Organocatalytic Asymmetric Direct Vinylogous Aldol Reactions of 2-Furanone and Application in the Synthesis of (+)-L-733,060, (+)-CP-99,994, (2*S*,3*R*)-3-Hydroxypipecolic Acid and (+)-Febrifugine

by

© **Eldho K. Paul**

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To my famil

ABSTRACT

The organocatalytic, direct vinylogous aldol reaction (ODVA) of 2-furanone (γ-crotonolactone) is of interest because the reaction provides direct access to γ-substituted butenolides, an important structural motif in several natural products and biologically active compounds. We have observed that this reaction is catalyzed by chiral aminothioureas and aminosquaramides. A detailed investigation of this method is described in Chapter 2. The ODVA reaction of γ-crotonolactone with aldehydes can be used for the synthesis of substance P receptor antagonist piperidines (+)-L-733,060 and (+)-CP-99,994, and also for the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid, which is a component of tetrazomine, an antitumor agent and an antibiotic. These results are presented in Chapter 3. This methodology is also useful for the total synthesis of the antimalarial alkaloid (+)-febrifugine and a formal synthesis of (+)-halofuginone, an antimalarial agent. The results of this work are described in Chapter 4.

ACKNOWLEDGEMENTS

First and foremost, I'd like to thank my thesis advisor, Professor Sunil V. Pansare, for his guidance, endless support, enthusiasm and encouragement throughout my doctoral studies. From the first day, his door was always open when I needed to discuss any topic, no matter how random or obscure. I am extremely grateful for his guidance, patience and creativity in approaching chemical problems.

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Finally, I want to give my deepest thanks to my family, especially my mom and dad. Thanks to my sisters for their continuous support throughout my life. This thesis certainly would not have been possible without the love and encouragement from them.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations and Symbols

Ac	acetyl
ADH	asymmetric dihydroxylation
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Boc	*tert*-butoxycarbonyl
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)-acetamide
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
dr	diastereomeric ratio
$(DHQ)_2$-PHAL	hydroquinine 1,4-phthalazinediyl diether
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess

EI	electrospray ionization
eq.	equivalent(s)
Et	ethyl
g	gram(s)
h	hour(s)
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	Hertz(s)
IBX	2-iodoxybenzoic acid
IR	infrared
iBu	isobutyl
J	coupling constant
L	ligand
LAH	lithium aluminium hydride
M	molar
M+	molecular ion
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
MOM	methoxymethyl ether

MsCl	methanesulfonyl chloride
mp	melting point
MS	mass spectrum
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
ODVA	organocatalytic direct vinylogous aldol
OVMA	organocatalytic vinylogous Mukaiyama aldol
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PTSA	*p*-toluenesulphonic acid
pyr	pyridine
RCM	ring-closing metathesis
rt	room temperature
SES	(2-Trimethylsilyl)ethanesulfonyl
SmI_2	samarium iodide
*t*Bu	*tert*-butyl
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*p*-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
UHP	urea hydrogen peroxide
UV	ultraviolet
VMA	vinylogous Mukaiyama aldol
^{o} C	degree Celsius
δ	chemical shift (spectroscopy)
α	alpha
β	beta
γ	gamma
δ	delta
ε	epsilon
π	pi

CHAPTER 1

Introduction

This chapter is based on the following publication:

Pansare, S. V., Kaur, G., & Paul, E. K. (2017). [Publication details illegible].

Contributions of authors

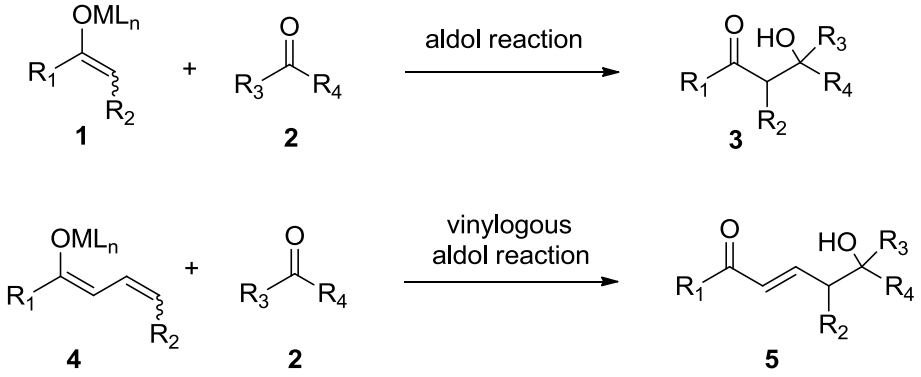
S. V. Pansare: research supervision, literature review, manuscript

E. K. Paul: literature review, manuscript

CHAPTER 1

Introduction

The aldol reaction is one of the most chemistry-carbon-carbon bond formation. With the vinylogous extension is of considerable i principle[1] to of extending effect of a polarized functional molecule that is separated from the functional allows the transmission of electronic effects carbon–carbon double bond. This has been applied t reactions employing α,β-unsaturated carbonyl compound component (Scheme 1.1).[2a]



Scheme 1.1 Classical aldol and vinylogous aldol rea

Over the years, the vinylogous aldol r Mukaiyama aldol reaction have been carried out the synthetic community.

vinylogous Mukaiyama aldol reaction (OVMA) have appeared in the literature, reviews available in the literature[2] on the (boron derived catalysts Ca(II) catalysts) and on the (metal free organic catalysts) have appeared in the literature[3]. There are a few reviews available in the literature[2a] on the organocatalytic version of the vinylogous aldol (OVA) reaction, which, as mentioned nucleophiles, is the most attractive vers regioselectivity issues associated with th

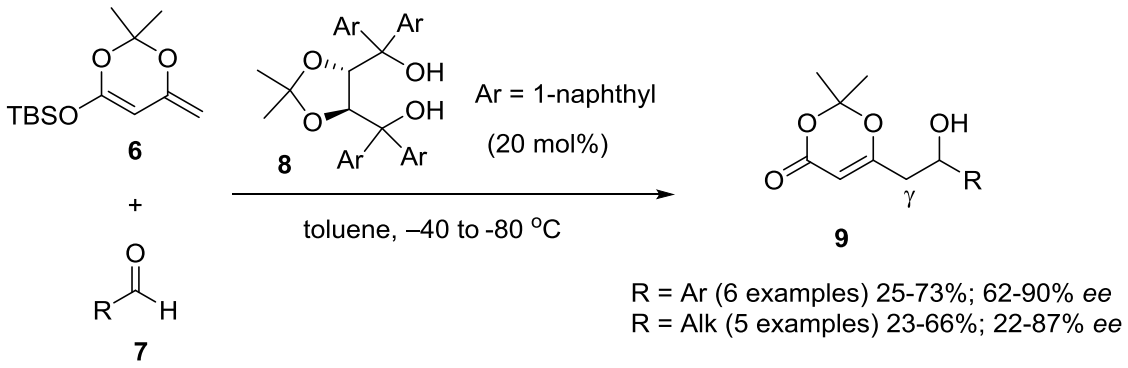
1.1 The organocatalytic vinylogous Mukaiyama aldol reaction (OVMA)

The interest in OVMA reactions is mainly importance in natural products synthesis[2,3a]. With the objective of developing asymmetric have been directed towards the development of vinylogous aldol reactions. The OVMA reac OVMA reactions of dienoic acid 2) OVMA rea silyloxydienes.

1.1.1 OVMA reactions of cyclic siloxydie

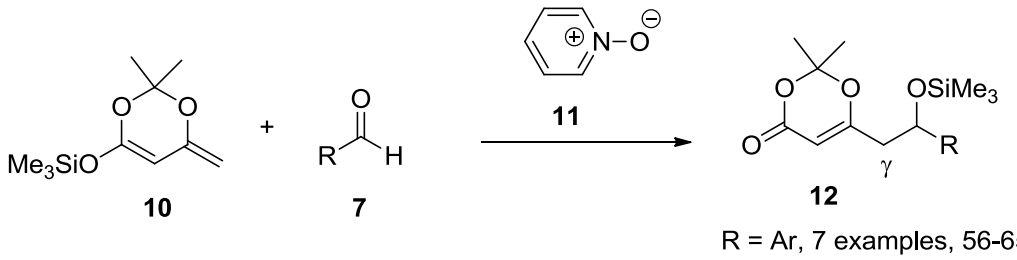
Rawal and co-workers[6] reported the first example of of silyloxyfuran (Scheme 1.2) to aldehydes using va catalysts. Prelimitary investigations revealed that 2 the el

t a r - t h e a r t i e A D D O B ($\alpha,\alpha,\alpha',\alpha'$ - t e t r - 1 a , 3 a d r i y o l x e 4 l , - d 5 i n m e t h a a s m a o l)
p r o m i s i n g T h u c s a , t a u l y s t e r . o p t i m i z e d 6 c r e a c t i t s i o w n i s t , h
v a r i e t y o f a l d e h y d e s i n p r e s e 8 n t c o e p o r f o v a i d e a t t
v i n y l o g o u s a l (S c h e m e 1 d . 2 p u) c o t i s n g o o d - 7 3 % e) d s a n d (2 3
e n a n t i o s e - 9 0 % e t e i . v i l t n y g (e 2 n 2 e r a l , a r o m a t i c a l d e h
a l i p h a t i c a l d e h y d e s i n t e r m s o f y i e l d a n d
s h o w e d c - o m p l e t e i v i t y .



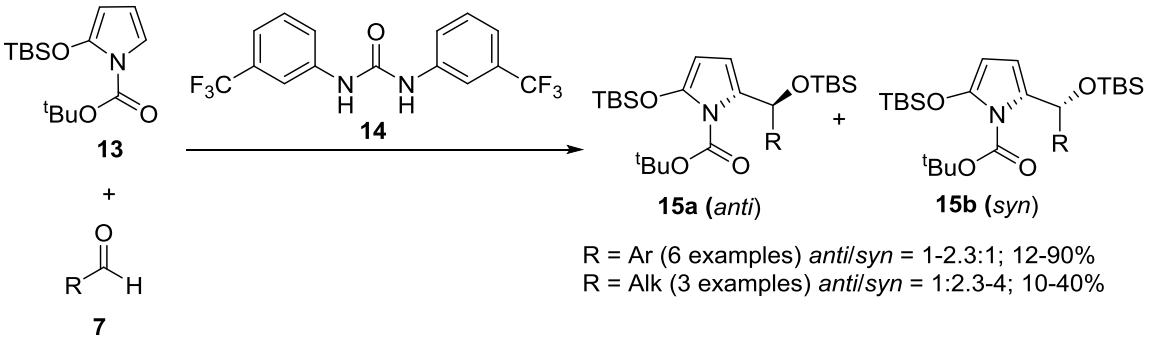
S c h e m e . T h e 2 f i r S V M A s y m m e t r i c s c a t a l y z e d b

Complementary to the TADDOL cat[7]alyzed
r e p o r t e d t h e V M A r 1 e C a a c t t a i l o y n z e o d f b s y i l a o x l y e d w i e s m e b a
I n i t i a l e x p e r i m 1 e 0 a n s m e 4 t i h y l b t e h n z a d l i d e e n h e y d e i n d i c
N - o x i d e i s t h e c a t a l y s t o f c h o i c e a m o n g o
(D M S O) , d i m e t h y l f o r m a m i d e (D M F) a n d h e x a m e
o f a r o m a t l d e h y d e s p r o 1 2 i m e o d d e t y h a i e e a d l s d . o l T h æ d a u s c y t
v e r s i o n o f t h i s r e a c t i o n w a s n o t i n v e s t i g a



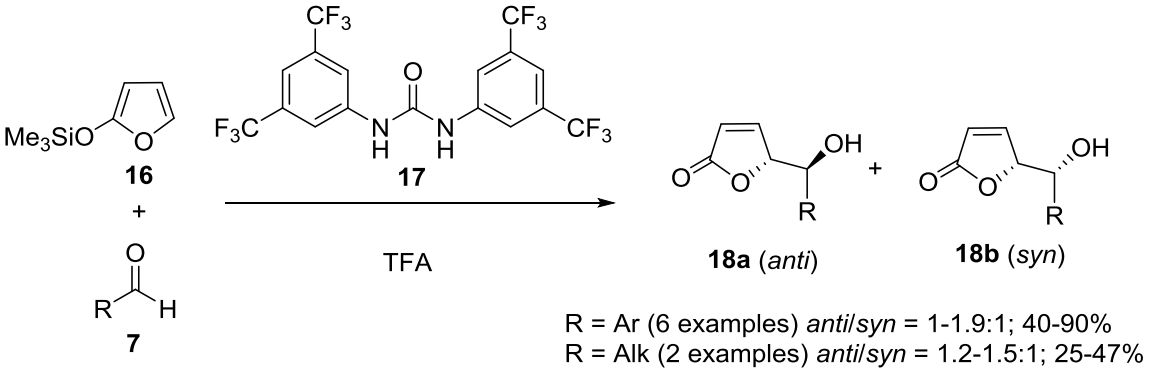
Scheme 3. The Lewis acid catalyzed vinylogous Mukaiyama aldol reaction

Zanardi and coworkers[8] have developed a classic catalyzed vinylogous Mukaiyama aldol reaction between tert-butyldimethylsilyloxyfuran and aldehydes to give the conjugate Subsequently, the corresponding thioureas was reported by Takemoto[9] and co-workers. The structure and stereochemistry of the obtained adducts (Scheme 1.4). Optimization studies the catalyst of choice and the (1,6)-vinylogous (1,5)-aldol products in high yields. The asymmetric version is not investigated in this study.



Scheme 4. The TBAF mediated reaction of thiourea 14 catalyst

The OVMA reaction was successfully applied to a variety of aromatic aldehydes by Soriente[10] in 2006. Several aromatic aldehydes were treated with 3-(trimethylsiloxy)furan (**16**) using 3-(3,5-bis(trifluoromethyl)phenyl)-1-(3,5-bis(trifluoromethyl)phenyl)urea (**17**) as a catalyst (10 mol%) in toluene at room temperature. The addition products were obtained in good yields (65-85%) (Scheme 1.5). The diastereoselectivity was found to be moderate in favor of the *anti* diastereomer in some cases.

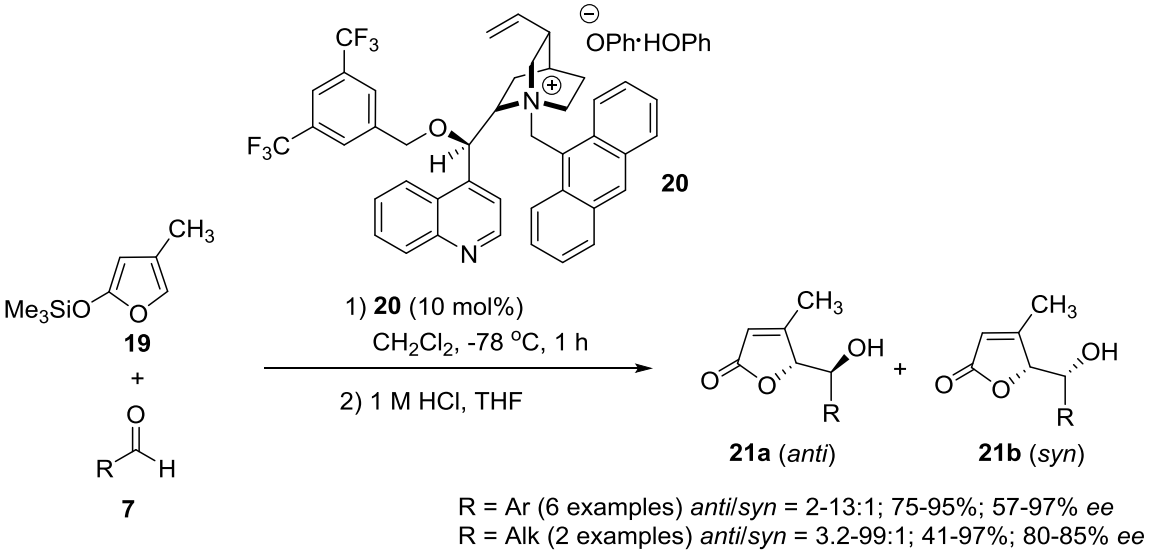


Scheme 1.5. Diarylureas as OVMA catalysts for the methanolysis of furfural

The same group reported the use of the bifunctional OVMA catalyst (**18**) as well as aliphatic aldehydes.[11] Diarylureas are known for their ability to bind anions through bonding interactions with the pyrrole NH f tested as catalysts, but these compounds (70%) showed moderate diastereoselectivities (2.3:1).

The first enantioselective 2-(trimethylsiloxy)furan addition to aldehydes was reported by Jacobsen[12] in 2007. The reaction proceeded with a variety of

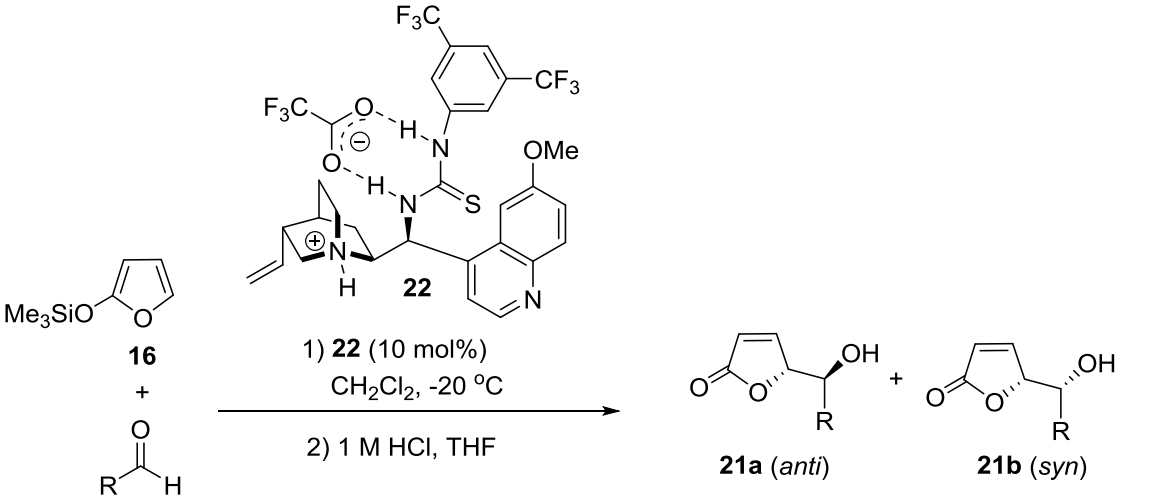
relies on the use of cinchona alkaloid derivatives as primary aminium organocatalyst (Scheme 1.6). Preliminary investigations of the reaction of 2-(trimethylsiloxy)furan (TMSOF) as a masked 1,4-dicarbonyl (trimethylsilyloxy) furan as a nucleophile in terms of yield and enantioselectivity. Reactions with a s were extremely slow at -78 °C, but proceeded to completion at room temperature with excellent diastereoselectivity (2:1 to 99:1 *anti*:*syn*), and high enantioselectivity was observed for the *anti* diastereomer (57-97% *ee*).



Scheme 1.6. Enantioselective reactions catalyzed by c

Deget[13] examined cinchona alkaloid-derived thiourea 22 as a catalyst for the reaction of 2-(trimethylsiloxy)furan with various aldehydes. The reaction is enantioselective, and both aromatic, as

moderate to excellent yields (58-98%) (Scheme 17).[14] In general, the diastereoselectivities were also moderate to excellent (4:1 to 49:1 *anti*/*syn*), with the *anti* diastereomer being the major product. The enantioselectivities were also moderate to excellent (71-98% *ee* for the major diastereomer). The best results were obtained with aryl substituted aldehydes (entries 1-12), while alkyl substituted aldehydes (entries 13-16) afforded lower diastereoselectivities (2.5:1 to 4.5:1 *anti*/*syn*) and enantioselectivities (80-93% *ee* for the major diastereomer).

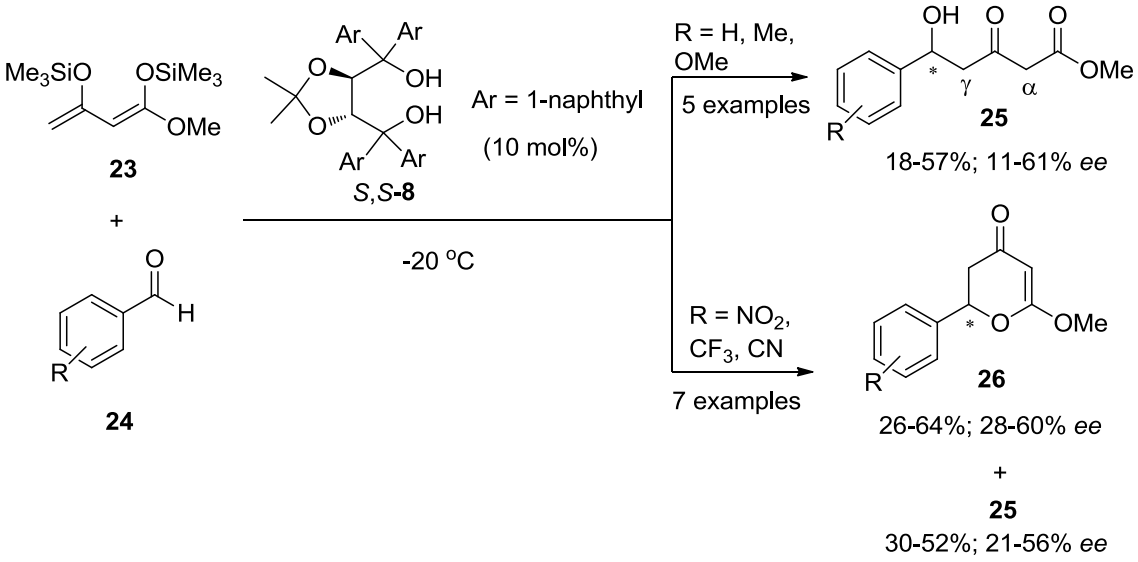


Scheme 17. CVMA reaction catalyzed by quinine

In a related study, we developed an asymmetric CVMA reaction of (trimethylsiloxy)furan with aldehydes catalyzed by a quinidine derived secondary amine (free base).[14] The results of this study are also presented in Table 2. These reactions are conducted in greater than 20 °C. Good diastereoselectivities and enantioselectivities were obtained (Table 2, entries 1-9). The results are comparable to those obtained with the trifluoroacetate

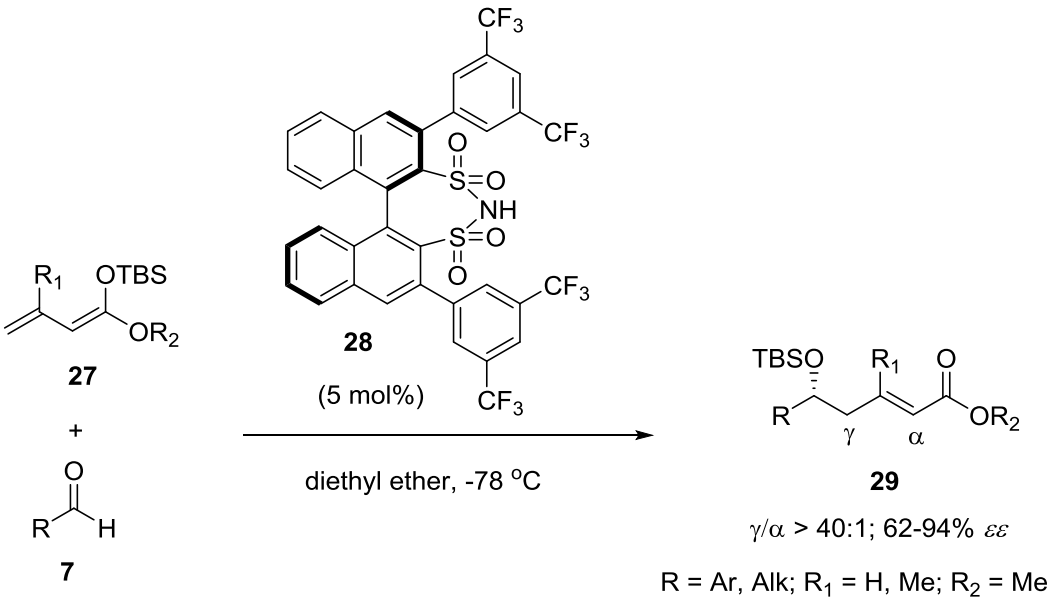
1.1.2 DVMA reactions of acyclic siloxydi

So far, use of acyclic siloxydienes in DVMA reactions has been less e organocatalytic conditions has been less e acyclic siloxydienes as have utilized Chan's diene[15] 23. [16] Vill as the vinylogous donor aldehyde was used, as de the vinylogous 25 (Scheme 1.8).[16] Notably, all t with complete γ-selectivity. Interestingly, aldehyde chiral 4-oxo-2-enoate was also obtained with expected 25. The DVMA ad authors suggested that the Diels–Alder reaction of th aldehyde.



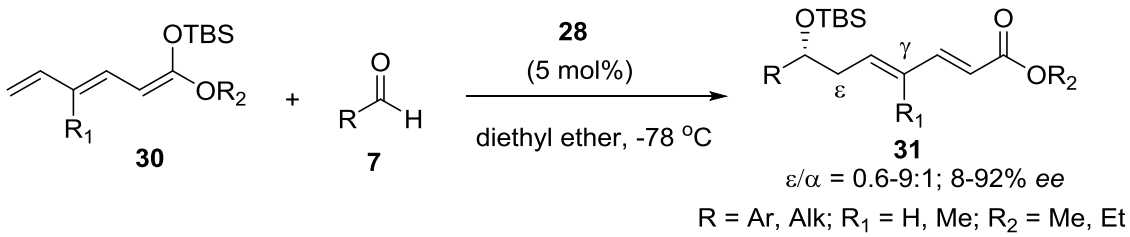
Scheme 1.8. The DVMA reaction catalyzed by TA

List et al.[17] developed an OVMA reaction using a disulfonimides as catalysts. The vinylogous aldol products were obtained in high γ/α ratio and excellent enantioselectivity (Scheme 19).



Scheme 19. Disulfonimide catalyzed OVMA reaction

In addition to the vinylogous[17] aldol reaction was also investigated (Scheme 20, example 1). The organocatalytic bisvinylogous aldol reaction enantioselectivity (ee) was 92% obtained with configuration. Many aldehydes were tested particularly suitable for aromatic additions were not detected in any of the reactions.



Scheme 1. Di(1s0ulfonimide catalyzed bisviny

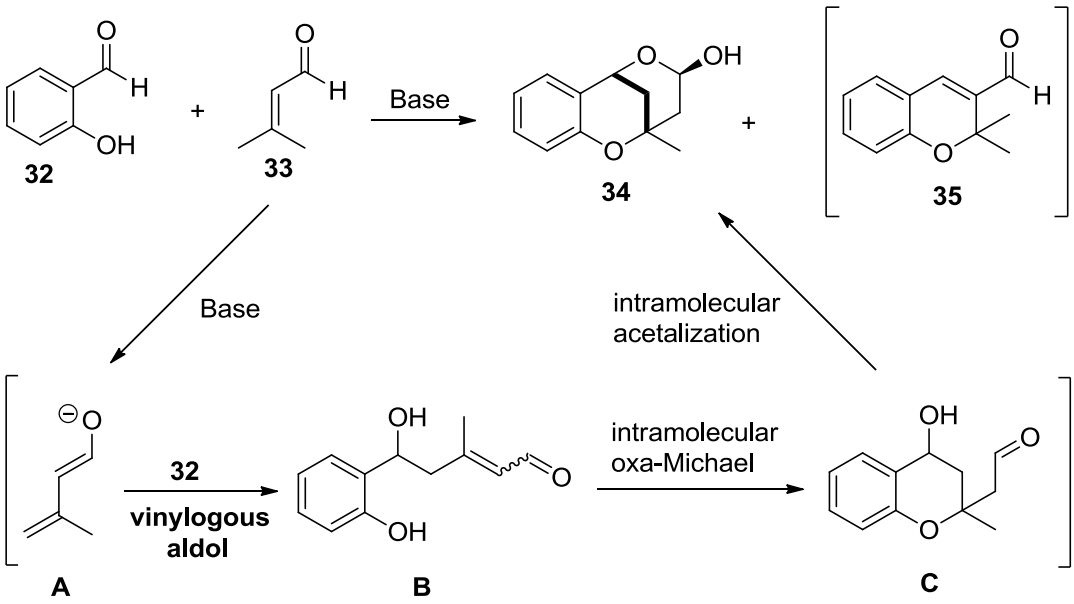
1.C2rganocatalytic vinylogous aldol reaction (ODV

The organocatalytic direct vinylogous a
version in terms[2] The reaction remains challe
diastereoselectivity, enantioselectivity, and regioselectivity with these reactions. So far, ODVA reacti
have examined the α,β-unsaturated aldehydes

1.2ODVA reactions of acyclic dien

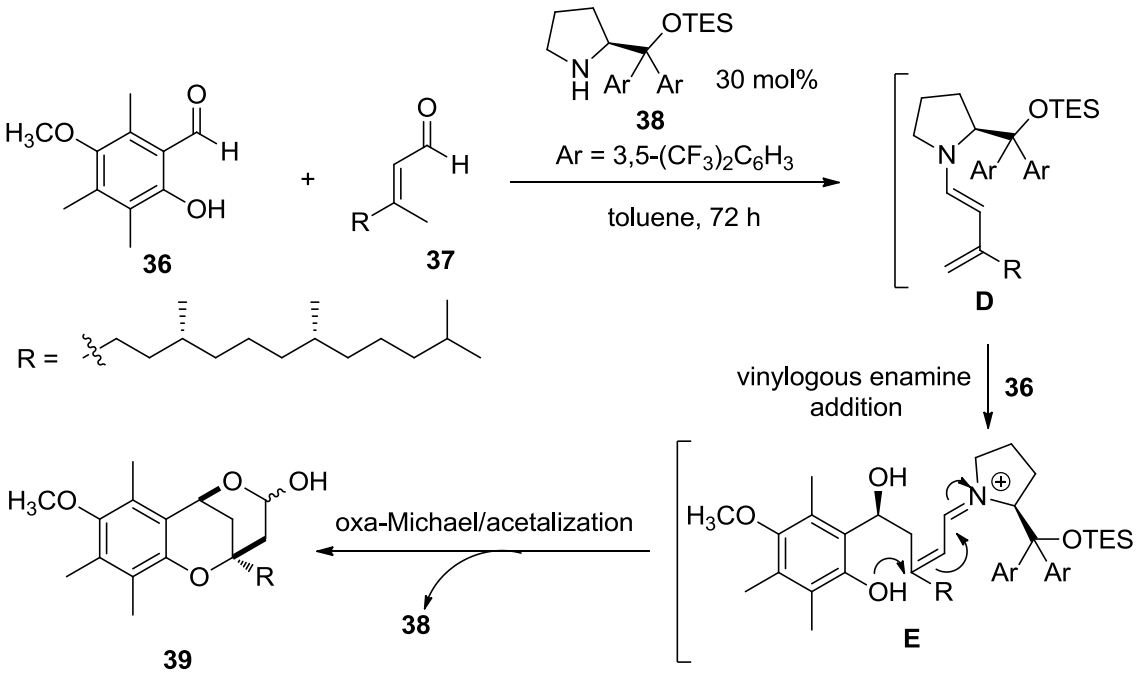
Bräse and[18] reported the ODVA reaction of 3-(2-methyl
senecial3l)-2-methylbenzaldehyde using DABCO (Scheme 1). The reaction
hemial3)4was obtained in moderate yield of 38after 7 days. The γ-substituted
methyl group followed by the vinylogous a
salicyl3a2A)dehyde and 4-methylcyclohexanone
by in turlaamrolactone (Figure 34.). Optimization of the re
revealed that stoichiometric amounts of 35are not necessary since product
use of triethylamine34 as the base provided the product.

h y d r o x y e b h e y n d z e a s l d w e r e c o o m t v h e r t t e r d i c e y 3 i t (t l i e 2 x r a m t p h l i e a s c , e
u p t o 6 1 % c y h i r e o l m 3 5) (n a e o x r a m t p h l e e s , u p t o 8 1 % y i e l d)



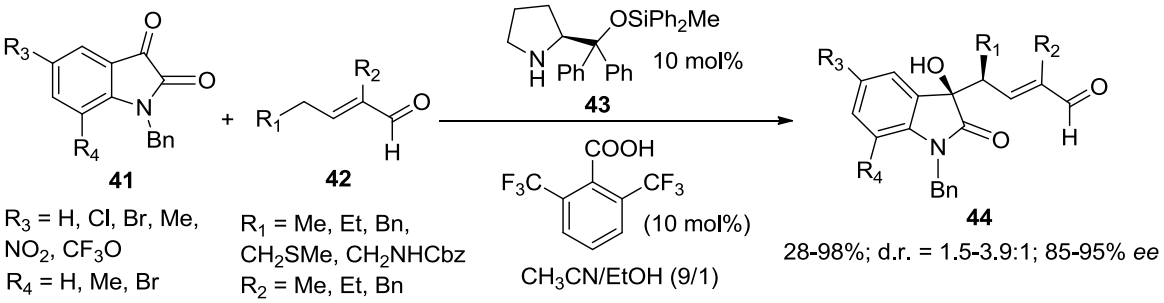
S c h e m e . 1 T h 1 e 1 b a s e p r o m o t e d v i n y l o g o u s a l d c

I n a r e l a t e d [19] S e t x u a d m y i , n e W d o g t g h o e n c h i r a l p y r r o l i
a l d o l r e a c t i $\alpha\beta$ r u n o s f a t a u m r a a t l e i d p h a a l t d i e c h y d e a n d t h i s
t h e s y n α - t h o e c s o i p s h e o r f o l . R e 3 a 6 v i t i o n p 3 7 h a m t h e e h y p d r e s e
o f a d i a r y l 3 8 g o e h i e r m a l t e d a t t a r l i 3 c 9 s y h t c r l o i u c g h h e a n i s a e c r e i t e a s
s u c h a s i m i n i u m i o n f o r m a t i o n , x v i n y l o g o u s
a d d i t i o n s a t r i d o n a (S t c h e m e 1 . 1 2) .



Scheme. 1A 1v2inylogo3us aldol route t

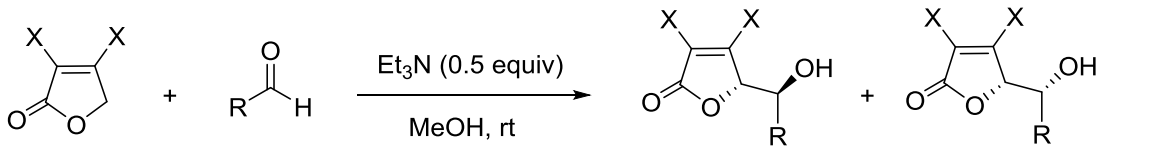
Recently,[20] Me pochtied re the OD-VA b sreteiaptcuttieodn unsaturated aldehydes with isatsiumbsst(i-Stcuhteemde hydroxyoxindo4l4widtehr igyaodvesstereocontrol. No proceeded wi-steHevcetriywitiygh



Scheme. 1T.h1e3 ODVAα-breanctchied enfals with is

1.2 ODVA reaction of cyclic dienes

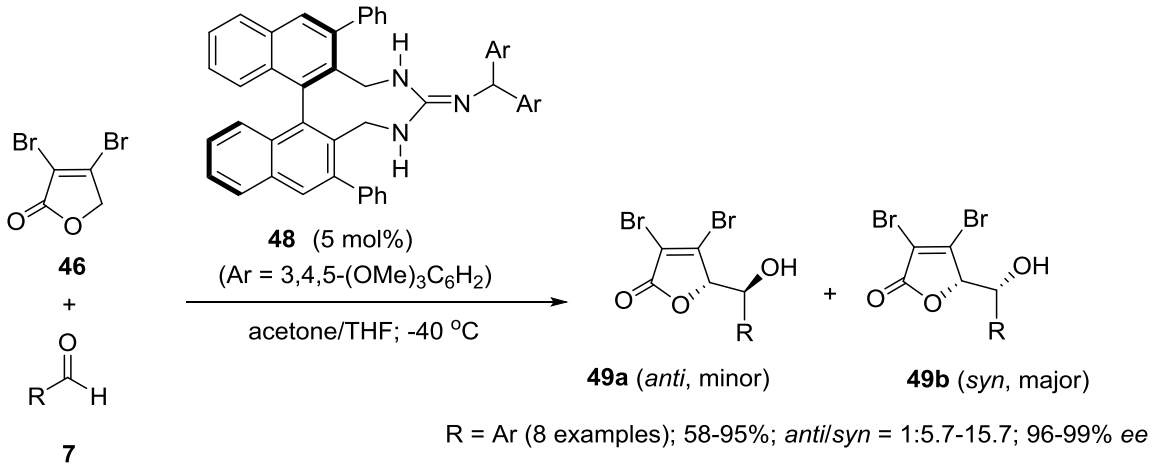
In the α,β-unsaturated carbonyl compounds s
dienolate protonation with mild acid the low acidity
γ-hydrogen atoms. However, the γ-carbon (or dienolate)
readily deprotonated, as in the this generates
As a result, there are usually two ODVA adducts
The first example of an ODVA of unsubstituted
and-workup[21]. Arsf.ew aromatic aldehydes were teste
DABCO to obtain the vinylogous Zest and[22] workup
the vinylogous aldol 45 and 46 in moderate to fair
(Scheme 1.14). Several aldehydes were examined in
reactions were found to be



Scheme 1.14 Triethylamine catalyzed ODVA

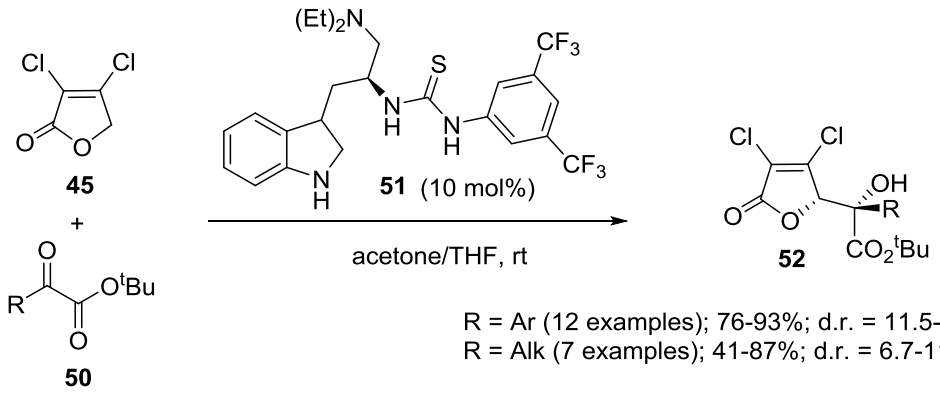
Terada and[23] developed a new class of chi
axially chiral, biaryl-2-ols (DAVN)

reac.Tihos was the fDVArte aecntainotni oosfe lhea4t5 gyeen at an4d6Variousatypelwyedreesf examined to aff4o9rbd the with upee(tSch9e9m%)el t1 .w1a5s also found4 6(tXhBa=t) dibr provides beatntde rendainatsitoesreeloectivity than the



Scheme. 1T.h1e5 ODVA reaction c4a8lyzed by

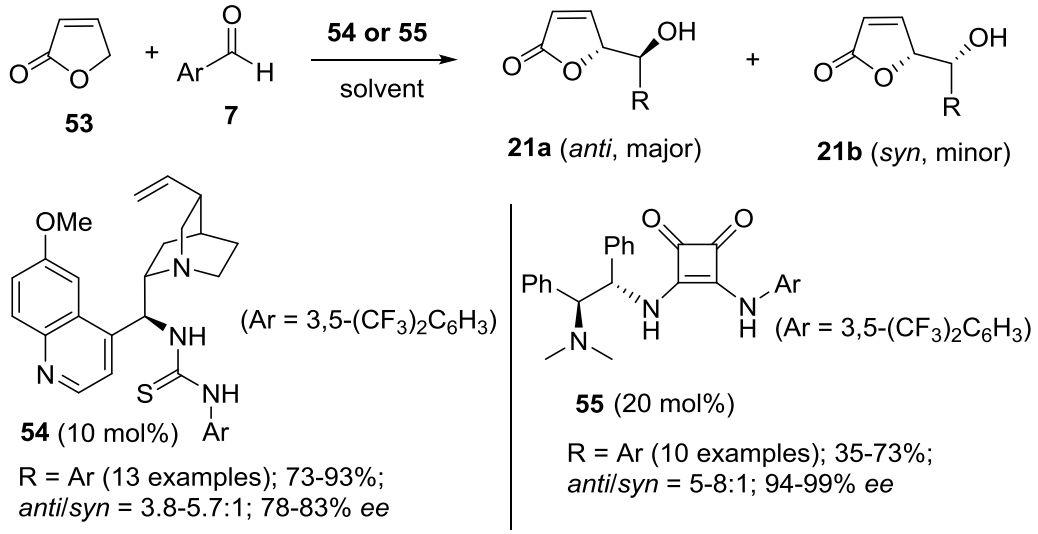
Recentely,[24] arepported the-ahmidgnaelty iodsiealsetoetrievoe vinylogous aldol reacti4o5nasmodkeemtpoles5Qwtiientrghs dtihoeh l tryptobeprhiavnied bifunct5i1o(nSacthemoeg a1nd1 6a)tallytstwas aromatic aldehydes exhibit better stereose method was also exten4d6ed to the dibromofur



Scheme 1.16 ODVA reaction-derivatized by Terada

It should be noted that the Terada gua
applicable in reactions with carbonyl compounds as the
nucleophile, since the 5d3 esonance of the
addition, the derivatized catalyst was found to be an
nucleophile (Scheme 1.16).

The first examples of ODVA reactions employ
crotonolactone were reported by Feringa and
derived from myrtenal, cyclohexanediamine and c
diamines were studied. Optimization revealed
amino thiourea 54 to be the catalyst of choice when t
diethyl ether (Scheme 1.17). Several aromatic
to provide the adduct as the major product (3 with a
5.7:1) and enantioselectivity (78

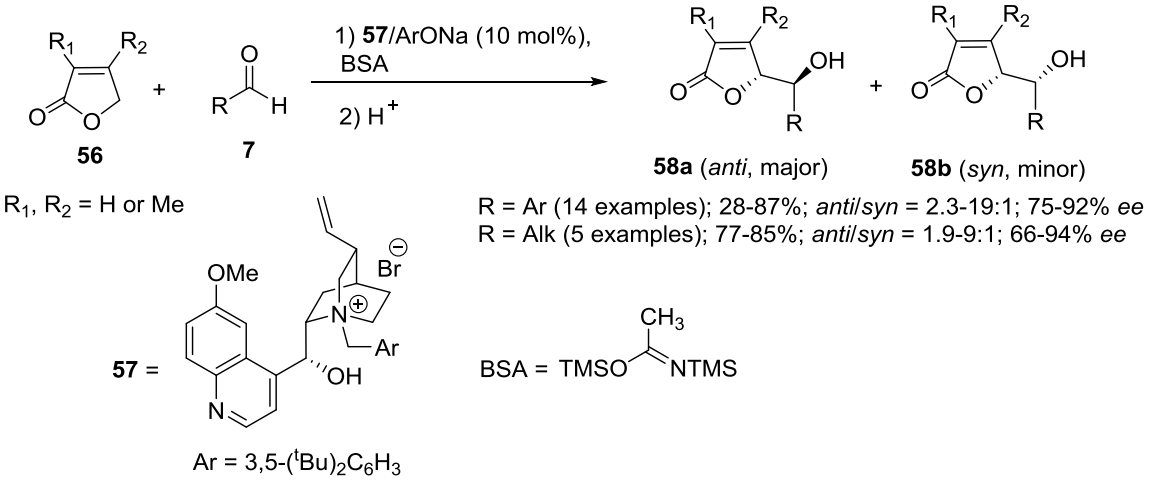


Scheme 1.10. ODVA reaction catalyzed by thio

Simultaneous with the Feng's study,[26] the a
reaction of lactone with various aromatic
various thiourea and squaramide catalysts
result. Overall, good diastereoselectivities
>99% ee) were obtained. The application
of this method.

Very recently, Ye and co-workers[27] reported the first enantioselective ODVA r
of H)-furan-2-ones (5) with aldehydes (Scheme 1.11). The N,O-chiral
ammonium amide obtained from the
bis(trimethylsilyl)
diastereoselectivities and enantioselectivities

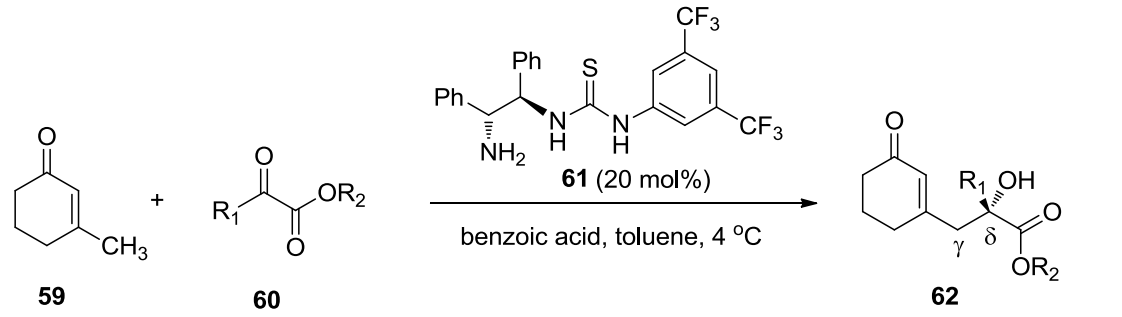
19:1-9, 2 examples, as well as the aliphatic 9:1-19:1 dr were observed. good.



Scheme 1.18 ODVA reaction catalyzed by the ammonium salt of (*S*)-*N*-(9-anthracenylmethyl)-*O*-(trimethylsilyl)-*N*-(trimethylsilyl)acetamide.

In a recent report,[28] we examined 2-methyl-2-OIDVA cyclohexenone with α-keto esters (Scheme 1.19). catalysts derived from cinchona alkaloid based diamines were studied. O diphenylethylene diamine was the best catalyst of aromatic as well as aliphatic aldehydes enantioselectivity (4 examples). It should be noted that the enolate is the nucleophile in this reaction contiguous (at the α and β positions) tertiary stereocenters

unsuccessful. Linear aldehydes were found to be a c
conditions.

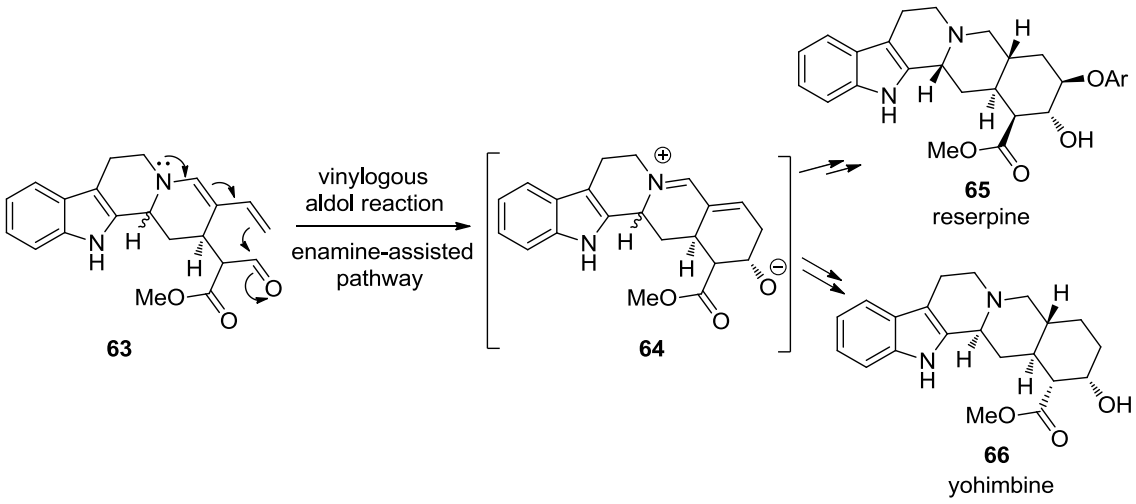


Scheme 1. The 1,9 ODVA reaction and initial synthetic

1.3 Applications of ODVA r

One of the main focuses in modern orga
efficient synthetic protocols that allow
construction of natural products with
reaction of α,β-unsaturated carbonyls to
unsaturated carbonyls. These functional a
synthesis of enantiomerically pure
of polyketides. The isoprenoids provided the impetus
stereoselective, catalytic vinylogous aldo
OVMA reactions, much effort has been directed
total synthesis of natural products to dem

In natural product synthesis, vinylogous aldol reactions are used to construct complex architectures in the forms of alkaloids. Biogenetic pathways to the pentacyclic indole alkaloids reserpine (**65**) and yohimbine (**66**) have been proposed to involve vinylogous aldol reactions.[29] In these proposed biogenetic pathways, the vinylogous aldol reaction of **63** can undergo an enamine assisted vinylogous aldol reaction to form **64**, which undergoes functional group transformations to form reserpine (**65**) and yohimbine (**66**) (Scheme 1.20).



Scheme 1.20 Proposed biogenetic synthesis of yohimbine and reserpine

The organocatalytic vinylogous aldol reaction is of interest because the reaction products, γ-butenolides, contain important structural motifs in several natural products. γ-Butenolide derivatives are potential intermediates for the synthesis of pure, functionalized polyhydroxylated pyran derivatives.

The DVA reaction of lactones with the substituted hydrocarbon substance P receptor (NK1R) antagonists, which have been associated with a variety of biological activities including neurogenic inflammation, and pain. Thus, the synthetic methodology is useful for the synthesis of a component of an antagonist. The results of this work are presented in Chapter 3.

Chapter 4 will describe a total synthesis of (+)-febrifugine and (−)-isofebrifugine, which are the active components of a traditional Chinese medicine for the treatment of malaria. The synthesis employs the organocatalytic direct vinylogous Mannich reaction. As such, the synthesis is a slightly modified version of the one described in Chapter 2. The contributions of all authors are explained

1.4 References

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9) De RMsTaa,loCt.Si;ar,iAe.Ot,Che.2n0,69 301

10De RMsCai,tLr.S;oriAeTeerahLed2n0,467 8.507

11Cafe GoDe RMskohnKe,SHor;iAn.T,æl,oCt.Va,leLn.ti,
Molec2u0l,e94s 2.594

12Nagaho Y;amaYneM,„ukaiyTaCmhae,me.2n0,376 . 8

13Sinkgh,FPox;mBan,DMen,LgJ.AmChe.Sno.2n,1103,2 9.558

14Zhu„M;aB,–C.Z;hanYgW,anWg,Ad.Syn Ctat.2a0,1305,2291

15Vil lRa.A;ooc,eMl lRas,saS,ceAtTreit,rah2e0,695n5.571

16Chan, T. H.; J.BheSmo.Cm,heGmm.1P9,7957 8

17Rat LeGa,á-Gaá,P.L;ayF„B;ecMk., EiSt A,ng.Cwhe,mn t
Ed2n,1507 5.4

18(a) Lesch, B.; ToränBr,äAsdeSy,nSCtahnt.2e0,5eide,
34,7 5(5)5; Lesch, B.; ToränSy,ntJ.2e0,5Nsie8g8e.r, M

19Liu, K.; ChugneDA,nAg.eCwhe,mnEtd2o0n,487,W5827.

20Melchiorre, OP.Ju.e,2C0a1,24s5i5,9C.

21Sudhan,K;undMu., KRed,dPy., MWah,enGd.rBah,aSt., SVy.nth
Comm.u2n0,322, 1.881

22Das SkaZ,mhaa,dC,urTa.nJ,Dr.Che.2n0,772, 3.311

23Ube„S;himNdTae,rMd.An,g.Cwhe,mnEtd2n,1409, 1.858

24Lud,W;ankd;HanX,.X;uL,–W.K;wiatkJ.Ws,kaiKgW,.L;uY,.
Ang.Cwhe,mnEtd2n,1510, 1.861

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CHAPTER 2

Organocatalytic Asymmetric Direct Vinylogous Aldol Reactions of γ-Crotonolactone with Aromatic Aldehydes

This Chapter is based on the following publication:

Pansare, S. V.; Paul, E. K. **hem** **m** **2011,n** , 1027-1029.

Contributions of authors

S. V. Pansare: research supervisor, manuscript preparation.

E. K. Paul: experimental work, manuscript preparation.

2.1 Introduction

The functionalized γ-butenolide (2(5**H**)-furanone) motif is found in several natural products and the synthesis of butenolides has therefore attracted considerable interest in recent years.[1] A popular approach to 5-substituted furanones involves the vinylogous Mukaiyama aldol reaction of silyloxyfurans[2] (Figure 2.1), and a number of asymmetric modifications of this reaction are known.[2f-n] In contrast, the alternative approach involving a direct vinylogous aldol reaction of furanones is less explored,[3] and asymmetric variants of this reaction employing chiral guanidine, aminothiourea and chiral ammonium amide as catalysts are reported.[4] A detailed account of these studies is provided in Chapter 1.

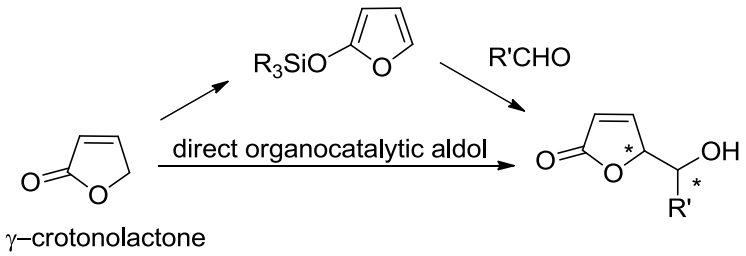


Figure 2.1. Direct aldol approach to butenolides.

The chiral guanidine-based system[4a] requires halolactones, and fails when crotonolactone is used as the substrate. The aminothiourea mediated reaction requires a fourfold excess of the nucleophile[4b] and there is scope for improvement of the stereoselectivity.[4b,c] Evidently, a catalytic system that addresses these issues would be desirable. The following sections describe our findings on the asymmetric, direct

vinylogous aldol reaction of crotonolactone with aromatic aldehydes mediated by aminothiourea and aminosquaramide catalysts.

2.2 Results and Discussions

We initially examined several classes of bifunctional, amine catalysts for the direct aldol reaction of crotonolactone: (a) cyclohexanediamine,[5a] diphenylethylenediamine,[5b] cinchonidine[5c,d] and cinchonine[5e,f] derived thioureas (**1, 2, 3** and **4**), (b) cyclohexanediamine and diphenylethylenediamine derived squaramides (**5, 6**)[5g-i] and (c) a proline-derived thiourea catalyst (**7**, Figure 2.2).

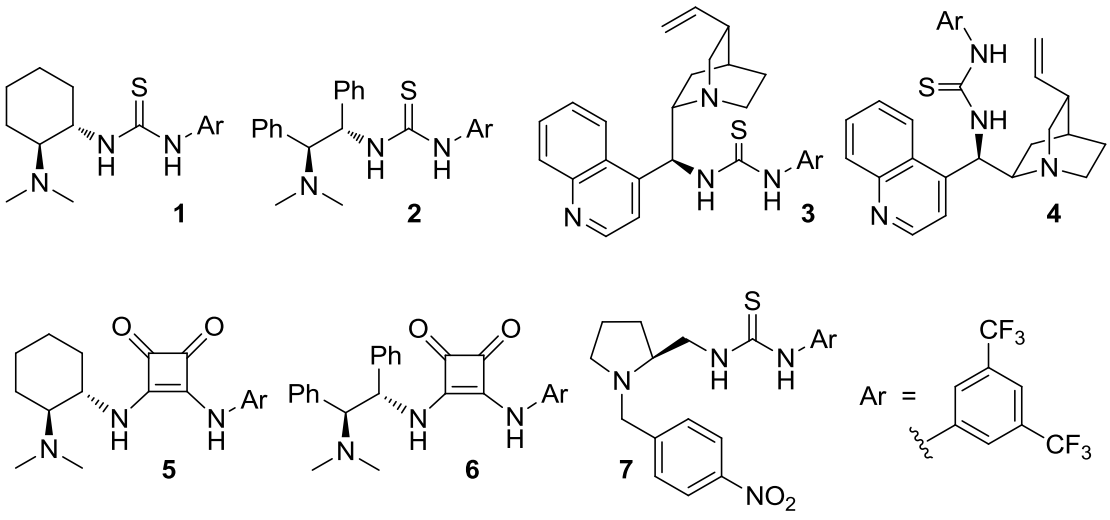
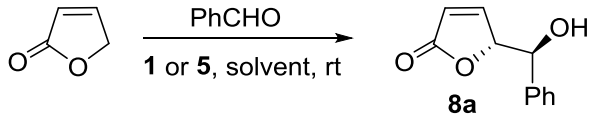


Figure 2.2. Bifunctional catalysts examined for the direct vinylogous aldol reaction of crotonolactone.

Orienting experiments were conducted with crotonolactone and benzaldehyde. Initially, the aldol reaction was examined with catalysts **1** and **5** in a variety of

solvents (Table 2.1).



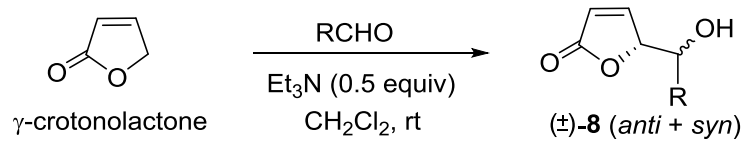
Entry[a]	Cat[b]	Solvent	t/h	Yield (%)	dr[c] (*anti/syn*)	ee[d] (%) (*anti*)
1	**1**	CH_2Cl_2	84	65	3.0/1	79
2	**1**	THF	84	78	5.8/1	76
3	**1**	toluene	84	89	1.0/1	78
4	**1**	EtOAc	84	72	3.2/1	72
5	**1**	$CHCl_3$	84	78	3.0/1	70
6	**1**	MeOH	84	81	2.6/1	40
7	**1**	DMF	84	63	3.6/1	45
8	**5**	CH_2Cl_2	12	88	2.0/1	49
9	**5**	THF	12	89	2.6/1	67
10	**5**	CH_2Cl_2[e]	168	76	5.3/1	94
11	**5**	THF[e]	168	92	5.0/1	90
12	**5**	$CHCl_3$[e]	168	98	5.9/1	91
13	**5**	toluene[e]	168	46	6.7/1	93
14	**5**	EtOAc[e]	168	32	5.6/1	96
15	**5**	DMF[e]	168	65	3.3/1	89
16	**5**	CH_3CN[e]	168	35	4.5/1	93

[a] 2 equiv. of crotonolactone. 20 mol%. Determined by ^{1}H NMR analysis of crude products. Chiral HPLC analysis. [e] Reaction at 0 ^{o}C.

Table 2.1. Solvent survey for the vinylogous aldol reaction of crotonolactone.

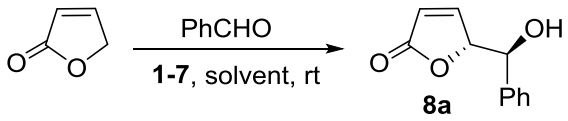
The reaction proceeded smoothly in most of the solvents examined (Table 2.1), and the expected aldol product **8a** was obtained as a mixture of *anti* and *syn* diastereomers, with the *anti* product predominating. Stereochemical assignments are based on the reported ^{1}H NMR data and the trend in chemical shifts for the *anti* and *syn* diastereomers of **8**.[2c] Overall, catalyst **1** provided moderate to good enantioselectivities for the *anti* product, except in methanol and DMF (entries 6 and 7, Table 2.1). Dichloromethane, THF and toluene emerged as promising solvents, when catalyst **1** was used, in terms of enantioselectivity, but the complete lack of diastereoselectivity in toluene precluded further studies in this solvent (entry 3, Table 2.1). At room temperature, **5** provided the aldol product **8a** with poor enantio- and diastereoselectivities in dichloromethane and THF as solvents (entries 8 and 9, Table 2.1). Much better results were obtained with **5** at 0 ^{o}C (entries 10-16, Table 2.1). Overall, good diastereoselectivities (3.3-6.7:1) and excellent enantioselectivities (89-96% *ee*) were obtained in most of the solvents for catalyst **5** at 0 ^{o}C. Low yields were obtained in ethyl acetate (32%) and acetonitrile (35%) (entries 14 and 16, Table 2.1), as solvents. From these studies, dichloromethane and THF emerged as promising solvents for further investigations.

The enantiomeric excess of **8a-l** was determined by chiral HPLC comparison with racemic samples. The racemic products in this study were prepared by adapting the triethylamine catalyzed reaction of dihalofuranones with aldehydes (Scheme 2.1).[3a]



Scheme 2.1. The triethylamine catalyzed reaction of γ-crotonolactone with aldehydes.

Subsequent studies, aimed at identifying the optimal catalyst, were therefore conducted in dichloromethane and THF. The results obtained from the catalyst survey are summarized in Table 2.2. The diphenylethylenediamine-thiourea catalyst (**2**) provided **8a** in relatively low yield and moderate enantioselectivity. In comparison, the cinchonidine and cinchonine based catalysts (**3** and **4**, respectively) generated **8a** in excellent yields, but the stereoselectivity was low (de: 1.8-4.8/1, **ee**: 50-71%). Much better results were obtained with the squaramide catalyst **5** in dichloromethane and THF at 0 ^{o}C (Table 2.2, entries 9 and 10, 94 and 91% **ee**). In comparison, the diphenylethylenediamine squaramide catalyst **6** was superior to **5** (Table 2.2, entries 11 and 12, 97 and 96% **ee**). At ambient temperature, **6** provided **8a** in excellent enantiomeric excess (97% **ee**) and good diastereoselectivity (7/1) in dichloromethane. Thus, two optimal catalytic systems, providing the ***anti*** diastereomer in greater than 90% **ee**, were identified from the catalyst and solvent survey, namely (a) the cyclohexanediamine squaramide catalyst **5** in dichloromethane at 0 ^{o}C (entry 9) and (b) the diphenylethylenediamine squaramide catalyst **6** in dichloromethane at ambient temperature (entry 11, Table 2.2).



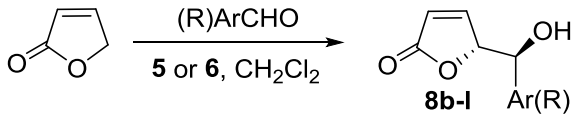
Entry[a]	Cat[b]	Solvent	T/h	Yield (%)	dr[c] (*anti/syn*)	ee[d] (%) (*anti*)
1	**1**	CH_2Cl_2	84	65	3/1	79
2	**1**	THF	84	78	5.8/1	76
3	**2**	CH_2Cl_2	96	32	6.7/1	77
4	**2**	THF	84	33	10/1	75
5	**3**	CH_2Cl_2	24	95	3.7/1	64
6	**3**	THF	48	95	2/1	50
7	**4**	CH_2Cl_2	24	98	1.8/1	65[e]
8	**4**	THF	48	95	4.8/1	71[e]
9	**5**	CH_2Cl_2	168	76	5.3/1	94
10	**5**	THF	84	46	4.3/1	91
11	**6**	CH_2Cl_2	120	35	7/1	97
12	**6**	THF	120	31	7/1	96
13	**7**	CH_2Cl_2	144	24	3.6/1	14
14	**7**	THF	144	25	4.5/1	14

[a] 2 equiv. of crotonolactone. 20 mol%. Determined by ^{1}H NMR analysis of crude products. Chiral HPLC analysis. [e] enantiomeric product. Reaction at 0 ^{o}C

Table 2.2. Catalyst survey for the vinylogous aldol reaction of crotonolactone.

