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Article

Michael Additions of Thiocompounds to α,β-Unsaturated Carbonyl Compounds in Aqueous Media: Stereoselectivity with Unambiguous Characterization by NMR

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As reações de crotonaldeído (**8**) com tiofenol (**2**) e benzalacetona (**10**) com 1,2-etanoditiol (**11**) levam aos produtos de adição de Michael. As reações de tiofenol (**2**) com (*R*)-carvona (**13**) e (*S*)-perilaldeído (**15**) levam aos produtos (2*S*,3*R*,5*S*)-5-isopropenil-2-metil-3-feniltio-cicloexanona (**14**) e (1*R*,2*R*,4*S*)-4-isopropenil-2-feniltio-cicloexano carbaldeído (**16**), respectivamente. Também é apresentada a elucidação inequívoca da estereoquímica de **14** e **16** por RMN.

The reactions of crotonaldehyde (**8**) with thiophenol (**2**) and benzalacetone (**10**) with ethane-1,2-dithiol (**11**) yield Michael addition products. The reactions of thiophenol (**2**) with (*R*)-carvone (**13**) and (*S*)-perillaldehyde (**15**) lead to (2*S*,3*R*,5*S*)-5-isopropenyl-2-methyl-3-(phenylthio)cyclohexanone (**14**) and (1*R*,2*R*,4*S*)-4-isopropenyl-2-(phenylthio)cyclohexanecarbaldehyde (**16**), respectively. An unambiguous elucidation of the stereochemistry of **14** and **16** by NMR is also presented.

Keywords: 1,4-additions, water, Green Chemistry, NMR

Introduction

At this century's threshold, the environmental conditions of our planet Earth are, and should be, one of our most serious concerns. Chemistry research may bring us great advances in the quality of life (e.g., medications, new materials, etc.), but on the other hand, it may also be responsible for several of our environmental pollution problems.

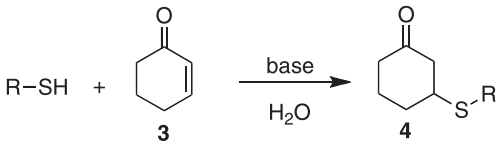
For *sustainable development*,[1] we must think about strategies to minimize the environmental impact of these technological activities. One of these strategies is known as *Green Chemistry*.[2-8] The objective of Green Chemistry is the development of methodologies that generate and use the lowest possible amounts of possibly toxic substances for the production of chemical compounds.[2-8]

Today, the study of organic reactions using water as a solvent is considered an important strategy in the area of Green Chemistry. Water is an innocuous solvent that is also abundant and inexpensive.[9-13] The Michael reaction, a widely used technique in organic synthesis,[14] is an important tool for the preparation of various polyfunctional compounds via carbon-carbon and carbon-heteroatom bond-forming reactions. In the literature, some examples of Michael reactions in aqueous media can be found. Water-tolerant Lewis acids,[15,20] Brϕnsted acids,[21] and bases can catalyze these reactions in the presence or absence of phase transfer agents.[22-27] Recently, it was reported that amphiphilic polymer-supported ammonium hydroxides are efficient heterogeneous catalysts for these reactions.[28] In some cases, the Michael additions may be carried out without any type of catalysis.[29-32] Moreover, it is interesting to point out that in the applications of these aqueous methodologies, many nucleophile types can be used, including organometallic regents.[33-36]

In our research, we have analyzed some studies of this type of reaction in water catalyzed by bases without phase transfer agents.[37-38] According to King and co-workers,[39] the control of pH is essential for the optimization of the nucleophilic reactions in aqueous media as lateral processes, such as reagent hydrolysis, compete with the desired reaction. Previously, we reported on the Michael additions of

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propane-1-thiol (**1**) and thiophenol (**2**) to cyclohex-2-enone (**3**) at three pH conditions in aqueous media (pH 7, 10, 13). The best condition for all of the tested reactions was at pH 7 using a 1 mol L^{-1} $NaHCO_3$ aqueous solution. The yields were 70% and 95%, respectively (Scheme 1).[38]



R	base (pH)	time/(h)	yield (%)
n-Pr **1**	NaOH (pH 14)	2	30
	Na_2CO_3 (pH 10)		50
	$NaHCO_3$ (pH 7)		70
C_6H_5 **2**	NaOH (pH 14)	0.75	30
	Na_2CO_3 (pH 10)		55
	$NaHCO_3$ (pH 7)		95

Scheme 1. Optimization of Michael addition of thiols in water.

Our research also showed that the Michael additions of thiophenol (**2**) to α,β-unsaturated nitroolefins like 1-nitrocyclohex-1-ene (**5**) in aqueous media have a good diastereoselectivity; this result is cited in the literature as the first example of this kind of reaction in water that presents diastereoselectivity (Scheme 2).[38,40]

Experimental

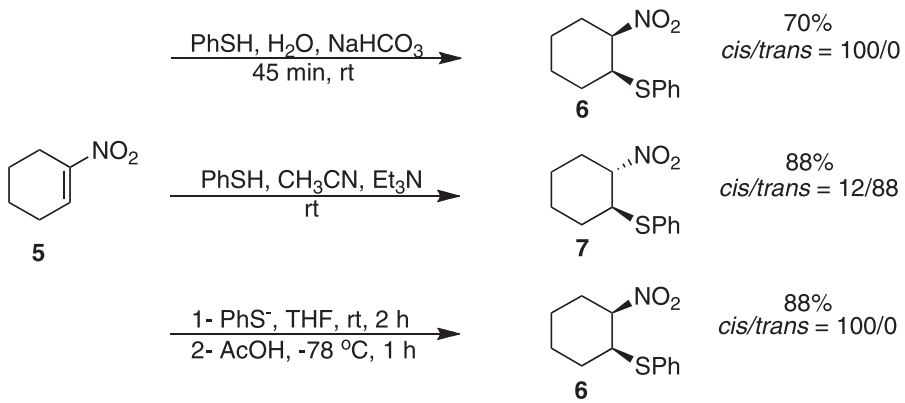
Thiophenol (**2**), crotonaldehyde (**8**), benzalacetone (**10**), ethane-1,2-dithiol (**11**), (*R*)-carvone (**13**) and (*S*)-perillaldehyde (**15**) were used as received (Aldrich). Some of the products were purified by radial chromatography in a Harrison Research Chromatotron. High resolution gas chromatography (HRGC) analyses were performed under two conditions: condition A) HP-5890-II gas chromatograph with FID, using a 30 m (length), 0.25 mm (ID) and 0.5 mm (phase thickness) RTX-5 silica capillary column with H_2 as the gas carrier and a flow division of 1/20; condition B) Varian Star 3400cx gas chromatograph with FID, using a 30 m (length), 0.25 mm (ID) and 0.5 mm (phase thickness) capillary column HP1 for injection on-column, and H_2 as the gas carrier. The analyses were performed in a BRUCKER-300 (^{1}H - 300 MHz, ^{13}C - 75 MHz) and in a Varian Mercury (^{1}H - 400 MHz, ^{13}C - 100 MHz) in $CDCl_3$ and C_6D_6 as solvents, with TMS as the internal standard.

The unambiguous ^{1}H and ^{13}C NMR assignments for compounds **14** and **16** were obtained from COSY90, HSQC, HMBC, TOCSY and nOe. All experiments were run with a relaxation delay of 1.5 s, 65K (^{1}H) and 32K (^{13}C) data points for 1D experiments and 2048 × 512 data matrixes for COSY90, TOCSY (mixing time of 25 ms), nOe (mixing time of 300 ms) HSQC and HMBC. Gradient selections were used in all 2D techniques. Zero filling and/or linear predictions were used in all 2D experiments. Pulse programs and data processing were performed using XWINMR 3.5 software from BRUKER.

The FT-IR spectra were recorded on a Nicolet Magna-IR-FT (NaCl film).

*3-(Phenylthio)butyraldehyde (**9**)*

To 10 mL of a 0.5 mol L^{-1} aqueous $NaHCO_3$ solution, 5 mmol of thiophenol (**2**) were added. Soon after, 0.4 mL of a 45% aqueous crotonaldehyde (**8**) solution (2.5 mmol)



Scheme 2. Comparison of the first example of diastereoselectivity of Michael addition in water with classical methods.

were also added. The reaction mixture was then stirred vigorously for 40 min at room temperature. Then, the reaction mixture was neutralized with concentrated hydrochloric acid and extracted with chloroform. The organic extract was dried (using anhydrous Na_2SO_4), and the solvent was evaporated under reduced pressure. The product was purified by radial chromatography using chloroform as a solvent. 0.34 g of product was obtained. The following spectroscopic data were obtained: IR (KBr) ν_{max}/cm^{-1} 2825, 2727, 1724, 748, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 1H, *J* 6.78 Hz), 2.58 (ddd, 1H, *J* 1.65, 7.60, 17.30 Hz), 2.70 (ddd, 1H, *J* 1.70, 6.00, 17.30 Hz), 3.69 (sextet, 1H, *J* 6.78 Hz), 7.27-7.44 (m, 5H), 9.75 (t, 1H, *J* 1.65 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 37.6, 50.1, 127.6, 129.1, 133.0, 133.5, 200.5; MS, *m/z* (%), 182 (1), 182 (2), 180 (23), 137 (4), 110 (100), 77 (6.1); t_R= 12.1 mim [condition A: column temperature: 50 °C (5 min) to 280 °C (5 min) (25 °C min^{-1}); injector temperature: 260 °C; detector temperature: 280 °C].

*4-(2-mercaptoethylthio)-4-phenylbutan-2-one (**12**)*

To 15 mL of a 0.3 mol L^{-1} aqueous $NaHCO_3$ solution, 5 mmol of ethane-1,2-dithiol (**11**) were added. Soon after, 5 mmol of benzalacetone (**10**) were also added. The reaction mixture was then stirred vigorously for 17 h at room temperature. Then, the reaction mixture was extracted with chloroform. The organic extract was dried (using anhydrous Na_2SO_4), and the solvent was evaporated under reduced pressure to obtain the pure product. 0.87 g of the product was obtained. The following spectroscopic data were obtained: ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.59 (bs, 1H), 2.08 (s, 3 H), 2.55 (m, 4H), 2.97 (d, *J* 7.21 Hz, 2H), 4.35 (t, *J* 7.21 Hz, 1H), 7.30 (m, 5H); ^{13}C RMN (50 MHz, $CDCl_3$) δ 23.90, 30.66, 31.06, 44.18, 49.98, 127.66, 127.75, 128.67, 141.57, 205.05; MS, *m/z* (%) 240 (15), 222 (9), 206 (20), 179 (25), 147 (41), 104 (30), 77 (18), 43 (100); t_R= 20.2 mim [condition B, column temperature: 40 °C (2 min) to 250 °C (15 min) (10 °C min^{-1}), injector temperature: room temperature (on column), detector temperature: 280 °C].

*Michael addition of thiophenol (**2**) to α,β-unsaturated terpenes*

To 10 mL of a 0.5 mol L^{-1} $NaHCO_3$ aqueous solution, 20 mmol of thiophenol (**2**) were added. Soon after, 10 mmol of the respective terpene were also added. The reaction mixture was then stirred vigorously for 24 h at room temperature. The products of each substrate were isolated and characterized as follows:

*For (R)-carvone (**13**)*

(2*S*,3*R*,5*S*)-5-Isopropenyl-2-methyl-3-(phenylthio) cyclohexanone (**14**): The solid product was isolated from the reaction media by filtration and purified by recrystalization using hexane as the solvent; 1.27 g were obtained. For NMR data, see Table 1 (^{1}H - 300 MHz, ^{13}C - 75 MHz), t_R= 20.7 min [condition A: column temperature: 70 °C to 250 °C (5 min) (8 °C/min), injector temperature: 220 °C, detector temperature: 250 °C]. mp, 63-65 °C (hexane); $[\alpha]_{24}^{D}$ = –91.0 (*c* 10, CH_2Cl_2).

*For (S)-perillaldehyde (**15**)*

(1*R*,2*R*,4*S*)-4-Isopropenyl-2-(phenylthio) cyclohexanecarbaldehyde (**16**): The solid product was isolated from the reaction media by filtration and crystallized using hexane as the solvent. 1.77 g of a sample of compound **16** and thiophenol were obtained. In order to obtain a pure sample, this mixture was purified by flash chromatography using hexane:ethyl acetate (9:1); 1.20 g were obtained. For NMR data, see Table 2 (^{1}H - 400 MHz, ^{13}C - 100 MHz), t_R= 20.5 min [condition A: column temperature: 70 °C to 250 °C (5 min) (8 °C min^{-1}), injector temperature: 220 °C, detector temperature: 250 °C]. mp, 75-76 °C (hexane), $[\alpha]_{24}^{D}$ = –58.0 (*c* 10, CH_2Cl_2).

Results and Discussion

Synthesis

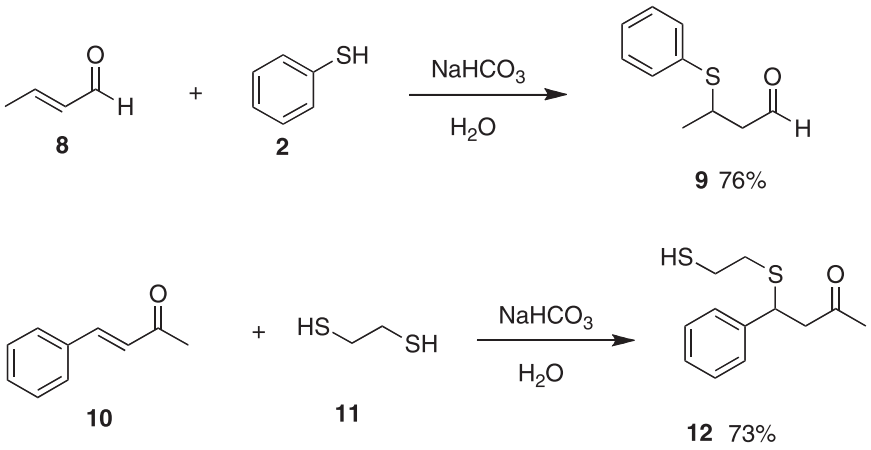
In this work, we extended our studies to other α,β-unsaturated carbonyl compounds.

The reactions of aliphatic acyclic carbonyl compounds like crotonaldehyde (**8**) with thiophenol (**2**) and benzalacetone (**10**) with ethane-1,2-dithiol (**11**) also yielded Michael addition products (Scheme 3).

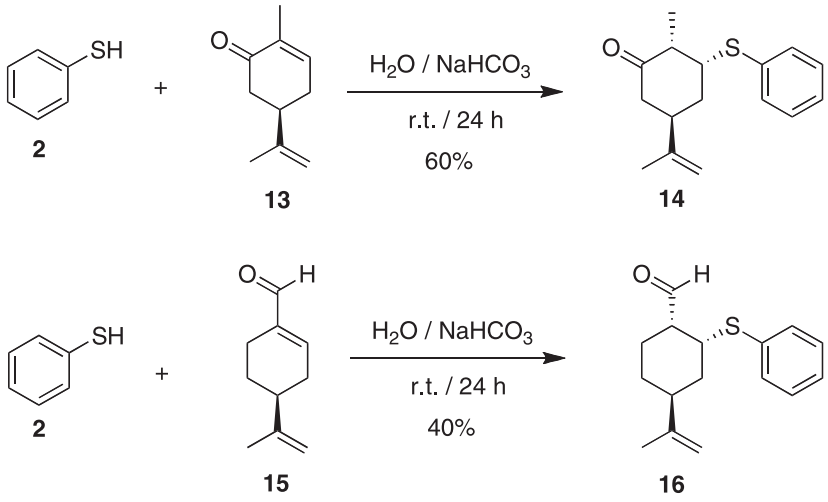
Some chiral terpenic substrates for this reaction type were also tested in order to analyze their stereoselectivity in aqueous media. It was observed that thiophenol (**2**) reacts with (*R*)-carvone (**13**) and (*S*)-perillaldehyde (**15**) at pH 7, leading to the kinetic products shown in Scheme 4.

