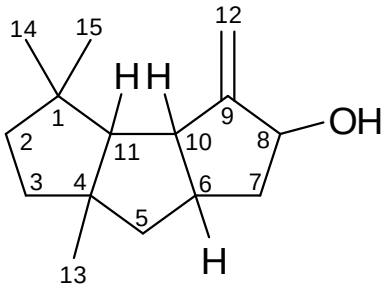
ii. The coupling constant data for H5 and H8a are given in the table. Use the Karplus curve below and your answer to (b)(i) to explain the size of the H5 coupling constant and assign the coupling constants for H8a to specific coupling partners. (5)



Hamigeran B

Atom	δ_H (ppm, mult, *J*/Hz)	NOE correlations
5	3.39, d, 9.3	H6, H7a, H8a, Me15
6	2.31, m	
7a	1.81, m	
7b	1.69, m	8b, H12, Me14
8a	2.63, ddd, 13.0, 9.6, 5.4	
8b	1.56, m	
9	-	
12	1.21, m	
13	0.53, d, 6.5	
14	0.45, d, 6.5	
15	1.29, s	

Jan 2008 EAQ1



Capnellene

Capnellene was isolated from the Indonesian soft coral *Capnella imbricata*. The ^{1}H NMR data has been provided below.

NMR data for capnellene at 400 MHz in $CDCl_3$

	δ^{1}H (mult, *J* Hz)	**NOE data**
H2	1.51 m	H2-H3b
H3a	2.09 m	
H3b	1.45 m	H3b-Me15, H3b-H2
H5a	1.79 dd 13.8, 8.4	
H5b	1.51 dd 13.8, 4.6	H5b-H6, H5b-Me15
H6	2.22 dddd 11.6, 8.4, 4.6, 3.5	H6-H5b
H7a	2.13 ddd 14.2, 8.4, 3.5	H7a-H11
H7b	1.39 dd 14.2, 4.2	
H8	4.74 dd 8.4, 4.2	
H10	2.36 dd 11.6, 3.3	
H11	1.75 d 3.3	H11-Me14, H11-H12a, H11-H7a, H11-Me13
H12a	5.05 d 2.5	H12a-H11,
H12b	4.96 d 2.5	
Me13	1.24 s	Me13-H11,
Me14	1.02 s	Me14-Me15, Me14-H11
Me15	0.82 s	Me15-Me14, Me15-H5b, Me15-H3b

a.) Draw the structure, labelling protons on carbons 5, 6, 7, 8, 10, 11. Use the data table above to indicate the coupling constants between these protons. Explain why one of the expected couplings between H6 and H7b is missing. (6)

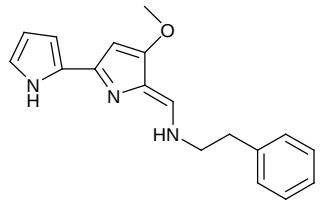
b.) Use the information from part a. to propose two possible relative stereochemistries between protons H6, H10, H11. A Karplus curve is given below. (6)

c.) Use the NOE data given to confirm the relative stereochemistry determined in part b. and the relative stereochemistry of Me13, Me14, Me15. What is the stereochemistry of the ring junctions? Draw a clear stereochemical diagram to explain your answer. (8)

2007 EAQ1

The alkaloid tambjamine F was isolated from the marine invertebrate *Sigillina signifera*. The ^{1}H, ^{13}C, HSQC, COSY and HMBC data are given in Table 1 below. Use this information to:

a.) Assign all ^{1}H NMR shifts explaining your reasoning. (6)
b.) Assign all ^{13}C NMR shifts explaining your reasoning. (8)
c.) Indicate how the COSY data are consistent with your assignments. (2)
d.) Indicate how the HMBC data are consistent with your assignments. (4)



Tambjamine F

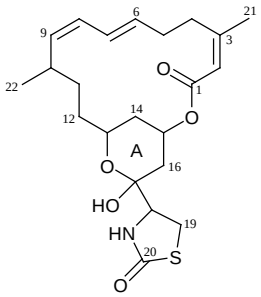
Table 1. 1D and 2D NMR spectral data for tambjamine F obtained in $CDCl_3$ at 400/100 MHz (δ in ppm).

