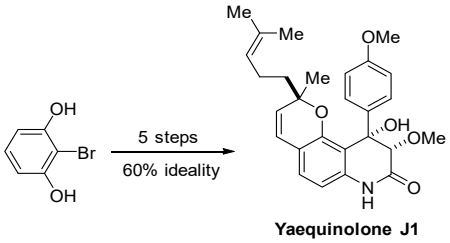
# Five-Step Synthesis of Yaequinolones J1 and J2

Johannes Schwan, Merlin Kleoff, Philipp Heretsch* and Mathias Christmann*

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany

Supporting Information Placeholder




**Yaequinolone J1**

**ABSTRACT:** A concise synthesis of yaequinolones J1 and J2 is reported. The route is based on the aryne insertion into the σ-C–N-bond of an unsymmetric imide followed by a diastereoselective aldol cyclization of the resulting *N*-acylated aminobenzophenone. The chromene motif is generated in the first step by an organocatalytic tandem Knoevenagel-electrocyclization of citral and 2-bromoresorcinol. The approach adheres to the ideality-principle, using almost exclusively strategic bond-forming reactions.

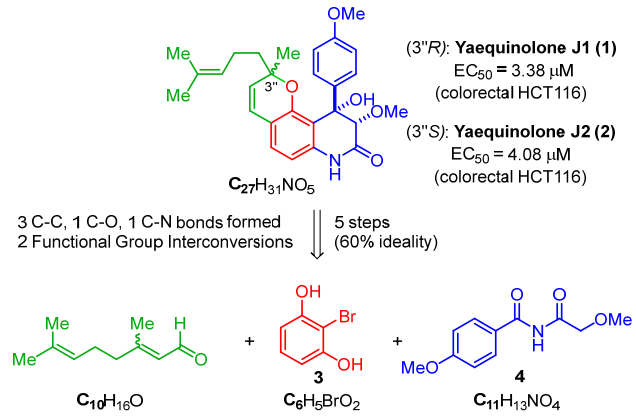
A natural product should be prepared from simple starting materials "linking them together directly, in a sequence of only successive construction reactions involving no intermediary refunctionalizations". This definition of the "ideal synthesis" by Hendrikson in 1975 already anticipates the concepts of atom, step and redox economy.[1,2] Accordingly, the focus of the synthetic community is shifting to step efficient syntheses providing natural products with a "minimum amount of labor and material expense."[2] The ideality of a synthesis can be expressed either numerically[2a] or graphically.[2b]

Some of the most step efficient syntheses have been enabled by specifically developed C-C and C-heteroatom bond formations.[3] Recently, our groups disclosed a general synthetic approach to 3,4-dioxygenated quinolinones by the insertion of arynes into unsymmetric imides.[4] We envisioned to employ the aryne approach to the synthesis of 3,4-dioxygenated quinolinones.

Yaequinolones J1 (**1**) and J2 (**2**), two diastereomeric meroterpenes, were isolated in 2005 from *Penicillium* sp. FKI-2140 in a screening program for new insecticides.[5] Biosynthetic studies indicate that the quinolone core is assembled from anthranilic acid and *O*-methyl-L-tyrosine.[6] Double prenylation in *ortho*-position of the phenol moiety affords a geranyl-substituted cationic intermediate that cyclizes forging the pyran motif in **1** and **2**.[7] In 2018, Hanessian and coworkers achieved the first enantioselective total synthesis of **1** and **2** and determined the absolute configuration of both diastereomers. It was also found that **1** and **2** display cytotoxicity against a melanoma A375 and a colorectal HCT116 cell line in the low μM range.[8]

Our retrosynthetic analysis divides **1** and **2** into three fragments (Scheme 1). The central aromatic ring was traced back to 2-bromoresorcinol (**3**). Annulation with citral affords the pyran motif while the quinolone is formed by aryne insertion of imide **4** followed by aldol cyclization.[9]

**Scheme 1. Step-Efficient Synthesis of Yaequinolones J1 and J2**




Our synthesis commenced with the tandem Knoevenagel-electrocyclization of citral and 2-bromoresorcinol (**3**) to construct the pyran. Similar reactions have been described for certain resorcinols with amine catalysts in toluene and xylene. However, under the reported conditions, annulation occurs predominantly in 2-position.[10] In anticipation of the pending aryne formation we employed 2-bromoresorcinol (**3**) instead. Since halogenated resorcinols have not been used in reactions with citral thus far, an initial catalyst screening was performed.

Ethylenediamine (**5a**) and ethylenediamine diacetate (EDDA, **5b**) were found to be the most active catalysts (Ta-

ble 1, entries 1 and 2). Other diamine-catalysts (**5c–f**) delivered chromene **6** in yields below 10%**,** whereas pyridine[10e] gave no conversion (entries 3–5). Pre-formation of the iminium-salt using piperidine and acetic anhydride[10a] resulted in a yield of 11% (entry 6). Applying conditions described by Lee,[10h] chromene **6** was obtained in 37% yield (entry 8). Further optimization (entries 7–11) revealed that chromene **6** can be prepared in 49% yield by increasing the amount of citral from one to two equivalents and the catalyst loading from 10 mol% to 20 mol%. Further increasing the amount of citral resulted in diminished yields.

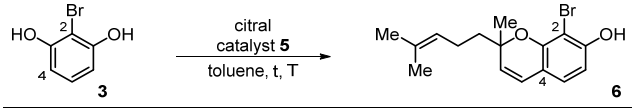
With the optimized protocol for chromene **6** in hand (entry 11), we focused on introducing the *ortho*-silyl triflate motif. Treating **6** with bis(trimethylsilyl)amine (HMDS) furnished the corresponding silyl ether. Halogen–metal exchange with *n*-butyllithium initiated a retro-Brook rearrangement upon which the resulting lithium phenolate was trapped with triflic anhydride.[11] Thus, aryne precursor **7** was prepared in 69% yield from **6** in one pot (Scheme 2).

Formation of the quinolone moiety started with the insertion of aryne-precursor **7** into unsymmetrical imide **4**. Treating **7** with imide **4** in the presence of dry cesium fluoride gave the desired benzophenone **8** in 31% yield, along with its regioisomer **9** (11%). Conducting the reaction in flow[4a] was not advantageous in this case due to the limited solubility of the starting materials in acetonitrile.

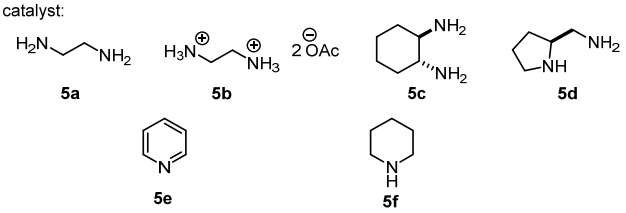
Racemic **8** was treated with potassium *tert*-butoxide in THF at 0 °C initiating the aldol cyclization to provide diastereomeric yaequinolones J1 and J2 in a ratio of 1:1.4 and 74% yield. It was possible to separate the two enantiomers of benzophenone **8** via chiral HPLC. Employing either (+)-**8** or (–)-**8**, enantiopure (+)-yaequinolone J2 in a yield of 40% or (–)-yaequinolone J1 in a yield of 30%, respectively.

To visualize the efficiency of syntheses, we recently developed a color-coded flow chart representation.[2b] Applied to this synthesis, it is evident that our route relies almost exclusively on construction reactions. With only two functional group interconversions that are performed in one pot, it directly translates into a high degree of ideality (Scheme 3).[12]

**Table 1. Optimization of the Tandem Knoevenagel-Electrocyclization**[a]




catalyst:

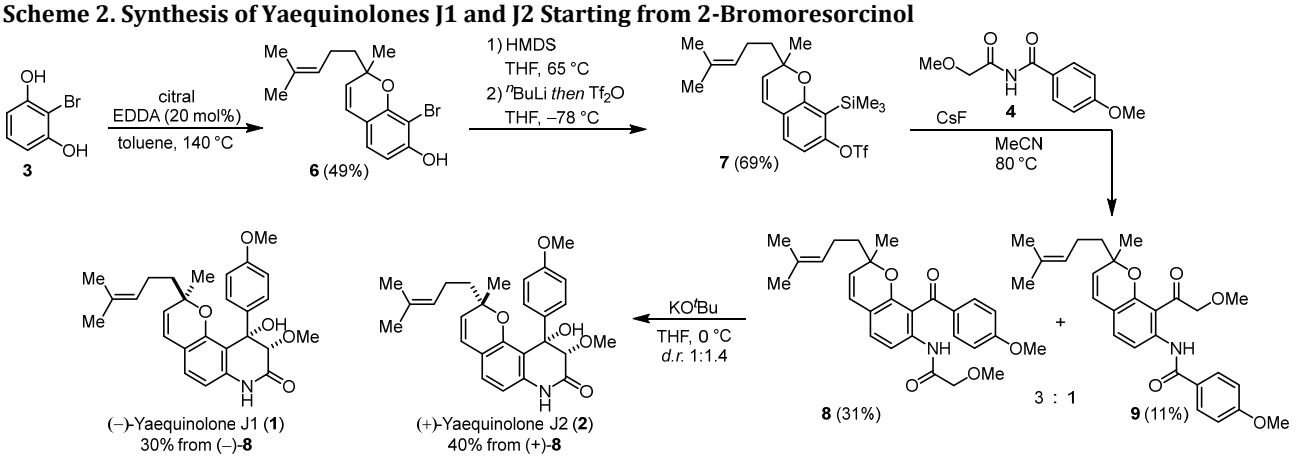



| Entry | Catalyst **5** [mol%] | Time [h] | Temp. [°C] | Citral [equiv.] | Yield [%] |
|---|---|---|---|---|---|
| 1 | **a** [30] | 0.5 | 150 | 1.5 | 26 |
| 2 | **b** [30] | 0.5 | 150 | 1.5 | 33 |
| 3 | **c** [30] | 0.5 | 150 | 1.5 | 8 |
| 4 | **d** [30] | 0.5 | 150 | 1.5 | 7 |
| 5[b,c] | **e** [200] | 18 | 90 | 1.0 | 0 |
| 6[b,d] | **f** [220] | 40 | 130 | 1.0 | 11 |
| 7 | **b** [10] | 5 | 140 | 1.0 | 29 |
| 8 | **b** [10] | 5 | 140 | 1.5 | 37 |
| 9 | **b** [10] | 5 | 140 | 2.0 | 42 |
| 10 | **b** [10] | 5 | 140 | 2.5 | 23 |
| 11 | **b** [20] | 5 | 140 | 2.0 | 49 (40)[b] |

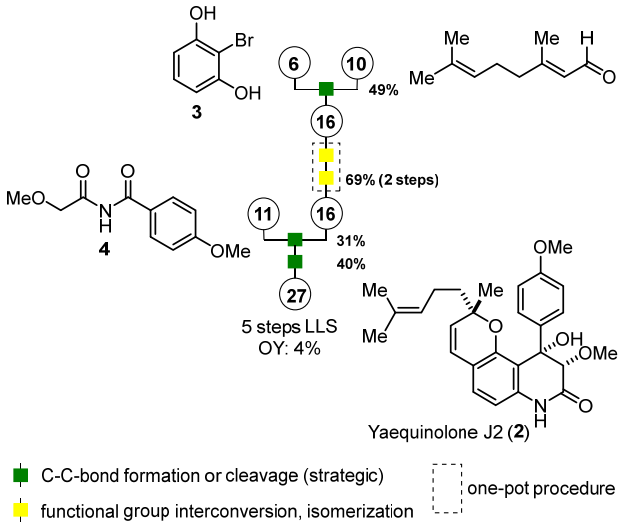
[a] Reactions were performed at 0.265 mmol scale in a sealed tube under microwave heating. [b] Performed under conventional heating using an oil bath. [c] Pyridine was used as solvent. [d] A mixture of EtOAc and toluene was used as solvent with acetic anhydride as additive.

