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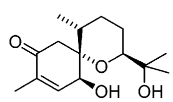
ABSTRACT



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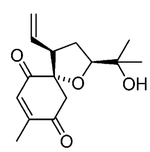

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From the medium, polar bioactive fractions of leaf aqueous extract of *Helianthus annuus* L., heliespirones B (2) and C (3) have been isolated. The structural elucidation was based on extensive spectral studies. A probable biogenesis of heliespirone skeleton is proposed and discussed. The structure of heliespirone B has been confirmed by X-ray diffraction analysis.

In 1998, we reported the isolation of heliespirone A (**1**), the first member of a new class of bioactive sesquiterpenes, named heliespirane.[1] The main constitutional characteristic of this compound is that the structure displays an unusual previously unknown spirosesquiterpene skeleton. Whereas spiroacetals are relatively common as natural products,[2] oxaspirocyclic compounds are rare. An example of this structure is the central part of the skeleton of oscillatoxin D,[3] a minor constituent of the marine blue-green alga *Lyngbya majuscule* (Oscillatoriaceae). This alga is the causative agent of a severe contact dermatitis in Hawaii and Okinawa.[4]

The structure elucidation of **1** was performed by homo- and heteronuclear 2D-NMR spectral data, and the relative stereochemistry was proposed by NOE experiments. In the course of our ongoing research on bioactive compounds from cultivars, we have isolated two new sesquiterpenes which contain six- and five-membered spiroheterocyclic skeletons heliespirones B (**2**) and C (**3**), respectively (Figure 1).

Leaves of *H. annuus* L. cv. SH-222 and Atila commercialized by Semillas Pacifico and SENASA (Peru), respectively, were collected during the third plant development stage (plants 1.2 m tall with flowers, 1 month before harvest).[5] They were provided by Rancho de la Merced, Agricultural Research Station, Junta de Andalucia, Jerez, Spain. The collection period was established on the basis of phytotoxic bioactivity exhibited by the different leaf aqueous extracts

† Universidad de Cádiz.
‡ Louisiana State University.
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Table 1. ^{1}H and ^{13}C NMR Spectroscopic Data (δ in ppm, J in Hz) of **2** and **3** (in $CDCl_3$)

	2		**3**	
position	δ_H	δ_C	δ_H	δ_C
1		81.8		86.9
2	4.48 dt (4.8, 2)	74.6		196.5
3	6.60 dt (4.8, 1.4)	143.9	6.63 q (1.5)	136.9
4		135.7		151.7
5		197.4		196.3
6	3.09 d (16.4)	40.2	2.95 d (16.2)	48.5
	2.44 d (16.4)		2.83 d (16.2)	
7	2.05 ddt (13.4, 4.1, 6.9)	33.8	5.61 ddd (16.4, 10.5, 8.5)	134.6
8	α 1.46 dddd (13.4, 13.3, 12.5, 3.5)	28.4	3.26 brddd (12.2, 10.5, 7.1)	47.0
	β 1.64 dddd (4.1, 13.3, 3.9, 2.9)			
9	α 1.60 dddd (3.5, 2.9, 12.5, 2.3)	25.2	α 2.04 ddd (12.2, 7.1, 5.1)	32.4
	β 1.37 dddd (12.5, 3.9, 12.5, 11.7)		β 1.92 ddd (12.2, 12.2, 10.7)	
10	3.26 dd (11.7, 2.3)	76.5	3.95 dd (10.7, 5.1)	86.7
11		72.0		70.3
12	1.11 s	26.2	1.12 s	27.5
13	1.09 s	24.3	1.23 s	24.5
14	0.82 d (6.9)	18.7	5.12 dd (8.5, 1.1)	119.6
			5.09 dd (16.4, 1.1)	
15	1.75 dd (2, 1.4)	15.0	1.98 d (1.5)	16.1

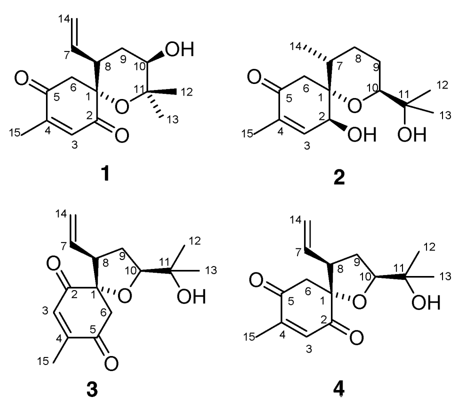


Figure 1. Heliespirones isolated from *Helianthus annuus*.

corresponding to four different plant development stages.[6] The phytochemical study was made following a biodirected fractionation methodology.

Fresh leaves of sunflower cv. Atila (5.0 Kg) and SH-222 (6.0 Kg) were soaked with H_2O (weight of plant/volume of solvent 1:3) for 24 h at 25 °C in the dark. Each of the H_2O extracts were reextracted with CH_2Cl_2 (0.5 L per 1.0 L of water extract, 8×), and the organic extracts were dried over Na_2SO_4 and evaporated in a vacuum to yield 11.5 and 16.0 g of crude extract for the Atila and SH-222 cultivars, respectively.

Atila extract was fractionated by column chromatography (CC) on silica gel using hexane, ethyl ether, EtOAc, methanol, and water yielding fractions A1 (0.3 g), A2 (4.7 g), A3 (3.1 g), A4 (1.9 g), A5 (1.0 g), and A6 (0.8 g). The bioactive fraction A3 was chromatographed using silica gel and eluting with $CHCl_3$/acetone 9:1. After purification by HPLC with a Hibar Si 60 (Merck) column of less polar fractions using $CHCl_3$/methanol 19:1, heliespirone B (**2**) (22 mg) was isolated.

SH-222 extract was fractionated by CC on silica gel using hexanes−EtOAc mixtures of increasing polarity, yielding 170 × 50 mL fractions which were reduced to 26 fractions after comparison by thin layer chromatography (TLC), termed from A to Z by increasing polarity. The bioactive fraction Q was chromatographed using silica gel and eluting with $CHCl_3$/*t*-BuOH 98:2 (2 L) and 96:4 (1 L). After purification by HPLC with a Hibar Si 60 (Merck) column of less polar fractions, heliespirone C (**3**) (2 mg) was obtained.