The optimized conditions were employed in a study of the scope of the reaction with a variety of aldehydes. These investigations indicated that the choice of

catalyst **5** or **6** is determined by the nature of the aldehyde, and high enantioselectivities are obtained by proper pairing of the catalyst and aldehyde. Nonetheless, for most of the reactions, the diphenylethylenediamine derived catalyst **6** provided higher enantioselectivities than **5**. All isomers of methoxybenzaldehyde (entries 3-5, Table 2.3) provide high enantioselectivity. The diastereoselectivity for all of the reactions is moderate.[7] Overall, the level of stereoselection (average dr = 6/1, average **ee** = 94%) is higher than that obtained with cinchona alkaloid-thiourea catalysts.[4b] The aldol products **8a-l** exhibited spectral data in agreement with literature reports.[2,4] The results of these studies are summarized in Table 2.3.



Entry[a]	8	R	Cat[b]	Yield (%)[c]	dr[d] *(anti/syn)*	ee[e]% *anti (syn)*
1	b	4-MeC_6H_4	6	51	8/1	95 (32)
2	c	4-BrC_6H_4	6	62	8/1	95 (55)
3	d	4-$MeOC_6H_4$	6	35	8/1	97 (48)
4	e	2-$MeOC_6H_4$	6	58	8/1	96 (84)
5	f	3-$MeOC_6H_4$	6	54	6/1	96 (72)
6	g	4-ClC_6H_4	5	50	6/1	94 (83)
7	h	4-$NO_2C_6H_4$	6	50	5/1	>99 (50)
8	i	4-$CF_3C_6H_4$	6	60	6/1	95 (nd)
9	j	2-Naphthyl	6	73	6/1	95 (>99)
10	k	Cyclohexyl	5	50	3/1	>99 (>99)
11	l	1-Naphthyl	6	68	2/1	77 (80)

[a] 2 equiv of crotonolactone; 20 mol%. 144 h at 0 °C for **5** and 240 h at rt for **6**; [1]H NMR of crude products. [e] Chiral HPLC analysis.

Table 2.3. Vinylogous aldol reaction of crotonolactone with various aldehydes.

The stereochemical outcome of the reaction is presumably governed by hydrogen bonding[8] of the aldehyde with the squaramide[5g-j] functionality and an ionic interaction of the deprotonated nucleophile and the resultant ammonium group in the catalyst (Figure 2.3). We have observed that the triethylamine catalyzed reaction of

crotonolactone with aldehydes (used for the preparation of racemic products in this study) has an intrinsic preference for the **anti** diastereomer (dr = ~2/1). The present results suggest that the hydrogen bonding functionality in the catalyst enhances this diastereoselectivity.

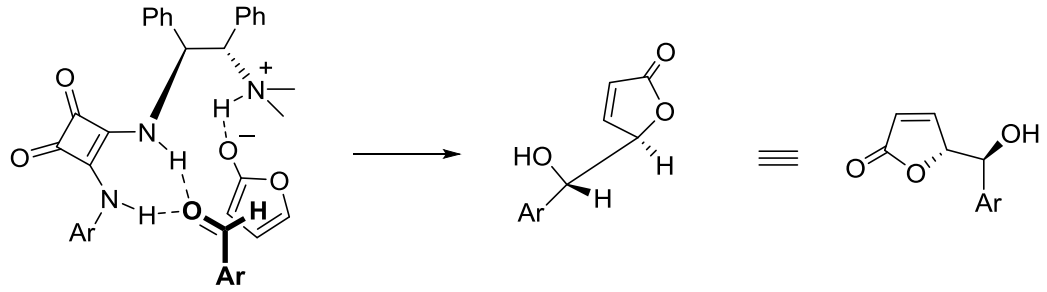
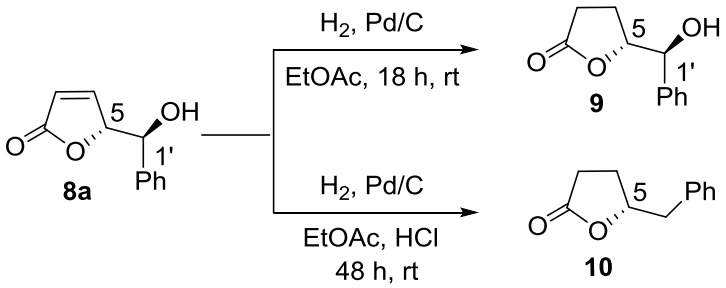


Figure 2.3. A proposed transition state assembly for the ODVA reaction leading to the **anti** aldol product.

2.2.1 Determination of the absolute configuration of 8a

Hydrogenation (Pd/C) of aldol product **8a** in ethyl acetate provided **9** (Scheme 2.2) which was dextrorotatory ($[\alpha]^{23}_D$ = +50.7 (= 1.0, $CHCl_3$), 88% **ee**). The positive rotation indicates that lactone **9** is enantiomeric to the previously reported[2g] (5**S**,1') isomer ($[\alpha]^{25}_D$ = -53.3 (= 0.22, $CHCl_3$) for **9** with 92% **ee**). Hydrogenation of **8a** in the presence of HCl, by adaptation of the literature procedure,[4a] provided **10** (Scheme 2.2) which was assigned the configuration on the basis of chiral HPLC retention times[7] (Chiralcel OD-H, hexanes/2-propanol 80/20, 1 mL/min, 214 nm, $_S$ = 5.95 min, $_R$ = 6.74

min). Lactone **9** is therefore assigned the (5 ,1'**S**) configuration, and compounds **8a-l** are also assigned the (5 ,1'**S**) configuration by analogy.



Scheme 2.2. Hydrogenation and hydrogenolysis of aldol product.

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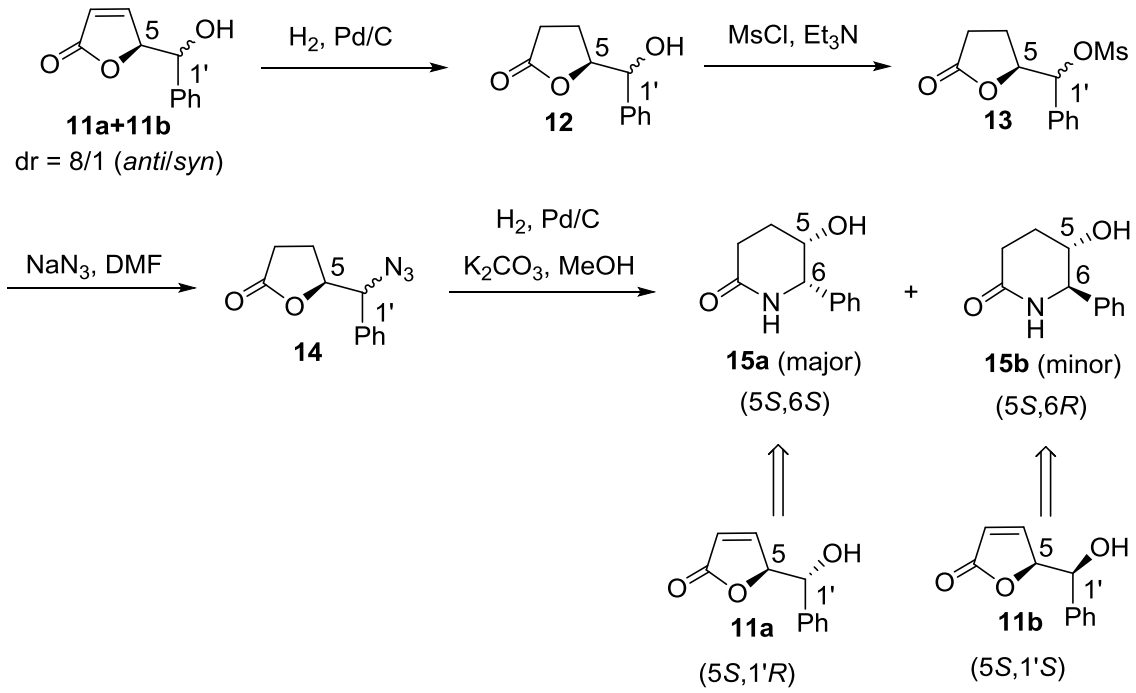
It was also shown that the aldol products **11a** and **11b** are diastereomeric at C-1', and not at C-5, by converting the aldol products **11a** and **11b** into lactam **15a** and **15b** via a series of simple transformations (Scheme 2.3). Hydrogenation of **11** (8/1 mixture of **11a**/**11b**) to the butyrolactone **12**, subsequent mesylation of the secondary alcohol to give **13** and displacement of the mesylate, with inversion of configuration, by azide anion gave the azido butyrolactone **14**. Reduction of the azide (H_2, Pd/C), in the presence of a base (K_2CO_3), generated the required piperidones **15a** and **15b**. At this stage, **15a** (**i** isomer) was easily separated from the minor **15b** (**a**isomer) by flash column chromatography. The optical rotation of **15a** (**i** isomer) was consistent with that reported for the (5**S**,6**S**) isomer in the literature ($[\alpha]_D^{23}$ = +55.3 (= 1.1, CH_2Cl_2), 97% **ee**; lit. $[\alpha]_D^{25}$ = +52.0 (= 1.1, CH_2Cl_2),[8] for a 99% **ee** sample). The optical rotation of the **15b** (**a**isomer) was opposite to that reported for the (5 ,6**S**) isomer in the literature ($[\alpha]_D^{23}$ = +26.0 (1.0 , MeOH), 96% **ee**; lit. $[\alpha]_D^{20}$ = –25.9 (= 0.27, MeOH),[9] for a 92% **ee** sample). Therefore, **15b** is assigned the (5**S**,6) absolute configuration. These

observations indicate that **15b** is obtained from the (5**S**,1'**S**) isomer of **11b** which is diastereomeric to **11a** at C-1'. The aldol reaction therefore generates aldol products which are diastereomeric at the secondary alcohol stereocenter.



Scheme 2.3. Conversion of aldol product into lactam.

2.3 Conclusions

In conclusion, a highly enantioselective, catalytic aldol reaction of crotonolactone with aldehydes was developed. A notable outcome of this study is the superior performance of the squaramide catalysts over the conventional aminothiourea catalysts.

2.4 Experimental section

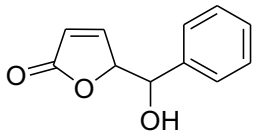
General: All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

General Procedure for the organocatalytic direct vinylogous aldol reaction:

To the catalyst (0.10 mmol, in a 2.0 mL Reacti-Vial™ or a standard 3.0 mL vial) was added the aldehyde (0.50 mmol) followed by γ-crotonolactone (2-(5**H**)-furanone) (1.0 mmol) and dichloromethane (0.50 mL). The suspension was stirred for 10 d at room temperature (for catalyst **6**) or kept for 7 d at 0 ^{o}C with occassional shaking (for catalyst **5**). The mixture was then diluted with ethyl acetate (1.0 mL) and aqueous HCl (2 N) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10/1). The diastereomeric composition (**an** / **i**) **n**was determined by ^{1}H NMR analysis of the crude product. The enantiomeric excess was determined by HPLC (Chiralpak AD-H or AS-H column, flow

rate 1.0 mL/min, UV detection at 210 or 254 nm) by comparison with reported retention times[4b] for compounds **8a-l,** and also by comparison with racemic standards (prepared by using triethylamine as the catalyst) for compounds **8h, 8i** and **8l**. The absolute configuration of **8a** was assigned by correlation. Absolute configurations of **8b-l** are assigned by analogy within the series.

5-[Hydroxy(phenyl)methyl]furan-2(5*H*)-one (8a):

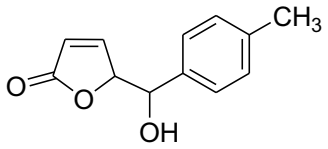


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with benzaldehyde (53 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 34 mg (35%) of **8a** as a white solid.

IR: 3432, 1728, 1167, 1039, 820 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.43-7.34 (m, 6H, Ar**H** and COCH=C**H**), 6.19 (dd, 1H, = 5.8, 1.9 Hz, COC**H**=CH), 5.19-5.18 (br m, 1H, CH=CHC**H**), 5.09 (br t, 1H, = 4.1 Hz, ArC**H**OH), 2.25 (d, 1H, = 3.8 Hz, O**H**); ***Syn* diastereomer:** δ 7.42-7.36 (m, 5H, Ar**H**), 7.17 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 6.13 (dd, 1H, = 5.8, 2.0 Hz, COC**H**=CH), 5.17 (apparent dt, 1H, = 7.0, 1.5 Hz, CH=CHC**H**), 4.71 (d, 1H, = 7.0 Hz, ArC**H**OH), 2.78 (s, 1H, O**H**); MS (APCI pos.): **m** 191.0 (M+1).

HPLC: Chiralpak AS-H, hexanes/2-propanol 90/10, 254 nm, $_1$ = 27.8 min (major **an**),**i** $_2$ = 36.2 min, ( ),**n**$_3$ = 49.6 min ( ),**n**$_4$ = 66.8 min (minor **an**).**i**Ee: 97% (**an**).**i**

5-[Hydroxy(*p*-tolyl)methyl]furan-2(5*H*)-one (8b):

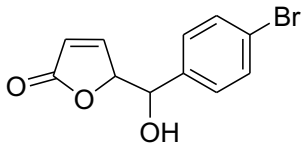


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 4-methylbenzaldehyde (59 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 52 mg (51%) of **8b** as a white solid.

IR: 3401, 1736, 1325, 1170, 1102, 1079, 1039, 917, 877 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.36 (dd, 1H, = 5.8, 1.4 Hz, COCH=C**H**), 7.28 (d, 2H, = 8.0 Hz, Ar**H**), 7.22 (d, 2H, = 8.0 Hz, Ar**H**, ortho to CH_3), 6.18 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.17-5.15 (m, 1H, CH=CHC**H**), 5.04 (br t, 1H, = 4.0 Hz, ArC**H**OH), 2.37 (3H, C**H**$_3$), 2.22 (d, 1H, = 4.0 Hz, O**H**), 2.37 (3H, C**H**$_3$); ***Syn* diastereomer:** δ 7.28 (d, 2H, = 8.0 Hz, Ar**H**), 7.22 (d, 2H, = 8.0 Hz, ortho to CH_3), 7.16 (dd, 1H, = 5.8, 1.6 Hz, COCH=C**H**), 6.13 (dd, 1H, = 5.8, 2.0 Hz, COC**H**=CH), 5.15-5.17 (m, 1H, CH=CHC**H**), 4.66 (dd, 1H, = 6.9, 3.0 Hz, ArC**H**OH), 2.58 (d, 1H, = 3.0 Hz, O**H**), 2.37 (3H, C**H**$_3$); MS (APCI pos.): **m** 205.0 (M+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 95/5, 254 nm, $_1$ = 20.0 min (major **an**),**i** $_2$ = 22.2 min, (minor **an**),**i** $_3$ = 26.8 min (minor),**n**$_4$ = 29.0 min (major).**m**Ee: 95% (**an**).**i**

5-[Hydroxy(4-bromophenyl)methyl]furan-2(5*H*)-one (8c):

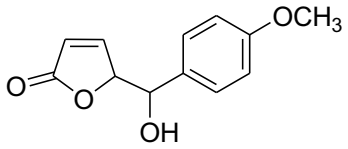


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 4-bromobenzaldehyde (93 mg, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 83 mg (62%) of **8c** as a white solid.

IR: 3343, 1742, 1486, 1399, 1191, 1176, 1095, 1074, 1041, 1008, 917, 880, 831, 808 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.55 (d, 2H, = 8.4 Hz, Ar**H**, ortho to Br), 7.32 (dd, 1H, = 5.8, 1.4 Hz, COCH=C**H**), 7.29 (d, 2H, = 8.5 Hz, Ar**H**), 6.19 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.15-5.13 (m, 1H, CH=CHC**H**), 5.04 (t, 1H, = 4.0 Hz, ArC**H**OH), 2.48 (d, 1H, = 4.0 Hz, O**H**); ***Syn* diastereomer:** δ 7.55 (d, 2H, = 8.4 Hz, Ar**H**, ortho to Br), 7.29 (d, 2H, = 8.4 Hz), 7.20 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 6.14 (dd, 1H, = 5.8, 2.0 Hz, COC**H**=CH), 5.15-5.13 (m, 1H, CH=CHC**H**), 4.73 (dd, 1H, = 6.7, 3.3 Hz, ArC**H**OH), 2.73 (d, 1H, = 3.3 Hz, O**H**); MS (APCI pos.): **m** 269.1 (M^+).

HPLC: Chiralpak AD-H, hexanes/2-propanol 88/12, 254 nm, $_1$ = 9.6 min (major **an**),**i** $_2$ = 10.4 min (minor),**n**$_3$ = 10.8 min (minor **an**),**i** $_4$ = 11.6 min (major).**n**Ee: 95% (**an**).**i**

5-[Hydroxy(4-methoxyphenyl)methyl]furan-2(5*H*)-one (8d):

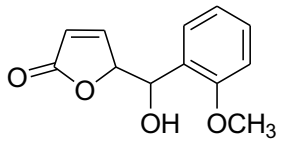


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 4-methoxybenzaldehyde (63 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 39 mg (35%) of **8d** as a white solid.

IR: 3357, 1742, 1585, 1510, 1242, 1171, 1101, 1085, 1029, 1008, 877, 827, 814 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.39 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 7.32 (d, 2H, = 8.7 Hz, Ar**H**), 6.93 (d, 2H, = 8.7 Hz, ortho to OCH_3), 6.18 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.15-5.14 (m, 1H, CH=CHC**H**), 5.0 (t, 1H, = 4.0 Hz, ArC**H**OH), 3.82 (s, 3H, OC**H**$_3$), 2.26 (d, 1H, = 4.0 Hz, O**H**); ***Syn* diastereomer:** δ 7.32 (d, 2H, = 8.7 Hz, Ar**H**), 7.16 (dd, 1H, = 5.8, 1.6 Hz, COCH=C**H**), 6.93 (d, 2H, = 8.7 Hz, ortho to OCH_3), 6.13 (dd, 1H, = 5.8, 2.1 Hz, COC**H**=CH), 5.15-5.14 (m, 1H, CH=CHC**H**), 4.65 (dd, 1H, = 7.1, 3.0 Hz, ArC**H**OH), 3.82 (s, 3H, OC**H**$_3$), 2.61 (d, 1H, = 3.0 Hz, O**H**); MS (APCI pos.): **m** 221.0 (M+1), 203.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 90/10, 254 nm, $_1$ = 15.1 min (major **an**),**i** $_2$ = 17.7 min, (minor **an**),**i** $_3$ = 19.0 min (minor),**n** $_4$ = 20.7 min (major).**n**Ee: 97% (**an**).**i**

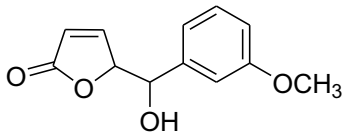
5-[Hydroxy(2-methoxyphenyl)methyl]furan-2(5*H*)-one (8e):



Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 2-methoxybenzaldehyde (63 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 64 mg (58%) of **8e** as a colorless liquid.

IR: 3418, 1733, 1601, 1491, 1462, 1238, 1160, 1095, 1036, 1022, 816 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.40 (dd, 1H, = 5.8, 1.0, COCH=C**H**), 7.34-7.31 (m, 2H, Ar**H** ortho and para to OCH_3), 7.03 (t, 1 H, = 7.5 Hz, Ar**H**, meta to OCH_3), 6.92 (d, 1H, = 8.3, Ar**H**), 6.15 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.38-5.37 (m, 1H, CH=CHC**H**), 5.31 (t, 1H, = 5.7 Hz, ArC**H**OH), 3.89 (s, 3H, OC**H**$_3$), 2.82 (d, 1H, = 5.7 Hz, O**H**); ***Syn* diastereomer:** δ 7.34-7.31 (m, 2H, Ar**H** ortho and para to OCH_3), 7.18 (dd, 1H, = 5.8, 1.1, COCH=C**H**), 7.03 (t, 1 H, = 7.5 Hz, Ar**H**, meta to OCH_3), 6.92 (d, 1H, = 8.3, Ar**H**), 6.12 (dd, 1H, = 5.8, 2.0 Hz, COC**H**=CH), 5.24-5.23 (br dt, 1H, = 6.6, 1.5, CH=CHC**H**) 5.02 (t, 1H, = 5.7 Hz, ArC**H**OH), 3.85 (s, 3H, OC**H**$_3$), 3.06 (d, 1H, = 5.7 Hz, O**H**); MS (APCI neg.): **m** 219 (M^+); APCI pos. m/z 203.0 ((M-H_2O)+1). HPLC: Chiralpak AD-H, hexanes/2-propanol 85/15, 254, $_1$ = 8.4 min (major **an**),**i** $_2$ = 11.0 min, (minor **an**),**i** $_3$ = 12.9 min (major),**n**$_4$ = 16.3 min (minor).**n**Ee: 96% (**an**).**i**

5-[Hydroxy(3-methoxyphenyl)methyl]furan-2(5*H*)-one (8f):

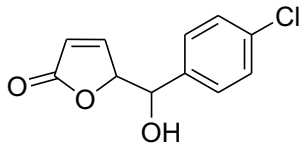


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 3-methoxybenzaldehyde (63 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0. 10 mmol) according to the general procedure provided 60 mg (54%) of **8f** as a colorless liquid.

IR: 3420, 1735,1600, 1585, 1489, 1456, 1435, 1256, 1157, 1034, 825 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.35-7.29 (m, 2H, Ar**H**, COCH=C**H**), 6.97-6.87 (m, 3H, Ar**H**), 6.17 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.18-5.15 (m, 1H, CH=CHC**H**), 5.08 (t, 1H, = 4.0 Hz, ArC**H**OH), 3.82 (s, 3H, OC$\mathbf{H}_3$), 2.73(d, 1H, = 4.0 Hz, O**H**); ***Syn* diastereomer:** δ 7.35-7.29 (m, 1H, Ar**H**), 7.18 (dd, 1H, = 5.8, 1.4 Hz, COCH=C**H**), 6.97-6.87 (m, 3H, Ar**H**), 6.12 (dd, 1H, = 5.8,1.9 Hz, COC**H**=CH), 5.18-5.15 (m, 1H, CH=CHC**H**), 4.68 (dd, 1H, = 7.0, 3.1 Hz, ArC**H**OH), 3.82 (s, 3H, OC$\mathbf{H}_3$), 2.94 (d, 1H, = 3.1 Hz, O**H**); MS (APCI pos.): **m** 221.0 (M+1), 203.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 90/10, 210 nm, $_1$ = 14.2 min (major **an**),**i** $_2$ = 18.3 min, (minor **an**),**i** $_3$ = 20.0 min (minor),**n**$_4$ = 21.4 min (major).**n**Ee: 96% (**an**).**i**

5-[Hydroxy(4-chlorophenyl)methyl]furan-2(5*H*)-one (8g):

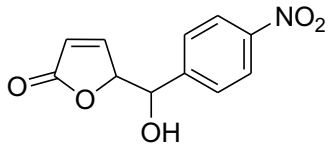


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 4-chlorobenzaldehyde (70 mg, 0.50 mmol) catalyzed by **5** (45 mg, 0.10 mmol) according to the general procedure provided 56 mg (50%) of **8g** as a white solid.

IR: 3420, 1732, 1491, 1175, 1093, 1078, 1042, 917, 852, 812 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.40-7.31 (m, 5H, Ar**H**, COCH=C**H**), 6.20 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.15-5.13 (m, 1H, CH=CHC**H**), 5.05 (t, 1H, = 4.0 Hz, ArC**H**OH), 2.38 (d, 1H, = 4.0 Hz, O**H**); ***Syn* diastereomer:** δ 7.40-7.31 (m, 4H, Ar**H**), 7.20 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 6.14 (dd, 1H, = 5.8,2.0 Hz, COCH=C**H**), 5.15-5.13 (m, 1H, CH=CHC**H**), 4.74 (dd, 1H, = 6.8, 3.2 Hz, ArC**H**OH), 2.67 (d, 1H, = 3.2 Hz, O**H**); MS (APCI pos.): **m** 225.0 (M+1), 207.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H hexanes/2-propanol 95/5, 210 nm, $_1$ = 21.1 min (major **an**),**i** $_2$ = 24.2 min, (minor **an**),**i** $_3$ = 25.9 min (major),**n**$_4$ = 29.4 min (minor).**n**Ee: 94% (**an**).**i**

5-[Hydroxy(4-nitrophenyl)methyl]furan-2(5*H*)-one (8h):

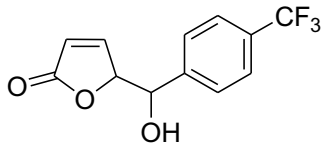


Reaction of *γ*-crotonolactone (70 μL, 1.0 mmol) with 4-nitrobenzaldehyde (76 mg, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 59 mg (50%) of **8h** as a yellow solid.

IR: 3438, 1746, 1515, 1348, 1169, 1103, 1039, 916, 833 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 8.26 (d, 2H, = 8.7 Hz, Ar**H**, ortho to NO_2), 7.63 (d, = 8.7, 2H, Ar**H**), 7.30 (dd, 1H, = 5.9,1.6 Hz, COCH=C**H**), 6.17 (dd, 1 H, = 5.9, 1.8 Hz, COC**H**=CH), 5.21-5.19 (m, 2H, CH=CHC**H**, ArC**H**OH), 2.77 (d, 1H, = 3.7 Hz, O**H**); ***Syn* diastereomer:** δ 8.29 (d, 2H, = 8.7 Hz, Ar**H**, ortho to NO_2), 7.66-7.59 (m, 2H, Ar**H**), 7.21 (m, 1H, COCH=C**H**), 6.24 (dd, 1 H, = 5.8, 1.4 Hz, COC**H**=CH), 5.0-4.98 (m, 2H, CH=CHC**H**, ArC**H**OH), 2.59 (d, 1H, = 3.5 Hz, O**H**); MS (APCI pos.): **m** 236.1 (M+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 95/5, 254 nm, $_1$ = 52.4 min (major **an**),**i** $_2$ = 59.1 min, (major),**n**70.5 (minor).**m**Ee: >99% (**an**).**i**

5-[Hydroxy(4-trifluoromethylphenyl)methyl]furan-2(5*H*)-one (8i):

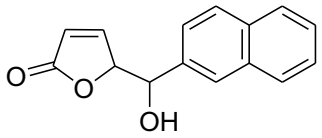


Reaction of γ-crotonolactone (70 L, 1.0 mmol) with 4-trifluoromethylbenzaldehyde (67 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 78 mg (60%) of **8i** as a colorless solid.

IR: 3413, 1739, 1322, 1161, 1100, 1065, 1040, 1016, 816 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.68 (d, 2H, = 8.1 Ar**H**), 7.55 (d, 2H, = 8.1, Ar**H**), 7.31 (dd, 1H, = 5.8, 1.4 Hz, COCH=C**H**), 6.21 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.19-5.14 (m, 2H, CH=CHC**H**O, ArC**H**OH), 2.38 (d, 1H, = 3.9 Hz, O**H**); ***Syn* diastereomer:** δ 7.68 (d, 2H, = 5.7, Ar**H**), 7.55 (d, 2H, = 5.7, Ar**H**), 7.24 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 6.15 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.19-5.14 (m, 1H, CH=CHC**H**), 4.91 (m, 1H, ArC**H**OH), 2.38 (d, 1H, = 3.4 Hz, O**H**); MS (APCI pos.): **m** 259.2 (M+1), 241.1 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 97/3, 254 nm, $_1$ = 28.9 min (major **an**),**i** $_2$ = 32.4 min, (minor **an**).**i**Ee: 95% (**an**).**i**

5-[Hydroxy (naphthalen-2-yl)methyl]furan-2(5*H*)-one (8j):

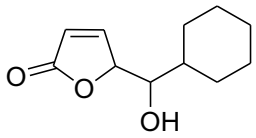


Reaction of γ-crotonolactone (70 L, 1.0 mmol) with 2-naphthaldehyde (78 mg, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 88 mg (73%) of **8j** as a pale yellow solid.

IR: 3359, 1752, 1731, 1172, 1077, 1041, 824 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.90-7.85 (m, 4H, Ar**H**), 7.53-7.50 (m, 3H, Ar**H**), 7.36 (dd, 1H, = 5.8, 1.4 Hz COCH=C**H**), 6.19 (dd, 1 H, = 5.8, 1.9 Hz, COC**H**=CH), 5.29-5.26 (m, 2H, CH=CHC**H**, ArC**H**OH), 2.51 (d, 1H, = 3.7 Hz, O**H**); ***Syn* diastereomer:** δ 7.90-7.85 (m, 4H, Ar**H**), 7.53-7.50 (m, 3H, Ar**H**), 7.18 (dd, 1H, = 5.8, 1.6 Hz, COCH=C**H**), 6.13 (dd, 1H, = 5.8, 2.0 Hz, COC**H**=CH), 5.29-5.26 (m, 2H, CH=CHC**H**), 4.88 (dd, 1H, = 7.1, 3.1 Hz, ArC**H**OH), 2.81 (d, 1H, = 3.1 Hz, O**H**); MS (APCI pos.): **m** 241.0 (M+1), 223.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 85/15, 254 nm, $_1$ = 9.5 min (major **an**),**i** $_2$ = 11.8 min, (minor **an**),**i** $_3$ = 12.6 min (major),**n**$_4$= 13.6 min (minor).**n**Ee: 95% (**an**).**i**

5-[Hydroxy(cyclohexyl)methyl]furan-2(5*H*)-one (8k):

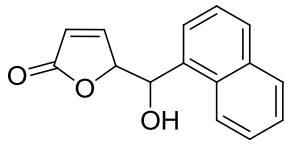


Reaction of γ-crotonolactone (70 L, 1.0 mmol) with cyclohexanecarboxaldehyde (60 L, 0.50 mmol) catalyzed by **5** (45 mg, 0.10 mmol) according to the general procedure provided 49 mg (50%) of **8k** as a white solid.

IR: 3420, 1747, 1715, 1154, 1112, 1096, 1029, 1004, 870, 845 829 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.59 (dd, 1H, = 5.8, 1.4 Hz, COCH=C**H**), 6.19 (dd, 1 H, = 5.8, 1.9 Hz, COC**H**=CH), 5.10 (dt, 1H, = 5.7, 1.6 Hz, CH=CHC**H**), 3.61 (apparent q, 1H, = 5.6 Hz, ArC**H**OH), 1.98-1.96 (m, 1H, C**H**CH_2), 1.82-1.54 (m, 4H, C**H**$_2$), 1.33-1.10 (m, 6H, C**H**$_2$); ***Syn* diastereomer:** δ 7.45 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 6.19 (dd, 1H, = 5.8, 1.9 Hz, COC**H**=CH), 5.18 (m, 1H, CH=CHC**H**), 3.49-3.45 (m, 1H, ArC**H**OH), 1.98-1.96 (m, 1H, C**H**CH_2), 1.82-1.54 (m, 4H, C**H**$_2$), 1.33-1.10 (m, 6H, C**H**$_2$); MS (APCI pos.): **m** 197.0 (M+1), 179.1 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 95/5, 210 nm, $_1$= 15.4 min (major **an**),**i** $_2$ = 17.5 min (major).**m**Ee: >99% (**an**).**i**

5-[Hydroxy(naphthalen-1-yl)methyl]furan-2(5*H*)-one (8l):



Reaction of *γ*-crotonolactone (70 L, 1.0 mmol) with 1-naphthaldehyde (68 L, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 82 mg (68%) of **8k** as a yellow solid.

IR: 3414, 1730, 1165, 1102, 1081, 1042, 882, 823, 797, 775 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 8.02 (d, 1H, = 8.5 Hz, Ar**H**), 7.93 (d, 1H, = 7.6 Hz, Ar**H**), 7.88 (d, 1H, = 8.0 Hz, Ar**H**), 7.74 (d, 1H, = 7.2 Hz, Ar**H**), 7.59-7.53 (m, 3H, Ar**H** & COCH=C**H**), 7.27-7.25 (m, 1H, Ar**H**), 6.20 (dd, 1 H, = 5.8, 2.0 Hz, COC**H**=CH), 5.98 (t, 1H, = 3.5 Hz, CH=CHC**H**), 5.44-5.43 (m, 1H, ArC**H**OH), 2.57 (d, 1H, = 3.8 Hz, O**H**); ***Syn* diastereomer:** δ 7.98 (m, 1H, Ar**H**), 7.88-7.87 (m, 2H, Ar**H**), 7.74 (d, 1H, = 7.0 Hz, Ar**H**), 7.59-7.53 (m, 3H, Ar**H** & COCH=C**H**), 7.27-7.25 (m, 1H, Ar**H**), 6.95 (dd, 1H, = 5.8, 1.5 Hz, COCH=C**H**), 6.14 (dd, 1H, = 5.8, 2.0 Hz, COC**H**=CH), 5.46-5.45 (m, 1H, CH=CHC**H**), 5.39 (dt, 1H, = 3.4, 1.6 Hz, ArC**H**OH), 2.92 (d, 1H, = 3.2 Hz, O**H**); MS (APCI pos.): **m** 241.0 (M+1), 223.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 85/15, 254 nm, $_1$= 8.7 min (major **an**),**i** $_2$ = 9.5 min (minor **an**),**i** $_3$ = 13.8 min (major),**n**$_4$= 17.3 min (minor).**n**Ee: 77% (**an**).**i**

2.5 References:

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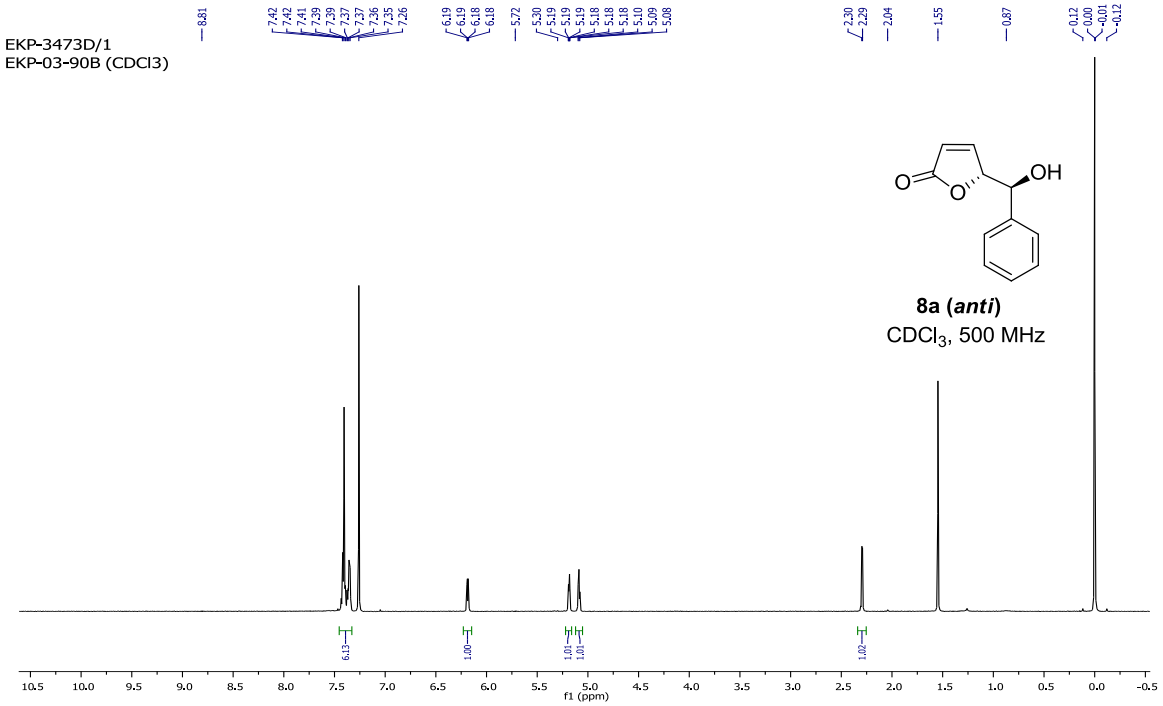
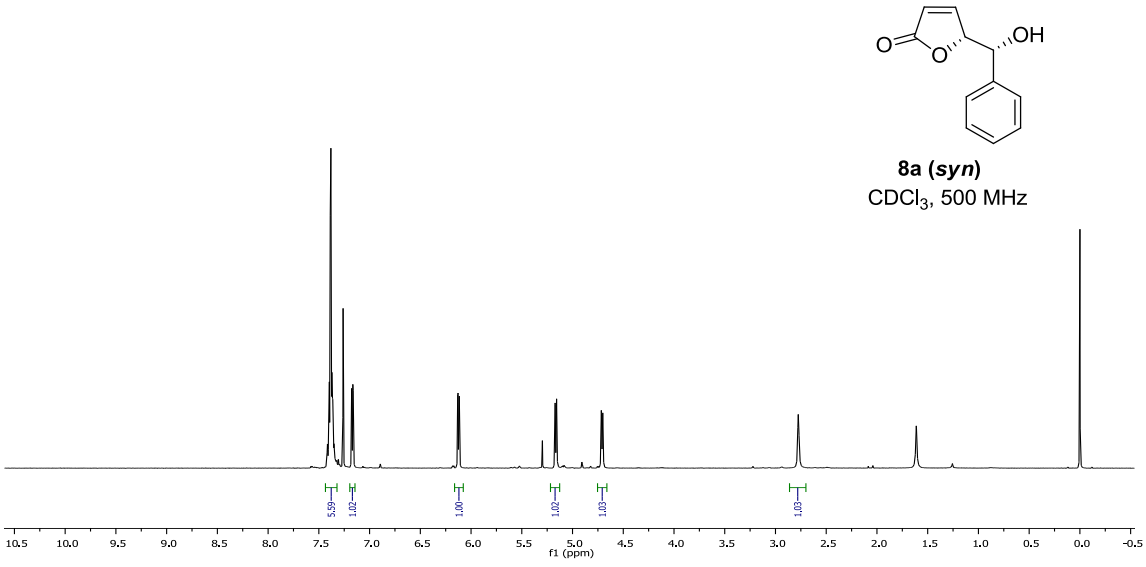
2.6 Selected ^{1}H NMR spectra

EKP-3473D/1
EKP-03-90B (CDCl3)

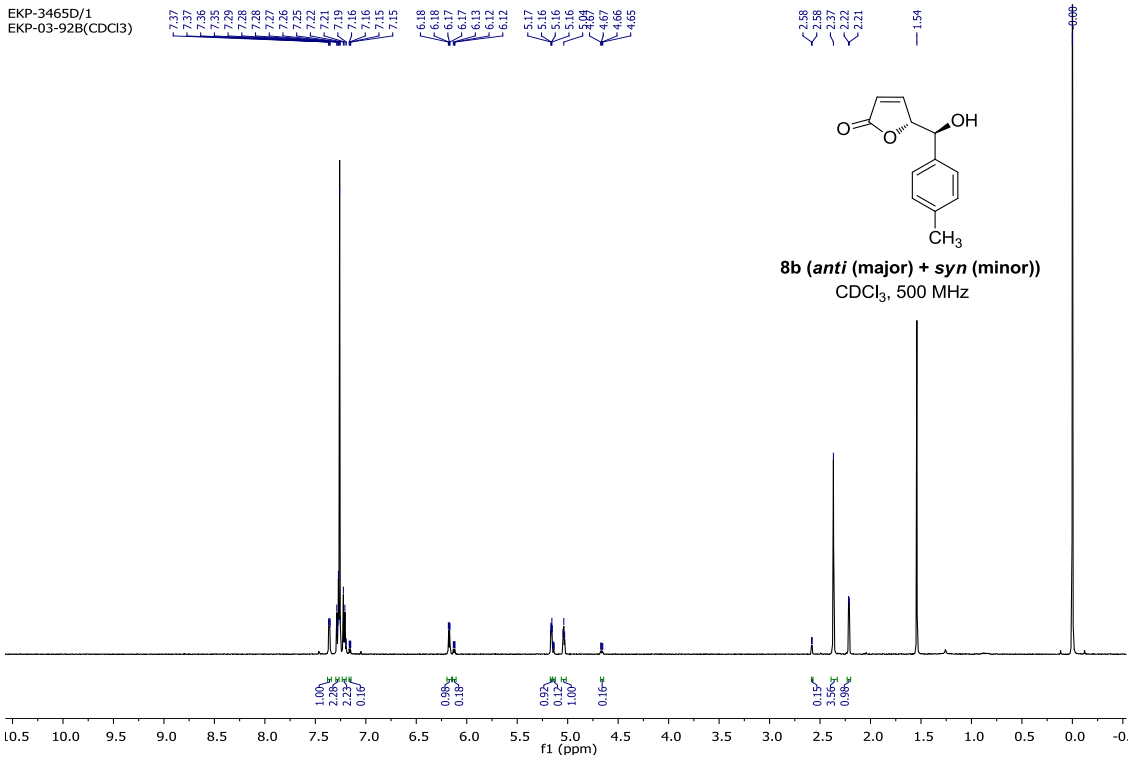


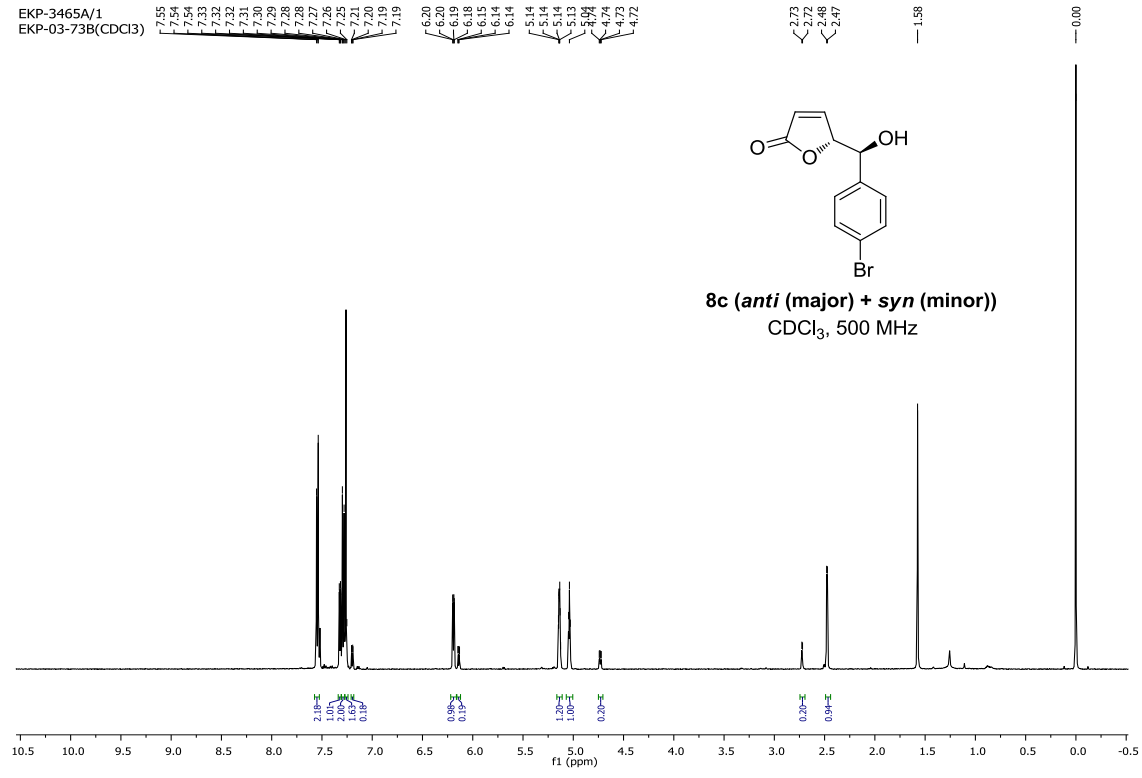
8a (*anti*)
$CDCl_3$, 500 MHz

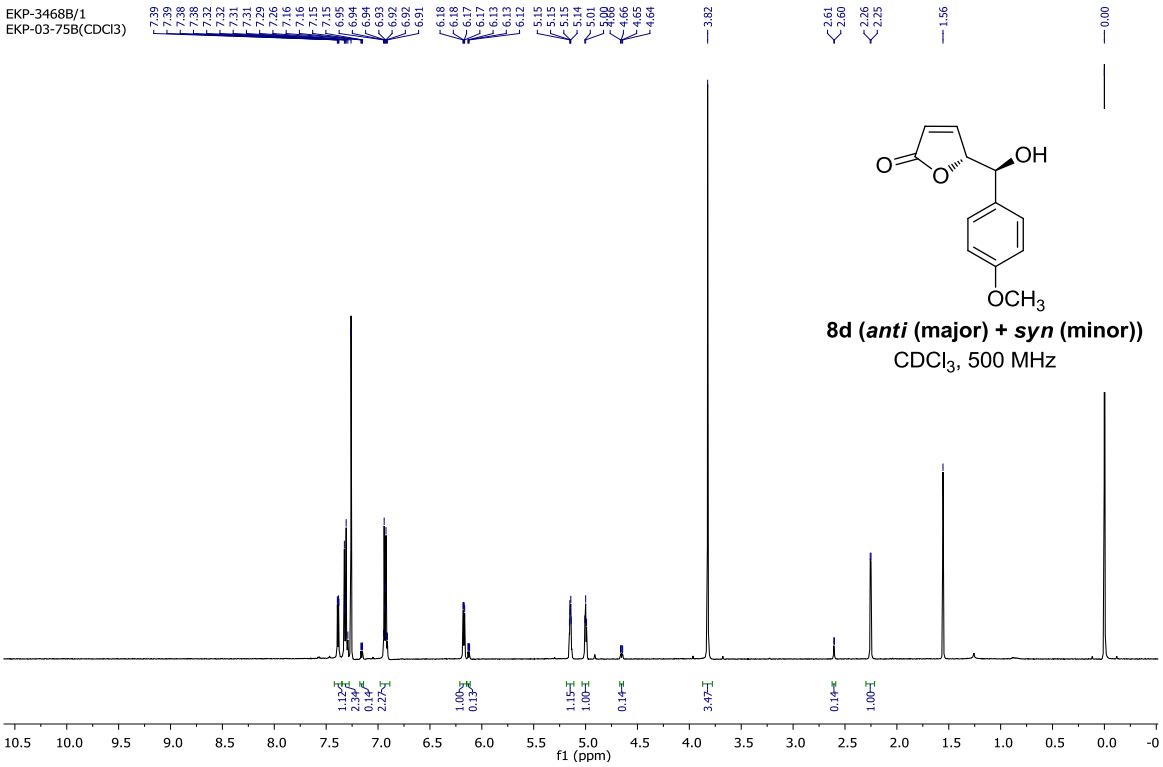
EKP-3421D/1
EKP-03-38C (CDCl3)



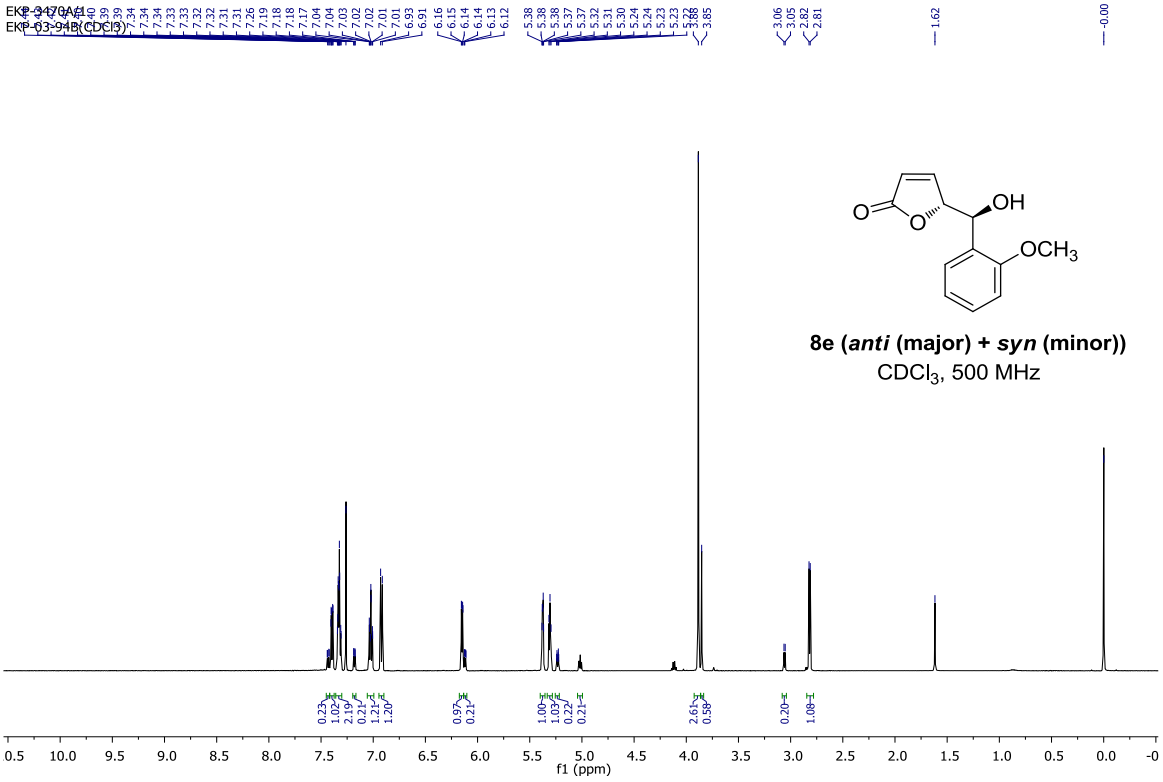
8a (*syn*)
$CDCl_3$, 500 MHz


EKP-3465D/1
EKP-03-92B(CDCl3)
OH
CH3
8b (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

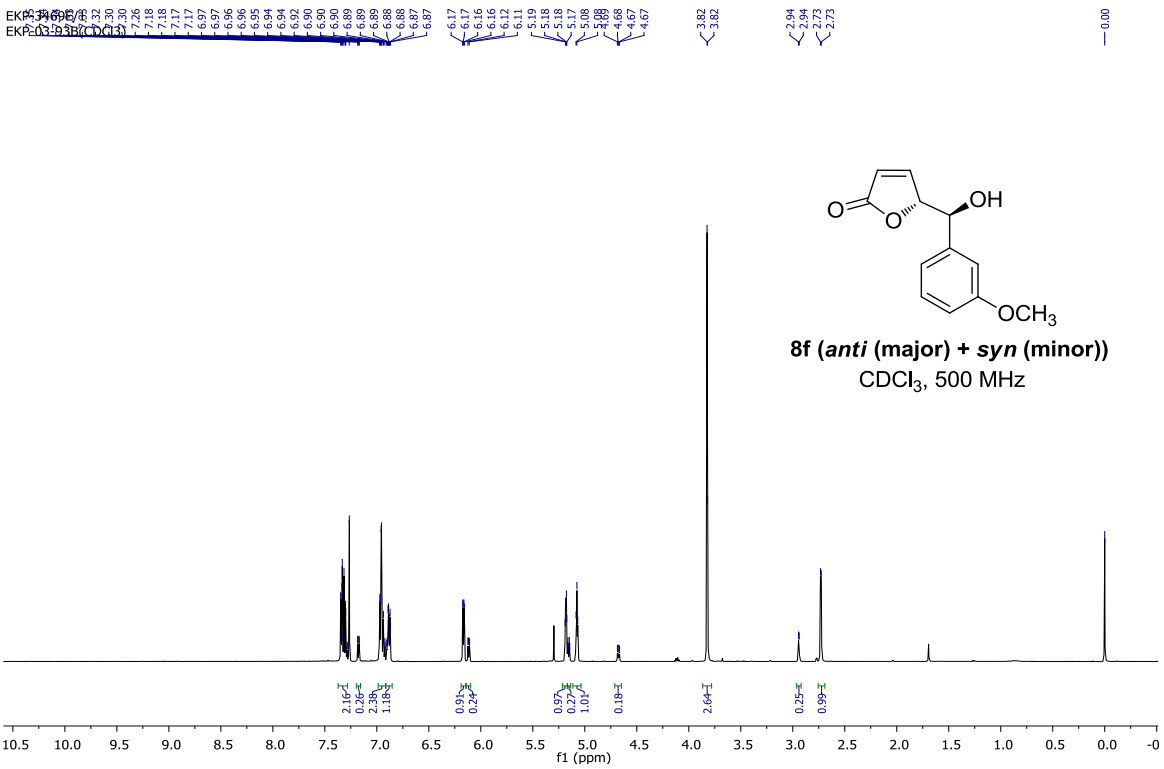

EKP-3465A/1
EKP-03-73B(CDCl3)
OH
Br
8c (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

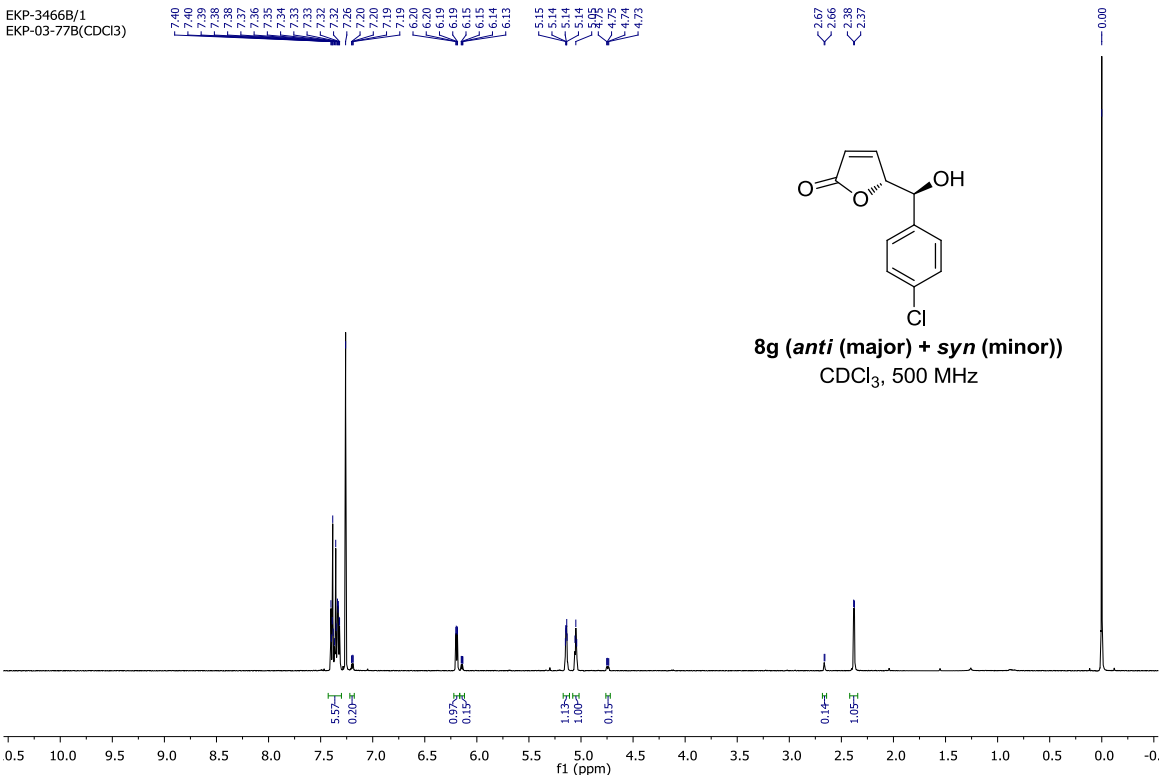


8d (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz

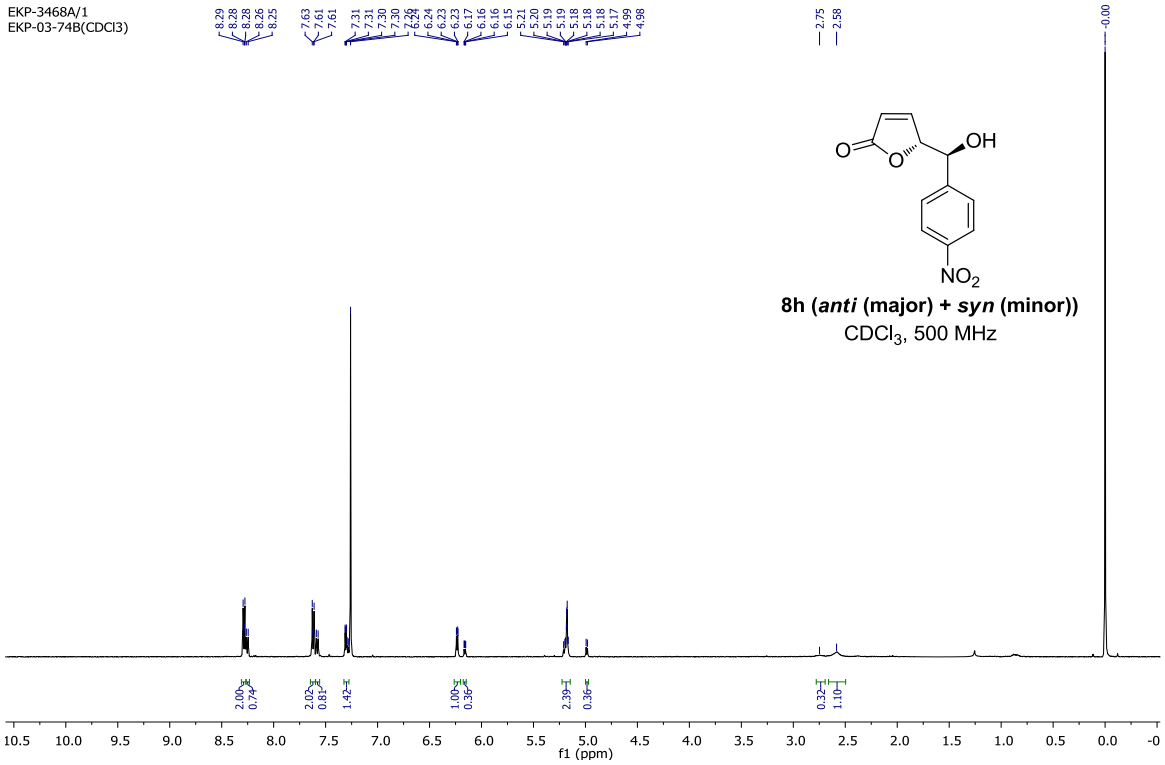


8e (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz


EKP-3466B/2
EKP-03-93B(CDCl3)
O
O
OH
OCH3
8f (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

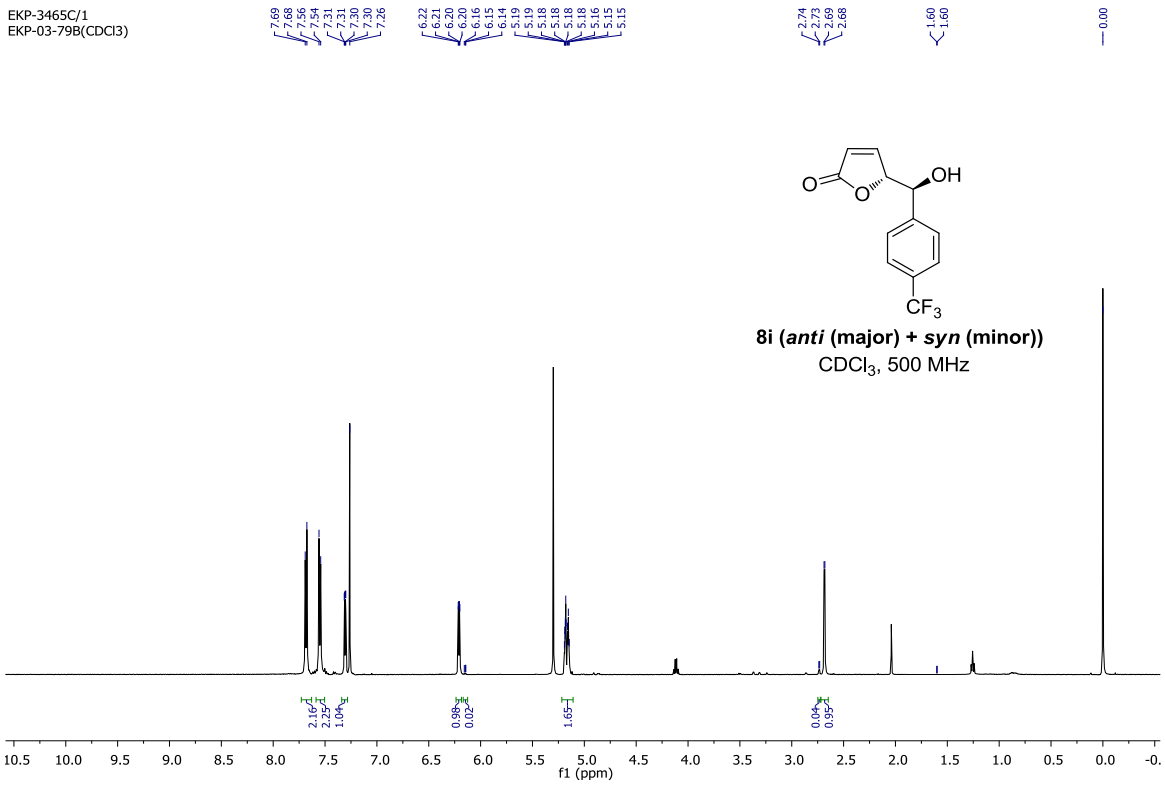

EKP-3466B/1
EKP-03-77B(CDCl3)
O
O
OH
Cl
8g (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

EKP-3468A/1
EKP-03-74B(CDCl3)

