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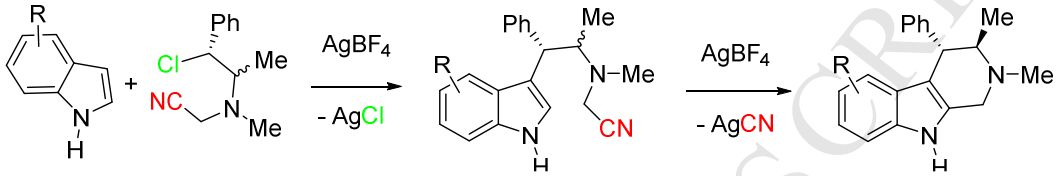

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Alkylation of Indoles by Aziridinium ions: New Rapid Access to Tetrahydro-β-Carbolines (THBCs)

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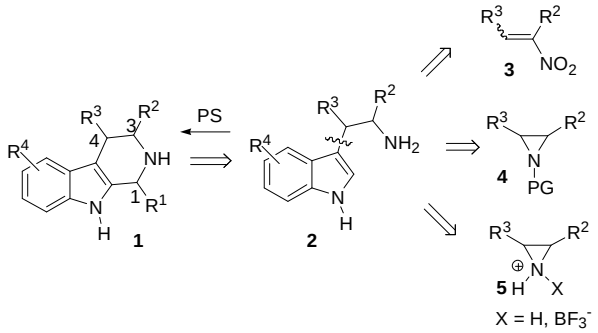
ABSTRACT

The alkylation of indoles by aziridinium ions generated *in-situ* from β-amino chlorides was explored. The outcome of this reaction strongly relied on the substitution pattern of the starting β-amino chloride and requires silver tetrafluoroborate activation to proceed in reasonable yield. Ephedrine- and pseudoephedrine-derived *N*-cyanomethyl-β-amino chlorides afforded the corresponding tryptamines in a regio- and stereoselective manner and subsequent silver(I)-promoted Pictet-Spengler reactions produced 4-phenyl substituted THBCs in good yields. Unexpected epimerization at C-3 was found in these reactions, producing *trans*-3,4-disubstituted THBCs stereoselectively.

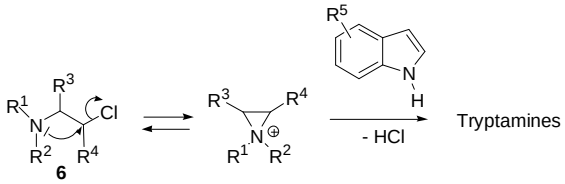
1. Introduction

Tetrahydro-β-carbolines **1** (THBCs) belong to a family of extensively studied alkaloids due to their strong biological activity in the CNS and their privileged binding to serotonin receptors.[1] Classical access to this skeleton involves a Pictet-Spengler (P-S) reaction of the required tryptamine **2**, allowing predictable stereocontrol of the produced C-1 stereocenter.[2] Therefore, synthetic routes to substituted tryptamines have been particularly scrutinized, and the most direct ones rely on Friedel-Crafts (F-C) reactions of the corresponding indoles with either nitroalkenes **3** or aziridines **4** as electrophilic partners, both reactions being promoted by Lewis acids and/or organocatalysts. While the former route has been extensively studied, culminating in enantioselective versions allowing introduction of substituents at C-4 and/or C-3,[3] this route still requires an extra reduction step of the nitro group before performing the P-S reaction. On the other hand, F-C reactions of indoles with aziridines **4** are particularly sensitive to the nature of substituents on the aziridine ring, and require specific Lewis acids activation, together with electron withdrawing groups on the aziridine heterocycle.[4] A much less explored route is the direct reaction of aziridinium ions such as **5** with indoles, which might be due to the difficulties in generating and controlling the reactivity of these electrophilic species,[5] though this way offers the advantage of directly furnishing the target tryptamine devoid of a protecting group on the nitrogen atom and ready for the ensuing P-S step (Scheme 1).



Scheme 1. Synthetic routes to TBHCs **1**

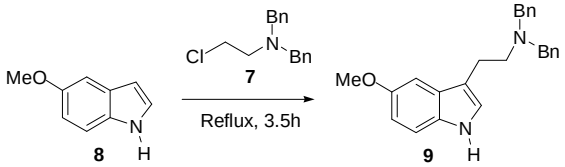
To the best of our knowledge, β-chloroamines **6** are as yet unexplored electrophilic partners in such F-C reactions. These compounds are prone to generate aziridinium ions through intramolecular substitution[6] that could further react with indoles. We report herein the behaviour of such halides in F-C reactions with indoles (Scheme 2).



Scheme 2. β-Chloroamines as aziridinium precursors for F-C reactions.

2. Results and discussion

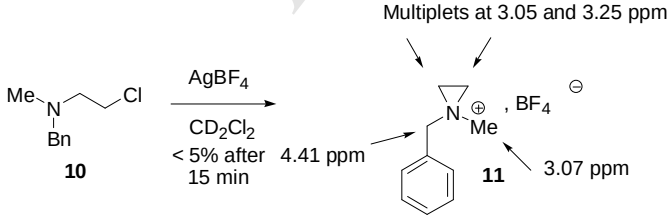
N,*N*-Dibenzyl amino chloride **7** was first examined as the electrophilic partner in such F-C reactions. 5-Methoxyindole **8**, with a nucleophilicity parameter *N* of 6.22, was selected as a suitable nucleophilic indole.[7] Refluxing these compounds (2 equiv. of chloride) in acetonitrile did not lead to any reaction, however, addition of $AgBF_4$ (2 equiv.) as a chloride scavenger led, after 3h at reflux, to the expected tryptamine **9** in a low isolated yield, that could not be improved by the use of other refluxing solvents (Scheme 3). In order to gain a better understanding of the reaction between chloride **7** and $AgBF_4$, it was monitored by NMR in CD_2Cl_2. Thus, chloride **7** was added to a solution of $AgBF_4$ (1.2 equiv.) in CD_2Cl_2 and samples were examined by ^1H NMR, showing that aziridinium ion was produced almost quantitatively after 10 min, as shown by the appearance of two singlets at 4.50 and 3.09 ppm, and proved to be stable in solution for at least 40 min.



Additive	Solvent	Yield (%)
None	MeCN	0
$AgBF_4$	MeCN	26
$AgBF_4$	THF	7
$AgBF_4$	DCM	9
$AgBF_4$	Toluene	15

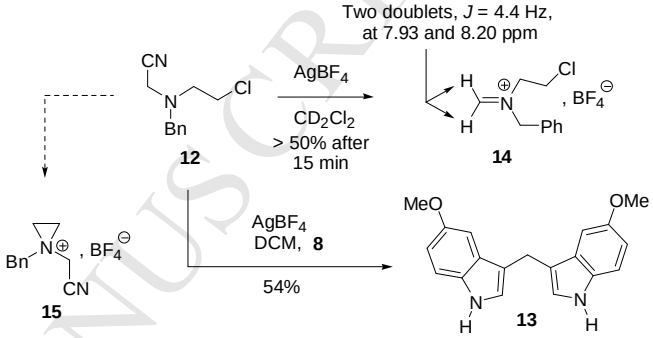
Scheme 3. F-C reaction of β-amino chloride **7** with indole **8** requires silver tetrafluoroborate as additive.

Addition of 5-methoxy indole **8** to this solution (rt) showed that formation of the tryptamine was not rapid since after 15min, no appreciable reaction was observed and after 2h, 32% of starting indole was still present. We thus modified our protocol by adding **8** to a preformed solution of aziridinium (1.2 equiv.) in DCM followed by stirring for 72h at rt and isolated **9** in 42% yield. However, switching to *N*-benzyl-*N*-methyl amino chloride **10** surprisingly gave no trace of the expected tryptamine under these conditions. We thus monitored formation of aziridinium **11** by NMR and found that, in sharp contrast with **7**, only trace amounts of aziridinium **11** could be detected in the solution, together with the starting chloride, after 30 min. Leaving the mixture to stand overnight led to a complex mixture of products. Other solvents (MeCN, DMSO, acetone) were tried with no success (Scheme 4). Clearly, lower steric crowding around the nitrogen atom compared to **7** is a critical parameter and complexation of the amine with Ag (I), as suggested by broadening of the signals in ^1H NMR, probably competes with chloride abstraction and hampers formation of the aziridinium ion.



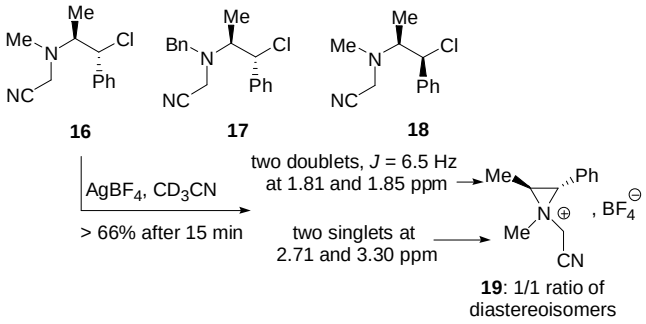
Scheme 4. Aziridinium **11** is not efficiently produced upon reaction with $AgBF_4$.

Having learned through these experiments, we next turned to the use of β-amino chlorides with a *N*-cyanomethyl substituent for two reasons. First, it is known that the lone pair of the nitrogen atom in amino nitriles is deactivated by the anomeric effect, thus preventing competitive complexation of the lone pair of the nitrogen atom with Ag(I), which slows down formation of the aziridinium ion. In addition, amino nitriles are direct precursors of iminium ions by abstraction of cyanide anion, which are intermediates in P-S reactions.[8] Thus these compounds appear at first sight to be ideal candidates in the Ag(I)-promoted F-C reaction. The β-amino chloride **12** was tested first under previously standardized conditions, yielding bis-indolylmethane **13** in 54% isolated yield. This product is formed through a Mannich reaction[9] which implies the competitive formation of an iminium ion **14** from **12,** upon activation with $AgBF_4$, which was produced more efficiently than the aziridinium ion **15** required for the F-C reaction. This was confirmed by monitoring the reaction of **12** with $AgBF_4$ by NMR, as depicted in Scheme 5:



Scheme 5. $AgBF_4$ promotes formation of iminium **14** and not aziridinium **15**.

In order to circumvent this problem, we next examined ephedrine-derived and pseudoephedrine derived β-amino chlorides **16**-**18**,[10] hoping that the benzylic chloride atom in these substrates would be more reactive towards intramolecular substitution. Gratifyingly, monitoring of the reaction of **16** in CD_3CN unambiguously showed selective formation of the aziridinium ion **19**, instead of an iminium ion (Scheme 6):

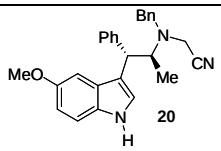
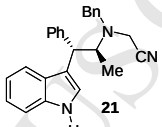
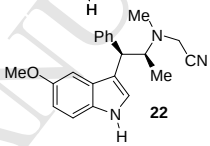
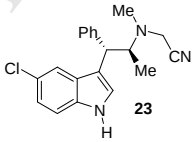
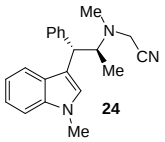
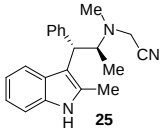
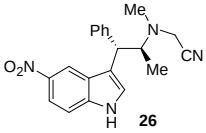
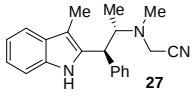
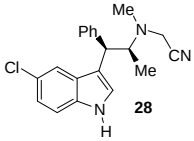
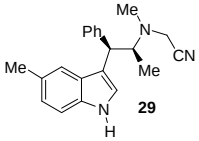


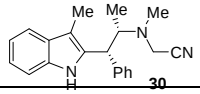
Scheme 6. $AgBF_4$ promotes formation of aziridinium **19**.

Reaction of these halides with different indoles was thus studied under various conditions (solvent, Lewis acid), and these experiments are shown in Table 1. The first three entries conducted with *N*-Bn chloride **17** demonstrate that the best conditions were with MeCN as solvent, with a slight excess of preformed aziridinium ion. Under these conditions, tryptamine **20** was isolated in 51% yield and was produced regio- and stereoselectively (entry 3). In contrast, tryptamine **21** was produced in low yield and stereoselectivity. It should be mentioned that other halide scavengers, such as $AlCl_3$, or $[(MeCN)_4Cu]PF_6$ were tested without success. Next the reaction of *N*-Me chloride **16** was examined under these conditions with a series of indoles (entries 5-10). In all cases, tryptamines were

produced with high regio- and stereoselectivity except for indole **8** (entry 5) albeit in modest yields. The main by-products found were unreacted indoles and β-amino alcohols resulting from the opening of the aziridinium ion by water. Nucleophilic indoles such as 2-Me indole (N = 6.91,[7] entry 8) reacted well, while electron deficient 5-nitro indole reacted with poor yield (entry 9). Pseudoephedrine-derived chloride **18** showed similar behaviour, yielding epimeric tryptamines **28**-**30** at the benzylic position. It should be noted that 3-methyl indole yielded the corresponding 2-substituted indoles (entries 10,14). The structure of tryptamine **23** was determined by X-ray crystallography[11] showing that inversion had occurred at the benzylic position.

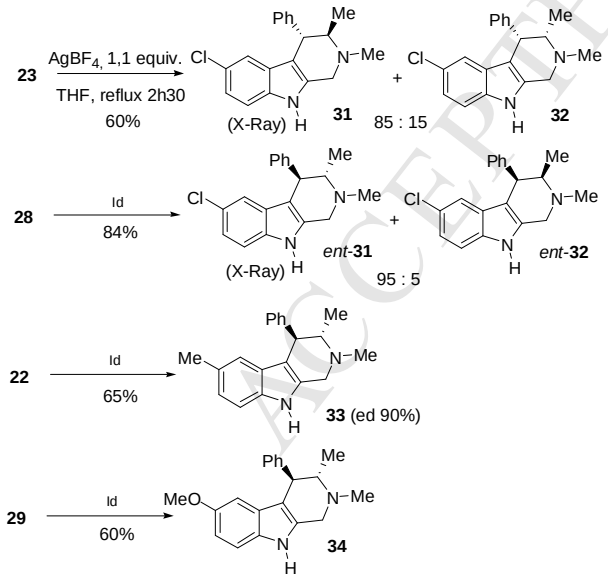
Table 1. Friedel-Crafts reactions of ephedrine-derived chlorides.

Entry	Halide	Indole	Conditions	Product	Yield (de) (%)
1	**17**	**8**	No additive, MeCN, Reflux, 40h	 **20**	4 (>95)
2	**17**	**8**	$AgBF_4$ (1.2 equiv.), DCM, 2h30	**20**	41 (22)
3	**17**	**8**	$AgBF_4$ (1.2 equiv.), MeCN, 2h30	**20**	51 (> 95)
4	**17**	indole	Id.	 **21**	25 (20)
5	**16**	**8**	Id.	 **22**	34 (50)
6	**16**	5-Chloro indole	Id.	 **23**	32 (>95)
7	**16**	*N*-Methyl indole	Id.	 **24**	25 (>95)
8	**16**	2-Methyl indole	Id.	 **25**	40 (>95)
9	**16**	5-Nitro indole	Id.	 **26**	5 (>95)
10	**16**	3-Methyl indole	Id.	 **27**	21 (>95)
11	**18**	5-Chloro indole	Id.	 **28**	40 (>95)
12	**18**	5-Methyl indole	Id.	 **29**	44(>95)

13	**18**	5-Methoxy indole	Id.	**22**	28(>95)
14	**18**	3-Methyl indole	Id	 **30**	18 (>95)

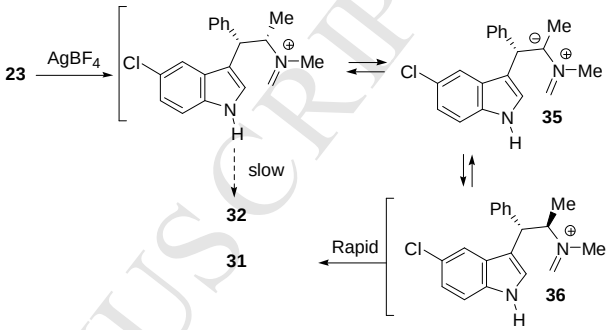
It appears that this reaction is extremely sensitive to both the nature of the β-amino chloride and of the indole. When the first efficiently produces an intermediate aziridinium ion, and the reacting indole is sufficiently nucleophilic, then tryptamines are produced regio- and stereoselectively through an S_N2 opening of the aziridinium ion. Otherwise, an S_N1 reaction competes, leading to partial or extensive (entry 5) epimerization at the benzylic position.

Next the Pictet-Spengler reaction of the prepared tryptamines was studied. Simple heating in THF of tryptamines **23, 28**, **22** and **29**, bearing a *N*-cyanomethyl group, in the presence of 1.1 equiv. of $AgBF_4$ led to the corresponding THBCs **31**, *ent*-**31**, **33** and **34** in good yield (Scheme 7). However, we were surprised to notice that epimerization had occurred when ephedrine-derived chloro-indole **23** was reacted under these conditions. The major isomer **31** produced gave suitable crystals for X-ray analysis and allowed us to conclude that epimerization had occurred quite surprisingly at C-3 and that the expected *cis* isomer **32** was present in only 15% yield in the mixture. It should be noted that the absolute configuration of the stereocenters was unambiguously determined by X-ray crystallography, due to the presence of the chloride atom on the aromatic ring and convergence of the Flack parameter.[12] Pseudoephedrine-derived tryptamine **28** gave as the major product *ent*-**31** but still minor amounts (ca 5%) of the epimer at C-3 were detected in the crude reaction mixture. The structure of the major epimer *ent*-**31** was again secured by X-ray crystallography,[11] thereby confirming the absolute and relative configurations in **31** and *ent*-**31**.



Scheme 7. Pictet-Spengler reactions of *N*-cyanomethyl tryptamines.

This unexpected epimerization at C-3, which leads to the more stable (*trans*) THBC **31** has seldom been reported in the literature[13] and may occur through an intermediate azomethine ylide **35**,[14] though additional mechanistic studies need to be performed to clarify this point (Scheme 8). This epimerization leads to interesting questions on how simple amino nitriles can be the precursors of azomethine ylides, and alerts the synthetic community on possible epimerization at C-3 occurring during the synthesis of THBCs through a Pictet-Spengler reaction.



Scheme 8. Epimerization at C-3 may occur *via* an azomethine ylide.

3. Conclusion

In conclusion, we have demonstrated for the first time that β-chloroamines are suitable precursors of aziridinium ions upon chloride abstraction by $Ag(BF_4)$ and are able to react with indoles through Friedel-Crafts reactions leading directly to tryptamines. The nature of the substituents on the nitrogen atom is a crucial factor since its lone pair needs to be deactivated either by bulky substituents (Bn) or by a cyanomethyl group, to avoid interaction between the silver salt and the nitrogen atom that can hamper halide abstraction. With reactive benzylic chlorides, the reaction gives tryptamines often with high regio- and stereoselectivity, although yields are modest. Finally, the produced *N*-cyanomethyl tryptamines can be efficiently transformed into TBHCs through a Pictet-Spengler reaction mediated by $AgBF_4$. During the course of this reaction, unexpected epimerization was observed at C-3.

4. Experimental section

General information: *N*-cyanomethyl-β-chloroamines **16-18** were prepared following our previously reported procedures respectively from (1*R*,2*S*)-ephedrine, (1*R*,2*S*)-norephedrine, (1*S*,2*S*)-pseudoephedrine.[10] Chlorides **7** and **10** were obtained after respectively benzylation of ethanolamine[15] and methylation of benzylaminoethanol.[16] All chemicals were used as received. Acetonitrile and dichloromethane was freshly distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Purifications were performed by column chromatography on silica gel 230-400 mesh or by preparative TLCs. ^1H and ^{13}C NMR spectra were collected on a Bruker Avance spectrometer respectively at 300 and 75 MHz. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δTMS = 0), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad), coupling constant (J/Hz), integration and attribution. High resolution mass spectra (HR-MS) were obtained on a Waters Micromass Q-Tof Micro instrument. Optical rotations were determined on a Perkin Elmer 341 polarimeter.

4.1. General procedure using $AgBF_4$ for the synthesis of tryptamine derivatives

Silver tetrafluoroborate was quickly weighed (185 mg, 0,96 mmol, 1.24 eq.) and dissolved in 5 mL of MeCN under an argon atmosphere and stirred for 10 min at room temperature. β–Chlorinated amines (0,9 mmol, 1.16 eq.), dissolved in MeCN (1 mL) was added dropwise leading to the formation of a precipitate. After 30 min, the indole (0,77 mmol, 1 eq.) was added and the mixture was monitored by TLC (EtOAc/PE). The reaction was worked-up after 2.5 hours with 3 mL of a saturated aqueous solution of $NaHCO_3$ and 3 mL of 15% aqueous NH_3 solution. The mixture was then filtered on Celite and rinsed with EtOAc. After usual workup (H_2O/EtOAc), the residue was purified by column chromatography (silica gel; PE/EtOAc).

*4.2. Dibenzyl-(5-methoxy-1H-indol-3-ylethyl)-amine (**9**):*

Colorless oil (30 mg, 42%); R_f =0.43 (EtOAc/PE : 15/85); ^{1}H RMN (300 MHz, $CDCl_3$) : δ (ppm) : 7.97 (bs, 1H, NH), 7.47-7.23 (m, 11H, HAr), 6.95 (bs, 1H, HAr), 6.82-6.79 (m, 2H, HAr), 3.76 (bs, 7H, H-3, H-4, $ArOCH_3$), 3.02-2.98 (bm, 2H, H-1), 2.85-2.80 (bm, 2H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 153.8, 139.9, 131.3, 128.9, 128.5, 128.3, 127.8, 126.9, 122.4, 112.3, 111.8, 100.4 (CqAr, CHAr), 58.26 (C-3, C-4), 55.90 ($ArOCH_3$), 53.68 (C-1), 23.08 (C-2); HRMS (ESI) m/z calcd for $C_{25}H_{26}N_2O$ $[M+H]^+$: 371.2123, found: 371.2127.

*4.3. (1S,2S) and (1S,2R)-{benzyl-[2-(5-Methoxy-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-amino}-acetonitrile (**20**):*

Dark red amorphous solid (102 mg, 41%); R_f =0.62 (EtOAc/PE : 30/70); NMR of major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.11 (bs, 1H, NH), 7.43-6.80 (m, 14H, Ph, H-2, H-4, H-6, H-7), 4.32 (d, *J* = 9Hz, 1H, H-2), 4,00 (d, A part of AB syst., *J* = 14Hz, 1H, H-4a), 3.90 (s, 3H, $ArOCH_3$), 3.93-3.80 (m, 1H, H-1), 3.61 (d, B part of AB syst., *J* = 17Hz, 1H, H-4b), 3.46 (d, A part of AB syst., *J* = 17Hz, 1H, H-5a), 3.30 (d, B part of AB syst., *J* = 17Hz, 1H, H-5b), 1.33 (d, *J* = 6Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 154.0, 143.8, 137.5, 131.4, 127.5, 117.6, 117.5 (CqAr), 128.7, 128.4, 128.3, 128.2, 127.4, 126.0, 122.2, 112.0, 111.9, 101.3 (CHAr), 61.8 (C-1), 56.0 ($ArOCH_3$), 53.3 (C-4), 48.3 (C-2), 38.3 (C-5), 13.0 (C-3). NMR of minor epimer: ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 7.43-6.80 (m, 15H, Ph, H-2, H-4, H-6, H-7), 4.20 (d, *J* = 15Hz, 1H, H4-a), 4.04 (d, *J* = 14Hz , 2H, H-4b, H-5a), 3.98 (d, *J* = 10Hz, 1H, H-2), 3.93 (s, 3H, OCH_3), (d, *J* = 14Hz ,1H, H-5b), 3.12-3.03 (m, 1H, H-1), 1.19 (d, *J* = 6Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.7, 137.2, 132.6, 130.0, 129.7, 129.1, 128.9, 128.6, 127.8, 127.1, 127.0, 126.3, 126.0, 125.9, 114.8 (CqAr, CHAr), 60.2 (C-1), 54.6 (C-4), 56.0 ($ArOCH_3$), 53.1 (C-2), 42.2 (C-5), 16.2 (C-3). HRMS (ESI) m/z calcd for $C_{27}H_{28}N_3O$ $[M+H]^+$: 410.2232, found: 410.2234.

*4.4. (1S,2S) and (1S,2R)-{benzyl-2-[1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-amino}-acetonitrile (**21**):*

Dark red oil (102 mg, 25%); R_f =0.3 (EtOAc/PE : 20/80); NMR of major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.02 (bs, 1H, NH), 7.58 (d, *J* = 8Hz, 1H, HAr), 7.30-7.00 (m, 12H, HAr), 6.80-6.77 (m, 2H, HAr), 4.26 (d, *J* = 11Hz, 1H, H-2), 3.92 (d, A part of AB syst., *J* = 14Hz, 1H, H-4a), 3.83-3.73 (m, 1H, H-1), 3.57 (d, B part of AB syst., *J* = 14Hz, 1H, H-4b), 3.34 (d, A part of AB syst., *J* = 18Hz, 1H, H-5a), 3.18 (d, B part of AB syst., *J* = 18Hz, 1H, H-5b), 1.21 (d, *J* = 6Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.7, 137.2, 136.0 (CqAr), 129.5, 128.7, 128.6, 128.4, 128.3, 128.2, 127.4, 126.0, 122.1, 121.2, 119.5, 119.0, 111.2, (CHAr), 61.9 (C-1), 53.2 (C-4), 48.2 (C-2), 38.2 (C-5), 13.0 (C-3). NMR of minor epimer: ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 7.86 (bs, 1H, NH), 7.30-7.00 (m, 14H, HAr), 6.64 (d, 1H, HAr), 4.17 (d, A part of AB syst., *J* = 15Hz, 1H, H4-a), 3.97 (d, B part of AB syst., *J* = 15Hz , 1H, H-4b), 3.96 (d, A part of AB syst., *J* = 17Hz, 1H, H-5), 3.91 (d, *J* = 9Hz 1H, H-2), 3.63 (d, B part of AB syst., *J* = 17Hz ,1H, H-5b), 3.15-3.03 (m, 1H, H-1), 1.14 (d, *J* = 6Hz, 3H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 142.9, 136.6, 113.8 (CqAr), 129.9, 129.0, 127.3, 127.1, 127.0, 126.5, 125.8, 117.9, 117.4 (CHAr), 60.5 (C-1), 54.4 (C-4), 52.3 (C-2), 41.7 (C-5), 15.9 (C-3). HRMS (ESI) m/z calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127, found: 380.2127.