Atom	δ ^{13}C/ppm	mult	δ ^{1}H/ppm, integral, mult, *J*/Hz	^{1}H-^{1}H COSY (H $\rightarrow$ H)	^{13}C-^{1}H HMBC (C $\rightarrow$ H)
C1	164.5	C			H-14
C2	143.7	C			H-10
C3	140.3	CH	7.07 (1H, d, 14.7)	NH2	H-15
C4	137.4	C			H-15, H-16, H-6
C5 (2C)	129.1	CH	7.18 (2H, m)	H-6, H-7	H-6, H-7
C6 (2C)	129.0	CH	7.26 (2H, m)	H-5	H-16, H-5, H-7
C7	127.1	CH	7.19 (1H, m)	H-5	H-5
C8	124.8	CH	7.07 (1H, bs)	H-12	
C9	122.5	C			H-8
C10	114.1	CH	6.72 (1H, bs)	H-12	H-8
C11	110.9	C			H-13, H-3
C12	110.9	CH	6.30 (1H, m)	H-10, H-8	H-8
C13	91.8	CH	5.92 (1H, d, 1.2)		
C14	58.5	CH_3	3.85 (3H, s)		
C15	52.7	CH_2	3.66 (2H, m)	NH2, H-16	H-16
C16	36.7	CH_2	2.98 (2H, t, 7.2)	H-15	H-15
NH1			11.60 (1H, bs)		
NH2			9.80 (1H, bs)	H-3, H-15	

2007 EAQ2

Latrunculin A is a complex metabolite isolated from the sponge *Latrunculia* and the seaslugs that feed on it. There are 5 stereocentres in this molecule and different approaches need to be employed to determine their relative stereochemistry. For the A ring the ^{1}H NMR data and coupling constants are given in the extract of the data table below.

a.) In some conformationally constrained systems, expected couplings may be missing. Using the Karplus curve below explain why this is the case. (3)
b.) Draw a diagram of ring A in your answer book and indicate the couplings between the protons. (4)
c.) Use the information from part a.) in conjunction with the Karplus curve to assign the correct relative stereochemistry at C-13 and C-15, and assign the diastereotopic protons at C-14 and C-16. Draw a clear conformational diagram to explain your answer. (8)
d.) An NOE correlation is observed between H16' and H18. Use this information to suggest the relative stereochemistry at C17. (3)
e.) Suggest how you might determine the relative stereochemistry at C-11. (2)



Latrunculin A

Table 1. Selected ^{1}H NMR and coupling data for latrunculin A obtained in DMSO-d_6 at 400 MHz.

No.	δ_H/ppm (integral, mult., *J*/Hz)
12	1.22 (2H, m)
13	4.28 (1H, t, 11.0)
14	1.42 (1H, d, 14.4)
14′	1.32 (1H, ddd, 3.2, 11.0, 14.4)
15	4.99 (1H, dd, 3.2, 4.8)
16	1.97 (1H, d, 14.8)
16′	1.53 (1H, dd, 4.8, 14.8)

2006 EAQ1

Spectroscopic data is given below for a potential drug molecule. The molecule contains two amides and a phenol-OH.

Use this information:

a.) To determine the molecular formula (4)
b.) Determine the correct structure of the molecule using the 1D and 2D NMR data. Draw structures indicating the COSY and HMBC correlations to confirm your conclusions. (10)
c.) Assign all the ^{1}H and ^{13}C NMR data. (6)

MS data: M^{+} at 250.1317 *m/z*

(C = 12.0000, H = 1.0078, N = 14.0031; O = 15.9949)

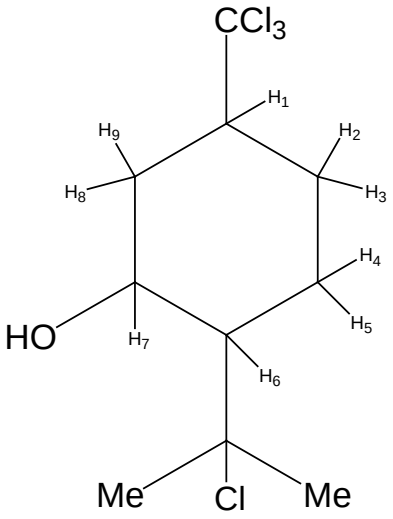
The IR spectrum shows major bands at 3630, 3314, 3256, 1692, 1608 cm^{-1}