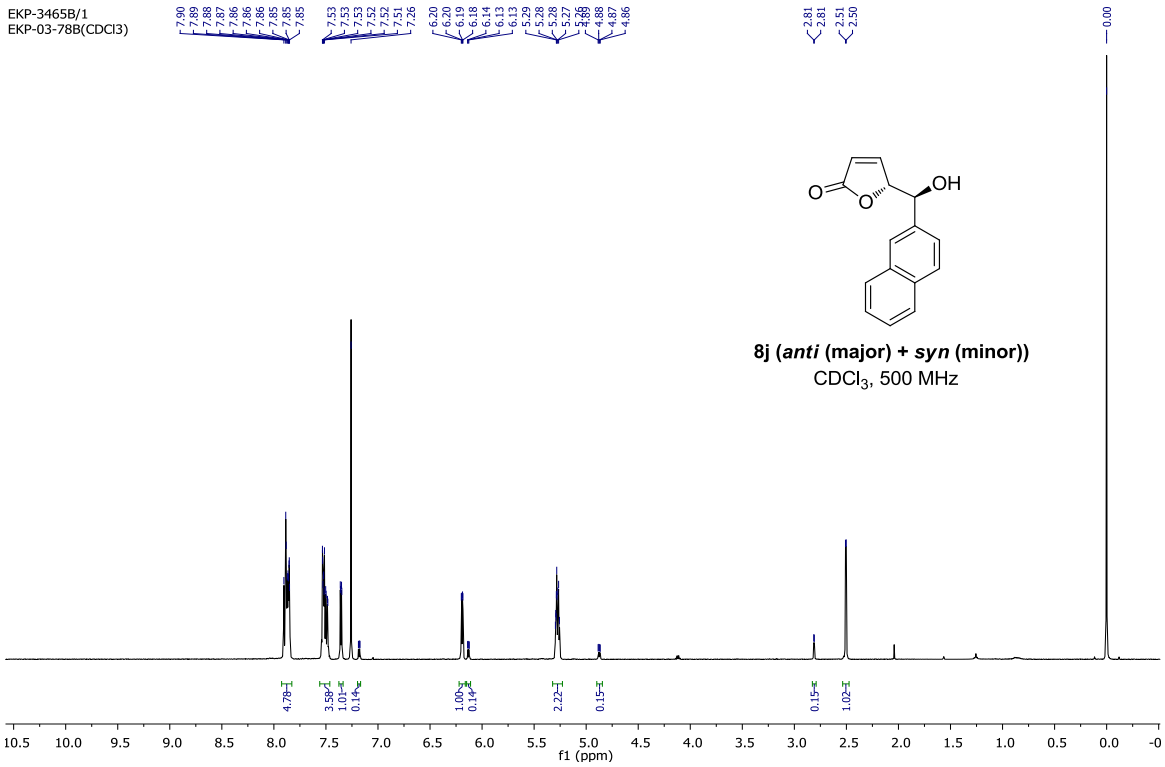


8h (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz

EKP-3465C/1
EKP-03-79B(CDCl3)



8i (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz


EKP-3465B/1
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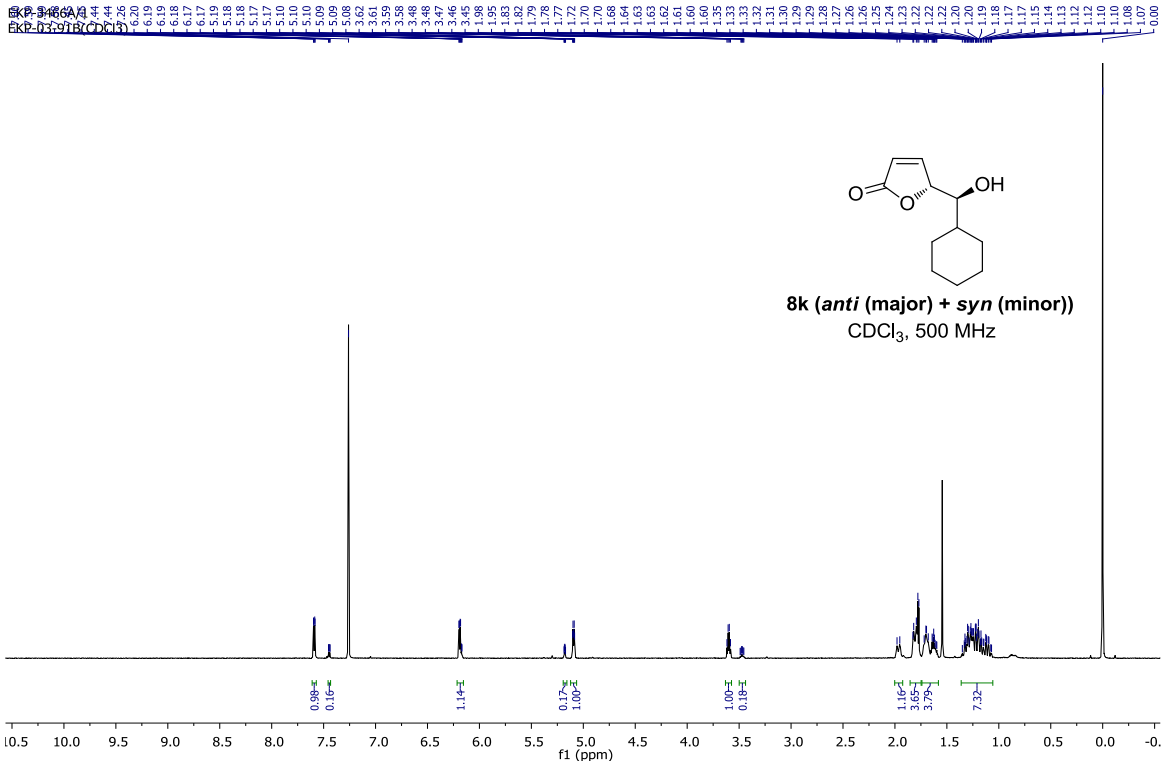
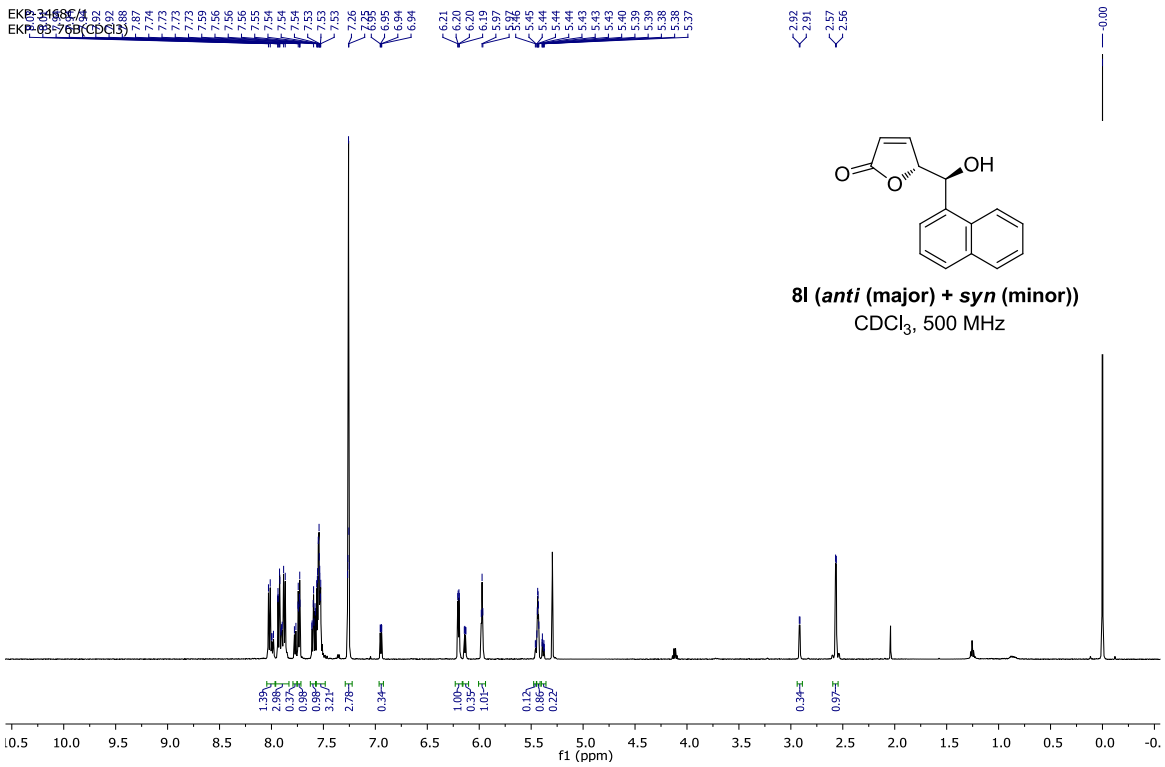
OH
8j (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

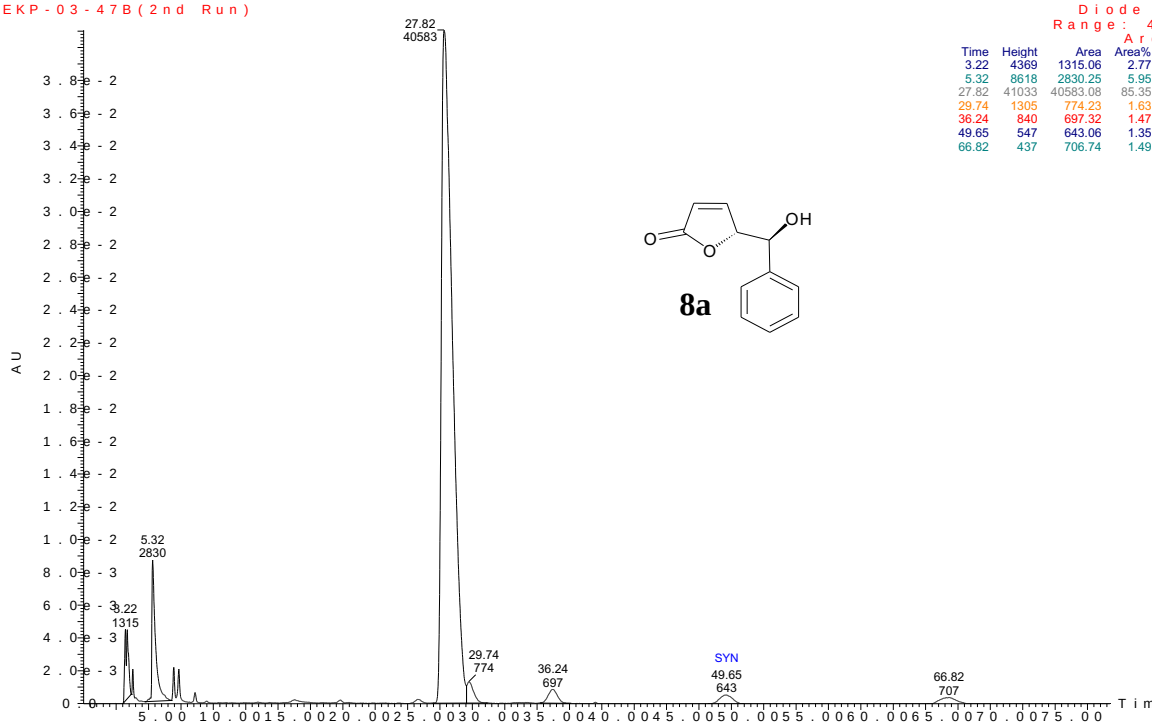

OH
8k (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)


O
O
OH
8l (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

2.7 Selected HPLC chromatograms

AS-H 90hex 10ipa 254nm 90 min

EKP-03-47B(2nd Run)



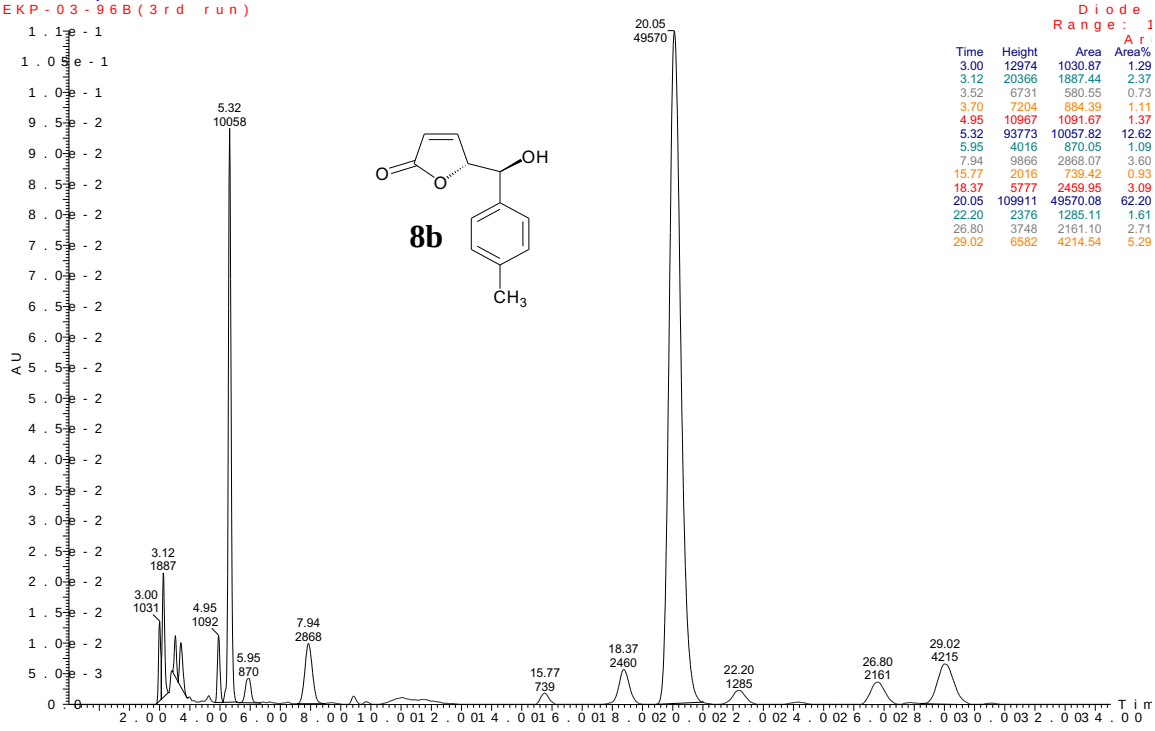
Diode Range: 4

Time	Height	Area	Area%
3.22	4369	1315.06	2.77
5.32	8618	2830.25	5.95
27.82	41033	40583.08	85.35
29.74	1305	774.23	1.63
36.24	840	697.32	1.47
49.65	547	643.06	1.35
66.82	437	706.74	1.49

8a

AD-H 95hex5ipa 254nm 60 min

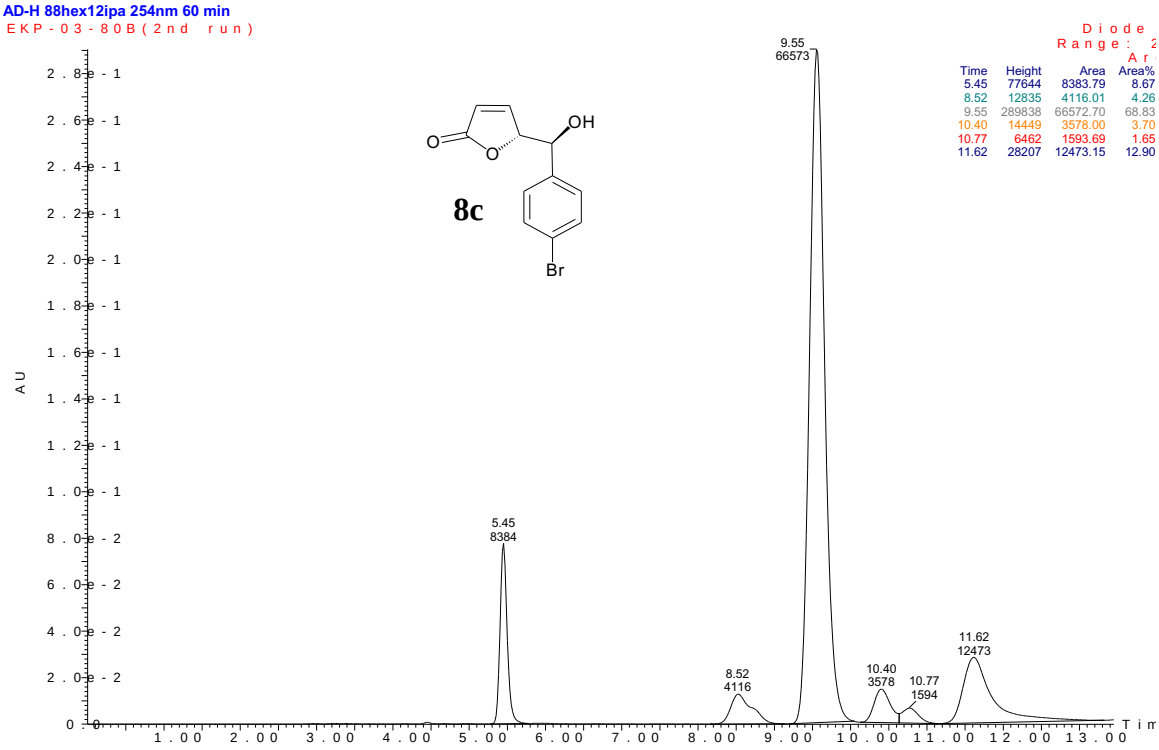
EKP-03-96B(3rd run)

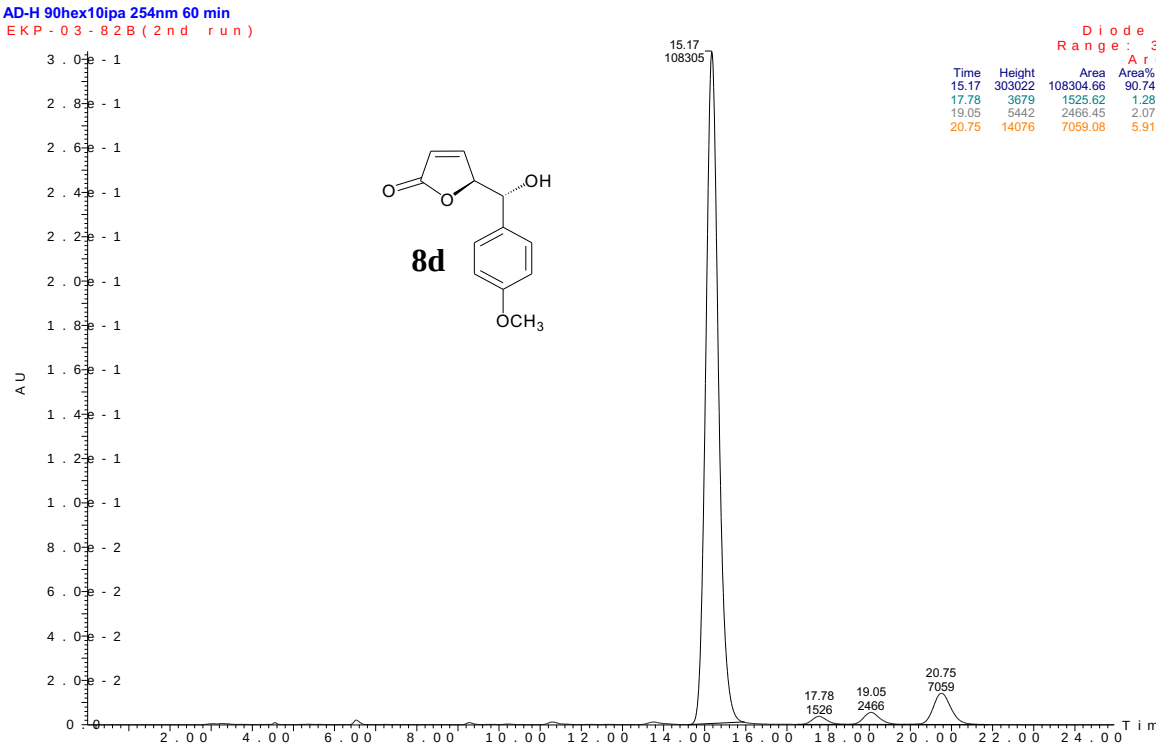


Diode Range: 1

Time	Height	Area	Area%
3.00	12974	1030.87	1.29
3.12	20366	1887.44	2.37
3.52	6731	580.55	0.73
3.70	7204	884.39	1.11
4.95	10967	1091.67	1.37
5.32	93773	10057.82	12.62
5.95	4016	870.05	1.09
7.94	9866	2868.07	3.60
15.77	2016	739.42	0.93
18.37	5777	2459.95	3.09
20.05	109911	49570.08	62.20
22.20	2376	1285.11	1.61
26.80	3748	2161.10	2.71
29.02	6582	4214.54	5.29

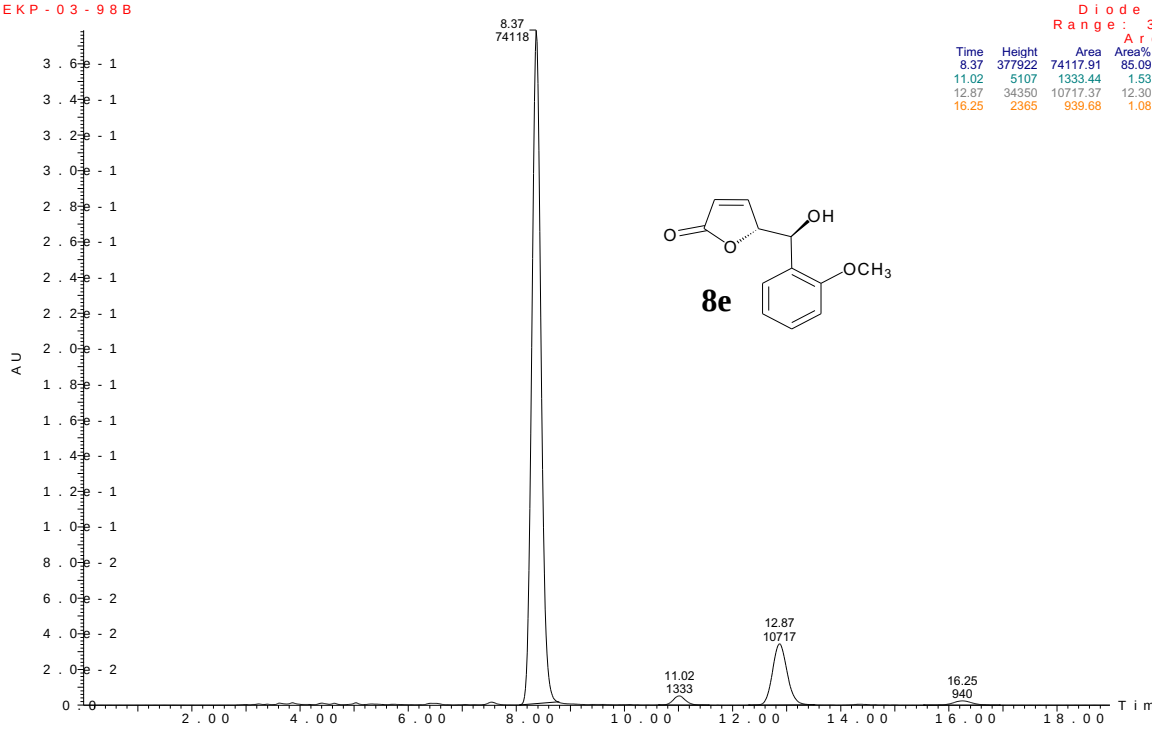
8b


AD-H 88hex12ipa 254nm 60 min
EKP-03-80B(2nd run)
Diode
Range:
Ar
Time Height Area Area%
5.45 77644 8383.79 8.67
8.52 12835 4116.01 4.26
9.55 289838 66572.70 68.83
10.40 14449 3578.00 3.70
10.77 6462 1593.69 1.65
11.62 28207 12473.15 12.90
8c
OH
O
O
Br
9.55
66573
5.45
8384
8.52
4116
10.40
3578
10.77
1594
11.62
12473
AU
Tim


AD-H 90hex10ipa 254nm 60 min
EKP-03-82B(2nd run)
Diode
Range:
Ar
Time Height Area Area%
15.17 303022 108304.66 90.74
17.78 3679 1525.62 1.28
19.05 5442 2466.45 2.07
20.75 14076 7059.08 5.91
8d
OH
O
O
OCH3
15.17
108305
17.78
1526
19.05
2466
20.75
7059
AU
Tim

AD-H 85hex15ipa 254nm 60 min

EKP-03-98B

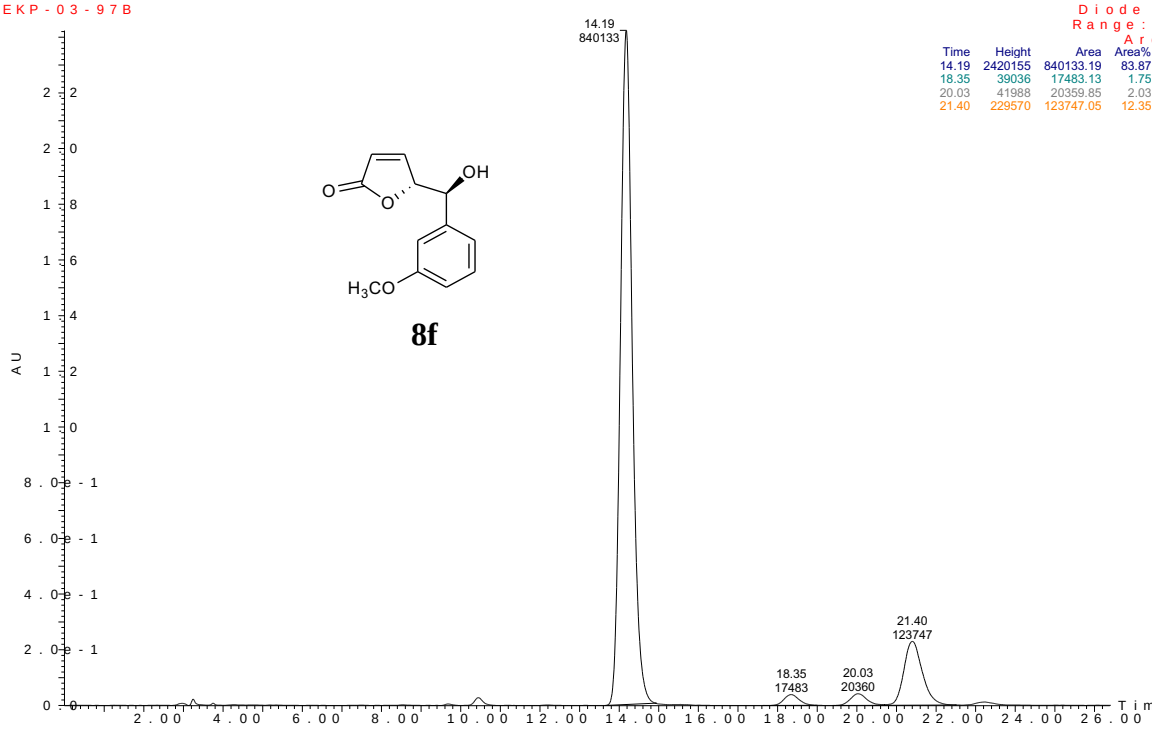


Time	Height	Area	Area%
8.37	377922	74117.91	85.09
11.02	5107	1333.44	1.53
12.87	34350	10717.37	12.30
16.25	2365	939.68	1.08

8e

AD-H 90hex10ipa 210nm 60 min

EKP-03-97B

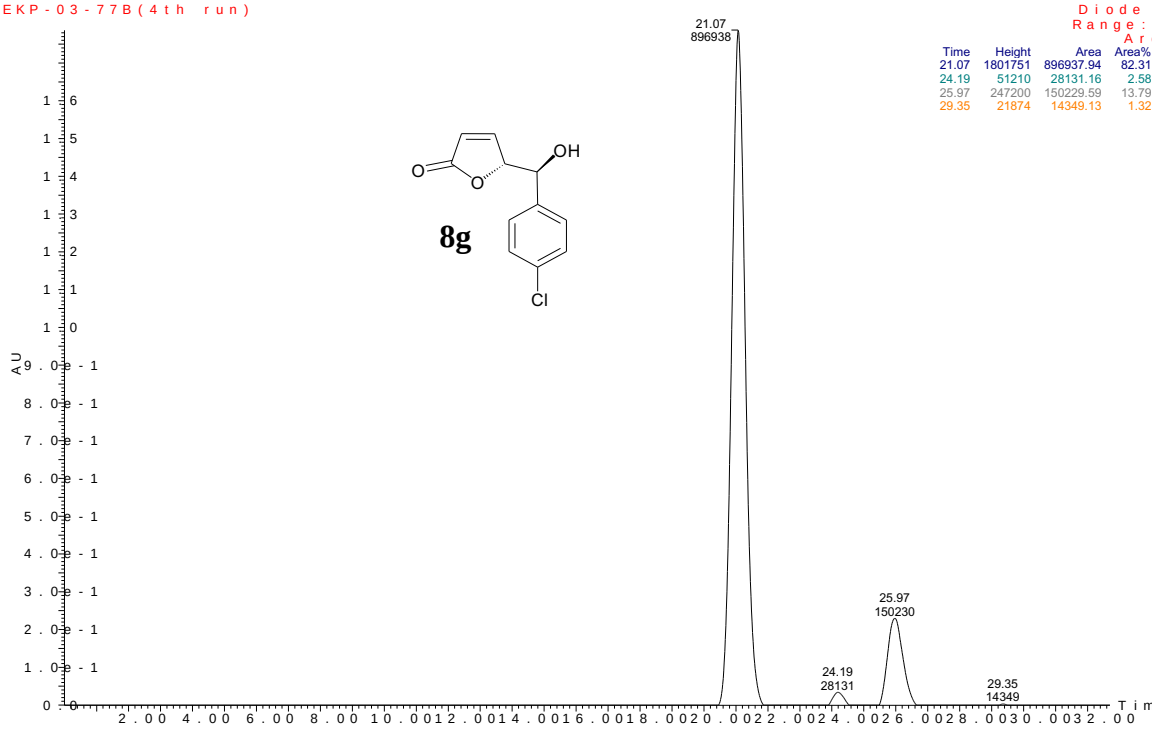


Time	Height	Area	Area%
14.19	2420155	840133.19	83.87
18.35	39036	17483.13	1.75
20.03	41988	20359.85	2.03
21.40	229570	123747.05	12.35

8f

AD-H 95hex 5ipa 210nm 60 min

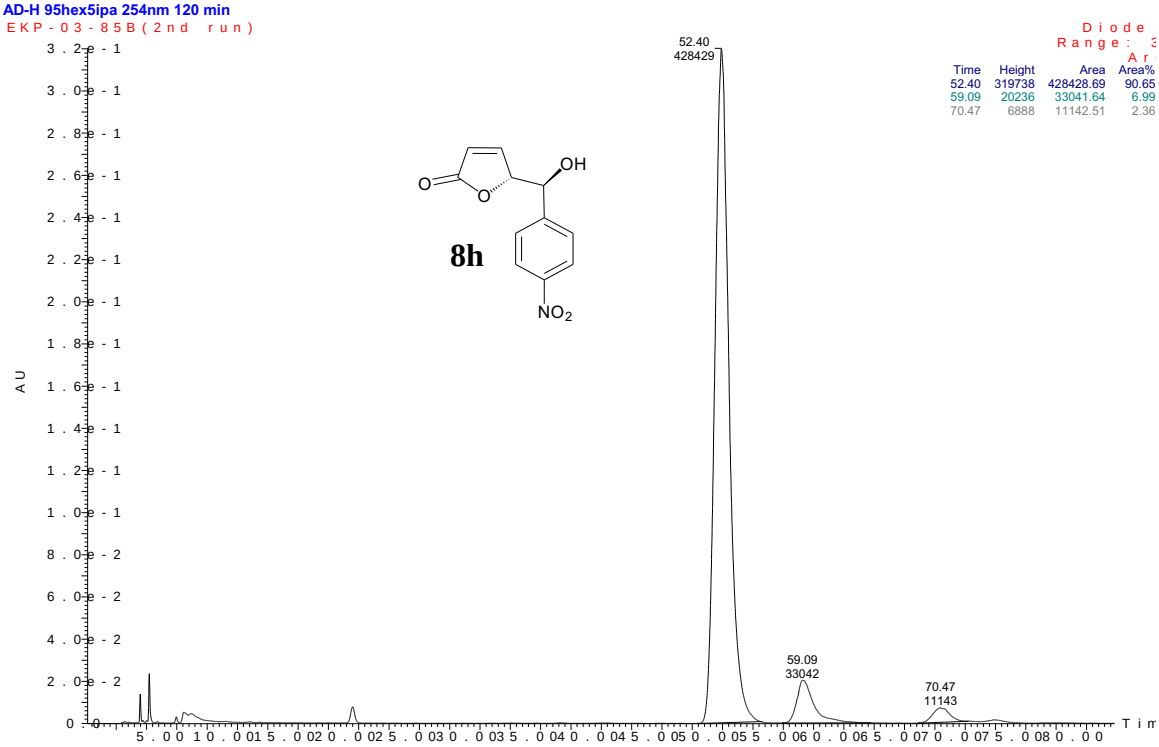
EKP-03-77B(4th run)



8g

AD-H 95hex5ipa 254nm 120 min

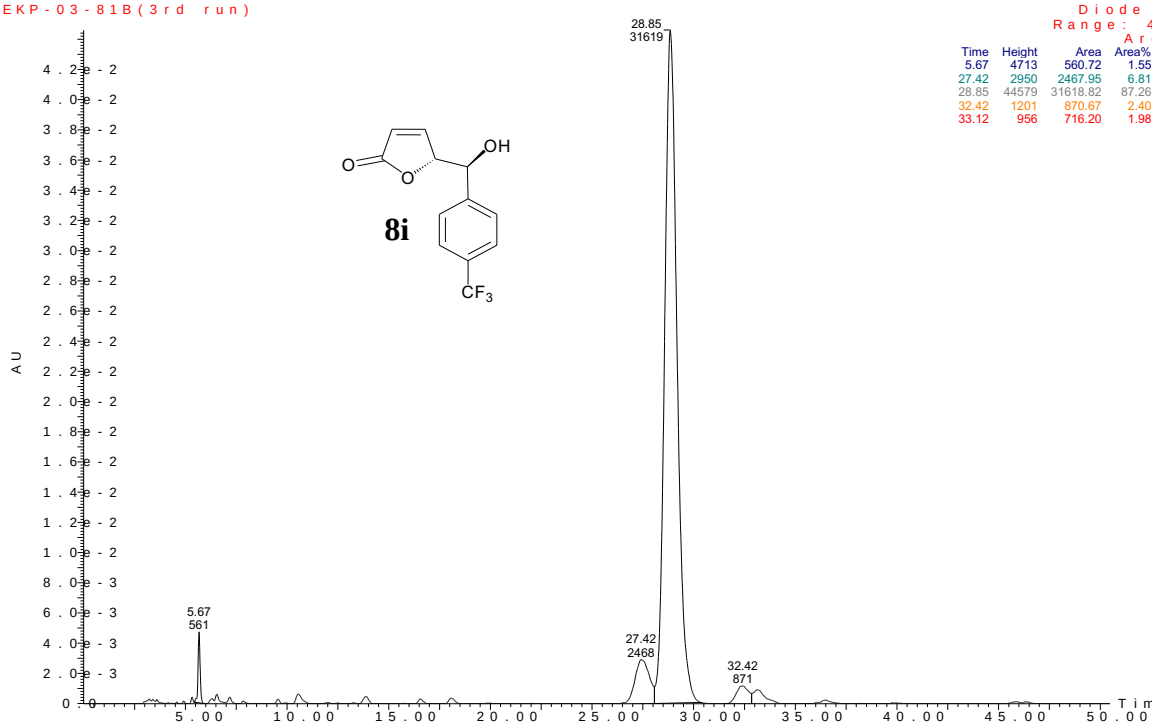
EKP-03-85B(2nd run)



8h

AD-H 97hex3ipa 254nm 60 min

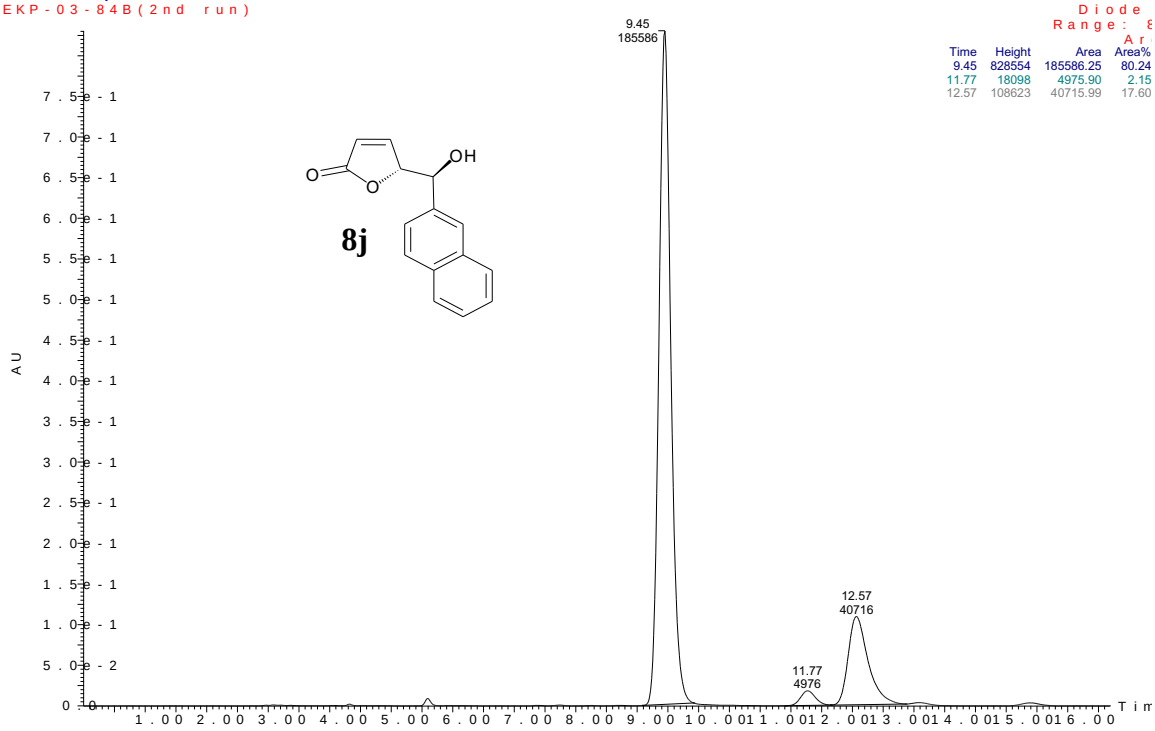
EKP-03-81B(3rd run)



8i

AD-H 85hex15ipa 254nm 60 min

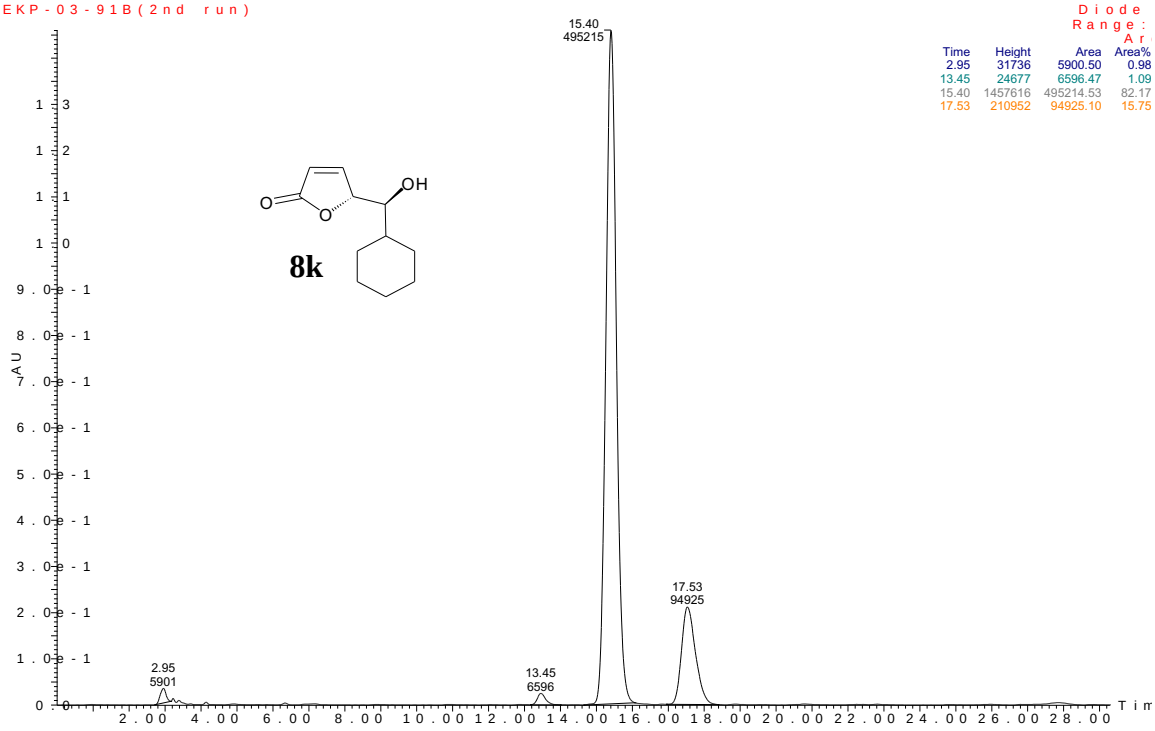
EKP-03-84B(2nd run)



8j

AD-H 95hex 5ipa 210nm 60 min

EKP-03-91B(2nd run)



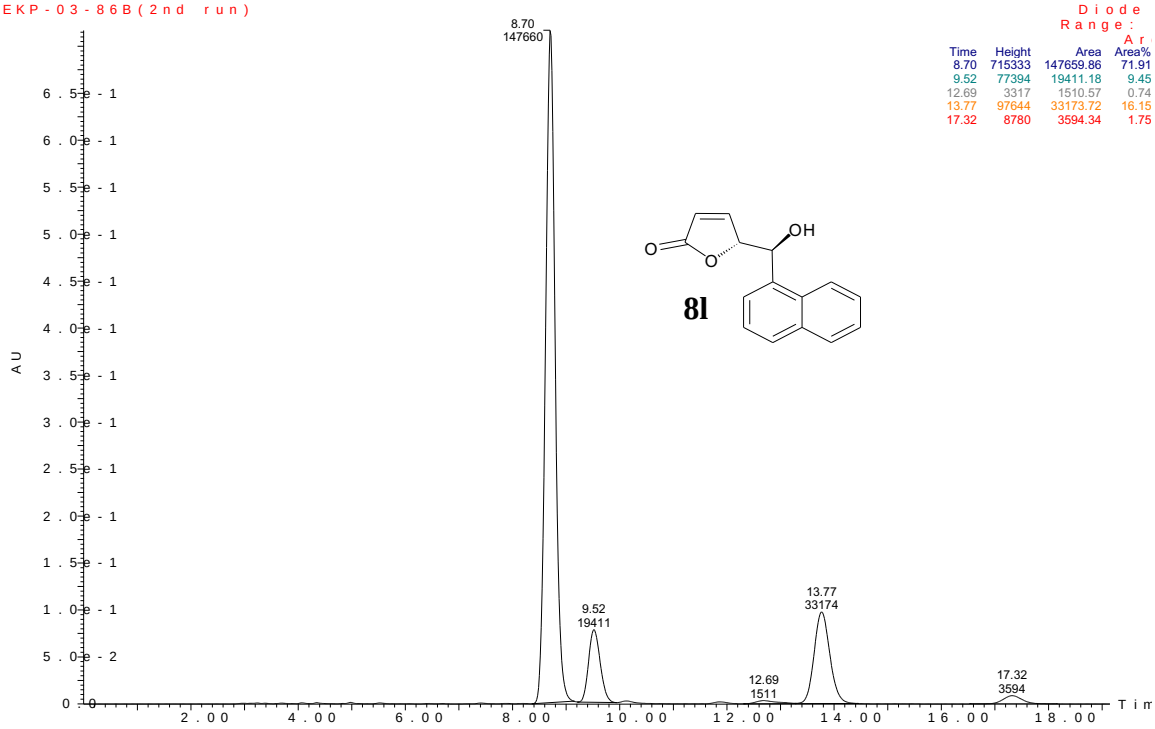
Diode Range: Ar

Time	Height	Area	Area%
2.95	31736	5900.50	0.98
13.45	24677	6596.47	1.09
15.40	1457616	495214.53	82.17
17.53	210952	94925.10	15.75

8k

AD-H 85hex15ipa 254nm 60 min

EKP-03-86B(2nd run)



Diode Range: Ar

Time	Height	Area	Area%
8.70	715333	147659.86	71.91
9.52	77394	19411.18	9.45
12.69	3317	1510.57	0.74
13.77	97644	33173.72	16.15
17.32	8780	3594.34	1.75

8l

CHAPTER 3

Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-Hydroxypipecolic Acid: Application of an Organocatalytic Direct Vinylogous Aldol Reaction

This Chapter is based on the following publication:

Pansare, S. V.; Paul, E. K. *Org. Biomol. Chem.* **2012**, *10*, 2119–2125.

Contributions of authors

S. V. Pansare: research supervisor, manuscript preparation.

E. K. Paul: experimental work, manuscript preparation.

3.1 Introduction

The piperidine motif is found in numerous biologically relevant natural products[1] as well as in medicinal and pharmaceutical agents,[2] and the synthesis of functionalized piperidines has therefore continued to engage synthetic chemists over the years.[3] Stereoselective routes to aryl substituted[4] and hydroxylated piperidines[5] have been extensively investigated. In particular, the biological activity and the synthesis of a variety of 2,3-disubstituted piperdines has attracted considerable interest. This is perhaps best exemplified by the synthetic efforts directed towards the neurokinin receptor antagonists (+)-L-733,060[6] and (+)-CP-99,994;[7] as well as (2*S*,3*R*)-3-hydroxypipecolic acid,[8] a constituent of the antibiotic tetrazomine (Figure 3.1). The following sections describe organocatalysis based enantioselective syntheses of these three targets.

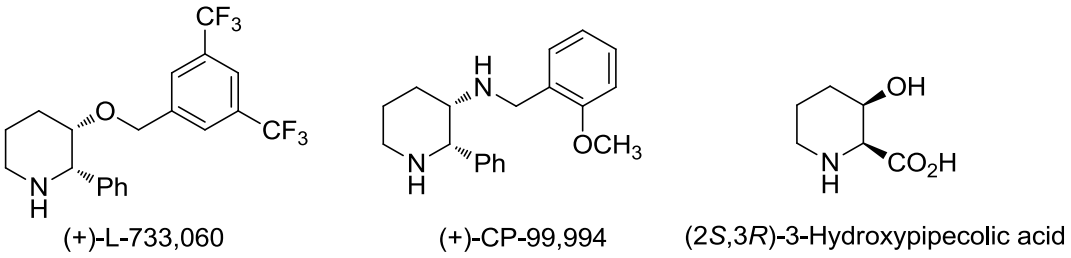


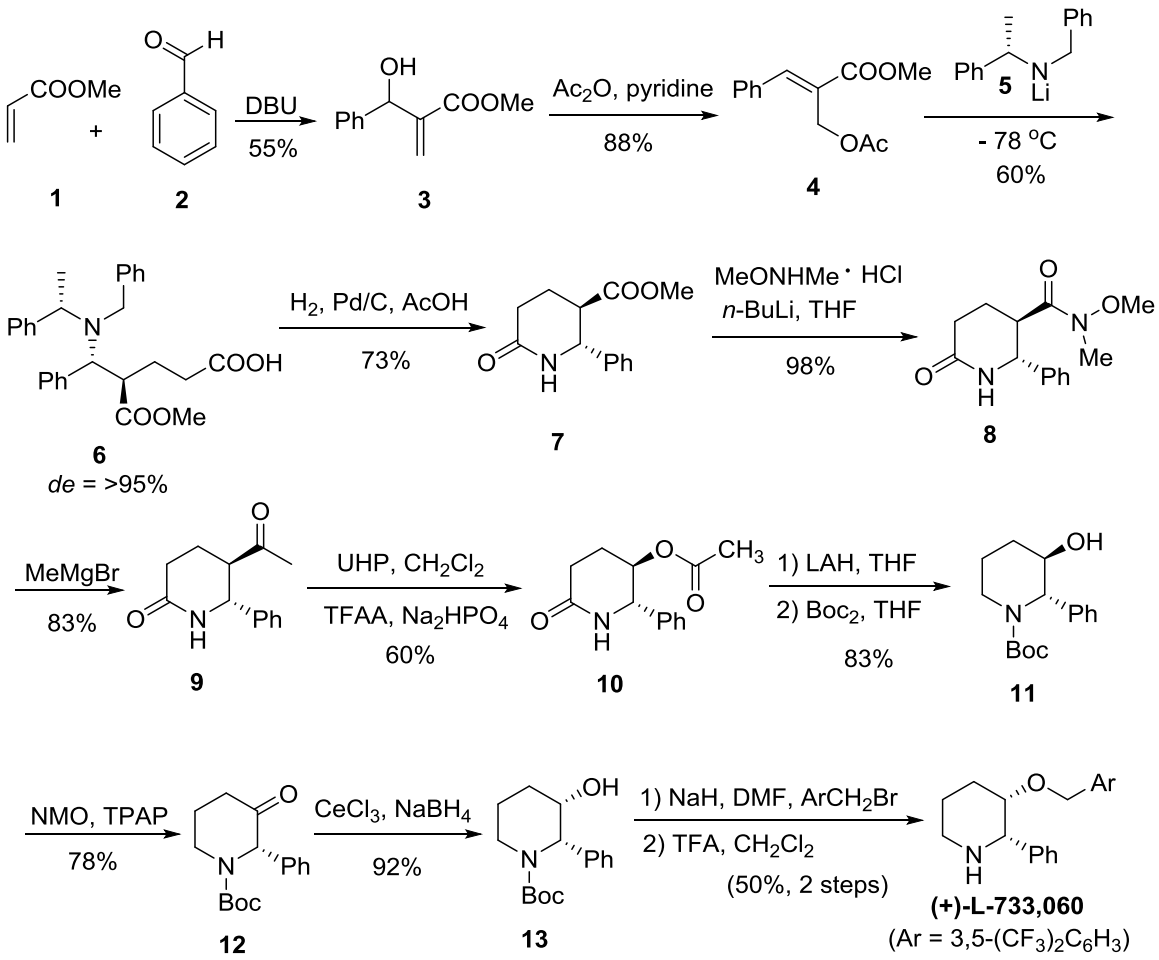
Figure 3.1. Biologically active 2,3-disubstituted piperidines targeted in this study.

3.2 Known synthetic routes to (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid

The following summary provides an overview of the reported syntheses of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid from 2010 onwards.

3.2.1 Synthesis of (+)-L-733,060

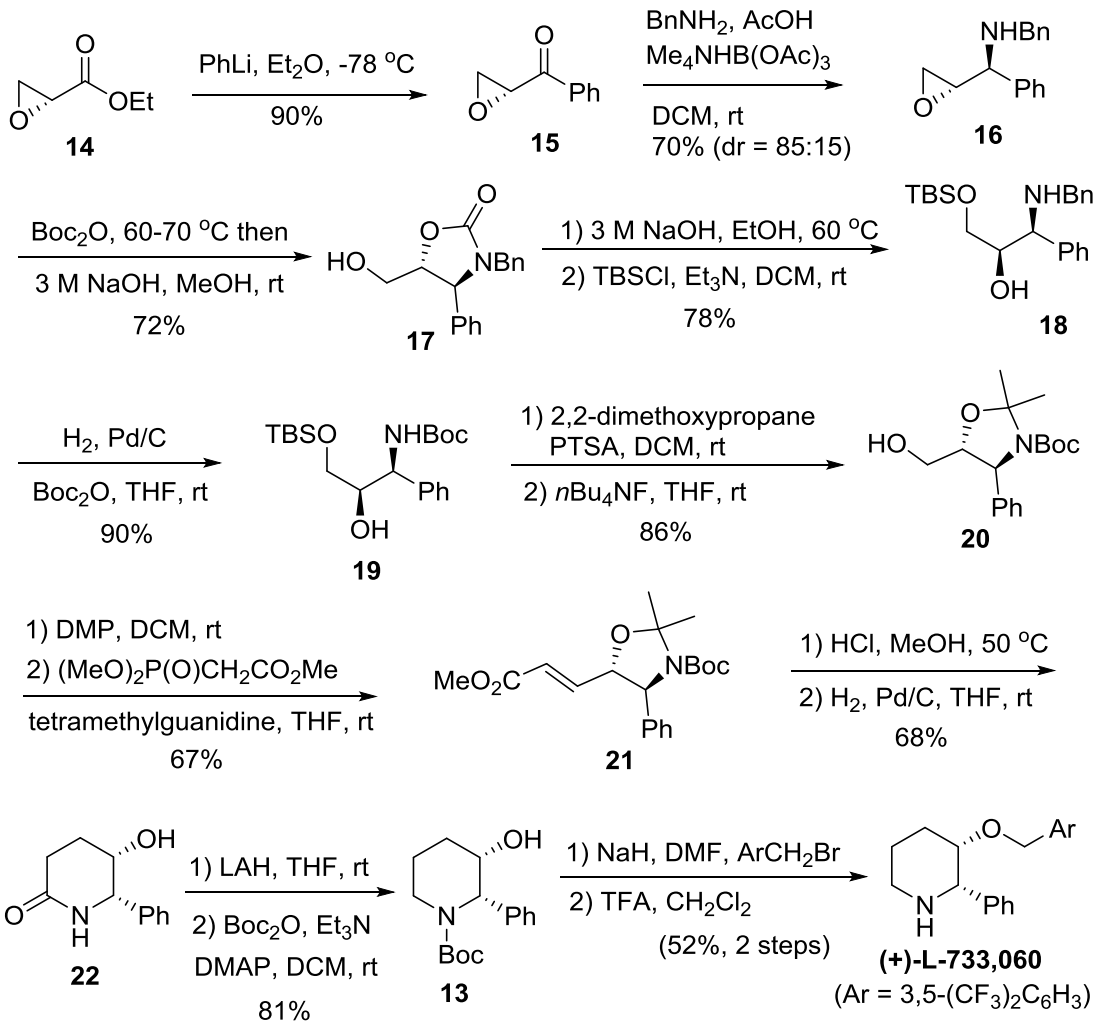
In 2010, Garrido and coworkers reported[6a] an enantioselective synthesis of (+)-L-733,060. The synthesis starts with the Baylis-Hillman reaction of methylacrylate **1** and benzaldehyde **2** (Scheme 3.1). The Baylis-Hillman adduct **3** obtained was treated with acetic anhydride and pyridine to give **4**. A domino reaction (stereoselective Ireland-Claisen rearrangement of the enolate derived from **4** followed by a Michael addition of **5** to the resulting compound) of **4** and chiral lithium amide **5** afforded optically pure γ-substituted δ-aminoacid **6**. Hydrogenolysis of **6** using Pd/C in AcOH and subsequent in situ lactamization gave **7**. The methyl ketone **9** was obtained by converting the piperidin-2-one **7** into Weinreb amide **8** followed by addition of methylmagnesium bromide. Baeyer-Villiger oxidation of **9** with urea hydrogen peroxide (UHP) provided lactam **10**. The lactam **10** was reduced using $LiAlH_4$ and subsequent treatment with $(Boc)_2O$, afforded the N-Boc amino alcohol **11**. The inversion of hydroxyl group is necessary for the synthesis of (+)-L-733,060. Oxidation of **11** with NMO/TPAP followed by stereoselective reduction using $CeCl_3$ and $NaBH_4$, gave the desired piperidine **13**. O-Alkylation of **13** with 3,5-bis(trifluoromethyl)benzyl bromide followed by deprotection provided (+)-L-733,060 (12 steps from Baylis-Hillman adduct **3**, 5.6% overall yield).



Scheme 3.1. Synthesis of (+)-L-733,060 by Garrido.

In the same year, Haddad and coworkers reported[6b] the synthesis of (+)-L-733,060 (Scheme 3.2). The synthesis began with the addition of phenyllithium to ethyl glycidate **14** to provide epoxyketone **15**. Reductive amination of **15** gave the corresponding anti-aminoepoxide **16** as a single diastereomer after flash chromatography. The aminoepoxide was treated with di-*tert*-butyldicarbonate to provide the oxazolidinone **17** through regioselective intramolecular epoxide opening. The oxazolidinone **17** was

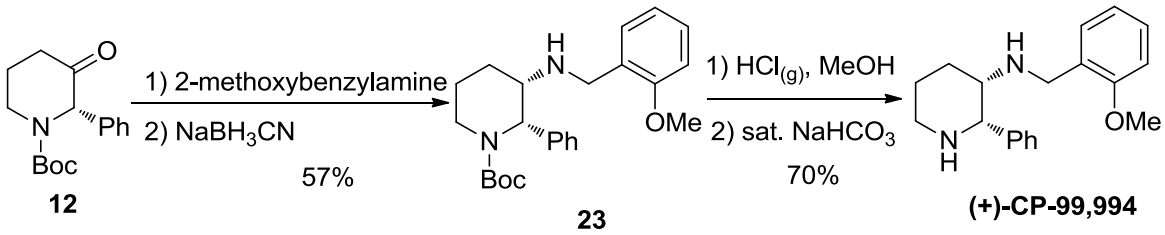
treated with NaOH/EtOH followed by a selective protection of the primary alcohol as *t*-butyldimethylsilyl ether to provide the amino alcohol **18**. Hydrogenolysis of **18** with Pd/C in the presence of di-*t*-butyldicarbonate afforded **19**. Oxazolidine **20** was obtained by the treatment of **19** with 2,2-dimethoxypropane followed by the deprotection of primary alcohol. Oxidation of **20** using Dess-Martin periodinane (DMP) gave the corresponding aldehyde, which was then subjected to a Horner-Wadsworth-Emmons reaction to provide the ester **21**. Unmasking of the 1,2-amino alcohol moiety in **21** followed by hydrogenation provided the saturated ester, which underwent *in situ* cyclization to form the piperidinone **22**. Reduction of **22** using $LiAlH_4$ followed by treatment with $(Boc)_2O$, provided the *N*-Boc aminoalcohol **13**. *O*-Alkylation of **13** with 3,5-bis(trifluoromethyl)benzyl bromide followed by deprotection provided (+)-L-733,060 (16 steps from ethyl glycidate **14**, 5.3% overall yield).



Scheme 3.2. Synthesis of (+)-L-733,060 by Haddad.

3.2.2 Synthesis of (+)-CP-99,994

Garrido and coworkers reported[6a] an enantioselective synthesis of (+)-CP-99,994 (Scheme 3.3). The ketone **12** undergoes reductive amination followed by deprotection provided (+)-CP-99,994. The synthesis of ketone **12** is described in Scheme 3.1.



Scheme 3.3. Synthesis of (+)-CP-99,994 by Garrido.

In 2012, Bhat and coworkers reported[7d] an enantioselective synthesis of (+)-CP-99,994 (Scheme 3.4). The synthesis began with enantiomerically pure L-ornithine **24**, which was protected with benzyl chloroformate to afford **25** in excellent yield. Compound **25** was converted to *N*-methoxy-*N*-methylamide **26** which was treated with phenylmagnesium bromide at -78 ^{o}C in THF to provide ketone **27**. The diaminophenylketone **27** was treated with trimethylsilyl triflate and triethylsilane at -78 ^{o}C to afford the piperidine derivative **28** with good diastereoselectivity (24/1) resulting from cyclization of **27** via an *N*-acyliminium ion. Deprotection of **28** followed by reductive *N*-alkylation of the primary amine with 2-methoxybenzaldehyde provided CP-99,994 (7 steps from L-ornithine **24**, 40% overall yield).

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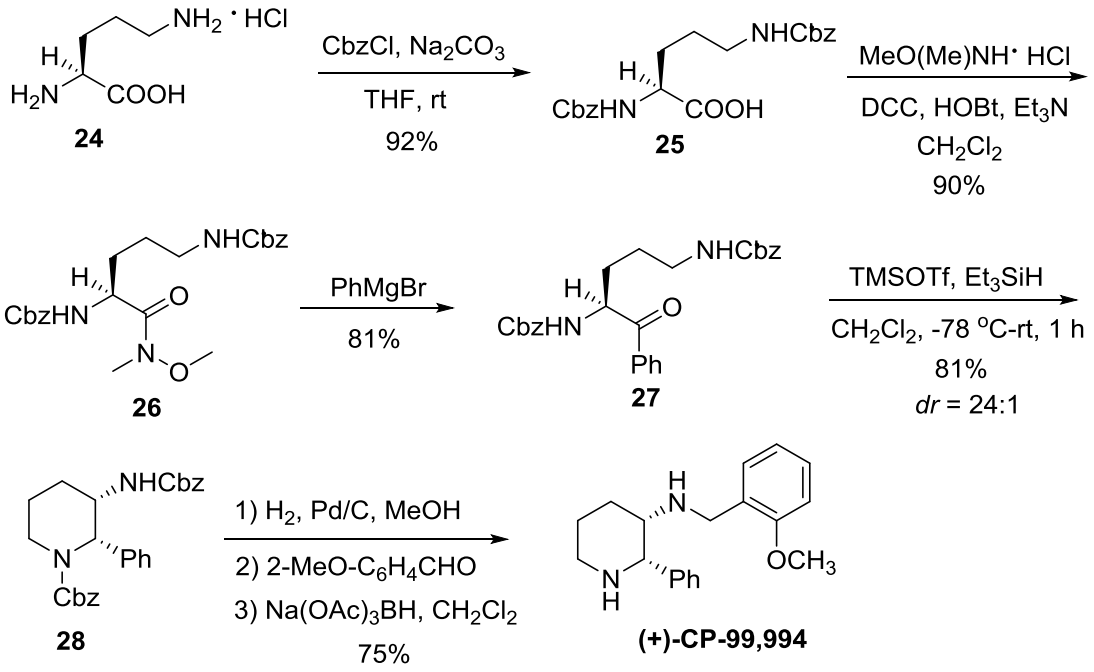
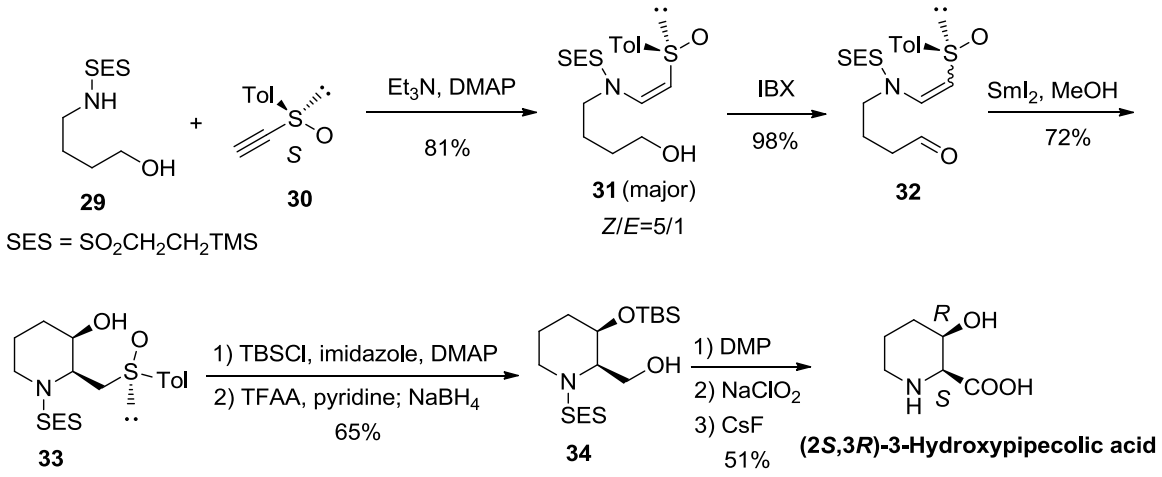


Scheme 3.4. Synthesis of (+)-CP-99,994 by Bhat.

