Enantioselective Synthesis of (+)-Homocitric Acid Lactone, (+)-Antofine and (+)-Cryptopleurine Involving Organocatalytic Conjugate Addition Reactions

by

© **Rajendar Dyapa**

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To my family

ABSTRACT

The organocatalytic, asymmetric conjugate addition of carbon nucleophiles and heteroatom nucleophiles to electron-deficient alkenes (Michael acceptors) such as nitroalkenes, enones, and vinyl sulfones, is of interest because the products are useful synthetic intermediates. The present study examines the enantioselective, iminium ion catalyzed vinylogous Mukaiyama-Michael reaction of 5-triisopropylsilyloxy furan-2-carboxylates with acrolein. The stereoselectivity of this reaction is dependent on the nature of the furan nucleophile and the secondary amine catalyst. The Michael adduct obtained in this methodology was employed in the synthesis of (*S*)-homocitric acid lactone. The details of this study are described in Chapter 2.

In a separate study, the *γ*-nitroketone obtained from an organocatalytic Michael addition of *β*-nitrostyrene and 1,4-cyclohexanedione mono ethylene ketal has been utilized in alkaloid synthesis. Thus, a total synthesis of indolizidine alkaloid (+)-antofine and quinolizidine alkaloid (+)-cryptopleurine was achieved from the γ-nitroketone. Details of these investigations are described in Chapter 3 and Chapter 4.

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List of Abbreviations

Ac	acetyl
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Boc	*tert*-butoxycarbonyl
Bn	benzyl
br	broad
BuLi	butyl lithium
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisoproyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEAD	di-2-methoxyethyl azodicarboxylate

DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNBA	2,4-dinitrobenzoic acid
dr	diastereomeric ratio
ds	diastereoselectivity
ee	enantiomeric excess
EI	electrospray ionization
eq.	equivalent(s)
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
g	gram
h	hour
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
i-Bu	isobutyl
i-Pr	isopropyl
IR	infrared
J	coupling constant

LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
M	molar
M^+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
min	minute
mL	milliliter
mmol	millimole
mp	melting point
Ms	methanesulfonyl
MS	mass spectrum
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNBA	*para*-nitrobenzoic acid

Pr	propyl
psi	pounds per square inch
PTSA	*para*-toluenesulphonic acid
pyr	pyridine
rt	room temperature
S_N2	bimolecular nucleophilic substitution
t-Bu	tertiary butyl
TEA	triethylamine
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	tetramethylsilyl
TMEDA	tetramethylethylenediamine
Ts	*p*-toluenesulfonyl

Chapter 1

Introduction

1.1 Organocatalytic conjugate addition reactions

The conjugate addition of nucleophiles to the *β*-position of *α,β*-unsaturated carbonyl compounds (Michael reaction) is an important method to make a carbon–carbon bond.[1] Due to the high demand for optically active compounds, much effort has been devoted to the development of asymmetric Michael reactions, since stereogenic centers can be constructed in the course of the Michael reaction.[2] Although asymmetric conjugate additions have over the years been dominated by using chiral catalysts containing metals, small organic molecules (organocatalysts) have been developed recently as efficient catalysts for these reactions.[1,2]

Carbon nucleophiles with active methylene groups are extensively used in direct Michael additions, whereas simple carbonyl compounds need to be activated as enol ethers or enamines prior to addition to a Michael acceptor (Figure 1.1). In this case, direct addition of unmodified carbonyl compounds to Michael acceptors would avoid unwanted chemical transformations and also reduce the overall synthetic effort.

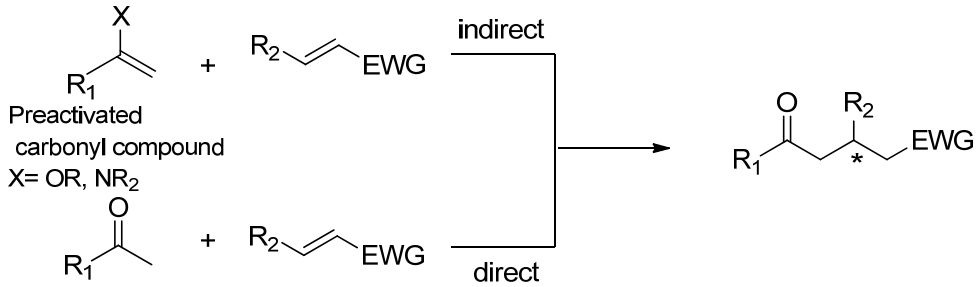


Figure 1.1 Direct and indirect Michael addition

In this context, the concept of aminocatalysis has received considerable attention in recent years. Catalytic activation of the Michael donor may take place through enamine or enolate formation for the addition to a Michael acceptor (Figure 1.2 paths a and b). Alternatively, carbonyl containing Michael acceptors can be activated by the formation of an iminium species.

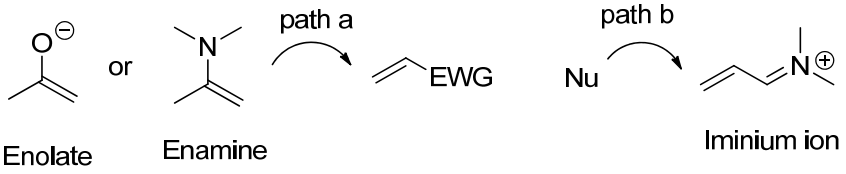
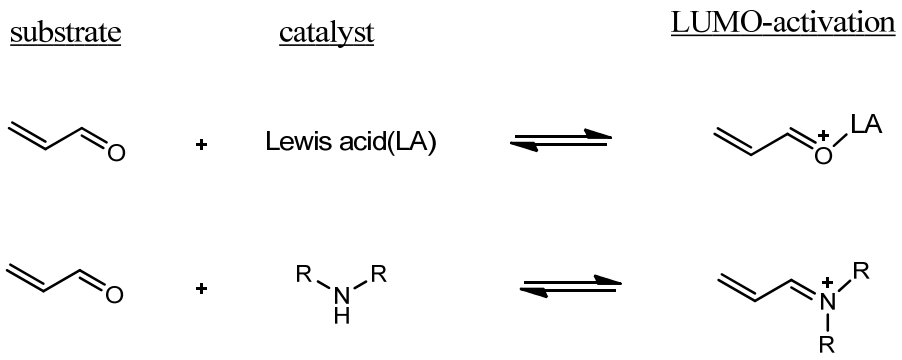


Figure 1.2 Activation of a Michael donor and Michael acceptor

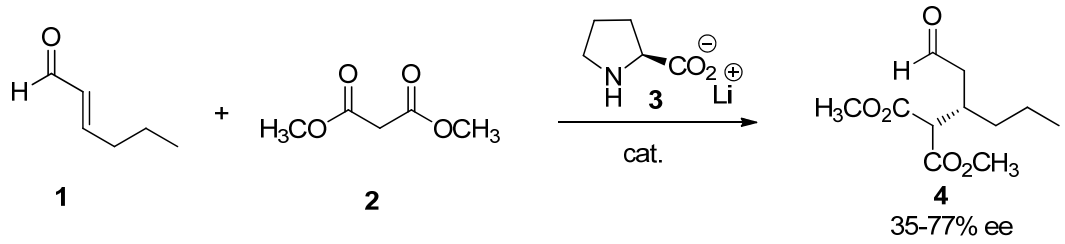
1.1.1 Organocatalytic conjugate addition reactions via iminium catalysis

In 2000, MacMillan reported the activation of unsaturated aldehydes and ketones by reversible iminium ion formation with chiral amines as a highly generalized strategy for conjugate addition reactions.[3,4] The formation of the iminium ion lowers the LUMO energy of the carbonyl substrate with respect to the HOMO of the nucleophile. This activation effect is similar to that associated with reactions involving metal-based Lewis acids (Scheme 1.1).[1]



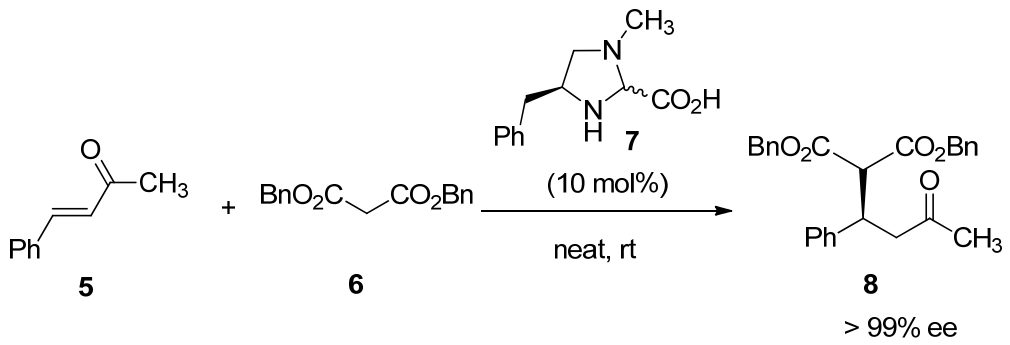
Scheme 1.1

Iminium catalysis forms the basis for several conjugate addition reactions of various Michael donors such as malonates,[6,7] nitroalkanes[8,9] and thiols[10] to enones as well as for Mukaiyama-Michael reactions of silyloxyfurans with enals.[4,5] The first iminium-catalyzed conjugate addition (malonate **2** to enone **1**) was reported by Yamaguchi and co-workers[11] in 1991 using the lithium salt of *S*-proline **3** to obtain moderate-to-good enantioselectivities (Scheme 1.2).



Scheme 1.2

In 2003, Jørgensen developed the highly enantioselective organocatalytic Michael addition[12] of malonates such as **6** to *α,β*-unsaturated enones such as **5** using an imidazolidine catalyst **7**, which was readily prepared from phenylalanine (Scheme 1.3).

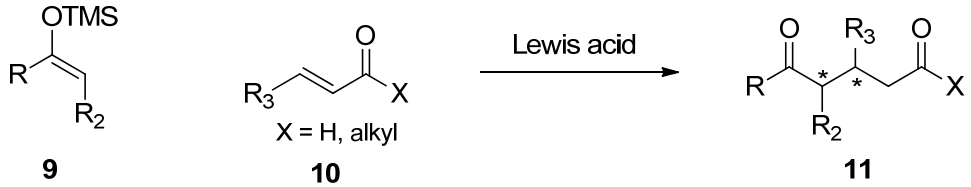


Scheme 1.3

The following is a brief summary of the iminium ion catalyzed Mukaiyama-Michael reactions of silyloxyaromatic compounds with enals catalyzed by organic molecules (organocatalytic reactions).

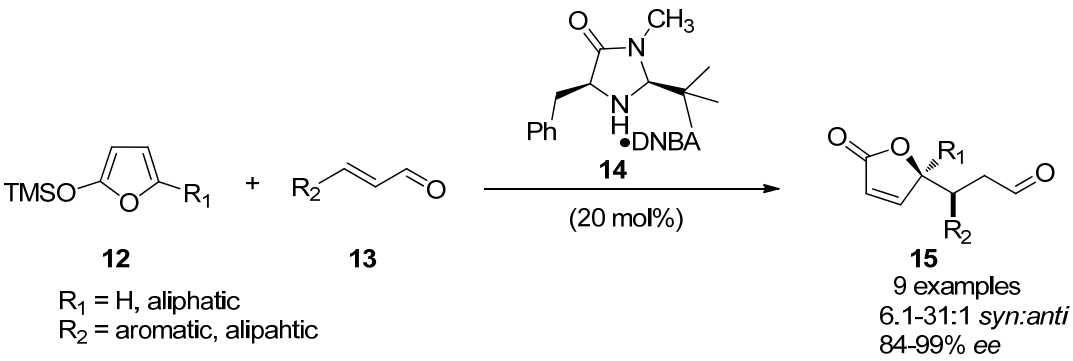
1.1.2 Organocatalytic Mukaiyama-Michael Reaction

The Mukaiyama-Michael reaction has become a powerful method for stereoselective carbon-carbon bond formation, since it was discovered by Mukaiyama in 1974.[13] The classical version of this reaction involves the addition of silyl enol ethers such as **9** to *α,β*-unsaturated carbonyl compounds **10** for the stereoselective construction of acyclic frameworks such as **11** (Scheme 1.4). The use of silyl enol ethers for additions to *α,β*-unsaturated carbonyls provides mild reaction conditions increasing the functional group tolerance for these Michael additions.



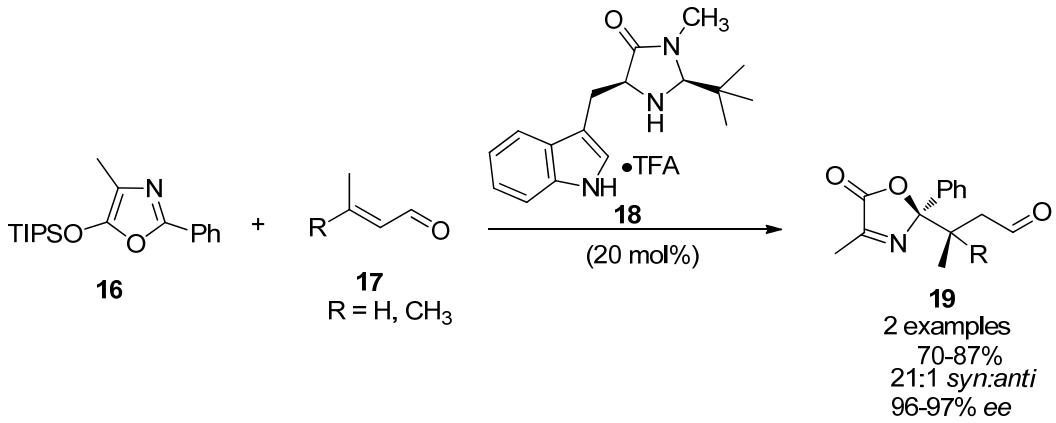
Scheme 1.4

In 2003, MacMillan and co-workers reported the first organocatalytic Mukaiyama-Michael-type reactions, using 5-silyloxyfurans **12** as nucleophiles to obtain products with the butenolide framework **15**.[14] The 2,4-dinitrobenzoic acid (DNBA) salt of imidazolidinone **14** catalyzed the reactions of different enals with silyloxyfurans with excellent selectivites and yields (Scheme 1.5).



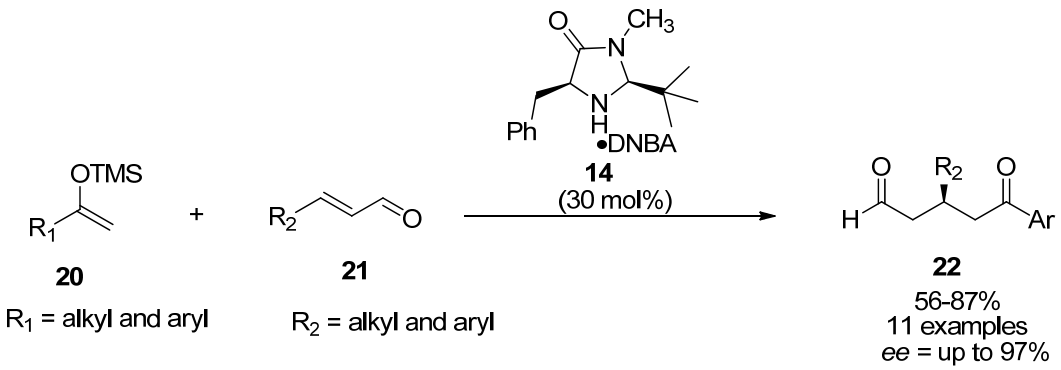
Scheme 1.5

The same group also utilized silyloxyoxazoles **16** as nucleophiles. These reactions are promoted by the tryptophan derived catalyst **18** in good yields and high enantioselectivities[15] (Scheme 1.6).



Scheme 1.6

Wang and co-workers demonstrated that aryl-substituted TMS enol ethers **20** could also be used as nucleophiles in Mukaiyama-Michael type reactions.[16] Several alkyl and aryl TMS enol ethers **20** were added to crotanaldehyde as well as to cinnamaldehyde and its derivatives to provide the adducts **22** in moderate yields and moderate to high enantioselectivities (Scheme 1.7).

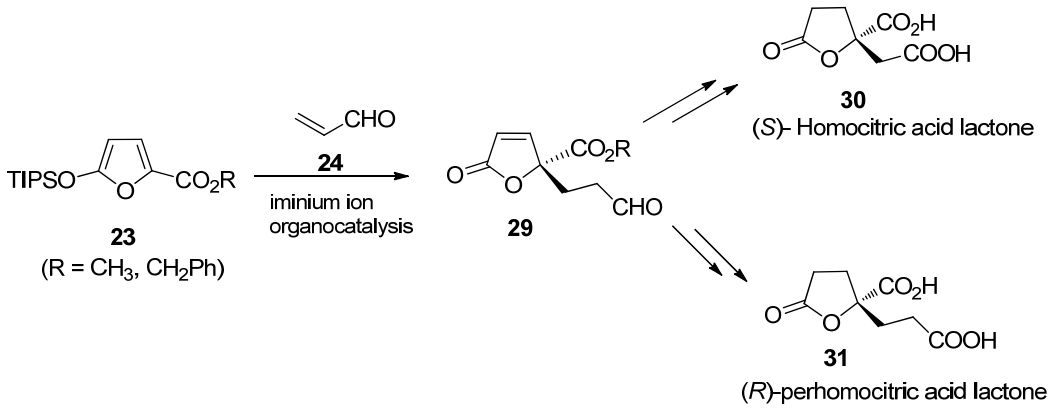


Scheme 1.7

Our strategy was to develop an enantioselective organocatalytic Mukaiyama-Michael addition of TIPS furan **23** to acrolein **24**, to establish the γ-butenolide framework **29** (Scheme 8). The γ-butenolide skeleton is represented in numerous natural products.[17]

The objective of these investigations was to utilize the γ-butenolide framework, obtained from the organocatalytic Mukaiyama-Michael reaction, in the synthesis of (*S*)-homocitric acid lactone (enantiomer of the natural product) and its homolog (*R*)-perhomocitric acid lactone.[18] It is noteworthy that only a few examples of enantioselective organocatalytic Mukaiyama-Michael conjugate additions of furans related to **23** and β-substituted α,β-unsaturated aldehydes are known, and the use of acrolein **24** as a Michael acceptor in these reactions has not been reported. Conversion of

29 to (*S*)-homocitric acid lactone **30** provided a new synthesis of this natural product enantiomer, and also established the stereochemistry of the Michael addition of **23** to **29**.



Scheme 1.8 Enantioselective synthesis of (*S*)-homocitric acid lactone and (*R*)-perhomocitric acid lactone.

1.1.3 Organocatalytic conjugate addition reactions via enamine catalysis

Chiral amines can catalyze the asymmetric conjugate addition of aldehydes and ketones to electron-deficient alkenes (Michael acceptors) such as nitroalkenes, enones, and vinyl sulfones, by the *in situ* formation of enamines from the starting aldehydes and ketones.[2] The enamine catalysis relies on reversible formation of enamines from a catalytic amount of the amine. The formation of an iminium ion is the first step of the catalytic cycle (Figure 1.3). This results in a significant increase in α-C-H acidity which facilitates enamine formation. [1e]

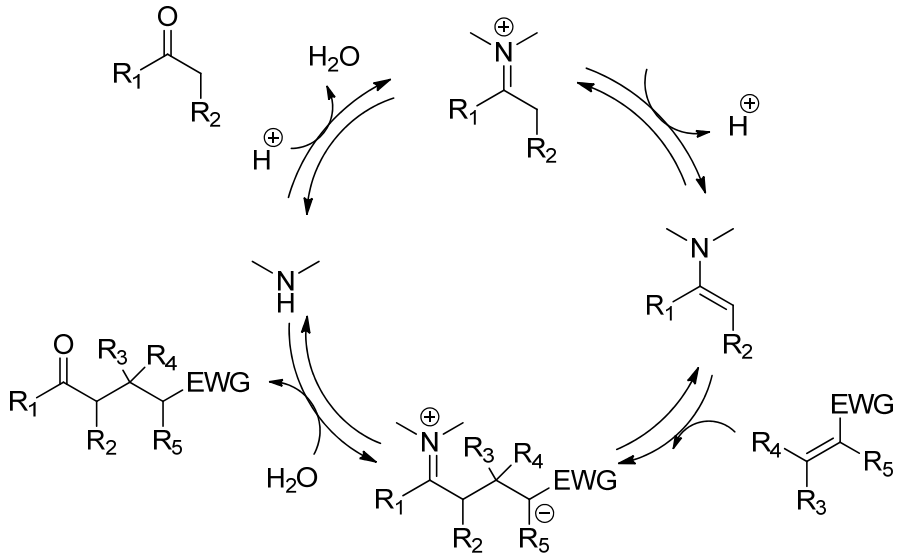
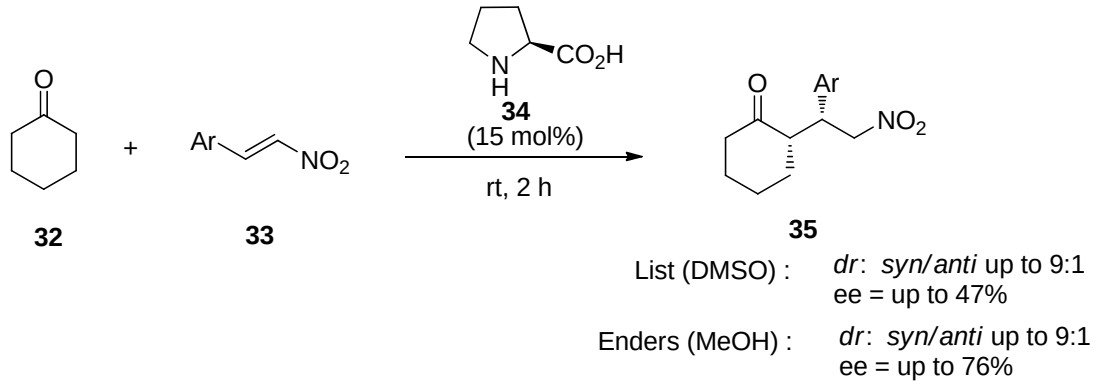


Figure 1.3 Enamine-Catalyzed Michael Reaction.[1e]

Although asymmetric conjugate additions have, over the years, been dominated by the application of chiral Lewis acids as catalysts, [19,20] more recently organocatalysts have been added as efficient tools.[2]

The following is a brief summary of organocatalytic conjugate addition of ketones to nitroalkenes using enamine catalysis.

In 2001, List *et al.* developed the first enamine-catalyzed asymmetric Michael reaction of ketone **32** to nitroalkenes **33**.[21] The reaction was catalyzed by (*S*)-proline (**34**) in DMSO to afford the desired *γ*-nitroketones **35** in high yields and good diastereoselectivities, but only low enantioselectivities (Scheme 1.9). In a related study, Enders used methanol as the solvent to obtain better enantio- and diastereoselectivities.[22]

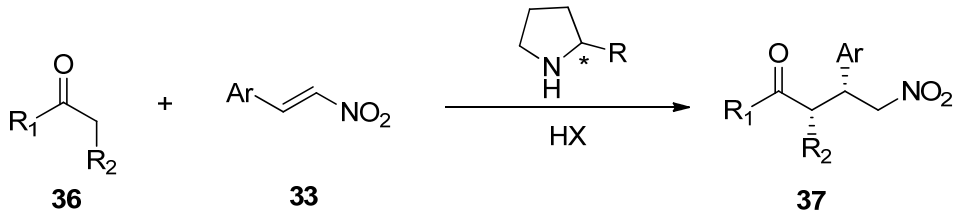


Scheme 1.9

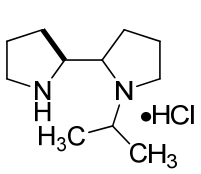
Since these reports, several methods have been developed for the organocatalytic Michael addition of ketones to nitroalkenes.[1,2] For the vast majority of these reactions, chiral amines are used as catalysts.

1.2 Functionalized pyrrolidines as organocatalysts for the ketone-nitroalkene conjugate addition reaction

Several catalysts having an *N*-containing side chain or heterocycle were developed (Figure 1.4), and either the free amine or the corresponding salts were shown to promote the highly *syn*-selective addition of cyclic and acyclic ketones **36** to nitroalkenes **33**[2e,g] (Scheme 1.10). Quite often the role of the acid co-catalyst (HX, Scheme 1.10) is to promote iminium ion formation, and consequently enamine formation, which results in an overall rate acceleration and increased conversion. Numerous secondary amine based catalysts[23-29] have been reported for these reactions. A selection of catalysts reported in the early days of the reaction (organocatalytic ketone-nitroalkene conjugate addition) are shown in Figure 1.4.

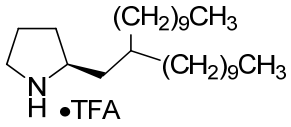


Scheme 1.10



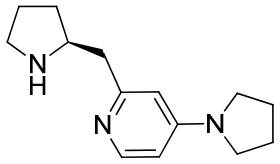
38

9 examples
dr: up to *syn/anti* = 95/5
ee = up to 74%
Alexakis



39

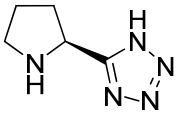
11 examples
dr: up to *syn/anti* = 98/2
ee = up to 90%
Barbas II



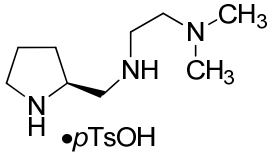
•2,4-dinitrobenzenesulfonic acid

40

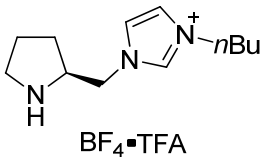
15 examples
dr: up to *syn/anti* = 98/2
ee = up to 99%
Kotsuki



41
6 examples
dr: up to *syn/anti* = 19/1
ee = up to 91%
Ley



42
17 examples
dr: up to *syn/anti* = 19/1
ee = up to 99%
Pansare

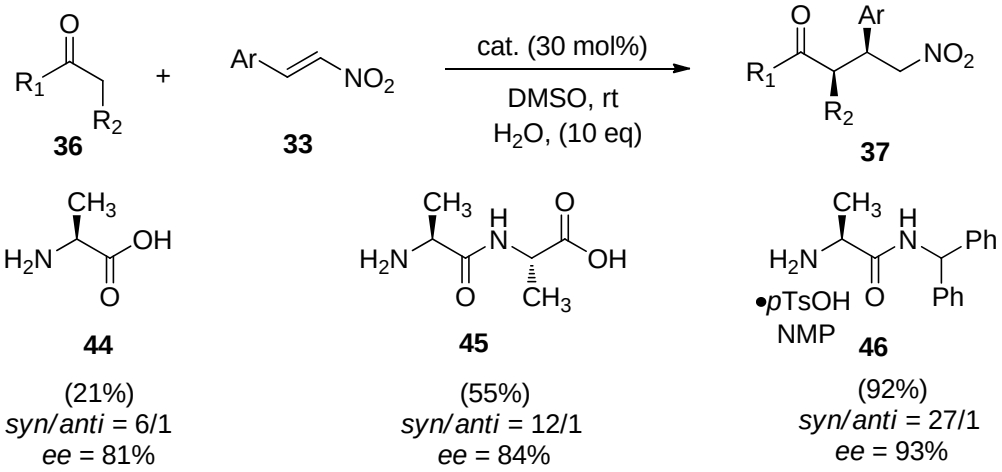


43
10 examples
dr: up to *syn/anti* = 99/1
ee = up to 99%
Luo,Cheng

Figure 1.4 Selected organocatalysts for ketone-nitroalkene conjugate addition

1.3 Chiral primary amines as organocatalysts for the ketone-nitroalkene conjugate addition reaction

Alanine **44** and alanine-containing small oligopeptides have also shown good stereoselectivities in the addition of ketones **36** to nitroalkenes **33**[30] (Scheme 1.11). The L-ala-L-ala dipeptide **45** was more selective than the monomer **44**, while the alanine derivative **46** is a much better catalyst than **44** and **45**.[31]

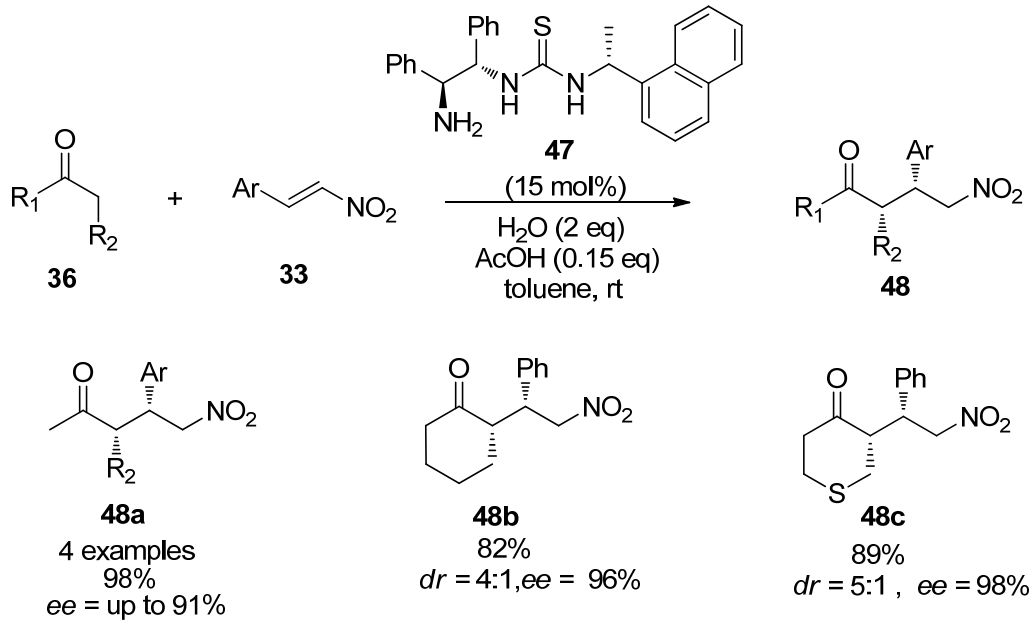


Scheme 1.11

1.4 Chiral amino-thioureas and amino-squaramides as organocatalysts for the ketone-nitroalkene conjugate addition reaction

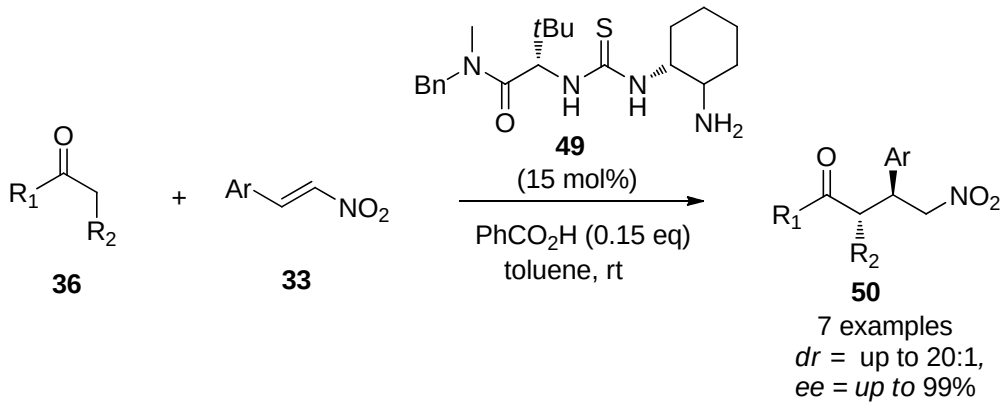
Tsogoeva, Schmatz, and co-workers utilized primary amine derived chiral thiourea catalysts in the Michael reaction of ketones **36** nitroalkenes **33**.[32,33] Thiourea **47** bearing a primary amine promoted the addition of ketones to nitroalkenes (Scheme 1.12)

with moderate diastereoselectivities (up to 6:1 *dr*) but excellent enantioselectivities (up to 99% ee). Water plays an important role in the regeneration of the catalyst and enamine formation is accelerated by acidic additives.



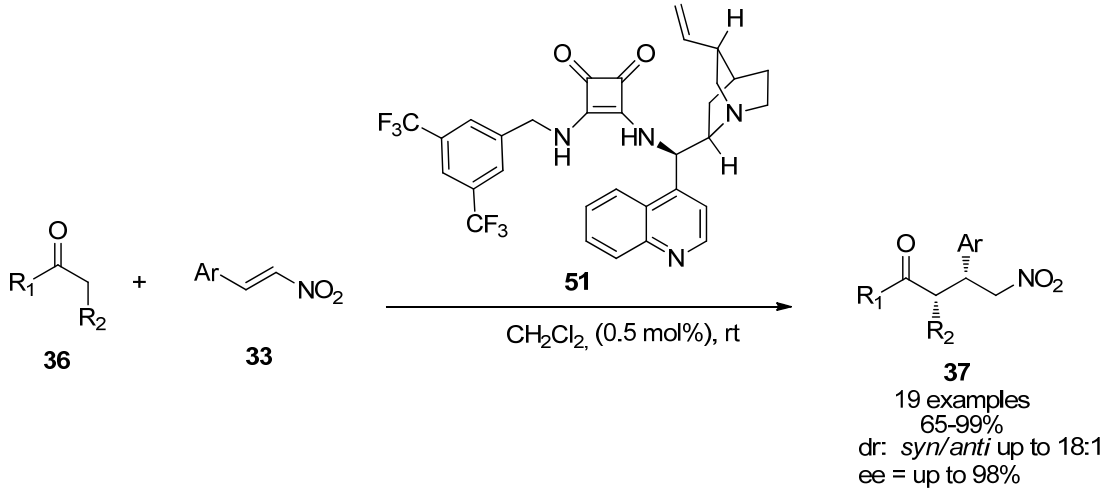
Scheme 1.12

Huang and Jacobsen used a similar primary amine thiourea catalyst **49** for the conjugate addition of ketones **36** to nitroalkenes **33**.[34] While reactions performed in polar and/or protic solvents proceeded slowly, nonpolar solvents and high concentrations turned out to be beneficial. Thiourea containing catalyst **49** furnished the Michael adducts with excellent *anti*-selectivity (up to 20:1 *dr*) and enantioselectivities (up to 99%). A (*Z*)-enamine intermediate was proposed for the observed *anti*-diastereoselectivity (Scheme 1.13).



Scheme 1.13

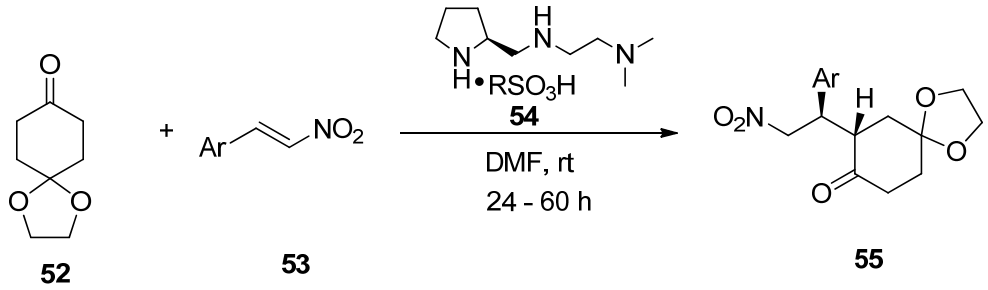
A chiral squaramide derivative catalyst **51** was reported by Rawal and co-workers for the Michael addition of ketones **36** to nitroalkenes **33** (Scheme 1.14). The squaramide derivative afforded the desired Michael adducts with high diastereo- and enantioselectivities.[35]



Scheme 1.14

The objective of our study was to utilize the enantiomerically-enriched γ-nitroketone **55**, for the stereoselective synthesis of selected alkaloids. The γ-nitroketone can be obtained from the organocatalytic Michael addition of an appropriate cyclic

ketone **52** and nitroalkene **53** via an enamine based Michael addition reaction (Scheme 1.15).



Scheme 1.15

The full potential of the organocatalytic ketone-nitroalkene conjugate addition reactions described above will be realized when the enantiomerically-enriched *γ*-nitroketone products find applications in other synthetic endeavours.[36-39] We therefore chose to examine the application of *γ*-nitroketone **55** (1.2.4) in the synthesis of the indolizidine alkaloid (+)-antofine and the quinilozidine alkaloids (+)-julandine and (+)-cryptopleurine.[40]

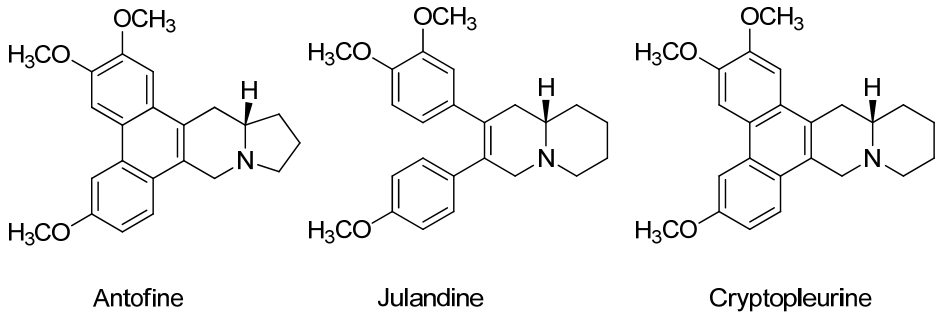


Figure 1.5 Indolizidine and quinolizidine alkaloids synthesized in this study.

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Chapter 2

Enantioselective Synthesis of (*S*)-Homocitric Acid Lactone and (*R*)-Per-homocitric Acid Lactone Involving Organocatalysis

This chapter is based on the following publication:

Pansare, S.V.; Adsool, S.V.; Dyapa, R. *Tetrahedron: Asymmetry* **2010**, *21*, 771–773

Contribution of authors

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

S. V. Adsool: Initial synthetic experimental work.

R. Dyapa: Synthetic experimental work for a major portion of the publication.

2.1 Introduction

(*R*)-Homocitric acid (**1**, Figure 2.1) is a key intermediate in the biosynthesis of L-lysine, an essential amino acid in some yeast and fungi,[1] and it is also a component of the Fe-Mo cofactor in nitrogenase.[2] The unique biological profile of homocitric acid is of interest in the development of antifungal therapies[3] and in the elucidation of the details of nitrogen fixation.[4] Studies toward these objectives require access to enantiomerically enriched (*R*)-homocitric acid and its analogues,[5] neither of which are commercially available in significant amounts. Consequently, the enantioselective synthesis of homocitric acid, invariably isolated as its γ-lactone, has been actively investigated in recent years.[6] Syntheses of racemic homocitrate[7] and per-homocitrate[7a] have also been reported. Close congeners of homocitrate such as the alkyl citrate, isocitrate, or α-alkyl malate motifs are key pharmacophoric units in several bioactive alkaloids, glycosides and antifungal agents.[8] This has added to the interest in substituted α-hydroxy di- and tricarboxylic acid derivatives in recent years.

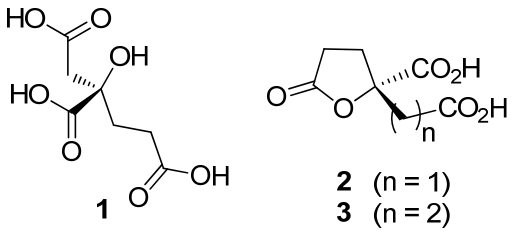
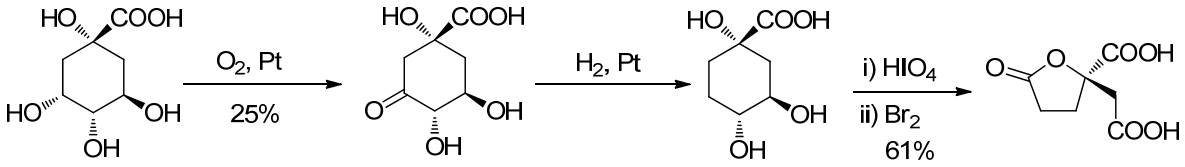


Figure 2.1 (*R*)-Homocitric acid (**1**), (*S*)-homocitric acid lactone (**2**) and (*R*)-per-homocitric acid lactone (**3**).

The following summary provides an overview of the stereoselective methods for the syntheses of (*S*)-homocitric acid.

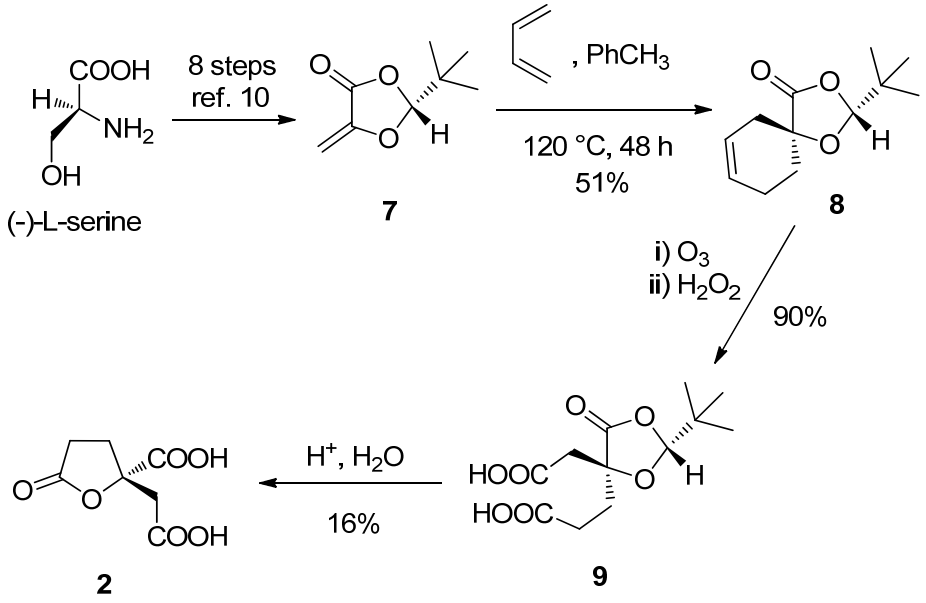
2.2 Known synthetic routes to (*S*)-homocitric acid

The first enantioselective synthesis of (*S*)-homocitric acid lactone was reported by Thomas and co-workers in 1966 (Scheme 2.1).[6g] The synthesis was carried out primarily to establish the absolute configuration of (*R*)-homocitric acid by the synthesis of its optical isomer, which could be obtained by degradation of (-)-quinic acid. In the first step of this endeavour, quinic acid was oxidized to the ketone **5** using a catalytic oxidation protocol reported by Haslam,[9] followed by complete reduction of the ketone moiety in **5** to generate the diol **6**.[10] Periodate cleavage of the diol followed by *in situ* oxidation of the dialdehyde provided (*S*)-homocitric acid lactone.



Scheme 2.1

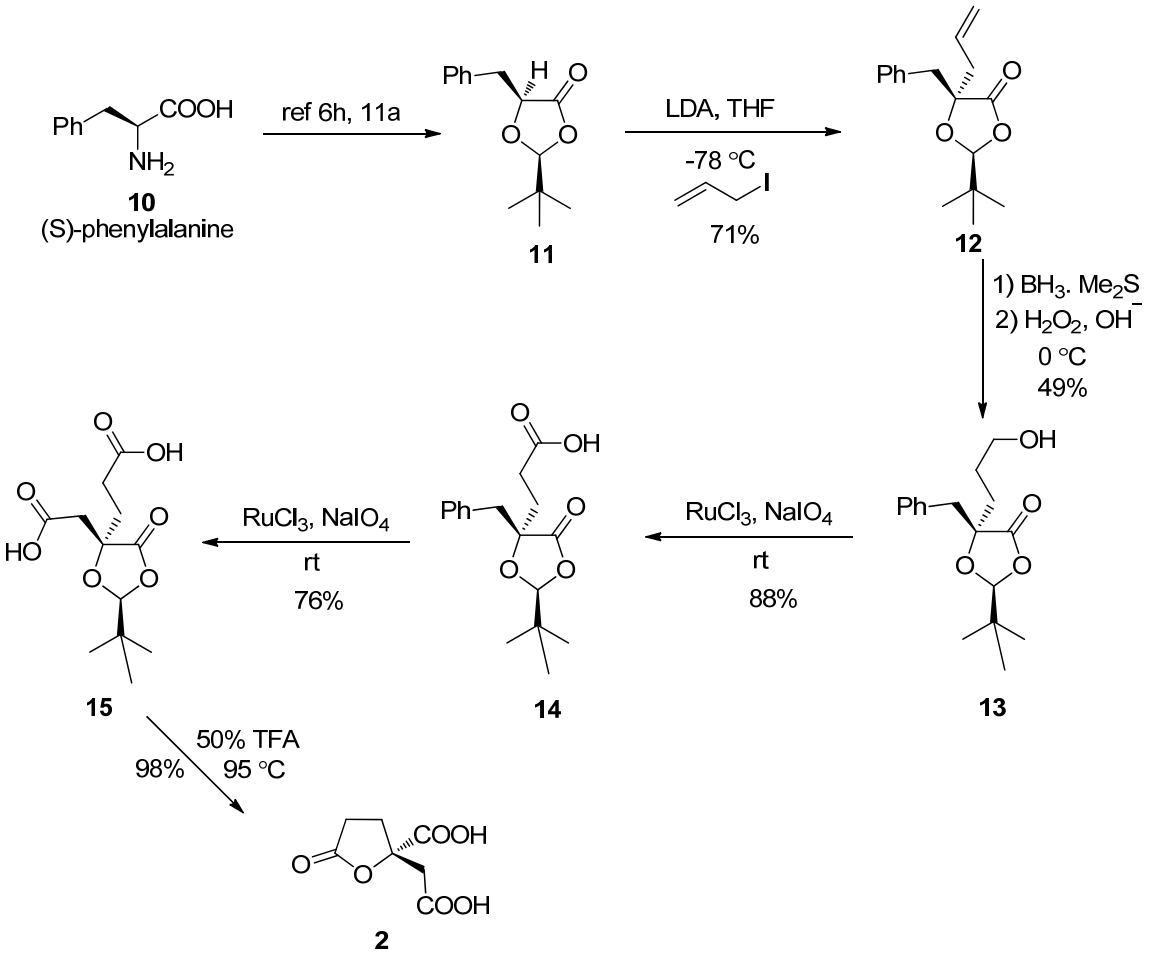
In 1996, Biellmann and co-workers reported the enantioselective synthesis of (*S*)-homocitric acid lactone **2** starting from (*S*)-serine (Scheme 2.2).[6f] In a sequence centered around a stereoselective Diels-Alder reaction, the authors used reported methods[11] to make the key starting material **7** from (-)-L-serine.



Scheme 2.2

Dioxolanone **7** was subjected to a Diels-Alder reaction with 1,3-butadiene to obtain the cyclohexene derivative **8**. Ozonolysis of **8** followed by oxidative workup provided the diacid **9**. Hydrolysis of the dioxolanone **9** provided (*S*)-homocitric acid lactone **2** in a low yield (16%, 96% ee). In the same report, the authors also describe the synthesis of (*R*)-homocitric acid lactone *ent*-**2**, which was prepared from (-)-L-lactic acid.

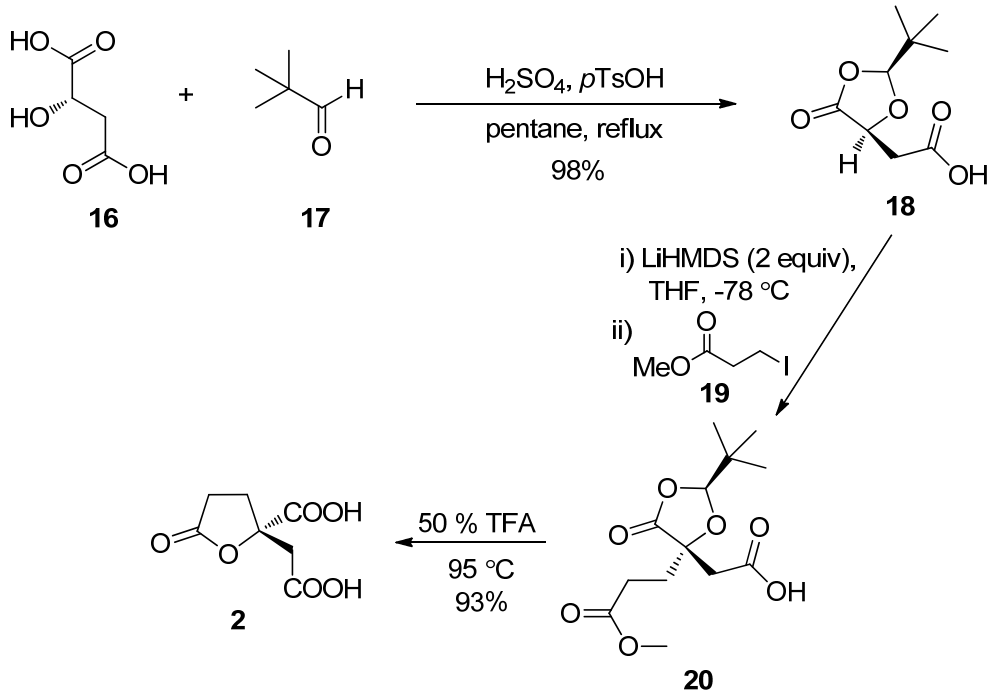
Huang and Li reported the synthesis of (*S*)-homocitric acid lactone, using Seebach's SRS (self-regeneration of stereocenters) methodology,[11a] from (*S*)-phenylalanine (Scheme 2.3).[6a] This strategy depends on using the phenyl group as a latent carboxyl group.[12]



Scheme 2.3

Thus, compound **11** was prepared from (*S*)-phenylalanine using a known procedure[6h,11a] and then stereoselectively alkylated with allyl iodide to give dioxolanone **12**. Oxidative hydroboration of compound **12** afforded corresponding alcohol **13**. Compound **15** was obtained from the sequential oxidation of alcohol **13** using $RuCl_3/NaIO_4$. Compound **15** was then converted to (*S*)-homocitric acid lactone by using a known procedure.[6b]

Tatsumi and co-workers reported a convenient route for the synthesis of (*S*)-homocitric acid (Scheme 2.4).[6b] The synthesis starts with readily available L-malic acid which was first reacted with pivalaldehyde to provide compound **18**. Alkylation of the dianion of compound **18** with the iodide **19** afforded compound **20**. The synthesis concluded with the hydrolysis of **20** to give the (*S*)-homocitric acid lactone **2**.



Scheme 2.4

2.3 Objective

The objective of this study was to utilize the γ-butenolide framework, obtained from organocatalytic Mukaiyama-Michael reaction, in the synthesis (*S*)-homocitric acid lactone (enantiomer of natural product) and its homolog (*R*)-per-homocitric acid lactone.

2.4 Results and discussion

Our approach to homocitric acid lactone is based on the Mukaiyama-Michael reaction[13] of silyloxy furans and α,β-unsaturated aldehydes and ketones, which is a useful method for the construction of butenolides. The iminium ion catalyzed version of this reaction was pioneered by MacMillan[14a,b] and other organocatalytic variants have since been developed.[14e-g] We reasoned that the use of acrolein as the Michael acceptor in a conjugate addition reaction with an appropriately substituted furan would lead directly to the homocitrate lactone motif (Figure 2.2). It may be noted that only β-substituted enals had previously been examined as substrates in this reaction.[14] We anticipated that acrolein would be a more challenging Michael acceptor since the stereoselectivity of the reaction appeared to depend on a β-substituent in the enal.[14]

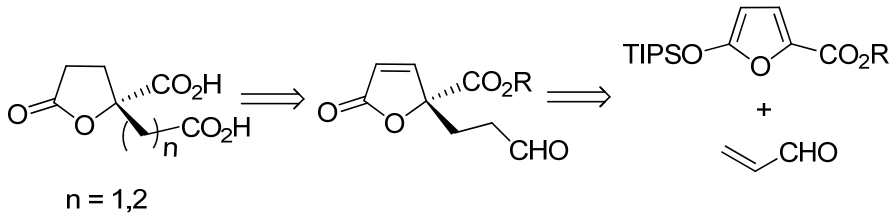
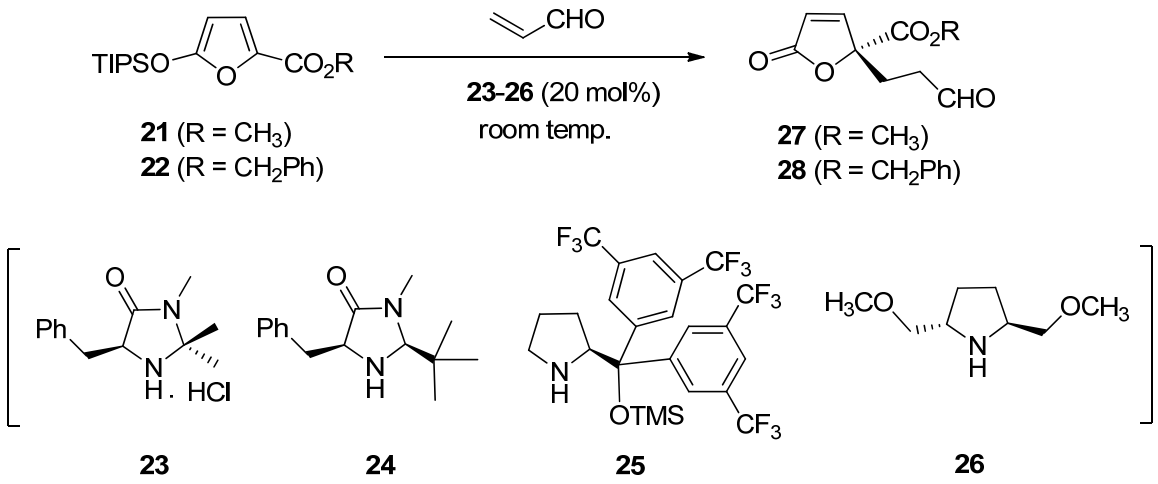


Figure 2.2 Retrosynthesis of (*S*)-homocitric acid lactone

With this objective in mind, the furans **21**[15a] and **22** were readily prepared from commercially available γ-crotonolactone by adapting a literature procedure.[15b] Secondary amines **23-26** were chosen as potential catalysts for the organocatalytic conjugate addition reaction of **21** and **22** with acrolein (Scheme 2.5). Orienting experiments were conducted with furan **21** and acrolein in the presence of the MacMillan first generation

catalyst **23** (Table 2.1). Although the required product was not obtained in ethereal solvents, the use of halogenated solvents was beneficial and **27** was obtained in modest yield and in 73% ee in chloroform, with water as an additive (Table 1, Entry 5). The enantioselectivity with the MacMillan catalyst **24** was low. Interestingly, a change in the ester alkyl group had a beneficial effect on enantioselection. Thus, the use of furan **22**[16] (benzyl ester) as the nucleophile in $CHCl_3/H_2O$ provided the Michael adduct **28**[16] in 80% ee and 40% yield. Increasing the amount of acrolein (20 eq., Entry 9) was not beneficial and provided only 19% of **28** with significantly lowered enantiomeric excess (69% ee). As with **21**, changing the solvent to THF was detrimental (1% ee). This observation suggests that the reaction is notably sensitive to changes in the solvent and ethereal solvents, in particular, are detrimental to enantioselection. Reactions of **22** in the presence of amines **24**, **25** and **26** also provided the butenolide **28** (Table 1, entries 10-18). When **24** was used under the conditions optimized for **23** ($CHCl_3/H_2O$ as the solvent) **28** was not obtained. The use of TFA as an additive (instead of water) had a pronounced effect and **28** was obtained, but with low ee (39%, entry 12). In summary, the best conditions for the synthesis of **28** employ the ester **22** with an excess (3 equivalents) of acrolein and catalyst **23** in $CHCl_3/H_2O$ as the solvent.



