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Divergent Two-Step Total Synthesis of Sclerotioloid A and B

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

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A two-step divergent total synthesis of the structurally unique N-propargylated alkaloids sclerotioloid A and sclerotioloid B has been achieved. The synthesis relies on a robust aldol-propargylation domino reaction yielding the key divergent intermediate. Single crystal x-ray structure studies of the natural product sclerotioloid A shows that it exists as a helically chiral racemate in the solid state.

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Divergent Two-Step Total Synthesis of Sclerotioloid A and B

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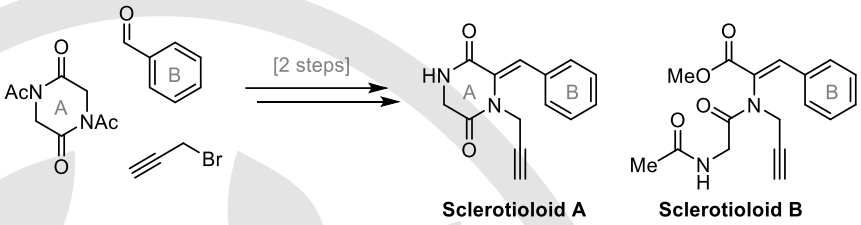
Click here to insert a dedication.



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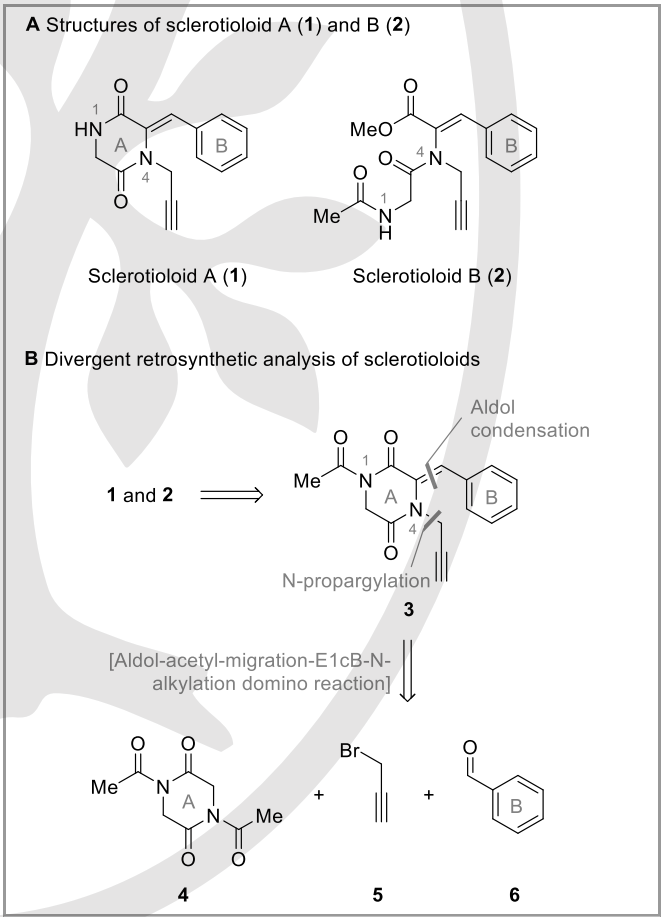
Abstract A two-step divergent total synthesis of the structurally unique N-propargylated alkaloids sclerotioloid A and sclerotioloid B has been achieved. The synthesis relies on a robust aldol-propargylation domino reaction yielding the key divergent intermediate. Single crystal x-ray structure studies of the natural product sclerotioloid A shows that it exists as a helically chiral racemate in the solid state.

Key words Alkaloids, natural products, total synthesis, domino reaction

2,5-Diketopiperazines are an abundant class of alkaloids with a broad range of biological activities.[1] Recently, an unusual 2,5-diketopiperazine substitution pattern was observed in sclerotioloid A (**1**) and its seco form sclerotioloid B (**2**), both alkaloids having been isolated from the marine fungus *Aspergillus sclerotiorum* ST0501 in 2023 (Scheme 1A).[2] Namely, sclerotioloids A (**1**) and B (**2**) represent the first natural isolates to contain an *N*-propargyl motif. This is in stark contrast to other known terminal acetylide natural products, which are common motifs in fungal secondary metabolites.[3] Furthermore, we expected the highly congested benzylidene motif of sclerotioloid A (**1**) to be significantly folded, rendering sclerotioloid A helically chiral. While helically chiral molecules are well-established in catalysis and nanoscience, they are rare in the realm of alkaloids and in particular alkaloids of such low molecular weight as sclerotioloids.[4,5] Intrigued by these structural features, we targeted the total synthesis of sclerotioloid A (**1**) and B (**2**).

To gain synthetic access to these natural products, we considered the diketopiperazine imide **3** as a potential point of divergence (Scheme 1B) with N-deacetylation of the imide **3** giving sclerotioloid A (**1**) and methanolysis of ring A giving sclerotioloid B (**2**). The side chains of the divergent intermediate **3** were envisioned to be disconnected by N-alkylation and aldol condensation to reveal *N*,*N*'-diacetyl glycine anhydride (**4**), propargyl bromide (**5**) and benzaldehyde (**6**) (Scheme 1B) as the starting materials.



Scheme 1 A: Structure of sclerotioloid A (**1**) and B (**2**). B: Divergent retrosynthesis of sclerotioloid A (**1**) and B (**2**).

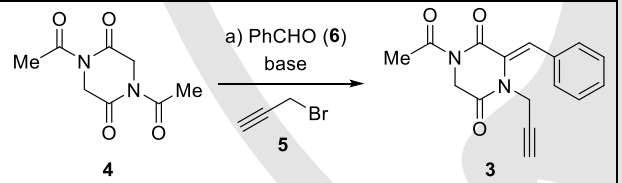
The synthesis plan requires differentiation of the ketopiperazine **3** nitrogens N4 and N1. In particular, the alkylation must be achieved on the sterically more congested N4 amide flanking the *Z*-benzylidene motif. Such proximal differentiation can be achieved by an aldol–acyl migration–E1cB domino reaction

which has precedence in diacetylated ketopiperazines.[6] In 2016, the groups of Li and Liu developed a one-pot method using this chemistry to access 1,3,6-trisubstituted 3,6-diunsaturated (3*Z*,6*Z*)-2,5-diketopiperazine derivatives (of type **10**, Scheme 2).[7] The method involved heating (95 °C) aryl aldehydes, diacetyl glycine anhydride and allyl bromide in the presence of Cs_2CO_3 and 3 Å molecular sieves in DMF. This method provided a highly promising starting point for our synthesis, as the Li–Liu sequence could potentially be interrupted at mono-aldol stage and deployed using propargyl bromide instead of allyl bromide to achieve a one-step synthesis of the divergent intermediate **3**.

In the synthetic direction, we attempted to employ the Li–Liu conditions to our system but opted to run the reaction at room temperature and with only 1.1 equiv. of benzaldehyde (**6**) to favor the mono-aldol product. Exposing *N*,*N*'-diacetyl glycine anhydride (**4**, 1.0 equiv.) to benzaldehyde (**6**, 1.1 equiv.), Cs_2CO_3 (2.5 equiv.), propargyl bromide (**5**, 5.0 equiv.) and 3 Å molecular sieves in anhydrous DMF at room temperature gratifyingly led to the desired aldol–acetyl–migration–E1cB–N-alkylation domino reaction (*via* **7** → **8** → **9** → **3**) delivering **3** as a highly crystalline solid in a 58% yield over 2 hours (Table 1, Entry 1).[8,9] Using alternative bases, such as Na_2CO_3 and K_2CO_3 resulted in lower yields and longer reaction times (30%, 23 h and 51%, 24 h respectively) (Table 1, Entries 2 and 3). We also noted that when the molecular sieves were not freshly activated, the yield dropped significantly to 28%, although full conversion to the aldol condensation product **9** was observed by TLC. Attempts at improving the yield by heating the reaction mixture to 60°C led to complex mixtures based on TLC – presumably starting to favor the double-aldol product **10**.

