약학석사학위논문

# Synthesis of (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one Isolated from a Korean Marine Sponge of the Family Irciniidae

## 해양 해면 Irciniidae과에서 분리된 천연물 (*S*)-4-(1H-indol-3-yl)-3-methyl-1- (2-methylbutyl)-1H-pyrrol-2(5H)-one의 합성

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약학대학 약학과

**김 형 준**

Abstract

# Synthesis of (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one Isolated from a Korean Marine Sponge of the Family Ircinidae

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An indole alkaloidal natural product was isolated from a Korean marine sponge of the family Ircinidae collected off the coast of Chuja island. The natural compound was structurally determined through the combined spectroscopic analysis to be (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one. However, spectroscopic data were not decisively determine the absolute configuration of the compound.

Organic synthesis was used to prepare the novel compound and compare its

spectroscopic data to determine the absolute configuration of the natural product. Retrosynthesis of the target compound was carried out. The initial mode of approach was to synthesize the lactam and indole moiety separately and conjugate them subsequently. Several schemes were devised and performed. However, this approach proved to be unsuccessful, particularly with the conjugation of the two moieties.

An alternative approach was to cyclize the lactam ring moiety onto the indole group. Several schemes were devised and attempted with this, but none have been able to produce the final product. Future studies based on different approaches will be required for the successful synthesis of the natural product.

Key word: sponge, indole alkaloid, synthesis

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# Introduction

Nature has served as a source of medicinal compounds throughout human history. Natural products, mainly isolated from terrestrial plants, have served various therapeutical purposes with the advent of modern medicine. As new sources for natural products began to dwindle from terrestrial sources, marine natural products sprouted up as a new source in recent decades. Starting with unusual nucleoside derivatives isolated from sea sponges in the 1950s [1], marine natural products research initially had a slow growth. During the 1980s, through the collaborative efforts of researchers from various fields, marine environments began gaining attention as a potential source for novel compounds with therapeutic properties [2] and research into the field gained momentum.

By 2010, over 15,000 new marine natural products have been discovered, with over half of these surfacing in the last decade. Of these new compounds, those isolated from marine sponges account for almost 30% of the total.[3] Numerous studies have shown that these marine natural products have a broad spectrum of biological activities which includes but is not limited to anticancer, antibacterial, immunosuppressive, anti-inflammatory and antifungal.[4] The sedentary, almost immobile nature of marine sponges, and other marine animals that serve as potential sources of new natural products, is thought to be responsible for their huge diversity in secondary metabolites as chemical defense becomes the most

likely evolutionary option.[5]

Previously from our group, natural products were isolated from a Korean sponge from the family Ircinidae that was collected from off the coast of Chuja Island, Republic of Korea. Several bioactive terpenoids and polyketides have previously been isolated from Ircinidae sponges before, revealing its potential as a source of bioactive natural products.[6] From this sample was isolated five new compounds, two sesterterpenes and three indole alkaloids, all of which have been structurally defined via spectroscopic analyses.

Spectroscopic analyses, particularly NMR, are powerful tools for determining the total structure of compounds, both planar and absolute configuration. However, there are some shortcomings, as such analyses are not able to fully determine the structure of compounds at times. Such was the case here with one of the indole alkaloids, (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one (Figure 1), where the absolute configuration of the methyl group in the N-conjugated alkyl chain was not definitively determined. In such cases, organic synthesis of the hypothesized compound followed by spectroscopic comparison can serve to help determine absolute configuration with certainty.

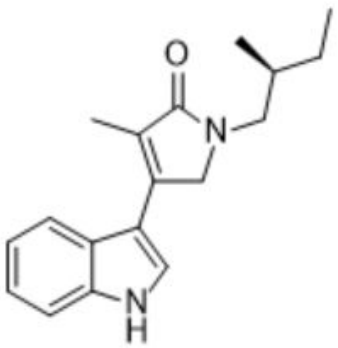



**Figure 1.** (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one

The purpose of this study began with two goals: the primary goal was to determine the absolute configuration of the target compound through chemical synthesis. If the primary goal was achieved, the secondary goal was to synthesize analogues of the target compounds with the hopes of producing a bioactive lead compound.

# Results and Discussion

## 1. Design and retrosynthesis

As described in the introduction, the purpose of this research was to confirm (or deny) the absolute stereochemistry of the natural compound (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one. Initially, retrosynthesis seemed to dictate that the simplest approach to synthesizing the target compound was by conjugating the indole and lactam ring constituents together (Figure 2).

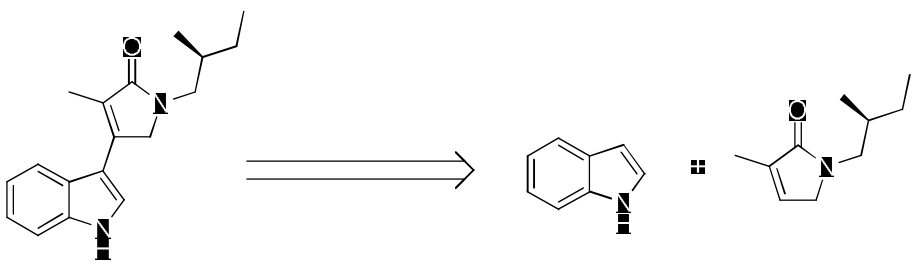
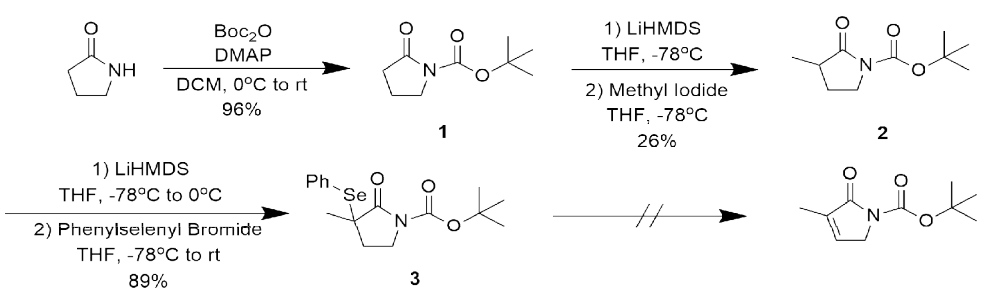


**Figure 2.** Retrosynthesis of target compound

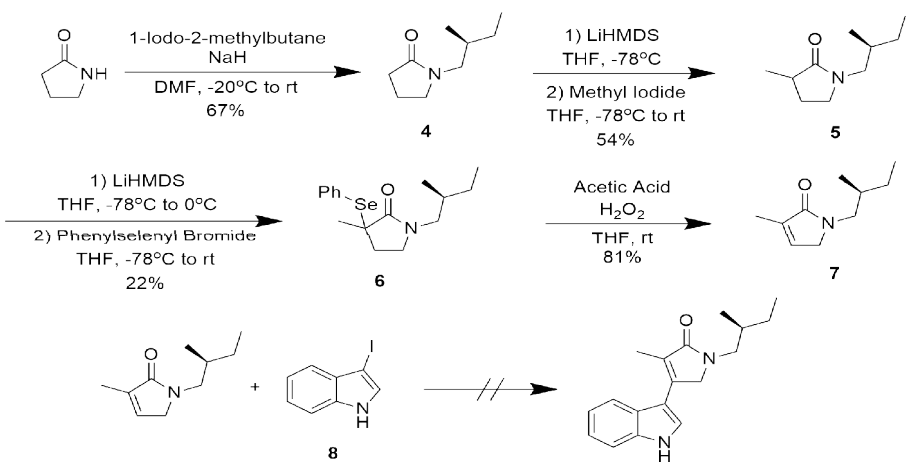
## 2. Conjugation of separate lactam and indole moieties




**Scheme 1.** Initial scheme with Boc protected lactam ring.

The first approach was to synthesize a complete lactam ring structure and conjugate it with an indole in the final step (Scheme 1). The lactam ring began with a Boc protection on the lactam ring of a 2-pyrrolidinone. This allowed for the selective methylation of the 3 position.[7] The 3 position was then conjugated with a phenylselenyl group in order to prepare the lactam ring for hydrogenation.[8]

The Boc protecting group seemed to have an adverse effect on the reactivity of the lactam ring. The methylation of the 3 position was 26%, much lower than originally expected. Hydrogenation of the phenylselenyl conjugated lactam ring did not produce any detectable amounts of products.




**Scheme 2.** Scheme involving Heck reaction between indole and lactam.

Assuming that the Boc protecting group was responsible for the reduced reactivity in the remaining part of the lactam ring, another scheme that circumvented the protection of the lactam group was devised (Scheme 2). Instead of preventing the

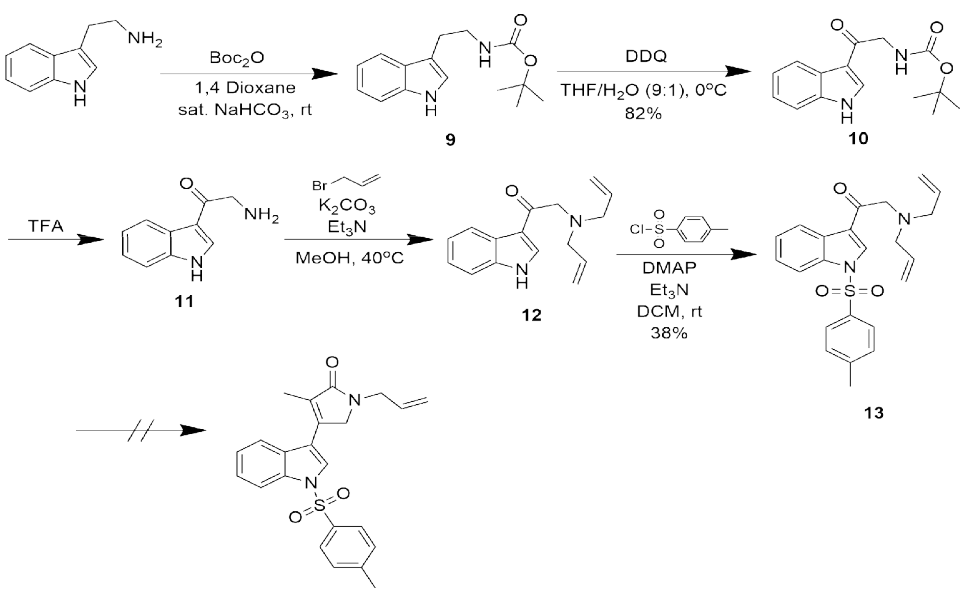
nitrogen from reacting via its protection, the first step was to alkylate it.[9] Methylation and phenylselenyl conjugation in the 3 position followed, and the hydrogenation utilizing the phenylselenyl conjugate as a leaving group allowed the formation of a double bond between the 3,4 position, completing the lactam ring.[7,8] Iodoindole was synthesized through halogenation of indole in preparation for the conjugation of indole and the lactam ring.[10] The final conjugation reaction was attempted via the Heck reaction.[11,12,13]

Previously, it was hypothesized that the Boc protecting group on the lactam ring acted to reduce reactivity in the rest of the ring. Here, with the N-conjugation of an alkyl chain, which is nonpolar as opposed to the more polar Boc protecting group, reactivity seemed to increase, as indicated by the increase in product yield of the methylation. While the alkylation and methylation produced yields of 67% and 54%, respectively, the actual yield is thought to be higher than this because the boiling point of these products decreased noticeably compared to 2-pyrrolidinone.

