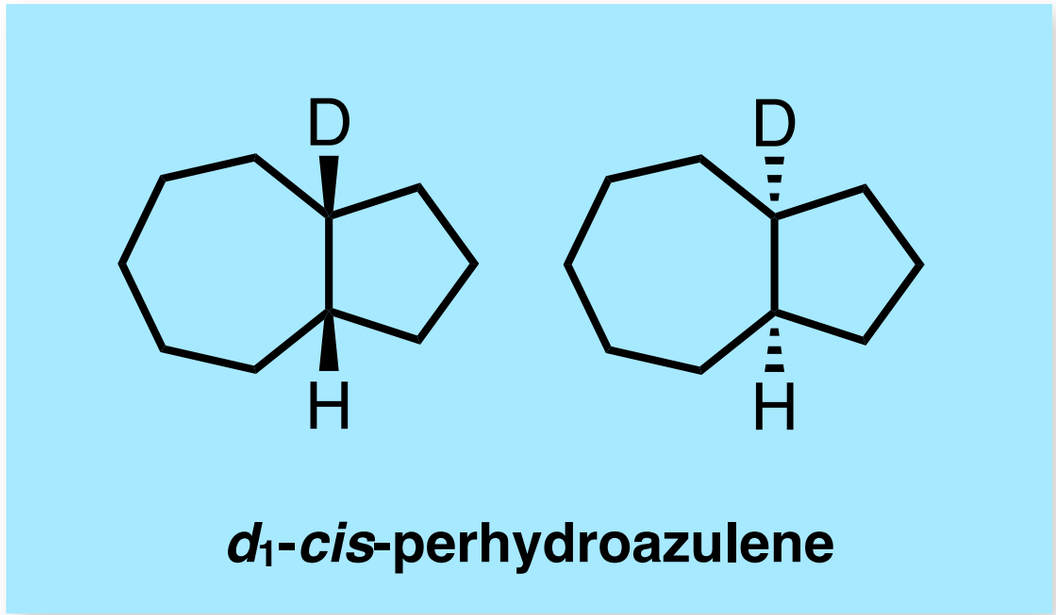
Crypto-Optically Active Monodeuterated cis-Perhydroazulene

Group Seminar

November 6, 2020

Fumito Saito

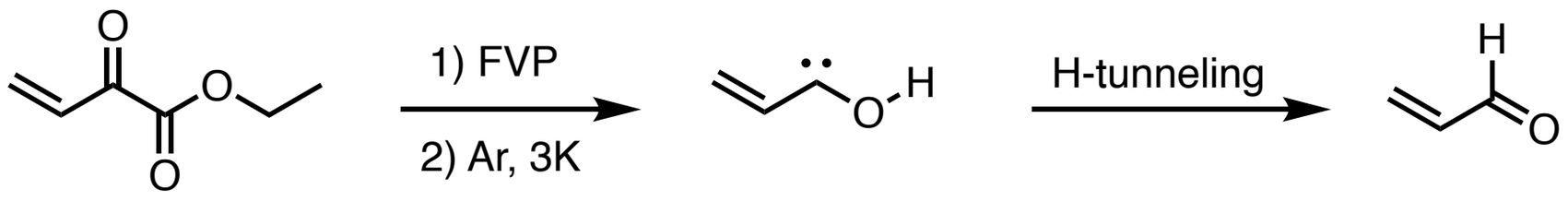
Institut für Organische Chemie
Justus-Liebig-Universität
35392 Giessen, Germany

