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Youssef Nassar, Fabienne Fache, Beatrice Pelotier, Olivier Piva. Access to Hexahydroindeno[2,1-c]pyran-based Propellanes by a Domino Prins/Friedel-Crafts Cyclization. *Synthesis: Journal of Synthetic Organic Chemistry*, In press, 10.1055/a-1882-8128 . hal-03720442

HAL Id: hal-03720442

<https://hal.science/hal-03720442v1>

Submitted on 12 Jul 2022

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Synthesis

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DOI: 10.1055/a-1882-8128

Please cite this article as: NASSAR Y, Fache F, Pelotier B et al. Access to Hexahydroindeno[2,1-c]pyran-based Propellanes by a Domino Prins/Friedel-Crafts Cyclization. Synthesis 2022. doi: 10.1055/a-1882-8128

Conflict of Interest: The authors declare that they have no conflict of interest.

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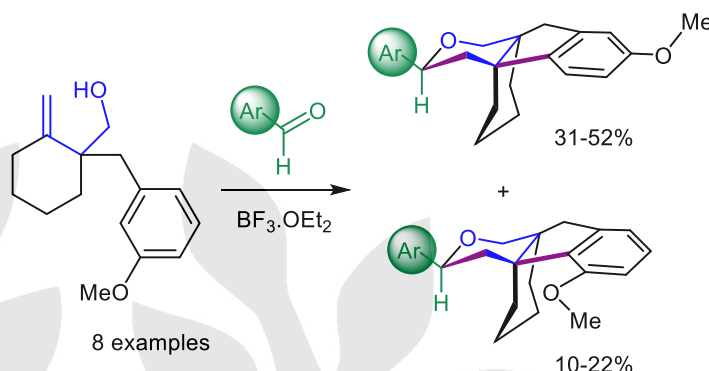
Access to Hexahydroindeno[2,1-c]pyran-based Propellanes by a Domino Prins/Friedel-Crafts Cyclization

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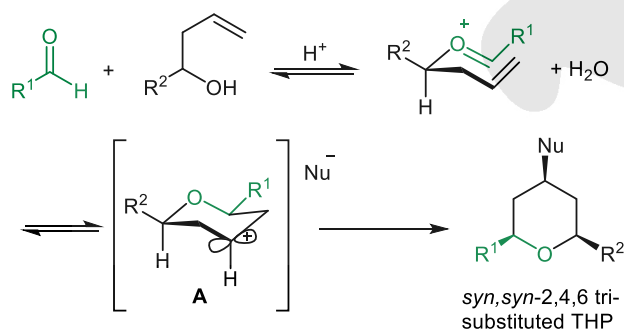


Received:
 Accepted:
 Published online:
 DOI:

Abstract Starting from readily available cyclic homoallylic alcohols, Prins reaction allowed the formation of a bicyclic tetrahydropyranyl carbocation intermediate which was only trapped by electron rich aromatic rings according a further intramolecular Friedel-Crafts reaction leading to new [4.4.3]propellane structures.

Key words Prins reaction; tetrahydropyrans; Friedel-Crafts reaction; tandem; propellanes

Tetrahydropyran (THP) ring is frequently found as a subunit in numerous natural or biological active compounds. Among the very large number of methods to access these structures, oxa-Michael reactions,¹⁻⁴ hetero-Diels-Alder cycloadditions^{5,6} and Prins cyclizations⁷⁻¹⁰ have been extensively considered. Prins reaction is highly appealing, at first because Prins reaction is a three component reaction allowing the creation of libraries of compounds. The three reagents are usually commercially or readily available. The reaction requires also friendly catalysts to generate the carbocation intermediate and in some cases can be performed under neat conditions (Scheme 1).



Scheme 1. Mechanism of Prins cyclization

Furthermore, the reaction occurs under mild conditions leading to a carbocation intermediate which is trapped by a nucleophile species. Usually the reaction is highly stereoselective leading to the *syn,syn*-2,4,6 trisubstituted adducts.¹⁰⁻¹³ Recent reports also describe the control of the configuration of the newly created stereogenic centers by using chiral phosphoric acids or borates.¹⁴⁻¹⁷

Indenopyrans represent an interesting subclass of oxygenated heterocycles for which an indene and a pyran subunit are fused. Some of them have been reported to exhibit fluorescent properties and have been considered for the fabrication of OLEDs.¹⁸ The same indenopyran subunit has been also found in different natural products which exhibit promising biological activities. For example, brazilin **1** isolated from sappanwood is used in traditional south-east Asian medicine.^{19,20} It has been preconized for treatment of diabetes and against cancer diseases. Nodulisporic acid **2** which also contains an indenopyran substructure has been the subject of intensive research due to its insecticidal activities.²¹⁻²²

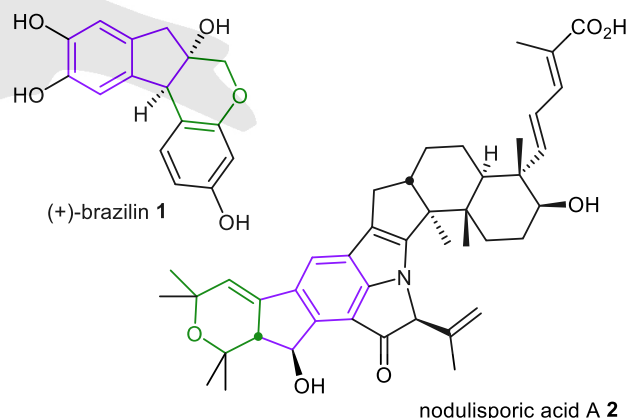
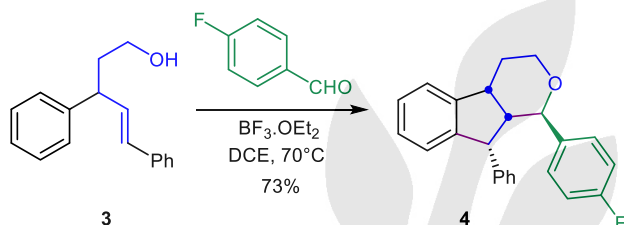


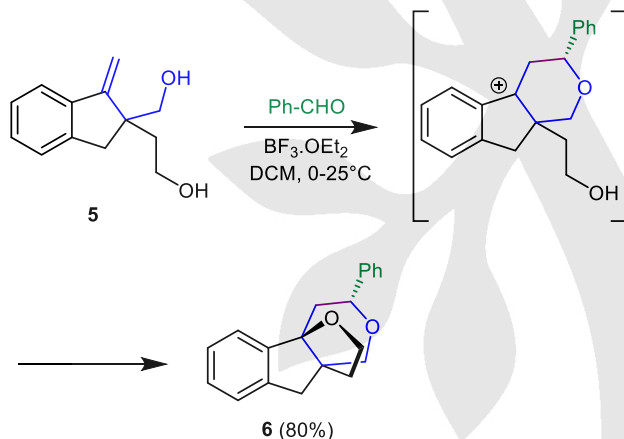
Figure 1. Natural products possessing an indenopyran subunit.

Prins reaction has been obviously considered to access indenopyrans. It was anticipated that the transient carbocation could be intercepted by aromatic derivatives to build the five-membered ring. Such a strategy combining both Prins reaction and Friedel-Crafts cyclization has been recently reviewed²³ and is still under investigation.²⁴⁻²⁹ For example, Reddy *et al.* described a concise and practical synthesis of indenopyran scaffolds from (*E*)-3,5-diphenylpent-4-en-1-ol **3**, various aldehydes and through the activation of $\text{BF}_3 \cdot \text{OEt}_2$ at 70°C (Scheme 2).³⁰



Scheme 2. Tandem Prins / Friedel-Crafts reaction.

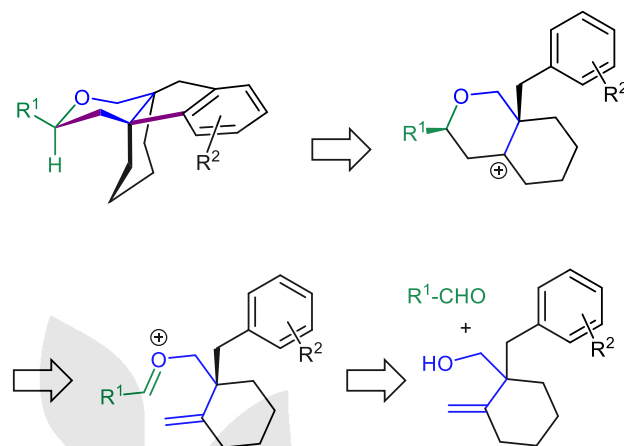
The intermediate carbocation obtained during the Prins cyclization, can also be trapped by other nucleophilic species such as an oxygen atom as depicted on Scheme 3. By this way, a straightforward synthesis of indeno [2,1-*c*]pyran scaffolds possessing a propellane substructure was achieved by the same group.³¹



Scheme 3. Prins reaction and intramolecular trapping of the carbocation. Access to propellane structures

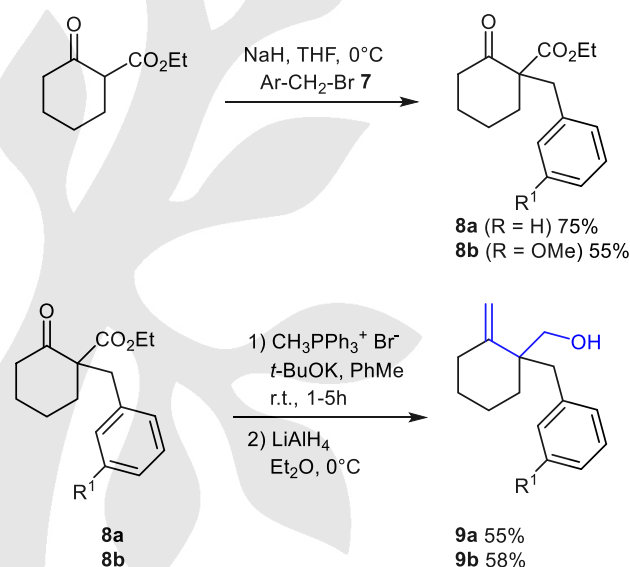
For a long time, we have been interested in the Prins reaction and its application to the synthesis of natural products and various analogues.³²⁻³⁴ Moreover, we recently described the access to propellane derivatives from easily available bicyclic hydroxylactones.^{35,36} Here, we report the synthesis of a new class of propellanes which contain a hexahydroindeno[2,1-*c*]pyran-subunit from unsaturated alcohols **9a-b**.

The strategy was based on the retrosynthesis depicted on Scheme 4. The propellane could result from an intramolecular Friedel-Crafts reaction from the aryl counterpart on the carbocation generated during the Prins reaction. This intermediate could result itself from the condensation and further nucleophilic attack of the oxonium intermediate by the exo-methylene group.



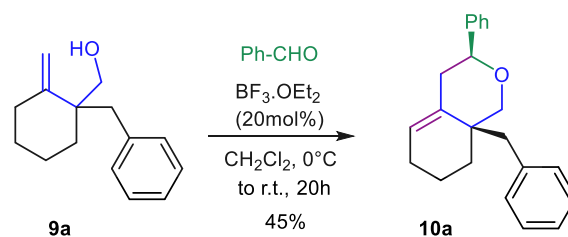
Scheme 4. Retrosynthetic approach to new indeno [2,1-*c*]pyrans

The starting materials have been prepared by a three step sequence from commercially available ethyl cyclohexanone carboxylate³⁷⁻³⁹ (Scheme 5).



