Electronic Supplementary Information

Concise Two-Step Chemical Synthesis of Molnupiravir

Vinícius R. D. Pereira,[a] Marco A. M. Bezerra,[b] Mauro R. B. P. Gomez,[b] Guilherme M. Martins,[c] Adilson D. da Silva,[a] Kleber T. de Oliveira,[c] Rodrigo O. M. A. de Souza [b*] and Giovanni W. Amarante [a*]

Contents:

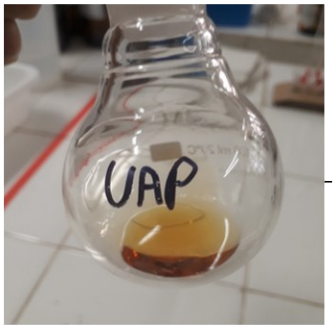
1. Images

1.1 Images from one-pot cetalization/esterification step to compound (**4**)

Cetalization reaction
after 1 h

Esterification reaction
after 1 h

Solvent removal under
reduced pressure



Compound (**4**)

Liquid/liquid extraction
followed by solvent removal
under reduced pressure

1.2 Images from one-pot oxyamination/deprotection step to molnupiravir (**2**).

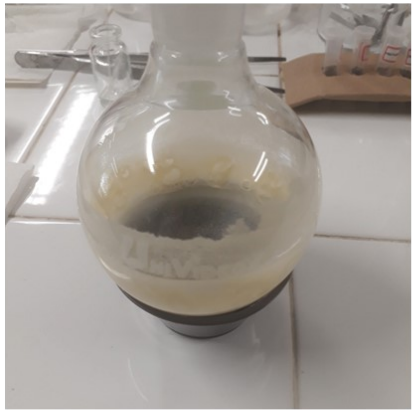
Oxyamination reaction
after 2 h

Deprotection reaction
after 30 min

Neutralization with Na_2CO_3 (pH around 7-8)
followed by the extraction with AcOEt

molnupiravir (**2**)

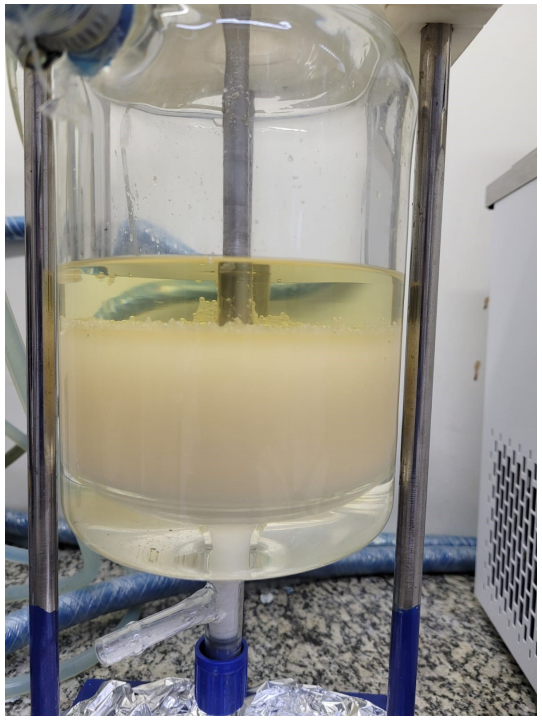
After recrystallization
(AcOEt 1:1 MeCN)