The stereochemistry of these reactions is controlled by the axial addition of thiophenol in the first step and by the axial protonation in the next step (Scheme 5).

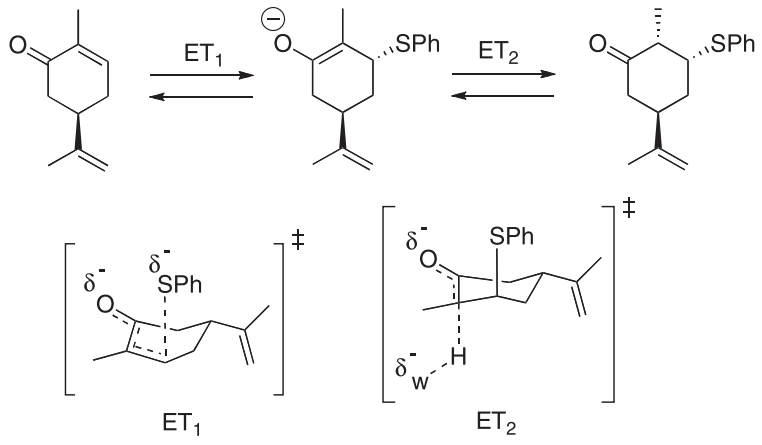
These reactions (Scheme 4) are reported in the literature using CH_2Cl_2 or hexane at 0 °C as the solvent and triethylamine as the catalyst, leading to the same products.[41,42] However, in the literature, the determination of the stereochemistry of the products was not clear. We report here the unambiguous elucidation of the stereochemistry of **14** and **16**.



Scheme 3. Michael addition in water.



Scheme 4. Stereoselectivity of Michael addition in water.



Scheme 5. Transitions states in the formation of compound **14**.

The methodology developed in this paper presents as an advantage the substitution of a toxic and inflammable organic solvent for water. Furthermore, no temperature control was necessary. Also, in operational work-up, our methodology reduces the product isolation procedure to a filtration step, as these products are insoluble in water.

*Stereochemical elucidation with unambiguous spectral assignments of compounds **14** and **16** by NMR*

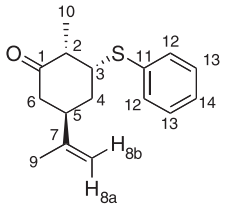
The ^{1}H NMR spectrum for compound **16** was fully assigned by a combination of homo- and heteronuclear 2D NMR methods, including DQF-COSY, HSQC, HMBC, nOe experiments and 1D-TOCSY. Some important details of the experiments will be commented on.

*(2S,3R,5S)-5-Isopropenyl-2-methyl-3-(phenylthio)cyclohexanone (**14**)*

The ^{1}H and ^{13}C NMR assignments of compound **14** are listed in Table 1. The DQF-COSY experiment of compound **14** demonstrates that H-2 at δ 2.89 (qdd) shows cross signals with the methyl H-10 at δ 1.22 (d) and H-3 at δ 3.9 (bdt). The H-3 hydrogen shows cross signals with H-2, H-4_{eq} at δ 2.06 (dtd) and H-4_{ax} at δ1.89 (ddd) (Figure 1).

In the nOe difference experiment, the relative configuration of the H-2 and H-3 hydrogens was

Table 1. Summary of the ^{1}H and ^{13}C data for compound **14**



Assignment	δ ^{1}H (J / Hz)	δ ^{13}C
1	--	209.6
2	2.89 (qdd, $J_{2\text{-}10}$ 6.73, $J_{2\text{-}3}$ 4.80, $J_{2\text{-}6ax}$ 1.15, 1H)	48.2
3	3.9 (bdt, $J_{3\text{-}2}$ 4.80, $J_{3\text{-}4eq} \approx J_{3\text{-}4ax}$ 3.50, 1H)	53.2
4 eq	2.06 (dtd, $J_{4eq\text{-}4ax}$ 13.85, $J_{4eq\text{-}3} \approx J_{4eq\text{-}5}$ 3.65, $J_{4eq\text{-}6eq}$ 2.06, 1H)	35.0
4 ax	1.89 (ddd, $J_{4ax\text{-}4eq}$ 13.85, $J_{4ax\text{-}5}$ 11.60, $J_{4ax\text{-}3}$ 3.13, 1H)	
5	3.03 (btt, $J_{5\text{-}4ax} \approx J_{5\text{-}6ax}$ 12.05, $J_{5\text{-}4eq} \approx J_{5\text{-}6eq}$ 3.85, 1H)	40.1
6 eq	2.53 (ddd, $J_{6eq\text{-}6ax}$ 13.70, $J_{6eq\text{-}5}$ 4.30, $J_{6eq\text{-}4eq}$ 2.06, 1H)	45.7
6 ax	2.28 (ddd, $J_{6ax\text{-}6eq}$ 13.70, $J_{6ax\text{-}5}$ 12.53, $J_{6ax\text{-}2}$ 1.15, 1H)	
7	--	146.7
8a	4.76 (app quint d, $J_{8a\text{-}9} = J_{8a\text{-}5}$ 1.38, $J_{8a\text{-}8b}$ 0.44, 1H)	109.9
8b	4.69 - 4.72 (m, 1H)	
9	1.66 (app d, J 0.60, 3H)	20.6
10	1.22 (d, $J_{10\text{-}2}$ 6.73, 3H)	12.6
11	--	134.3
12	7.38 -7.43 (m, 2H)	132.3
13/14	7.21-7.33 (m, 3H)	128.9 127.2

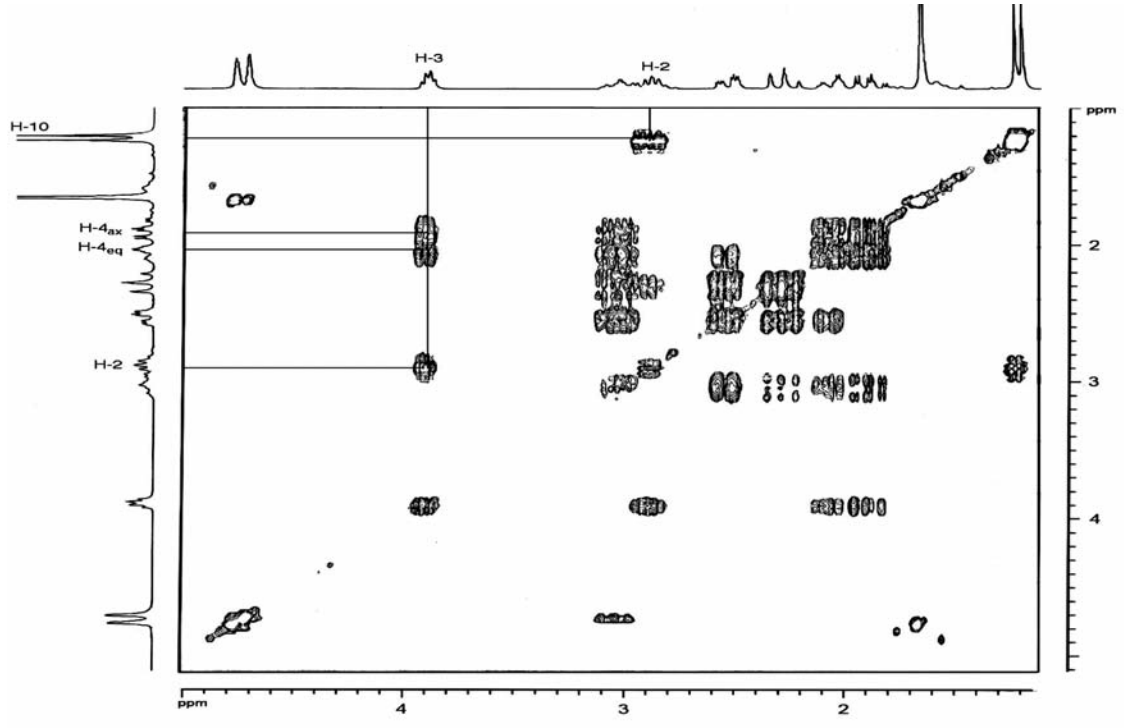


Figure 1. COSY spectra showing cross signals in chloroform for compound **14**.

established. The selective irradiation of H-2 produces nOe enhancements at H-3 and H-10, and a slight effect at axial hydrogens H-6 and H-4, while the selective saturation of H-3 produces nOe enhancements at H-2 and both H-4 and H-10. The nOe effect on axial and equatorial hydrogen H-4 is very similar. These nOe indicate that hydrogen H-3 is at the equatorial position, because if it were in the axial position this difference would be greater (Figure 2).

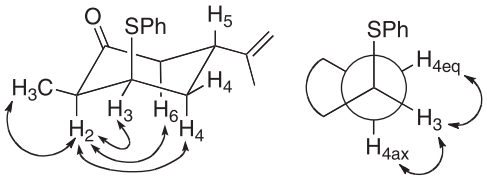


Figure 2. nOe for compound **14**.

*(1R,2R,4S)-4-isopropenyl-2-(phenylthio)cyclohexanecarbaldehyde (**16**)*

The determination of the stereochemistry of compound **16** was only possible with a NMR study in $CDCl_3$ and C_6D_6 (Table 2).

In $CDCl_3$ (Figure 3a), the H-2 and H-5 hydrogens are overlapped as a multiplet in 2.49-2.58 dby DQF-COSY spectrum (Figure 4). On the other hand, in C_6H_6 (Figure 3b), H-5 appears as a triplet of triplets in 2.50 d ($J_{5\text{-}4eq} \approx J_{5\text{-}6eq}$ 3.10 Hz, $J_{5\text{-}4ax} \approx J_{5\text{-}6ax}$ 12.00 Hz), but the H-2 is overlapped with H-7eq in 1.77-1.88 d (m, 2H).

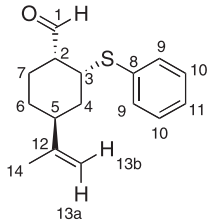
With the TOCSY experiment, it was possible to determine the multiplicity of hydrogen H-2 (δ 2.49-2.58). Hydrogen H-3 (δ 3.98) was selectively saturated in $CDCl_3$. The spectrum was obtained with a mixing time of 25 ms at 20 °C. The irradiation changes the multiplet to a double triplet with $J_{2\text{-}7ax}$ 12.37 Hz and $J_{2\text{-}7eq} \approx J_{2\text{-}3}$ 3.10 Hz (Figure 5). These couplings are consistent with H-2 in the axial position.

Finally, the relative configurations of H-3 and H-5 were examined with ^{1}H nOe difference spectroscopy. Saturation of H-3 in $CDCl_3$ produces nOe enhancements at H-2 and H-4 axial, while the saturation of H-5 in the C_6D_6 solvent shows nOe at H-4 equatorial. With this result, it is possible to suggest that H-3 and H-2 are *synclinal*, as shown in Figure 6.

Conclusions

The present work is an additional relevant contribution to the study of organic reactions in water. The Michael addition reactions of thiophenol to α,β-unsaturated terpenes in aqueous media show high stereoselectivity in the formation of the products at room temperature, with

Table 2 . Summary of the ^{1}H and ^{13}C data for compound **16**



Assig.	$CDCl_3$		C_6D_6	
	δ ^{1}H (J / Hz)	δ ^{13}C	δ ^{1}H (J / Hz)	δ ^{13}C
1	9.70 (s, 1H)	202.4	9.48 (s, 1H)	200.7
2	2.49-2.58 (m, 1H)	53.1	1.77-1.88 (m, 1H)	53.0
3	3.98 (app dd, $J_{3\text{-}4eq}$ 5.97 $J_{3\text{-}4ax} \approx J_{3\text{-}2}$ 3.10, 1H)	48.0	3.52 (app dd, $J_{3\text{-}4eq}$ 5.98, $J_{3\text{-}4ax} \approx J_{3\text{-}2}$ 3.33, 1H)	48.2
4 ax.	1.63 (ddd, $J_{4ax\text{-}4eq}$ 13.50, $J_{4ax\text{-}5}$ 12.11, $J_{4ax\text{-}3}$ 3.35, 1H)	36.7	1.20 (ddd, $J_{4ax\text{-}4eq}$ 13.40, $J_{4ax\text{-}5}$ 12.00, $J_{4ax\text{-}3}$ 3.33, 1H)	36.9
4 eq.	2.08 (ddd, $J_{4eq\text{-}4ax}$ 13.50, $J_{4eq\text{-}3}$ 5.14, $J_{4eq\text{-}5}$ 3.10, 1H)		1.92 (ddd, $J_{4eq\text{-}4ax}$ 13.40, $J_{4eq\text{-}3}$ 5.10, $J_{4eq\text{-}5}$ 3.10, 1H)	
5	2.49-2.58 (m, 1H)	39.0	2.50 (tt, $J_{5\text{-}4eq} \approx J_{5\text{-}6eq}$ 3.10, $J_{5\text{-}4ax} \approx J_{5\text{-}6ax}$ 12.00, 1H)	39.3
6 ax.	1.22 (qd, $J_{6ax\text{-}6eq} \approx J_{6ax\text{-}5} \approx J_{6ax\text{-}7ax}$ 12.70, $J_{6ax\text{-}7eq}$ 3.65, 1H)	30.0	0.86 (qd, $J_{6ax\text{-}6eq} \approx J_{6ax\text{-}5} \approx J_{6ax\text{-}7ax}$ 12.20, $J_{6ax\text{-}7eq}$ 3.60, 1H)	30.2
6 eq.	1.98-2.05 (m, 1H)		1.63-1.72 (m, 1H)	
7 eq.	1.91-2.03 (m, 2H)	21.8	1.77-1.88 (m, 1H)	22.1
7 ax.			1.63-1.72 (m, 1H)	
8	--	135.2	--	135.9
9	7.41-7.46 (m, 2H)	132.4	7.27-7.73 (m, 2H)	132.6
10	7.19 - 7.34 (m, 3H)	127.5	6.80-7.07 (m, 3H)	127.5
11		129.1		129.2
12	--	149.1	--	149.3
13a	4.73 (app quint, $J_{13a\text{-}14} \approx J_{13a\text{-}5}$ 1.30, 1H)	109.1	4.75 (app quint, $J_{13a\text{-}14} \approx J_{13a\text{-}5}$ 1.38, 1H)	109.3
13b	4.71 (app s, 1H)		4.71 (app s, 1H)	
14	1.72 (bs, 3H)	21.2	1.56 (s, 3H)	21.1

