

**Asymmetric One-Pot Synthesis of
(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-ol: A Key Component of
Current HIV Protease Inhibitors**

Adrian Sevenich^{§†}, Gong-Qing Liu^{§†}, Anthony J. Arduengo III[‡], B. Frank Gupton^{||} and Till Opatz^{*†}

[†] Institute of Organic Chemistry, Johannes Gutenberg University, Duesbergweg 10–14, 55128 Mainz, Germany

[‡]Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487, USA

^{||} Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284, United States

E-mail: opatz@uni-mainz.de

[§] Both authors contributed equally.

Table of Contents

1. Light sources and reaction setup for irradiations	S1
2. Comparison with Doan's route	S1
3. Comparison with reported enzymatic resolutions	S2
4. Copies of NMR spectra.....	S3
5. Chiral GC data	S9

1. Light sources and reaction setup for irradiations

Light Sources: USHIO G8T5E UV-B low pressure mercury lamp, 7.2 W, $\lambda_{\text{max}} = 306$ nm

<http://www.ushio.com/products/uv/uv-illumination/low-pressure-mercury-arc-blacklight.php>

Reaction Setup:

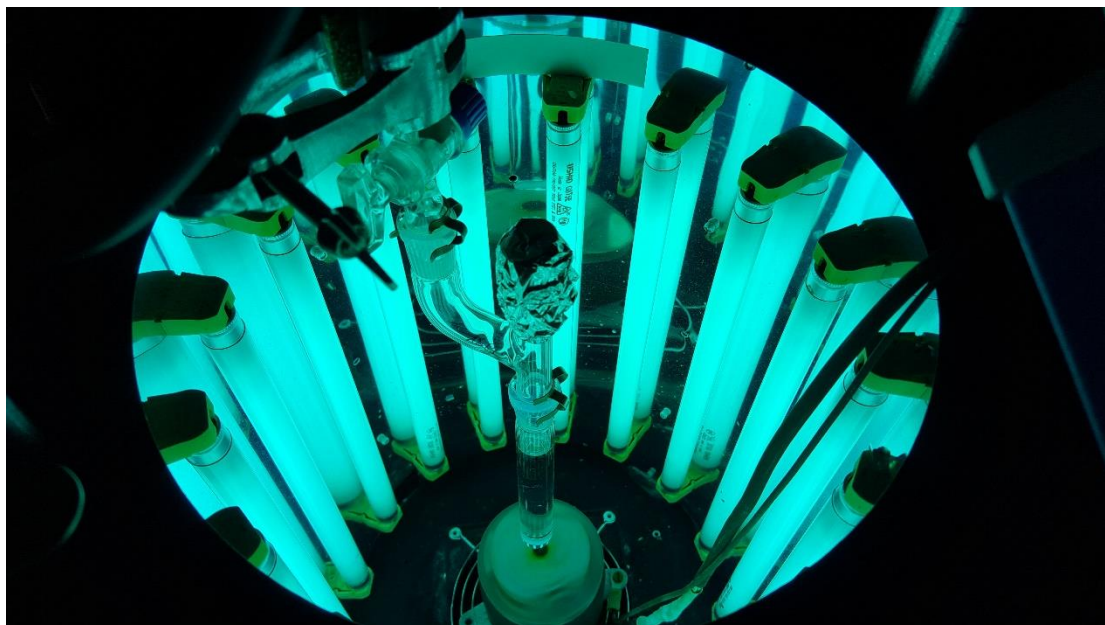
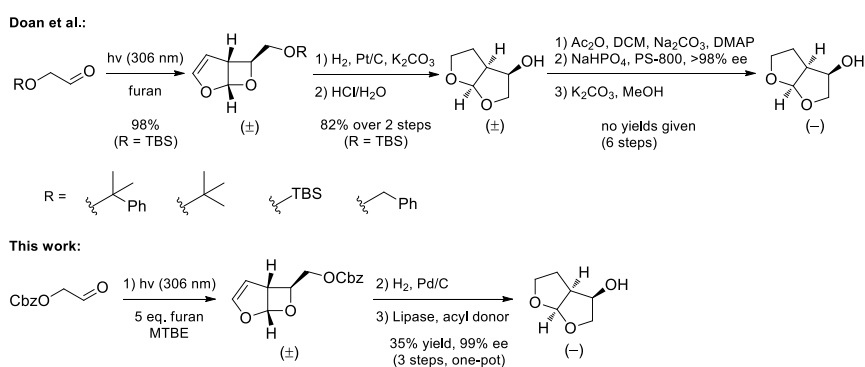


Figure S1: Typical reaction setup for irradiation in the Rayonet Photochemical Reactor (Southern New England Ultraviolet Company)

2. Comparison with Doan's route



Comparison of starting materials and protecting groups:

Doan et al.:

TBS:

[+] Aldehyde commercially available

[+] Complete route described for this aldehyde (including yields and scale)

[-] Expensive protecting group

1-Methyl-1-phenylethyl:

[-] Low yield for the aldehyde (29% over 2 steps, Doan et al.)

[-] One additional chromatographic step

Benzyl:

[+] Aldehyde commercially available

[+] Removable during hydrogenation

[+] Only toluene as by-product

[-] Competing Norrish-type II reaction during irradiation

[-] Not further described by Doan et al. after the irradiation step

This work:

Cbz:

[+] Readily synthesized from sustainable resources

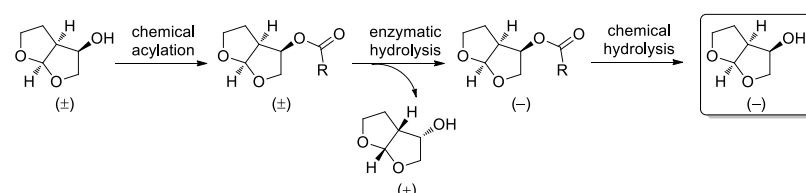
[+] Besides the benzyl group one of the cheapest protecting groups available

[+] Removable during hydrogenation

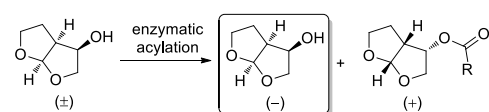
[+] Only toluene and CO₂ as byproducts

3. Comparison with reported enzymatic resolutions

Strategy #1:



Strategy #2:



Scheme S1. Two possible strategies for the enzymatic resolution of racemic bis-THF alcohol.