In conclusion, we developed a five-step synthesis of yaequinolones J1 and J2 starting from commercial 2-bromoresorcinol (**3**) and citral. Enantiomerically pure natural products were obtained by separation of the enantiomers of (±)-**8** via chiral HPLC. This route provides a rapid access to yaequinolones J1 and J2, compared to the previously reported 18-step synthesis.[8]

**Scheme 2. Synthesis of Yaequinolones J1 and J2 Starting from 2-Bromoresorcinol**



**Scheme 3. Flow-Chart Presentation of the Synthesis of Yaequinolone J2**




## ASSOCIATED CONTENT

### Supporting Information.

Experimental procedures and characterization data including $^{1}H$ and $^{13}C$ NMR spectra, IR and high-resolution mass spectral data are given for all compounds as well as a comparison of NMR data with those reported for natural **1** and **2**.
(PDF)

## AUTHOR INFORMATION


### Corresponding Authors

* E-mail: philipp.heretsch@fu-berlin.de
* E-mail: mathias.christmann@fu-berlin.de


### Notes

The authors declare no competing financial interest.

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# Five-Step Synthesis of Yaequinolones J1 and J2

Johannes Schwan, Merlin Kleoff, Philipp Heretsch* and Mathias Christmann*

*Freie Universität Berlin, Institut für Chemie und Biochemie, Takustraße 3, 14195 Berlin, Germany*

# Supporting Information

## General Methods

Analytical data were obtained using the following equipment:

**NMR spectroscopy:** $^{1}H$ and $^{13}C$ NMR spectra were acquired on a JEOL ECP 500 (500 MHz), BRUKER Avance 500 (500 MHz), VARIAN Inova 600 (600 MHz), and a BRUKER Avance 700 (700 MHZ) in the reported deuterated solvents. The chemical shifts were reported relative to the deuterated solvents' residual shifts. The multiplicities of the signals are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, br = broad and combinations thereof.
The spectra were processed with the software MESTREC 9.0.

**Mass spectra** were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian)

**IR spectroscopy:** IR Spectra were recorded on a JASCO FT/IR-4100 spectrometer. Characteristic absorption bands are reported in wavelengths $\tilde{\nu}$ in $cm^{-1}$ and were analyzed with the software Spectral Manager from JASCO.

**Flash column and thin layer chromatography:** Reaction progress was monitored by thin layer chromatography (silica gel 60 F 254, E. Merck) using UV light ($\lambda$ = 254 nm) for visualization or vanillin staining agent (170 mL methanol, 20.0 ml conc. acetic acid, 10.0 mL conc. sulfuric acid, 1.0 g vanillin). Flash column chromatography was performed using silica gel M60 from MACHEREY & NAGEL (particle size: 40–63 µm).

**HPLC** was conducted on a modular KNAUER HPLC system with a UV detector at 254 nm and differential refractometer. For chiral separations, a ChiralPAK® IA (Daicel) 32 x 250 mm column was used.

**MPLC** was performed with a TELEDYNE ISCO Combi-Flash Rf or a TELEDYNE ISCO Combi-Flash Rf200 using prepacked $SiO_2$-columns and cartridges from TELEDYNE. UV response was monitored at 254 nm and 280 nm. As eluents, cyclohexane (99.5%+ quality) and EtOAc (HPLC grade) were used.

**Optical rotations** were measured on a JASCO P-2000 polarimeter at 589 nm using 100 mm cells and the solvent and concentration (g/100 mL) indicated

**Microwave reactions:** A BIOTAGE Initiator+ microwave reactor (400 W) was used to perform microwave heated reactions

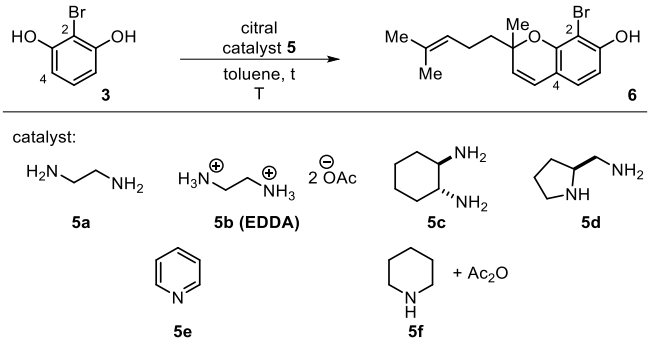
**Reagents and solvents:** Reactions with air or moisture sensitive substances were carried out under an argon atmosphere using standard Schlenk techniques. All reagents and solvents were used as purchased from commercial suppliers unless otherwise noted. Anhydrous solvents were purified with the solvent purification system MB-SPS-800 (BRAUN). Dry acetonitrile was purchased from ACROS Organics in AcroSeal©-bottles under argon atmosphere with molecular sieves (3 Å). HPLC-grade acetonitrile was purchased from Fischer Scientific. The solvents used for column chromatography (EtOAc, *n*-pentane, *n*-hexane) and work up were purified from commercially available technical grade solvents by distillation under reduced pressure with the help of rotatory evaporators (HEIDOLPH or IKA) at 40 °C bath temperature.
2-Bromoresorcinol was purchased from SIGMA ALDRICH. Imide **4** was prepared according to ref. 1.

Compound names are derived from CHEMDRAW 18.0 and are not necessarily identical with the IUPAC nomenclature.

Room temperature refers to 23 °C.

## Synthesis of Compounds

**Optimization of the Tandem Knoevenagel-Electrocyclization[a]**




| Entry | Catalyst **5** [mol%] | Time [h] | Temp. [°C] | Citral [equiv.] | Yield [%] |
|---|---|---|---|---|---|
| 1 | **a** [30] | 0.5 | 150 | 1.5 | 26 |
| 2 | **b** [30] | 0.5 | 150 | 1.5 | 33 |
| 3 | **c** [30] | 0.5 | 150 | 1.5 | 8 |
| 4 | **d** [30] | 0.5 | 150 | 1.5 | 7 |
| 5[b] | **e** [200] | 18 | 90 | 1.0 | 0 |
| 6[b,c] | **f** [220] | 40 | 130 | 1.0 | 11 |
| 7 | **b** [10] | 5 | 140 | 1.0 | 29 |
| 8 | **b** [10] | 5 | 140 | 1.5 | 37 |
| 9 | **b** [10] | 5 | 140 | 2.0 | 42 |
| 10 | **b** [10] | 5 | 140 | 2.5 | 23 |
| 11 | **b** [20] | 5 | 140 | 2.0 | 49 (40)[b] |

Reactions were performed using general procedure 1. [a] Performed under conventional heating using an oil bath. [b] Pyridine was used as solvent. c Performed according to procedure 2.

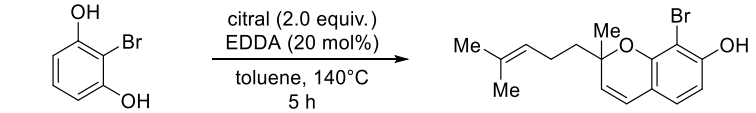
**Procedure 1:**

2-Bromoresorcinol (50 mg, 0.27 mmol, 1.0 equiv.) was dissolved in the solvent stated (3.0 mL). Amine catalyst **5** (0.1 equiv. to 0.2 equiv.) and citral (1.0 to 2.5 equiv.) were added. The mixture was heated to the temperature stated in a sealed tube using microwave or conventional heating for the time stated. After cooling to room temperature, all volatile compounds were removed under reduced pressure. The residue was purified by MPLC (dry loading on Celite®, cyclohexane/EtOAc = 100:0 to 0:100) to yield the title compound **6** as a yellow oil.

**Procedure 2:**

Citral (282 mg, 1.85 mmol, 1.0 equiv.) and piperidine (0.40 mL, 4.1 mmol, 2.2 equiv.) were dissolved in EtOAc (3.5 mL). Next, acetic anhydride (0.41 mL, 4.3 mmol, 2.3 equiv.) was added dropwise at 0 °C and the mixture was then heated to 90 °C for 1 h. After cooling to r.t., the mixture was added to a stirred solution of 2-bromoresorcinol (525 mg, 2.78 mmol, 1.5 equiv.) in toluene (7.5 mL) and heated to 150 °C in a sealed tube for 40 h. The reaction mixture was quenched with $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by MPLC (dry loading on Celite®, cyclohexane/EtOAc = 100:0 to 0:100) to yield the title compound **6** (66 mg, 0.20 mmol, 11% based on citral) as a yellow oil.

**8-Bromo-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-7-ol (6)**



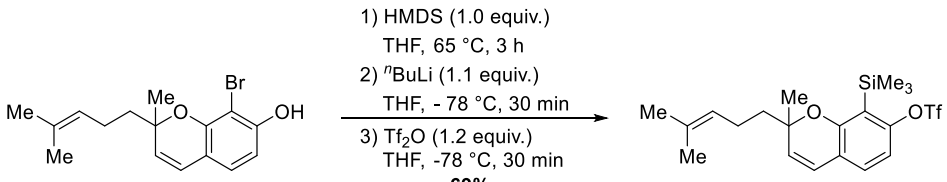

**3**
$C_6H_5BrO_2$ (189.01)

**6**
$C_{16}H_{19}BrO_2$ (323.23)

2-Bromoresorcinol (50 mg, 0.27 mmol, 1.0 equiv.) was dissolved in toluene (3.0 mL). Ethylenediamine-*N*,*N*'-diacetic acid (9.5 mg, 0.053 mmol, 0.2 equiv.) and citral (92 µL, 0.53 mmol, 2.0 equiv.) were added. The mixture was heated to 140 °C in a sealed tube using microwave heating for 5 h. After cooling to room temperature, all volatile compounds were removed under reduced pressure. The residue was purified by MPLC (dry loading on Celite®, cyclohexane/EtOAc = 100:0 to 0:100) to yield the title compound **6** as a yellow oil (42 mg, 0.13 mmol, 49%).

**$R_f$** = 0.26 (*n*-hexane/EtOAc 95:5); **$^1$H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 6.81 (d, J = 8.2 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.27 (d, J = 9.8 Hz, 1H), 5.44 (d, J = 9.8 Hz, 1H), 5.12 – 5.08 (m, 1H), 2.17 – 2.11 (m, 2H), 1.75 – 1.67 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.43 (s, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 153.2, 150.8, 132.0, 127.3, 125.9, 124.1, 122.2, 115.3, 107.4, 99.5, 80.3, 41.3, 26.6, 25.8, 22.7, 17.7; **IR** (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3506, 3040, 2969, 2921, 2856, 1637, 1604, 1530, 1516, 1499, 1479, 1438, 1384, 1338, 1306, 1246, 1182, 1120, 1077, 1031, 983, 952, 915, 901, 810, 762, 715; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{19}BrNaO_2^+$ ([M+Na]$^+$): 345.0460; found: 345.0461.

