## Supporting Information

# Mechanistic Study of the Biomimetic Synthesis of Flavonolignan Diastereoisomers in Milk Thistle

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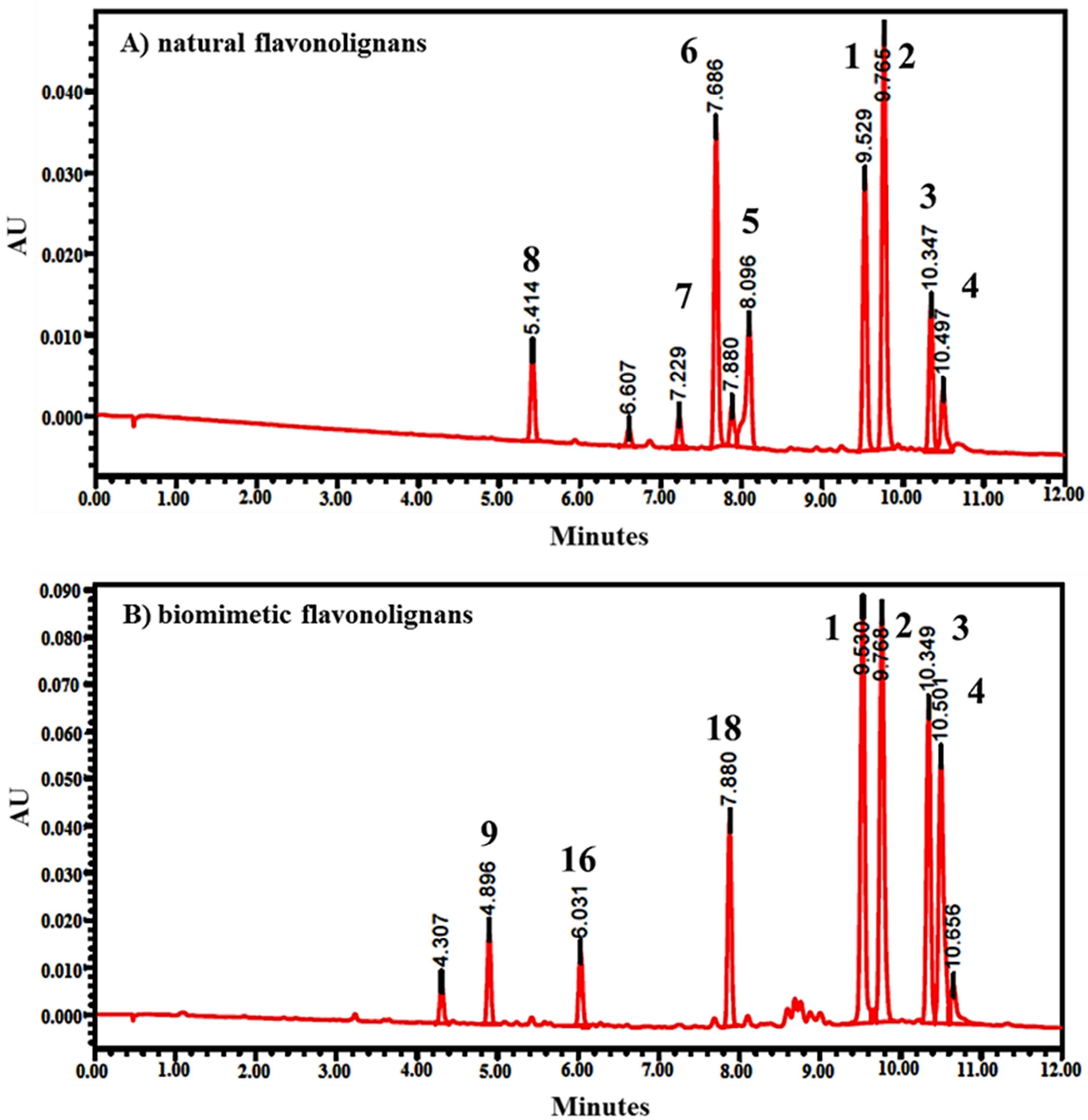
**Figure S1.** UPLC chromatograms of natural flavonolignans in silymarin compared with the product of the biomimetic reaction (Scheme 2)

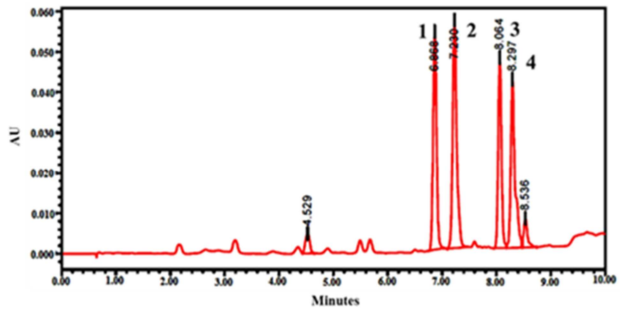



(**A**) natural flavonolignans; (**B**) reaction of taxifolin (1 equiv), *trans*-coniferyl alcohol (2 equiv), and $Ag_2O$ (4 equiv) in ethyl acetate (0.04 M) at 75 °C for 96 h. Compounds are silybin A (**1**); silybin B (**2**); isosilybin A (**3**); isosilybin B (**4**); silydianin (**5**); silychristin (**6**); isosilychristin (**7**); taxifolin (**8**); *trans*-coniferyl alcohol (**9**); coniferyl aldehyde (**16**); dehydrodiconiferyl alcohol (**18**).

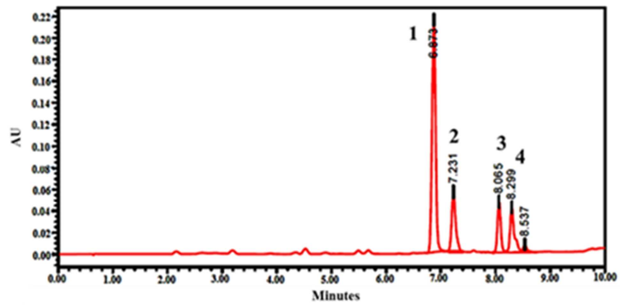
**Method:** UPLC was conducted using a $CH_3OH/H_2O$ (0.1% formic acid) gradient that initiated at 5:95 and increased to 50:50 over 10 min and held with that ratio for 2 min at a flow rate of 0.6 mL/min (50 °C) using an HSST3 column (1.8 µm, 2.1 × 100 mm) monitored at 288 nm.

**Figure S2.** UPLC chromatograms of biomimetic synthesis of flavonolignans (Scheme 2)

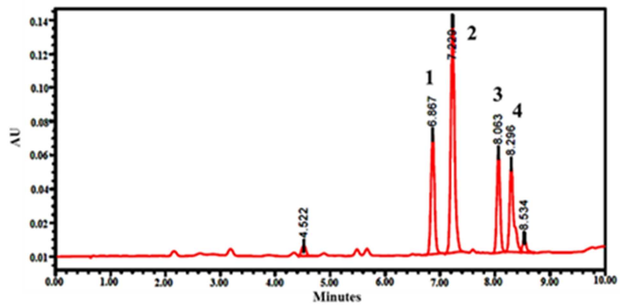
**A**) Crude reaction



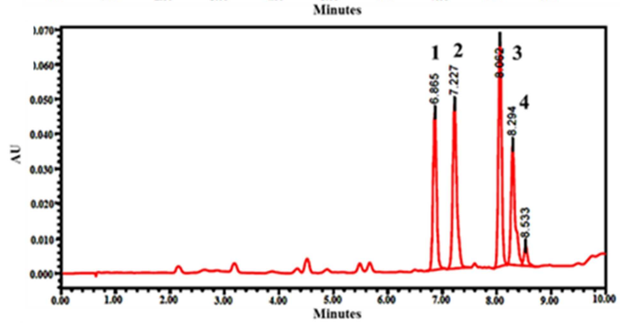

**B**) Co-injection of **1**



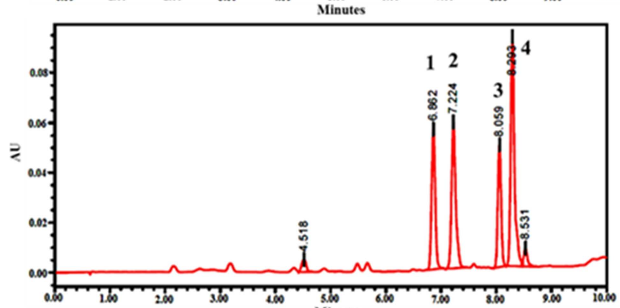

**C**) Co-injection of **2**




**D**) Co-injection of **3**



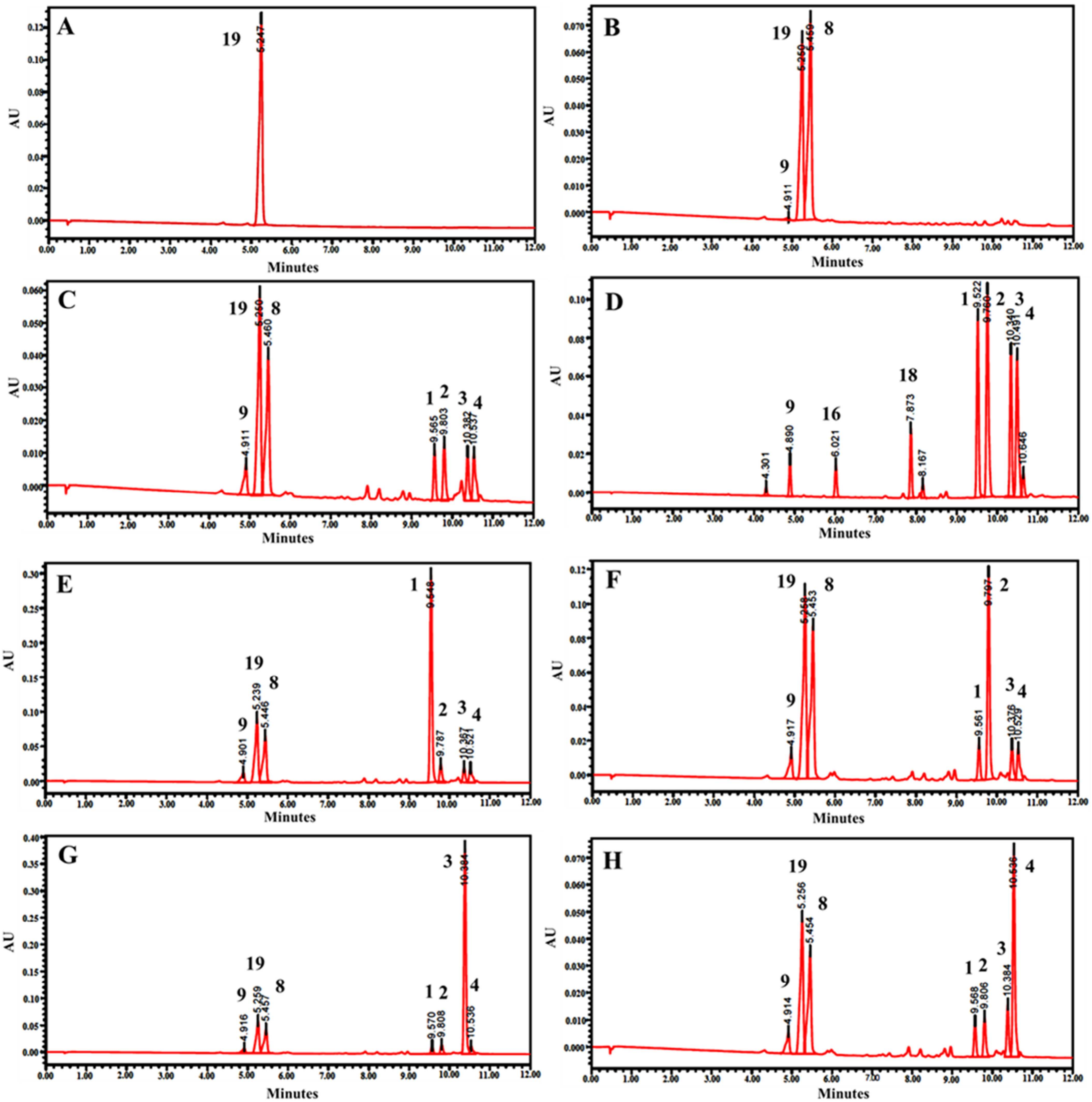

**E**) Co-injection of **4**




(**A**) reaction of taxifolin (1 equiv), *trans*-coniferyl alcohol (2 equiv), and $Ag_2O$ (4 equiv) in ethyl acetate (0.06 mM) at 75 °C for 96 h; with co-injection (**B**) of **1**; (**C**) of **2**; (**D**) of **3**; (**E**) of **4**. (*Note*: More dilute reaction resulted in more selective formation of the flavonolignans and minimization of the byproducts.)