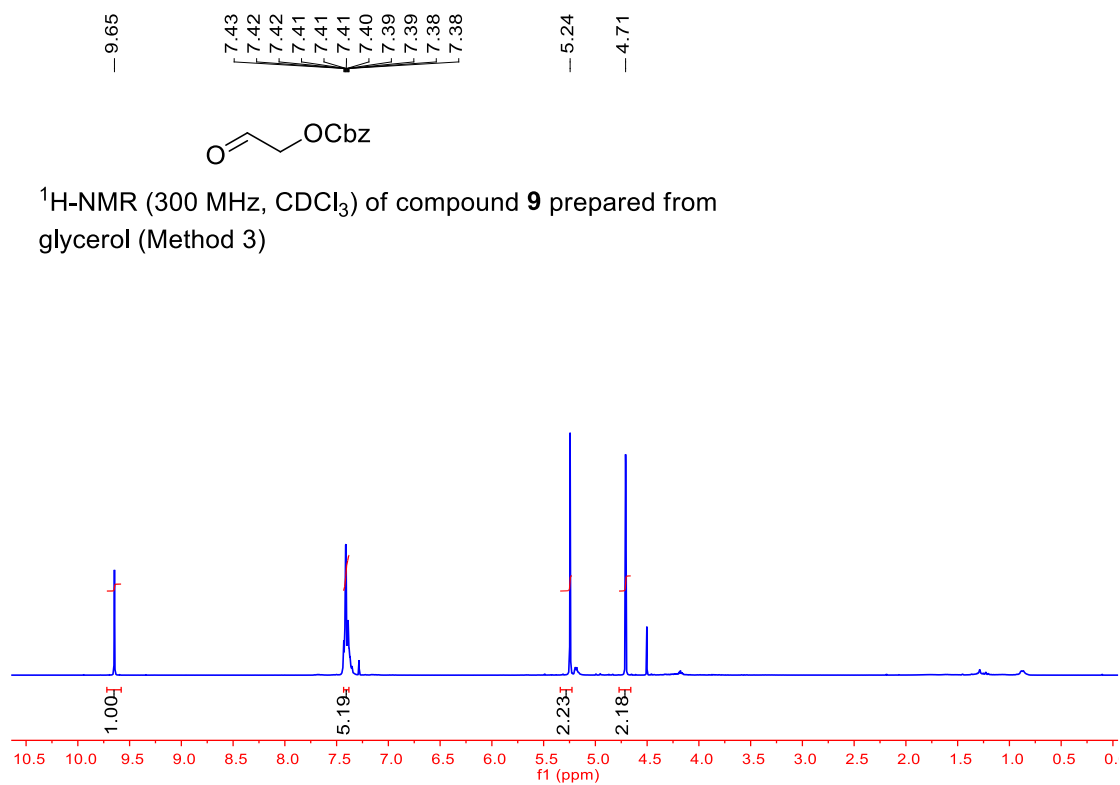
Comparison of strategies used in the literature:

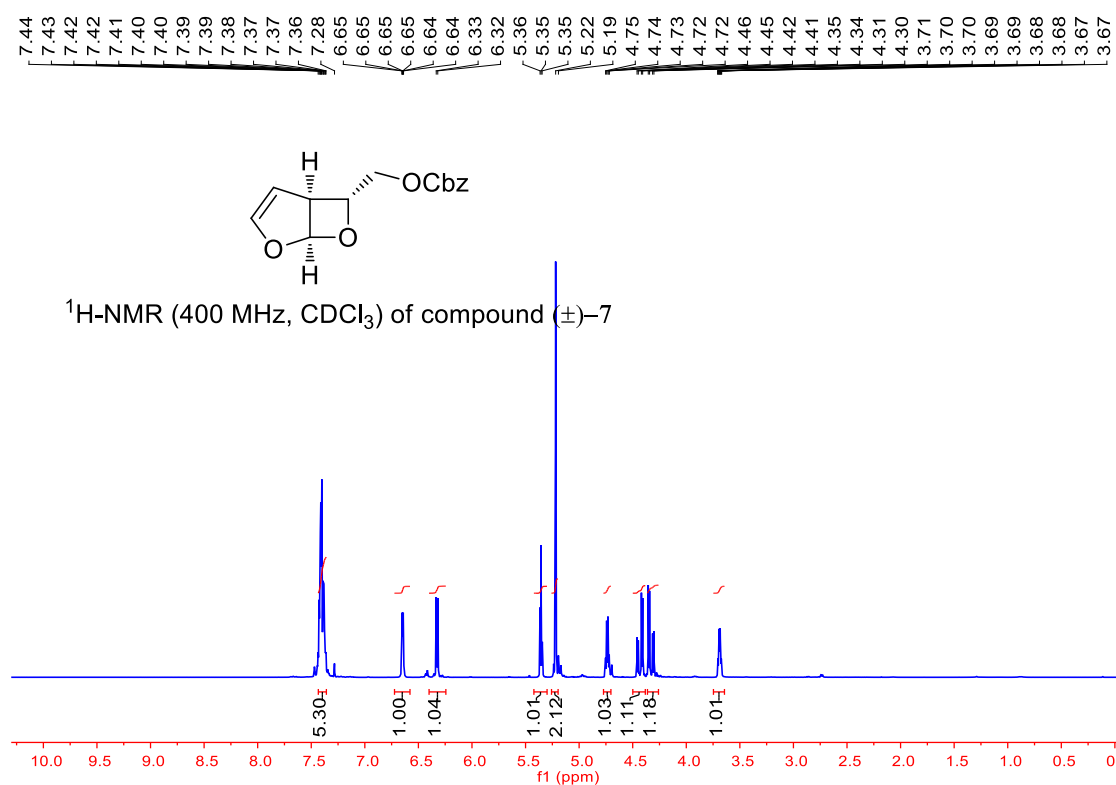
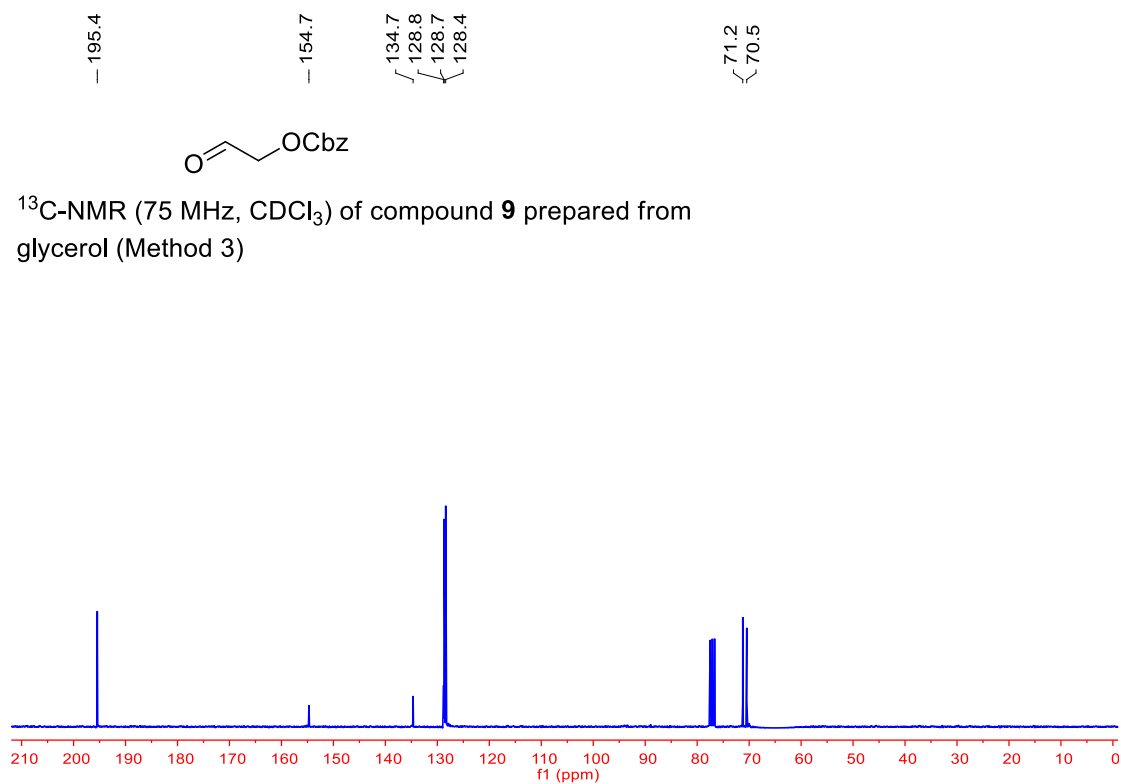
Literature	Strategy	Enzyme	Acyl donor	Solvent	Yield	ee
<i>Tetrahedron Lett.</i> 1995 , 36, 505-508;	#2	Lipase PS-30	Ac ₂ O	DME	42%	95%
<i>Bioorg. Med. Chem. Lett.</i> 1996 , 6, 2847-2852.	#1	LPL-80	-	H ₂ O/buffer	47%	98%
<i>J. Med. Chem.</i> 1996 , 39, 3278-3290.	#2	Lipase PS-30	Ac ₂ O	DME	42%	95%
<i>Org. Process Res. Dev.</i>	#2	Lipase PS-CI	Ac ₂ O	DME	33–42%	97–98%

