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Article

Iodine-Catalyzed Prins Cyclization of Aliphatic and Aromatic Ketones

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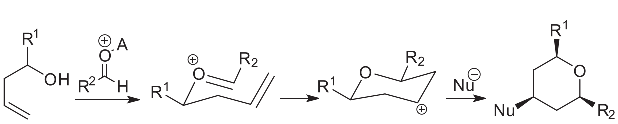
A ciclização de Prins catalisada por iodo entre álcoois homoalílicos e cetonas foi investigada. Condições anidras e atmosfera inerte não são necessárias neste protocolo ausente de metais. A reação do 2-(3,4-di-hidronaftalen-1-il)propan-1-ol com seis cetonas simétricas alifáticas levou ao produto desejado em 67-77% de rendimento. A ciclização foi realizada com quatro cetonas alifáticas assimétricas, levando aos correspondentes piranos em 66-76% de rendimento. A ciclização de Prins também foi alcançada com quatro cetonas aromáticas com 37-66% de rendimento. Finalmente, a ciclização de Prins do monoterpeno isopulegol e acetona foi realizada com sucesso.

Iodine-catalyzed Prins cyclization of homoallylic alcohols and ketones was investigated. Anhydrous conditions and inert atmosphere are not required in this metal-free protocol. The reaction of 2-(3,4-dihydronaphthalen-1-yl)propan-1-ol with six aliphatic symmetric ketones gave the desired products in 67-77% yield. Cyclization was performed with four aliphatic unsymmetric ketones, leading to corresponding pyrans in 66-76% yield. Prins cyclization was also accomplished with four aromatic ketones in 37-66% yield. Finally, Prins cyclization of the monoterpene isopulegol and acetone was successfully achieved.

Keywords: iodine, Prins cyclization, ketones, pyrans, spiro compounds

Introduction

Prins cyclization constitutes a powerful tool to obtain tetrahydropyrans (Scheme 1),[1-3] including the key step in several total syntheses.[4-14] Typically, Prins cyclization is performed mixing a homoallylic alcohol and an aldehyde in the presence of excess of an acid under anhydrous conditions. The use of ketones as the carbonyl components is restricted to a relatively small number of examples.[15-22] Additionally, only aliphatic symmetric ketones were usually employed. Herein, we describe the Prins cyclization of homoallylic alcohols **1a**-**b** (Figure 1) with several ketones (aliphatic and aromatic, symmetric and non symmetric) catalyzed by 5 mol% of iodine[23,24] without using anhydrous conditions and inert atmosphere.[25-27]



Scheme 1. General mechanism for Prins cyclization using aldehydes.

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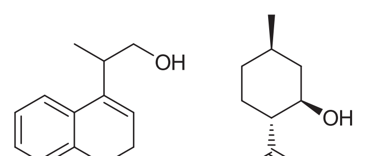


1a **1b**

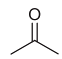
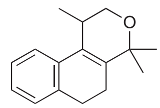
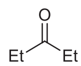
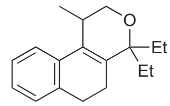
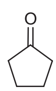
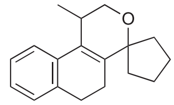
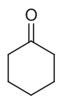
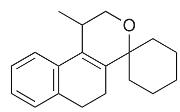
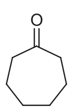
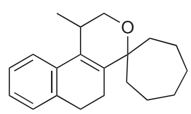
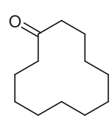
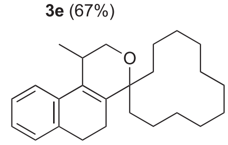
Figure 1. Structure of Homoallylic Alcohols **1a**-**b**.

Results and Discussion

We start our study investigating the reaction of the readily available homoallylic alcohol **1a**[28] with 1 equiv of acetone (**2a**) in CH_2Cl_2. The desired Prins cyclization product **3a** was obtained in 76% yield using 5 mol% of iodine (Table 1, entry 1). Under similar conditions, the Prins cyclization could also be performed with 2-pentanone (**2b**, entry 2), as well as with a series of cyclic ketones (**2c**-**f**, entries 3-6).

The next step was the study of unsymmetrical ketones (Table 2). The iodine-catalyzed Prins cyclization of **1a** with ketone **2g** gave the chromene derivative **3g** in 71% isolated yield, as a 1:1.25 mixture of diastereomers (entry 1). A similar result was obtained using the ketone **2h**, although in a slightly higher diastereoselectivity (entry 2).

Table 1. Iodine-catalyzed Prins cyclization of **1a** with aliphatic symmetric ketones **2a-f**[a]

entry	Ketone	Product (Yield / %)
1	 **2a**	 **3a** (76%)
2	 **2b**	 **3b** (75%)
3	 **2c**	 **3c** (77%)
4	 **2d**	 **3d** (75%)
5	 **2e**	 **3e** (67%)
6	 **2f**	 **3f** (70%)

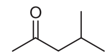
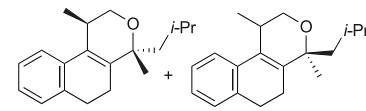
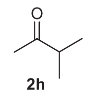
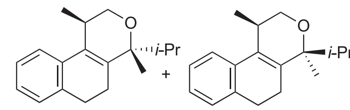
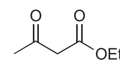
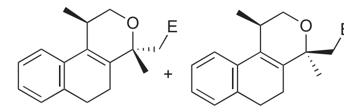
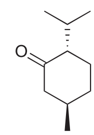
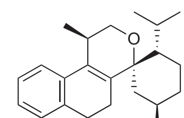
[a]Conditions: **1a** (1.0 equiv), ketone **2a-f** (1.0 equiv), I_2 (5 mol%), CH_2Cl_2.

Ethyl acetoacetate (**2i**) was also used as the carbonyl component, giving **3i** in 75% yield (entry 3). In such a case, the diastereoselectivity was higher than using **2g-h**. The reaction of **1a** with menthone **2j** gave the spirocyclic compound **3j** in 22% yield, as a single diastereomer. This low yield is analogous to that previously reported for Prins cyclizations using menthone.[22]

Considering the results obtained with aliphatic ketones, we tuned our attention to the less reactive aromatic ketones (Table 3). The coupling of acetophenone (**2k**) and **1a** gave **3k**, as a 1:5 mixture of diastereomers in 66% yield (entry 1). Using benzophenone (**2l**) as the carbonyl component, the desired product **3l** was isolated in 43% yield (entry 2). The spirocyclic compound **3m** was obtained in 52% yield as a single diastereomer, using 1-tetralone (**2m**), as substrate (entry 3). Chromanone **2n** gave the spiro cyclic compound **3n** in 37% yield (entry 4).

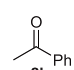
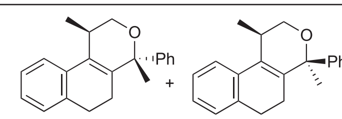
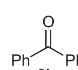
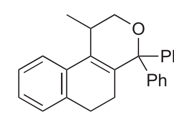
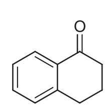
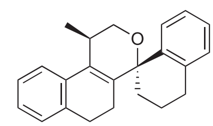
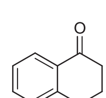
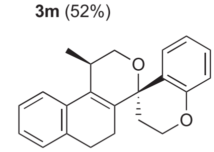
Based on the results in Tables 1-3, it is possible to conclude that lower yields were observed for the more bulky ketones, either aliphatic (Table 2, entry 4) or aromatic (Table 3, entries 2-4). Additionally, the relative configuration

Table 2. Iodine-Catalyzed Prins cyclization of **1a** with aliphatic unsymmetric ketones **2g-j**[a]

entry	Ketone	Product (Yield / %)
1	 **2g**	 **3g** (71%, *cis*:*trans* = 1:1.25)
2	 **2h**	 **3h** (66%, *cis*:*trans* = 1:2.5)
3	 **2i**	 **3i** (76%, *cis*:*trans* = 1:4.8) E=CO_2Et
4	 **2j**	 **3j** (22%)

[a]Conditions: **1a** (1.0 equiv), ketone **2g-j** (1.0 equiv), I_2 (5 mol%), CH_2Cl_2.

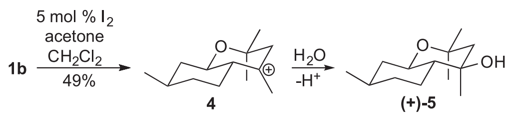
Table 3. Iodine-catalyzed Prins cyclization of **1a** with aromatic ketones **2k-2n**[a]

entry	Ketone	Product (Yield / %)
1	 **2k**	 **3k** (66%, *cis*:*trans* = 1:5)
2	 **2l**	 **3l** (43%)
3	 **2m**	 **3m** (52%)
4	 **2n**	 **3n** (37%)

[a]Conditions: **1a** (1.0 equiv), ketone **2k-n** (1.0 equiv), I_2 (5 mol%), CH_2Cl_2.

of the Prins cyclization products (**3g-k** and **3m-n**) shows that the bulkier group is *cis* to the methyl group. This agrees with the mechanism proposed for the iodine-catalyzed Prins cyclization.[25] The relative configurations were assigned by nuclear magnetic resonance (NMR) analysis, including Overhauser effect spectroscopy (NOESY) experiments.

The Prins cyclization of the monoterpene isopulegol **1b** was also investigated, because it has very different structural features when compared to **1a**. Treatment of a mixture of **1b** and acetone (**2a**) with iodine gave the functionalized bicyclic compound **5**, as a single diastereoisomer. It is important to note that in this case the carbocation intermediate **4** reacts with water (formed *in situ*), instead of losing a proton like in previous cases. The attack of water occurs through the equatorial face, explaining the formation of a single diastereoisomer (Scheme 2).[25,29]



Scheme 2. Prins cyclization of isopulegol (**1b**) and acetone (**2a**).

Conclusions

The iodine-catalyzed Prins cyclization of homoallylic alcohols and several ketones (aliphatic and aromatic, symmetric and unsymmetric) furnishes the desired hydropyrans in good to moderate yield. This protocol can be useful to prepare *O*-heterocycles under very mild conditions. In the case of hindered ketones, the desired products were obtained in lower yield.

Experimental

All commercially available reagents were used without further purification unless otherwise noted. Commercially available isopulegol was purified by flash column chromatography (15% AcOEt in hexanes). Tetrahydrofuran (THF) and benzene were freshly distilled from sodium/benzophenone. CH_2Cl_2 was freshly distilled over CaH_2. Thin layer chromatography (TLC) analyses were performed in silica gel plates, using UV and/or *p*-anisaldehyde solution for visualization. Flash column chromatography was performed using silica gel 200-400 mesh. Melting points are uncorrected. All NMR analyses were recorded using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal pattern. The experimental procedures for the preparation of compounds **3a** and **3c-e** were previously reported.[25]

4,4-Diethyl-1-methyl-1,4,5,6-tetrahydro-2H-benzo[f] isochromene (**3b**). General procedure for iodine-catalyzed prins cyclization: I_2 (0.030, 0.076 mmol) was added to a stirred solution of **1a** (0.113 g, 0.600 mmol) and **2b** (0.06 mL, 0.6 mmol) in CH_2Cl_2 (5 mL). The mixture was refluxed for 3 h. Na_2SO_3 (0.0075 g, 0.60 mmol) and H_2O (10 mL) were added. The aqueous phase was extracted with AcOEt (3 × 5 mL). The combined organic phase was washed with brine (5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (5% AcOEt in hexanes), affording **3b** (0.115 g, 0.450 mmol, 75%) as white solid; mp 58-60 °C; R_f = 0.56 (hexanes:EtOAc, 9:1); IR (film) ν/cm^{-1} 3061, 2963, 2930, 1487, 1452, 765, 733; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, *J* 7.4 Hz, 3H), 1.25 (d, *J* 6.8 Hz, 3H), 1.47-1.62 (m, 2H), 1.71-1.85 (m, 2H), 2.06-2.13 (m, 2H), 2.56-2.64 (m, 1H), 2.69-2.79 (m, 2H), 3.62 (dd, *J* 11.2, 1.7 Hz, 1H), 3.90 (dd, *J* 11.1, 3.2 Hz, 1H), 7.10-7.14 (m, 2H), 7.16-7.28 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.4, 8.7, 18.6, 24.1, 28.0, 28.5, 28.6, 28.7, 65.3, 79.6, 122.2, 126.2, 126.4, 127.4, 131.4, 134.1, 136.0, 136.9; LRMS *m/z* (rel. int.) 256 ($M^{+\bullet}$, 0.32), 228 (10), 227 (100); HRMS [ESI(+)] calcd. for $[C_{18}H_{24}O + Na]^+$ 279.1725, found 279.1718.

1-Methyl-1,2,5,6-tetrahydrospiro[benzo[*f*]isochromene-4,1'-cyclododecane] (**3f**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2f** (0.110 g, 0.600 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). Compound **3f** (0.148 g, 0.420 mmol, 70%) was obtained as colorless oil; R_f = 0.76 (hexanes-EtOAc, 9.5:0.5); IR (film) ν/cm^{-1} 3063, 2926, 2932, 2861, 1469, 765, 733; ^{1}H NMR (200 MHz,$CDCl_3$) δ 1.21 (d, *J* 6.8 Hz, 3H), 1.40-1.47 (m, 18H), 1.69-1.79 (m, 4H), 2.06-2.31 (m, 2H), 2.62-2.70 (m, 3H), 3.59 (dd, *J* 2.4, 11.0 Hz, 1H), 3.87 (dd, *J* 3.3, 11.1 Hz, 1H), 7.09-7.28 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.3, 20.2, 21.1, 22.8, 23.0, 23.3, 23.6, 24.7, 25.7, 27.0, 27.1, 28.7, 29.1, 31.6, 35.8, 65.2, 78.6, 122.4, 126.0, 126.3, 127.2, 130.0, 134.3, 136.0,139.5; LRMS *m/z* (rel. int.) 352 ($M^{+\bullet}$, 27.0), 337 (7.3), 309 (4.36), 281 (6.0), 226 (16.8), 225 (100); HRMS [ESI(+)] calcd. for $[C_{25}H_{36}O + H]^+$ 353.2839, found 353.2841.

2,4,5,6-Tetrahydro-4-isobutyl-1,4-dimethyl-1*H*-benzo[*f*] isochromene (**3g**): the reaction was performed following the general procedure, but using **1a** (0.090 g, 0.48 mmol), **2g** (0.060 mL, 0.48 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0061 g, 0.024 mmol). Compound **3g** (1:1.25 *cis:trans*, 0.092 g, 0.34 mmol, 71%) was obtained as a pale yellow oil; R_f = 0.63 (hexanes-EtOAc, 9:1); IR (film) ν/cm^{-1} 3061, 2950, 2928, 1488, 1451, 1126, 766, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ *trans*-**3g** 0.95 (d, *J* 6.6 Hz, 6H), 1.18 (d, *J* 6.9 Hz, 3H), 1.39 (s, 3H), 1.42-1.71 (m, 2H), 1.80-1.90 (m, 1H), 2.04-2.16 (m, 2H), 2.67-2.78 (m, 3H), 3.58 (dd, *J* 11.1, 3.3 Hz, 1H), 3.91 (dd, *J* 11.4, 3.6 Hz, 1H), 7.11-7.13 (m, 2H), 7.15-7.29 (m, 2H); *cis*-**3g** 9.07 (d, *J* 6.6 Hz, 3H), 1.02 (d, *J* 6.6 Hz, 3H), 1.271 (s, 3H), 1.274 (d, *J* 6.9 Hz, 3H), 3.65 (dd, *J* 11.1, 1.5 Hz, 1H), 3.94 (dd, *J* 11.4, 3.0 Hz, 1H). Other signals overlap with the major diastereomer; ^{13}C NMR (50 MHz, $CDCl_3$) δ *trans*-**3g** 18.0, 24.0, 24.1, 24.2, 24.8, 25.2, 28.8, 43.9, 65.6, 77.2, 122.5, 126.1, 126.3, 127.3, 130.1, 134.1, 136.0, 139.4; *cis*-**3g** 18.5, 24.1, 24.4, 24.7, 25.1, 25.6, 28.3, 48.4, 65.4, 78.1, 122.2, 126.2, 126.4, 127.4, 130.7, 135.7, 137.5 ; LRMS *m/z* (rel. int.) 270 ($M^{+\bullet}$, 2.03), 255 (20), 214 (17), 213 (100); HRMS [ESI(+)] calcd. for $[C_{19}H_{26}O + H]^+$ 271.2062, found 271.2053.

2,4,5,6-Tetrahydro-4-isopropyl-1,4-dimethyl-1*H*-benzo[*f*]isochromene (**3h**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2h** (0.064 mL, 0.60 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). Compound *cis*-**3h** (0.0271, 0.106 mmol, 18%) and *trans*-**3h** (0.0675 g, 0.264 mmol, 44%) were obtained as white solid and colorless viscous oil, respectively. (±)-(1*R*,4*R*)-2,4,5,6-tetrahydro-4-isopropyl-1,4-dimethyl-1*H*-benzo[*f*]isochromene (*cis*-**3h**); mp 61-63 °C; R_f = 0.34 (hexanes-EtOAc, 9.5:0.5); IR (film) ν/cm^{-1} 3060, 2967, 2934, 1451, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, *J* 6.9 Hz, 3H), 1.03 (d, *J* 6.6 Hz, 3H), 1.09 (d, *J* 6.6 Hz, 3H), 1.40 (s, 3H), 1.86-1.95 (m, 1H), 2.07-2.15 (m, 2H), 2.61-2.80 (m, 2H), 2.82-2.84 (m, 1H), 3.58 (dd, *J* 11.2, 6.0 Hz, 1H), 3.99 (dd, *J* 11.1, 4.5 Hz, 1H), 7.11-7.15 (2H), 7.22-7.23 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 17.1, 18.6, 24.5, 24.7, 28.6, 28.7, 34.4, 67.1, 78.3, 123.0, 125.9, 126.1, 127.1, 131.4, 134.2, 136.1, 139.4; LRMS *m/z* (rel. int.) 256 ($M^{+\bullet}$, 0.08), 241 (0.87), 213 (100); HRMS [ESI(+)] calcd. for $[C_{18}H_{25}O + H]^+$ 257.1900, found 257.1899. (±)-(1*R*,4*S*)-2,4,5,6-tetrahydro-4-isopropyl-1,4-dimethyl-1*H*-benzo[*f*] isochromen (*trans*-**3h**); R_f = 0.31 (hexanes-EtOAc, 9.5:0.5); IR (film) ν/cm^{-1} 3061, 2964, 2931, 1451, 766; ^{1}H NMR (300MHz, $CDCl_3$) δ 0.92 (d, *J* 6.8 Hz, 3H), 1.04 (d, *J* 6.8 Hz, 3H), 1.28 (d, *J* 7.0 Hz, 3H), 1.30 (s, 3H), 1.88-2.02 (m, 1H), 2.08-2.18 (m, 2H), 2.54-2.59 (m, 1H), 2.71-2.80 (m, 2H), 3.66 (dd, *J* 0.8, 11.0 Hz, 1H), 3.90 (dd, *J* 3.1, 11.1 Hz, 1H), 7.10-7.13 (m, 2H), 7.17-7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 18.47, 18.51, 21.2, 23.8, 28.5, 28.8, 34.6, 65.3, 78.6, 122.1, 126.2, 126.4, 127.4, 130.3, 134.2, 135.8, 138.1; LRMS *m/z* (rel. int.) 256 ($M^{+\bullet}$, 0.5), 241 (4.1), 213 (100); HRMS [ESI(+)] calcd. for $[C_{18}H_{24}O + Na]^+$ 279.1719, found 279.1679.

Ethyl 2-(2,4,5,6-tetrahydro-1,4-dimethyl-1*H*-benzo[*f*] isochromen-4-yl)acetate (**3i**): the reaction was performed following the general procedure, but using **1a** (0.89 g, 0.47 mmol), **2i** (0.060 mL, 0.47 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0060, 0.024 mmol). Compound **3i** (1:4.8, *cis:trans* 0.108 g, 0.36 mmol, 76%) was obtained as colorless viscous oil; R_f = 0.26 ((hexanes-EtOAc, 9:1); IR (film) ν/cm^{-1} 3060, 2975, 2932, 2900, 2870, 1732, 1488, 1463, 1450, 1034, 1060, 1075, 768, 735. ^{1}H NMR (300 MHz, $CDCl_3$) δ *trans*-**3i** 1.75 (d, *J* 4.2 Hz, 3H), 1.20 (t, *J* 4.2 Hz, 3H), 1.39 (s, 3H), 2.13-2.28 (m, 2H), 2.63-2.66 (m, 1H), 2.66 (d, *J* 7.8 Hz, 1H), 2.69-2.74 (m, 1H), 2.79 (d, *J* 8.1 Hz, 3H), 2.85-2.94 (m, 1H), 3.70 (dd, *J* 6.75, 1.0 Hz, 1H), 3.92 (dd, *J* 6.9, 1.8 Hz, 3H), 4.09 (q, *J* 4.2 Hz, 2H), 7.12-7.13 (m, 2H), 7.18-7.22 (m, 1H), 7.24 (br, 1H). *cis*-**3i** 1.23 (d, *J* 3.9 Hz, 3H), 1.24 (d, *J* 4.2 Hz, 3H), 1.54 (s, 3H), 4.15 (d, *J* 4.2 Hz, 2H) 7.14 -7.15 (m, 2H). Other signals overlap with the major diastereomer; ^{13}C NMR (50 MHz, $CDCl_3$) δ *trans*-**3i** 14.2, 18.0, 23.3, 24.6, 28.1, 28.5, 45.4, 45.4, 60.3, 65.6, 77.2, 122.3, 126.3, 126.5, 127.5, 131.1, 133.7, 135.6, 136.1, 170.2, *cis*-**3i** 13.9, 18.1, 24.3, 25.9, 28.5, 28.7, 41.8, 60.4, 66.0, 75.7, 122.5, 125.4, 126.6, 128.6, 130.9, 134.0, 135.8, 136.7, 170.5; LRMS *m/z* (rel. int.) 300 ($M^{+\bullet}$, 2.3), 213 (60.8), 165 (16.0), 153 (17.4), 141 (23.0), 128 (22.5), 115 (19.9), 43 (100); HRMS [ESI(+)] calcd. for $[C_{19}H_{24}O_3+Na]^+$ 323.1623, found.323.1625.