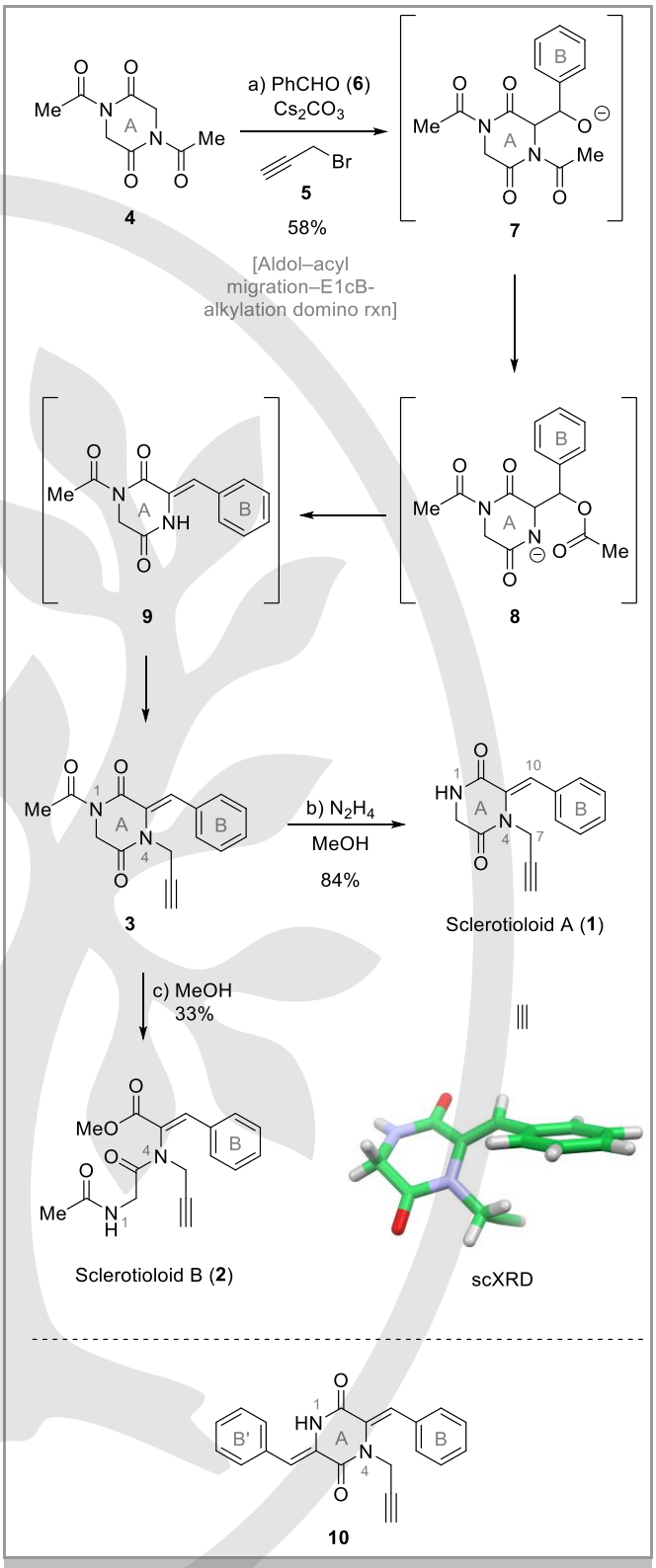
The key divergent intermediate **3** was now accessible in a single step from commercially available starting materials and set the stage for completing the total syntheses. First focusing on sclerotioloid A (**1**), the N1 acetyl group of imide **3** was removed using hydrazine hydrate to give sclerotioloid A (**1**) in 84% yield after flash purification (Scheme 1).[10,11] The spectroscopic data for the thus obtained synthetic sclerotioloid A (**1**) were identical to those reported for the isolated material.[2]

Table 1 Optimization of synthesis of **3**.



Entry	Base	Notes	Time (h)	Yield (%)[b]
1	Cs_2CO_3	–	2 h	58%
2	Na_2CO_3	–	23 h	30%
3	K_2CO_3	–	24 h	51%
4	Cs_2CO_3	MS not freshly activated	2 h	28%

[a] Reaction carried out on a 1.0 mmol scale, base (2.5 equiv.), **4** (1.0 equiv.), **5** (5.0 equiv.), **6** (1.1 equiv.), DMF, rt. [b] Isolated yields after flash column chromatography.

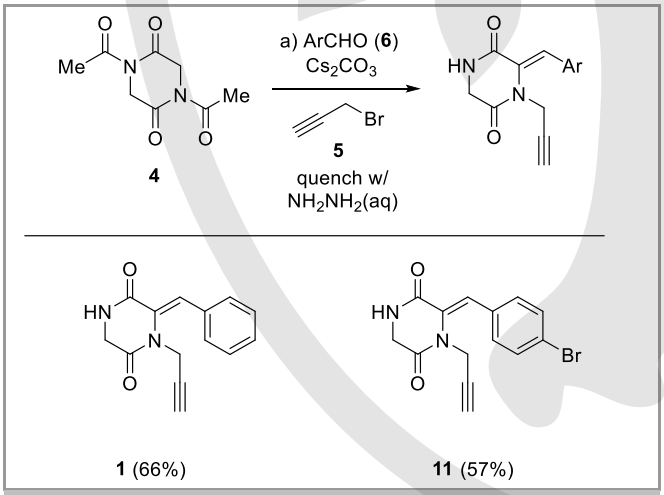


Scheme 2 Total synthesis of sclerotioloid A (**1**) and sclerotioloid B (**2**) and hypothetical mechanism of the domino reaction. a) **4** (1.0 equiv.) PhCHO (**6**, 1.1 equiv.), Cs_2CO_3 (2.5 equiv.), propargyl bromide (**5**, 5.0 equiv.), 3 Å MS (425 wt-%), DMF, rt, 2 h, 58%. b) Hydrazine hydrate (80% aq. solution, 20 equiv.), MeOH, rt, 5 min, 84% c) MeOH (anhydrous), 50 °C, 2 days, 33%.

We then approached the synthesis of sclerotioloid B (**2**) from the divergent intermediate **3**. This would require the ring A C2 carbonyl of the imide **3** to react with methanol as opposed to the N–Ac group. Attempted methanolysis of the ring A of **3** with refluxing MeOH and 0.1 equiv. of *p*-toluenesulfonic acid as a catalyst resulted simply in the deacetylation of the material, giving **1** in 57% yield in 2 hours. Under milder conditions, just heating at 50 °C with methanol, a similar deacetylation to **1** occurred but more slowly – taking several days to complete. Re-evaluating our stance, we recognized that trace amounts of water could function as a competing nucleophile to methanol and attack the undesired N–Ac carbonyl of **3**. Following this line of thought, we used anhydrous methanol as the reaction solvent. With this change the desired methanolysis of the diketopiperazine ring A took place, yielding sclerotioloid B (**2**) in 33% yield in conjunction with **1** in 36% yield over 2 days at 50 °C (Scheme 1).[12] The spectroscopic data for the thus obtained synthetic sclerotioloid B (**2**) were identical to those reported for the isolated material.[2]

As hypothesized at the outset of the study, the single crystal X-Ray structure of sclerotioloid A (**1**) (Scheme 2, Inset) showcased significant folding of the benzylidene system with the $\theta_{C7-N4-C3-C10}$ dihedral angle being 39.3°. Also, the diketopiperazine ring of **1** was observed to be in a boat conformer.[13] The highly folded arrangement of the benzylidene and propargyl motifs in **1** result in the crystal lattice comprising of a packing unit of two helical enantiomers *M*-**1** and *P*-**1**, rendering crystalline **1** racemic.[14]

Finally, we attempted a telescoped one-pot synthesis of sclerotioloid A (**1**) by first carrying out the domino reaction followed by quenching with hydrazine hydrate (Scheme 3). This approach yielded sclerotioloid A (**1**) in 66% yield in one-pot. The method was also amenable to facile synthesis of sclerotioloid A derivatives as demonstrated by the synthesis of **11** in 57% yield using *p*-bromobenzaldehyde as the starting material.



Scheme 3 One-pot synthesis of sclerotioloid A (**1**) and sclerotioloid A analogue **11**.

In conclusion, we have achieved a divergent two-step total synthesis of the first reported N-propargylated alkaloids sclerotioloid A (**1**) and sclerotioloid B (**2**) using a domino reaction to construct the divergent intermediate **3**. Considering that sclerotioloid A (**1**) is an entirely unique structure in both the 2,5-diketopiperazine and alkyne alkaloid space, the possible biogenetic origins of this alkaloid warrant further studies.

Funding Information

J.H.S acknowledges funding from Aalto University, FinnCERES and the Research Council of Finland (project 354458).

Acknowledgment

We thank M.Sc. Anton Bannykh and Prof. Petri Pihko for their assistance with the scXRD characterization of **1** and **3**.

Supporting Information

YES.