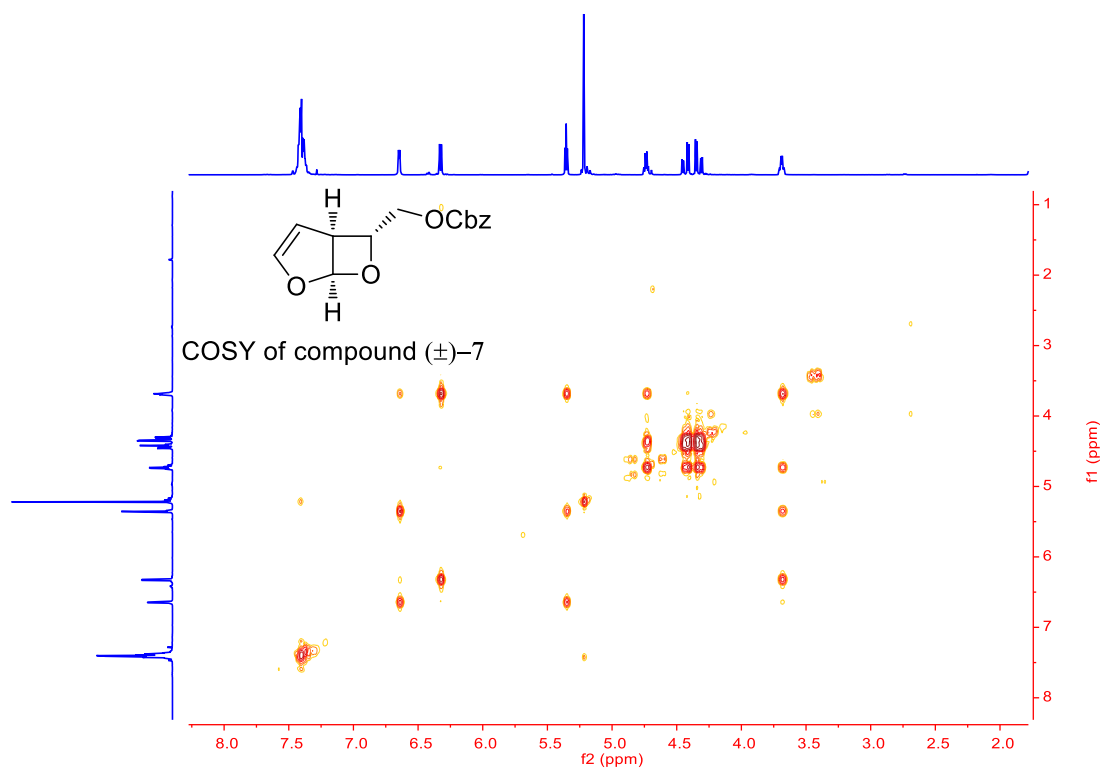
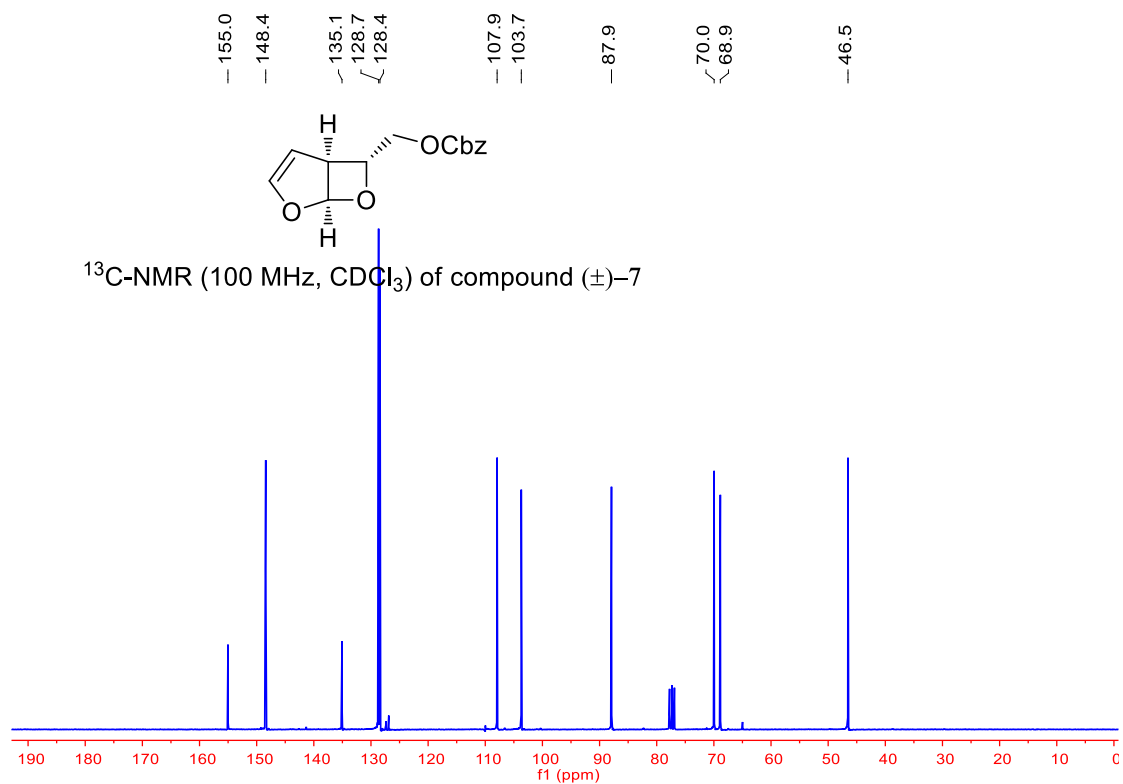
2007, 11, 972-980.						
<i>Org. Lett.</i> 2008 , 10, 1103-1106	#1	Novozyme 435	-	H ₂ O/buffer	Not given	>99%
<i>Org. Process Res. Dev.</i> 2011 , 15, 279-283.	#2	PS-CI, PS-CII, PS-DI, AK-CI	VA, VB, IPA	DME, MTBE	Not given	>99%
<i>Eur. J. Org. Chem.</i> 2016 , 1874 - 1880	#2	Lipase AS, AK, PS	VA	DCM/HFIP	30–37%	28–99%
WO2003024974A2	#1	PS-800	-	H ₂ O/buffer	Not given	>98%
This work	#2	CALA, CALB, RML, TLL, PFL, PPL, PCL	VA, IPA, Ac ₂ O, (EtCO) ₂ O, (nPrCO) ₂ O	MTBE	43%	99%