After solvent removal
under reduced pressure

1.3 Images from 10g scale-up

10g scale apparatus

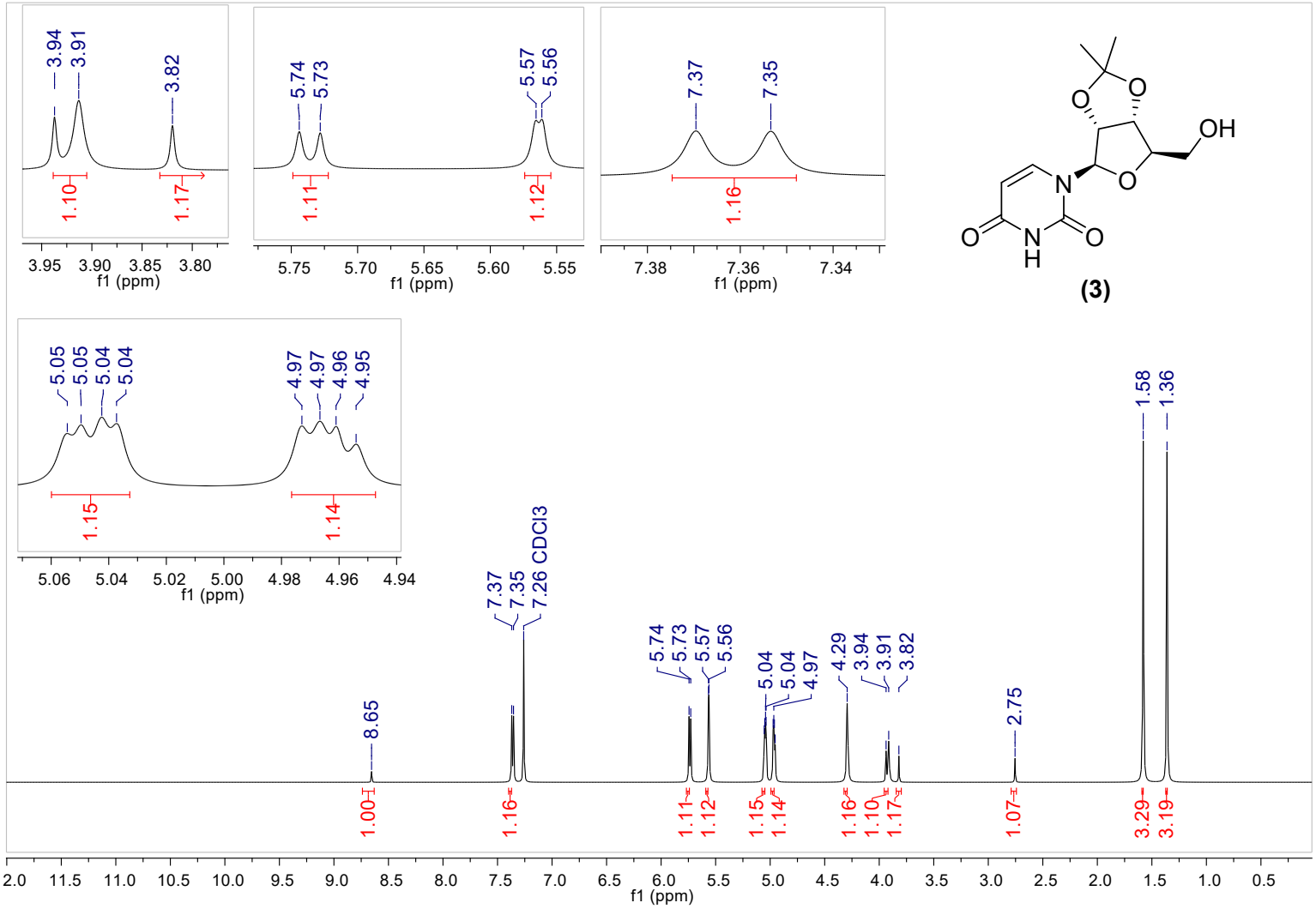


Work-up