Heliespirone B (**2**) was isolated as colorless crystals (mp 129−130 °C, *n*-hexane/ethyl acetate 1:8; $[\alpha]_D$ +19.6; c = 0.1, $CHCl_3$, 25 °C). Its HRMS spectrum with a molecular ion at m/z 268.1674 suggested a sesquiterpene with four unsaturations, with a molecular formula $C_{15}H_{24}O_4$, (calcd 268.1675) plus fragments at m/z 250 $[M - H_2O]^+$, and 235 $[M - CH_3 - H_2O]^+$. The IR, ^{1}H NMR, and ^{13}C NMR (Table 1) data present some analogies with those previously described for **1**, which suggested a heliespirane skeleton type for this compound. Thus, the ^{1}H NMR spectrum showed two doublets corresponding to the geminal protons, H-6 and H-6′ (δ 3.09; d and δ 2.44; d, J = 16.4 Hz) only coupled with each other and two singlets assigned to two methyl groups H-12 and H-13 (δ 1.11 and δ 1.09). The IR spectrum showed absorptions at 3448 cm^{-1} (hydroxyl group) and 1677 cm^{-1} (carbonyl group).

The ^{1}H NMR-2D-COSY spectrum presents a signal corresponding to a proton geminal to a hydroxyl group at 4.48 (dt, $J_{2,3}$ = 4.8, $J_{2,15}$ = 2, H-2), which is coupled with a proton at δ 6.60 (dt, $J_{2,3}$ = 4.8, $J_{3,15}$ = 1.4, H-3) assignable

(6) Macías, F. A.; Castellano, D.; Molinillo, J. M. G. *J. Agric. Food Chem.* **2000**, *48*, 2512−2521.

to a proton attached to a double bond conjugated with a carbonyl group. This signal is correlated with another at δ 1.75 (3H, dd, $J_{2,15} = 2$, $J_{3,15} = 1.4$, H-15) corresponding to a methyl moiety attached to a C−C double bond. The chemical shift of C-5 at δ 197.4 and correlation observed in the HMBC experiment with proton H-3 confirm the presence of a carbonyl group at position C-5.

The spectrum shows a second correlation series: H-14 (δ 0.82, 3H, d, $J_{7,14} = 6.9$) couples with H-7 (δ 2.05, ddt, $J_{7,8\alpha} = 13.4$, $J_{7,8\beta} = 4.1$, $J_{7,14} = 6.9$). H-7 is coupled with H-8α (δ 1.46, dddd, $J_{7,8\alpha} = 13.4$, $J_{8\alpha,8\beta} = 13.3$, $J_{8\alpha,9\beta} = 12.5$, $J_{8\alpha,9\alpha} = 3.5$) and H-8$\beta$ (δ 1.64, dddd, $J_{7,8\beta} = 4.1$, $J_{8\alpha,8\beta} = 13.3$, $J_{8\beta,9\beta} = 3.9$, $J_{8\beta,9\alpha} = 2.9$). Both protons appeared coupled with H-9β (δ 1.37, dddd, $J_{8\alpha,9\beta} = 12.5$, $J_{8\beta,9\beta} = 3.9$, $J_{9\beta,9\alpha} = 12.5$, $J_{9\beta,10} = 11.7$) and H-9α (δ 1.60, dddd, $J_{8\alpha,9\alpha} = 3.5$, $J_{8\beta,9\beta} = 2.9$, $J_{9\beta,9\alpha} = 12.5$, $J_{9\alpha,10} = 2.3$). These data, together with the chemical shift in the ^{13}C NMR of C-1 (δ 81.8), C-10 (δ 76.5), and C-11 (δ 72.0), allow us to propose the structure **2** for this compound (Figure 2).

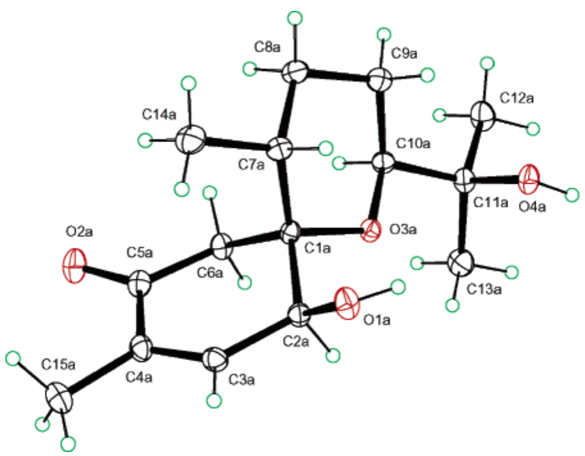


Figure 2. Single-crystal X-ray structure of **2** (ORTEP).

The relative stereochemistry of C-7 and C-10 can be deduced by the coupling constants that imply axial positions for H-7 and H-10 in a six-membered ring with a chair conformation. The stereochemistry of C-1 can be easily deduced from the NOE effects observed between H-10 and H-6. The stereochemistry of C-2 and the structure of heliespirone B was confirmed by X-ray diffraction analysis.

Heliespirone C (**3**) was isolated as colorless oil ($[\alpha]_D$ +14.4; $c = 0.1$, $CHCl_3$, 25 °C). Its HRMS spectrum with a molecular ion at *m/z* 264.1337 suggested a molecular formula $C_{15}H_{20}O_4$. The IR, ^{1}H NMR, and ^{13}C NMR (Table 1) data are very similar to those previously reported for **1**. Thus, the IR spectrum showed absorptions at 3458 cm^{-1} (hydroxyl group), 1692 and 1682 cm^{-1} (two carbonyl groups), and 1651 (double bond) and 1250 cm^{-1} (C−O−C asymmetric stretching).

The ^{13}C NMR spectrum confirmed this hypothesis with two signals corresponding to two carbonyl carbons C-2 (δ 196.5) and C-5 (δ 196.3) and four signals in the area of olefinic carbons C-3 (δ 136.9), C-4 (δ 151.7), C-7 (δ 134.6), and C-14 (δ 119.6).

The ^{1}H NMR spectrum showed a deshielded singlet (δ 6.63, q, $J_{3,15} = 1.5$, H-3) corresponding to a proton attached to a double bond conjugated with a carbonyl group and a doublet (δ 1.98, 3H, d, $J_{3,15} = 1.5$, H-15) which was assigned to a methyl group attached to the double bond.