**Method:** UPLC was conducted using a $CH_3OH/H_2O$ gradient that initiated at 30:70 and increased to 60:40 over 10 min at a flow rate of 0.4 mL/min (40 °C) using an HSST3 column (1.8 µm, 2.1 × 100 mm) monitored at 288 nm.

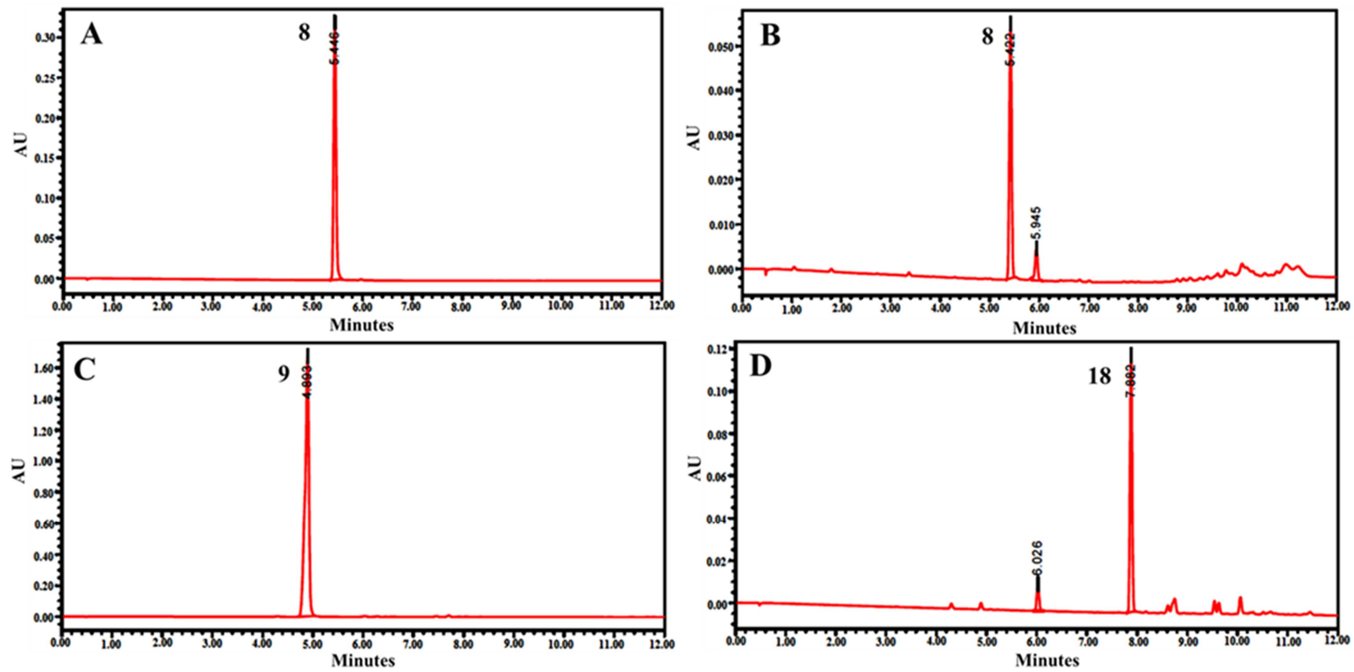
**Figure S3.** UPLC chromatograms of *cis*-coniferyl alcohol and its reaction with taxifolin (Scheme 3)




(**A**) *cis*-coniferyl alcohol; (**B**) reaction of *cis*-coniferyl alcohol (2 equiv) with with taxifolin (1 equiv) and $Ag_2O$ (4 equiv) in ethyl acetate (0.001 M) at 75 °C after 10 min.; (**C**) after 2.5 h; (**D**) after 96 h; (**E**) after 2.5 h with co-injection of silybin A ; (**F**) after 2.5 h with co-injection of silybin B; (**G**) after 2.5 h with co-injection of isosilybin A; (**H**) after 2.5 h with co-injection of isosilybin B.

**Method:** UPLC conditions same as in **Figure S1**.

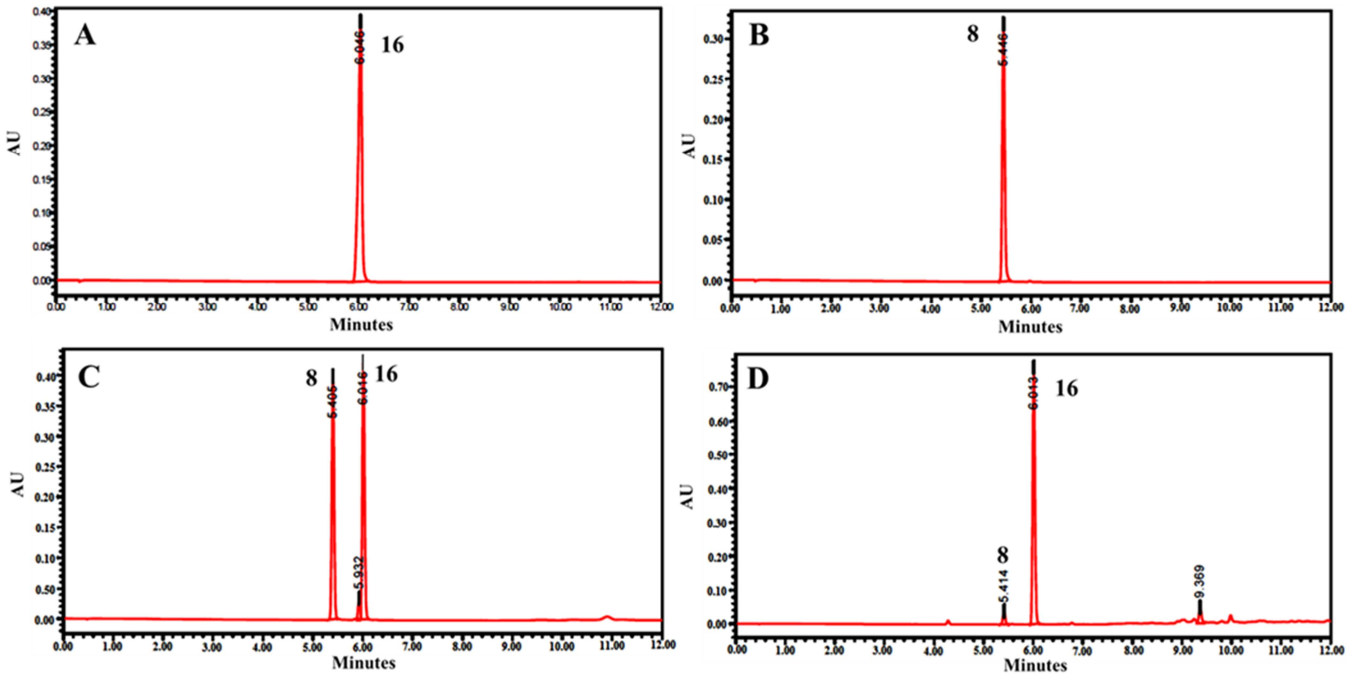
**Figure S4.** UPLC chromatograms of oxidation reactions of taxifolin and coniferyl alcohol (Scheme 4)




(**A**) taxifolin; (**B**) reaction of taxifolin (1 equiv) with $Ag_2O$ (4 equiv) in ethyl acetate (0.001 M) for 96 h at 75 °C; (**C**) *trans*-coniferyl alcohol; (**D**) reaction of *trans*-coniferyl alcohol (1 equiv) with $Ag_2O$ (2 equiv) in ethyl acetate (0.001 M) for 115 h at 75 °C.

**Method:** UPLC conditions same as in **Figure S1**.

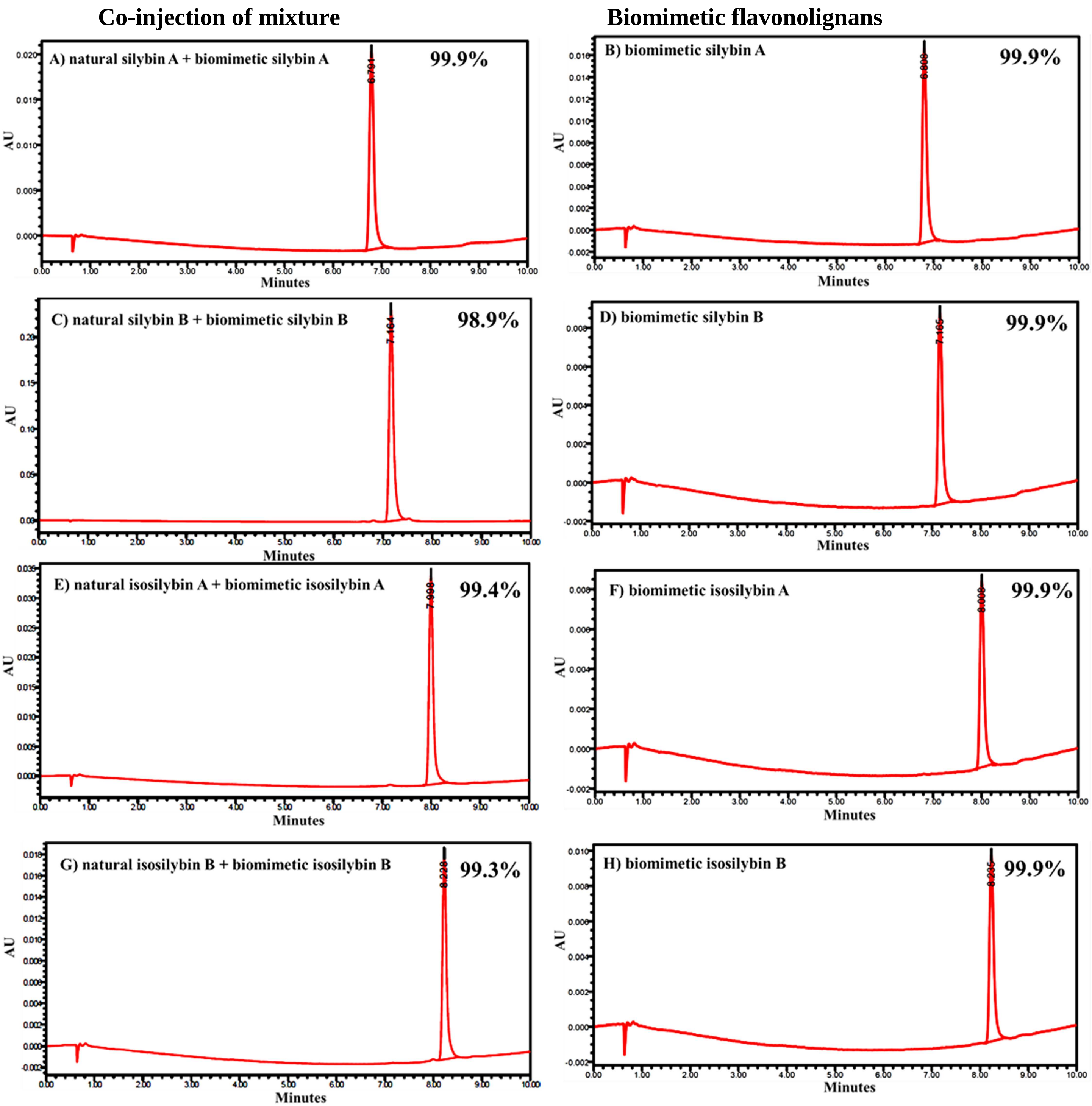
**Figure S5.** UPLC chromatograms of reactions of taxifolin and coniferyl aldehyde (Scheme 5)




(**A**) coniferyl aldehyde; (**B**) taxifolin; (**C**) reaction of coniferyl aldehyde (2 equiv) with taxifolin (1 equiv) without $Ag_2O$ in ethyl acetate (0.0005 M) for 96 h at 75 °C; (**D**) Reaction of coniferyl aldehyde (2 equiv) with taxifolin (1 equiv) and $Ag_2O$ (4 equiv) in ethyl acetate (0.0005 M) for 96 h at 75 °C.

