Supplementary Material

### Overexpression of Secondary Metabolism Regulator and Enzyme Leads to the Discovery of Anti-inflammatory Meroterpenoids from *Alternaria alternata* JJY-32

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# **The aLaeA gene sequences of *Alternaria sp.* JJY-32**

ATGGCTGATATTGAAGCTCAGGTTGCTGTTGTGCGTCTTTCTCTCCCCCCAACTCTCGATTTCTTCACTGGCGCATTCACAAACTAATCCGACAACTCCAGGACTCGGATGAAACCGACTCGGCATTTGGCGACGACTCGGCATCGTAAGTCTCTCCCGTGAGACGCGGAGCCGCCTTCTGACACGCCATCAAAGCGAGACCACGTCCCTCAAGTCCGCCGTATACAACTACAAGTACCGTAACGGCCGGCGATACCATGCGTACAAGGAAGGAGCATATTGTTAGCATATCCGCTCGCTGTACATCCAATGCAGTTCCTAAGTGGGCGCAGGGGGTCCGAATGACGAGACACAATCAGATCAGTTGGATATAACGTATGTTCTGCGACCAGTTTGCTTCTACGTCGTGTGTTGACCTGGACGAAAGGCATCATATCTGTCTCCTCTTGCTCGACGGCGAGCTGTTTTTGGCTCCGATCAAGGAACAGCCTATGGTATGTAATGATGTGCATGGGGGGGTGCGACATGTTGGTACATGCTGACGGTTGGTCTACGGAATAGCATGTCTTGGATCTGGGAACGGGCACTGGTACGCAGACAGTAATCCGCCTGAGGCAACGCATGAGCTGACACATTCAGGAATCTGGGCTATCGACTTTGCCGATAGATATCCATCAGCCGAGGTCAGTGCACTTTGCAGCAGGCAGTCGAGTGAGTATCACTTTATTGATGTGAACAGGTCATAGGAACCGATCTTAGCCCCACCCAACCATCCATGGTCCCACCCAACGTGCGCTTCGAAATCGACGACTTCACTGAGCCGTGGCTATTCAAGAAAGATCATTTCGACTTCATACACATGCGATCGCTATATGGGTGTGTAGCGAACTGGGCGACCTTCTATAGAGAAGCACTGGAGTAAGTGAAGCCCCCATACATCACCTTGGCTCGCCTGTTAGACATTGCAACAGCTGACCATACGCTTCTGTCATTAGTGCCCTCCAACCCGGCGGATACGTCGAACAGCTCGAAATCAGCGTTGTACTAAAATCCGACGACGGCACCGTCACCTCCGGTTCCATCTTCGACCGCTGGGGCAAAATCTCCCTCGAACTCGGTGACCAATTCGGCAAATCTCTCCGCACAGTCGACGAATCGCGTGCGGGGCTCGAAGCAGCAGGCTTTGTCAACGTGGTAGAACGGCGCTGGAAGCTGCCGGTAGGAGGATGGCCGGCGGATAAGAGATTCAAGGAGTTGGGCCAGTACAATCGGATTAACTGGGAGCAGGGCATCGAAGGGTGGAGCTTGTACCTGTTGACGACGGTGATGAAGTGGAGTAAGGAGGAGGTTGAGGTTTATCTTGCGCATATGAGGACAGCGCTGAGGGATCGGAGTATCCATGCTTATCAGGAGGTGTAAGTTTATCATGTTTCTTTTGTAATGATGTTGATGATGGGTGGGGGAGCGTGGAATAAGAGAAGATGCAGGTTCAGGTGAGAGATGGCATTTTTTGCTAATTGATGTGCAGATCGCTGGTCTATGGACAGAAGCCGCCGAGGCCAAGGAAGGATGACGATGAGTGA

# **The aMpaB gene sequences of *Alternaria sp.* JJY-32**

ATGAGGGAAGTCCAAACAACTCAGATCAACGACGACACACCGCCAACTGACACAAAACTCCTATCATTTTCTTCATACGGTCCCAAAGTCTGGACTTGTCTCGCTCTTGCTGCCTACTGGCTTCTTGTTCGCGTTCTCCGTTACAAGCGTCGTGATGGTGTTTCTCGTCGCCTCGATGTAAGCAAATTACAACTAATGCTGATCAAATTAGGACTCTGACAGACCATTCAGTACTCTGATCGCTCGTCGTGGAGTCGTATGACACTTCAAGATGCGCATTCCATGCAGCTCGCTCTTGCCGAATTAGAGTTTCCGACCGTGTTTTCTGTTTCCGTGTTCTTCGCTCTCTTCAAGACATATGGCATCCCCAGCATTTCTAAGCTGCTAGTCGCAACAGGAAAGTTGTCAGCTCCTGAAACTGCATCCAAACGGGCCGCGGATACTGGTGTCGTGATCACCGAGGTAGTGCTAAATAAACCAGATTCTGAAAGAGCGATTAGTGGCATAGCACTTATGAATTACCTTCATGGTCGATACATCAAGGCTGGGAAGATATCGAATGACGATATGTTATACACCCTTAGTCTTTTCGTGCTCGAGCCAATCAGATGGACGGCCAAATACGAGTGGCGTGGTGTAACGGACTTTGAGAGATGCGCCATGGGCGTCTACTGGAAAGATCTGGGTGAGGCGATGAAGATATCGTACGATACTCTACCCTCTGCGGACCAAGGGTGGCGAGACGGGTTACACTGGCTCGAAGAATTGGAGGCGTGGAGCCTGGGGTACGAAAATCGGAATATGGTGCCCGCAAATACGAATGCAACACTCGCTCGCGGCACGTTCGACATTGCCTTGTTCAATGTGCCTTCTATTCTCAAACCGTATGGGTTCACCATAGCTTCTTCGTTGCTCGAGCCACGTTTACAGAAGGCGATGAAGTGAGTAAAAAAAGCCCTTTCGCATGATGTGTATACCATACTGACCATGCCCCAGGCTGCCACAACCACCAGCCGTATACACACAGATCCTTGAAACTGTCGTCGAGATTCGGAAATTTGCATTGCGAAACTTCTTTCTCCCTCGACCGCACTTCCTACGTAAGGAATGGTTCACAGAACTCGATGGAAAGACTGGACGTGCTCACTTCGGCCAATACATTGCTCACCCATGGTATATAAAGCCAACATTCATCACGAGATGGGGTCCGAAGGCGTTGTTACTGCGACTTATTGGGGGCGCCGTTCCAGGAGATGAGAAGTACCATCCAGATGGATACCGGATTCATGAGCTCGGTCCATCAGAGCTCGTAGGAAAGGATGACACTGAGATGAGTGAAACGAGAGAAGAGCTAAGAGCGCGAAGAATGGGGTGTGTTTTCTCTGGACGATGAGTCGCATTAACACAGGATTATGTTCGGGAAACGGAAGGTCTTGTTGAGATATCCAAGGGTCTACGGAATGGTTCCGCAGCTGCATCCACATGACGGAACGCTAACCCCGCGCGTCCACCCCGCGGTGATACATATAGACCGTTTGCTCTCCAATGTATAACAAAAAATCTCGCTTCAGTATCTTTGTTCCCTGTATCATCAATAACTCGTTATGGCGACCACAAAAGTAGCATTGATTACAGCTAGCTCGGCAGGATTAGGGGCACAGATAGCACGAGTATTTGCGCCAGACTTCCGTGTGGTATGTGTAAAACGCCTCGAATCACATATCCCCCCATATTTGAATACTGAGAGTGGTAGCTAACATCACCTAGGTAATCAACTATTCATCAAACTCGGATCGGGCACAATCTCTCATGAAGGAACTATCATCCATACCAGGCCCATCCTCAGAAGCAAACCCACGCTTCCACCTGGTTCAAGCAGACATGTCCTCAAAACCGTCAGTCCAAAATCTTGTAAAAGAAACAATCGAAAAGATGGGCCGATTGGACGTCGTCGTTTCTAACGCAGGCTGGACGCGCATGACGACCTTTACCGATATTGAGCAGCAAGTCAATGACGACGACTGGGACAAGTGTTTCACCATGAACGTCAAAACGCACATGTGGCTGGCATATGCCGCGAAAGATGCCTTGGCCGAAAACGAAGGATGTTTTATTTCGACAGCGAGTGTGGCGGGTGTGAAGCCTAGTGGAAGCAGCGTTCCTTATGCTGTTACCAAAGCAGCGCAAATTCATCTTGCAAAGAGTCTTGCTGTCATTCTGGCACCGAAGATTCGTGTGAACAGCATCAGTCCGGGTATGCTACTCACAGAATGGGGGCTCAAGTTCCCAGAAGCGAAGCGTAATGCTGCGATCAACAACACCAAGTTGAAGAGGCTGGCTACAGTGGAAGATTGTGCGGATCAGGTCAGAGTGCTGGCGCTGAGTAGAAGTATCACTGGGCAGAACATCTCGATAGATGGCGGTTCATCGGTCTAG

**Table S1.** Strain and plasmid used in this study

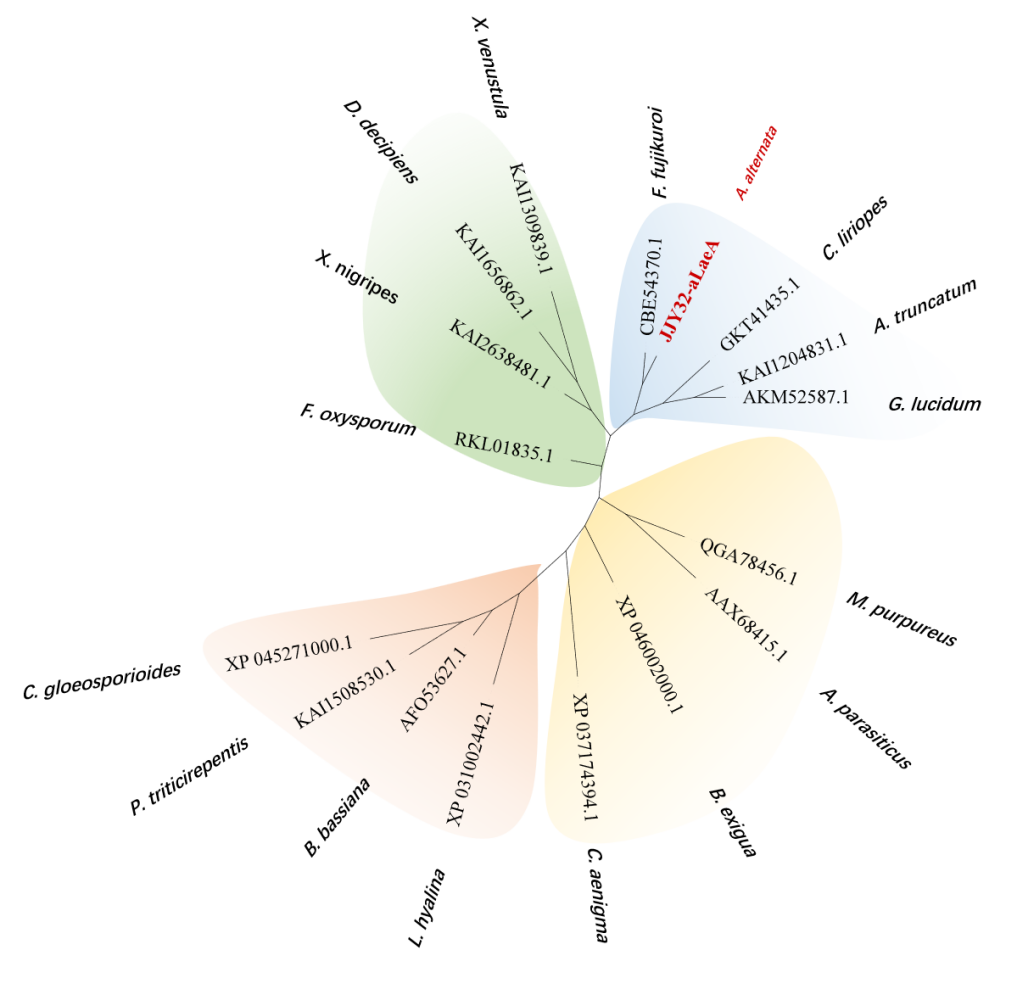
|  |  |  |
| --- | --- | --- |
| Strains  or plasmids | Characteristics | Sources |
| Strains |  |  |
| *Alternaria alternata* JJY-32 | Isolated from a sponge-derived sample collected in Qionghai, Hainan (China). | Preserved in our laboratory |
| *Escherichia*  *coli* DH10B | Cloning host | Solarbio life sciences |
| Plasmids |  |  |
| pHyg | Hygromycin resistance gene carrier | Preserved in our laboratory |
| pHyg-aLaeA | pHYG carrying aLaeA gene fragments | This study |
| pHyg-aMpaB | pHYG carrying aMpaB gene fragments | This study |

# **Table S2.** The primers used in this study. (5’ to 3’)

|  |  |
| --- | --- |
| **Primers** | **Sequences** |
| KZ-JJY32-LaeA-F | GGggtaccTCACTCATCGTCATCCTTCCTTGG |
| KZ-JJY32-LaeA-R | GCtctagaATGGCTGATATTGAAGCTCAGGTTG |
| YZ-JJY32-LaeA-F | GCGATCGCATGTGTATGAAGTCG |
| YZ-JJY32-LaeA-R | TACAGACAAGCTGTGACCGTCTC |
| JJY32-MpaB’-OE-F | TCCCcccgggCTAGACCGATGAACCGCCATC |
| JJY32-MpaB’-OE-R | CTAGtctagaATGAGGGAAGTCCAAACAACTC |
| PHYG-F | TCTCCGAAGTAGGTAGAGCG |
| PHYG-R | GCTTGCAAATTAAAGCCTTCG |
| JJY32-MpaB’-YZ-F1 | ATCTGGTTAGCTCCATGGCCTC |
| JJY32-MpaB’-YZ-F2 | CAGCCTTGATGTATCGACCAT |

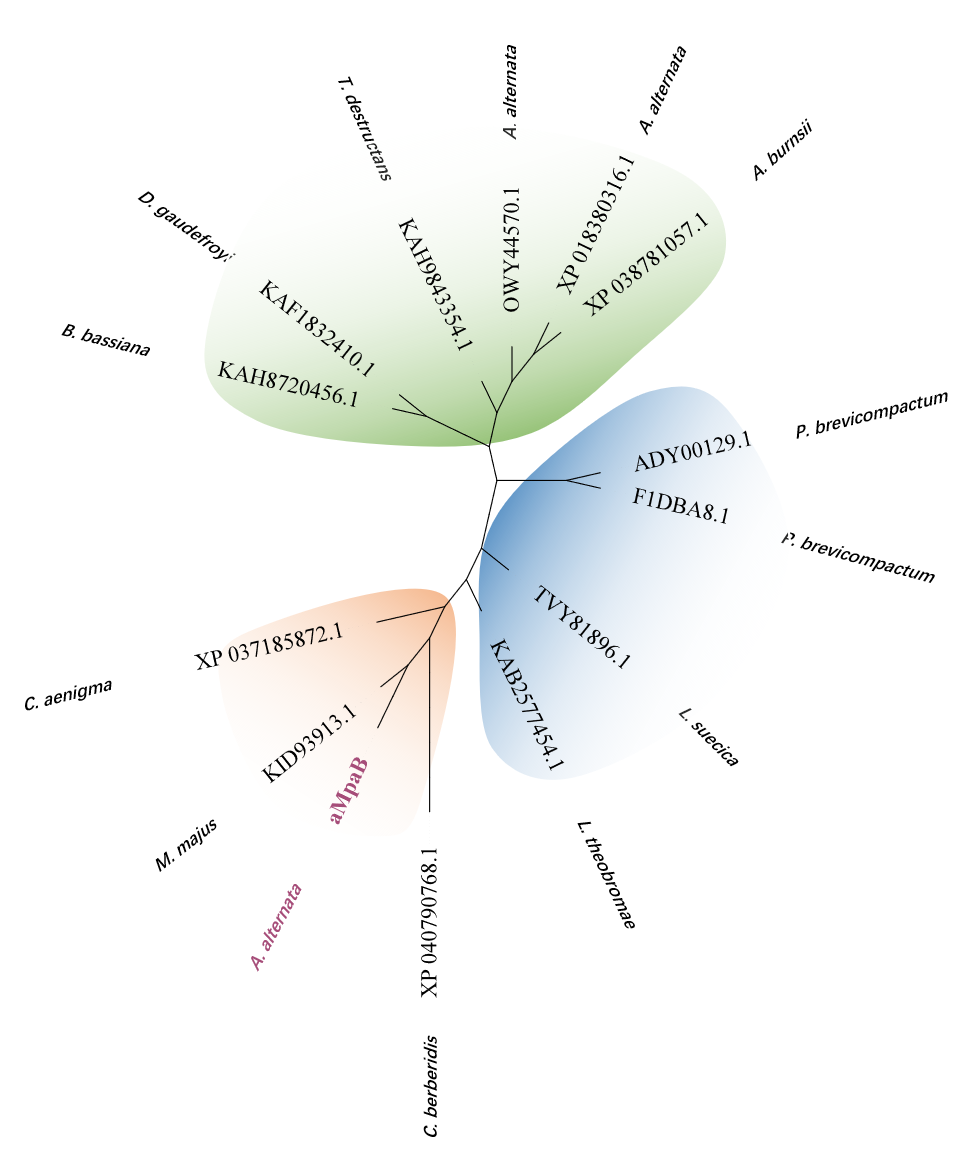
Note: The sites of the restriction endonucleases are represented by lowercase letters.

# **Figure S1.** Phylogenetic analysis of aLaeA



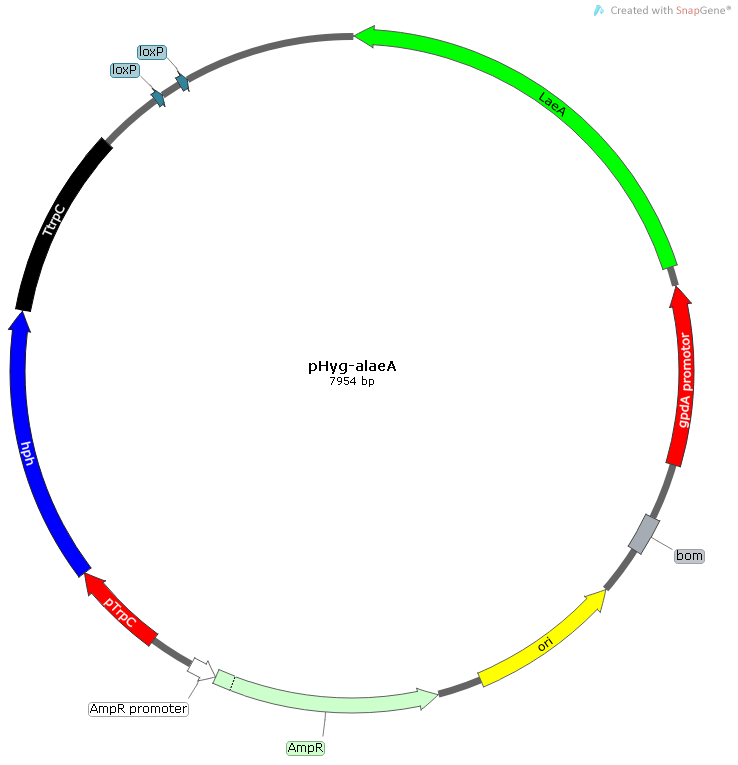
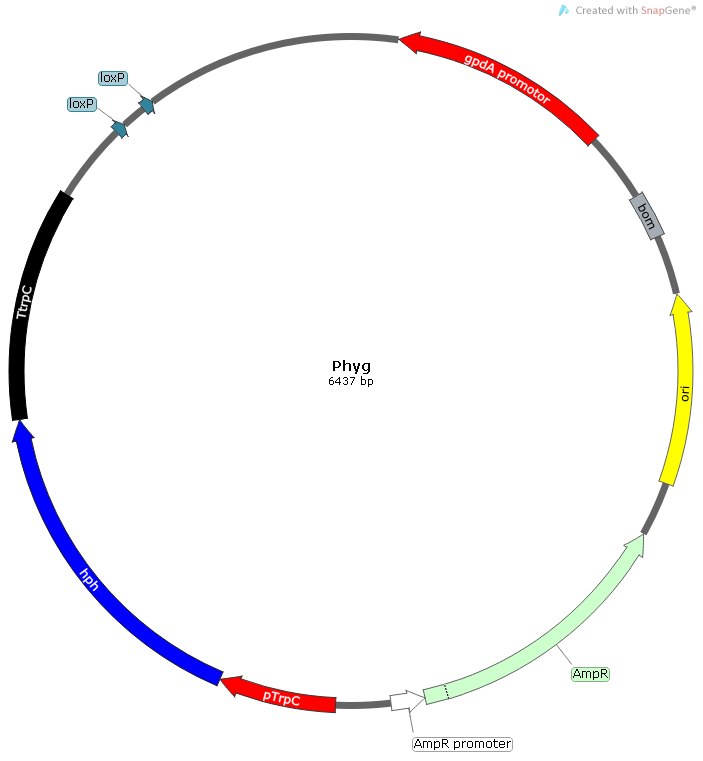
Note: The figure highlights the uniqueness of the aLaeA (in bold) among the ones reported in the NCBI database. The phylogenetic tree was generated by the maximum likelihood method based on the Poisson correction model. aLaeA homologues sources: RKL01835.1 from Fusarium oxysporum, KAI2638481.1 from Xylaria nigripes, AKP07636.1 from Aspergillus fumisynnematus, XP 037174394.1 from Colletotrichum aenigma, XP 045259354.1 from Colletotrichum gloeosporioides, KAI1501145.1 from Biscogniauxia marginata, AFO53627.1 from Beauveria bassiana, KAI1508530.1 from Pyrenophora tritici-repentis, XP 045271000.1 from Colletotrichum gloeosporioides

# **Figure S2.** Phylogenetic analysis of aMpaB

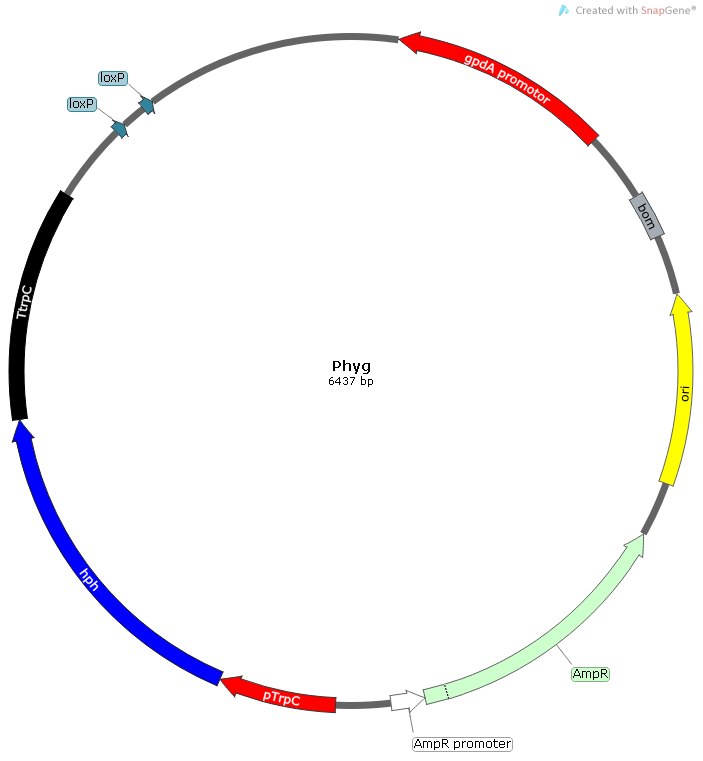


Note: The figure highlights the uniqueness of the aMpaB (in bold) among the ones reported in the NCBI database. The phylogenetic tree was generated by the maximum likelihood method based on the Poisson correction model. aMpaB homologues sources: KAF1832410.1 from Decorospora gaudefroyi, KAH9843354.1 from Teratosphaeria destructans, F1DBA8.1 from Penicillium brevicompactum, KAG7420302.1 from Fusarium oxysporum, TVY81896.1 from Lachnellula suecica, KAB2577454.1 from Lasiodiplodia theobromae, XP 037185872.1 from Colletotrichum aenigma, KID93913.1 from Metarhizium majus, XP 033528765.1 from Dothidotthia symphoricarpi, KZM26171.1 from Ascochyta rabiei, KAH7080647.1 from Paraphoma chrysanthemicola,

# **Figure S3.** Map of the vector pHyg backbone and the constructed plasmid of pHyg-aLaeA

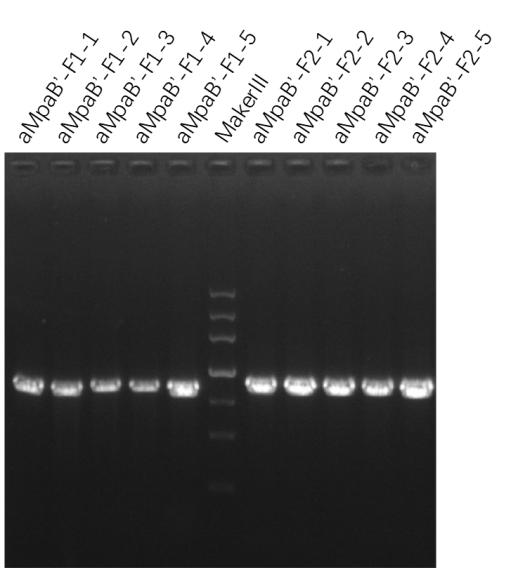
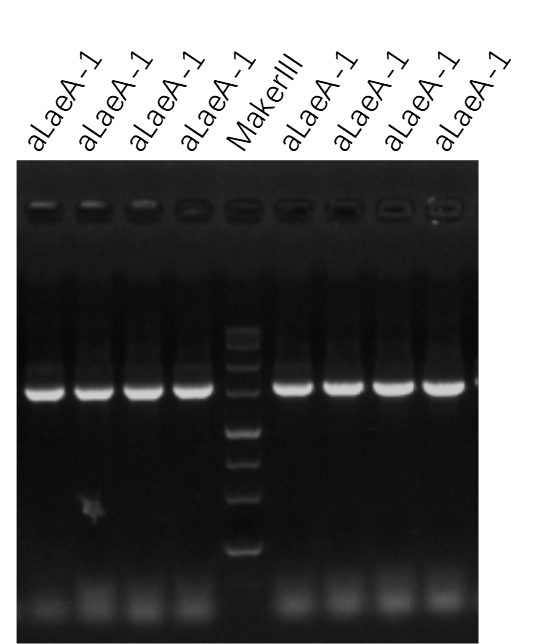


# **Figure S4.** Map of the vector pHyg backbone and the constructed plasmid of pHyg-aMpaB





# **Figure S5.** PCR analysis of gene insertion



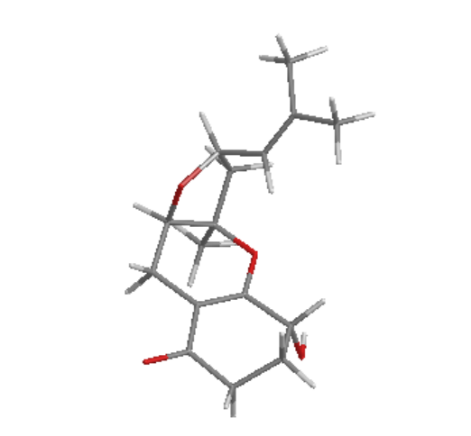
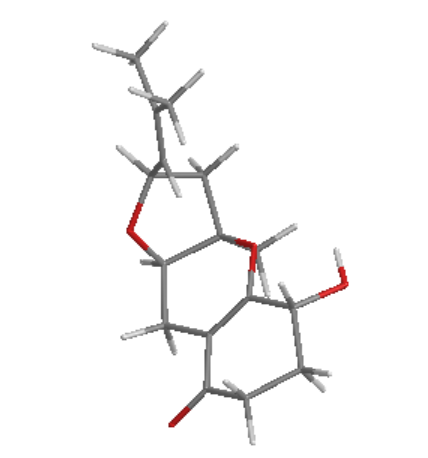
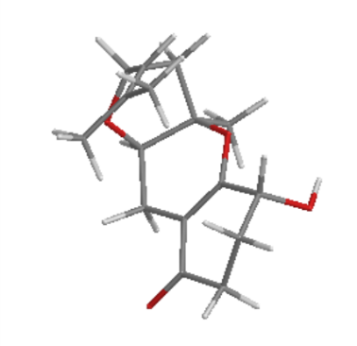
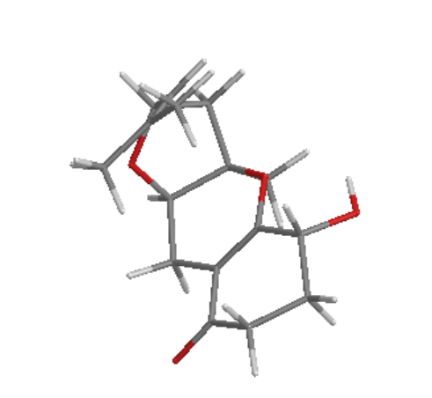
Note: The mutant strain HDN19120-OE::aLaeA showed correct-sized products verified by PCR and aMpaB showed correct-sized products verified by PCR.

