

# Multicomponent Hosomi-Sakurai reaction on Isosorbide Derivatives

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## **SUPPORTING INFORMATION**

Summary:

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## Discussion on relative configuration of the main diastereomers

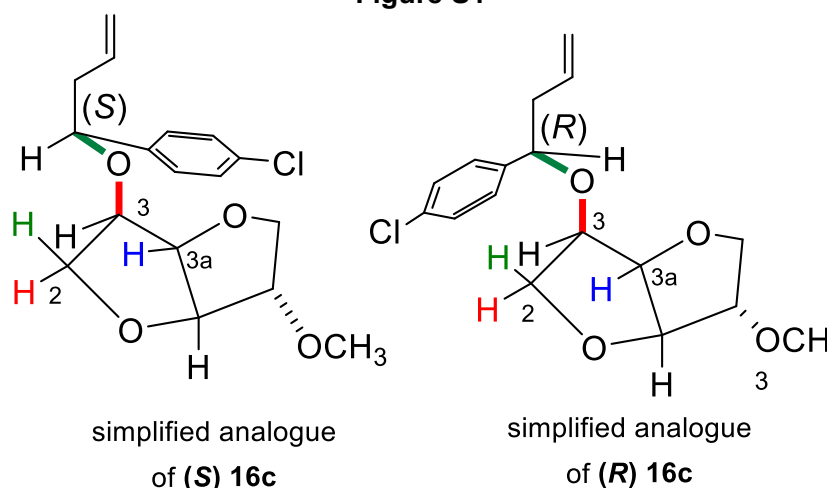
First of all, we noticed some  $^1\text{H}$  NMR trends that were constant along the whole series, at least for the products **16a-16j**, derived from aromatic aldehydes. As shown in the following Table S1, we noticed regular significant differences in chemical shift for *H*-3a and *H*-2. *H*-3a is shifted upfield in the major isomer. On the contrary, both *H*-2, but especially the one falling at higher  $\delta$ , are shifted upfield for the minor isomer. The two *H*-2 may be differentiated by the coupling constant with *H*-3. In both the major and minor isomers, the upfield (lower  $\delta$ ) *H*-2 has  $J \approx 8.4$  Hz, whereas the downfield (higher  $\delta$ ) *H*-2 has  $J \approx 7.0$  Hz. The downfield *H*-2 (lower  $J$ ) is the one that experiences the highest difference. It is probably the one placed on the opposite side of the oxygen bound at C-3 (down, coloured in red in the following Figure S1).

| Table S1. Characteristic Chemical shifts ( $^1\text{H}$ NMR) of the two diastereomers         |                   |              |       |                         |                                      |            |
|-----------------------------------------------------------------------------------------------|-------------------|--------------|-------|-------------------------|--------------------------------------|------------|
| Compound                                                                                      | Major             | Minor        | Diff. | Major                   | Minor                                | Diff.      |
|                                                                                               | <i>H</i> -3a      | <i>H</i> -3a |       | <i>H</i> -2             | <i>H</i> -2                          |            |
| <b>16a</b>                                                                                    | 4.45              | 4.73         | 0.28  | 3.86, 3.49              | 3.58, 3.39                           | 0.28, 0.10 |
| <b>16b</b>                                                                                    | 4.32 <sup>a</sup> | 4.68         | 0.36  | 3.88, <sup>a</sup> 3.47 | 3.53, 3.40                           | 0.35, 0.07 |
| <b>16c</b>                                                                                    | 4.35              | 4.67         | 0.32  | 3.82, 3.47              | 3.52, 3.39                           | 0.30, 0.08 |
| <b>16d</b>                                                                                    | 4.36              | 4.68         | 0.32  | 3.86, 3.47              | 3.52, 3.40                           | 0.34, 0.07 |
| <b>16e</b>                                                                                    | 4.34              | 4.76         | 0.32  | 3.89, <sup>a</sup> 3.50 | 3.57, 3.42                           | 0.32, 0.08 |
| <b>16f</b>                                                                                    | 4.42              | 4.76         | 0.34  | 3.83, 3.53              | 3.56, <sup>b</sup> 3.45 <sup>b</sup> | 0.37, 0.08 |
| <b>16g</b>                                                                                    | 4.34              | 4.68         | 0.34  | 3.84, 3.44              | 3.50, 3.35                           | 0.34, 0.09 |
| <b>16h</b>                                                                                    | 4.51              | 4.81         | 0.30  | 3.97, 3.52              | 3.62, 3.48                           | 0.35, 0.04 |
| <b>16i</b>                                                                                    | 4.44              | 4.66         | 0.22  | 3.82, <sup>a</sup> 3.47 | 3.54, 3.39                           | 0.28, 0.08 |
| <b>16k</b>                                                                                    | 4.62              | 4.61         | -0.01 | 3.79, 3.37              | 3.79, 3.40                           | 0, -0.03   |
| <b>16l</b>                                                                                    | 4.63              | 4.63         | 0     | 3.82, 3.39              | 3.82, 3.39                           | 0, 0       |
| <sup>a</sup> Determined by HSQC. <sup>b</sup> Determined on the spectrum of the crude product |                   |              |       |                         |                                      |            |

The other protons of the bicyclic system show little differences in  $\delta$  among the two isomers. Interestingly, **this trend is only valid for the products derived from aromatic aldehydes**, and it is not present in the two products derived from aliphatic aldehydes (**16k** and **16j**). Thus, this difference is surely due to anisotropic effects given by the aromatic ring.

If we compare the chemical shifts in the aromatic products with those in the aliphatic ones, it is clear that ***H*-3a is shielded in the major diastereomer, whereas one of the two *H*-2 is shielded in the minor isomer**. Thus, they should fall in the shielding cone of the aromatic ring.

Figure S1



In order to try to understand this behaviour, we used Chem3D<sup>TM</sup> with the AM1 algorithm (MOPAC) to search for the likely more stable conformations of the products. For the sake of simplicity (in order to avoid too many local minima) and for a clearer visualization, we carried out minimization on a simplified analog of **16c**, by substituting the TBDPS group with a methyl group, since it is reasonable that this would not influence the conformational equilibrium, being this group very far away from the new stereogenic center.

Fortunately, the bicyclic scaffold is pretty rigid and thus the only two important rotatable bonds are the ones coloured in red and green in Figure S1.

As far as it regards the red bond, the preferred conformations, without any doubt, are those that place the bulky substituent outside the bicyclic ring, in order to minimize steric strain. Less obvious are the preferred conformations deriving from rotation of the green bond. Considering only the three staggered conformations, one of the three substituents at the new stereogenic centre should be *anti* ( $180^\circ$  dihedral angle) with C3-O bond.

The ones placing the hydrogen in this position were definitely less favoured by our minimizations, as expected, being "doubly gauche" conformations. Moreover, the presence of a nOe between the "blue" hydrogen and the "purple" one are against this possibility.

Also conformations placing the aryl group upside are less favoured by our minimization, but, most of all, they are in contrast with the absence of any nOe between the protons of the allyl group and the various protons of the bicyclic system.

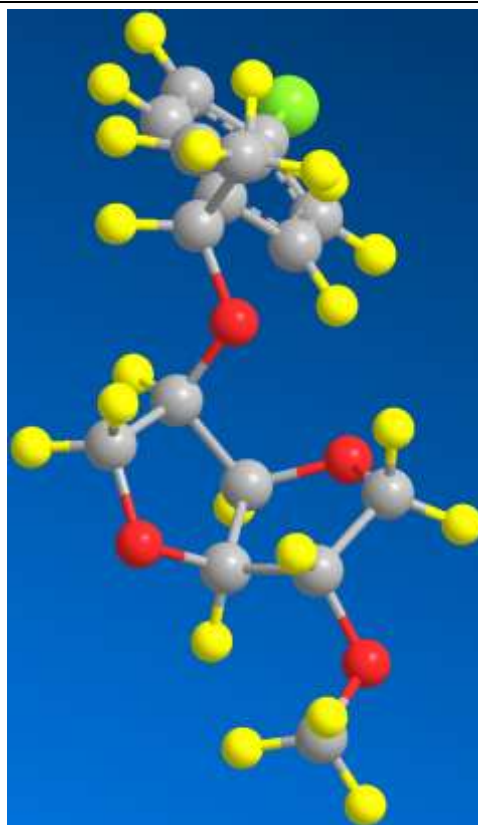
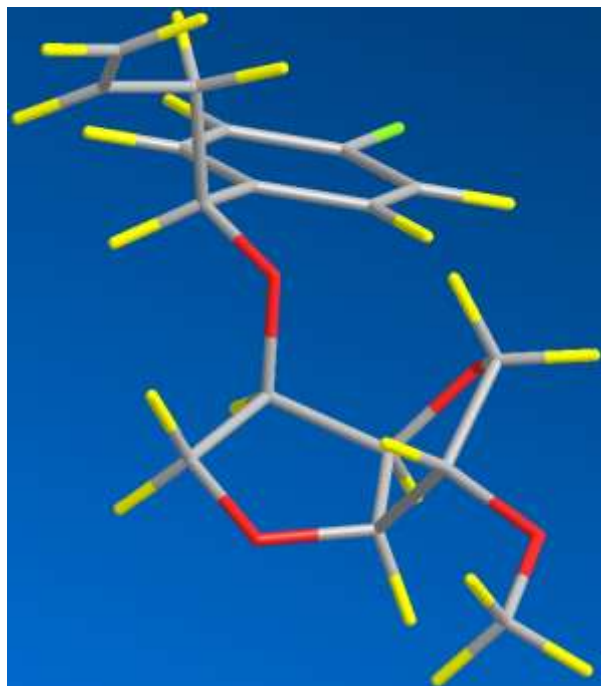
Therefore, the best ones turned out to be, for both isomers, those placing the allyl group at  $180^\circ$  dihedral angle with the red bond and upside. These conformations, shown in Figures S1, are in agreement with the absence of nOe between the allyl group hydrogens and any of the bicyclic system, and with nOe experiments showing a close distance between blue and purple hydrogens in both isomers (the distance is similar).

If these are the preferred conformations, the shielding anisotropic effect of the aryl group would act differently in the two isomers. In the (*S*) isomer this effect is expected to move upfield *H*-3a, whereas in the (*R*) isomer this effect will act on both *H*-2 hydrogens, but especially the lower one (drawn in red). This may be better seen by the following images of the minimized conformations (Figures S2 and S3). In this hypothesis, the major diastereoisomer would be the (*S*) one.

Arguments based on the shielding effect of aromatic rings have been often used in assigning relative configurations, for example in the well known Mosher's method.

It should be stressed that this is just an hypothesis, based on the accordance between experimental spectroscopic data and conformational minimization with MOPAC, and thus we can not state with 100% certainty that this assignment is correct.

**Figure S2. Preferred conformation for the (*S*) simplified product 16a.** These are simply different views of the same conformation. grey: carbon; yellow: hydrogen; red: oxygen; green: chlorine



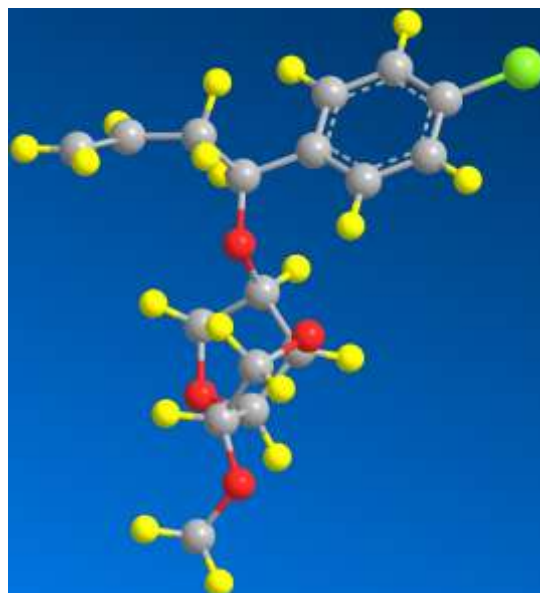
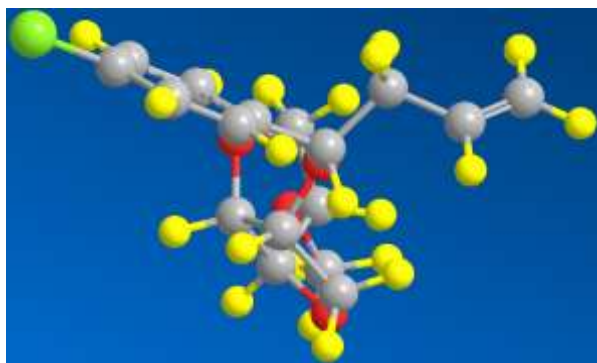
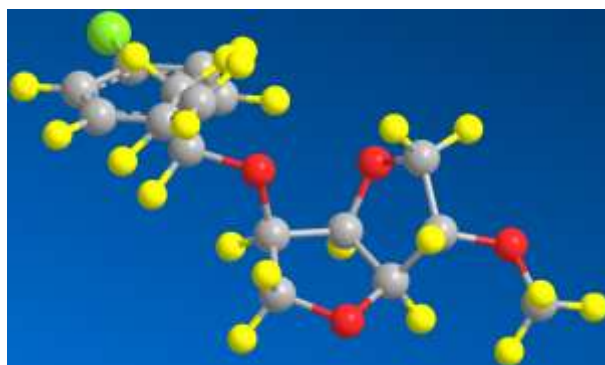
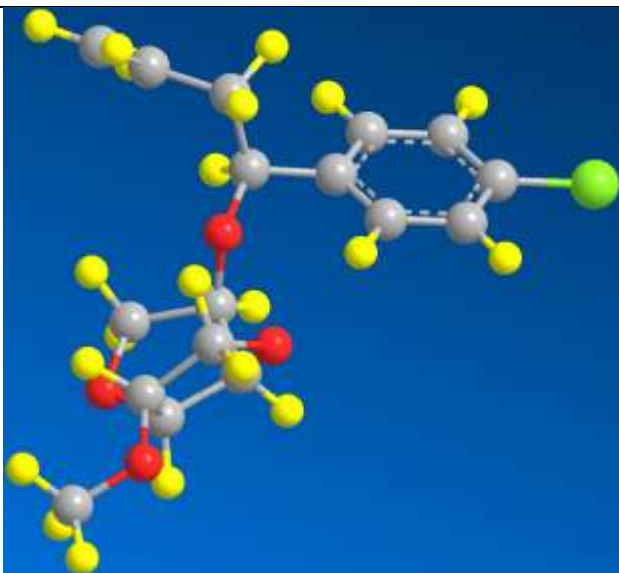
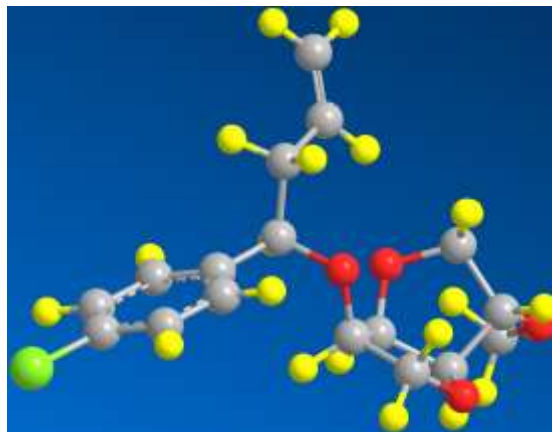
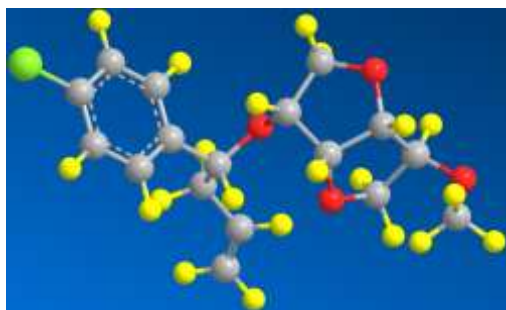
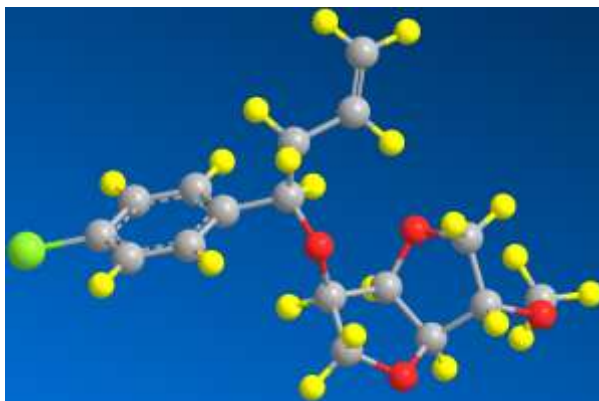
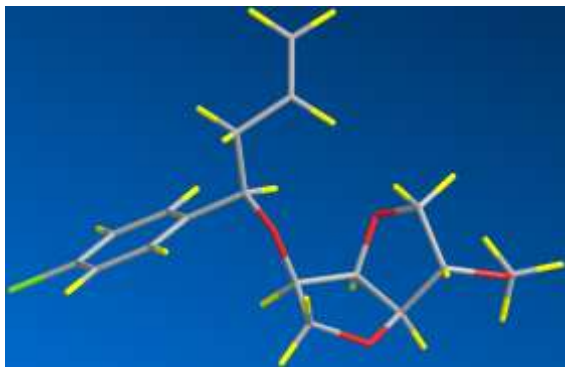
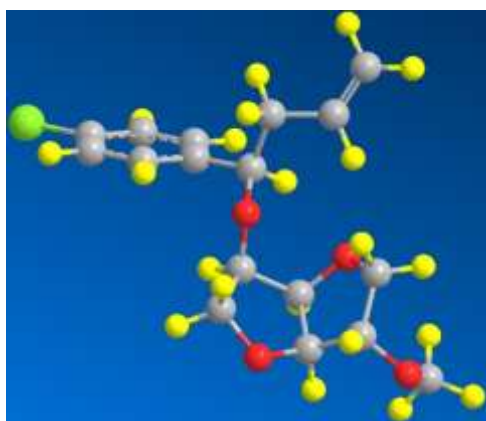
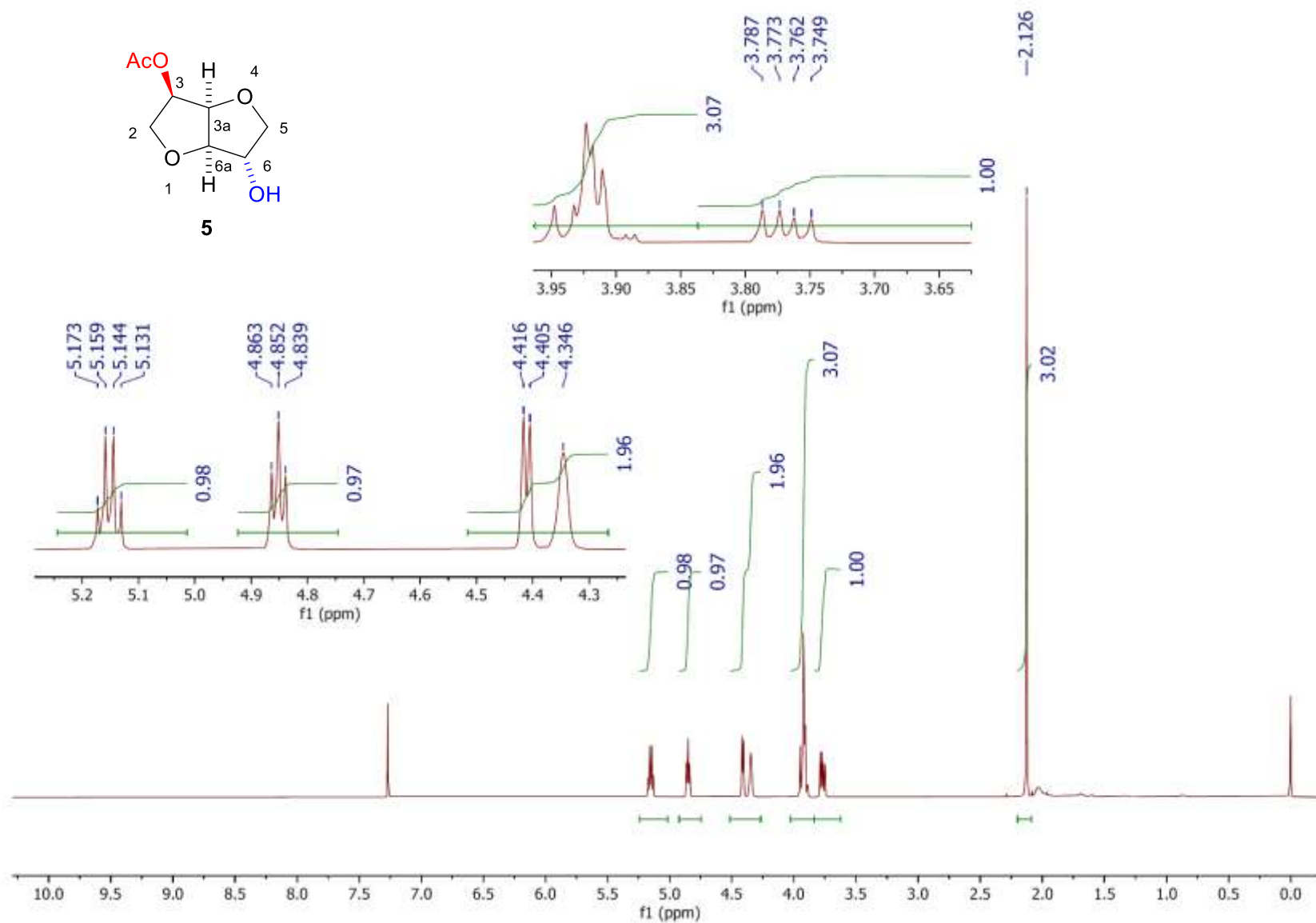


