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PII: S0040-4020(14)00826-6

DOI: 10.1016/j.tet.2014.05.108

Reference: TET 25657

To appear in: *Tetrahedron*

Received Date: 9 April 2014

Revised Date: 22 May 2014

Accepted Date: 29 May 2014

Please cite this article as: Gao Y, Shan D, Jia Y, Intramolecular Larock Indole Synthesis for the Preparation of Tricyclic Indoles and Its Application in the Synthesis of Tetrahydropyrroloquinoline and Fargesine, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.05.108.

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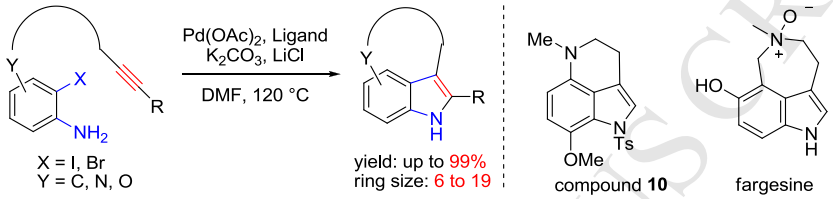
Yan Gao, Dong Shan, Yanxing Jia*

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing 100191, China.



Tetrahedron
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Intramolecular Larock Indole Synthesis for the Preparation of Tricyclic Indoles and Its Application in the Synthesis of Tetrahydropyrroloquinoline and Fargesine

Yan Gao[a], Dong Shan[a], and Yanxing Jia[a,b,*]

[a] State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing 100191, China
[b] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1 Palladium-catalyzed
Keyword_2 Total synthesis
Keyword_3 Natural product
Keyword_4 Indole alkaloids
Keyword_5 Tetrahydropyrroloquinoline

ABSTRACT

A general and efficient strategy for fused tricyclic indoles from substituted 2-halogenanilines via the palladium-catalyzed intramolecular Larock indolization process has been developed. Using this strategy, a number of 3,4- and 3,5-fused indoles with a variety of ring sizes can been prepared. The utility of this method is demonstrated through the synthesis of the known tetrahydropyrrolo[4,3,2-de]quinoline **10** and the first total synthesis of fargesine.

1. Introduction

The indole nucleus is present in many biological important natural products and pharmaceuticals.[1] The family of the 3,4-fused indoles (those in which the 3-position of the indole is bridged to the 4-position) also comprise a number of biologically active natural and unnatural products.[2] These include the well-known dehydrobufotenine,[3] lysergic acid,[4] welwistatin,[5] communesin F,[6] dragmacidin E,[7] decursivine,[8] penitrem D,[9] indolactam V,[10] and diazonamide A,[11] where the indole is bridged with different ring sizes (6-, 7-, 8-, 9-, and 12-membered rings) and various tethers linked by carbon, nitrogen, and oxygen atoms in different positions (Figure 1). Accordingly, lysergic acid is a representative natural product of the ergot alkaloid family and is also a precursor for a wide range of ergoline alkaloids, its derivatives, such as α-ergocryptine, bromocryptine, and ergometrine are clinically used. Indolactam V, the core structure of tumor-promoting teleocidins, can not only selectively activate the protein kinase C (PKC), but also direct differentiation of human embryonic stem cells (ESCs) into pancreatic progenitors. Diazonamide A exhibits potent antimitotic activity.

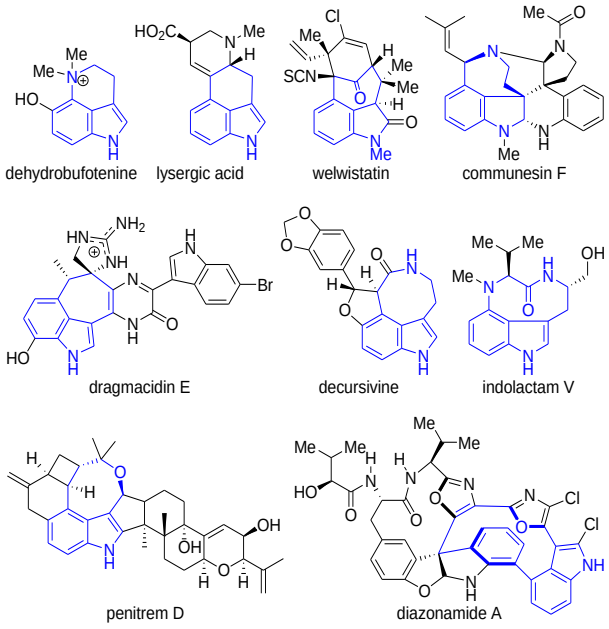
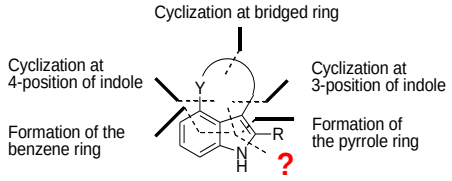


Figure 1. Selected examples of 3,4-fused indole alkaloids.

The synthesis of 3,4-fused indole moieties have been investigated by many organic chemists, and various strategies have been developed (Scheme 1): 1) cyclization at 4-position of indole starting from 3-substituted indole derivatives;[12] 2) cyclization at 3-position of indole starting from 4-substituted indole derivatives;[13] 3) cyclization at bridged ring starting from 3,4-substituted indole derivatives;[14] 4) formation of the benzene ring starting from substituted pyrrole derivatives;[15] 5) Formation of the pyrrole ring starting from substituted benzene derivatives.[16] However, most of the synthesis of 3,4-fused indole

* Corresponding author. Tel.: +86-10-8280-5166; fax: +86-10-8280-2724; e-mail: yxjia@bjmu.edu.cn

adopted the strategy 1-3, which are based on the introduction of functional groups to the 3- and/or 4-positions of existing indoles followed by cyclization. As a further complication, the direct functionalization of the indole 4-position is extremely difficult since most electrophiles prefer attacking the 5- or 7-position. The preparation of 4-substituted indole derivatives, the precursor of 3,4-fused tricyclic indoles, normally requires multi-step synthesis. Thus, the development of general synthetic methods for the rapid synthesis of these skeletons in a single operation remains an important challenge facing organic chemists. We[17] have recently reported a palladium-catalyzed intramolecular Larock indolization process.[18] Herein, we report a full account of our exploration in the developing this method.

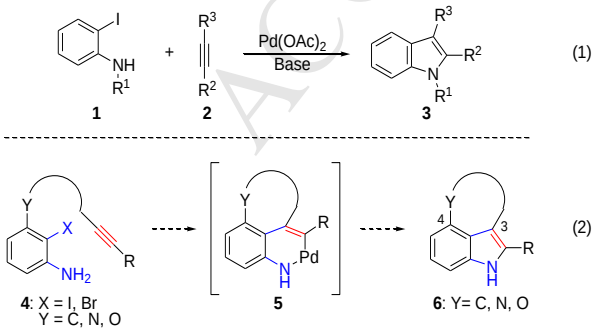


Scheme 1. Strategy for the synthesis of 3,4-fused tricyclic indoles.

2. Results and discussions

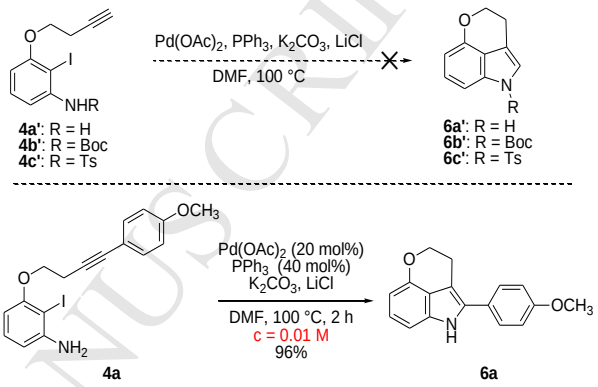
2.1. Preparation of allylic alcohol substrates

In connection with some of our work on the total synthesis of 3,4-fused indole alkaloids,[4a,4b,8b-d,10a,14a-d] we have synthesized the 3,4-briged ring by using Witkop photocyclization, Heck reaction, S_N2 reaction et al. It is almost one molecular, one strategy. We then envisaged if we could identify a general approach for the rapid access to a variety of 3,4-fused tricyclic indoles, which would not only expedite the total synthesis of 3,4-fused indole alkaloids, but also enable the modular construction of a library of their analogues for further medicinal chemistry studies. Further considering palladium-catalyzed transformations generally require only a catalytic amount of a metal complex and tolerate a large number of functional groups, and have thus made a major impact on the synthesis of indoles. We were curious whether a palladium-catalyzed intramolecular Larock indolization process could be applied for the preparation of such polycyclic indoles (Scheme 2).[19] To the best of our knowledge, although intramolecular Larock indolization has been reported in the literaure,[20] the synthesis of 3,4-fused tricyclic indole moieties via intramolecular Larock indole synthesis has never been reported.



Scheme 2. Synthesis of 3,4-fused tricyclic indoles via intramolecular Larock indolization.

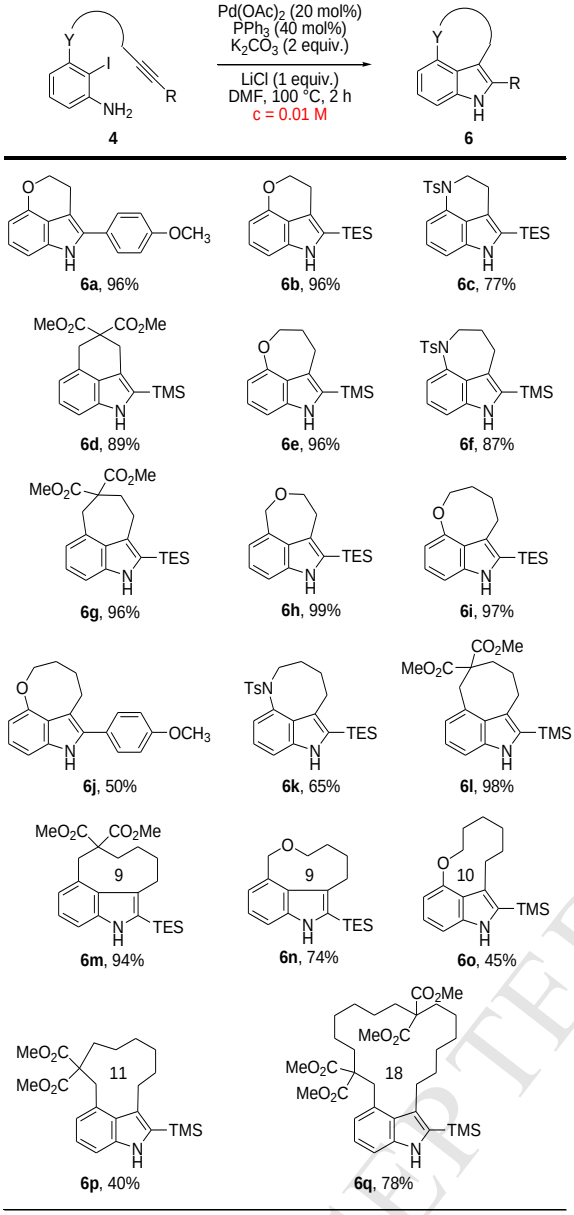
To test the feasibility of this concept, terminal alkynes compound **4a′-4c′** were initially prepared and subjected to the typical Larock indolization condition (Scheme 3). Unfortunately, no desired product **6a′-6c′** was obtained. We gradually realize that the terminal alkynes don't work well for the Larock indole synthesis.[19] Thus, the internal alkyne **4a** was then prepared and subjected to the typical Larock indolization condition. Gratifyingly, the desired 3,4-fused tricyclic indole product **6a** was obtained cleanly in 96% yield as the only product (Scheme 3). It is worth to mention that although the use of $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) at the same substrate concentration gave **6a** in 87% yield, the use of a lower amount of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) or higher substrate concentration (0.05 M) resulted in decreased reaction efficiency.



Scheme 3. Realization of the intramolecular Larock indolization.

With this encouraging initial result in hand, we examined the substrate scope by using different sets of 2-iodoanilines containing carbon, oxygen or nitrogen tethers (Table 1). In all cases, good to excellent yields of the desired tricyclic indoles (**6a-6q**) were obtained. The substrates leading to six- and seven-membered ring fused indoles were first examined and the desired cyclization products were obtained in excellent yield (Table 1, **6a-6h**). The intramolecular reaction was next applied to generate 3,4-medium-ring (8- to 11-membered rings) fused indoles, which were thought to be more hard to prepare.[21] To our surprise, the desired 3,4-fused tricyclic indole products could be still obtained in good to excellent yield (Table 1, **6i-6n**), although the 10-membered and 11-membered tricyclic products **6o** and **6p** were formed in moderate yield. Our method could be also applied to the synthesis of 3,4-macrocycle (>12-membered rings) indoles. In this case, the 18-membered tricyclic product **6q** could be obtained in 78% yield.

Table 1
Synthesis of 3,4-fused tricyclic indole systems via an intramolecular Larock indole synthesis[a,b]

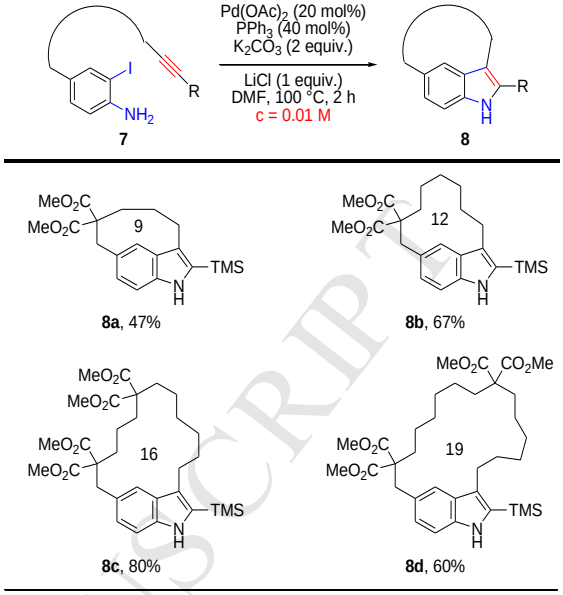


[a] General reaction conditions: concentration 0.01M in DMF, 0.20 equiv of $Pd(OAc)_2$, 0.40 equiv of Ph_3P, 2.0 equiv of K_2CO_3, 1.0 equiv of LiCl, 100 °C.

[b] Isolated yield.

Encouraged by the results for the 3,4-fused tricyclic indoles, without individual optimization, the scope of the intramolecular larock reaction was examined for the preparation of 3,5-fused tricyclic indoles from their corresponding precursor **7** (Table 2). The reaction was found to be compatible with a variety of ring sizes. The medium-ring (9-membered rings) fused indoles **8a** could be obtained in 47% yield. The macrocycle (12-membered rings) fused indoles **8b** was obtained in 67% yield. Again surprisingly, the macrocycle (16 or 19-membered rings) 3,5-fused tricyclic indoles **8c** and **8d** could be obtained in 80% and 60% yield, respectively.

Table 2
Synthesis of 3,5-fused tricyclic indole systems via an intramolecular Larock indole synthesis[a,b]

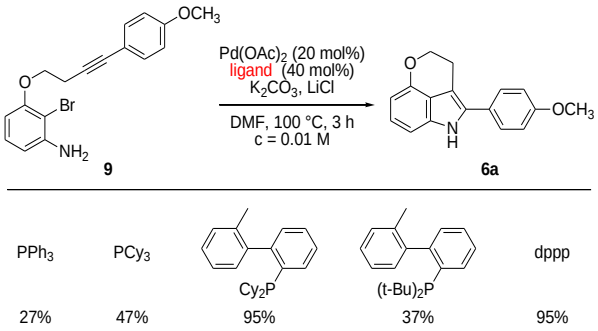


[a] General reaction conditions: concentration 0.01M in DMF, 0.20 equiv of $Pd(OAc)_2$, 0.40 equiv of Ph_3P, 2.0 equiv of K_2CO_3, 1.0 equiv of LiCl, 120 °C.

[b] Isolated yield.

After examining the reaction of 2-iodoaniline derivatives, we next investigated the substrate scope by using the inert 2-bromoaniline derivatives, because of their lower cost and the wider of diversity of available compounds. Compound **9** was synthesized and used as a model compound. When compound **9** was subjected to the optimal reaction condition, the desired product was obtained in only 27% yield along with recovery of some starting material. Thus, a variety of electron-rich bulky phosphine ligands were screened to increase the yield.[22] As shown in Table 3, Me-phos and dppp turned out to be the ligands of choice and gave the desired product in 95% yield, although all tested ligands could furnish the desired product.

Table 3
Reaction optimization of 2-bromoaniline derivative **9**



2.2. Synthesis of compound 10

To probe the utility of our method, conversion of compound **6c** to known tetrahydropyrroloquinoline **10** was firstly made.[23] The 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system was first recognized as an important structural motif of natural products when the structure of the toad poison dehydrobufotenine was elucidated (Figure 2).[23] Since then, several marine alkaloids, such as damirones, discorhabdines, and makaluvamines, have been isolated and characterized based on the tetrahydropyrroloquinoline nucleus.

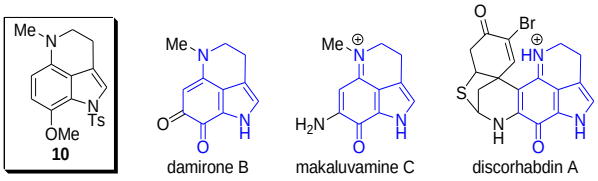
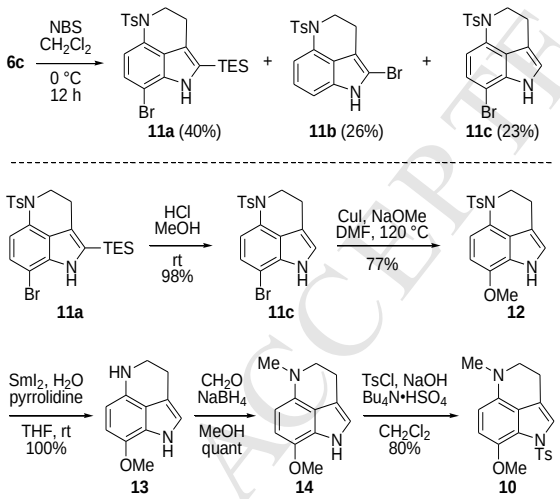


Figure 2. Selected examples of 3,4-fused indole alkaloids.

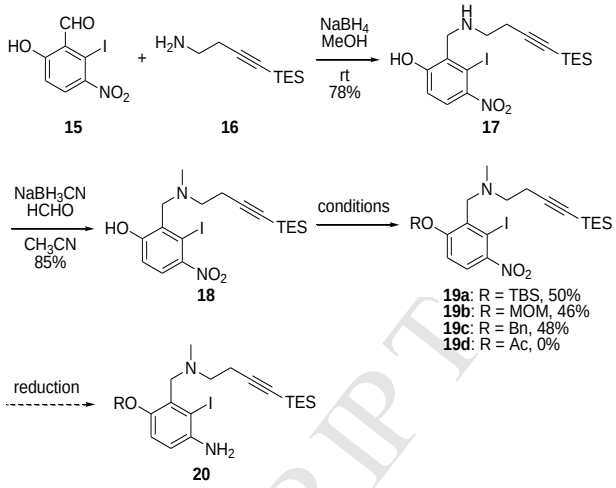
Bromination of compound **6c** gave the desired 7-bromide **11a** in 40% yield, 2-bromide **11b** in 26% yield as well as 2-de-TES 7-bromide **11c** in 23% yield (Scheme 4).[24] It is worth to mention that this bromination reaction is very sensitive to the reaction condition. When the reaction was conducted at room temperature, the main product was 2-bromine product **11b**. Compound **11a** could be readily converted to **11c** by treatment with HCl in MeOH. Ullmann reaction of **11c** with NaOMe provided the corresponding product **12** in 77% yield.[25] Reductive removal of Ts group gave the compound **13** in quantitative yield. Finally, reductive amination of **13** with formaldehyde with $NaBH_4$ followed by protection of indole NH with TsCl gave the known product **10** in 80% yield.



Scheme 4. Synthesis of compound **10**.

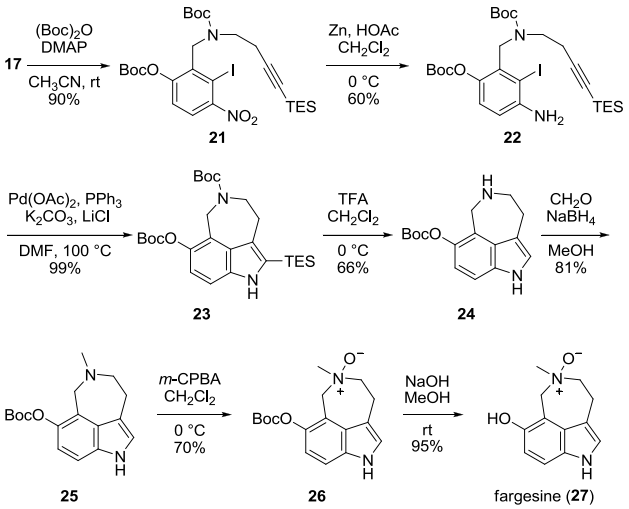
2.3. Total synthesis of fargesine

To further probe the utility of our method, we applied it to the total synthesis of the natural product fargesine. Fargesine, a new *N*-oxide alkaloid, was isolated by Zhu and co-workers from the root and stem of *Evodia fargesii* Dode, whose fruits are employed as a traditional medicine used as an analgesic against bellyache and to relieve cough after measles.[26] In addition, the total synthesis of fargesine has not been reported.



Scheme 5. Preparation of allylic alcohols **3a**-**3h**.

Our synthesis of fargesine was illustrated in Scheme 5. Reductive coupling of the known aldehyde **15**[27] and the primary amine **16** afforded the secondary amine **17** in 78% yield. Reductive amination of **17** with formaldehyde with $NaBH_3CN$ provided tertiary amine **18** in 85% yield. Firstly, protection of phenol with TBSCl gave the desired product **19a** in 50% yield. However, attempts to reduction of the nitro group with Zn in HOAc did not give the desired aniline **20**. Changing the protection group to MOM or Bn gave the same results. We gradually realize the reason might be the special structure of compounds **19** and/or **20**, which is liable to undergo an elimination of protonated amino group under acidic conditions to generate the chemically labile ortho-quinone methide intermediates. Attempt to protection of phenol using Ac did not afford the desired product due to compound **18** is a good leaving group. Taking these problems into consideration, an electron-withdrawing group was next planned to be introduced at the secondary amine **17** to reduce these effects.



Scheme 6. Total synthesis of fargesine.

The completion of the synthesis of fargesine is depicted in Scheme 6. Protection of both phenol and nitrogen of amine **17**

with Boc_2O gave **21** in 90% yield. Gratefully, reduction of the nitro group of **21** with Zn in HOAc provided the desired cyclization precursor 2-iodoaniline **22** in 60% yield. Treatment of **22** under our optimized reaction condition successfully afforded the desired tricyclic product **23** in nearly quantitative yield. Selective deprotection of *N*-Boc and TES with TFA gave **24** in 66% yield. Reductive amination of **24** followed by oxidation of **25** with *m*-CPBA provided the desired *N*-oxide **26** in 70% yield.[28] Finally, removal of *O*-Boc of **26** under basic condition gave fargesine (**27**) in 95% yield, whose physical properties (NMR, MS) were essentially identical to those reported for the natural material.[26] Thus, our first total synthesis of fargesine was achieved in eight steps and in 15% overall yield from the known aldehyde **15**.

3. Conclusion

In conclusion, we have developed a new and general strategy for the construction of 3,4-fused and 3,5-fused tricyclic indoles, the key structural motif of a number of natural products and bioactive molecules, via an intramolecular Larock indolization reaction. The scope and generality of the reaction was examined. The utility of this method is demonstrated through the synthesis of the known tetrahydropyrroloquinoline **10** and the first total synthesis of fargesine. The application of this methodology in the total synthesis of other natural products and related systems for bioactivity studies is in progress in our laboratory and will be reported in due course.

4. Experimental Section

4.1. General

Infrared spectra were recorded on Thermo Nicolet Nexus-470 FT-IR spectrometers. Mass spectra were recorded on a Bruker APEX IV FT-MS (ESI) spectrometer. ^{1}H NMR spectra were recorded at Bruker Avance III 400 MHz NMR spectrometer, ^{13}C NMR spectra were obtained by using the same NMR spectrometers unless otherwise stated. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in the deuterated solvent as an internal standard. Flash column chromatography was performed using silica gel (200-300 mesh) with solvents distilled prior to use. Visualization was achieved under a UV lamp (254 nm and 365 nm), and by developing the plates with phosphomolybdic acid in ethanol.

4.2. Preparation of 3,5-fused tricyclic indoles 8a-8d

To a stirred solution of the 2-iodo aniline (0.10 mmol) in anhydrous DMF (10 mL) was added PPh_3 (0.04 mmol), K_2CO_3 (0.20 mmol) and LiCl (0.10 mmol) successively under argon atmosphere. After discharging oxygen with argon for 0.5 h, $Pd(OAc)_2$ (0.02 mmol) was added under argon, then the solution was heated at 100 ^{o}C for 2 h. The mixture was cooled down to room temperature, diluted with EtOAc, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC to give the pure products.

4.2.1. The preparation of indole 8a.

White solid. Isolated yield: 47%. Mp 168-169 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.56 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 6.81 (dd, J = 1.2, 8.4 Hz, 1H), 3.69 (s, 6H), 3.40 (s, 2H), 2.89 (t, J = 8.4 Hz, 2H), 2.12-2.08 (m, 2H), 0.90-0.84 (m, 2H), 0.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 137.5, 133.4, 128.8, 126.4, 124.8, 124.1, 120.0, 110.9, 58.7, 52.2, 36.7, 30.8, 27.1, 27.0, -0.8; HRMS (ESI) *m/z* calcd for $C_{40}H_{54}N_2NaO_8Si_2$ (2M + Na)$^+$ 769.3311, found: 769.3279; IR (KBr) 3411, 2951, 2172, 1732, 1253, 1163, 840, 758, 636 cm^{-1}.

4.2.2. The preparation of indole 8b.

White solid. Isolated yield: 67%. Mp 119-121 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.82 (br s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 0.8, 8.0 Hz, 1H), 3.74 (s, 6H), 3.48 (s, 2H), 3.05 (m, 2H), 1.59-0.84 (m, 10H), 0.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.8, 134.4, 128.8, 125.8, 123.5, 123.0, 121.7, 110.7, 58.9, 52.3, 37.9, 29.4, 26.9, 26.2, 25.7, 21.3, 19.3, -0.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}NO_4Si$ (M + H)$^+$ 416.2252, found 416.2247; IR (KBr) 3420, 2951, 2917, 1728, 1635, 1431, 1035, 855, 648 cm^{-1}.

4.2.3. The preparation of indole 8c.

White solid. Isolated yield: 80%. Mp 105-106 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br s, 1H), 7.29 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.67 (dd, J = 1.2, 8.4 Hz, 1H), 3.74 (s, 6H), 3.70 (s, 6H), 3.33 (s, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.03-1.99 (m, 2H), 1.89-1.84 (m, 2H), 1.77-1.73 (m, 2H), 1.57-1.15 (m, 6H), 1.13-1.11 (m, 4H), 0.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.8, 137.3, 133.1, 128.9, 126.0, 125.6, 123.0, 120.1, 111.0, 59.2, 57.2, 52.4, 52.3, 37.3, 31.1, 30.4, 30.1, 29.9, 27.4, 27.3, 25.7, 21.4, 18.6, -0.6; HRMS (ESI) *m/z* calcd for $C_{31}H_{46}NO_8Si$ (M + H)$^+$ 588.2987, fonud 588.2991; IR (KBr) 3465, 2950, 2927, 2171, 1735, 1365, 1218, 843, 753 cm^{-1}.

4.2.4. The preparation of indole 8d.

White solid. Isolated yield: 60%. Mp 127-128 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.29 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.75 (dd, J = 1.5, 8.4 Hz, 1H), 3.74 (s, 6H), 3.70 (s, 6H), 3.37 (s, 2H), 2.76 (t, J = 7.9 Hz, 2H), 1.95-1.87 (m, 4H), 1.77-1.75 (m, 2H), 1.68-1.61 (m, 2H), 1.51-1.20 (m, 10H), 1.19-1.08 (m, 4H), 0.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 172.1, 137.4, 133.2, 128.6, 126.0, 125.8, 123.6, 120.7, 110.7, 58.8, 57.2, 52.3, 52.1, 39.3, 32.1, 32.0, 30.6, 30.2, 30.0, 29.8, 29.5, 28.8, 26.7, 24.3, 23.3, 22.6, -0.6; HRMS (ESI) *m/z* calcd for $C_{34}H_{52}NO_8Si$ (M + H)$^+$ 630.3457, found 630.3464; IR (KBr) 3412, 2950, 2931, 2172, 1731, 1434, 1219, 841, 758 cm^{-1}.