Computational Details

**Methods:** Conformational searches of **1**−**2**, **4** and **6** were carried out by employing the “systematic” procedure implemented in Spartan′14 using MMFF (Merck molecular force field). The conformational optimizations were obtained and the major conformers (>5% population) of conformational distribution were selected for further optimization with DFT calculations at the B3LYP/6-31+G(d) level using the Gaussian09 program. The conformers were subjected to ECD calculation by the TDDFT method at the B3LYP/6-31+G(d) level. The hybrid B3LYP functions were chosen to run the TDDFT calculations. The final calculated ECD spectra were obtained according to the Boltzmann-calculated contribution of each conformer1-3.



**Figure S6**. DFT-optimized structures for low-energy conformers of (8*R*, 10*R*, 11*R,* 15*R*)-**1a** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).

Conf. 1 46.7% Conf. 2 3.2% Conf. 3 3.3% Conf. 4 46.8%

**Table S3.** Harmonic frequencies (cm\*\*-1a) of **1a1** - **1a4**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **1a1** | 11.7119 | 21.8547 | 41.9339 |
| **1a2** | 25.2353 | 28.7839 | 38.6170 |
| **1a3** | 25.0819 | 28.8046 | 38.4368 |
| **1a4** | 11.6972 | 21.8478 | 41.9080 |

**Table S4**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **1a** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **1a1** | -923.513548 | -923.563007 | 46.7% |
| **1a2** | -923.511856 | -923.560489 | 3.2% |
| **1a3** | -923.511857 | -923.560500 | 3.3% |
| **1a4** | -923.513548 | -923.563007 | 46.8% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

**Table S5**. Cartesian coordinates of the low-energy reoptimized conformers of (15*R*, 8*R*, 10*R*, 11*R*)-**1a** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 1a1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 2.76994 | -2.03323 | -2.54223 |
| 2 | C | 2.92601 | -1.96124 | -1.03543 |
| 3 | C | 2.64619 | -0.55352 | -0.52549 |
| 4 | C | 1.33922 | -0.00696 | -1.05279 |
| 5 | C | 0.73579 | -0.47987 | -2.15643 |
| 6 | C | 1.41427 | -1.52412 | -2.98127 |
| 7 | O | 0.81253 | 0.99639 | -0.26291 |
| 8 | C | -0.37608 | 1.6693 | -0.71686 |
| 9 | C | -1.31507 | 0.8127 | -1.56239 |
| 10 | C | -0.6031 | -0.0069 | -2.62661 |
| 11 | C | -1.24687 | 1.90346 | 0.50822 |
| 12 | C | -1.99581 | 0.5793 | 0.66143 |
| 13 | O | -2.00942 | -0.0495 | -0.63641 |
| 14 | O | 0.90822 | -1.90045 | -4.03724 |
| 15 | C | 0.04621 | 2.96816 | -1.39461 |
| 16 | C | -1.3422 | -0.37682 | 1.6197 |
| 17 | C | -1.61225 | -0.53515 | 2.93083 |
| 18 | C | -0.87858 | -1.56787 | 3.74572 |
| 19 | C | -2.62186 | 0.26732 | 3.70289 |
| 20 | O | 2.60866 | -0.60637 | 0.89904 |
| 21 | H | 3.5384 | -1.43536 | -3.04437 |
| 22 | H | 2.87279 | -3.0742 | -2.86714 |
| 23 | H | 3.935 | -2.27298 | -0.73999 |
| 24 | H | 2.24174 | -2.67364 | -0.55395 |
| 25 | H | 3.45706 | 0.12665 | -0.81027 |
| 26 | H | -2.09206 | 1.426 | -2.03707 |
| 27 | H | -0.45329 | 0.60816 | -3.52223 |
| 28 | H | -1.22871 | -0.86381 | -2.90309 |
| 29 | H | -0.68268 | 2.17865 | 1.40598 |
| 30 | H | -1.97673 | 2.69917 | 0.31098 |
| 31 | H | -3.03902 | 0.7553 | 0.94184 |
| 32 | H | 0.64956 | 3.58027 | -0.71475 |
| 33 | H | 0.67006 | 2.76866 | -2.2727 |
| 34 | H | -0.8177 | 3.55903 | -1.71562 |
| 35 | H | -0.57934 | -1.01339 | 1.17224 |
| 36 | H | -0.33126 | -1.0871 | 4.5631 |
| 37 | H | -1.58676 | -2.28451 | 4.17435 |
| 38 | H | -0.15484 | -2.13232 | 3.14825 |
| 39 | H | -3.06592 | 1.07709 | 3.11859 |
| 40 | H | -3.43277 | -0.38109 | 4.0501 |
| 41 | H | -2.1483 | 0.72639 | 4.57732 |
| 42 | H | 2.01896 | 0.1184 | 1.18124 |

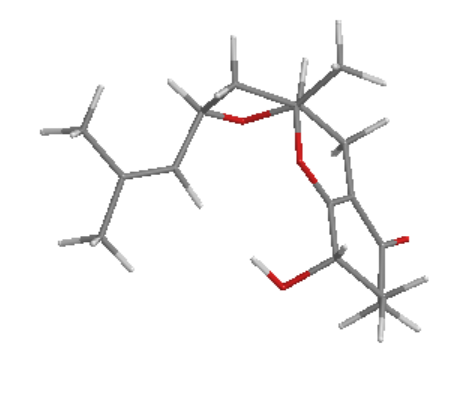
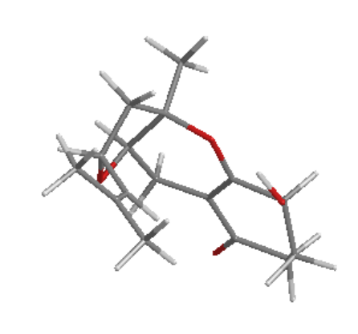
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| --- | --- | --- | --- | --- |
| **Conformer 1a2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 2.67915 | -2.94116 | -0.95181 |
| 2 | C | 2.74948 | -2.78329 | 0.55843 |
| 3 | C | 1.64218 | -1.86726 | 1.06763 |
| 4 | C | 1.49984 | -0.60278 | 0.25718 |
| 5 | C | 2.00502 | -0.44996 | -0.97849 |
| 6 | C | 2.71634 | -1.59012 | -1.62879 |
| 7 | O | 0.79296 | 0.3779 | 0.92007 |
| 8 | C | 0.70493 | 1.68378 | 0.32339 |
| 9 | C | 0.7717 | 1.70748 | -1.2022 |
| 10 | C | 1.84436 | 0.80012 | -1.78332 |
| 11 | C | -0.71722 | 2.17487 | 0.54538 |
| 12 | C | -1.48749 | 1.54529 | -0.61507 |
| 13 | O | -0.53478 | 1.31107 | -1.67131 |
| 14 | O | 3.28222 | -1.43056 | -2.70886 |
| 15 | C | 1.74593 | 2.57489 | 0.99243 |
| 16 | C | -2.12488 | 0.22309 | -0.28744 |
| 17 | C | -3.33247 | 0.01803 | 0.27505 |
| 18 | C | -3.84483 | -1.37808 | 0.51132 |
| 19 | C | -4.26583 | 1.11082 | 0.71618 |
| 20 | O | 0.39912 | -2.56206 | 1.02656 |
| 21 | H | 3.53857 | -3.52786 | -1.2942 |
| 22 | H | 1.76504 | -3.45939 | -1.2609 |
| 23 | H | 3.72453 | -2.35908 | 0.83083 |
| 24 | H | 2.6735 | -3.77117 | 1.02726 |
| 25 | H | 1.84801 | -1.62004 | 2.11568 |
| 26 | H | 0.92063 | 2.72899 | -1.57549 |
| 27 | H | 2.80633 | 1.32672 | -1.79006 |
| 28 | H | 1.58546 | 0.553 | -2.81966 |
| 29 | H | -1.12946 | 1.90764 | 1.52435 |
| 30 | H | -0.76274 | 3.26697 | 0.4455 |
| 31 | H | -2.23876 | 2.23911 | -1.00682 |
| 32 | H | 1.60362 | 2.58709 | 2.07896 |
| 33 | H | 2.75864 | 2.19727 | 0.81367 |
| 34 | H | 1.6952 | 3.6055 | 0.62666 |
| 35 | H | -1.53246 | -0.6462 | -0.5707 |
| 36 | H | -3.13611 | -2.14308 | 0.17685 |
| 37 | H | -4.02773 | -1.53905 | 1.57877 |
| 38 | H | -4.78326 | -1.53392 | -0.03071 |
| 39 | H | -3.84498 | 2.11174 | 0.59003 |
| 40 | H | -5.19712 | 1.06553 | 0.14229 |
| 41 | H | -4.50771 | 0.99314 | 1.77779 |
| 42 | H | -0.2849 | -1.90499 | 1.25354 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 1a3** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 1.65394 | -2.47733 | -1.99591 |
| 2 | C | 2.25752 | -2.70593 | -0.61926 |
| 3 | C | 1.49621 | -1.92623 | 0.44654 |
| 4 | C | 1.25245 | -0.48848 | 0.05942 |
| 5 | C | 1.30858 | -0.04215 | -1.20673 |
| 6 | C | 1.59395 | -1.00087 | -2.31516 |
| 7 | O | 0.96111 | 0.3148 | 1.14212 |
| 8 | C | 0.85042 | 1.73297 | 0.93069 |
| 9 | C | 0.37093 | 2.1443 | -0.45738 |
| 10 | C | 1.03431 | 1.37683 | -1.58928 |
| 11 | C | -0.31934 | 2.21734 | 1.77328 |
| 12 | C | -1.53168 | 1.91316 | 0.88556 |
| 13 | O | -1.05507 | 1.93233 | -0.46773 |
| 14 | O | 1.73707 | -0.59007 | -3.46563 |
| 15 | C | 2.17306 | 2.37426 | 1.33571 |
| 16 | C | -2.20293 | 0.60199 | 1.23128 |
| 17 | C | -2.68799 | -0.37609 | 0.43775 |
| 18 | C | -3.2822 | -1.62531 | 1.03747 |
| 19 | C | -2.72479 | -0.34123 | -1.06556 |
| 20 | O | 0.23684 | -2.55239 | 0.67302 |
| 21 | H | 2.27621 | -2.97268 | -2.74922 |
| 22 | H | 0.64056 | -2.88749 | -2.06419 |
| 23 | H | 3.3067 | -2.38355 | -0.62626 |
| 24 | H | 2.23992 | -3.77835 | -0.3932 |
| 25 | H | 2.06037 | -1.9703 | 1.38527 |
| 26 | H | 0.51018 | 3.22077 | -0.62145 |
| 27 | H | 1.98944 | 1.85164 | -1.84422 |
| 28 | H | 0.38981 | 1.41245 | -2.47556 |
| 29 | H | -0.37707 | 1.7444 | 2.75946 |
| 30 | H | -0.25578 | 3.3031 | 1.92255 |
| 31 | H | -2.27767 | 2.70805 | 0.99947 |
| 32 | H | 2.42888 | 2.11312 | 2.3688 |
| 33 | H | 2.99408 | 2.01017 | 0.70844 |
| 34 | H | 2.13819 | 3.46546 | 1.25466 |
| 35 | H | -2.30404 | 0.45498 | 2.30712 |
| 36 | H | -3.19491 | -1.64601 | 2.12882 |
| 37 | H | -4.34542 | -1.69851 | 0.78638 |
| 38 | H | -2.77087 | -2.51193 | 0.64854 |
| 39 | H | -2.78466 | 0.67377 | -1.46473 |
| 40 | H | -1.8461 | -0.84446 | -1.47977 |
| 41 | H | -3.61668 | -0.85851 | -1.4372 |
| 42 | H | -0.32368 | -1.88797 | 1.11622 |

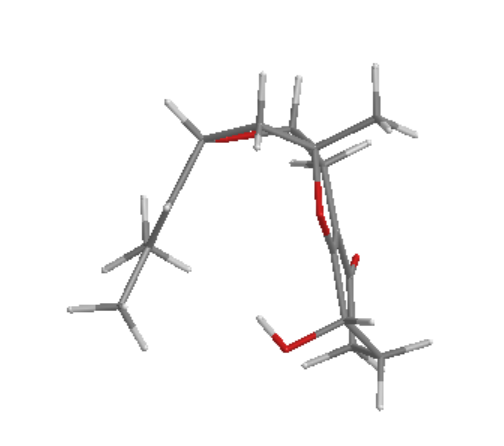
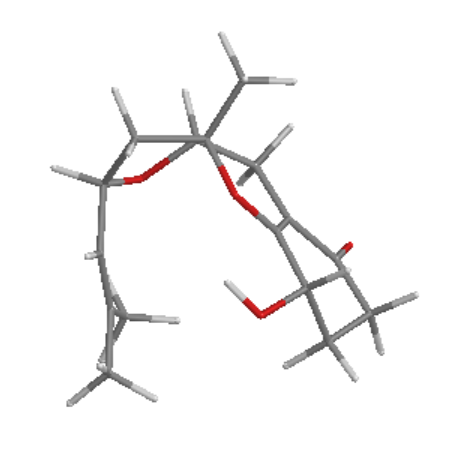
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| --- | --- | --- | --- | --- |
| **Conformer 1a4** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 3.19138 | -1.55087 | -0.90367 |
| 2 | C | 2.33274 | -2.12035 | 0.2089 |
| 3 | C | 1.88127 | -1.02264 | 1.16332 |
| 4 | C | 1.26509 | 0.14828 | 0.43023 |
| 5 | C | 1.50122 | 0.40914 | -0.86658 |
| 6 | C | 2.48646 | -0.42108 | -1.62187 |
| 7 | O | 0.40423 | 0.88883 | 1.21612 |
| 8 | C | -0.20191 | 2.06525 | 0.65154 |
| 9 | C | -0.38369 | 2.04309 | -0.86332 |
| 10 | C | 0.82084 | 1.50721 | -1.61923 |
| 11 | C | -1.65756 | 2.06906 | 1.09346 |
| 12 | C | -2.32039 | 1.12534 | 0.08341 |
| 13 | O | -1.54729 | 1.23062 | -1.12177 |
| 14 | O | 2.76865 | -0.13763 | -2.78509 |
| 15 | C | 0.5714 | 3.27831 | 1.15556 |
| 16 | C | -2.3926 | -0.3028 | 0.57714 |
| 17 | C | -2.17035 | -1.46682 | -0.06853 |
| 18 | C | -2.21841 | -2.77565 | 0.67776 |
| 19 | C | -1.87673 | -1.60816 | -1.53648 |
| 20 | O | 0.93508 | -1.59439 | 2.06458 |
| 21 | H | 4.13856 | -1.16668 | -0.50951 |
| 22 | H | 3.41254 | -2.34053 | -1.62982 |
| 23 | H | 2.88293 | -2.89283 | 0.75941 |
| 24 | H | 1.45519 | -2.62659 | -0.2168 |
| 25 | H | 2.72634 | -0.66107 | 1.76019 |
| 26 | H | -0.63369 | 3.04127 | -1.24558 |
| 27 | H | 1.54576 | 2.31543 | -1.77433 |
| 28 | H | 0.49834 | 1.14616 | -2.60302 |
| 29 | H | -1.80324 | 1.7586 | 2.13357 |
| 30 | H | -2.08738 | 3.07223 | 0.975 |
| 31 | H | -3.34176 | 1.46265 | -0.12551 |
| 32 | H | 0.60036 | 3.29066 | 2.25097 |
| 33 | H | 1.61223 | 3.24824 | 0.81511 |
| 34 | H | 0.12545 | 4.2173 | 0.81216 |
| 35 | H | -2.65853 | -0.37207 | 1.63226 |
| 36 | H | -2.39589 | -2.63872 | 1.74962 |
| 37 | H | -3.02104 | -3.40844 | 0.28523 |
| 38 | H | -1.2678 | -3.30773 | 0.56617 |
| 39 | H | -2.27313 | -0.7817 | -2.13067 |
| 40 | H | -0.79884 | -1.69063 | -1.70393 |
| 41 | H | -2.35097 | -2.51309 | -1.93308 |
| 42 | H | 0.24517 | -0.9172 | 2.19707 |



**Figure S7**. DFT-optimized structures for low-energy conformers of (15*S*, 8*R*, 10*R*, 11*R*)-**1b** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).



Conf. 1 39.1% Conf. 2 11.3%

Conf. 3 11.2% Conf. 4 38.5%

**Table S6**. Harmonic frequencies (cm\*\*-1a) of **1b1** – **1b4**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **1b1** | 18.8118 | 30.4676 | 42.8589 |
| **1b2** | 20.7364 | 31.4881 | 44.9729 |
| **1b3** | 20.7588 | 31.4982 | 44.9177 |
| **1b4** | 18.8545 | 30.5297 | 42.9542 |

**Table S7**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **1b** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **1b1** | -923.513403 | -923.562117 | 39.1% |
| **1b2** | -923.512397 | -923.560945 | 11.3% |
| **1b3** | -923.512394 | -923.560938 | 11.2% |
| **1b4** | -923.513398 | -923.562102 | 38.5% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

**Table S8**. Cartesian coordinates of the low-energy reoptimized conformers of (15*S*, 8*R*, 10*R*, 11*R*)-**1b** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 1b1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 0.86169 | -3.7778 | 1.69304 |
| 2 | C | 2.19075 | -3.09038 | 1.44629 |
| 3 | C | 1.99038 | -1.61123 | 1.14311 |
| 4 | C | 0.93676 | -1.37724 | 0.08475 |
| 5 | C | -0.0156 | -2.27582 | -0.21888 |
| 6 | C | -0.07818 | -3.56907 | 0.52642 |
| 7 | O | 1.06613 | -0.15629 | -0.55008 |
| 8 | C | 0.26424 | 0.08544 | -1.72101 |
| 9 | C | -1.10449 | -0.58886 | -1.70468 |
| 10 | C | -1.06727 | -2.04097 | -1.25661 |
| 11 | C | -0.14932 | 1.54914 | -1.68182 |
| 12 | C | -1.39185 | 1.54019 | -0.79011 |
| 13 | O | -1.91922 | 0.19798 | -0.81084 |
| 14 | O | -0.91273 | -4.41913 | 0.22174 |
| 15 | C | 1.10278 | -0.25372 | -2.94879 |
| 16 | H | -1.59097 | -0.52498 | -2.68681 |
| 17 | C | -1.10687 | 1.88985 | 0.64346 |
| 18 | H | -2.16626 | 2.19154 | -1.20614 |
| 19 | H | -0.7344 | 1.05854 | 1.24043 |
| 20 | C | -1.28071 | 3.0813 | 1.24983 |
| 21 | C | -0.97577 | 3.24858 | 2.71533 |
| 22 | C | -1.76827 | 4.33047 | 0.57003 |
| 23 | O | 3.23841 | -1.08159 | 0.70247 |
| 24 | H | 1.02808 | -4.853 | 1.81986 |
| 25 | H | 0.37852 | -3.39372 | 2.598 |
| 26 | H | 2.84964 | -3.20797 | 2.31492 |
| 27 | H | 2.7126 | -3.57412 | 0.60897 |
| 28 | H | 1.7044 | -1.07089 | 2.05305 |
| 29 | H | -0.84365 | -2.68225 | -2.11786 |
| 30 | H | -2.05195 | -2.32589 | -0.86764 |
| 31 | H | 0.63387 | 2.22 | -1.31209 |
| 32 | H | -0.43943 | 1.89117 | -2.68365 |
| 33 | H | 2.03749 | 0.31833 | -2.94785 |
| 34 | H | 1.38435 | -1.31234 | -2.95359 |
| 35 | H | 0.56727 | -0.03814 | -3.87899 |
| 36 | H | -0.6301 | 2.31783 | 3.1774 |
| 37 | H | -0.19246 | 4.00046 | 2.8565 |
| 38 | H | -1.87215 | 3.57366 | 3.25357 |
| 39 | H | -2.74441 | 4.62129 | 0.97141 |
| 40 | H | -1.06507 | 5.15208 | 0.74395 |
| 41 | H | -1.8678 | 4.22198 | -0.51263 |
| 42 | H | 3.02155 | -0.26442 | 0.21555 |

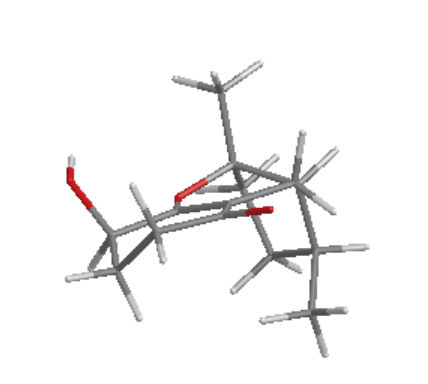
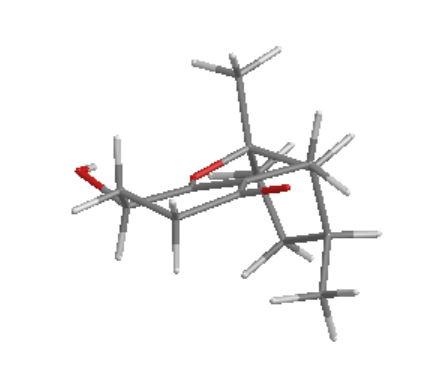
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| --- | --- | --- | --- | --- |
| **Conformer 1b2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -0.28894 | -4.10292 | 1.25921 |
| 2 | C | 1.02594 | -3.34453 | 1.34082 |
| 3 | C | 1.23727 | -2.47782 | 0.1049 |
| 4 | C | 0.02499 | -1.65119 | -0.24081 |
| 5 | C | -1.21007 | -1.92358 | 0.21332 |
| 6 | C | -1.44712 | -3.16209 | 1.01389 |
| 7 | O | 0.3202 | -0.57813 | -1.05676 |
| 8 | C | -0.77514 | 0.19152 | -1.58597 |
| 9 | C | -1.99422 | 0.27613 | -0.67152 |
| 10 | C | -2.39757 | -1.05735 | -0.06319 |
| 11 | C | -0.3335 | 1.64755 | -1.59164 |
| 12 | C | -0.64785 | 2.11677 | -0.17033 |
| 13 | O | -1.64661 | 1.22229 | 0.36084 |
| 14 | O | -2.58113 | -3.43498 | 1.40513 |
| 15 | C | -1.0901 | -0.33079 | -2.98374 |
| 16 | H | -2.85532 | 0.71012 | -1.1964 |
| 17 | C | 0.53523 | 2.07108 | 0.75538 |
| 18 | H | -1.09394 | 3.11565 | -0.18725 |
| 19 | H | 0.73436 | 1.08667 | 1.17659 |
| 20 | C | 1.33305 | 3.09394 | 1.12239 |
| 21 | C | 2.46093 | 2.87634 | 2.0966 |
| 22 | C | 1.20676 | 4.50641 | 0.62324 |
| 23 | O | 1.5393 | -3.30938 | -1.01101 |
| 24 | H | -0.27165 | -4.84426 | 0.45298 |
| 25 | H | -0.461 | -4.62731 | 2.20552 |
| 26 | H | 1.02115 | -2.70789 | 2.235 |
| 27 | H | 1.84752 | -4.06221 | 1.44795 |
| 28 | H | 2.1014 | -1.82593 | 0.27904 |
| 29 | H | -3.05384 | -1.59123 | -0.76131 |
| 30 | H | -2.95756 | -0.88099 | 0.86275 |
| 31 | H | 0.71843 | 1.78942 | -1.86265 |
| 32 | H | -0.94315 | 2.22889 | -2.29534 |
| 33 | H | -0.19844 | -0.29371 | -3.61973 |
| 34 | H | -1.40691 | -1.3789 | -2.95063 |
| 35 | H | -1.88229 | 0.25083 | -3.4661 |
| 36 | H | 3.41952 | 3.12311 | 1.62858 |
| 37 | H | 2.32856 | 3.51357 | 2.9771 |
| 38 | H | 2.51752 | 1.83892 | 2.44282 |
| 39 | H | 0.46462 | 4.61898 | -0.17073 |
| 40 | H | 0.92569 | 5.17272 | 1.44517 |
| 41 | H | 2.16394 | 4.84769 | 0.21443 |
| 42 | H | 1.60996 | -2.7134 | -1.77857 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 1b3** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 1.06769 | -3.27601 | 1.05933 |
| 2 | C | 1.48757 | -2.04261 | 1.84212 |
| 3 | C | 1.97797 | -0.94256 | 0.90827 |
| 4 | C | 1.03571 | -0.69351 | -0.24135 |
| 5 | C | 0.10586 | -1.57827 | -0.63875 |
| 6 | C | 0.04885 | -2.9279 | -0.00241 |
| 7 | O | 1.20889 | 0.54768 | -0.81599 |
| 8 | C | 0.37625 | 0.9154 | -1.92943 |
| 9 | C | -0.96932 | 0.19901 | -2.01172 |
| 10 | C | -0.89257 | -1.28855 | -1.71215 |
| 11 | C | -0.09472 | 2.33968 | -1.6774 |
| 12 | C | -1.28955 | 2.14025 | -0.73819 |
| 13 | O | -1.84331 | 0.85839 | -1.07151 |
| 14 | O | -0.77512 | -3.75689 | -0.38673 |
| 15 | C | 1.21272 | 0.78419 | -3.1969 |
| 16 | H | -1.43499 | 0.34556 | -2.99482 |
| 17 | C | -0.91288 | 2.21623 | 0.72566 |
| 18 | H | -2.04538 | 2.90958 | -0.93207 |
| 19 | H | -0.16484 | 2.98223 | 0.93118 |
| 20 | C | -1.34429 | 1.4897 | 1.77818 |
| 21 | C | -0.75537 | 1.70417 | 3.14838 |
| 22 | C | -2.42552 | 0.44538 | 1.72881 |
| 23 | O | 3.24728 | -1.30463 | 0.37321 |
| 24 | H | 1.92626 | -3.74854 | 0.57001 |
| 25 | H | 0.61994 | -4.0025 | 1.74622 |
| 26 | H | 0.63188 | -1.67335 | 2.42209 |
| 27 | H | 2.27575 | -2.31954 | 2.55173 |
| 28 | H | 2.11193 | -0.02414 | 1.49196 |
| 29 | H | -0.59294 | -1.83224 | -2.61613 |
| 30 | H | -1.88444 | -1.64681 | -1.41226 |
| 31 | H | 0.67818 | 2.99261 | -1.25829 |
| 32 | H | -0.45143 | 2.79174 | -2.61203 |
| 33 | H | 2.12657 | 1.38427 | -3.12132 |
| 34 | H | 1.53091 | -0.25301 | -3.34926 |
| 35 | H | 0.66067 | 1.10781 | -4.08515 |
| 36 | H | 0.04636 | 2.45007 | 3.14599 |
| 37 | H | -1.52691 | 2.04712 | 3.8454 |
| 38 | H | -0.3334 | 0.76741 | 3.52735 |
| 39 | H | -1.98695 | -0.55361 | 1.64725 |
| 40 | H | -3.02699 | 0.4778 | 2.64433 |
| 41 | H | -3.1281 | 0.59984 | 0.90661 |
| 42 | H | 3.47663 | -0.60709 | -0.26712 |