In the 2D-COSY-^{1}H NMR spectrum the following correlations were observed: H-14 (δ 5.12, dd, $J_{7,14} = 8.5$, $J_{14,14'} = 1.1$) with H-14′ (δ 5.09, dd, $J_{7,14'} = 16.4$, $J_{14,14'} = 1.1$) and H-7 (δ 5.61, ddd, $J_{7,8} = 10.5$, $J_{7,14} = 16.4$, $J_{7,14'} = 8.5$); H-7 showed coupling with H-8 (δ 3.26; brddd, $J_{8,9\alpha} = 7.1$; $J_{8,9\beta} = 12.2$, $J_{7,8} = 10.5$) and H-8 with H-9α (δ 2.04; ddd, $J_{9\alpha,9\beta} = 12.2$; $J_{9\alpha,10} = 5.1$ Hz, $J_{8,9\alpha} = 7.1$) and H-9β (δ 1.92; ddd, $J_{9\beta,10} = 10.7$, $J_{9\alpha,9\beta} = 12.2$, $J_{8,9\beta} = 12.2$) and both coupled with the signal corresponding to H-10 (δ 3.95; dd, $J_{9\beta,10} = 10.7$; $J_{9\alpha,10} = 5.1$).

Additionally, ^{1}H NMR spectrum showed the following signals: two doublets corresponding to two geminal protons H-6 and H-6′ (δ 2.95; d and δ 2.83; d, $J = 16.2$ Hz) only coupled with each other and two singlets assigned to two methyl groups H-12 and H-13 (δ 1.12 and δ 1.23). These data suggest that its structure is very similar to that assigned for **1**. Only slight differences in chemical shifts and coupling constants can be observed. Thus, the differences may be due to some stereochemical differences between these compounds.

The relative stereochemistry of heliespirone C was established using NOE difference experiments. The main observed effects by irradiation of signals corresponding to H-7, H-8, and H-10 are represented in Figure 3. These effects are

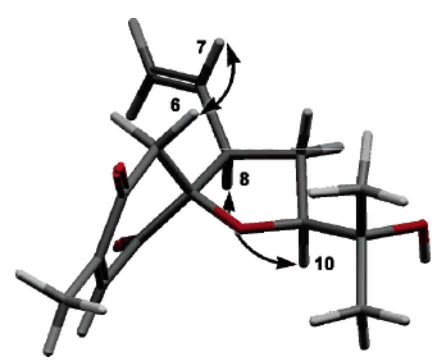


Figure 3. NOE effects for **3** on the minimum energy conformer obtained with theoretical PM3 calculations.

explained by the most stable conformation obtained using semiempirical PM3 calculations[7] with this stereochemistry. Irradiation of H-8 provoked a NOE effect over the signal corresponding to H-10 that indicated that both protons presented the same α-orientation. Irradiation of H-7 provoked an effect on the signal corresponding to H-6 was observed.

(7) (a) Stewart, J. P. P. *J. Comput. Chem.* **1989**, *10*, 209−220. (b) Stewart, J. P. P. *J. Comput. Chem.* **1989**, *10*, 221−264.

This stereochemistry is supported by the good correlation observed between calculated angles and observed coupling constants (Table 2). Thus, we conclude that heliespirone C is the C-1 epimer isomer of heliespirone A.

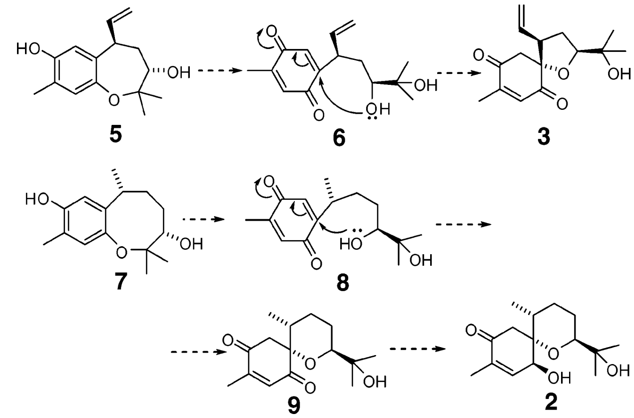
Table 2. Observed Coupling Constants vs Calculated Angles for **3**

protons	calcd Φ	obsd J (Hz)
8−9β	164.3	12.2
8−9α	41.8	7.1
9α−10α	48.8	5.1
9β−10α	171.9	10.7

The NOE data and coupling constants alone, however, cannot necessarily distinguish between a spiro-5 structure (**3**) and a spiro-6 structure (cf. **1**). Comparison of the chemical shifts observed in the ^{13}C NMR spectra of compounds **2** and **3** for C-10 and C-11 suggest that the ether function must be placed at position 10 instead 11 as was proposed originally for compound **1**. This is supported by those chemical shifts observed in the corresponding ^{13}C NMR spectra of heliannuols B, D,[8] E,[9] and F,[10] which present this functionalization at this position. Additionally, comparison of calculated ^{13}C chemical shifts for both structures **1** and **3** with the experimental ^{13}C NMR data for heliespirones A and C show better agreement with the spiro-5 structure.[11] This suggests that the structure of heliespirone A must be revised to **4**. Finally, the lack of reactivity of heliespirone A under usual acetylation conditions also supports the presence of a tertiary alcohol and the spiro-5 structure rather than a secondary hydroxyl as would be found in the spiro-6 structure **1**.

The biogenesis of these three compounds could proceed through oxidation of the corresponding heliannuols C (**5**) and A (**7**) to quinones (**6** and **8**) and a subsequence intramolecular conjugated addition (Scheme 1). In the case of **2**, further reduction of the intermediate **9** is required.

Scheme 1. Proposed Biogenesis of Heliespiranes



The levels of activity shown by heliespirones B (43% inhibition) and C (56% inhibition) at 10^{-3} M (all significant inhibition at $P < 0.01$) in the coleoptiles bioassay,[12] relative to controls, suggest that they may be lead compounds for new agrochemicals.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of heliespirones B (**2**) and C (**3**), a table comparing calculated shifts with experimental data for heliespirone A and heliespirone C (**3**), gHSQC spectrum of heliespirone B (**2**), ^{1}H 2DCOSY spectrum of heliespirone C (**3**), and additional X-ray crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Macías, F. A.; Varela. R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett.* **1999**, *40*, 4725−4728.

