# Electronic supplementary information

# Experimental lipophilicity scale for coded and noncoded amino acid residues

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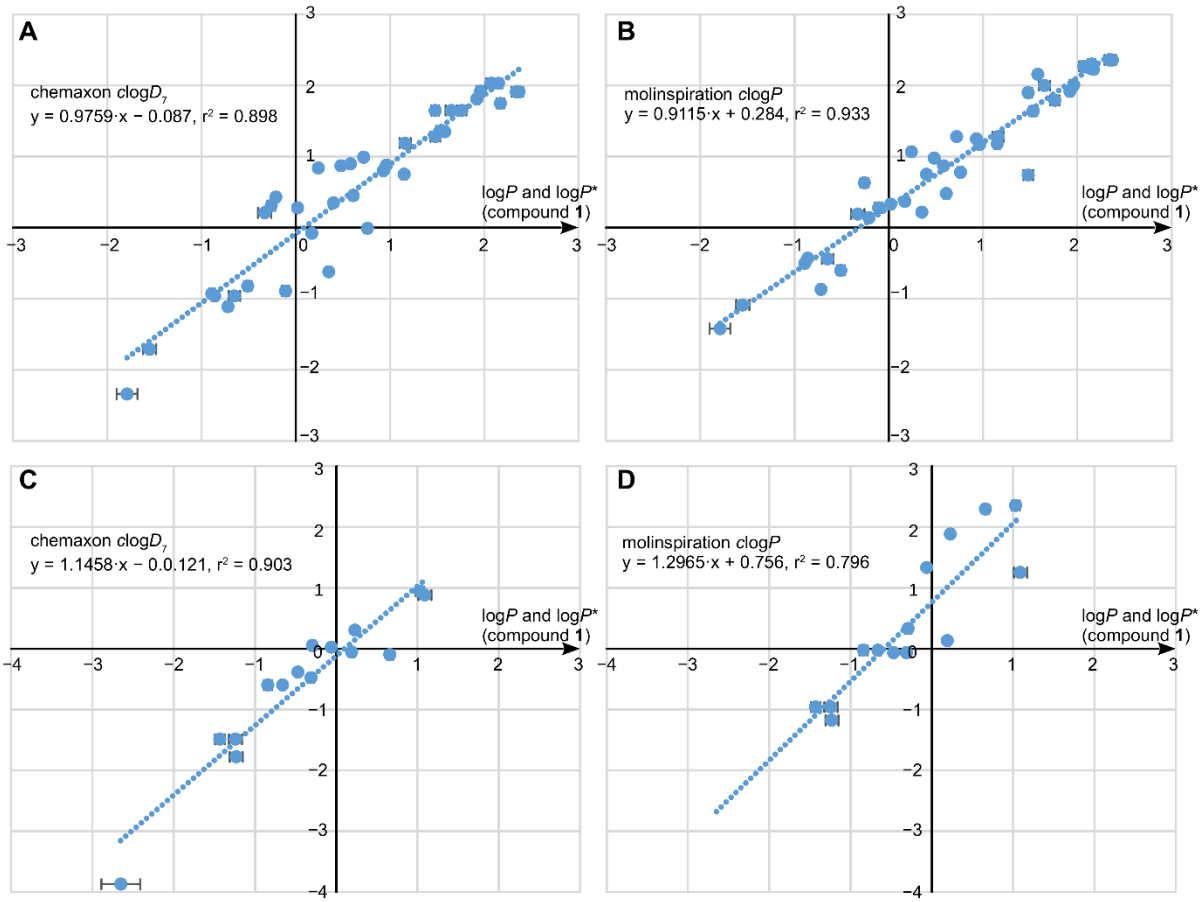


**Fig. S1** Correlations between experimental (x axes) and computed (y axes) log*P* (log$D_7$) values for noncoded amino acid residues. Panels A and B show correlations for 38 noncoded amino acids based on alanine core structure (aromatic, Phe, Tyr, Trp, Met, Lys and others in Table S1). Panels C and D show correlations for 15 proline analogues separately.

The set of analogues:

General (panels A, B): α-Nal, β-Nal, Azu, 4-$CF_3$-Phe, 4-Br-Phe, 4-Cl-Phe, 4-$N_3$-Phe, 4-F-Phe, (Me)Tyr, 4-CN-Phe, 4-AcNH-Phe, 4-$NH_2$-Phe, 3-I-Tyr, 3-$NO_2$-Tyr, 3-F-Tyr, Dopa, 6-Br-Trp, 5-Br-Trp, 5-Cl-Trp, 5-$CH_3$-Trp, 1-$CH_3$-Trp, 5-F-Trp, 5-OH-Trp, 5-$NH_2$-Trp, Nle, Tfnle, Nva, Sem, Aha, Mox, MetO, (Boc)Lys, Sac, (Pro)Lys, (Ac)Lys, (Me)Glu, (Me)Asp, Citr.

Proline analogues (panels C, D): (Bn)Hyp, Oic, (Boc)Amp, 4TfmPro, Ash, Mep, Cys[ΨPro], Dfp, Dhp, Flp, flp, (Ac)Amp, Hyp, hyp, Amp (panel C only).



*OBC,* doi: 10.1039/d1ob01213d

## Protocols

All reactions and manipulations were performed at the room temperature: 21-23°C. The starting amino acids and the reagents were of commercial grade. The solvents were of standard grade ("ACS certified"), and they were used without additional purification. NMR spectra were measured at a spectrometer machine operating at 500 MHz $^{1}$H and 471 MHz $^{19}$F frequencies at 298 K.

Preparation of compounds **1**:

*N*-acetylation:

**Protocol 1:** An amino acid (1 mmol) was mixed with dichloromethane (10 ml), and acetic anhydride was added either as one equivalent (0.1 ml) or in excess (0.5 ml) depending from the presence of the other reactive groups in the structure. The mixture was stirred for a few hours or overnight (5-20 h). A successful reaction produced a clear solution of the product (unreacted amino acids are not soluble in dichloromethane). The reaction vial was left open under a fume hood overnight (20 h) to allow dichloromethane to fully evaporate. Optionally, the residue was dissolved in water or water-acetonitrile (10-20 ml) and freeze-dried.

**Protocol 2:** An amino acid (1 mmol) was mixed with dichloromethane (10 ml), and an excess of acetic anhydride (0.5 ml) was added. *N,N*-Diisopropylethylamine (0.5 ml) was added, and the reaction was stirred overnight (20 h). A successful reaction produced a clear solution (unreacted amino acid is not soluble in dichloromethane). The reaction vial was left open under a fume hood overnight (20 h) allowing the solvent to dry out. Optionally, the residue was dissolved in water or water-acetonitrile (10-20 ml) and freeze-dried, otherwise the material was used in the next step without purification.

**Protocol 3:** An amino acid (1 mmol) was mixed with dichloromethane (10 ml) and *N,N*-diisopropylethylamine (0.7 ml, 4 equiv.). Trimethylsilylchloride (0.4 ml, 3.2 equiv.) was added, and the mixture was stirred for about 15 min. Typically, the reaction produced a clear or slightly turbid solution (unreacted amino acid is not soluble in dichloromethane). Acetic anhydride was added either as one equivalent (0.1 ml) or in excess (0.5 ml) depending from the presence of other potential reactive groups in the structure. The reaction mixture was stirred for about 2-3 h, and then the reaction vial was left open under a fume hood overnight (20 h) allowing the solvent to evaporate. Optionally, the residue was dissolved in water or water-acetonitrile (10-20 ml) and freeze-dried.

*N.B.*: unless a substance contained acetylatable groups in the side-chain, the substance was first acetylated using Protocol 1. If the solution did not clear overnight, the protocol was changed to Protocol 2. If this did not lead to clearance of the solution, the substance was processed by Protocol 3. Protocol 3 was chosen for all substances that contained side-chain groups susceptible to acetylation: thiol, phenol, etc.

Ion-exchange:

**Protocol 4:** The product of the freeze-drying was dissolved in either water (for polar amino acids) or acetonitrile-water 1:1 mixture (for nonpolar amino acids). A cation exchange resin was pre-washed with 1:2 hydrochloric acid and then thoroughly washed with water until a neutral reaction was observed in the eluate (by pH paper). The substance solution was placed on the column and eluted with the solvent. Acidic fractions were collected and freeze-dried affording the *N*-acetylamino acid as a powder.



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*N.B.*: Passing through a cation-exchange column removes *N,N*-diisopropylethylamine and (if any) remaining non-reacted amino acid. The step was not essential, but highly desirable, as it significantly simplified the next esterification and purification steps. A material coming out from the cation-exchange column is typically acidic, such that relatively small amounts of trimethylsilylchloride were sufficient for methanol acidification in Protocol 5. In contrast, material containing *N,N*-diisopropylethylamine required much higher amounts of added acid and prolonged reaction times. Though, for moderately hydrophilic amino acids (log*P* of threonine derivative or lower), a cation-exchange step was essential, since silica gel purification (Protocol 6) was not efficient of separating target product **1** from remaining Hünig's base.

Esterification:

**Protocol 5:** A product from the Protocol 1-4 was dissolved in methanol (2-5 ml). Trimethylsilylchloride was added to create acidic reaction of the medium. Typically, 0.2-0.5 ml of the reagent was added. The strongly acidic reaction of the medium was checked on a pH paper. The solution was stirred overnight (20 h). The solvent was removed under reduced pressure on a rotary evaporator using bath temperature of about 30-35°C.

**Protocol 6:** The residue from the esterification step was purified on a short silica gel column (about 20 g) using ethyl acetate – methanol 20:1 mixture as a starting eluent. For polar amino acids, the original elution with the 20:1 mixture was continued with a changing solvent ratio 20:1 → 5:1 → 2:1. Alternatively, the elution was continued with dichloromethane – methanol 9:1 → 2:1 mixture. The fractions were collected and analysed by thin layer chromatography, which was visualized in an iodine chamber. Iodine visualization worked only for intermediate and nonpolar substances (log*P* ≥ −0.5). Alternatively, the fractions were analysed by dry weight after drying the fraction vials under the fume hood overnight. Fractions were checked by taking a tiny amount in a capillary tube and placing it on a pH paper. If some fraction gave an acidic reaction, their purification was repeated typically resulting in non-acidic material. Compound **1** was obtained as either solid or an oily material in 100-300 mg amount depending from the molecular weight. The identity of the compounds was checked by $^{1}$H NMR spectra in methanol-$d_4$ or DMSO-$d_6$ solution.

Preparation of compounds **2**:

Esterification:

**Protocol 7:** Commercial Fmoc-amino acids were taken on 0.3 mmol amount: Fmoc-(Boc)Lys-OH, Fmoc-(Pbf)Arg-OH, Fmoc(tBu)Asp-OH, Fmoc-(tBu)Glu-OH, Fmoc-(tBu)Ser-OH, and Fmoc-(Boc)Amp-OH, where Amp stands for (*4R*)-aminoproline. The substances were mixed with chloroform (5 ml each). Difluoroethylamine (0.4 g) was mixed with chloroform (30 ml) and *tert*-butyl nitrite (0.8 ml) was added. The solution was stirred for 10 min, and then 5 ml portions were added in every vial containing the Fmoc-amino acids. After about one hour a clear or slightly turbid solution was observed in each reaction vial (unreacted material is poorly soluble in chloroform) indicating successful completion of the reactions. The reaction vials were left open under a fume hood overnight to allow the solvent to dry out. Each crude material was purified on a short silica gel column (20 g) using ethyl acetate – methanol 20:1 mixture as an eluent. Fractions were analysed by thin layer chromatography (iodine chamber) and dry weight after drying the fraction vials overnight. Esters of the Fmoc-amino acids were collected as either solid or greasy material in about 150 mg amount each.

Deprotection:



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**Protocol 8:** A purified product of the previous step (50 mg) was dissolved in dichloromethane (100 μl) and trifluoroacetic acid (100 μl) was added. The solution was stirred for one hour, and 50 μl aliquots were taken to 4 ml vials. The volatiles were blown off by an intense argon stream affording compounds **2**, which were launched directly into the partition measurements. Buffer (2 ml, pH 7) and octan-1-ol (2 ml) was added and the mixture was vigorously shaken for over two hours. The NMR samples were prepared as described in Protocol 9. The measurements of relative concentrations were accomplished by $^{19}F\{^{1}H\}$ NMR in 60-degree pulse experiments below the Ernst angle (acquisition+recycling time either 0.5 or 0.8 s).

In the case of (Pbf)Arg, the deprotection was performed by mixing with 200 μl pure trifluoroacetic acid for two hours.

Partitioning:

**Protocol 9:** A substance (5-10 mg) was placed in a 4 ml glass vial with a screw cap. Water (1 ml) and octan-1-ol (1 ml) was added and the mixture was intensively shaken for over two hours. The vials were let to stand still for a few minutes to allow phase separation, otherwise a quick centrifugation was used to sped up the process. Fractions of each phase were carefully taken using 1 ml plastic syringes (accuracy 0.01 ml) with needles. 0.35 ml of each fraction were placed in identical type 5 mm NMR tubes and 0.20 ml of same deuterated solvent (DMSO-$d_6$, methanol-$d_4$, or acetonitrile-$d_3$) was placed in each tube, creating the total volume of 0.55 ml, which corresponds to over 4 cm height of the solution in the tube. The solutions in the tubes were mixed, and the samples were subjected to the NMR measurements. For each chemical structure the operation was performed in triplicate.

Distribution:

**Protocol 10:** The distribution between buffer (1-2 ml) and octan-1-ol (1 ml) was performed in the same manner as described in Protocol 9. The aqueous phase was either of the buffers:

pH 6: 150 mM 2-(*N*-morpholino)ethanesulfonic acid (MES) buffer adjusted by hydrochloric acid;

pH 7: 150 mM potassium phosphate buffer adjusted by concentrated potassium hydroxide;

pH 8: 150 mM tris(hydroxymethyl)aminomethane (Tris) buffer adjusted by hydrochloric acid;

pH 9: 150 mM borate buffer adjusted by concentrated potassium hydroxide.

The pH accuracy was ±0.1.

It was observed that for non-ionized molecules the experimental log*D* values obtained in this way were slightly higher compared to the log*P* values by ≤ 0.1 units. This observation may be caused by the salting-out effect that occurs in the measurements against 150 mM buffers.

NMR measurements:

**Protocol 11:** NMR tubes were placed in the NMR probes at the conventional depth. The samples were locker, tuned, and shimmed for every sample. All measurements were performed at 298 K. The datasets were copied and applied for measurements without re-adjustment of acquisition or processing parameters (except zero-order phase) and without readjustment of the receiver gain. $^{1}H$ NMR spectra were recorded for all samples, $^{19}F$ NMR and $^{19}F\{^{1}H\}$ NMR spectra were recorder for fluorine-containing analytes (inverse-gated decoupling for decoupled spectra). One-scan and multi-scan measurement were performed on the samples. A single 90-degree pulse experiment with no dummy scans was used for single scan experiments, and a 30-degree pulse experiment with 8 dummy scans was used



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for multiscan measurements. In case when the amount of the substance in two phases was drastically different (log*P*/*D* > 2 or log*P*/*D* < −2), 16-64 scans were used to acquire the spectrum for the concentrated phase, and up to 8,000 scans were used for the less concentrated phase. In this case, the comparison between the phases was made taking into account linear dependence of the resonance intensity from the number of scans.

The spectra were processed in a conventional manner using Fourier transform with 1-2 Hz line broadening and a 5-degree polynomial baseline correction. Baseline correction in selected region of the spectra was used whenever possible. The comparison of the relative analyte concentration in the phases was made by comparison of the absolute integral values and/or by overlaying resonances from two spectra on each other. *P/D* values were read out for several separate resonances for each sample. Averaging these values produced the final log*P/D* value and the standard deviation. An example of the spectra analysis is shown in a dedicated section below.

Distribution of the Dopa derivative **1** in the presence of iron ions:

**Protocol 12:** Dopa derivative **1** was placed in 4 ml glass vials, 5 mg in each vial. Fresh 30 mM iron (II) sulphate solution in deionized water was prepared. Aliquotes of this solution (1 ml, 0.66 ml, 0.33 ml, and 0.17 ml) were placed in the vials containing **1** and water was added to adjust the total volume of the aqueous phase to 1 ml. The final concentration of the iron ions was 5, 10, 20, 30 mM, while one equivalent of **1** corresponded to 1 ml of 20 mM solution. Octan-1-ol (1 ml) was added to each vial and the vials were shaken vigorously for over two hours. Samples of each phase (0.35 ml) were taken by 1 ml plastic syringes into NMR tubes. DMSO-$d_6$ (0.20 ml) was added to each tube. The measurements were performed according to the Protocol 11. The results are summarised in Table S5.

Special additions to the protocols:

For histidine derivative **1**: in the column chromatography purification (Protocol 6), the substance was placed in the original (20:1 ethyl acetate – methanol) eluent. After few fraction, the elution was continued with the eluent mixed with some amount of trimethylamine solution (45 w%, about 0.5 ml).

For cysteine derivative **1**: partitioning and distribution (Protocol 9 and Protocol 10) were performed in the presence of 1-1.5 μl of mercaptoethanol.

For derivatization of 3,5-diiodotyrosine using Protocol 3, the substance was taken as a dihydrate. The substance produced a jelly in the first step. Solution cleared after two more equivalents of *N,N*-diisopropylethylamine and trimethylsilylchloride were added to compensate for the water molecules, then processed as usual.

In case of amino-tryptophan and amino-phenylalanine, the acetylation was performed with one equivalent of acetic anhydride. The reaction produced a mixture of amino- and *N*-acetylamino derivatives, which was used for partitioning without separation. *N*-acetylamino derivatives were slightly more lipophilc as seen using by the resonance of the additional acetyl group.

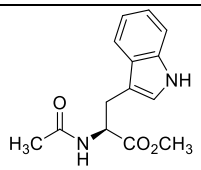
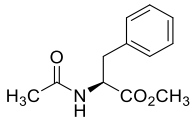
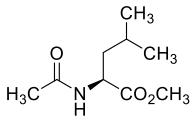
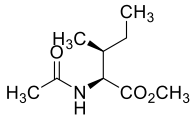
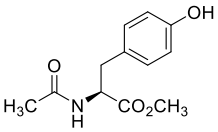
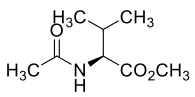
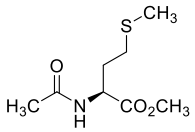
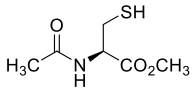
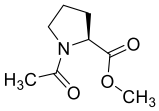
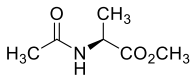
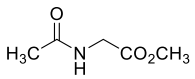
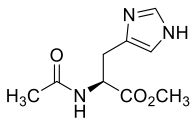
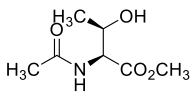
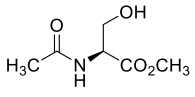
Esterification (Protocol 7) for amino acids containing *N*-butyloxycarbonyl moiety in the side-chain (Boc-lysine or Boc-aminoproline). The substance was filtered on an ion-exchange column after *N*-acetylation. After freeze-drying, the substance was taken up in methanol, and a couple of small drops of trimethylsilylchloride was added (less than 0.025 ml). The mixture was left for prolonged time (about few days), then processed as usual.



*OBC,* doi: 10.1039/d1ob01213d

## Experimental lipophilicity values

**Table S1** Summarized experimental log*P* data for model compounds **1**.

| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| coded | Trp |  | +1.20±0.05 | - |
| coded | Phe |  | +0.92±0.03 | [S1] |
| coded | Leu |  | +0.84±0.04 | [S1] |
| coded | Ile |  | +0.77±0.04 | [S1] |
| coded | Tyr |  | +0.29±0.02 | - |
| coded | Val |  | +0.26±0.03 | [S1] |
| coded | Met |  | +0.13±0.03 | - |
| coded | Cys |  | −0.19±0.05 | - |
| coded | Pro |  | −0.50±0.02 | ([S2]) |
| coded | Ala |  | −0.54±0.03 | [S1] |
| coded | Gly |  | −0.92±0.05 | [S1] |
| coded | His |  | −0.99±0.04 | - |
| coded | Thr |  | −1.01±0.06 | - |
| coded | Ser |  | −1.31±0.05 | - |



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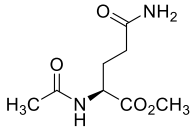
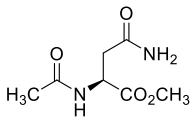
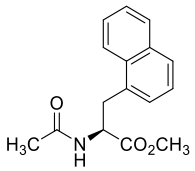
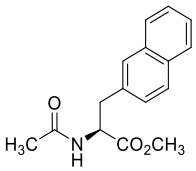
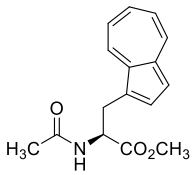
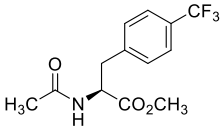
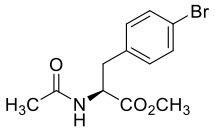
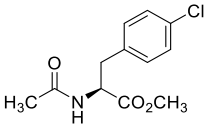
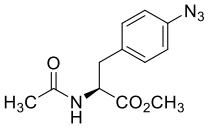
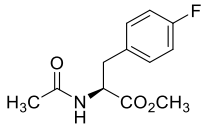
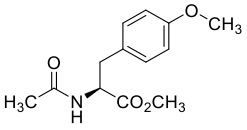
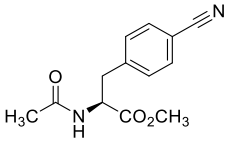
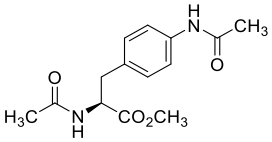
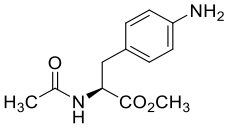
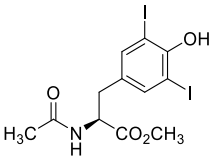
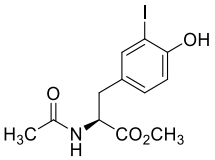
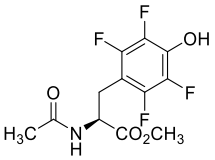
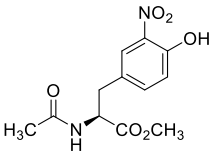
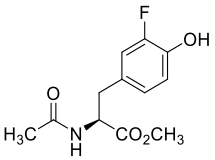
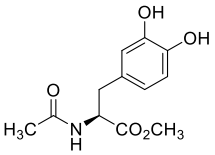
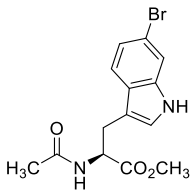
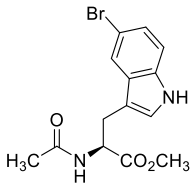
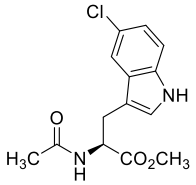
| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| coded | Gln |  | −1.60±0.04 | - |
| coded | Asn |  | −1.74±0.06 | - |
| aromatic | α-Nal |  | +2.08±0.06 | - |
| aromatic | β-Nal |  | +2.15±0.04 | - |
| aromatic | Azu |  | +2.07±0.04 | - |
| Phe analogues | 4-$CF_3$-Phe |  | +1.96±0.04 | - |
| Phe analogues | 4-Br-Phe |  | +1.92±0.03 | - |
| Phe analogues | 4-Cl-Phe |  | +1.76±0.05 | - |
| Phe analogues | 4-$N_3$-Phe |  | +1.58±0.02 | - |
| Phe analogues | 4-F-Phe |  | +1.16±0.06 | - |
| Phe analogues | (Me)Tyr |  | +0.92±0.01 | - |
| Phe analogues | 4-CN-Phe |  | +0.58±0.02 | - |
| Phe analogues | 4-AcNH-Phe |  | +0.02±0.03 | - |

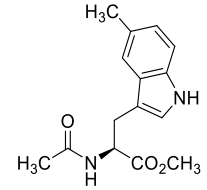
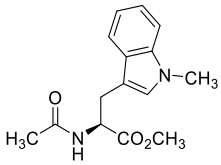
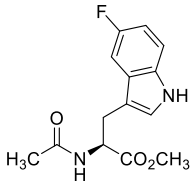
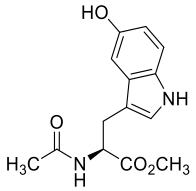
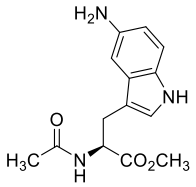
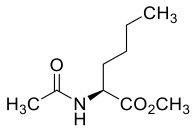
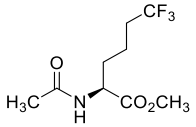
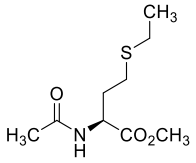
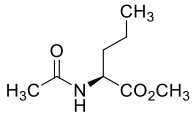
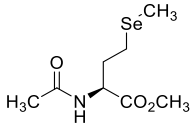
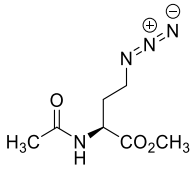


*OBC*, doi: 10.1039/d1ob01213d

| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| Phe analogues | 4-$NH_2$-Phe |  | −0.33±0.07 | - |
| Tyr analogues | 3,5-diI-Tyr |  | +1.58±0.15 | |
| Tyr analogues | 3-I-Tyr |  | +1.48±0.04 | - |
| Tyr analogues | 2,3,5,6-tetraF-Tyr |  | +0.98±0.12 | - |
| Tyr analogues | 3-$NO_2$-Tyr |  | +0.76±0.03 | - |
| Tyr analogues | 3-F-Tyr |  | +0.48±0.02 | - |
| Tyr analogues | Dopa |  | −0.21±0.02 | - |
| Trp analogues | 6-Br-Trp |  | +2.37±0.04 | - |
| Trp analogues | 5-Br-Trp |  | +2.34±0.05 | - |
| Trp analogues | 5-Cl-Trp |  | +2.17±0.04 | - |

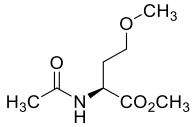
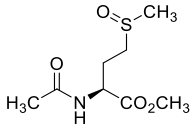
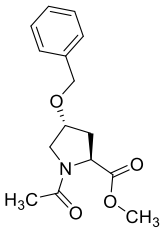
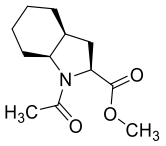
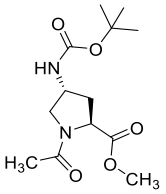
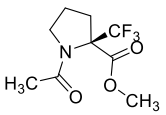
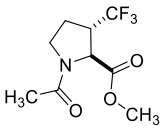
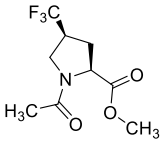
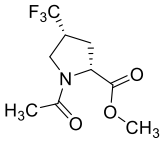
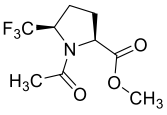
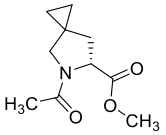
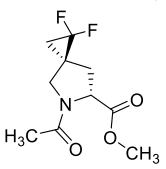


*OBC*, doi: 10.1039/d1ob01213d

| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| Trp analogues | 5-$CH_3$-Trp |  | +1.65±0.06 | - |
| Trp analogues | 1-$CH_3$-Trp |  | +1.53±0.04 | - |
| Trp analogues | 5-F-Trp |  | +1.48±0.05 | - |
| Trp analogues | 5-OH-Trp |  | +0.24±0.02 | - |
| Trp analogues | 5-$NH_2$-Trp |  | −0.26±0.04 | - |
| Met analogues | Nle |  | +0.93±0.01 | - |
| Met analogues | Tfnle |  | +0.72±0.02 | - |
| Met analogues | Eth |  | +0.56±0.03 | - |
| Met analogues | Nva |  | +0.40±0.02 | - |
| Met analogues | Sem |  | +0.35±0.02 | - |
| Met analogues | Aha |  | −0.11±0.04 | - |

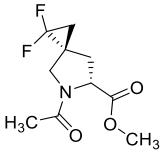
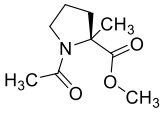
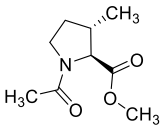
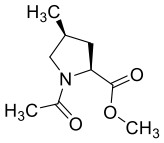
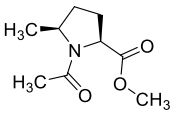
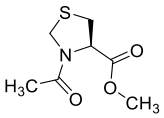
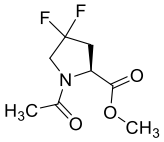
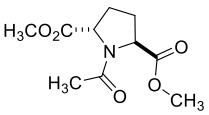
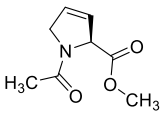
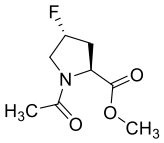
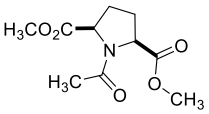
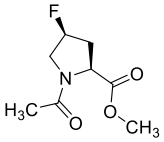
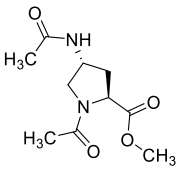


*OBC*, doi: 10.1039/d1ob01213d

| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| Met analogues | Mox |  | −0.65±0.06 | - |
| Met analogues | MetO |  | −1.79±0.11 | - |
| Pro analogues | (Bn)Hyp |  | +1.09±0.08 | - |
| Pro analogues | Oic |  | +1.03±0.05 | [S1] |
| Pro analogues | (Boc)Amp |  | +0.66±0.04 | - |
| Pro analogues | 2TfmPro |  | +0.41±0.04 | [S3] |
| Pro analogues | 3TfmPro |  | +0.35±0.05 | [S3] |
| Pro analogues | 4TfmPro |  | +0.23±0.02 | [S3,S4] |
| Pro analogues | 4TfmPro |  | +0.24±0.01 | [S4] |
| Pro analogues | 5TfmPro |  | +0.28±0.06 | [S3] |
| Pro analogues | Ash |  | +0.19±0.03 | [S4] |
| Pro analogues | c$F_2$Ash |  | +0.18±0.03 | [S4] |

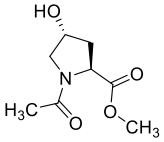
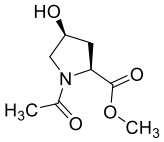
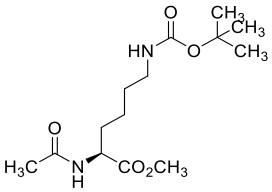
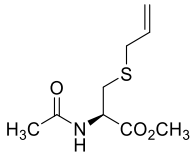
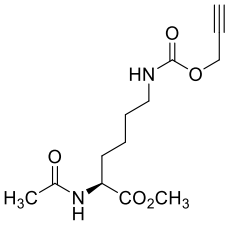
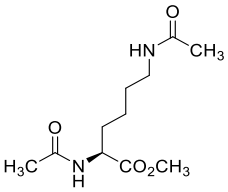
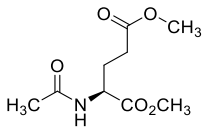
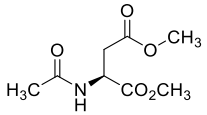
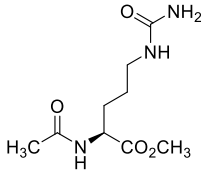
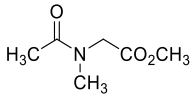


*OBC*, doi: 10.1039/d1ob01213d

| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| Pro analogues | *t*$F_2$Ash |  | +0.03±0.02 | [S4] |
| Pro analogues | 2Mep |  | −0.06±0.06 | [S3] |
| Pro analogues | 3Mep |  | −0.04±0.05 | [S3] |
| Pro analogues | Mep |  | −0.06±0.02 | [S3] |
| Pro analogues | 5Mep |  | −0.14±0.07 | [S3] |
| Pro analogues | Cys[ΨPro] |  | −0.31±0.04 | - |
| Pro analogues | Dfp |  | −0.29±0.04 | - |
| Pro analogues | (Me)*r*Prc |  | −0.43±0.03 | [S2] |
| Pro analogues | Dhp |  | −0.47±0.02 | - |
| Pro analogues | Flp |  | −0.66±0.03 | [S3,S4] |
| Pro analogues | (Me)*m*Pdc |  | −0.74±0.05 | [S2] |
| Pro analogues | flp |  | −0.84±0.05 | [S3,S4] |
| Pro analogues | (Ac)Amp |  | −1.23±0.08 | - |



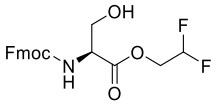
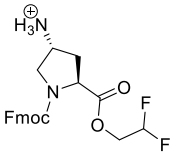
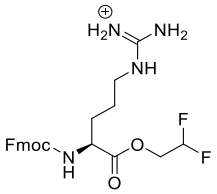
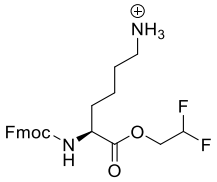
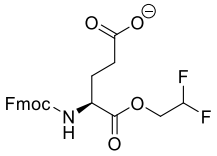
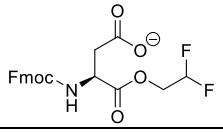
*OBC*, doi: 10.1039/d1ob01213d

| group | amino acid code | structure | log*P* | reference |
|---|---|---|---|---|
| Pro analogues | Hyp |  | −1.24±0.08 | [S3] |
| Pro analogues | hyp |  | −1.43±0.06 | [S3] |
| Lys analogues | (Boc)Lys |  | +1.15±0.03 | - |
| Lys analogues | Sac |  | +0.61±0.03 | - |
| Lys analogues | (Pro)Lys |  | +0.17±0.02 | - |
| Lys analogues | (Ac)Lys |  | −0.89±0.03 | - |
| miscellaneous | (Me)Glu |  | −0.51±0.04 | - |
| miscellaneous | (Me)Asp |  | −0.72±0.03 | - |
| miscellaneous | Citr |  | −1.55±0.07 | - |
| miscellaneous | Sar |  | −0.86±0.03 | [S1] |



*OBC*, doi: 10.1039/d1ob01213d

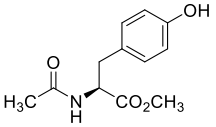
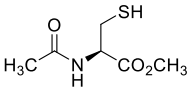
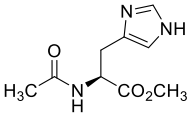
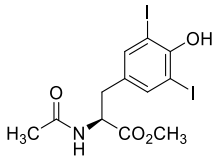
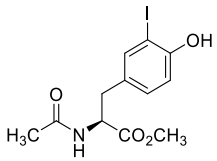
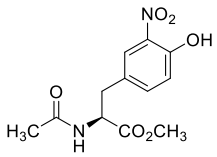
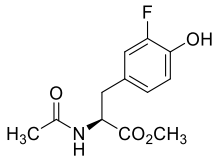
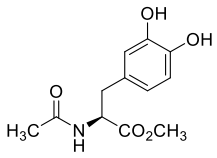
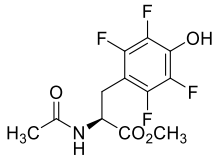
**Table S2** Summarized experimental log$D_7$ data for compounds **2**.

| amino acid code | structure | experimental log$D_7$ |
|---|---|---|
| Ser |  | +3.50±0.13 |
| Amp |  | +2.16±0.06 |
| Arg |  | +1.56±0.04 |
| Lys |  | +1.54±0.06 |
| Glu |  | +1.28±0.12 |
| Asp |  | +0.92±0.06 |



*OBC*, doi: 10.1039/d1ob01213d

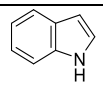
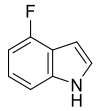
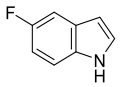
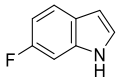
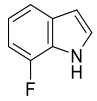
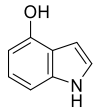
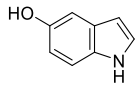
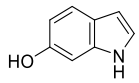
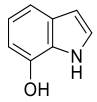
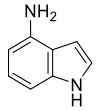
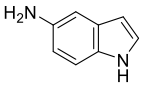
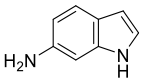
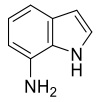
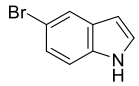
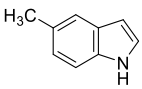
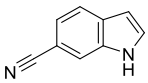
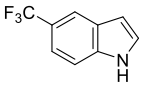
**Table S3** Summarized experimental log*D* data for compounds **1**.

| amino acid code | structure | log$D_6$ | log$D_7$ | log$D_8$ | log$D_9$ |
|---|---|---|---|---|---|
| Tyr |  | - | +0.43±0.08 | +0.29±0.03 | +0.32±0.03 |
| Cys |  | - | −0.10±0.11 | −0.24±0.06 | −0.58±0.06 |
| His |  | −1.33±0.05 | −0.98±0.04 | −0.97±0.06 | - |
| 3,5-diI-Tyr |  | +2.18±0.05 | +1.95±0.05 | +0.85±0.04 | 0.00±0.04 |
| 3-I-Tyr |  | - | +1.58±0.04 | +1.29±0.02 | +0.79±0.03 |
| 3-$NO_2$-Tyr |  | +0.77±0.03 | +0.56±0.02 | −0.30±0.02 | −1.03±0.02 |
| 3-F-Tyr |  | - | +0.58±0.06 | +0.35±0.04 | −0.02±0.03 |
| Dopa |  | - | −0.11±0.02 | −0.19±0.04 | −2.10±0.12 |
| 2,3,5,6-tetraF-Tyr |  | - | −0.06±0.02 | −0.74±0.08 | −2.68±0.04 |



*OBC*, doi: 10.1039/d1ob01213d

**Table S4** Summarized experimental log*P* / log$D_7$ data for substituted indoles.

| chemical structure | substituent | log*P* | log$D_7$ | reference |
|---|---|---|---|---|
|  | - | +2.20±0.04 | - | [S5] |
|  | 4-F | +2.58±0.13 | - | [S5] |
|  | 5-F | +2.56±0.07 | - | [S5] |
|  | 6-F | +2.61±0.06 | - | [S5] |
|  | 7-F | +2.66±0.05 | - | [S5] |
|  | 4-OH | +1.19±0.03 | - | - |
|  | 5-OH | +1.24±0.02 | - | - |
|  | 6-OH | +1.34±0.03 | - | - |
|  | 7-OH | +1.68±0.04 | - | - |
|  | 4-$NH_2$ | +0.71±0.01 | +0.82±0.02 | - |
|  | 5-$NH_2$ | +0.63±0.03 | +0.67±0.03 | - |
|  | 6-$NH_2$ | +0.86±0.03 | +0.92±0.02 | - |
|  | 7-$MH_2$ | +1.34±0.06 | +1.41±0.04 | - |
|  | 5-Br | +3.40±0.20 | - | - |
|  | 5-$CH_3$ | +2.71±0.09 | - | - |
|  | 6-CN | +2.47±0.07 | - | - |
|  | 5-$CF_3$ | +3.65±0.03 | - | - |



*OBC*, doi: 10.1039/d1ob01213d

**Table S5** Distribution of Dopa derivative **1** in the presence of iron

| [$Fe^{2+}$] | log$D_{Fe}$ |
|---|---|
| 5 mM | −0.16±0.07 |
| 10 mM | −0.12±0.10 |
| 20 mM (1 equivalent) | −0.13±0.06 |
| 30 mM | −0.12±0.08 |

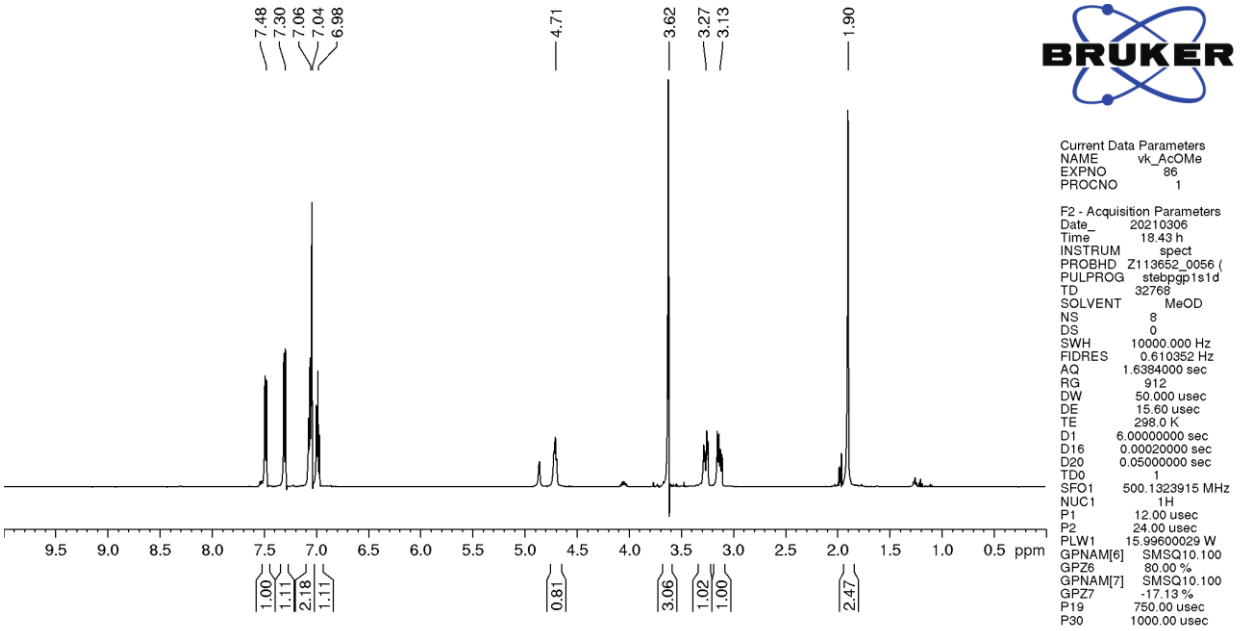


*OBC*, doi: 10.1039/d1ob01213d

## NMR spectra of model compounds 1

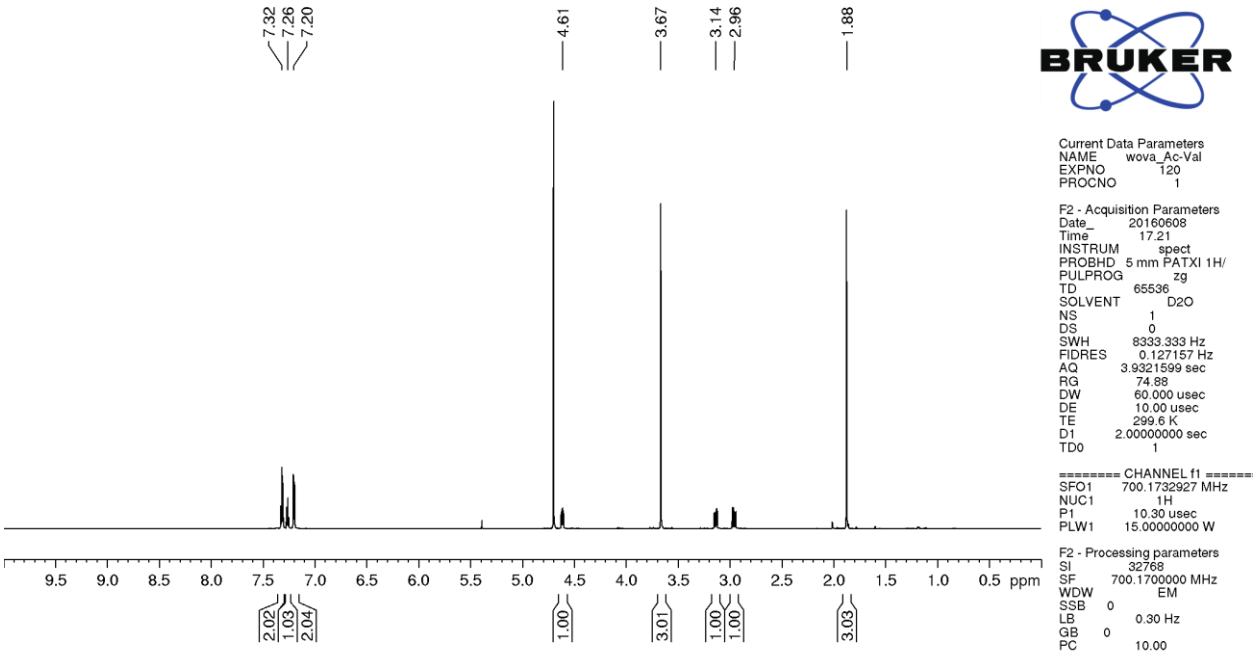
Ac-Trp-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.48 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 7.04 (s, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 4.71 (m, 1H), 3.62 (s, 3H), 3.27 (dd, *J* = 14.5 and 5.4 Hz, 1H), 3.13 (dd, *J* = 14.6 and 7.6 Hz, 1H), 1.90 (s, 3H).