*4.5. (1S,2S) and (1S,2R)-{[2-(5-Methoxy-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**22**):*

Orange oil (19 mg, 34%); R_f= 0.45 (EtOAc/PE: 30/70); NMR of major epimer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.03 (bs, 1H, NH), 7.35-7.12 (m, 7H, Ph, H-2, H-7), 6.96 (d, *J* = 2Hz, 1H, H-4), 6.82 (dd, *J* = 9Hz, *J* = 2Hz, 1H, H-6), 4.20 (d, *J* = 9Hz, 1H, H-2), 3.81 (s, 3H, $ArOCH_3$), 3.59-3.48 (m, 1H, H-1), 3.42 (bs, AB syst., 2H, H-5a, H-5b), 2.40 (s, 3H, H-4), 1.15 (d, *J* = 7Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 153.9, 143.4, 131.3, 129.9, 127.9, 127.7, 126.0, 122.6, 117.1, 117.0, 101.6 (CqAr, CHAr), 128.3, 128.2 (CHPh), 62.0 (C-1), 56.0 ($ArOCH_3$), 47.5 (C-2), 42.8 (C-5), 37.2 (C-4), 12.4 (C-3); NMR of minor epimer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.21 (bs, 1H, NH), 7.35-7.12 (m, 7H, Ph, H-2, H-7), 6.74 (dd, *J* = 9Hz, *J* = 2Hz, 1H, H-6), 6.30 (d, *J* = 2Hz, 1H, H-4), 4.39 (d, *J* = 5Hz, 1H, H-2), 3.93 (d, A part of AB syst., *J* = 15Hz, 1H, H-5a,), 3.58 (s, 3H, OCH_3), 3.64 (d, B part of AB syst., *J* = 15Hz , 1H, H-5b), 3.23-3.14 (m, 1H, H-1), 2.51 (s, 3H, H-4), 0.85 (d, *J* = 7Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 153.5, 131.5, 127.2, 126.6, 111.9, 111.8, 111.4, 111.0, 102.4 (CqAr, CHAr), 60.2 (C-1), 55.7 ($ArOCH_3$), 43.7 (C-2), 48.2 (C-5), 42.1 (C-4), 11.7 (C-3). Major epimer was obtained pure starting from 200 mg of **18**. White solid (84 mg, 28%); R_f= 0.41 (EtOAc/PE : 30/70); Mp 127°C; $[\alpha]_D^{20}$ = -12.2 (c 0.3, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O$ $[M+H]^+$: 334.1919, found: 334.1928.

*4.6. (1S,2S)-{[2-(5-Chloro-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**23**):*

Orange oil (82 mg, 32%); R_f= 0.22 (EtOAc/PE : 30/70); $[\alpha]_D^{20}$ = -69.8 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.19 (bs, 1H, NH), 7.55 (d, 1H, H-4), 7.36-7.11 (m, 8H, Ph, H-2, H-6, H-7), 4.22 (d, *J* = 9Hz, 1H, H-2), 3.63-3.53 (m, 1H, H-1), 3.46 (d, A part of AB syst., *J* = 18Hz, 1H, H-5a), 3.39 (d, B part of AB syst., *J* = 18Hz, 1H, H-5b), 2.41 (s, 3H, H-4), 1.15 (d, *J* = 7Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.1, 134.3, 128.1, 125.2, 117.2, 117.1 (CqAr), 126.2, 123.1, 122.4, 118.5, 112.3 (CHAr), 128.3, 128.2 (CHPh), 62.0 (C-1), 47.4 (C-2), 42.9 (C-5), 36.9 (C-4), 12.4 (C-3); HRMS (ESI) m/z calcd for $C_{20}H_{21}N_3Cl$ $[M+H]^+$: 338.1424, found: 338.1421.

*4.7. (1S,2S)-{[2-(1-Methyl-indol-1H-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**24**):*

Orange needles (60 mg, 25%); R_f =0.35 (EtOAc/PE : 30/70); Mp 132°C; $[\alpha]_D^{20}$ = -33.9 (c 0.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 7.64 (d, 1H, ArH), 7.43-7.07 (m, 9H, Ar), 4.33 (d, *J* = 9Hz, 1H, H-2), 3.77 (s, 3H, NCH_3 of indole), 3.69-3.60 (m, 1H, H-1), 3.47 (s, 2H, H-5), 2.46 (s, 3H, H-4), 1.21 (d, *J* = 7Hz , 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.8, 136.8, 127.7, 126.5, 126.0, 121.7, 119.3, 118.0, 117.2, 115.9, 109.3 (CqAr, CHAr), 128.3, 128.3 (CHPh), 62.2 (C-1), 47.5 (C-2), 42.8 (C-5), 37.2 (C-4), 32.8 (NCH_3 of indole), 12.4 (C-3); HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3$ $[M+H]^+$: 318.1970, found: 318.1973.

*4.8. (1S,2S)-{[2-(2-Methyl-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**25**):*

Brown amorphous solid (98 mg, 40%); R_f =0.42 (EtOAc/PE : 30/70); Mp 80°C; $[\alpha]_D^{20}$ = +29.5 (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 7.75 (bd, 2H, NH, Ar), 7.47 (d, 2H, Ar), 7.32-7.12 (m, 6H, Ar), 4.18 (d, *J* = 10Hz, 1H, H-2), 4.18-4.05 (m, 1H, H-1), 3.53 (d, A part of AB syst., *J* = 17Hz, 1H, H-5a), 3.44 (d, B part of AB syst., *J* = 17Hz, 1H, H-5b), 2.46, (s, 3H, $ArCH_3$), 2.43 (s, 3H, H-4), 1.06 (d, *J* = 7Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.6, 135.4, 131.5, 127.2, 125.8, 120.9, 119.4, 119.2, 117.7, 113.1, 110.6 (CqAr, CHAr), 128.2, 128.1 (CHPh), 59.7 (C-1), 47.1 (C-2), 42.4 (C-5), 36.1 (C-4), 12.4, 11.8 (C-3, $ArCH_3$); HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3$ $[M+H]^+$: 318.1970, found: 318.1972.

*4.9. (1S,2R)-{[2-(3-Methyl-1H-indol-2-yl)-1-Methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**27**):*

Orange oil (51mg, 21%); R_f =0.50 (EtOAc/PE : 30/70); ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.39 (bs, 1H, NH), 7.54-7.09 (m, 9H, Ar), 4.31 (d, *J* = 9Hz, 1H, H-2), 3.65-3.56 (m, 1H, H-1), 3.41 (bs, 2H, H-5), 2.43 (s, 3H, H-4), 2.29 (s, 3H, $ArCH_3$), 1.15 (d, *J* = 6Hz , 3H, H-3); ^{13} C NMR (75 MHz, $CDCl_3$) : δ (ppm): 140.4, 135.6, 135.0, 129.0, 117.0, 108.0 (CqAr) 126.8, 121.5, 119.2, 118.4, 110.6, (CHAr), 128.7, 128.3 (CHPh), 60.7 (C-1), 47.1 (C-2), 42.9 (C-5), 37.6 (C-4), 11.8 (C-3), 9.0 ($ArCH_3$); HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3$ $[M+H]^+$: 318.1970, found: 318.1969.

*4.10. (1S,2R)-{[2-(5-Chloro-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**28**):*

Starting from 175 mg of **18**. Yellow solid (61 mg, 40%); R_f= 0.49 (EtOAc/PE : 30/70); Mp 164°C; $[\alpha]_D^{20}$ = +2.5 (c 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) : δ (ppm) : 8.14 (bs, 1H, NH), 7,53 (d, *J* = 2Hz, 1H, H-4), 7.36-7.09 (m, 9H, Ph, H-2, H-6, H-7), 4.20 (d, *J* = 10Hz, 1H, H-2), 3.68-3.43 (m, 1H, H-1), 3.47 (d, A part of AB syst., *J* = 18Hz, 1H, H-5a), 3.38 (d, B part of AB syst., *J* = 18Hz, 1H, H-5b), 2.40 (s, 3H, H-4), 1.15 (d, *J* = 6Hz, 3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.0, 134.3, 128.3, 125.2, 117.2, 117.1 (CqAr), 126.2, 123.0, 122.4, 118.4, 112.1 (CHAr), 128.2, 128.0 (CHPh), 61.9 (C-1), 47.3 (C-2), 42.8 (C-5), 37.0 (C-4), 12.3 (C-3); HRMS (ESI) m/z calcd for $C_{20}H_{21}N_3Cl$ $[M+H]^+$: 338.1424, found: 338.1427.

*4.11. (1S,2R)-{[2-(5-Methyl-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**29**):*

Starting from 200 mg of **18**. Orange solid (128 mg, 44%); R_f= 0.40 (EtOAc/PE : 30/70); Mp 139°C; $[\alpha]_D^{20}$ = -32.3 (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 7.96 (bs, 1H, NH), 7.39-6.97 (m, 9H, Ph, H-2, H-4, H-6, H-7), 4.23 (d, *J* = 12Hz, 1H, H-2), 3.63-3.54 (m, 1H, H-1), 3.51 (d, A part of AB syst., *J* = 18Hz, 1H, H-5a), 3.41 (d, B part of AB syst., *J* = 18Hz, 1H, H-5b), 2.44 (s, 3H, $ArCH_3$), 2.42 (s, 3H, H-4), 1.04 (d, *J* = 6Hz, 3H, H-3); ^{13} C NMR (75 MHz, $CDCl_3$) : δ (ppm): 143.3, 134.3, 127.5, 117.4, 116.6 (CqAr), 126.2, 123.4, 121.7, 118.6, 110.7 (CHAr), 128.6, 128.4 (CHPh), 61.5 (C-1), 47.8 (C-2), 42.1 (C-5), 37.3 (C-4), 21.5 ($ArCH_3$), 12.0 (C-3); HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3$ $[M+H]^+$: 318.1970, found : 318.1971.

*4.12. (1S,2S)-{[2-(3-Methyl-1H-indol-2-yl)-1-Methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (**30**):*

Starting from 500 mg of **18**. White solid (124 mg, 18%); R_f= 0.81 (EtOAc/PE : 30/70); Mp 51°C; $[\alpha]_D^{20}$ = -58.6 (c 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) : δ (ppm) : 8.87 (bs, 1H, NH), 7.50 (d, 1H, HAr), 7.39-7.08 (m, 8H, HAr), 4.21 (d, *J* = 9Hz, 1H, H-2), 3.67-3.58 (m, 1H, H-1), 3.41(d, A part of AB syst., *J* = 17Hz, 1H, H-5a), 3.29 (d, B part of AB syst., *J* = 17Hz, 1H, H-5b), 2.40 (s, 3H, H-4), 2.15 (s, 3H, $ArCH_3$), 1.10 (d, *J* = 7Hz ,3H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ (ppm): 141.8, 135.5, 134.7, 129.1, 116.9, 108.5 (CqAr), 126.7, 121.1, 118.9, 118.1, 110.7 (CHAr), 128.7, 128.0 (CHPh), 61.3 (C-1), 48.1 (C-2), 42.6 (C-5), 37.7 (C-4), 13.1 (C-3), 9.0 ($ArCH_3$); HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3$ $[M+H]^+$: 318.1970, found: 318.1967.

4.13. General procedure using $AgBF_4$ for the synthesis of tetrahydro-β-carboline

To a solution of tryptamine derivative (0.54 mmol) in dry THF (5 mL) was added silver tetrafluoroborate (127 mg, 0.59 mmol, 1.1 eq.) under argon atmosphere. The suspension was heated to reflux for 3h and monitored by TLC (CH_2Cl_2/EtOH, 9/1). The reaction was quenched with 1 mL of a saturated aqueous solution of $NaHCO_3$, filtered through Celite and rinsed with EtOAc. After usual workup (H_2O/EtOAc), the residue was purified by column chromatography (silica gel; CH_2Cl_2/EtOH, 13/1 to 9/1). Samples were then crystallized from small volume of EtOAc.

*4.14. (3R,4S)-6-Chloro-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (**31**):*

Starting from 180 mg of **23**. White needles (101 mg, 60%); R_f= 0.33 (CH_2Cl_2/EtOH : 90/10); Mp 236°C; $[\alpha]_D^{20}$ = -69.4 (c 0.2, acetone); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) : δ (ppm) : 11.08 (bs, 1H, NH), 7.29-7.18 (m, 6H, HAr), 6.92 (dd, *J* = 9Hz, *J* = 2Hz, 1H, HAr), 6.53 (d, *J* = 2Hz, 1H, HAr), 3.90 (d, A part of AB syst., *J* = 15Hz, 1H, H-1a), 3.81 (d, *J* = 6Hz, 1H, H-4), 3.72 (d, B part of AB syst., *J* = 15Hz, 1H, H-1b), 2.83-2.74 (m, 1H, H-3), 2.35 (s, 3H, NCH_3), 1.00 (d, *J* = 6Hz, 3H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) : δ (ppm): 144.2, 134.9, 134.5, 127.5, 122.6, 108.8 (CqAr), 126.2, 119.8, 116.9, 112.3 (CHAr), 128.5, 128.0 (CHPh), 61.9 (C-4), 50.0 (C-1), 45.2 (C-3), 39.8 (NCH_3), 14.2 (C-5); HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2Cl$ $[M+H]^+$: 311.1315, found: 311.1317.

*4.15. (3S,4R)-6-Chloro-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (ent-**31**):*

Starting from 60 mg of **28**. White needles (46 mg, 84%); R_f= 0.33 (CH_2Cl_2/EtOH : 90/10); Mp 233°C; $[\alpha]_D^{20}$ = +71.3 (c 0.2, acetone); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) : δ (ppm) : 11.10 (bs, 1H, NH), 7.29-7.18 (m, 6H, HAr), 6.92 (dd, *J* = 8Hz, *J* = 2Hz, 1H, HAr), 6.53 (d, *J* = 2Hz, 1H, HAr), 3.92 (d, A part of AB syst., *J* = 16Hz, 1H, H-1a), 3.82 (d, *J* = 7Hz, 1H, H-4), 3.73 (d, B part of AB syst., *J* = 16Hz, 1H, H-1b), 2.86-2.77 (m, 1H, H-3), 2.37 (s, 3H, NCH_3), 1.01 (d, *J* = 6Hz, 3H, H-5); ^{13} C NMR (75 MHz, $(CD_3)_2SO$) : δ (ppm): 144.3, 134.9, 134.8, 127.7, 122.8, 109.0 (CqAr), 126.4, 120.1, 117.1, 112.6 (CHAr), 128.7, 128.3 (CHPh), 62.1 (C-4), 50.3 (C-1), 45.4 (C-3), 40.0 (NCH_3), 14.4 (C-5); HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2Cl$ $[M+H]^+$: 311.1315, found: 311.1311.

*4.16. (3S,4R)-6-Methyl-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (**33**):*

Starting from 100 mg of **22**. Pale yellow solid (59 mg, 65%); R_f= 0.33 (CH_2Cl_2/EtOH : 90/10); Mp 262°C; $[\alpha]_D^{20}$ = +44.4 (c 0.1, acetone); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) : δ (ppm) : 10.68 (bs, 1H, NH), 7.27-7.12 (m, 6H, HAr), 6.74 (bd, *J* = 8Hz , 1H, HAr), 6.43 (bs, 1H, HAr), 3.86 (A part of AB syst., *J* = 15Hz, 1H, H-5a), 3.79 (d, *J* = 6Hz, 1H, H-2), 3.64 (B part of AB syst., *J* = 15Hz, 1H, H-5b), 2.83-2.75 (m, 1H, H-1), 2.34 (s, 3H, $ArCH_3$), 2.13 (s, 3H, H-4), 1.01 (d, *J* = 7Hz, 3H, H-3); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) : δ (ppm): 144.9, 134.4, 126.2, 125.9, 108.0 (CqAr), 140.2, 117.6, 110.5 (CHAr), 128.5, 127.8 (CHPh), 62.0

(C-3), 49.8 (C-1), 45.5 (C-4), 36.6 (NCH_3), 21.2 ($ArCH_3$), 13.7 (C-5); HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2$ $[M+H]^+$: 291.1861, found: 291.1870.

*4.17. (3S,4R)-6-Methoxy-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (**34**):*

Starting from 40 mg of **29**. White needles (22 mg, 60%); R_f= 0.29 (CH_2Cl_2/EtOH : 90/10); Mp 236°C; $[\alpha]_D^{20}$ = +78.0 (c 0.2, acetone); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) : δ (ppm) : 10.66 (bs, 1H, NH), 7.33-7.13 (m, 6H, HAr), 6.57 (dd, *J* = 9Hz , *J* = 3Hz, 1H, HAr), 6.05 (bd, 1H, HAr), 3.89 (d, A part of AB syst., *J* = 15Hz, 1H, H-5a), 3.79 (d, *J* = 6Hz, 1H, H-2), 3.71 (d, B part of AB syst., *J* = 15Hz, 1H, H-5b), 3.45 (s, 3H, OCH_3), 2.85-2.77 (m, 1H, H-1), 2.37 (s, 3H, H-4), 1.02 (d, *J* = 6Hz, 3H, H-3); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) : δ (ppm): 152.5, 144.5, 133.5, 131.3, 126.9, 108.7 (CqAr), 126.0, 111.3, 109.1, 100.8 (CHAr), 128.7, 128.0 (CHPh), 62.1 (C-3), 55.0 (OCH_3), 50.4 (C-1), 45.6 (C-4), 39.9 (NCH_3), 14.3 (C-5); HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$: 307.1810, found: 307.1814.

Acknowledgments

University of Versailles St-Quentin-en-Yvelines and CNRS are acknowledged for financial support.

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Supplementary Material

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. All compounds appear following the numbering in the experimental section.

Cry

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Supporting information

Alkylation of Indoles by Aziridinium ions: New Rapid Access to Tetrahydro-β-Carbolines (THBCs)

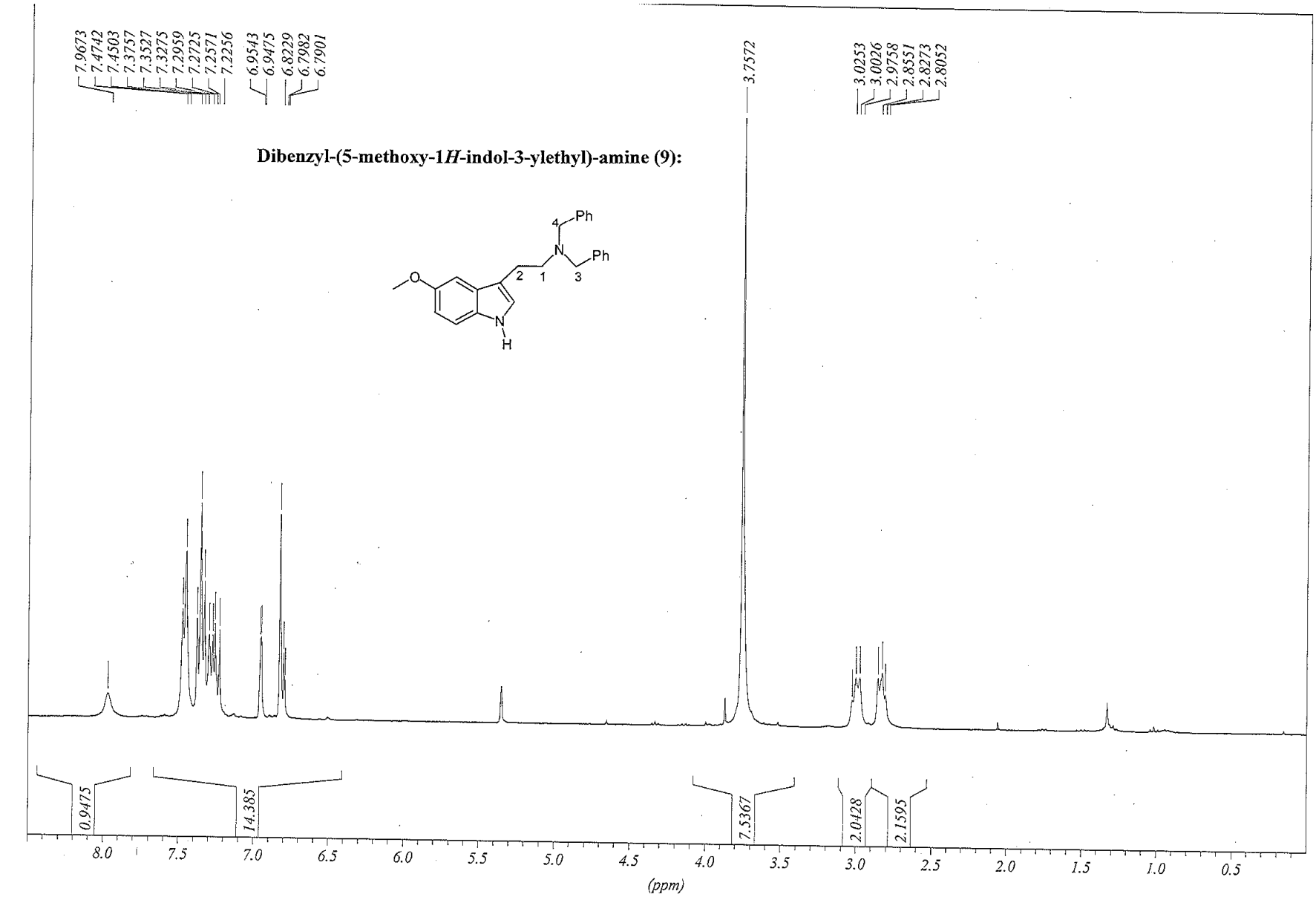
Laurence Menguy,[a] Cheikh Lo,[a] Jérôme Marrot[a] and François Couty*[a]

[a]*Institut Lavoisier, Université de Versailles St Quentin-en-Yvelines, UMR 8180, 45 avenue des Etats-Unis, 78035, Versailles, France*

Corresponding author. e-mail: couty@chimie.uvsq.fr

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds.
All compounds appear following numbering of experimental section.