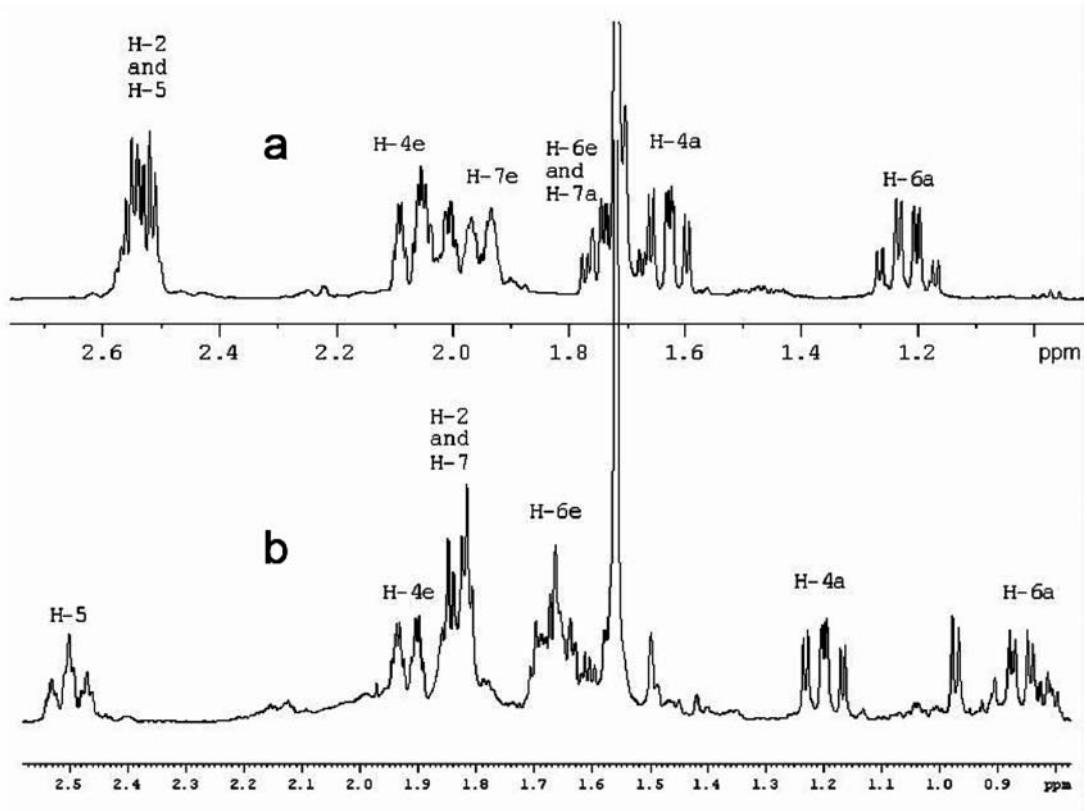


Figure 3. ^{1}H NMR spectra of compound **16** in (a) a chloroform solvent and (b) a benzene solvent.

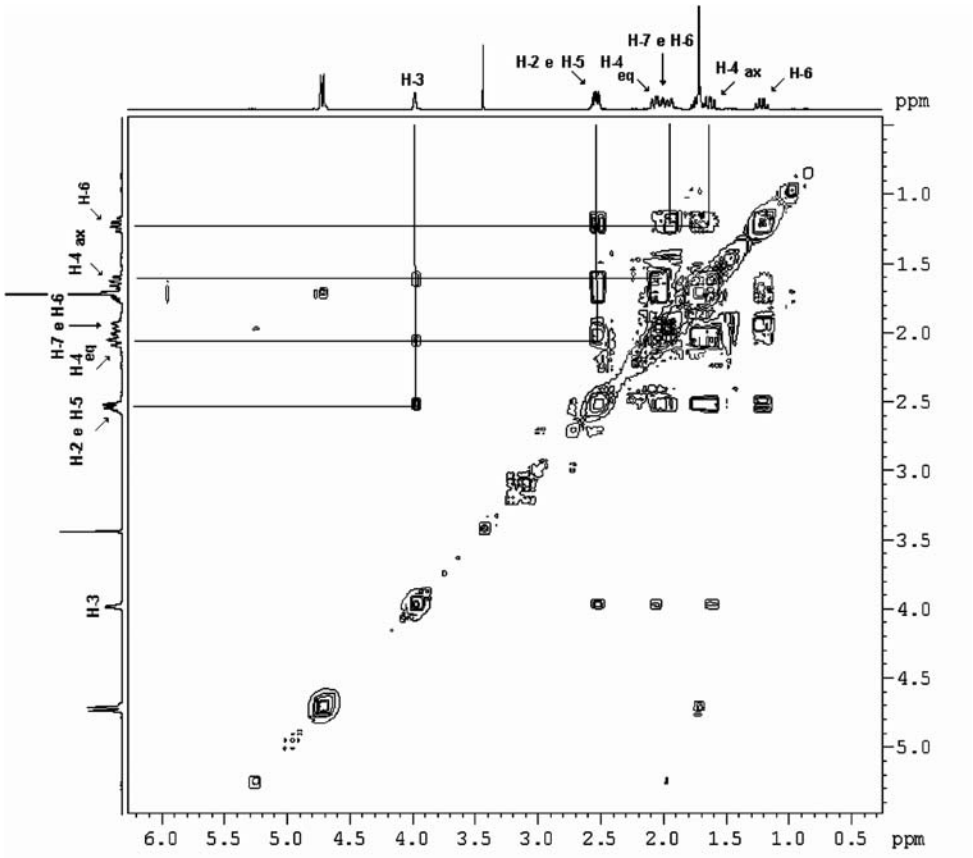


Figure 4. COSY spectra showing a cross signals for compound **16** in a chloroform solvent.

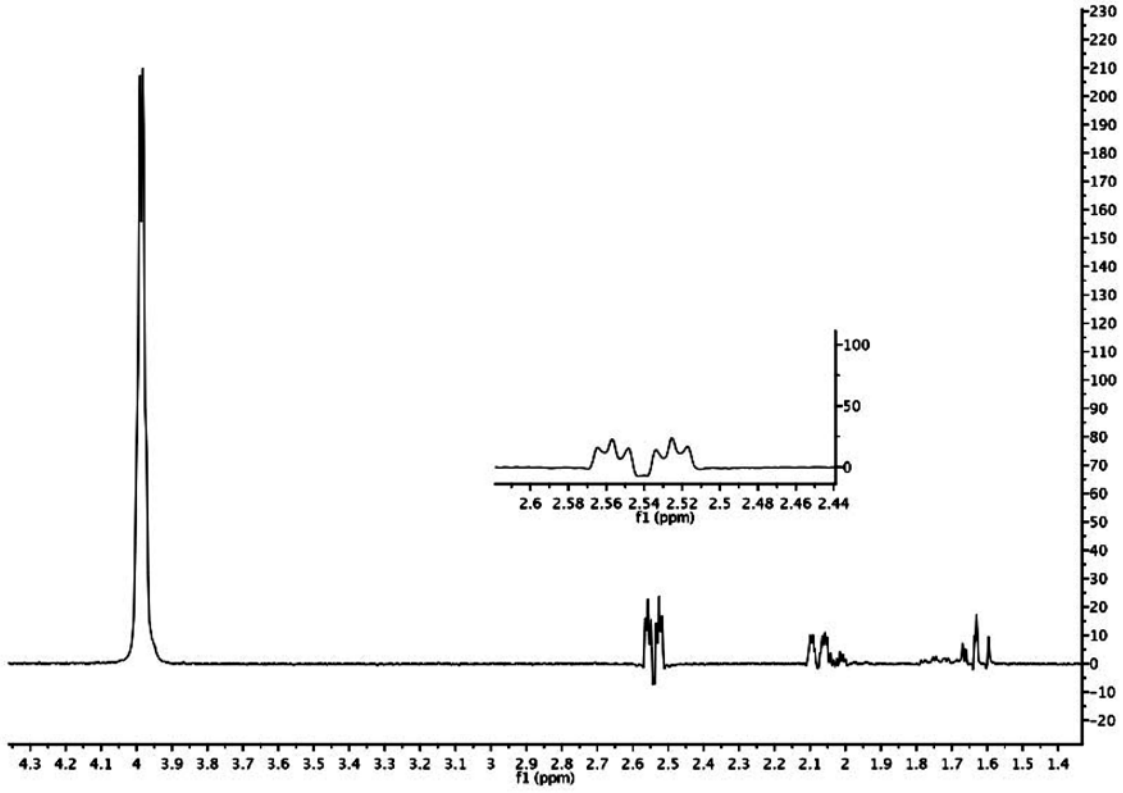


Figure 5. Selective excitation of hydrogen H-3 in the TOCSY experiment.

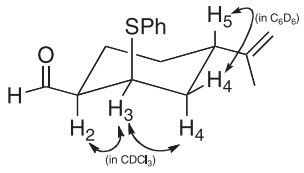


Figure 6. nOe for compound **16**.

good yields. This methodology represents an improvement over previous methods available in the literature in that it: a) uses a non-aggressive solvent; b) substitutes $NaHCO_3$ for triethylamine as the base; c) can be carried out at room temperature (while in previous procedures low temperatures were needed); and d) the isolation step was reduced to a simple filtration. All of these advantages show progress toward the goal of Green Chemistry.

Supplementary Information

NMR spectra for the compounds **14** and **16** are available free of charge as PDF file at http://jbcs.sbq.org.br.

Acknowledgments

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Michael Additions of Thiocompounds to α,β-Unsaturated Carbonyl Compounds in Aqueous Media: Stereoselectivity with Unambiguous Characterization by NMR

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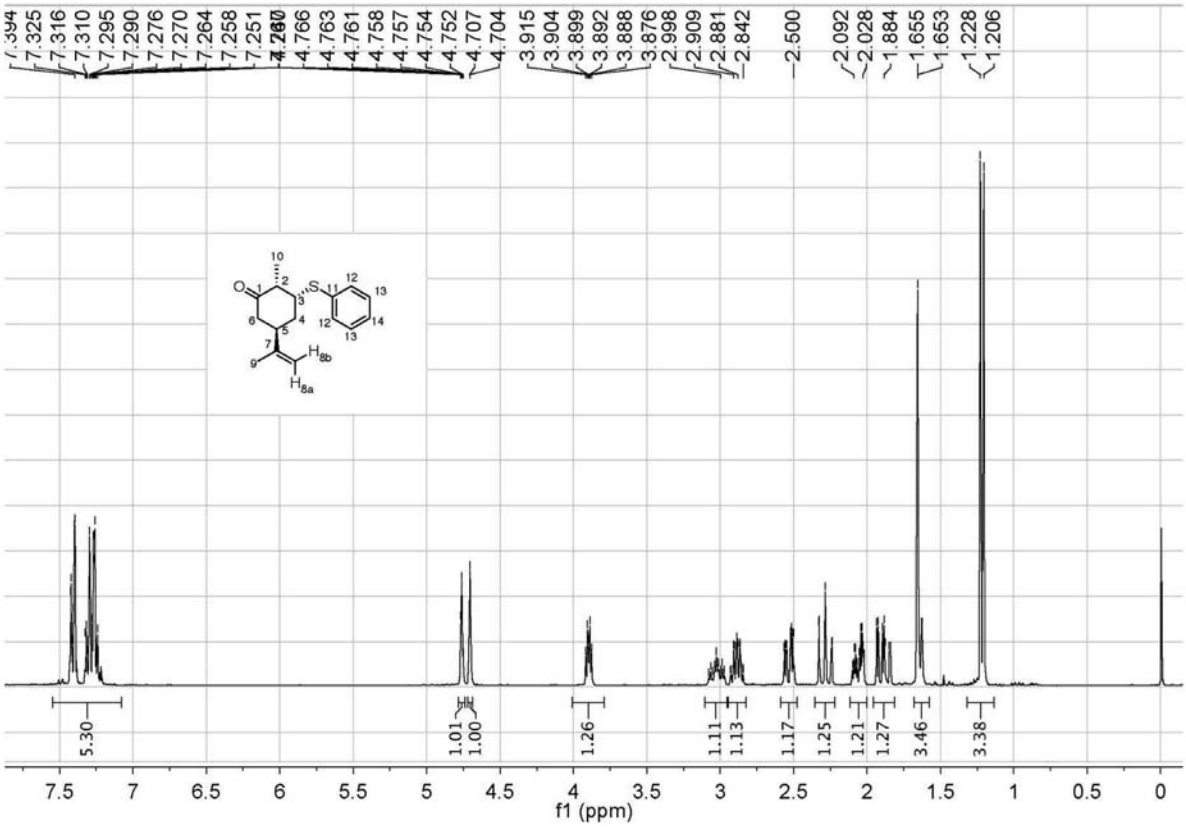


Figure S1. ^{1}H NMR spectrum of compound **14** (400 MHz, $CDCl_3$).

*e-mail: soa@iq.ufrj.br

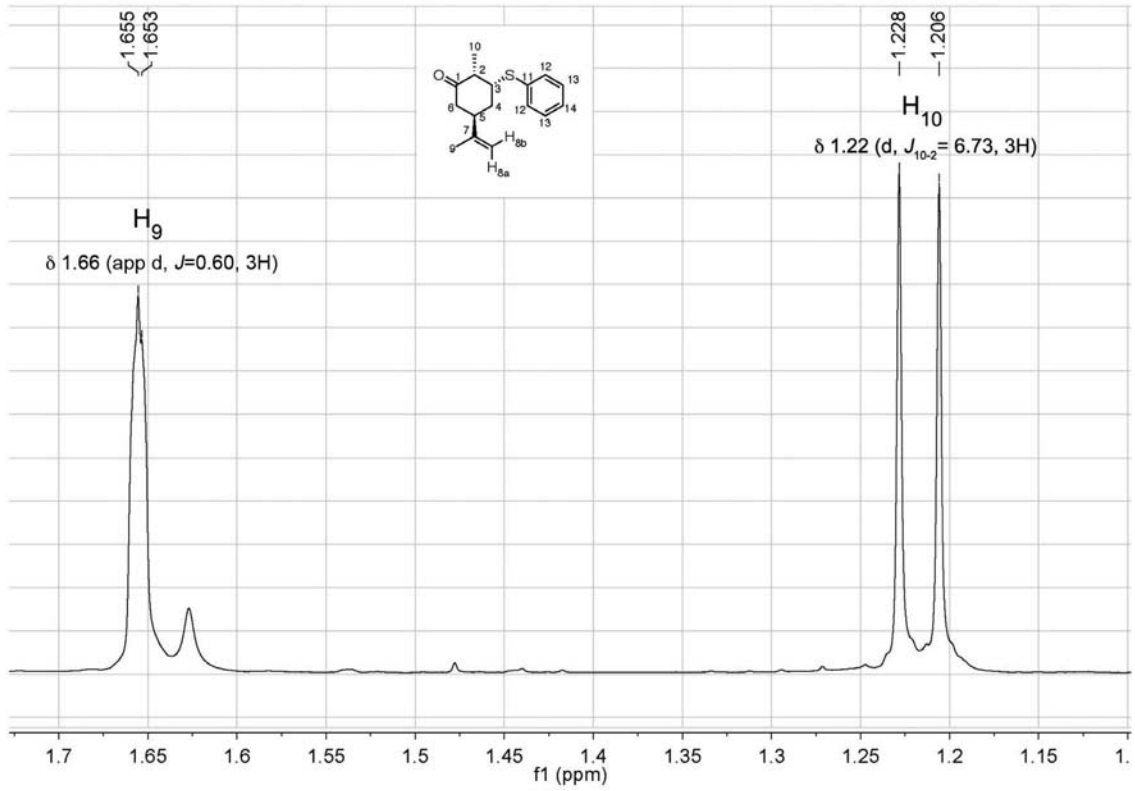


Figure S2. ^{1}H NMR spectrum of compound **14** between δ 1.15-1.70 (400 MHz, $CDCl_3$).