	δ ^{13}C/ppm, mult	δ ^{1}H/ppm, mult, *J*	^{1}H-^{1}H COSY data	HMBC data C→H
1	176.5 s			C1-H7, 11, 14
2	172.0 s			C2-H8, 10, 13
3	152.9 s			C3-H5, 6
4	133.4 s			C4-H5, 6, 13
5	121.8 d (2C)	7.47 2H d 8 Hz	H5-H6	C5-H6, 13
6	115.9 d (2C)	6.71 2H d 8 Hz	H6-H5	C6-H5
7	36.5 t	2.18 2H t 7 Hz	H7-H11	C7-H9, 11, 14
8	33.9 t	2.23 2H t 7Hz	H8-H10	C8-H9, 10, 13
9	28.3 t	1.29 2H quint 7 Hz	H9-H10, H9-H11	C9-H7, 8, 10, 11
10	25.3 t	1.67 2H quint 7 Hz	H10-H8, H10-H9	C10-H8, 9, 11
11	25.0 t	1.57 2H quint 7 Hz	H11-H7, H11-H9	C11-H7, 9, 10
12		11.0 1H s		
13		8.0 1H bs		
14		6.0 2H bs		

2006 EAQ2

The ^{1}H NMR spectrum of the compound below has been analysed and selected ^{1}H-^{1}H coupling data has been reported.

H	mult	J/Hz
1	dddd	12.3, 12.3, 3.3, 3.2
2	dddd	14.5, 4.6, 3.6, 3.3
3	dddd	14.5, 12.3, 10.6, 3.3
4	dddd	15.1, 12.4, 10.6, 3.6
5	dddd	15.1, 4.6, 4.3, 3.3
6	ddd	12.4, 10.4, 3.3
7	ddd	11.3, 10.4, 4.3
8	ddd	14.1, 12.3, 11.3
9	ddd	14.1, 4.3, 3.2



a.) Copy the structure into your answer book and indicate all the mutual coupling constants. (6)

b.) Use the information from part a.) together with the Karplus curve given below to assign the stereochemistry of H_1-H_9. Draw a conformational diagram to exaplain your reasoning and indicate the stereochemistry of the side groups. (10)

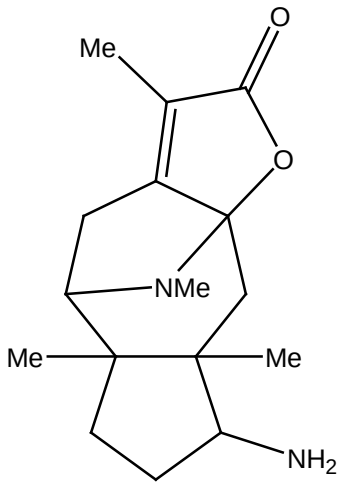
c.) NOE data shows enhancements for: H1-H4, H1-H-7, H3-H6, H4-H7, H6-H8, H8-H3. rationalise this information using the conformation derived in part b.).

2006 EAQ 3

Hederacine B is a compound isolated from ground ivy (*Glechoma hederaceae*). The ^{1}H, ^{13}C and HMBC NMR data are given below. Using this information:

a.) Assign the ^{1}H and ^{13}C NMR data to the structure indicating your reasoning. Draw a structure indicating the HMBC correlations to confirm your conclusions. (14)
b.) Selected NOE correlations are given below. Use this information to assign the relative stereochemistry in the lower five-membered ring in hederacine B. (6)

NOE data: 3.11 – 1.40; 2.88 – 1.49; 2.13 – 1.29; 1.49 – 2.13; 1.29 – 1.40; 1.40 – 2.88



Hederacine B

Atom No	δ ^{1}H/ppm, mult	δ ^{13}C/ppm, mult	HMBC H→C
1	–	170.5 s	–
2	–	130.5 s	–
3	–	156.0 s	–
4	2.82 m, 1H 2.37 m, 1H	22.5 t	C-2, C-12
5	3.37 m, 1H	59.0 d	C-12
6	–	46.5 s	
7	2.13 m, 1H 1.26 m, 1H	35.1 t	C-9, C-10
8	2.01 m, 1H 1.49 m, 1H	24.5 t	C-6, C-10
9	2.88 m, 1H	67.5 d	C-6, C-11, C-14
10	–	55.5 s	–
11	2.85 m, 1H 1.30 m, 1H	48.2 t	C-6, C-9
12	–	110.0 s	–
13	3.11 s, 3H	49.5 q	C-12
14	1.40 s, 3H	17.0 q	C-6, C-9, C-11
15	1.29 s, 3H	15.0 q	C-5, C-7
16	1.90s, 3H	7.5 q	C-1, C-3

NH_2 data not shown

2006 EAQ4

A water-soluble compound containing an guanidinium group (HN-(C=NH)-NH_2, δ_C ~157 ppm) was isolated from a New Zealand hydroid.