Scheme 2.5

Among the remaining catalysts, the imidazolidinone **24** was superior. Reactions with the prolinol derivative **25** were found to be very capricious in terms of enantioselectivity and the C_2-symmetric pyrrolidine **26** was not especially effective as a catalyst (Table 2.1). Overall, the higher efficiency of **23** over **24** is notable in this study. It may be noted that the facial selectivity for the reaction of **21** with β-substituted acroleins is known to depend on the nature of the β-substitutent and this substitutent is often necessary for good stereoselectivity.[14a,d] Since these studies[14a] were conducted with catalyst **24**, an unambiguous stereochemical assignment for adducts **27** and **28** was not possible by analogy to the reported results. However, subsequent reactions of **28** were useful in determining the sense of asymmetric induction in the Mukaiyama-Michael reaction.

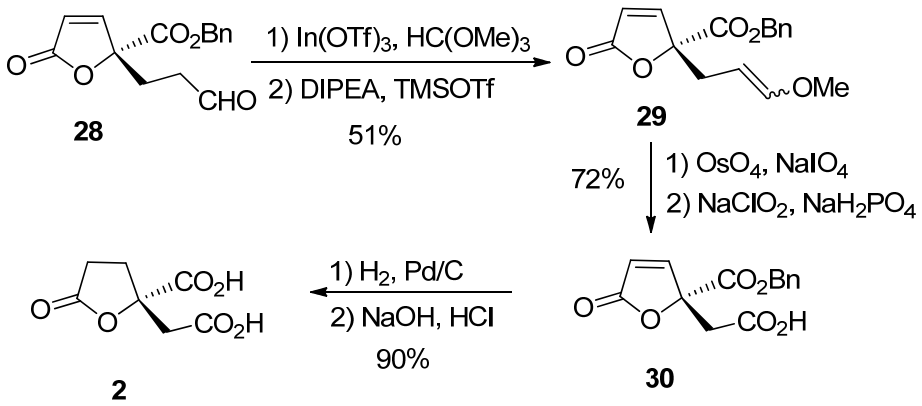
Entry	Cat.	Solvent	Add.	Time (h)	Yield (%)		ee (%)[a]
					27	**28**	
1	23	THF	H_2O[b]	16	-		-
2	23	dioxane	H_2O	16	-		-
3	23	CH_2Cl_2	H_2O	156	18		52
4	23	$CHCl_3$	H_2O	156	12		45
5	**23**	**$CHCl_3$**	**H_2O**	**72**	**24**		**73**
6	24	THF	TFA[c]	72	21		13
7	24	CH_2Cl_2	TFA	3[d]	9		20
8	**23**	**$CHCl_3$**	**H_2O**	**72**		**40**	**80**
9	23	$CHCl_3$	H_2O	20		19[e,f]	69
10	23	THF	H_2O	20		16	1
11	24	$CHCl_3$	H_2O	144		-	-
12	24	$CHCl_3$	TFA	48		33[e]	39
13	24	$CHCl_3$	TFA	72[f]		47	72
14	24	THF	TFA	50		50	59
15	24	CH_2Cl_2	TFA	48[f]		41	41
16	25	$CHCl_3$	H_2O	120		36	50
17	25	THF	-	91		74	35
18	25	CH_2Cl_2	-	120		33	44
19	26	$CHCl_3$	H_2O	168		27	1
20	26	$CHCl_3$	MeOH	192		35	3

[a]Chiral HPLC analysis of **28** and of the acetal with (2*R*,3*R)*-2,3-butanediol for **27**. [b]2 equiv water. [c]0.2 equiv TFA. [d]reaction at -40 °C. [e]20 equiv acrolein. [f]reaction at 0 °C.

Table 2.1 Catalyst survey for the Mukaiyama-Michael reaction of acrolein with furan nucleophiles

With the ester **28** (80% ee) in hand, we proceeded to convert it into the target homocitric acid lactone *via* a dehomologation/oxidation protocol (Scheme 2.6).

Acetalization of **28** with trimethylorthoformate followed by treatment of the crude acetal with Hunig's base provided the enol ether **29** as a mixture of stereoisomers (*trans/cis* = 2/1).[16] Oxidative cleavage of the enol ether (OsO_4/$NaIO_4$) provided the acid **30**.



Scheme 2.6

Hydrogenation of **30** was anticipated to proceed with concommitant debenzylation. However, the benzyl ester in **30** was resistant to hydrogenolysis (Pd/C, 2 atm. H_2) which invariably led to mixtures containing a trace of **2** and the dihydro analog of **30**. Nonetheless, selective reduction of the double bond in **30** was possible (1 atm. H_2), which was followed by base hydrolysis of the ester and subsequent acidification to provide (*S*)-homocitric acid lactone **2** (90% from **30**, Scheme 2.6).

The lactone **2** obtained in this study is dextrorotatory and is therefore assigned the (*S*) configuration ($[\alpha]_D^{23}$ = +39.0 (c 1, H_2O); lit.[6c] $[\alpha]_D^{23}$ = -48.9, c 0.38, H_2O) for the (*R*) enantiomer). This assignment also establishes the sense of asymmetric induction in the organocatalytic Michael addition reaction leading to **28**.

The proposed mechanism for the organocatalytic Mukaiyama-Michael addition to acrolein is shown in Figure 2. According to MacMillan, the imidazoline salt **23** forms an iminium ion such as **31.** Two factors for stereocontrol can be identified in the reaction.[14a,b]

1) Selective formation of *E* iminium ion **31** (Figure 2.3)

2) The benzyl group on the catalyst shields the *si*-face of the iminium ion.

Taking into consideration these aspects, the furan nucleophile should approach from the less hindered *re*-face of the iminium ion as shown in **31**, which will lead to the enamine **32**. Hydrolysis of enamine **32** will give aldehyde **28** and regenerate the catalyst for further catalytic cycles.

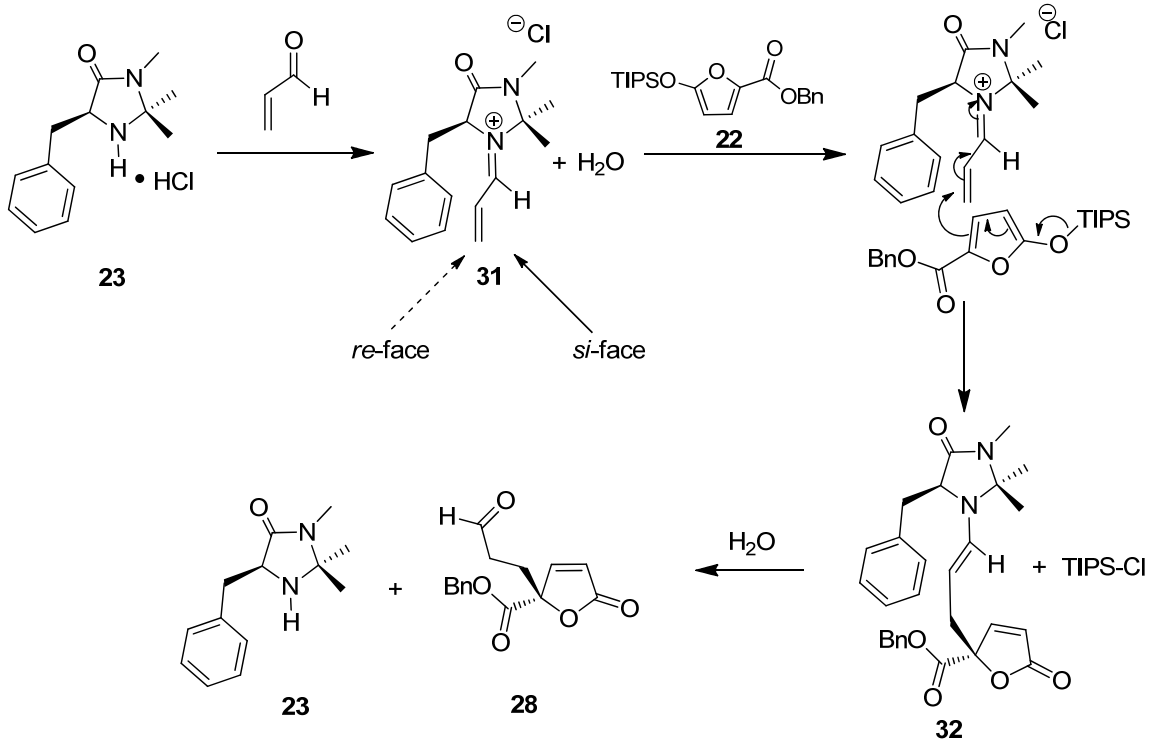
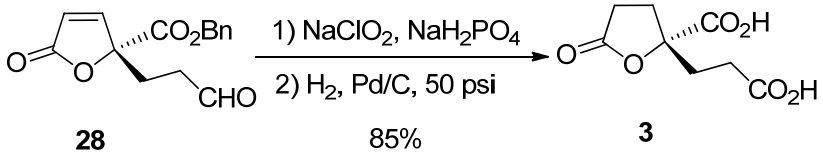


Figure 2.3 The proposed mechanism for the organocatalytic Mukaiyama-Michael addition to acrolein

Given the recent interest in the higher homologue of (*S*)-homocitric acid (per-homocitric acid),[5d,6a] we converted lactone **28** to a homologue of **2**. Oxidation of aldehyde **28** provided the corresponding acid which was hydrogenated to provide the target (*R*)-per-homocitric acid lactone (**3**)[16] in good yield (85%, Scheme 2.7). It may be noted that **3** is a desymmetrized derivative of the parent, achiral triacid.



28 85% **3**

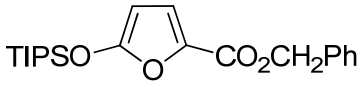
Scheme 2.7

2.5 Conclusion

Expedient, organocatalysis-based, enantioselective syntheses of (*S*)-homocitric acid lactone and its homologue have been developed. Notably, the methodology also provides several butenolide intermediates that offer opportunities for chemoselective functionalization. Such reactions may find applications in the synthesis of functionalized, oxygen and nitrogen heterocycles with applications in biology and medicine.[17]

2.6 Experimental section

Benzyl-5-triisopropylsiloxy-2-furoate (22):

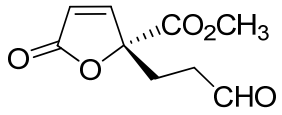


A solution of *s*-BuLi (11.6 mL, 10.5 mmol, 0.900 M solution in cyclohexanes) was added dropwise to a stirred solution of (furan-2-yloxy) triisopropylsilane (2.42 g, 10.1 mmol) in THF (12.0 mL) at -78 ^{o}C under nitrogen and the mixture was stirred at -78 ^{o}C for an hour. A solution of benzyl chloroformate (1.48 mL, 10.5 mmol) in THF (13.0 mL, cooled at -78 ^{o}C) was added, the mixture was stirred for 90 min and then warmed to room temperature. The mixture was concentrated and the residue was dissolved in ethyl acetate (20.0 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 x 10.0 mL) followed by brine (20.0 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (97/3 hexanes/ether). The product obtained contained a volatile impurity which was removed at 120 ^{o}C (0.2 mmHg) to provide 1.50 g (40%) of pure **22** as an orange oil.

IR (neat): 2947, 2869, 1720, 1604, 1531, 1303, 1123 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.31 (m, 5H, Ar*H*), 7.13 (d, 1H, *J* = 3.5, C*H*=CC=O), 5.30 (d, 1H, *J* = 3.5, C*H*=CO), 5.28 (s, 2H, PhCH_2), 1.34-1.29 (sept, 3H, SiC*H*), 1.10 (d, 18H, *J* = 7.5, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9 (*C*OSi), 158.4 (*C*=O), 136.43 (*C*C=O), 133.9 (Ar*Cipso*), 128.7 (Ar*C*), 128.3 (2 x Ar*C*), 122.2 (*C*=CC=O), 87.7 (*C*=CO), 66.0

(Ph*C*), 17.7 (*C*H_3CH), 12.4 (CH_3*C*H); HRMS (CI+): *m/z* 375.1999 (375.1992 Calc. for $C_{21}H_{31}O_4Si$, $[M+H]^+$).

(*R*)-Methyl 2-(formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (27):

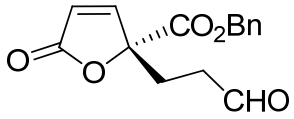


To a solution of the imidazolidinone **23** (9.00 mg, 0.030 mmol, 20 mol% with respect to ester **21**) in chloroform (0.500 mL) was added water (6.00 μL, 0.330 mmol, 2 equiv. with respect to ester **21**), acrolein (0.030 mL, 0.500 mmol) and the ester **21** (50.0 mg, 0.170 mmol) at room temperature. The mixture was stirred at room temperature for 72 h. Water (5.0 mL) was added and the mixture was extracted with dichloromethane (2 x 5.0 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 6/4) to provide 8 mg (24%) of aldehyde **27** as a yellow gum.

IR (neat): 3096, 2923, 2853, 1772, 1740, 1722, 1437, 1255, 1178, 1104 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1H, C*H*O), 7.43 (d, 1H, C*H*=CHC=O, J = 5.6), 6.19 (d, 1H, J = 5.6), 3.81 (s, 3H, CH_3), 2.61 (m, 2H, CH_2CHO), 2.55-2.50 (m, 1H, C$H_2$$CH_2$CHO), 2.31-2.25 (m, 1H, C$H_2$$CH_2$CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.4 (*C*HO), 171.0 (O*C*=O), 167.6 (*C*O_2CH_3), 154.3 (*C*=CC=O), 122.4 (C=*C*C=O), 88.6 (O*C*CO_2CH_3), 53.5 (O*C*H_3), 37.7 (*C*H_2CHO), 27.5 (*C*$H_2$$CH_2$); HRMS (CI+): *m/z* 199.0605 (199.0606 Calc. for $C_9H_{11}O_5$, $[M+H]^+$); *ee* (acetal with(2*R*,3*R)*-2,3-butanediol):

73% (t_{major}: 16.7 min; t_{minor}: 18.1 min; Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 92/8, 1 mL/min).

(*R*)-Benzyl-2-(formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (28):



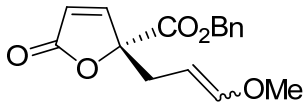
To a solution of the imidazolidinone salt **23** (122 mg, 0.47 mmol, 20 mol% with respect to ester **22**) in chloroform (9.0 mL) and water (86.0 μL, 3.80 mmol, 2 equiv. with respect to ester **22**) was added acrolein (0.460 mL, 7.20 mmol) and ester **5** (0.90 g, 2.40 mmol) at room temperature. The mixture was stirred at room temperature for 72 h. Dichloromethane (10.0 mL) was added the mixture was washed with water (1 x 10.0 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 1/1) to provide 260 mg (40%) of the aldehyde **28** as a viscous brown liquid.

IR (neat): 3092, 2929, 2735, 1768, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.70 (s, 1H, C*H*O), 7.41 (d, 1H, C*H*=CHC=O, J = 5.0), 7.39-7.32 (m, 6H, Ar*H*), 6.17 (d, 1H, J = 5.0), 5.21 (s, 2H, CH_2Ph), 2.59-2.47 (m, 3H, CH_2CHO, CH_2CH$_2$CHO), 2.30-2.22 (m, 1H, CH_2CH$_2$CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6 (*C*HO), 171.1 (O*C*=O), 167.1 (*C*O$_2$Bn), 154.4 (*C*=CC=O), 134.7(Ar*C*ipso), 129.0 (Ar*C*), 129.0 (Ar*C*), 128.6 (Ar*C*), 122.7 (C=*C*C=O), 88.9 (O*C*C=O), 68.5 (*C*H$_2$Ar), 37.8 (*C*H$_2$CHO), 27.7 (*C*H$_2$CH$_2$); HRMS (CI+): *m/z* 275.0917 (275.0919 Calc. for $C_{15}H_{15}O_5$, $[M+H]^+$); *ee*: 80%

(t_{minor}: 50 min; t_{major}: 67.6 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

Other reactions of **22** with acrolein, employing different solvents and/or catalysts at selected temperatures, were carried out according to the procedure described above.

(*R*)-Benzyl 2,5-dihydro-2-(3-methoxyallyl)-5-oxofuran-2-carboxylate (29):



Indium triflate (1.7 mg, 0.0030 mmol) was added to a solution of the aldehyde **28** (165 mg, 0.60 mmol) and trimethyl orthoformate (0.130 mL, 1.20 mmol) in dichloromethane (8.0 mL) at room temperature. The mixture was stirred for 4 min, a second portion of indium triflate (1.70 mg, 0.003 mmol) was added and the stirring was continued further for 6 min. The reaction mixture was then filtered through a plug of neutral alumina and the plug was washed with dichloromethane. The filtrate was concentrated under vacuum to provide 159 mg (83%) the dimethyl acetal of **28** as colourless oil. This was used further without purification.

IR (neat): 2932, 1773, 1456, 1128, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, 3H, J = 3.1, C*H*=CHC=O), 7.40-7.30 (m, 6H, Ar*H*), 6.16 (d, 1H, J = 3.1, CH=C*H*C=O), 5.21 (s, 2H, CH_2Ar), 4.32 (t, 1H, J = 5.0, C*H*$(OCH_3)_2$), 3.28 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.30-2.24 (m, 1H, CH_2C$(OCH_3)_2$), 2.0-1.90 (m, 1H,CH_2C$(OCH_3)_2$), 1.70-1.50 (m, 2H, CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2 (C=C*C*O), 167.3 (*C*O_2CH2Ph), 154.4 (*C*H=CHCO), 134.6 (Ph*C*ipso), 128.7 (Ph*C*), 128.7

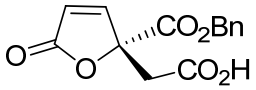
(Ph*C*), 128.3 (Ph*C*), 122.4 (CH=*C*HCO), 103.6 (*C*H(OCH_3)$_2$), 89.5 (O*C*CO_2CH_2Ph), 68.1 (*C*H_2Ph), 53.3 (O*C*H_3), 52.9 (O*C*H_3), 30.5 (CH_2*C*H(OCH_3)$_2$), 26.6 (*C*H_2CH(OCH_3)$_2$); HRMS (CI+): *m/z* 320.1255 (320.1260 Calc. for $C_{17}H_{20}O_6$, M^+).

The above acetal (150 mg, 0.470 mmol) was dissolved in dichloromethane (0.8 mL) and *N*,*N*-diisopropylethylamine (97.0 μL, 0.560 mmol) was added at room temperature. The mixture was cooled to -20 ^oC and TMSOTf (93.0 μL, 0.52 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 2.5 h after which it was concentrated and filtered through a short silica gel column (hexanes/ethyl acetate, 7/3) to provide 84 mg (62%) of **29** as a 2:1 mixture of *E:Z* isomers.

IR (neat): 2936, 1768, 1655, 1456, 1213, 1107, 1027, 922 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): Major isomer: δ 7.40 (d, 1H, *J* = 5.0, C*H*=CHC=O), 7.36-7.32 (m, 5H, Ar*H*), 6.33 (d, 1H, *J* = 12.7, CH=C*H*OMe), 6.16 (d, 1H, *J* = 5.6, CH=C*H*C=O), 5.2 (m, 2H, OCH_2Ph), 4.54-4.49 (m, 1H, C*H*=CHOMe), 3.43 (s, 3H, OCH_3), 2.75 (dd, 1H, *J* = 14, 8, CH_2C=CHOMe), 2.56 (dd, 1H, *J* = 14.0, 7.0, CH_2C=CHOMe). Visible peaks of minor isomer: δ 6.12 (d, 1H, *J* = 5.6, CH=C*H*C=O), 5.99 (d, 1H, *J* = 7.3, CH=C*H*OMe), 4.24-4.20 (q, 1H, *J* = 7.3, C*H*=CHOMe), 3.55 (s, 3H, OCH_3), 2.85 (dd, 1H, *J* = 14.50, 7.30 CH_2), 2.82 (dd, 1H, *J* = 14.5, 7.30, CH_2C=CHOMe); ^{13}C NMR (125 MHz, $CDCl_3$): Major isomer: δ 171.4 (C=C*C*O), 167.3 (*C*O_2CH_2Ph), 154.4 (*C*=CCO), 151.7 (C=*C*OMe), 150.2 (Ph*C*ipso), 134.9 (Ph*C*), 128.9 (Ph*C*), 128.6 (Ph*C*), 122.8 (C=*C*CO), 93.1 (*C*=COMe), 90.2 (O*C*CO_2Bn), 68.1 (*C*H_2Ph), 56.1 (C=CO*C*H_3), 35.0 (*C*H_2C=CHOMe). Visible peaks of the minor isomer: δ 171.7 (C=C*C*O), 167.5 (*C*O_2CH_2Ph), 154.6 (*C*=CCO), 121.9 (Ph*C*), 128.8 (Ph*C*), 128.8 (Ph*C*), 128.4 (*C*Ph),

122.2 (C=*C*CO), 96.5 (*C*=COMe), 89.9 (O*C*CO_2Bn), 68.1 (*C*H_2Ph), 59.9 (C=CO*C*H_3), 30.5 (*C*H_2C=CHOMe); HRMS (CI+): *m/z* 288.1000 (288.0998 Calc. for $C_{16}H_{16}O_5$, M^+).

2-((*R*)-2-((Benzyloxy) carbonyl)-2,5-dihydro-5-oxofuran-2-yl)acetic acid (30):



A solution of osmium tetroxide (4% in water, 86.0 μL, 0.014 mmol) was added to a stirred solution of the enol ethers **29** (0.080 g, 0.28 mmol) in acetone (4.3 mL) and water (0.50 mL). The mixture was stirred for 10 min and sodium periodate (0.118 g, 0.55 mmol) was added. The mixture was stirred for 20 min and filtered through a pad of Celite. The Celite was washed with acetone and the filtrate was concentrated to provide an aqueous solution which was extracted with ethyl acetate (3 x 5.0 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 64 mg (95%) of (*R*)-benzyl-2-(formylmethyl)-2,5-dihydro-5-oxofuran-2-carboxylate as a gum. This was used further without purification.

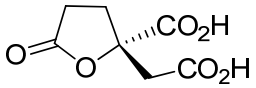
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (s, 1H, C*H*O), 7.56 (d, 1H, *J* = 5.6, C*H*=CHCO), 7.38-7.30 (m, 5H, Ar*H*), 6.24 (d, 1H, *J* = 5.6, CH=C*H*CO), 5.24-5.18 (AB, 2H, *J* = 15.0, OCH_2Ph), 3.23-3.13 (AB, 2H, *J* = 20.0, CH_2CHO).

The above aldehyde (0.064 g, 0.26 mmol) was dissolved in *t*-butyl alcohol (5.20 mL) and 2-methyl-2-butene (0.55 mL of a 2 M solution in THF, 1.10 mmol). To this was added a solution of $NaClO_2$ (0.071 g, 0.79 mmol) and NaH_2PO_4 (0.033 g, 0.28 mmol) in water (1.30 mL). The mixture was stirred at room temperature for 3 h and concentrated.

The aqueous solution obtained was extracted with ether (3 x 5.0 mL). The ether layer was separated and the aqueous layer was cooled (<5 ^{o}C) and acidified (0.5 M HCl, 3.0 mL) and the acidic solution was extracted with ether (3 x 5.0 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 64 mg (95%) of the acid **30**. This was used further without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.0-8.0 (br. 1H, CO_2H), 7.56 (d, 1H, J = 5.6, COCH=C*H*), 7.37-7.29 (m, 5H, Ph*H*), 6.24 (d, 1H, J = 5.6, COC*H*=CH), 5.22 (s, 2H, PhCH_2O), 3.20-3.05 (AB, 2H, J = 16.9, CH_2COOH).

(*S*)-2-(Carboxymethyl)-tetrahydro-5-oxofuran-2-carboxylic acid ((*S*)-Homocitric acid) (2):



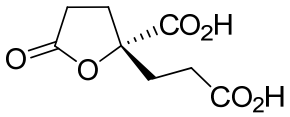
The acid **30** (47 mg, 0.17 mmol) was dissolved in ethyl acetate (3.0 mL), Pd/C (10%, 10 mg) was added and the mixture was stirred under hydrogen at atmospheric pressure for 48 h. The reaction mixture was filtered through Celite, the Celite was washed with ethyl acetate (10 mL) and the combined filtrates were concentrated to provide 40 mg (85%) of 2-((*S*)-2-((benzyloxy)carbonyl)-tetrahydro-5-oxofuran-2-yl)acetic acid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.33 (m, 5H, Ar*H*), 5.24 (AB, 2H, J = 12.0, OCH_2Ph), 3.19 (d, 1H, J = 17.1, CH_2COOH), 3.04 (d, 1H, J = 17.1, CH_2COOH), 2.65-2.50, (m, 3H, CH_2CH_2), 2.36-2.29 (m, 1H, COCH_2CH$_2$).

The above ester (38 mg, 0.14 mmol) was dissolved in THF (0.50 mL), aqueous NaOH (2 M, 0.50 mL) was added and the mixture was stirred at ambient temperature for 15 h. The THF was removed under reduced pressure and the resulting aqueous solution was extracted once with dichloromethane. The aqueous solution was cooled, acidified with HCl (0.50 M) to pH 1 and extracted with dichloromethane (3 x 5.0 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 25 mg (97%) of (*S*)-homocitric acid (**2**) that was pure by ^{1}H NMR.

IR (solid): 3500-2800 (br), 1717, 1416, 1170, 1064, 942, 870 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39 (d, 1H, J = 17.5, CH_2COOH), 3.05 (d, 1H, J = 17.5, CH_2COOH), 2.75-2.69 (m, 2H, CH_2C=O), 2.60-2.54 (m, 1H, CH_2CH_2), 2.47-2.40 (m, 1H, CH_2CH_2); MS (APCI negative): *m/z* 187 [M-H]$^-$); (APCI positive): *m/z* 189 [M+H]$^+$); $[\alpha]_D^{23}$: + 39.0 (c 1, H_2O).

(*R*)-2-(2-Carboxyethyl)-tetrahydro-5-oxofuran-2-carboxylic acid ((*R*)-Per-homocitric acid) (3):



To a solution of the aldehyde **28** (500 mg, 1.82 mmol) in *t*-butyl alcohol (8.0 mL) was added 2-methyl-2-butene (3.82 mL of 2 M soln. in THF, 7.65 mmol) followed by dropwise addition of a solution of $NaClO_2$ (494 mg, 5.46 mmol) and NaH_2PO_4 (219 mg, 1.82 mmol) in water (32.0 mL). The mixture was stirred at ambient temperature for 3 h and the *t*-butyl alcohol was removed under reduced pressure. The resulting mixture was extracted with ether (2 x 10.0 mL). The aqueous layer was cooled

to 0 ˚C and acidified with HCl (0.50 M). The acidic solution was extracted with ethyl acetate (2 x 10.0 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide 500 mg (94%) of the acid as a white solid. This was pure by ^{1}H NMR (500 MHz) and was used further without purification.

IR (neat): 3091, 1734, 1706, 1499, 1456, 1236, 1172, 1088, 1053, 905, 819, 750 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.40 (d, 1H, J = 5.60, COCH=C*H*), 7.37-7.26 (m, 5H, Ph*H*), 6.19-6.18 (d, 1H, J = 5.6, COC*H*=CH), 5.21 (s, 2H, PhCH_2O), 2.59-2.53 (m, 1H, C*H*CH_2COOH), 2.44-2.40 (m, CH_2COOH), 2.31-2.25 (m, C*H*CH_2COOH). HRMS (CI+): *m/z* 291.0871 (291.0869 Calc. for $C_{15}H_{14}O_6$, $[M+H]^+$); $[\alpha]_D^{20}$: + 86.0 (c 1, CH_2Cl_2).

To a solution of the above acid (100 mg, 0.34 mmol) in THF (15.0 mL) was added Pd/C (10%, 30 mg) and the mixture was shaken under hydrogen at 50 psi for 7 h. The mixture was filtered through a pad of Celite and the Celite was washed with THF (2x10.0 mL). The combined filtrates were concentrated under reduced pressure to provide 62 mg (90%) of per-homocitric acid lactone (**14**) that was pure by ^{1}H NMR. If necessary, further purification can be achieved by sonication of a mixture of the diacid and chloroform (10 mg/mL) for 10-15 min. followed by decantation of the chloroform layer to remove the dissolved impurities.

IR (neat): 2938, 1733, 1709, 1243, 1169, 1074, 1044 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 9.25-8.25 (br, CO_2H), 2.70-2.60 (m, 1H, CH_2CO), 2.60-2.50 (m, 3H, CH_2CO), 2.48-2.38 (m, 2H, *C*H_2CH_2CO), 2.22-2.14 (m, 2H, *C*H_2CH_2CO); ^{13}C NMR (125 MHz, $CDCl_3$+ DMSO-d_6): δ 175.9 (*C*=O), 174.8 (*C*=O), 173.1 (*C*=O), 85.6 (*C*-O),

32.4 (CH_2CO), 31.8 (CH_2CO), 29.0 (CH_2), 28.1 (CH_2); MS (APCI negative): *m/z* 200.6 (M-2); HRMS (CI+): *m/z* 203.0554 (203.0556 Calc. for $C_8H_{11}O_6$, $[M+H]^+$).; $[\alpha]_D^{23}$: -3.8 (c 1, THF).

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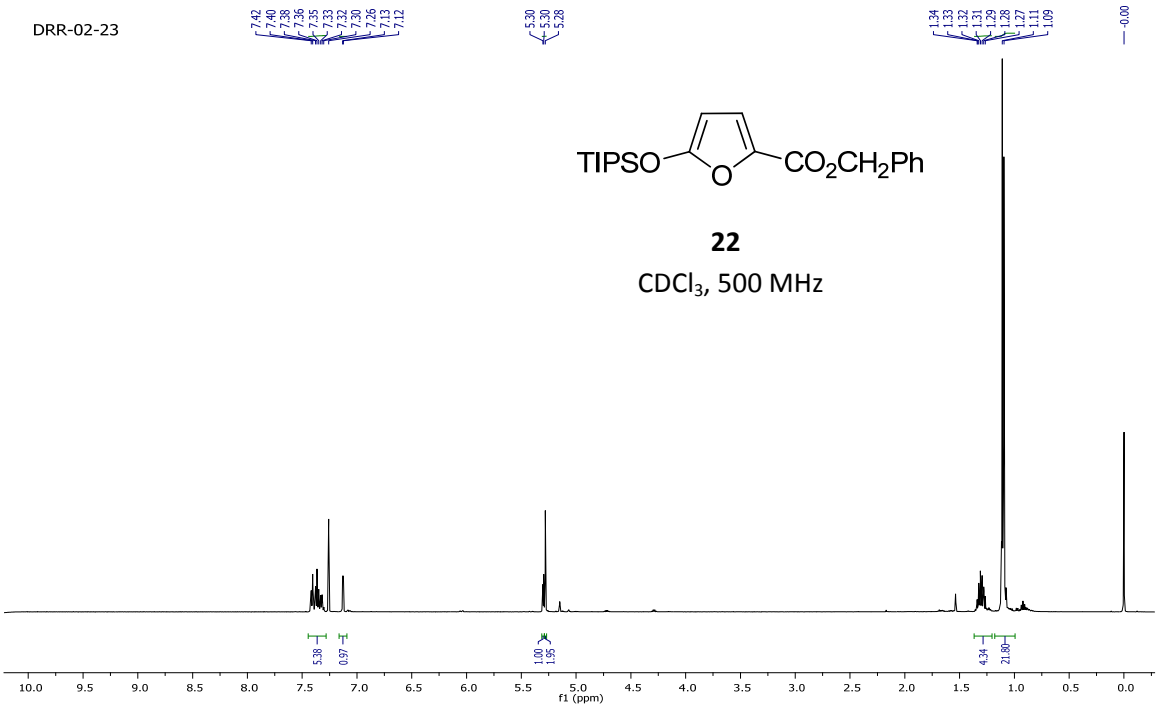
2.8 Selected ^{1}H NMR and ^{13}C NMR spectral data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7.40
7.38
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7.30
7.26
7.13
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5.30
5.30
5.28
1.34
1.33
1.32
1.31
1.29
1.28
1.27
1.11
1.09
0.00
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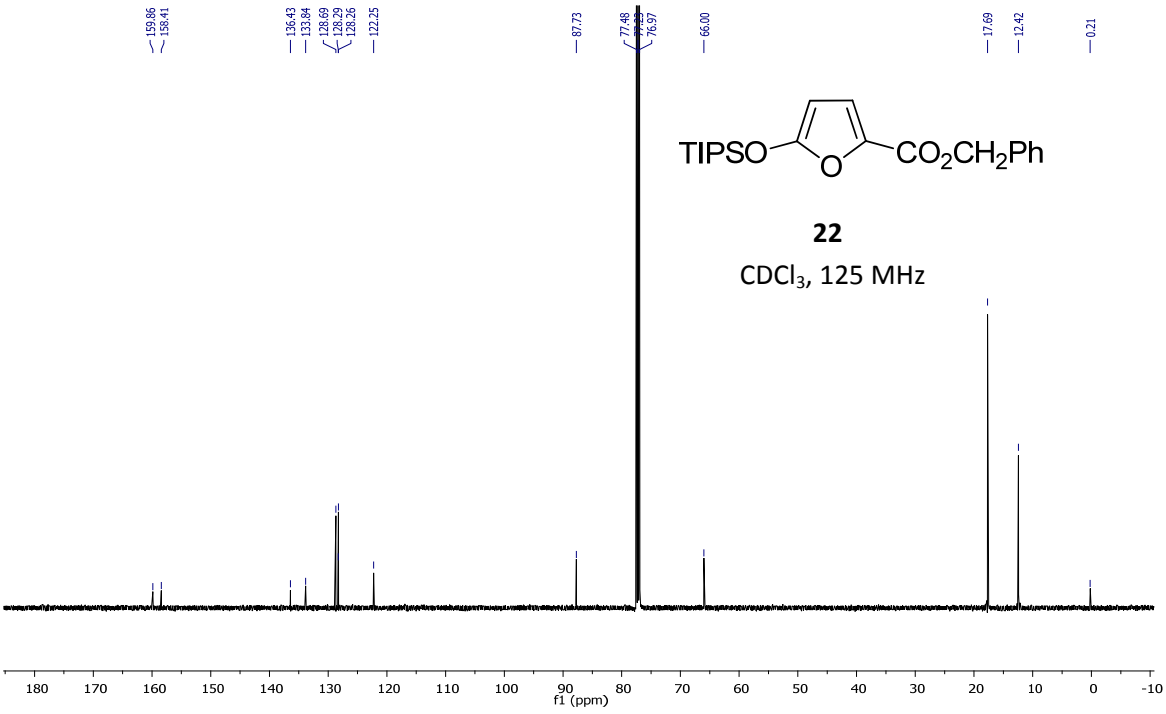
4.34
21.80
f1 (ppm)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158.41
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77.48
77.23
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O
CO2CH2Ph
22
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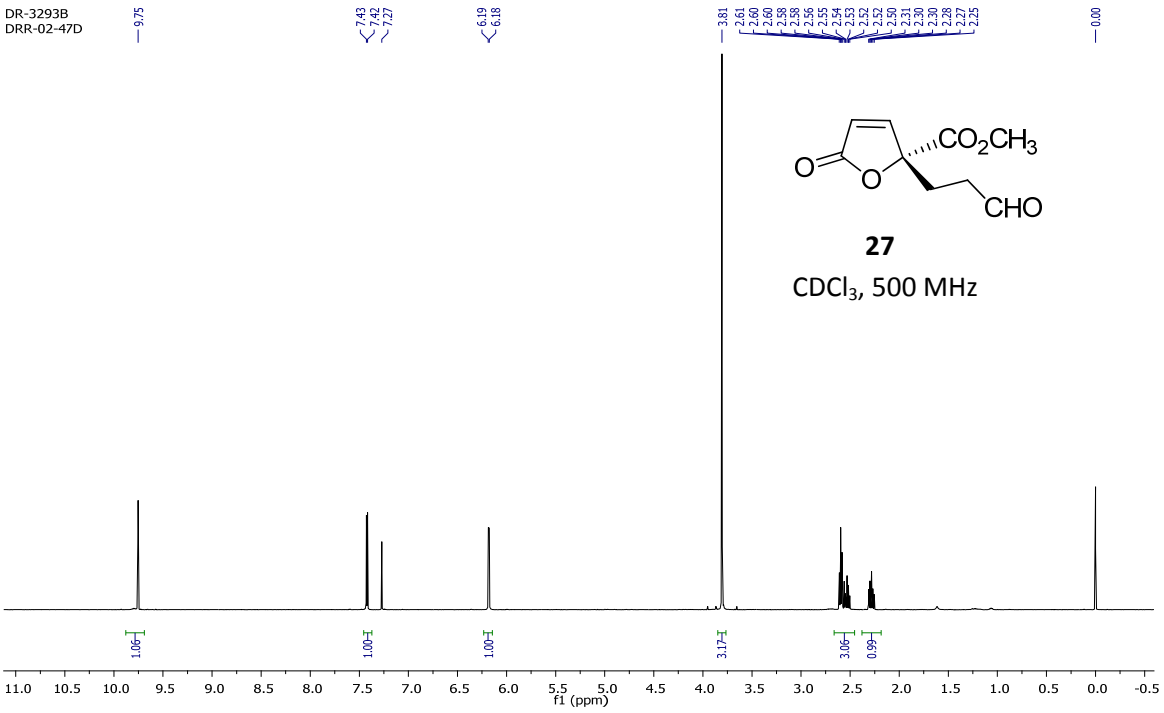
f1 (ppm)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7.42
7.27
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6.18
3.81
2.61
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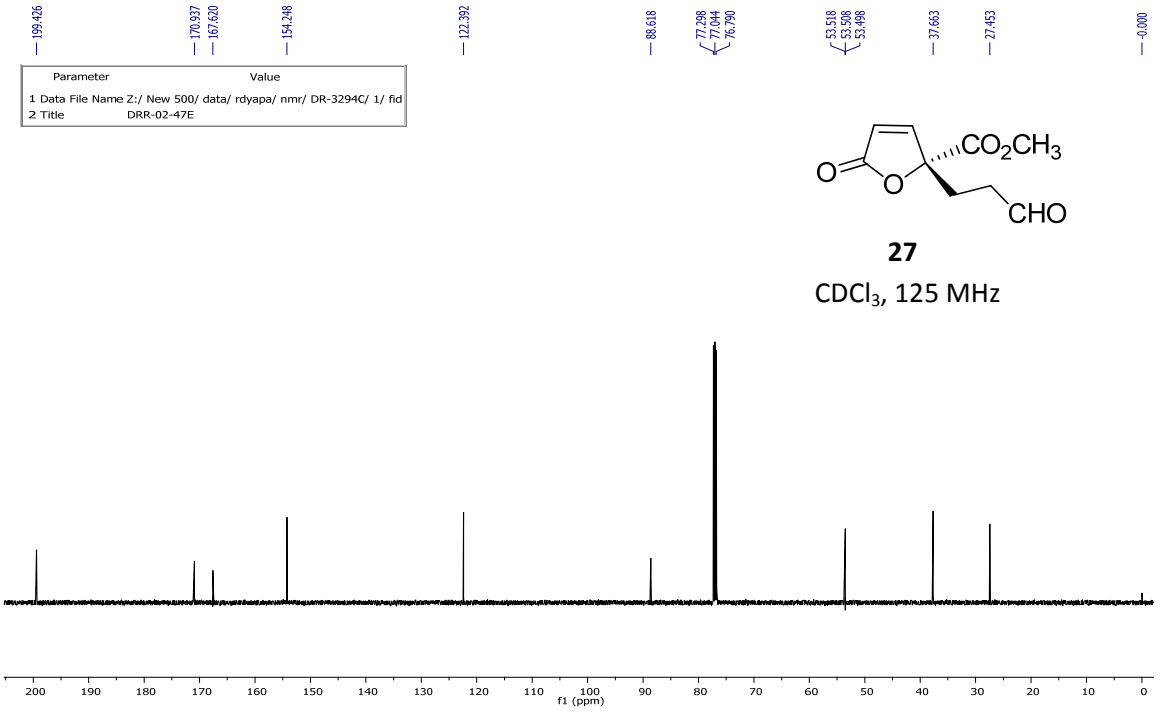
2.56
2.55
2.54
2.53
2.52
2.52
2.50
2.31
2.30
2.30
2.28
2.27
2.25
0.00
CO2CH3
O
O
CHO
27
CDCl3, 500 MHz
1.06
1.00
1.00
3.17
3.06
0.99
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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167.620
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37.663
27.453
0.000
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Value
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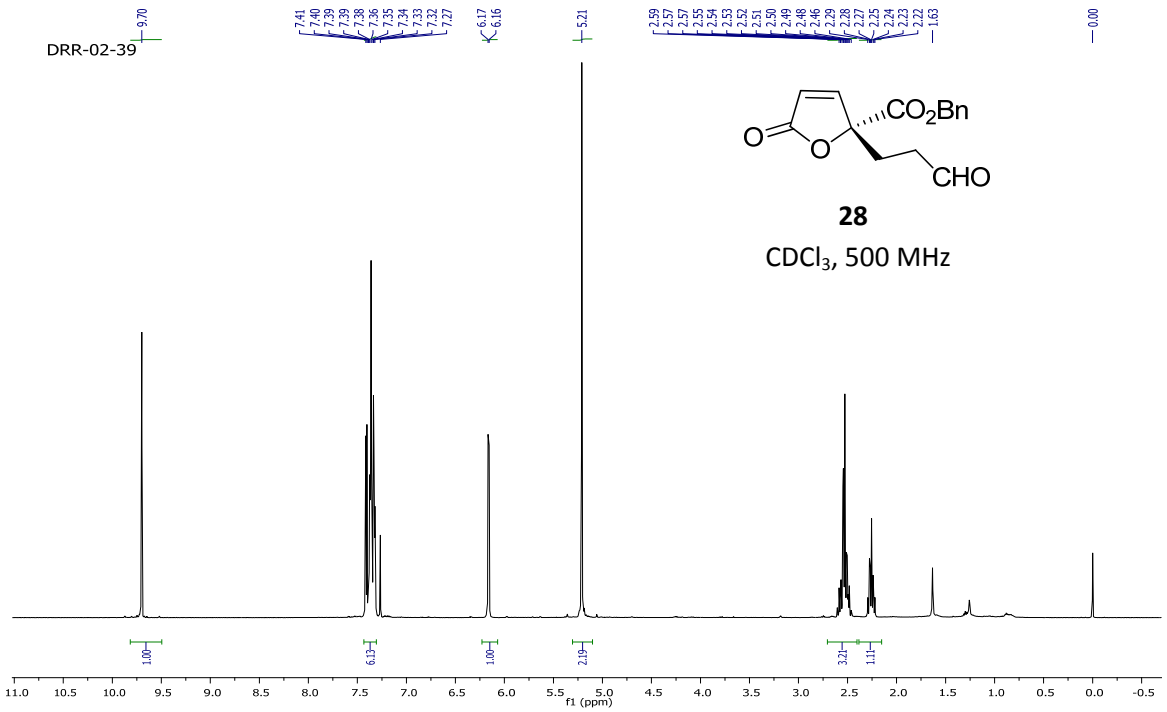
f1 (ppm)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CHO
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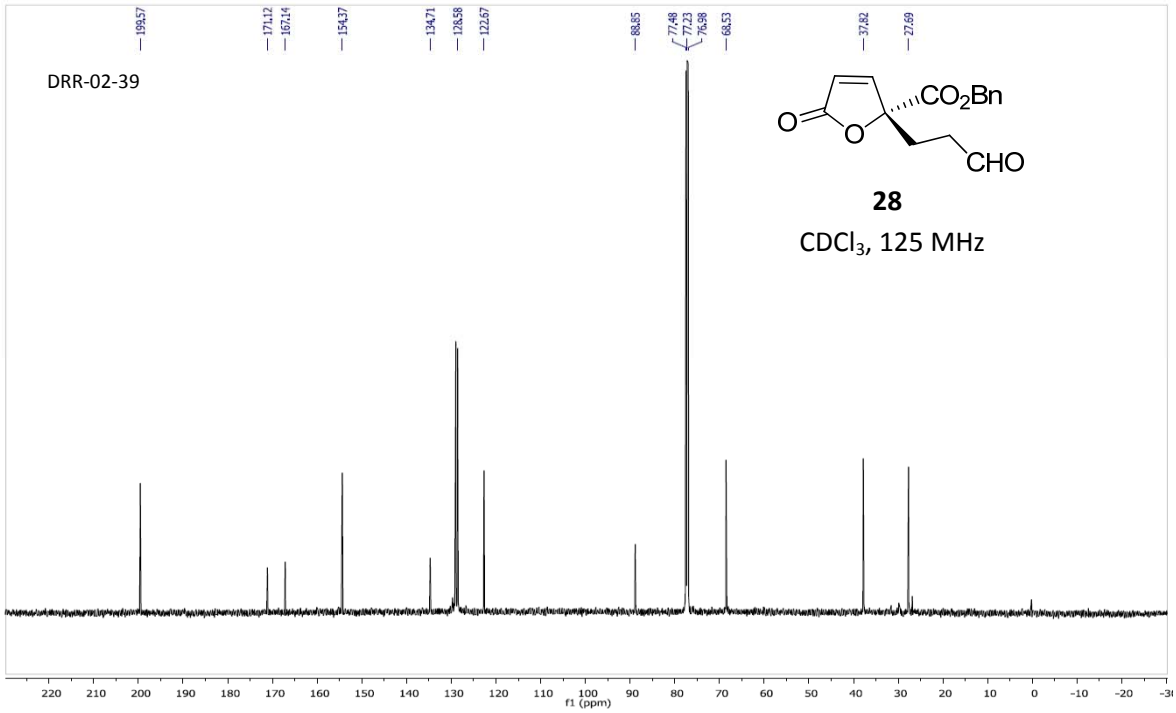
f1 (ppm)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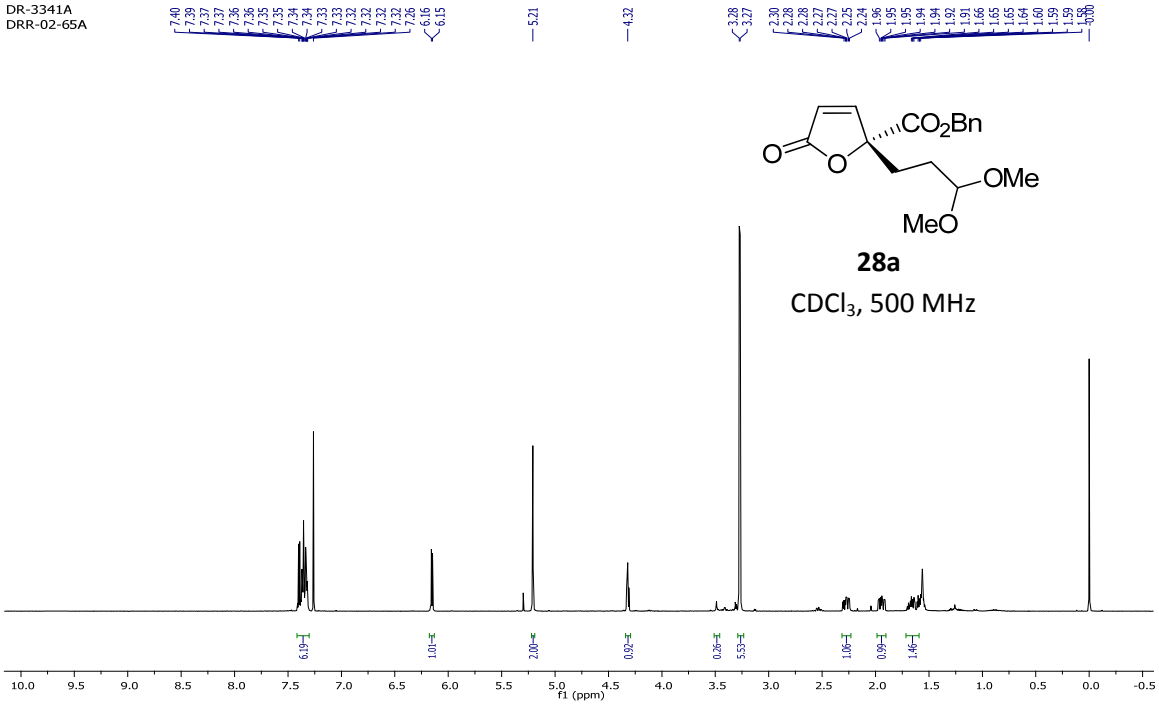
O
O
CHO
28
CDCl3, 125 MHz
f1 (ppm)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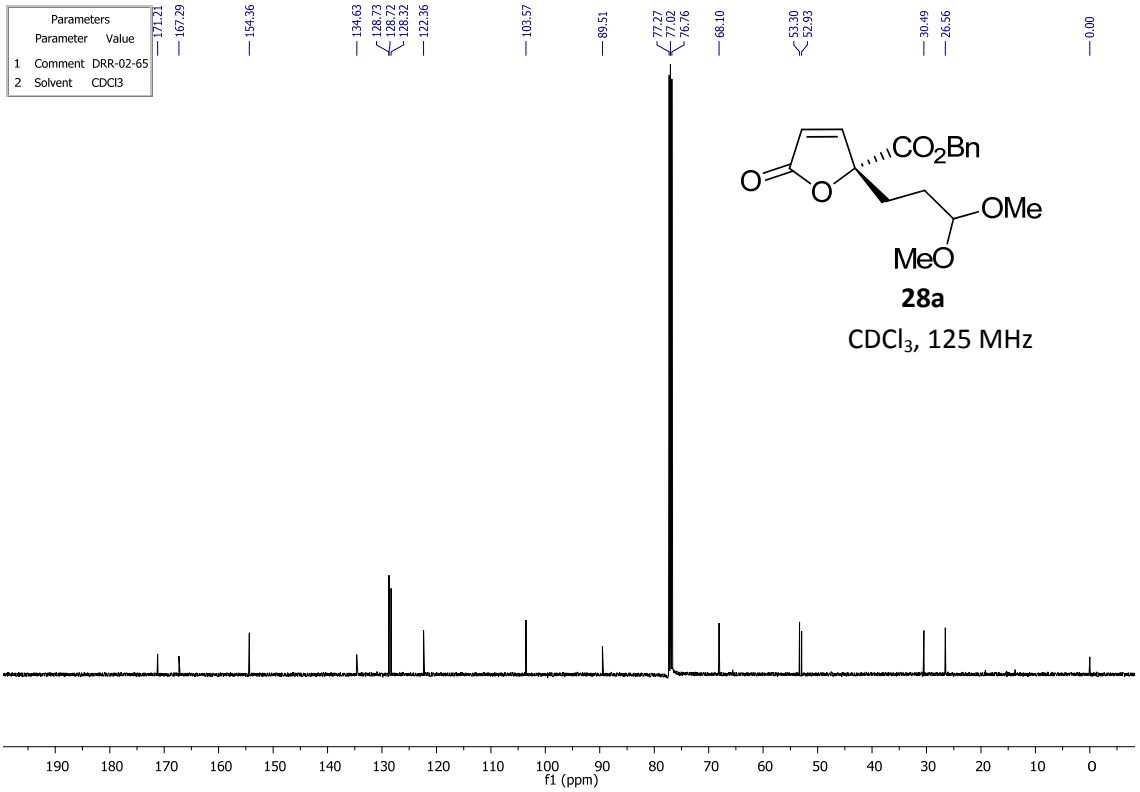
5.21
4.32
3.28 3.27
2.30 2.28 2.28 2.27 2.27 2.25 2.24 1.96 1.95 1.95 1.94 1.94 1.92 1.91 1.66 1.65 1.64 1.60 1.59 1.59 1.58 0.00
CO2Bn
O
O
OMe
MeO
28a
CDCl3, 500 MHz
6.19 1.01 2.00 0.92 0.26 5.53 1.08 0.99 1.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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CO2Bn
O
O
OMe
MeO
28a
CDCl3, 125 MHz
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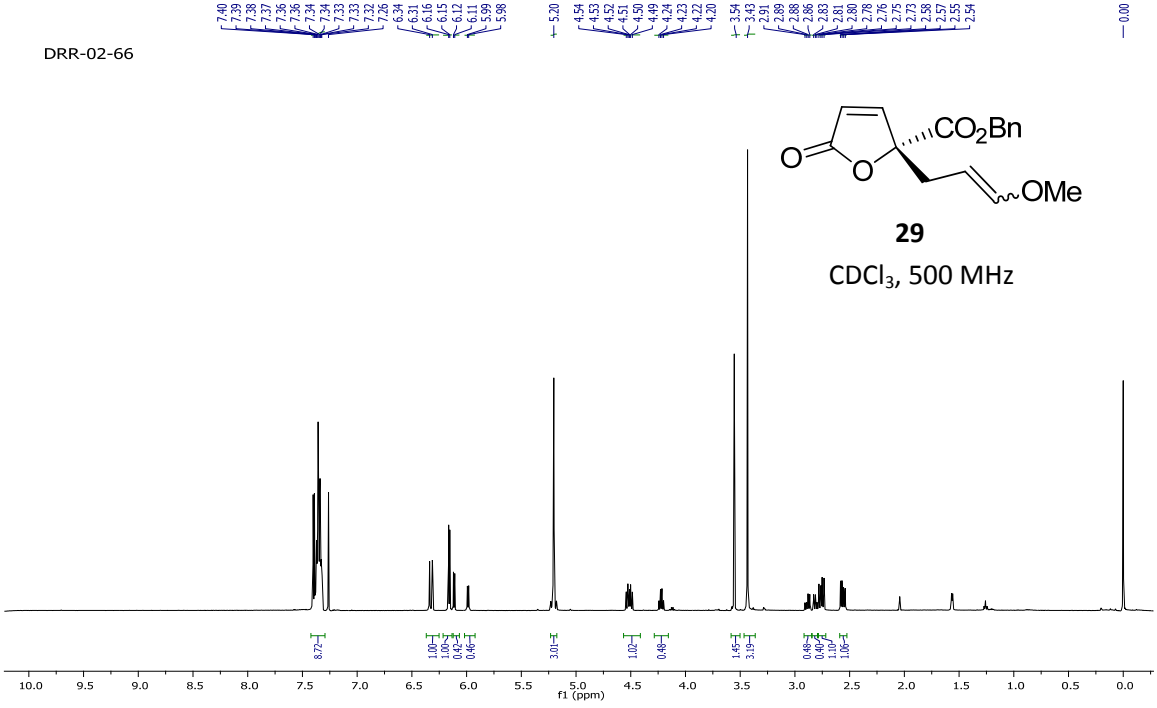
f1 (ppm)