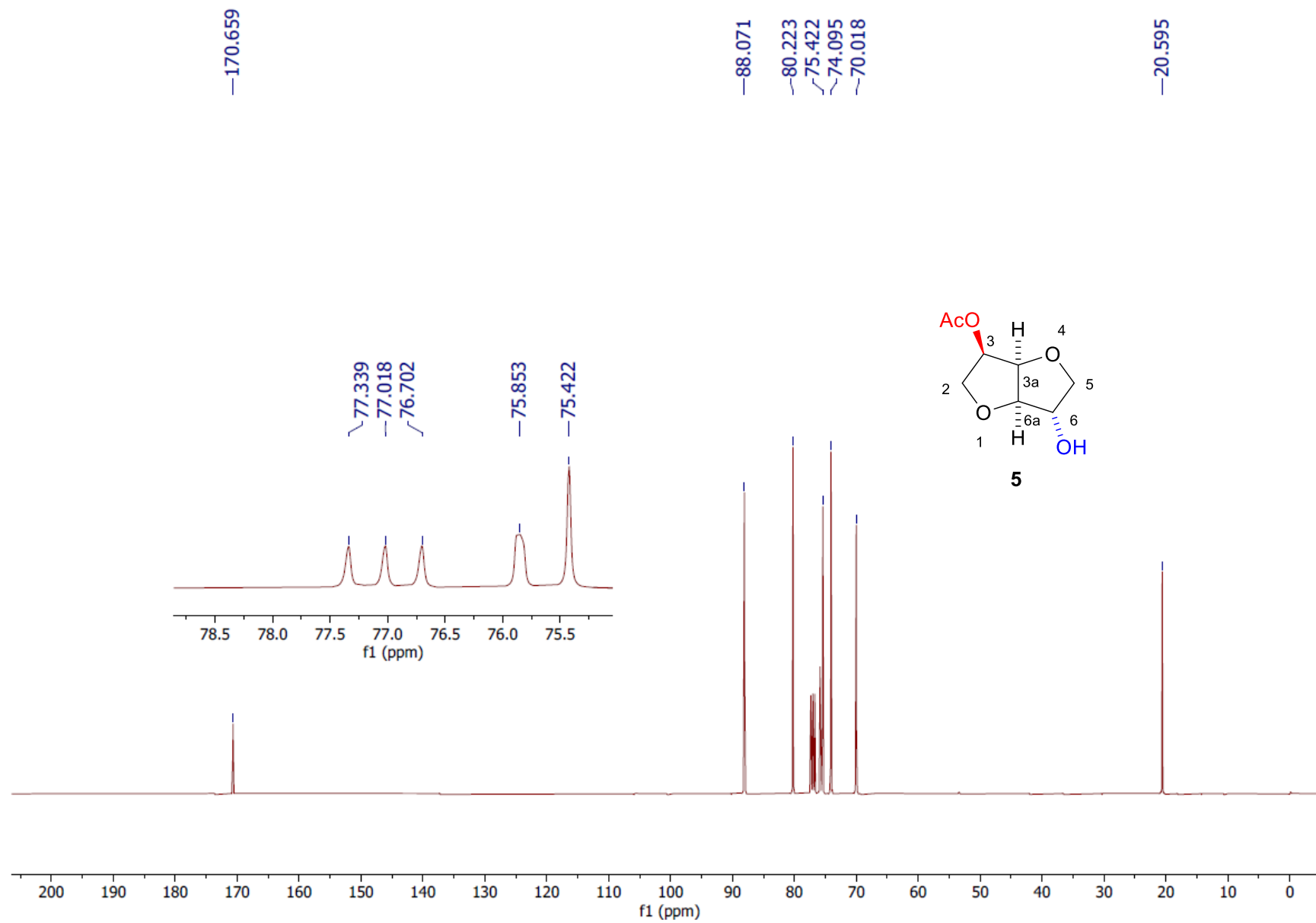
**Figure S3. Preferred conformation for the (*R*) simplified product 16a.** These are simply different views of the same conformation. grey: carbon; yellow: hydrogen; red: oxygen; green: chlorine



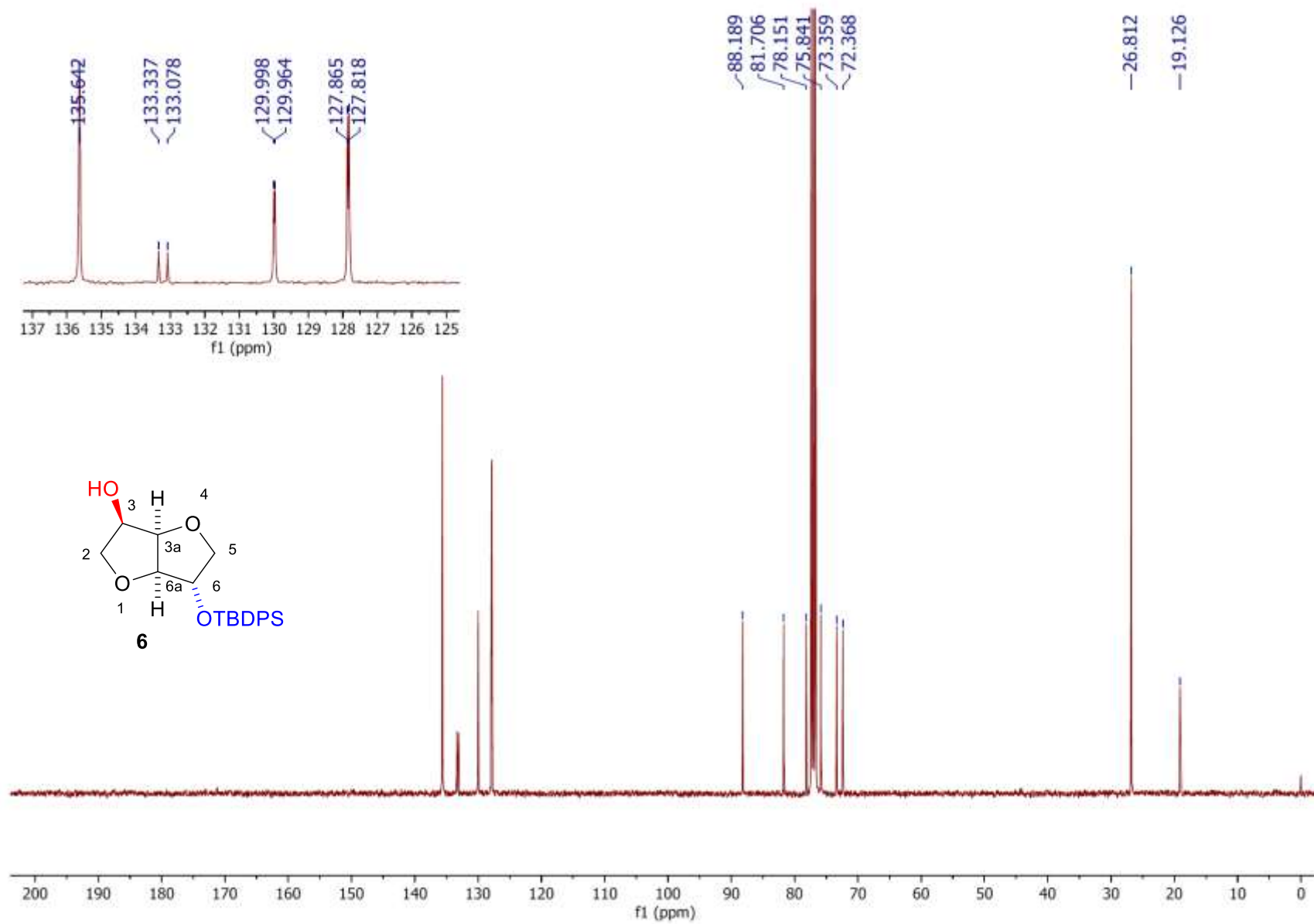


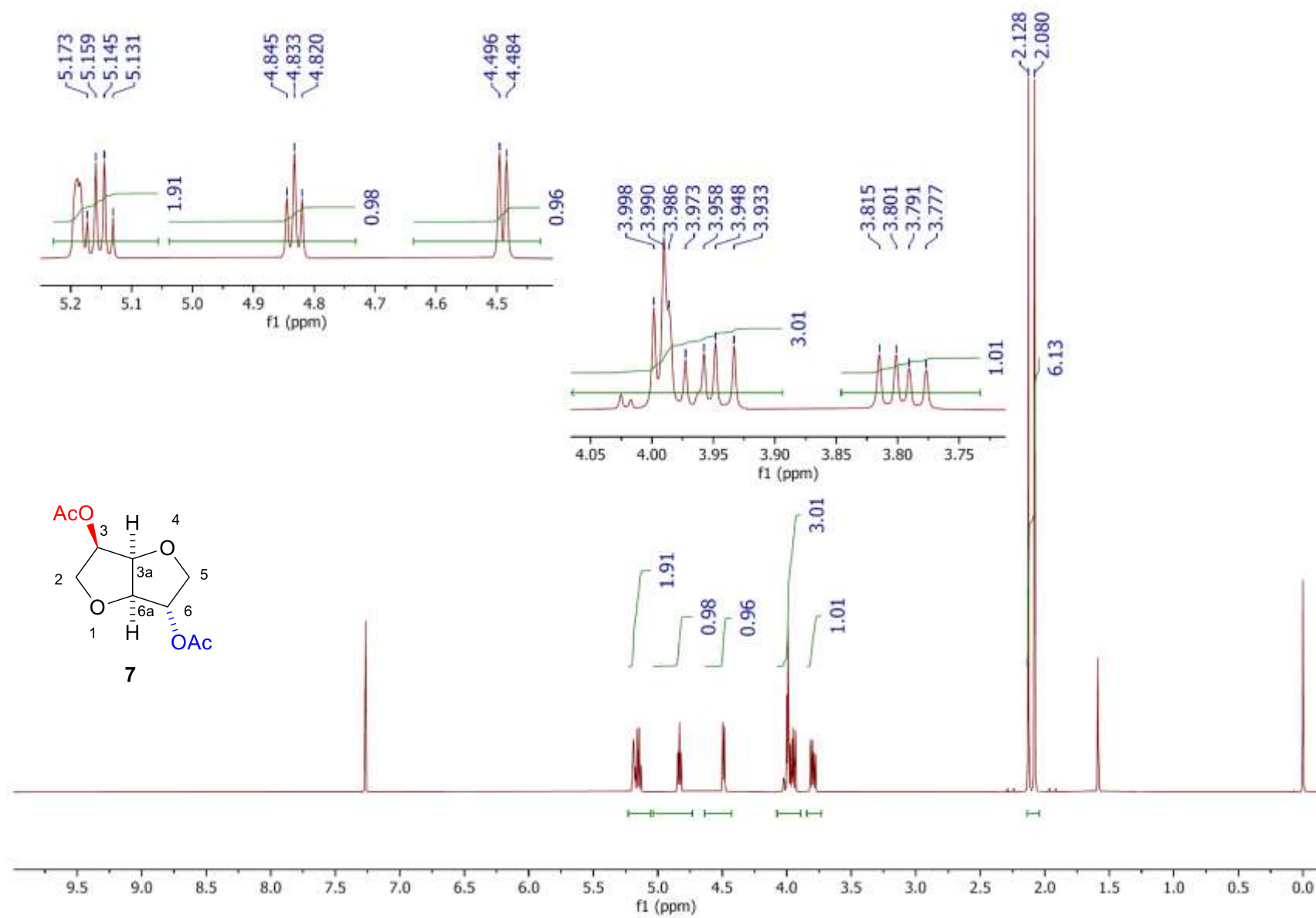
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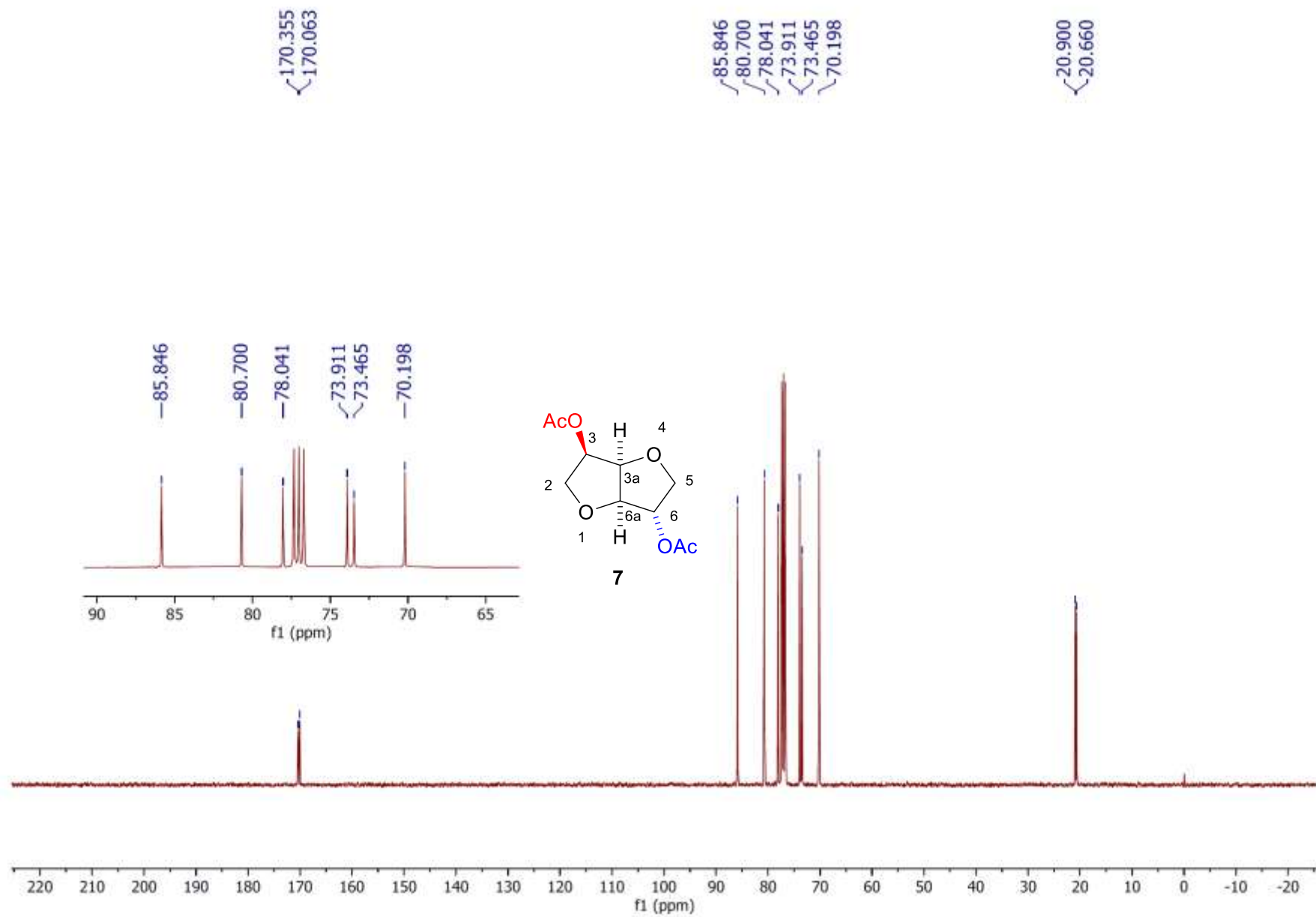


