Structure Elucidation of the Photooxygenation Products of 1,2-Dihydronaphthalenes[†]

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Photooxygenation of 1,2-dihydronaphthalenes resulted in diendoperoxides and hydroperoxides via [4 + 2] cyclo-addition and ene reactions, respectively. The relative configuration and stereochemistry of the products were eluci-dated by various ^{1}H and ^{13}C NMR methods. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

In connection with the synthesis of analogues of podophyllotoxin (**1**) (for a recent review, see Ref. 1), we investigated the photooxygenation of the chiral 1,2-dihydronaphthalenes **2** (Scheme 1).[2] Products of both [4 + 2] cycloadditions (**3**) and ene reaction (**4**) were obtained. Interestingly, the diendoperoxides **3** and hydroperoxides **4** were formed as single diastereomers in all reactions. Hence it was important to establish the relative configuration of all stereocentres. Elucidation of the stereochemistry of the diendoperoxides **3** and hydroperoxides **4**, and the corresponding hydroxy analogues **5a** and **6a**, and their complete ^{1}H and ^{13}C NMR assignments are discussed.

RESULTS AND DISCUSSION

Structure elucidation of compounds **3–6** is based on the NMR spectroscopic assignments which were confirmed by ^{1}H,^{1}H COSY, ^{1}H,^{13}C HMQC,[3] ^{1}H,^{13}C HMBC[4] and phase-sensitive NOESY[5] experiments. The ^{1}H and ^{13}C chemical shifts and proton–proton coupling constants are summarized in Tables 1 and 2 and the results of HMBC measurements are given in Table 3.
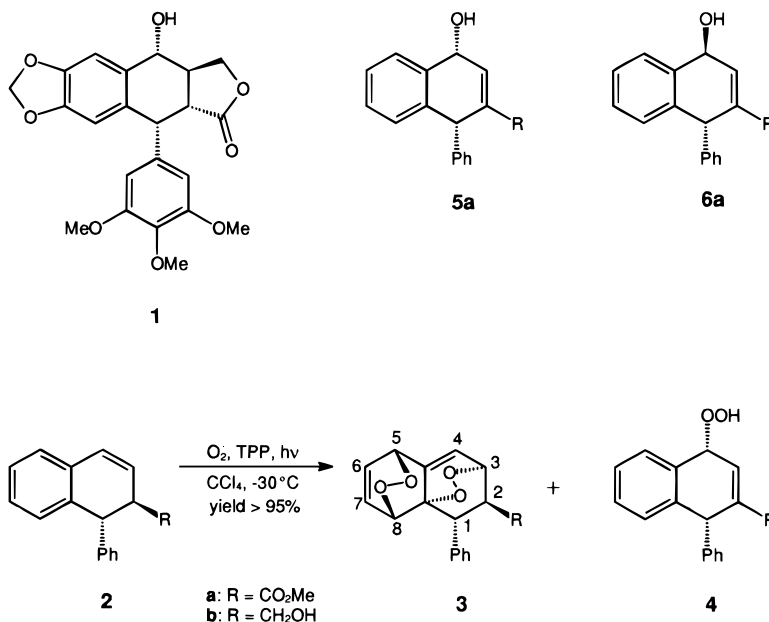
1

5a 6a

2 **a**: R = CO₂Me **b**: R = CH₂OH 3 4

Scheme 1

Table 1. ^{1}H chemical shifts (ppm) and proton–proton couplings (Hz) of compounds 3–6

	3a	3b	4b	5a	6a[a]
1-H	3.76	2.76	5.60	5.42	5.50
2-H	3.64	2.93	6.31	7.26	7.26
3-H	5.15	5.02	—	—	—
4-H	6.54	6.55	4.62	5.04	5.13
5-H	5.19	5.20	7.11	7.13	7.22
6-H	6.83	6.83	7.23	7.21	7.22
7-H	6.50	6.51	7.26	7.25	7.28
8-H	4.21	4.18	7.57	7.51	7.68
11-H$_a$	—	3.36	4.05	—	—
11-H$_b$	—	3.65	4.05	—	—
OH	—	1.57	1.60	2.18	2.35
CH$_3$O	3.67	—	7.97	3.67	3.70
ortho	7.57	7.54	7.31	7.30	7.10
meta	7.39	7.37	7.26	7.24	7.20
para	7.31	7.31	7.18	7.15	7.13
$J_{1,2}$	5.6	5.7	4.7	4.8	2.4
$J_{2,3}$	3.6	3.4			
$J_{3,4}$	5.8	5.8			
$J_{5,6}$	6.2	6.2			
$J_{6,7}$	8.1	8.3			
$J_{7,8}$	6.1	6.2			
$J_{2,11a}$	—	10.1			
$J_{2,11b}$	—	5.0			
$J_{4,5}$	1.0	1.1			
$J_{5,7}$	1.3	1.4			
$J_{6,8}$	1.3	1.4			
$J_{1,4}$	—	—	2.9	2.9	2.9