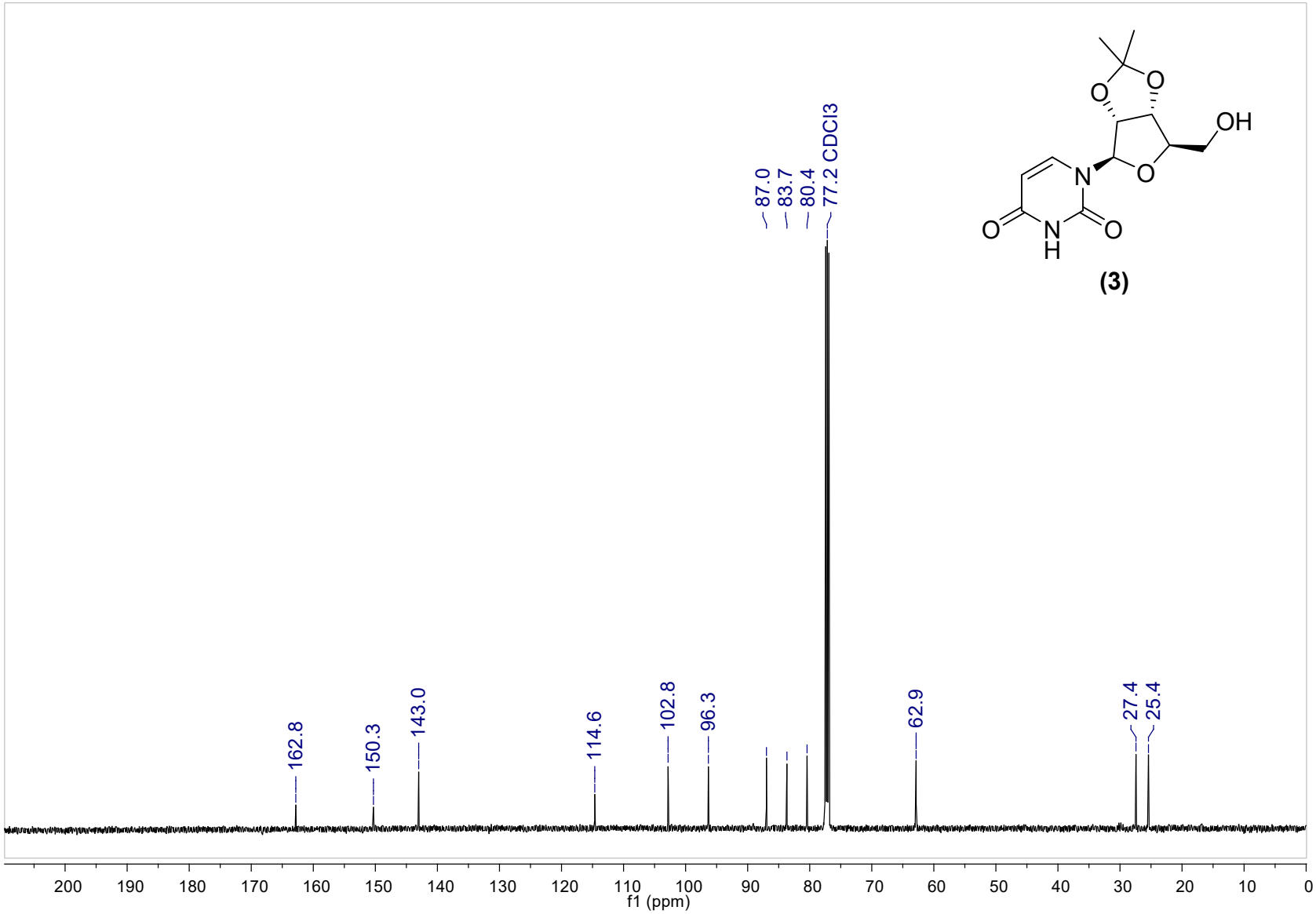
Isolation

2. NMR spectra

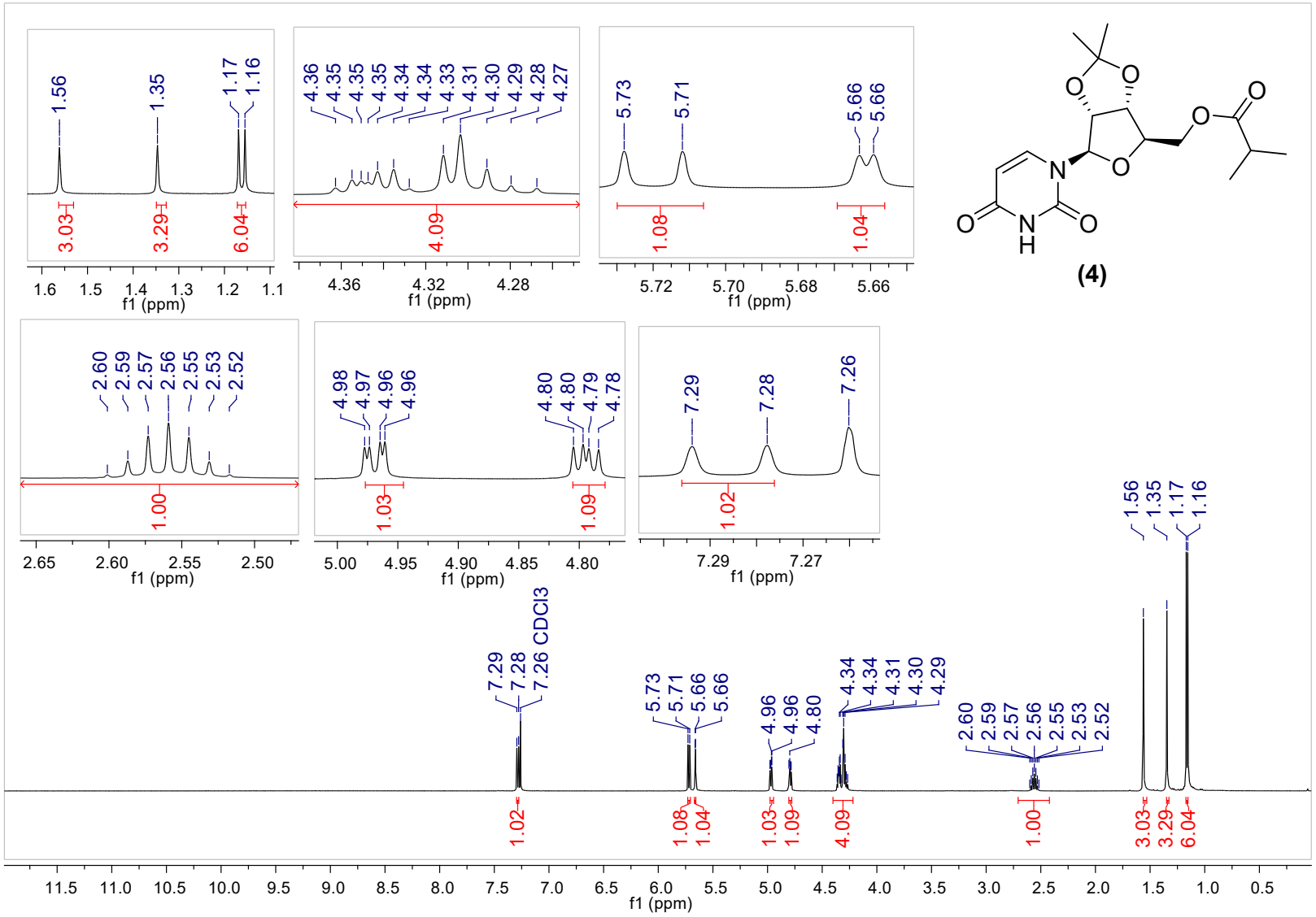
2.1 ^{1}H-NMR (500 MHz, $CDCl_3$) spectrum of compound (**3**).