**Method:** UPLC conditions same as in **Figure S1**.

**Figure S6.** UPLC chromatograms of co-injection of biomimetic and natural flavonolignans (left column) and purified biomimetic flavonolignans (right column)




(**A**) natural silybin A and biomimetic silybin A; (**B**) biomimetic silybin A; (**C**) natural silybin B and biomimetic silybin B; (**D**) biomimetic silybin B (**E**) natural isosilybin A and biomimetic isosilybin A; (**F**) biomimetic isosilybin A; (**G**) natural isosilybin B and biomimetic isosilybin B; (**H**) biomimetic isosilybin B.

**Method:** UPLC conditions same as in **Figure S2**.

**Figure S7.** $^{1}$H NMR spectra (500 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) silybin A

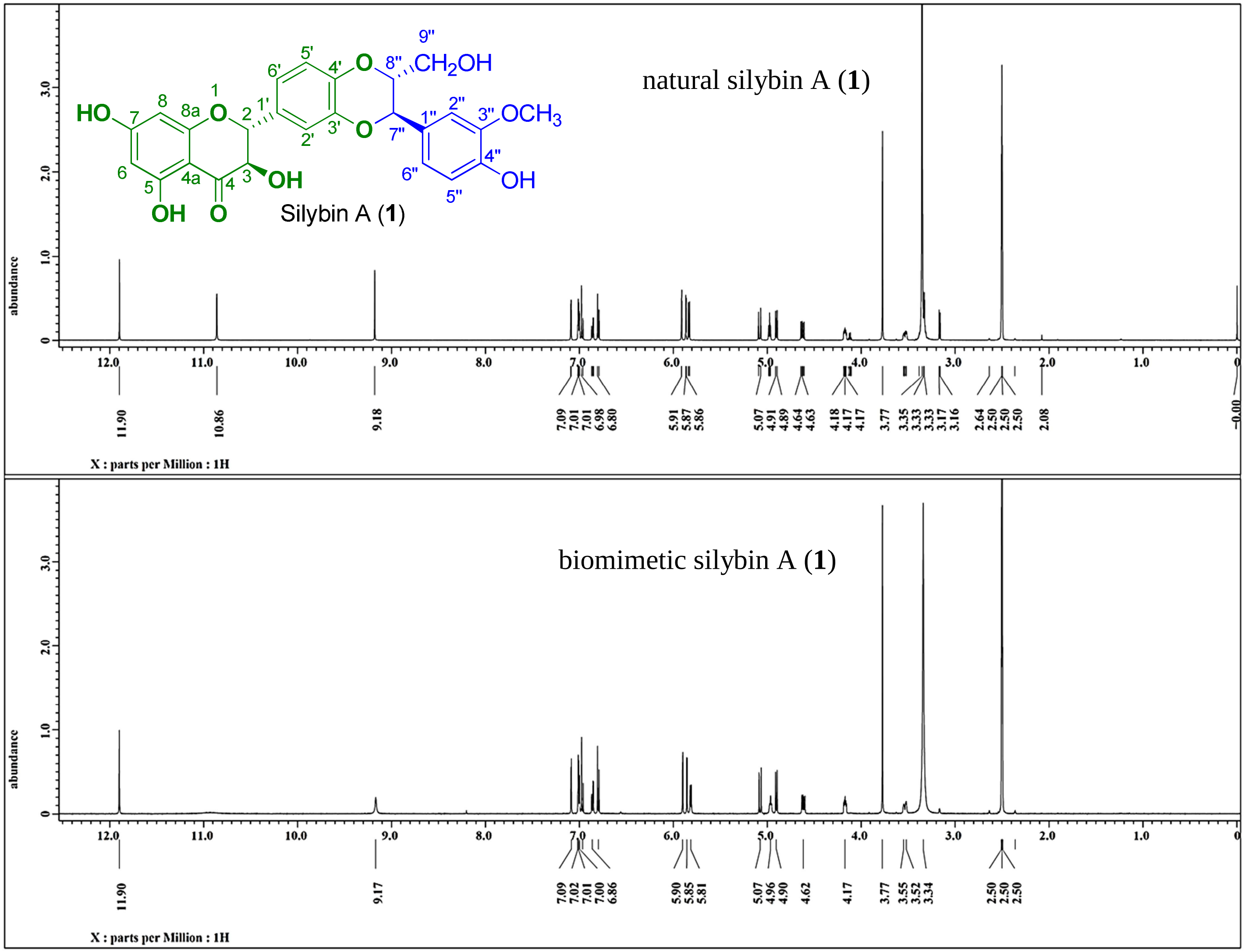


**Figure S8.** $^{13}$C NMR spectra (125 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) silybin A

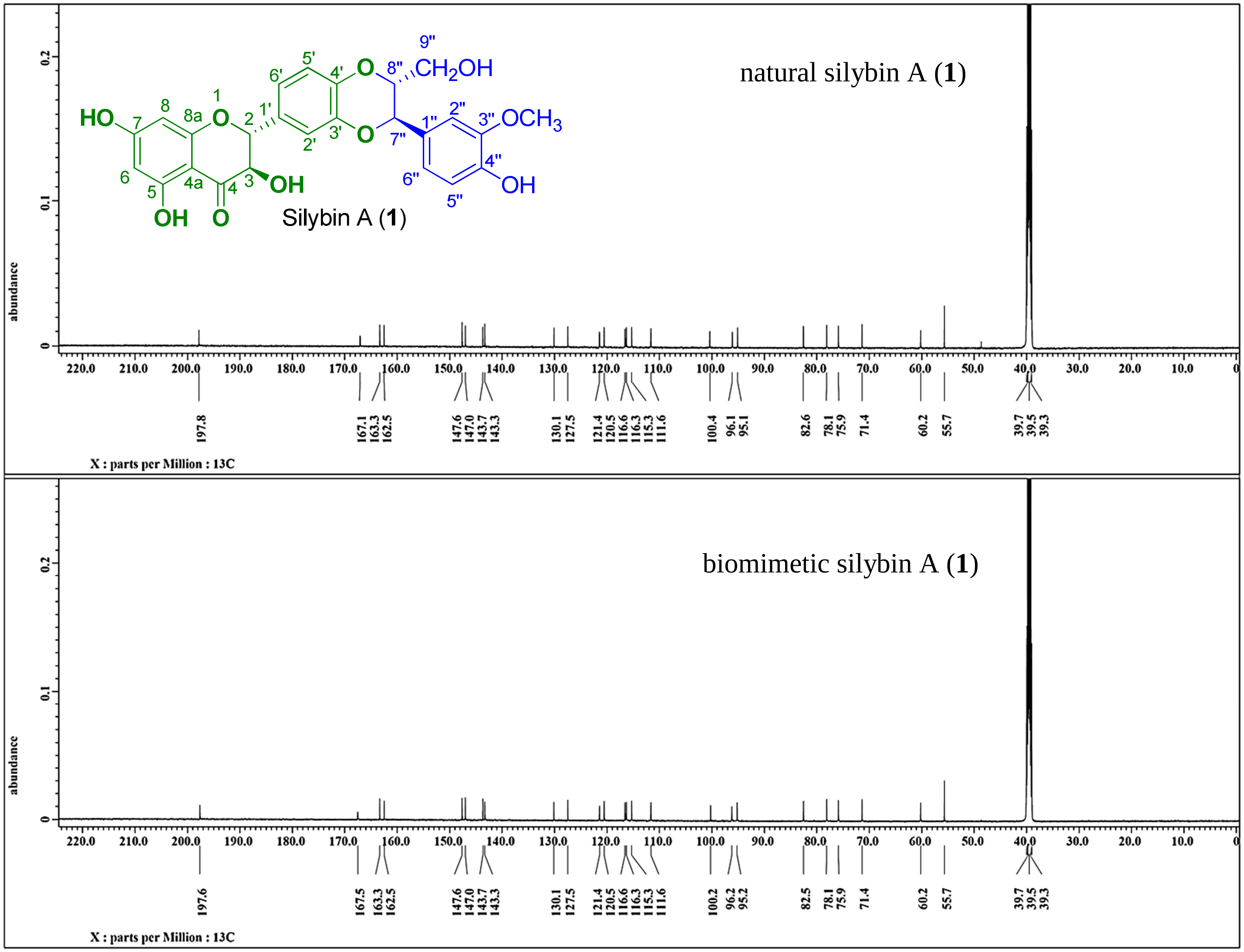


**Figure S9.** $^1$H NMR spectra (500 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) silybin B

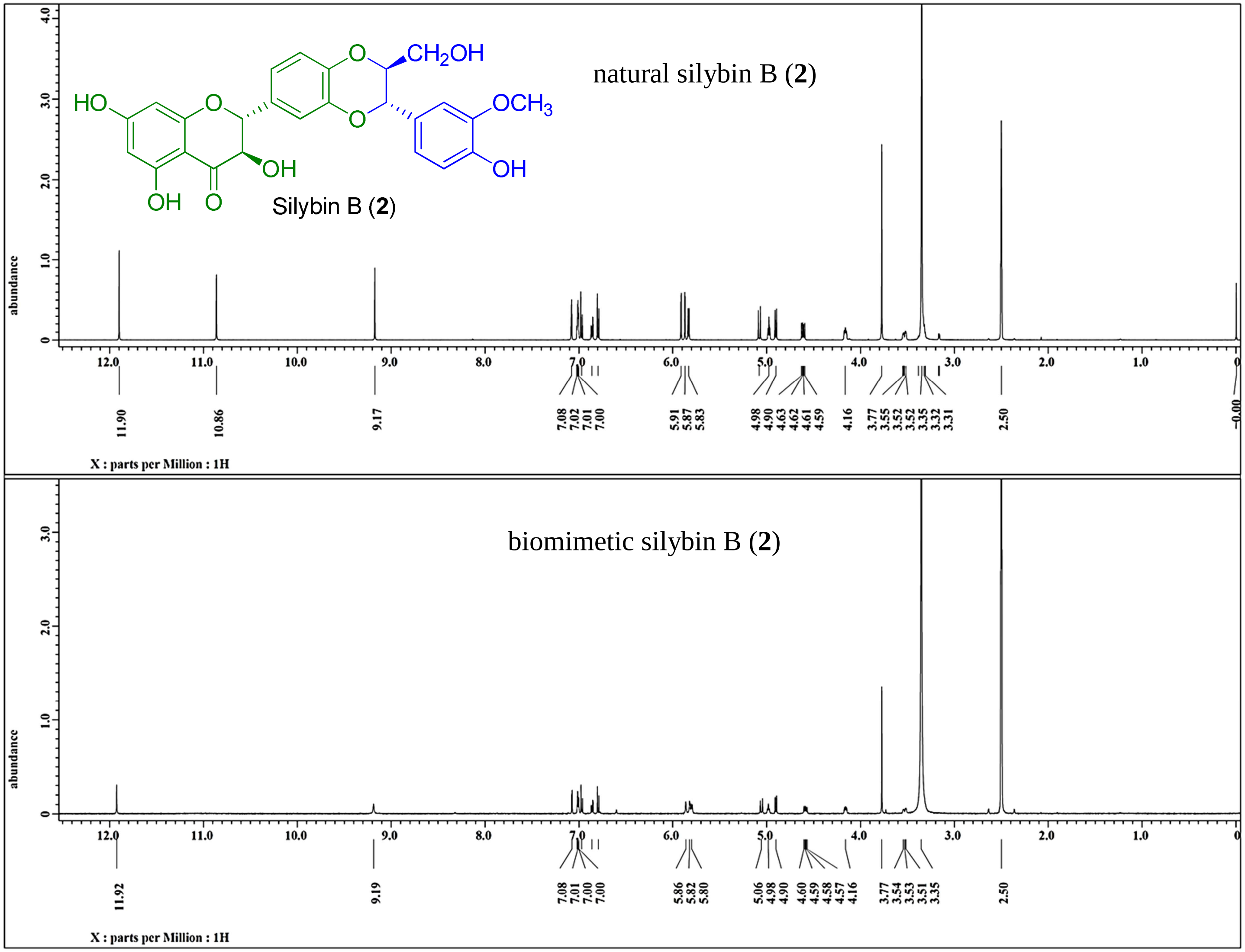


**Figure S10.** $^{13}$C NMR spectra (125 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) silybin B

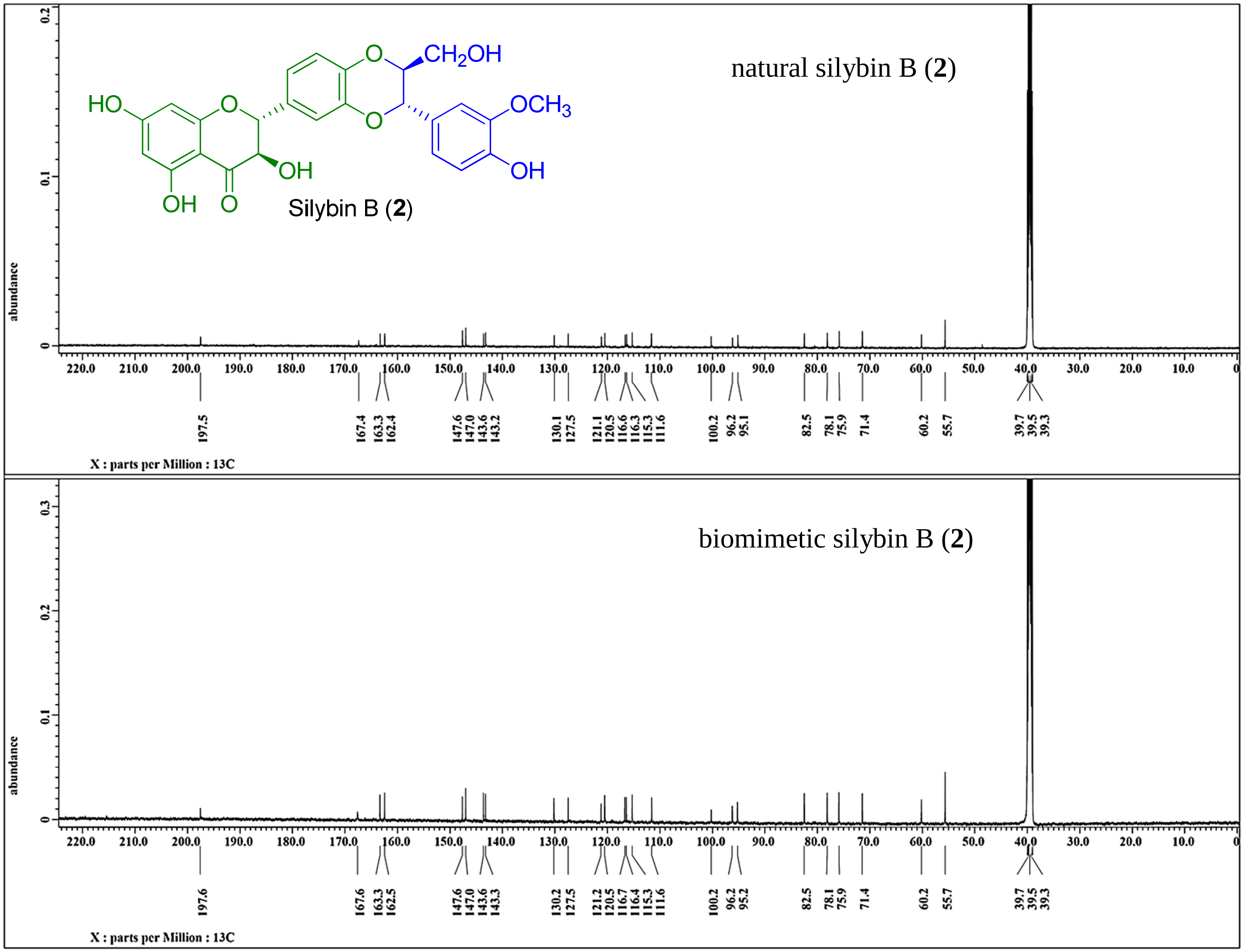


**Figure S11.** $^{1}$H NMR spectra (500 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) isosilybin A

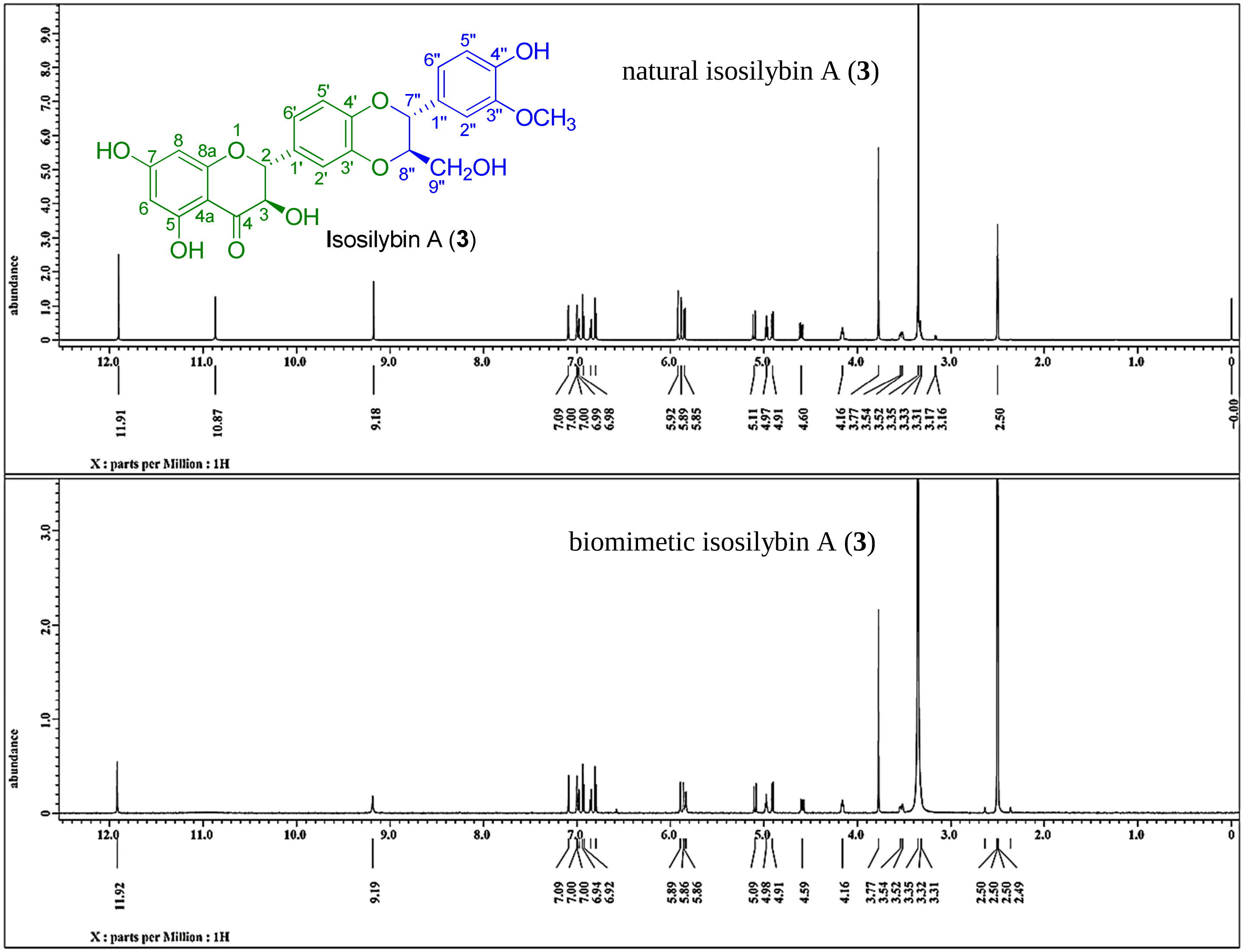


**Figure S12.** $^{13}$C NMR spectra (125 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) isosilybin A

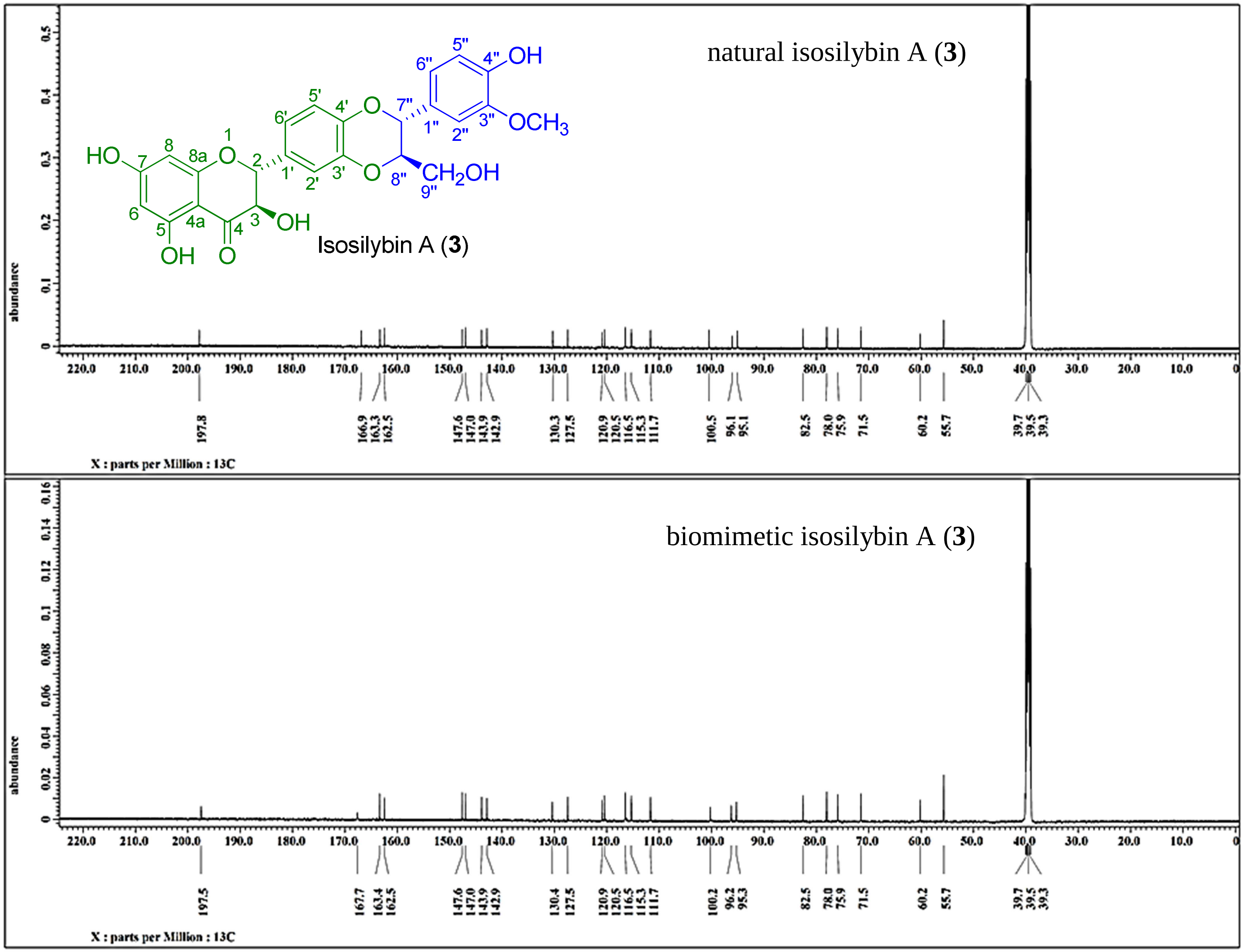


**Figure S13.** $^{1}$H NMR spectra (500 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) isosilybin B

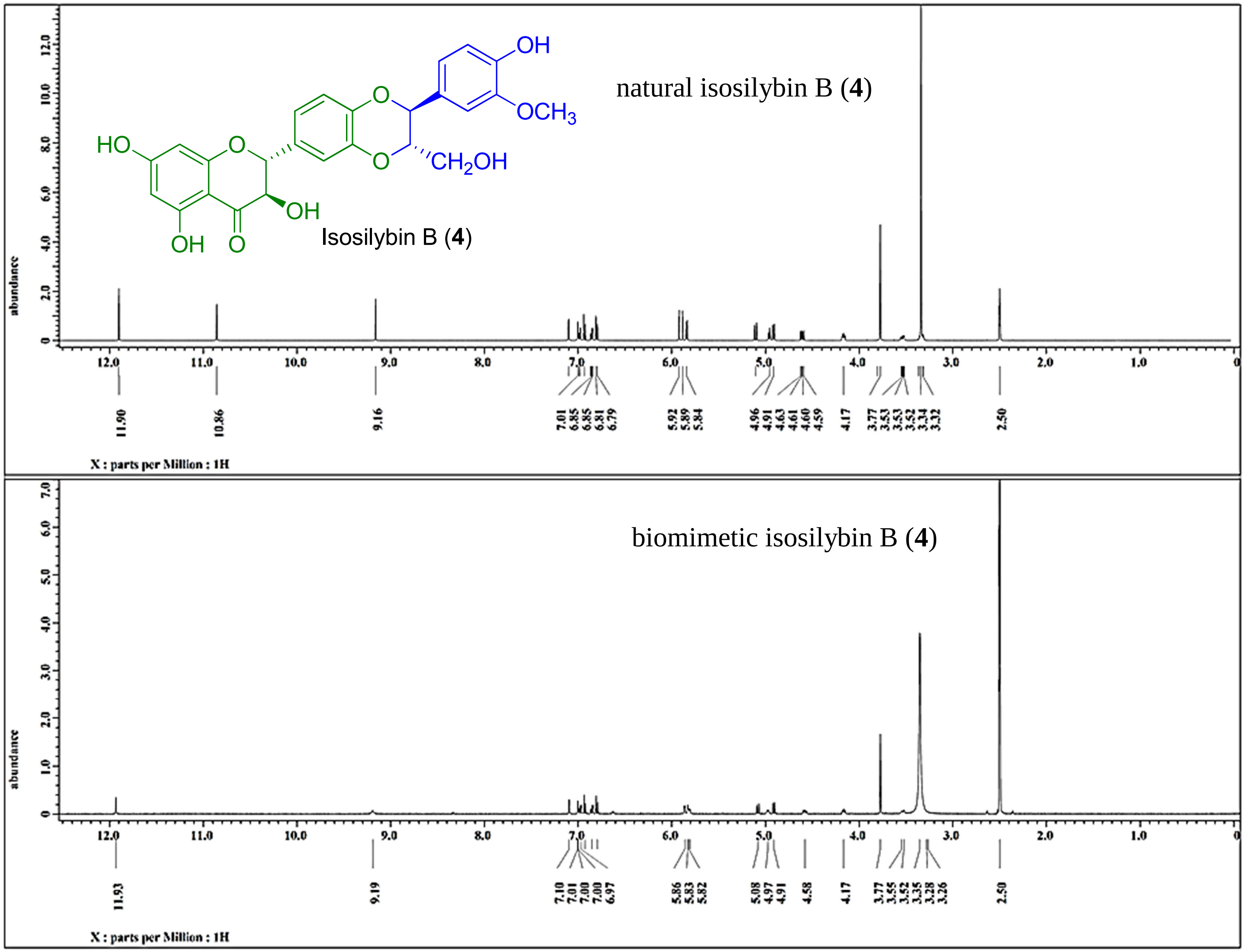


**Figure S14.** $^{13}$C NMR spectra (125 MHz in DMSO-$d_6$) of natural (top) and biomimetic (bottom) isosilybin B

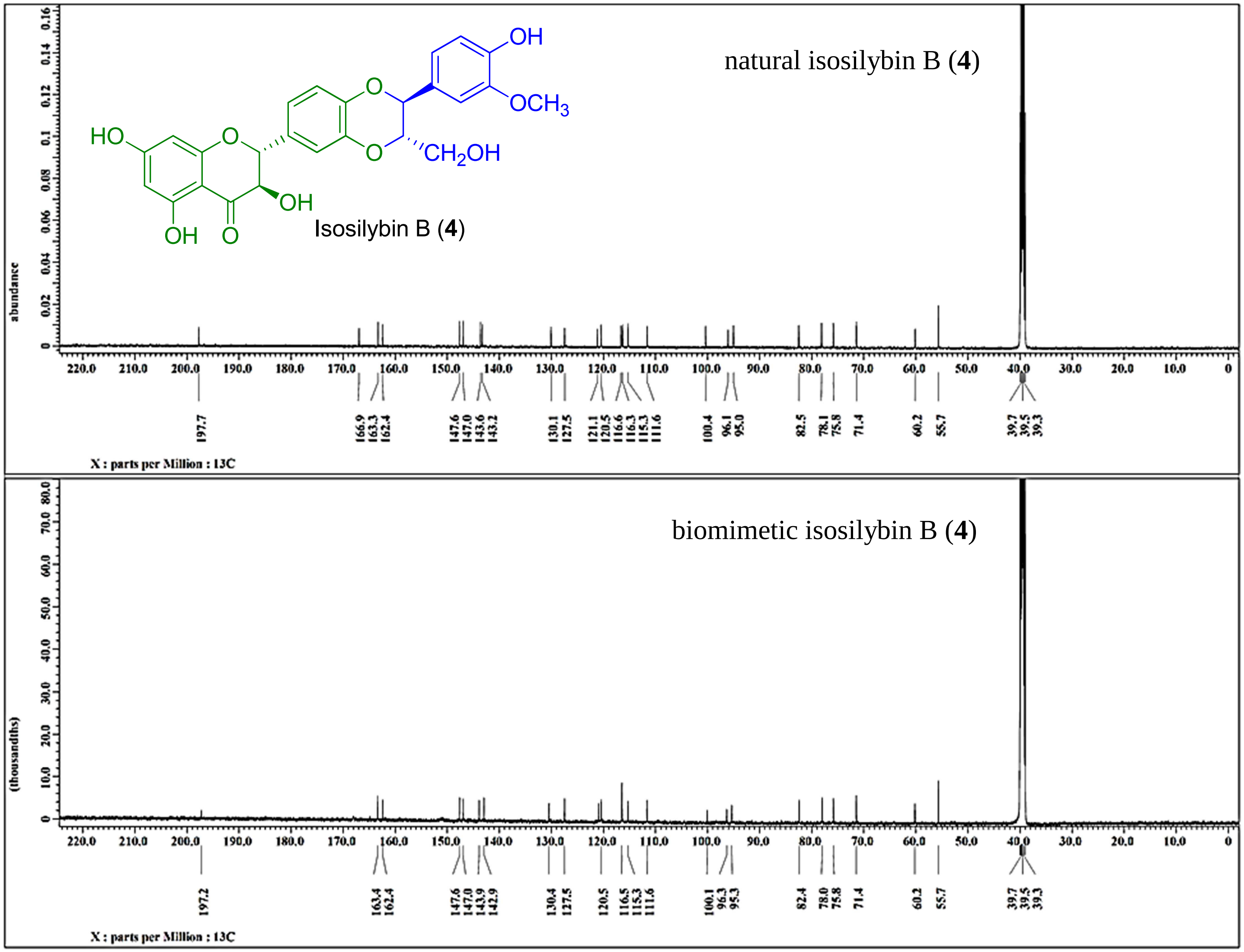