The 1D and 2D NMR data is given below. The accurate mass measurement obtained by ESI-MS is $[M+H]^+ = 279.1452$ *m/z.*

(C = 12.0000, H = 1.0078, N = 14.0031; O = 15.9949)

Use this information:

d.) To determine the molecular formula (4)
e.) To determine the correct structure of the molecule using the 1D and 2D NMR data and assign all the ^1H and ^{13}C NMR data. Draw structures indicating the COSY and HMBC correlations to confirm your conclusions.(12)
f.) To explain the NOESY correlations observed for this compound. (4)

	δ_C/ppm mult	δ_H/ppm (H, mult, J/Hz)	^1H-^1H COSY	HMBC (C→H)	NOESY
1	189.4 s			H-9	
2	166.2 s			H-7, H-11	
3	164.1 s			H-9, H-10	
4	157.3 s			H-6	
5	125.0 s			H-10	
6	41.0 t	3.06 (2H, d, 6.0)	H-8, H-12		H-8, H-12
7	38.5 t	3.17 (2H, d, 6.0)	H-8, H-11	H-8, H-11	H-8, H-11
8	26.6 t (2C)	1.40 (4H, t, 2.8)	H-7, H-6	H-7, H-6	H-7, H-6, H-9
9	133.2 d (2C)	7.80 (2H, d, 8.8)	H-10		
10	116.3 d (2C)	6.80 (2H, d, 8.8)	H-9	H-9	H-9, H-13
11		8.70 (1H, t, 5.6)	H-7		H-7, H-9
12		7.40 (1H, t, 5.6)	H-6		H-6
13		10.80 (1H, bs)			H-10

Note: 3 additional exchangable H are not visible in the ^1H NMR

2005 EAQ1

The Antarctic alga *Pantoneura plocamioides* produces an interesting monobrominated monoterpene called pantoisofuranoid A. The mass spectrometric and 1D and 2D NMR data are given below. To simplify your workings, you may assume that C3 and C6 are linked by an ether bridge.

MS data: M^+ at 264.0361*m/z*

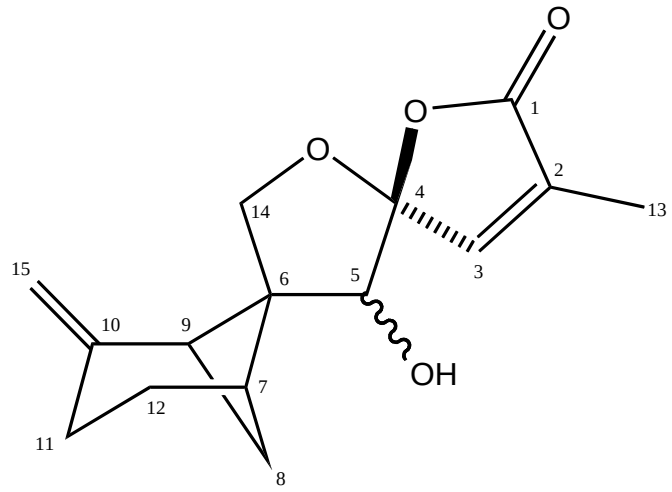
(C = 12.0000, H = 1.0078, O = 15.9949, ^{79}Br = 78.9180)

Label	$\delta\ ^{13}C$ (ppm), mult	$\delta\ ^{1}H$ (ppm), mult, *J* (Hz)	COSY data (H-H)	HMBC data (H to C)
1	105.9 d	6.31 d 13.6	H1-H2	H1-C2, H1-C3
2	141.3 d	6.17 d 13.6	H2-H1	H2-C1
3	88.3 s			
4	75.4 d	3.84 m	H4-H5	H4-C3, H4-C6
5	34.7 t	2.30 m	H5-H4,	H5-C3, H5-C6
		1.94 dd 14.0, 3.1	H5-H6	
6	83.4 d	3.84 m	H6-H5	H6-C3
7	71.7 s			
8	26.4 q	1.09 s		H8-C6, H8-C7, H8-C9
9	27.6 q	0.78 s		H9-C6, H9-C7, H9-C8
10	21.0 q	1.32 s		H10-C2, H10-C3, H10-C4

a.) Determine the molecular formula of pantoisofuranoid A. (4)
b.) Calculate the number of double bond equivalents. (2)
c.) What are the functional groups present in pantoisofuranoid A? Present your evidence for each one. (4)
d.) Using the 1D and 2D NMR data determine the structure of pantoisofuranoid A. Explain your reasoning at all stages. (10)