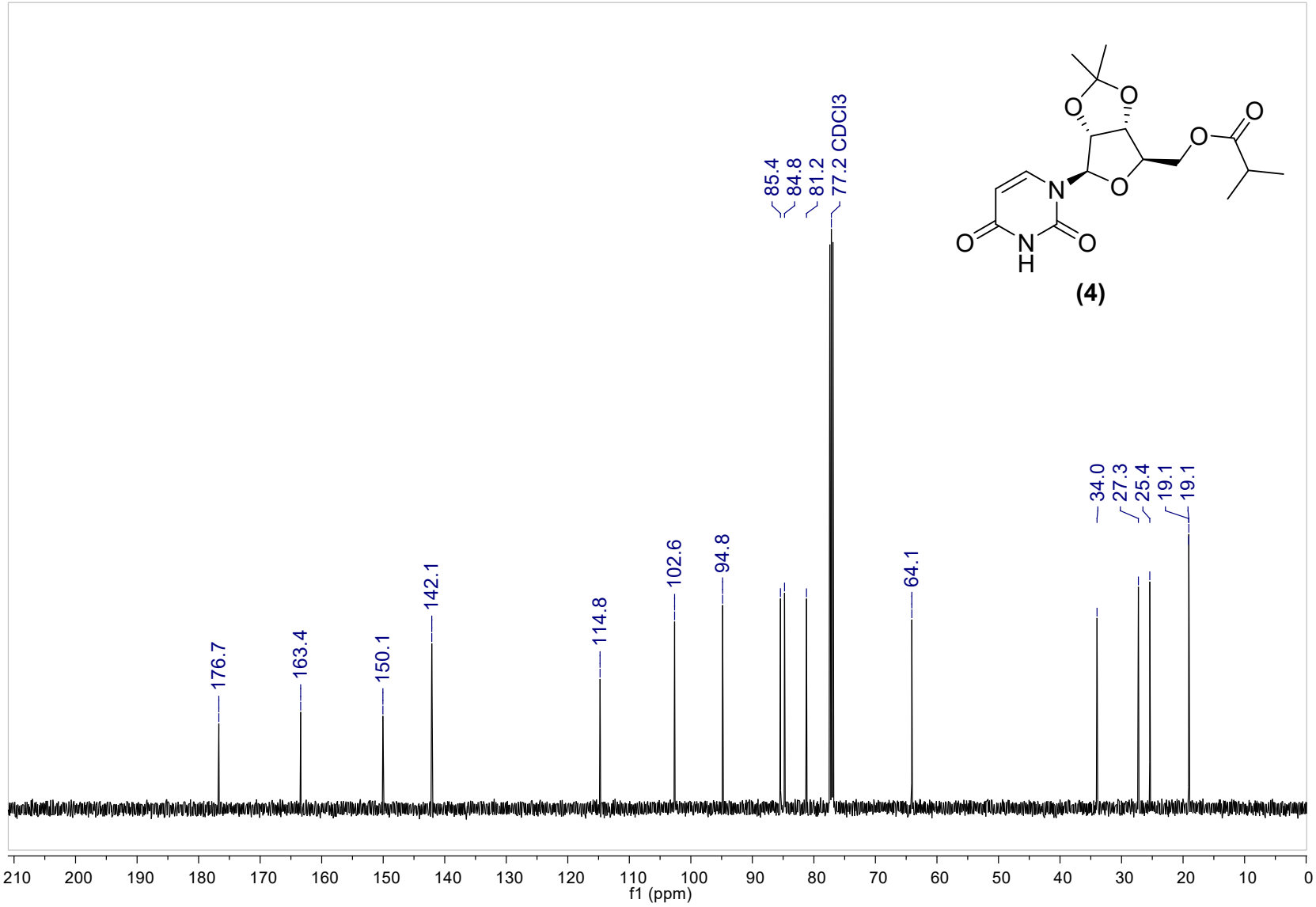
2.2 ^{13}C-NMR (125 MHz, $CDCl_3$) spectrum of compound (**3**).