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(8) (*Z*)-1-acetyl-3-benzylidene-4-(prop-2-yn-1-yl)piperazine-2,5-dione (**3**) A mixture of **4** (200 mg, 1.01 mmol, 1.00 equiv.), Cs_2CO_3 (822 mg, 2.52 mmol, 2.50 equiv.), benzaldehyde (**6**, 0.11 mL, 1.11 mmol, 1.10 equiv., vacuum distilled), propargyl bromide (**5**, 0.38 mL, 5.05 mmol, 5.00 equiv.) and flame-dried 4 Å MS (840 mg, 425 wt-%) in dry DMF (8 mL) was stirred at room temperature for 2 h under argon. The resulting brown suspension was concentrated under reduced pressure followed by addition of DI water (50 mL) and EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The thus obtained crude product was purified using flash column chromatography (SiO_2, 30% EtOAc/Hexane) to yield **3** as a yellow crystalline solid (166 mg, 58%).
R_f (25% EtOAc/Hex): 0.29 (UV, $KMnO_4$). MP: 173.1–174.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (s, 1H), 7.43– 7.36 (m, 5H), 4.56 (s, 2H), 4.27 (d, *J* = 2.5 Hz, 2H), 2.65 (s, 3H), 2.14 (t, *J* = 2.5 Hz, 1H). {^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): 171.6, 164.7, 164.1, 132.5, 130.0, 129.6, 129.05, 128.95, 127.8, 77.0, 73.1, 45.3, 33.8, 26.8. FTIR (ATR, cm^{-1}): 2921,

2851, 1698, 1628, 1354, 1192, 936, 743. HRMS (ESI+): m/z calcd. For $C_{16}H_{14}N_2O_3$ [M+Na+] 305.0897 measured 305.0899.

(9) CCDC 2338001 contains the supplementary crystallographic data for **3**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.

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(11) Sclerotioloid A (**1**) To a stirred suspension of **3** (20 mg, 1.0 equiv.) in MeOH (1 mL) hydrazine hydrate (60 µL, 62 mmol, 80% v/v solution in water, 22 equiv.) was added. The resulting suspension was allowed to stir at room temperature for 5 min. TLC showed full conversion and all material had dissolved. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography (SiO_2, 75% EtOAc/Hexane) to yield sclerotioloid A (**1**) as a white solid (14.3 mg, 84%). Spectroscopic data matched those reported previously.[2]
R_f (25% EtOAc/Hex): 0.29 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (s, 1H), 7.46 – 7.35 (m, 5H), 4.56 (s, 2H), 4.27 (d, *J* = 2.5 Hz, 2H), 2.65 (s, 3H), 2.14 (t, *J* = 2.5 Hz, 1H). {^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): 171.6, 164.7, 164.1, 132.5, 130.0, 129.6, 129.05, 128.95, 127.8, 77.0, 73.1, 45.3, 33.8, 26.8.

(12) Sclerotioloid B (**2**) A solution of **3** (32 mg, 0.113 mmol, 1.00 equiv.) in anhydrous MeOH (2 mL) was stirred at 50 °C for 2 days. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography (SiO_2, EtOAc) to yield sclerotioloid B (**2**) as a white crystalline solid (11.7 mg, 33%). Spectroscopic data matched those reported previously.[2]
R_f (75% EtOAc/Hex): 0.16 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, DMSO-d_6): 8.06 (t, *J* = 5.58 Hz, 1H), 7.85 (s, 1H), 7.75 (d, *J* = 1.2 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.45 – 7.50 (m, 3H), 4.38 (dd, *J* = 17.6 Hz, 2.6 Hz, 1H), 4.25 (dd, *J* = 17.6 Hz, 2.6 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 17.0 Hz, 5.7 Hz, 1H), 3.56 (dd, *J* = 17.0 Hz, 5.6 Hz, 1H), 3.14 (t, *J* = 2.6 Hz, 1H), 1.77 (s, 3H). {^{1}H}^{13}C NMR (101 MHz, DMSO-d_6): 169.3, 168.7, 164.7, 139.7, 131.8, 131.3, 130.5, 129.1, 126.9, 77.8, 76.1, 52.8, 40.7, 35.8, 22.2.

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(14) CCDC 2338002 contains the supplementary crystallographic data for **1**.

Supporting Information

Divergent Two-Step Total Synthesis of Sclerotioloid A and B

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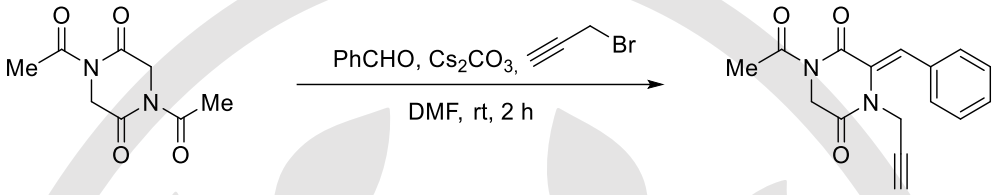
Contents

1 General Procedures

All reactions were carried out in non-dried glassware open to air and at room temperature (22 °C) unless otherwise noted. Solvents and reagents were used as obtained from the supplier unless otherwise noted. Analytical TLC was performed using Merck silica gel 60G F_{254} plates and analyzed by UV light or by staining upon heating with ninhydrin solution (0.3 g of ninhydrin, 3 mL AcOH, 100 mL EtOH), iodine (I_2 in powdered silica gel) or potassium permanganate solution (1.0 g $KMnO_4$, 2.0 g Na_2CO_3, 100 mL DI H_2O). For flash chromatography purifications, silica (RediSep Rf Gold, spherical silica 20–40 µm) and p.a. grade solvents were used with Combi*Flash* NextGen 300 automated chromatography unit. The NMR spectra were recorded in $CDCl_3$ and *d*6-DMSO on a Bruker Avance 400 spectrometer. The chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ 7.26) and DMSO (δ 2.50) for ^{1}H NMR and $CDCl_3$ (δ 77.16) and DMSO-d_6 (δ 39.52) for ^{13}C NMR. Melting points (mp) were determined in open capillaries using a Mettler Toledo MT50 melting point apparatus and are uncorrected. High-resolution mass spectrometric data were measured using an Agilent LC-QTOF 6540 working in positive mode using internal calibration. FTIR data was acquired using a Perkin Elmer Spectrum 100 FTIR spectrometer with an ATR attachment. Structures were assigned based on *J*-coupling constant data, 135-DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, and ^{1}H-^{1}H NOESY.

2 Synthetic Procedures

1.1 (*Z*)-1-Acetyl-3-benzylidenepiperazine-2,5-dione (3)



A mixture of *N*,*N*'-diacetylglycine anhydride (**4**, 200 mg, 1.01 mmol, 1.00 equiv.), Cs_2CO_3 (822 mg, 2.52 mmol, 2.50 equiv.), benzaldehyde (**6**, 0.11 mL, 1.11 mmol, 1.10 equiv., vacuum distilled prior to use), propargyl bromide (**5**, 0.38 mL, 5.05 mmol, 5.00 equiv.) and flame-dried 4 Å MS (840 mg) in dry DMF (8 mL) was stirred at room temperature for 2 h under argon. The resulting brown suspension was concentrated under reduced pressure followed by addition of DI water (50 mL) and EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The thus obtained crude product was purified using flash column chromatography (SiO_2, 30% EtOAc/Hexane) to yield **3** as a yellow crystalline solid (166 mg, 58%).

***R*f** (25% EtOAc/Hex): 0.29 (UV).

MP: 173.1–174.0 °C.

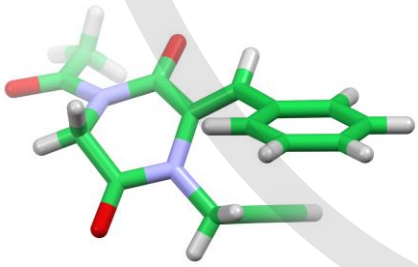
^{1}H NMR (400 MHz, $CDCl_3$): 7.46 – 7.44 (m, 1H), 7.46 – 7.35 (m, 5H), 4.56 (s, 2H), 4.27 (d, *J* = 2.5 Hz, 2H), 2.65 (s, 3H), 2.14 (t, *J* = 2.5 Hz, 1H).

{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): 171.6, 164.7, 164.1, 132.5, 130.0, 129.6, 129.05, 128.95, 127.8, 77.0, 73.1, 45.3, 33.8, 26.8.

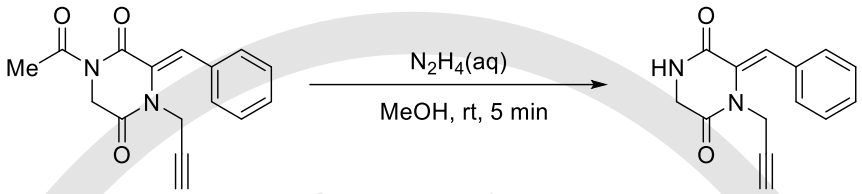
FTIR (ATR, cm^{-1}): 2921, 2851, 1698, 1628, 1354, 1192, 936, 743.