Scheme 5. Synthesis of homoallylic alcohols **9a-b**

Attempts to reach propellane structures were first carried out with alcohol **9a**. In the presence of benzaldehyde and by using $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst, its rapid conversion was observed in dichloromethane, at 0°C under argon atmosphere. The newly created structure exhibited an olefinic proton at 5.53 ppm and was therefore identified as isochromene derivative **10a**. This compound clearly resulted from the Prins cyclization leading to the expected tertiary carbocation intermediate. However, instead of the planned Friedel-Crafts reaction, a competitive elimination occurred to give **10a** (Scheme 6).



Scheme 6. Prins reaction/elimination observed with substrate **9a**

In order to favor the cyclization, isolated compound **10a** was stirred in the presence of triflic acid for 16h at r.t. in deuterated chloroform. No further reaction was observed by $^1\text{H-NMR}$ even after additional heating at 40°C for 3 additional hours. This fruitless sequence could be correlated to the weak nucleophilic character of the sole phenyl ring. Therefore, compound **9b** was next considered. It possesses one additional methoxy group which considerably enhances the electron density of the aromatic ring as already pointed out for tandem Prins/intermolecular Friedel-Crafts reactions.

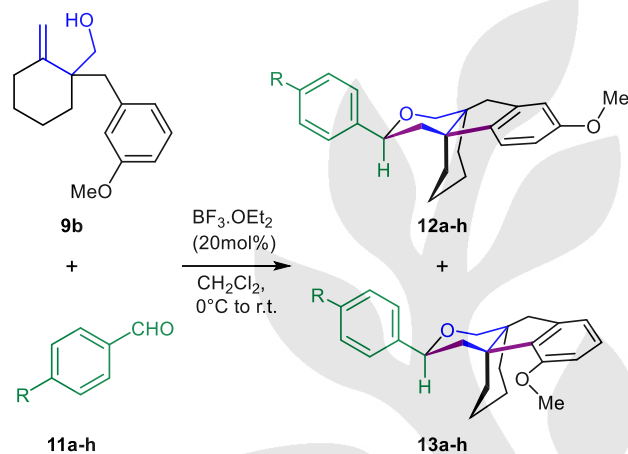


Table 1. Tandem Prins reaction/FC condensation with **9b**.

11	R	t(h)	12 ^a	13 ^a
11a	-NO ₂	15	12a 40	13a 13
11b	-F	20	12b 51	13b 17
11c	-Cl	57	12c 52	13c 17
11d	-Br	15	12d 44	13d 13
11e	-CF ₃	70	12e 31	13e 10
11f	-CO ₂ Me	19	12f 50	13f 22
11g	-H	21	12g 33	13g ^b
11h	-CH ₃	15	12h traces	13h traces

^a Isolated yields

^b Degradation over silica

The reaction was carried out at first with *p*-nitrobenzaldehyde **11a** at 0°C , in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst (20 mol%) under stirring at r.t. for 21h (Table 1). After treatment two new compounds **12a** and **13a** were isolated in 53% as a 3:1 mixture and separated by flash-chromatography on silica. In contrast with the previous attempt performed with **9a**, no olefinic protons were detected on the $^1\text{H-NMR}$ spectra excluding the isolation of isochromene derivatives. Mass spectroscopy revealed the compounds are isomers and correspond both to propellane derivatives. Examination of the multiplicity of the protons attached on the methoxyphenyl ring allowed to assign the structure for each isomer (Fig. 2). For the minor isomer **13a**, hydrogen atom H_7 appears at 7.06 ppm as a doublet of doublet ($J = 7.4$ and 8.3 Hz) while the two other aromatic hydrogen atoms resonate respectively at 6.62 (H_6 , d, $J = 7.4$ Hz) and 6.79 ppm (H_8 , d, $J = 8.3$ Hz).

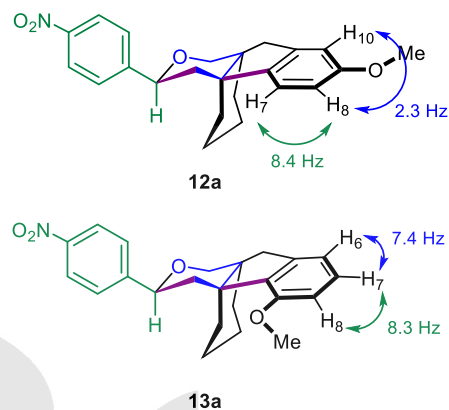


Fig. 2. Selective NMR data for indenopyrans **12a** and **13a**

In contrast, the major isomer **12a** exhibits a complete different NMR spectrum. Aromatic proton H_{10} appears at 6.85 ppm as a doublet with a small coupling constant ($J = 2.3$ Hz), while hydrogen atoms H_7 and H_8 are coupled together with a larger value ($J = 8.4$ Hz). These data are in correlation with a structure for which the methoxy group is para relative to the newly created C-C bond.

According to the reaction pathway (scheme 1), it was assumed that compounds **12** and **13** resulted from the attack of the aromatic ring onto the same carbocationic intermediate. Therefore, they should present the same relative configuration. 2D COSY NMR experiments conducted on compound **13a** allowed the attribution of the hydrogen atom on carbon atoms 1, 4 and 12 (Figure 3 and 4). On the 2D NOESY NMR spectra, a strong correlation between H_{4b} and H_{12a} was observed which is in full agreement with the relative configuration as depicted on Figure 2.

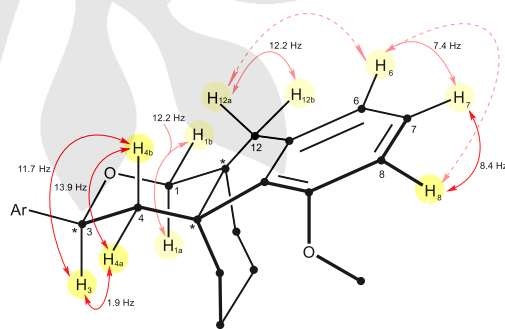


Figure 3. 2D-COSY correlations measured on **13a**.

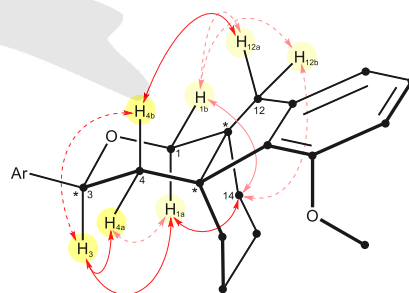


Figure 4. NOESY correlations measured on **13a**.

The reaction was carried out with other aldehydes and results are collected in Table 1. With aldehydes **11a-f** possessing an electron withdrawing group in *para* position, the overall yields of propellane structures are on the range of 41-72%, which could

easily be separated by flash-chromatography. In all cases, the same selectivity in favor of structures **12** was observed, resulting probably from a minimization of steric hindrance between the methoxy group and the propellane substructure. With aldehydes **11g-h**, the reaction was not so efficient. Solely compound **12g** (R=H) was isolated in only 33% yields, while other expected adducts detected by TLC, were degraded during isolation on silica.

In conclusion, we have prepared new propellane derivatives from readily available starting materials by using as key step a tandem Prins reaction/Friedel-Crafts cyclization. To be successful, the presence of an electron donating group such as a methoxy group was required to favor the trapping of the carbocation intermediate instead of a competitive elimination process.

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All commercially available compounds were used without further purification. Solvent were dried according to standard procedures. Petroleum ether (PE) refers to a hydrocarbon mixture with a boiling range of 40-60°C. Column chromatography was performed with silica gel (0.040-0.063 mm). NMR spectra were recorded at 293 K, using a 300 MHz spectrometer (Bruker AMX 300) or a 500 MHz spectrometer (Bruker DRX 500). Shifts are referenced relative to deuterated solvent residual peaks. Low and high resolution (LR and HRMS) mass spectra were recorded in the positive mode using a Bruker MicroTOF-Q II XL spectrometer.

Procedures

Compound **8a** was prepared according to known procedures.³⁷

Ethyl 1-(3-methoxybenzyl)-2-oxocyclohexane-1-carboxylate **8b**

To a suspension of 60% sodium hydride (140 mg, 3.5 mmol) in THF was added a solution of ethyl 2-cyclohexanonecarboxylate (500 mg, 2.9 mmol) in THF (100 mL) at 0 °C and the mixture was stirred for 3 hours. To this solution was added *m*-methoxybenzyl bromide (0.49 mL, 3.5 mmol) and then the mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched by adding water, extracted with ether, washed with aqueous NaHCO₃ solution and then dried over MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give **8b** (469 mg, 1.61 mmol).

Colorless oil; yield: 55%. Rf = 0.37 (silica gel, petroleum ether: EtOAc (90:10)).

¹H NMR (300 MHz, CDCl₃) δ = 7.14 (t, *J* = 8.0 Hz, 1H), 6.76 – 6.67 (m, 3H), 4.15 – 4.06 (m, 2H), 3.77 (s, 3H), 3.27 (d, *J* = 13.6 Hz, 1H), 2.85 (d, *J* = 13.6 Hz, 1H), 2.47 – 2.40 (m, 3H), 2.04–1.99 (m, 1H), 1.72 – 1.67 (m, 3H), 1.52 – 1.36 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 207.4, 171.1, 159.4, 138.3, 129.0, 122.9, 116.3, 112.1, 62.2, 61.4, 55.2, 41.4, 40.6, 36.0, 27.7, 22.6, 14.1.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₇H₂₂NaO₄: 313.1410; found 313.1410.

Access to homoallylic alcohols **9a** and **9b**

General procedure: To a well stirred suspension of methyltriphenylphosphonium bromide (2.0 equiv.) in anhydrous toluene under argon was added *t*-BuOK (2.0 equiv.). The mixture was stirred at room temperature for 2 hours then the solution of ketoester **8** (1.0 equiv., 1.24 M) in toluene was added. The mixture was then stirred for one more hour. After being poured to cold ether water, the mixture was extracted by ethyl acetate, then dried over MgSO₄. Evaporation of the solvent gave a crude mixture, which was used without further purification. To a well stirred solution of the crude mixture (1.0 equiv., 0.5 M) in anhydrous

diethyl ether under argon was added LiAlH₄ (2.0 equiv.) at 0 °C. The mixture was then stirred for 1.5-18 hours. At the end of the reaction, water was added to decompose the excess of the reagent. It is important to ensure that all the excess reagent is destroyed before continuing. The organic layer was separated and washed with sulfuric acid (0.1M), brine, dried over Na₂SO₄, filtered and concentrated. After column chromatography on silica gel, the desired alcohol was isolated

(1-Benzyl-2-methylenecyclohexyl)methanol **9a**

Colorless oil; yield: 55% (for 2 steps) (1.01 g isolated from **8a** (2.2 g)). Rf = 0.64 (silica gel, petroleum ether: EtOAc (85:15)). ¹H NMR (400 MHz, CDCl₃) δ = 7.28 – 7.16 (m, 5H), 4.96 (d, *J* = 1.2 Hz, 1H), 4.68 (d, *J* = 1.2 Hz, 1H), 3.58 (d, *J* = 11.0 Hz, 1H), 3.38 (d, *J* = 11.0 Hz, 1H), 3.16 (d, *J* = 13.1 Hz, 1H), 2.56 (d, *J* = 13.1 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.31 – 2.22 (m, 1H), 1.67 – 1.41 (m, 6H), 1.31 (Brs, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 151.2, 138.3, 130.8, 127.9, 126.2, 110.1, 64.6, 45.1, 40.2, 34.1, 33.8, 28.0, 22.0. HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₅H₂₀NaO: 239.1406; found 239.1403.