DRR-02-66



29

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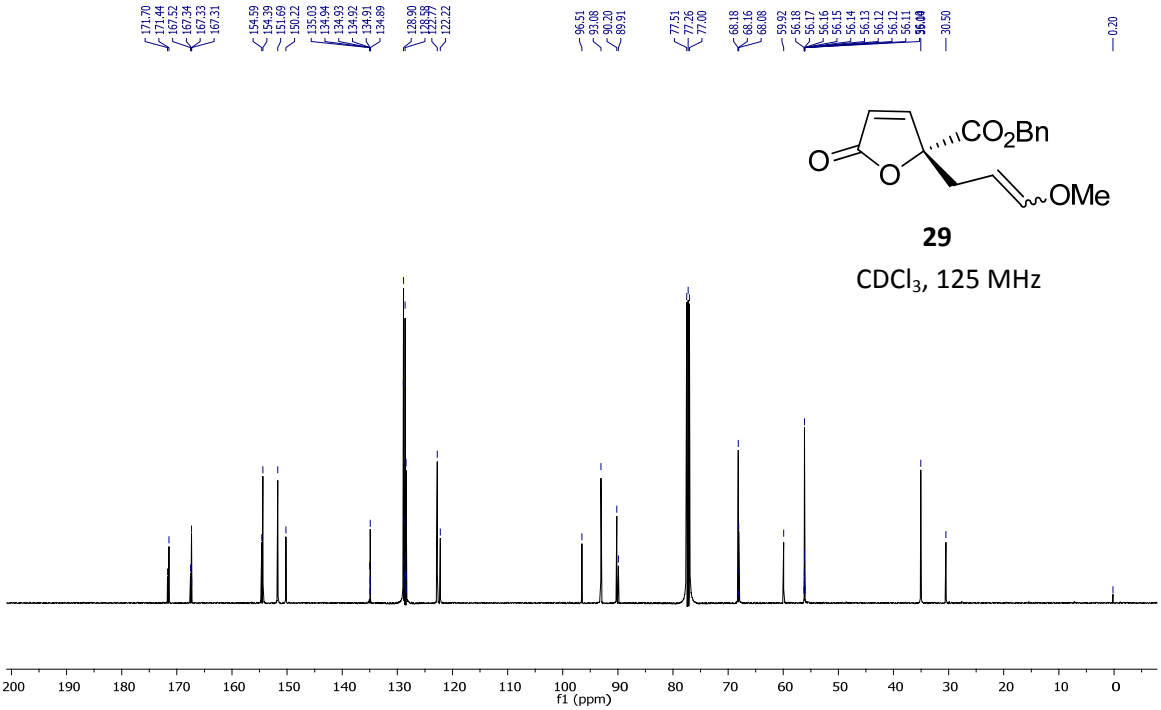
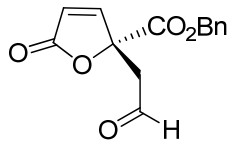


29

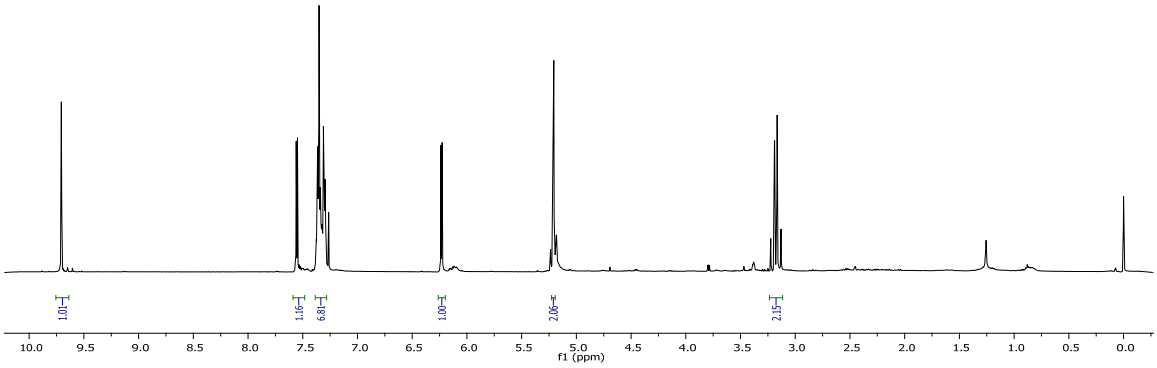
$CDCl_3$, 125 MHz

DRR-02-67



29a

$CDCl_3$, 500 MHz



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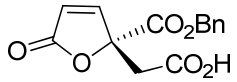

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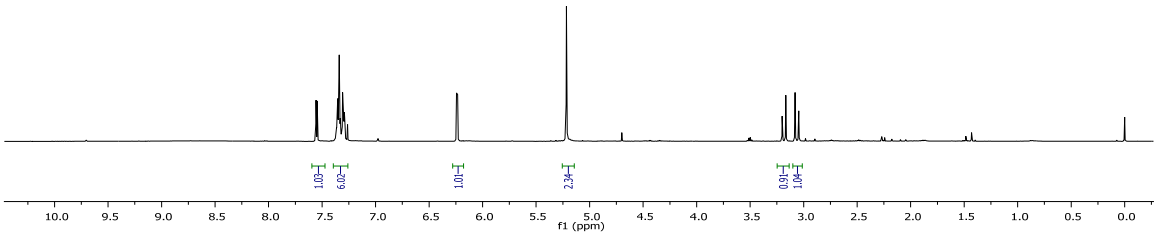

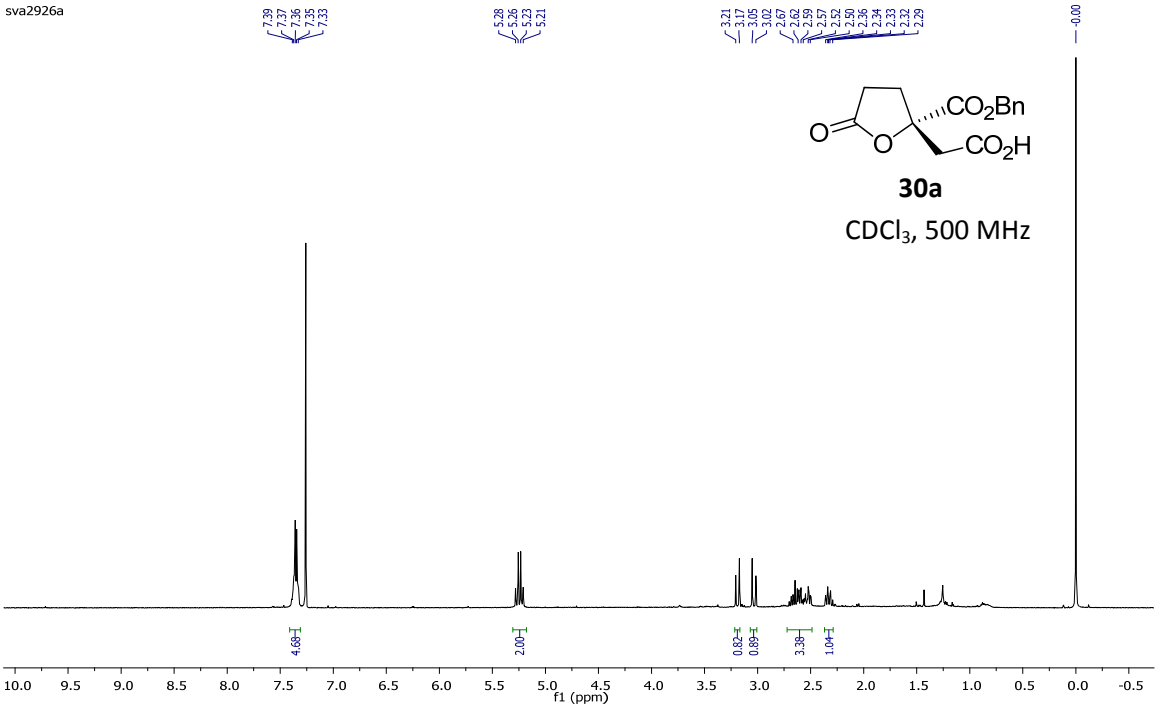
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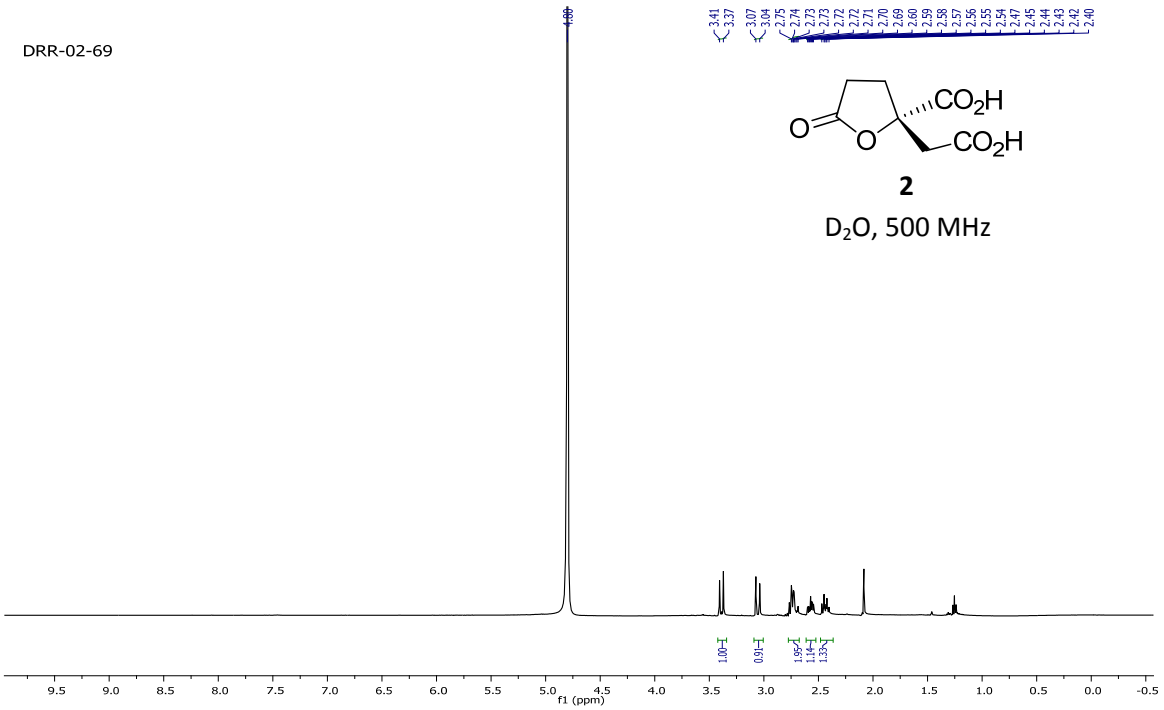
7.37
7.36
7.35
7.33
5.28
5.26
5.23
5.21
3.21
3.17
3.05
3.02
2.67
2.62
2.59
2.57
2.52
2.50
2.36
2.34
2.33
2.32
2.29
0.00
CO2Bn
O
O
CO2H
30a
CDCl3, 500 MHz
4.68
2.00
0.82
0.89
3.38
1.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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3.07
3.04
2.75
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2.73
2.72
2.71
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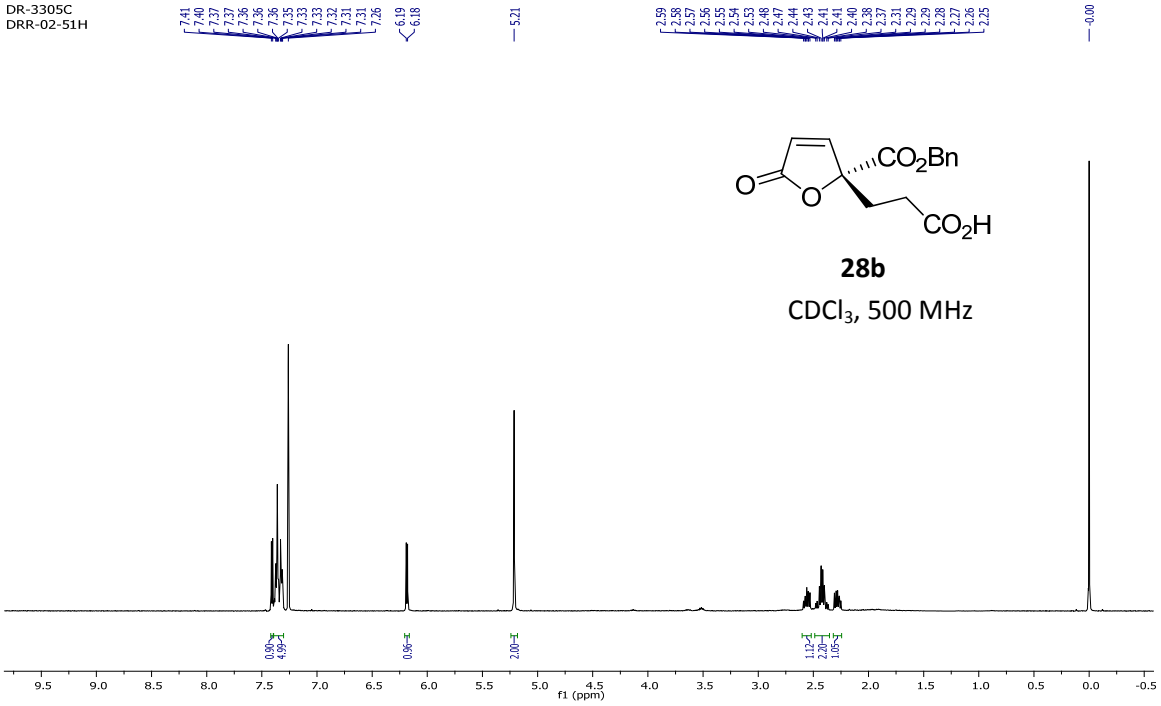
2.60
2.59
2.58
2.57
2.56
2.55
2.54
2.47
2.45
2.44
2.43
2.42
2.40
CO2H
O
O
CO2H
2
D2O, 500 MHz
1.00
0.91
1.95
1.34
1.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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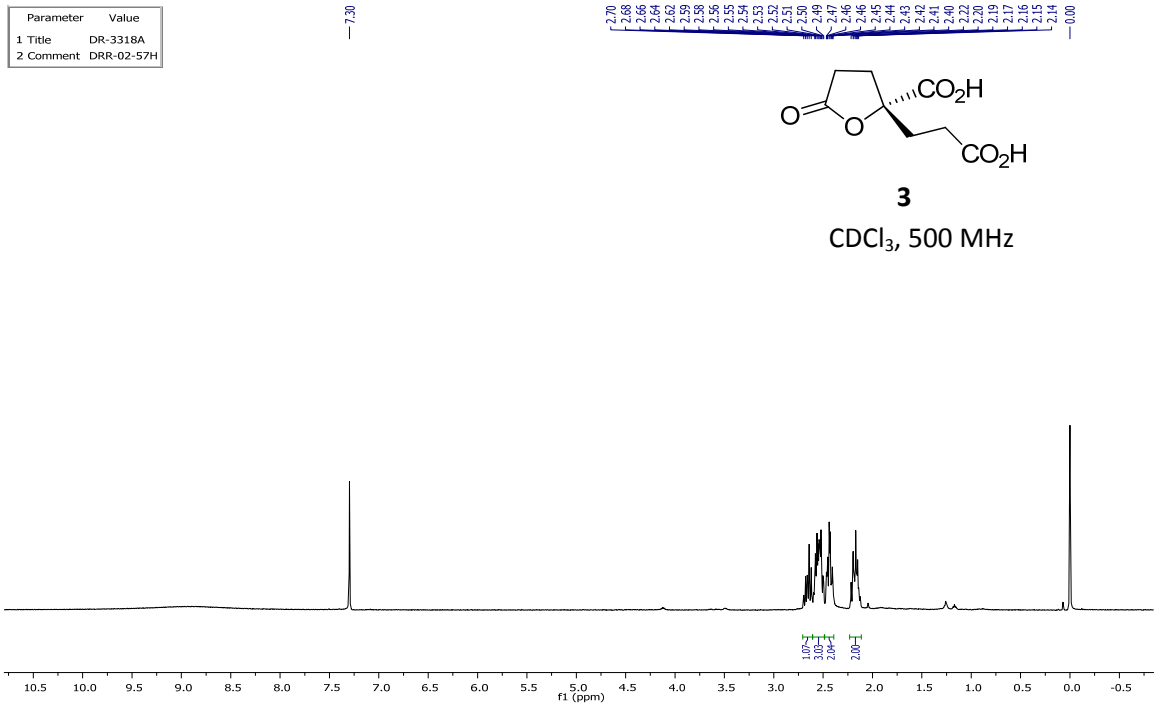
5.21
2.59 2.58 2.57 2.56 2.55 2.54 2.53 2.48 2.47 2.44 2.43 2.41 2.41 2.40 2.38 2.37 2.31 2.29 2.29 2.28 2.27 2.26 2.25
0.00
CO2Bn
O
O
CO2H
28b
CDCl3, 500 MHz
0.90 4.99 0.96 2.00 1.12 2.01 1.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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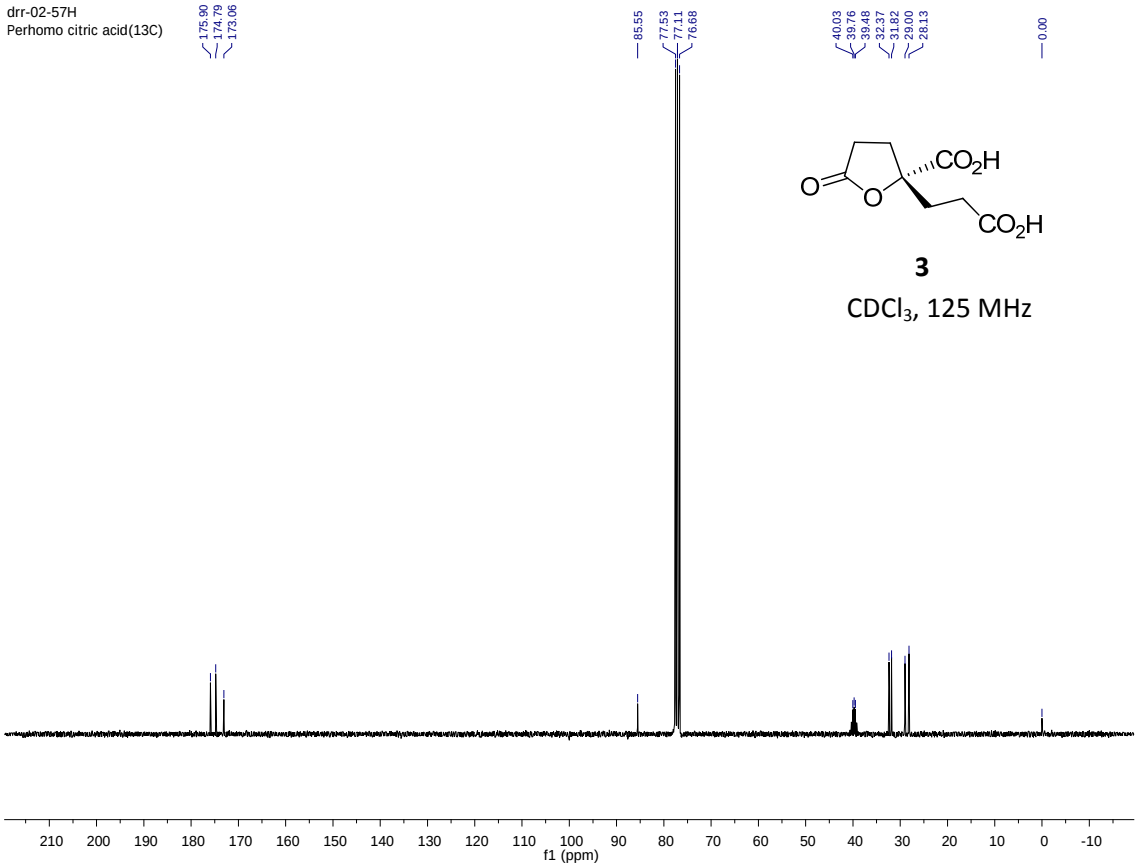
0.00
CO2H
O
O
CO2H
3
CDCl3, 500 MHz
1.07 3.03 2.04 2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


drr-02-57H
Perhomo citric acid(13C)
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174.79
173.06
85.55
77.53
77.11
76.68
40.03
39.76
39.48
32.37
31.82
29.00
28.13
0.00
CO2H
O
O
CO2H
3
CDCl3, 125 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Chapter 3

A Simple Enantioselective Route to Functionalized Indolizidines. Synthesis of (+)-Antofine

This chapter is based on the following publication:

Pansare, S.V.; Lingampally, R.; Dyapa, R. *Eur. J. Org. Chem.* **2011**, 2235–2238

Contribution of authors

S. V. Pansare: Research supervisor, manuscript preparation

R. Lingampally: Synthetic experimental work on ipalbidine, which is the second target molecule prepared in the above publication, and manuscript preparation

R. Dyapa: Synthetic experimental work and manuscript preparation

3.1 Introduction

The indolizidine motif is a prominent structural unit in numerous alkaloids[1] and also constitutes a major class of glycosidase inhibitors.[2] In addition, several indolizidines have an interesting biological profile which includes antibacterial, antiviral, antitumor and antidiabetic properties.[3] Aryl-substituted indolizidines are also of interest; either as bioactive natural products[4] or as peptidomimetics.[5] Accordingly, the synthesis of arylindolizidines continues to be intensely investigated and general synthetic strategies toward aryl-fused[6a-c] or aryl-substituted indolizidines[6d-h] as well as other functionalized indolizidines have been reported.[7] The phenanthroindolizidine alkaloid (-)-antofine, an enantiomer of (+)-antofine, has potent anticancer activity.[8] The anticancer activity may occur through the inhibition of protein and nucleic acid synthesis.[9] Antofine has also shown other medicinal properties, including antibiotic, antifungal and antiviral activity.[10]

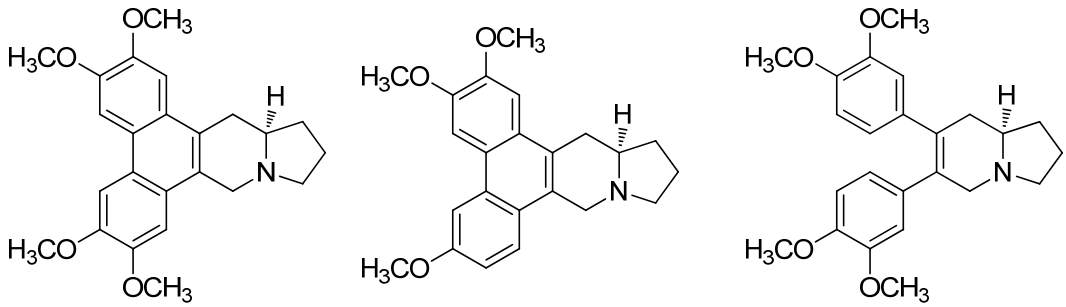
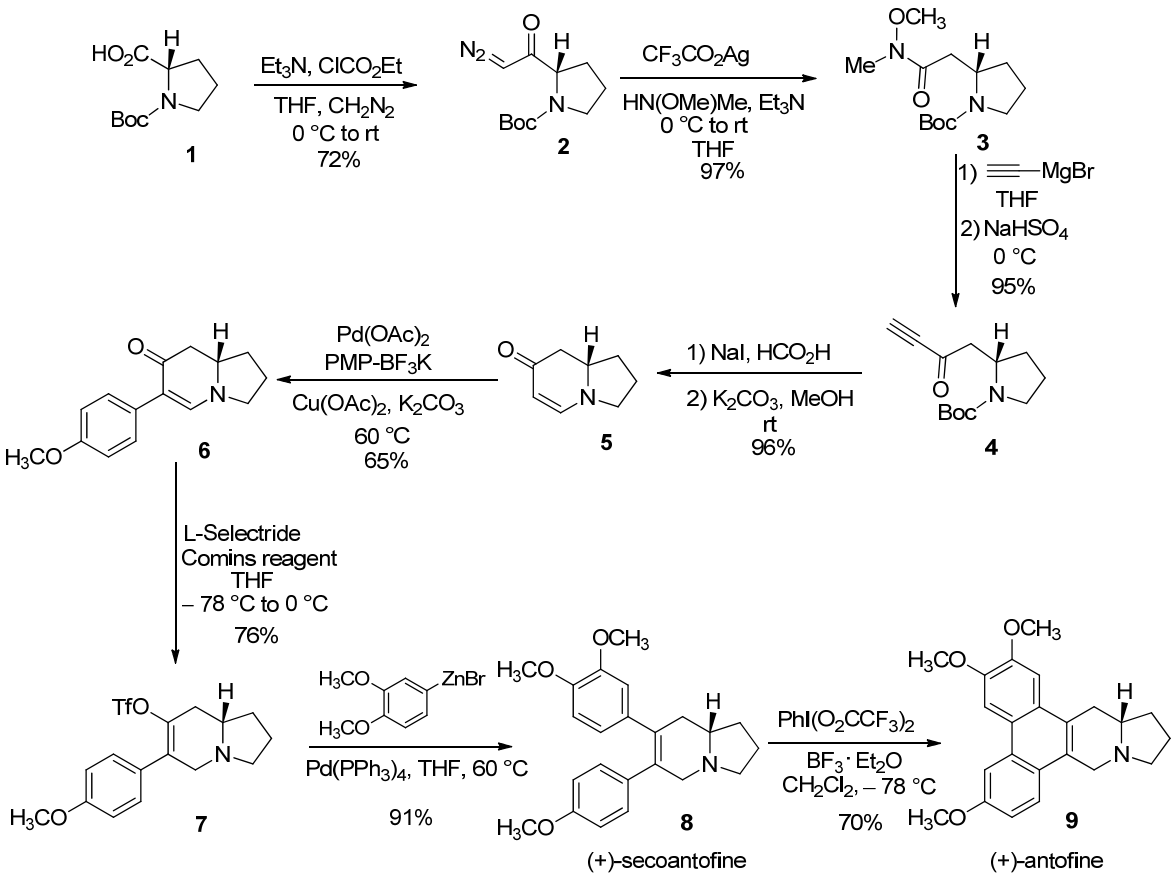


Figure 3.1 Structures of selected phenanthroindolizidine alkaloids

3.2 Recent syntheses of (+)-antofine

The following summary provides an overview of the recent reports since 2010 on the synthesis of enantiomerically pure antofine.

In 2010, Georg and co-workers reported an enantioselective total synthesis of (+)-antofine (Scheme 3.1).[11a] Their synthesis starts with Boc-*S*-proline (**1**), which was homologated using standard Arndt-Eistert reaction conditions. The acid was first converted into diazoketone **2** which was then subjected to a Wolff rearrangement with catalytic CF_3CO_2Ag in the presence of freshly distilled *N*,*O*-dimethylhydroxylamine to provide the Weinreb amide **3**. Ynone **4** was prepared by treatment of **3** with ethynylmagnesium bromide.

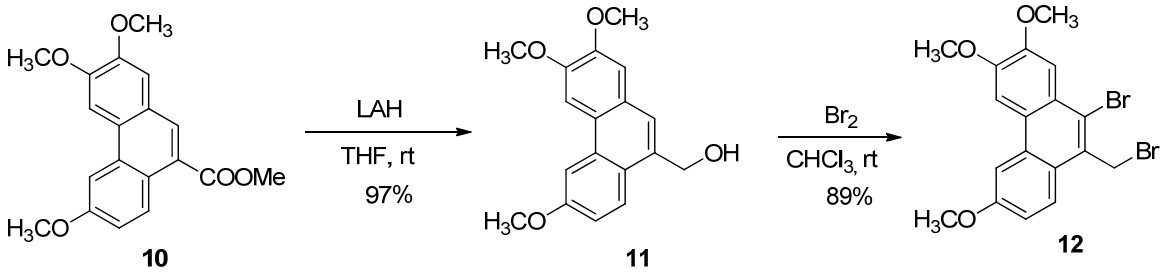


Scheme 3.1

Initially, enaminone **5** was prepared from the ynone **4** by stepwise treatment with aqueous HCl in dioxane followed by addition of methanolic K_2CO_3. However, this protocol led to racemization of **4**. Alternatively, a milder deprotection protocol (formic acid and NaI) was used to minimize racemization of **4**. Treatment of the obtained vinyl iodide with K_2CO_3 gave enaminone **5**. A Pd(II)-catalyzed C-H arylation of **5** with an appropriate organotrifluoroborate produced the arylindolizidinone **6**. 1,4-Reduction of enaminone **6** using L-selectride and trapping of the resulting enolate with 2-(*N*,*N*-bis(trifluoromethanesulfonyl)amino)-5-chloropyridine (Comins reagent) provided the

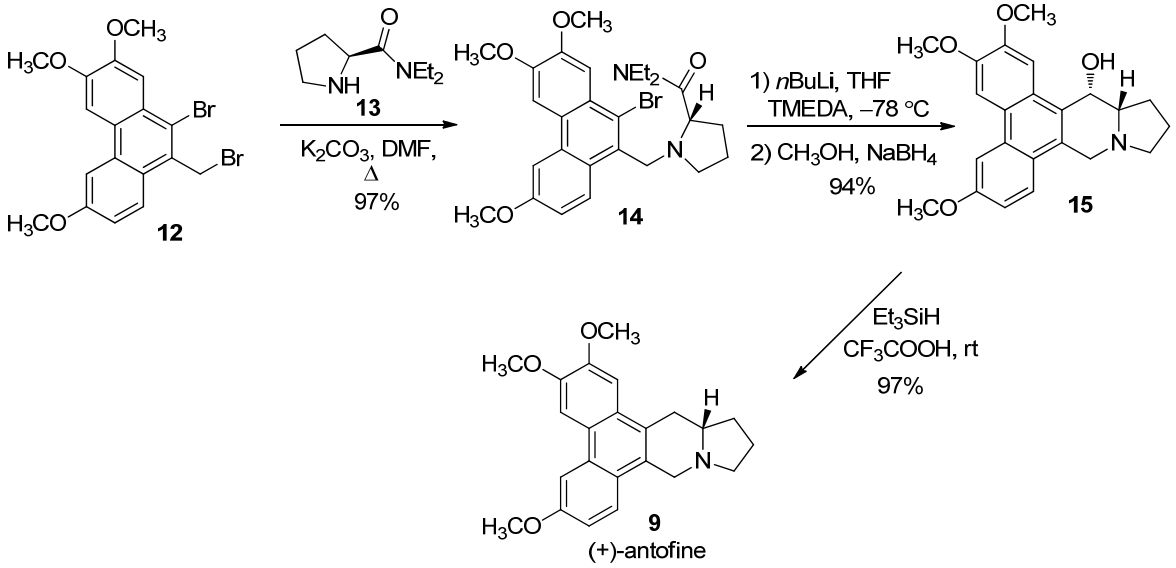
triflate **7**. (+)-Secoantofine (**8**) was prepared from 3,4-dimethoxyphenylzinc bromide and triflate **7**, using the Negishi cross-coupling protocol. In the final step, the phenanthrene framework was constructed with a $PhI(O_2CCF_3)_2$ mediated oxidative cyclization involving the aryl groups to provide the title compound (+)-antofine.

Wang and coworkers reported a short and efficient route to enantiomerically pure antofine, involving Parham-type cycloacylation as the key step.[11b] The synthesis began with ester **10** which was prepared by a procedure described by Wang and co-workers.[12,13] Reduction of ester **10** using LAH provided alcohol **11**. Alcohol **11** was brominated to afford the dibromo compound **12**. Amide **14** was prepared from the alkylation of (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (**13**) with dibromide **12**, using K_2CO_3 as a base (Scheme 3.2).



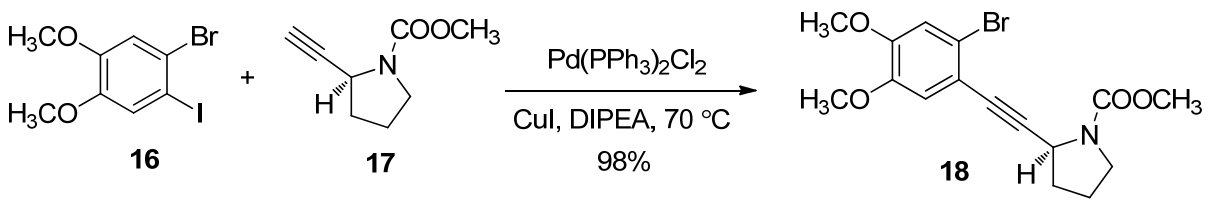
Scheme 3.2

Amide **14** was treated with *n*BuLi to effect ring closure. Subsequent reduction of the ketone ($NaBH_4$) obtained in the cyclization step provided the aminol **15** stereoselectively. Dehydroxylation of **15** using triethylsilane and trifluoroacetic acid provided the title compound (+)-antofine (Scheme 3.3).



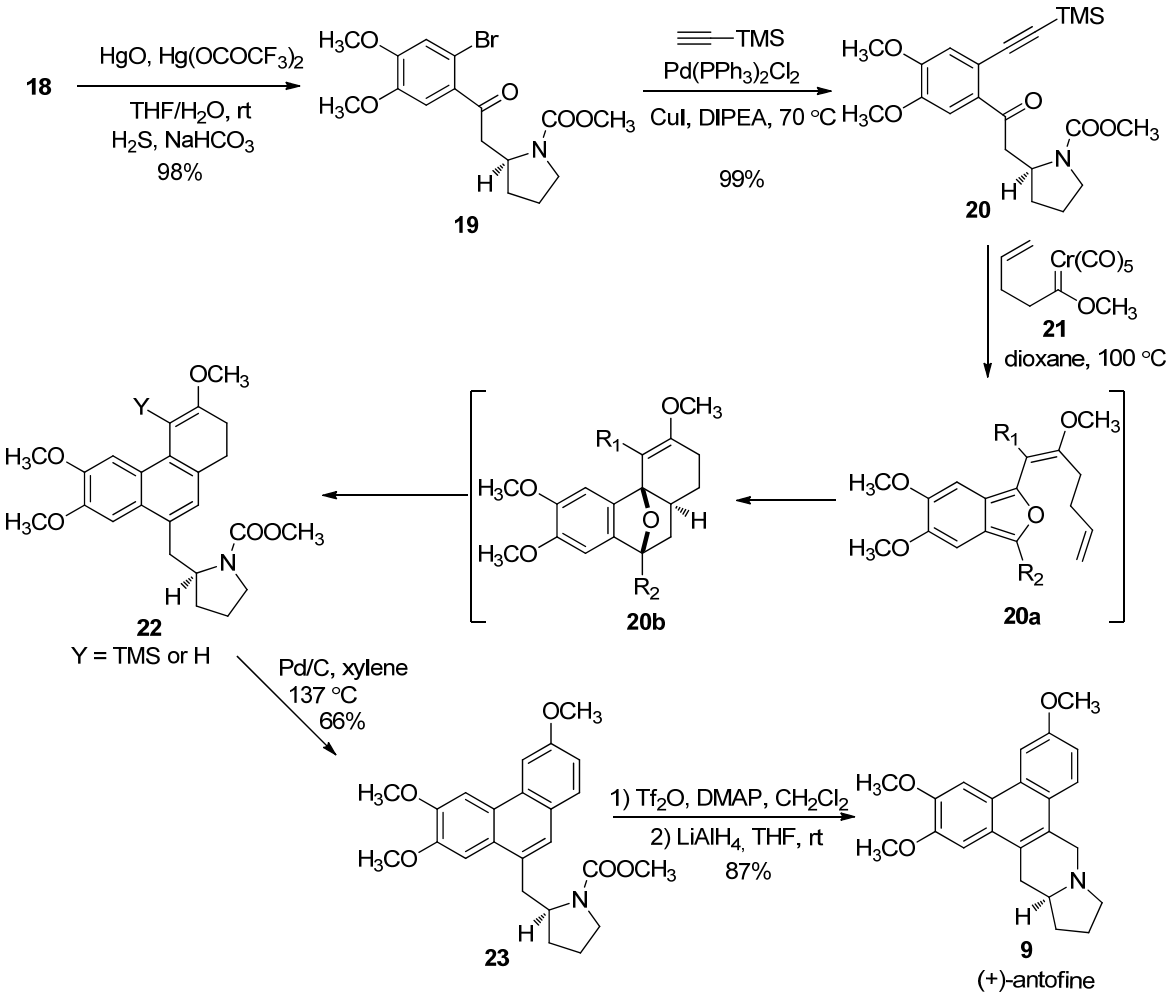
Scheme 3.3

Herndon and co-workers reported an enantioselective synthesis of (+)-antofine. The key steps in their synthesis are alkyne hydration, a chromium-carbene complex mediated net [5 + 5] cycloaddition process and a Bischler-Napieralski cyclization reaction.[14] The synthesis began with enantiomerically pure 2-ethynylpyrrolidine derivative **17** which was prepared in seven steps from Boc protected proline by using previously reported methods.[15] Sonogashira coupling of dihaloveratrole derivative **16** with **17** provided the bromoalkyne **18** (Scheme 3.4).



Scheme 3.4

Hydration of bromoalkyne **18** using mercuric trifluoroacetate, mercuric oxide and sodium hydrogen carbonate afforded the ketone **19** regioselectively. Sonagashira coupling of TMS-acetylene with bromoketone **19** afforded the ketone **20**. Phenanthrene derivative **23** was obtained from a net [5 + 5] cycloaddition of ketone **20** and the carbene complex **21** involving a tandem process (isobenzofuran **20a** formation followed by exo-selective intramolecular Diels-Alder reaction to form benzo-oxanorbornene **20b,** opening of the benzo-oxanorbornene ring system followed by dehydration step).

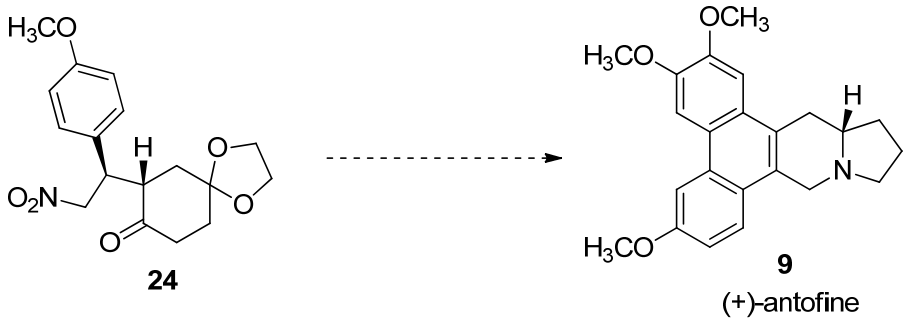


Scheme 3.5

Dehydrogenation of compound **22** using palladium on carbon provided **23**. Bischler-Napieralski-type cyclization of phenantherene derivative **23**, using triflic anhydride, provided the corresponding cyclic amide which was reduced to the title compound (+)-antofine (Scheme 3.5).

3.3 Objective

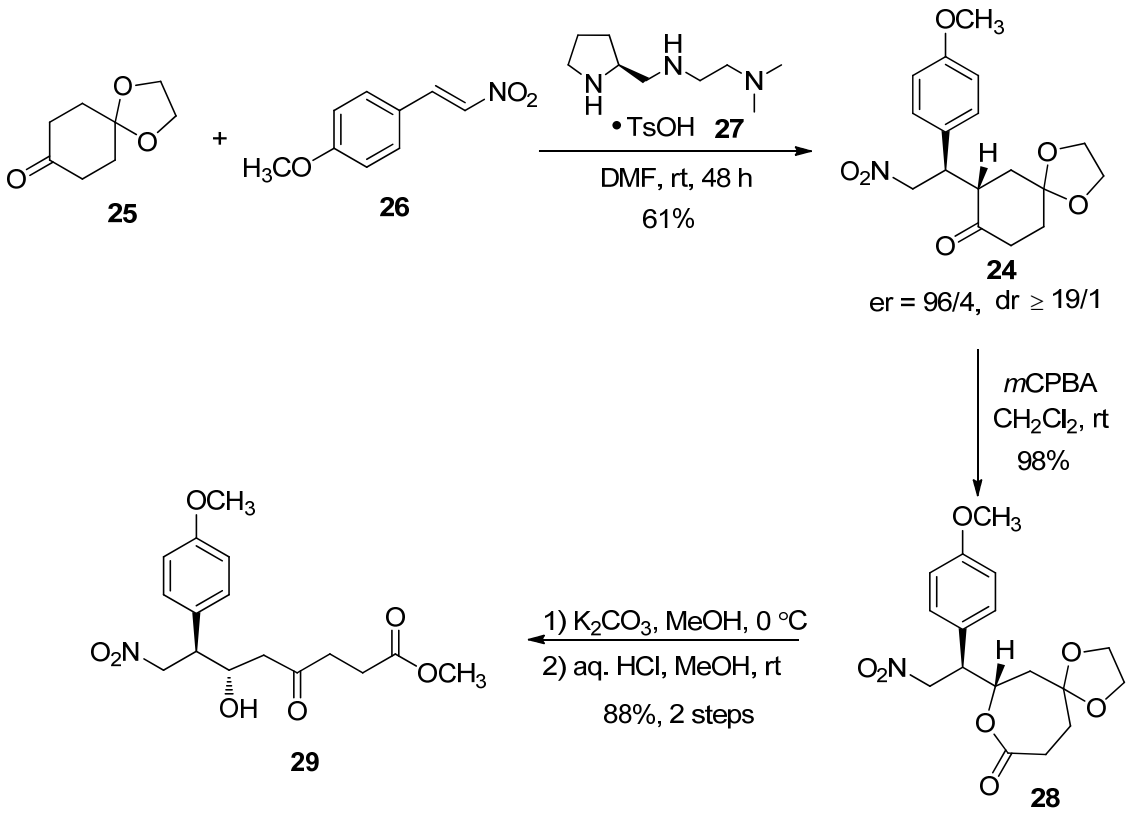
Our interest in indolizidines stems from our studies on the organocatalytic synthesis of *γ*-nitroketones from cyclic ketones and 2-nitrovinylarenes via an enamine-based Michael addition reaction.[16] This reaction has been extensively studied and the development of new catalysts for the process continues at a remarkable pace.[17] Undoubtedly, the full potential of the organocatalytic ketone-nitroalkene Michael reaction will be realized only when the *γ*-nitroketone products are utilized in target oriented synthesis, but this has been relatively unexplored.[18] We therefore chose to examine the application of *γ*-nitroketone **24** (Scheme 3.6) in the synthesis of (+)-antofine (**9**).



Scheme 3.6

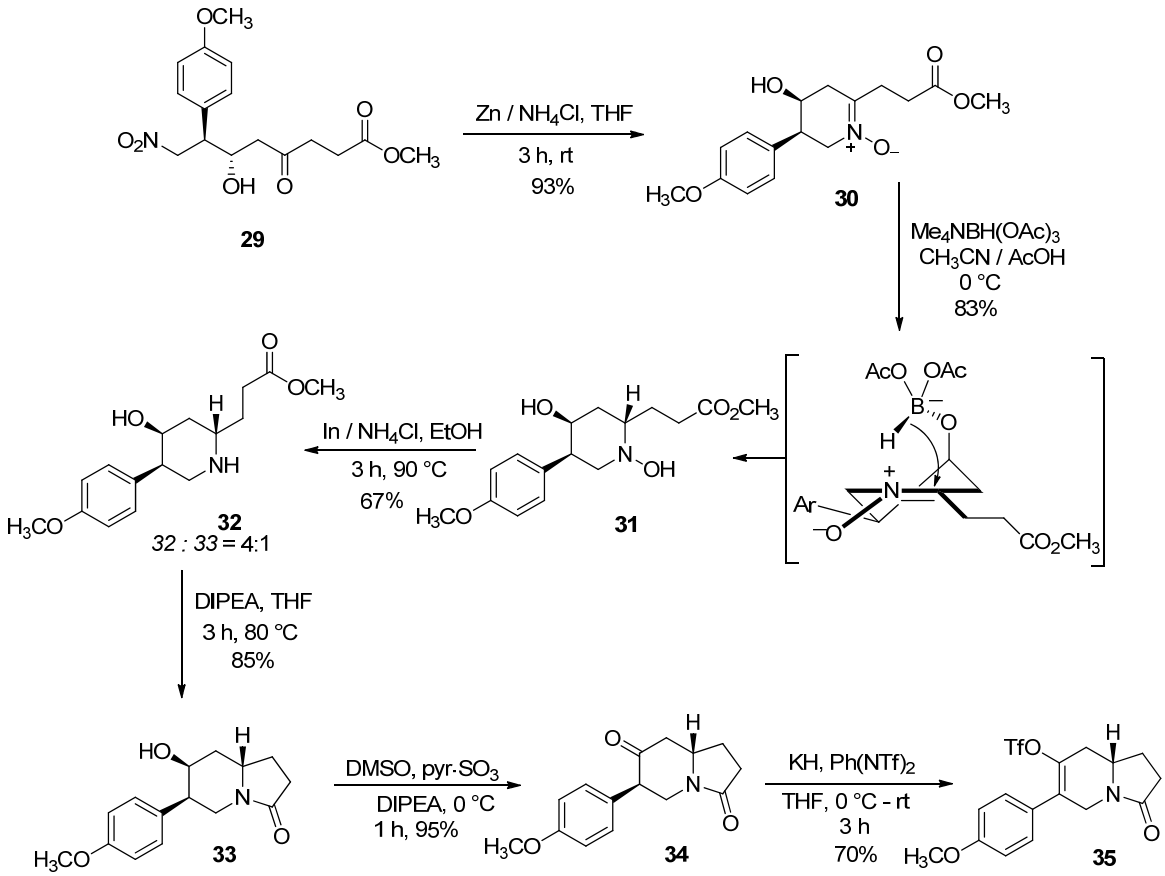
3.4 Results and discussion

Our studies began with the synthesis of the appropriate *γ*-nitroketone starting material for (+)-antofine (**9**).[11] The organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal and 4-methoxy-*β*-nitrostyrene, employing the triamine salt catalyzed protocol[16a] developed in the Pansare group, provided the nitroketone **24** in good yield and stereoselectivity (er = 96/4, dr >19/1). Baeyer-Villiger oxidation of **24** provided the lactone **28** in excellent yield (98%). Methanolysis of **28** and subsequent hydrolysis of the ketal generated the highly functionalized octanoate **29** (Scheme 3.7, 88% over two steps) that has all the required carbon atoms for the indolizidine framework.



Scheme 3.7

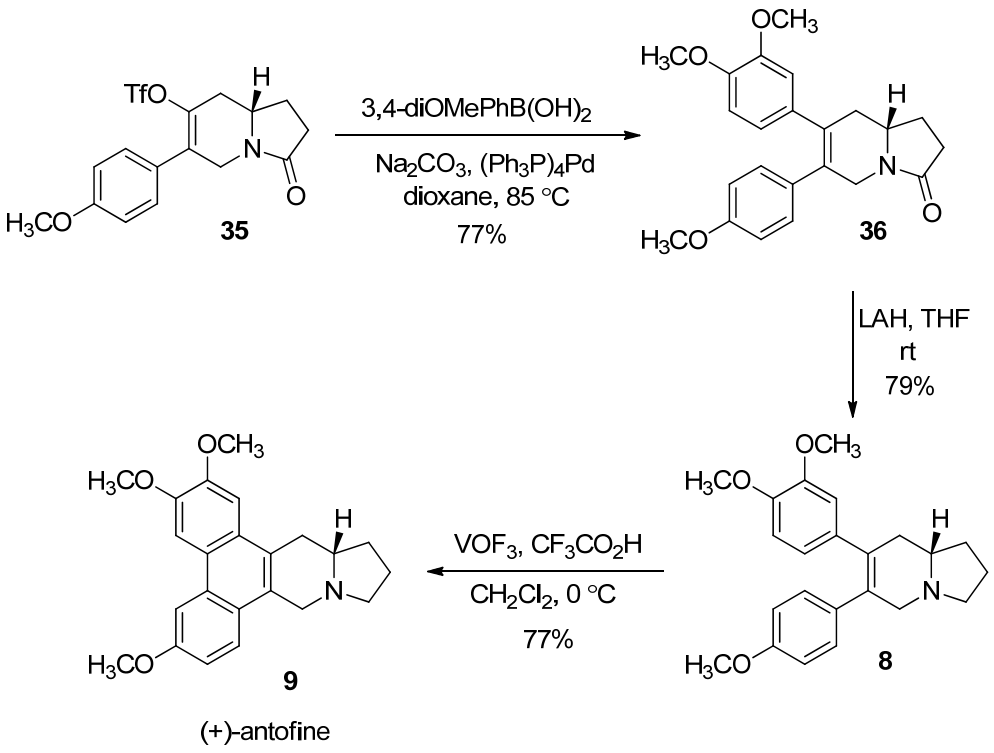
Reduction of the nitroketone **29** with zinc in aq. ammonium chloride provided the nitrone **30** which was anticipated to undergo a stereoselective reduction due to the 1,3 disposition with the secondary alcohol stereocenter. Treatment of **30** with L-Selectride® or LAH at -78 ^{o}C resulted in reduction of the ester. Reduction with $NaBH_4$ was stereorandom and also led to reduction of the ester, indicating the need for a milder reducing agent. Accordingly, $Me_4NBH(OAc)_3$ was examined which gratifyingly provided the hydroxylamine **31** (83%) as a single diastereomer, presumably via a hydroxyl-directed reduction (Scheme 3.8). At this stage, **31** was assigned the shown stereochemistry which was assumed to derive from an intramolecular, hydroxyl directed reduction of **30**.[19] Reduction of the N-O bond in **31** was achieved with indium metal to provide a mixture of the amino ester **32** and the corresponding indolizidinone **33** resulting from cyclization of the amino ester. This product mixture was treated with DIPEA in refluxing isopropyl alcohol to complete the lactamization (Scheme 3.8).



Scheme 3.8

The synthesis of (+)-antofine (**9**) was achieved from the lactam **33**. Oxidation of **33** (pyridine.SO_3) provided the ketolactam **34**. Conversion of **34** to the enol triflate **35** followed by a Suzuki-Miyaura coupling[20] of **35** with 3,4-dimethoxyphenylboronic acid furnished the lactam **36**. Reduction of the amide in **36** provided secoantofine **8**. Finally, oxidative biaryl coupling in **8** employing VOF_3 provided (+)-antofine (Scheme 3.9)

(**9**, 77%)



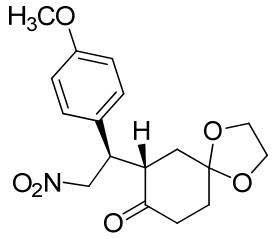
Scheme 3.9

3.5 Conclusion

In conclusion, an organocatalytic Michael addition based enantioselective synthesis of the indolizidine framework was developed. This approach has potential applications in the synthesis of congeners and analogs of the target alkaloids[1a] by a) variation in the ketone, nitrostyrene and the aryl cross-coupling partner, and b) embellishment of the propanoate side chain in **31**. The utility of our strategy is augmented by the large number of methods available for the stereoselective synthesis of a variety of *γ*-nitroketones.[21]

3.6 Experimental section

(7*S*)-7-[(1*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-one (24):

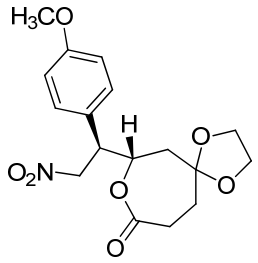


To a solution of 1,4-cyclohexanedione monoethylene ketal (13.0 g, 83.7 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine[16] (572 mg, 3.34 mmol) and *p*-toluenesulfonic acid monohydrate (634 mg, 3.34 mol) was added a solution of 4-methoxy-*β*-nitrostyrene (3.00 g, 16.7 mmol) in DMF (30 mL) and the resulting solution was stirred at ambient temperature for 48 h. Ethyl acetate (100 mL) was added and the solution washed with water, aq. HCl (3 N), dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash chromatography on silica gel to provide 4.60 g of a solid. This was dissolved in ethyl acetate (23 mL) and precipitated by addition of hexanes (70 mL). The procedure was repeated once to provide 3.50 g (62%) of **24** with 96% ee. In repeated runs, **24** was obtained in 90-96% ee.

IR (neat): 2897, 2360, 1712, 1548, 1512, 1247, 1132, 1026, 950, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.91 (dd, 1H, J = 12.3, 4.8, CH_2NO_2), 4.56 (dd, 1H, J = 12.3, 9.9, CH_2NO_2), 4.00-3.83 (m, 4H, OCH_2CH_2O), 3.78 (s, 3H, OCH_3), 3.04-2.98 (m, 1H, ArC*H*), 2.72-2.66 (dt, 1H, J = 13.8, 6.4, COC*H*), 2.48-2.43 (m, 1H, COCH_2), 2.07-2.01 (m, 1H, COCH_2), 1.98-1.92 (dt, 1H, J = 13.3, 5.2, CHCH_2), 1.72-1.68 (m, 1H, CHCH_2), 1.57-1.51 (apparent t, 2H, J = 13.4,

CH_2CH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.4 (*C*O), 159 (Ar*C*), 129.2 (2xAr*C*), 129.0 (Ar*C*), 114.4 (2xAr*C*), 107.1 (O*C*O), 79.1 (CH_2NO_2), 64.8 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 55.2 (OCH_3), 48.3 (CO*C*H), 42.7 ($CHCH_2NO_2$), 39.3 ($COCH_2$), 38.6 (CH_2), 35.1 (CH_2); MS (APCI, pos.): *m/z* 336 (M+1); HRMS (EI): *m/z* 335.1367 (335.1369 calc. for $C_{17}H_{21}NO_6$ (M^+)); HPLC (Chiralpak AS-H, hexane/2- propanol: 60/40, flow rate 1.0 mL/min, 254 nm): t_{minor} = 9.45 min, t_{major} = 12.97 min, ee = 93%, dr = 20:1 (average values from multiple reactions).

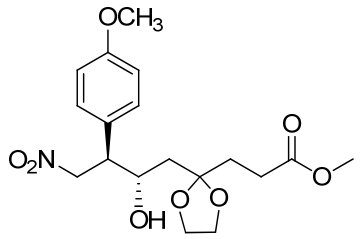
(*S*)-7-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (28):



To a solution of the nitroketone **24** (3.10 g, 9.24 mol) in anhydrous dichloromethane (60 mL) at ambient temperature, was added solid sodium phosphate (3.21 g, 12.0 mol) followed by *m*-chloroperbenzoic acid (~77%, 4.94 g, 28.7 mmol). The resulting white slurry was stirred vigorously for 16 h. Dichloromethane (100 mL) was added and the solution was washed with 5% aq. NaOH (2 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 3.20 g (98%) of **28** as a white, solid foam. This material was pure by ^1H NMR (500 MHz) and was directly used further.