3.2.3. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid

In 2010, Lee and coworkers reported[8b] a synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid. The synthesis started from monoprotected amino alcohol **29** (Scheme 3.5), which was obtained from butane-1,4-diol in three steps. The amino alcohol **29** was added to optically active acetylenic sulfoxide **30** under basic conditions (Et_3N, DMAP) to afford sulfonamide **31** as a 5/1 *Z*:*E* mixture. After separation, *Z*-**31** was oxidized to aldehyde **32** with 2-iodoxybenzoic acid (IBX). A highly diastereoselective radical cyclization took place, when aldehyde **32** was treated with SmI_2 in methanol and the only product formed was the 3-hydroxypiperidine **33** (*d*.*r*. = 100:0, 72%). After protection of the alcohol as a *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMAP), a Pummerer rearrangement

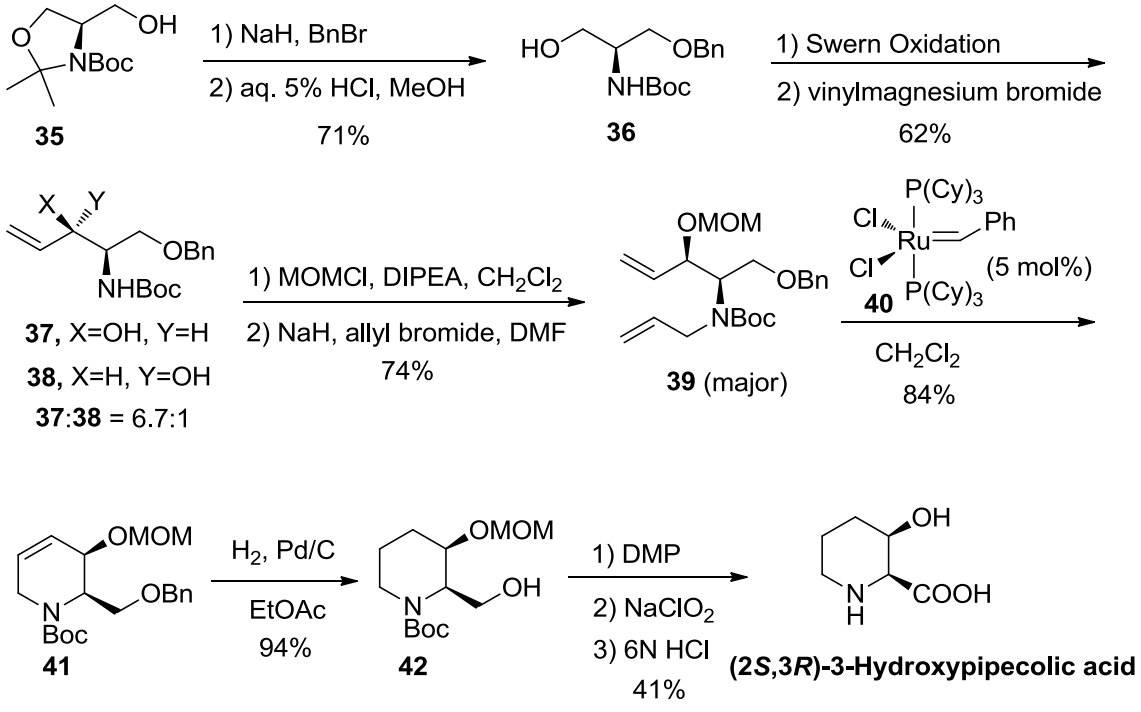
was performed and reduction of the Pummerer product gave the primary alcohol **34**. The hydroxypiperidine **34** was oxidized in two steps (DMP, followed by $NaClO_2$) to the corresponding carboxylic acid. After a deprotection with cesium fluoride, (2*S*,3*R*)-3-hydroxypipecolic acid was obtained (8 steps from **29**, 19% overall yield).



Scheme 3.5. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid by Lee.

A strategy involving ring-closing metathesis (RCM) to build the piperidine core of 3-hydroxypipecolic acid by C–C bond formation was reported recently by Chattopadhyay.[8f] Serinol derivative **35** was protected as a benzyl ether followed by the oxazolidine ring opening under acidic conditions to provide **36** (Scheme 3.6). Swern oxidation of **36** provided the corresponding aldehyde. Treatment of the aldehyde with vinylmagnesium bromide afforded *syn*-allylic alcohol **37** as the major isomer (*d.r.* = 6.7:1). Unfortunately, the *syn* isomer could not be separated from the minor *anti* isomer **38**. After conversion of the mixture of **37** and **38** into their MOM ether derivatives and *N*-

allylation (NaH, allyl bromide), the pure *syn* isomer **39** was separated by column chromatography. Ring-closing metathesis (RCM) of **39** with the first-generation Grubbs catalyst **40** gave the desired dehydropiperidine derivative **41**. Hydrogenation of **41** afforded the piperidine derivative **42**, which was subjected to a two-step oxidation (DMP and Pinnick oxidation) to furnish the carboxylic acid. Deprotection of the Boc and MOM groups under acidic conditions provided the desired (2*S*,3*R*)-3-hydroxypipecolic acid (11 steps from **35**, 10.5% overall yield).



Scheme 3.6. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid by Chattopadhyay.

3.3 Results and Discussions

The 2-substituted 3-hydroxy piperidine motif **A** is accessible by the rearrangement of 5-(1-aminoalkyl or -aminoaryl) butyrolactones **B** (Figure 3.2).[9] The aminobutyrolactones can, in turn, be obtained from the corresponding hydroxy precursors **C**, which are typically obtained by stereoselective vinylogous Mukaiyama aldol reactions of 2-siloxyfurans and aldehydes.[10] However, a much simpler route to stereodefined 5-(1-hydroxyalkyl/aryl) butenolides involves the organocatalytic, direct vinylogous aldol reaction of γ-crotonolactone (2(5*H*)-furanone) with aldehydes, a reaction that has received attention only recently.[11] Given the structural similarities in the targets of the present study (Figure 3.1), it appeared that a suitably functionalized butyrolactone could potentially be employed as a common synthetic precursor to achieve most of the objectives. In addition, this synthetic strategy would also highlight the utility of the organocatalytic direct vinylogous aldol (ODVA) reaction (Figure 3.2).

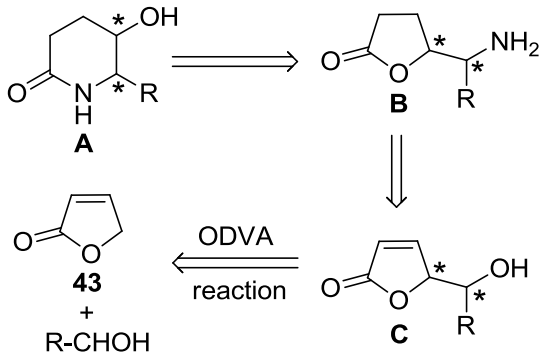
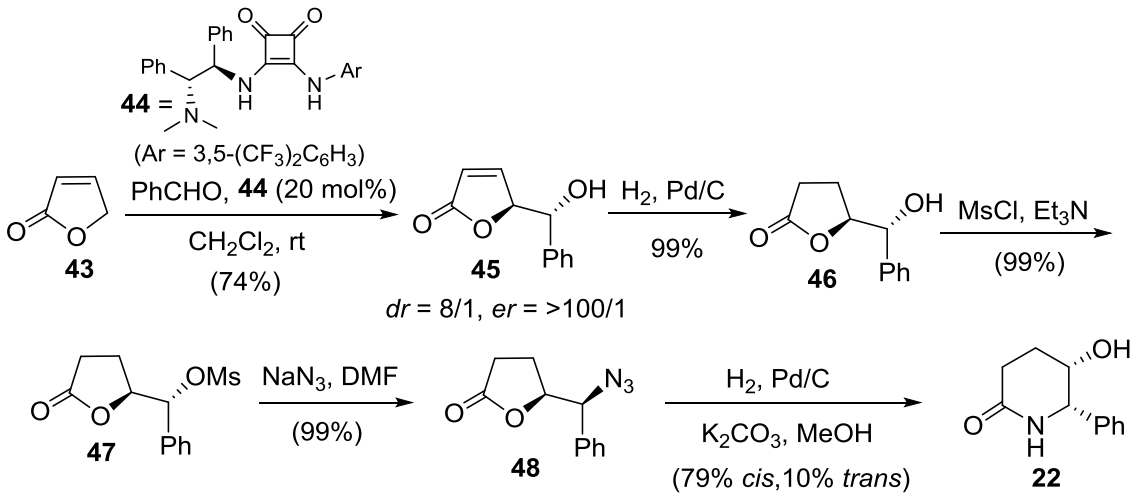


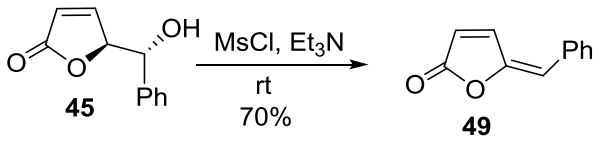
Figure 3.2. The organocatalytic direct vinylogous aldol route to functionalized piperidines.

Our studies therefore began with the synthesis of **45** (Scheme 3.7) and its conversion to (5*S*,6*S*)-5-hydroxy-6-phenylpiperidin-2-one (**22**) which is an advanced precursor to (+)-L-733,060 and (+)-CP-99,994. Initially, the direct vinylogous aldol reaction of commercially available γ-crotonolactone and benzaldehyde was examined in the presence of selected aminothiourea and aminosquaramide catalysts derived from diphenylethylenediamine, 1,2-cyclohexane diamine and amines obtained from cinchona alkaloids. The details of these studies were described in Chapter 2 (pages 27-32). Extensive optimization studies with these catalysts revealed the aminosquaramide **44**[12] as the most efficient catalyst in terms of the yield, diastereoselectivity and enantioselectivity for the aldol product.[11c] Thus, the direct vinylogous aldol reaction of γ-crotonolactone with benzaldehyde provided the butenolide **45** in good yield and diastereoselectivity (74%, *anti*/*syn* = 8/1) and excellent enantiomeric excess (>99% ee for the *anti* diastereomer) when the reaction was conducted in dichloromethane at ambient temperature (Scheme 3.7).



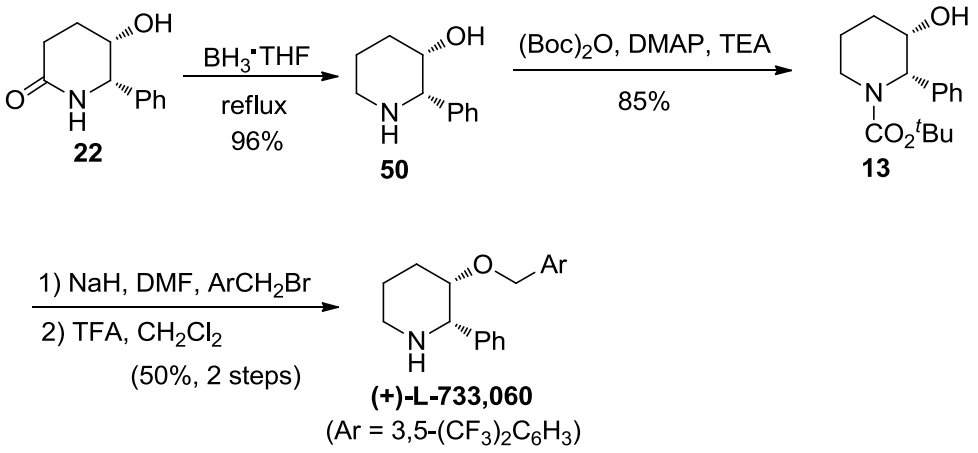
Scheme 3.7. Conversion of aldol product to lactam employing ODVA reaction.

The aldol product **45** (as a diastereomeric mixture) was easily converted to the lactam **22** via a series of simple transformations. Hydrogenation of **45** to the butyrolactone **46**, subsequent mesylation of the secondary alcohol to give **47** and displacement of the mesylate, with inversion of configuration, by azide anion gave the azido butyrolactone **48**. It should be mentioned that the attempted mesylation of **45** exclusively resulted in its dehydration (Scheme 3.8).



Scheme 3.8. Dehydration of aldol product.

The unwanted dehydration side reaction is effectively prevented by prior reduction of the double bond in **44**. Reduction of the azide (H_2, Pd/C) generated a mixture of the corresponding amino butyrolactone and the required piperidone **22** resulting from an intramolecular *N*-acylation of the amino lactone. Notably, hydrogenation of the azide in the presence of a base (K_2CO_3) significantly facilitated this rearrangement to directly provide **22** without any residual amino lactone. At this stage, *cis*-**22** was easily separated from the minor (*trans*) diastereomer by flash chromatography and all further transformations were carried out with diastereomerically pure *cis*-**22**. The overall conversion of **44** to **22** is quite efficient (76% yield over four steps) and can be conducted without purification of any of the intermediates.

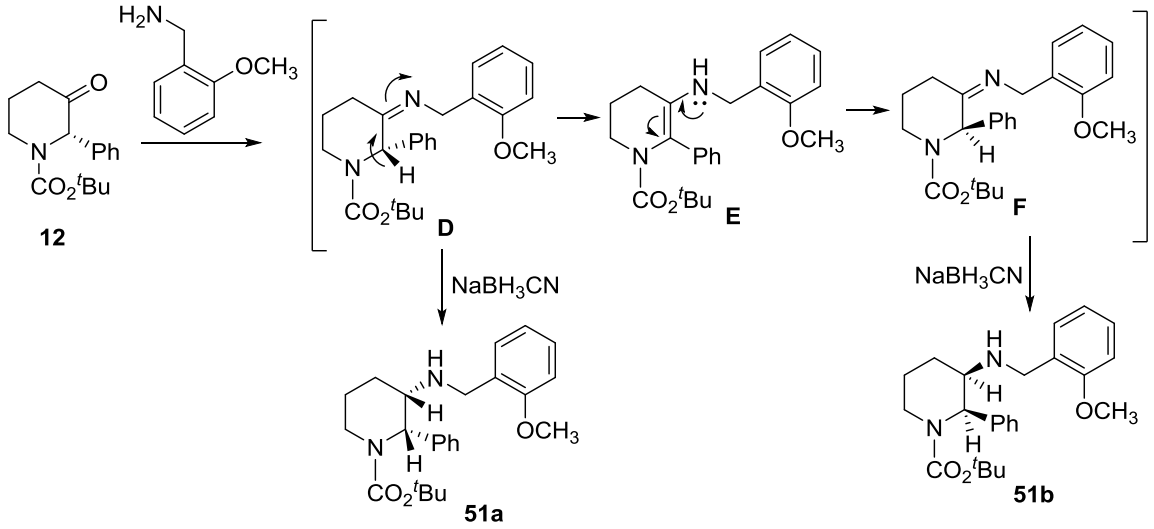


Scheme 3.9. Synthesis of (+)-L-733,060.

Reduction of the piperidinone **22** with borane[6e] provided the corresponding piperidine (**50**, 96%) (Scheme 3.9), which was converted to the *N*-Boc derivative **13**. The conversion of **13** to the neurokinin receptor antagonist targets was achieved by adaptation and some modification of previously described methods (Scheme 3.9). *O*-Alkylation of **13** with 3,5-bis(trifluoromethyl)benzylbromide followed by deprotection provided (+)-L-733,060 (9 steps from benzaldehyde, 24.8% overall yield).

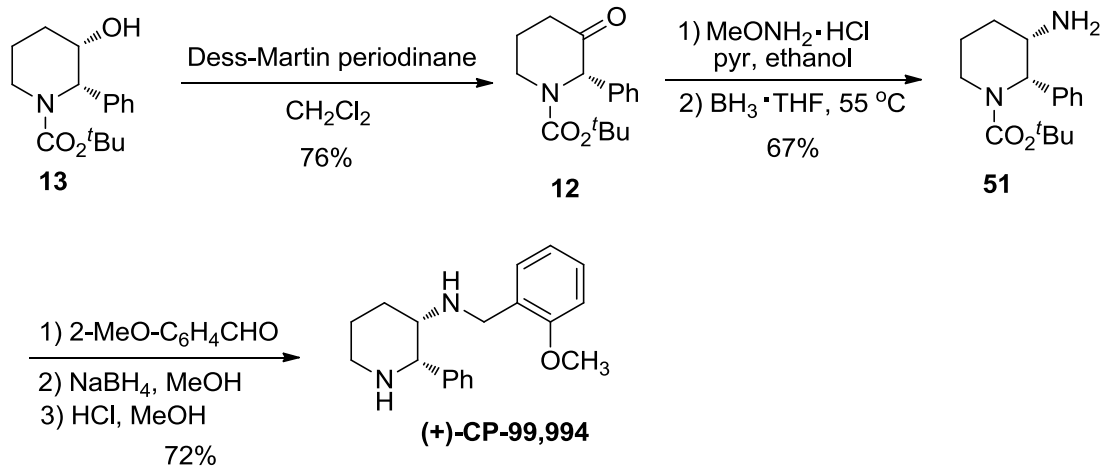
The synthesis of (+)-CP-99,994 required the synthesis of ketone **12** and subsequent reductive amination (Scheme 3.11), and both of these steps required detailed attention to the reaction conditions. Oxidation of **13** with Dess-Martin periodinane provided the 3-piperidinone **12** (77%, 94% ee). Notably, in our hands, the enantiomeric excess of **12** was dependent on the method of oxidation and the DMP procedure[13] is by far the best for obtaining **12** in good yield and high enantiomeric excess. Oxidation of **13** with IBX or IBX/DMSO with heating led to **12** with diminished ees compared to **13**. Swern oxidation of **13** is reported to provide **12** without racemization.[14] In the present

study, Swern oxidation of **13** (96% e.e.) provided **12** with 76% e.e. Oximation of **12** obtained from this Swern oxidation of **13** (e.e. of **13** = 93%), eventually provided CP-99,994 with 60% e.e. Similarly, the reaction of **12** (87% e.e.) with methoxylamine hydrochloride in pyridine as the solvent[13] subsequently provided CP-99,994 with 50% e.e. Changing the solvent to ethanol and employing only the necessary amount of pyridine was found to be important for minimizing the racemization of **12**. Likewise, direct imination of **12** with the appropriate amine (see the reported conversion of **12** to **23** described in Scheme 3.3, page 73),[6a] with or without Lewis acid catalysis, eventually provided racemic CP-99,994. These observations suggest that **12** is prone to racemization if it is heated or exposed to excess base and that the extent of racemization, under these conditions, may depend on variables that are difficult to regulate. A proposed mechanism for the racemization of **12** is shown in Scheme 3.10.



Scheme 3.10. A proposed mechanism for the racemization of **12**.

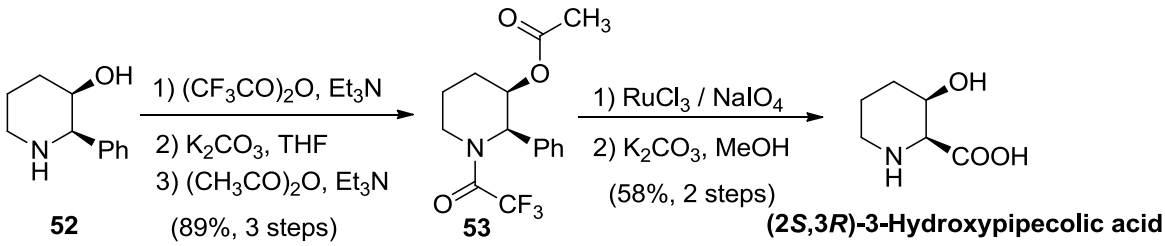
Oximation of **12** with methoxylamine by a significant modification of the reported procedure[13] (ethanol instead of pyridine as the solvent) gave the corresponding oxime ether which was reduced stereoselectively to the amine **51** (Scheme 3.11). Reductive *N*-alkylation of **51** with 2-methoxybenzaldehyde followed by deprotection provided (+)-CP-99,994 (11 steps from benzaldehyde, 16.9% overall yield).



Scheme 3.11. Synthesis of (+)-CP-99,994 employing ODVA reaction.

We next investigated the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid. This particular diastereomer of 3-hydroxypipecolic acid has been the subject of numerous investigations and it continues to attract interest from synthetic chemists.[8a-f] At the outset, it seemed reasonable that direct oxidation of the phenyl ring in the *O*-acetyl derivative of *N*-Boc-(2*R*,3*R*)-2-phenyl-3-hydroxypiperidine (*ent*-**13**), which was obtained by employing the enantiomer of catalyst **44**, would lead us to the pipecolic acid target.

However, attempted oxidation[15] ($RuCl_3/NaIO_4$) of this substrate invariably led to a mixture of products, none of which corresponded to the required carboxylic acid. Interestingly, a change in the *N*-protecting group[8c,16] was beneficial. Accordingly, (2*R*,3*R*)-2-phenyl-3-hydroxypiperidine **52** was first converted to the *N*,*O*-bis (trifluoroacetyl) derivative and the trifluoroacetate ester was selectively replaced with an acetate to provide **53** (Scheme 3.12). Oxidation of the phenyl ring in **53**, with $RuCl_3/NaIO_4$, now proceeded smoothly to provide the corresponding carboxylic acid. Methanolysis of the trifluoroacetamide and the acetate in this intermediate gave (2*S*,3*R*)-3-hydroxypipecolic acid (10 steps from benzaldehyde, 28.1% overall yield).



Scheme 3.12. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid from **52**.

3.4 Conclusions

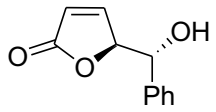
In conclusion, we have achieved the synthesis of three representative members of the 2,3-disubstituted class of bioactive piperidines from the butenolide **45**. The syntheses developed in this study are based on an organocatalytic vinylogous aldol reaction as the pivotal step. Notably, ketone **12** is also a starting material in the synthesis of spirocyclic NK-1 receptor antagonists.[14b,17] The methodology presented here has potential use in the

preparation of libraries of antagonists, related to the those described here, by variation of the aldehyde in the direct vinylogous aldol step.

3.5 Experimental section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. Compounds **45**, **13**, **13a** and **51a** were prepared by literature methods. The conversion of **13a** to (+)-L-733,060 and of **51a** to (+)-CP-99,994 was achieved by literature methods.

(*S*)-5-[(*R*)-Hydroxy(phenyl)methyl]furan-2(5*H*)-one (45):

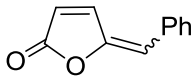


To the catalyst (20 mol %, 1.0 g) in a 25 mL round bottom flask was added benzaldehyde (970 µL, 9.14 mmol) followed by 2-(5*H*)-furanone **43** (1.28 mL, 18.3 mmol) and dichloromethane (5.0 mL). The mixture was stirred for 10 days at room temperature. The mixture was diluted with ethyl acetate (30 mL) and aqueous 2 N HCl (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined extracts were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10/1) to give **45** as a pale yellow solid (1.73 g, 74%). The diastereomeric composition (anti:syn=8/1) was determined by

^{1}H NMR analysis of the crude product. The enantiomeric excess was determined by HPLC (Chiralpak AS-H, hexanes/2-propanol 90/10, 254 nm, t_R = 32.6 min (minor anti), t_R = 37.7 min (minor syn), t_R = 53.1 min (major syn), t_R = 70.5 min (major anti). The ee: > 99% (anti)). In repeated experiments an ee range of 97 to > 99% was observed.

IR: 3432, 3084, 2877, 2360, 2342, 1727, 1453, 1167, 1083, 1067, 1039, 820 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.43-7.34 (m, 6H, ArH and COCH=CH), 6.19 (dd, 1H, J = 5.8, 1.9 Hz, COCH=CH), 5.19-5.18 (br m, 1H, CH=CHCH), 5.09 (br t, 1H, J= 4.1 Hz, ArCHOH), 2.25 (d, 1H, J= 3.8 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (C=O), 152.9 (CH=CH-C=O), 138.3 (ArC), 128.8 (ArC), 128.6 (ArC), 126.1 (ArC), 123.2 (CH=CH-C=O), 86.6 (CH-O-C=O), 73.1 (CH-OH); ***Syn* diastereomer:** δ 7.42-7.36 (m, 5H, ArH), 7.17 (dd, 1H, J = 5.8, 1.5 Hz, COCH=CH), 6.13 (dd, 1H, J= 5.8, 2 Hz, COCH=CH), 5.17 (apparent dt, 1H, J= 7.0, 1.5 Hz, CH=CHCH), 4.71 (d, 1H, J= 7.0 Hz, ArCHOH), 2.78 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (C=O), 153.0 (CH=CH-C=O), 137.7 (ArC), 129.1 (ArC), 128.8 (ArC), 126.8 (ArC), 123.1 (CH=CH-C=O), 86.9 (CH-O-C=O), 75.8 (CH-OH); MS (APCI, pos.): m/z 191.0 (M+1).

5-Benzylidenefuran-2(2*H*)-one (49):

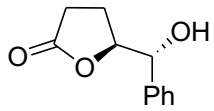


Triethylamine (292 µL, 2.10 mmol) was added slowly to an ice cold solution of **45** (200 mg, 1.05 mmol) in CH_2Cl_2, followed by the addition of methane sulfonyl chloride (122 µL, 1.57 mmol). The reaction mixture was stirred for 1 h at 0 ^{o}C and water (20 mL) was

added at 0 ^{o}C. The mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 130 mg (72%) of **49** as a yellow oil.

IR: 3064, 1705, 1630, 1492, 1214, 1164, 819, 699 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl3) ***E* isomer:** δ 7.82 (1H, d, J= 5.6 Hz), 7.38-7.36 (5H, m), 6.80 (1H, s), 6.35 (1H, dd, J= 5.5, 1.8 Hz), ***Z* isomer**: δ 7.80 (2H, d, J= 7.4 Hz), 7.50 (1H, d, J= 5.3 Hz), 7.49-7.33 (3H, m), 6.23 (1H, d, J= 5.3 Hz), 6.04 (1H, s); MS (APCI pos.): m/z 192.3 (M+1).

(*S*)-Dihydro-5-[(*R*)-(hydroxy(phenyl)methyl]furan-2(3*H*)-one (45):

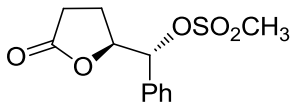


Pd/C (10%, 75 mg) was added to a stirred solution of **45** (750 mg, 3.94 mmol) in EtOAc (10.0 mL). The reaction mixture was stirred for 4 h at room temperature under a balloon filled with H_2. The mixture was filtered through Celite and the filter cake was washed with EtOAc (2 x 30 mL). The combined filtrates were concentrated under reduced pressure to provide 758 mg (99%) of **46** as a white solid (syn:anti=8:1). This was pure by ^{1}H NMR and was used in the next step without purification.

IR: 3391, 1753, 1453, 1370, 1182, 1042, 992 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.39-7.32 (m, 5H, ArH), 5.13 (d, 1H, J= 2.7 Hz, CHOH), 4.72-4.65 (m, 1H, CHCH$_2$), 2.59-2.50 (m, 2H, CH$_2$C=O, CHCH$_2$), 2.5-2.4 (m, 1H, CH$_2$C=O), 2.32-2.24 (m, 1H, CH$_2$CH-O), 1.97-1.90 (m, 1H, CH$_2$CH-O); **Visible peaks for the *syn* diastereomer:** δ 4.65-4.60 (m, 1H, CHCH$_2$), 2.06-2.01 (m, 1H, CH$_2$CHO). ^{13}C NMR (75

MHz, $CDCl_3$): ***Anti* diastereomer:** δ 177.6 (CH_2CO), 138.4 (ArC), 128.7 (ArC), 128.2 (ArC), 126.0 (ArC), 83.3 (CH_2CHO), 73.5 (CHOH), 28.6 (CH_2CO), 20.7 (CH_2CHO); **Visible peaks for the *syn* diastereomer:** δ 176.8 (CH_2CO), 138.3 (ArC), 128.8 (ArC), 128.2 (ArC), 127.0 (ArC), 83.4 (CH_2CHO), 77.2 (CHOH), 28.5 (CH_2CO), 24.0 (CH_2CHO); MS (EI pos): m/z 193.1 (M+1).

(*S*)-Dihydro-5-[(*R*)-(methylsulfonyl)(phenyl)methyl]furan-2(3*H*)-one (47):

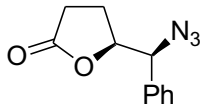


Triethyl amine (626 µL, 4.50 mmol) was added slowly to an ice cold solution of **46** (720 mg, 3.75 mmol) in CH_2Cl_2, followed by the addition of methane sulfonyl chloride (349 µL, 4.50 mmol). The reaction mixture was stirred for 1 h at 0 ^oC and water (20 mL) was added at 0 ^oC. The mixture extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 1.10 g (>99%) of **47** as a yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 3027, 2938, 1775, 1351, 1171, 1031, 944, 912, 874, 836 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.35 (m, 5H, ArH), 5.73 (d, 1H, J = 3.9 Hz, HC-OSO_2Me), 4.86-4.80 (m, 1H, $CHCH_2$), 2.91 (s, 3H, CH_3), 2.50-2.40 (m, 2H, $CH_2C=O$), 2.28-2.09 (m, 2H, $CHCH_2$); **Visible peaks for the *syn* diastereomer:** δ 5.52 (d, 1H, J= 5.7 Hz, $HCOSO_2Me$), 2.89 (s, 3H, CH_3); 13C NMR (75 MHz, CDCl3): ***anti***: δ 176.1, 133.5, 129.6, 129.1, 126.9, 82.8, 80.4, 39.0, 27.7, 22.1; ***syn***: δ 176.0, 133.7, 130.0, 129.2,

127.5, 84.3, 80.3, 39.3, 27.9, 24.2; MS (API-ES) m/z 270.4 (M^+); HRMS (CI): 271.0640 (271.0640 calc. for $C_{12}H_{15}O_5S$, M + H).

(S)-5-[(S)-Azido(phenyl)methyl]-dihydrofuran-2(3*H*)-one (48):

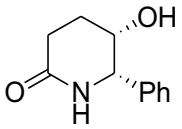


Sodium azide (1.22 g, 18.7 mmol) was added to the crude mesylate **47** (1.10 g, 4.07 mmol) in DMF (5.0 mL) and the mixture was stirred at 80 ^oC for 4 h. The mixture was cooled to room temperature and EtOAc (30 mL) was added followed by water (30 mL). The resulting biphase was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to provide 838 mg (>99%) of **48** as a yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 2101, 1774, 1455, 1250, 1175, 1148, 1066, 990, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): ***Syn* diastereomer:** δ 7.44-7.35 (m, 5H, Ar*H*), 4.71-4.61 (m, 1H, C*H*-CH_2), 4.60 (d, 1H, *J* = 5.9 Hz, C*H*N_3), 2.48-2.34 (m, 2H, CH_2C=O), 2.15-2.05 (m, 1H, CHCH_2), 2.05-1.95 (m, 1H, CHCH_2); **Visible peaks for the *anti* diastereomer:** δ 4.90 (d, 1H, *J* = 4.2 Hz, C*H*N_3), 2.58-2.45 (m, CH_2C=O), 2.25-2.15 (m, CHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): ***Syn* diastereomer:** δ 176.2 (*C*=O), 134.5 (ArC_{ipso}), 129.2 (Ar*C*), 127.8 (Ar*C*), 127.2 (Ar*C*), 81.2 (O-*C*H), 68.5 (H*C*N_3), 28.0 (*C*H_2C=O), 24.6 (*C*H_2CH); **Visible peaks for the *anti* diastereomer:** δ 176.4 (*C*=O), 134.6 (ArC_{ipso}), 129.1 (Ar*C*), 129.0 (Ar*C*),

81.4 (O-CH), 67.8 (HCN$_3$), 28.1 (CH$_2$C=O), 22.3 (CH$_2$CH); MS (EI pos.): m/z 218.1 (M+1); HRMS (APCI pos.): m/z 218.0972 (218.0930 calc. for $C_{11}H_{12}N_3O_2$ (M+H)).

(5*S*,6*S*)-5-Hydroxy-6-phenylpiperidin-2-one (22):

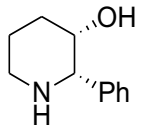


To a stirred solution of **48** (810 mg, 4.24 mmol) in methanol (5.0 mL) was added K_2CO_3 (160 mg, 1.16 mmol) followed by Pd/C (10%, 81 mg). The reaction mixture was stirred for 4 h at room temperature under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with MeOH (2 x 30 mL) and the combined filtrates were concentrated under reduced pressure to provide a yellow gum. This was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95/5 as the eluant) to provide 543 mg (76%) of *cis*-**22** as a fluffy white solid and 91.0 mg (13 %) of *trans*-**22** as a white solid.

***Cis* diastereomer:** Mp: 99 °C (lit.[6b] mp. 92 °C); IR: 3360, 3197, 2945, 1643, 1461, 1399, 1351, 1318, 1197, 1069, 986, 942 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H, ArH), 7.37-7.33 (m, 3H, ArH), 5.85 (br s, 1H, CONH), 4.67 (d, 1H, *J*= 2.7 Hz, CHAr), 4.08 (br s, 1H, CHOH), 2.76-2.69 (m, 1H, CH$_2$C=O), 2.41-2.37 (m, 1H, CH$_2$C=O), 2.15-2.13 (m, 1H, CHCH$_2$), 2.04-2.01 (m, 1H, CHCH$_2$), 1.69 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (C=O), 137.9 (ArC$_{ipso}$), 129.2 (ArC), 128.7 (ArC), 127.0 (ArC), 66.2 (CHOH), 61.9 (CHAr), 26.7 (CHCH$_2$), 26.07 (CH$_2$C=O); MS (APCI, pos.) m/z 192.1 (M+1); HRMS (EI): 191.0950 (191.0946 calc. for $C_{11}H_{13}NO_2$ (M+H)); $[\alpha]_D^{23}$ = +55.3 (*c* 1.06, CH_2Cl_2), lit. $[\alpha]_D^{25}$ = +52.0 (*c* 1.1, CH_2Cl_2).[6b]

***Trans* diastereomer**: IR: 3237, 2364, 1631, 1581, 1485, 1446, 1349, 1333, 1175, 1076, 945, 801 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45-7.40 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH), 5.70 (br s, 1H, CONH), 4.69 (d, J= 2.8 Hz, 1H, CHAr), 4.10 (br s, 1H, CHOH), 2.77 (ddd, 1H, J= 18.0, 11.9, 6.5 Hz, CH_2CO), 2.43 (ddd, 1H, J= 18.0, 6.2, 2.8 Hz, CH_2CO), 2.19-2.15 (m, 1H, $CHCH_2$), 2.07-2.03 (m, 1H, $CHCH_2$), 1.47 (br t, 1H, J= 1.5 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (C=O), 137.8 ($Ar C_{ipso}$), 129.2 (ArC), 128.8 (ArC), 127.0 (ArC), 66.3 (CHOH), 61.9 (CHAr), 26.7 ($CHCH_2$), 26.1 (CH_2C=O); MS (APCI pos.): m/z 192.3 (M^+); $[\alpha]_D^{23}$ = +26.0 (c 1.0 , MeOH); lit. $[\alpha]_D^{23}$ = +31.6 (c 0.75, MeOH).[18]

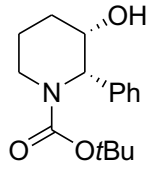
(2*S*,3*S*)-2-Phenylpiperidin-3-ol (50):



Borane-THF complex (4.70 mL, 4.68 mmol) was added to c-122s (300 mg, 1.56 mmol), and the mixture was heated to reflux for 5 h. The mixture was cooled to 0 °C, aqueous HCl (3 M, 12.0 mL) was added and the mixture was stirred for 30 min. at room temperature. The mixture was then concentrated to dryness under reduced pressure and the residue was basified with 5% aqueous NaOH at 0 °C to pH~10. The resulting mixture was extracted with EtOAc, dried (Na_2SO_4) and concentrated to provide **50** as a white solid (267 mg, 96%). This was pure by ^1H NMR and was used in the next step without purification.

Mp: 90-93 ^{o}C; IR: 3274, 2926, 2851, 1447, 1323, 1089, 1054, 1053, 989 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H, ArH), 7.32-7.24 (m, 2H, ArH), 3.86 (br s, 1H, CHAr), 3.78 (br s, 1H, CHOH), 3.22-3.19 (m, 1H, NCH_2), 2.81 (dt, 1H, J= 12.1, 2.8 Hz, NCH_2), 2.02-1.92 (m, 1H, $CHCH_2$), 1.89-1.84 (m, 1H, $CHCH_2$), 1.74-1.67 (m, 1H, CH_2CH_2N), 1.52-1.48 (m, 1H, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0 ($Ar C_{ipso}$), 128.5 (ArC), 127.3 (ArC), 126.6 (ArC), 68.9 (CHOH), 65.0 (CHAr), 47.5 (NCH_2), 32.0 ($CHCH_2$), 19.9 (CH_2CH_2N); MS (APCI, pos.): m/z 178.1 (M+1); HRMS (EI): 177.1153 (177.1154 calcd for $C_{11}H_{15}NO$); $[\alpha]_D^{23}$ = +66.45 (c 0.62, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (13):

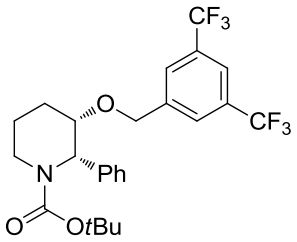


To a solution of **50** (500 mg, 2.82 mmol) in CH_2Cl_2 (5.0 mL) were added di-*tert*-butyl dicarbonate (616 mg, 2.82 mmol), 4-(dimethylamino)pyridine (25 mg, 0.20 mmol) and triethylamine (431 µL, 3.10 mmol) at 0 ^{o}C. The solution was stirred at room temperature for 3 h, saturated aqueous NH_4Cl was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 7/3) afforded 663 mg (85%) of **13** as colorless oil.

IR: 3452, 2937, 1661, 1413, 1362, 1255, 1175, 1141, 1074, 1024, 962, 871 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 7.45 (d, 2H, J= 7.6 Hz, ArH), 7.34 (t, 2H, J= 7.6 Hz, ArH),

7.28-7.26 (m, 1H, ArH), 5.33 (d, 1H, J= 5.4 Hz, CHAr), 4.1-4.06 (m, 1H, CHOH), 4.01 (dd, J= 4.9 Hz, 13.2 Hz, 1H, NCH$_2$), 3.04 (dt, J= 3.9 Hz, 13.2, 1H, NCH$_2$), 1.84-1.67 (m, 3H, CH$_2$CH$_2$), 1.67-1.62 (m, 1H, CH$_2$CH$_2$), 1.58 (s, 1H, OH), 1.37 (s, 9H, C(CH$_3$)$_3$) ; ^{13}C NMR (500MHz, $CDCl_3$): δ 155.4 (C=O), 138.4 (ArC_{ipso}), 128.4 (ArC), 127.2 (ArC), 79.9 (C(CH$_3$)$_3$), 70.1 (CHOH), 59.3 (CHAr), 39.5 (CH$_2$N), 28.3 ((CH$_3$)$_3$, 27.7 (CHCH$_2$), 23.1 (NCH$_2$CH$_2$); MS (APCI, pos.): m / z 378.1 ((M-Boc)+1); $[\alpha]_D^{23}$ = +42.3 (c 1.0, $CHCl_3$), lit. $[\alpha]_D^{24}$ = +42.6 (c0.54, $CHCl_3$).[6b]

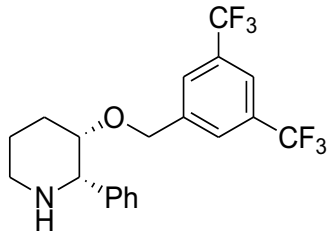
(2*S*,3*S*)-*tert*-Butyl-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-phenylpiperidine-1-carboxylate (13a):



To a solution of **13** (60 mg, 0.22 mmol) in DMF/THF (3:1, 1.0 mL) under N_2 at 0 ^oC was added sodium hydride (95%, 16 mg, 0.65 mmol). The mixture was stirred at room temperature for 30 min. and 3,5-bis(trifluoromethyl)benzyl bromide (0.10 g, 0.33 mmol) was added at 0 ^oC. The mixture was stirred 16 h at room temperature, after which water (5.0 mL) added at 0 ^oC and the mixture was extracted with Et_2O (2 x 10 mL) The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 9/1) to give 57 mg (52%) of **13a** as colorless oil.

IR: 2939, 1686, 1411, 1357, 1276, 1175, 1128, 885 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.77 (s, 1H, Ar*H*), 7.71 (s, 2H, Ar*H*), 7.55 (d, 2H, *J*= 7.7 Hz, Ar*H*), 7.33 (t, 2H, *J*= 7.7 Hz, Ar*H*), 7.27-7.25 (m, 1H, Ar*H*), 5.69 (br s, 1H, C*H*Ar), 4.73 (AB system, 2H, *J*= 12.6 Hz, CH_2Ar), 3.96-3.90 (m, 1H, NCH_2 or C*H*O), 3.90-3.86 (m, 1H, NCH_2 or C*H*O), 2.77 (dt, *J* = 13.1, 3.2 Hz, 1H, NCH_2), 2.01-1.96 (m, 2H, CHCH_2), 1.74-1.70 (m, 1H, CH_2CH_2N), 1.70-1.60 (m, 1H, CH_2CH_2N), 1.46 (s, 9H, C(CH_3)$_3$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3 (*C*=O), 141.0 (Ar*C*), 138.01 (Ar*C*), 131.6 (q, *J*= 33.3 Hz, *C*F_3), 128.4 (Ar*C*), 128.3 (Ar*C*), 127.2 (br, Ar*C*), 127.1 (Ar*C*), 125.1 (Ar*C*), 121.5-121.4 (br, Ar*C*), 80.1 (*C*(CH$_3$)$_3$), 78.7 (*C*H-O), 69.2 (*C*H_2Ar), 55.5 (*C*HAr), 39.2 (N*C*H_2), 28.4 (C(*C*H$_3$)$_3$), 25.9 (CH*C*H_2), 24.2 (*C*H_2CH_2N); MS (APCI, pos.): *m* / *z* 204.2 ((M-Boc)+1); $[\alpha]_D^{23}$ = +39.1 (*c*1.0, $CHCl_3$), lit. $[\alpha]_D^{25}$ = +27.9 (*c*0.8, $CHCl_3$).[6e]

(2*S*,3*S*)-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-phenylpiperidine ((+)-L-733,060):

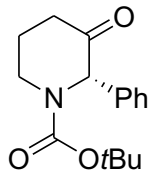


To a solution **13a** (46 mg, 0.09 mmol) in CH_2Cl_2 (1.0 mL) was added trifluoroacetic acid (70 µL, 0.91 mmol) at 0 ^oC. The mixture was stirred at room temperature for 18 h and 10% aqueous NaOH was added at 0 ^oC. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to

afford 34 mg (92%) of (+)-L-733,060 as a colorless oil that was pure by ^{1}H NMR (500 MHz).

IR: 2936, 2858, 1374, 1342, 1276, 1174, 1126, 883, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 7.69 (s, 1H, ArH), 7.44 (s, 2H, ArH), 7.37 (br d, 2H, J= 7.3 Hz, ArH), 7.32 (br t, J= 7.2 Hz, 2H, ArH), 7.27 (m, 1H, ArH), 4.52 (d, 1H, J= 12.5 Hz, CH_2Ar), 4.14 (d, 1H, J= 12.5 Hz, CH_2Ar), 3.85 (s, 1H, CHAr), 3.68 (s, 1H, $CHOCH_2$Ar), 3.30-3.27 (m, 1H, NCH_2), 2.85 (dt, J = 12.4, 2.8 Hz, 1H, NCH_2), 2.22 (d, 1H, J = 13.9 Hz, $CHCH_2$), 1.89-1.82 (m, 1H, $CHCH_2$), 1.77-1.70 (m, 1H, CH_2CH_2CH-O), 1.54-1.51 (m, 1H, CH_2CH_2CH-O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4 (ArC), 141.1 (ArC), 131.33 (q, J= 33.2 Hz, CF_3), 128.2 (ArC), 127.5 (ArC), 127.3 (ArC), 126.8 (ArC), 125.1 (ArC), 121.5-121.2 (m, ArC), 77.1 (CH-O), 70.1 (CH_2Ar), 64.2 ($CHAr$), 46.9 (NCH_2), 28.4 (CH_2CH-O), 20.3 (CH_2CH_2N); MS (APCI pos.): m / z 404.4 (M^+); HRMS (CI): m / z 404.1447 (404.1449 calcd for $C_{20}H_{20}F_6NO$, M+H); $[\alpha]_D^{23}$ = +48.6 (c 0.51, $CHCl_3$); lit. $[\alpha]_D^{24}$ = +31.7 (c 0.5, $CHCl_3$)[6e].

(*S*)-*tert*-Butyl-3-oxo-2-phenylpiperidine-1-carboxylate (12):

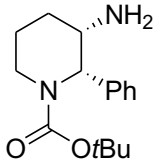


Dess-Martin periodinane (1.07 g, 2.50 mmoles) was added to a solution of alcohol **13** (0.14 g, 0.50 mmol) in CH_2Cl_2 (3.0 mL) and the mixture was stirred at room temperature for 1 h. Saturated aqueous sodium bicarbonate (10 mL) was added, the organic layer was

separated and the aqueous layer was extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 8/2) to give 106 mg (76%) of **12** as a pale yellow liquid.

IR: 2974, 1690, 1401, 1361, 1247, 1154 (br), 1105, 1031, 967 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.37-7.20 (m, 5H, ArH), 5.65 (br s, 1H, CHAr), 4.08 (br s, 1H, CH_2N), 3.34-3.30 (br m, 1H, CH_2N), 2.51-2.40 (m, 2H, $CH_2C=O$), 1.98-1.88 (m, 2H, $CH_2CH_2C=O$), 1.43 (br s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 ($CH_2C=O$), 155.0 (N-C=O), 135.6 (ArC), 128.9 (ArC), 127.6 (ArC), 125.4 (ArC), 80.7 ($C(CH_3)_3$), 65.9 (br, CHAr), 40.1 (br, NCH_2), 37.3 ($CH_2C=O$), 28.2 ($C(CH_3)_3$), 22.8 (CH_2CH_2N); HRMS (EI pos.): 275.1525 (275.1521 calcd for $C_{16}H_{21}NO_3$); HPLC: Chiralpak AD-H, hexanes/2-propanol 99/1, 254 nm, t_{major} = 35.7 min, t_{minor} = 37.6 min.; ee = 96% ee.

(2*S*,3*S*)-*tert*-Butyl 3-amino-2-phenylpiperidine-1-carboxylate (51):

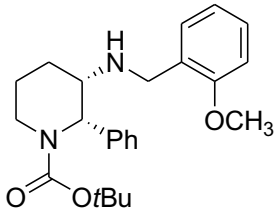


To a stirred solution of ketone **12** (60 mg, 0.22 mmoles) in ethanol (0.50 mL) at room temperature, was added anhydrous pyridine (26 μL, 0.33 mmol) followed by methoxylamine hydrochloride (27 mg, 0.33 mmol) and the mixture was stirred at room temperature for 30 min. Saturated aqueous NH_4Cl (10 mL) was added, the mixture was stirred for 30 min, and then extracted with diethyl ether (3 x 30 mL). The combined

organic layers were dried (Na_2SO_4), and concentrated to provide the crude oxime methyl ether of **51** (70 mg). This was treated with BH_3-THF (1 M soln. in THF, 0.65 mL, 0.63 mmoles) under N_2 and the solution was stirred at 50 ^oC for 4h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 30 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 9/1) to provide 40 mg (67%) of **51** as pale yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 2931, 1682, 1407, 1362, 1252, 1147, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.44 (d, 2H, J= 7.3 Hz, ArH), 7.31-7.28 (m, 2H, ArH), 7.26-7.23 (m, 1H, ArH), 5.20 (d, 1H, J = 6.0 Hz, CHAr), 4.01 (br d, 1H, J= 10.9 Hz, CHNH$_2$), 3.20-3.11 (m, 2H, NCH$_2$), 1.88-1.65 (m, 4H, CH$_2$CH$_2$CH), 1.45 (br s, 2H, NH$_2$), 1.36 (s, 9H, C(CH$_3$)$_3$); 13C NMR (75 MHz, CDCl3): δ 155.4 (CO$_2$^{t}Bu), 139.1 (ArC), 129.4 (2 × ArC), 128.2 (2 × ArC), 127.2 (ArC), 79.7 (OC(CH$_3$)$_3$), 60.6 (NCH), 51.2 (CHNH$_2$), 39.8 (NCH$_2$), 29.2 (NH$_2$CHCH$_2$), 28.3 (C(CH$_3$)$_3$), 24.4 (NCH$_2$CH$_2$); MS (EI pos.): m /z 277.2 (M + 1).

(2*S*,3*S*)-*tert*-Butyl 3-(2-methoxybenzylamino)-2-phenylpiperidine-1-carboxylate (51a):

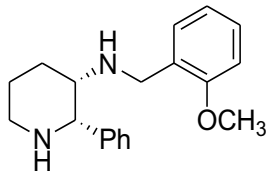


To a solution of amine **51** (16 mg, 0.06 mmol) in THF (1.0 mL) was added 2-methoxybenzaldehyde (21 μL, 0.17 mmol) and the mixture was stirred at room

temperature for 22 h. The solvent was removed under reduced pressure and the residue was dissolved in methanol (1.0 mL). Sodium borohydride (13 mg, 0.35 mmoles) was added to this solution and the mixture was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (pH~8) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/ EtOAc, 9/1) to provide 18 mg (78%) of **51a** as pale yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 2933, 1685, 1494, 1457, 1407, 1359, 1241, 1178, 1144, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, J= 7.3 Hz, ArH), 7.33-7.28 (m, 2H, ArH), 7.26-7.18 (m, 3H, ArH), 6.89 (t, 1H, J= 7.4 Hz, ArH), 6.81 (d, 1H, J= 8.5 Hz, ArH), 5.47 (s, 1H, CHAr), 3.95 (d, 1H, J= 11.1 Hz, NCH_2), 3.77 (AB system, 2H, J= 13.4 Hz, CH_2Ar), 3.71 (s, 3H, OCH_3), 3.07-3.03 (m, 1H, CHNH), 2.97 (dt, 1H, J= 13.0, 2.3 Hz, NCH_2), 1.85-1.75 (m, 3H, CH_2CHNH), 1.66-1.53 (m, 2H, CH_2CH_2N), 1.41 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (CO), 155.2 (ArC), 139.2 (ArC), 129.5 (ArC), 129.2 (ArC), 128.4 (ArC), 128.1 (ArC), 128.0 (ArC), 126.9 (ArC), 120.4 (ArC), 110.1 (ArC), 79.6 (C(CH$_3$)$_3$), 57.2 (CHAr), 55.0 (CHNH, OCH$_3$), 46.6 (CH$_2$Ar), 39.5 (NCH$_2$), 28.4 (C(CH$_3$)$_3$, 26.8 (CH$_2$CHNH), 24.3 (CH$_2$CH$_2$N); MS (EI pos.): m/z 397.5 (M+1); HRMS (EI): m/z 396.2412 (396.2413 calcd for $C_{24}H_{32}N_2O_3$); HPLC (Chiralpak OD-H, hexanes/2-propanol 90/10, 210 nm, t_{minor} = 4.64 min, t_{major} = 5.20 min; ee = 93.4%.

(2*S*,3*S*)-*N*-(2-Methoxybenzyl)-2-phenylpiperidin-3-amine ((+)-CP-99,994):

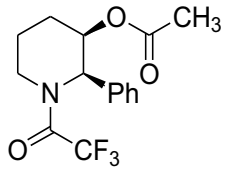


To a solution of **51a** (18 mg, 0.05 mmol) in MeOH (0.50 mL) was added 1:1 mixture of conc. aqueous HCl and methanol (1.0 mL) at 0 ^{o}C and the mixture was stirred at room temperature for 22 h. Saturated aqueous $NaHCO_3$ was added (pH~8), and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4), and concentrated to give 12 mg (92%) of CP-99,994 as a pale yellow oil that was pure by ^{1}H NMR (500 MHz).

IR: 2935, 2846, 1647, 1595, 1492, 1451, 1239, 1111, 1027, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.12 (m, 6H, ArH), 6.97 (d, 1H, J= 7.3 Hz, ArH), 6.80 (t, 1H, J= 7.3 Hz, ArH), 6.67 (d, J= 8.2 Hz, 1H, ArH), 3.87 (s, 1H, CHAr), 3.67 (d, 1H, J= 13.9 Hz, CH_2Ar), 3.44 (s, 3H, OCH_3), 3.41 (d, 1H, J= 13.9 Hz, CH_2Ar), 3.28-3.25 (m, 1H, CHNH), 2.82-2.76 (m, 2H, NCH_2), 2.14 (br d, 1H, J= 13.5 Hz, CH_2CHNH), 1.95-1.91 (m, 1H, CH_2CH_2NH), 1.77 (br s, 2H, NH), 1.63-1.57 (m, 1H, CH_2CHNH), 1.39 (br d, 1H, J= 13.1 Hz, CH_2CH_2NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6 (ArC), 142.4 (ArC), 129.5 (ArC), 128.2 (ArC), 128.1 (ArC), 127.8 (ArC), 126.5 (ArC), 126.3 (ArC), 119.9 (ArC), 109.7 (ArC), 63.9 (CHAr), 54.7 (NCH), 54.6 (OCH_3), 47.7 (CH_2Ar), 46.7 (NCH_2), 28.2 (CH_2CHN), 20.3 (CH_2CH_2NH); MS (APCI pos.): *m/z* 297.4 (M+1); HRMS (EI): 296.1898 (296.1889 calcd for $C_{19}H_{24}N_2O$, M^+); $[\alpha]_D^{23}$ = +68.0 (*c* 1.1,

$CHCl_3$); lit. $[\alpha]_D^{20}$ = +67.2 (c1, $CHCl_3$);[13] HPLC (Chiralpak OD-H, hexanes/2-propanol 90/10, 210 nm, t_{major} = 6.07 min, t_{minor} = 8.94 min; ee = 94.8%.

_N_-Trifluoroacetyl-(2*S*,3*R*)-3-acetoxy-2-phenylpiperidine (53):

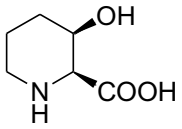


To an ice cold solution of the aminoalcohol **52** (e r50t, 500 mg, 2.82 mmol; prepared as described for **50**, but with the enantiomer of catalyst **44**) in CH_2Cl_2 (30.0 mL) containing Et_3N (2.30 mL, 16.9 mmol) and 4-(dimethylamino)pyridine (17 mg, 0.14 mmol) was added triflouroacetic anhydride (1.60 mL, 11.3 mmol). The solution was stirred at room temperature for 12 h, water was added and the solution was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4), and concentrated. The residue was dissolved in THF (30.0 mL), K_2CO_3 (770 mg, 5.57 mmol) was added and the mixture was stirred for 36 h at room temperature. Water was added and the mixture was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 7/3) to provide 715 mg (93%) of the trifluoroacetamide derivative of **52**. This was dissolved in CH_2Cl_2 (30.0 mL), Et_3N (1.57 mL, 11.3 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.12 mmol) were added and the solution was cooled to 0 ^oC. Acetic anhydride (530 μL, 5.19 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and

concentrated. The crude product was purified by flash chromatography (hexanes/ EtOAc, 8/2) to provide 795 mg (89%) of **53** as a pale yellow oil.

IR: 1743, 1687, 1451, 1370, 1235, 1193, 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**: Major rotamer:** δ 7.49-7.26 (m, 5H, ArH), 5.99 (d, 1H, J= 5.7 Hz, CHAr), 5.25-5.20 (m, 1H, CHOAc), 3.83 (br d, 1H, J= 14.0 Hz, NCH_2), 3.19-3.13 (m, 1H, NCH_2), 2.17-2.11 (m, 2H, CH_2CHOAc), 2.0 (s, 3H, $COCH_3$), 1.85-1.83 (m, 2H, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 ($COCH_3$), 135.4 ($COCF_3$), 128.9 (ArC), 128.7 (ArC), 128.0 (ArC), 128.0 (ArC), 127.8 (ArC), 116.6 (q, J= 288.0 Hz, CF_3), 55.5(CHAr), 41.2 (q, J= 3.4 Hz, CH_2N), 24.9 (CH_2CH-O), 23.9 (CH_3), 21.1 (CH_2CH_2N); **Minor rotamer:** ^{1}H NMR (500 MHz, $CDCl_3$)**,** visible peaks: 5.55 (d, J= 5.3 Hz, 1H, CHAr), 4.37 (d, J= 11.8 Hz, 1H, CH_2N), 2.75 (dt, 1H, J = 13.3, 4.1 Hz, NCH_2N). ^{13}C NMR (75 MHz, $CDCl_3$), visible peaks: δ 169.7 ($COCH_3$), 156.5 (q, J= 36.1 Hz, CF_3), 135.0 ($COCF_3$), 72.4 (CH-O), 70.6 (CHO), 57.7 (CHAr), 38.8 (CH_2CH-O), 23.5 (CH_3), 21.1 (CH_2CH_2N); MS (APCI pos.): m /z 216.1 (M+1).

(2*R*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid:



To a mixture of **53** (0.15 g, 0.48 mmol) in carbon tetrachloride (0.75 mL), acetonitrile (0.75) mL and water (1.1 mL), were added sodium periodate (1.53 g, 7.13 mmol) and ruthenium chloride (5.0 mg, 0.02 mmol) and the mixture was stirred vigorously at ambient temperature for 20 h. The mixture was filtered through a pad of Celite and the

residue was rinsed several times with CH_2Cl_2. The black filtrates were combined, dried (Na_2SO_4) and concentrated. The residue obtained was dissolved in methanol (5.0 mL), K_2CO_3 (393 mg, 2.84 mmol) was added and the mixture was stirred at room temperature for 12 h. The resulting solution was concentrated and the residue was dissolved in aqueous 1 N HCl (1.0 mL). This solution was applied to a column of Dowex 50Wx8 resin (200-400 dry mesh) and the column was eluted with deionized water (250 mL) followed by 5% aqueous ammonia. The ninhydrin positive fractions were combined and concentrated to provide 40 mg (58%) of (2*R*,3*R*)-3-hydroxypiperidine-2-carboxylic acid as a white solid.