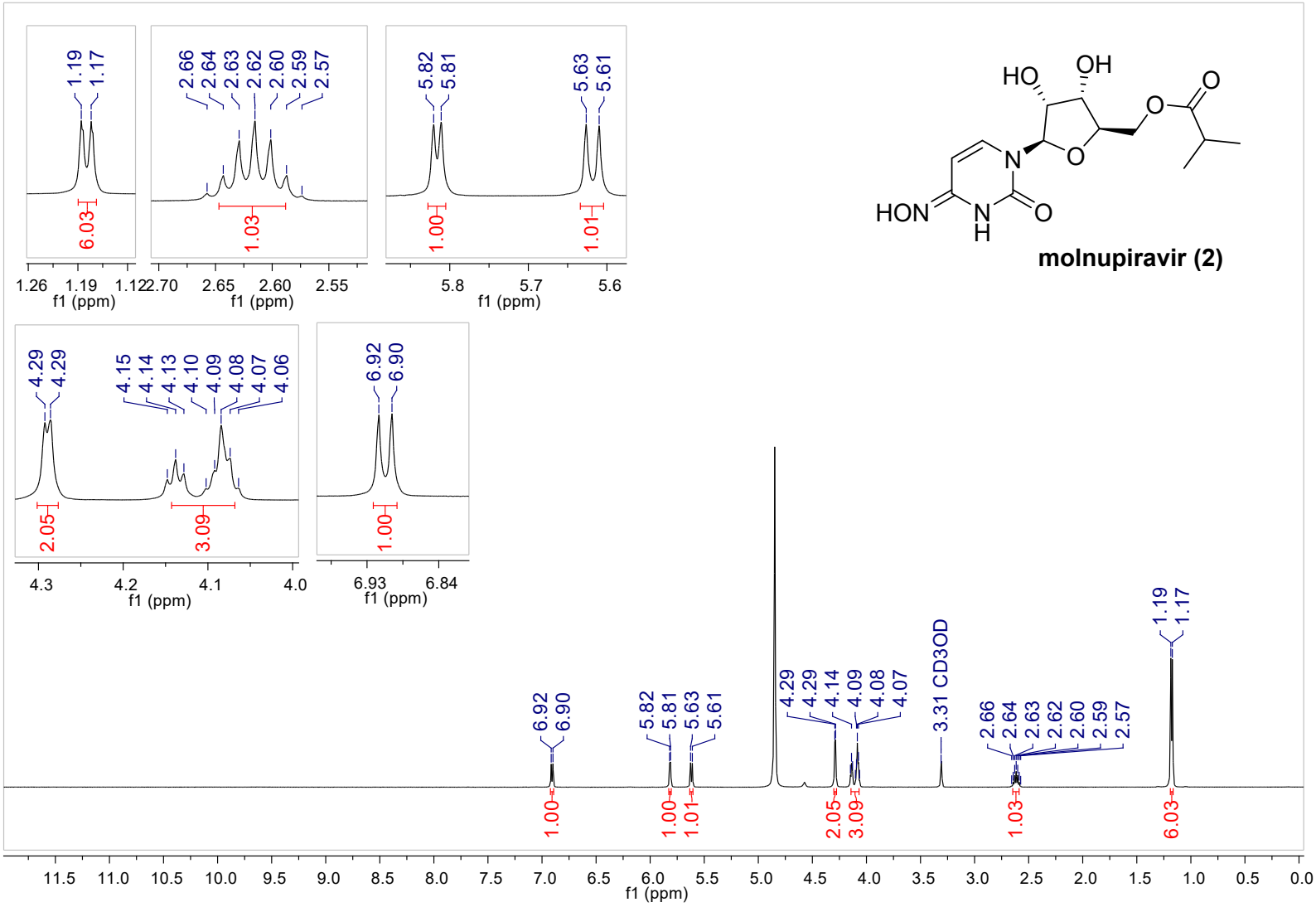
2.3 ^{1}H-NMR (500 MHz, $CDCl_3$) spectrum of compound (**4**).