(1-(3-Methoxybenzyl)-2-methylenecyclohexyl)methanol **9b**

Colorless oil; yield: 69% (63 mg isolated from **8b** (107 mg)). Rf = 0.275 (silica gel, petroleum ether: EtOAc (80:20)).

¹H NMR (400 MHz, CDCl₃) δ = 7.20 – 7.15 (m, 1H), 6.79 – 6.74 (m, 3H), 4.96 (d, *J* = 1.2 Hz, 1H), 4.68 (d, *J* = 1.2 Hz, 1H), 3.79 (s, 3H), 3.60 (d, *J* = 11.0 Hz, 1H), 3.41 (d, *J* = 11.0 Hz, 1H), 3.14 (d, *J* = 13.1 Hz, 1H), 2.55 (d, *J* = 13.1 Hz, 1H), 2.41 – 2.35 (m, 1H), 2.30 – 2.24 (m, 1H), 1.67 – 1.42 (m, 6H), 1.35 (Brs, 1H).

¹³C NMR (101 MHz, CDCl₃) δ = 159.2, 151.3, 139.9, 128.7, 123.3, 116.6, 111.4, 110.0, 64.7, 55.2, 45.0, 40.2, 34.2, 33.8, 28.0, 21.9.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₆H₂₂NaO₂: 269.1512; found 269.1509.

Tandem Prins reaction/Friedel-Crafts cyclization:

General procedure: To a stirred solution of the exo-olefinic alcohol **9** (0.25 mmol) and aldehyde **11** (0.25 mmol) in anhydrous dichloromethane (1.0 mL) was added BF₃·OEt₂ (0.05 mmol) at 0°C under argon atmosphere. The reaction mixture was stirred at room temperature for the specified time. The reaction mixture was then quenched with aqueous saturated NaHCO₃ (3 mL) and extracted with ethyl acetate (20 mL, 10 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated. The crude product was purified by flash-chromatography.

(3*R**,8*aR**)-8a-Benzyl-3-phenyl-3,4,6,7,8,8a-hexahydro-1H-isochromene **10a**

Viscous oil; yield: 45% (63 mg isolated from **8a** (100 mg)). Rf = 0.81 (silica gel, petroleum ether: EtOAc (85:15)).

¹H NMR (300 MHz, CDCl₃) δ = 7.46 – 7.17 (m, 10H), 5.56 – 5.53 (m, 1H), 4.38 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.84 (d, *J* = 11.3 Hz, 1H), 3.26 (dd, *J* = 13.4, 1.1 Hz, 1H), 3.02 (dd, *J* = 11.3, 1.1 Hz, 1H), 2.78 (dd, *J* = 13.4, 1.1 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.25 (dd, *J* = 14.1, 3.0 Hz, 1H), 2.03 – 1.99 (m, 2H), 1.66 – 1.50 (m, 3H), 0.89 – 0.79 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 142.9, 139.0, 138.5, 131.1, 128.5, 128.0, 127.6, 126.2, 125.9, 122.7, 82.0, 75.6, 40.6, 39.4, 39.0, 27.8, 25.7, 17.9.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₂H₂₄NaO: 327.1719; found 327.1721.

(4*aR**,9*aR**,12*R**)-7-Methoxy-12-(4-nitrophenyl)-1,2,3,4-tetrahydro-9H-4*a*,9*a*-(ethanooxymethano)fluorene **12a**

Viscous oil; Rf = 0.39 (silica gel, Petroleum ether: EtOAc (90:10)).

¹H NMR (400 MHz, CDCl₃) δ = 8.14 (d, *J* = 9.7 Hz, 2H), 7.48 (d, *J* = 9.7 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.63 (dd, *J* = 11.5, 2.9 Hz, 1H), 4.00 (d, *J* = 12.1 Hz, 1H), 3.85 (d, *J* = 12.1 Hz, 1H), 3.78 (s, 3H), 3.48 (dt, *J* = 15.4, 1.2 Hz, 1H), 2.32 (d, *J* = 15.4 Hz, 1H), 2.09 – 2.00 (m, 2H), 1.62 – 1.25 (m, 8H).

^{13}C NMR (75 MHz, CDCl_3) δ = 159.0, 150.4, 142.9, 141.9, 126.5, 123.7, 123.6, 122.00, 112.3, 111.9, 74.7, 70.1, 55.5, 46.5, 46.2, 44.3, 41.4, 31.2, 28.5, 22.6, 22.4.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NNaO}_4$: 402.1676; found 402.1676.

(*4aR**,*9aS**,*12S**)-5-Methoxy-12-(4-nitrophenyl)-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **13a**

Yellow oil; Rf = 0.43 (silica gel, petroleum ether: EtOAc (90:10)).

^1H NMR (500 MHz, CDCl_3) δ = 8.13 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.12 (dd, J = 8.3, 7.4 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 4.67 (dd, J = 11.9, 2.2 Hz, 1H), 4.02 (d, J = 12.2 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.76 (s, 3H), 3.47 (d, J = 15.2 Hz, 1H), 2.78 (d, J = 15.2 Hz, 1H), 2.34 (d, J = 15.2 Hz, 1H), 1.93 – 1.88 (m, 2H), 1.69 – 1.22 (m, 7H).

^{13}C NMR (126 MHz, CDCl_3) δ = 157.0, 150.7, 147.1, 143.6, 135.5, 128.0, 126.6, 123.47, 118.9, 109.3, 74.3, 69.9, 55.3, 49.0, 44.0, 43.5, 41.6, 31.8, 28.1, 23.4, 22.8.

HRMS (EI): m/z [M] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_4$: 379.1778; found 379.1777.

(*4aR**,*9aR**,*12R**)-12-(4-Fluorophenyl)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **12b**

Colorless oil; Rf = 0.32 (silica gel, Petroleum ether: EtOAc (95:5)).

^1H NMR (300 MHz, CDCl_3) δ = 7.32 – 7.27 (m, 2H), 7.00 – 6.95 (m, 3H), 6.86 (bd, J = 2.3 Hz, 1H), 6.72 (dd, J = 8.2, 2.3 Hz, 1H), 4.51 (dd, J = 10.4, 3.6 Hz, 1H), 4.00 (d, J = 12.1 Hz, 1H), 3.82 (d, J = 12.1 Hz, 1H), 3.80 (s, 3H), 3.52 (d, J = 15.4 Hz, 1H), 2.31 (d, J = 15.4 Hz, 1H), 2.07 – 1.99 (m, 2H), 1.65 – 1.26 (m, 8H).

^{13}C NMR (75 MHz, CDCl_3) δ = 162.1 (d, J_{CF} = 245 Hz), 158.9, 143.1, 142.3, 138.6, 127.7 (d, J_{CF} = 8.1 Hz), 122.0, 115.1 (d, J_{CF} = 21.4 Hz), 112.2, 111.8, 75.0, 70.2, 55.5, 46.5, 46.2, 44.3, 41.5, 31.5, 28.5, 22.7, 22.4.

^{19}F NMR (282 MHz, CDCl_3) δ = -115.39.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{FNaO}_2$: 375.173079; found 375.173132

(*4aR**,*9aS**,*12S**)-12-(4-Fluorophenyl)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **13b**

Pale yellow oil; Rf = 0.46 (silica gel, petroleum ether: EtOAc (95:5)).

^1H NMR (300 MHz, CDCl_3) δ = 7.30 (dd, J = 8.6, 5.6 Hz, 2H), 7.13 (dd, J = 8.2, 7.3 Hz, 1H), 6.96 (t, J = 8.8 Hz, 2H), 6.87 (d, J = 7.1 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 4.56 (dd, J = 11.8, 2.2 Hz, 1H), 4.02 (d, J = 12.1 Hz, 1H), 3.83 – 3.78 (m, 1H), 3.76 (s, 3H), 3.50 (d, J = 15.1 Hz, 1H), 2.75 (dt, J = 14.0, 3.4 Hz, 1H), 2.32 (d, J = 14.8 Hz, 1H), 1.97 – 1.83 (m, 2H), 1.68 – 1.64 (m, 2H), 1.42–1.20 (m, 5H).

^{13}C NMR (101 MHz, CDCl_3) δ = 161.7 (d, J_{CF} = 245 Hz), 157.0, 143.8, 138.8, 136.0, 127.8, 127.7 (d, J_{CF} = 8.1 Hz), 118.9, 115.2 (d, J_{CF} = 21.4 Hz), 109.2, 74.6, 69.7, 55.3, 49.1, 44.0, 43.6, 41.9, 31.9, 28.1, 23.5, 22.8.

^{19}F NMR (282 MHz, CDCl_3) δ = -115.58.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{FNaO}_2$: 375.1731; found 375.1730.

(*4aR**,*9aR**,*12R**)-12-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **12c**

Viscous oil; Rf = 0.38 (silica gel, petroleum ether: EtOAc (95:5)).

^1H NMR (300 MHz, CDCl_3) δ = 7.26 (s, 4H), 6.97 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.72 (dd, J = 8.2, 2.3 Hz, 1H), 4.51 (dd, J = 8.9, 5.0 Hz, 1H), 3.99 (d, J = 12.1 Hz, 1H), 3.82 (d, J = 12.1 Hz, 1H), 3.80 (s, 3H), 3.51 (dt, J = 15.3, 1.2 Hz, 1H), 2.31 (d, J = 15.3 Hz, 1H), 2.06 – 1.99 (m, 2H), 1.68 – 1.57 (m, 1H), 1.41 – 1.25 (m, 7H).

^{13}C NMR (75 MHz, CDCl_3) δ = 158.9, 143.0, 142.3, 141.3, 133.0, 128.5, 127.3, 122.0, 112.2, 111.8, 74.9, 70.2, 55.5, 46.5, 46.0, 44.3, 41.4, 31.5, 28.5, 22.7, 22.4.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{ClNaO}_2$: 391.1435; found 391.1438.

(*4aR**,*9aS**,*12S**)-12-(4-chlorophenyl)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **13c**

Pale yellow oil; Rf = 0.45 (silica gel, petroleum ether: EtOAc (95:5)).

^1H NMR (300 MHz, CDCl_3) δ = 7.25 – 7.24 (m, 4H), 7.12 (dd, J = 8.2, 7.3 Hz, 1H), 6.87 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 8.3 Hz, 1H), 4.55 (dd, J = 12.2, 2.2 Hz, 1H), 4.01 (d, J = 12.2 Hz, 1H), 3.78 (d, J = 13.2 Hz, 1H), 3.76 (s, 3H), 3.48 (d, J = 15.2 Hz, 1H), 2.75 (d, J = 13.9 Hz, 1H), 2.32 (d, J = 15.2 Hz, 1H), 1.96 – 1.83 (m, 2H), 1.68 – 1.64 (m, 1H), 1.56 – 1.51 (m, 1H), 1.42 – 1.21 (m, 5H).