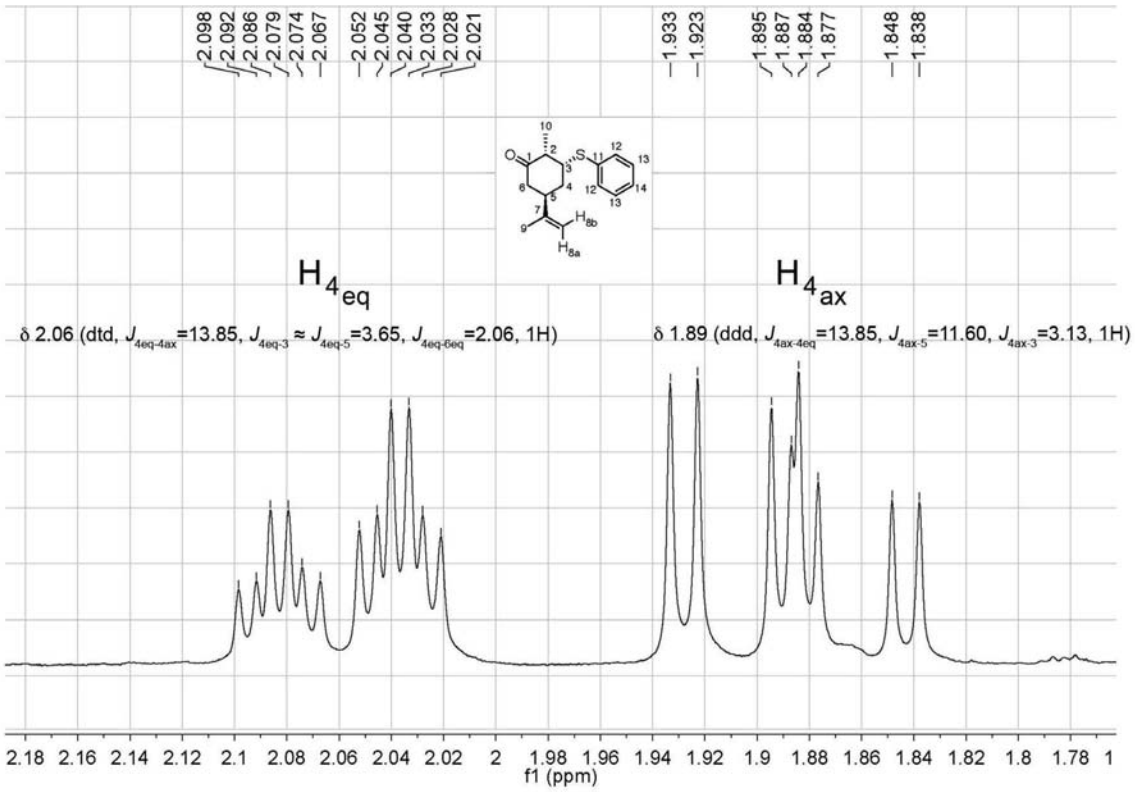


Figure S3. ^{1}H NMR spectrum of compound **14** between δ 1.78-2.18 (400 MHz, $CDCl_3$).

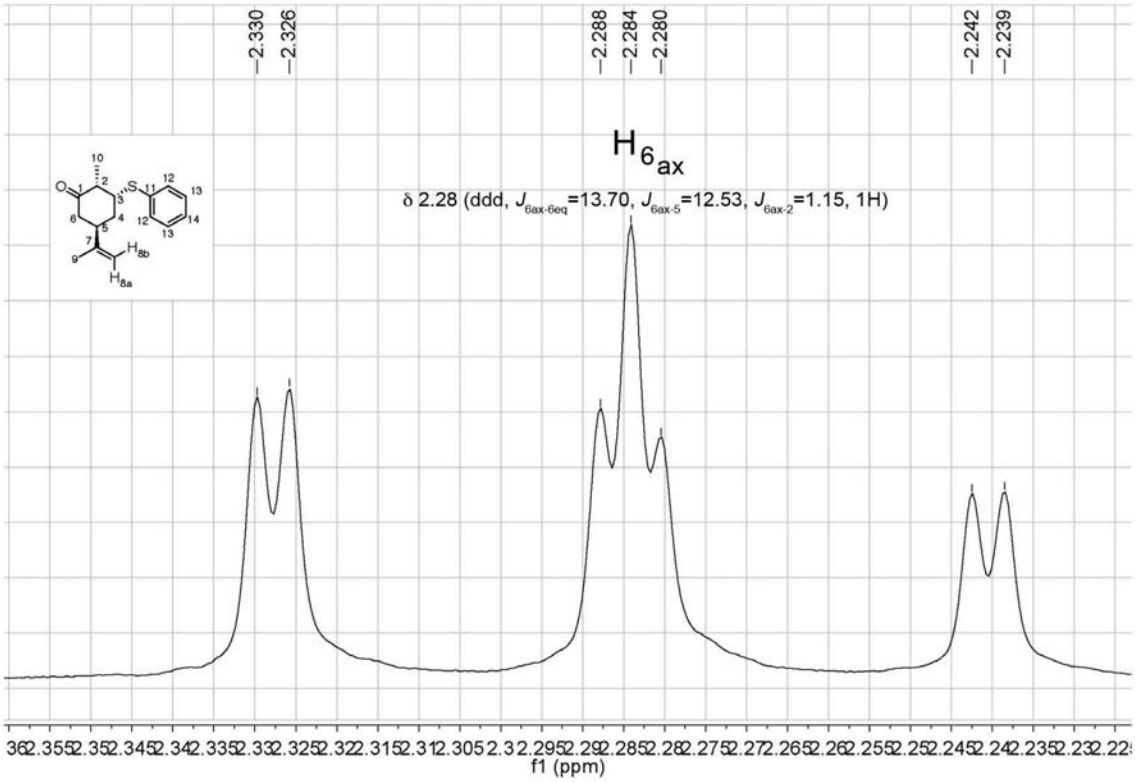


Figure S4. [1]H NMR spectrum of compound **14** between δ 2.22-2.35 (400 MHz, $CDCl_3$).

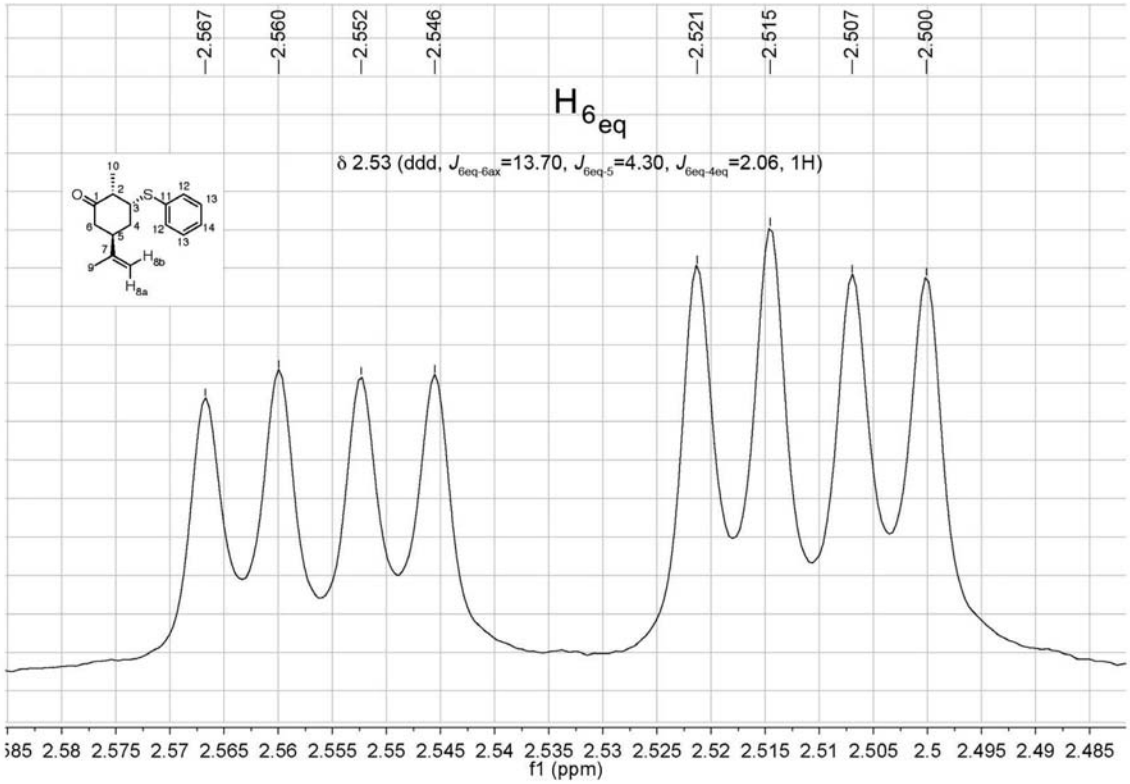


Figure S5. [1]H NMR spectrum of compound **14** between δ 2.48-2.58 (400 MHz, $CDCl_3$).

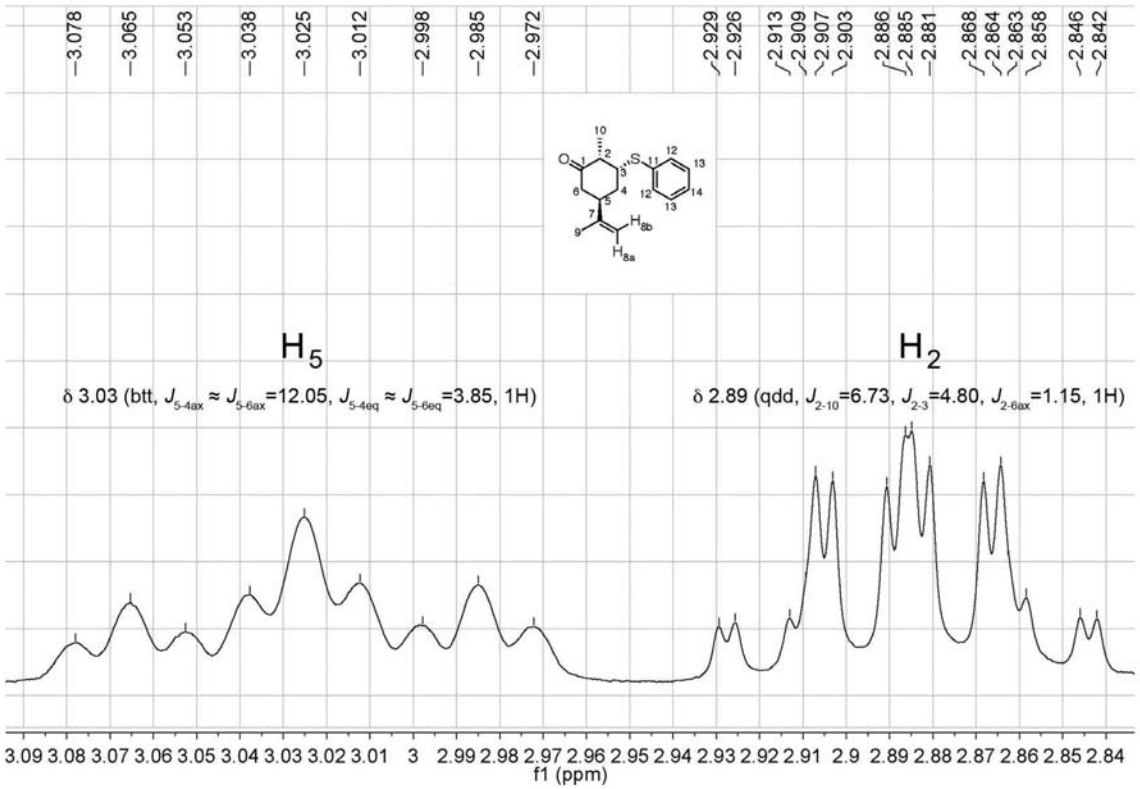


Figure S6. ^{1}H NMR spectrum of compound **14** between δ 2.84-3.09 (400 MHz, $CDCl_3$).

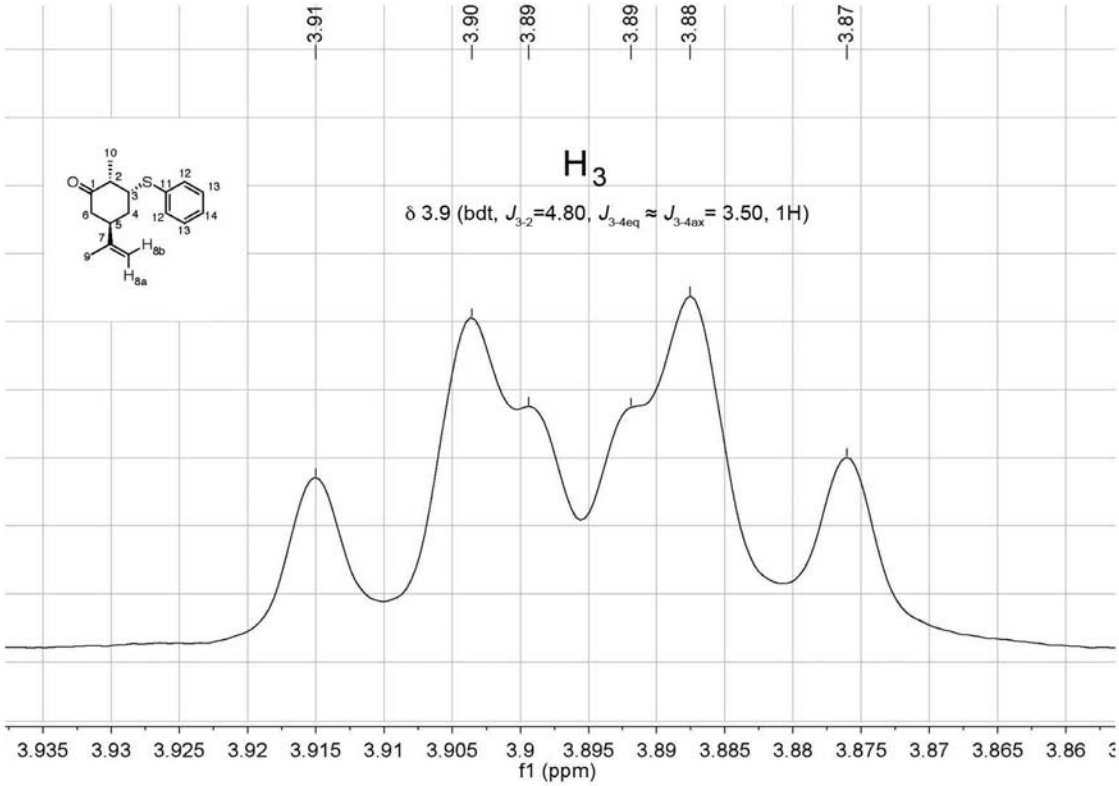


Figure S7. ^{1}H NMR spectrum of compound **14** between δ 3.86-3.93 (400 MHz, $CDCl_3$).