Ac-Phe-$OCH_3$ in deuterium oxide:

$^1$H NMR (700 MHz): 7.32 (m, 2H), 7.26 (m, 1H), 7.20 (m, 2H), 4.61 (dd, *J* = 8.7 and 5.9 Hz, 1H), 3.67 (s, 3H), 3.14 (dd, *J* = 14.0 and 5.8 Hz, 1H), 2.96 (dd, *J* = 14.0, 8.9 Hz, 1H), 1.88 (s, 3H).

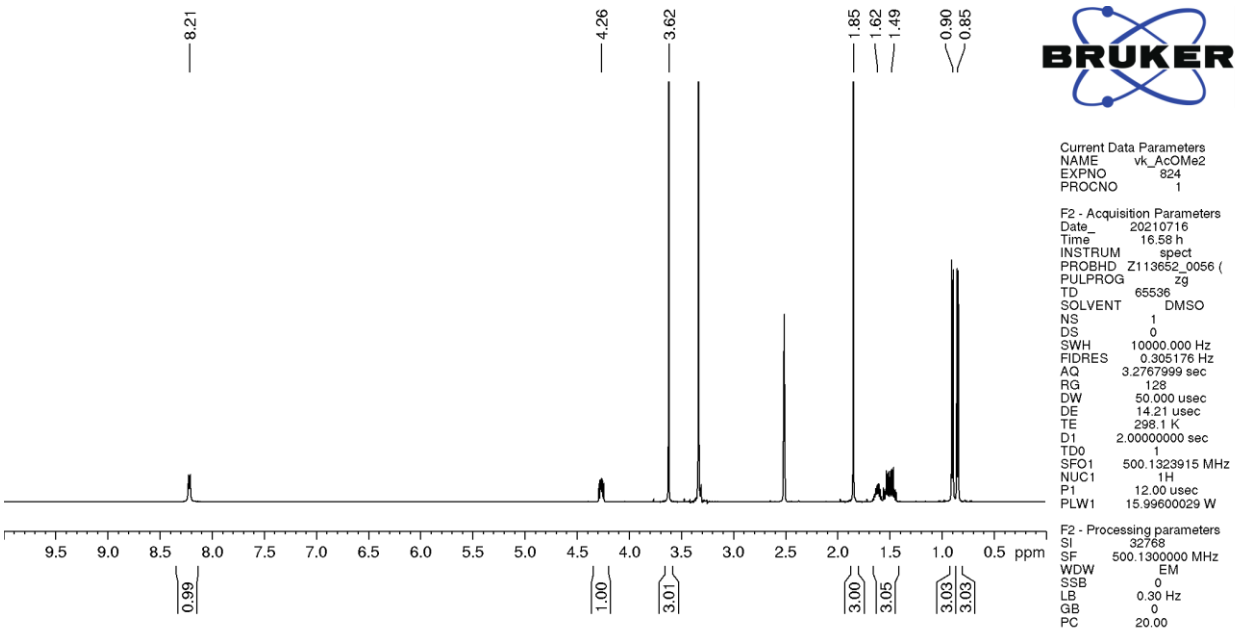





*OBC,* doi: 10.1039/d1ob01213d

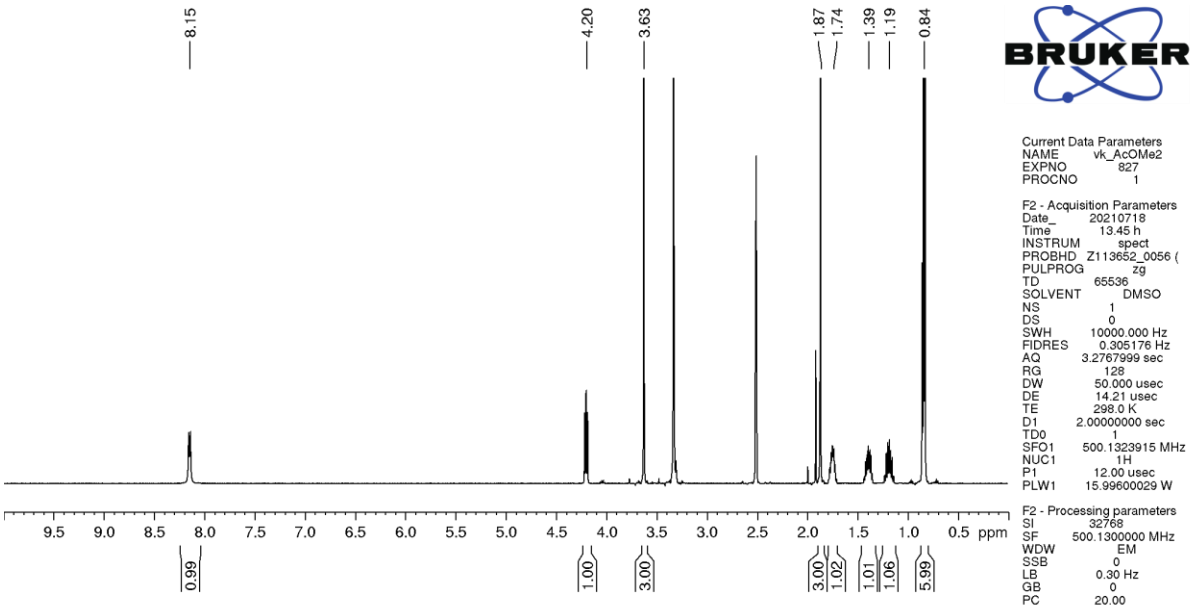
Ac-Leu-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.21 (d, *J* = 7.9 Hz, 1H), 4.26 (dt, *J* = 7.8 and 5.0 Hz, 1H), 3.62 (s, 3H), 1.85 (s, 3H), 1.62 (m, 1H), 1.49 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H).




Ac-Ile-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.15 (d, *J* = 8.0 Hz, 1H), 4.20 (dd, *J* = 7.8 and 6.8 Hz, 1H), 3.63 (s, 3H), 1.87 (s, 3H), 1.74 (m, 1H), 1.39 (m, 1H), 1.19 (m, 1H), 0.84 (m, 6H).

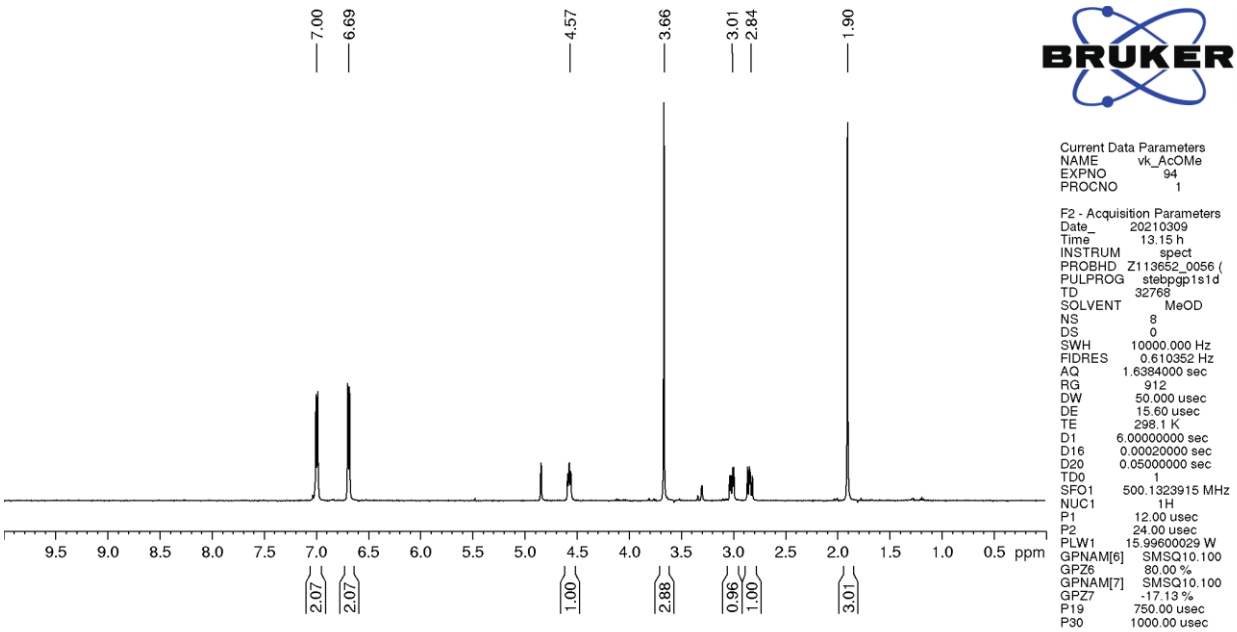





*OBC,* doi: 10.1039/d1ob01213d

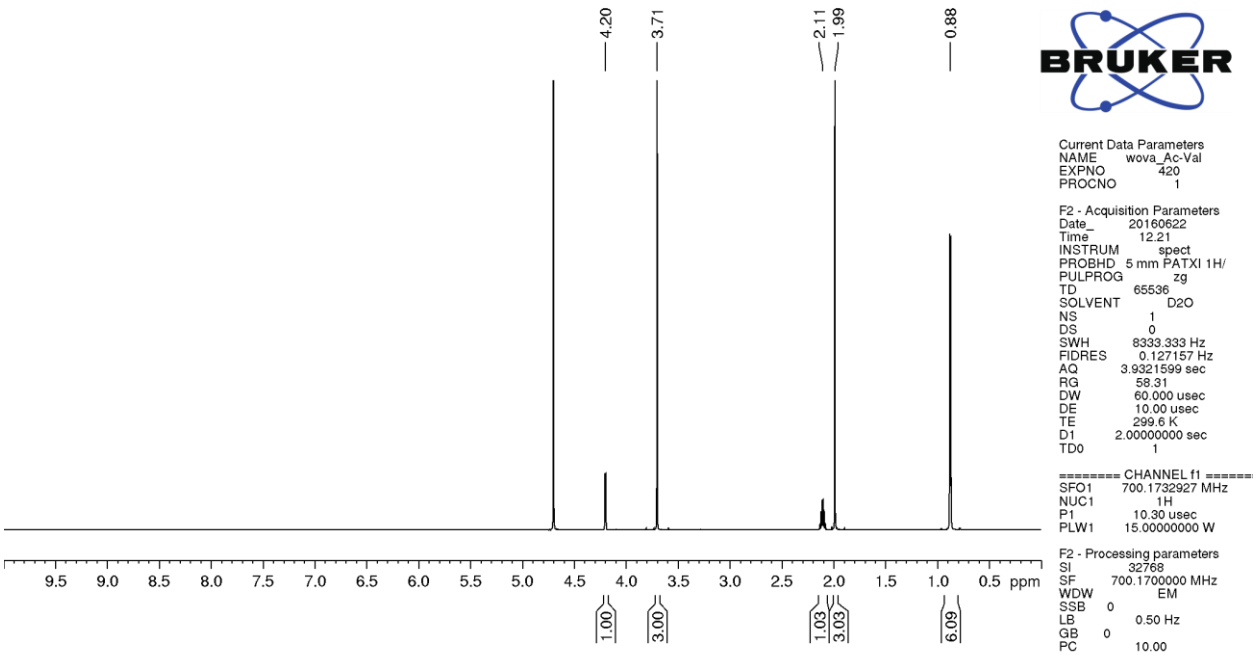
Ac-Tyr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.00 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.2 Hz, 2H), 4.57 (dd, *J* = 8.0 and 6.6. Hz, 1H), 3.66 (s, 3H), 3.02 (dd, *J* = 14.0 and 6.4 Hz, 1H), 2.84 (dd, *J* = 14.0 and 8.7 Hz, 1H), 1.91 (s, 3H).




Ac-Val-$OCH_3$ in deuterium oxide:

$^1$H NMR (700 MHz): 4.20 (d, *J* = 6.0 Hz, 1H), 3.71 (s, 3H), 2.11 (m, 1H), 1.99 (s, 3H), 0.88 (m, 6H).

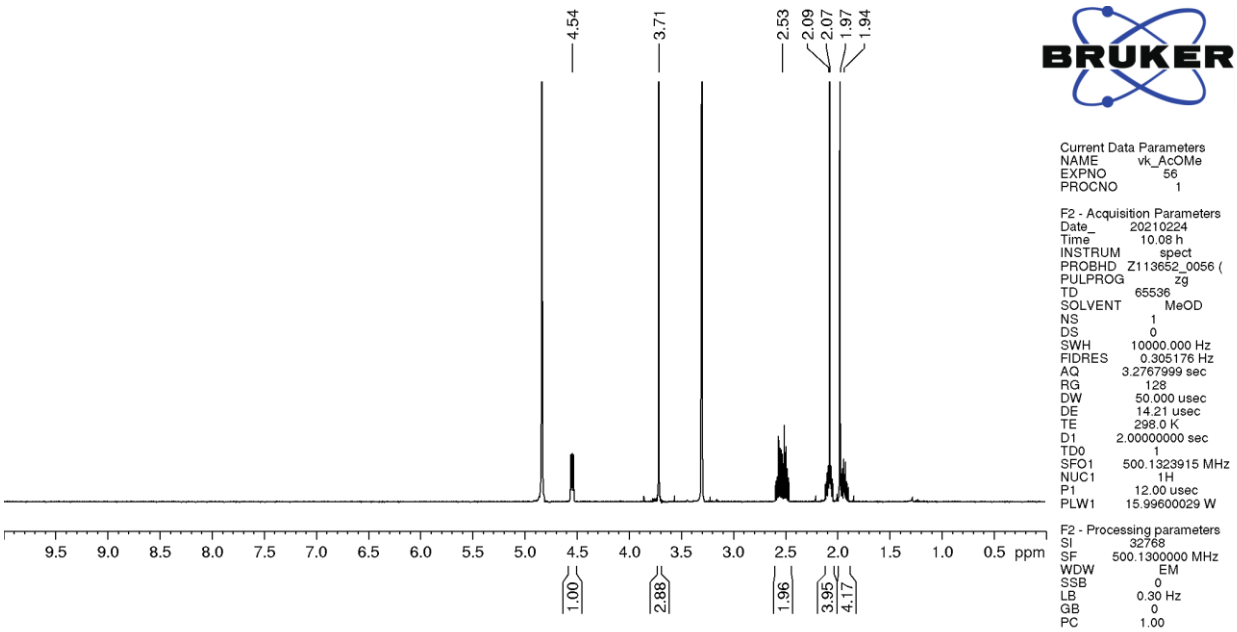





*OBC,* doi: 10.1039/d1ob01213d

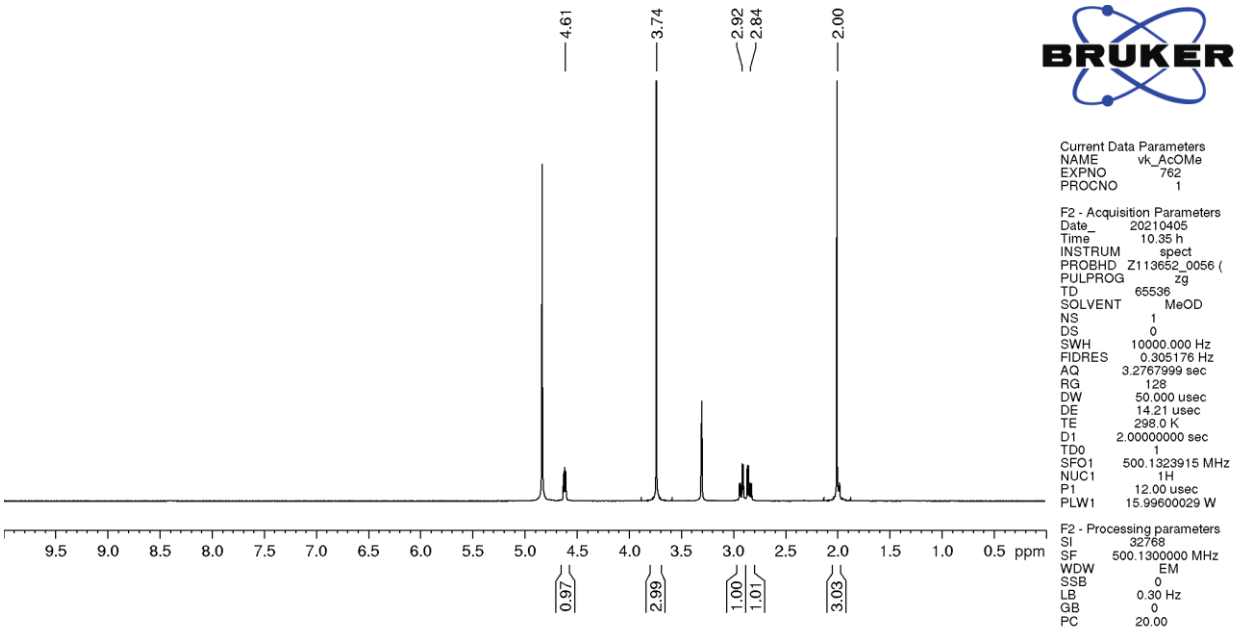
Ac-Met-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.54 (dd, *J* = 9.0 and 4.8 Hz, 1H), 3.71 (s, 3H), 2.53 (m, 2H), 2.09 (m, 1H), 2.07 (s, 3H), 1.97 (s, 3H), 1.94 (m, 1H).




Ac-Cys-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.61 (dd, *J* = 6.7 and 5.0 Hz, 1H), 3.74 (s, 3H), 2.92 (dd, *J* = 13.9 and 4.8 Hz, 1H), 2.84 (dd, *J* = 14.0 and 6.9 Hz, 1H), 2.00 (s, 3H).

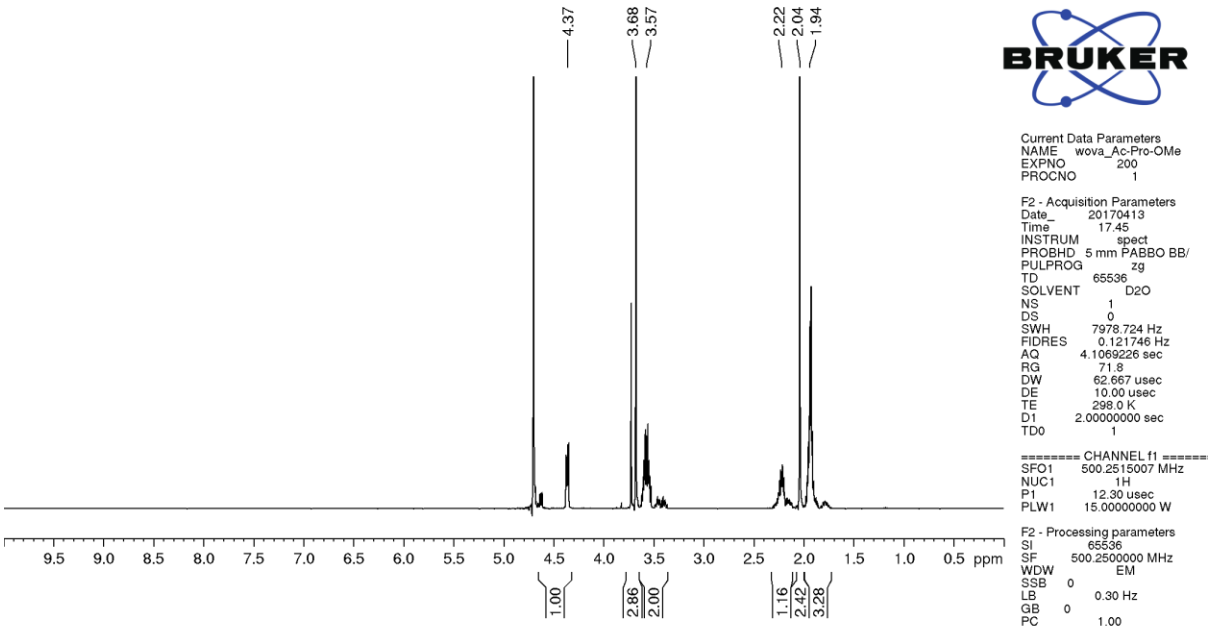





*OBC,* doi: 10.1039/d1ob01213d

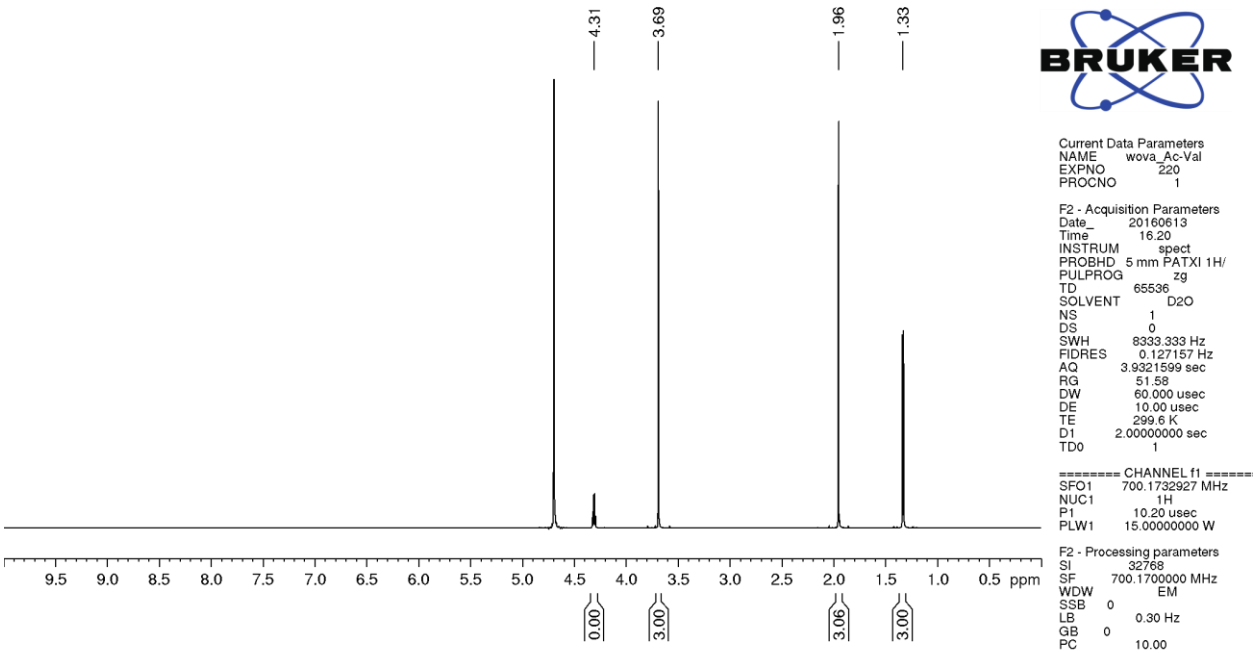
Ac-Pro-$OCH_3$ in deuterium oxide, major rotamer:

$^1$H NMR (500 MHz): 4.37 (dd, *J* = 8.4 and 4.4 Hz, 1H), 3.68 (s, 3H), 3.57 (m, 2H), 2.22 (m, 1H), 2.04 (s, 3H), 1.94 (m, 3H).




Ac-Ala-$OCH_3$ in deuterium oxide:

$^1$H NMR (700 MHz): 4.31 (q, *J* = 7.3 Hz, 1H), 3.69 (s, 3H), 1.96 (s, 3H), 1.33 (d, *J* = 7.3 Hz).

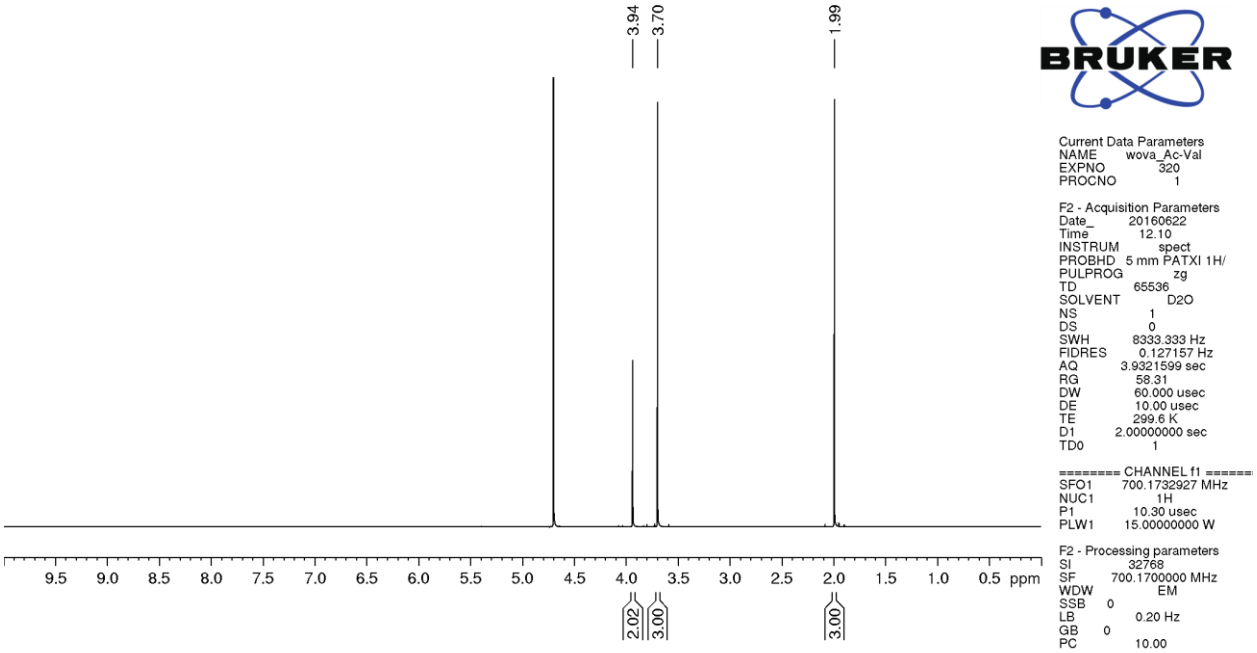





*OBC,* doi: 10.1039/d1ob01213d

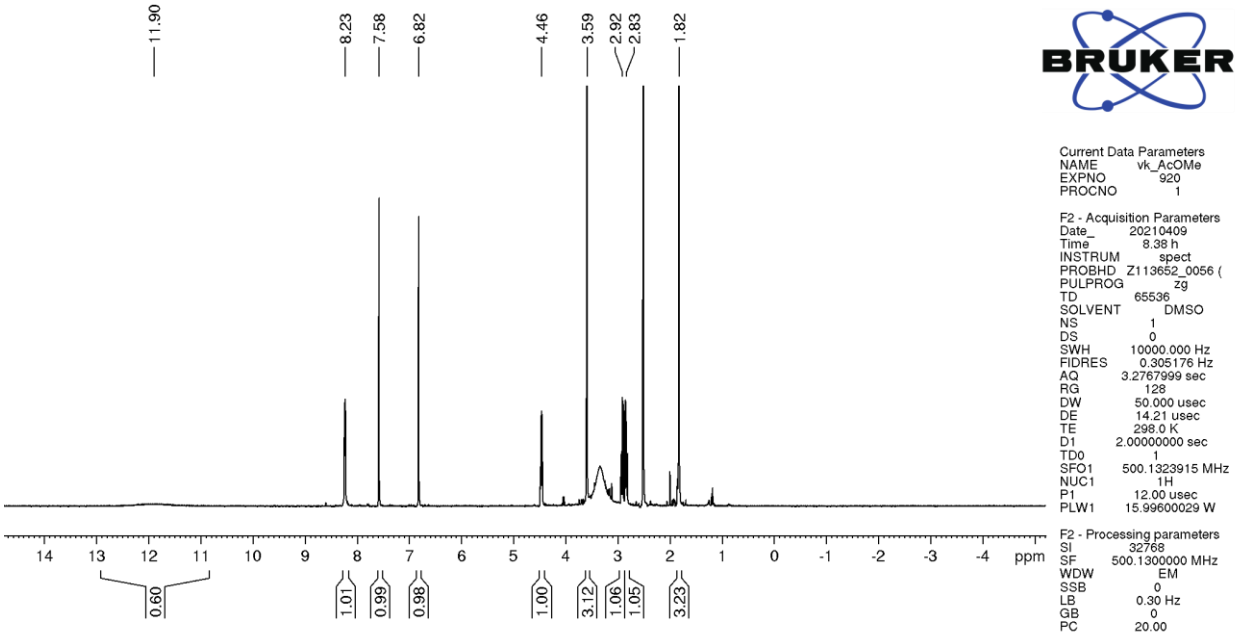
Ac-Gly-$OCH_3$ in deuterium oxide:

$^1$H NMR (700 MHz): 3.94 (s, 2H), 3.70 (s, 3H), 1.99 (s, 3H).




Ac-His-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 11.9 (broad s, 1H), 8.24 (d, *J* = 7.4 Hz, 1H), 7.58 (s, 1H), 6.82 (s, 1H), 4.46 (m, 1H), 3.59 (s, 3H), 2.92 (dd, *J* = 14.6 and 5.7 Hz, 1H), 2.83 (dd, *J* = 14.5 and 8.3 Hz, 1H), 1.82 (s, 3H).

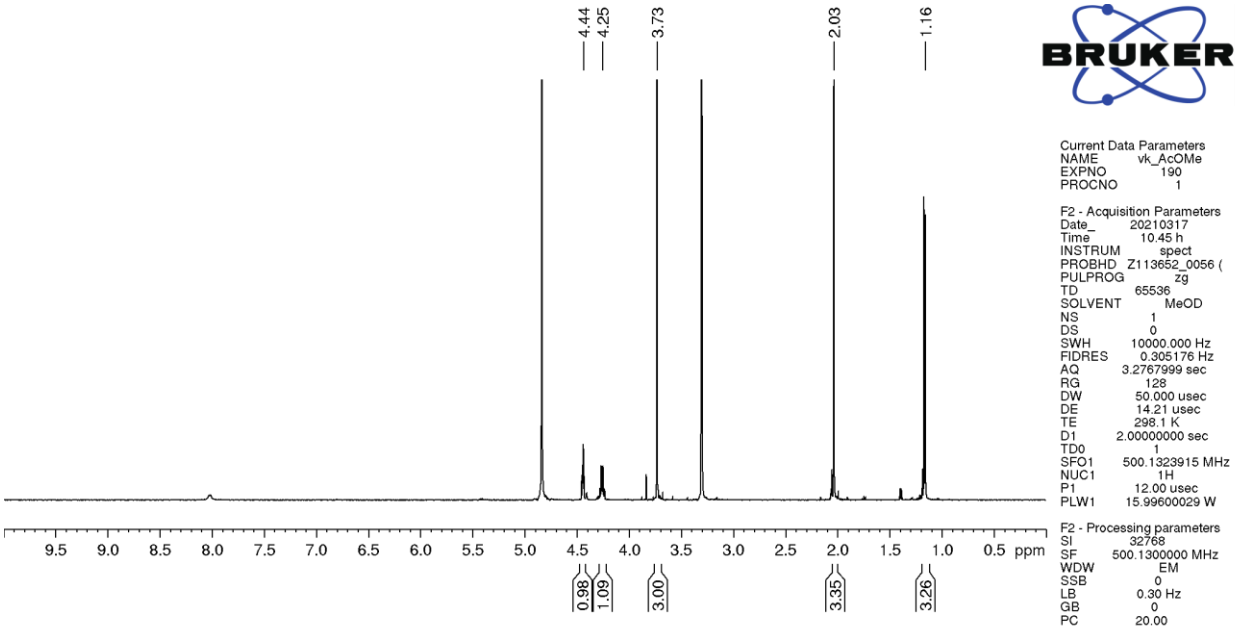





*OBC*, doi: 10.1039/d1ob01213d

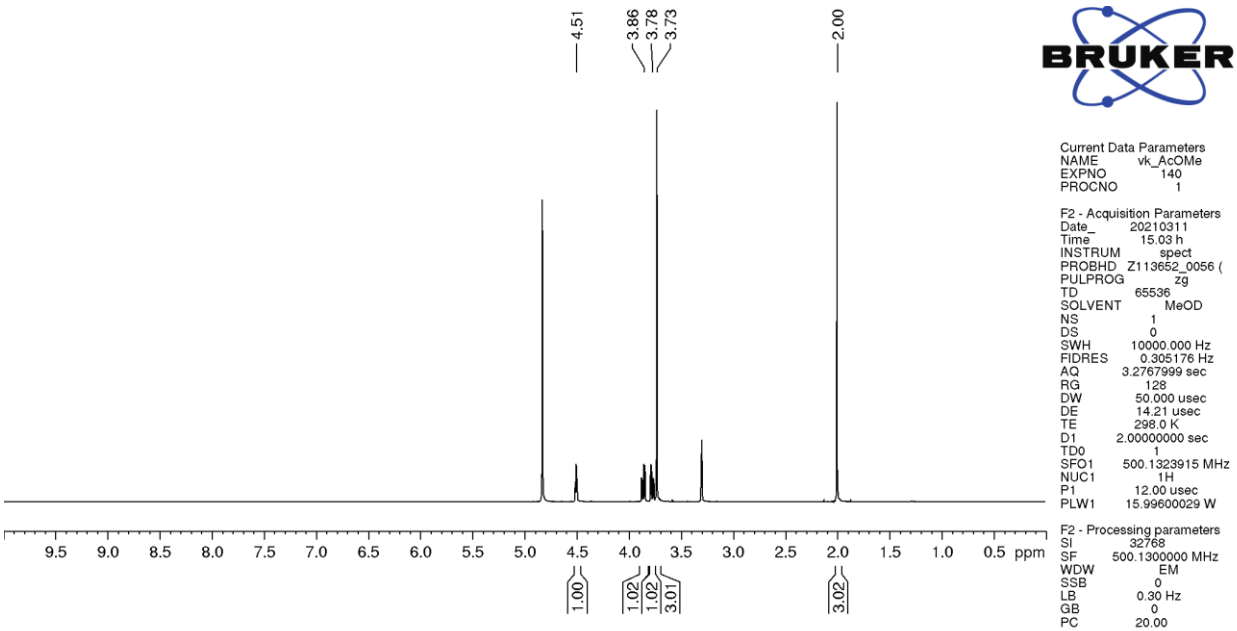
Ac-Thr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.44 (m, 1H), 4.25 (m, 1H), 3.73 (s, 3H), 2.03 (s, 3H), 1.16 (d, 6.5 Hz).




Ac-Ser-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.51 (t, *J* = 4.6 Hz, 1H), 3.86 (dd, *J* = 11.3 and 5.0 Hz, 1H), 3.78 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.73 (s, 3H), 2.00 (s, 3H).