HRMS (ESI+): m/z calcd. For $C_{16}H_{14}N_2O_3$ [M+Na$^+$] 305.0897 measured 305.0899.

scXRD:



1.2 Sclerotioloid A (1)



To a stirred suspension of **3** (20 mg, 1.0 equiv.) in MeOH (1 mL) hydrazine hydrate (60 µL, 62 mmol, 80% v/v solution in water, 22 equiv.) was added. The resulting mixture was allowed to stir at room temperature for 5 min. TLC (EtOAc) showed full conversion. The reaction mixture was concentrated under reduced pressure and purified using flash column chromatography (SiO_2, 75% EtOAc/Hexane) to yield sclerotioloid A (**1**) as a white crystalline solid (14.3 mg, 84%).

***R*f** (EtOAc): 0.56 (UV, $KMnO_4$).

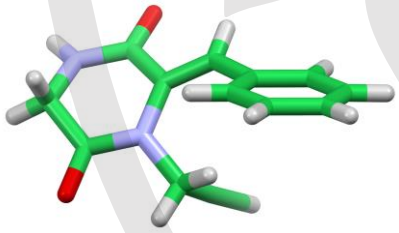
^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (s, 1H), 7.40 – 7.32 (m, 5H), 7.34 (s, 1H), 7.24 (br. s, 1H), 4.26 (d, *J* = 2.5 Hz, 1H), 4.15 (d, *J* = 2.3 Hz, 1H), 2.12 (t, *J* = 2.5 Hz, 1H).

{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): 165.14, 165.10, 133.2, 129.5, 129.3, 128.9, 128.8, 123.8, 77.4, 72.7, 45.5, 34.4.

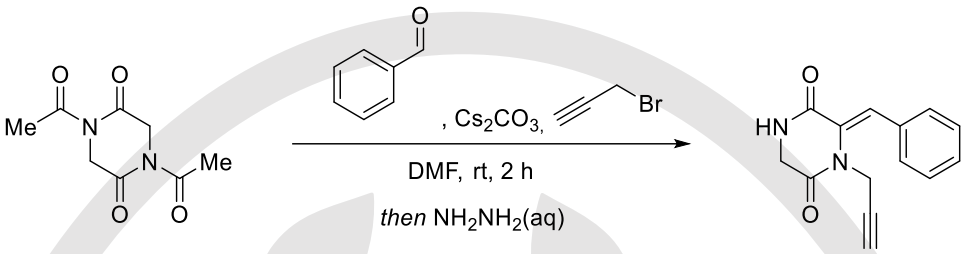
^{1}H NMR (400 MHz, DMSO-d_6): 7.40 – 7.32 (m, 5H), 7.34 (s, 1H), 7.24 (br. s, 1H), 4.26 (d, *J* = 2.5 Hz, 1H), 4.15 (d, *J* = 2.3 Hz, 1H), 2.12 (t, *J* = 2.5 Hz, 1H).

{^{1}H}^{13}C NMR (101 MHz, DMSO-d_6): 165.6, 163.3, 133.3, 129.9, 129.3, 128.7, 128.5, 120.7, 78.2, 74.4, 44.5, 32.9.

scXRD:



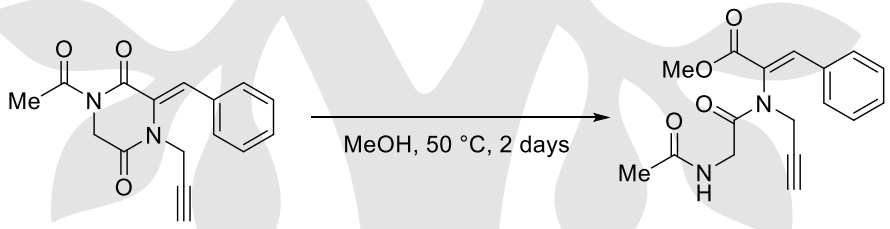
2.1 Sclerotioloid A (1) telescoped protocol



A mixture of *N*,*N*'-diacetylglycine anhydride (**4**, 200 mg, 1.01 mmol, 1.00 equiv.), Cs_2CO_3 (822 mg, 2.52 mmol, 2.50 equiv.), benzaldehyde (**6**, 0.11 mL, 1.11 mmol, 1.10 equiv., vacuum distilled prior to use), propargyl bromide (**5**, 0.38 mL, 5.05 mmol, 5.00 equiv.) and flame-dried 4 Å MS (840 mg) in dry DMF (8 mL) was stirred at room temperature for 2 h under argon. The resulting brown suspension was filtered to remove 4 Å MS and Cs2CO3. The resulting filtrate was transferred to a round bottom flask and hydrazine hydrate (1.26 mL, 20.18 mmol, 80% v/v solution in water, 20 equiv.) was added. The resulting mixture was allowed to stir at room temperature for 3 h. TLC (EtOAc) showed full conversion. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography (SiO_2, 75% EtOAc/Hexane) to yield sclerotioloid A (**1**) as a white crystalline solid (159 mg, 66%).

Spectroscopic data matched those reported in 1.2.

2.2 Sclerotioloid B (2)



A solution of **3** (32 mg, 0.113 mmol, 1.00 equiv.) in anhydrous MeOH (2 mL) was stirred at 50 °C for 2 days under argon. The reaction mixture was concentrated under reduced pressure and purified using flash column chromatography (SiO_2, 100% EtOAc) to yield sclerotioloid B (**2**) as a white crystalline solid (11.7 mg, 33%) and sclerotioloid A (**1**, 9.2 mg, 36%).

***R*f** (75% EtOAc/Hex): 0.16 (UV, $KMnO_4$).

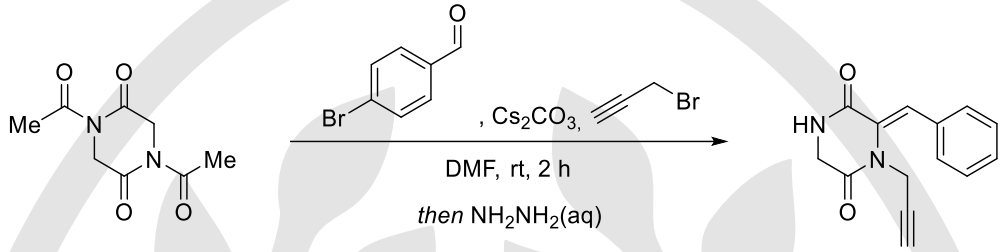
^{1}H NMR (400 MHz, $CDCl_3$): 7.84 (s, 1H), 7.63 – 7.58 (m, 2H), 7.45 – 7.37 (m, 3H), 6.33 (s, 1H), 4.63 (dd, *J* = 17.5, 2.6 Hz, 1H), 4.31 (dd, *J* = 17.5, 2.6 Hz, 1H), 3.91 (dd, *J* = 18.0, 4.2 Hz, 1H), 3.87 (s, 3H), 3.71 (dd, *J* = 18.0, 4.0 Hz, 1H), 2.17 (t, *J* = 2.6 Hz, 1H), 1.96 (s, 3H).

{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): 170.0, 168.9, 165.0, 141.8, 131.8, 131.6, 130.7, 129.4, 126.1, 77.0, 74.1, 53.1, 42.1, 36.8, 23.1.

^{1}H NMR (400 MHz, DMSO-d_6): 8.06 (t, *J* = 5.6 Hz, 1H), 7.85 (s, 1H), 7.75 (d, *J* = 1.2 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.45 – 7.50 (m, 3H), 4.38 (dd, *J* = 17.6 Hz, 2.6 Hz, 1H), 4.25 (dd, *J* = 17.6 Hz, 2.6 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 17.0 Hz, 5.7 Hz, 1H), 3.56 (dd, *J* = 17.0 Hz, 5.6 Hz, 1H), 3.14 (t, *J* = 2.6 Hz, 1H), 1.77 (s, 3H).

{^{1}H}^{13}C NMR (101 MHz, DMSO-d_6): 169.3, 168.7, 164.7, 139.7, 131.8, 131.3, 130.5, 129.1, 126.9, 77.8, 76.1, 52.8, 40.7, 35.8, 22.2.