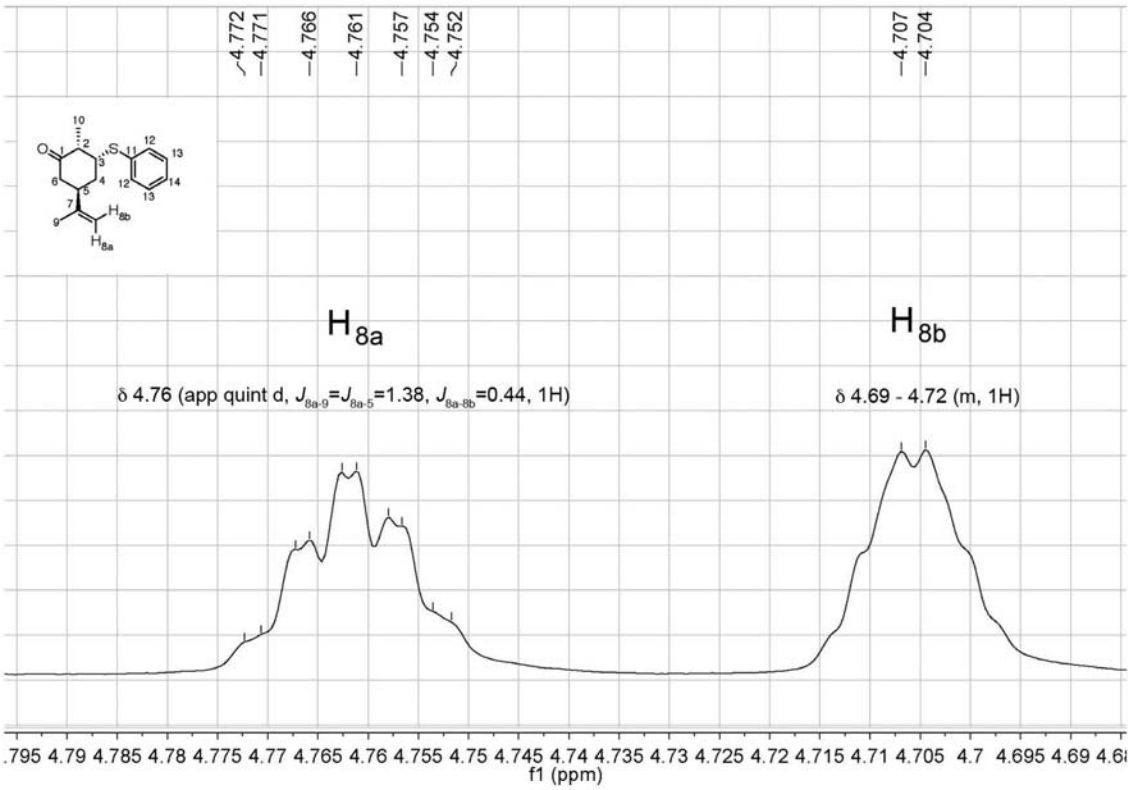


Figure S8. [1]H NMR spectrum of compound **14** between δ 4.69-4.79 (400 MHz, $CDCl_3$).

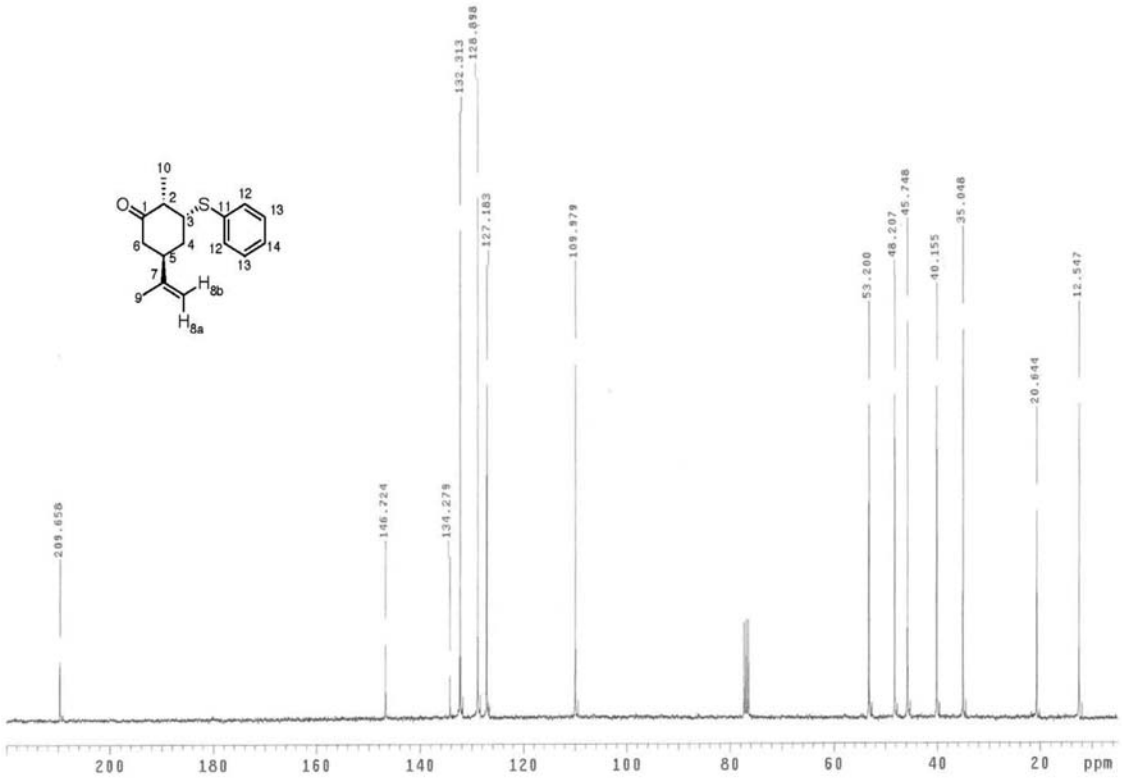


Figure S9. [13]C NMR spectrum of compound **14** (100 MHz, $CDCl_3$).

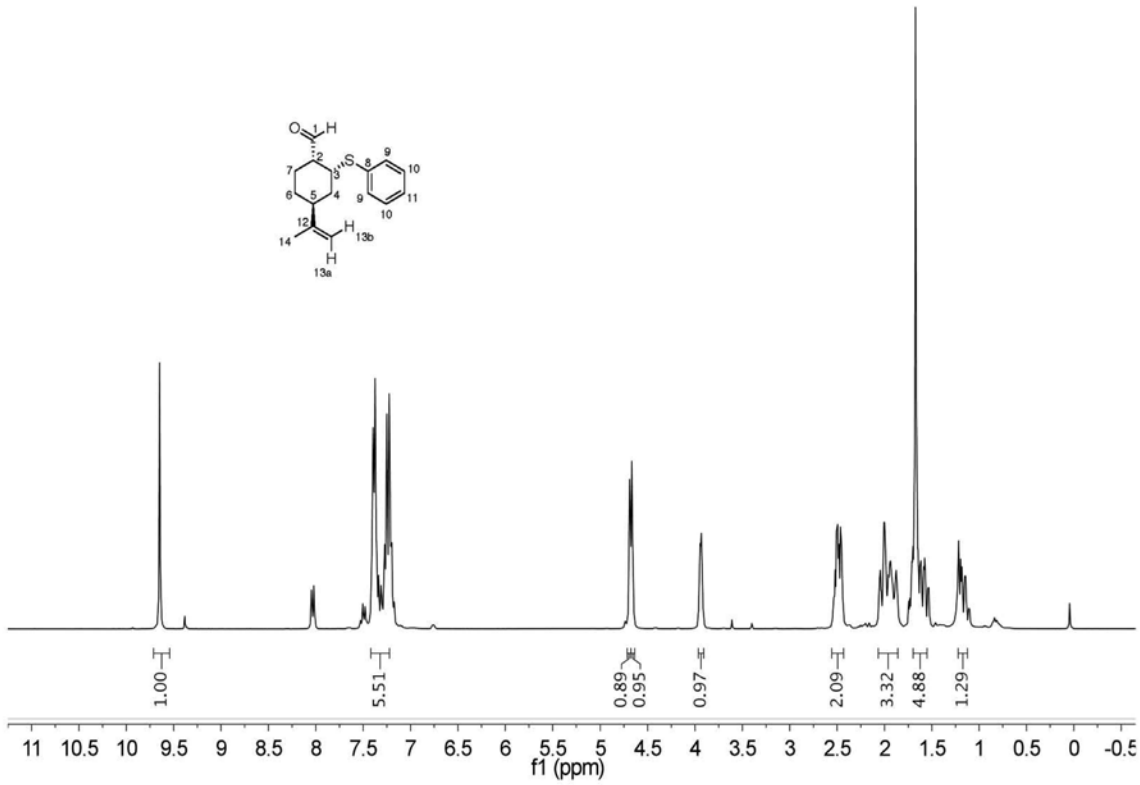


Figure S10. ^{1}H NMR spectrum of compound **16** (400 MHz, $CDCl_3$).

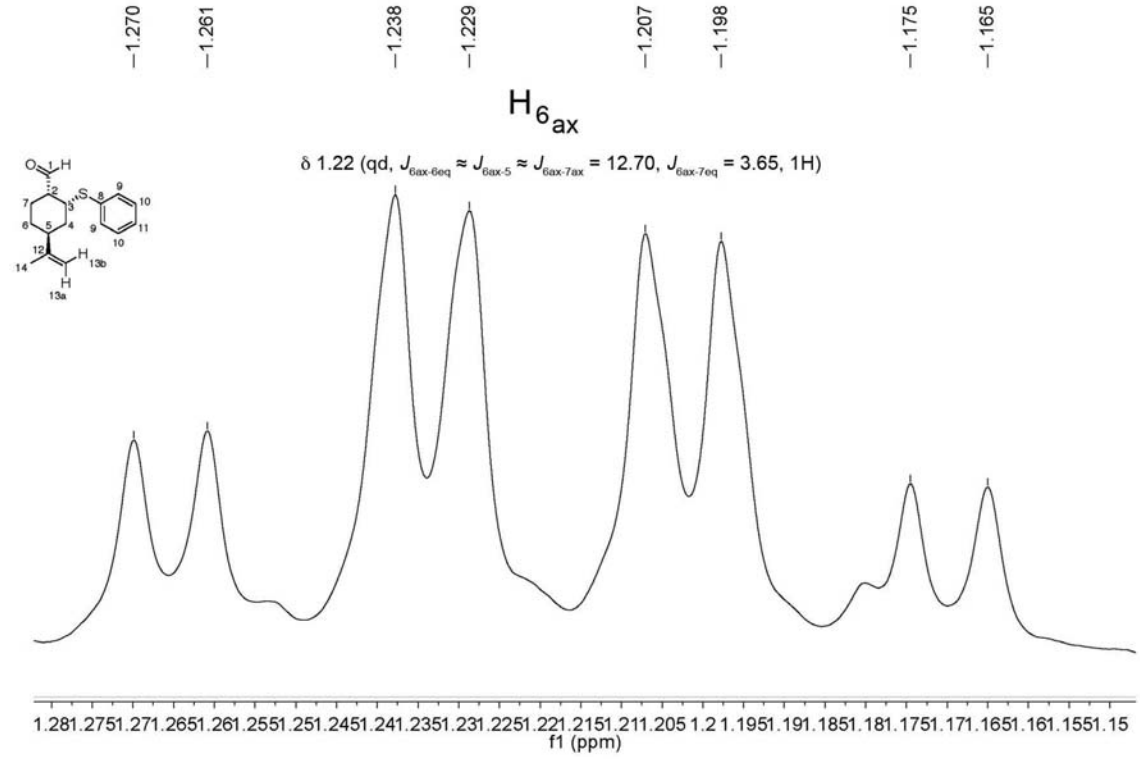


Figure S11. ^{1}H NMR spectrum of compound **16** between δ 1.15-1.28 (400 MHz, $CDCl_3$).

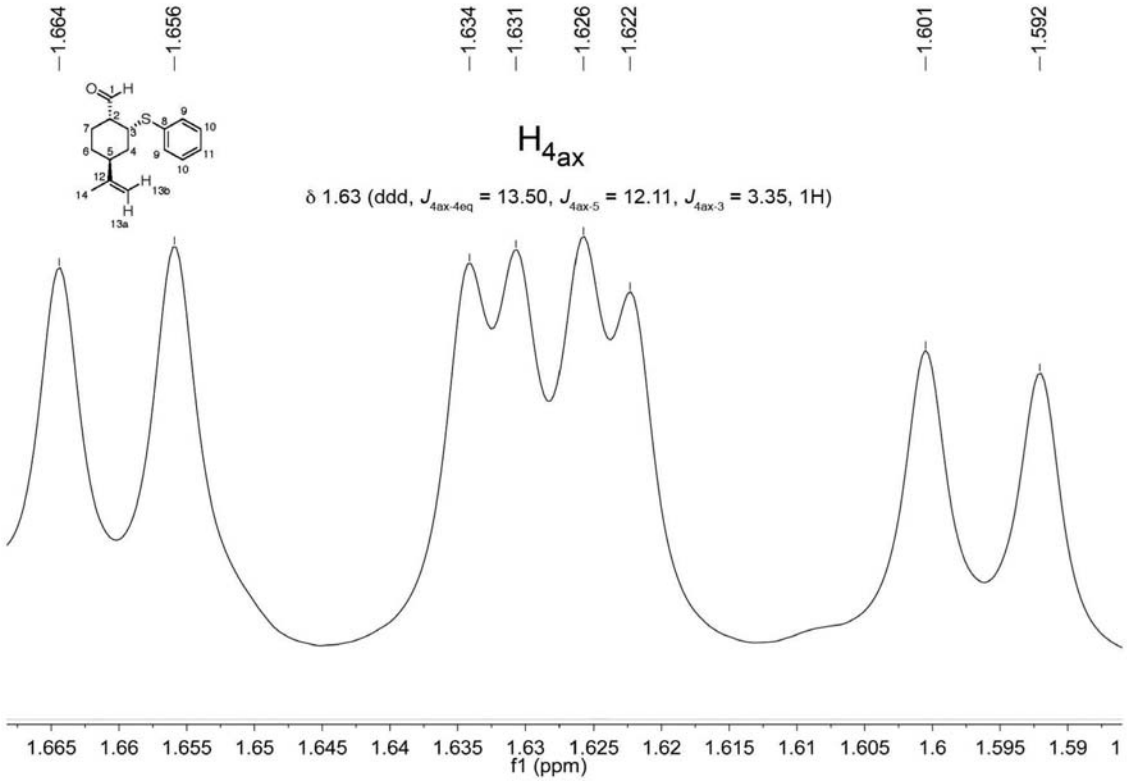


Figure S12. ^{1}H NMR spectrum of compound **16** between δ 1.59-1.67 (400 MHz, $CDCl_3$).