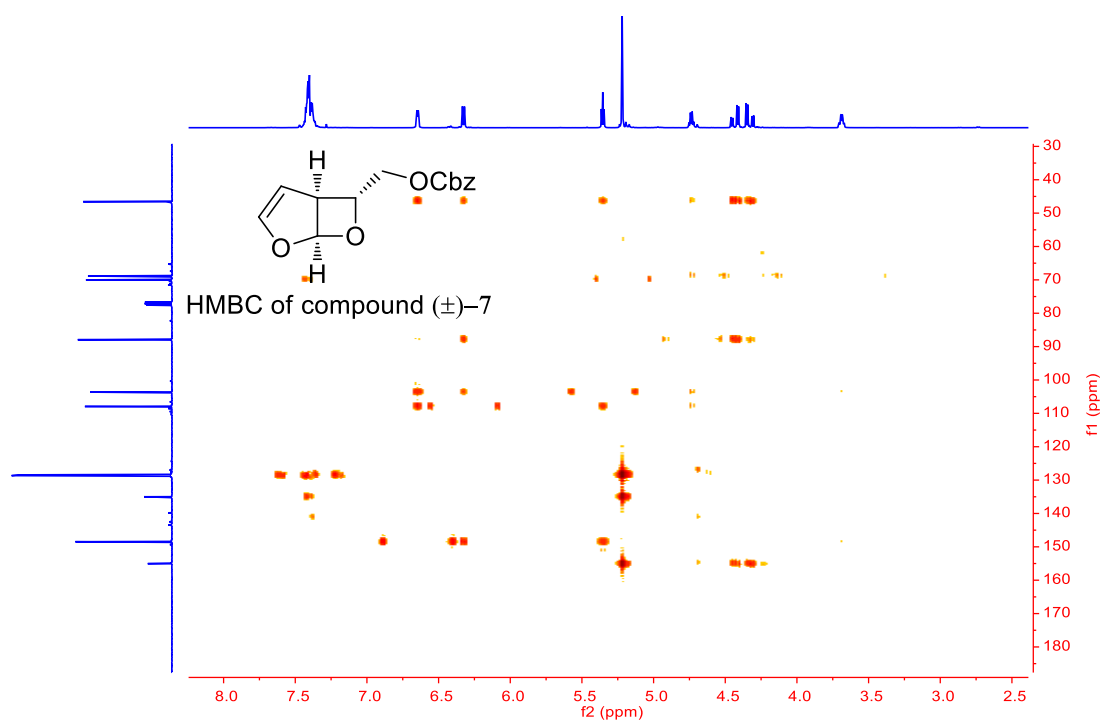
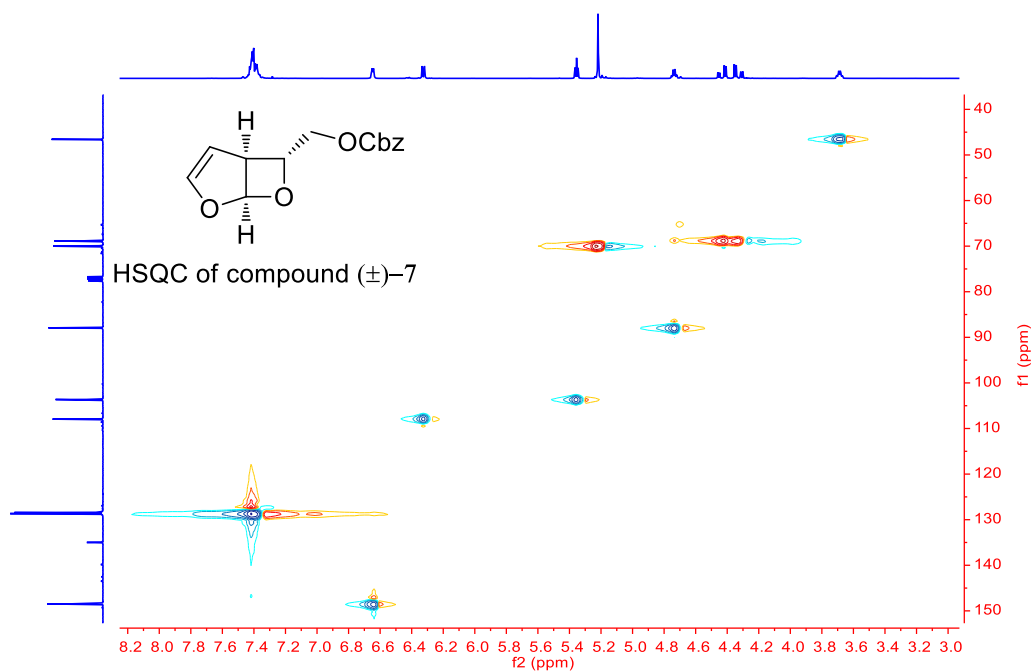
VA = vinyl acetate, VB = vinyl butyrate, IPA = isopropenyl acetate