(1*R*,2'*R*,5'*R*)-2'-isopropyl-1,5-diMethyl-1,2,5,6-etrahydrospiro[benzo[*f*]issochrom-ene-4,1'cyclohexane] (**3j**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2j** (0.103 mL, 0.600 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). Compound **3j** (0.0429 g, 0.132 mmol, 22%) was obtained as colorless oil; R_f = 0.41 (hexanes-EtOAc, 9.5:0.5); IR (film) ν/cm^{-1} 3061, 3030, 2936, 2924, 2856, 1453, 1090, 748, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, *J* 7.2 Hz, 3H), 0.85 (d, *J* 6.8 Hz, 3H), 0.90 (d, *J* 6.4 Hz, 3H), 0.99 (d, *J* 6.8 Hz, 3H), 1.13-1.29 (m, 2H), 1.32-1.37 (m, 1H), 1.42-1.68 (m, 4H), 1.75-1.82 (m, 2H), 1.91-2.05 (m, 2H), 2.12-2.20 (m, 1H), 2.55-2.73 (m, 2H), 2.90-2.97 (m, 1H), 3.48 (dd, *J* 11.4, 8.4 Hz, 1H), 3.92 (dd, *J* 11.4, 5.7 Hz, 1H), 7.12-7.15 (m, 2H), 7.21-7.23 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8, 18.7, 20.5, 22.5, 24.0, 24.7, 27.2, 27.5, 28.3, 28.8, 35.3, 42.4, 46.1, 65.5, 80.0, 123.5, 125.7, 125.9, 127.0, 132.4, 134.5, 136.4, 140.2; LRMS *m/z* (rel. int.) 324 ($M^{+\bullet}$, 10), 309 (3.37), 240 (17), 239 (100); HRMS [ESI(+)] calcd. for $[C_{23}H_{32}O + H]^+$ 325.2526, found 325.2532.

1,4-Dimethyl-4-phenyl-1,4,5,6-tetrahydro-2*H*-benzo[*f*] isochromene (**3k**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2k** (0.070 mL, 0.60 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). The crude product was purified by flash column chromatography (2% AcOEt in hexanes). Compounds *cis*-**3k** (0.0186 g, 0.0641 mmol, 11%) as a white solid and *trans*-**3k** (0.097 g, 0.33 mmol, 55%) as colorless viscous oil were obtained. (±)-(1*R*,4*R*)-

1,4-dimethyl-4-phenyl-1,4,5,6-tetrahydro-2*H*-benzo[*f*]isochromene (*cis*-**3k**); mp 98-100 °C; R_f = 0.38 (hexanes-EtOAc, 9.5:0.5); IR (film) ν/cm^{-1} 3059, 2929, 2247, 1489, 764, 699; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, *J* 6.8 Hz, 3H), 1.80 (s, 3H), 1.94-2.10 (m, 1H), 2.19-2.35 (m, 1H), 2.65-2.70 (m, 1H), 2.74-2.96 (m, 2H), 3.47 (dd, *J* 1.8, 11.2 Hz, 1H), 3.70 (dd, *J* 3.0, 11.2 Hz, 1H), 7.15-7.17 (m, 2H), 7.23-7.38 (m, 5H), 7.49-7.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.8, 25.6, 26.1, 28.3, 29.1, 65.3, 78.1, 122.6, 126.5, 126.6, 127.2, 127.47. 127.55, 128.0, 132.2, 133.9, 135.8, 135.9, 143.0; LRMS *m/z* (rel. int.) 290 ($M^{+\bullet}$), 275 (87), 77 (100); HRMS [ESI(+)] calcd. for $[C_{21}H_{22}O + Na]^+$ 313.1563, found 313.1559. (±)-(1*R*,4*S*)-2,4,5,6-tetrahydro-1,4-dimethyl-4-phenyl-1*H*-benzo[*f*]isochromene (*trans*-**3k**); R_f = 0.41 (hexanes-EtOAc, 9.5-0.5); IR (film) ν/cm^{-1} 3069, 2930, 2244, 1489, 766, 700; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, *J* 7.0 Hz, 3H), 1.71 (s, 3H), 1.80-1.94 (m, 1H), 2.05-2.28 (m, 1H), 2.61-2.72 (m, 2H), 2.85-2.96 (m, 1H), 3.51 (dd, *J* 4.7, 11.5 Hz, 1H), 4.02 (dd, *J* 4.5, 11.5 Hz, 1H), 7.12-7.19 (m, 2H), 7.28-7.40 (m, 5H), 7.56-7.61 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 22.3, 25.3, 28.2, 28.4, 66.3, 79.0, 126.3, 126.4, 127.2, 127.46, 127.53, 128.1, 131.4, 133.8, 136.1, 137.5, 144.5; LRMS *m/z* (rel. int.) 290 ($M^{+\bullet}$, 19), 275 (100); HRMS [ESI(+)] calcd. for $[C_{21}H_{23}O + H]^+$ 291.1743, found 291.1755.

1-Methyl-4,4'-diphenyl-2,4,5,6-tetrahydro-1*H*-benzo[*f*]isochromene (**3l**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2l** (0.109 g, 0.60 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). The crude product was purified by flash column chromatography (5% AcOEt in hexanes). Compound **3l** (0.0925 g, 0.258 mmol, 43%) was obtained as colorless viscous oil; R_f = 0.71 (hexanes-EtOAc, 1:9); IR (film) ν/cm^{-1} 3059, 3023, 2957, 2870, 2246, 1488, 1447, 761, 732, 700; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (d, *J* 6.6 Hz, 3H), 1.86-1.94 (m, 2H), 2.61-2.70 (m, 2H), 2.86-2.95 (m, 1H), 3.47 (dd, *J* 4.8, 11.4 Hz, 1H), 3.81 (dd, *J* 11.6, 4.4 Hz, 1H), 7.10-7.47 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6, 26.8, 28.2, 28.7, 66.1, 85.0, 123.1, 126.3, 126.6, 127.4, 127.5, 127.60, 127.62, 129.2, 129.4, 132.8, 134.0, 135.7, 136.1, 143.3, 144.2; LRMS *m/z* (rel. int.) 352 ($M^{+\bullet}$, 9), 310 (61), 288 (16), 275 (53), 105 (63), 77 (100); HRMS [ESI(+)] calcd. for $[C_{26}H_{24}O + H]^+$ 353.1900, found 353.1884.

(1*R*,1'*S*)-1-methyl-1,2,3',4',5,6-hexahydro-2'*H*-spiro[benzo[*f*]isochromene-4,1'-napthalene] (**3m**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2m** (0.080 mL, 0.60 mmol), CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). Compound **3m** (0.0998 g, 0.312 mmol, 52%) was obtained as colorless viscous oil; R_f = 0.63 (hexanes-EtOAc, 9:1); IR (film) ν/cm^{-1} 3061, 3017, 2928, 2868, 2244, 1487, 1450, 762, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, *J* 6.9 Hz, 3H), 1.75-1.90 (m, 2H), 2.01-2.11 (m, 3H), 2.20-2.36 (m, 1H), 2.64-2.72 (m, 2H), 2.76-2.96 (m, 3H), 3.56 (dd, *J* 2.7, 11.4 Hz, 1H), 4.00 (dd, *J* 3.3, 11.4 Hz, 1H), 7.06-7.29 (m, 6H), 7.32-7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.3, 18.7, 25.5, 28.4, 29.1, 29.7, 34.6, 64.8, 75.8, 122.5, 125.3, 126.4, 126.5, 127.5, 127.6, 128.2, 129.6, 132.9, 134.1, 136.1, 136.4, 137.4, 137.8; LRMS *m/z* (rel. int.) 316 ($M^{+\bullet}$, 75), 301 (3.89), 288 (16), 287 (30), 274 (28), 273 (100); HRMS [ESI(+)] calcd. for $[C_{23}H_{24}O + H]^+$ 317.1900, found 317.1902.

(1*R*,4*S*)-1-methyl-1,2,5,6-tetrahydrospiro[benzo[*f*]isochromene-4,4'-chroman] (**3n**): the reaction was performed following the general procedure, but using **1a** (0.113 g, 0.600 mmol), **2n** (0.089 g, 0.60 mmol) CH_2Cl_2 (5 mL) and I_2 (0.0076, 0.030 mmol). Compound **3n** (0.071 g, 0.22 mmol, 37%) was obtained as colorless viscous oil; R_f = 0.64 (hexanes-EtOAc, 9:1); IR (film) ν/cm^{-1} 3064, 3029, 2928, 2948, 1484, 1447, 766, 731; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, *J* 6.6 Hz, 3H), 1.72-2.14 (m, 3H), 2.32-2.48 (m, 1H), 2.32-2.48 (m, 1H), 2.64-2.75 (m, 2H), 2.78-2.84 (m, 1H), 3.60 (dd, *J* 1.8, 11.2 Hz, 1H), 4.06 (dd, *J* 3.0, 11.2 Hz, 1H), 4.29-4.38 (m, 1H), 4.50-4.63 (m, 1H), 6.77-6.90 (1H), 7.14-7.30 (m, 5H), 7.38 (d, *J* 7.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.9, 24.8, 28.4, 29.2, 33.2, 62.1, 64.8, 72.1, 117.3, 119.6, 122.5, 123.5, 126.5, 126.8, 127.6, 128.8, 129.5, 133.8, 134.0, 134.2, 136.0, 155.0; LRMS *m/z* (rel. int.) 316 ($M^{+\bullet}$, 75), 290 (35), 289 (80), 273 (68), 247 (39), 231 (53, 32 (100); HRMS [ESI(+)] calcd. for $[C_{22}H_{22}O_2+Na]^+$ 341.1512, found 341.1516.

(+)-(4*S*,4a*S*,7*R*,8a*S*)-2,2,4,7-tetramethyloctahydro-2*H*-chromen-4-ol (**5**): the reaction was performed following the general procedure, but using **1b** (0.154 g, 1.00 mmol), acetone (0.089 mL, 1.2 mmol), CH_2Cl_2 (5 mL) and I_2 (0.013, 0.050 mmol). Compound **5** (0.103 g, 0.486 mmol, 49%) was obtained as a white solid; mp 105-106 °C; $[\alpha]_D^{20}$ 5.8 (*c* 1.00, $CHCl_3$); R_f = 0.12 (hexanes:EtOAc, 9:1); IR (film) ν/cm^{-1} 3465, 3004, 2933, 2883, 1375, 1159; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, *J* 6.6 Hz, 3H), 1.01-1.13 (m, 5H), 1.18 (s, 6H), 1.39 (s, 3H), 1.47 (br, 1H), 1.54 (br, 1H), 1.60 (br, 1H), 1.67-1.94 (m, 3H), 3.51-3.64 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3, 22.4, 24.4, 29.6, 31.3, 32.8, 34.4, 41.8, 49.1, 49.4, 68.6, 69.9, 71.2; LRMS *m/z* (rel. int.) 198 (2.8), 197 (25.5), 194 (7.2), 179 (7.2), 139 (21.1), 121 (16.1), 95 (18.7), 93 (17.1), 81 (61.0), 71 (35), 67 (47.7), 59 (69.2), 55 (100); HRMS [ESI(+)] calcd. for $[C_{13}H_{24}O_2 + H]^+$ 213.1849, found 213.1854.

Supplementary Information

NMR copies are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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Supplementary Information

Iodine-Catalyzed Prins Cyclization of Aliphatic and Aromatic Ketones

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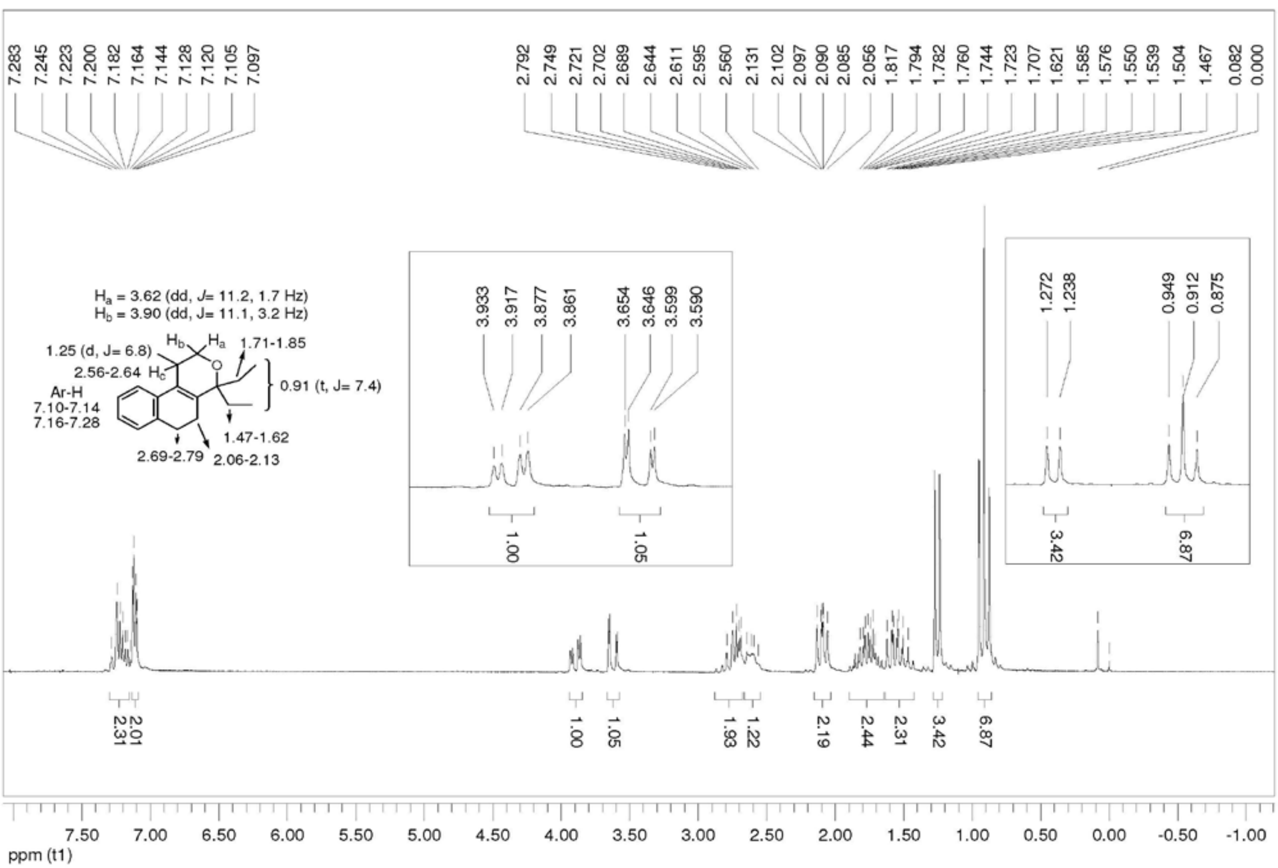

Figure S1. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3b**.

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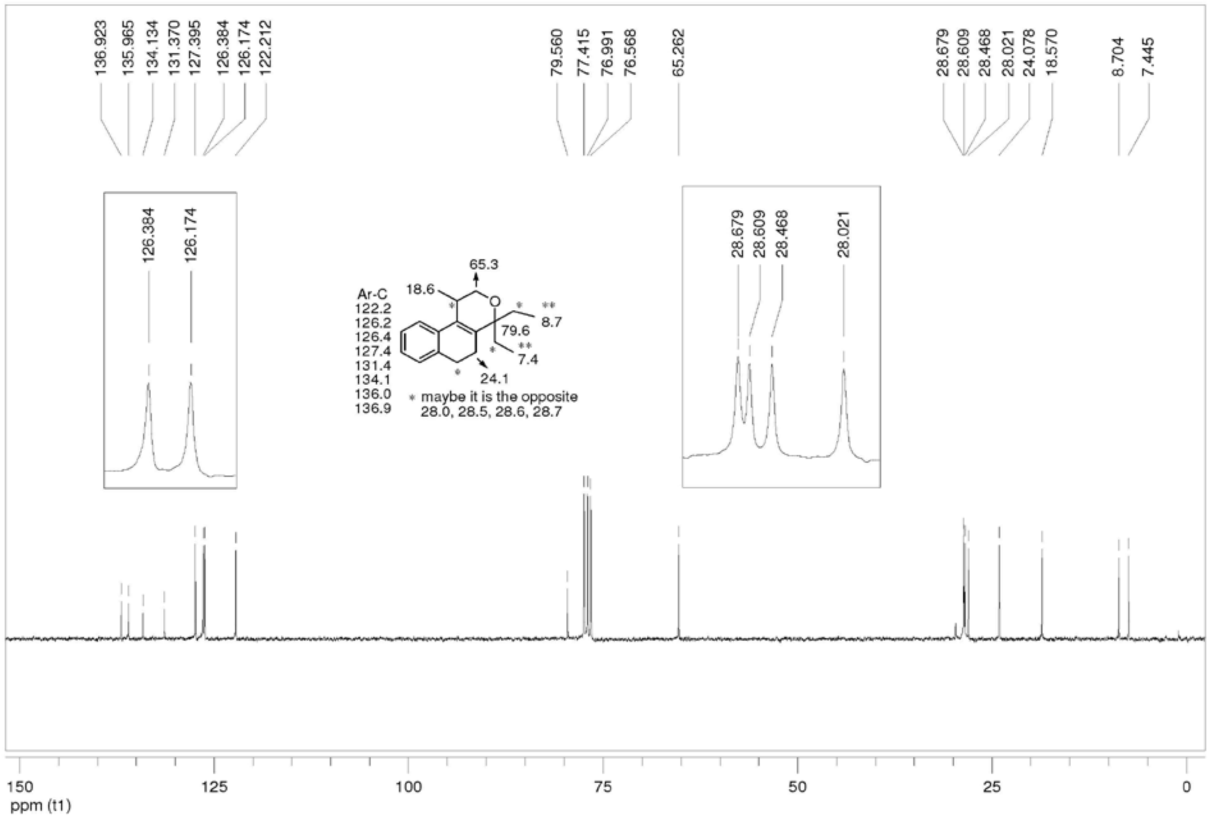

Figure S2. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3b**.

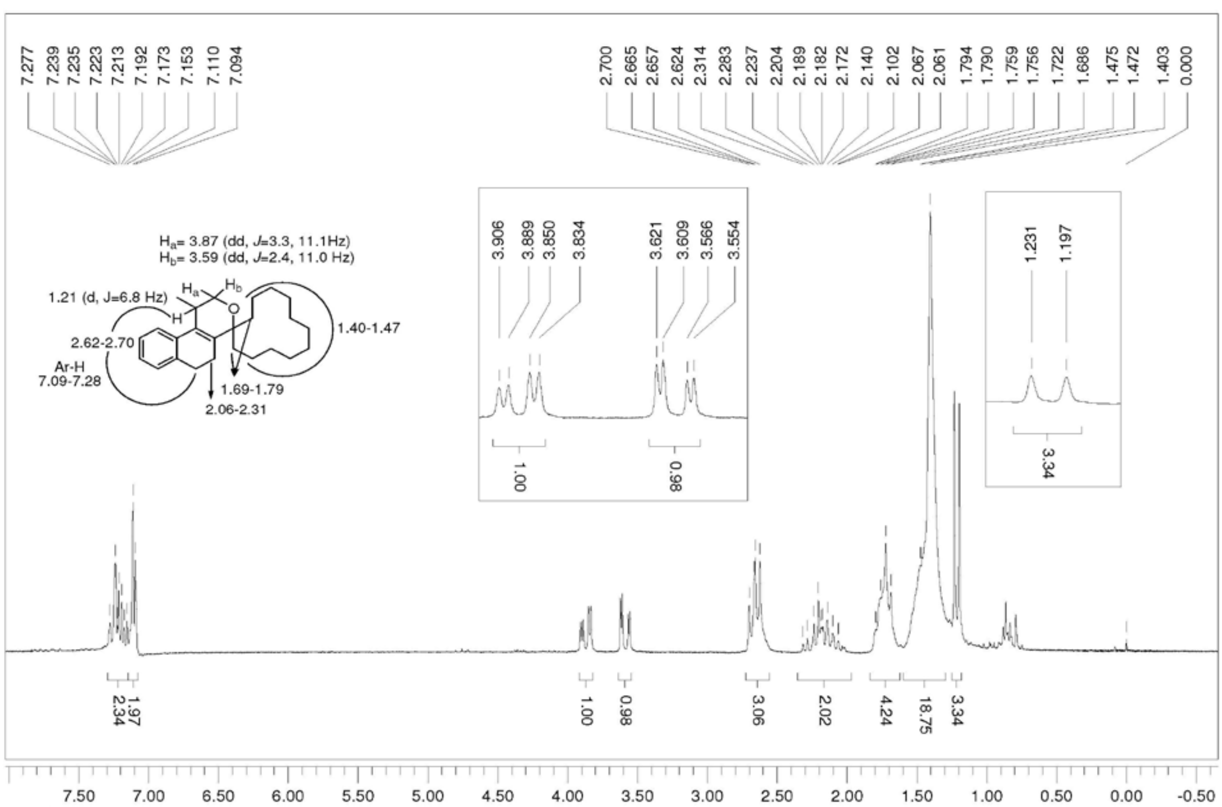

Figure S3. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3f**.