Crystallographic data for compounds 23, 31 and *ent*-31.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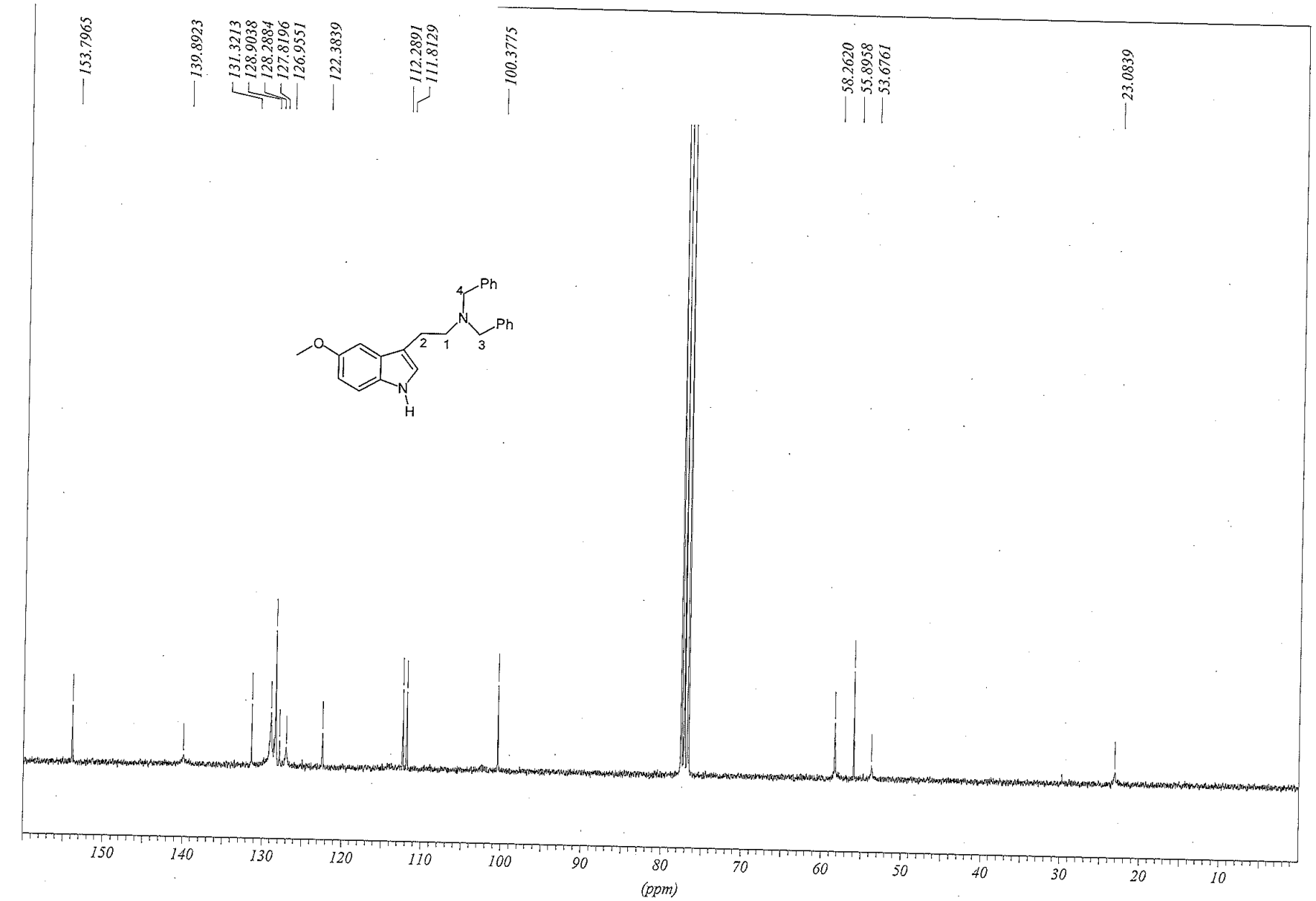
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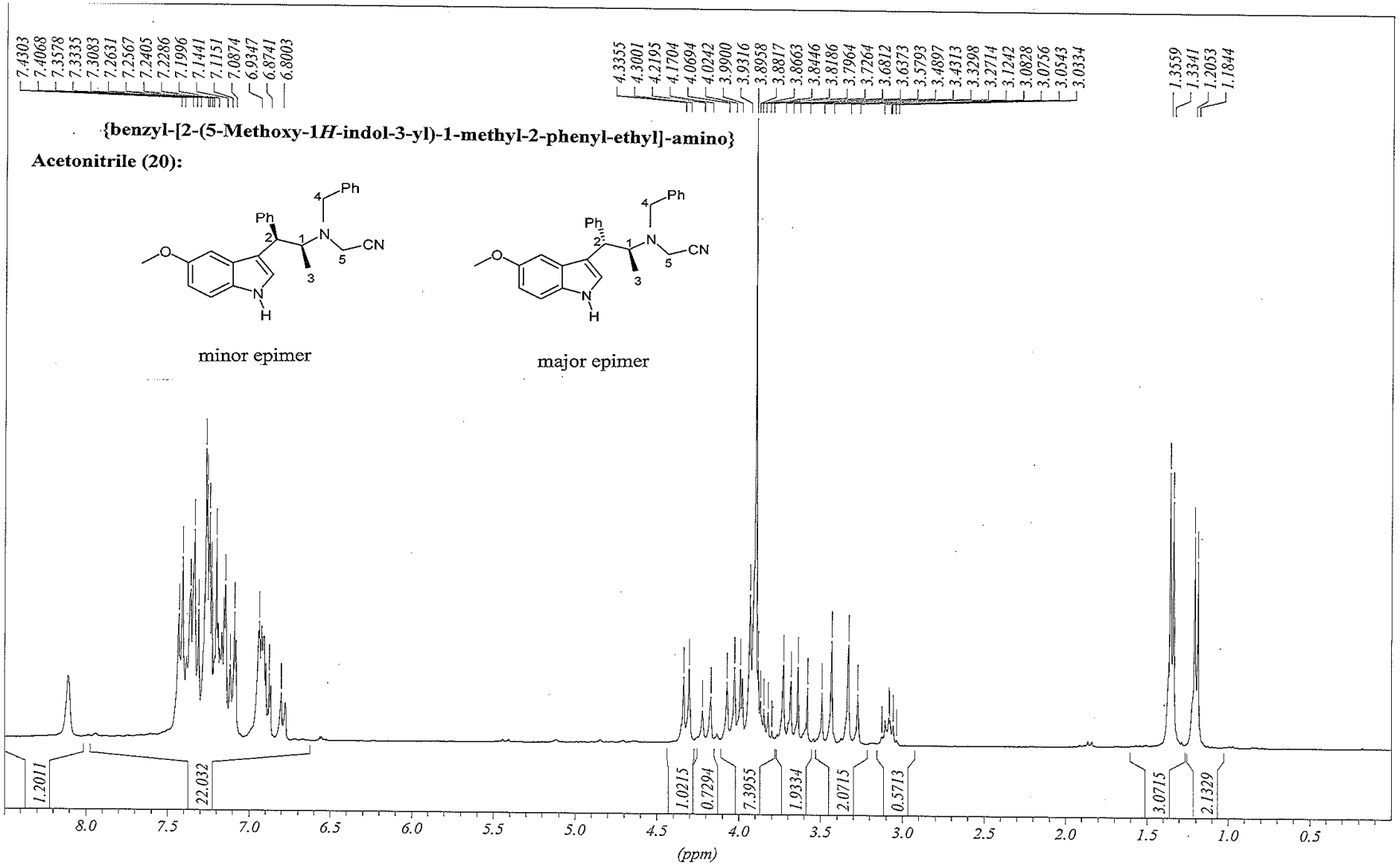
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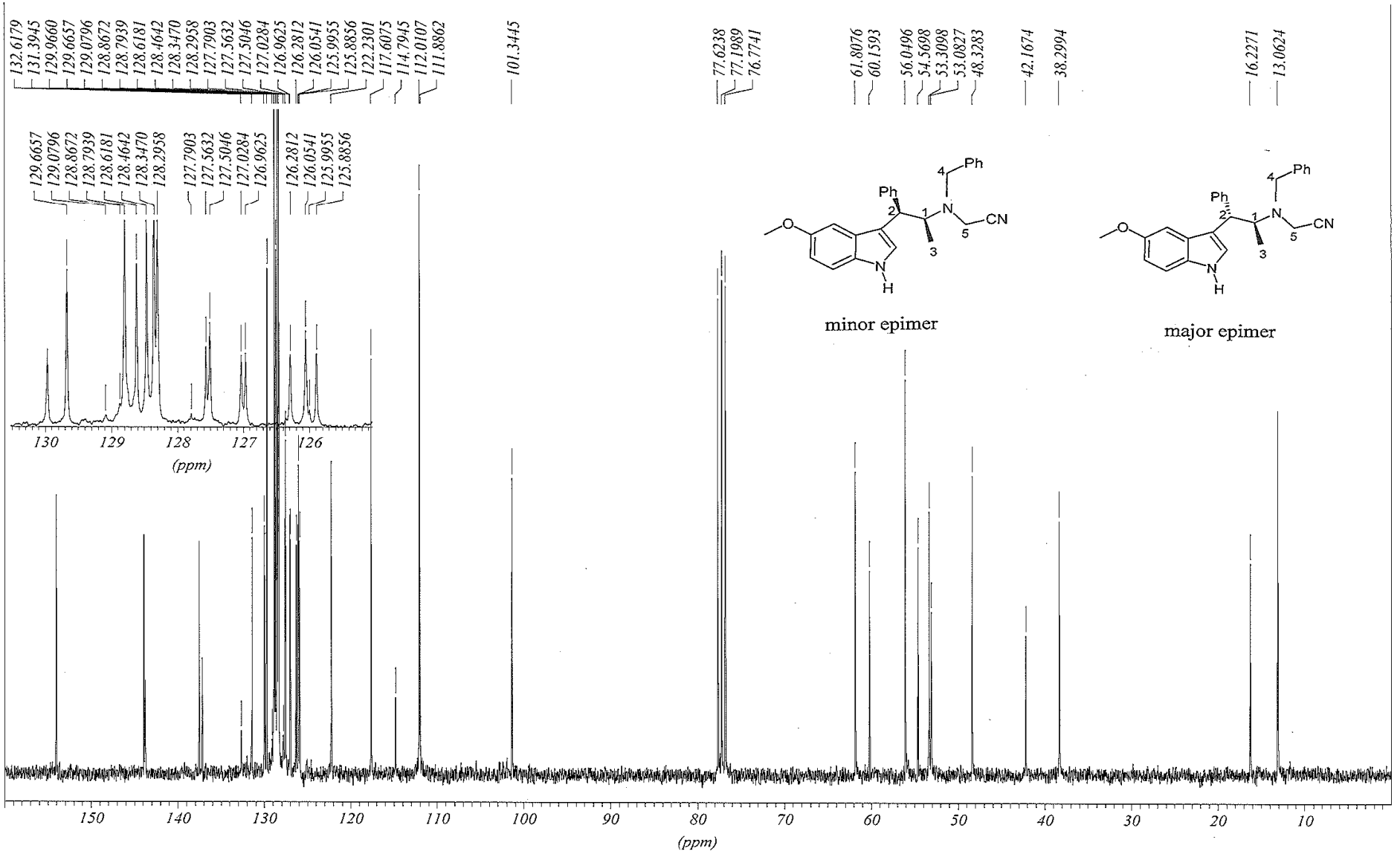
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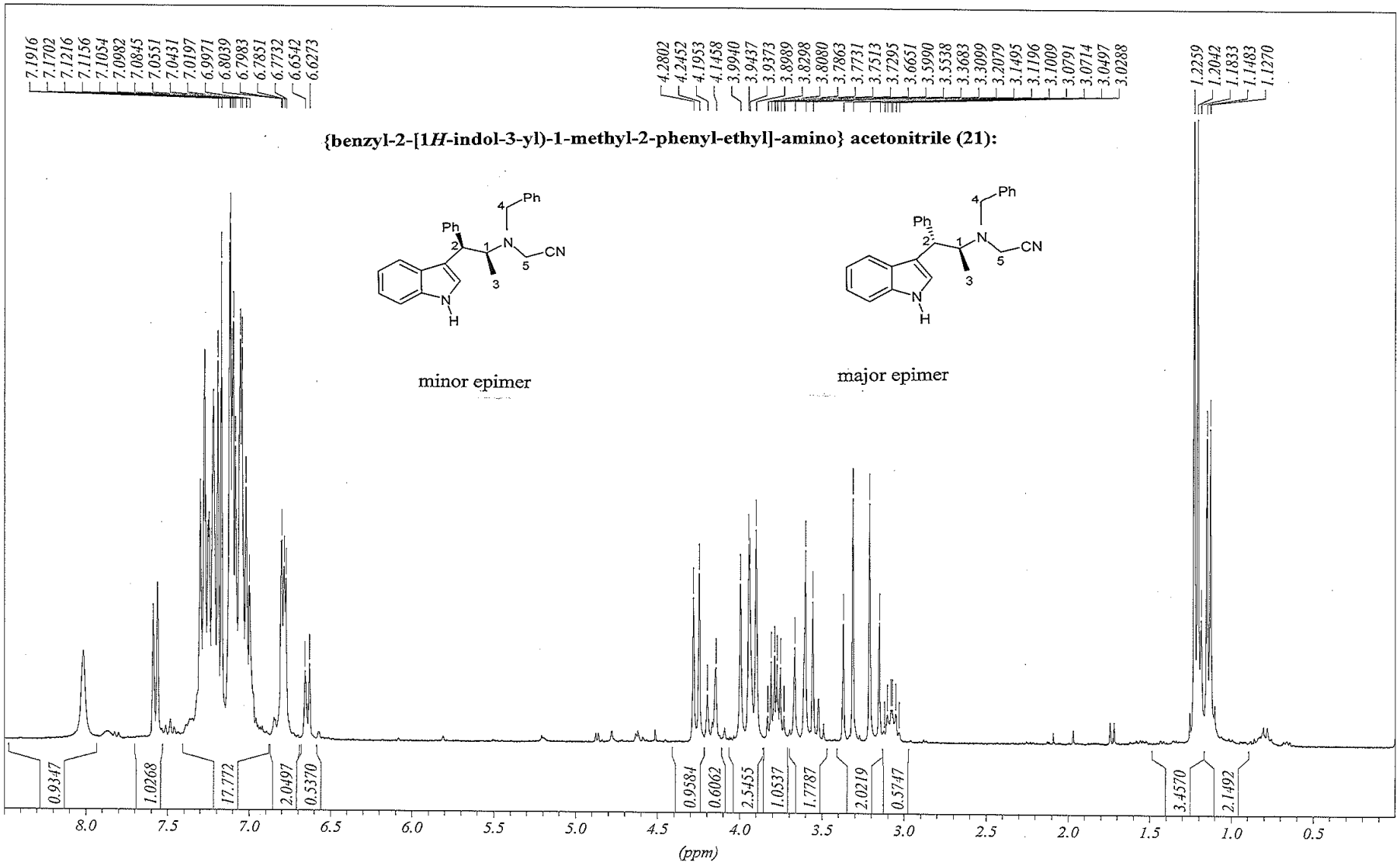
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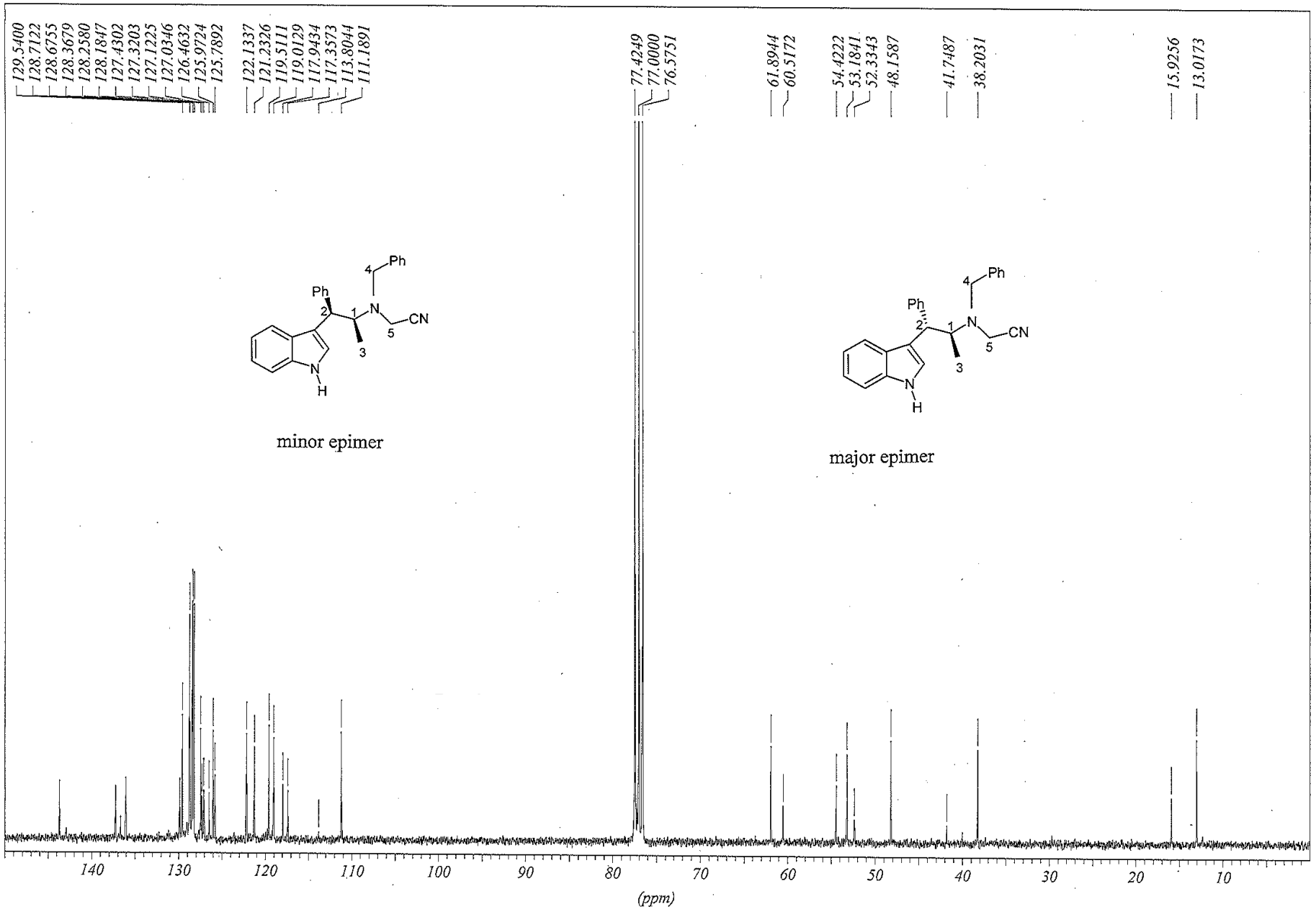