The phenylselenyl conjugation consistently resulted with product yields of around 20%, with most of the starting material remaining unreacted. This did not change even when the equivalency of phenylselenyl bromide, lithium hexamethyldisilazide or both was increased. These results gave credence to the hypothesis that the 3 position was not being properly activated to allow for a nucleophilic attack, conjugating the phenylselenyl group to the lactam.

The final step of the scheme was the conjugation of a halogenated indole with the synthesized 3-methyl-1H-pyrrol-2(5H)-one. It was determined that the Heck reaction would be appropriate for this reaction. However, none of the various types of conditions attempted with this reaction produced any detectable amount of the final product. In most cases, the starting materials would not react at all, and in one case a conjugation had occurred, but it was between the 4 position of the lactam ring and the 2 position of the indole instead of the expected 3 position. Although usually the 3 position of the indole is the most reactive, in this case neither the halogen nor the palladium catalysts were successful in activating it in preparation for conjugation.

### 3. Formation of lactam moiety



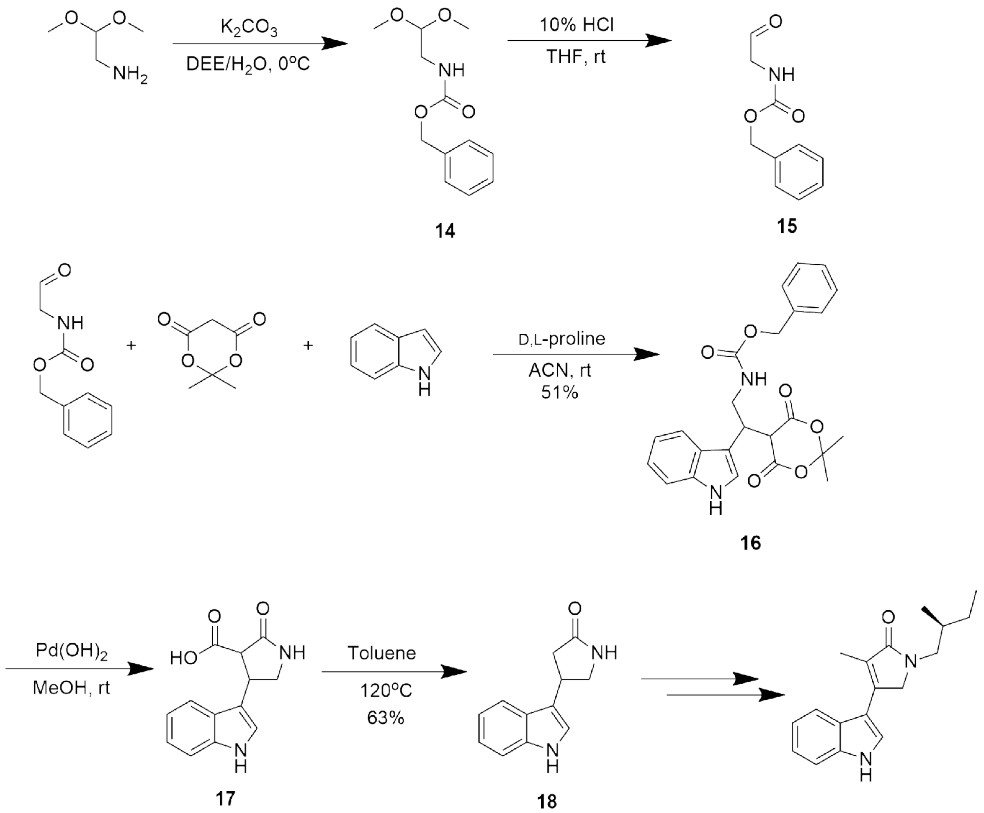

**Scheme 3.** First attempt at cyclization of lactam ring.

Conjugating the indole and lactam moieties proved to be a difficult method, and another approach was deemed necessary. Instead of starting with two different moieties and conjugating them towards the end, a method with a chain attached to an indole that would later become cyclized was thought of. A reaction scheme starting from tryptamine was devised. The amine would be protected to prevent it from reacting during the formation of a ketone. Allylation was then carried out on the deprotected amine group, then cyclization of the chain was attempted after protecting the pyrrole ring of indole.[14]

The first five steps of this scheme proved to be simple, even if the yield was not very promising. With the exception of the second step, no purification was required. The deprotection step seemed to be the reason for the relatively low yield of around 20% in the fifth step. While deprotection is simple, the product seemed to have formed a salt crystal with the acid. Triethylamine was used as a base to nullify the acid, and the product went from being crystals to an oily residue, giving credence to the idea of salt crystals. Even so, the yield of the reaction increased only to 38%, which was lower than expected.

The final cyclization was a four part reaction. The first part involved the addition of LDA to ethyl 2,2-dibromopropionate at -78°C. After 20 minutes, this was followed by the addition of *tert*-butyllithium. After 1.5 hours, the reaction was warmed up to room temperature, and **13** was transferred at 0°C. After another 30 minutes, the temperature was lowered to -10°C and thionyl chloride was added

before running the reaction overnight at room temperature. This reaction, as complicated as it was proved, proved to be just as difficult, and no detectable amount of product was produced.




**Scheme 4.** Second attempt at cyclization of lactam ring.

Another scheme involving the cyclization of the lactam ring after conjugation with the indole moiety was found.[15,16] At the core of this scheme, a synthesized aldehyde was condensed with an indole and 2,2-dimethyl-1,3-dioxane-4,6-dione using D,L-proline as a catalyst to produce **16**. Then debenzylation via hydrogenolysis using $H_2$ gas was carried out, resulting in a cyclized lactam

conjugated to an indole in compound **17**. After decarboxylation on the lactam ring to synthesize **18**, the compound resembled the 2-pyrrolidinone used as a starting material in scheme 2, with the addition of an indole conjugated at the 4 position. Synthesis of the final product was not completed in this study. However, the completion of **18** enables the possibility to successfully terminate this study because the lactam ring is identical to the starting point of Scheme 2 with the exception of an indole being conjugated to its 4 position. Although differences in reactivity are expected due to this difference, the lactam ring appears to be a likely starting point in conducting the remaining reactions towards the successful completion of the synthesis of (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one .

## Conclusion

The primary purpose of this study was to organically synthesize the target compound (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one, with the synthesis of structural analogues as set as a secondary goal. The reason for the primary goal was to determine if the previously isolated and structurally determined target natural product compound was indeed in the configuration deciphered using the spectroscopic data available.

The primary objective of the study was not achieved, as various difficulties were encountered in our attempt to synthesize the target compound. As the primary goal was not achieved, there was no progress on the secondary goal as well.

The final scheme attempted in this study (Scheme 4) is has been successful in synthesizing an indole conjugated to a lactam ring. This proves to be promising, as the lactam ring is identical in structure to the starting point of a previous attempt (Scheme 2) where the lactam ring moiety was successfully synthesized. However, further studies will be required to synthesize the target compound.

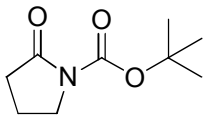
# Experimental Section

## 1. General Experimental Procedures

All reagents purchased from commercial sources were used unpurified. All solvents used were of reagent grade or distilled from glass prior to use. Organic solvents were concentrated under reduced pressure with the use of a Büchi rotary evaporator. TLC analyses were performed using Merck precoated TLC plate (silica gel 60 $GF_{254}$, 0.25 mm). Flash chromatography was carried out using E. Merck Kieselgel 60 (230~400 mesh). Proton and carbon nuclear magnetic resonance spectra were recorded using the Varian 300 [300 MHz ($^{1}H$), 75 MHz ($^{13}C$)] spectrometer and Bruker Avance 500 [500 MHz ($^{1}H$), 125 MHz ($^{13}C$)] spectrometer. The compounds were dissolved using either $CHCl_3$-*d*, $CH_3OH$-*d* or DMSO-*d* as solvents and reported in ppm relative to $CHCl_3$ (δ 7.26), $CH_3OH$ (δ 3.30), DMSO (δ 2.50) for $^{1}H$-NMR and relative to $CHCl_3$ (δ 77.0), $CH_3OH$ (δ 49.0), DMSO (δ 39.5) resonance for $^{13}C$-NMR. Low-resolution ESI-LC/MS data were recorded on an Agilent Technologies 6130 quadrupole mass spectrometer with an Agilent Technologies 1200 series HPLC. Infrared spectra were recorded on a JASCO FT/IR-300E spectrometer.

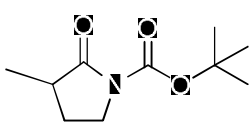
## 2. Synthesis of the Indole Alkaloid

*Tert*-butyl 2-oxopyrrolidine-1-caboxylate (**1**)



DMAP (91.7 mg, 0.75 mmol) was added to a 1-neck round bottom flask and $N_2$ flushed. Dry $CH_2Cl_2$ (5.5 mL) was added to the flask, then 2-pyrrolidinone (190 μL, 2.5 mmol) dropwise, then cooled to 0°C. In a separate flask, $Boc_2O$ (1,091 mg, 5.0 mmol) was added, flushed with $N_2$, and dissolved in dry $CH_2Cl_2$ (2.0 mL) and transferred to the 2-neck flask dropwise. The reaction was run overnight, warming up from 0°C to room temperature. The solvent was then evaporated, then filtered through silica (eluent: EtOAc/Hex, 1:1) to give *tert*-butyl 2-oxopyrrolidine-1-caboxylate (0.72 mmol, 96% yield) as a yellowish oil. $^1$H NMR (300 MHz, $CDCl_3$) δ: 3.70 (2H, t, *J*=7.2 Hz), 2.46 (2H, t, *J*=7.8 Hz), 1.95 (2H, p, *J*=8.1 Hz), 1.48 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 174.2 (C=O), 150.0 (C=O), 82.6 (C), 46.4 ($CH_2$), 32.8 ($CH_2$), 27.9 (C), 17.3 ($CH_2$). $[M + H]^+$ calculated for $C_9H_{15}NO_3$ 186.2, found 186.1 on low-resolution ESI-LC/MS.

