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Dr. Claudio Palomo Nicolau con N.I.F. 37655199-J como Director de la Tesis Doctoral: "Asymmetric α-Functionalization of Barbituric Acids *via* Brønsted Base Catalysis" realizada en el Programa de Doctorado Química Sintética e Industrial por la Doctoranda Doña. Sandra Rodríguez del Pozo,

autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia-San Sebastián a 5 de Noviembre de 2018

EL DIRECTOR DE LA TESIS

Fdo.: Claudio Palomo Nicolau

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Dr. Juan Miguel Oyarbide Garmendia con N.I.F. 15968197-X como Director de la Tesis Doctoral:"Asymmetric α-Functionalization of Barbituric Acids *via* Brønsted Base Catalysis" realizada en el Programa de Doctorado Química Sintética e Industrial por la Doctoranda Doña. Sandra Rodríguez del Pozo,

autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia-San Sebastián a 5 de Noviembre de 2018

EL DIRECTOR DE LA TESIS

Fdo.: Juan Miguel Oyarbide Garmendia.

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AUTORIZACIÓN DEL DEPARTAMENTO

El Consejo del Departamento de Química Orgánica I en la reunión celebrada el día 7 de Noviembre de 2018 ha acordado dar la conformidad a la admisión a trámite de presentación de la Tesis Doctoral titulada: "Asymmetric α-Functionalization of Barbituric Acids *via* Brønsted Base Catalysis" dirigida por el Dr. Claudio Palomo Nicolau y el Dr. Juan Miguel Oyarbide Garmendia y presentada por Doña. Sandra Rodríguez del Pozo ante este Departamento.

En Vitoria-Gasteiz a 7 de Noviembre de 2018

VºBº DIRECTOR DEL DEPARTAMENTO	SECRETARIA DEL DEPARTAMENTO
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AUTORIZACIÓN DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO

La Comisión Académica del Programa de Doctorado en **Química Sintética e Industrial** en la reunión celebrada el día 5 de Noviembre de 2018,
ha acordado dar la conformidad a la presentación de la Tesis Doctoral titulada: "Asymmetric α-Functionalization of Barbituric Acids *via* Brønsted Base Catalysis" dirigida por el Dr. Claudio Palomo Nicolau y el Dr. Juan Miguel Oyarbide Garmendia y presentada por Dña. Sandra Rodríguez del Pozo adscrita al Departamento de Química Orgánica I.

En Leioa, a 5 de Noviembre de 2018

LA RESPONSABLE DEL PROGRAMA DE DOCTORADO

KIMIKA ORGANIKOA II SAILA
DEPARTAMENTO DE QUÍMICA ORGÁNICA II

Fdo.: Esther Lete

Universidad del País Vasco Euskal Herriko Unibertsitatea

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ACTA DE GRADO DE DOCTOR O DOCTORA
ACTA DE DEFENSA DE TESIS DOCTORAL

DOCTORANDA DÑA. **Sandra Rodríguez del Pozo**

TITULO DE LA TESIS: **“Asymmetric *α*-Functionalization of Barbituric Acids *via* Brønsted Base Catalysis”**

El Tribunal designado por la Comisión de Postgrado de la UPV/EHU para calificar la Tesis Doctoral arriba indicada y reunido en el día de la fecha, una vez efectuada la defensa por el/la doctorando/a y contestadas las objeciones y/o sugerencias que se le han formulado, ha otorgado por___________________la calificación de:

unanimidad ó mayoría

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SOBRESALIENTE / NOTABLE / APROBADO / NO APTO

Idioma/s de defensa (en caso de más de un idioma, especificar porcentaje defendido en cada idioma):

Castellano ____
Euskera ____
Otros Idiomas (especificar cuál/cuales y porcentaje) ____________________

En Donostia-San Sebastián a 18 de enero de 2019

EL/LA PRESIDENTE/A, EL/LA SECRETARIO/A,

Fdo.: Fdo.:

Dr/a: ____________________ Dr/a: ____________________

VOCAL 1º, VOCAL 2º, VOCAL 3º,

Fdo.: Fdo.: Fdo.:

Dr/a: ____________________Dr/a:____________________Dr/a:____________________

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Fdo.: ____________________

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Universidad del País Vasco
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Asymmetric α-Functionalization of Barbituric Acids *via* Brønsted Base Catalysis

DOCTORAL THESIS

Sandra Rodríguez del Pozo

Donostia-San Sebastián, 2019

Dedicado a la memoria de mi abuelo,

Agradecimientos

Esta tesis doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Ciencias Químicas de San Sebastián, Universidad del País Vasco (UPV-EHU), bajo la dirección del Dr. Claudio Palomo Nicolau y el Dr. Mikel Oiarbide Garmendia, a quienes expreso mi más sincero agradecimiento, primero por darme la oportunidad de desarrollar esta tesis doctoral en este departamento, por su dedicación, esfuerzo y paciencia durante todo el desarrollo de este trabajo. La financiación de este trabajo ha provenido de una beca predoctoral de la UPV-EHU, organismo al cual, me gustaría agradecer su colaboración.

También me gustaría agradecer al resto de profesores que forman parte del departamento, en especial, a Silvia Vera.

Noski, nola ez, nire laborategiko lagunei, Amaiur, Aneto, Julen, Iñakudo, Odeitxus, Igortxos, Joseba, Ugaitz eta Paula, zuen pazientziagatik eta pasa ditugun une on eta txarrengatik, eskerrik asko denoi, munduko onenak zarete!!! Baita nire laborategiko lagun zaharrei ere: Haizea, Iurre, Eider, Nerea, Irati eta Diane. Eskerrik asko neskak, gauza asko ikasi ditut zuengatik!!! Baina berezik eskerrak eman dizkiot Olatxiri bere familia eta kuadrillan ni integratzeagatik eta, momentu on asko nirekin konpartitzeagatik. Eskerrik asko Olatxi, zurekin lau urte hauetan etxean bezala sentitu naiz!!!

Bestalde, eskerrik Mikelei ere bere aholkuengatik eta azkeen bi urteetan egunero nire txapak josateagatik.

Y por último, me gustaría agradecer a mi familia todo el apoyo que me ha dado. Gracias en especial, a mi madre y a mi padre, por ayudarme siempre en la manera en la que lo he necesitado. Y por supuesto, a mi hermano y a mis tías Sole y Beatriz.

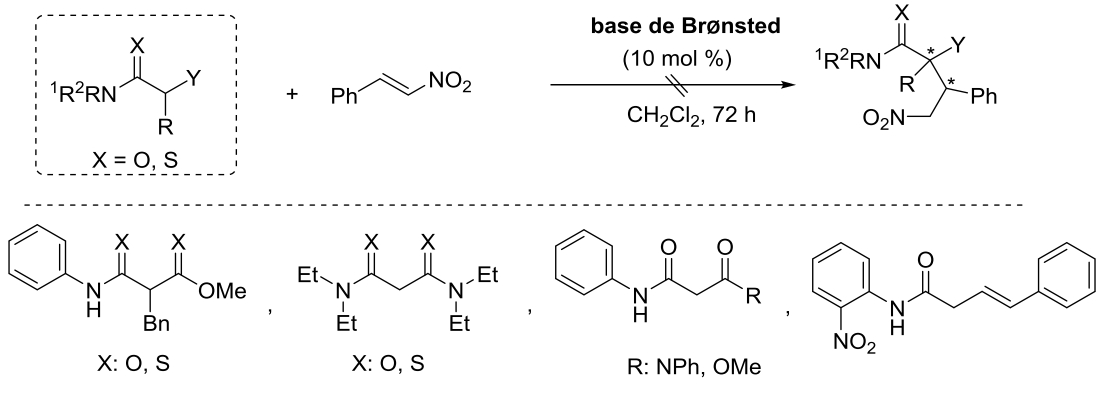
RESUMEN

Las amidas pueden catalogarse entre los compuestos carbonílicos menos reactivos. Esta estabilidad ha contribuido a su utilidad como productos funcionales finales, constituyendo por ejemplo la estructura base de las proteínas y otras moléculas bioactivas de menor peso molecular. A su vez, esta estabilidad cinética las convierte en sustratos recalcitrantes para llevar a cabo procesos de *C*-funcionalización catalítica. En concreto, la formación directa de nuevos enlaces *C-C* en *α* de una amida de forma enantioselectiva sigue siendo un reto.

En esta tesis doctoral se han investigado nuevos procedimientos para la *α*-funcionalización enantioselectiva de amidas mediante el uso de organocatalizadores, y, más concretamente, bases de Brønsted.

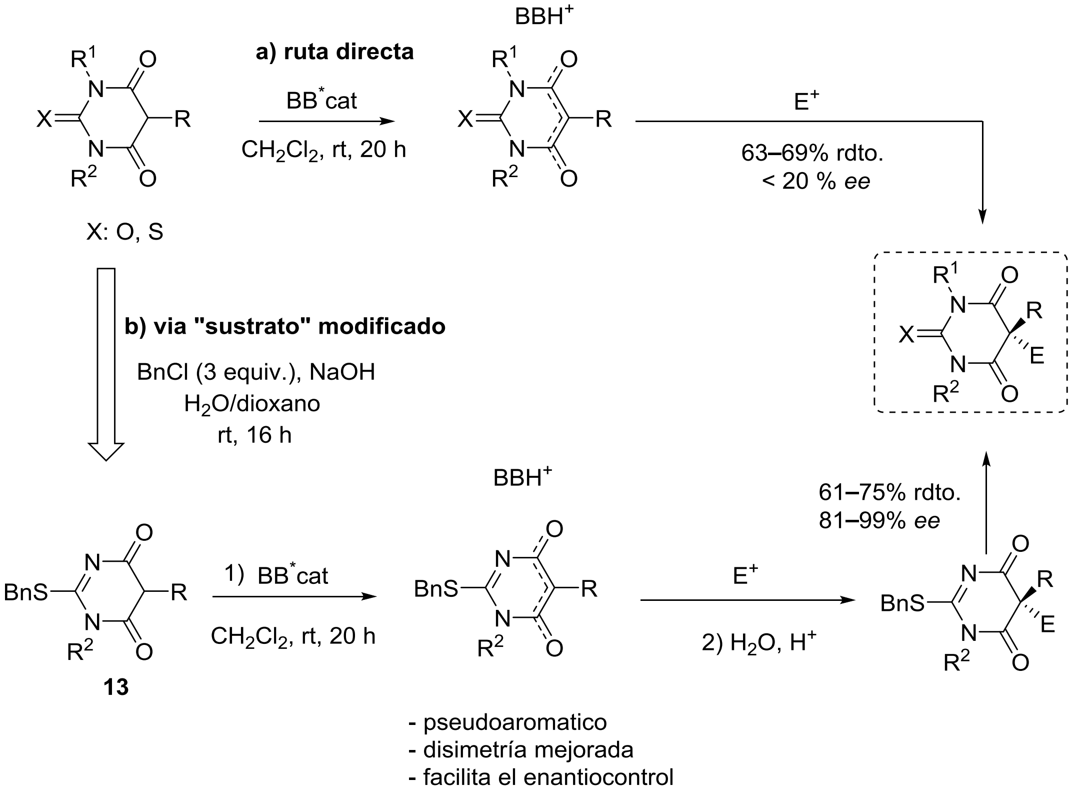
El estudio se ha centrado en dos tipos de amidas: los derivados del ácido barbitúrico y las *α*-iminoamidas, debido a que ambos tipos de amidas son la estructura base de compuestos de interés farmacológico.