[a] J(1-H,OH) = 9.5 Hz.

Table 2. ^{13}C chemical shifts of compounds 3–6

	3a	3b	4b	5a	6a
C-1	43.5	43.3	78.6	65.4	65.9
C-2	50.3	48.1	118.4	135.2	139.8
C-3	73.5	75.0	146.4	129.8	132.7
C-4	121.0	121.1	46.9	45.3	45.6
C-5	71.8	72.1	129.6	129.5	128.6
C-6	132.8	132.6	128.7	128.4	128.3
C-7	131.9	132.1	126.5	127.0	127.0
C-8	71.3	71.6	129.4	128.6	126.7
C-9	76.0	76.2	130.7	133.8	135.4
C-10	141.8	141.0	140.2	138.5	136.8
C-11	171.4	64.5	64.6	166.5	166.3
CH$_3$O	52.3	—	—	51.9	52.0
ipso	137.2	137.6	142.7	142.9	143.3
ortho	129.8	132.1	128.8	128.6	127.9
meta	128.6	128.6	128.8	128.6	128.6
para	127.6	127.5	126.9	126.6	128.6

shielding effect of the 1-phenyl group in the starting material **2**, the attack of ^{1}O$_2$ should be directed to the opposite side of the ring, but the attractive interactions between the terminal oxygen and the allylic hydrogen in an intermediate with peroxide geometry over-compensate the effect of the 1-phenyl group.[2,6] Thus, attack of singlet oxygen occurs exclusively *cis* to the 1-phenyl group. In the resulting 1,4(here 3,9)-oxygen bridged product, the *trans* 1-Ph and 2-R substituents can be arranged ax/eq or eq/ax in the boat-type cyclohexene ring. The primary endoperoxides undergo a fast second addition of a singlet oxygen, which *a priori* can proceed *cis* or *trans* to the endoperoxide bridge. Hence we should consider structures I–IV for compounds **3** (Scheme 2). The arrows indicate the important steric proximities which give evidence for structure type IV for compounds **3**. The characteristic proton–proton responses resulting from the NOESY experiment are compiled in Table 4.

The NOESY cross peak between 1-H and 4-H proves the equatorial arrangement of the phenyl group in position 1, furthermore supporting the assignment of 8-H. 8-H is located above the plane of the 1-Ph group, resulting in a characteristic upfield shift of this signal (δ8-H = 4.21 and 4.18, respectively). In **3a** the cross peak between CO$_2$CH$_3$ and 4-H protons whereas in the case of **3b** the observed steric proximity between 11-Ha and 4-H are in accordance with the preservation of the

The HMBC measurements were very useful not only for the unambiguous assignment of the quaternary carbon atoms, but in particular for the assignment of proton-bearing sp^2 carbon atoms with overlapping signals of the attached protons. An additional advantage of this method is that it provides a bridge between separated spin systems. In the case of **3a**, we utilized the three-bond HMBC correlation of 4-H with C-5, thus allowing the assignment of 5-H via the HMQC experiment. In this way, all protons of **3** could be assigned.

To elucidate the relative configuration of all six stereocentres in bisendoperoxides **3a** and **3b**, phase-sensitive NOESY spectra were recorded. In the case of 1,2-dihydronaphthalenes **2a** and **2b**, the [4 + 2] cycloaddition of ^{1}O$_2$ may proceed either *cis* to the phenyl group or on the opposite side. Considering the steric

Table 3. ^{1}H–^{13}C long-range correlations for compounds 3a, 5a and 5b observed by 2D HMBC measurements [J(C,H) = 7 Hz]