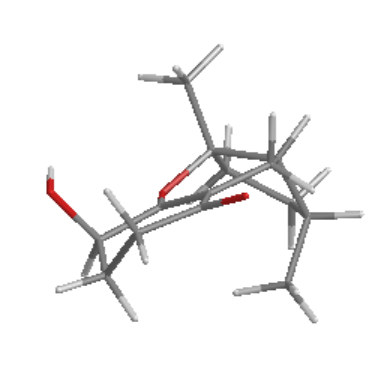
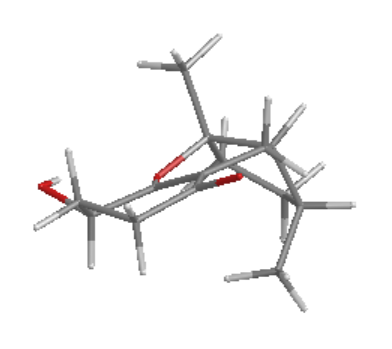
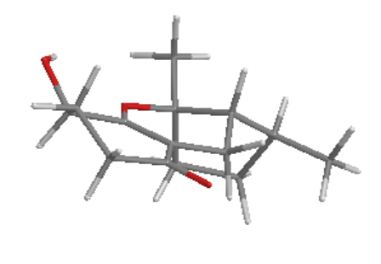
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 1b4** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 0.81972 | -2.97707 | 1.68441 |
| 2 | C | 2.16829 | -2.31746 | 1.47156 |
| 3 | C | 2.0007 | -0.87101 | 1.02565 |
| 4 | C | 1.02155 | -0.72724 | -0.1167 |
| 5 | C | 0.08825 | -1.64937 | -0.40786 |
| 6 | C | -0.03144 | -2.87407 | 0.43852 |
| 7 | O | 1.19221 | 0.443 | -0.82964 |
| 8 | C | 0.37343 | 0.67026 | -1.98999 |
| 9 | C | -0.96992 | -0.05414 | -2.00149 |
| 10 | C | -0.89664 | -1.49368 | -1.52138 |
| 11 | C | -0.10183 | 2.11351 | -1.9195 |
| 12 | C | -1.30912 | 2.02734 | -0.97907 |
| 13 | O | -1.85646 | 0.71245 | -1.15974 |
| 14 | O | -0.8437 | -3.75089 | 0.14943 |
| 15 | C | 1.22645 | 0.38796 | -3.22132 |
| 16 | H | -1.42298 | -0.02968 | -3.00096 |
| 17 | C | -0.95268 | 2.28194 | 0.46939 |
| 18 | H | -2.06318 | 2.76498 | -1.27573 |
| 19 | H | -0.20344 | 3.06452 | 0.59094 |
| 20 | C | -1.40433 | 1.69224 | 1.59632 |
| 21 | C | -0.8347 | 2.07111 | 2.93885 |
| 22 | C | -2.49144 | 0.65478 | 1.65854 |
| 23 | O | 3.27996 | -0.38477 | 0.62515 |
| 24 | H | 0.96752 | -4.03638 | 1.92061 |
| 25 | H | 0.27586 | -2.51059 | 2.51306 |
| 26 | H | 2.76408 | -2.35841 | 2.39125 |
| 27 | H | 2.74324 | -2.87454 | 0.71892 |
| 28 | H | 1.65961 | -0.25187 | 1.86361 |
| 29 | H | -0.58455 | -2.14358 | -2.34765 |
| 30 | H | -1.89315 | -1.81388 | -1.19498 |
| 31 | H | 0.66496 | 2.81438 | -1.57285 |
| 32 | H | -0.44623 | 2.44764 | -2.90687 |
| 33 | H | 2.13899 | 0.9946 | -3.20722 |
| 34 | H | 1.54705 | -0.65942 | -3.2427 |
| 35 | H | 0.68592 | 0.60035 | -4.14932 |
| 36 | H | -0.0283 | 2.80748 | 2.85736 |
| 37 | H | -1.61446 | 2.50065 | 3.57619 |
| 38 | H | -0.42453 | 1.18611 | 3.43664 |
| 39 | H | -2.05797 | -0.34855 | 1.70832 |
| 40 | H | -3.10723 | 0.80294 | 2.55288 |
| 41 | H | -3.17969 | 0.70939 | 0.81185 |
| 42 | H | 3.1002 | 0.37897 | 0.04548 |



**Figure S8**. DFT-optimized structures for low-energy conformers of (7*S*, 10*R*, 11*S*, 15*S*)-**2a** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).

Conf. 1 12.3% Conf. 2 38.6%

Conf. 3 3.5% Conf. 4 11.7% Conf. 5 33.9%

**Table S9**. Harmonic frequencies (cm\*\*-1a) of **2a1** – **2a2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **2a1** | 36.5838 | 59.9013 | 74.0207 |
| **2a2** | 33.16 | 58.2068 | 71.6768 |
| **2a3** | 49.3372 | 53.4882 | 78.0701 |
| **2a4** | 47.9469 | 54.6158 | 77.3732 |
| **2a5** | 42.0417 | 62.2597 | 76.3911 |

**Table S10**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **2a** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **2a1** | -770.922207 | -770.964612 | 12.3% |
| **2a2** | -770.923251 | -770.965687 | 38.6% |
| **2a3** | -770.921144 | -770.963421 | 3.5% |
| **2a4** | -770.922223 | -770.964565 | 11.7% |
| **2a5** | -770.922999 | -770.965564 | 33.9% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

**Table S11**. Cartesian coordinates of the low-energy reoptimized conformers of (7*S*, 10*R*, 11*S*, 15*R*)-**2a** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2a1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -2.22042 | -1.16908 | 2.33121 |
| 2 | C | -1.4002 | -0.37036 | 3.33177 |
| 3 | C | -0.03576 | -0.03941 | 2.77044 |
| 4 | C | 0.09353 | 0.2062 | 1.30315 |
| 5 | C | -0.97872 | 0.05697 | 0.50629 |
| 6 | C | -2.31427 | -0.44318 | 0.9938 |
| 7 | C | 1.43215 | 0.6339 | 0.79397 |
| 8 | C | 1.50866 | 0.5933 | -0.72902 |
| 9 | C | 0.18086 | 1.01775 | -1.38121 |
| 10 | O | -0.96462 | 0.32843 | -0.84805 |
| 11 | C | 1.87539 | -0.75877 | -1.40689 |
| 12 | C | 0.97327 | -0.8539 | -2.65111 |
| 13 | C | 0.36782 | 0.53494 | -2.82289 |
| 14 | O | 0.94345 | 0.08233 | 3.50484 |
| 15 | O | -3.18582 | 0.67564 | 1.12424 |
| 16 | C | -0.08561 | 2.52092 | -1.32813 |
| 17 | H | 2.29227 | 1.30327 | -1.03443 |
| 18 | C | 1.78628 | -2.0275 | -0.56571 |
| 19 | H | -1.75061 | -2.14959 | 2.1802 |
| 20 | H | -3.22171 | -1.33972 | 2.74332 |
| 21 | H | -1.26749 | -0.96338 | 4.24325 |
| 22 | H | -1.89927 | 0.56684 | 3.60075 |
| 23 | H | -2.75442 | -1.12421 | 0.25606 |
| 24 | H | 1.60059 | 1.66619 | 1.12861 |
| 25 | H | 2.23907 | 0.03635 | 1.23051 |
| 26 | H | 2.91716 | -0.67823 | -1.74687 |
| 27 | H | 0.17281 | -1.5891 | -2.50278 |
| 28 | H | 1.5365 | -1.15898 | -3.53906 |
| 29 | H | -0.57353 | 0.48185 | -3.37961 |
| 30 | H | 1.06515 | 1.17952 | -3.37155 |
| 31 | H | -3.14554 | 1.14779 | 0.27261 |
| 32 | H | -1.00798 | 2.76737 | -1.86627 |
| 33 | H | -0.22638 | 2.86501 | -0.29799 |
| 34 | H | 0.73554 | 3.09374 | -1.77095 |
| 35 | H | 2.0636 | -2.89981 | -1.16826 |
| 36 | H | 2.4737 | -1.9918 | 0.28441 |
| 37 | H | 0.77456 | -2.2013 | -0.18869 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2a2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -2.47174 | 0.01313 | 2.54478 |
| 2 | C | -1.30191 | -0.54332 | 3.33364 |
| 3 | C | 0.01577 | -0.04785 | 2.77926 |
| 4 | C | 0.12195 | 0.21577 | 1.31272 |
| 5 | C | -0.96227 | 0.07717 | 0.52991 |
| 6 | C | -2.32598 | -0.29809 | 1.06086 |
| 7 | C | 1.46892 | 0.58364 | 0.77796 |
| 8 | C | 1.53435 | 0.47867 | -0.74246 |
| 9 | C | 0.21615 | 0.91553 | -1.40491 |
| 10 | O | -0.94582 | 0.28284 | -0.83804 |
| 11 | C | 1.85628 | -0.91057 | -1.36577 |
| 12 | C | 0.94463 | -1.02927 | -2.60099 |
| 13 | C | 0.37945 | 0.36879 | -2.82646 |
| 14 | O | 1.00173 | 0.07963 | 3.50307 |
| 15 | O | -3.33194 | 0.42938 | 0.36026 |
| 16 | C | -0.00555 | 2.42687 | -1.41269 |
| 17 | H | 2.33688 | 1.15163 | -1.08075 |
| 18 | C | 1.73333 | -2.14037 | -0.47265 |
| 19 | H | -3.41665 | -0.3962 | 2.92178 |
| 20 | H | -2.53868 | 1.10006 | 2.69164 |
| 21 | H | -1.29463 | -1.63846 | 3.30808 |
| 22 | H | -1.38406 | -0.22203 | 4.37759 |
| 23 | H | -2.49846 | -1.36446 | 0.8748 |
| 24 | H | 1.66788 | 1.62342 | 1.06979 |
| 25 | H | 2.26322 | -0.01734 | 1.23261 |
| 26 | H | 2.8981 | -0.87586 | -1.71328 |
| 27 | H | 0.12367 | -1.73372 | -2.41926 |
| 28 | H | 1.49352 | -1.38672 | -3.47831 |
| 29 | H | -0.56666 | 0.32109 | -3.37556 |
| 30 | H | 1.09199 | 0.96929 | -3.40479 |
| 31 | H | -3.00523 | 0.51859 | -0.55498 |
| 32 | H | -0.9241 | 2.67812 | -1.95512 |
| 33 | H | -0.12871 | 2.81736 | -0.39694 |
| 34 | H | 0.82894 | 2.95623 | -1.88374 |
| 35 | H | 1.98078 | -3.04477 | -1.03985 |
| 36 | H | 2.42605 | -2.0908 | 0.37247 |
| 37 | H | 0.7188 | -2.26742 | -0.08467 |

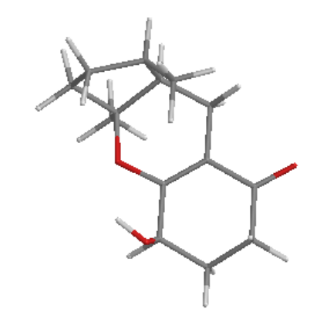
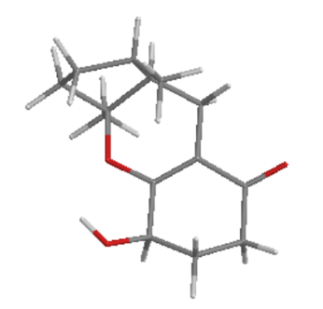
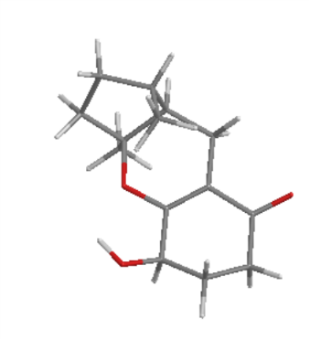
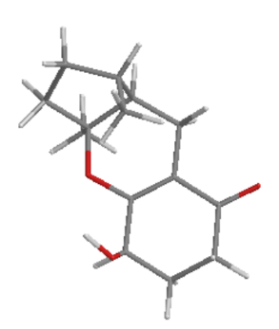
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2a3** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -2.12537 | -1.59035 | 2.27507 |
| 2 | C | -1.46644 | -0.70763 | 3.32306 |
| 3 | C | -0.13568 | -0.18584 | 2.83009 |
| 4 | C | 0.02365 | 0.10546 | 1.37379 |
| 5 | C | -0.9823 | -0.17068 | 0.52742 |
| 6 | C | -2.2571 | -0.85802 | 0.94443 |
| 7 | C | 1.31302 | 0.72166 | 0.93814 |
| 8 | C | 1.44084 | 0.82218 | -0.57766 |
| 9 | C | 0.09144 | 1.00684 | -1.2908 |
| 10 | O | -0.94198 | 0.12173 | -0.82116 |
| 11 | C | 2.09723 | -0.37426 | -1.29654 |
| 12 | C | 1.74629 | -0.09434 | -2.76022 |
| 13 | C | 0.38437 | 0.61101 | -2.75409 |
| 14 | O | 0.7856 | 0.04986 | 3.61036 |
| 15 | O | -3.27876 | 0.12887 | 1.04821 |
| 16 | C | -0.44327 | 2.43815 | -1.20105 |
| 17 | H | 2.07945 | 1.69214 | -0.79561 |
| 18 | C | 1.65403 | -1.7751 | -0.87959 |
| 19 | H | -1.52057 | -2.49536 | 2.13335 |
| 20 | H | -3.11157 | -1.9025 | 2.63768 |
| 21 | H | -1.29553 | -1.29452 | 4.23215 |
| 22 | H | -2.09912 | 0.14869 | 3.58032 |
| 23 | H | -2.56611 | -1.57809 | 0.17774 |
| 24 | H | 1.35765 | 1.73419 | 1.36069 |
| 25 | H | 2.16961 | 0.17364 | 1.34759 |
| 26 | H | 3.18514 | -0.3258 | -1.16202 |
| 27 | H | 1.73604 | -0.99554 | -3.38193 |
| 28 | H | 2.49464 | 0.58383 | -3.18974 |
| 29 | H | -0.38665 | -0.06008 | -3.15038 |
| 30 | H | 0.4331 | 1.48243 | -3.41731 |
| 31 | H | -3.26745 | 0.61648 | 0.20449 |
| 32 | H | -1.38373 | 2.53405 | -1.75563 |
| 33 | H | -0.66352 | 2.71739 | -0.16508 |
| 34 | H | 0.27159 | 3.16257 | -1.60473 |
| 35 | H | 2.22127 | -2.52686 | -1.44033 |
| 36 | H | 1.84402 | -1.95566 | 0.18236 |
| 37 | H | 0.59615 | -1.96052 | -1.08309 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2a4** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -2.56459 | -0.44545 | 2.47927 |
| 2 | C | -1.37153 | -0.84488 | 3.32629 |
| 3 | C | -0.10775 | -0.16637 | 2.84493 |
| 4 | C | 0.03655 | 0.12974 | 1.38752 |
| 5 | C | -0.97617 | -0.14603 | 0.54886 |
| 6 | C | -2.29973 | -0.71454 | 1.0037 |
| 7 | C | 1.34552 | 0.68886 | 0.93211 |
| 8 | C | 1.48541 | 0.71566 | -0.58574 |
| 9 | C | 0.14686 | 0.90559 | -1.31706 |
| 10 | O | -0.91452 | 0.07277 | -0.81486 |
| 11 | C | 2.1111 | -0.53148 | -1.24334 |
| 12 | C | 1.77775 | -0.31029 | -2.72109 |
| 13 | C | 0.43716 | 0.43379 | -2.75814 |
| 14 | O | 0.81344 | 0.08431 | 3.62016 |
| 15 | O | -3.35918 | -0.12483 | 0.25415 |
| 16 | C | -0.34697 | 2.35417 | -1.29819 |
| 17 | H | 2.15049 | 1.55578 | -0.83872 |
| 18 | C | 1.62435 | -1.89779 | -0.76492 |
| 19 | H | -3.46191 | -0.98627 | 2.80306 |
| 20 | H | -2.78923 | 0.61983 | 2.62827 |
| 21 | H | -1.21189 | -1.92822 | 3.29596 |
| 22 | H | -1.55121 | -0.55048 | 4.36593 |
| 23 | H | -2.31179 | -1.79204 | 0.80283 |
| 24 | H | 1.41508 | 1.71794 | 1.30871 |
| 25 | H | 2.18546 | 0.13796 | 1.37118 |
| 26 | H | 3.19911 | -0.50834 | -1.10293 |
| 27 | H | 1.74493 | -1.2389 | -3.30021 |
| 28 | H | 2.54836 | 0.32503 | -3.176 |
| 29 | H | -0.35077 | -0.23231 | -3.12877 |
| 30 | H | 0.51566 | 1.2716 | -3.46064 |
| 31 | H | -3.00243 | 0.01502 | -0.64334 |
| 32 | H | -1.28124 | 2.4505 | -1.86309 |
| 33 | H | -0.56473 | 2.68815 | -0.27803 |
| 34 | H | 0.39064 | 3.03812 | -1.7305 |
| 35 | H | 2.17143 | -2.69122 | -1.28695 |
| 36 | H | 1.80406 | -2.03448 | 0.30534 |
| 37 | H | 0.5623 | -2.0609 | -0.96576 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2a5** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -2.47344 | 0.54518 | 2.97492 |
| 2 | C | -1.66768 | -0.6254 | 3.50465 |
| 3 | C | -0.3418 | -0.74986 | 2.78608 |
| 4 | C | -0.25247 | -0.30655 | 1.36218 |
| 5 | C | -1.33143 | 0.21221 | 0.75504 |
| 6 | C | -2.64492 | 0.44879 | 1.4645 |
| 7 | C | 1.04613 | -0.50287 | 0.65713 |
| 8 | C | 1.16485 | 0.41712 | -0.56343 |
| 9 | C | -0.15729 | 0.50413 | -1.3508 |
| 10 | O | -1.35296 | 0.59314 | -0.56912 |
| 11 | C | 2.15612 | -0.10065 | -1.62465 |
| 12 | C | 1.33411 | -1.09504 | -2.46285 |
| 13 | C | -0.14391 | -0.78126 | -2.19183 |
| 14 | O | 0.62948 | -1.26812 | 3.33436 |
| 15 | O | -3.22376 | 1.67028 | 1.0115 |
| 16 | C | -0.19465 | 1.73972 | -2.26652 |
| 17 | H | 1.4675 | 1.41179 | -0.20976 |
| 18 | C | 3.45573 | -0.69172 | -1.09627 |
| 19 | H | -3.45538 | 0.58513 | 3.46148 |
| 20 | H | -1.975 | 1.48988 | 3.23291 |
| 21 | H | -2.21414 | -1.56662 | 3.37979 |
| 22 | H | -1.47287 | -0.47673 | 4.57223 |
| 23 | H | -3.33828 | -0.36075 | 1.20877 |
| 24 | H | 1.88703 | -0.29139 | 1.32884 |
| 25 | H | 1.12051 | -1.56009 | 0.37472 |
| 26 | H | 2.43511 | 0.74089 | -2.27242 |
| 27 | H | 1.5473 | -2.13531 | -2.19178 |
| 28 | H | 1.5694 | -0.98223 | -3.52699 |
| 29 | H | -0.60575 | -1.61128 | -1.64281 |
| 30 | H | -0.71156 | -0.67881 | -3.12338 |
| 31 | H | -2.97527 | 1.74886 | 0.07107 |
| 32 | H | -1.14958 | 1.79083 | -2.80337 |
| 33 | H | -0.12692 | 2.65775 | -1.67139 |
| 34 | H | 0.6066 | 1.75236 | -3.01033 |
| 35 | H | 4.11977 | -0.9516 | -1.92766 |
| 36 | H | 3.97815 | 0.03125 | -0.4615 |
| 37 | H | 3.29126 | -1.60301 | -0.51332 |



**Figure S9**. DFT-optimized structures for low-energy conformers of (7*R*, 10*S*, 11*R*, 15*R*)-**2b** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).

Conf. 1 65.8% Conf. 2 14.1% Conf. 3 16.7% Conf. 4 3.3%

**Table S12**. Harmonic frequencies (cm\*\*-1a) of **2b1** – **2b4**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **2b1** | 35.0028 | 57.9724 | 74.6505 |
| **2b2** | 28.6056 | 58.4328 | 77.6332 |
| **2b3** | 45.8661 | 58.962 | 78.4739 |
| **2b4** | 34.7039 | 61.6217 | 71.6346 |

**Table S13**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **2b** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **1b1** | -770.923339 | -770.965689 | 65.8% |
| **2b2** | -770.921644 | -770.964238 | 14.1% |
| **2b3** | -770.922244 | -770.964396 | 16.7% |
| **2b4** | -770.920293 | -770.962864 | 3.3% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

**Table S14.** Cartesian coordinates of the low-energy reoptimized conformers of (7*R*, 10*S*, 11*R*, 15*R*)-**2b** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2b1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 1.19559 | -3.07019 | 0.87823 |
| 2 | C | 2.46595 | -2.70091 | 0.13615 |
| 3 | C | 2.52764 | -1.21376 | -0.13571 |
| 4 | C | 1.24946 | -0.4697 | -0.34416 |
| 5 | C | 0.07669 | -1.12114 | -0.25811 |
| 6 | C | -0.03593 | -2.57712 | 0.12938 |
| 7 | C | 1.34695 | 0.99108 | -0.64589 |
| 8 | C | -0.00224 | 1.69321 | -0.52984 |
| 9 | C | -1.15423 | 0.80786 | -1.03704 |
| 10 | O | -1.14862 | -0.51733 | -0.47536 |
| 11 | C | -0.45659 | 2.17653 | 0.87821 |
| 12 | C | -1.96331 | 1.86834 | 0.95342 |
| 13 | C | -2.38146 | 1.53083 | -0.47347 |
| 14 | O | 3.6057 | -0.63343 | -0.25132 |
| 15 | O | -1.16682 | -2.76396 | 0.97698 |
| 16 | C | -1.22604 | 0.69265 | -2.55838 |
| 17 | H | 0.04686 | 2.59755 | -1.15522 |
| 18 | C | 0.27806 | 1.6252 | 2.09537 |
| 19 | H | 1.13733 | -4.15598 | 1.02026 |
| 20 | H | 1.21365 | -2.63838 | 1.88857 |
| 21 | H | 3.33369 | -2.98046 | 0.74331 |
| 22 | H | 2.52913 | -3.22772 | -0.82223 |
| 23 | H | -0.19823 | -3.17393 | -0.77552 |
| 24 | H | 1.71284 | 1.09436 | -1.67609 |
| 25 | H | 2.08686 | 1.48586 | -0.00822 |
| 26 | H | -0.33076 | 3.26786 | 0.90149 |
| 27 | H | -2.53235 | 2.71597 | 1.34894 |
| 28 | H | -2.15814 | 1.00947 | 1.60742 |
| 29 | H | -3.28169 | 0.90754 | -0.47691 |
| 30 | H | -2.59006 | 2.45351 | -1.02837 |
| 31 | H | -1.82652 | -2.10416 | 0.6904 |
| 32 | H | -2.10359 | 0.10912 | -2.85915 |
| 33 | H | -1.28522 | 1.67561 | -3.03672 |
| 34 | H | -0.35244 | 0.16848 | -2.9602 |
| 35 | H | -0.14619 | 2.04554 | 3.01419 |
| 36 | H | 1.3381 | 1.89448 | 2.07755 |
| 37 | H | 0.19595 | 0.53711 | 2.16802 |