Mp. 231-235 ^oC (lit.[8a] mp 233-238 ^oC); IR: 3600-2859 (br), 1618 (br), 1461, 1399, 1312, 1205, 1137, 1083, 1042, 996 cm^{-1}; ^1H NMR (500 MHz, D_2O): δ 4.44 (s, 1H, C*H*COOH), 3.60 (d, 1H, *J*= 1.4 Hz, C*H*-OH), 3.37-3.33 (m, 1H, C*H*$_2$NH), 2.94 (dt, 1H, *J*= 3.5, 12.9 Hz, C*H*$_2$NH), 1.95-1.84 (m, 2H, C*H*$_2$CHOH), 1.76-1.66 (m, 2H, C*H*$_2$CH$_2$N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (*C*OOH), 64.1 (*C*H-OH), 62.2 (*C*HCOOH), 43.6 (*C*H$_2$N), 28.7 (*C*H$_2$CHOH), 15.9 (*C*H$_2$CH$_2$N); MS (APCI pos.): *m*/*z* 146.1 (M+H); $[\alpha]_D^{23}$ = -53.5 (*c* 0.6, H_2O); lit. $[\alpha]_D^{24}$ = - 52.8 (*c* 0.6, H_2O). [8f]

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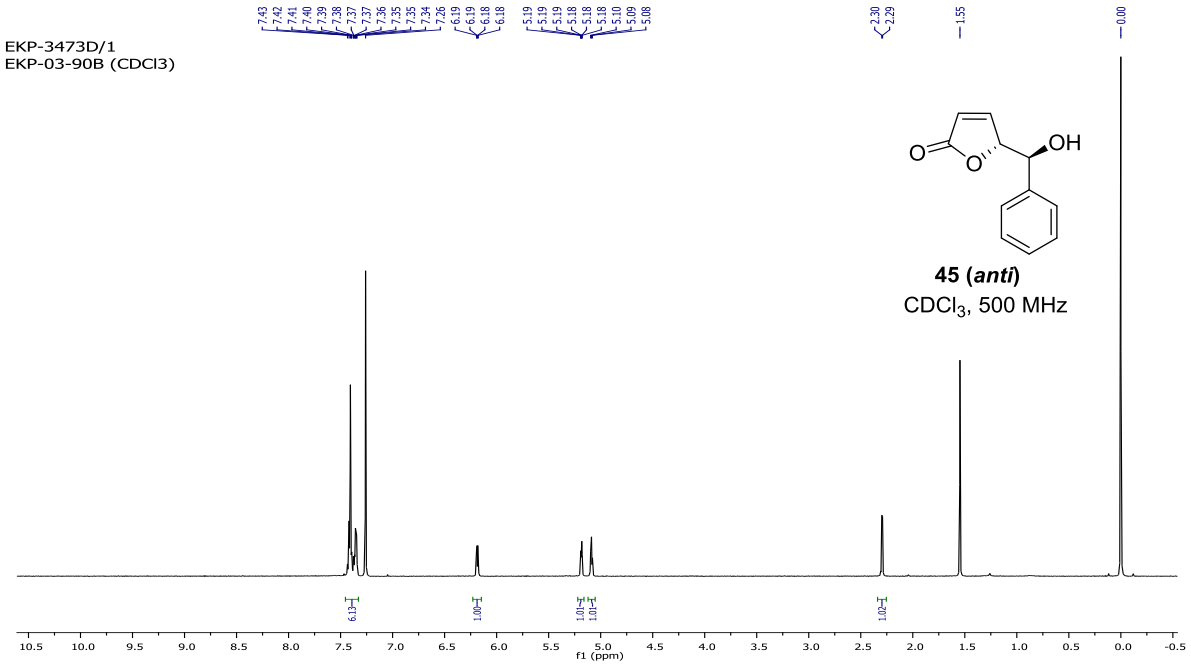
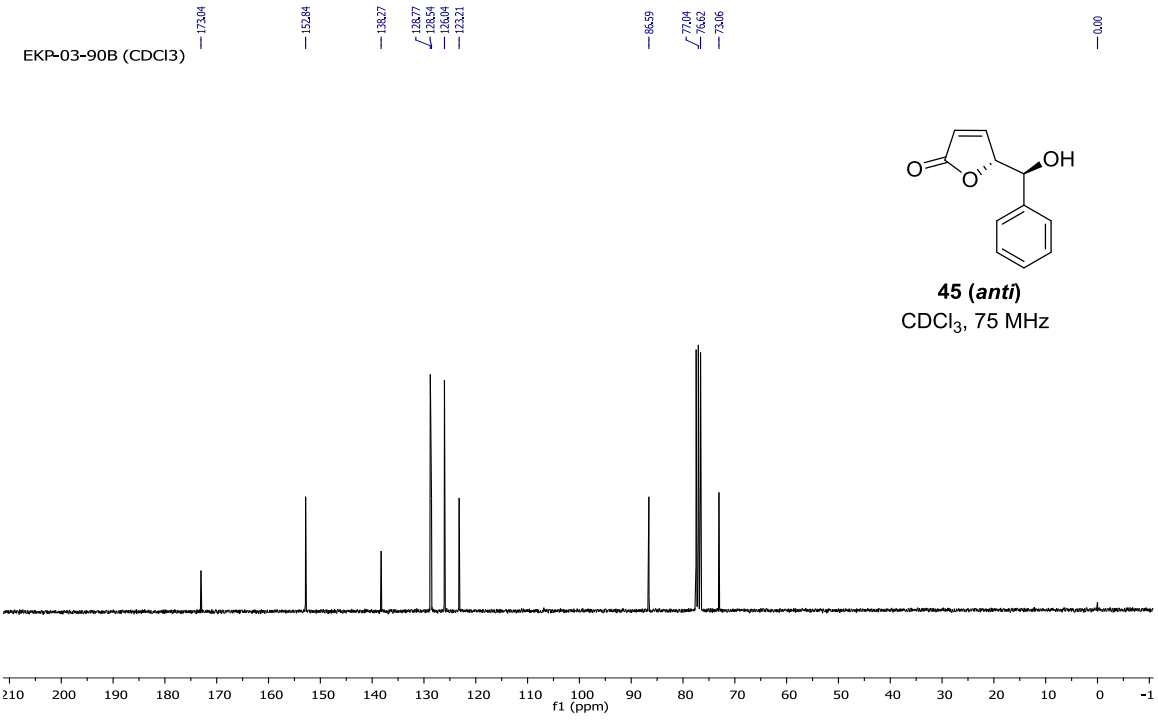
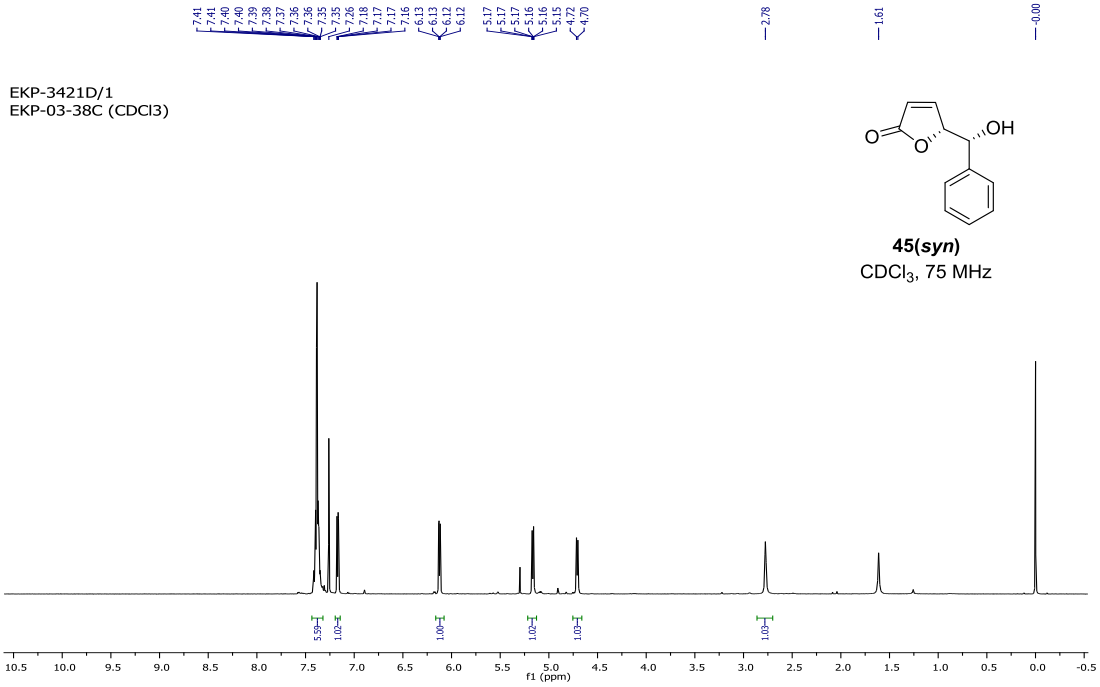
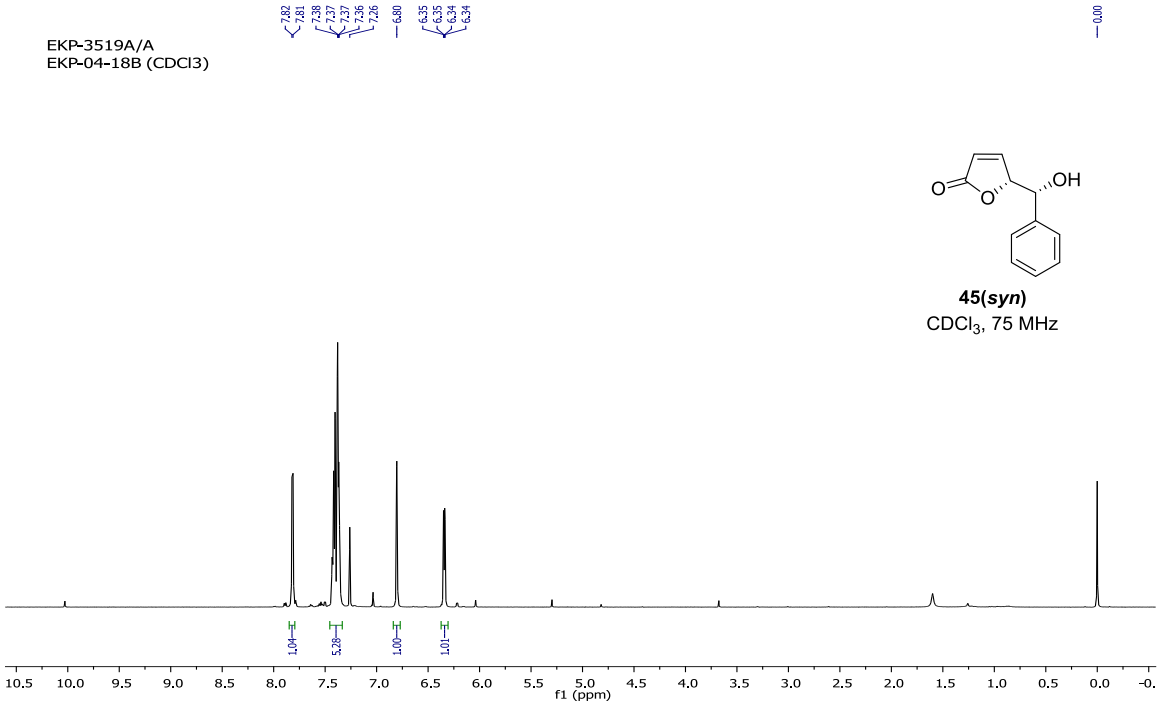
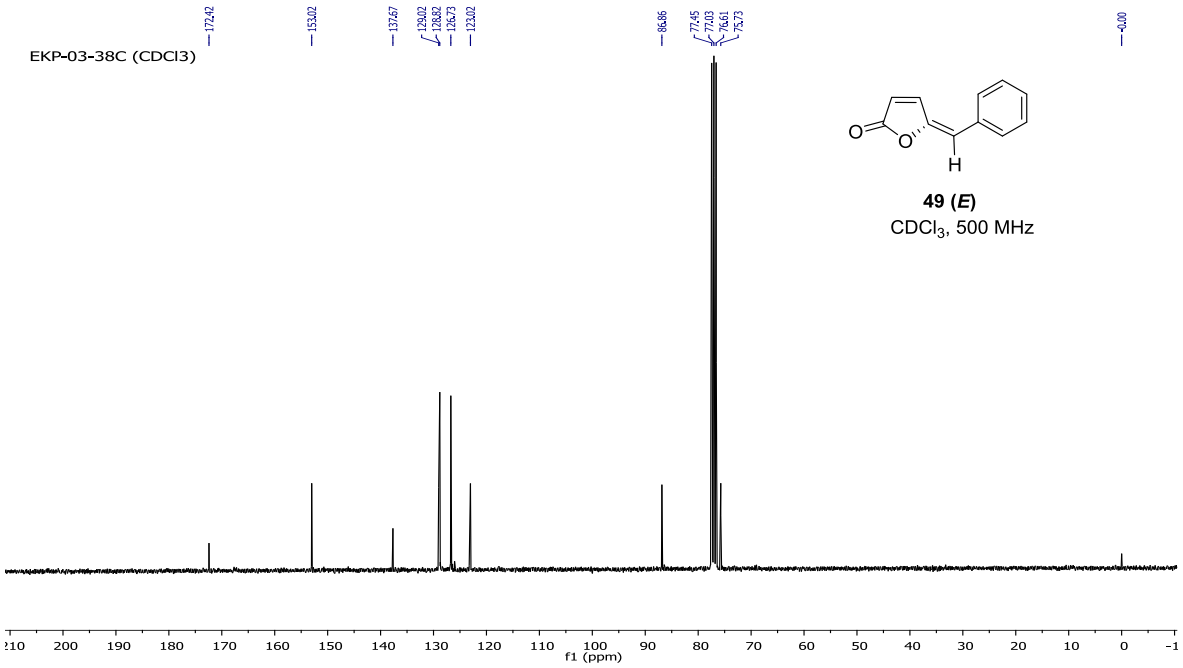
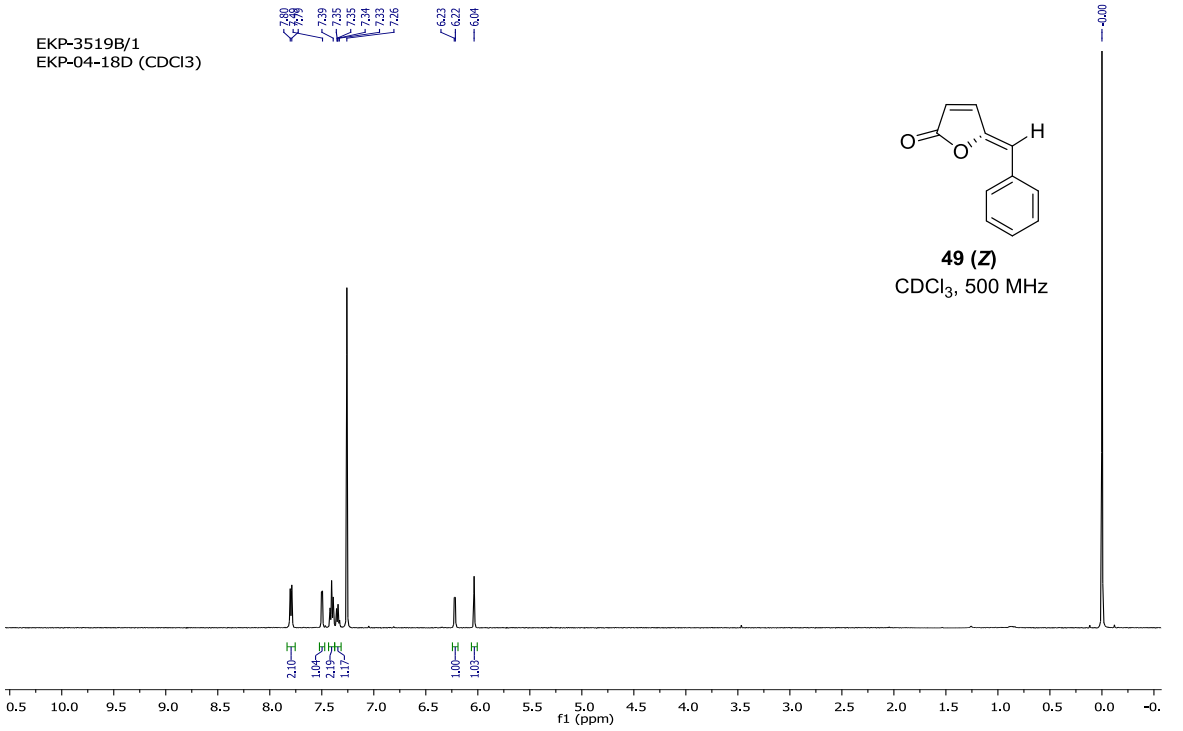

EKP-3473D/1
EKP-03-90B (CDCl3)
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.37
7.36
7.35
7.35
7.24
7.26
6.19
6.19
6.18
6.18
5.19
5.19
5.19
5.18
5.18
5.18
5.10
5.09
5.08
2.30
2.29
1.55
0.00
O
O
OH
45 (anti)
CDCl3, 500 MHz
6.13
1.00
1.01
1.01
1.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

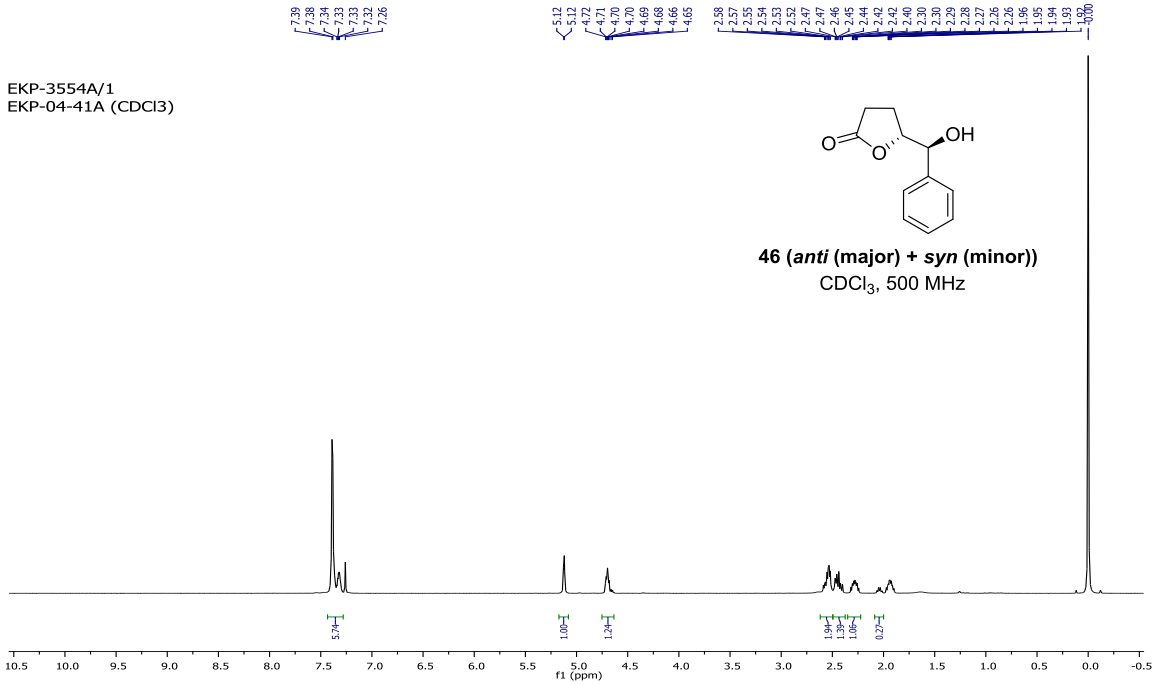

EKP-03-90B (CDCl3)
173.04
152.84
138.27
128.77
128.54
126.04
123.21
86.59
77.04
76.62
73.06
0.00
O
O
OH
45 (anti)
CDCl3, 75 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

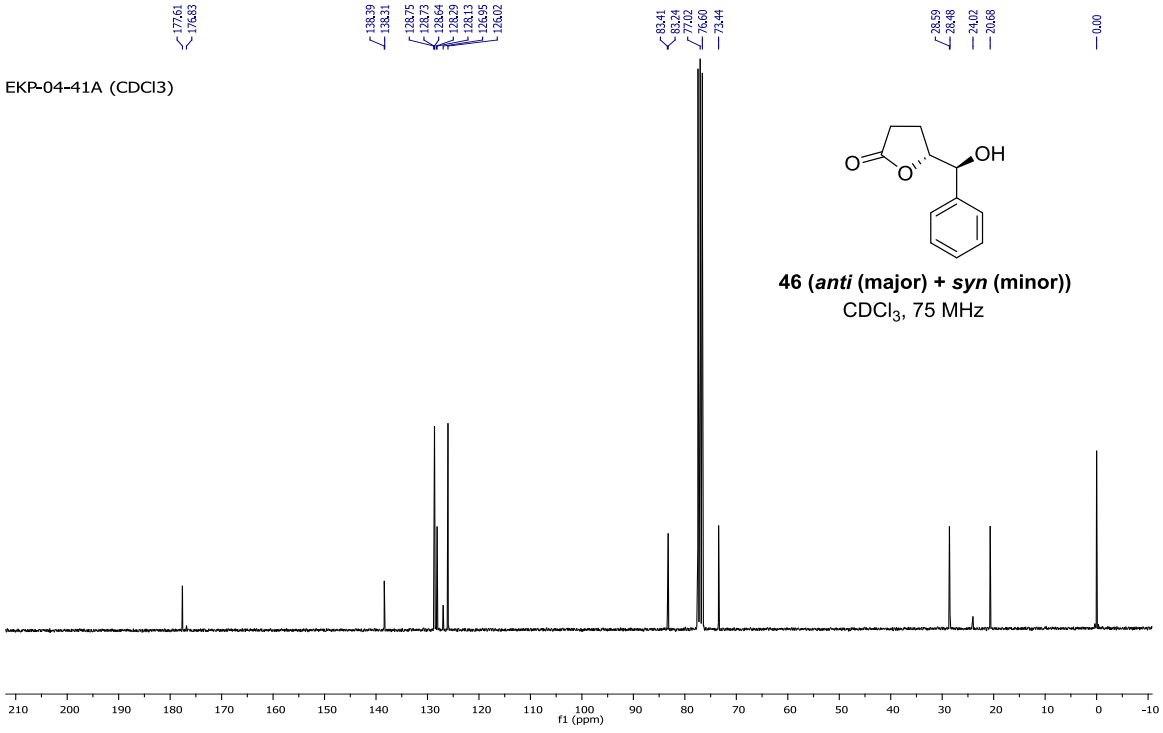

EKP-3421D/1
EKP-03-38C (CDCl3)
OH
O
O
45(syn)
CDCl3, 75 MHz
f1 (ppm)

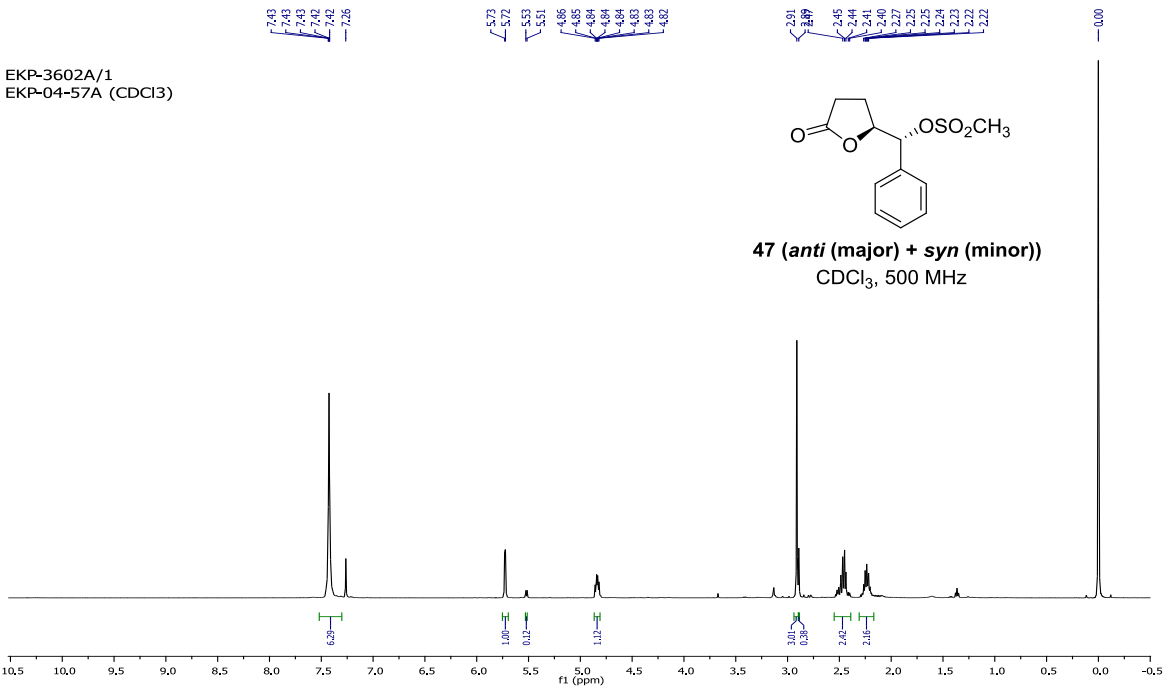

EKP-3519A/A
EKP-04-18B (CDCl3)
OH
O
O
45(syn)
CDCl3, 75 MHz
f1 (ppm)

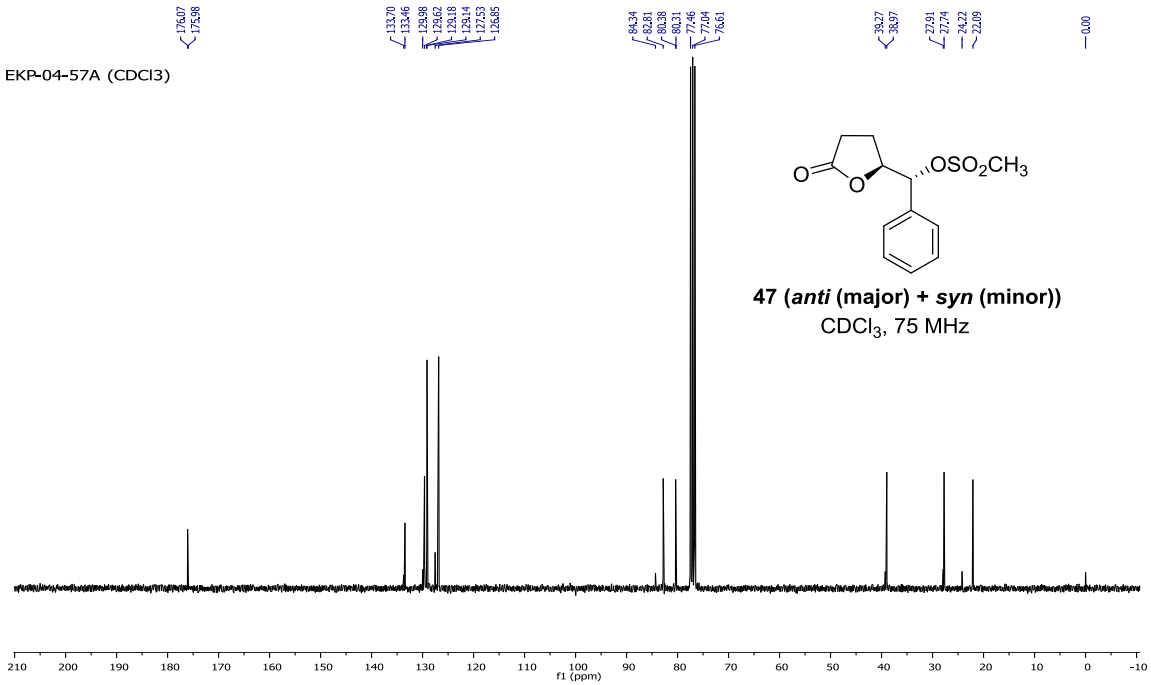

EKP-03-38C (CDCl3)
177.42
153.02
137.67
129.02
128.82
126.73
123.02
86.86
77.45
77.03
76.61
75.73
0.00
O
O
H
49 (E)
CDCl3, 500 MHz
f1 (ppm)

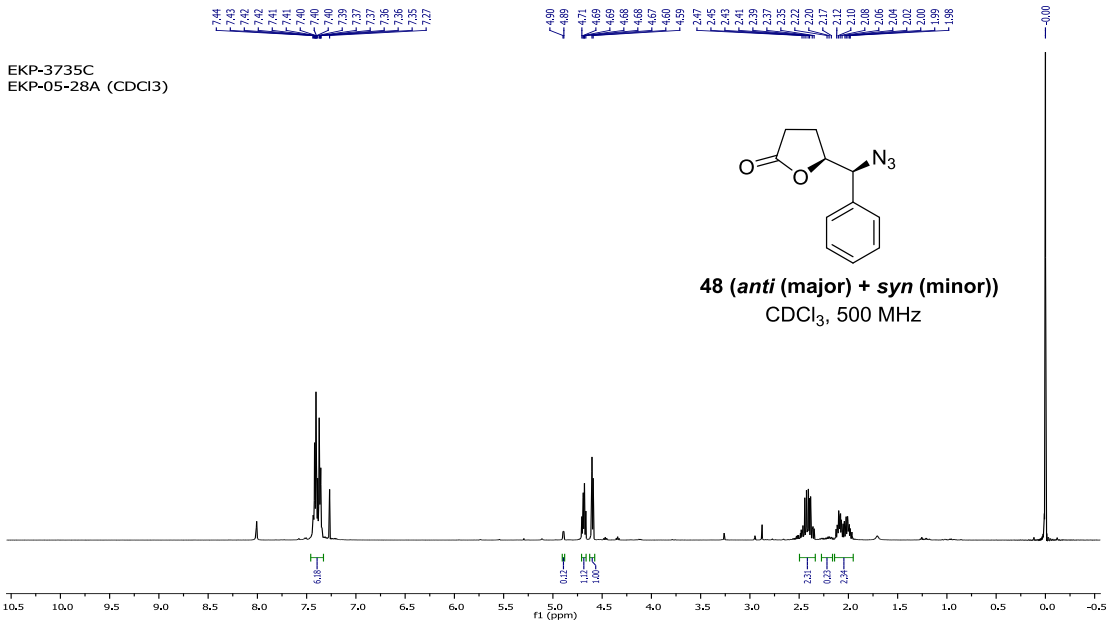

EKP-3519B/1
EKP-04-18D (CDCl3)
7.80
7.79
7.39
7.35
7.35
7.34
7.33
7.26
6.23
6.22
6.04
0.00
2.10
1.04
2.19
1.17
1.00
1.03
O
O
H
49 (Z)
CDCl3, 500 MHz
f1 (ppm)

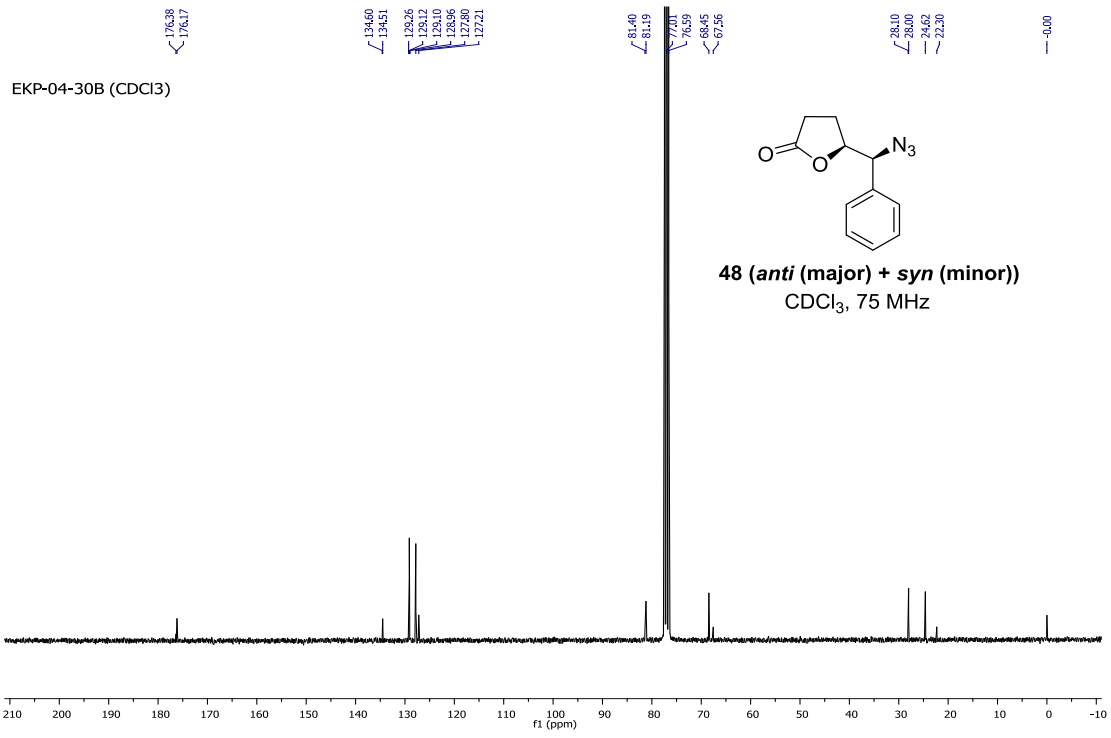

EKP-3554A/1
EKP-04-41A (CDCl3)
OH
O
O
46 (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)


EKP-04-41A (CDCl3)
OH
O
O
46 (anti (major) + syn (minor))
CDCl3, 75 MHz
f1 (ppm)

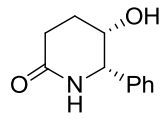

EKP-3602A/1
EKP-04-57A (CDCl3)
OSO2CH3
47 (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)


EKP-04-57A (CDCl3)
OSO2CH3
47 (anti (major) + syn (minor))
CDCl3, 75 MHz
f1 (ppm)

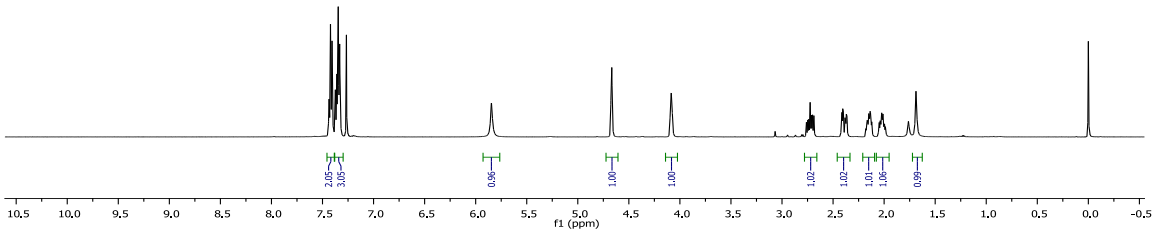

EKP-3735C
EKP-05-28A (CDCl3)
O
O
N3
48 (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)


EKP-04-30B (CDCl3)
O
O
N3
48 (anti (major) + syn (minor))
CDCl3, 75 MHz
f1 (ppm)

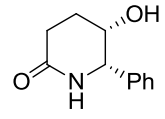
EKP-3622A/1
EKP-04-45C (CDCl3)



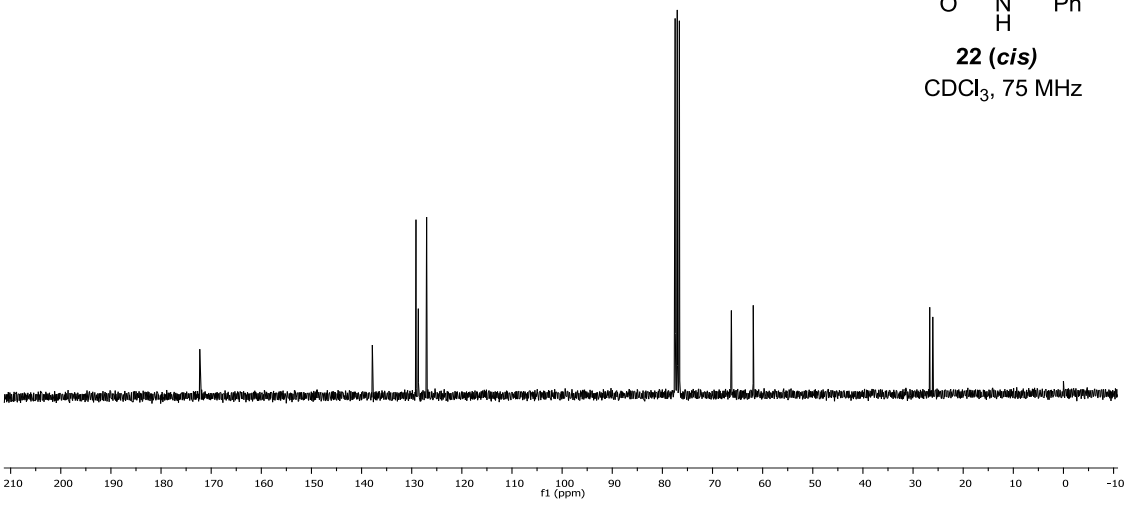
22 (*cis*)
$CDCl_3$, 500 MHz



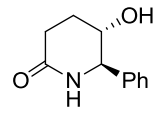
EKP-04-45C (CDCl3)



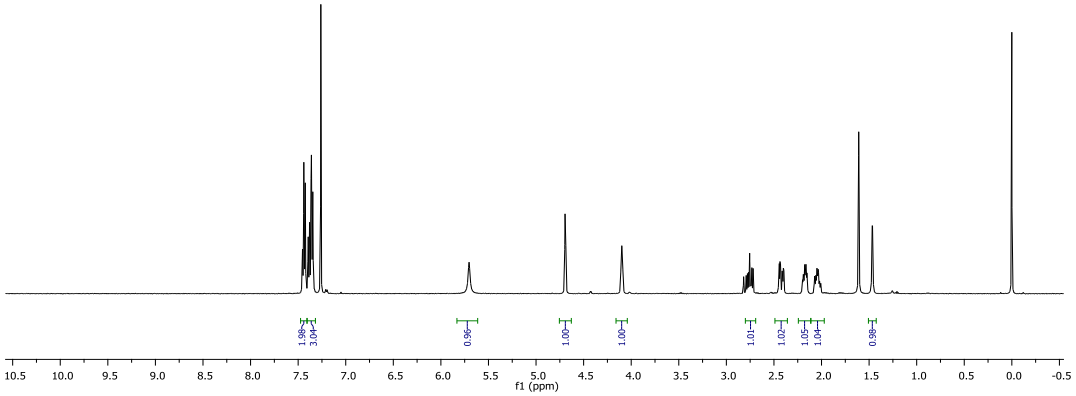
22 (*cis*)
$CDCl_3$, 75 MHz



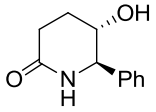
EKP-3552B/1
EKP-04-32C (CDCl3)



22 (*trans*)
$CDCl_3$, 500 MHz

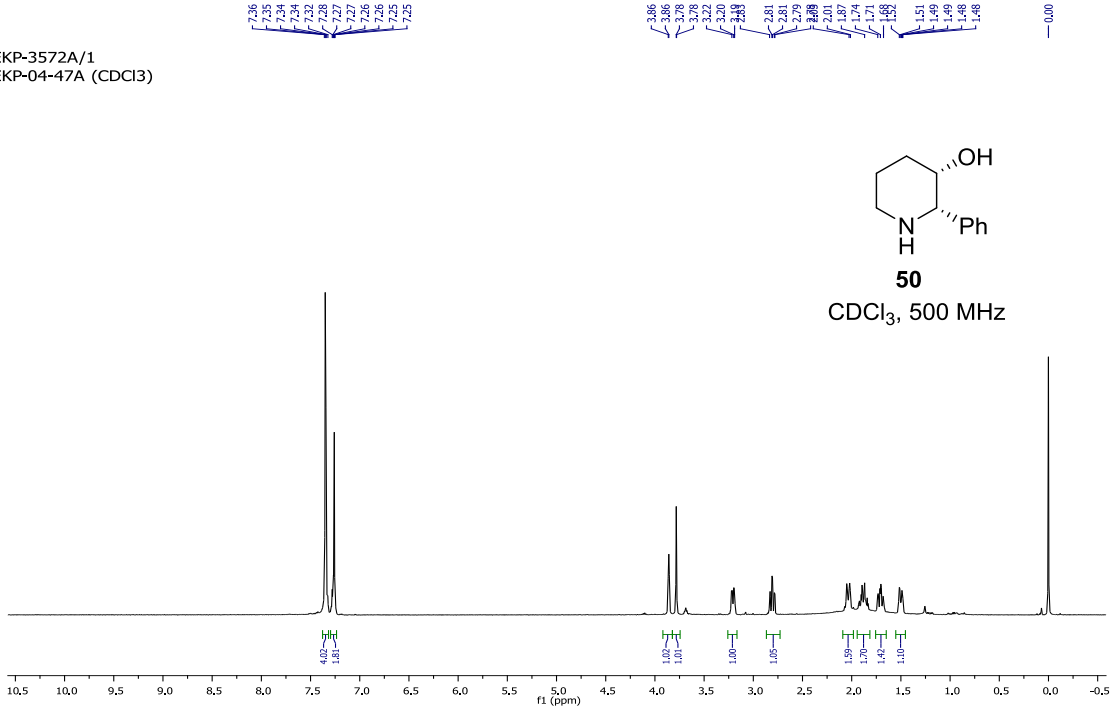


EKP-04-32C (CDCl3)



22 (*trans*)
$CDCl_3$, 75 MHz

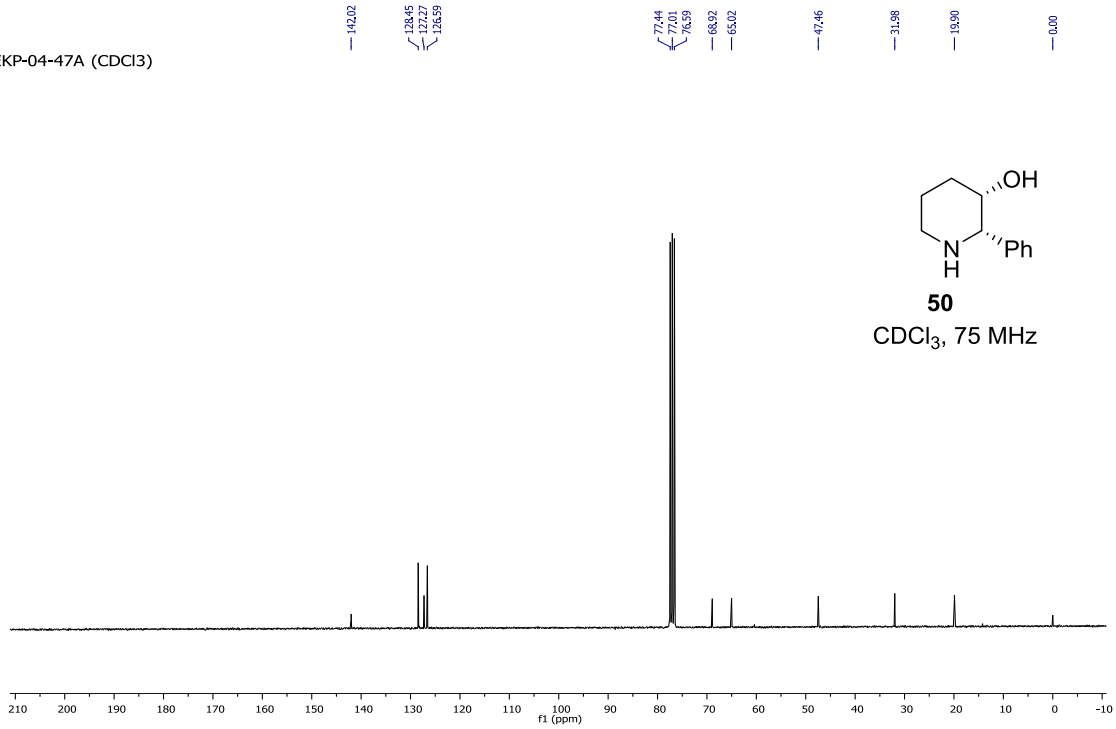
EKP-3572A/1
EKP-04-47A (CDCl3)



50

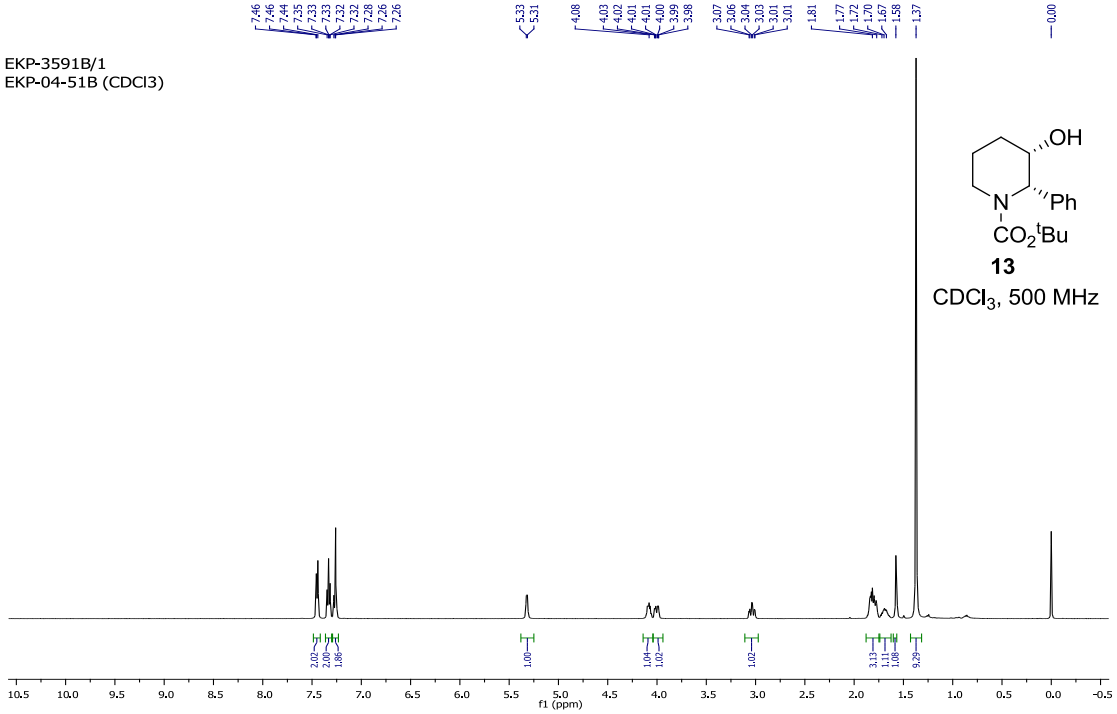
$CDCl_3$, 500 MHz

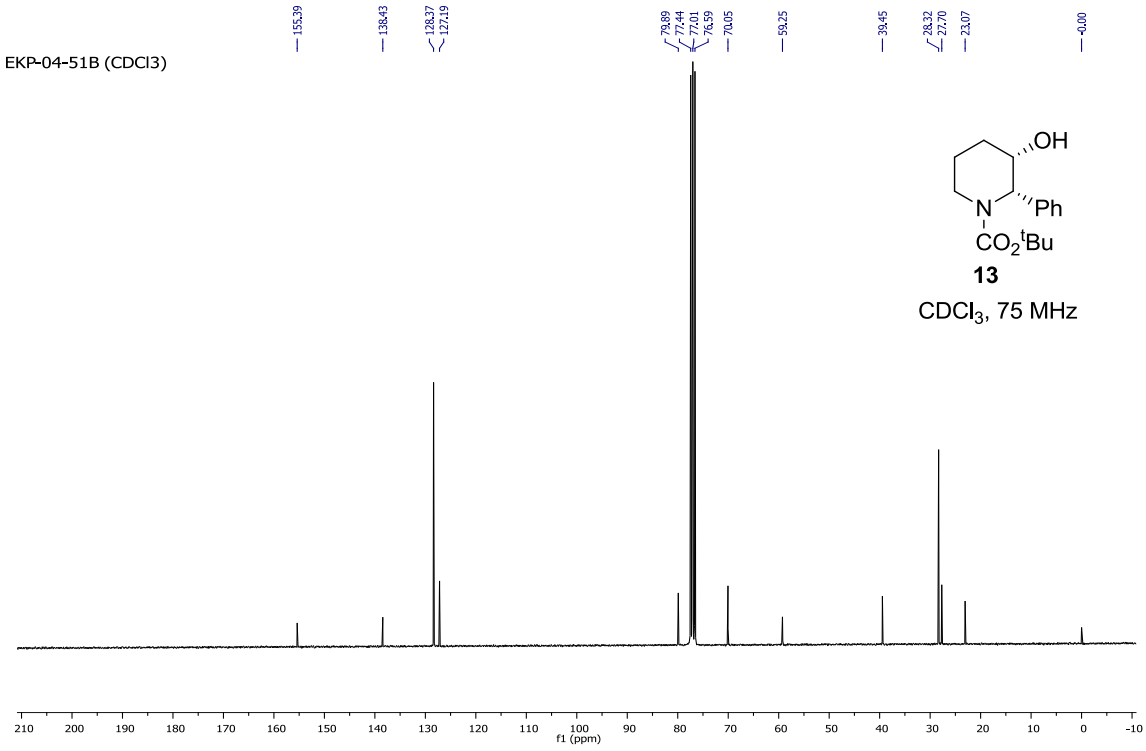
EKP-04-47A (CDCl3)

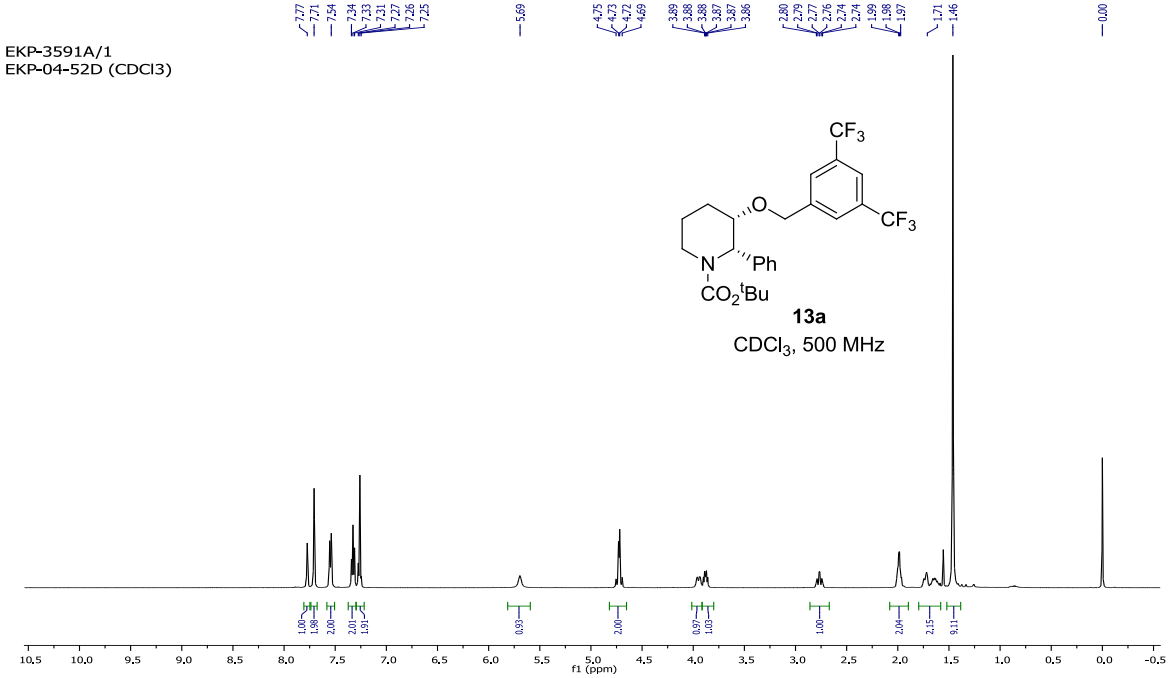


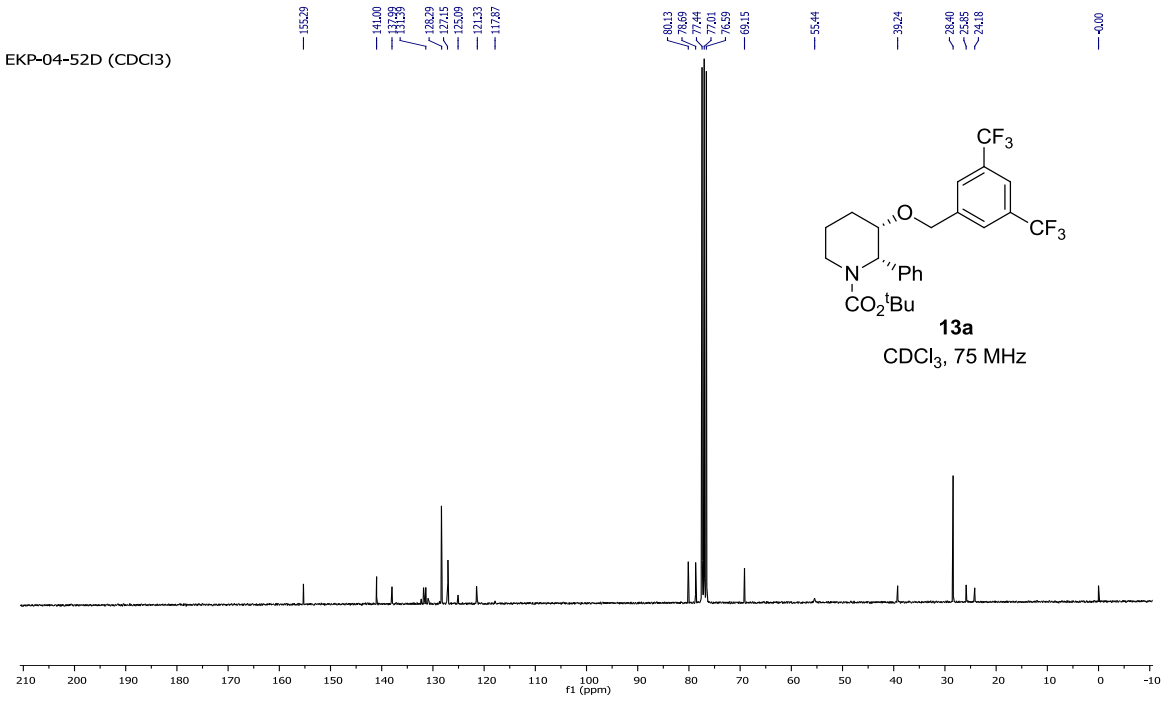
50

$CDCl_3$, 75 MHz

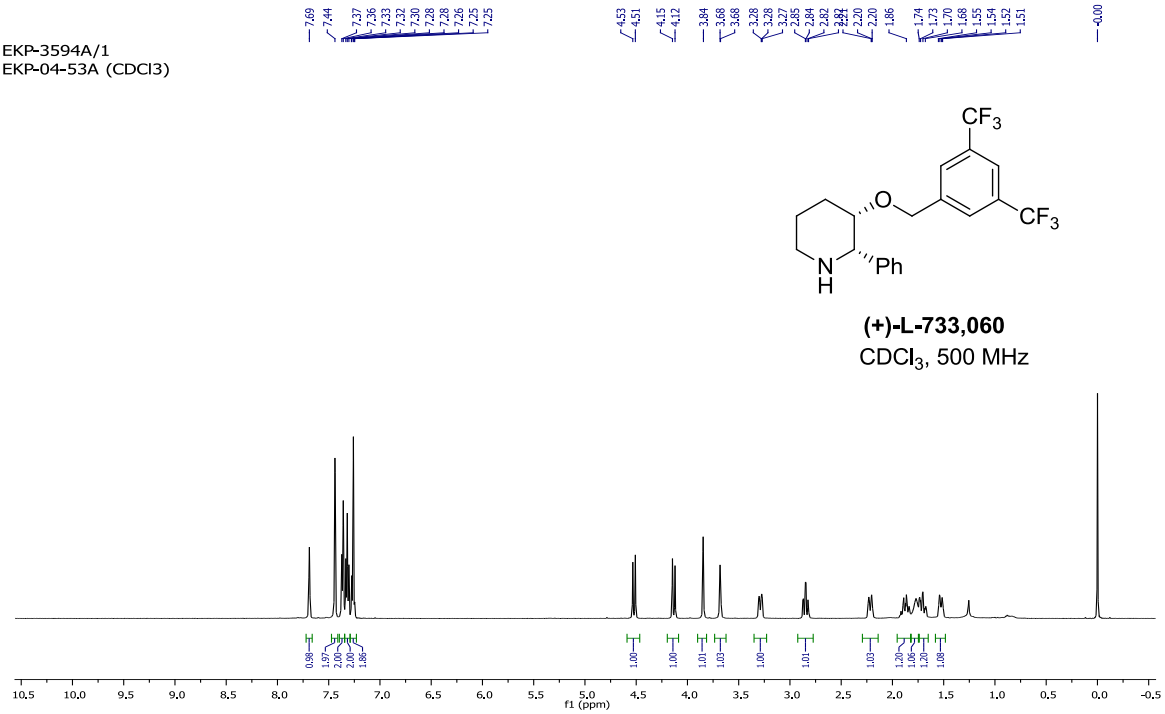

EKP-3591B/1
EKP-04-51B (CDCl3)
OH
Ph
N
CO2tBu
13
CDCl3, 500 MHz
f1 (ppm)


EKP-04-51B (CDCl3)
OH
Ph
N
CO2tBu
13
CDCl3, 75 MHz
f1 (ppm)


EKP-3591A/1
EKP-04-52D (CDCl3)
CF3
CF3
O
N
Ph
CO2tBu
13a
CDCl3, 500 MHz
f1 (ppm)

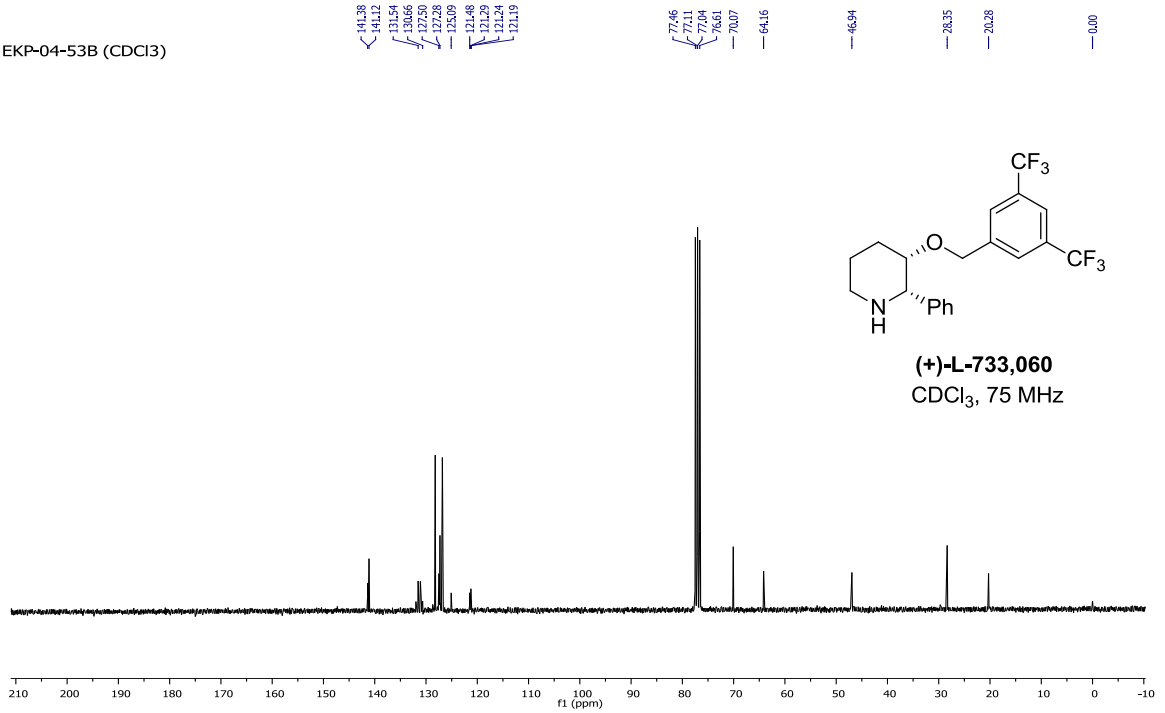

EKP-04-52D (CDCl3)
CF3
CF3
O
N
Ph
CO2tBu
13a
CDCl3, 75 MHz
f1 (ppm)

EKP-3594A/1
EKP-04-53A (CDCl3)

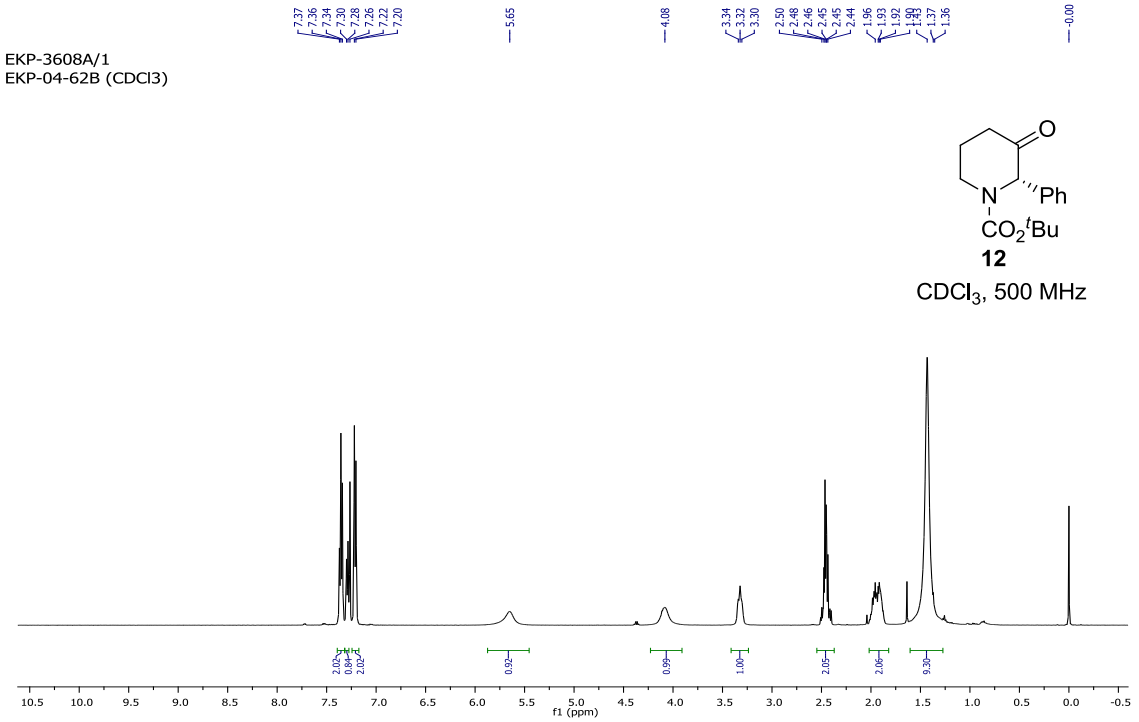


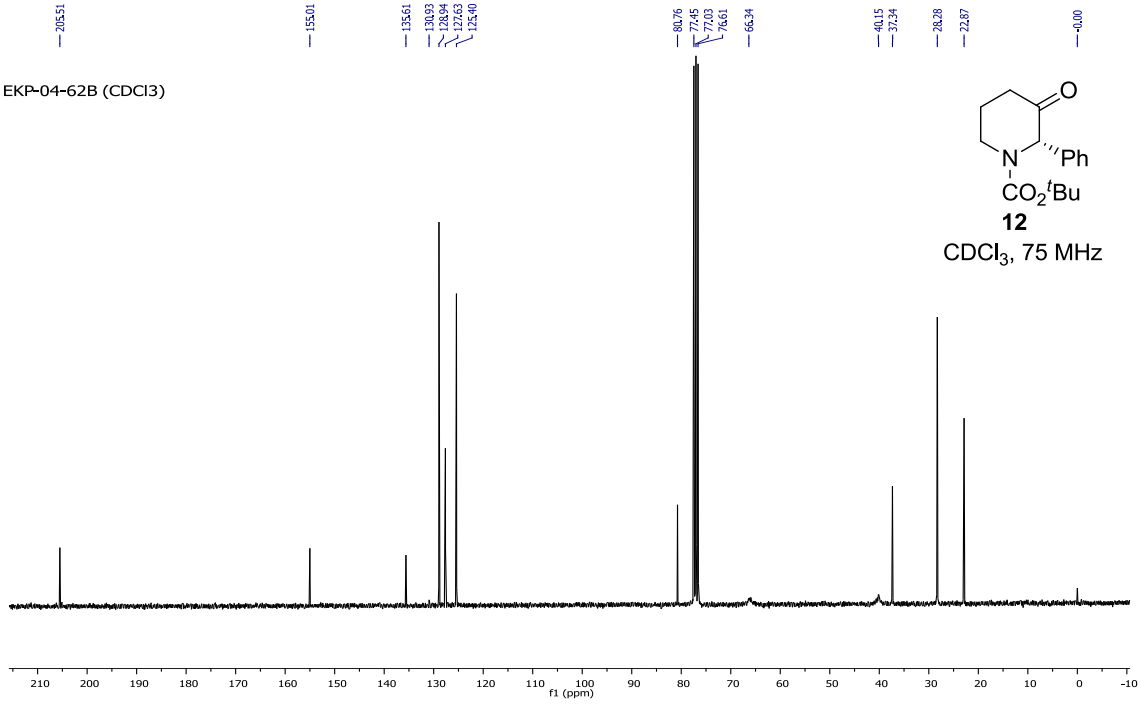
(+)-L-733,060
$CDCl_3$, 500 MHz

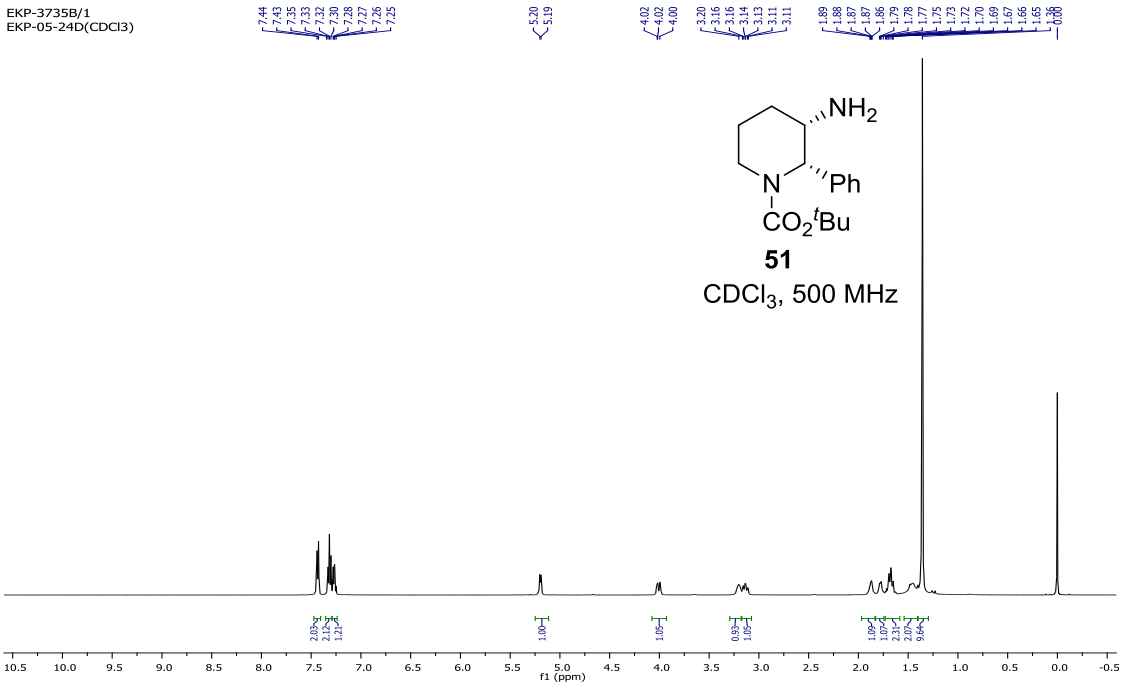
EKP-04-53B (CDCl3)