Inicialmente, se ha estudiado la viabilidad de la reacción de adición conjugada de diversas amidas y tioamidas activadas derivadas de ácido malónico a nitroestireno en presencia de un catalizador bifuncional tipo base de Brønsted/enlace de H. Se ha comprobado que la citada reacción es inviable, también para el caso de amidas *β,γ*-insaturadas, recuperándose los productos de partida inalterados (Scheme 1).



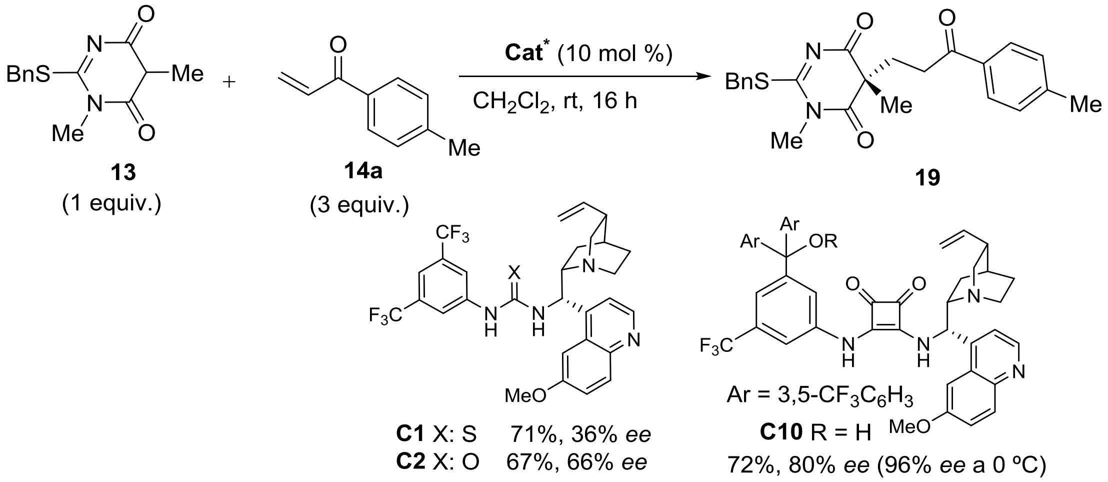
Scheme 1. Listado de amidas y tioamidas.

Una vez realizado este estudio, se pensó en el uso de derivados del ácido barbitúrico, cuyo esqueleto es una *pseudo* diamida. De esta manera, se ha estudiado la *α*-funcionalización enantioselectiva de ácidos barbitúricos y derivados. En un primer intento se ensayó la reacción directa de (thio)barbituratos con aril vinil cetonas en presencia de diversas bases de Brønsted bifuncionales obteniéndose rendimientos buenos, 63–69%, pero principalmente racémicos. A la vista de estos resultados insatisfactorios, se decidió la modificación de los sustratos y su conversión en los SBn derivados **13** que resultaron ser mucho más eficaces. La idea subyacente es que el enolato intermedio que se genera mejora la disimetría estructural en comparación con los (thio)barbituratos facilitando de esta manera el enantiocontrol de la reacción (Scheme 2).


a) ruta directa
BB*cat
CH2Cl2, rt, 20 h
BBH+
E+
63–69% rdto.
< 20 % ee
X: O, S
b) via "sustrato" modificado
BnCl (3 equiv.), NaOH
H2O/dioxano
rt, 16 h
13
1) BB*cat
CH2Cl2, rt, 20 h
BBH+
E+
2) H2O, H+
61–75% rdto.
81–99% ee
- pseudoaromatico
- disimetría mejorada
- facilita el enantiocontrol

Scheme 2.

Se probaron distintos derivados bencilados **13**, con la aril metil cetona **14a** y los catalizadores **C1** y **C2** (10 mol%) obteniéndose rendimientos de 71% y 67% y excesos de 36% y 66% respectivamente (Scheme 3).



Scheme 3.

A partir de estos resultados preliminares, se hizo un estudio con distintos catalizadores y temperaturas para poder optimizar la reacción. Los mejores resultados se obtuvieron con **C10**, un nuevo catalizador derivado de esquaramida y con un alto impedimento estérico, y bajando la temperatura a 0 °C. De esta manera, se consiguió un rendimiento del 72% y un *ee* del 96%.

Una vez encontradas las mejores condiciones para la reacción, se utilizaron diferentes (thio)barbitúricos derivados y electrófilos para estudiar su alcance: aril vinil cetonas, α-sililoxienona, vinil sulfona y diazocarboxilato (Figure 1). La reacción funciona muy bien con distintas aril vinil cetonas, obteniéndose rendimientos del 61–75% y excesos enantioméricos de 90–97%. Utilizando la α-sililoxienona también se obtienen muy buenos resultados, rendimientos de entre 61–72% y 83–94% de *ee*. No obstante, con la vinil sulfona y con el diazocarboxilato se obtuvieron rendimientos moderados pero excesos enantioméricos que no son suficientemente buenos (Figure 1).

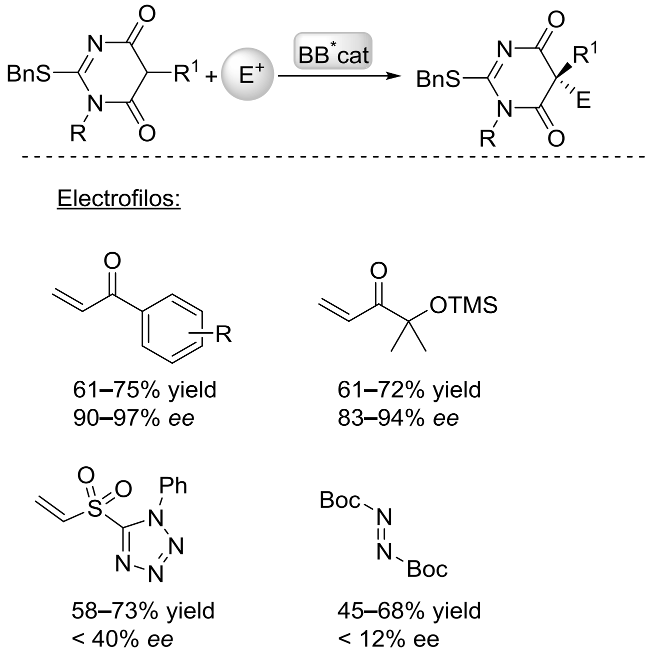
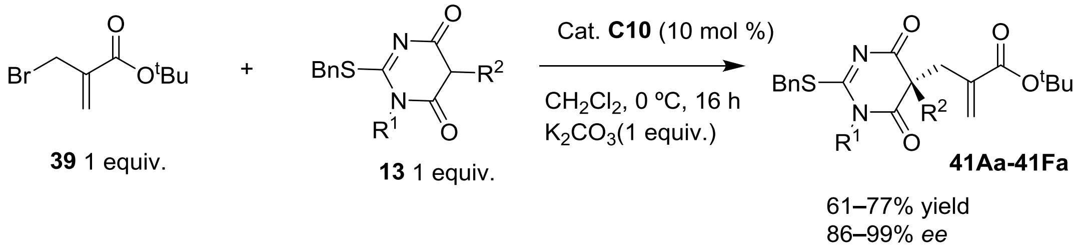

BnS
N
O
R
R1
E+
BB*cat
E
Electrofilos:
OTMS
Ph
Boc
61–75% yield
90–97% ee
61–72% yield
83–94% ee
58–73% yield
< 40% ee
45–68% yield
< 12% ee

Figure 1.

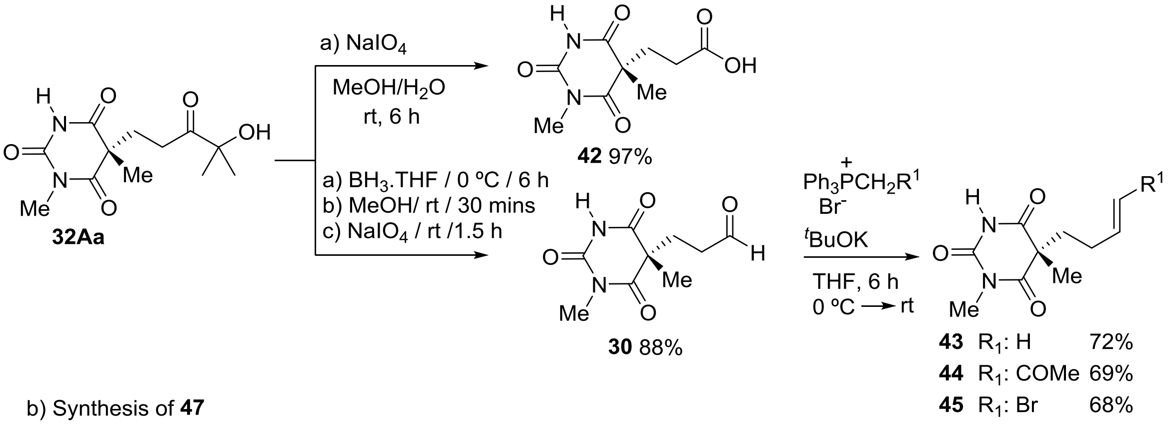
Por otro lado, se estudió la alquilación de los derivados bencilados utilizando (*pseudo*)halogenuros del tipo Morita-Baylis-Hillmann (Scheme 4). Tras un estudio con diferentes bases, se concluyó que el uso de K_2CO_3 era la mejor opción. De esta manera, se obtuvo un gran abanico de compuestos derivados del ácido barbitúrico con muy buenos rendimientos (61–77%) y muy buenos excesos enantiómericos (86–99%).


Br
O
O^tBu
39 1 equiv.
+
BnS
N
R1
R2
13 1 equiv.
Cat. C10 (10 mol %)
CH2Cl2, 0 ºC, 16 h
K2CO3(1 equiv.)
41Aa-41Fa
61–77% yield
86–99% ee

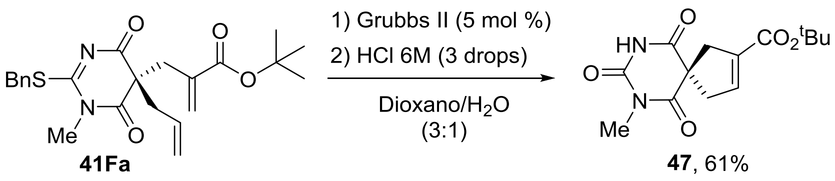
Scheme 4.