IR (neat): 2962, 1736, 1550, 1514, 1249, 1154, 1117, 1099, 1029, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, 2H, J = 11.6, Ar*H*), 6.89 (d, 2H, J = 11.6, Ar*H*), 4.94 (dd, 1H, J = 12.6, 4.7, C*H*$_2$NO$_2$), 4.76-4.69 (m, 2H, C*H*$_2$NO$_2$, (CO)OC*H*)), 3.89-3.85 (m, 2H, OC*H*$_2$CH$_2$O), 3.80 (4H, OC*H*$_3$, OCH$_2$C*H*$_2$O), 3.62-3.58 (dt, 1H, J = 9.3, 4.7, Ar-C*H*), 3.54-3.51 (m, 1H, OCH$_2$C*H*$_2$O), 2.88-2.81 (m, 1H, C*H*$_2$CO), 2.65-2.60 (m, 1H, C*H*$_2$CO), 1.93-1.89 (m, 2H, C*H*$_2$(C)CH$_2$), 1.86-1.79 (m, 2H, CH$_2$(C)C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5 (*C*O), 159.5 (Ar*C*), 129.3 (2xAr*C*), 127.8 (Ar*C*), 114.6 (2xAr*C*), 107.2 (O*C*O), 77.7 (*C*H$_2$NO$_2$), 75.8 (*C*OC(O)), 65.0 (OCH$_2$*C*H$_2$O), 64.3 (O*C*H$_2$CH$_2$O), 55.3 (O*C*H$_3$), 48.1 (OCH*C*H$_2$), 41.5 (*C*HCH$_2$NO$_2$), 33.1 (*C*H$_2$(C)CH$_2$), 29.3 (CH$_2$(C)*C*H$_2$); HRMS (CI): *m/z* 351.1308 (351.1318 calc. for $C_{17}H_{21}NO_7$ $[M+H]^+$).

Methyl 3-(2-((2*S*, 3*R*)-2-hydroxy-3-(4-methoxyphenyl)-4-nitrobutyl)-1, 3-dioxolan-2-yl) propanoate (28a):

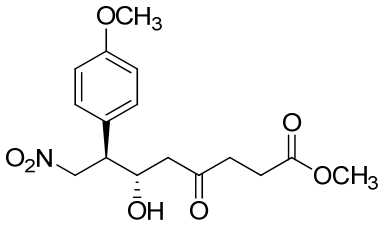


A solution of the lactone **28** (3.4 g, 9.7 mmol) in methanol (70 mL) was cooled to 0 °C and potassium carbonate (2.67 g, 19.4 mmol) was added. The mixture was stirred at room temperature for 30 min. The mixture was cooled to 0 °C, neutralized with aq. HCl (0.5 M) and the solution was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 3.5 g (95%) of the

nitroketal **28a** as a light brown gum. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3501, 2956, 1732, 1548, 1514, 1249, 1179, 1134, 1030, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, J = 8.6, Ar*H*), 6.85 (d, 2H, J = 8.6, Ar*H*), 5.04 (dd, 1H, J = 12.7, 5.2, CH_2NO$_2$), 4.58 (dd, 1H, J = 9.7, 12.7, CH_2NO$_2$), 4.05-4.02 (m, 1H, Ar-C*H*) 4.01-3.91 (m, 4H, OCH_2CH_2O), 3.86 (s, 1H, CHO*H*), 3.78 (s,3H, ArOCH_3) 3.64 (s,3H, OCH_3), 3.42-3.37 (dt, 1H, J = 5.3, 9.5, C*H*OH), 2.25-2.16 (m, 2H, CO_2CH_2), 2.02-1.97 (m, 1H, CH_2(C)CH$_2$), 1.79-1.85 (m, 1H, CH_2(C)CH$_2$),1.64-1.62 (m, 2H, CH$_2$(C)CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (CO_2CH_3), 159.2 (Ar*C*), 129.2 (Ar*C*), 129.1 (Ar*C*), 114.5 (Ar*C*), 110.9 (O*C*O), 78.5 (CH_2NO_2), 70.0 (*C*HOH), 65.1 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 55.2 (ArO*C*H$_3$), 51.7 (CO_2CH_3), 50.3 (HO-C*C*H$_2$), 40.5 (Ar-*C*H), 31.7 (*C*H$_2$CH$_2$CO$_2$CH$_3$), 28.5 (*C*H$_2$CO$_2$CH$_3$); MS (APCI, pos.): *m/z* 366 (M-OH); HRMS (CI): *m/z* 384.1647 (384.1658 calc. for $C_{18}H_{26}NO_8$ [M+H]$^{+}$).

(6*S*,7*R*)-Methyl 6-hydroxy-7-(4-methoxyphenyl)-8-nitro-4-oxooctanoate (29):

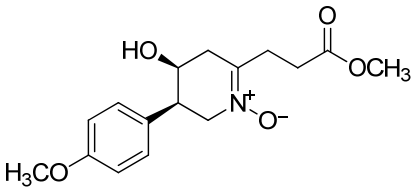


To a solution of the nitroketal **28a** (3.50 g, 10.3 mmol) in methanol (70 mL) at 0 °C, was added aq. HCl (6 N, 40 mL), and the mixture was stirred at room temperature overnight. The methanol was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried

(Na_2SO_4) and concentrated to provide 2.90 g (95%) of the nitroketone **29** as a light brown solid. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3436, 2953, 1723, 1710, 1553, 1514, 1380, 1251, 1204, 1179, 1157, 1102, 1032, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, J = 6.6, Ar*H*), 6.87 (d, 2H, J = 6.6, Ar*H*), 5.07 (dd, 1H, J = 5.1, 12.8, CH_2NO$_2$), 4.60 (dd, 1H, J = 9.9, 12.8, CH_2NO$_2$), 4.24-4.19 (m, 1H, Ar-C*H*), 3.79 (s, 3H, ArOCH_3) 3.65 (s, 3H, OCH_3), 3.55 (d, 1H, J = 4, CHO*H*) 3.51-3.46 (dt, 1H, J = 5.2, 9.8, C*H*OH), 2.57-2.64 (m, 4H, CH_2COCH_2), 2.41-2.52 (m, 2H, CH_2CO$_2$CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.7 (*C*O), 173.1 (*C*O$_2$CH$_3$), 159.3 (Ar*C*) 129.0 (2xAr*C*), 128.6 (Ar*C*), 114.6 (O*C*O), 78.4 (*C*H$_2$NO$_2$), 69.8 (*C*HOH), 55.2 (ArCO*C*H$_3$), 51.9 (CO$_2$*C*H$_3$), 49.2 (HO-C*C*H$_2$CO), 47 (Ar-*C*H), 37.7 (CO*C*H$_2$), 27.4 (*C*H$_2$CO$_2$CH$_3$); MS (APCI, pos.): *m/z* 322 (M-OH); HRMS (CI): *m/z* 322.1284 (322.1291 calc. for $C_{16}H_{20}NO_6$ (M-OH)).

(3*R*,4*S*)4-Hydroxy-6-(3-methoxy-3-oxopropyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-1-oxide (30):

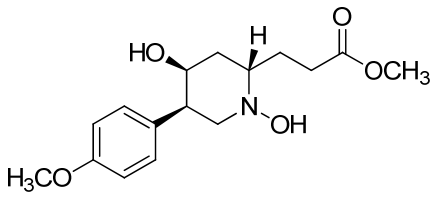


A solution of NH_4Cl (0.37g, 6.0 mmol) in water (5 mL) was added to a solution of the nitroketone **29** (2.3 g, 6.0 mmol) in THF (20 mL). Activated Zn powder (4.4 g, 0.060 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered (Celite), the residue was washed with

THF, and the combined filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and the mixture was washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 2.0 g, (95%) of **30** as brown foam. This material was pure by ^{1}H NMR (500 MHz) and was directly used further. An analytical sample was obtained by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95/5).

IR (neat): 2953, 1738, 1612, 1512, 1434, 1249, 1175, 1134, 1070, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.6, Ar*H*), 6.88 (d, 2H, J = 8.6, Ar*H*), 4.34-4.29 (br t, 1H, J = 13.3, ArC*H*), 4.18 (br s, 1H, C*H*OH), 3.89 (dd, 1H, J = 14.9, 5.5, CH_2N), 3.79 (s, 3H, ArOCH_3), 3.68 (s, 3H, CO_2CH_3), 3.20 (dd, 1H, J = 11.9, 4.8, CH_2N), 2.94-2.68 (m, 6H, CH_2C=N, COCH$_2$CH_2, COCH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7 (*C*O), 159.1 (Ar*C*), 144.7 (*C*=NO), 129.7 (Ar*C*), 128.8 (2xAr*C*), 114.3 (2 x Ar*C*), 65.2 (*C*H$_2$NO), 57.8 (Ar-*C*H), 55.3 (O*C*H$_3$), 51.8 (CO_2CH_3), 43.7 (*C*HOH), 38.7 (*C*H$_2$CO$_2$CH$_3$), 28.3 (N=C*C*H$_2$), 27.5 (N=C*C*H$_2$); MS (APCI, pos.): *m/z* 308 (M+1); HRMS (CI): *m/z* 308.1499 (308.1498 calc. for $C_{16}H_{22}NO_5$ $[M+H]^+$).

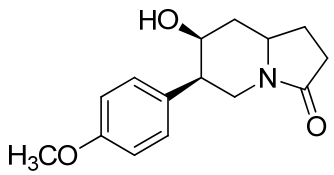
Methyl 3-(2*R*,4*S*,5*S*)-4-hydroxy-5-(4-methoxyphenyl)-*N*-hydroxypiperidin-2-yl)propanoate (31):



To a solution of tetramethylammonium triacetoxyborohydride (3.2 g, 0.012 mol) in acetonitrile (10 mL) was added acetic acid (10 mL). The mixture was stirred at 0 °C for 5 min and a solution of the nitrone **30** (1.9 g, 0.006 mol) in acetonitrile (5 mL) was added. The mixture was stirred at 0 °C for 1 h and the pH of the solution was adjusted (pH 7 to 8) with aqueous NaOH (5% solution). The mixture was extracted with dichloromethane (2 x 50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to give 1.59 g (83%) of **31** as a white solid. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3518, 3203, 2920, 1715, 1511, 1437, 1245, 1205, 1175, 1105, 1025, 981, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, 2H, J = 8.7, Ar*H*), 6.88 (d, 2H, J = 8.7, Ar*H*), 3.93 (d, 1H, J = 12.3 ArC*H*), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, COCH_3), 3.52-3.44 (t, 1H, J = 10.1, C*H*OH), 3.31-3.13 (m, 1H, ArCHCH_2), 3.07-2.9 (m, 1H, ArCHCH_2), 2.53-2.32 (m, 2H, COCH_2), 2.22-2.14 (m, 1H, NC*H*), 2.04-1.98 (dt, 1H, J = 13.3, 5.2, OHCHCH_2), 1.92-1.84 (m, 1H, OHCHCH_2), 1.74-1.66 (m, 1H, NCHCH_2), 1.54-1.50 (m, 1H, NCHCH_2); MS (APCI, pos.): *m/z* 272 (M-OCH$_3$+1), 310 (M+1); HRMS (CI): *m/z* 310.1636 (310.1654 calc. for $C_{16}H_{24}NO_5$ [M+H]).

(6*R*,7*S*,8a*S*)-Hexahydro-7-hydroxy-6-(4-methoxyphenyl)indolizin-3(5H)-one (33):

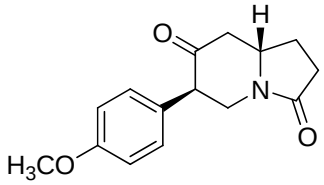


The hydroxylamine **31** (1.65 g, 5.34 mmol) was dissolved in a mixture of EtOH (20 mL) and saturated aqueous NH_4Cl (10 mL). Indium powder (1.2 g, 0.01 mol) was added and the mixture was heated to reflux for 4 h. The mixture was cooled, filtered through a pad of Celite, and the filtrate was concentrated. The residue was diluted with dichloromethane (40 mL) and the aqueous layer was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 10 mL) dried (Na_2SO_4) and concentrated to give 1.04 g of a yellow gum. This material is a mixture of the amino ester and the cyclization product (lactam **33**, ~30%). The mixture was therefore directly converted to the lactam as follows:

To a solution of the crude amino ester **32** and lactam **33** mixture (1.00 g) in THF (15 mL) was added diisopropylethyl amine (1.5 mL, 0.0080 mol) and the solution was heated to reflux for 5 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 0.82 g (60% from **31**) of the lactam (**33**) as a pale yellow foam. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3356, 2923, 1652, 1510, 1453, 1242, 1175, 1027, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.13 (br s, 1H, C*H*OH), 4.12 (dd, 1H, J = 4.7, 12.6, NCH_2), 3.97-3.91 (m, 1H, ArC*H*), 3.8 (s, 3H, OCH_3), 3.37-3.32 (t, 1H, J = 12.6, NCH_2), 2.81-2.77 (dt, 1H, J = 4.6, 1.8, NC*H*), 2.44-2.41 (br t, 2H, J = 7.1, COCH_2), 2.29-2.22 (m, 1H, CH_2CHOH), 2.21-2.16 (m, 1H, NCHCH_2), 1.65-1.61 (m, 2H, CHCH_2CH), 1.6-1.52 (dt, 1H, J = 2.4, 9.6, NCHCH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6 (*C*O), 158.8 (ArC_{ipso}), 131.5 (ArC_{ipso}), 128.6 (Ar*C*), 114.2 (Ar*C*), 69.1 (*C*HOH), 55.3 (O*C*H_3), 50.8 (N*C*H), 44.8 (N*C*H_2), 39.6 (Ar*C*H), 38.1 (HOCH*C*H_2), 30.6 (NCO*C*H_2), 24.7 (NCH*C*H_2); MS (APCI, pos.): *m/z* 262 (M+1); HRMS (EI): *m/z* 261.1364 (261.1365 calc. for $C_{15}H_{19}NO_3$ (M^+).

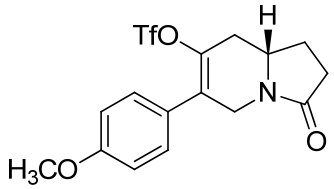
(6*R*,8a*S*)-Hexahydro-6-(4-methoxyphenyl)indolizine-3,7-dione (34):



To a stirred solution of the alcohol **31** (0.20 g, 0.77 mmol) in dichloromethane (7 mL) was added DMSO (3.5 mL) followed by DIPEA (1 mL) at 0 °C. Solid SO_3 pyridine (365 mg, 2.30 mmol) was added portion wise and the mixture was stirred at 0 ^oC for 1 h. Water (3 mL) was added and the mixture was diluted with dichloromethane (10 mL). The mixture was washed with water (2 x 15 mL) and the organic layer was dried (Na_2SO_4) and concentrated to provide a brown solid which was purified by flash chromatography on silica gel (EtOAc) to provide 0.14 g (70%) of **34** as a white solid.

IR (neat): 2955, 1714, 1673, 1515, 1455, 1239, 1186, 1036, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, 2H, J = 8.7, Ar*H*), 6.90 (d, 2H, J = 8.7, Ar*H*), 4.59 (dd, 1H, J = 13.1, 6.9, ArCC*H*), 4.01-3.96 (m, 1H, NC*H*) 3.80 (s, 3H, OCH_3), 3.63 (dd, 1H, J = 12.0, 6.9, NCH_2), 3.11-3.06 (t, 1H, J = 12.5, NCH_2), 2.74 (dd, 1H, J = 3.8, 13.6, $COCH_2$), 2.56-2.46 (m, 2H, $COCH_2$, $NCOCH_2$) 2.44-2.40 (m, 2H, $NCOCH_2CH_2$, $COCH_2CH_2$), 1.83-1.79 (m, 1H, $COCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (*C*O), 173.5 (N*C*O), 159.1 (Ar*C*OCH_3), 130.0 (Ar*C*H), 126.4 (Ar*C*), 114.1 (Ar*C*H), 57.2 (N*C*H), 55.3 (OCH_3), 54.9 (ArC*C*H), 48.6 (NCH_2), 45.1 ($COCH_2$), 29.7 ($NCOCH_2$), 24.7 ($COCH_2CH_2$); MS (APCI pos.): *m/z* 260.1 (M+1); HRMS (CI+): *m/z* 259.1214 (259.1208 calc. for $C_{15}H_{17}NO_3$ M^+).

(*S*)-1,2,3,5,8,8a-Hexahydro-6-(4-methoxyphenyl)-3-oxoindolizin-7-yl trifluoromethanesulfonate (35):

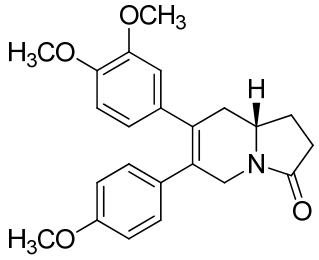


To a suspension of KH (54 mg, 0.39 mmol) in THF (2 mL) was added ketone **34** (0.10 g, 0.39 mmol) at 0 ºC. The mixture was stirred at room temperature for 2 h and *N*-phenyl bis-trifluoromethanesulfonimide (152 mg, 0.42 mmol) was added in one portion and the mixture was stirred for 1h at room temperature. Water (5 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a brown gum, which was purified by flash

chromatography on silica gel (EtOAc) to provide 105 mg (70%) of **35** as a pale brown liquid.

IR (neat): 2962, 2840, 1693, 1609, 1243, 1201, 1000, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, 2H, J = 8.8, Ar*H*), 6.92 (d, 2H, J = 8.8, Ar*H*), 4.75 (dd, 1H, J = 2.3, 18.0, NCH_2) 3.95-3.92 (m, 1H, NC*H*), 3.82 (s, 3H, OCH_3), 3.73-3.69 (br d, 1H, J = 18.0, NCH_2), 2.70 (dd, 1H, J = 4.3, 16.3, COCH_2), 2.61-2.55 (m, 1H, COCH_2), 2.53-2.49 (m, 2H, C=CCH_2) 2.45-2.38 (m, 1H, $COCH_2CH_2$), 1.88-1.81(m, 1H, $COCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (*C*=O), 160.0 (TfO*C*=C), 139.5 (Ar*C*OCH_3), 129.6 (Ar*C*), 127.9 (Ar*C*H), 124.8 (TfOC=*C*), 115.2 (q, J = 109.4, *C*F_3), 114.1 (Ar*C*H), 55.3 (O*C*H_3), 53.3 (N*C*H), 43.0 (N*C*H_2), 35.5 (C=C*C*H_2CH), 29.6 ($COCH_2CH_2$), 24.3 (CO*C*H_2); MS (APCI pos.): *m/z* 392.1 (M+1); HRMS (CI+): *m/z* 391.0704 (391.0701 calc. for $C_{16}H_{16}NO_5SF_3$, M^+).

(*S*)-1,2,8,8a-Tetrahydro-7-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)indolizin-3(5H)-one (36):

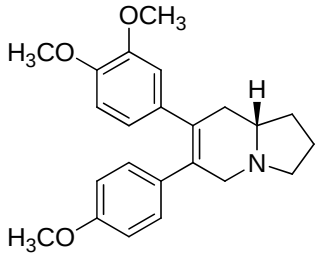


To a stirred solution of the enol triflate **35** (85 mg, 0.22 mmol) and 3,4-dimethoxyphenyl boronic acid (44 mg, 0.24 mmol) in dioxane (4 mL) was added aq. Na_2CO_3 (69 mg, 0.65 mmol; degassed with N_2 for 20 min) and the mixture was degassed

with nitrogen for 15 min. $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) was added and the mixture was heated with stirring at 85 ºC for 90 min. The mixture was cooled to ambient temperature, diluted with EtOAc (15mL) and the mixture was washed with water (2 x 5ml). The organic layer was dried (Na_2SO_4) and concentrated to give a brown gum, which was purified by flash chromatography on silica gel (EtOAc) to provide 67 mg (80%) of **36** as a pale yellow gum.

IR (neat): 2965, 2834, 1729, 1674, 1510, 1454, 1243, 1027, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, 2H, J = 8.7, Ar*H*), 6.70 (d, 3H, J = 8.7, Ar*H*), 6.62 (dd, 1H, J = 1.9, 8.3, Ar*H*), 6.42 (d, 1H, 1.9, Ar*H*), 4.71 (dd, 1H, J = 2.2, 18.4, NCH_2), 3.93-3.88 (m, 1H, NC*H*), 3.82 (s, 3H, OCH_3), 3.78 (br s, 1H, NCH_2), 3.74 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 2.74 (dd, 1H, J = 3.1, 16.7, COCH_2), 2.52-2.49 (t, 2H, J = 7.9, COCH_2, C=CCH_2), 2.45-2.37 (m, 2H, C=CCH_2,COCH2CH_2), 1.88-1.77 (m, 1H, $COCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (*C*=O), 158.4 (Ar*C*OCH_3), 148.1 (Ar*C*OCH_3), 147.5 (Ar*C*OCH_3), 134.3 (Ar*C*C=C), 131.8 (C=*C*CH_2CH), 131.5 (C=*C*CH_2N), 130.6 (Ar*C*), 130.2 (Ar*C*H), 120.8 (Ar*C*H), 113.6 (Ar*C*H), 112.9 (Ar*C*H), 110.6 (Ar*C*H), 55.7 (N*C*H), 55.6 (OCH_3), 55.2 (OCH_3), 53.4 (OCH_3), 44.4 (NCH_2), 38.7 (C=CCH_2CH), 30.1 ($COCH_2CH_2$), 24.9 (COCH_2); MS (APCI positive): *m/z* 380.2 (M+1); HRMS (CI+): *m/z* 379.1791 (379.1784 calc. for $C_{23}H_{25}NO_4$, M^+).

(*S*)-1,2,3,5,8,8a-Hexahydro-7-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)indolizine (secoantofine, 8):

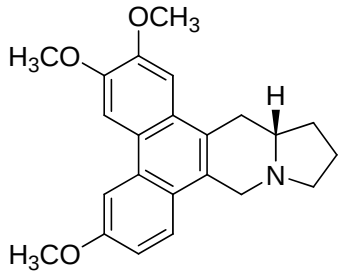


To a suspension of $LiAlH_4$ (16 mg, 0.42 mmol) in dry THF (1.5 mL) at 0 °C was slowly added a solution of the lactam **36** (0.04 g, 0.1 mmol) in THF (1 mL). After stirring for an hour at 0 ^{o}C, the mixture was stirred at ambient temperature for 24 h. It was then cooled to 0 °C and water (8 μL, 0.42 mmol), 1 N NaOH (8 μL) and water (24 μL), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and washed with dichloromethane. The combined filtrates were dried (Na_2SO_4) and concentrated to provide 31 mg (80%) of **8** as a pale yellow gum. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 2962, 1606, 1509, 1458, 1243, 1168, 1139, 1022, 832, 810 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, 2H, J = 8.7), 6.69-6.66 (m, 4H), 6.47 (br d, 1H, J = 1.1), 3.86 (d, 1H, J = 15.8), 3.81 (s, 3H), 3.73 (s, 3H), 3.54 (s, 3H), 3.30 (dt, 1H, J = 7.0, 1.6), 3.07 (dt, 1H, J = 16.0, 3.2), 2.77-2.68 (m, 1H), 2.45-2.35 (m, 2H), 2.24 (apparent q, 1H, J = 9.0), 2.14-2.06 (m, 1H), 1.97-1.90 (m, 1H), 1.87-1.80 (m, 1H), 1.60-1.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 147.9, 147.1, 135.1, 133.6, 132.7, 132.6, 130.2, 120.7, 113.4, 113.1, 110.4, 60.4, 57.9, 55.7, 55.5, 55.1, 54.3, 38.6, 30.9, 21.5; MS (APCI

positive): *m/z* 366.4 (M+1); HRMS (CI+): *m/z* 365.1986 (365.1999 calcd. For $C_{23}H_{27}NO_3$ (M^+)); $[\alpha]^{23}_D$ = +148 (*c* = 0.4, $CHCl_3$; Lit.[22] $[\alpha]^{25}_D$ = +169 (*c* 1, $CHCl_3$, for the *S* enantiomer)).

(*S*)-2,3,6-Trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinoline ((+)-antofine) (9):



To a solution of **8** (25 mg, 0.068 mmol) in dichloromethane (1.5 mL) at 0 °C was added VOF_3 (40 mg, 0.32 mmol) and the mixture was stirred for 15 min. Trifluoroacetic acid (70 μL, 0.90 mmol) was added and stirring was continued for 75 min at 0 °C. Aqueous NaOH (10%, 2 mL) was added and the mixture was warmed to room temperature. The biphase was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product. Purification by flash chromatography on silica gel (CH_2Cl_2/methanol, 97.5/2.5) provided 19 mg (77%) of **9** as a pale cream colored solid.

IR (neat): 2961, 1616, 1510, 1469, 1418, 1257, 1233, 1203, 1169, 1127, 1032, 913, 843, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 1H, Ar*H*), 7.91 (d, 1H, *J* = 2.4, Ar*H*), 7.82 (d, 1H, *J* = 9.0, Ar*H*), 7.32 (s, 1H, Ar*H*), 7.20 (dd, 1H, *J* = 9.0, 2.4, Ar*H*), 4.7 (d, 1H, *J* = 14.6), 4.11 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.70 (brd,

1H, J = 14.6), 3.47 (dt, 1H, J = 8.5, 1.6), 3.35 (brd, 1H), 2.90 (m, 1H), 2.51-2.44 (m, 2H), 2.26-2.24 (m, 1H), 2.04-2.02 (m, 1H), 1.95-1.85 (m, 1H), 1.82-1.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 149.4, 148.4, 130.2, 127.1, 126.6, 125.5, 124.3, 124.1, 123.5, 114.9, 104.7, 104.0, 103.9, 60.3, 56.0, 55.9, 55.5, 55.1, 53.8, 33.7, 31.3, 21.6; MS (APCI, pos.): *m/z* 364.4 (M+1); HRMS (CI+): *m/z* 364.1922 (364.1913 calc. for $C_{23}H_{26}NO_3$ $[M+H]^+$); $[\alpha]^{23}_D$ = +118 (*c* = 0.4, $CHCl_3$; Lit.[22] $[\alpha]^{25}_D$ = +111 (*c* 1, $CHCl_3$, for the *S* enantiomer)).

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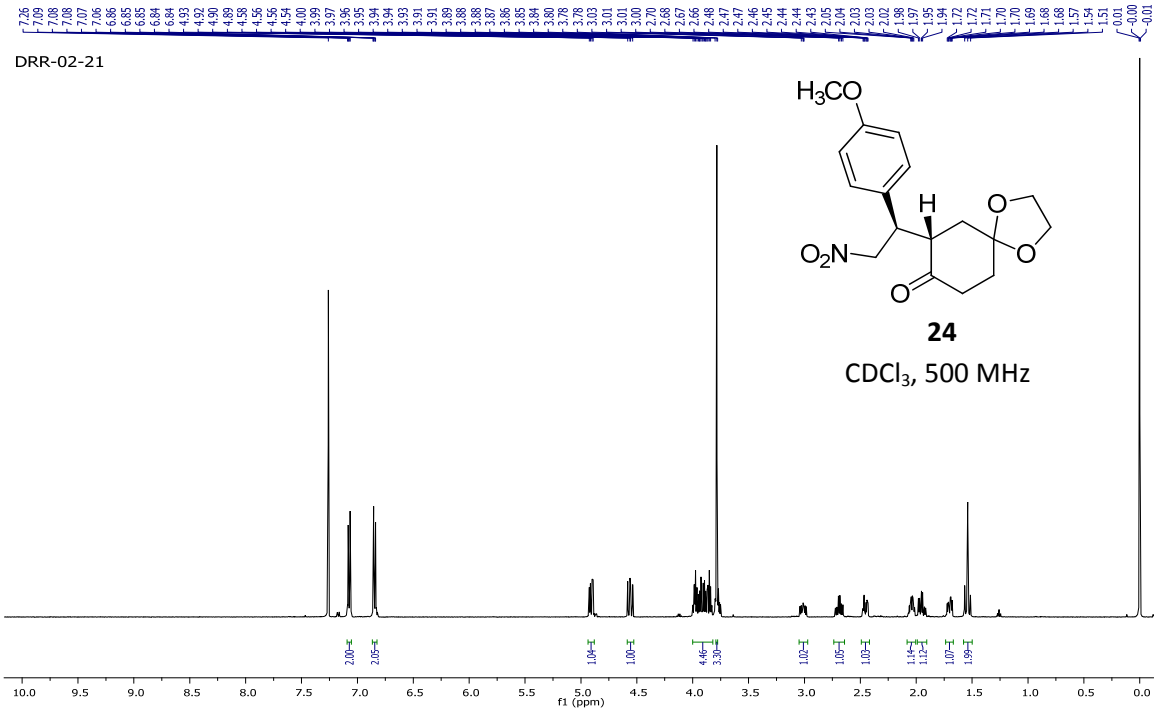
3.8 Selected ^{1}H NMR and ^{13}C NMR spectral data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H
O
O2N
O
O
24
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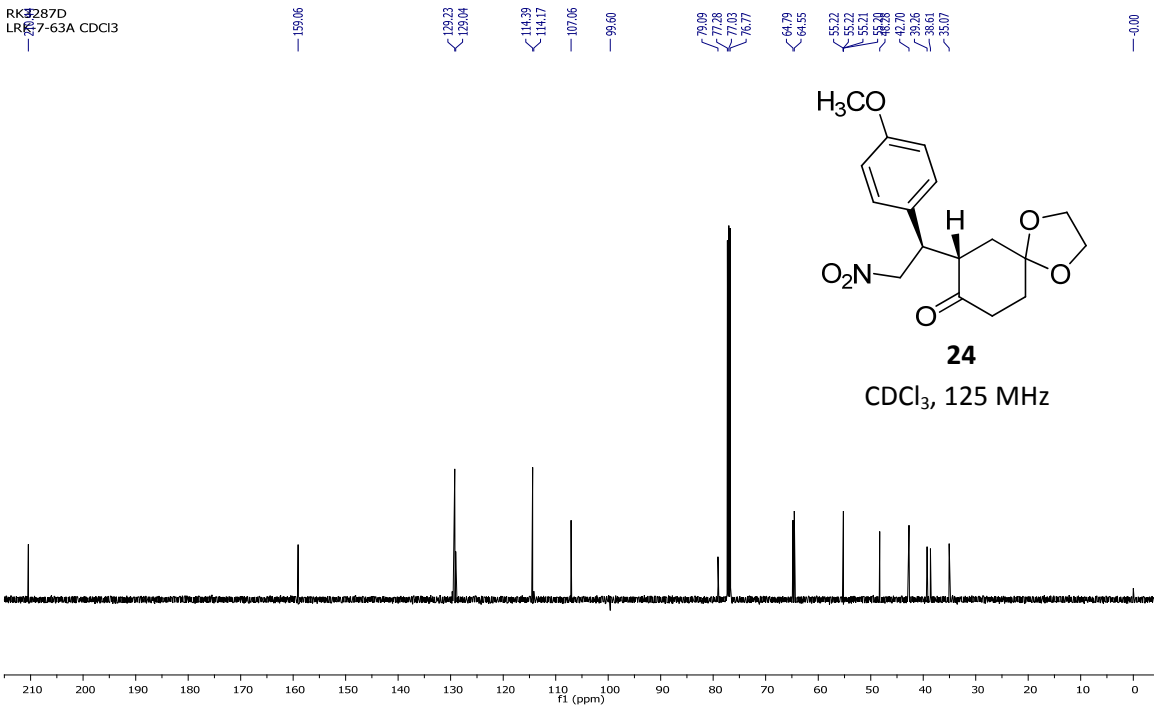
f1 (ppm)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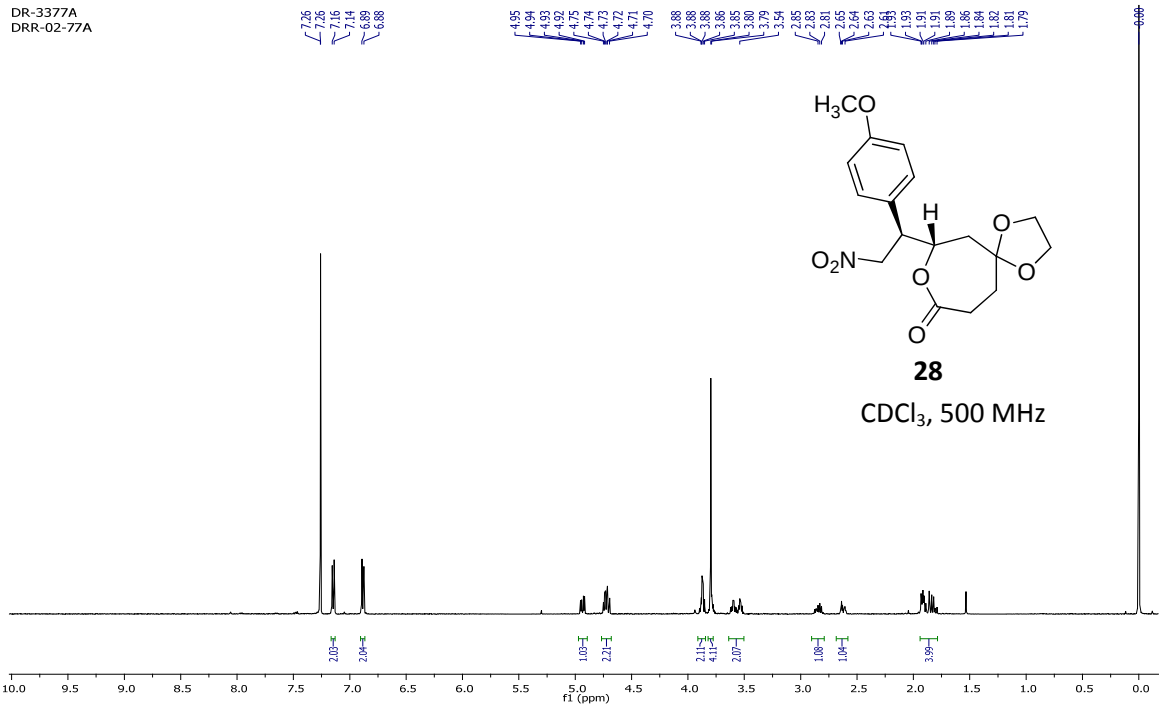
LRK7-63A CDCl3
H3CO
H
O
O2N
O
O
24
CDCl3, 125 MHz
f1 (ppm)

DR-3377A
DRR-02-77A



28

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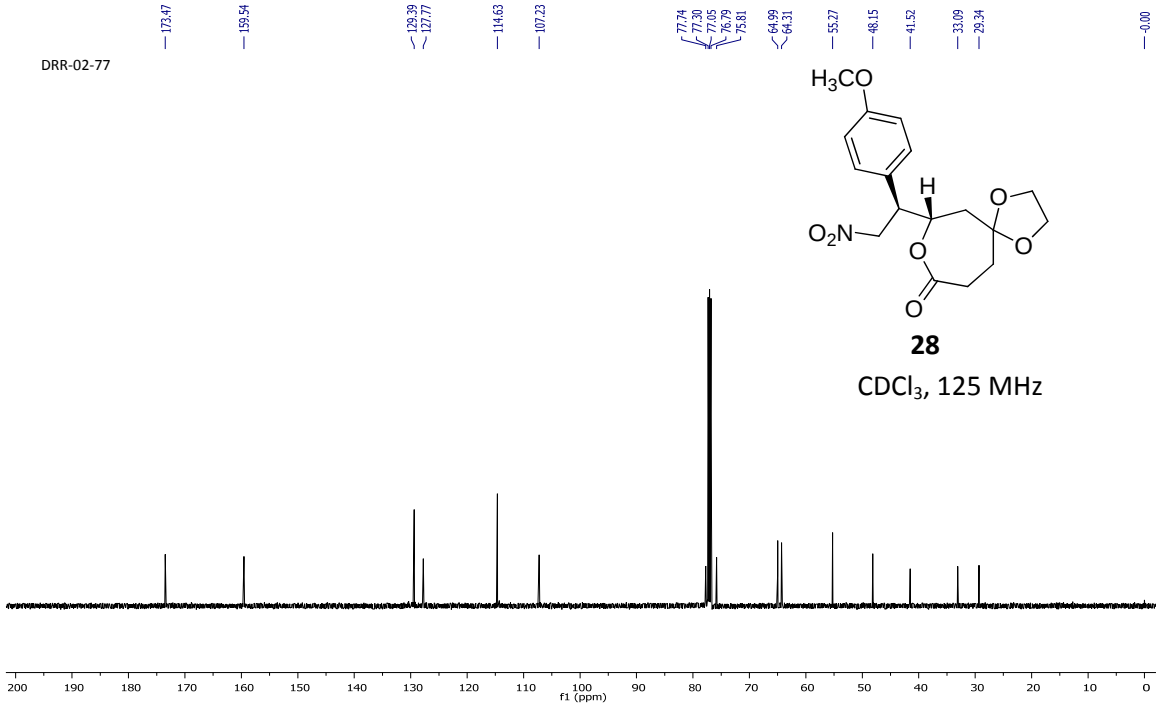
DRR-02-77



28

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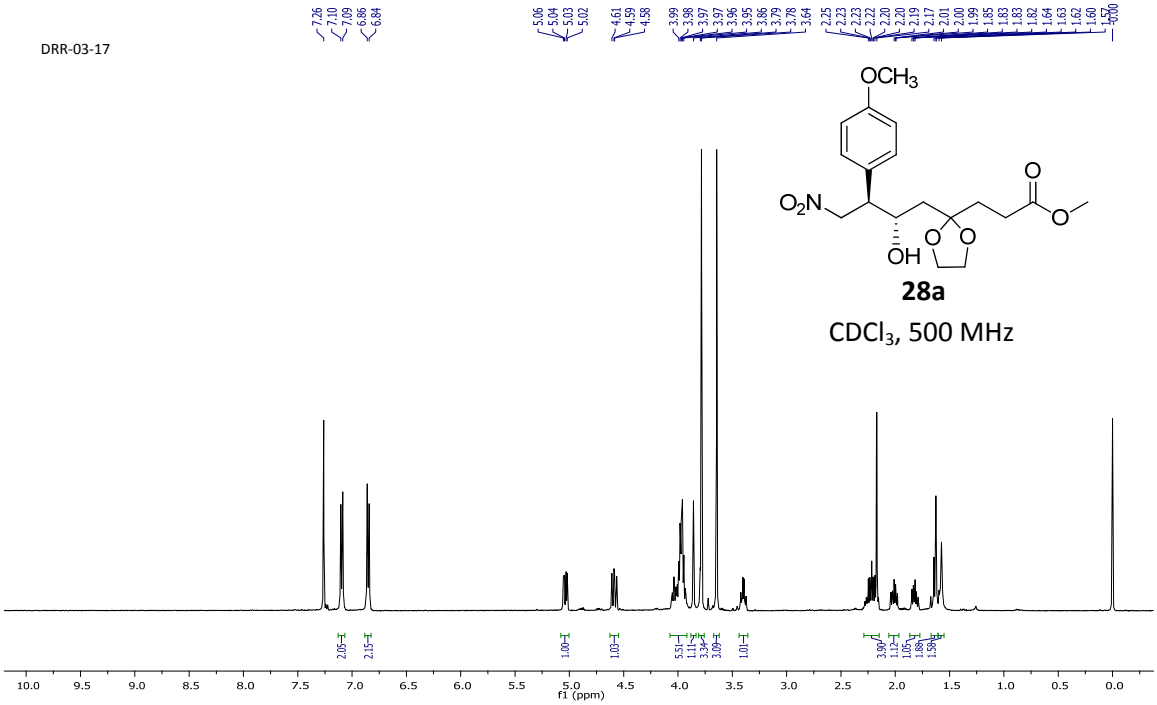
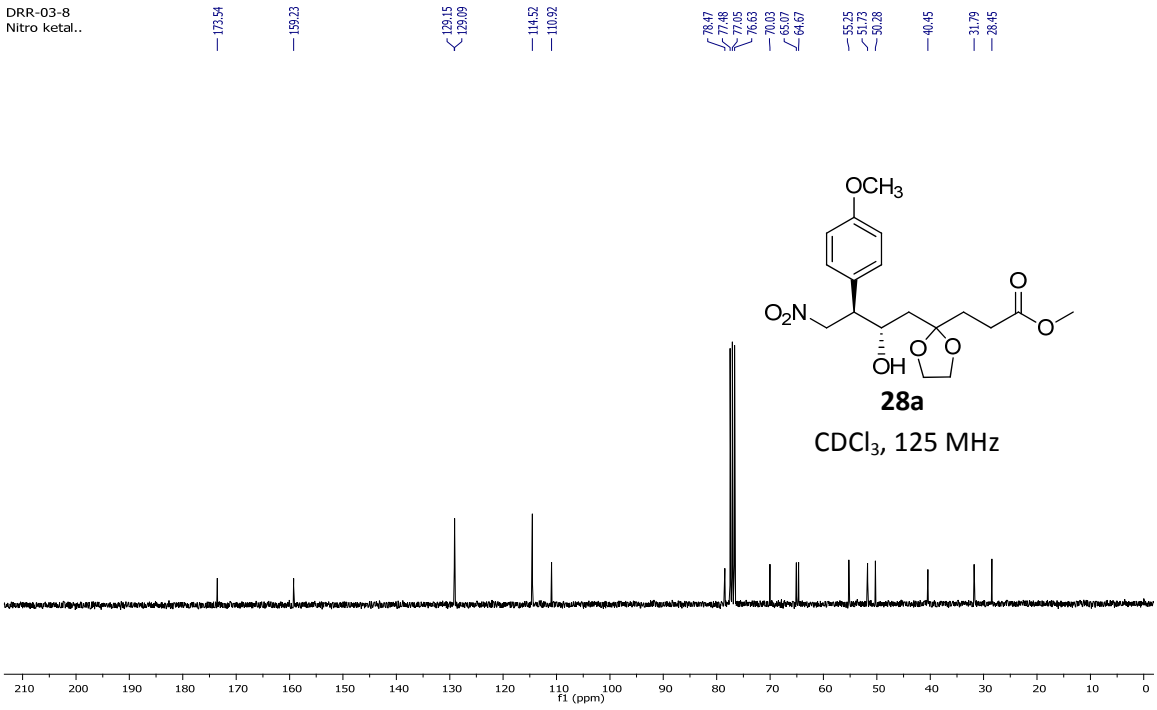
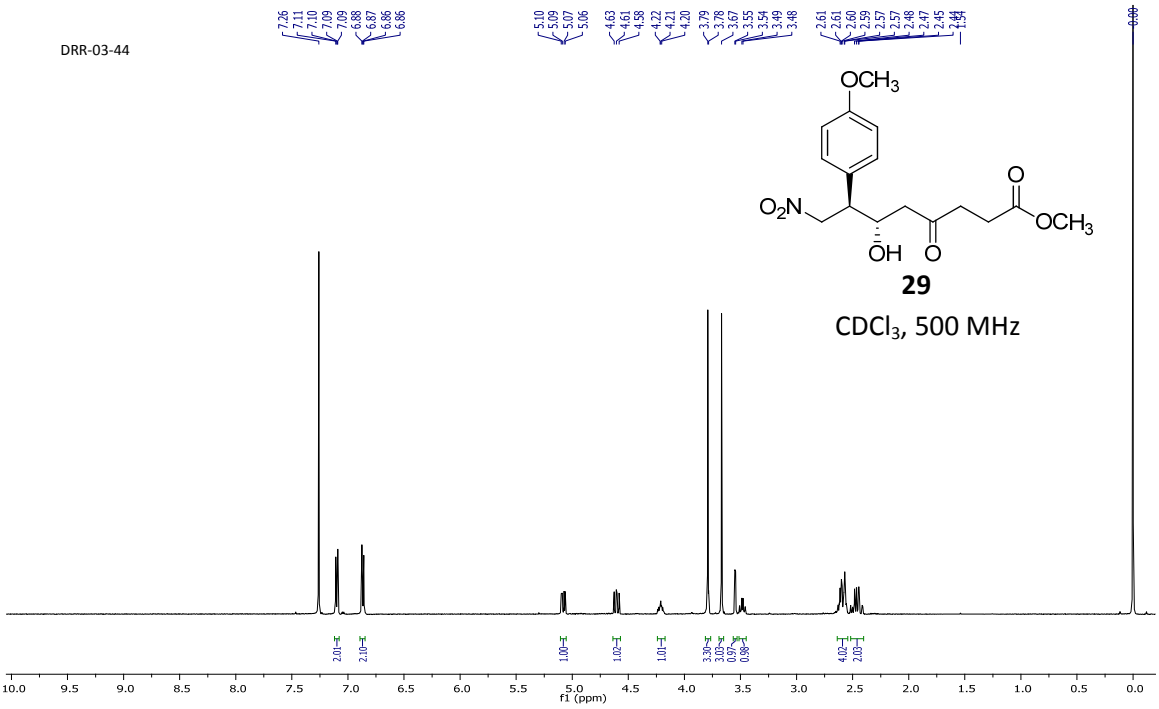


DRR-03-8
Nitro ketal..

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7.11
7.10
7.09
7.09
6.88
6.87
6.86
6.86
5.10
5.09
5.07
5.06
4.63
4.61
4.58
4.22
4.21
4.20
3.79
3.78
3.67
3.55
3.54
3.49
3.48
2.61
2.61
2.60
2.59
2.57
2.57
2.48
2.47
2.45
1.44
1.43
0.00
OCH3
O2N
OH
O
O
OCH3
29
CDCl3, 500 MHz
2.01
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1.00
1.02
1.01
3.30
3.03
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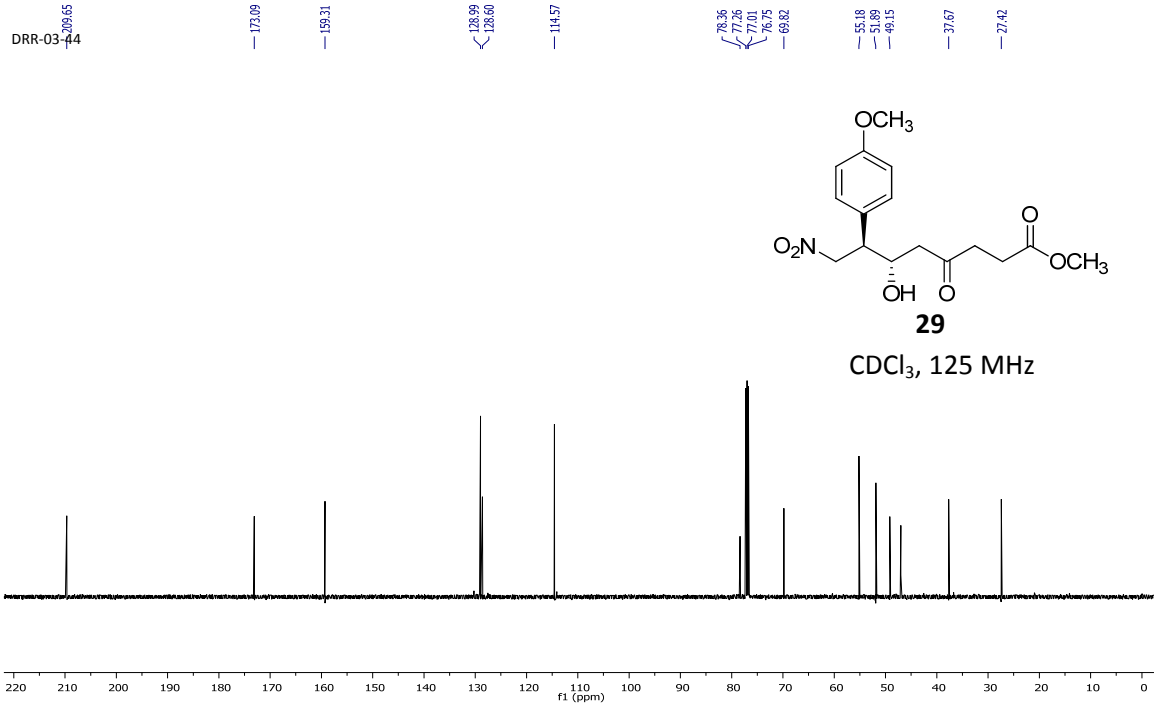
0.98
4.03
2.03
f1 (ppm)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114.57
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77.01
76.75
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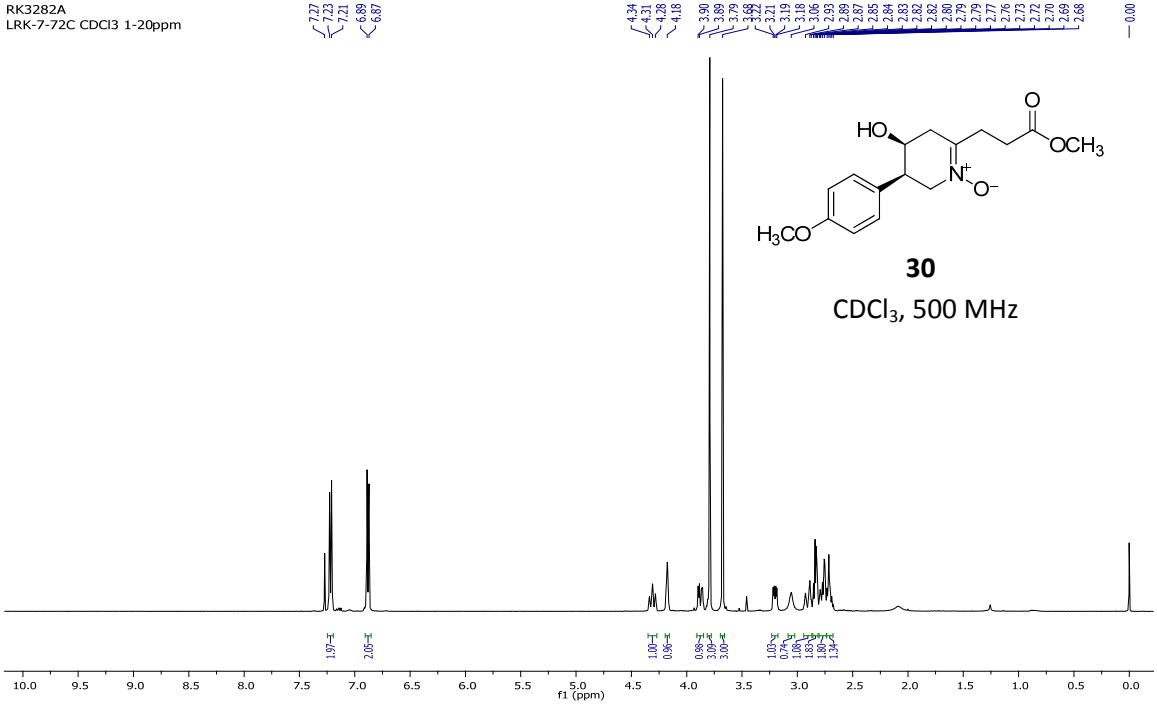
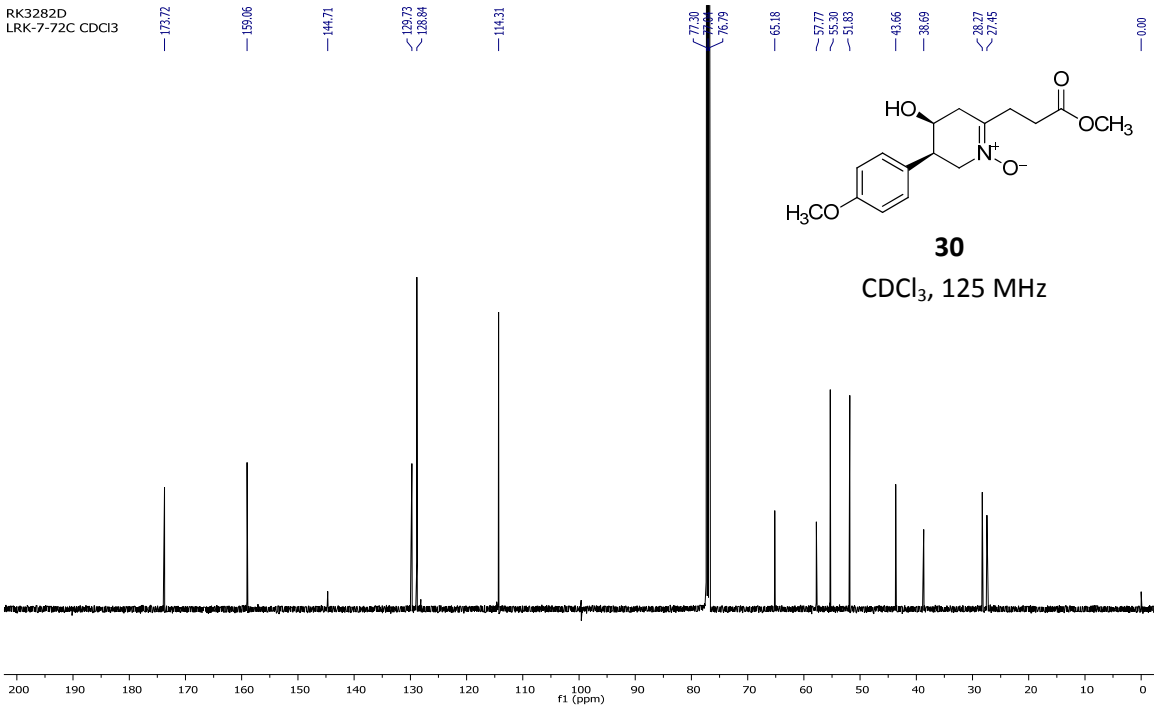
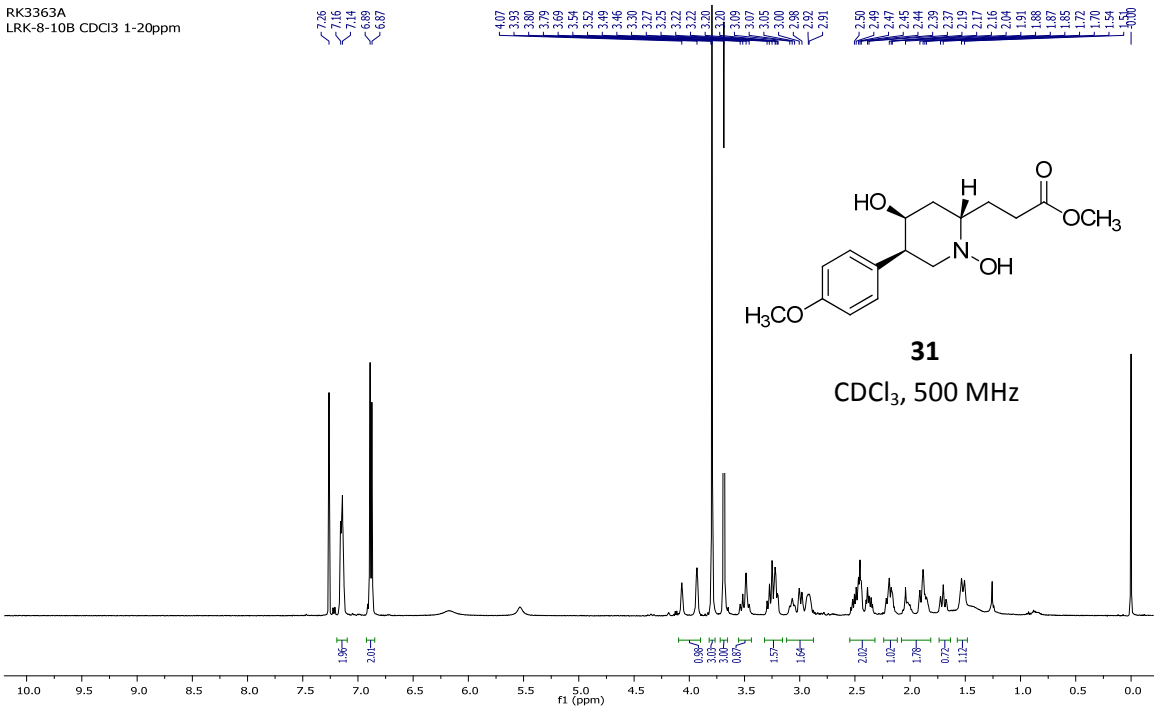
OCH3
29
CDCl3, 125 MHz
f1 (ppm)