**Table S1.** $^{1}$H NMR data (500 MHz in DMSO-$d_6$) comparing natural flavonolignans to the biomimetic counterparts

| **Position** | natural **1** | biomimetic **1** | natural **2** | biomimetic **2** | natural **3** | biomimetic **3** | natural **4** | biomimetic **4** |
|---|---|---|---|---|---|---|---|---|
| 2 | 5.08, d (11.5) | 5.07, d (11.5) | 5.08, d (11.5) | 5.06, d (11.5) | 5.11, d (10.9) | 5.10, d (10.9) | 5.11, d (11.5) | 5.08, d (10.9) |
| 3 | 4.63, dd (11.5, 6.3) | 4.60, dd (11.5, 6.3) | 4.61, dd (11.5, 6.3) | 4.59, dd (11.5, 6.3) | 4.60, dd (10.9, 6.3) | 4.58, dd (10.9, 6.3) | 4.61, dd (11.5, 5.9) | 4.58, dd (10.9, 6.3) |
| 6 | 5.91, d (1.7) | 5.90, d (1.7) | 5.91, d (2.3) | 5.86, br d (1.7) | 5.92, d (2.3) | 5.89, d (1.7) | 5.92, d (2.0) | 5.86, d (2.3) |
| 8 | 5.86, d (1.7) | 5.86, d (1.7) | 5.87, d (2.3) | 5.82, br d (1.7) | 5.89, d (2.3) | 5.86, d (1.7) | 5.89, d (2.0) | 5.83, d (2.3) |
| 2' | 7.09, d (1.7) | 7.09, d (1.7) | 7.08, d (1.8) | 7.07, d (1.7) | 7.09, d (2.3) | 7.09, d (2.3) | 7.10, d (1.8) | 7.10, d (1.8) |
| 5' | 6.97, d (8.0) | 6.97, d (8.0) | 6.97, d (8.1) | 6.97, d (8.6) | 6.93, d (8.6) | 6.93, d (8.6) | 6.93, d (8.0) | 6.93, d (8.0) |
| 6' | 7.00, dd (8.0, 1.7) | 7.00, dd (8.0, 1.7) | 7.02, dd (8.1, 1.8) | 7.01, dd (8.6, 1.7) | 6.98, dd (8.6, 2.3) | 6.98, dd (8.6, 2.3) | 6.98, dd (8.0, 1.8) | 6.98, dd (8.0, 1.8) |
| 2" | 7.01, d (1.8) | 7.01, d (1.8) | 7.02, d (1.7) | 7.02, d (1.7) | 7.00, d (1.7) | 7.00, d (1.7) | 7.00, d (2.3) | 7.00, d (1.8) |
| 5" | 6.80, d (8.6) | 6.80, d (8.0) | 6.79, d (8.6) | 6.79, d (8.0) | 6.80, d (8.6) | 6.80, d (8.0) | 6.80, d (8.6) | 6.80, d (8.0) |
| 6" | 6.86, dd (8.6, 1.8) | 6.85, dd (8.0, 1.7) | 6.86, dd (8.6, 1.7) | 6.86, dd (8.0, 1.7) | 6.86, dd (8.6, 1.7) | 6.86, dd (8.0, 1.7) | 6.86, dd (8.6, 2.3) | 6.85, dd (8.0, 1.8) |