El estudio de las reacciones de adición enantioselectiva se completó abordando la posterior elaboración de los aductos en estructuras de interés. Por ejemplo, se transformó el derivado **32Aa** en el ácido **42** y en el aldehído **30**. Este último, se sometió a distintas reacciones de Wittig dando como resultado los aductos **43**, **44** y **45** (Scheme 5, a).

a) Synthesis of **30** and **42-45**


a) NaIO4
MeOH/H2O
rt, 6 h
32Aa
42 97%
a) BH3.THF / 0 ºC / 6 h
b) MeOH/ rt / 30 mins
c) NaIO4 / rt /1.5 h
30 88%
Ph3PCH2R1 Br-
tBuOK
THF, 6 h
0 ºC → rt
43 R1: H 72%
44 R1: COMe 69%
45 R1: Br 68%

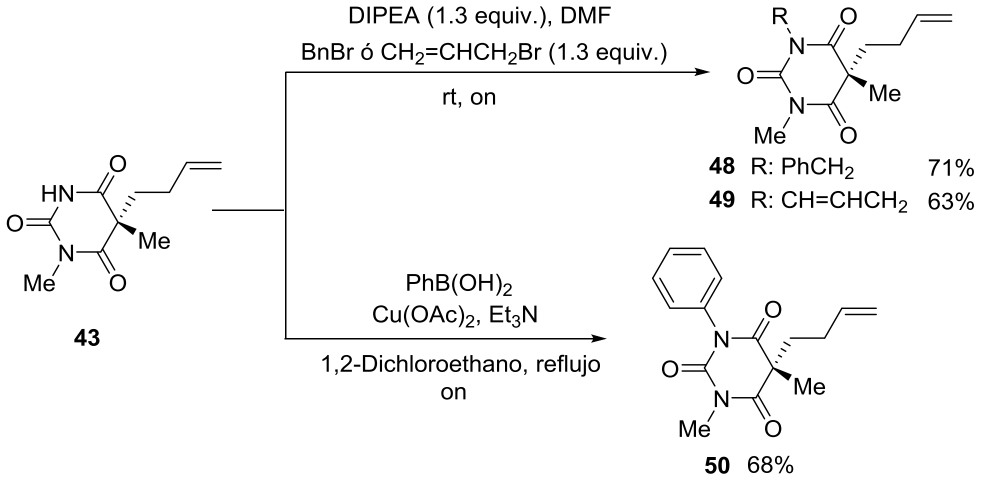
b) Synthesis of **47**


BnS
41Fa
1) Grubbs II (5 mol %)
2) HCl 6M (3 drops)
Dioxano/H2O
(3:1)
CO2tBu
47, 61%

Scheme 5.

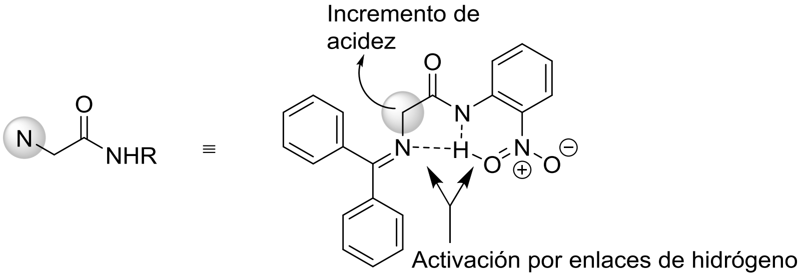
Por otro lado, sobre el compuesto **41Fa** se realizó una metátesis con el catalizador de Grubbs II, y tras una hidrólisis ácida, se obtuvo el compuesto derivado espirocíclico **47** con un 61% de rendimiento (Scheme 5, b).

Por último, se han desarrollado distintas *N* alquilaciones sobre el compuesto derivatizado **43** dando como resultado los compuestos *N* disustituídos **48** y **49** con muy buenos rendimientos. Además, se consiguió la arilación de este sustrato **43** obteniéndose el compuesto **50** con un 68% de rendimiento (Scheme 6).


DIPEA (1.3 equiv.), DMF
BnBr ó CH2=CHCH2Br (1.3 equiv.)
rt, on
48 R: PhCH2 71%
49 R: CH=CHCH2 63%
43
PhB(OH)2
Cu(OAc)2, Et3N
1,2-Dichloroethano, reflujo
on
50 68%

Scheme 6.

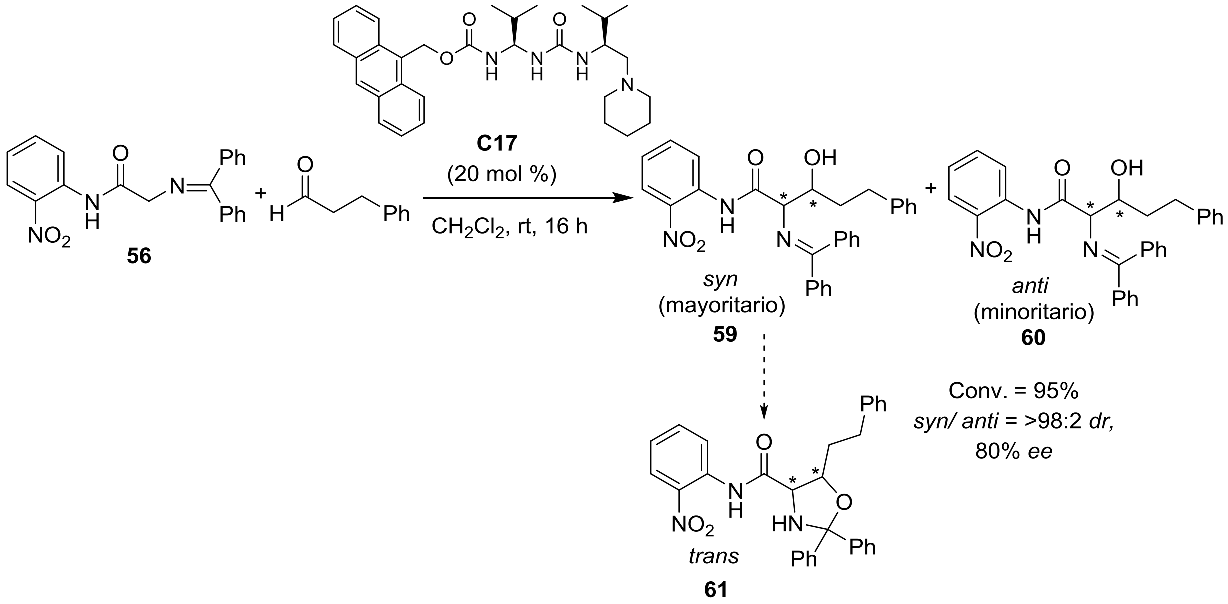
En la segunda parte de la tesis se pensó en la síntesis de un nucleófilo derivado de amida con elementos activantes para aumentar su reactividad en la posición *α*. Con estas propiedades, se sintetizó la acetamida **56** pensando que la formación de enlaces de hidrógeno intramoleculares podrían facilitar la reactividad del nucleófilo (Figure 2).


Incremento de acidez
NHR
≡
Activación por enlaces de hidrógeno

56

Figure 2. Estructura de la acetamida **14**.

La reacción aldólica de **56** con hidrocinamaldehído transcurrió de manera deseada con el catalizador **C17**, obteniéndose el correspondiente aducto *syn* (**60**) con un 95% de conversión, *dr* >98:2 y un 80% de *ee* (Scheme 7). Actualmente se está llevando a cabo el scope de esta reacción en el laboratorio.


C17
(20 mol %)
CH2Cl2, rt, 16 h
56
syn
(mayoritario)
59
anti
(minoritario)
60
trans
61
Conv. = 95%
syn/ anti = >98:2 dr,
80% ee

Scheme 7.

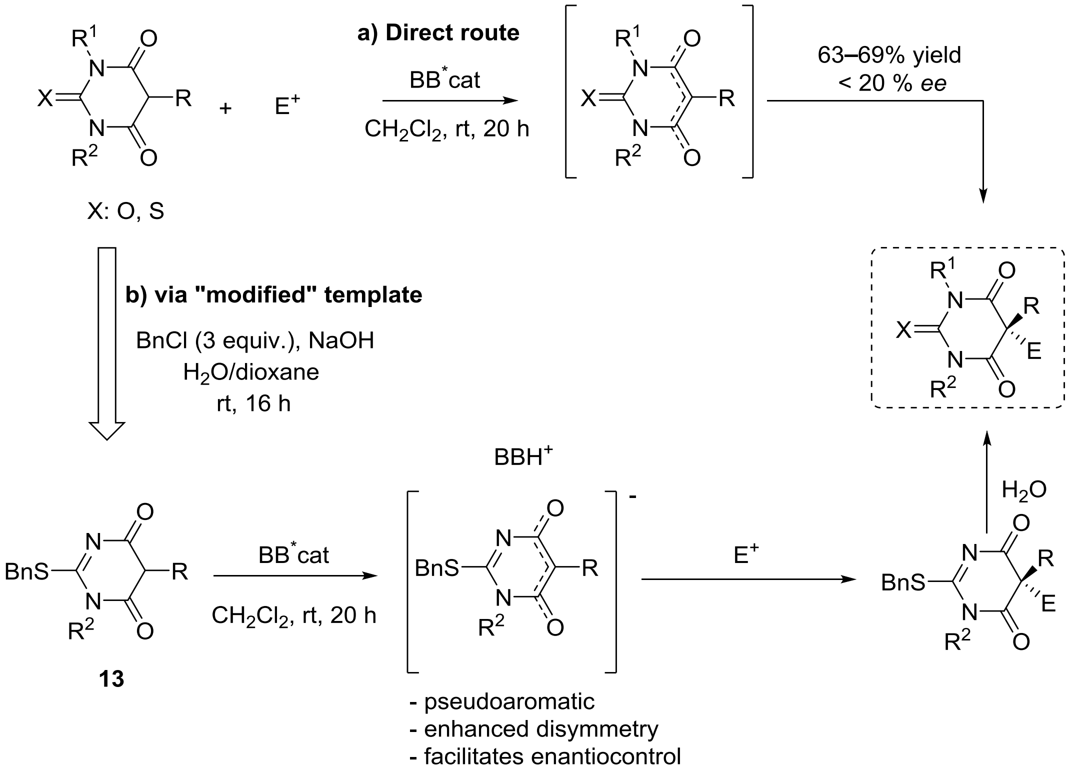
.

SUMMARY

The aim of this thesis has been the development of new organocatalytic methods for achieving the enantioselective *α*-functionalization of amides.