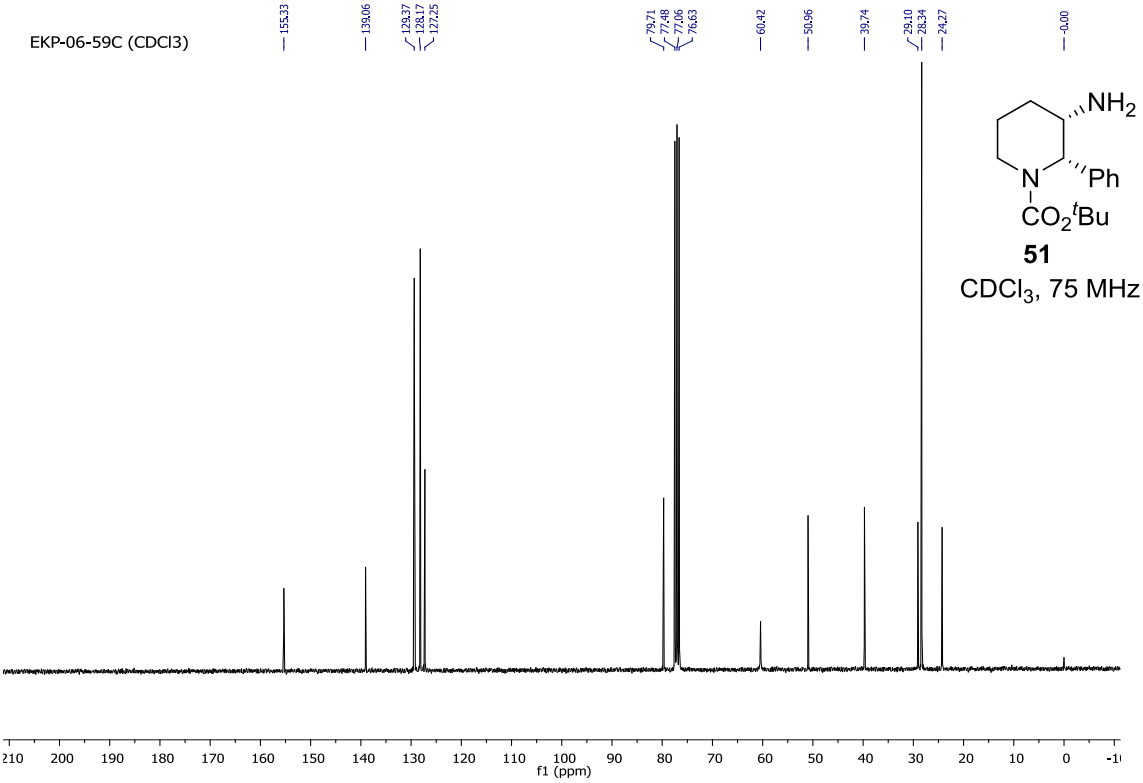


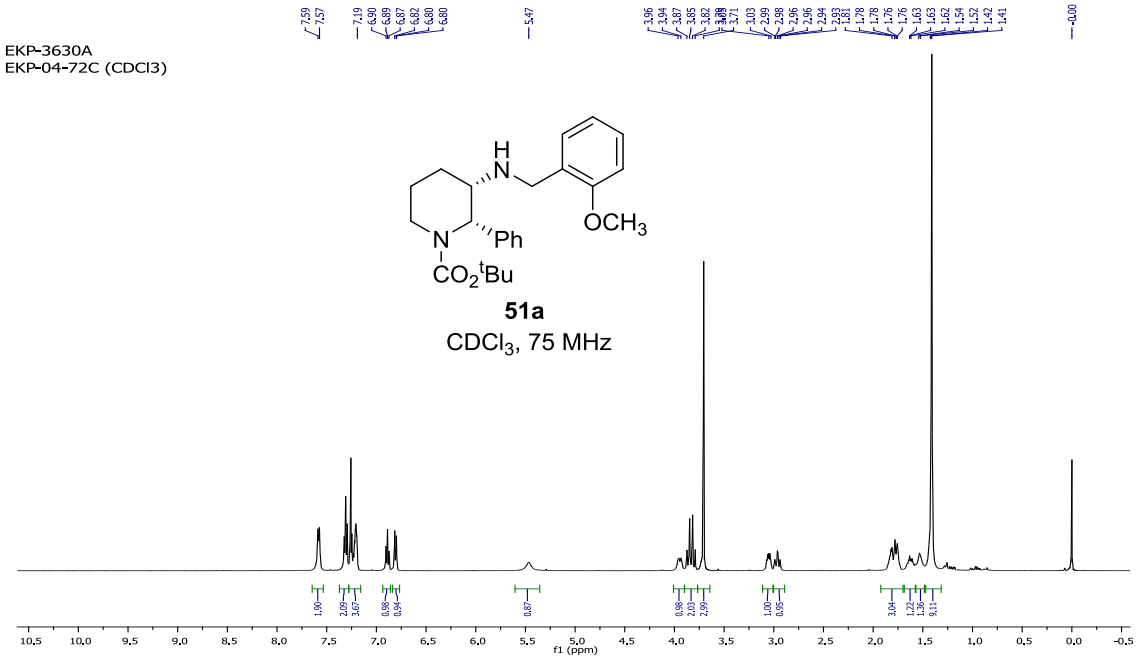
(+)-L-733,060
$CDCl_3$, 75 MHz

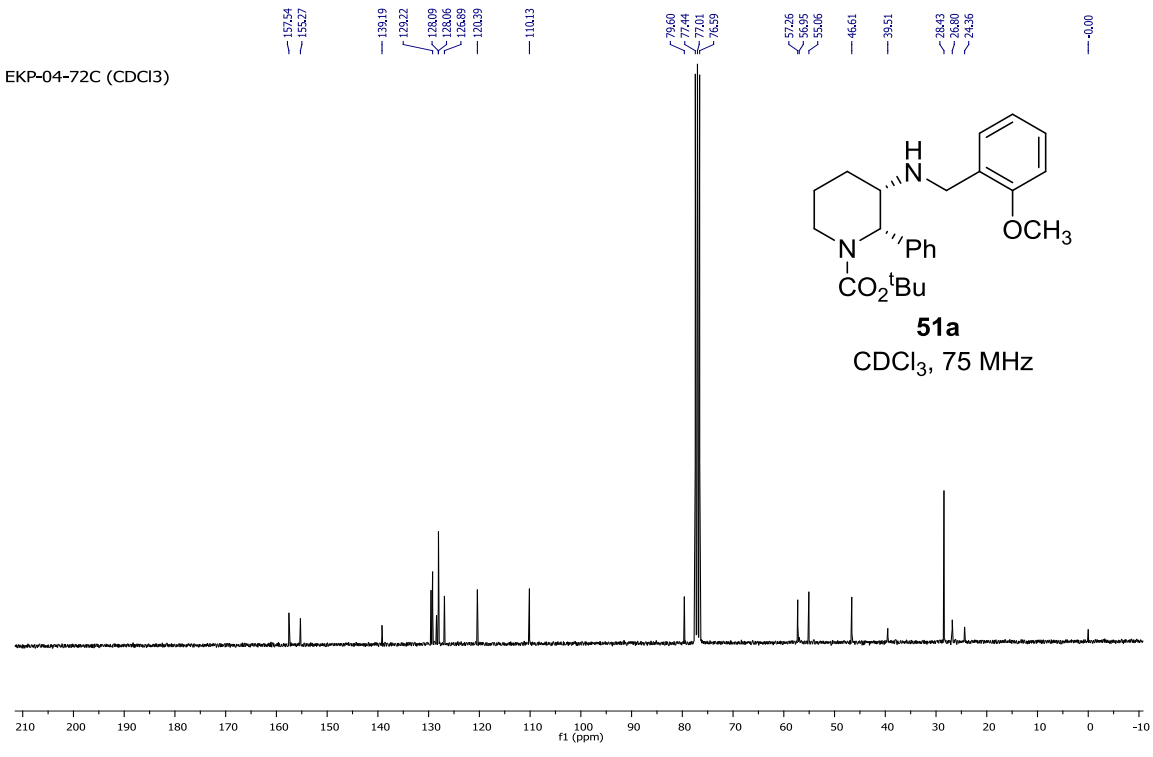

EKP-3608A/1
EKP-04-62B (CDCl3)
O
N
Ph
CO2tBu
12
CDCl3, 500 MHz
f1 (ppm)


EKP-04-62B (CDCl3)
O
N
Ph
CO2tBu
12
CDCl3, 75 MHz
f1 (ppm)

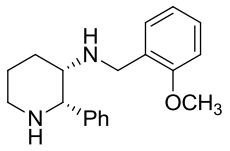

EKP-3735B/1
EKP-05-24D(CDCl3)
NH2
Ph
N
CO2tBu
51
CDCl3, 500 MHz
f1 (ppm)


EKP-06-59C (CDCl3)
NH2
Ph
N
CO2tBu
51
CDCl3, 75 MHz
f1 (ppm)

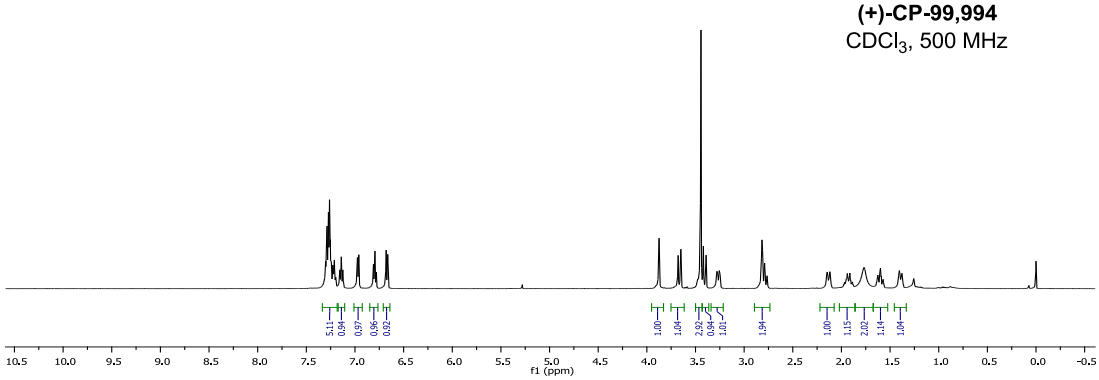

EKP-3630A
EKP-04-72C (CDCl3)
H
N
OCH3
N
Ph
CO2tBu
51a
CDCl3, 75 MHz
f1 (ppm)


EKP-04-72C (CDCl3)
H
N
OCH3
N
Ph
CO2tBu
51a
CDCl3, 75 MHz
f1 (ppm)

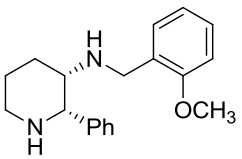
EKP-3634A/1
EKP-04-74A (CDCl3)



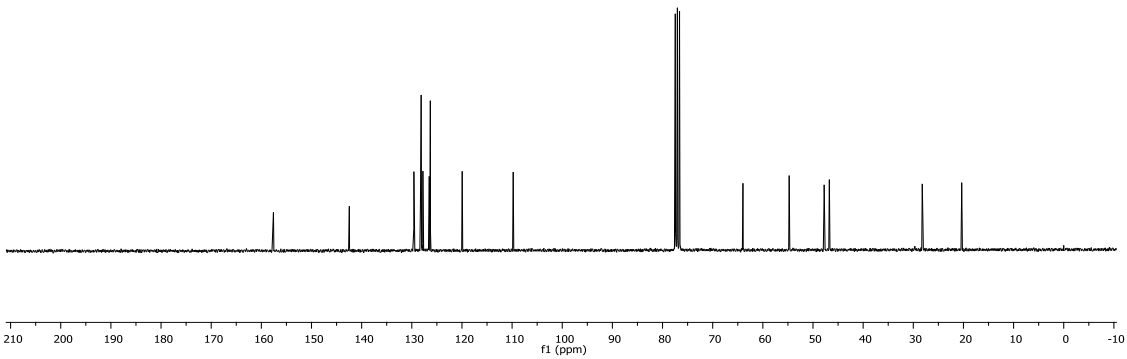
(+)-CP-99,994
$CDCl_3$, 500 MHz

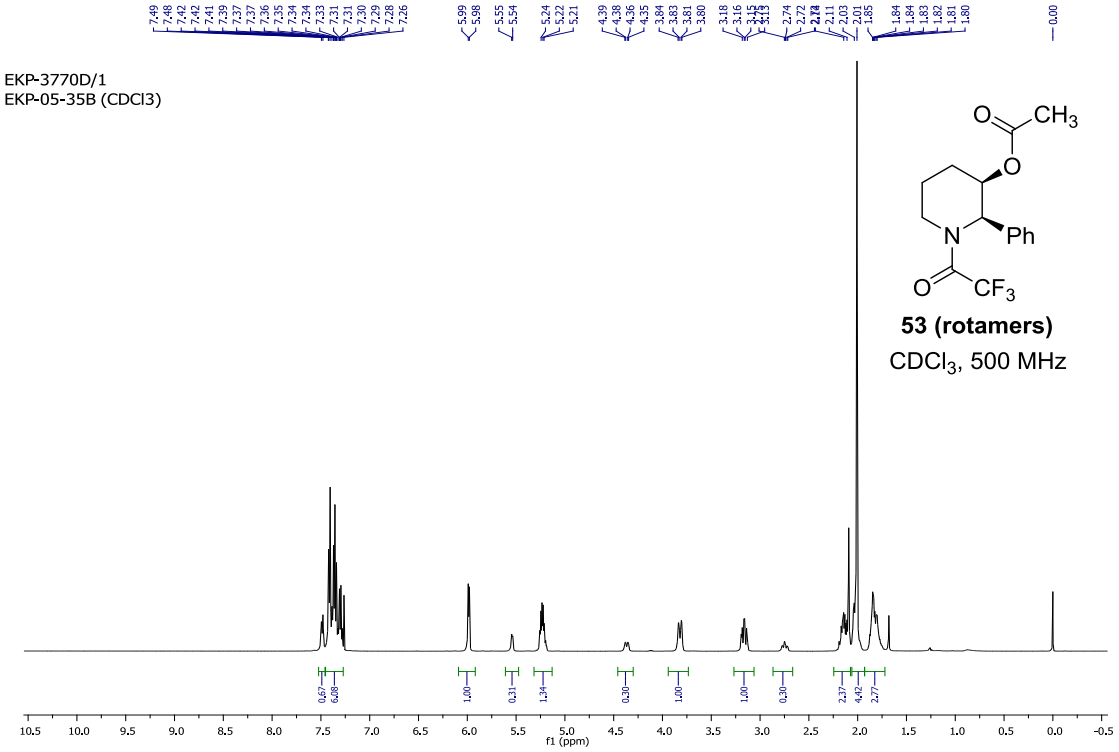


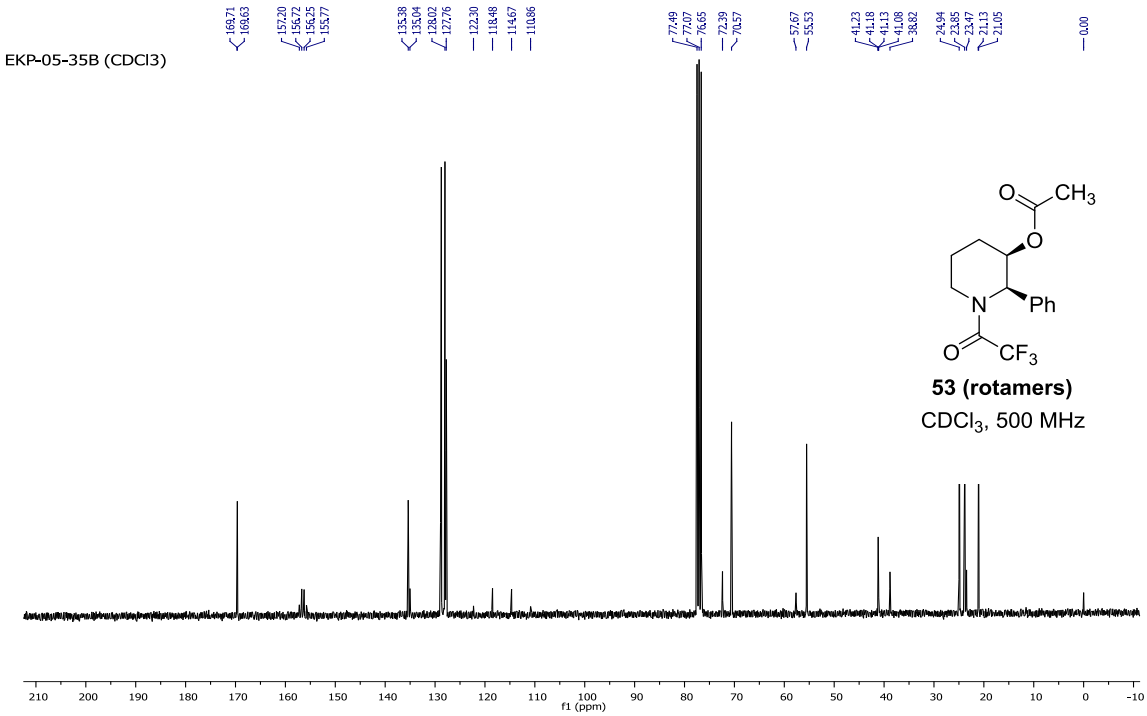
EKP-04-74A (CDCl3)



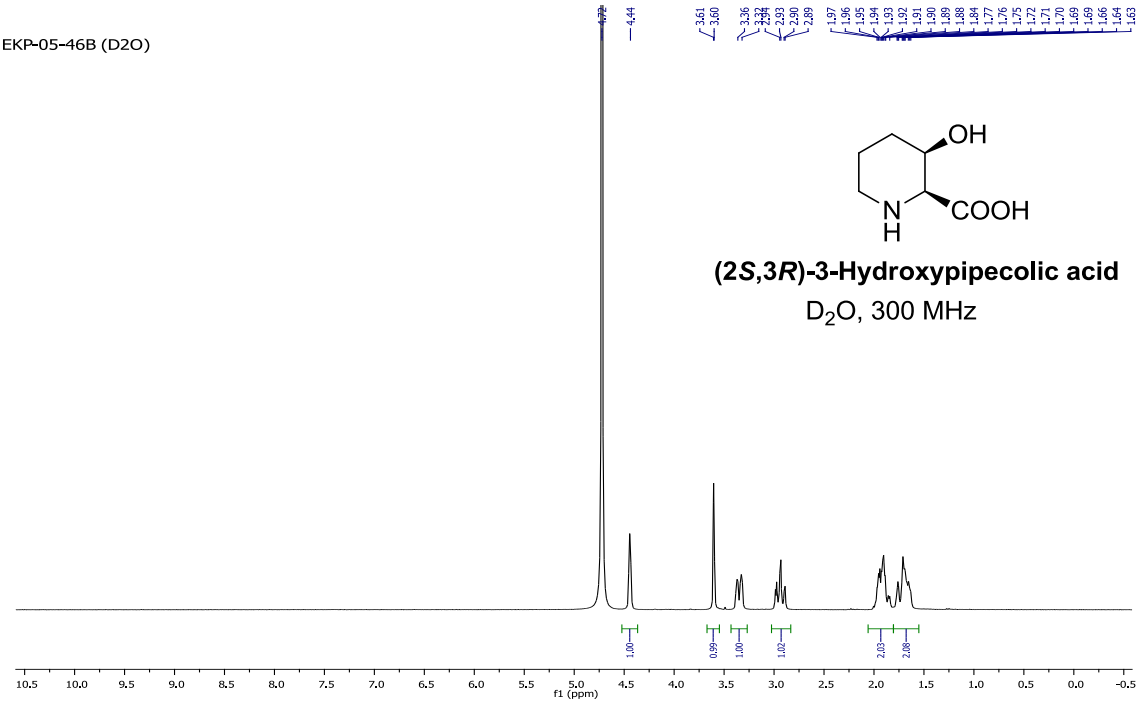
(+)-CP-99,994
$CDCl_3$, 75 MHz




EKP-3770D/1
EKP-05-35B (CDCl3)
O
CH3
O
N
Ph
O
CF3
53 (rotamers)
CDCl3, 500 MHz
f1 (ppm)


EKP-05-35B (CDCl3)
O
CH3
O
N
Ph
O
CF3
53 (rotamers)
CDCl3, 500 MHz
f1 (ppm)

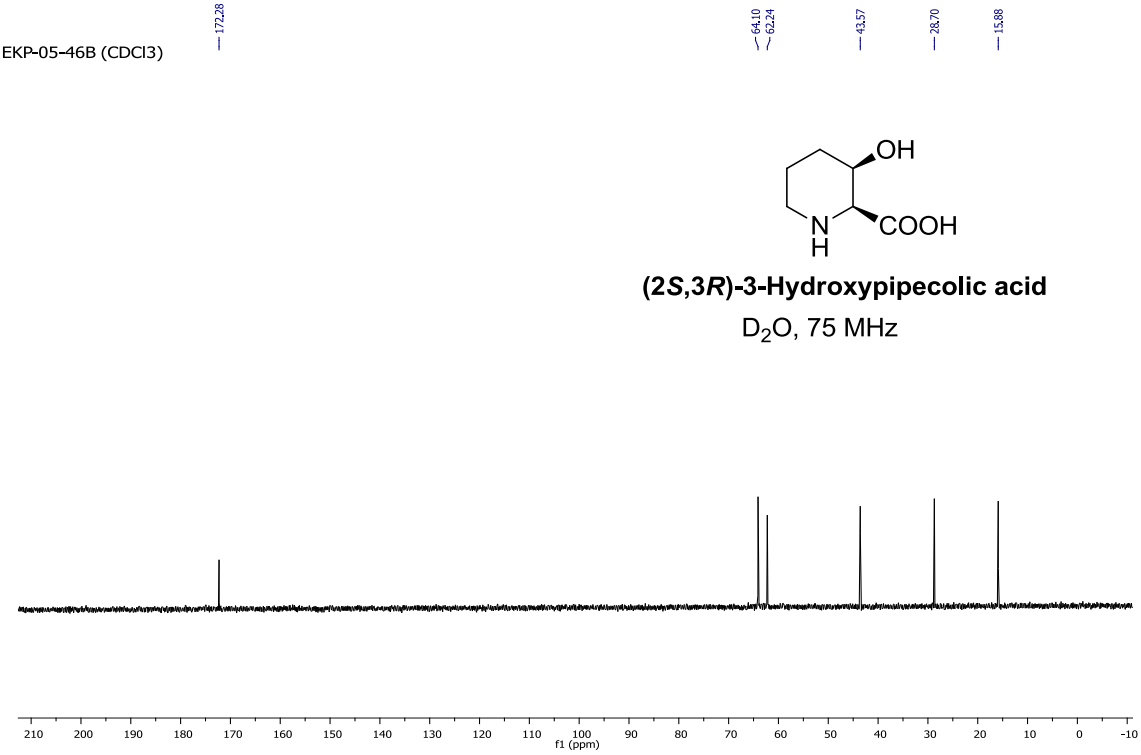
EKP-05-46B (D2O)



(2*S*,3*R*)-3-Hydroxypipecolic acid

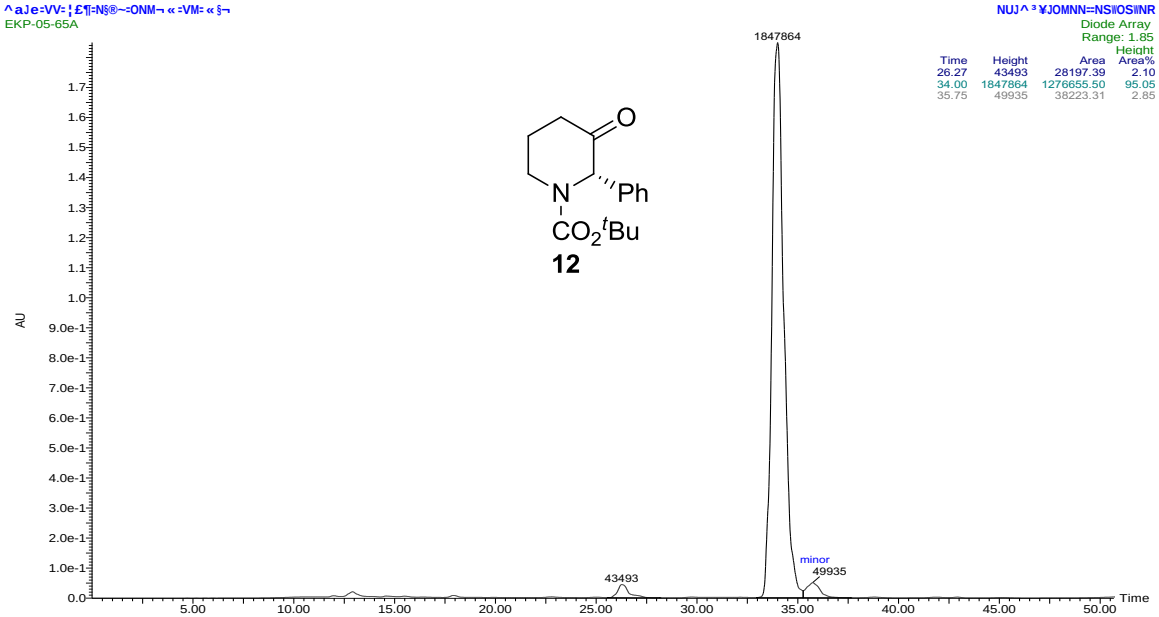
D_2O, 300 MHz

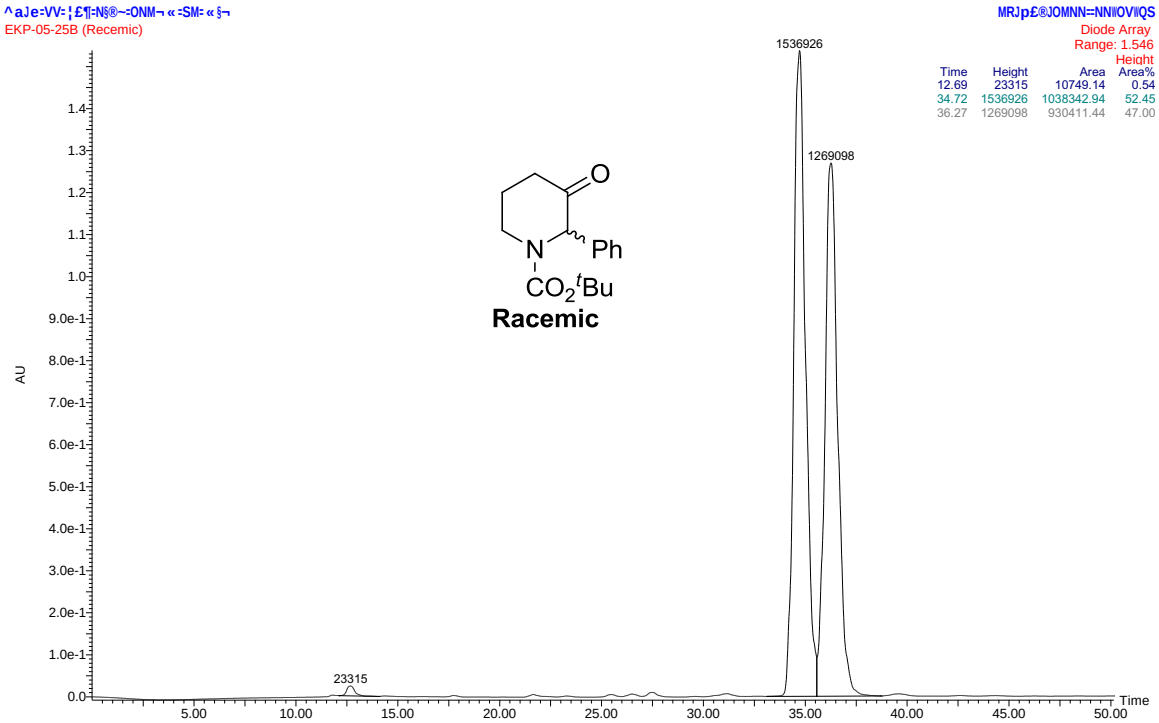
EKP-05-46B (CDCl3)

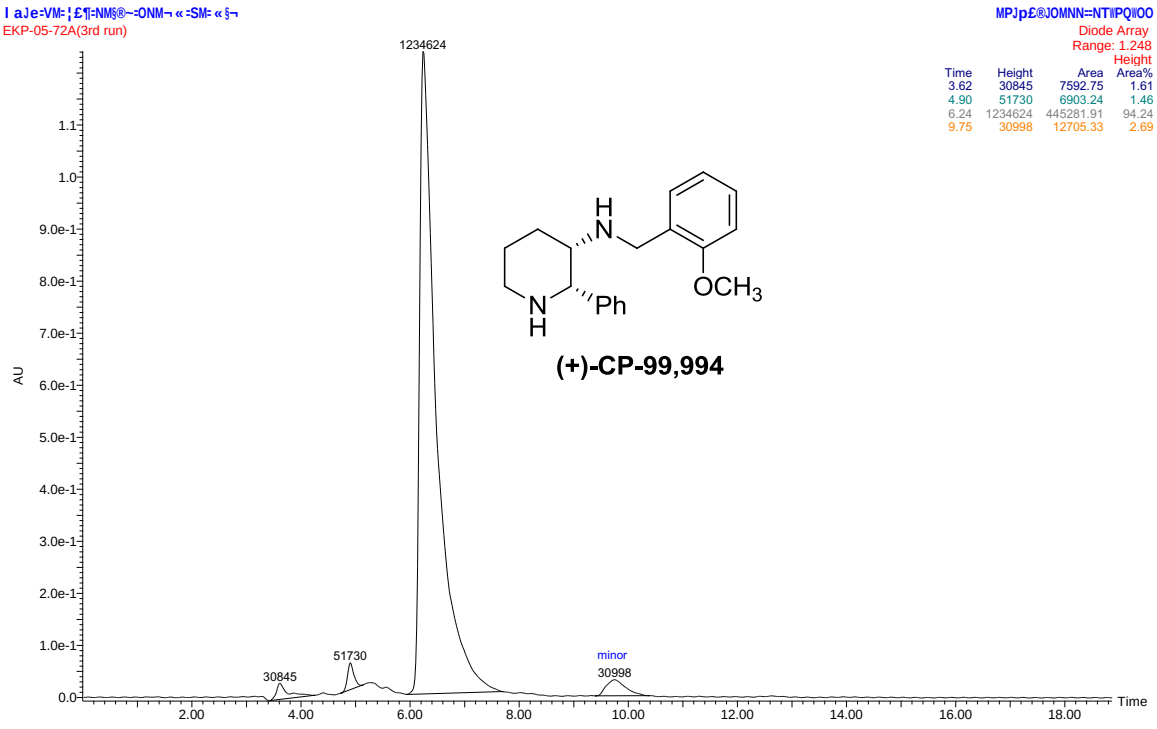


(2*S*,3*R*)-3-Hydroxypipecolic acid

D_2O, 75 MHz


EKP-05-65A
Diode Array
Range: 1.85
Time Height Area Area%
26.27 43493 28197.39 2.10
34.00 1847864 1276655.50 95.05
35.75 49935 38223.31 2.85
1847864
minor
43493
49935
AU
Time
12


EKP-05-25B (Recemic)
Diode Array
Range: 1.546
Time Height Area Area%
12.69 23315 10749.14 0.54
34.72 1536926 1038342.94 52.45
36.27 1269098 930411.44 47.00
1536926
1269098
23315
AU
Time
Racemic


EKP-05-72A(3rd run)
Diode Array
Range: 1.248
Height
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3.62 30845 7592.75 1.61
4.90 51730 6903.24 1.46
6.24 1234624 445281.91 94.24
9.75 30998 12705.33 2.69
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CHAPTER 4

Synthesis of (+)-Febrifugine and a Formal Synthesis of (+)-Halofuginone Employing an Organocatalytic Direct Vinylogous Aldol Reaction

This chapter is based on the following publica

Pansare, S. V.; Paul, E. K. *Synthesis* **2013**, *45*, 1-13.

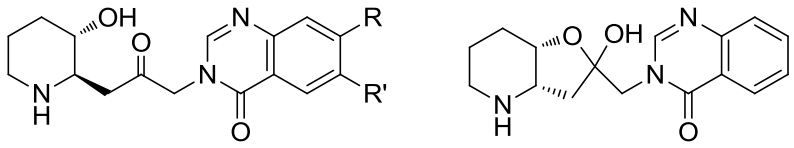
Contributions of authors

S. V. Pansare: research supervisor, manusc

E. K. Paul: experimental work, manuscript

4.1 Introduction

The prevalence of malaria in tropical r
combat malaria have resulted in a persist
antimalarial agents (e.g., quinine, artemisinin, 1 Figure 4.1) and the alo
attracted considerable interest.[2] Thus, both the
febrifugine (dually conveyed by the Dichroa
exhibits antimalarial activity, and the synthetic
febrifugine continues to be actively investigated
showcase new methodology for stereoselective construction
piperidine ring in the targets. Of the five
reported. Febrifugine and halofuginone, which
have contributed to a continued interest
antimalarial properties, halofuginone[5] has
also an anti-inflammatory activity and has been approved for the tr
it is active against Coccidiosis. Recently, its immo
mechanism of action of febrifugine[8] and ha
These studies highlighted the use of febrifugine
treatment of multiple sclerosis, scleroder
important consideration in devising a synt
the approach for making analogs of febrifu



1: R = R' =H **2**: R = Br, R' = Cl **3**

Figure 4.1. (+)-Febrifugine (**1**), halofuginone (**2**) and isofebrifugine (**3**)

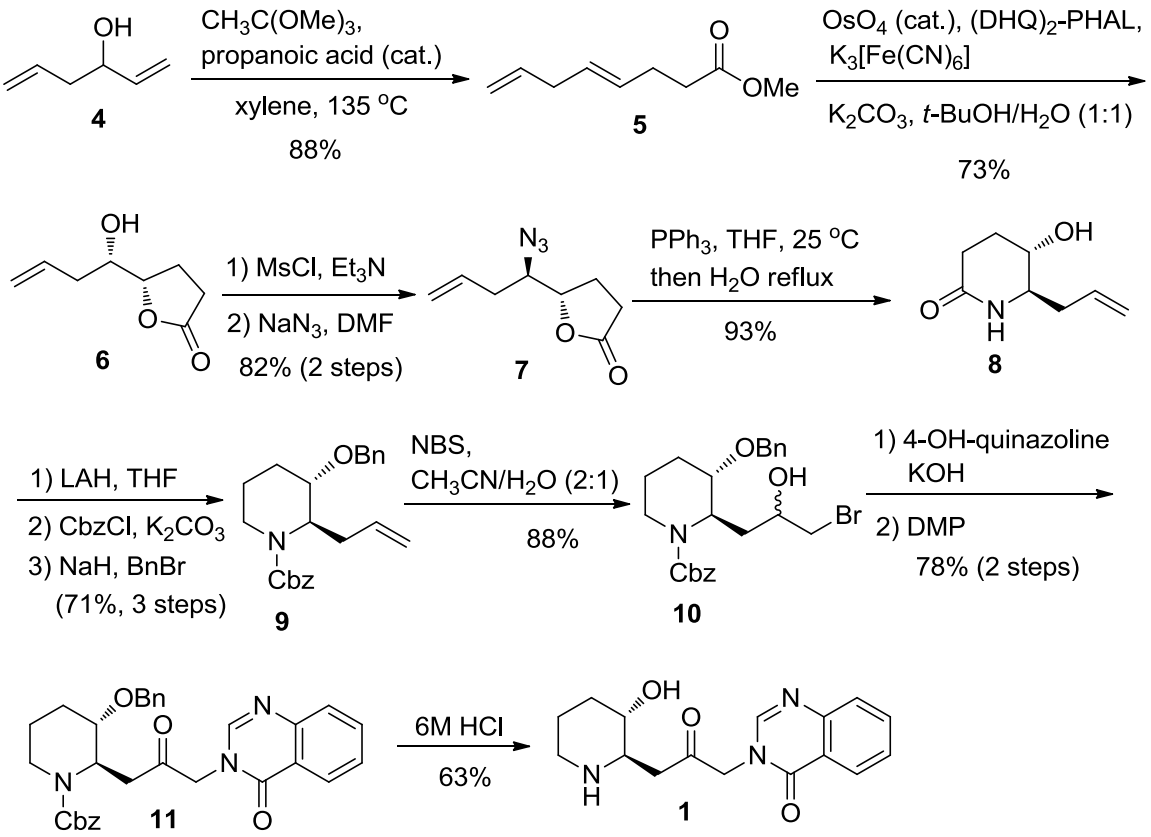
4.2 Known synthetic routes to (+)-Febrifugine

The following summary provides an overview of the synthetic routes to (+)-febrifugine and its analogues from 2009 onwards.

4.2.1 The Sudalai synthesis of (+)-Febrifugine

Sudalai and co-workers reported the first synthesis of (+)-febrifugine (**1**) in 2009. The synthesis started from the readily available, commercially available 4-chloroacetoacetate (**4**) which underwent Johnson-Claisen rearrangement with (*S*)-allyl alcohol (**5**) to afford the ester (**6**). This was catalyzed by the Grubbs-Hoveyda 2nd generation catalyst (**7**) to afford the cyclic olefin (**8**). The chloride was displaced by sodium azide to provide the azide (**9**). The azide was then reduced by zinc and ammonium chloride to afford the amine (**10**) which underwent spontaneous cyclization to afford the lactam (**11**). Reduction of the lactam (**11**) with $LiAlH_4$ provided the corresponding piperidine, which was protected as the chloroformate. Subsequent benzylation of the alcohol afforded the ketone (**12**). The ketone was then subjected to Noyori asymmetric transfer hydrogenation conditions to provide the alcohol (**13**) as a mixture of diastereomers (dr

with 4-hydroxyquinazoline in the presence of secondary alcohol-Mitsunobu reagents. Desired product febrifugine (6) and subsequent neutral febrifugine (4) (12.5% overall yield).

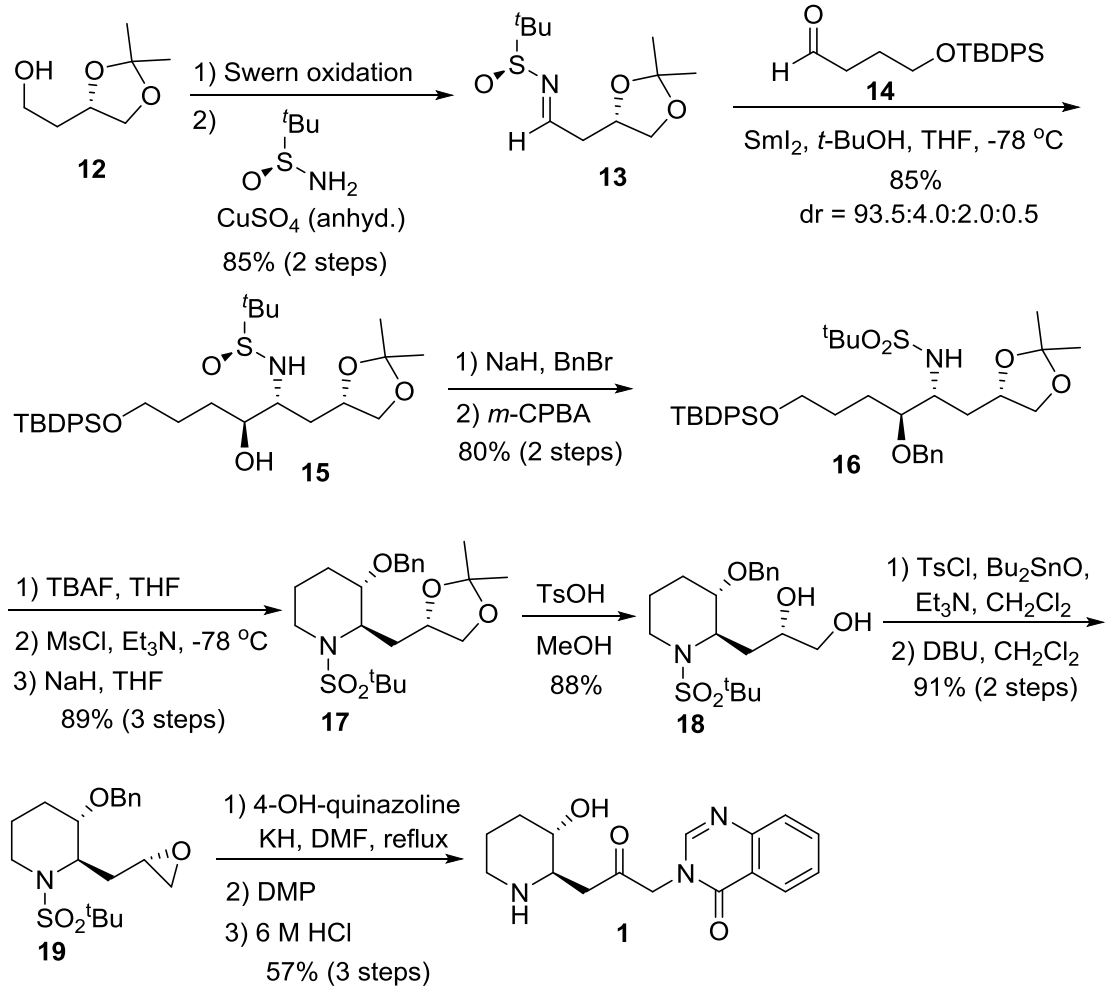


Scheme 4.1. Synthesis of (+)-febrifugine by Sudalai.

4.2.2 The Lin synthesis of (+)-Febrifugine

In 2009, Lin and co-workers[3b] reported a stereoselective total synthesis of (+)-febrifugine. The synthesis started from the readily

which was *tert*-butylated to afford the primary alcohol (Stephenson et al.). SmI_2-mediated reductive coupling of this aldehyde with -78°C afforded the anti diol and diast (93.5:4.0:2.0:0.5). Protection of the hydroxyl group as the subsequent *m*-CPBA mediated epoxidation of the double bond. After removal of the group with TBAF, mesylation of the secondary alcohol and cyclization in refluxing toluene provided the tricyclic ether. Treatment with *p*-toluenesulfonic acid in methanol to effect deprotection of the acetonide followed by base mediated cyclization provided the epoxide. Oxidation of the secondary alcohol with 4-hydroxyquinazoline followed by the Dess-Martin periodinane gave the desired ketone. Deprotection of the TBS ether with HF-pyridine provided (+)-ecteinascidin 12 (243.5 mg, 12% overall yield).

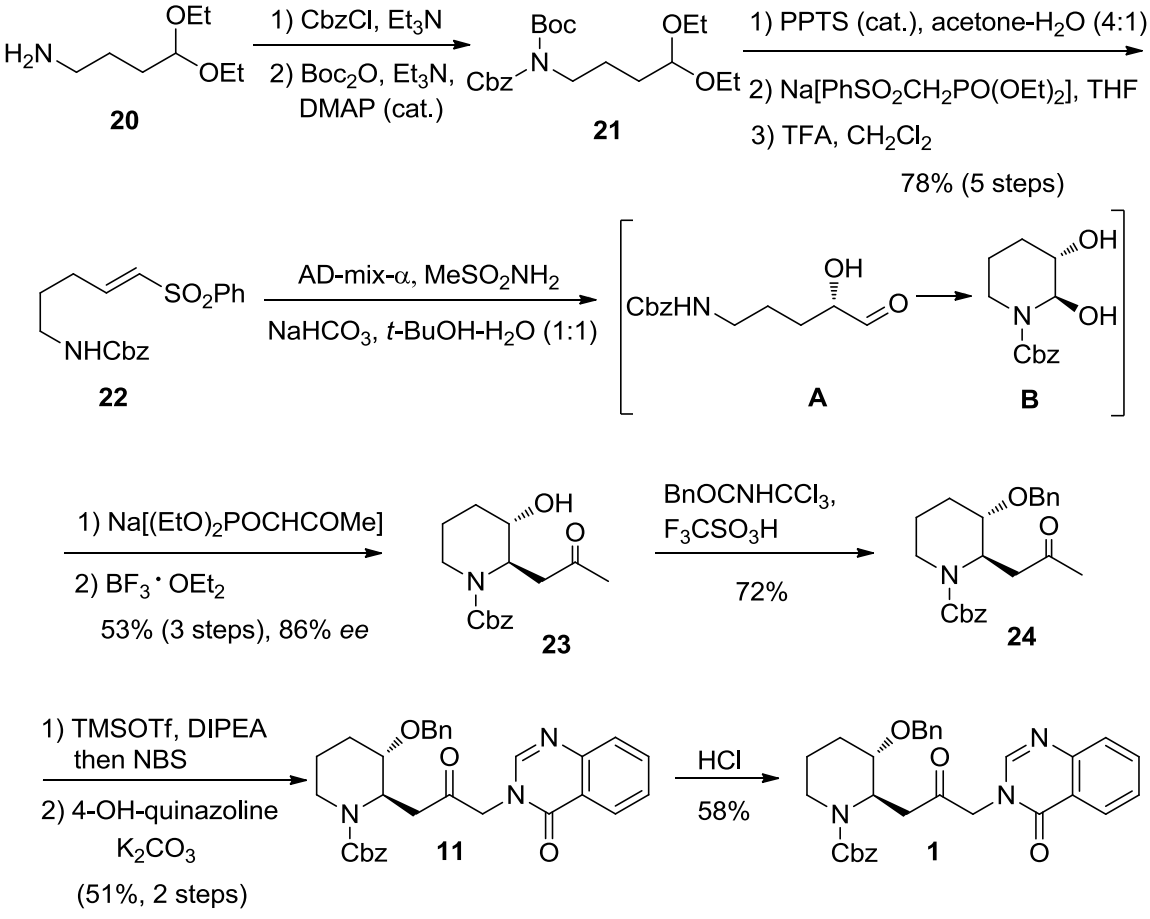


Scheme 4.2. Synthesis of (+)-febrifugine by Lin.

4.2.3 The Evans synthesis of (+)-Febrifugine

Evans and coworkers[3a] envisaged an anti-selective aldol reaction as the key step in their synthesis of (+)-febrifugine. The synthesis commenced with the aldol reaction of oxazolidinone **20** with aldehyde **21** (Scheme 4.3). The aldol product was then protected as the benzyl carbonate **22** and the chiral auxiliary was removed by reduction with lithium borohydride to afford alcohol **23**. Oxidation of the primary alcohol with *para*-toluenesulfonic acid and pyridinium dichromate furnished carboxylic acid **24**. Treatment of the carboxylic acid with

diethyl ester in presence of NaH followed by Horner-Wadsworth-Emmons olefination of the hemiaminal ether to afford the piperidine 23 as a single diastereomer. The hydroxyl group directed the bromination of piperidine 23 (TfOH, DBDMH, then NBS) to afford bromide 24 in 72% yield. Deprotection of the carbamate (TMSOTf, DIPEA then NBS) and condensation with 4-hydroxyquinazoline provided febrifugine (20) and isofebrifugine (21) in 58% yield.



Scheme 4.3. Synthesis of (+)-febrifugine by Evans.

4.3 Results and Discussion

We decided to develop a synthesis of f
precursor that couldgaiasnoebeandcopvertetedia ht
linked piperidines by simple coupling with
common prlecu2irssoar stuoitably protec[3]isedkCpaisperi
(Figure 4.2) whfochcdieoriavleisZDefdrTmieptedIpdeirnidnie
can be obtaine[9]dobfyanisaommenroizaaltKiyolrUllaEmtaeelys
derives from the fFuwnhcitcihonlaelaidzsedtdoutleeoobrgd
vinylogous [10]adodlotlcomooelaacctticoone and an approp
vinylogous [11]adlidroelctrleyacsteitosn the ab5soilutethest
piperidine ring of the -6tairsgeitn.diTrheectsltyercoon
aldol reaction amidulastiacmierfvedtheysmeaondary
the aldol adduct (Figure 4.2).

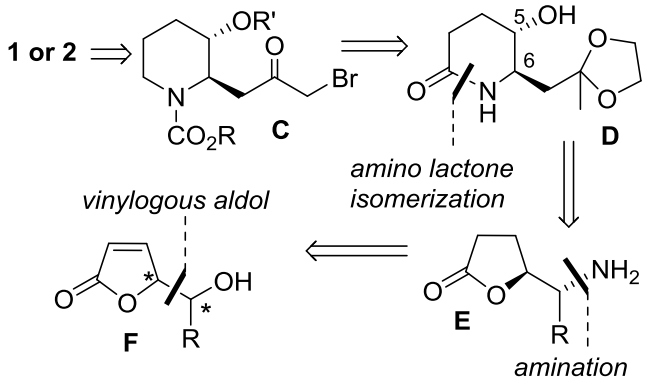


Figure 4.2. The organocatalytic direct vinylo

Our investigations based on the Schreiner's thiourea catalyst 24 (Scheme 4.14) in the direct vinylogous aldol reaction of 2-(trimethylsiloxy)furan 26 and 2-octynal 27 as the aldehyde was examined in the presence of diphenylethylenediamine derived aminothiourea (25a, 25b, 25c) and squaramide (25d and 25e) catalysts (Figure 4.3).

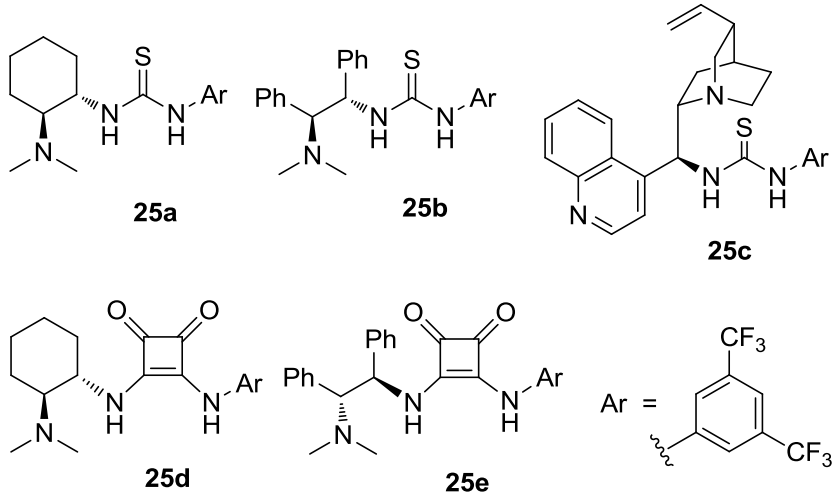
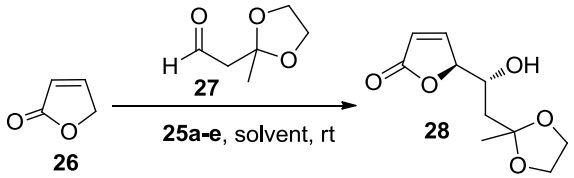


Figure 4.3 .Selected aminothiourea and aminos

Orienting experiments suggested that the use of toluene as solvent for further studies based on the catalyst 24 (Table 4.1 entries 1-4) was ideal. Although lower temperature (0 °C) increased the enantiomeric excess, it also drastically slowed down the reaction (Table 4.1 entry 4). The phenylethylenediamine derived aminothiourea 25a was ineffective as a catalyst in this reaction and provided the product in poor yield and low enantiomeric excess (Table 4.1 entries 5-8). The squaramide catalysts 25d and 25e also provided

(Table 4.1, entry 9). Reaction was slower, but provided higher enantioselectivity. The aminothiourea catalyst was tested in a set of dichloromethane solvent provided the highest enantioselectivity and diastereoselectivity. Further studies catalyst with ethyl acetate provided enantiomeric excess diastereoselectivity and yield as synthetic more useful when dichloromethane was used

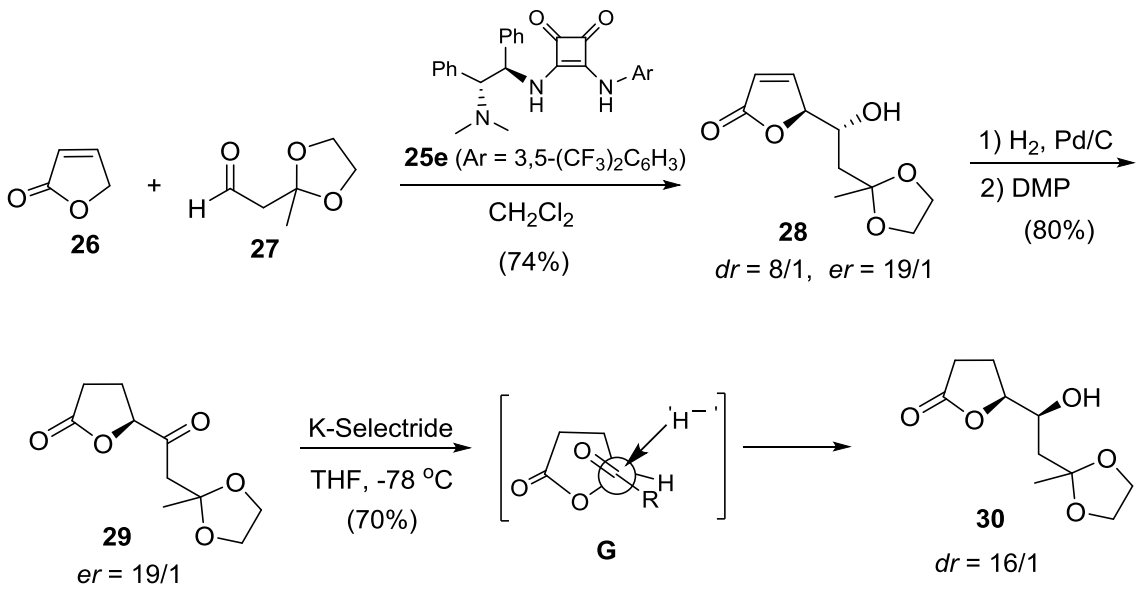


Entry[a]	Cat[b]	Solvent	T/h	Yield (%)	dr[c] (*anti/syn*)	ee[d] (%) (*anti*)[e]
1	**25a**	CH_2Cl_2	24	59	1.1/1	−55
2	**25a**	tolu	24	68	1/1	−18
3	**25a**	EtOA	24	31	1.1/1	−58
4	**25a**	DMF	24	12	1/1	−30
5	**25a**	CH_2Cl_2	14[f]4	8	4.2/1	−62
6	**25b**	CH_2Cl_2	144	2	-	−61
7	**25b**	EtOA	14	0	-	-
8	**25b**	tolu	144	0	-	-
9	**25c**	CH_2Cl_2	48	13	1.5/1	−74
10	**25d**	CH_2Cl_2	48	31	1.9/1	−90
11	**25d**	CH_2Cl_2	14[f]4	16	2.2/1	−93
12	**25d**	EtOA	48	20	1.6/1	−88
13	**25d**	tolu	48	39	1.5/1	−88
14	**25e**	EtOA	120	18	2.4/1	95
15	**25e**	CH_2Cl_2	192	74	8/1	91
16	**25e**	tolu	120	27	2.9/1	90

[a] 2 equiv. of 2c0r omto hfo.lNaMcRtoonfe.crudCheirparlodHuRctLCs
[e] yes'iisn.dicates formatio28nReafctticoen eantaOtiome

Table 4.1 .Optimization of the ODVA dela27tion of

Thus the direct vinylogous addition reaction of **27** using **25** as the catalyst provided good yields and diastereoselectivity (anti:syn = 8:1) and excellent enantioselectivity (anti diastereomer) when the reaction was carried out at −78 °C (Table 4.4). Following the planned synthetic strategy, the *trans* substitution in the target amino lactone would involve an inversion of configuration at the carbon bearing the hydroxyl group. Therefore, the aldol product was first hydrogenated and then subjected to a Mitsunobu reaction. However, the hydrogenation of **28** under a variety of conditions (Scheme 4.4) led to complex mixtures and hence an alternate strategy was examined. Accordingly, the alcohol was first reduced to the corresponding amine **29** with Selectride® as the reductant to give **30** (70%) with good *syn* selectivity (*syn*:*anti* = 16:1), presumably via a chelation controlled pathway[15,16] (Scheme 4.4).

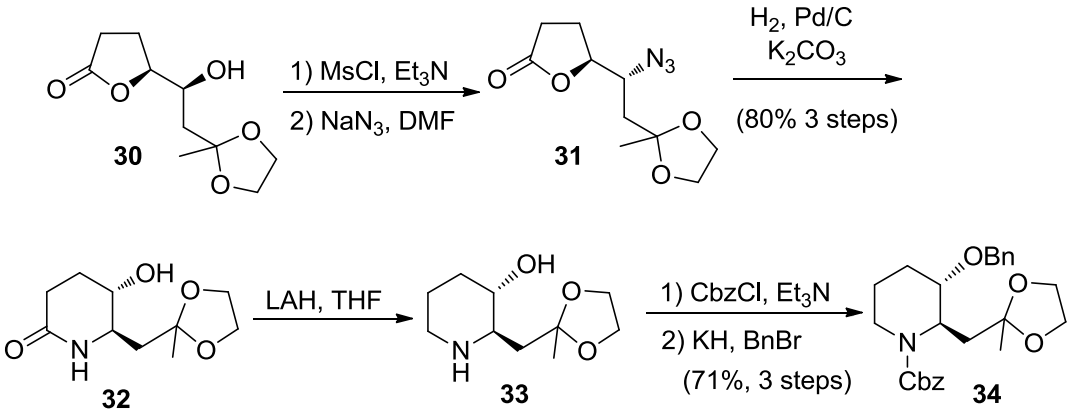


Scheme 4.4. Synthesis of **30** via DVA reaction.

The stereochemical assignments of the early organocatalytic vinylogous aldol reactions involving aldehydes that afforded the major 4,6-*anti* diastereomer (the *anti* and *syn* assignments in this report refer to the relative stereochemistry of the C4 and C6 protons) in these aldol products (see compound **28**, ref. 10) formed by the (+)-proline catalyst configuration.

The lactones **30** were readily converted to the desired azido alcohols **31** (major diastereomer) by azidation with inversion of configuration at C6 (Scheme 4.5). Reduction of the azide (H$_2$, Pd/C) then afforded a mixture of butyrolactone and 3,2-hemiketal **32**. Both of these intermediates were acylated with the amino acid **33** using DCC as the coupling agent,

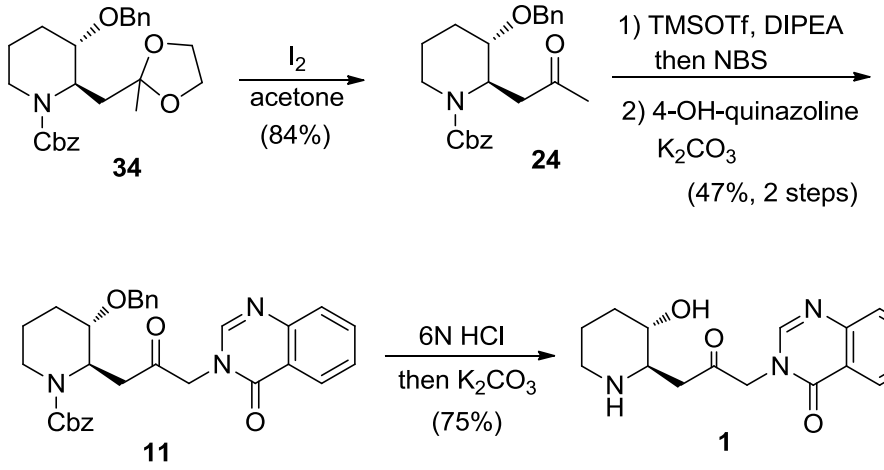
significantly facilitated the isolation of the product from any residual amino lactam starting material. Reduction of the piperidine ring was isolated as a single diastereomer of *trans* isomer during the *N*-protection with the carbobenzyloxy followed by protection of the key intermediate, as shown in Scheme 4.5).



Scheme 4.5. Synthesis of piperidine

With the piperidine, the final steps of the ketone was unmasked by treatment of the ketal (Scheme 4.6). Comparison of the ^{1}H and ^{13}C NMR data of the *trans* orientation of the substituents on the initial stereochemical assignment was confirmed by the unreported by Honda [3] (a TMSOTf, DBU bromoketone was reduced in to provide

derivative (6 mg, 0.011 mmol) and subsequent neutr
febrifugine. ($[\alpha]_D^{23}$ = +170.76, (EtOH); lit. $[\alpha]_D^{25}$ = +141.60, (EtOH), 86%



Scheme 4.6. Total synthesis of (+)-febrifugine.