RK3282A
LRK-7-72C CDCl3 1-20ppm
HO
O
OCH3
N+
O−
H3CO
30
CDCl3, 500 MHz
f1 (ppm)


RK3282D
LRK-7-72C CDCl3
HO
O
OCH3
N+
O−
H3CO
30
CDCl3, 125 MHz
f1 (ppm)


RK3363A
LRK-8-10B CDCl3 1-20ppm
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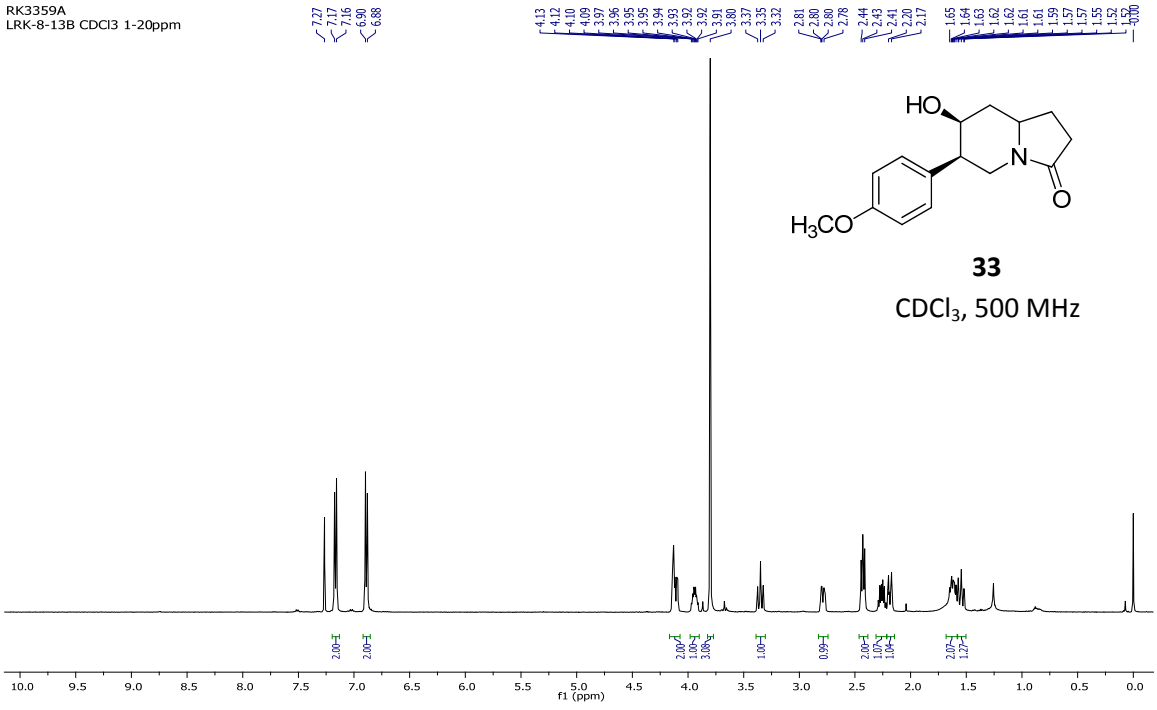
H
O
OCH3
N
OH
H3CO
31
CDCl3, 500 MHz
f1 (ppm)


RK3359A
LRK-8-13B CDCl3 1-20ppm
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O
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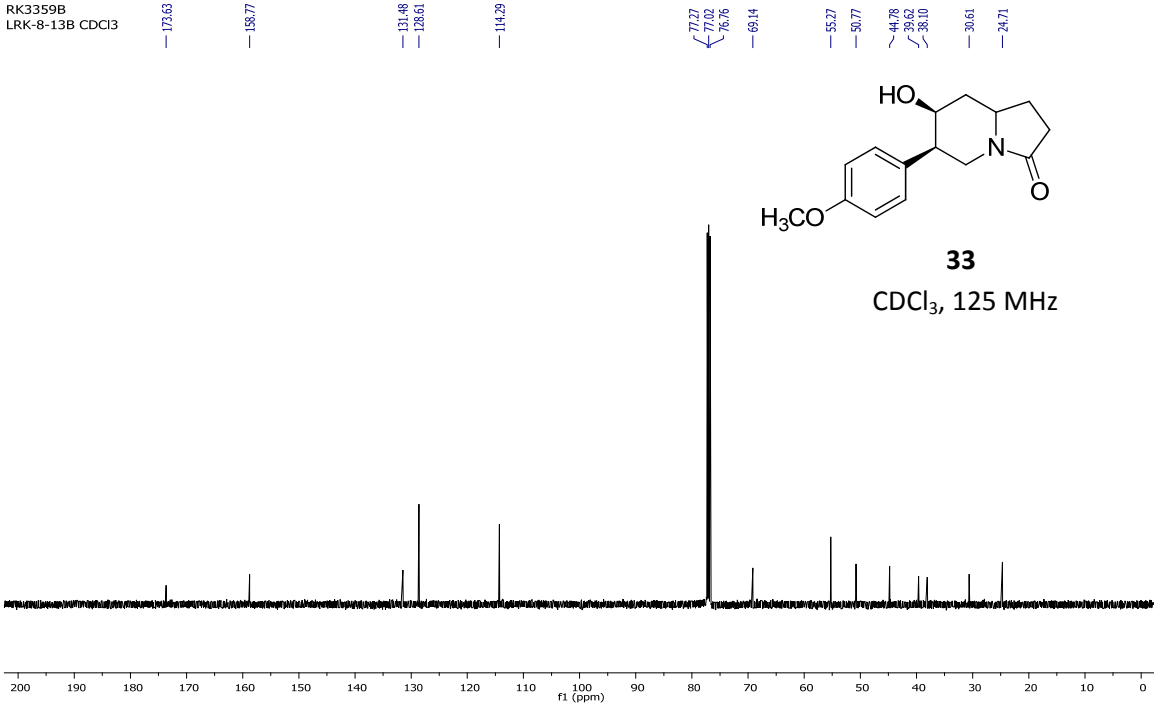
33
CDCl3, 500 MHz
f1 (ppm)

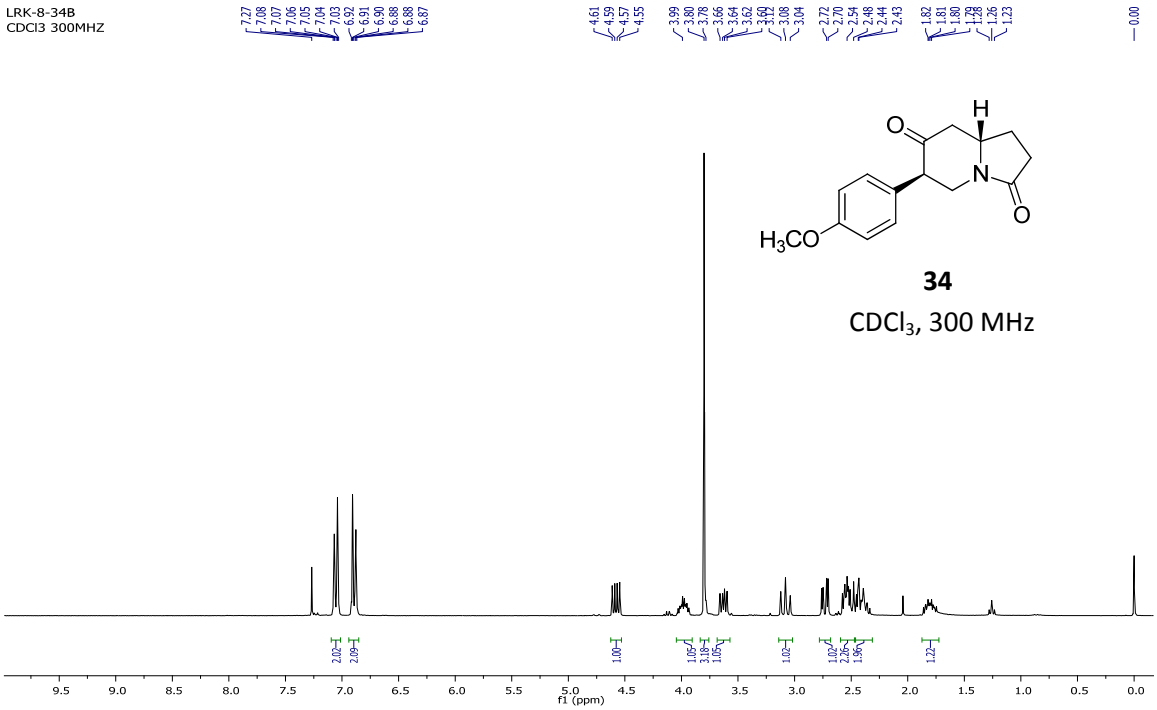
RK3359B
LRK-8-13B CDCl3



33

$CDCl_3$, 125 MHz

LRK-8-34B
CDCl3 300MHZ



34

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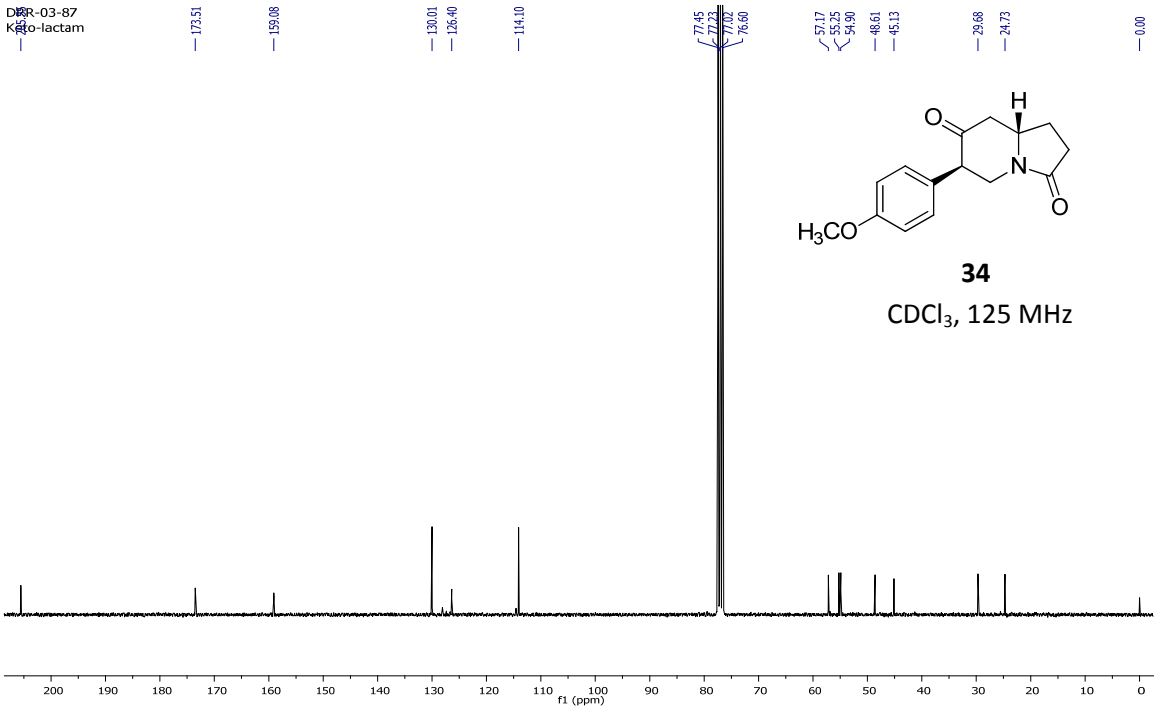

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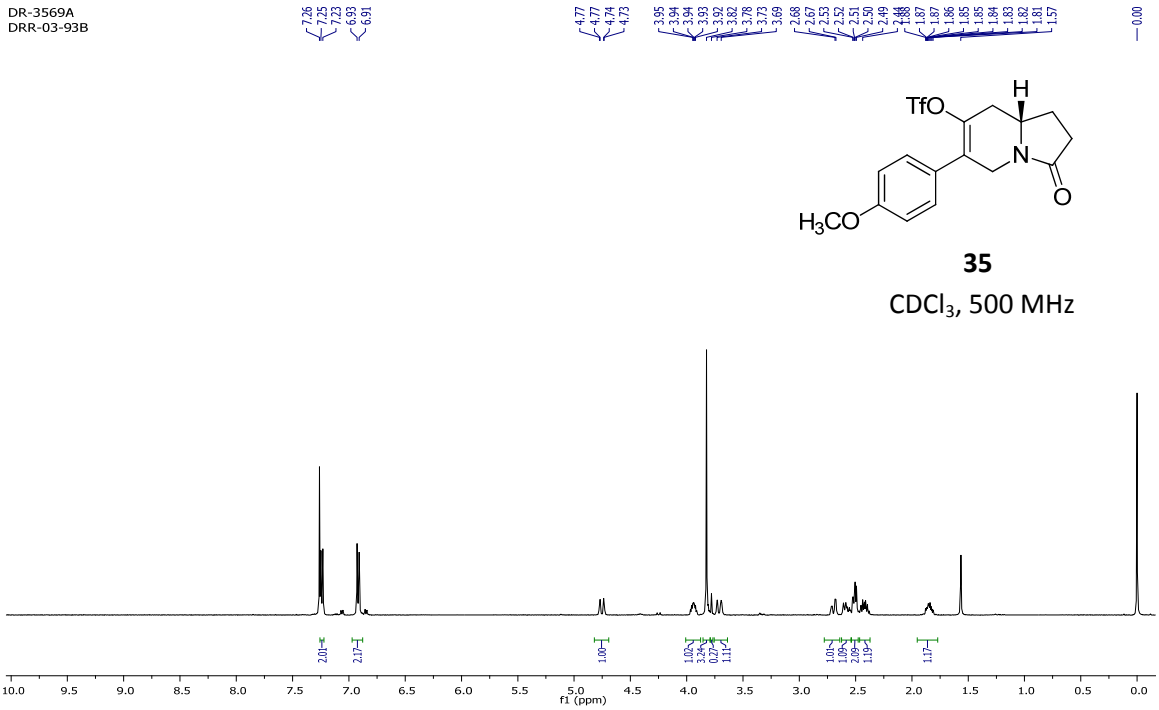

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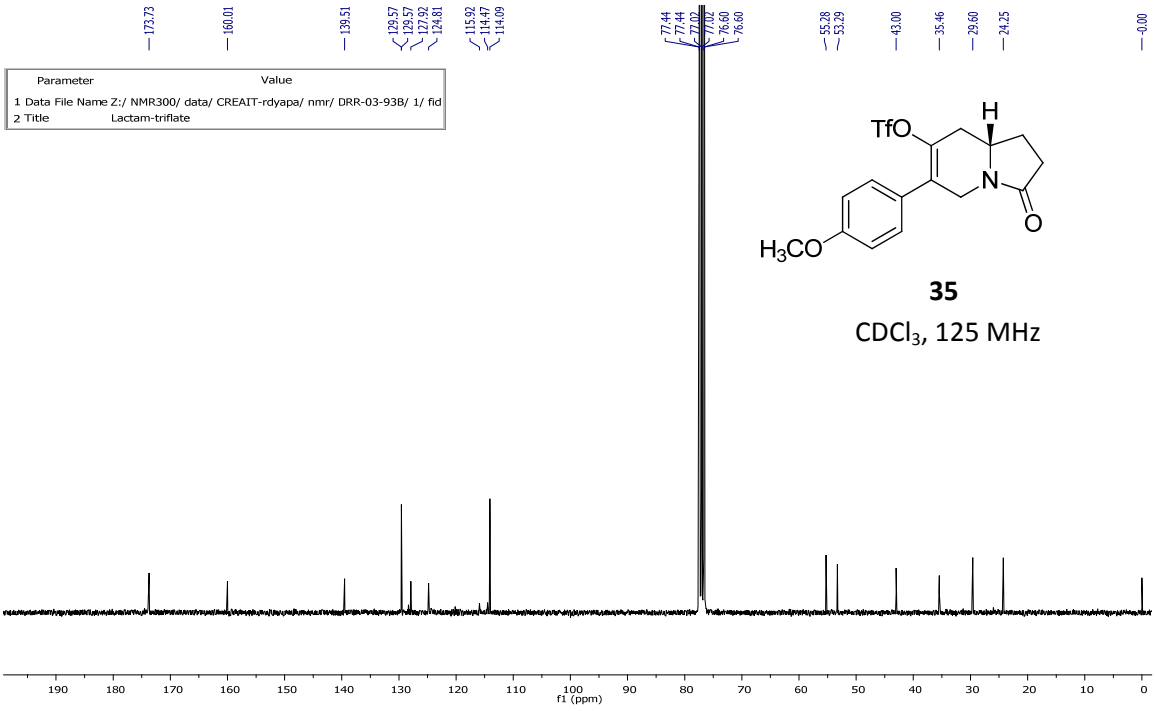
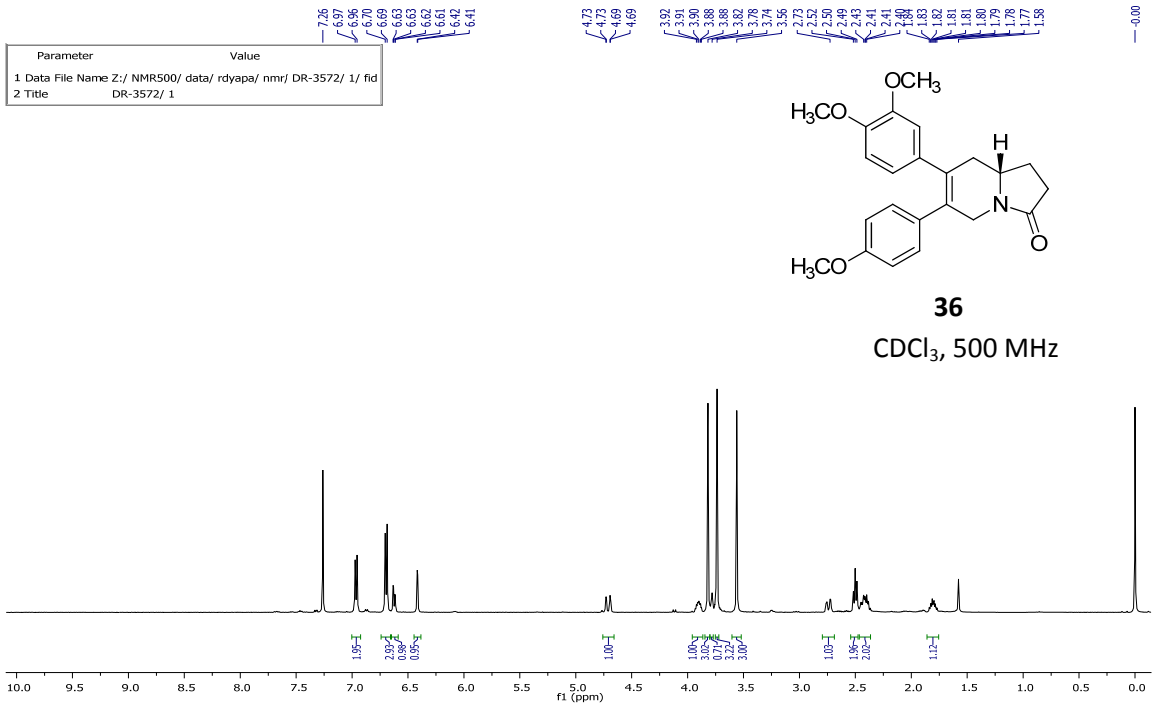


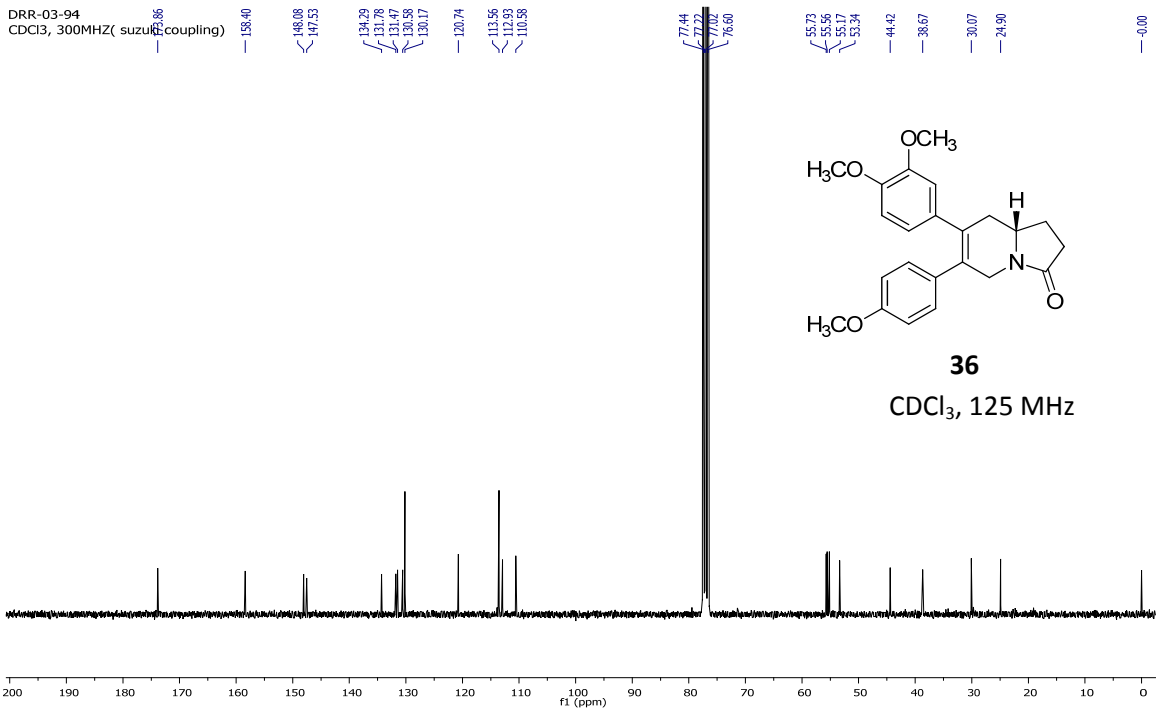
35

$CDCl_3$, 125 MHz



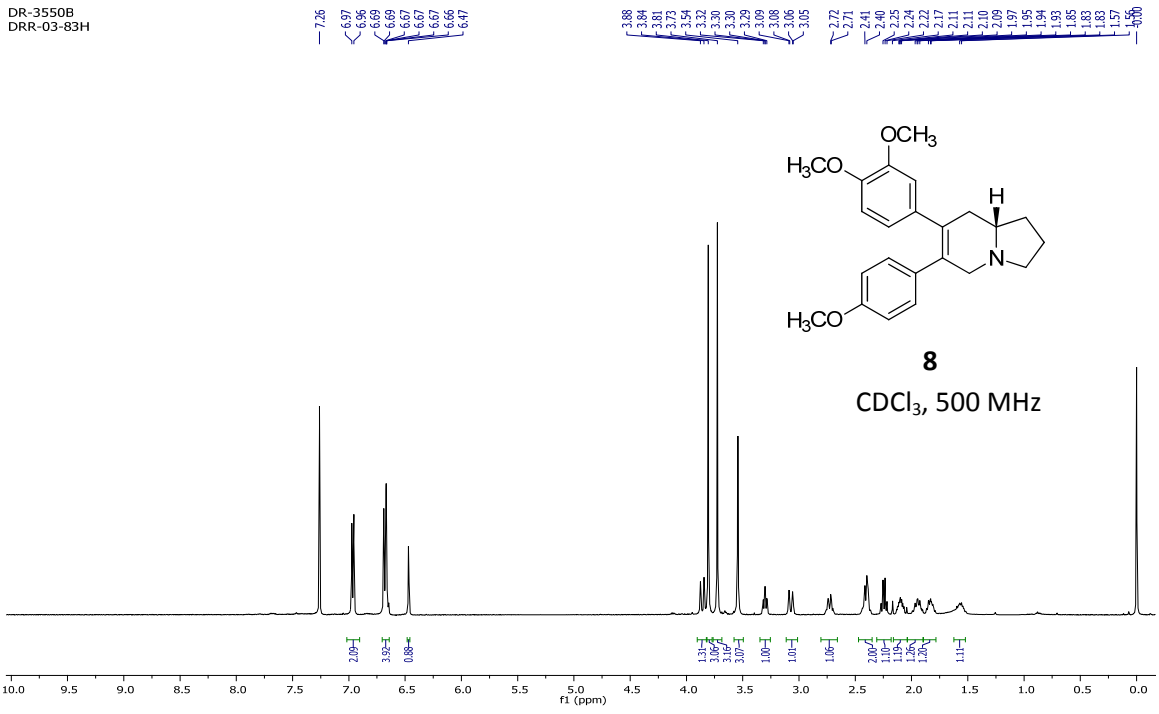
36

$CDCl_3$, 500 MHz



36

$CDCl_3$, 125 MHz



8

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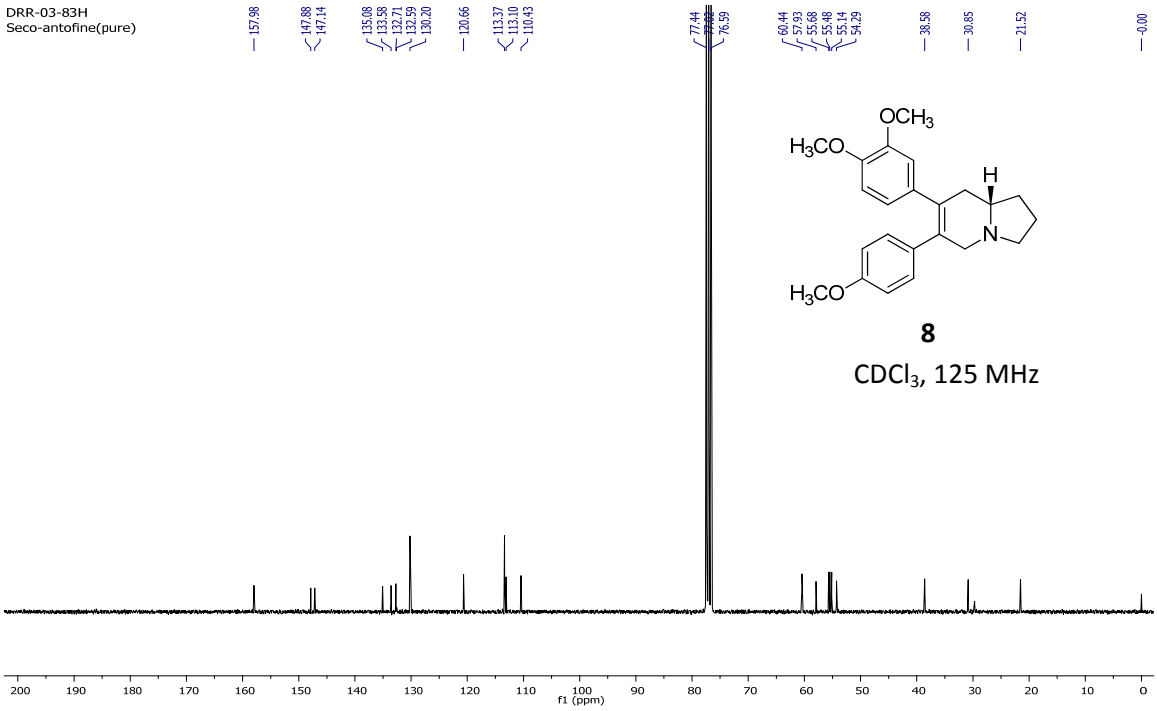

8

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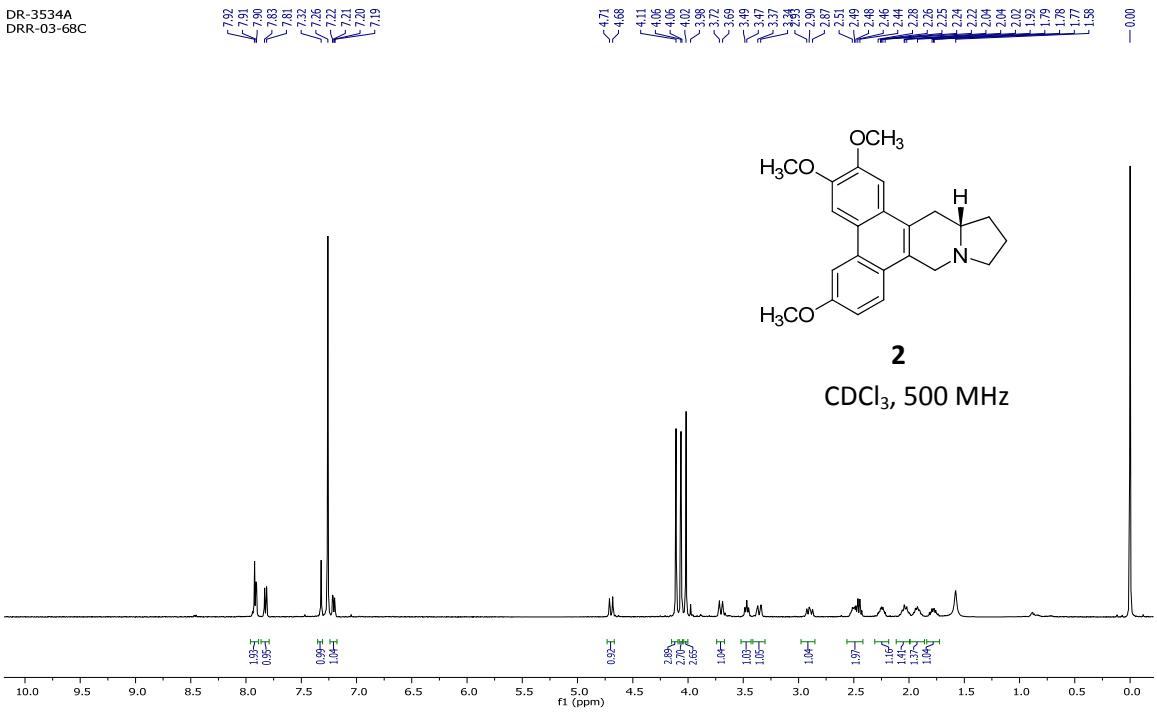

2

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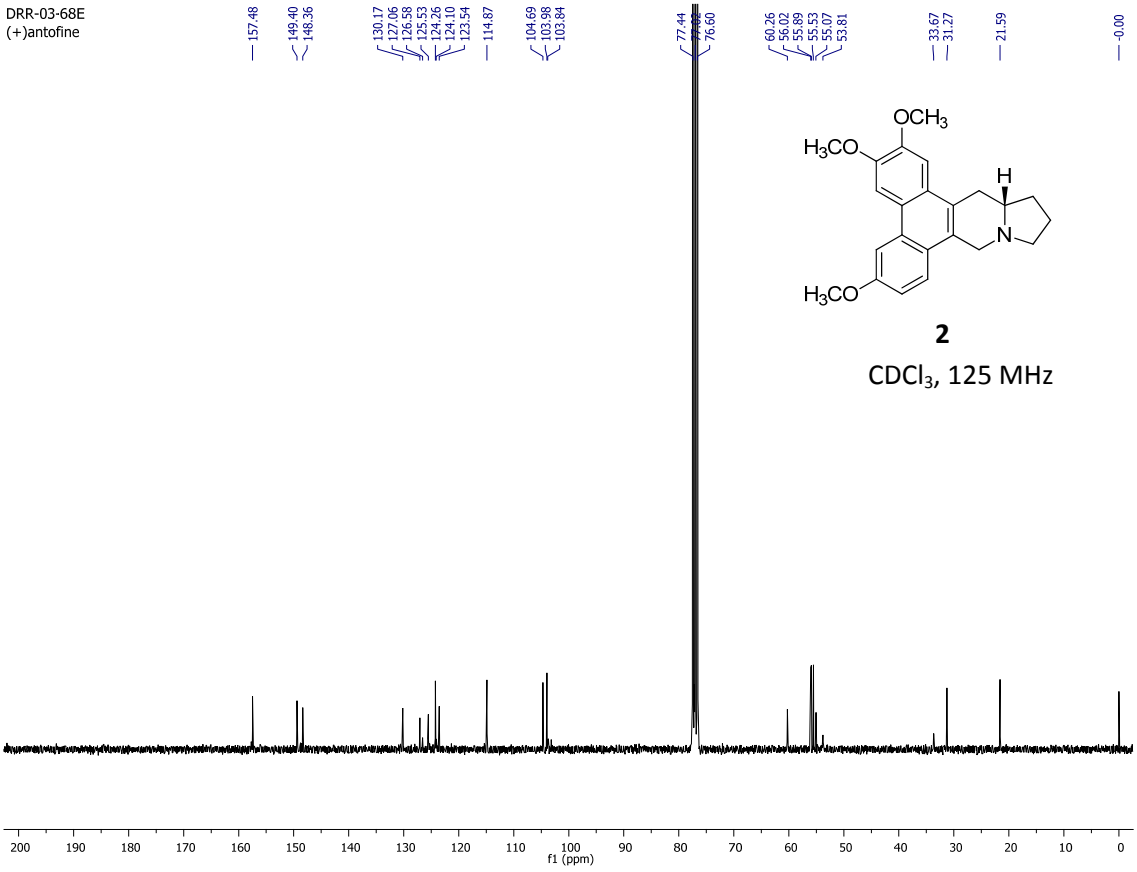
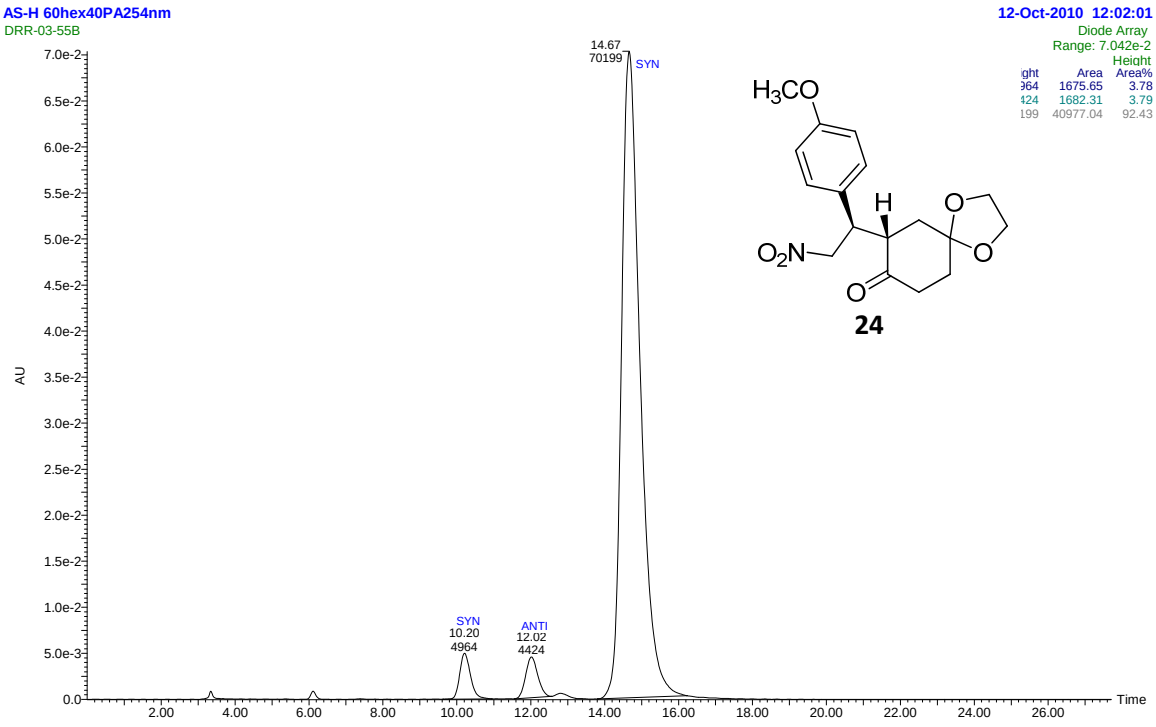


2

$CDCl_3$, 125 MHz

3.9 HPLC chromatogram for nitroketone **24**



Chapter 4

Enantioselective approach to functionalized quinolizidines: synthesis of (+)-julandine and (+)-cryptopleurine

This chapter is based on the following publication:

Pansare, S.V.; Dyapa, R. *Org. Biomol. Chem.* **2012**, *10*, 6776–6784

Contribution of authors

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

R. Dyapa: Synthetic experimental work and manuscript preparation.

4.1 Introduction

The quinolizidine motif is a prominent structural unit in numerous alkaloids.[1] The structurally related phenanthroquinolizidine alkaloids[2] are also well known and these have attracted considerable interest due to their anticancer,[3] antiviral,[4] amoebicidal[5] and anti-inflammatory[6] activities. For example, the secophenanthroquinolizidine alkaloid (+)-julandine (**1**)[7] has antimicrobial activity[8] and the corresponding phenanthroquinolizidine (-)-cryptopleurine (**2**),[9] an enantiomer of (+)-cryptopleurine, has also shown excellent biological activities such as antiviral,[10] amoebicidal[11] and anticancer activity.[3] The synthesis of quinolizidines,[13] aryl-fused quinolizidines[14] and phenanthroquinolizidines[12] has therefore continued to engage synthetic chemists over the years.

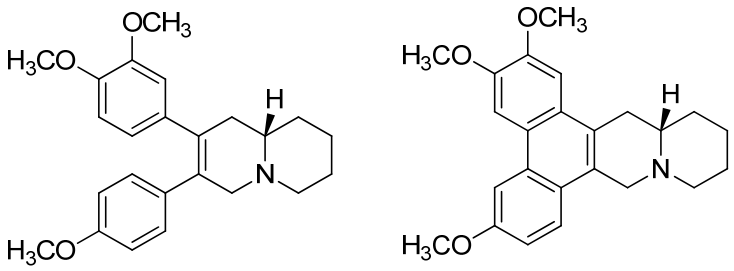
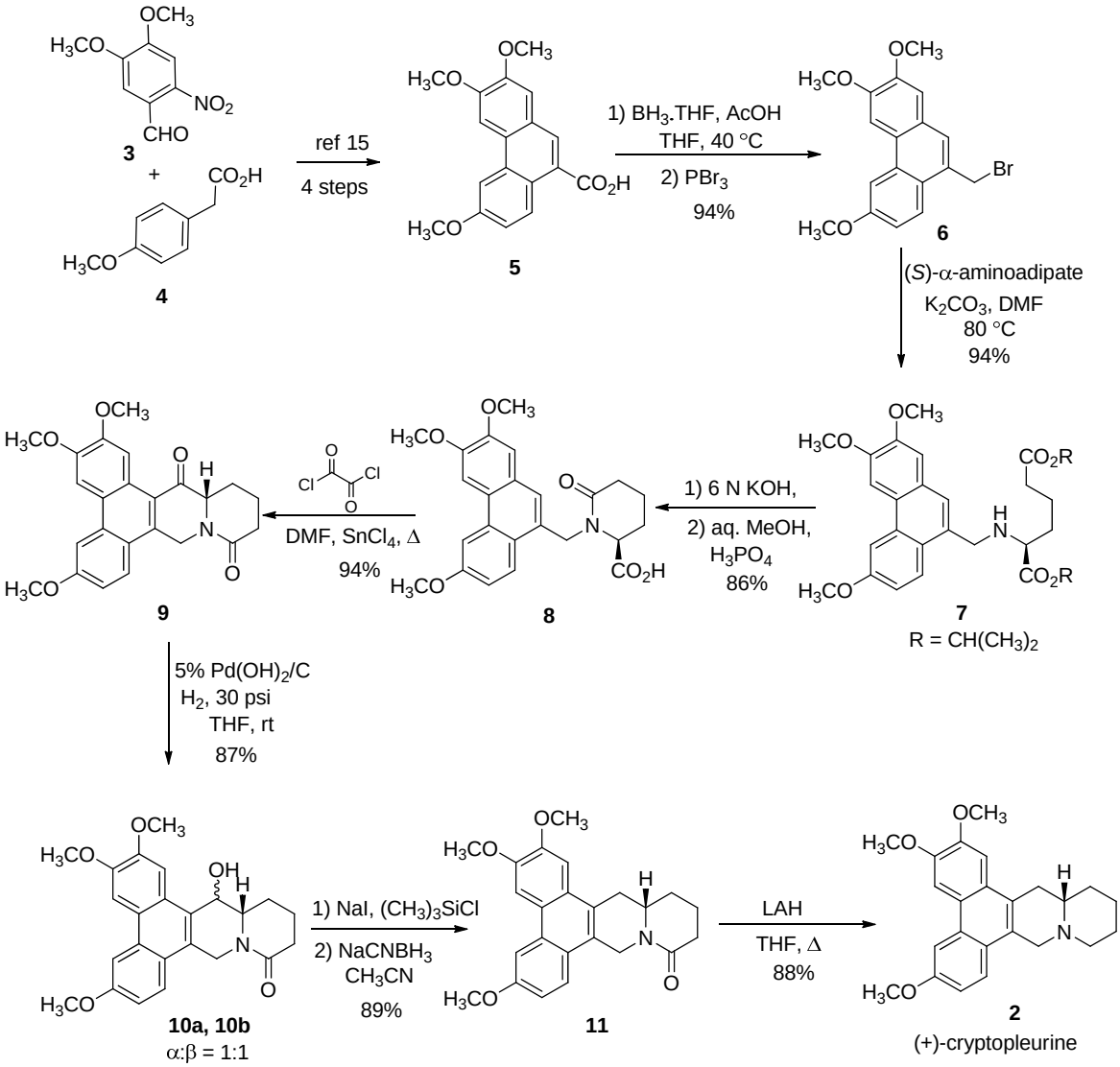


Figure 4.1 (+)-Julandine (**1**) and (+)-Cryptopleurine (**2**)

4.2 Reported syntheses of (+)-cryptopleurine

The following summary provides an overview of the syntheses of cryptopleurine in enantiomerically enriched form.

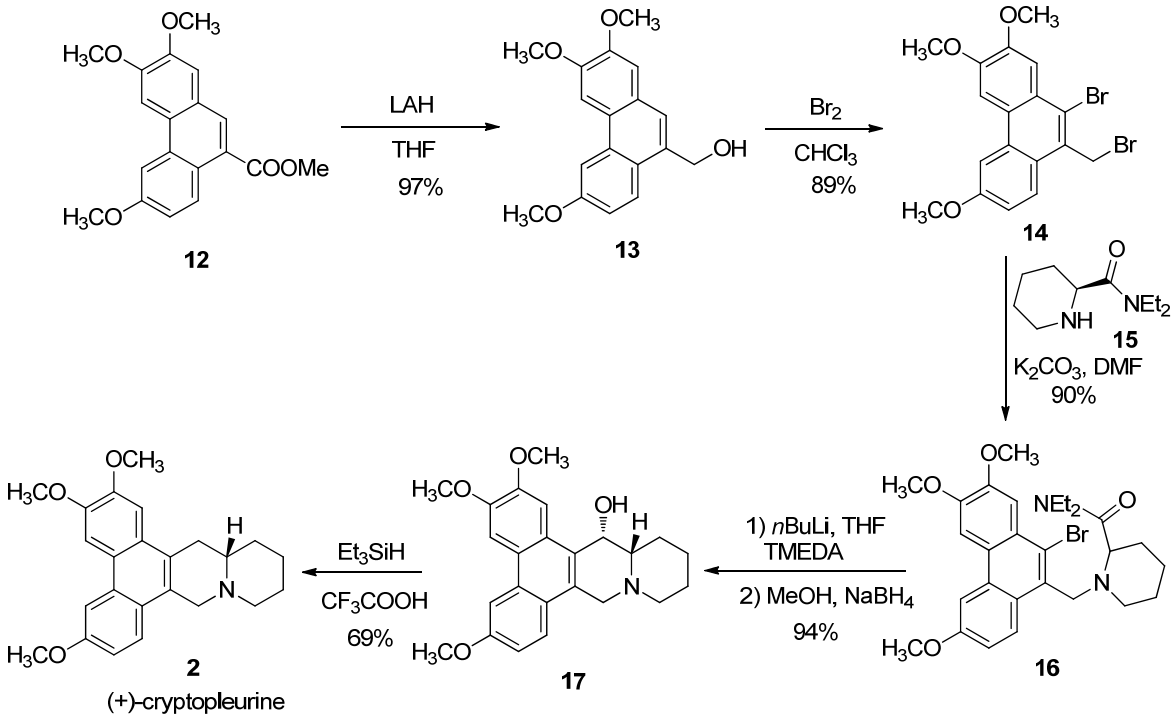
Rapoport and co-workers reported an enantioselective synthesis of (+)-cryptopleurine (Scheme 1).[12d] The key step in their synthesis is an intramolecular Friedel-Crafts acylation reaction. The synthesis began with phenanthrene carboxylic acid **5**, which was prepared from **3** and **4** according to the reported procedure.[15] Reduction of **5** to the alcohol and subsequent bromination provided the bromide **6**. Optically pure diisopropyl α-aminoadipate was coupled with the bromide **6** to provide the alkylated diester **7** which was treated with 6 N KOH to provide the amido acid **8** (Scheme 4.1).



Scheme 4.1

Amido ketone **9** was obtained by the cyclization of the amido acid **8** using oxalyl chloride in DMF followed by $SnCl_4$ treatment. Hydrogenation of **9** ($Pd(OH)_2/C$) provided a mixture of amido alcohols **10a,b** which was converted to the phenanthraquinolizidinone **11** by a two step dehydroxylation involving conversion to the corresponding iodide and subsequent dehalogenation. Finally the amide in **11** was reduced with LAH to provide the title compound (+)-cryptopleurine.

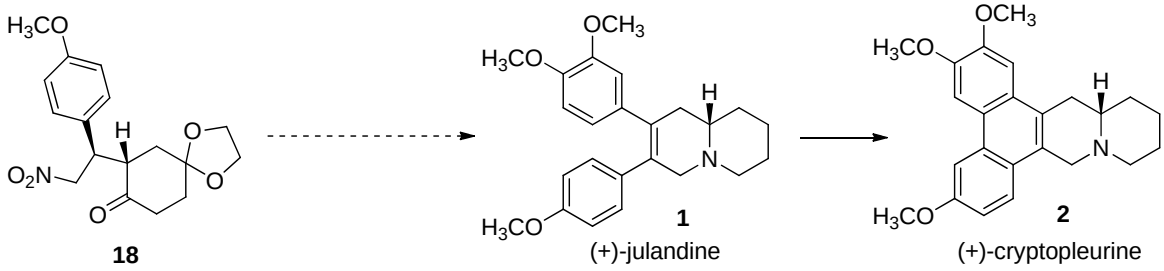
Wang and co-workers reported a short and efficient route (Scheme 4.2) to enantiomerically pure (+)-cryptopleurine, involving Parham-type cycloacylation as the key step.[9a] The synthesis begins with reduction of ester **12** with LAH to provide the alcohol **13**. Alcohol **13** was brominated to afford the dibromo compound **14**. Amide **16** was prepared from the alkylation of (*S*)-*N*,*N*-diethylpiperidinedine-2-carboxamide (**15**) with dibromide **14**, using K_2CO_3 as base. Amide **16** was treated with *n*BuLi to effect cyclization to provide the intermediate ketone which was subsequently reduced to **17**. Dehydroxylation of aminol **17** using triethylsilane and trifluoroacetic acid provided the title compound (+)-cryptopleurine.



Scheme 4.2

4.3 Objective

The interest in quinolizidines is an outcome of our ongoing studies on the development and application of the organocatalytic ketone-nitroalkene Michael addition reaction.[16] This reaction has been extensively studied and although the development of new catalysts for the process continues at a significant pace, further application of the nitroketone Michael adducts has progressed relatively slowly.[16] It was therefore decided to examine the utility of a suitable *γ*-nitroketone in a general approach to the quinolizidine motif. The initial target of the investigation was the naturally occurring (+)-julandine, since only one enantioselective synthesis of the unnatural (-)-julandine has been reported.[10a] In addition, cryptopleurine can be obtained in one step by the oxidative cyclization of julandine[10e] and hence a route to julandine would also establish an access to cryptopleurine (**2**).



Scheme 4.3

4.4 Retrosynthetic analysis for the diaryl quinolizidine motif

Retrosynthetically, the 2,3-diaryl quinolizidine motif of julandine may be accessible by aryl cross coupling from a 7-aryl quinolizidinone such as **A** (Figure 4.2) which derives from the functionalized piperidine **B**. This piperidine intermediate can be

made from the reductive cyclization of the nitroketone **C** which can be obtained by the reductive opening of the lactone **D**. Ultimately, lactone **D** derives from a Baeyer-Villiger oxidation of the corresponding γ-nitroketone which leads us to the organocatalytic, ketone-nitroalkene Michael addition of an appropriate cyclic ketone and nitroalkene.

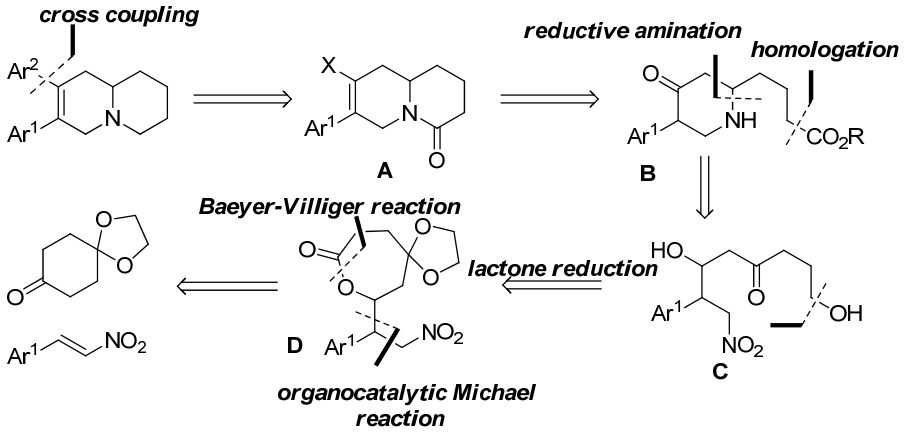
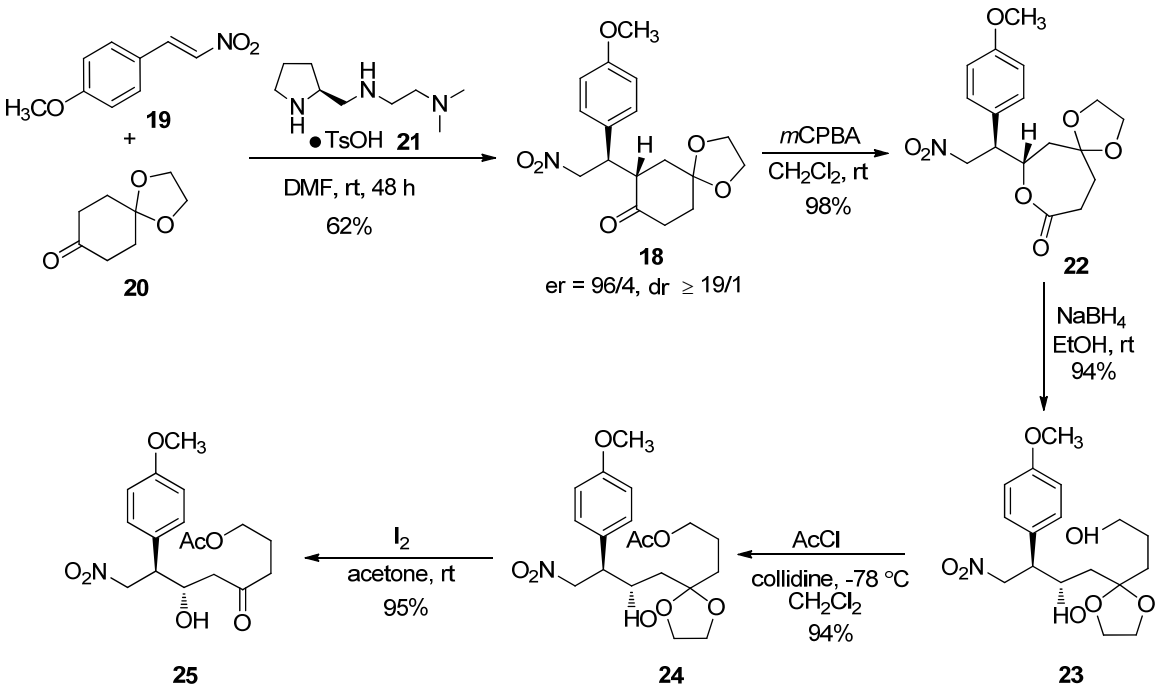


Figure 4.2

4.5 Results and Discussion

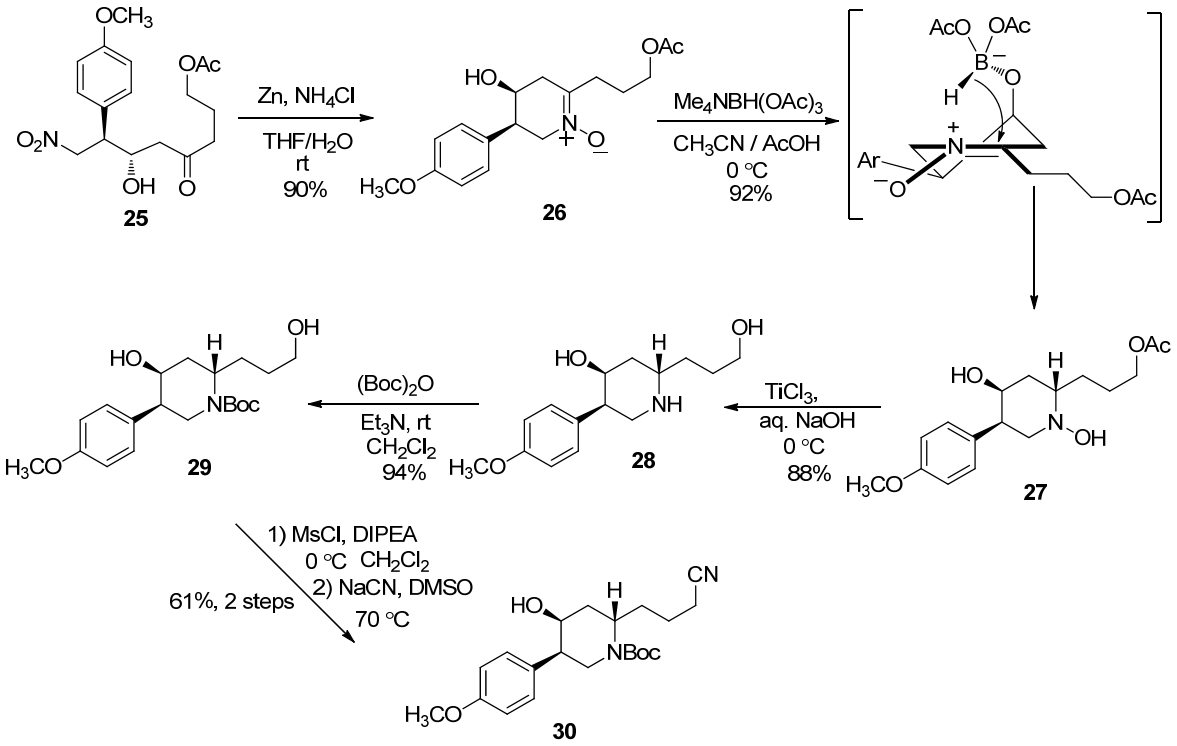
The organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal and 4-methoxy-β-nitrostyrene employing a chiral pyrrolidine-based triamine catalyst[14a,17j] provided the requisite γ-nitroketone **18** in good yield and stereoselectivity (er = 96/4, dr >19/1, Scheme 4.4). Baeyer-Villiger oxidation of **18** provided the corresponding lactone **22** which was reduced with sodium borohydride to the nitrodiol **23** (92%, 2 steps). The primary alcohol in **23** was then selectively acetylated to provide the acetate **24** (94%) which was converted to the nitroketone **25** (Scheme 4.4) by deketalization with iodine in acetone (95%).[18]



Scheme 4.4

With the nitroketone **25** in hand, the construction of the quinolizidine framework was initiated. This process involved the preparation of a suitably substituted piperidine from **25** and then constructing the quinolizidine by cyclization. Reduction of the nitroketone **25** with zinc in aq. ammonium chloride provided the nitrone **26**, presumably from the hydroxylamine derived from **26**. Reduction of the nitrone **26** with tetramethylammonium triacetoxyborohydride provided the *N*-hydroxy piperidine **27** as a single diastereomer (Scheme 4.5). The stereoselectivity of this reduction is presumably due to an intramolecular, hydroxyl-directed reduction of **26**. Reduction of the N-O bond in **27** ($TiCl_3$ followed by aqueous NaOH[19]) provided the corresponding amino alcohol **28** which was protected to provide **29**. Conversion of **29** into the quinolizidine motif

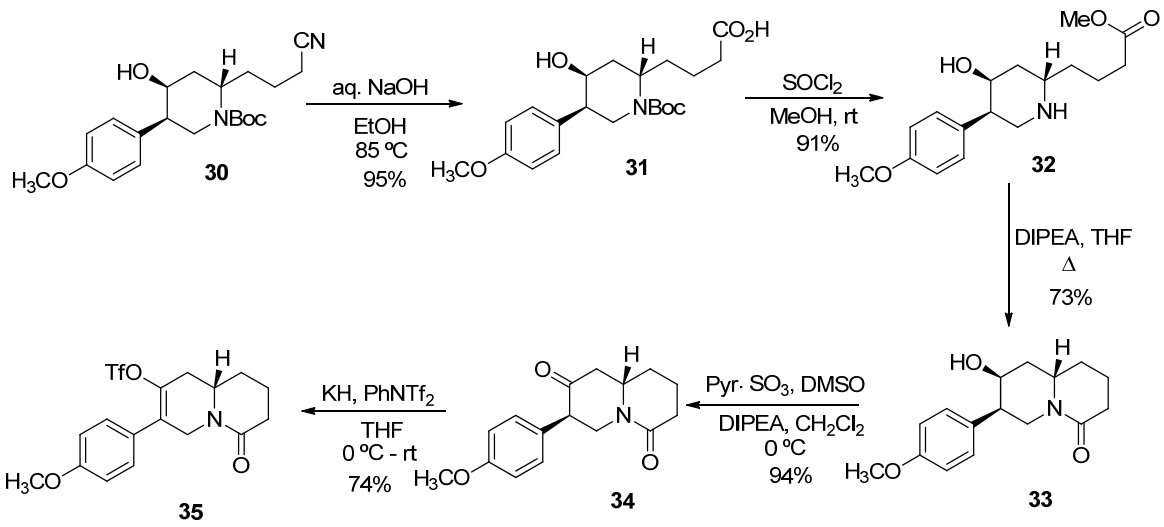
required a one carbon homologation. This was achieved by conversion of the primary alcohol of **29** to the mesylate and subsequent cyanation to provide **30**.