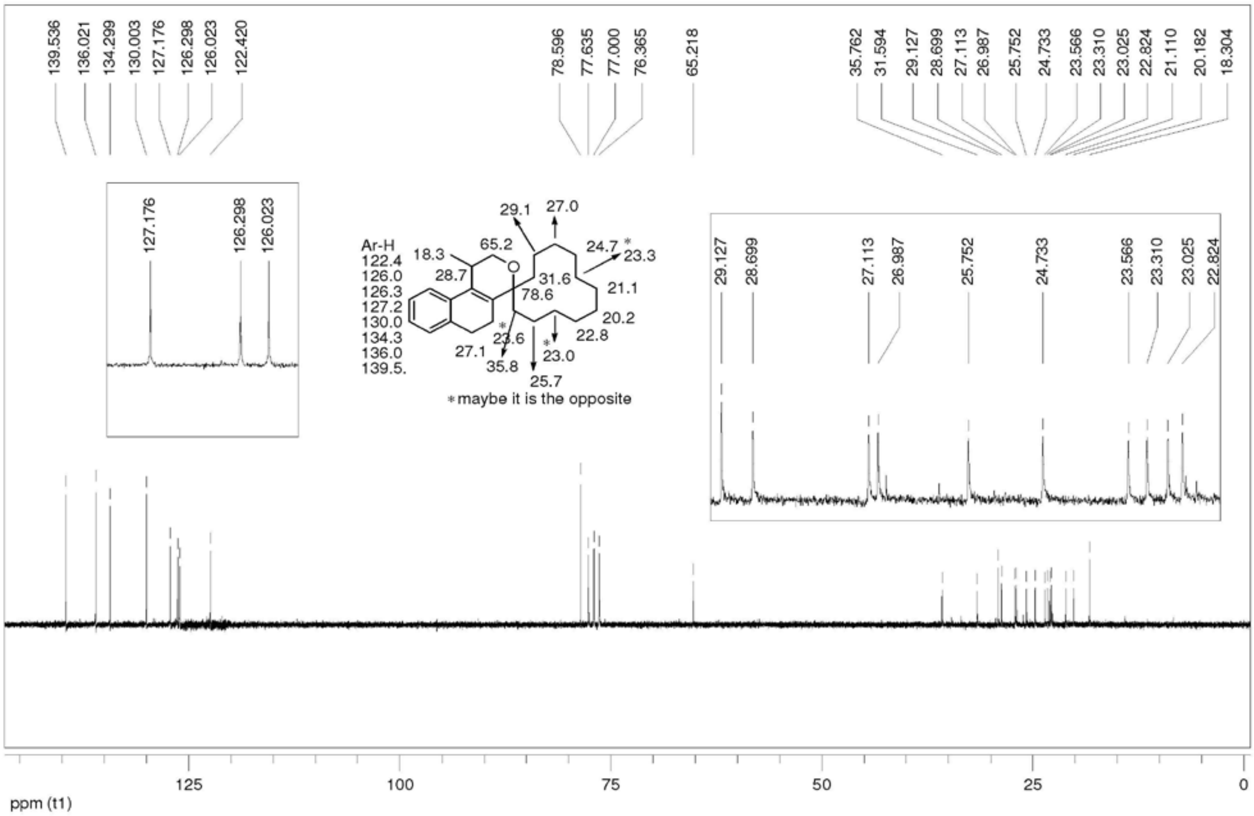

Figure S4. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **3f**.

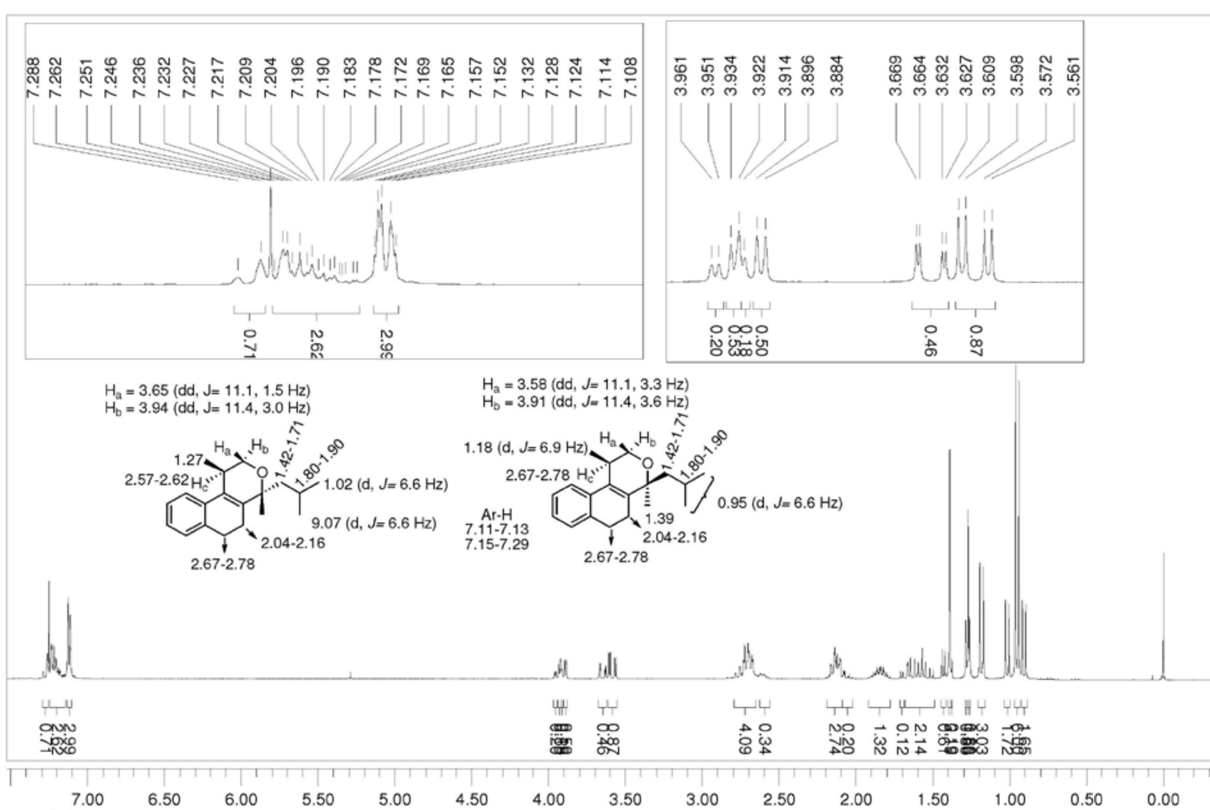

Figure S5. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **3g**.

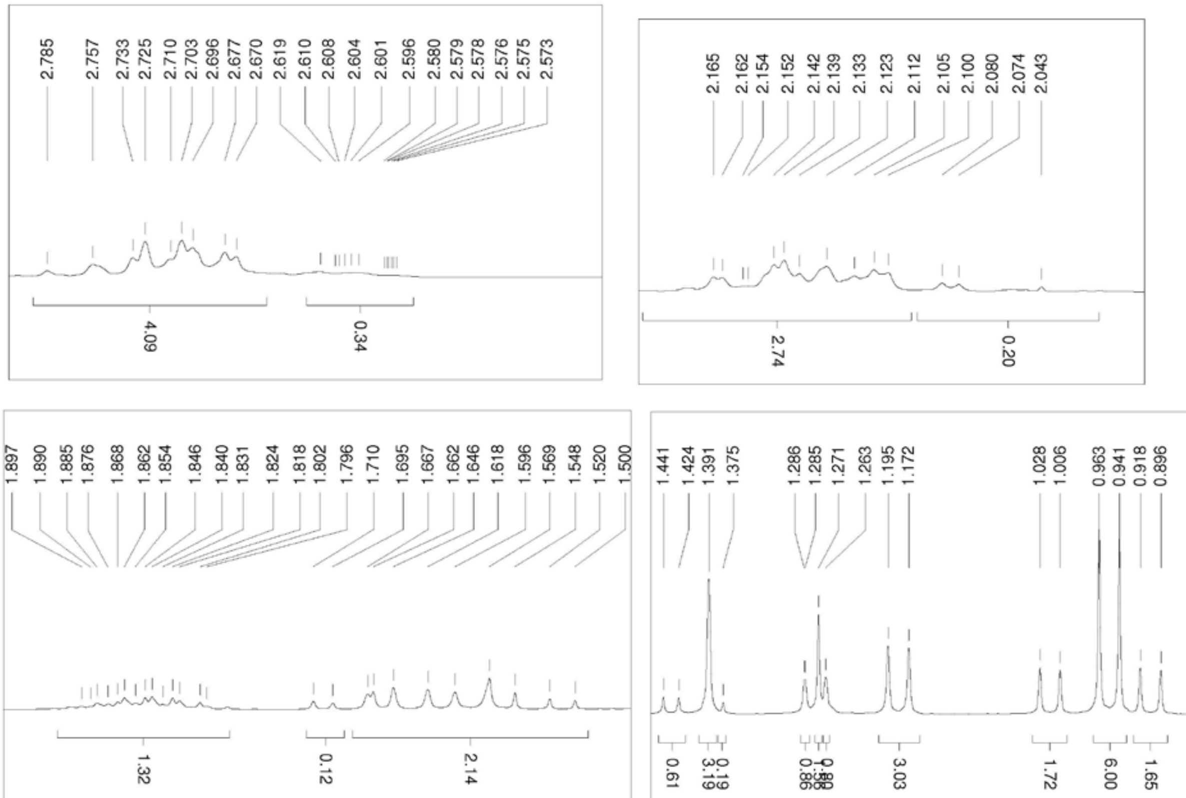

Figure S6. ^{1}H NMR (300 MHz, $CDCl_3$) selected expansions of **3g**.

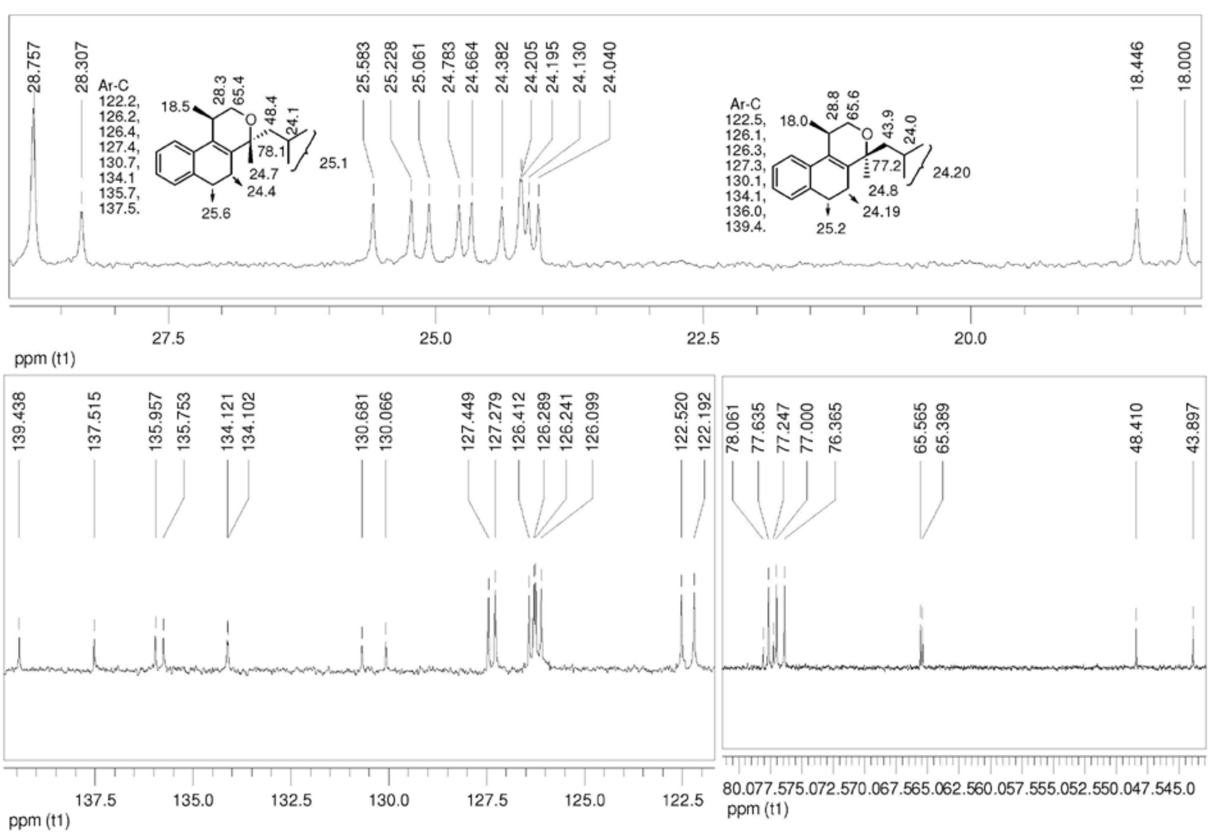

Figure S7. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3g**.

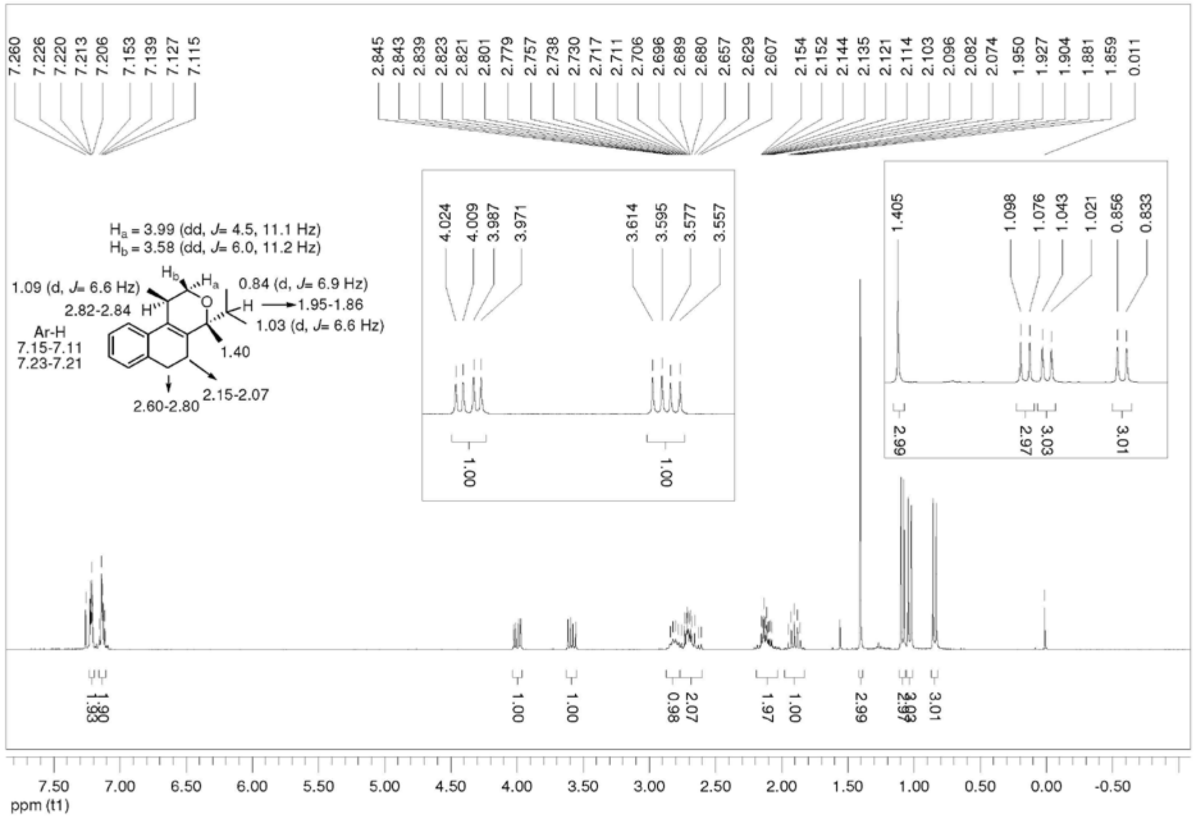

Figure S8. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ***cis*-3h**.

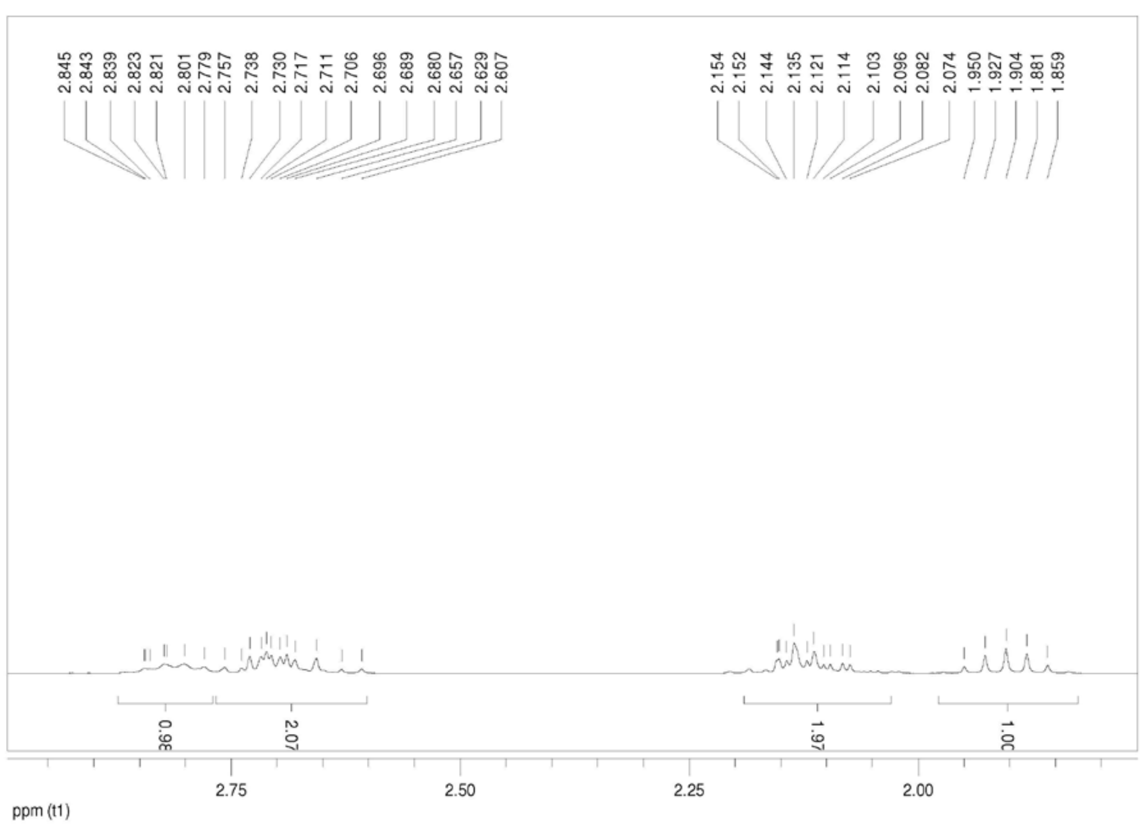

Figure S9. ^{1}H NMR (200 MHz, $CDCl_3$) selected expansions of ***cis*-3h**.

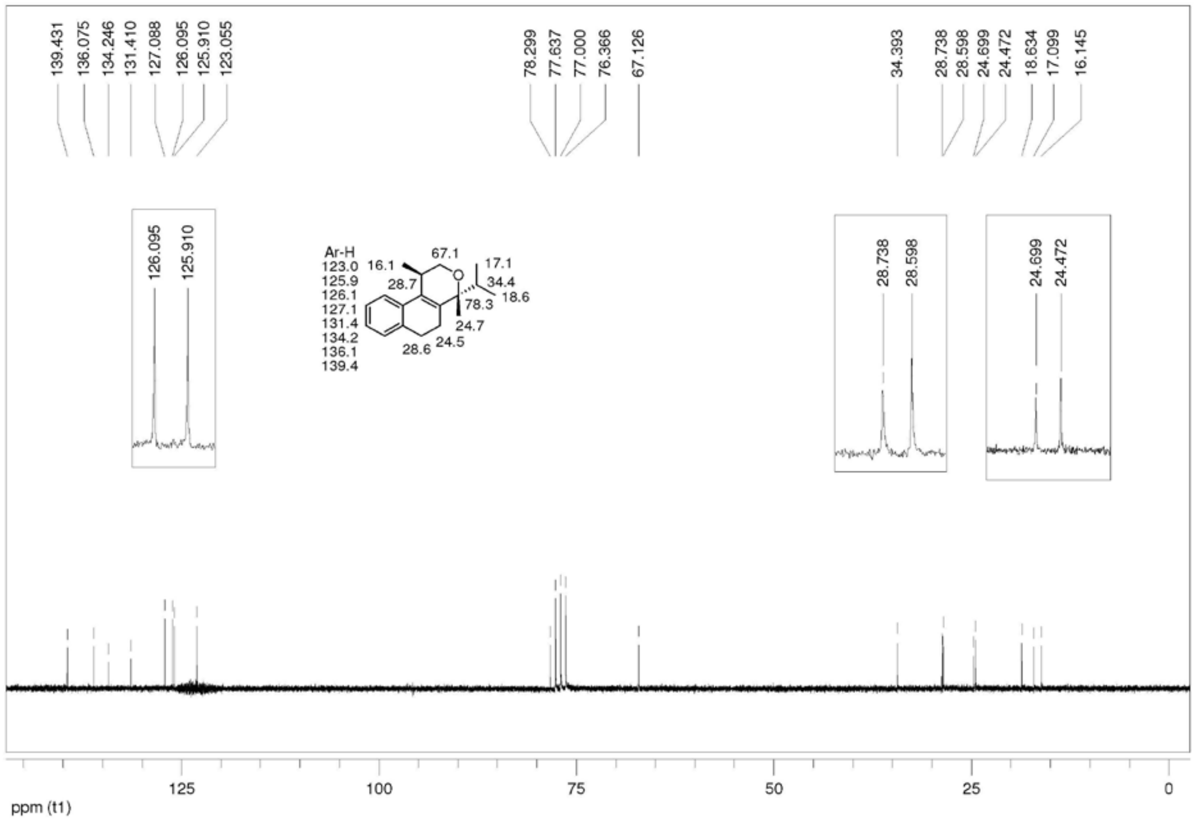

Figure S10. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of ***cis*-3h**.