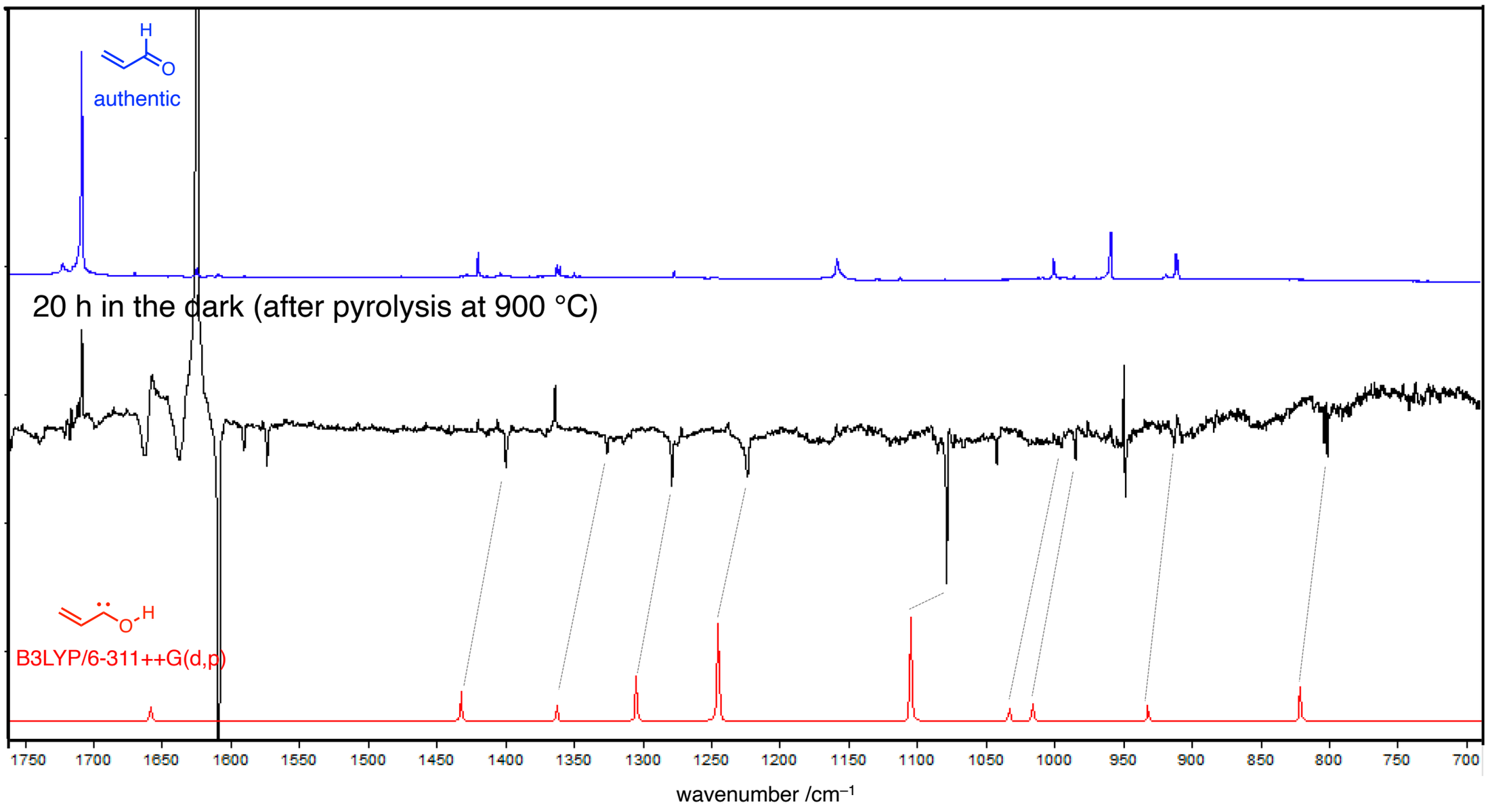


***d*$_1$-*cis*-perhydroazulene**

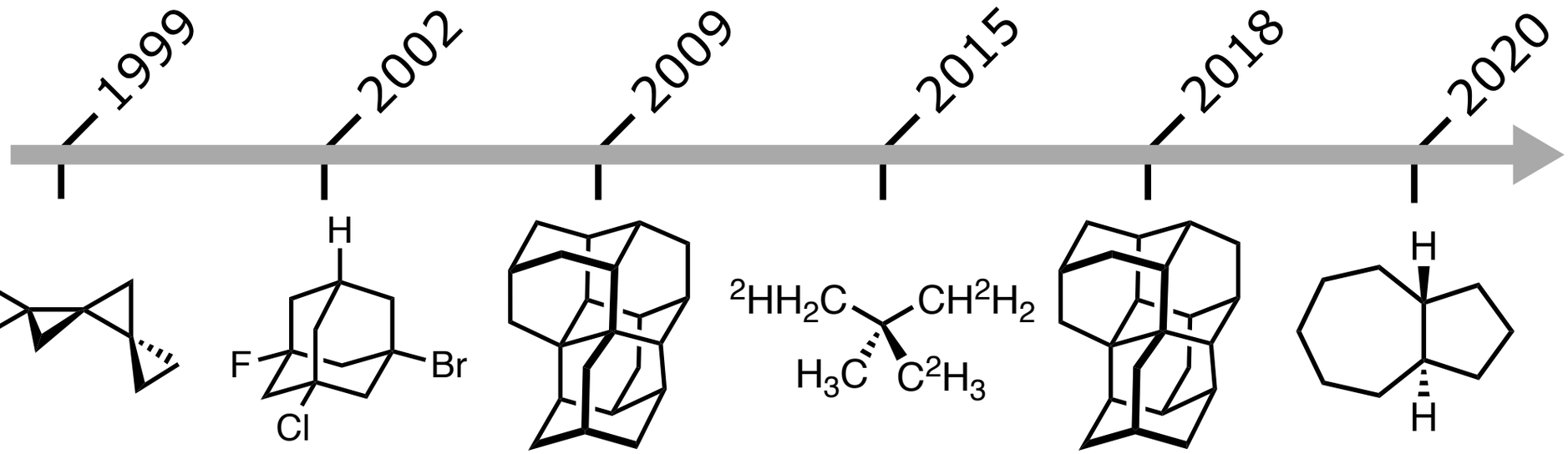
I had a serious problem – What made me so depressed

Target reaction





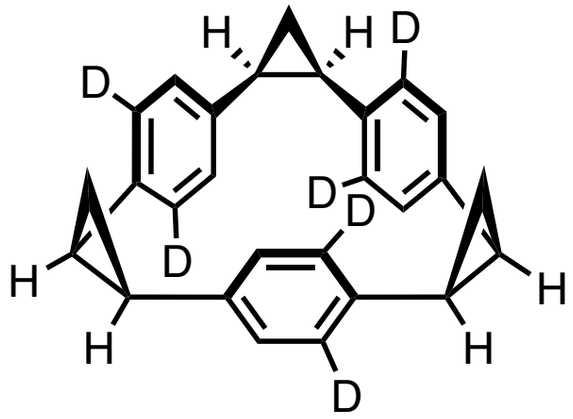
Absolute Configuration Determination



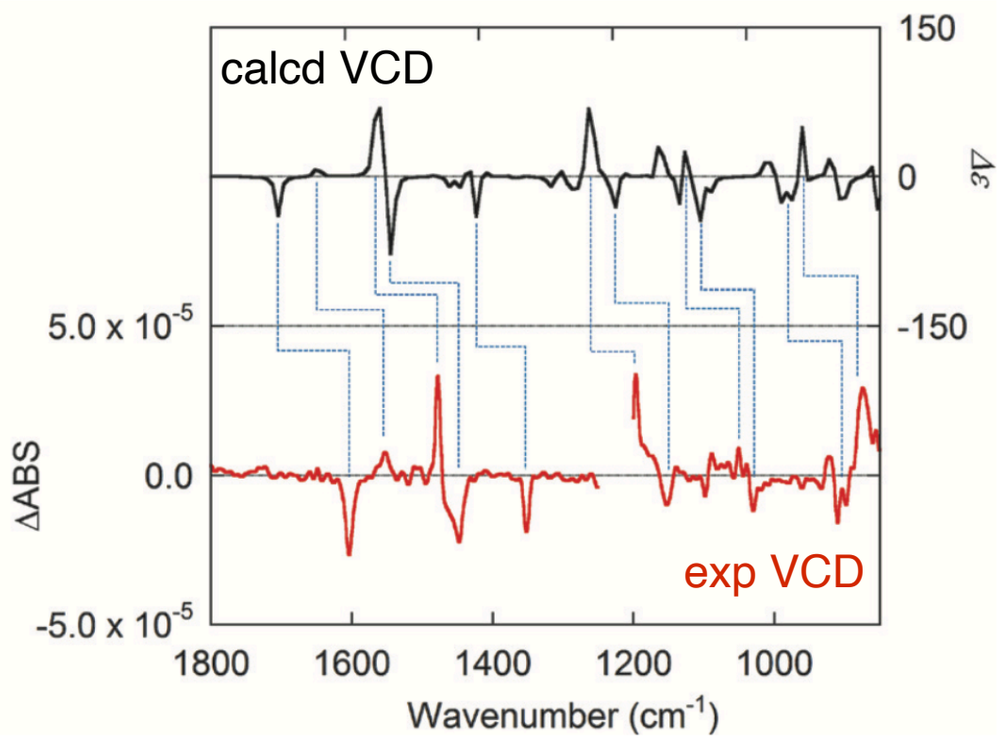
ORD | ECD | ORD VCD X-ray | VCD | AFM | ORD VCD X-ray

F. Saito, P. R. Schreiner *Eur. J. Org. Chem.* **2020**, 6328.

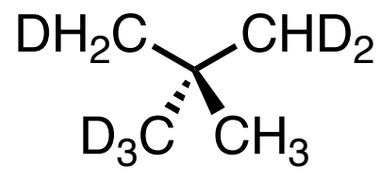
Encounter with one paper



isotopically chiral hydrocarbon

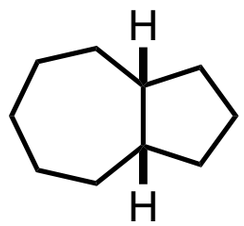


"There is a class of chiral hydrocarbons that owe their chirality only to asymmetric distribution of masses of the hydrogen nuclei. Studies on the chemistry of such deuterium (D)-labeled chiral hydrocarbons are limited to those on D_6-neopentane [$C(CH_3)(CH_2D)(CHD_2)(CD_3)$], probably owing to ***the synthetic difficulties****. Furthermore,* ***determination of the absolute configuration*** *of D-labeled chiral hydrocarbons is also a challenge."*



T. Miura, T. Nakamuro, S. G. Stewart, Y. Nagata, M. Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 3334

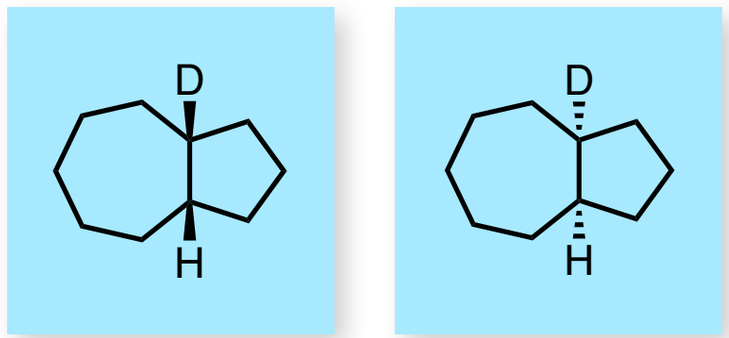
I came up with an idea!



cis-perhydroazulene

meso (achiral)

***d*-substitution**



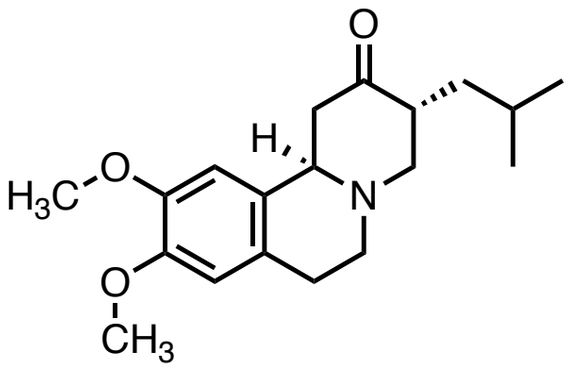
d_1-*cis*-perhydroazulene

chiral

- **synthesis**
- **absolute configuration**

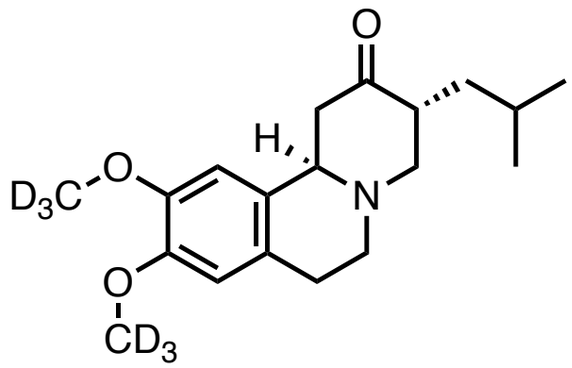
Why AC of deuterium-labeled compounds?