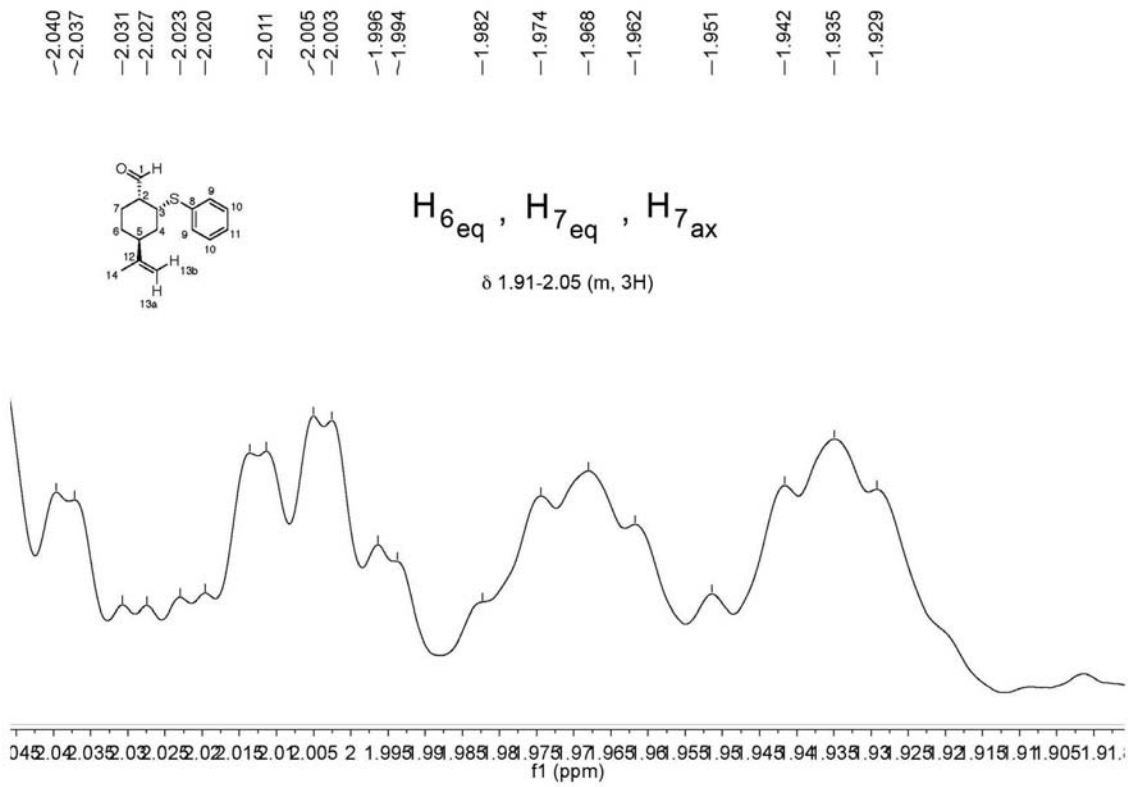


Figure S13. ^{1}H NMR spectrum of compound **16** between δ 1.91-2.05 (400 MHz, $CDCl_3$).

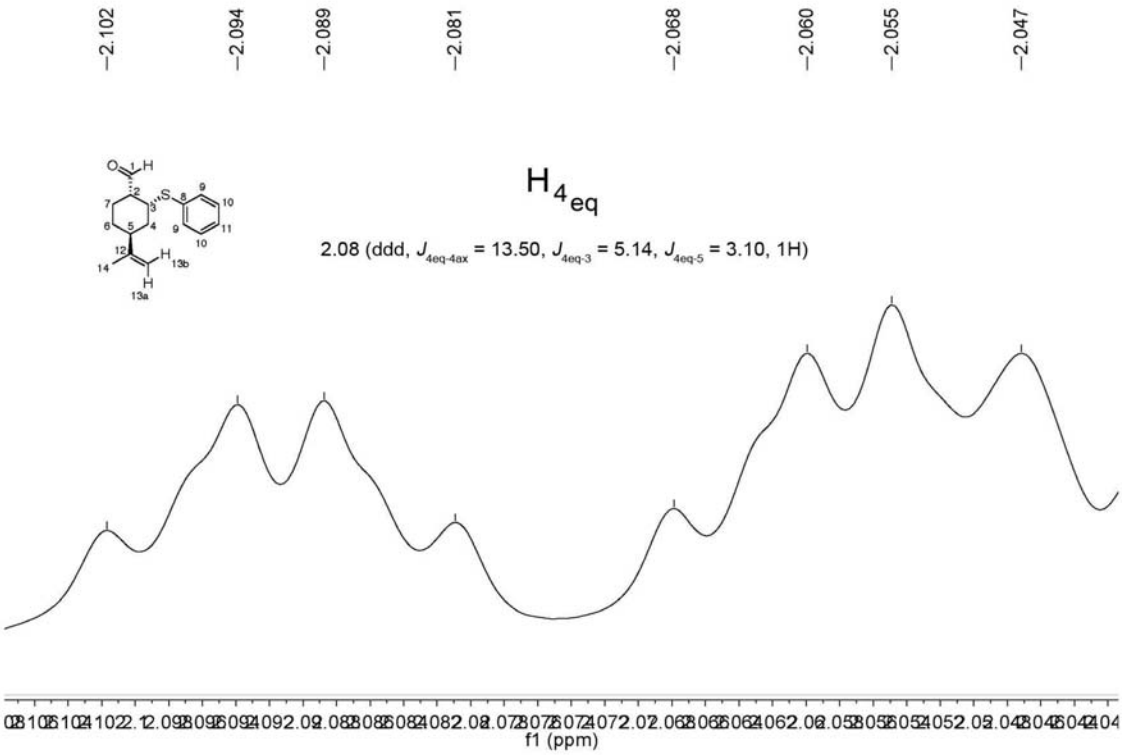


Figure S14. [1]H NMR spectrum of compound **16** between δ 2.04-2.11 (400 MHz, $CDCl_3$).

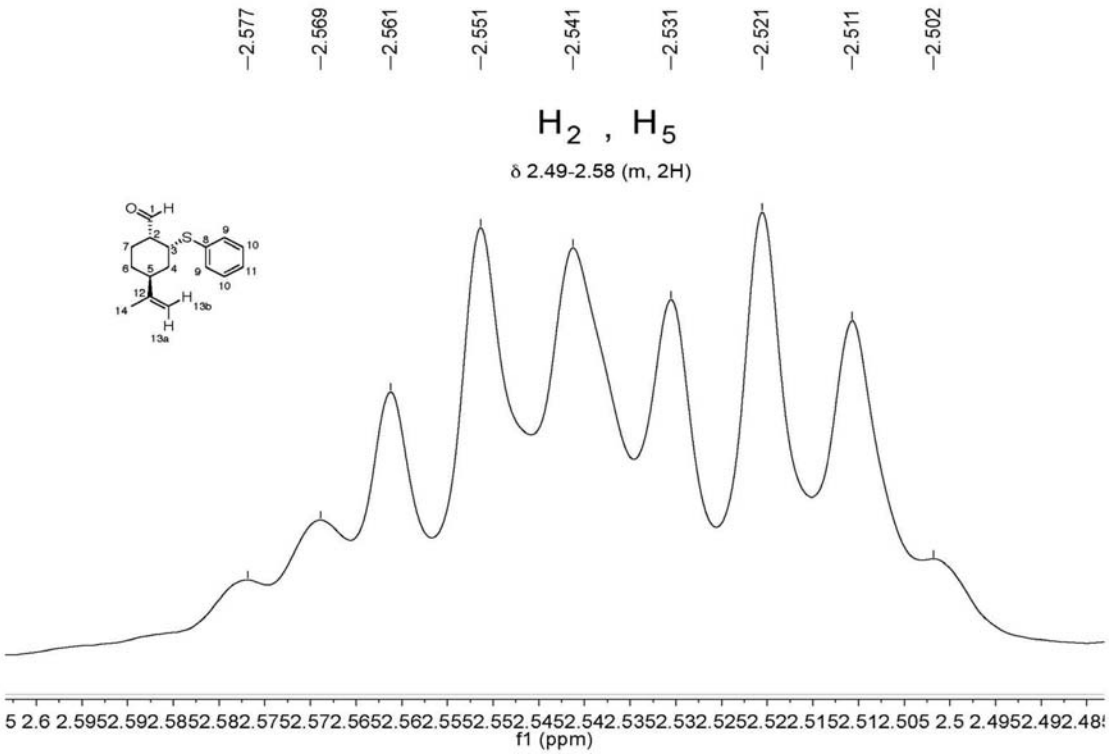


Figure S15. [1]H NMR spectrum of compound **16** between δ 2.49-2.60 (400 MHz, $CDCl_3$).

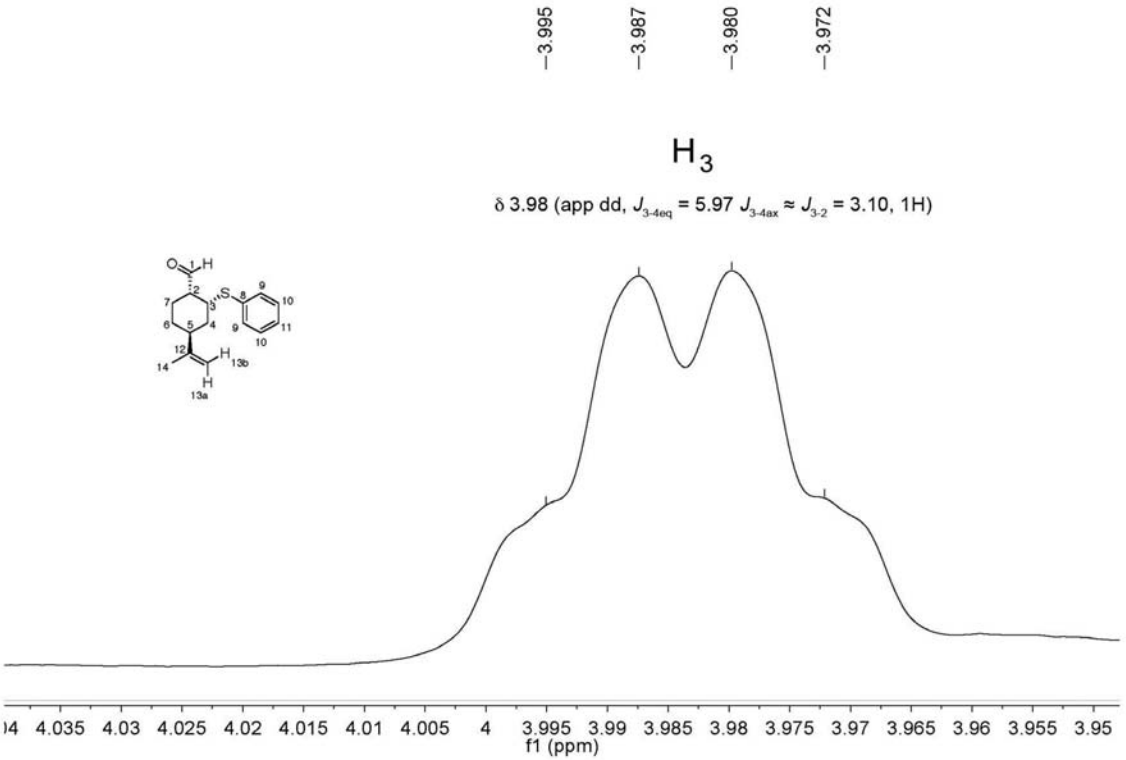


Figure S16. [1]H NMR spectrum of compound **16** between δ 3.95-4.03 (400 MHz, $CDCl_3$).

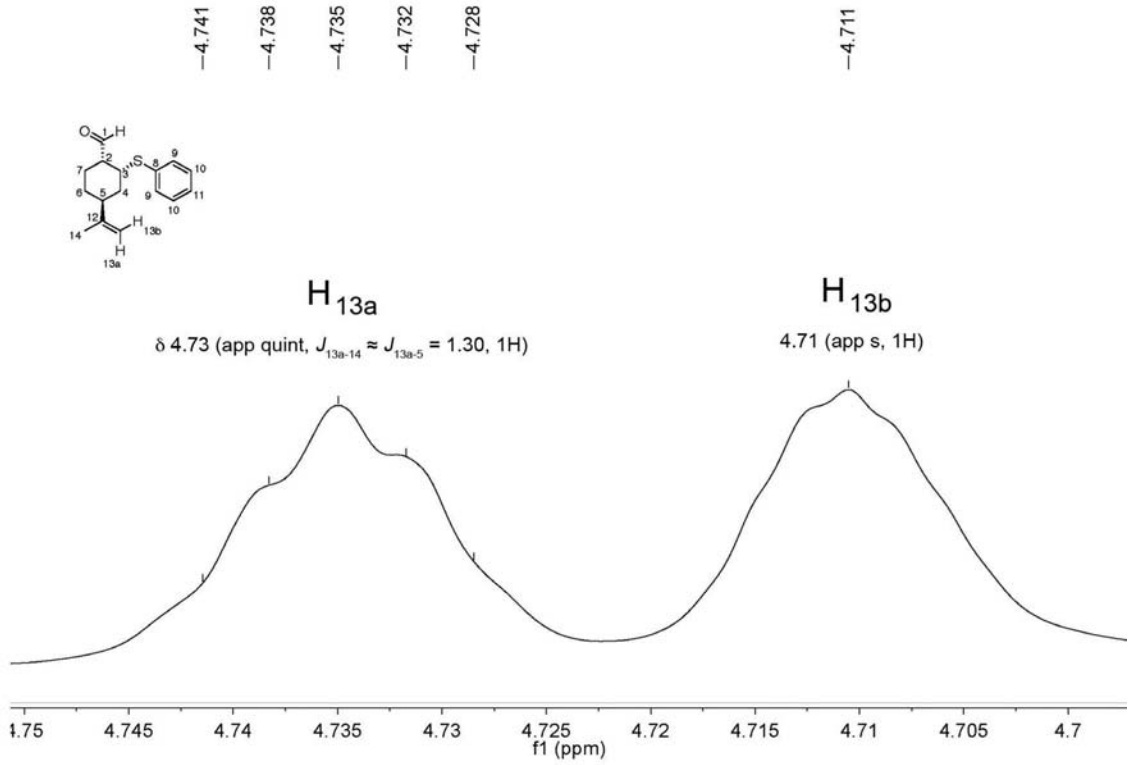


Figure S17. [1]H NMR spectrum of compound **16** between δ 4.70-4.75 (400 MHz, $CDCl_3$).

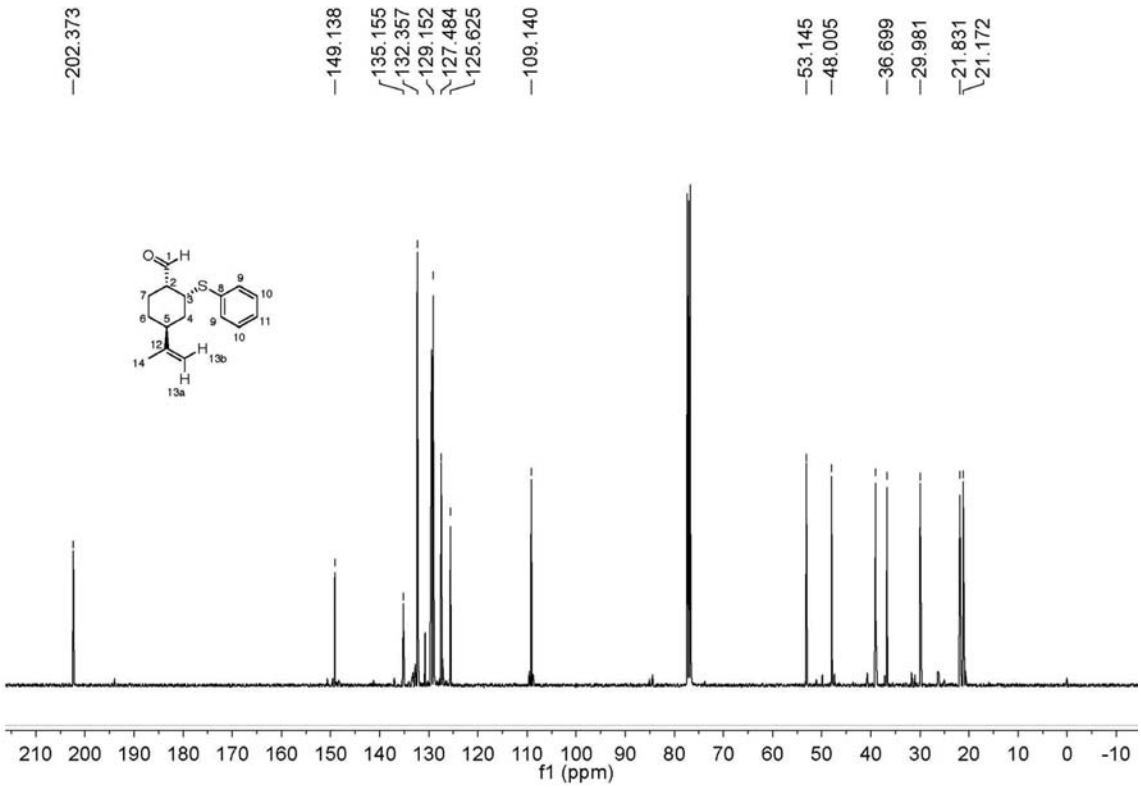


Figure S18. ^{13}C NMR spectrum of compound **16** (100 MHz, $CDCl_3$).