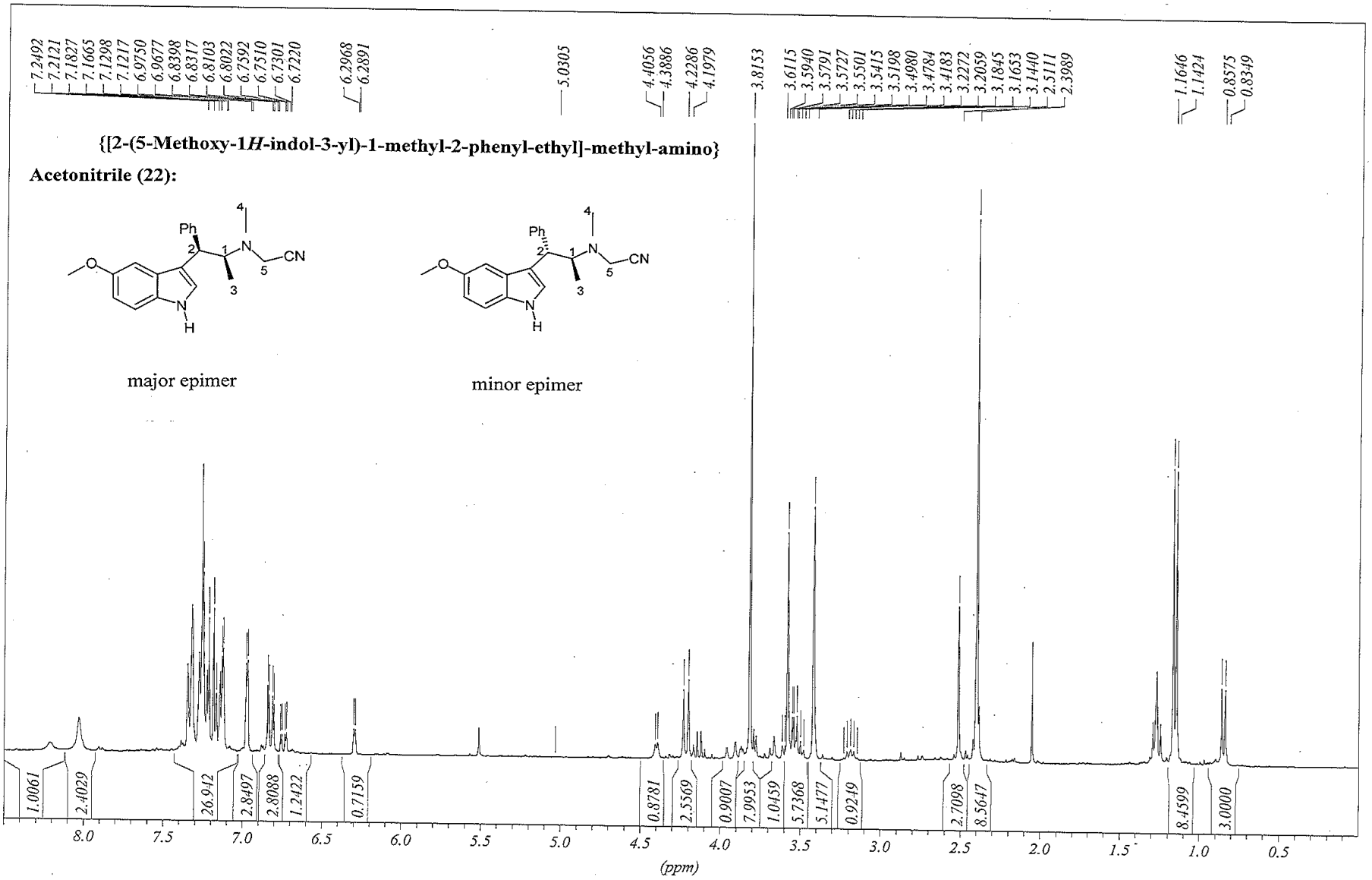
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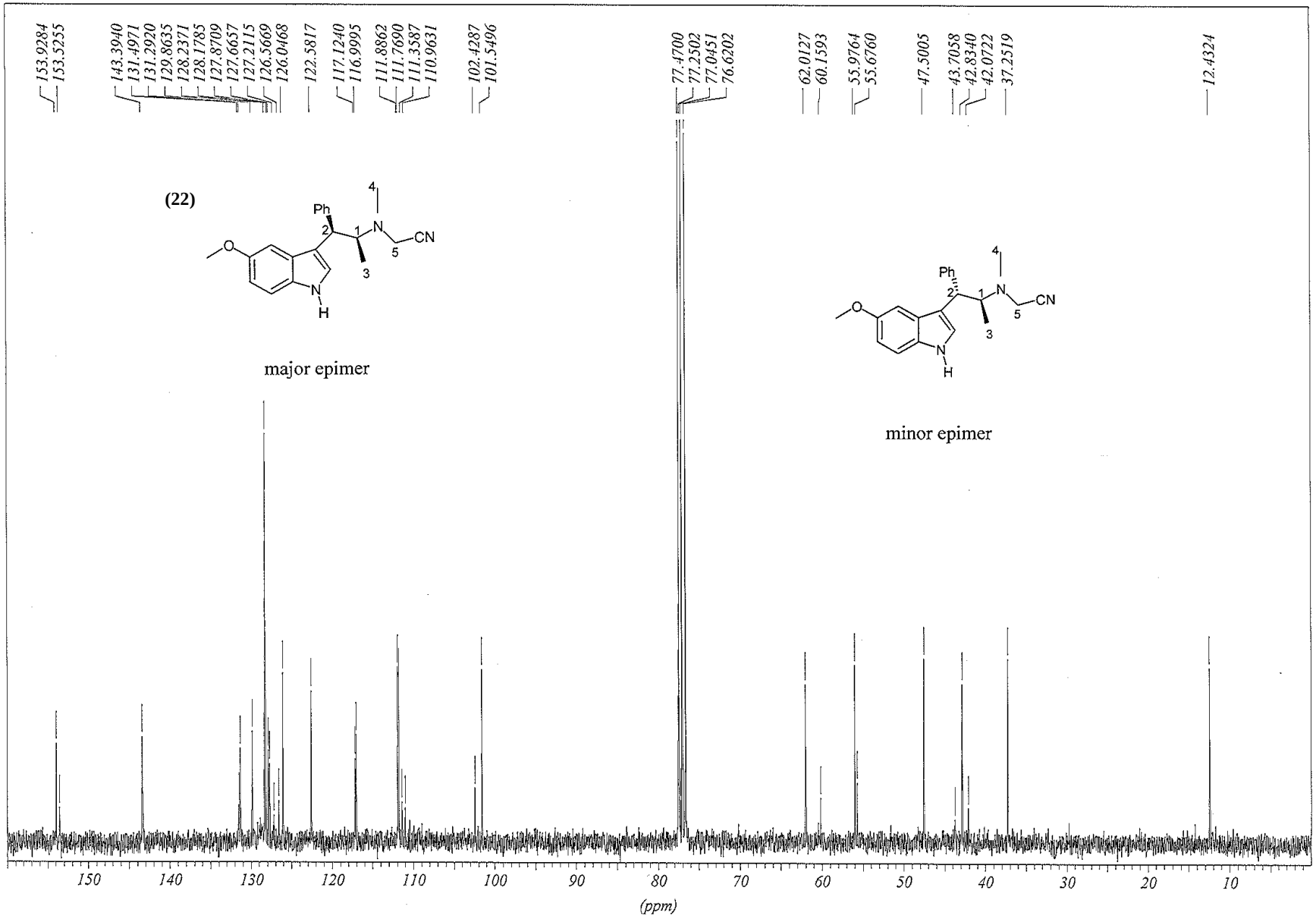
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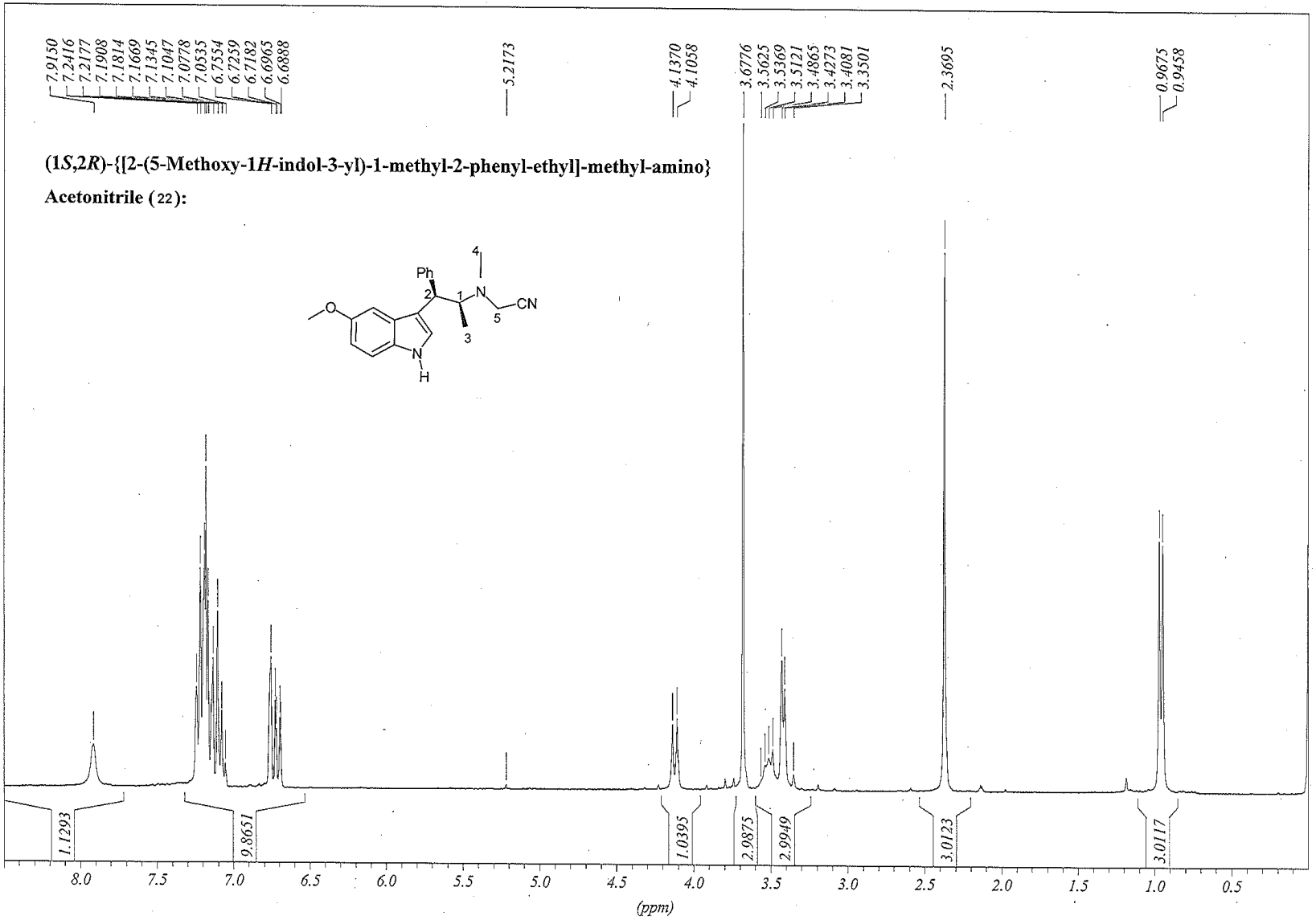
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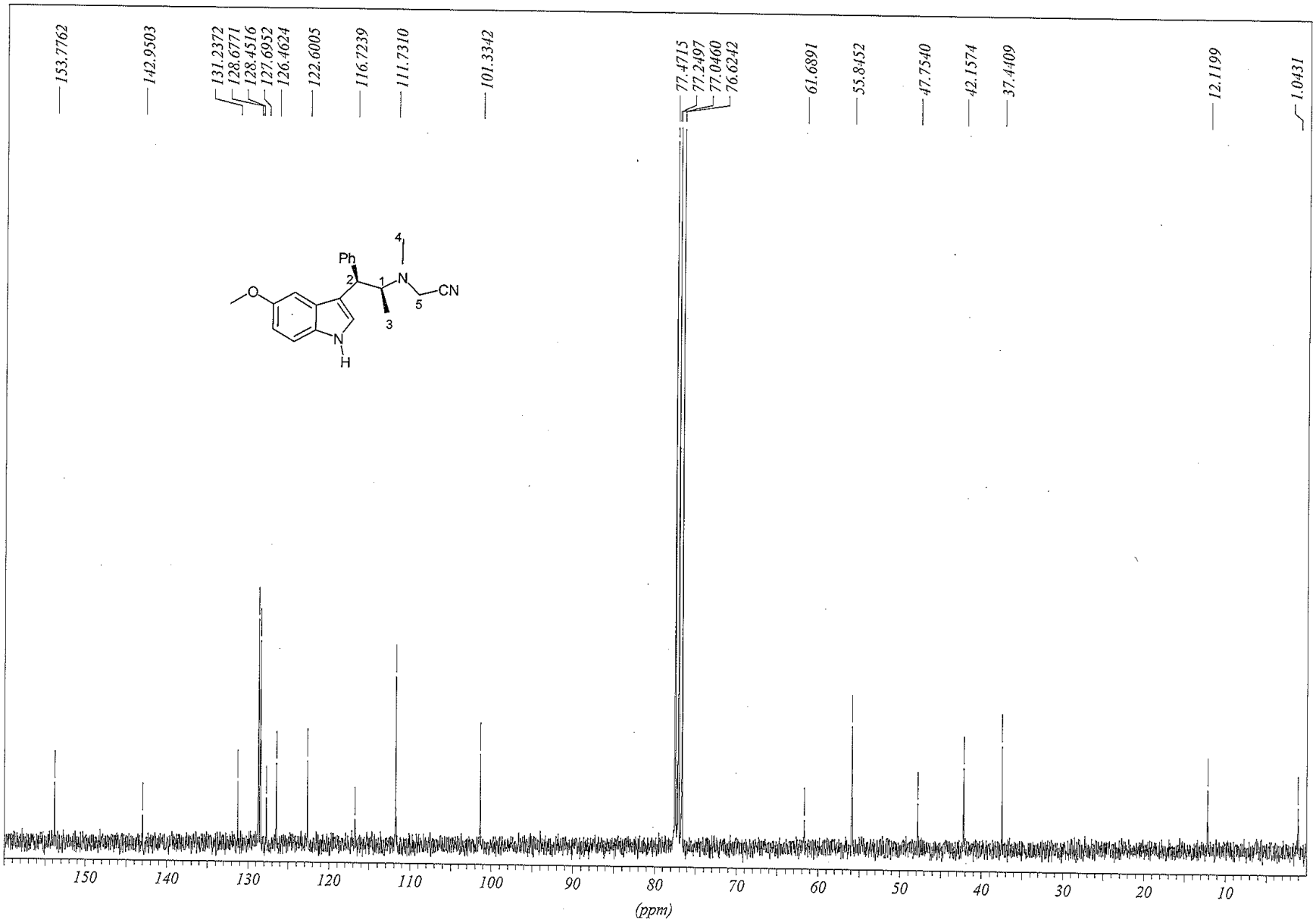
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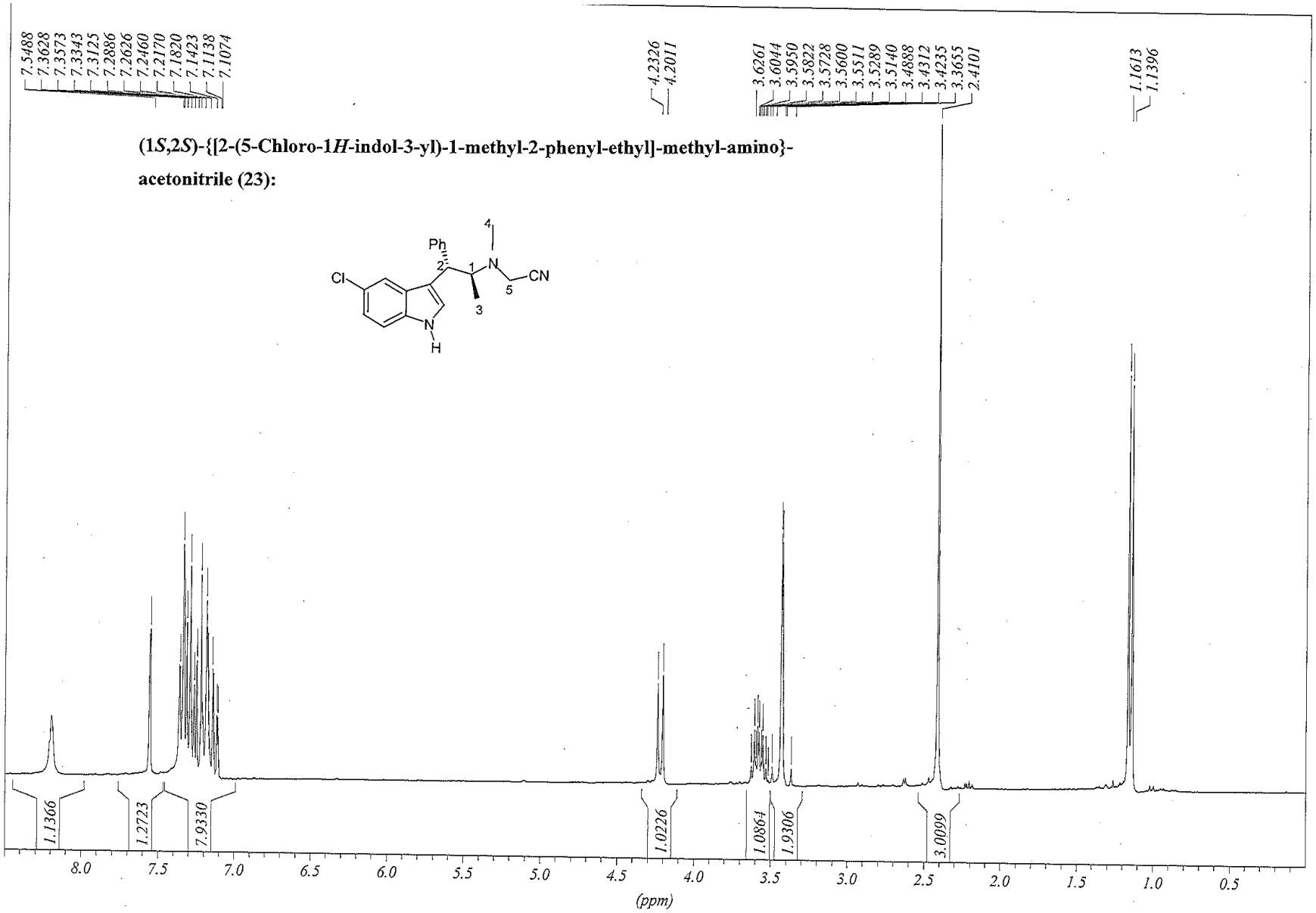
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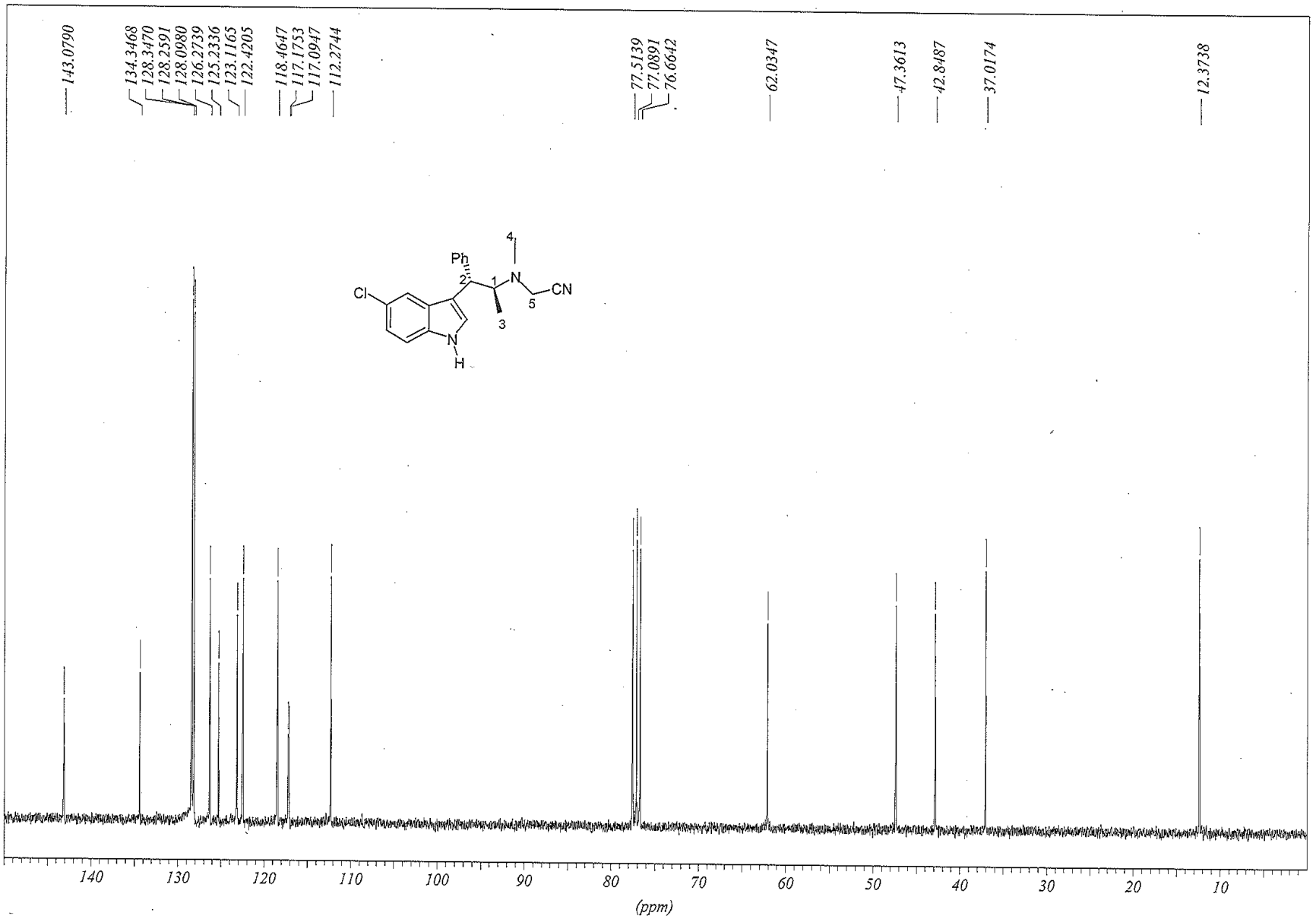
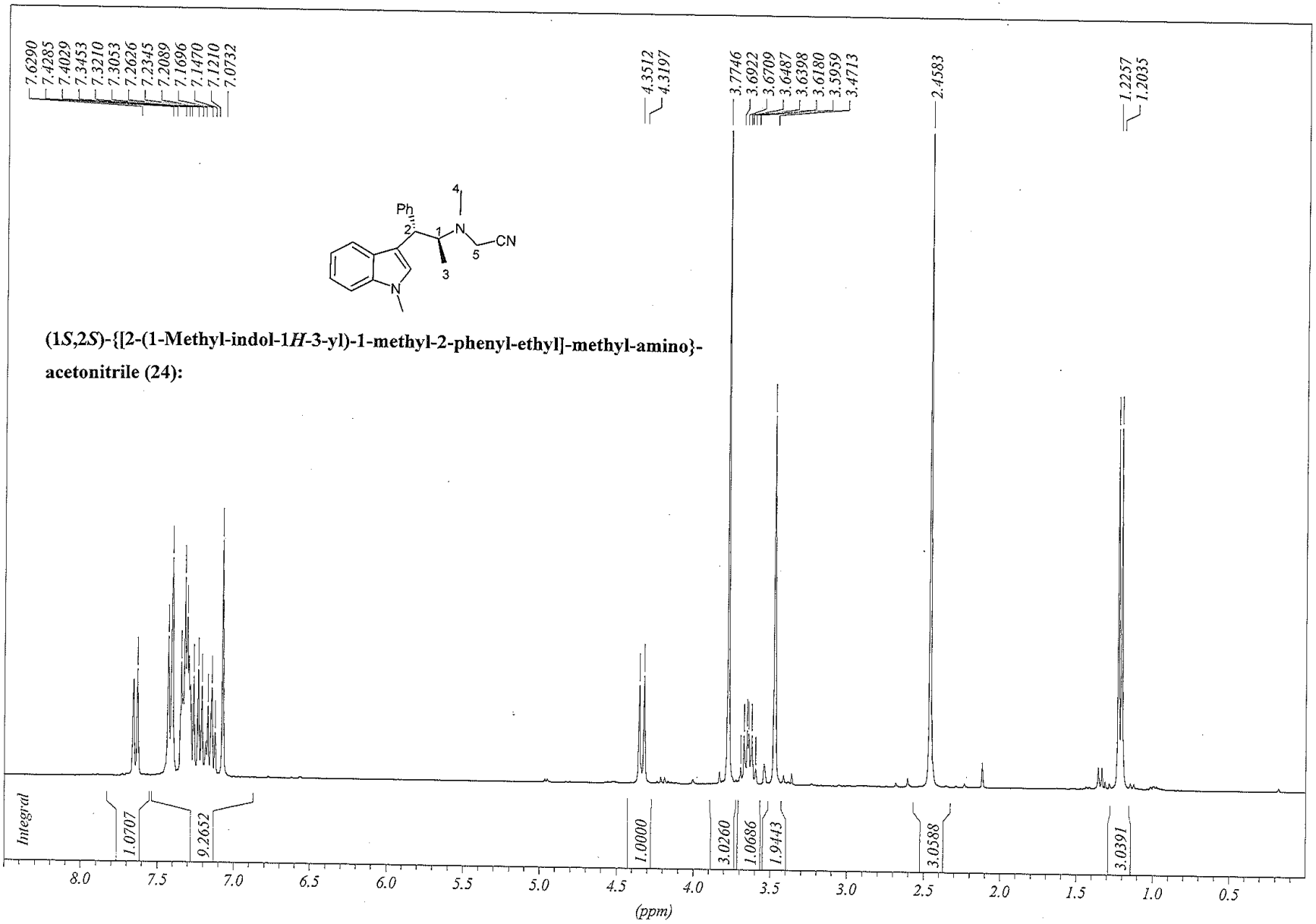
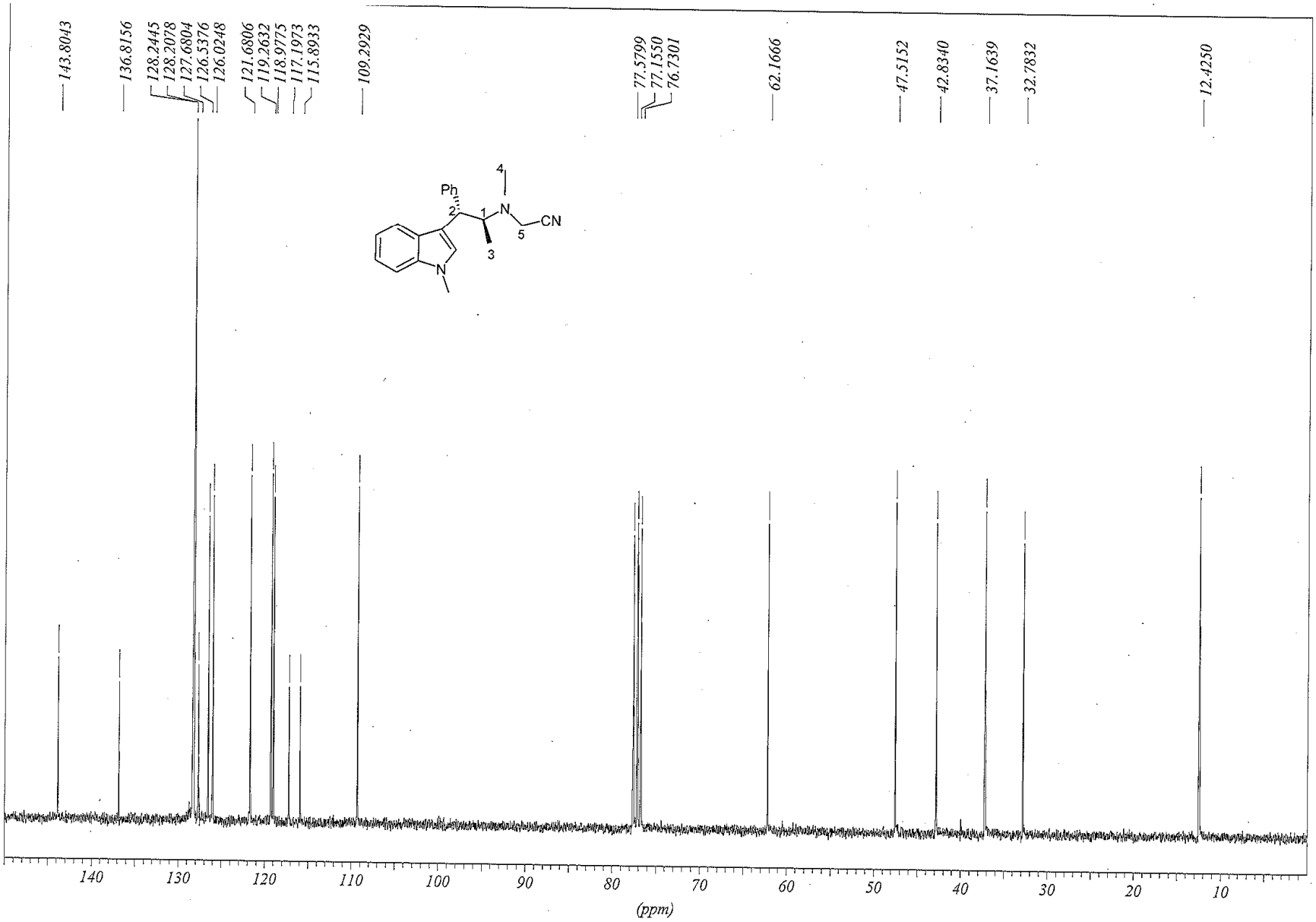
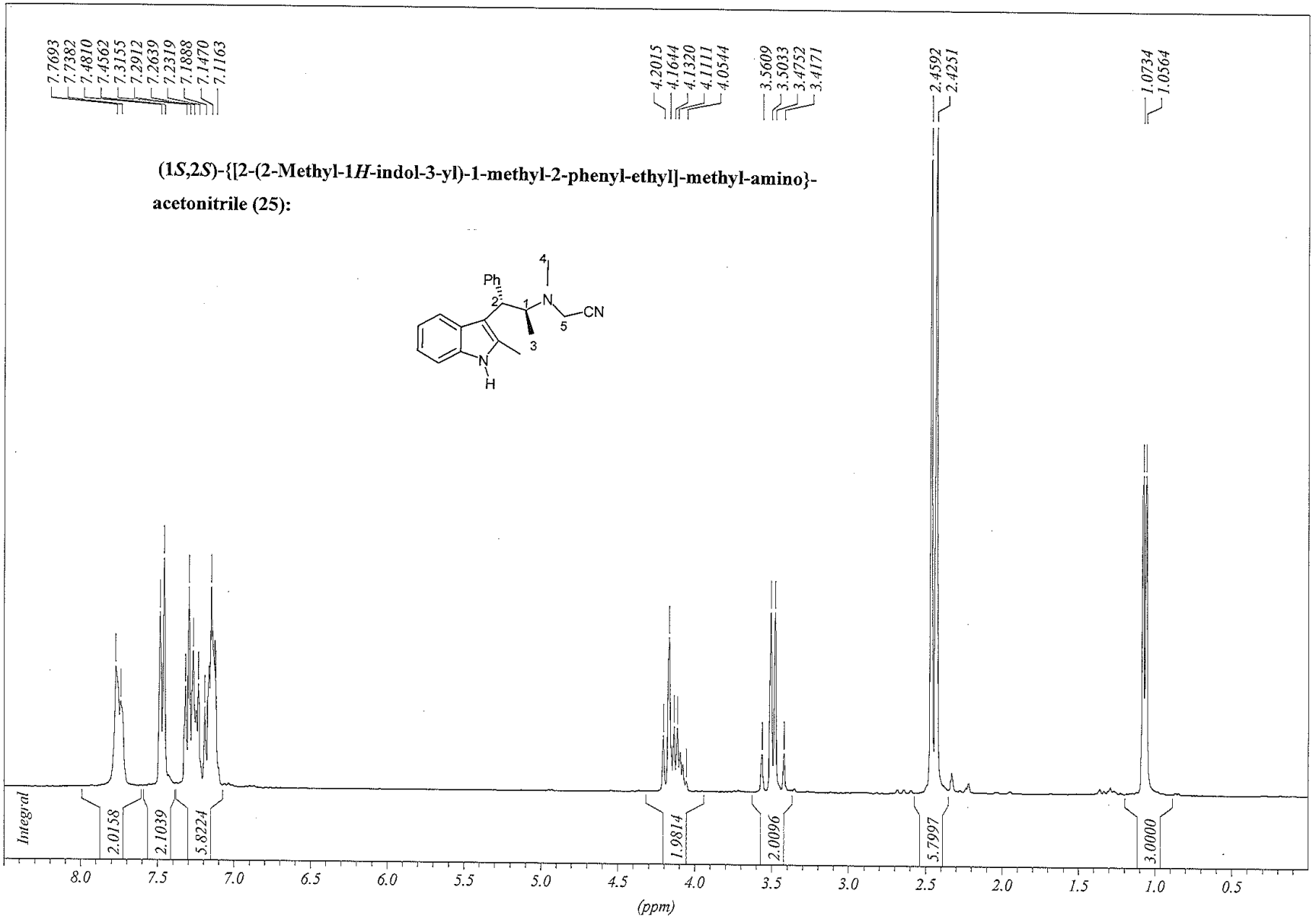
0.5
(ppm)

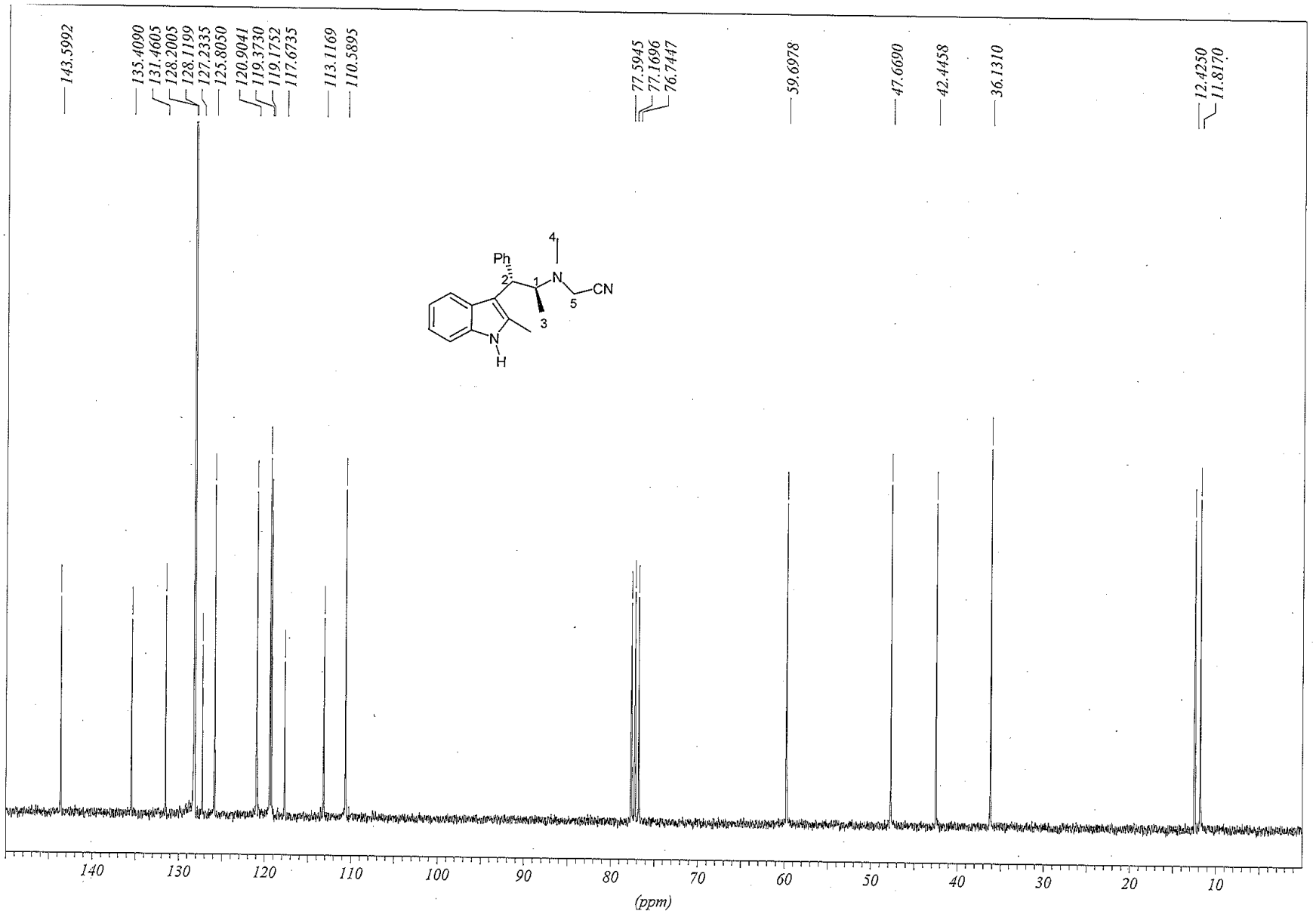

143.0790
134.3468
128.3470
128.2591
128.0980
126.2739
125.2336
123.1165
122.4205
118.4647
117.1753
117.0947
112.2744
77.5139
77.0891
76.6642
62.0347
47.3613
42.8487
37.0174
12.3738
Ph
Cl
CN
N
H
1
2
3
4
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



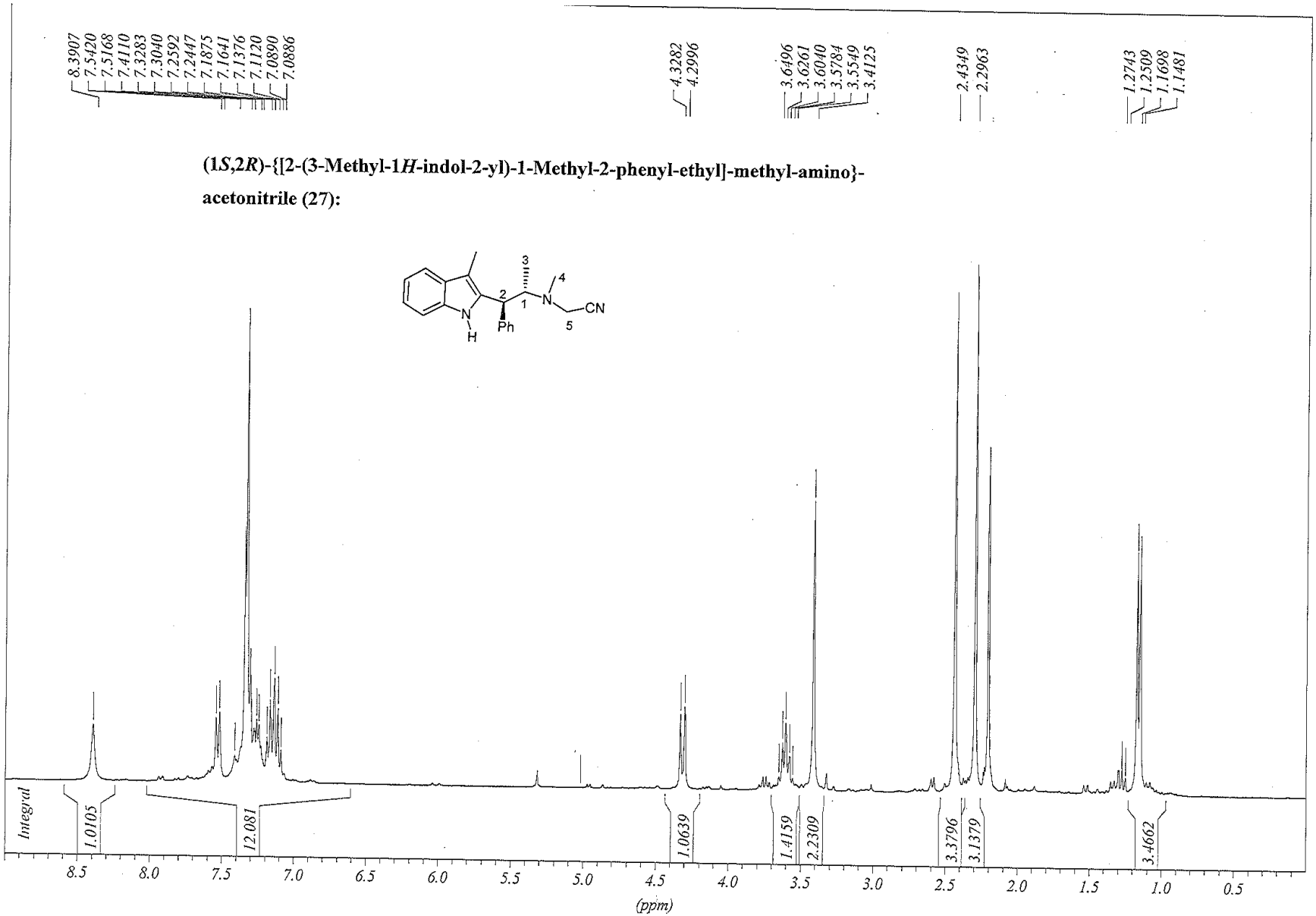
(1*S*,2*S*)-{[2-(1-Methyl-indol-1*H*-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (24):