D-labeled drugs



tetrabenazine

***d*-substitution**



deutetrabenazine

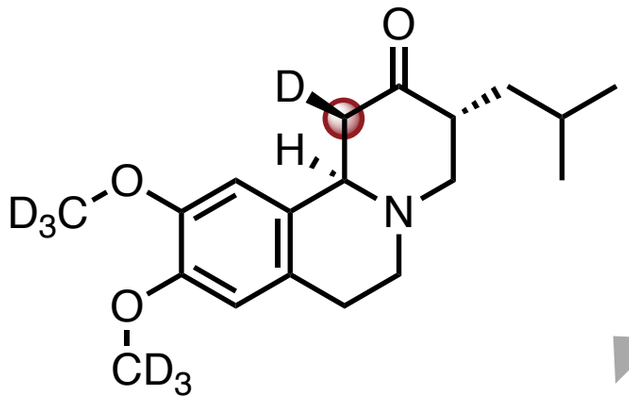
- **a longer half-life**
- **reduced or less frequent dosing**
- **reduced toxicity**

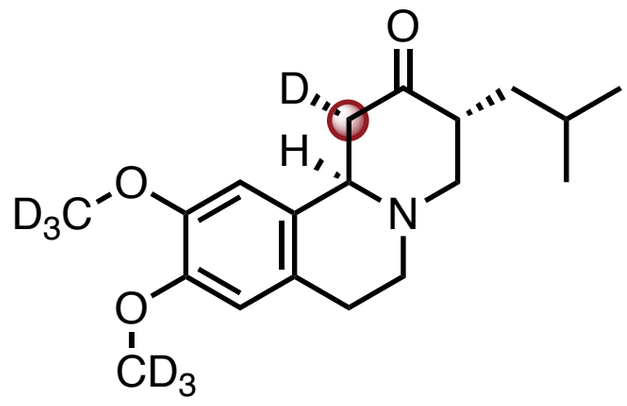
What needs to be considered

- **Where to put deuterium? – position**
- **How many deuteriums? – number**
- **In which orientation? – stereochemistry**

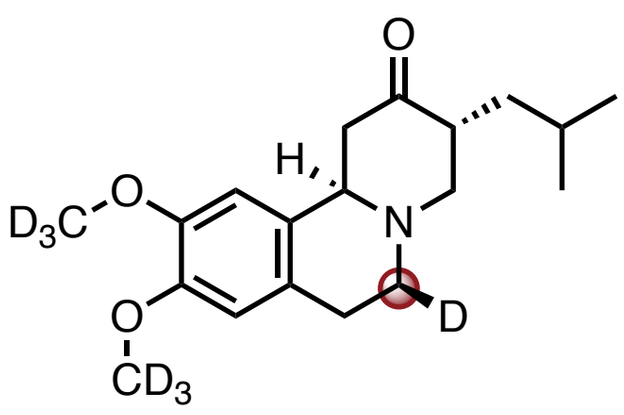
We will need to determine the AC of isotopically chiral D-labeled drugs in the future

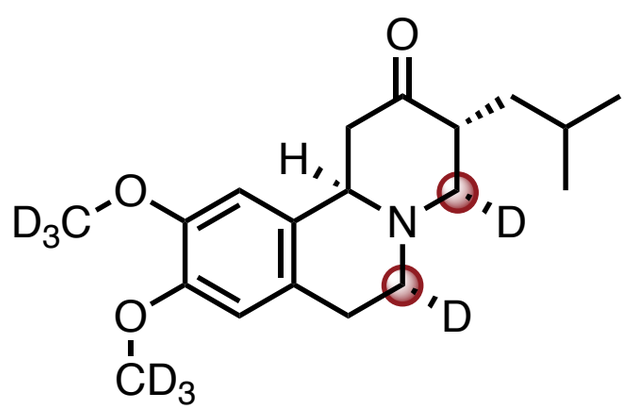
isotopically chiral stereogenic center





distinct pharmacokinetic properties

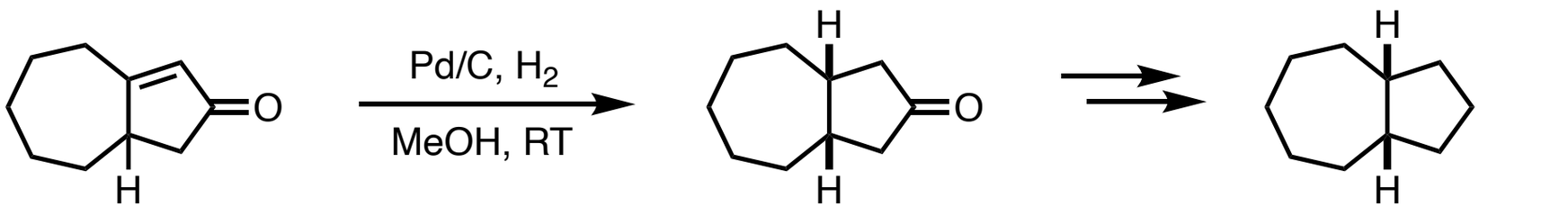




Challenge: determination of absolute stereochemistry

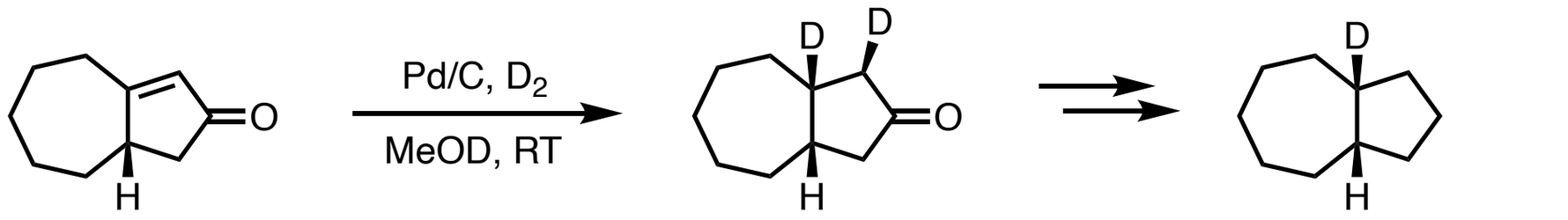
I was very optimistic about synthesis

What I knew:



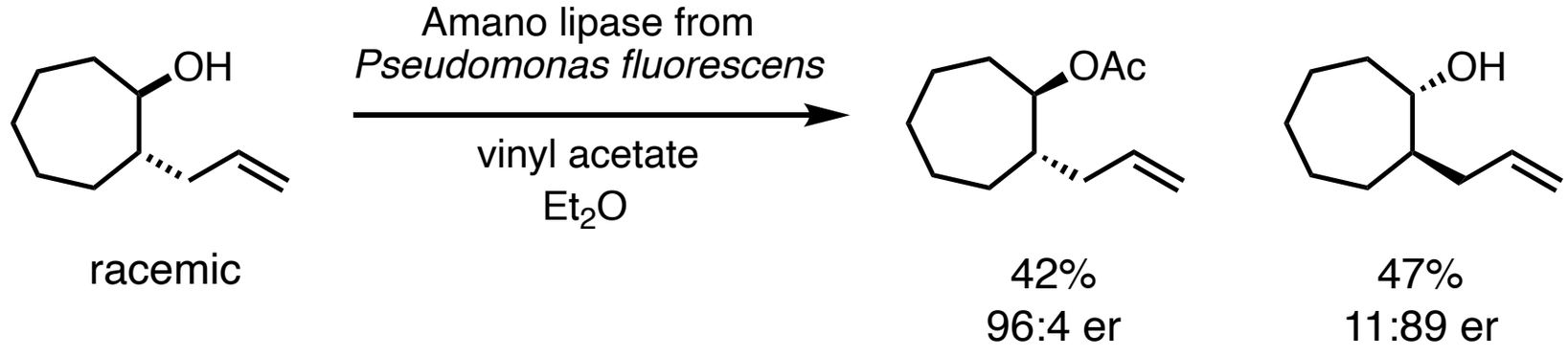
rac dr 20:1 *cis*-perhydroazulene

What I believed it to happen:



enantioenriched dr 20:1 d_1-*cis*-perhydroazulene

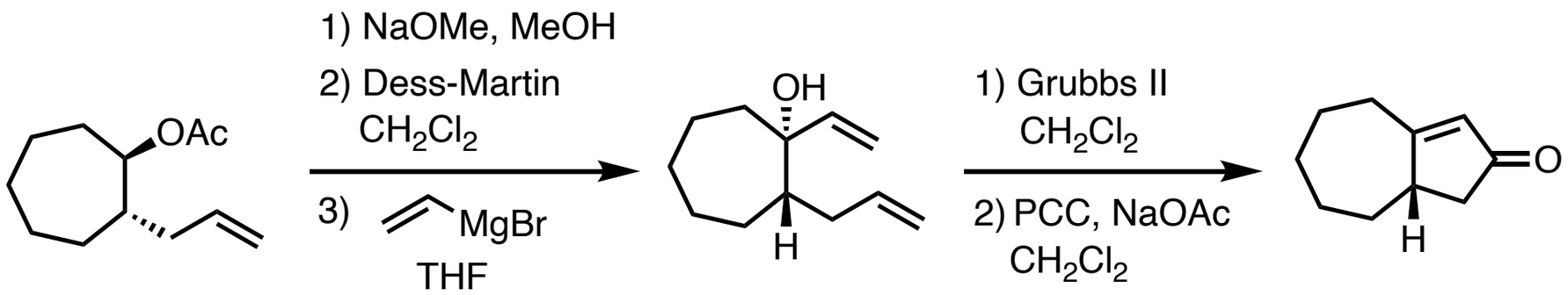
Synthesis of the key intermediate cyclopentenone



racemic

42%
96:4 er

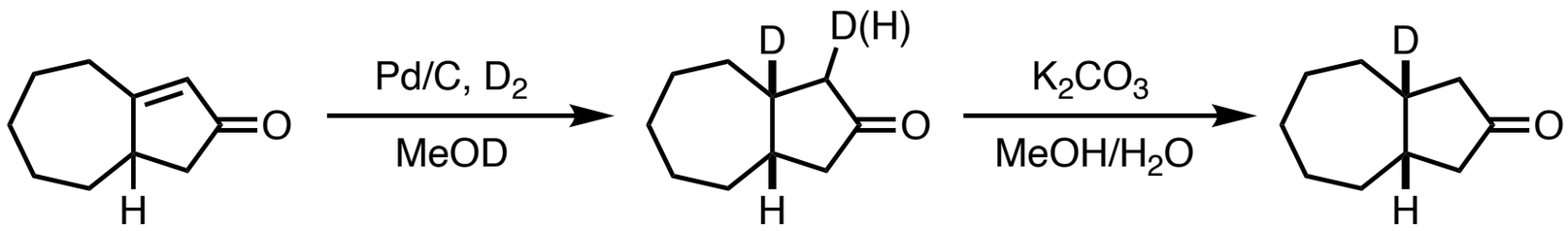
47%
11:89 er

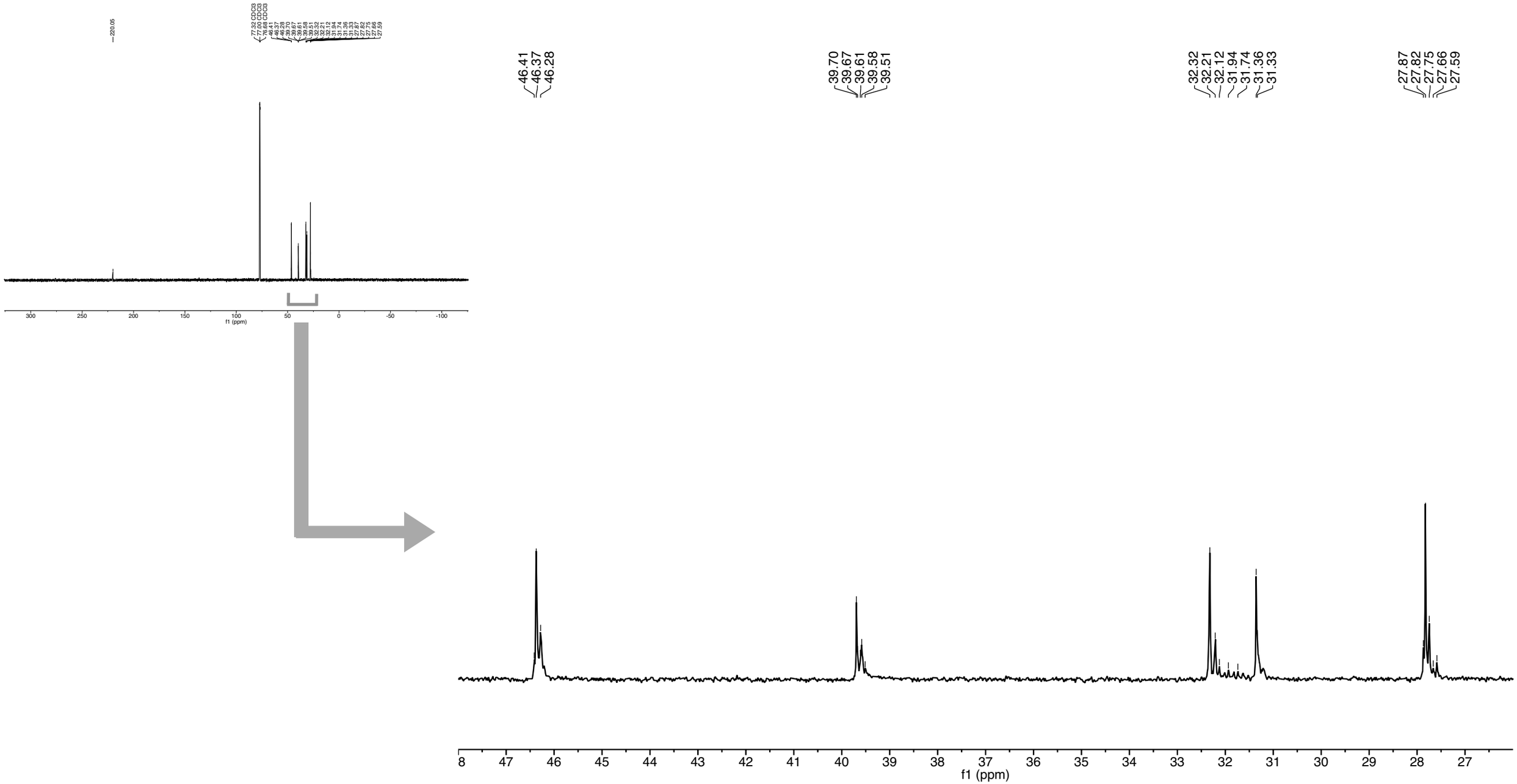


93%
(3 steps)

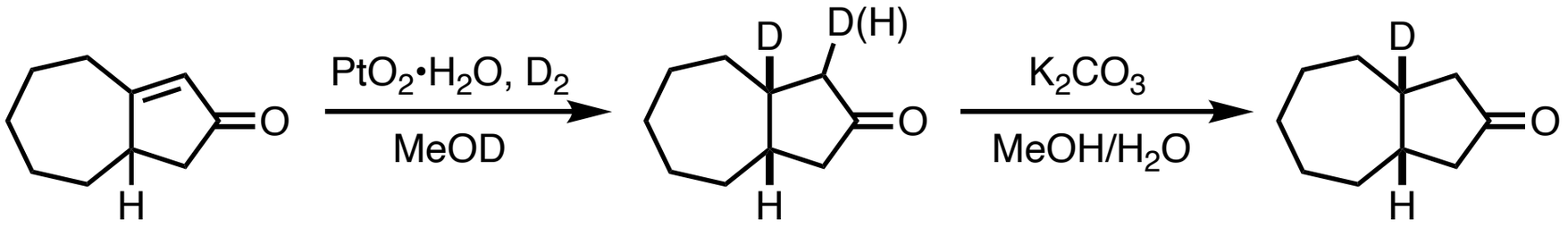
39%
(2 steps)