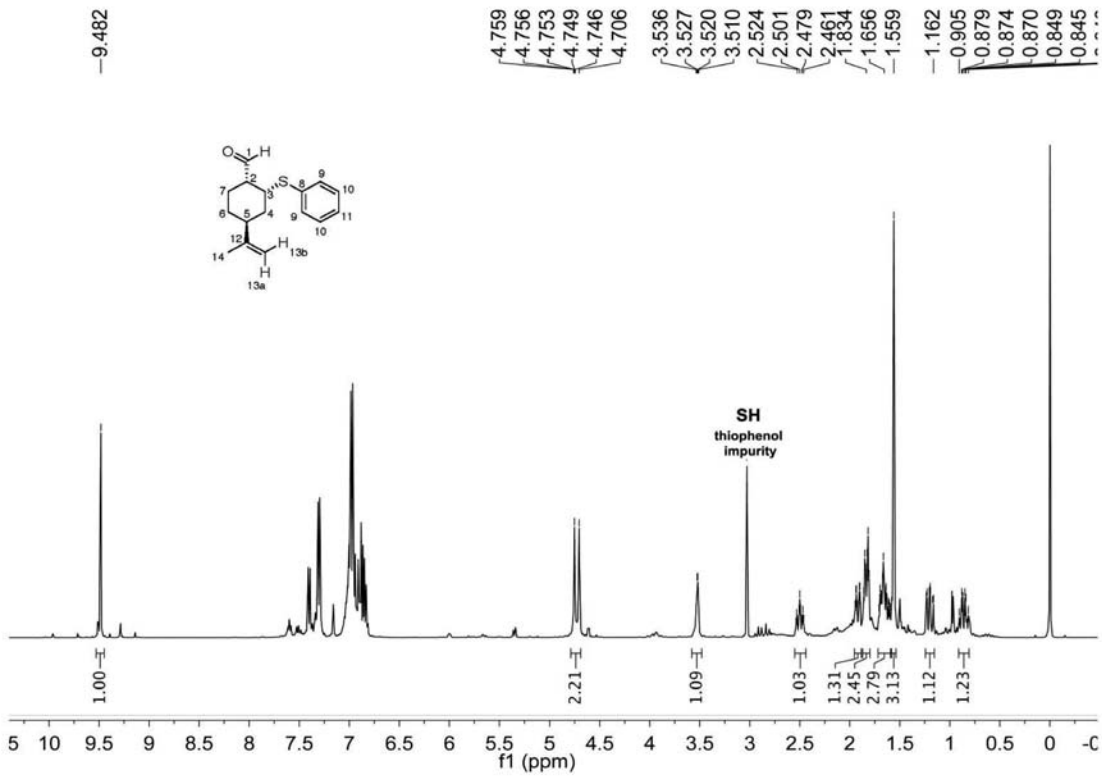


Figure S19. ^{1}H NMR spectrum of compound **16** (400 MHz, C_6D_6).

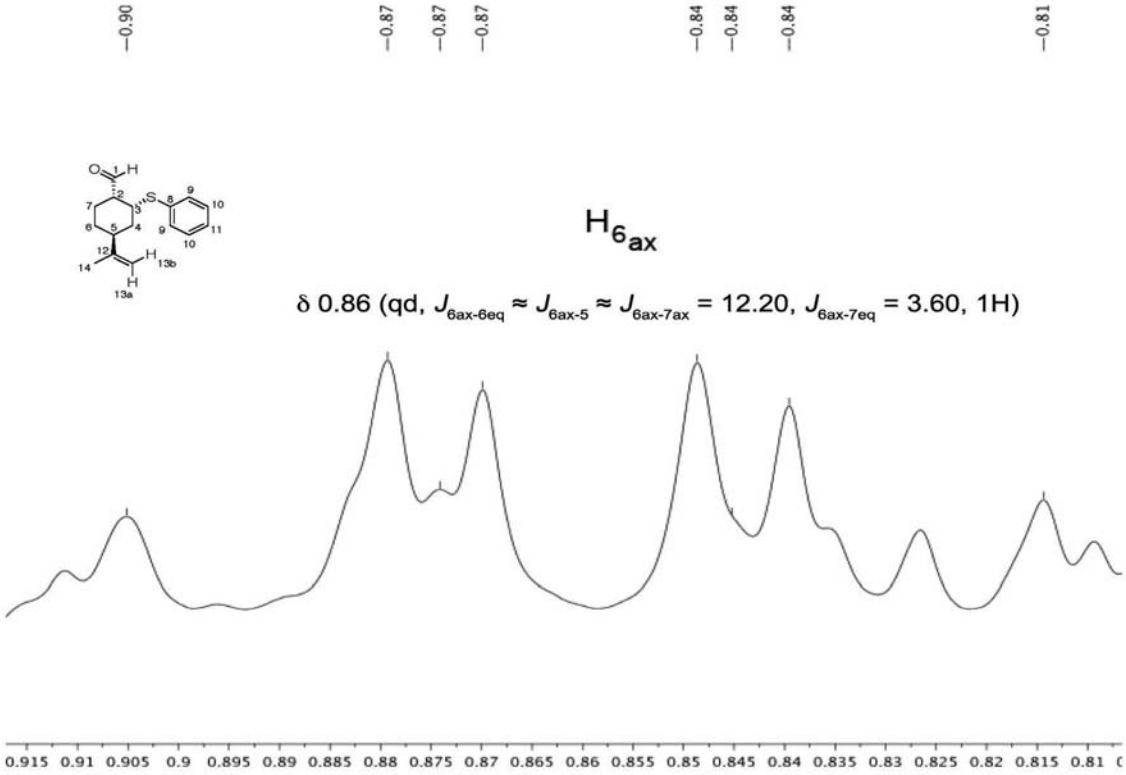


Figure S20. ^{1}H NMR spectrum of compound **16** between δ 0.80-0.91 (400 MHz, C_6D_6).

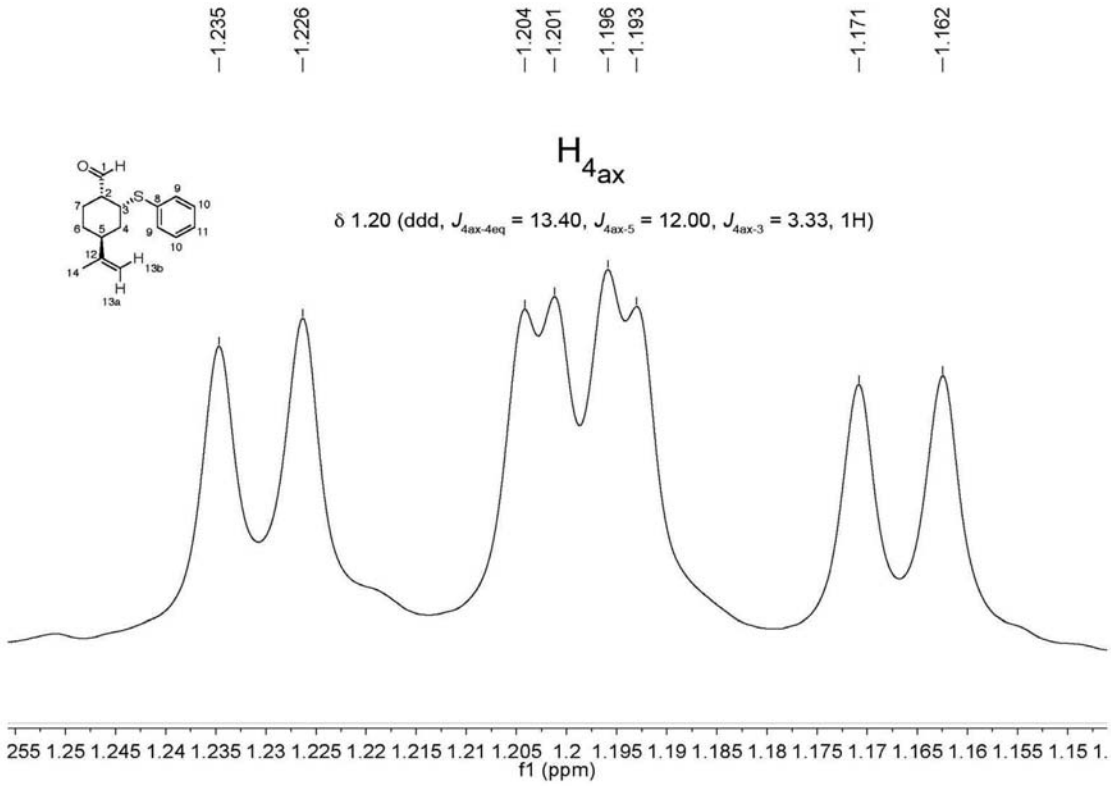


Figure S21. ^{1}H NMR spectrum of compound **16** between δ 1.15-1.25 (400 MHz, C_6D_6).

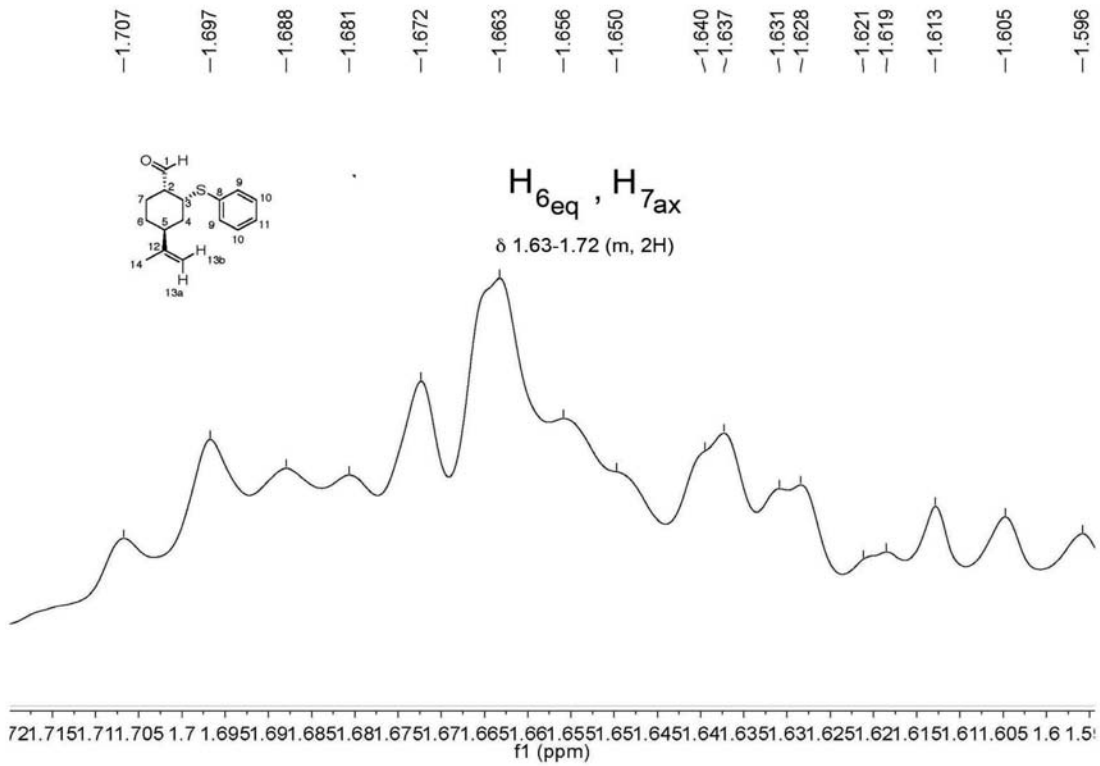


Figure S22. ^{1}H NMR spectrum of compound **16** between δ 1.59-1.72 (400 MHz, C_6D_6).

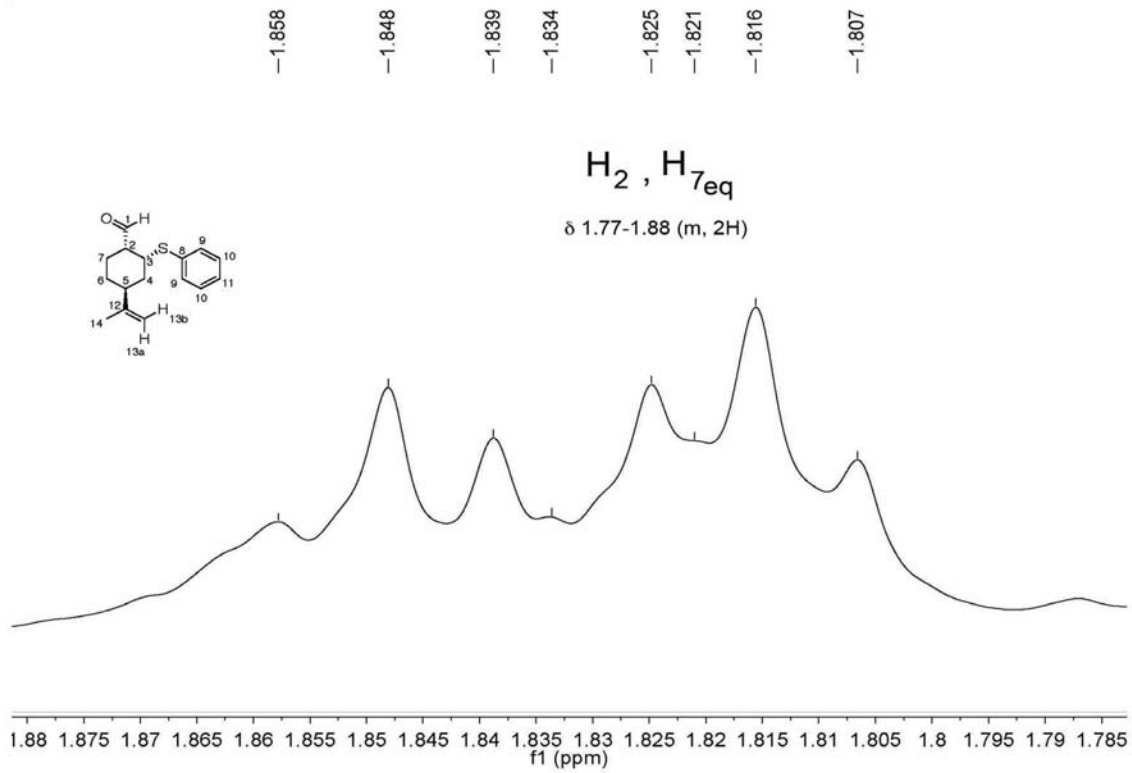


Figure S23. ^{1}H NMR spectrum of compound **16** between δ 1.77-1.88 (400 MHz, C_6D_6).