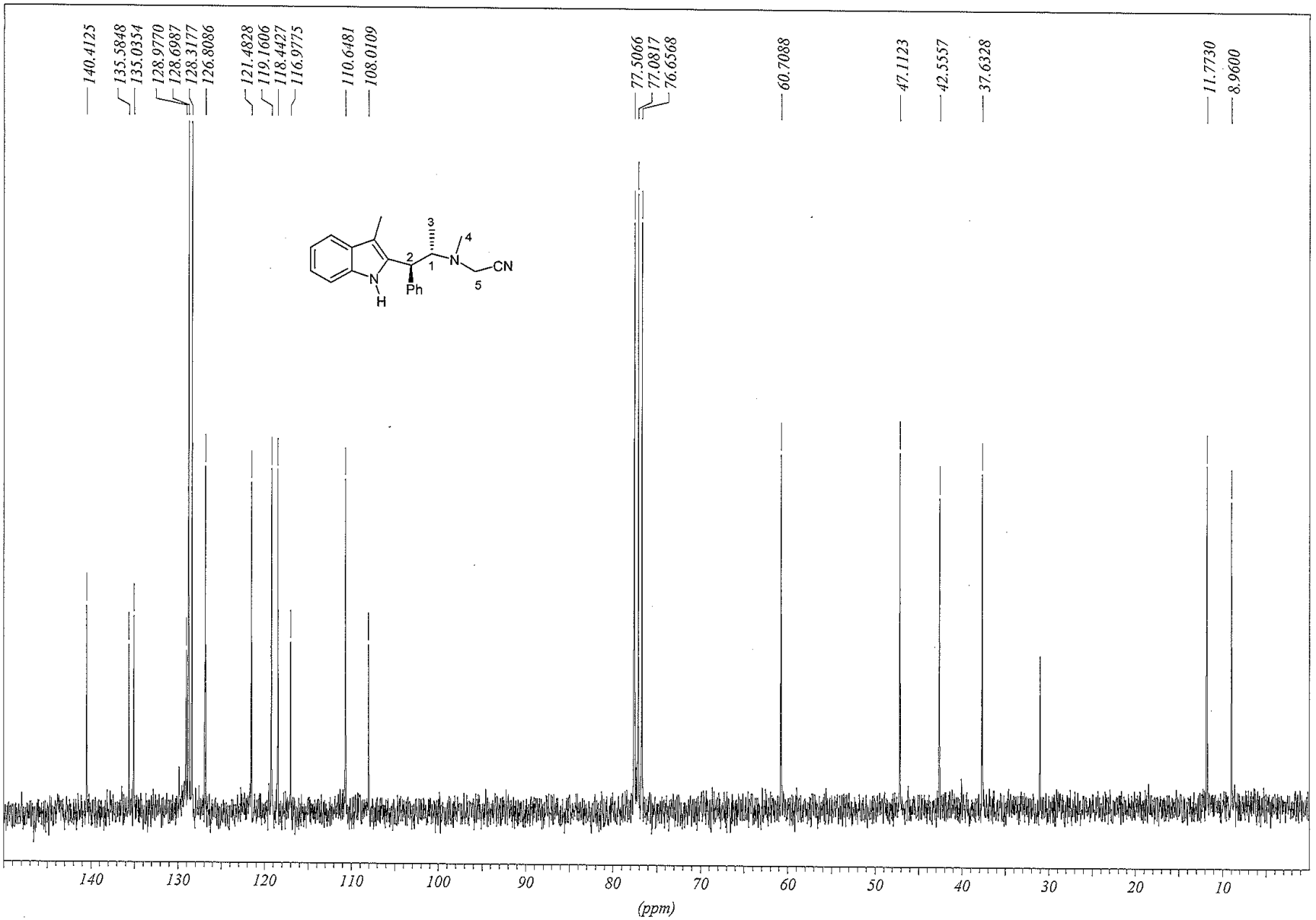

143.8043
136.8156
128.2445
128.2078
127.6804
126.5376
126.0248
121.6806
119.2632
118.9775
117.1973
115.8933
109.2929
77.5799
77.1550
76.7301
62.1666
47.5152
42.8340
37.1639
32.7832
12.4250
Ph
2
1
N
4
CN
5
3
N
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

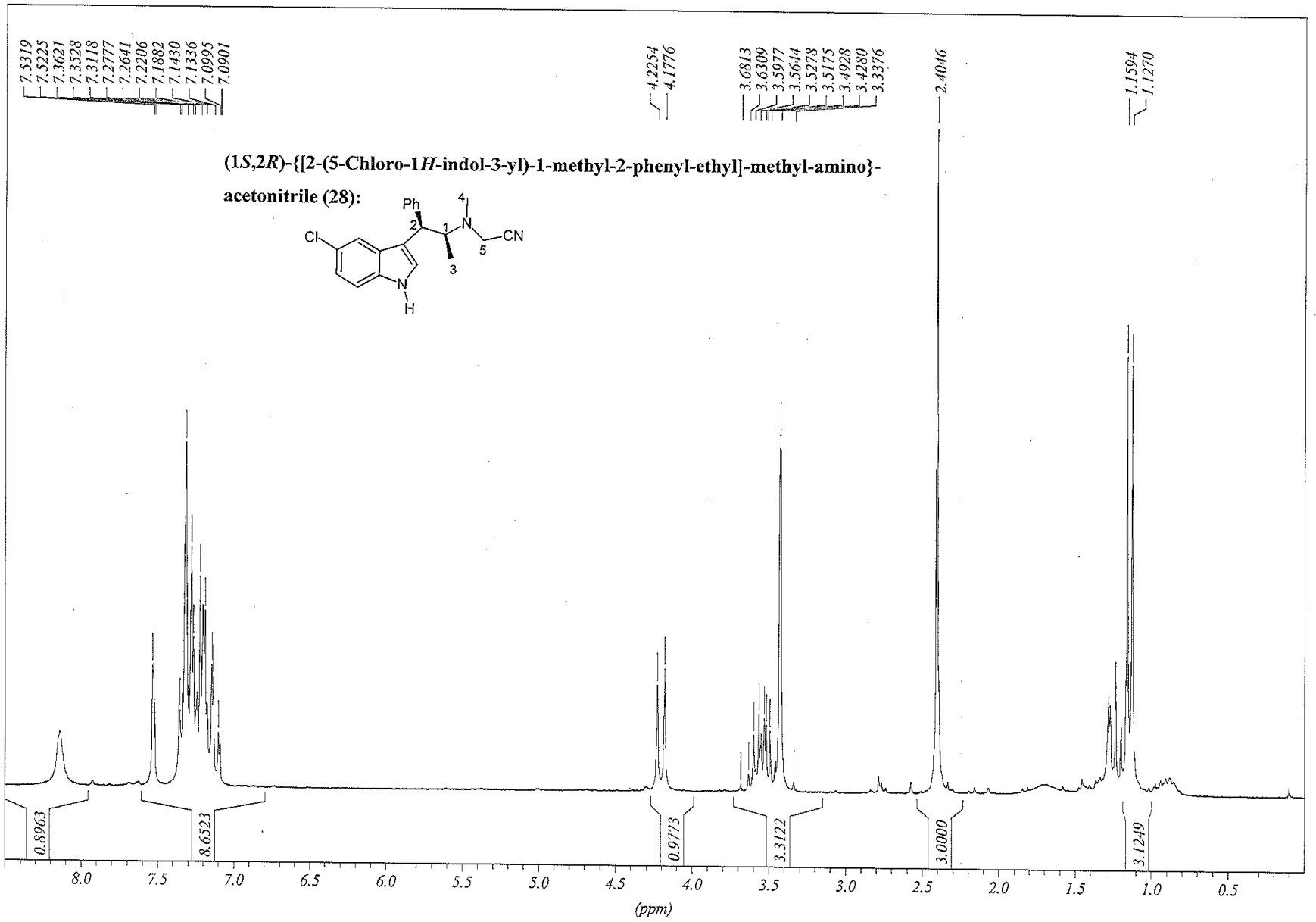

7.7693
7.7382
7.4810
7.4562
7.3155
7.2912
7.2639
7.2319
7.1888
7.1470
7.1163
4.2015
4.1644
4.1320
4.1111
4.0544
3.5609
3.5033
3.4752
3.4171
2.4592
2.4251
1.0734
1.0564
(1S,2S)-{[2-(2-Methyl-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (25):
Ph
4
2
1
N
CN
5
3
N
H
Integral
2.0158
2.1039
5.8224
1.9814
2.0096
5.7997
3.0000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

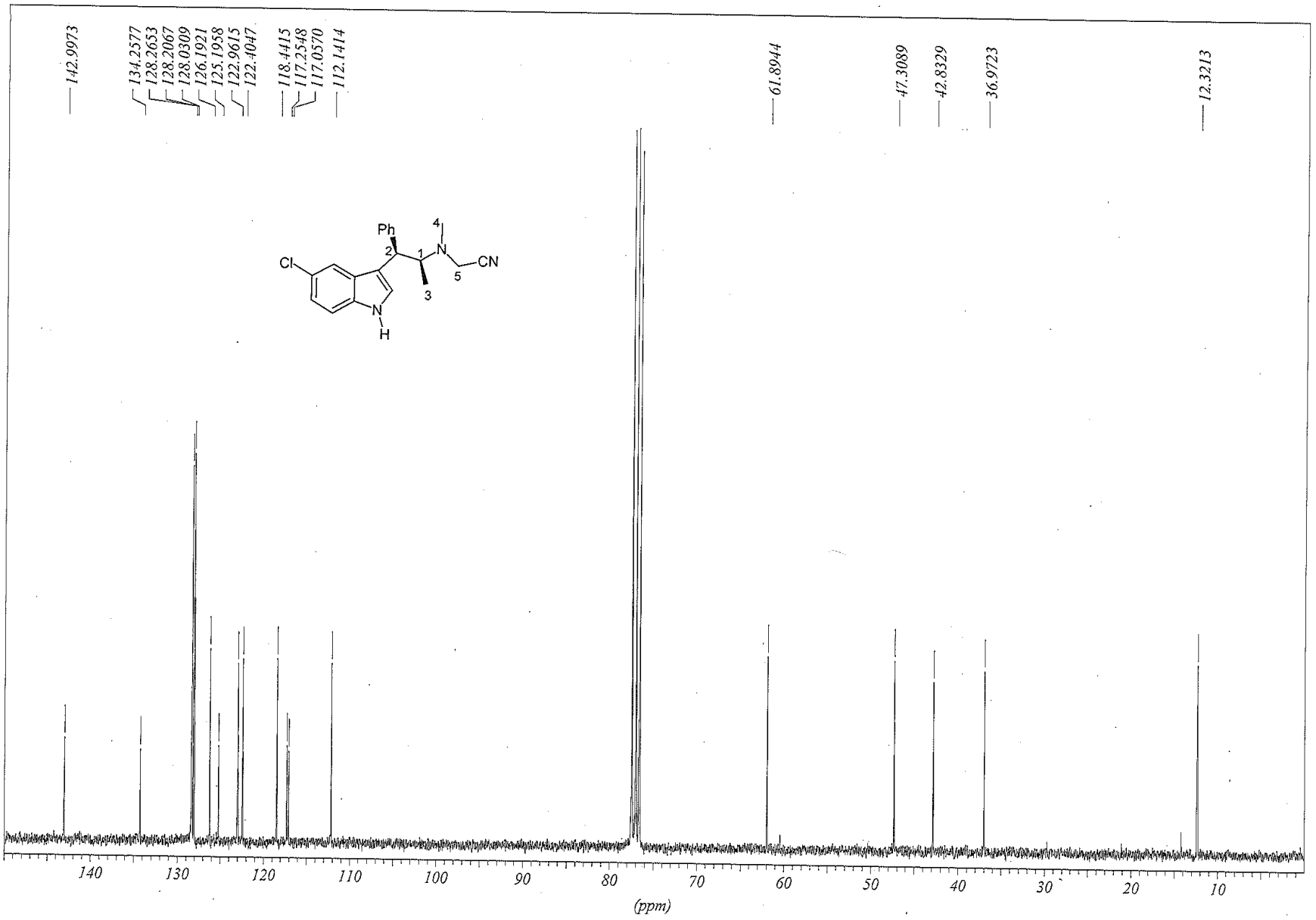

143.5992
135.4090
131.4605
128.2005
128.1199
127.2335
125.8050
120.9041
119.3730
119.1752
117.6735
113.1169
110.5895
77.5945
77.1696
76.7447
59.6978
47.6690
42.4458
36.1310
12.4250
11.8170
Ph
2
1
N
4
5
CN
3
N
H
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

(1*S*,2*R*)-{[2-(3-Methyl-1*H*-indol-2-yl)-1-Methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (27):

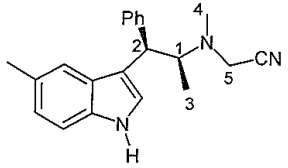


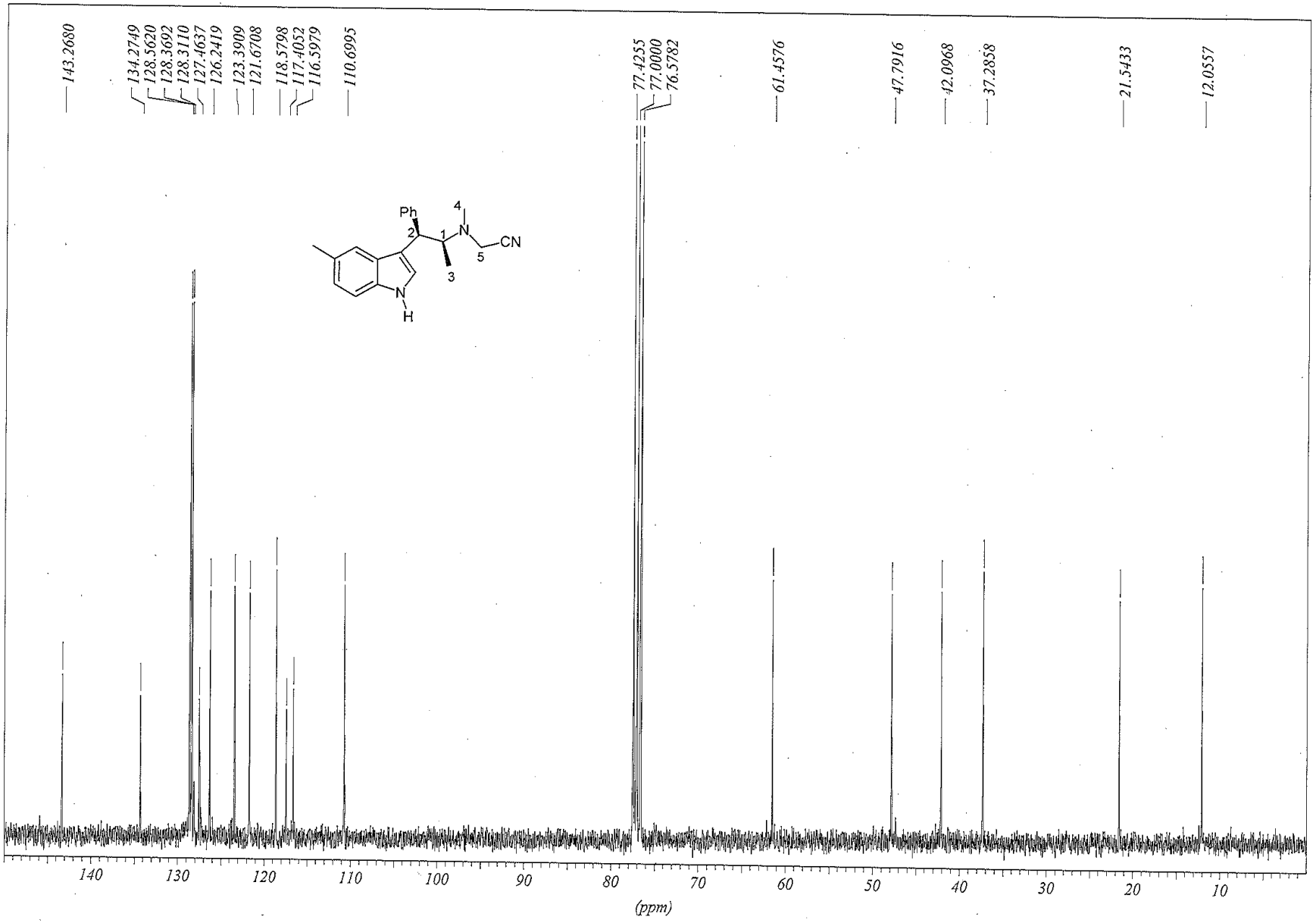

140.4125
135.5848
135.0354
128.9770
128.6987
128.3177
126.8086
121.4828
119.1606
118.4427
116.9775
110.6481
108.0109
77.5066
77.0817
76.6568
60.7088
47.1123
42.5557
37.6328
11.7730
8.9600
N
H
Ph
CN
1
2
3
4
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

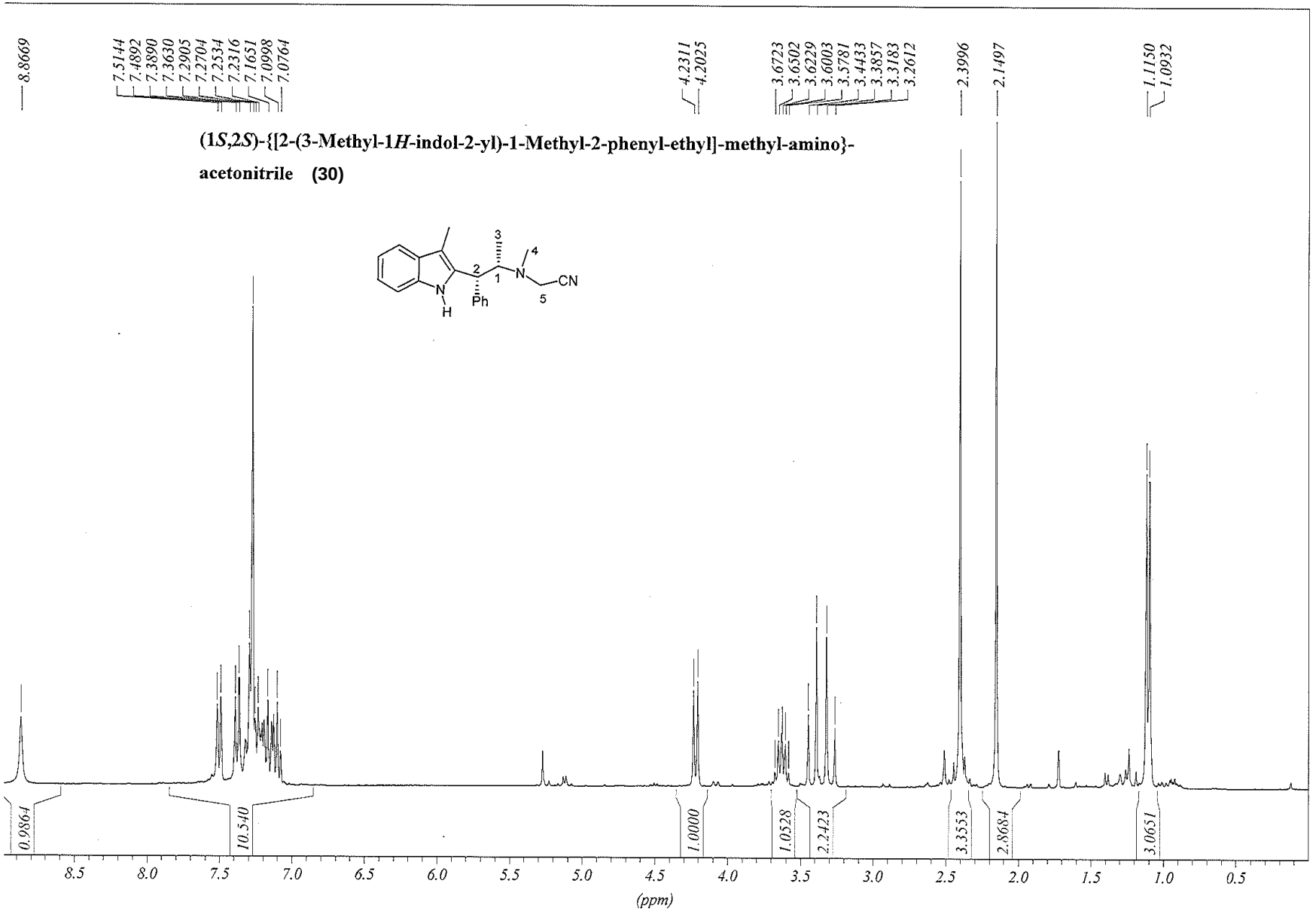

7.5319
7.5225
7.3621
7.3528
7.3118
7.2777
7.2641
7.2206
7.1882
7.1430
7.1336
7.0995
7.0901
4.2254
4.1776
3.6813
3.6309
3.5977
3.5644
3.5278
3.5175
3.4928
3.4280
3.3376
2.4046
1.1594
1.1270
(1S,2R)-{[2-(5-Chloro-1H-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (28):
Ph
2
1
4
N
CN
5
3
Cl
N
H
0.8963
8.6523
0.9773
3.3122
3.0000
3.1249
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

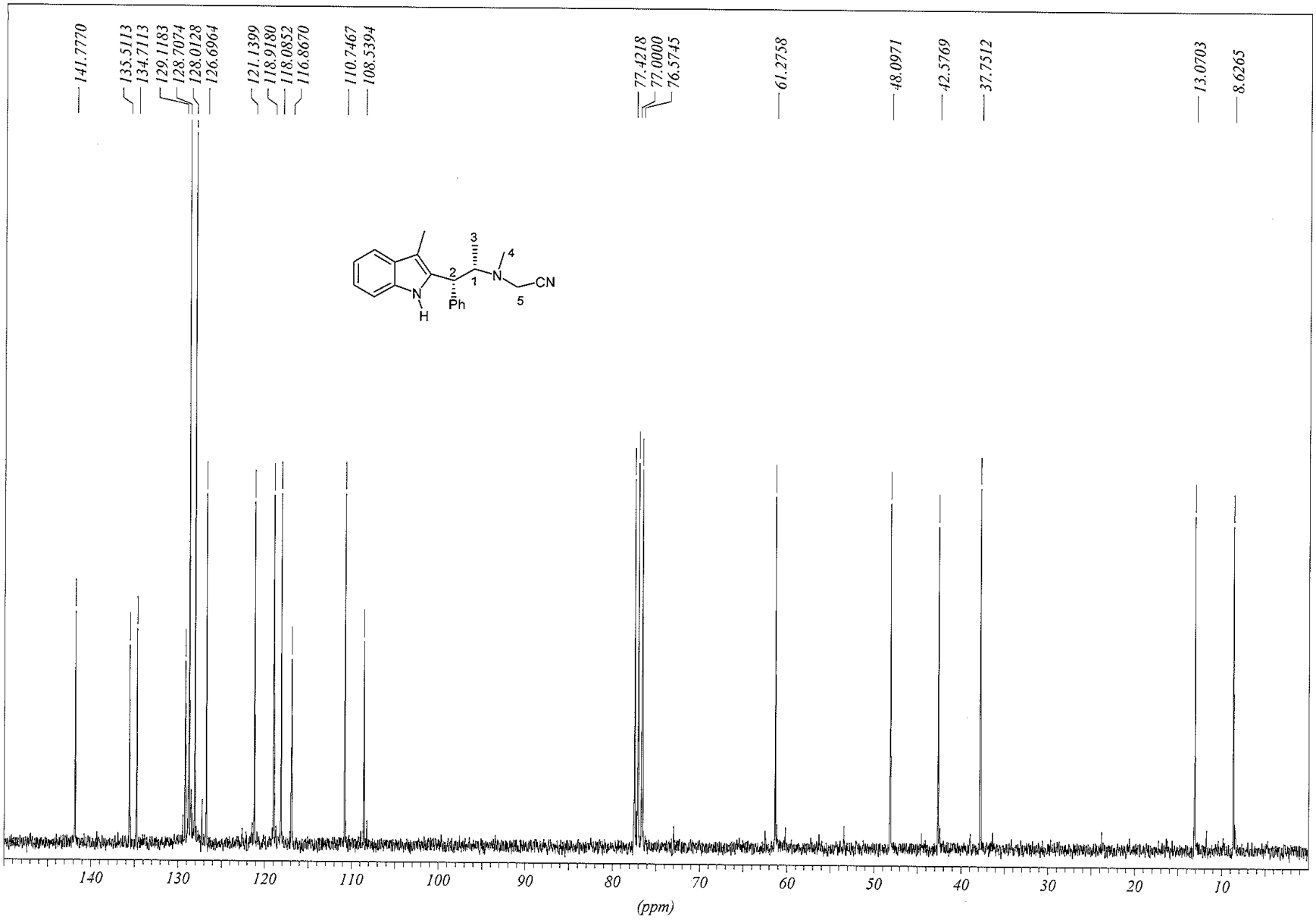

142.9973
134.2577
128.2653
128.2067
128.0309
126.1921
125.1958
122.9615
122.4047
118.4415
117.2548
117.0570
112.1414
61.8944
47.3089
42.8329
36.9723
12.3213
Ph
2
1
N
4
CN
5
3
Cl
N
H
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

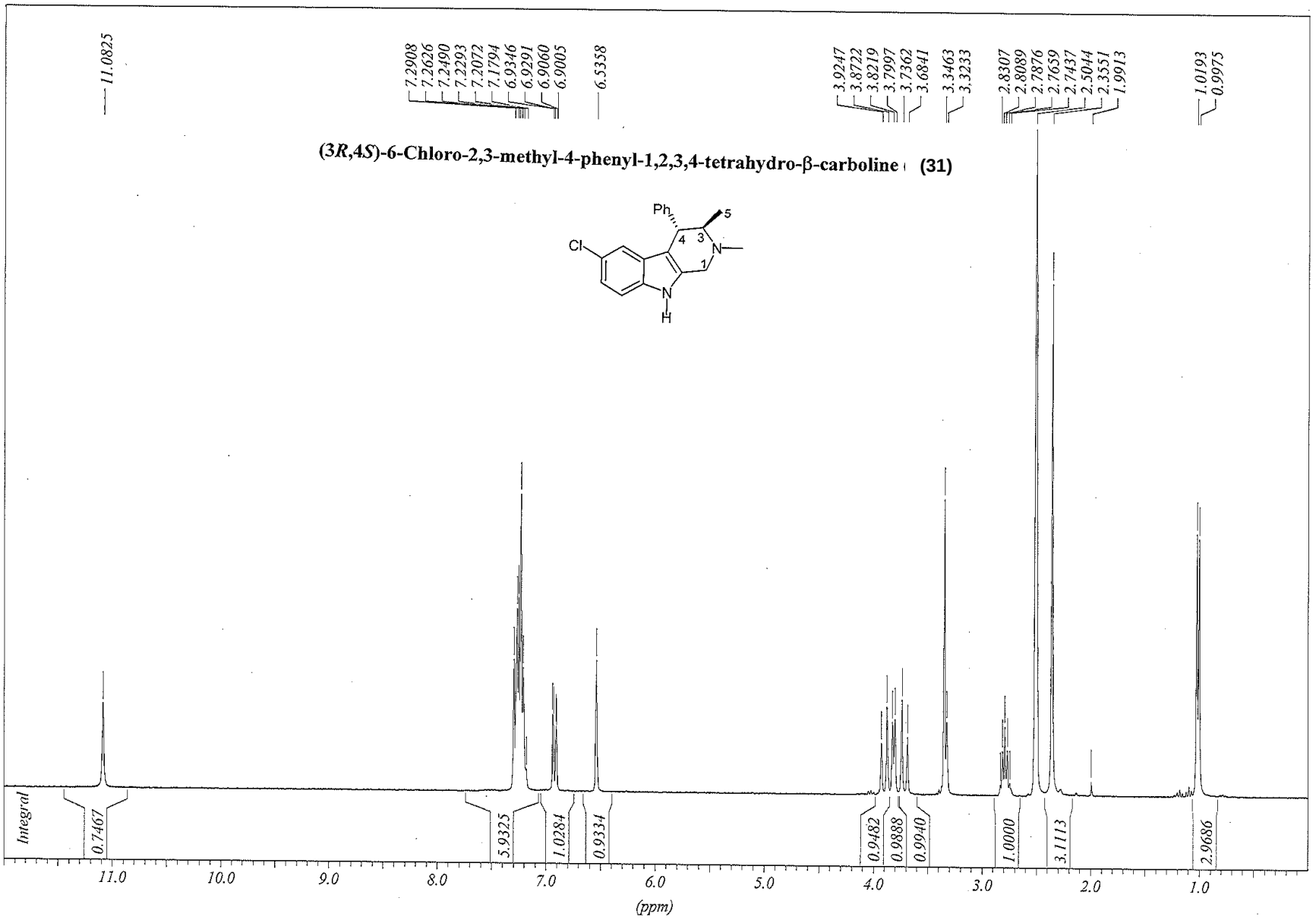
(1*S*,2*R*)-{[2-(5-Methyl-1*H*-indol-3-yl)-1-methyl-2-phenyl-ethyl]-methyl-amino}-acetonitrile (29):