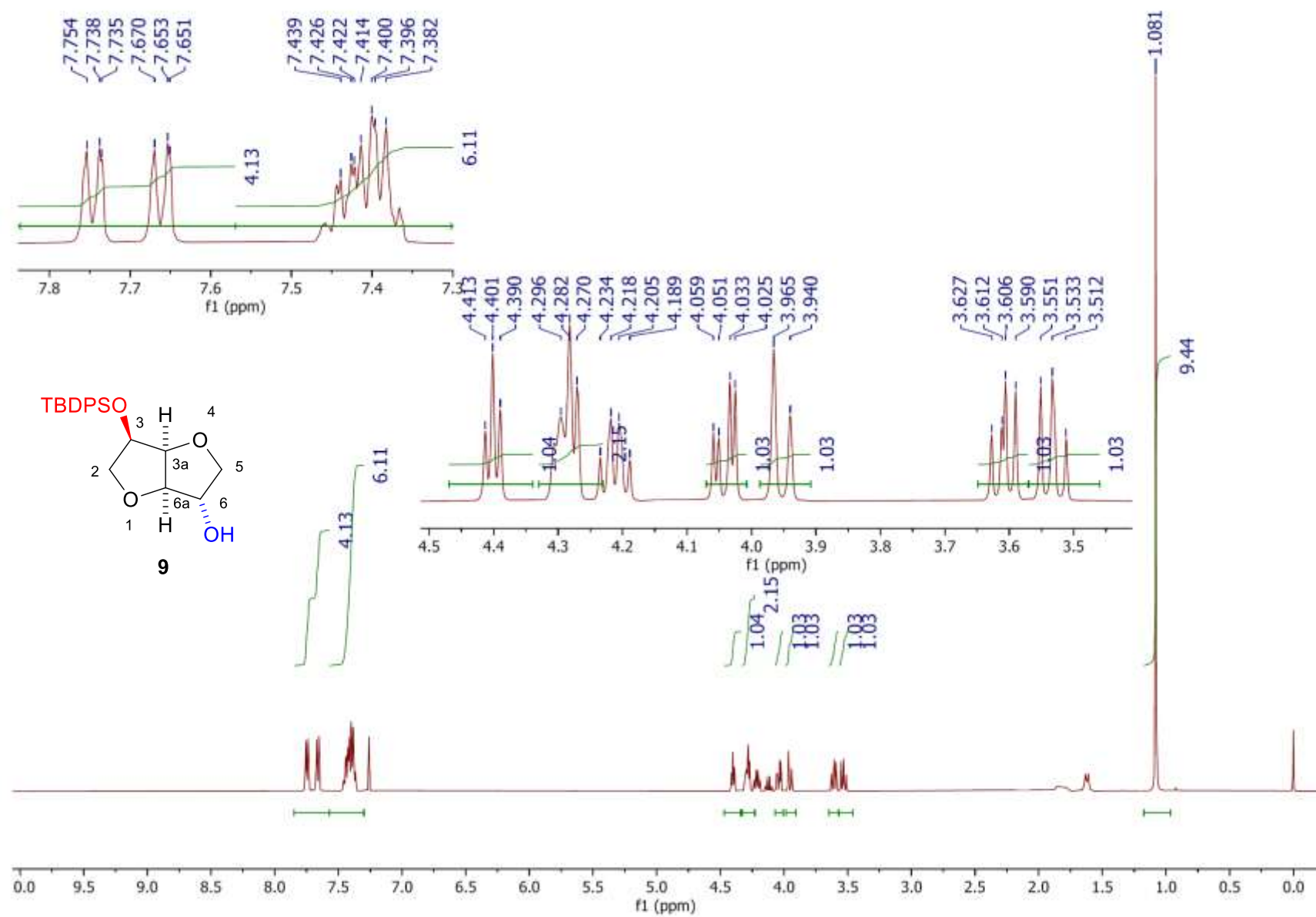


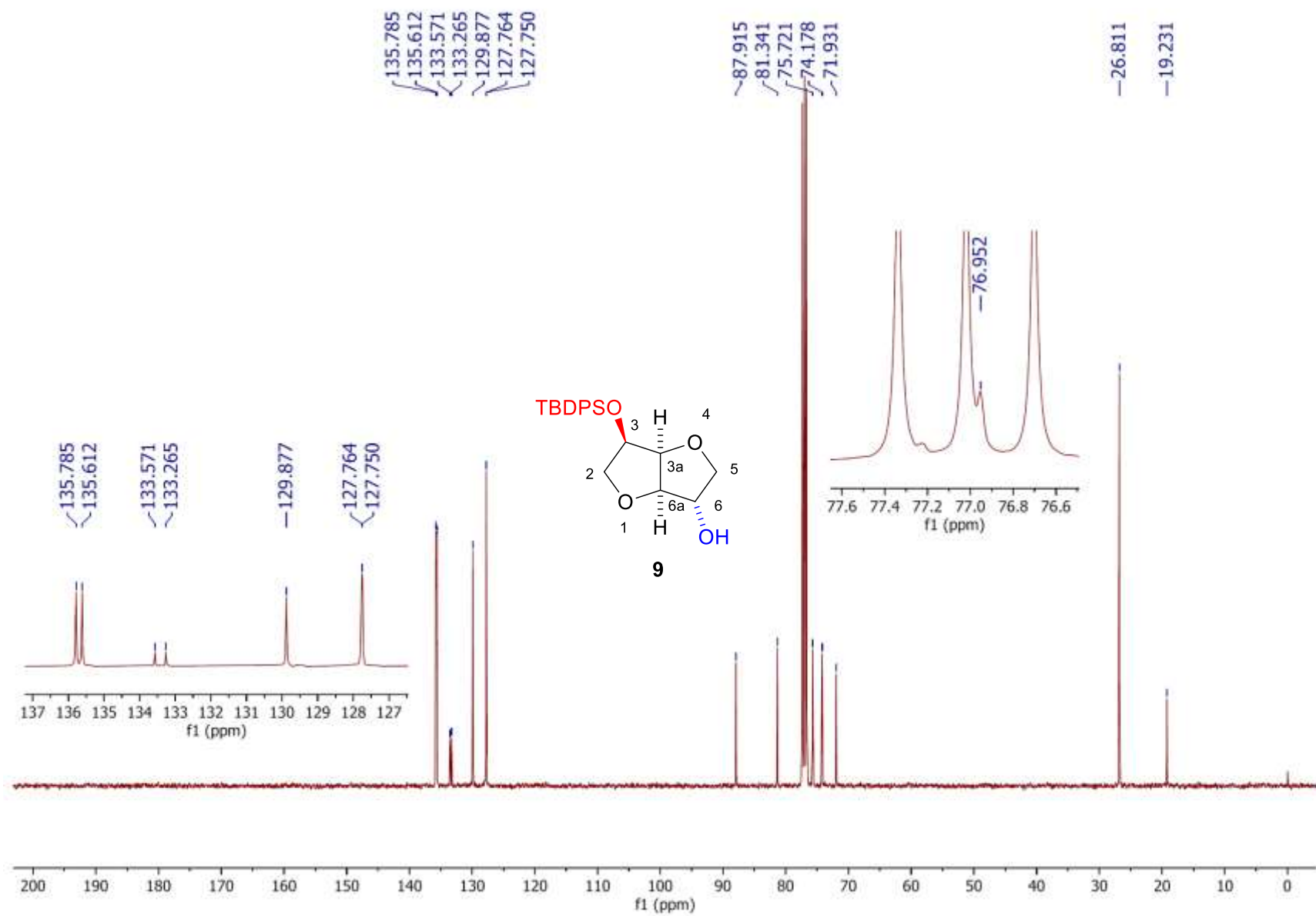


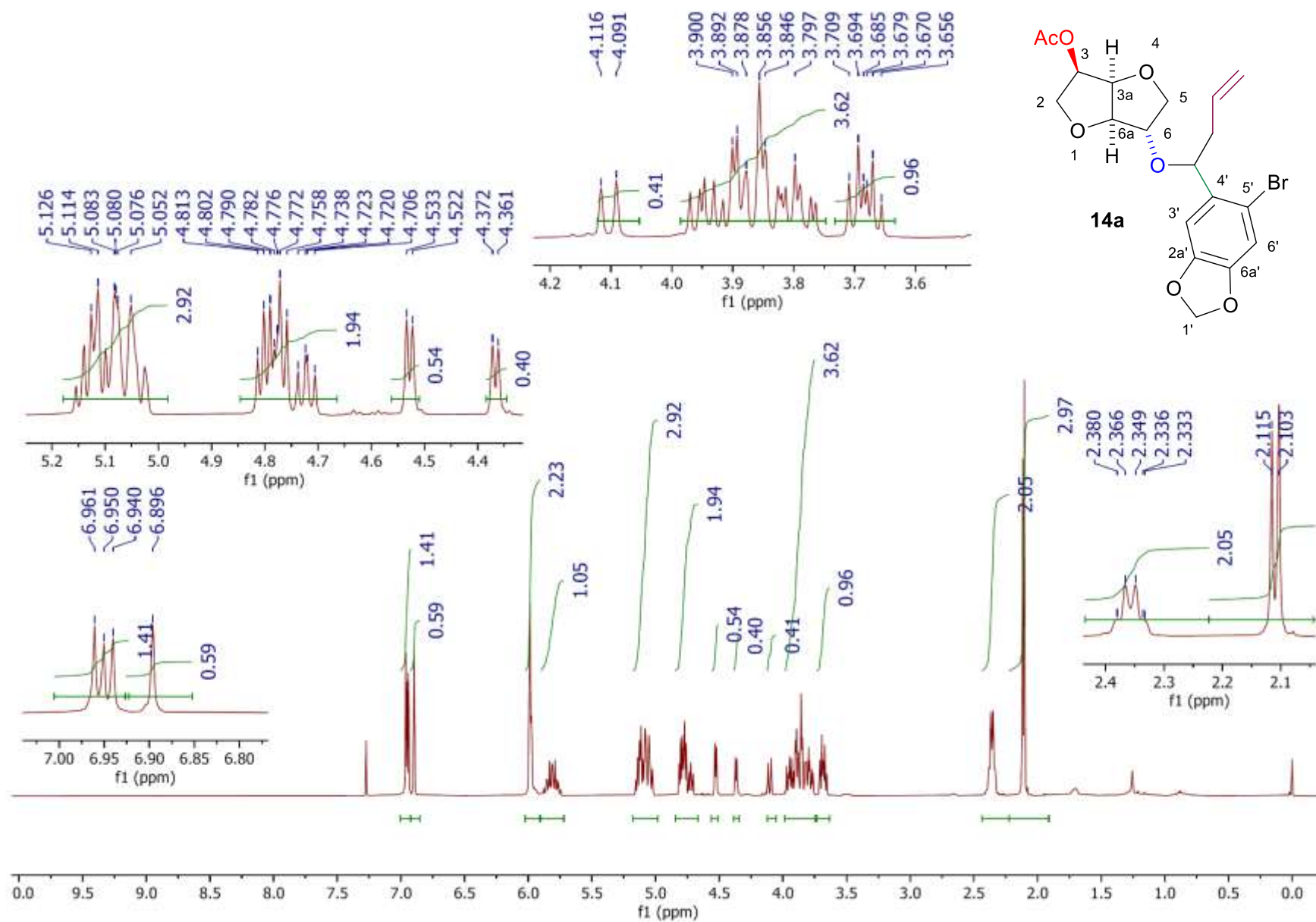


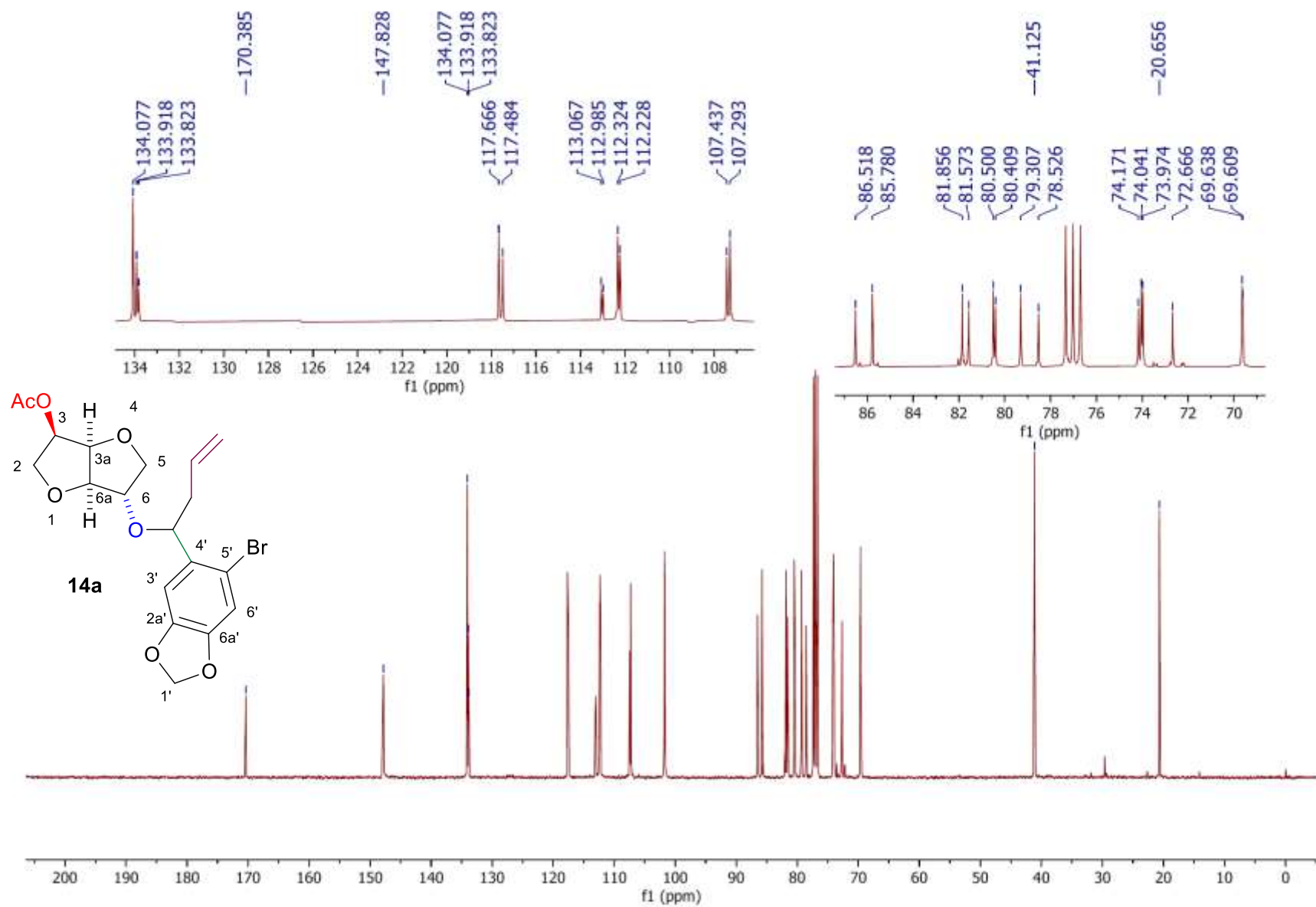


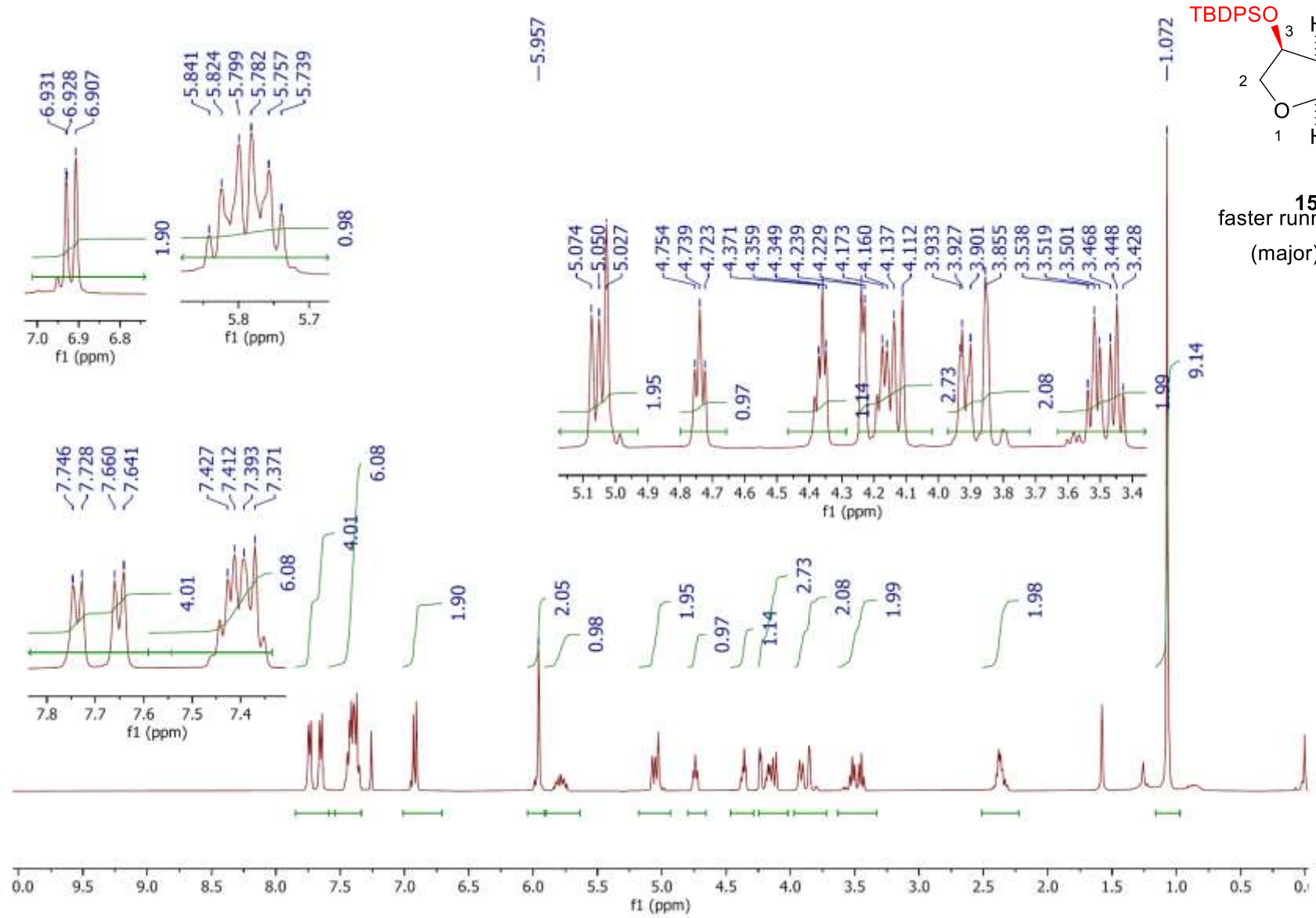


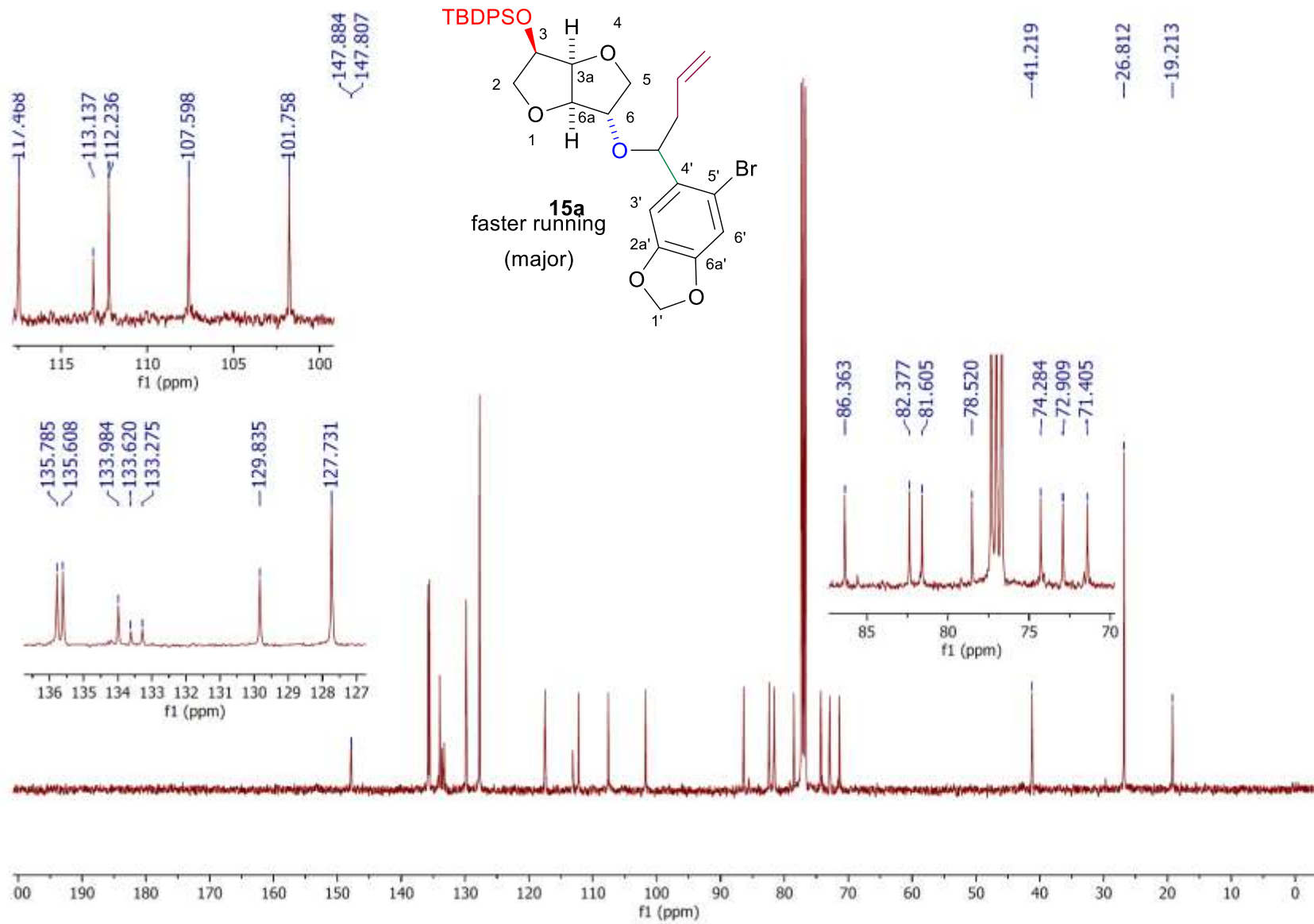


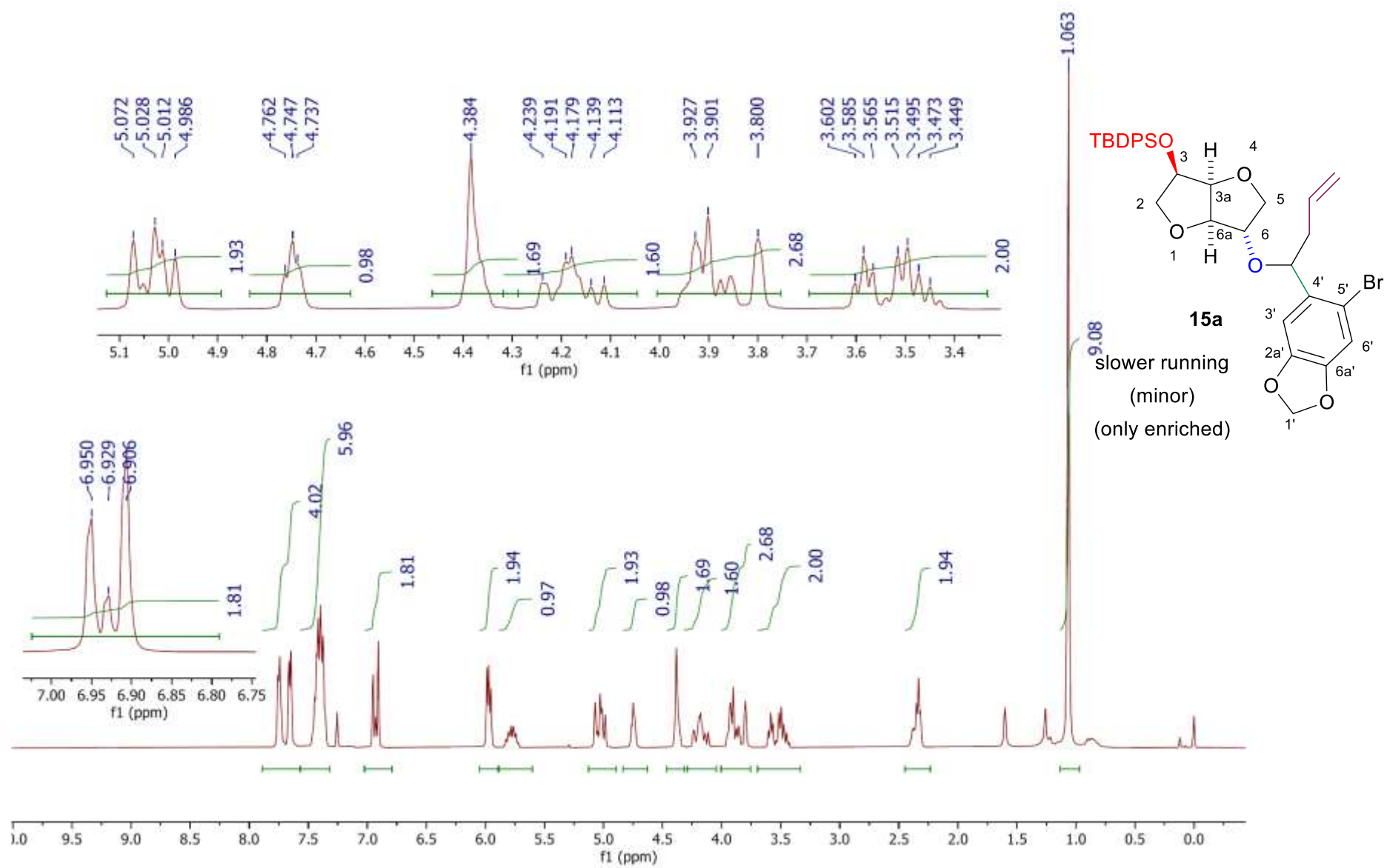


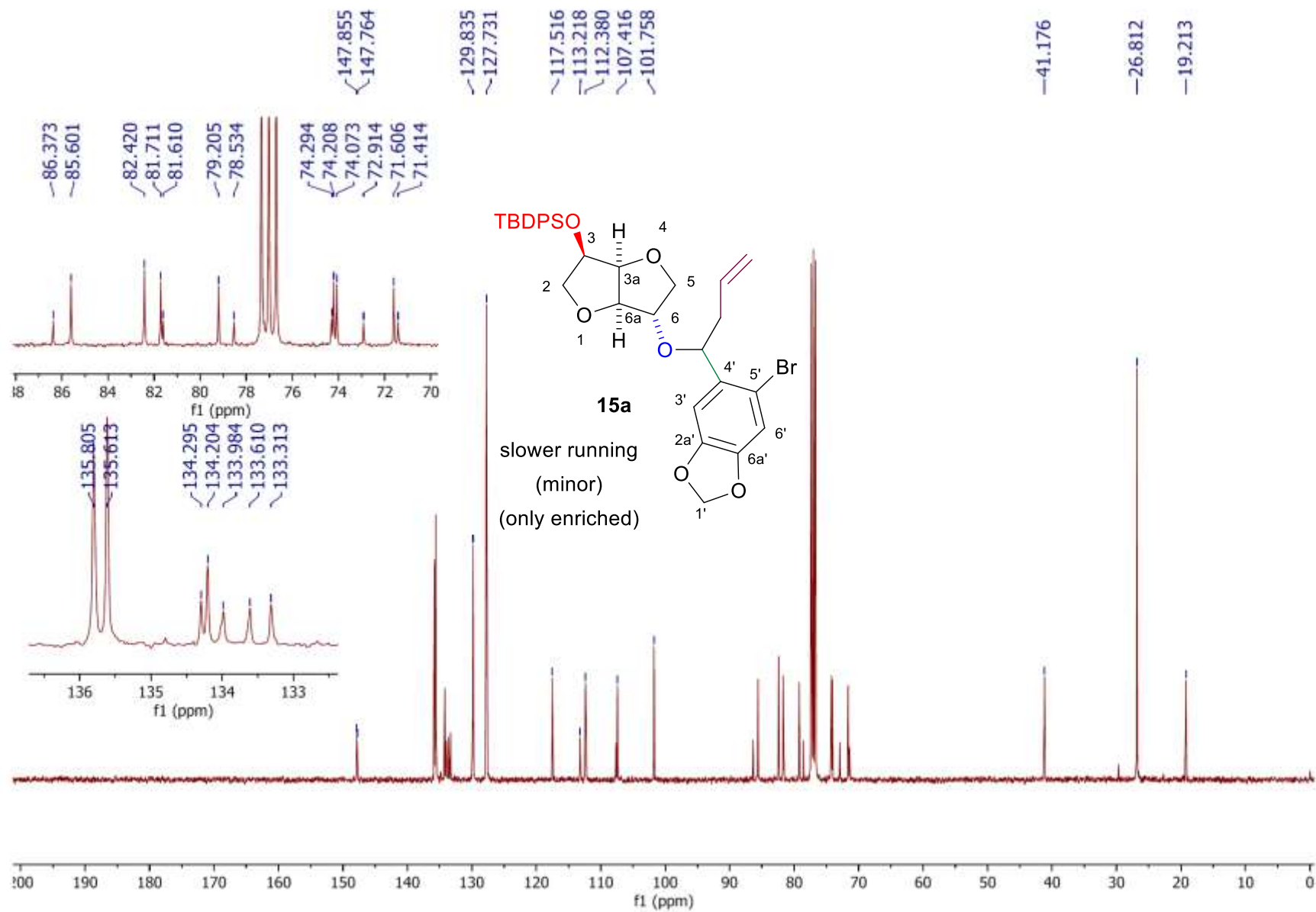


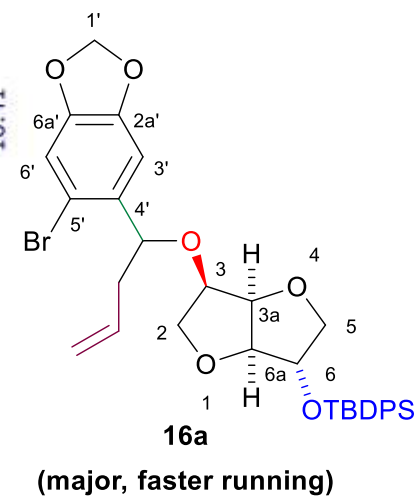
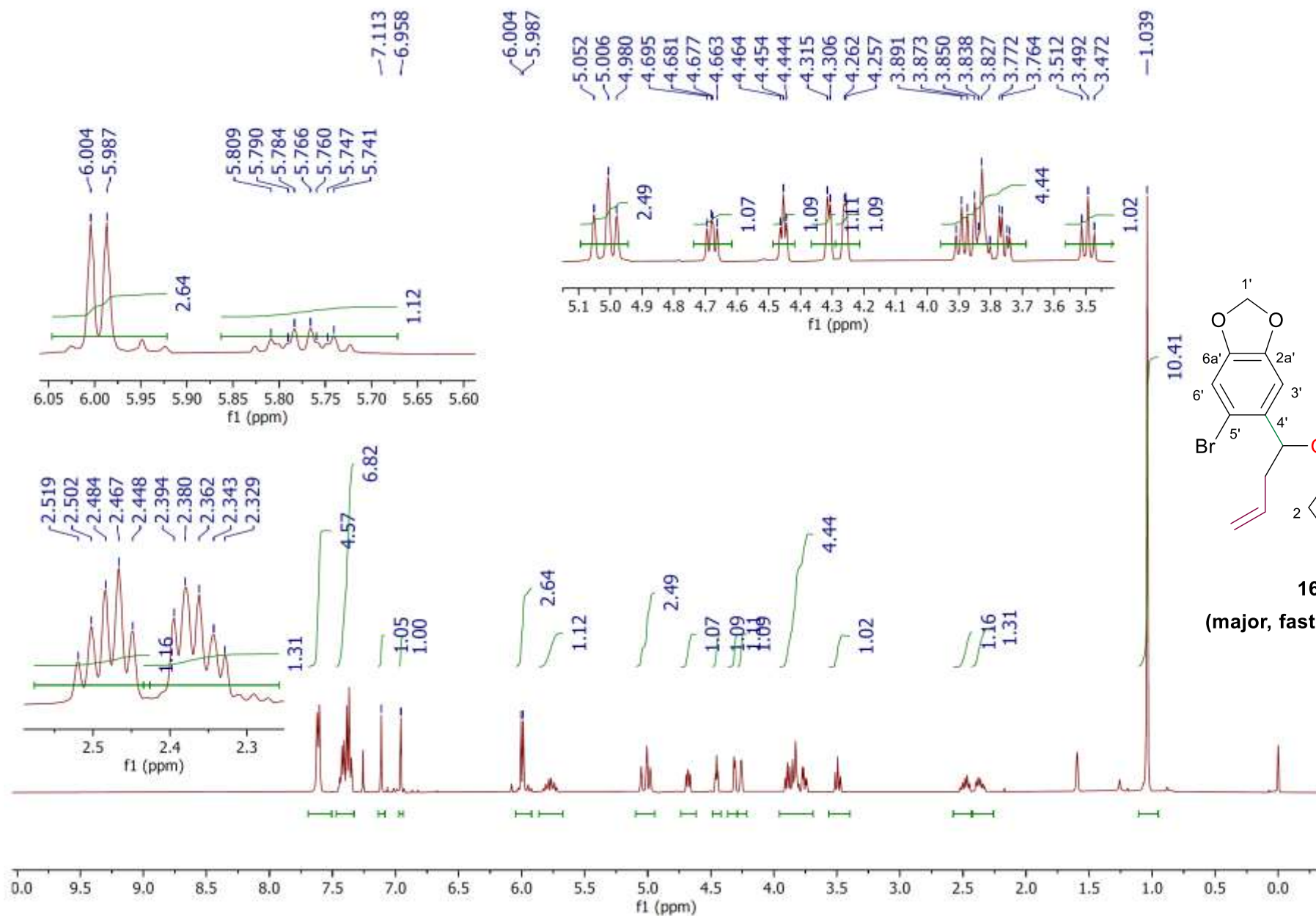