^{13}C NMR (101 MHz, CDCl_3) δ = 157.0, 143.8, 141.6, 135.9, 132.9, 128.4, 127.8, 127.3, 118.9, 109.2, 74.5, 69.8, 55.3, 49.1, 44.0, 43.6, 41.9, 31.8, 28.1, 23.5, 22.8.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{ClNaO}_2$: 391.1435; found 391.1439.

(*4aR**,*9aR**,*12R**)-12-(4-Bromophenyl)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **12d**

Colorless oil; Rf = 0.425 (silica gel, Petroleum ether: EtOAc (90:10)).

^1H NMR (300 MHz, CDCl_3) δ = 7.41 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.71 (dd, J = 8.3, 2.3 Hz, 1H), 4.49 (dd, J = 8.5, 5.5 Hz, 1H), 3.98 (d, J = 12.1 Hz, 1H), 3.81 (d, J = 12.1 Hz, 1H), 3.79 (s, 3H), 3.50 (d, J = 15.3 Hz, 1H), 2.30 (d, J = 15.3 Hz, 1H), 2.11 – 1.93 (m, 2H), 1.70 – 1.54 (m, 2H), 1.47 – 1.21 (m, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ = 158.9, 143.0, 142.3, 141.9, 131.4, 127.7, 122.0, 121.1, 112.2, 111.8, 75.0, 70.2, 55.5, 46.5, 46.1, 44.3, 41.5, 31.5, 28.5, 22.7, 22.4.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{BrNaO}_2$: 435.0930; found 435.0927.

(*4aR**,*9aS**,*12S**)-12-(4-Bromophenyl)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **13d**

White solid; Rf = 0.52 (silica gel, petroleum ether: EtOAc (90:10)).

^1H NMR (300 MHz, CDCl_3) δ = 7.39 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.12 (dd, J = 8.1, 7.4 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 4.53 (dd, J = 12.0, 2.4 Hz, 1H), 4.01 (d, J = 12.0 Hz, 1H), 3.83 – 3.72 (m, 2H), 3.76 (s, 3H), 3.48 (d, J = 15.1 Hz, 1H), 2.32 (d, J = 15.1 Hz, 1H), 1.96 – 1.80 (m, 2H), 1.67 – 1.16 (m, 7H).

^{13}C NMR (126 MHz, CDCl_3) δ = 157.0, 143.8, 142.2, 135.9, 131.4, 127.8, 127.7, 121.1, 118.9, 109.3, 74.5, 69.8, 55.3, 49.1, 44.0, 43.6, 41.9, 31.9, 28.1, 23.5, 22.8.

HRMS (EI): m/z [M] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{BrO}_2$: 412.1032; found 412.1024.

(*4aR**,*9aR**,*12R**)-7-Methoxy-12-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **12e**

Colorless oil; Rf = 0.378 (silica gel, Petroleum ether: EtOAc (95:5)).

^1H NMR (300 MHz, CDCl_3) δ = 7.54 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.71 (dd, J = 8.2, 2.3 Hz, 1H), 4.58 (dd, J = 8.8, 5.3 Hz, 1H), 4.00 (d, J = 12.1 Hz, 1H), 3.84 (d, J = 12.1 Hz, 1H), 3.80 (s, 3H), 3.50 (d, J = 15.3 Hz, 1H), 2.31 (d, J = 15.3 Hz, 1H), 2.07–2.02 (m, 2H), 1.65–1.50 (m, 3H), 1.43–1.26 (m, 5H).

^{13}C NMR (101 MHz, CDCl_3) δ = 158.9, 154.4, 146.9, 143.0, 142.1, 129.6 (q, J = 42.3 Hz), 126.2, 125.3 (q, J = 4 Hz), 122.0, 112.3, 111.8, 75.0, 70.2, 55.5, 46.5, 44.3, 41.5, 31.5, 28.5, 22.7, 22.4, 20.7.

^{19}F NMR (376 MHz, CDCl_3) δ = -62.44.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₄H₂₅F₃NaO₂: 425.1699; found 425.1706.

(4*aR**,9*aS**,12*S**)-5-Methoxy-12-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-9H-4*a*,9*a*-(ethanooxymethano)fluorene **13e**

Yellow oil; R_f = 0.600 (silica gel, petroleum ether: EtOAc (90:5)).

¹H NMR (400 MHz, CDCl₃) δ = 7.53 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.12 (dd, *J* = 8.3, 7.3 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 4.02 (d, *J* = 12.1 Hz, 1H), 3.80 (d, *J* = 12.1 Hz, 1H), 3.75 (s, 3H), 3.49 (d, *J* = 15.1 Hz, 1H), 2.76 (d, *J* = 13.7 Hz, 1H), 2.34 (d, *J* = 15.3 Hz, 1H), 1.90 – 1.84 (m, 2H), 1.71 – 1.61 (m, 1H), 1.45 – 1.17 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ = 159.5, 146.9, 140.0, 138.4, 129.7 (q, *J* = 42.3 Hz), 129.0, 126.1, 125.5 (q, *J* = 4 Hz), 123.6, 123.3, 117.1, 111.3, 81.1, 77.4, 75.8, 55.3, 40.5, 39.4, 39.1, 28.0, 25.7, 17.9.

¹⁹F NMR (376 MHz, CDCl₃) δ = -62.44.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₄H₂₅F₃NaO₂: 425.1699; found 425.1695.

Methyl 4-((4*aR**,9*aR**,12*R**)-7-methoxy-1,2,3,4-tetrahydro-9H-4*a*,9*a*-(ethanooxymethano)fluoren-12-yl)benzoate **12f**

Viscous oil; R_f = 0.30 (silica gel, petroleum ether: EtOAc (90:10)).

¹H NMR (300 MHz, CDCl₃) δ = 7.96 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.58 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.99 (d, *J* = 12.1 Hz, 1H), 3.89 (s, 3H), 3.83 (d, *J* = 12.1 Hz, 1H), 3.78 (s, 3H), 3.51 (d, *J* = 15.2 Hz, 1H), 2.31 (d, *J* = 15.2 Hz, 1H), 2.13 – 1.95 (m, 2H), 1.70 – 1.58 (m, 1H), 1.45 – 1.25 (m, 7H).

¹³C NMR (76 MHz, CDCl₃) δ = 167.1, 158.9, 148.0, 143.0, 142.2, 129.7, 129.1, 125.8, 122.0, 112.2, 111.8, 75.2, 70.1, 55.5, 52.2, 46.5, 46.1, 44.3, 41.5, 31.5, 28.5, 22.7, 22.4.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₅H₂₈NaO₄: 415.1879; found 415.1879.

Methyl 4-((4*aR**,9*aS**,12*S**)-5-methoxy-1,2,3,4-tetrahydro-9H-4*a*,9*a*-(ethanooxymethano)fluoren-12-yl)benzoate **13f**

Pale yellow oil; R_f = 0.37 (silica gel, petroleum ether: EtOAc (90:10)).

¹H NMR (300 MHz, CDCl₃) δ = 7.95 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.12 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 4.63 (dd, *J* = 12.0, 2.2 Hz, 1H), 4.02 (d, *J* = 12.1 Hz, 1H), 3.89 (s, 3H), 3.79 (d, *J* = 12.1 Hz, 1H), 3.76 (s, 3H), 3.50 (d, *J* = 15.2 Hz, 1H), 2.76 (d, *J* = 14.1 Hz, 1H), 2.35 (d, *J* = 15.2 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.72 – 1.60 (m, 1H), 1.46 – 1.16 (m, 6H).

¹³C NMR (126 MHz, CDCl₃) δ = 167.2, 157.0, 148.4, 143.8, 135.8, 129.7, 129.1, 127.8, 125.8, 118.9, 109.3, 74.8, 69.8, 55.3, 52.1, 49.1, 44.0, 43.6, 41.9, 31.8, 28.1, 23.5, 22.8.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₅H₂₈NaO₄: 415.187980; found 415.187921.

(4*aR**,9*aR**,12*R**)-7-methoxy-12-phenyl-1,2,3,4-tetrahydro-9H-4*a*,9*a*-(ethanooxymethano)fluorene **12g**

Colorless oil; R_f = 0.350 (silica gel, petroleum ether: EtOAc (95:5)).

¹H NMR (500 MHz, CDCl₃) δ = 7.34 – 7.27 (m, 4H), 7.24 – 7.19 (m, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.53 (dd, *J* = 11.3, 2.6 Hz, 1H), 4.00 (d, *J* = 12.2, 1H), 3.83 (d, *J* = 12.2, 1H), 3.79 (s, 3H), 3.54 (d, *J* = 15.1 Hz, 1H), 2.31 (d, *J* = 15.2 Hz, 1H), 2.13 – 1.96 (m, 1H), 1.66 – 1.48 (m, 1H), 1.44 – 1.22 (m, 5H).

¹³C NMR (126 MHz, CDCl₃) δ = 158.8, 143.2, 142.8, 142.5, 128.4, 127.5, 126.0, 122.0, 112.2, 111.8, 75.7, 70.2, 55.5, 46.6, 46.1, 44.4, 41.5, 31.5, 28.5, 22.7, 22.5.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₃H₂₆NaO₂: 357.1825; found 357.1823.

Funding Information

Y.N. thanks MESRI for a Ph-D grant (2019-2021)