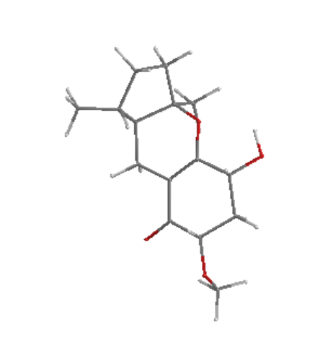
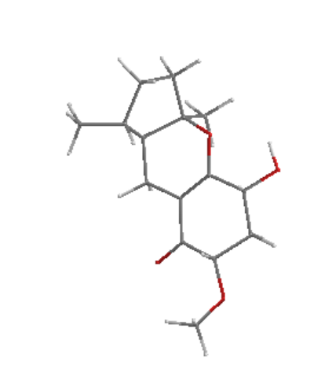
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2b2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 1.23091 | -3.33831 | -0.10847 |
| 2 | C | 2.42539 | -2.59617 | 0.46943 |
| 3 | C | 2.49228 | -1.18303 | -0.06401 |
| 4 | C | 1.21377 | -0.46137 | -0.33681 |
| 5 | C | 0.04354 | -1.11184 | -0.21623 |
| 6 | C | -0.06407 | -2.57276 | 0.13867 |
| 7 | C | 1.30407 | 0.99233 | -0.67242 |
| 8 | C | -0.04043 | 1.69859 | -0.52959 |
| 9 | C | -1.20799 | 0.80572 | -0.98542 |
| 10 | O | -1.18556 | -0.50973 | -0.40205 |
| 11 | C | -0.45174 | 2.20865 | 0.88235 |
| 12 | C | -1.95522 | 1.9021 | 1.00971 |
| 13 | C | -2.4171 | 1.53969 | -0.39737 |
| 14 | O | 3.56975 | -0.61253 | -0.22665 |
| 15 | O | -0.41366 | -2.6694 | 1.51605 |
| 16 | C | -1.3264 | 0.66475 | -2.5018 |
| 17 | H | -0.0091 | 2.59105 | -1.1729 |
| 18 | C | 0.32009 | 1.68063 | 2.08676 |
| 19 | H | 1.37528 | -3.4687 | -1.18874 |
| 20 | H | 1.176 | -4.3358 | 0.34269 |
| 21 | H | 2.37786 | -2.55031 | 1.5628 |
| 22 | H | 3.34551 | -3.1195 | 0.18729 |
| 23 | H | -0.86577 | -3.04384 | -0.44193 |
| 24 | H | 1.63854 | 1.07187 | -1.71526 |
| 25 | H | 2.06296 | 1.50152 | -0.06935 |
| 26 | H | -0.32585 | 3.30023 | 0.88091 |
| 27 | H | -2.51204 | 2.75663 | 1.40775 |
| 28 | H | -2.12929 | 1.05487 | 1.68441 |
| 29 | H | -3.31728 | 0.91733 | -0.36218 |
| 30 | H | -2.64226 | 2.4526 | -0.96188 |
| 31 | H | -1.17739 | -2.07679 | 1.64183 |
| 32 | H | -2.21285 | 0.0768 | -2.76561 |
| 33 | H | -1.40002 | 1.63947 | -2.99476 |
| 34 | H | -0.46557 | 0.13323 | -2.92119 |
| 35 | H | -0.07579 | 2.11877 | 3.00991 |
| 36 | H | 1.37905 | 1.94904 | 2.03119 |
| 37 | H | 0.24036 | 0.59418 | 2.18284 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2b3** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 1.19933 | -3.12147 | 0.97225 |
| 2 | C | 2.45716 | -2.79888 | 0.18838 |
| 3 | C | 2.5528 | -1.31778 | -0.10558 |
| 4 | C | 1.29046 | -0.54008 | -0.28934 |
| 5 | C | 0.10398 | -1.15694 | -0.16092 |
| 6 | C | -0.03903 | -2.60323 | 0.25235 |
| 7 | C | 1.42526 | 0.91127 | -0.61765 |
| 8 | C | 0.09532 | 1.65517 | -0.57678 |
| 9 | C | -1.10435 | 0.77797 | -0.96981 |
| 10 | O | -1.10843 | -0.5191 | -0.34564 |
| 11 | C | -0.3077 | 2.27733 | 0.77592 |
| 12 | C | -1.78296 | 2.61248 | 0.54137 |
| 13 | C | -2.32538 | 1.54173 | -0.41331 |
| 14 | O | 3.64304 | -0.76955 | -0.25813 |
| 15 | O | -1.14933 | -2.74536 | 1.1351 |
| 16 | C | -1.22368 | 0.56897 | -2.4812 |
| 17 | H | 0.16814 | 2.49497 | -1.28502 |
| 18 | C | -0.12754 | 1.41978 | 2.02686 |
| 19 | H | 1.11445 | -4.20312 | 1.13139 |
| 20 | H | 1.25929 | -2.6768 | 1.97536 |
| 21 | H | 3.33417 | -3.09538 | 0.7738 |
| 22 | H | 2.47706 | -3.3397 | -0.76405 |
| 23 | H | -0.24501 | -3.20789 | -0.63835 |
| 24 | H | 1.83806 | 0.98629 | -1.63235 |
| 25 | H | 2.14393 | 1.40091 | 0.04989 |
| 26 | H | 0.26063 | 3.20265 | 0.93333 |
| 27 | H | -1.85958 | 3.59305 | 0.0545 |
| 28 | H | -2.36598 | 2.66732 | 1.46649 |
| 29 | H | -3.00674 | 0.87173 | 0.12409 |
| 30 | H | -2.90398 | 2.03188 | -1.20486 |
| 31 | H | -1.79543 | -2.06652 | 0.86232 |
| 32 | H | -2.11282 | -0.0259 | -2.71945 |
| 33 | H | -1.29147 | 1.52154 | -3.01672 |
| 34 | H | -0.36459 | 0.01605 | -2.87613 |
| 35 | H | -0.41743 | 1.9926 | 2.91523 |
| 36 | H | 0.91673 | 1.12384 | 2.16232 |
| 37 | H | -0.7484 | 0.52017 | 2.01433 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 2b4** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 1.16306 | -3.40874 | -0.24097 |
| 2 | C | 2.38588 | -2.75375 | 0.38117 |
| 3 | C | 2.50882 | -1.3125 | -0.05896 |
| 4 | C | 1.26001 | -0.52425 | -0.28306 |
| 5 | C | 0.06603 | -1.13454 | -0.20263 |
| 6 | C | -0.10023 | -2.60972 | 0.05844 |
| 7 | C | 1.41368 | 0.9412 | -0.52913 |
| 8 | C | 0.09328 | 1.69842 | -0.44596 |
| 9 | C | -1.11857 | 0.86058 | -0.88561 |
| 10 | O | -1.13676 | -0.47182 | -0.34147 |
| 11 | C | -0.30036 | 2.25007 | 0.93968 |
| 12 | C | -1.77021 | 2.61928 | 0.72425 |
| 13 | C | -2.32911 | 1.60388 | -0.27986 |
| 14 | O | 3.60812 | -0.77514 | -0.18469 |
| 15 | O | -0.45351 | -2.78141 | 1.42744 |
| 16 | C | -1.24449 | 0.74486 | -2.4066 |
| 17 | H | 0.17695 | 2.57531 | -1.10644 |
| 18 | C | -0.13348 | 1.32047 | 2.1399 |
| 19 | H | 1.30241 | -3.47435 | -1.32776 |
| 20 | H | 1.06825 | -4.43043 | 0.14465 |
| 21 | H | 2.34006 | -2.77763 | 1.4753 |
| 22 | H | 3.28457 | -3.29349 | 0.06316 |
| 23 | H | -0.92003 | -3.0099 | -0.54943 |
| 24 | H | 1.82805 | 1.06641 | -1.53817 |
| 25 | H | 2.13782 | 1.38546 | 0.16377 |
| 26 | H | 0.28148 | 3.15661 | 1.14844 |
| 27 | H | -1.83183 | 3.62311 | 0.28497 |
| 28 | H | -2.35154 | 2.63854 | 1.65183 |
| 29 | H | -3.01086 | 0.91191 | 0.22845 |
| 30 | H | -2.91104 | 2.13828 | -1.03965 |
| 31 | H | -1.19332 | -2.16863 | 1.59306 |
| 32 | H | -2.14068 | 0.17503 | -2.67742 |
| 33 | H | -1.30343 | 1.72881 | -2.8832 |
| 34 | H | -0.39246 | 0.20779 | -2.83714 |
| 35 | H | -0.41668 | 1.84566 | 3.0593 |
| 36 | H | 0.90648 | 1.003 | 2.25871 |
| 37 | H | -0.76639 | 0.43161 | 2.07563 |



**Figure S10**. DFT-optimized structures for low-energy conformers of (7*S*, 10*S*, 11*R*, 15*R*, 17*S*)-**4a** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).



Conf. 1 91.6% Conf. 2 8.4%

**Table S15**. Harmonic frequencies (cm\*\*-1a) of **4a1** – **4a2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **4a1** | 32.5615 | 40.1366 | 59.9401 |
| **4a2** | 25.9366 | 37.5103 | 58.811 |

**Table S16**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **4a** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **4a1** | -885.414699 | -885.461392 | 91.6% |
| **4a2** | -885.412340 | -885.459143 | 8.4% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

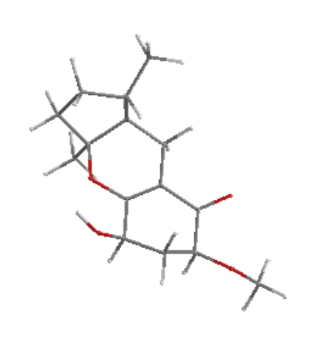
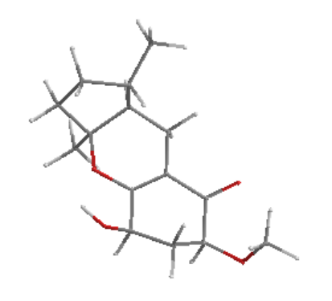
**Table S17**. Cartesian coordinates of the low-energy reoptimized conformers of (7*S*, 10*S*, 11*R*, 15*R*, 17*S*)-**4a** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 4a1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 2.44643 | -2.05411 | 0.68162 |
| 2 | C | 1.16156 | -2.85386 | 0.84986 |
| 3 | C | 0.09381 | -2.2916 | -0.11178 |
| 4 | C | 0.0473 | -0.80897 | -0.31372 |
| 5 | C | 1.01638 | -0.03396 | 0.20335 |
| 6 | C | 2.20346 | -0.57921 | 0.96063 |
| 7 | C | -1.11777 | -0.25867 | -1.07644 |
| 8 | C | -1.22705 | 1.2577 | -0.93838 |
| 9 | C | 0.15215 | 1.92945 | -0.9012 |
| 10 | O | 1.04226 | 1.34361 | 0.0671 |
| 11 | C | -1.87951 | 1.72139 | 0.38312 |
| 12 | C | -1.29936 | 3.12155 | 0.64327 |
| 13 | C | -0.1994 | 3.33496 | -0.40011 |
| 14 | O | -0.74705 | -2.99744 | -0.6679 |
| 15 | O | 3.37734 | 0.14139 | 0.59276 |
| 16 | O | 1.49731 | -4.22271 | 0.64316 |
| 17 | C | 0.8597 | 1.98112 | -2.25373 |
| 18 | H | -1.81491 | 1.64928 | -1.78055 |
| 19 | C | 0.54967 | -5.12572 | 1.19774 |
| 20 | C | -3.402 | 1.72663 | 0.32242 |
| 21 | H | 3.23 | -2.43815 | 1.34771 |
| 22 | H | 2.85196 | -2.19258 | -0.33102 |
| 23 | H | 0.78559 | -2.72309 | 1.87349 |
| 24 | H | 2.04203 | -0.41746 | 2.0328 |
| 25 | H | -0.98464 | -0.51468 | -2.13521 |
| 26 | H | -2.05249 | -0.72801 | -0.74944 |
| 27 | H | -1.57923 | 1.06528 | 1.21035 |
| 28 | H | -0.87512 | 3.16166 | 1.65353 |
| 29 | H | -2.05062 | 3.91596 | 0.57695 |
| 30 | H | 0.65769 | 3.85573 | 0.03993 |
| 31 | H | -0.59591 | 3.95305 | -1.21507 |
| 32 | H | 3.09002 | 1.0607 | 0.43623 |
| 33 | H | 1.80087 | 2.53692 | -2.17418 |
| 34 | H | 1.12101 | 0.97807 | -2.60718 |
| 35 | H | 0.23866 | 2.46079 | -3.01712 |
| 36 | H | 0.8977 | -6.14427 | 1.00483 |
| 37 | H | 0.47847 | -4.98626 | 2.2808 |
| 38 | H | -0.43494 | -5.00816 | 0.73979 |
| 39 | H | -3.82315 | 2.08701 | 1.26683 |
| 40 | H | -3.79086 | 0.71933 | 0.14397 |
| 41 | H | -3.7674 | 2.37731 | -0.47922 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 4a2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 2.25462 | -2.16785 | 0.8233 |
| 2 | C | 0.94367 | -2.9249 | 0.99716 |
| 3 | C | -0.13332 | -2.3328 | 0.06491 |
| 4 | C | -0.13689 | -0.84914 | -0.13285 |
| 5 | C | 0.86648 | -0.10587 | 0.36657 |
| 6 | C | 2.0523 | -0.6852 | 1.1035 |
| 7 | C | -1.3018 | -0.26127 | -0.86708 |
| 8 | C | -1.36433 | 1.25658 | -0.71769 |
| 9 | C | 0.03407 | 1.88827 | -0.70963 |
| 10 | O | 0.93051 | 1.2709 | 0.23285 |
| 11 | C | -1.97188 | 1.73032 | 0.62156 |
| 12 | C | -1.3449 | 3.11111 | 0.87654 |
| 13 | C | -0.26475 | 3.29991 | -0.19195 |
| 14 | O | -0.99788 | -3.01692 | -0.48092 |
| 15 | O | 3.23844 | 0.00058 | 0.7076 |
| 16 | O | 1.12789 | -4.33546 | 0.94951 |
| 17 | C | 0.71009 | 1.92844 | -2.07857 |
| 18 | H | -1.96041 | 1.67017 | -1.54341 |
| 19 | C | 1.59655 | -4.85018 | -0.28904 |
| 20 | C | -3.49456 | 1.78052 | 0.59652 |
| 21 | H | 3.03034 | -2.57679 | 1.48285 |
| 22 | H | 2.6485 | -2.29854 | -0.19378 |
| 23 | H | 0.56971 | -2.73344 | 2.01201 |
| 24 | H | 1.91754 | -0.51651 | 2.17826 |
| 25 | H | -1.19885 | -0.51437 | -1.92989 |
| 26 | H | -2.24234 | -0.70581 | -0.52255 |
| 27 | H | -1.67199 | 1.06018 | 1.4376 |
| 28 | H | -0.89524 | 3.1315 | 1.87635 |
| 29 | H | -2.07395 | 3.92751 | 0.83385 |
| 30 | H | 0.61729 | 3.79311 | 0.23019 |
| 31 | H | -0.6629 | 3.93439 | -0.9934 |
| 32 | H | 2.97916 | 0.93374 | 0.58644 |
| 33 | H | 1.66831 | 2.45691 | -2.01874 |
| 34 | H | 0.93426 | 0.9206 | -2.44373 |
| 35 | H | 0.08478 | 2.43023 | -2.82405 |
| 36 | H | 1.54777 | -5.94174 | -0.24027 |
| 37 | H | 0.98202 | -4.51816 | -1.12928 |
| 38 | H | 2.64071 | -4.56995 | -0.45214 |
| 39 | H | -3.88292 | 2.14654 | 1.55274 |
| 40 | H | -3.91688 | 0.78626 | 0.42095 |
| 41 | H | -3.85917 | 2.44712 | -0.1923 |



**Figure S11**. DFT-optimized structures for low-energy conformers of (7*R*, 10*R*, 11*S*, 15*R*, 17*S*)-**4b** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).

Conf. 1 96.4% Conf. 2 3.6%

**Table S18**. Harmonic frequencies (cm\*\*-1a) of **4b1** – **4b2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **4b1** | 23.3972 | 35.4642 | 57.8095 |
| **4b2** | 32.986 | 36.4378 | 56.9024 |

**Table S19**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **4b** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **4b1** | -885.414844 | -885.461873 | 96.4% |
| **4b2** | -885.412303 | -885.458763 | 3.6% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

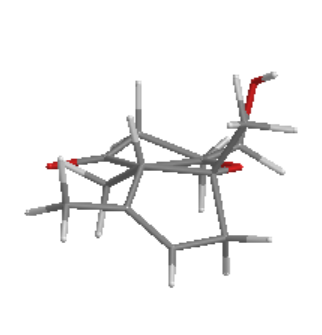
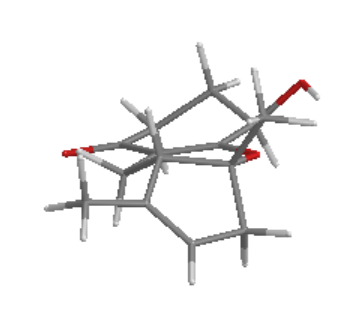
**Table S20**. Cartesian coordinates of the low-energy reoptimized conformers of (7*R*, 10*R*, 11*S*, 15*R*, 17*S*)-**4b** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 4b1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 0.77709 | -2.66689 | 1.44618 |
| 2 | C | 1.79107 | -2.67539 | 0.31015 |
| 3 | C | 1.90953 | -1.24912 | -0.26721 |
| 4 | C | 0.66488 | -0.42047 | -0.34651 |
| 5 | C | -0.47993 | -0.88259 | 0.18541 |
| 6 | C | -0.5764 | -2.17794 | 0.95529 |
| 7 | C | 0.77015 | 0.91293 | -1.01969 |
| 8 | C | -0.46611 | 1.77487 | -0.77604 |
| 9 | C | -1.75235 | 0.93815 | -0.76205 |
| 10 | O | -1.6815 | -0.19862 | 0.11819 |
| 11 | C | -0.48319 | 2.4709 | 0.60352 |
| 12 | C | -1.97253 | 2.66612 | 0.93322 |
| 13 | C | -2.75656 | 1.92182 | -0.15074 |
| 14 | O | 2.96015 | -0.79522 | -0.71988 |
| 15 | O | -1.42215 | -1.99957 | 2.08904 |
| 16 | O | 2.99961 | -3.21205 | 0.83999 |
| 17 | C | -2.2046 | 0.465 | -2.14182 |
| 18 | H | -0.52386 | 2.54215 | -1.56097 |
| 19 | C | 3.87947 | -3.71381 | -0.15752 |
| 20 | C | 0.28991 | 3.78393 | 0.61323 |
| 21 | H | 0.67855 | -3.66918 | 1.88302 |
| 22 | H | 1.13657 | -2.03854 | 2.27384 |
| 23 | H | 1.42601 | -3.32761 | -0.49462 |
| 24 | H | -1.04334 | -2.93454 | 0.31401 |
| 25 | H | 0.88463 | 0.74371 | -2.09785 |
| 26 | H | 1.66488 | 1.44886 | -0.68345 |
| 27 | H | -0.04405 | 1.81806 | 1.36895 |
| 28 | H | -2.18967 | 2.23628 | 1.91831 |
| 29 | H | -2.26997 | 3.71973 | 0.96804 |
| 30 | H | -3.63304 | 1.42346 | 0.27686 |
| 31 | H | -3.10285 | 2.64392 | -0.90043 |
| 32 | H | -2.0911 | -1.33946 | 1.82589 |
| 33 | H | -3.16503 | -0.05834 | -2.07322 |
| 34 | H | -2.31604 | 1.301 | -2.83985 |
| 35 | H | -1.49336 | -0.24741 | -2.57305 |
| 36 | H | 4.76388 | -4.11868 | 0.34217 |
| 37 | H | 3.40025 | -4.52311 | -0.71691 |
| 38 | H | 4.20373 | -2.92669 | -0.84178 |
| 39 | H | 0.23155 | 4.25716 | 1.59903 |
| 40 | H | 1.34675 | 3.61833 | 0.38213 |
| 41 | H | -0.11106 | 4.48883 | -0.12289 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 4b2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 0.89738 | -2.79691 | 1.16014 |
| 2 | C | 1.88708 | -2.73331 | 0.00331 |
| 3 | C | 1.95709 | -1.29594 | -0.55264 |
| 4 | C | 0.68746 | -0.50339 | -0.58541 |
| 5 | C | -0.4306 | -1.01003 | -0.036 |
| 6 | C | -0.47745 | -2.32554 | 0.70711 |
| 7 | C | 0.7381 | 0.84397 | -1.23662 |
| 8 | C | -0.51792 | 1.66357 | -0.95189 |
| 9 | C | -1.77755 | 0.78767 | -0.92337 |
| 10 | O | -1.6523 | -0.35914 | -0.06226 |
| 11 | C | -0.52533 | 2.33676 | 0.439 |
| 12 | C | -2.01229 | 2.48279 | 0.80307 |
| 13 | C | -2.79732 | 1.7307 | -0.27484 |
| 14 | O | 2.98948 | -0.80295 | -1.00502 |
| 15 | O | -1.29697 | -2.18798 | 1.86609 |
| 16 | O | 3.12552 | -3.35822 | 0.32215 |
| 17 | C | -2.24594 | 0.32159 | -2.30014 |
| 18 | H | -0.61647 | 2.44105 | -1.72259 |
| 19 | C | 3.86994 | -2.74392 | 1.36484 |
| 20 | C | 0.20932 | 3.67161 | 0.4543 |
| 21 | H | 0.83599 | -3.81524 | 1.56412 |
| 22 | H | 1.23921 | -2.17779 | 2.00067 |
| 23 | H | 1.4846 | -3.33287 | -0.82432 |
| 24 | H | -0.94376 | -3.07907 | 0.0618 |
| 25 | H | 0.83433 | 0.69685 | -2.3198 |
| 26 | H | 1.62353 | 1.40077 | -0.90984 |
| 27 | H | -0.05106 | 1.68485 | 1.18401 |
| 28 | H | -2.19531 | 2.03309 | 1.78621 |
| 29 | H | -2.33985 | 3.52649 | 0.85942 |
| 30 | H | -3.64832 | 1.1992 | 0.16415 |
| 31 | H | -3.18233 | 2.45281 | -1.00541 |
| 32 | H | -2.00733 | -1.5652 | 1.62012 |
| 33 | H | -3.18813 | -0.23218 | -2.21869 |
| 34 | H | -2.39854 | 1.1642 | -2.98226 |
| 35 | H | -1.52313 | -0.36187 | -2.75816 |
| 36 | H | 4.85136 | -3.22491 | 1.40649 |
| 37 | H | 4.0203 | -1.67651 | 1.18606 |
| 38 | H | 3.38114 | -2.89908 | 2.33042 |
| 39 | H | 0.15819 | 4.1272 | 1.44877 |
| 40 | H | 1.26538 | 3.54086 | 0.19861 |
| 41 | H | -0.22751 | 4.37602 | -0.26161 |



**Figure S12**. DFT-optimized structures for low-energy conformers of (10*R*, 11*S*, 15*R*)-**6a** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).



Conf. 1 79.0% Conf. 2 21.0%

**Table S21**. Harmonic frequencies (cm\*\*-1a) of **6a1** - **6a2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **6a1** | 38.6368 | 54.6771 | 71.1043 |
| **6a2** | 42.0834 | 55.8521 | 78.0123 |

**Table S22**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **3a** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **6a1** | -769.724807 | -769.767326 | 79.0% |
| **6a2** | -769.723741 | -769.766076 | 21.0% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

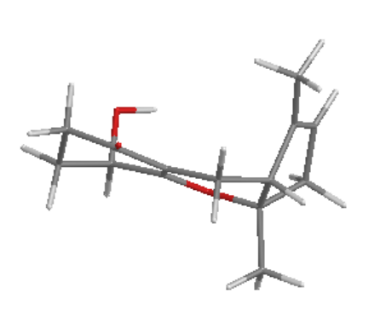
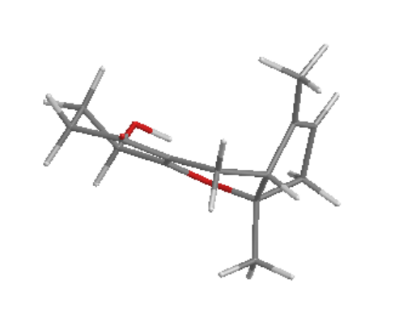
**Table S23**. Cartesian coordinates of the low-energy reoptimized conformers of (10*R*, 11*S*, 15*R*)-**6a** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 6a1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 0.50661 | 1.44713 | -3.43821 |
| 2 | C | -0.74145 | 0.63322 | -3.71901 |
| 3 | C | -1.46479 | 0.27948 | -2.438 |
| 4 | C | -0.66498 | 0.09068 | -1.18965 |
| 5 | C | 0.66445 | 0.27179 | -1.21514 |
| 6 | C | 1.41257 | 0.72815 | -2.44739 |
| 7 | C | -1.39399 | -0.34564 | 0.03395 |
| 8 | C | -0.62335 | -0.00242 | 1.30731 |
| 9 | C | 0.91557 | -0.14072 | 1.16754 |
| 10 | O | 1.48518 | 0.06686 | -0.1297 |
| 11 | C | -0.9334 | -0.99528 | 2.40652 |
| 12 | C | 0.07051 | -1.8674 | 2.57352 |
| 13 | C | 1.20808 | -1.58183 | 1.64286 |
| 14 | O | -2.67897 | 0.08429 | -2.43062 |
| 15 | O | 2.45108 | 1.62993 | -2.07237 |
| 16 | C | 1.62335 | 0.86935 | 2.09271 |
| 17 | H | -0.8809 | 1.0165 | 1.62448 |
| 18 | C | -2.22793 | -0.96553 | 3.13902 |
| 19 | H | 1.05188 | 1.64506 | -4.36882 |
| 20 | H | 0.22901 | 2.43315 | -3.04053 |
| 21 | H | -0.4946 | -0.29765 | -4.24113 |
| 22 | H | -1.41874 | 1.21643 | -4.35223 |
| 23 | H | 1.88369 | -0.14124 | -2.9204 |
| 24 | H | -2.37749 | 0.13777 | 0.09289 |
| 25 | H | -1.58373 | -1.42434 | -0.04647 |
| 26 | H | 0.06972 | -2.69057 | 3.27561 |
| 27 | H | 2.172 | -1.65492 | 2.15689 |
| 28 | H | 1.2131 | -2.29671 | 0.81249 |
| 29 | H | 2.78456 | 1.30929 | -1.21339 |
| 30 | H | 1.31111 | 0.77469 | 3.13767 |
| 31 | H | 2.71118 | 0.74187 | 2.04498 |
| 32 | H | 1.41889 | 1.89507 | 1.76413 |
| 33 | H | -2.27959 | -1.75598 | 3.89478 |
| 34 | H | -2.35399 | -0.00483 | 3.64774 |
| 35 | H | -3.06466 | -1.10565 | 2.44797 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 6a2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | 0.70891 | 0.23933 | -3.72413 |
| 2 | C | -0.70358 | 0.79613 | -3.65441 |
| 3 | C | -1.422 | 0.2826 | -2.42736 |
| 4 | C | -0.63383 | 0.06463 | -1.17709 |
| 5 | C | 0.69887 | 0.22127 | -1.19482 |
| 6 | C | 1.48077 | 0.5418 | -2.44483 |
| 7 | C | -1.38258 | -0.30615 | 0.05589 |
| 8 | C | -0.62955 | 0.10523 | 1.31939 |
| 9 | C | 0.9106 | -0.04839 | 1.21117 |
| 10 | O | 1.50009 | 0.07648 | -0.08764 |
| 11 | C | -0.96231 | -0.82019 | 2.46955 |
| 12 | C | 0.03443 | -1.68486 | 2.70415 |
| 13 | C | 1.18812 | -1.4596 | 1.77684 |
| 14 | O | -2.63714 | 0.09277 | -2.43449 |
| 15 | O | 1.81527 | 1.92607 | -2.41344 |
| 16 | C | 1.61024 | 1.01239 | 2.08419 |
| 17 | H | -0.88568 | 1.14213 | 1.5733 |
| 18 | C | -2.26852 | -0.74244 | 3.17738 |
| 19 | H | 0.66196 | -0.8473 | -3.87195 |
| 20 | H | 1.22268 | 0.67128 | -4.59073 |
| 21 | H | -1.26017 | 0.4791 | -4.54312 |
| 22 | H | -0.70273 | 1.89096 | -3.62208 |
| 23 | H | 2.41817 | -0.02654 | -2.46013 |
| 24 | H | -2.36721 | 0.17789 | 0.07649 |
| 25 | H | -1.57063 | -1.38777 | 0.02969 |
| 26 | H | 0.01802 | -2.46541 | 3.45313 |
| 27 | H | 2.14323 | -1.50562 | 2.31012 |
| 28 | H | 1.20308 | -2.22302 | 0.99098 |
| 29 | H | 2.24441 | 2.07998 | -1.55219 |
| 30 | H | 1.2817 | 0.9826 | 3.12803 |
| 31 | H | 2.6979 | 0.87699 | 2.06109 |
| 32 | H | 1.41659 | 2.01731 | 1.69113 |
| 33 | H | -2.33622 | -1.48664 | 3.97752 |
| 34 | H | -2.39843 | 0.2471 | 3.62635 |
| 35 | H | -3.09447 | -0.9201 | 2.48201 |



**Figure S13**. DFT-optimized structures for low-energy conformers of (10*S*, 11*R*, 15*R*)-**6b** at B3LYP/6-31+G(d) level in methanol (CPCM) (Conformer populations were calculated using the Gibbs free energy and Boltzmann population at 298 K estimated thereof).

Conf. 1 17.3% Conf. 2 82.7%

**Table S24**. Harmonic frequencies (cm\*\*-1a) of **6b1** – **6b2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **Frequencies** | | |
|
| 1 | 2 | 3 |
| **6b1** | 37.1905 | 53.3588 | 72.7842 |
| **6b2** | 36.3635 | 53.6060 | 75.8656 |

**Table S25**. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **6b** at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Conformations** | **E+ZPE** | **G** | **%** |
| **6b1** | -769.725577 | -769.767865 | 17.3% |
| **6b2** | -769.727099 | -769.769342 | 82.7% |

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy at B3LYP/6-31G+(d) level of theory with PCM solvent model for MeOH. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

**Table S26**. Cartesian coordinates of the low-energy reoptimized conformers of (10*S*, 11*R*, 15*R*)-**6b** calculated at B3LYP/6-31+G(d) level of theory with PCM solvent model for MeOH.