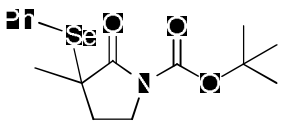
*Tert*-butyl 3-methyl-2-oxopyrrolidine-1-carboxylate (**2**)



*Tert*-butyl 2-oxopyrrolidine-1-caboxylate (133.4 mg, 0.72 mmol) was added to a 2-neck round bottom flask and $N_2$ flushed. The flask was cooled down to -78°C before 1.0M lithium hexamethyldisilazide in THF (1.51 mL, 1.51 mmol) was added dropwise and the reaction allowed to run for 30 minutes. Iodomethane (100.41 μL, 1.61 mmol) was

subsequently added dropwise into the reaction mixture and the reaction was run at -78°C for 45 minutes. The reaction was quenched with saturated ammonium chloride solution (5 mL) and allowed to warm up to room temperature. The reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1/1 to 100% EtOAc) to afford the product (0.19 mmol, 26% yield) as a yellowish oil. $^1$H NMR (300 MHz, $CDCl_3$) δ: 3.74 (m, 1H), 3.55 (1H, m), 2.52 (1H, m), 2.19 (1H, m), 1.62 (1H, m), 1.50 (9H, s), 1.20 (3H, d, *J*=7.5 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 176.5 (C=O), 150.3 (C=O), 82.6 (C), 44.2 (CH), 38.5 ($CH_2$), 27.9 (C), 26.3($CH_2$), 15.3($CH_3$). $[M + H]^+$ calculated for $C_{10}H_{17}NO_3$ 199.2, found 199.1 on low-resolution ESI-LC/MS.

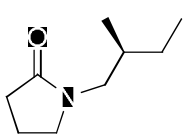
*Tert*-butyl 3-methyl-2-oxo-3-(phenylselanyl)pyrrolidine-1-carboxylate (**3**)



*Tert*-butyl 3-methyl-2-oxopyrrolidine-1-carboxylate (37.9 mg, 0.19 mmol) was added into a 2-neck round bottom flask and $N_2$ flushed. The compound was dissolved in dry THF (2 mL) before cooling to -78°C. 1.0M lithium hexamethyldisilazide in THF (1.51 mL, 1.51 mmol) was added dropwise and the reaction allowed to run at -78°C for 30 minutes, then warmed up to 0°C and run for 30 minutes. Meanwhile, phenylselenyl bromide (134.5 mg, 0.57 mmol) was added into a separate flask, $N_2$

flushed, and dissolved in THF (1 mL). The reaction mixture was cooled back down to -78°C and the phenylselenyl bromide solution was transferred over dropwise. The reaction was run at -78°C, then transferred over to an ice bath and warmed up to 0°C. The reaction was quenched with saturated ammonium chloride solution (5 mL) and allowed to warm up to room temperature. The reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 4/1) to afford the product (0.17 mmol, 89% yield) as a brown solid. $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.62 (2H, d, *J*=7.8 Hz), 7.36 (1H, d, *J*=7.2 Hz), 7.29 (2H, t, *J*=4.5 Hz), 3.56 (1H, t, *J*=9.9 Hz), 3.31 (1H, m), 2.21 (1H, m), 2.03 (1H, m), 1.56 (3H, s), 1.49 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 173.8 (C=O), 150.1 (C=O), 137.6 (CH), 129.4 (CH), 128.8 (CH), 126.1 (C), 82.6 (C), 49.6 (C), 42.9 ($CH_2$), 33.5 ($CH_3$), 27.9 ($CH_3$), 24.0 ($CH_2$). $[M + H]^+$ calculated for $C_{16}H_{21}NO_3Se$ 355.3, found 355.2 on low-resolution ESI-LC/MS.

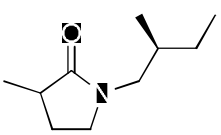
(*S*)-1-(2-methylbutyl)pyrrolidin-2-one (**4**)



Sodium hydride (474 mg, 19.74 mmol) was added into a 2-neck round bottom flask and $N_2$ flushed. The compound was dissolved in dry THF (5 mL) before being cooled down to 0°C. 2-pyrrolidinone

(500 μL, 6.58 mmol) was added into the flask dropwise and the reaction was run at 0°C for 30 minutes. Next, (*S*)-1-iodo-2-methylbutane (1.7 mL, 12.16 mmol) was added into the reaction dropwise, and the reaction was run for another 1 hour at 0°C. The reaction was quenched with saturated ammonium chloride solution (5 mL) and allowed to warm up to room temperature. The reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc) to afford the product (4.41 mmol, 67% yield) as a yellowish oil. $^1$H NMR (300 MHz, $CDCl_3$) δ: 3.36 (2H, t, *J*=6.3 Hz), 3.12 (2H, d, *J*=7.5 Hz), 2.41 (2H, t, *J*=8.1 Hz), 2.01 (2H, t, *J*=7.8 Hz), 1.65 (1H, m), 1.34 (1H, m), 1.12 (1H, m), 0.90 (3H, t, *J*=7.5 Hz), 0.85 (3H, d, *J*=6.9 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 175.2 (C=O), 48.7 ($CH_2$), 47.7 ($CH_2$), 32.9 (CH), 31.1 ($CH_2$), 26.9 ($CH_2$), 18.2 ($CH_3$), 16.8 ($CH_2$), 11.2 ($CH_3$). $[M + H]^+$ calculated for $C_9H_{17}NO$ 156.2, found 156.2 on low-resolution ESI-LC/MS.

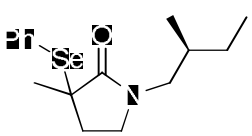
3-methyl-1-((*S*)-2-methylbutyl)pyrrolidin-2-one (**5**)



(*S*)-1-(2-methylbutyl)pyrrolidin-2-one (419.1 mg, 2.70 mmol) was placed in a 2-neck round bottom flask and $N_2$ flushed. The compound was dissolved in dry THF (2.5 mL) before being cooled down to -78°C. After cooling, 1.0M lithium hexamethyldisilazide in THF (5.4 mL,

5.40 mmol) was added to the solution dropwise, and the reaction was run for 2 hours at -78°C. Next, iodomethane (378 μL, 6.07 mmol) was sequentially added to the solution dropwise, and the reaction was run overnight starting from -78°C and being allowed to warm up to room temperature. The reaction was quenched with saturated ammonium chloride solution (5 mL). The reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1/1) to afford the product (1.46 mmol, 54% yield) as a yellowish oil. $^1$H NMR (300 MHz, $CDCl_3$) δ: 3.27 (2H, m), 3.12 (2H, m), 2.48 (1H, dd, *J*=7.5 Hz), 2.22 (2H, m), 1.65 (1H, m), 1.20 (3H, d, *J*=7.5 Hz), 1.12 (2H, m), 0.90 (3H, t, *J*=7.5 Hz), 0.84 (3H, d, *J*=6.9 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 156.4 (C=O), 48.8 ($CH_2$), 45.6 ($CH_2$), 36.8 (CH), 32.9 (C), 27.3 ($CH_2$), 26.9 ($CH_2$), 16.8 ($CH_3$), 16.5 ($CH_3$), 11.2 ($CH_3$). $[M + H]^+$ calculated for $C_{10}H_{19}NO$ 170.3, found 170.2 on low-resolution ESI-LC/MS.

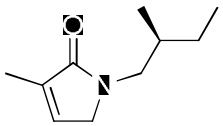
3-methyl-1-((*S*)-2-methylbutyl)-3-(phenylselanyl)pyrrolidin-2-one (**6**)



3-methyl-1-((*S*)-2-methylbutyl)pyrrolidin-2-one (247.1 mg, 1.46 mmol) was placed in a 2-neck round bottom flask and $N_2$ flushed. The compound was dissolved in dry THF (2 mL) before being cooled down to 0°C. After cooling, 1.0M lithium hexamethyldisilazide in THF (2.19 mL,

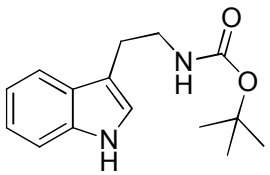
2.19 mmol) was added to the solution dropwise, and the reaction was run for 30 minutes at 0°C, cooled down to -20°C and run for 15 minutes, warmed back up to 0°C and run additionally for 15 minutes. In a separate 1-neck pear bottom flask, phenylselenyl bromide (516.8 mg, 2.19 mmol) was weighed, added and $N_2$ flushed. THF (1 mL) was added to the phenylselenyl bromide, and the solution was added to the reaction mixture dropwise, and the reaction was run at 0°C for 1 hour. The reaction was quenched with saturated ammonium chloride solution (5 mL), and the reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 4/1 to 1/1) to afford the product (0.263 mmol, 22% yield) as a brown amorphous solid. $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.68 (2H, d, *J*=8.1 Hz), 7.31 (1H, m), 7.22 (2H, t, *J*=6.9 Hz), 3.04 (2H, m), 2.93 (1H, m), 2.25 (1H, m), 1.98 (1H, m), 1.56 (1H, m), 1.28 (1H, m), 1.08 (1H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 175.2 (C=O), 137.8 (CH), 129.0 (CH), 128.8 (CH), 126.4 (C), 491. (C), 48.9 ($CH_2$), 44.2 ($CH_2$), 34.5 (CH), 32.7 ($CH_2$), 26.4 ($CH_3$), 24.9 ($CH_2$), 17.3 ($CH_3$), 12.1 ($CH_3$). $[M + H]^+$ calculated for $C_{16}H_{23}NOSe$ 325.3, found 326.1 on low-resolution ESI-LC/MS.

(*S*)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one (**7**)



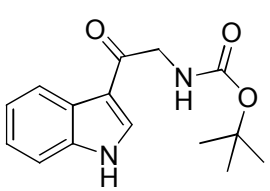
3-methyl-1-((*S*)-2-methylbutyl)-3-(phenylselanyl)pyrrolidin-2-one (85.3 mg, 0.263 mmol) was added to a 1-neck round bottom flask and $N_2$ flushed. THF (2 mL) was added to the flask and stirred at room temperature. Acetic acid (190 μL) and 30% $H_2O_2$ (1.7 mL) was added to the solution consecutively and the reaction was run for 1 hour at room temperature. The reaction was quenched with the addition of 1.0M solution of $NaHCO_3$ (300 μL). The reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2/1) to afford the product (0.213 mmol, 81% yield) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ: 6.64 (1H, s), 3.81 (2H, s), 3.29 (2H, m), 1.89 (3H, s), 1.69 (1H, m), 1.38 (1H, m), 1.13 (1H, m), 0.89 (3H, t, *J*=7.5 Hz), 0.85 (3H, d, *J*=6.6 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 172.3 (C), 135.8 (C), 134.7 (CH), 51.3 ($CH_2$), 48.6 ($CH_2$), 34.3 (CH), 26.9 ($CH_2$), 16.9 ($CH_3$), 11.3 ($CH_3$), 11.2 ($CH_3$). $[M + H]^+$ calculated for $C_{10}H_{17}NO$ 168.2, found 168.2 on low-resolution ESI-LC/MS.