Acknowledgment

CNRS and Université de Lyon1 are warmly thanked for financial support.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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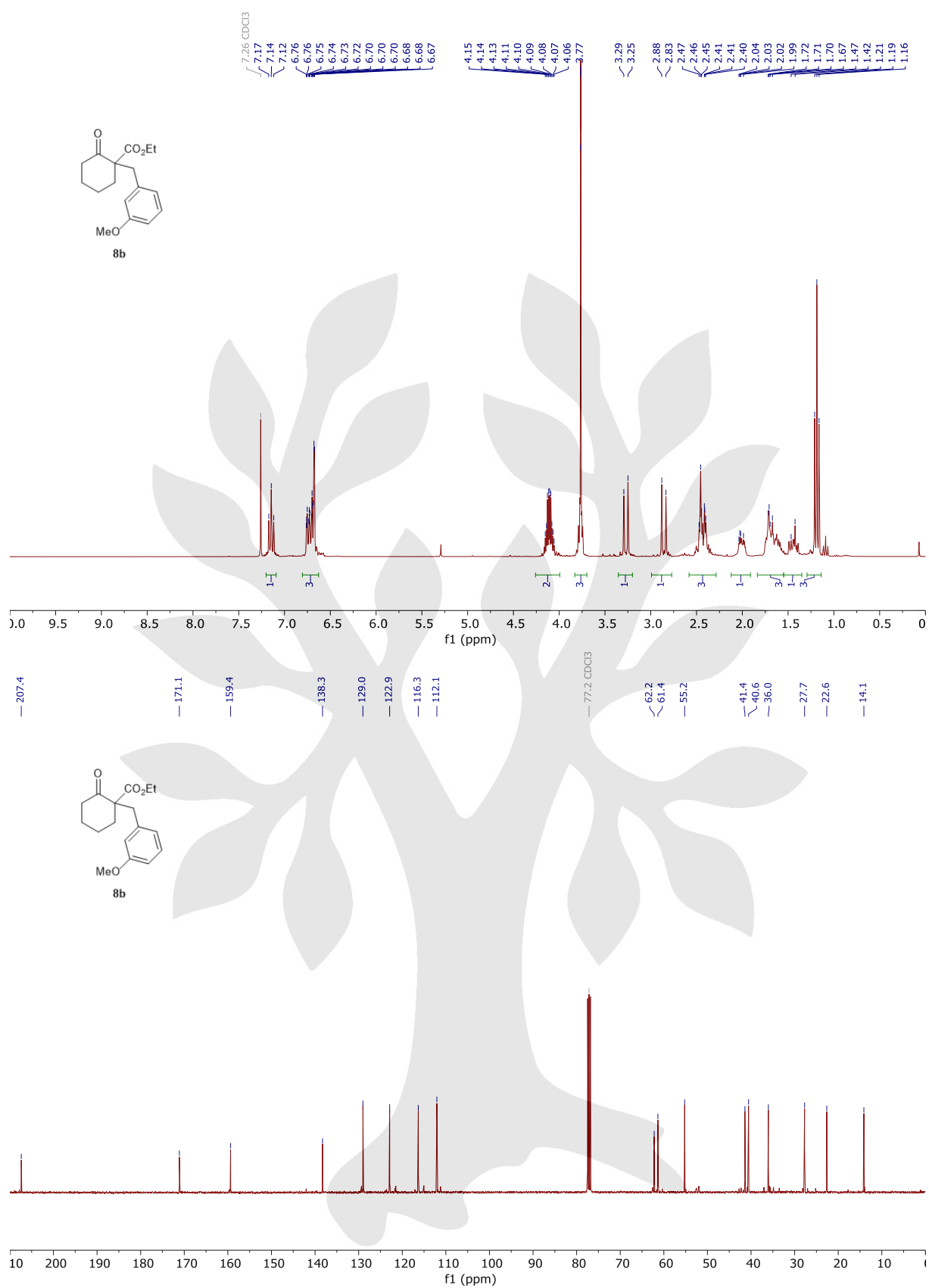
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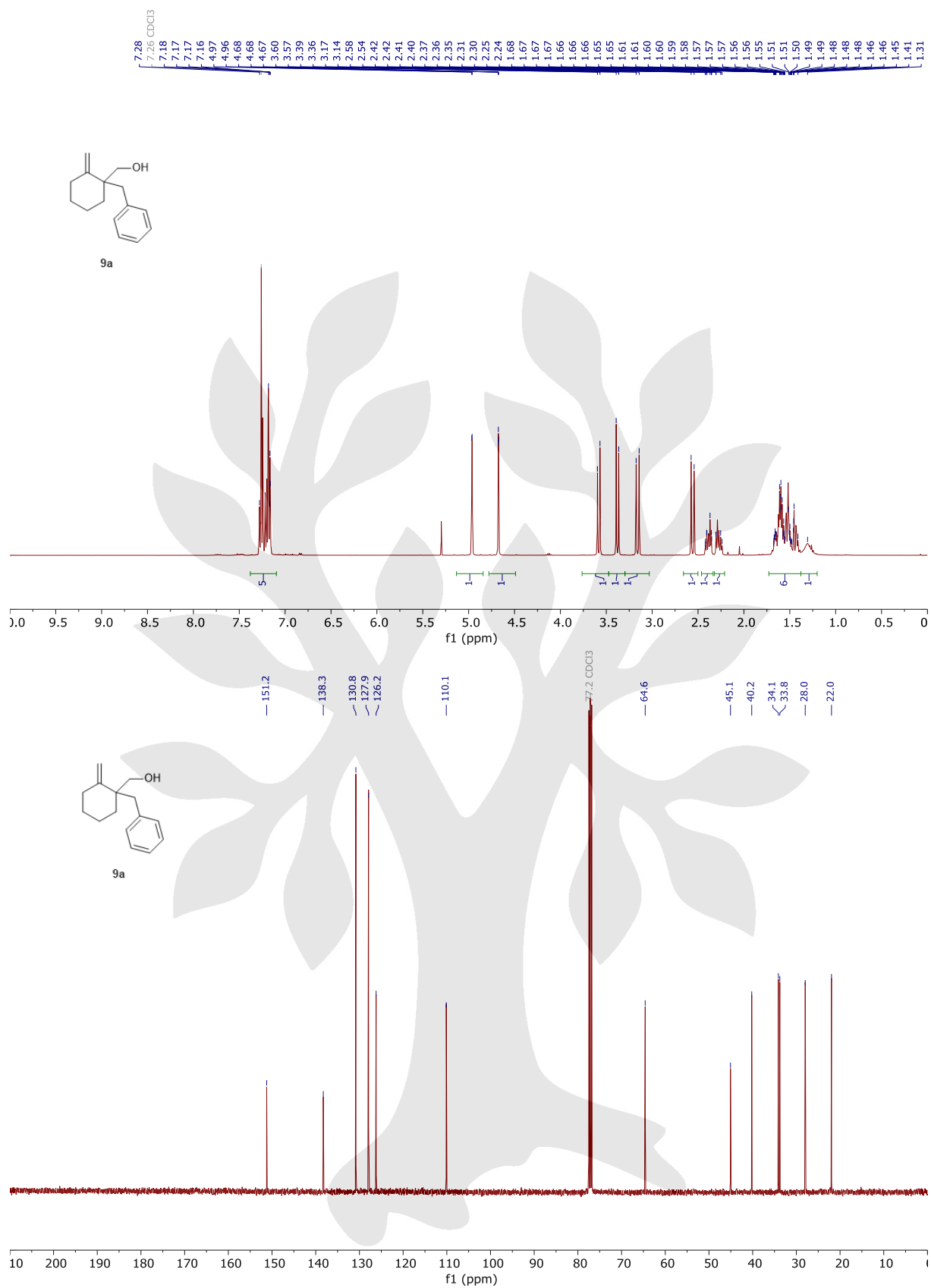
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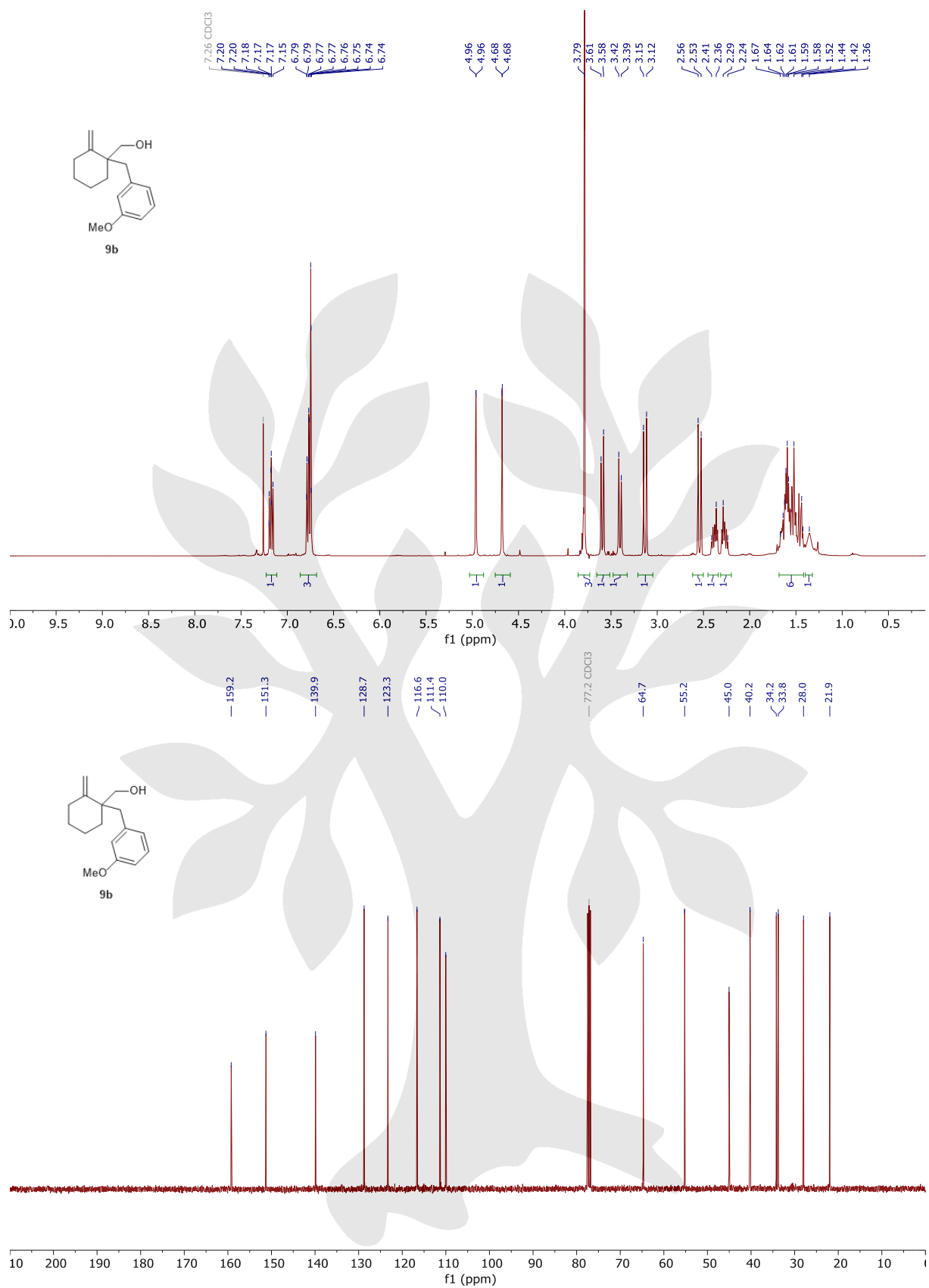
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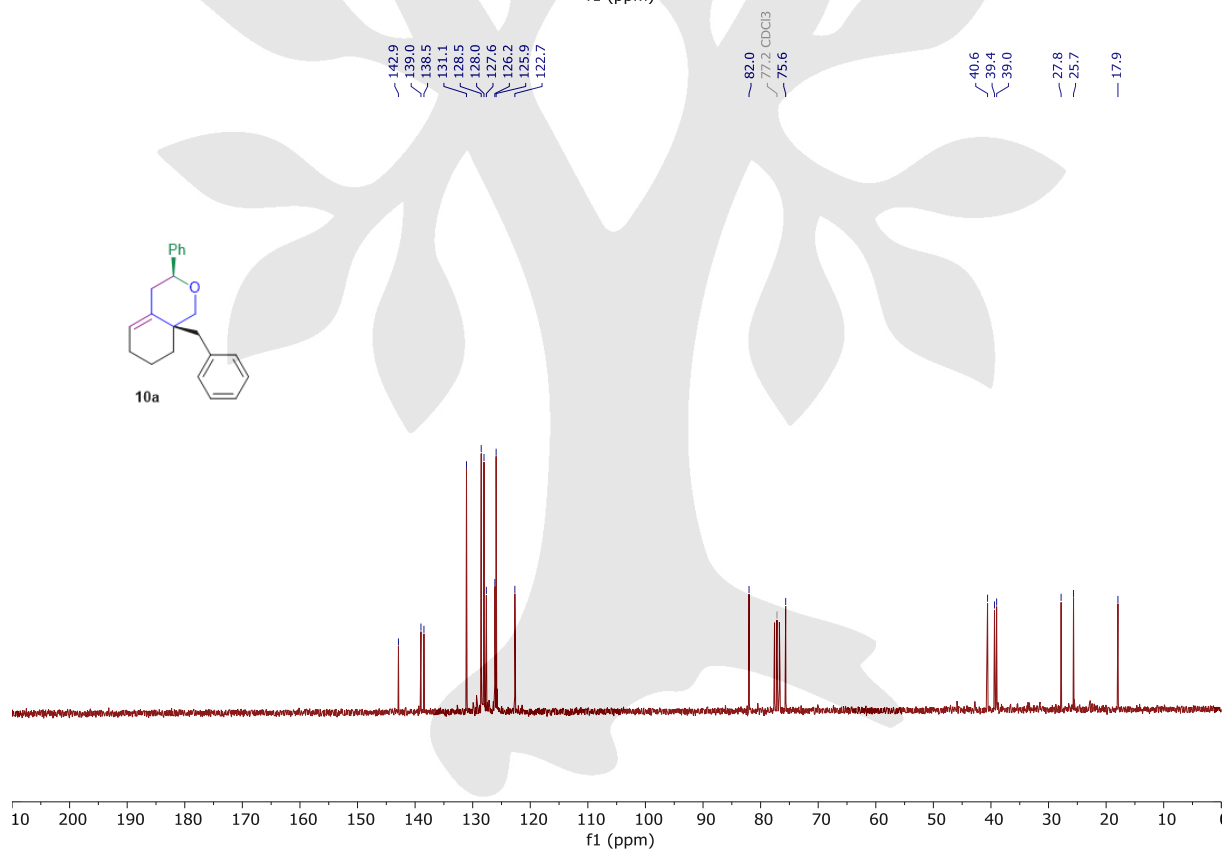
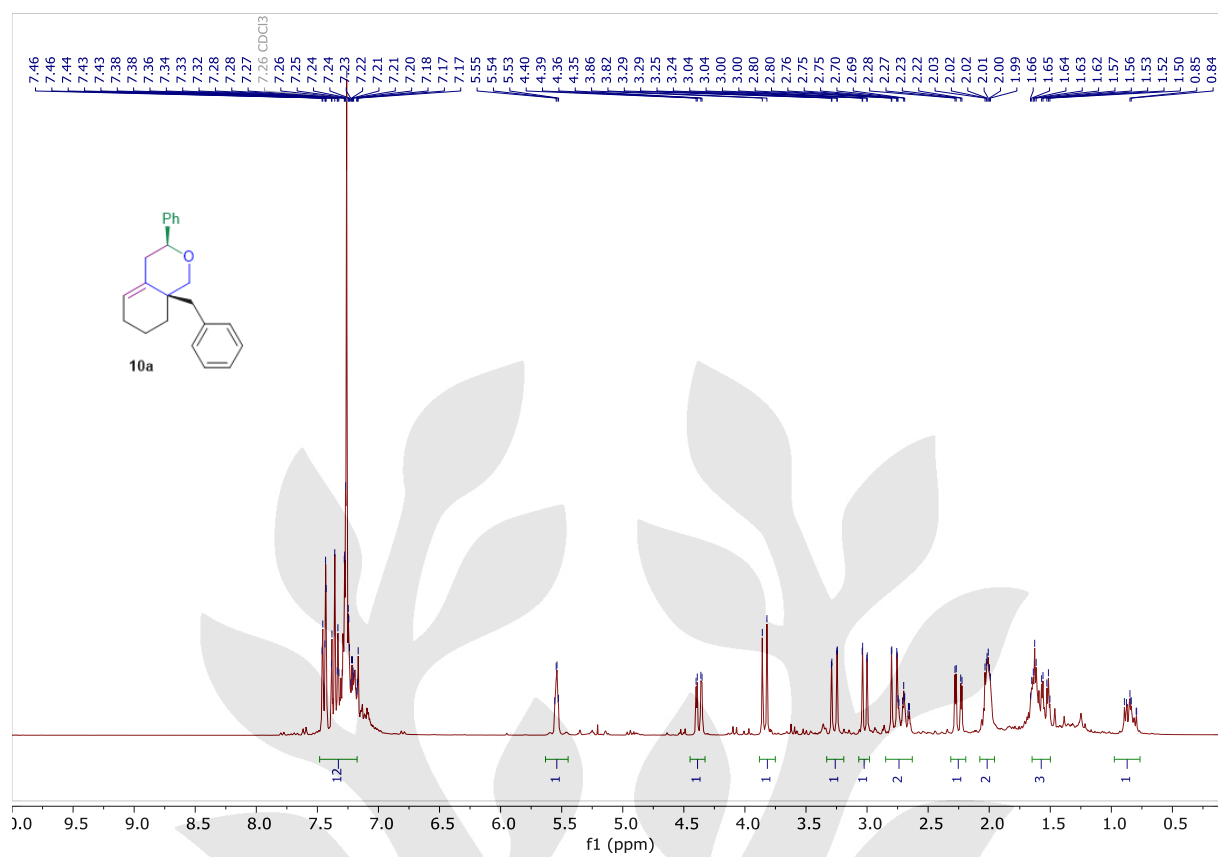
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¹ H-NMR and ¹³ C-NMR spectra for compound 13c	page 15
¹ H-NMR and ¹³ C-NMR spectra for compound 12d	page 16
¹ H-NMR and ¹³ C-NMR spectra for compound 13d	page 17
¹ H-NMR and ¹³ C-NMR spectra for compound 12e	page 18
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¹⁹ F-NMR spectra for compound 13e	page 21
¹ H-NMR and ¹³ C-NMR spectra for compound 12f	page 22
¹ H-NMR and ¹³ C-NMR spectra for compound 13f	page 23
¹ H-NMR and ¹³ C-NMR spectra for compound 12g	page 24