**2-Methyl-2-(4-methylpent-3-en-1-yl)-8-(trimethylsilyl)-2H-chromen-7-yl trifluoromethanesulfonate (7)**




**6**
$C_{16}H_{19}BrO_2$ (323.23)

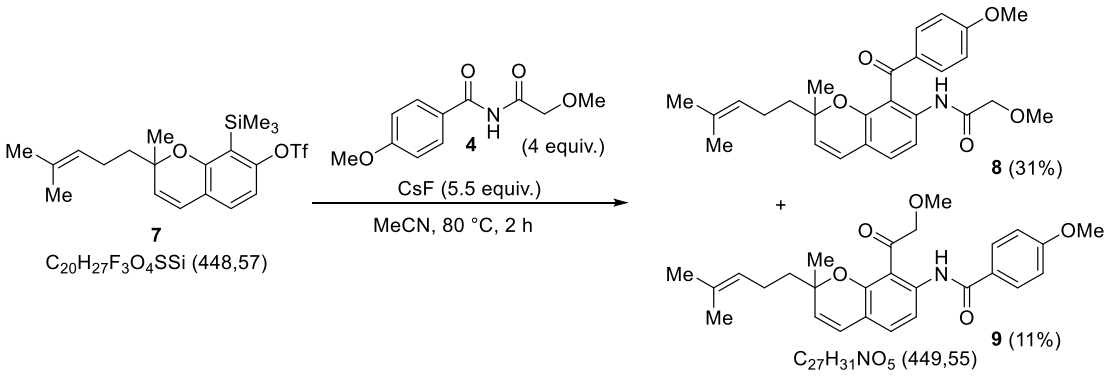
**7**
$C_{20}H_{27}F_3O_4SSi$ (448.57)

Compound **6** (100 mg, 0.309 mmol, 1.0 equiv.) was dissolved in THF (1.0 mL) and hexamethyldisilazane (66 µL, 0.31 mmol, 1.0 equiv.) was added. The mixture was heated to 65 °C for 3 h. After cooling to room temperature, all volatile compounds were removed under vacuum. The residue was dissolved in THF (1.0 mL) and *n*-butyllithium (0.14 mL, 2.5 M, 0.34 mmol, 1.1 equiv.) was added dropwise at –78 °C. After stirring at –78 °C for 30 min, trifluoromethanesulfonic anhydride (62 µL, 0.37 mmol, 1.2 equiv.) was added and stirring was continued for 30 min. $NaHCO_3$ (sat. aq., 10 mL) was added at –78 °C and the mixture was extracted with EtOAc (3x50 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified via column chromatography ($SiO_2$, *n*-pentane/EtOAc 98:2) to yield the title compound **7** (95 mg, 0.21 mmol, 69%) as a colorless oil.

**$R_f$** = 0.61 (*n*-hexane/EtOAc 95:5); **$^1$H NMR** (500 MHz, $CDCl_3$): δ [ppm] = 6.98 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.33 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 9.9 Hz, 1H), 5.11 (tdd, *J* = 5.7, 2.8, 1.4 Hz, 1H), 2.23 – 2.01 (m, 2H), 1.86 (ddd, *J* = 13.9, 11.6, 5.2 Hz, 1H), 1.68 (s, 3H), 1.67 – 1.61 (m, 1H), 1.59 (s, 3H), 1.40 (s, 3H), 0.40 (s, 9H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 159.3, 154.2, 132.2, 129.6, 128.5,

123.9, 122.3, 119.9, 119.2, 118.8 (q, *J* = 320.8 Hz), 112.4, 80.2, 42.1, 27.1, 25.8, 23.4, 17.8, 1.2; **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ [ppm] = –72.8; **IR** (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2970, 2926, 2858, 1647, 1576, 1445, 1407, 1370, 1341, 1286, 1247, 1206, 1163, 1139, 1076, 1016, 988, 923, 907, 840, 694, 668; **HRMS** (ESI): *m/z* calculated for $C_{20}H_{27}F_3NaO_4SSi^+$ ([M+Na]$^+$): 471.1243; found: 471.1245.

**2-Methoxy-N-(8-(4-methoxybenzoyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-7-yl)acetamide (8) and 4-Methoxy-N-(8-(2-methoxyacetyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-7-yl)benzamide (9)**




Cesium fluoride (93 mg, 0.61 mmol, 5.5 equiv.) was dried at $10^{-3}$ mbar and 500 °C for 5 min. After cooling to room temperature, acetonitrile (1.5 mL) and imide **4** (100 mg, 0.45 mmol, 4.0 equiv.) were added. After adding aryne precursor **7** (50 mg, 0.11 mmol, 1.0 equiv.), the mixture was heated to 80 °C for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by MPLC (dry loading on Celite®, cyclohexane/EtOAc 100:0 to 0:100), yielding **8** (15 mg, 34 µmol, 31%) and **9** (5.7 mg, 13 µmol, 11%) as yellow oils. The thus obtained racemic mixture of **8** can be separated into its enantiomers by chiral HPLC (chiralPAK® IA, *n*-hexane/*i*-PrOH 95:5, flow: 18 mL·min$^{-1}$; 90 bar; *ee* ≥ 99% [HPLC]).

*(+)*-**8**: $[\alpha]_D^{24}$ = +128.6° (c = 0.22, $CHCl_3$); *(–)*-**8**: $[\alpha]_D^{24}$ = –146.3° (c = 0.19, $CHCl_3$)

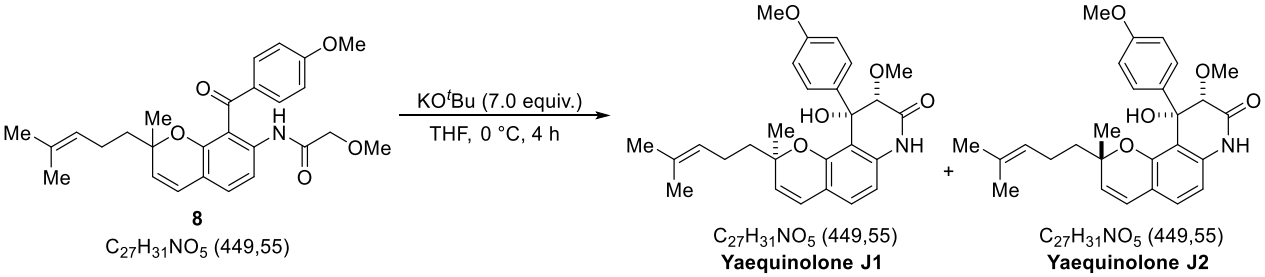
**$R_f$** = 0.22 (*n*-hexane/EtOAc = 4:1); **$^1$H NMR** (700 MHz, $CDCl_3$) δ [ppm] = 9.25 (s, 1H), 7.83 – 7.78 (m, 3H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.87 (m, 2H), 6.33 (d, *J* = 9.9 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 4.90 (ddt, *J* = 7.1, 5.7, 1.4 Hz, 1H), 3.90 (d, *J* = 0.6 Hz, 2H), 3.85 (s, 3H), 3.37 (s, 3H), 1.83 – 1.76 (m, 1H), 1.75 – 1.68 (m, 1H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.45 (d, *J* = 1.4 Hz, 3H), 1.43 – 1.38 (m, 2H), 1.12 (s, 3H); **$^{13}$C NMR** (176 MHz, $CDCl_3$) δ [ppm] = 195.3, 168.3, 163.8, 151.6, 135.9, 132.0, 131.9, 131.8, 129.0, 128.7, 124.0, 122.1, 118.1, 117.7, 114.1, 113.6, 79.7, 72.3, 59.6, 55.6, 41.5, 26.5, 25.7, 22.5, 17.7; **IR** (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3356, 2966, 2924, 2852, 1717, 1700, 1683, 1669, 1662, 1653, 1647, 1635, 1596, 1577, 1540, 1533, 1521, 1517, 1507, 1457, 1430, 1418, 1399, 1307, 1285, 1257, 1192, 1170, 1153, 1112, 1083, 1029, 987, 947, 890, 843, 793, 762, 741, 720; **HRMS** (ESI): *m/z* calculated for $C_{27}H_{31}NNaO_5^+$ ([M+Na]$^+$): 472.2094; found: 472.2091.

**9**:

**$R_f$** = 0.35 (*n*-hexane/EtOAc = 4:1); **$^1$H NMR** (700 MHz, $CDCl_3$) δ [ppm] = 12.37 (s, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 8.06 – 8.02 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.37 (d, *J* = 9.9 Hz, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 5.12 – 5.08 (m, 1H), 4.74 (d, *J* = 18.0 Hz, 1H), 4.71 (d, *J* = 18.0 Hz, 1H), 3.88

(s, 3H), 3.51 (s, 3H), 2.21 – 2.07 (m, 2H), 1.90 (ddd, *J* = 14.0, 11.1, 5.4 Hz, 1H), 1.73 (ddd, *J* = 14.1, 11.3, 5.2 Hz, 1H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.57 (d, *J* = 1.3 Hz, 3H), 1.49 (s, 3H); **$^{13}$C NMR** (176 MHz, $CDCl_3$) δ [ppm] = 202.1, 165.6, 162.8, 155.6, 141.9, 132.5, 132.5, 129.6, 127.4, 127.2, 123.5, 122.7, 116.4, 114.2, 113.3, 111.9, 81.6, 80.3, 59.5, 55.6, 42.0, 27.3, 25.8, 23.3, 17.8; **IR** (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2957, 2924, 2853, 1680, 1650, 1596, 1507, 1454, 1408, 1376, 1306, 1254, 1181, 1124, 1081, 1030, 925, 842, 756; **HRMS** (ESI): *m/z* calculated for $C_{27}H_{31}NNaO_5^+$ ([M+Na]$^+$): 472.2094; found: 472.2080.

**Yaequinolone J1 (1) and Yaequinolone J2 (2)**




**8**
$C_{27}H_{31}NO_5$ (449,55)

$C_{27}H_{31}NO_5$ (449,55)
**Yaequinolone J1**

$C_{27}H_{31}NO_5$ (449,55)
**Yaequinolone J2**

Compound **8** (25 mg, 56 µmol, 1.0 equiv.) was dissolved in anhydrous THF (3.0 mL) and a solution of KO$^t$Bu (0.78 mL, 0.39 mmol, 0.5 M in THF, 7.0 equiv.) was added at 0 °C. The mixture was stirred at 0 °C until complete consumption of starting material was observed via TLC (4 h). The reaction was quenched by addition of water and extracted with EtOAc (3x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified via column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH 97:3) to yield a mixture of yaequinolone J1 and J2 (18 mg, 0.41 mmol, *d.r.* = 1 : 1.4 [$^1$H NMR], 74%) as a colorless oil. The two diastereomers were separated by preparative TLC ($SiO_2$, $CH_2Cl_2$/MeOH 98:2), to yield pure yaequinolone J1 (7.3 mg, 16 µmol, 29%) and yaequinolone J2 (10 mg, 22 µmol, 40%) as colorless oils.

According to the synthesis of racemic yaequinolones J1 and J2, (–)-yaequinolone J1 (2.5 mg, 5.6 µmol, 30%) was obtained starting from (–)-**8** (8.2 mg, 18 µmol) and KO$^t$Bu (0.26 mL, 0.13 mmol, 0.5 M in THF). (+)-yaequinolone J2 (2.1 mg, 4.7 µmol, 40%) was obtained starting from (+)-**8** (5.3 mg, 12 µmol) and KO$^t$Bu (0.17 mL, 83 µmol, 0.5 M in THF).