*Tert*-butyl (2-(1H-indol-3-yl)ethyl)carbamate (**9**)



Tryptamine (200 mg, 1.25 mmol) was added into a round bottom flask and dissolved in 1,4-dioxane (5 mL). Saturated $NaHCO_3$ solution (2.5 mL) and di-tert-butyl carbonate (409.2 mg, 1.87 mmol) was added to the solution and the reaction was run at room temperature for 2 hours. The reaction mixture was concentrated in vacuo, then worked up with distilled water and EtOAc three times. The combined organic layer was again worked up with distilled water, washed with brine, dried with $MgSO_4$, and concentrated in vacuo to afford the crude product. The product was used directly in the next reaction. $[M + H]^+$ calculated for $C_{15}H_{20}N_2O_2$ 261.3, found 261.2 on low-resolution ESI-LC/MS.

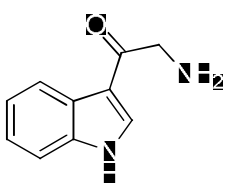
*Tert*-butyl (2-(1H-indol-3-yl)-2-oxoethyl)carbamate (**10**)



*Tert*-butyl (2-(1H-indol-3-yl)ethyl)carbamate (325.4 mg, 1.25 mmol) from the previous reaction was flushed with $N_2$ in a round bottom flask. A solvent mixture of THF/$H_2O$ (9/1, 20 mL) was added to the flask before cooling down to 0°C. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (567.5 mg, 2.50 mmol) was added to the solution, and reaction was carried out at 0°C for 2 hours. The reaction mixture

was concentrated in vacuo, then extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2/1) to afford the product (1.03 mmol, 82% yield) as a pale yellow crystal. $^1$H NMR (300 MHz, DMSO) δ: 11.9 (1H,s ), 8.38 (1H, s), 8.14 (1H, d, *J*=6.6 Hz), 7.47 (1H, d, *J*=6.6 Hz), 7.18 (2H, t, *J*=3.9 Hz), 6.99 (1H, t, *J*=6.3 Hz), 4.28 (2H, d, *J*=5.7 Hz), 1.40 (9H, s); $^{13}$C NMR (75 MHz, DMSO) δ: 190.7 (C=O), 155.9 (C=O), 136.3 (C), 133.3 (CH), 125.3 (C), 122.8 (CH), 121.7 (CH), 121.1 (CH), 113.9 (C), 112.1 (CH), 90.8 (CH), 77.8 (C), 46.8 ($CH_2$), 28.2 ($CH_3$). $[M + H]^+$ calculated for $C_{15}H_{18}N_2O_3$ 275.3, found 275.2 on low-resolution ESI-LC/MS.

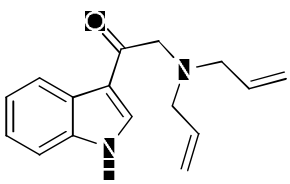
2-amino-1-(1H-indol-3-yl)ethanone (**11**)



*Tert*-butyl (2-(1H-indol-3-yl)-2-oxoethyl)carbamate (282.5 mg, 1.03 mmol) was added to a round bottom flask and $N_2$ flushed. The flask was cooled down to 0°C and trifluoroacetic acid (5 mL) was added into the flask while stirring. The reaction was allowed to run at 0°C for 40 minutes. The reaction mixture was concentrated in vacuo, then dissolved in methanol (5 mL), before cooling down to 0°C. Triethylamine (5 mL) was added to the flask, and the solution was allowed to stir for 30 minutes. The reaction mixture was concentrated in vacuo, then extracted with EtOAc three

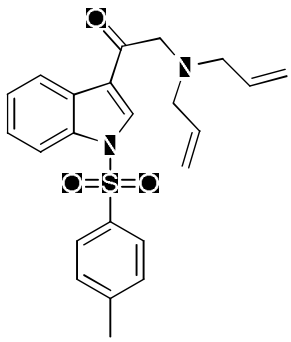
times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The product was used directly in the next reaction without further purification. $[M + H]^+$ calculated for $C_{10}H_{10}N_2O$ 175.2, found 175.1 on low-resolution ESI-LC/MS.

2-(diallylamino)-1-(1H-indol-3-yl)ethanone (**12**)



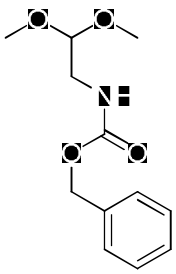
2-amino-1-(1H-indol-3-yl)ethanone (179.4 mg, 1.03 mmol) and potassium carbonate (355.9 mg, 2.58 mmol) was added to a 2-neck round bottom flask and $N_2$ flushed. Dry methanol (10 mL) and allyl bromide (187 μL, 2.16 mmol) were added sequentially to the flask, and the reaction was refluxed at 80°C overnight. The reaction mixture was then cooled down to room temperature. The solids were filtered out, and the filtrate was extracted with DCM twice. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The product was used directly in the next reaction without further purification. $[M + H]^+$ calculated for $C_{16}H_{18}N_2O$ 255.3, found 255.2 on low-resolution ESI-LC/MS.

2-(diallylamino)-1-(1-tosyl-1H-indol-3-yl)ethanone (**13**)



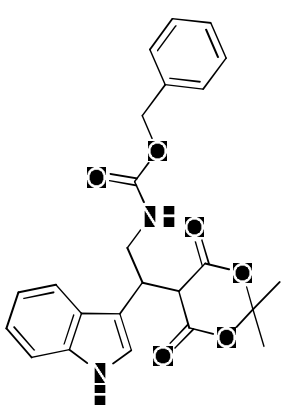
2-(diallylamino)-1-(1H-indol-3-yl)ethanone (261.9 mg, 1.03 mmol), p-toluenesulfonyl chloride (196.4 mg, 1.03 mmol), and 4-dimethylaminopyridine (18.9 mg, 0.154 mmol) was added to a round bottom flask and $N_2$ flushed. Dry DCM (8 mL) and trimethylamine (187 μL, 1.34 mmol) was added sequentially to the flask, and the reaction was run at room temperature overnight. The reaction mixture was concentrated in vacuo then extracted with EtOAc three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2/1) to afford the product (0.391 mmol, 38% yield) as a pale yellow crystal. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.62 (1H, s), 8.29 (1H, d, *J*=8.9 Hz), 7.91 (1H, d, *J*=8.9 Hz), 7.85 (1H, d, *J*=10.2 Hz), 7.36 (2H, m), 7.23 (2H, m), 5.92 (2H, m), 5.21 (4H, t, *J*=6.7 Hz), 3.76 (2H, s), 3.35 (4H, s), 2.34 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 145.9 (C=O), 134.6 (C), 134.4 (C), 132.9 (CH), 130.2 (CH), 127.9 (C), 127.1, 125.6 (CH), 124.8 (CH), 122.9 (CH), 119.3 (C), 113.0 (CH), 57.4 ($CH_2$), 21.6 ($CH_3$). $[M + H]^+$ calculated for $C_{23}H_{24}N_2O_3S$ 409.5, found 409.1 on low-resolution ESI-LC/MS.

Benzyl (2,2-dimethoxyethyl)carbamate (**14**)



Diethyl ether (10 mL) and aminoacetaldehyde dimethyl acetal (1.00 mL, 9.18 mmol) was added to a round bottom flask and stirred at room temperature. Potassium carbonate (3.81 mg, 27.54 mmol) and distilled water (10 mL) was added to the solution and cooled down to 0°C. Benyl chloroformate (1.31 mL, 9.18 mmol) was added to the solution dropwise, and the reaction was allowed to warm up to room temperature and stirred overnight. The organic layer was separated from the aqueous layer, and the aqueous layer was washed twice with diethyl ether. The combined organic layers were then washed with 5% citric acid solution three times, twice with brine, dried with $MgSO_4$, and concentrated in vacuo, and used directly in the next step.

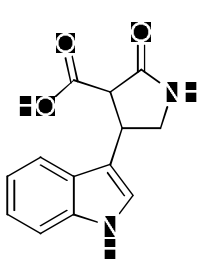
benzyl (2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-(1H-indol-3-yl)ethyl)carbamate (**16**)



To the benzyl (2,2-dimethoxyethyl)carbamate (2196 mg, 9.18 mmol) was added THF (20 mL) and 10% HCl solution (10 mL). The reaction was stirred at room temperature overnight. The organic solvent was evaporated in vacuo, and the aqueous solution was extracted with diethyl ether three times. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in

vacuo leaving a small amount of solvent (approx. 5 mL). To the resulting solution containing **15** was added acetonitrile (25 mL) and dissolved. To this solution was added indole (1075 mg, 9.18 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (1322 mg, 9.18 mmol), and D,L-proline (105 mg, 0.918 mmol) consecutively and $N_2$ flushed. The reaction was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue was directly purified by column chromatography (silica gel, hexane/acetone 9/5) to afford the product (0.523 mmol, 57% yield) as a pale brown solid. $^1$H NMR (500 MHz, DMSO) δ: 8.65 (1H, s), 8.29 (1H, d, *J*=7.4 Hz), 7.91 (1H, d, *J*=7.4 Hz), 7.81 (2H, d, *J*=8.4 Hz), 7.33 (2H, m), 7.25 (2H, d, *J*=8.1 Hz), 5.92 (2H, m), 5.21 (4H, t, *J*=11.2 Hz), 3.76 (2H, s), 3.29 (4H, s), 2.35 (3H, s); $^{13}$C NMR (125 MHz, DMSO) δ: 145.9 (C), 134.6 (C), 134.4 (C), 132.9 ($CH_2$), 130.2 (CH), 127.9 (C), 127.1 (CH), 125.6 (CH), 124.8 (CH), 123.0 (CH), 119.3 (C), 113.0 (CH), 57.4 ($CH_2$), 21.6 ($CH_3$). IR (KBr) 3705, 2980, 2938, 2864, 2826, 1740, 1346, 1054, 1013 cm$^{-1}$. $[M + H]^+$ calculated for $C_{24}H_{24}N_2O_6$ 437.5, found 437.2 on low-resolution ESI-LC/MS.

