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# $^{12}C/^{13}C$ isotope exchange for the synthesis of D-[$^{13}$C]phenylalanine by using [$^{13}$C]$CO_2$ and binol chiral aldehyde receptor

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**Abstract**
Isotope labeling of α-amino acids is a crucial tool for drug discovery and understanding biochemical processes. The goal for this work was to develop a fast exchange condition to prepare D-[$^{13}$C]phenylalanine in a short time with high incorporation of $^{13}$C isotope, which could be translated to $^{11}$C-α-amino acid. In this work the exchange reactions on preformed imine carboxylate by using [$^{13}$C]$CO_2$ gave some evidence that the fast exchange to enable direct radiolabeling of α-amino acids, using [$^{11}$C]$CO_2$, could be possible.

**Keywords** (±)-phenylalanine · Carbon-13 · Binol chiral aldehyde receptors · Isotopically-labeled enantioenriched α-amino acids · Resolution/isotopic labeling

## Introduction

Isotopically labeled α-amino acids and their derivatives have widespread use in structural and mechanistic biochemistry [1], quantitative proteomics [2], absorption distribution metabolism and excretion (ADME) profiling [3, 4], and as image agents in positron emission tomography (PET) techniques [5–7]. The short half-life of $^{11}$C (20 min) makes the multi-step preparation of $^{11}$C-labeled α-amino acids targets needed for PET problematic. Current approaches are restricted to cyanation/hydrolysis reactions using [$^{11}$C]$CN^-$ (Fig. 1a) [8], Another approach includes the use of [$^{11}$C]$CH_3I$; an example of this is methylation of methionine with [$^{11}$C]$CH_3I$ to get [S-methyl-$^{11}$C]methionine (Fig. 1b) [9–11]. [$C_1$-$^{11}$C]glutamine or glutamate can be prepared by conjugate additions to $^{11}$C-acrylates (Fig. 1c) [12]. All these methods occur with low to moderate radiochemical yields and require time-consuming, multi-step approaches.

In general, the literature methods to prepare isotopically-labeled enantioenriched α-amino acids depend on the insertion of labeled carbon via classical methods, followed by resolution [13]. The incorporation of $^{13/14}$C into the α-amino acids can be done by using classical methods. General approaches include the cyanation of electrophiles with [$^{13}$C]CN, followed by hydrolysis [14–16], carboxylation of organometallic with [$^{13}$C]$CO_2$ [17, 18], the use of C-labeled acetate as a precursor [19, 20], and alkylations with $^{13}$C-labeled electrophiles [21]. These methods can be utilized to prepare enantioenriched isotopically labeled α-amino acids via an enzymatic approach after the insertion of labeled carbon. The enzymatic approach includes enzymatic kinetic resolution, such as acylase [14–16] and the use of lyases for stereoselective C–N bond formation [19, 20]. It also can be done by using chiral auxiliaries for α-alkylation or α-amination [21] and enantioselective hydrogenation of enamines [22]. Recently, Lundgren et.al reported that achiral aryl aldehyde catalyst can catalyze carboxylate exchange in α-amino acids to produce the isotopically labeled racemic α-amino acids. They also showed that this methodology can be used to prepare racemic $^{11}$C-isotopically labelled α-amino acids [23, 24]. Then after that they reported that using uryl-based binol aldehyde receptors catalyst can catalyze carboxylate exchange in α-amino acids Fig. 2 [25]. These uryl-based binol aldehyde receptors are known catalysts for the inversion of L-amino acids to D-amino acids via shift base intermediate epimerization [26–30].

Lundgren *et.al*. reported that using uryl-based binol aldehyde receptors as catalysts can catalyze carboxylate exchange in α-amino acids to prepare $^{13}$C and $^{14}$C-isotopically labelled α-amino acids. Nevertheless, they did not demonstrate that this technology is suitable for the

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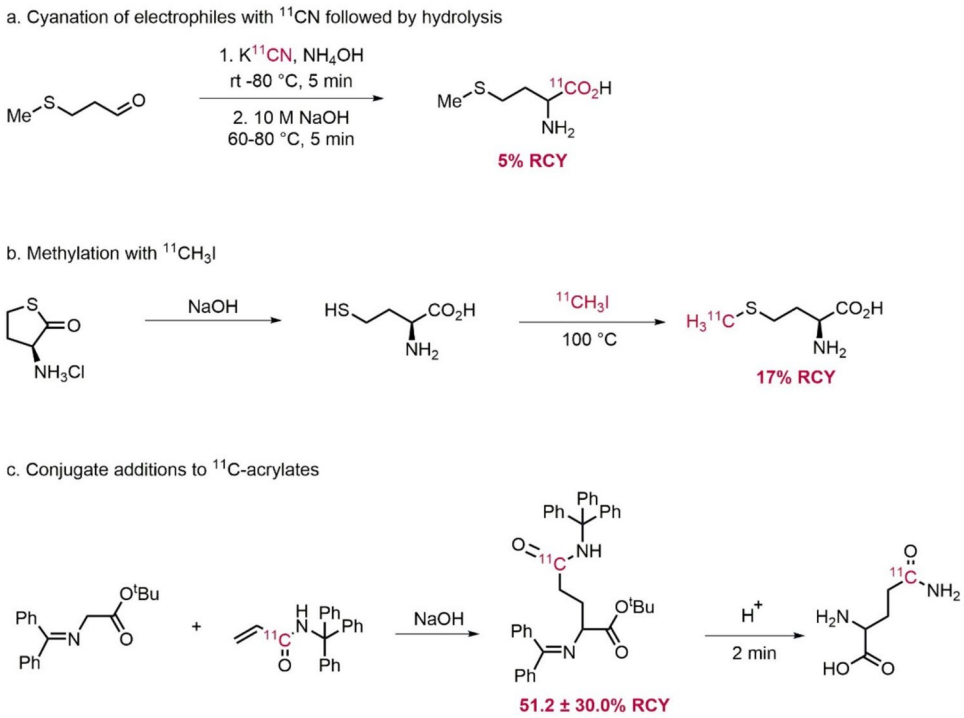