2.3 (*Z*)-6-(4-bromobenzylidene)-1-(prop-2-yn-1-yl)piperazine-2,5-dione (11)



A mixture of *N*,*N*'-diacetylglycine anhydride (**4**, 0.25 g, 1.26 mmol, 1.00 equiv.), Cs_2CO_3 (1.03 g, 3.15 mmol, 2.50 equiv.), 4-bromobenzaldehyde (0.26 g, 1.40 mmol, 1.10 equiv.), propargyl bromide (**5**, 0.48 mL, 6.31 mmol, 5.00 equiv.) and flame-dried 4 Å MS (840 mg) in dry DMF (10 mL) was stirred at room temperature for 24 h under argon. The resulting brown suspension was filtered to remove 4 Å MS and Cs_2CO_3. The resulting filtrate was transferred to a round bottomed flask and hydrazine hydrate (1.53 mL, 25 mmol, 80% v/v solution in water, 20 equiv.) was added. The resulting mixture was allowed to stir at room temperature for 3 h. TLC (EtOAc) showed full conversion. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography (SiO_2, 5% MeOH/DCM) to yield derivative **11** as a thick yellow oil (230 mg, 57%).

R$_f$ (EtOAc): 0.60 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.47 (br. s, 1H), 4.26 (d, *J* = 2.5 Hz, 2H), 4.14 (d, *J* = 2.3 Hz, 2H), 2.14 (t, *J* = 2.5 Hz, 1H).

{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): 164.9, 164.3, 132.1, 131.0, 129.2, 123.5, 122.5, 77.1, 73.1, 45.6, 34.5.

FTIR (ATR, cm^{-1}): 3280, 1681, 1631, 1485, 1433, 1403, 1378, 1321, 1177, 1110, 1070, 896, 723, 682, 638, 544.

HRMS (ESI+): m/z calcd. For $C_{14}H_{11}BrN_2O_2$ [M+H$^+$] 319.0077 measured 319.0078.

3 NMR Comparison of Sclerotioloid A (1) to Isolated Material

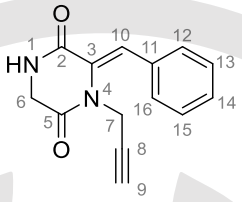


Table S1. Comparison of NMR data for isolated and synthetic Sclerotioloid A (**1**) in DMSO-d_6.

Atom No.	Isolated (1)		Synthetic (1)		ΔC (ppm)
	H	C	H	C	
1	8.42 (s, 1H)	–	8.41 (s, 1H)	–	–
2	–	163.4	–	163.3	0.1
3	–	129.9	–	129.9	0.0
4	–	–	–	–	–
5	–	165.7	–	165.6	0.1
6	4.01 (d, *J* = 2.4 Hz, 2H)	44.5	4.10 (d, *J* = 2.3 Hz, 2H)	44.5	0.0
7	4.13 (d, *J* = 2.4 Hz, 2H)	32.9	4.13 (d, *J* = 2.4 Hz, 2H)	32.9	0.0
8	–	78.2		78.2	0.0
9	3.10 (t, *J* = 2.4 Hz, 1H)	74.5	3.09 (t, *J* = 2.4 Hz, 1H)	74.4	0.1
10	7.10 (s, 1H)	120.8	7.10 (s, 1H)	120.7	0.1
11	–	133.4	–	133.3	0.1
12		128.6		128.6	0.0
13		129.4		129.3	0.1
14	7.35–7.40 (m, 5H)	128.8	7.35–7.40 (m, 5H)	128.7	0.1
15		129.4		129.3	0.1
16		128.6		128.6	0.0

4 NMR Comparison of Sclerotioloid B (2) to Isolated Material

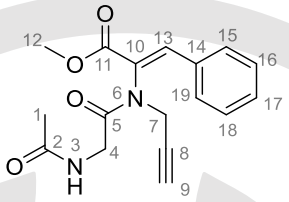


Table S2. Comparison of NMR data for isolated and synthetic Sclerotioloid B (**2**) in DMSO-d_6.

Atom No.	Isolated (2)		Synthetic (2)		ΔC (ppm)
	H	C	H	C	
1	1.77 (s, 3H)	21.9	1.77 (s, 3H)	22.2	0.3
2	–	169.0	–	169.3	0.3
3	8.06 (s, 1H)	–	8.06 (t, *J* = 5.58 Hz, 1H)	–	–
4	3.56 (dd, *J* = 17.0 Hz, 5.7 Hz, 1H), 3.66 (dd, *J* = 17.1 Hz, 5.7 Hz, 1H)	40.4	3.56 (dd, *J* = 17.0 Hz, 5.6 Hz, 1H) 3.67 (dd, *J* = 17.0 Hz, 5.7 Hz, 1H)	40.7	0.3
5	–	168.4	–	168.7	0.3
6	–	–	–	–	–
7	4.24 (dd, *J* = 17.6 Hz, 2.5 Hz, 1H) 4.38 (dd, *J* = 17.5 Hz, 2.5 Hz, 1H)	35.5	4.25 (dd, *J* = 17.6 Hz, 2.6 Hz, 1H) 4.38 (dd, *J* = 17.6 Hz, 2.6 Hz, 1H)	35.8	0.3
8	–	77.5	–	77.8	0.3
9	3.15 (s, 1H)	75.8	3.14 (t, *J* = 2.6 Hz, 1H)	76.1	0.3
10	–	126.6	–	126.9	0.3
11	–	164.5	–	164.7	0.2
12	3.81 (s, 3H)	52.5	3.81 (s, 3H)	52.8	0.3
13	7.84 (s, 1H)	139.5	7.85 (s, 1H)	139.7	0.2
14	–	131.5	–	131.8	0.3
15	7.75 (s, 1H)	130.2	7.75 (d, *J* = 1.2 Hz, 1H)	130.5	0.3
16	7.46 (d, *J* = 7.6 Hz, 1H)	128.8	7.45 – 7.50 (m, 3H)	129.1	0.3
17	7.49 (d, *J* = 6.9 Hz, 1H)	131.0		131.3	0.3
18	7.46 (d, *J* = 7.6 Hz, 1H)	128.8		129.1	0.3
19	7.73 (s, 1H)	130.2	7.73 (d, *J* = 1.8 Hz, 1H)	130.5	0.3

5 scXRD report for 1 and 3

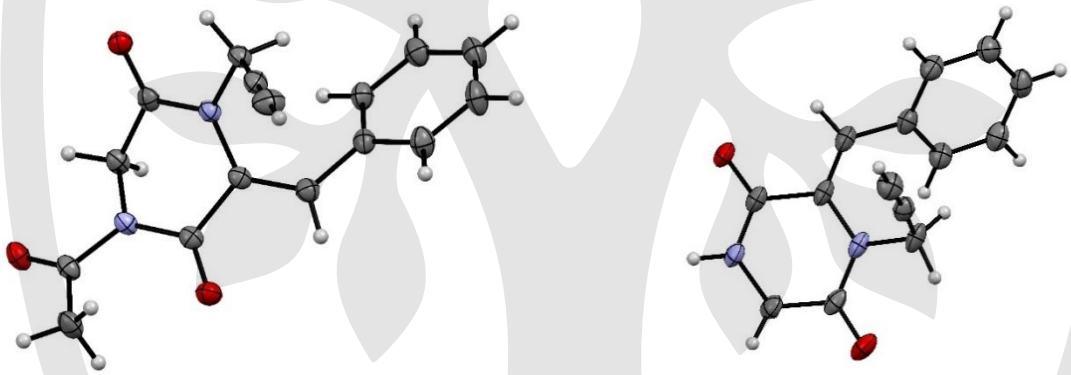
Single-crystal X-ray diffraction analyses were performed at 120 K on Agilent SuperNova, Dualflex, HyPix-Arc 100 and Rigaku XtaLAB Synergy R with CuKα (λ = 1.54184 Å) radiation. Crystals were obtained by slow cooling of hot acetone solution of **3** and evaporation from $CDCl_3$ of **1**, then suspended in protective oil and were mounted on MiTeGen loop for measurement. The data reduction and absorption corrections were made by program CrysAlisPro[1]. The structures were solved by using SHELXT[2] in OleX 2-1.5[3] and refined with SHELXL[4]. All non-hydrogen atoms were refined anisotropicaly. The hydrogen atoms were calculated to their idealised positions as riding atoms with isotropic thermal parameters as 1.2 × C for C(H) and C(H,H) and 1.2 × C for the C(H,H,H) for **3** and 1.2 x N for amide nitrogen for **1**. The structures were drawn with Mercury[5]. Crystallographic data was deposited with the accession numbers **2338001** and **2338002** can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Table S3. Crystallographic data