4.3. Preparation of compound 10

4.3.1. The preparation of compound 11a.

To a stirred solution of compound **6c** (86 mg, 0.20 mmol) in CH_2Cl_2 (9 mL) at 0 ^{o}C was added NBS (36 mg, 0.20 mmol). The solvent was stirred until completion of the reaction. The reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated in vacuo and purified by FCC (PE/EtOAc, 15 : 1) to give the product **11a** (40.3 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 5.2 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 4.02 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 5.6 Hz, 2H), 2.30 (s, 3H), 0.90 (t, J = 8.0 Hz, 9H), 0.75 (q, J = 8.0 Hz, 6H).

4.3.2. The preparation of compound 11c.

To a stirred solution of compound **11a** (40.3 mg, 0.08 mmol) in anhydrous MeOH (1.7 mL) at room temperature was added concentrated hydrochloric acid (0.02 mL). After stirred for 5 h, the mixture was evaporated under reduced pressure and purified by FCC (PE/EtOAc, 15 : 1) to give the product **11c** (30.6 mg, 98%) as a white solid. Mp 197-198 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 6.79 (s, 1H), 4.04 (t, J = 5.6 Hz, 2H), 2.65 (t, J = 5.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 136.9, 133.3, 130.8, 129.6, 126.8, 125.4, 121.6, 117.9, 112.5, 110.3, 99.2, 47.7, 21.5, 21.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}BrN_2O_2S$ (M + H)$^+$

391.0117, found 391.0110; IR (KBr) 3355, 2922, 2851, 1740, 1347, 1221, 1162, 806, 671 cm^{-1}.

4.3.3. The preparation of compound 12.

To a round bottom flask containing anhydrous MeOH (0.12 mL) was added compound **11c** (19 mg, 0.05 mmol) in DMF (1 mL) and CuI (19 mg, 0.10 mmol) in which metallic sodium (11.5 mg, 0.5 mmol) was dissolved, then the solution was heated at reflux for 1 h. After cooled down to room temperature, the mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was evaporated under reduced pressure, washed with 2% NaOH, extracted with EtOAc, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 4 : 1) to give the product **12** (13 mg, 77%) as a white solid. Mp 227-229 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.70 (s, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.02 (t, J = 5.6 Hz, 2H), 3.94 (s, 3H), 2.56 (t, J = 5.2 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 143.2, 137.3, 129.5, 126.9, 124.5, 124.4, 122.5, 117.2, 112.1, 109.6, 103.1, 55.5, 47.8, 21.5, 21.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}N_2O_3S$ $(M + H)^+$ 343.1111, found 343.1113; IR (KBr) 3368, 2969, 2928, 1738, 1348, 1217, 1088, 803, 672 cm^{-1}.

4.3.4. The preparation of compound 13.

Preparation of SmI_2 in THF (0.13 M): To a stirred solution of the Sm (230 mg) in anhydrous THF (10 mL) was added I_2 (330 mg) under argon atmosphere. Then the solution was heated at reflux until the color became deep-blue.

To a round bottom flask containing compound **12** (13 mg, 0.038 mmol) was added the solution of SmI_2 (3 mL, 0.13 M, 0.38 mmol), H_2O (0.02 mL) and pyrrolidine (0.07 mL). The solution was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 4:1) to give product **13** (7 mg, quant) as a white solid. Mp 140-143 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 6.74 (s, 1H), 6.45 (d, J = 7.6 Hz, 1H), 6.14 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.45 (t, J = 6.0 Hz, 2H), 2.99 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 135.3, 125.1, 119.9, 115.6, 111.2, 103.9, 99.3, 56.0, 43.9, 23.1; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_2O$ $(M + H)^+$ 189.1022, found 189.1027; IR (KBr) 3352, 2955, 2926, 2854, 1738, 1713, 1366, 1216, 1051, 797 cm^{-1}.

4.3.5. The preparation of compound 14.

To a stirred solution of compound **13** (5 mg, 0.027 mmol) in MeOH was added CH_2O (9 μL), $NaBH_4$ (4 mg, 0.108 mmol). The solution was stirred at room temperature for 0.5 h. The mixture was diluted with EtOAc, washed with water, extracted with EtOAc, dried over Na_2SO_4 and filtered to give the product **14** (5.4 mg, quant) as a colorless oil without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 6.73 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 6.09 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.22 (t, J = 6.0 Hz, 2H), 3.07 (t, J = 5.2 Hz, 2H), 2.91 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2O$ $(M + H)^+$ 203.1180, found 203.1184.

4.3.6. The preparation of compound 10.

To a solution of **14** (2 mg, 0.01 mmol), $Bu_4N{\cdot}HSO_4$ (3.4 mg, 0.01 mmol) in CH_2Cl_2 (1 mL) was added powered NaOH (1.6 mg, 0.04 mmol) and TsCl (2.9 mg, 0.02 mmol). The reaction mixture was stirred under argon overnight. Water was added and the mixture was extracted with EtOAc, dried over Na_2SO_4 and filtered. The resulting residue was purified by FCC (CH_2Cl_2/ MeOH, 99 : 1) to give product **10** (2.7 mg, 80%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.24(d, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.18 (t, J = 6.0 Hz, 2H), 2.99 (t, J = 5.6 Hz, 2H), 2.87 (s, 3H), 2.37 (s, 3H); HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2O_3S$ $(M + H)^+$ 357.1277, found 357.1273.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (Nos. 21372017, 21290183), the National Basic Research Program of China (973 Program, NO. 2010CB833200).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: .

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Supporting Information

Intramolecular Larock Indole Synthesis for the Preparation of Tricyclic Indoles and Its Application in the Synthesis of Tetrahydropyrroloquinoline and Fargesine

Yan Gao,[†] Dong Shan,[†] Yanxing Jia*[,†,‡]

[†]*State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing 100191, China, and* [‡]*State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

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General Experimental

All reagents were obtained from commercial sources unless otherwise mentioned. N, N-Dimethylformamide (DMF) was distilled from magnesium sulfate under vacuum. Tetrahydrofuran (THF) was distilled from potassium sodium alloys. Acetonitrile and dichloromethane were distilled from calcium hydride. Flasks were flame-dried under vacuum and cooled under argon atmosphere.

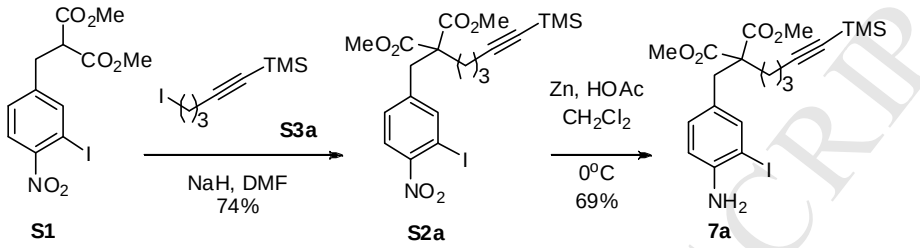
The following abbreviations are used: **Boc**: *tert*-butoxycarbonyl; **DCM**: dichloromethane; **DMF**: N, N-dimethylformamide; **DMAP**: 4-dimethylaminopyridine; **DMSO**: dimethyl sulfoxide; **DEAD**: diethyl azodicarboxylate; **EtOAc**: ethyl acetate; **FCC**: flash column chromatography; **HMPA**: hexamethylphosphoramide; **HOAc**: acetic acid; ***m*-CPBA**: *meta*-chloroperoxybenzoic acid; **PE**: petroleum ether; **TFA**: trifluoroacetic acid; **THF**: tetrahydrofuran.

^{1}H NMR spectra were recorded at Bruker Avance III 400 MHz NMR spectrometer; ^{13}C NMR spectra were obtained by using the same NMR spectrometers unless otherwise stated. Mass spectra were recorded on a Bruker APEX IV FT-MS (ESI) spectrometer. Infrared spectra were recorded on Thermo Nicolet Nexus-470 FT-IR spectrometers.

Preparation of starting materials.

For all analytical data of the compounds in Table 1 and Scheme 6, see our previous communication paper (Ref. [17]).

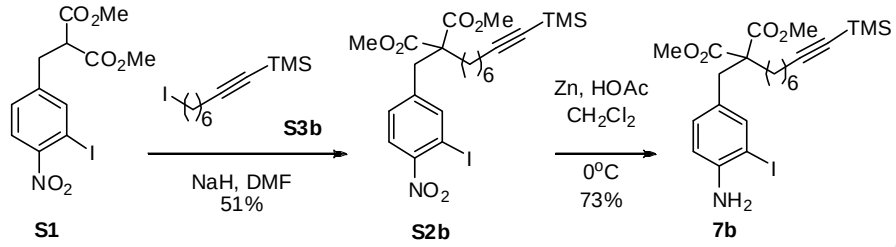
Synthesis of compound **7a**



To a stirred solution of **S1** (254 mg, 0.65 mmol) in anhydrous DMF (6.5 mL) was added NaH (28 mg, 0.71 mmol) at room temperature. The reaction mixture was stirred for 1 h and the iodide **S3a** (344 mg, 1.30 mmol) was added dropwisely. The solution was stirred until completion of the reaction. The mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 10 : 1) to afford compound **S2a** (253 mg, 74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 7.25 (dd, J = 1.72, 8.56 Hz, 1H), 3.72 (s, 6H), 3.22 (s, 2H), 2.24 (t, J = 7.0 Hz, 2H), 1.93-1.87 (m, 2H), 1.53-1.45 (m, 2H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.5, 143.3, 142.9, 130.6, 125.2, 105.9, 86.2, 85.4, 58.7, 52.6, 37.9, 32.2, 23.7, 19.9, 0.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}INO_6Si$ $(M + H)^+$ 532.0647; found 532.0651; IR (KBr) 2955, 2173, 1578, 1528, 1250, 1175, 844, 760 cm^{-1}.

To a stirred solution of the 2-indo nitrobenzene **S2a** (252 mg, 0.47 mmol) in CH_2Cl_2 (5.8 mL) was added activated zinc dust (1.76 g, 28.2 mmol). The solution was cooled down to 0 ^{o}C and HOAc (0.43 mL) was added dropwisely. After stirred for 10 min at 0 ^{o}C, the mixture was filtered through a pad of Celite and the Celite was washed with EtOAc. The filtrate was neutralized with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 8 : 1) to afford **7a** (163 mg, 69%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 1.8 Hz, 1H), 6.86 (dd, J = 1.8, 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.02 (br s, 2H), 3.71 (s, 6H), 3.07 (s, 2H), 2.22 (t, J = 7.2 Hz, 2H), 1.87-1.83 (m, 2H), 1.52-1.44 (m, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 145.7, 139.9, 130.8, 127.3, 114.4, 106.4, 85.0, 83.9, 58.9, 52.3, 37.2, 31.5, 23.8, 20.0, 0.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}INO_4Si$ $(M + H)^+$ 502.0905; found 502.0905; IR (KBr) 3465, 3371, 2953, 1732, 1619, 1501, 1250, 843, 665 cm^{-1}.

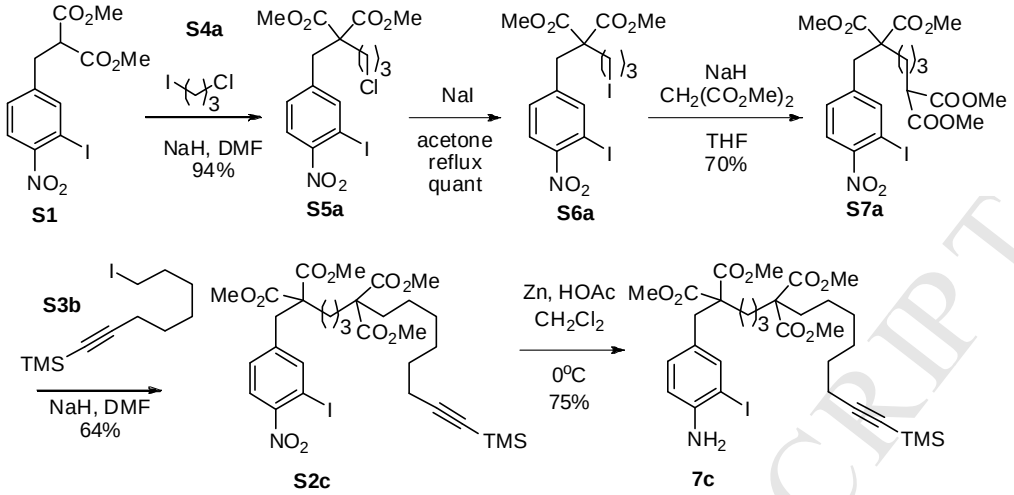
Synthesis of compound **7b**



To a stirred solution of **S1** (275 mg, 0.70 mmol) in anhydrous DMF (7 mL) was added NaH (30.8 mg, 0.77 mmol) at room temperature. The reaction mixture was stirred for 1 h and the iodide **S3b** (320 mg, 1.04 mmol) was added dropwisely. The solution was stirred until completion of the reaction. The mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 10 : 1) to afford compound **S2b** (203 mg, 51%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.20 (dd, J = 1.8, 8.3 Hz, 1H), 3.72 (s, 6H), 3.22 (s, 2H), 2.22 (t, J = 7.0 Hz, 2H), 1.80-1.76 (m, 2H), 1.54-1.47 (m, 2H), 1.43-1.23 (m, 6H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.5, 143.4, 143.1, 130.5, 125.3, 107.3, 86.2, 84.5, 58.9, 52.6, 37.7, 32.6, 29.1, 28.4, 24.1, 19.8, 0.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{33}INO_6Si$ $(M + H)^+$ 574.1116; found 574.1120; IR (KBr) 2952, 2931, 2171, 1730, 1527, 1249, 844, 759, 698 cm^{-1}.

To a stirred solution of the 2-indo nitrobenzene **S2b** (135.5 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added activated zinc dust (922 mg, 14.20 mmol). The solution was cooled down to 0 °C and HOAc (0.2 mL) was added dropwisely. After stirred for 10 min at 0 °C, the mixture was filtered through a pad of Celite and the Celite was washed with EtOAc. The filtrate was neutralized with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 8 : 1) to afford **7b** (93.5 mg, 73%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 1.8 Hz, 1H), 6.82 (dd, J = 1.8, 8.1 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 4.01 (br s, 2H), 3.71 (s, 6H), 3.08 (s, 2H), 2.21 (t, J = 7.0 Hz, 2H), 1.77-1.73 (m, 2H), 1.55-1.47 (m, 2H), 1.42-1.21 (m, 6H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 145.7, 140.0, 130.7, 127.5, 114.4, 107.5, 84.4, 83.9, 59.1, 52.3, 37.0, 31.8, 29.7, 29.2, 28.5, 24.0, 19.8, 0.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}INNaO_4Si$ $(M + Na)^+$ 566.1194; found 566.1195; IR (KBr) 3463, 3369, 2928, 2171, 1732, 1618, 1204, 841, 759 cm^{-1}.

Synthesis of compound **7c**



To a suspension of NaH (22 mg, 0.85 mmol) in DMF (2.0 mL) was added **S1** (305 mg, 0.78 mmol) in DMF (1.5 mL). After 10 min at room temperature, **S4a** (0.20 mL, 1.53 mmol) was added to this mixture, and the reaction mixture was stirred at room temperature for 6 h, diluted with ether, washed with water and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 8 : 1) gave the chloride **S5a** (344 mg, 94%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 1.8 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.24 (dd, J = 1.8, 7.9 Hz, 1H), 3.74 (s, 6H), 3.54 (t, J = 6 Hz, 2H), 3.23 (s, 2H), 1.98-1.94 (m, 2H), 1.80-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 151.7, 143.4, 142.6, 130.6, 125.3, 86.3, 58.4, 52.7, 44.4, 37.9, 30.3, 27.6.

A solution of **S5a** (312 mg, 0.66 mmol) and NaI (199 mg, 1.33 mmol) in acetone (2.5 mL) was refluxed overnight. The mixture was then cooled to room temperature and partitioned between hexanes and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give iodide **S6a** (367 mg, quant) without further purification.

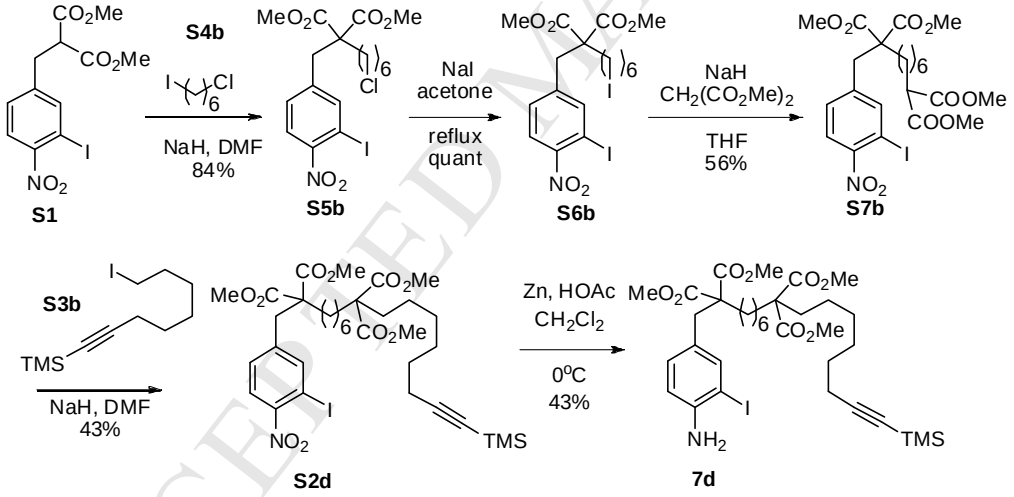
To a slurry of NaH (14.4 mg, 0.60 mmol) in THF (2 mL) was added dimethylmalonate (63 μL, 0.55 mmol) via syrige. The reaction mixture was stirred until no more gas was evolved and a solution of crude iodide **S6a** (306 mg, 0.55 mmol) in THF (1 mL) was added. The resulting mixture was stirred at room temperature overnight, diluted with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 8 : 1) gave compound **S7a** (213 mg, 70%) as a yellow solid. Mp 71-72 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.23 (dd, J = 1.8, 8.3 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 6H), 3.36 (t, J = 7.4 Hz, 1H), 3.20 (s, 2H), 1.93-1.87 (m, 2H), 1.83-1.78 (m, 2H), 1.34-1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.5, 151.6, 143.3, 142.8, 130.6, 125.3, 86.3, 58.7, 52.7, 52.6, 51.1, 37.7, 32.2, 28.7, 22.0; IR (KBr) 3649, 2953, 1730, 1527, 1435, 1157, 1033, 871, 699 cm^{-1}.

To a suspension of NaH (4.2 mg, 0.17 mmol) in DMF (1 mL) was added **S7a** (84.6 mg, 0.15 mmol) in DMF (0.5 mL). After 10 min at room temperature, iodide **S3b** (92.4 mg, 0.30 mmol) was added, and the reaction mixture was stirred at room temperature for 4 h, diluter with ether, washed with water and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 6 : 1) gave compound **S2c** (71 mg, 64%) as a yellow solid. Mp 105-106 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 1.6 Hz, 1H), 7.20 (dd, J = 1.6, 8.3 Hz, 1H), 3.71 (s, 6H), 3.70 (s, 6H), 3.19 (s, 2H), 2.19 (t, J = 7.04 Hz, 2H), 1.87-1.81 (m, 4H), 1.78-1.74 (m, 2H), 1.52-1.44 (m, 2H),

1.40-1.14 (m, 8H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.7, 151.6, 143.3, 142.9, 130.5, 125.3, 107.4, 86.2, 84.4, 58.7, 57.5, 52.5, 52.3, 37.8, 33.1, 33.0, 32.8, 29.2, 28.4, 24.0, 19.7, 19.3, 0.1; HRMS (ESI) *m/z* calcd for $C_{31}H_{44}INNaO_{10}Si$ $(M + Na)^+$ 768.1671; found 768.1667; IR (KBr) 3469, 2953, 1739, 1527, 1255, 1029, 844, 760, 639 cm^{-1}.

To a stirred solution of the 2-indo nitrobenzene **S2c** (71 mg, 0.10 mmol) in CH_2Cl_2 (1.2 mL) was added activated zinc dust (374 mg, 5.76 mmol). The solution was cooled down to 0 ^{o}C and HOAc (0.09 mL) was added dropwisely. After stirred for 10 min at 0 ^{o}C, the mixture was filtered through a pad of Celite and the Celite was washed with EtOAc. The filtrate was neutralized with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 7 : 1) to gave compound **7c** (51 mg, 75%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 1.6 Hz, 1H), 6.80 (dd, J = 1.6, 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.02 (br s, 2H), 3.71 (s, 6H), 3.70 (s, 6H), 3.05 (s, 2H), 2.20 (t, J = 7.0 Hz, 2H), 1.87-1.82 (m, 4H), 1.76-1.72 (m, 2H), 1.53-1.46 (m, 2H), 1.42-1.25 (m, 4H), 1.18-1.07 (m, 4H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.4, 145.7, 140.0, 130.7, 127.2, 114.4, 107.5, 84.4, 83.9, 58.9, 57.5, 52.3, 52.3, 37.1, 32.8, 32.7, 32.1, 29.3, 28.5, 28.5, 24.0, 19.8, 19.2, 0.2; HRMS (ESI) *m/z* calcd for $C_{31}H_{47}INO_8Si$ $(M + H)^+$ 716.2110; found 716.2117; IR (KBr) 3370, 2951, 2171, 1732, 1500, 1249, 1113, 842, 760 cm^{-1}.

Synthesis of compound **7d**



To a suspension of NaH (19.4 mg, 0.77 mmol) in DMF (2.0 mL) was added **S1** (273 mg, 0.70 mmol) in DMF (1.5 mL). After 10 min at room temperature, **S4b** (0.22 mL, 1.40 mmol) was added to this mixture, and the reaction mixture was stirred at room temperature for 6 h, diluted with ether, washed with water and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 8 : 1) gave chloride **S5b** (299 mg, 84%) as a yellow solid. Mp 72-73 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.20 (dd, J = 1.5, 8.3 Hz, 1H), 3.72 (s, 6H), 3.53 (t, J = 6.6 Hz, 2H), 3.22(s, 2H), 1.80-1.73 (m, 4H), 1.49-1.41 (m, 2H), 1.37-1.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 151.5, 143.4, 143.1, 130.5, 125.3, 86.2, 58.8, 52.6, 44.9, 37.7, 32.5, 32.4, 28.9, 26.5, 24.1.

A solution of **S5b** (289 mg, 0.57 mmol) and NaI (170 mg, 1.13 mmol) in acetone (2 mL) was refluxed overnight. The mixture was then cooled to room temperature and partitioned between

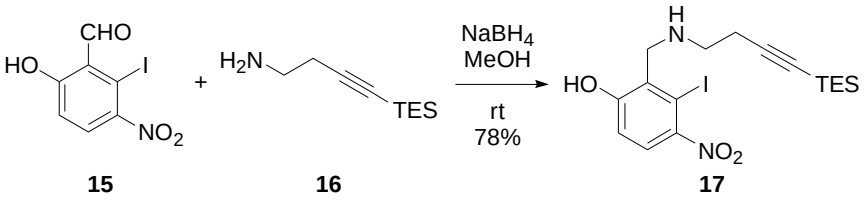
hexanes and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give iodide **S6b** (344 mg, quant) without further purification.

To a slurry of NaH (14.0 mg, 0.59 mmol) in THF (2 mL) was added dimethylmalonate (61 μL, 0.53 mmol) via syrige. The reaction mixture was stirred until no more gas was evolved and a solution of crude iodide **S6b** (320 mg, 0.53 mmol) in THF (1 mL) was added. The resulting mixture was stirred at room temperature overnight, diluted with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 6 : 1) gave compound **S7b** (181 mg, 56%) as a yellow solid. Mp 88-89 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.21 (dd, J = 1.8, 8.3 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 6H), 3.35 (t, J = 7.5 Hz, 1H), 3.22 (s, 2H), 1.92-1.88 (m, 2H), 1.79-1.75 (m, 2H), 1.32-1.24 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.8, 151.5, 143.4, 143.1, 130.5, 125.3, 86.2, 58.9, 52.5, 52.4, 51.6, 37.7, 32.5, 29.2, 28.8, 28.7, 27.1, 24.0; IR (KBr) 3467, 2952, 2259, 1735, 1527, 1347, 1202, 844, 698 cm^{-1}.

To a suspension of NaH (2.8 mg, 0.11 mmol) in DMF (0.6 mL) was added **S7b** (60.4 mg, 0.10 mmol) in DMF (1.0 mL). After 10 min at room temperature, iodide **S3b** (61.6 mg, 0.20 mmol) was added, and the reaction mixture was stirred at room temperature overnight, diluter with ether, washed with water and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 7 : 1) gave compound **S2d** (34 mg, 43%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 7.20 (dd, J = 1.7, 8.3 Hz, 1H), 3.71 (s, 6H), 3.70 (s, 6H), 3.20 (s, 2H), 2.19 (t, J = 7.0 Hz, 2H), 1.87-1.83 (m, 4H), 1.79-1.74 (m, 2H), 1.52-1.45 (m, 2H), 1.40-1.24 (m, 10H), 1.17-1.13 (m, 4H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 170.9, 151.5, 143.4, 143.1, 130.5, 125.3, 107.5, 86.2, 84.4, 58.9, 57.6, 52.5, 52.2, 37.7, 32.6, 29.5, 29.3, 29.2, 28.5, 24.1, 24.0, 24.0, 19.8, 0.1; HRMS (ESI) *m/z* calcd for $C_{34}H_{50}INNaO_{10}Si$ $(M + Na)^+$ 810.2141; found 810.2125; IR (KBr) 3466, 2950, 2260, 1734, 1528, 1245, 1048, 843, 697 cm^{-1}.

To a stirred solution of the 2-indo nitrobenzene **S2d** (80 mg, 0.10 mmol) in CH_2Cl_2 (1.3 mL) was added activated zinc dust (390 mg, 6 mmol). The solution was cooled down to 0 ^oC and HOAc (0.09 mL) was added dropwisely. After stirred for 10 min at 0 ^oC, the mixture was filtered through a pad of Celite and the Celite was washed with EtOAc. The filtrate was neutralized with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by FCC (PE/EtOAc, 7 : 1) to give compound **7d** (33 mg, 43%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 1.8 Hz, 1H), 6.81 (dd, J = 1.8, 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.02 (br s, 2H), 3.69 (s, 12H), 3.06 (s, 2H), 2.19 (t, J = 7.1 Hz, 2H), 1.87-1.83 (m, 4H), 1.75-1.71 (m, 2H), 1.52-1.45 (m, 2H), 1.40-1.11 (m, 14H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.6, 145.7, 140.0, 130.7, 127.5, 114.4, 107.5, 84.4, 83.9, 59.0, 57.6, 52.2, 36.9, 32.5, 32.5, 31.8, 29.7, 29.5, 29.4, 29.3, 28.5, 24.1, 24.0, 19.8, 0.2; HRMS (ESI) *m/z* calcd for $C_{34}H_{52}INNaO_8Si$ $(M + Na)^+$ 780.2399; found 780.2406; IR (KBr) 3464, 2926, 2170, 1731, 1249, 1014, 843, 796, 761 cm^{-1}.

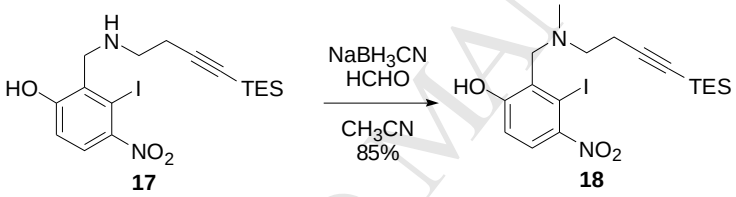
Synthesis of compound **17**



15 **16** **17**

To a stirred solution of the aldehyde **15** (645 mg, 2.2 mmol) and amine **16** (403 mg, 2.2 mmol) in methanol (6.6 mL) at room temperature was added $NaBH_4$ (171 mg, 4.4 mmol). The mixture was stirred at room temperature for 1 h. The reactioin mixture was extracted with EtOAc and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 2 : 1) gave compound **17** (790 mg, 78%) as a yellow solid. Mp 75-77 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.36 (s, 2H), 2.83 (t, J = 6.0 Hz, 2H), 2.55 (t, J = 6.0 Hz, 2H), 0.98 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 146.4, 126.1, 125.4, 116.8, 103.7, 92.8, 85.1, 58.0, 46.2, 20.0, 7.5, 4.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}IN_2O_3Si$ $(M + H)^+$ 461.0752; found 461.0750; IR (KBr) 2954, 2874, 2174, 1524, 1453, 1338, 1243, 829, 727 cm^{-1}.