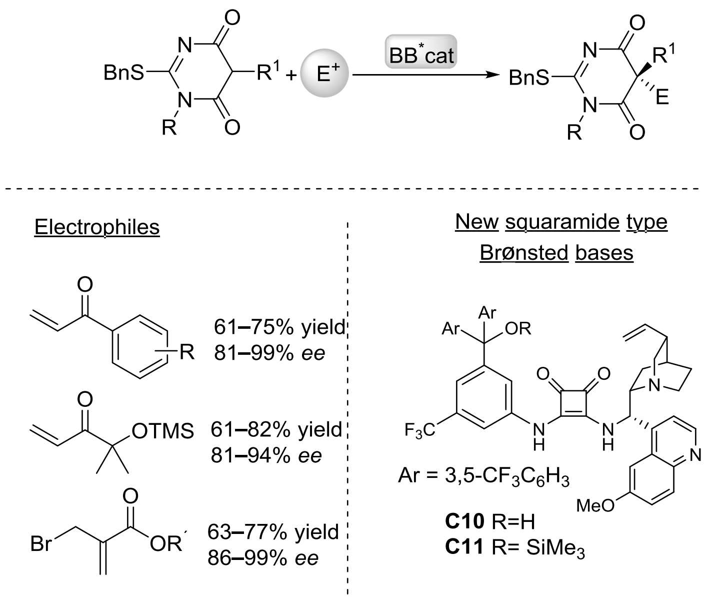
The study is focused on two types of amide subsets: barbituric acid derivatives and *α*-iminoamides. Both structures bear considerable practical interest, as they are the core structure of biologically relevant compounds.

On one hand, to achieve the desymmetrization of barbituric acids we propose two different approaches. First, a direct route using (thio)barbiturates as nucleophiles, aryl vinyl ketone as electrophile and a Brønsted base as catalyst in CH_2Cl_2 was raised. The adducts in this case, were obtained in good yields (between 63 and 69%), but basically as racemic compounds. Secondly, using the SBn derivatives **13** to break the symmetry of the initial barbituric acid, in this way, a 61–65% yield and 81–99% *ee* was obtained (Scheme 1).


R1
O
N
X
R
N
R2
O
+
E+
X: O, S
a) Direct route
BB*cat
CH2Cl2, rt, 20 h
63–69% yield
< 20 % ee
b) via "modified" template
BnCl (3 equiv.), NaOH
H2O/dioxane
rt, 16 h
BnS
13
BB*cat
CH2Cl2, rt, 20 h
BBH+
E+
H2O
E
- pseudoaromatic
- enhanced disymmetry
- facilitates enantiocontrol

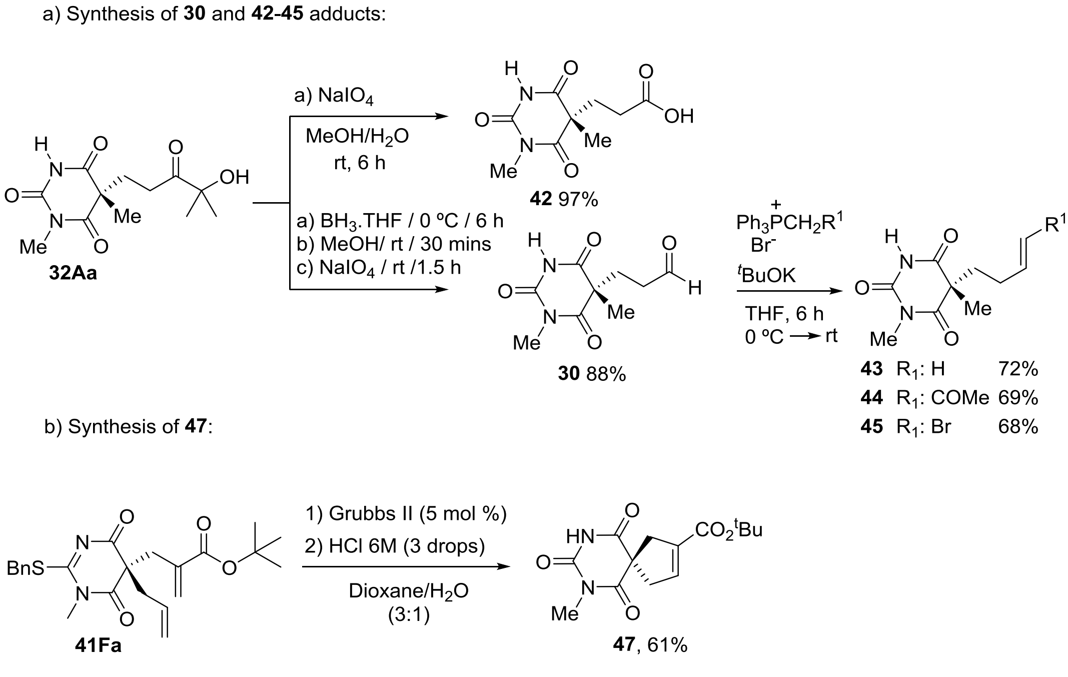
Scheme 1.

We chose different Brønsted bases and, at the same time, new ones were synthetized (**C10** and **C11**), in addition, several electrophiles were used for this purpose (Scheme 2), aryl vinyl ketones, oxy enones and Morita-Baylis-Hillmann type (*pseudo*)halogenides. In this way, a wide family of derivatives of barbituric acid was obtained with good yield and good enantiomeric excesses.


BB*cat
BnS
R
E+
R1
E
Electrophiles
New squaramide type Brønsted bases
61–75% yield
81–99% ee
OTMS
61–82% yield
81–94% ee
Br
OR´
63–77% yield
86–99% ee
Ar = 3,5-CF3C6H3
C10 R=H
C11 R= SiMe3
MeO

Scheme 2.

Furthermore, some selected transformations of adducts were tested to show the versatility of the approach. For example, aduct **32Aa** was transformed into the carboxylic acid **42** through oxidative treatment with $NaIO_4$. On the other hand, applying a reduction /1,2-diol cleavage sequence, aldehyde **30** was produced in 88% overall yield (Scheme 3, path a).


a) Synthesis of 30 and 42-45 adducts:
32Aa
a) NaIO4
MeOH/H2O
rt, 6 h
42 97%
a) BH3.THF / 0 ºC / 6 h
b) MeOH/ rt / 30 mins
c) NaIO4 / rt /1.5 h
30 88%
Ph3PCH2R1 Br-
tBuOK
THF, 6 h
0 ºC → rt
43 R1: H 72%
44 R1: COMe 69%
45 R1: Br 68%
b) Synthesis of 47:
41Fa
1) Grubbs II (5 mol %)
2) HCl 6M (3 drops)
Dioxane/H2O
(3:1)
47, 61%

Scheme 3.

Adduct **41Fa** was transformed into a spiranic compound through metathesis reaction with Grubbs 2^nd generation catalyst in good yield. Subsequent, acid hydrolysis afforded spiranic barbituric acid **47** in 61% (Scheme 3, path b).

On the other hand, a new *α*-iminoamide with preactivation elements have been designed. As shown in Figure 1, in this design it is expected that the intramolecular hydrogen bonds could facilitate the deprotonation of the amide *α*-carbon and rigidify the TS of the subsequent reactions.

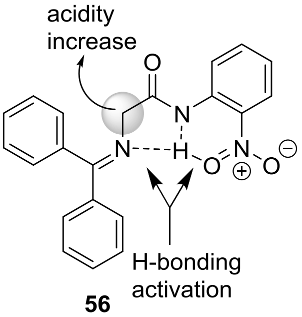
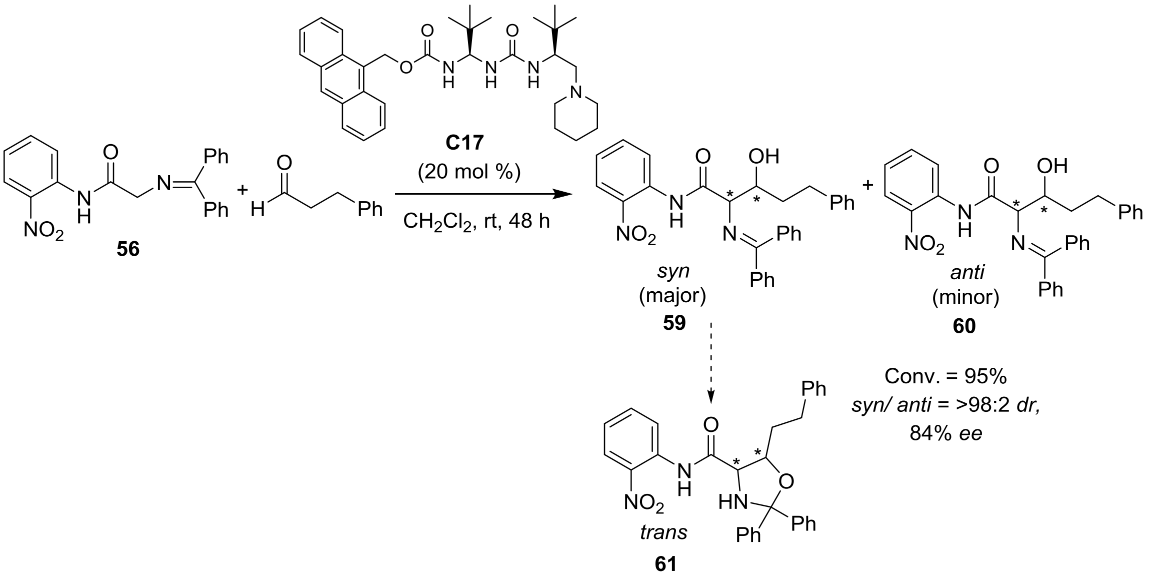

acidity
increase
O
N
N
H
O
N
O
H-bonding
activation
56

Figure 1.

With the newly designed iminoamide **56**, their aldol reaction has been studied using this new nucleophile design (Scheme 4), setting the base for further developments, and after optimization, we obtained, after 48 hours, 95% of conversion, > 98:2 *dr* ratio and 80% *ee* using an ureidopeptide type catalyst **C17** (Scheme 4). This work is currently being developed in the laboratory.


C17
(20 mol %)
CH$_2$Cl$_2$, rt, 48 h
NO$_2$
56
Ph
Ph
H
Ph
syn
(major)
59
anti
(minor)
60
OH
Conv. = 95%
syn/ anti = >98:2 dr,
84% ee
trans
61
HN
Ph
Ph

Scheme 4.