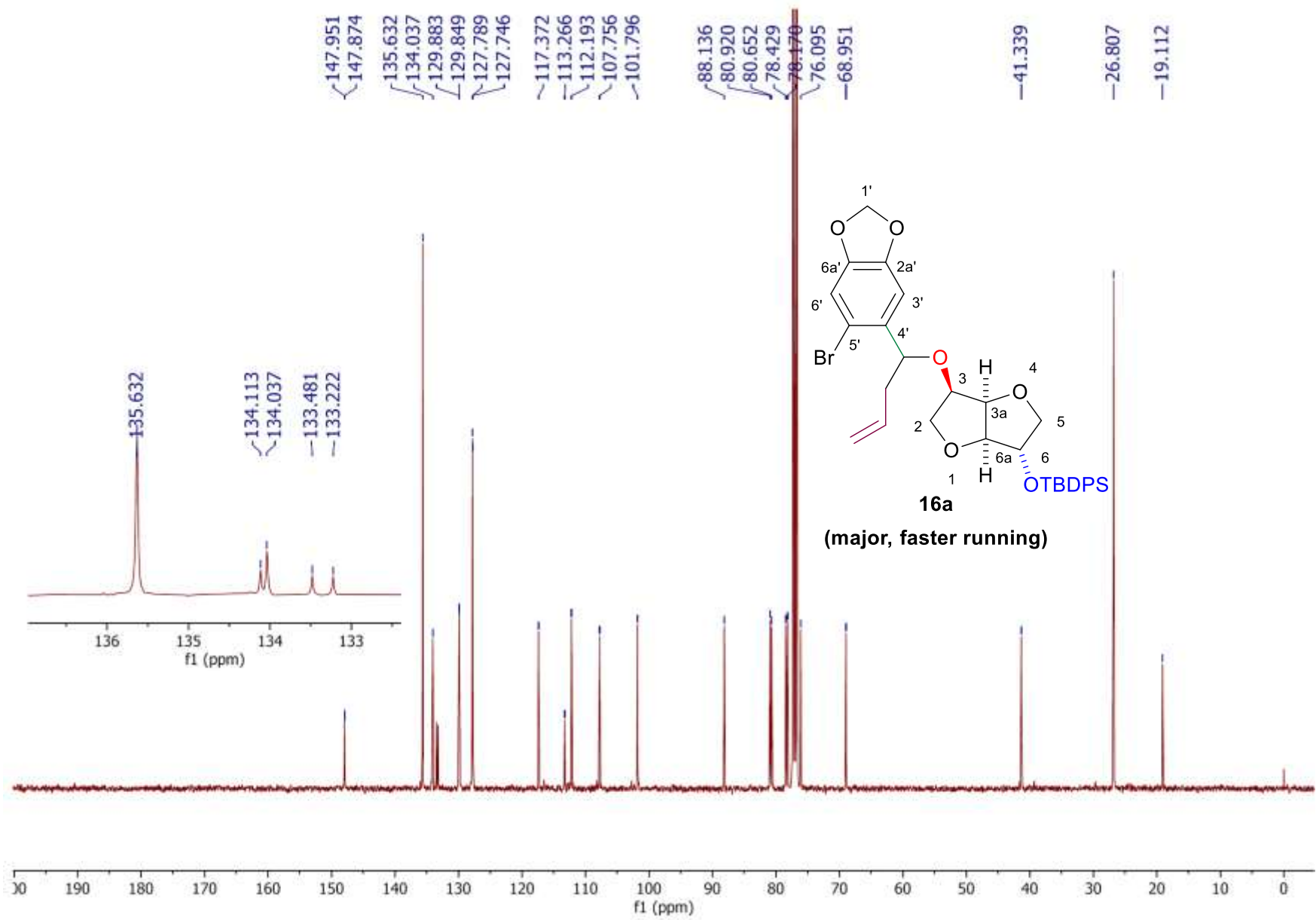


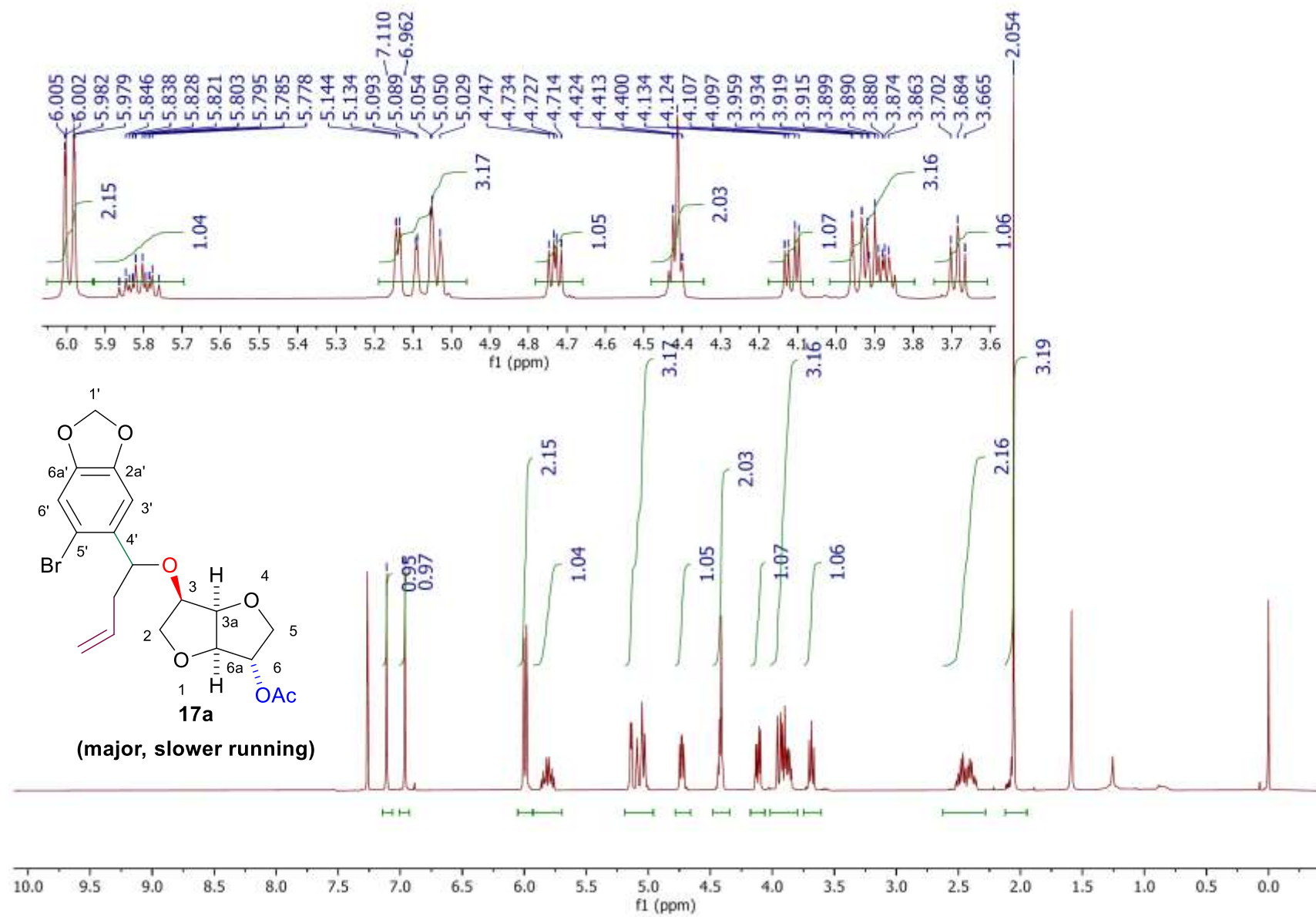


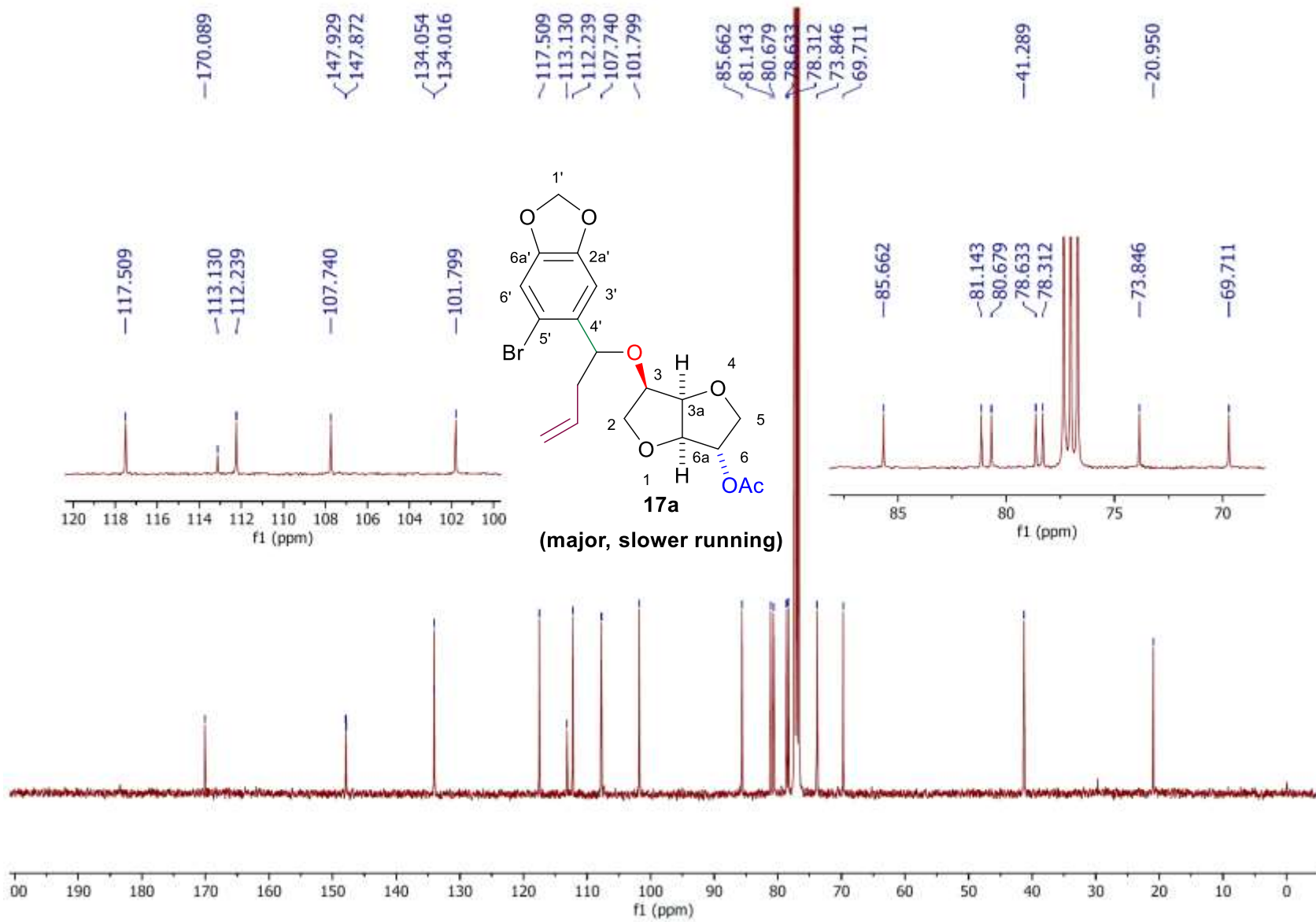




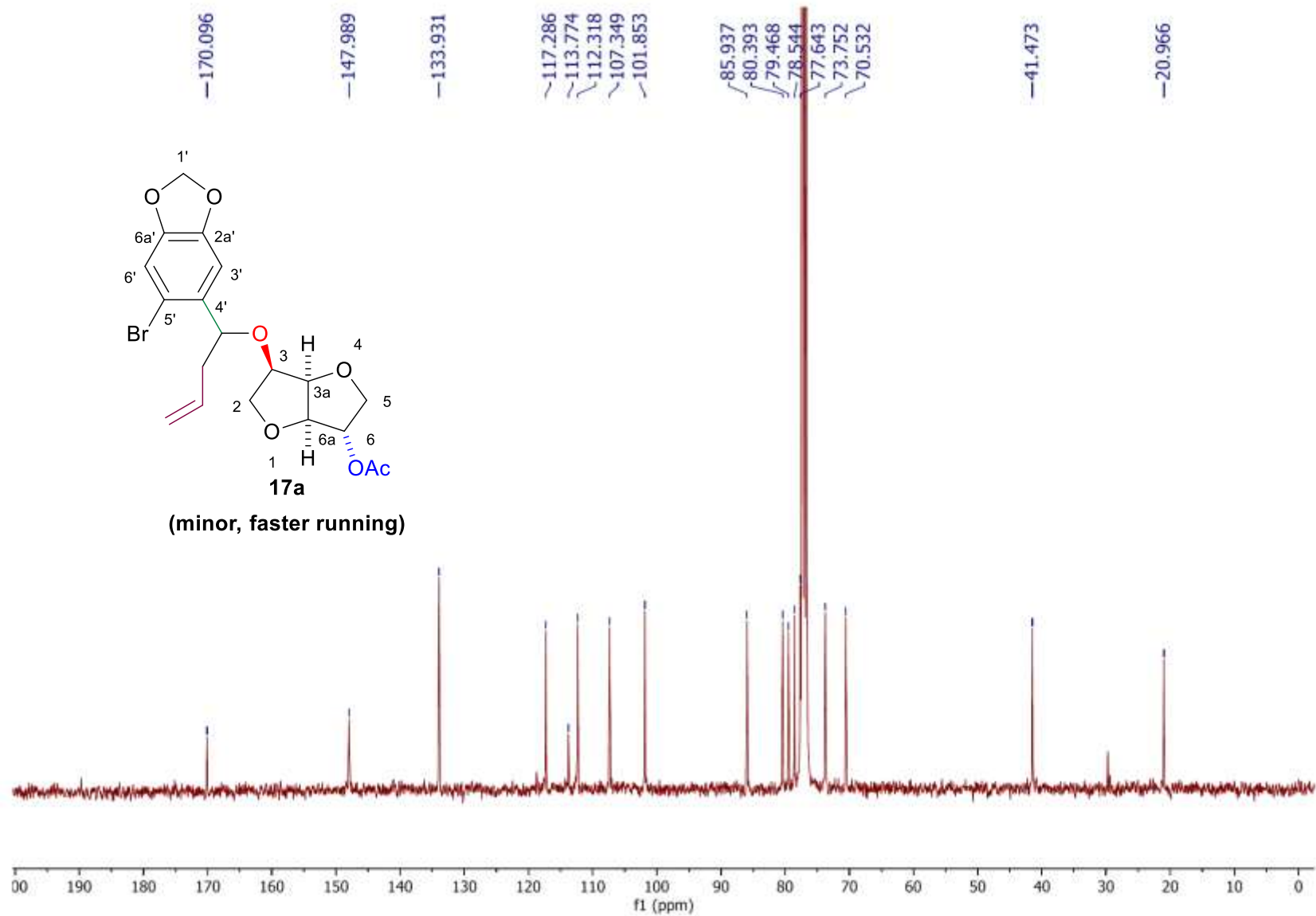


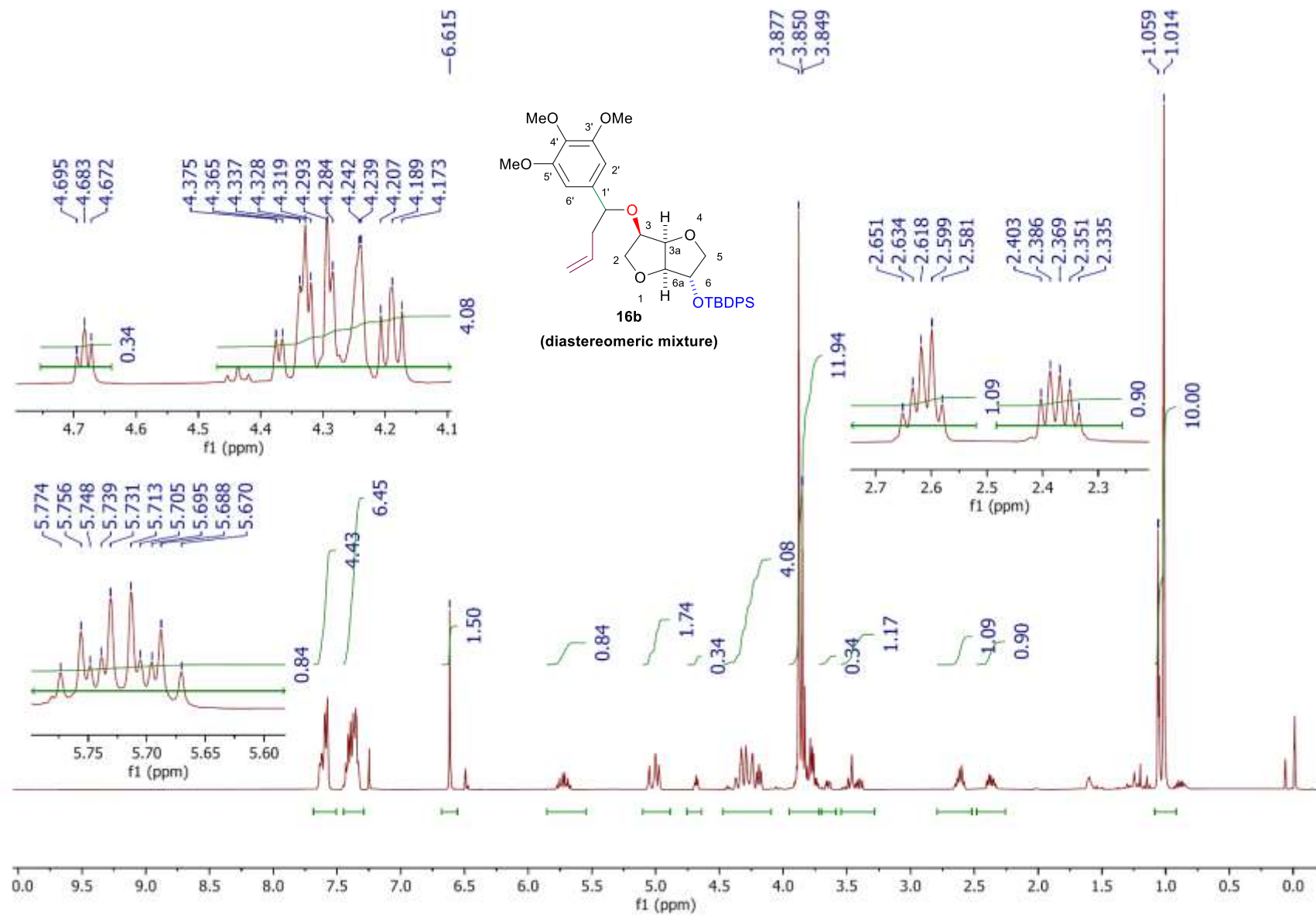