(10) Macías. F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Nat. Prod.* **1999**, *62*, 1636−1639.

(11) Data calculated using NMR Predict program ccss v. 3.0.25 by Modgraph Consultants Ltd v. 2.0. A table comparing calculated shifts with experimental data can be found in the Supporting Information.

(12) (a) Cutler, H. G.; Le Files, J. H.; Crumley, F. G.; Cox, R. H *J. Agric. Food Chem.* **1978**, *26*, 632−635. (b) Castellano, D. Standard bioassays for the evaluation of the allelopathic potential of natural product models. Doctoral Thesis, University of Cadiz, Spain, 2002.

Supporting Information

Heliespirones B and C, two New Plant Heliespiranes with a Novel Spiro Heterocyclic Sesquiterpene Skeleton

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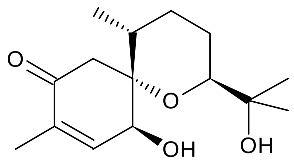
Figure S1. ^{1}H NMR of Heliespirone B (**2**, $CDCl_3$, 600 MHz)



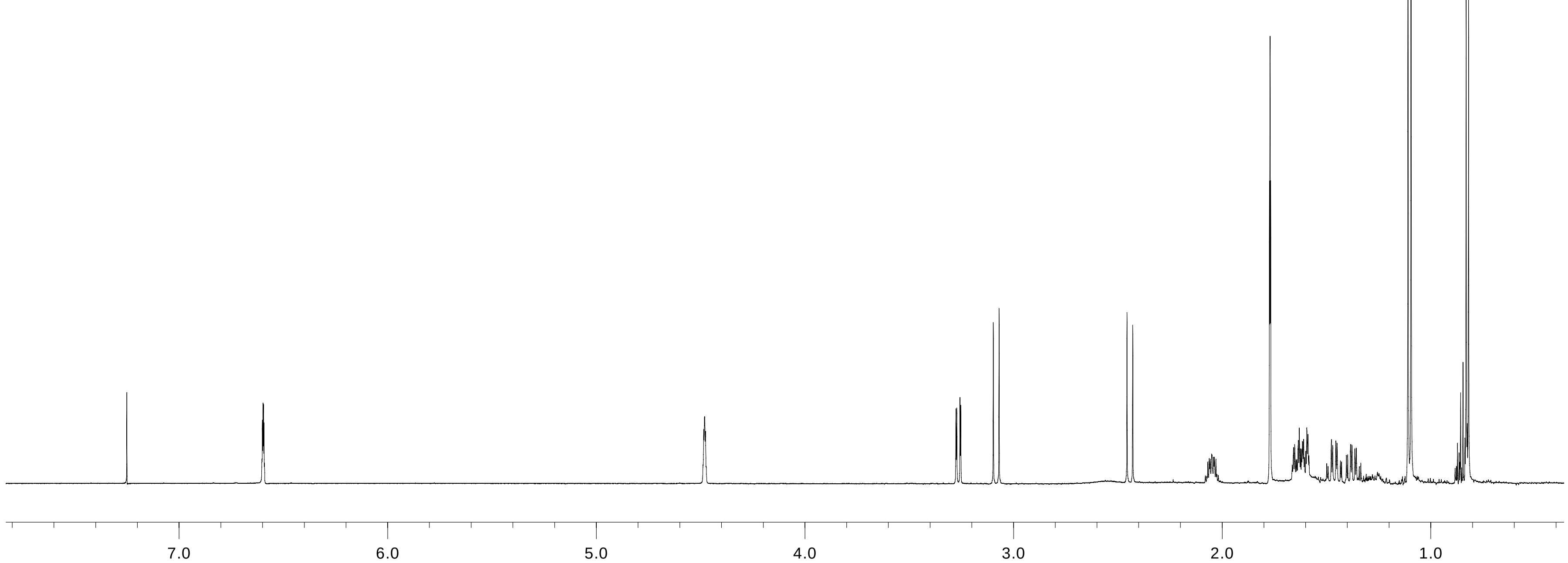
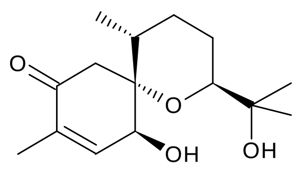


Figure S2. ^{13}C NMR of Heliespirone B (**2**, $CDCl_3$, 100 MHz)



