SLOVAK UNIVERSITY OF TECHNOLOGY IN BRATISLAVA
FACULTY OF CHEMICAL AND FOOD TECHNOLOGY

Pyrrolidine analogs of arylceramide HPA-12

22nd International Electronic Conference
on
Synthetic Organic Chemistry

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Authors: Jozef Markus, Dušan Berkeš

Bratislava **2018**

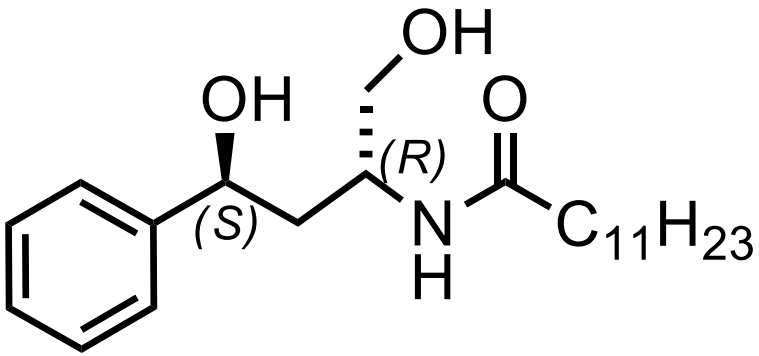
Goals of project

1. Total synthesis of pyrrolidine HPA-12 analogs and their characterisation

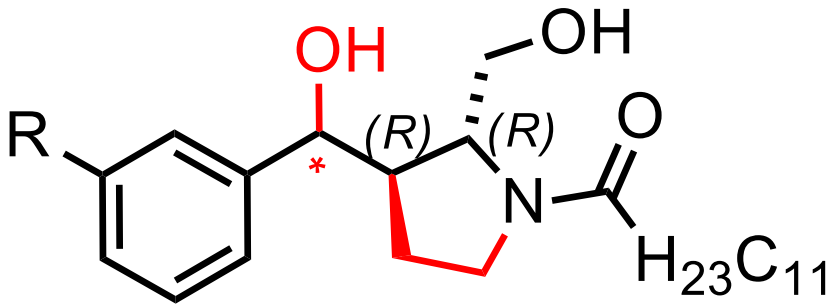
2. Study of stereoselective reduction of oxo group and its application in the synthesis of HPA-12 analogs

HPA-12 and a target constrained analog

HPA-12



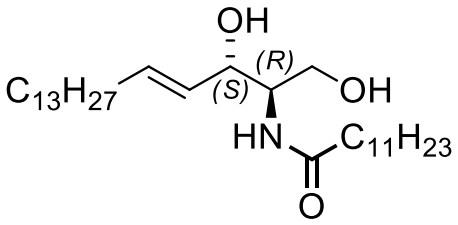
Conformational constrained analogs of HPA-12



R = Ph, m-Alk-Ph

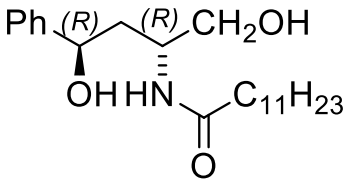
Ceramids, HPA-12, biological activity

Ceramide



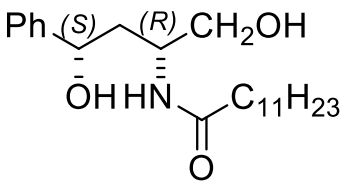
HPA-12

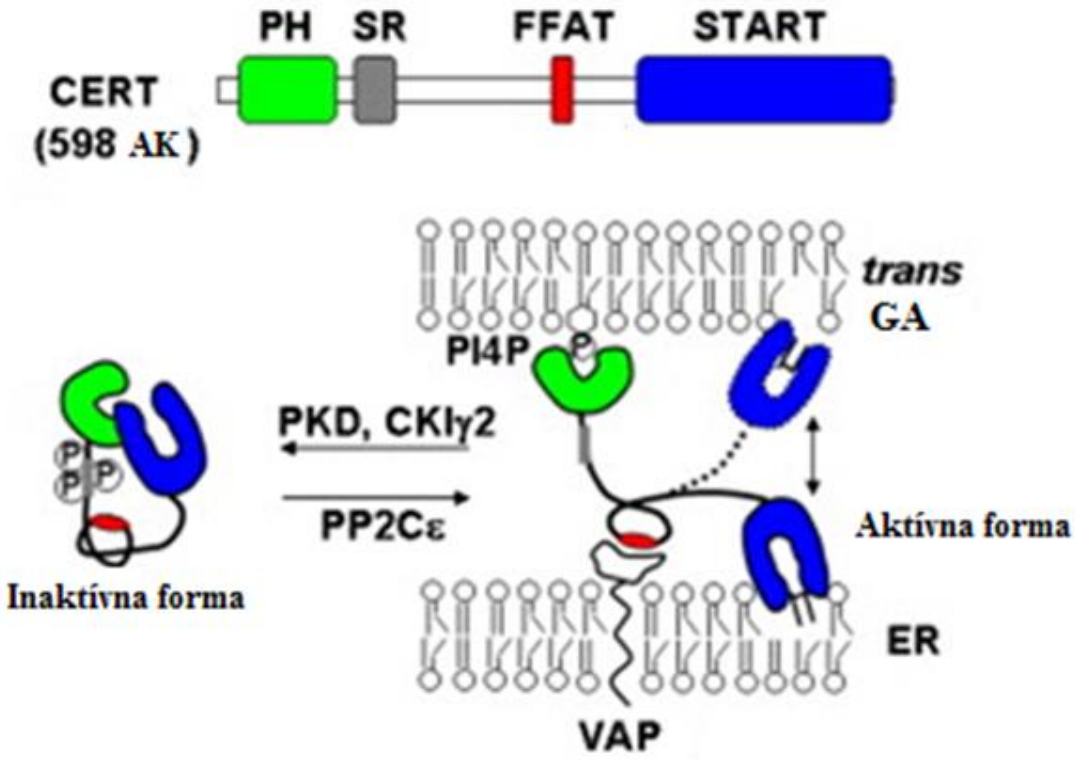
(before 2011)



HPA-12

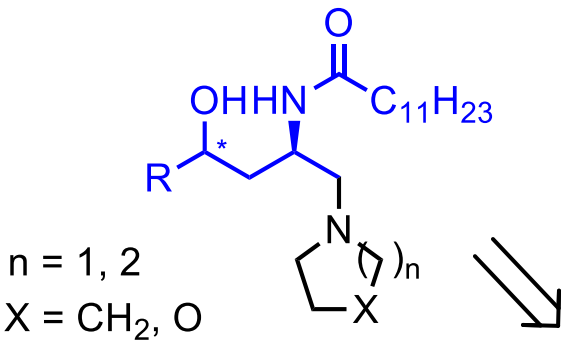
(from 2011)

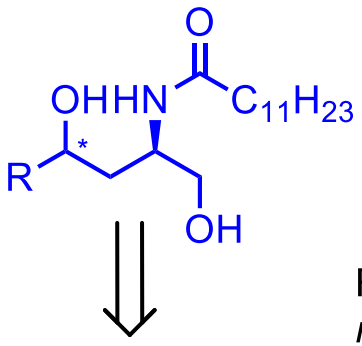




Hanada, K. et al *Nature* **2003**, *426*, 803-809.
Hanada, K. et al *Biochim. Biophys. Acta* **2009**, 684-691.
Hanada, K. P*roc. Jpn. Acad. Ser. B.* **2010**, *86*, 426-437.
Hanada, K. et al *Biochim. Biophys. Acta* **2014**, *1841*, 704-719.
Yamaji, T.; Hanada, K. *Traffic* **2015**, *16* , 101-122.
Berkeš, D.; Ďuriš, A.; Moravčíková, D. *Org. Lett.* **2011**. *13*, 1642-1645.
Berkeš, D.; Daïch, A.; Santos, C.; Ballereau, S.; Génisson, Y. *Chem. Eur. J.* **2016**, *22*, 17514-17525.

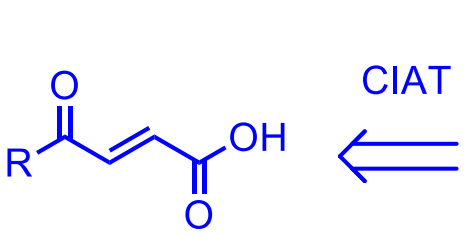
Synthesis of ceramides and their new analogs



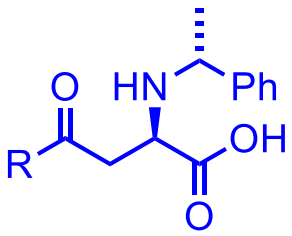


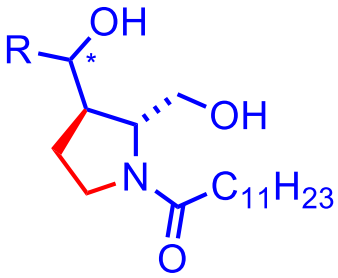
Ďuriš, A. *Dissertation project*, FCHPT-19989-22979, **2012**.