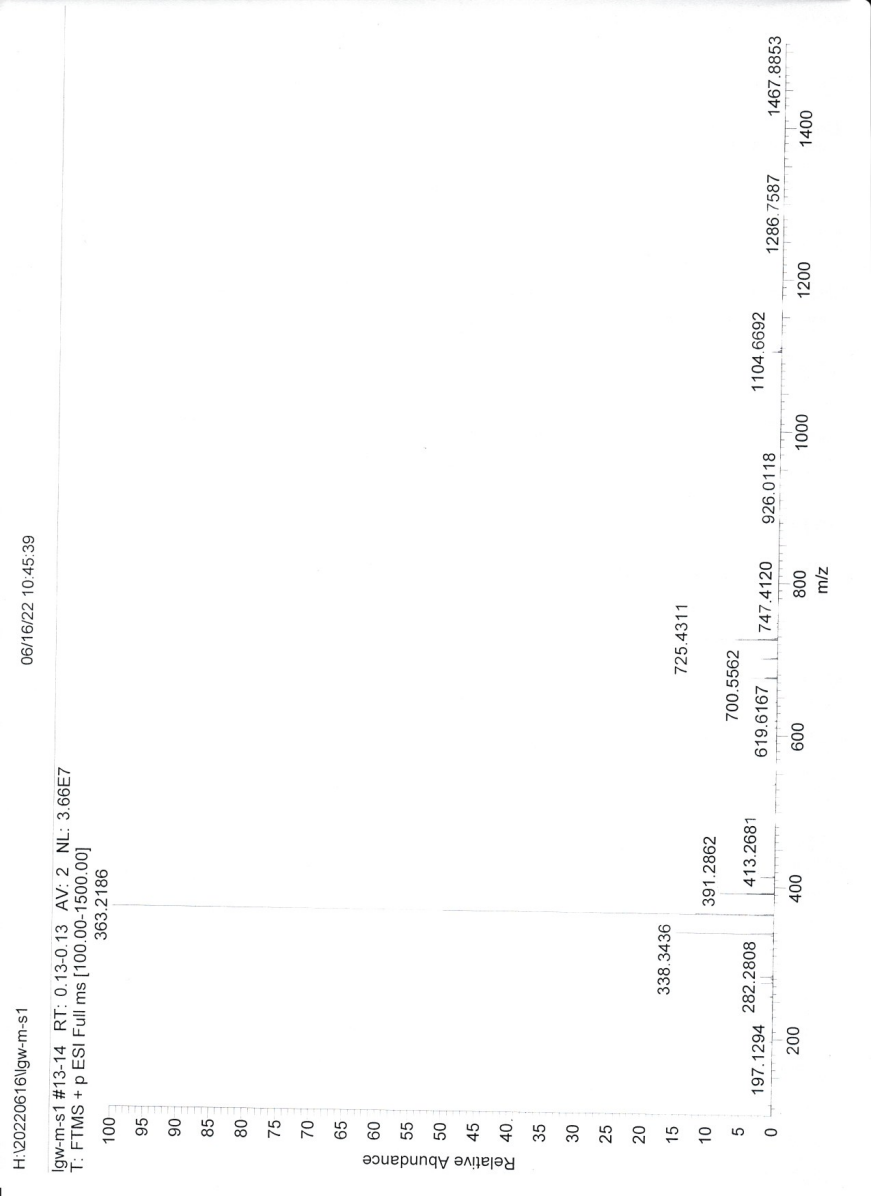
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 6b1** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -3.51773 | -0.01693 | -0.44672 |
| 2 | C | -3.33528 | 0.81854 | 0.81023 |
| 3 | C | -2.11937 | 0.36469 | 1.58578 |
| 4 | C | -0.93106 | -0.12789 | 0.82757 |
| 5 | C | -1.00403 | -0.26948 | -0.50503 |
| 6 | C | -2.25605 | -0.00203 | -1.30216 |
| 7 | C | 0.31581 | -0.39367 | 1.60078 |
| 8 | C | 1.561 | -0.40332 | 0.71937 |
| 9 | C | 1.30492 | -1.0433 | -0.66695 |
| 10 | O | 0.05114 | -0.67801 | -1.28825 |
| 11 | C | 2.14803 | 0.9394 | 0.3312 |
| 12 | C | 2.63003 | 0.90303 | -0.91969 |
| 13 | C | 2.40999 | -0.43606 | -1.55835 |
| 14 | O | -2.08199 | 0.43812 | 2.81311 |
| 15 | O | -2.1244 | 1.27322 | -1.92336 |
| 16 | C | 1.3703 | -2.5684 | -0.64146 |
| 17 | H | 2.35506 | -0.94294 | 1.25559 |
| 18 | C | 2.23886 | 2.08447 | 1.27708 |
| 19 | H | -3.7521 | -1.05088 | -0.16245 |
| 20 | H | -4.36932 | 0.37298 | -1.01619 |
| 21 | H | -4.2184 | 0.7064 | 1.44869 |
| 22 | H | -3.21642 | 1.88105 | 0.57215 |
| 23 | H | -2.36276 | -0.74898 | -2.09738 |
| 24 | H | 0.43965 | 0.33271 | 2.41183 |
| 25 | H | 0.21024 | -1.37615 | 2.07922 |
| 26 | H | 3.14178 | 1.7183 | -1.41335 |
| 27 | H | 2.08304 | -0.31815 | -2.59649 |
| 28 | H | 3.34256 | -1.00992 | -1.53066 |
| 29 | H | -1.23281 | 1.29107 | -2.31775 |
| 30 | H | 2.3245 | -2.92622 | -0.24168 |
| 31 | H | 0.56273 | -2.9848 | -0.02952 |
| 32 | H | 1.24221 | -2.97873 | -1.64953 |
| 33 | H | 2.8091 | 2.91492 | 0.84787 |
| 34 | H | 1.24146 | 2.45932 | 1.52578 |
| 35 | H | 2.73928 | 1.77764 | 2.20071 |

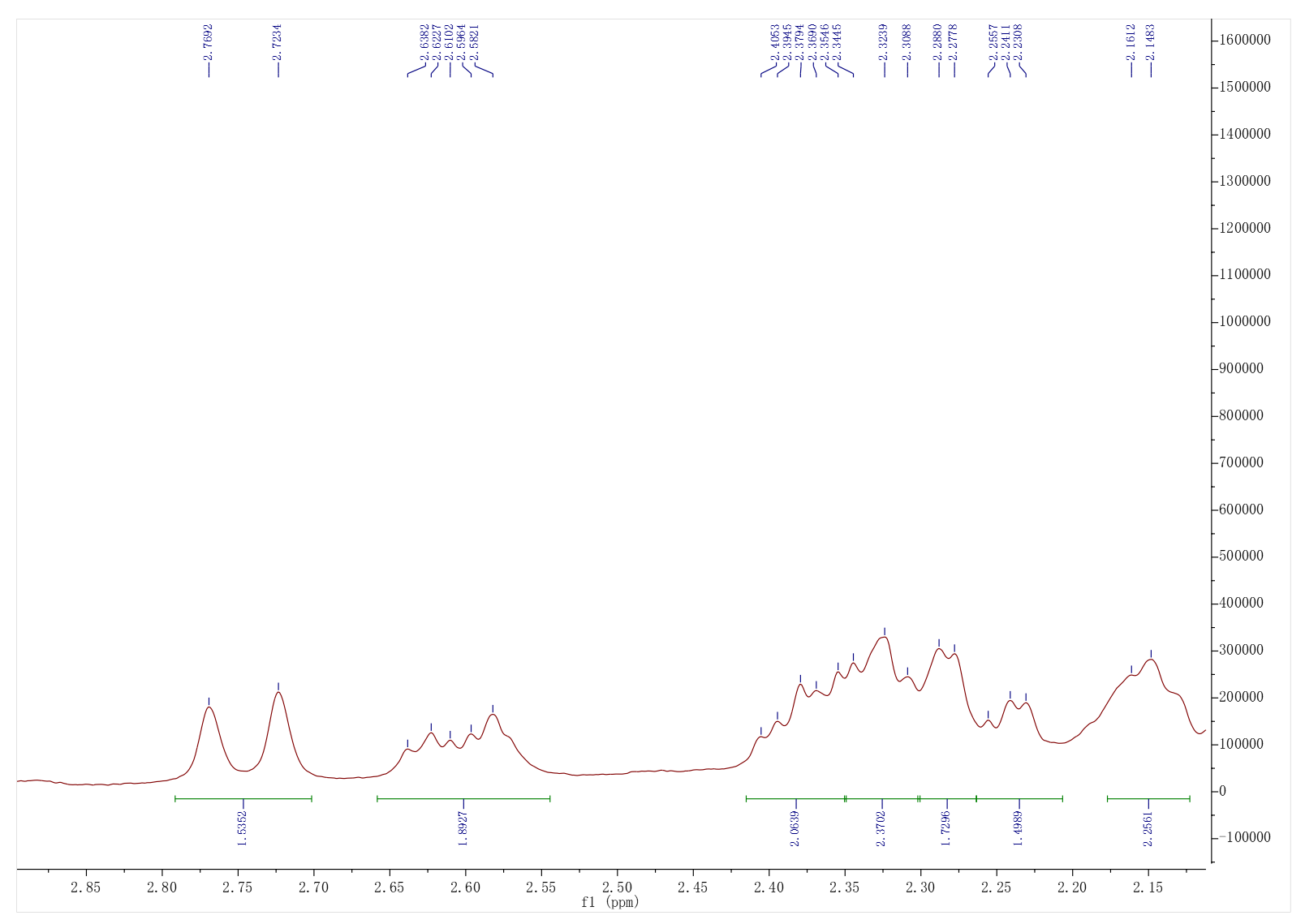
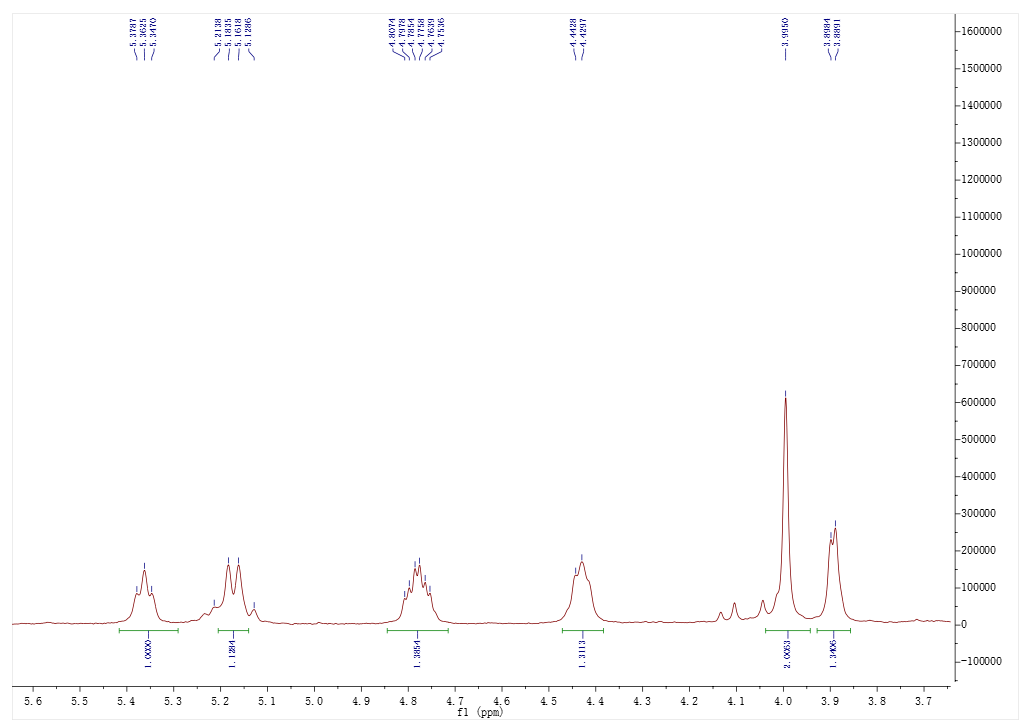
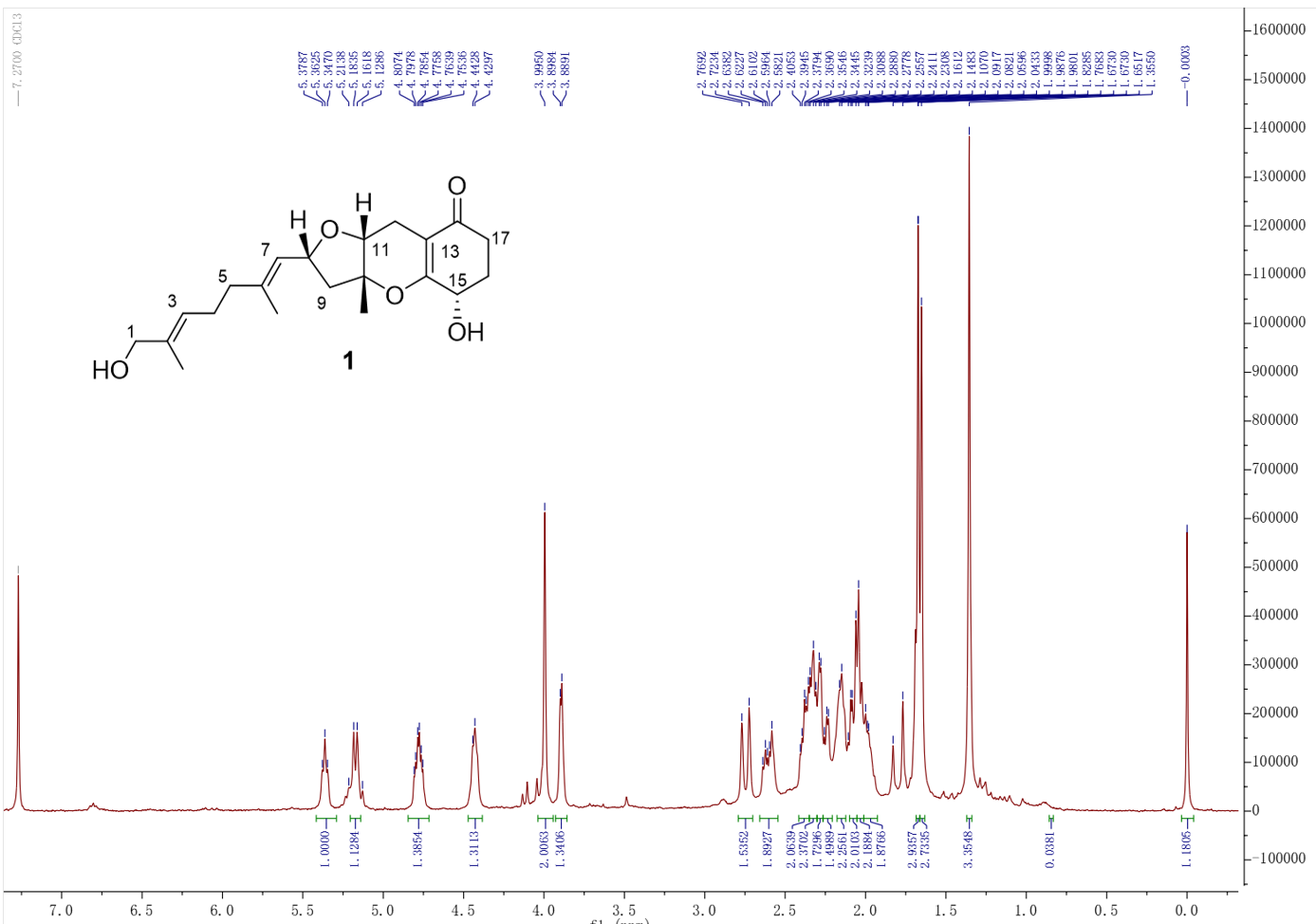
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Conformer 6b2** | | Standard Orientation  (Ångstroms) | | |
| I | Atom | X | Y | Z |
| 1 | C | -3.14407 | 1.15544 | -0.58287 |
| 2 | C | -3.4494 | 0.67605 | 0.82308 |
| 3 | C | -2.17895 | 0.38014 | 1.58966 |
| 4 | C | -0.97898 | -0.0928 | 0.83639 |
| 5 | C | -1.03831 | -0.22457 | -0.49788 |
| 6 | C | -2.25023 | 0.16254 | -1.3145 |
| 7 | C | 0.2423 | -0.41781 | 1.62807 |
| 8 | C | 1.49656 | -0.51376 | 0.76494 |
| 9 | C | 1.2198 | -1.14432 | -0.62175 |
| 10 | O | 0.0038 | -0.69776 | -1.26552 |
| 11 | C | 2.17668 | 0.78452 | 0.37887 |
| 12 | C | 2.67528 | 0.70745 | -0.86365 |
| 13 | C | 2.37734 | -0.61838 | -1.49814 |
| 14 | O | -2.14679 | 0.45717 | 2.81681 |
| 15 | O | -1.83817 | 0.76666 | -2.53844 |
| 16 | C | 1.18138 | -2.6701 | -0.58766 |
| 17 | H | 2.24568 | -1.1009 | 1.3158 |
| 18 | C | 2.32787 | 1.92823 | 1.3185 |
| 19 | H | -4.07301 | 1.30811 | -1.14527 |
| 20 | H | -2.65428 | 2.13838 | -0.54493 |
| 21 | H | -4.05782 | -0.23473 | 0.80408 |
| 22 | H | -4.00583 | 1.45359 | 1.35751 |
| 23 | H | -2.81174 | -0.74433 | -1.56689 |
| 24 | H | 0.39496 | 0.31344 | 2.42983 |
| 25 | H | 0.07546 | -1.38544 | 2.1194 |
| 26 | H | 3.24621 | 1.48431 | -1.35446 |
| 27 | H | 2.07579 | -0.48623 | -2.54226 |
| 28 | H | 3.26901 | -1.2528 | -1.45146 |
| 29 | H | -0.96726 | 0.37918 | -2.74798 |
| 30 | H | 2.10291 | -3.08912 | -0.17104 |
| 31 | H | 0.3382 | -3.02742 | 0.0135 |
| 32 | H | 1.04143 | -3.07684 | -1.59559 |
| 33 | H | 2.95913 | 2.71567 | 0.89362 |
| 34 | H | 1.35365 | 2.37041 | 1.54771 |
| 35 | H | 2.79144 | 1.59601 | 2.25252 |

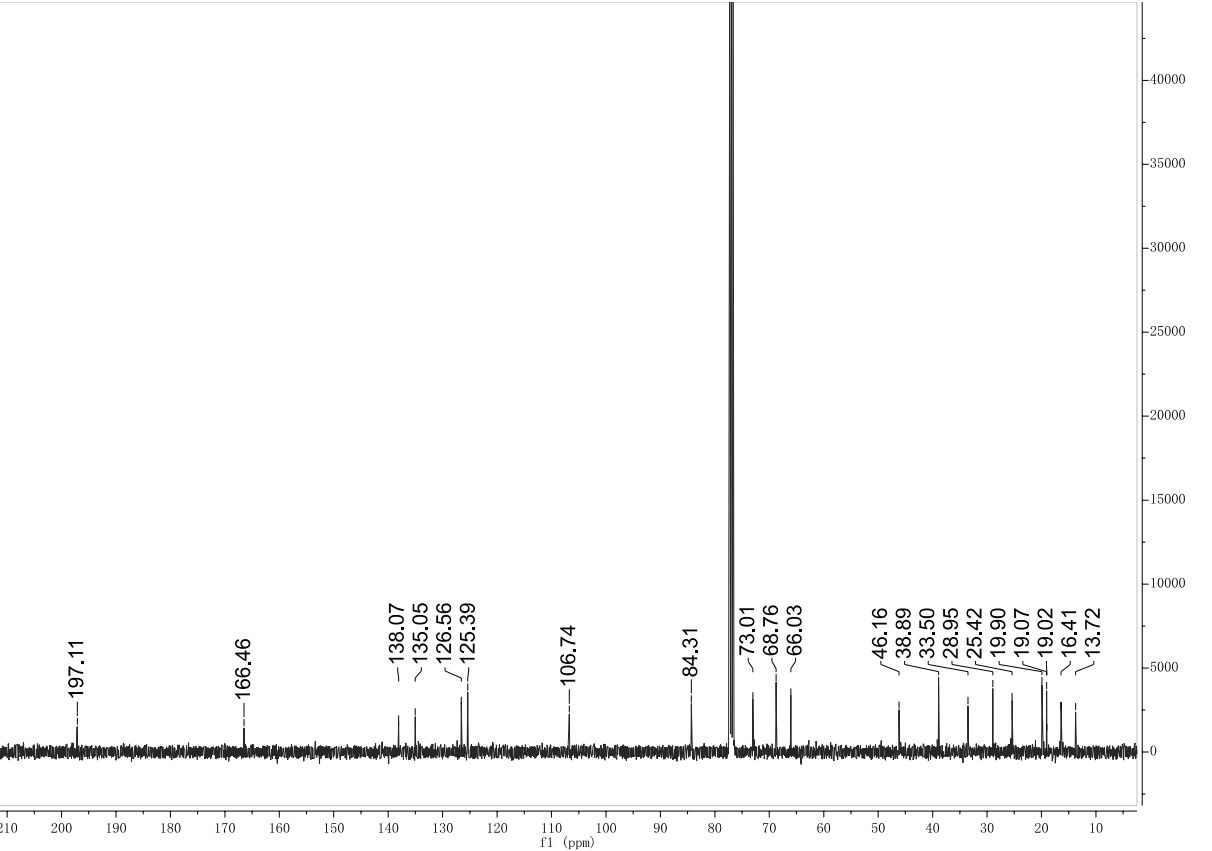
**References:**

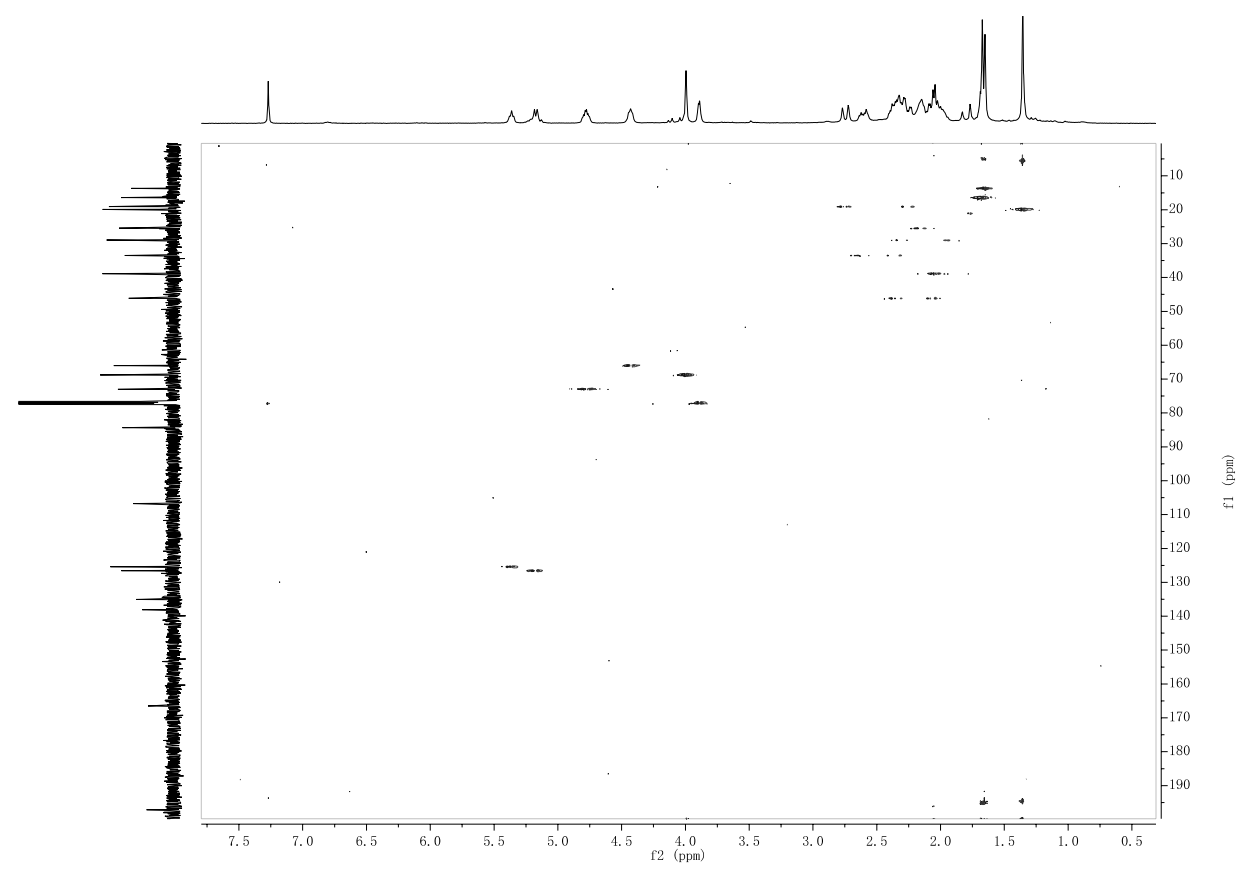
1. Nugroho AE, Morita H. *J Nat Med*. **2014**, 68, 1**-**10.
2. Farkas V, Nagy A, Menyhárd DK, Perczel A. *Chemistry*. **2019**, 25, 14890**-**14900.
3. Nugroho AE, Morita H. *J Nat Med*. **2019**, 73, 687**-**695.