Unexpectedly, Pd/C-catalyzed deuteration was not selective

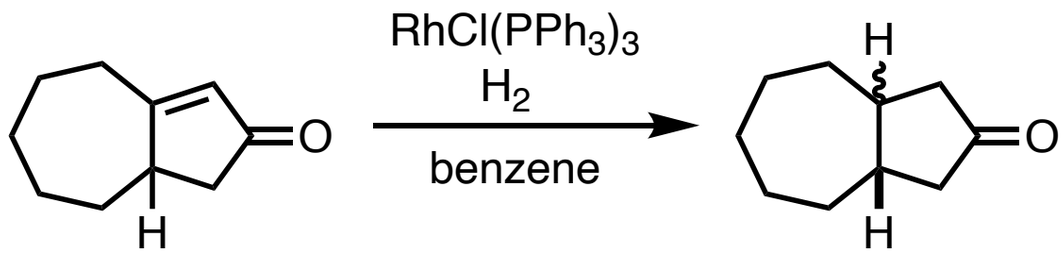




$PtO_2 \cdot H_2O$ and $RhCl(PPh_3)_3$ did not solve the problem



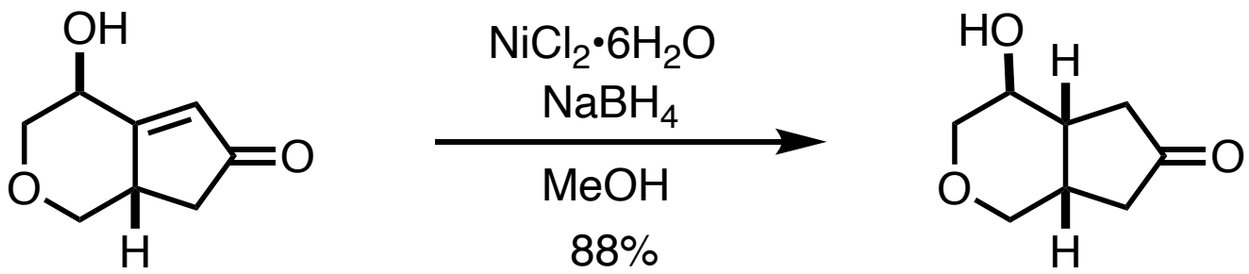
- <20% yield
- inseparable impurities incl. the trans isomer



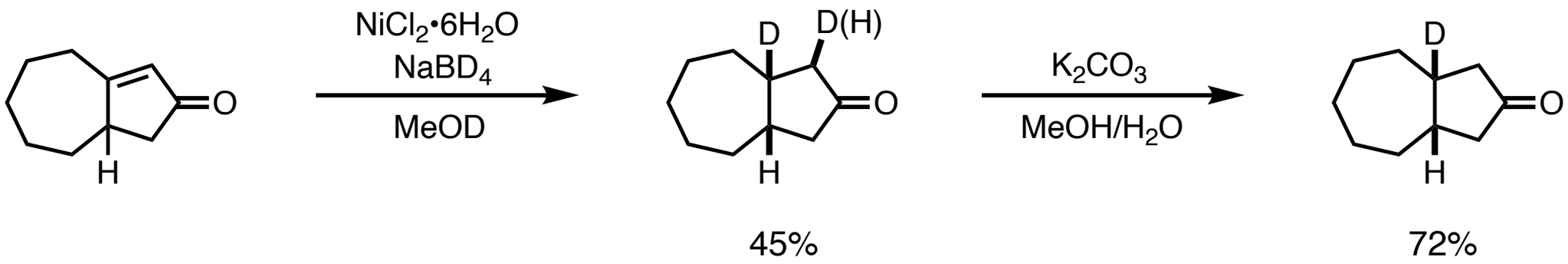
- very slow reaction
- trans:cis 3:1

I found a hope in the literature... and it worked (with a problem)!

Khan et al. *ChemistrySelect* **2018**, *3*, 5566–5570.



in situ generation of nickel boride

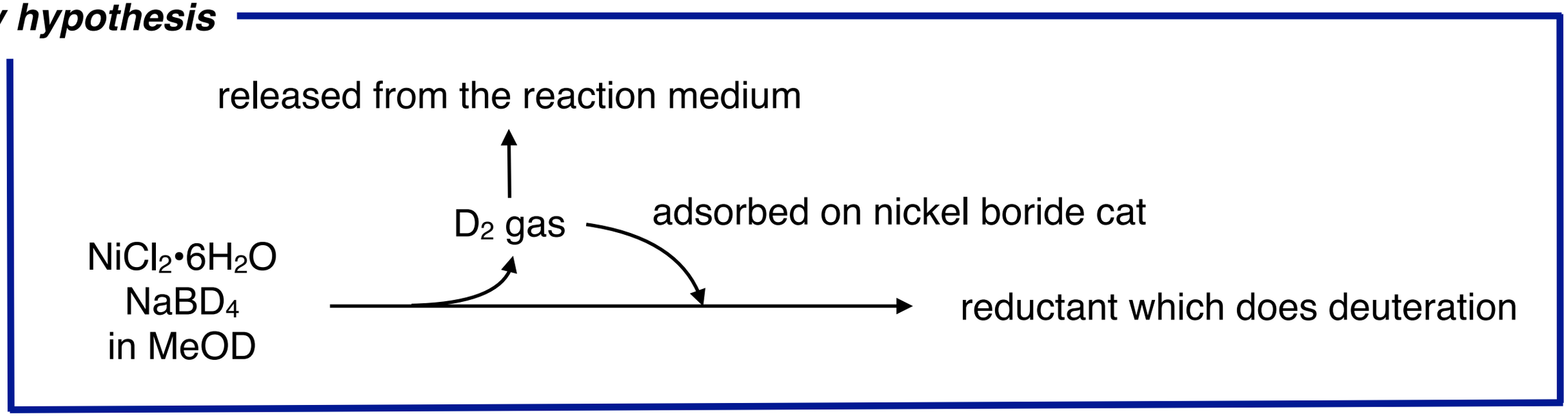


But: the deuteration reaction is not reproducible in terms of yield

Why do the yields vary almost always?

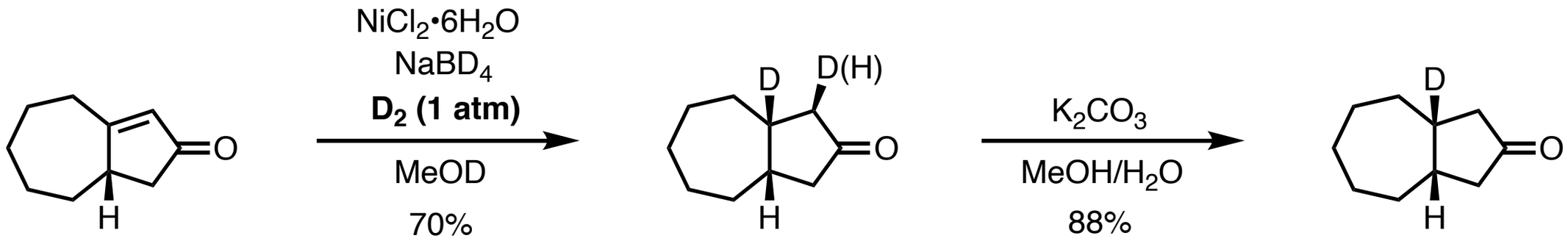
- nickel boride can be used as a hydrogenation catalyst (i.e., under H_2 atmosphere)
- I observed D_2 gas generation when $NiCl_2 \cdot 6H_2O$ and $NaBD_4$ were mixed