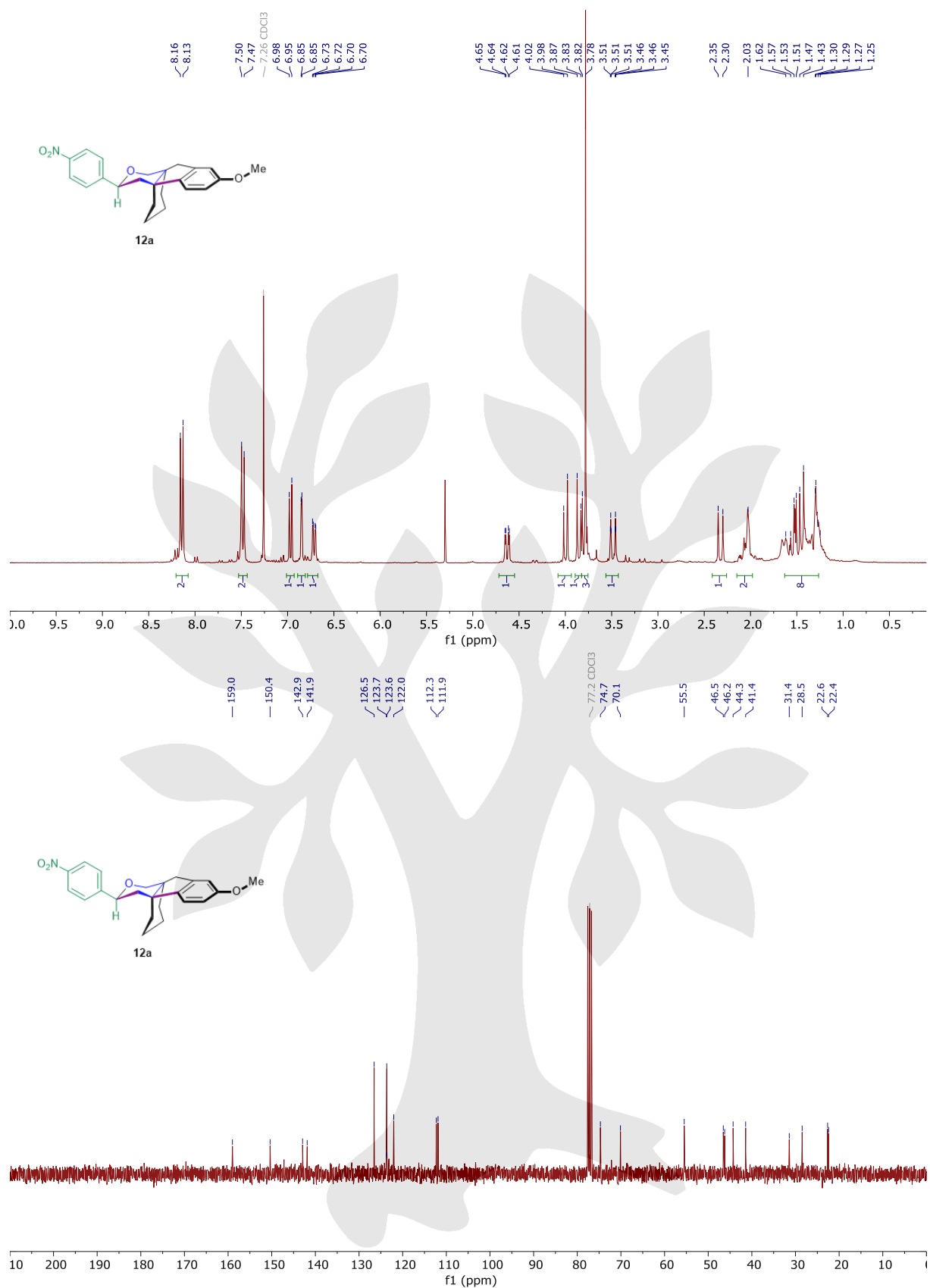


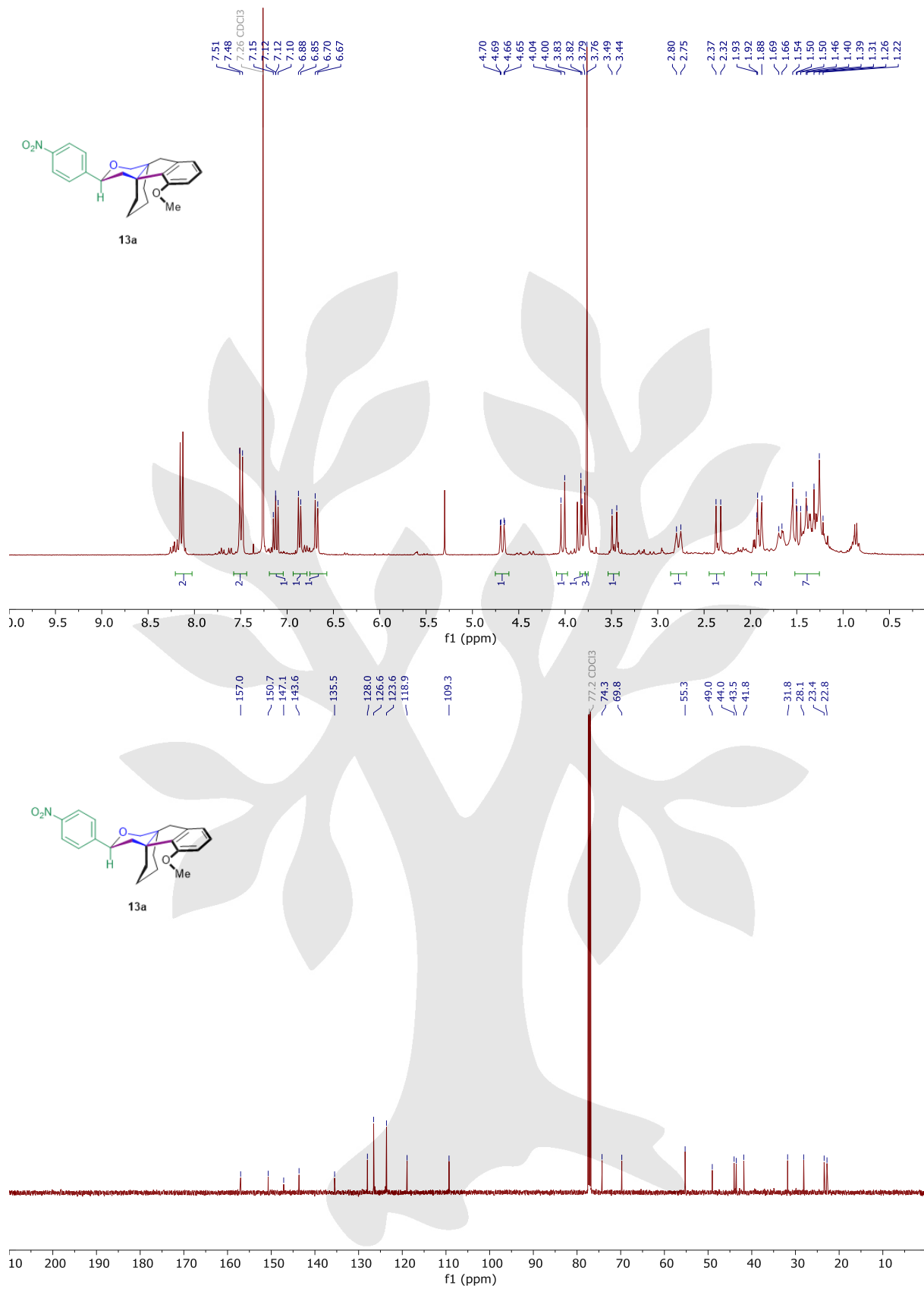




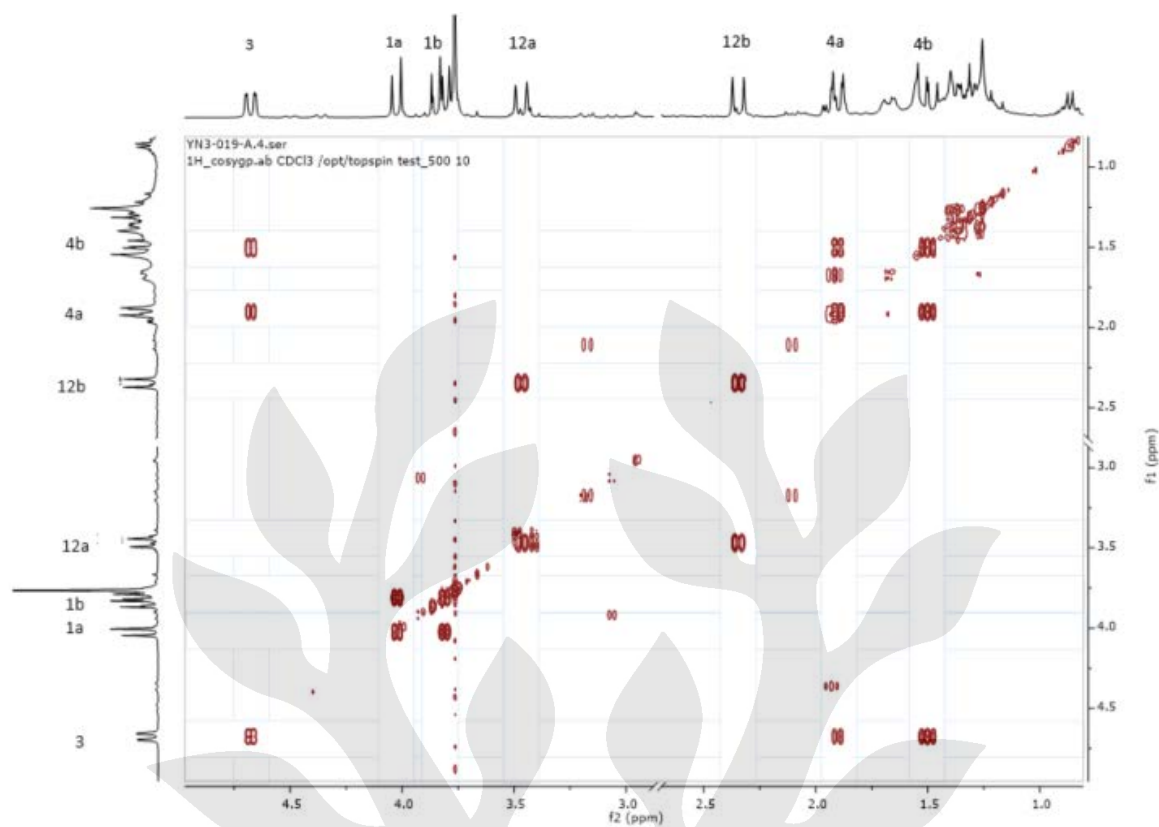




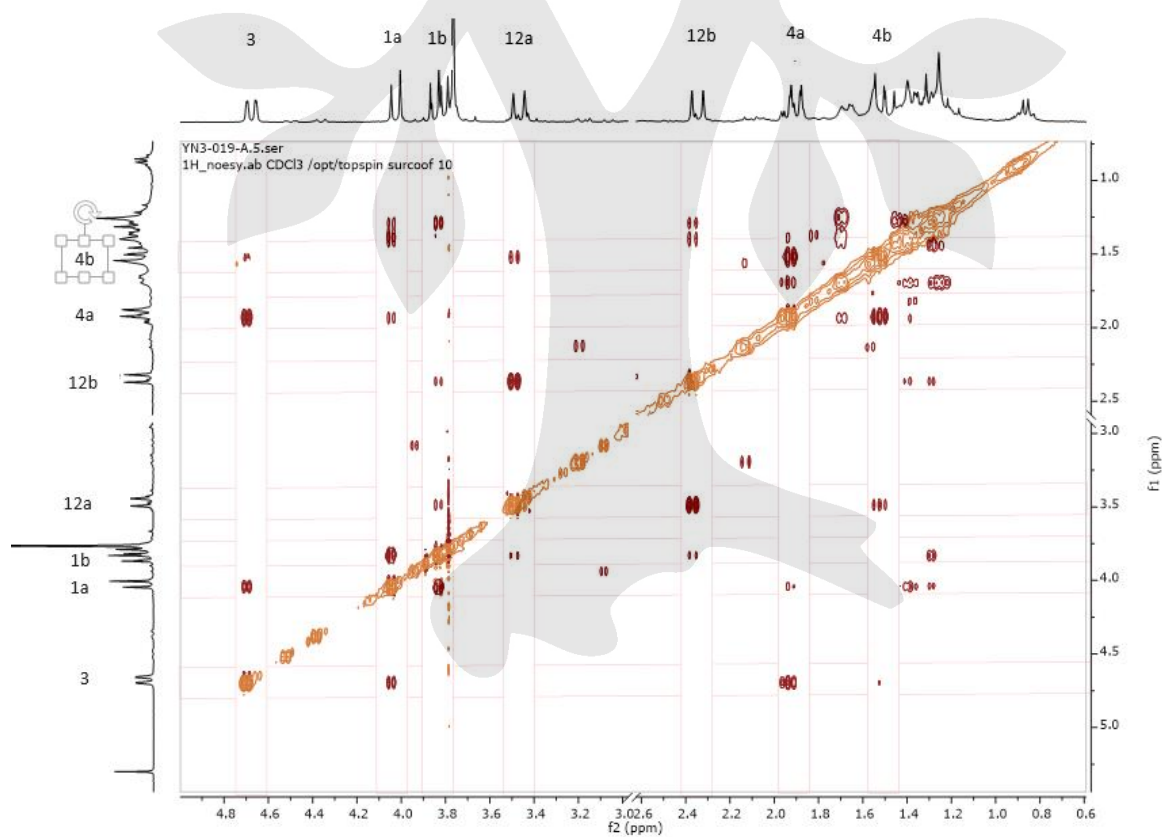


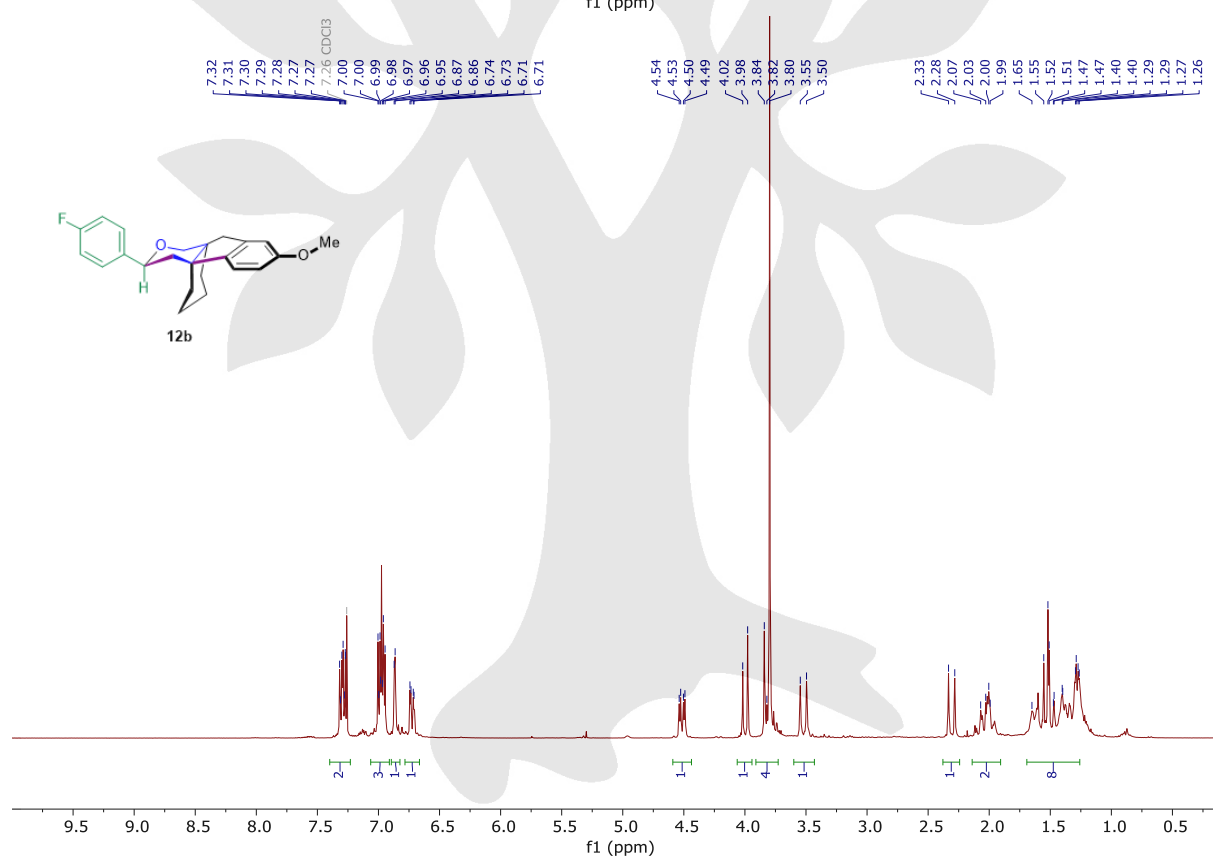
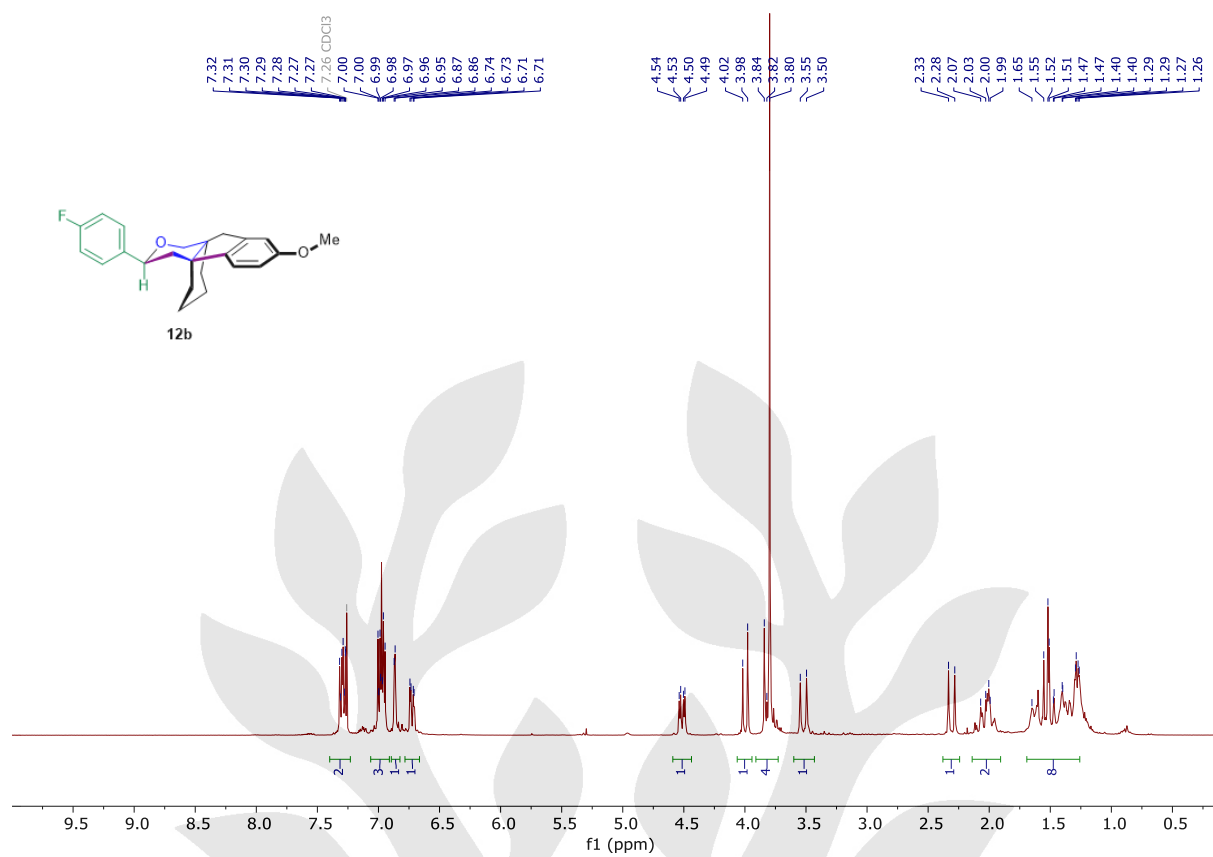