Abbreviations and acronyms

AA	Amino Acid
Ac	Acetyl
Aq.	Aqueous
Ar	Aryl
Å	Angstrom
BA	Benzoic Acid
BB*	Chiral Brønsted base
Bn	Benzyl
Boc	*Tert*-Butoxycarbonyl
^{i}Bu	Isobutyl
^{t}Bu	*Tert*-Butyl
Cat	Catalyst
Cbz	Benzyloxicarbonyl
CDI	1,1-Carbonyldiimidazol
*m*CPBA	*meta*-Chloroperbenzoic acid
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dicloroethane
DCM	Dichloromethane
$(DHQD)_2$PYR	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
$(DHQD)_2$PHAL	Hidroquinine 1,4-phthalazinediyl diether
DIBALH	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimetoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl Acetate

EWG	Electron-withdrawing group
h	Hour(s)
HOBT	1-hydroxybenzotriazole
HPLC	High-performance liquid chromatography
Im	Imidazole
L	Ligand
LA	Lewis Acid
LDA	Lithium diisopropylamide
LG	Leaving group
M	Metal
Me	Methyl
m. p.	Melting point
min	Minutes
MS	Mass spectrometry
M.S.	Molecular sieves
MTBE	Methyl *tert*-butyl ether
MVK	Methyl vinyl ketone
Naph	Naphthyl
n. d.	Not determined
n. r.	No reaction
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o.n.	Overnight
PG	Protecting group
Ph	Phenyl
^{n}Pr	*n*-Propyl
^{i}Pr	Isopropyl
pyr	Pyridine
quant	Quantitative
Rac	Racemic
Ref.	Reference
rt	Room temperature
t	Time
t_R	Retention time
T	Temperature
TEA	Triethylamine
Tf	Trifluoroacetate
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
UV	Ultraviolet

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CHAPTER 1

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1. **Introduction**

1.1. **Catalytic enantioselective synthesis**

Many important molecules required for life exist in two forms that are non-superimposable mirror images one another. The two forms are called enantiomers (from the Greek word for opposite) or optical isomers, because they rotate plane-polarised light either to the right or to the left. This tridimensional structure is very important when an exogenous molecule interacts with any bio-system, particularly, with the human body. Thus, a single-enantiomer drug can be pharmacologically interesting whereas its mirror image can be inactive or display a different desirable or non-desirable activity. One representative example about the different effect of the two enantiomers of a given molecule is Thalidomide (Figure 1). Since the tragedy of Thalidomide,[1] the demand of enantiomerically pure compounds (EPC)[2] has growth sharply in the pharmaceutical industry and also in other areas including agrochemicals, flavors, fragances and new materials.

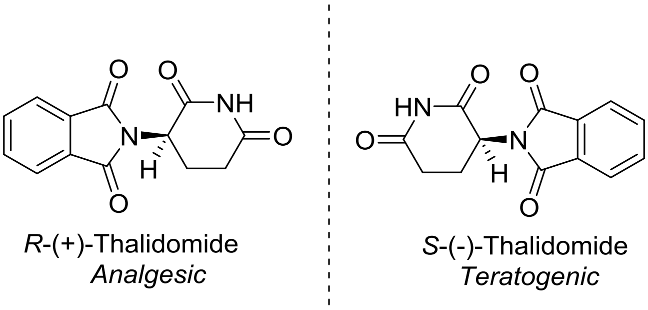


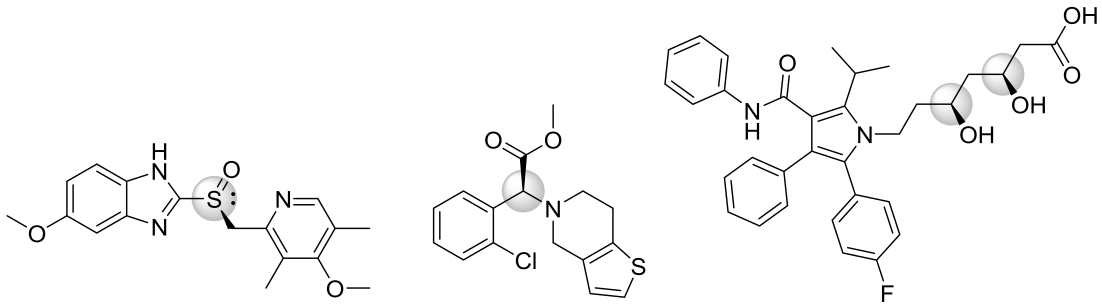
Figure 1. Both enantiomers of Thalidomide and their biological properties.

The administration of enantiopure drugs brings benefits in terms of improved efficacy, more predictable pharmacokinetics and reduced toxicity. These advantages forced pharmaceutical companies and health authorities to place stereochemically pure substances in a privileged position. Around 95% of the most-selling drugs worldwide are commercialized in enantiopure form. For example, this is the case of Nexium (esomeprazole), Lipitor (atorvastatin) and Plavix (clopidogrel) to mention some blockbuster drugs (Figure 2).

---

[1] Stephens, T.; Brynner, R. *Dark Remedy: The impact of thalidomide and its revival as a vital medicine,* **2001**, Perseus, Cambridge, MA.

[2] Seebach, D.; Hungerbühler, E. *Synthesis of enantiomerically pure compounds (EPC-Synthesis) in modern synthetic methods,* Scheffold, R., Ed., **1980**, p 94, Salle + Sauerländer, Frankfurt.


H
N
O
S
N
N
O
O
O
N
Cl
S
OH
O
O
N
H
N
OH
OH
F

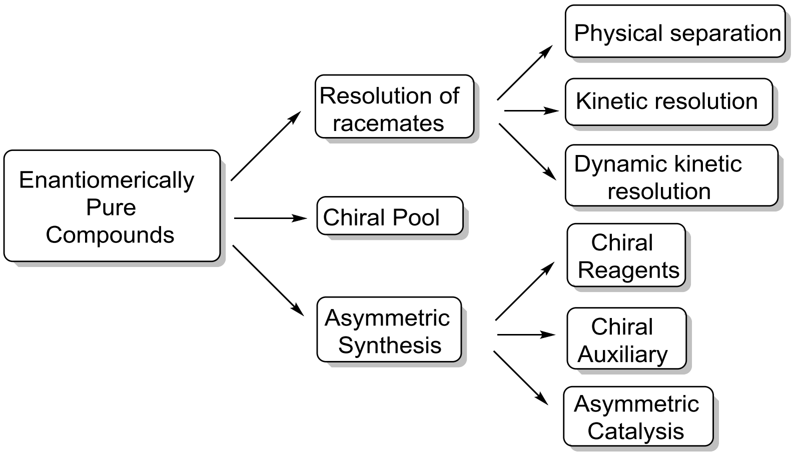
Nexium (esomeprazole) *Gastroesophageal reflux disease*

Plavix (clopidogrel) *Heart disease*

Lipitor (atorvastatin) *Lipid-lowering agent*

Figure 2. Commercial enantiopure drugs.

The great demand of enantiopure compounds incentivized the development of asymmetric synthesis. Traditionally, enantiomerically pure compounds were isolated from natural sources. However, this approach depends on natural products availability, which is limited. Owing to the importance of the chiral molecules in life, synthetic chemists have made great efforts in developing protocols to obtain enantiomerically enriched compounds. In general, there are three strategies for this purpose (Scheme 1): (i) resolution of mixtures of enantiomers,[3] (ii) the "chiral pool" approach,[4] and (iii) asymmetric synthesis.


Enantiomerically Pure Compounds
Resolution of racemates
Chiral Pool
Asymmetric Synthesis
Physical separation
Kinetic resolution
Dynamic kinetic resolution
Chiral Reagents
Chiral Auxiliary
Asymmetric Catalysis

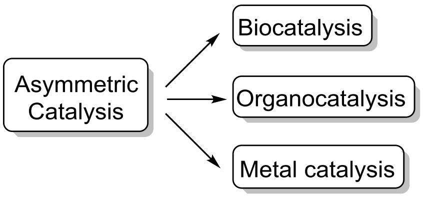
Scheme 1. Strategies for the synthesis of Enantiomerically Pure Compounds (EPC).

---

[3] For general reviews on resolution methods, see: a) Synoradzki, L.; Bernás, U.; Ruśkowski, P. *Org. Prep Proced. Inc.* **2008**, *40*, 163–200. b) Anderson, N. G. *Org. Proc. Res. Dep*. **2005**, *9*, 800–813. For general reviews on kinetic dynamic resolution, see: a) Pellissier, H. *Chirality from Dynamic Kinetic Resolution*, **2011**, RSC, Cambridge. b) Matute, B. M. *An. Quim*. **2006**, *102*, 46–52.

[4] For general reviews on "chiral pool" methods, see: a) Nicolau, K. C.; Snyder, S. A. *Classics in Total Synthesis II*, **2003**, Wiley.-VCH. b) Nicolau, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, **1996**, Wiley-VCH. c) Hanessian, S. P. *Appl. Chem*. **1993**, *65*, 1189–1204. Hanessian, S.; Giroux, S.; Merner, B. L. "*Design and Strategies in Organic Chemistry"*, **2013**, Wiley-VCH.

In asymmetric synthesis, an achiral substance is transformed into a chiral one with concomitant generation of new chemical bonds stereoselectively. The asymmetric induction during the new bond forming process can come from a chiral reagent,[5] a chiral auxiliary,[6] or a chiral catalyst.[7] While the utilization of chiral reagents and chiral auxiliaries require the use of stoichiometric amounts of the inductor, asymmetric catalysis is based on the use of substoichiometric quantities of a chiral enantiopure substance that accelerates the reaction and controls the stereochemistry of the reaction.



Scheme 2. The three pillars of asymmetric catalysis.

In the field of asymmetric catalysis, three different groups can be distinguished: biocatalysis, metal catalysis and organocatalysis (Scheme 2).[8]

The present work is centered on organocatalytic methods. Organocatalysis is defined as the acceleration of chemical reactions by small organic molecules in the absence of metals and among its features are:

---

[5] For more information about chiral ligands, see: a) *Privileged Chiral Ligands and Catalyst*, Ed. Zhou, Q.L. **2011**, Wiley-VCH, Weinheim. b) Schütz, T. *Synlett*, **2003**, *6*, 901–902.

[6] For more information about chiral auxiliaries, see: a) Roos, G. *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York. b) Glorious, F.; Gnass, Y. *Synthesis*, **2006**, *12*, 1899–1930. c) Roos, G. *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York.

[7] For general references on asymmetric catalysis, see: a) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*, **2007**, Wiley-VCH, Weihhelm. b) Trost, B. M. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5348–5255. c) *Comprehensive Asymmetric Catalysis I-III*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds. Springer-Verlag Berlin Heidelberg, **1999**.

[8] For general reviews on biocatalysis, see: a) De Gonzalo, G.; Lavandera, I.; Gotor, V. *Catalytic Methods in Asymmetric Synthesis. Advanced Material, Techniques, and Applications*, Ed. M. Gruttadauria, F. Giacalone, John Wiley and Sons, **2011**, 391–527. b) Zagrebelny, N. *Russ. Chem. Rev.* **2005**, *74*, 285–296. c) Reetz, M. T.; Brunner, B.; Schnerider, F.; Schulz, C. M.; Clouthier, M. M.; Kayser, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4075–4078. For general reviews on organometallic catalysis, see: a) Leenders, S. H. A. M.; Gramage-Doria, R.; de Bruin, B.; Reek, J. N. H. *Chem. Soc. Rev.* **2015**, *44*, 433–448. b) Steinborn, D. *Fundamentals of Organometallic catalysis*, **2011**, Wiley-VCH, Germany. c) Astruc, D. *Organometallic Chemistry and Catalysis*, **2007**, Springer-Verlag Berlin Heidelberg. Ref. 7c.

- Organocatalysts usually are non-sensitive to the humidity and the atmospheric oxygen, easy to handle without the need of dry boxes, inert atmospheres or anhydrous solvents.
- Many organocatalysts are directly available from nature in both enantiomeric series, or can be obtained through straight chemical manipulations.
- The organocatalysts are low or non-toxic, respectful with the environment and can be easily isolated from the reaction mixtures avoiding the contamination of the final product.