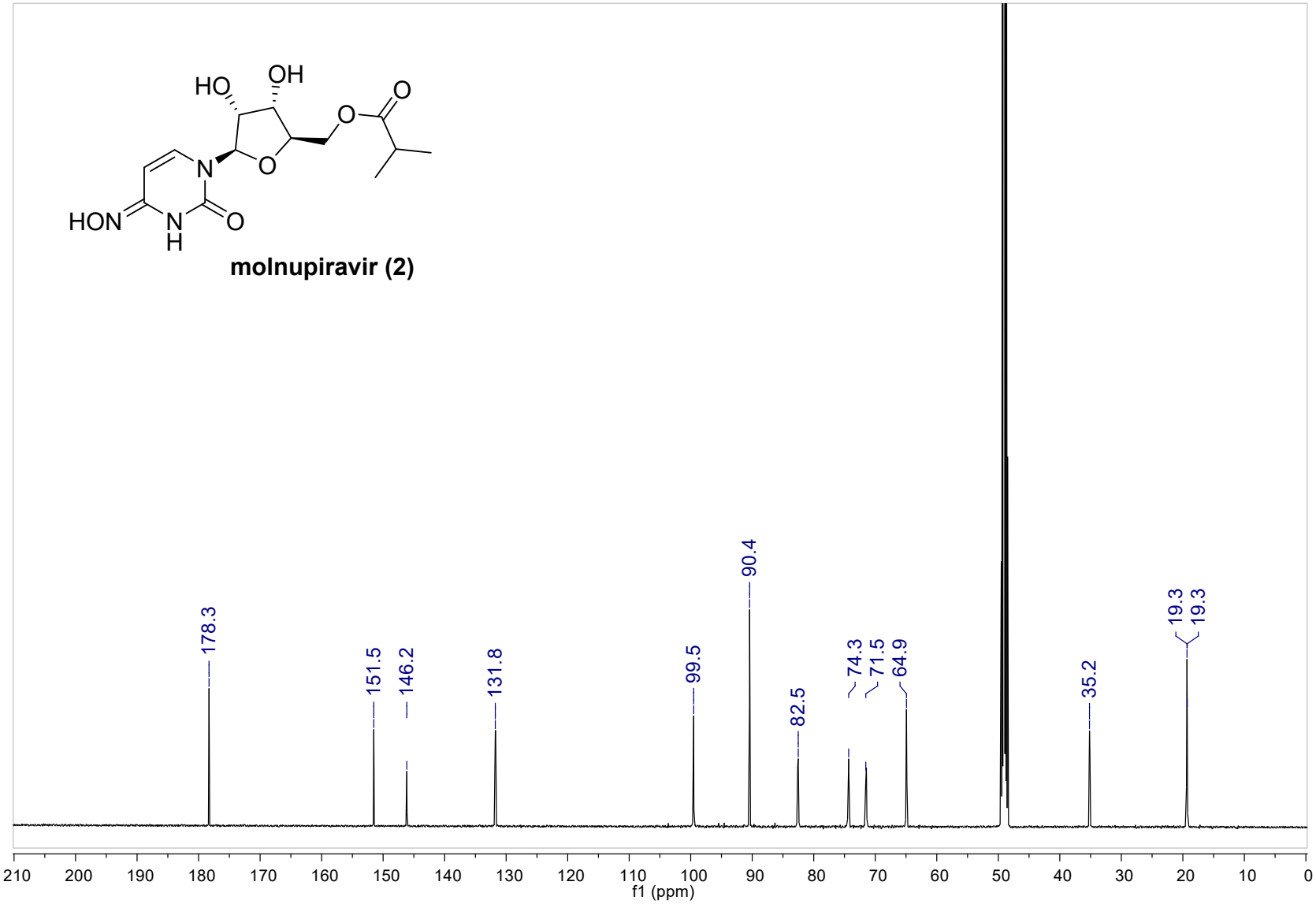
2.4 ^{13}C-NMR (125 MHz, $CDCl_3$) spectrum of compound (**4**).