	3a	4b	5a	6a
1-H	C-2; C-3; C$_{ipso}$; C$_{ortho}$;	C-2; C-3	C-2	
2-H	C-1; C-3; C-4; C$_{ipso}$; C-11	C-1; C-4; C-8; C-9; C-11	C-1; C-3; C-4; C-9; C-11	C-4; C-9; C-11
3-H	C-1; C-4; C-10	—	—	—
4-H	C-2; C-3; C-5; C-9	C-2; C-3; C-9; C-10; C$_{ipso}$; C$_{ortho}$	C-2; C-9; C-10; C$_{ipso}$; C$_{ortho}$	C-2; C-3; C-9; C-10; C$_{ipso}$; C$_{ortho}$
5-H	C-4; C-6; C-7; C-9; C-10	C-4; C-7; C-9	C-4; C-7; C-9	
6-H	C-5; C-8; C-10	—	—	—
7-H	C-5; C-8; C-9	—	—	—
8-H	C-6; C-7; C-9; C-10	C-1; C-6; C-10	C-1; C-6; C-10	C-1; C-6; C-10
OCH$_3$	C-11	—	C-11	C-11
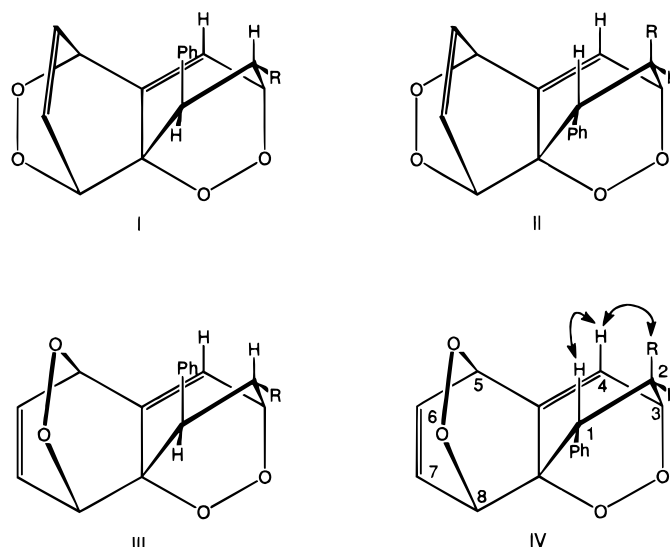
Scheme 2

trans configuration of the 1-Ph and 2-R substituents, that is, R-2 is axial.

A cross peak could even be detected between 6-H and 8-H, (interproton distance *ca.* 4.4 Å). In structures I and II, the interproton distance between 1-H and 7-H is *ca.* 3 Å, and so a strong NOESY cross peak should appear.

Table 4. Characteristic proton–proton proximities resulting from 2D NOESY measurements for compounds 3–6

Compound	Proton	NOE observed (%)
3a	1-H	3-H; 4-H; 8-H; H_{ortho}
	2-H	3-H; H_{ortho}
	3-H	1-H; 2-H; 4-H;
	4-H	1-H; 3-H; 5-H; CH_3O
	5-H	4-H; 6-H; 7-H
	6-H	5-H; 7-H; 8-H;
	7-H	5-H; 6-H; 8-H
	8-H	1-H; 6-H; 7-H; H_{ortho}
3b	1-H	2-H; 4-H; 8-H; 11-H_a; 11-H_b; H_{ortho}
	2-H	1-H; 3-H; 11-H_a; 11-H_b; H_{ortho}
	3-H	2-H; 4-H; 11-H_a; 11-H_b;
	4-H	1-H; 3-H; 5-H; 11-H_a
	5-H	4-H; 6-H; 7-H
	6-H	5-H; 7-H; 8-H
	7-H	5-H; 6-H; 8-H
	8-H	1-H; 6-H; 7-H
4b	1-H	2-H; 4-H; 8-H
	2-H	1-H; 4-H; 11-H;
	4-H	1-H; 2-H; 5-H; 11-H; H_{ortho}
	5-H	4-H;
	8-H	1-H
	11-H	2-H; 4-H; 8-H
5a	1-H	2-H; 4-H; 8-H; OH
	4-H	1-H; 5-H; H_{ortho}; CH_3O
	8-H	1-H; OH
	CH_3O	2-H; 4-H; H_{ortho};
	OH	1-H; 2-H; 8-H; H_{ortho}
6a	1-H	2-H; 8-H; OH; H_{ortho}
	4-H	5-H; H_{ortho}
	8-H	1-H; 7-H; OH
	CH_3O	2-H
	OH	1-H; 2-H; 8-H

The lack of any observable cross peak between 1-H and 7-H thus points to the *trans* arrangement of the two endoperoxyldic bridges and we conclude that structure IV describes the relative configuration of the diendoperoxides **3a** and **3b**.