Scheme 4.5

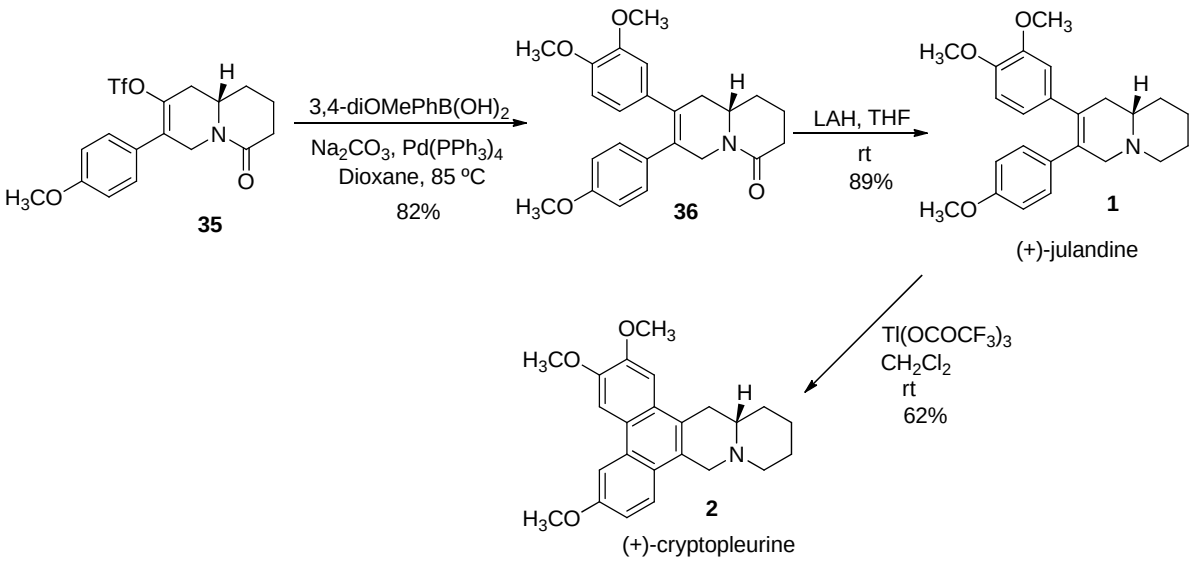
Conversion of **30** to the corresponding quinolizidinone **33** could be accomplished by hydrolysis of the nitrile **30** to the acid **31**, followed by esterification with concommitant removal of the Boc group and subsequent cyclization of the resulting aminoester **32** (63% overall). The overall conversion of **30** to **33** could also be achieved in one step (30%) by treatment of **30** with HCl in methanol followed by basification of the crude product. However, the multi-step procedure proceeds with higher overall yield (63%) and is therefore the method of choice. Oxidation of **33** provided the ketolactam **34**

which was then converted to the enol triflate **35** (Scheme 4.6). This is the key intermediate for the target alkaloids.



Scheme 4.6

The conversion of **35** to (+)-julandine (**1**) was achieved by a Suzuki cross-coupling reaction with 3,4-dimethoxyphenyl boronic acid to generate the lactam **36** followed by reduction with LAH to give **1** (73%, 2 steps). As expected, oxidative cyclization of **1** with thallium trifluoroacetate[10e] provided (+)-cryptopleurine (**2**, 62%, Scheme 4.7).



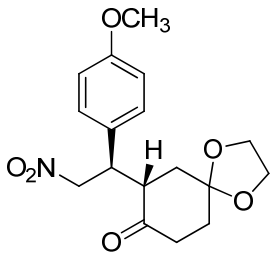
Scheme 4.7

4.6 Conclusion

In conclusion, an efficient synthesis of functionalized quinolizidines was developed from a simple *γ*-nitroketone starting material which is readily available from the organocatalytic ketone-nitroalkene Michael addition reaction. The methodology was applied in the first total synthesis of the natural enantiomer of the diarylquinolizidine alkaloid (+)-julandine and the structurally related phenanthroquinolizidine alkaloid (+)-cryptopleurine. The synthetic strategy should be particularly amenable to the preparation of focused libraries of analogs of these alkaloids by judicious selection of the nitroalkene and the aryl component in the cross-coupling step. This possibility as well as other synthetic applications of nitroketones and nitrones related to **18** and **26** are the focus of ongoing investigations in the Pansare group.

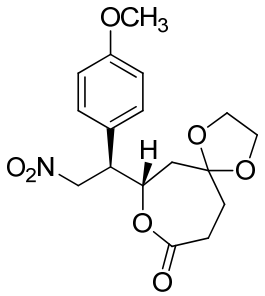
4.7 Experimental section

(7*S*)-7-[(1*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-one (18):



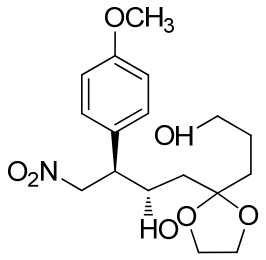
To a solution of 1,4-cyclohexanedione monoethylene ketal (13.0 g, 83.7 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine[16a] (572 mg, 3.34 mmol) and *p*-toluene sulfonic acid monohydrate (634 mg, 3.34 mol) was added a solution of 4-methoxy-*β*-nitrostyrene (3.00 g, 16.7 mmol) in DMF (30 mL) and the resulting solution was stirred at ambient temperature for 48 h. Ethyl acetate (100 mL) was added and the solution washed with water, aq. HCl (3 N), dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash chromatography on silica gel to provide 4.60 g of a solid. This was dissolved in ethyl acetate (23 mL) and precipitated by addition of hexanes (70 mL). The procedure was repeated once to provide 3.50 g (62%) of **18** with 96% ee. In repeated runs, **18** was obtained in 90-96% ee. Spectroscopic data for **18** is in agreement with that reported in the literature.[17j]

(*S*)-7-((*R*)-1-(4-methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (22):



To a solution of the nitroketone **18** (3.10 g, 9.25 mmol) in anhydrous dichloromethane (60 mL) at ambient temperature, was added solid sodium phosphate (3.21 g, 12.0 mol) followed by *m*-chloro perbenzoic acid (~77%, 4.94 g, 28.7 mmol). The resulting white slurry was stirred vigorously for 16 h. Dichloromethane (100 mL) was added and the solution was washed with 5% aq. NaOH (2 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 3.20 g, (98%) of **22** as a white, solid foam. This material was pure by ^1H NMR (500 MHz) and was used in the next step without purification. Spectroscopic data for **22** is in agreement with that reported in the literature.[17j] $[\alpha]^{23}_D$ = + 58.3 (*c* 1, $CHCl_3$).

(2*S*,3*R*)-1-(2-(3-Hydroxypropyl)-1,3-dioxolan-2-yl)-3-(4-methoxyphenyl)-4-nitrobutan-2-ol (23):

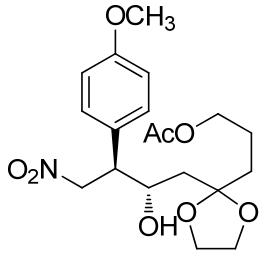


To a solution of the lactone **22** (2.85 g, 8.11 mmol) in ethanol (30 mL), was added sodium borohydride (0.46 g, 12.1 mmol). The mixture was stirred at room temperature for 3 h, then cooled to 0 °C and the solution was acidified (pH~5) with aq. HCl (0.5 M). The acidic solution was extracted with EtOAc (2 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to provide 2.70 g (94%) of the diol **23** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc).

IR (neat): 3493, 2960, 2837, 1550, 1511, 1378, 1248, 1059 1028, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, J = 8.6, Ar*H*), 6.85 (d, 2H, J = 8.6, Ar*H*), 5.04 (dd, 1H, J = 5.2, 12.7, C*H*$_2$NO$_2$), 4.59 (dd, 1H, J = 9.7, 12.7, C*H*$_2$NO$_2$), 4.05-3.99 (m, 1H, Ar-C*H*), 3.99-3.93 (m, 5H, CHO*H*, OC*H*$_2$C*H*$_2$O), 3.78 (s, 3H, OC*H*$_3$), 3.55 (t, 2H, J = 6.2, C*H*$_2$OH), 3.42-3.38 (td,1H, J = 5.2, 9.5, C*H*OH), 1.70-1.57 (m, 4H, *CH*$_2$CHOH, C*H*$_2$C$_{ketal}$), 1.50-1.39 (m, 2H, C*H*$_2$CH$_2$OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2 (Ar*C*-OCH$_3$), 129.3 (Ar*C*$_{ipso}$), 129.1 (2 x Ar*C*), 114.5 (2 x Ar*C*), 111.8 (O*C*O), 78.5 (*C*H$_2$NO$_2$), 70.1 (*C*HOH), 64.9 (O*C*H$_2$CH$_2$O), 64.6 (OCH$_2$*C*H$_2$O), 62.6 (*C*H$_2$OH), 55.3 (ArO*C*H$_3$),

50.3 (HO-CH*C*H_2), 40.3 (Ar-*C*HCH$_2$), 33.3 (CH_2C*C*H_2), 26.7 (*C*H_2CH_2OH); MS (API-ES): *m/z* 378 (M+Na); MALDI-TOF MS: 378.1611 (378.1529 calc. for $C_{17}H_{25}NO_7Na$ (M+Na)); $[\alpha]^{23}_D$ = + 40.5 (*c* 1, $CHCl_3$).

3-(2-((2*S*,3*R*)-2-Hydroxy-3-(4-methoxyphenyl)-4-nitrobutyl)-1,3-dioxolan-2-yl)propyl acetate (24):



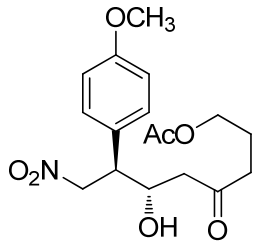
A solution of the diol **23** (2.10 g, 5.91 mmol) in dry dichloromethane (35 mL) was cooled to -78 °C and acetyl chloride (0.50 mL, 7.09 mmol) and collidine (1.43 mL, 11.8 mmol) were added. The solution was stirred at -78 ^oC for 4 h and then diluted with dichloromethane (50 mL). The resulting solution was warmed to ambient temperature and washed with aq. HCl (0.5 M, 2 x 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 2.20 g (94%) of the acetate **24** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc/hexanes, 6:4).

IR (neat): 3496, 2961, 1731, 1550, 1513, 1375, 1242, 1141, 1032, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J* = 8.7, Ar*H*), 6.85 (d, 2H, *J* = 8.7, Ar*H*), 5.04 (dd, 1H, *J* = 5.3, 12.7, C*H*$_2$NO$_2$), 4.59 (dd, 1H, *J* = 9.6, 12.7, C*H*$_2$NO$_2$), 3.99-3.92 (m, 8H, Ar-

C*H,* CHO*H*, OC*H*$_2$C*H*$_2$O, C*H*$_2$OAc) 3.78 (s, 3H, ArOC*H*$_3$), 3.42-3.38 (td, 1H, *J* = 5.3, 9.5, C*H*OH), 2.03 (s, 3H, COC*H*$_3$) 1.67-1.64 (m, 3H, CHC*H*$_2$C$_{ketal}$, C$_{ketal}$C*H*$_2$), 1.50-1.46(m, 3H, CHC*H*$_2$C$_{ketal}$, C*H*$_2$CH$_2$OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6 (*C*(O)CH$_3$), 159.7 (Ar*C*-OCH$_3$), 129.8 (Ar*C*$_{ipso}$), 129.6 (2 x Ar*C*), 115.0 (2 x Ar*C*), 112.0 (O*C*O), 79.0 (*C*H$_2$NO$_2$), 70.6 (*C*H$_2$OAc), 65.5 (*C*HOH) 65.2 (OCH$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 55.8 (O*C*H$_3$), 50.8 (CH*C*H$_2$C$_{ketal}$) 40.9 (Ar-*C*H), 33.8 (C$_{ketal}$*C*H$_2$CH$_2$), 23.5 (OC(O)*C*H$_3$) 21.5 (*C*H$_2$CH$_2$O); MS (API-ES, pos.): *m/z* 420.4 (M+Na); MALDI-TOF MS: 420.1704 (420.1634 calc. for $C_{19}H_{27}NO_8Na$ (M+Na));

$[\alpha]^{23}_D$ = + 23.6 (*c* 0.5, $CHCl_3$).

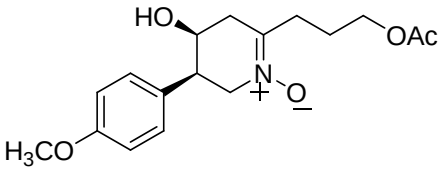
(6*S*,7*R*)-6-Hydroxy-7-(4-methoxyphenyl)-8-nitro-4-oxooctyl acetate (25):



A solution of the ketal **24** (2.20 g, 5.50 mmol) and iodine (0.070 g, 0.55 mmol) in acetone (20 mL) was stirred at ambient temperature for 1 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane. The resulting solution was washed successively with aqueous $Na_2S_2O_3$ (5% w/v, 2 x 25 mL) and brine (1 x 25mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.85 g (95%) of the nitroketone **25** as a yellow solid. This material was pure by ^{1}H NMR and was used in the next step without purification. Mp:77-80 ºC;

IR (neat): 3402, 2955, 1735, 1708, 1548, 1380, 1253, 1227, 1111, 1036, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, 2H, J = 8.7, Ar*H*), 6.87 (d, 2H, J = 8.7, Ar*H*), 5.07 (dd, 1H, J = 5.1, 12.8, CH_2NO_2), 4.60 (dd, 1H, J = 9.8, 12.8, CH_2NO_2), 4.21-4.18 (m, 1H, ArC*H,*), 4.03-4.01 (br t, 2H, J = 6.3, CH_2OAc), 3.79 (s, 3H, OCH_3), 3.49-3.44 (m, 2H, C*H*OH, CHO*H*), 2.43-2.37 (m, 4H, CH_2COCH_2) 2.01 (s, 3H, COCH_3,), 1.86-1.82 (m, 2H, C$H_2$$CH_2$O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6 (*C*O) 171.0 (O*C*(O)CH_3), 159.4 (Ar*C*-OCH_3), 129.0 (2 x Ar*C*), 128.6 (ArC_{ipso}), 114.7 (2 x Ar*C*), 78.4 (*C*H_2NO_2), 69.6 (*C*HOH), 63.3 (*C*H_2OAc), 55.3 (O*C*H_3), 49.1 (*C*H_2C(O)), 46.8 (Ar*C*H), 39.7 (C(O)*C*H_2), 22.4 (*C*H_2CH_2CO), 20.9 (OC(O)*C*H_3); MS (API-ES, pos.): *m/z* 376 (M+Na); MALDI-TOF MS: 376.1443 (376.1372 calc. for $C_{17}H_{23}NO_7Na$, (M+Na).

(3*R*,4*S*)-4-Hydroxy-6-(3-acetoxypropyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-1-oxide (26):

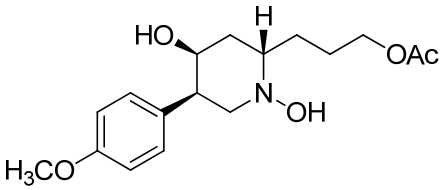


A solution of NH_4Cl (0.297 g, 5.55 mmol) in water (5 mL) was added to a solution of the nitroketone **25** (1.96 g, 5.55 mmol) in THF (24 mL). Activated Zn powder (3.51 g, 55.5 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered through Celite, the residue was washed with THF, and the combined filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and the solution was

washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.60 g (90%) of **26** as a pale yellow foam. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 2948, 1735, 1611, 1509, 1459, 1230, 1140, 1031, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, 2H, J = 8.7, Ar*H*), 6.90 (d, 2H, J = 8.7, Ar*H*), 4.37-4.32 (apparent br t, 1H, J = 13.4, ArC*H*), 4.20-4.19 (br s, 1H, CHO*H*), 4.14-4.11 (t, 2H, J = 6.5, CH_2OAc), 3.92 (dd, 1H, J = 5.5, 14.9, CH_2N), 3.80 (s, 3H, OCH_3), 3.25-3.21 (m, 1H, CH_2N), 2.89-2.53 (m, 4H, CH_2C=N, C=NCH_2CH$_2$) 2.01 (s, 3H, COCH_3,), 1.99-1.92 (m, 2H, CH_2CH$_2$OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (*C*OCH$_3$), 159.0 (Ar*C*-OCH$_3$), 145.0 (*C*=NO) 129.4 (ArC_{ipso}), 128.7 (2 x Ar*C*), 114.3 (2 x Ar*C*), 65.1 (*C*HOH), 63.8 (O*C*H$_2$), 57.5 (O*C*H$_3$), 55.2 (*C*H$_2$NO), 43.5 (Ar-*C*H), 37.6 (*C*H$_2$C=N), 28.1 (*C*H$_2$CH$_2$O), 23.5 (CO*C*H$_3$) 20.9 (N=C*C*H$_2$); MS (APCI, pos.): *m/z* 322.4 (M+1); MALDI-TOF MS: 344.1557 (344.1474 calcd for $C_{17}H_{23}NO_5Na$ (M+Na)).

3-((2*R*,4*S*,5*S*)-4-Hydroxy-5-(4-methoxyphenyl)-*N*-hydroxypiperidin-2-yl)propylacetate (27):

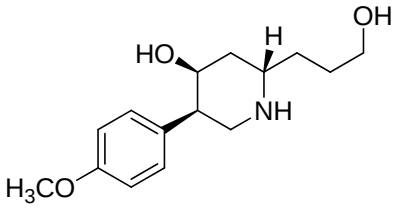


To a solution of tetramethylammonium borohydride (2.62 g, 9.96 mmol) in acetonitrile (14 mL) was added acetic acid (14 mL). The mixture was stirred at 0 °C for 5 min and a solution of the nitrone **26** (1.6 g, 4.98 mmol) in acetonitrile (6 mL) was added.

The mixture was stirred at 0 °C for 1 h and then basified (pH ~ 8) with aqueous NaOH (5% solution). The mixture was extracted with dichloromethane (2 x 60 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to give 1.48 g (92%) of **27** as a brown viscous material. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2).

IR (neat): 3415, 2923, 1731, 1512, 1238, 1032, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.7, Ar*H*), 6.88 (d, 2H, J = 8.5, Ar*H*), 4.10-4.07 (t, 2H, J = 6.7, OCH_2), 3.91 (br s, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.58-3.48 (m, 1H, NC*H*), 3.31-3.20 (m, 2H, NCH_2, CHO*H*), 3.03 (br d, J = 12.4, 1H, CH_2N), 2.86-2.82 (m, 1H, ArC*H*), 2.11-2.00 (m, 5H, COCH_3, CHCH_2CH), 1.74-1.55 (m, 2H, CH_2CH$_2$OAc), 1.50-1.42 (m, 2H, NCHCH_2); MS (APCI, pos.): *m/z* 324.2 (M+1); HRMS (CI): *m/z* 324.1812 (324.1811 calc. for $C_{17}H_{26}NO_5$ [M+H]$^+$); $[\alpha]^{23}_D$ = + 39.1 (*c* 0.7, $CHCl_3$).

(2*S*,4*S*,5*R*)-2-(3-Hydroxypropyl)-5-(4-methoxyphenyl)piperidin-4-ol (28):

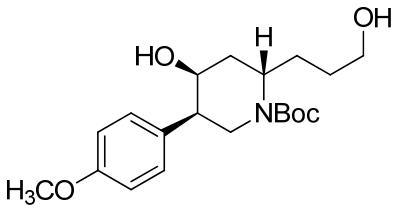


To a stirred solution of the hydroxylamine **27** (0.90 g, 2.8 mmol) in methanol (20 mL) was added aq. $TiCl_3$ (3.77 mL, 4.17 mmol) at 0 °C and the mixture was stirred at 0 ^{o}C for 4 h. Aqueous NaOH (20% w/v, 27 mL) was added and the mixture was filtered to remove inorganic salts. The residue washed with methanol and the combined filtrates

were concentrated under reduced pressure. The resulting aqueous solution was extracted with dichloromethane (3 x 40 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to provide 0.65 g (88%) of the amino alcohol **28** as a yellow solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

Mp:138-140 ºC; IR (neat): 3554, 2910, 2843, 1511, 1461, 1240, 1182, 1056, 1026, 817 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.10 (d, 1H, J = 2.32, C*H*OH), 3.79 (s, 3H, OCH_3), 3.64-3.54 (m, 2H, CH_2OH), 3.38-3.35 (t, 1H, J = 12.5, NCH_2), 3.08-3.03 (m, 1H, NC*H*) 3.00 (dd ,1H, J = 4, 12.5, NCH_2), 2.79-2.74 (m, 1H, ArC*H*), 1.96-1.92 (dt, 1H, J = 13.8, 3.0, CHCH_2CH), 1.79-1.75 (m, 1H, CHCH_2CH), 1.65-1.57 (m, 3H, NCHCH_2, CH_2CH$_2$OH), 1.42-1.39 (m, 1H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6 (Ar*C*-OCH$_3$), 132.8 (ArC_{ipso}), 128.77 (2 x Ar*C*), 114.2 (2 x Ar*C*), 69.3 (*C*HOH), 62.8 (*C*H$_2$OH), 55.3 (OCH$_3$), 49.8 (*C*HNH), 46.7 (*C*H$_2$NH), 44.1 (Ar-*C*H), 39.4 (CH*C*H$_2$CH), 35.6 (NHCH*C*H$_2$) 30.4 (*C*H$_2$CH$_2$OH); MS (APCI, pos.): *m/z* 266.2 (M+1); MALDI-TOF MS: 266.1796 (266.1756 calc. for $C_{15}H_{24}NO_3$ $[M+H]^+$).

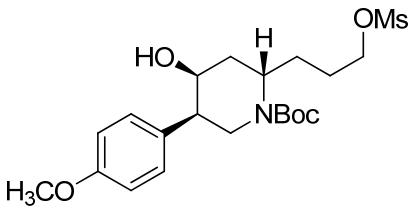
(2*S*,4*S*,5*R*)-*tert*-Butyl 4-hydroxy-2-(3-hydroxypropyl)-5-(4-methoxyphenyl) piperidine-1-carboxylate (29):



To a solution of the aminol **28** (0.850 g, 3.21 mmol) and triethylamine (0.54 mL, 3.84 mmol) in dry dichloromethane (10 mL) at 0 °C was slowly added a solution of the $(Boc)_2O$ (0.706 g**,** 3.24 mmol) in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 16 h, saturated $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with aqueous HCl (0.5 M, 2 x 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 1.1 g (94%) of **29** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was obtained by purification by flash chromatography on silica gel (EtOAc).

IR (neat): 3403, 2936, 1658, 1511, 1420, 1246, 1164, 1067, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.48-4.46 (br m, 1H, NC*H*), 4.32 (br dd, 1H, J = 3.4, 14.1 NCH_2,), 4.21-4.14 (m, 1H, C*H*OH), 3.80 (s, 3H, OCH_3), 3.72-3.70 (m, 2H, CH_2OH), 3.35 (dd, 1H, J = 4.2, 14.1, NCH_2), 3.06 (br m, 1H, ArC*H*), 1.89-1.53 (m, 6H, $CHCH_2CH$, $NCHCH_2$, CH_2CH_2OH), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (Ar*C*-OCH_3), 155.3 ($CO_2{}^t$Bu), 130.8 (2 x Ar*C*), 130.2 (ArC_{ipso}), 113.8 (2 x Ar*C*) 80.1 ($C(CH_3)_3$), 66.4 (*C*HOH), 62.6 (CH_2OH), 55.3 (OCH_3), 50.8 (N*C*H), 44.4 (CH_2N), 42.8 (Ar*C*H), 33.0 ($CHCH_2CH$), 29.3 ($NCHCH_2$), 28.5 ($C(CH_3)_3$), 27.6 (CH_2CH_2OH); MS (APCI, pos.): *m/z* 266.2 (M-Boc+2); HRMS (CI): *m/z* 266.1751 (266.1756 calc. for $C_{15}H_{24}NO_3$ (M-Boc +2H); $[\alpha]^{23}_D$ = + 68.2 (*c* 1, $CHCl_3$).

3-((2*S*,4*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)propyl methanesulfonate (29a):

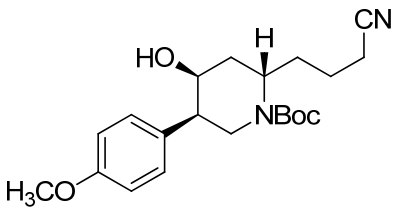


To a stirred solution of **29** (1.10 g, 3.01 mmol) in dichloromethane (15 mL) was added DIPEA (0.53 mL) followed by methanesulfonyl chloride in dichloromethane (10 mL) over 15 min. at 0 °C. The mixture was stirred at 0 °C for 3 h. Cold water (10 mL) was added and the organic layer was separated, washed with water (3 x 25 mL), brine (1 x 25 mL) dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 2:8) to provide 0.85 g (64%) of **29a** as a white solid.

Mp: 140-144 ºC; IR (neat): 3441, 2937, 1676, 1511, 1418, 1353, 1247, 1167, 915, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.46 (br m, 1H, NC*H*), 4.29-4.18 (m, 3H, NCH_2, OCH_2), 4.16-4.14 (m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.33 (dd, 1H, J = 4.1, 14.2, NCH_2), 3.07-3.05 (m, 1H, ArC*H*) 3.02 (s, 3H, SO_2CH_3), 1.92-1.61 (m, 6H, CHCH_2CH, NCHCH_2, CH_2CH_2O), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (Ar*C*-OCH_3), 155.0 ($CO_2{}^t$Bu), 130.8 (2 x Ar*C*), 130.1 (ArC_{ipso}), 113.9 (2 x Ar*C*), 80.2 (*C*(CH_3)$_3$), 69.7 (*C*H_2O), 66.4 (*C*HOH), 55.3 (O*C*H_3), 50.4 (N*C*H), 44.4 (*C*H_2N), 42.8 (Ar*C*H), 37.4 (SO_2CH_3), 33.0 (CH*C*H_2CH), 28.5 (C(*C*H_3)$_3$), 27.2 (NCH*C*H_2), 26.3 (*C*H_2CH_2OMs); MS (APCI, pos.):

m/z 344.1 (M-Boc+2); HRMS (CI): *m/z* 344.1538 (344.1532 calc. for $C_{16}H_{26}NO_5S$ (M-Boc+2H).

(2*S*,4*S*,5*R*)-*tert*-Butyl-2-(3-cyanopropyl)-4-hydroxy-5-(4-methoxyphenyl)piperidine-1-carboxylate (30):

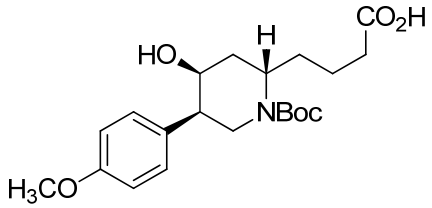


To a solution of the mesylate **29a** (0.820 g, 1.85 mmol) in anhydrous DMSO (15 mL), at ambient temperature, was added NaCN (18.0 g, 3.69 mmol). The mixture was stirred at 70 ºC for 2 h and cooled to ambient temperature. Ethyl acetate (40 mL) was added and the mixture was washed with water (3 x 30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 0.65 g (95%) of **30** as a yellow solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 3447, 2934, 2248, 1678, 1511, 1416, 1246, 1162, 1113, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.46 (br s, 1H, NC*H*), 4.32 (br dd, 1H, J = 2.2, 14.2, NCH_2), 4.19-4.13 (m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.33 (dd, 1H, J = 4.0, 14.2, NCH_2), 3.07-3.05 (m, 1H, ArC*H*), 2.44 (t, 2H, J = 6.8, CH_2CN), 2.04-1.96 (m, 1H, CHCH_2CH), 1.80-1.77 (m, 1H, CHCH_2CH), 1.70-1.62 (m, 4H, NCHCH_2, CH_2CH$_2$CN) 1.46 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (Ar*C*-OCH$_3$), 155.0 (*C*O$_2^t$Bu), 130.7 (2 x Ar*C*), 130.0 (ArC_{ipso}), 119.5 (*C*N), 113.8

(2 x Ar*C*), 80.2 (*C*(CH_3)$_3$), 66.3 (*C*HOH), 55.3 (O*C*H_3), 50.0 (N*C*H), 44.4 (*C*H_2N), 42.8 (Ar-*C*H), 33.1 (CH*C*H_2CH), 30.2 (NCH*C*H_2), 28.4 (C(*C*H_3)$_3$), 22.5 (*C*H_2CH$_2$CN), 17.0 (*C*H_2CN); MS (APCI, pos.): *m/z* 275.3 (M-Boc+2); HRMS (CI): *m/z* 375.2292 (375.2284 calc. for $C_{21}H_{31}N_2O_4$ $[M+H]^+$); $[\alpha]^{23}_D$ = + 27.0 (*c* 0.6, $CHCl_3$).

4-((2*S*,4*S*,5*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)-butanoic acid (31):

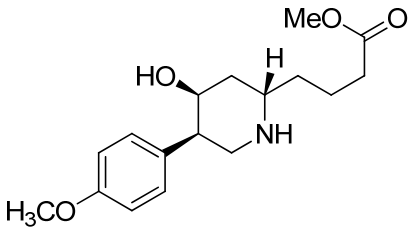


A solution of the nitrile **30** (0.610 g, 1.63 mmol) in aqueous NaOH (2 M, 6 mL) and ethanol (6 mL) was heated at 85 ºC for 16 h. The ethanol was removed under reduced pressure and resulting solution was acidified (pH ~ 4) with aqueous HCl (0.5 M). The acidic solution was extracted with dichloromethane (2 x 50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide 0.61 g (95%) of **31** as a brown solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

Mp: 88-90 ^{o}C; IR (neat): 3423, 2933, 1666, 1511, 1418, 1245, 1160, 1033, 829, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 2H, *J* = 7.9, Ar*H*), 6.84 (d, 2H, *J* = 7.9, Ar*H*), 4.42 (br s, 1H, NC*H*), 4.31 (br d, 1H, *J* = 13.9, NCH_2), 4.14-4.12 (br m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.32 (br dd, 1H, *J* = 2.7, 13.9, NCH_2), 3.03 (br s, 1H, ArC*H*), 3.0-2.5 (br, CO_2H), 2.39 (br s, 2H, CH_2COOH), 1.79-1.61 (m, 6H, CHCH_2CH, NCHCH_2,

CH_2CH$_2$COOH), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4 (CO_2H), 158.7 (Ar*C*-OCH$_3$ or *C*O$_2$^{t}Bu), 155.1 (Ar*C*-OCH$_3$ or *C*O$_2$^{t}Bu), 130.8 (2 x Ar*C*), 130.3 (ArC_{ipso}), 113.7 (2 x Ar*C*), 80.1 (*C*(CH$_3$)$_3$), 66.3 (*C*HOH), 55.2 (ArO*C*H$_3$), 50.7 (N*C*H), 44.2 (*C*H$_2$N), 42.8 (Ar-*C*H), 34.1 (*C*H$_2$CO$_2$H), 32.3 (CH*C*H$_2$CH), 30.2 (NCH*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$), 21.8 (*C*H$_2$CH$_2$CO$_2$H); MS (APCI, pos.): *m/z* 294.2 (M-Boc+2); HRMS (CI pos.): *m/z* 294.1711 (294.1705 calc. for $C_{16}H_{24}NO_4$ (M-Boc+2H).

Methyl 4-((2*S*,4*S*,5*R*)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)butanoate (32):

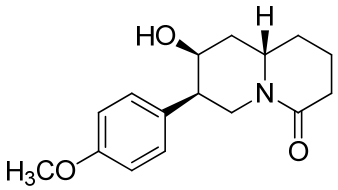


To a solution of the acid **31** (0.600 g, 1.53 mmol) in methanol (12 mL) at 0 ºC was added $SOCl_2$ (0.510 mL, 7.02 mmol) and the mixture was stirred at ambient temperature for 16 h. The methanol was removed under reduced pressure, the residue was diluted with dichloromethane (25 mL) and the resulting solution was washed with water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 0.43 g, (91%) of **32** as an off white solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 3123, 2940, 1727, 1610, 1510, 1433, 1240, 1168, 1030, 828 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, *J* = 8.6, Ar*H*), 6.87 (d, 2H, *J* = 8.6, Ar*H*), 4.08-4.07 (br m, 1H, C*H*OH), 3.79 (s, 3H, ArOCH_3), 3.67 (s, 3H, CO_2CH_3), 3.39-3.31 (t, 1H, *J* = 12.0, NCH_2), 3.00-2.91 (m, 2H, NC*H*, ArC*H*), 2.84-2.79 (m, 1H, NCH_2), 2.37-2.32 (t, 2H, *J* =

7.4, CH_2CO$_2$CH$_3$), 1.99-1.92 (dt, 1H, J = 2.9, 13.6, CHCH_2CH), 1.73-1.63 (m, 4H, CHCH_2CH, CH_2CH$_2$CO, CHNH), 1.49-1.35 (m, 2H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (CO$_2$CH$_3$), 158.5 (ArC-OCH$_3$), 133.3 (ArC_{ipso}), 128.8 (2 x ArC), 114.1 (2 x ArC), 69.3 (CHOH), 55.3 (ArOCH$_3$), 51.6 (CO$_2$$CH_3$), 49.4 (NH$C$H), 47.0 ($CH_2$N), 44.8 (Ar$C$H), 39.5 (CH$CH_2$CH), 36.4 (NHCH$CH_2$), 34.1 ($CH_2CO_2CH_3$), 21.4 ($CH_2CH_2CO_2CH_3$); MS (APCI, pos.): *m/z* 308.3 (M+1); HRMS (CI): *m/z* 308.1861 (308.1862 calc. for $C_{17}H_{26}NO_4$ $[M+H]^+$)

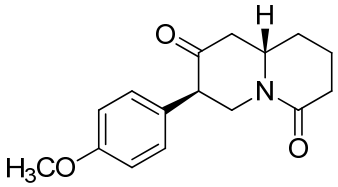
(7*R*,8*S*,9a*S*)-hexahydro-8-hydroxy-7-(4-methoxyphenyl)-1H-quinolizin-4(6H)-one (33):



To a solution of the amino ester **32** (0.380 g, 1.23 mmol) in THF (6 mL) was added diisopropylethyl amine (752 μL, 4.31 mmol) and the solution was heated to reflux for 16 h. Additional diisopropylethylamine (0.250 mL, 1.43 mmol) was added and the mixture was refluxed for 2 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 246 mg (73%) of the lactam **33** as a pale yellow foam. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 3349, 2945, 1606, 1514, 1478, 1442, 1245, 1171, 1035, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.76 (dd, 1H, J = 4.2, 12.8, NCH_2), 4.1 (br m, 1H, C*H*OH), 3.8 (s, 3H, OCH_3), 3.78-3.74 (m, 1H, NC*H*), 3.20-3.15 (t, 1H, J = 12.8, NCH_2), 2.85-2.81 (br m, 1H, ArC*H*), 2.48-2.40 (m, 1H, NCOCH_2), 2.38-2.31 (m, 1H, NCOCH_2), 2.02-1.97 (m, 2H, CHCH_2CH, CHO*H*), 1.86-1.82 (m, 1H, NCHCH_2CH$_2$), 1.74-1.68 (m, 3H, CHCH_2CH, COCH$_2$CH_2) 1.55-1.48 (m, 1H, CHCH_2CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (N*C*O), 158.7 (Ar*C*-OCH$_3$), 131.9 (ArC_{ipso}), 128.6 (2 x Ar*C*), 114.2 (2 x Ar*C*), 68.7 (*C*HOH), 55.3 (O*C*H$_3$), 50.0 (N*C*H), 45.3 (*C*H$_2$N), 40.3 (Ar-*C*H), 39.6 (CH*C*H$_2$CH), 33.0 (CO*C*H$_2$), 29.7 (NCH*C*H$_2$), 19.1 (*C*H$_2$CH$_2$CO); MS (APCI, pos.): *m/z* 276.5 (M+1); HRMS (CI): *m/z* 275.1526 (275.1521 calc. for $C_{16}H_{21}NO_3$ (M+)).

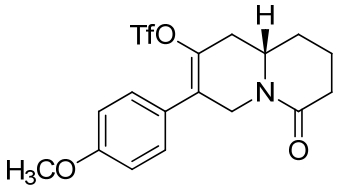
(3*R*,9a*S*)-Hexahydro-3-(4-methoxyphenyl)-1*H*-quinolizine-2,6-dione (34):



To a stirred solution of the alcohol **33** (0.45 g, 1.63 mmol) in dichloromethane (15 mL) was added DMSO (8 mL) followed by DIPEA (2.4 mL) at 0 °C. Solid SO_3.pyridine (781 mg, 4.90 mmol) was added in small portions and the mixture was stirred at 0 ºC for 1 h. Water (10 mL) was added and the mixture was diluted with dichloromethane (20 mL). The mixture was washed with water (2 x 30 mL) and the organic layer was dried (Na_2SO_4) and concentrated to provide 420 mg (94%) of **34** as a brown solid.

Mp: 88-90 ^{o}C; IR (neat): 2921, 1719, 1624, 1514, 1447, 1338, 1242, 1171, 1022, 826 cm^{-1}; ^{1}H NMR (500 MHz,$CDCl_3$): δ 7.06 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 5.12 (dd, 1H, J = 12.7, 6.2, NCH_2), 3.85-3.82 (m, 1H, NC*H*) 3.79 (s, 3H, OCH_3), 3.64 (dd, 1H, J = 12.7, 6.2, NCH_2), 3.00-2.91 (t, 1H, J = 12.4, ArC*H*), 2.58-2.55 (m, 2H, COCH_2), 2.50-2.46 (m, 2H, NCOCH_2), 2.18-2.09 (m, 1H, NCHCH_2), 1.97-1.78 (m, 2H,$COCH_2CH_2$), 1.72-1.63 (m, 1H, NCHCH_2) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2 (*C*O), 169.4 (N*C*O), 159.0 (Ar*C*OCH_3),129.9 (2 x Ar*C*), 126.8 (Ar*C*), 114.1 (2 x Ar*C*), 56.0 (N*C*H), 55.4 (O*C*H_3), 55.3 (ArC*C*H), 48.3 (N*C*H_2), 47.7 (CO*C*H_2), 32.8 (NCO*C*H_2), 29.6 ($COCH_2CH_2$), 18.9 (NCH*C*H_2); MS (APCI pos.): *m/z* 274.1 (M+1); HRMS (CI+): *m/z* 273.1371 (273.1365 calc. for $C_{16}H_{19}NO_3$, M^+).

(*S*)-4,6,7,8,9,9a-Hexahydro-3-(4-methoxyphenyl)-6-oxo-1*H*-quinolizin-2-yl trifluoromethanesulfonate (35):

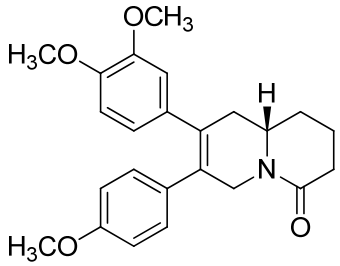


To a suspension of KH (66 mg, 0.50 mmol) in THF (2 mL) was added the ketone **34** (136 mg, 0.50 mmol) at 0 ºC. The mixture was stirred at room temperature for 2 h and a solution of *N*-phenylbistrifluoromethanesulfonimide (195 mg, 0.55 mmol) in THF (2 mL) was added dropwise at 0 ºC. The mixture was then stirred for 0.5 h at room temperature. Water (7 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a brown

viscous material which was purified by flash chromatography on silica gel (EtOAc) to provide 150 mg (74%) of **35** as a yellow gum.

IR (neat): 2942, 1642, 1512, 1412, 1206, 1138, 1036, 833 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 8.8, Ar*H*), 6.91 (d, 2H, J = 8.8, Ar*H*), 5.28 (d, 1H, J = 18.4, NCH_2), 3.82 (s, 3H, OCH_3), 3.82-3.77 (m, 1H, NC*H*), 3.64 (d, 1H, J = 18.4, NCH_2), 2.79-2.72 (m, 1H, COCH_2), 2.52-2.49 (m, 1H, COCH_2), 2.49-2.43 (m, 2H, C=CCH_2) 2.20-2.11 (m, 1H, $COCH_2CH_2$), 1.99-1.89 (m, 1H, $COCH_2CH_2$), 1.81-1.61 (m, 2H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (*C*=O), 160.0 (TfO*C*=C), 139.3 (Ar*C*OCH_3), 129.7 (2 x Ar*C*), 128.0 (Ar*C*), 124.8 (TfOC=*C*), 122.5 (q, J = 346.4, *C*F_3), 114.0 (2 x Ar*C*), 55.3 (O*C*H_3), 52.7 (N*C*H), 45.5 (N*C*H_2), 35.6 (C=C*C*H_2CH), 32.8 (CO*C*H_2), 28.3 (NCH*C*H_2), 18.2 ($COCH_2CH_2$); MS (APCI pos.): *m/z* 406.1 (M+1); HRMS (CI+): *m/z* 405.0865 (405.0858 calc. for $C_{17}H_{18}NO_5SF_3$, M^+).

(*S*)-2,3,9,9a-Tetrahydro-8-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1*H*-quinolizin-4(6H)-one (36):

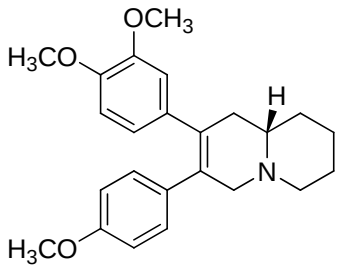


To a stirred solution of the enol triflate **35** (150 mg, 0.370 mmol) and 3,4-dimethoxyphenyl boronic acid (74 mg, 0.41 mmol) in dioxane (6 mL) was added a degassed, aqueous solution of Na_2CO_3 (118 mg, 1.11 mmol, in 0.50 mL water) and the

mixture was degassed with a stream of nitrogen for 15 min. $Pd(PPh_3)_4$ (21 mg, 0.019 mmol) was added and the mixture was heated with stirring at 85 ºC for 90 min. The mixture was then cooled to ambient temperature, diluted with EtOAc (15mL) and the resulting mixture was washed with water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a brown gum. This was purified by flash chromatography on silica gel (CH_2Cl_2/methanol, 98.5:1.5) to provide 120 mg (82%) of **36** as a white solid.

Mp: 94-101 ºC; IR (neat): 2944, 1635, 1510, 1454, 1245, 1173, 1028, 824 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.0 (d, 2H, J = 8.7, Ar*H*), 6.71-6.68 (m, 3H, Ar*H*), 6.62 (dd, 1H, J = 8.3, 2, Ar*H*), 6.43 (s, 1H, Ar*H*), 5.20 (d, 1H, J = 18.7 NCH_2), 3.81 (s, 3H, OCH_3), 3.81-3.79 (m, 1H, NC*H*), 3.73 (s, 3H, OCH_3), 3.72-3.68 (d, 1H, J = 18.7, NCH_2), 3.55 (s, 3H, OCH_3), 2.60-2.57 (m, 2H, C=CCH_2), 2.48-2.46 (t, 2H, J = 12.7, COCH_2), 2.16-2.11 (m, 1H, NCHCH_2) 1.91-1.88 (m, 1H, $COCH_2CH_2$), 1.81-1.72 (m, 2H, $COCH_2CH_2$, NCHCH_2) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (*C*=O), 158.4 (Ar*C*-OCH_3), 148.1 (Ar*C*-OCH_3), 147.5 (Ar*C*-OCH_3), 133.9 (Ar*C*C=C), 131.9 (C=*C*CH_2CH), 131.2 (C=*C*CH_2N), 131.1 (Ar*C*), 130.4 (2 x Ar*C*) 120.6 (Ar*C*H), 113.5 (2 x Ar*C*), 113.0 (Ar*C*), 110.6 (Ar*C*), 55.7 (N*C*H), 55.6 (O*C*H_3), 55.2 (O*C*H_3), 52.8 (O*C*H_3), 46.8 (N*C*H_2), 38.9 (C=C*C*H_2CH), 33.0 (CO*C*H_2), 28.7 (NCH*C*H_2), 18.5 ($COCH_2CH_2$); MS (APCI pos.): *m/z* 394.2 (M+1); HRMS (CI+): *m/z* 394.2016 (394.2018 calc. for $C_{24}H_{28}NO_4$, $[M+H]^+$).

(*S*)-4,6,7,8,9,9a-Hexahydro-2-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-1H-quinolizine ((+)-Julandine, 1):

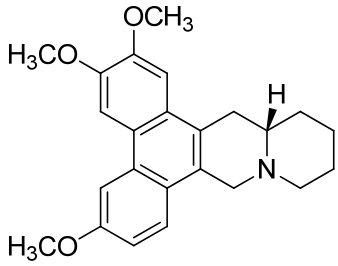


To a suspension of $LiAlH_4$ (38 mg, 0.096 mmol) in dry THF (1.5 mL) at 0 °C was slowly added a solution of the lactam **36** (0.10 g, 0.25 mmol) in THF (2 mL). The mixture was stirred for an hour at 0 ˚C and then at ambient temperature for 24 h. It was then cooled to 0 °C and water (18 μL, 1 mmol), 1 N NaOH (1 mL) and water (48 μL), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and washed with dichloromethane. The combined filtrates were dried (Na_2SO_4) and concentrated to give a yellow gum. This was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 99:1) to provide 63 mg (89%) of **1** as a pale yellow gum.

IR (neat): 2928, 1604, 1509, 1458 1242, 1172, 1029, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.98 (d, 2H, J = 8.6, Ar*H*), 6.69-6.67 (m, 4H, Ar*H*), 6.46 (br s, 1H, Ar*H*), 3.81 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.62-3.59 (br d, 1H, J = 16.5), 3.53 (s, 3H, OCH_3) 3.10-3.03 (m, 2H), 2.55-2.51 (br d, 1H, J = 18.1), 2.41-2.30 (m, 2H), 2.11-2.10 (m, 1H), 1.86-1.80 (m, 2H), 1.75-1.70 (br m, 2H), 1.36-1.35 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 147.9, 147.2, 134.5, 133.2, 131.5, 131.3, 130.2, 120.5, 113.4, 113.0, 110.5, 62.8, 60.4, 57.9, 55.7, 55.6, 55.5, 55.2, 39.6, 33.3, 30.0, 25.9, 24.4; MS (APCI pos.): *m/z* 380.5 (M+1); HRMS (CI+): *m/z* 379.2151 (379.2147 calc. for $C_{24}H_{29}NO_3$, M^+).

$[\alpha]^{23}_{D}$ = +88.8° (*c* 0.5, $CHCl_3$, Lit.[7a] $[\alpha]^{26}_{D}$ = -71.6 ° (*c* 0.33, $CHCl_3$ for the *R*-enantiomer).

(*S*)-2,3,6-Trimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinoline ((+)-Cryptopleurine) (2):



A modification of the literature procedure was employed.[7e] To a stirred solution of **1** (65 mg, 0.17 mmol) in dichloromethane (10 mL) at ambient temperature was added thallium (III) trifluoroacetate (94 mg, 0.17 mmol) and the mixture was stirred for 30 min. The volatiles were removed under reduced pressure, water (5 mL) was added to the residue and the mixture was basified with saturated aqueous sodium carbonate. The mixture was then extracted with chloroform (2 x 15 mL). The combined extracts were dried and concentrated. The residue obtained was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to give a yellow solid which was recrystallized from chloroform/acetone to give 40 mg (62%) of **2** as a white crystalline solid.

Mp: 190-194 ^{o}C (Lit.[20] mp. 197-198 ^{o}C (benzene); IR (neat): 2926, 1610, 1509, 1467, 1253, 1141, 1040, 846, 748, 632 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.9 (d, 1H *J* = 2.6), 7.26 (s, 1H), 7.20 (dd, 1H, *J* = 2.6, 9), 4.44 (d, 1H, *J* =15.5), 4.10 (s, 3H), 4.06 (s, 3H), 4.01(s, 3H), 3.64 (d, 1H, *J* = 15.3), 3.28 (d, ,1H, *J* = 10.8), 3.11 (dd, 1H, *J* =

4, 16.3), 2.92-2.86 (m, 1H), 2.43-2.39 (t, 1H, J = 10.3), 2.34-2.28 (td, 1H, J = 3.8, 11.5), 2.04 (d, 1H, J = 13.9), 1.89 (d, 1H, J = 12.3), 1.81-1.77 (m, 2H), 1.56-1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 149.4, 148.3, 130.1, 126.5, 125.7, 124.5, 124.1, 123.7, 123.4, 114.8, 104.7, 103.9, 103.9, 57.6, 56.3, 56.2, 56.0, 55.9, 55.5, 34.8, 33.9, 26, 24.4; MS (APCI pos.): *m/z* 378.1 (M+1); HRMS (CI+): *m/z* 377.1990 (377.1991 calc. for $C_{24}H_{29}NO_3$, M^+); $[\alpha]^{23}_D$ = +104.6 º (*c* 0.55, $CHCl_3$); Lit.[9d] $[\alpha]^{23}_D$ = +106 º (*c* 1, $CHCl_3$)).