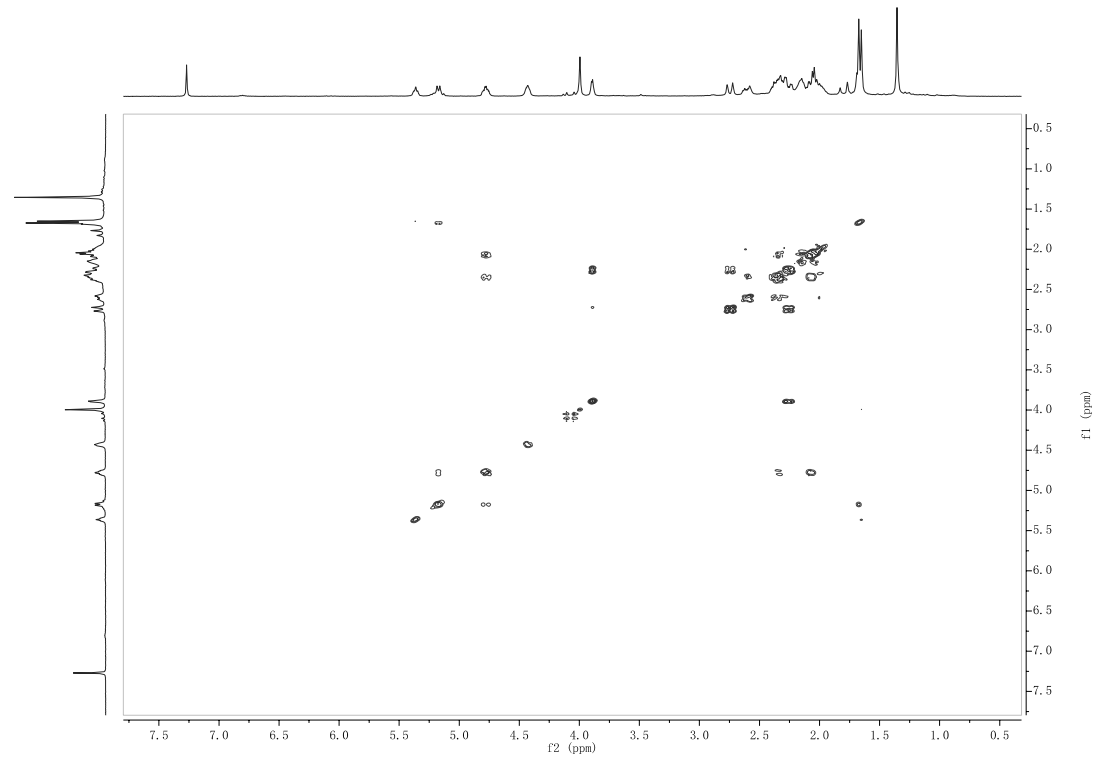
# **Figure S 14.** HRESIMS spectrum of tricycloalternarene O (**1**)

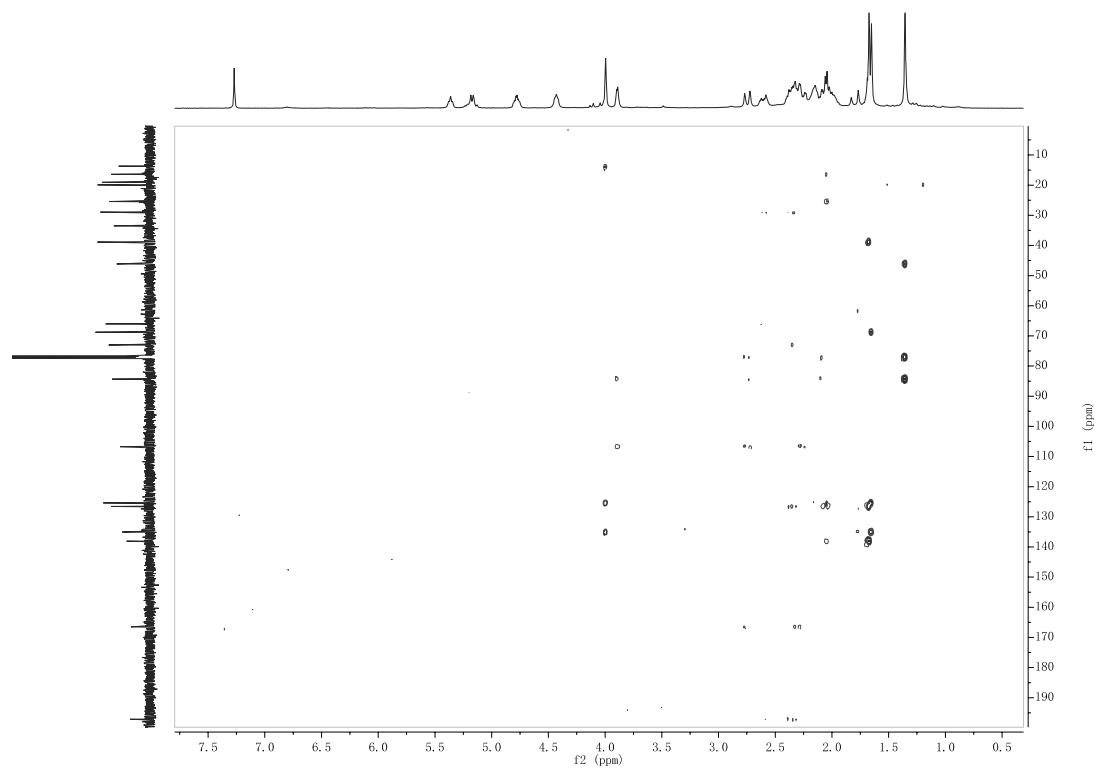


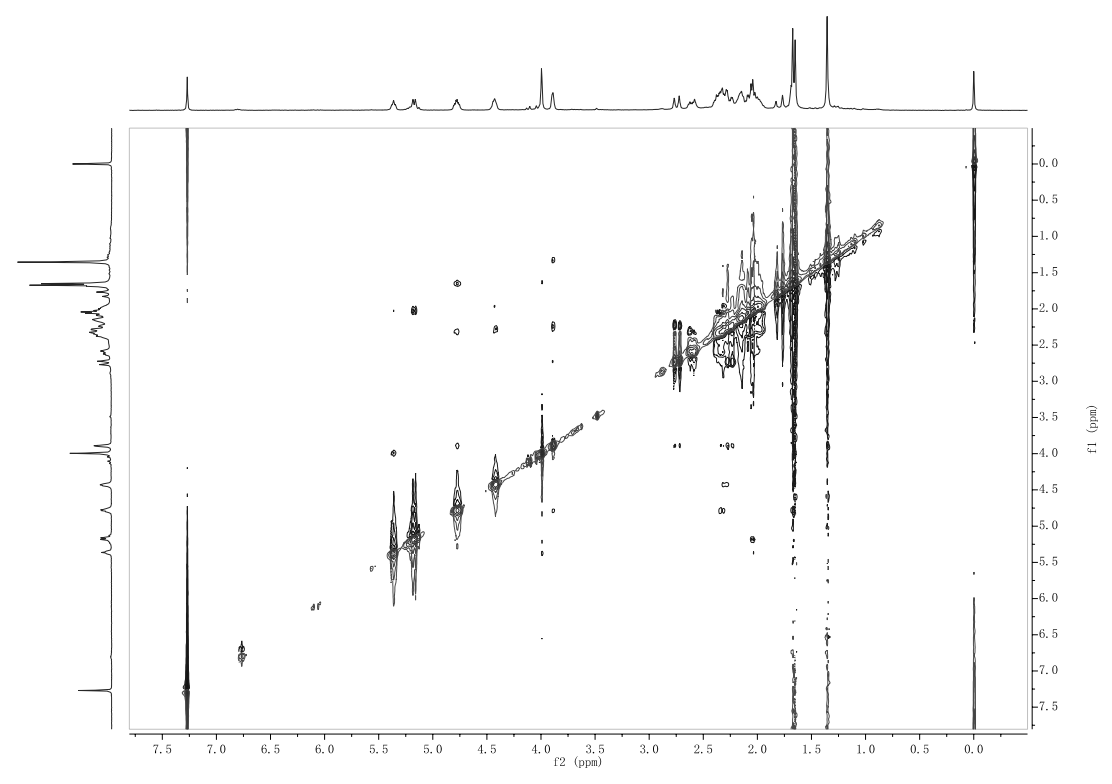
**Figure S 15.** 1H-NMR (600, 150 MHz, CDCl3) spectrum of tricycloalternarene O (**1**) 

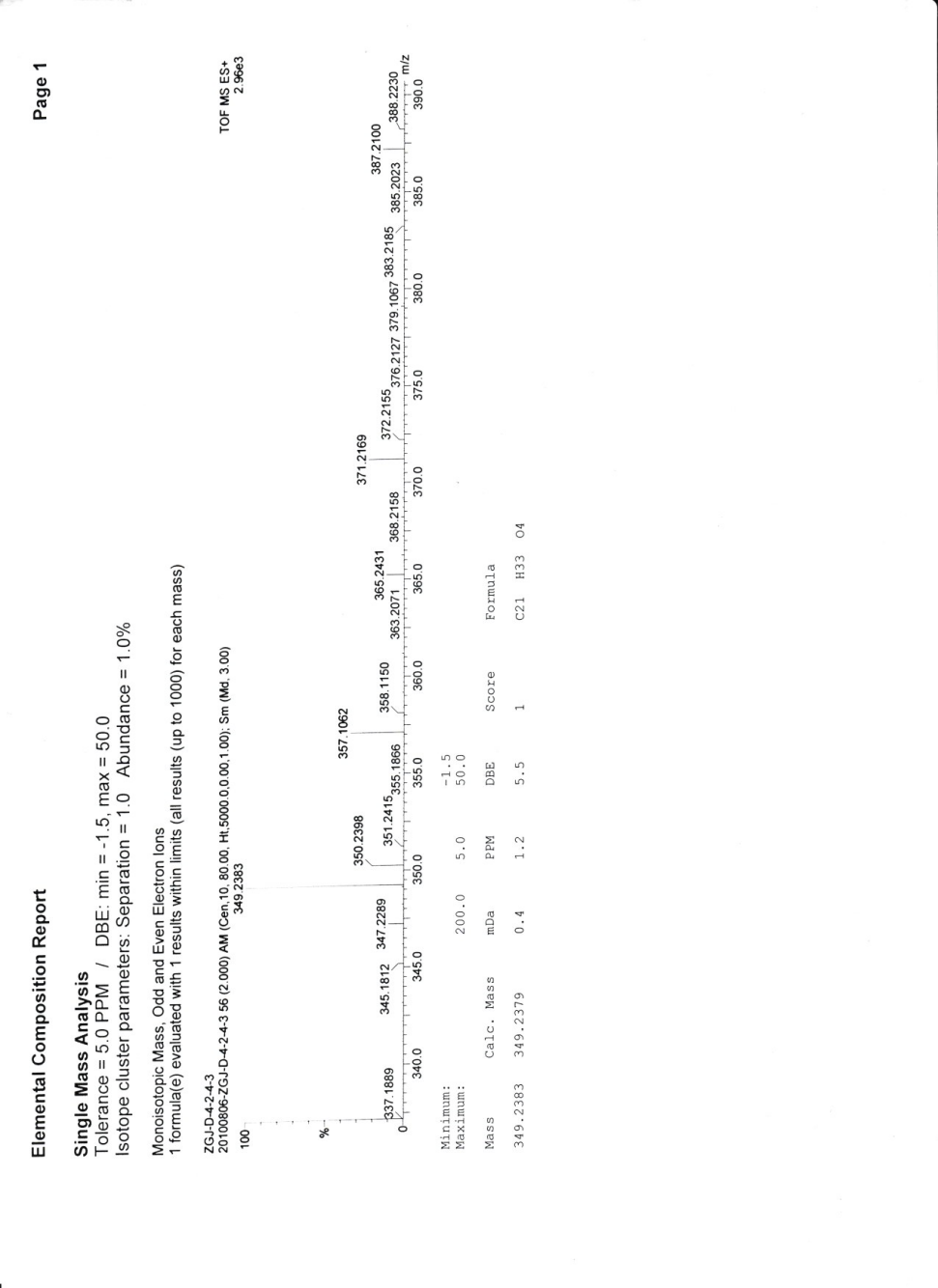
**Figure S 16.** 13C-NMR (600, 150 MHz, CDCl3) spectrum of tricycloalternarene O (**1**) 

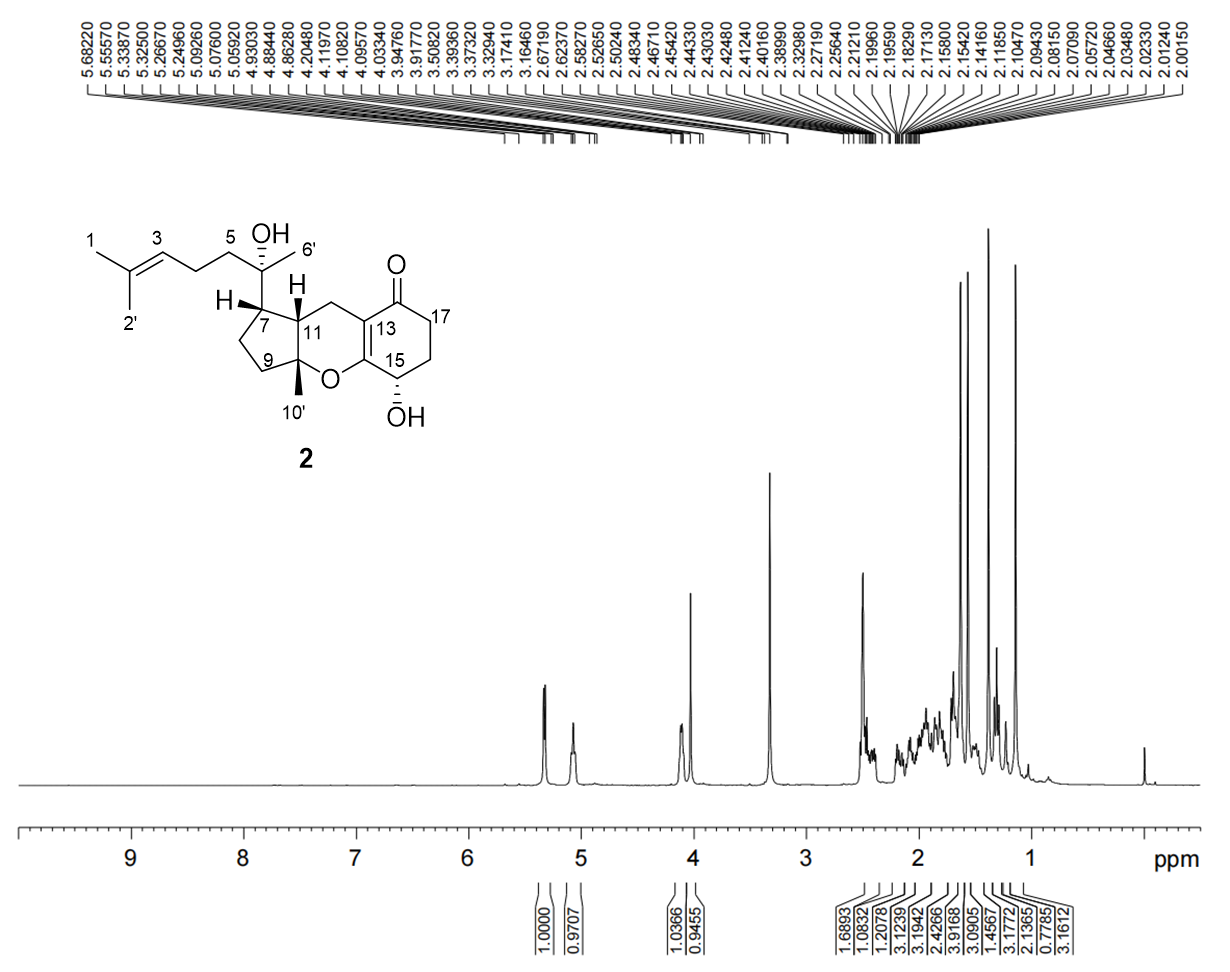
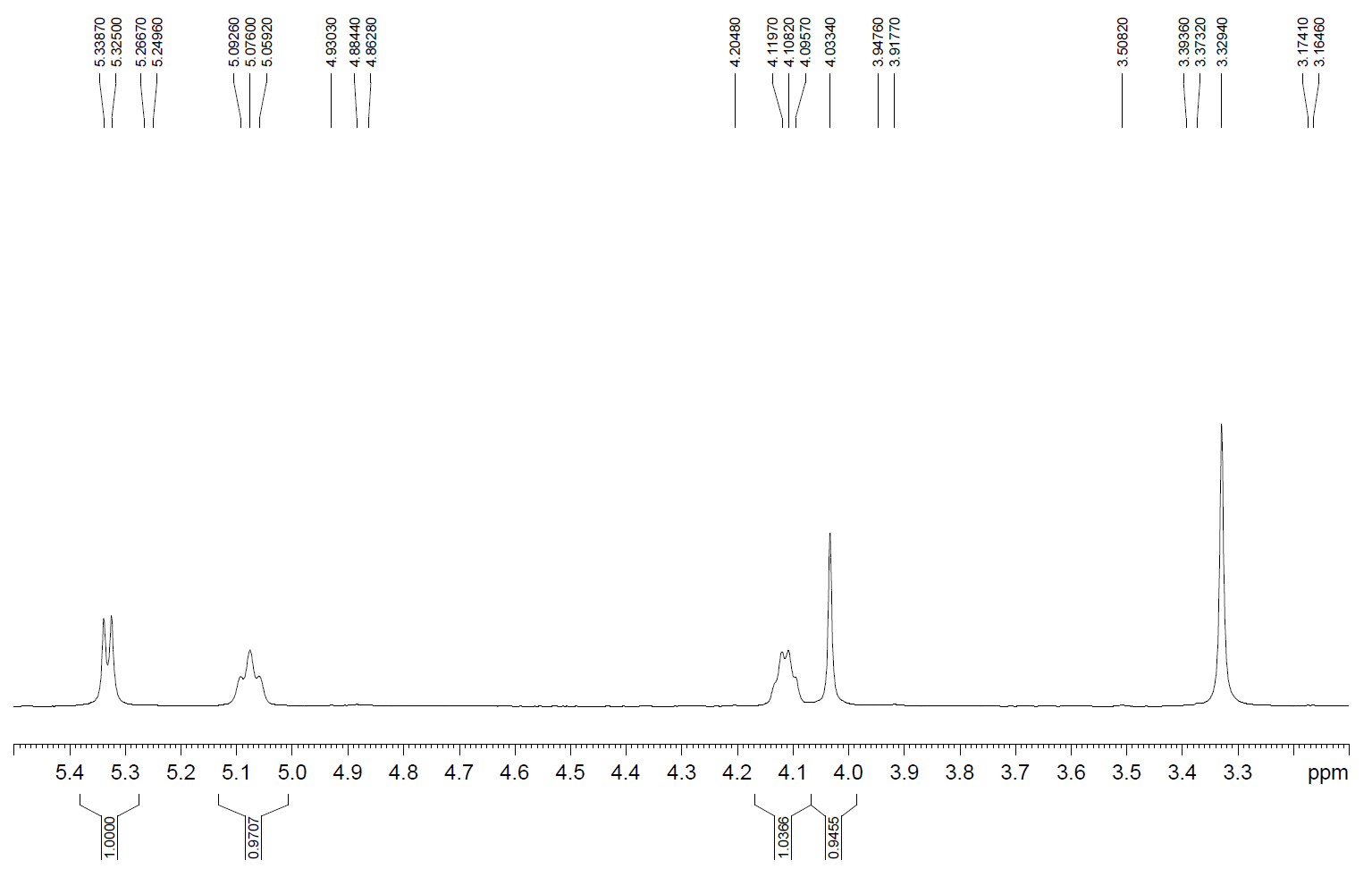
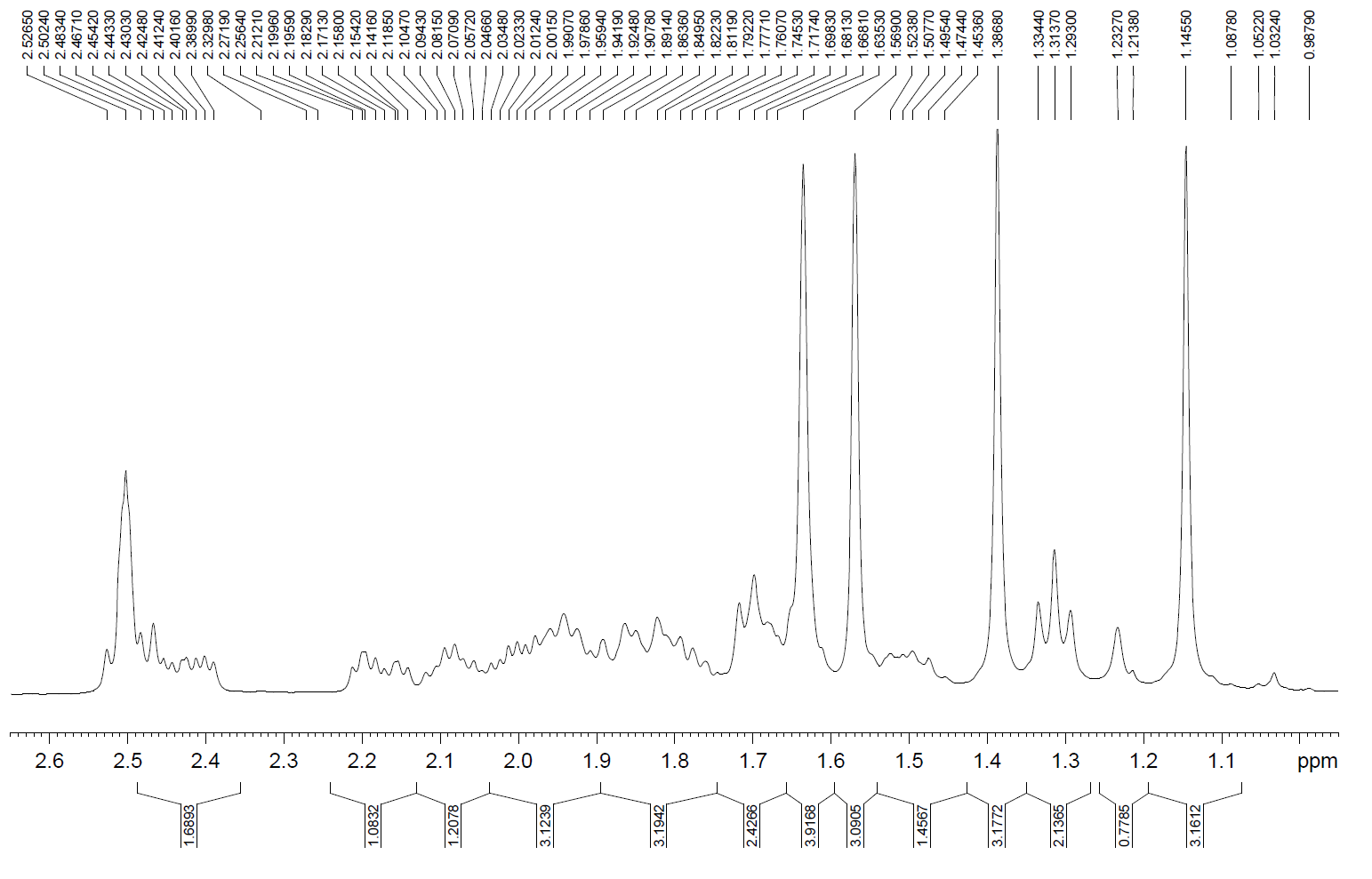
**Figure S 17.** HSQC (600, 150 MHz, CDCl3) spectrum of tricycloalternarene O (**1**)

**Figure S 18.** 1H-1H COSY (600, 150 MHz, CDCl3) spectrum of tricycloalternarene O (**1**)

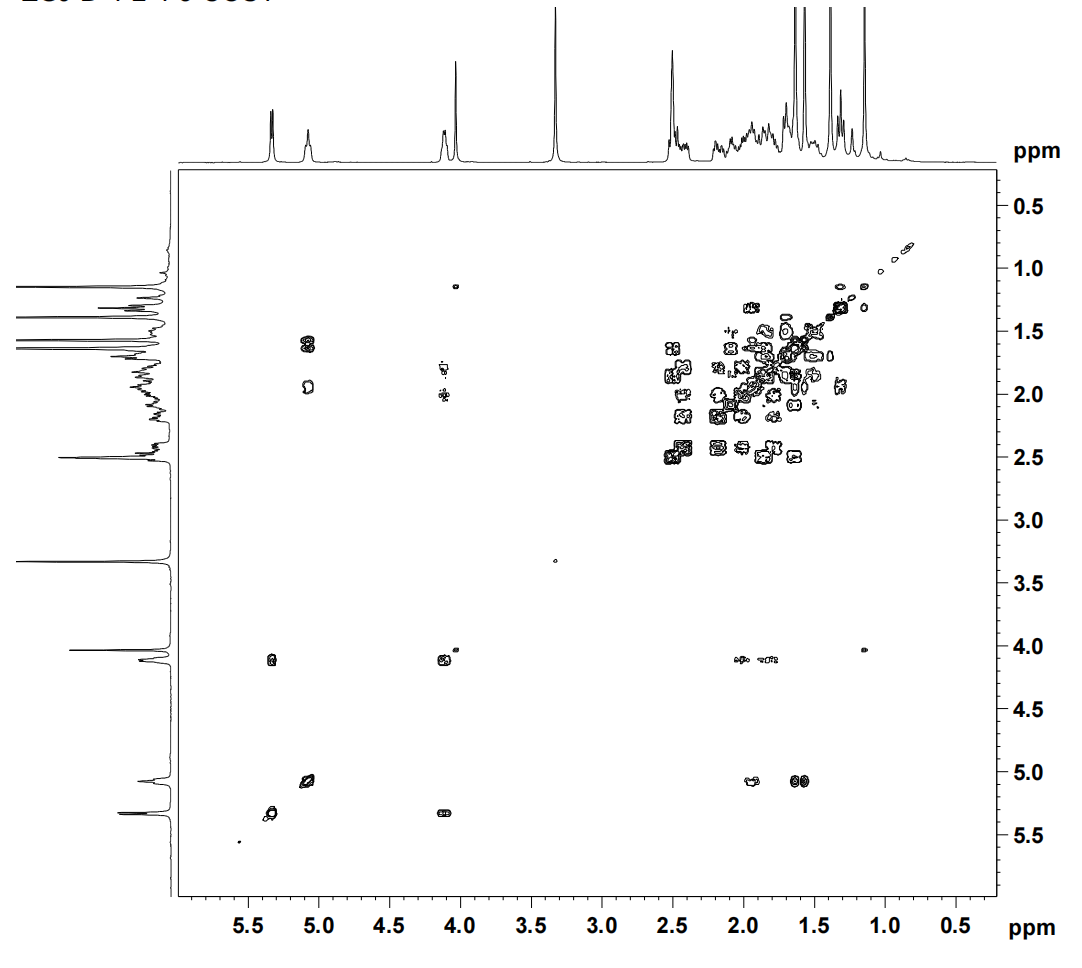
**Figure S 19.** HMBC (600, 150 MHz, CDCl3) spectrum of tricycloalternarene O (**1**)

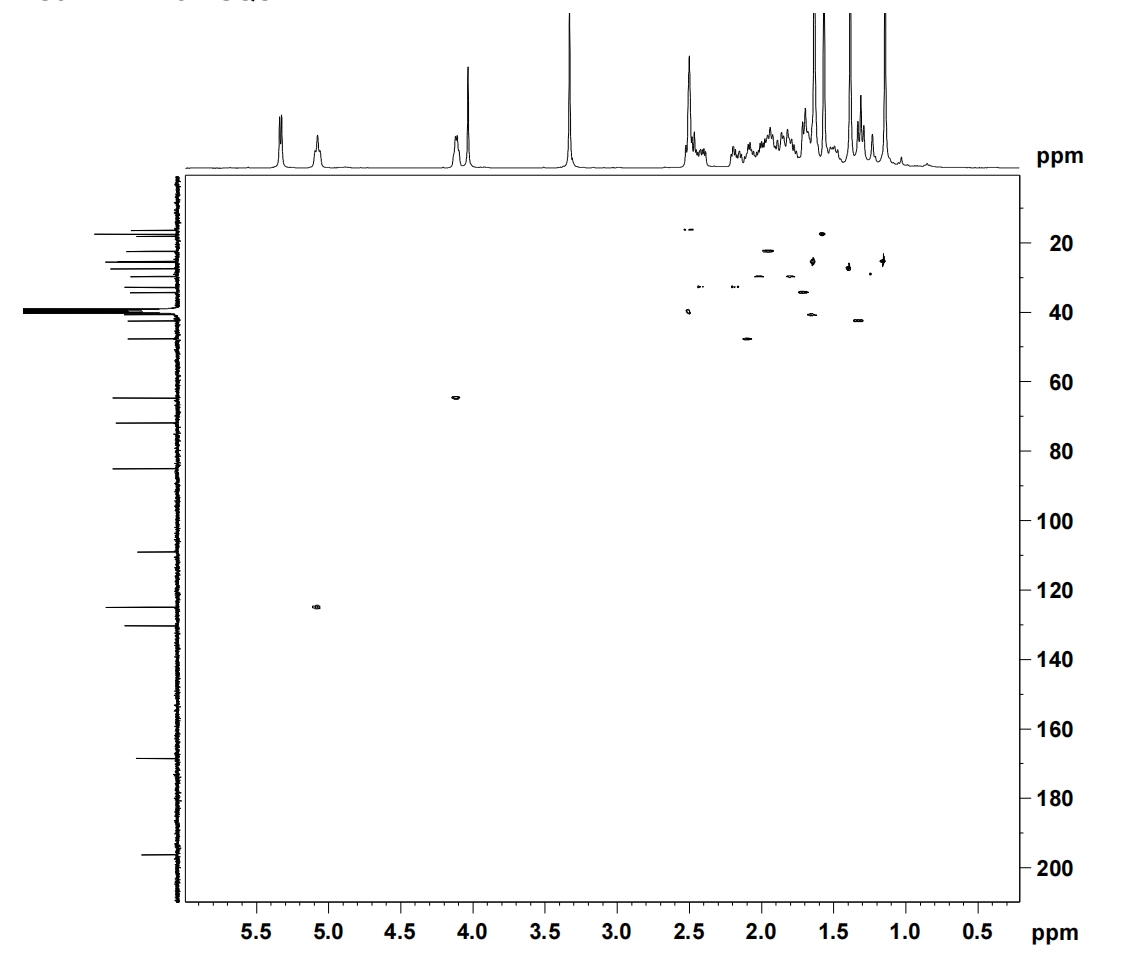
**Figure S 20.** ROESY (600, 150 MHz, CDCl3) spectrum of tricycloalternarene O (**1**)