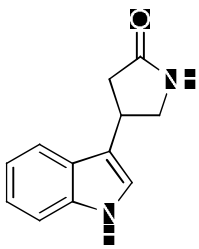
4-(1H-indol-3-yl)-2-oxopyrrolidine-3-carboxylic acid (**17**)



Benzyl (2-oxoethyl)carbamate (228 mg, 0.523 mmol) was added to a round bottom flask and dissolved in dry methanol (10 mL). 10% Pd/C (34 mg) was added to the solution before being flushed several times with $H_2$ gas. The reaction was run at room

temperature overnight while under $H_2$ at atmospheric pressure. The suspension was filtered through Celite® and washed with methanol. The solution was evaporated in vacuo, and the resulting mixture was used directly in the next reaction.

4-(1H-indol-3-yl)pyrrolidin-2-one (**18**)



Toluene (10 mL) was added to 4-(1H-indol-3-yl)-2-oxopyrrolidine-3-carboxylic acid (127.7 mg, 0.523 mmol) in a 2-neck round bottom flask. The solution was refluxed at 120°C overnight. The solution was cooled down to room temperature and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, methanol/DCM 1/9) to afford the product (0.330 mmol, 63% yield) as a white solid. $^1$H NMR (300 MHz, $CD_3OD$) δ: 7.53 (1H, d, *J*=7.8 Hz), 7.33 (1H, d, *J*=7.2 Hz), 7.11 (2H, m), 7.00 (1H, t, *J*=7.5 Hz), 3.97 (1H, dd, *J*=7.2 Hz, 8.4 Hz), 3.84 (1H, t, *J*=7.8 Hz), 3.49 (1H, dd, *J*=2.7 Hz, 7.2 Hz), 3.31 (1H, m), 2.76 (1H, dd, *J*=8.1 Hz, 8.7 Hz), 2.56 (1H, dd, *J*=8.1 Hz, 8.7 Hz); $^{13}$C NMR (125 MHz, $CD_3OD$) δ: 180.7 (C=O), 138.6 (C), 127.5 (C), 126.3 (CH), 122.7 (CH), 121.9 (CH), 119.8 (CH), 117.2 (C), 112.5 (CH), 50.2 ($CH_2$), 38.6 ($CH_2$), 33.5 (CH). IR (KBr) 3263, 2446, 2074, 1487, 1422, 1267, 1131, 1038, 983, 743 $cm^{-1}$. $[M + H]^+$ calculated for $C_{12}H_{12}N_2O$ 201.24, found 201.1 on low-resolution ESI-LC/MS.

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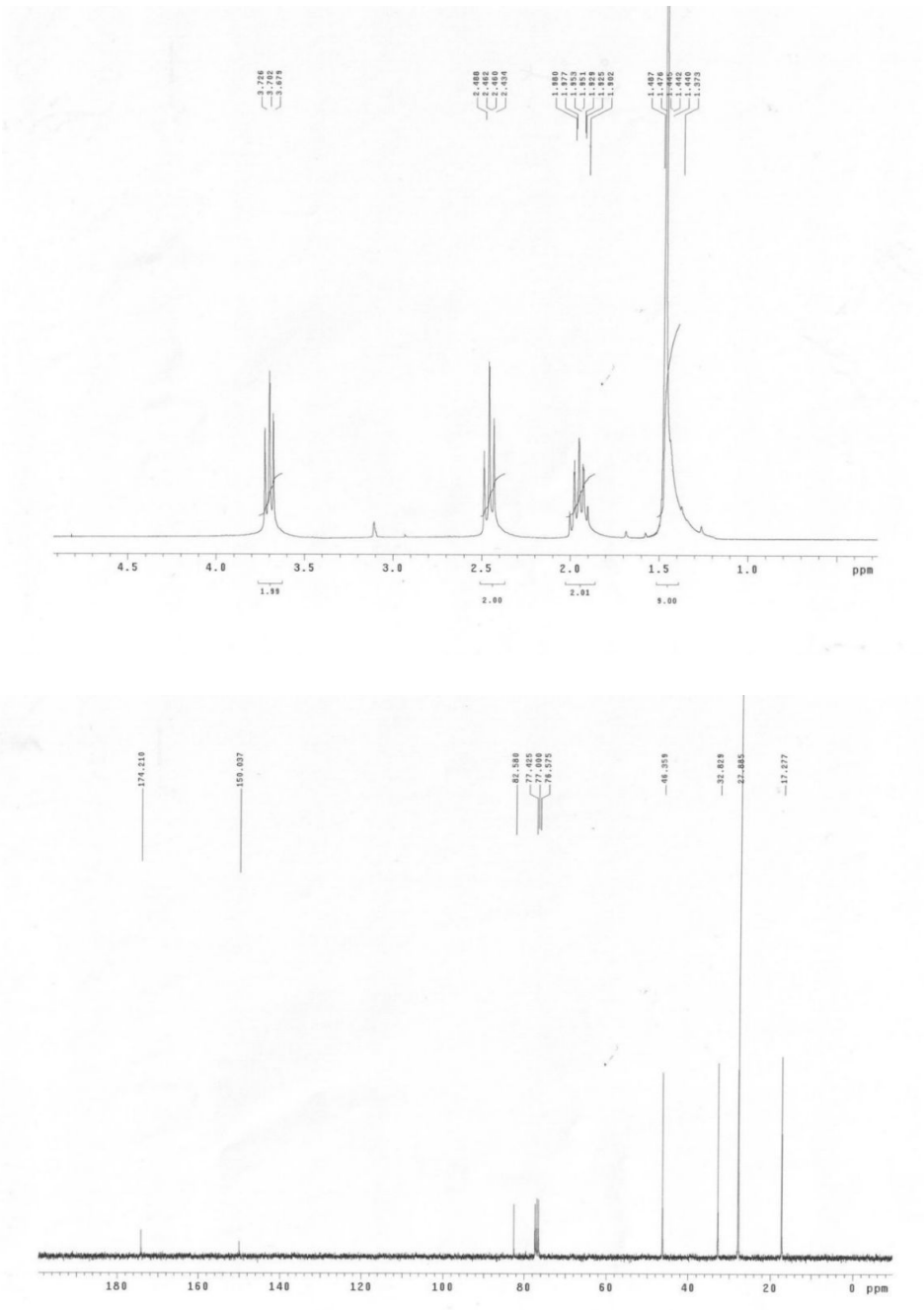