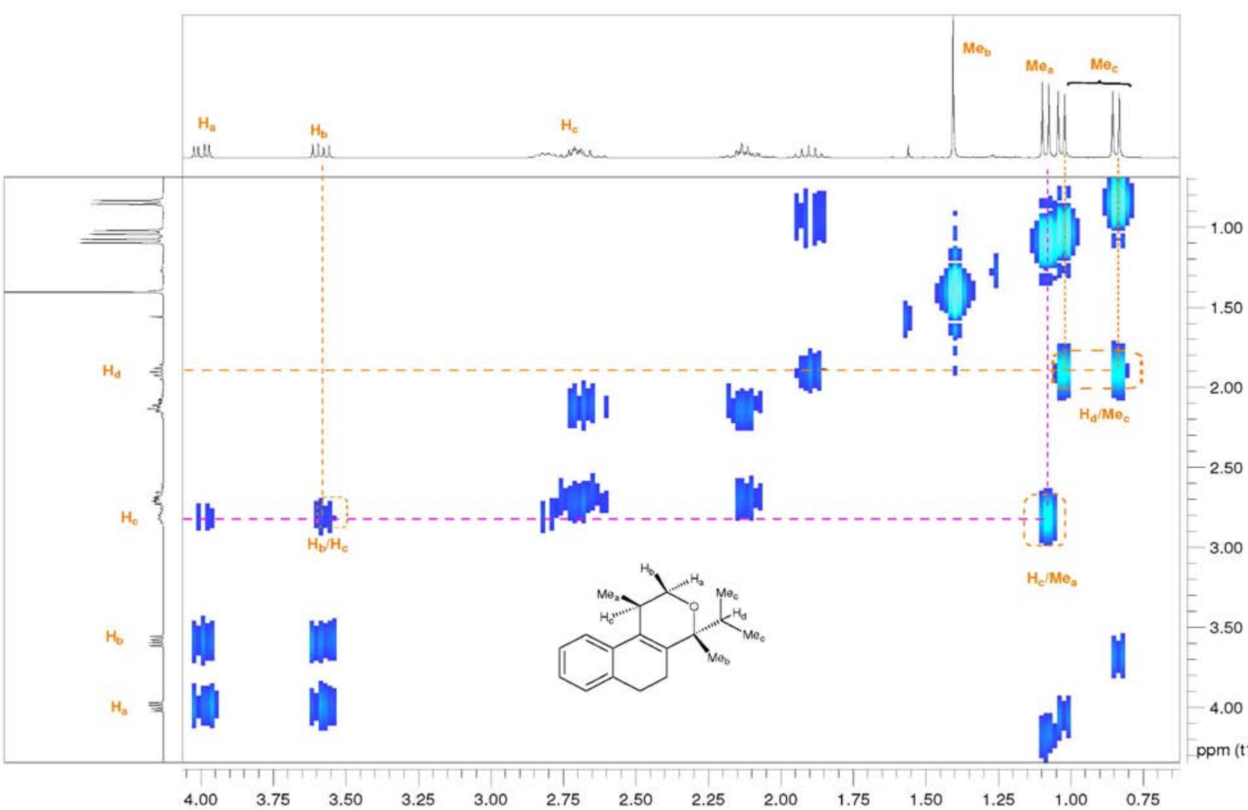

Figure S11. Selected COSY (300 MHz, $CDCl_3$) correlated spectrum of ***cis*-3h**.

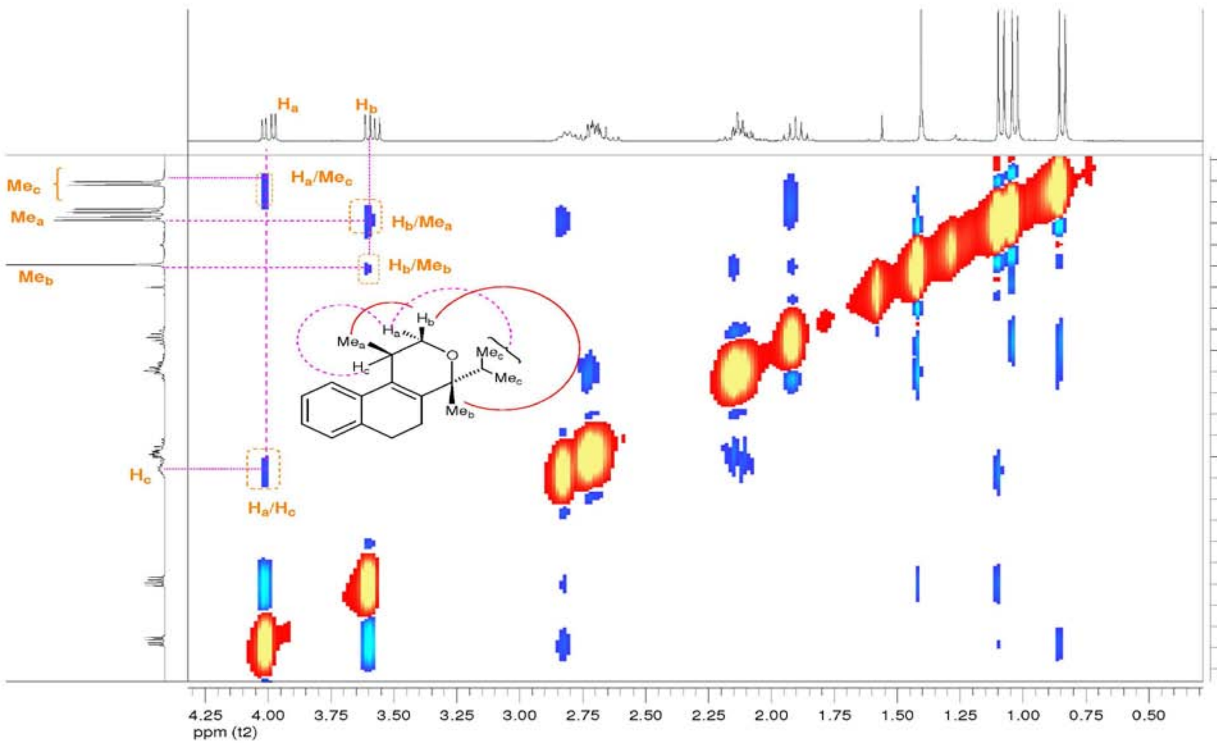

Figure S12. Selected NOESY (300 MHz, $CDCl_3$) correlated spectrum of ***cis*-3h**.

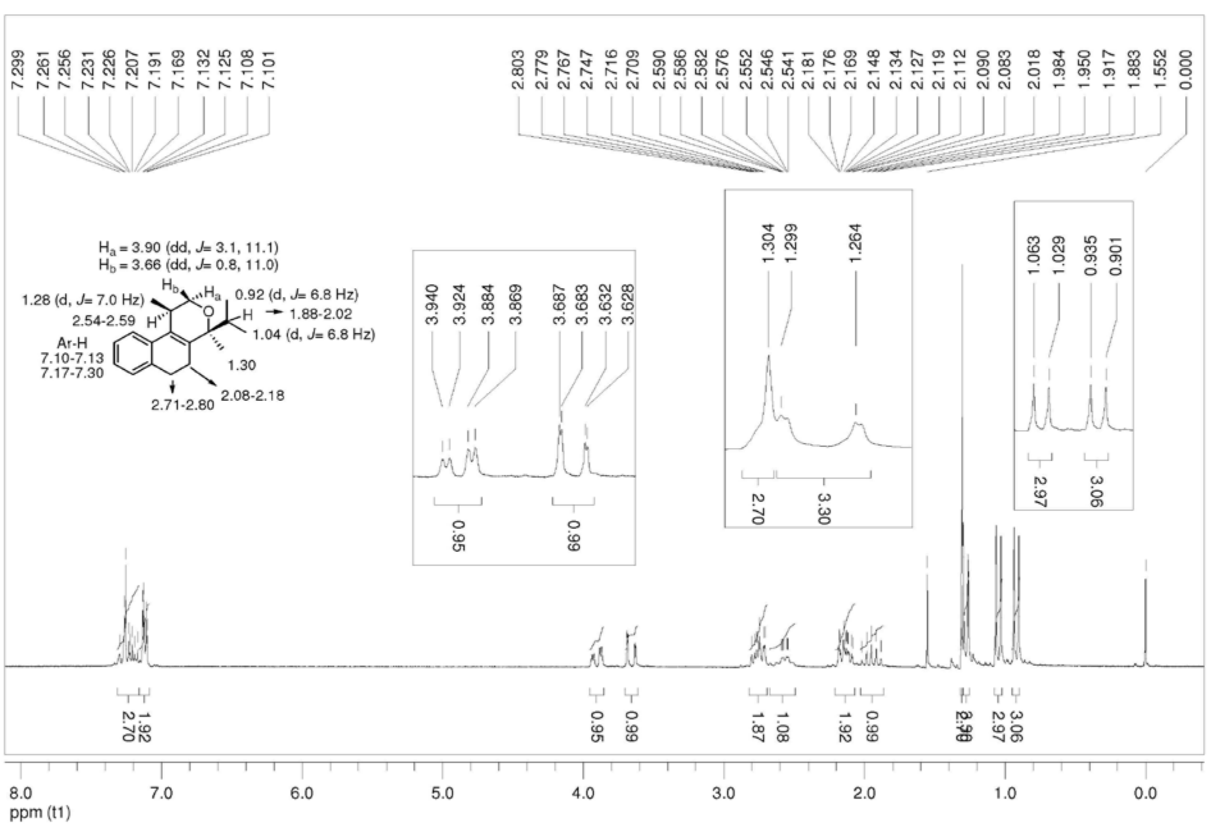

Figure S13. [1]H NMR (200 MHz, $CDCl_3$) spectrum of ***trans*-3h**.

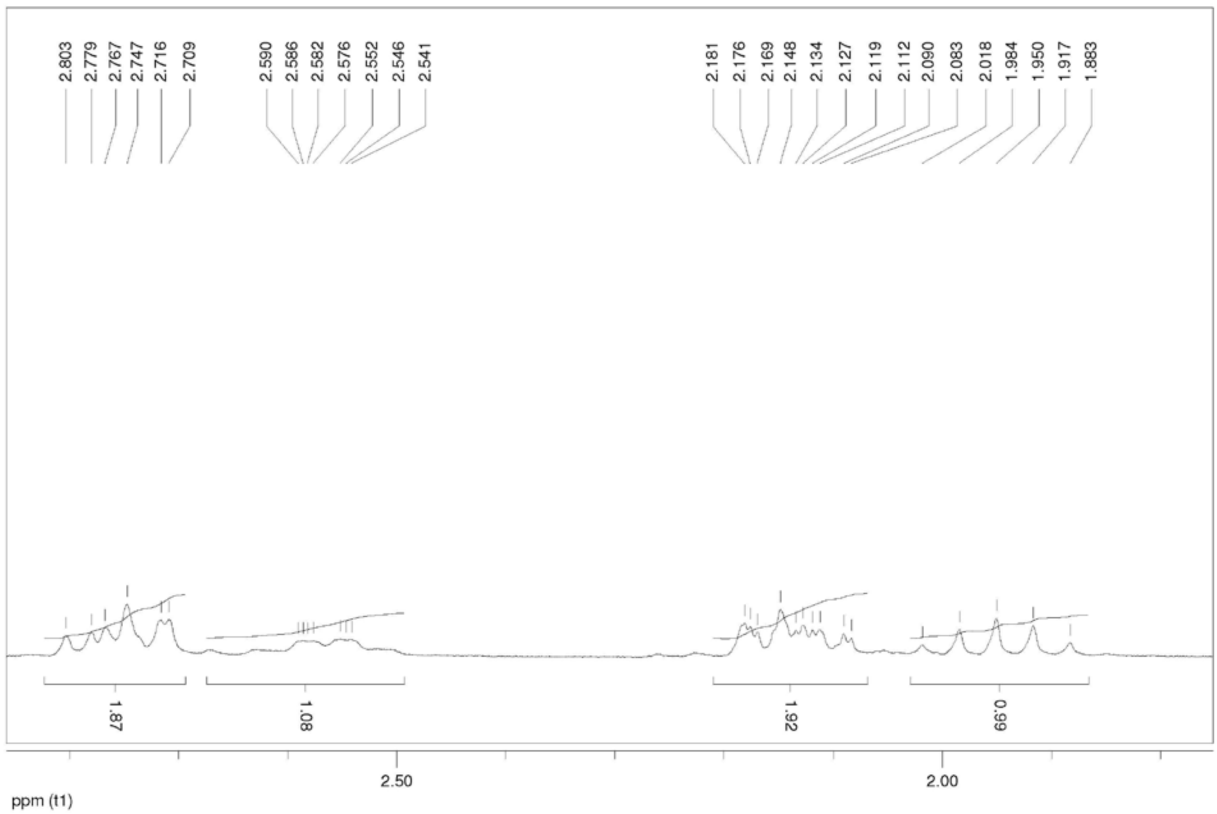

Figure S14. [1]H NMR (200 MHz, $CDCl_3$) selected expansions of ***trans*-3h**.

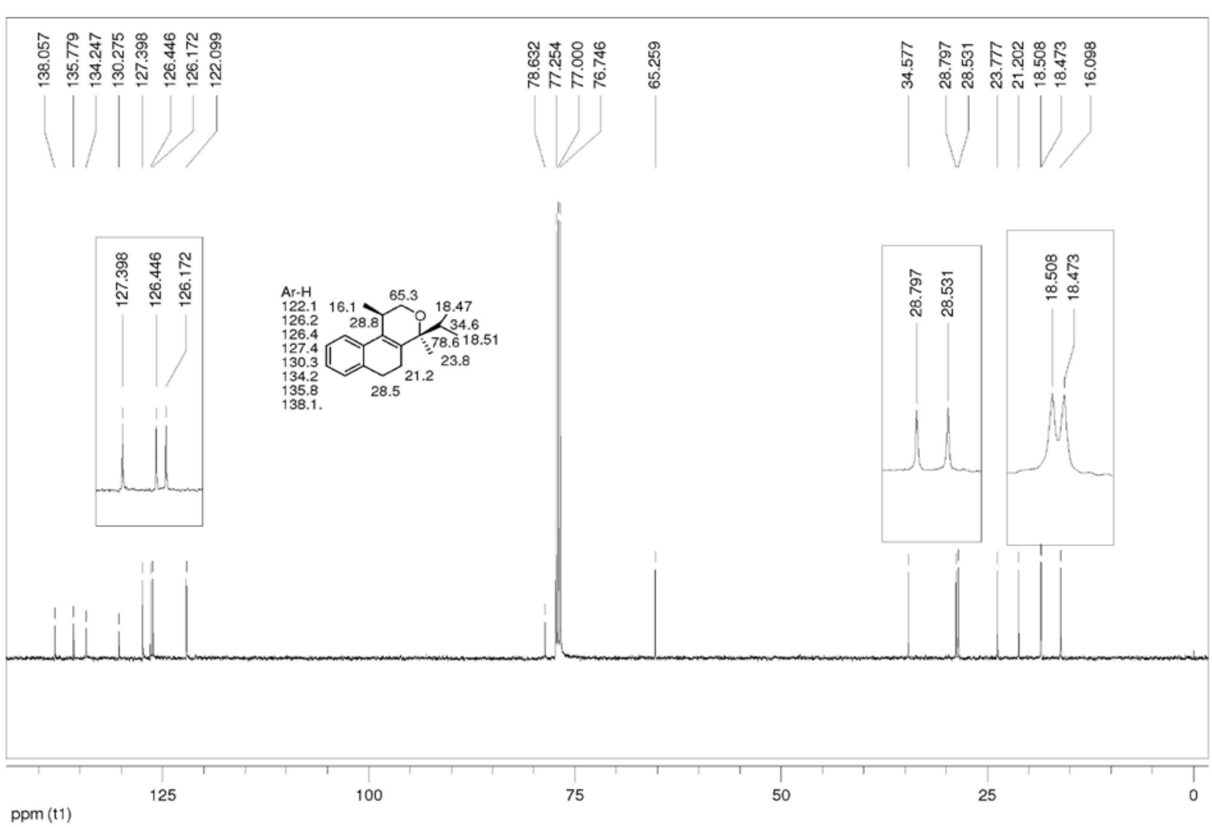

Figure S15. [13]C NMR (75 MHz, $CDCl_3$) spectrum of ***trans*-3h**.

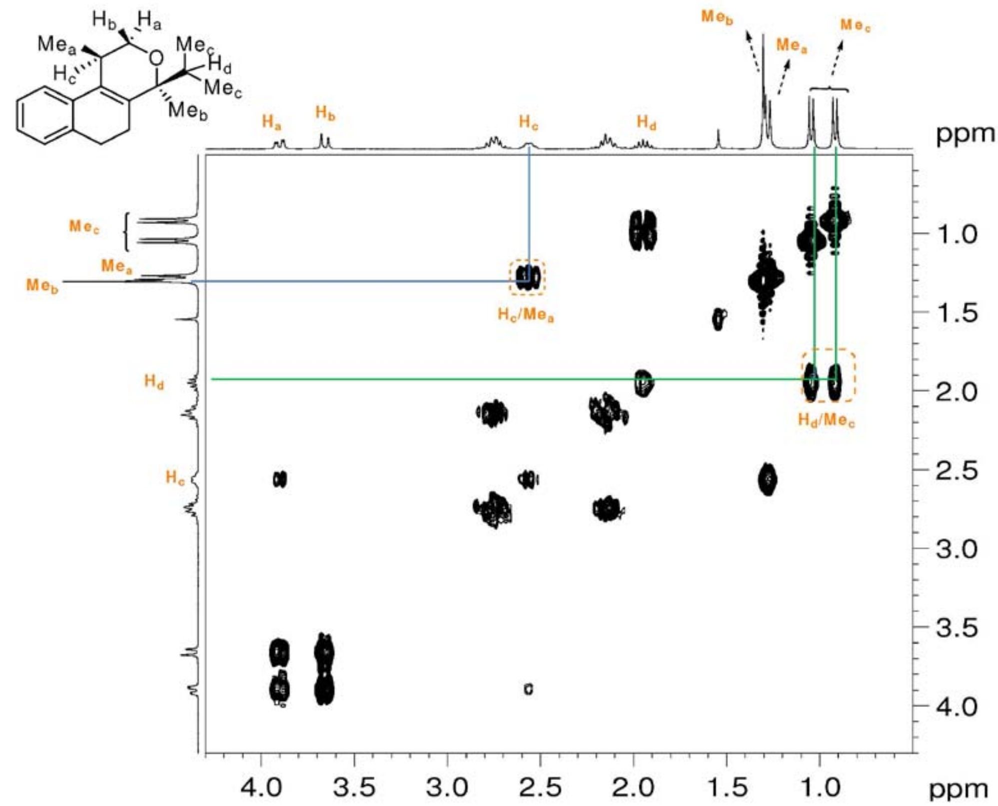

Figure S16. Selected COSY (300 MHz, $CDCl_3$) correlated spectrum of ***trans*-3h**.