**Fig. 1** Classical methods for synthesis of $^{11}$C-labeled α-amino acids

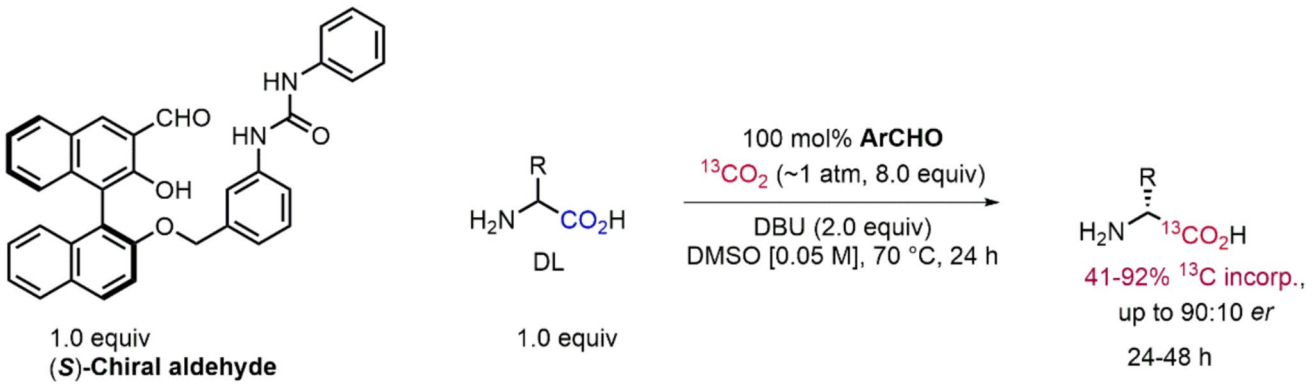



**Fig. 2** The usage of uryl-based binol aldehyde receptors catalyst can catalyze carboxylate exchange in α-amino acids

preparation of $^{11}$C-isotopically labelled α-amino acids, as the reaction duration was 24–48 h [25]. The short half-life of $^{11}$C (20 min) makes the multi-step preparation of $^{11}$C-α-amino acid targets needed for PET problematic [31]. This question emerges: is it feasible to devise a method for $^{13}$C labelling of α-amino acids that is time-efficient, utilizes a low equivalent of [$^{13}$C]$CO_2$, achieves high incorporation, and ensures good recovery, which could subsequently be used for 11C labelling of α-amino acids. Although Lundgren *et.al* reported that using uryl-based binol aldehyde receptors catalyst can catalyze carboxylate exchange in α-amino acids with *er* (enantiomeric ratio) up to 90:10 and 41–92% $^{13}$C incorporation in 24–48 h as shown in Fig. 2 [25]. The modification of the reaction conditions is needed to provide some evidence that direct radiolabeling of α-amino acids, using [$^{11}$C]$CO_2$, under the fast exchange conditions could be possible.

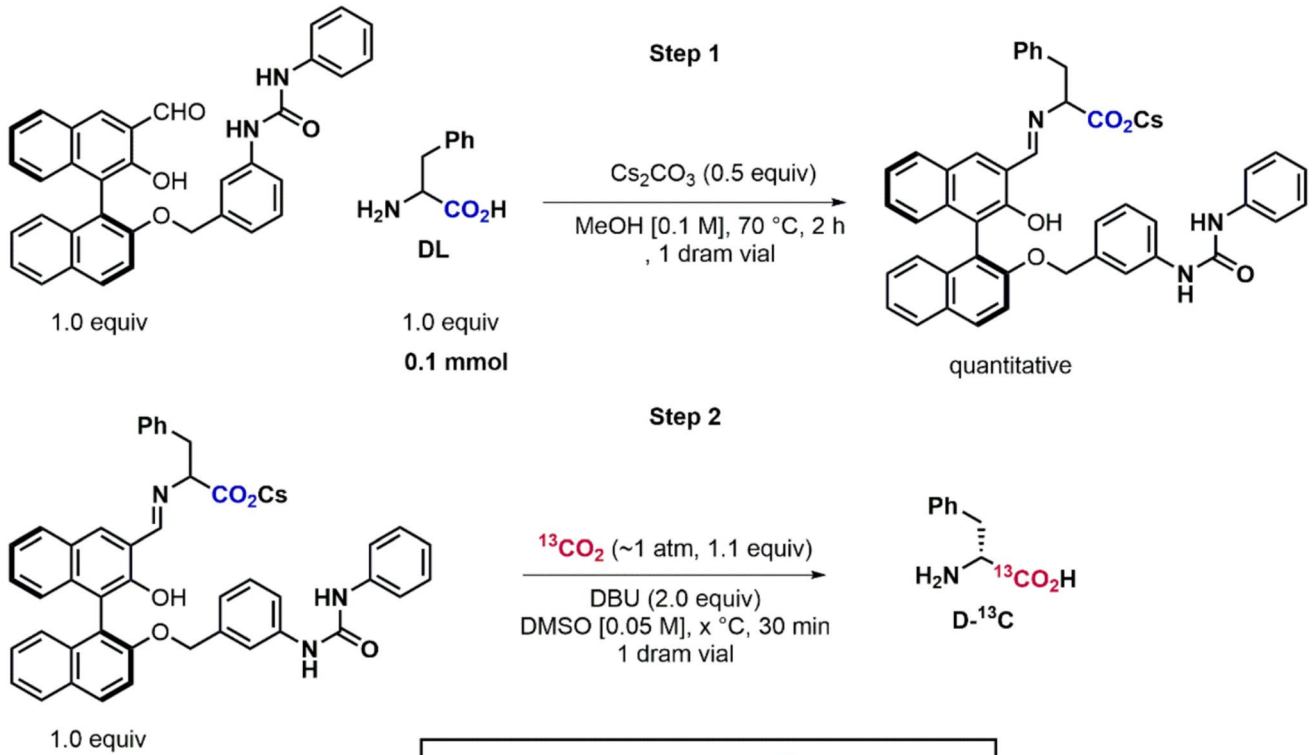
## Results and discussion

Lundgren et al. suggested in their previous work that imine carboxylates are the intermediates in their mechanistic cycle, so the aim of this work was to prepare the imine carboxylate salt in a separate step and then subject it to various reaction conditions to get the maximum $^{13}$C incorporation in the shortest time and by using a low equivalent of [$^{13}$C]

$CO_2$, which could be applicable to direct radiolabelling of α-amino acids, using [$^{11}$C]$CO_2$ [23–25].

Initially, pre-formed imine carboxylate was prepared quantitatively by condensation of α-amino acids with uryl-based binol aldehyde in basic MeOH [32] and examined as reagents for carboxylate exchange. Initial screens were performed at various temperatures, as can be seen in Fig. 3 Modified reaction conditions are carried out for the formation of the Cs-imine carboxylate intermediate by performing the reaction at 0.1 M of MeOH to increase the solubility of chiral aldehyde, and the reaction was run for 2 h. The carboxylate exchange conditions of Cs-imine carboxylate were initially carried out for 30 min by using 1.1 equiv. of [$^{13}$C]$CO_2$ and 2.0 equiv. of DBU in 0.05 M of DMSO at various temperatures, as can be seen in Fig. 3. The highest anticipated $^{13}$C incorporation, based on the headspace of the one-dram vial, is 60%. At 70 °C, 85% of phenylalanine was identified via NMR, with a 22% incorporation of $^{13}$C and an er of 85:15 (D:L). At 80 °C, similar results were observed. To enhance incorporation within the same duration, the reaction was conducted at 90 °C, yielding a slightly increased $^{13}$C incorporation to 26%, but with a reduced er of 73:27. Elevating the temperature to 100 °C resulted in a further increase in incorporation to 39% and an er of 69:31, as illustrated in Fig. 3 Despite achieving a carboxylate exchange of 39% $^{13}$C at 100 °C, the er was inferior to the normal reaction conditions documented by Lundgren et al., which reported an er of 90:10, 71% $^{13}$C incorporation, and a 65% yield with 8.0 equivalents of [$^{13}$C] $CO_2$ under their standard conditions [25].