Photooxygenation of **2** affords, in addition to the bisendoperoxides **3**, 1,4-dihydronaphthalenes **4** via an ene reaction. This reaction again exhibits a very high degree of stereoselectivity. Attack of $^1O_2$ *cis* to the 1-Ph group results in the *cis*-**4** isomer, whereas *trans*-**4** results from the opposite arrangement. The elucidation of the isomeric structures is rendered difficult because of a rapid ring inversion, resulting in an equilibrium of the two boat conformers (A/B) (Scheme 3).[7]

In the *cis* isomers, the 1-Ph and 4-OOH substituents are in the 1eq,4eq or 1ax,4ax positions; in the *trans* isomer they are arranged 1eq,4ax or 1ax,4eq. Care must be taken in evaluating the preferred steric position of the C-1 and C-4 substituents, as the energies of the two conformers are expected to be close to each other owing to an unfavourable steric interaction (1,3-allylic strain)[8] between the substituent and the fused aromatic ring in the equatorial case. The 1,3-γ-*gauche* interaction, destabilizing the axial position of substituents, is considerably reduced owing to the boat conformation of the dihydrocyclohexa-1,4-diene ring. In the case of **4a**, because of its tendency to decompose, the hydroperoxide was directly reduced with triphenylphosphine to the corresponding **5a** hydroxy compound. As a

	R	R^1	R^2
4b	CH_2OH	H	OOH
5a	CO_2Me	H	OH
6a	CO_2Me	OH	H
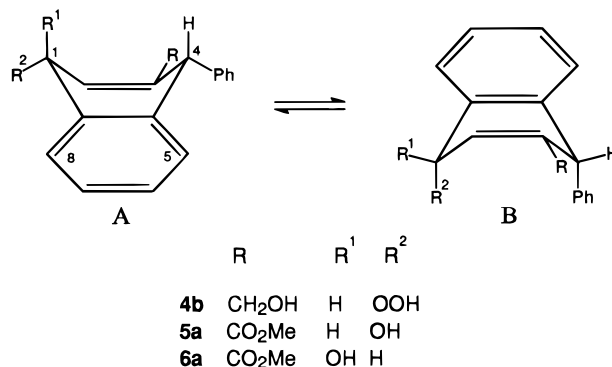
Scheme 3

model compound, the isomeric **6a** was also synthesized and investigated.

It has been found previously that δ5-H may be indicative of the steric arrangement of the 1-phenyl group, since the planes of the two aromatic groups are nearly perpendicular, owing to the steric interaction between the equatorial 1-Ph and the fused aromatic ring.[7] This results in an upfield shift of the 5-H signal. Furthermore, it is known that in cyclohexa-1,4-dienes and in their fused-ring analogues the ^5J(1-H,4-H) homoallylic coupling constants may provide confirmatory evidence for the steric arrangement of 1-H and 4-H protons.[9] For the isomeric compounds **5a** and **6a** neither characteristic differences in the chemical shifts of 5-H (7.13 and 7.22) nor in ^5J(1-H,4-H) homoallylic couplings (2.9 and 3.3 Hz) could be observed. In conformer A the dihedral angle between 1-H and 2-H bonds should be around 90°, whereas that in conformer B is ca. 30°. Considering the couplings for **4b**, **5a** and **6a** [^3J(1-H,2-H) = 4.7, 4.8 and 2.4 Hz, respectively], we conclude that these compounds exist in $CDCl_3$ at room temperature in an equi-

librium of conformers A and B, and their rapid interconversion leads to averaged chemical shifts and couplings. The considerably smaller allylic coupling (2.4 Hz) in **6a** indicates that in this case the population of conformer B should be higher than those of compounds **4b** and **5a**. The cis configuration of **4b** is substantiated by the 1-H/4-H NOESY cross peak (Fig. 1). The cross-peak (see Table 4) between 1-H and 4-H in the phase-sensitive 2D NOESY spectrum of **5a** proves the cis configuration and the participation of conformer A in the A/B conformational equilibrium, whereas the NOE between OH and ortho-protons verifies the same for conformer B. In case of the isomeric **5a**, the observed NOESY cross peak between 1-H and ortho-protons proves the trans configuration and the existence of conformer A in the conformational equilibrium.