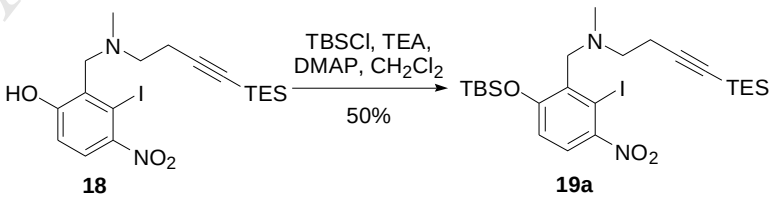
Synthesis of compound **18**



17 **18**

To a stirred solution of amine **17** (100 mg, 0.22 mmol) and HCHO (30%) (44 mg, 0.44 mmol) in anhydrous CH_3CN (2.2 mL) at room temperature was added $NaBH_3CN$ (21 mg, 0.33 mmol). The mixture was stirred at room temperature for 1 h. The reactioin mixture was extracted with EtOAc and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 5 : 1) gave compound **18** (89 mg, 85%) as a yellow solid. Mp 71-73 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 4.11 (s, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.39 (s, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 146.3, 126.3, 125.1, 116.6, 103.8, 93.0, 84.5, 66.9, 55.3, 40.8, 18.3, 7.4, 4.3; HRMS (ESI) *m/z* calcd for $C_{18}H_{28}IN_2O_3Si$ $(M + H)^+$ 475.0909; found 475.0910; IR (KBr) 2954, 2912, 2873, 2174, 1572, 1337, 1242, 1017, 726, 650 cm^{-1}.

Synthesis of compound **19a**

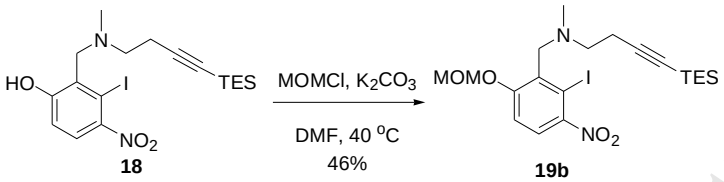


18 **19a**

To a stirred solution of compound **18** (20 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (1 mL) was added DMAP (2 mg, 0.01 mmol). The solution was cooled to 0 ^oC, then TEA (18 μL) and TBSCl (13 mg,

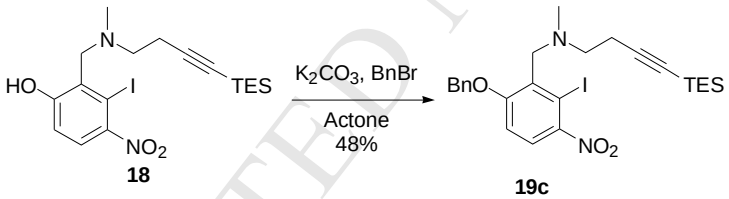
0.08 mmol) was added. The mixture was stirred at 0 °C for 1 h. The mixture was quenched with water and extracted with CH_2Cl_2 and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 7 : 1) gave compound **19a** (12.5 mg, 50%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 3.73 (s, 2H), 2.74 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 8.0 Hz, 2H), 2.22 (s, 3H), 1.03 (s, 9H), 0.97 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H), 0.29 (s, 6H).

Synthesis of compound **19b**



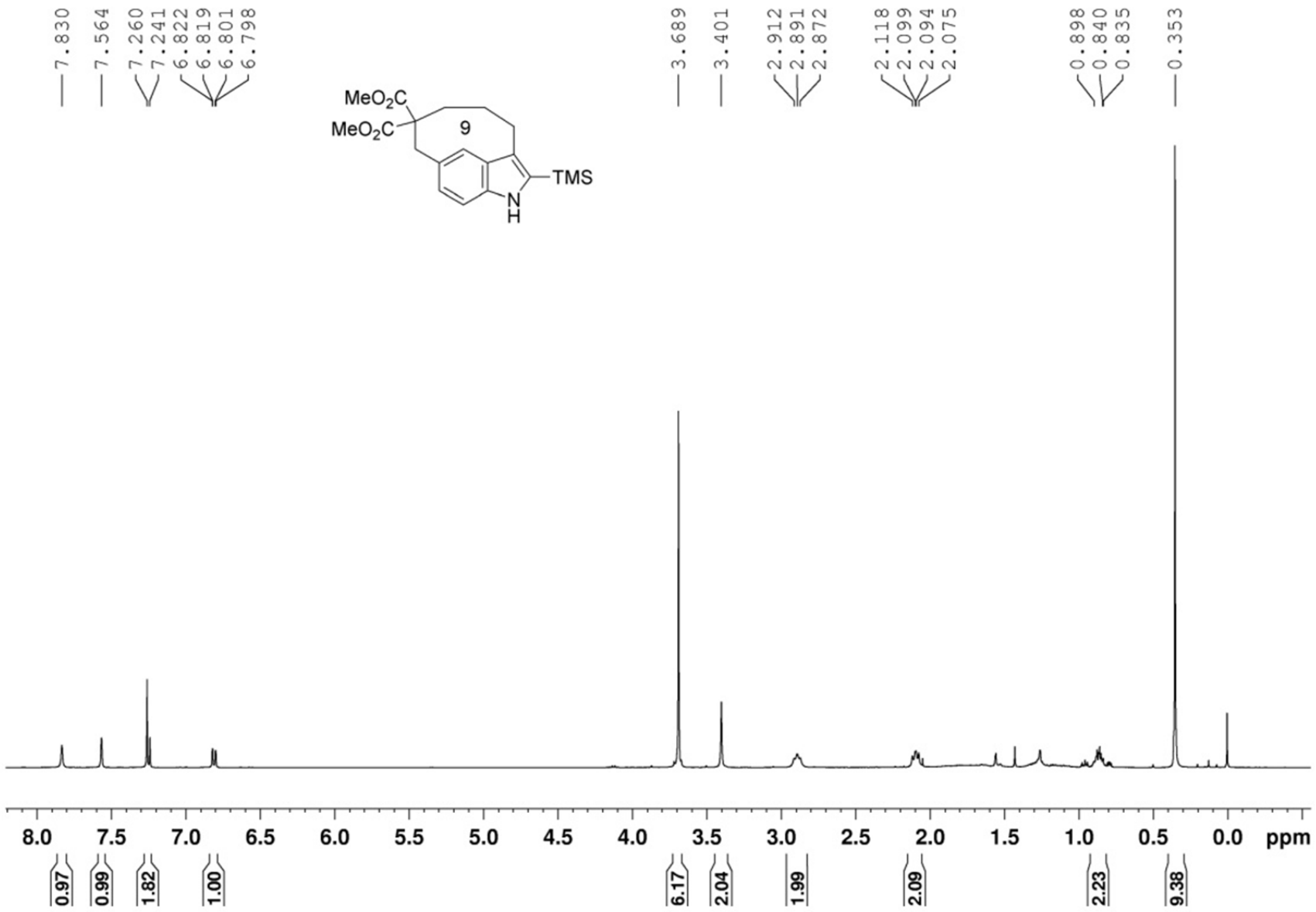
To a solution of compound **18** (15 mg, 0.03 mmol) in anhydrous DMF (1 mL) were added K_2CO_3 (5.3 mg, 0.04 mmol) and MOMCl (5 μL) at 40 °C. The mixture was stirred at that temperature for an hour. Water was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 10 : 1) gave compound **19b** (7.6 mg, 46%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 9.2 Hz, 1H), 7.18 (d, J = 9.2 Hz, 1H), 5.26 (s, 2H), 3.80 (s, 2H), 3.49 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.48 (t, J = 8.0 Hz, 2H), 2.29 (s, 3H), 0.97 (t, J = 7.6 Hz, 9H), 0.55 (q, J = 7.6 Hz, 6H).

Synthesis of compound **19c**

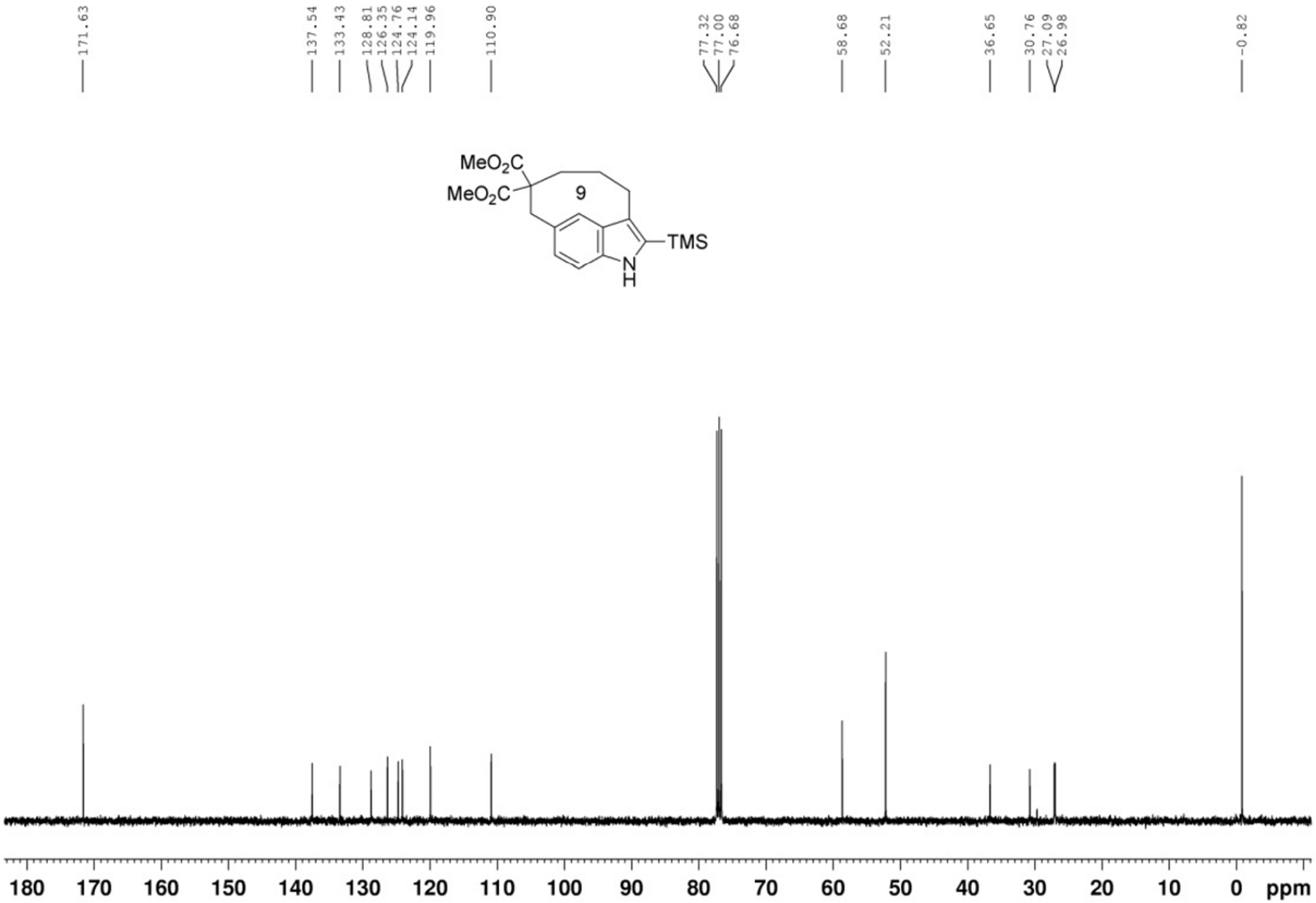


To a stirred solution of compound **18** (14 mg, 0.03 mmol) in anhydrous acetone (1 mL) at room temperature was added K_2CO_3 (8.3 mg, 0.06 mmol) and BnBr (4 μL). After stirring at room temperature overnight, the solvent was neutralized with NH_4Cl solution, extracted with EtOAc and dried over Na_2SO_4. Purification by FCC (PE/EtOAc, 7 : 1) gave compound **19c** (8 mg, 48%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 9.0 Hz, 1H), 7.42-7.37 (m, 5H), 6.95 (d, J = 8.8 Hz, 1H), 5.15 (s, 2H), 3.84 (s, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.43 (t, J = 8.0 Hz, 2H), 2.28 (s, 3H), 0.97 (t, J = 7.6 Hz, 9H), 0.56 (q, J = 7.6 Hz, 6H).

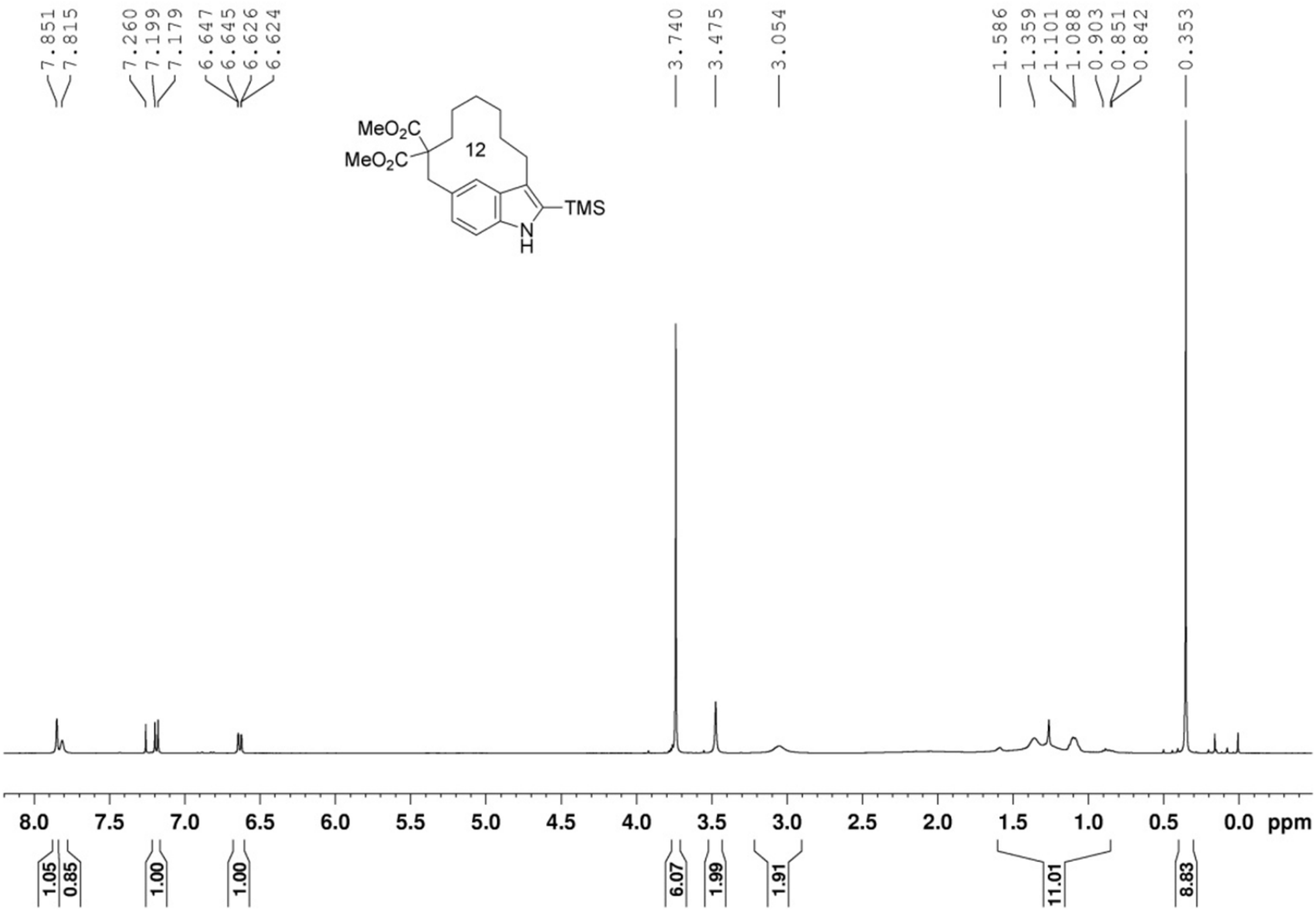
^{1}H NMR of compound 8a ($CDCl_3$, 400 MHz)



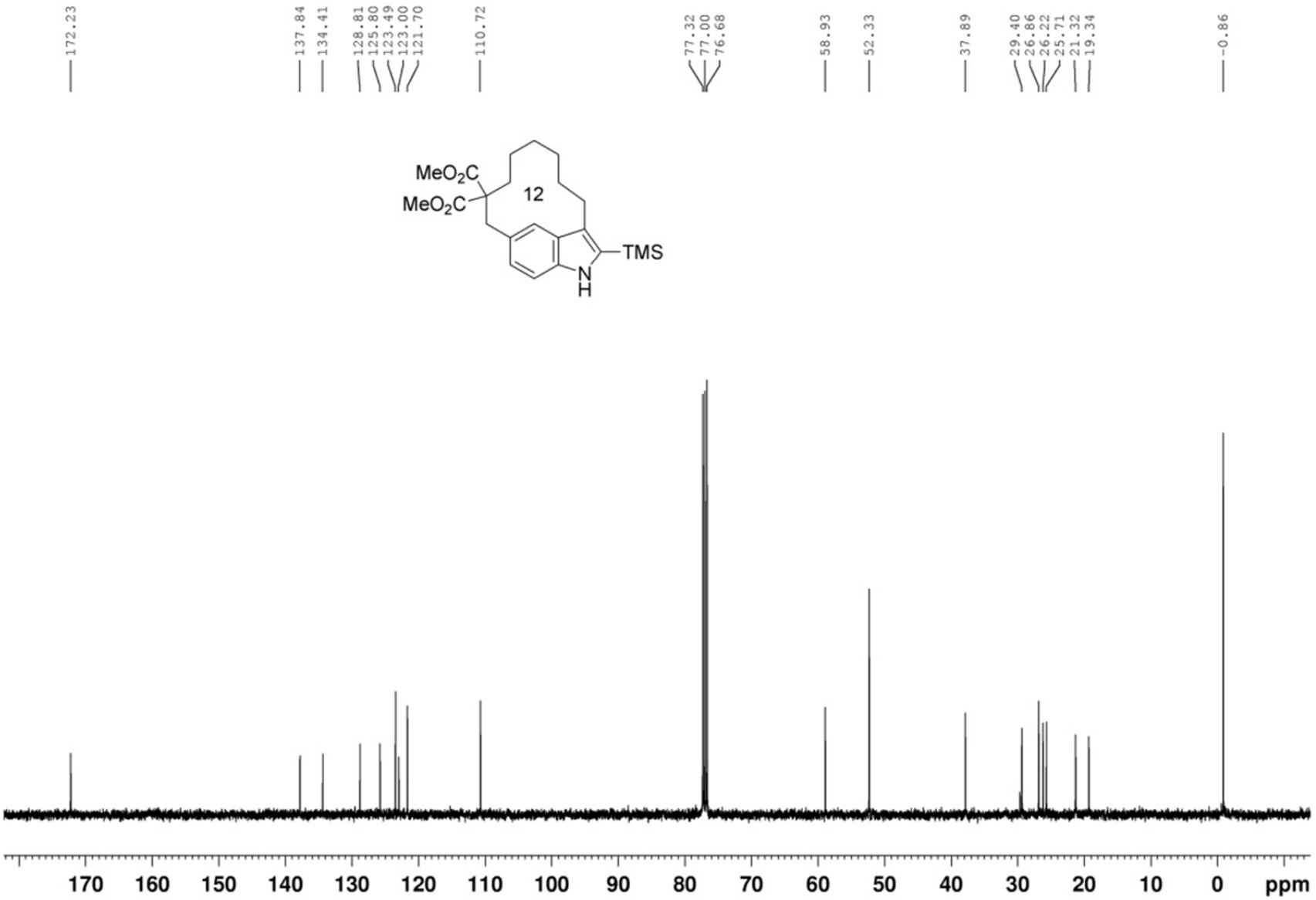
^{13}C NMR of compound 8a ($CDCl_3$, 100 MHz)



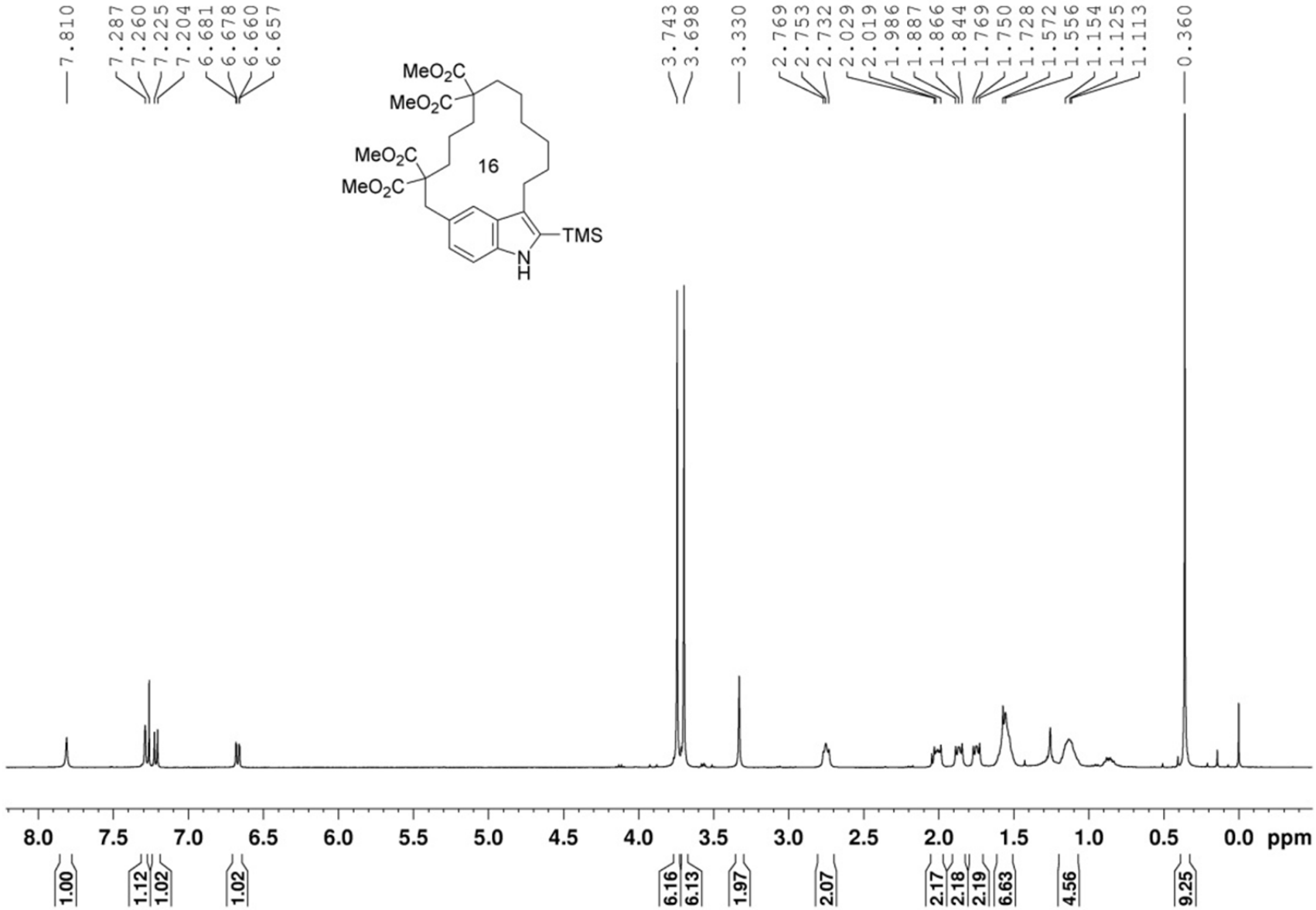
^{1}H NMR of compound 8b ($CDCl_3$, 400 MHz)



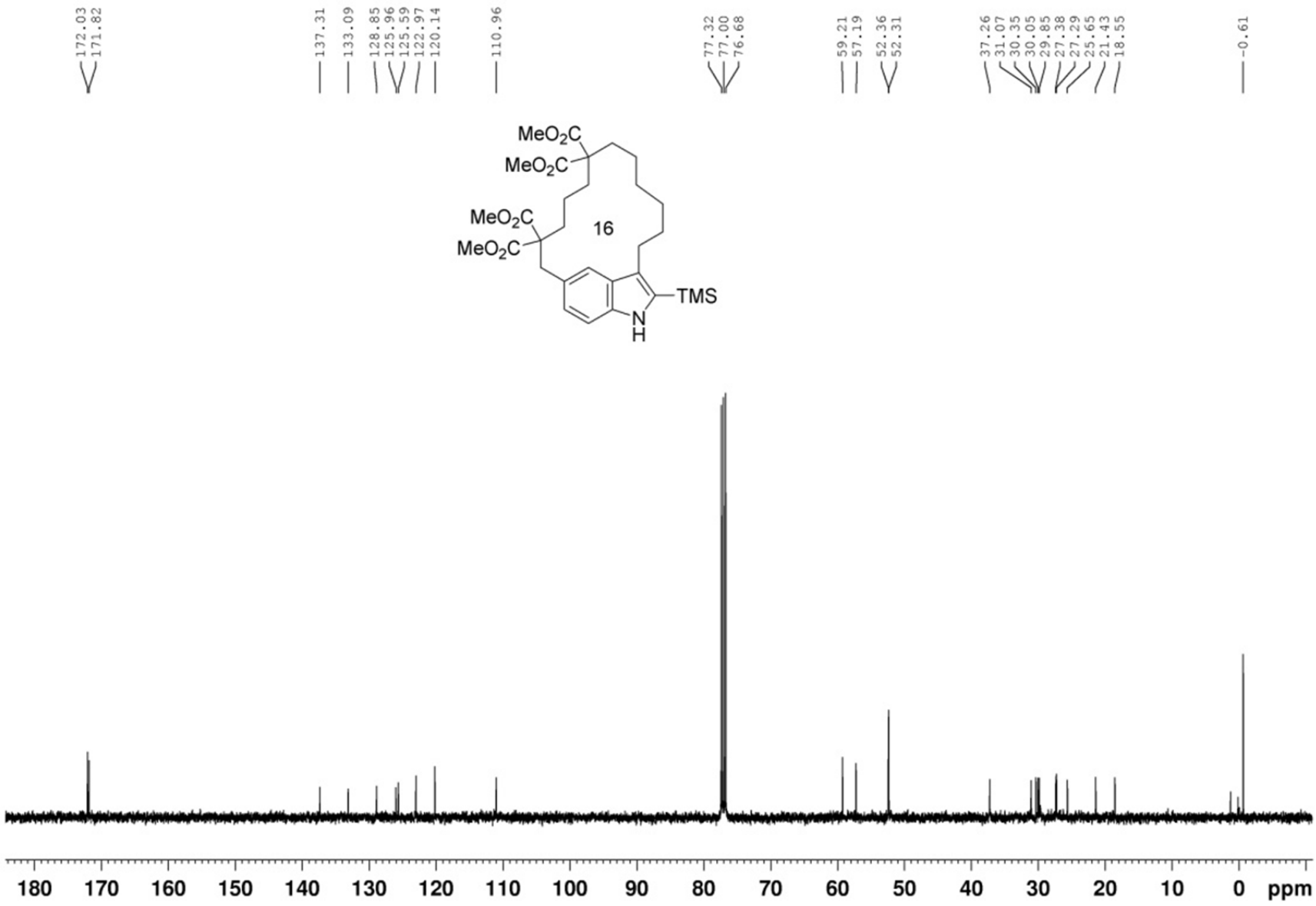
^{13}C NMR of compound 8b ($CDCl_3$, 100 MHz)