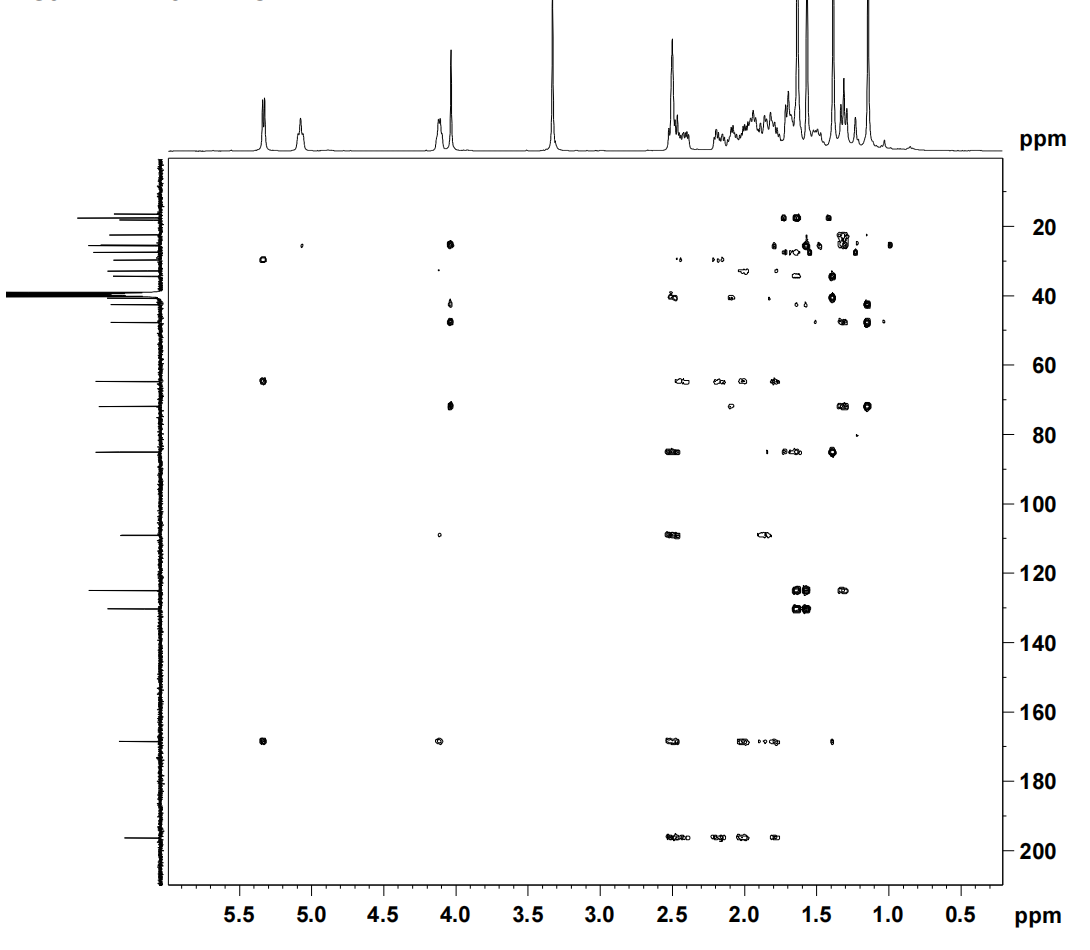
**Figure S 21.** HRESIMS spectrum of tricycloalternarene P (**2**)

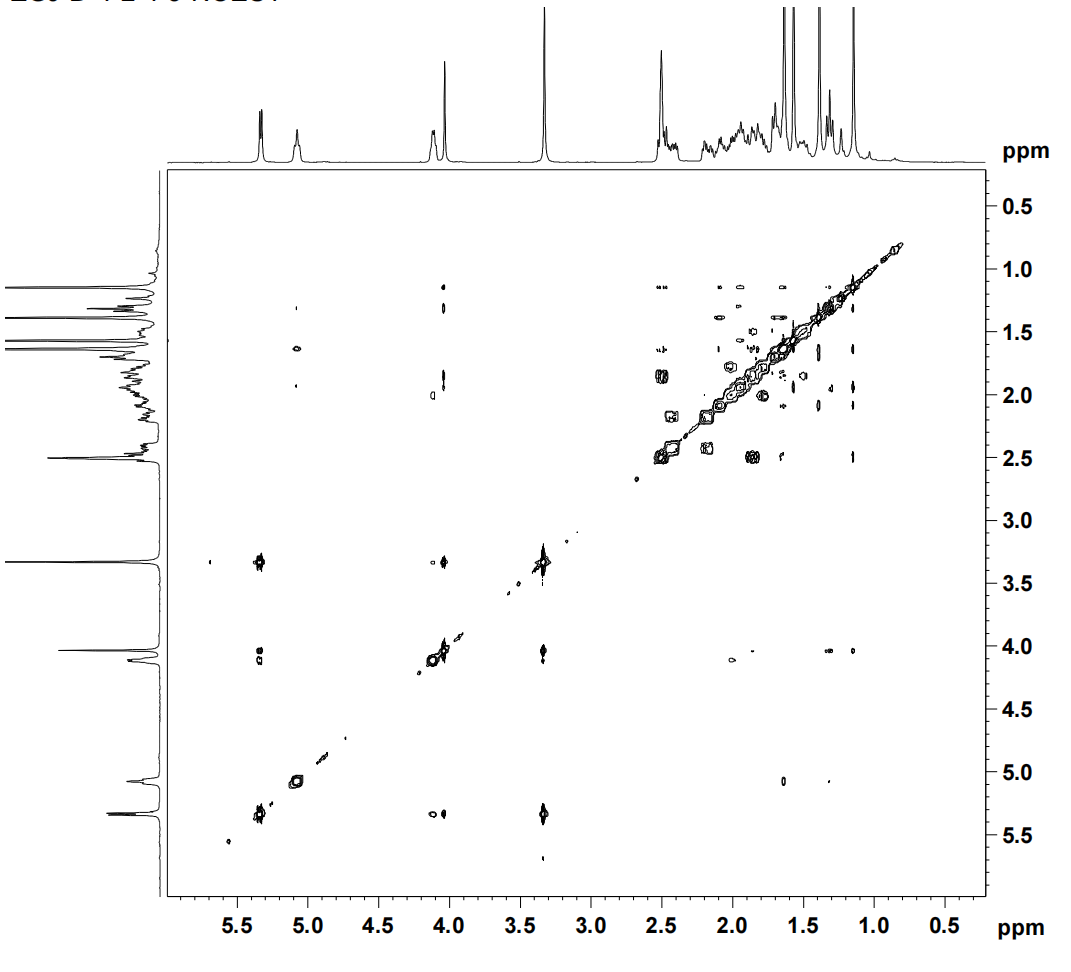
**Figure S 22.** 1H-NMR (400, 150 MHz, DMSO) spectrum of Tricycloalternarene P (**2**)  

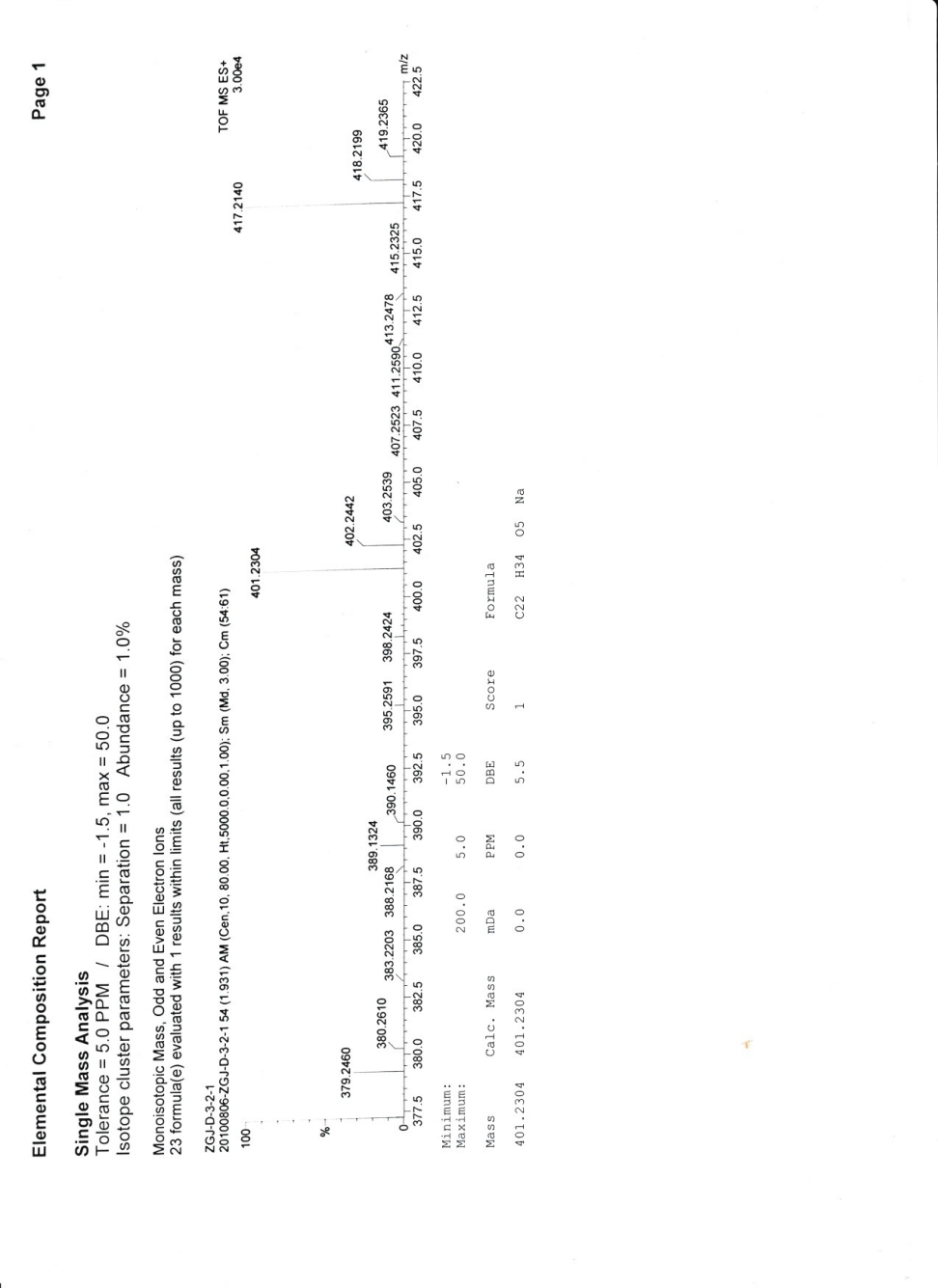
# **Figure S 23.** 13C-NMR (400, 150 MHz, DMSO) spectrum of tricycloalternarene P (**2**)

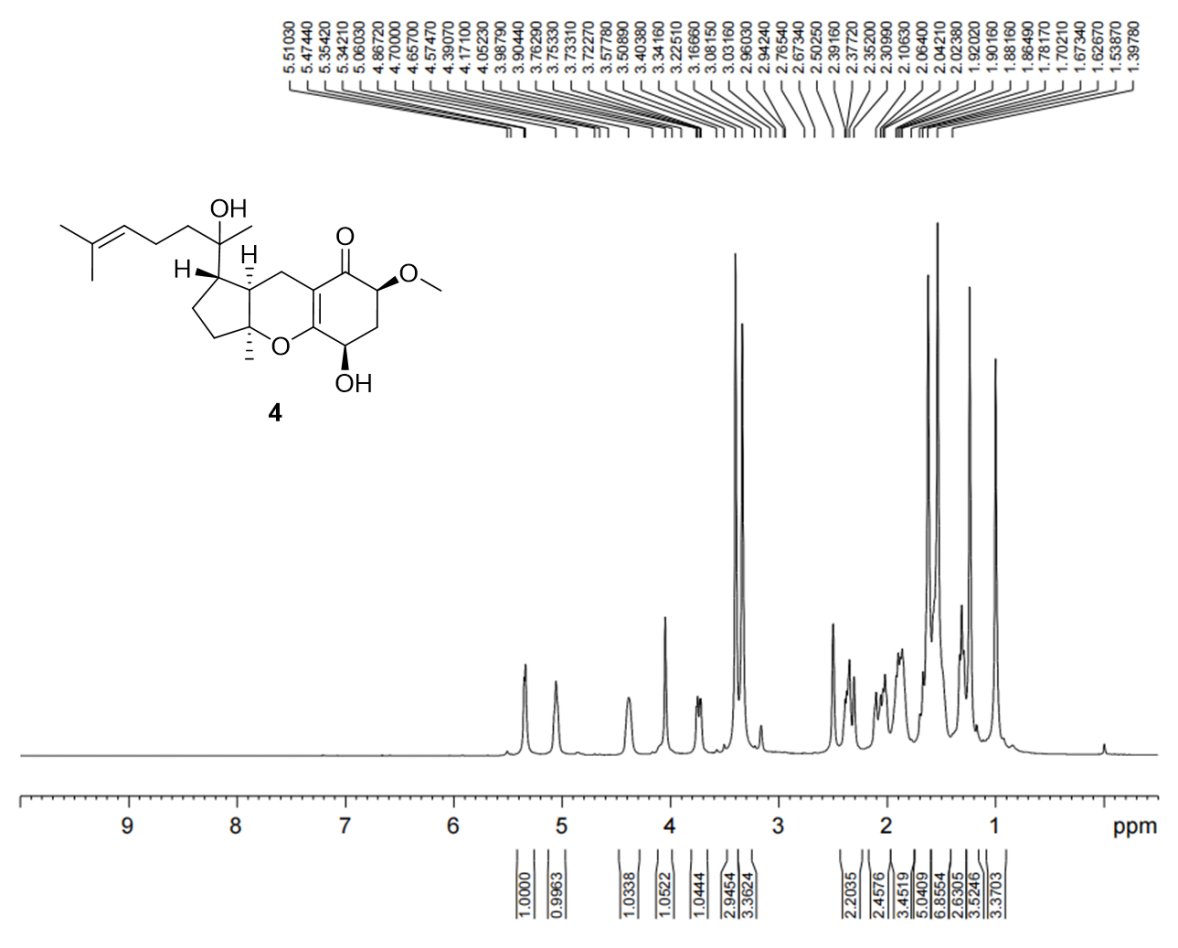
**Figure S 24.** 1H-1H COSY (400, 150 MHz, DMSO) spectrum of tricycloalternarene P (**2**)

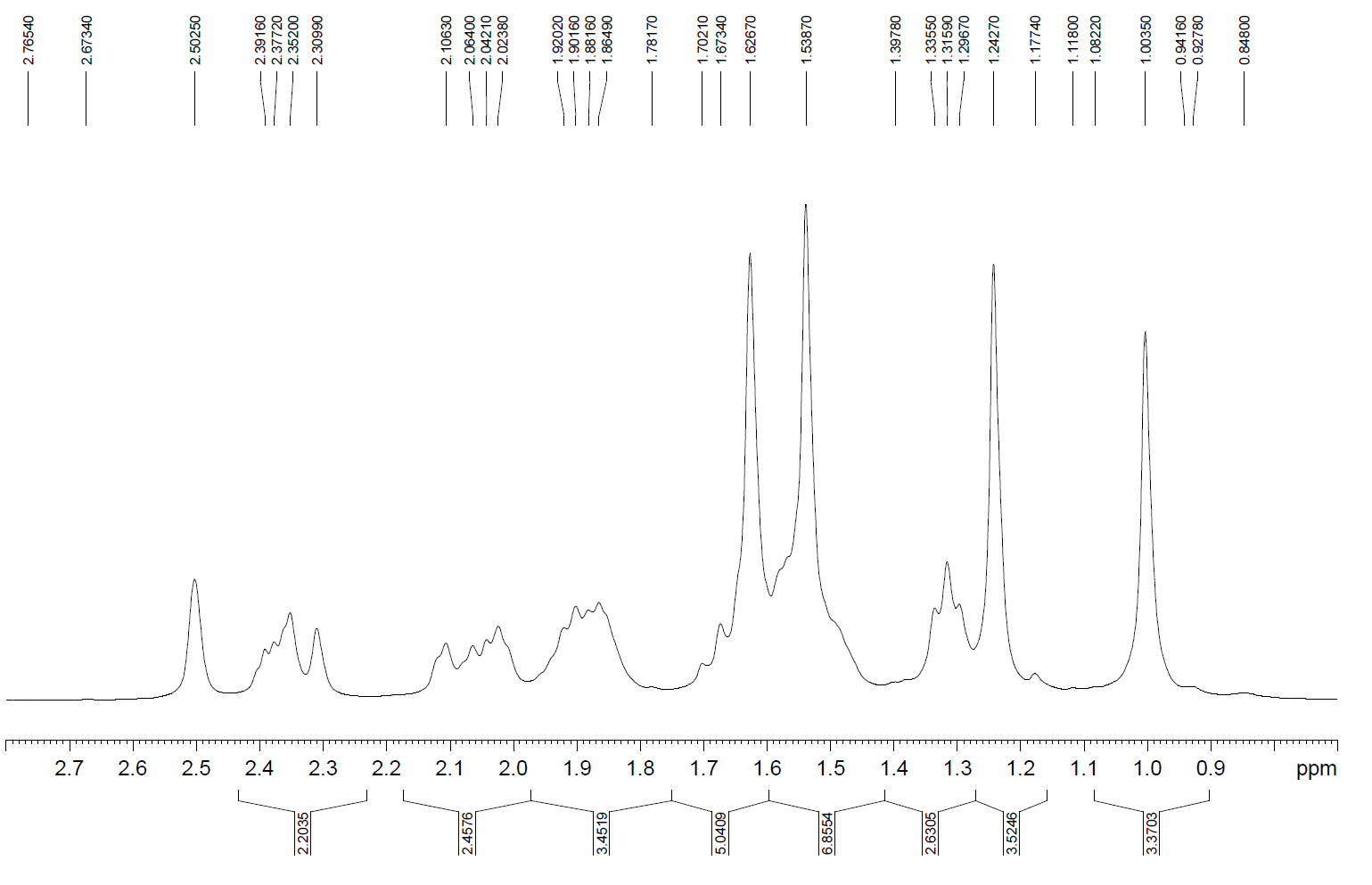
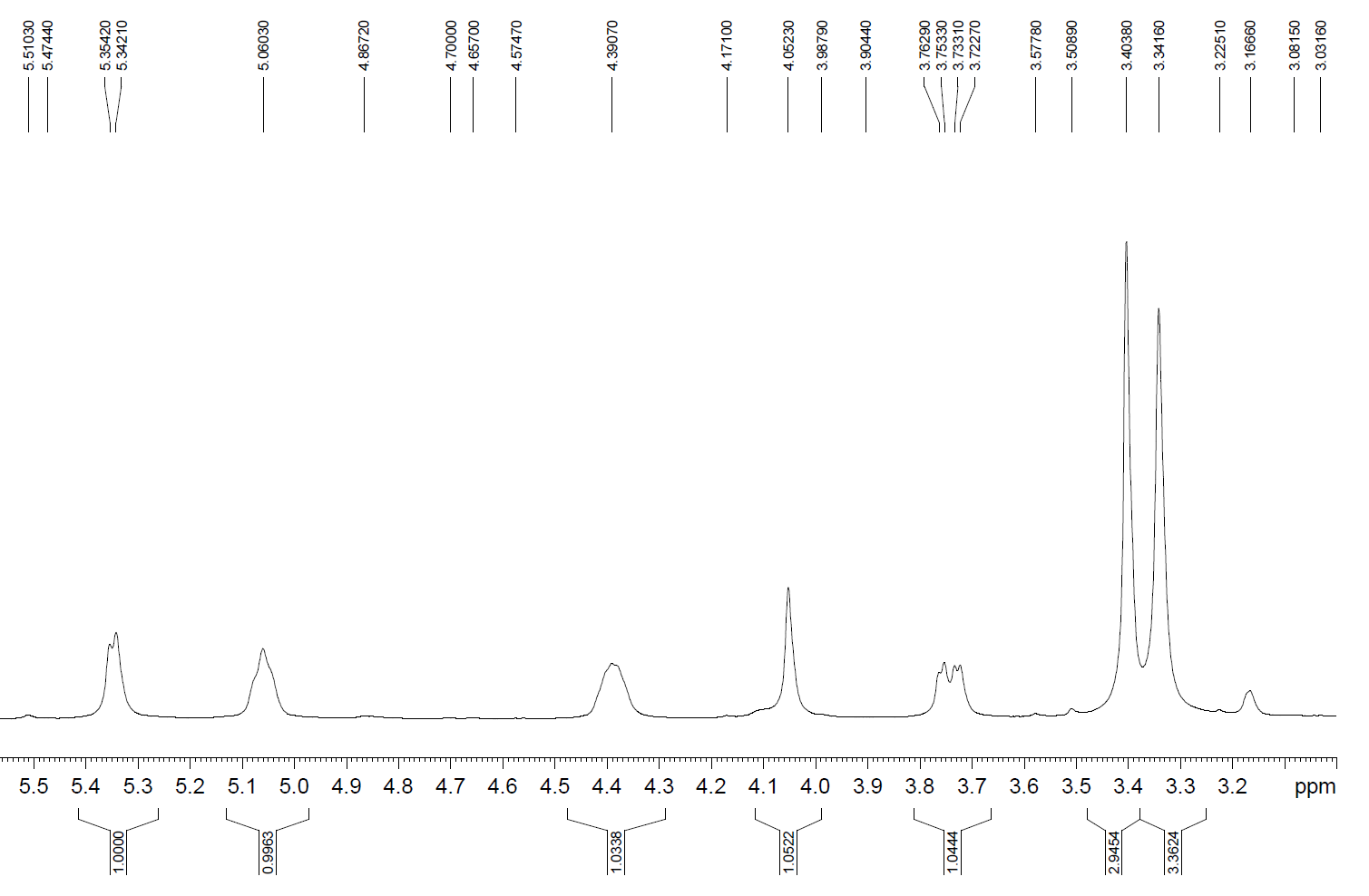
**Figure S 25.** HSQC (400, 150 MHz, DMSO) spectrum of tricycloalternarene P (**2**)

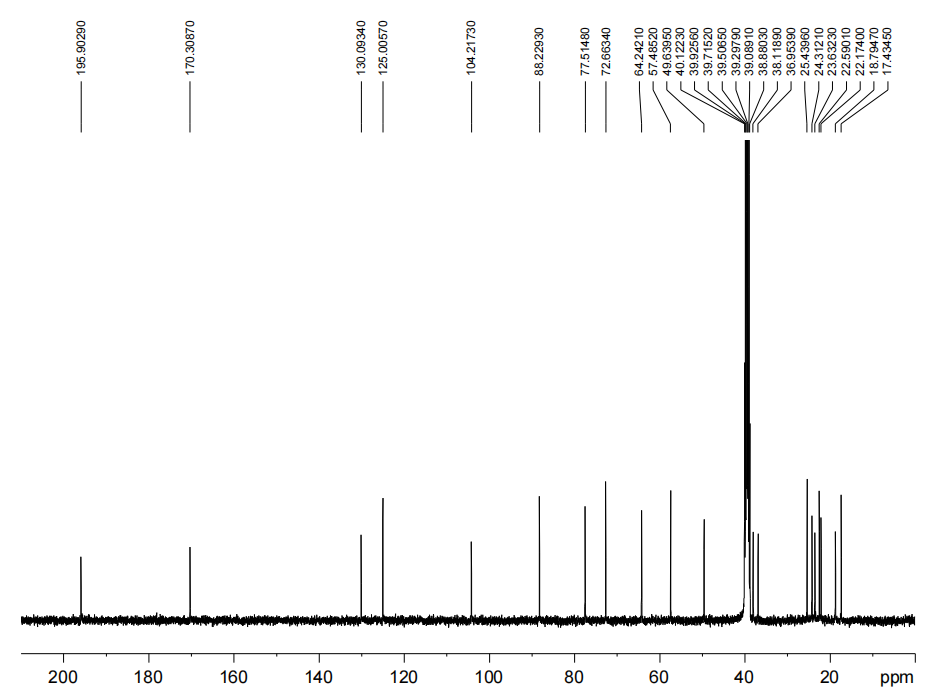
**Figure S 26.** HMBC (400, 150 MHz, DMSO) spectrum of tricycloalternarene P (**2**)

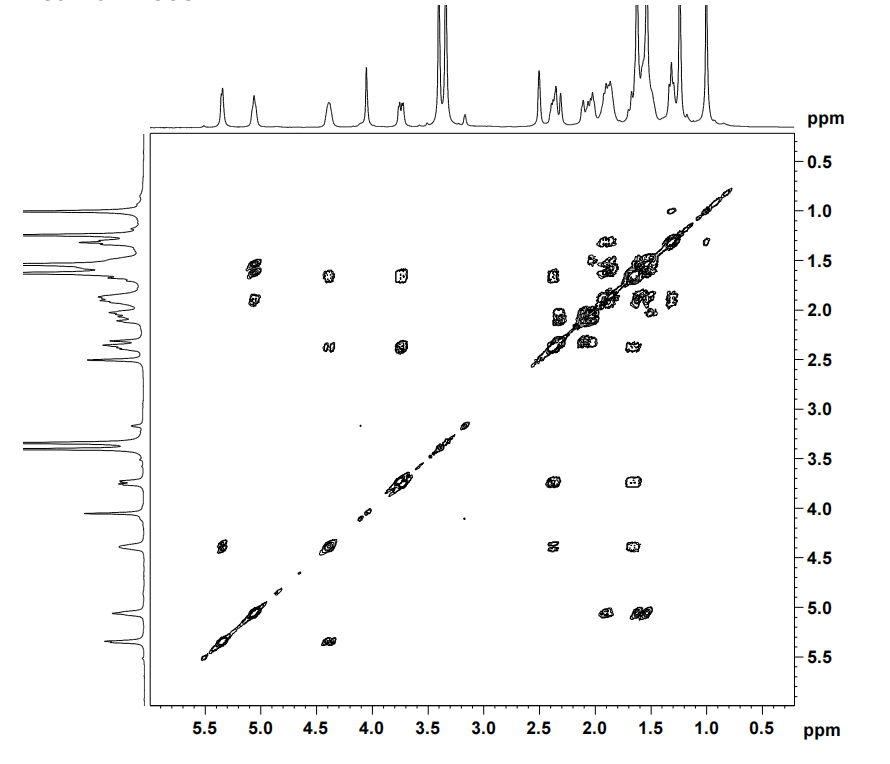
**Figure S 27**. NOESY (400, 150 MHz, DMSO) spectrum of tricycloalternarene P (**2**)