R = Ph, *p*-Me-Ph, *p*-OMe-Ph, *p*-Alk-Ph, *m*-Alk-Ph, Alk

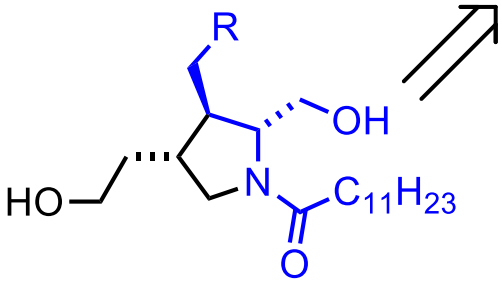


CIAT

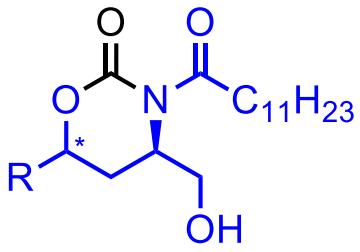




R = Ph, *m*-Alk-Ph



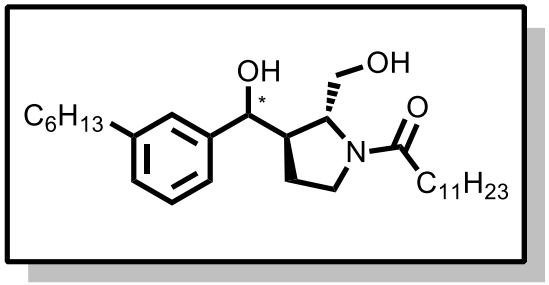
R = Ph, *p*-Me-Ph, *p*-OMe-Ph, *p*-Alk-Ph, *m*-Alk-Ph



Moravčíková, D. *Dissertation project*, FCHPT-19989-16212, **2013**.

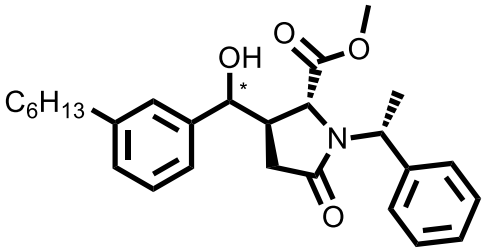
R = Ph, *p*-Me-Ph, *p*-OMe-Ph, *p*-Alk-Ph, *m*-Alk-Ph

Retrosynthetic analysis



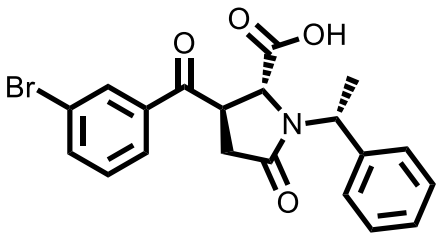
Conformational restricted analogue of HPA-12

FGI

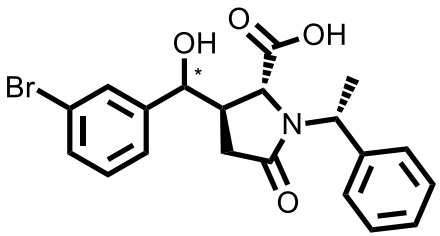


Sonogashira

FGI



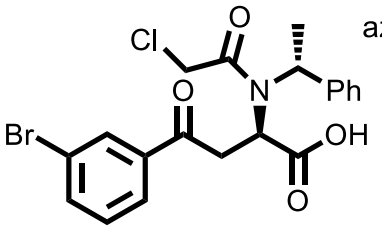
reduction

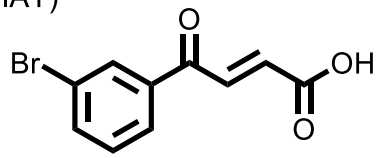


cyclisation

acetylation

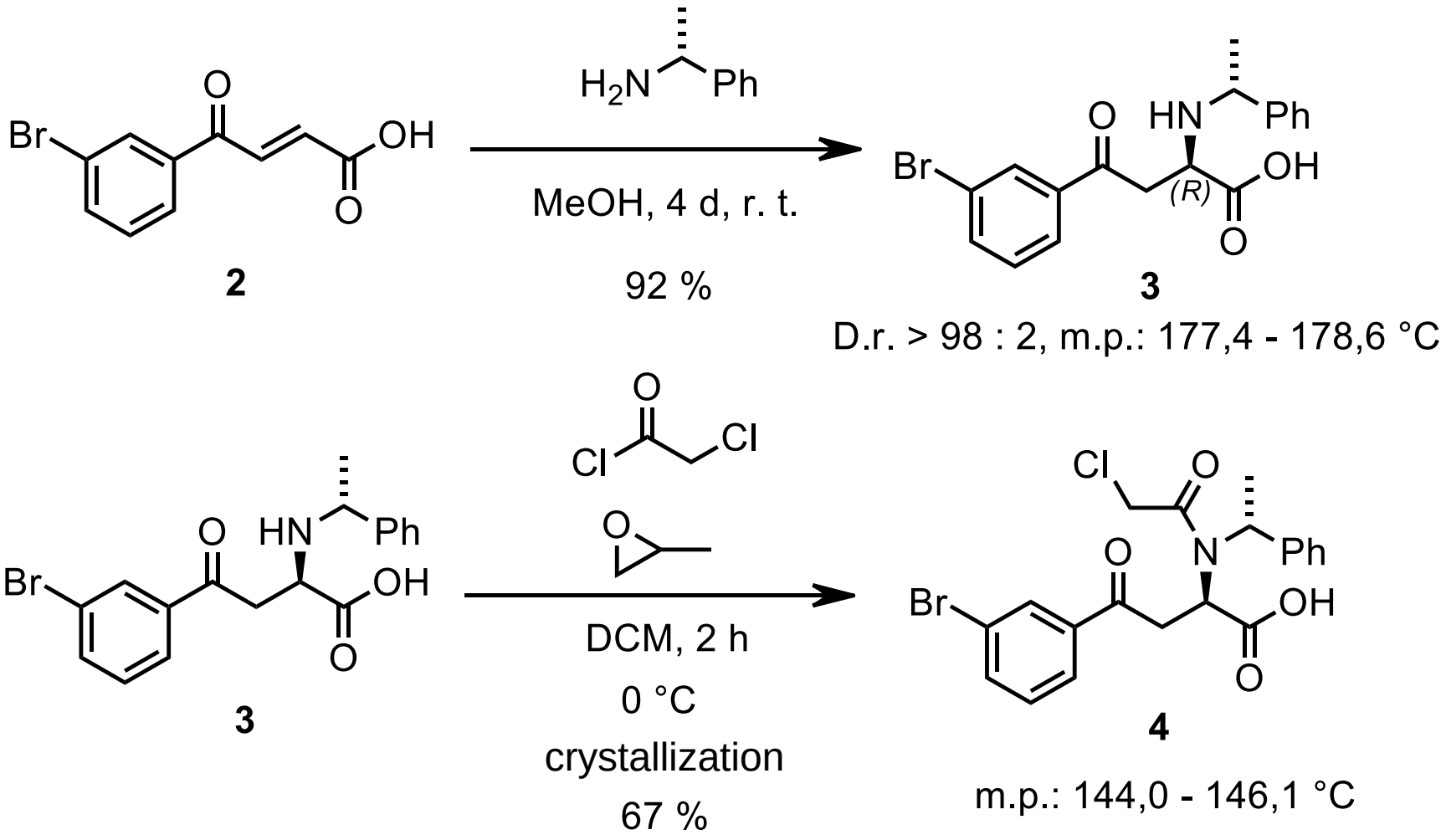
aza-Michael addition (CIAT)