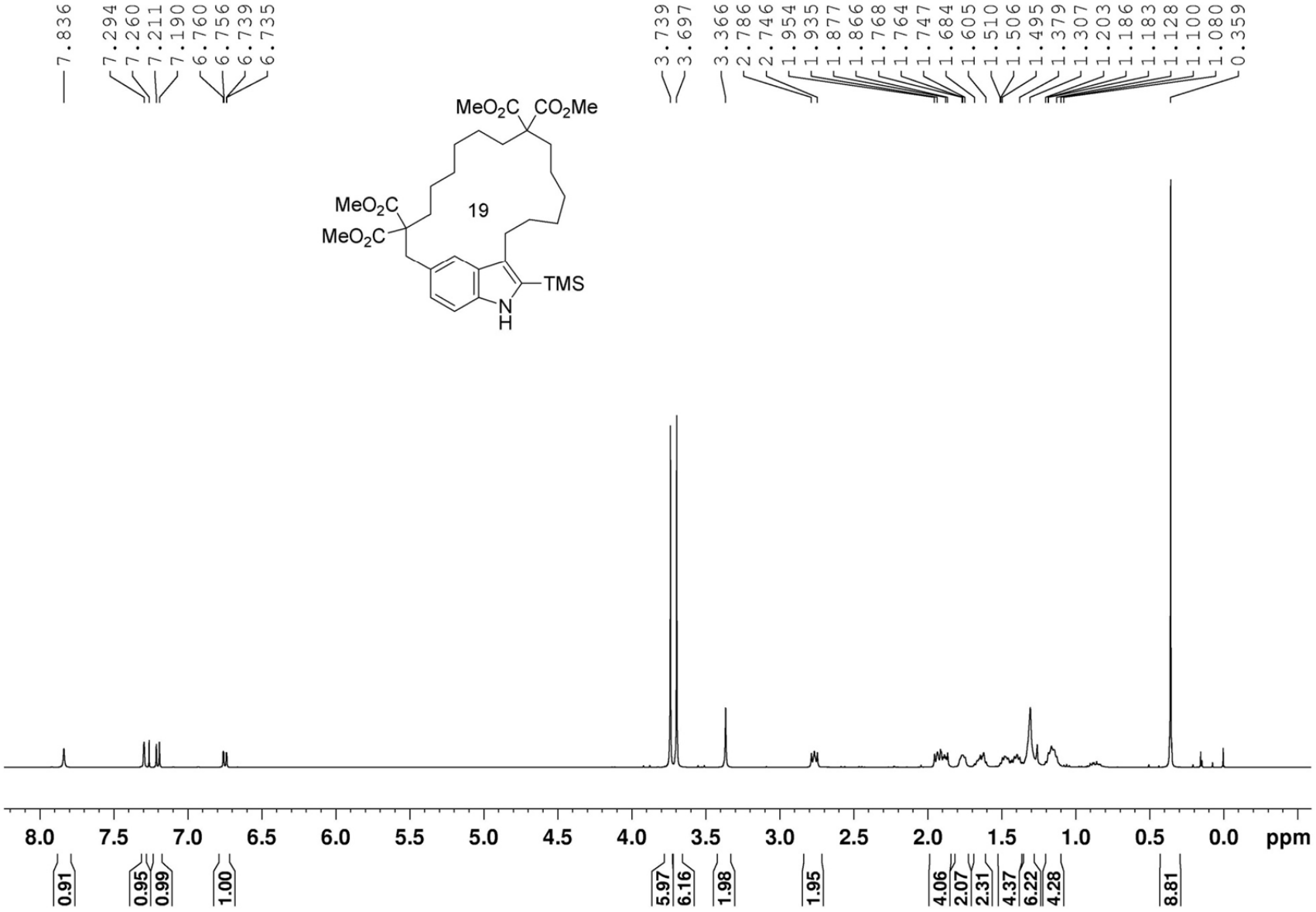
^{1}H NMR of compound 8c ($CDCl_3$, 400 MHz)



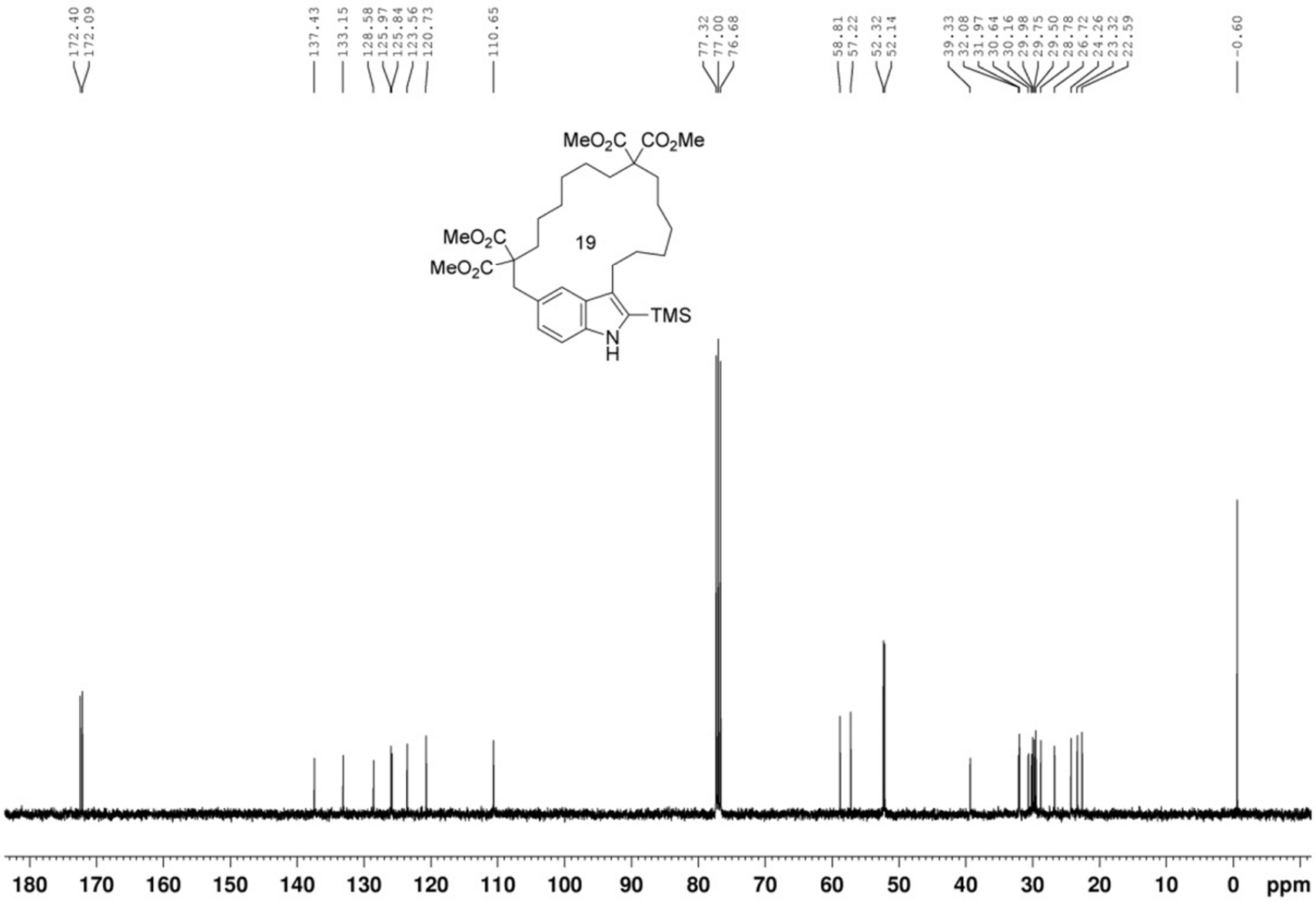
^{13}C NMR of compound 8c ($CDCl_3$, 100 MHz)



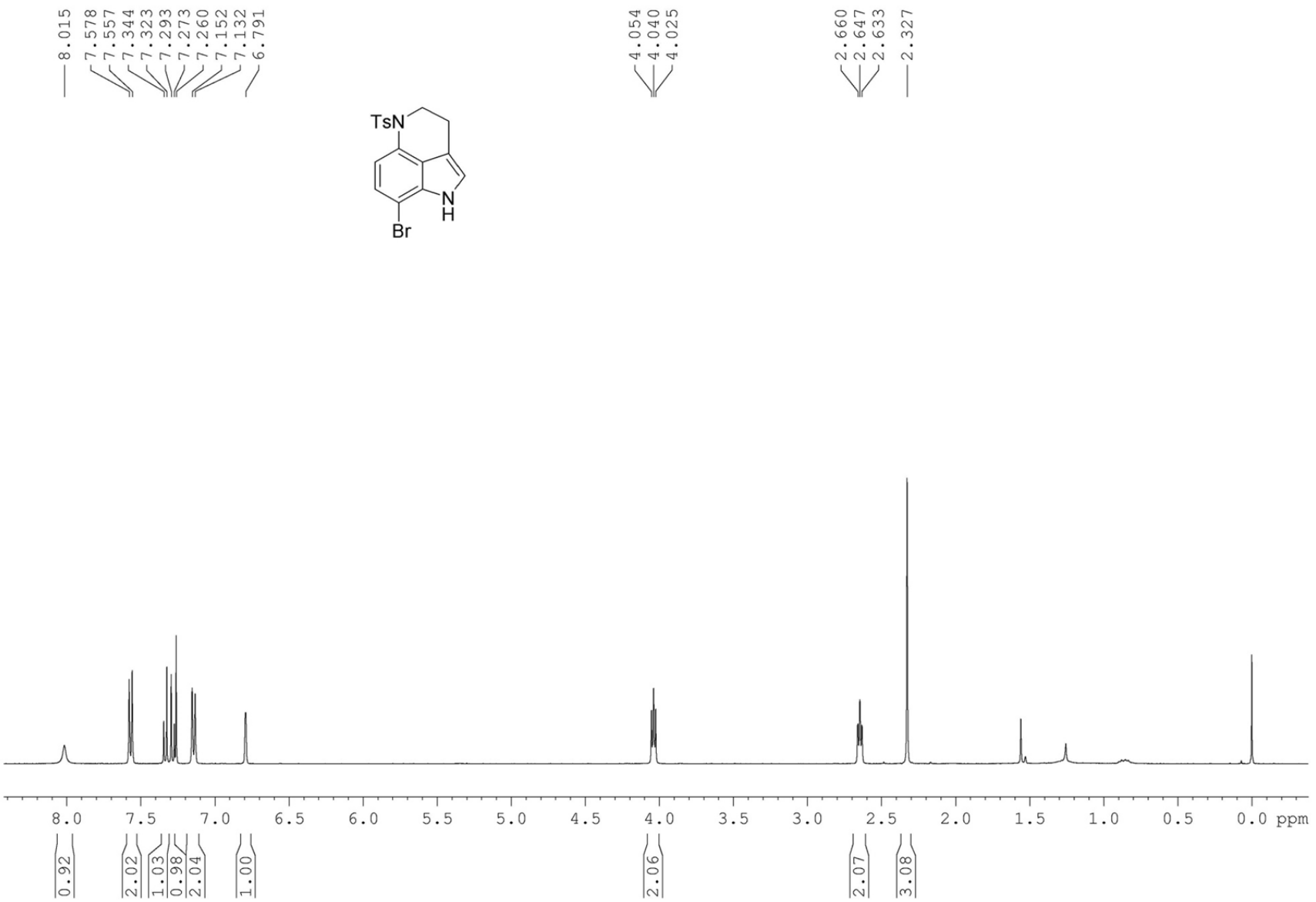
^{1}H NMR of compound 8d ($CDCl_3$, 400 MHz)



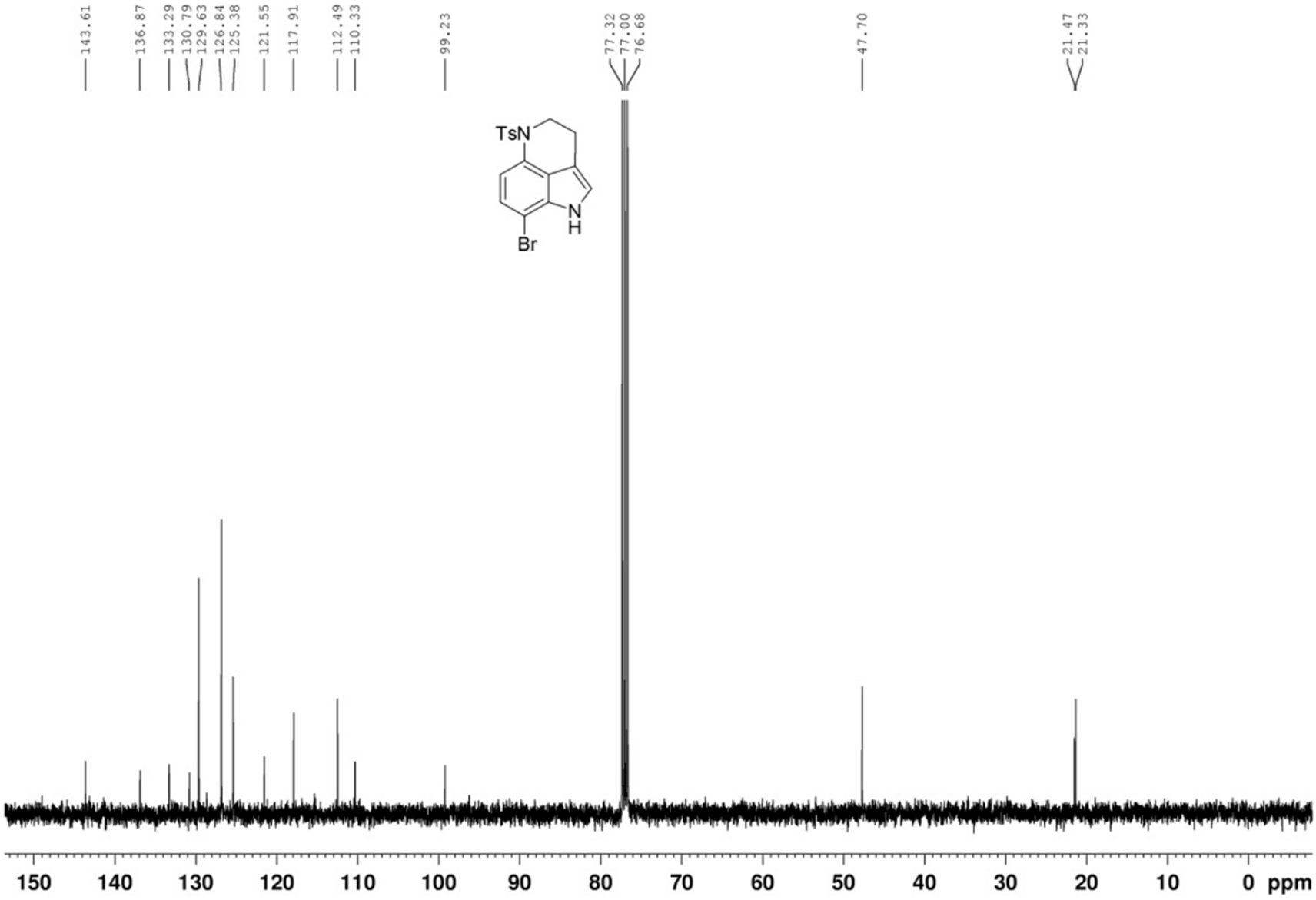
^{13}C NMR of compound 8d ($CDCl_3$, 100 MHz)



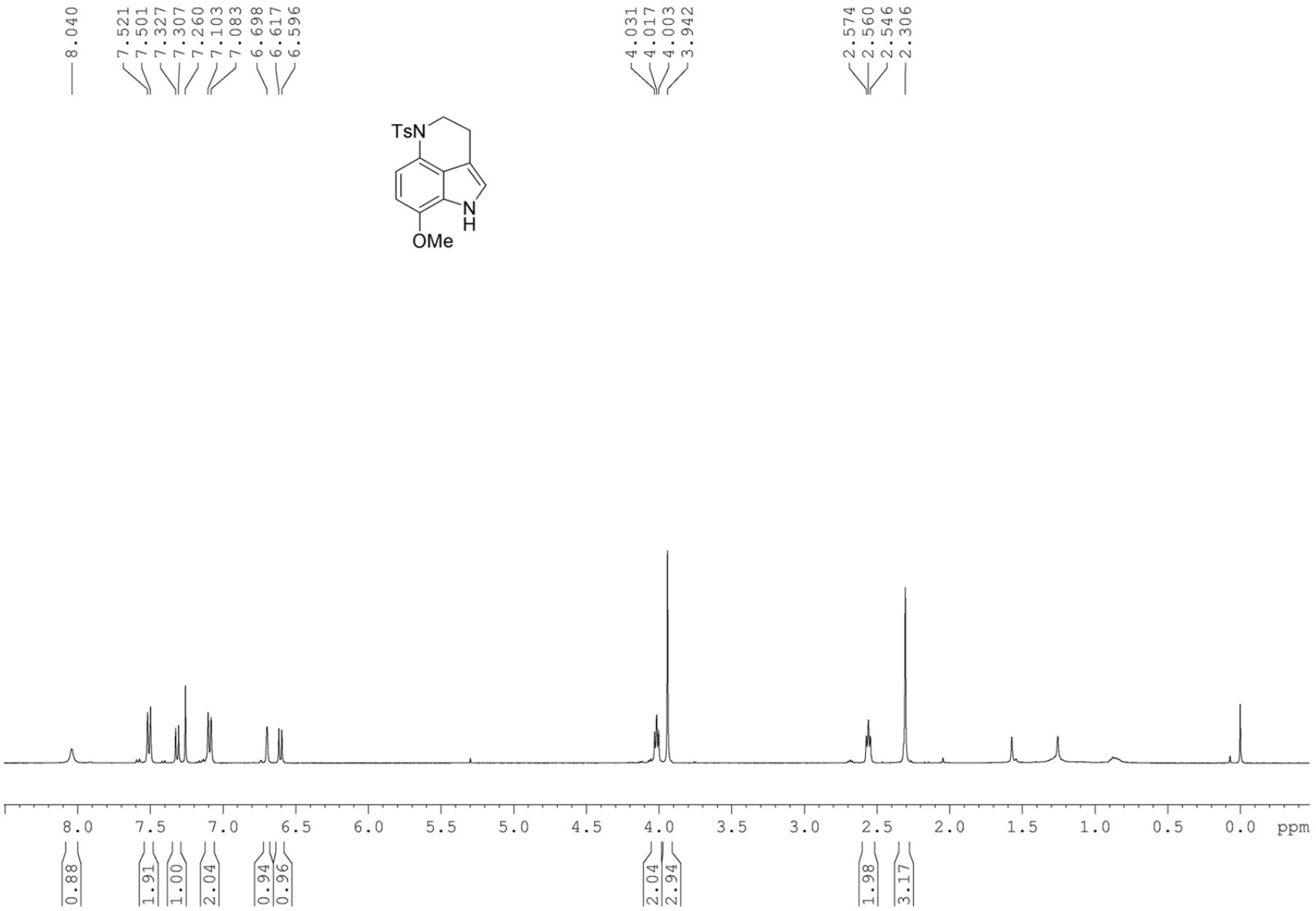
^{1}H NMR of compound 11c ($CDCl_3$, 400 MHz)



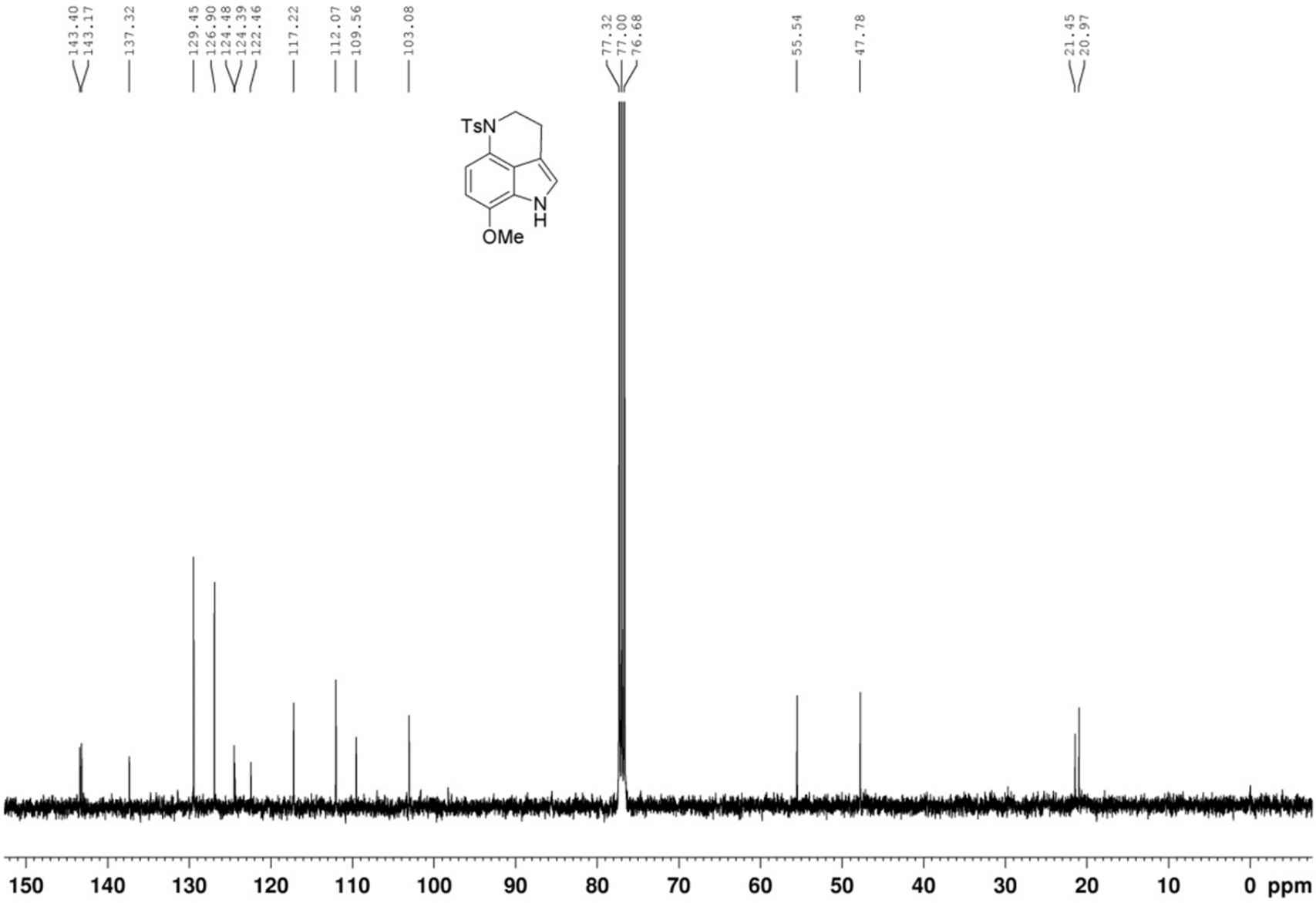
^{13}C NMR of compound 11c ($CDCl_3$, 100 MHz)



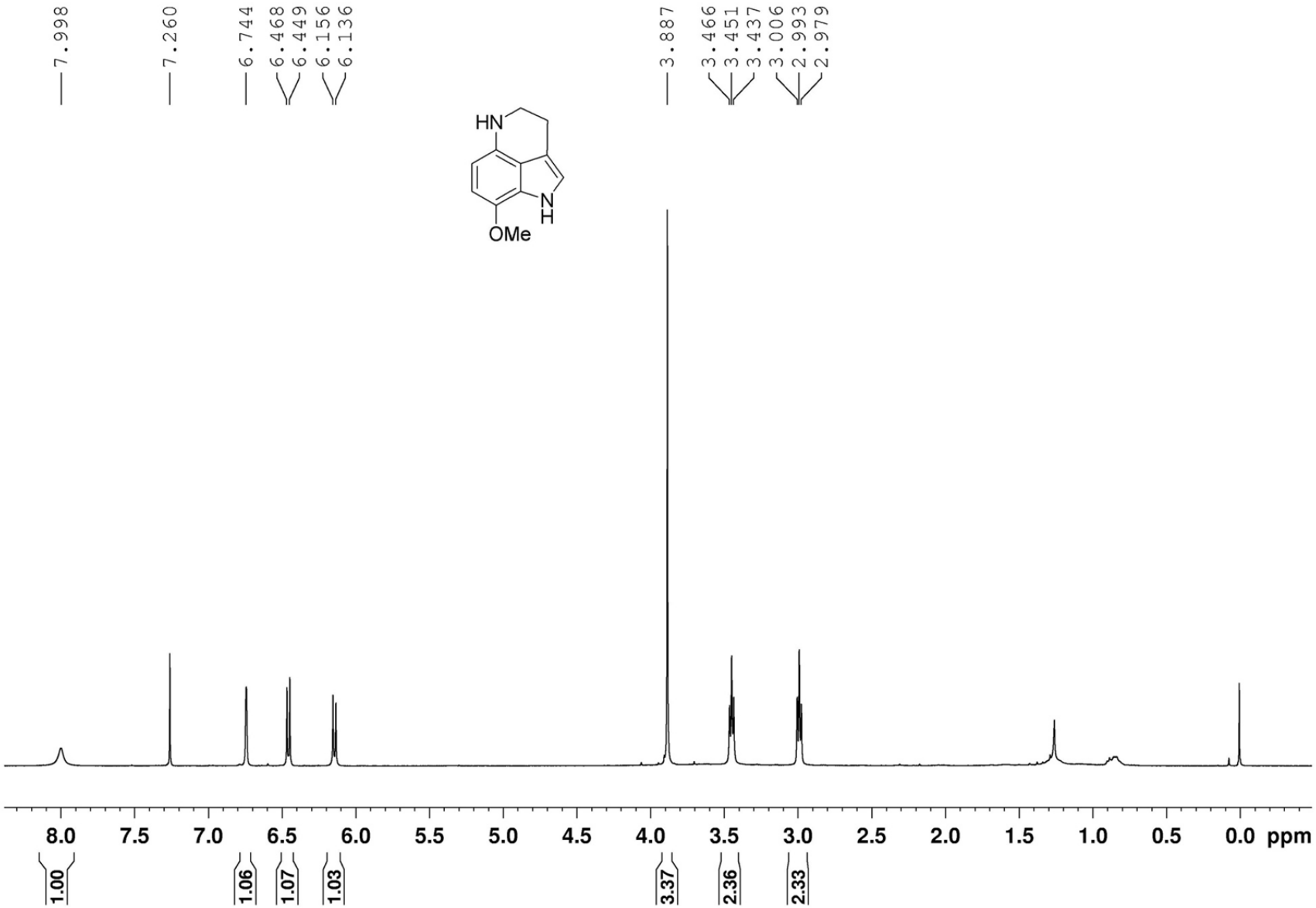
^{1}H NMR of compound 12 ($CDCl_3$, 400 MHz)



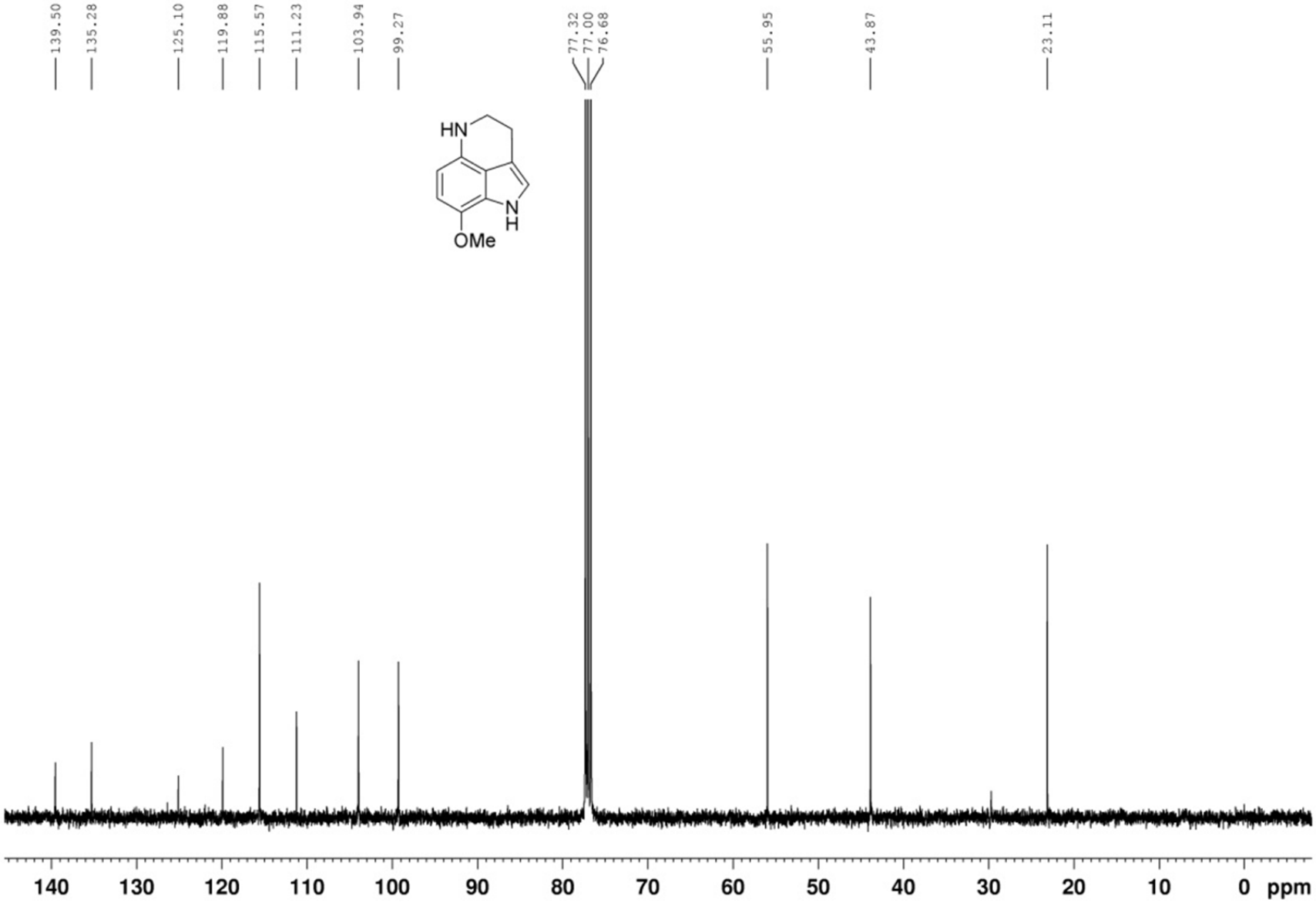
^{13}C NMR of compound 12 ($CDCl_3$, 100 MHz)