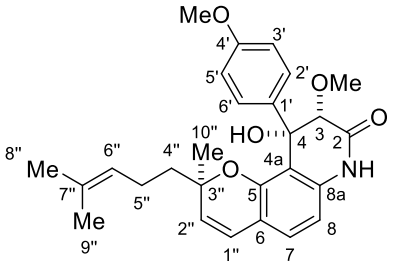
**(–)-Yaequinolone J1:**

$[\alpha]_D^{21}$ = –61.9° (c = 0.21, EtOH) [Lit:[2b] $[\alpha]_D^{23}$ = –65.6° (c = 0.1, EtOH)]; **$R_f$** = 0.37 ($CH_2Cl_2$/MeOH 95:5); **$^1$H NMR** (700 MHz, $CDCl_3$) δ [ppm] = 7.67 (s, 1H), 7.21 – 7.18 (m, 2H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.34 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 10.0 Hz, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 5.34 (s, 1H), 4.72 (tdd, *J* = 6.9, 3.0, 1.5 Hz, 1H), 3.80 (d, *J* = 1.4 Hz, 1H), 3.74 (s, 3H), 3.58 (s, 3H), 1.73 – 1.66 (m, 1H), 1.60 – 1.52 (m, 5H), 1.43 – 1.39 (m, 4H), 1.32 (s, 3H); **$^{13}$C NMR** (176 MHz, $CDCl_3$) δ [ppm] = 167.5, 159.7, 152.5, 136.4, 133.8, 131.9, 127.9, 127.5, 127.0, 123.6, 122.2, 117.8, 114.4, 114.1, 108.1, 85.1, 80.8, 78.0, 59.6, 55.3, 41.1, 26.7, 25.7, 22.1, 17.5; **IR** (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3495, 3225, 2965, 2929, 2857, 2836, 1694, 1606, 1510, 1492, 1377, 1252, 1176, 1102, 1046, 827, 742, 716 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{27}H_{31}NNaO_5^+$ ([M+Na]$^+$): 472.2094; found: 472.2092. The spektroscopic data matches those reported for (–)-Yaequinolone J1.[2]

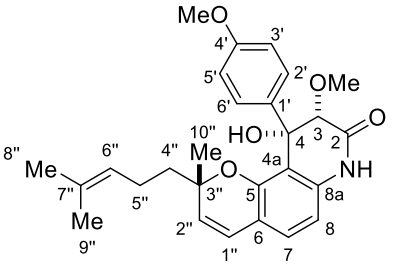
**(+)-Yaequinolone J2:**

$[\alpha]_D^{21}$ = +176.5° (c = 0.18, EtOH) [Lit:[2b] $[\alpha]_D^{23}$ = +187.1° (c = 0.1, EtOH)]; **$R_f$** = 0.39 ($CH_2Cl_2$/MeOH 95:5); **$^1$H NMR** (700 MHz, $CDCl_3$) δ [ppm] = 7.81 (s, 1H), 7.21 – 7.18 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.81 – 6.77 (m, 2H), 6.36 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 10.0 Hz, 1H), 5.50 (d, *J* = 9.9 Hz, 1H), 5.20 (s, 1H), 5.04 (tdd, *J* = 5.7, 2.8, 1.4 Hz, 1H), 3.83 (d, *J* = 1.4 Hz, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 2.09 (dq, *J* = 12.4, 6.6 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.70 – 1.60 (m, 5H), 1.57 (s, 3H), 0.95 (s, 3H); **$^{13}$C NMR** (176 MHz, $CDCl_3$) δ [ppm] = 167.7, 159.6, 152.6, 136.3, 134.2, 132.4, 128.3, 127.5, 127.0, 123.7, 122.6, 118.3, 114.9, 113.9, 108.2, 85.0, 80.5, 78.0, 59.7, 55.4, 41.4, 25.8, 25.7, 23.1, 17.8; **IR** (neat): $\tilde{\nu}$ [$cm^{-1}$]= 3507, 3235, 3062, 3043, 2967, 2925, 2853, 2836, 1694, 1641, 1605, 1510, 1491, 1462, 1377, 1303, 1252, 1222, 1175, 1104, 1081, 1046, 998, 916, 883, 830, 753, 734; **HRMS** (ESI): *m/z* calculated for $C_{27}H_{31}NNaO_5^+$ ($[M+Na]^+$): 472.2094; found: 472.2093. The spektroscopic data matches those reported for (+)-Yaequinolone J2.[2]

## $^{1}H$ and $^{13}C$ NMR comparisons ($CDCl_3$)

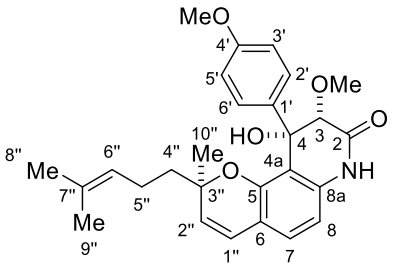



**Yaequinolone J1**

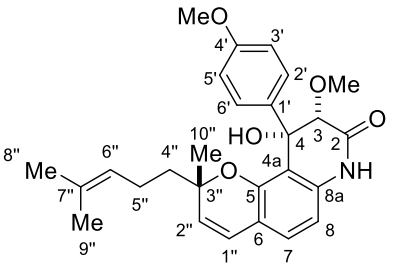



**Yaequinolone J2**

| **$^{1}H$ NMR Data** | **Synthetic (700 MHz)** | **Natural[2b] (600 MHz)** | **$^{1}H$ NMR Data** | **Synthetic (700 MHz)** | **Natural[2b] (600 MHz)** |
|---|---|---|---|---|---|
| **Position** | **δH (*J* in Hz)** | | **Position** | **δH (*J* in Hz)** | |
| 1-NH | 7.67, br s | 7.40, br s | 1-NH | 7.81, br s | 7.49, br s |
| 3 | 3.80, d (1.4) | 3.80, d (1.1) | 3 | 3.83, d (1.4) | 3.83, d (0.9) |
| 7 | 6.90, d (7.9) | 6.90, d (8.0) | 7 | 6.91, d (8.0) | 6.93, d (8.0) |
| 8 | 6.34 (8.0) | 6.34, d (8.0) | 8 | 6.36, d (8.0) | 6.36, d (8.0) |
| 2', 6' | 7.19, m | 7.19, d (8.4) | 2', 6' | 7.19, m | 7.19, d (8.8) |
| 3', 5' | 6.78, m | 6.78, d (8.4) | 3', 5' | 6.79, m | 6.79, d (8.8) |
| 1'' | 6.28, d (10.0) | 6.28, d (9.6) | 1'' | 6.31, d (10.0) | 6.31, d (9.7) |
| 2'' | 5.44, d (10.0) | 5.44, d (9.6) | 2'' | 5.50, d (9.9) | 5.50, d (9.7) |
| 4'' | 1.41, m | 1.40, m | 4'' | 1.65, m | 1.67, m |
| | | | | 1.65, m | 1.62, m |
| 5'' | 1.69, m | 1.69, m | 5'' | 2.09, dq (12.4, | 2.09, m |
| | 1.56, m | 1.56, m | | 6.6) | |
| | | | | 2.00, m | 2.01, m |
| 6'' | 4.72, tdd (6.9, | 4.71, t (7.1) | 6'' | 5.04, tdd (5.7, | 5.04, t (7.3) |
| | 3.0, 1.5) | | | 2.8, 1.4) | |
| 8'' | 1.56, m | 1.56, s | 8'' | 1.65, m | 1.66, s |
| 9'' | 1.32, s | 1.31, s | 9'' | 1.57, s | 1.57, s |
| 10'' | 1.41, m | 1.41, s | 10'' | 0.95, s | 0.95, s |
| 3-OMe | 3.58, s | 3.58, s | 3-OMe | 3.58, s | 3.58, s |
| 4'-OMe | 3.74, s | 3.74, s | 4'-OMe | 3.76, s | 3.77, s |
| 4-OH | 5.34, s | 5.36, s | 4-OH | 5.20, s | 5.22, s |




**Yaequinolone J1**




**Yaequinolone J2**

| $^{13}$C NMR Data | Synthetic (176 MHz) | Natural[2b] (150 MHz) | $^{13}$C NMR Data | Synthetic (176 MHz) | Natural[2b] (150 MHz) |
|---|---|---|---|---|---|
| **Position** | **δH (*J* in Hz)** | | **Position** | **δH (*J* in Hz)** | |
| 2 | 167.5 | 167.2 | 2 | 167.7 | 167.4 |
| 3 | 85.1 | 85.1 | 3 | 85.0 | 85.0 |
| 4 | 78.0 | 78.1 | 4 | 78.0 | 78.0 |
| 4a | 114.4 | 114.3 | 4a | 114.9 | 114.6 |
| 5 | 152.5 | 152.5 | 5 | 152.6 | 152.6 |
| 6 | 117.8 | 118.0 | 6 | 118.3 | 118.5 |
| 7 | 127.0 | 127.2 | 7 | 127.0 | 127.1 |
| 8 | 108.1 | 108.1 | 8 | 108.2 | 108.2 |
| 8a | 136.4 | 136.2 | 8a | 136.3 | 136.2 |
| 1’ | 133.8 | 133.7 | 1’ | 134.2 | 134.1 |
| 2’, 6’ | 127.5 | 127.5 | 2’, 6’ | 127.5 | 127.4 |
| 3’, 5’ | 114.1 | 114.2 | 3’, 5’ | 113.9 | 113.9 |
| 4’ | 159.7 | 159.8 | 4’ | 159.6 | 159.8 |
| 1’’ | 122.2 | 122.2 | 1’’ | 122.6 | 122.5 |
| 2’’ | 127.9 | 128.0 | 2’’ | 128.3 | 128.4 |
| 3’’ | 80.8 | 80.8 | 3’’ | 80.5 | 80.5 |
| 4’’ | 41.1 | 41.1 | 4’’ | 41.4 | 41.3 |
| 5’’ | 22.1 | 22.2 | 5’’ | 23.1 | 23.0 |
| 6’’ | 123.6 | 123.7 | 6’’ | 123.7 | 123.8 |
| 7’’ | 131.9 | 131.9 | 7’’ | 132.4 | 132.4 |
| 8’’ | 25.7 | 25.6 | 8’’ | 25.8 | 25.8 |
| 9’’ | 17.5 | 17.4 | 9’’ | 17.8 | 17.7 |
| 10’’ | 26.7 | 26.7 | 10’’ | 25.7 | 25.6 |
| 3-OMe | 59.6 | 59.5 | 3-OMe | 59.7 | 59.7 |
| 4’-OMe | 55.3 | 55.3 | 4’-OMe | 55.4 | 55.4 |

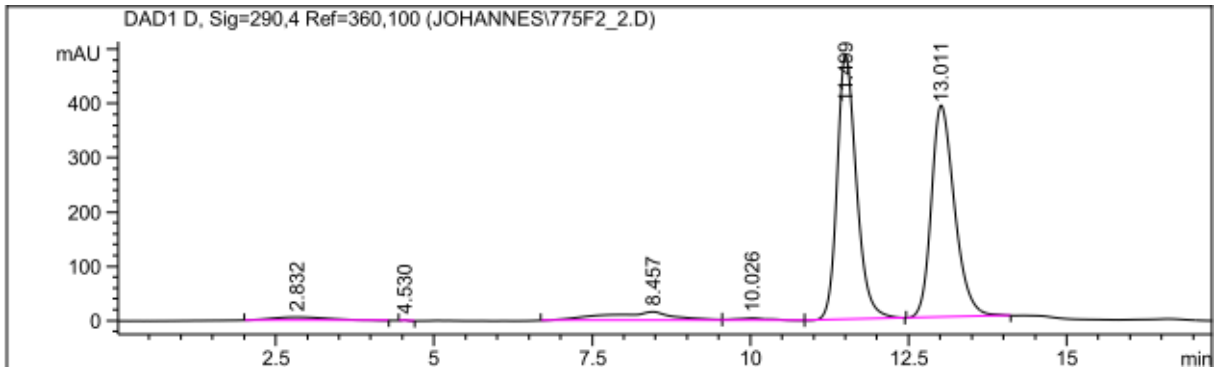
## References


(1) Schwan, J.; Kleoff, M.; Hartmayer, B.; Heretsch, P.; Christmann, M. Synthesis of Quinolinone Alkaloids via Aryne Insertions into Unsymmetric Imides in Flow. *Org. Lett.* **2018**, *20*, 7661–7664.

(2) (a) Vece, V.; Jakkepally, S.; Hanessian, S. Total Synthesis and Absolute Stereochemical Assignment of the Insecticidal Methabolites Yaequinolones J1 and J2. *Org. Lett.* **2018**, *20*, 4277–4280. (b) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Ōmura, S. Yaequinolones J1 and J2, Novel Insecticidal Antibiotics from *Penicillium* sp. FKI-2140. *Org. Lett.* **2005**, *7*, 5701–5704.