The next challenge was how to obtain high %$^{13}$C incorporation which is close to the equilibrium incorporation which

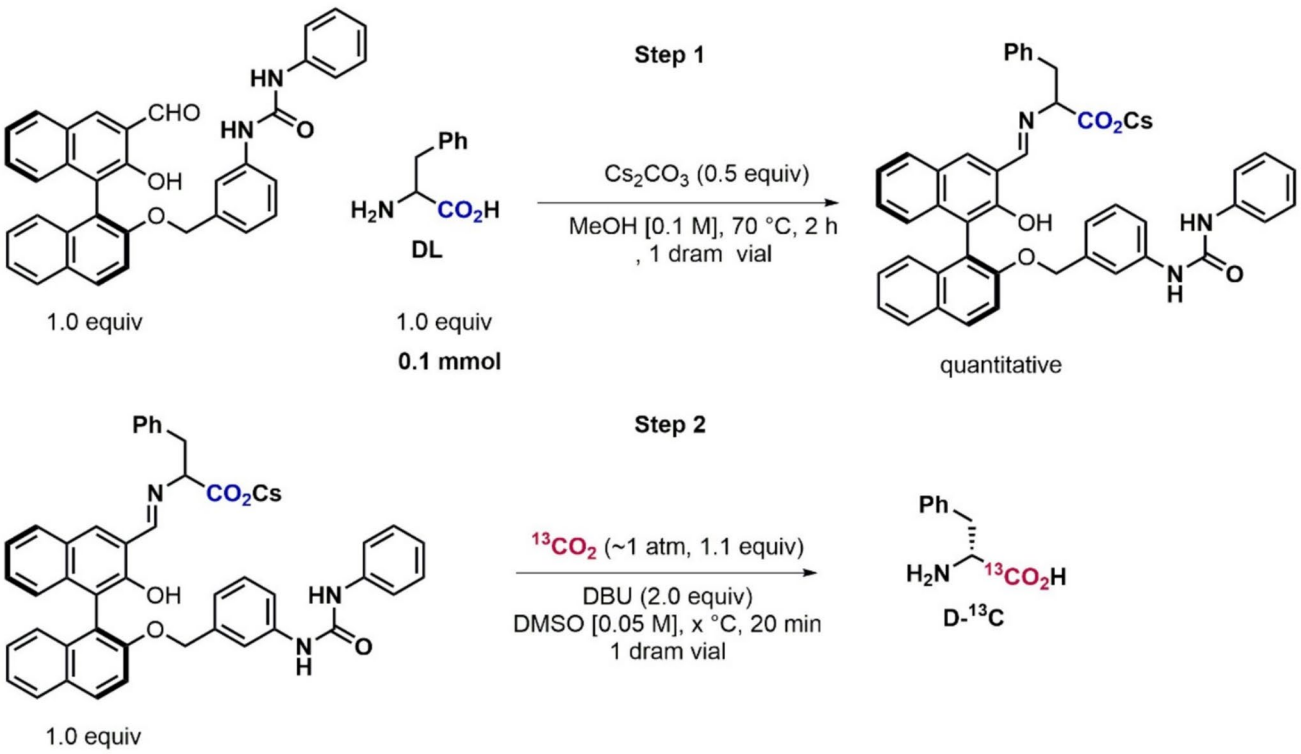



| Temperature | Recovery | $^{13}$C | *er* |
|---|---|---|---|
| 70 | 85 | 22 | 85:15 |
| 80 | 74 | 20 | 85:15 |
| 90 | 79 | 26 | 73:27 |
| 100 | 80 | 39 | 69:31 |

**Fig. 3** Development of fast conditions for enantioenriched carboxylate exchange. $^{1}$H NMR yields were determined from crude reaction mixtures, using 3-(trimethylsilyl)-1-propanesulfonic acid (DSS) as an internal standard. LC–MS analysis was used to determine the crude $^{13}$C% incorporation of the amino acid. The *er*% was obtained through chiral HPLC analysis of the products (General Procedure A)

is around 60% $^{13}C$ with *er* close to that reported in previous report which is 90:10 *er* [25]. The idea was to run the reaction at high temperature to get high incorporation then cool it down to get good *er*. Running the exchange at 110 °C for 10 min to get 24% $^{13}C$ incorporation with 76:24 *er*, followed by a cool-down to 70 °C for another 10 min to get the equilibrium ratio of D to L (90:10), 24% incorporation, and 77% NMR yield. The reaction was carried out at even higher temperature which is 120 °C, and this was the best result. Running the exchange at 120 °C for 10 min to get 44% $^{13}C$ incorporation with 77:23 *er*, followed by a cool-down to 70 °C for another 10 min to get the equilibrium ratio of D to L (90:10), 47% incorporation, and 62% NMR yield (Fig. 4).

In summary, to promote faster reactions with [$^{13}C$]$CO_2$, pre-formed imine carboxylates were generated quantitatively by condensation of α-amino acids with chiral aldehyde in basic MeOH [32] and examined as reagents for carboxylate exchange. The best conditions were by running the exchange




1. 110 °C

| Time | Recovery | $^{13}C$ | *er* |
|---|---|---|---|
| 10 min | - | 21 | 76:24 |

Cool to 70 °C for 10 min

| Time | Recovery | $^{13}C$ | *er* |
|---|---|---|---|
| 20 min | 77 | 24 | 91:9 |

- 20 min time point means 10 min at 110 °C and 10 min at 70 °C

2. 120 °C

| Time | Recovery | $^{13}C$ | *er* |
|---|---|---|---|
| 10 min | - | 44 | 77:23 |

Cool to 70 °C for 10 min

| Time | Recovery | $^{13}C$ | *er* |
|---|---|---|---|
| 20 min | 62 | 47 | 90:10 |

- 20 min time point means 10 min at 120 °C and 10 min at 70 °C

**Fig. 4** Development of fast conditions for enantioenriched carboxylate exchange by heating the reaction for the first interval of time then cool it down (General Procedure B)

at 120 °C for 10 min to get 47% $^{13}C$ incorporation with 77:23 *er*, followed by a cool-down to 70 °C for another 10 min to get the equilibrium ratio of D to L (90:10), 47% incorporation, and 62% NMR yield (Fig. 4). As a result of this work, the future studies at a level close to that of [$^{11}C$]$CO_2$ could be done, to see if the direct radiolabeling of α-amino acids, using [$^{11}C$]$CO_2$, could be possible to achieve with high enantiomeric ratio (90:10).