aza-Michael addition(CIAT), chloroacetylation

Preparation of γ-oxo-α-aminoacid and its chloroacetylation

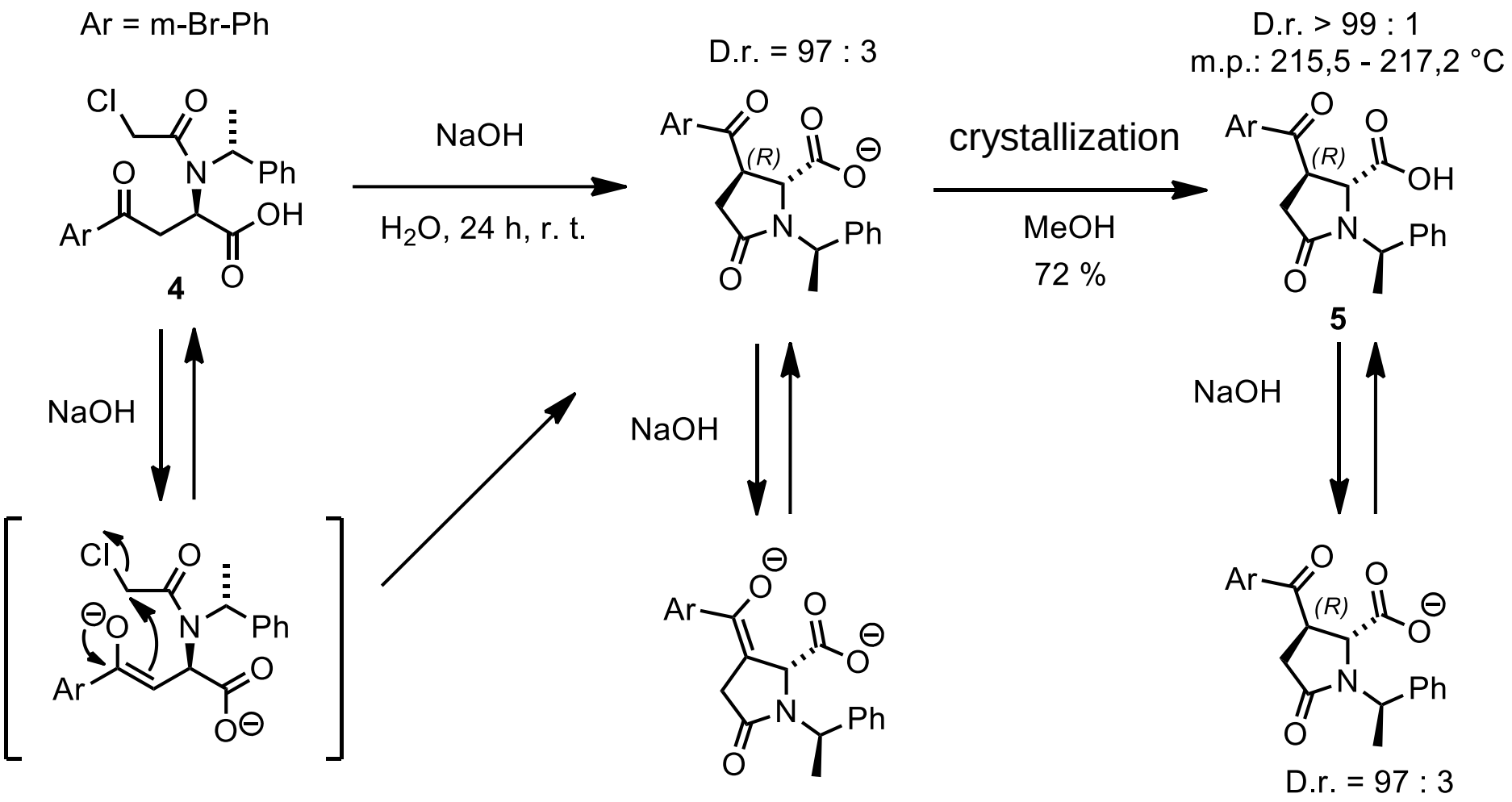


Markus, J. *Dissertation project*, FCHPT-19989-40437, **2016**.

Bonache, M. A.; Garcia-Lopez, M. T.; Gerona-Navarro, G.; Gonzalez-Muniz, R.; Herranz, R. *J. Org. Chem.*, **2001**, *66*, 3538 – 3547.

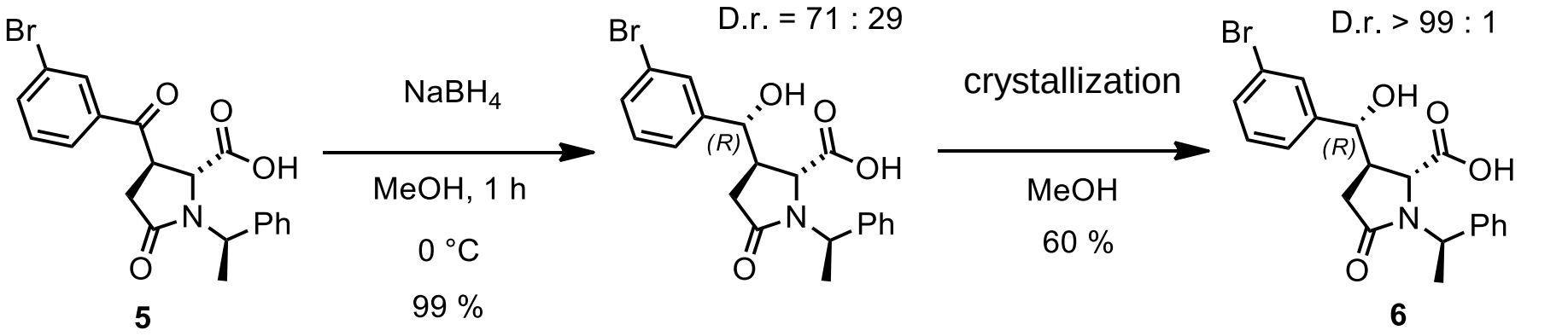
Cyclisation

Intramolecular alkylation – preparation of oxoproline derivative



Reduction of oxo group of oxoproline derivative

Preparation of hydroxy derivative



Markus, J. *Dissertation project*, FCHPT-19989-40437, **2016**.

Reduction of oxo group of oxoproline derivative

Preparation of hydroxy derivative

Reduction agent / Solvent	D.r. (R : S)
PMHS, Pd / MeOH	a*
$NaBH_3CN$ / MeOH	**2** : 1
BH_3 / THF	**2** : 1
CBS – BH_3/ H_2O	**2** : 1
$NaBH_4$, $MnCl_2$ / MeOH	**80** :20
$NaBH_4$, $CeCl_3$ / MeOH	**78** : 22
$NaBH_4$, AcOH / DCM	**85** : 15
$LiBHEt_3$ / THF	**98** : 2
L-Selectride / THF	**98** : 2

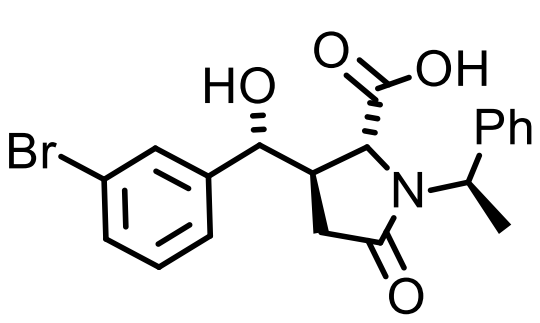
Reactions were monitored by HPLC.

a - debromination

Hudlický, M. *Reductions in Organic Chemistry Second Edition*, **1990**.