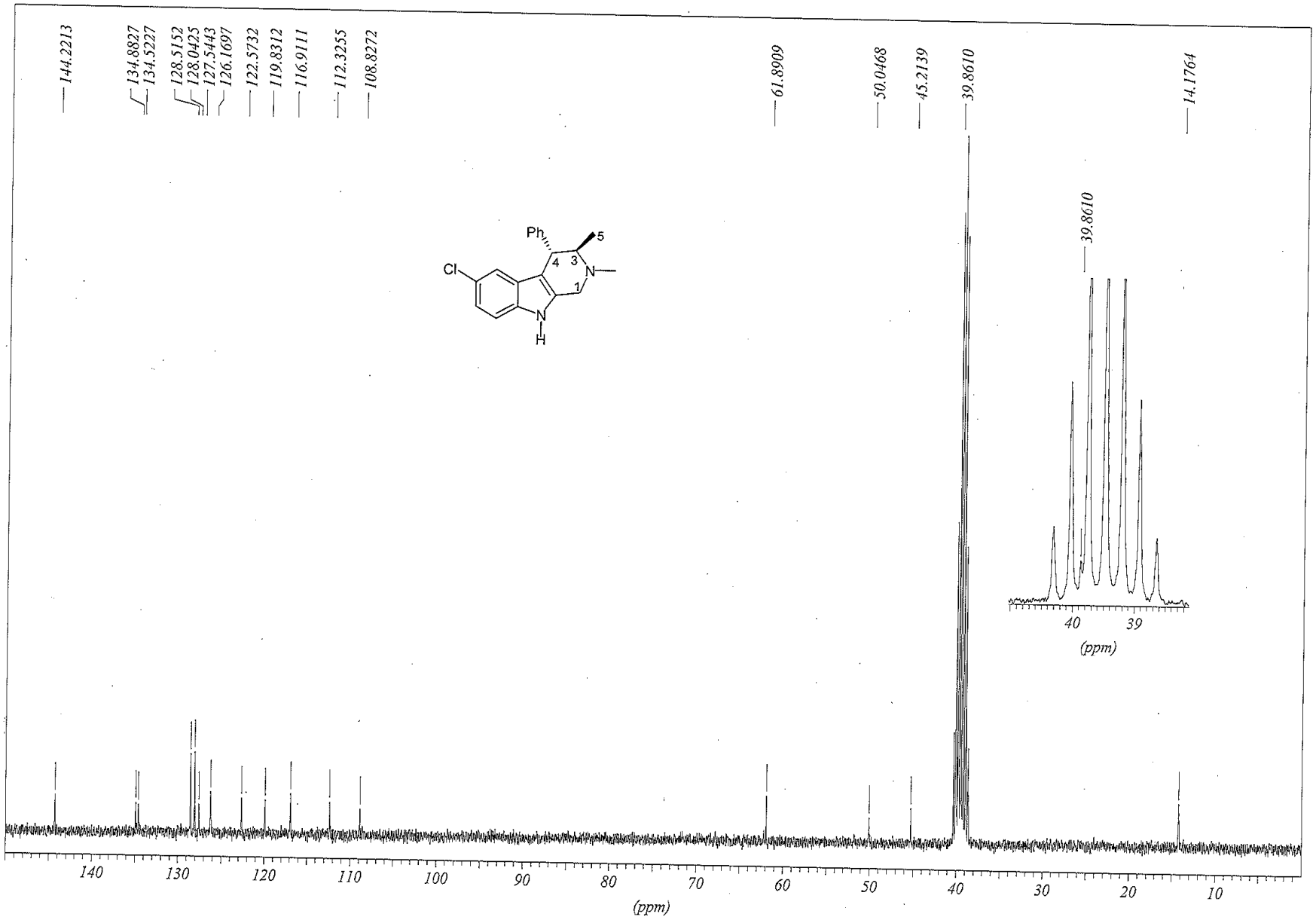


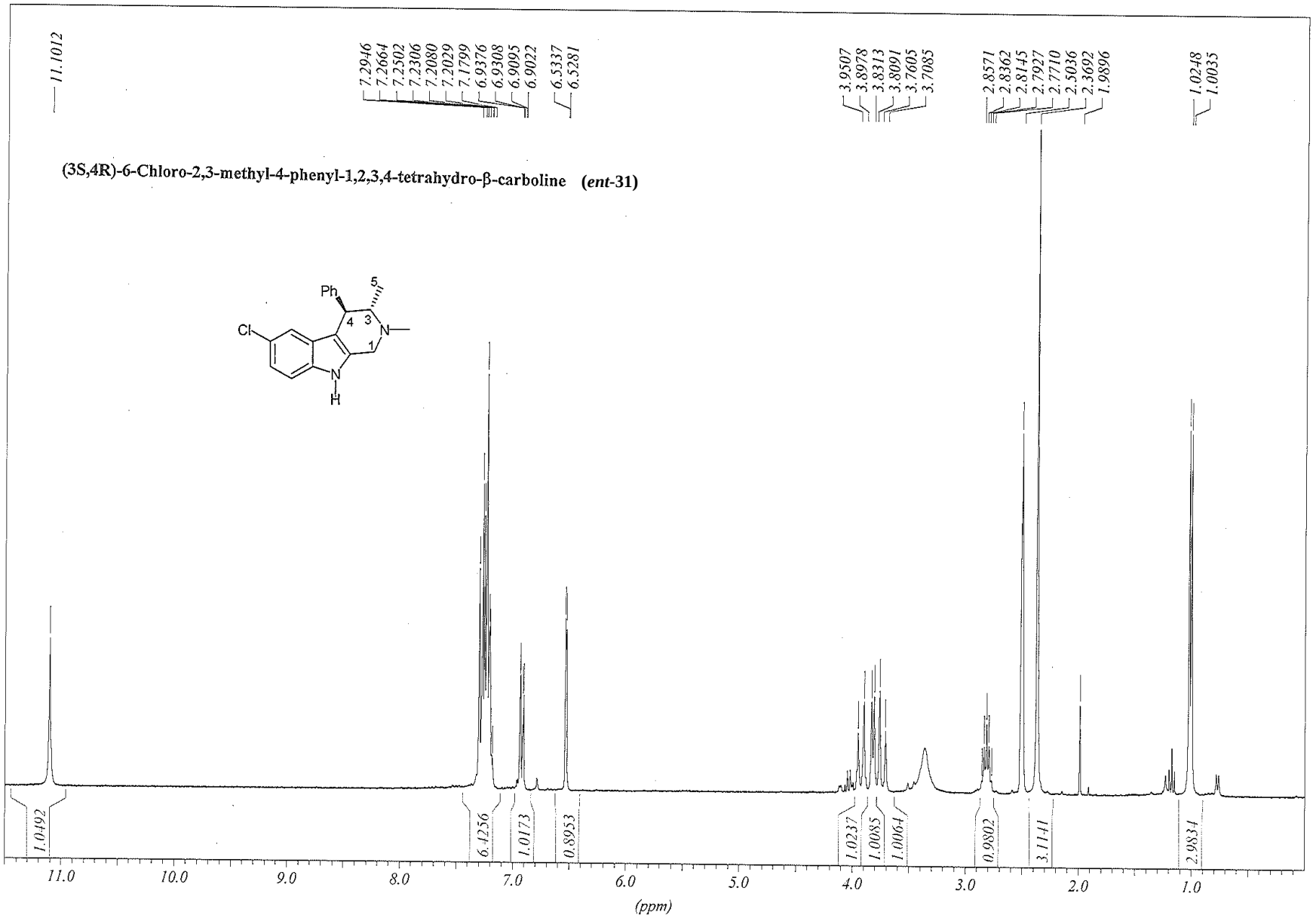

143.2680
134.2749
128.5620
128.3692
128.3110
127.4637
126.2419
123.3909
121.6708
118.5798
117.4052
116.5979
110.6995
77.4255
77.0000
76.5782
61.4576
47.7916
42.0968
37.2858
21.5433
12.0557
Ph
2
1
N
4
CN
5
3
N
H
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

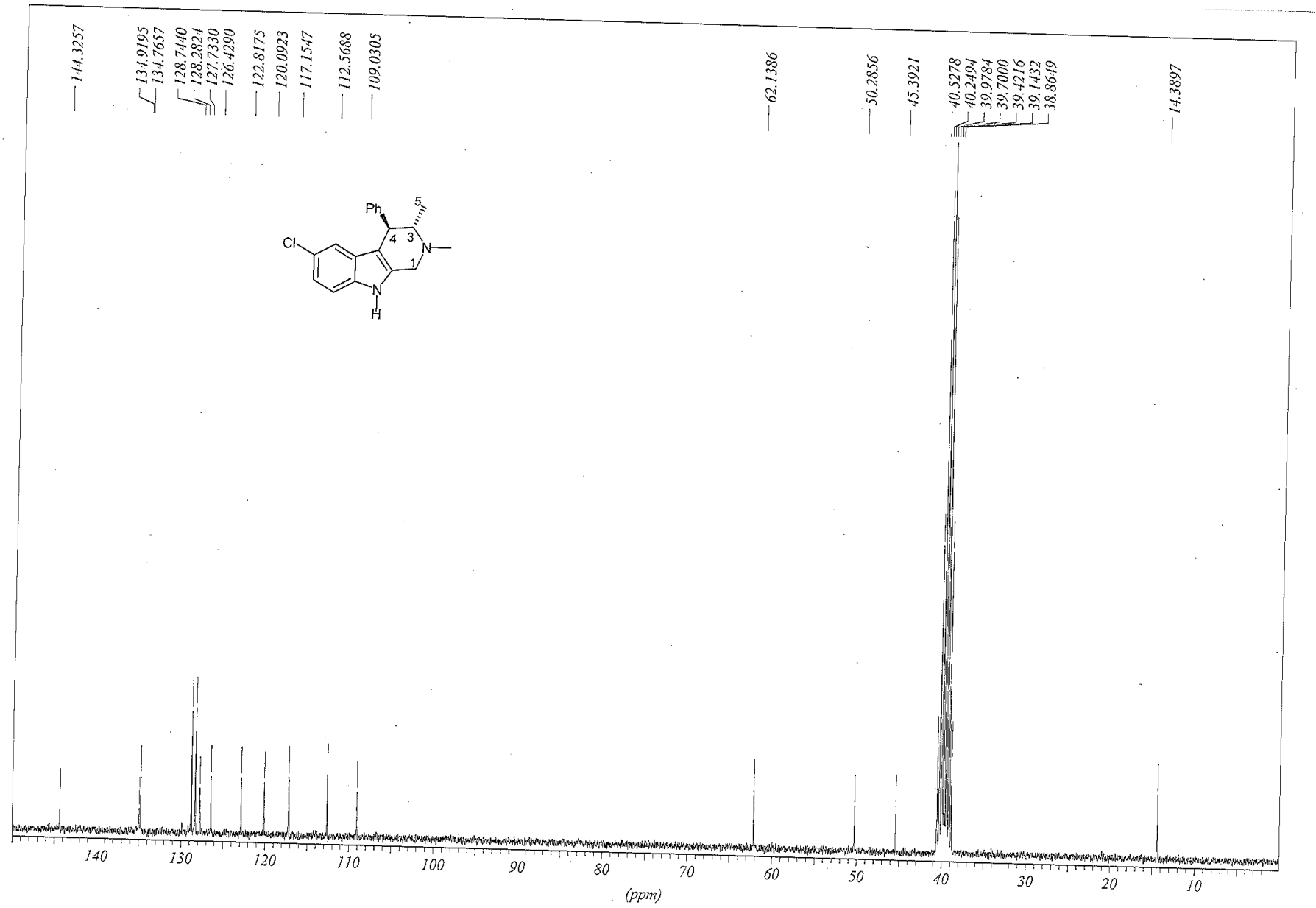

8.8669
7.5144
7.4892
7.3890
7.3630
7.2905
7.2704
7.2534
7.2316
7.1651
7.0998
7.0764
4.2311
4.2025
3.6723
3.6502
3.6229
3.6003
3.5781
3.4433
3.3857
3.3183
3.2612
2.3996
2.1497
1.1150
1.0932
(1S,2S)-{[2-(3-Methyl-1H-indol-2-yl)-1-Methyl-2-phenyl-ethyl]-methyl-amino}-
acetonitrile (30)
N
H
Ph
CN
0.9864
10.540
1.0000
1.0528
2.2423
3.3553
2.8684
3.0631
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

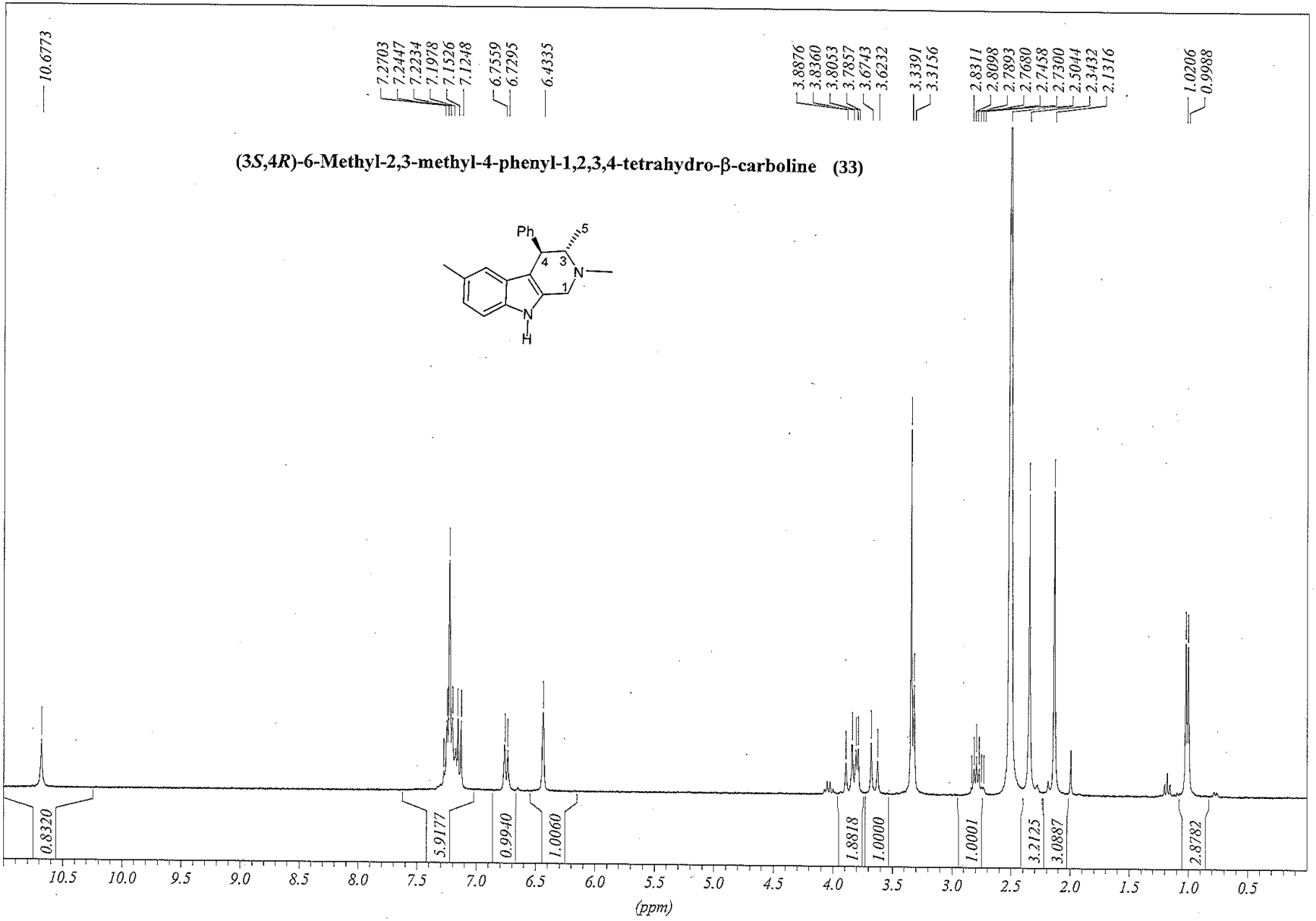

141.7770
135.5113
134.7113
129.1183
128.7074
128.0128
126.6964
121.1399
118.9180
118.0852
116.8670
110.7467
108.5394
77.4218
77.0000
76.5745
61.2758
48.0971
42.5769
37.7512
13.0703
8.6265
N
H
Ph
CN
1
2
3
4
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

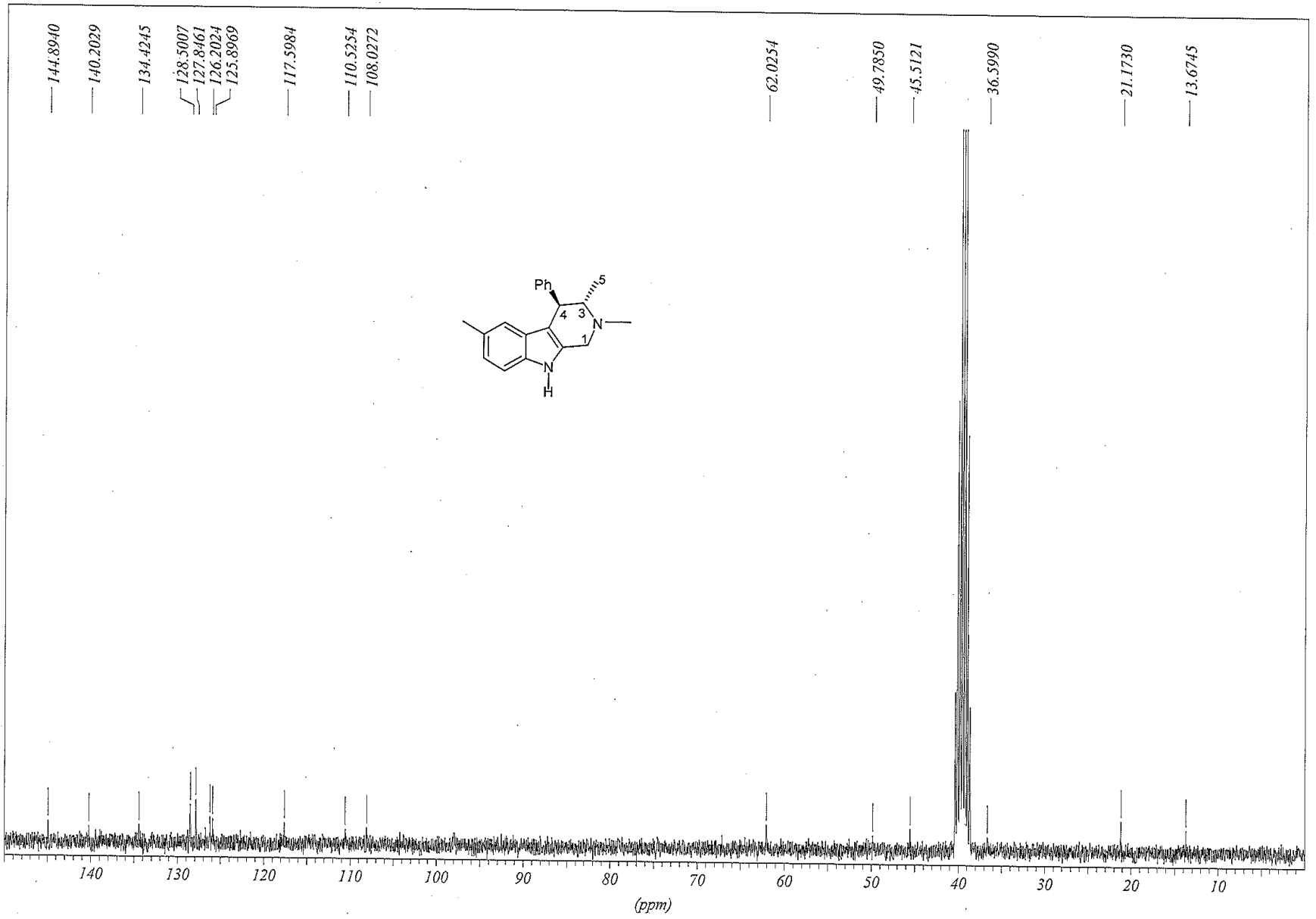

11.0825
7.2908
7.2626
7.2490
7.2293
7.2072
7.1794
6.9346
6.9291
6.9060
6.9005
6.5358
3.9247
3.8722
3.8219
3.7997
3.7362
3.6841
3.3463
3.3233
2.8307
2.8089
2.7876
2.7659
2.7437
2.5044
2.3551
1.9913
1.0193
0.9975
(3R,4S)-6-Chloro-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (31)
Ph
5
4
3
N
1
Cl
N
H
Integral
0.7467
5.9325
1.0284
0.9334
0.9482
0.9888
0.9940
1.0000
3.1113
2.9686
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

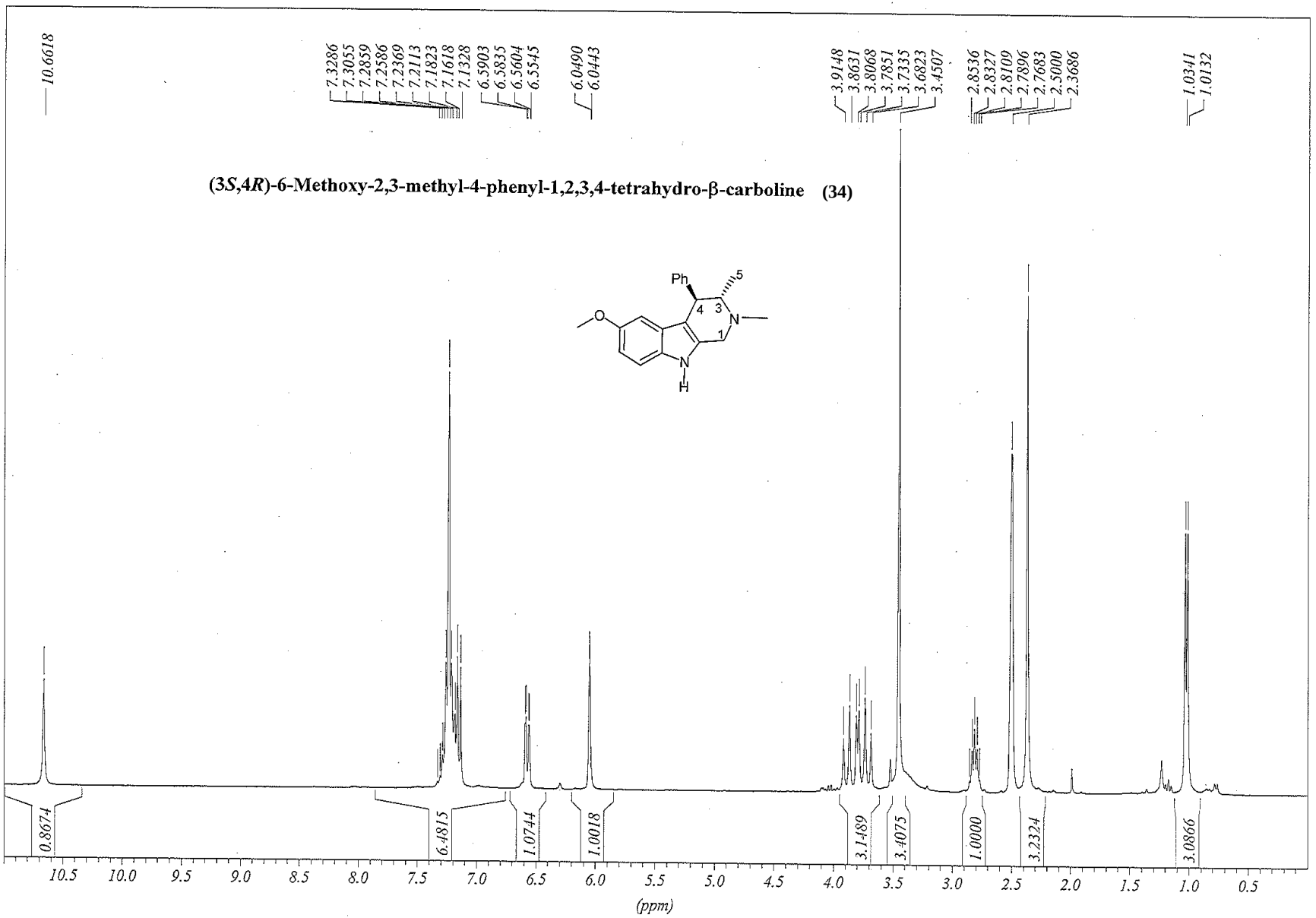

144.2213
134.8827
134.5227
128.5152
128.0425
127.5443
126.1697
122.5732
119.8312
116.9111
112.3255
108.8272
61.8909
50.0468
45.2139
39.8610
14.1764
Ph
5
4
3
N
1
Cl
N
H
39.8610
40
39
(ppm)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