## Conclusion and outlook

In summary, a modified strategy is reported for the resolution/isotopic labeling of α-amino acids mediated by using a uryl-based binol aldehyde receptor with conjunction of [$^{13}C$]$CO_2$ via reversible decarboxylation/carboxylation event of an imine carboxylate intermediate. The method provides access to C1-enantioenriched-labeled products in a direct and operationally trivial manner in a short time from pre-formed imine carboxylates. The modification of the reaction conditions provides some evidence that the fast exchange conditions to enable direct radiolabeling of α-amino acids, using [$^{11}C$]$CO_2$, could be possible. Given the widespread use of enantiomerically-labeled α-amino acids in discovery science, drug development, and medical imaging, we expect this finding to have immediate application. The future studies at a level close to that of [$^{11}C$]$CO_2$ will be done.

## Experimental

### General procedure A and B

#### General procedure A

Standard reaction using the pre-formed imine from the corresponding amino acid and chiral aldehyde:

In an atmosphere-controlled glovebox, amino acid (0.10 mmol, 1.0 equiv.), chiral aldehyde (53.8 mg, 0.10 mmol, 1.0 equiv.), $Cs_2CO_3$ (16.3 mg, 0.05 mmol, 0.50 equiv.), and anhydrous MeOH (1.0 mL) were sequentially added to a dried 1-dram vial charged with a stir bar. The vial was sealed with a PTFE-lined cap and removed from the glovebox. The reaction was stirred at 70 °C for 2 h in an aluminum block, and then the reaction was cooled to room temperature. The solvent was evaporated in vacuo to isolate the imine salt. Then put under a Schlenk line at 50 °C overnight in an aluminum block. The vial was then evacuated and refilled with $N_2$ on a Schlenk line. This cycle was repeated 3 times. After the purging cycle, the vial was taken back into the glovebox and sodium trimethylsilylpropanesulfonate internal standard (DSS) was added, followed by the addition of anhydrous DMSO (2.0 mL) and DBU (29.8 ul, 0.20 mmol, 2.0 equiv.). The vial was sealed with a PTFE-lined cap and removed from the glovebox. The reaction headspace was evacuated (~ 300 mTorr) using a 25-gauge needle. The vial headspace was then carefully refilled with 15 psi $^{13}CO_2$ through the PTFE-lined cap using a 25-gauge needle, until the internal pressure reached ~ 1 atm (requires 20–60 s, depending on the pressure of the [$^{13}C$]$CO_2$ tank). This provides ~ 1.1 equivalents of (~ 0.11 mmol) $^{13}CO_2$ which would result in an equilibrium exchange incorporation of ~ 60%. The vial cap was then sealed with parafilm and electrical tape, and the reaction was stirred (at the corresponding temp) in an aluminum block. Upon completion of the reaction (30 min), the vial was cooled to room temperature. To determine the percent recovery of the amino acid, a small aliquot (~ 5 µL) of the reaction was placed in 0.70 mL DMSO for calibrated $^1H$ NMR analysis, using DSS as the reference signal. a small aliquot of the reaction (~ 5 µL) was placed in 1.0 mL of 1:1 MeOH:$H_2O$/0.1% $HCO_2H$ for LC–MS analysis to determine the crude $^{13}C$% incorporation of the amino acid. The reaction mixture was quenched (at the corresponding temp) with 1 ml of 2 M FA then diluted with $H_2O$ (5 mL). The aqueous layer was then washed with DCM (5 × 5 mL). The aqueous layer was lyophilized to remove the $H_2O$. The crude mixture was then purified by reverse phase chromatography. The *er%* was obtained through chiral HPLC analysis of the products. The $^{13}C$% incorporation was obtained through high resolution mass spectrometry (HRMS) analysis of the products.

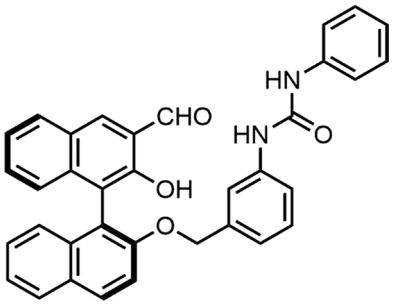
#### General procedure B

Standard reaction using the pre-formed imine from the corresponding amino acid and chiral aldehyde:

In an atmosphere-controlled glovebox, amino acid (0.10 mmol, 1.0 equiv.), chiral aldehyde (53.8 mg, 0.10 mmol, 1.0 equiv.), $Cs_2CO_3$ (16.3 mg, 0.05 mmol, 0.50 equiv.), and anhydrous MeOH (1.0 mL) were sequentially added to a dried 1-dram vial charged with a stir bar. The vial was sealed with a PTFE-lined cap and removed from the glovebox. The reaction was stirred at 70 °C for 2 h in an aluminum block, and then the reaction was cooled to room temperature. The solvent was evaporated in vacuo to isolate the imine salt. Then put under a Schlenk line at 50 °C overnight in an aluminum block. The vial was then evacuated and refilled with $N_2$ on a Schlenk line. This cycle was repeated 3 times. After the purging cycle, the vial was taken back into the glovebox and sodium trimethylsilylpropanesulfonate internal standard (DSS) was added, followed by the addition of anhydrous DMSO (2.0 mL) and DBU (29.8 ul, 0.20 mmol, 2.0 equiv.). The vial was sealed with a PTFE-lined cap and removed from the glovebox. The reaction headspace was evacuated (~ 300 mTorr) using a 25-gauge needle. The vial headspace was then carefully refilled

with 15 psi [$^{13}$C]$CO_2$ through the PTFE-lined cap using a 25-gauge needle, until the internal pressure reached ~ 1 atm (requires 20 – 60 s, depending on the pressure of the $^{13}CO_2$ tank). This provides ~ 1.1 equivalents of (~ 0.11 mmol) [$^{13}$C]$CO_2$ which would result in an equilibrium exchange incorporation of ~ 60%. The vial cap was then sealed with parafilm and electrical tape, and the reaction was stirred (at the corresponding temp) in an aluminum block. Upon completion of the reaction (10 min), the vial was cooled to 70 °C for 10 min. To determine the percent recovery of the amino acid, a small aliquot (~ 5 µL) of the reaction was placed in 0.70 mL DMSO for calibrated $^1$H NMR analysis, using DSS as the reference signal. a small aliquot of the reaction (~ 5 µL) was placed in 1.0 mL of 1:1 MeOH:$H_2O$/0.1% $HCO_2H$ for LC–MS analysis to determine the crude $^{13}$C% incorporation of the amino acid. The reaction mixture was quenched (at the corresponding temp) with 1 ml of 2 M FA then diluted with $H_2O$ (5 mL). The aqueous layer was then washed with DCM (5 × 5 mL). The aqueous layer was lyophilized to remove the $H_2O$. The crude mixture was then purified by reverse phase chromatography. The *er%* was obtained through chiral HPLC analysis of the products. The $^{13}$C% incorporation was obtained through high resolution mass spectrometry (HRMS) analysis of the products.