1.2. **Brønsted base catalysis**

The field of organocatalysis has developed so considerably in a relatively short period of time owing to the identification of a few generic mechanism of substrate activation and stereochemical induction which provided effective tools for reaction invention. Organic catalysts can exert their functions by following two different substrate activation patterns: covalent and non-covalent based modes of activation.[9]

Catalysis by covalent activation is based on the ability of some organic catalysts to bind the substrate covalently in a reversible manner to yield a reactive intermediate that can participate in a subsequent *C*-*C* or *C*-X bond forming reaction enantioselectively. Chiral primary and secondary amines belong to this class, and have the ability to activate carbonyl substrates *via* the formation of nucleophilic enamines from enolizable aldehydes and ketones (Scheme 3a),[10] electrophilic iminium ions from unsaturated carbonyl compounds (Scheme 3b),[11] and α-iminylradical cation intermediates in SOMO catalysis with the assistance of a (photo)chemical oxidant (Scheme 3c).[12] Heterocyclic carbene catalysts offer an alternative activation mechanism for aldehydes, conferring an inverted reactivity

---

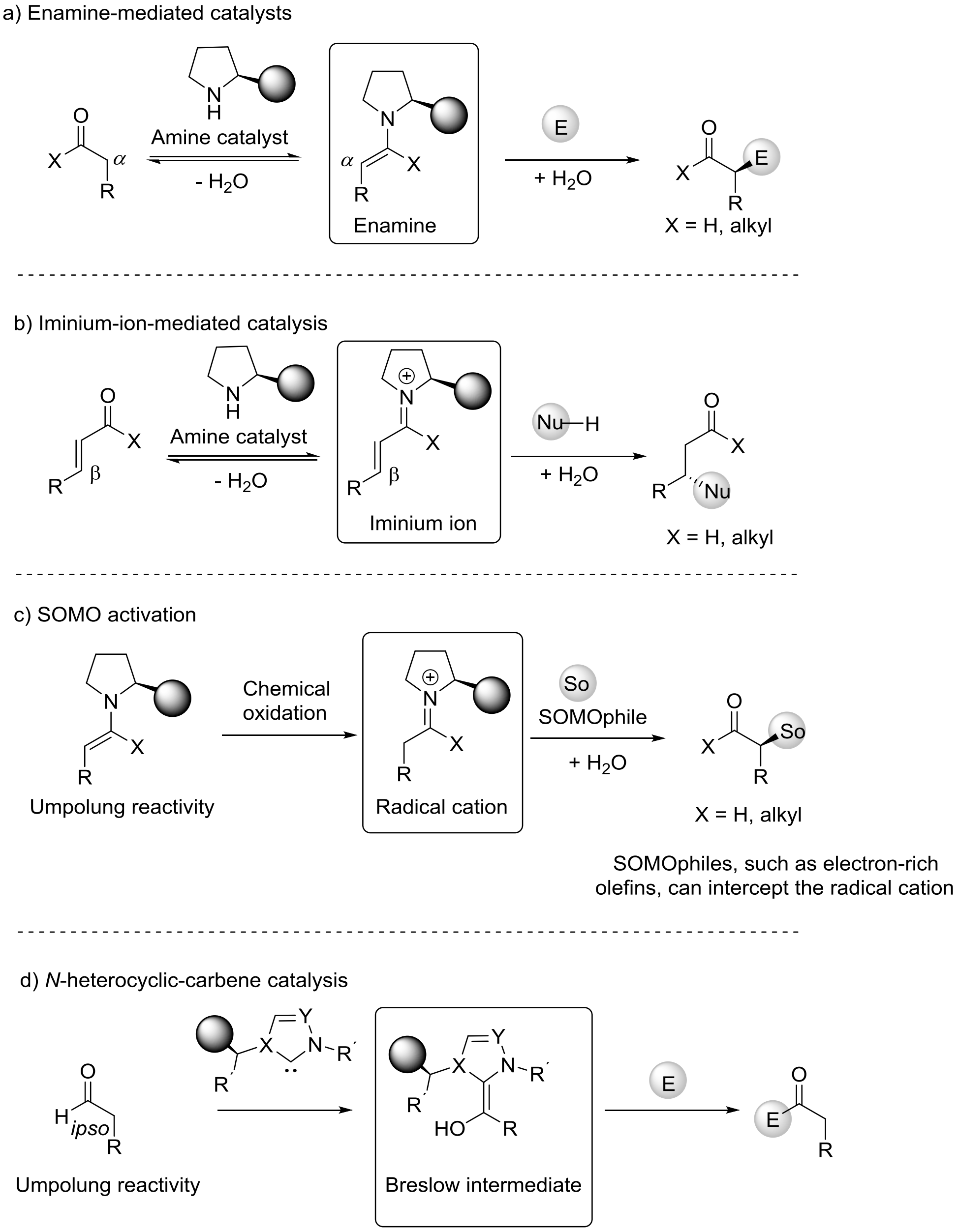
[9] For a classification of generic mechanisms of organocatalytic reactivity: Silvi, M.; Melchiorre, P. *Nature*, **2018**, *554*, 41–49.

[10] For general reviews on enamine-mediated catalysis: a) Fu, N.; Zhang, L.; Luo, S. *Org. Biomol. Chem.* **2018**, *16*, 510–520. b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Ed. Springer, New York **2007**, vol. B, 46–55. c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

[11] For general reviews on iminium-ion-mediated catalysis: a) Liu, Y.; Melchiorre, P. *Science of Synthesis, 1: Asymmetric Organocatalysis*, **2012**, *1*, 403–38. b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. b) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79–87.

[12] For general reviews on SOMO catalysis: a) McMillan, D. W. C.; Rendler, S. *Asymmetric Synthesis II*, **2012**, 87–94. b) MacMilan, D. W. C.; Beeson, T. D. *Science of Synthesis, Asymmetric Organocatalysis*, **2012**, *1*, 271–307. c) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science*, **2007**, *316*, 582–585.

(umpolung) to the normally electrophilic carbonyl carbon atom upon formation of Breslow intermediates (Scheme 3d),[13] which acts as an acyl anion equivalent.


a) Enamine-mediated catalysts
Amine catalyst
- H2O
Enamine
E
+ H2O
X = H, alkyl
b) Iminium-ion-mediated catalysis
Amine catalyst
- H2O
Iminium ion
Nu—H
+ H2O
X = H, alkyl
c) SOMO activation
Umpolung reactivity
Chemical oxidation
Radical cation
So
SOMOphile
+ H2O
X = H, alkyl
SOMOphiles, such as electron-rich olefins, can intercept the radical cation
d) N-heterocyclic-carbene catalysis
ipso
Umpolung reactivity
Breslow intermediate
E

Scheme 3. Covalent-based mechanisms.

---

[13] For general reviews on *N*-heterocyclic-carbene catalysis: a) Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040–5052. b) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Rev.* **2008**, *37*, 2691–2698. c) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.***2007**, *107*, 5606–5655.

Non-covalent catalysis approaches are based on, usually many cooperative, weak attractive interactions between the catalysts and the substrate.[14] Although the catalyst-substrate interactions are generally weaker and less directional than their covalent counterparts, non-covalent interactions operate in concert to ensure a high level of transition state organization, ultimately resulting in efficient activation and a high degree of enantioselectivity. Hydrogen-bonding activation (Scheme 4a),[15] phase-transfer catalysis (Scheme 4b),[16] anion binding activation (Scheme 4c),[17] Brønsted acid catalysis (Scheme 4d),[18] and Brønsted base catalysis (Scheme 4e) [19] are all useful organocatalytic strategies for making chiral molecules.

---

[14] For general reviews on non-covalent catalysis: a) Quitavalla, A.; Cerisoli, L.; Elisa, M. *Current Organocatalysis*, **2014**, *1*, 107–171. b) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 20678–20685.

[15] For general reviews on hydrogen-bonding catalysis: a) Nishikawa, Y. *Tetrahedron Lett.* **2018**, *59*, 216–223. b) Doyle, A.; Jacobsen, E. N. *Chem. Rev*. **2007**, *107*, 5713–5743. c) Schreiner, P. R.; *Chem. Soc. Rev.* **2003**, *32*, 289–296. d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.

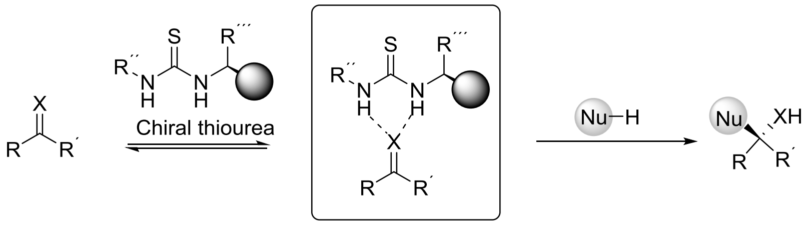
[16] For general reviews on phase transfer catalysis: a) Tan, J.; Yasuda, N. *Org. Process Res. Dev.* **2015**, *19*, 1731–1746. b) Maruoka, K.; Takashi, O. *Chem. Rev.* **2003**, *103*, 3013–3028. c) Takashi, O.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *23*, 4222–4266. d) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. e) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.

[17] For general reviews on anion-binding catalysis: a) Visco, M. D.; Attard, J.; Guan, Y.; Mattson, A. E. *Tetraedron Lett.* **2017**, *58*, 2623–2628. b) Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52,* 534–561.

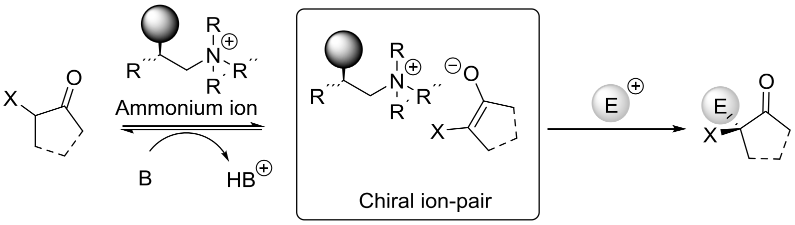
[18] For general reviews on Brønsted acid catalysis: a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev*. **2014**, *114*, 9047–9153. b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568

[19] For general reviews on Brønsted base catalysis: a) Teng, B. Lim, W. C.; Tan, C. H. *Synlett*, **2017**, *28*, 1272–1277. b) Palomo, C.; M. Oiarbide, M.; Lopez, R. *Chem. Soc. Rev.* **2009**, *38*, 632. c) Ojima, I. *Catalytic Asymmetric Synthesis*, Ed. John Wiley and Sons, New York, **2010**. d) A. Ting, Gross, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem***. 2010**, *291*, 145–200. e) Maruoka, K. *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*; Ed. Thieme, Stuttgart, **2012**.