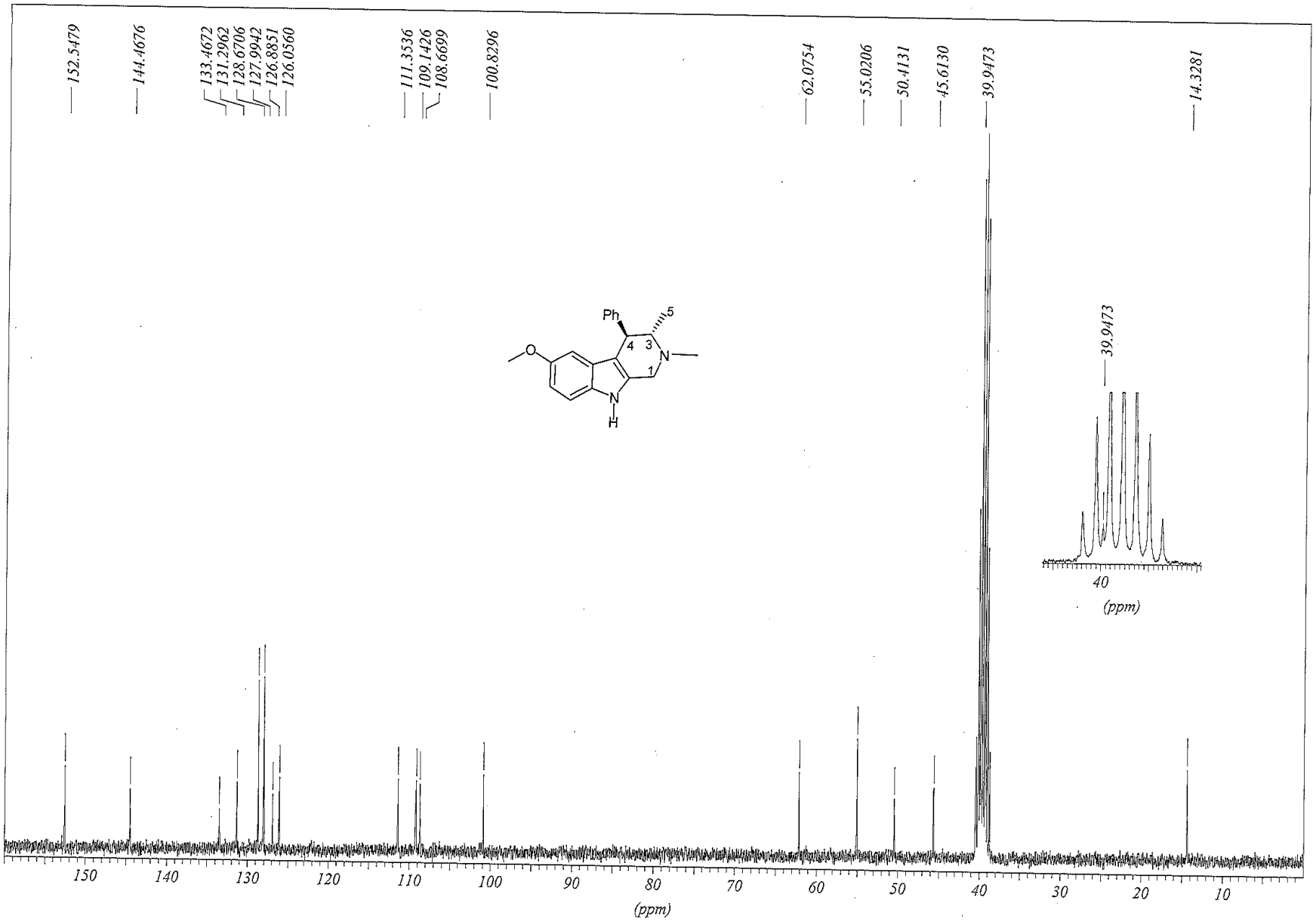

11.1012
7.2946
7.2664
7.2502
7.2306
7.2080
7.2029
7.1799
6.9376
6.9308
6.9095
6.9022
6.5337
6.5281
3.9507
3.8978
3.8313
3.8091
3.7605
3.7085
2.8571
2.8362
2.8145
2.7927
2.7710
2.5036
2.3692
1.9896
1.0248
1.0035
(3S,4R)-6-Chloro-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (ent-31)
Ph
5
4
3
N
1
Cl
N
H
1.0492
6.4256
1.0173
0.8953
1.0237
1.0085
1.0064
0.9802
3.1141
2.9834
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)


144.3257
134.9195
134.7657
128.7440
128.2824
127.7330
126.4290
122.8175
120.0923
117.1547
112.5688
109.0305
62.1386
50.2856
45.3921
40.5278
40.2494
39.9784
39.7000
39.4216
39.1432
38.8649
14.3897
Ph
5
4
3
N
1
Cl
N
H
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


10.6773
7.2703
7.2447
7.2234
7.1978
7.1526
7.1248
6.7559
6.7295
6.4335
3.8876
3.8360
3.8053
3.7857
3.6743
3.6232
3.3391
3.3156
2.8311
2.8098
2.7893
2.7680
2.7458
2.7300
2.5044
2.3432
2.1316
1.0206
0.9988
(3S,4R)-6-Methyl-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (33)
Ph
5
4
3
N
1
N
H
0.8320
5.9177
0.9940
1.0060
1.8818
1.0000
1.0001
3.2125
3.0887
2.8782
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


144.8940
140.2029
134.4245
128.5007
127.8461
126.2024
125.8969
117.5984
110.5254
108.0272
62.0254
49.7850
45.5121
36.5990
21.1730
13.6745
Ph
5
4
3
N
1
N
H
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


10.6618
7.3286
7.3055
7.2859
7.2586
7.2369
7.2113
7.1823
7.1618
7.1328
6.5903
6.5835
6.5604
6.5545
6.0490
6.0443
3.9148
3.8631
3.8068
3.7851
3.7335
3.6823
3.4507
2.8536
2.8327
2.8109
2.7896
2.7683
2.5000
2.3686
1.0341
1.0132
(3S,4R)-6-Methoxy-2,3-methyl-4-phenyl-1,2,3,4-tetrahydro-β-carboline (34)
Ph
5
4
3
N
1
O
N
H
0.8674
6.4815
1.0744
1.0018
3.1489
3.4075
1.0000
3.2324
3.0866
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


152.5479
144.4676
133.4672
131.2962
128.6706
127.9942
126.8851
126.0560
111.3536
109.1426
108.6699
100.8296
62.0754
55.0206
50.4131
45.6130
39.9473
14.3281
Ph
5
4
3
N
1
O
N
H
39.9473
40
(ppm)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

structure report

Alkylation of Indoles by Aziridinium ions: Straightforward Access to Tetrahydro-
β-Carbolines (THBCs)

Laurence Menguy, Cheikh Lo, Jerome Marrot and Francois Couty*
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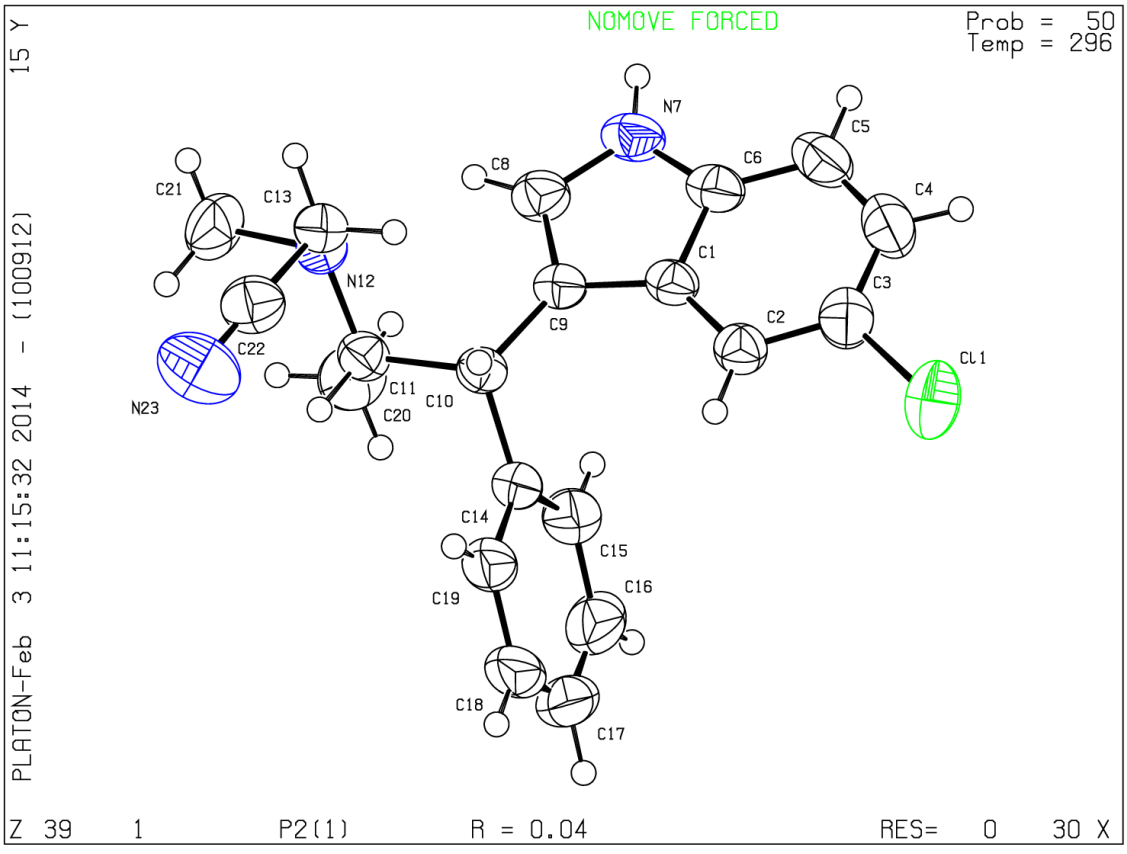
Cedex, France
Correspondence email: couty@chimie.uvsq.fr

Computing details
For all compounds, data collection: Bruker *APEX2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*;
program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97*
(Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker
SHELXTL.

Compound 23



Crystal data
$C_{20}H_{20}ClN_3$ $F(000) = 356$
$M_r = 337.84$ $D_x = 1.242$ Mg m^{-3}

Monoclinic, $P2_1$ Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 9.1886 (13) Å Cell parameters from 9883 reflections
b = 9.6741 (13) Å θ = 2.7–27.3°
c = 10.4245 (15) Å μ = 0.22 mm^{-1}
β = 102.791 (7)° T = 296 K
V = 903.7 (2) $Å^3$ Parallelepiped, brown
Z = 2 0.30 × 0.24 × 0.18 mm

Data collection

Bruker APEX-II CCD
diffractometer 5222 independent reflections
Radiation source: fine-focus sealed tube 4372 reflections with $I > 2\sigma(I)$
Graphite monochromator R_{int} = 0.044
Detector resolution: 512x512 pixels mm^{-1} θ_{max} = 30.0°, θ_{min} = 2.0°
φ and ω scans h = −12→12
Absorption correction: multi-scan
SADABS (Sheldrick, V2.10) k = −13→13
T_{min} = 0.938, T_{max} = 0.962 l = −14→14
67580 measured reflections

Refinement

Refinement on F_2 Secondary atom site location: difference Fourier map
Least-squares matrix: full Hydrogen site location: inferred from neighbouring sites
$R[F_2 > 2\sigma(F_2)]$ = 0.040 H atoms treated by a mixture of independent and constrained refinement
$wR(F_2)$ = 0.102 $w = 1/[\sigma^2(F_o^2) + (0.0498P)^2 + 0.114P]$
where $P = (F_o^2 + 2F_c^2)/3$
S = 1.02 $(\Delta/\sigma)_{max} < 0.001$
5222 reflections $\Delta\rho_{max}$ = 0.23 e $Å^{-3}$
223 parameters $\Delta\rho_{min}$ = −0.20 e $Å^{-3}$
1 restraint Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
Primary atom site location: structure-invariant direct methods Absolute structure parameter: −0.06 (5)

Special details

Refinement

Refinement of F_2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F_2, conventional R-factors R are based on F, with F set to zero for negative F_2. The threshold expression of $F_2 > \sigma(F_2)$ is used only for calculating R-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. R-factors based on F_2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

x y z U_{iso}*/U_{eq}

Cl1 0.70296 (5) 0.47448 (6) 0.41178 (5) 0.07569 (16)
C1 0.25920 (16) 0.43888 (14) 0.29366 (13) 0.0408 (3)
C2 0.41296 (17) 0.40709 (16) 0.32412 (14) 0.0449 (3)
H2 0.4467 0.3186 0.3113 0.054*
C3 0.51130 (19) 0.51158 (19) 0.37344 (16) 0.0543 (4)
C4 0.4662 (2) 0.64601 (19) 0.39247 (19) 0.0631 (5)
H4 0.5369 0.7136 0.4247 0.076*
C5 0.3158 (2) 0.67876 (18) 0.36324 (17) 0.0601 (4)
H5 0.2838 0.7679 0.3758 0.072*
C6 0.21447 (19) 0.57537 (16) 0.31487 (14) 0.0469 (3)
N7 0.06173 (17) 0.57809 (14) 0.28097 (14) 0.0535 (3)
H7 0.004 (2) 0.650 (2) 0.285 (2) 0.064 (6)*
C8 0.00976 (18) 0.44977 (16) 0.23873 (15) 0.0486 (3)
H8 −0.0905 0.4266 0.2108 0.058*
C9 0.12605 (16) 0.36033 (14) 0.24335 (13) 0.0398 (3)
C10 0.12246 (15) 0.20725 (14) 0.21517 (13) 0.0385 (3)
H10 0.1629 0.1619 0.2996 0.046*

C11 −0.03646 (16) 0.14487 (15) 0.16326 (14) 0.0433 (3)
H11 −0.0249 0.0443 0.1593 0.052*
N12 −0.13378 (13) 0.17296 (13) 0.25548 (13) 0.0459 (3)
C13 −0.07790 (19) 0.11720 (16) 0.38539 (16) 0.0488 (3)
H13A −0.1452 0.1425 0.4412 0.059*
H13B 0.0187 0.1579 0.4226 0.059*
C14 0.22234 (16) 0.16307 (15) 0.12326 (15) 0.0455 (3)
C15 0.2434 (2) 0.2427 (2) 0.01852 (17) 0.0593 (4)
H15 0.2006 0.3301 0.0056 0.071*
C16 0.3271 (2) 0.1943 (3) −0.0671 (2) 0.0777 (6)
H16 0.3389 0.2489 −0.1375 0.093*
C17 0.3929 (2) 0.0663 (3) −0.0490 (2) 0.0825 (8)
H17 0.4488 0.0337 −0.1069 0.099*
C18 0.3752 (2) −0.0124 (2) 0.0549 (3) 0.0782 (7)
H18 0.4204 −0.0988 0.0682 0.094*
C19 0.29020 (19) 0.03459 (19) 0.1414 (2) 0.0583 (4)
H19 0.2790 −0.0206 0.2117 0.070*
C20 −0.1088 (2) 0.1938 (3) 0.02471 (17) 0.0671 (5)
H20A −0.2013 0.1456 −0.0060 0.101*
H20B −0.0431 0.1752 −0.0331 0.101*
H20C −0.1276 0.2913 0.0260 0.101*
C21 −0.28857 (19) 0.1282 (2) 0.2072 (2) 0.0685 (5)
H21A −0.2901 0.0332 0.1804 0.103*
H21B −0.3350 0.1843 0.1334 0.103*
H21C −0.3421 0.1378 0.2760 0.103*
C22 −0.0628 (2) −0.0348 (2) 0.38463 (17) 0.0582 (4)
N23 −0.0553 (3) −0.1509 (2) 0.3719 (2) 0.0881 (6)

Atomic displacement parameters (Å²)

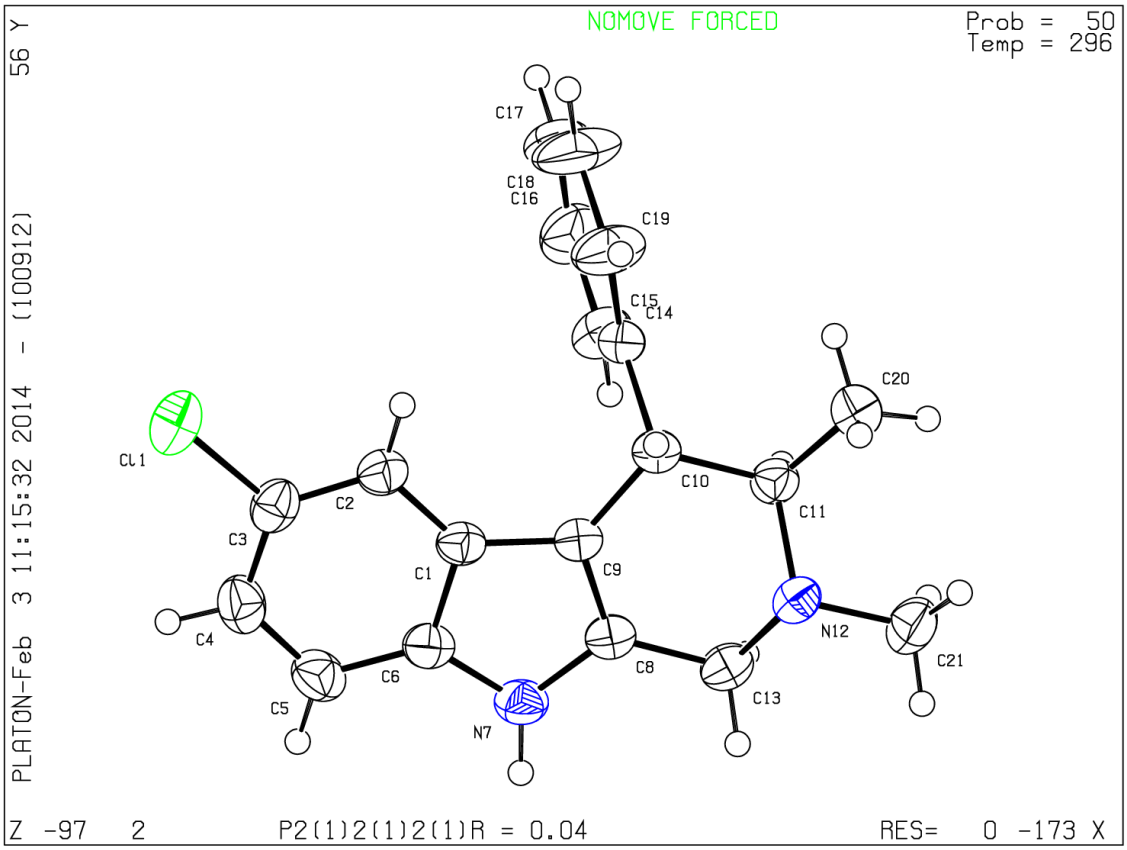
U_{11} U_{22} U_{33} U_{12} U_{13} U_{23}
Cl1 0.0519 (2) 0.0856 (4) 0.0843 (3) −0.0160 (2) 0.0036 (2) 0.0057 (3)
C1 0.0503 (7) 0.0386 (7) 0.0354 (6) 0.0012 (6) 0.0137 (5) −0.0029 (5)
C2 0.0495 (7) 0.0432 (7) 0.0430 (7) −0.0004 (6) 0.0126 (6) −0.0007 (5)
C3 0.0560 (9) 0.0594 (10) 0.0472 (8) −0.0095 (7) 0.0108 (7) −0.0003 (7)
C4 0.0785 (12) 0.0542 (10) 0.0584 (9) −0.0214 (9) 0.0187 (8) −0.0098 (8)
C5 0.0871 (13) 0.0385 (8) 0.0598 (9) −0.0060 (8) 0.0272 (9) −0.0081 (7)
C6 0.0626 (9) 0.0391 (7) 0.0429 (7) 0.0038 (6) 0.0201 (6) −0.0006 (6)
N7 0.0650 (9) 0.0387 (6) 0.0606 (8) 0.0135 (6) 0.0222 (7) −0.0002 (6)
C8 0.0504 (8) 0.0424 (7) 0.0542 (8) 0.0091 (6) 0.0142 (6) 0.0032 (6)
C9 0.0435 (7) 0.0376 (7) 0.0397 (7) 0.0050 (5) 0.0124 (5) −0.0008 (5)
C10 0.0389 (6) 0.0362 (6) 0.0403 (6) 0.0045 (5) 0.0082 (5) −0.0008 (5)
C11 0.0408 (7) 0.0426 (8) 0.0448 (7) 0.0021 (6) 0.0054 (5) −0.0057 (6)
N12 0.0384 (6) 0.0430 (6) 0.0572 (7) 0.0026 (5) 0.0120 (5) −0.0043 (5)
C13 0.0516 (8) 0.0468 (8) 0.0515 (8) −0.0019 (6) 0.0191 (7) −0.0075 (6)
C14 0.0415 (7) 0.0430 (7) 0.0532 (8) −0.0008 (6) 0.0133 (6) −0.0108 (6)
C15 0.0645 (10) 0.0594 (10) 0.0581 (9) −0.0056 (8) 0.0227 (8) −0.0076 (8)
C16 0.0690 (12) 0.1064 (18) 0.0654 (11) −0.0259 (12) 0.0310 (9) −0.0265 (11)
C17 0.0504 (10) 0.116 (2) 0.0871 (15) −0.0145 (12) 0.0273 (10) −0.0545 (15)
C18 0.0435 (8) 0.0705 (13) 0.1178 (17) 0.0044 (9) 0.0119 (9) −0.0473 (13)
C19 0.0444 (8) 0.0485 (9) 0.0809 (11) 0.0032 (7) 0.0118 (7) −0.0143 (8)
C20 0.0556 (10) 0.0923 (15) 0.0474 (8) 0.0044 (10) −0.0018 (7) −0.0043 (9)
C21 0.0370 (8) 0.0747 (12) 0.0915 (14) 0.0028 (8) 0.0094 (8) 0.0008 (10)
C22 0.0591 (9) 0.0559 (10) 0.0598 (9) 0.0095 (8) 0.0136 (7) 0.0047 (8)
N23 0.1113 (16) 0.0562 (10) 0.0917 (13) 0.0244 (10) 0.0117 (11) 0.0091 (9)

Geometric parameters (Å, º) for (1)

Cl1—C3 1.7545 (19) N12—C13 1.443 (2)
C1—C2 1.412 (2) N12—C21 1.465 (2)
C1—C6 1.415 (2) C13—C22 1.477 (3)
C1—C9 1.437 (2) C13—H13A 0.9700
C2—C3 1.377 (2) C13—H13B 0.9700
C2—H2 0.9300 C14—C15 1.384 (2)
C3—C4 1.392 (3) C14—C19 1.385 (2)
C4—C5 1.384 (3) C15—C16 1.382 (3)
C4—H4 0.9300 C15—H15 0.9300
C5—C6 1.384 (2) C16—C17 1.373 (4)
C5—H5 0.9300 C16—H16 0.9300

C6—N7 1.370 (2) C17—C18 1.362 (4)
N7—C8 1.367 (2) C17—H17 0.9300
N7—H7 0.88 (2) C18—C19 1.393 (3)
C8—C9 1.368 (2) C18—H18 0.9300
C8—H8 0.9300 C19—H19 0.9300
C9—C10 1.5086 (19) C20—H20A 0.9600
C10—C14 1.5272 (19) C20—H20B 0.9600
C10—C11 1.5620 (19) C20—H20C 0.9600
C10—H10 0.9800 C21—H21A 0.9600
C11—N12 1.4759 (19) C21—H21B 0.9600
C11—C20 1.525 (2) C21—H21C 0.9600
C11—H11 0.9800 C22—N23 1.135 (3)
C2—C1—C6 118.62 (14) C13—N12—C11 113.68 (11)
C2—C1—C9 134.08 (13) C21—N12—C11 113.81 (14)
C6—C1—C9 107.30 (13) N12—C13—C22 112.43 (14)
C3—C2—C1 117.73 (14) N12—C13—H13A 109.1
C3—C2—H2 121.1 C22—C13—H13A 109.1
C1—C2—H2 121.1 N12—C13—H13B 109.1
C2—C3—C4 123.19 (17) C22—C13—H13B 109.1
C2—C3—Cl1 118.52 (14) H13A—C13—H13B 107.8
C4—C3—Cl1 118.28 (14) C15—C14—C19 118.04 (15)
C5—C4—C3 119.76 (16) C15—C14—C10 123.19 (14)
C5—C4—H4 120.1 C19—C14—C10 118.71 (15)
C3—C4—H4 120.1 C16—C15—C14 121.0 (2)
C6—C5—C4 118.25 (16) C16—C15—H15 119.5
C6—C5—H5 120.9 C14—C15—H15 119.5
C4—C5—H5 120.9 C17—C16—C15 120.5 (2)
N7—C6—C5 130.45 (15) C17—C16—H16 119.7
N7—C6—C1 107.11 (13) C15—C16—H16 119.7
C5—C6—C1 122.44 (16) C18—C17—C16 119.14 (18)
C8—N7—C6 109.30 (13) C18—C17—H17 120.4
C8—N7—H7 124.1 (14) C16—C17—H17 120.4
C6—N7—H7 126.6 (14) C17—C18—C19 121.0 (2)
N7—C8—C9 110.40 (14) C17—C18—H18 119.5
N7—C8—H8 124.8 C19—C18—H18 119.5
C9—C8—H8 124.8 C14—C19—C18 120.3 (2)
C8—C9—C1 105.88 (13) C14—C19—H19 119.9
C8—C9—C10 129.12 (14) C18—C19—H19 119.9
C1—C9—C10 124.77 (12) C11—C20—H20A 109.5
C9—C10—C14 113.99 (12) C11—C20—H20B 109.5
C9—C10—C11 115.16 (11) H20A—C20—H20B 109.5
C14—C10—C11 108.67 (11) C11—C20—H20C 109.5
C9—C10—H10 106.1 H20A—C20—H20C 109.5
C14—C10—H10 106.1 H20B—C20—H20C 109.5
C11—C10—H10 106.1 N12—C21—H21A 109.5
N12—C11—C20 111.08 (13) N12—C21—H21B 109.5
N12—C11—C10 110.98 (11) H21A—C21—H21B 109.5
C20—C11—C10 112.72 (13) N12—C21—H21C 109.5
N12—C11—H11 107.3 H21A—C21—H21C 109.5
C20—C11—H11 107.3 H21B—C21—H21C 109.5
C10—C11—H11 107.3 N23—C22—C13 173.7 (2)
C13—N12—C21 109.20 (14)

Compound 31:



Crystal data

$C_{19}H_{19}ClN_2$ D_x = 1.251 Mg m^{-3}
M_r = 310.81 Mo $K\alpha$ radiation, λ = 0.71073 Å
Orthorhombic, $P2_12_12_1$ Cell parameters from 9836 reflections
a = 6.4404 (15) Å θ = 2.6–29.4°
b = 15.894 (4) Å μ = 0.23 mm^{-1}
c = 16.125 (3) Å T = 296 K
V = 1650.6 (6) Å$_3$ Parallelepiped, yellow
Z = 4 0.30 × 0.10 × 0.06 mm
F(000) = 656

Data collection

Bruker APEX-II CCD
diffractometer 4806 independent reflections
Radiation source: fine-focus sealed tube 4115 reflections with $I > 2\sigma(I)$
Graphite monochromator R_{int} = 0.048
Detector resolution: 512x512 pixels mm^{-1} θ_{max} = 30.1°, θ_{min} = 1.8°
φ and ω scans h = −9→9
Absorption correction: multi-scan
SADABS (Sheldrick, V2.10) k = −22→22
T_{min} = 0.934, T_{max} = 0.986 l = −22→22
80184 measured reflections

Refinement

Refinement on F_2 Secondary atom site location: difference Fourier map
Least-squares matrix: full Hydrogen site location: inferred from neighbouring sites
$R[F_2 > 2\sigma(F_2)]$ = 0.039 H atoms treated by a mixture of independent and constrained refinement
$wR(F_2)$ = 0.097 $w = 1/[\sigma_2(F_o{}_2) + (0.0476P)_2 + 0.2381P]$
where $P = (F_o{}_2 + 2F_c{}_2)/3$

S = 1.04 $(\Delta/\sigma)_{max}$ < 0.001
4806 reflections $\Delta\rho_{max}$ = 0.21 e Å^{-3}
205 parameters $\Delta\rho_{min}$ = −0.16 e Å^{-3}
0 restraints Absolute structure: Flack H D (1983), Acta Cryst.
A39, 876-881
Primary atom site location: structure-invariant direct
methods Absolute structure parameter: −0.01 (5)