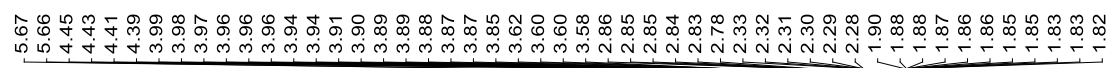
4. Copies of NMR spectra



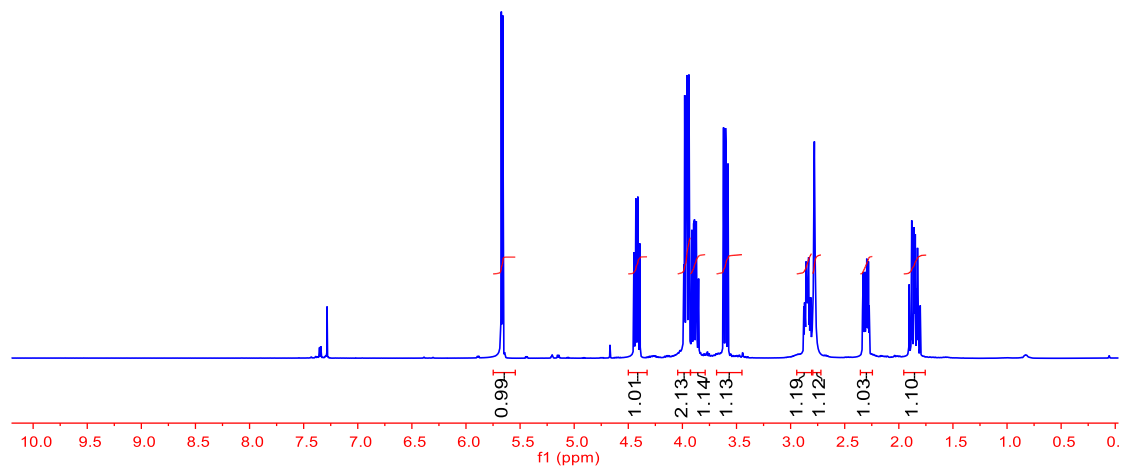




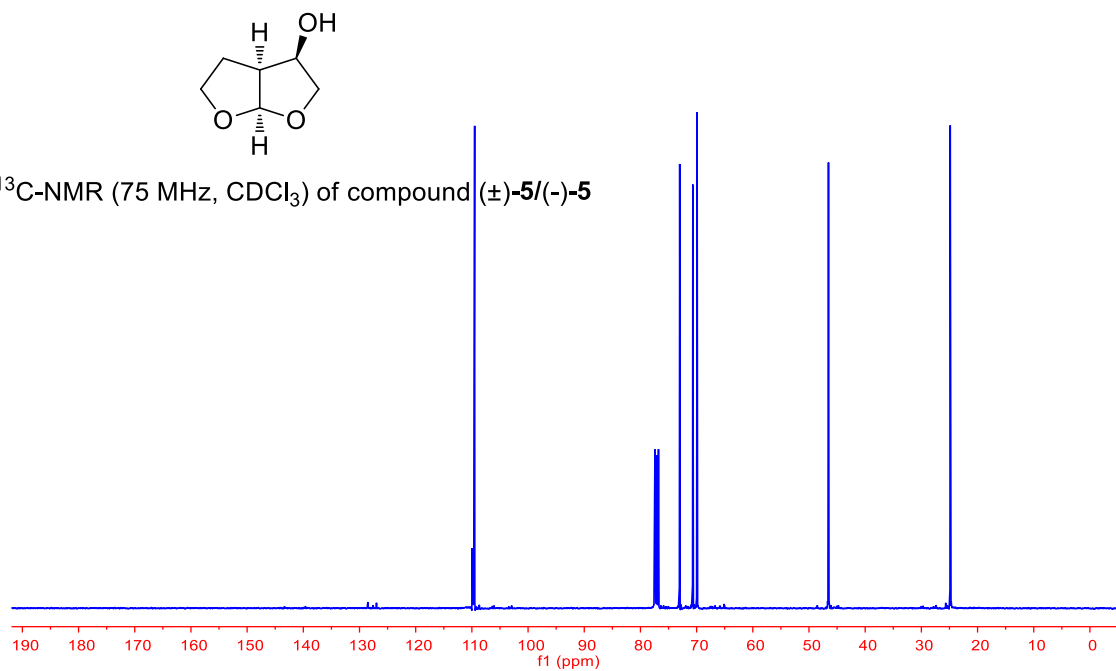


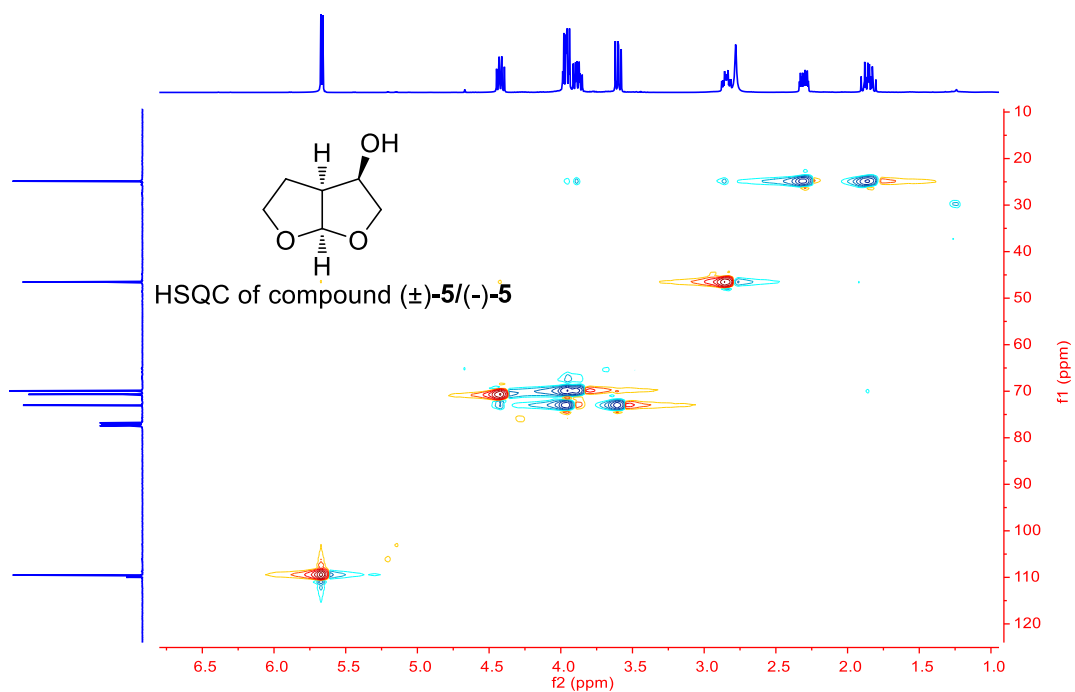
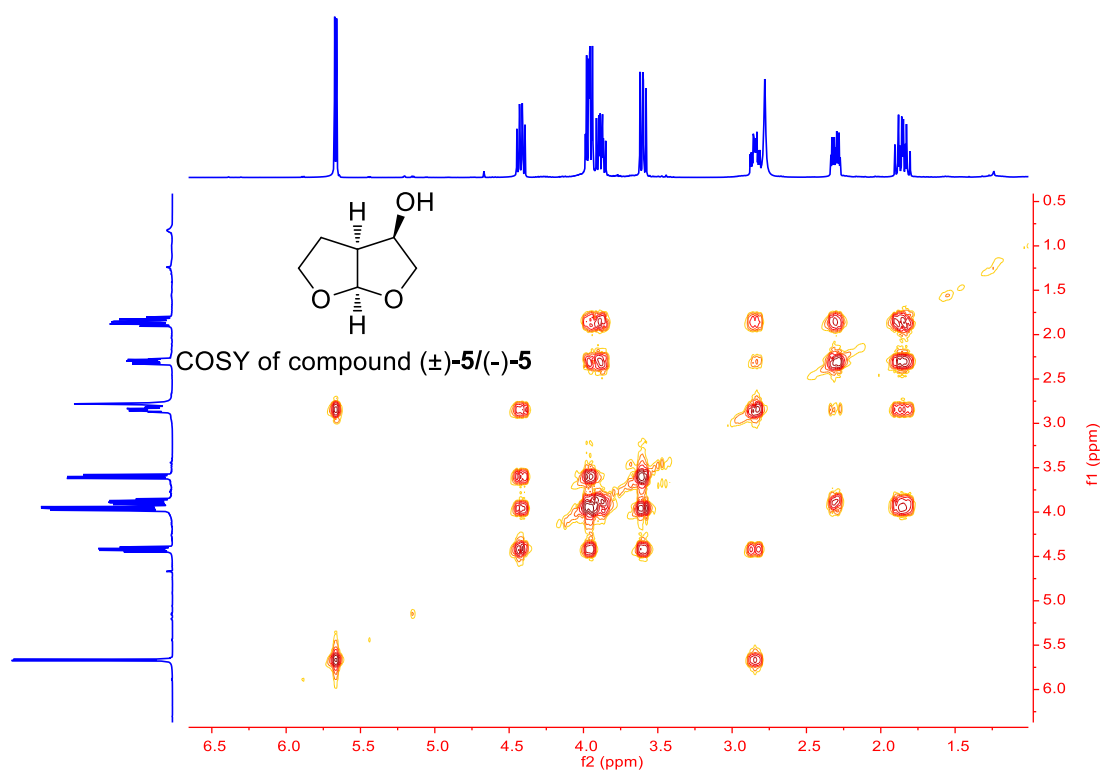