## Appendix

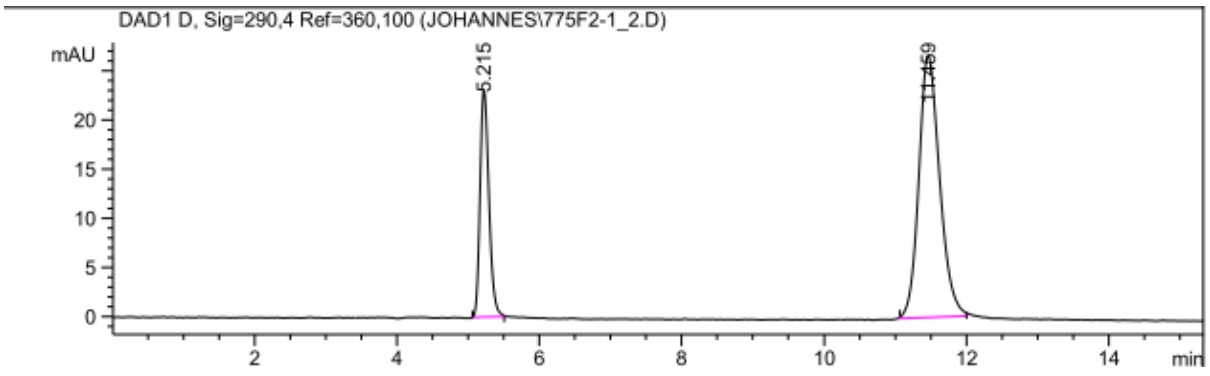
HPLC chromatogram of *rac*-**8** (ChiralPAK IA, 10% IPA/hexane, 34 bar, 0.8 mL/min):




Signal 2: DAD1 D, Sig=290,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 2.832 | BB | 0.7588 | 383.23703 | 5.98713 | 1.7278 |
| 2 | 4.530 | BB | 0.0855 | 7.06715 | 1.34046 | 0.0319 |
| 3 | 8.457 | BV | 0.9825 | 1241.70569 | 16.05212 | 5.5982 |
| 4 | 10.026 | VV | 0.5045 | 160.19423 | 4.16720 | 0.7222 |
| 5 | 11.499 | VB | 0.3243 | 1.03764e4 | 487.50809 | 46.7814 |
| 6 | 13.011 | BB | 0.3911 | 1.00120e4 | 390.47000 | 45.1385 |

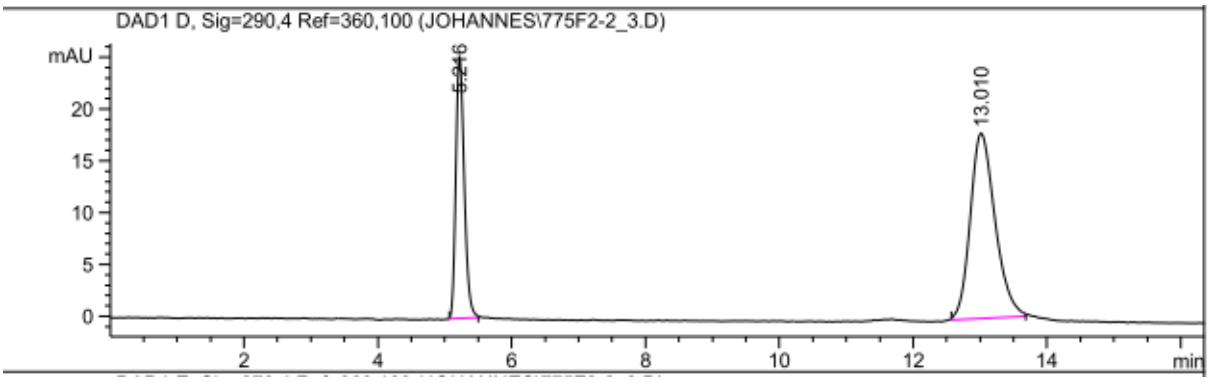
HPLC chromatogram of (+)-**8** (ChiralPAK IA, 10% IPA/hexane, 34 bar, 0.8 mL/min):




Signal 2: DAD1 D, Sig=290,4 Ref=360,100

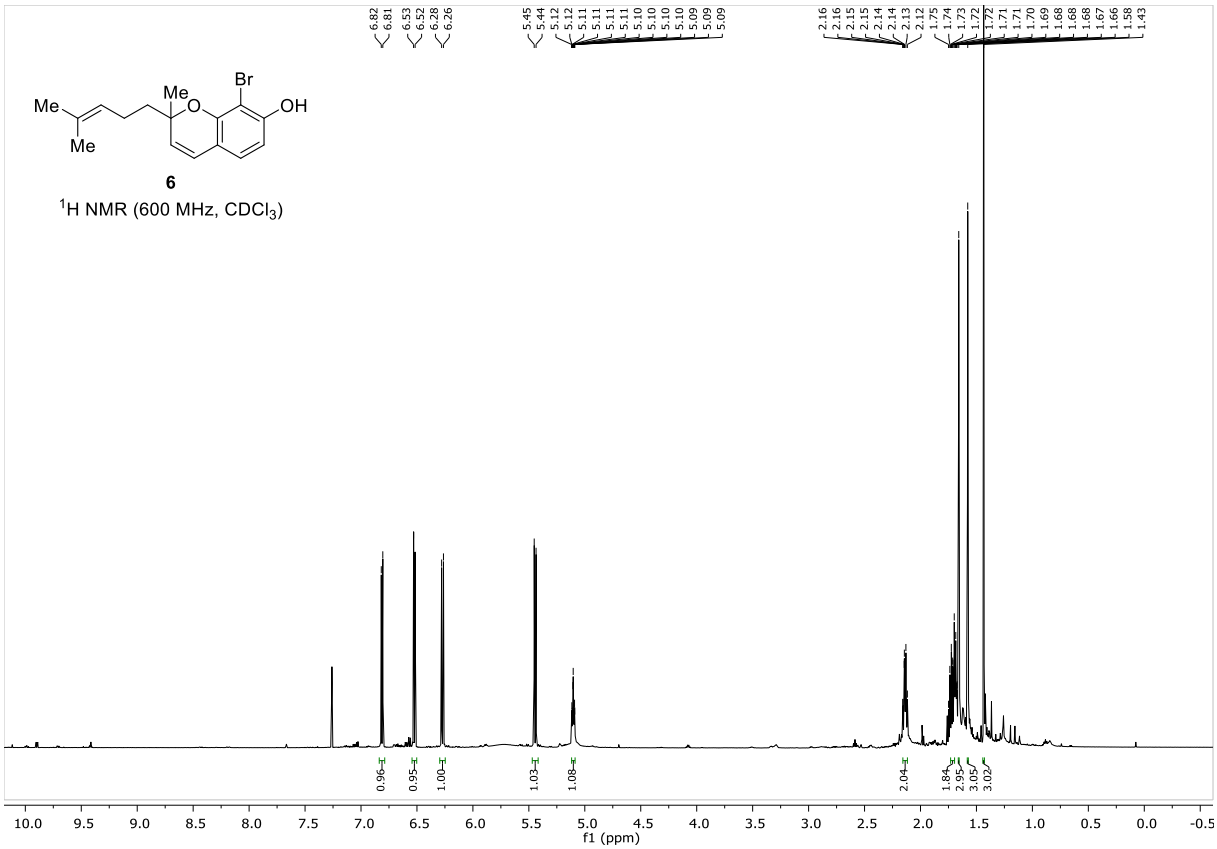
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.215 | BB | 0.1357 | 201.69472 | 23.14871 | 27.1269 |
| 2 | 11.459 | BB | 0.3073 | 541.82794 | 26.64318 | 72.8731 |

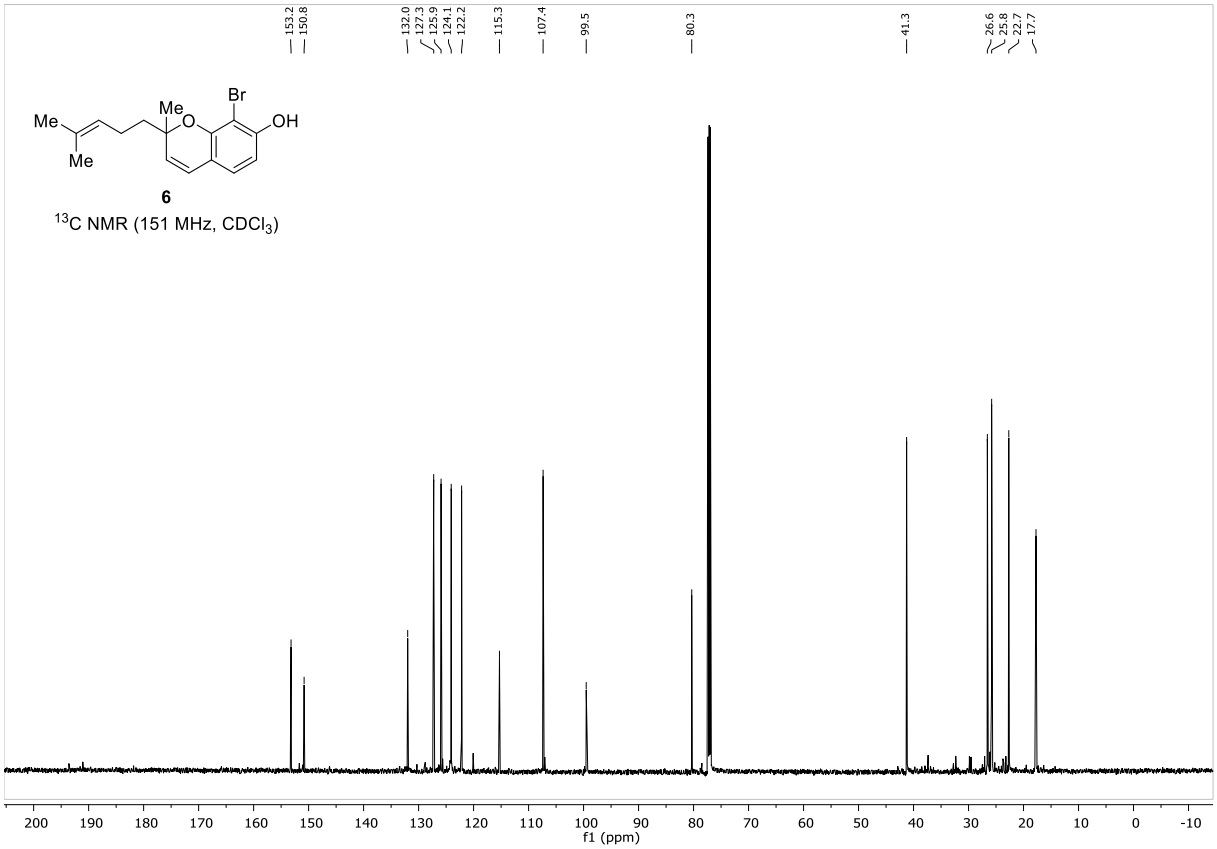
HPLC chromatogram of (–)-**8** (ChiralPAK IA, 10% IPA/hexane, 34 bar, 0.8 mL/min):