| 7" | 4.90, d (7.5) | 4.90, d (8.0) | 4.90, d (7.5) | 4.90, d (7.5) | 4.91, d (8.1) | 4.91, d (8.0) | 4.91, d (7.5) | 4.91, d (8.0) |
| 8" | 4.17, ddd | 4.17, ddd | 4.16, ddd | 4.16, ddd | 4.16, ddd | 4.16, ddd | 4.17, ddd | 4.17, ddd |
| | (7.5, 4.6, 2.3) | (8.0, 4.6, 2.3) | (7.5, 4.1, 2.3) | (7.5, 4.1, 2.3) | (8.1, 4.6, 2.3) | (8.0, 4.6, 2.3) | (7.5, 4.6, 2.3) | (8.0, 4.6, 2.3) |
| 9"a | 3.53, ddd | 3.53, ddd | 3.53, ddd | 3.52, ddd | 3.53, ddd | 3.53, ddd | 3.54, ddd | 3.53, ddd |
| | (10.3, 5.2, 2.3) | (10.3, 5.2, 2.3) | (9.8, 4.6, 2.3) | (9.7, 5.2, 2.3) | (12.0, 4.6, 2.3) | (12.0, 5.2, 2.3) | (11.9, 5.2, 2.3) | (11.9, 5.2, 2.3) |
| 9"b | 3.33, m | 3.32, m | 3.33, m | 3.31, m | 3.33, m | 3.33, m | 3.33, m | 3.33, m |
| 3"-$OCH_3$ | 3.77, s | 3.77, s | 3.77, s | 3.77, s | 3.78, s | 3.77, s | 3.77, s | 3.77, s |
| 3-OH | 5.83, d (6.3) | 5.81, d (6.3) | 5.83, d (6.3) | 5.80, d (6.3) | 5.83, d (6.3) | 5.84, d (6.3) | 5.84, d (5.9) | 5.81, d (6.3) |
| 5-OH | 11.90, s | 11.90, s | 11.90, s | 11.90, s | 11.90, s | 11.92, s | 11.90, s | 11.93, s |
| 7-OH | 10.86, s | - | 10.86, s | - | 10.85, s | - | 10.86, s | - |
| 4"-OH | 9.18, s | 9.18, s | 9.17, s | 9.19, s | 9.15, s | 9.19, s | 9.16, s | 9.19, s |
| 9"-OH | 4.97, dd (5.7, 5.2) | 4.96, dd (5.7, 5.2) | 4.98, dd (5.7, 4.6) | 4.99, dd (5.7, 5.2) | 4.95, dd (5.7, 4.6) | 4.98, dd (5.7, 5.2) | 4.96, dd (5.5, 5.0) | 4.97, dd (5.7, 5.2) |

chemical shifts in δ, coupling constants in Hz

**Table S2.** $^{13}$C NMR data (125 MHz in DMSO-$d_6$) comparing natural flavonolignans to the biomimetic counterparts

| **Position** | **type** | natural **1** | biomimetic **1** | natural **2** | biomimetic **2** | natural **3** | biomimetic **3** | natural **4** | biomimetic **4** |
|---|---|---|---|---|---|---|---|---|---|
| 2 | CH | 82.6 | 82.5 | 82.5 | 82.5 | 82.5 | 82.5 | 82. 5 | 82. 4 |
| 3 | CH | 71.4 | 71.4 | 71.4 | 71.4 | 71.5 | 71.5 | 71.5 | 71.4 |