Compound	**3**	**1**
CCDC deposition number	2338001	2338002
Empirical formula	$C_{16}H_{14}N_2O_3$	$C_{14}H_{12}N_2O_2$
Formula weight	282.29	240.26
Temperature (K)	119.8(4)	120.00(10)
Crystal system, space group	Triclinic, P-1	Monoclinic, $P2_1/n$
a, b, c (Å)	8.6786(3), 9.0117(2), 9.5238(3)	9.5832(2), 12.0168(2), 11.0539(2)
α, β, γ (°)	82.592(2), 72.214(3), 78.865(2)	90, 102.493(2), 90
Volume (Å^3)	693.94(4)	1242.82(4)
Z	2	4
ρ_{calc} (g/cm^3)	1.351	1.284
μ (mm^{-1})	0.780	0.715
F(000)	296.0	504.0
Crystal size (mm^3)	0.234 × 0.176 × 0.076	0.271 × 0.181 × 0.065
Diffractometer	Agilent SuperNova, Dualflex	Rigaku XtaLAB Synergy R
Detector	HyPix-Arc 100	HyPix-Arc 100
Radiation	Cu Kα (λ = 1.54184)	Cu Kα (λ = 1.54184)
2Θ range for data collection (°)	9.78 to 152.784	11.02 to 158.276
Index ranges	-10 ≤ h ≤ 10, -10 ≤ k ≤ 11, -11 ≤ l ≤ 8	-12 ≤ h ≤ 11, -15 ≤ k ≤ 15, -10 ≤ l ≤ 14

[1] CrysAlisPro 1.171.42.80a, **2023**, Rigaku Oxford Diffraction.
[2] Sheldrick, G.M. (**2015**). *Acta Cryst*. A71, 3-8.
[3] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (**2009**), *J. Appl. Cryst*. 42, 339-341.
[4] Sheldrick, G.M. (**2015**). *Acta Cryst*. C71, 3-8.
[5] Mercury 2022.3.0 (Build 364735).

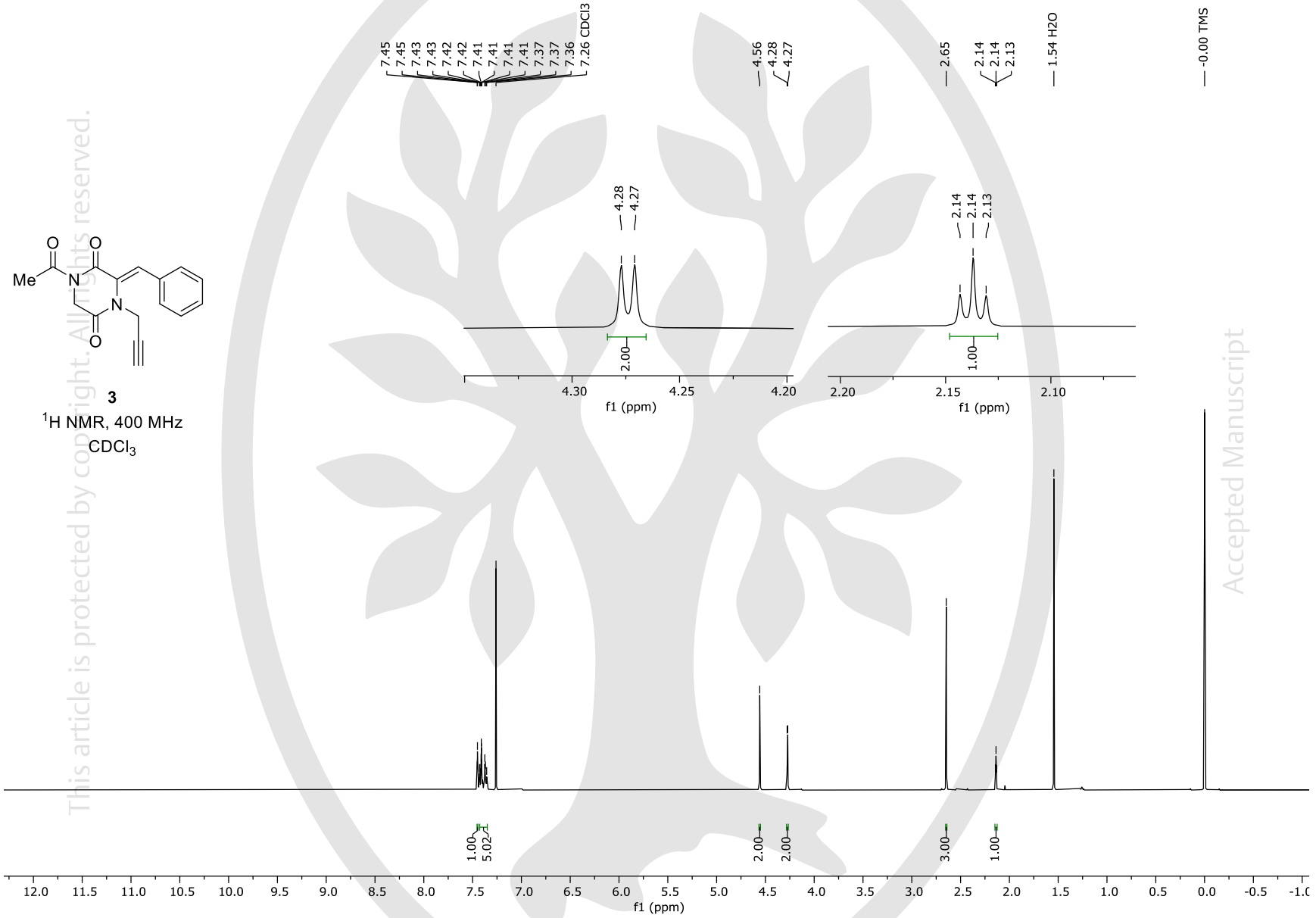
Reflections collected	8347	12381
Independent reflections	2844 [R_{int} = 0.0189, R_{sigma} = 0.0205]	2690 [R_{int} = 0.0239, R_{sigma} = 0.0199]
Data/restraints/parameters	2844/0/191	2690/0/167
Goodness-of-fit on F^2	1.068	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0337, wR_2 = 0.0880	R_1 = 0.0345, wR_2 = 0.0901
Final R indexes [all data]	R_1 = 0.0354, wR_2 = 0.0894	R_1 = 0.0373, wR_2 = 0.0921
Largest diff. peak/hole (e Å^{-3})	0.22/-0.24	0.20/-0.21
Absorption correction	Multi-scan, CrysAlisPro 1.171.42.80a (Rigaku Oxford Diffraction, 2023). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.85768, 1.00000	0.88305, 1.00000
R_{int}	0.0189	0.0239