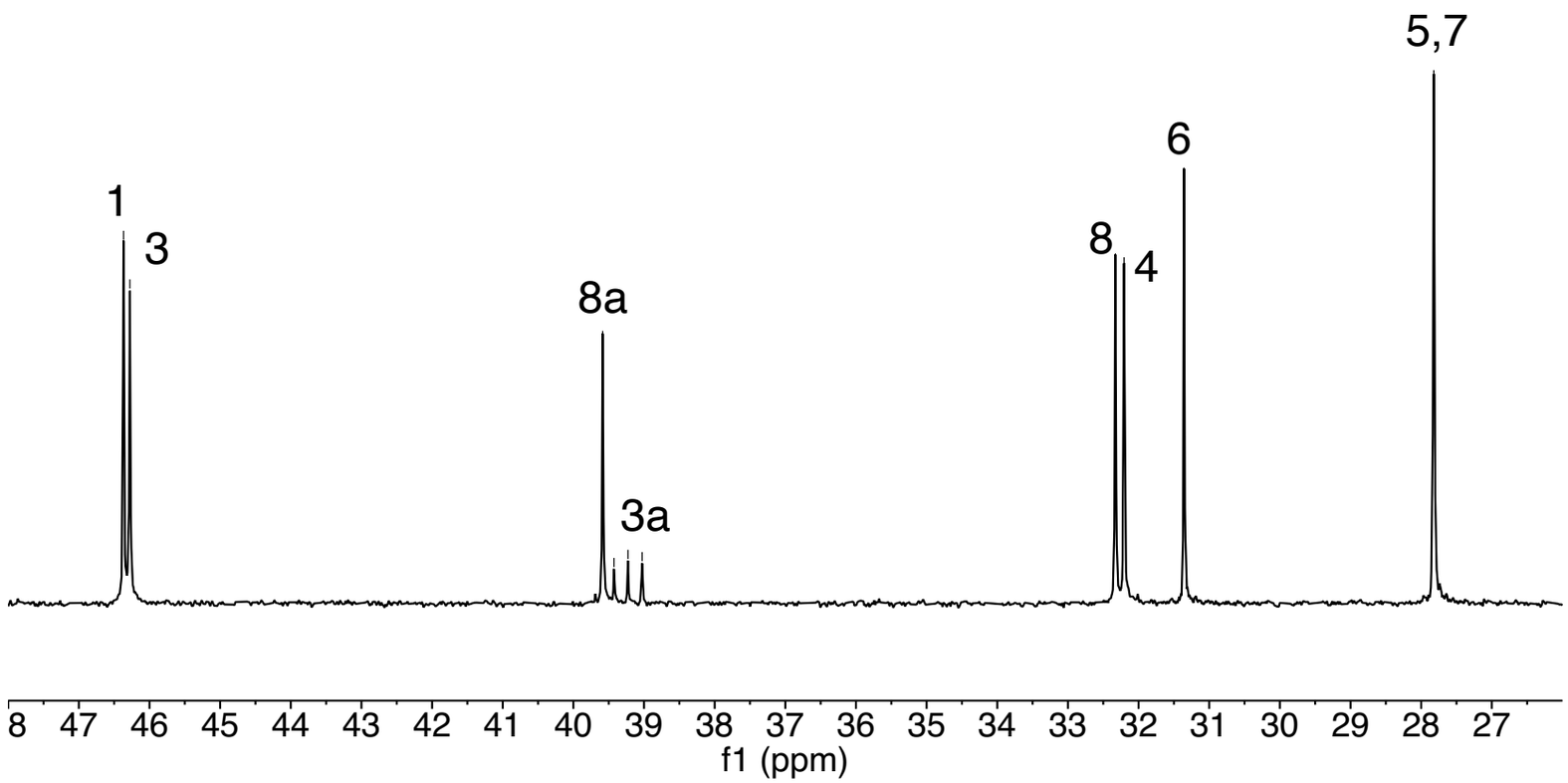
my hypothesis

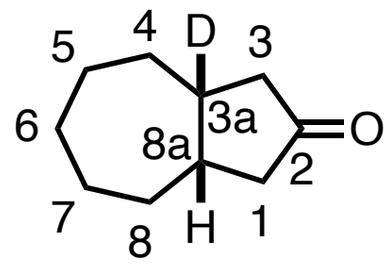


Solution: Supplying D_2 gas externally

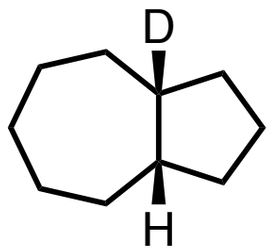
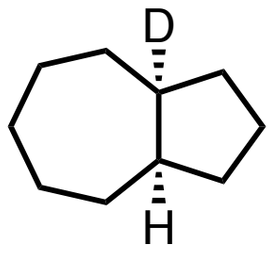
External supply of D_2 gas solved the problem!





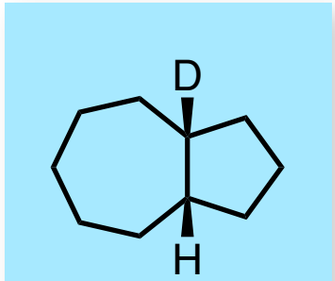


Monodeuterated *cis*-perhydroazulene is crypto-optically active

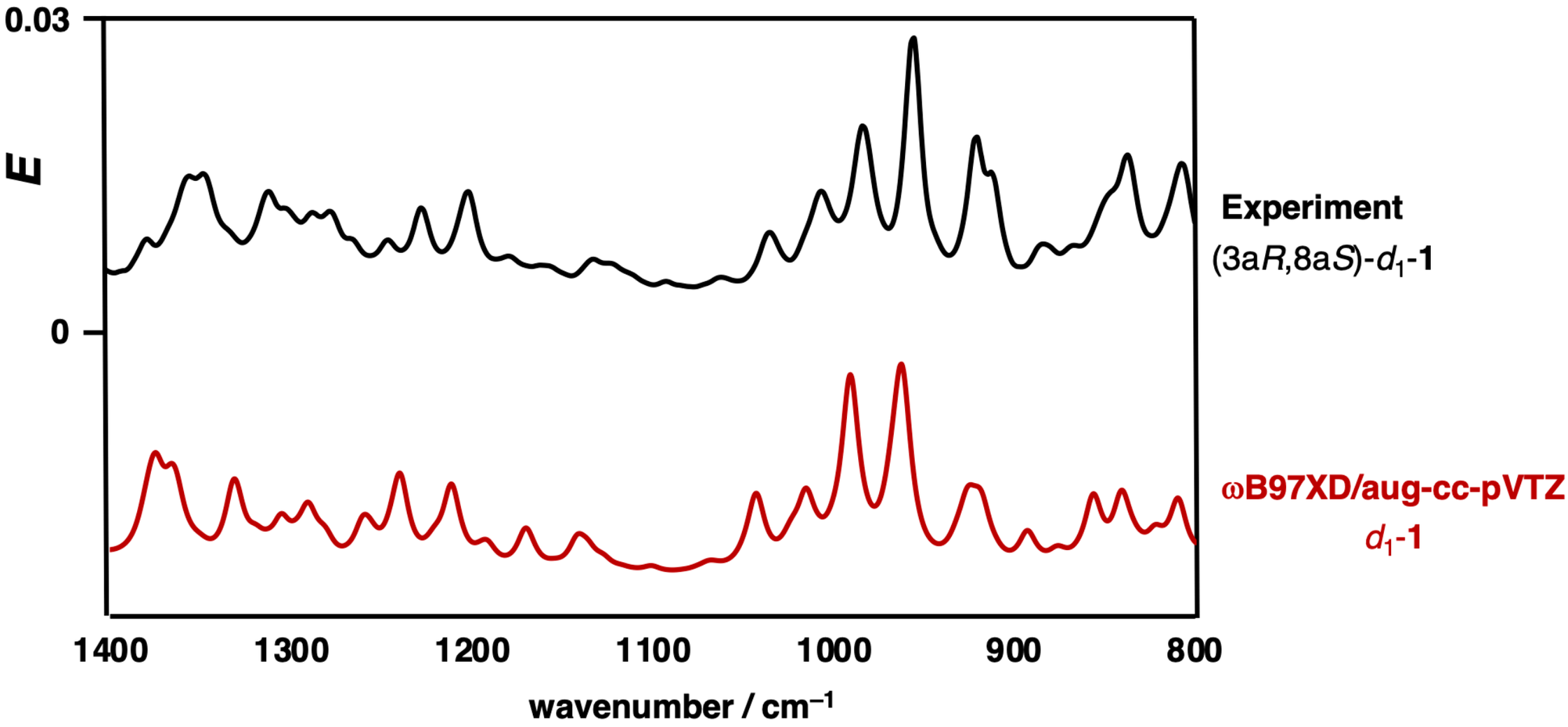
	$[\alpha]_D^{25}$		
	run 1	run 2	run 3
	+0.3±0.4	+0.5±1.1	+0.1±0.1
	0.0±0.1	0.0±0.1	–0.1±0.1