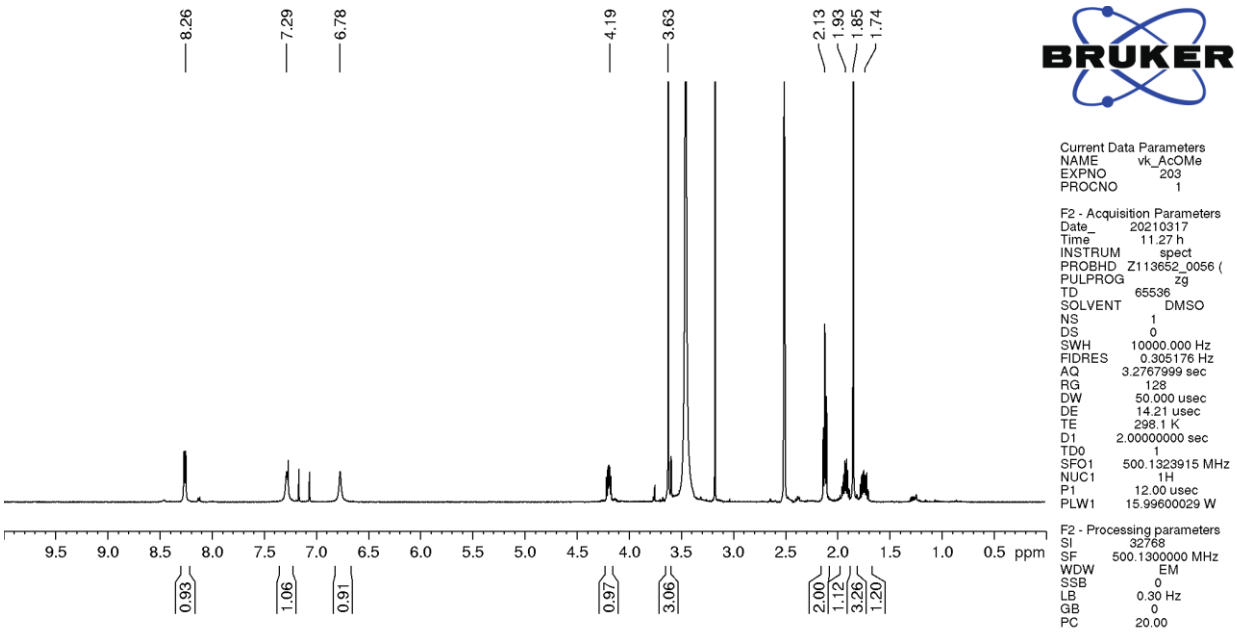





*OBC,* doi: 10.1039/d1ob01213d

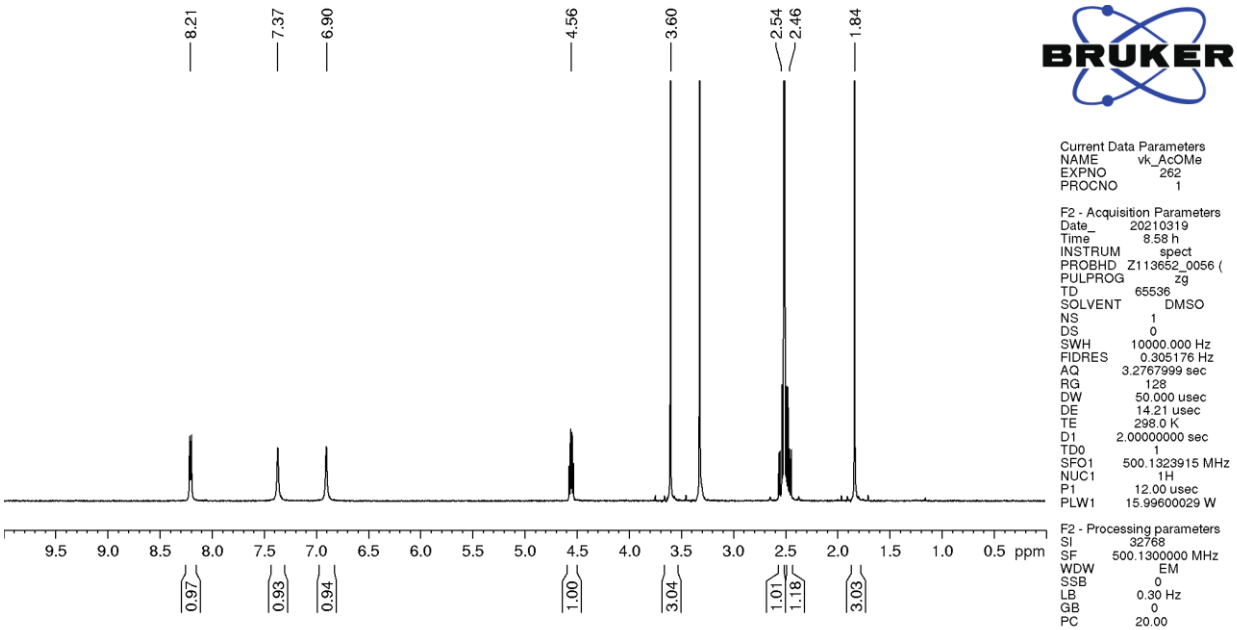
Ac-Gln-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.26 (d, *J* = 7.4 Hz, 1H), 7.29 (broad s, 1H), 6.78 (broad s, 1H), 4.19 (m,1H), 3.63 (s, 3H), 2.13 (t, *J* = 7.7 Hz, 2H), 1.93 (m, 1H), 1.85 (s, 3H), 1.20 (m, 1H).




Ac-Asn-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.21 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 6.90 (s, 1H), 456 (m, 1H), 3.60 (s, 3H), 2.54 (dd, *J* = 15.7 and 5.8 Hz, 1H), 2.46 (dd, *J* = 15.6 and 7.1 Hz, 1H), 1.84 (s, 3H).

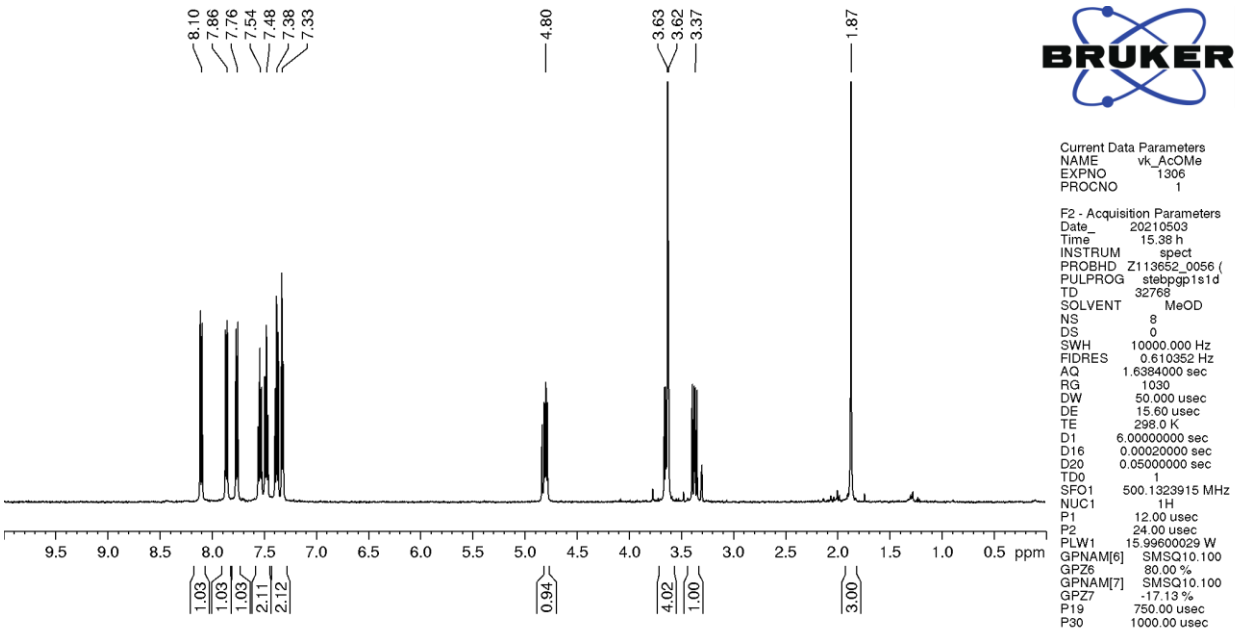





*OBC,* doi: 10.1039/d1ob01213d

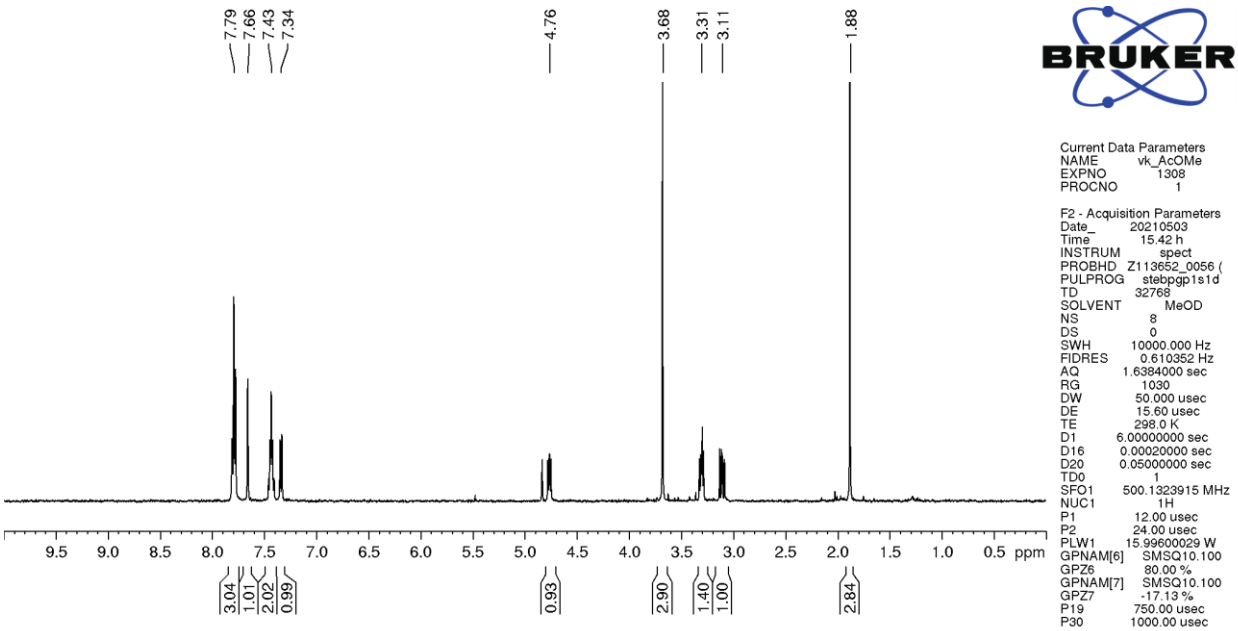
Ac-α-Nal-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 8.10 (d, *J* = 8.6 Hz0, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.3 Hz), 7.54 (t, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 6.9 Hz, 1H), 4.80 (m, 1H), 3.63 (m, 1H), 3.62 (s, 3H), 3.37 (dd, *J* = 14.4 and 8.6 Hz, 1H), 1.87 (s, 3H).




Ac-β-Nal-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.79 (m, 3H), 7.66 (s, 1H), 7.43 (m, 2H), 7.34 (dd, *J* = 8.5 and 1.2 Hz, 1H), 4.76 (dd, *J* = 9.0 and 6.0 Hz, 1H), 3.68 (s, 3H), 3.30 (dd, *J* = 13.8 and 6.0 Hz, 1H), 3.11 (dd, *J* = 13.9 and 9.1 Hz, 1H), 1.88 (s, 3H).

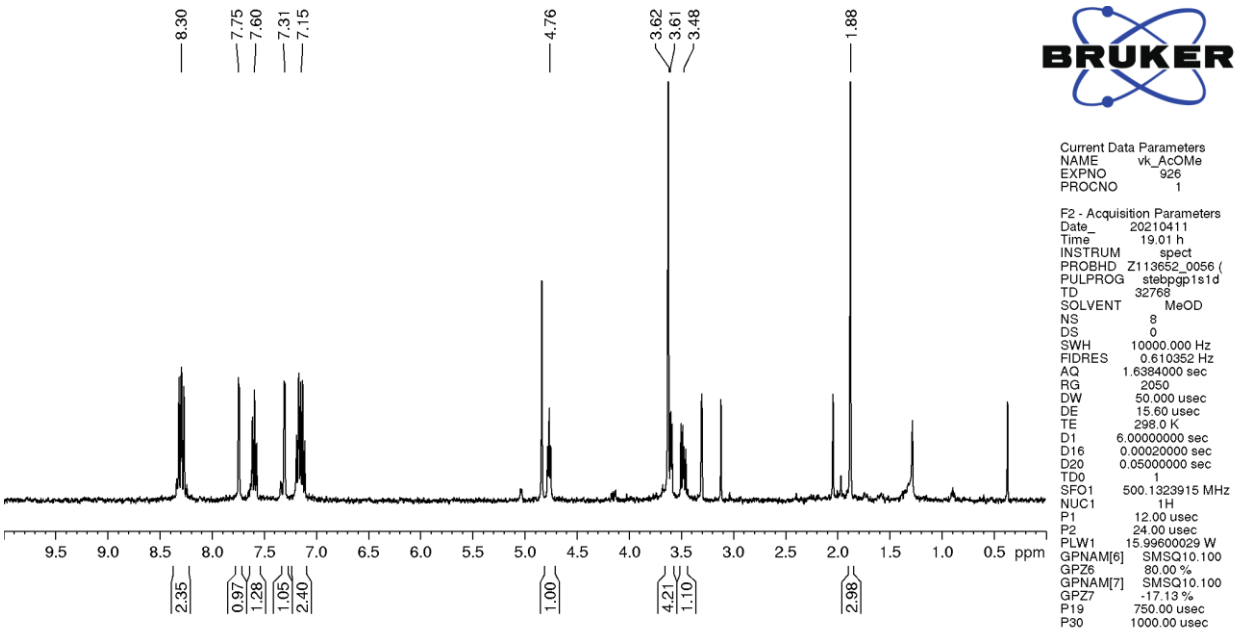





*OBC,* doi: 10.1039/d1ob01213d

Ac-Azu-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 8.30 (dd, *J* = 13.5 and 10.4 Hz, 2H), 7.75 (d, *J* = 3.5 Hz, 1H), 7.60 (t, *J* = 10.0 Hz, 1H), 7.31 (d, *J* = 3.9 Hz, 1H), 7.15 (m, 2H), 4.76 (t, *J* = 7.2 Hz, 1H), 3.62 (s, 3H), 3.61 (m, 1H), 3.48 (dd, *J* = 14.3 and 7.7. Hz, 1H), 1.88 (s, 3H).

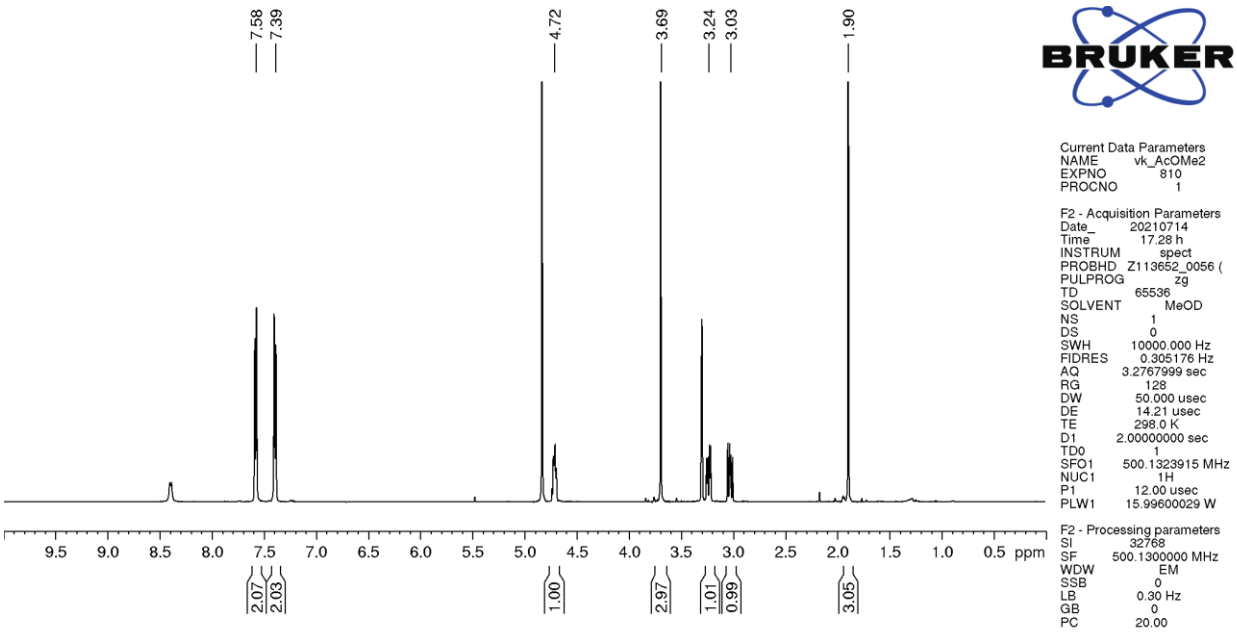




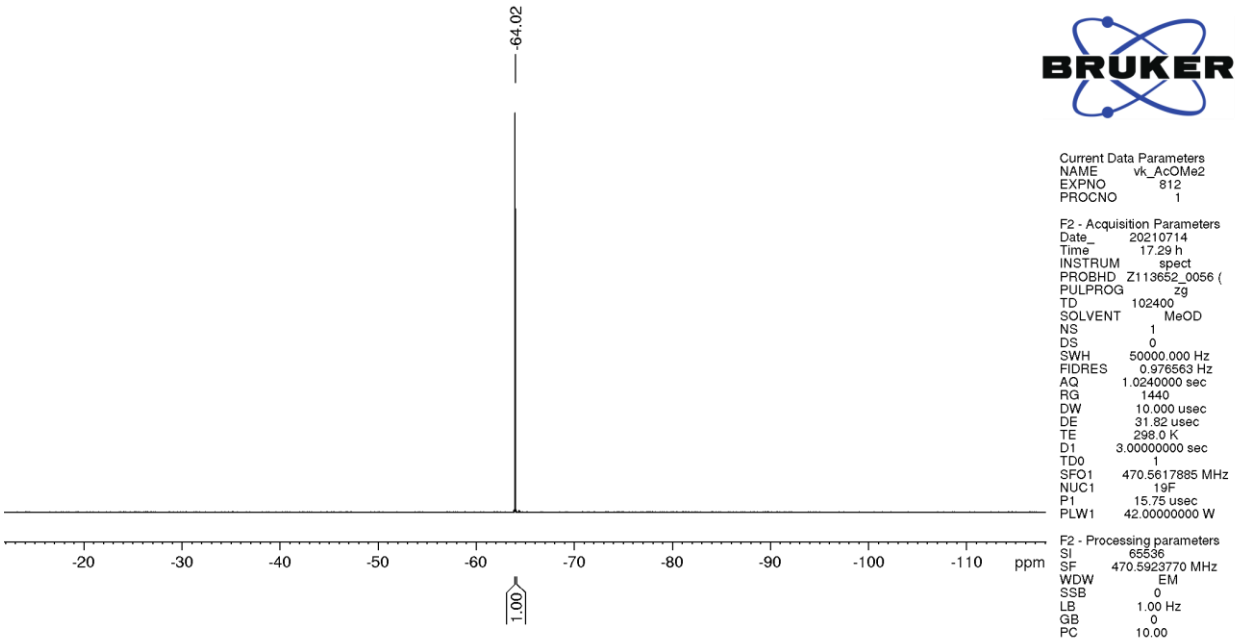

*OBC,* doi: 10.1039/d1ob01213d

Ac-4-$CF_3$-Phe-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.58 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 4.72 (m, 1H), 3.69 (s, 3H), 3.24 (dd, *J* = 14.0 and 5.6 Hz, 1H), 3.03 (dd, *J* = 13.0 and 8.9 Hz, 1H), 1.90 (s, 3H).




$^{19}$F NMR (471 MHz): −64.0 (s).

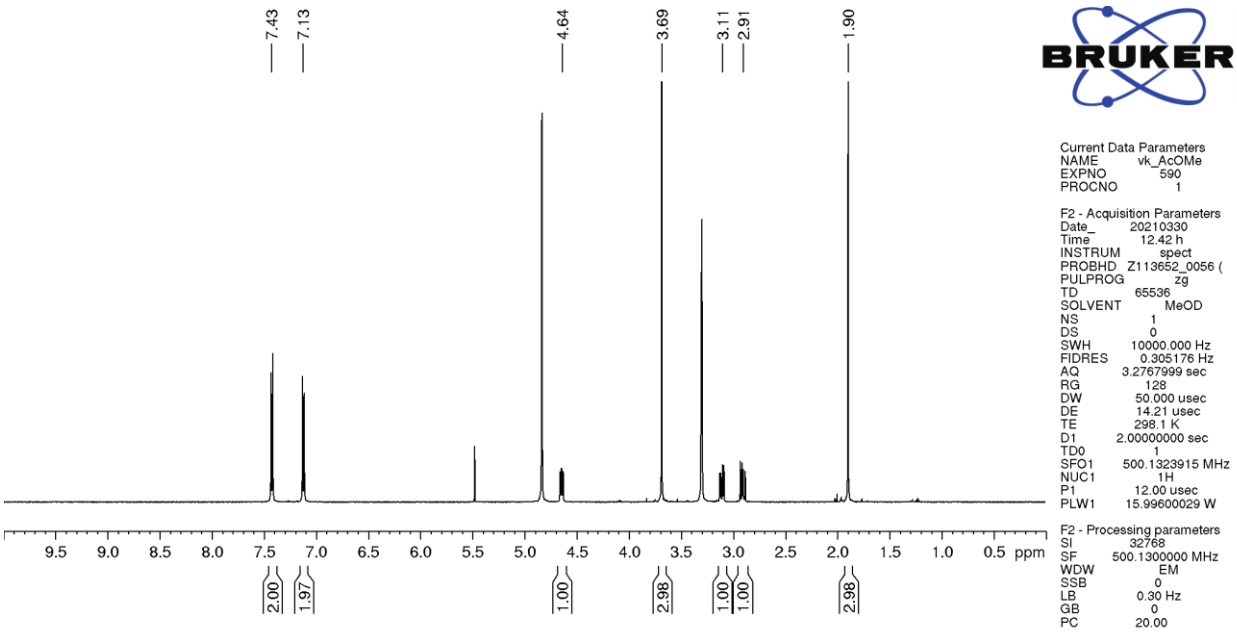





*OBC*, doi: 10.1039/d1ob01213d

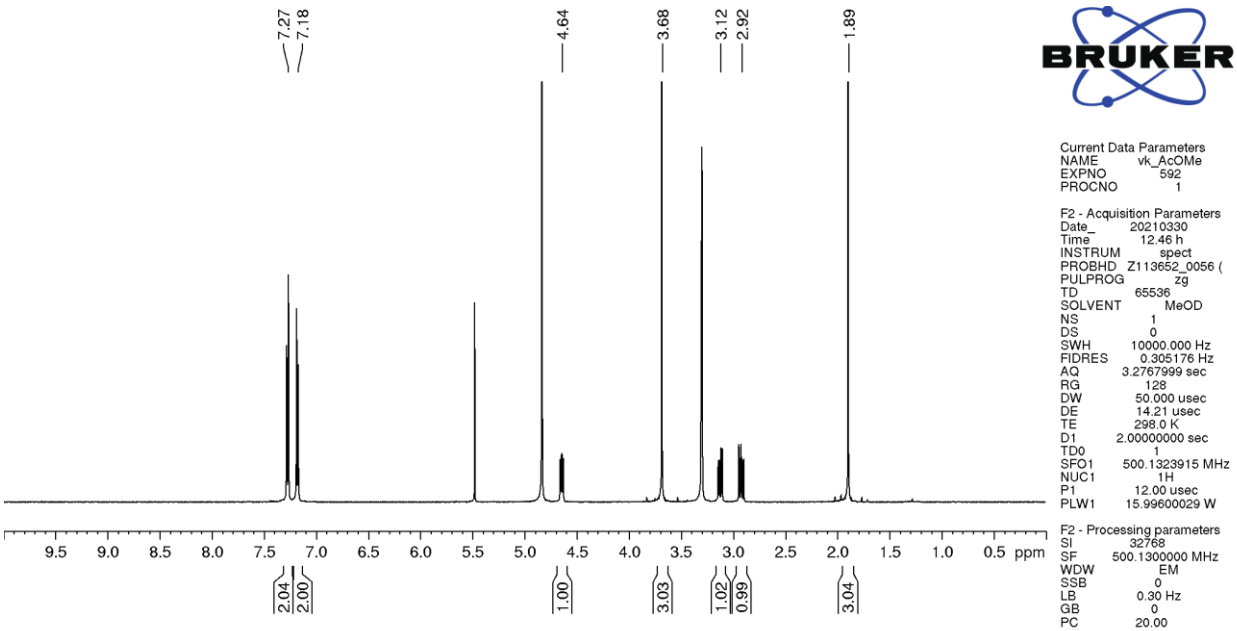
Ac-4-Br-Phe-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.43 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.64 (dd, *J* = 9.0 and 5.7 Hz, 1H), 3.69 (s, 3H), 3.11 (dd, *J* = 14.0 and 5.7 Hz, 1H), 2.91 (dd, *J* = 14.0 and 8.9 Hz, 1H), 1.90 (s, 3H).




Ac-4-Cl-Phe-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.27 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 4.64 (dd, *J* = 9.0 and 5.8 Hz, 1H), 3.68 (s, 3H), 3.12 (dd, *J* = 14.0 and 5.8 Hz, 1H), 2.92 (dd, *J* = 14.0 and 9.0 Hz, 1H), 1.89 (s, 3H).

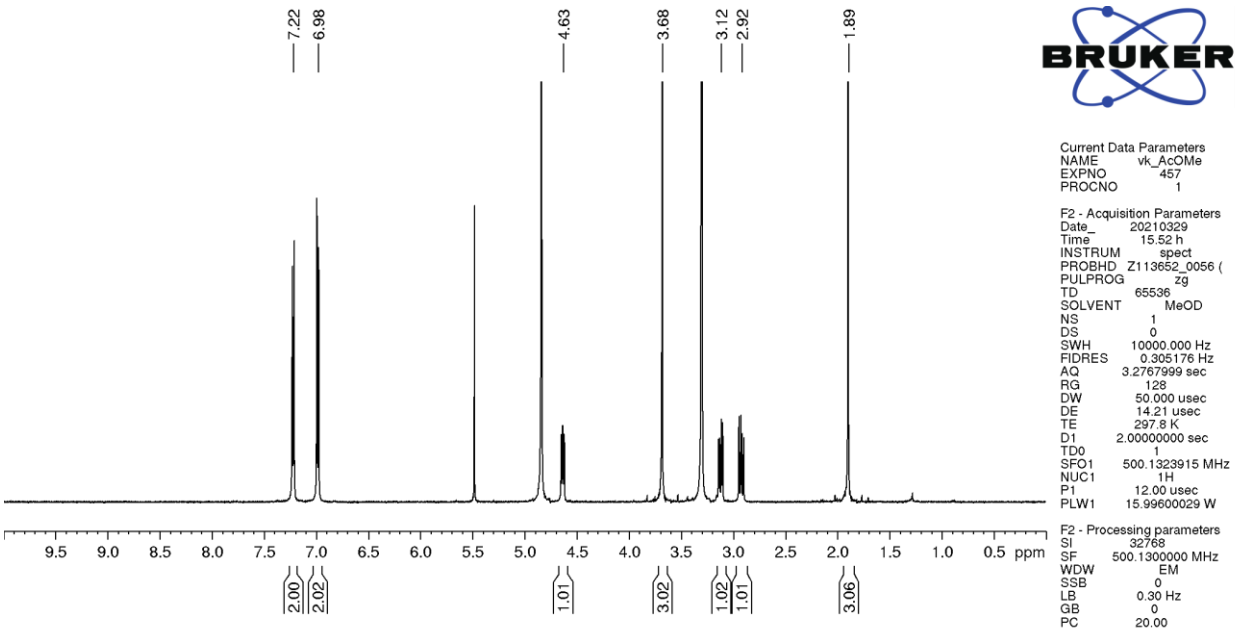





*OBC,* doi: 10.1039/d1ob01213d

Ac-4-$N_3$-Phe-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.22 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.63 (dd, *J* = 9.0 and 5.7 Hz, 1H), 3.68 (s, 3H), 3.12 (dd, *J* = 13.9 and 5.7 Hz, 1H), 2.92 (dd, *J* = 14.0 and 8.9 Hz, 1H), 1.89 (s, 3H).

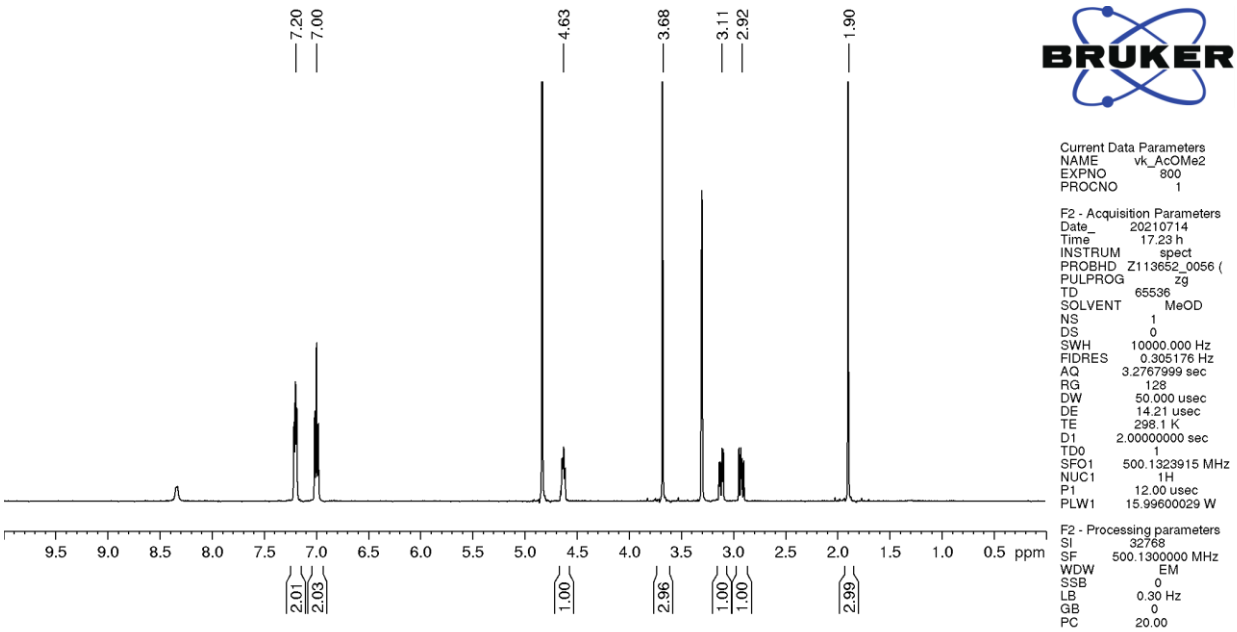




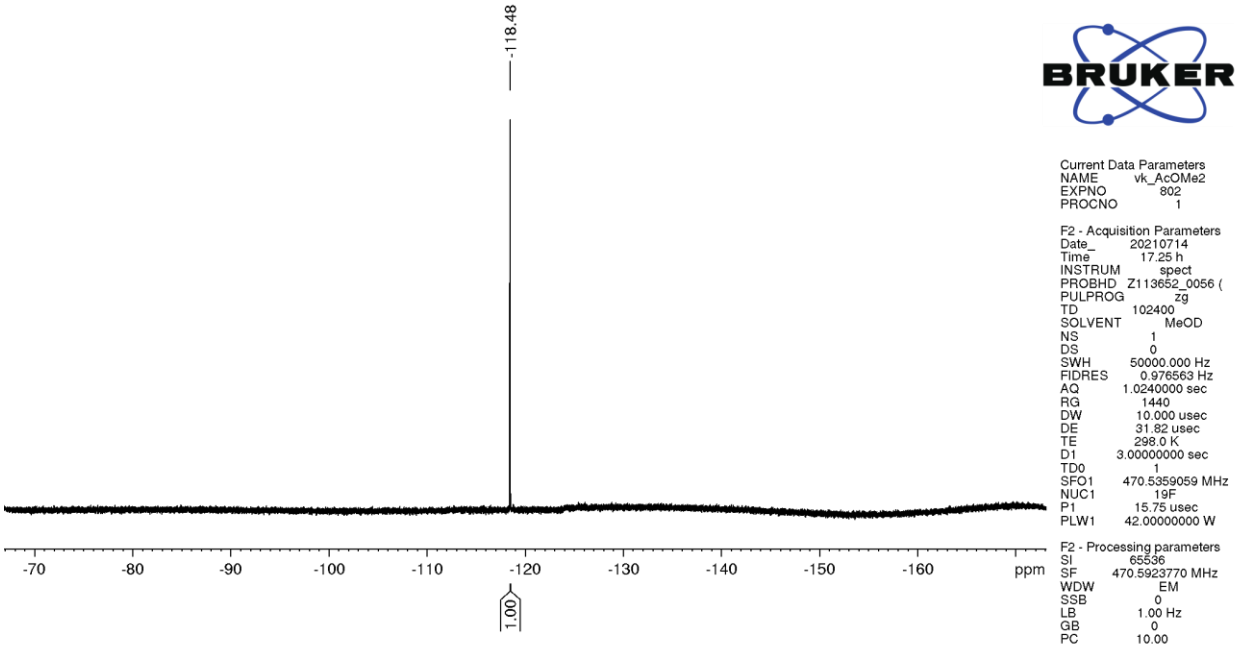

*OBC,* doi: 10.1039/d1ob01213d

Ac-4F-Phe-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.20 (m, 2H), 7.00 (m, 2H), 4.63 (m, 1H), 3.68 (s, 3H), 3.11 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.92 (dd, *J* = 14.0 and 8.9 Hz, 1H), 1.90 (s, 3H).




$^{19}$F NMR (471 MHz): −118.5 (m).

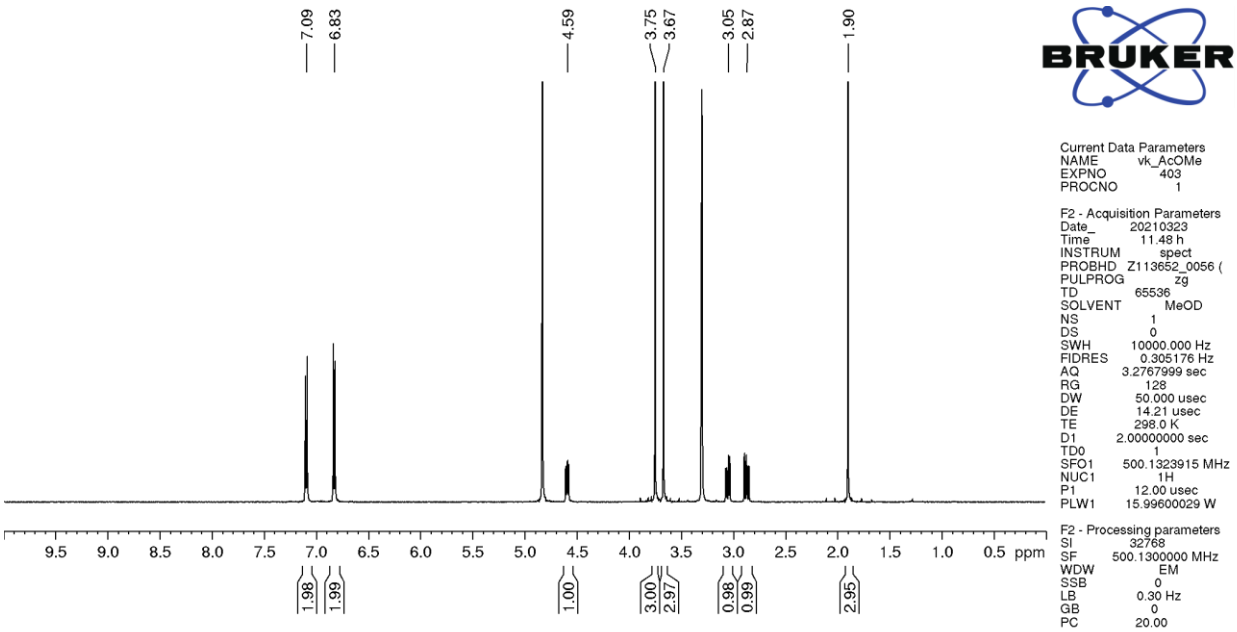





*OBC*, doi: 10.1039/d1ob01213d

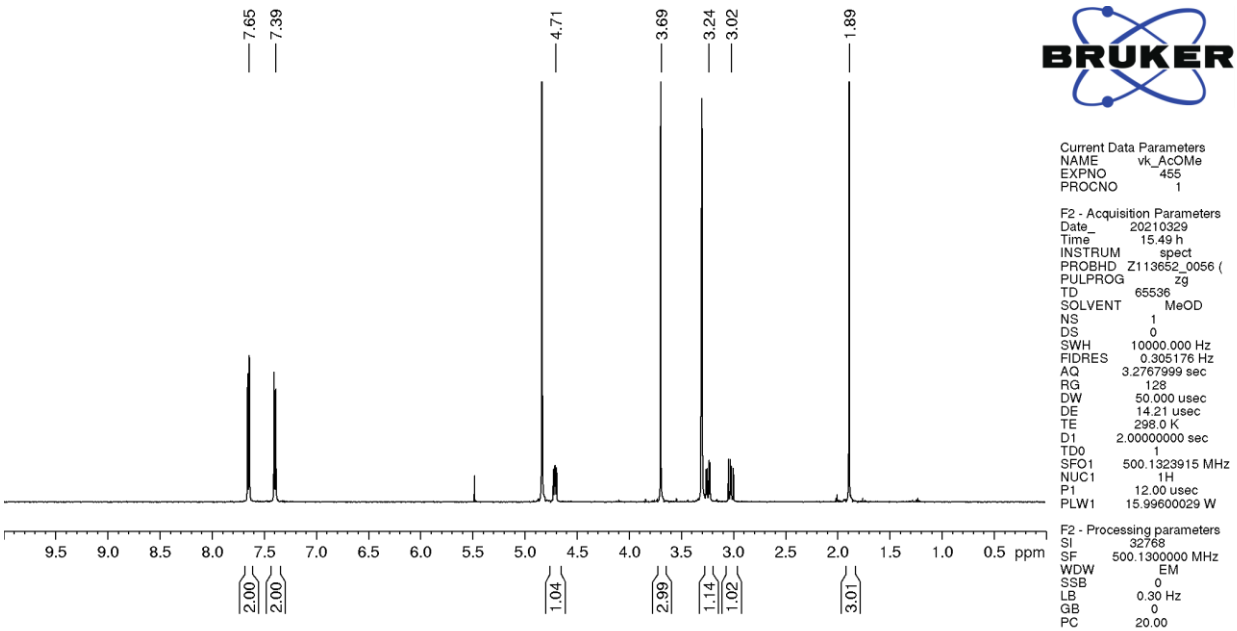
Ac-(Me)Tyr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.09 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.59 (dd, *J* = 8.7 and 5.9 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.05 (dd, *J* = 14.0 and 5.9 Hz, 1H), 2.87 (dd, *J* = 13.9 and 8.8 Hz, 1H), 1.90 (s, 3H).




Ac-4-CN-Phe-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.65 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 4.71 (dd, *J* = 9.1 and 5.6 Hz, 1H), 3.69 (s, 3H), 3.24 (dd, *J* = 13.8 and 5.6 Hz, 1H), 3.02 (dd, *J* = 13.9 and 9.2 Hz, 1H), 1.89 (s, 3H).