**Figure 3.** NMR spectrum of compound 1

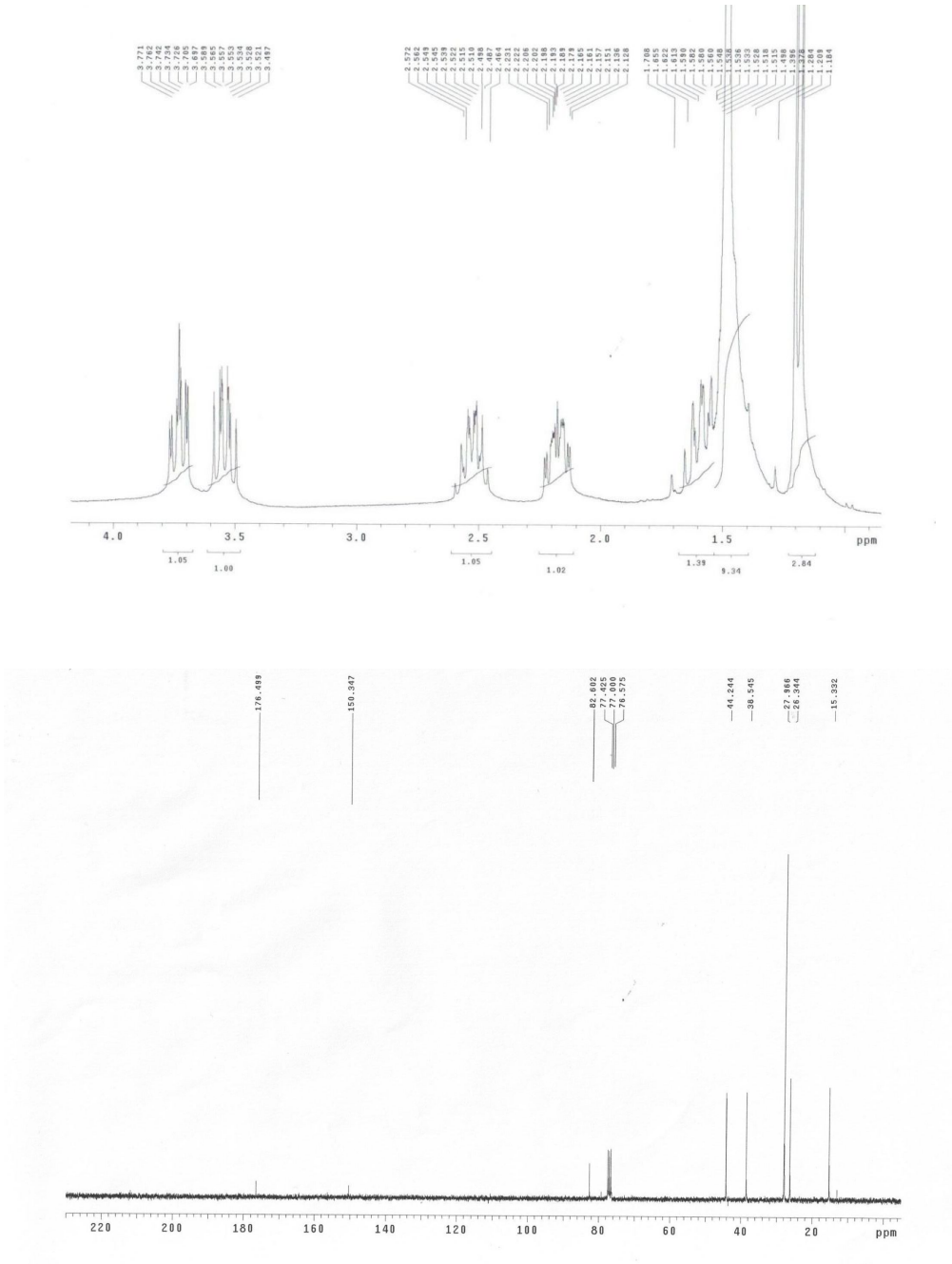


**Figure 4.** NMR spectrum of compound **2**

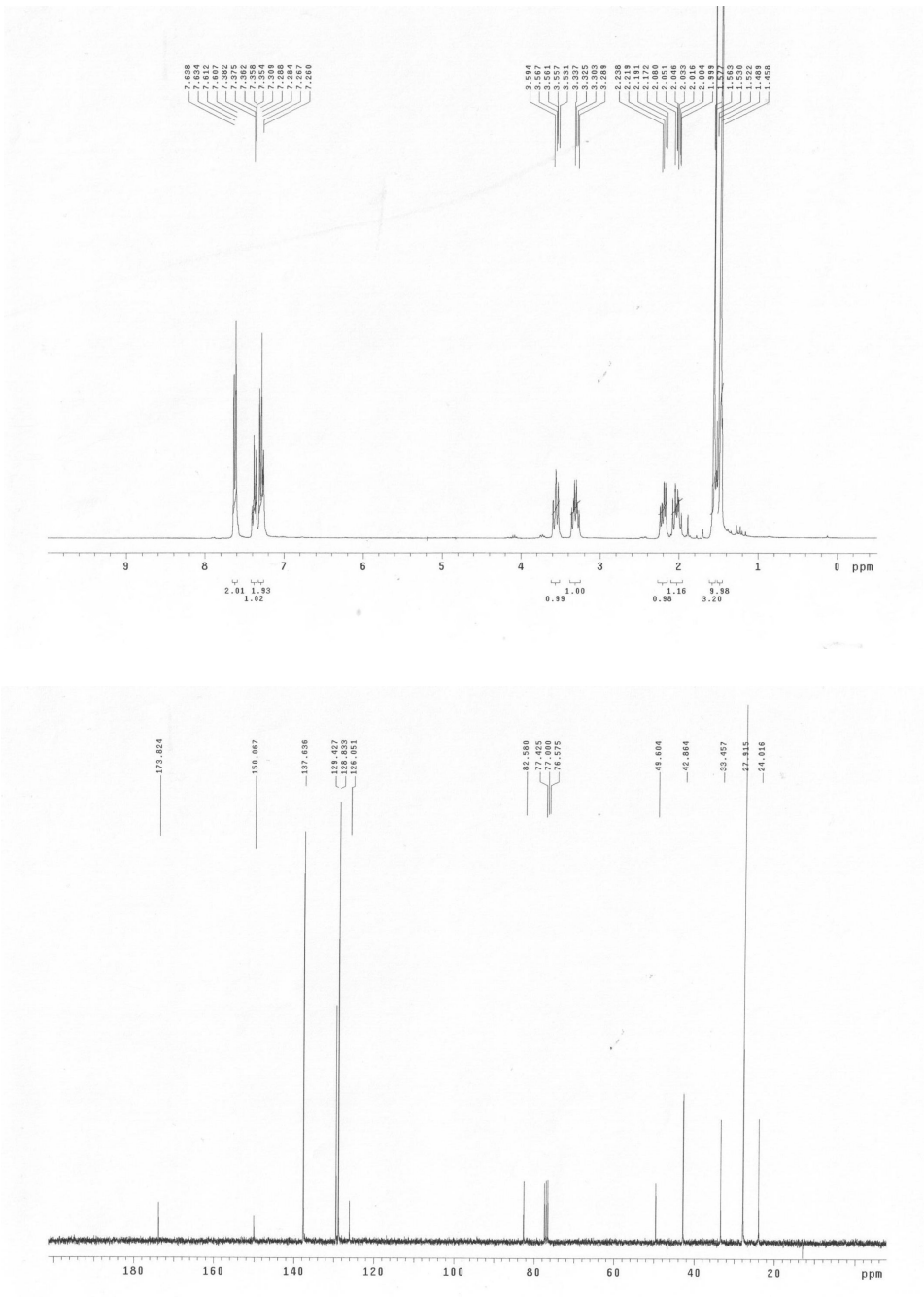


**Figure 5.** NMR spectrum of compound **3**

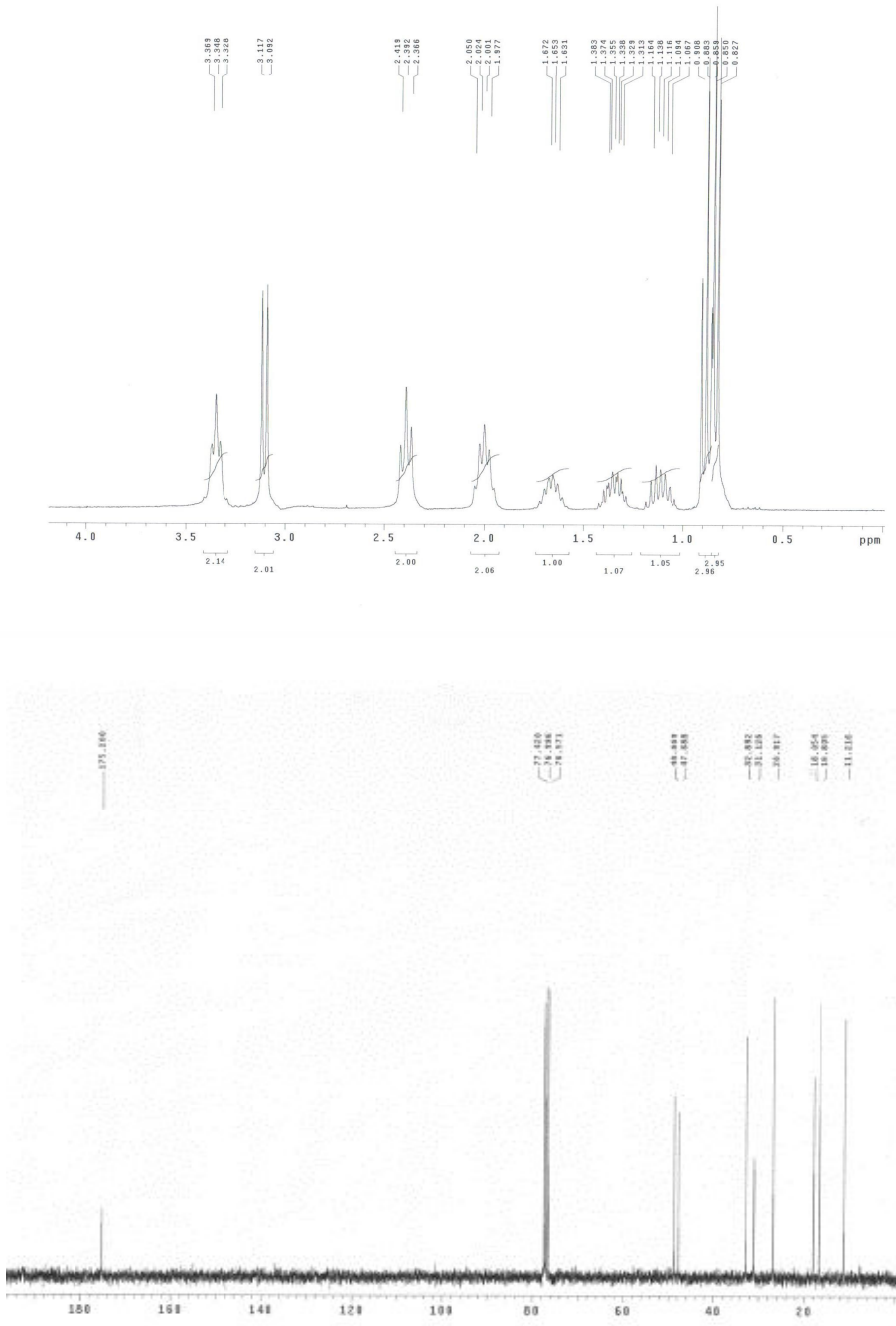


**Figure 6.** NMR spectrum of compound **4**

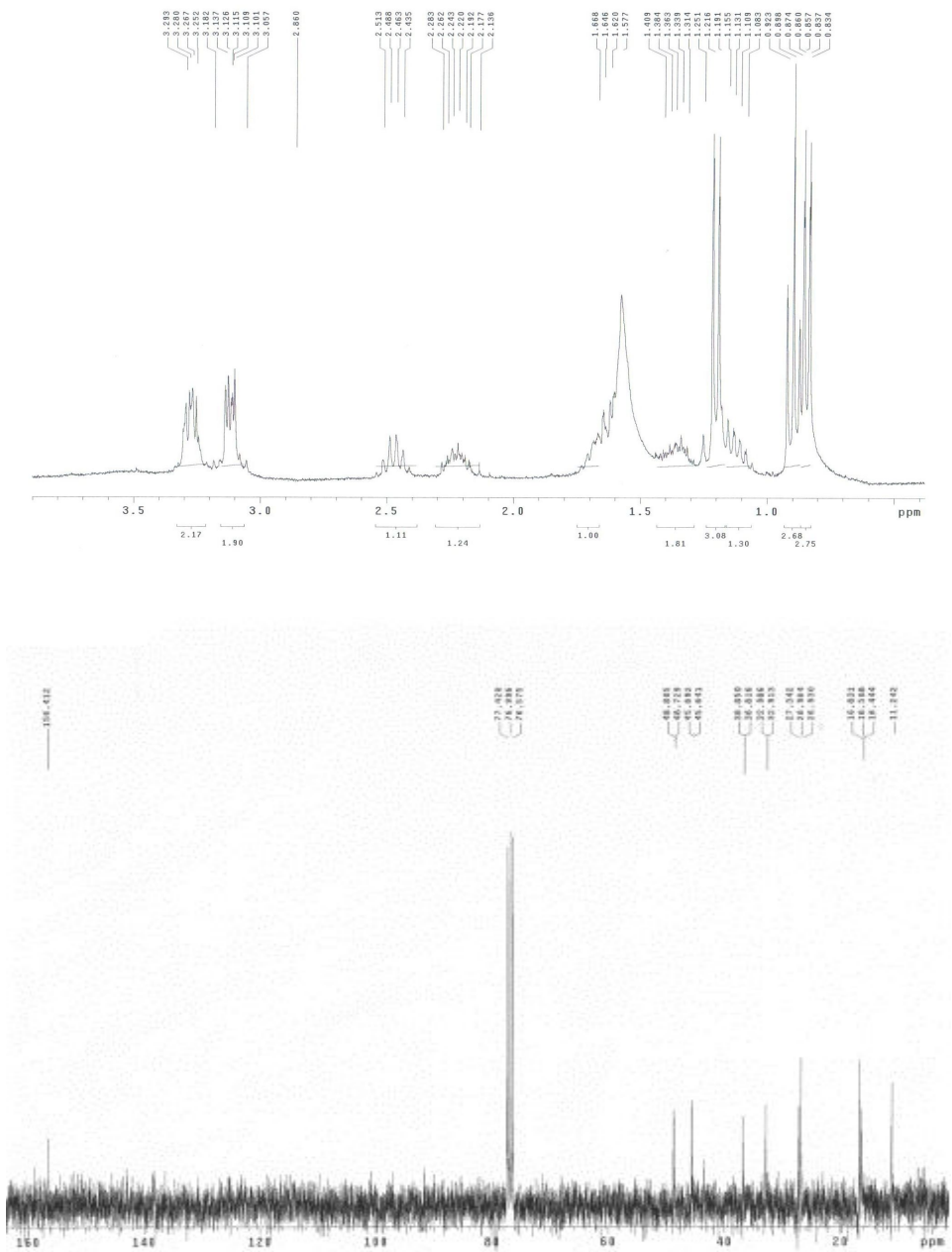

**Figure 7.** NMR spectrum of compound **5**

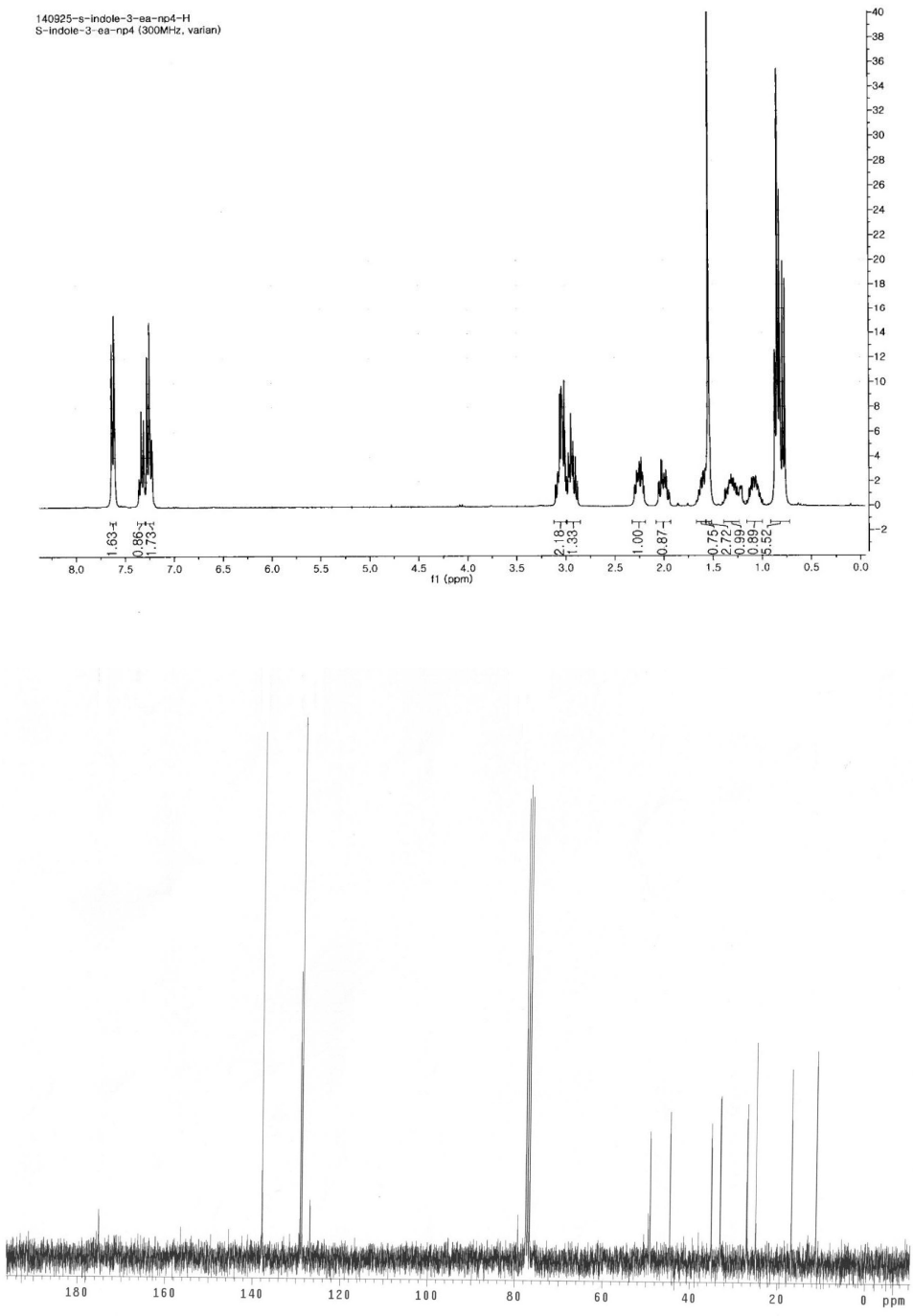


**Figure 8.** NMR spectrum of compound **6**

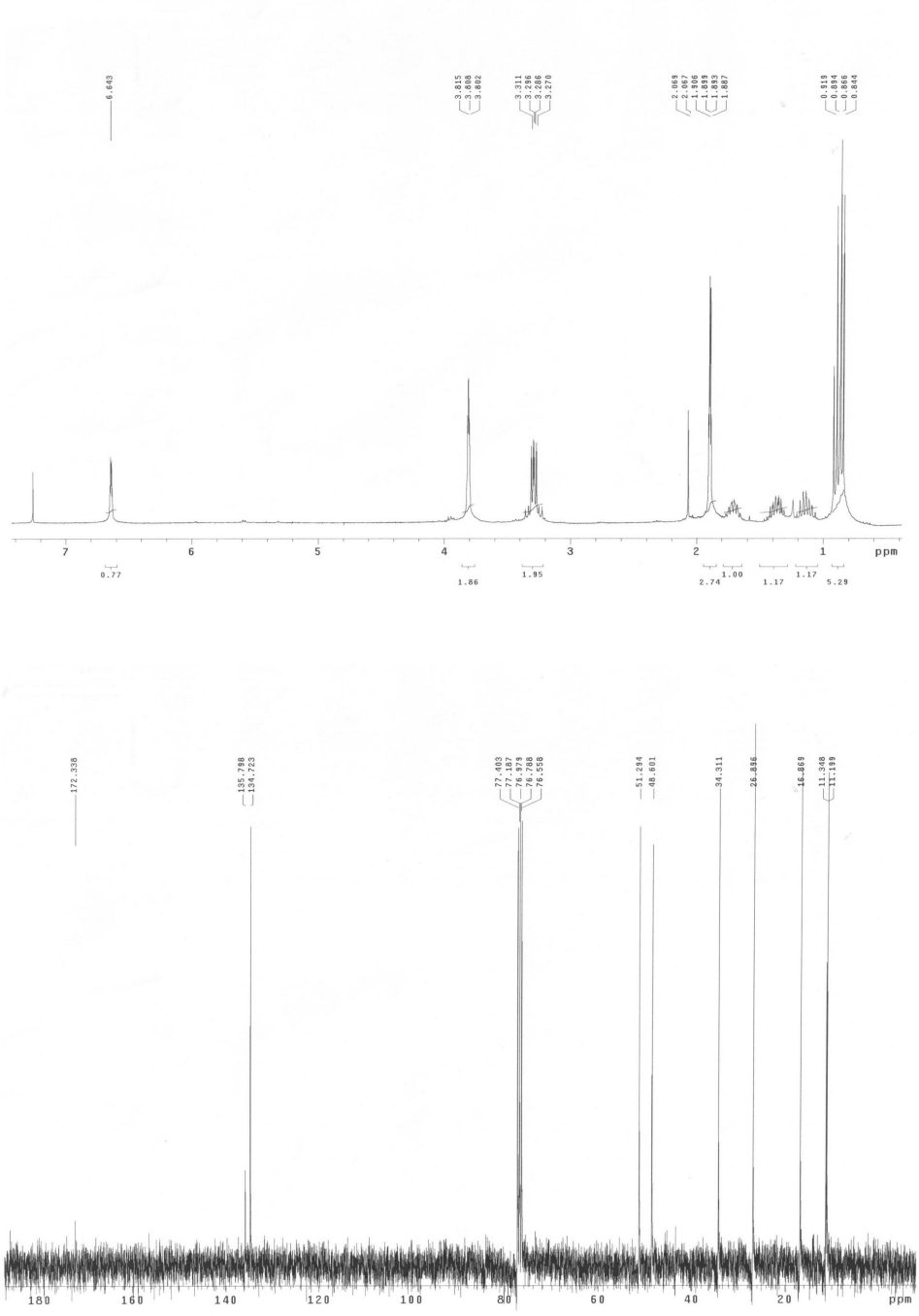


**Figure 9.** NMR spectrum of compound **7**

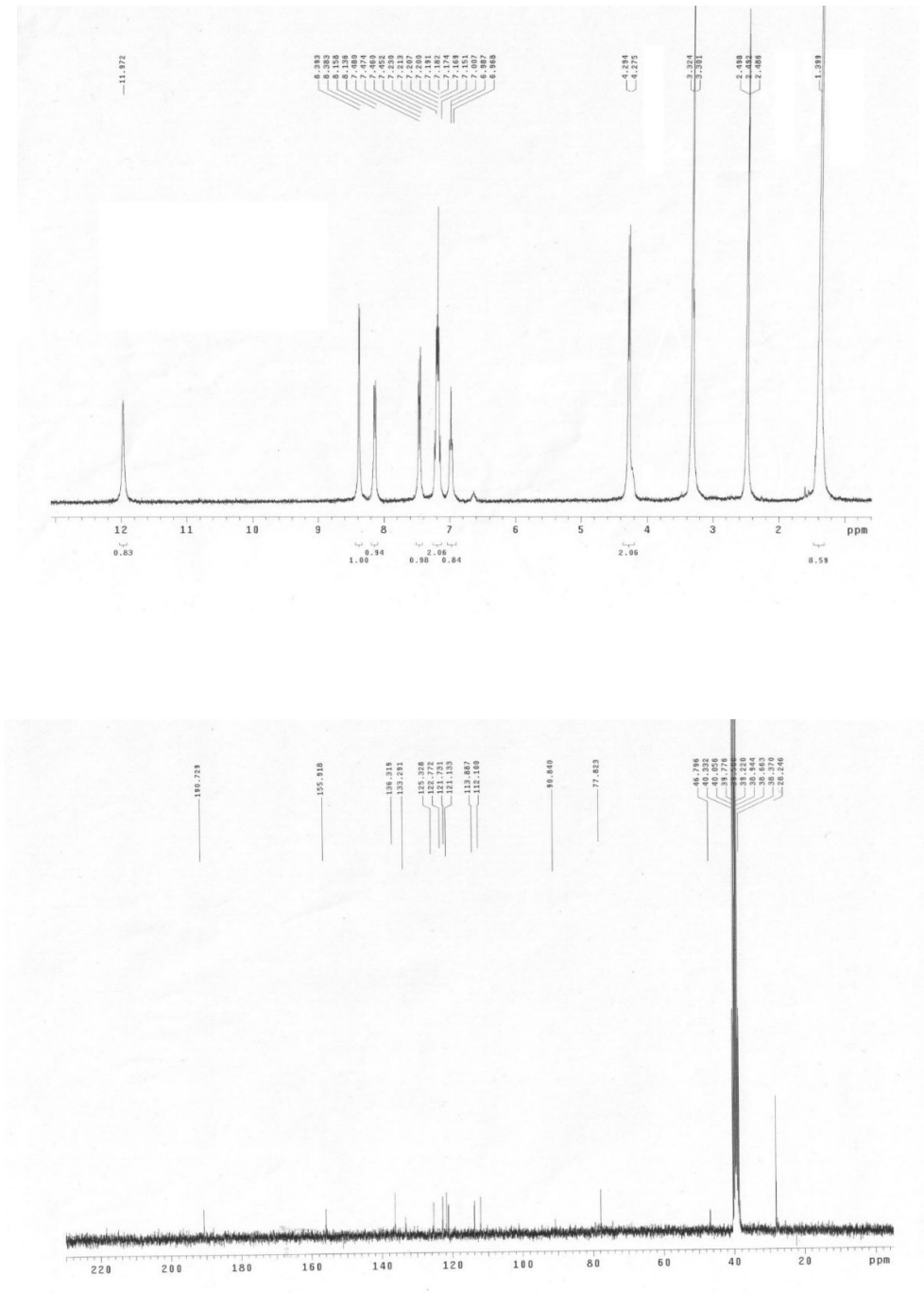