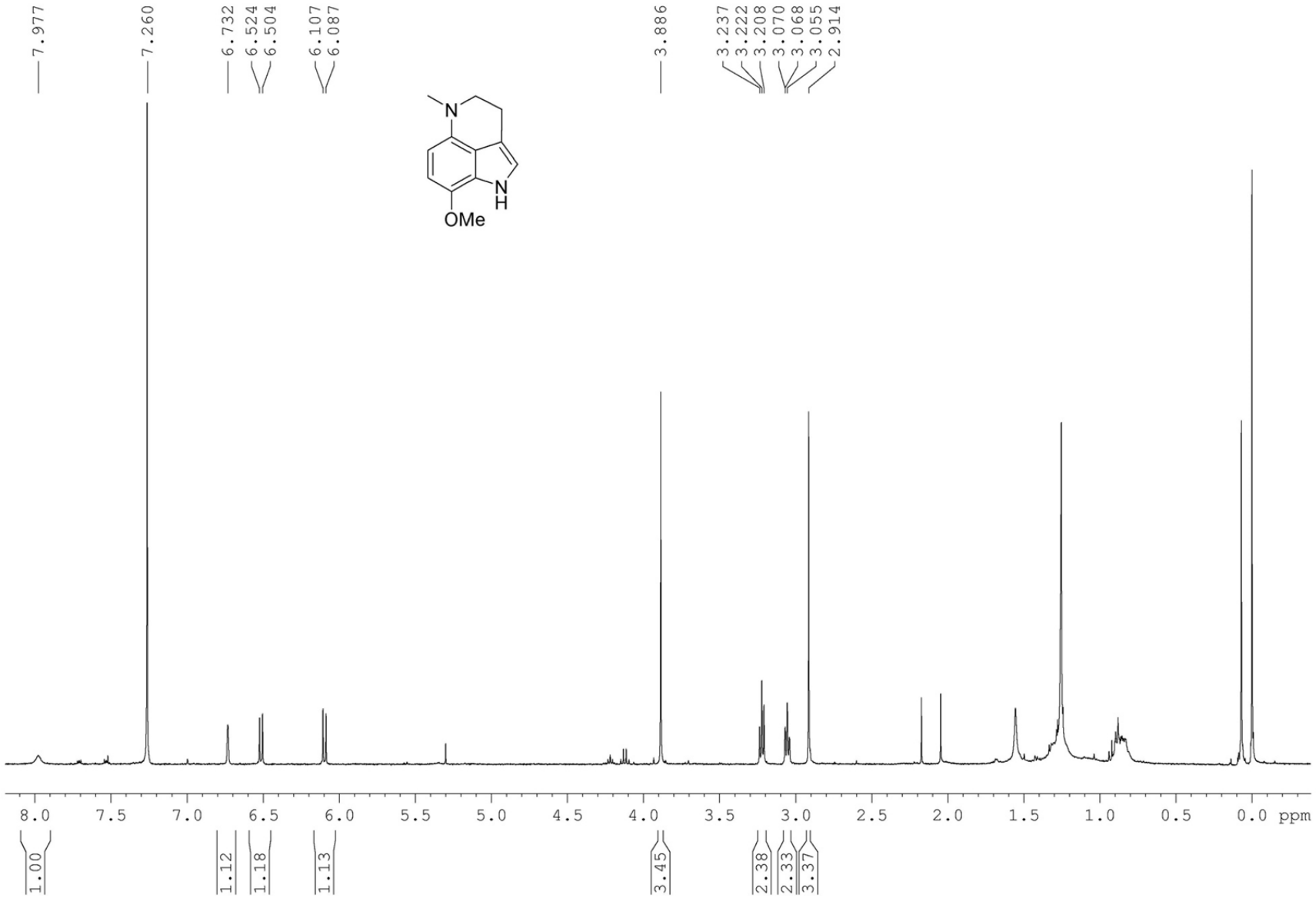
^{1}H NMR of compound 13 ($CDCl_3$, 400 MHz)



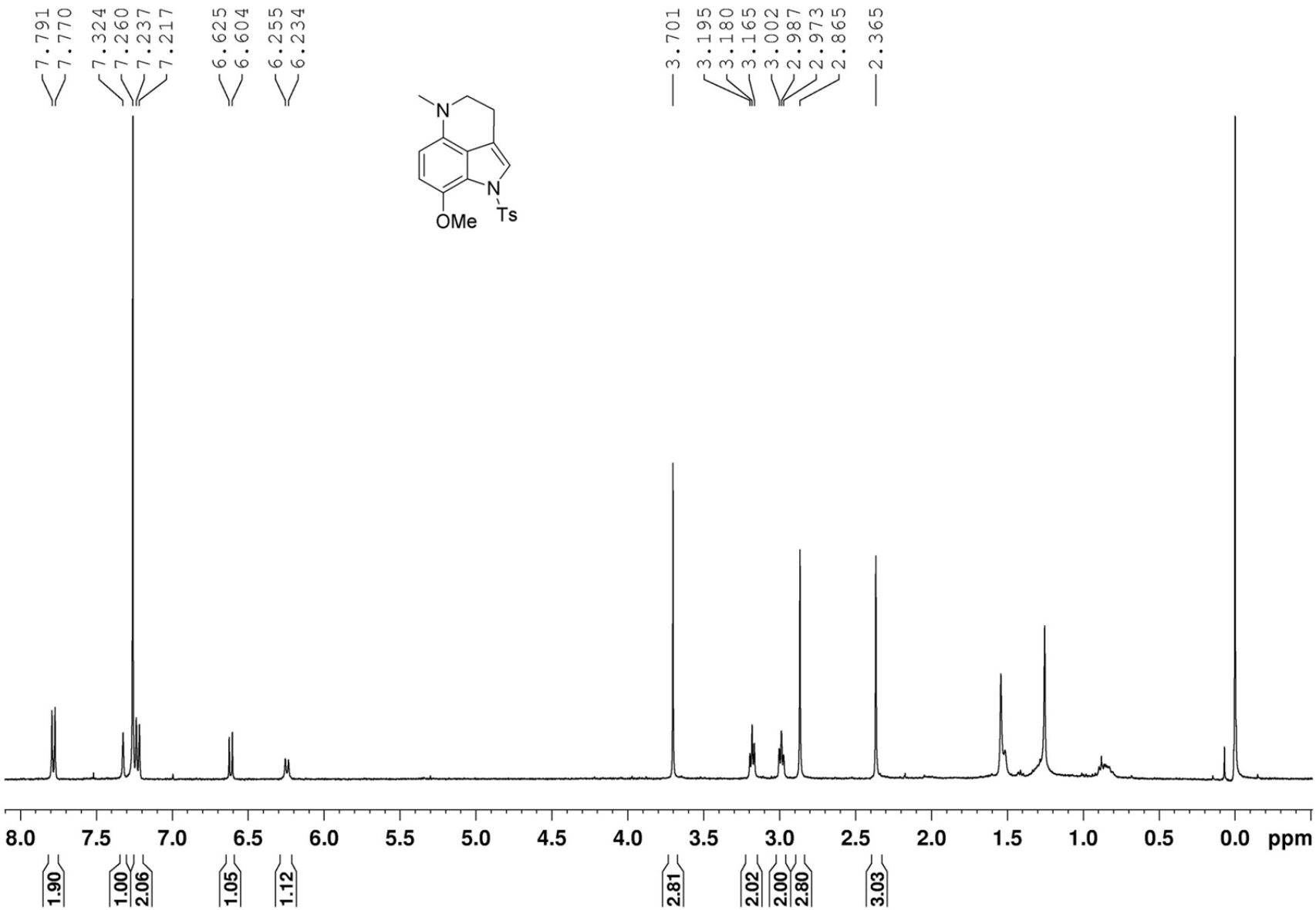
^{13}C NMR of compound 13 ($CDCl_3$, 100 MHz)



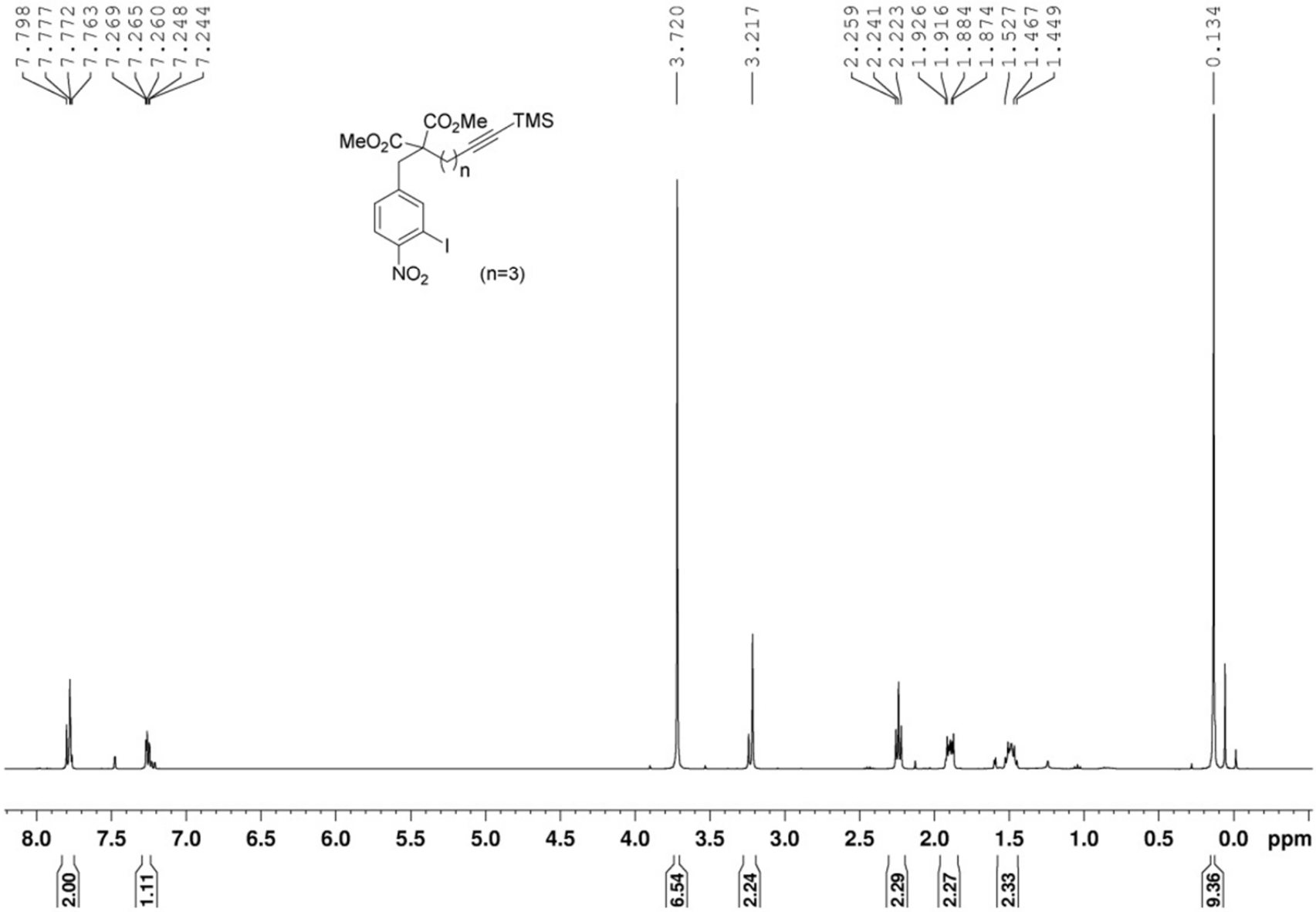
^{1}H NMR of compound 14 ($CDCl_3$, 400 MHz)



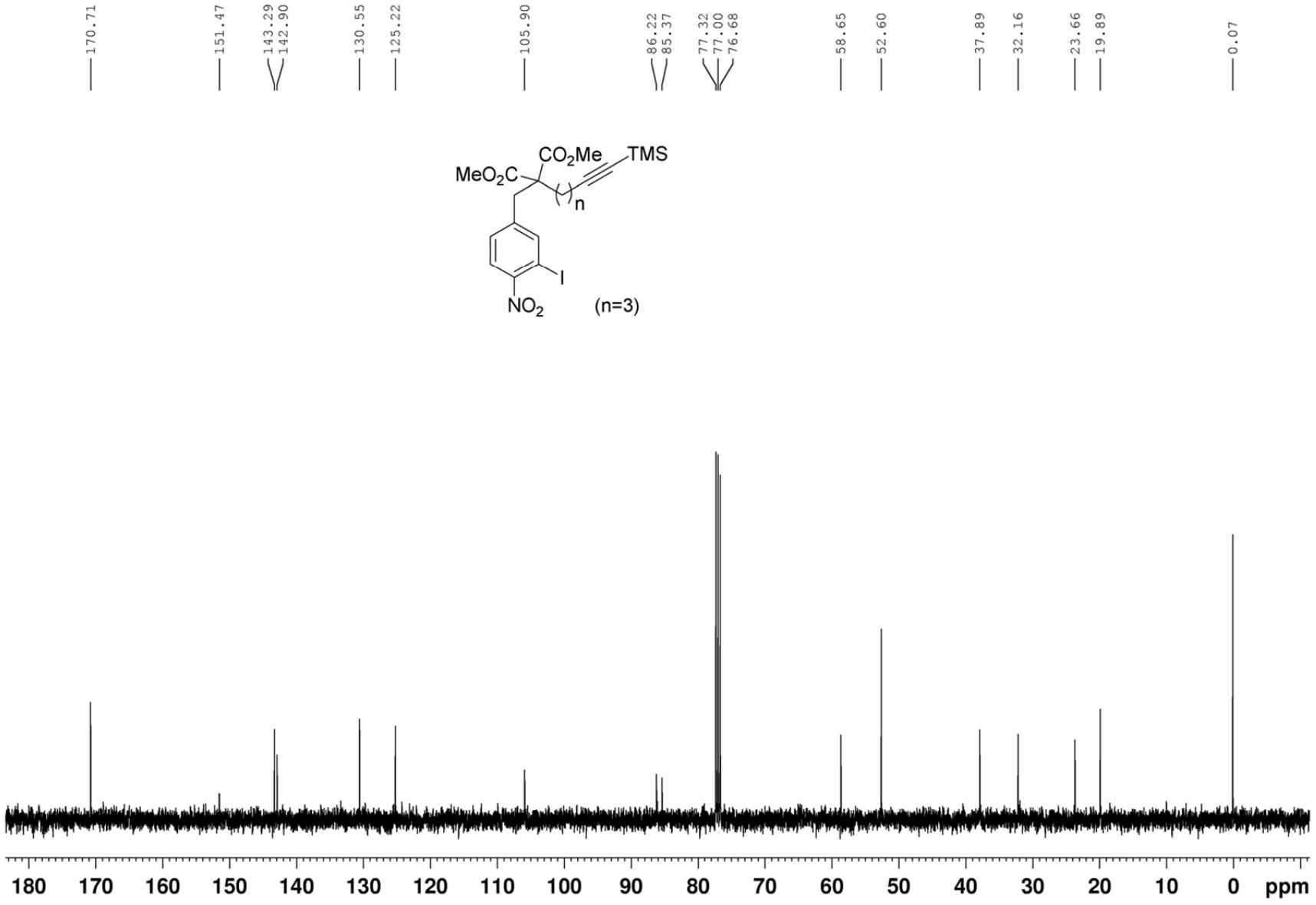
^{1}H NMR of compound 10 ($CDCl_3$, 400 MHz)



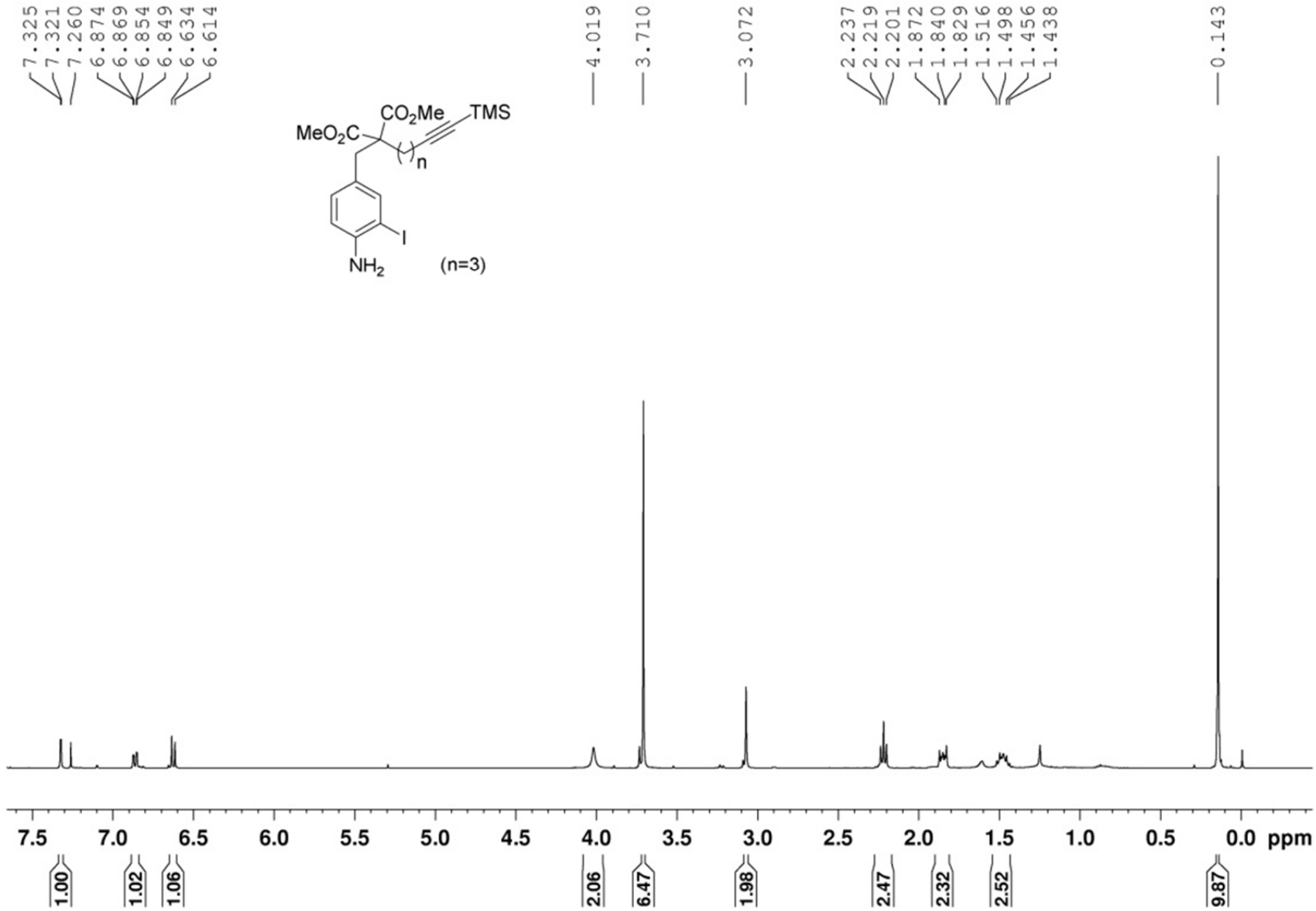
^{1}H NMR of compound S2a ($CDCl_3$, 400 MHz)



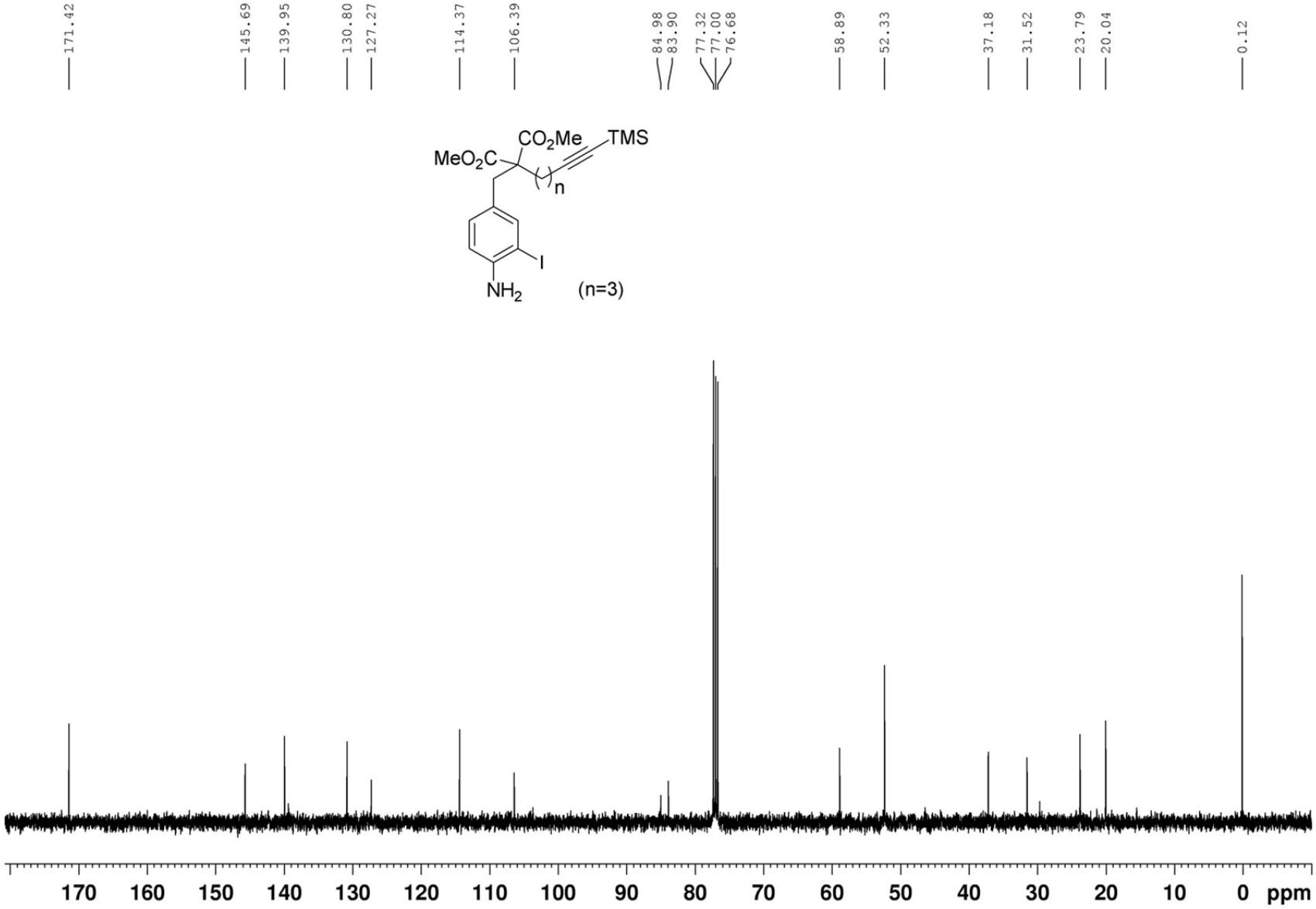
^{13}C NMR of compound S2a ($CDCl_3$, 100 MHz)



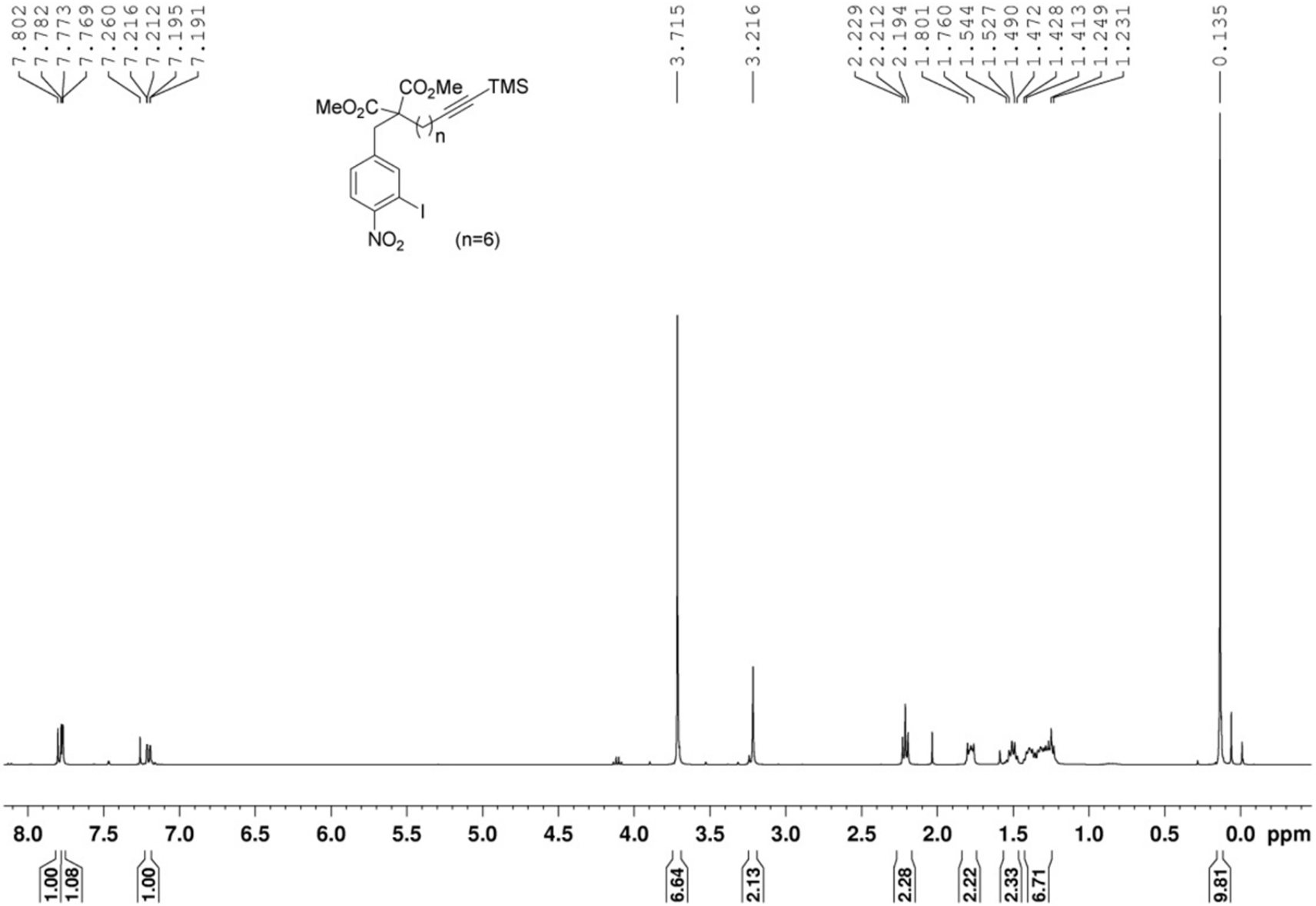
^{1}H NMR of compound 7a ($CDCl_3$, 400 MHz)