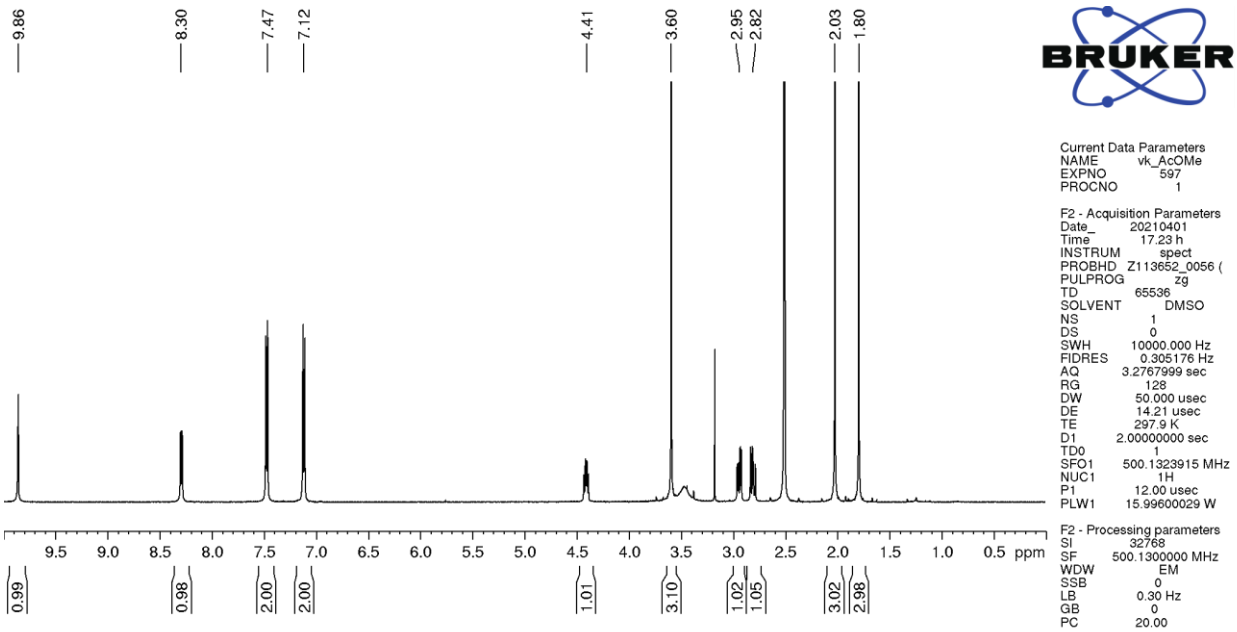





*OBC,* doi: 10.1039/d1ob01213d

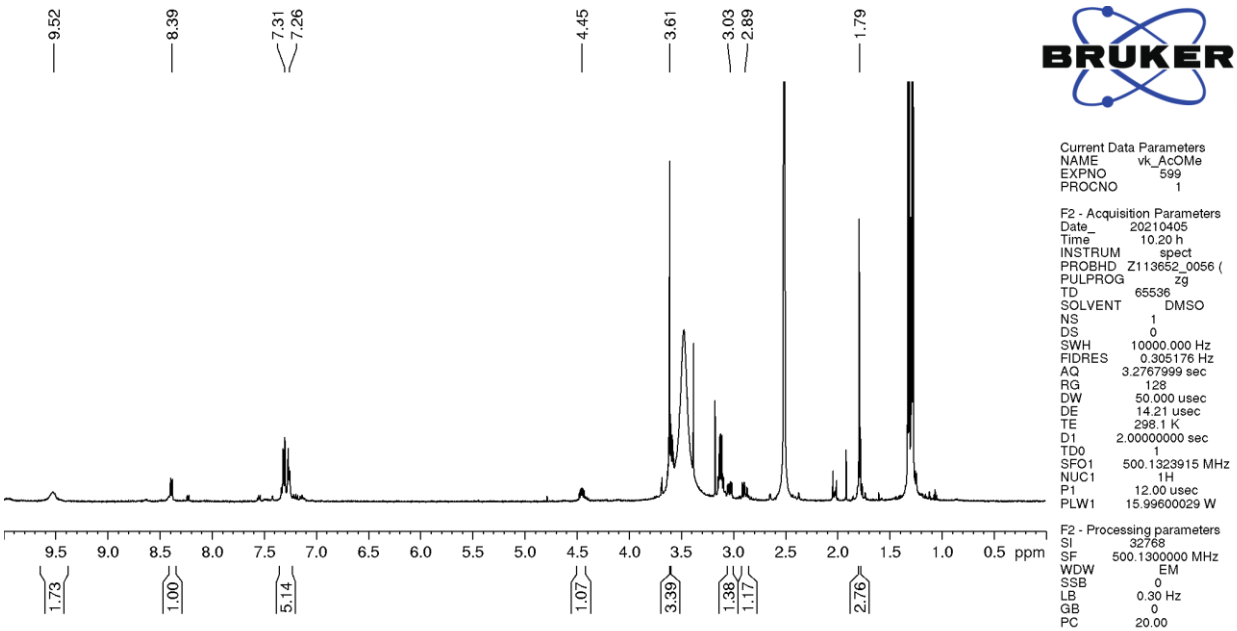
Ac-4-AcNH-Phe-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 9.86 (s, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 4.41 (m, 1H), 3.60 (s, 3H), 2.95 (dd, *J* = 13.7 and 5.6 Hz, 1H), 2.82 (dd, *J* = 13.8 and 9.1 Hz, 1H), 2.03 (s, 3H), 1.80 (s, 3H).




Ac-4-$NH_2$-Phe-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 9.52 (broad s, 2H), 8.39 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 4.45 (m, 1H), 3.61 (s, 3H), 3.03 (dd, *J* = 13.8 and 5.5 Hz, 1H), 2.89 (dd, *J* = 13.8 and 9.3 Hz, 1H), 1.79 (s, 3H).



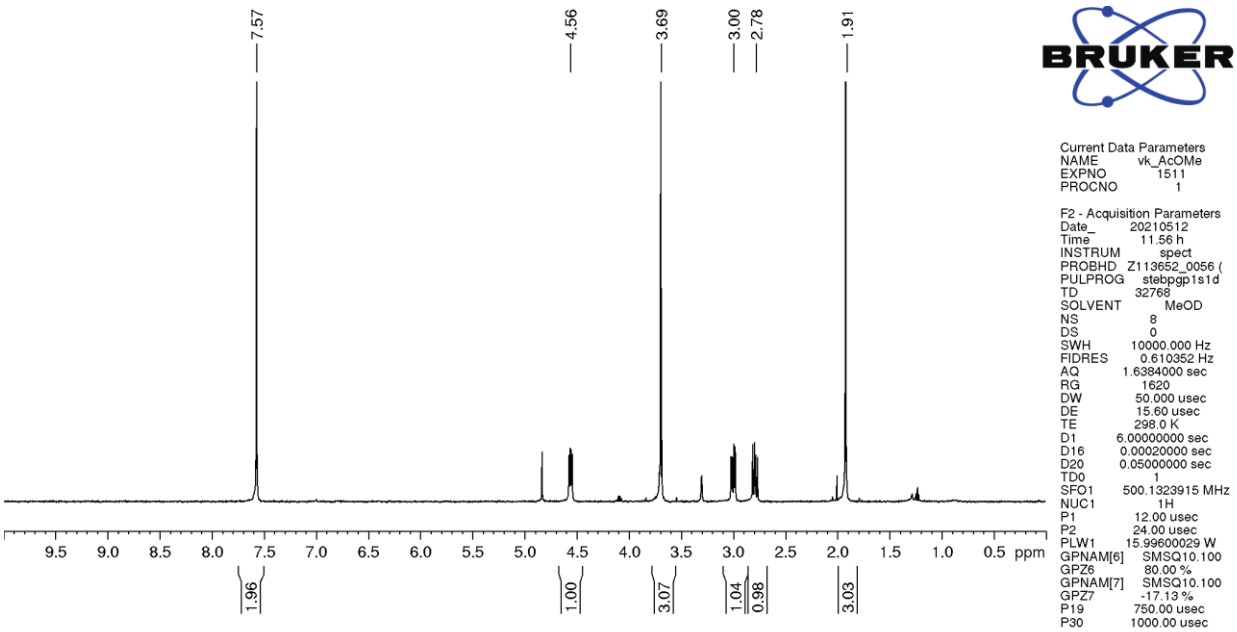

*n.b.*: the spectrum demonstrates presence of diisopropylethylamine.



*OBC,* doi: 10.1039/d1ob01213d

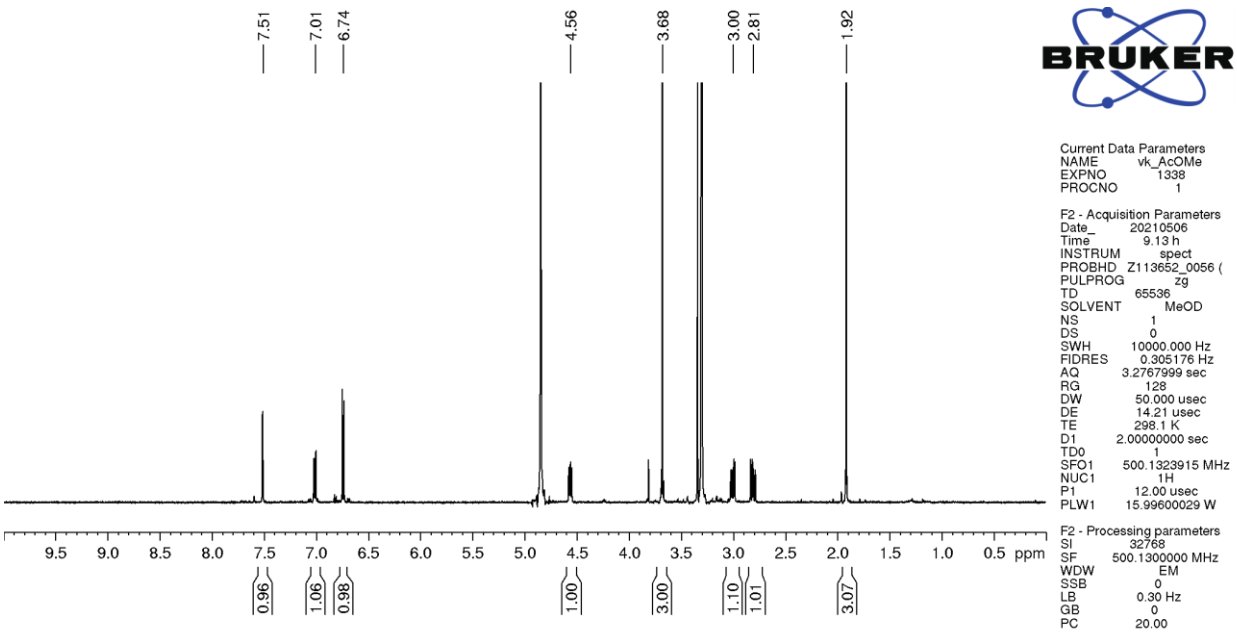
Ac-3,5-diI-Tyr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.57 (s, 2H), 4.56 (dd, *J* = 8.9 and 5.7 Hz, 1H), 3.69 (s, 3H), 3.00 (dd, *J* = 14.0 and 5.6 Hz, 1H), 2.79 (dd, *J* = 14.0 and 8.9 Hz, 1H), 1.92 (s, 3H).




Ac-3-I-Tyr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.51 (d, 2.2 Hz, 1H), 7.01 (dd, *J* = 8.3 and 2.2. Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 4.56 (dd, *J* = 8.9 and 5.9 Hz, 1H), 3.68 (s, 3H), 3.00 (dd, *J* = 13.7 and 5.8 Hz, 1H), 2.81 (dd, *J* = 13.9, 8.9 Hz, 1H), 1.92 (s, 3H).

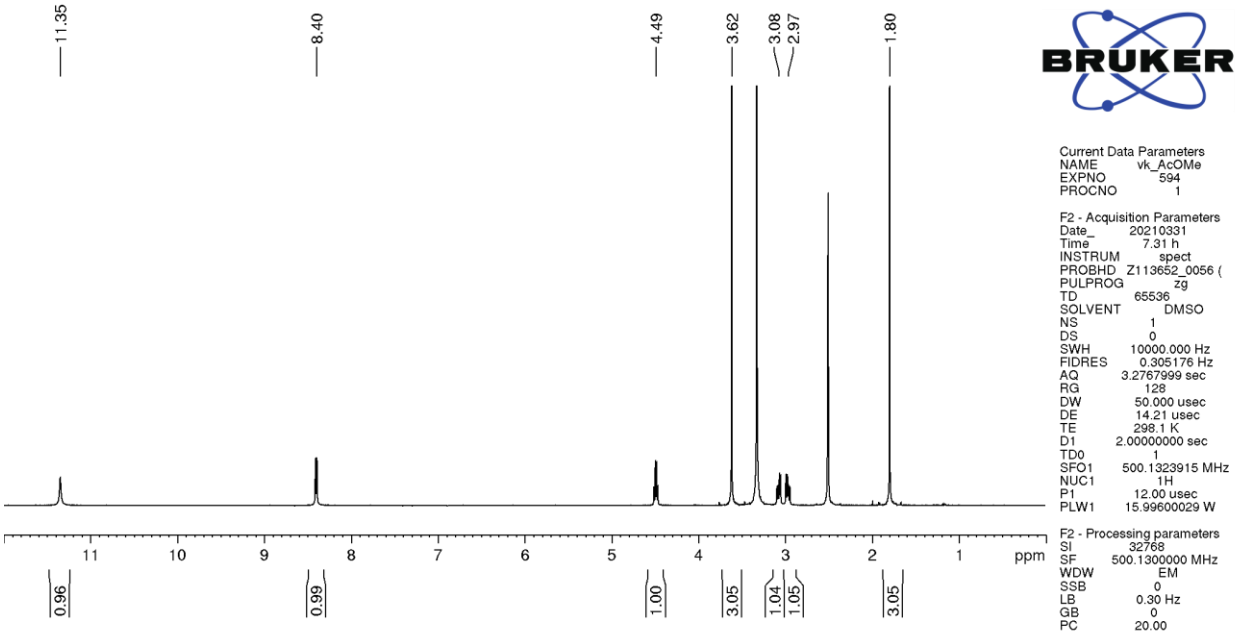




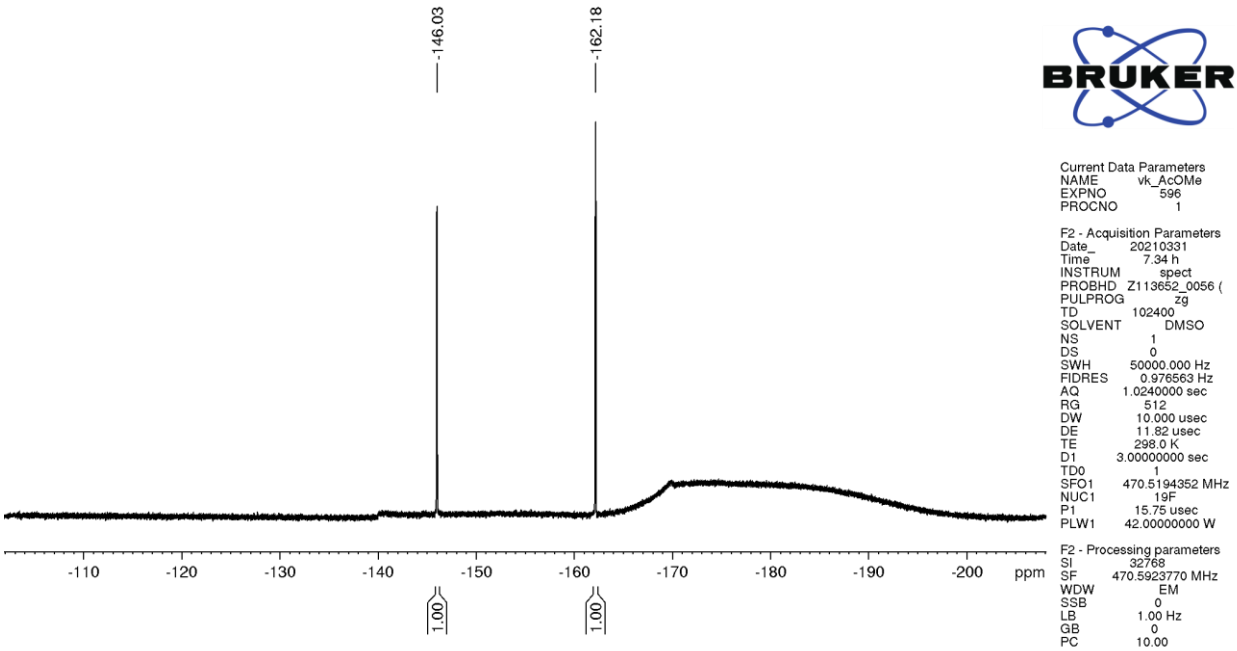

*OBC,* doi: 10.1039/d1ob01213d

Ac-2,3,5,6-tetraF-Tyr-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 11.3 (s, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 4.49 (m, 1H), 3.62 (s, 3H), 3.08 (dd, *J* = 14.1 and 6.5 Hz, 1H), 2.97 (dd, *J* = 14.1 and 7.9 Hz, 1H), 1.80 (s, 3H).




$^{19}$F NMR (471 MHz): −146.0 (m, 2F), −162.2 (m, 2F).

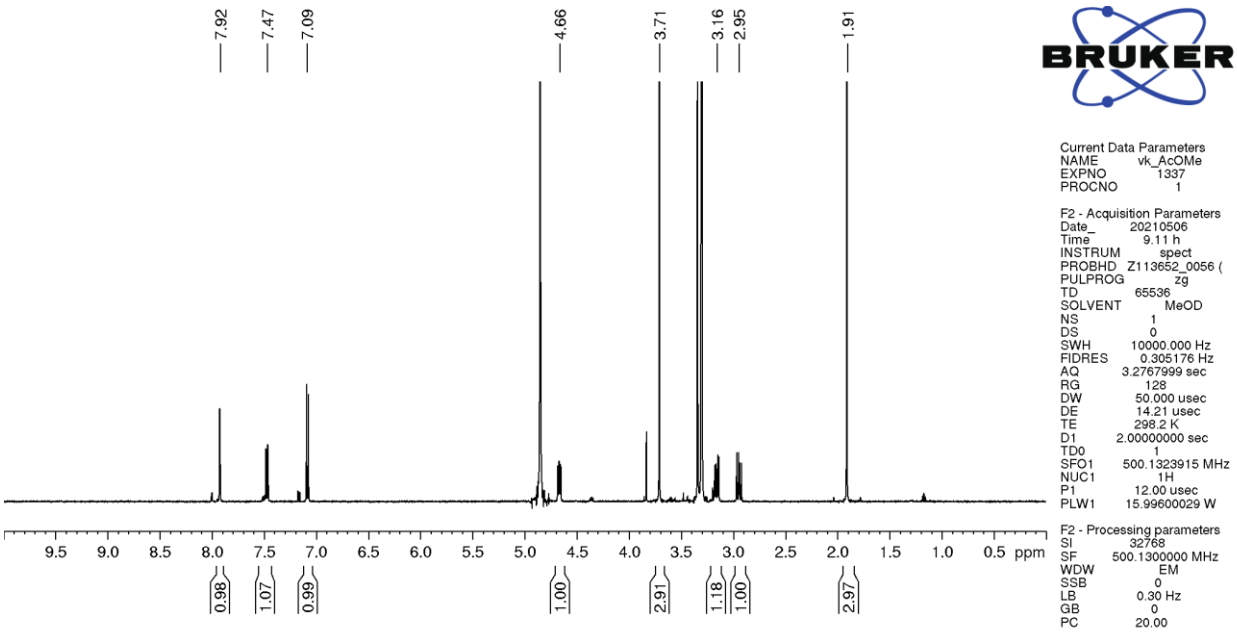





*OBC,* doi: 10.1039/d1ob01213d

Ac-3-$NO_2$-Tyr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.92 (d, *J* = 2.2 Hz, 1H), 7.47 (dd, *J* = 8.6 and 2.2. Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 4.66 (dd, *J* = 9.0 and 5.6 Hz, 1H), 3.71 (s, 3H), 3.16 (dd, *J* = 14.1 and 5.5. Hz, 1H), 2.95 (dd, *J* = 14.1 and 9.1 Hz, 1H), 1.91 (s, 3H).

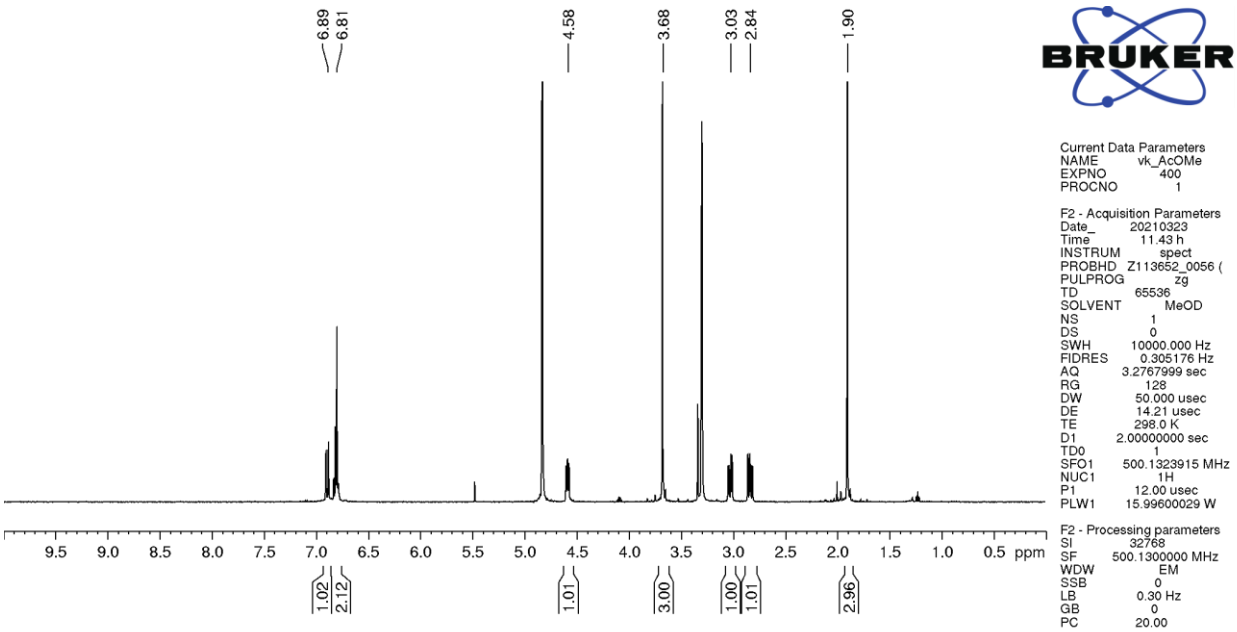




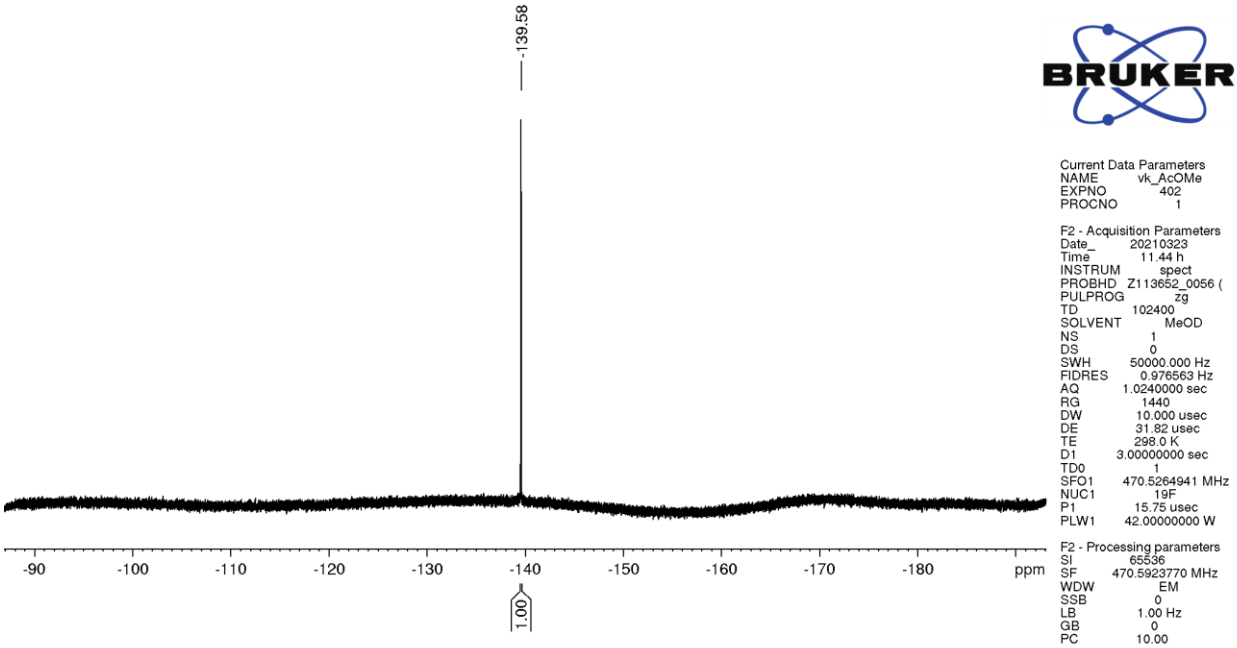

*OBC,* doi: 10.1039/d1ob01213d

Ac-3-F-Tyr-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 6.89 (m, 1H), 6.81 (m, 2H), 4.58 (dd, *J* = 8.8 and 5.8 Hz, 1H), 3.68 (s, 3H), 3.03 (dd, *J* = 14.0 and 5.7 Hz, 1H), 2.84 (dd, *J* = 14.0 and 8.8. Hz, 1H), 1.90 (s, 3H).




$^{19}$F NMR (471 MHz): −139.6 (dd, *J* = 12 and 7 Hz).

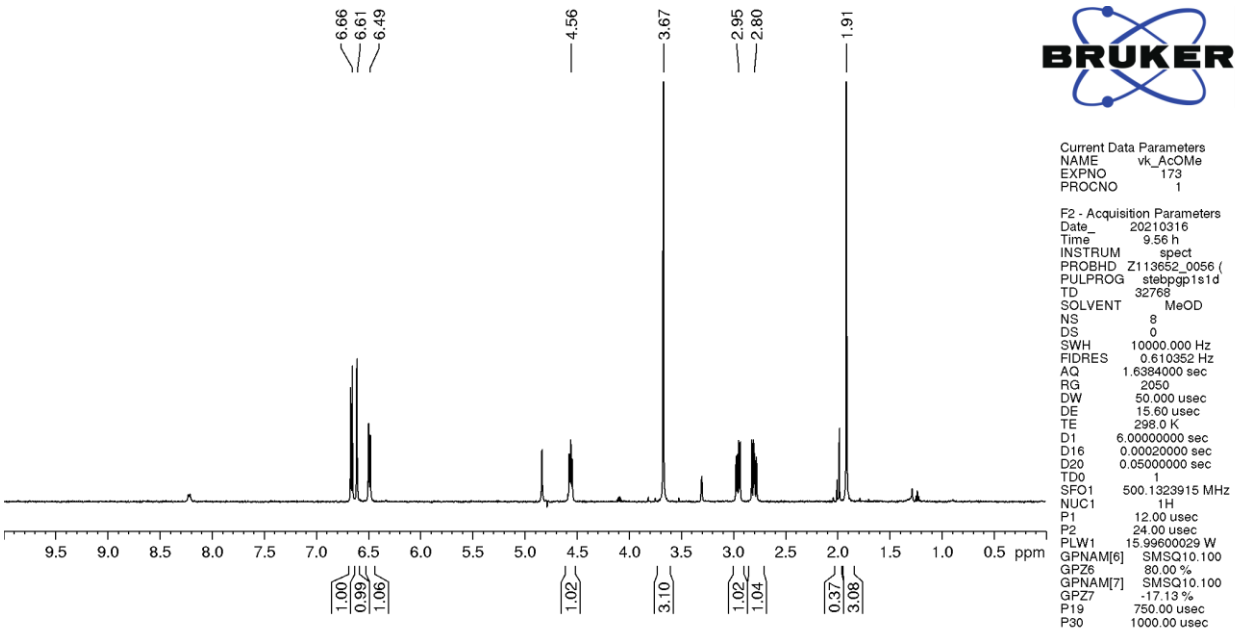





*OBC,* doi: 10.1039/d1ob01213d

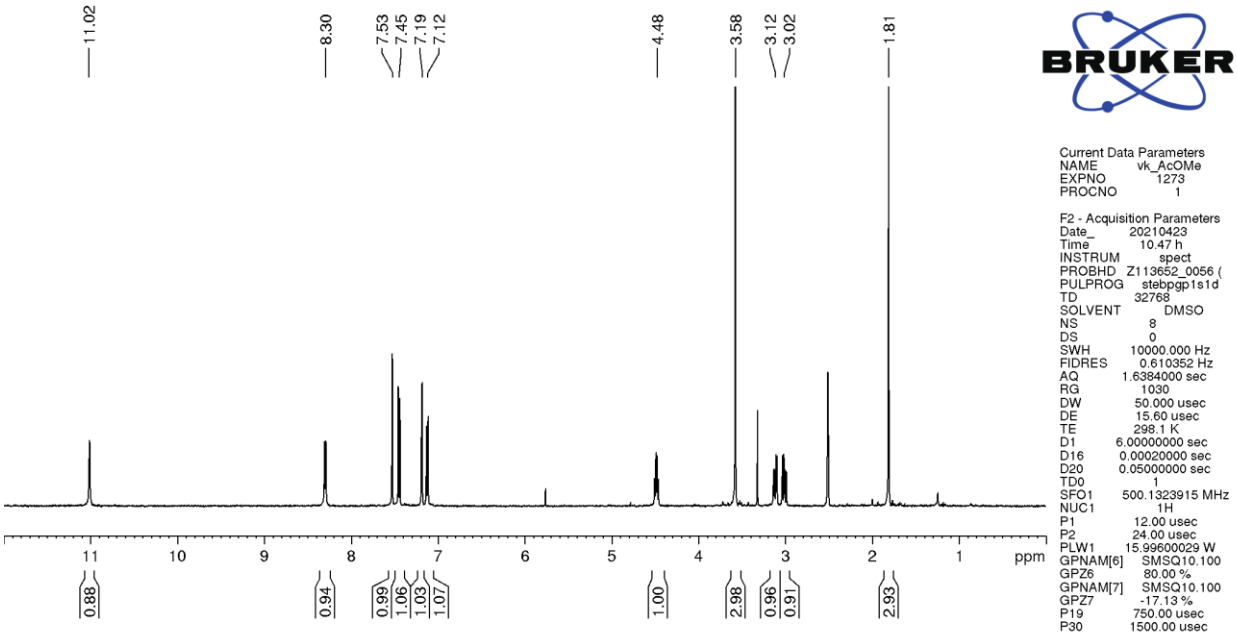
Ac-Dopa-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 6.66 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 1.7 Hz, 1H), 6.49 (dd, *J* = 8.0 and 1.7 Hz, 1H), 4.56 (dd, *J* = 8.6 and 6.2 Hz, 1H), 3.67 (s, 3H), 2.95 (dd, *J* = 14.0 and 6.2 Hz, 1H), 2.80 (dd, *J* = 14.0 and 8.4 Hz, 1H), 1.91 (s, 3H).




Ac-6-Br-Trp-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 11.02 (s, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 8.6 and 1.7 Hz, 1H), 4.48 (m, 1H), 3.57 (s, 3H), 3.12 (dd, *J* = 14.7 and 5.9 Hz, 1H), 3.02 (dd, *J* = 14.6 and 8.6 Hz, 1H), 1.81 (s, 3H).

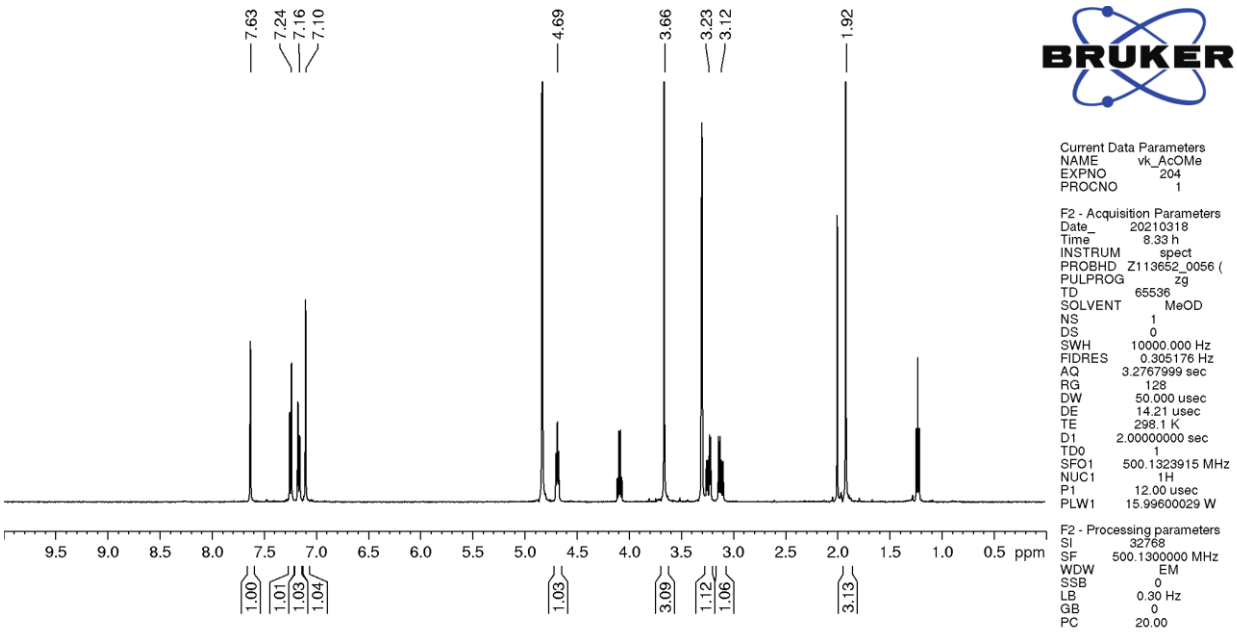





*OBC,* doi: 10.1039/d1ob01213d

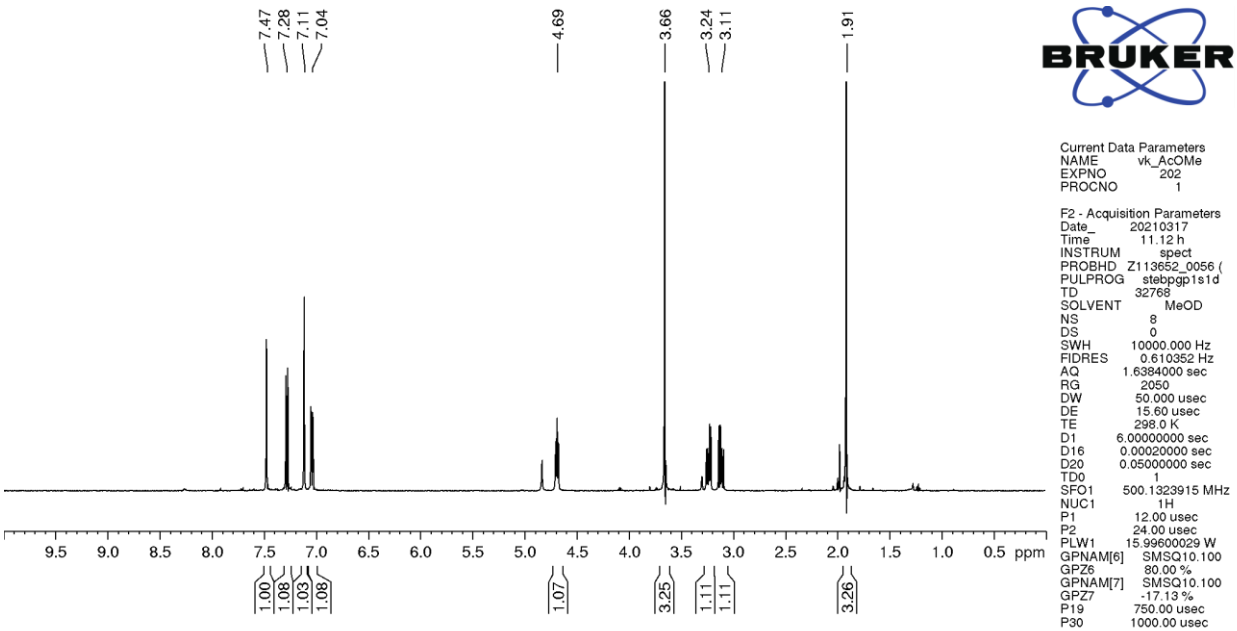
Ac-5-Br-Trp-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.63 (s, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.10 (s, 1H), 4.69 (t, *J* = 6.7 Hz, 1H), 3.66 (s, 3H), 3.23 (dd, *J* = 14.7 and 6.1 Hz, 1H), 3.12 (dd, *J* = 14.7 and 7.5 Hz, 1H), 1.92 (s, 3H).




Ac-5-Cl-Trp-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.47 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.11 (s, 1H), 7.04 (dd, *J* = 8.6 and 2.0 Hz, 1H), 4.69 (dd, *J* = 7.7 and 5.8 Hz, 1H), 3.65 (s, 3H), 3.23 (dd, *J* = 14.7 and 5.9 Hz, 1H), 3.11 (dd, *J* = 14.7 and 7.8 Hz, 1H), 1.91 (s, 3H).

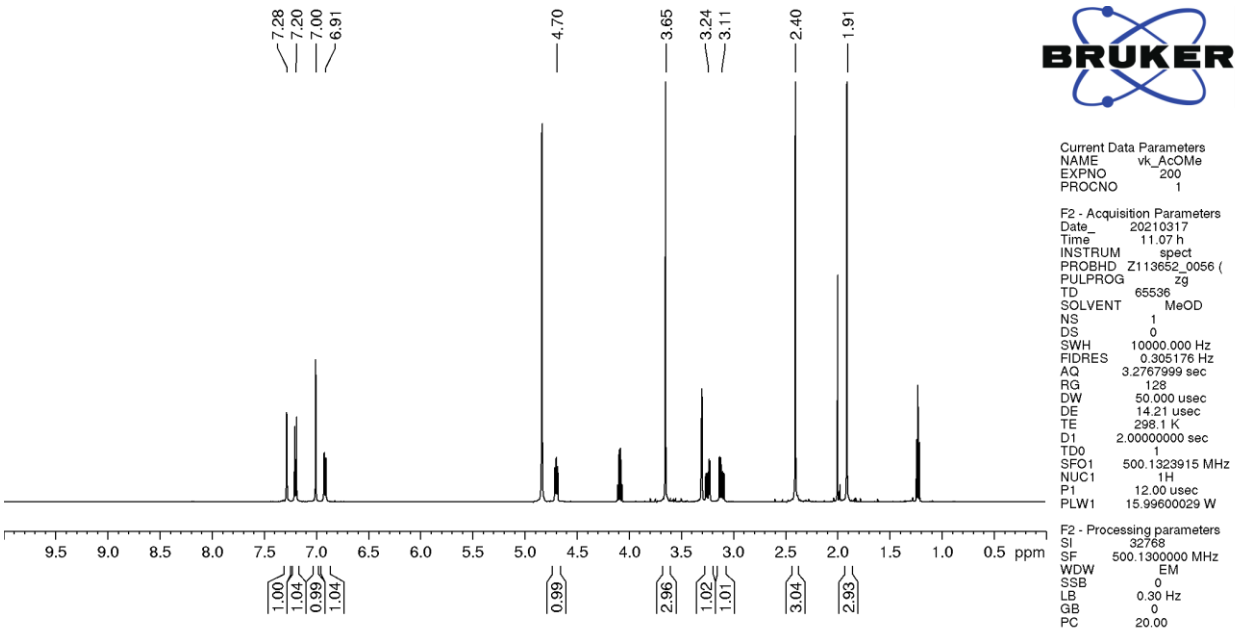





*OBC,* doi: 10.1039/d1ob01213d

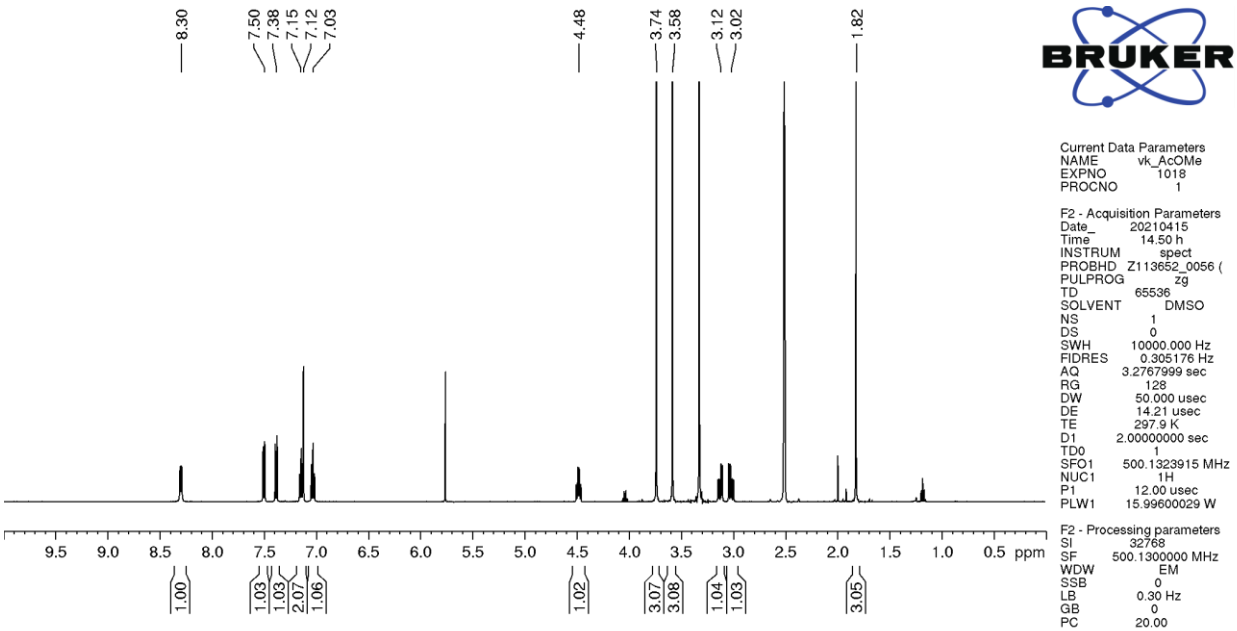
Ac-5-$CH_3$-Trp-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.28 (s, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.00 (s, 1H), 6.91 (dd, *J* = 8.4 and 1.5 Hz), 4.70 (dd, *J* = 7.6 and 5.8 Hz, 1H), 3.65 (s, 3H), 3.24 (ddd, *J* = 14.7, 5.9 and 0.7 Hz, 1H), 3.11 (dd, *J* = 14.7 and 7.8 Hz, 1H), 2.40 (s, 3H), 1.91 (s, 3H).