**Figure 10.** NMR spectrum of compound **10**

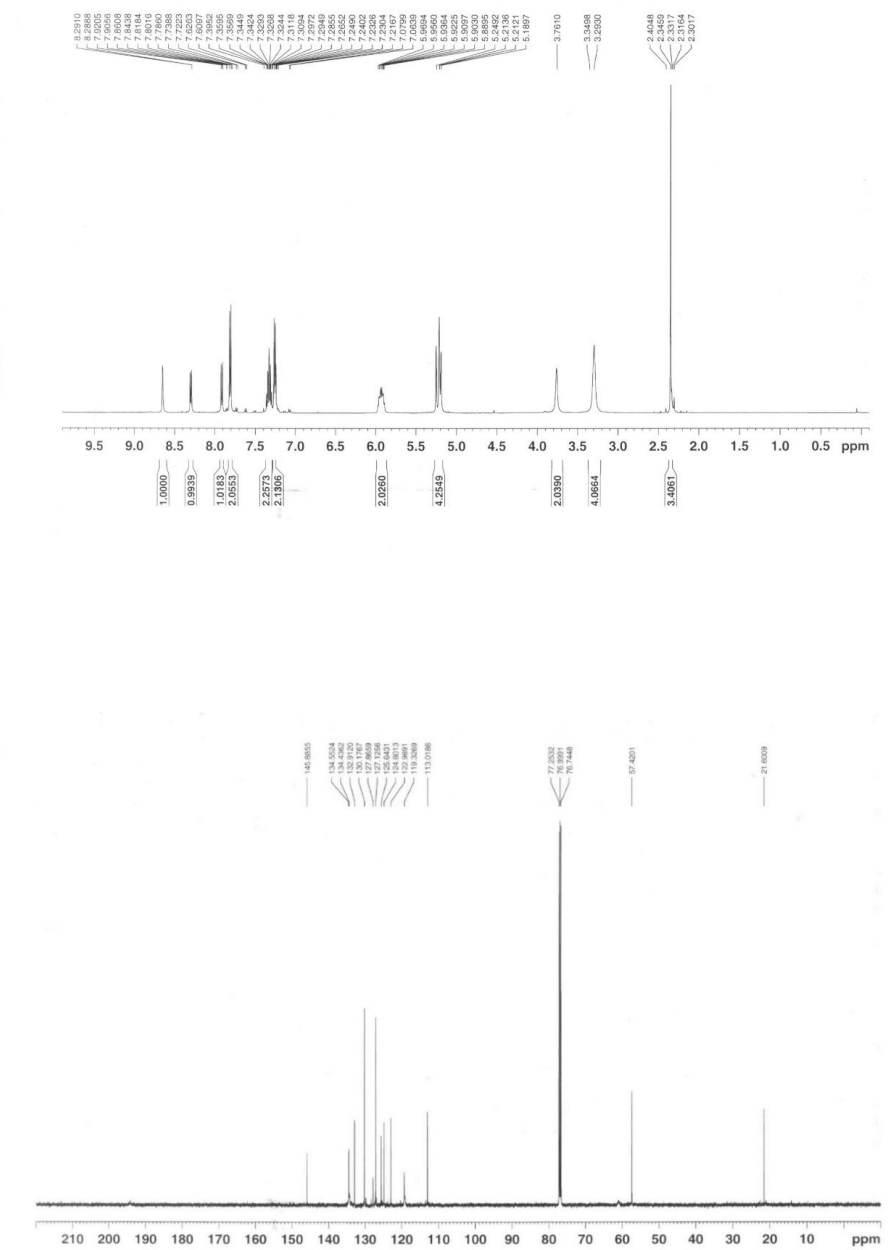

**Figure 11.** NMR spectrum of compound **13**

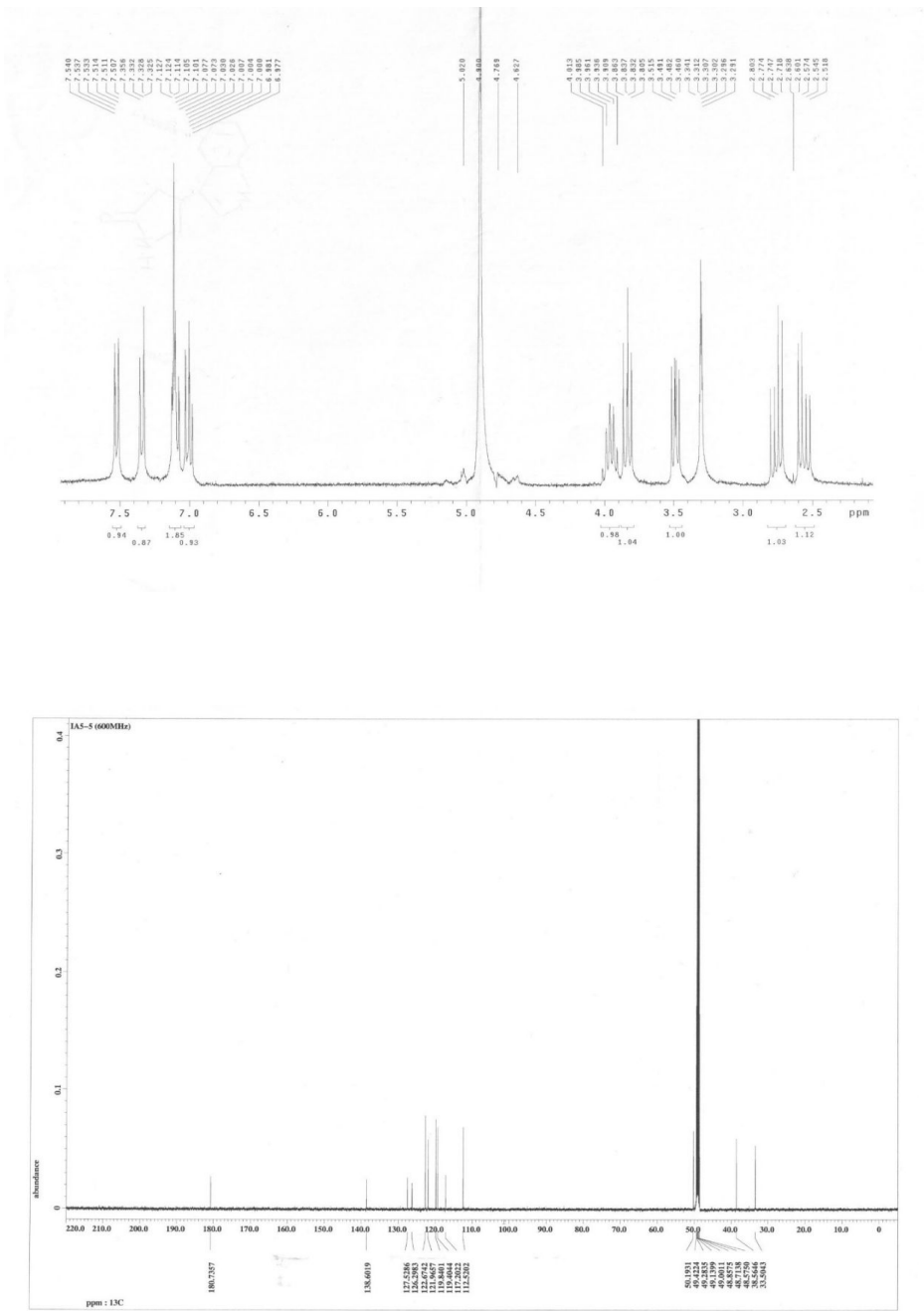


**Figure 12.** NMR of compound **18**

국문초록

# 해양 해면 Irciniidae과에서 분리된 천연물 (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one의 합성

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약학과

천연물과학 전공

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우리나라 남해안 추자도 인근 해역에서 채집된 해면동물로부터 인돌계 알칼로이드 천연물이 분리되었다. 