The cis configuration of **4b** and **5a** proves that the attack of $^1O_2$ proceeds cis to the 1-Ph group also in the ene-reaction. The same degree of stereoselectivity of the ene and [4 + 2] cycloaddition provides strong evidence that both reaction modes exhibit a common interme-
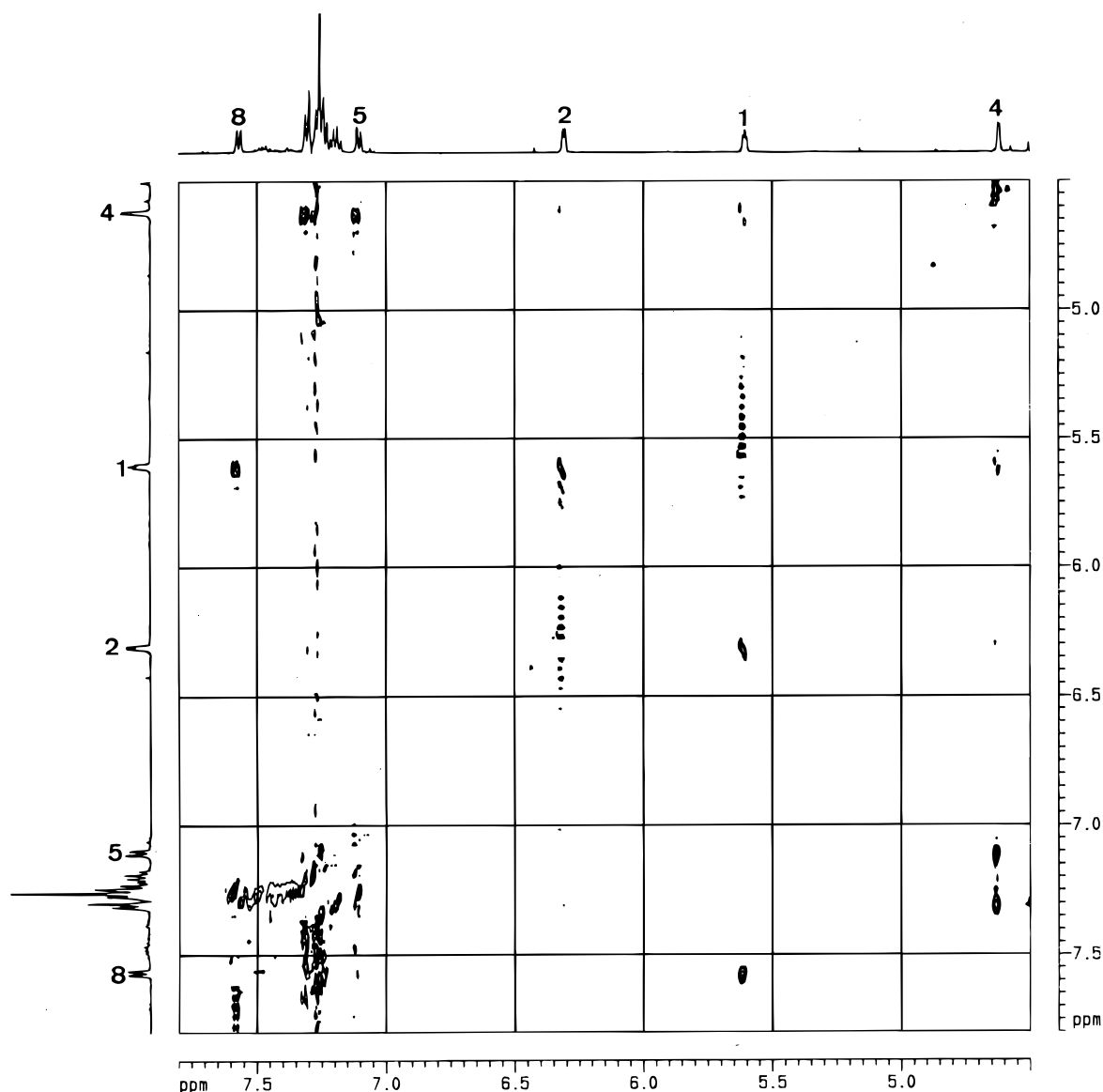