Esterification , Mitsunobu inversion

Preparation of methylester and inversion of hydroxyl group



6

D.r. > 99 : 1

$KHCO_3$

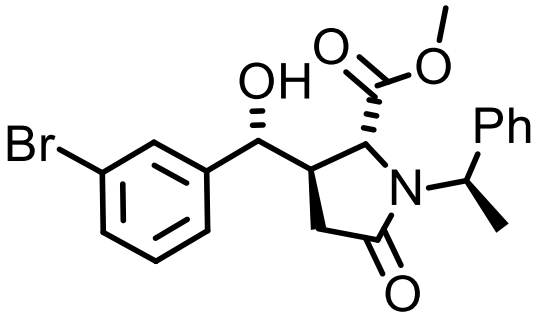
MeI

Me_2CO, 24 h

reflux

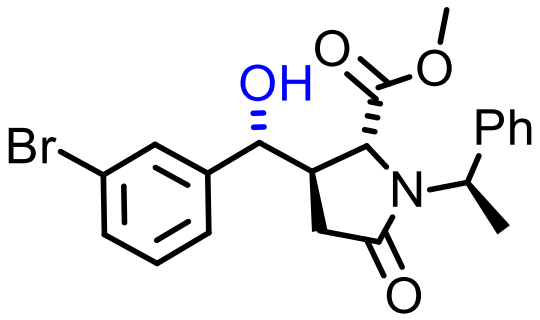
crystallization

80 %



7

D.r. > 99 : 1, m.p.: 150,5 - 152,6 °C



7

D.r. > 99 : 1

DEAD, PPh_3

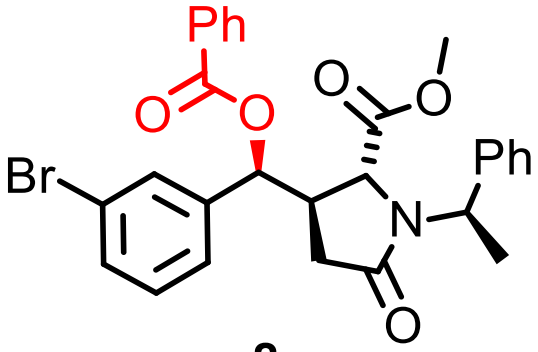
PhCOOH

THF, 4 h

- 5 °C

column chromatography

87 %



8

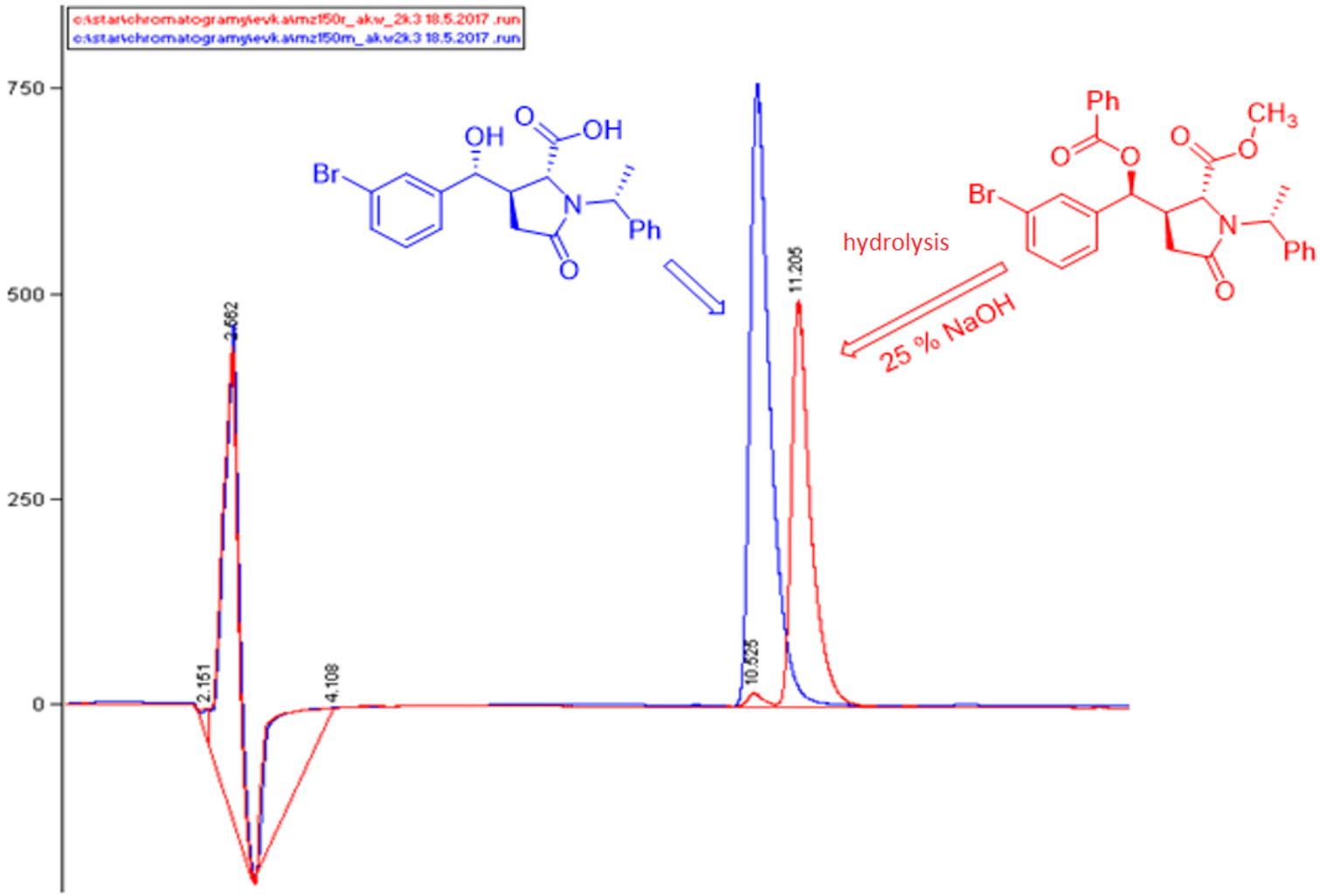
D.r. > 1 : 99, m.p.: 132,4 - 133,7 °C

Markus, J. *Dissertation project*, FCHPT-19989-40437, **2016.**

But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.*, **2006**, *128*, 9636-9637.

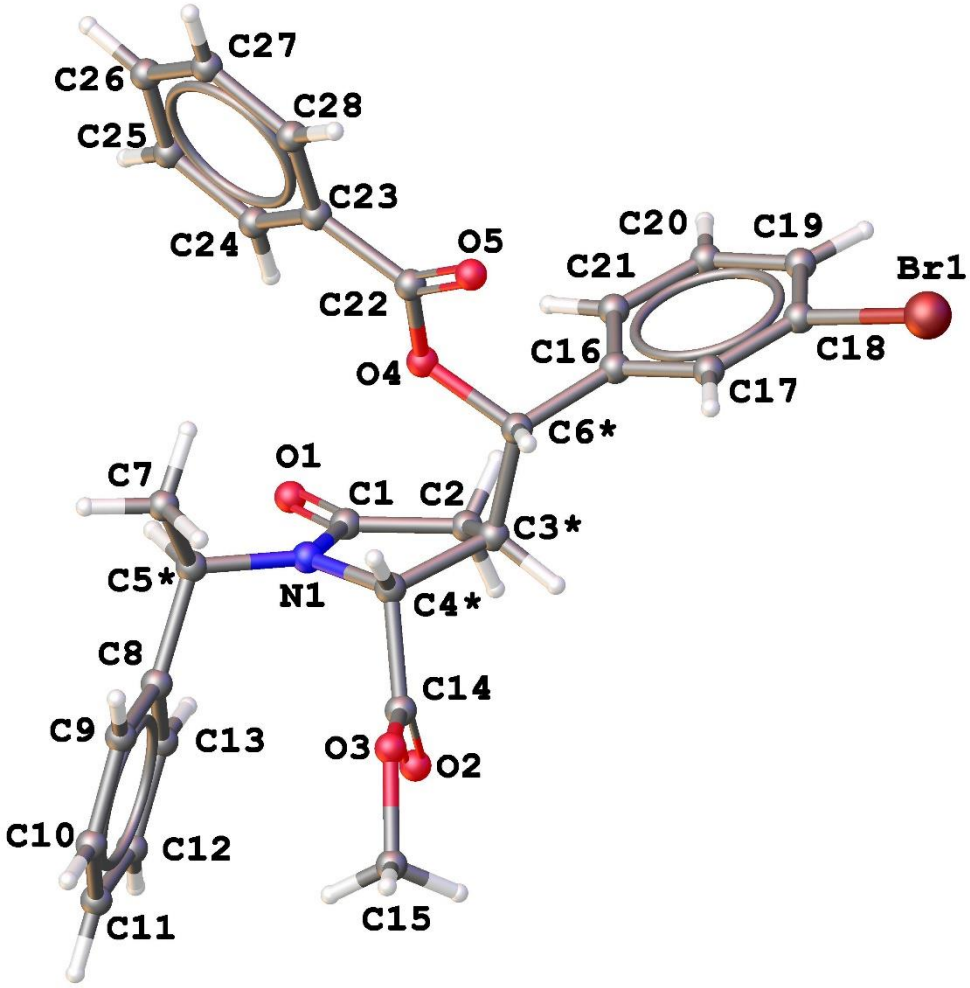
Determination of configuration of hydroxy stereogenic centre

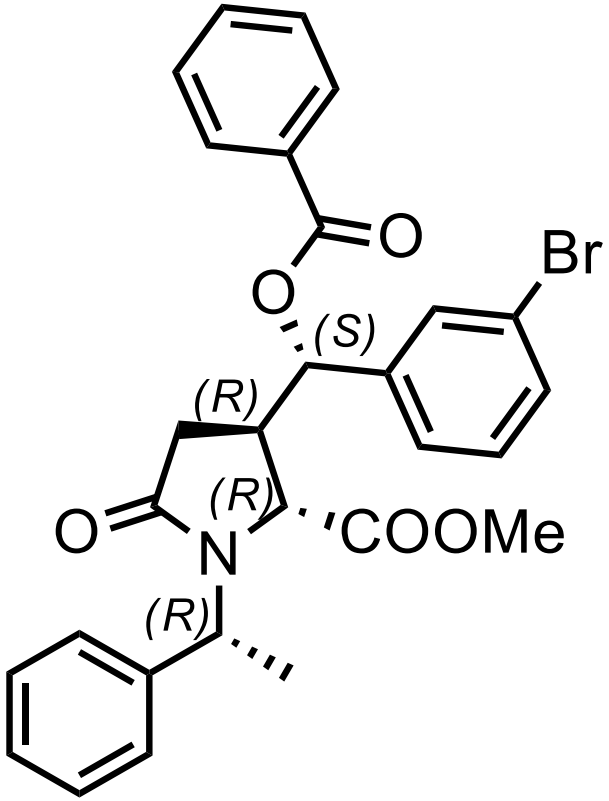
HPLC analysis: Basic hydrolysis of ester + hydroxy derivative



Determination of configuration of hydroxy stereogenic centre

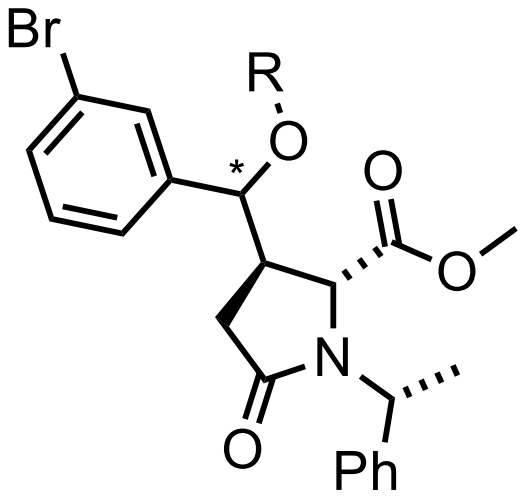
X-ray analysis of crystal of Mitsunobu inversion product





Sonogashira coupling

Substititution of bromine for alkynyl



7 R = H

* = *(R)*

8 R = Bz

* = *(S)*

$Pd(PPh_3)_4$

CuI

C_4H_9—≡—H

TEA, 12 h

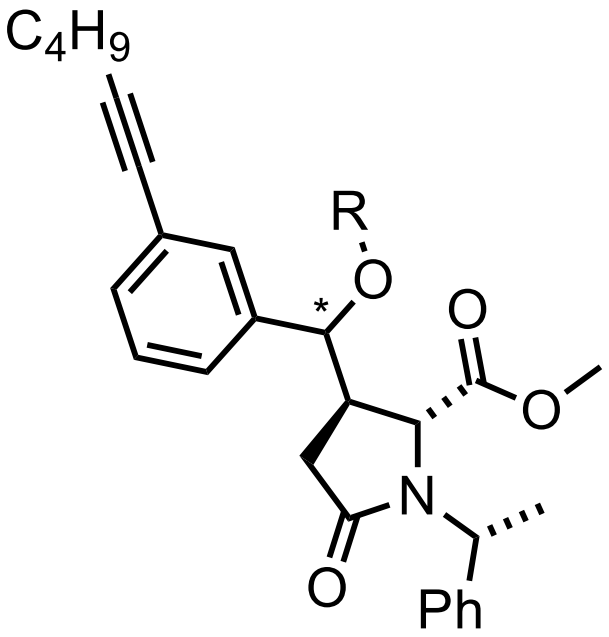
65 °C

column chromatography

(90 %)

column chromatography

(82 %)