## Characterization of the products



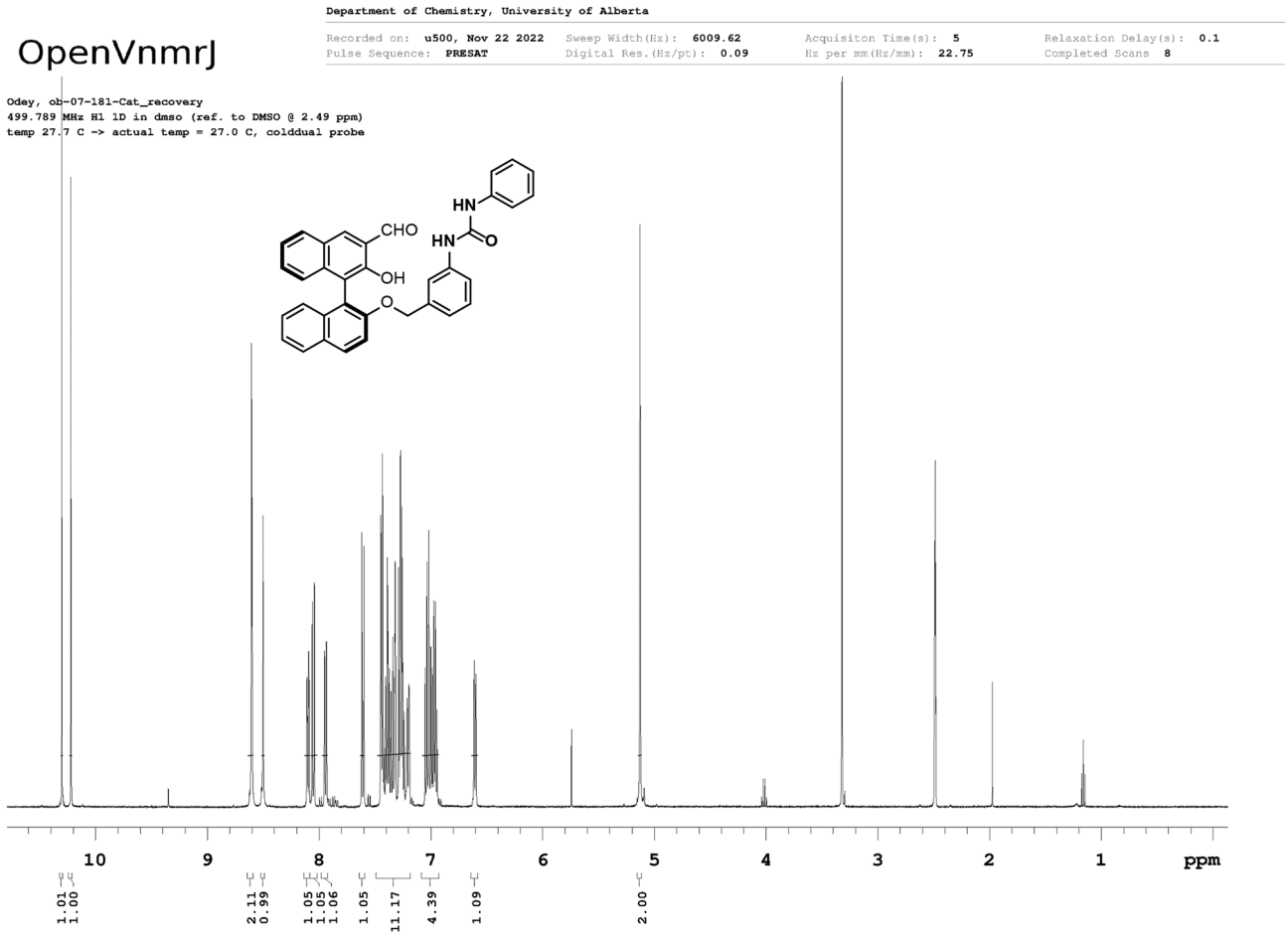

Prepared according to reported literature procedure [26] and isolated in 70% as a yellow solid after purification by normal phase column chromatography (7% EtOAc in DCM).

**$^1$H NMR** ($d_6$-DMSO, 500 MHz), δ 10.30 (s, 1H), 10.22 (s, 1H), 8.61 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.09–8.11 (m, 1H), 8.05 (d, $J$ = 9.2 Hz, 1H), 7.94 (d, $J$ = 8.2 Hz, 1H), 7.61 (d, $J$ = 9.2 Hz, 1H), 7.20–7.45 (m, 11H), 6.96–7.05 (m, 4H), 6.60 (d, $J$ = 8.2 Hz, 1H), 5.13 (s, 1H);

**$^{13}$C NMR** ($d_6$-DMSO, 125 MHz), δ 196.9, 154.1, 152.9, 152.3, 139.6, 139.5, 137.9, 136.9, 136.6, 133.3, 130.1, 130.0, 129.7, 128.9, 128.7, 128.5, 128.1, 127.2, 126.6, 124.5, 124.3, 124.0, 123.6, 122.7, 121.8, 120.2, 118.1, 117.6, 117.5, 117.4, 116.8, 115.7, 70.1;