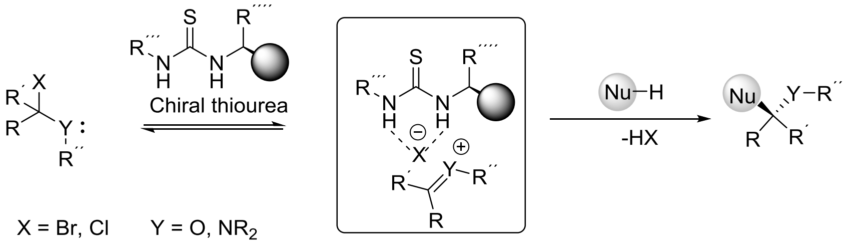
a) Hydrogen-bonding catalysis


Chiral thiourea
Nu–H

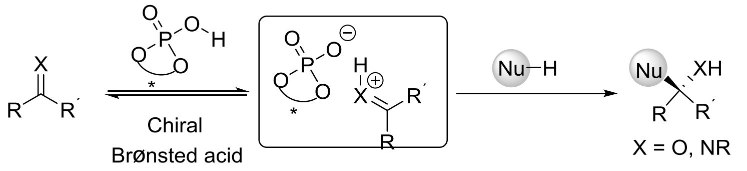
b) Phase transfer catalysis


Ammonium ion
B
HB
Chiral ion-pair

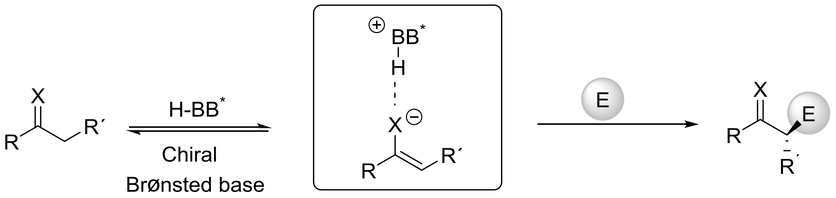
c) Anion-binding catalysis


Chiral thiourea
Nu–H
-HX
X = Br, Cl
Y = O, NR$_2$

d) Brønsted acid catalysis


Chiral
Brønsted acid
Nu–H
X = O, NR

e) Brønsted base catalysis


H-BB*
Chiral
Brønsted base

Scheme 4. Non covalent-activation mechanisms.

According to the IUPAC, a Brønsted base (BB) can be defined as a molecular entity capable of accepting a hydron (or proton) from an acid or the corresponding chemical species. Figure 3 shows a simplified catalytic cycle followed in these reactions. The catalytic cycle is initiated *via* deprotonation of the pro-nucleophile by the basic catalyst, forming a chiral ionic pair. The anionic species reacts with the corresponding electrophile in an enantioselective way to provide a Nu-E adduct as the ultimate reaction product and liberation of free base catalyst.

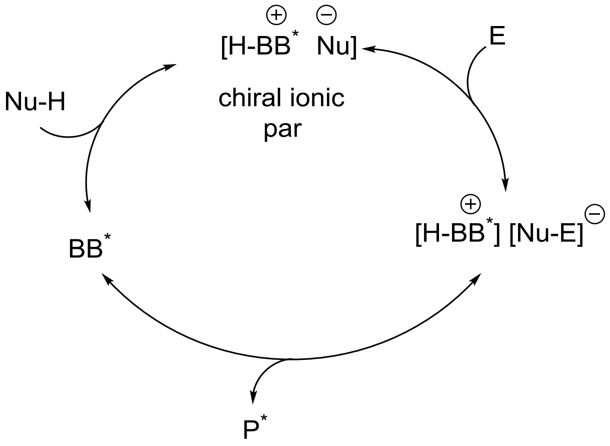
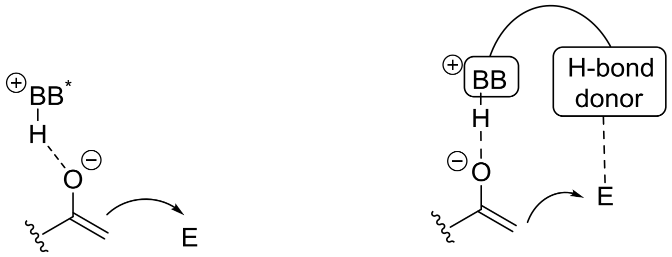


Figure 3. Catalytic cycle promoted by Brønsted bases.

From the perspective of the organic transformations, proton transfer is often considered a key activation step that precedes the new bond formation. Chirality transfer during the new bond forming process occurs in a chiral ion-pair systems. The intrinsic nondirectional nature of electrostatic interactions in these ion-pair complexes makes difficult to predict the sense of the stereoinduction exerted from the catalyst. Catalysts that combine a site acting as a base and another site with hydrogen-bond donor ability, namely bifunctional Brønsted base/H-bond donor catalysts,[20] can anchor both nucleophilic and electrophilic components in the transition state. As a result, more active catalysts are obtained, and a higher degree of stereochemical order is achieved in the transition state (Figure 4).

---

[20] For further information on the concept of bifunctional organocatalysts see: L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, *23*, 490–508.



Brønsted base catalyst

Bifunctional Brønsted base/H-bond donor catalyst

Figure 4.

Various nitrogen-containing functionalities have been used for the design of chiral BB catalysts. Among them, tertiary amines, guanidines,[21] amidines, and imidazoles are the most prominent (Figure 5a). Stronger bases, such as phosphazines have also been developed recently in an attempt to gather less acidic substrates.[22] In this context, alkaloids, particularly those of the cinchona family, are a source of enantiopure BB catalyst candidates providing access to various BBs which display reasonable constitutional and stereochemical diversity (Figure 5b).[23] Another type of BB catalysts are derived from α-amino acids, which are cheap starting materials. Other non-natural sources, such as synthetic 1,2-diamines and binaphthols, have also been employed as enantiopure materials precursor for the designed Brønsted base catalyst. Figure 5c displays three representative examples of chiral Brønsted base catalysts.

---

[21] For general reviews on guanidines in asymmetric synthesis, see: a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752. b) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553–557.

[22] Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

[23] For general reviews on cinchona alkaloids in asymmetric organocatalysis see: a) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504. b) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229–1279. c) Yeboah, E.M.O.; Yeboah, S. O.; Singh, G. S.; *Tetrahedron.* **2011**, 1725–1762. d) Bryant, L.A.; Fanelli, R.; Cobb, A. *Beilstein J. Org. Chem.* **2016**, *12*, 429–443.

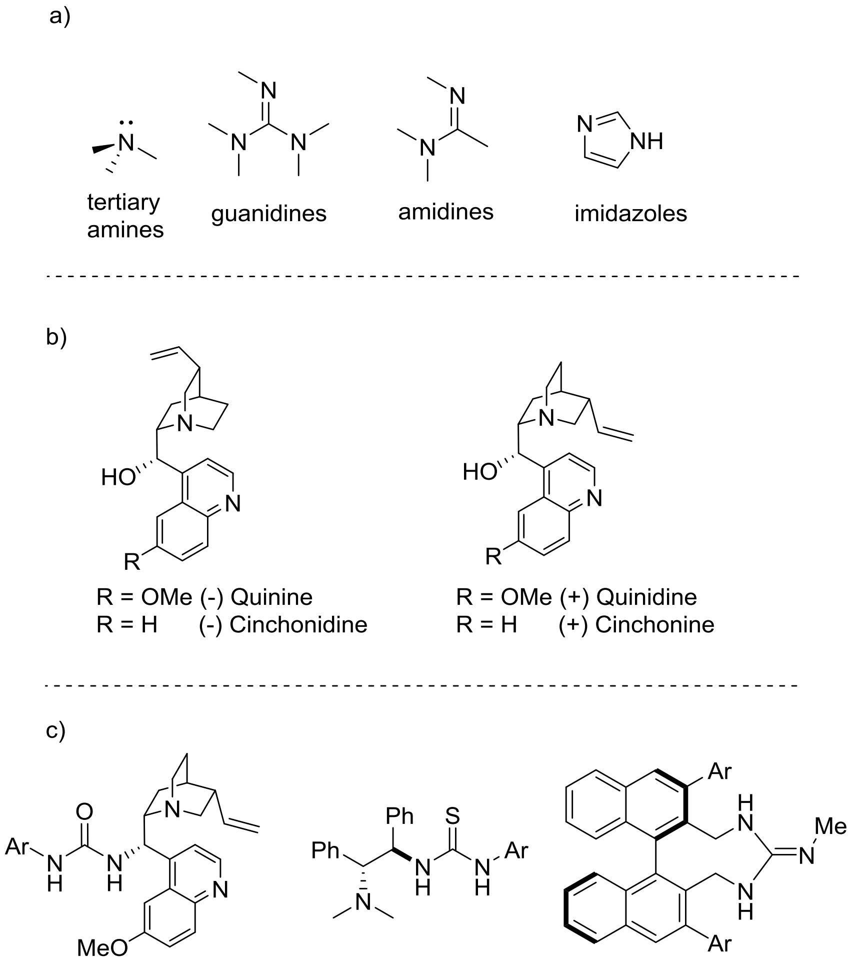
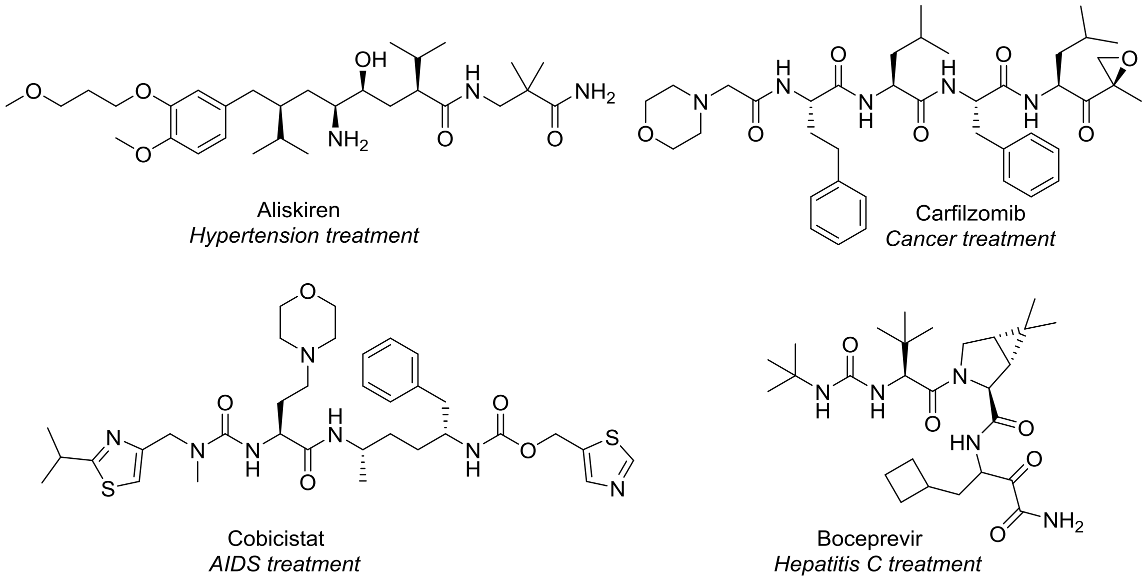

a)
N
tertiary amines
N
N N
guanidines
N
N
amidines
N
NH
imidazoles
b)
N
HO
N
R
R = OMe (-) Quinine
R = H (-) Cinchonidine
N
HO
N
R
R = OMe (+) Quinidine
R = H (+) Cinchonine
c)
O
Ar
N
H
N
H
N
N
MeO
Ph
S
Ph
N
H
N
H
Ar
N
Ar
H
N
Me
N
N
H
Ar

Figure 5. a) Chiral BB catalysts. b) Alkaloids from cinchona family. c) Some representative chiral Brønsted base catalysts.