Ac-1-$CH_3$-Trp-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.30 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.15 (m, 1H), 7.12 (s, 1H), 7.03 (m, 1H), 4.47 (m, 1H), 3.74 (s, 3H), 3.58 (s. 3H), 3.12 (dd, *J* = 14.7 and 6.0 Hz, 1H), 3.02 (dd, *J* = 14.6 and 8.2 Hz, 1H), 1.82 (s, 3H).

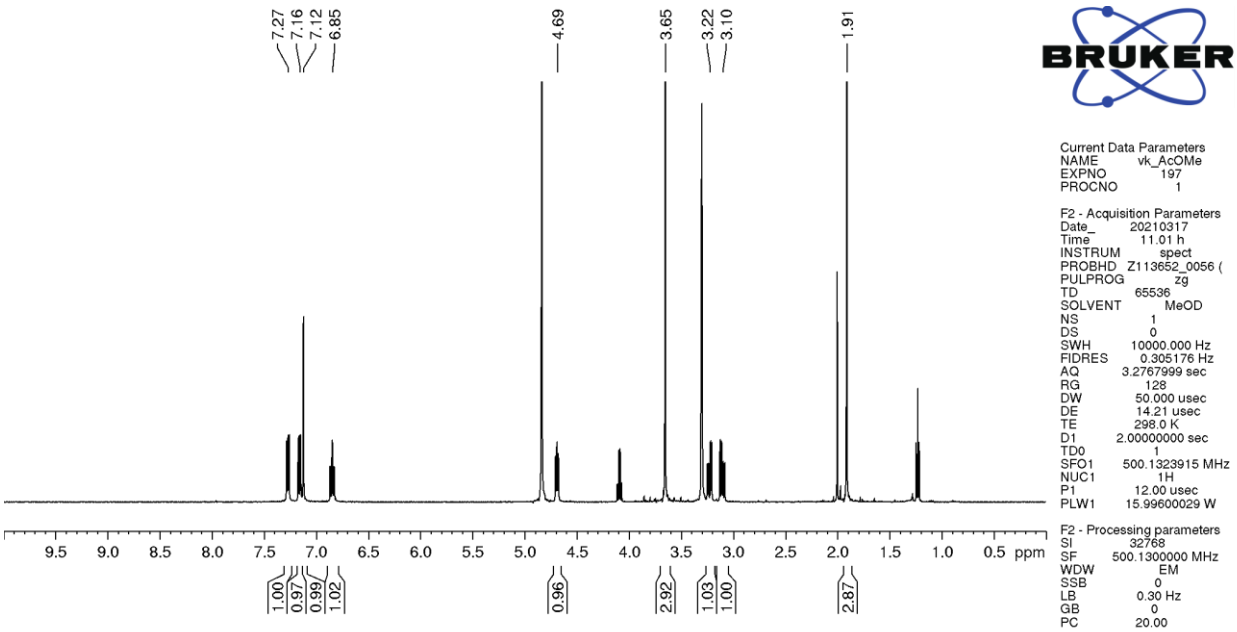




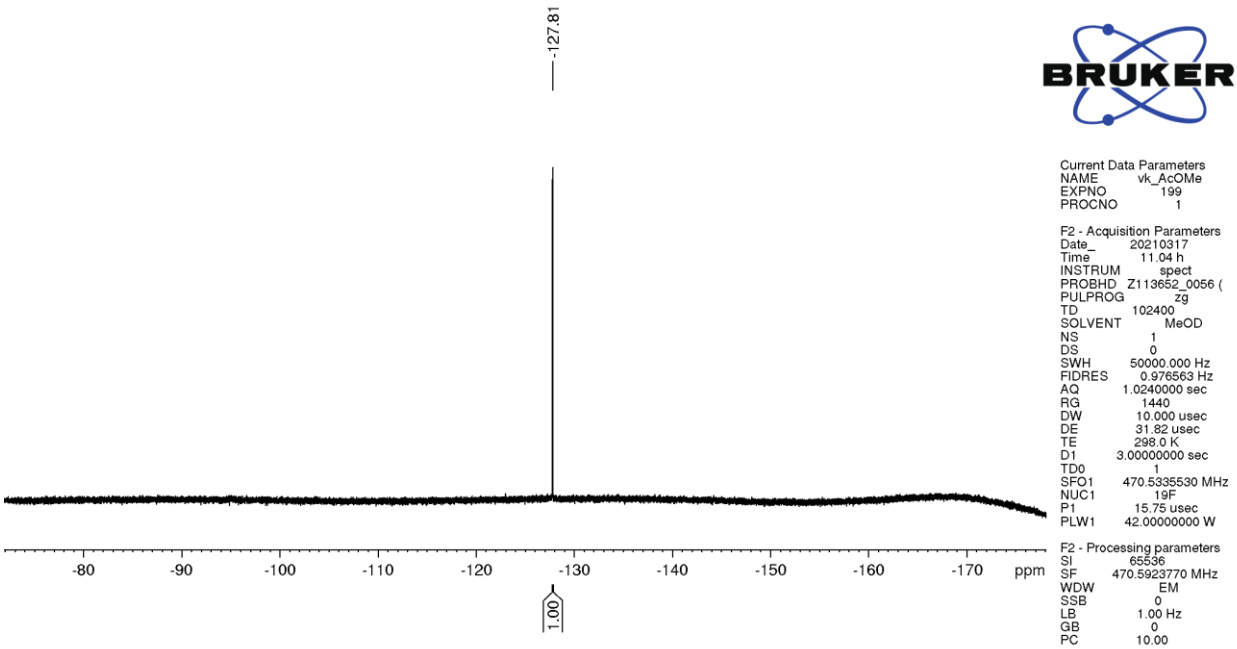

*OBC,* doi: 10.1039/d1ob01213d

Ac-5-F-Trp-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.27 (dd, *J* = 8.8 and 4.5 Hz, 1H), 7.16 (dd, *J* = 10.0 and 2.6 Hz, 1H), 7.12 (s, 1H), 6.85 (td, *J* = 9.2 and 2.5 Hz, 1H), 4.69 (dd, *J* = 7.7. and 5.8 Hz, 1H), 3.65 (s, 3H), 3.22 (dd, *J* = 14.7 and 5.9 Hz, 1H), 3.10, (dd, *J* = 14.7 and 7.8 Hz, 1H), 1.91 (s, 3H).




$^{19}$F NMR (471 MHz): −127.8 (td, *J* = 10 and 5 Hz).

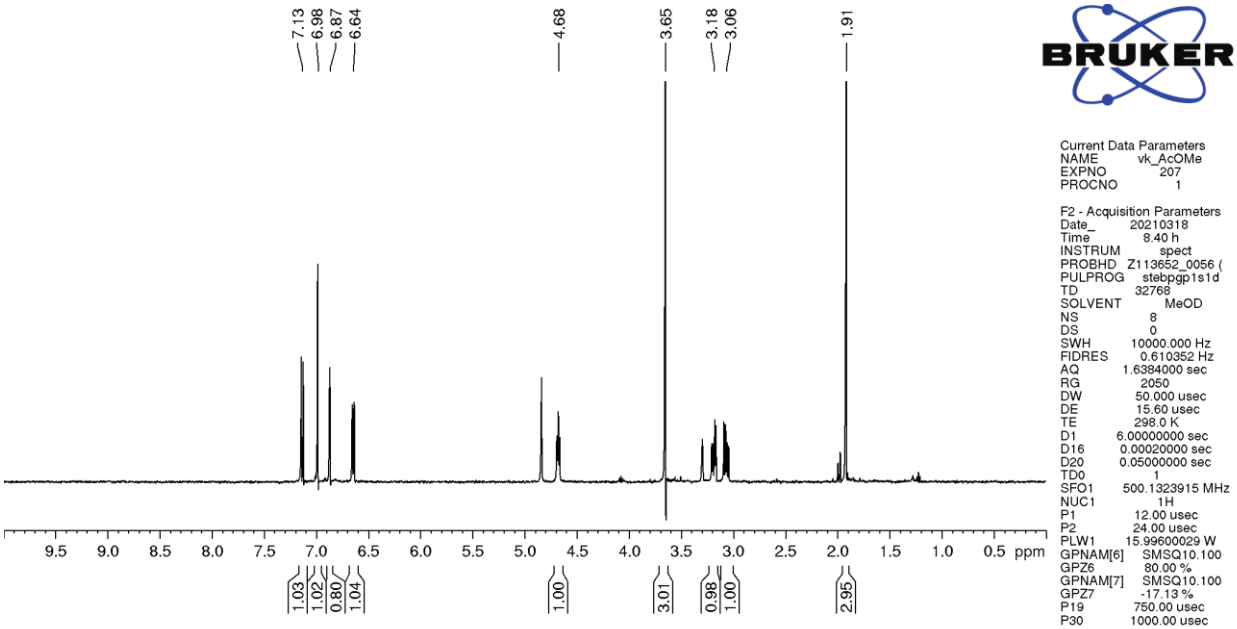





*OBC,* doi: 10.1039/d1ob01213d

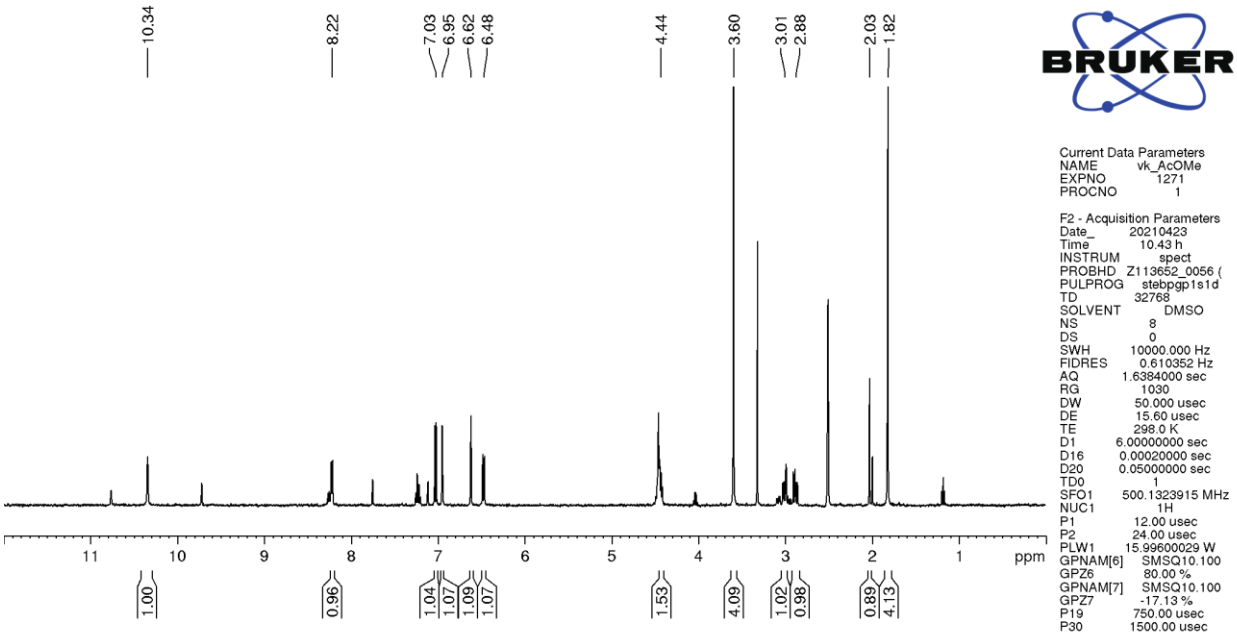
Ac-5-OH-Trp-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 7.14 (d, *J* = 8.9 Hz, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 4.68 (t, *J* = 6.6 Hz, 1H), 3.65 (s, 3H), 3.19 (dd, *J* = 14.7 and 5.9 Hz, 1H), 3.07 (dd, *J* = 14.5 and 7.7 Hz, 1H), 1.92 (s, 3H).




Ac-5-$NH_2$-Trp-$OCH_3$ (with Ac-5-AcNH-Trp-$OCH_3$) in DMSO-$d_6$:

$^1$H NMR (500 MHz): 10.34 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 2.2 Hz, 1H), 6.62 (d, *J* = 1.5 Hz, 1H), 6.48 (dd, *J* = 8.6 and 2.0 Hz, 1H), 4.44 (m, 1H), 3.60 (s, 3H), 3.01 (dd, *J* = 14.6 and 5.8 Hz, 1H), 2.88 (dd, *J* = 14.6 and 8.8 Hz, 1H), 1.82 (s, 3H).

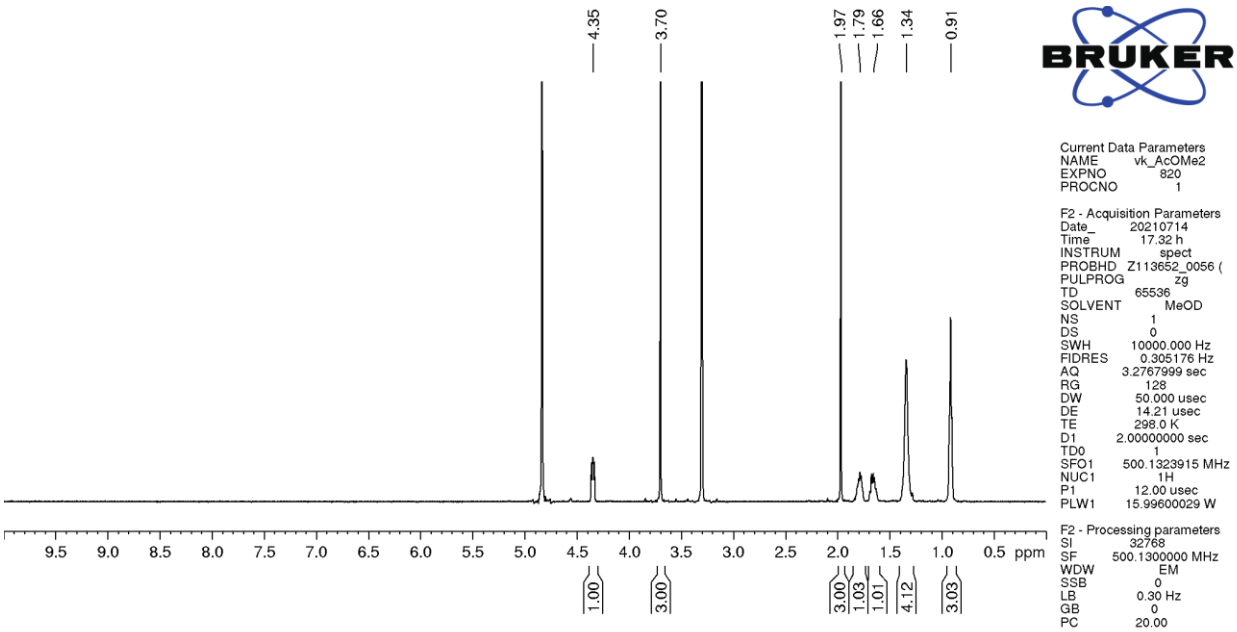





*OBC,* doi: 10.1039/d1ob01213d

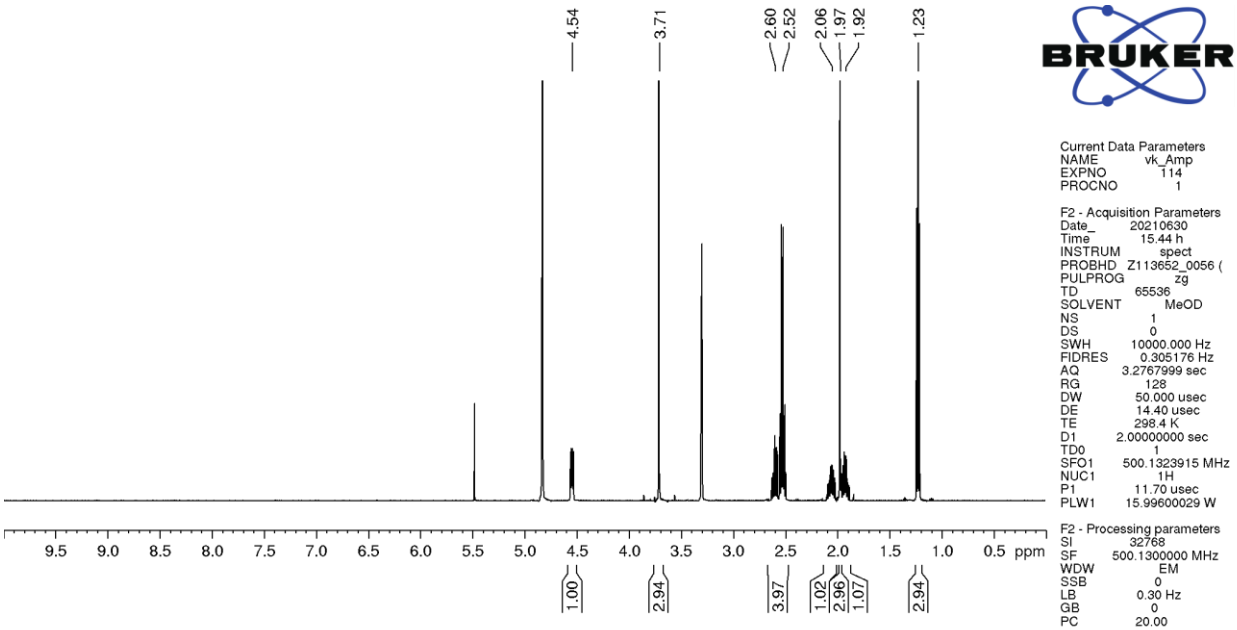
Ac-Nle-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.35 (dd, *J* = 8.5 and 5.4 Hz, 1H), 3.70 (s, 3H), 1.97 (s, 3H), 1.79 (m, 1H), 1.66 (m, 1H), 1.34 (m, 4H), 0.91 (t, *J* = 5.8 Hz, 3H).




Ac-Eth-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.54 (dd, *J* = 9.0 and 4.9 Hz, 1H), 3.71 (s, 3H), 2.60 (m, 1H), 2.53 (m, 1H), 2.52 (q, *J* = 7.4 Hz, 2H), 2.06 (m, 1H), 1.97 (s, 3H), 1.92 (m, 1H), 1.23 (t, *J* = 7.4 Hz, 3H).

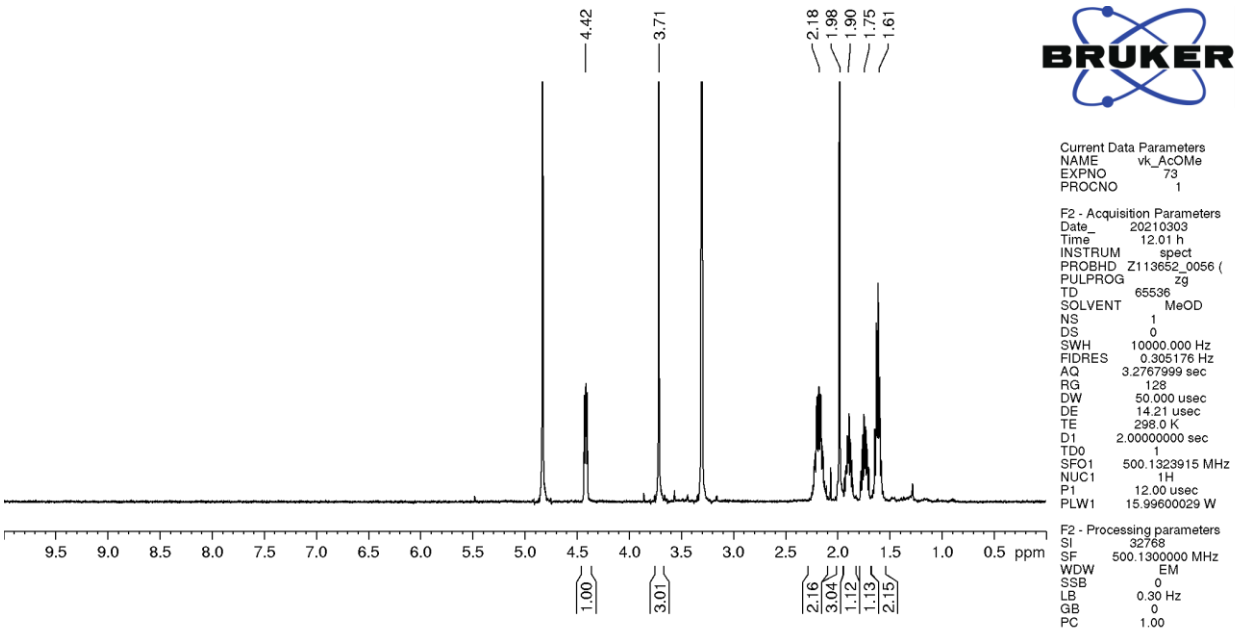




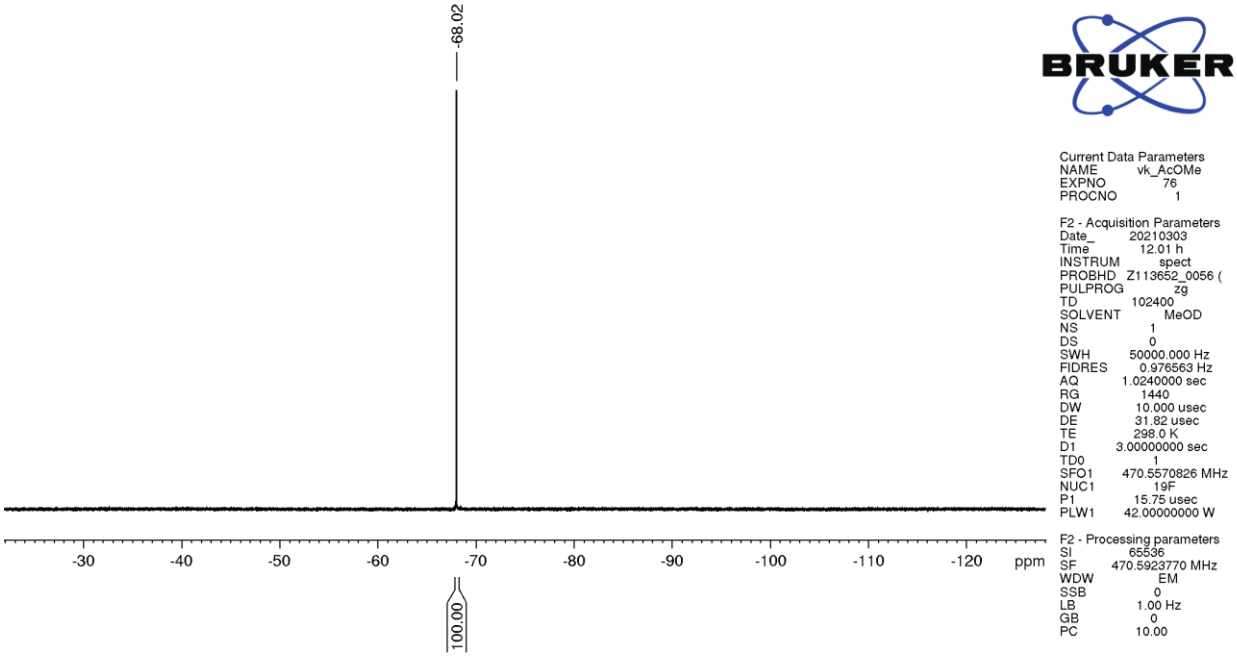

*OBC,* doi: 10.1039/d1ob01213d

Ac-Tfnle-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.42 (dd, *J* = 8.9 and 5.1 Hz, 1H), 3.71 (s, 3H), 2.18 (m, 2H), 1.98 (s, 3H), 1.90 (m, 1H), 1.75 (m, 1H), 1.61 (m, 2H).




$^{19}$F NMR (471 MHz): −68.0 (t, *J* = 11 Hz).

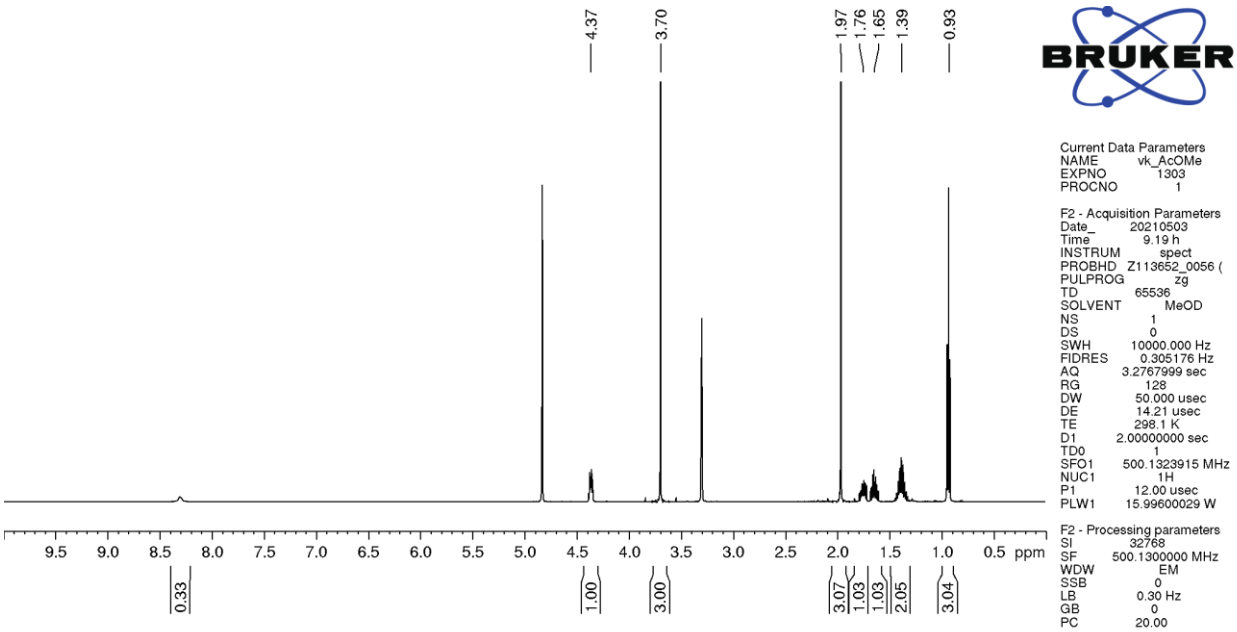





*OBC,* doi: 10.1039/d1ob01213d

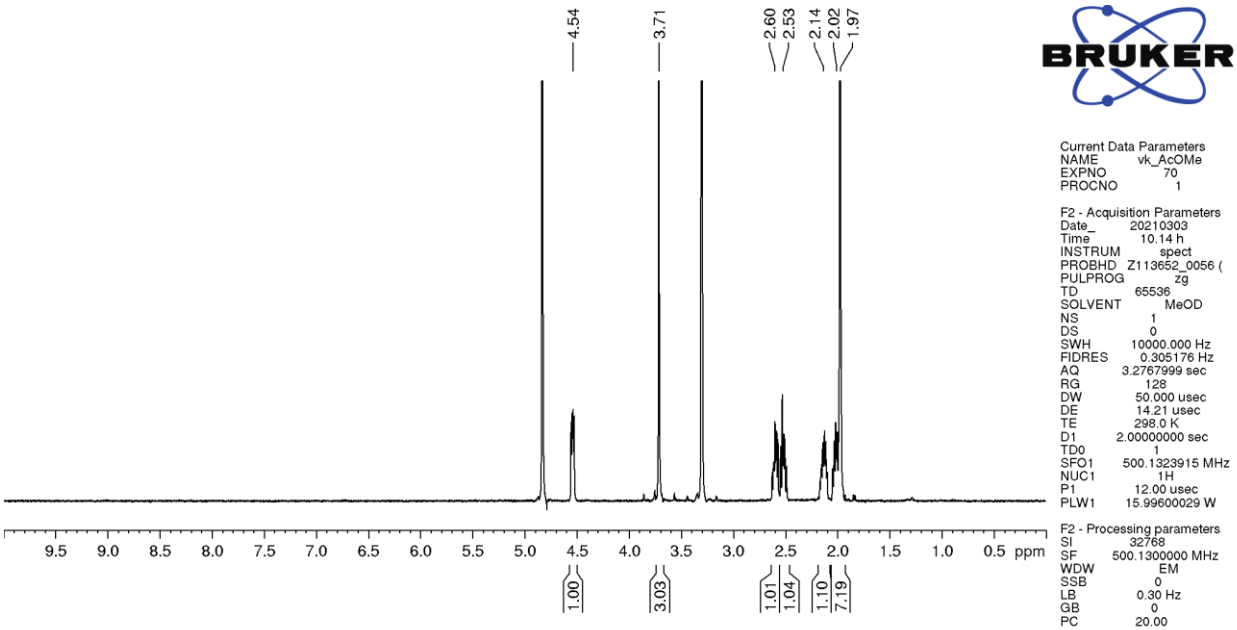
Ac-Nva-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.37 (m, 1H), 3.70 (s, 3H), 1.97 (s, 3H), 1.76 (m, 1H), 1.64 (m, 1H), 1.39 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).




Ac-Sem-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.54 (dd, *J* = 9.0 and 4.9 Hz, 1H), 3.71 (s, 3H), 2.60 (m, 1H), 2.53 (m, 1H), 2.14 (m, 1H), 2.02 (m, 1H), 1.97 (two s, 6H).

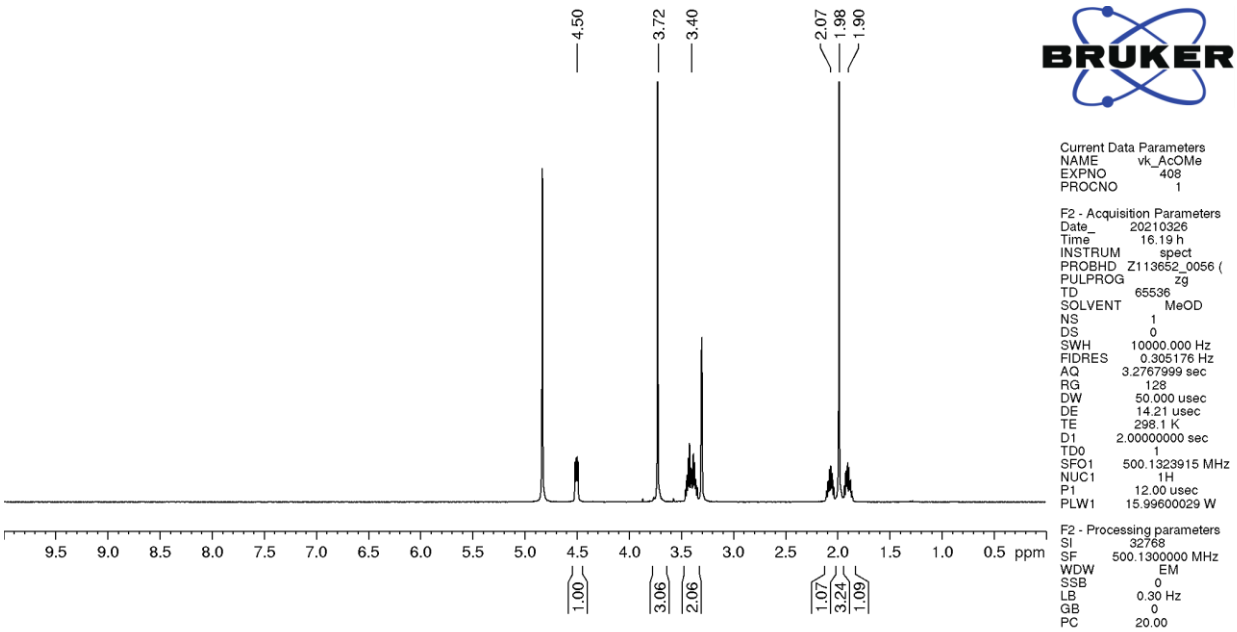





*OBC,* doi: 10.1039/d1ob01213d

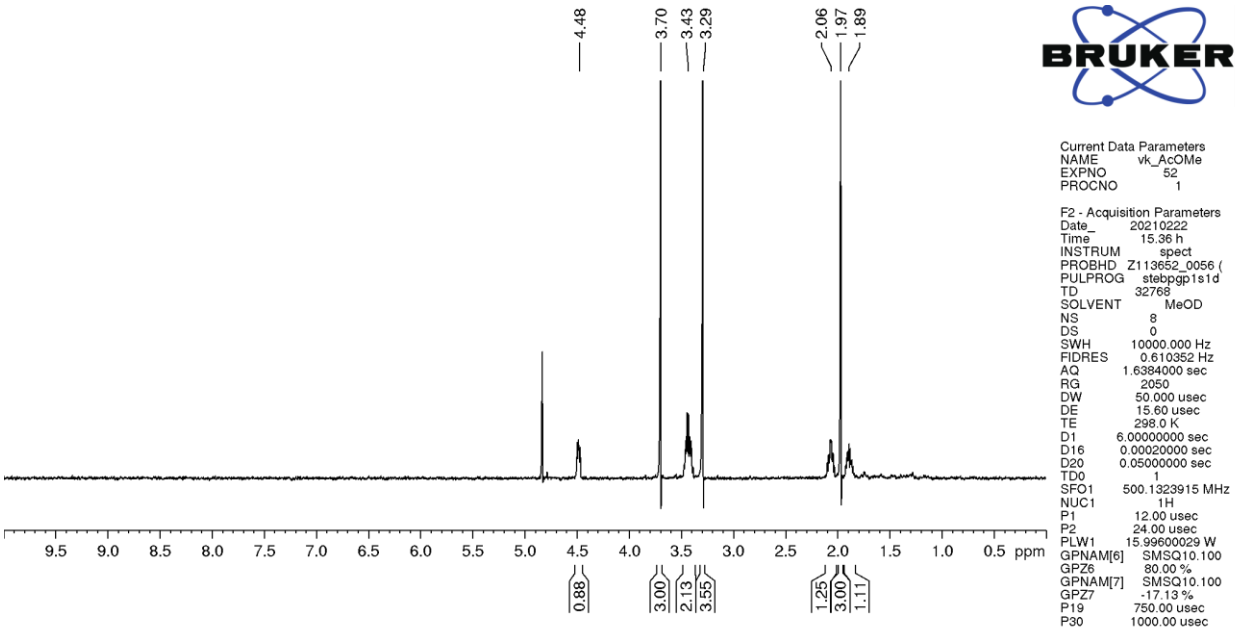
Ac-Aha-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.50 (dd, *J* = 8.8 and 5.2 Hz, 1H), 3.72 (s, 3H), 3.40 (m, 2H), 2.07 (m, 1H), 1.98 (s, 3H), 1.90 (m, 1H).




Ac-Mox-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.48 (dd, *J* = 8.6 and 5.6 Hz, 1H), 3.70 (s, 3H), 3.42 (m, 2H), 3.29 (s, 3H), 2.06 (m, 1H), 1.97 (s, 3H), 1.89 (m, 1H).

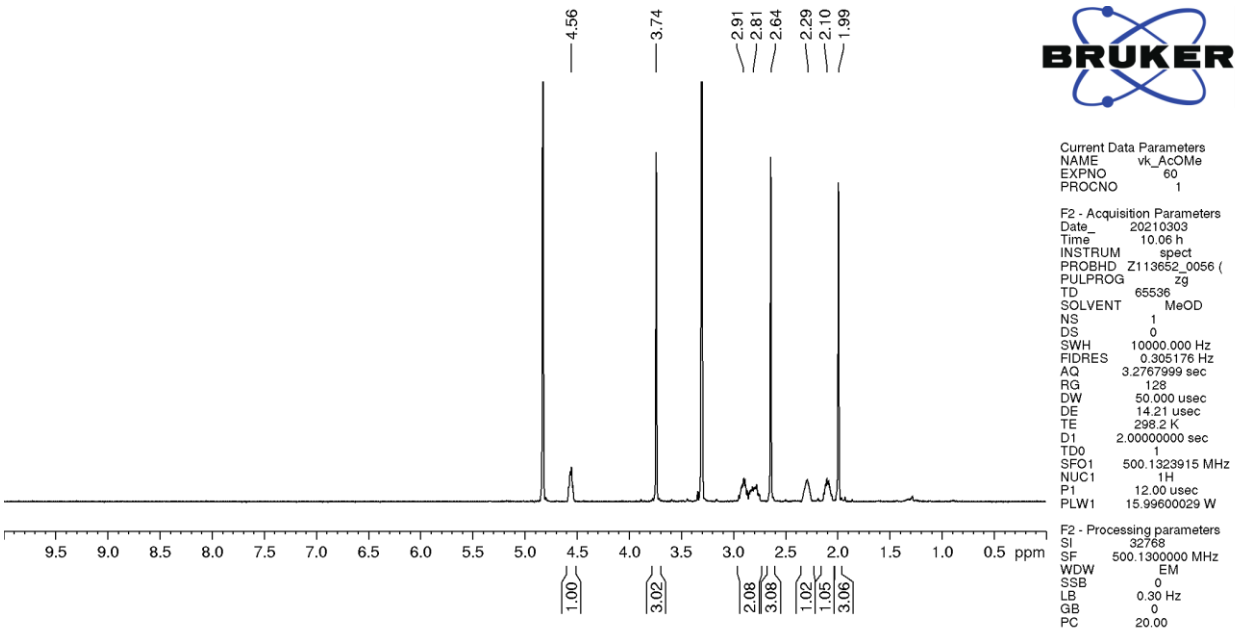





*OBC,* doi: 10.1039/d1ob01213d

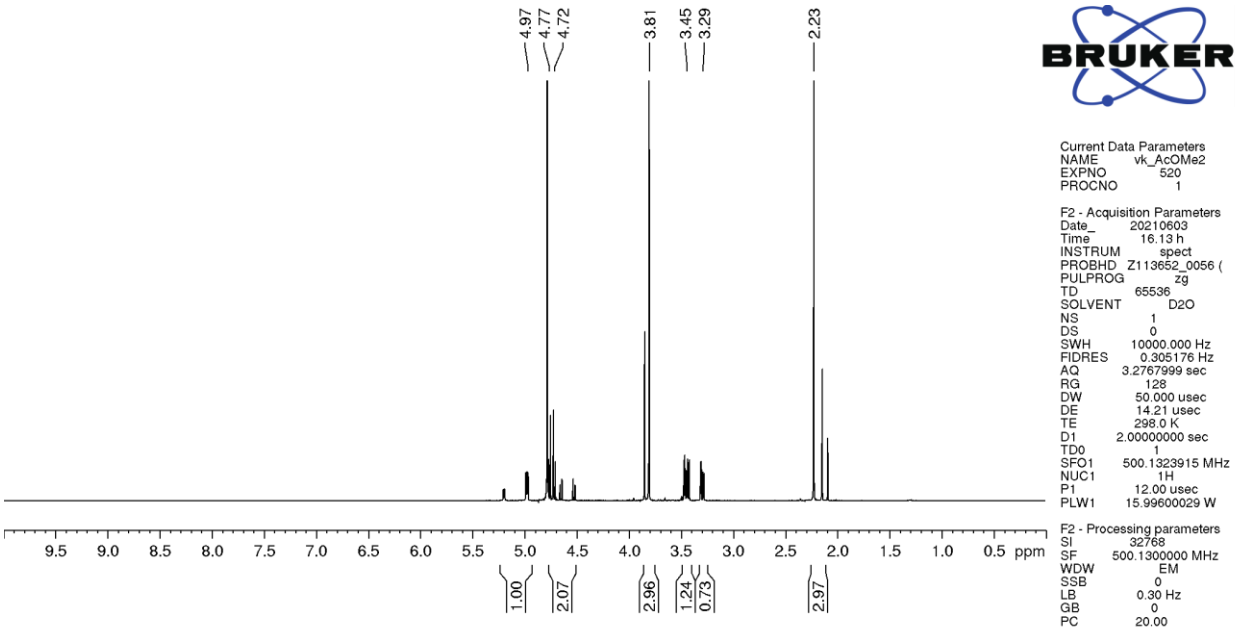
Ac-MetO-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.56 (m, 1H), 3.74 (s, 3H), 2.91 (m, 1H), 2.81 (m, 1H), 2.64 (s, 3H), 2.29 (m, 1H), 2.10 (m, 1H), 1.99 (s, 3H).