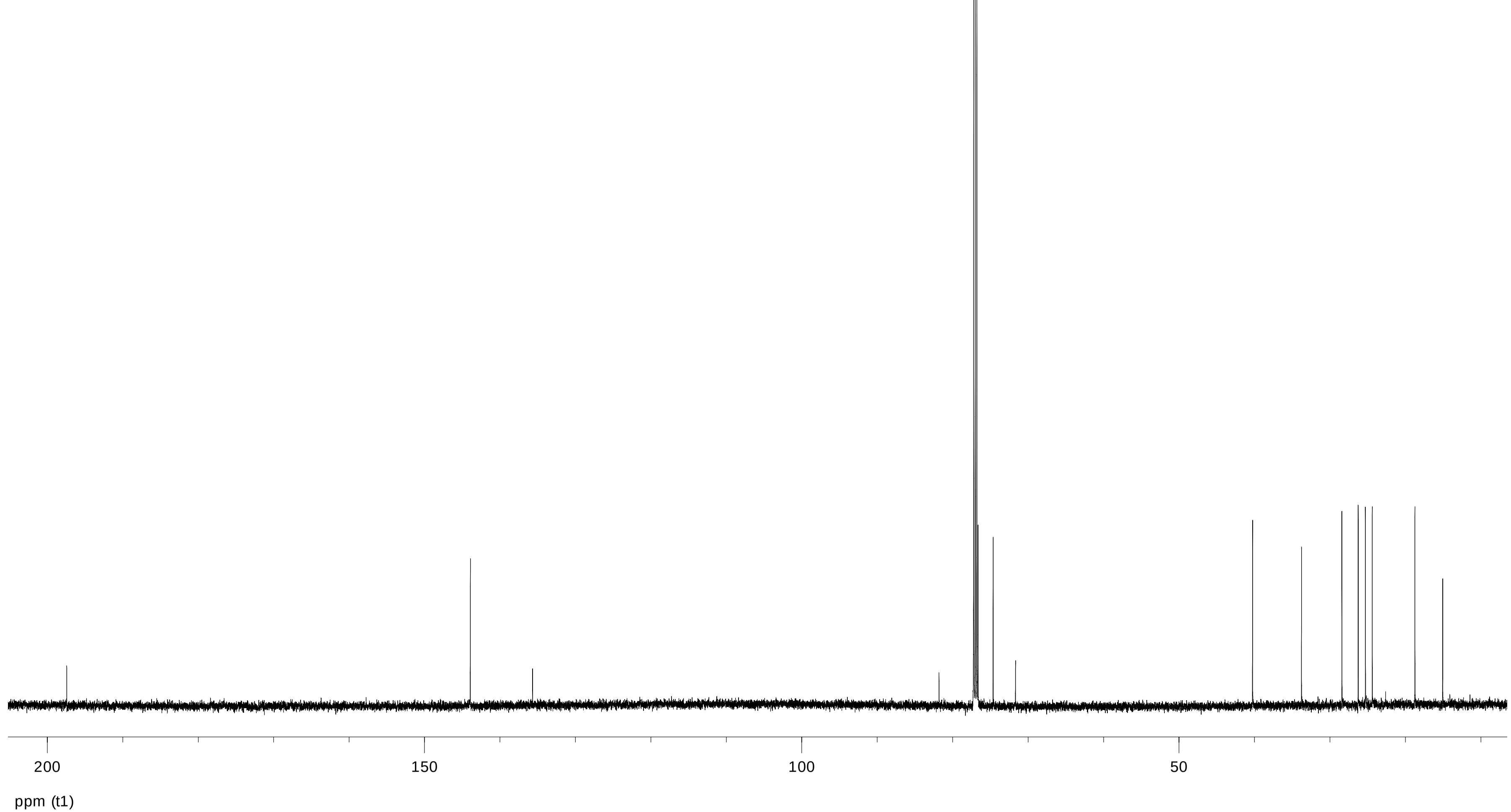


Figure S3. gHSQC of Heliespirone B (**2**, $CDCl_3$, 600 MHz)

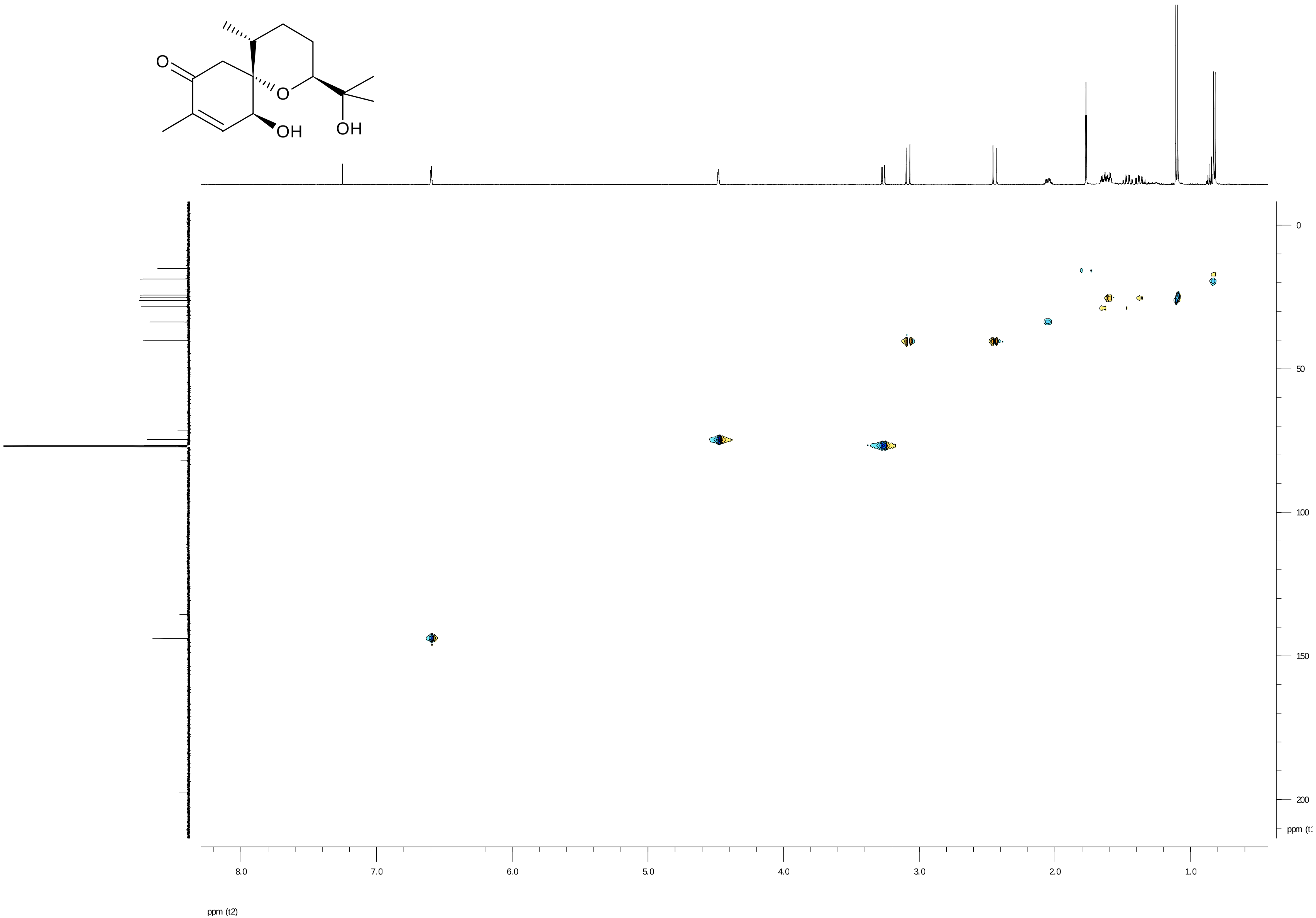


Figure S4. ^{1}H NMR of Heliespirone C (**3**, $CDCl_3$, 400 MHz)