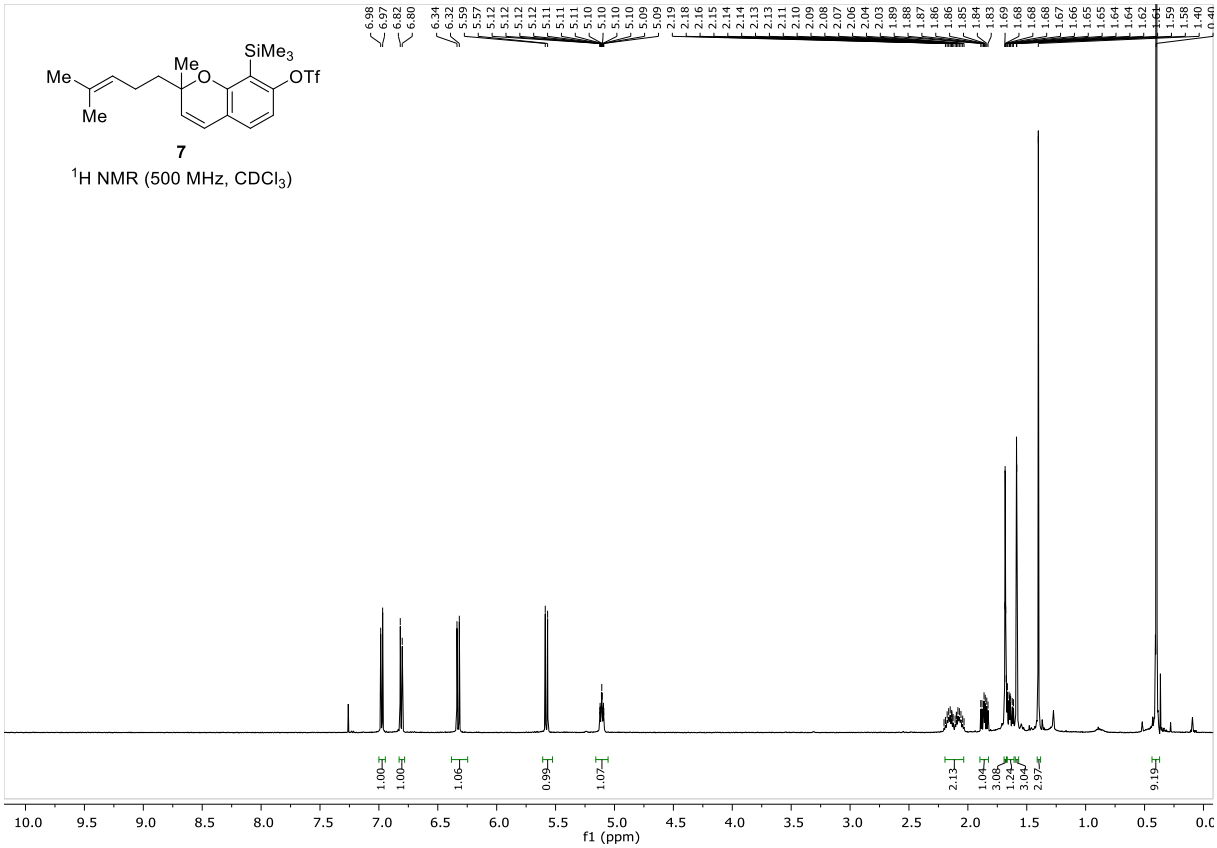


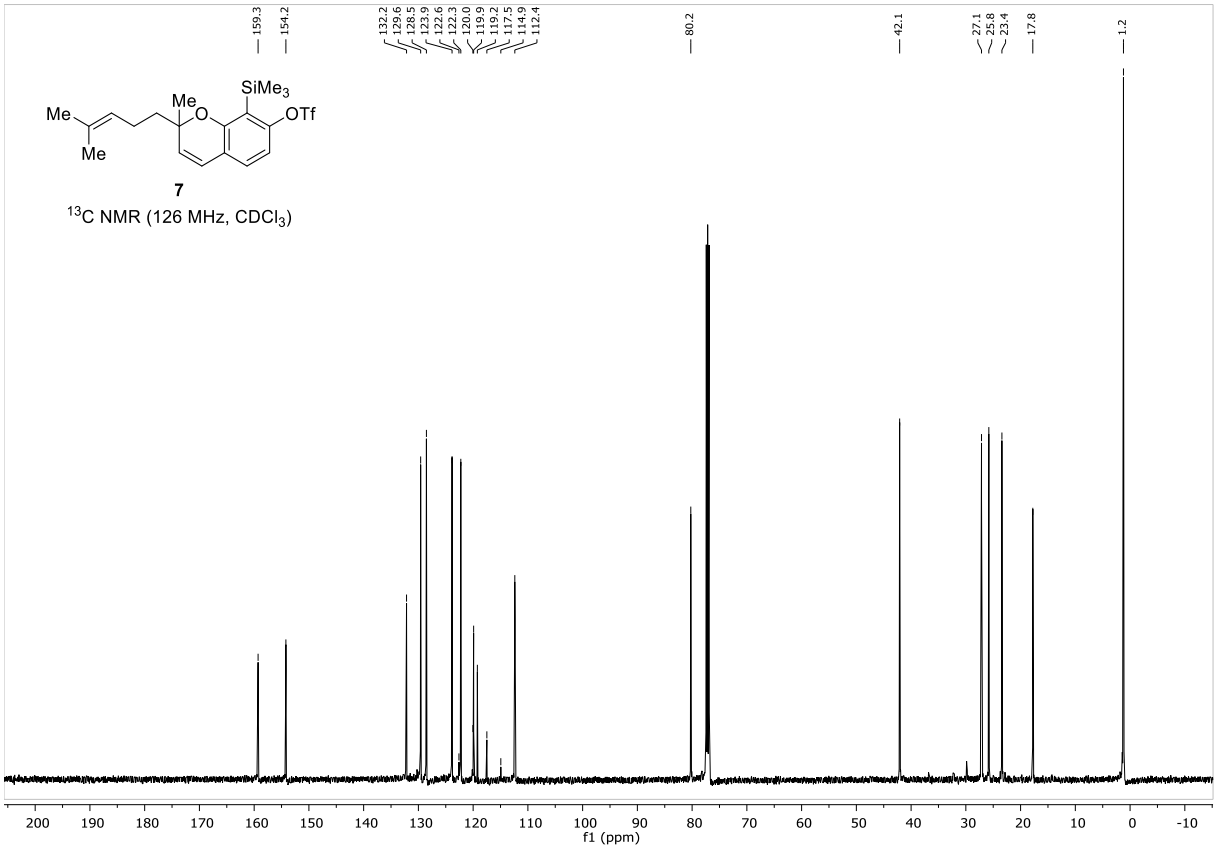

Signal 2: DAD1 D, Sig=290,4 Ref=360,100

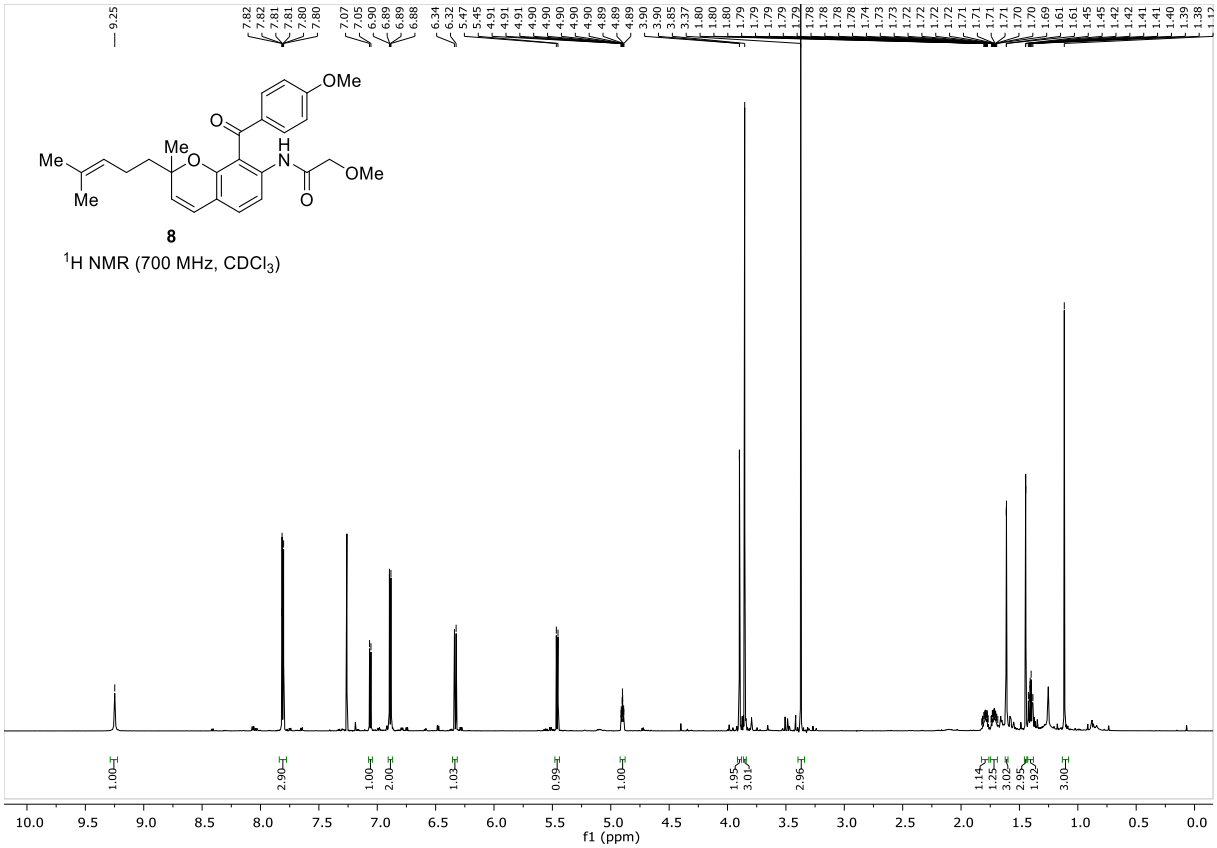
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.216 | BB | 0.1357 | 220.38380 | 25.29259 | 32.1903 |
| 2 | 13.010 | BB | 0.3924 | 464.24362 | 17.91024 | 67.8097 |


Me
Me
Me
O
Br
OH
6
$^1$H NMR (600 MHz, $CDCl_3$)
6.82
6.81
6.53
6.52
6.28
6.26
5.45
5.44
5.12
5.11
5.11
5.11
5.11
5.10
5.10
5.10
5.09
5.09
5.09
2.16
2.16
2.15
2.15
2.14
2.14
2.13
2.12
1.75
1.74
1.73
1.72
1.72
1.71
1.71
1.70
1.69
1.68
1.68
1.68
1.67
1.66
1.58
1.43
0.96
0.95
1.00
1.03
1.08
2.04
1.84
2.95
3.05
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


Me
Me
Me
O
Br
OH
6
$^{13}$C NMR (151 MHz, $CDCl_3$)
153.2
150.8
132.0
127.3
125.9
124.1
122.2
115.3
107.4
99.5
80.3
41.3
26.6
25.8
22.7
17.7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