9 R = H

m.p.: 107,7 - 109,4 °C

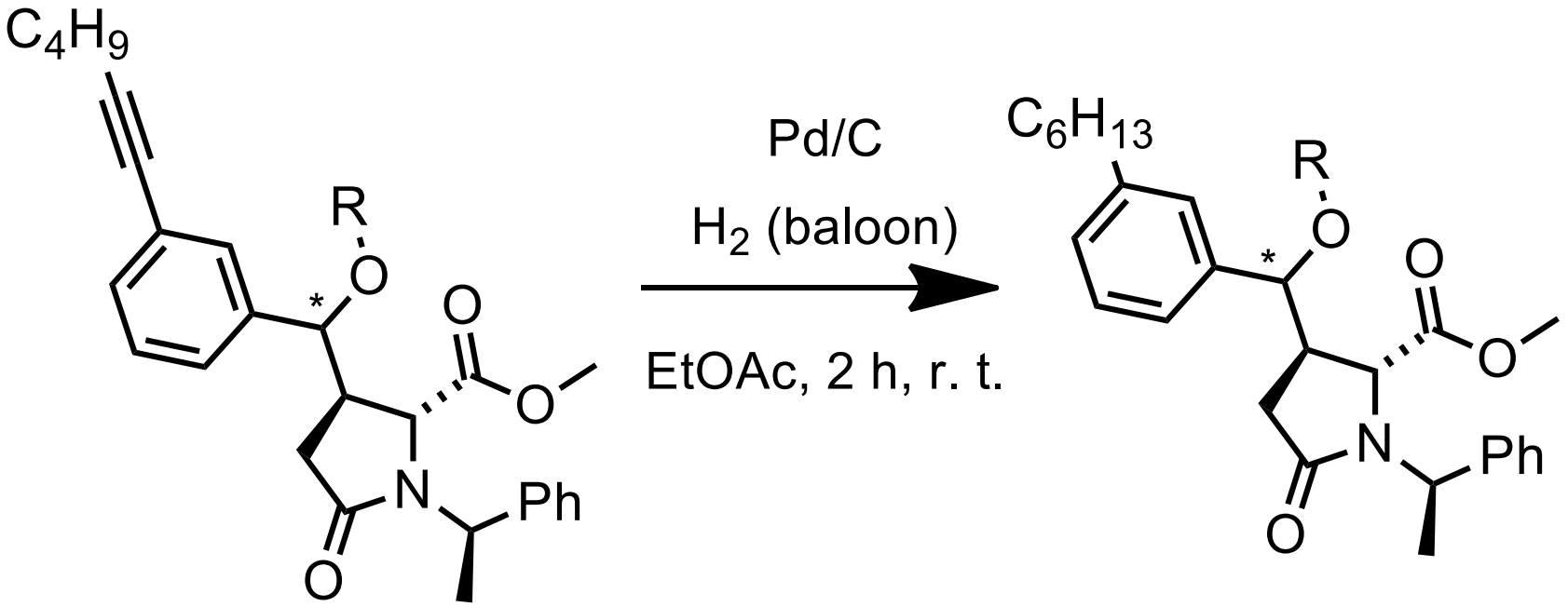
10 R = Bz

m.p.: 59,0 - 64,1 °C

Markus, J. *Dissertation project*, FCHPT-19989-40437, **2016**.