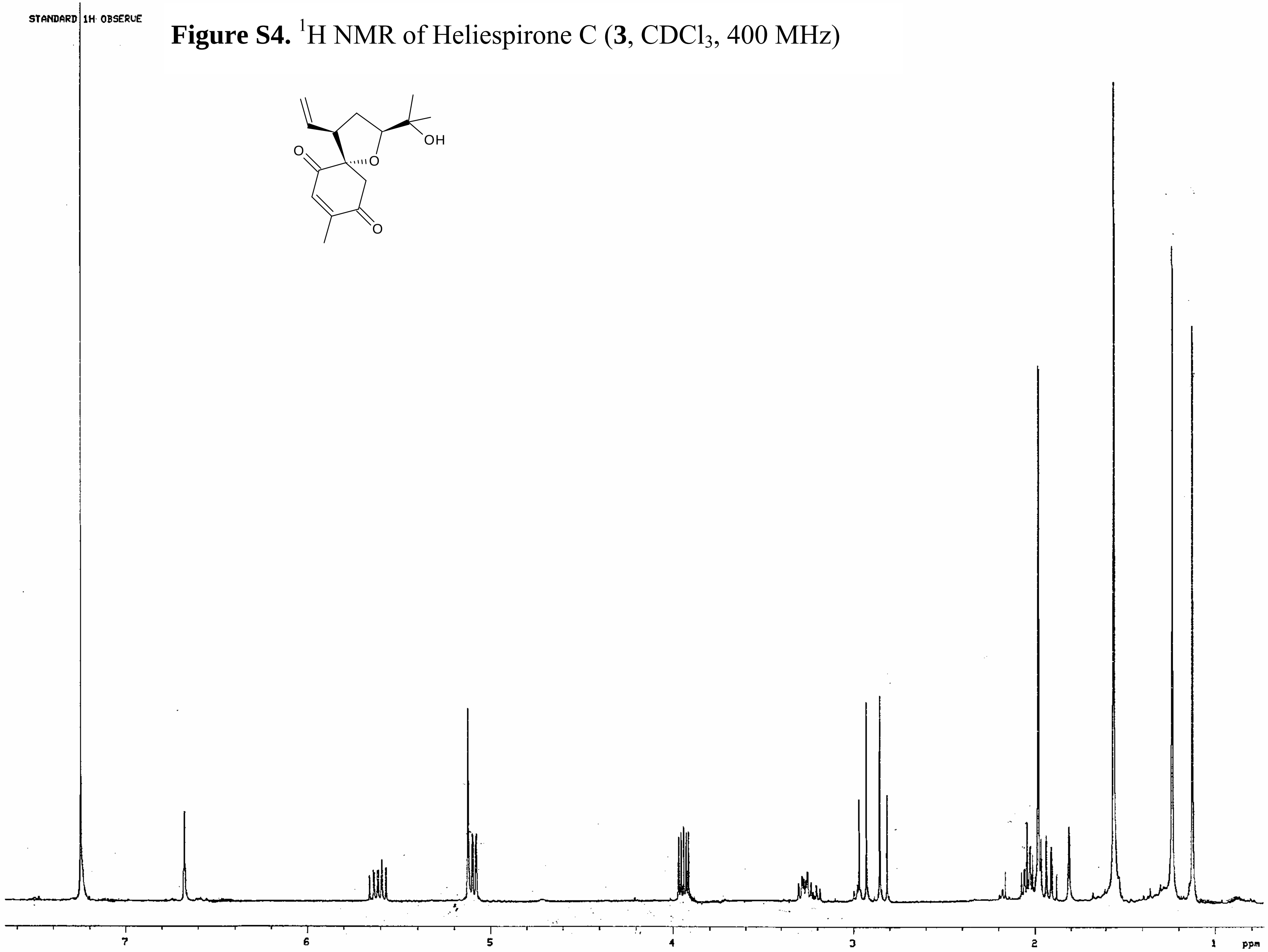


Figure S5. ^{13}C NMR of Heliespirone C (**3**, $CDCl_3$, 100 MHz)

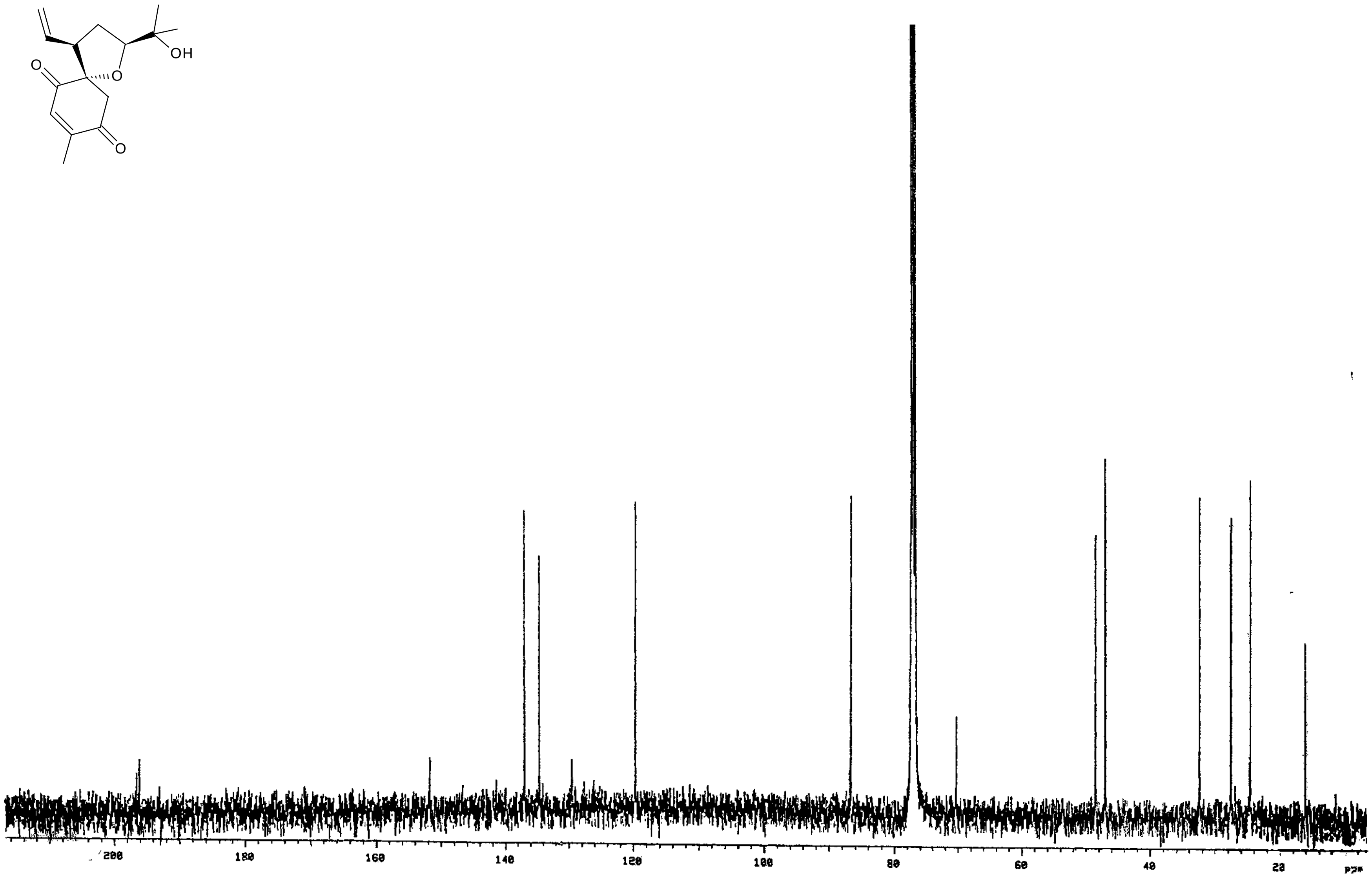
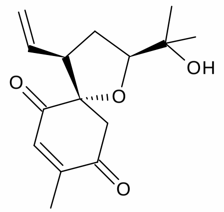