**HRMS (ESI):** calcd. for $C_{35}H_{27}N_2O_4$ $[M + H]^+$: 539.1965. Found 539.1973.

## $^{1}H$ and $^{13}C$ spectra of chiral aldehyde

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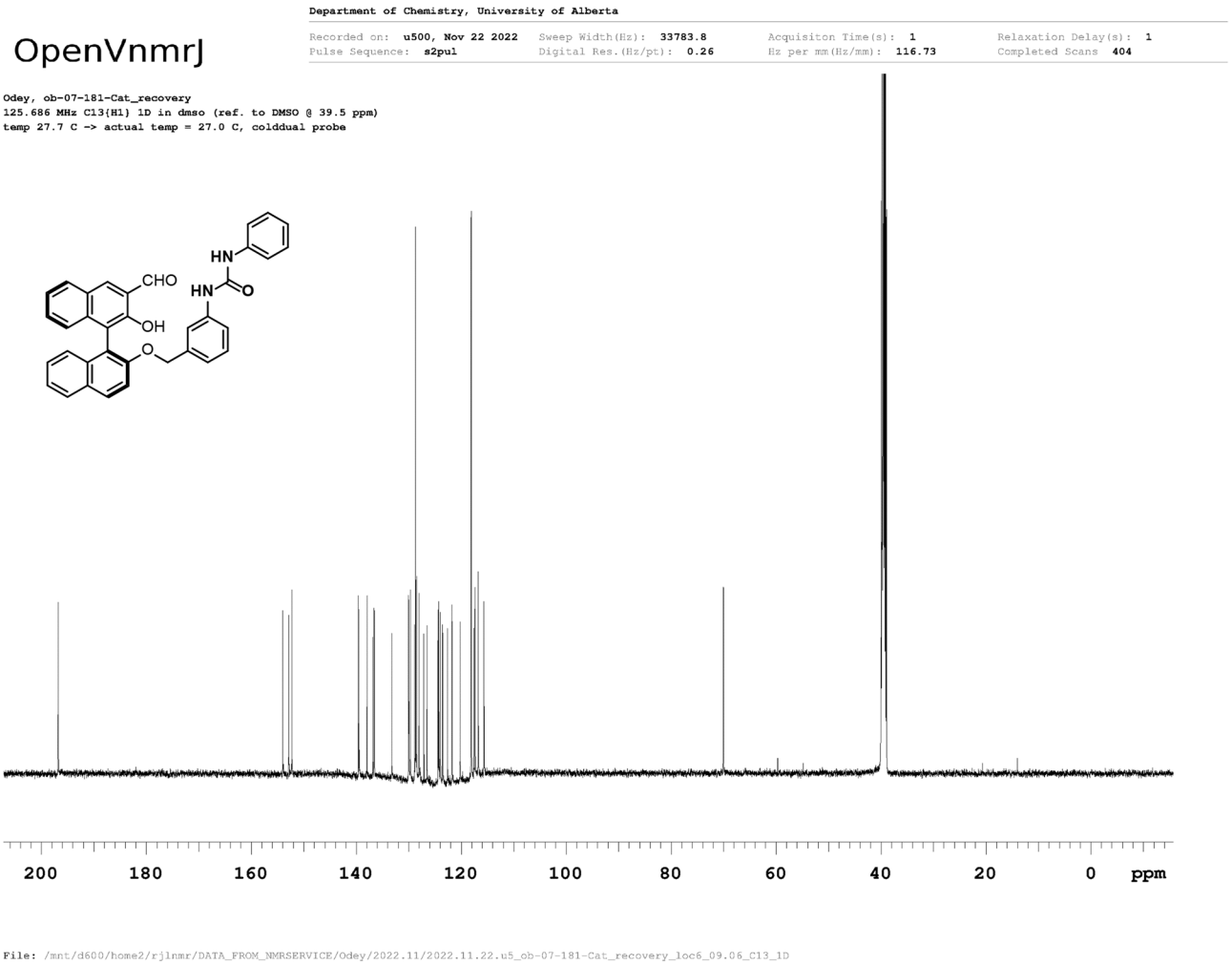


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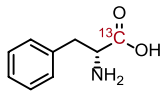


Prepared according to the literature procedure [25]. DL-$^{12}$C-phenylalanine (33.0 mg, 0.20 mmol, 1.0 equiv.), chiral aldehyde ((***S***)**-4A**) (107.7 mg, 0.2 mmol, 1.00 equiv.), and DBU (59.6 µL, 0.4 mmol, 2.0 equiv.) in DMSO (4.0 mL). The reaction mixture was allowed to stir for 24 h. $^{1}$H NMR yield: 61%. Isolated in 52% yield, *er:* 88:12, 88% $^{13}$C incorporation (HRMS) as an off-white solid after purification by preparative-HPLC (Agilent Prep-C18 column, 2.5% MeOH in $H_2O$, 25 mL/min).

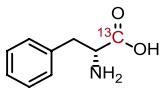
**$^{1}$H NMR** ($D_2O$, 500 MHz) δ 7.40–7.38 (m, 2H), 7.35–7.32 (m, 1H), 7.30–7.29 (m, 2H), 3.93 (m, 1H), 3.23 (brs, 1H), 3.09 (brs, 1H);

**$^{13}$C NMR** ($D_2O$, 125 MHz) δ 175.3, 136.2, 130.3, 130.0, 128.6, 56.9 (d, $J$ = 56.2 Hz), 37.5;

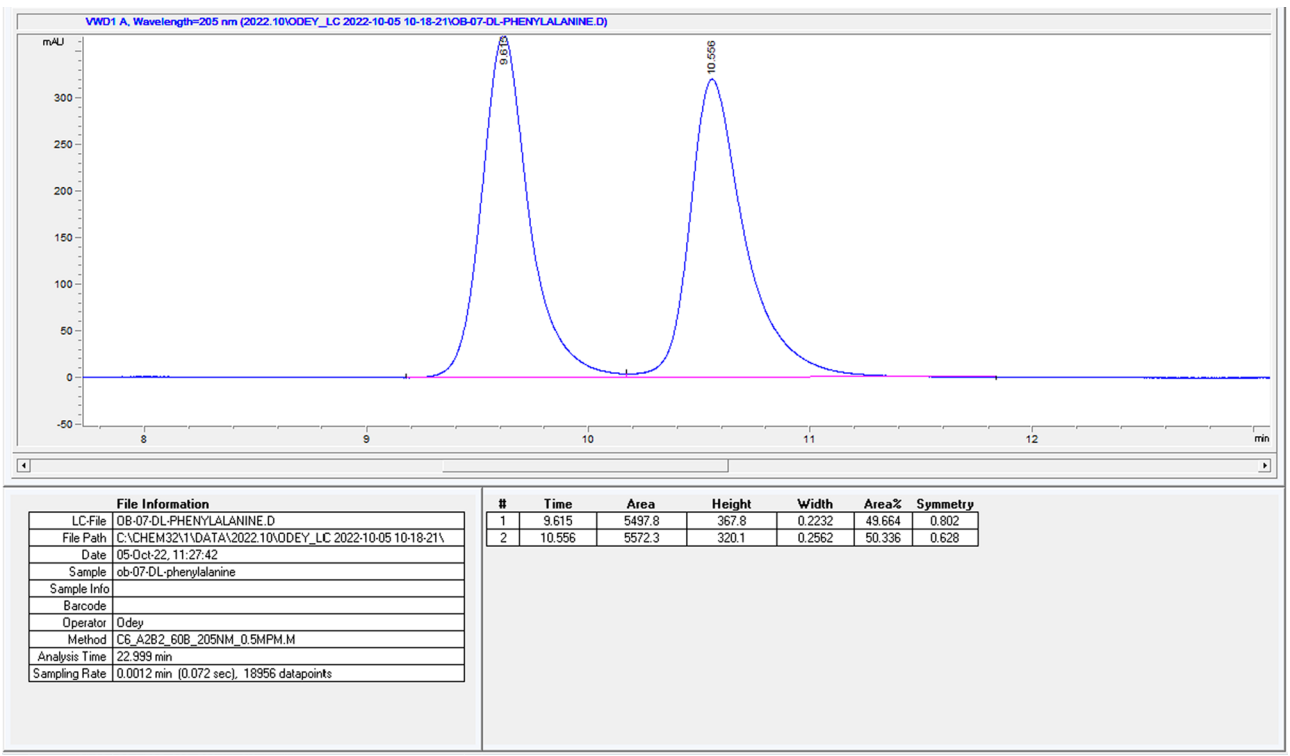
**HRMS (ESI):** calcd. for $C_8[^{13}C]H_{10}NO_2$ $[M-H]^-$: 165.0751. Found 165.0751;