| 4 | C | 197.8 | 197.6 | 197.7 | 197.6 | 197.8 | 197.5 | 197.8 | 197.2 |
| 4a | C | 100.4 | 100.2 | 100.4 | 100.2 | 100.5 | 100.2 | 100.5 | 100.1 |
| 5 | C | 163.3 | 163.3 | 163.3 | 163.3 | 163.3 | 163.4 | 163.3 | 163.4 |
| 6 | CH | 96.1 | 96.2 | 96.1 | 96.2 | 96.1 | 96.2 | 96.1 | 96.3 |
| 7 | C | 167.1 | 167.5 | 166.9 | 167.6 | 166.9 | 167.7 | 166.9 | 167.0 |
| 8 | CH | 95.1 | 95.2 | 95.0 | 95.2 | 95.1 | 95.3 | 95.1 | 95.3 |
| 8a | C | 162.5 | 162.5 | 162.4 | 162.5 | 162.5 | 162.5 | 162.5 | 162.4 |
| 1' | C | 130.1 | 130.1 | 130.1 | 130.2 | 130.3 | 130.4 | 130.3 | 130.4 |
| 2' | CH | 116.6 | 116.6 | 116.6 | 116.7 | 116.5 | 116.5 | 116.5 | 116.5 |
| 3' | C | 143.3 | 143.3 | 143.2 | 143.3 | 142.9 | 142.9 | 142.9 | 142.9 |
| 4' | C | 143.7 | 143.7 | 143.6 | 143.6 | 143.9 | 143.9 | 143.9 | 143.9 |
| 5' | CH | 116.3 | 116.3 | 116.3 | 116.4 | 116.4 | 116.5 | 116.5 | 116.5 |
| 6' | CH | 121.4 | 121.4 | 121.4 | 121.2 | 120.9 | 120.9 | 120.9 | 120.9 |
| 1" | C | 127.5 | 127.5 | 127.5 | 127.5 | 127.5 | 127.5 | 127.5 | 127.5 |
| 2" | CH | 111.6 | 111.6 | 111.6 | 111.6 | 111.7 | 111.7 | 111.7 | 111.6 |
| 3" | C | 147.6 | 147.6 | 147.6 | 147.6 | 147.6 | 147.6 | 147.6 | 147.6 |
| 4" | C | 147.0 | 147.0 | 147.0 | 147.0 | 147.0 | 147.0 | 147.0 | 147.0 |
| 5" | CH | 115.3 | 115.3 | 115.3 | 115.3 | 115.3 | 115.3 | 115.3 | 115.3 |
| 6" | CH | 120.5 | 120.5 | 120.5 | 120.5 | 120.5 | 120.5 | 120.5 | 120.5 |
| 7" | CH | 75.9 | 75.9 | 75.8 | 75.9 | 75.9 | 75.9 | 75.9 | 75.8 |
| 8" | CH | 78.1 | 78.1 | 78.1 | 78.1 | 78.0 | 78.0 | 78.0 | 78.0 |
| 9" | $CH_2$ | 60.2 | 60.2 | 60.2 | 60.2 | 60.2 | 60.2 | 60.2 | 60.2 |
| 3"-$OCH_3$ | $CH_3$ | 55.7 | 55.7 | 55.7 | 55.7 | 55.7 | 55.7 | 55.7 | 55.7 |

chemical shifts in δ

**Figure S15.** $^{1}$H NMR spectra (500 MHz in acetone-$d_6$) of purchased (top) and synthetic (bottom) coniferyl aldehyde (**16**)