Catalytic hydrogenation

Reduction of alkynyl



9 R = H

* = *(R)*

10 R = Bz

* = *(S)*

column chromatography

94 %

column chromatography

90 %

11 R = H

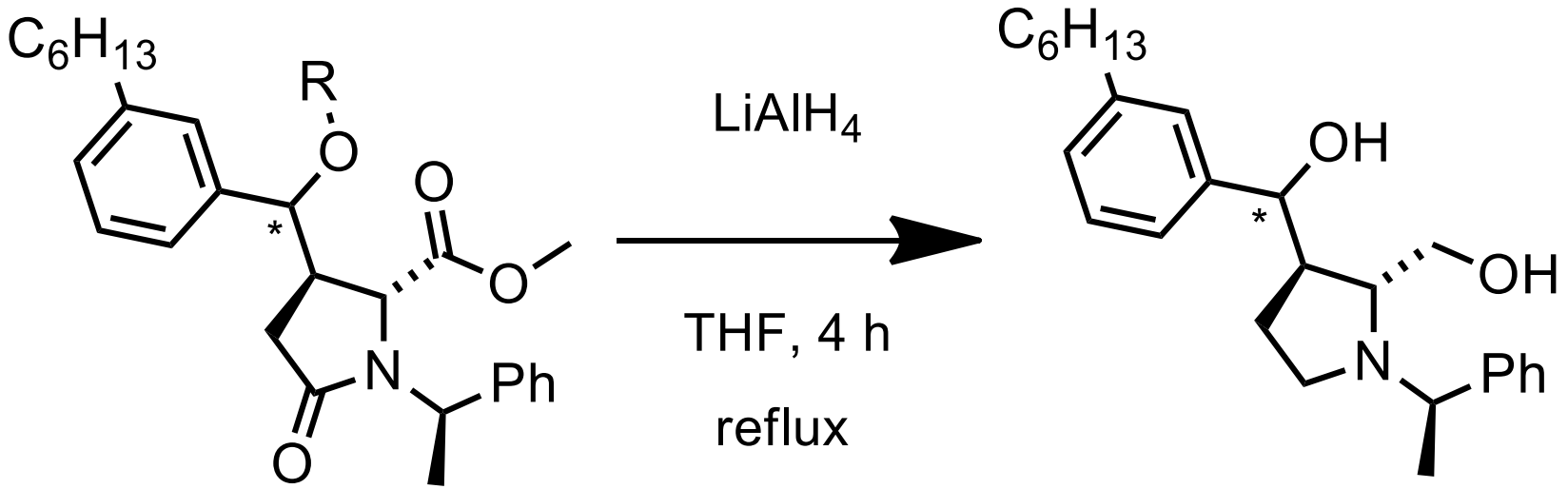
* = *(R)*

12 R = Bz

* = *(S)*

Reduction of ester and lactame

Preparation of aminodiol



11 R = H

* = *(R)*

column chromatoraphy

88 %

13 * = *(R)*

12 R = Bz

* = *(S)*

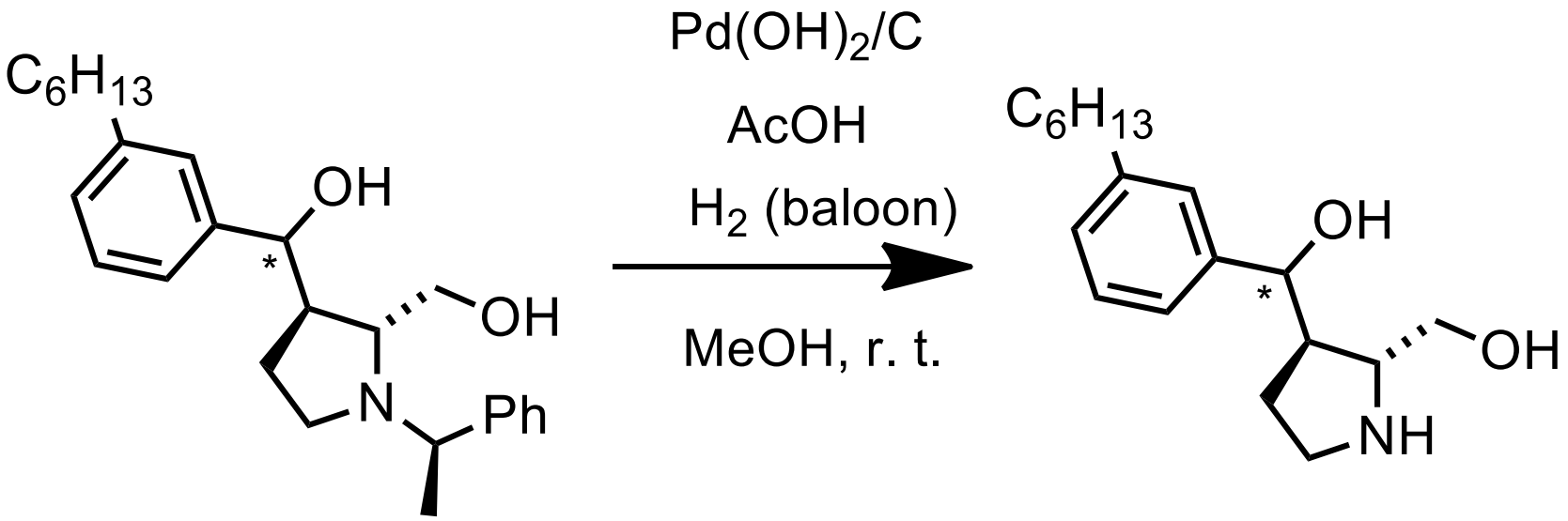
column chromatography

73 %

14 * = *(S)*

Catalytic hydrogenation

Debenzylation of aminodiol



13 * = *(R)*

20 h

column chromatography

62 %

15 * = *(R)*

14 * = *(S)*

3 h

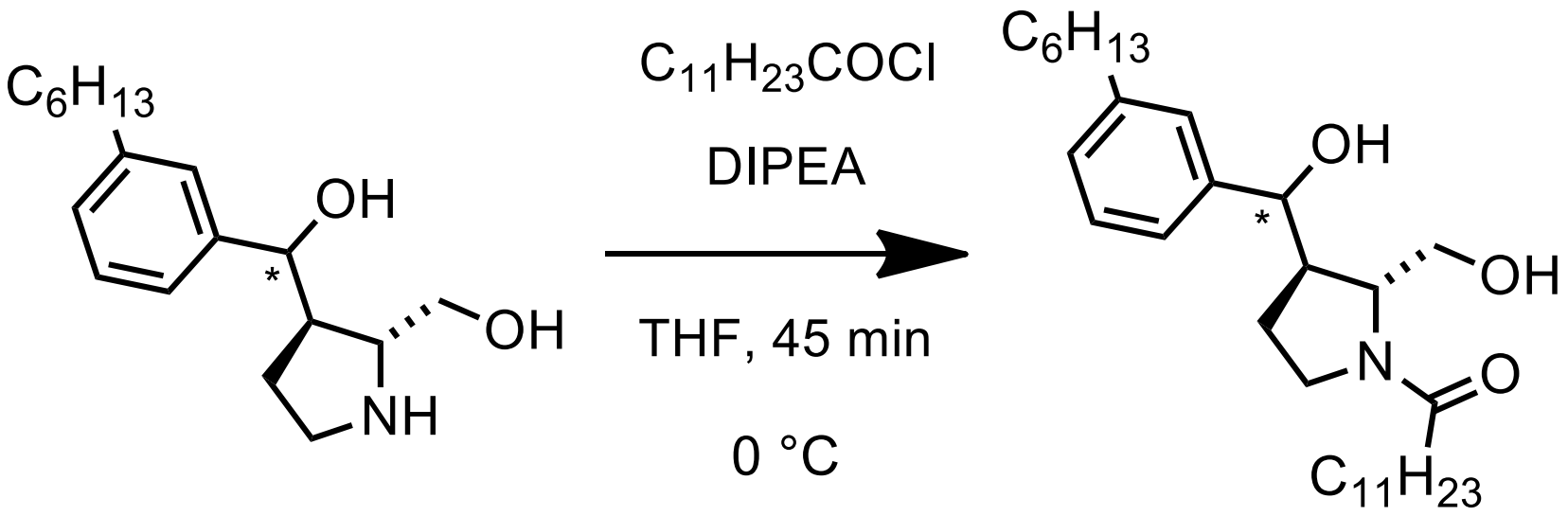
column chromatography

85 %

16 * = *(S)*

N - acylation

Preparation of target HPA-12 analog



15 * = *(R)* column chromatography **17** * = *(R)*

60 %

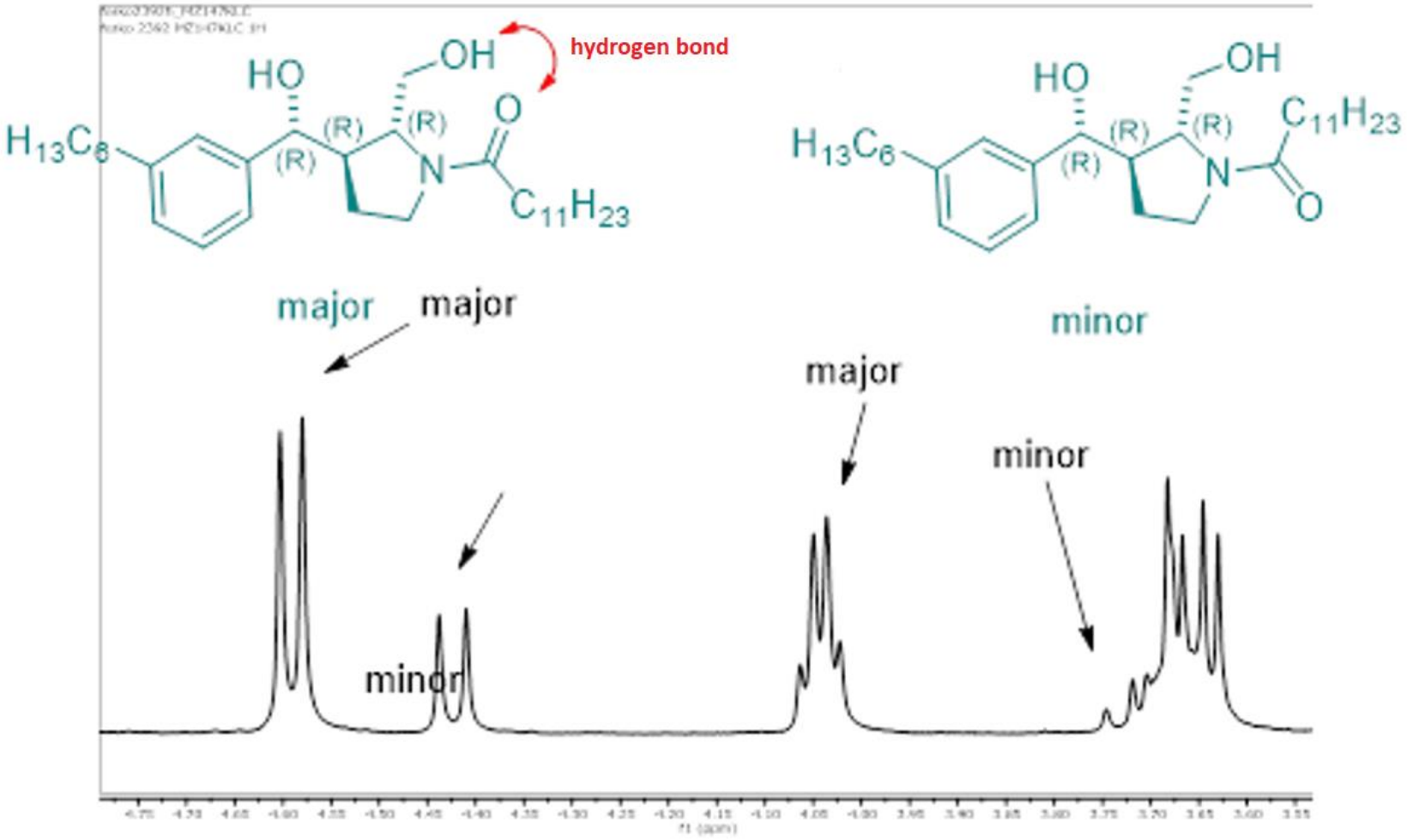
16 * = *(S)* column chromatography **18** * = *(S)*