4.8 References:

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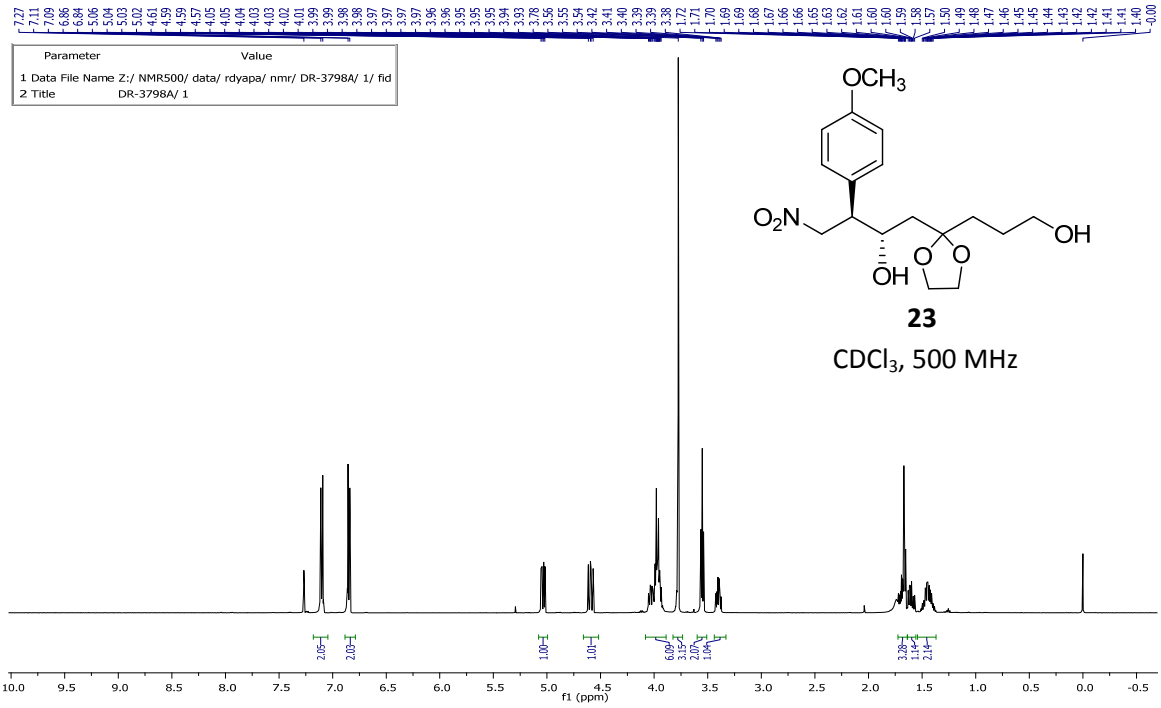
4.9 Selected ^{1}H NMR and ^{13}C NMR spectral data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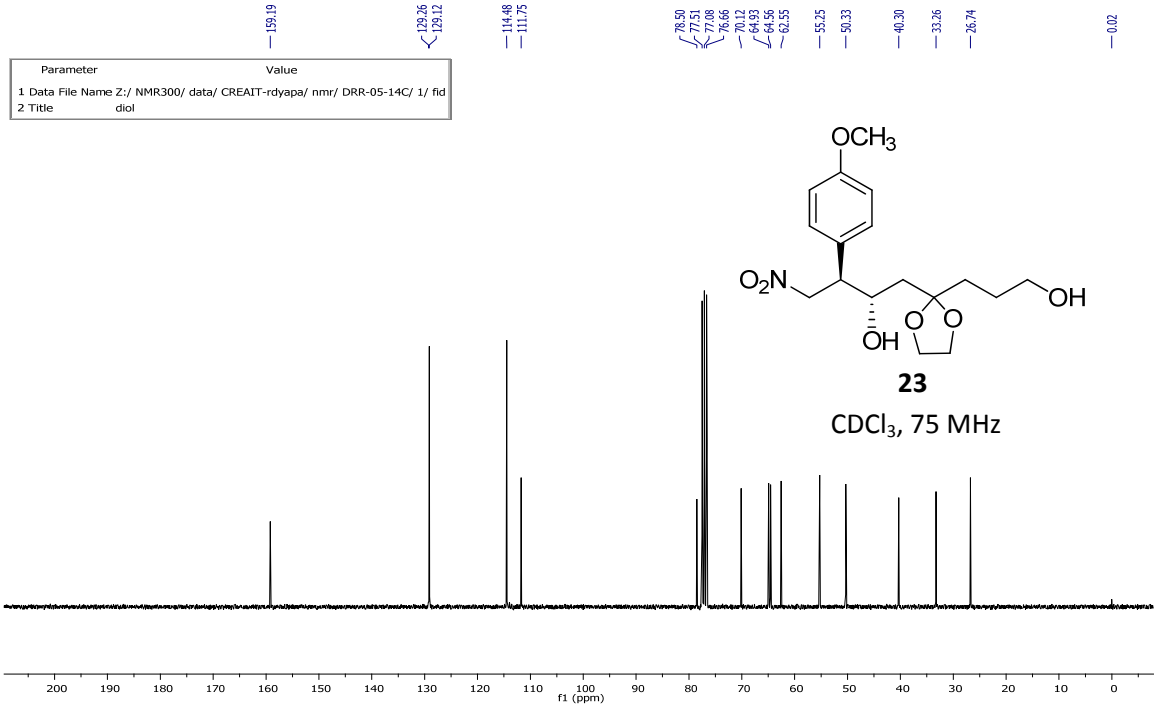
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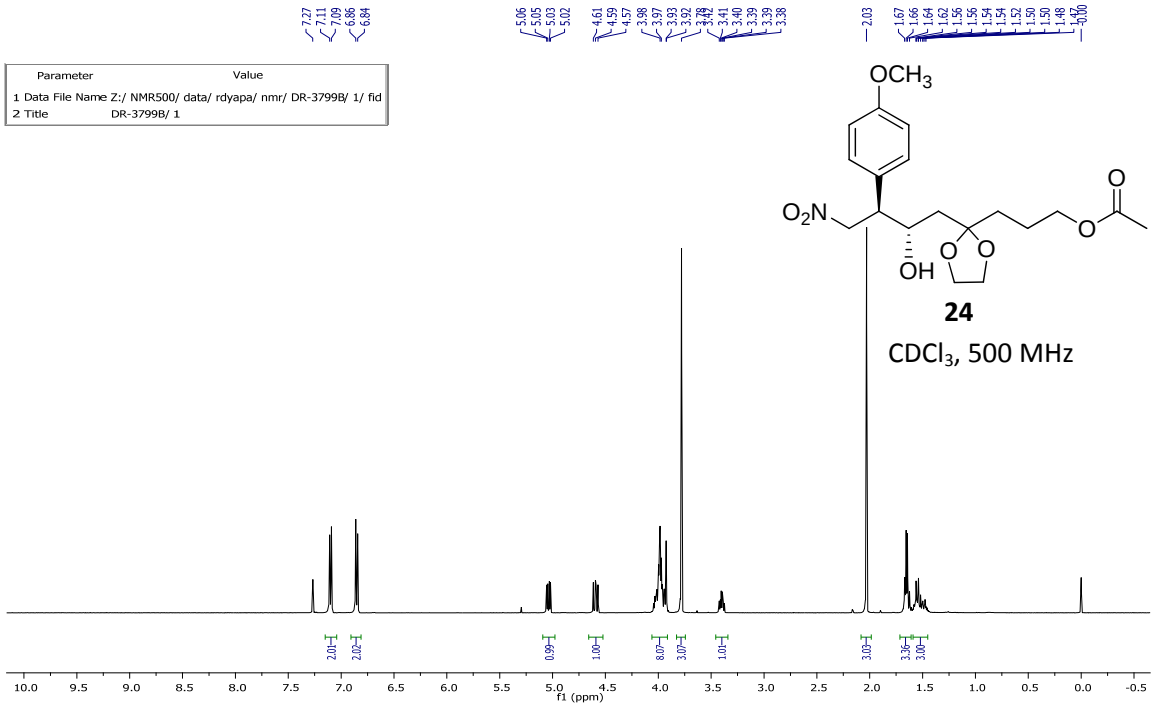
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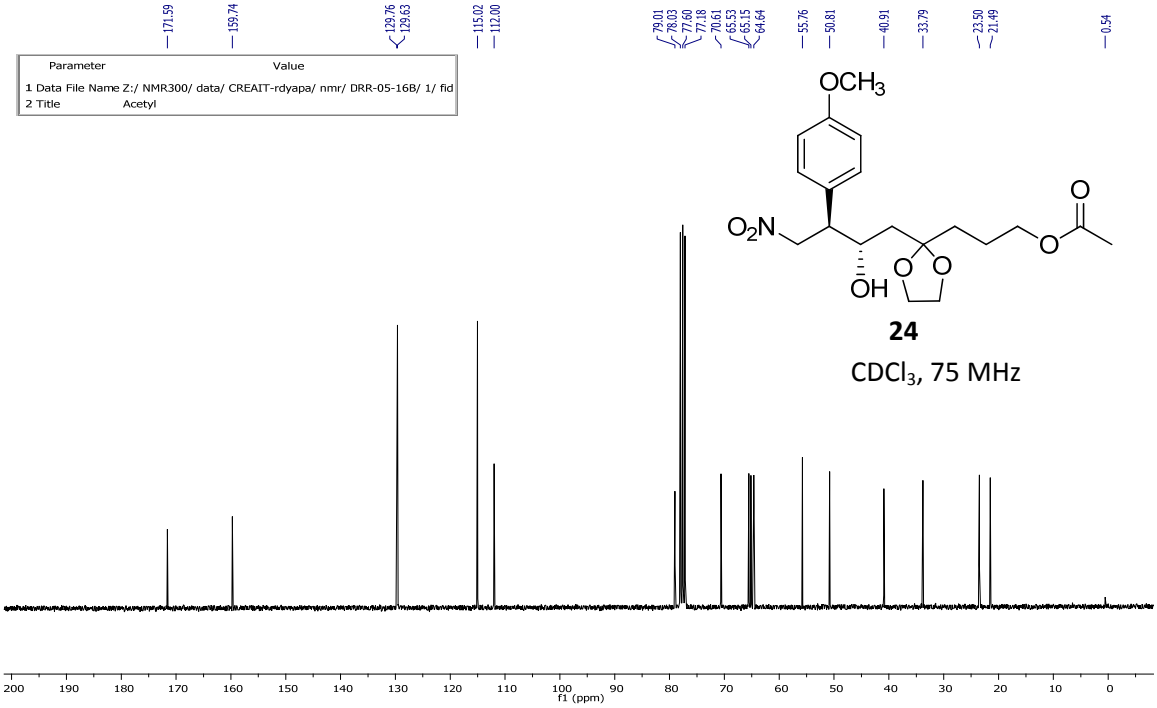
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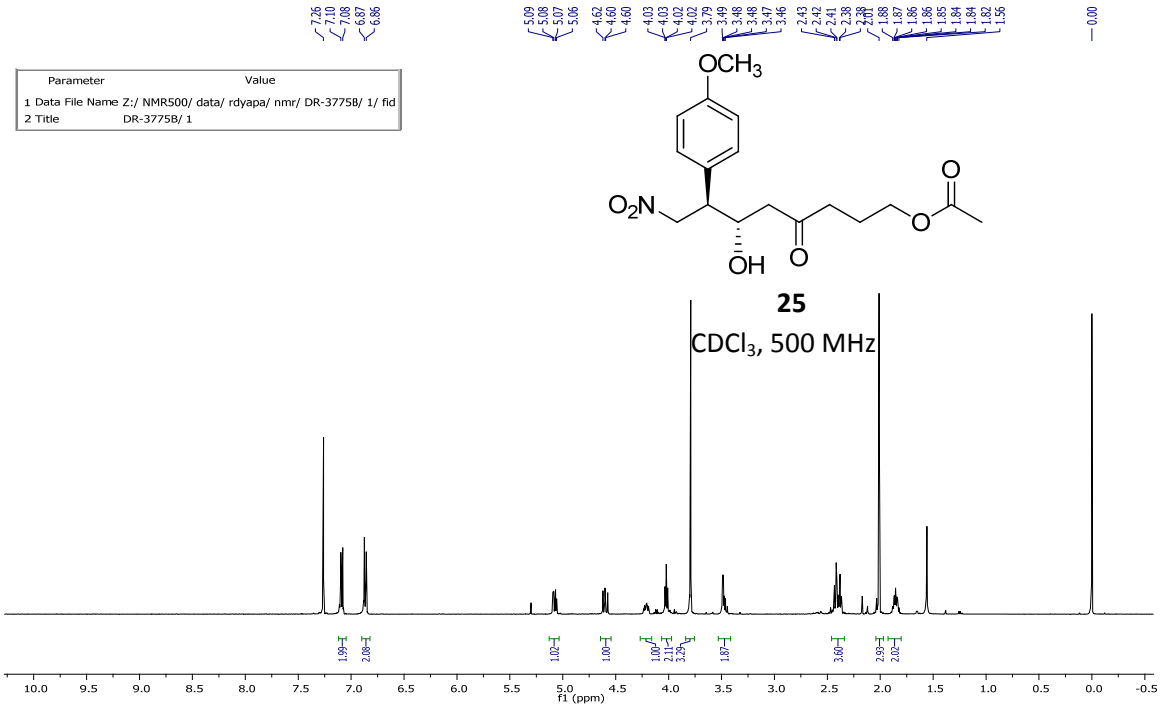
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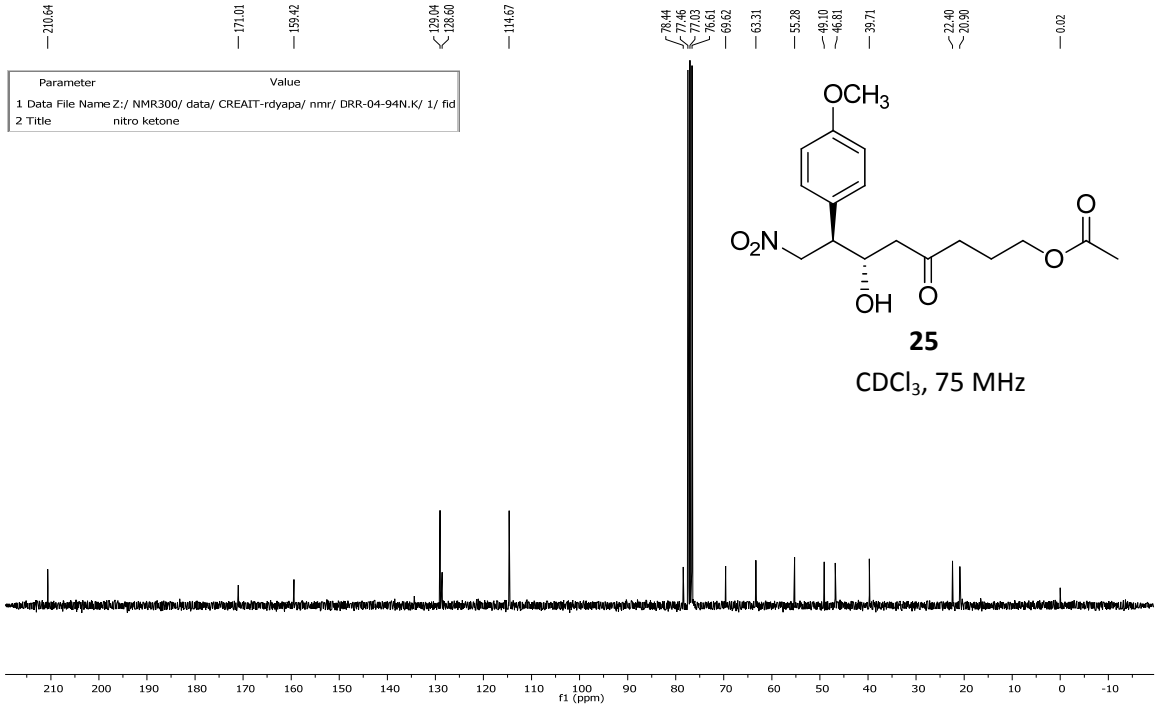
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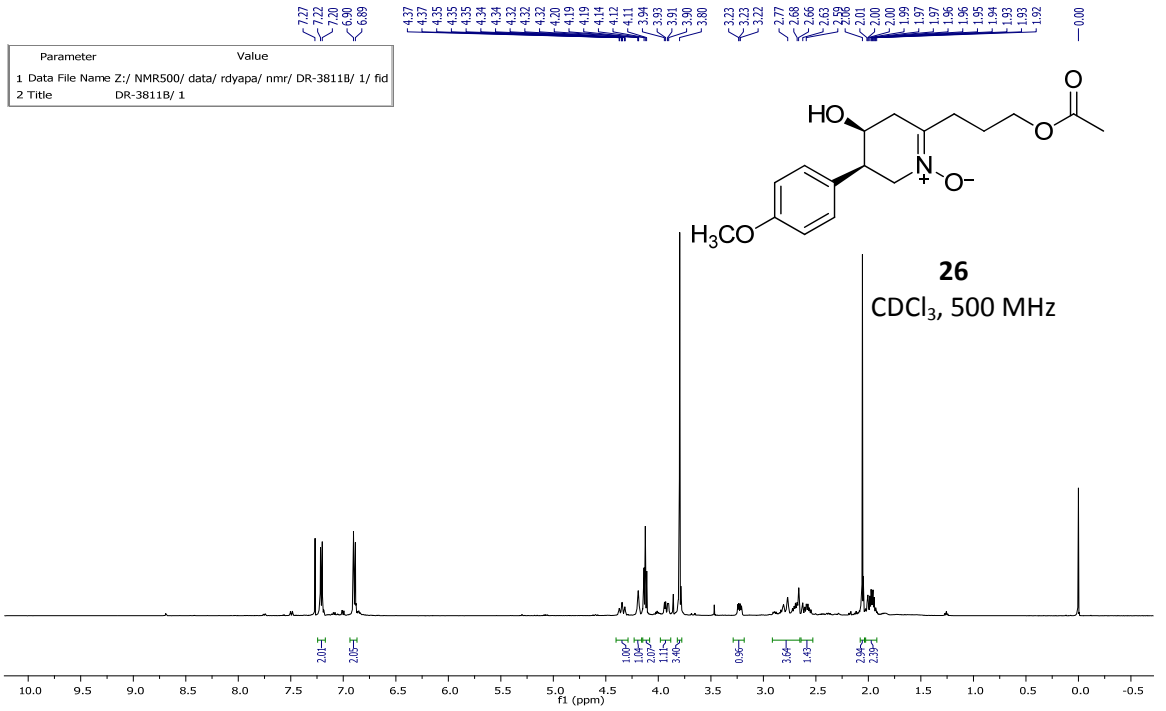
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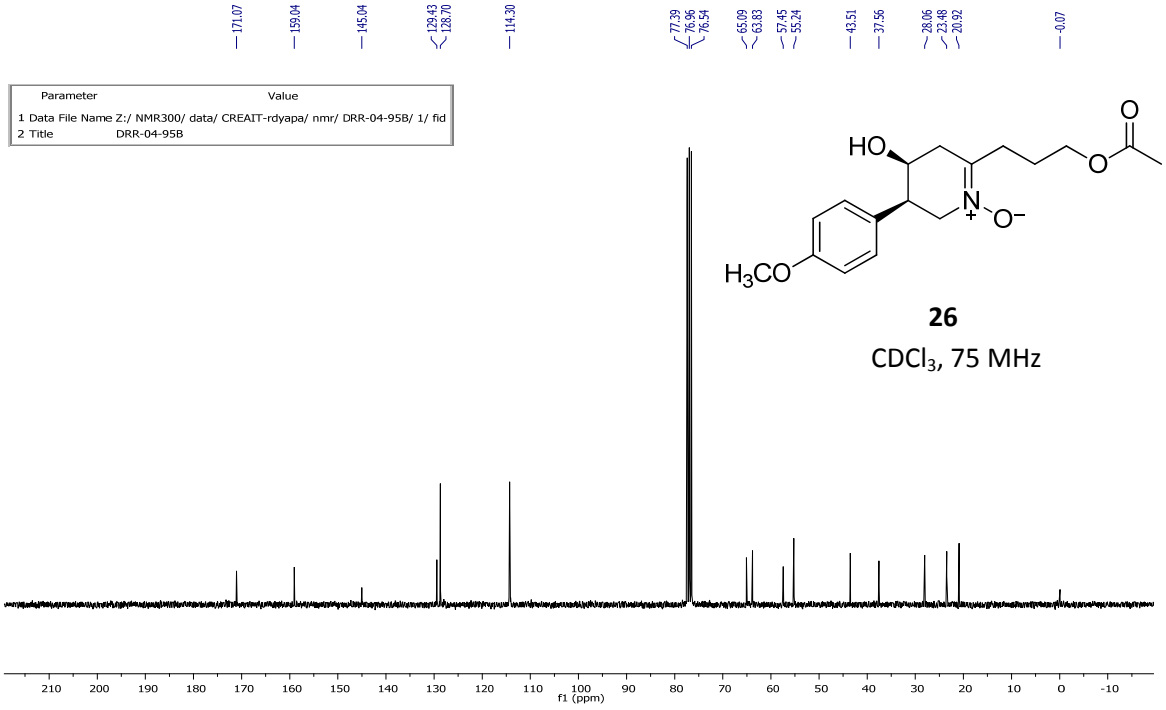
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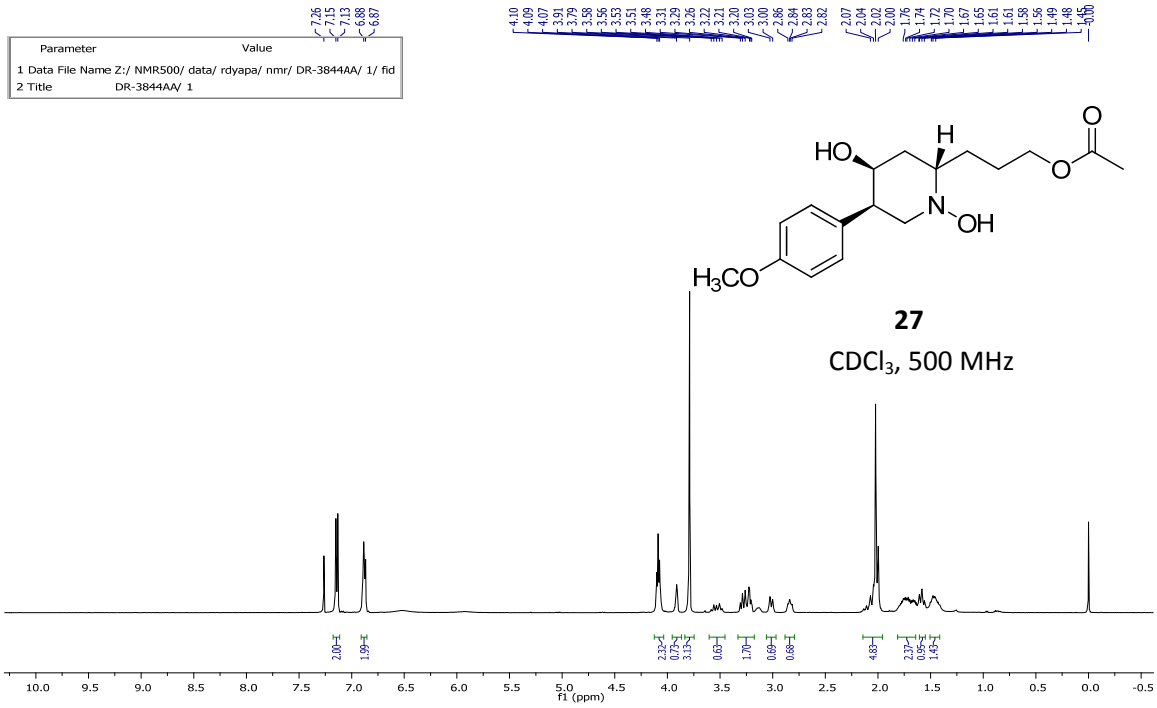

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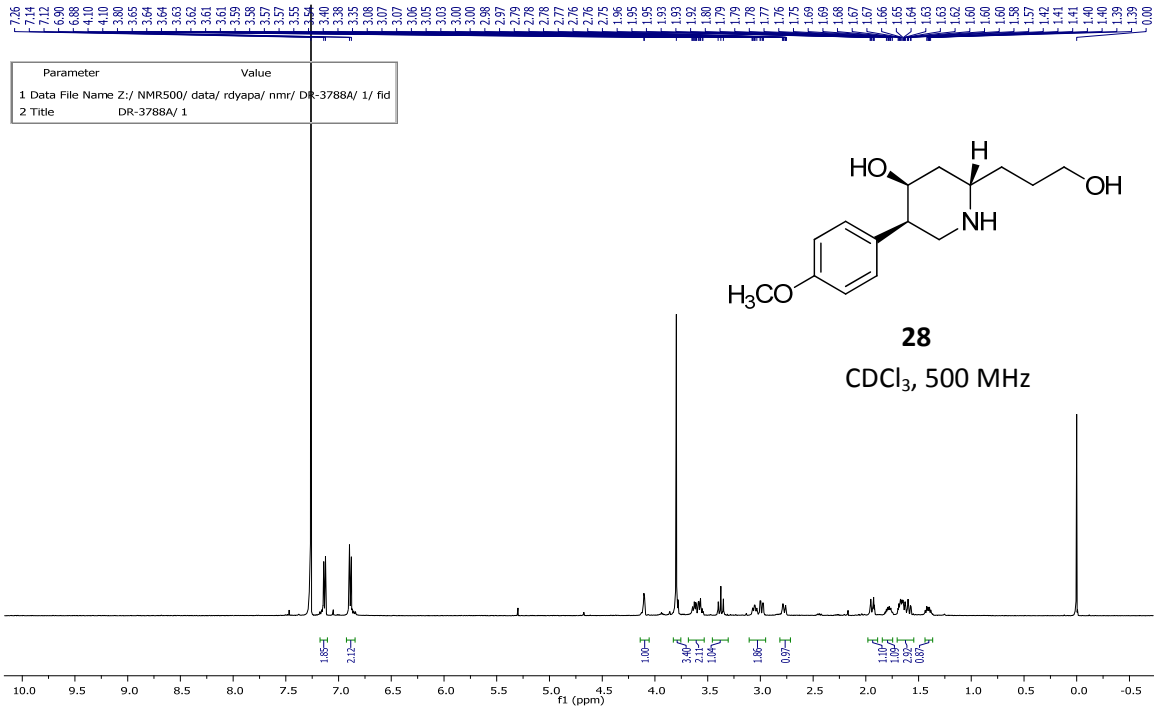

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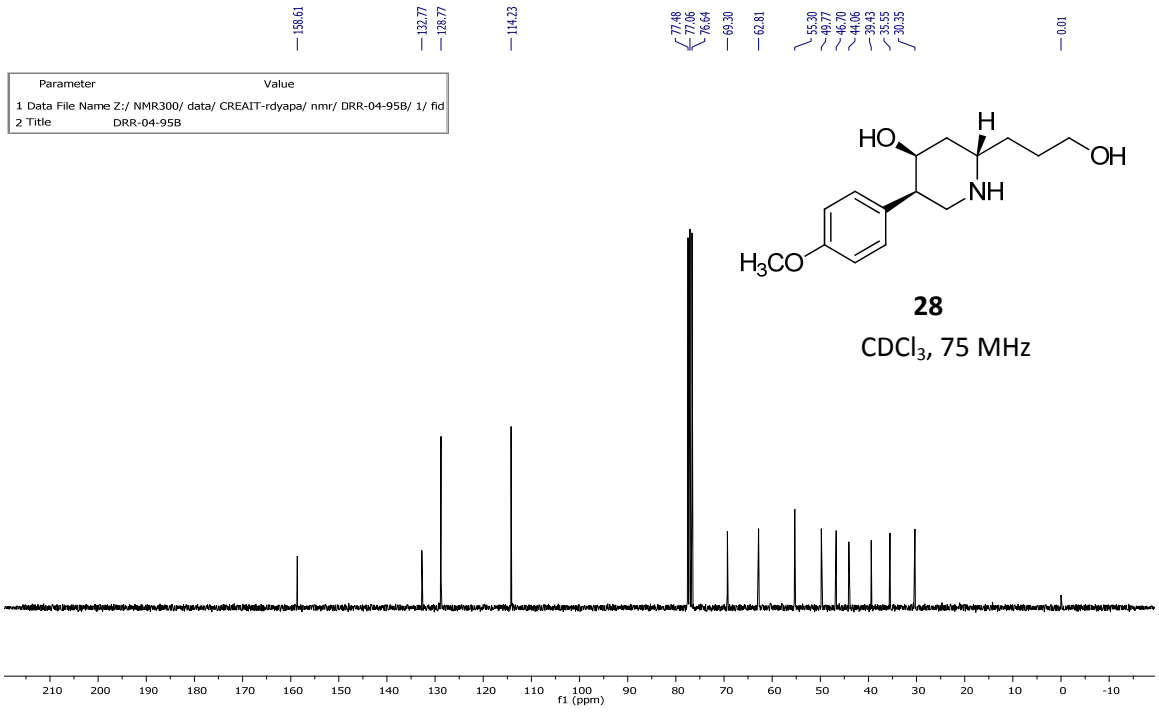

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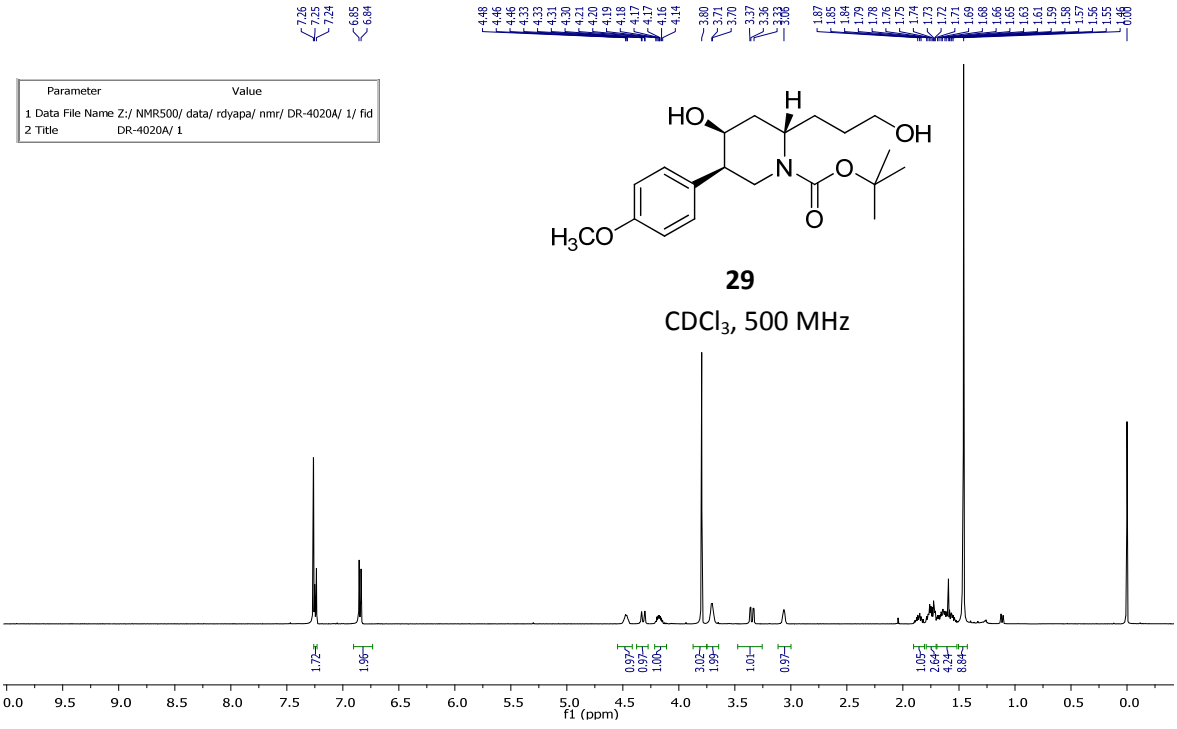

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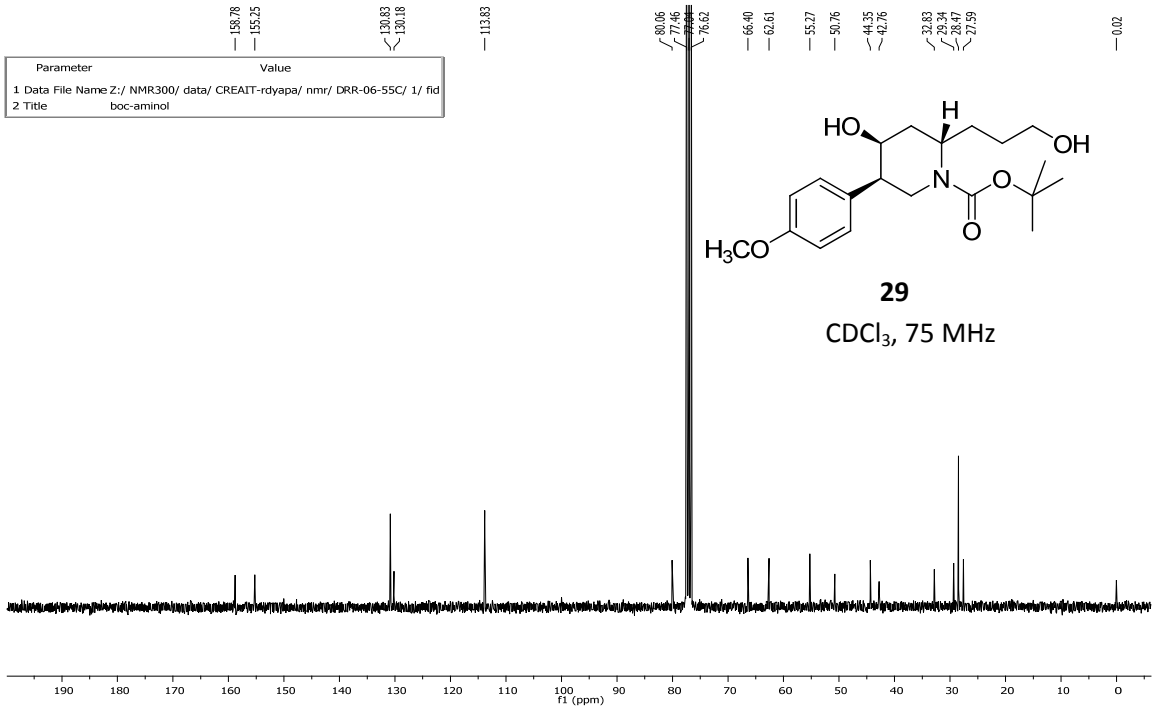
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OH
N
O
O
H3CO
29
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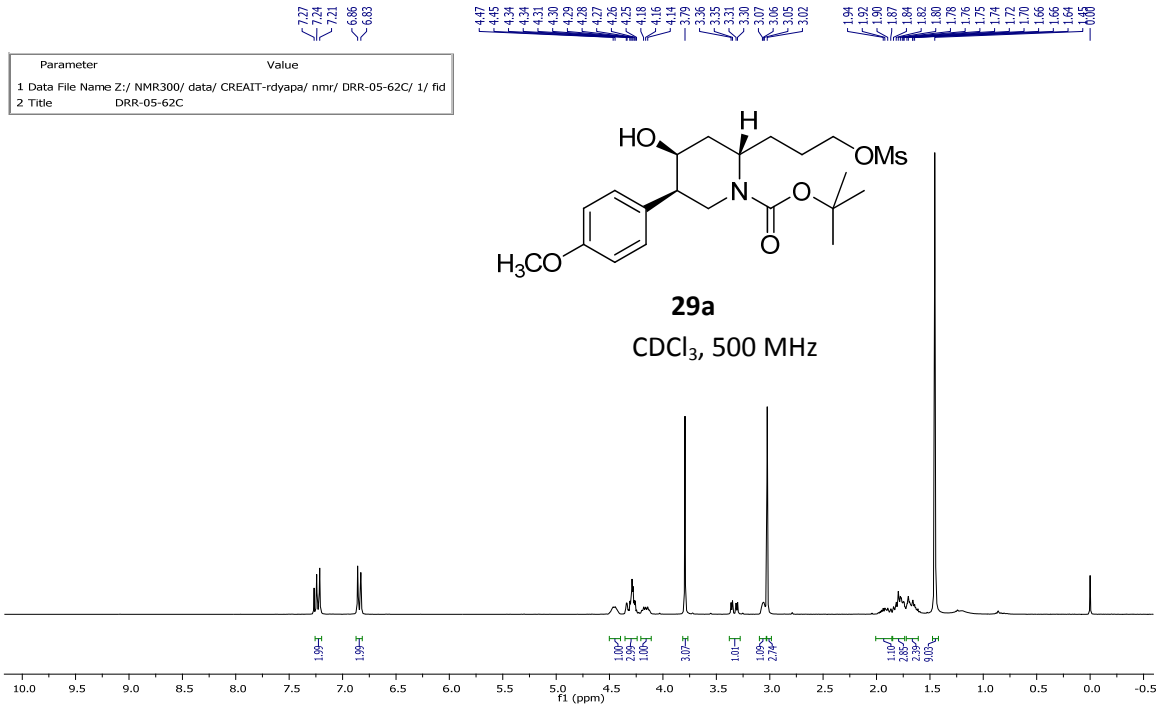
f1 (ppm)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7.24
7.21
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6.83
4.47
4.45
4.34
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4.31
4.30
4.29
4.28
4.27
4.26
4.25
4.18
4.16
4.14
3.79
3.36
3.35
3.31
3.30
3.07
3.06
3.05
3.02
1.94
1.92
1.90
1.87
1.84
1.82
1.80
1.78
1.76
1.75
1.74
1.72
1.70
1.66
1.66
1.64
1.45
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OMs
N
O
O
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29a
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1.99
1.99
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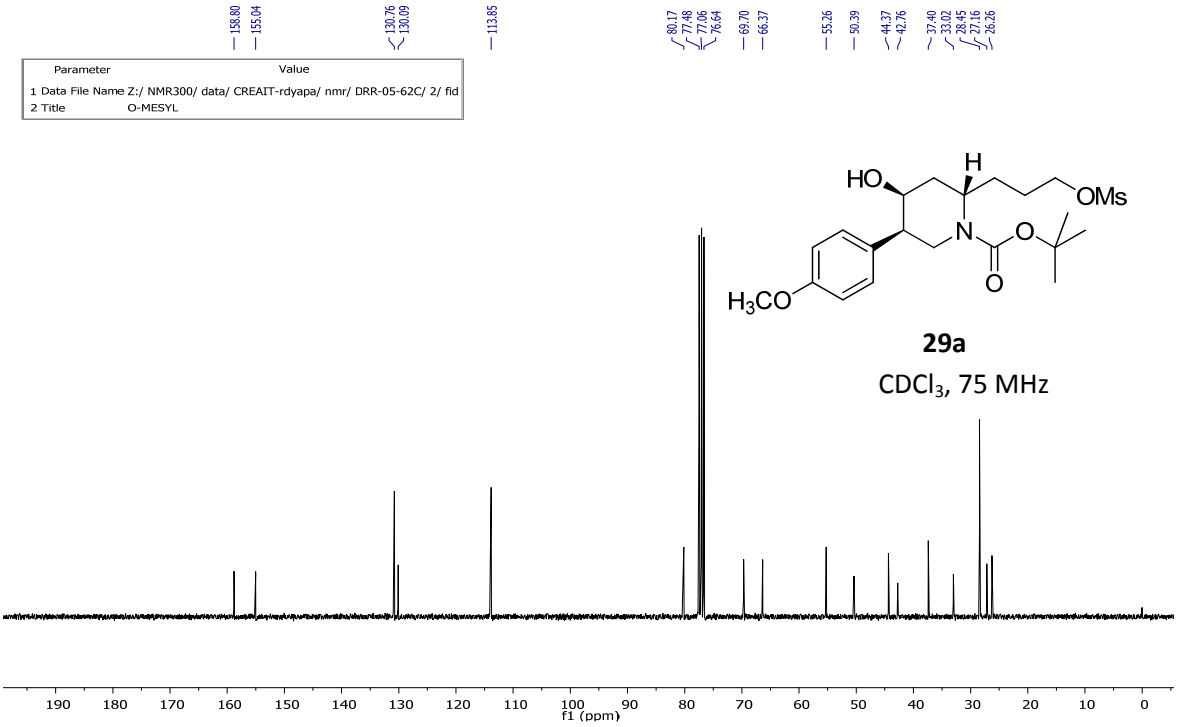
3.07
1.01
1.05
2.74
1.10
2.85
2.39
9.05
f1 (ppm)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50.39
44.37
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37.40
33.02
28.45
27.16
26.26
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Value
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OMs
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O
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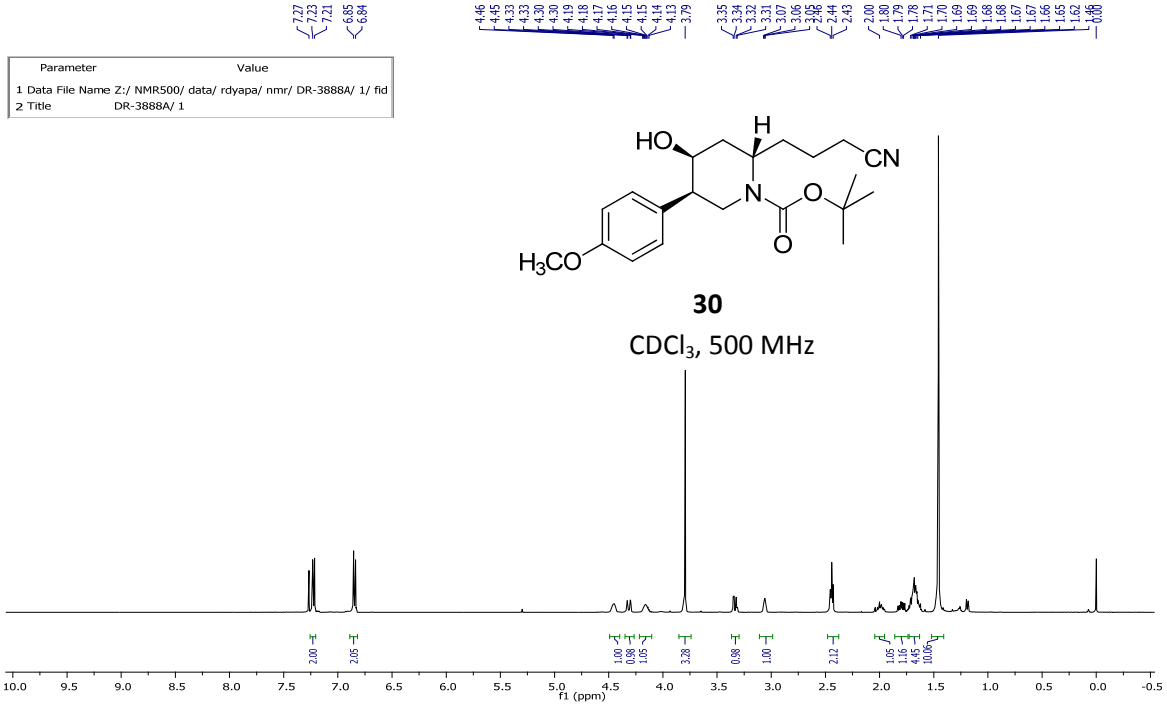
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4.46
4.45
4.33
4.30
4.30
4.19
4.18
4.17
4.16
4.15
4.15
4.14
4.13
3.79
3.35
3.34
3.32
3.31
3.07
3.06
2.46
2.44
2.43
2.00
1.80
1.79
1.78
1.71
1.70
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.65
1.62
1.46
0.00
Parameter
Value
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2 Title DR-3888A/ 1
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CN
N
O
O
H3CO
30
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2.00
2.05
1.00
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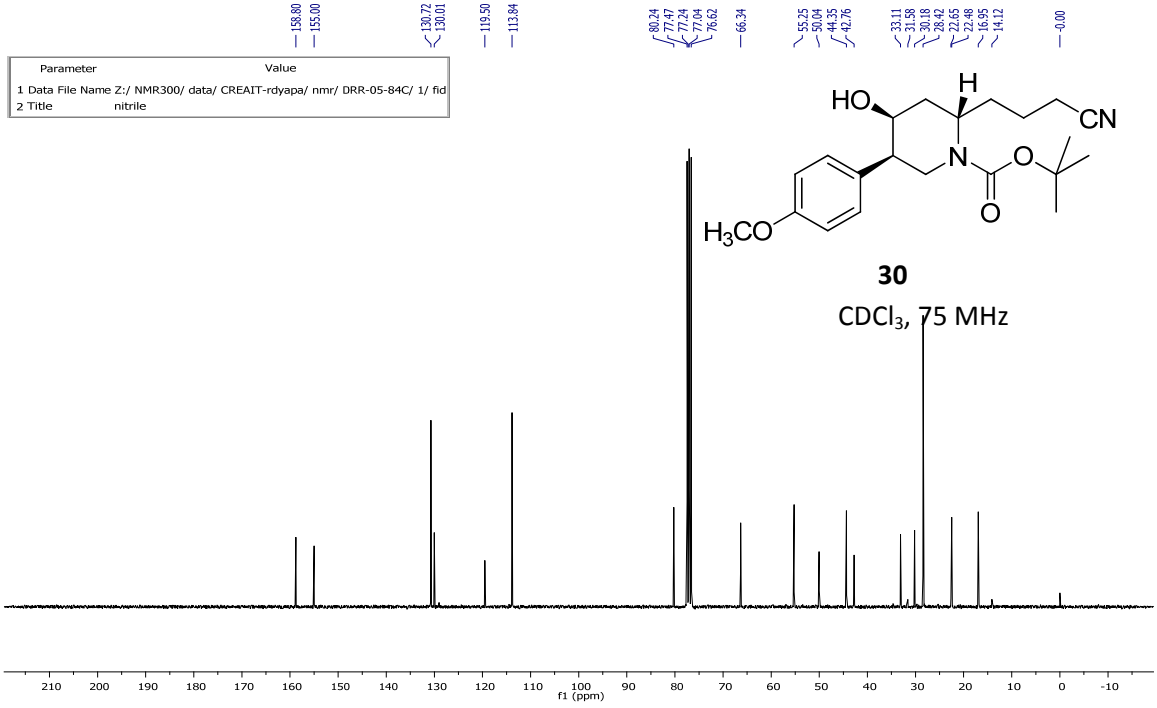
3.28
0.98
1.00
2.12
1.05
1.16
4.45
10.06
f1 (ppm)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130.72
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80.24
77.47
77.24
77.04
76.62
66.34
55.25
50.04
44.35
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33.11
31.58
30.18
28.42
22.65
22.48
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14.12
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O
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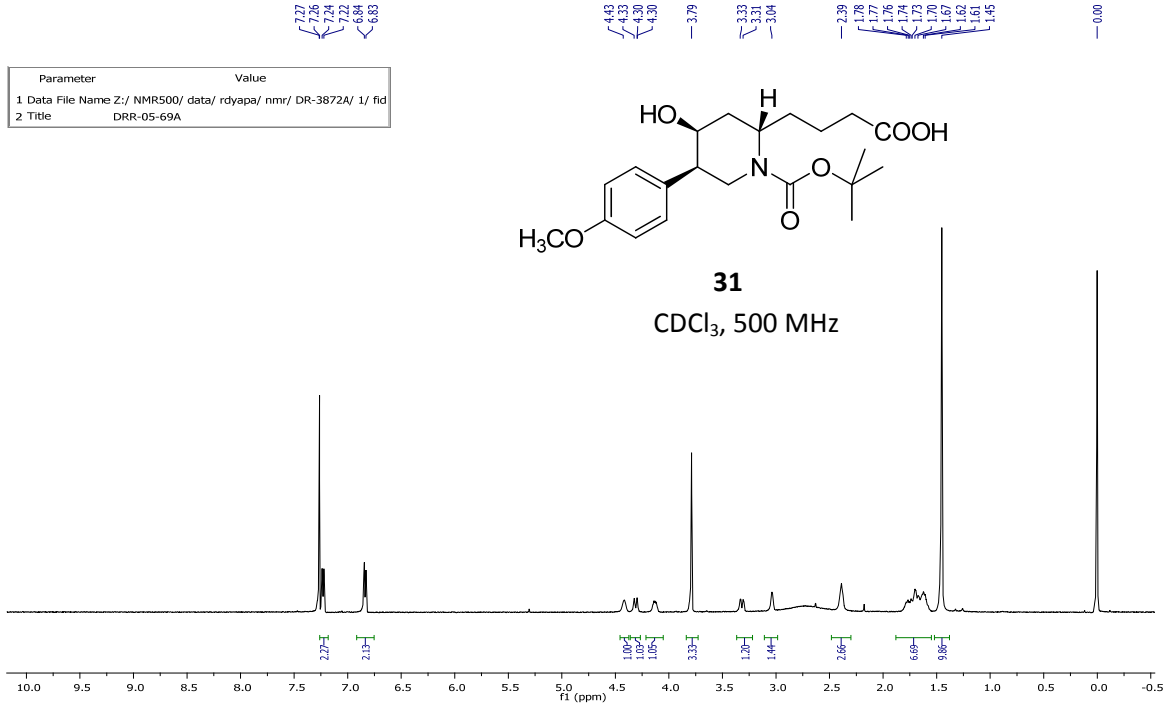
f1 (ppm)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6.83
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4.33
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4.30
3.79
3.33
3.31
3.04
2.39
1.78
1.77
1.76
1.74
1.73
1.70
1.67
1.62
1.61
1.45
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COOH
N
O
O
H3CO
31
CDCl3, 500 MHz
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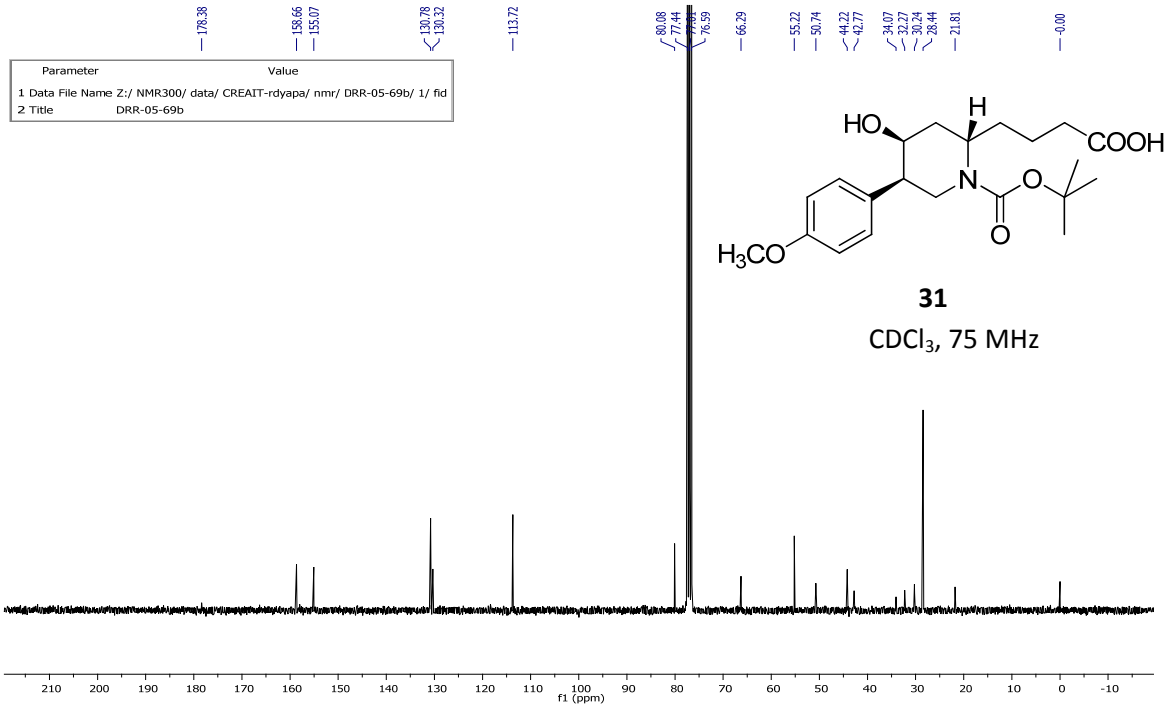
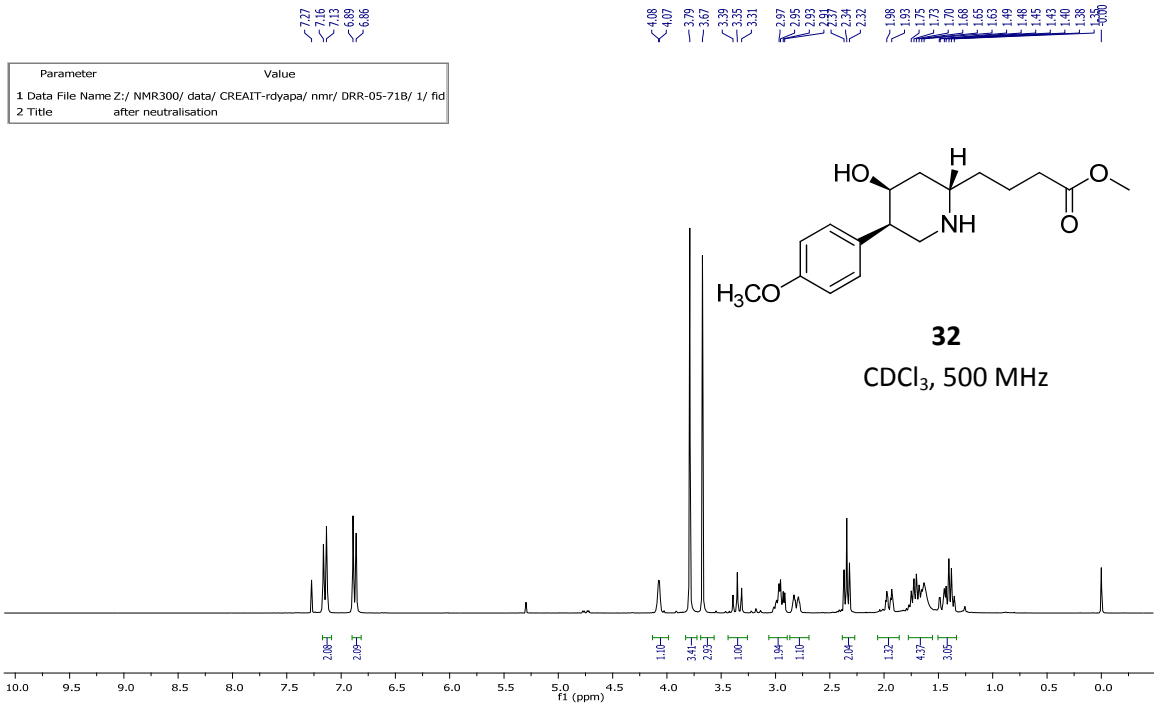
3.33
1.20
1.44
2.66
6.69
9.86
f1 (ppm)