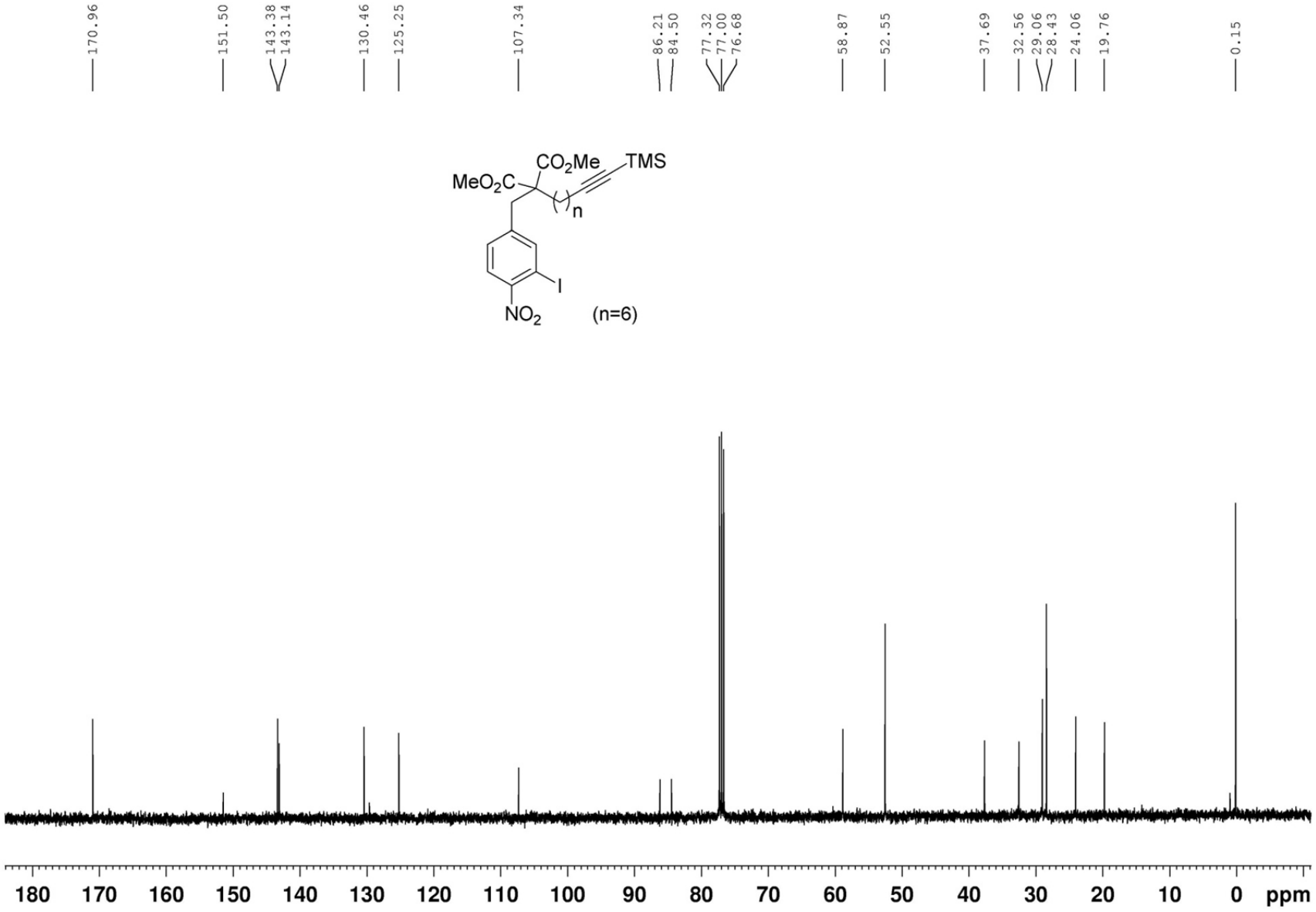
^{13}C NMR of compound 7a ($CDCl_3$, 100 MHz)



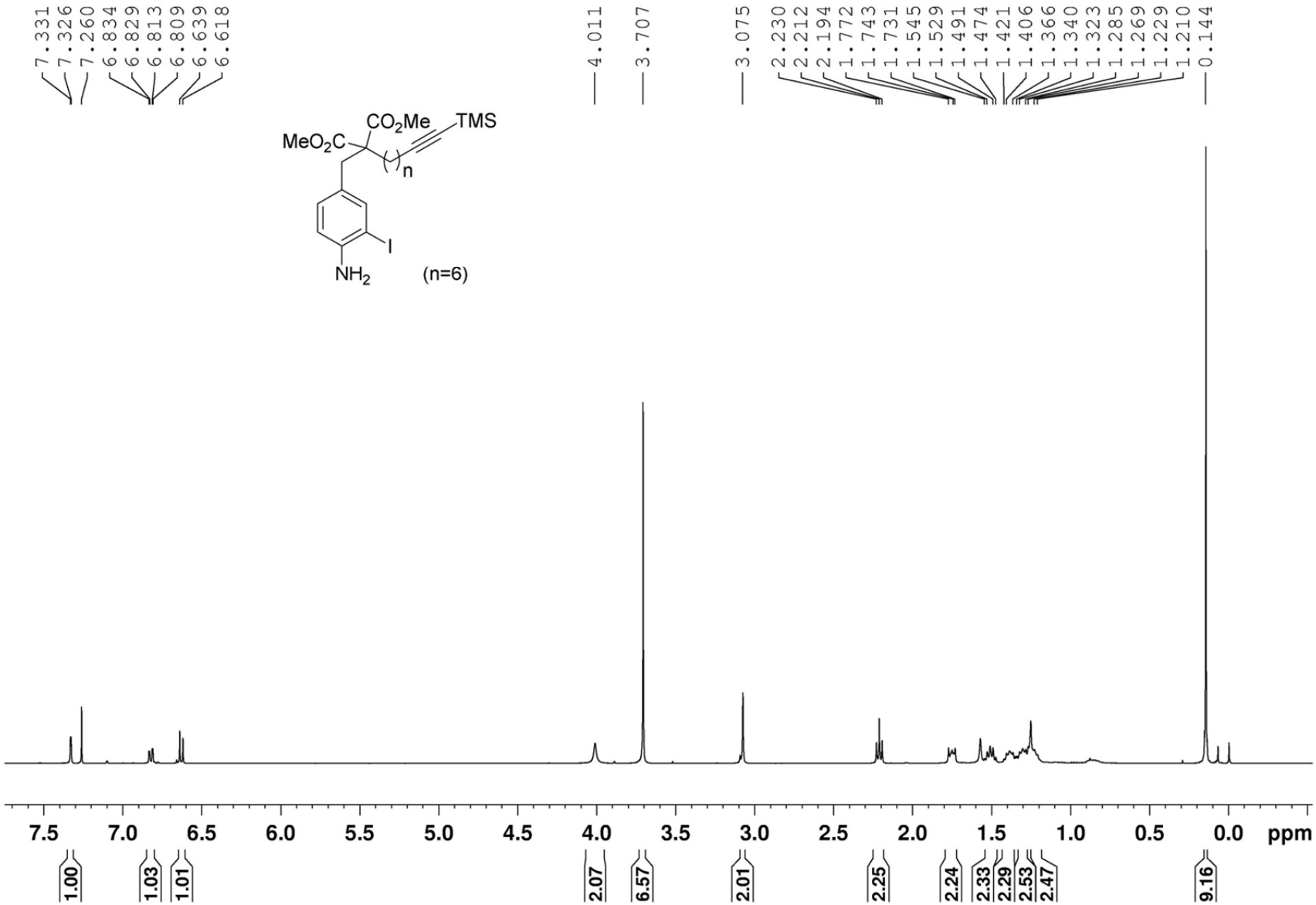
^{1}H NMR of compound S2b ($CDCl_3$, 400 MHz)



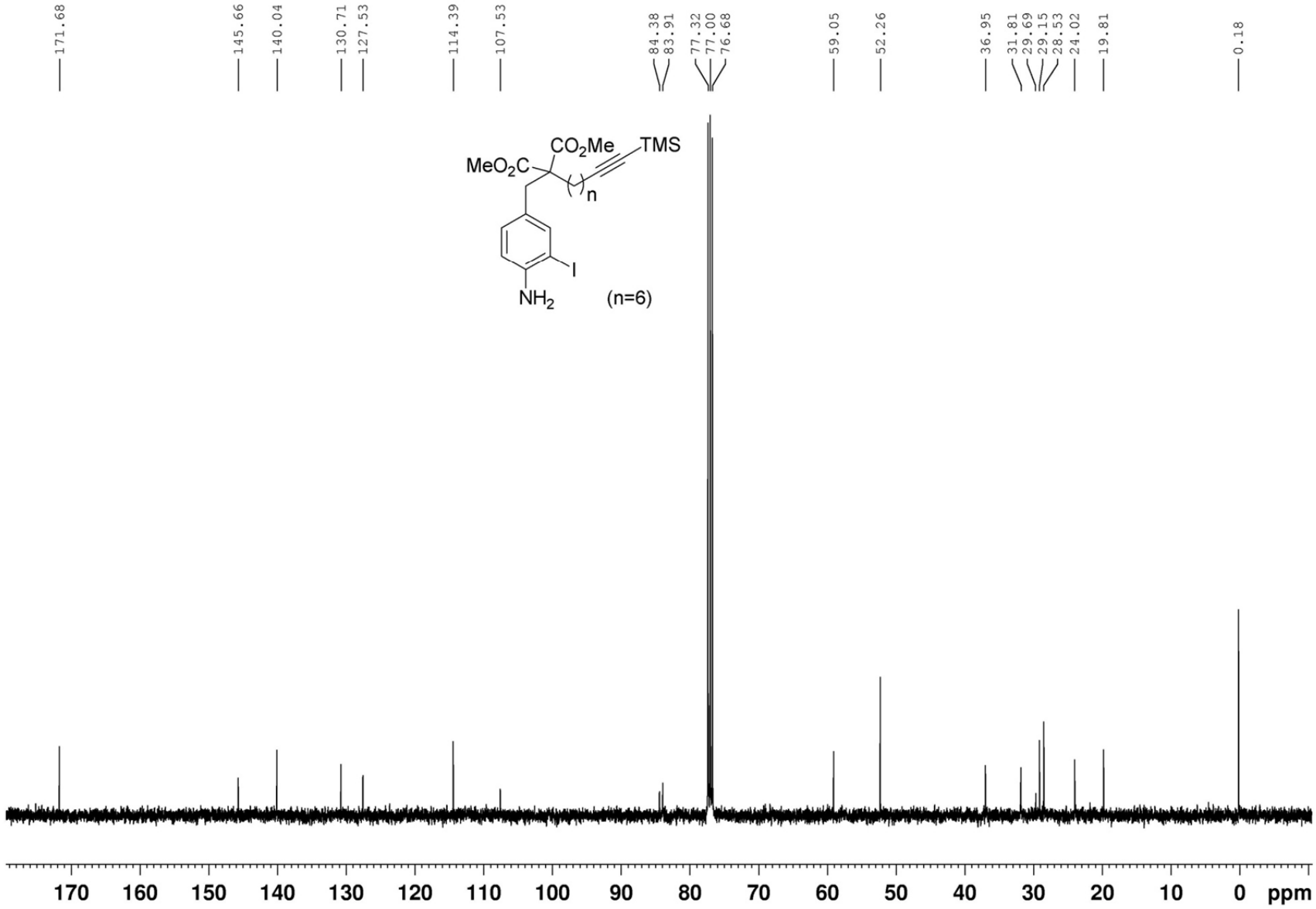
^{13}C NMR of compound S2b ($CDCl_3$, 100 MHz)



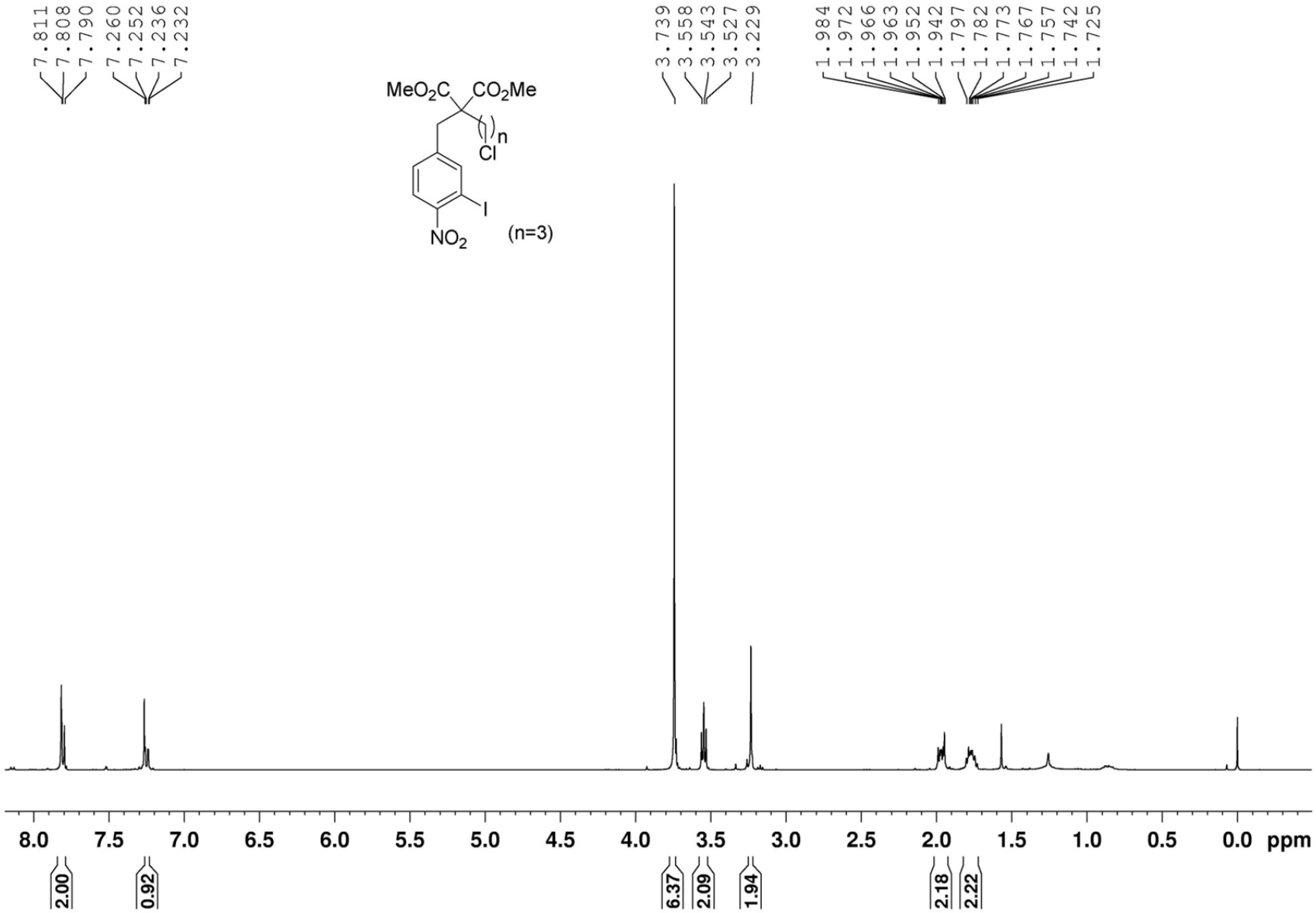
^{1}H NMR of compound 7b ($CDCl_3$, 400 MHz)



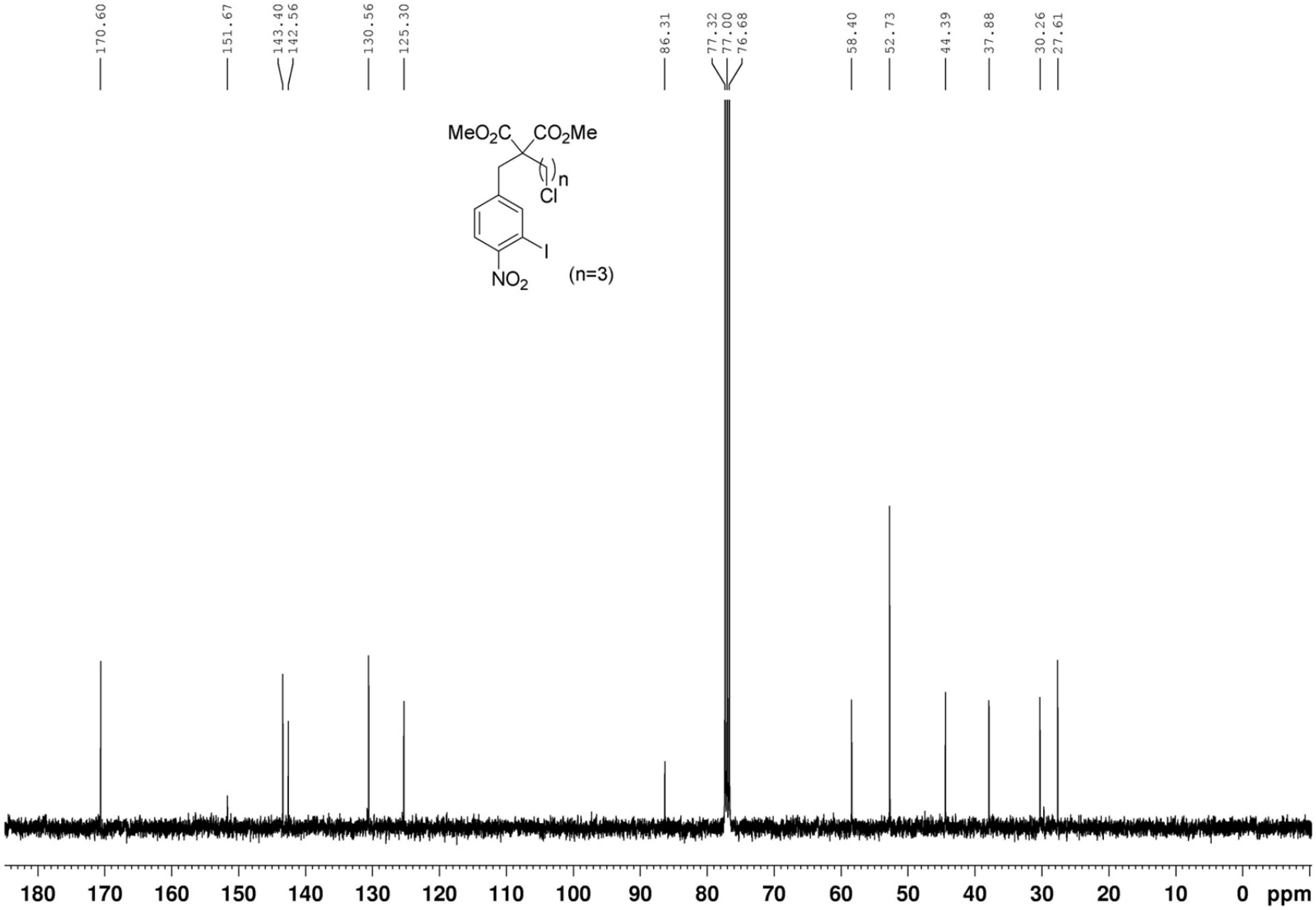
^{13}C NMR of compound 7b ($CDCl_3$, 100 MHz)



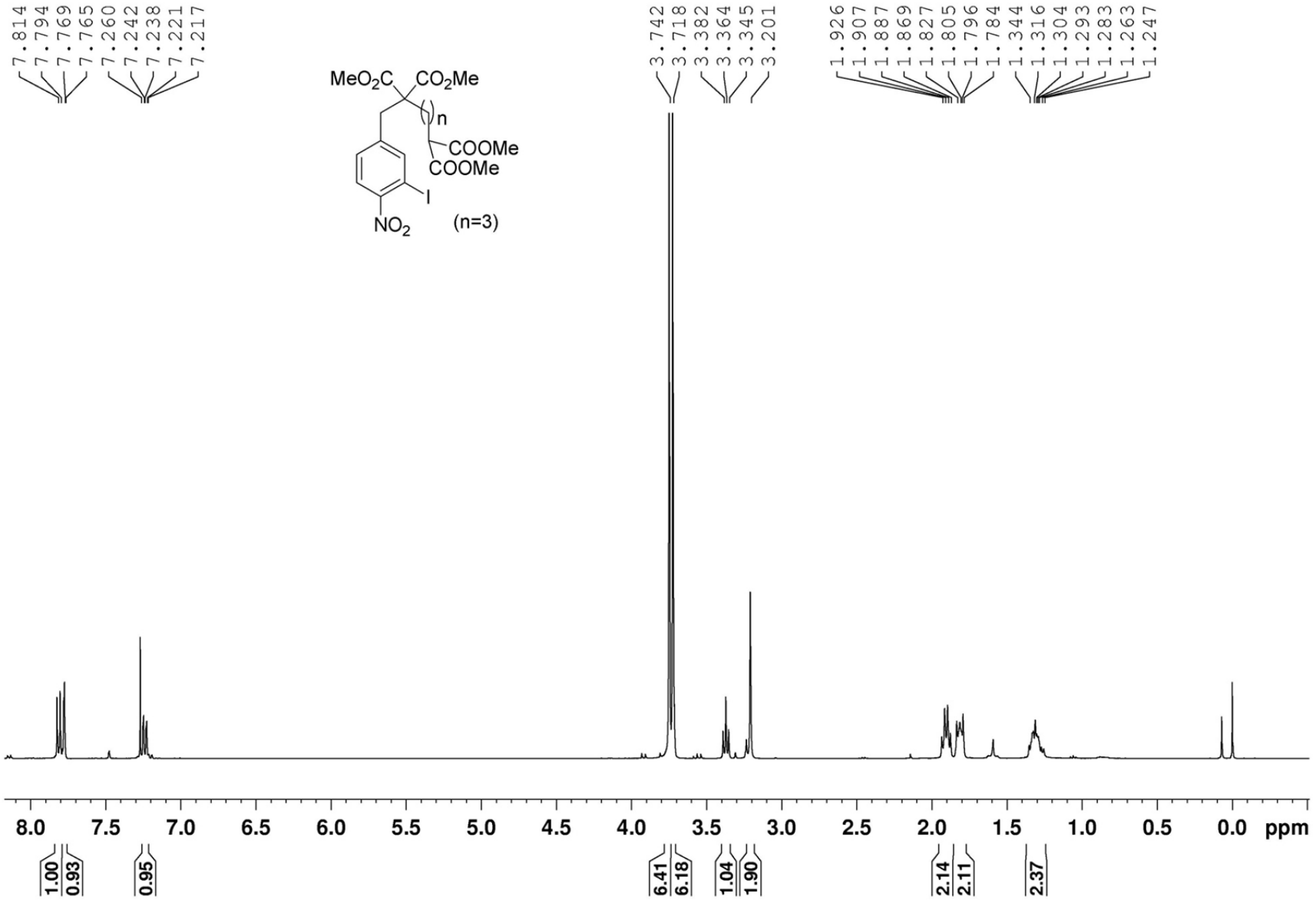
^{1}H NMR of compound S5a ($CDCl_3$, 400 MHz)



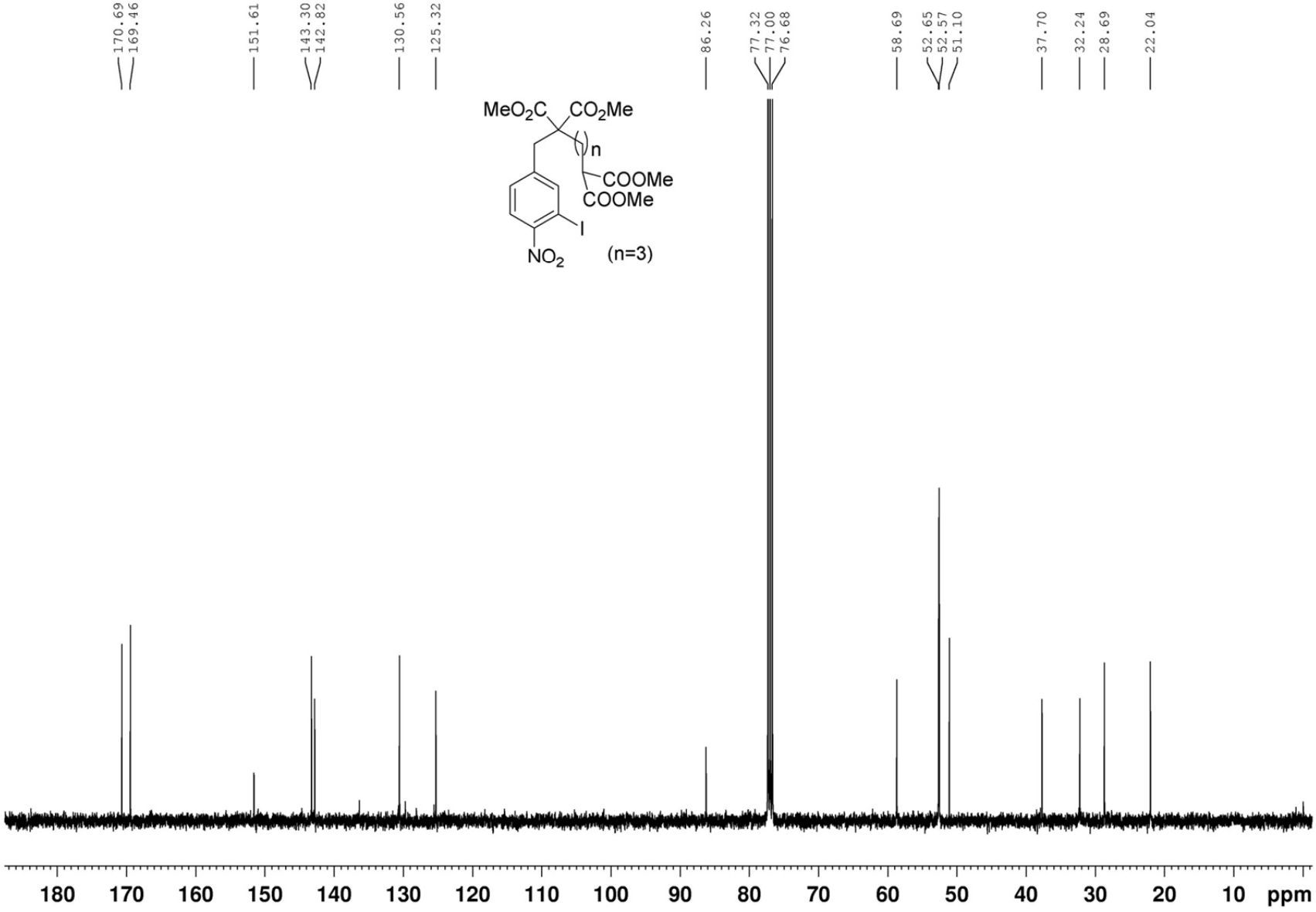
^{13}C NMR of compound S5a ($CDCl_3$, 100 MHz)



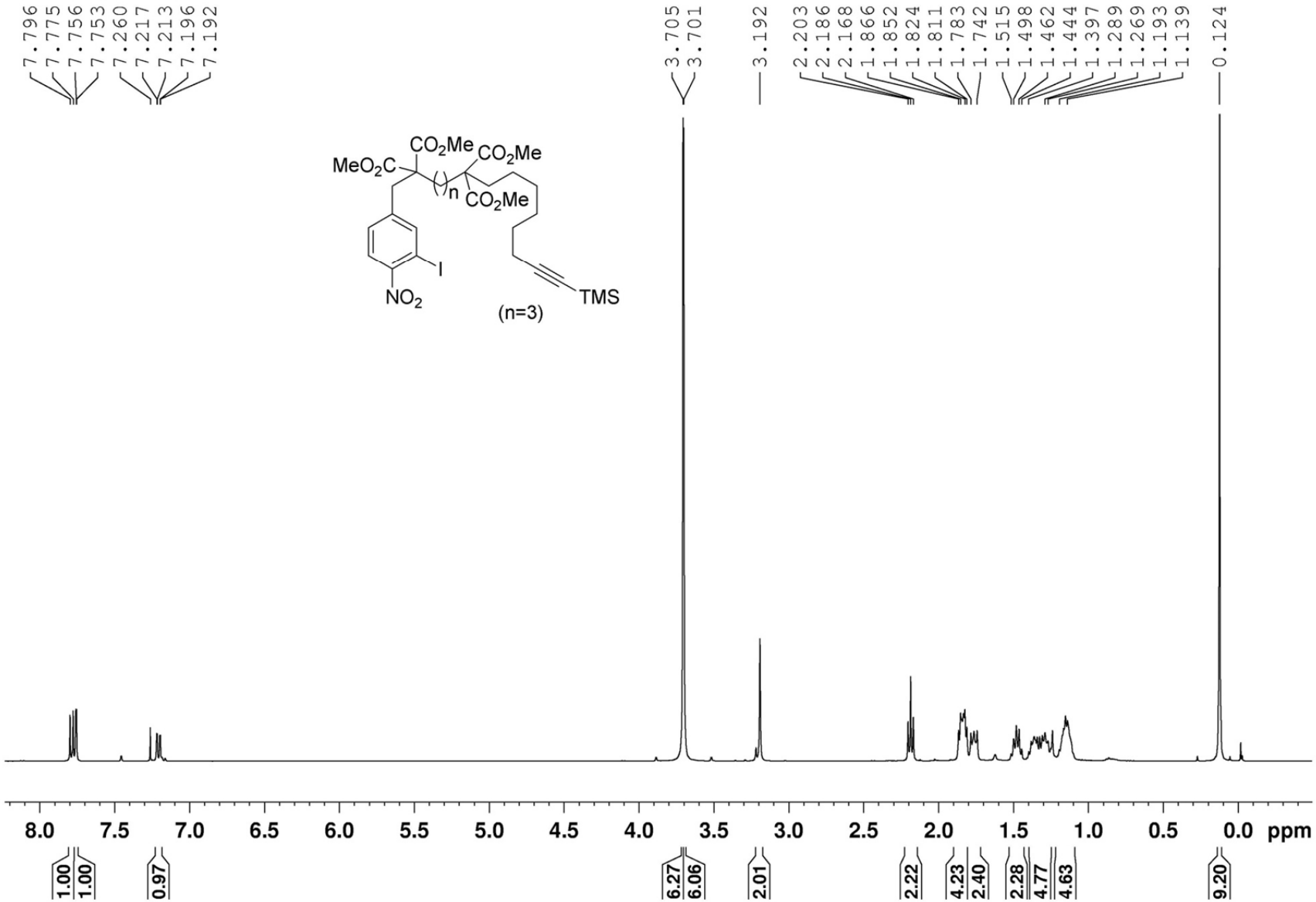
^{1}H NMR of compound S7a ($CDCl_3$, 400 MHz)