2005 EAQ2

Massarinolin A, a sesquiterpene isolated from an aquatic fungus *Massarina tunicata*, is shown below. ^{1}H NMR data and selective NOEs are given in the table below.



Position	^{1}H NMR data (δ/ppm, mult, *J*/Hz)	NOE correlations
3	6.95, q, 1.3	4.22
5	4.22, broad s	2.27, 3.14, 6.95
7	2.63, m	
8	2.27, ddd, 10.0, 5.7, 5.7	4.22
	1.57, d, 10.0	1.64
9	3.14, d, 5.7	4.22, 4.87
11	2.58, m	4.84
	2.22, ddd, 17.0, 9.4, 1.2	4.84
12	1.98, dddd, 12.0, 9.4, 4.2, 2.4	
	1.64, m	3.93
13	1.94, d, 1.5	
14	3.99, d, 9.6	1.98, 2.58, 3.14, 4.84, 4.87
	3.93, d, 9.6	2.63, 1.64
15	4.87, m	3.14, 3.99
	4.84, m	2.22, 3.99

a.) Using the Karplus curve below, assign the diastereotopic chemical shifts for positions 11 and 12 to equatorial and axial protons. Indicate the chemical shifts and all the coupling constants you can assign on a clear conformational drawing of the relevant part of the molecule. (5)

b.) Confirm your answer to part a.) using the NOE information provided. Indicate the relevant NOE correlations on a separate clear conformational drawing. (3)

c.) Using the coupling constant information, assign the diastereotopic protons at position 8. Explain why why the signal at δ 1.57 ppm is only a doublet. Rationalise your assignments using the NOE information. (5)

d.) Use the NOE information provided to assign the diastereotopic protons at position 14. (4)

e.) Use the NOE information provided to determine the stereochemistry at position 5. (3)

2004 EAQ1

A natural product containing a chlorinated double bond shows a molecular ion cluster at *m/z* 188/190 in its mass spectrum. The ^{1}H and ^{13}C NMR data are given in the table below, as well as the ^{1}H-^{1}H COSY and HMBC (C $\rightarrow$ H, 2 and 3 bonds only) data.

(Hint – there are two isotopes of Cl, ^{35}Cl and ^{37}Cl)

^{13}C NMR (δ/ppm, multiplicity) at 100MHz and ^{1}H NMR (δ/ppm, proton count, multiplicity, *J*/Hz) at 400 MHz and ^{1}H-^{1}H COSY and HMBC data in $CDCl_3$

	^{13}C	^{1}H	COSY	HMBC
			H-H	C→H
A	139.2 d	5.76 1H m	d/d', f	f, h
B	133.0 s			c, e, j
C	127.6 d	5.75 1H m	e, j	e, g, j
D	114.1 t	4.94 dq 17.1 1.8	a, f	a, f
		4.88 dquint 10.3 1.0		
E	66.9 t	4.12 1H s	c, OH	c
F	33.7 t	2.00 2H q 7.1	a, d/d', h	a, d/d'
G	29.2 t	1.27 2H m	i, j	i, j
H	28.7 t	1.33 2H m	f, i	
I	28.4 t	1.36 2H m	g, h	h
J	28.1 t	2.16 2H q 7.2	c, g	c

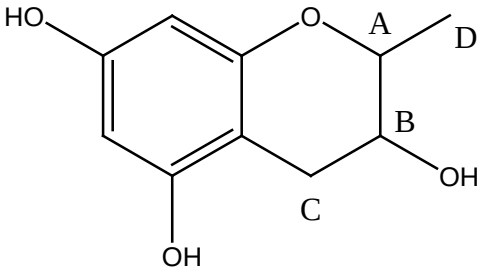
a. The accurate mass of the molecule is 188.0968. Using the NMR data and the accurate mass, calculate the molecular formula. (4)