Figure S6. COSY of Heliespirone C (**3**, $CDCl_3$, 400 MHz)



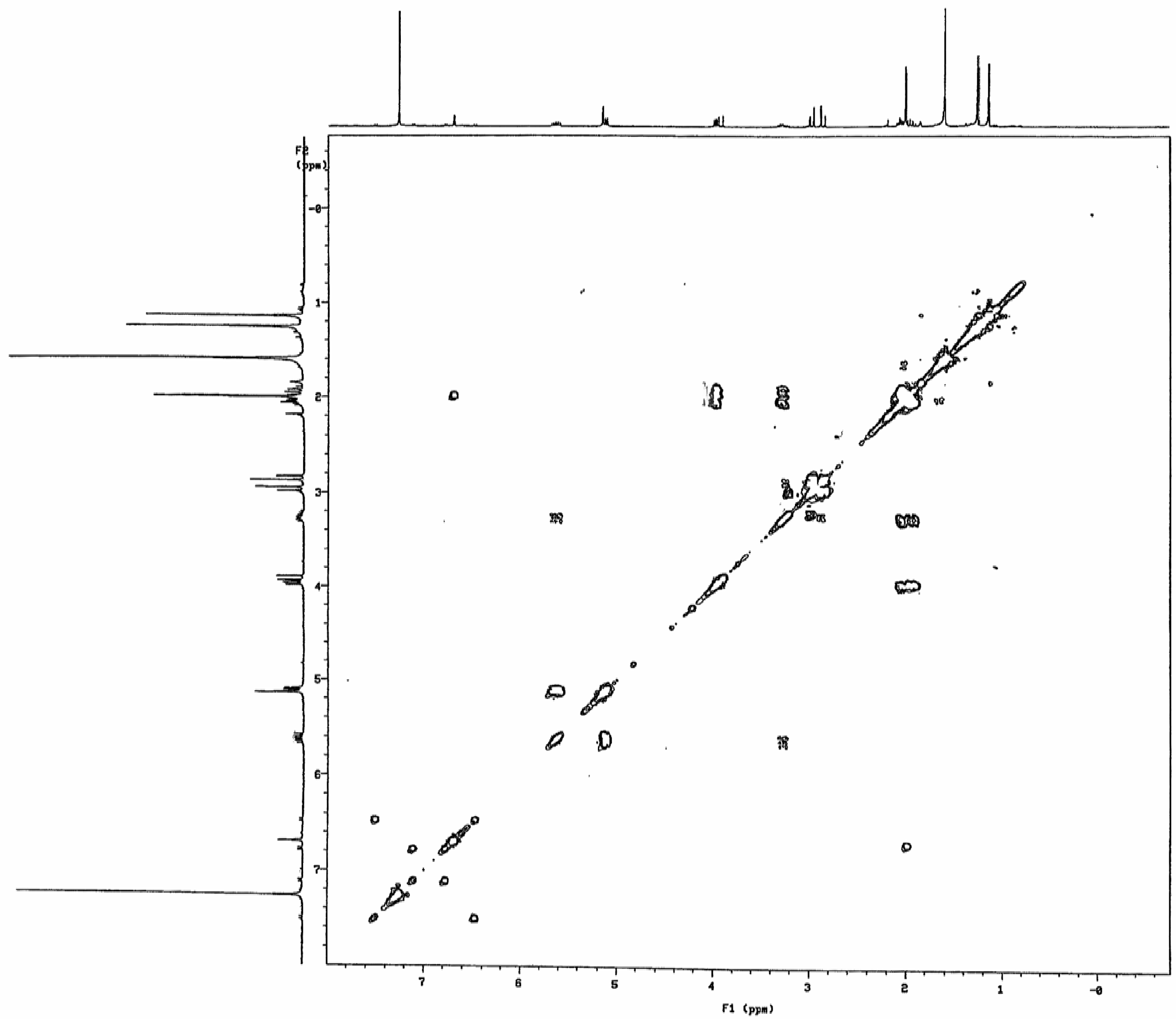


Table S1. ^{13}C NMR calculated and experimental data of heliespirones A and C (**3**). Calculation of the chemical shifts using NMRPredict program ccss v. 3.0.25 by Modgraph Consultants Ltd v. 2.0.