2.5 ^{1}H-NMR (500 MHz, CD_3OD) spectrum of molnupiravir (**2**).



2.6 ^{13}C-NMR (125 MHz, CD_3OD) spectrum of molnupiravir (**2**).



3. Tables 1, 2 and 3

3.1 Table 1: Comparison of synthetic routes starting from uridine

Parameter	**Painter *et al*., 2019** **WO pat. WO2019113462, 2019.**	**Fier *et al*., 2021** **Org. Process Res. Dev. 2021, 25, 2806−2815**	**Dey *et al*., 2021** **ACS Omega 2021, 6, 28366−28372**	**Our work**
Overall yield	<17%	57%	62%	68%
Steps	5	5	2	2
Total time	>40 h	>35 h	>12 h	4,5 h
Purification protocols	Includes column chromatography	Solvent washes and liquid-liquid extractions	Includes column chromatography	Only liquid-liquid extractions and recrystallization
Activation step	Insertion of 1,2,4-triazole	Insertion of 1,2,4-triazole	Formation of a thionated intermediate	No need of any extra activation step

3.2 Oxyamination step comparison to refs 10 and 11

Parameter	**Benkovics *et al.*, 2020 (T. Benkovics, J. McIntosh, S. Silverman, J. Kong, P. Maligres, T. Itoh, H. Yang, M. Huffman, D. Verma and W. Pan, *ChemRxiv*, 2020.)** **McIntosh *et al.* 2021 (*ACS Central Science*, 2021, 7, 1980-1985.)**	**Our work**
Oxyamination yield	86%	84%
Total time	6 h	2 h
Purification protocols	Several solvent washes, extractions and pH adjusts	Only one and simple liquid-liquid extraction

3.3 Comparison of synthetic routes to refs 10 and 11

Parameter	**Benkovics *et al.*, 2020 (T. Benkovics, J. McIntosh, S. Silverman, J. Kong, P. Maligres, T. Itoh, H. Yang, M. Huffman, D. Verma and W. Pan, *ChemRxiv*, 2020.)** **McIntosh *et al.* 2021 (*ACS Central Science*, 2021, 7, 1980-1985.)**	**Our work**
Overall yield	69%	68%
Steps	3	2
Total time	36 h	4,5 h
Purification protocols	Solvent washes, extractions and pH adjusts	Only liquid-liquid extractions and recrystallization

4. Total ion chromatogram (TIC) and high-resolution mass spectrum of monulpiravir sample in positive and negative ionization modes

4.1 C18 column