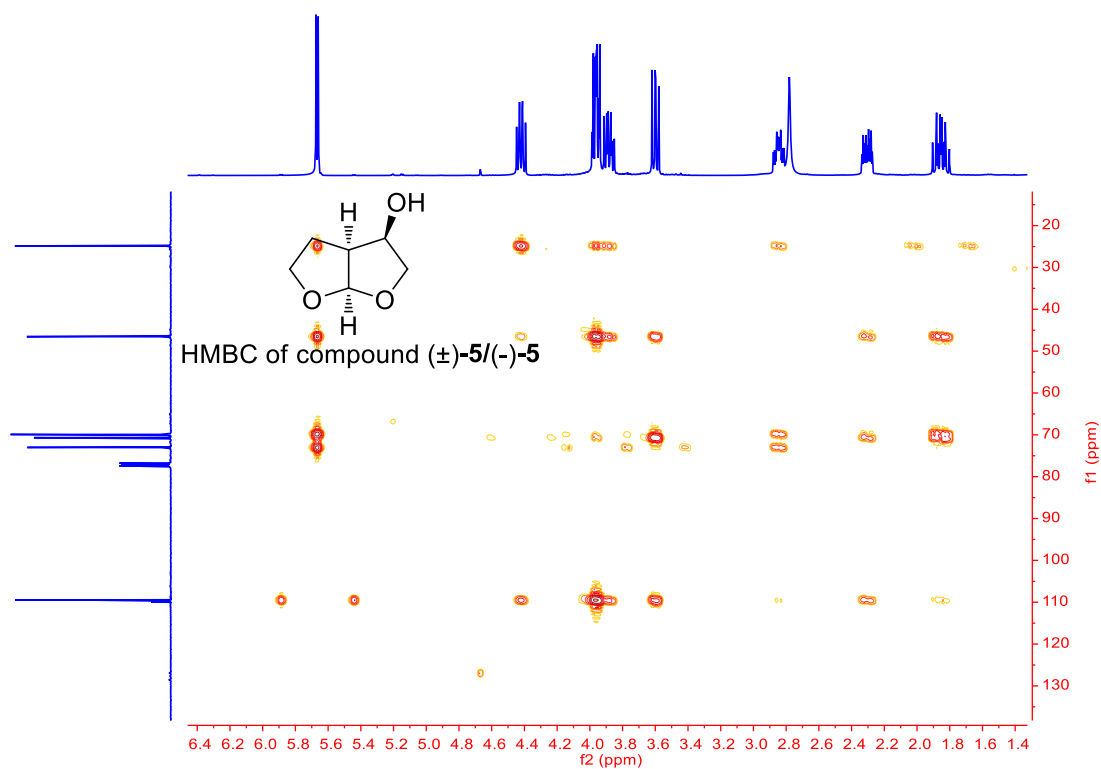
^1H -NMR (300 MHz, CDCl_3) of compound (±)-5/(-)-5