Ac-Cys[ψPro]-$OCH_3$ in deuterium oxide, major rotamer:

$^1$H NMR (500 MHz): 4.97 (dd, *J* = 7.2 and 3.5 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 4.72 (d, *J* = 9.0 Hz, 1H), 3.81 (s, 3H), 3.45 (m, 1H), 3.29 (dd, *J* = 12.4 and 3.5 Hz, 1H), 2.23 (s, 3H).

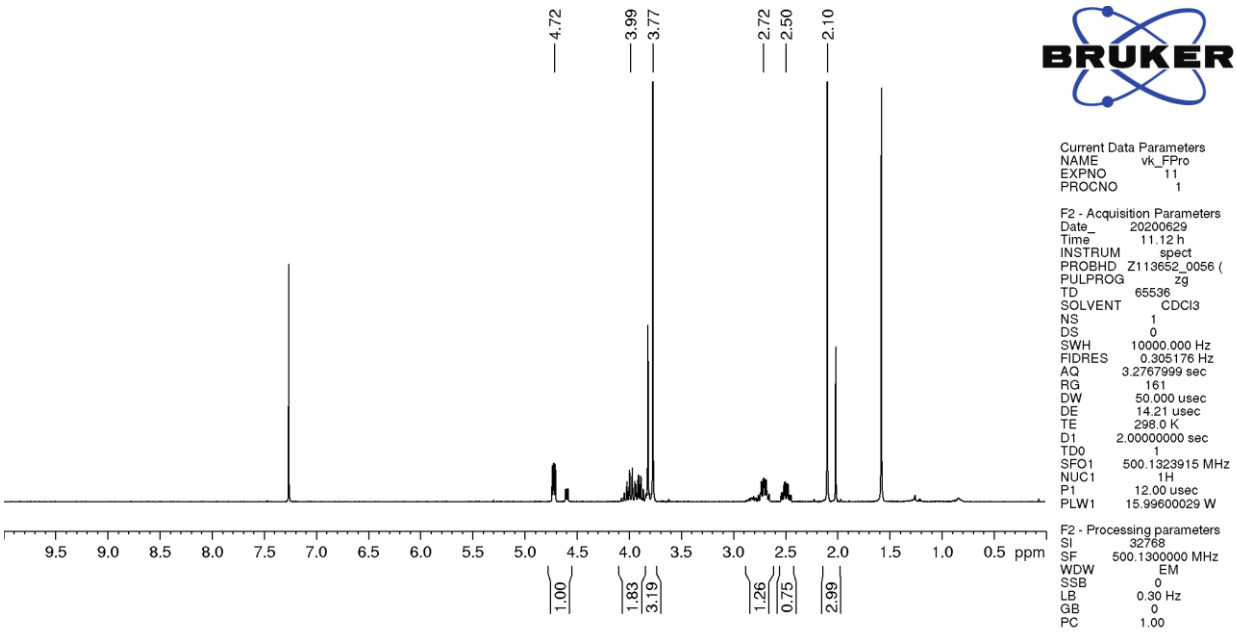




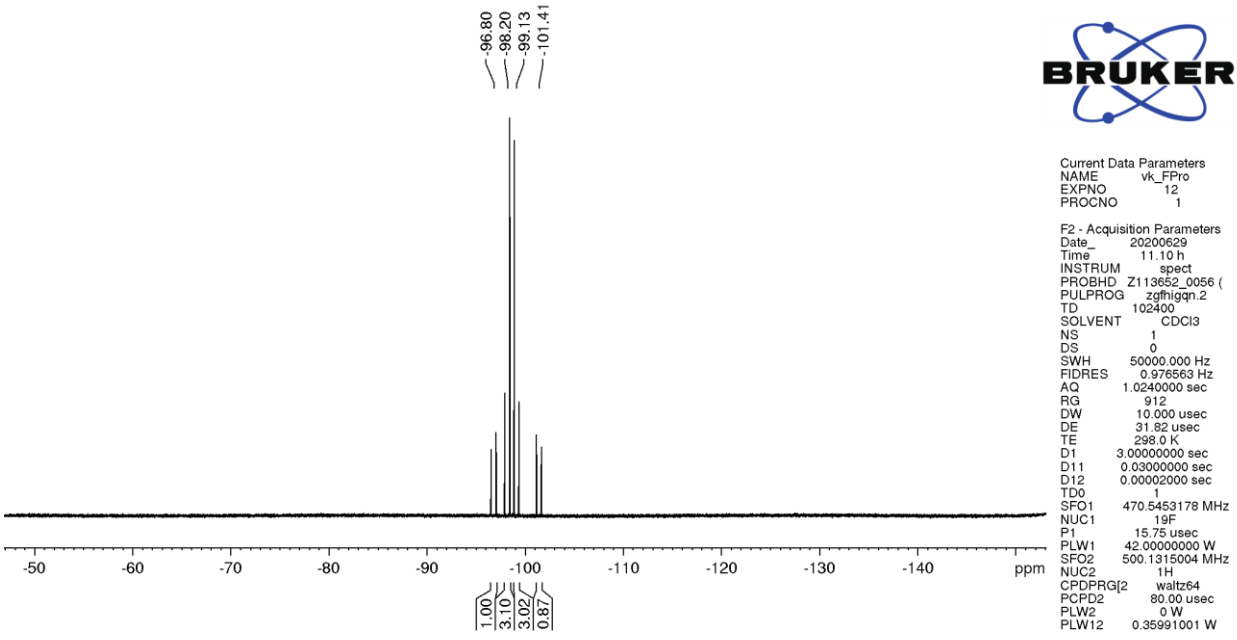

*OBC,* doi: 10.1039/d1ob01213d

Ac-Dfp-$OCH_3$ in deuterochloroform:

$^1$H NMR (500 MHz): 4.72 (dd, *J* = 9.3, 5.3, 1H), 3.99 (m, 2H), 3.77 (s, 3H), 2.72 (m, 1H), 2.50 (m, 1H), 2.10 (s, 3H).




$^{19}$F{$^1$H} NMR (471 MHz): −98.8 (minor, d, *J* = 236 Hz, 1F), −98.2 (major, d, *J* = 235 Hz, 1F), −99.1 (major, d, *J* = 234 Hz, 1F), −101.4 (minor, d, *J* = 236 Hz, 1F).

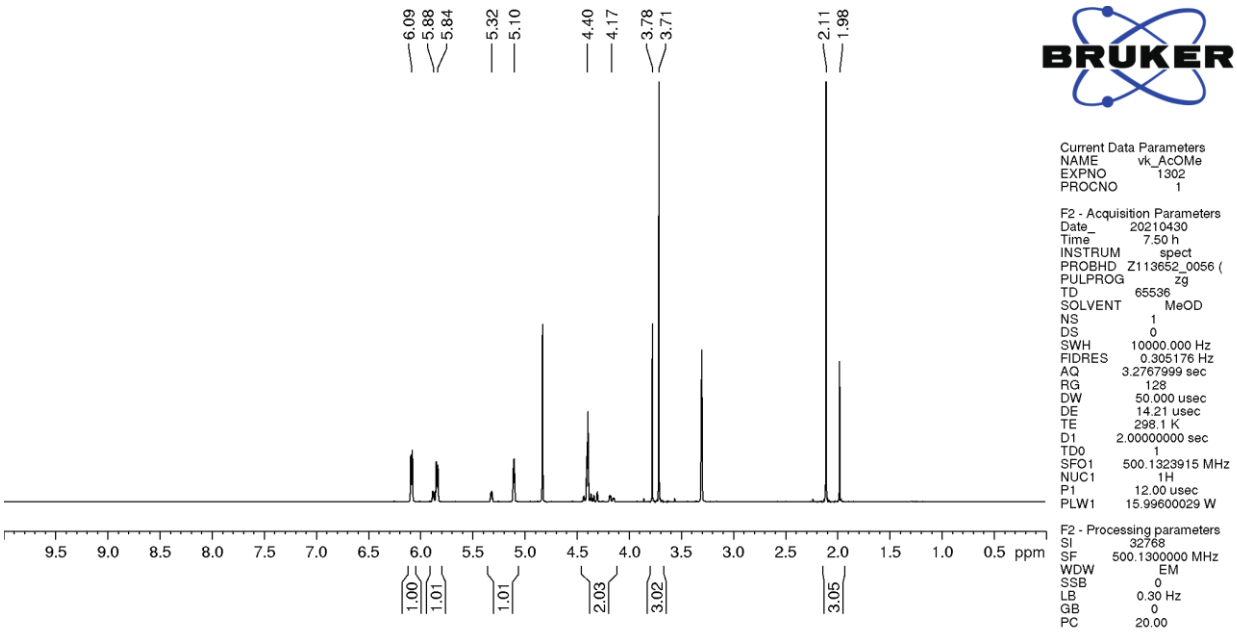





*OBC,* doi: 10.1039/d1ob01213d

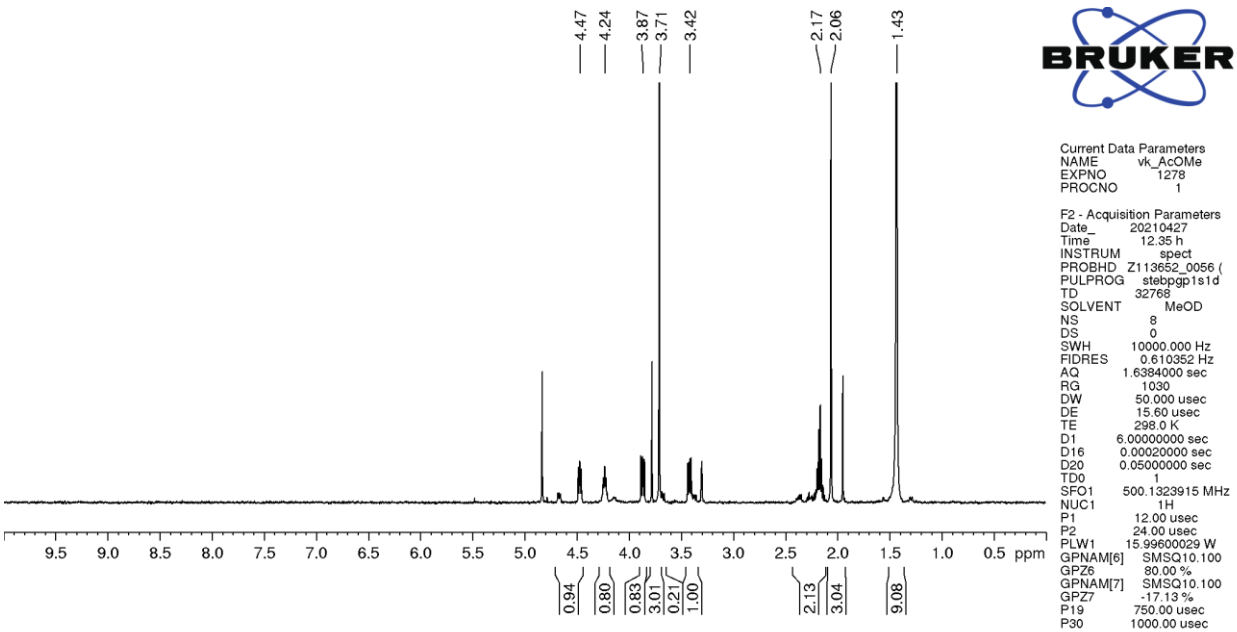
Ac-Dhp-$OCH_3$ in methanol-$d_4$, major rotamer:

$^1$H NMR (500 MHz): 6.09 (m, 1H), 5.84 (m, 1H), 5.10 (m, 1H), 4.40 (m, 2H), 3.71 (s, 3H), 2.11 (s, 3H).




Ac-(Boc)Amp-$OCH_3$ in methanol-$d_4$, major rotamer:

$^1$H NMR (500 MHz): 4.47 (dd, *J* = 8.4 and 6.0 Hz, 1H), 4.23 (m, 1H), 3.86 (dd, *J* = 10.6 and 6.5 Hz, 1H), 3.71 (s, 3H), 3.42 (dd, *J* = 10.4 and 5.4 Hz, 1H), 2.17 (m, 2H), 2.06 (s, 3H), 1.44 (s, 9H).

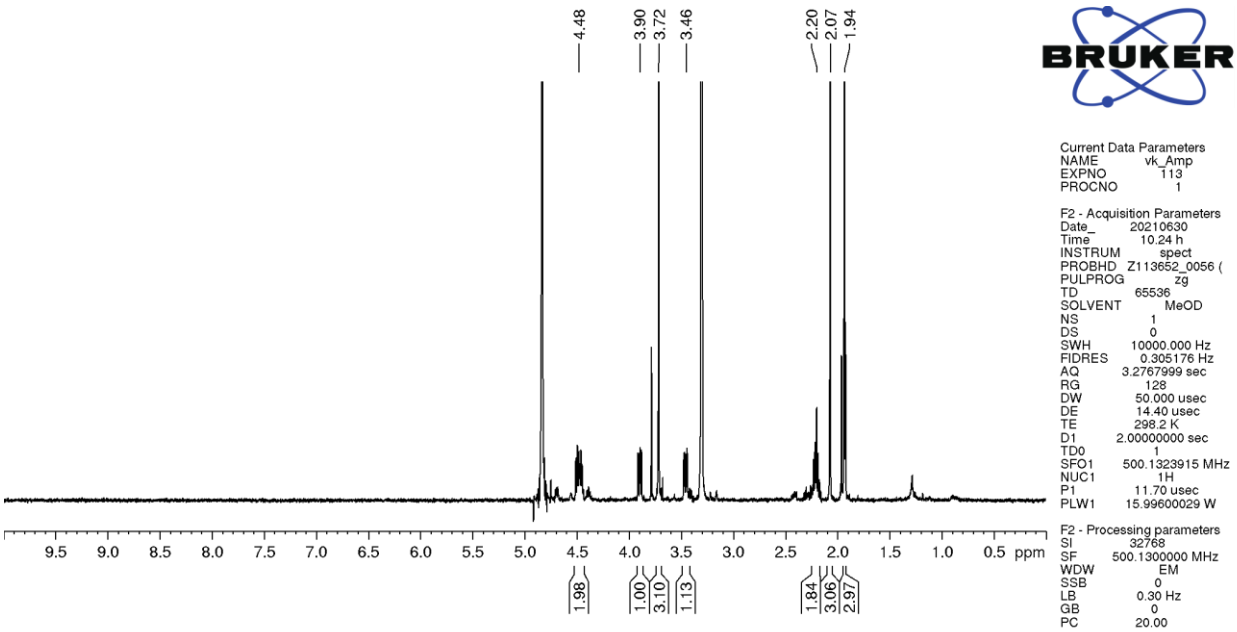





*OBC,* doi: 10.1039/d1ob01213d

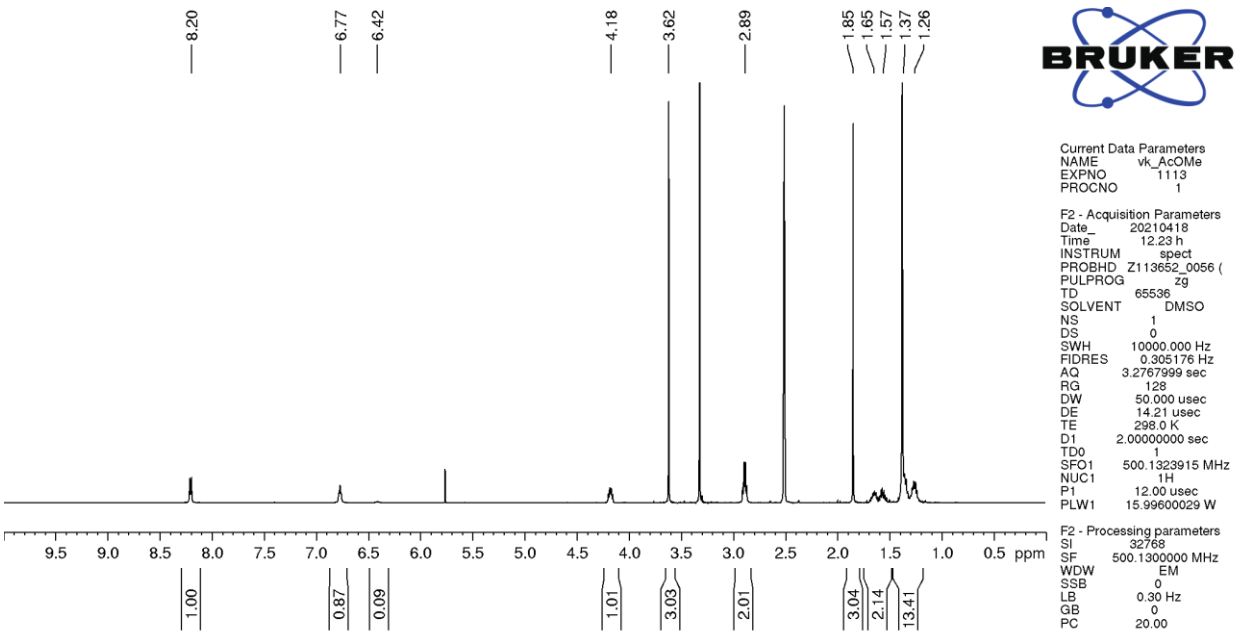
Ac-(Ac)Amp-$OCH_3$ in methanol-$d_4$, major rotamer:

$^1$H NMR (500 MHz): 4.48 (m, 2H), 3.90 (dd, *J* = 10.7 and 6.4 Hz, 1H), 3.72 (s, 3H), 3.46 (dd, *J* = 10.6 and 4.8 Hz, 1H), 2.20 (m, 2H), 2.07 (s, 3H), 1.94 (s, 3H).




Ac-(Boc)Lys-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.20 (d, *J* = 7.4 Hz, 1H), 6.77 (t, *J* = 5.4 Hz, 1H), 4.18 (m, 1H), 3.62 (s, 3H), 2.89 (q, *J* = 6.5 Hz, 2H), 1.85 (s, 3H), 1.65 (m, 1H), 1.57 (m, 1H), 1.37 (s, 9H), 1.38-1.23 (m, 4H).

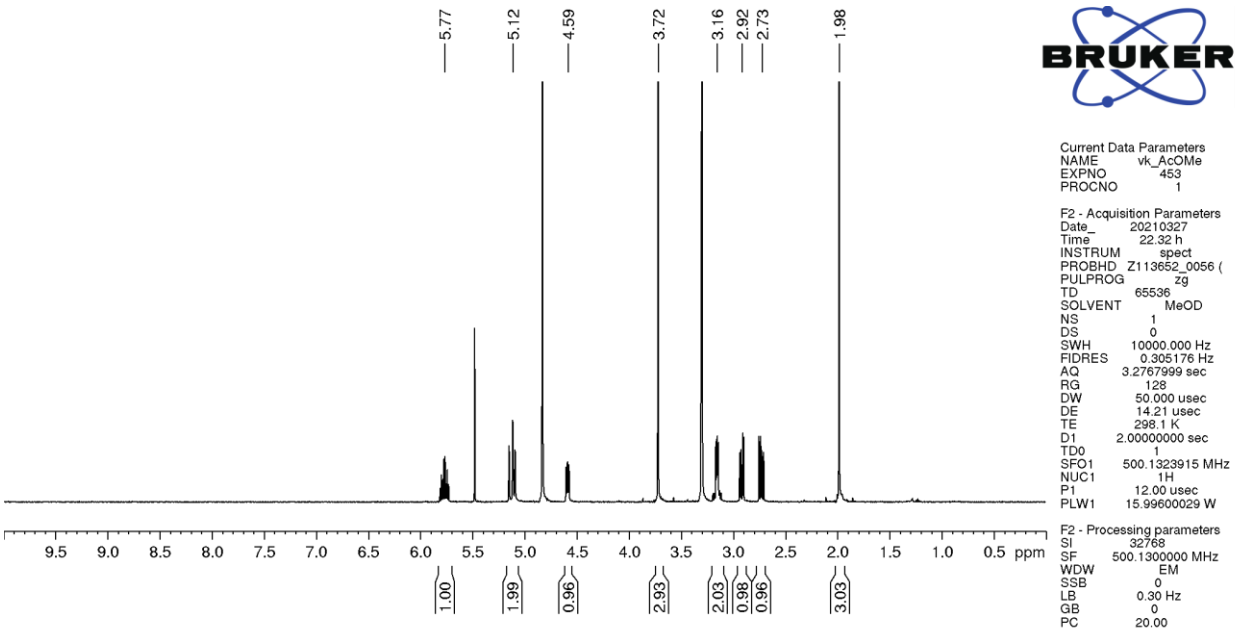





*OBC,* doi: 10.1039/d1ob01213d

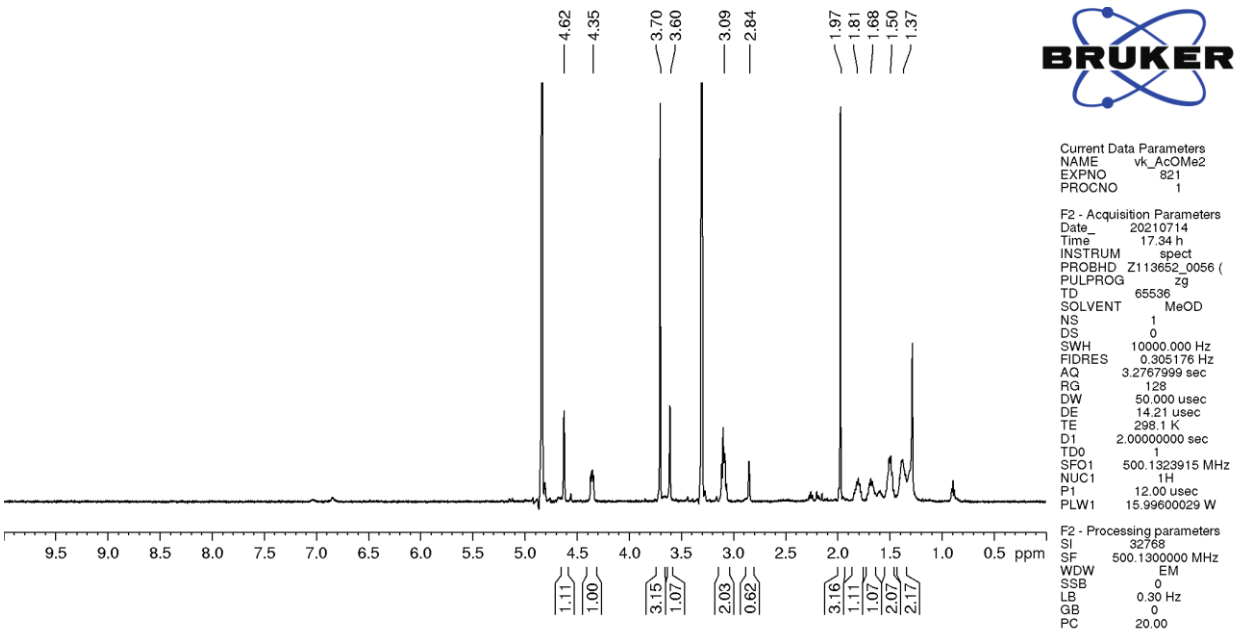
Ac-Sac-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 5.77 (m, 1H), 5.12 (m, 2H), 4.59 (dd, *J* = 8.2 and 5.4 Hz, 1H), 3.72 (s, 3H), 3.16 (m, 2H), 2.92 (dd, *J* = 13.8 and 5.3 Hz, 1H), 2.73 (dd, *J* = 13.9 and 8.2 Hz, 1H), 1.98 (s, 3H).




Ac-(Pro)Lys-$OCH_3$ in methanol-$d_4$:

$^1$H NMR (500 MHz): 4.62 (s, 1H), 4.35 (dd, *J* = 8.5 and 5.4 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 1H), 3.09 (m, 2H), 2.84 (s, 1H), 1.97 (s, 3H), 1.81 (m, 1H), 1.68 (m, 1H), 1.50 (m, 2H), 1.37 (m, 2H).

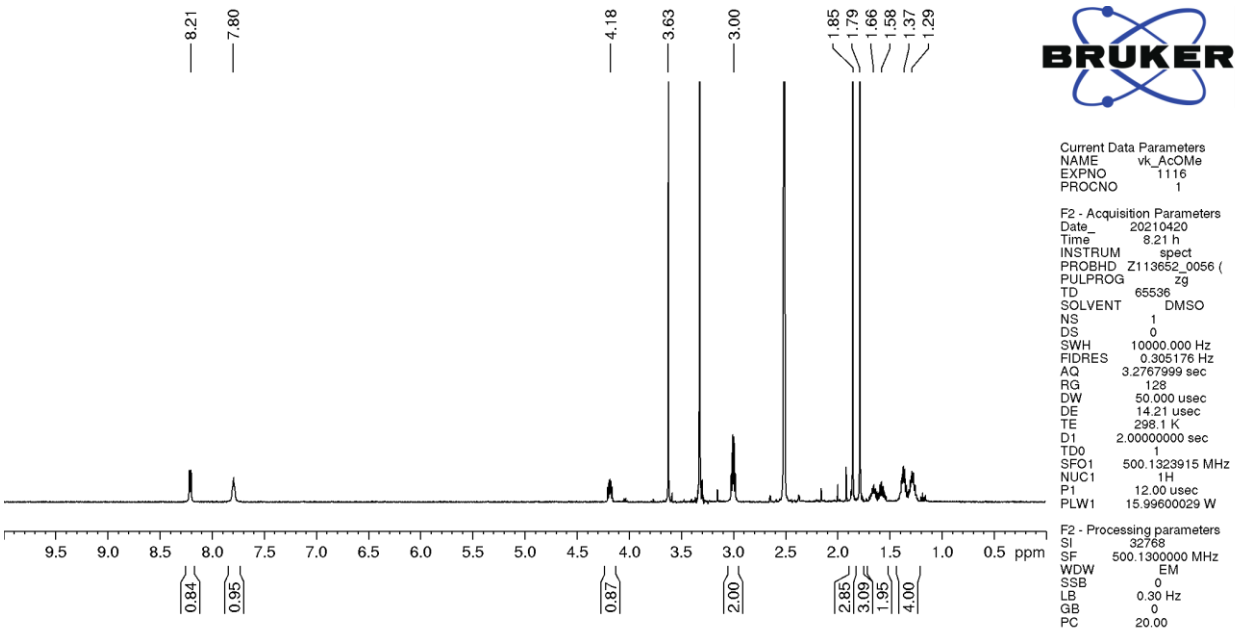





*OBC,* doi: 10.1039/d1ob01213d

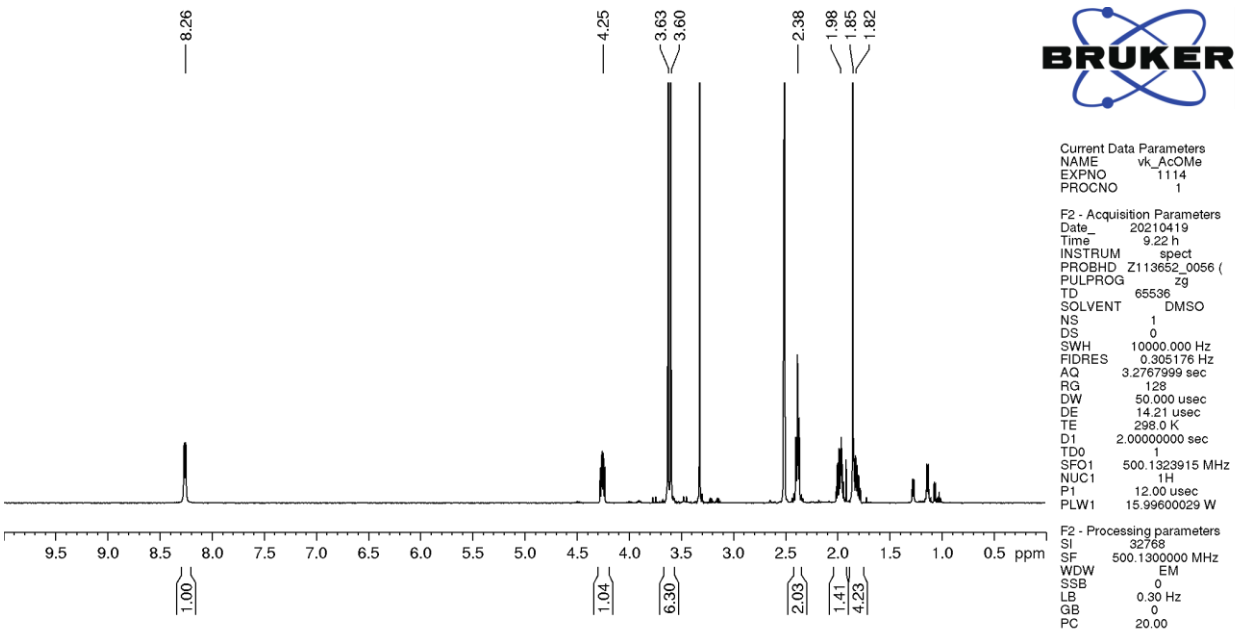
Ac-(Ac)Lys-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.21 (d, *J* = 7.4 Hz, 1H), 7.80 (m, 1H), 4.18 (m, 1H), 3.63 (s, 3H), 3.00 (q, *J* = 6.5 Hz, 2H), 1.85 (s, 3H), 1.79 (s, 3H), 1.66 (m, 1H), 1.58 (m, 1H), 1.37 (m, 2H), 1.29 (m, 2H).




Ac-(Me)Glu-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.26 (d, *J* = 7.6 Hz, 1H), 4.25 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 2.38 (m, 2H), 1.98 (m, 1H), 1.85 (s, 3H), 1.82 (m, 1H).

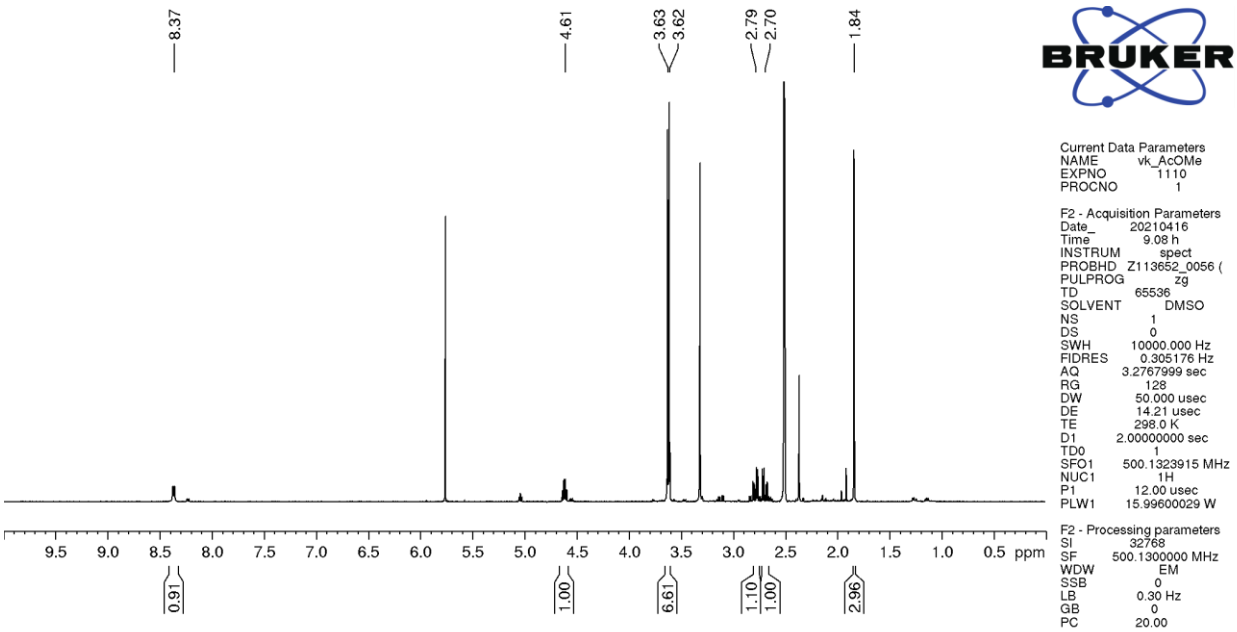





*OBC,* doi: 10.1039/d1ob01213d

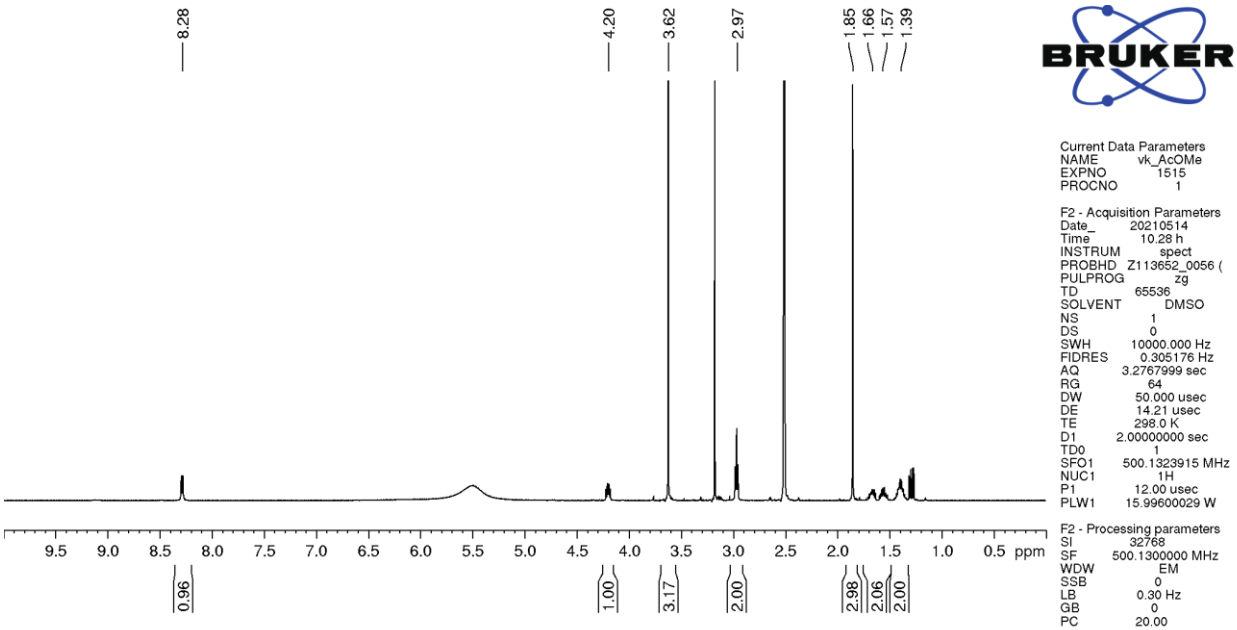
Ac-(Me)Asp-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.37 (d, *J* = 8.4 Hz, 1H), 4.61 (m, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 2.79 (dd, *J* = 16.4 and 6.1 Hz, 1H), 2.70 (dd, *J* = 16.4 and 7.2 Hz, 1H), 1.84 (s, 3H).




Ac-Citr-$OCH_3$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 8.28 (d, *J* = 7.4 Hz, 1H), 4.20 (m, 1H), 3.62 (s, 3H), 3.00 (t, *J* = 6.9 Hz, 2H), 1.85 (s, 3H), 1.66 (m, 1H), 1.57 (m, 1H), 1.39 (m, 2H).

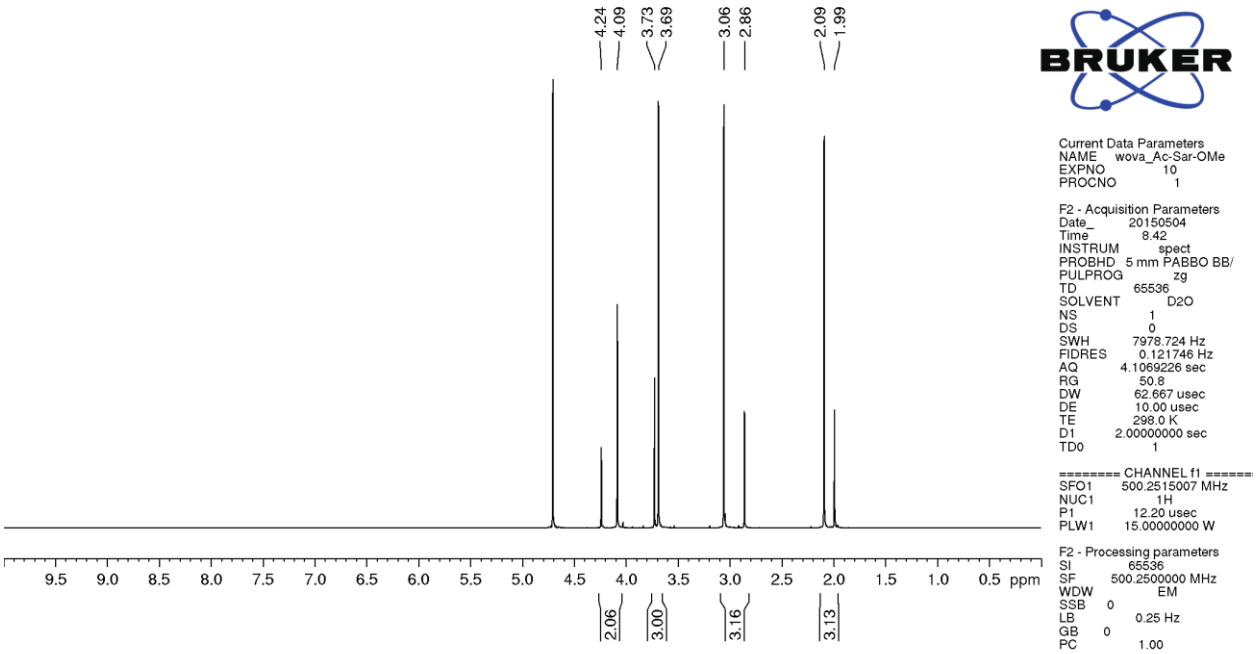





*OBC,* doi: 10.1039/d1ob01213d

Ac-Sar-$OCH_3$ in deuterium oxide:

$^1$H NMR (500 MHz): major rotamer, 4.08 (s, 2H), 3.69 (s, 3H), 3.06 (s, 3H), 2.09 (s, 3H); minor rotamer, 4.24 (s, 2H), 3.73 (s, 3H), 2.86 (s, 3H), 1.99 (s, 3H).