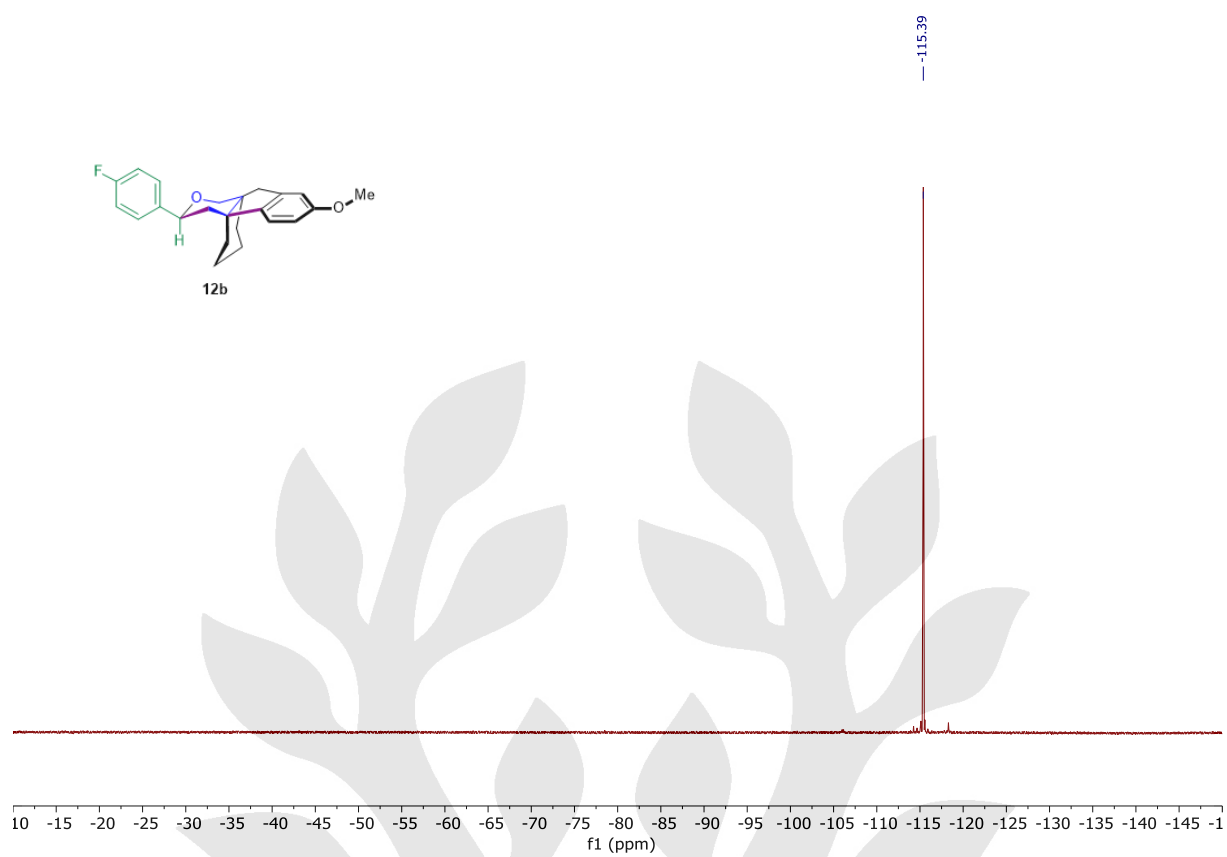
2D-COSY NMR for **13a** (500MHz, C₆D₆)

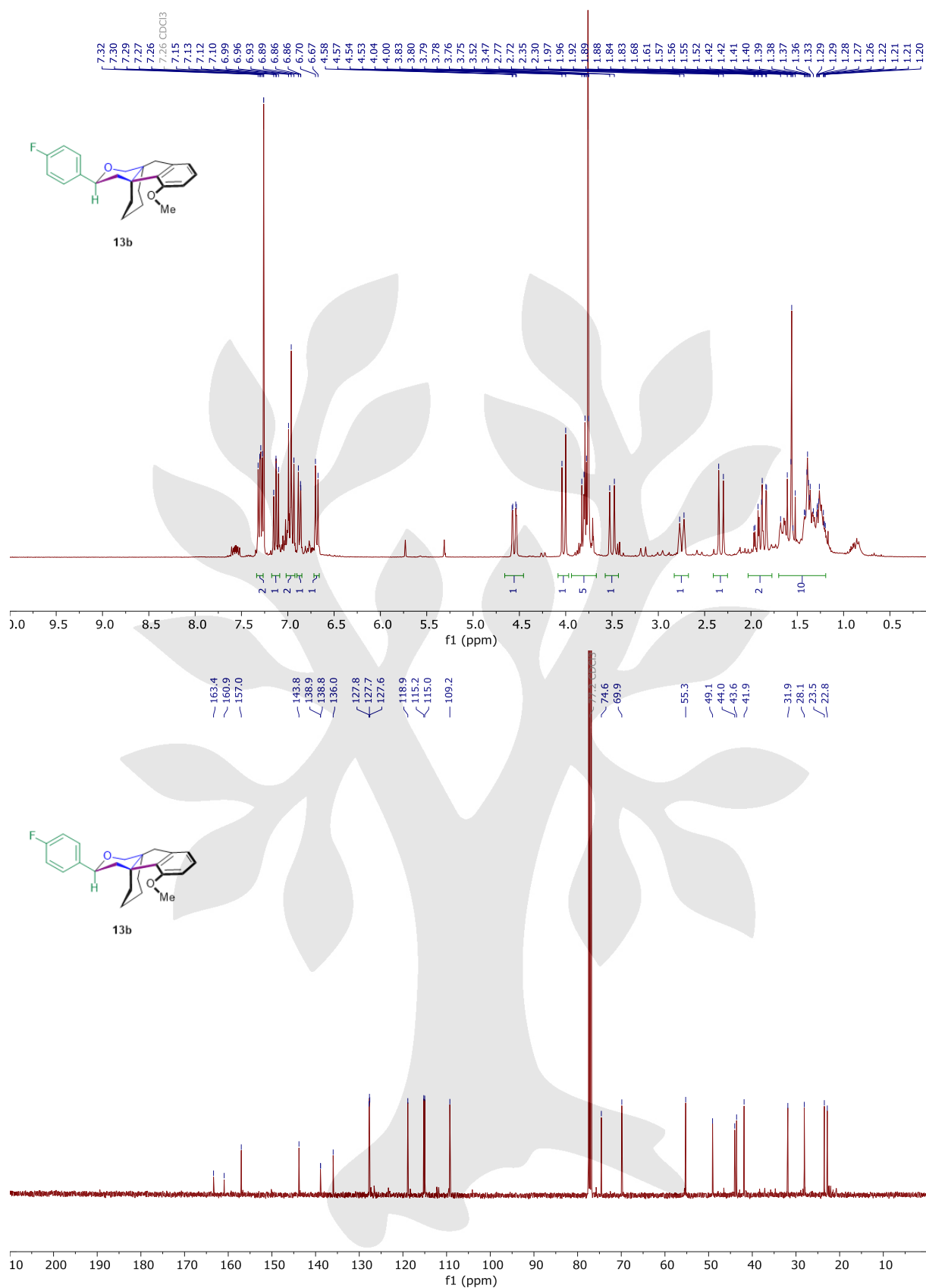


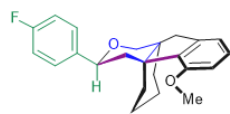
NOESY NMR spectra for **13a** (500MHz, C₆D₆)











13b