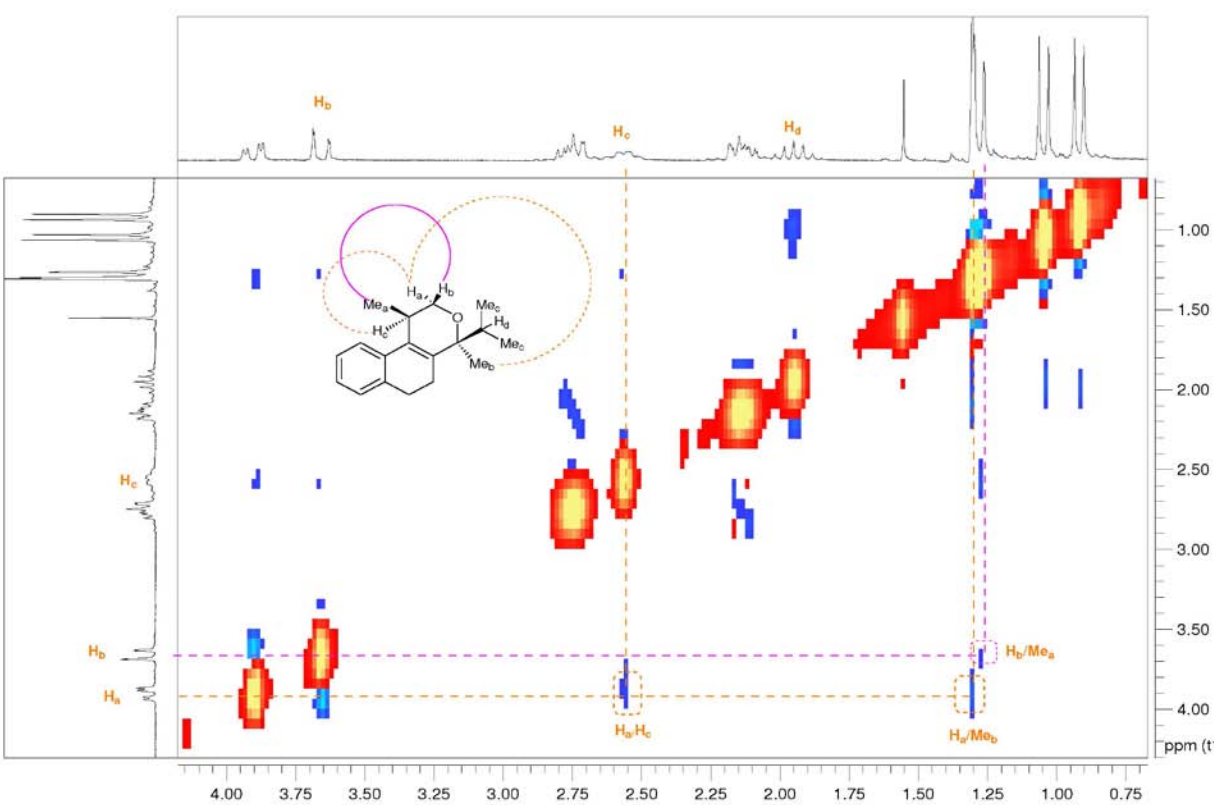

Figure S17. Selected NOESY (300 MHz, $CDCl_3$) correlated spectrum of ***trans*-3h**.

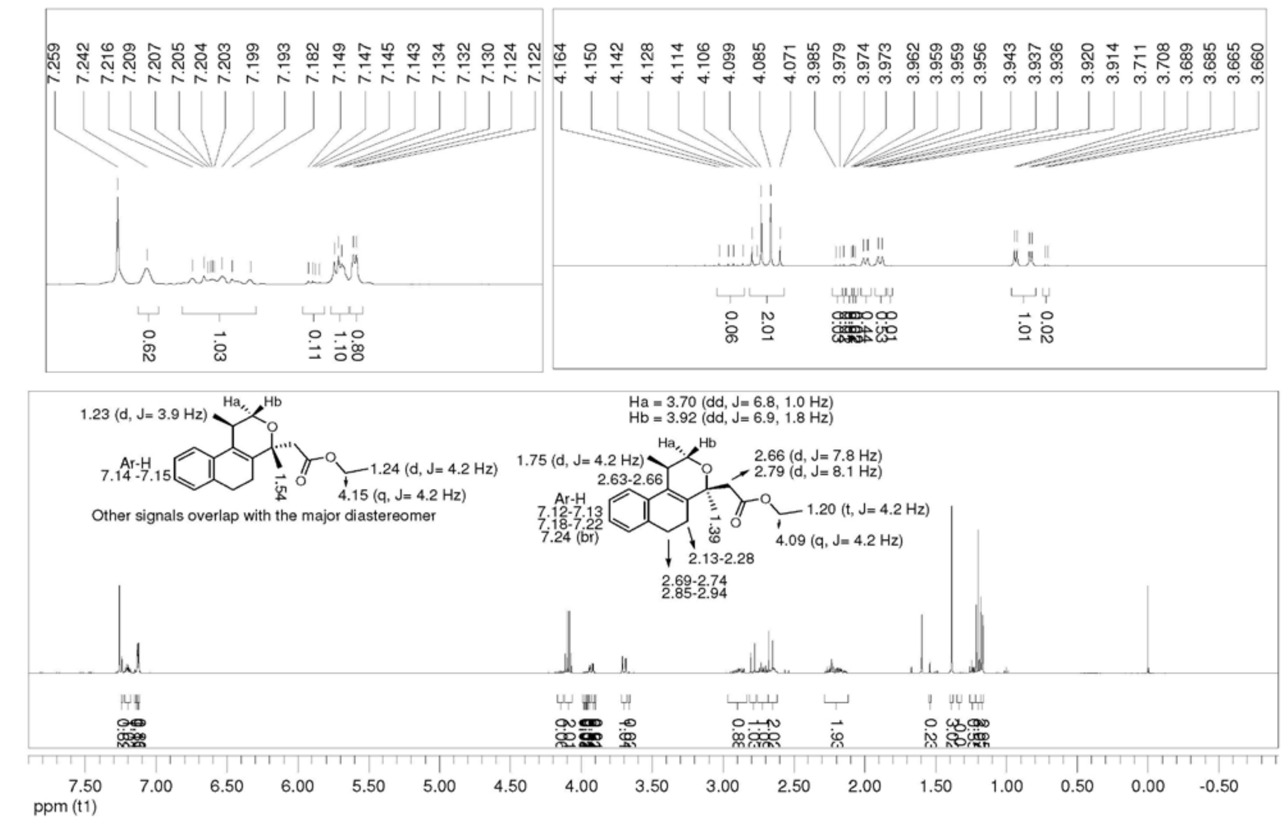

Figure S18. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **3i**.

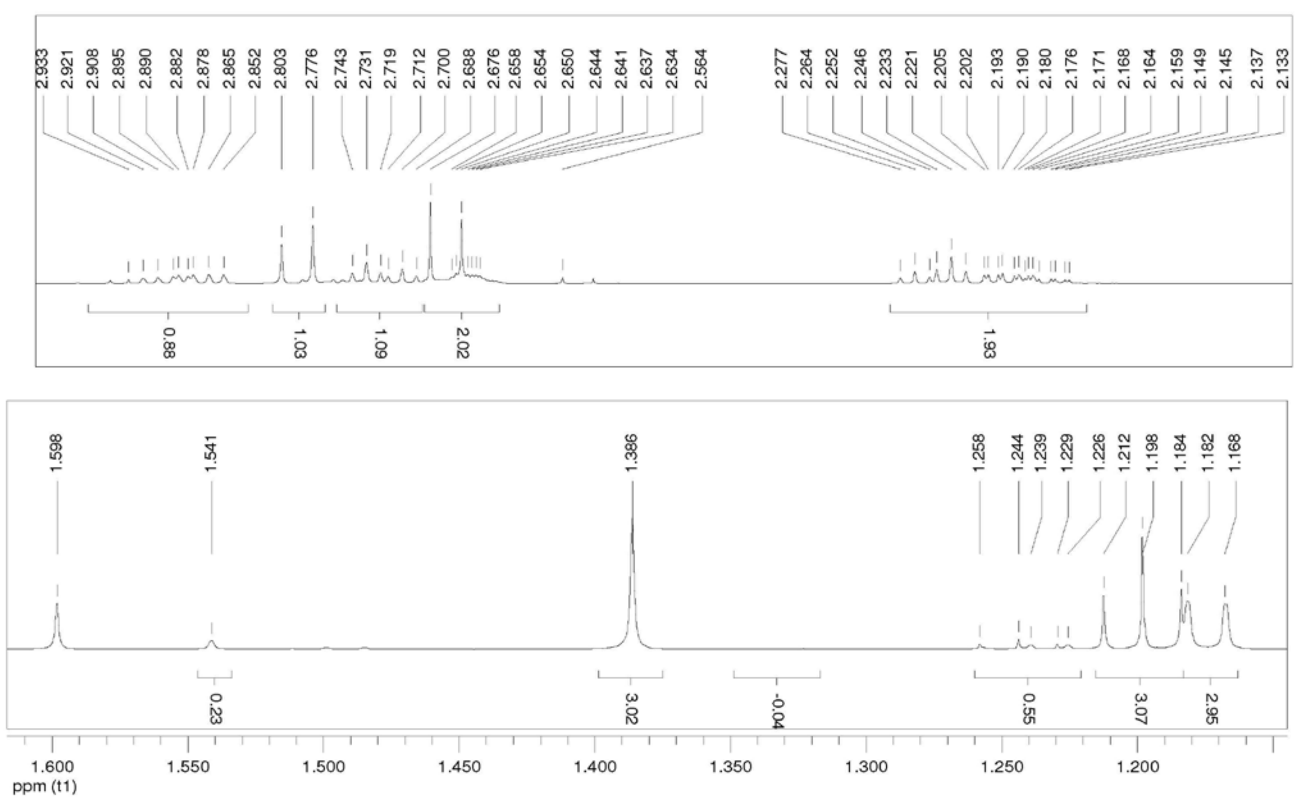

Figure S19. ^{1}H NMR (300 MHz, $CDCl_3$) selected expansions of **3i**.

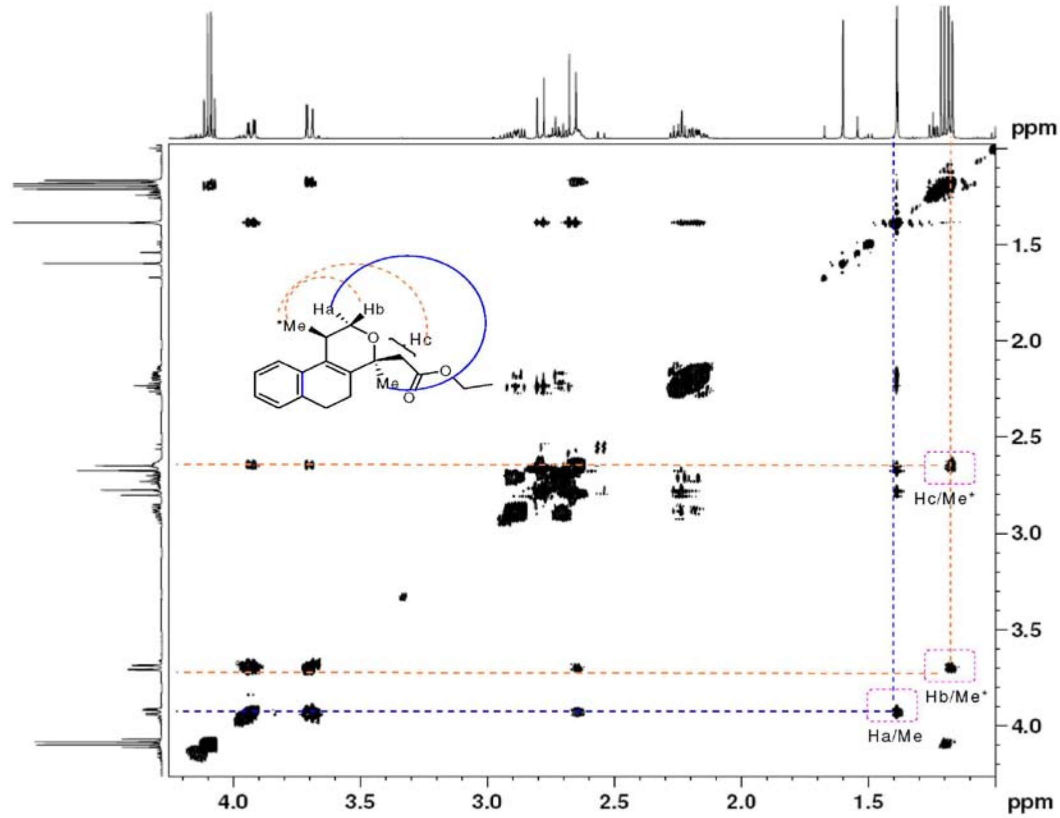

Figure S20. Selected NOESY (300 MHz, $CDCl_3$) correlated spectrum of **3i**.

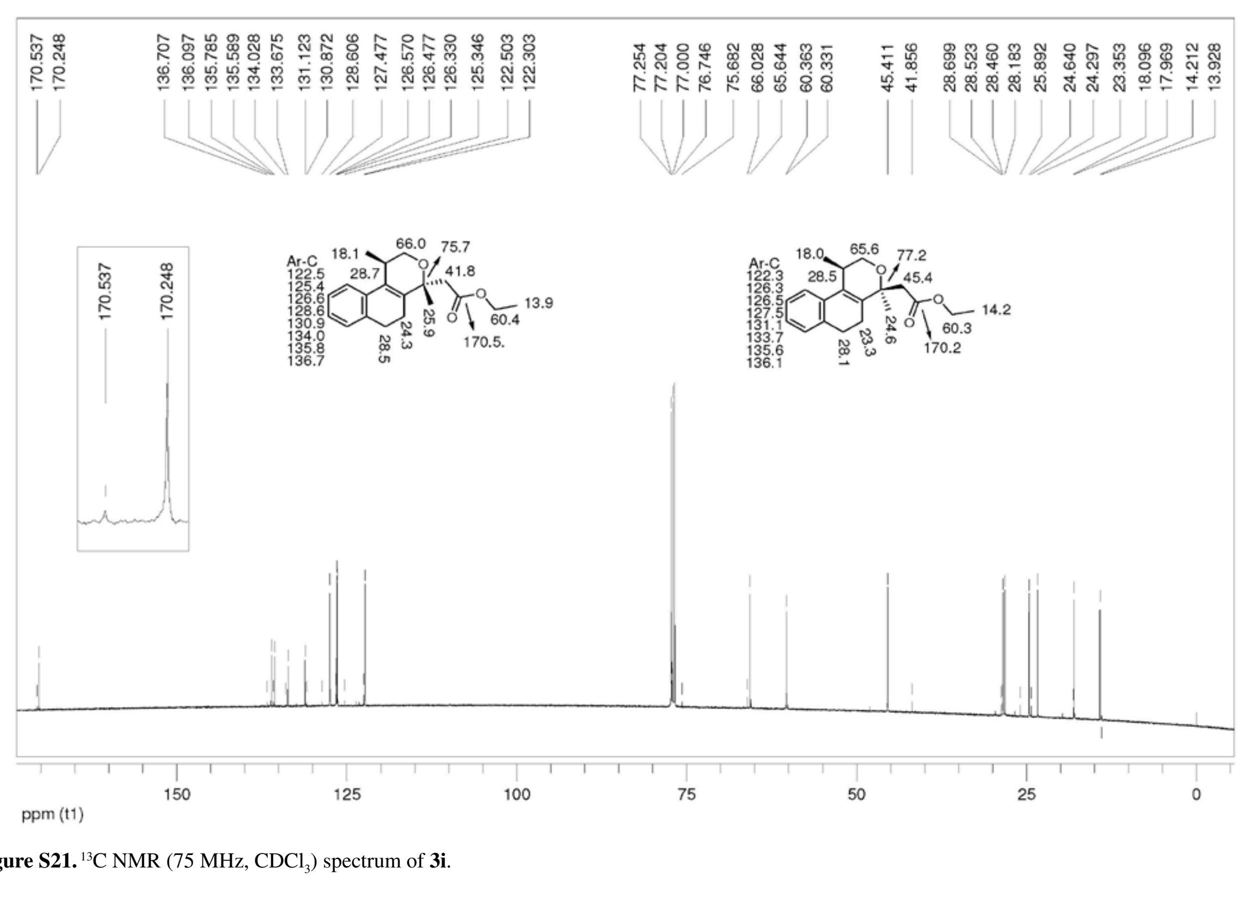

Figure S21. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3i**.

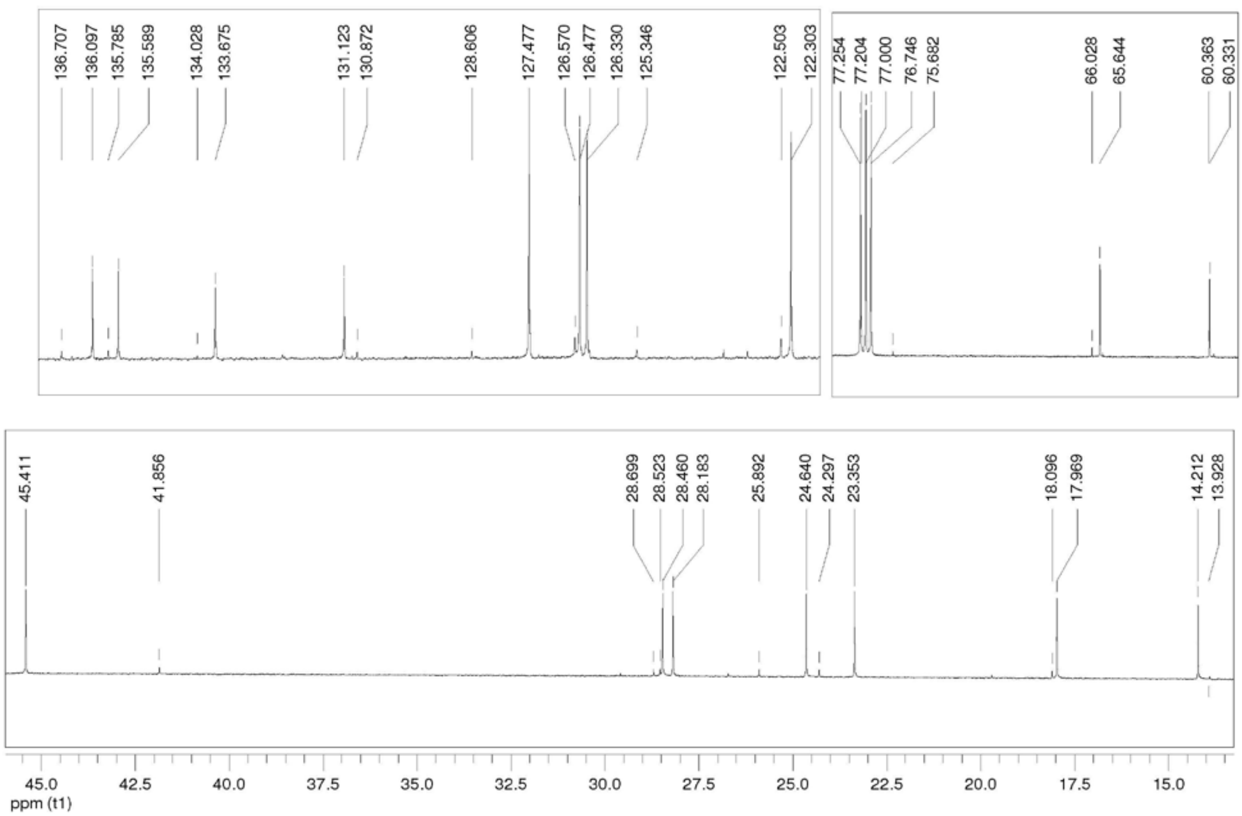

Figure S22. ^{13}C NMR (75 MHz, $CDCl_3$) selected expansions of **3i**.

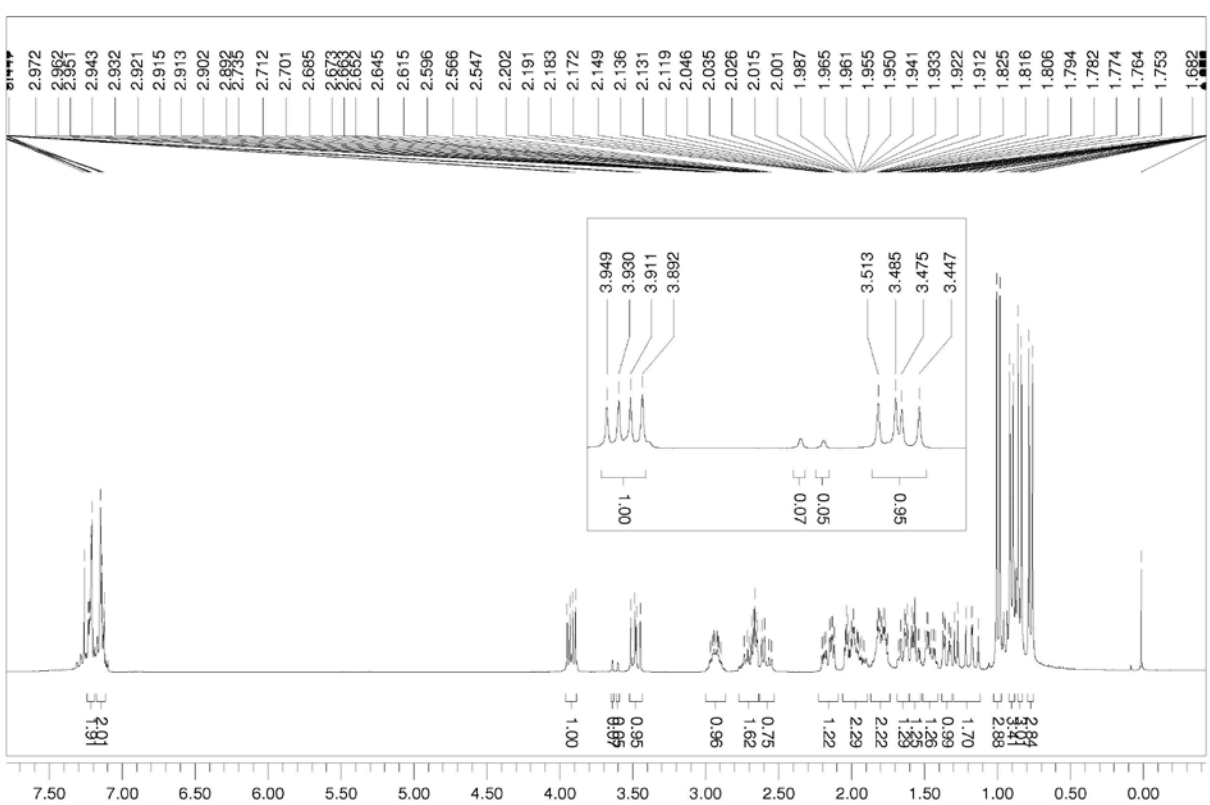

Figure S23. ^1H NMR (200 MHz, $CDCl_3$) spectrum of **3j**.