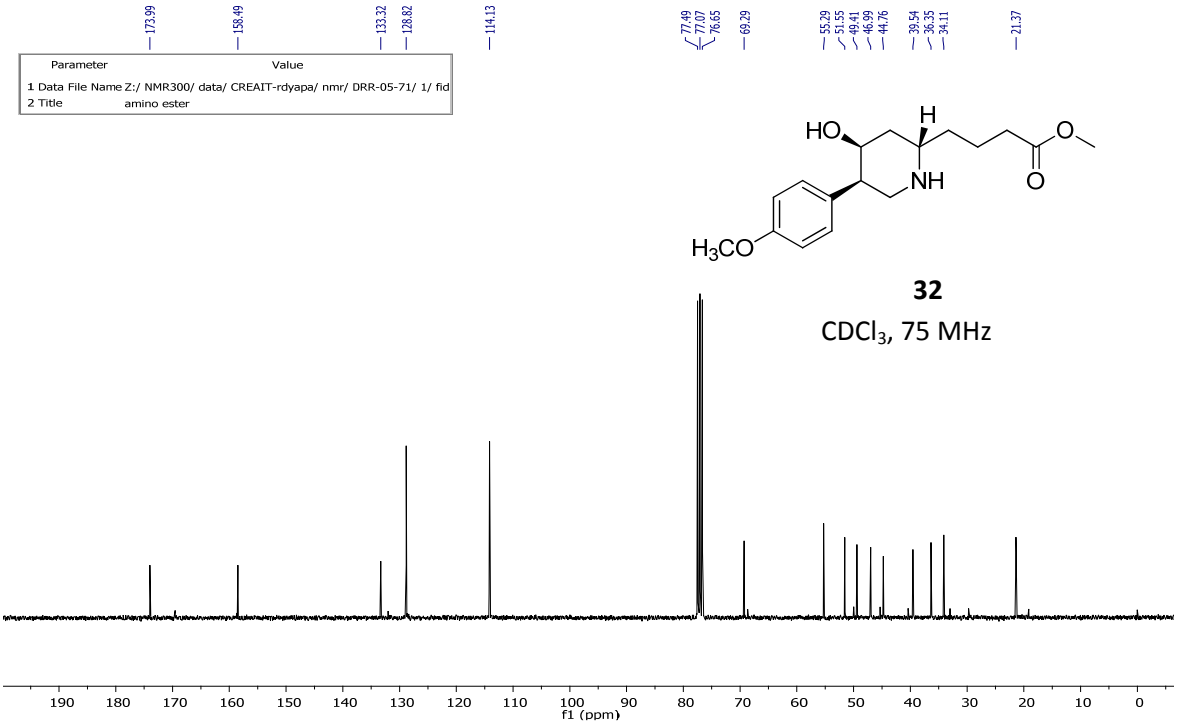
31

$CDCl_3$, 75 MHz



32

$CDCl_3$, 500 MHz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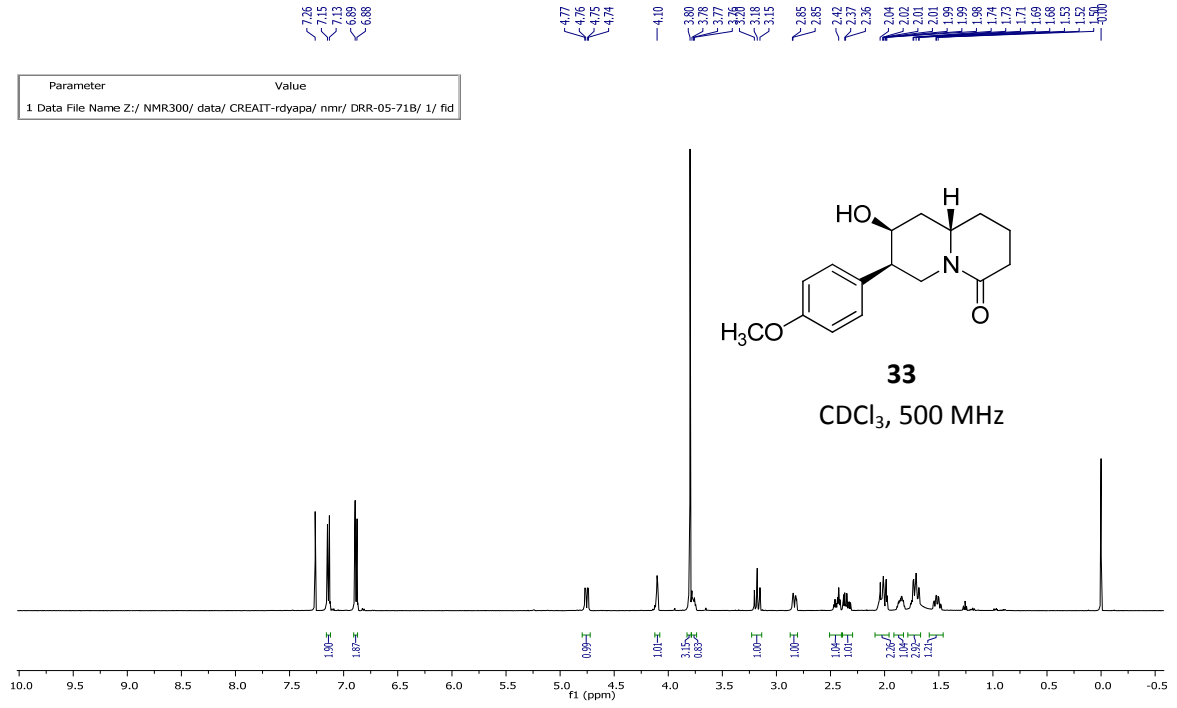
O
NH
O
H3CO
32
CDCl3, 75 MHz
f1 (ppm)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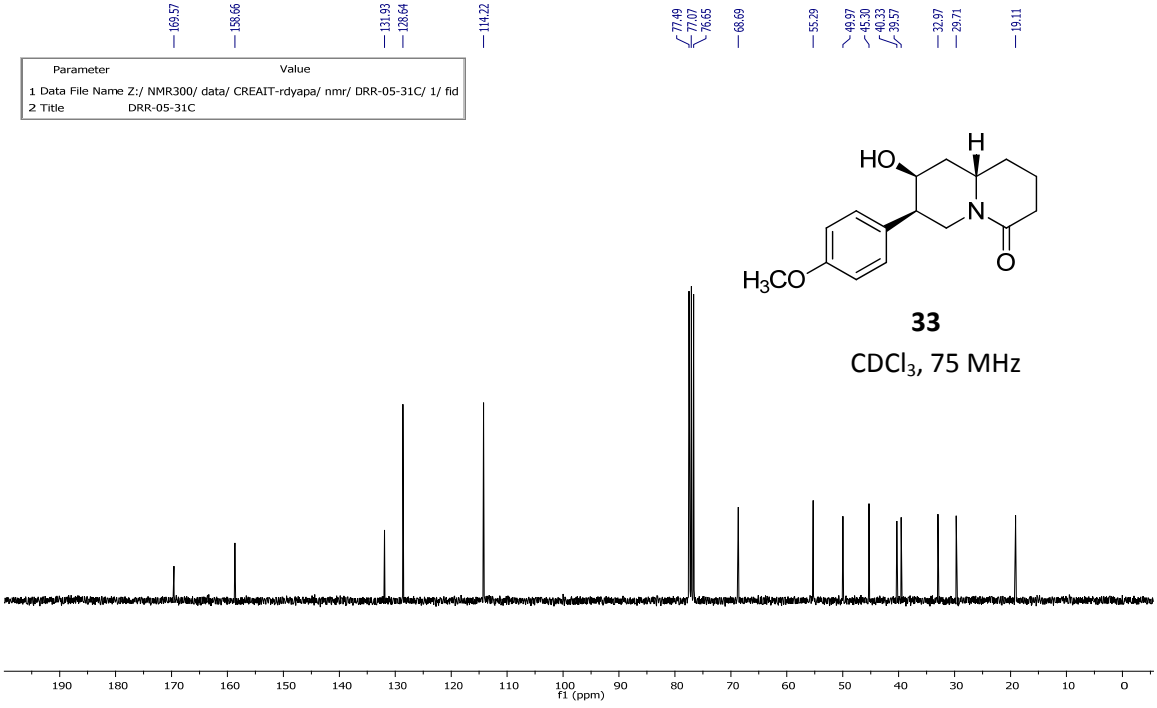
N
O
H3CO
33
CDCl3, 500 MHz
f1 (ppm)



33

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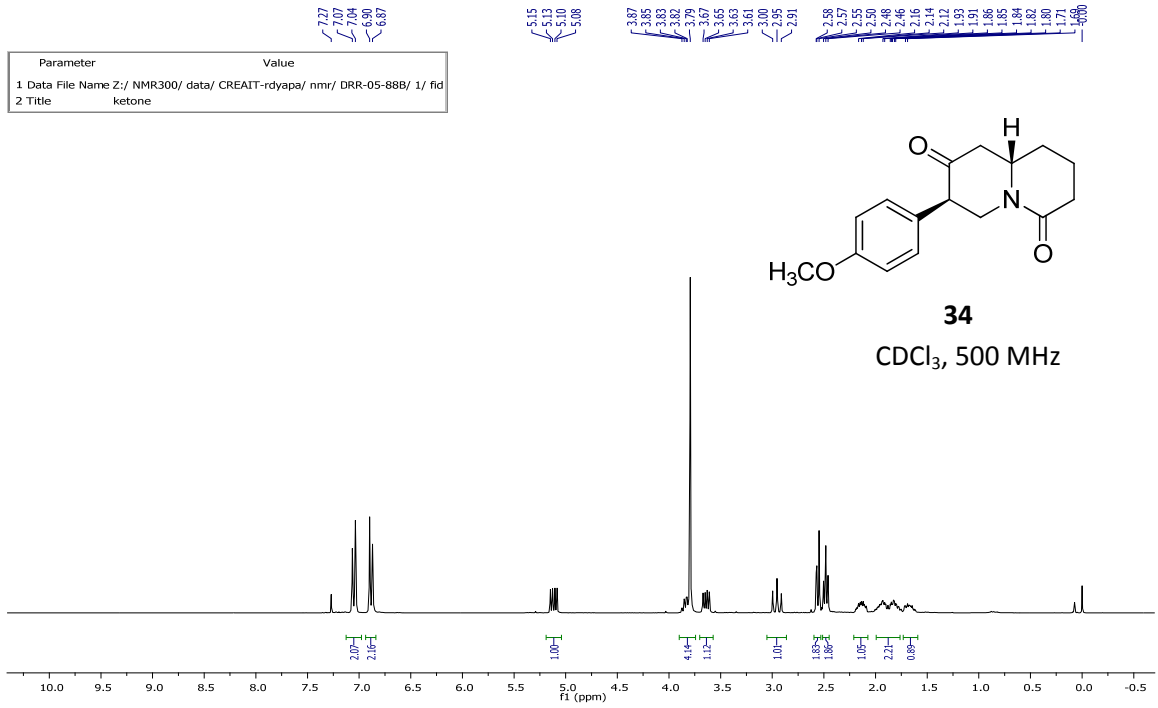

34

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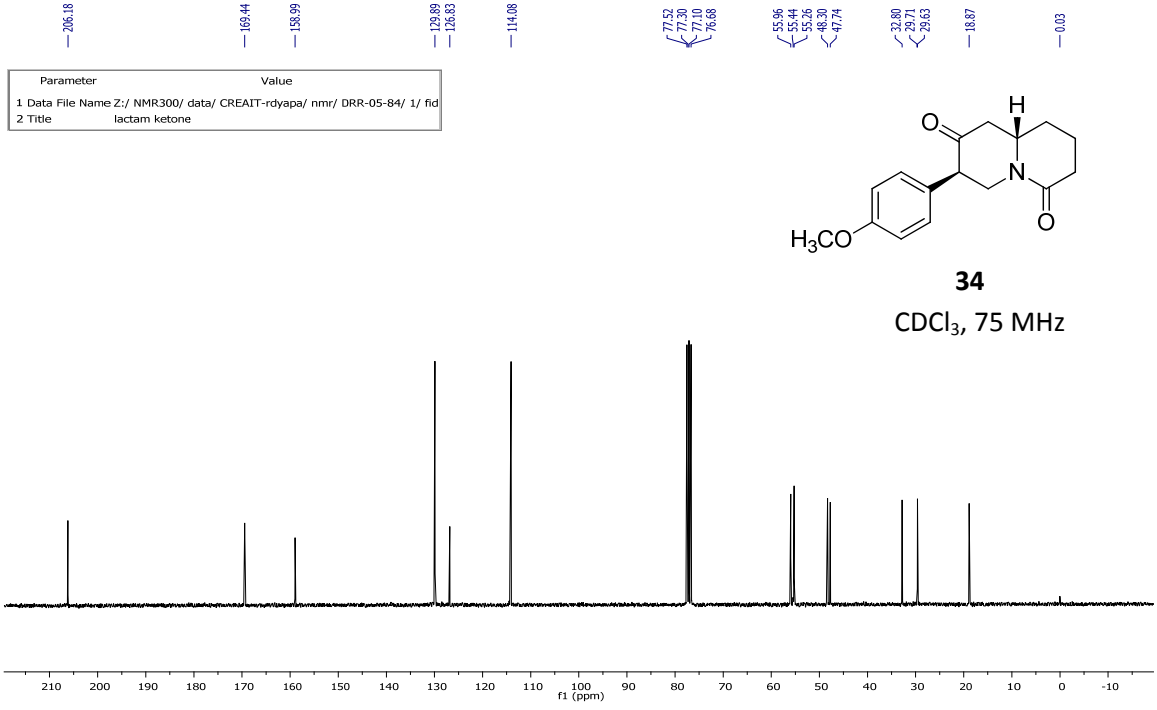

34

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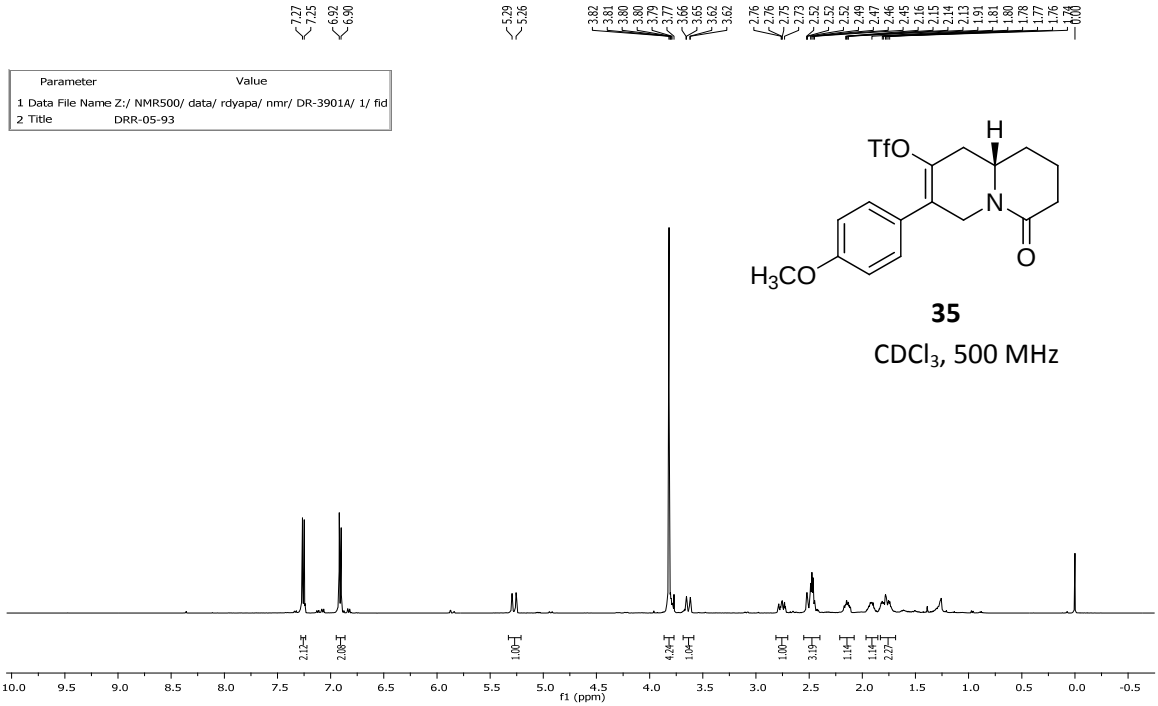
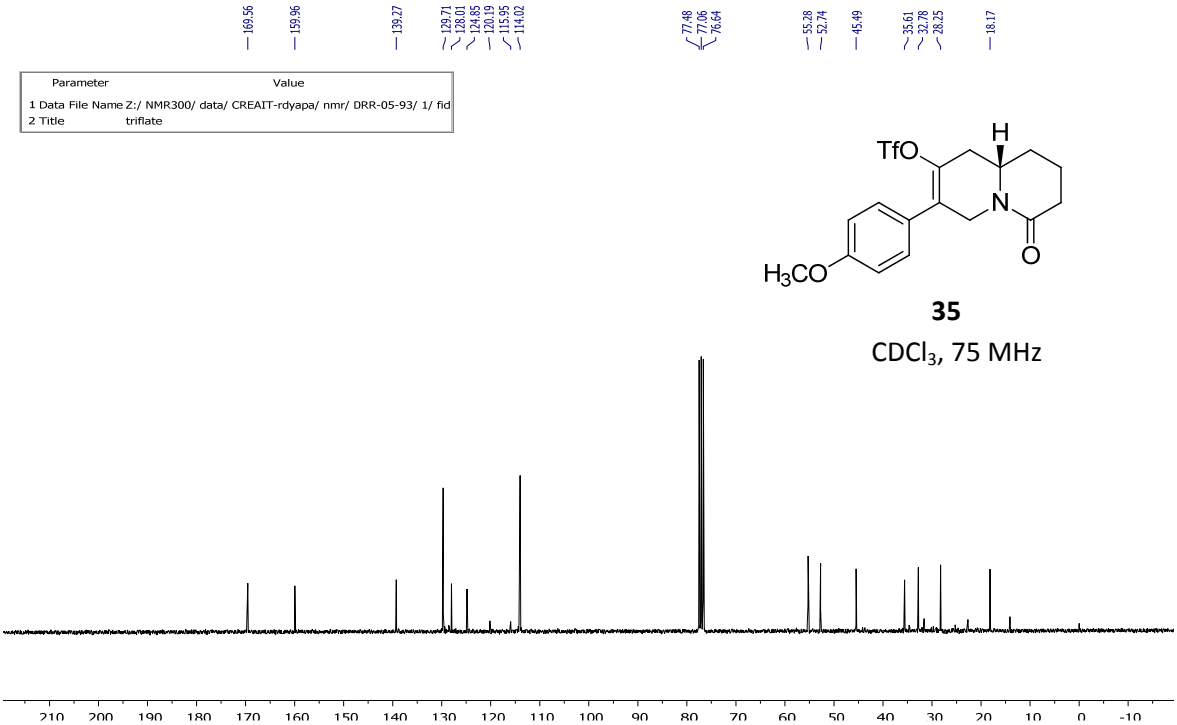


35

$CDCl_3$, 500 MHz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128.01
124.85
120.19
115.95
114.02
77.48
77.06
76.64
55.28
52.74
45.49
35.61
32.78
28.25
18.17
Parameter Value
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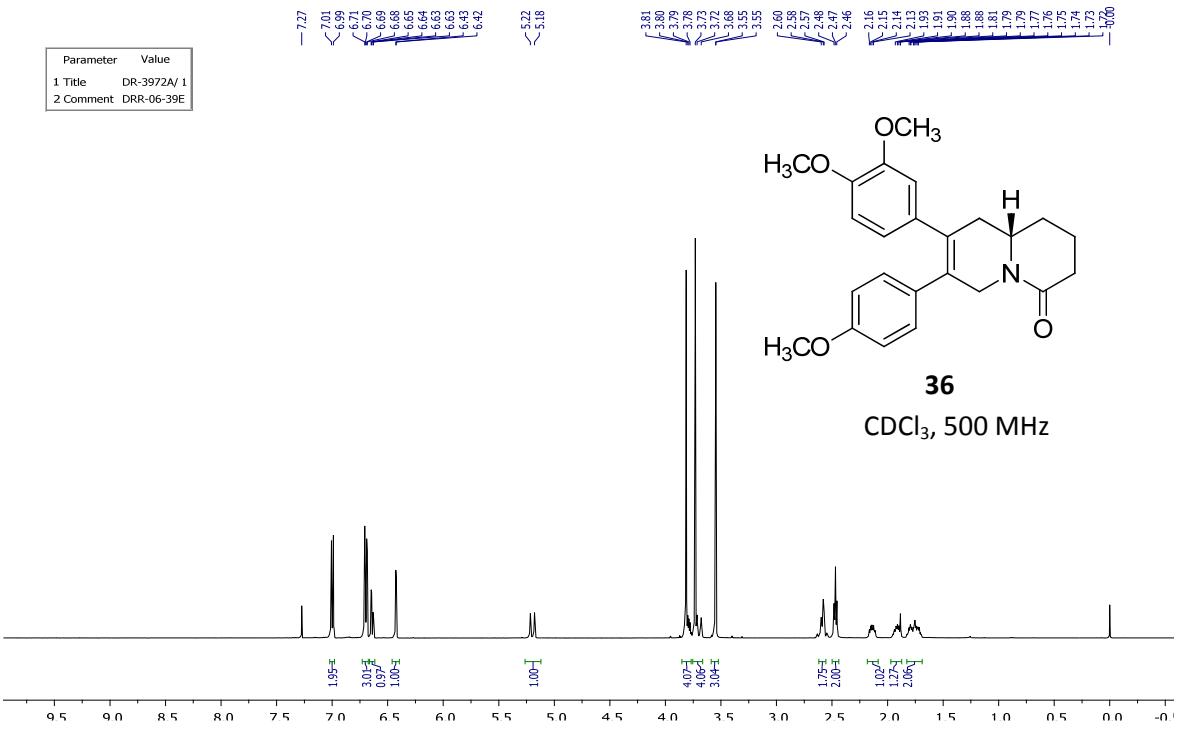
TfO
H
N
O
H3CO
35
CDCl3, 75 MHz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7.01
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6.71
6.70
6.69
6.68
6.65
6.64
6.63
6.63
6.43
6.42
5.22
5.18
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3.80
3.79
3.78
3.73
3.72
3.68
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2.46
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2.15
2.14
2.13
1.93
1.91
1.90
1.88
1.88
1.81
1.79
1.79
1.77
1.76
1.75
1.74
1.73
1.70
Parameter Value
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2 Comment DRR-06-39E
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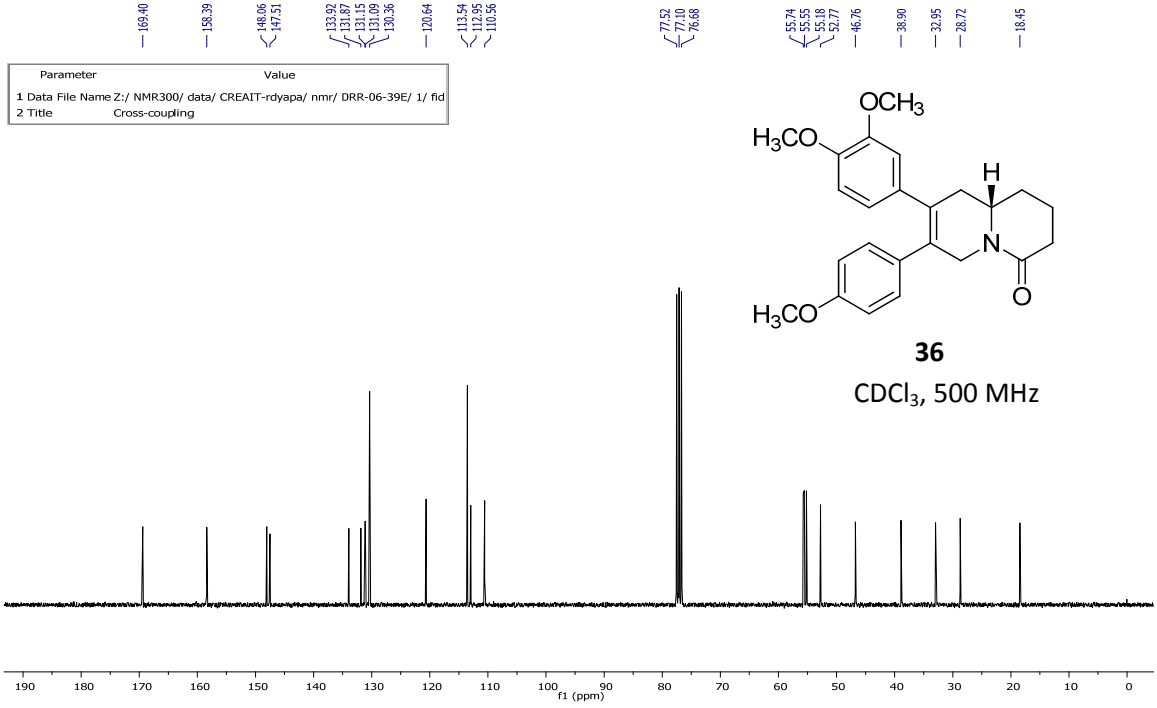
H3CO
H
N
O
H3CO
36
CDCl3, 500 MHz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158.39
148.06
147.51
133.92
131.87
131.15
131.09
130.36
120.64
113.54
112.95
110.56
77.52
77.10
76.68
55.74
55.55
55.18
52.77
46.76
38.90
32.95
28.72
18.45
Parameter Value
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2 Title Cross-coupling
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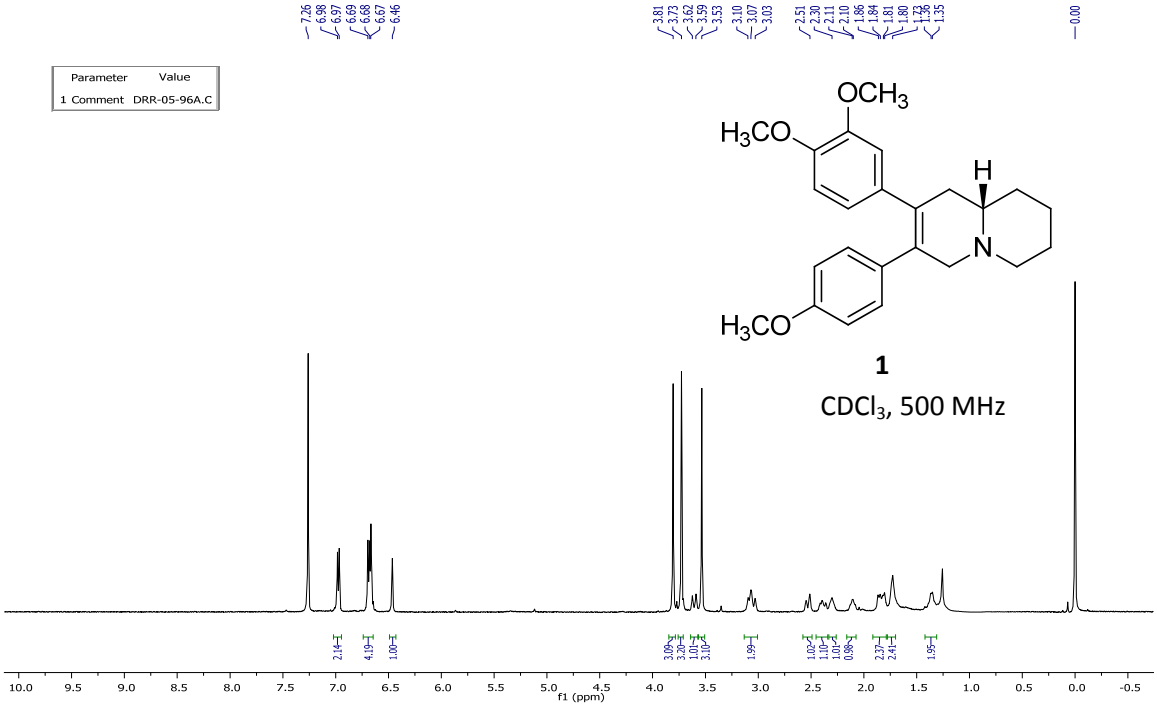
H3CO
H
N
O
H3CO
36
CDCl3, 500 MHz
f1 (ppm)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6.98
6.97
6.69
6.68
6.67
6.46
3.81
3.73
3.62
3.59
3.53
3.10
3.07
3.03
2.51
2.30
2.11
2.10
1.86
1.84
1.81
1.80
1.73
1.36
1.35
0.00
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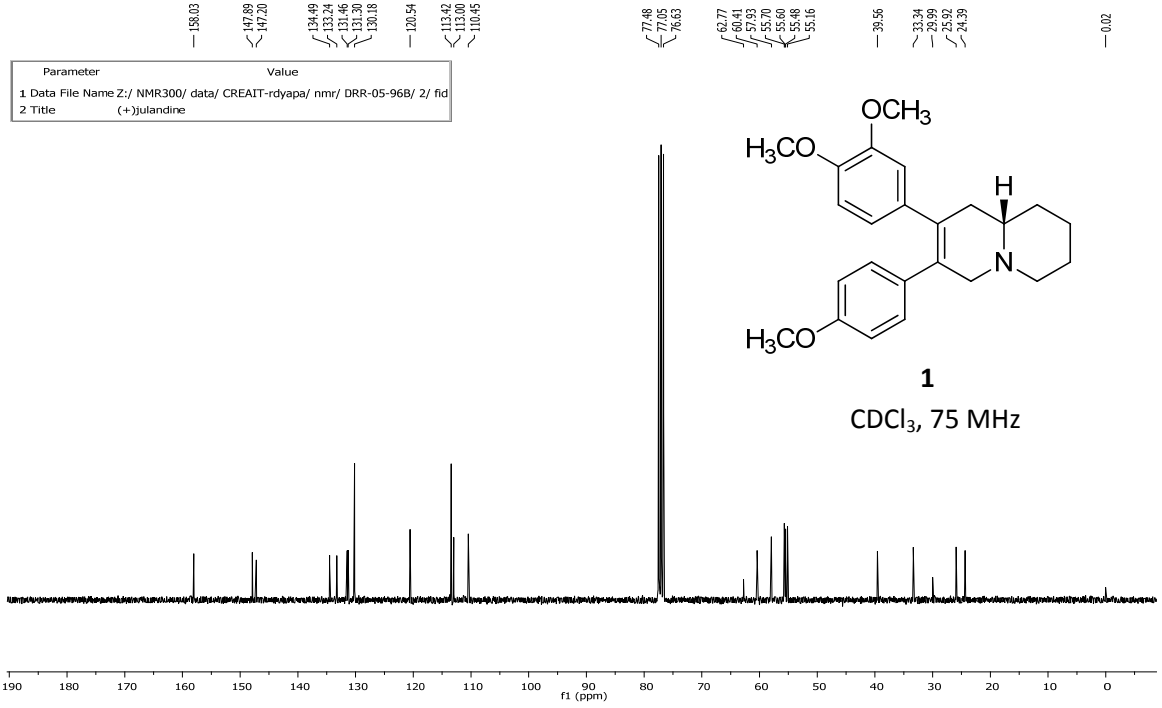
H3CO
H
N
H3CO
1
CDCl3, 500 MHz
f1 (ppm)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134.49
133.24
131.46
131.30
130.18
120.54
113.42
113.00
110.45
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77.05
76.63
62.77
60.41
57.93
55.70
55.60
55.48
55.16
39.56
33.34
29.99
25.92
24.39
0.02
Parameter Value
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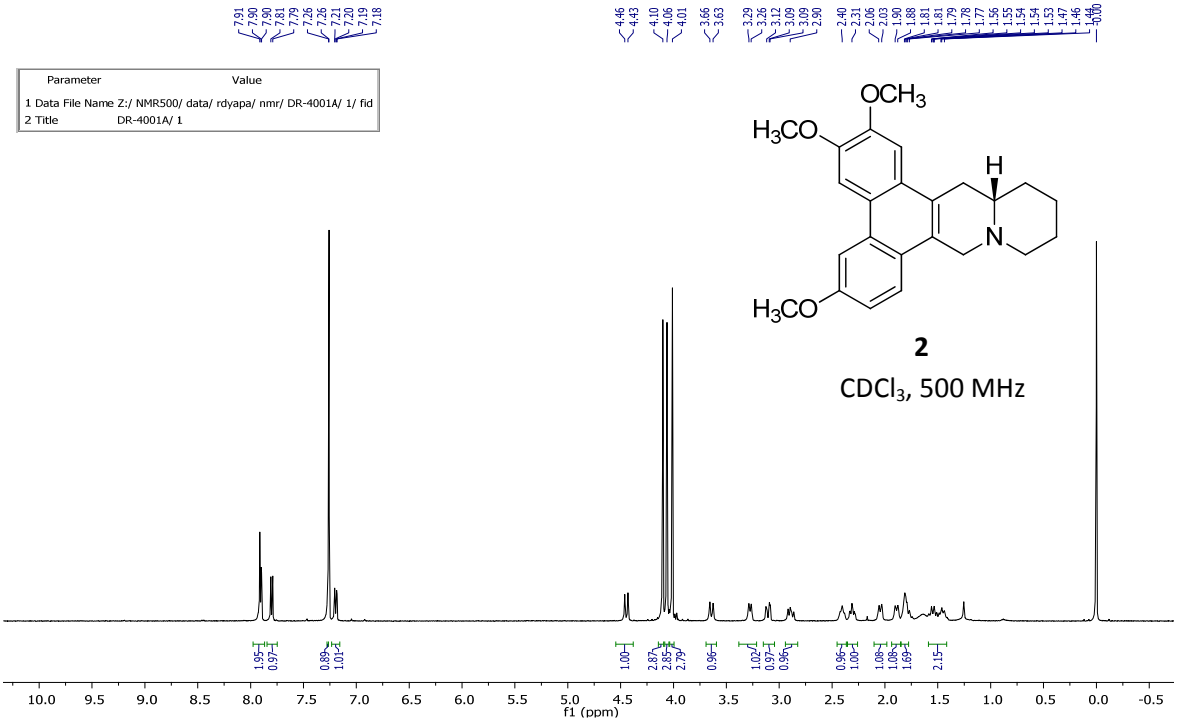
H
N
H3CO
1
CDCl3, 75 MHz
f1 (ppm)


7.91
7.90
7.90
7.81
7.79
7.26
7.26
7.21
7.20
7.19
7.18
4.46
4.43
4.10
4.06
4.01
3.66
3.63
3.29
3.26
3.12
3.09
3.09
2.90
2.40
2.31
2.06
2.03
1.90
1.88
1.81
1.81
1.79
1.78
1.77
1.56
1.55
1.54
1.54
1.53
1.47
1.46
1.44
1.00
Parameter Value
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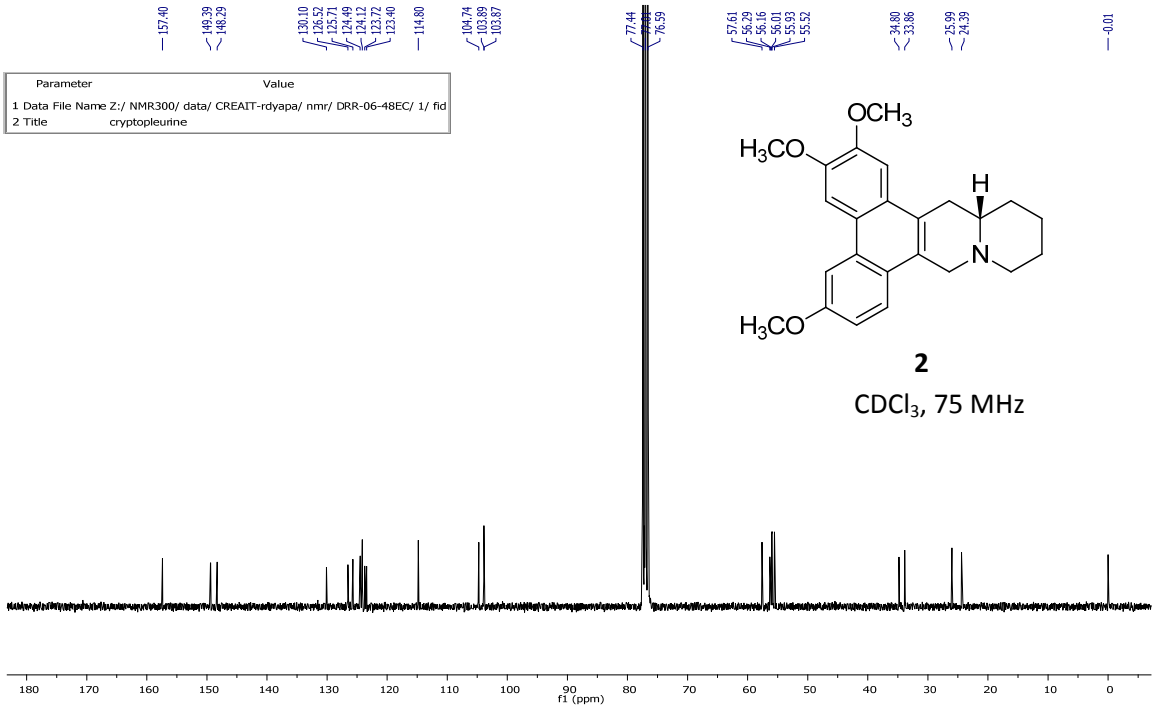
H3CO
H
N
H3CO
2
CDCl3, 500 MHz
1.95
0.97
0.89
1.01
1.00
2.87
2.85
2.79
0.96
1.02
0.97
0.96
0.96
1.00
1.08
1.08
1.69
2.15
f1 (ppm)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148.29
130.10
126.52
125.71
124.49
124.12
123.72
123.40
114.80
104.74
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77.44
77.03
76.59
57.61
56.29
56.16
56.01
55.93
55.52
34.80
33.86
25.99
24.39
-0.01
Parameter
Value
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2 Title cryptopleurine
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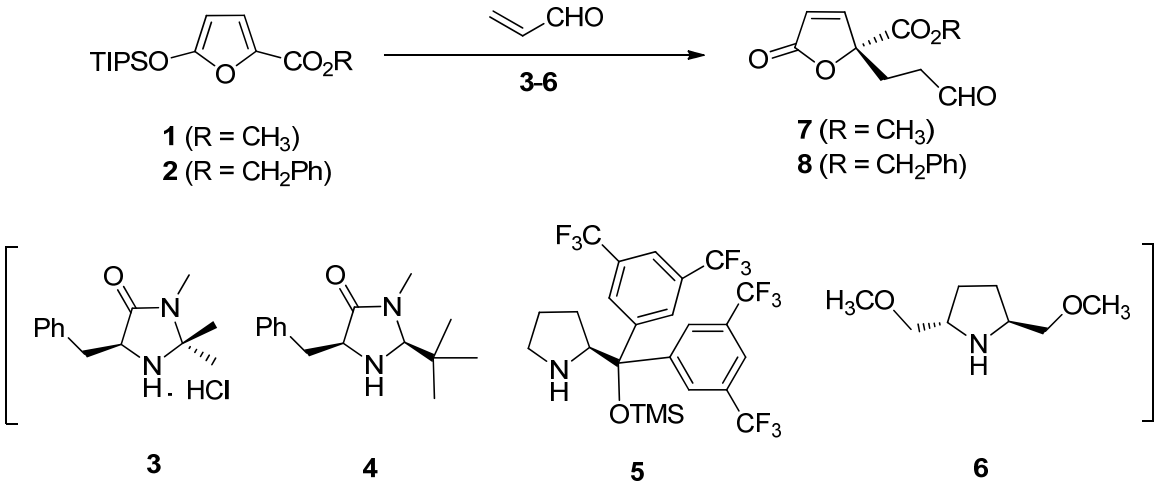
H3CO
H
N
H3CO
2
CDCl3, 75 MHz
f1 (ppm)

Chapter 5

Conclusions

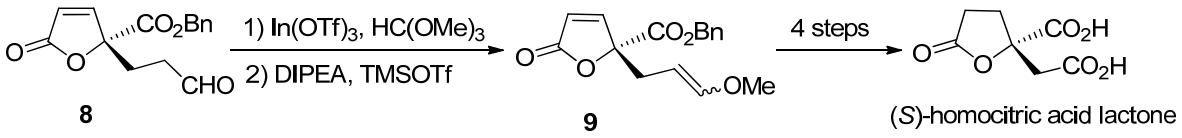
5.1 Summary of the thesis

The organocatalytic, enantioselective Mukaiyama-Michael reaction of silyloxy furans (**1** & **2**) and acrolein was developed. The methodology was used in an enantioselective syntheses of (*S*)-homocitric acid lactone and its homologue. Secondary amines **3-6** were chosen as potential catalysts for the organocatalytic conjugate addition reaction of **1** and **2** with acrolein (Scheme 5.1). After an extensive optimization study using various solvents and additives, the use of furan **2** (benzyl ester) as the nucleophile in $CHCl_3/H_2O$ provided the Michael adduct **8** in 80% ee and 40% yield using **3** as the catalyst.



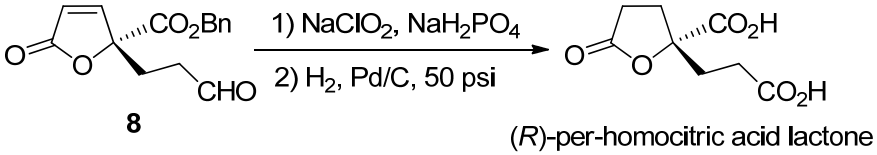
Scheme 5.1

Using the Michael adduct **8** (80% ee) as the starting material, the synthesis of the target homocitric acid lactone was completed *via* a dehomologation/oxidation protocol (Scheme 5.2).



Scheme 5.2

Michael adduct **8** was also used in the synthesis of (*R*)-per-homocitric acid lactone (Scheme 5.3), which is a desymmetrized version of parental achiral triacid.

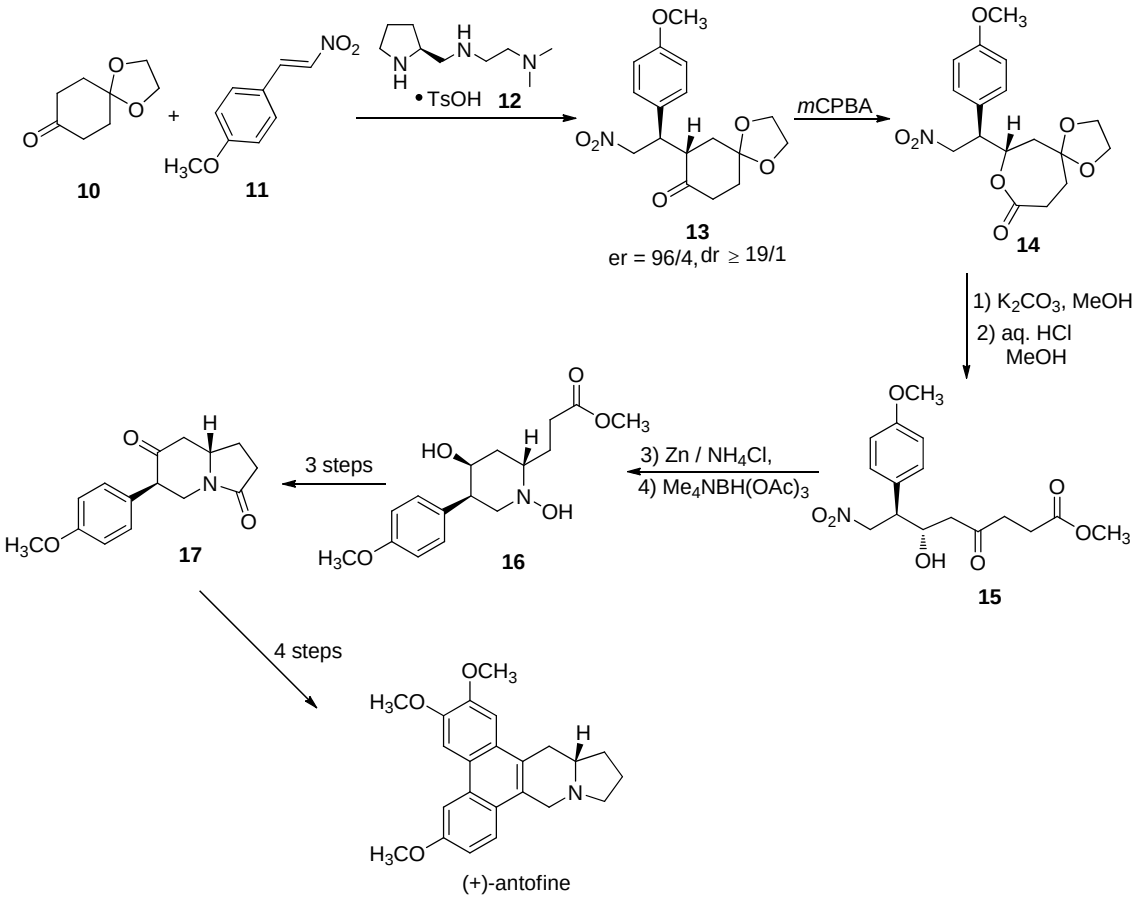


Scheme 5.3

In summary, an expedient, organocatalysis-based, enantioselective syntheses of (*S*)-homocitric acid lactone and its homologue have been developed. Notably, the methodology also provides several butenolide intermediates that offer opportunities for chemoselective functionalization. Such reactions may find applications in the synthesis of functionalized, oxygen and nitrogen heterocycles with applications in biology and medicine.

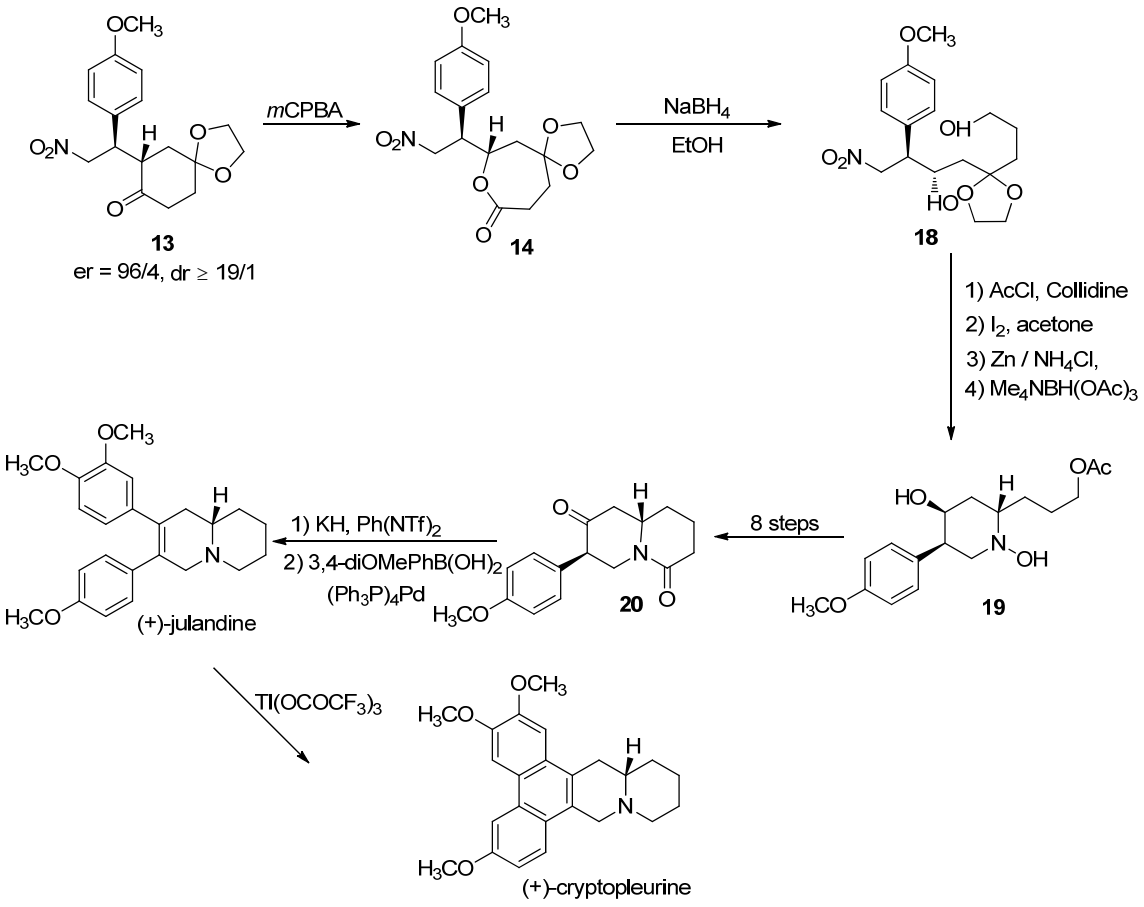
In the second project, an enantioselective synthesis of the indolizidine alkaloid (+)-antofine was developed from an enantiomerically enriched γ-nitroketone.

Enantiomerically pure *γ*–nitroketones and their derivatives are an important class of organic compounds due to their utility as building blocks for the asymmetric synthesis of natural products and biologically active molecules. The organocatalytic Michael addition of a monoprotected cyclohexane 1,3-dione and selected 4-methoxy-*β*-nitro styrenes in the presence of a proline-derived triamine catalyst provided the enantioenriched *γ*-nitroketone **13** (*ee* = 90%, *dr* ≥19/1). Oxidative ring expansion of the nitroketone and subsequent methanolysis provided a 8-nitro-4-oxooctanoate **15**. This is stereoselectively transformed to the key, functionalized piperidine intermediate **16** which is readily converted to (+)-antofine (Scheme 5.4).



Scheme 5.4

In the third project, we have used the enantioenriched γ-nitroketone **13** in the syntheses of quinolizidine alkaloids (+)-julandine and (+)-cryptopleurine. Oxidative ring expansion of the nitroketone **13,** followed by reductive ring-opening, leads to a suitably functionalized nitrodiol **18** which was stereoselectively converted to the functionalized piperidine **19**. (+)-Julandine was obtained by employing a homologation/cross coupling reaction sequence on piperidine derivative **19**. Oxidative cyclization of (+)-julandine using thallium trifluoroacetate provided the title compound (+)-cryptopleurine (Scheme 5.5).

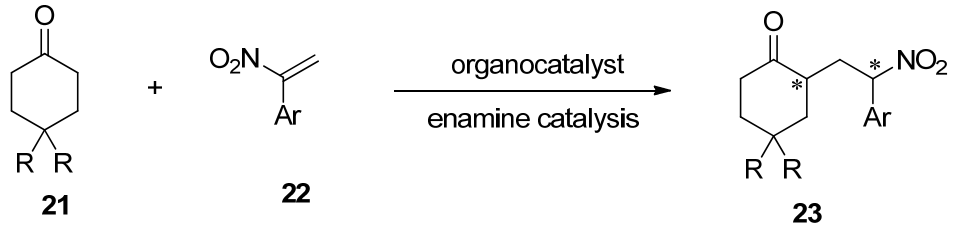


Scheme 5.5

In summary, an efficient synthesis of functionalized indolizidines and quinolizidines was developed from a simple γ-nitroketone starting material which is readily available from the organocatalytic ketone–nitroalkene Michael addition reaction. The methodology was applied in the total synthesis of indolizidine alkaloid (+)-antofine and the first total synthesis of the natural enantiomer of the diaryl quinolizidine alkaloid (+)-julandine. The structurally related phenanthroquinolizidine alkaloid (+)-cryptopleurine was prepared from (+)-julandine. The synthetic strategy should be particularly amenable to the preparation of focused libraries of analogs of these alkaloids by judicious selection of the nitroalkene and the aryl component in the cross-coupling step.

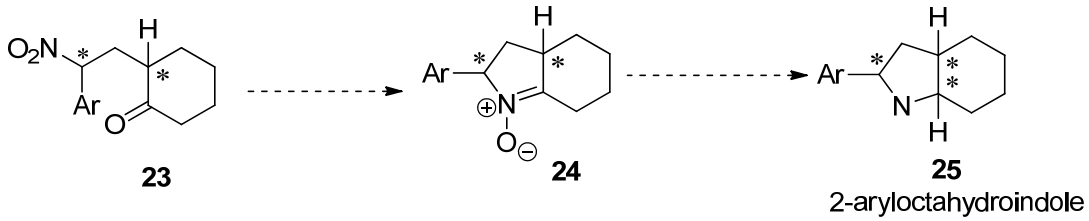
5.2 Future work

Organocatalytic Michael addition of cyclic ketones **21** and *α*-nitrostyrenes **22** (prepared by *in situ* elimination of the corresponding nitroacetates[1]) would be an interesting methodology to synthesize enantiomerically pure *γ*–nitroketones **23** (Scheme 5.6). These *γ*–nitroketones and their derivatives may be useful as building blocks for the asymmetric synthesis of natural products and biologically active compounds as detailed below.



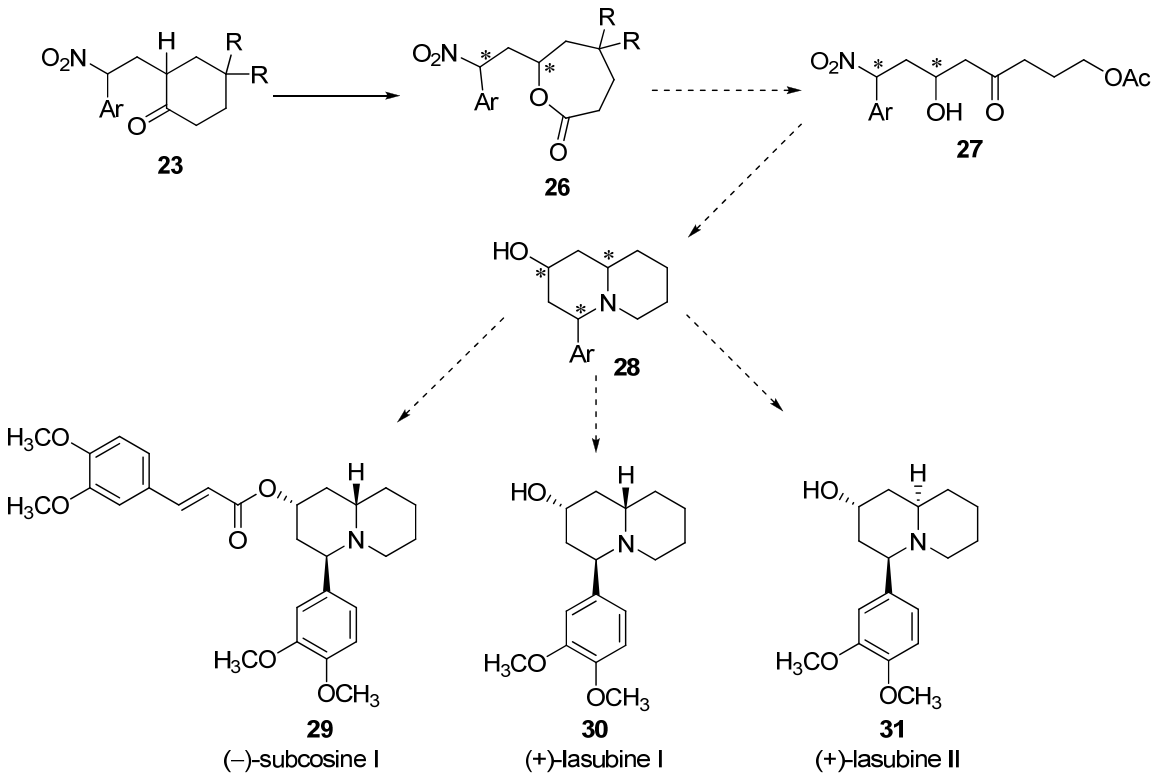
Scheme 5.6

The Michael adducts **23** can be potentially converted to the corresponding nitrones **24**. These nitrones would be useful in the stereoselective synthesis of 2-aryl octahydroindoles **25** (Scheme 5.7). These octahydroindoles may have applications in diversity oriented synthesis[2] and medicinal chemistry[3-5].



Scheme 5.7

In addition, the octahydroindoles **25** may also have applications in target oriented synthesis. Oxidative ring expansion of the *γ*-nitroketone **23** followed by reductive ring opening would lead to the 8-nitro-4oxooctonate **27**. This is a potential precursor of functionalized quinolizidines such as **28**. These quinolizidines could be transformed into natural products such as subcosine I (**29**), lasubine I (**30**) and lasubine II (**31**) (Scheme 5.8).



Scheme 5.8

5.3 References

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