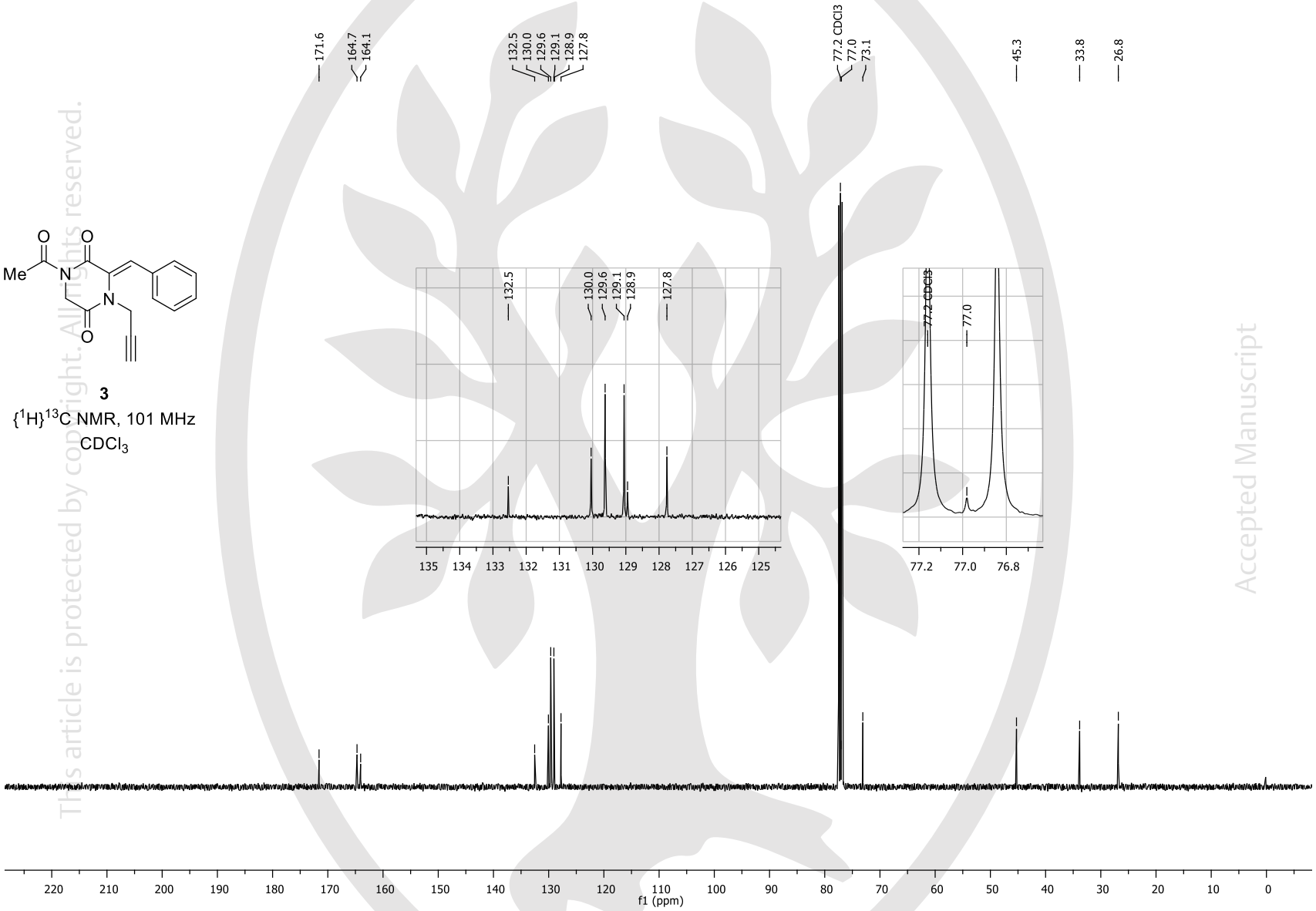


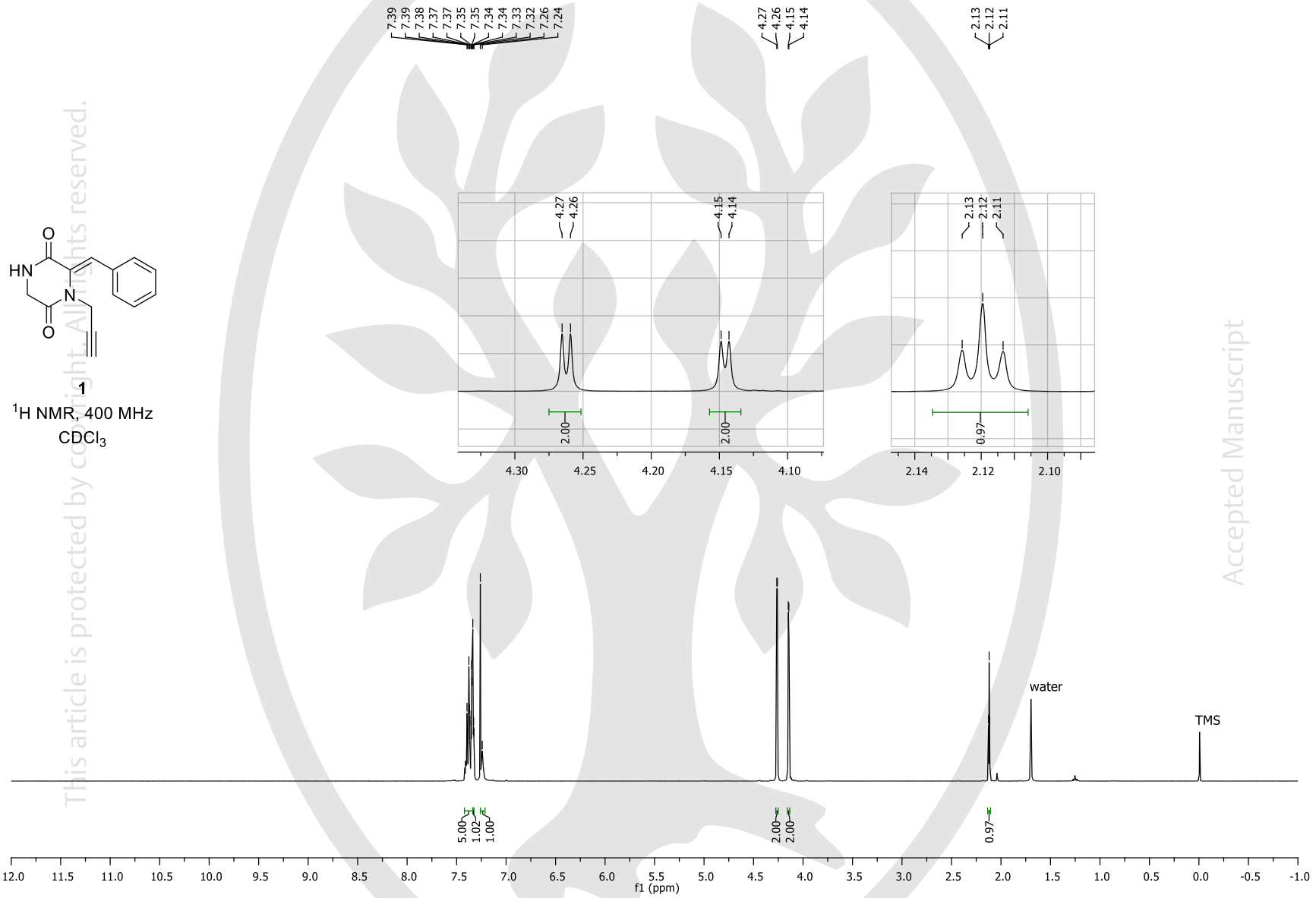
3 **1**

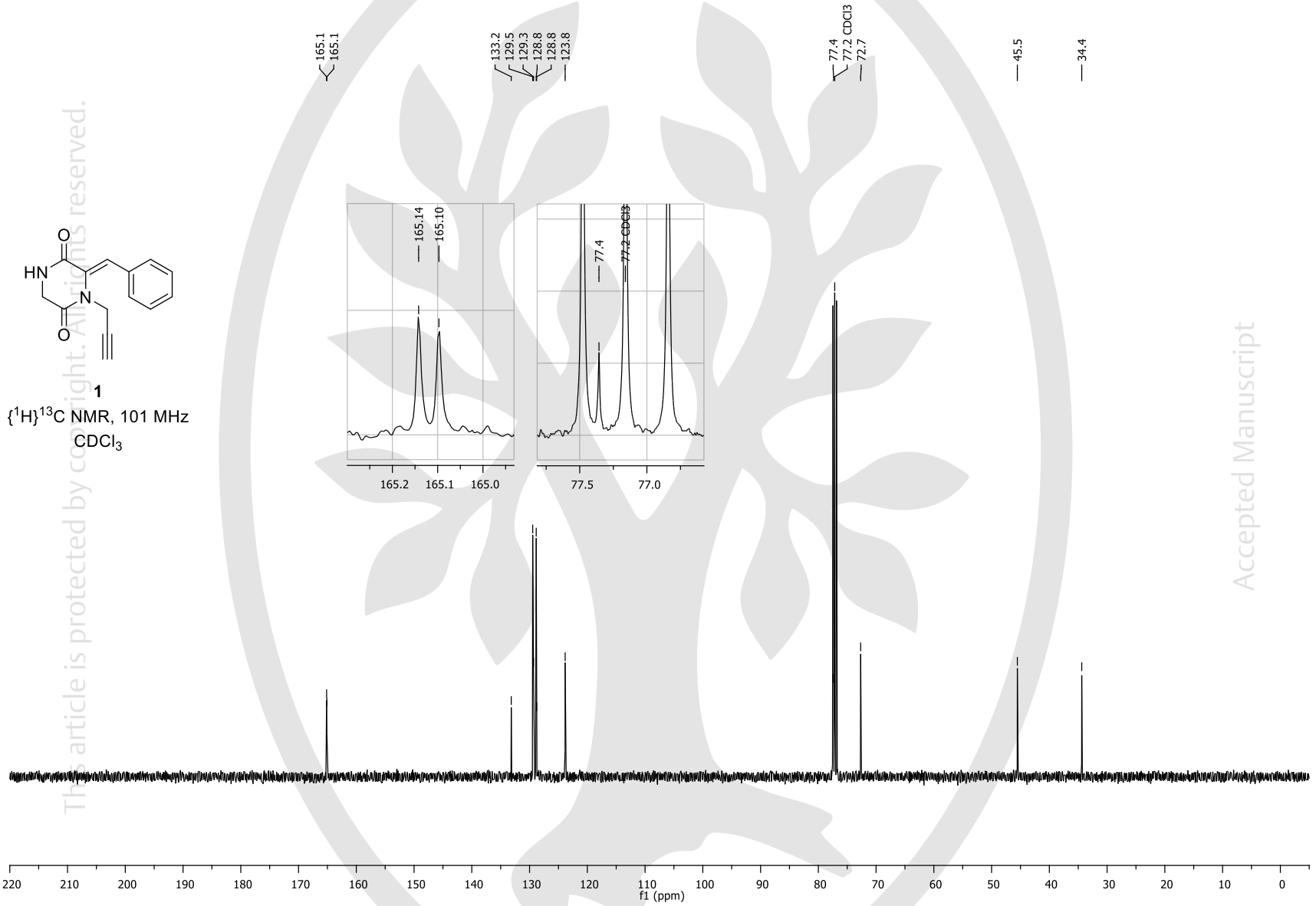
Figures S1 and S2. The ORTEP plots of **3** and **1.** The thermal displacement parameters are shown at 50% probability level.