(^{1}H = 1.0078, ^{12}C = 12.0000, ^{16}O = 15.9949, ^{35}Cl = 34.9689)

b. Calculate the double bond equivalents. (2)
c. Besides the chlorinated double bond, what are the other functional groups present? (2)
d. Generate a list of substructures consistent with your answer to c.) and the molecular formula. (4)
e. Propose a structure for the natural product that is consistent with all the 1D and 2D NMR data given. Show how you used the 2D NMR data to generate your final structure. (8)

2004 EAQ2

a. Explain the effect of chemical equivalence/magnetic non equivalence. Use chemical structures and draw spectra to illustrate your answer. (8)
b. Selected ^{1}H NMR data is given for the structure below. Determine the relative stereochemistry of the OH and the Me groups. Assign the diastereotopic protons at C to the equatorial or axial position. (8)
c. In addition, NOE spectra showed the following enhancements:
   Irradiation at 1.43 ppm enhanced a peak at 2.70 ppm
   Irradiation at 4.10 ppm enhance peaks at 3.94 and 2.32 ppm
   Rationalise this information with respect to your answer to part b.)



	δ_H/ppm	mult	J/Hz
A	3.94	dq	4.0, 6.8
B	4.10	ddd	10.3, 6.2, 4.0
C	2.70	dd	12.5, 10.3
	2.32	dd	12.6, 6.2
D	1.43	d	6.8

2003 EAQ1

^{1}H, ^{13}C, ^{1}H-^{1}H COSY NMR, IR and MS data for an unknown compound is summarised below. Using this information:

a	Determine the molecular formula of the unknown compound.	3
b	Determine the plane structure of the molecule. You may wish to use the ^{1}H-^{1}H COSY data to construct a spin system. Is there more than one possible structure that is consistent with the data given?	7
c	Assign the ^{1}H and ^{13}C chemical shifts to the structure.	4
d	Given that there is a strong NOE detectable between peaks in the ^{1}H NMR spectrum at 4.6 and 4.2 ppm, use this information to determine the relative stereochemistry of the compound in question.	3
e	Explain the formation of the *m/z* 86 fragment in the MS and explain the fragmentation.	3

Spectroscopic data:

IR: 3400 cm^{-1} (broad); 1620 cm^{-1} (strong)
MS: 131, 86 *m/z*
accurate mass: 131.0582
(C = 12.0000; H = 1.0078; O = 15.9949; N = 14.0031)

^{13}C NMR data (δ/ppm, mult): 175 (s); 69 (d); 60 (d); 53 (t); 38 (t).

^{1}H NMR data (δ/ppm, integral, mult, *J*/Hz)
4.55, H, m
4.18, H, dd, 10.6, 3.8
3.43, H, dm, 12.4
3.34, H, dd, 12.6, 3.8
2.47, ddd, H, 14.4, 10.2, 4.7
2.22, dm, H, 14.6

(dm = double multiplet, coupling constant given for doublet)

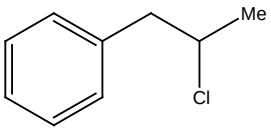
^{1}H-^{1}H COSY data. There are correlations between peaks at the following chemical shifts:
4.55-3.43; 4.55-3.34; 4.55-2.47; 4.55-2.22; 4.18-2.47; 4.18-2.22; 3.43-3.34; 2.47-2.22

2003 EAQ2

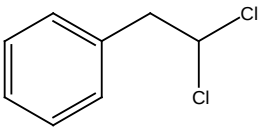
Many natural compounds contain chiral centres, and this complicates the interpretation of ^1H NMR spectra as CH_2 groups become diastereotopic.

a Using illustrative examples, briefly explain the terms homotopic, enantiotopic and diastereotopic. 4

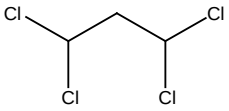
b For the three structures given below, indicate whether the CH_2 is homotopic, enantiotopic or diastereotopic. Draw the expected coupling pattern for the CH_2 in an achiral and in a chiral solvent. 8