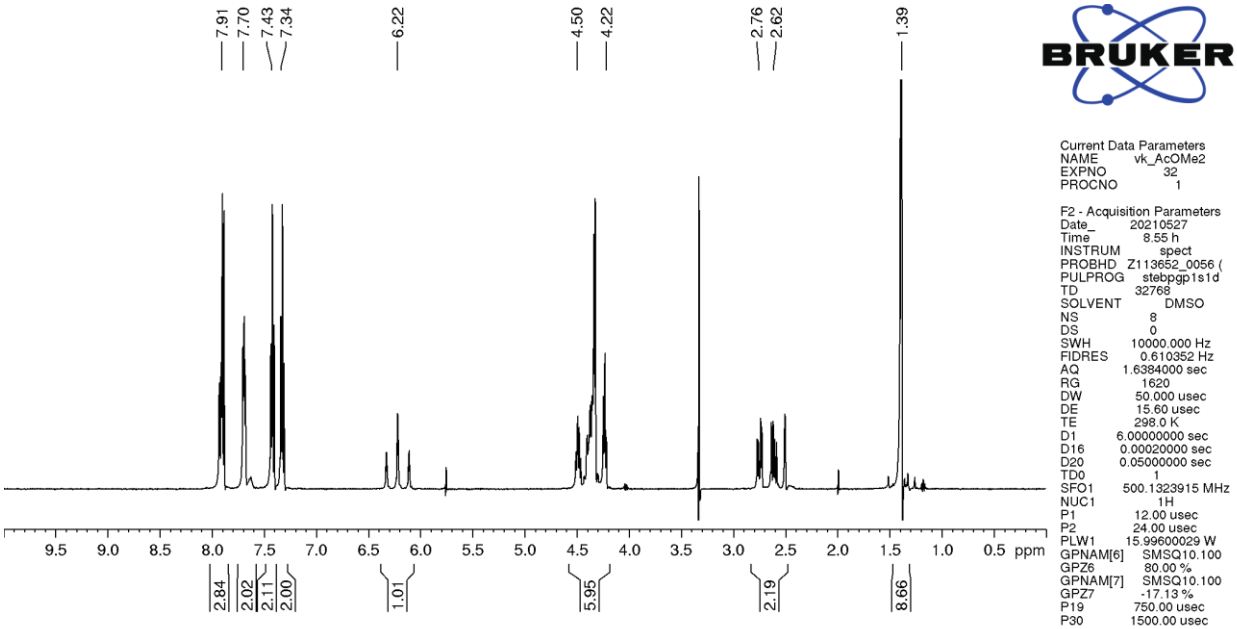



*OBC,* doi: 10.1039/d1ob01213d

## NMR spectra for difluoroethyl esters

Fmoc-($^t$Bu)Asp-$OCH_2CHF_2$ in DMSO-$d_6$:

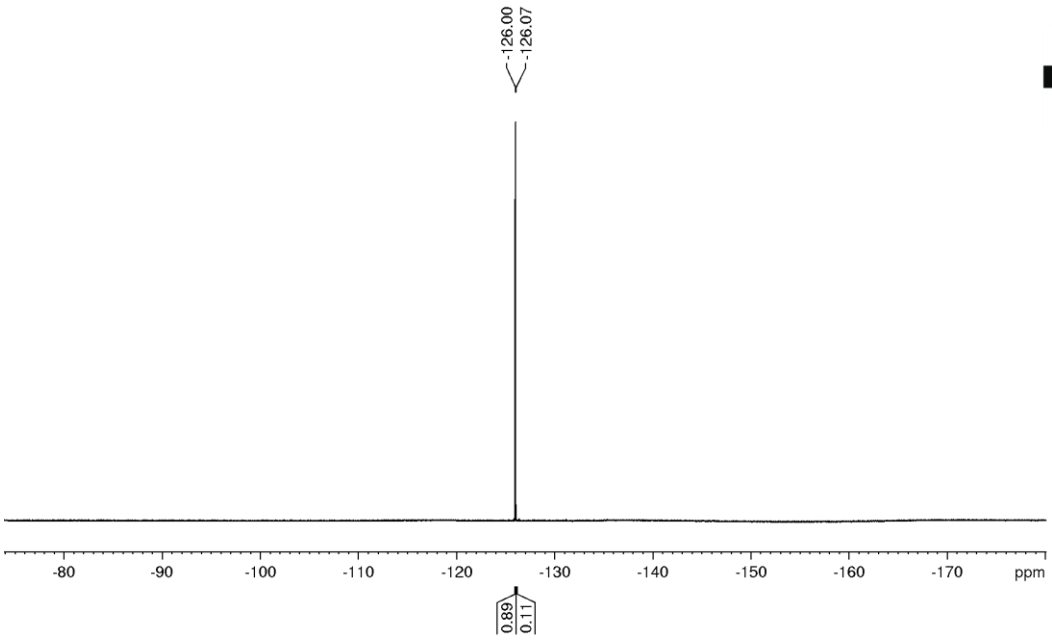
$^1$H NMR (500 MHz): 7.92 (d, *J* = 9.1 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.69 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 6.22 (tm, $J_{HF}$ = 54 Hz, 1H), 4.51-4.21 (m, 6H), 2.75 (dd, *J* = 16.3 and 5.8 Hz, 1H), 2.60 (dd, *J* = 16.4 and 8.8 Hz, 1H), 1.39 (s, 9H).

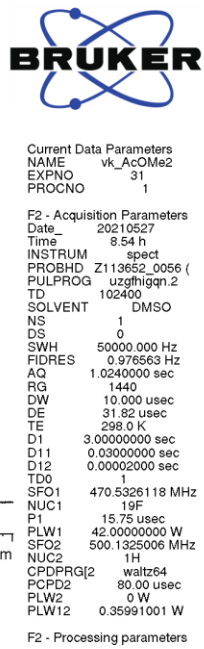






$^{19}$F{$^1$H} NMR (471 MHz), rotamers 9:1: −126.0 (s, major rotamer), −126.1 (broad s, minor rotamer).



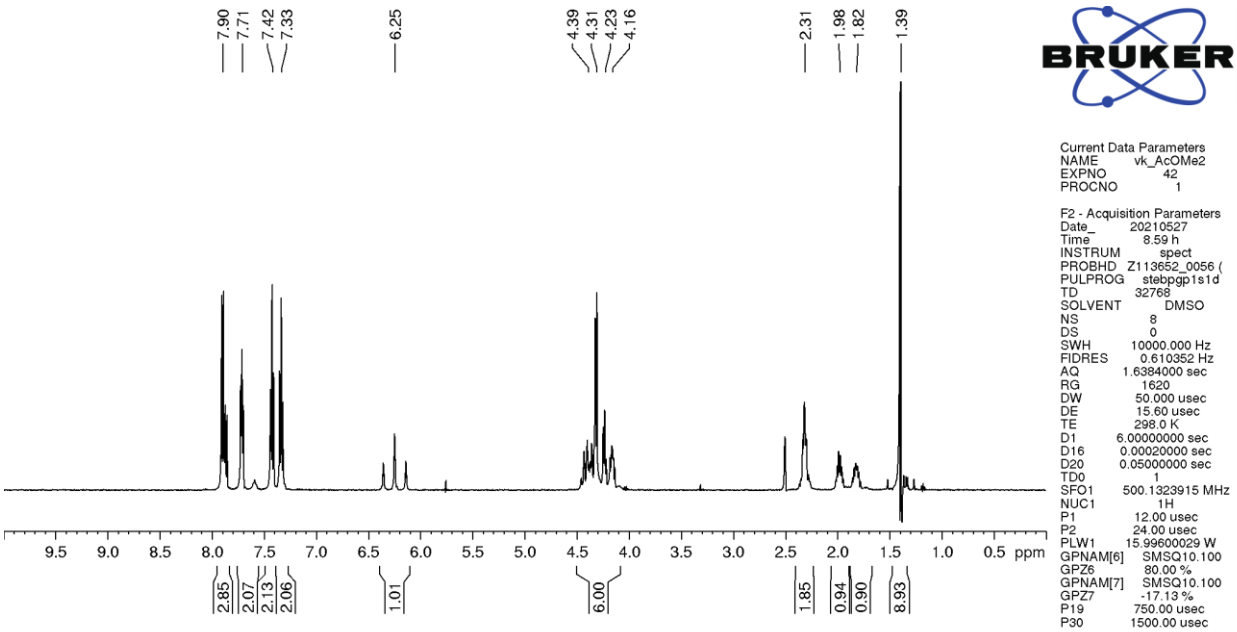





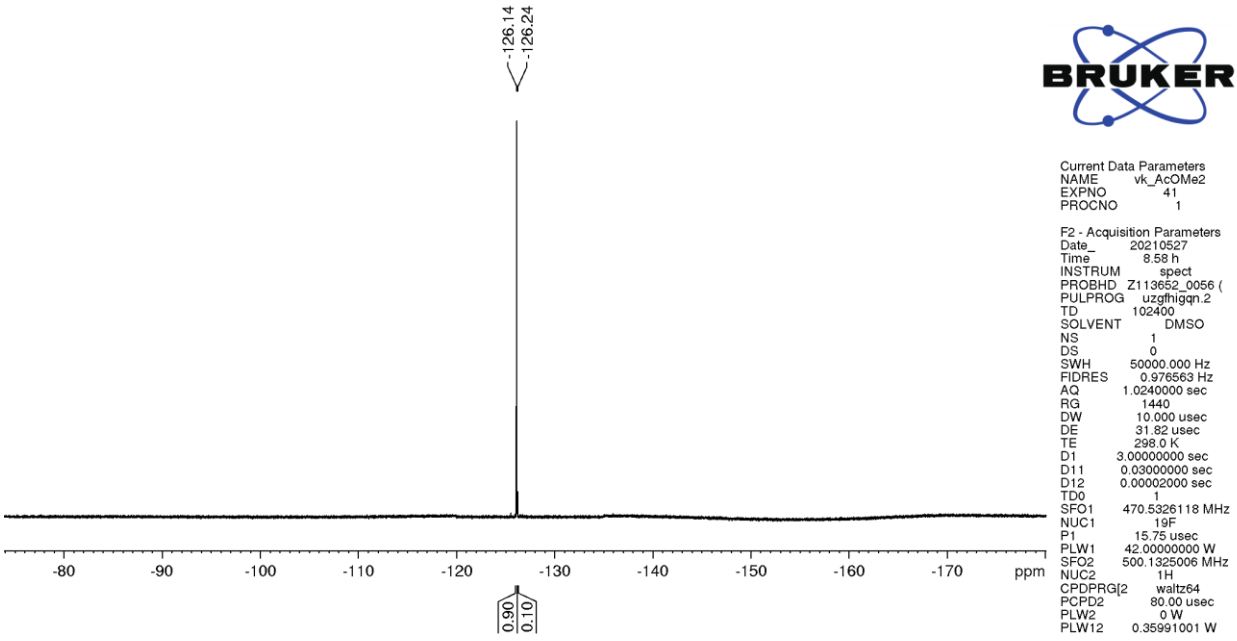

*OBC*, doi: 10.1039/d1ob01213d

Fmoc-($^t$Bu)Glu-$OCH_2CHF_2$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 7.90 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.71 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 6.25 (tm, $J_{HF}$ = 54 Hz, 1H), 4.46-4.13 (m, 6H), 2.32 (m, 2H), 1.98 (m, 1H), 1.82 (m, 1H), 1.39 (s, 9H).




$^{19}$F{$^1$H} NMR (471 MHz), rotamers 9:1 : −126.1 (two d, $J_{FF}$ = 289 Hz, major rotamer), −126.2 (broad s, minor rotamer).

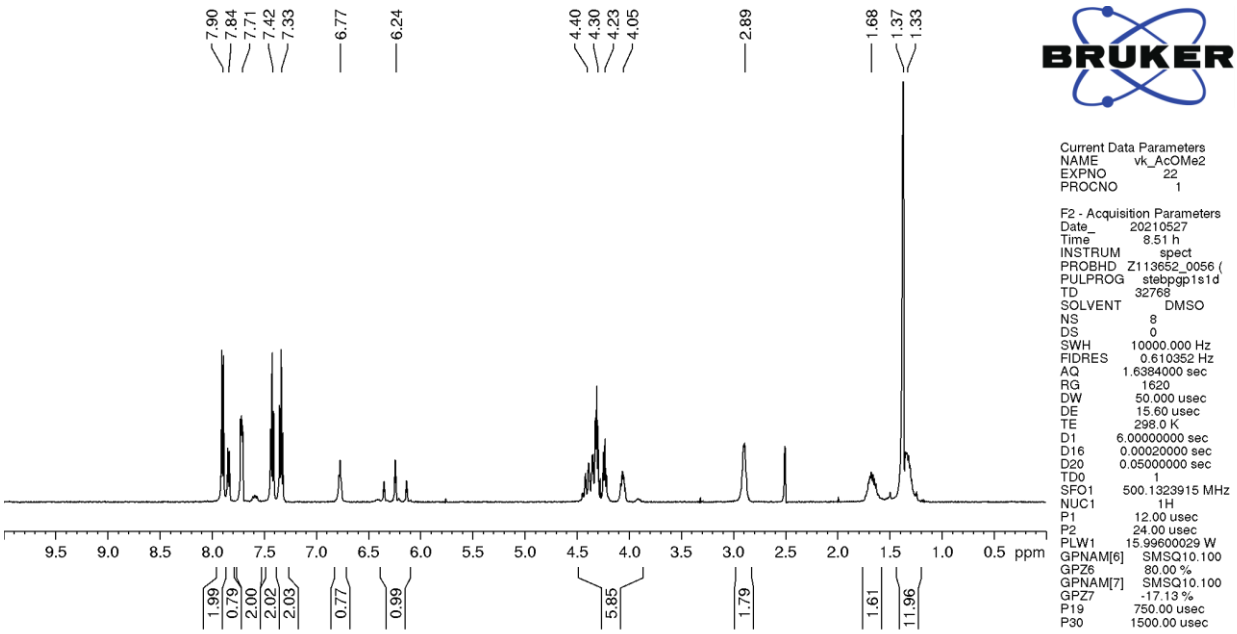




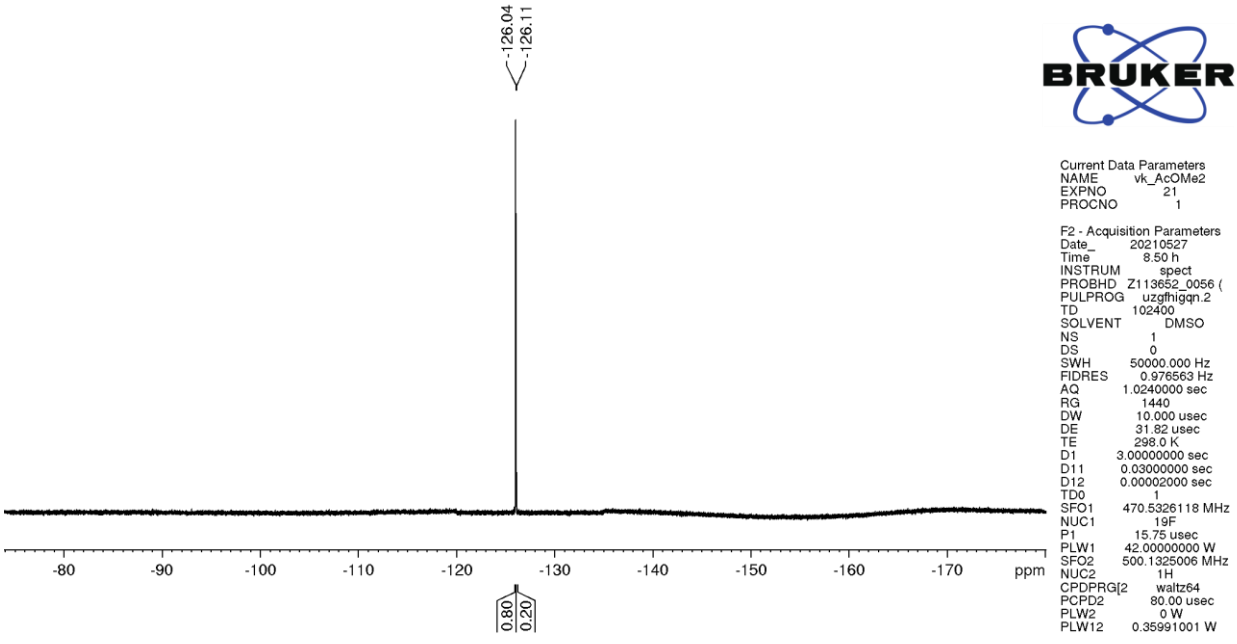

*OBC,* doi: 10.1039/d1ob01213d

Fmoc-(Boc)Lys-$OCH_2CHF_2$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 7.90 (d, *J* = 7.9 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.71 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 6.77 (t, *J* = 5.2 Hz, 1H), 6.24 (tm, $J_{HF}$ = 54 Hz, 1H), 4.44-4.03 (m, 6H), 2.89 (m, 2H), 1.68 (m, 2H), 1.37 (s, 9H), 1.33 (m, 2H).




$^{19}$F{$^1$H} NMR (471 MHz), rotamers 8:2 : −126.0 (s, major rotamer), −126.1 (s, minor rotamer).

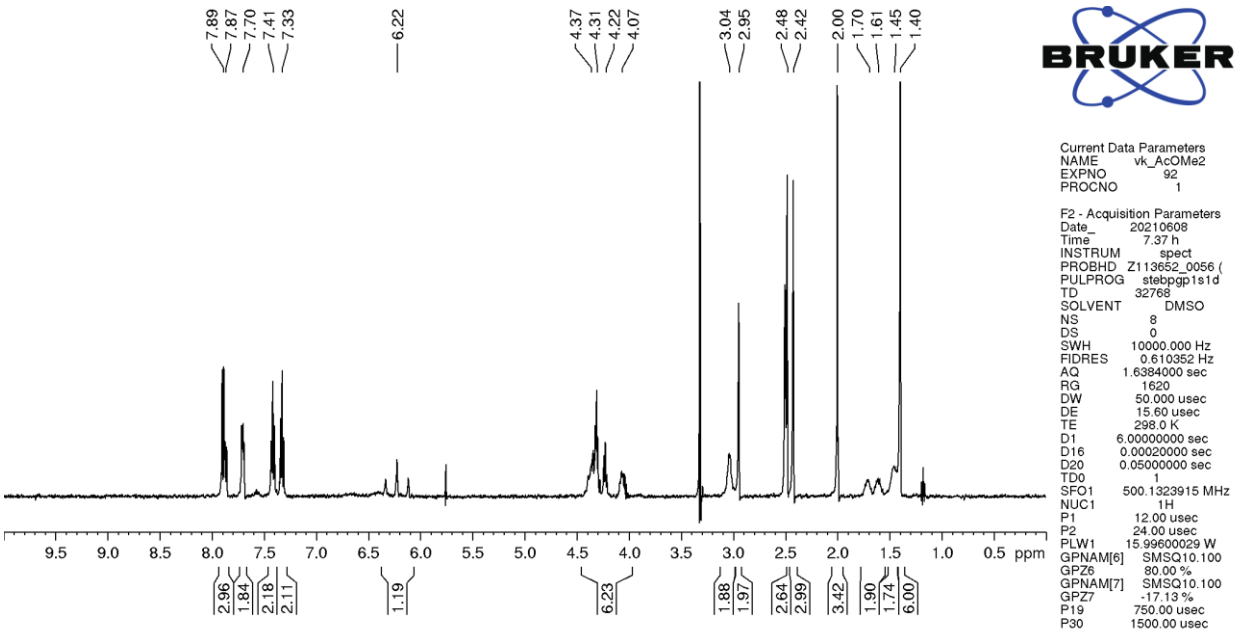




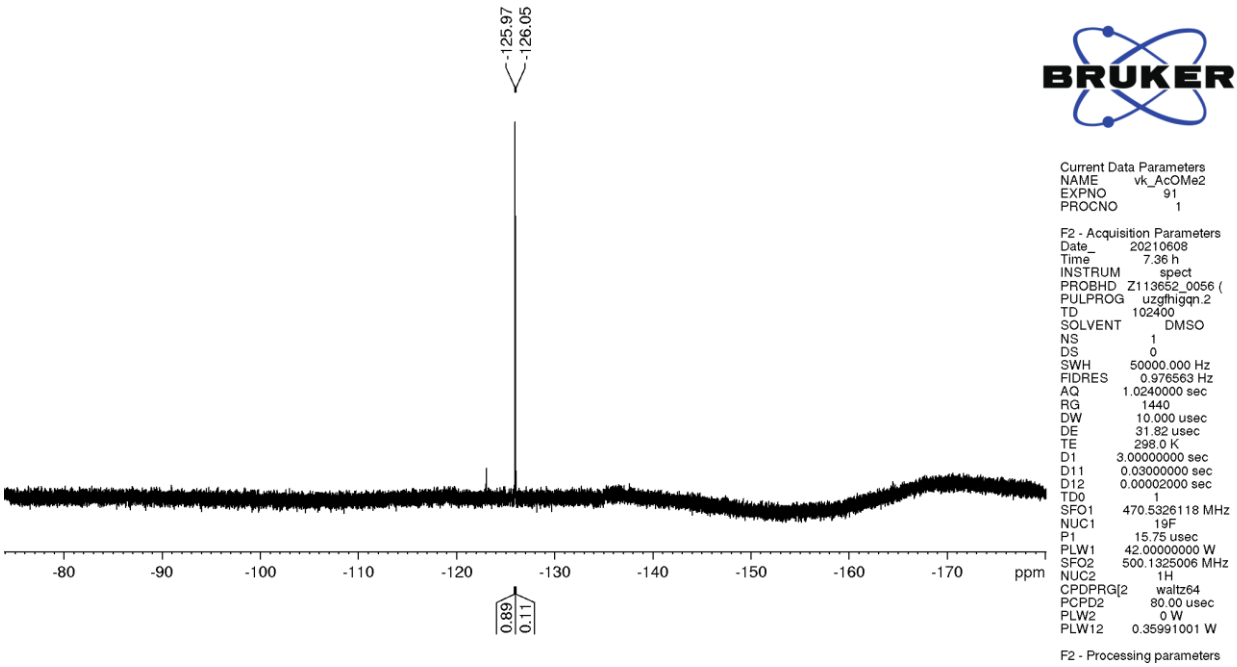

*OBC*, doi: 10.1039/d1ob01213d

Fmoc-(Pbf)Arg-$OCH_2CHF_2$ in DMSO-$d_6$:

$^1$H NMR (500 MHz): 7.90 (d, *J* = 7.8 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.71 (dd, *J* = 7.5 and 4.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.0-6.3 (broad, 3H), 6.23 (tt, $J_{HF}$ = 54 Hz, $J_{HH}$ = 3.0 Hz, 1H), 4.40-4.04 (multiplets, 6H), 3.04 (m, 2H), 2.95 (m, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.71 (m, 1H), 1.61 (m, 1H), 1.46 (m, 2H), 1.40 (m, 6H).




$^{19}$F{$^1$H} NMR (471 MHz), rotamers 9:1 : −126.0 (s, major rotamer), −126.1 (broad s, minor rotamer).

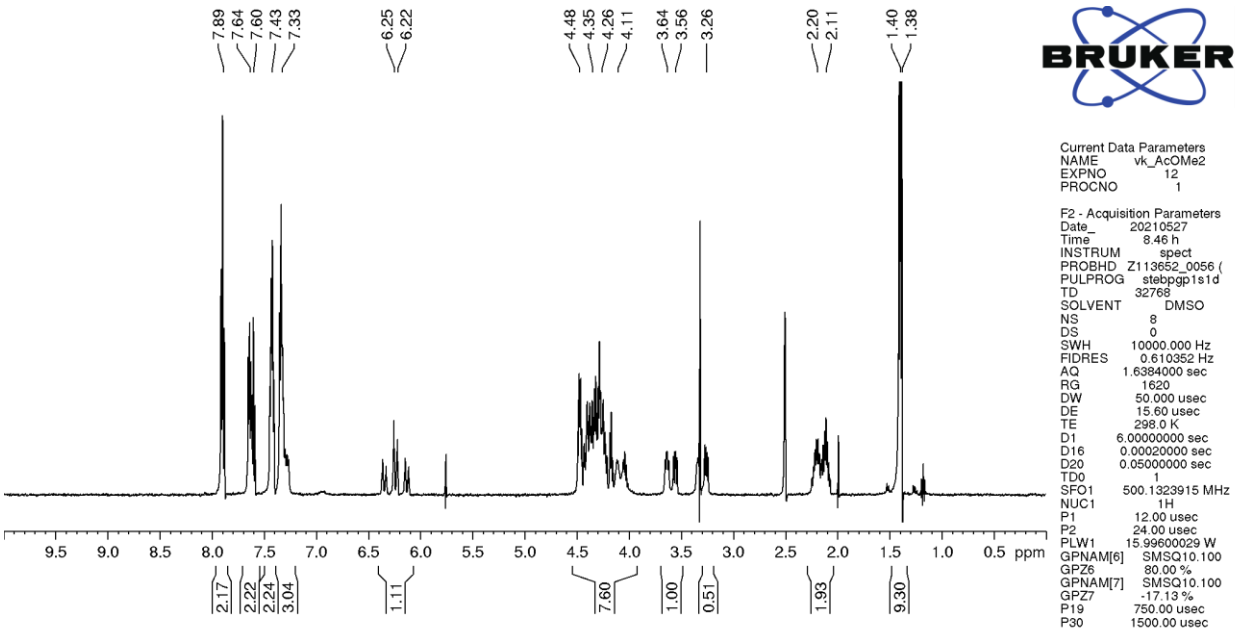




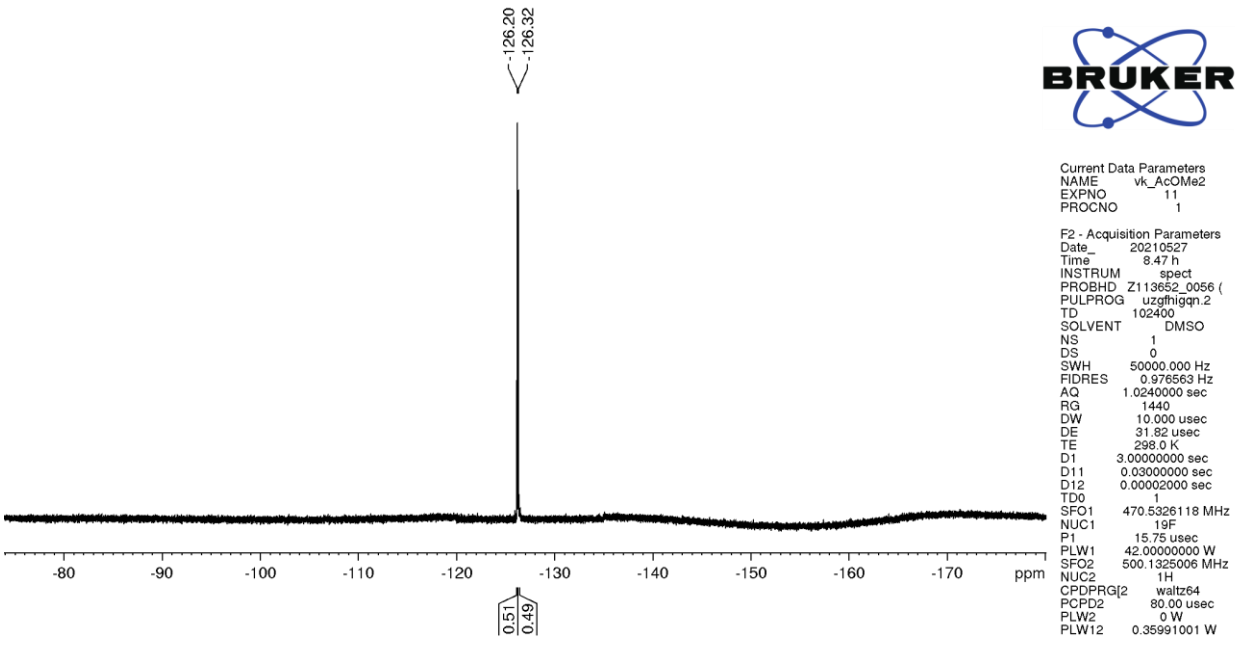

*OBC,* doi: 10.1039/d1ob01213d

Fmoc-(Boc)Amp-$OCH_2CHF_2$ in DMSO-$d_6$:

$^1$H NMR (500 MHz), two rotamers 1:1: 7.89 (m, 2H), 7.66-7.58 (m, 2H), 7.43 (m, 2H), 7.33 (m, 2H), 6.25 and 6.22 (two tm, $J_{HF}$ = 54 Hz, 1H), 4.40-4.03 (m, 7.5H), 3.64, 3.56, and3.25 (three m, 0.5H each), 2.20 and 2.11 (two m, 2H), 1.40 and 1.38 (two s, 9H).




$^{19}$F{$^1$H} NMR (471 MHz), rotamers 1:1 : −126.2 (s), −126.3 (s).

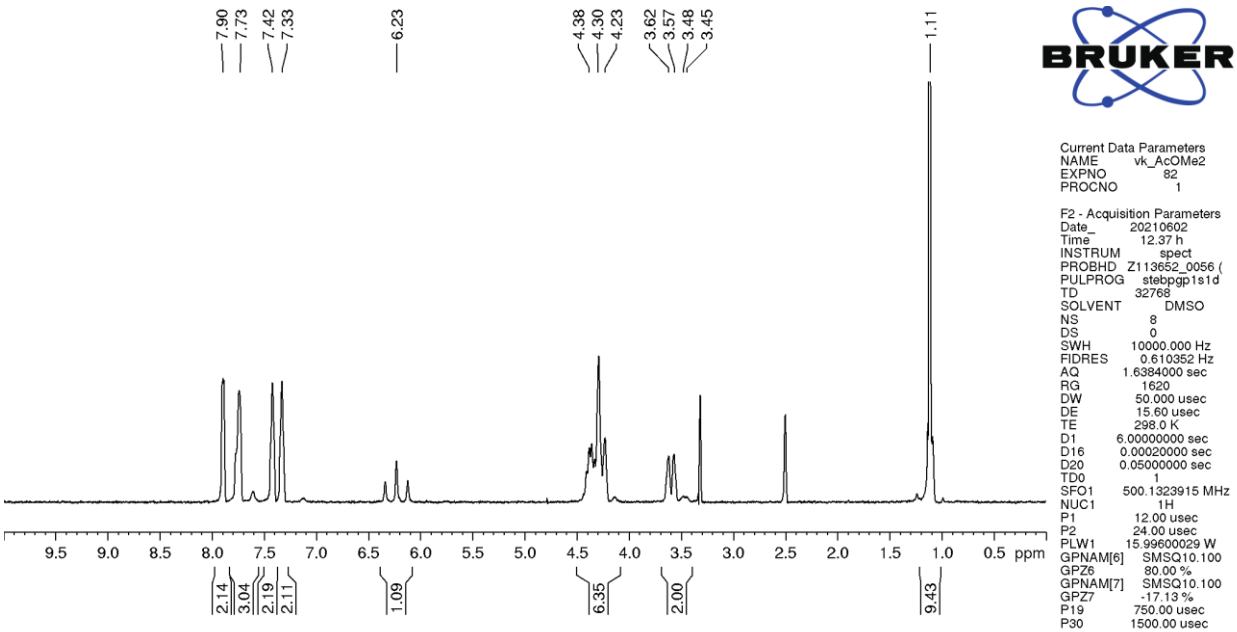




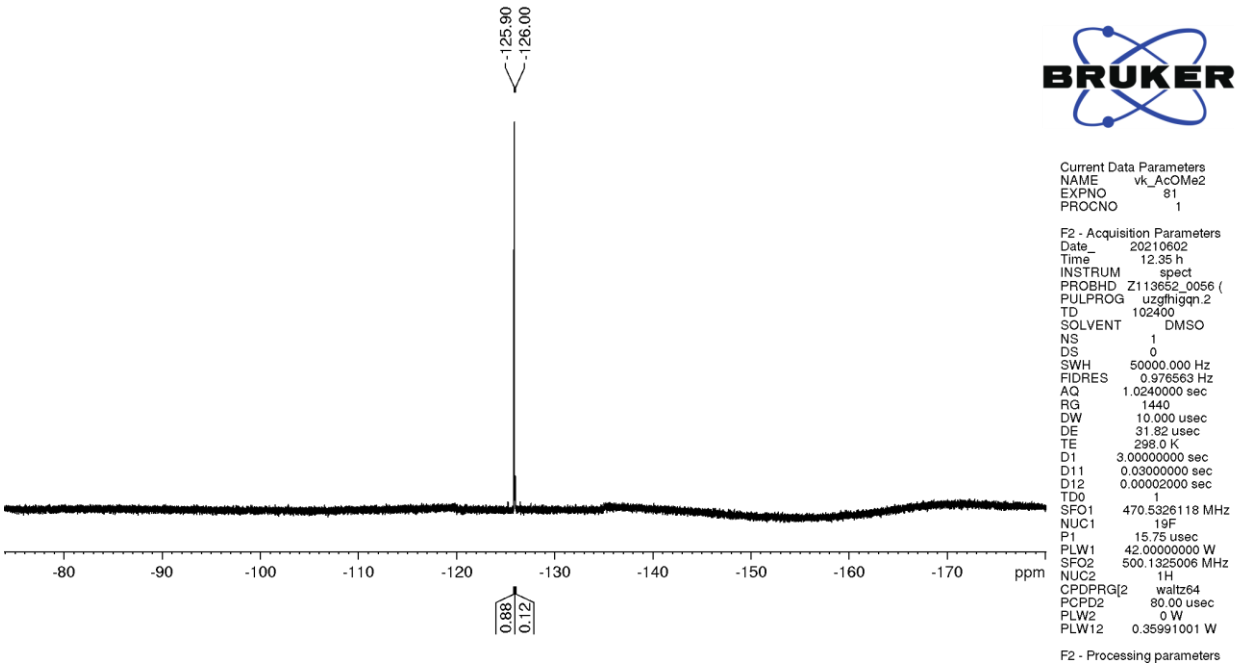

*OBC,* doi: 10.1039/d1ob01213d

Fmoc-($^t$Bu)Ser-$OCH_2CHF_2$ in DMSO-$d_6$:

$^1$H NMR (500 MHz), major rotamer: 7.90 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.74 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 6.24 (tm, $J_{HF}$ = 54 Hz, 1H), 4.44-4.21 (m, 6H), 3.63 (dd, *J* = 9.2 and 6.2 Hz, 1H), 3.57 (dd, *J* = 9.0 znd 4.9 Hz, 1H), 1.12 (s, 9H).




$^{19}$F{$^1$H} NMR (471 MHz), rotamers 9:1 : −125.9 (two d, $J_{FF}$ = 290 Hz, major rotamer), −126.0 (broad s, minor rotamer).

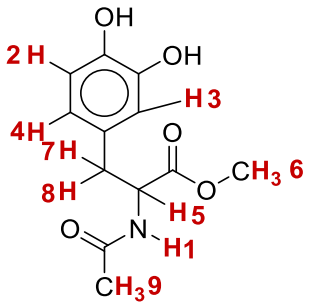





*OBC,* doi: 10.1039/d1ob01213d

## An example of spectra analysis

The example is given for the Dopa derivative Ac-Dopa-$OCH_3$ partitioning, log*P* = −0.21±0.02. Deuterated solvent – methanol-$d_4$. Three samples with 5-7 mg of the substance used in each. Acquisition parameters are shown on the spectra.

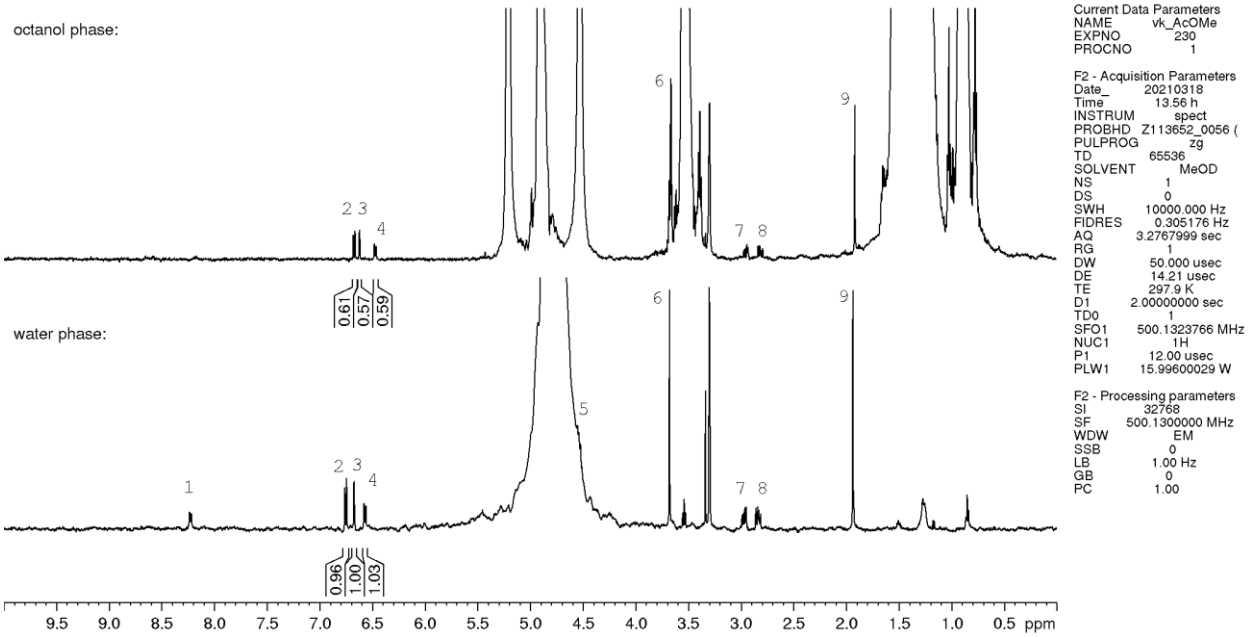



Single-scan spectra:

Both spectra were baseline-corrected over the entire range using a 5-degree polynomial. An additional baseline correction was applied between 7.2-6.2 ppm.