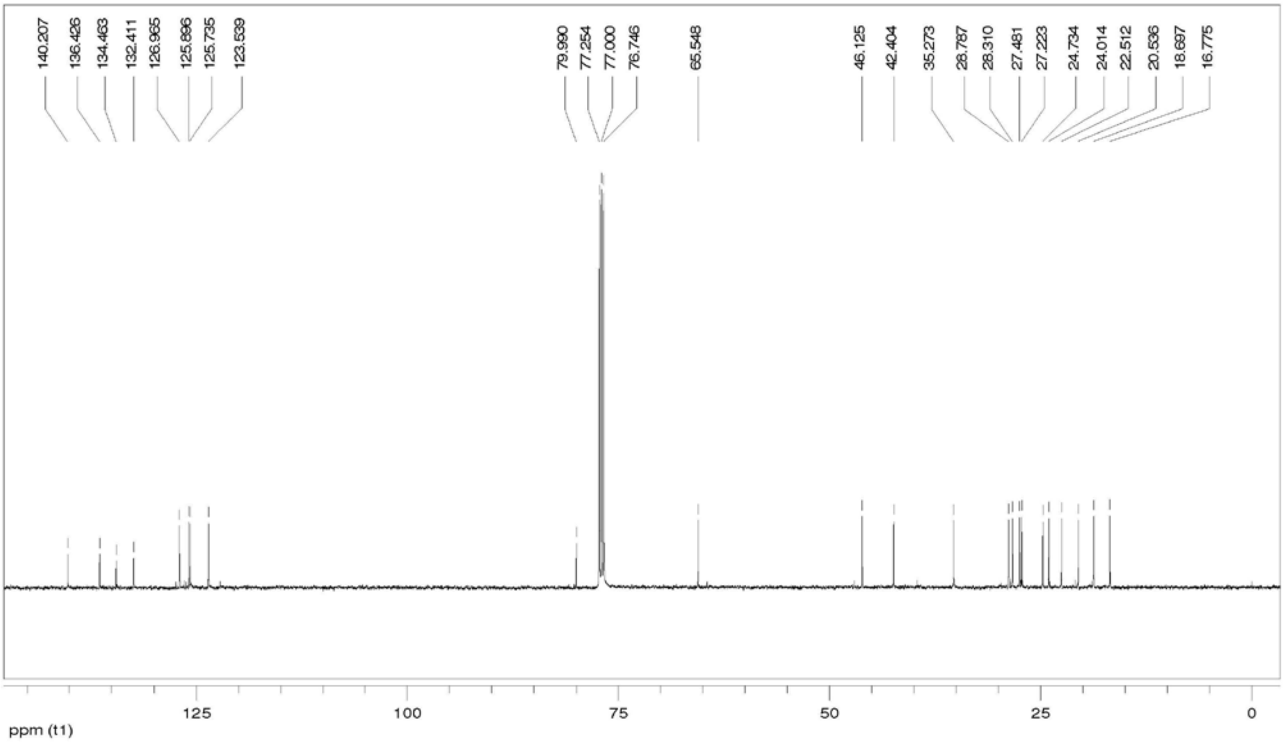

Figure S24. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3j**.

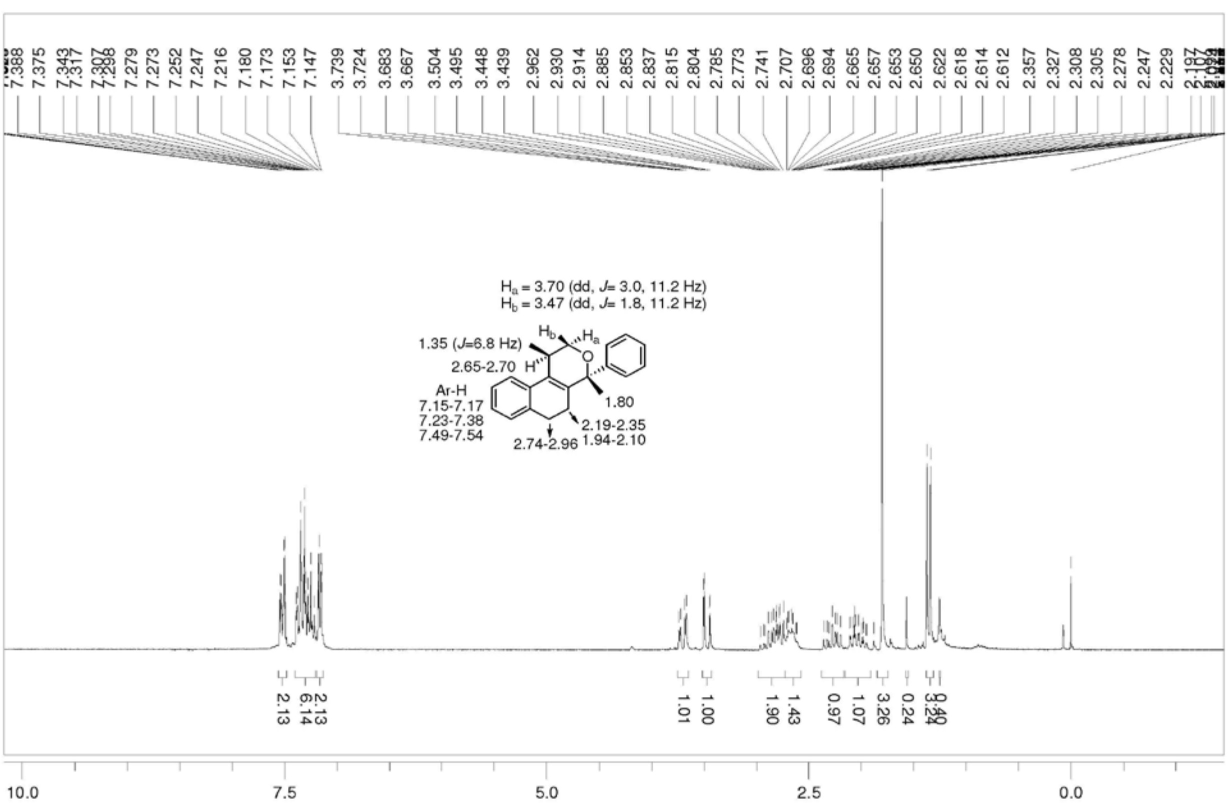

Figure S25. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of ***cis*-3k**.

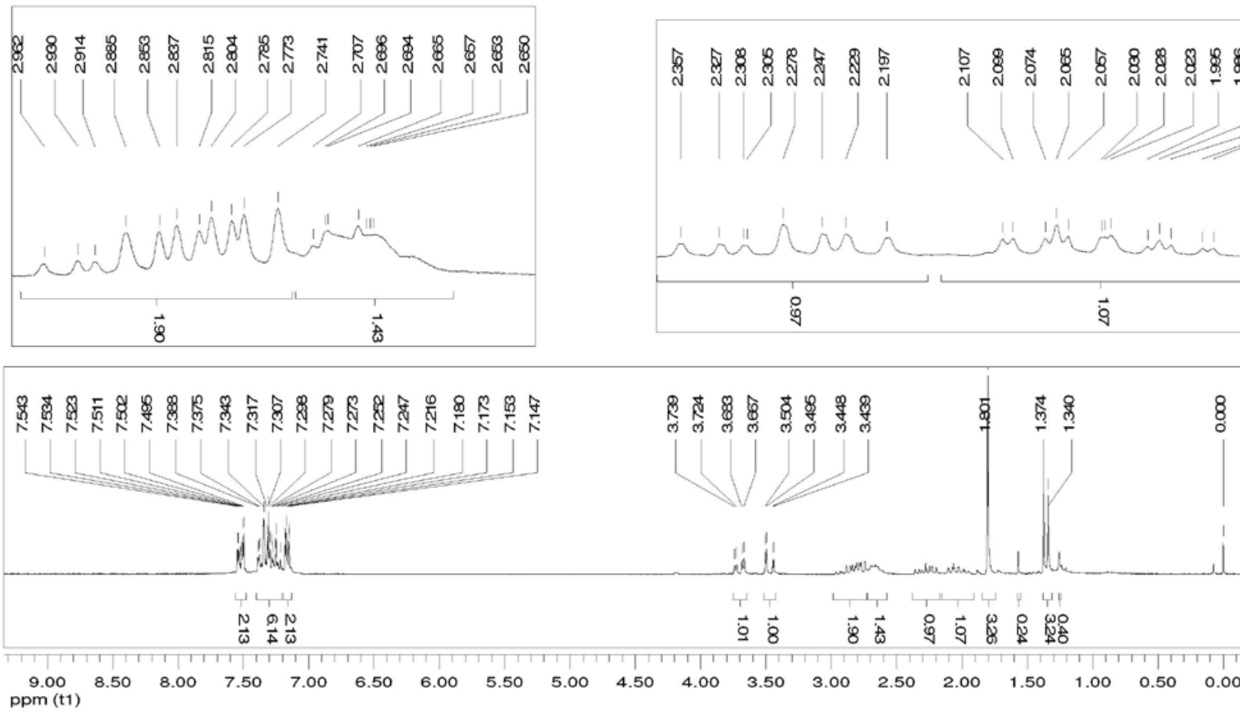

Figure S26. ^{1}H NMR (200 MHz, $CDCl_3$) selected expansion of ***cis*-3k**.

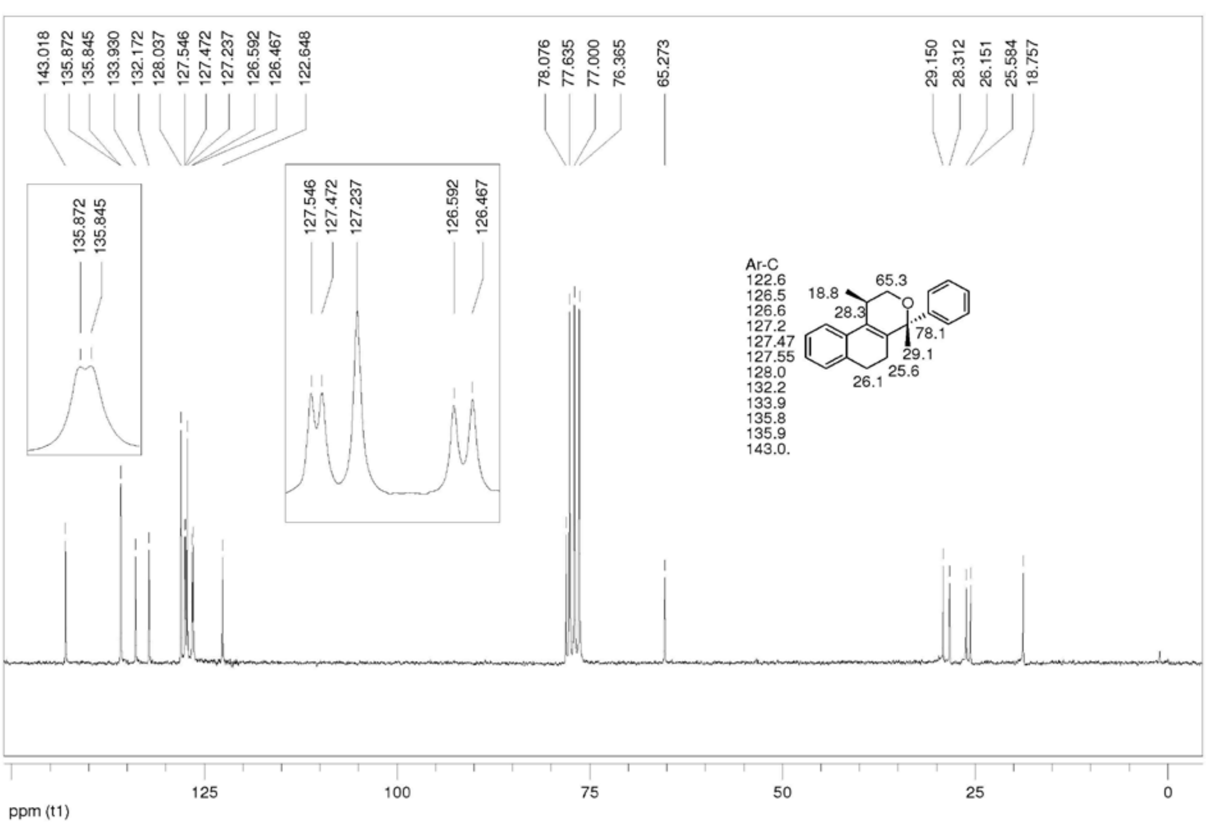

Figure S27. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ***cis*-3k**.

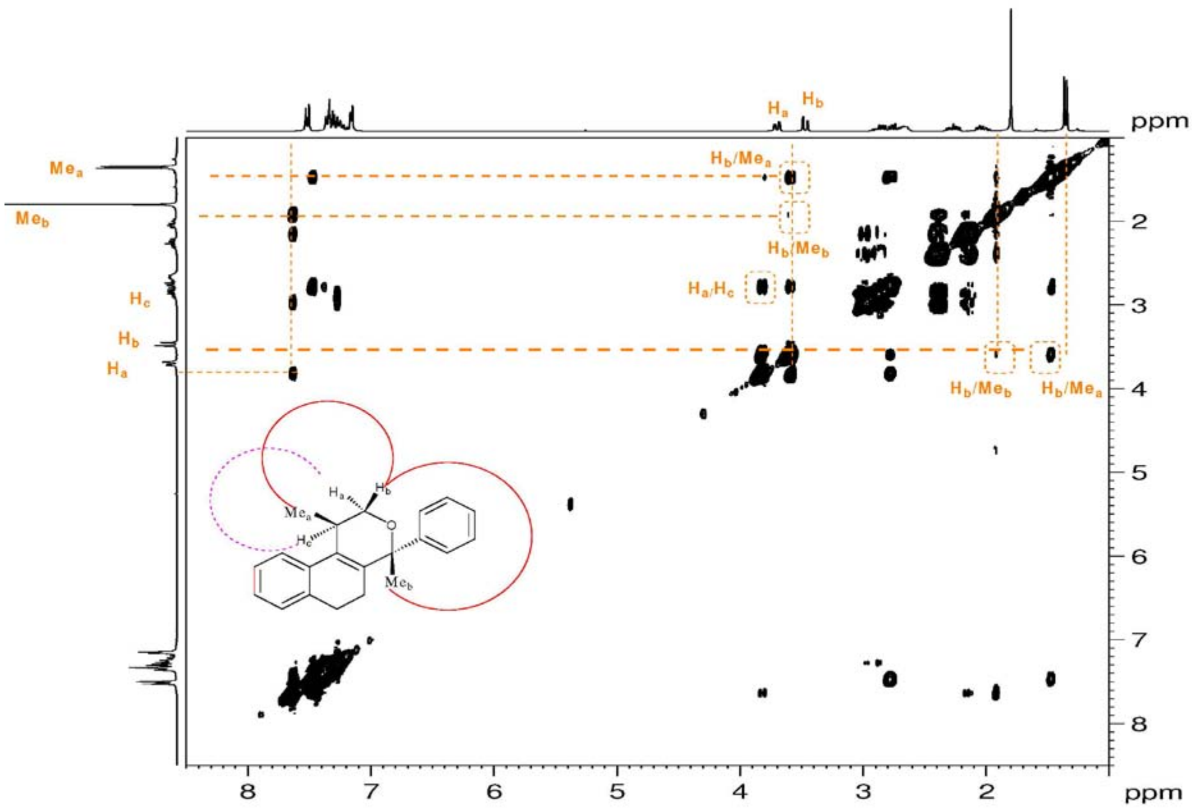

Figure S28. Selected NOESY (300 MHz, $CDCl_3$) correlated spectrum of ***cis*-3k**.

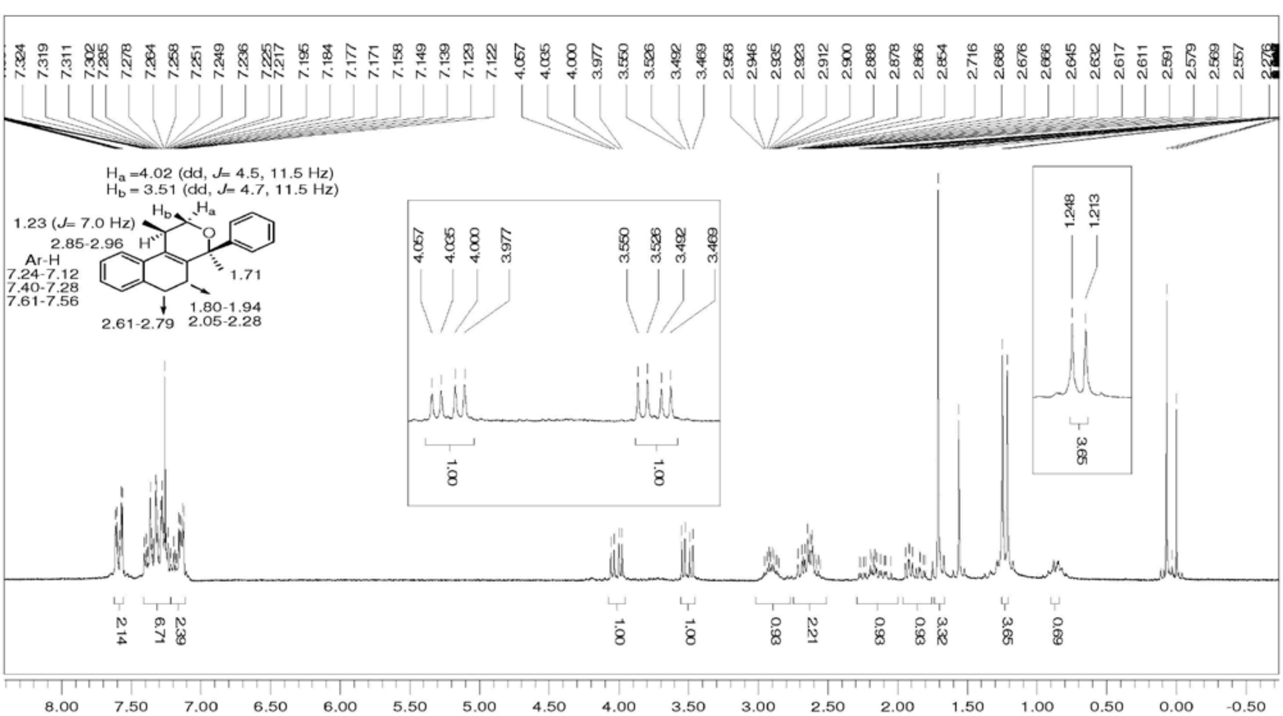

Figure S29. [1]H NMR (200 MHz, $CDCl_3$) spectrum of ***trans*-3k**.

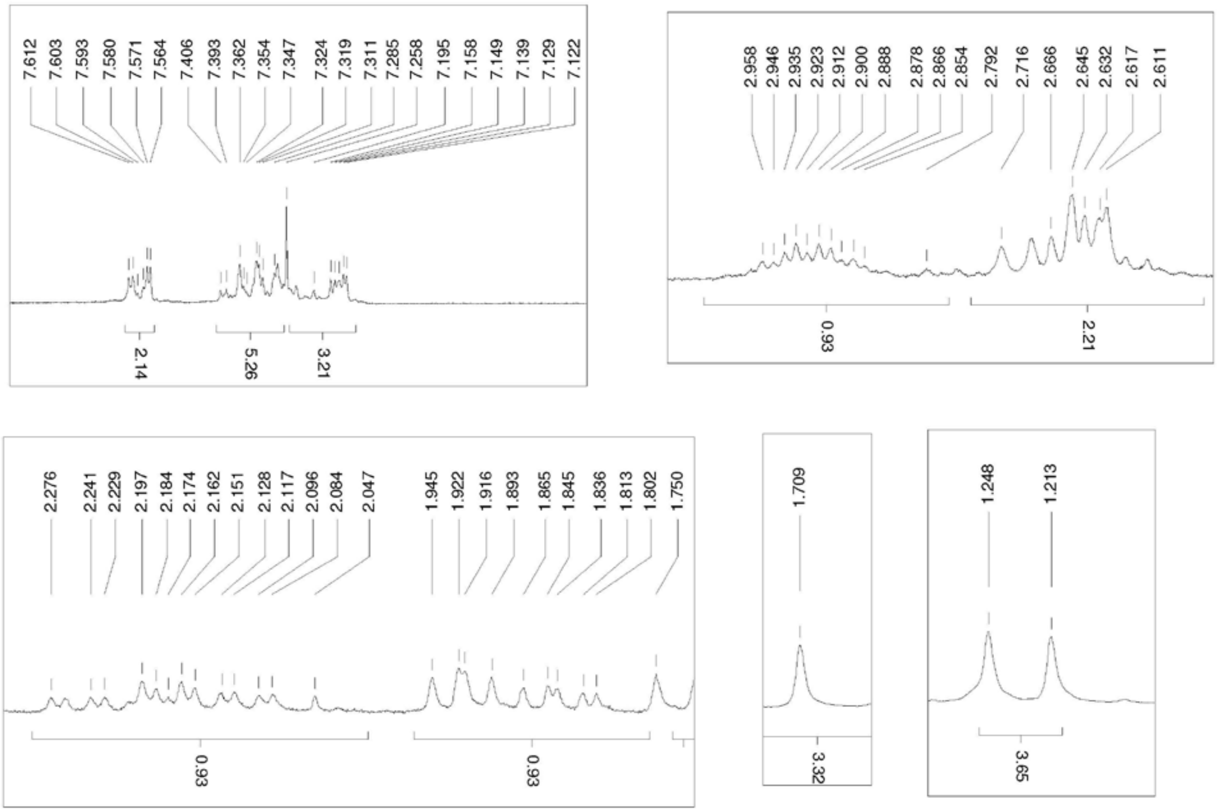

Figure S30. [1]H NMR (200 MHz, $CDCl_3$) selected expansion of ***trans*-3k**.