39 %

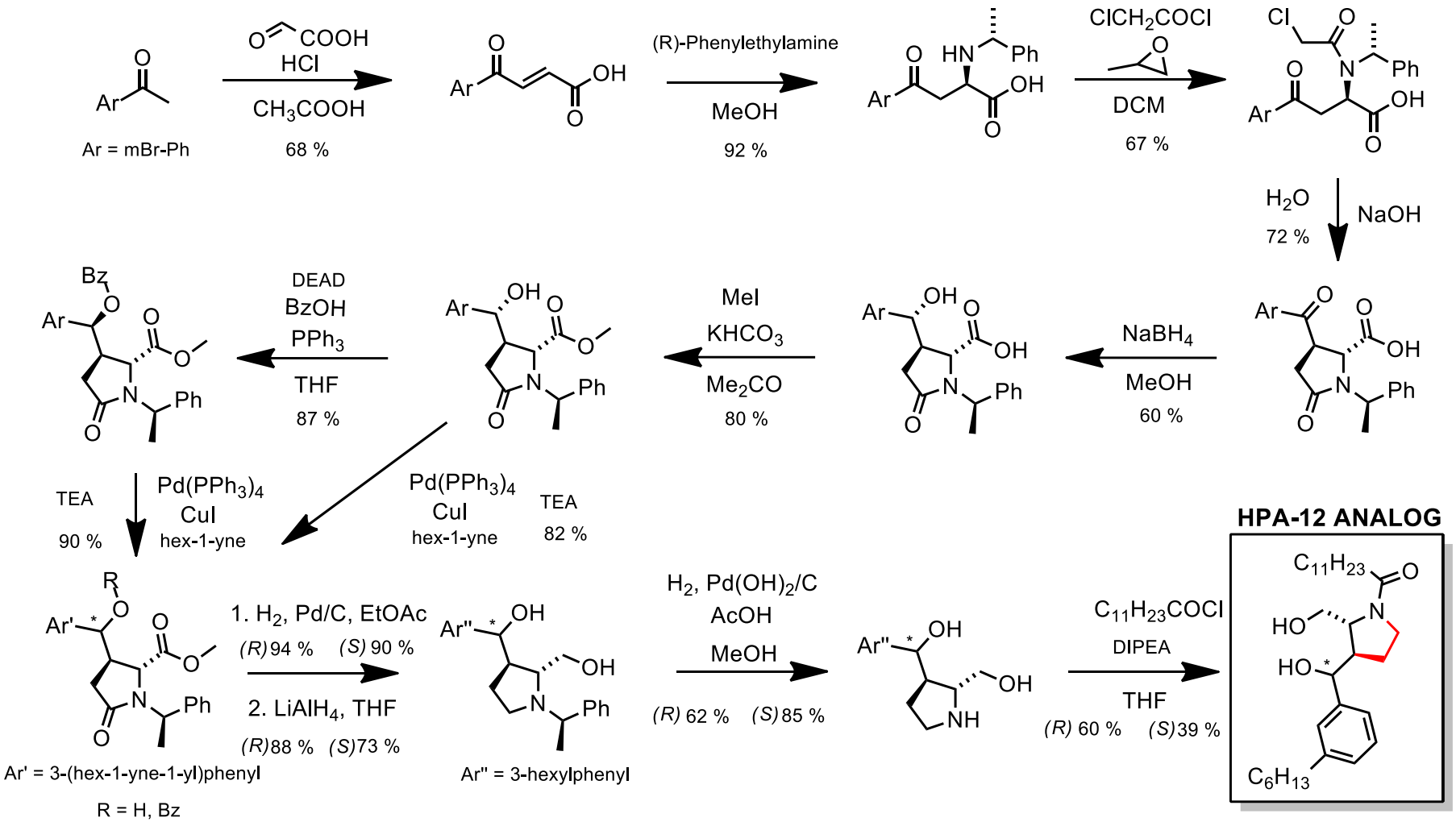
N - acylation

H NMR spectrum of HPA-12 analog

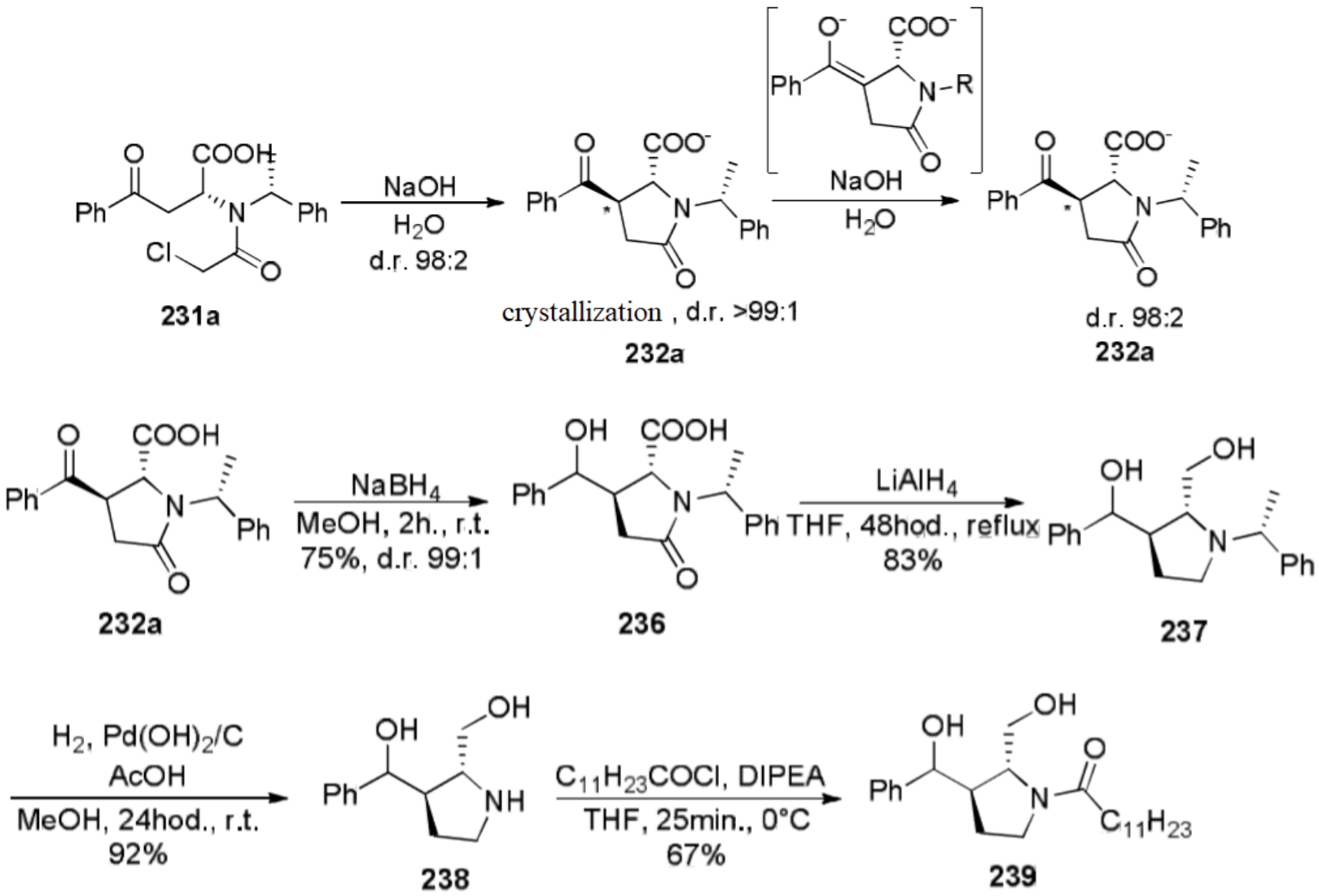
Major and minor rotamers



Synthesis scheme

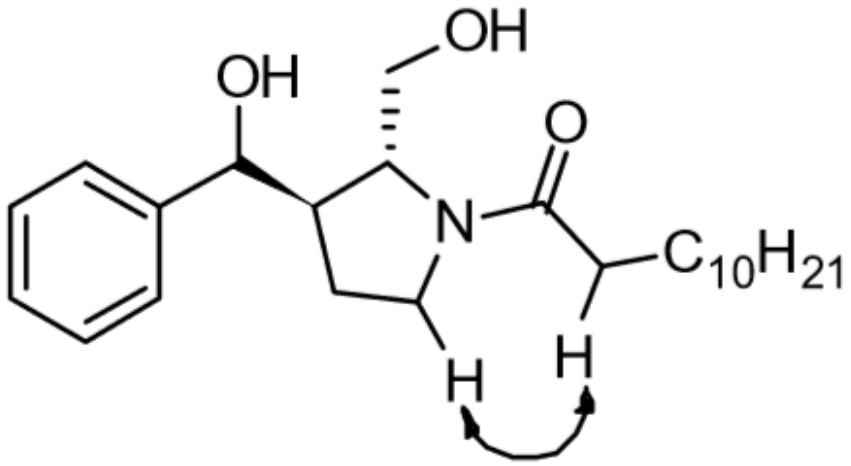


Phenyl analog

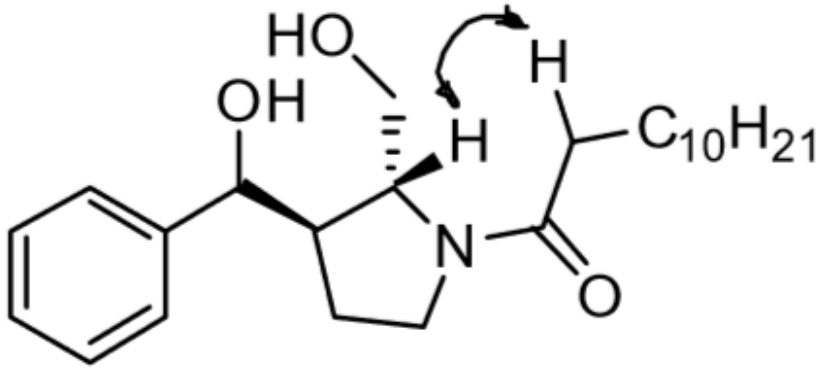


Markus, J. *Dissertation project*, FCHPT-19989-40437, **2016**.