Partitioning sample 1:

Full spectrum and integration:



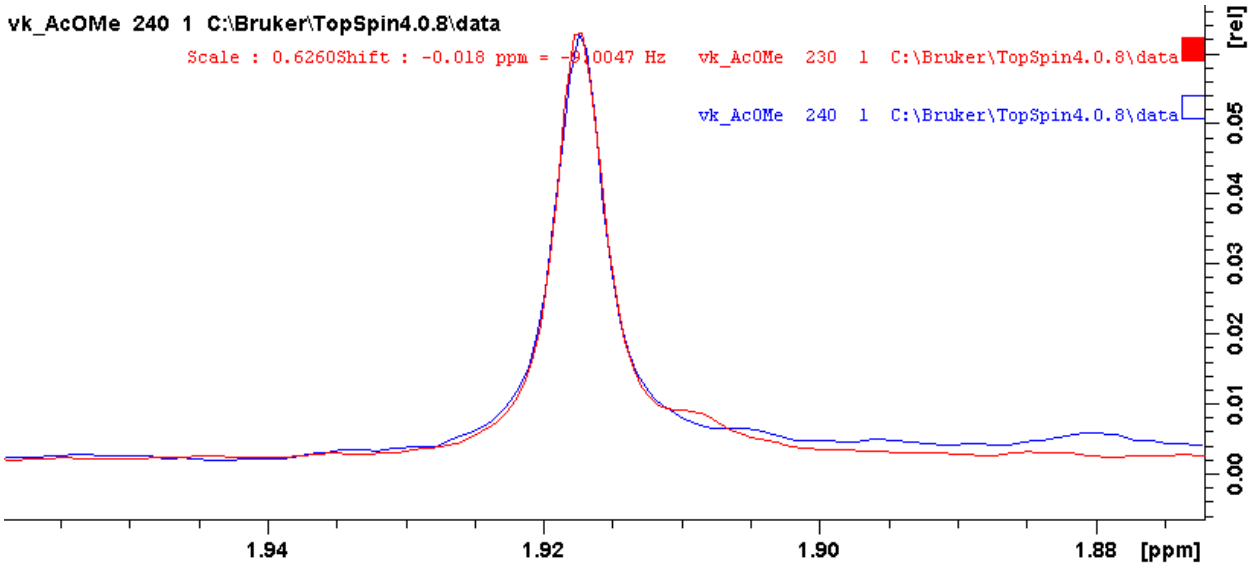

Absolute integrals:

| resonance | absolute integral, water | absolute integral, octan-1-ol | *P* |
|---|---|---|---|
| 2 | 5703 | 3378 | 0.592 |
| 3 | 5913 | 3483 | 0.589 |
| 4 | 6102 | 3611 | 0.592 |



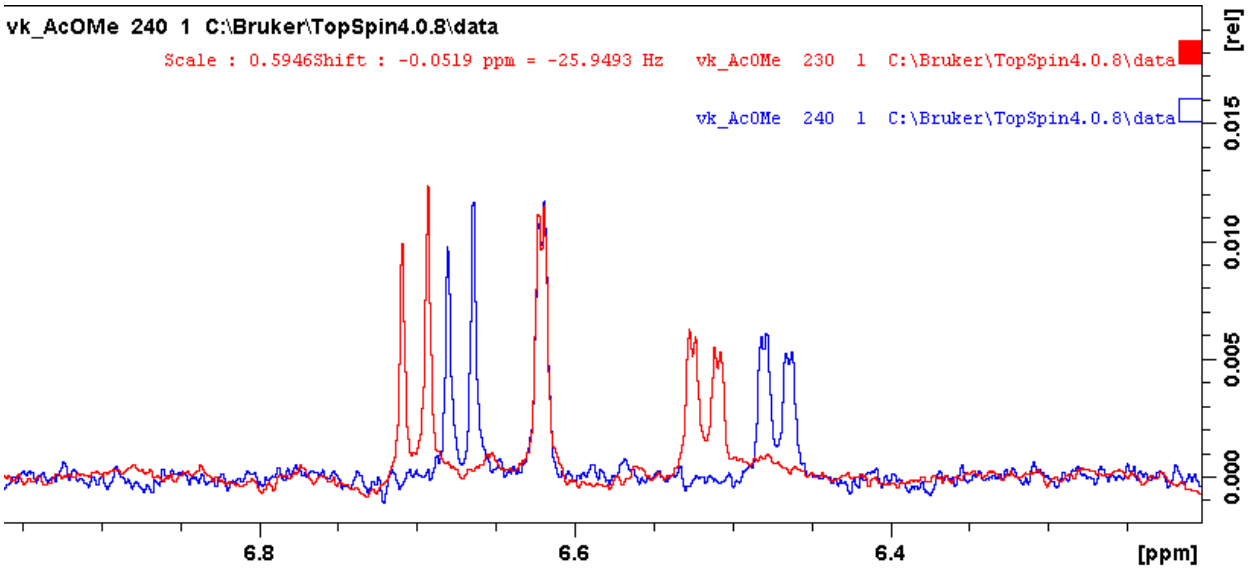
*OBC*, doi: 10.1039/d1ob01213d

Overlay acetyl resonance, 9:




⇨ Scale factor 0.626

Overlay aromatic resonances, 2-4:



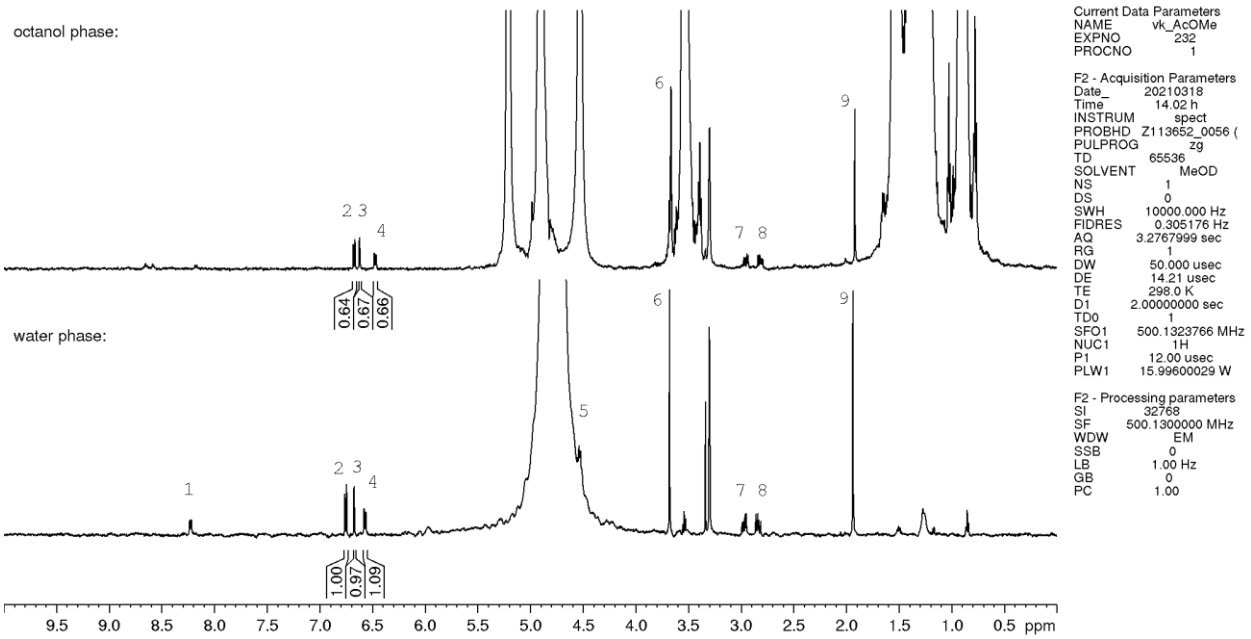

⇨ Scale factor 0.595



*OBC*, doi: 10.1039/d1ob01213d

Partitioning sample 2:

Full spectrum and integration:



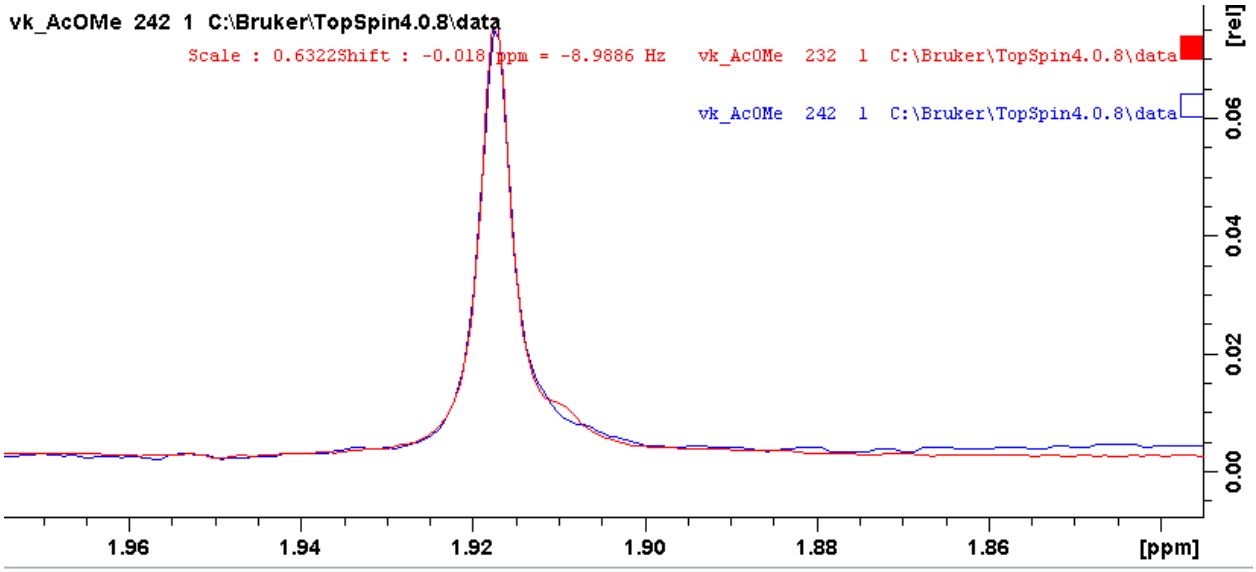

Absolute integrals:

| resonance | absolute integral, water | absolute integral, octan-1-ol | *P* |
|---|---|---|---|
| 2 | 6264 | 4135 | 0.660 |
| 3 | 6455 | 4263 | 0.660 |
| 4 | 7005 | 4323 | 0.617 |



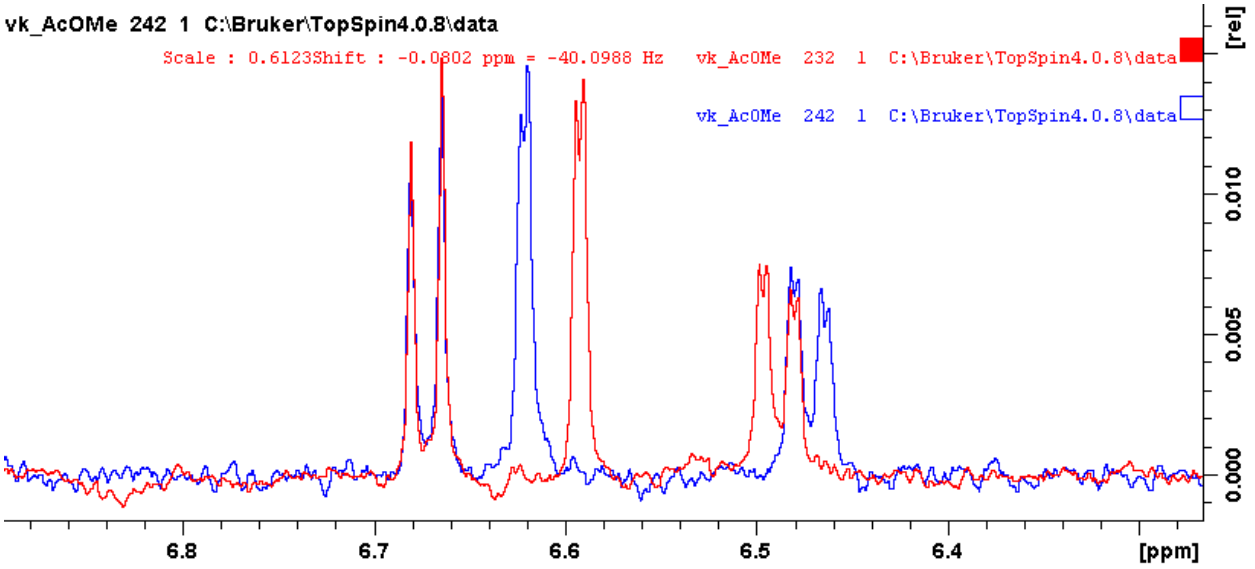
*OBC,* doi: 10.1039/d1ob01213d

Overlay acetyl resonance, 9:




⇨ Scale factor 0.632

Overlay aromatic resonances, 2-4:



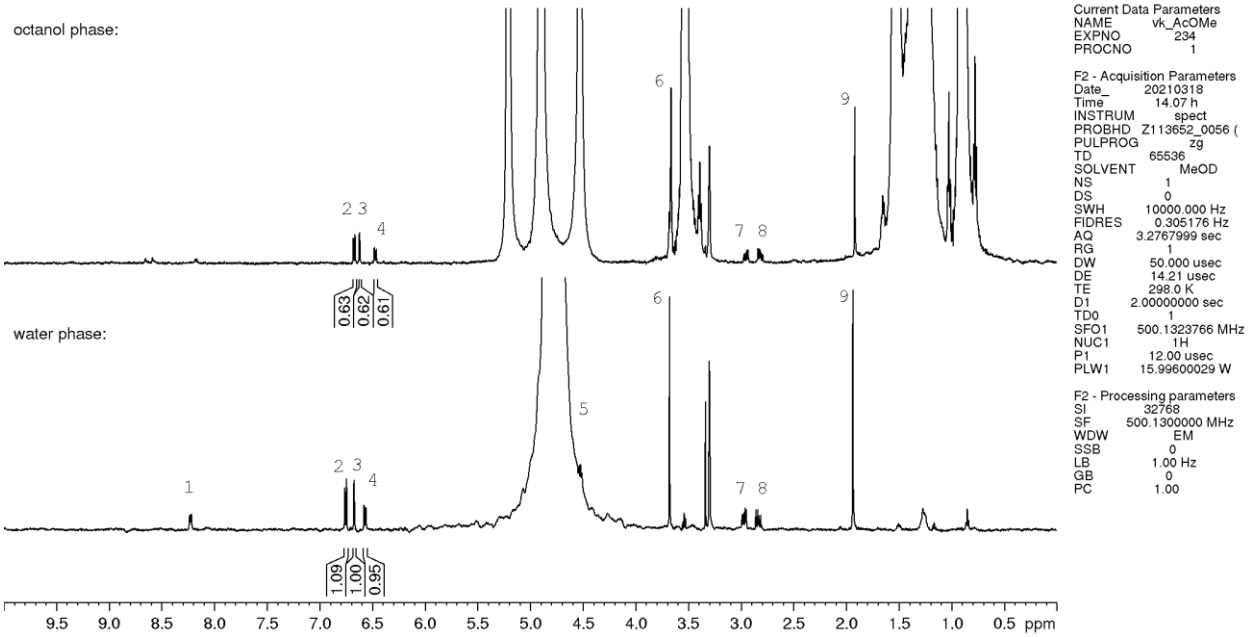

⇨ Scale factor 0.612



*OBC*, doi: 10.1039/d1ob01213d

Partitioning sample 3:

Full spectrum and integration:



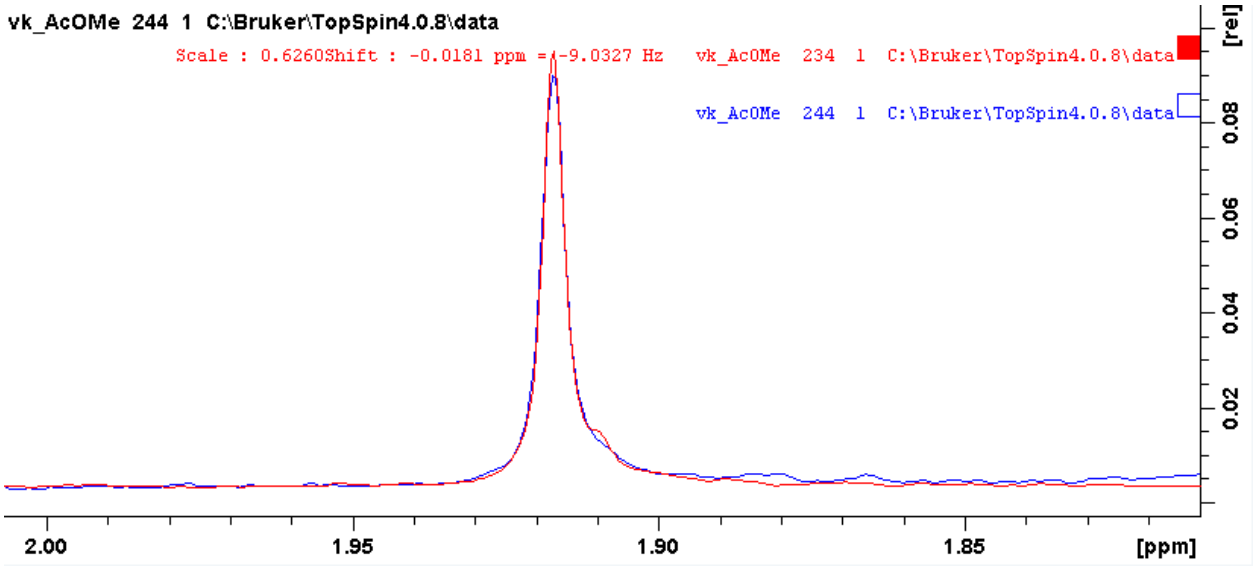

Absolute integrals:

| resonance | absolute integral, water | absolute integral, octan-1-ol | *P* |
|---|---|---|---|
| 2 | 7900 | 5070 | 0.642 |
| 3 | 8290 | 5164 | 0.623 |
| 4 | 9038 | 5261 | 0.582 |



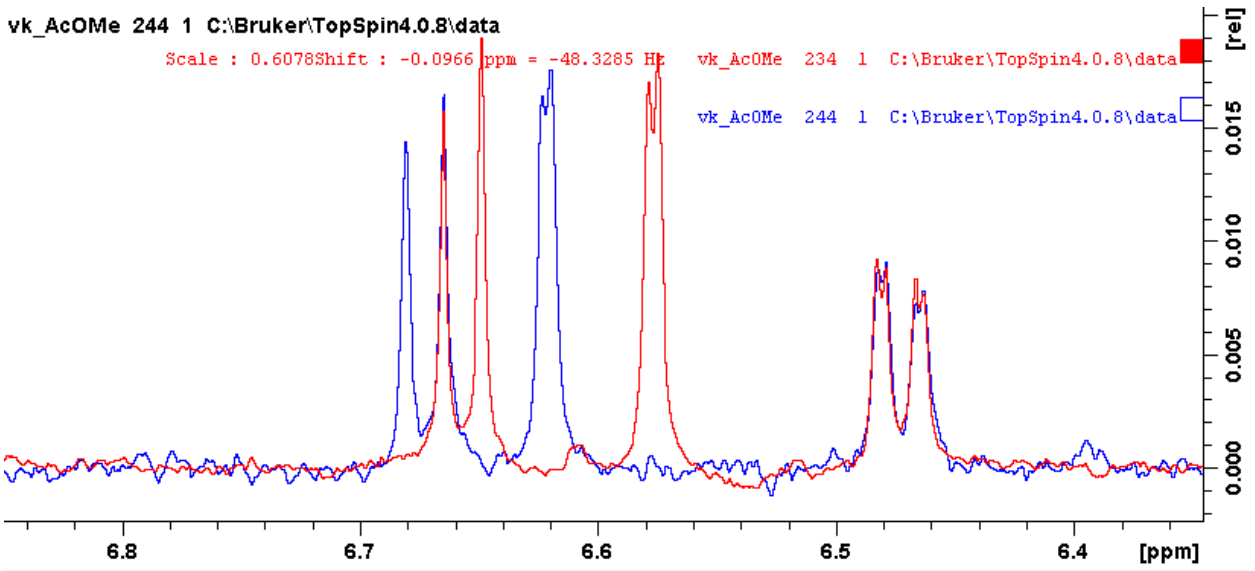
*OBC,* doi: 10.1039/d1ob01213d

Overlay acetyl resonance, 9:




⇨ Scale factor 0.626

Overlay aromatic resonances, 2-4:




⇨ Scale factor 0.608



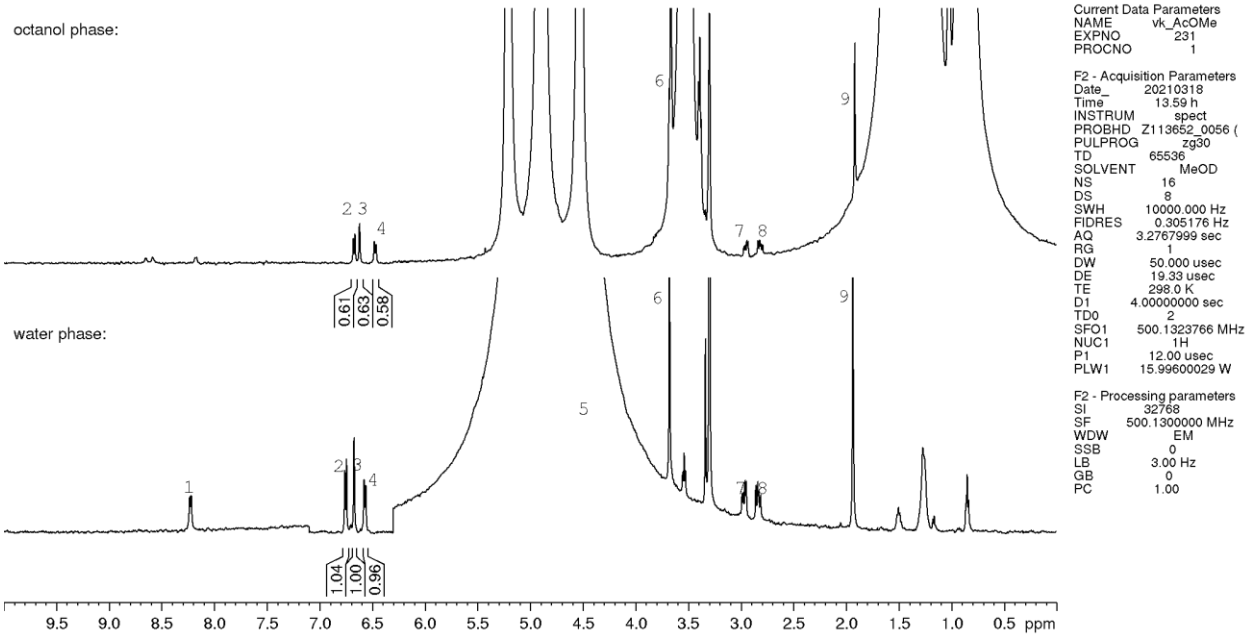
*OBC*, doi: 10.1039/d1ob01213d

16-scan spectra:

Both spectra were baseline-corrected over the entire range using a 5-degree polynomial. An additional baseline correction was applied between 7.1-6.3 ppm.

Partitioning sample 1:

Full spectrum and integration:



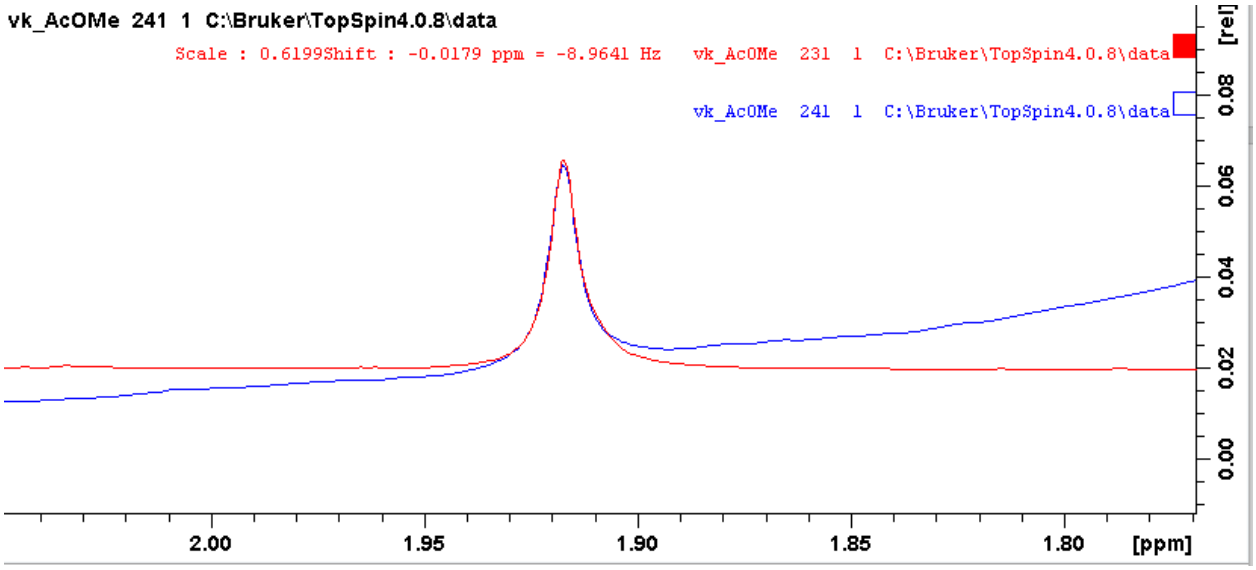

Absolute integrals:

| resonance | absolute integral, water | absolute integral, octan-1-ol | *P* |
|---|---|---|---|
| 2 | 42082 | 26738 | 0.635 |
| 3 | 43906 | 27978 | 0.637 |
| 4 | 45566 | 28760 | 0.631 |



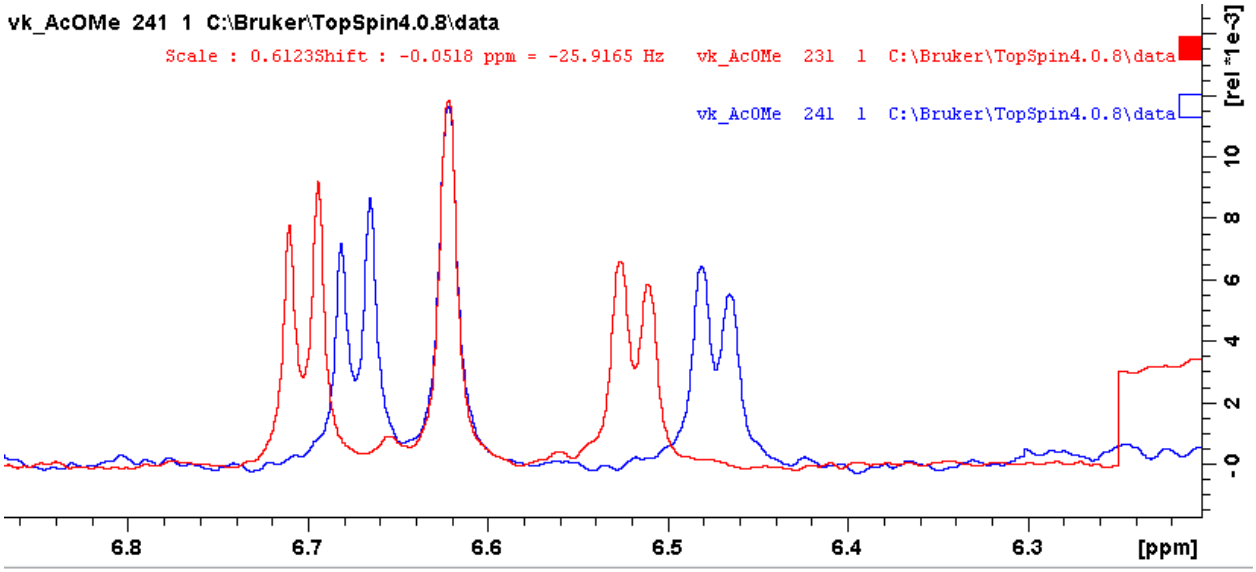
*OBC,* doi: 10.1039/d1ob01213d

Overlay acetyl resonance, 9:




⇨ Scale factor 0.620

Overlay aromatic resonances, 2-4:



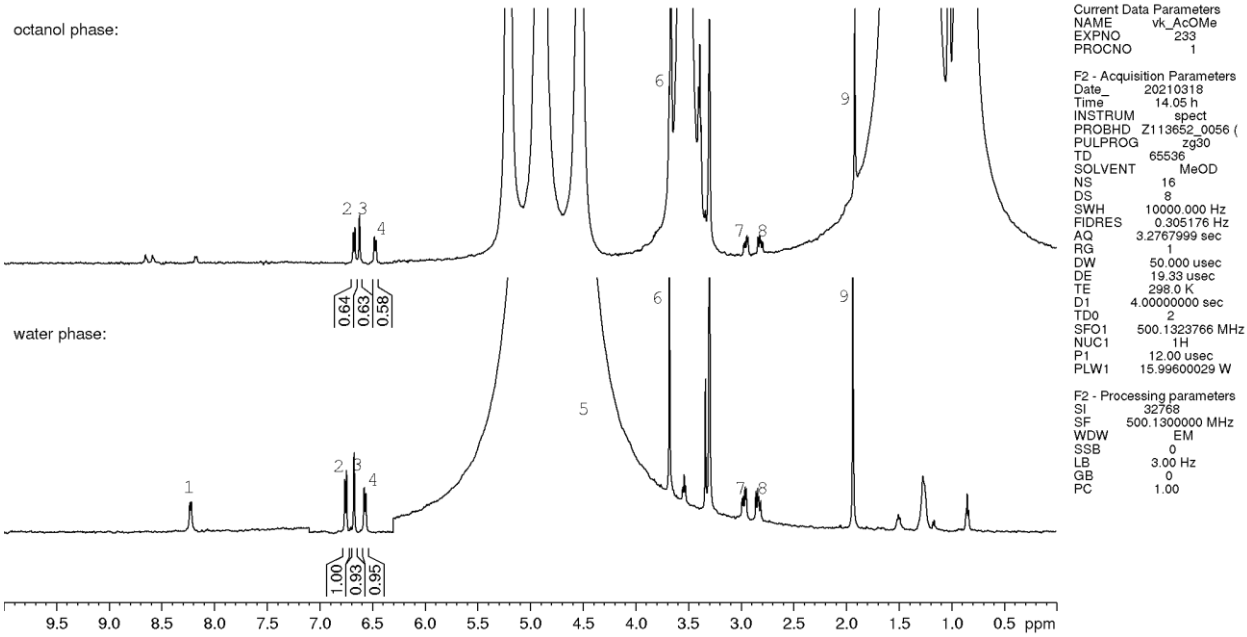

⇨ Scale factor 0.612



*OBC*, doi: 10.1039/d1ob01213d

Partitioning sample 2:

Full spectrum and integration:



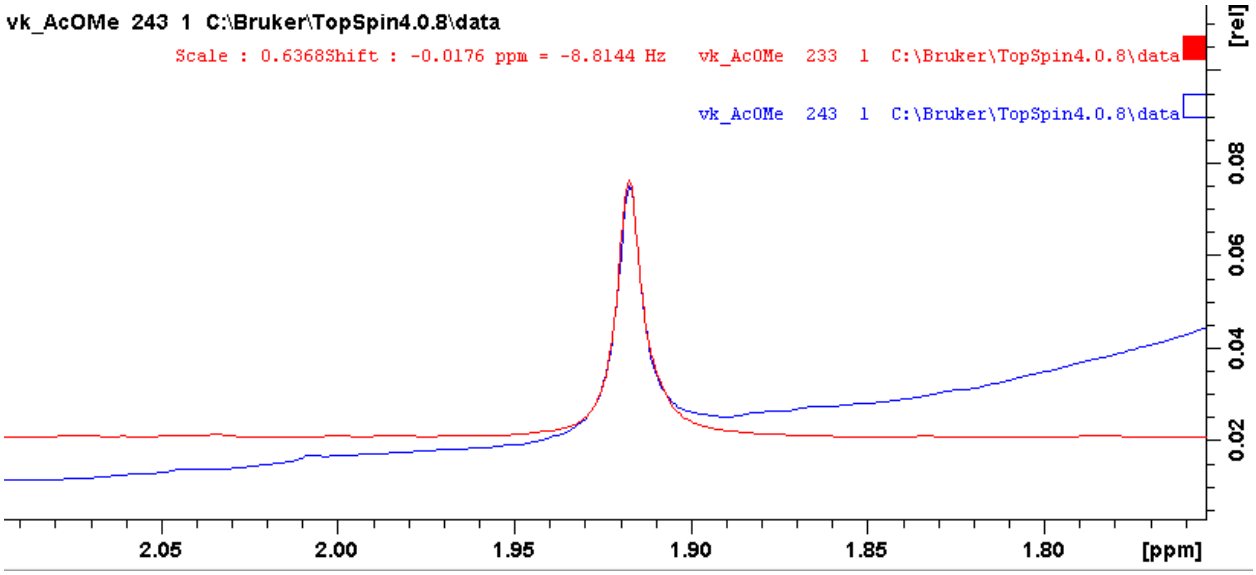

Absolute integrals:

| resonance | absolute integral, water | absolute integral, octan-1-ol | *P* |
|---|---|---|---|
| 2 | 50661 | 31289 | 0.618 |
| 3 | 51415 | 34202 | 0.665 |
| 4 | 54377 | 34530 | 0.635 |



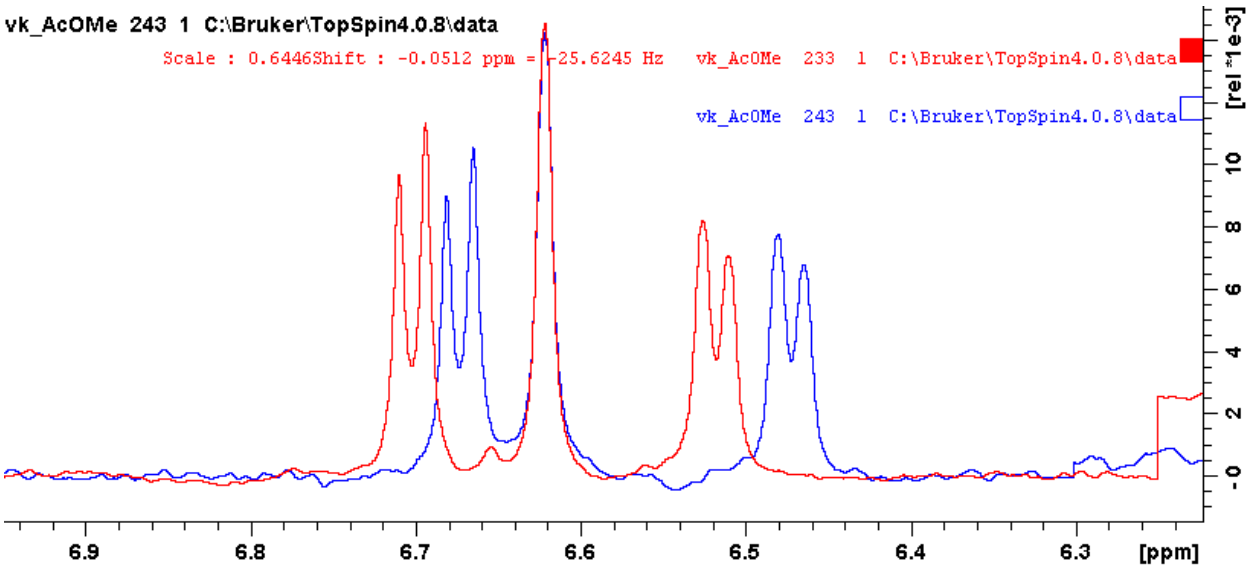
*OBC,* doi: 10.1039/d1ob01213d

Overlay acetyl resonance, 9:




⇨ Scale factor 0.637

Overlay aromatic resonances, 2-4:



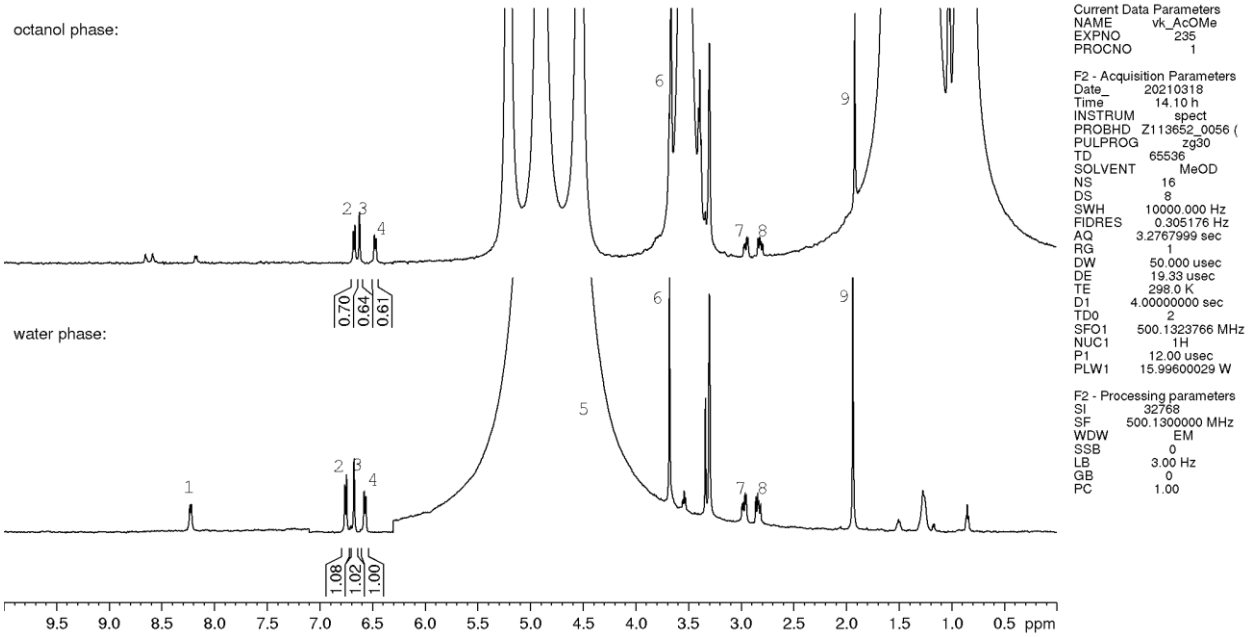

⇨ Scale factor 0.645



*OBC*, doi: 10.1039/d1ob01213d

Partitioning sample 3:

Full spectrum and integration:



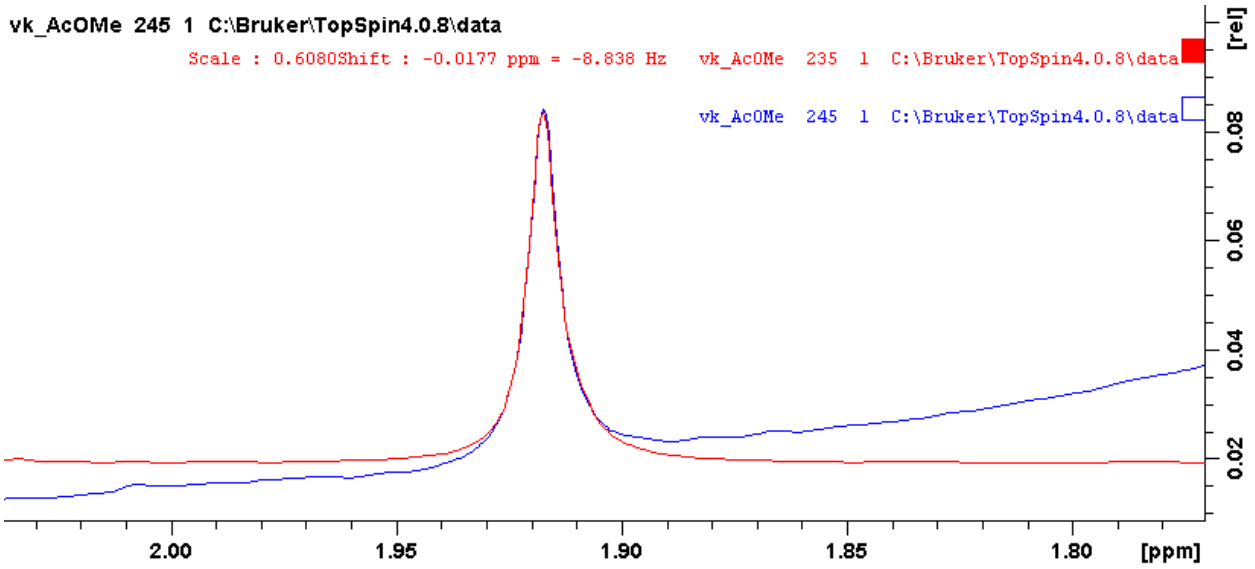

Absolute integrals:

| resonance | absolute integral, water | absolute integral, octan-1-ol | *P* |
|---|---|---|---|
| 2 | 64412 | 39336 | 0.611 |
| 3 | 65664 | 41080 | 0.626 |
| 4 | 69579 | 44838 | 0.644 |



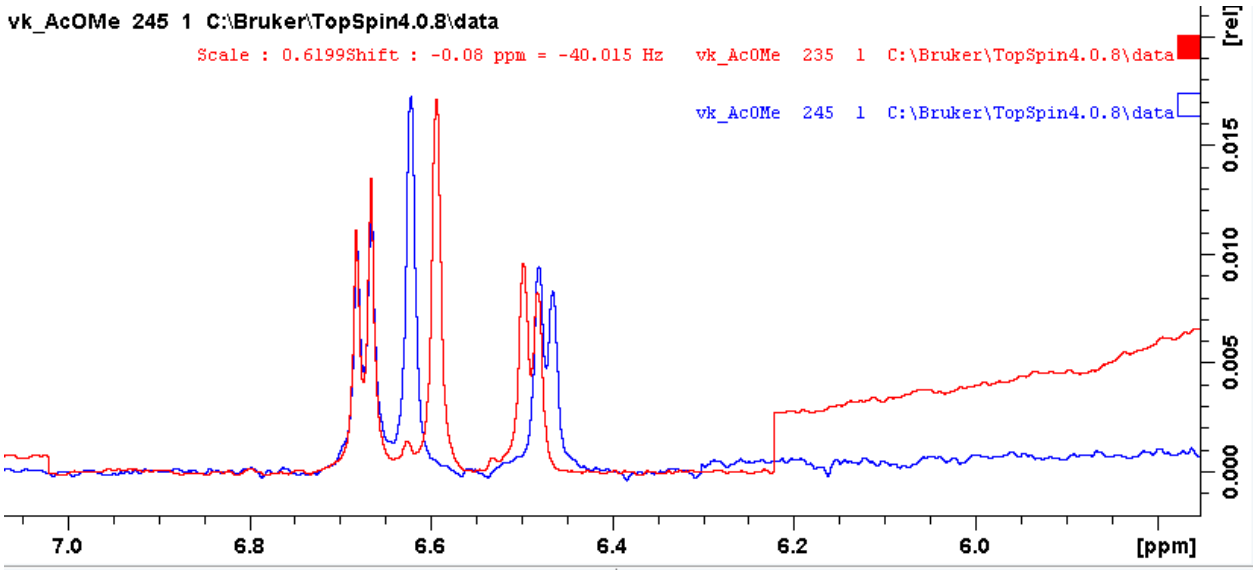
*OBC,* doi: 10.1039/d1ob01213d

Overlay acetyl resonance, 9:




⇨ Scale factor 0.608

Overlay aromatic resonances, 2-4:




⇨ Scale factor 0.620

Final average *P* = 0.623±0.021, or if expressed in logarithmic scale log*P* = −0.21±0.02



*OBC*, doi: 10.1039/d1ob01213d

## References

S1 V. Kubyshkin and N. Budisa, *J. Pept. Sci.*, 2018, **24**, e3076.

https://doi.org/10.1002/psc.3076

S2 V. Kubyshkin and N. Budisa, *Org. Biomol. Chem.*, 2017, **15**, 6764-6772.

https://doi.org/10.1039/C7OB01421J

S3 V. Kubyshkin, S. Pridma and N. Budisa, *New J. Chem.*, 2018, **42**, 13461-13470.

https://doi.org/10.1039/C8NJ02631A

S4 V. Kubyshkin, *Beilstein J. Org. Chem.*, 2020, **16**, 1837-1852.

https://doi.org/10.3762/bjoc.16.151

S5 F. Agostini, L. Sinn, D. Petras, C. J. Shipp, V. Kubyshkin, A. A. Berger, P. C. Dorrestein, J. Rappsilber, N. Budisa and B. Koksch, *ACS Cent. Sci.*, 2021, **7**, 81-92.

https://doi.org/10.1021/acscentsci.0c00679