1

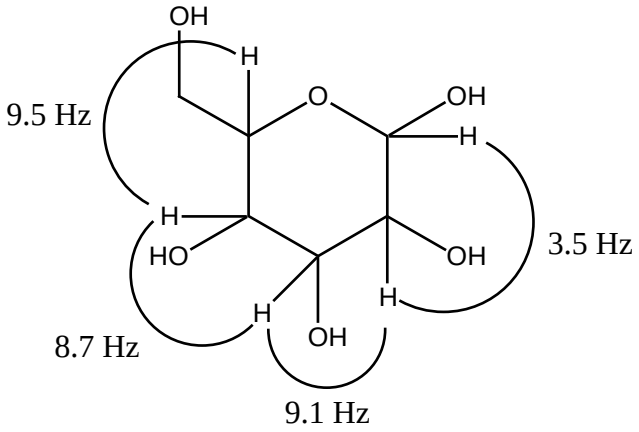


2



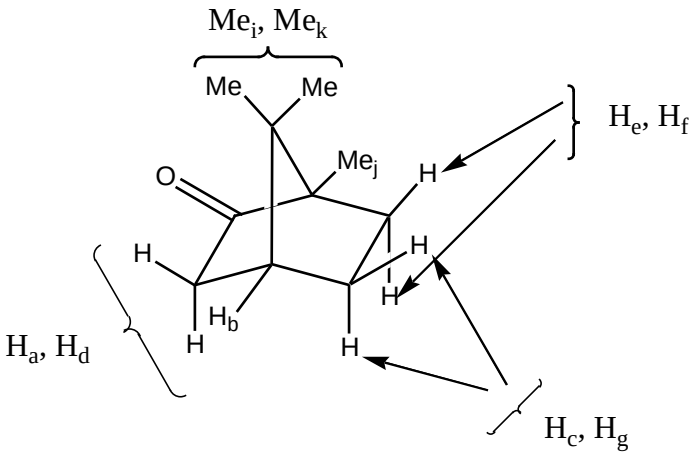
3

c The general structure of a sugar molecule with relevant coupling constants is given below. Using you knowledge of axial-axial, axial-equatorial and equatorial-equatorial coupling constants for six membered rings, determine the relative stereochemistry of the sugar molecule and produce a clear conformational drawing. 8



2002 EAQ1

a. Give a brief qualitative description of the origin of the NOE effect between two protons I and S. Diagrams should form a large part of your answer. (8).
b. Non-stereospecific assignments for camphor are given on the structure below. Data acquired from a difference NOE spectrum is tabulated below. Using this data assign H_a, H_c, H_d, H_e, H_f, H_g, Me_i and Me_k stereospecifically. Give your reasoning. (12)



Camphor

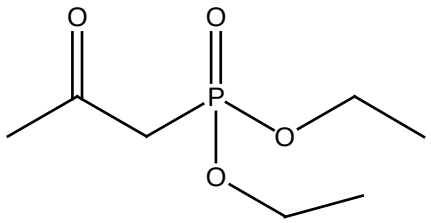
Irradiate	Enhancement
H_a	H_b, H_d, Me_k
H_c	H_b, H_e, H_f, H_g
Me_i	H_b, H_c, H_e
Me_k	H_a, H_b

2002 EAQ2

a. Which of the following nuclei is the most receptive in NMR at natural abundance? (4)

Nucleus	Natural abundance	Gyromagnetic ratio
^{13}C	1.1%	6.76
^{15}N	0.4%	2.70
^{19}F	100%	25.1
^{31}P	100%	10.8

b. Using your knowledge of ^{13}C NMR chemical shifts draw the expected ^{13}C NMR spectrum of the compound below. (8)

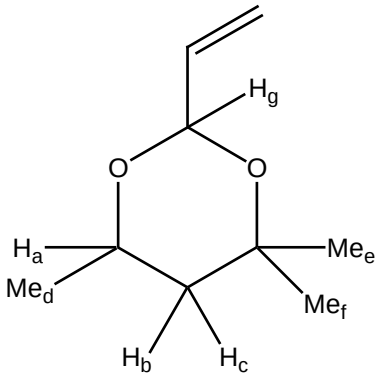


c. The ^{1}H NMR data for a compound $C_4H_{11}O_3P$ is given below. Determine the structure of the compound, and explain the coupling patterns observed. (8)

δ_H (ppm)	multiplicity (J, Hz)	No. of H
6.8	d, 692	1
4.2	dq, 9.1, 7.0	4
1.4	t, 7.0	6