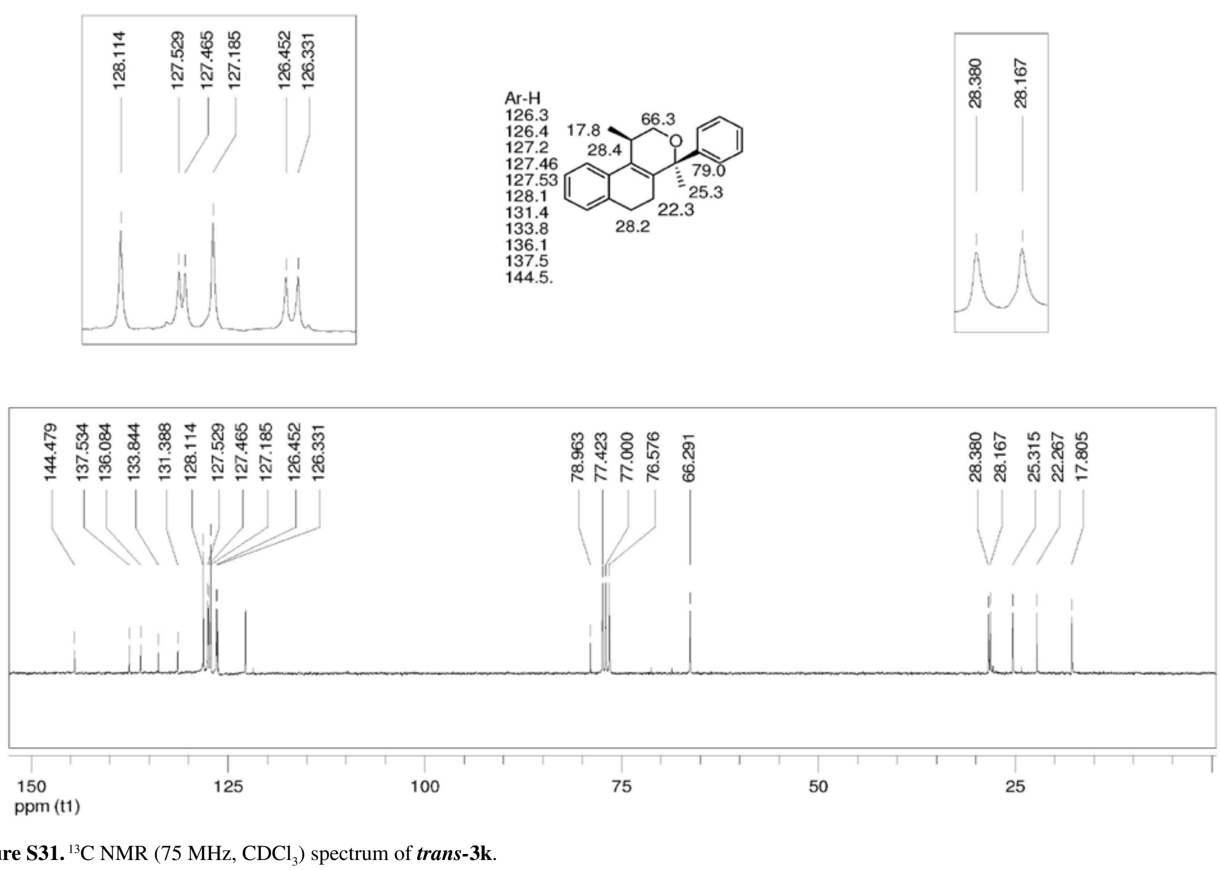

Figure S31. [13]C NMR (75 MHz, $CDCl_3$) spectrum of ***trans*-3k**.

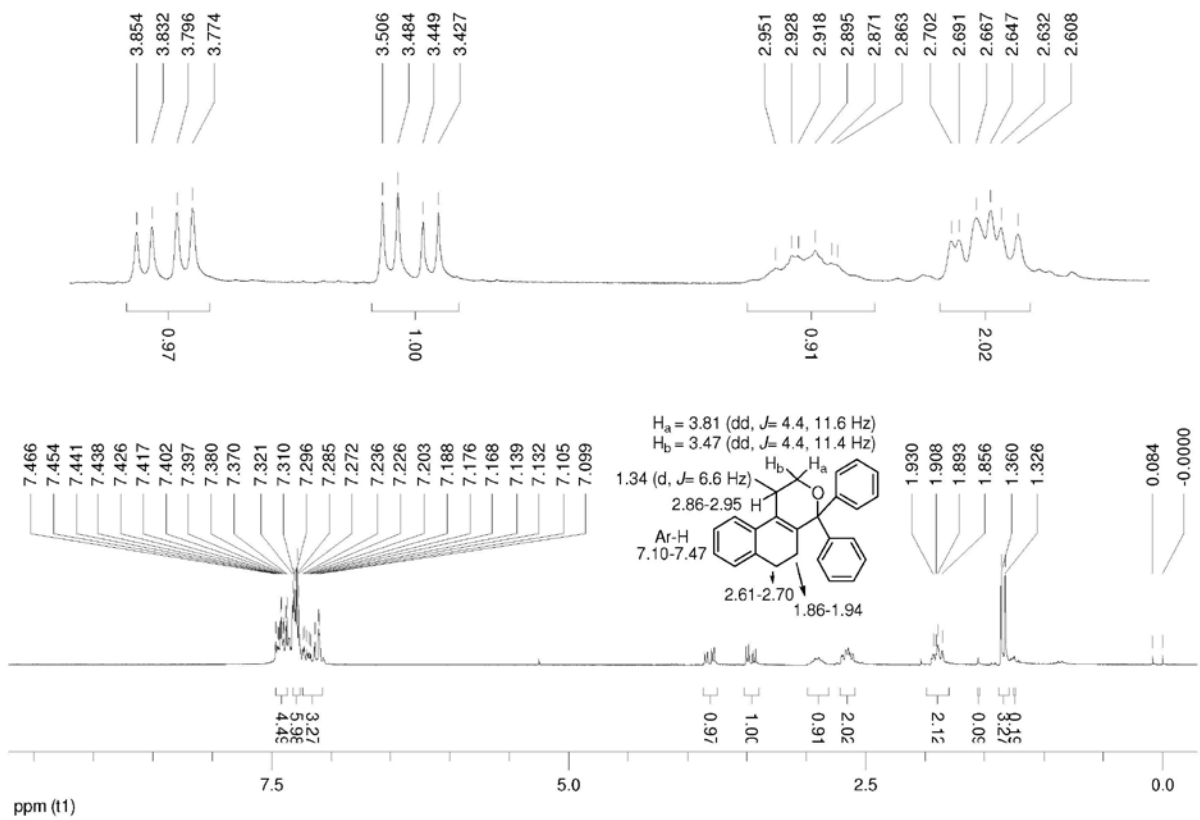

Figure S32. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3l**.

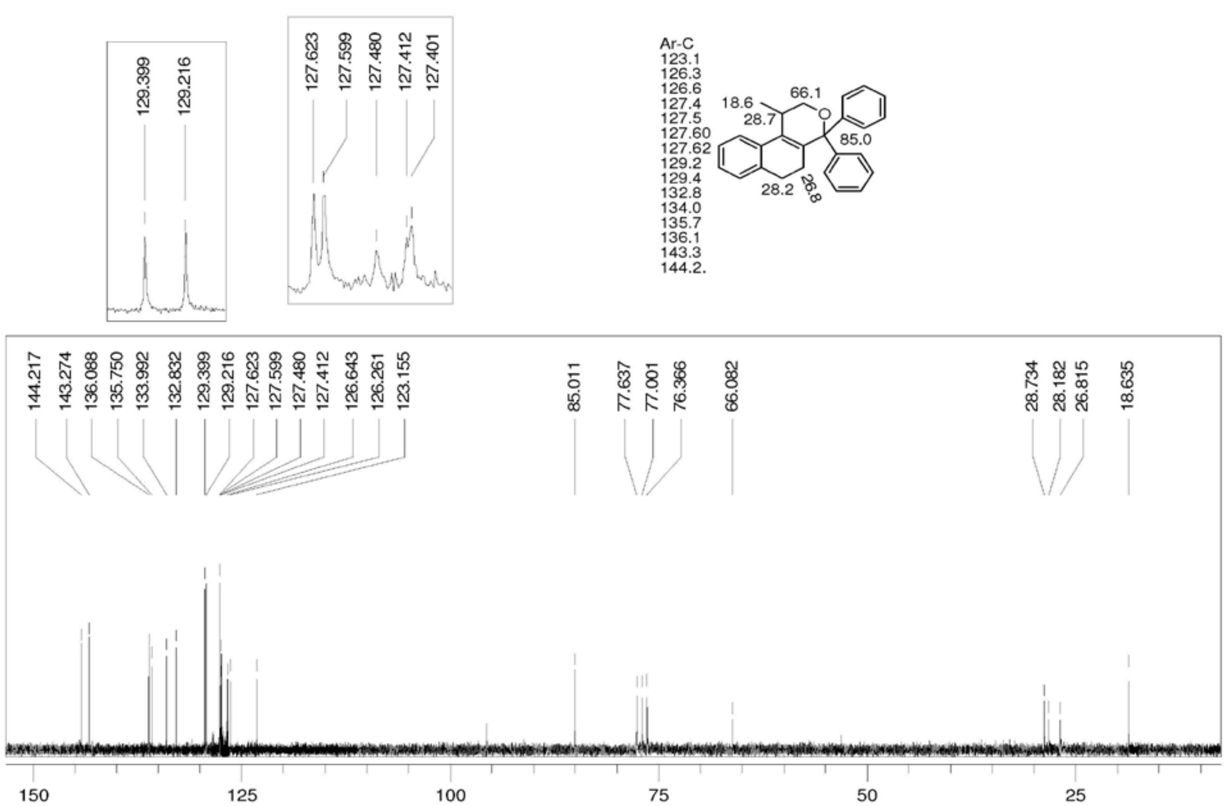

Figure S33. ^{1}H NMR (50 MHz, $CDCl_3$) spectrum of **3l**.

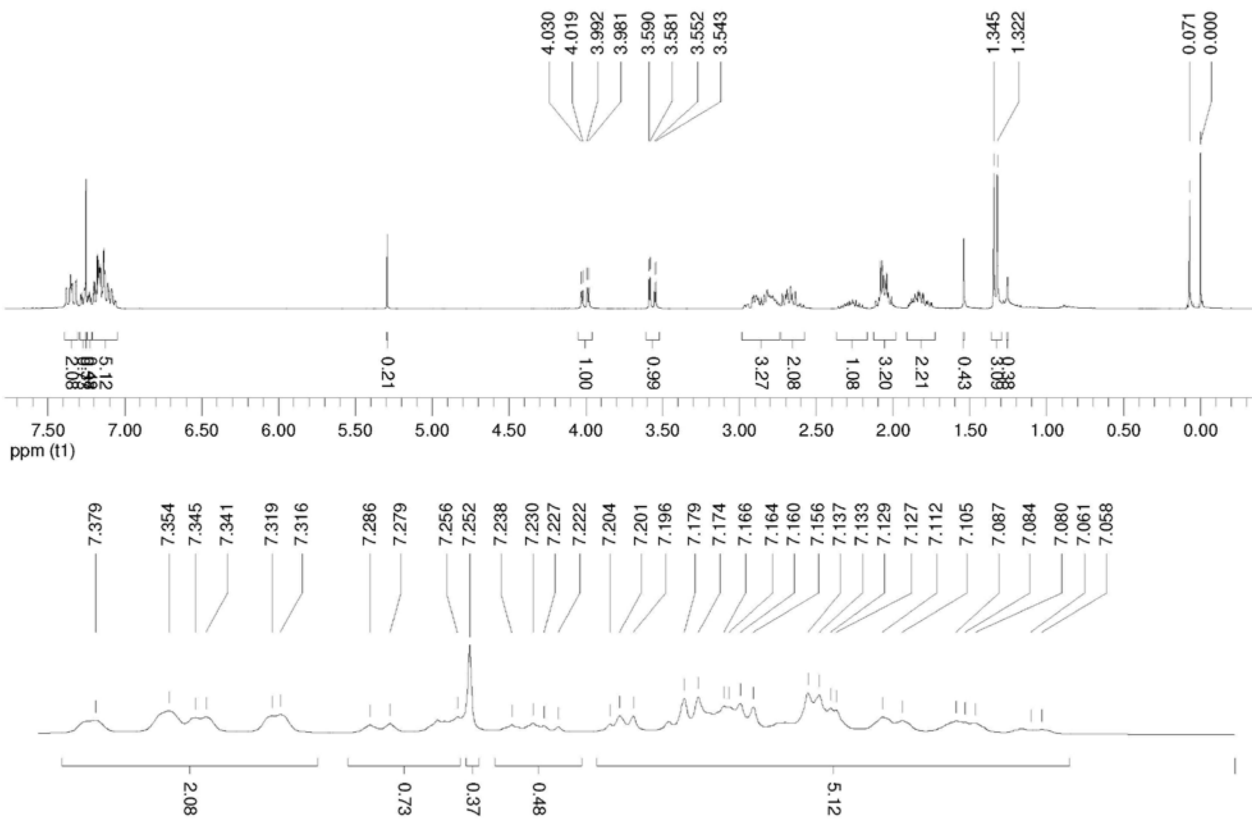

Figure S34. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **3m**.

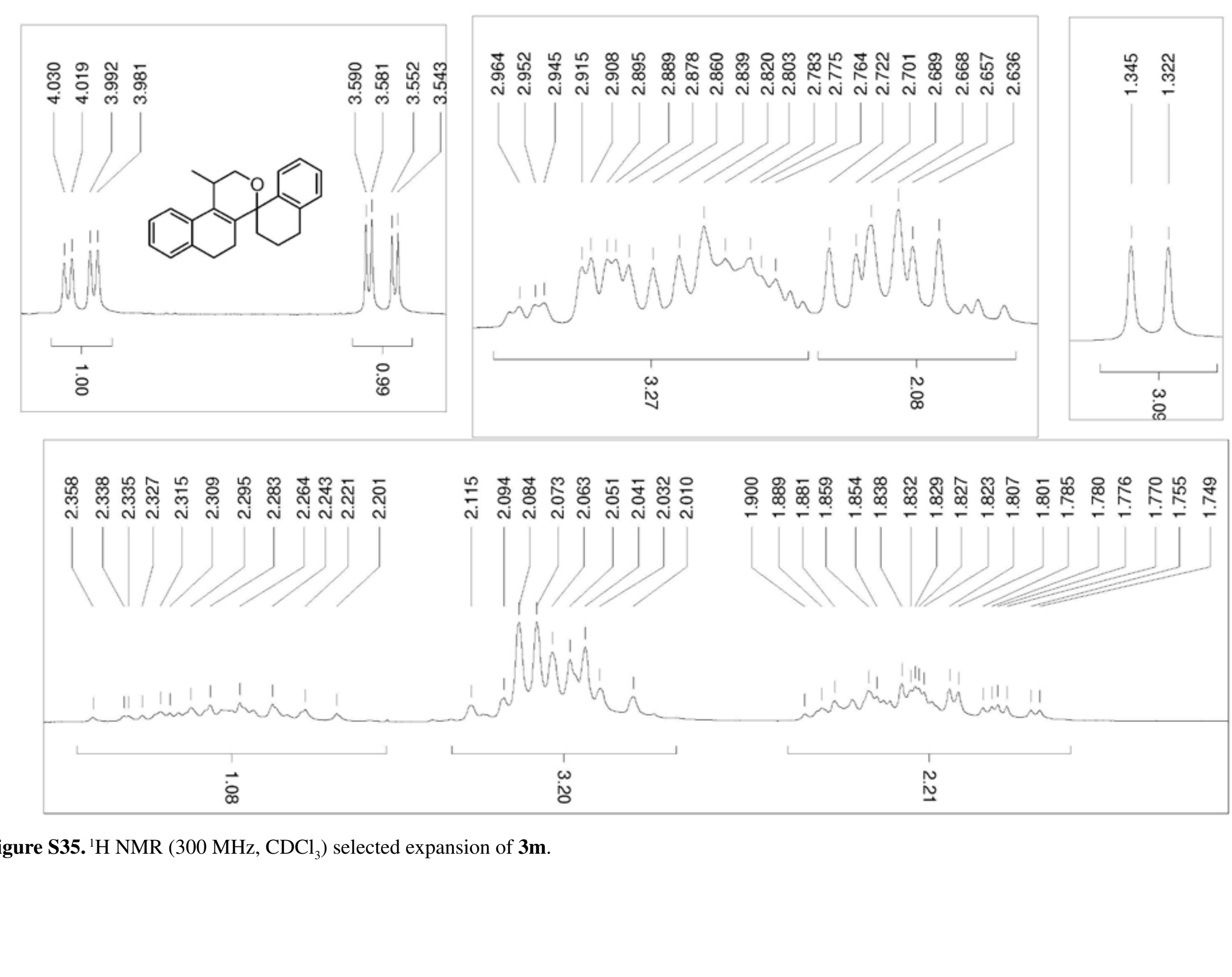

Figure S35. ^{1}H NMR (300 MHz, $CDCl_3$) selected expansion of **3m**.

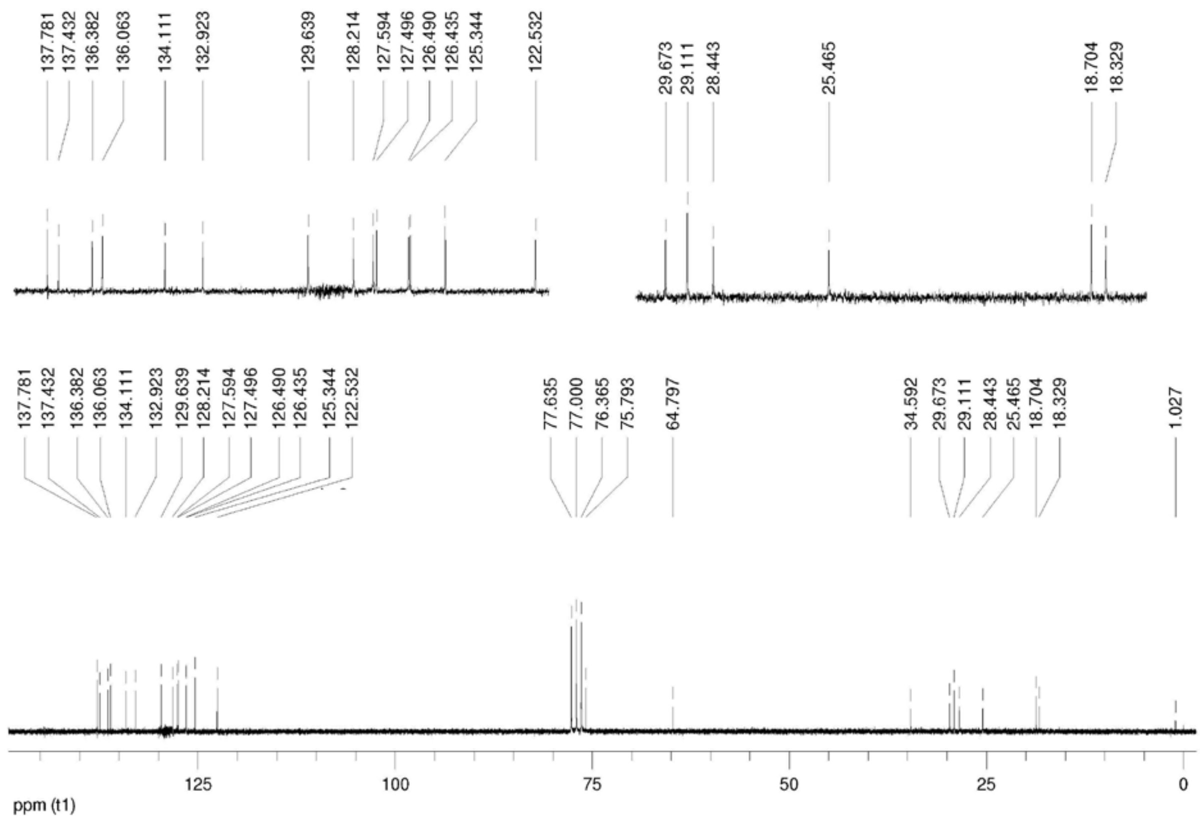

Figure S36. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **3m**.