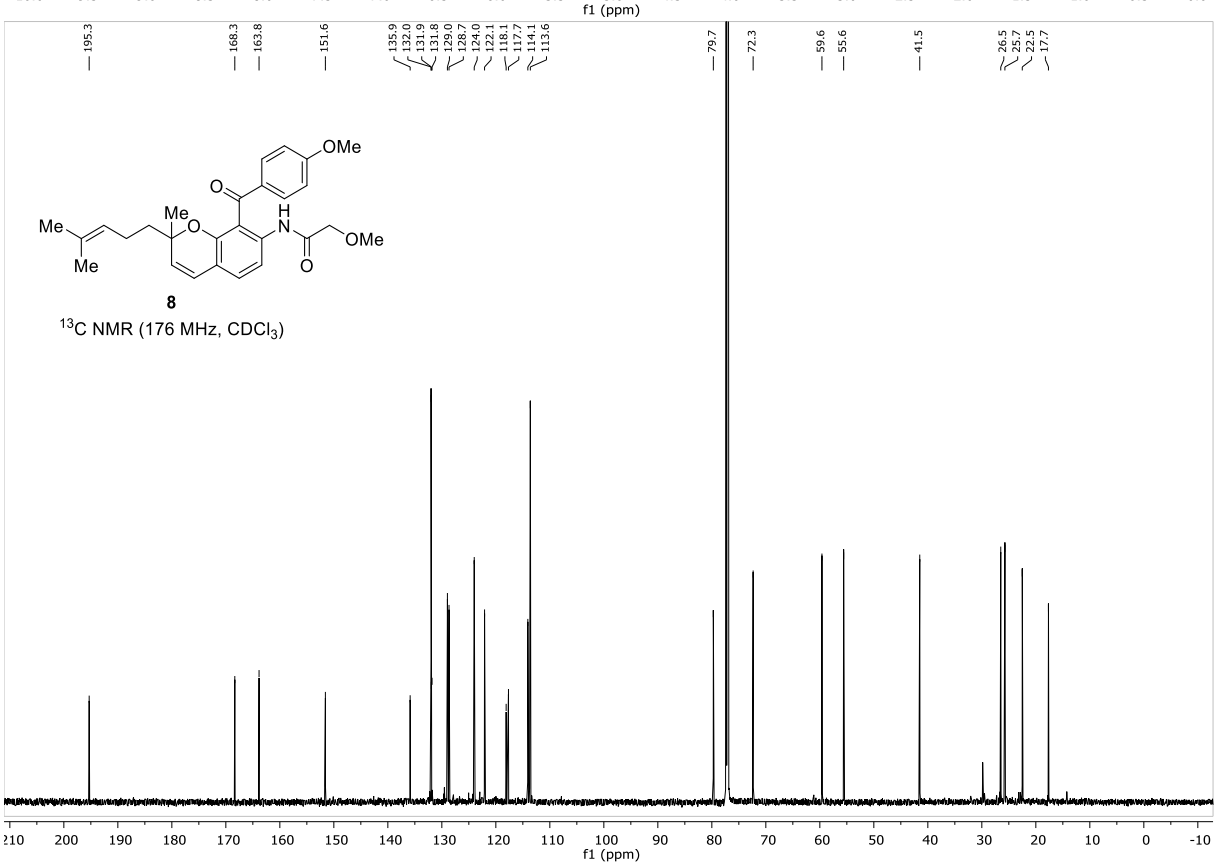

Me
Me
Me
O
SiMe3
OTf
7
1H NMR (500 MHz, CDCl3)
f1 (ppm)


Me
Me
Me
O
SiMe3
OTf
7
13C NMR (126 MHz, CDCl3)
f1 (ppm)



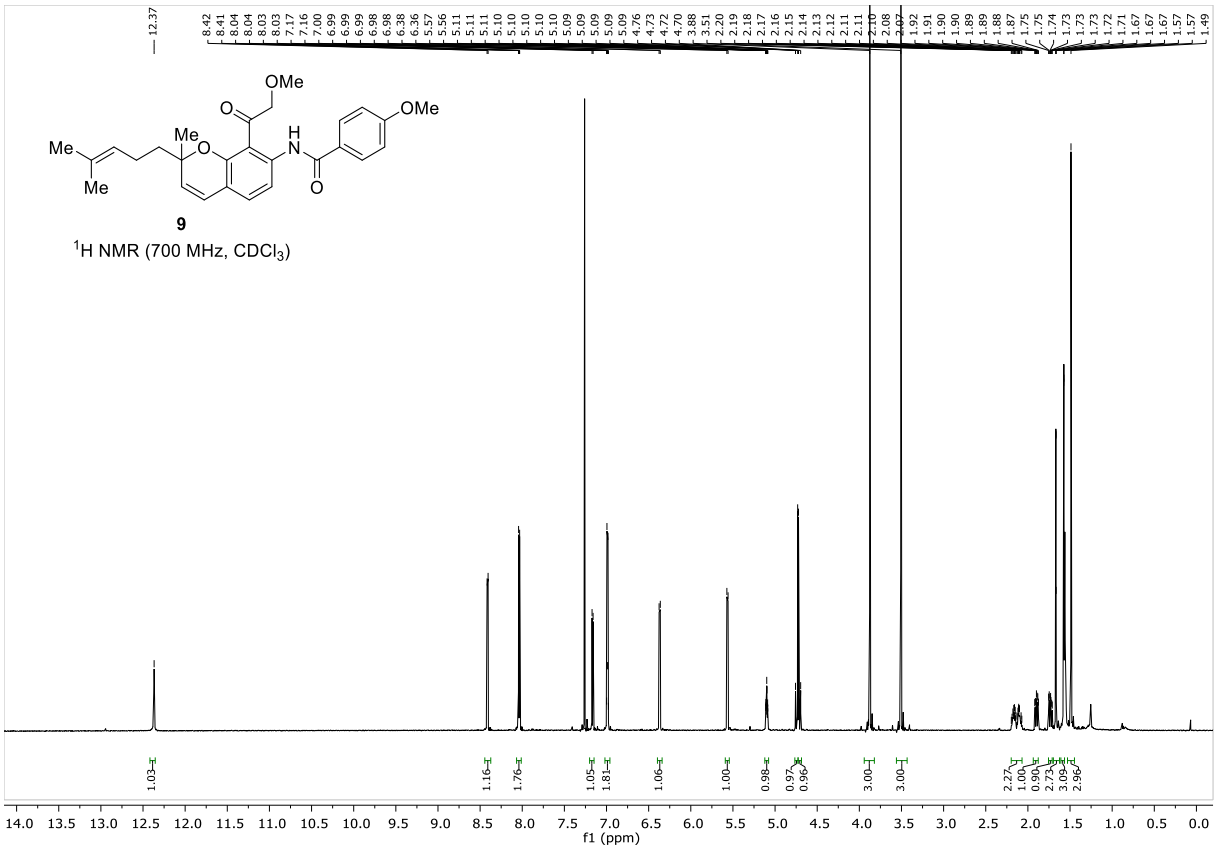

**8**

$^{1}$H NMR (700 MHz, $CDCl_3$)



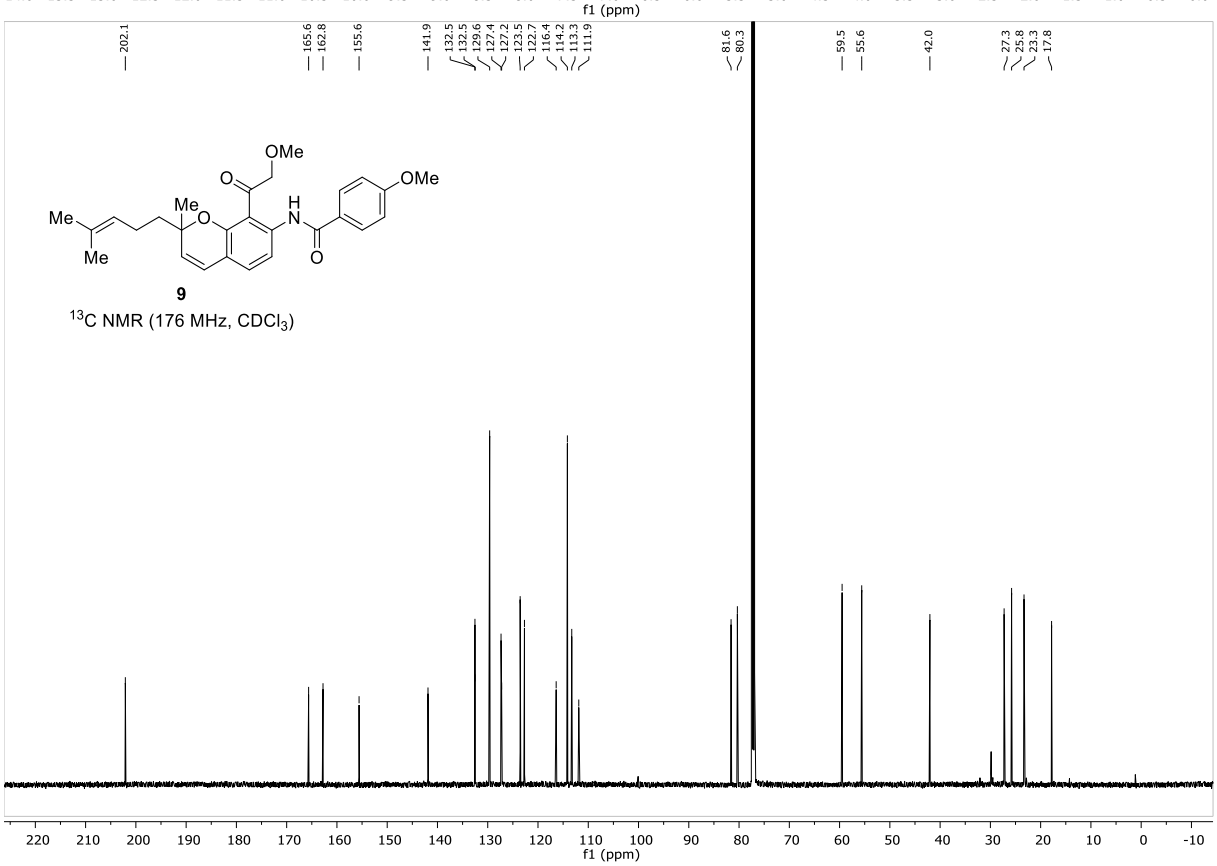

**8**

$^{13}$C NMR (176 MHz, $CDCl_3$)