carbon #	**calcd ^{13}C shifts for 1**	**exptl ^{13}C shifts for heliespirone A**	**exptl ^{13}C shifts for heliespirone C**	**calcd ^{13}C shifts for 3**
1	83.6	87.6	86.9	85.1
2	194.8	201.5	196.5	190.2
3	136.9	137.0	136.9	136.9
4	152.7	153.4	151.7	152.7
5	192.1	197.5	196.3	191.3
6	44.0	51.8	48.5	41.5
7	136.7	135.3	134.6	134.7
8	41.9	57.1	47.0	49.5
9	29.2	31.9	32.4	27.9
10	74.0	86.7	86.7	83.8
11	79.0	70.1	70.3	71.2
12	27.9	28.3	27.5	25.9
13	27.9	25.3	24.5	25.9
14	116.9	118.4	119.6	117.9
15	16.5	15.9	16.1	16.5

Table S2. Crystal Data and Structure Refinement for heliespirone B (**2**)

Crystal Data	
Empirical formula	$C_{15}H_{24}O_4$
Formula Weight	268.34
Temperature	105 K
Mo Kα radiation	
Wavelength	0.71073 Å
Cell parameters from 5178 reflections	
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	
	a = 10.3007 (14) Å
	b = 11.932 (2) Å
	c = 12.210 (2) Å
	α = 0º
	β = 106.984 (9)º
	γ = 0º
Volume	1435.3 (4) $Å^3$
Z	4
Calculated density	Dx = 1.242 Mg/m^3
	Dm not measured
Absorption coefficient	$\mu = 0.088\ mm^{-1}$
Crystal size	0.38 × 0.35 × 0.32 mm, colorless
Theta range for data collection	θ = 2.5– 32.6º

Data Collection

KappaCCD (with Oxford Cryostream) diffractometer

ω scans with κ offsets

Absorption correction: none

32482 measured reflections

5406 independent reflections

4753 reflections with $I > 2\sigma(I)$

$R_{int} = 0.025$

$h = -15 \rightarrow 15$

$k = -18 \rightarrow 14$

$l = -18 \rightarrow 18$

Intensity decay: <2%

Refinement

Refinement on F^2

$w=1/[\sigma^2(F_o^2) + (0.0421P)^2 + 0.2847P]$ where $P = (F_o^2 + 2Fc^2)/3$

$R[F^2 > 2\sigma(F^2)] = 0.038$

$wR(F^2) = 0.091$

$S = 1.029$

$(\Delta/\sigma)_{\mathrm{max}} = 0.000$

$\Delta\rho_{\mathrm{max}} = 0.32\ e\ Å^{-3}$

$\Delta\rho_{\mathrm{min}} = -0.25\ e\ Å^{-3}$

5406 reflections

364 parameters

Extinction correction: SHELXL

Extinction coefficient: 0.012 (2)

H atoms treated by a mixture of independent and constrain refinement

Scattering factors from *International Tables for Crystallography* (Vol. C)

Figure S6. X-Ray Model of Heliespirone B (**2**)

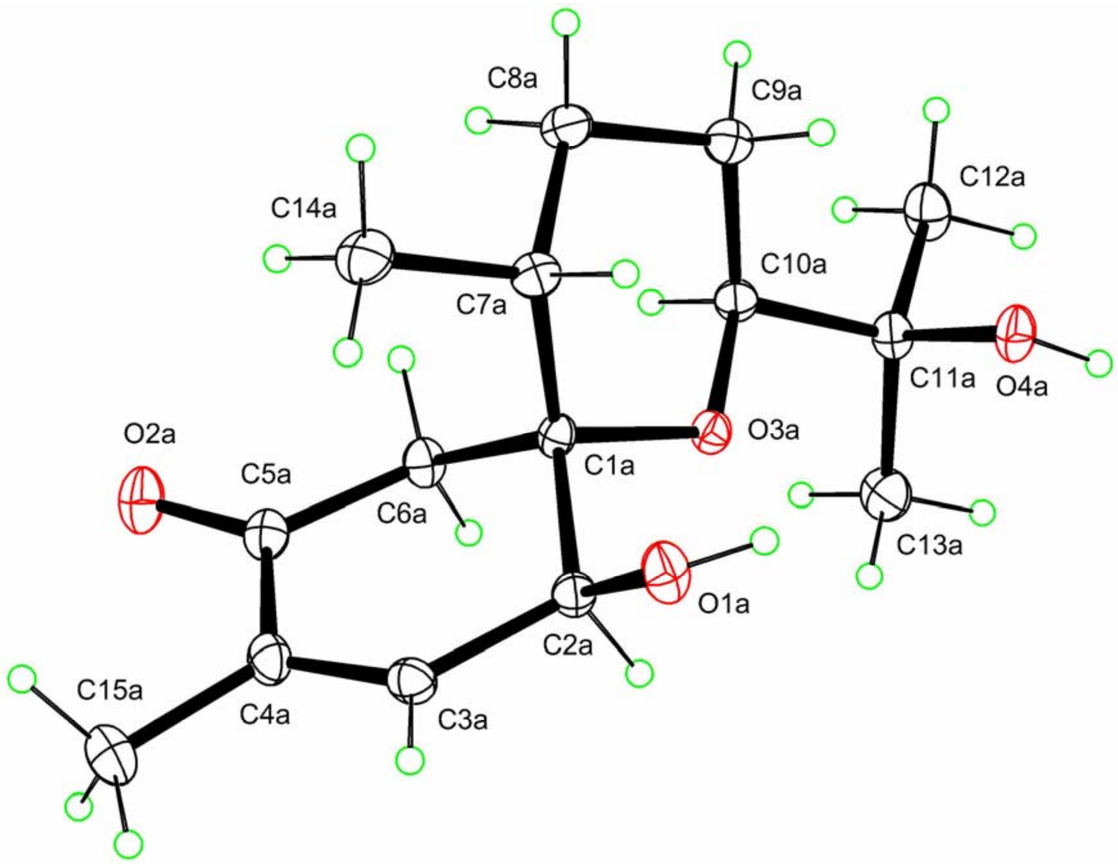


Figure S7. X-Ray Model of Heliespirone B (**2**). Showing Intermolecular Interactions in the Crystal.