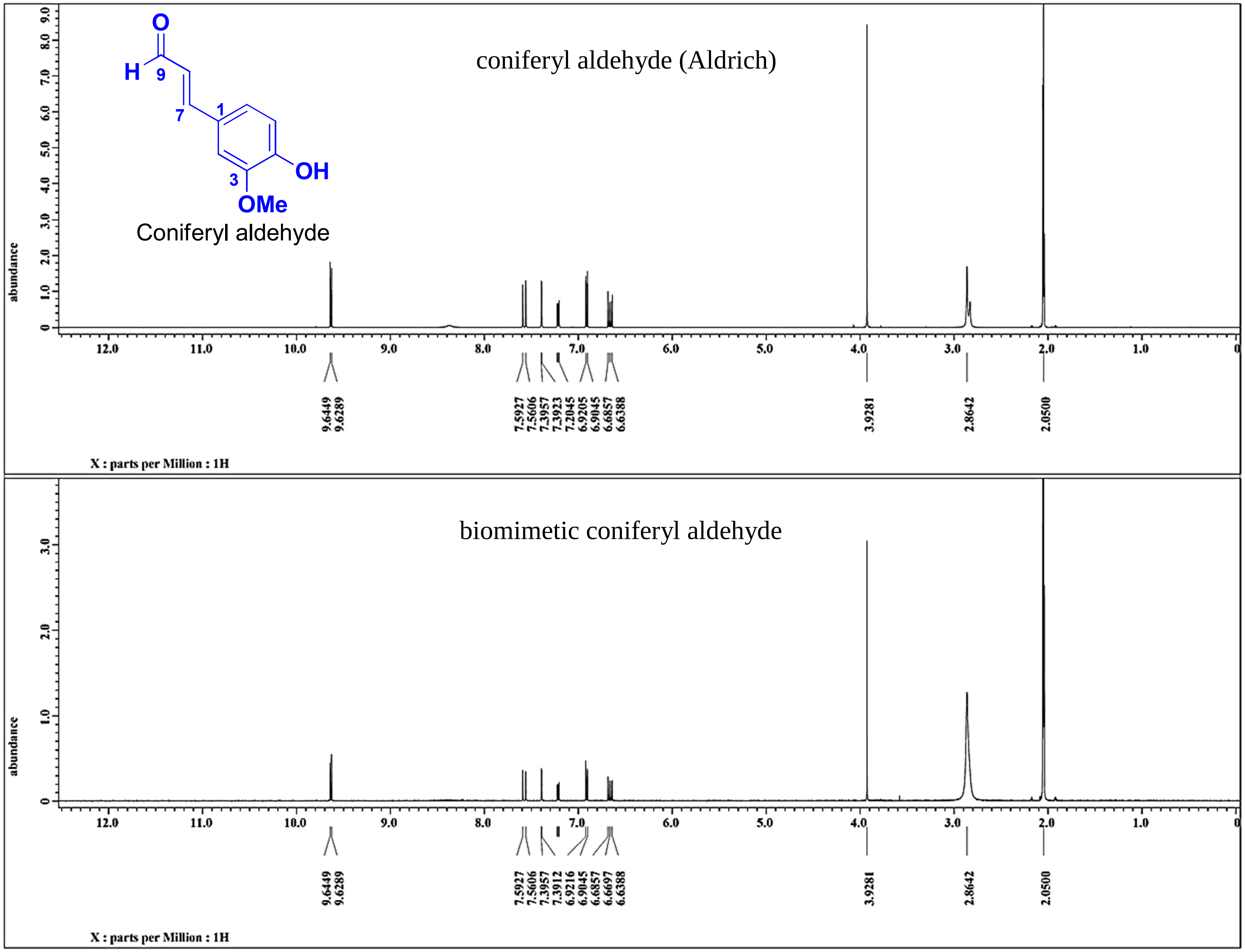


**Figure S16.** $^{1}$H NMR spectrum (500 MHz in acetone-$d_6$) of (±)-dehydrodiconiferyl alcohol (**18**)

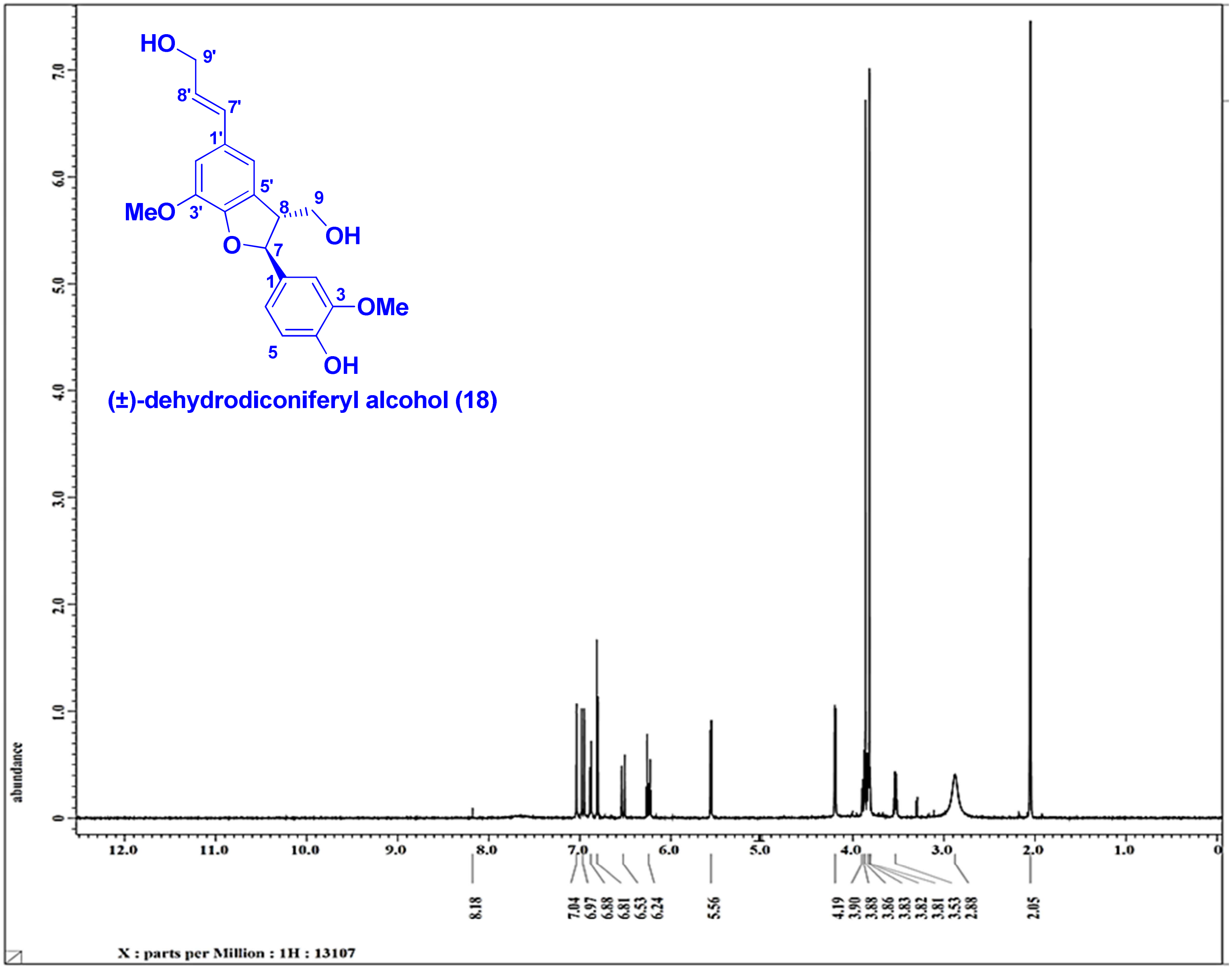


**Figure S17.** $^{13}$C NMR spectrum (125 MHz in acetone-$d_6$) of (±)-dehydrodiconiferyl alcohol (**18**)

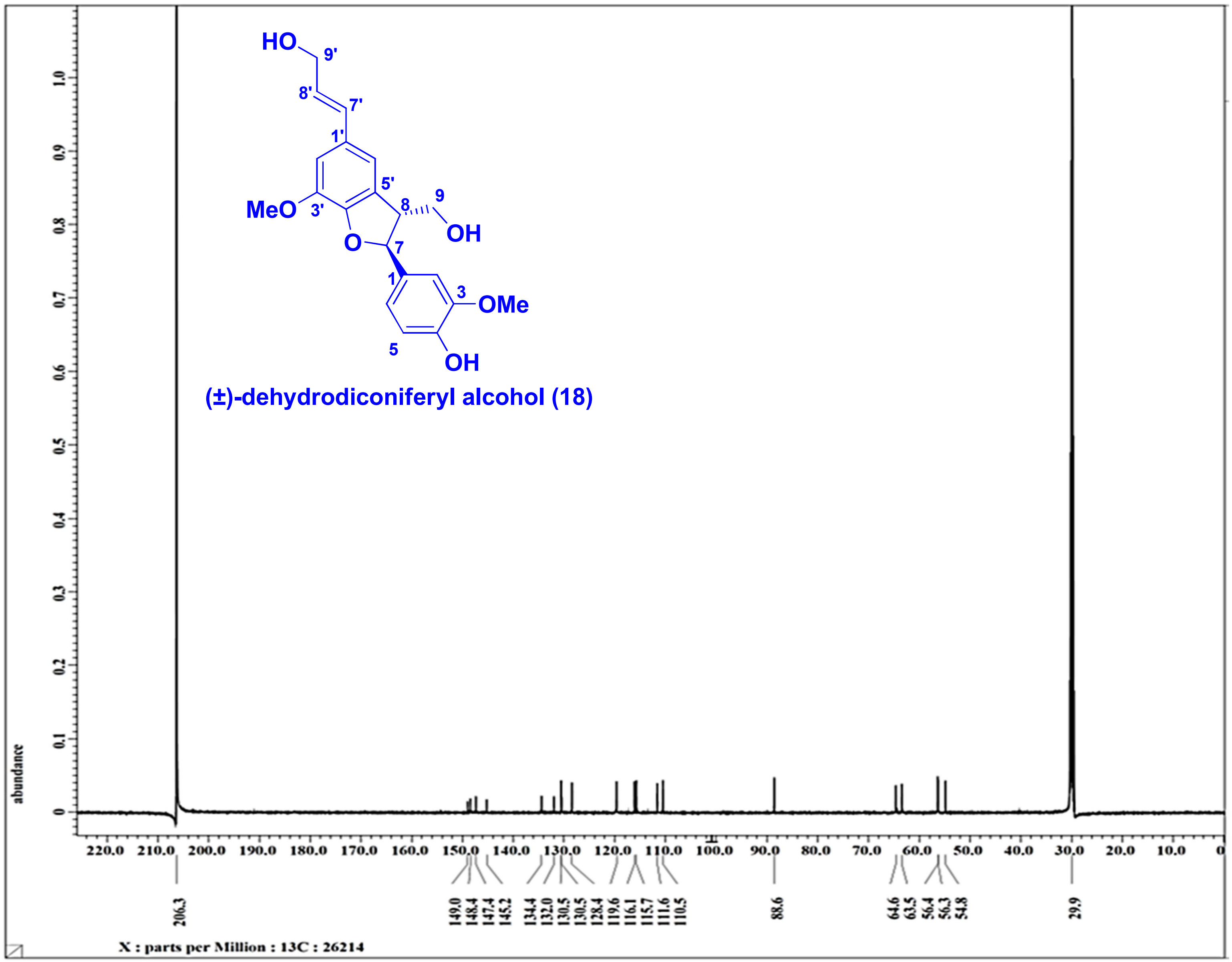


**Table S3.** $^{1}$H NMR data (500 MHz in acetone-$d_6$) comparing biomimetic (±)-dehydrodiconiferyl alcohol (**18**) to the literature data

| **Position** | **Type** | **Experimental** (shift, multiplicity, coupling) | **Literature**[a] (shift, multiplicity, coupling) |
|---|---|---|---|
| 2 | CH | 7.04, d (2.3) | 7.03, d (2.0) |
| 5 | CH | 6.81, d (8.0) | 6.80, d (8.1) |
| 6 | CH | 6.88, dd (8.0, 1.7) | 6.87, ddd (8.1, 2.0 and 0.5) |
| 7 | CH | 5.56, br d (6.3) | 5.56, dt (6.3, not given) |
| 8 | CH | 3.53, q (6.3) | 3.53 br q (not given) |
| 9a | $CH_2$ | 3.83, dd (10.3, 6.9) | 3.78 m |
| 9b | $CH_2$ | 3.88, dd (10.3, 5.2) | 3.88 m |
| $OCH_3$ | $CH_3$ | 3.82, s | 3.81, s |
| 2′ | CH | 6.95, d (1.7) | 6.94, br s |
| 6′ | CH | 6.98, br s | 6.97, br s |
| 7′ | CH | 6.52, dt (16.0, 1.7) | 6.52, dt (15.8, 1.5) |
| 8′ | CH | 6.23, dt (16.0, 5.2) | 6.23, dt (15.8, 5.5) |
| 9′ | $CH_2$ | 4.20, dd (5.7, 1.8) | 4.19, td (5.2, 1.5) |
| $OCH_3$ | $CH_3$ | 3.86, s | 3.85, s |

chemical shifts in δ, coupling constants in Hz

[a]Quideau, S.; John, R. *Holzforschung*, **1994**, *48*, 12-22.

**Table S4.** $^{13}$C NMR data (125 MHz in $CDCl_3$) comparing biomimetic (±)-dehydrodiconiferyl alcohol (**18**) to the literature data

| **Position** | **Type** | **Experimental** | **Literature**[a] |
|---|---|---|---|
| 1 | C | 134.4 | 134.4 |
| 2 | CH | 110.5 | 110.5 |
| 3 | C | 148.4 | 148.4 |
| 4 | C | 147.4 | 147.3 |
| 5 | CH | 115.7 | 115.7 |
| 6 | CH | 119.6 | 119.6 |
| 7 | CH | 88.6 | 88.5 |
| 8 | CH | 54.8 | 54.7 |
| 9 | $CH_2$ | 64.6 | 64.6 |
| $OCH_3$ | $CH_3$ | 56.3 | 56.3 |
| 1 | C | 132.0 | 131.9 |
| 2 | CH | 111.6 | 111.7 |
| 3 | C | 145.2 | 145.1 |
| 4 | C | 149.0 | 148.8 |
| 5 | C | 130.5 | 130.4 |
| 6 | CH | 116.1 | 116.1 |
| 7 | CH | 130.5 | 130.5 |
| 8 | CH | 128.4 | 128.3 |
| 9 | $CH_2$ | 63.5 | 63.4 |
| $OCH_3$ | $CH_3$ | 56.4 | 56.4 |

chemical shifts in δ

[a]Quideau, S.; John, R. *Holzforschung*, **1994**, *48*, 12-22.