concentration: 0.5 (g/100 mL); solvent: $CDCl_3$

Experimental vs computational IR spectra

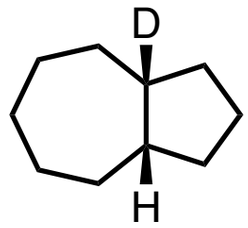


(3a*R*,8a*S*)-d_1-**1**

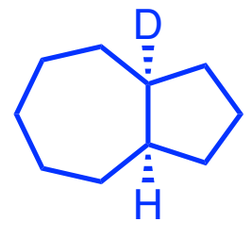


with Dennis

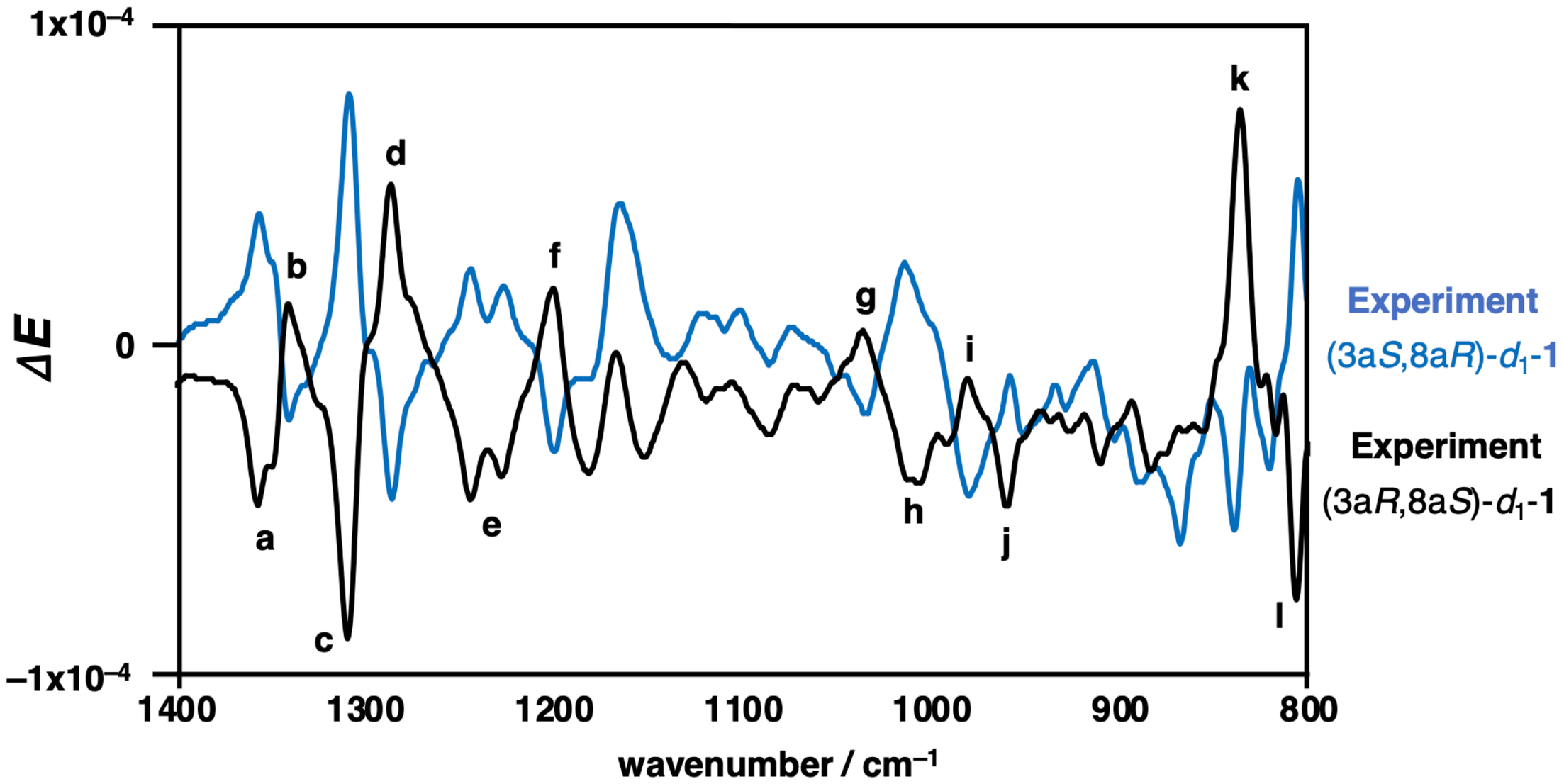
VCD spectra of the two enantiomers – Exciting results



(3a*R*,8a*S*)-d_1-**1**

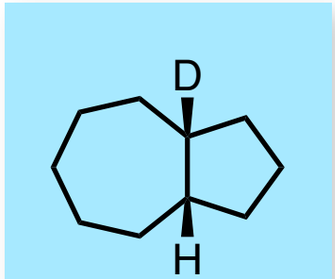


(3a*S*,8a*R*)-d_1-**1**

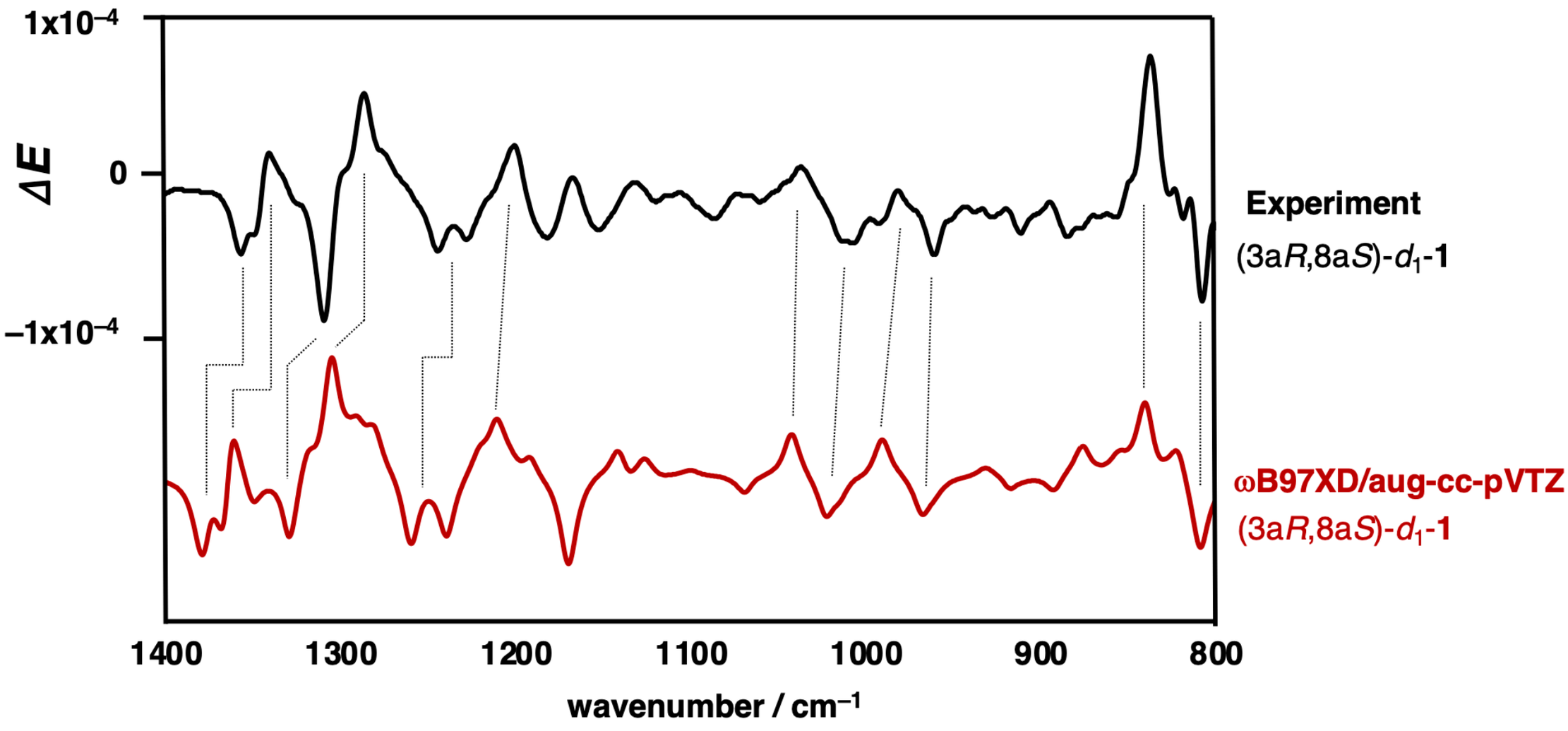


with Dennis

Experimental vs computational VCD spectra – simply beautiful

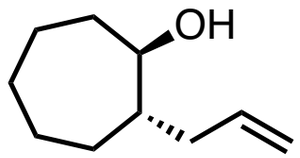


(3a*R*,8a*S*)-d_1-**1**

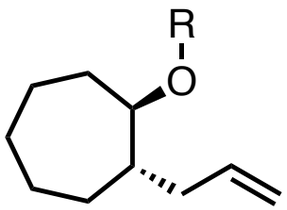


with Dennis

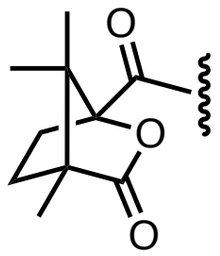
Additional evidence for AC assignment? – Efforts to get a crystalline sample



oil

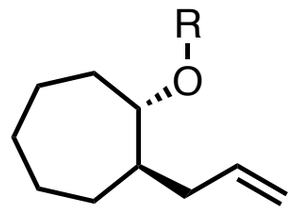


where R =

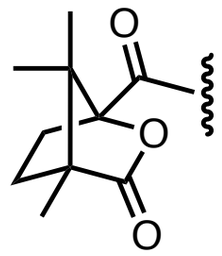


solid

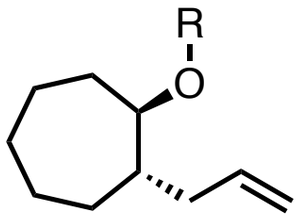
(but easily soluble in almost any common solvents)