^{13}C -NMR (75 MHz, CDCl_3) of compound (±)-5/(-)-5

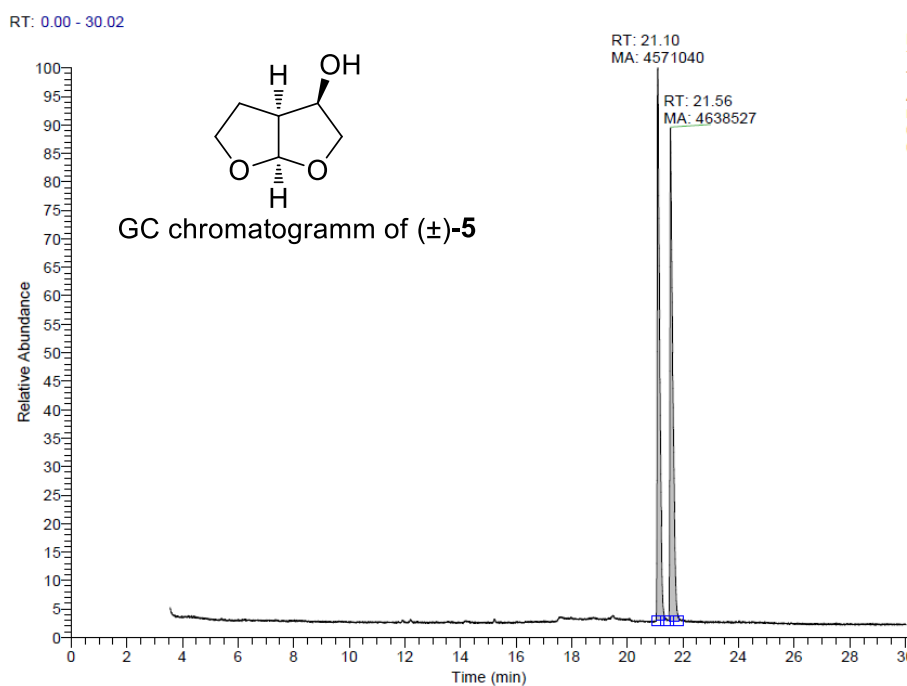




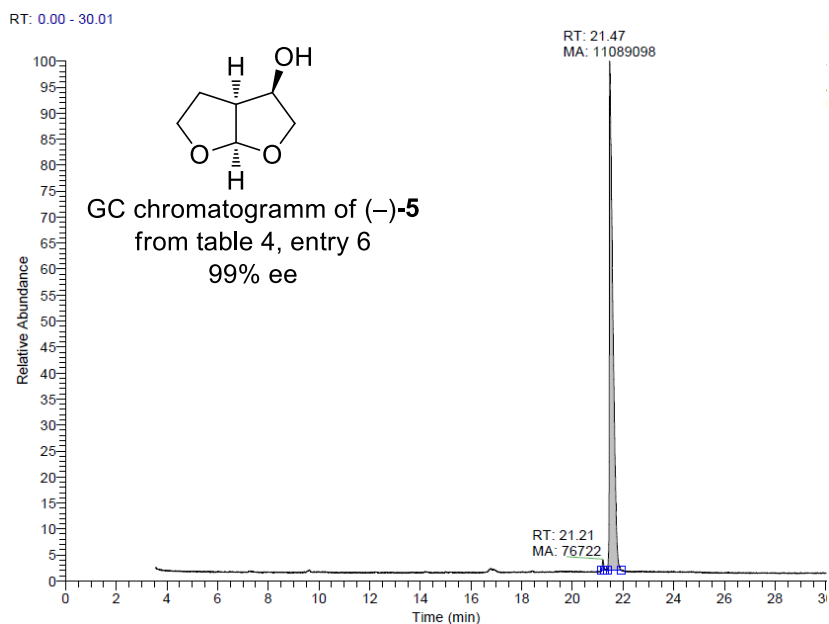


5. Chiral GC data

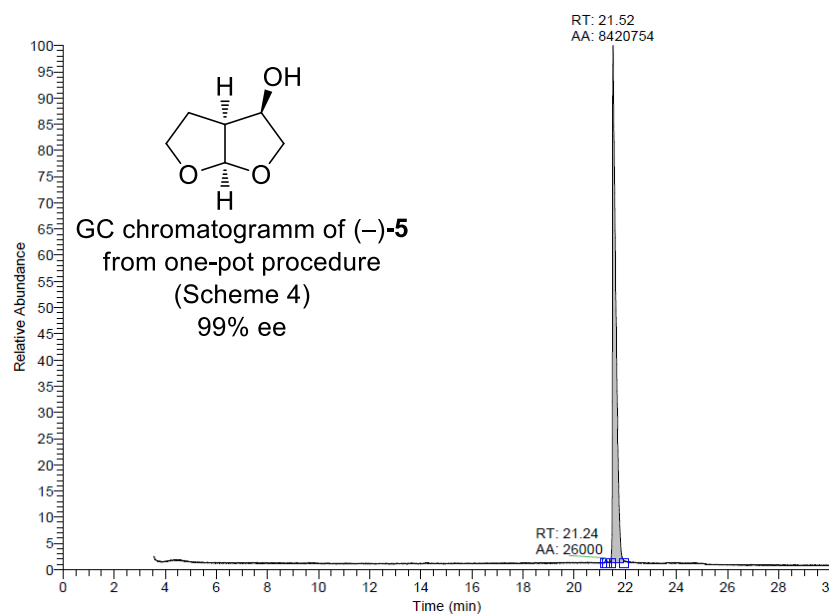
Condition: Chiraldex β -cyclodextrin trifluoroacetyl (BTA) capillary column, flow rate (helium) 1.0 mL/min, 90 °C (3 min hold) \rightarrow 140 °C (5 min hold) \rightarrow cooldown.



Peaks	Retention (min)	Areas	Areas%
1	21.10	4571040	49.58%
2	21.56	4648572	50.42%



Peaks	Retention (min)	Areas	Areas%
1	21.21	76722	0.68 %
2	21.47	11089098	99.32%



Peaks	Retention (min)	Areas	Areas%
1	21.24	26000	0.36%
2	21.52	8420754	99.64%