**Figure S18.** $^{1}$H NMR spectrum (500 MHz in $CDCl_3$)of 4-(3-hydroxyprop-1-yn-1-yl)-2-methoxyphenol

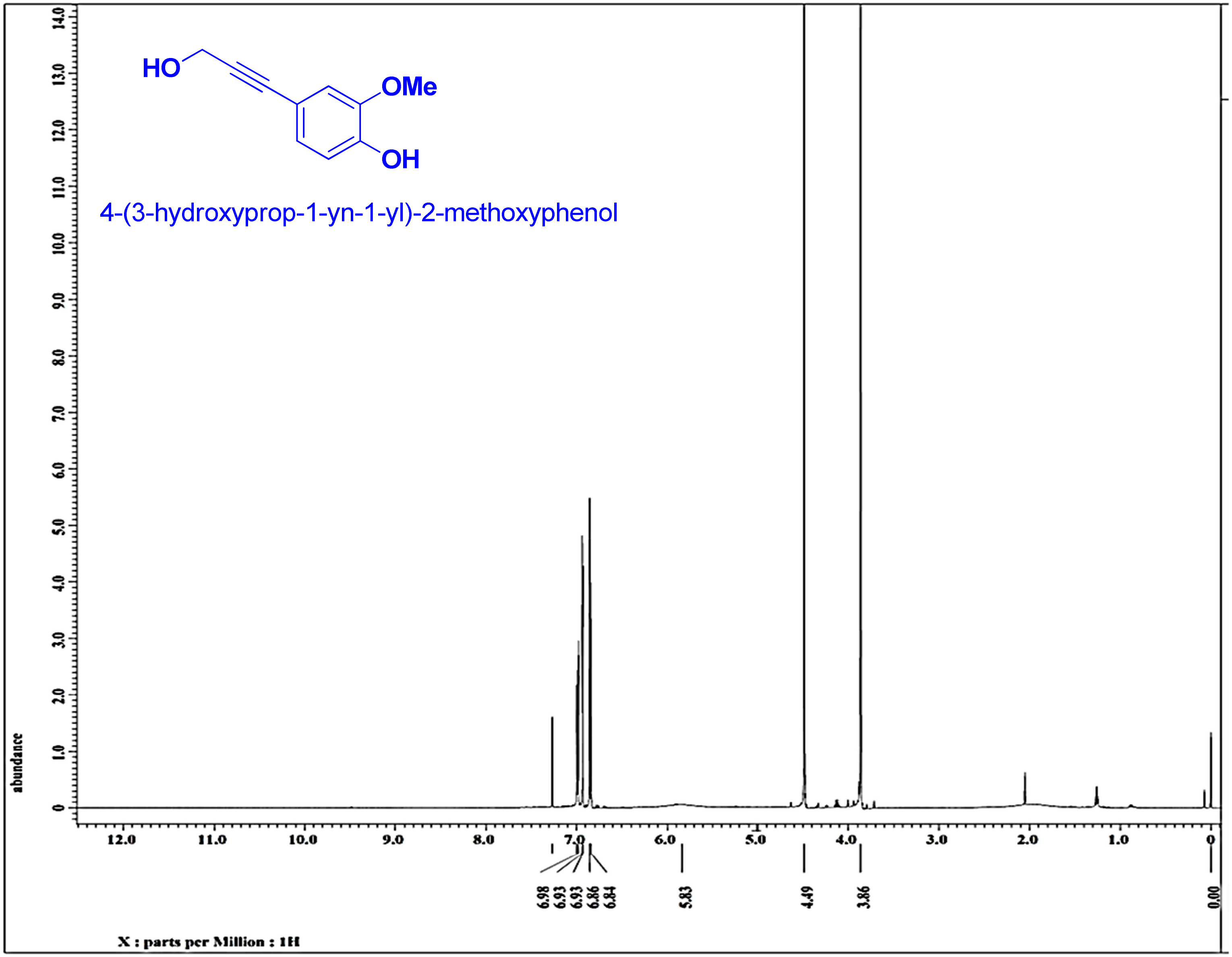


**Figure S19.** $^{13}$C NMR spectrum (125 MHz in $CDCl_3$) of 4-(3-hydroxyprop-1-yn-1-yl)-2-methoxyphenol

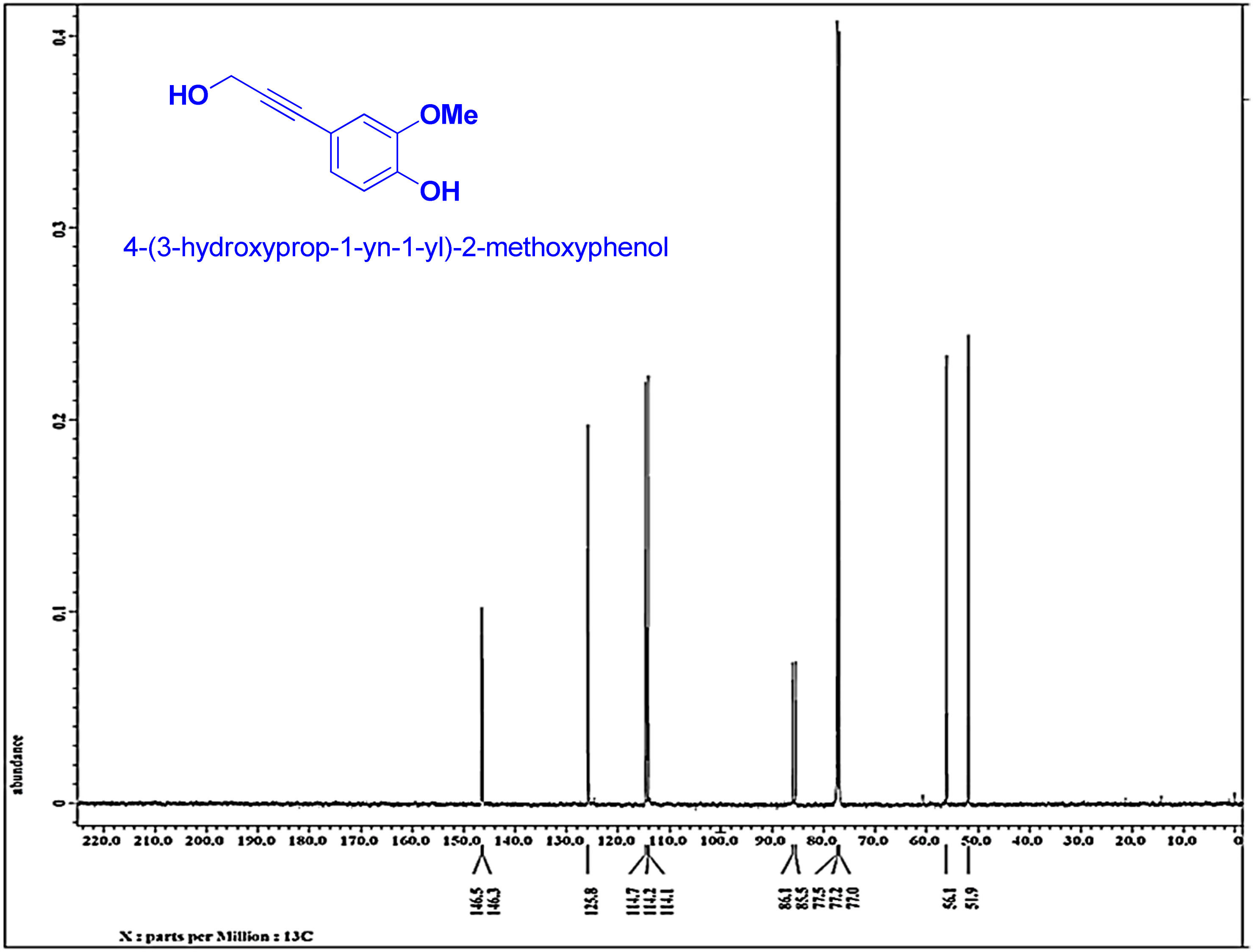


**Figure S20.** $^1$H NMR spectrum (500 MHz acetone-$d_6$) of *cis*-coniferyl alcohol (**19**)

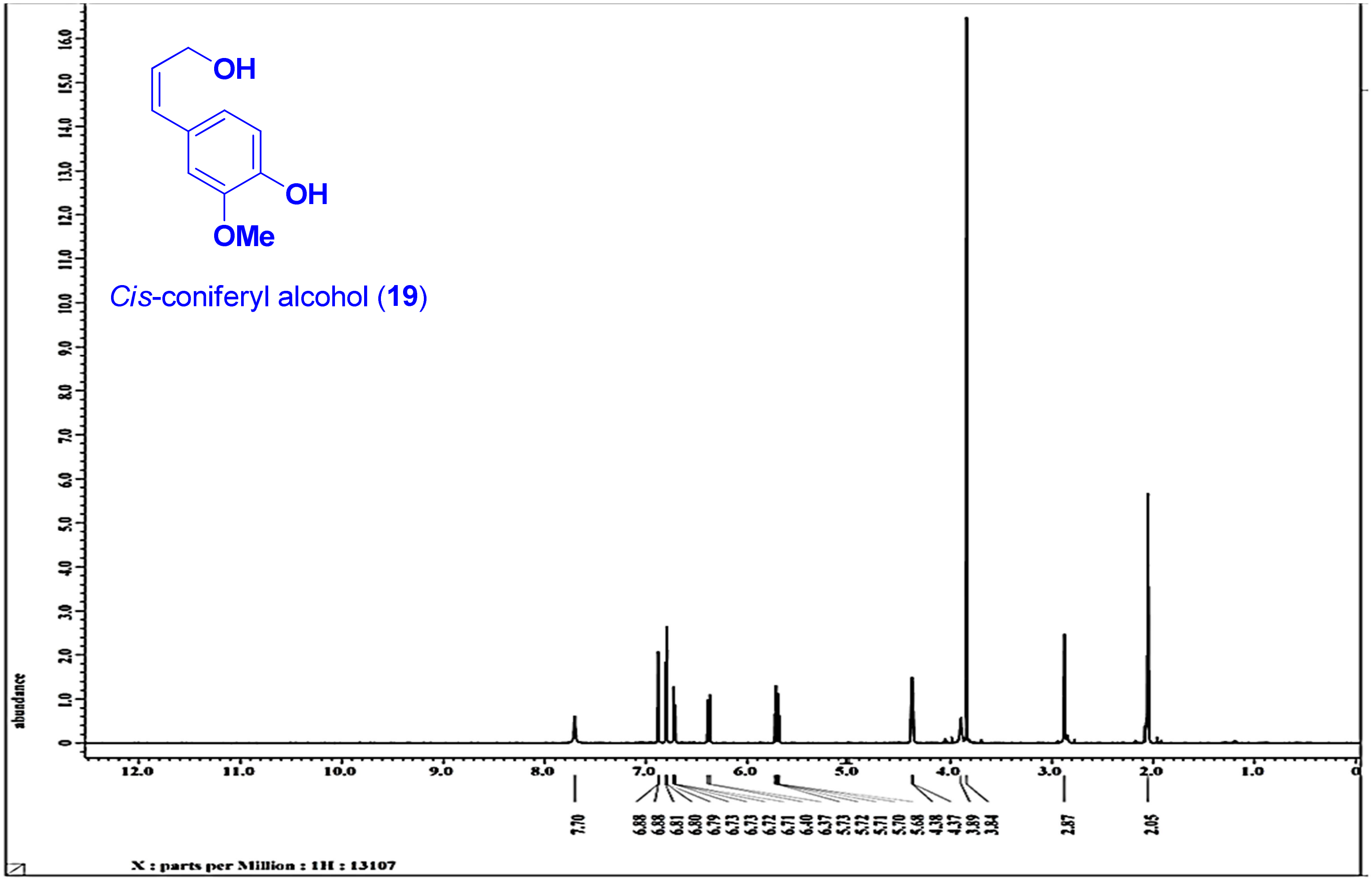


**Table S5.** $^{1}$H NMR data (500 MHz in acetone-$d_6$) comparing biomimetic *cis*-coniferyl alcohol (**19**) to the literature data

| Position | Type | Experimental (shift, multiplicity, coupling) | Literature[a] (shift, multiplicity, coupling) |
|---|---|---|---|
| 2 | CH | 6.88, d (1.7) | 6.87, d (2.0) |
| 5 | CH | 6.80, d (8.6) | 6.79, d (8.1) |
| 6 | CH | 6.72, dd (8.0, 1.7) | 6.72, dd (8.1, 2.0) |
| 7 | CH | 6.39, dt (12.0, 1.7) | 6.37, dt (11.8, 1.8) |
| 8 | CH | 5.71, dt (12.0, 6.3) | 5.70, dt (11.8, 6.2) |
| 9 | $CH_2$ | 4.37, br t (4.6) | 4.37, ddd (6.2, 5.4, 1.8) |
| $OCH_3$ | $CH_3$ | 3.84, s | 3.84, s |
| Ar-OH | OH | 7.70, br s | 7.60, br s |
| OH | OH | 3.89, t (5.2) | 3.81, t (5.4) |

[a] Ralph, J.; Zhang, Y. S. *Tetrahedron* **1998**, *54*, 1349-1354.