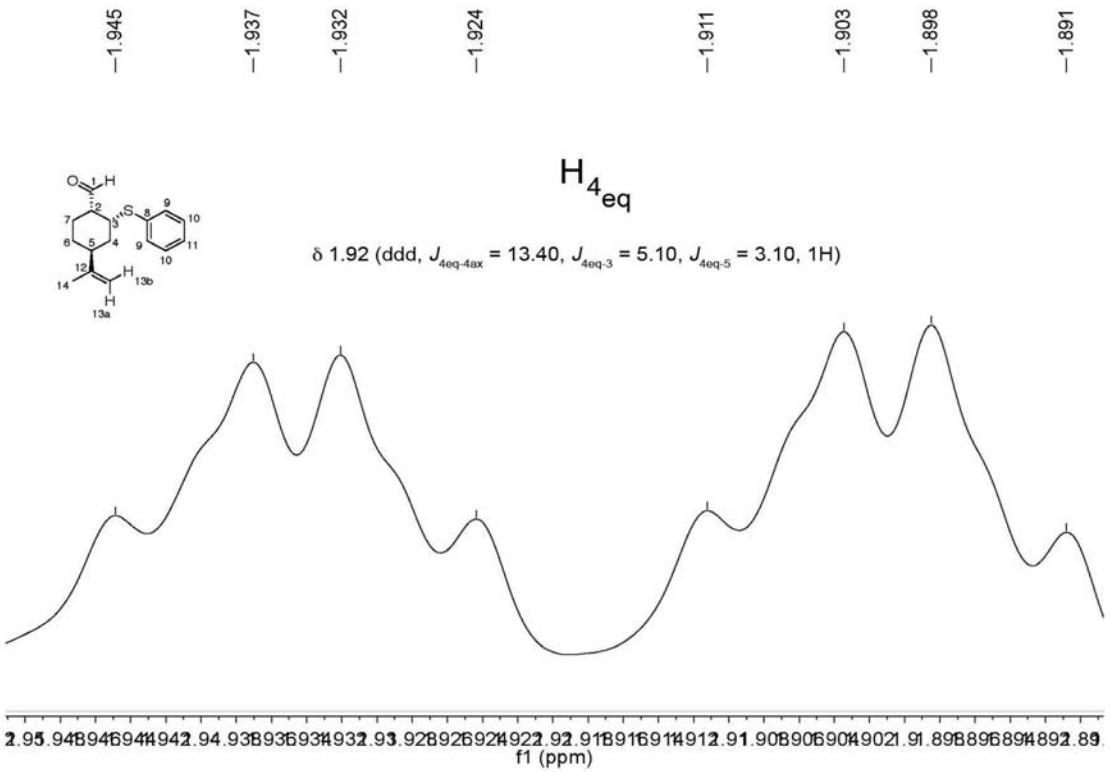


Figure S24. ^{1}H NMR spectrum of compound **16** between δ 1.88-1.95 (400 MHz, C_6D_6).

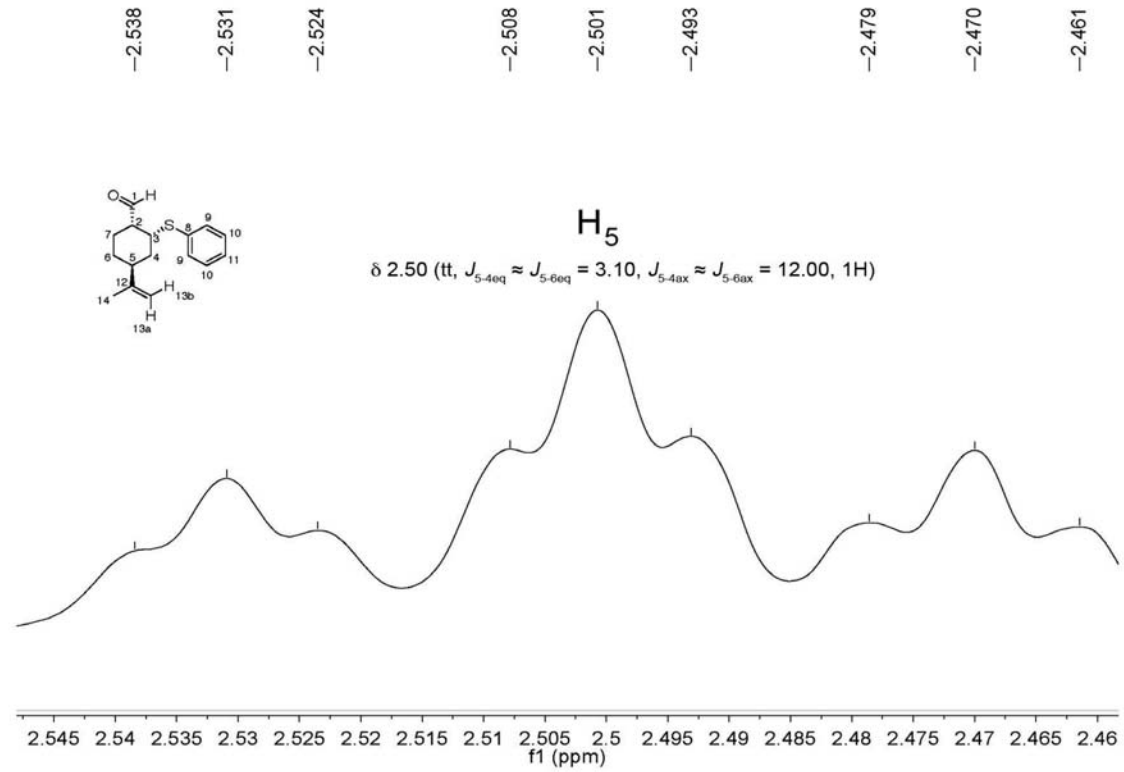


Figure S25. ^{1}H NMR spectrum of compound **16** between δ 2.45-2.54 (400 MHz, C_6D_6).

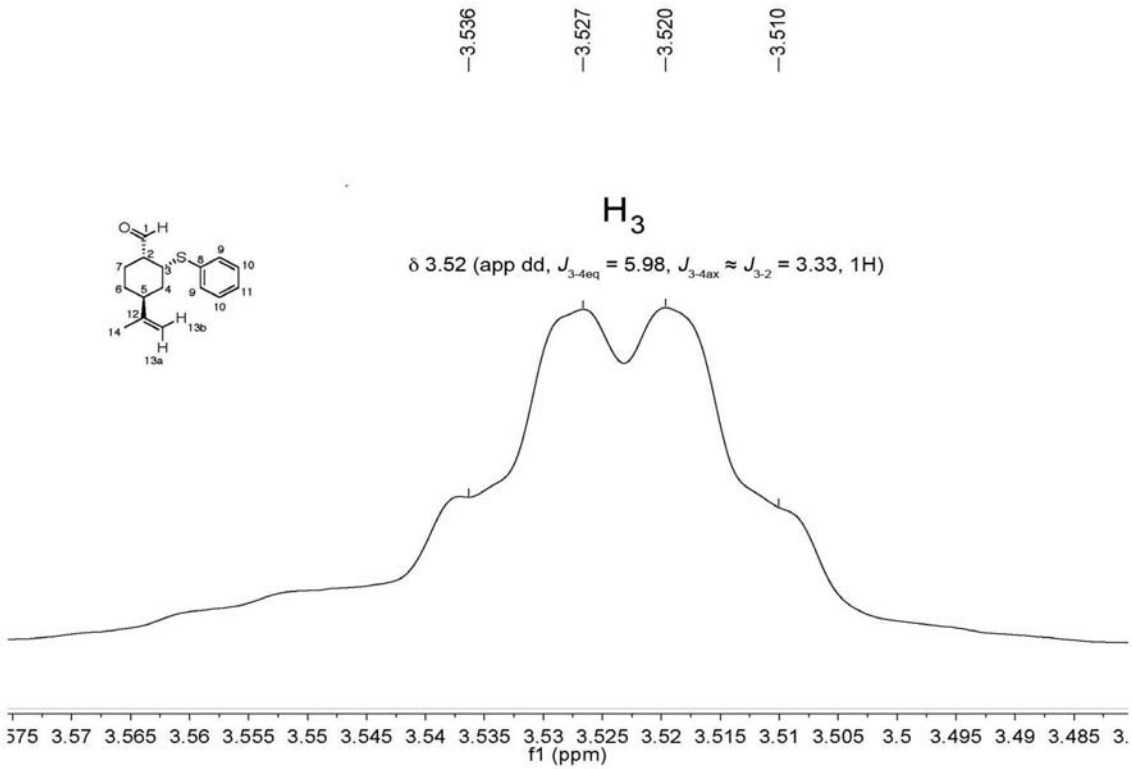


Figure S26. [1]H NMR spectrum of compound **16** between δ 3.49-3.57 (400 MHz, C_6D_6).

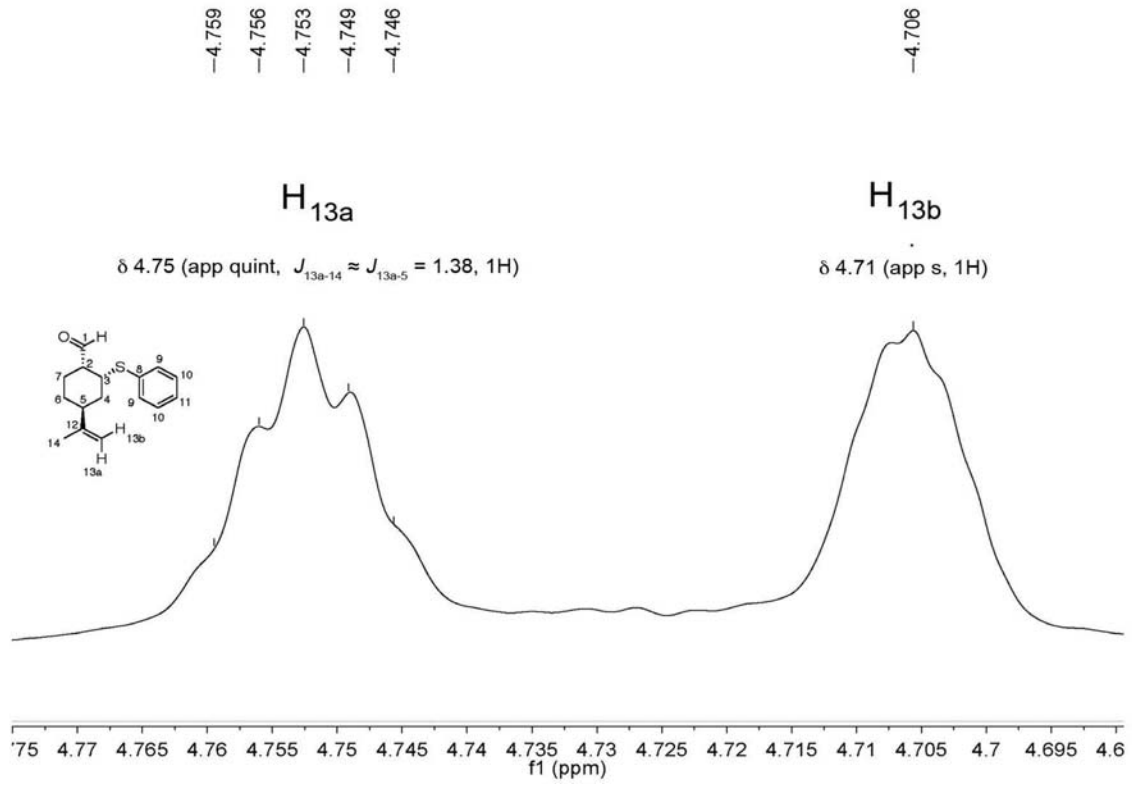


Figure S27. [1]H NMR spectrum of compound **16** between δ 4.69-4.78 (400 MHz, C_6D_6).

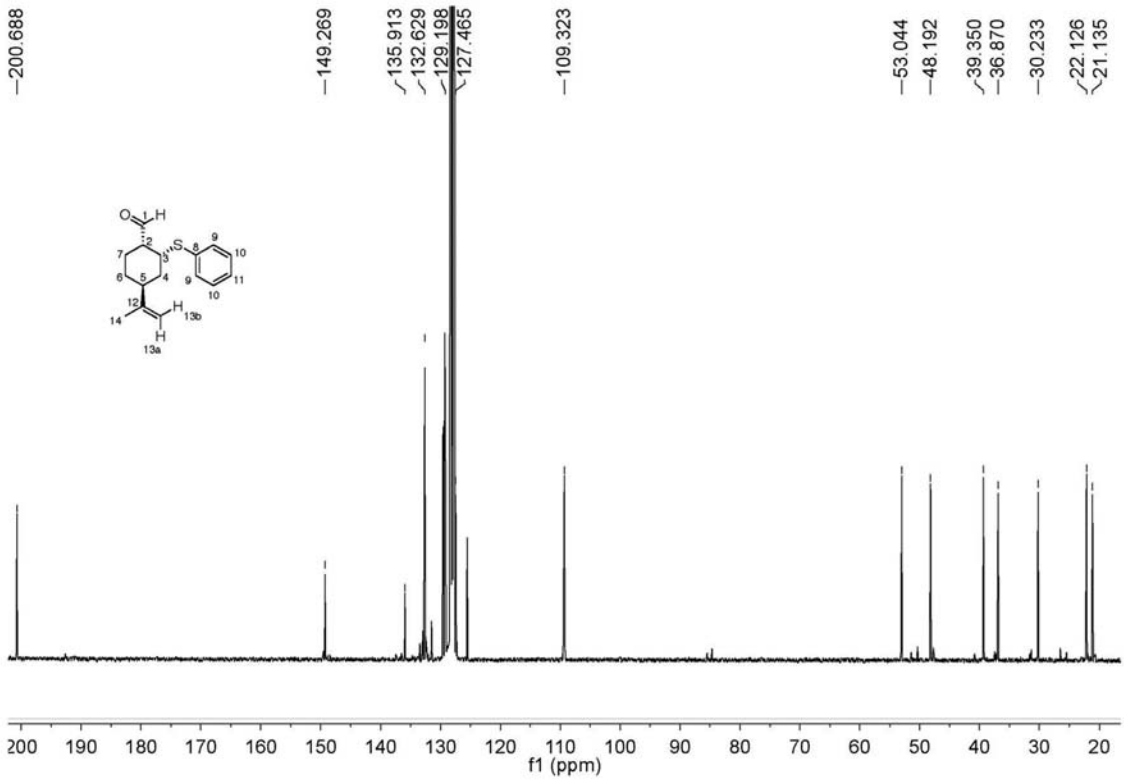


Figure S28. ^{13}C NMR spectrum of compound **16** (100 MHz, C_6D_6).