Phenyl analog

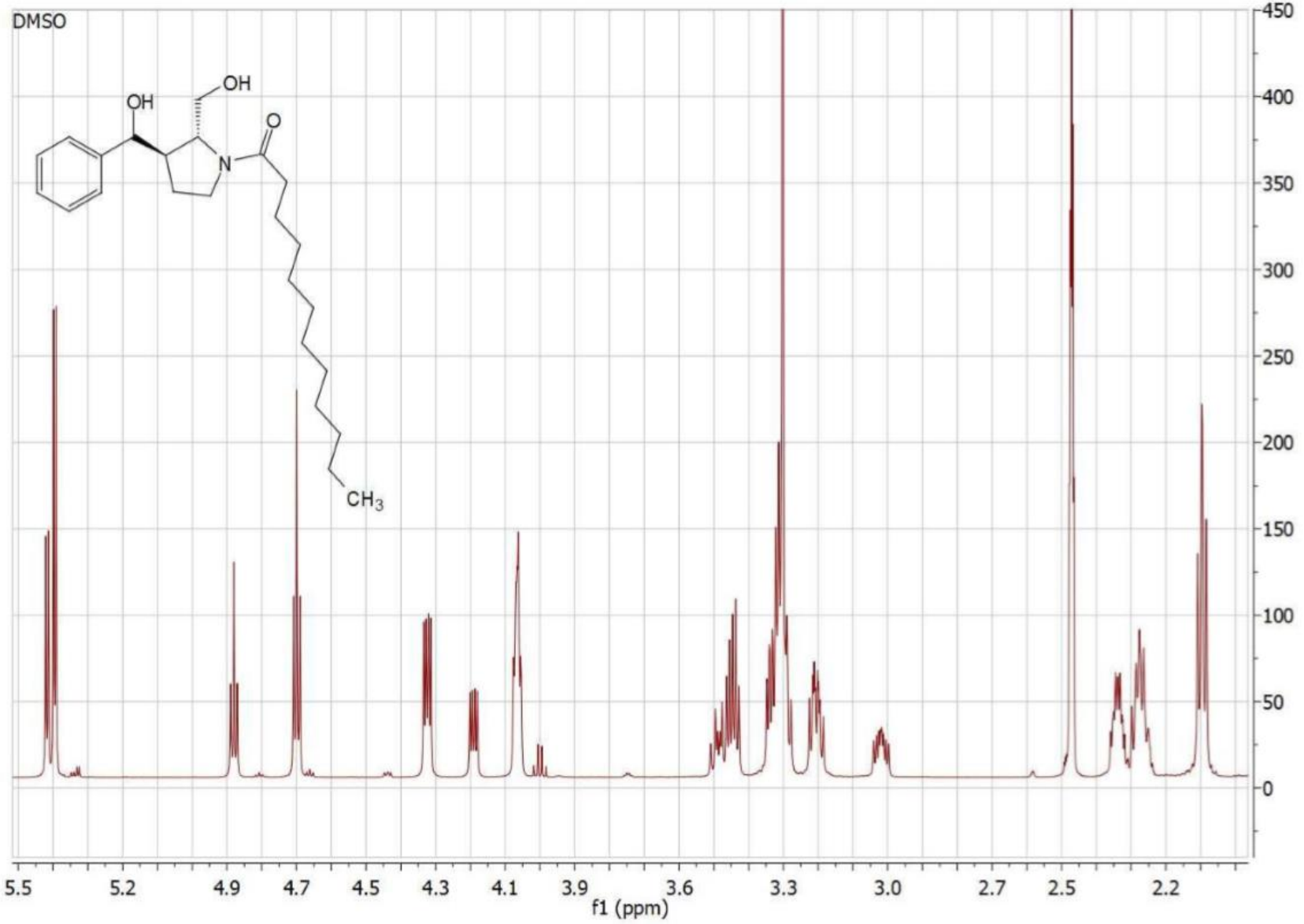


major

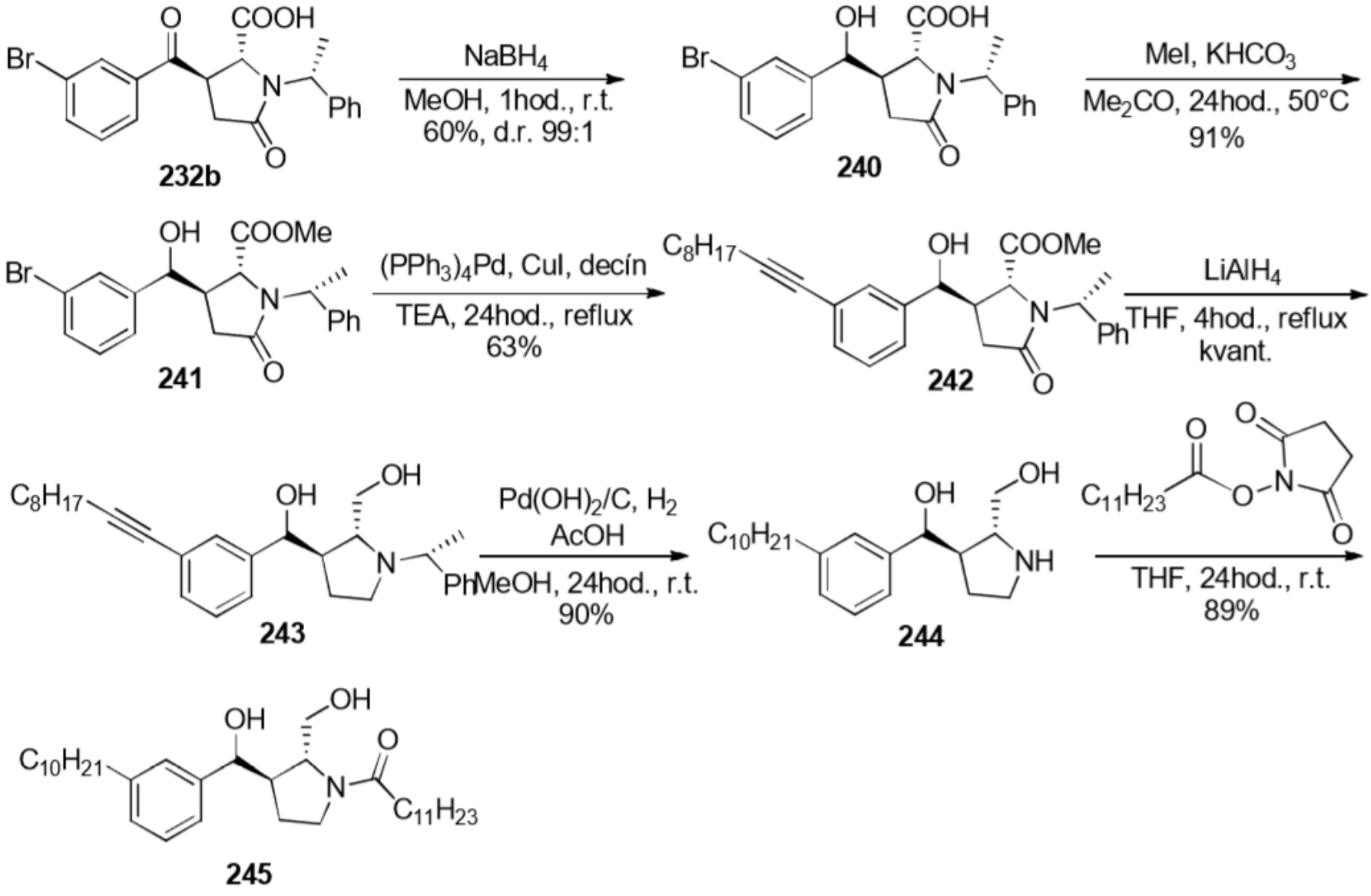


minor

Phenyl analog

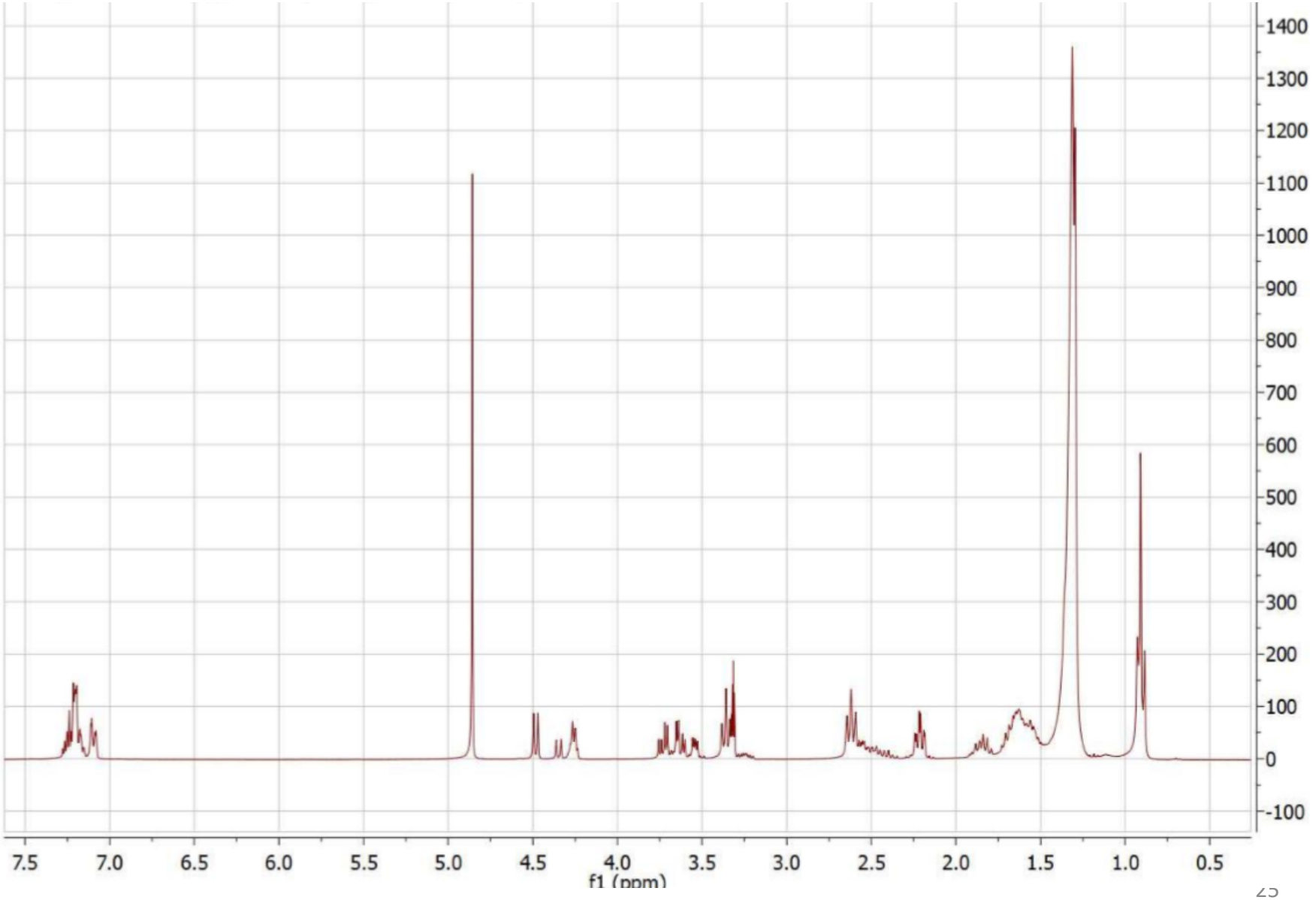


m-decyl analog



Markus, J. *Dissertation project*, FCHPT-19989-40437, **2016**.

m-decyl analog



Thank you!