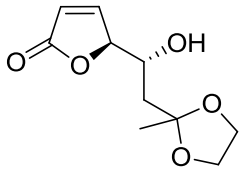
4.4 Conclusions

In conclusion, a stereoselective synthesis (6 steps, 14% overall yield) was achieved by employing a vinylogous aldol reaction and an intramolecular Mannich reaction of furanone-derived substrates to construct the 2,3-disubstituted piperidine core of the target bromoketone 24 obtained in one pot from commercially available 7-bromo-6-chloro-4-hydroxyquinazoline, a key intermediate in the synthesis of (+)-febrifugine. The study also

4.5 Experimental section

All commercially available reagents wer
requiring anhydrous conditions were perfo
using oven dried glassware and were stir
CaH_2 and sodium/benzophenone respectively. C
were used for TLC. Silica gel-400 mesh was
melting points are uncorrected and were
digital polarimeter at ambient temperature

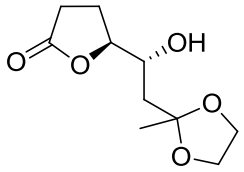
(*S*)-5-[(*R*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(5H)-one (28):



A mixture of (*E*)-4-(tert-butyldimethylsilyloxy)-2-hexenal
and 5-(5*H*)-furanone (10 mL, 21.5 mmol) in dichloromethane
for 192 h at ambient temperature. The mixture was
filtered and the filtrate was concentrated
chromatography (EtOAc/CH 10/1) to afford
solid (*anti*/*syn* = 8/1 determined by ^{1}H NMR analysis of the crude
IR (neat): 3467, 2988, 2889, 1749, 1758, NMR
(500 MHz, $CDCl_3$), ***anti* diastereomer:** δ 7.67 (dd, 1H, *J* = 5.8, 1.5 Hz), 6.
= 5.8, 1.5 Hz), 4.40–4.37 (m, 1H), 4.04–3.99 (m, 4H), 2.10,

7.0, 2.0 Hz) 8(6d, J=1H1s,4,.61,H)1,-1 92.9-1z (m, s1,H9)5, 1
3H)Visible resonances for the *syn* diastereomer: δ 7.52 (dd, J =1H5,.7, 1.5 Hz)
(part of -5dd,021(Hm),-4.52-5)4(mC,.2NBHR);(75 MHz, CDCl
diastereomer: δ 172.8, 154.9, 122.1, 110.0, 85.2, 69.6, 64.7, 64.3, 41.4, 24.1; Visible
resonances for the *syn* diastereomer: δ 172.9, 153.8, 122.7, 109.8, 84.9, 67.4, 64.8,
64.3, 40.1, 24 mC2,21MS1(AMCI,); pHRMS: (CI): 2
calcd1H1O5r(MCH)f=;0R30 (EtOAc/hexane; s,H:P4LC1);
Chiral-phase HPLC analysis: Chiralpak AS column, 2-propanol/hexane 10:90, 1.0 mL/min, 28 °C, 220 nm, (minor),
(major) *syn*-28: 57.9 min (major), 83.1 min (minor); *anti*-28: 42.4 min (minor), 88.3 min (major);
obtained 93% ee

(*S*)-5-[(*R*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]dihydrofuran-2(3H)-one (28a):



Pd/C (10%, 340 mg) was added to a solution of 28 (1.00 g, 7.93 mmol) in
methanol (80 mL). The mixture was stirred for 16 h under a hydrogen
balloon atmosphere and then filtered through a pad of Celite. The pad was
washed with methanol (2 × 30 mL). The combined filtrates were concentrated
under reduced pressure to give (99%) 5-[(*R*)-1-hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl

1 3 , - d i o x - 2 - y l a) n e f t u h r - 2 y a (n 3 - d H) 2 8 a a s a w h *a n t i s y n* = s o 8 l / i 1 d) . (T h i s

p u r H e N (M R) a n d w a s d i r e c t l y u s e d i n t h e n e x

I R (n e a t) : 3 5 0 0 , 2 9 8 5 , 2 8 9 2 , 1 7 7 0 , 1 6 5 8 ,

1 1 1 9 , 1 0 2 1 ; 7 H , N 9 M 9 R 6 (c 5 m 0 0 3) M 4 H n z d i a s t e r e o m e r : δ 4.37 - 4 . 3 2 (m ,

1 H) , - 3 4 9 0 9 6 (m , 5 H) , 0 3 (. d 5 d 8 d J , = b 1 H 7 , s 8 , 1 H 9) . 4 2 , . 2 4 6 8 6 4 H

(m , 1 H - 2) . , 2 3 2 . (2 m 8 1 (d 1 d H „ Y = 1 H 2 , 4 0 6 , 1 2 (. d 0 d , H = z 1) H 1 , 4 1 6 8 , 1 0 .

H z) , 1 . 3 V 8 i s i b l e (r e s o n a n c e s 3 H f o r t h e *s y n* d i a s t e r e o m e r : δ 4.43 - 4 . 4 0 (m , 1 H)

2 . - 2 8 6 4 (m , - 2 1 4 H 5) , (m 2 0 , 8 (4 d 6 d H „ Y = 1 H 2 , 4 . 9 , 1 7 0 (d 5 d „ J H = 1) H „ 1 .

1 4 . 8 , 1 . 8 H z 1 3 C , N 1 M R 3 7 (7 5 s M 8) H 2 z H d i a s t e r e o m e r : δ 177.2,

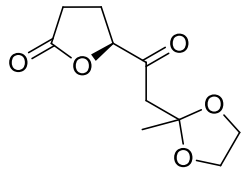
1 1 0 . 0 , 8 2 . 3 , 6 9 . 1 , 6 4 . V 6 i s i b l e 4 r e 3 s o n a n c e s , f o r 4 t h 0 e . 9 *s y n* , 2 8 . 3

diastereomer: δ 177.9, 109.9, 82.4, 69.8, 68.5, 64.8, 40.8, 28.3, 24.0, 23.9; MS (APCI,

p o s *m / z*) 2 1 7 . 1 (M + 1) ; H R M S (C I) : 2 1 6 1 7 5 . (M + H 2 f) ; 2 1 R 7 .

= 0 . 3 0 (E t O A c / h e x a n e s , 3 / 2) .

(*S*)-5-[2-(2-methyl-1,3-dioxolan-2-yl)acetyl]dihydrofuran-2(3H)-one (29):



T o a s o l u t i o n 2 8 a (9 0 0 m g , v 4 . 1 6 2 c (3 0 0 L)) w a s C H

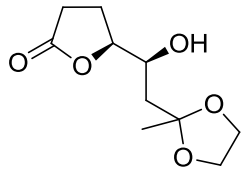
a d d e d - M D e t s i n p e r i g o , d i 8 n . a 3) 2 e a m (0 . l 5 3 e m i x t u r e w a s

t e m p t e u r r a e f o r 1 6 h . S a t u r a t e (3 0 a q u s e o u d s d e s o , d i t u

o r g a n i c l a y e r w a s s e p a r a t e d a n d 2 C 2 l t (h 2 e x a 3 u 0 e o

mL.) The combined organic (3 0 y, m L) r i $MgSO_4$ (w a s h e
c o n c e n t r a t e d r e s i d u e w a s p u r i f i e d b y f l a s h c
p r o v i d e 7 1 4 2 9 a m s g a (8 p 0 a % l) e o y f e l l o w l i q u i d .
I R (n e a t) : 2 9 9 6 , 2 8 9 3 , 1 7 6 9 , 1 7 1 ^{1} 3 H , N 1 M R 7 3 , 1
(5 0 0 M H z ,) δ 4 . 9 C D C B 8 (m , - 3 1 9 H 5) , (m 3 , . 9 4 9 H J) = 1 3 3 0 4 9 H (z d) ,
2 . 8 8 J (= d , 1 3 1 . H 4 - H z 4 , 5 2 (m 5 , - 2 5 . 3 1 H 3) , (m 2 , . 3 1 3 H) ^{1} ^{2} C , N 1 M R 4 4 (s
(7 5 M H z 3) ; δ 2 0 5 D . C 1 7 6 . 3 , 1 0 8 . 0 , 8 2 . 2 , 6 4 . 8 , 6 4 . 7 , 4 7 . 5 , 2 7 . 3 , 2 4 . 7 , 2 4 . 2 ; M S
(A P C I , *m/z* p 2 0 5 s l . (M + 1) , $[\alpha]_D^{23}$ = 8 - 1 8 0 . (9 2 , 3) C , H C - H R M S *m/z* (C I) :
2 1 4 . 0 8 0 8 (2 1 4 . H 0 8 1 2 4 5 4 1 , f = R a l 3 0 d (E r O A c / h e x a n e s , 1

(*S*)-5-[(*S*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(5H)-one (30):

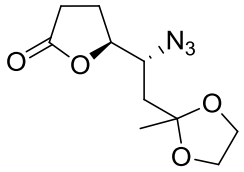


K - S e l e c ® (t 1 r . i 0 d e M i 0 m L T , H O F 2 m 8) 2 l . w a s a d d e d t o a s t i r
k e t 2 9 r (e 4 0 0 m g , 1 . 8 6 . 0 m 1 m) o - 7 a 8 C i a n d T H F h e (2 m i x t u r e w
- 7 8 ° C f o h r . 1 S a t u r a t e d a q u e o u s (a m 5 o m L) m a d d e d r
f o l l o w e d (2 0 . E t T O h A e c o r l g a y n e r w a s s e p a r a t e d a n d
e x t r a c t e d (w 2 i t x h 2 E O f T O m A e c) c o m b i n e d o r g a $MgSO_4$) c , l a y e
a n d c o n c e n t r a t e d . T h e r e s i d u e w a s p u r i f i e
1 / 1) t o p r o v i d 1 0 e a s 2 0 a 8 3 o m g e s (y s 7 l 0 i % d = q 1 u 0 6 i f d 1) (.

IR (neat): 3498, 2986, 2960, 2933, 2890, 1
cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) **Syn diastereomer:** δ 4.44-4.39 (m, 1H), 4.
(m, 4H), 3.95-3.90 (m, 1H), 2.67 (dd, 1H, *J* = 13.9, 7.4
2.25 (m, 2H), 1.65 (s, 3H), 1.48, 1.38 **Visible**
resonances for the *anti* diastereomer: δ 4.43-4.40 (m, 1H), 2.87 (dd, 1H,
1H, *J* = 14.6, 2.0 Hz), 1.37 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) **Syn diastereomer:** δ
177.9, 109.9, 82.4, 69.8, **Visible resonances for the**
***anti* diastereomer:** δ 177.2, 110.0, 82.2, 69.1, 64.8, 40.9, 28.3, 24.2
pos (*m/z*) 217.1 (M+1); HRMS (CI): $C_{10}H_{17}N_4O_5$ (M+H$^+$) (217.
= 0.30 (EtOAc/hexanes, 3/2).

(*S*)-5-[(*R*)-1-Azido-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-dihydrofuran-2(3H)-one

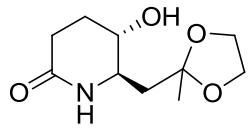
(31):



To a solution (100 mg, 2.7 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C under nitroge
added triethylamine (463 µL, 3.32 mmol) fo
3.32 mmol). The mixture was stirred at 0 °C for 1
mixture was extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic
(Na$_2$SO$_4$) and concentrated to give a yellow oil (
was used immediately in the next step with

Sodium azide (822 mg, 12.6 mmol) was added
mg, 2.53 mmol) in DMF (8 mL) and the mixture was heated at 90 °C for 16 hours.
The mixture was cooled to room temperature and poured into water (30 mL). The resulting biphase was separated with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to provide the azide as a yellow oil (631 mg, 100%). This was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56–4.52 (m, 1H), 4.16 (m, 1H), 3.91–3.86 (m, 1H), 3.43 (dd, J = 12.6, 10.2 Hz, 1H), 3.35 (dd, J = 12.6, 4.5 Hz, 1H), 2.27–2.19 (m, 1H), 2.10–2.04 (m, 1H), 1.99, 1.87 (d, J = 14.9 Hz, 1H), 1.49 (d, J = 14.9, 4.5 Hz, 1H). **Visible resonances for the *syn* diastereomer:** δ 4.60–4.57 (m, 1H), 3.54–3.48 (m, 1H), 2.37 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) **anti diastereomer:** δ 176.5, 108.1, 80.9, 64.7, 64.5, 60.5, 39.3, 28.2, 24.3, 22.2; **Visible resonances for the *syn* diastereomer:** δ 176.4, 108.2, 81.8, 64.64, 64.61, 60.5, 39.2, 28.1, 24.5, 22.2 m/z 242.1 MS (ESI+) (M + 1)$^+$ requires 242.1141, found 242.1145 HRMS (APCI+) (M + H)$^+$ requires for $C_{10}H_{16}NO_4$ (M + H)$^+$; R_f 0.50 (EtOAc/hexanes, 3

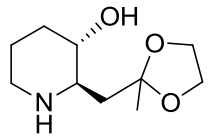
(5*S*,6*R*)-5-Hydroxy-6-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidin-2-one (32):



To a stirred solution of [illegible] in [illegible] at ambient temperature [illegible] was added [illegible] The mixture was stirred for 16 h at ambient temperature and then filtered through a pad of [illegible] and the combined filtrates were evaporated to a pale yellow gum. This was purified by [illegible] to provide [illegible] as a white solid. The overall yield from [illegible] is 80%.

IR (neat): 3352, 3229, 1623, 1467, 1420, 1379, 1197, 902 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) ***trans* diastereomer:** δ 6.63 (br s, 1H), 4.03–3.97 (m, 4H), 3.96 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.93 (m, 1H), 2.86 (ddd, *J* = 18.0, 6.3, 2.9 Hz, 1H), 2.41 (dd, *J* = 17.9, 2.1 Hz, 1H), 2.14 (dd, *J* = 14.5, 2.1 Hz, 1H), 2.03–1.88 (m, 3H), 1.83 (dd, *J* = 14.5, 9.8 Hz, 1H), 1.475 (s, 3H); **Visible resonances for the *cis* diastereomer:** 6.47 (s, 1H), 4.16 (m, 1H), 2.17 (m, 1H), 1.99 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ***trans* diastereomer:** δ 170.9, 109.7, 68.9, 64.7, 64.3, 55.1, 40.8, 29.1, 28.0, 24.2; **Visible resonances for the *cis* diastereomer:** δ 171.5, 109.4, 65.7, 64.6, 53.1, 40.5, 27.6, 25.8, 24.2; MS (APCI, pos *m/z* 216.1 (M+1); HRMS (CI): $C_{10}H_{18}NO_4$ (M+H)$^+$ requires 216.1236, found 216.1230. $[\alpha]_D^{25}$ −0.25 (*c* 1.0, MeOH, 4/1).

(2*R*,3*S*)-Benzyl-3-hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (33):

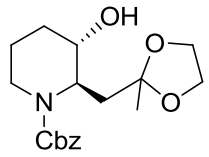


To a stirred solution of **32** (1.01 g, 2.66 mmol) in THF (30 mL) was added (0.199 g, 0.798 mmol) dissolved in THF (5 mL) and the mixture was 24 h. The mixture was cooled to 0 °C, water (50 mL) was added slowly and was stirred for 20 min. at 0 °C. Sodium periodate was added and the mixture was stirred for 10 min. The mixture was filtered through a Celite. The filter cake was washed with EtOAc (3 × 20 mL) and the combined were concentrated under reduced pressure to afford (2*R*,3*S*)-Benzyl-3-hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (**33**) as a pale white solid. This *trans* diastereomer (NMR) and was used in the purification.

IR (neat): 3316, 3122, 2928, 2862, 1682, 1424, 1378, 1246, 1128, 1040, 824, 1

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39 – 7.31 (m, 5H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.29 (d, *J* = 7.8 Hz, 1H), 4.12 – 4.02 (m, 2H), 3.92 – 3.82 (m, 2H), 3.73 – 3.64 (m, 1H), 3.58 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.47 (dd, *J* = 11.4, 7.8 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.32 (dd, *J* = 14.8, 4.8 Hz, 1H), 1.77 – 1.66 (m, 2H), 1.66 – 1.58 (m, 1H), 1.54 – 1.37 (m, 4H), 1.37 – 1.23 (m, 1H), 1.23 – 1.13 (m, 1H), 1.13 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ: 156.1, 136.8, 128.5, 128.1, 127.9, 110.1, 72.2, 64.6, 64.4, 59.9, 46.1, 46.1, 42.9, 36.1, 29.7, 25.8, 24.8, 23.8, 20.9; *m/z* 320.2 (M+1); 202.1 (M+1); HRMS (CI): calcd for C$_{18}$H$_{26}$NO$_5$ (M+H)$^+$ 336.1811, found 336.1847; (R_f = 0.3 (202.1443 C$_{10}$H$_{20}$NO$_3$ (M+H)$^+$; CH$_2$Cl$_2$/MeOH, 4/1).

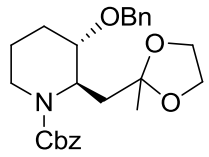
(2*R*,3*S*)-Benzyl 3-hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (33a):



To a solution of amino alcohol **32** (0.160 g, 0.679 mmol) in CH_2Cl_2 (11.0 mL) were added benzyl chloroformate (0.107 mL, 0.748 mmol) and pyridine (0.095 mL, 1.18 mmol). The solution was stirred at room temperature for 10 hr and then was diluted with CH_2Cl_2 (20 mL). The resulting solution was washed with 1 N HCl (2 x 20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (91% EtOAc/hexanes) to afford **33a** as a colorless oil.

IR (neat): 3466, 2944, 2883, 1702, 1257, 1153, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.28 (m, 5H), 5.15 (s, 2H), 3.98 (br s, 1H), 3.88–3.80 (m, 5H), 3.39 (br d, 1H, J = 11.4 Hz), 3.06 (br t, 1H, J = 11.4 Hz), 2.61 (br d, 1H, J = 14.1 Hz), 1.86–1.71 (m, 4H), 1.61–1.45 (m, 5H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3, 136.8, 128.4, 127.9, 127.8, 109.0, 68.2, 67.8, 67.3, 66.9, 53.2, 38.2, 25.7, 23.9, 23.1; ESI MS *m/z* 336.1 ($M + H^+$); HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NO_5$ ($M + H^+$) 336.1811, found 336.1816; $[\alpha]_D^{23}$ −20.9 (*c* 0.38, $CHCl_3$). R_f = 0.30 (EtOAc/hexanes, 3/2).

(2*R*,3*S*)-Benzyl-3-(benzyloxy)-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (34):



To a solution of **33a** (80 mg, 0.24 mmol) in dry THF at room temperature was added sodium hydride (60% dispersion in mineral oil, 0.24 mmol) and the mixture was stirred for 30 min. Tetrabutylammonium iodide (8 mg, 0.024 mmol) was added followed by benzyl bromide (29 mg, 0.24 mmol) and the mixture was stirred at ambient temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:1) to afford **34** as a colorless oil.

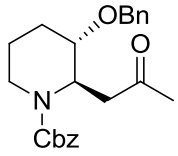
IR (neat): 2930, 2885, 1695, 1495, 1450, 1390, 1350, 1100, 1030, 735, 700 cm^{-1}.

^1H NMR (500 MHz, C_6D_6, 353 K) **Major rotamer:** δ 7.34-7.24 (m, 10H), 7.18-7.14 (m, 5H), 5.14 (AB system, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 45.6 Hz), 4.69 (dt, J_d = 14.1 Hz, J_t = 2.4 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.36 (d, J = 14.1 Hz, 1H), 3.85-3.82 (m, 1H), 3.73-3.71 (m, 1H), 3.71-3.68 (m, 1H), 3.46 (m, 1H), 3.29 (dt, J_d = 11.3 Hz, J_t = 2.9 Hz, 1H), 2.22 (m, 1H), 1.38-1.37 (m, 3H), 1.71-1.62 (m, 2H). **Visible resonances for the minor rotamer:** δ 5.19-5.14 (AB system, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 45.8 Hz), 4.70 (dt, J_d = 14.1 Hz, J_t = 2.3 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 14.1 Hz, 1H), 3.45 (m, 1H), 3.15 (dt, J_d = 11.5 Hz, J_t = 2.9 Hz, 1H).

^{13}C NMR (75 MHz, C_6D_6, 353 K) **Major rotamer:** δ 155.9, 138.9, 137.0, 128.3, 128.2 (2C), 127.9, 127.7, 1

39.1, 38.4, 19.9. Visible resonances for the minor rotamer: δ 155.7, 137.3, 128.4, 127.7, 127.6, 127.3, 109.2, 75.7, 7 19.9; (APCI *m/z* 426.2): (M+1); HRMS (CI): 426.2 $C_{25}H_{32}NO_5$ (M+H)$^+$ requires 426.2280. $[\alpha]_D^{23}$ = −12 *c* 0.48, CHCl$_3$. R_f = 0.60 (EtOAc/hexane

(2*R*,3*S*)-Benzyl 3-(benzyloxy)-2-(2-oxopropyl)piperidine-1-carboxylate (24):

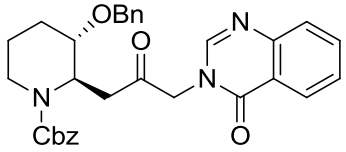


To a solution of 24 (64 mg, 0.15 mmol) was added a solution of I$_2$ (2 iodine (77.2 mg, 0.304 mmol, 10.5%) in anhydrous acetonitrile (0.6 mL) at room temper solution was stirred at ambient temperatur was dissolved in CH$_2$Cl$_2$ (1.0 mL) and Na$_2$S$_2$O$_3$ (5 mL) was added. The was stirred vigorously for a few minutes aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organ dried (Na$_2$SO$_4$), filtered and concentrated. The chromatography on silica gel (hexanes/EtOAc, 7 colorless oil.

IR (neat): 2943, 2866, 1689, 1422, 1355, 1 NMR (500 MHz, CDCl$_3$): δ 7.38–7.25 (m, 10H), 5.15 (s, 2H), 5.01 (br s, 1H), 4.66 (br s, 1H), 4.11 (br s, 1H), 2.84 (br s, 1H), 2.58 (m, 1H), 2.29–2.15 (m, 3H), 1.6 1H), 1.40 (br s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.9, 155.9, 138.

136.8, 128.4, 128.3, 127.9, 127.8, 127.5,
24.4, 19.5 *m/z* 3HRMS20(2Cl):382 $_{2}$H$_{2}$N$_{4}$(MeOH)^{2}= for C
−29 *c* 21.0, $_{3}$)C;HCl$_{3}$ t=−26 *c* 81.0, $_{3}$)CH$_{2}$Cwrth 86%f=Ree0.25
(hexanes/EtOAc, ^{1}H NMR (*d*, ^{13}C) NMR data is in agreem
data.

(2*R*,3*S*)-3-Benzyloxy-2-[2-oxoquinazolin-3(4*H*)-yl)propyl]piperidine-1-carbamic acid benzyl ester (11):

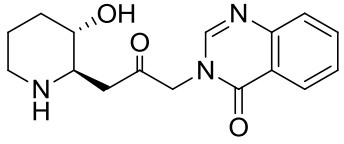


To a solut24 (040 mg, 0.11 mmo$_{2}$Cl$_{2}$) (2 mL) a^{0}C anhydrous and C
TMSOTf (40 µL, 0.22 mmol) and DIPEA (42 µL
stirr^{0}Cd for m0.5 and NBS (39 wmg, add2 2.mTmhe m
stirred at temperature for 3 h and then pour
mixture was extracted with EtOAc (2 x 10
washed with water (10 $_{2}$SO$_{4}$)), brine (1n0d mL), c
provide three corked tone which was used in the
To a solution of the bromoketone in anhyd
K_2CO_3 (15 mg, 0.11 hmydroxyquinazoline (16 mg,
mixture was stirred at room he and then pou
resulting mixture was extracted with EtOA
were washed with water (10 $_{2}$SO$_{4}$), brine a(n

concentrated. The brye sfi dause h wa s r opmua rt io fg ir eac p h y
(h e x a n e s / E t O A c , 2 / 3 1 1) a s t o a g d i v e o 2 7 e s m s g l (4 7 % i) d o
IR: 1726, 1674, 1610, 1424 $^{-1}$; ^{1}H 1 N M R , (5 0 5 7 , M H z
CDG;) l δ 8 .7 2 (d d , J = 1 H 8 , . 0 , 1 . 5) , 7 7 . . 9 7 2 3 ((b m r , - 7 s 2 , 4 H 9 1 , H ( ) 7 , . . 5 7
1 H) , - 7 7 . 2 3 5 2 (m , 7 (1 d 0 , H J) 1 , H 1 , 5 2 . . 4 0 (H d ,) J , = 1 H 5 1 , 2 1 . 4 - 4 H z 9 8 , 5 . 0
(m , 1 H) , 4 . 9 4 4 . 6 3 r (s m , 3 (0 1 H H)) d , = 4 1 1 . 5 5 9 H z) 1 , H) 4 , . 0 6
3 . 5 2 (b r s , 1 H) 6 (, d d 2 , J 9 = 1 7 H 1 , 4 b 7 , 2 s 8 7 . b 7 r H) H d z d) = , 2 1 2 4 H . , 7 ,
6 . 1 H z - 1) . , 8 8 1 . (9 b 4 r m , 2 H) , - 1 . 1 6 . 3 7 5 (m (, 4 b (r a 1 p s p) , a r 1 e d H n) t 4 , b 1 r
1 H J , = 1 2 . 1 5 2 C H N z M) R ; (7 5 M) 6 H z 0 0 C 0 0 C l 1 6 0 8 . . 9 2 , , 1 1 5 4 6 . . 2 5 , , 1 1 -
1 3 6 . 5 , 1 3 4 . 5 , 1 2 8 . 5 , 1 2 8 . 4 , 1 2 8 . 0 , 1 2 7 . 8 ,
7 0 . 4 , 6 7 . 4 , 5 3 . 9 , 5 0 . 6 , 4 1 m/z (5 2 6 3 9 2 . 6 (M + 2 1 4) ; 3 H R
(E I +) : 5 2 5 . 2 2 8 5 $_3$ (H 5 N 2 C 5 (M 2 + 6 H 4)] $^{2\ 3}$ = a [2 l 4 c d 8 1 . f 7 o , r $_3$) C ; H C l
l i [α] $_D^{2\ 5}$ = − 2 2 c 0 1 . (0 , $_3$) C ; H (= H 0 . 3 0 (E t O A c) ; $^{3\ a}$ (s l p H e , c t r o s c
N M R ^{1,2} C N M R) a n d o $^{3\ m}$ f t d 1 r c a a r l e r i o n t a a t g i r c e r e m e n t $^{3\ a}$, $^{3\ m}$ w i t h r

3-(3-[(2*R*,3*S*)-3-Hydroxypiperidin-2-yl)-2-oxopropyl]quinazolin-4(3*H*)-one

((+)-Febrifugine) (1):



A s t i r r e d 1 1 (s 1 o 7 l u m t g i , o n 0 . o 0 f 3 m m o M) , 0 m 2 L n) a w q a u s e o l u s a H C
r e f l u x f o r 1 h . T h e s ^{o} C o l a n d o w a s w a s $_2$ C $_3$ h t e i n e d c o w
p H - 1 0 . T s h i e c b s a o l u t i o n w a s (3 e x t r 3 a 0 c t m e L d) . w i T t h h e C d - H o C m l

layers were washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated ... mg (99%) of crude product. This was purif[ied] ... (CH_3CN/MeOH, 9/1) to provide 7.5 mg (75%) of (+)-... as a white solid. Mp: 133 °C; (lit.[1] mp 133–135 °C). IR (neat): 3306, 3052, ... 1669, 1607, 1468, 1136 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 7.9 Hz, 1H), 7.97–7.71 (m, 2H), 7.48 (s, 1H), 7.54–7.41 (m, 3H), (AB system, J = 12.5 Hz, 2H), 3.61 (dd, J = 11.9, 5 Hz, 1H), ... J = 11.9 Hz), 2.64 (dd, J = 11.9, 5 Hz, 1H), 2.53 ... Hz), 2.22 (s, 2H), 2.0 (br, 1H), 1.74–1.71 (m, 1H), 1.53–1.30 (m, 1H), 1. ... (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 148.2, 146. ... 126.8, 121.8, 72.2, 60.2; MS (APCI) m/z 302.0 (M+1, 100), 304.0 (M+1); HRMS (CI) m/z 302.1512 (302.1505 calcd for $C_{16}H_{20}N_3O_3$ (M + H)); $[\alpha]_D^{23}$ = +1.7 (c 0.6, EtOH); [lit.[3a] $[\alpha]_D^{25}$ = +1.1 (c 1.60, EtOH)]; R_f = 0.2 (CH_2Cl_2/MeOH/NEt_3 9.00/0.95/0.05). The ^{1}H NMR and ^{13}C NMR data is in agreement w[ith] [illegible] [3a, 3i]

4.6 References:

1)(a) Wells, T. N. C.; *Nat. Rev. Drug Discovery* **2009**, *8*, 879; (b) Burrows, J. N.; Chiba, S.; *Curr. Top. Med. Chem.* **2011**, *11*, 1226; Wright, D. L.; Gut, J.; Rosenthal, P. J.; *Expert Opin. Ther. Pat.* **2011**, *21*, 1741; (c) Winter, R. W.; Kelly, J. X.; Smilkstein, M. J.; Dodean, R.; Hinrichs, D.; *Int. J. Parasitol.* **2008**, *38*, 1379; Wu, Y.; Wang, X. L.; Liu, B. L.; Sun, X.; *Curr. Med. Chem.* **2011**, *18*, 1488; Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunter, R.; Ilett, K. F.; Jaffar, F. Y.; Kaminsky, W.; Klayman, D. L.; Kostewicz, E. S.; Krogstad, D. J.; Lanteri, C. A.; Lee, A. Y.; Leimanis, M. L.; Matile, H.; Monastyrskyi, A.; Nacer, A.; Nam, T.-G.; Navaratnam, V.; Olliaro, P. L.; Peters, W.; Rathod, P. K.; Ridley, R. G.; Saeed, M. E. M.; Scheurer, C.; Scheurer, K.; Steffan, J. J.; Steffan, N. L.; Stover, K. R.; Tasdemir, D.; Tidwell, R. R.; Tilley, L.; Vaillard, V. A.; Walker, L. A.; Wells, G. A.; Wittlin, S.; Woodland, J. G.; Yuthavong, Y.; *Nature* **2011**, *480*, 71.

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3) Enantioselective syntheses of febrifug

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Figéraed,*Angew. Chem., Int. Ed.* **2000**, *39*, 1799.
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Urbano, A.; *Org. Lett.* **2007**, *9*, 4M4.51C..
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153.
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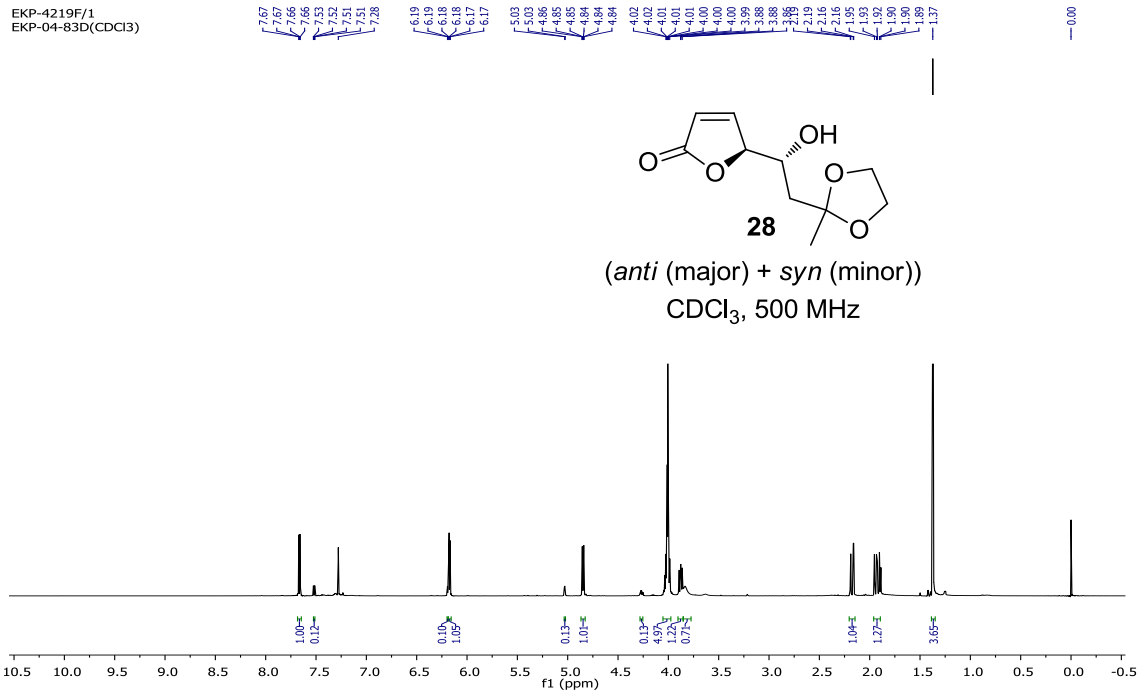
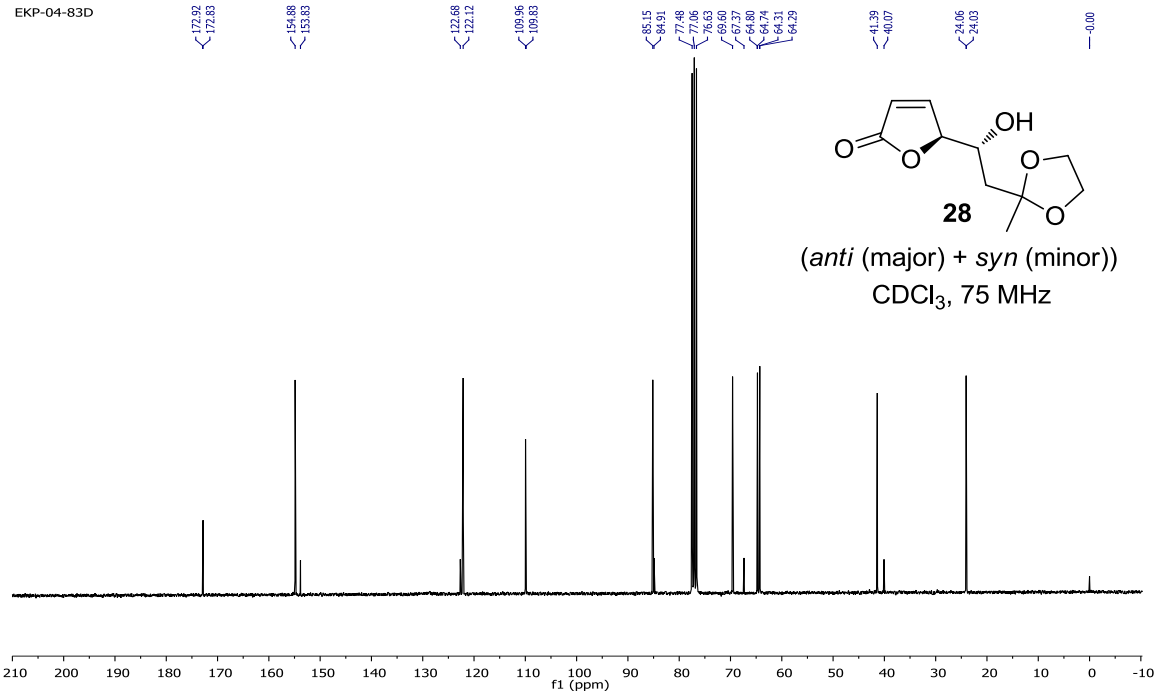
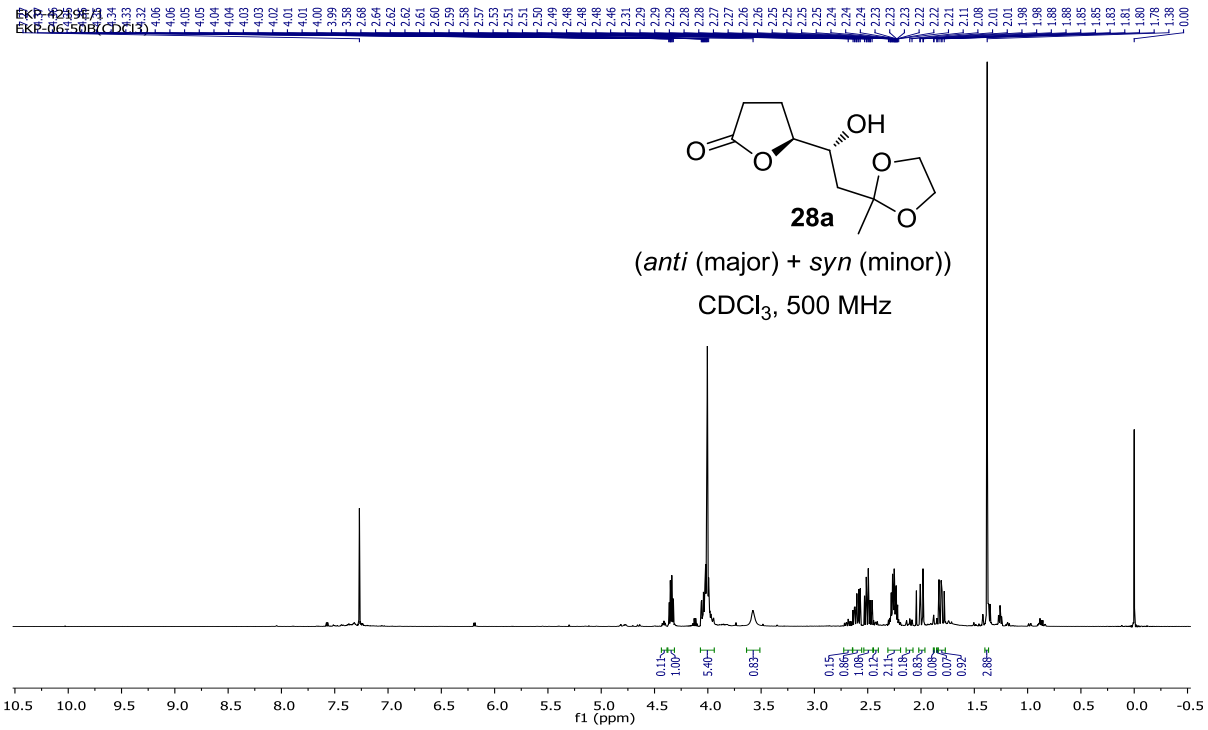
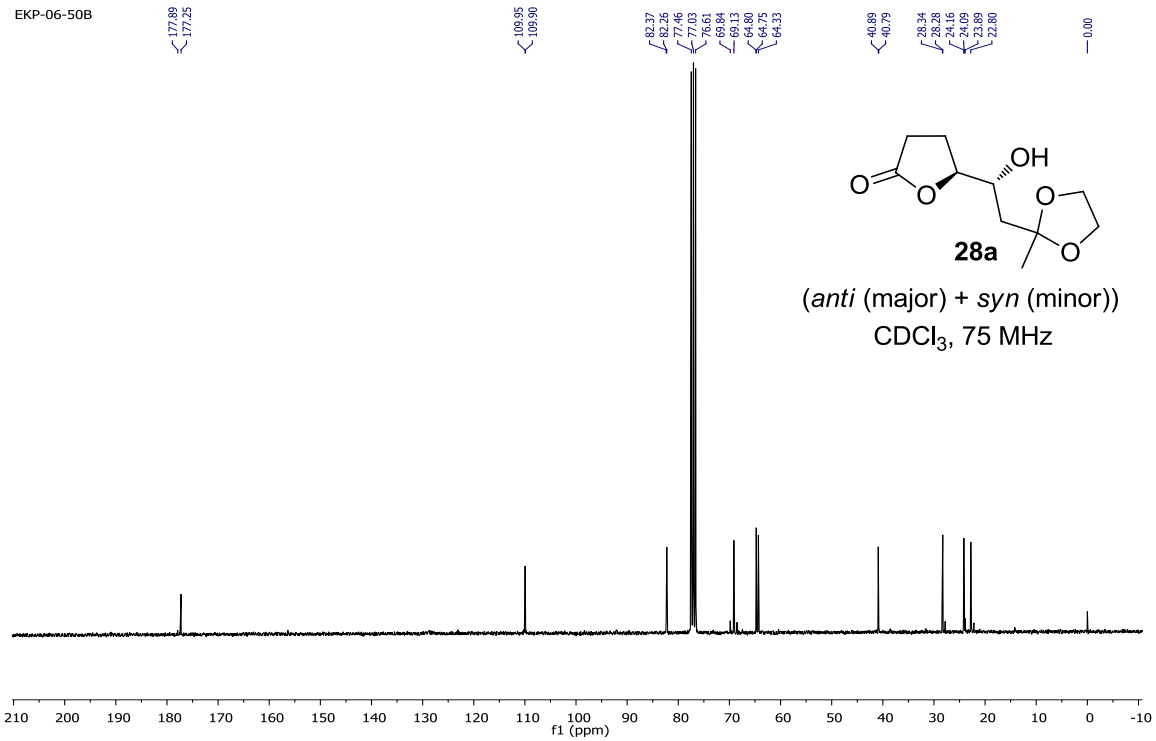
4.7 Selected ^{1}H and ^{13}C NMR spectra


EKP-4219F/1
EKP-04-83D(CDCl3)
OH
O
O
O
O
28
(anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)


EKP-04-83D
OH
O
O
O
O
28
(anti (major) + syn (minor))
CDCl3, 75 MHz
f1 (ppm)


OH
O
O
O
O
28a
(anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)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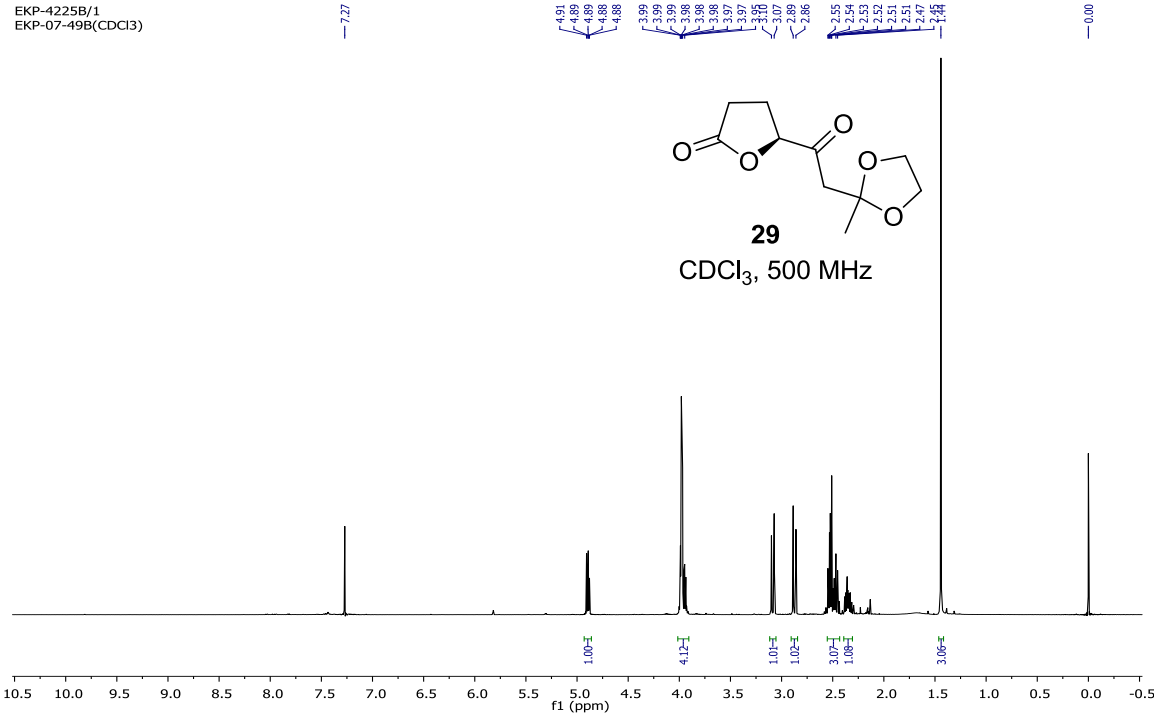
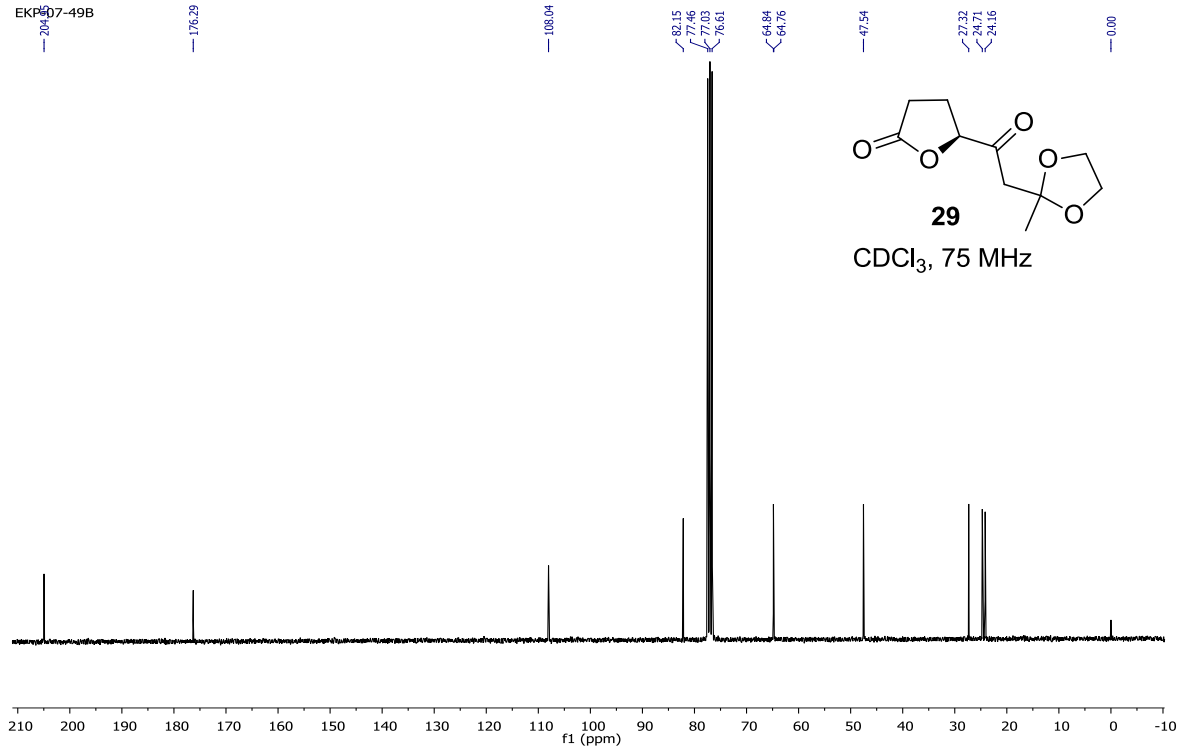
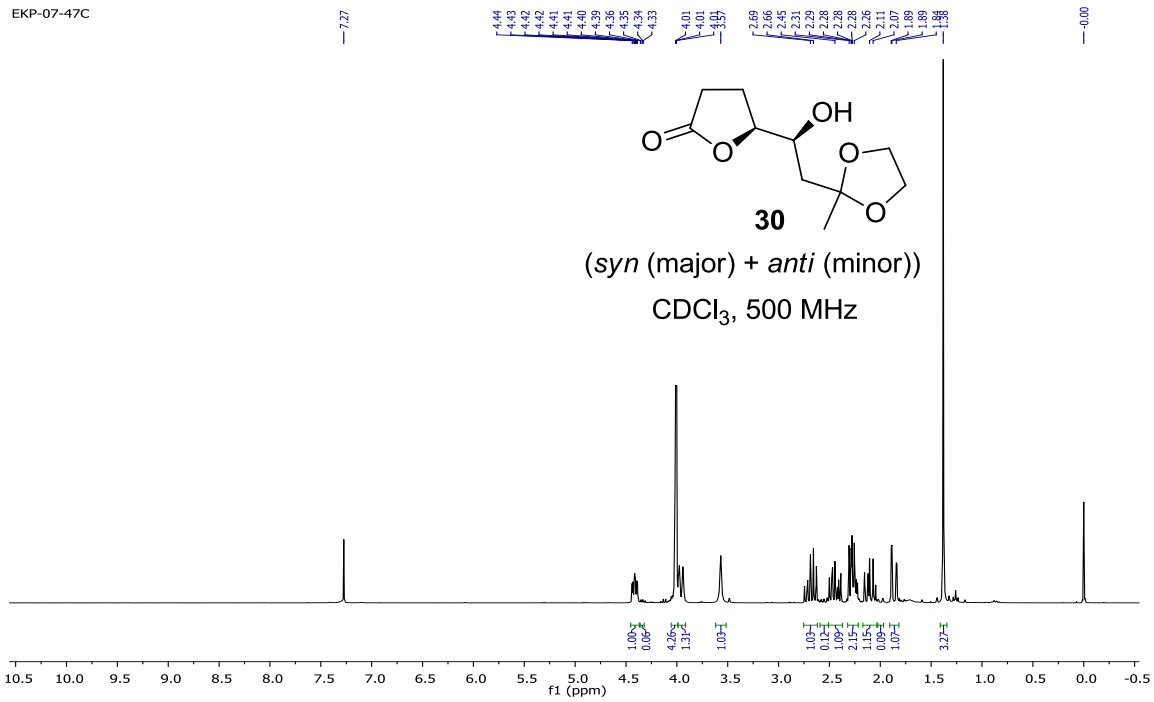
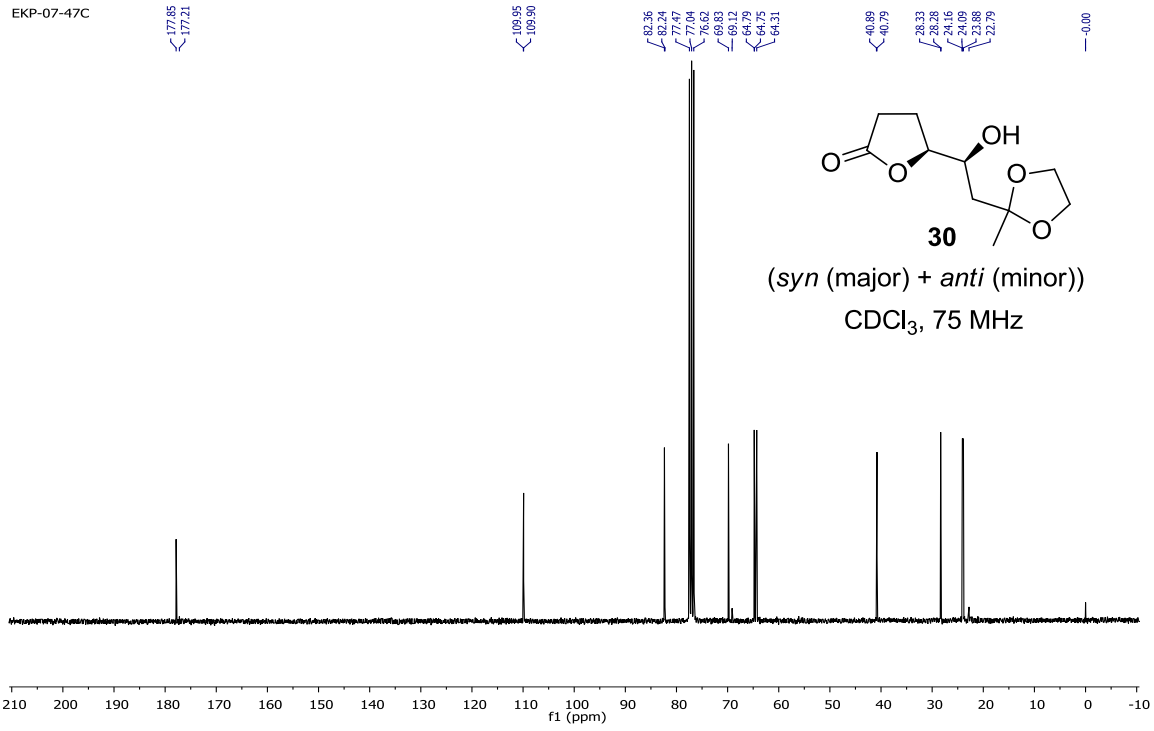
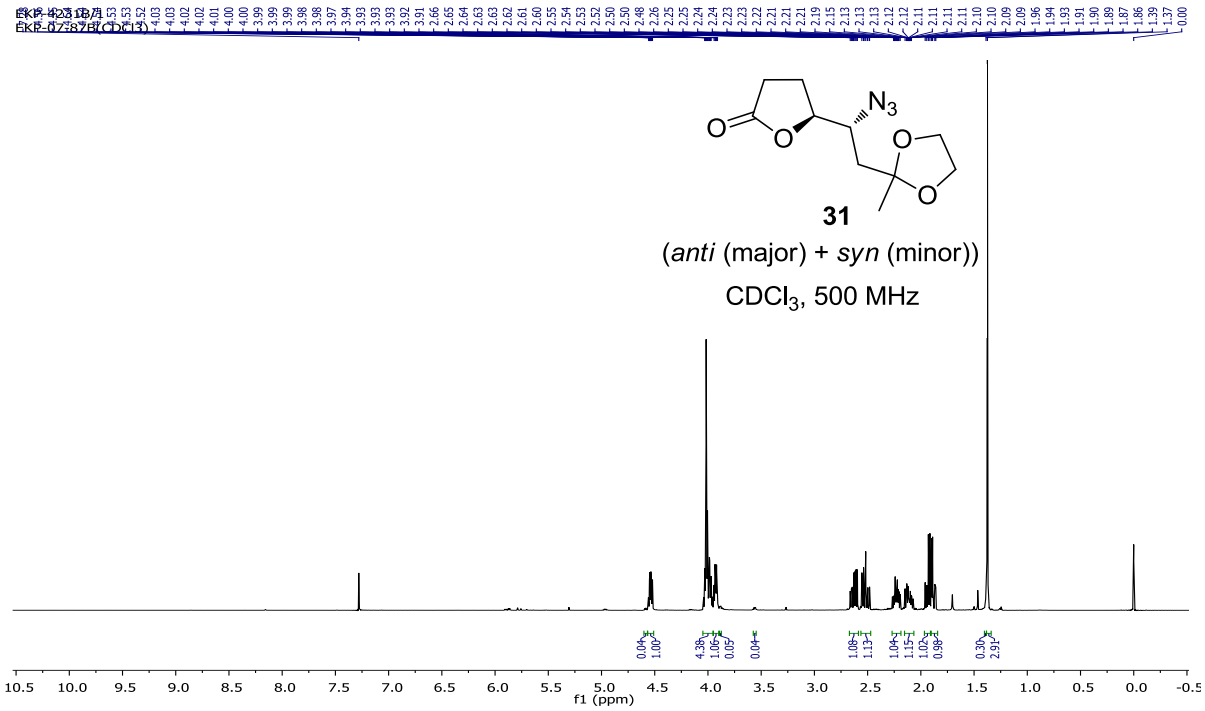
O
O
O
O
28a
(anti (major) + syn (minor))
CDCl3, 75 MHz
f1 (ppm)

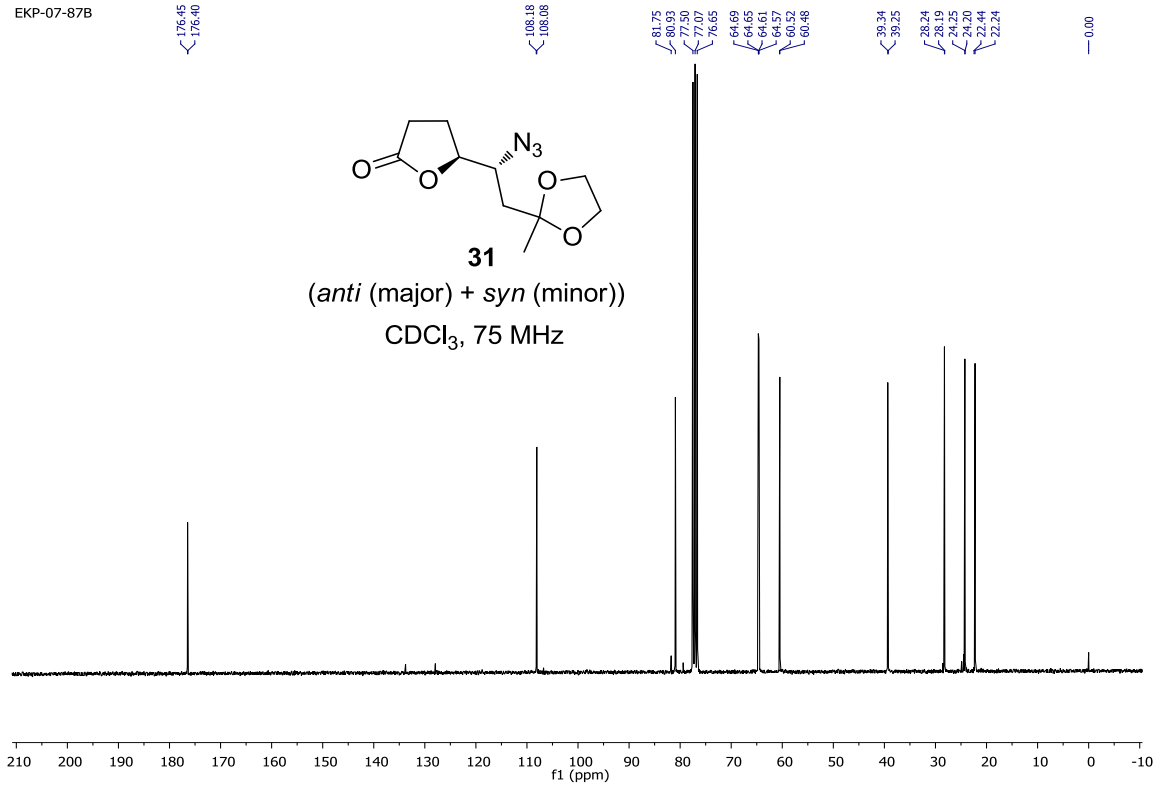

EKP-4225B/1
EKP-07-49B(CDCl3)
29
CDCl3, 500 MHz
f1 (ppm)


EKP-07-49B
29
CDCl3, 75 MHz
f1 (ppm)


EKP-07-47C
OH
O
O
O
O
30
(*syn* (major) + *anti* (minor))
$CDCl_3$, 500 MHz
f1 (ppm)


EKP-07-47C
OH
O
O
O
O
30
(*syn* (major) + *anti* (minor))
$CDCl_3$, 75 MHz
f1 (ppm)