6 Spectral data





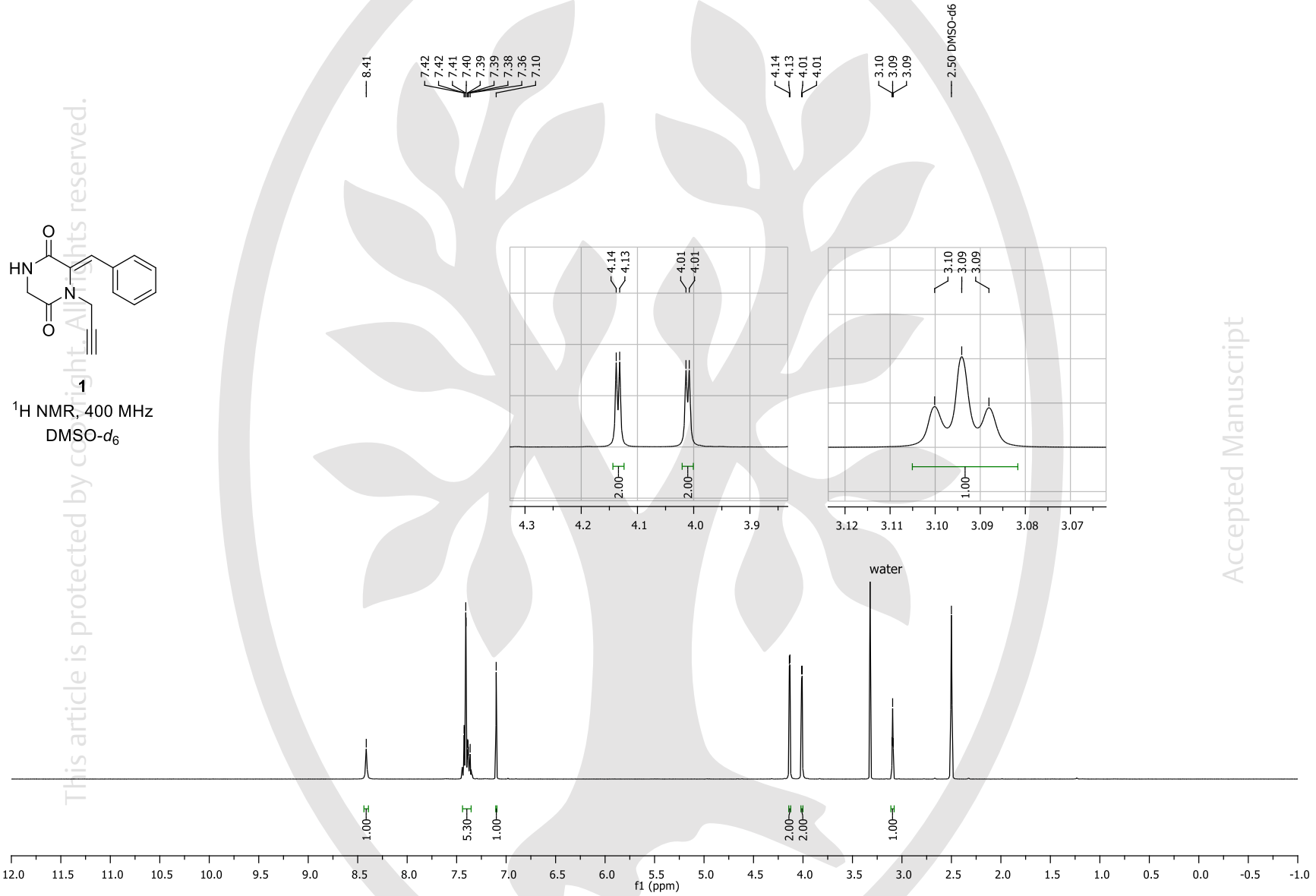




1

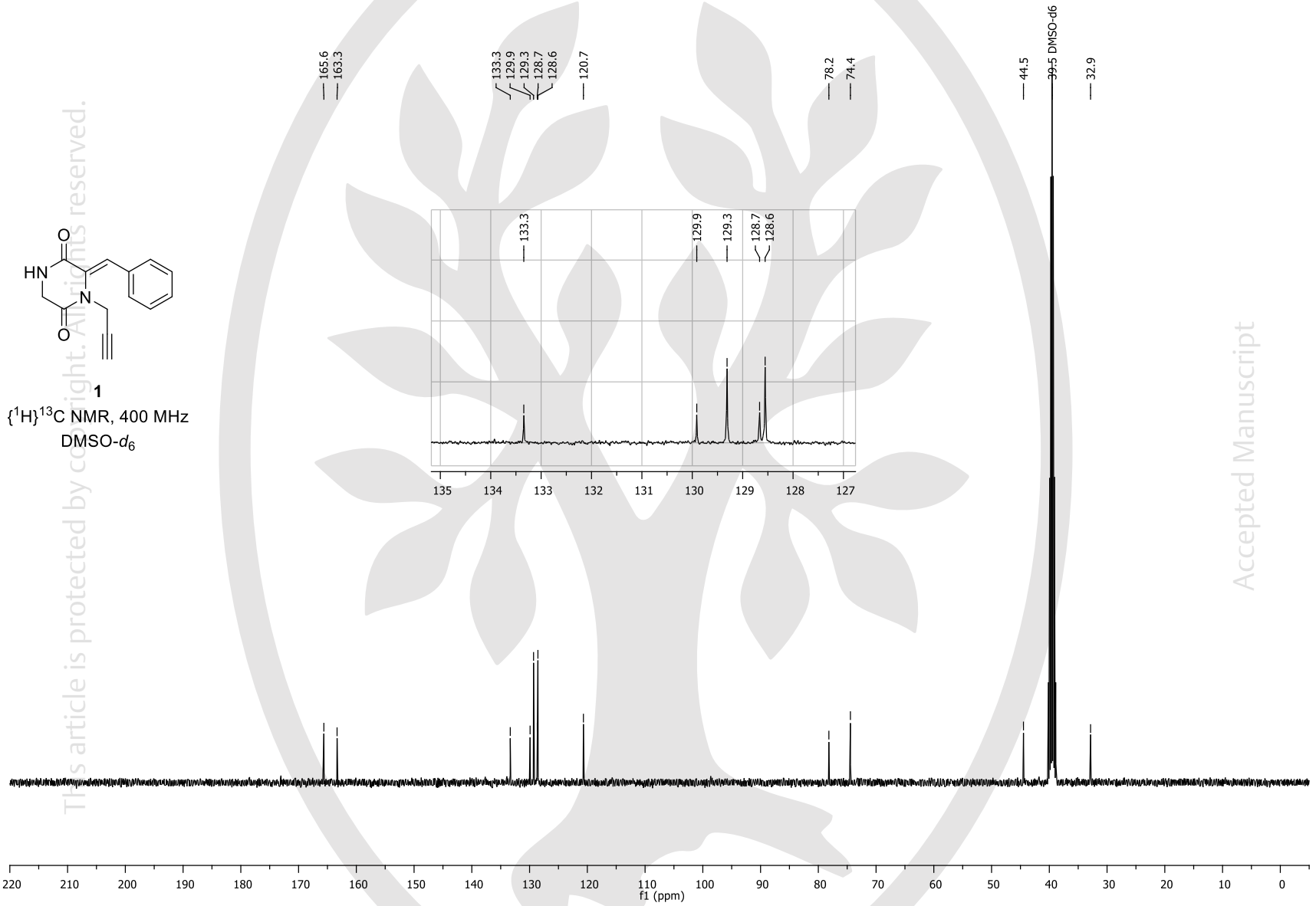
$\{^1H\}^{13}C$ NMR, 101 MHz

$CDCl_3$



1

^{1}H NMR, 400 MHz
DMSO-d_6



1

$\{^1H\}^{13}C$ NMR, 400 MHz

DMSO-d_6