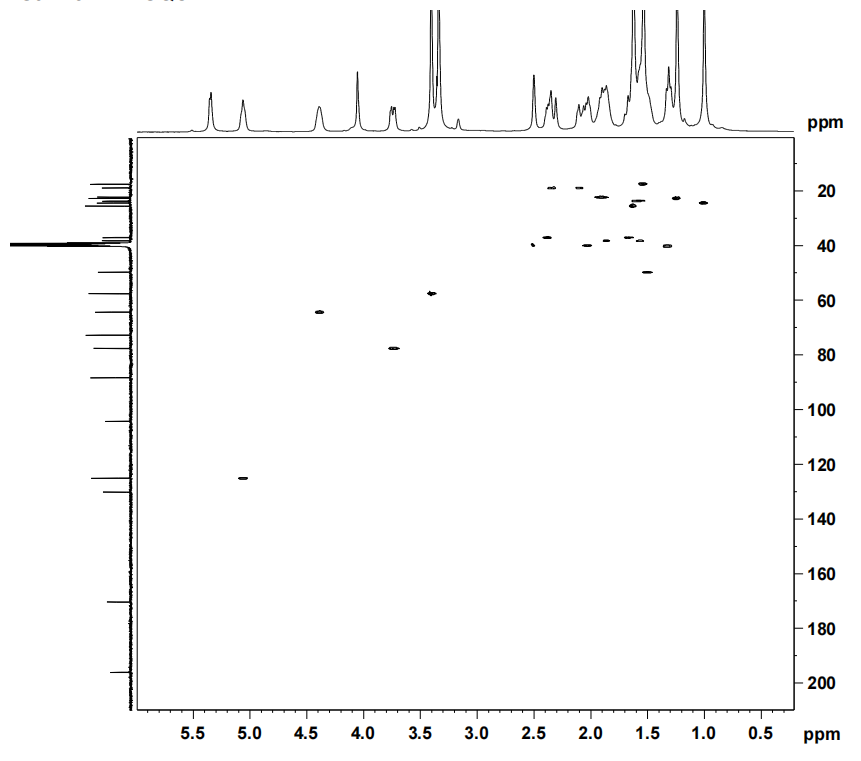
**Figure S 28.** HRESIMS spectrum of tricycloalternarene Q (**4**) ****

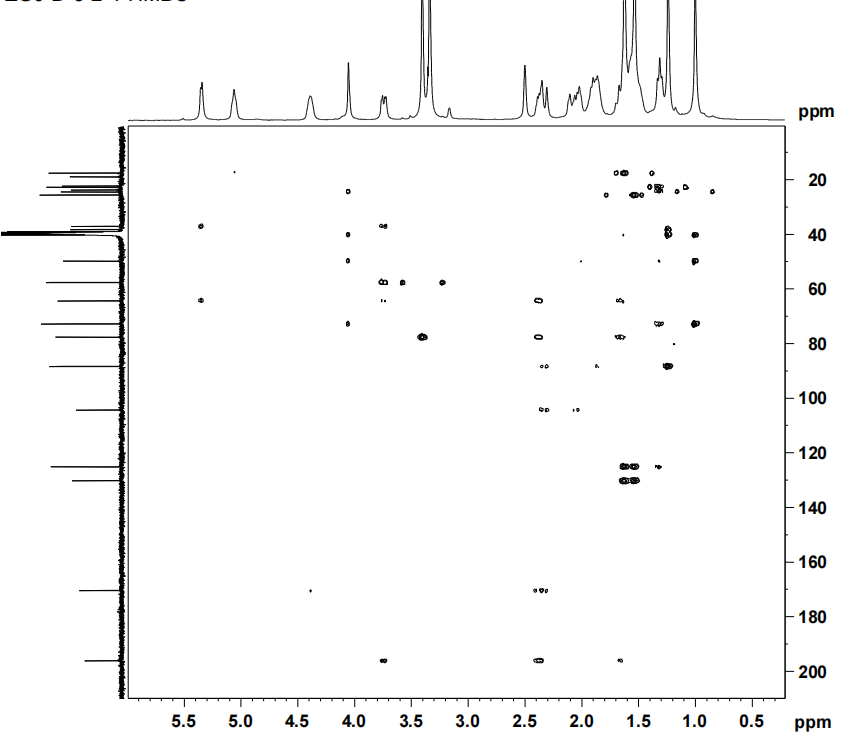
**Figure S 29.** 1H-NMR (400, 150 MHz, DMSO) spectrum of tricycloalternarene Q (**4**) 

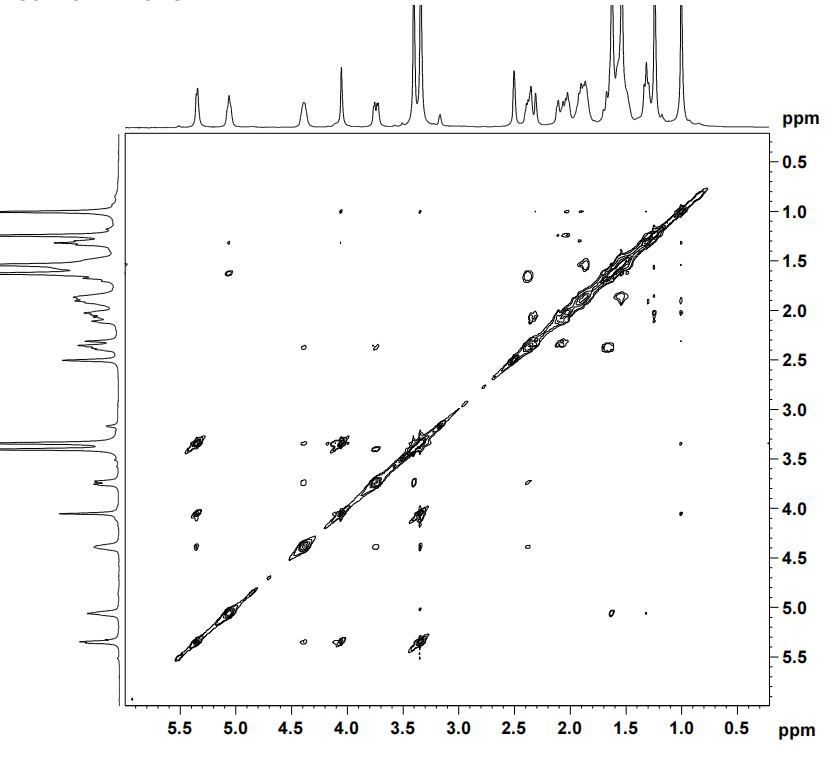


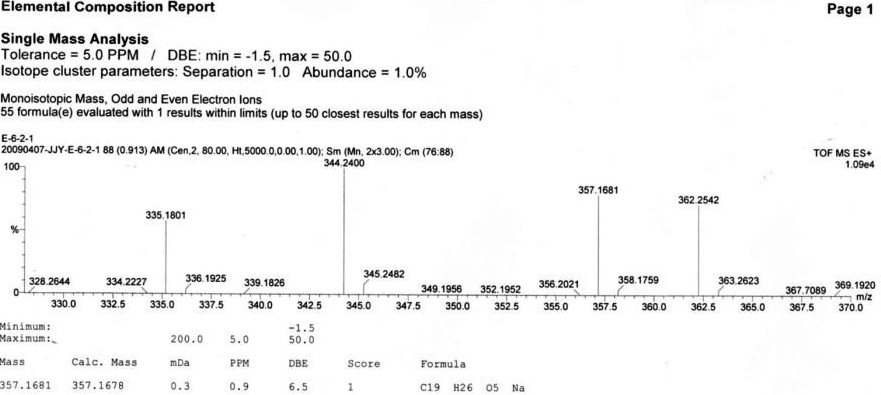
**Figure S 30.** 13C-NMR (400, 150 MHz, DMSO) spectrum of tricycloalternarene Q (**4**) 

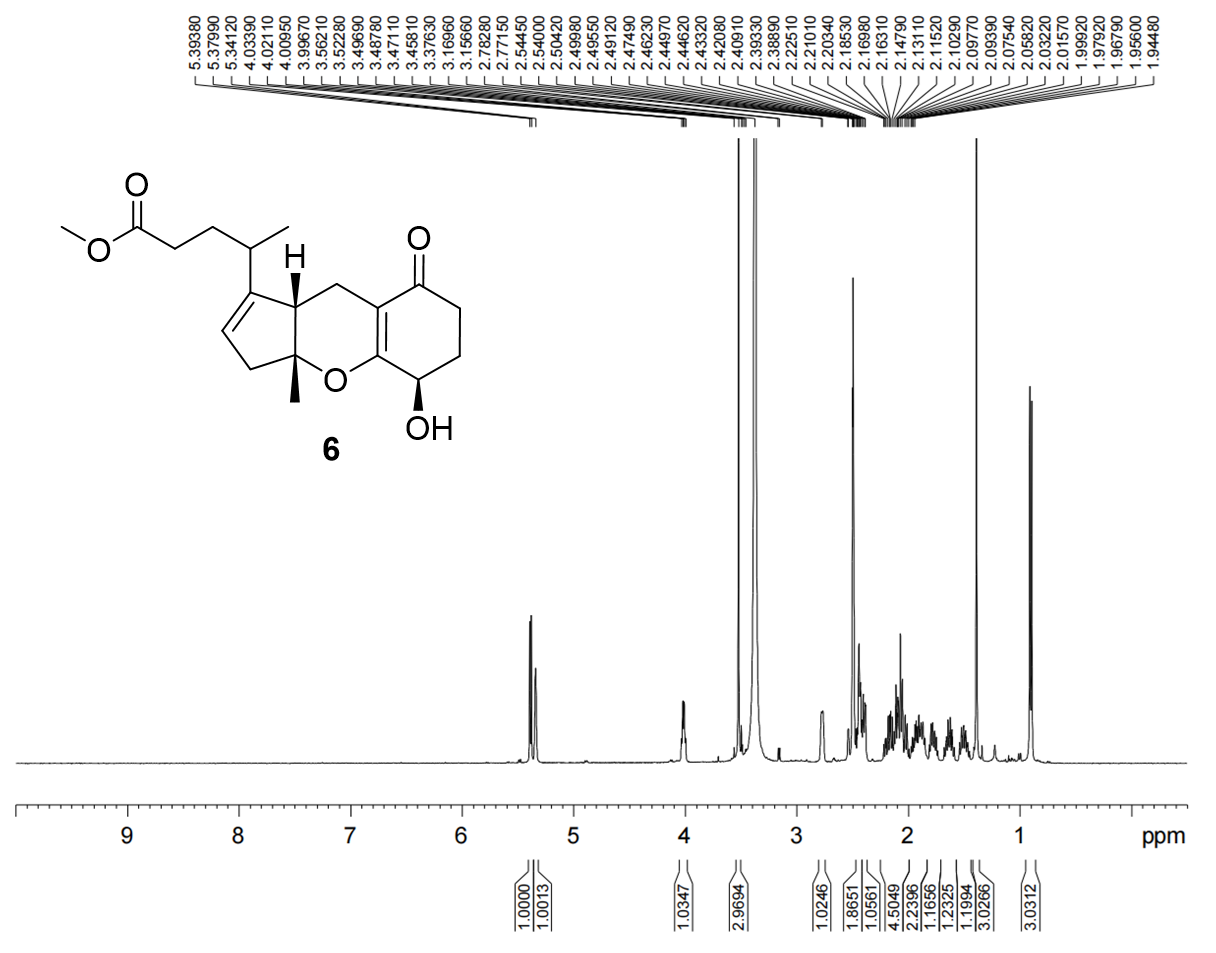
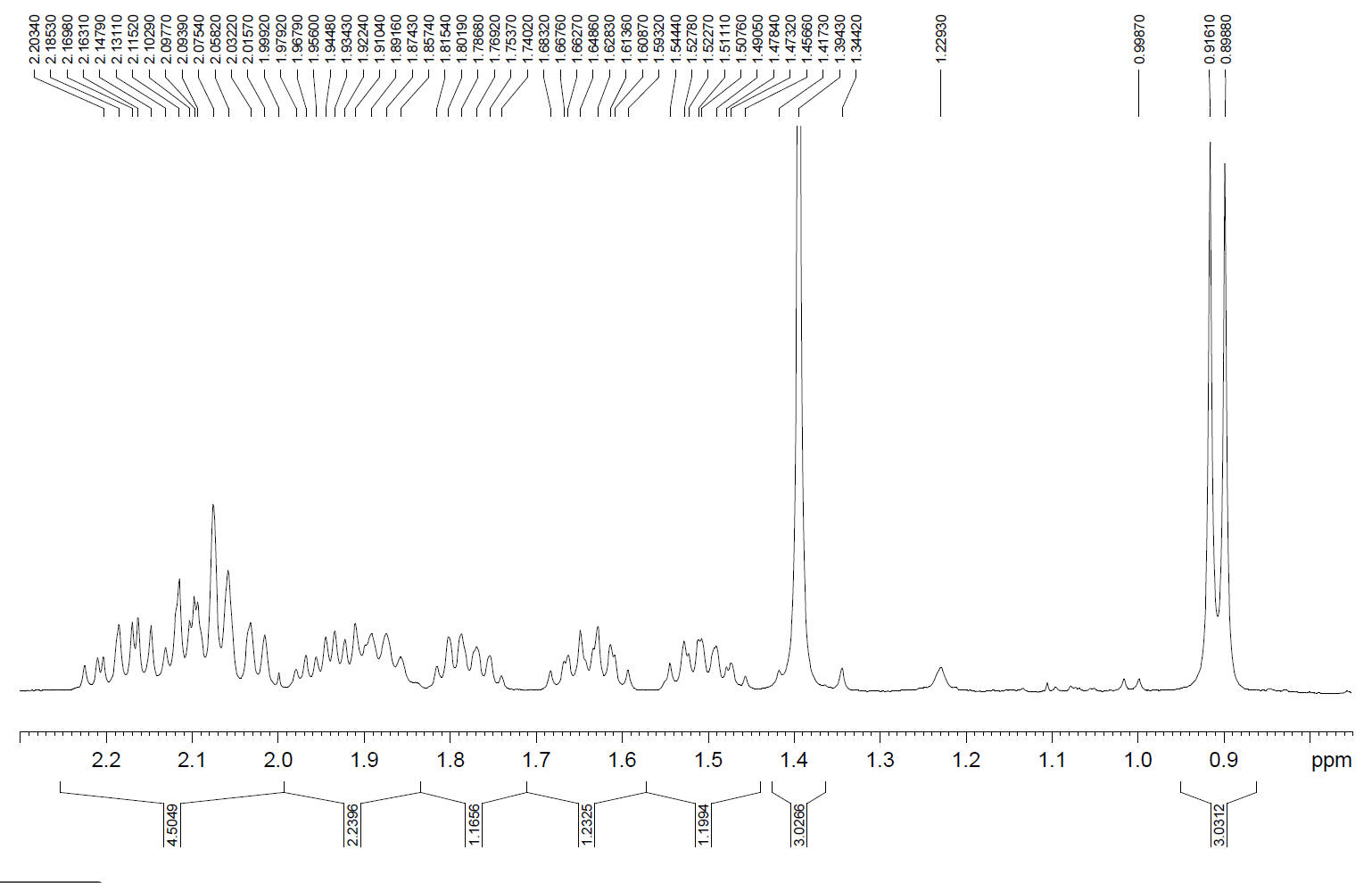
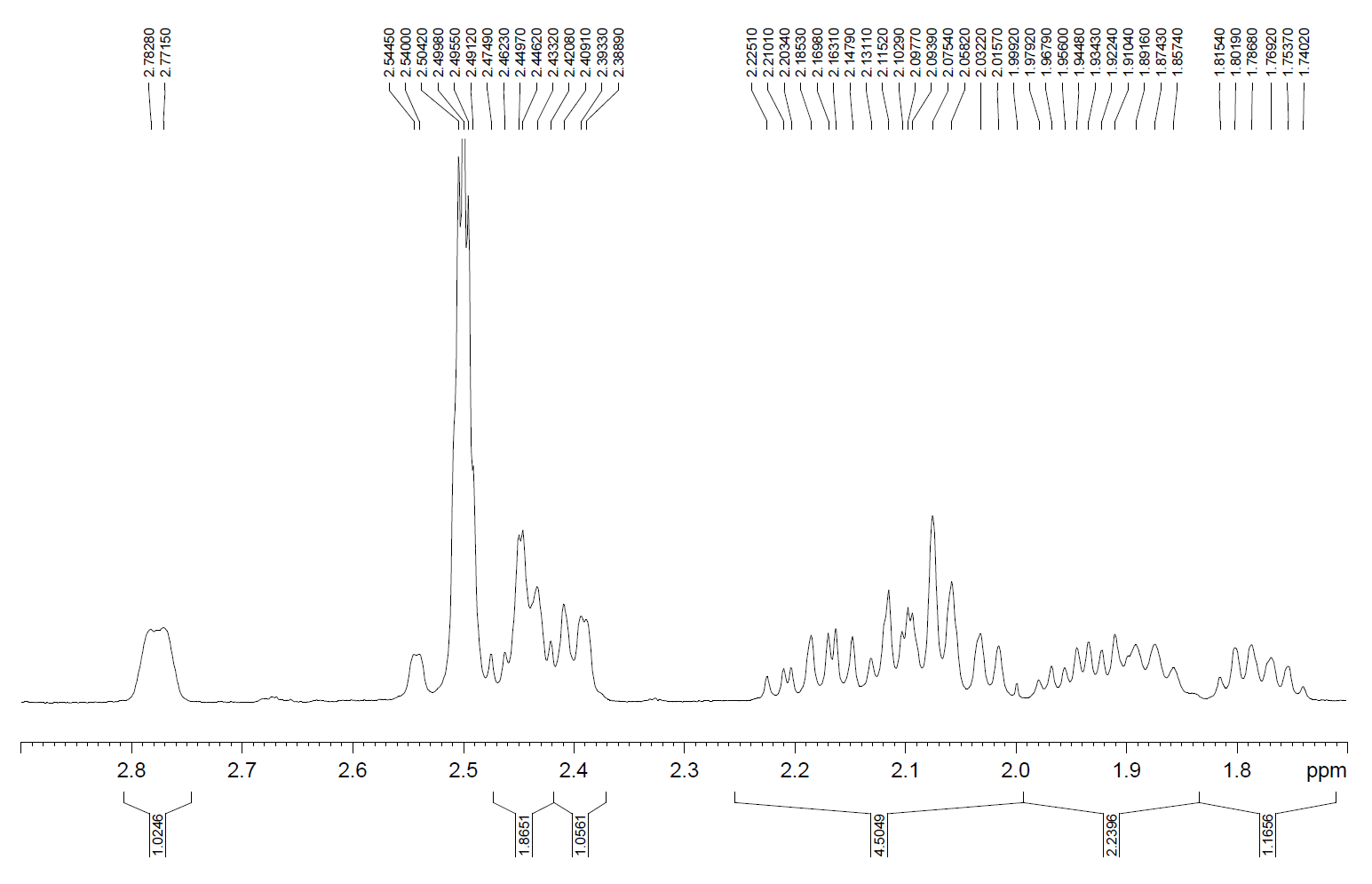
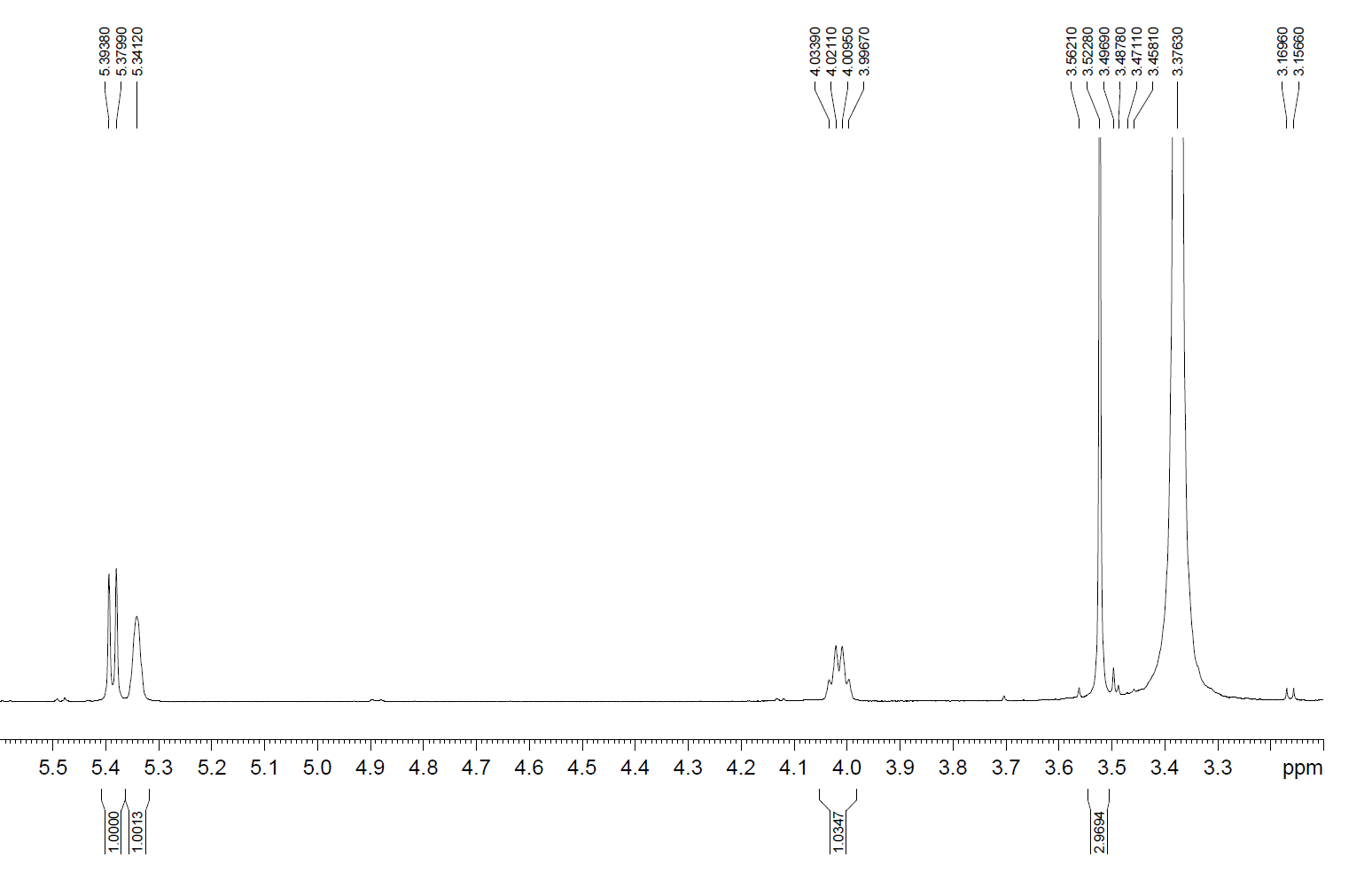
**Figure S 31.** 1H-1H COSY (400, 150 MHz, DMSO) spectrum of tricycloalternarene Q (**4**)

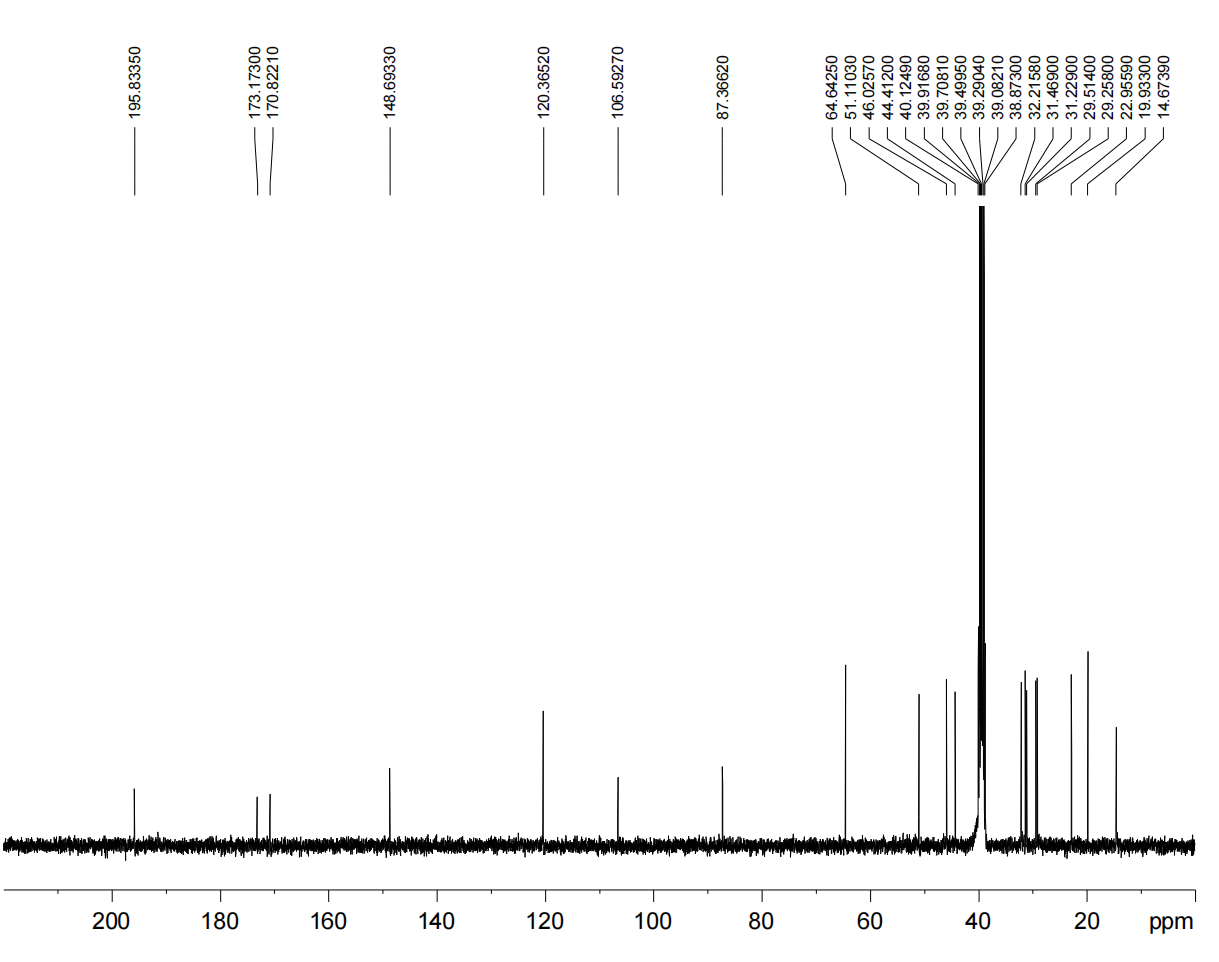
**Figure S 32.** HSQC (400, 150 MHz, DMSO) spectrum of tricycloalternarene Q (**4**)

**Figure S 33.** HMBC (400, 150 MHz, DMSO) spectrum of tricycloalternarene Q (**4**) 

**Figure S 34.** NOESY(400, 150 MHz, DMSO) spectrum of tricycloalternarene Q (**4**) 

**Figure S 35.** HRESIMS spectrum of tricycloalternarene R (**6**)

**Figure S 36.** 1H-NMR(400, 100 MHz, DMSO) spectrum of tricycloalternarene R (**6**) 

**Figure S 37.** 13C-NMR (400, 100 MHz, DMSO) spectrum of tricycloalternarene R (**6**)

**Figure S 38.** HSQC (400, 100 MHz, DMSO) spectrum of tricycloalternarene R (**6**)