N3
O
O
O
O
31
(anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)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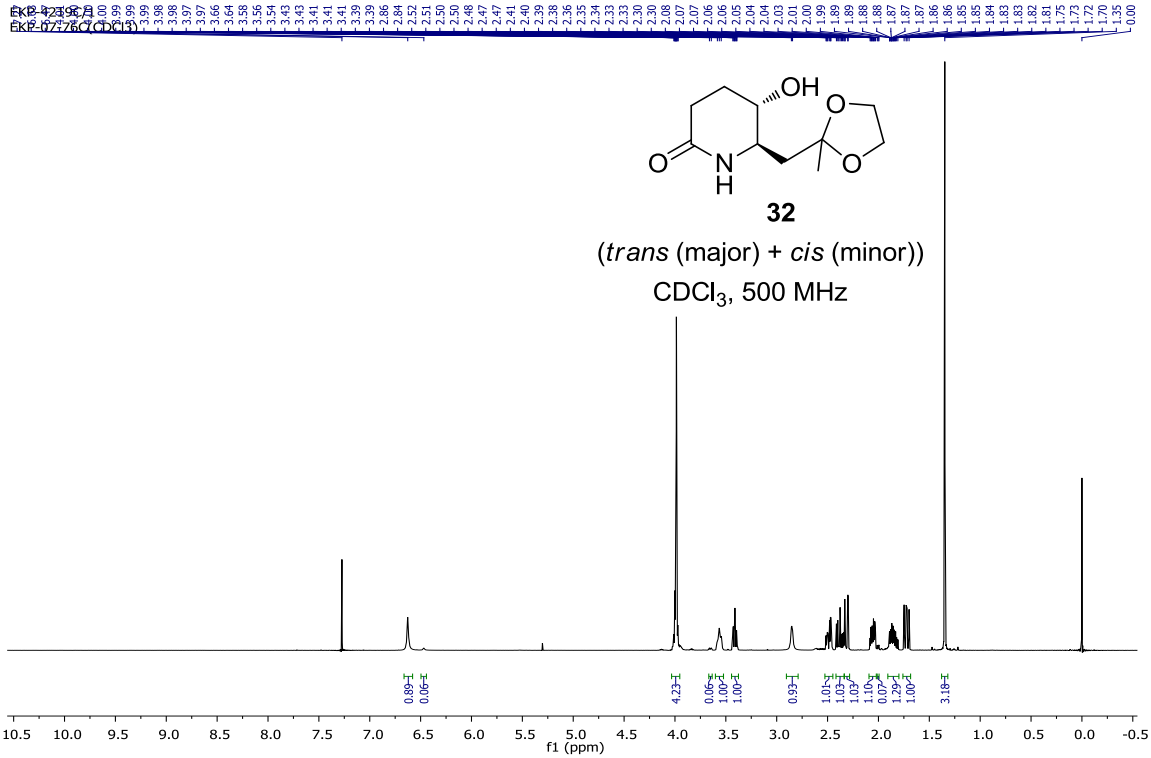
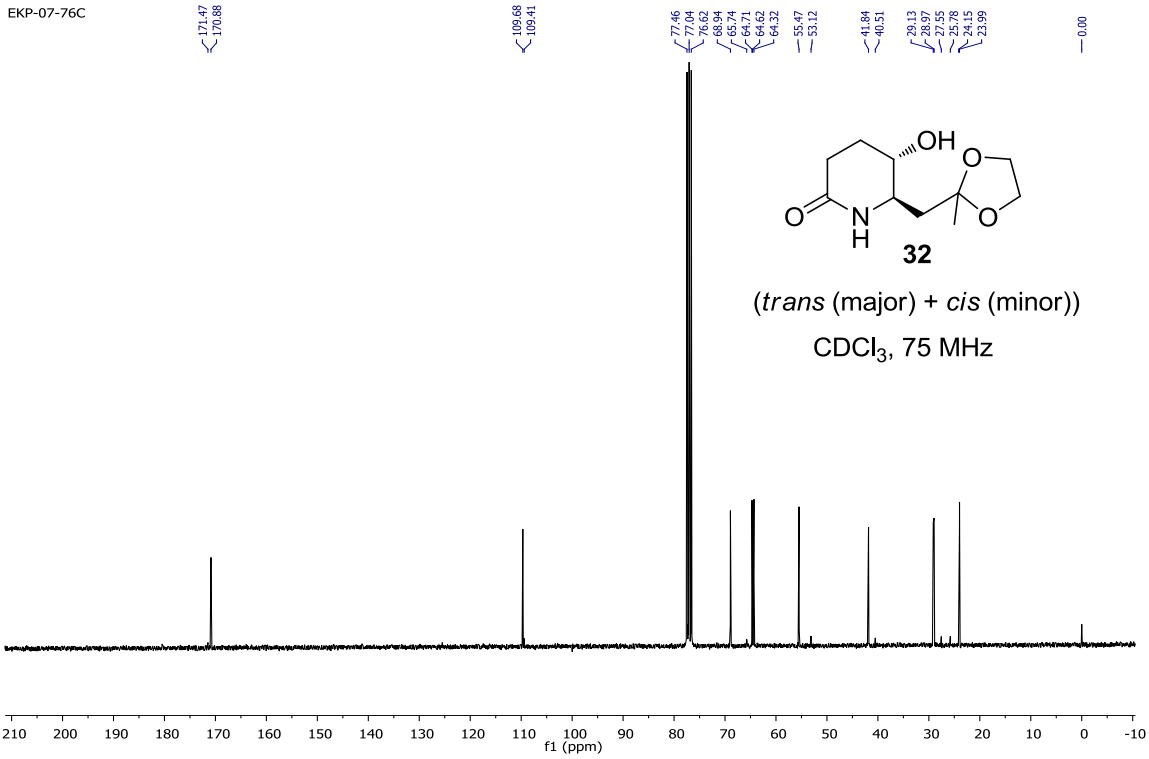
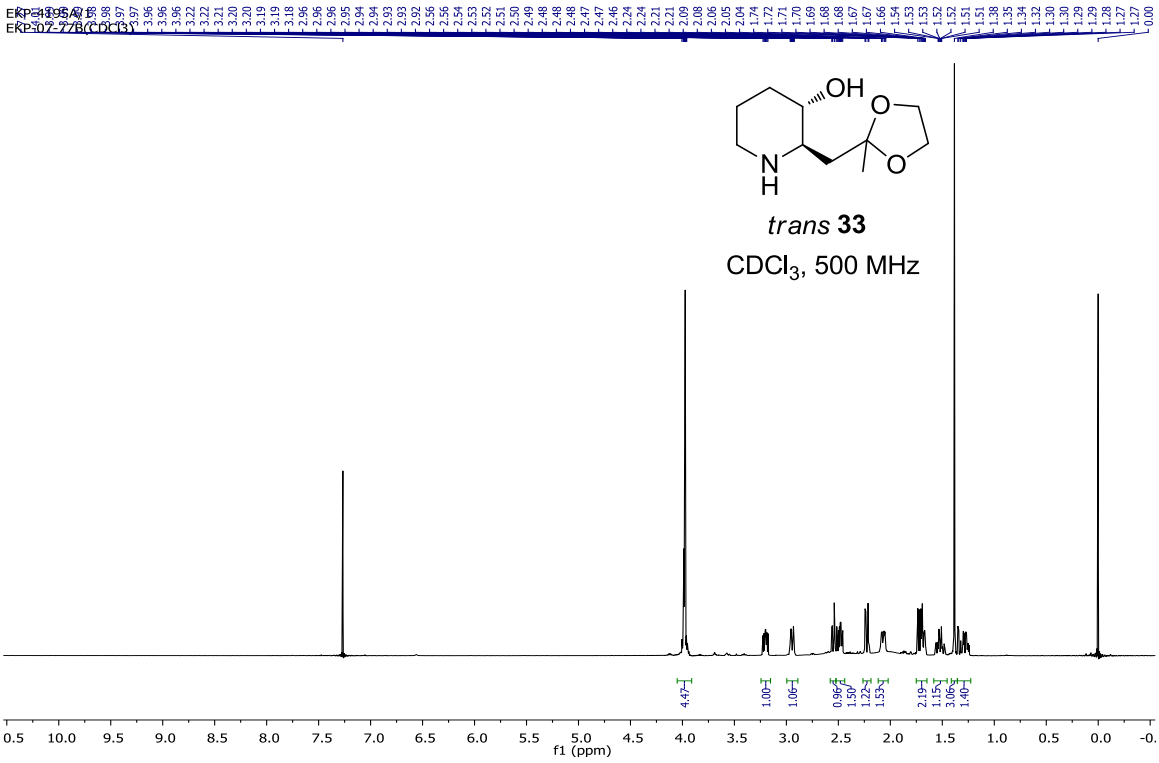
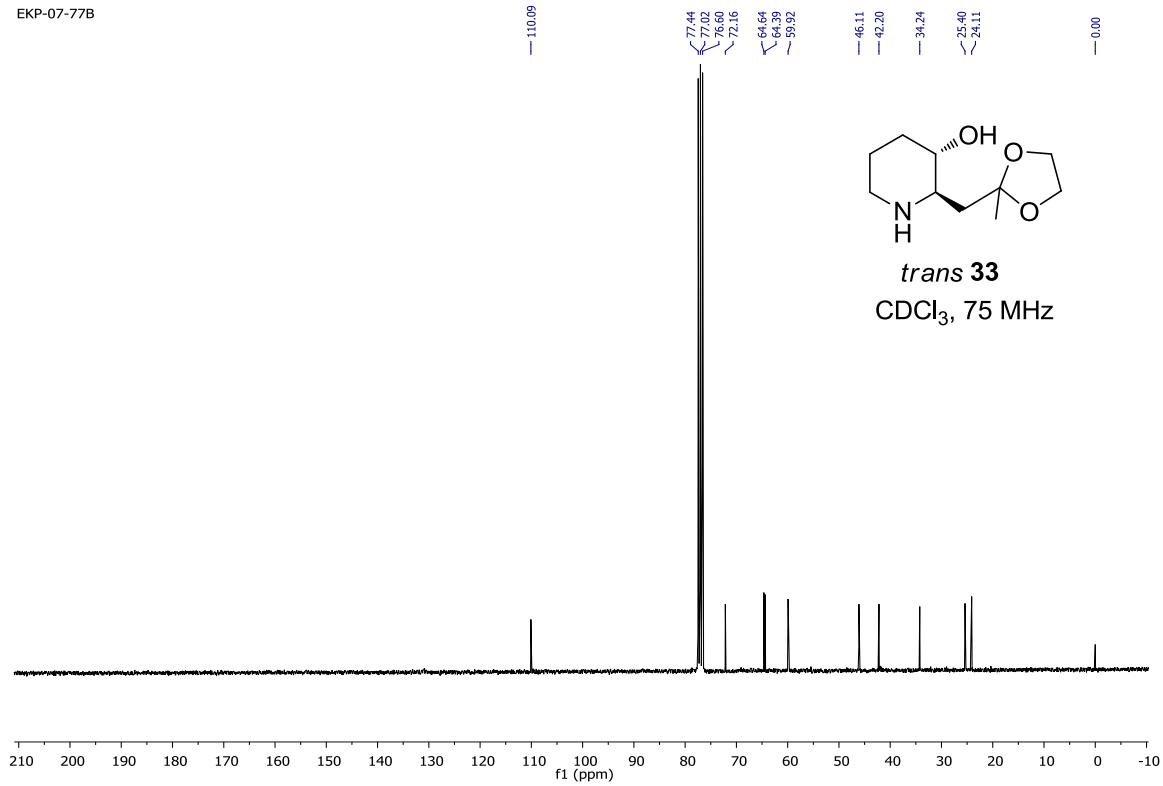
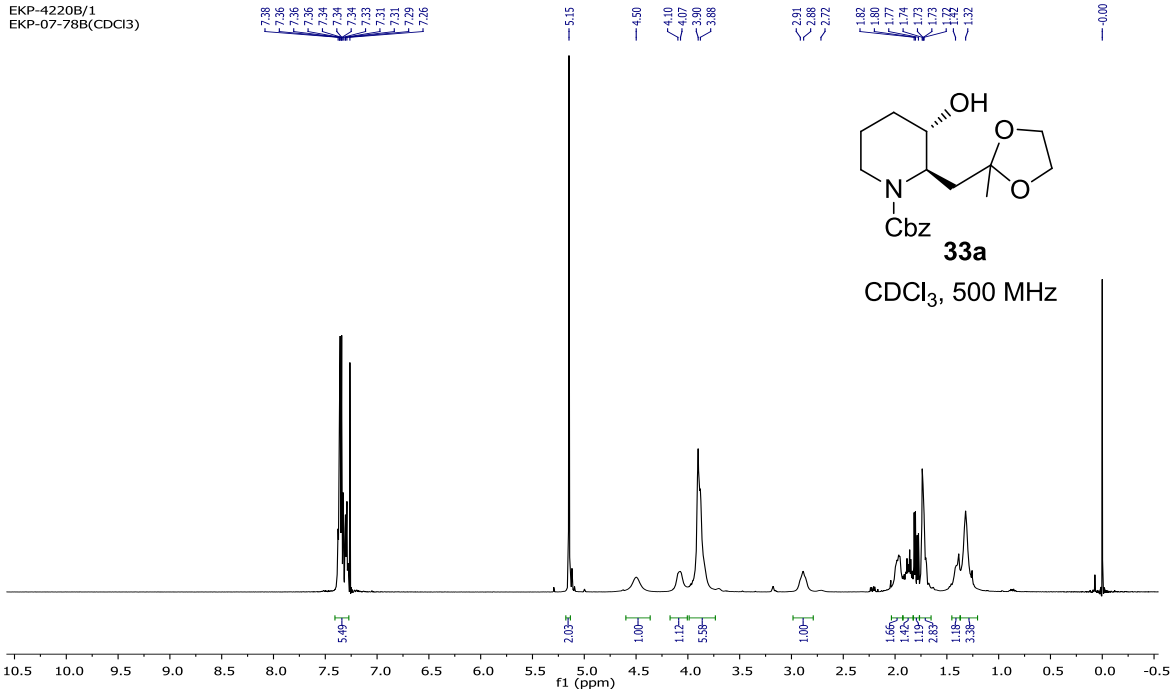
O
O
O
31
(anti (major) + syn (minor))
CDCl3, 75 MHz
f1 (ppm)

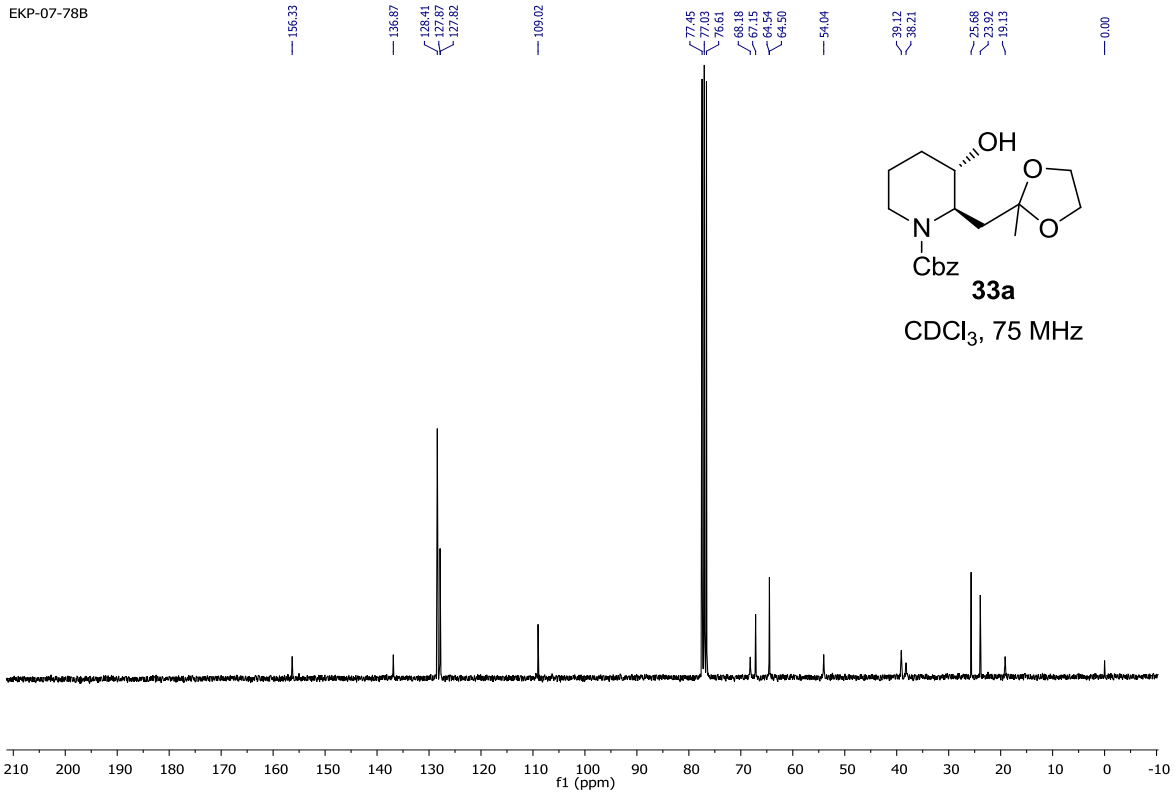

OH
O
O
N
H
O
32
(*trans* (major) + *cis* (minor))
$CDCl_3$, 500 MHz
f1 (ppm)

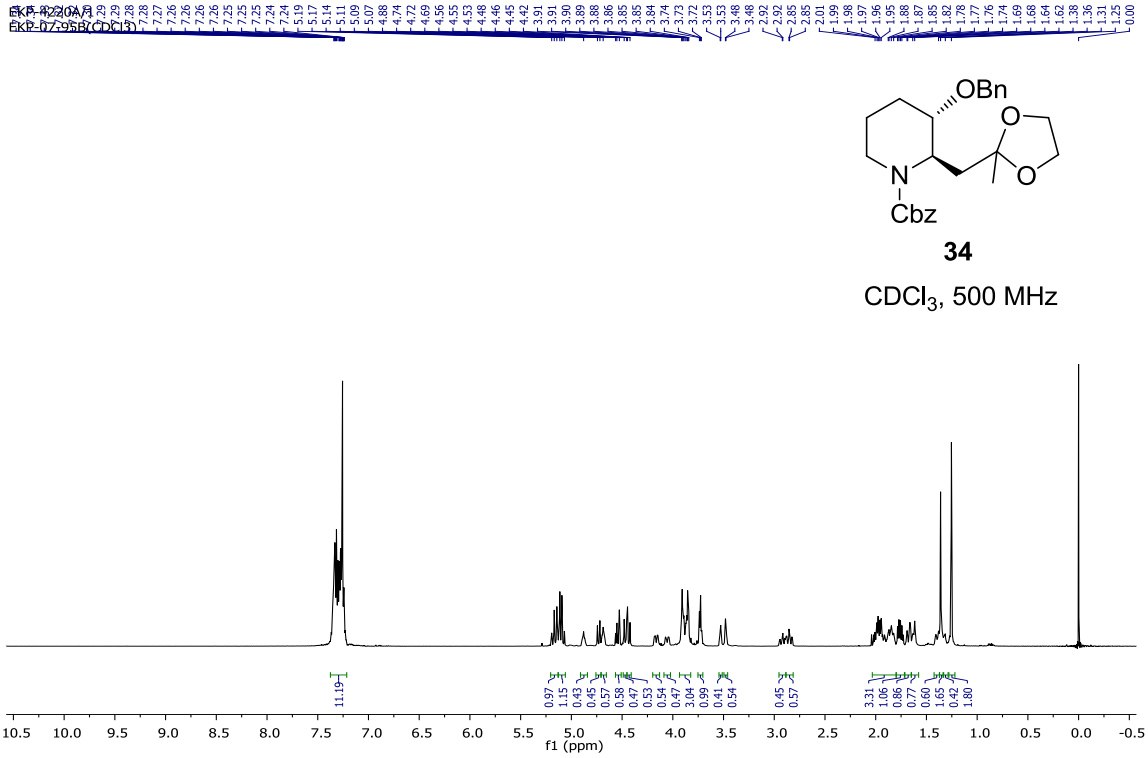

EKP-07-76C
OH
O
O
N
H
O
32
(*trans* (major) + *cis* (minor))
$CDCl_3$, 75 MHz
f1 (ppm)

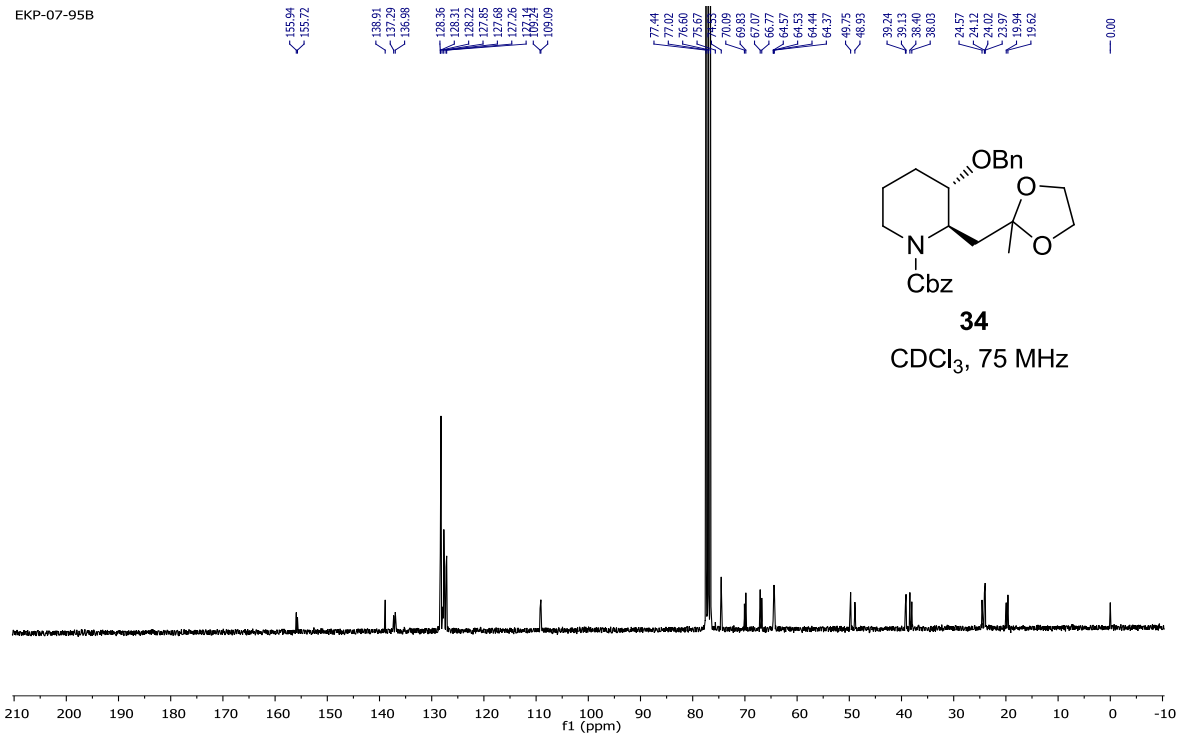

OH
O
N
H
O
trans 33
CDCl3, 500 MHz
4.47
1.00
1.06
0.96
1.50
1.22
1.53
2.19
1.15
3.06
1.40
f1 (ppm)


EKP-07-77B
110.09
77.44
77.02
76.60
72.16
64.64
64.39
59.92
46.11
42.20
34.24
25.40
24.11
0.00
OH
O
N
H
O
trans 33
CDCl3, 75 MHz
f1 (ppm)


EKP-4220B/1
EKP-07-78B(CDCl3)
OH
O
N
O
Cbz
33a
CDCl3, 500 MHz
f1 (ppm)


EKP-07-78B
OH
O
N
O
Cbz
33a
CDCl3, 75 MHz
f1 (ppm)


OBn
O
N
O
Cbz
34
CDCl3, 500 MHz
f1 (ppm)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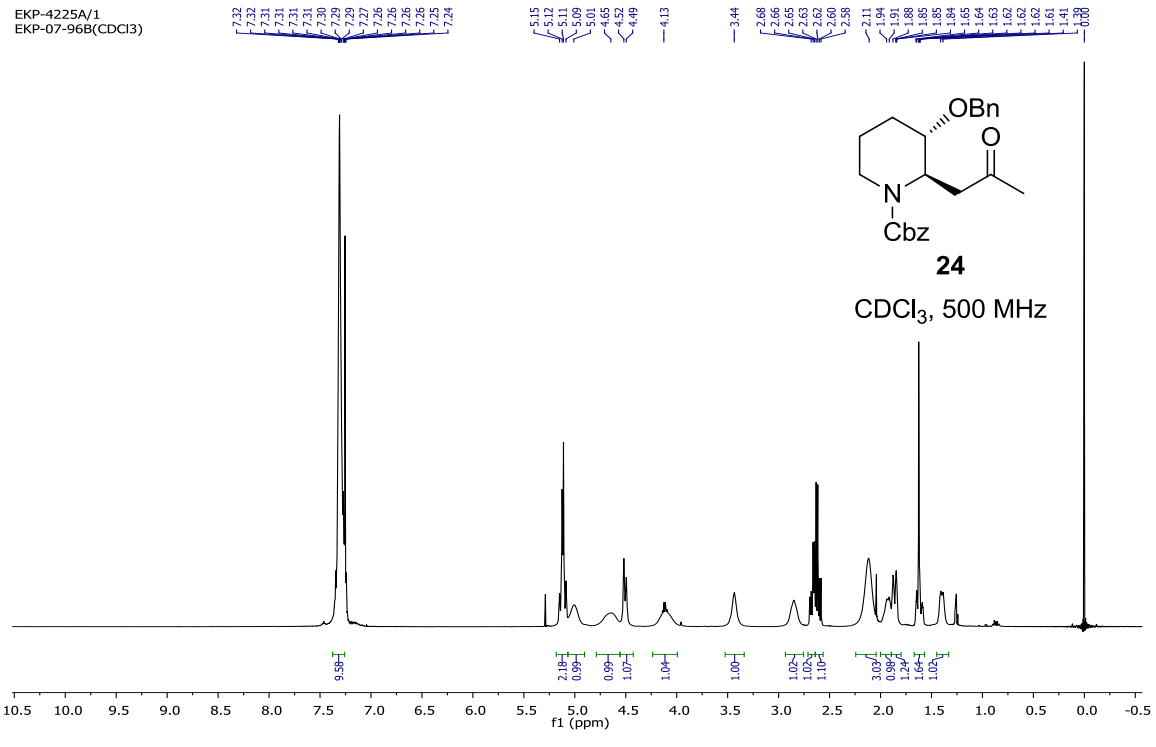
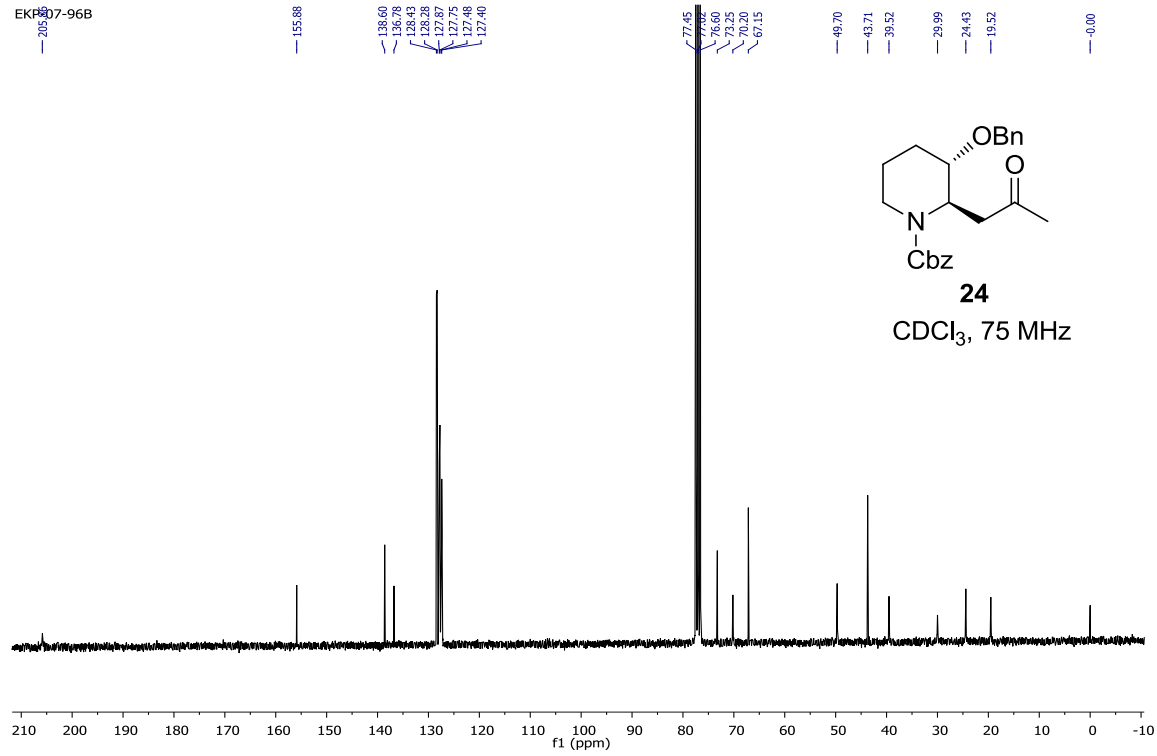
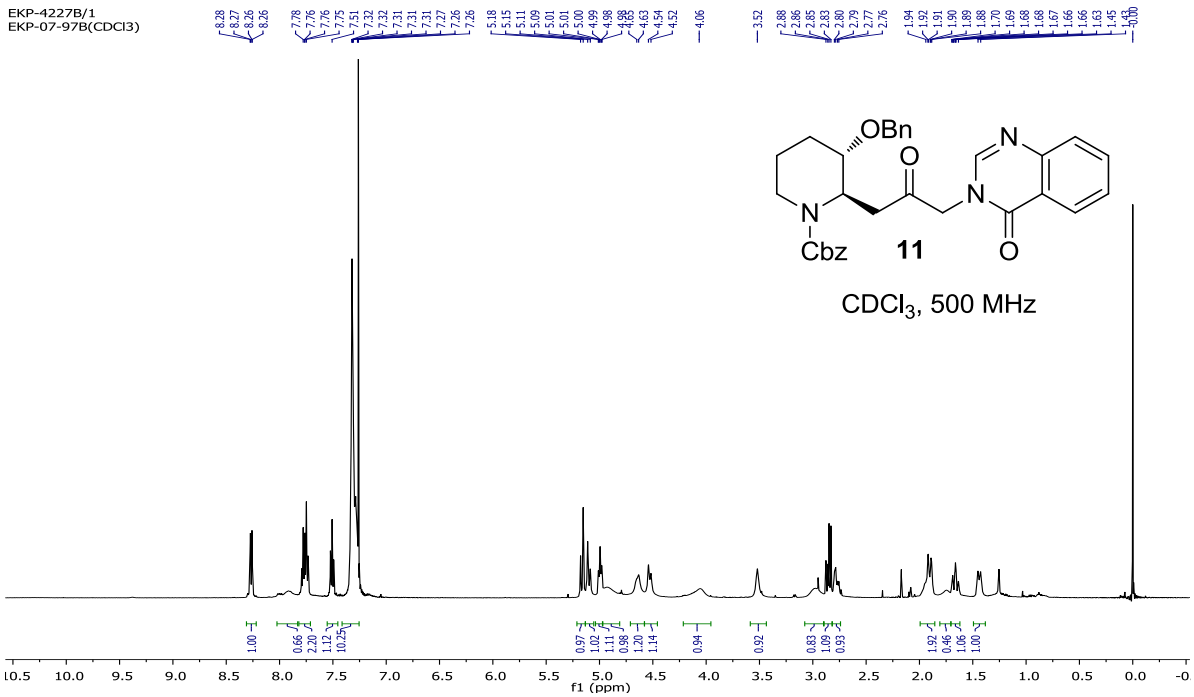
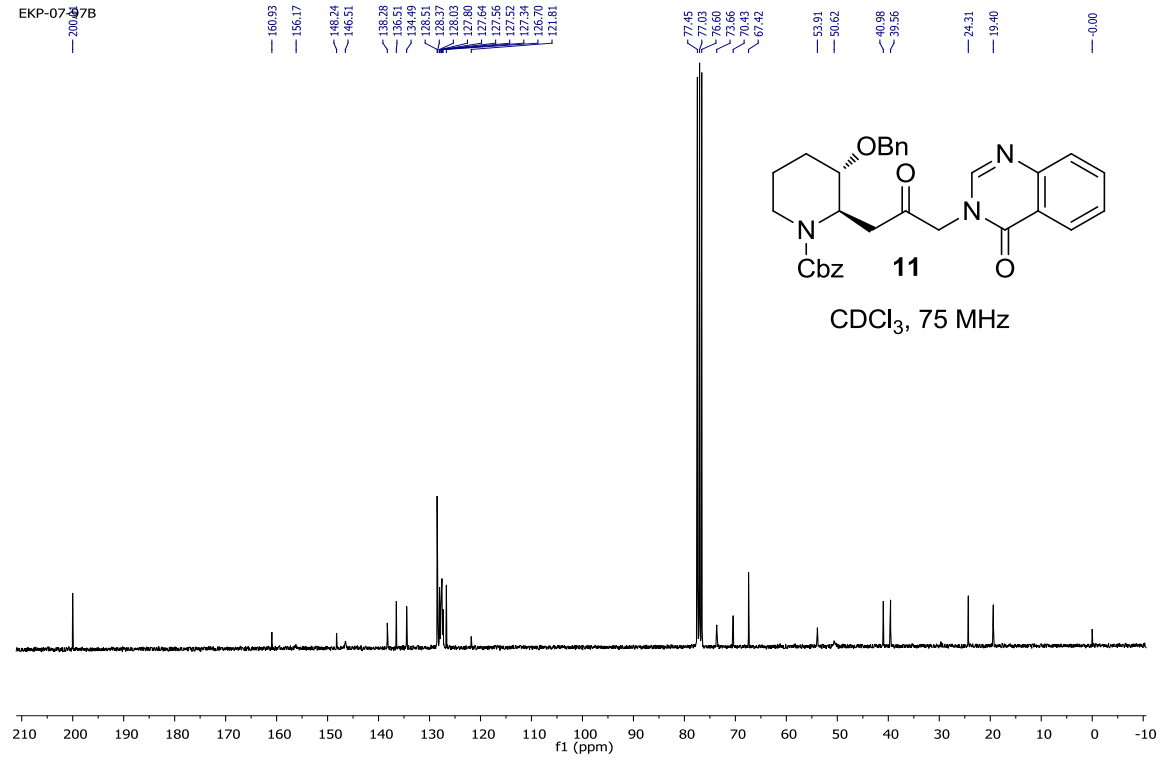
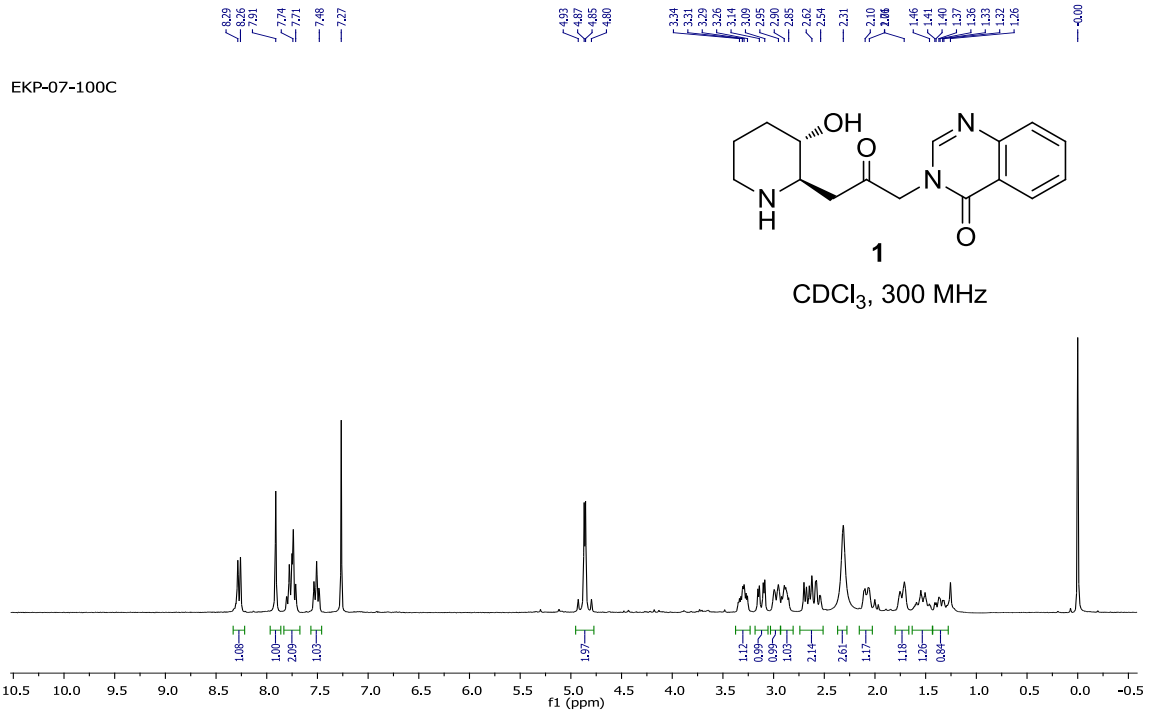
OBn
O
N
O
Cbz
34
CDCl3, 75 MHz
f1 (ppm)


EKP-4225A/1
EKP-07-96B(CDCl3)
OBn
O
N
Cbz
24
CDCl3, 500 MHz
f1 (ppm)


EKP-07-96B
OBn
O
N
Cbz
24
CDCl3, 75 MHz
f1 (ppm)


EKP-4227B/1
EKP-07-97B(CDCl3)
OBn
O
N
N
Cbz
11
O
CDCl3, 500 MHz
f1 (ppm)


EKP-07-97B
OBn
O
N
N
Cbz
11
O
CDCl3, 75 MHz
f1 (ppm)


EKP-07-100C
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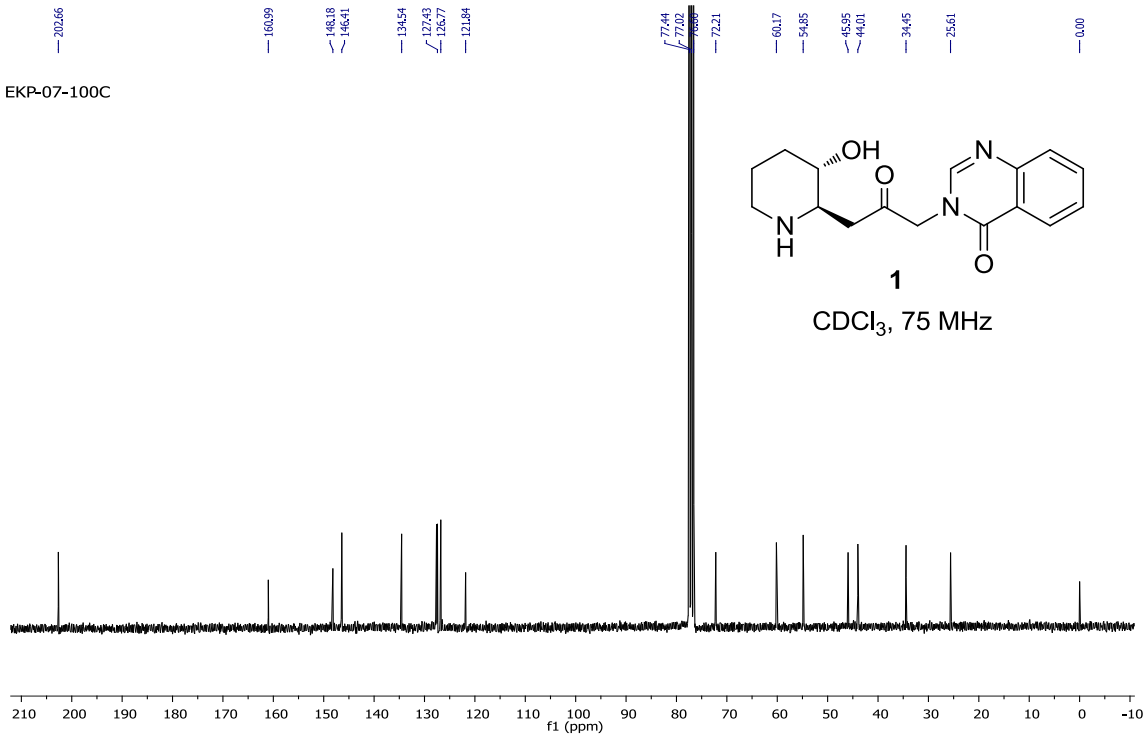
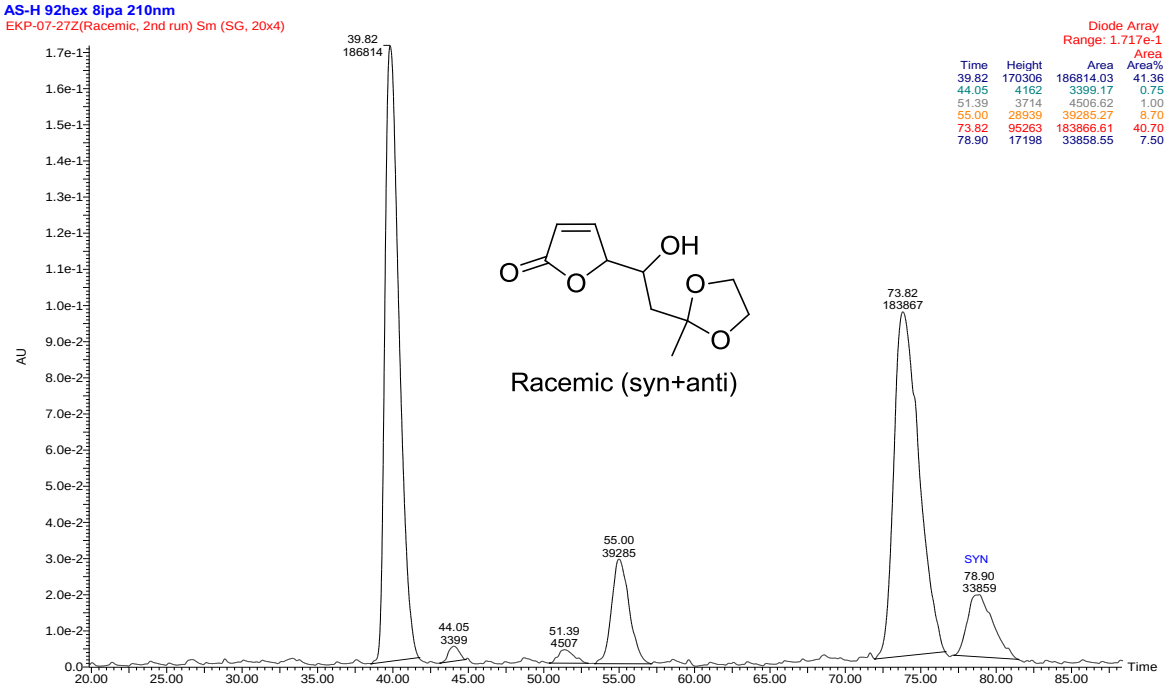
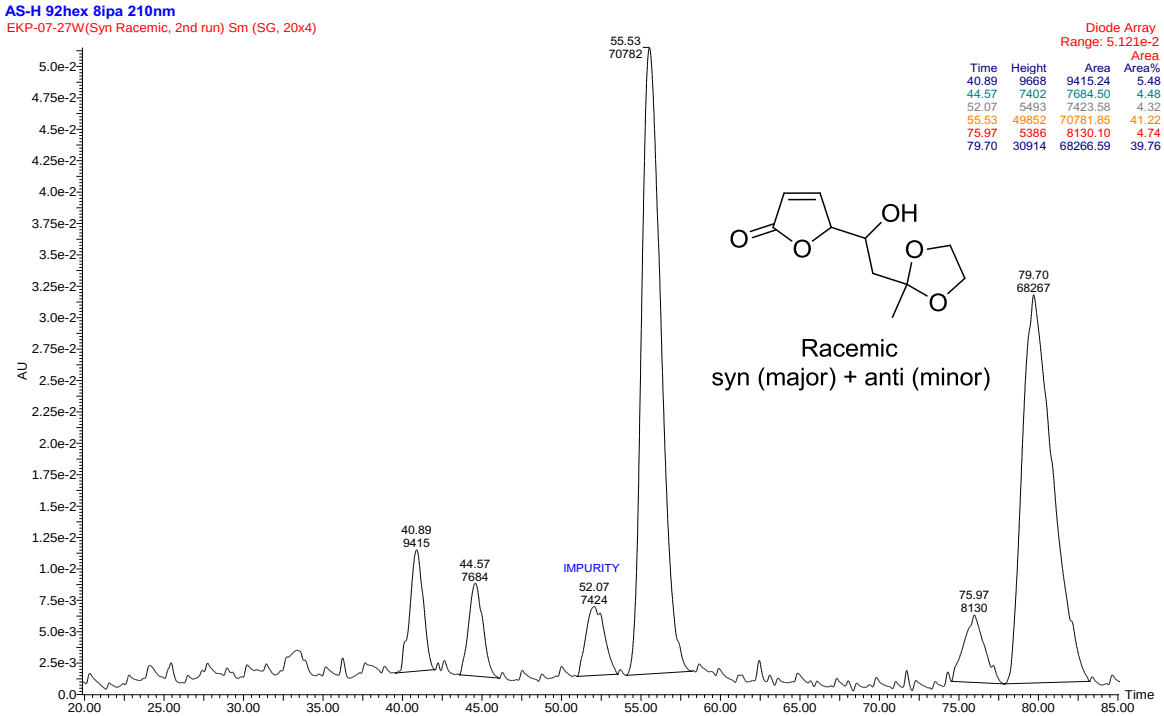
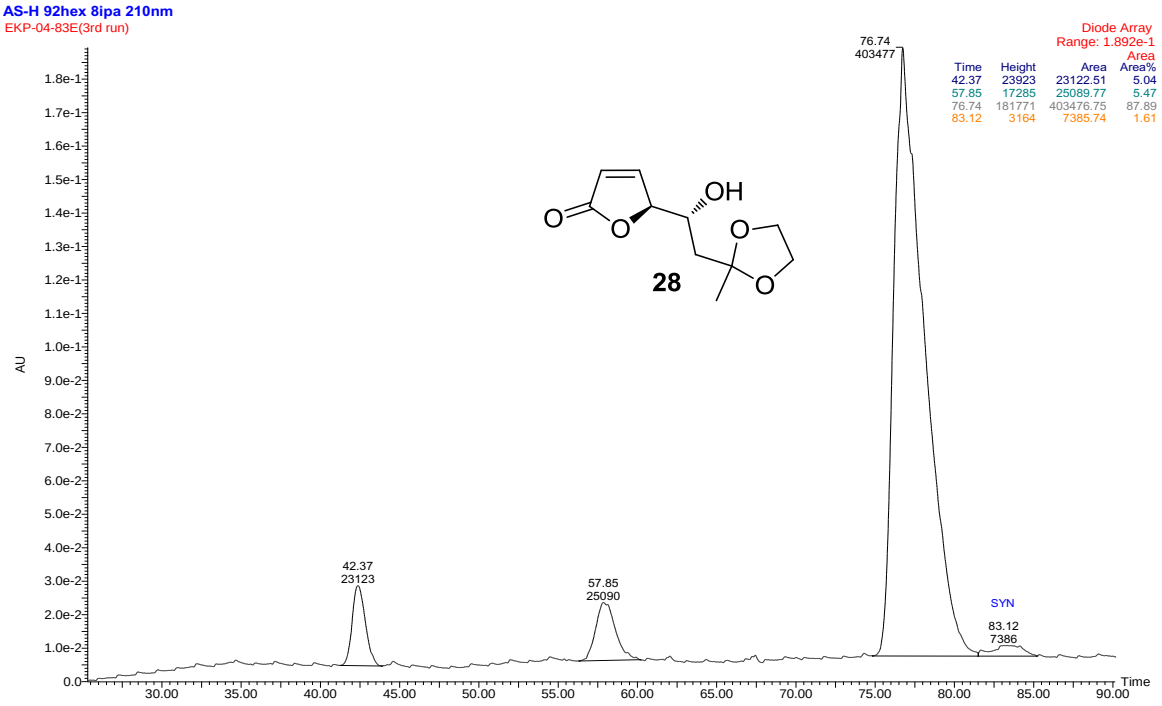
O
N
N
H
N
O
1
CDCl3, 300 MHz
f1 (ppm)

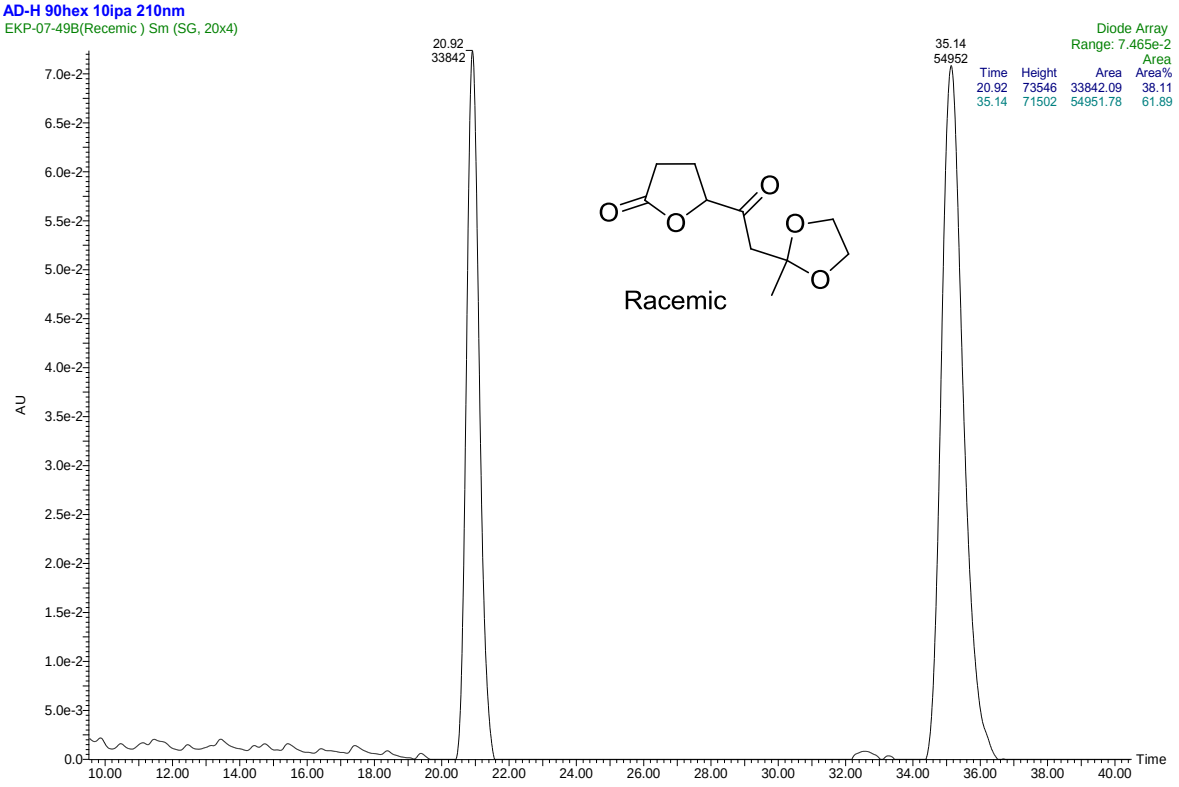

EKP-07-100C
OH
O
N
N
H
N
O
1
CDCl3, 75 MHz
f1 (ppm)

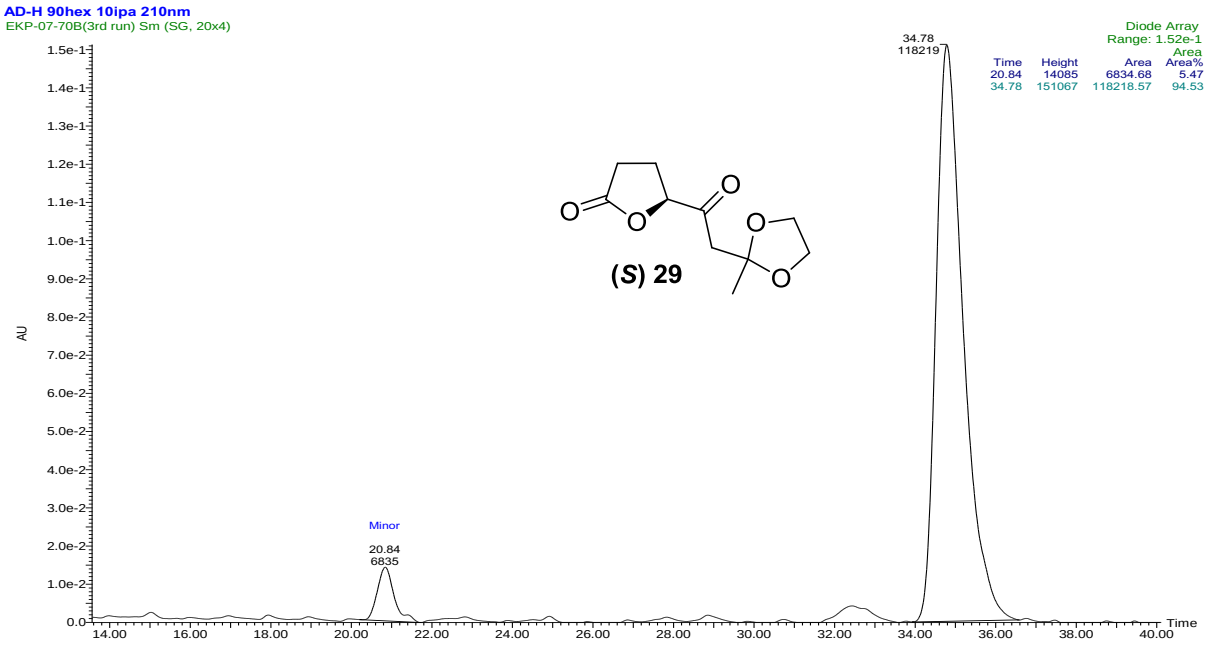
4.8 Selected HPLC chromatograms

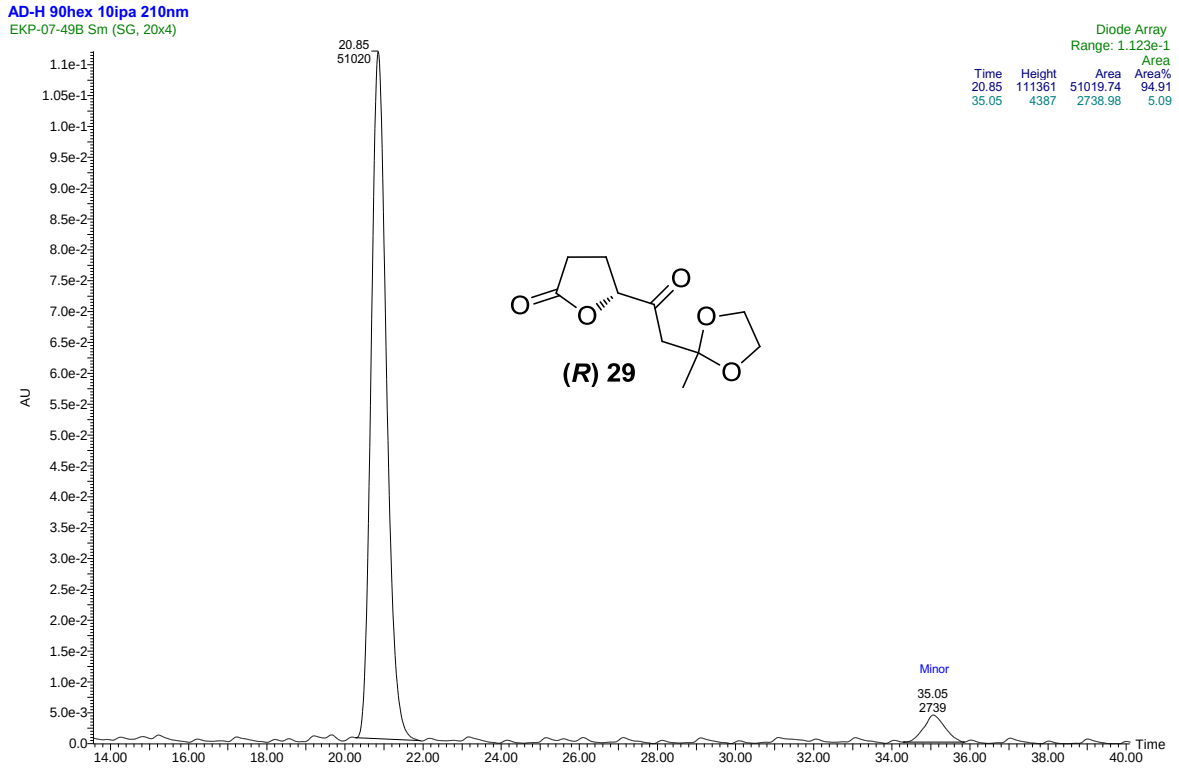

AS-H 92hex 8ipa 210nm
EKP-07-27Z(Racemic, 2nd run) Sm (SG, 20x4)
Diode Array
Range: 1.717e-1
Area
Time Height Area Area%
39.82 170306 186814.03 41.36
44.05 4162 3399.17 0.75
51.39 3714 4506.62 1.00
55.00 28939 39285.27 8.70
73.82 95263 183866.61 40.70
78.90 17198 33858.55 7.50
39.82
186814
44.05
3399
51.39
4507
55.00
39285
73.82
183867
SYN
78.90
33859
OH
O
O
O
O
Racemic (syn+anti)
AU
Time


AS-H 92hex 8ipa 210nm
EKP-07-27W(Syn Racemic, 2nd run) Sm (SG, 20x4)
Diode Array
Range: 5.121e-2
Area
Time Height Area Area%
40.89 9668 9415.24 5.48
44.57 7402 7684.50 4.48
52.07 5493 7423.58 4.32
55.53 49852 70781.85 41.22
75.97 5386 8130.10 4.74
79.70 30914 68266.59 39.76
55.53
70782
40.89
9415
44.57
7684
IMPURITY
52.07
7424
75.97
8130
79.70
68267
OH
O
O
O
O
Racemic
syn (major) + anti (minor)
AU
Time


AS-H 92hex 8ipa 210nm
EKP-04-83E(3rd run)
Diode Array
Range: 1.892e-1
Area
Time Height Area Area%
42.37 23923 23122.51 5.04
57.85 17285 25089.77 5.47
76.74 181771 403476.75 87.89
83.12 3164 7385.74 1.61
76.74
403477
42.37
23123
57.85
25090
SYN
83.12
7386
OH
28
AU
Time


AD-H 90hex 10ipa 210nm
EKP-07-49B(Recemic) Sm (SG, 20x4)
Diode Array
Range: 7.465e-2
Area
Time Height Area Area%
20.92 73546 33842.09 38.11
35.14 71502 54951.78 61.89
20.92
33842
35.14
54952
Racemic
AU
Time


AD-H 90hex 10ipa 210nm
EKP-07-70B(3rd run) Sm (SG, 20x4)
Diode Array
Range: 1.52e-1
Area
Time Height Area Area%
20.84 14085 6834.68 5.47
34.78 151067 118218.57 94.53
34.78
118219
Minor
20.84
6835
(S) 29
AU
Time


AD-H 90hex 10ipa 210nm
EKP-07-49B Sm (SG, 20x4)
Diode Array
Range: 1.123e-1
Area
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20.85 111361 51019.74 94.91
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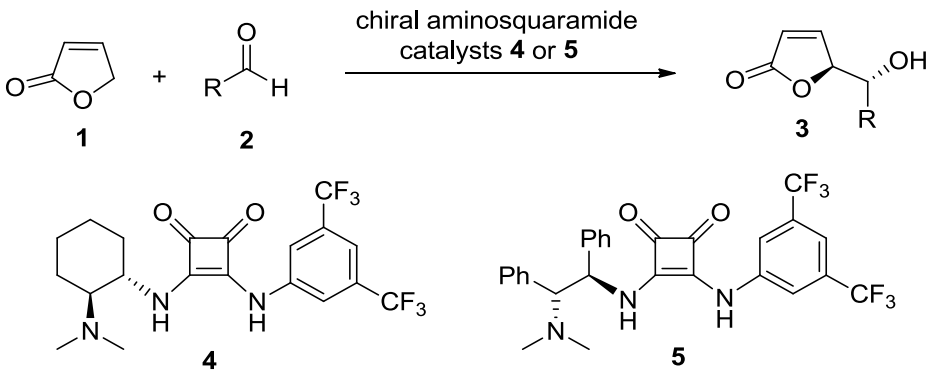
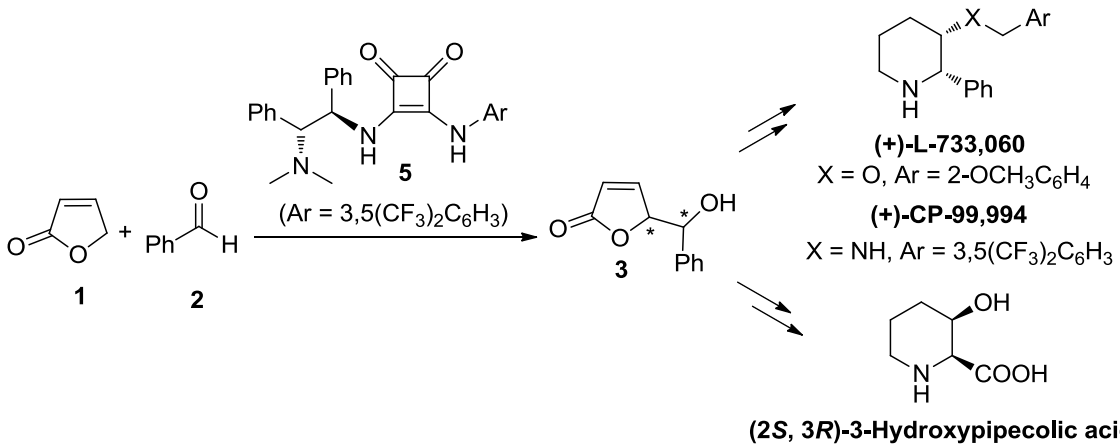
The organocatalytic direct vinylogous aldol (ODVA) reactions of γ-crotonolactone with various aromatic aldehydes (Scheme 5.1) were developed. It was observed that these reactions were catalyzed by several bifunctional chiral aminothioureas and aminosquaramides. A catalyst survey was carried out to find the optimal catalyst. Among various thiourea and squaramide catalysts, the squaramide catalysts gave the best result, providing the *anti* diastereomer as the major product. The optimized conditions were employed in a study of the scope of the reaction with a variety of aldehydes. These investigations indicated that the choice of catalyst or was determined by the nature of the aldehyde and high enantioselectivities were obtained by proper pairing of the catalyst and aldehyde. Overall, good diastereoselectivities (5-8:1) and excellent enantioselectivities (94- >99% *ee*) were obtained. Chapter 2 of this thesis describes details of the development of this method. E. K. Paul contributed to all of the synthetic work and was involved in the preparation of the manuscript for publication.



. The ODVA reaction catalyzed by squaramides and .

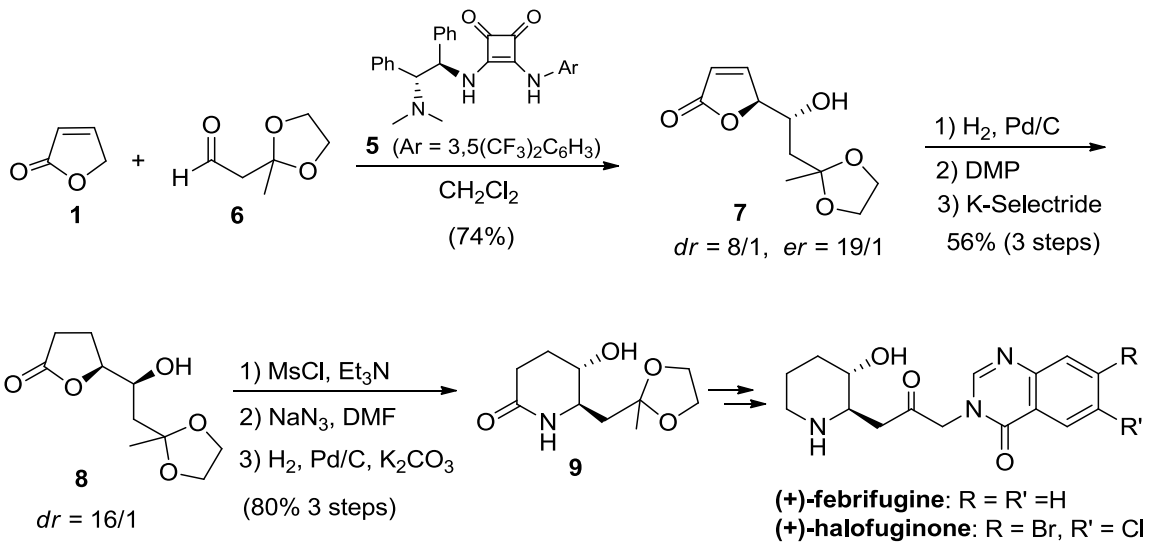
To demonstrate the synthetic importance of the organocatalytic direct vinylogous aldol (ODVA) reactions of *γ*-crotonolactone with aldehydes, application of the methodology in the synthesis of 2,3-disubstituted piperidines such as (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid was examined. The substance P receptor antagonists (+)-L-733,060 and (+)-CP-99,994, are associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission and (2*S*,3*R*)-3-hydroxypipecolic acid, is a component of tetrazomine, an antitumor agent and an antibiotic. In this project, ODVA reaction of *γ*-crotonolactone with benzaldehyde as the key step provided an efficient entry into piperidine derivatives (Scheme 5.2). The synthesis of (+)-L-733,060 was accomplished in 9 steps from the *γ*-crotonolactone ( ) in 24.8% overall yield. The synthesis of (+)-CP-99,994 was accomplished in 11 steps from the *γ*-crotonolactone ( ) in 16.9% overall yield. The synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid was accomplished in 10 steps from the *γ*-crotonolactone ( ) in 28.1% overall yield. The results of this work are presented in

Chapter 3 of this thesis. E. K. Paul contributed to all of the synthetic work and was involved in the preparation of the manuscript for publication.



. Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid.

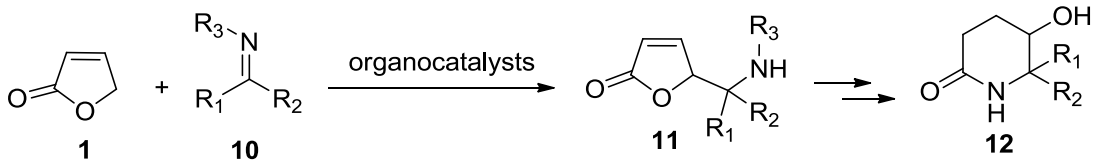
In the last project, the ODVA reaction was employed in the total synthesis of the antimalarial alkaloid (+)-febrifugine and a formal synthesis of (+)-halofuginone, an antimalarial agent (Scheme 5.3). The key steps in the synthesis involve the ODVA reaction of *γ*-crotonolactone with the aldehyde and the isomerization of a 2-aminoalkyl furanone to the 2,3-disubstituted piperidinone core of the target. The synthesis of the (+)-febrifugine was accomplished in 14 steps from the commercially available *γ*-crotonolactone ( ) in 6.8% overall yield. The results of this work are presented in Chapter 4 of this thesis. E. K. Paul contributed to all of the synthetic work and was involved in the preparation of the manuscript for publication.



. Synthesis of (+)-febrifugine and a formal synthesis of (+)-halofuginone employing the ODVA reaction.

In summary, the thesis work has developed a highly enantioselective, organocatalytic direct vinylogous aldol reaction of crotonolactone with aldehydes. This methodology was used in the synthesis of various biologically active compounds and natural products containing the 2,3-disubstituted piperidine motif.

Although the products of the 2-furanone in ODVA reaction can be converted into piperidines, a limitation of the methodology is the need for converting the aldol products into the corresponding amino lactone. An attractive alternative to this approach would be the direct synthesis of the amino lactones *via* an organocatalytic vinylogous Mannich reaction (Scheme 5.4) of imines with 2-furanone.



. Organocatalytic direct vinylogous Mannich-type reaction of crotonolactone.

It is anticipated that, the Mannich reaction will be catalyzed by hydrogen bonding donor catalysts or by chiral protic acids depending on the nature of the amine used to make the imines.

Alternatively, instead of using a chiral catalyst, chiral imines can be used as substrates. In addition, the organocatalytic vinylogous aldol as well as Mannich reactions can be examined with a variety of substituted crotonolactones.