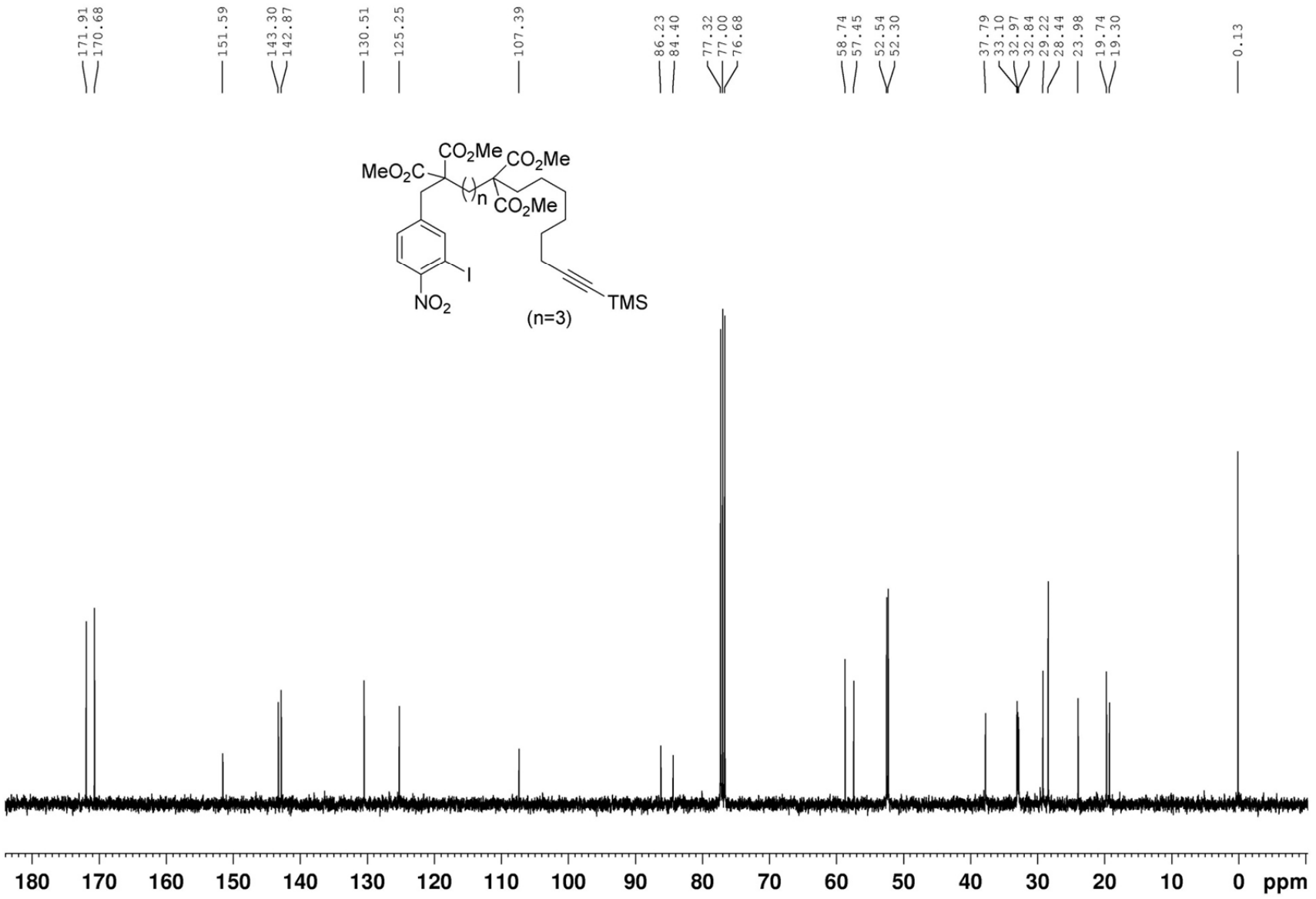
^{13}C NMR of compound S7a ($CDCl_3$, 100 MHz)



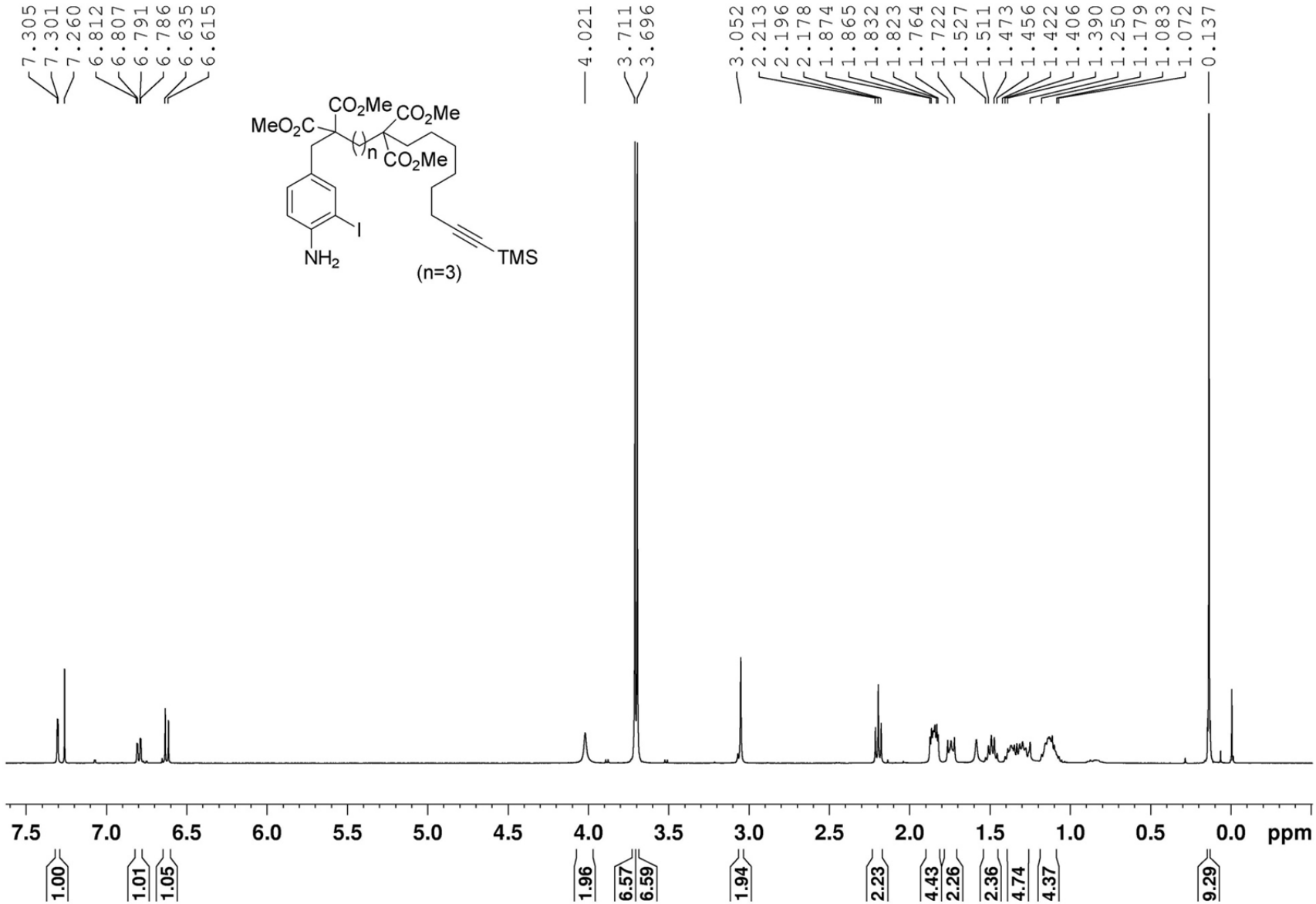
^{1}H NMR of compound S2c ($CDCl_3$, 400 MHz)



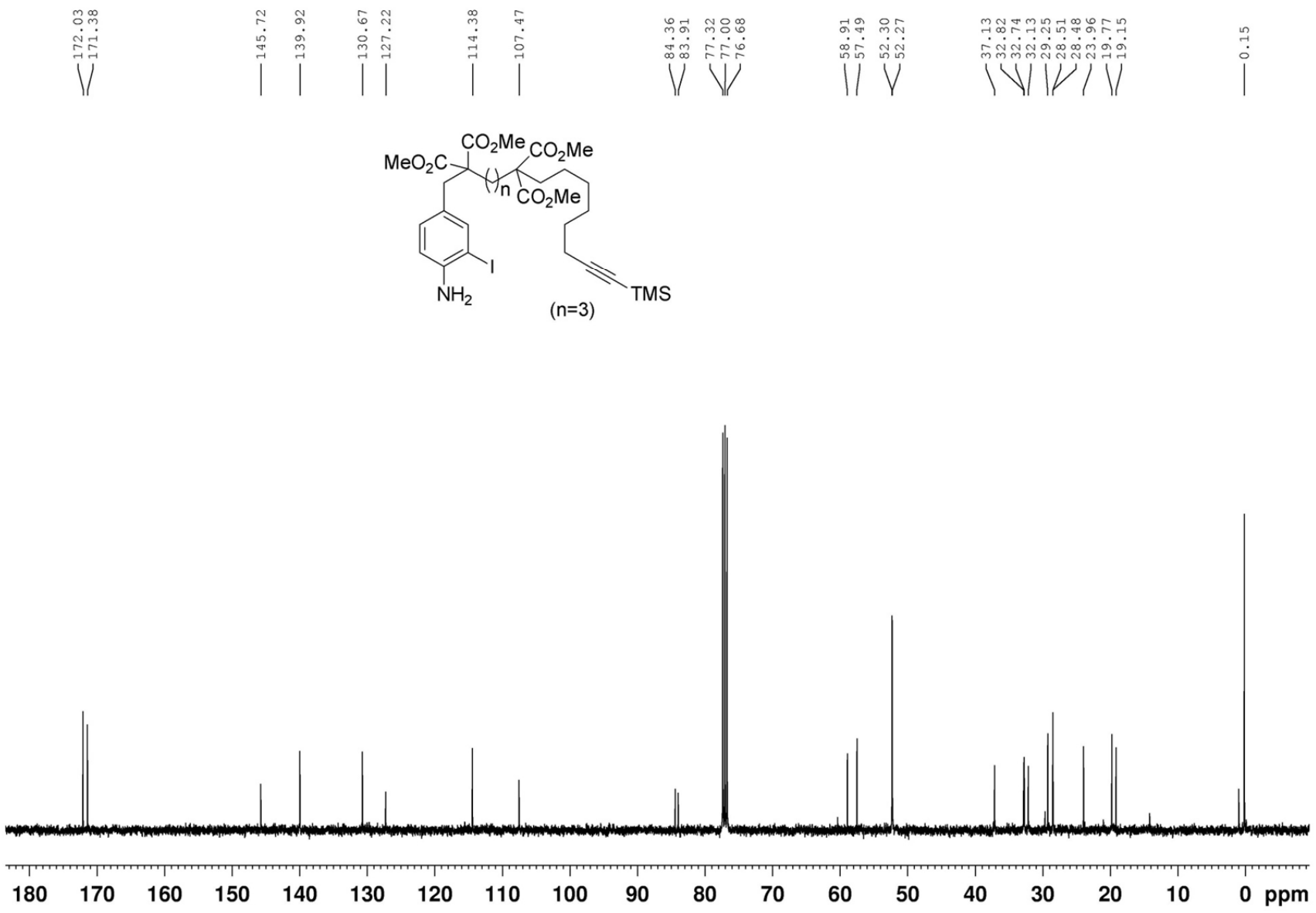
^{13}C NMR of compound S2c ($CDCl_3$, 100 MHz)



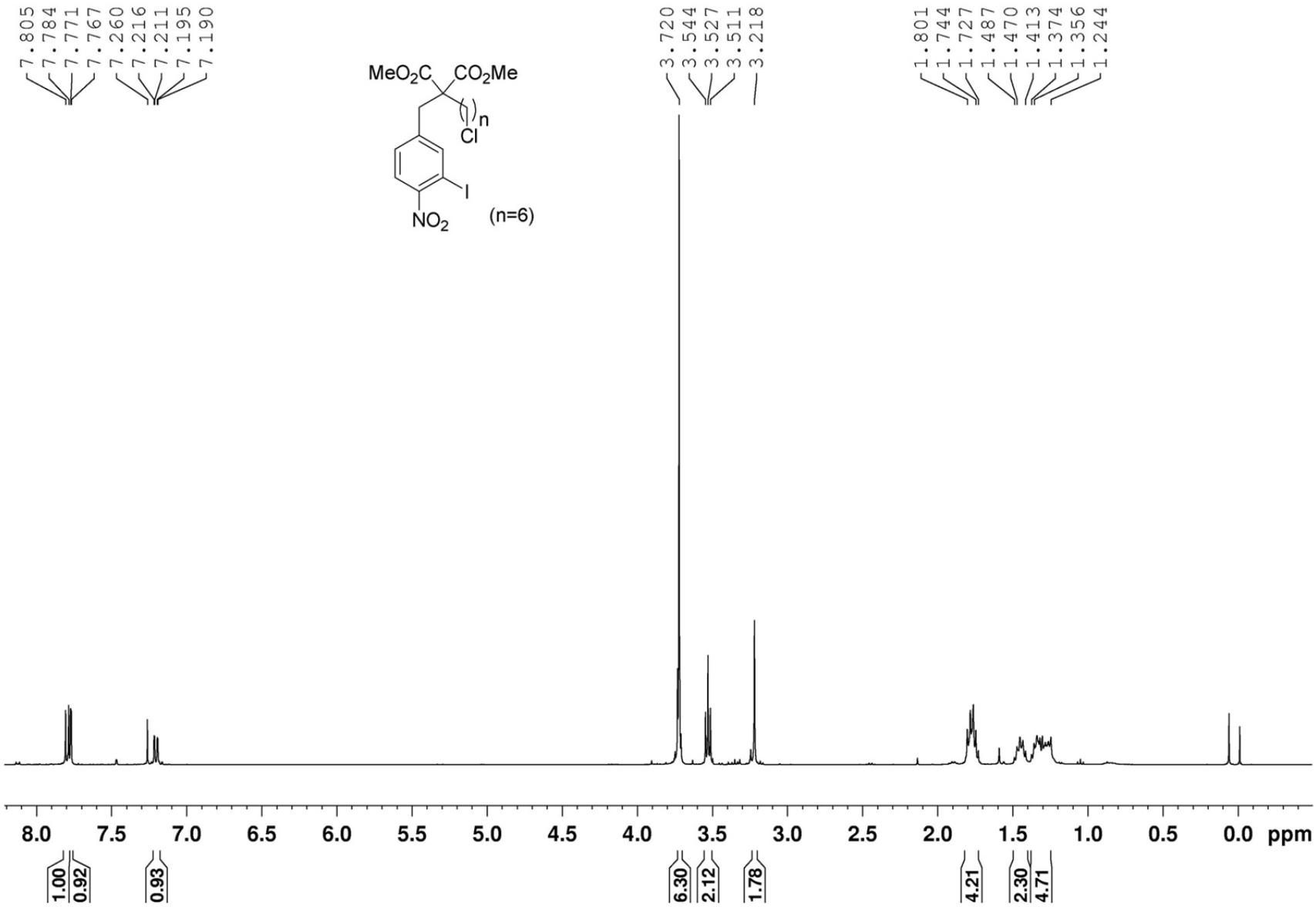
^{1}H NMR of compound 7c ($CDCl_3$, 400 MHz)



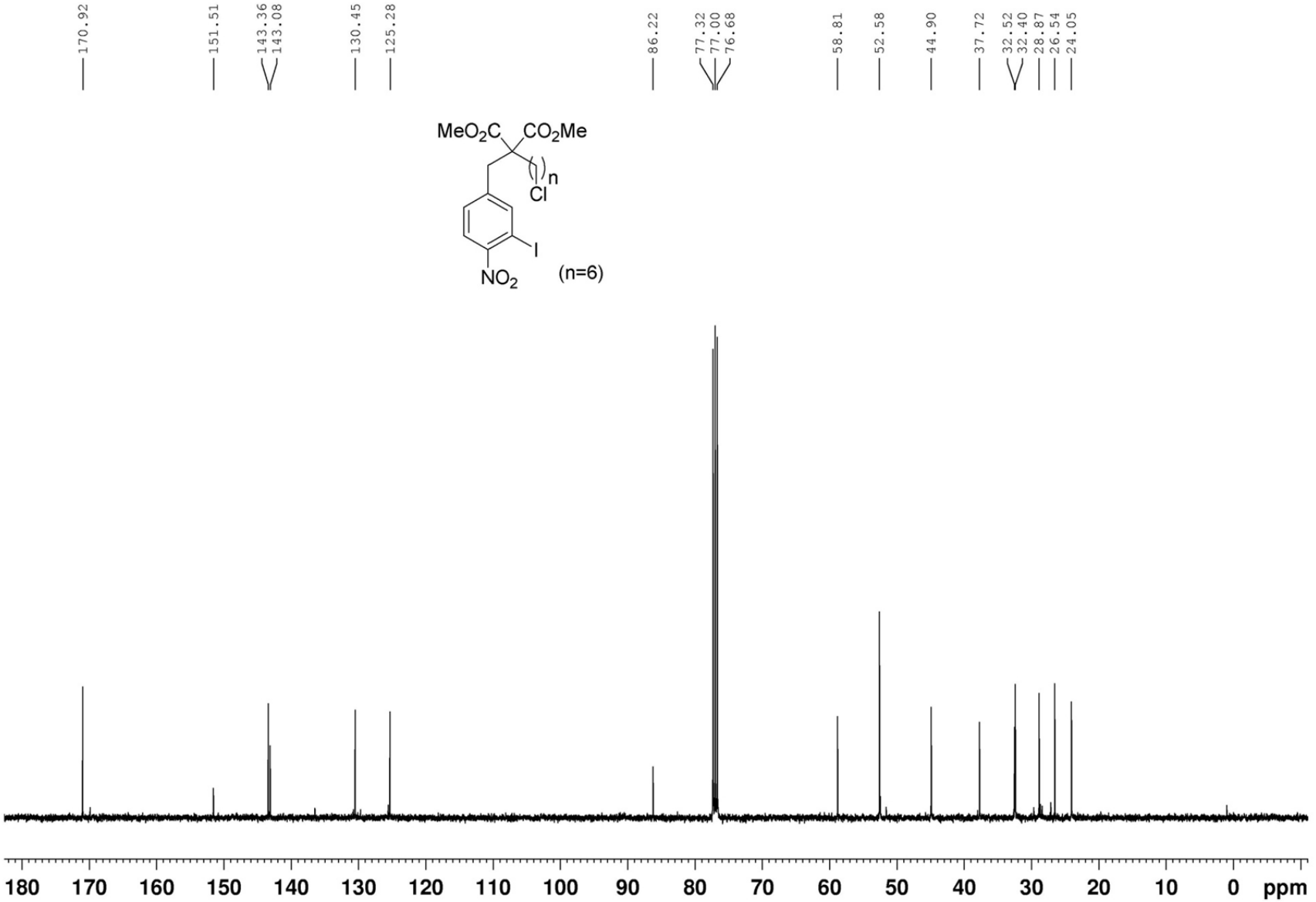
^{13}C NMR of compound 7c ($CDCl_3$, 100 MHz)



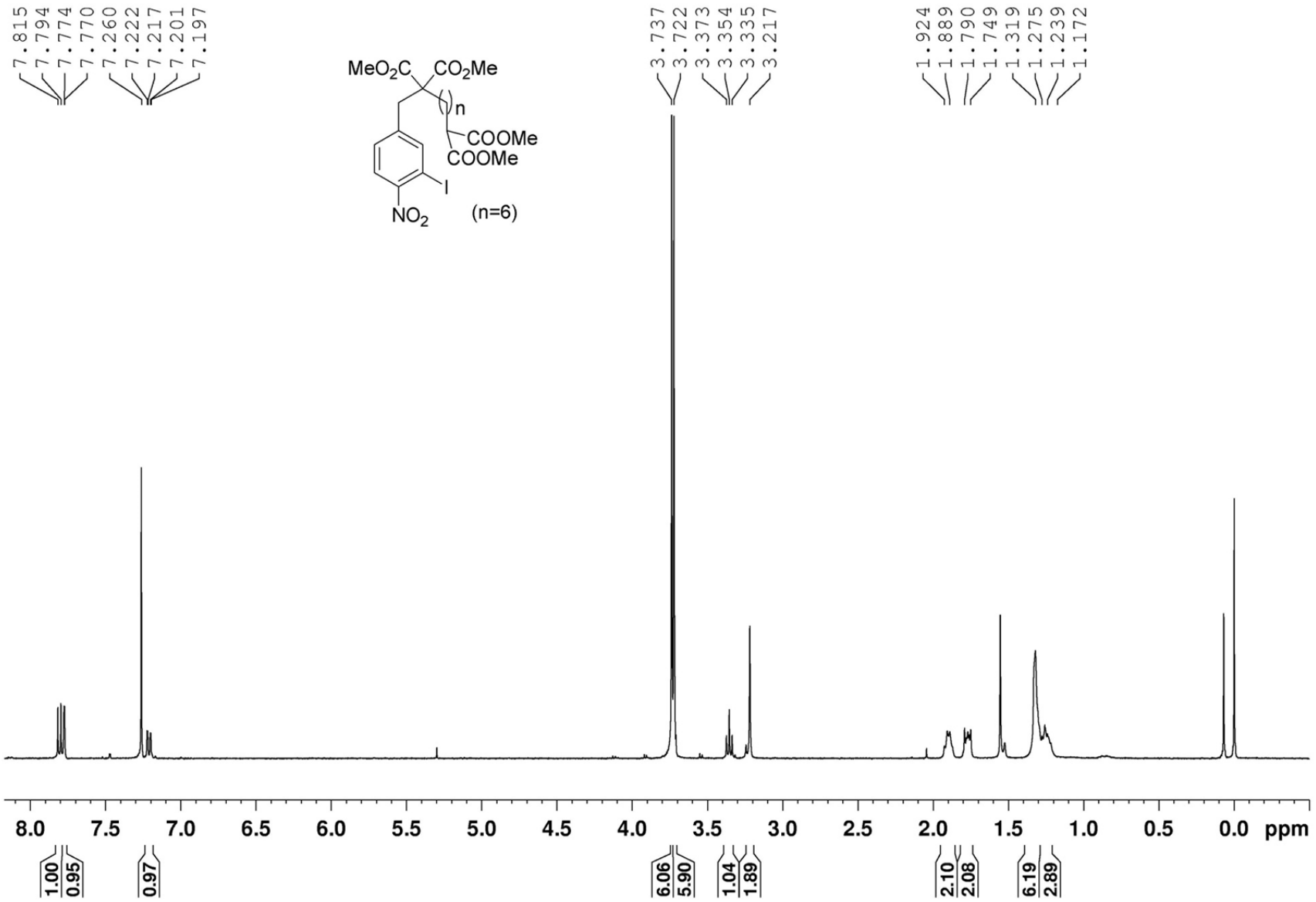
^{1}H NMR of compound S5b ($CDCl_3$, 400 MHz)



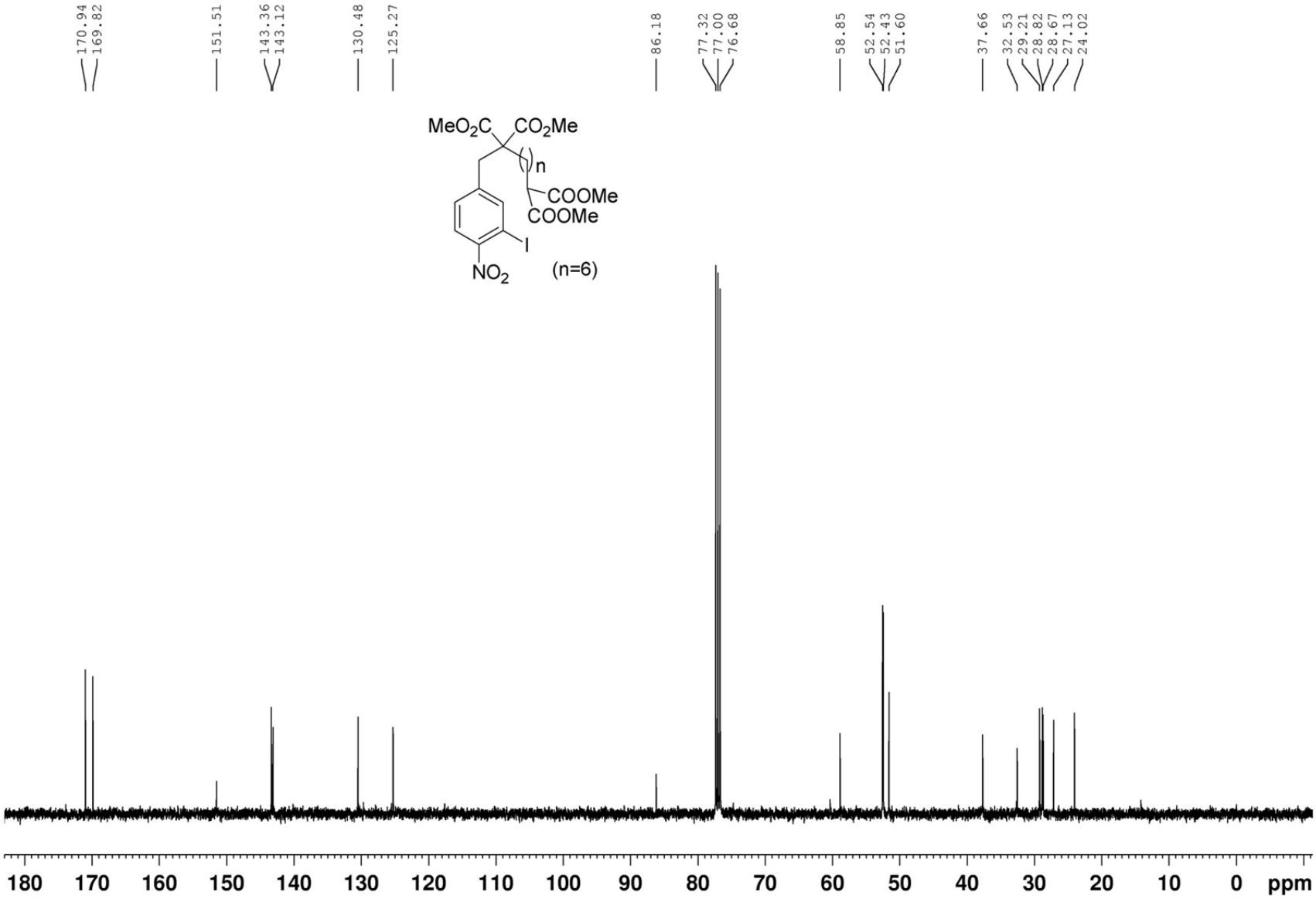
^{13}C NMR of compound S5b ($CDCl_3$, 100 MHz)



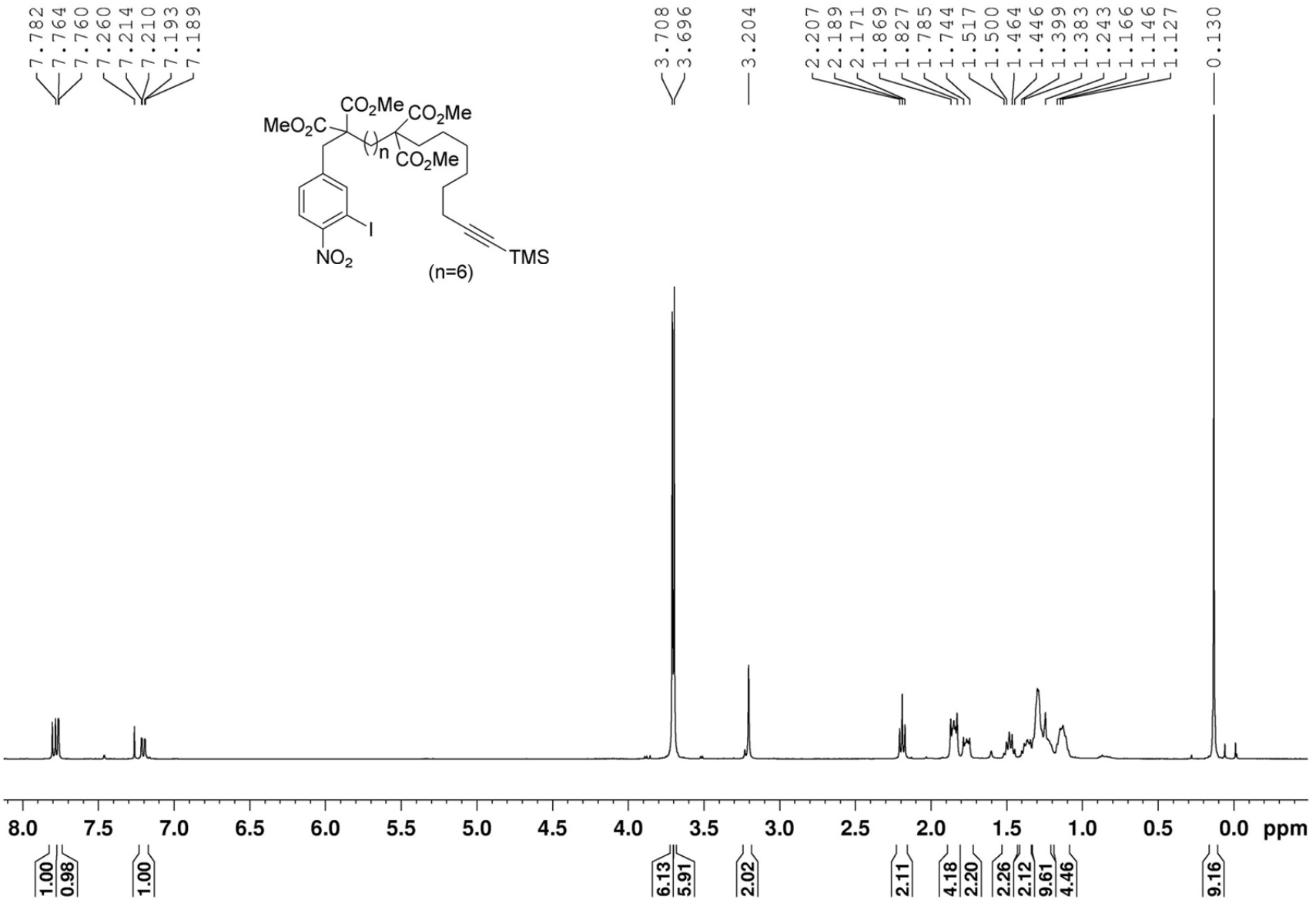
^{1}H NMR of compound S7b ($CDCl_3$, 400 MHz)