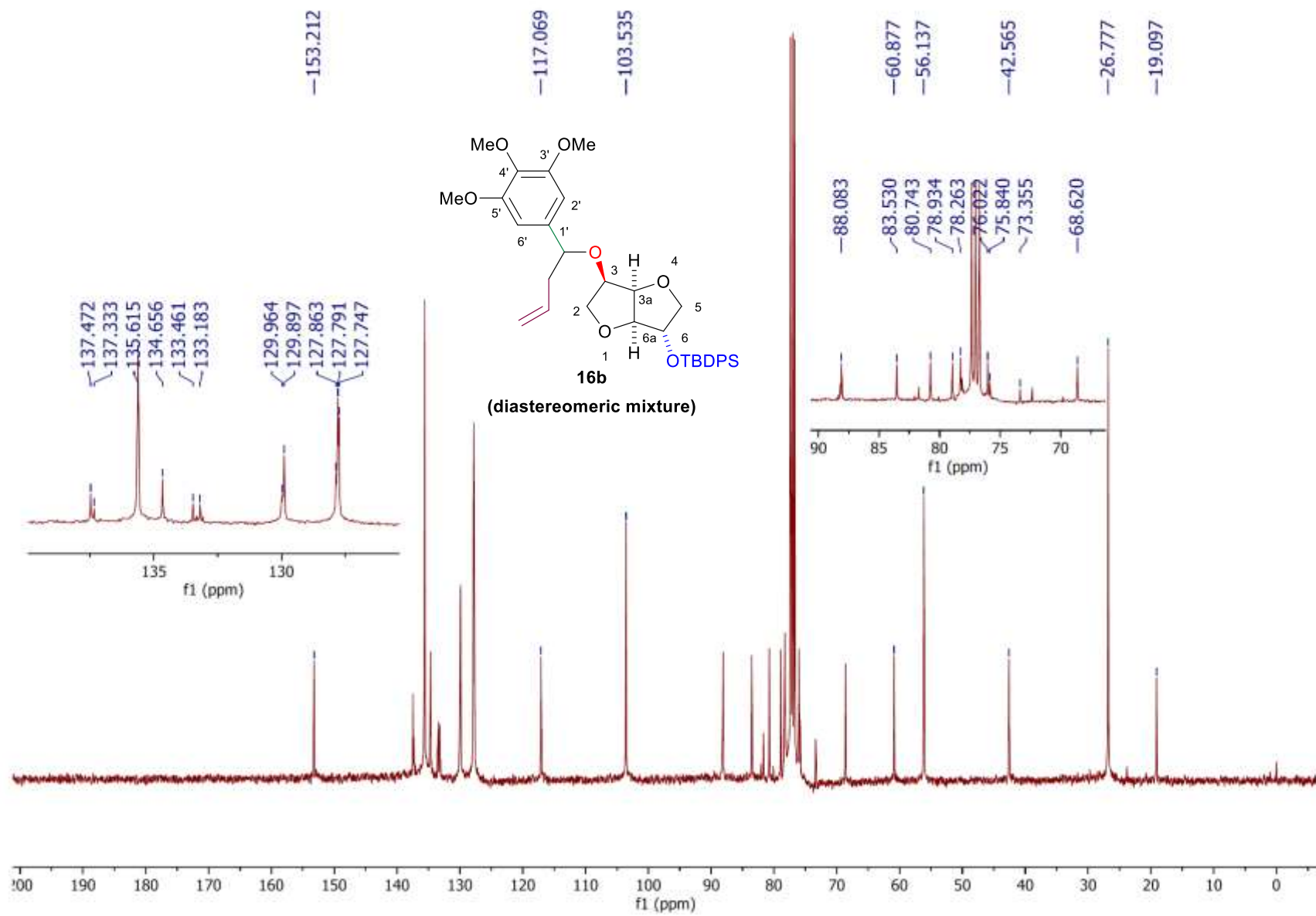


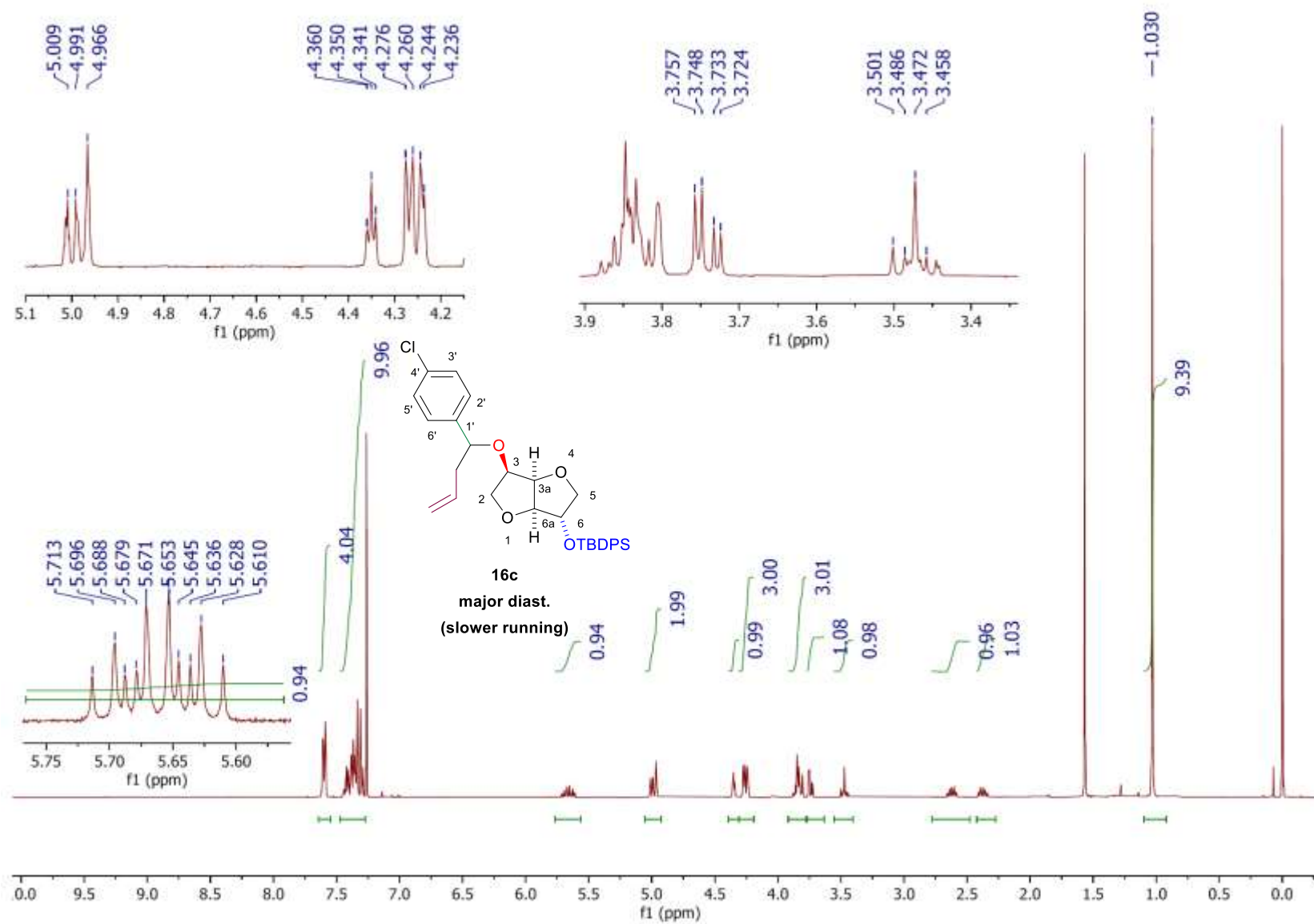


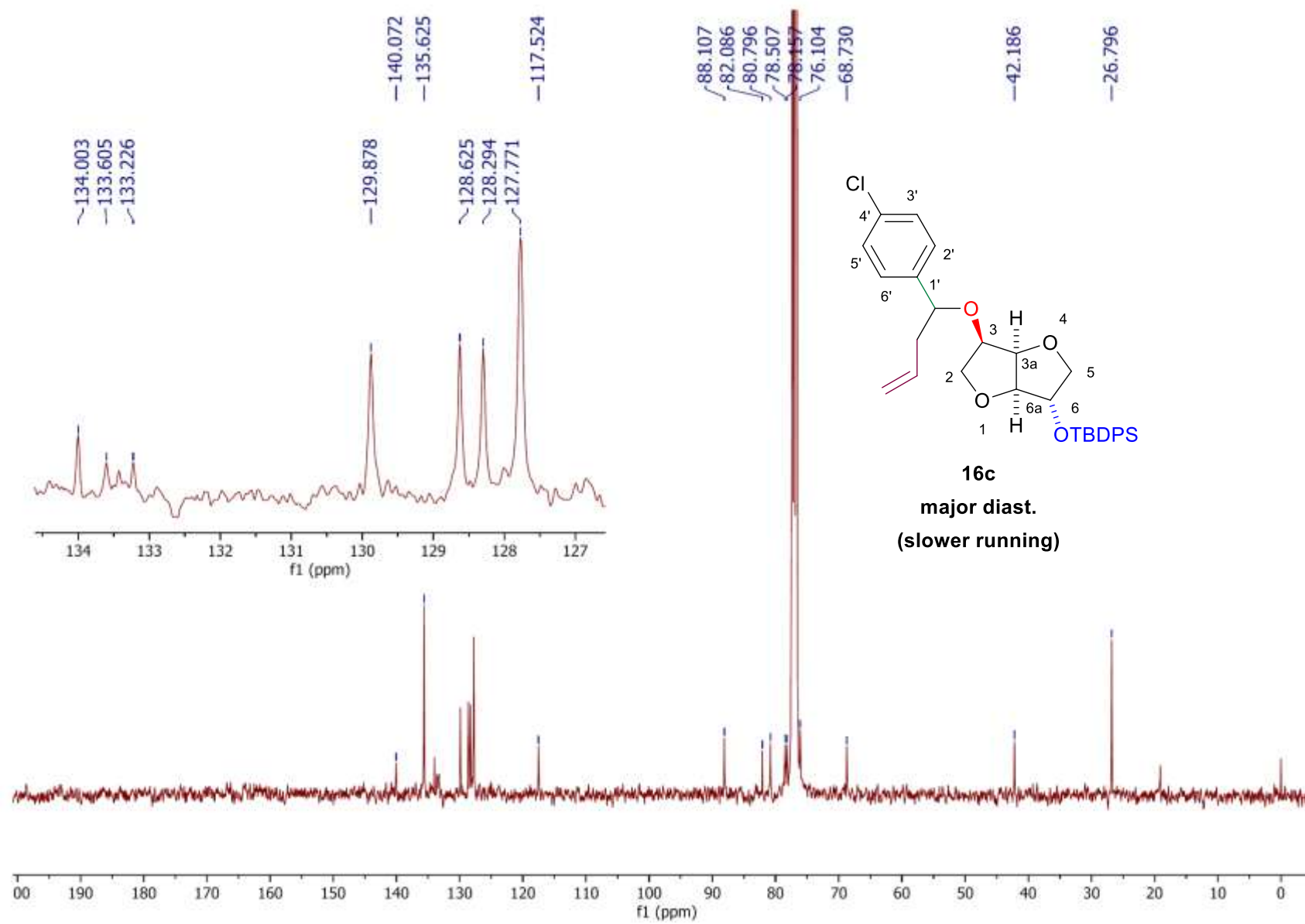




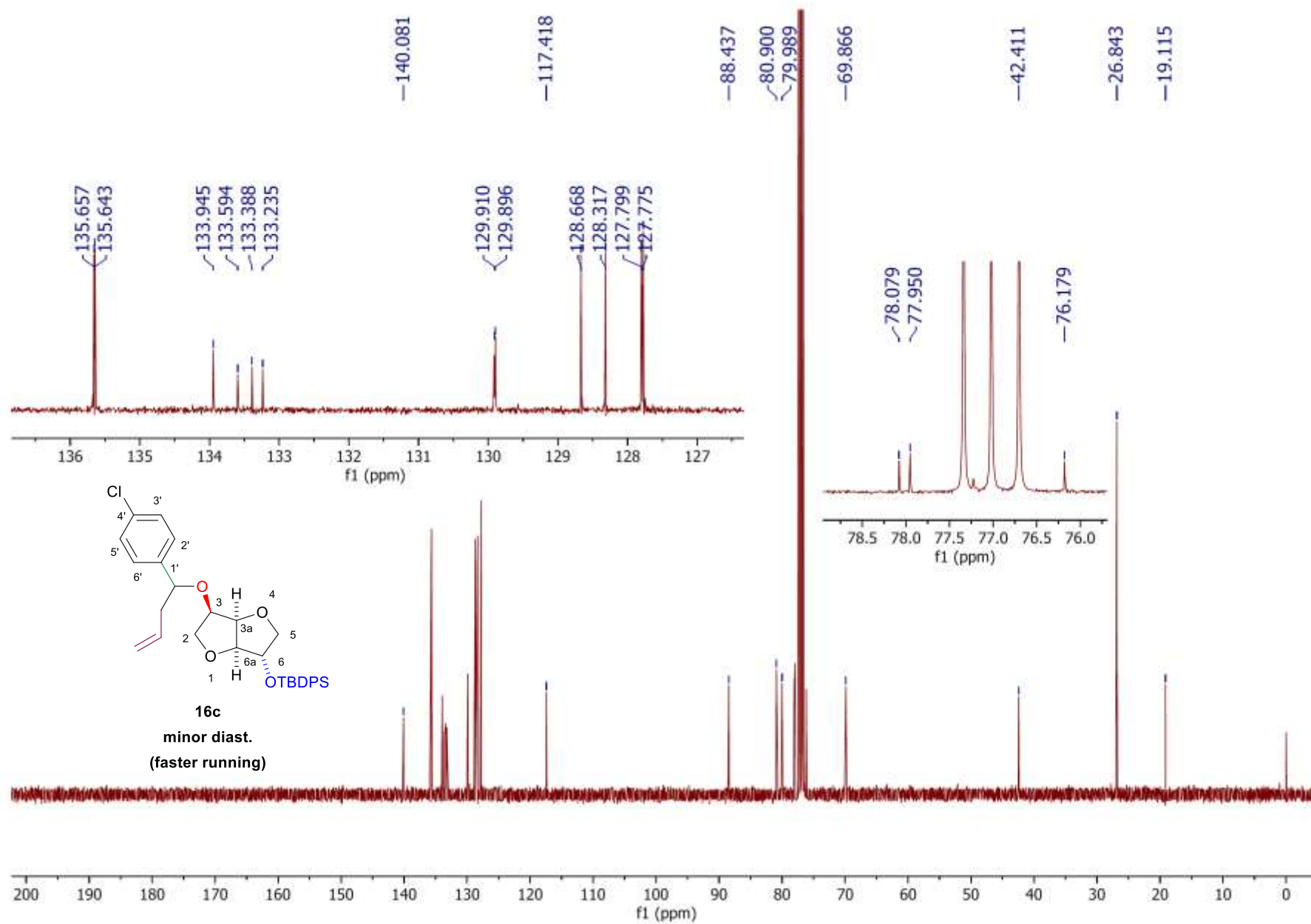


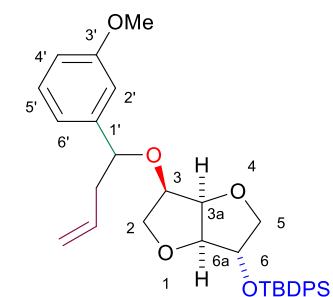
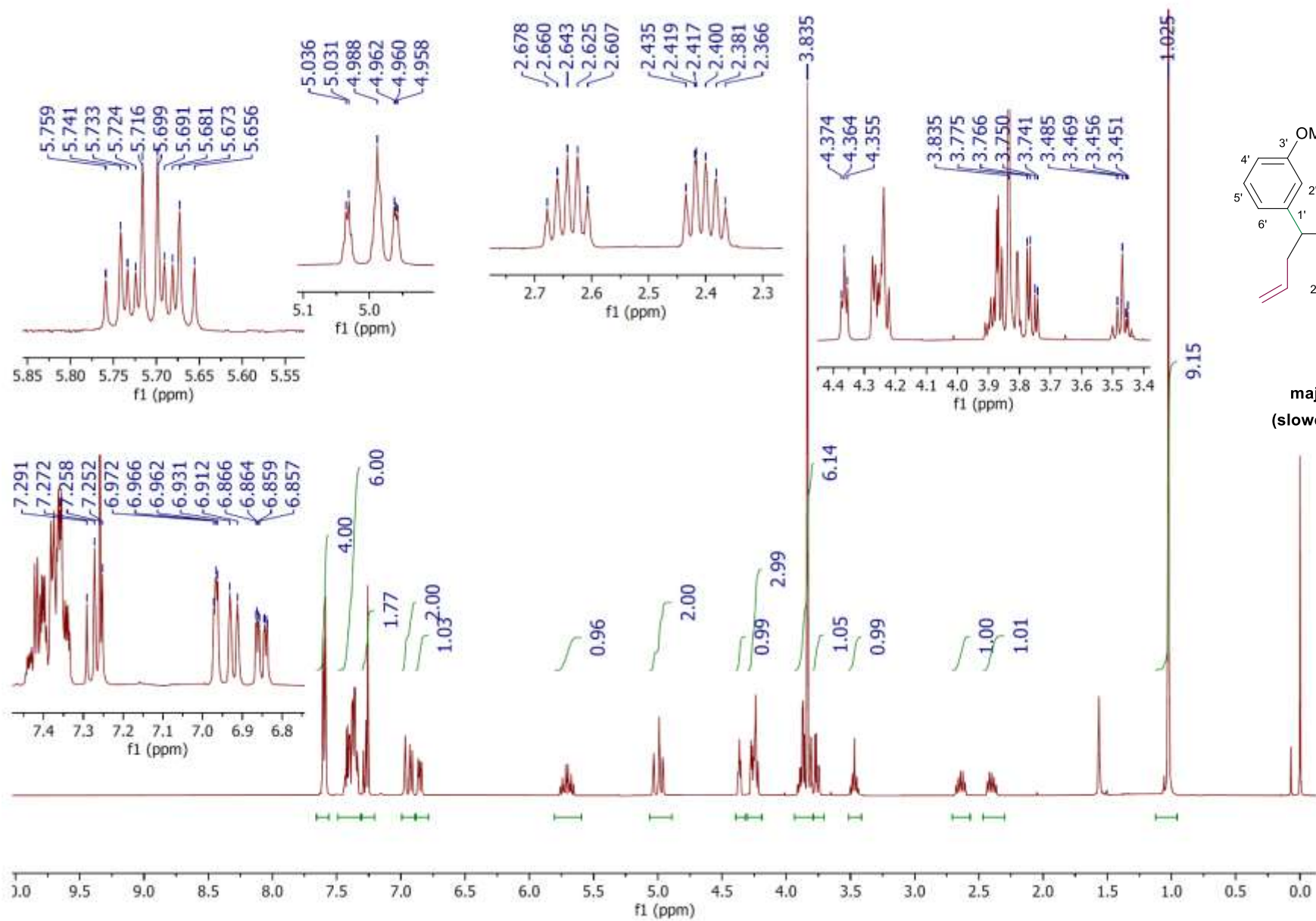