2001 EAQ1

a Briefly describe how the Karplus curve can be used to determine relative stereochemistry for rigid cyclic systems. 5



b For protons H_a, H_b and H_c in the molecule above the coupling constants are:
H_a, dd, J = 14.0, 4.5 Hz
H_b, dd, J = 15.0, 4.5 Hz
H_c, dd, J = 15.0, 14.0 Hz

i Copy the structure into your answer book and indicate indicate the magnitude of the couplings between H_a, H_b and H_c. 3

ii Use the Karplus curve below to determine the possible values for the two relevant dihedral angles. 3

iii Draw the above molecule in the chair conformation and indicate the relative stereochemistry of H_a, H_b and H_c. 4

c NOE difference experiments were performed. When H_g was irradiated, the ^1H NMR signals for H_a and Me_e were enhanced. In addition, irradiating H_c gave enhancements at H_b, Me_d and Me_f. Use this information to determine the relative stereochemistry of Me_d, Me_e, Me_f and H_g. 5

2001 EAQ2

A compound has the following IR, MS and NMR spectra:

IR:
2900-3000 cm^{-1} (s)
1600 cm^{-1} (s)
1200 cm^{-1} (s)

MS:
Low resolution electron impact m/z 100, 85, 56, 44
High resolution electron impact m/z 100.0888
(H = 1.0078; C = 12.0000; N = 14.0031; O = 15.9949)

^{1}H NMR:
6.44 ppm, 1H, dd *J* = 14.0, 7.0 Hz
4.18 ppm, 1H, dd *J* = 14.0, 1.5 Hz
3.94 ppm, 1H, dd *J* = 7.0, 1.5 Hz
3.61 ppm, 2H, t *J* = 7.0 Hz
1.63 ppm, 2H, quintet, *J* = 7.0 Hz
1.41 ppm, 2H, sextet, *J* = 7.0 Hz
0.97 ppm, 3H, triplet, *J* = 7.0 Hz

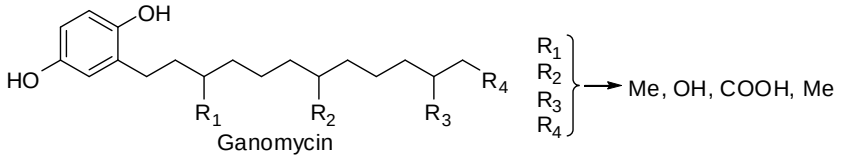
^{13}C NMR:
152 ppm CH
87 ppm CH_2
68 ppm CH_2
32 ppm CH_2
20 ppm CH_2
15 ppm CH_3

Use this information to:

a	i	Determine the molecular formula of the compound	4
	ii	Find the two functional groups present in the molecule	2
	ii	Elucidate the structure of the molecule	8
b		Assign all the ^{1}H and ^{13}C NMR data to the structure, and explain the low resolution mass spectral fragmentations.	6

One extra question:

The incomplete structure of ganomycin isolated from the basidiomycete fungus *Ganoderma pfeifferi* is given below. The side chain contains and additional three double bonds and groups R_1-R_4. Use the ^1H, ^{13}C, ^1H-^1H COSY and HMBC data, acquired in CD_3OD, to place the three double bonds and groups R_1 – R_4 in their correct positions and fully assign the ^1H and ^{13}C NMR data to this structure.



1D and 2D NMR spectral data for ganomycin obtained in $CDCl_3$ at 400/100 MHz (δ in ppm)

Atom	^{13}C (δ/ppm, mult)	^1H (δ/ppm, mult, *J*/Hz)	^1H-^1H COSY	HMBC (C-H, 2-3 bonds)
A	173 s			p
B	151 s			l
C	149 s			k, m, q
D	141 d	5.98 t 7.8	q	p
E	137 s			t
F	136 s			u
G	133 s			p, q
H	128 s			d
I	127 d	5.39 t 7.1	s	n, u
J	125 d	5.14 t 7.3	r	o, t
K	118 d	6.61 d 2.8	m	q
L	117 d	6.64 d 8.5	m	
M	115 d	6.52 dd 8.5 2.8	k, l	
N	69 t	3.94 s		i, u
O	40 t	2.00 t 7.8	s	j, t
P	36 t	2.33 t 7.2	r	d
Q	32 t	3.69 d 7.7	d	k
R	28 t	2.19 q 7.2	j, p	
S	27 t	2.10 q 7.5	i, o	
T	16 q	1.61 s		j, o
U	14 q	1.66 s		i, n