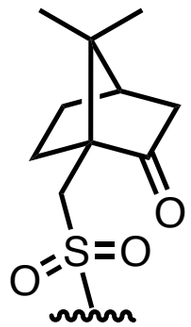
where R =



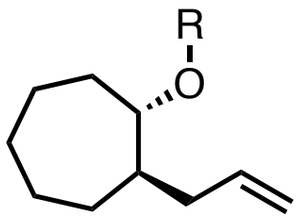
oil



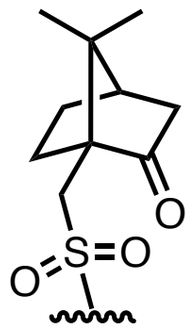
where R =



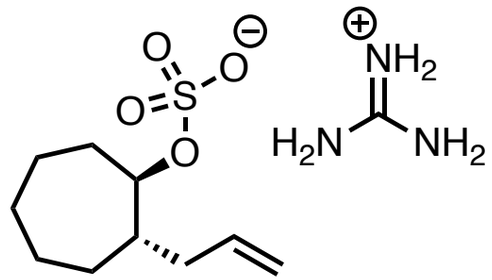
oil



where R =



oil

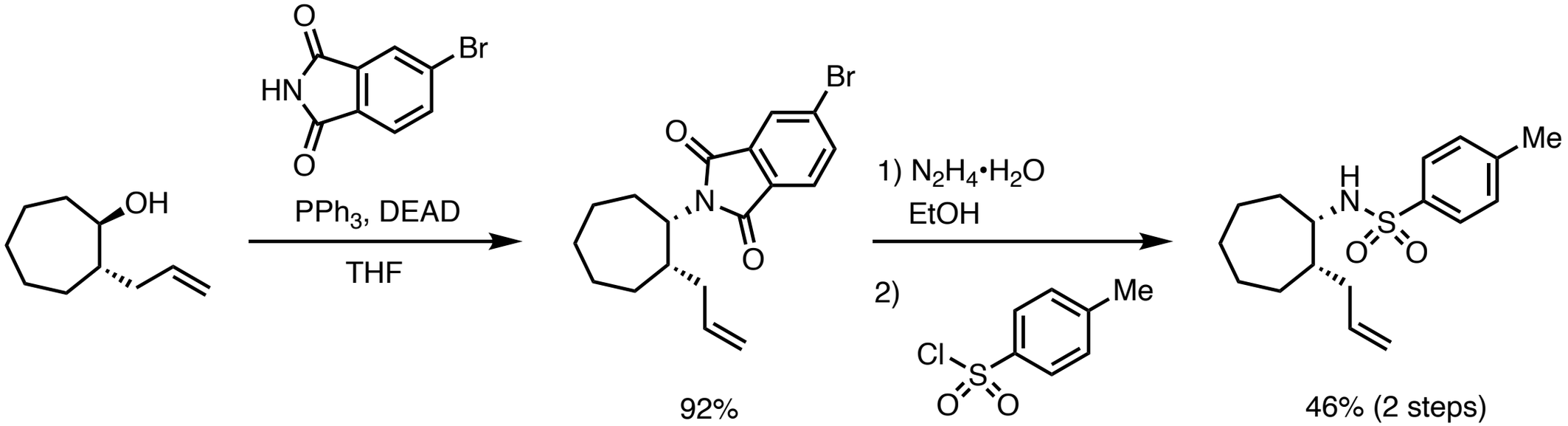


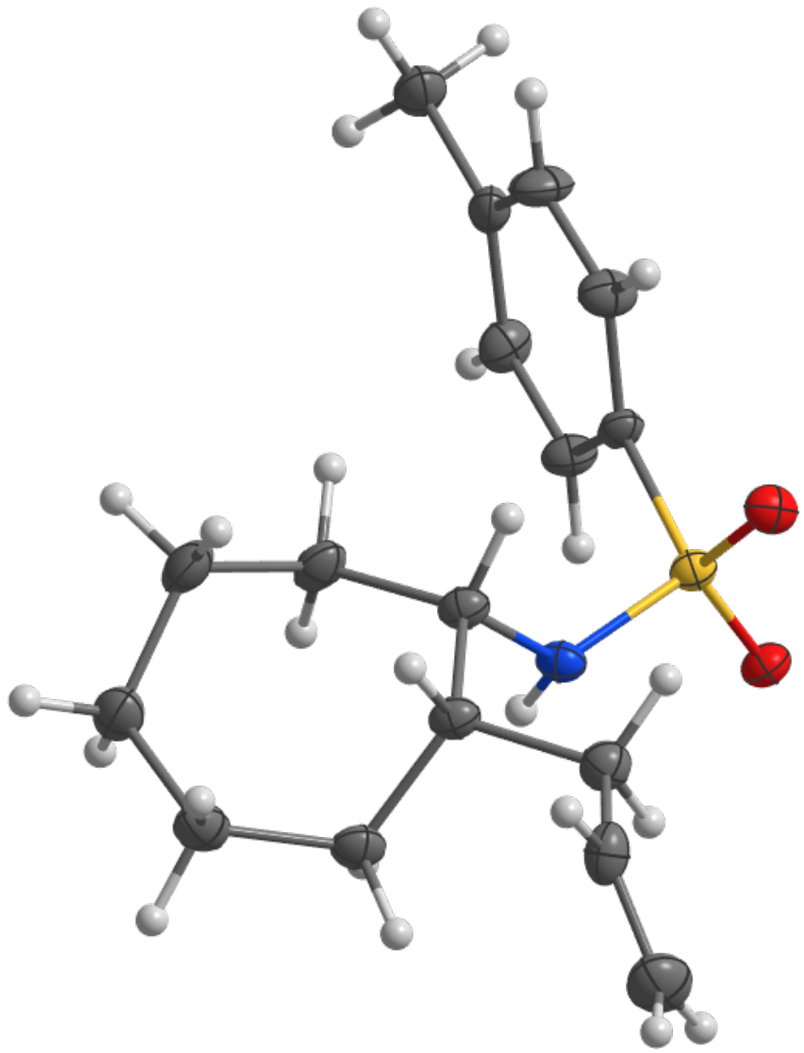
solid

no success (so far) in crystallization

OL **2019**, *21*, 9622

... and finally, X-ray crystal structure!

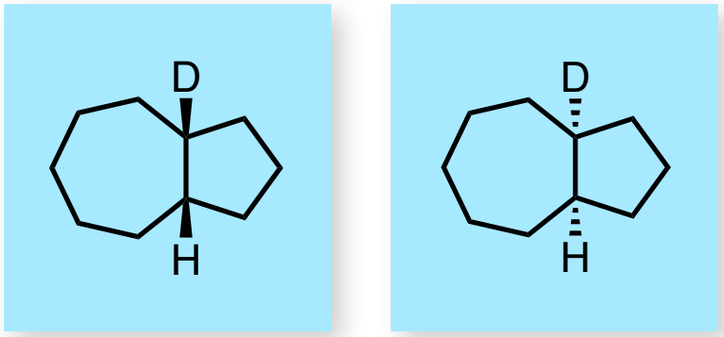




X-ray

with Jonathan

Summary



- synthesis → nickel boride catalyzed diastereoselective deuteration
- absolute configuration → VCD spectroscopy

What to do next...

- restart the vinylhydroxycarbene project
- move on to my next career step

Acknowledgements

- Prof. Dr. Peter R. Schreiner
- Dr. Dennis Gerbig
- Dr. Jonathan Becker
- Lab B218 (Vlad, Boryslav, Gowri, Kyangzi)
- PRS group