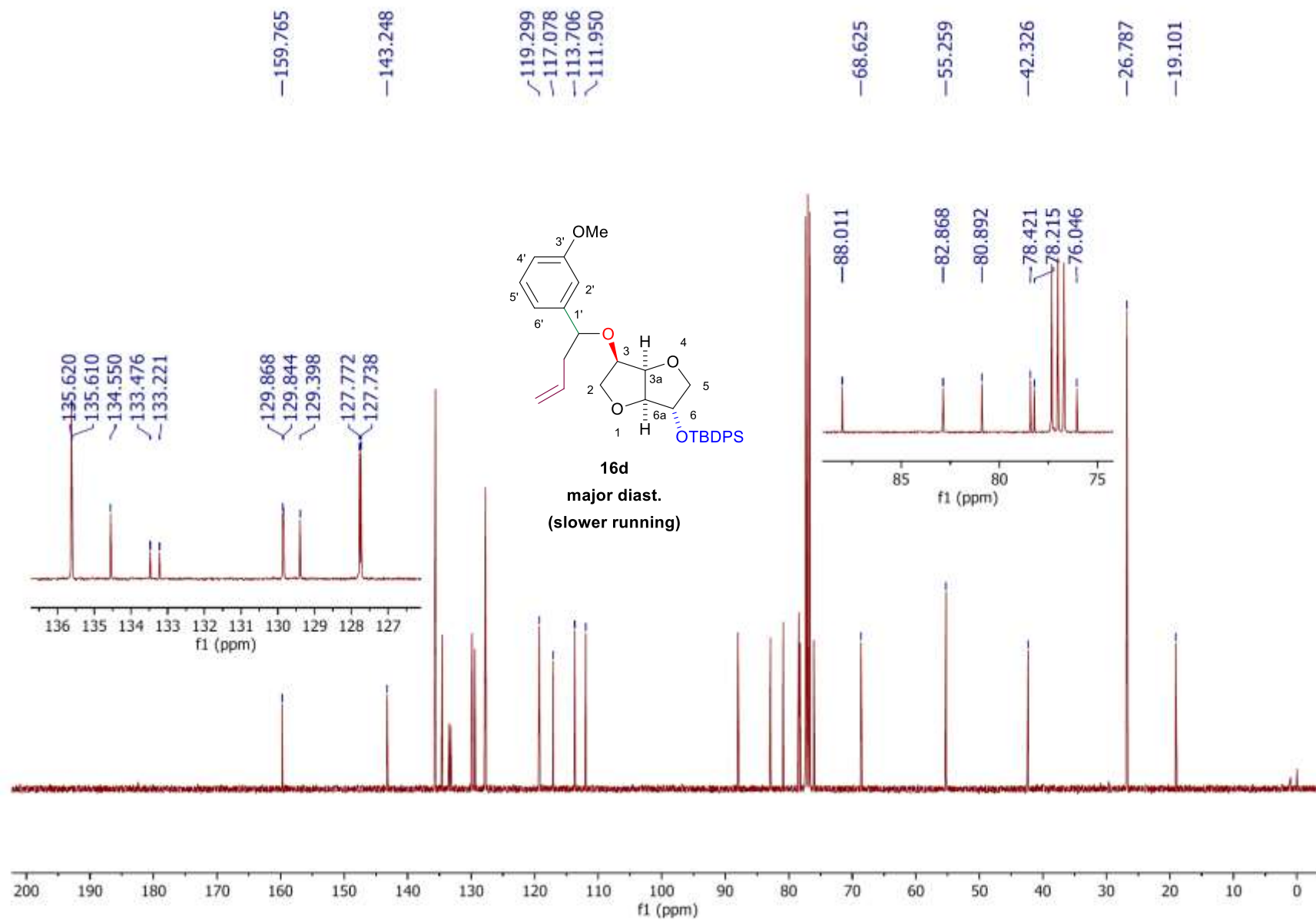


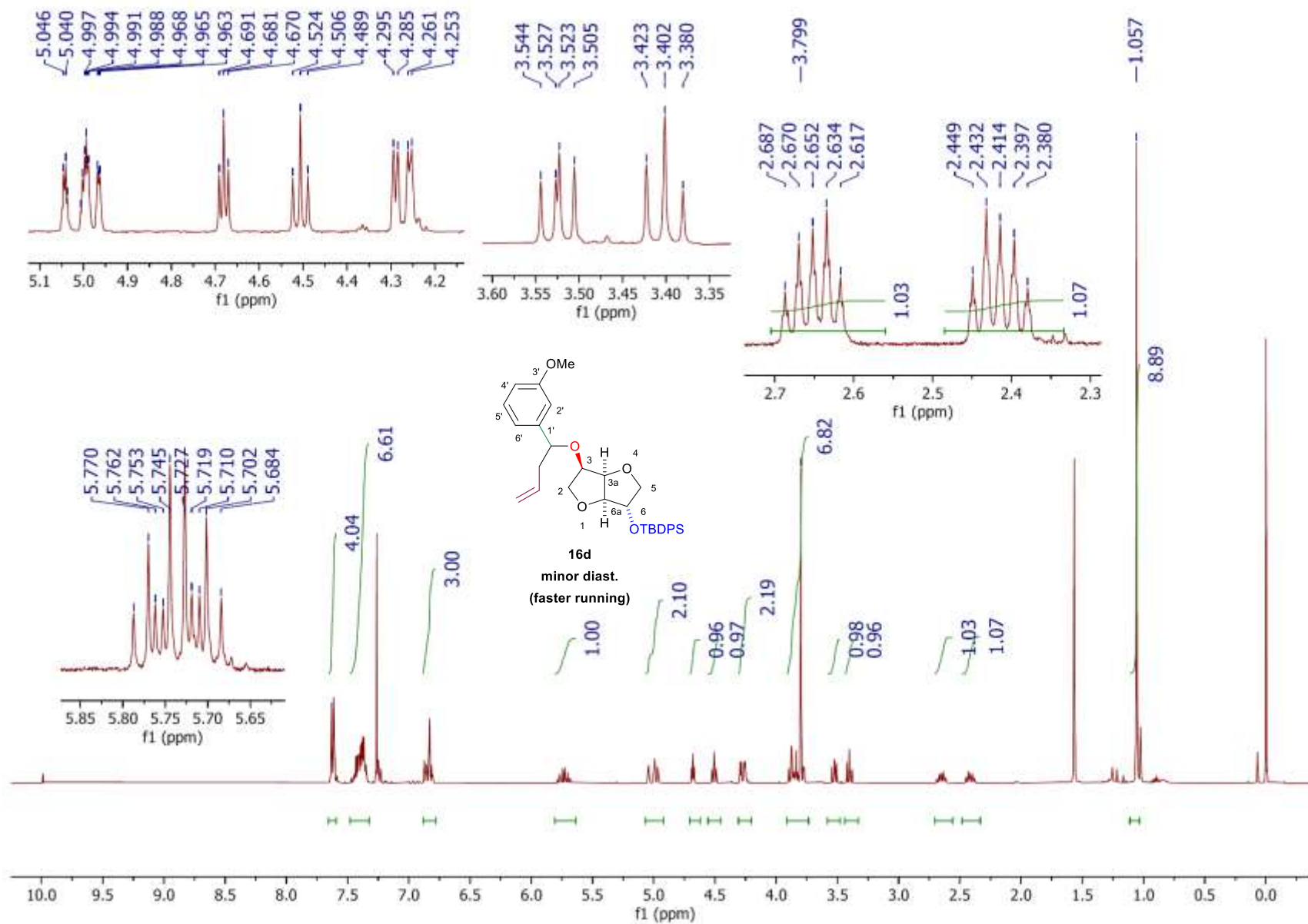


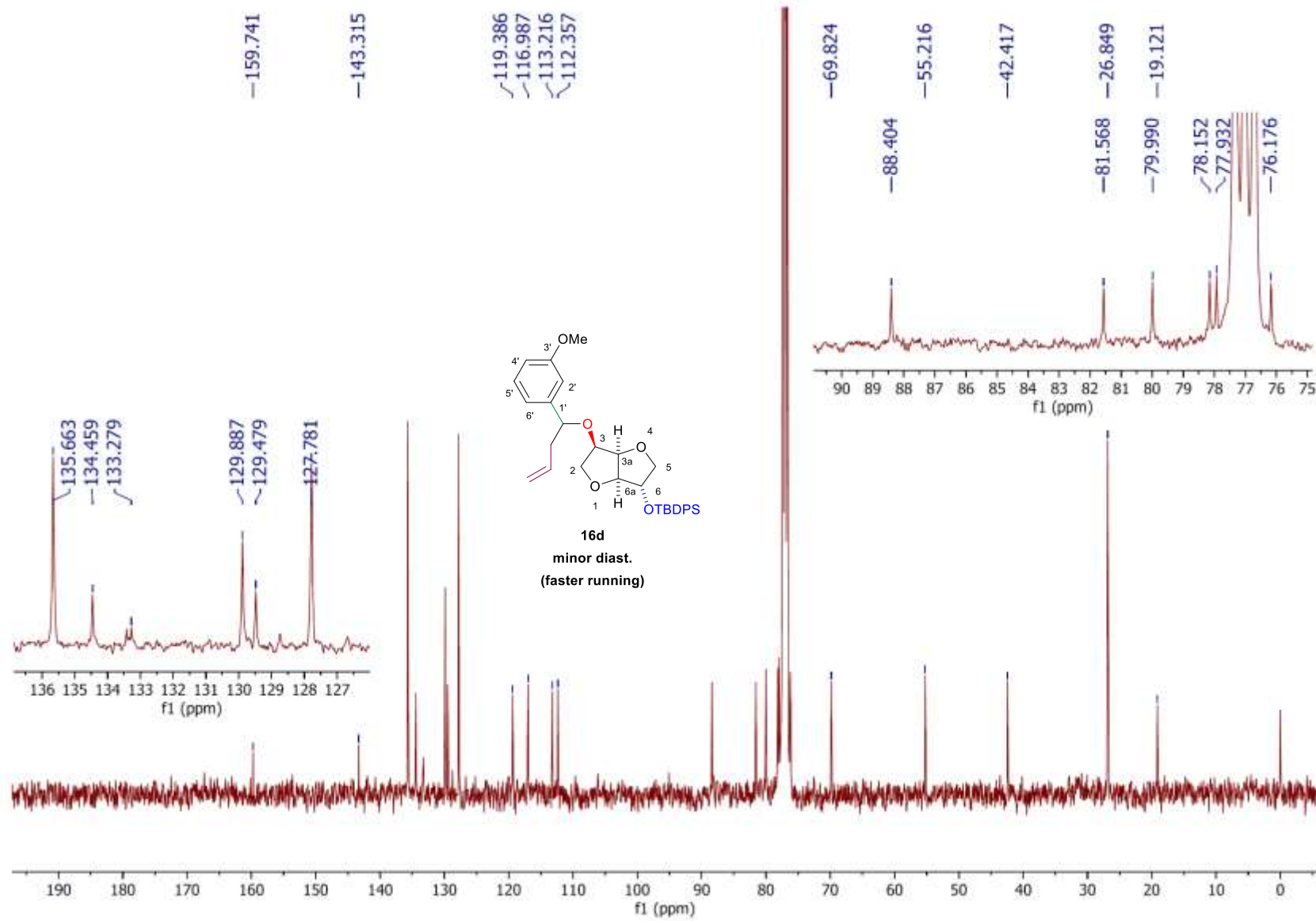


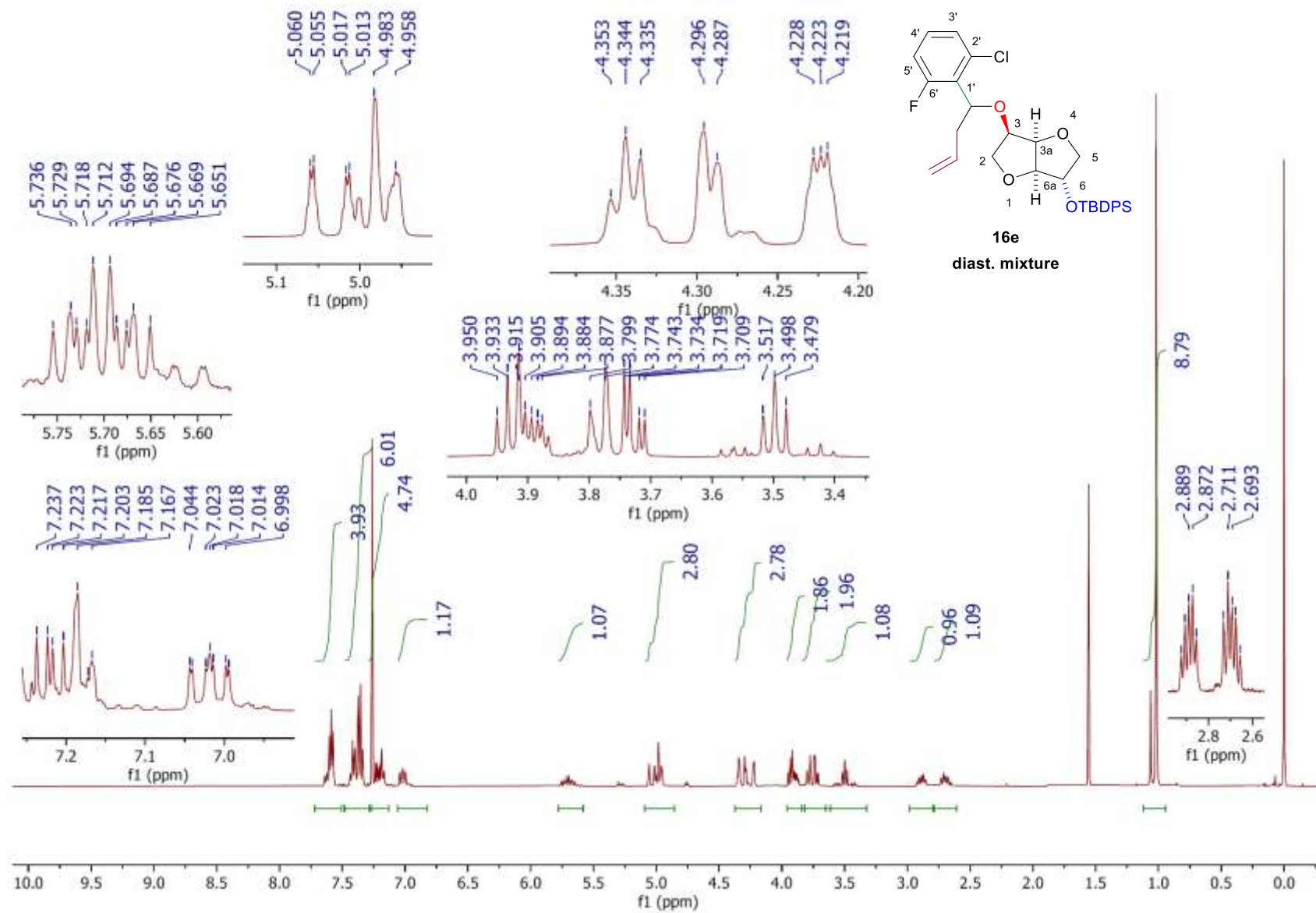


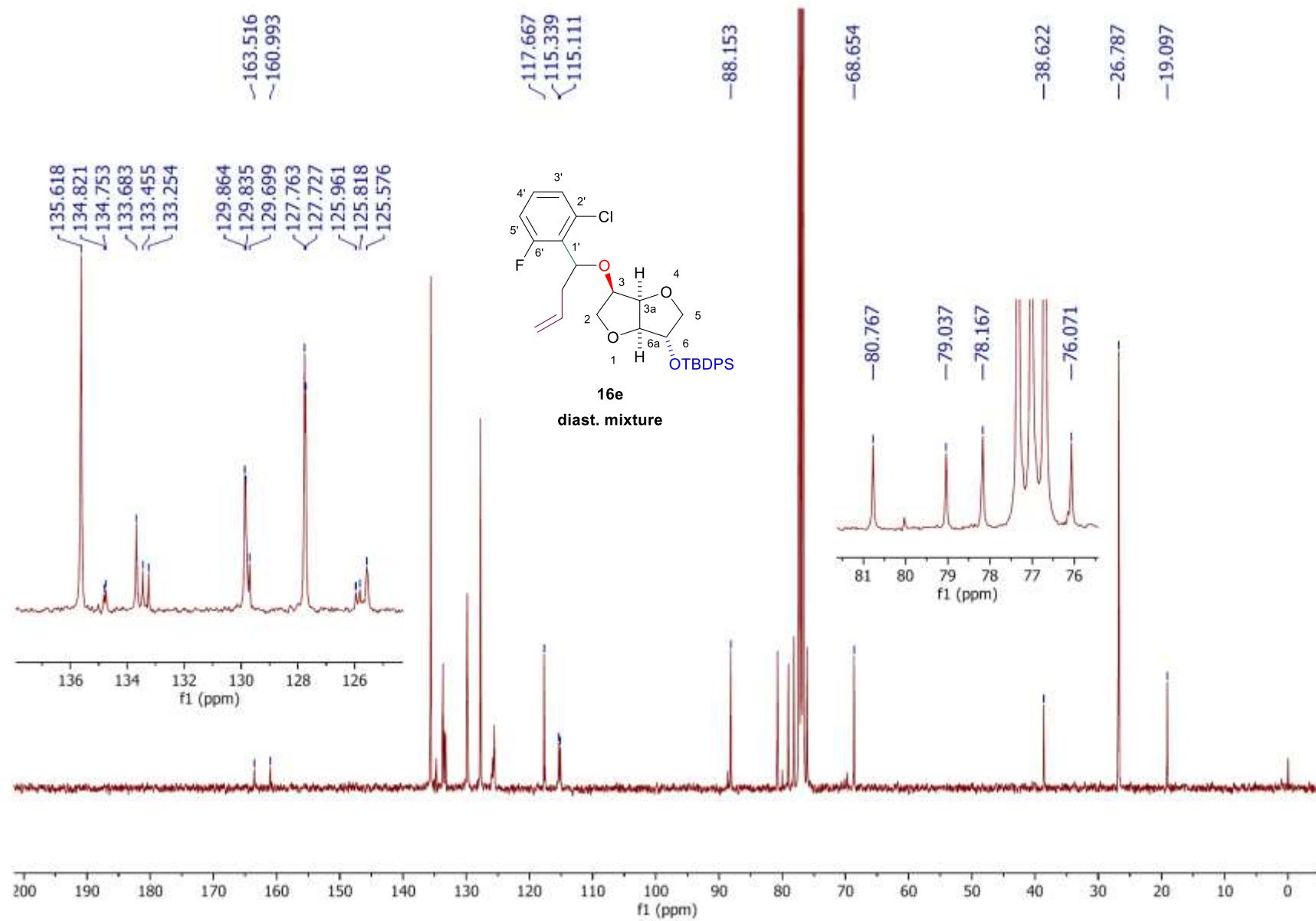
**16d**  
major diast.  
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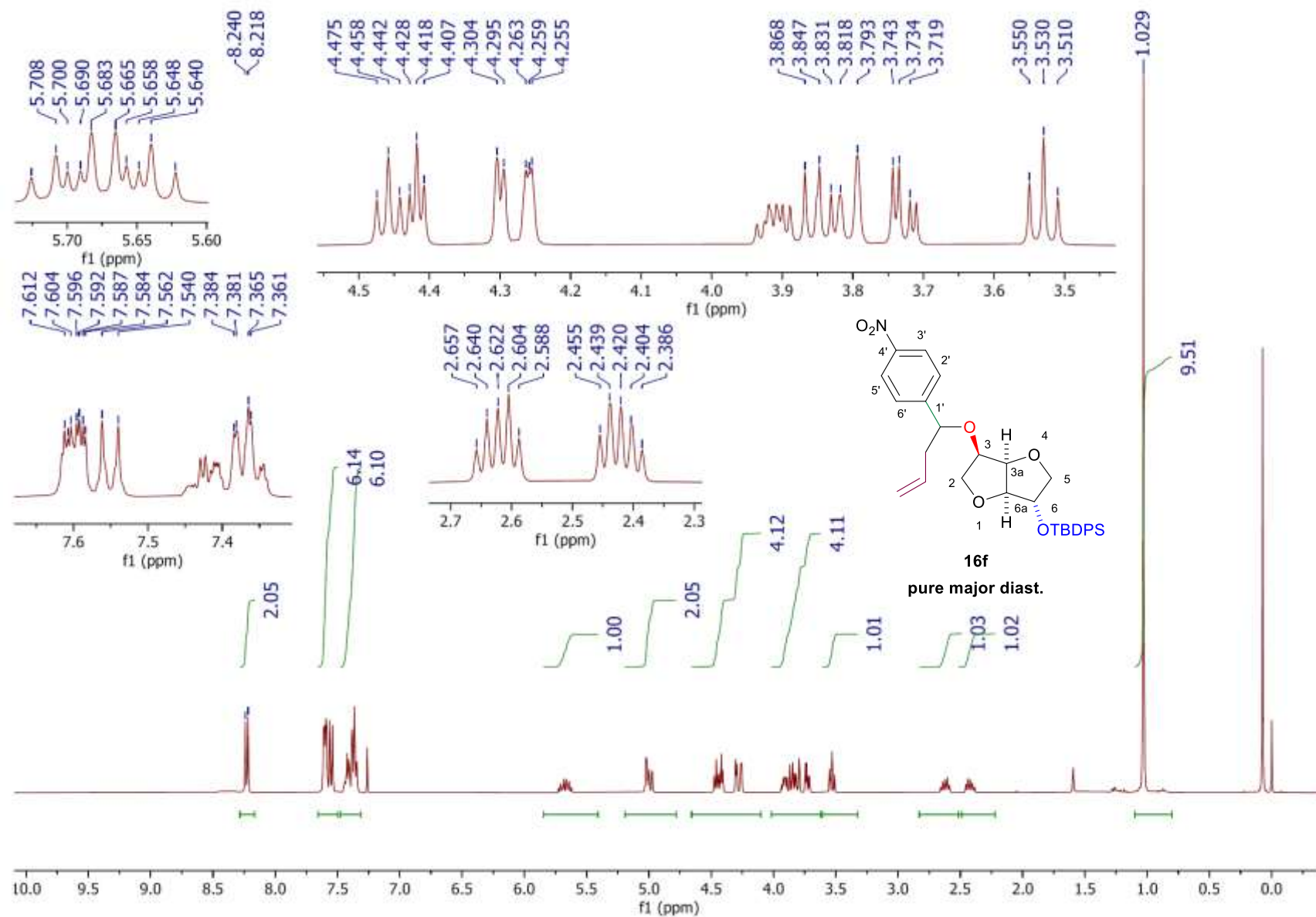