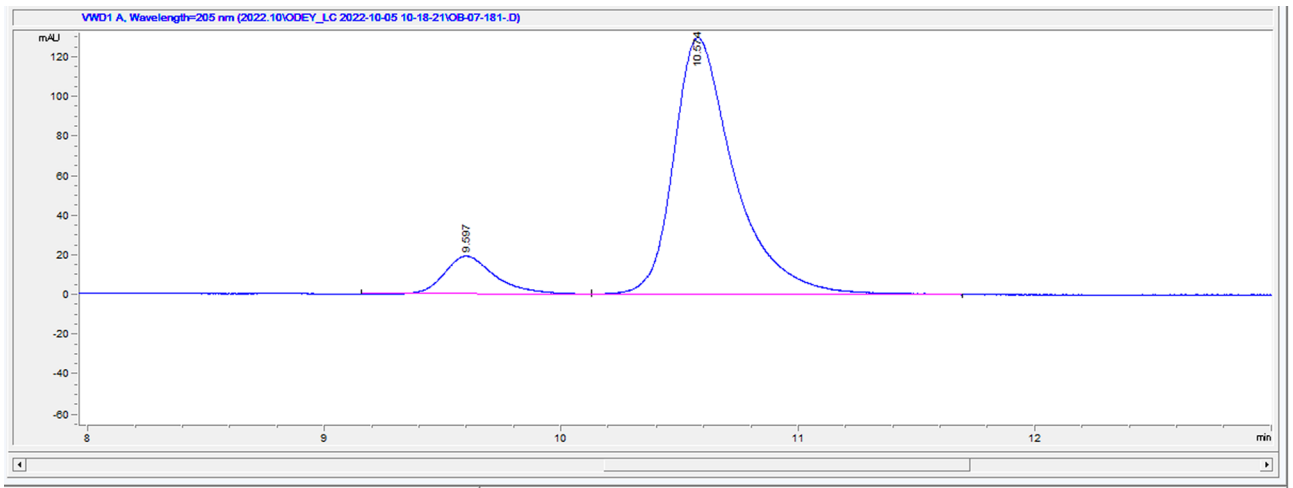
**Chiral HPLC:** 89:11 *er*. Determined on Astec Chirobiotic-T column (60% MeOH in $H_2O$ with 0.02% $HCO_2H$, 0.5 mL/min), $t_r$ = 9.6 min (minor), $t_r$ = 10.6 min (major).

## Chiral HPLC chromatogram of Racermic DL-phenylalnine and for $^{13}$C-D-phenylalanine



**Chiral HPLC:** 89:11 *er*. Determined on Astec Chirobiotic-T column (60% MeOH in $H_2O$ with 0.02% $HCO_2H$, 0.5 mL/min), $t_r$ = 9.6 min (minor), $t_r$ = 10.6 min (major).