Special details

Refinement

Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are
based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R-factors(gt) *etc*. and is
not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and
R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

x y z U_{iso}*/U_{eq}

Cl1 0.33525 (7) −0.10143 (2) 0.64759 (3) 0.05196 (12)
C1 0.0099 (2) 0.11002 (9) 0.61899 (8) 0.0336 (3)
C2 0.1640 (2) 0.05333 (9) 0.64425 (9) 0.0369 (3)
H2 0.2794 0.0712 0.6741 0.044*
C3 0.1376 (3) −0.03003 (9) 0.62308 (9) 0.0397 (3)
C4 −0.0376 (3) −0.05982 (10) 0.58102 (10) 0.0458 (4)
H4 −0.0520 −0.1170 0.5705 0.055*
C5 −0.1889 (3) −0.00428 (10) 0.55524 (10) 0.0450 (4)
H5 −0.3055 −0.0232 0.5268 0.054*
C6 −0.1629 (2) 0.08107 (9) 0.57291 (8) 0.0375 (3)
N7 −0.2841 (2) 0.14945 (9) 0.55240 (8) 0.0411 (3)
H7 −0.388 (3) 0.1468 (12) 0.5159 (11) 0.047 (5)*
C8 −0.1894 (2) 0.22030 (9) 0.58450 (8) 0.0346 (3)
C9 −0.0132 (2) 0.19978 (8) 0.62618 (8) 0.0325 (3)
C10 0.1208 (2) 0.26299 (9) 0.66936 (8) 0.0328 (3)
H10 0.2531 0.2669 0.6396 0.039*
C11 0.0156 (2) 0.35111 (9) 0.66805 (8) 0.0355 (3)
H11 −0.0892 0.3525 0.7121 0.043*
N12 −0.09072 (19) 0.36684 (7) 0.58754 (7) 0.0351 (3)
C13 −0.2654 (2) 0.30810 (10) 0.57521 (10) 0.0396 (3)
H13A −0.3239 0.3158 0.5203 0.047*
H13B −0.3732 0.3192 0.6158 0.047*
C14 0.1652 (3) 0.23556 (9) 0.75828 (9) 0.0380 (3)
C15 0.0028 (3) 0.21470 (11) 0.81091 (10) 0.0493 (4)
H15 −0.1330 0.2174 0.7915 0.059*
C16 0.0399 (4) 0.18980 (12) 0.89224 (11) 0.0600 (5)
H16 −0.0709 0.1763 0.9267 0.072*
C17 0.2372 (4) 0.18519 (14) 0.92144 (13) 0.0743 (7)
H17 0.2619 0.1685 0.9758 0.089*
C18 0.3985 (4) 0.20515 (18) 0.87068 (15) 0.0892 (9)
H18 0.5337 0.2020 0.8907 0.107*
C19 0.3636 (3) 0.23031 (14) 0.78875 (13) 0.0654 (6)
H19 0.4756 0.2435 0.7547 0.078*
C20 0.1766 (3) 0.41848 (10) 0.68662 (11) 0.0528 (4)
H20A 0.2683 0.4243 0.6400 0.079*
H20B 0.2552 0.4026 0.7347 0.079*
H20C 0.1080 0.4711 0.6969 0.079*
C21 −0.1770 (3) 0.45301 (10) 0.58495 (11) 0.0486 (4)
H21A −0.2602 0.4595 0.5360 0.073*
H21B −0.0654 0.4931 0.5840 0.073*
H21C −0.2613 0.4624 0.6332 0.073*

Atomic displacement parameters (Å^2)

U_{11} U_{22} U_{33} U_{12} U_{13} U_{23}

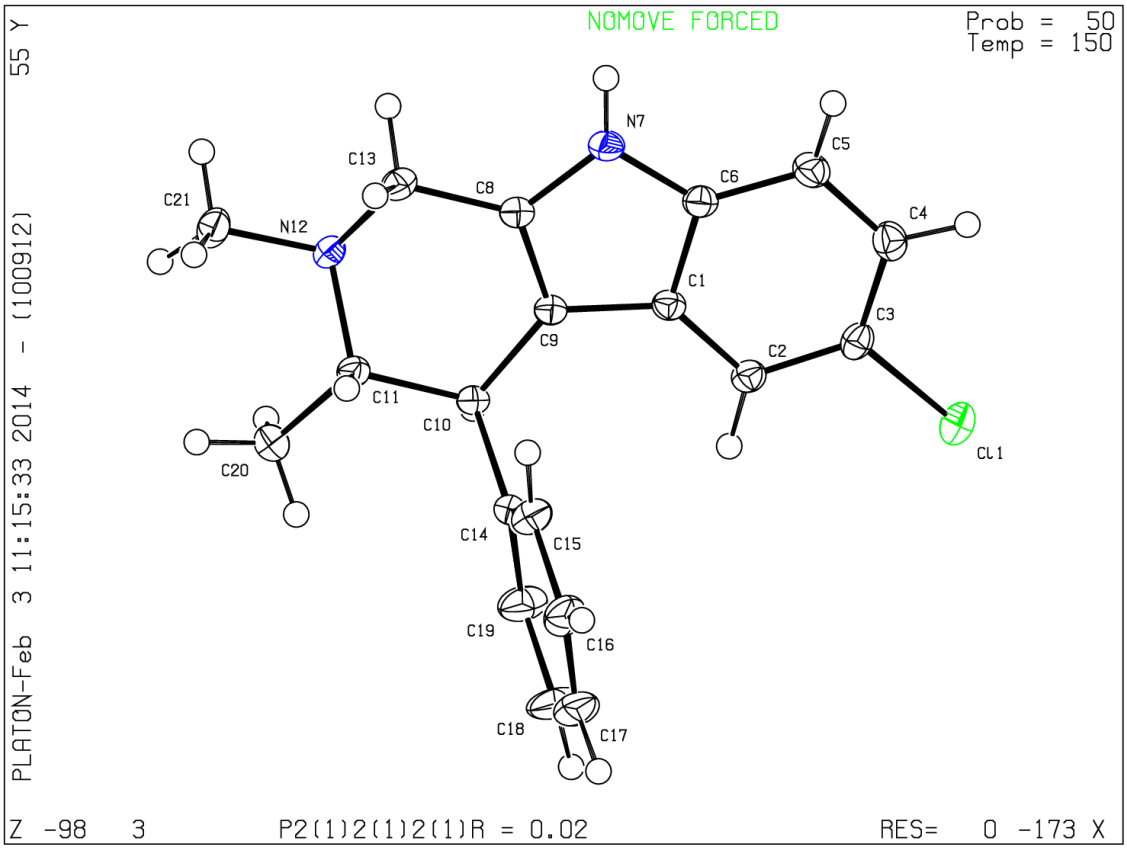
Cl1 0.0527 (2) 0.04360 (19) 0.0595 (2) 0.01043 (18) 0.0071 (2) 0.00947 (17)
C1 0.0341 (7) 0.0384 (7) 0.0283 (6) −0.0021 (6) −0.0009 (5) 0.0015 (5)
C2 0.0375 (7) 0.0404 (7) 0.0327 (6) −0.0004 (6) −0.0012 (6) 0.0031 (5)
C3 0.0449 (8) 0.0384 (7) 0.0359 (7) 0.0041 (6) 0.0070 (6) 0.0064 (5)

C4 0.0550 (10) 0.0354 (7) 0.0471 (8) −0.0061 (7) 0.0049 (8) 0.0002 (6)
C5 0.0437 (9) 0.0449 (8) 0.0464 (8) −0.0115 (7) −0.0038 (7) −0.0016 (6)
C6 0.0365 (7) 0.0421 (7) 0.0338 (6) −0.0052 (6) −0.0027 (6) 0.0026 (5)
N7 0.0348 (7) 0.0454 (7) 0.0431 (6) −0.0039 (6) −0.0094 (6) 0.0013 (5)
C8 0.0313 (7) 0.0404 (7) 0.0323 (6) 0.0002 (6) −0.0011 (6) 0.0017 (5)
C9 0.0317 (7) 0.0369 (7) 0.0291 (6) 0.0001 (6) −0.0016 (5) 0.0010 (5)
C10 0.0301 (7) 0.0377 (7) 0.0308 (6) −0.0004 (5) −0.0014 (5) 0.0005 (5)
C11 0.0392 (8) 0.0375 (7) 0.0297 (6) 0.0029 (6) −0.0003 (6) 0.0002 (5)
N12 0.0363 (6) 0.0368 (6) 0.0323 (5) 0.0043 (5) 0.0003 (5) 0.0044 (5)
C13 0.0320 (7) 0.0447 (8) 0.0420 (7) 0.0050 (6) −0.0042 (6) 0.0033 (6)
C14 0.0444 (8) 0.0340 (6) 0.0357 (6) −0.0024 (7) −0.0111 (7) 0.0009 (5)
C15 0.0511 (10) 0.0577 (10) 0.0390 (8) 0.0105 (8) −0.0013 (7) 0.0062 (7)
C16 0.0786 (14) 0.0587 (11) 0.0425 (9) 0.0042 (10) 0.0031 (9) 0.0121 (8)
C17 0.1023 (18) 0.0699 (13) 0.0506 (10) −0.0160 (12) −0.0321 (12) 0.0222 (9)
C18 0.0700 (15) 0.119 (2) 0.0788 (15) −0.0337 (14) −0.0470 (13) 0.0447 (14)
C19 0.0496 (11) 0.0827 (13) 0.0639 (11) −0.0204 (10) −0.0224 (9) 0.0271 (10)
C20 0.0614 (11) 0.0402 (8) 0.0568 (9) −0.0031 (8) −0.0147 (9) −0.0013 (7)
C21 0.0534 (9) 0.0421 (8) 0.0504 (8) 0.0112 (8) −0.0011 (8) 0.0059 (7)

Geometric parameters (Å, º) for (2)
Cl1—C3 1.7508 (16) C11—H11 0.9800
C1—C2 1.401 (2) N12—C13 1.475 (2)
C1—C6 1.415 (2) N12—C21 1.4785 (19)
C1—C9 1.4391 (19) C13—H13A 0.9700
C2—C3 1.379 (2) C13—H13B 0.9700
C2—H2 0.9300 C14—C19 1.372 (3)
C3—C4 1.399 (2) C14—C15 1.387 (2)
C4—C5 1.379 (2) C15—C16 1.390 (2)
C4—H4 0.9300 C15—H15 0.9300
C5—C6 1.396 (2) C16—C17 1.357 (3)
C5—H5 0.9300 C16—H16 0.9300
C6—N7 1.378 (2) C17—C18 1.360 (4)
N7—C8 1.3813 (19) C17—H17 0.9300
N7—H7 0.89 (2) C18—C19 1.399 (3)
C8—C9 1.359 (2) C18—H18 0.9300
C8—C13 1.486 (2) C19—H19 0.9300
C9—C10 1.4962 (19) C20—H20A 0.9600
C10—C14 1.5258 (19) C20—H20B 0.9600
C10—C11 1.556 (2) C20—H20C 0.9600
C10—H10 0.9800 C21—H21A 0.9600
C11—N12 1.4889 (18) C21—H21B 0.9600
C11—C20 1.520 (2) C21—H21C 0.9600
C2—C1—C6 120.04 (13) C13—N12—C21 107.22 (13)
C2—C1—C9 133.44 (14) C13—N12—C11 111.22 (11)
C6—C1—C9 106.45 (13) C21—N12—C11 110.68 (12)
C3—C2—C1 117.30 (14) N12—C13—C8 109.24 (12)
C3—C2—H2 121.3 N12—C13—H13A 109.8
C1—C2—H2 121.3 C8—C13—H13A 109.8
C2—C3—C4 123.01 (15) N12—C13—H13B 109.8
C2—C3—Cl1 118.50 (13) C8—C13—H13B 109.8
C4—C3—Cl1 118.46 (12) H13A—C13—H13B 108.3
C5—C4—C3 119.97 (15) C19—C14—C15 117.96 (15)
C5—C4—H4 120.0 C19—C14—C10 121.91 (16)
C3—C4—H4 120.0 C15—C14—C10 120.12 (15)
C4—C5—C6 118.39 (15) C14—C15—C16 121.03 (19)
C4—C5—H5 120.8 C14—C15—H15 119.5
C6—C5—H5 120.8 C16—C15—H15 119.5
N7—C6—C5 130.48 (15) C17—C16—C15 120.2 (2)
N7—C6—C1 108.36 (13) C17—C16—H16 119.9
C5—C6—C1 121.16 (15) C15—C16—H16 119.9
C6—N7—C8 107.64 (12) C16—C17—C18 119.60 (18)
C6—N7—H7 123.0 (12) C16—C17—H17 120.2
C8—N7—H7 128.1 (12) C18—C17—H17 120.2
C9—C8—N7 111.01 (13) C17—C18—C19 120.8 (2)
C9—C8—C13 123.38 (13) C17—C18—H18 119.6
N7—C8—C13 125.61 (13) C19—C18—H18 119.6
C8—C9—C1 106.53 (12) C14—C19—C18 120.4 (2)

C8—C9—C10 123.42 (13) C14—C19—H19 119.8
C1—C9—C10 130.04 (13) C18—C19—H19 119.8
C9—C10—C14 110.71 (11) C11—C20—H20A 109.5
C9—C10—C11 110.30 (12) C11—C20—H20B 109.5
C14—C10—C11 110.58 (11) H20A—C20—H20B 109.5
C9—C10—H10 108.4 C11—C20—H20C 109.5
C14—C10—H10 108.4 H20A—C20—H20C 109.5
C11—C10—H10 108.4 H20B—C20—H20C 109.5
N12—C11—C20 111.54 (12) N12—C21—H21A 109.5
N12—C11—C10 111.31 (11) N12—C21—H21B 109.5
C20—C11—C10 109.53 (13) H21A—C21—H21B 109.5
N12—C11—H11 108.1 N12—C21—H21C 109.5
C20—C11—H11 108.1 H21A—C21—H21C 109.5
C10—C11—H11 108.1 H21B—C21—H21C 109.5

Compound *ent*-31



Crystal data
$C_{19}H_{19}ClN_2$ D_x = 1.282 Mg m^{-3}
M_r = 310.81 Mo $K\alpha$ radiation, λ = 0.71073 Å
Orthorhombic, $P2_12_12_1$ Cell parameters from 9909 reflections
a = 6.4085 (5) Å θ = 2.6–29.8°
b = 15.7621 (13) Å μ = 0.24 mm^{-1}
c = 15.9379 (12) Å T = 150 K
V = 1609.9 (2) Å$_3$ Parallelepiped, colorless
Z = 4 0.30 × 0.16 × 0.06 mm
F(000) = 656
Data collection
Bruker APEX-II CCD
diffractometer 4706 independent reflections

Radiation source: fine-focus sealed tube 4605 reflections with $I > 2\sigma(I)$
Graphite monochromator $R_{int} = 0.033$
Detector resolution: 512x512 pixels mm^{-1} $\theta_{max} = 30.1°$, $\theta_{min} = 1.8°$
φ and ω scans $h = -9 \rightarrow 9$
Absorption correction: multi-scan
SADABS (Sheldrick, V2.10) $k = -22 \rightarrow 22$
$T_{min} = 0.933$, $T_{max} = 0.986$ $l = -21 \rightarrow 22$
85390 measured reflections

Refinement
Refinement on F_2 Secondary atom site location: difference Fourier map
Least-squares matrix: full Hydrogen site location: inferred from neighbouring sites
$R[F_2 > 2\sigma(F_2)] = 0.025$ All H-atom parameters refined
$wR(F_2) = 0.067$ $w = 1/[\sigma^2(F_o^2) + (0.0433P)^2 + 0.1827P]$
where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.05$ $(\Delta/\sigma)_{max} = 0.007$
4706 reflections $\Delta\rho_{max} = 0.27$ e Å^{-3}
275 parameters $\Delta\rho_{min} = -0.16$ e Å^{-3}
0 restraints Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
Primary atom site location: structure-invariant direct methods Absolute structure parameter: −0.08 (3)

Special details
Refinement
Refinement of F_2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F_2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F_2. The threshold expression of $F_2 > \sigma(F_2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F_2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Cl1	0.66231 (2)	1.101832 (7)	0.352218 (8)	0.02279 (3)
C1	0.99459 (8)	0.89011 (3)	0.38018 (3)	0.01587 (10)
C2	0.83771 (8)	0.94669 (3)	0.35506 (3)	0.01759 (10)
H2	0.7210 (11)	0.9281 (4)	0.3237 (4)	0.0189 (16)*
C3	0.86384 (8)	1.03104 (3)	0.37611 (3)	0.01823 (10)
C4	1.04086 (9)	1.06178 (3)	0.41811 (3)	0.02124 (11)
H4	1.0544 (13)	1.1218 (5)	0.4267 (5)	0.0297 (19)*
C5	1.19501 (9)	1.00603 (3)	0.44399 (3)	0.02104 (11)
H5	1.3124 (11)	1.0264 (4)	0.4720 (4)	0.0186 (16)*
C6	1.16903 (8)	0.91979 (3)	0.42628 (3)	0.01774 (10)
N7	1.29326 (7)	0.85125 (3)	0.44682 (3)	0.01913 (9)
H7	1.3888 (12)	0.8538 (5)	0.4827 (5)	0.0244 (18)*
C8	1.19814 (8)	0.77939 (3)	0.41492 (3)	0.01664 (10)
C9	1.01936 (8)	0.79981 (3)	0.37325 (3)	0.01547 (10)
C10	0.88420 (8)	0.73585 (3)	0.33048 (3)	0.01521 (9)
H10	0.7453 (12)	0.7310 (4)	0.3614 (5)	0.0222 (17)*
C11	0.99003 (8)	0.64709 (3)	0.33189 (3)	0.01642 (10)
H11	1.0954 (11)	0.6455 (4)	0.2875 (4)	0.0177 (16)*
N12	1.09899 (7)	0.63162 (3)	0.41310 (3)	0.01612 (9)
C13	1.27540 (8)	0.69087 (3)	0.42410 (3)	0.01865 (11)
H13A	1.3327 (13)	0.6840 (4)	0.4806 (5)	0.0247 (17)*
H13B	1.3917 (12)	0.6765 (4)	0.3820 (4)	0.0196 (17)*
C14	0.83981 (9)	0.76309 (3)	0.24032 (3)	0.01710 (10)
C15	1.00435 (9)	0.78569 (4)	0.18748 (3)	0.02224 (12)
H15	1.1370 (15)	0.7866 (5)	0.2098 (5)	0.036 (2)*
C16	0.96740 (11)	0.81015 (4)	0.10497 (3)	0.02665 (13)
H16	1.0768 (15)	0.8271 (5)	0.0699 (6)	0.039 (2)*
C17	0.76596 (12)	0.81298 (4)	0.07447 (4)	0.03203 (14)

H17 0.7466 (15) 0.8296 (5) 0.0215 (6) 0.046 (2)*
C18 0.60199 (11) 0.79131 (5) 0.12594 (4) 0.03854 (16)
H18 0.4631 (17) 0.7991 (6) 0.1053 (6) 0.047 (3)*
C19 0.63866 (10) 0.76664 (4) 0.20897 (4) 0.02908 (13)
H19 0.5181 (16) 0.7530 (6) 0.2440 (6) 0.040 (2)*
C20 0.82637 (10) 0.57891 (3) 0.31466 (4) 0.02443 (12)
H20A 0.7389 (13) 0.5715 (5) 0.3612 (6) 0.0303 (19)*
H20B 0.8868 (13) 0.5231 (5) 0.3015 (5) 0.031 (2)*
H20C 0.7528 (16) 0.5957 (6) 0.2682 (6) 0.043 (2)*
C21 1.18555 (9) 0.54505 (3) 0.41571 (3) 0.02229 (11)
H21A 1.0792 (13) 0.5005 (5) 0.4160 (5) 0.030 (2)*
H21B 1.2688 (12) 0.5385 (5) 0.4633 (5) 0.0233 (18)*
H21C 1.2734 (13) 0.5331 (5) 0.3672 (5) 0.0302 (19)*

Atomic displacement parameters (Å$_2$)
U_{11} U_{22} U_{33} U_{12} U_{13} U_{23}
Cl1 0.02302 (5) 0.01973 (5) 0.02562 (5) 0.00441 (5) 0.00280 (5) 0.00376 (4)
C1 0.01660 (19) 0.01741 (18) 0.01359 (18) −0.00137 (17) −0.00050 (16) 0.00009 (16)
C2 0.01865 (19) 0.01863 (18) 0.01548 (18) 0.00070 (17) −0.00057 (19) 0.00104 (16)
C3 0.0204 (2) 0.01732 (18) 0.01699 (19) 0.00209 (18) 0.00273 (17) 0.00326 (16)
C4 0.0253 (2) 0.0175 (2) 0.0210 (2) −0.00221 (19) 0.0018 (2) 0.00012 (18)
C5 0.0212 (2) 0.0206 (2) 0.0214 (2) −0.00469 (19) −0.00236 (18) −0.00015 (18)
C6 0.0177 (2) 0.01902 (19) 0.01647 (19) −0.00229 (18) −0.00167 (18) 0.00122 (16)
N7 0.01712 (18) 0.01998 (18) 0.02029 (18) −0.00197 (16) −0.00553 (15) 0.00064 (16)
C8 0.0163 (2) 0.01866 (19) 0.01499 (19) −0.00049 (17) −0.00103 (16) 0.00019 (16)
C9 0.01616 (19) 0.01664 (18) 0.01360 (18) −0.00009 (17) −0.00082 (16) −0.00010 (15)
C10 0.01491 (19) 0.01684 (18) 0.01387 (18) −0.00030 (17) −0.00168 (15) 0.00015 (15)
C11 0.0186 (2) 0.01712 (19) 0.01355 (18) 0.00107 (17) −0.00029 (16) 0.00043 (15)
N12 0.01708 (17) 0.01610 (16) 0.01518 (16) 0.00189 (15) −0.00010 (15) 0.00234 (14)
C13 0.0162 (2) 0.0203 (2) 0.0195 (2) 0.00185 (18) −0.00253 (17) 0.00212 (18)
C14 0.0204 (2) 0.01513 (17) 0.01576 (18) −0.00042 (19) −0.00387 (18) −0.00044 (15)
C15 0.0221 (2) 0.0259 (2) 0.0187 (2) 0.0041 (2) −0.00053 (19) 0.00282 (19)
C16 0.0340 (3) 0.0268 (2) 0.0192 (2) 0.0026 (2) 0.0016 (2) 0.0043 (2)
C17 0.0433 (3) 0.0312 (3) 0.0215 (2) −0.0045 (3) −0.0118 (2) 0.0095 (2)
C18 0.0315 (3) 0.0504 (3) 0.0337 (3) −0.0125 (3) −0.0193 (2) 0.0170 (3)
C19 0.0233 (2) 0.0364 (3) 0.0275 (2) −0.0086 (2) −0.0078 (2) 0.0105 (2)
C20 0.0277 (2) 0.0188 (2) 0.0268 (2) −0.0022 (2) −0.0068 (2) −0.00086 (19)
C21 0.0267 (2) 0.0175 (2) 0.0226 (2) 0.0049 (2) 0.0004 (2) 0.00226 (18)

Geometric parameters (Å, º) for (3)
Cl1—C3 1.7488 (5) C11—H11 0.979 (7)
C1—C2 1.4024 (7) N12—C21 1.4736 (7)
C1—C6 1.4172 (7) N12—C13 1.4768 (7)
C1—C9 1.4362 (7) C13—H13A 0.979 (8)
C2—C3 1.3813 (7) C13—H13B 1.028 (7)
C2—H2 0.946 (7) C14—C19 1.3836 (8)
C3—C4 1.4035 (8) C14—C15 1.3958 (8)
C4—C5 1.3851 (8) C15—C16 1.3906 (8)
C4—H4 0.960 (8) C15—H15 0.922 (9)
C5—C6 1.3982 (7) C16—C17 1.3801 (10)
C5—H5 0.932 (7) C16—H16 0.935 (9)
C6—N7 1.3813 (7) C17—C18 1.3761 (10)
N7—C8 1.3832 (7) C17—H17 0.892 (10)
N7—H7 0.839 (8) C18—C19 1.3992 (9)
C8—C9 1.3628 (7) C18—H18 0.957 (11)
C8—C13 1.4878 (7) C19—H19 0.977 (10)
C9—C10 1.4938 (7) C20—H20A 0.938 (9)
C10—C14 1.5264 (7) C20—H20B 0.983 (8)
C10—C11 1.5549 (7) C20—H20C 0.917 (10)
C10—H10 1.020 (8) C21—H21A 0.979 (8)
C11—N12 1.4907 (6) C21—H21B 0.933 (8)
C11—C20 1.5266 (8) C21—H21C 0.975 (8)
C2—C1—C6 120.23 (4) C21—N12—C13 107.10 (4)
C2—C1—C9 133.43 (5) C21—N12—C11 110.63 (4)

C6—C1—C9 106.25 (4) C13—N12—C11 110.99 (4)
C3—C2—C1 117.12 (5) N12—C13—C8 109.06 (4)
C3—C2—H2 121.4 (4) N12—C13—H13A 109.1 (4)
C1—C2—H2 121.4 (4) C8—C13—H13A 108.6 (4)
C2—C3—C4 123.11 (5) N12—C13—H13B 109.8 (4)
C2—C3—Cl1 118.15 (4) C8—C13—H13B 112.6 (4)
C4—C3—Cl1 118.71 (4) H13A—C13—H13B 107.7 (6)
C5—C4—C3 119.96 (5) C19—C14—C15 118.40 (5)
C5—C4—H4 121.2 (5) C19—C14—C10 121.67 (5)
C3—C4—H4 118.8 (5) C15—C14—C10 119.93 (5)
C4—C5—C6 118.15 (5) C16—C15—C14 120.84 (5)
C4—C5—H5 120.0 (4) C16—C15—H15 121.2 (5)
C6—C5—H5 121.9 (4) C14—C15—H15 117.9 (5)
N7—C6—C5 130.08 (5) C17—C16—C15 120.09 (6)
N7—C6—C1 108.62 (4) C17—C16—H16 118.8 (6)
C5—C6—C1 121.30 (5) C15—C16—H16 121.1 (6)
C6—N7—C8 107.42 (4) C18—C17—C16 119.75 (6)
C6—N7—H7 123.0 (5) C18—C17—H17 122.0 (6)
C8—N7—H7 127.7 (5) C16—C17—H17 118.2 (6)
C9—C8—N7 110.87 (4) C17—C18—C19 120.30 (6)
C9—C8—C13 123.31 (4) C17—C18—H18 118.2 (6)
N7—C8—C13 125.82 (4) C19—C18—H18 121.2 (6)
C8—C9—C1 106.83 (4) C14—C19—C18 120.62 (6)
C8—C9—C10 123.40 (4) C14—C19—H19 121.4 (6)
C1—C9—C10 129.78 (4) C18—C19—H19 118.0 (6)
C9—C10—C14 110.35 (4) C11—C20—H20A 110.8 (5)
C9—C10—C11 110.35 (4) C11—C20—H20B 113.4 (5)
C14—C10—C11 110.37 (4) H20A—C20—H20B 107.0 (7)
C9—C10—H10 109.6 (4) C11—C20—H20C 107.2 (6)
C14—C10—H10 108.2 (4) H20A—C20—H20C 111.6 (8)
C11—C10—H10 107.9 (4) H20B—C20—H20C 106.7 (7)
N12—C11—C20 111.27 (4) N12—C21—H21A 113.7 (5)
N12—C11—C10 111.35 (4) N12—C21—H21B 109.9 (5)
C20—C11—C10 109.34 (4) H21A—C21—H21B 108.4 (7)
N12—C11—H11 107.5 (4) N12—C21—H21C 112.0 (4)
C20—C11—H11 109.0 (4) H21A—C21—H21C 105.5 (6)
C10—C11—H11 108.3 (4) H21B—C21—H21C 107.1 (7)