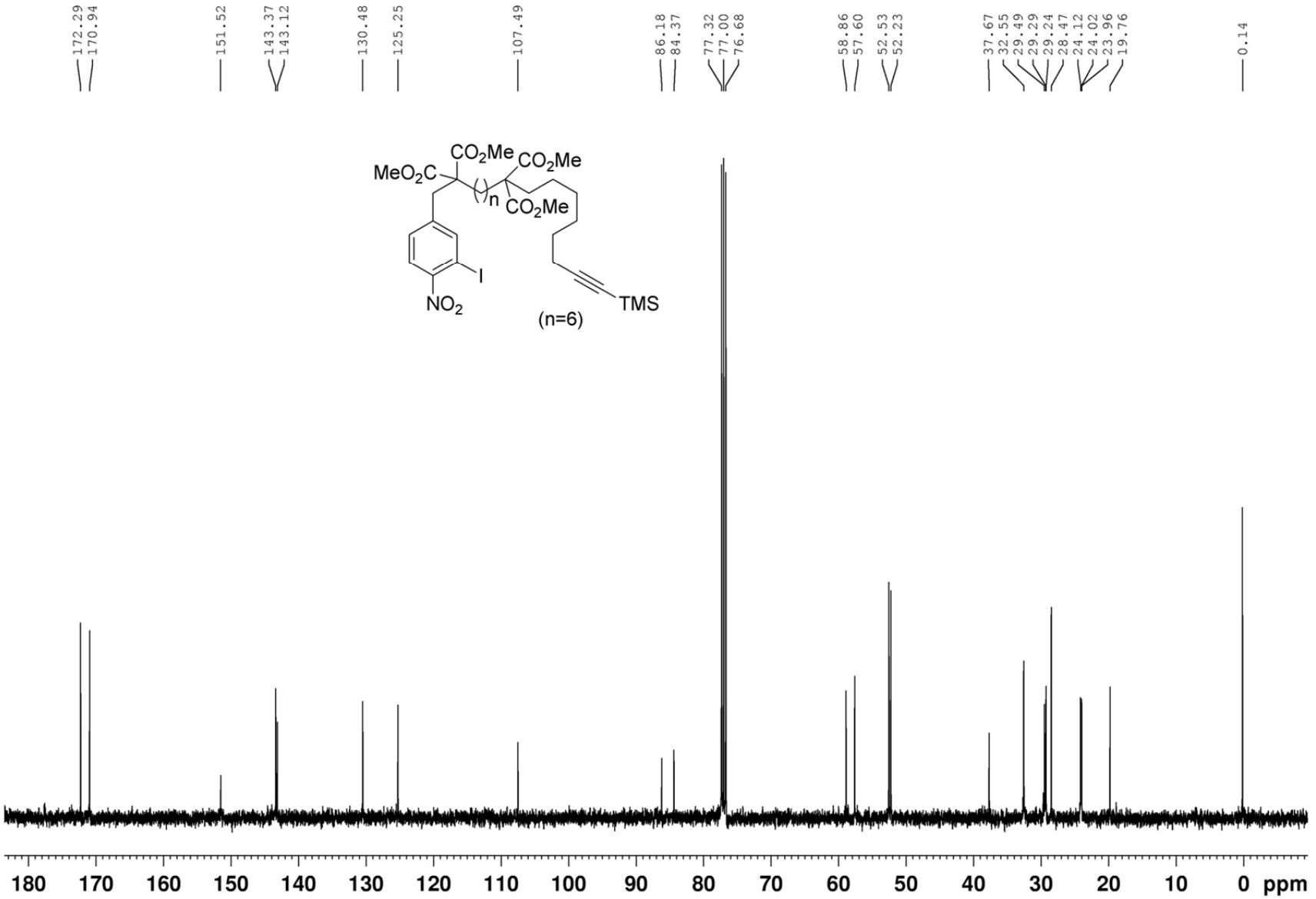
^{13}C NMR of compound S7b ($CDCl_3$, 100 MHz)



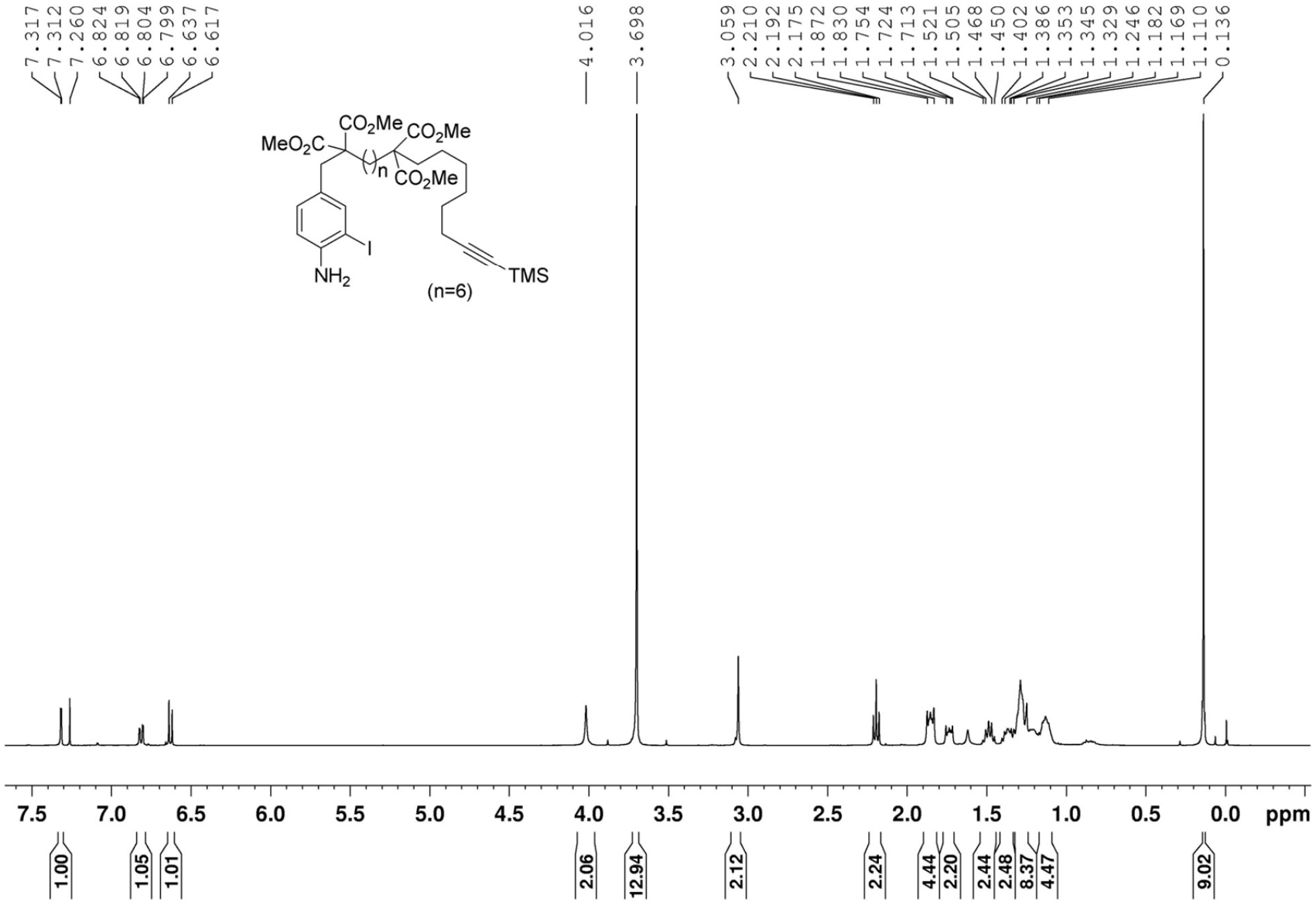
^{1}H NMR of compound S2d ($CDCl_3$, 400 MHz)



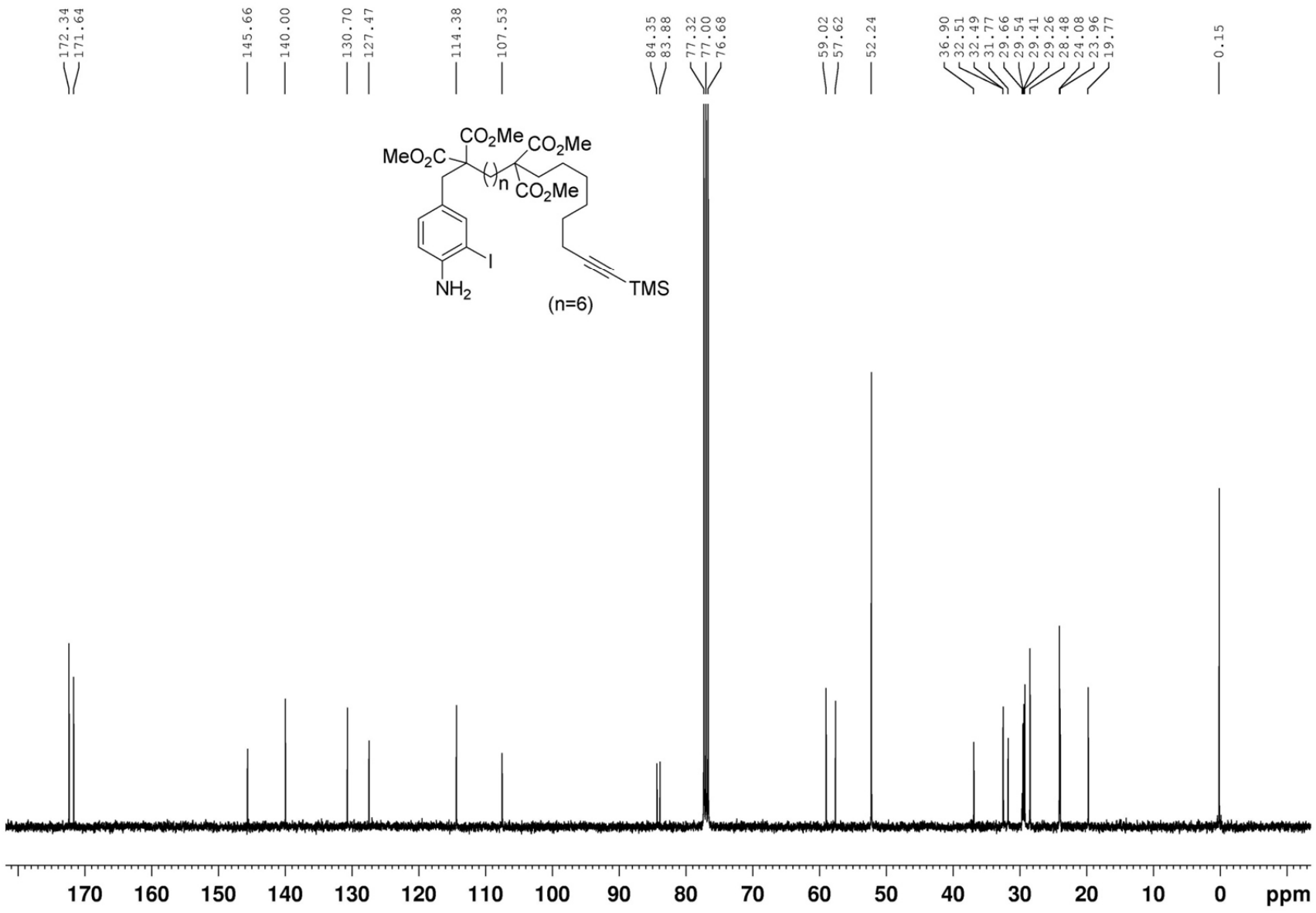
^{13}C NMR of compound S2d ($CDCl_3$, 100 MHz)



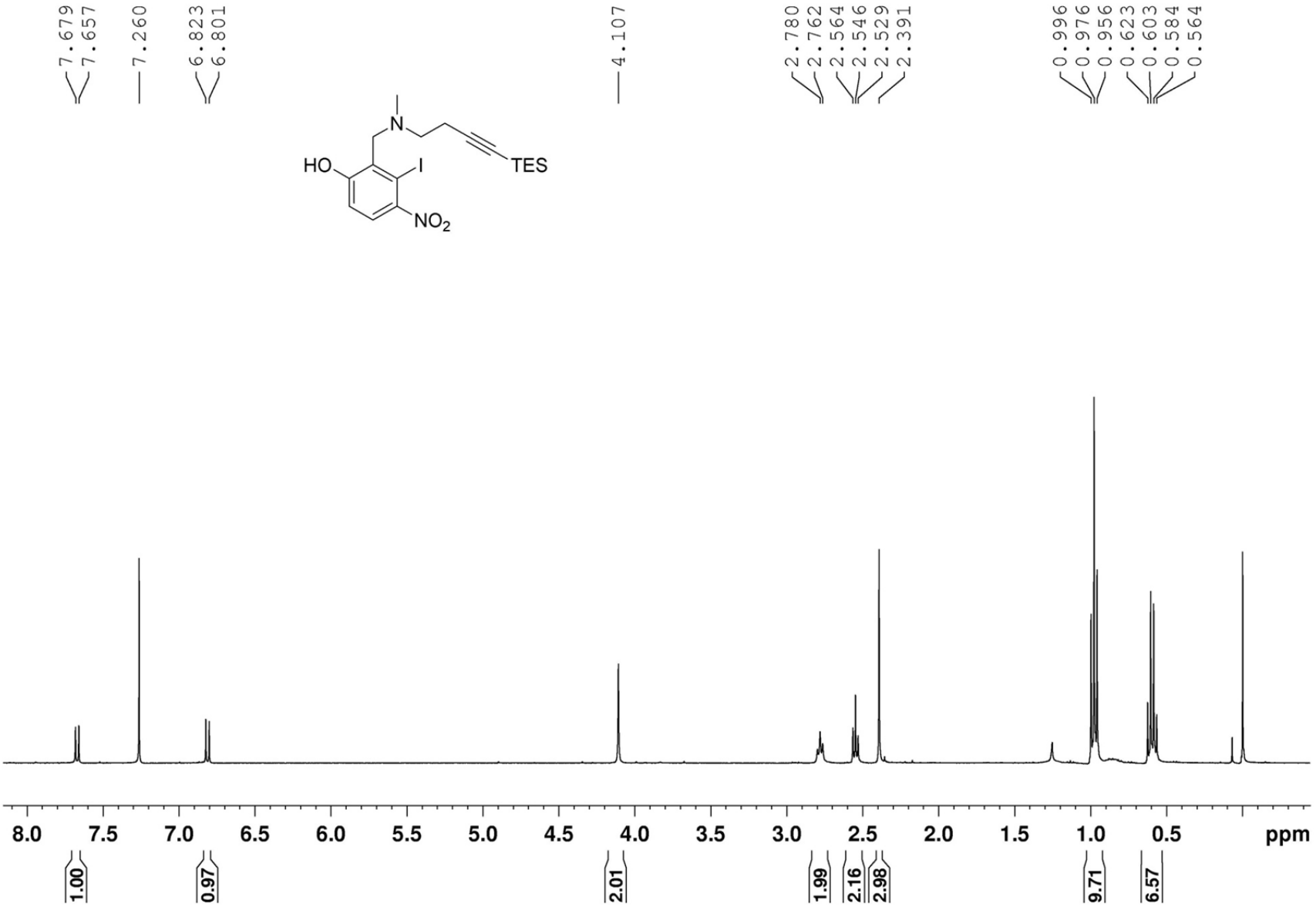
^{1}H NMR of compound 7d ($CDCl_3$, 400 MHz)



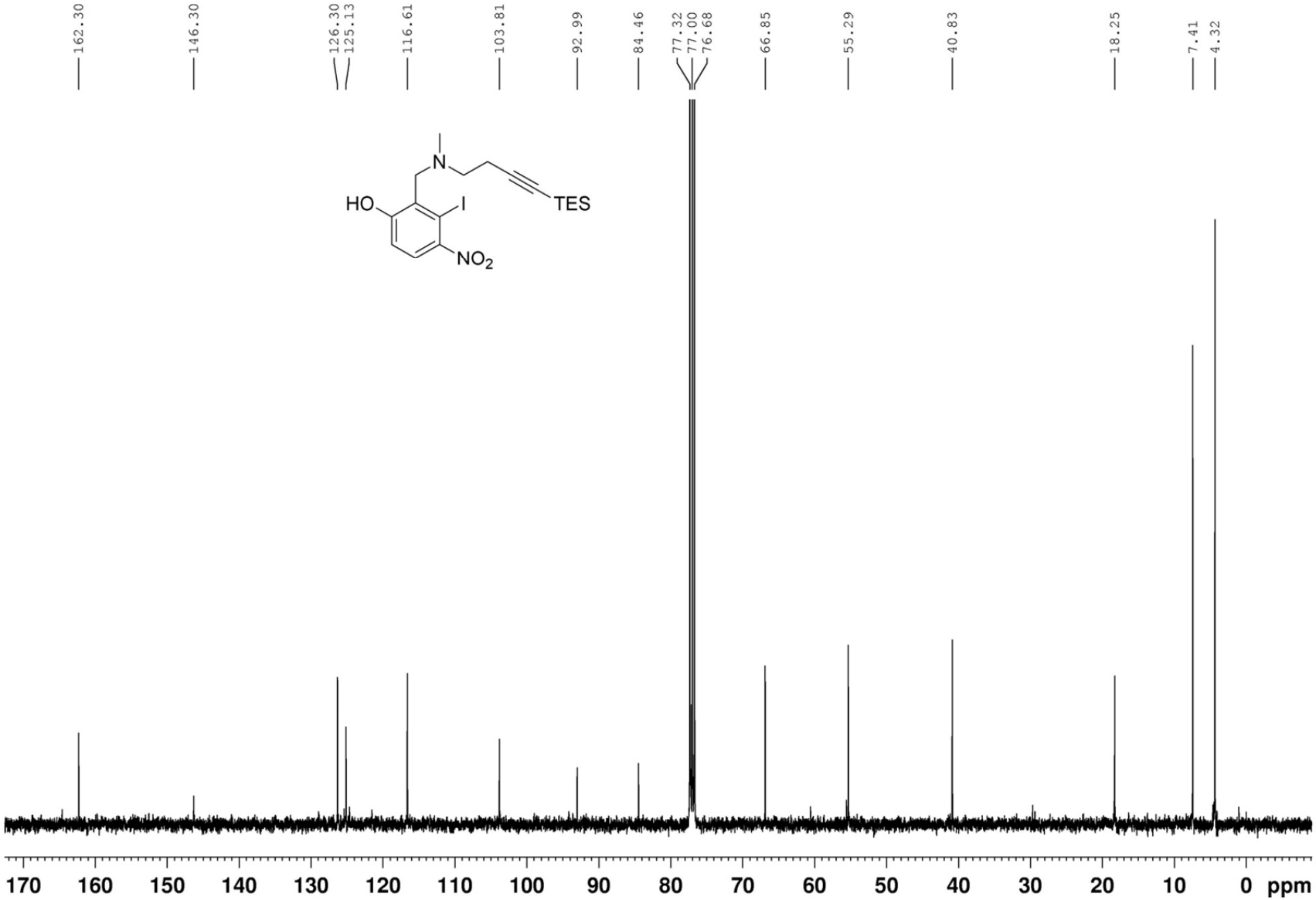
^{13}C NMR of compound 7d ($CDCl_3$, 100 MHz)



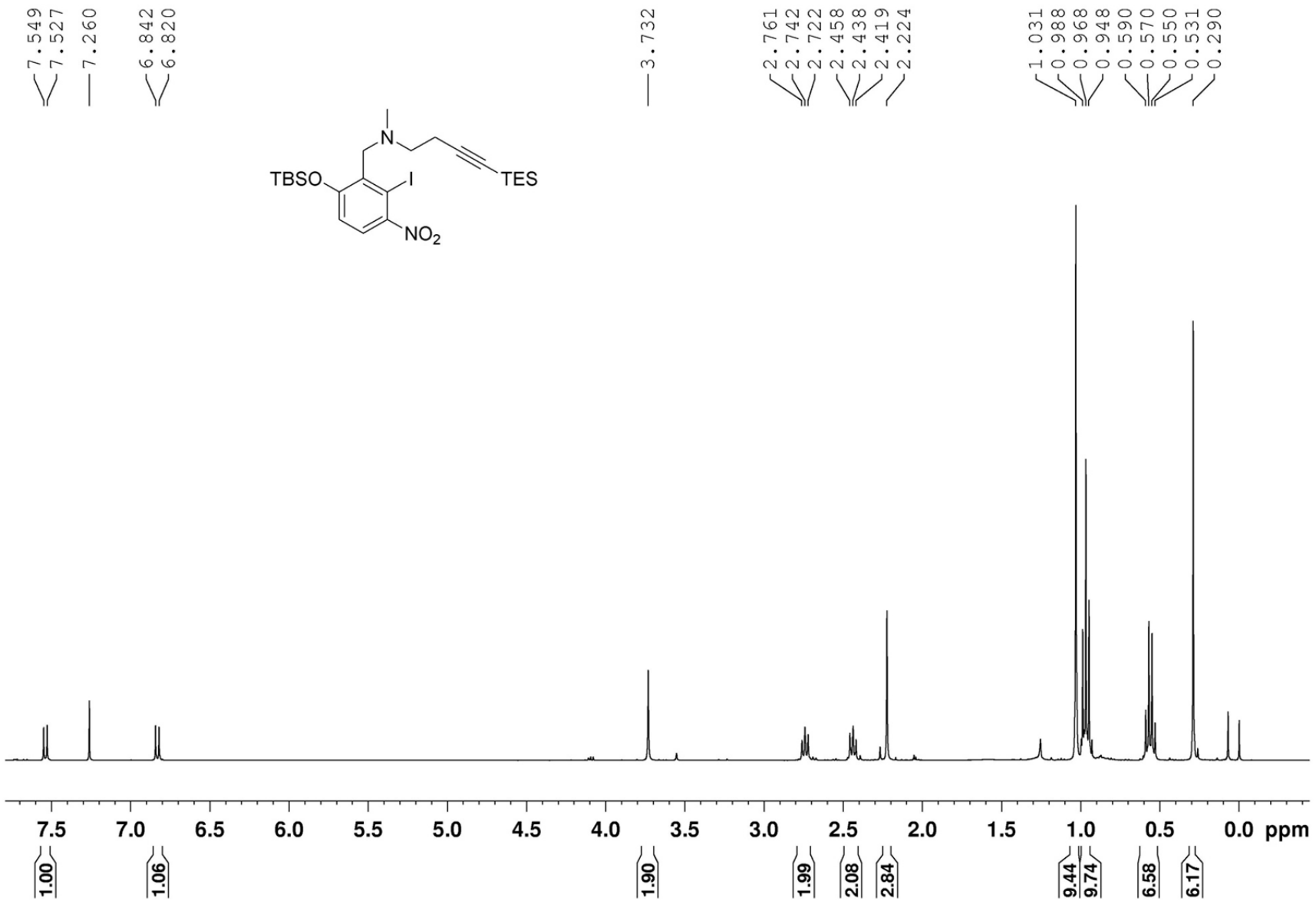
^{1}H NMR of compound 18 ($CDCl_3$, 400 MHz)



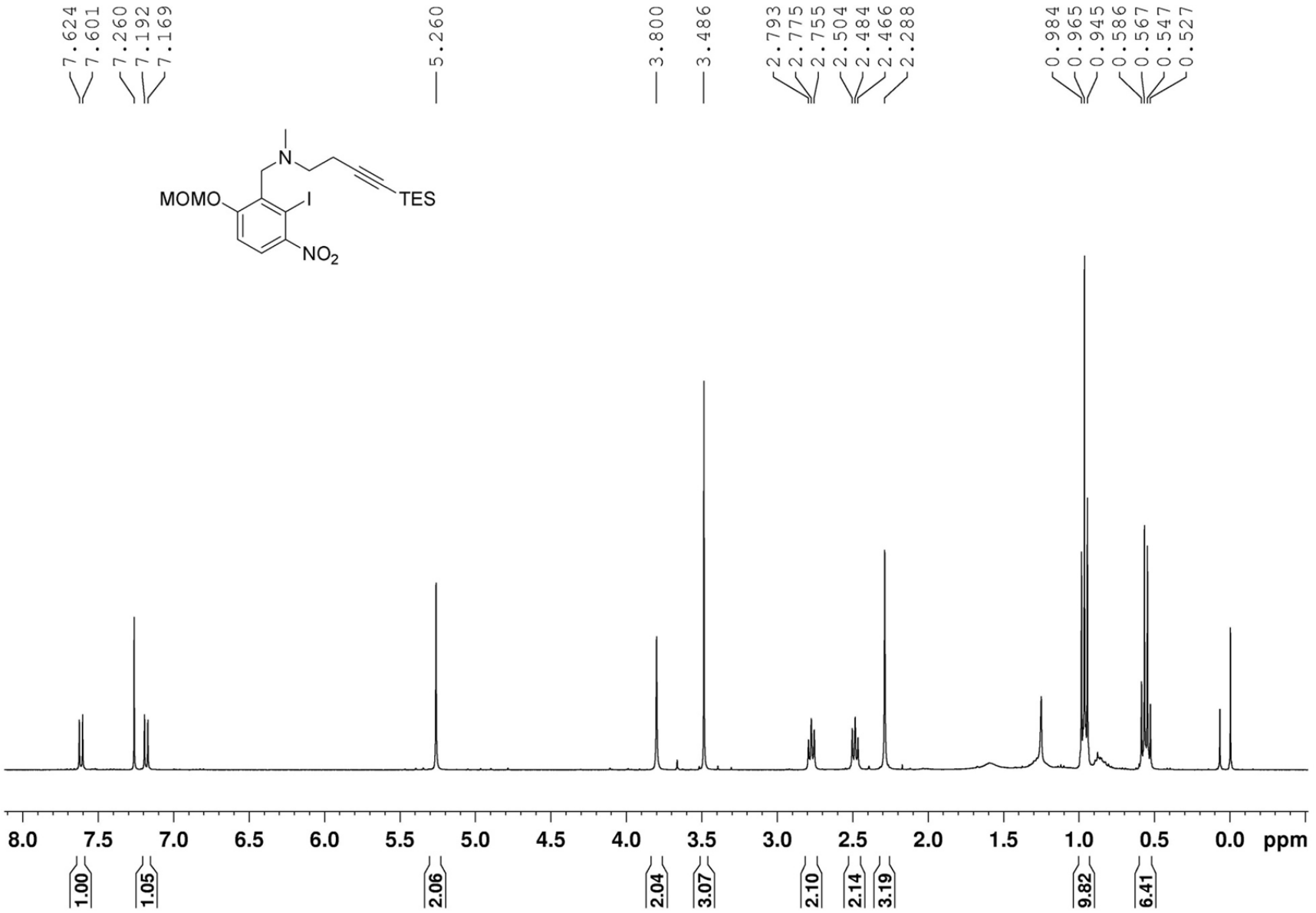
^{13}C NMR of compound 18 ($CDCl_3$, 100 MHz)



^{1}H NMR of compound 19a ($CDCl_3$, 400 MHz)



^{1}H NMR of compound 19b ($CDCl_3$, 400 MHz)



^{1}H NMR of compound 19c ($CDCl_3$, 400 MHz)