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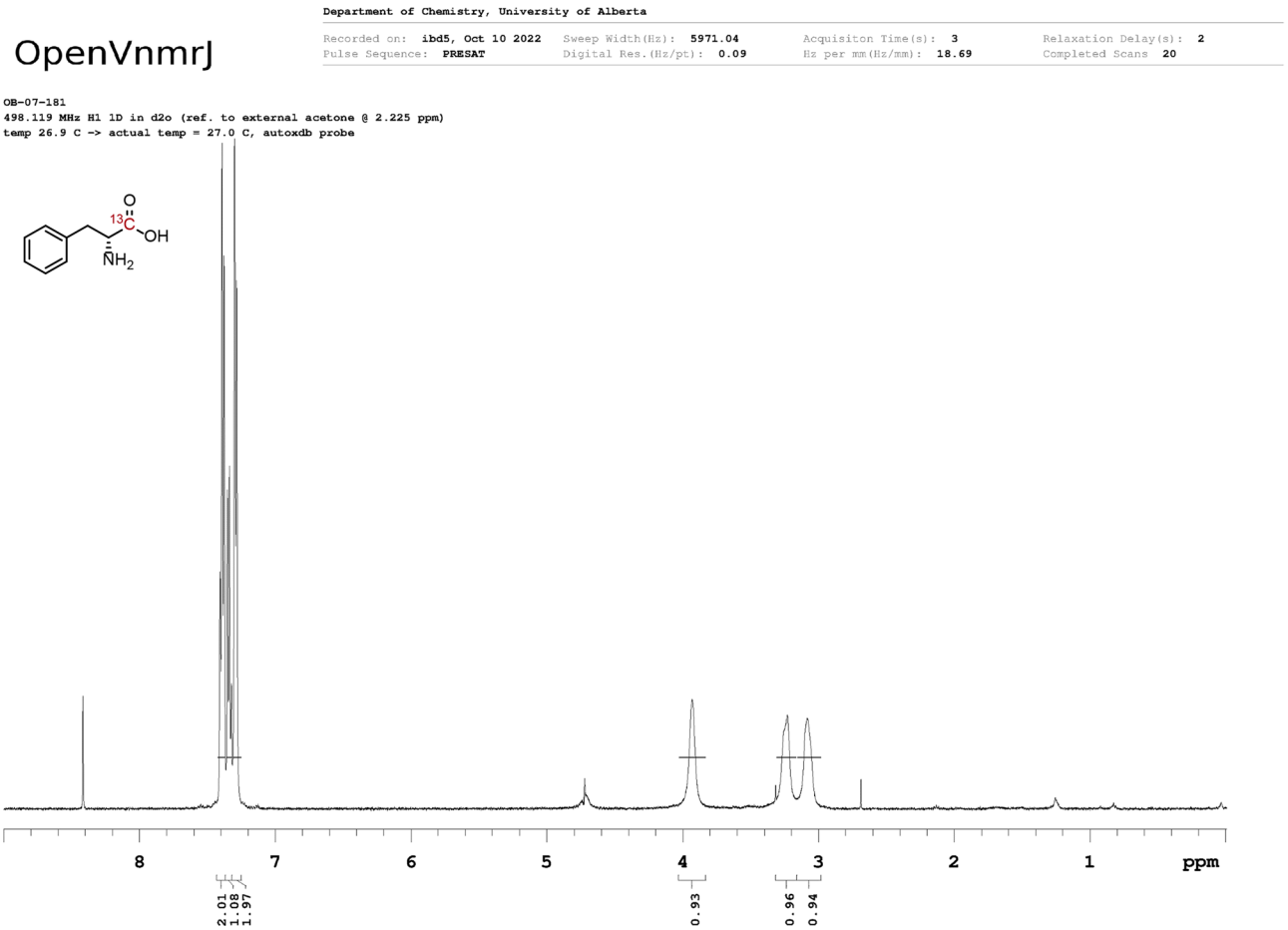
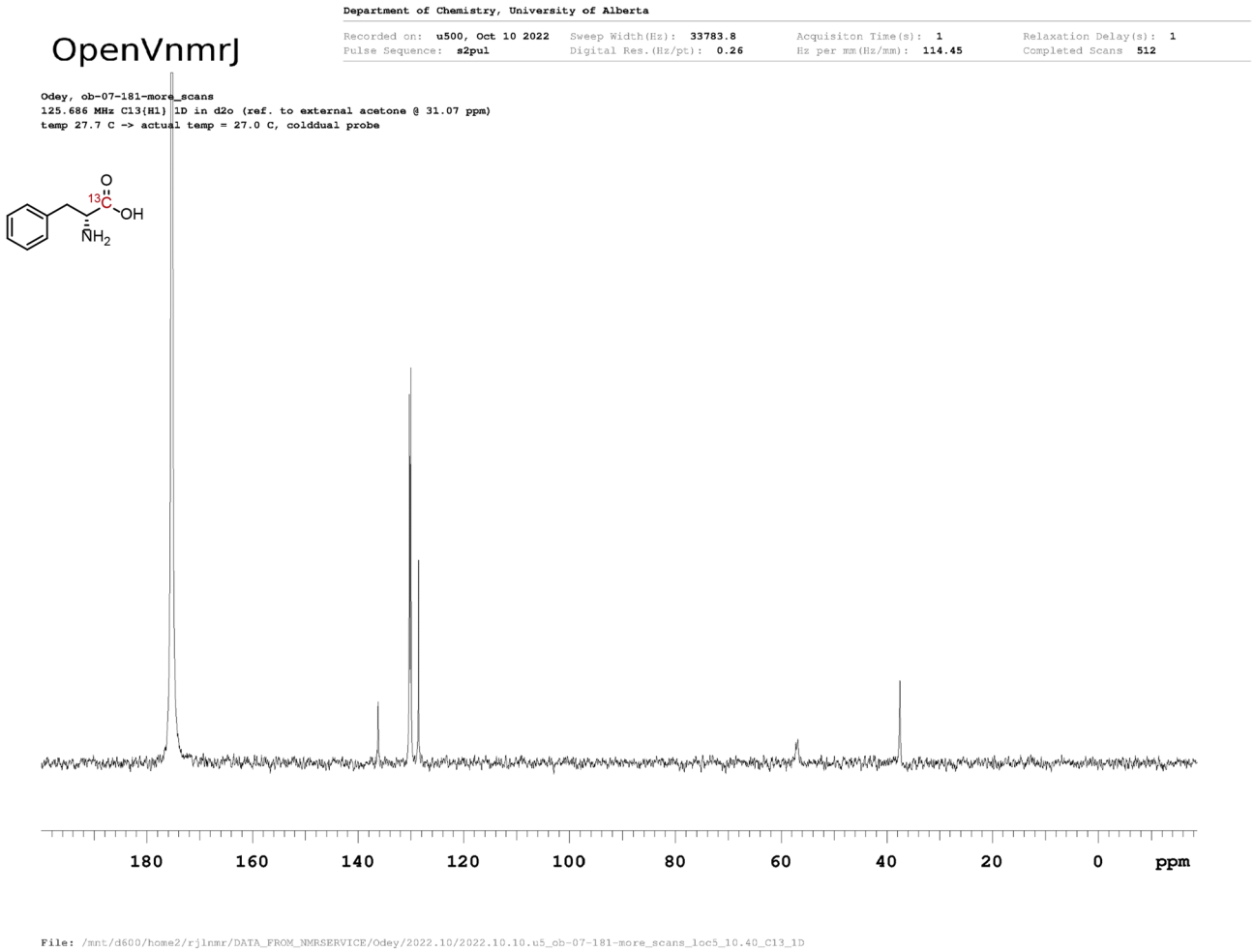
## $^{1}H$ and $^{13}C$ spectra of $^{13}C$-D-phenylalanine




Department of Chemistry, University of Alberta
OpenVnmrJ
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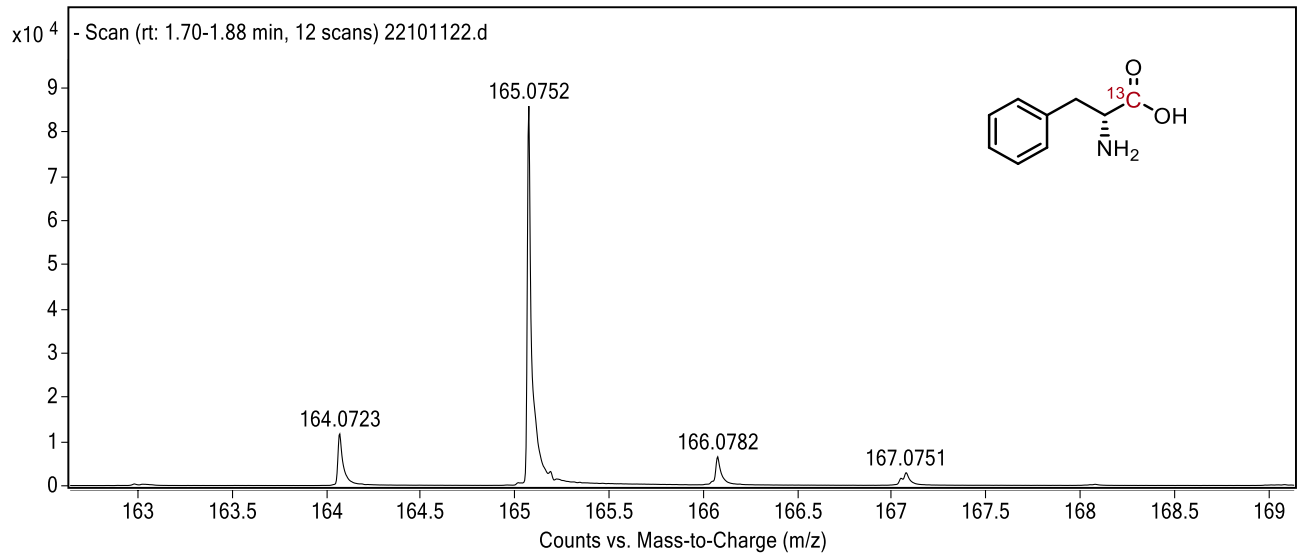
**High resolution mass spectrometry data of $^{13}$C-D-phenylalanine**




| m/z | Relative natural abundance (%) | Observed abundance (%) | Corrected abundance (%) | Isotopic enrichment relative (%) |
|---|---|---|---|---|
| [M-H]+0 | 100 | 11,749 | 11,749 | 12 |
| [M-H]+1 | 10.29 | 86,090 | 84,881 | 88 |

## Declarations

**Conflict of interest** There is no conflict of interest.

## References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