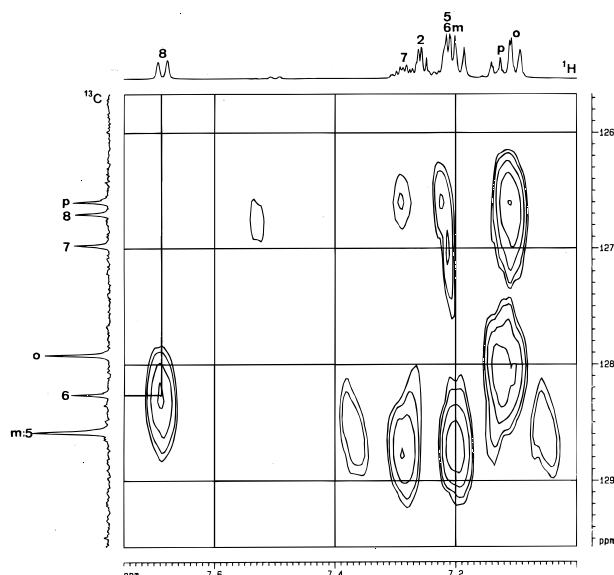**Figure 1.** 500 MHz ^{1}H,^{1}H Phase-sensitive 2D NOESY spectrum of **4b**.

Figure 2. 500/125 MHz ^{1}H, ^{13}C HMBC spectrum of **6a**.

diate with perepoxide geometry, and the reactions are controlled by favourable interactions between the allylic hydrogen and the terminal oxygen atom in the intermediate.[6]

To achieve an unambiguous ^{13}C signal assignment for the isomeric compounds **5a** and **6a**, HMQC and HMBC measurements were performed. In **6a**, the virtual isochrony of 5-H and 6-H did not allow the assignment of C-5 and C-6; however, this task could be accomplished by an HMBC experiment (Fig. 2).

The cross peak between 8-H and C-6 proved the δC-6 = 128.3 assignment. The similar ^{13}C chemical shifts for the *cis*-**5a** and *trans*-**6a** isomeric pair result from the rapid conformational interconversion of the A/B boat conformers.

EXPERIMENTAL

Syntheses

Synthesis of compounds **2–5**[2] and **6**[10] have been published previously.

Spectra

NMR spectra were measured on a Bruker DRX-500 spectrometer at room temperature in CDCl$_3$. Chemical shifts (ppm) are given on the δ scale; ^{1}H NMR spectra were referenced to internal TMS and ^{13}C NMR spectra to the solvent (δCDCl$_3$ = 77.0 ppm). In the 1D measurements, 64K data points were accumulated. Operating conditions were as follows.

500 MHz phase-sensitive NOESY spectrum. Relaxation delay D_1 = 1.5 s, mixing time 500 ms, 90° pulse 11.5 µs, sweep width 10 ppm in F_1 and F_2, 2 K points in t_2, 256 experiments in t_1, quadrature detection in t_2, TPPI in t_1, linear prediction to 512 and zero filling up to 1 K real points in F_1 and apodization with a $\pi/2$-shifted squared sine bell in both dimensions.

500/125 MHz HMQC spectrum with BIRD presaturation. Relaxation delay D_1 = 1.5 s, presaturation delay D_7 = 400 ms, evolution delay D_2 = 3.45 ms, 90° pulse 11.5 µs for ^{1}H, 12.5 µs for ^{13}C hard pulses and 65 µs ^{13}C GARP decoupling, 1K points in t_2, sweep width 10 ppm in F_2 and 160 ppm in F_1, 128 experiments in t_1, linear prediction to 256 and zero filling up to 512 real points in F_1 and apodization with a $\pi/2$-shifted squared sine bell in both dimensions.

500/125 MHz HMBC (DRX-500). Relaxation delay D_1 = 1.5 s, delay for evolution of long range coupling D_6 = 70 ms (J = 7 Hz), evolution delay D_2 = 3.45 ms, 90° pulse 11.5 µs for ^{1}H, 12.5 µs for ^{13}C hard pulses, 2K points in t_2, sweep width 10 ppm in F_2 and 220 ppm in F_1, 256 experiments in t_1, linear prediction to 512 real points in F_1 and apodization with a $\pi/2$-shifted squared sine bell in both dimensions.

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