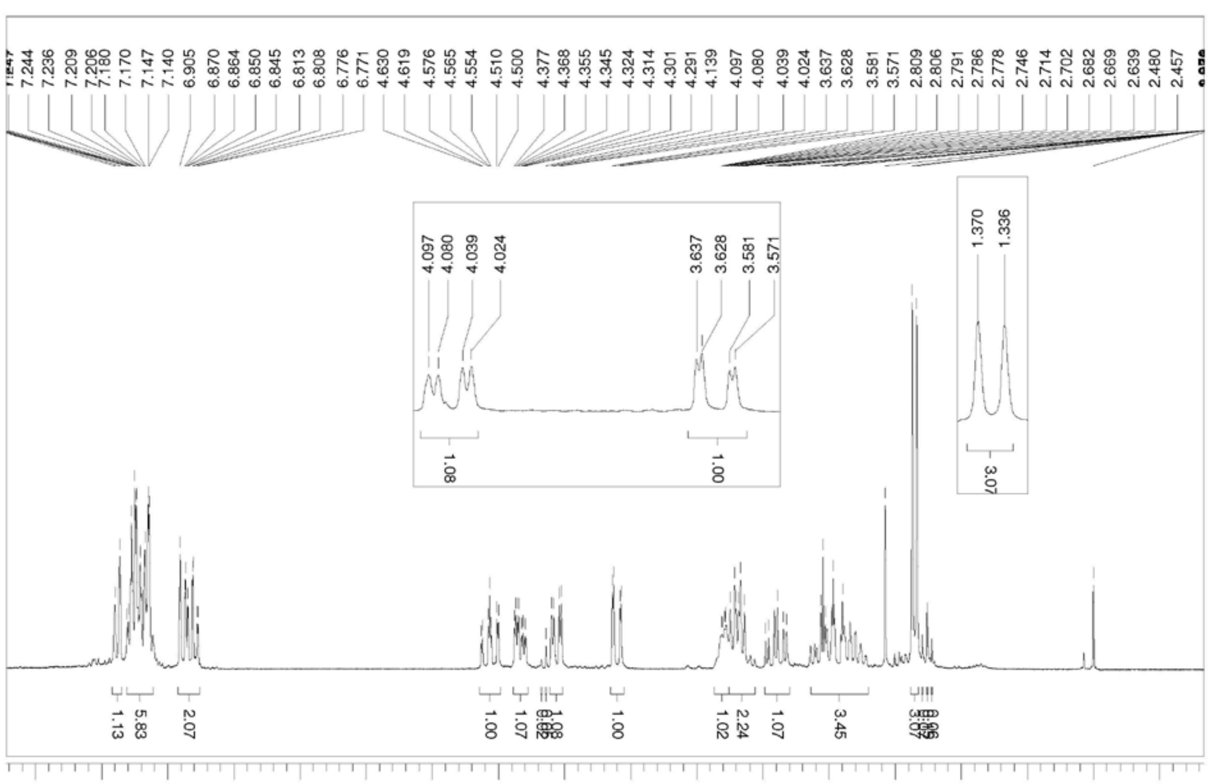

Figure S37. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3n**.

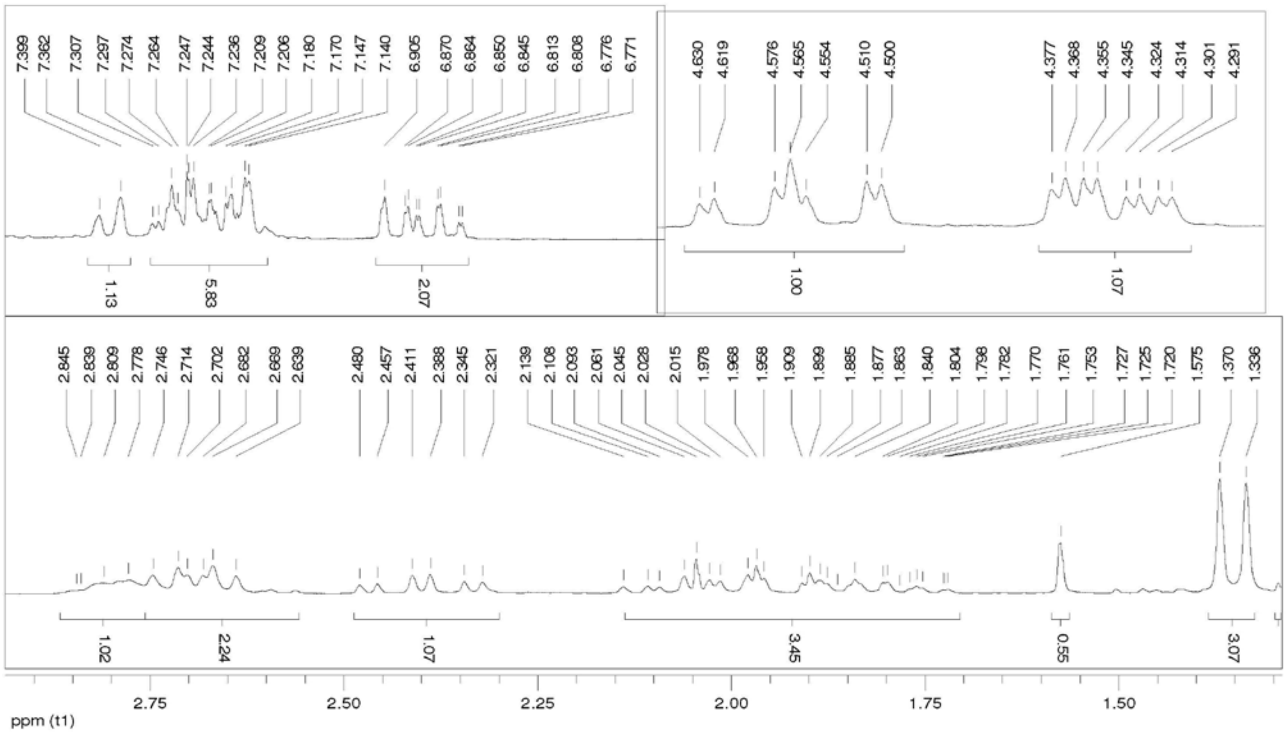

Figure S38. ^{1}H NMR (200 MHz, $CDCl_3$) selected expansions of **3n**.

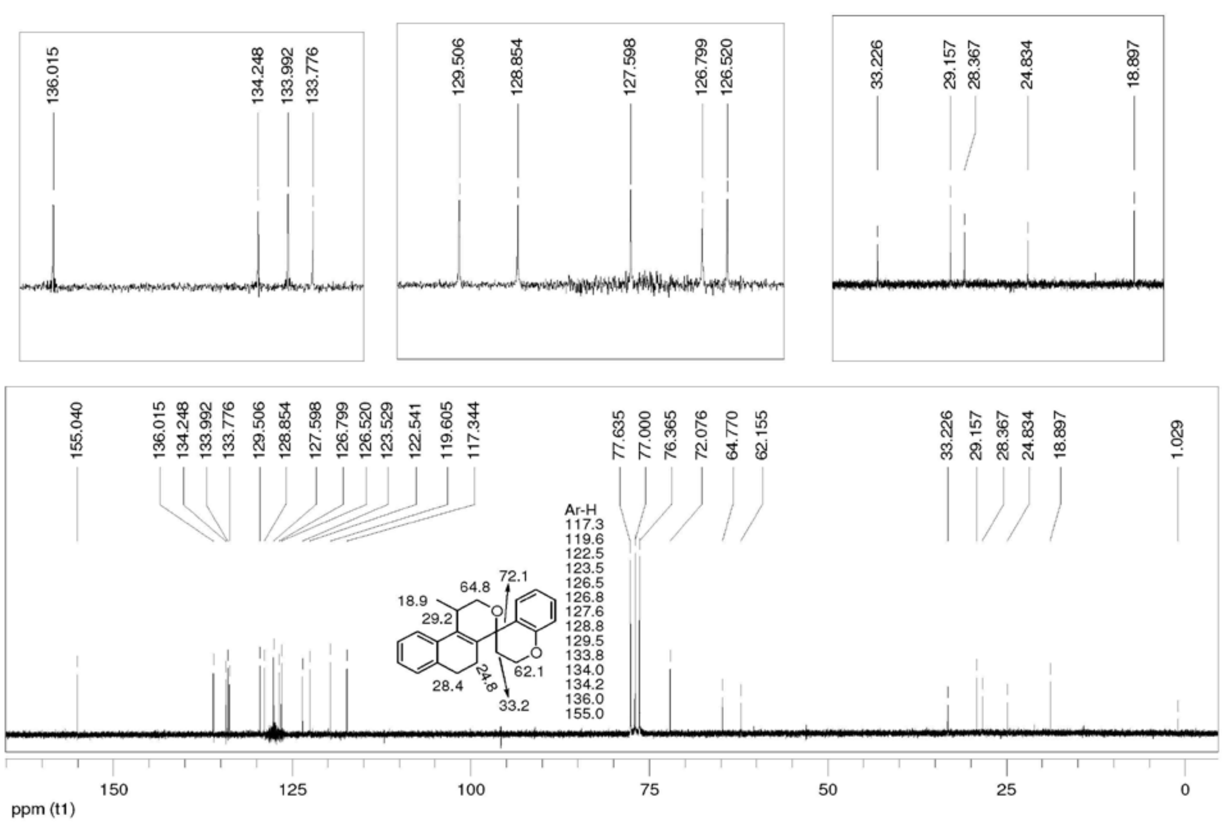

Figure S39. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **3n**.

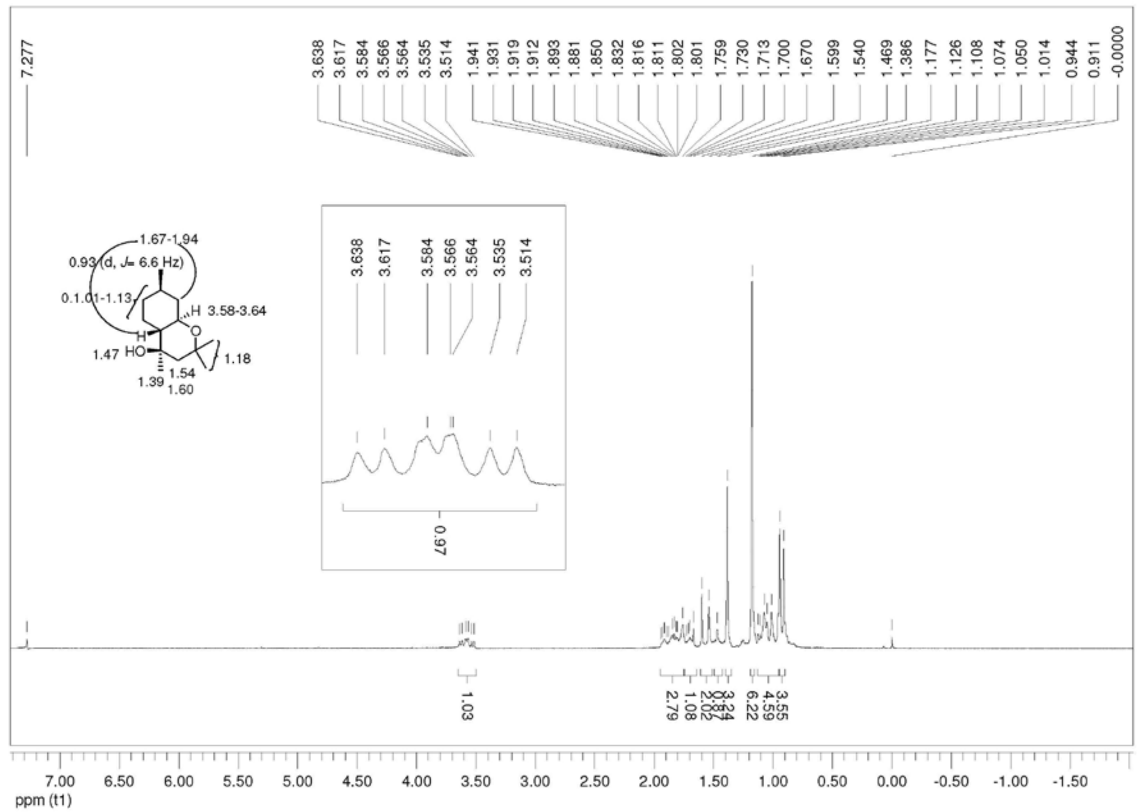

Figure S40. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **(+)-5**.

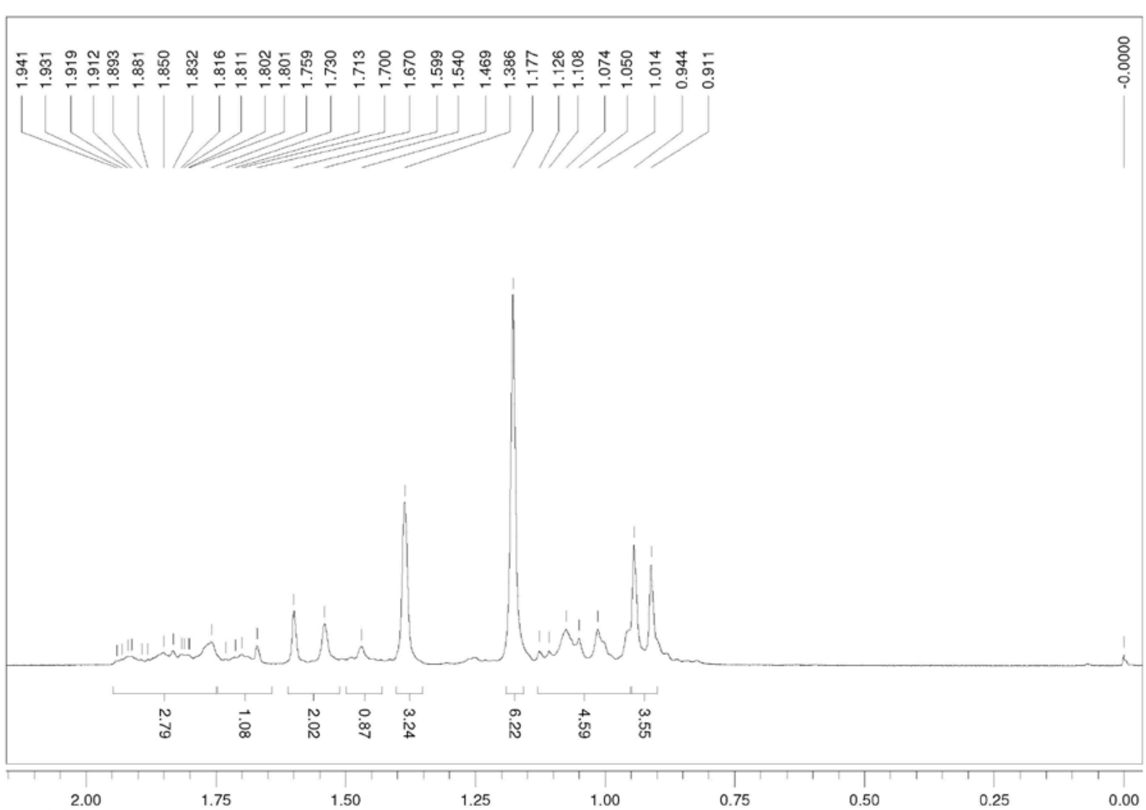

Figure S41. ^{1}H NMR (200 MHz, $CDCl_3$) selected expansions of **(+)-5**.

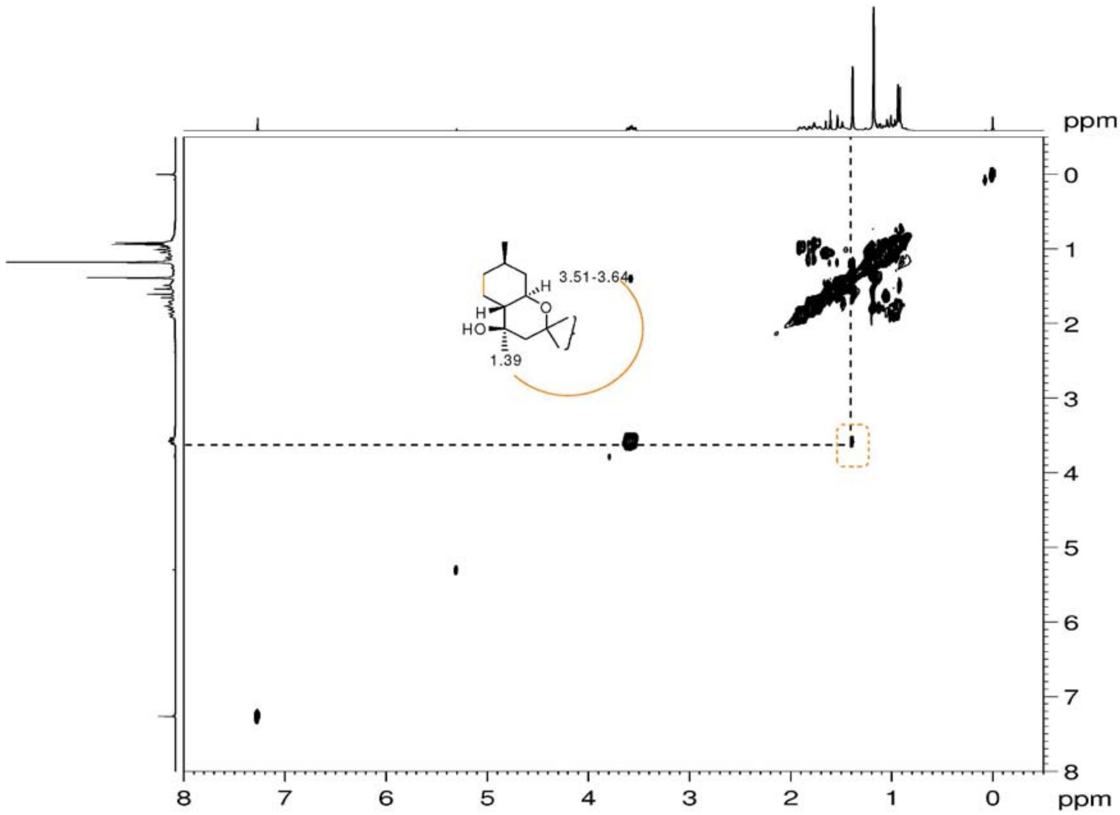

Figure S42. NOESY (300 MHz, $CDCl_3$) correlated spectrum of **(+)-5**.

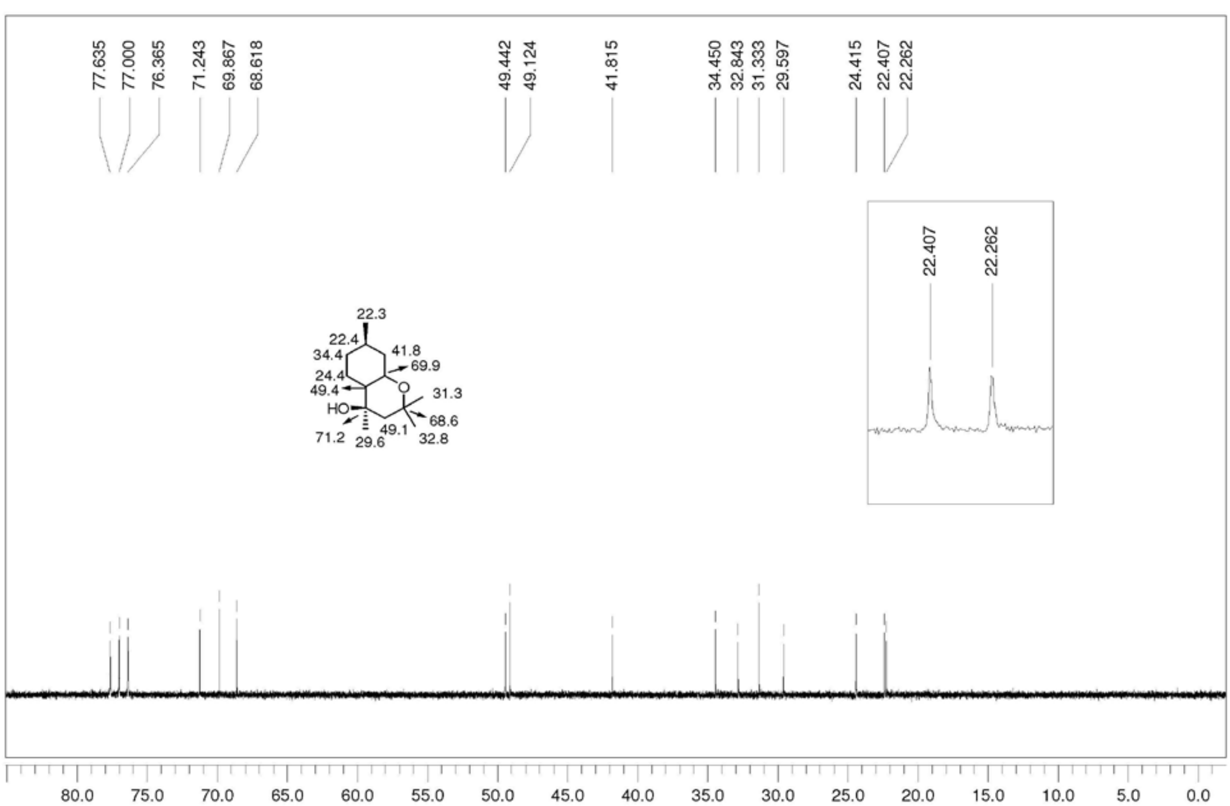

Figure S43. [13]C NMR (50 MHz, $CDCl_3$) spectrum of **(+)-5**.