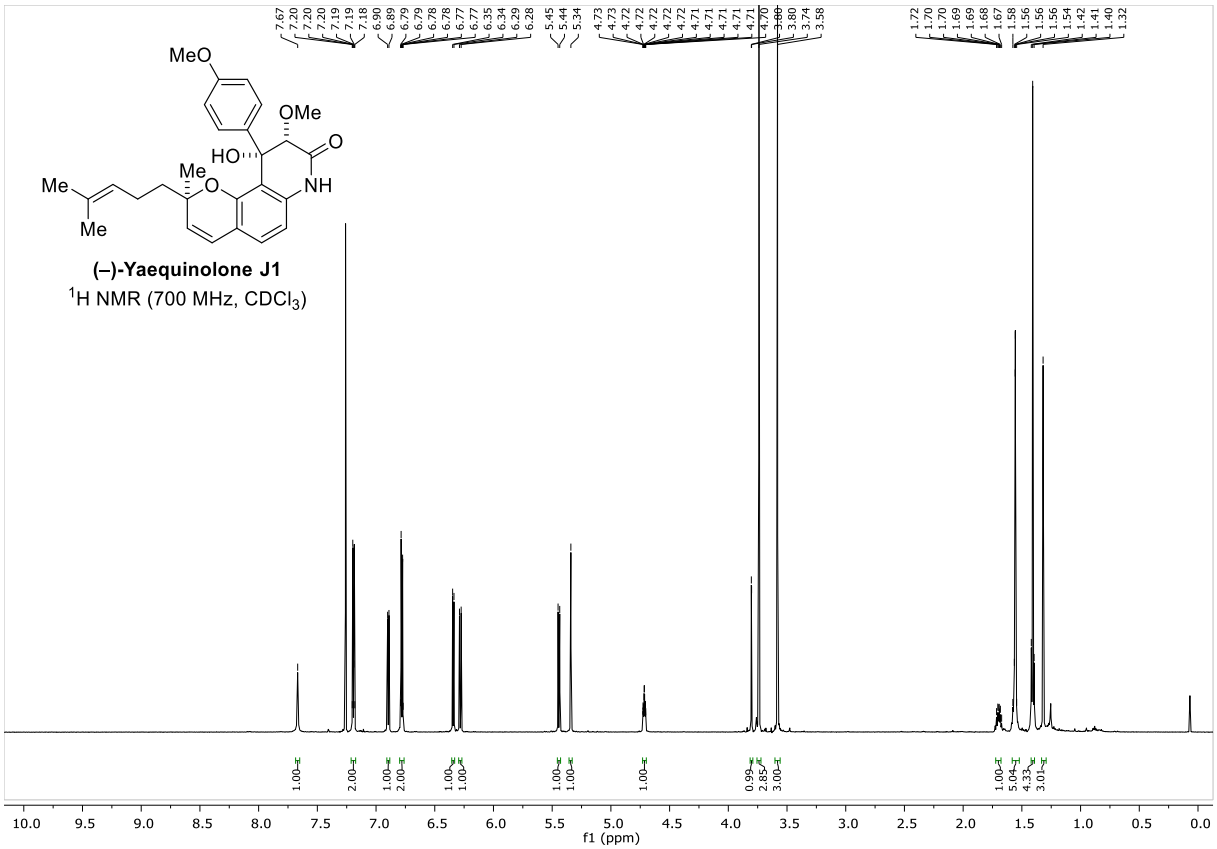

**9**

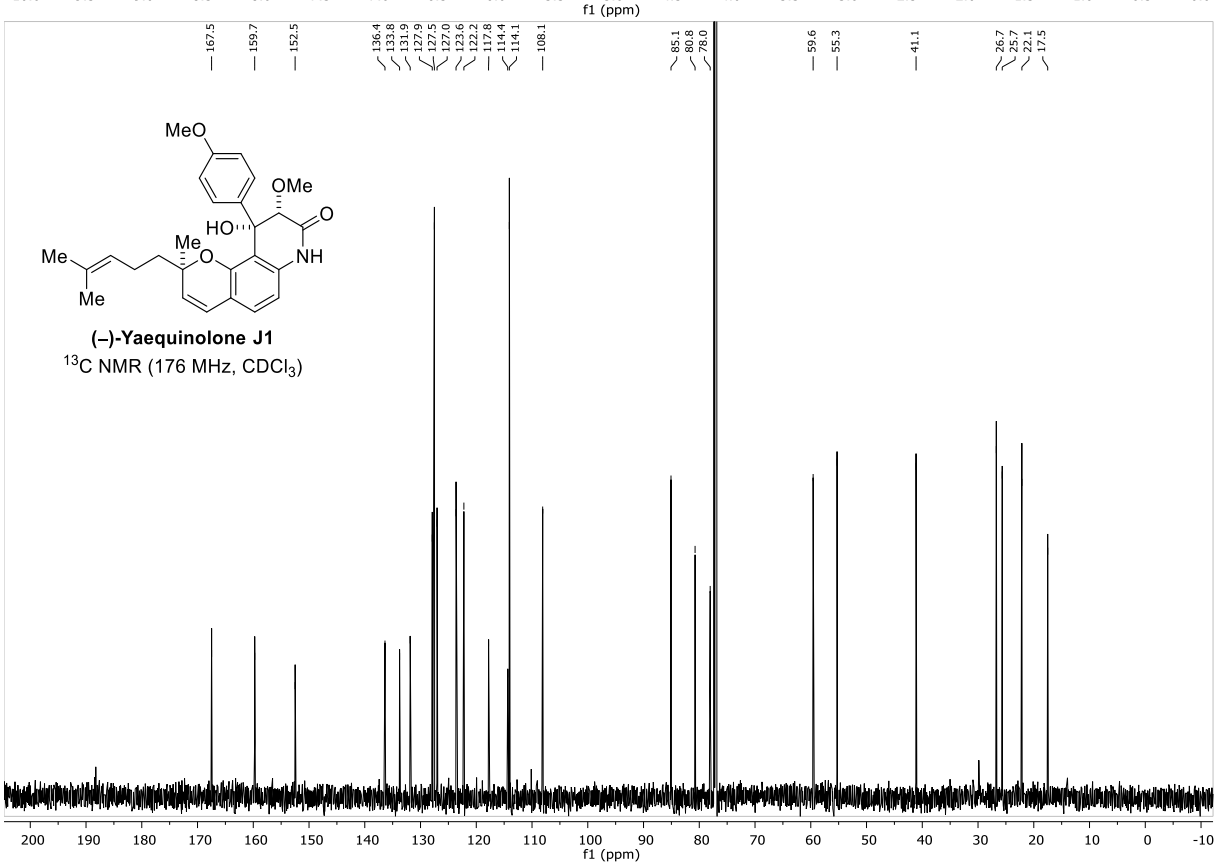
$^{1}$H NMR (700 MHz, $CDCl_3$)

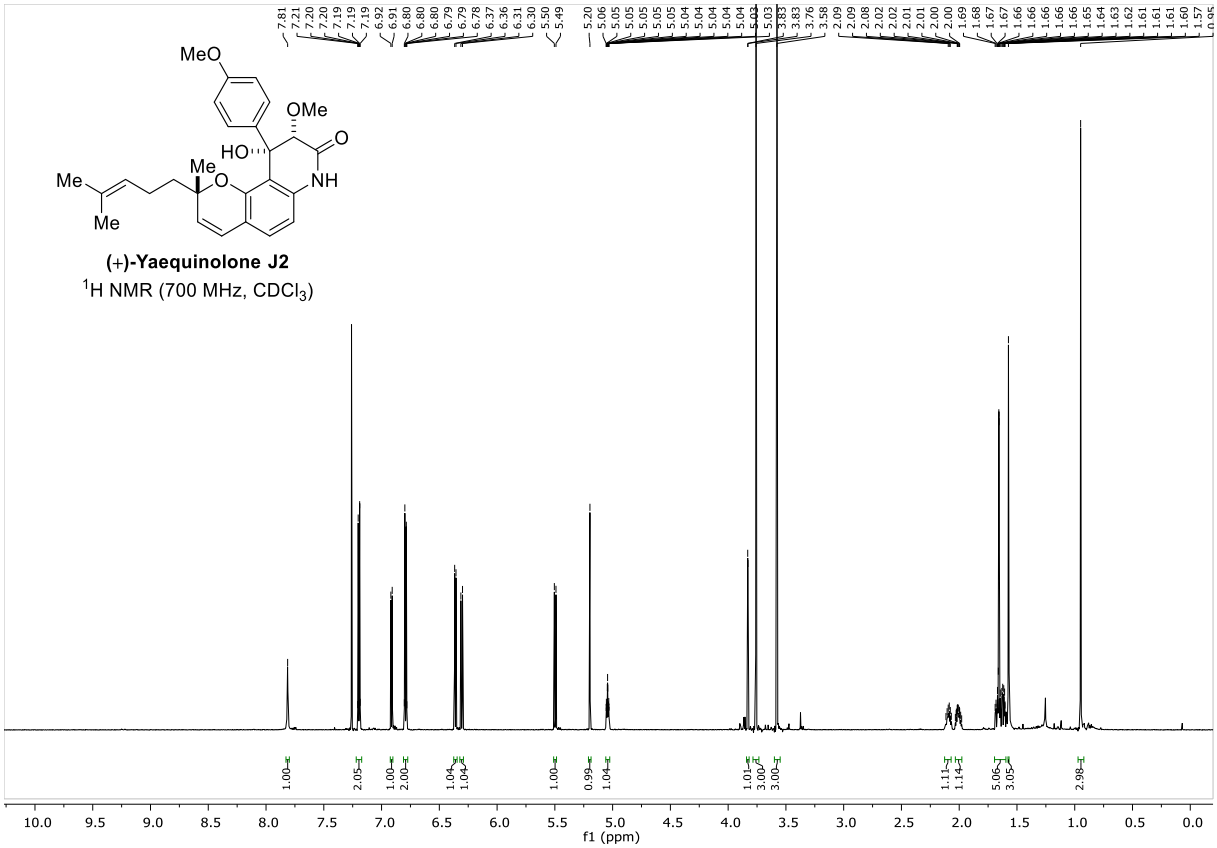


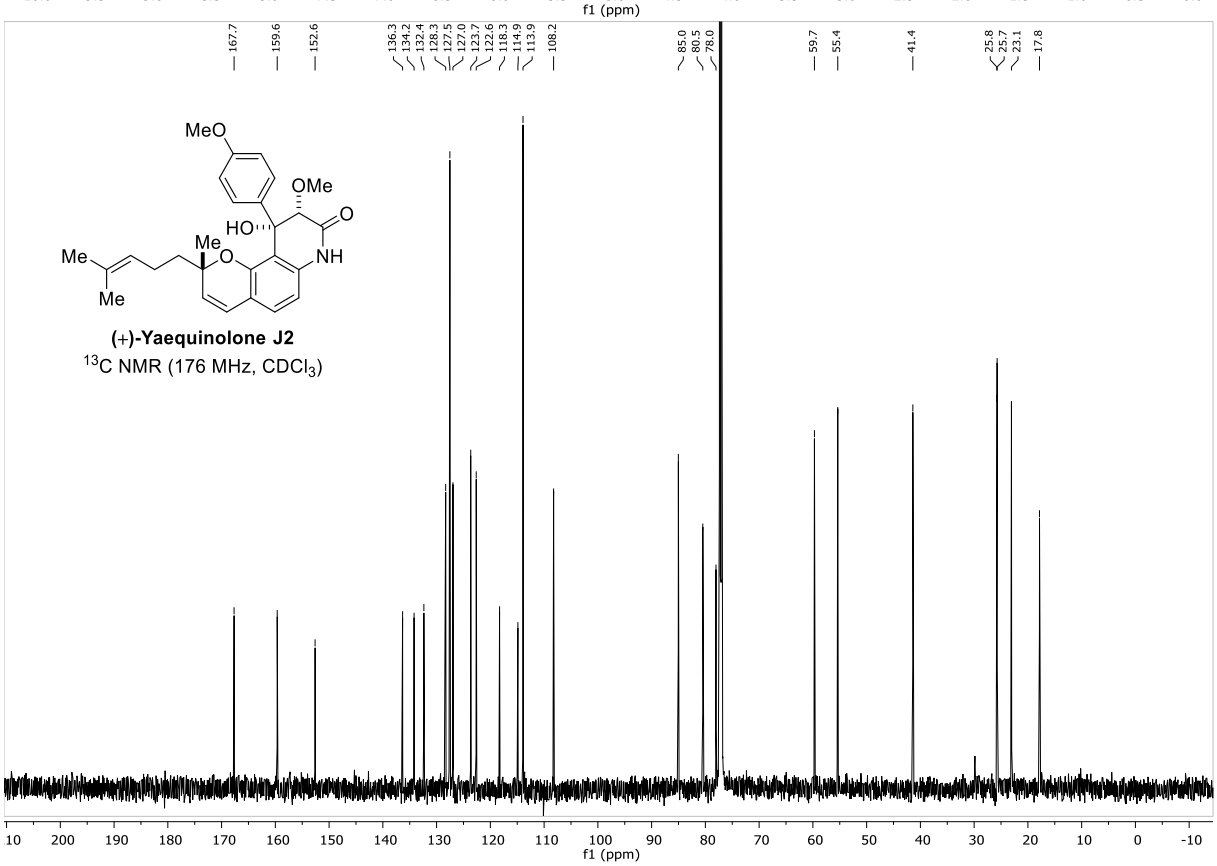

**9**

$^{13}$C NMR (176 MHz, $CDCl_3$)


MeO
OMe
HO
O
NH
Me
O
Me
Me
(–)-Yaequinolone J1
1H NMR (700 MHz, CDCl3)
f1 (ppm)


MeO
OMe
HO
O
NH
Me
O
Me
Me
(–)-Yaequinolone J1
13C NMR (176 MHz, CDCl3)
f1 (ppm)


MeO
OMe
HO
O
NH
Me
O
Me
Me
(+)-Yaequinolone J2
1H NMR (700 MHz, CDCl3)
f1 (ppm)


MeO
OMe
HO
O
NH
Me
O
Me
Me
(+)-Yaequinolone J2
13C NMR (176 MHz, CDCl3)
f1 (ppm)