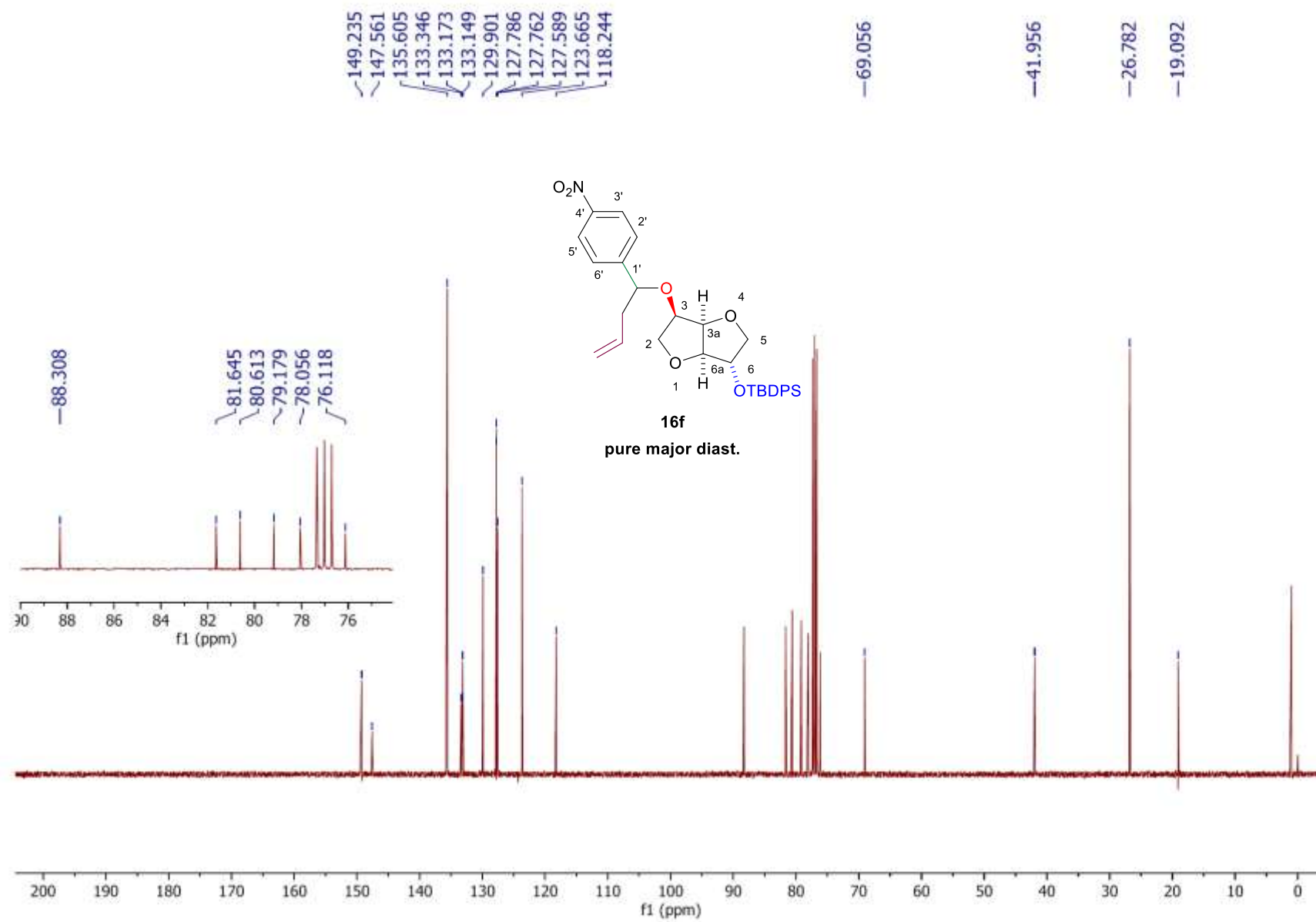


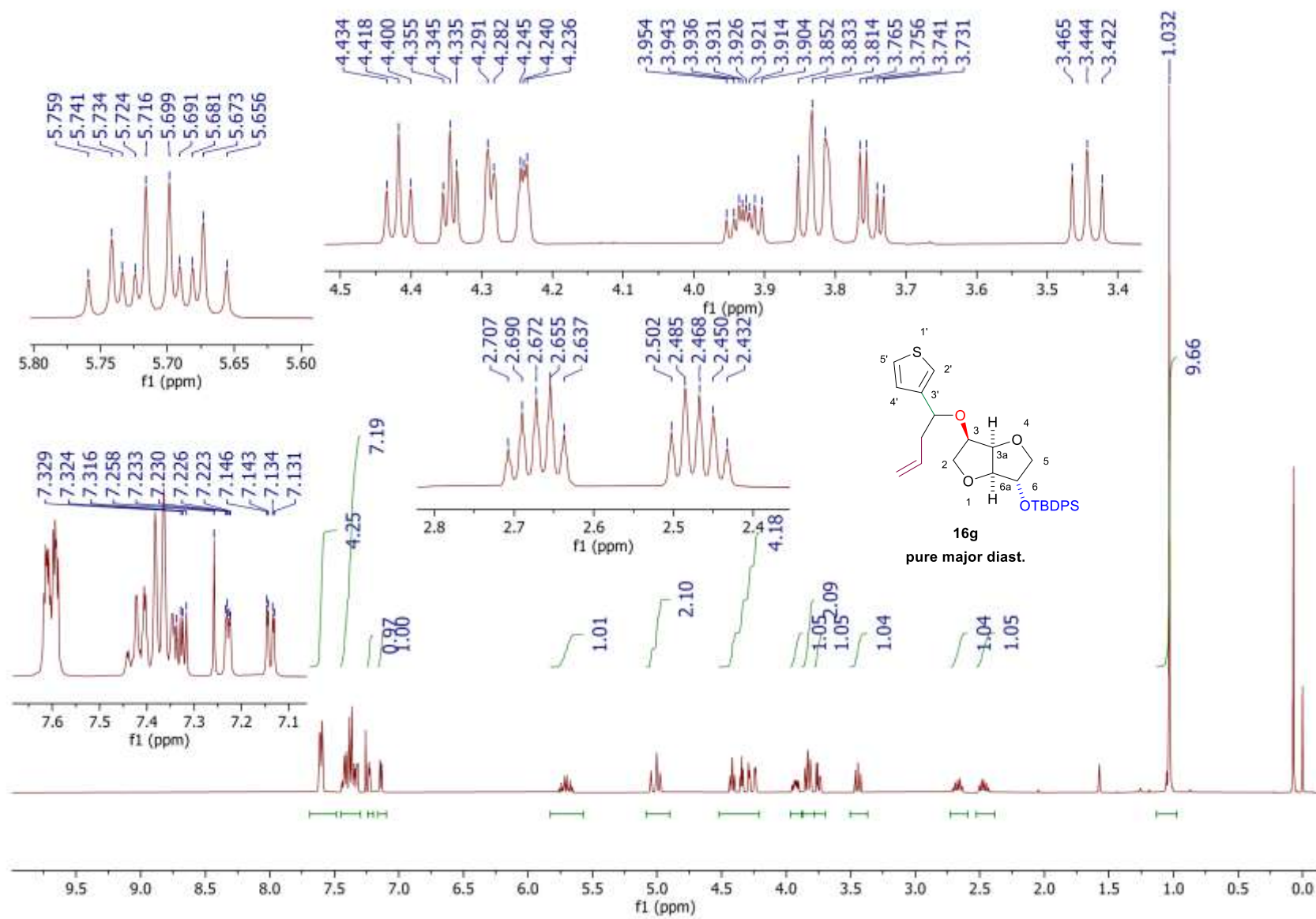


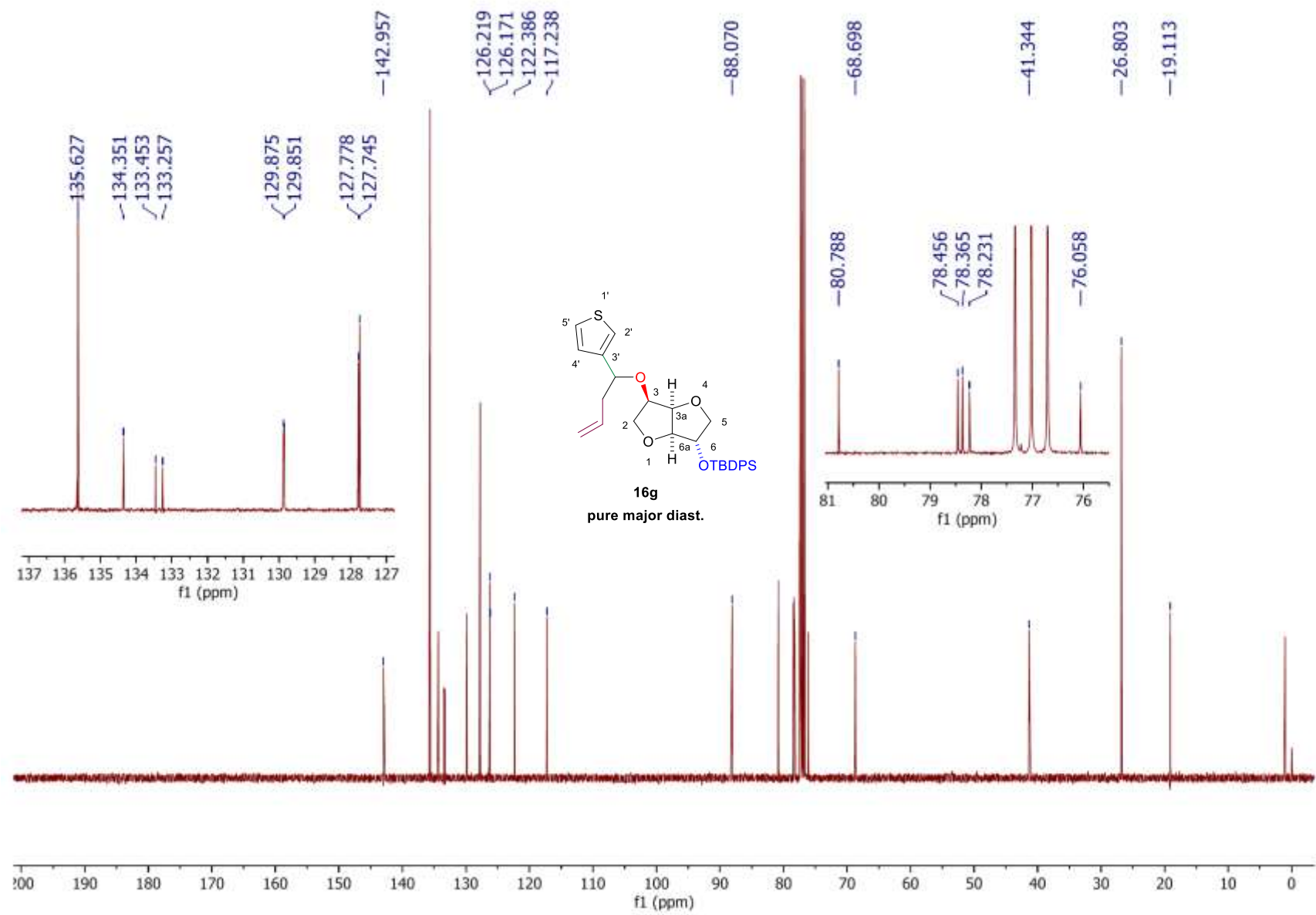


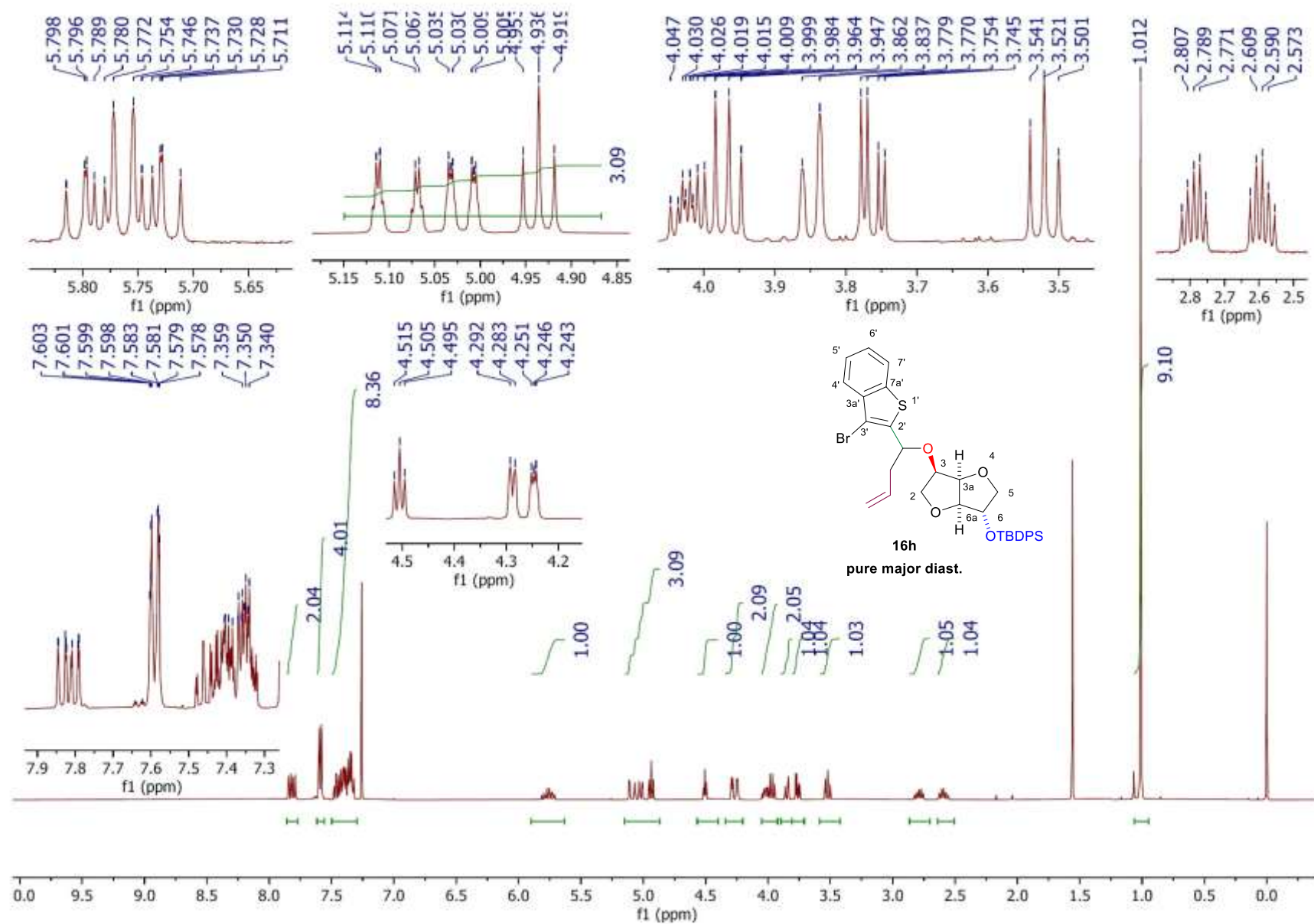


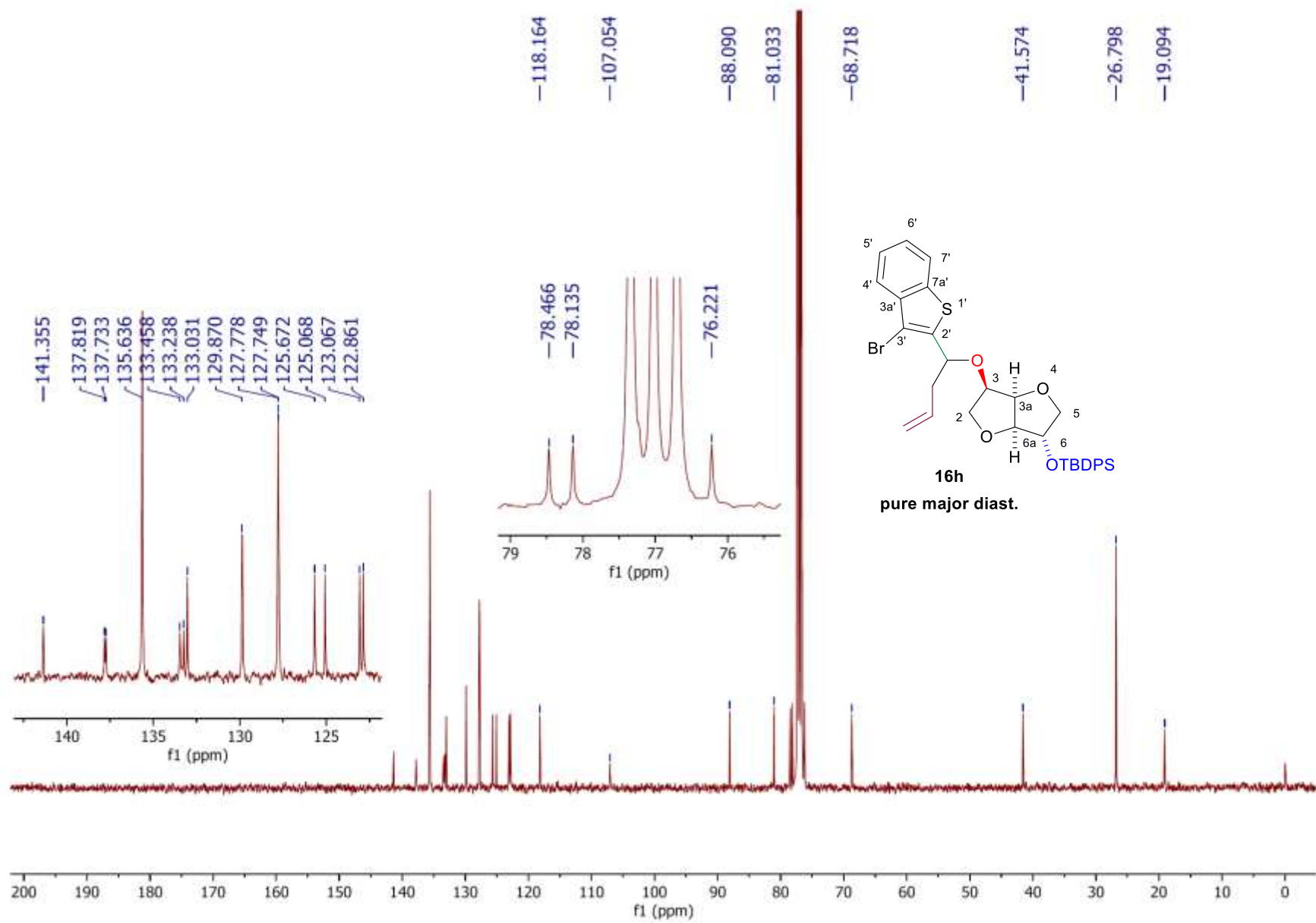


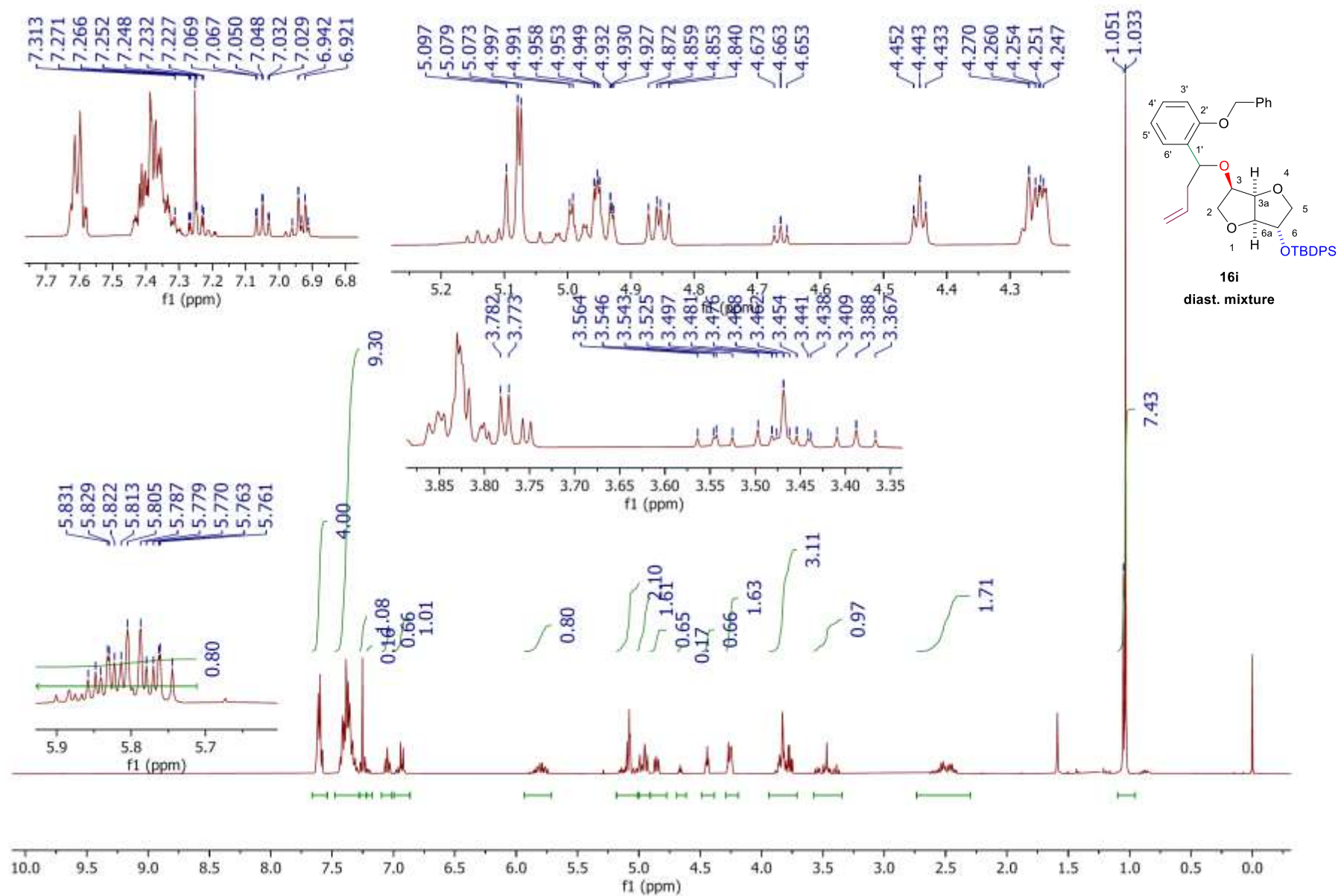