다양한 분광학적 기법으로 분석한 결과 해당 천연물의 구조는 (*S*)-4-(1H-indol-3-yl)-3-methyl-1-(2-methylbutyl)-1H-pyrrol-2(5H)-one으로 밝혀졌다. 그러나 분광학적 기법만으로는 해당 물질의 정확한 입체구조를 증명하기엔 부족하였다.

이러한 단점을 보완하기 위해 유기합성을 통하여 해당 물질을 만들고 합성물과 천연물의 분광학적 자료들을 비교하여 입체구조를 규명하기로

하였다. 해당 물질의 레트로 합성을 통하여 일단 물질의 인돌 부분과 락탐 부분으로 나눠서 따로 합성한 다음 이들을 첨가 반응으로 붙이기로 하였다. 그러나 다양한 시도에도 불구하고 이 접근 방법은 성공하지 못하였다.

이에 다음으로 전체 구조에서 락탐 부분을 인돌에 연결되어 있는 선형 구조를 고리화 반응을 통하여 합성하는 방법을 시도하였다. 하지만 이 방법을 실행하기 위하여 여러 가지 반응 계획이 시도되었지만 해당 물질을 합성하는 데에 이르지는 못하였다. 따라서 해당 물질을 성공적으로 합성하기 위해서는 새로운 접근방법이 요구될 것으로 보인다.

주요어: 해면동물, 인돌 알칼로이드, 유기합성

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