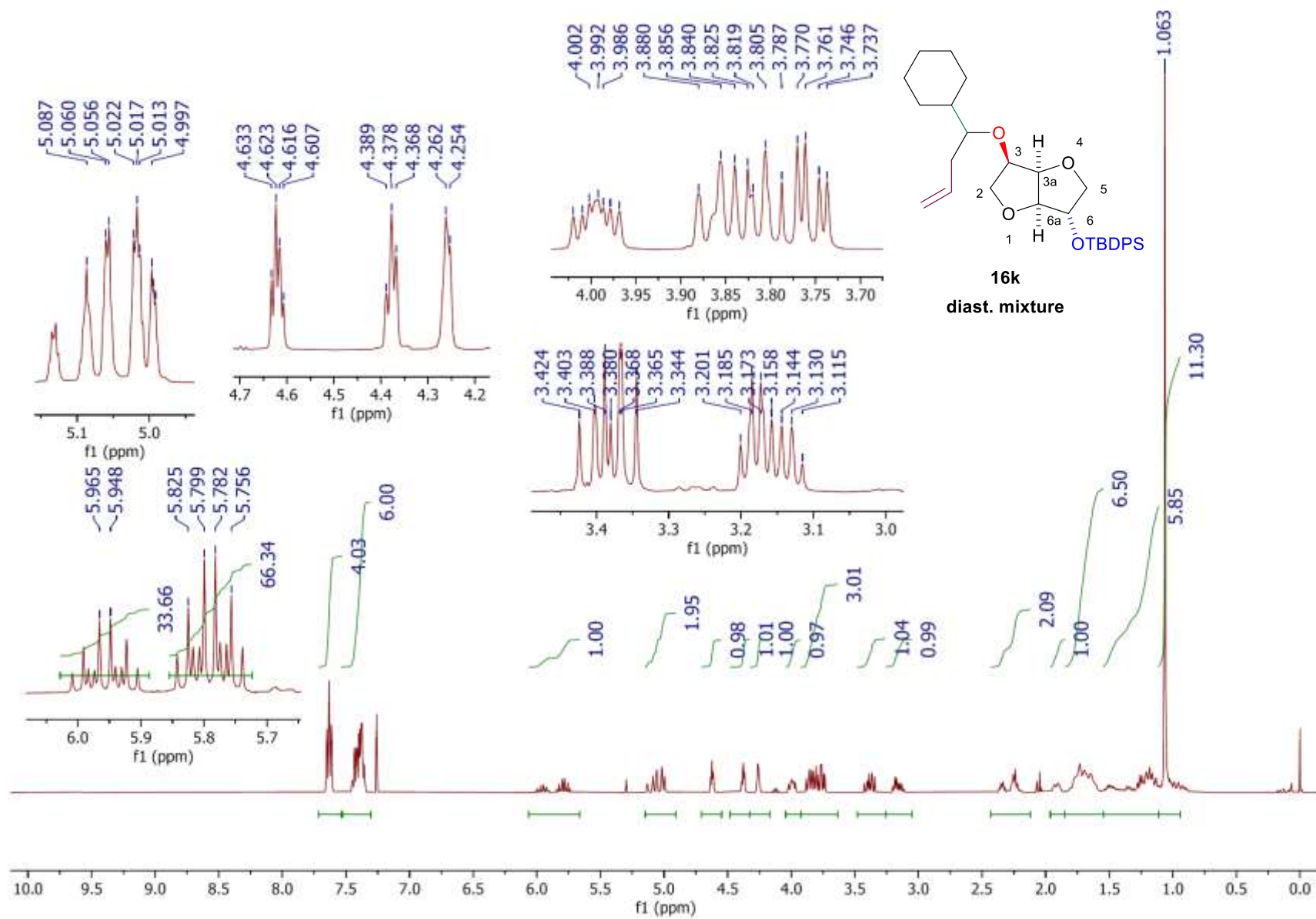


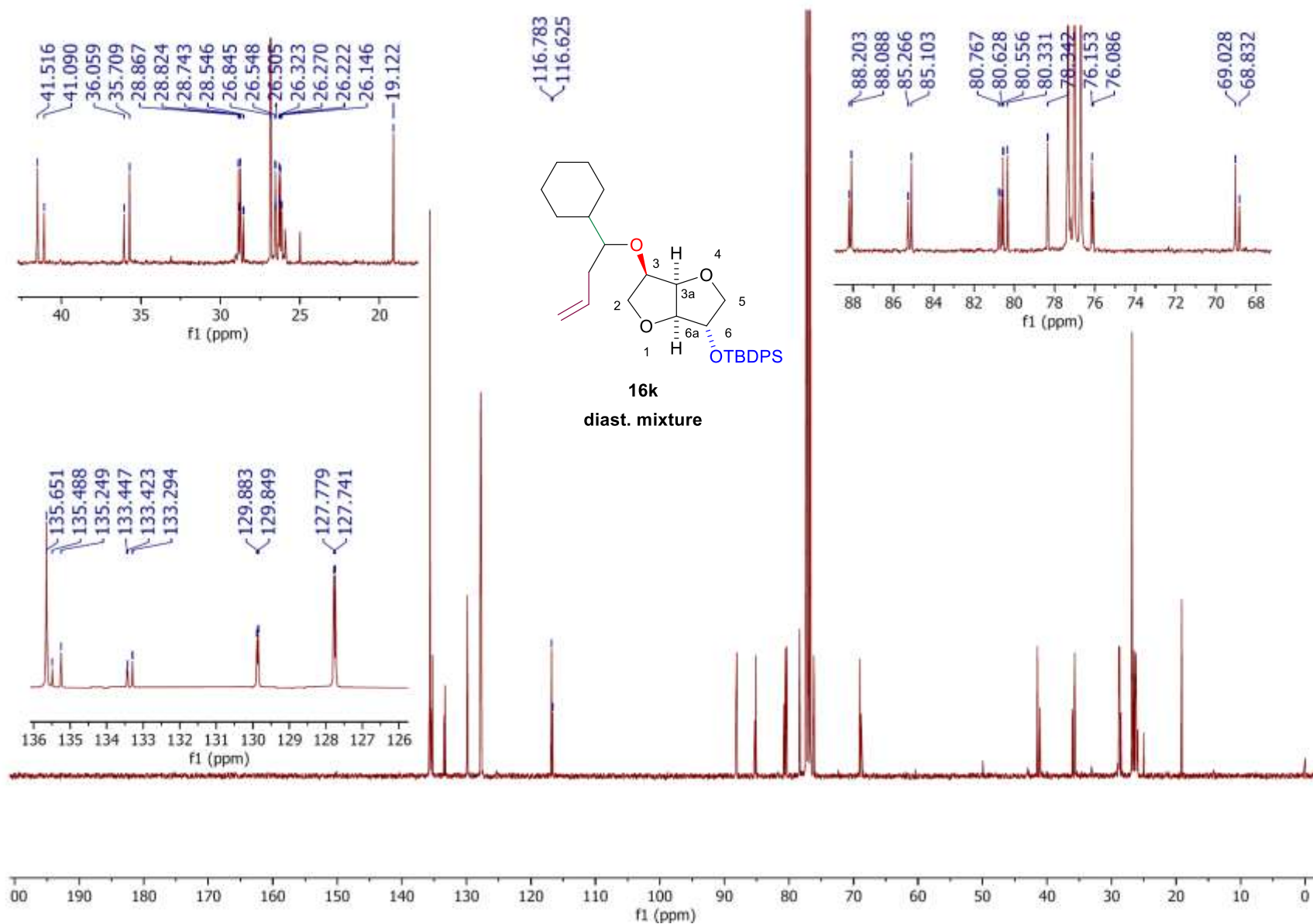


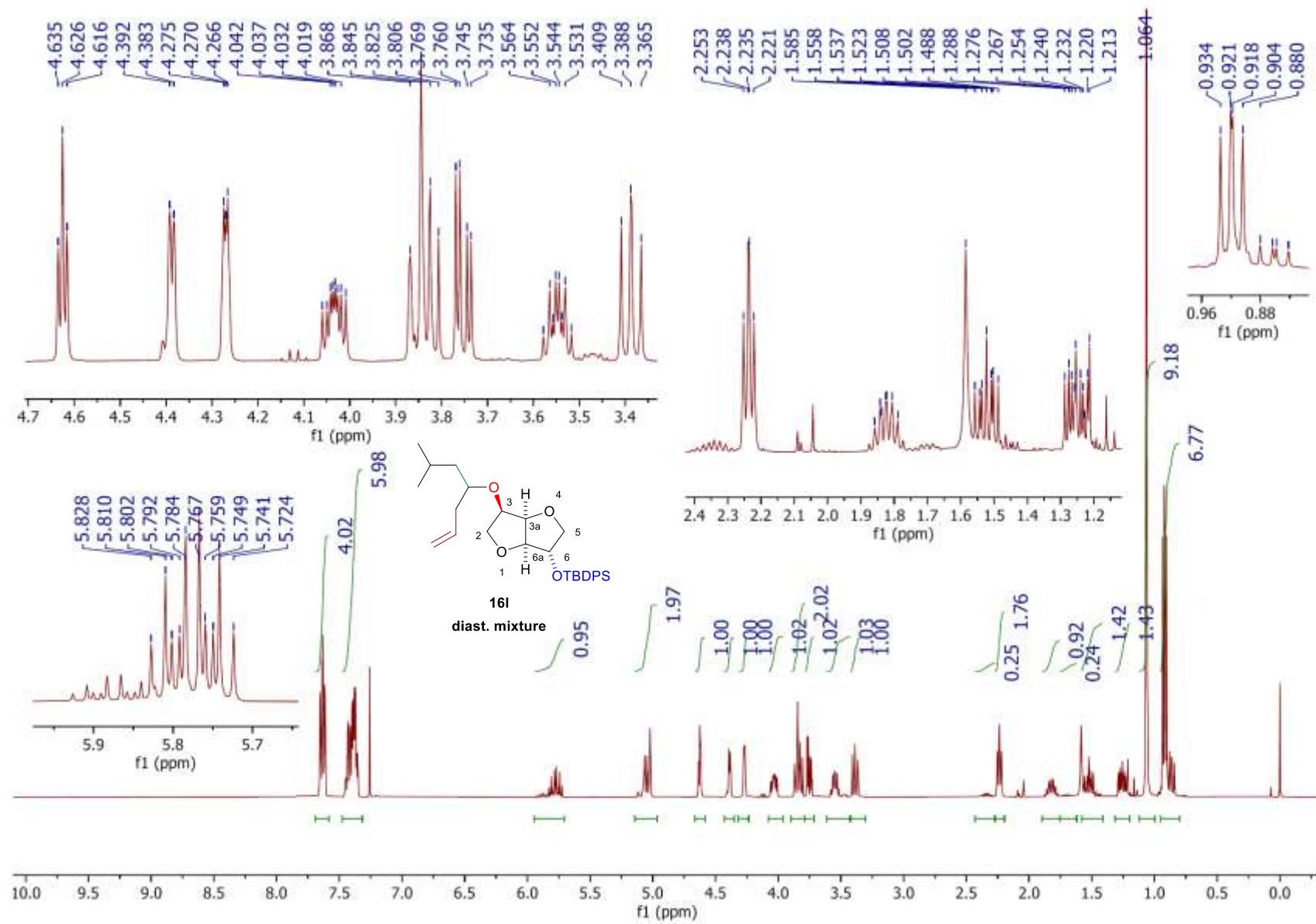


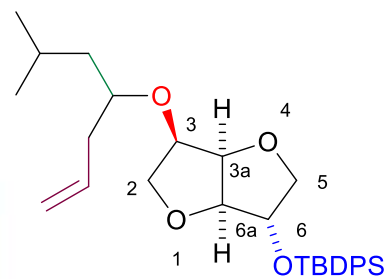
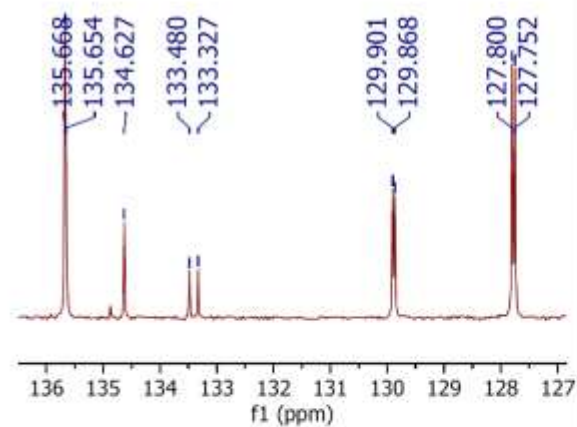
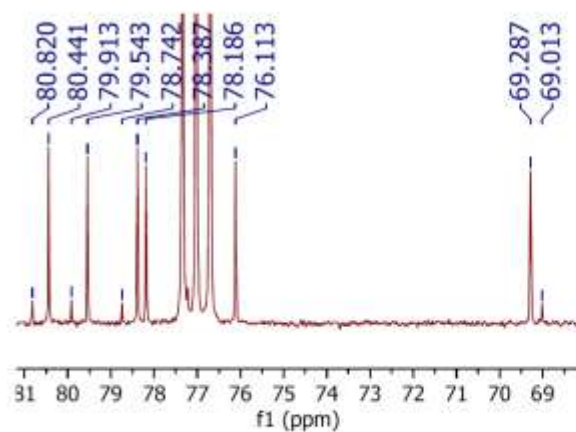












**16l**  
diast. mixture