1.3. **Amides as enolizable reagents in asymmetric catalysis**

The amide linkage is key in the structure of proteins, peptides, polymers and other biologically important molecules. Amide bonds are also present in a huge collection of molecules, including drugs.[24] For instance, amides are present in around 25% of top-selling pharmaceuticals and in many other medically important compounds (Figure 6).[25]


Aliskiren
Hypertension treatment

Carfilzomib
Cancer treatment

Cobicistat
AIDS treatment

Boceprevir
Hepatitis C treatment

Figure 6. Different drugs with amide bond.

Despite the huge importance of amides in organic chemistry, well-established methods for their asymmetric synthesis are relatively scarce.

1.3.1. **Chemical modifications of amides**

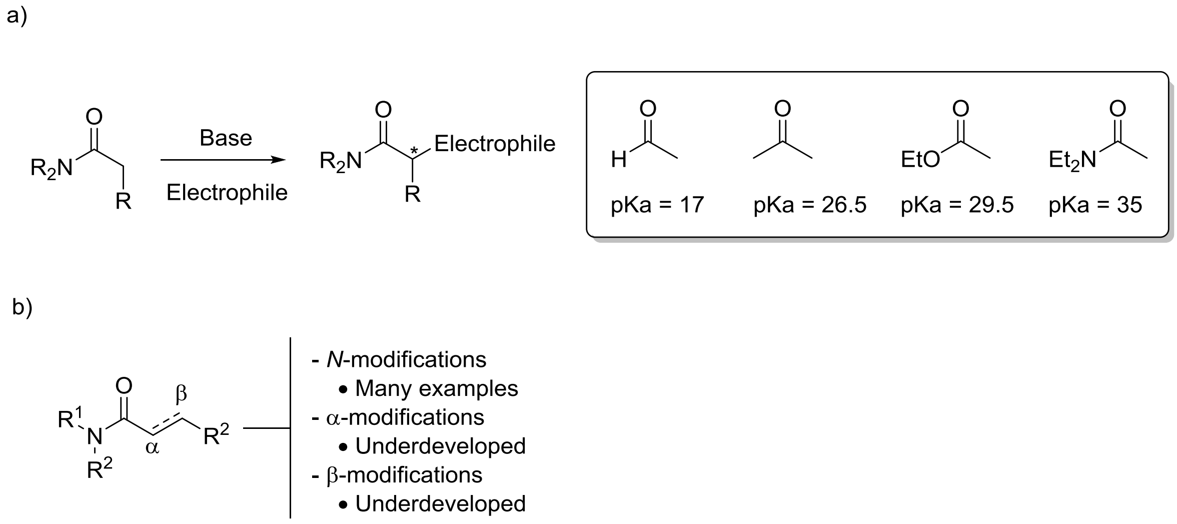
Carbonyl compounds can serve as nucleophiles through enolate formation or as electrophiles if they are conjugated with multiple bonds (Scheme 5). In general, the capacity to generate the corresponding enolate by proton abstraction depends on the type of carbonyl functional group (Scheme 5a). Thus, the carbon acidity of amides (pK_a in DMSO $\approx$ 35) and esters (pK_a in DMSO $\approx$ 31) are much lower than those of aldehydes or ketones (pK_a in DMSO $\approx$ 27).[26] This is the reason why the *C-C* bond formation in α-position of carbonyl compounds is mostly developed for aldehydes and ketones in sharp contrast to esters and amides. In addition, whereas aldehydes and ketones are suitable for enamine catalysis, esters and amides are not.

---

[24] Roughley, D. S.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479.

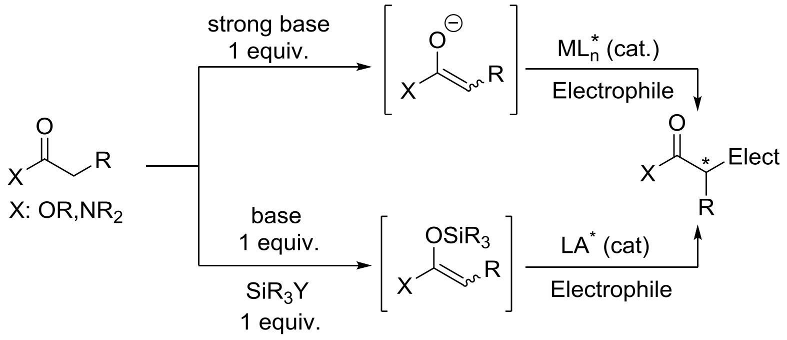
[25] Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55–68.

[26] Based on the Bordwell pK_a table (see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm).


a)
Base
Electrophile
Electrophile
pKa = 17
pKa = 26.5
pKa = 29.5
pKa = 35
b)
- N-modifications
• Many examples
- α-modifications
• Underdeveloped
- β-modifications
• Underdeveloped

Scheme 5. Reactivity of amide group.

The most popular method for *C-C* bond formations using amides or esters as nucleophiles involves irreversible generation of metal enolates using stoichiometric amounts of strong bases such as lithium diisopropylamide (LDA), potassium hexamethyldisilazide (KHMDS) or alternatively isolable silyl enolates generated from stoichiometric amounts of silicon reagents and bases (Scheme 6).[27]


X: OR,NR2
strong base
1 equiv.
base
1 equiv.
SiR3Y
1 equiv.
MLn* (cat.)
Electrophile
LA* (cat)
Electrophile
Elect

Scheme 6. Conventional methods for catalyst-controlled nucleophilic reactions of simple amides and esters.

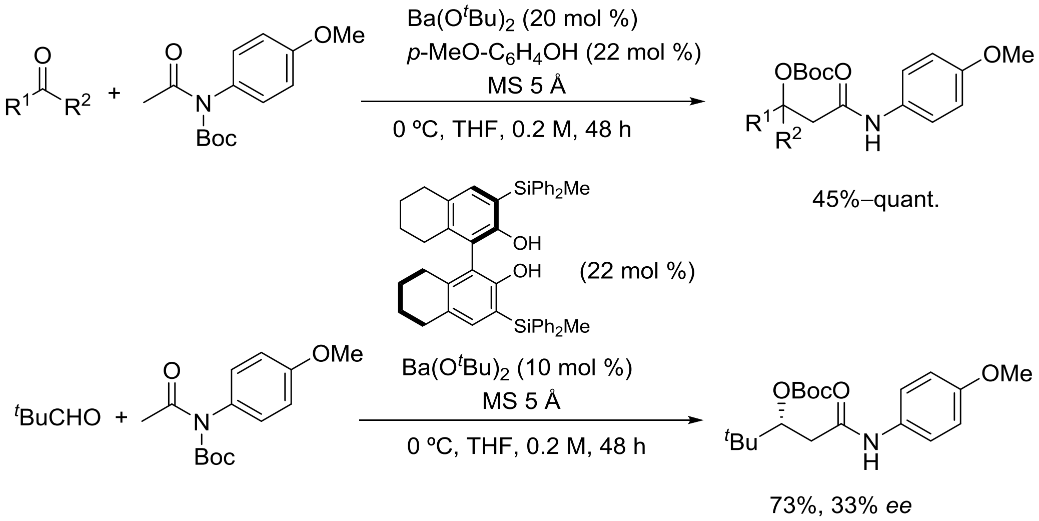
---

[27] For general examples of C-C bond formation using amides, see: a) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132–157. b) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 2060–2061. c) Yamamoto, Y.; Suzuki, H.; Yasuda, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **2008**, *49*, 4582.

1.3.2. **Enantioselective *α*-functionalization of amides**

The most widespread method for the *C-C* bond formation in *α* position to an amide group is still the use of stoichiometric amounts of metal enolates with strong bases, the use of isolable silicon enolates with stoichiometric amounts of silicon reagents and bases (Mukaiyama-type reactions) or the use of modified amides. [28] The main problem to design an efficient method for the generation of enolates from amides is that strong bases (e.g. lithium diisopropylamide or alkyl lithium) are generally required. Thus, implementation of catalytic variants of these procedures is precluded by the difficulties in catalyst turnover. In spite of these reasons, some catalytic methods for the enolate mediated *Cα* functionalization of amides have been described.

In 2006, Kobayashi and co-workers described a highly *anti*-selective aldol reaction of amides and aldehydes using catalytic amounts of barium phenoxide under mild conditions (at 0 °C for 24–48 h in most of cases). However, implementation of the asymmetric version has remained challenging (Scheme 7).[29]



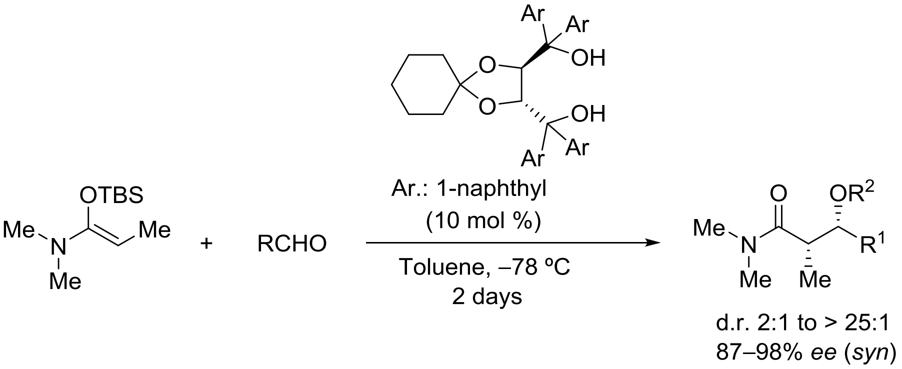
Scheme 7. Aldol reaction of amides with aldehydes.

---

[28] For more details, see: a) Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2016**, *22*, 15192–15200. b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236. c) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartoli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127. d) Oare, D.; Henderson, M. A.; Sanner, M. A.; Heathcock, H. *J. Org. Chem.* **1990**, *55*, 132–137.

[29] c

In the same year, Rawal and co-workers reported the first example of a metal-free Mukaiyama type aldol reaction of an amide derivative with high diastereo and enantioselectivities. They used as catalyst tetraaryl-1,3-dioxolane-4,5-dimethanol (taddol) (Scheme 8).[30] X-ray crystal structure elucidation of a catalyst-aldehyde complex revealed the presence of an intramolecular hydrogen bond between the two hydroxy groups of the catalyst and an intermolecular hydrogen bond to the carbonyl oxygen atom of *p*-anisaldehyde. This complex was consistent with the suggested mode of activation of the carbonyl group through a single-point hydrogen bond to a preorganized catalyst. This mode of activation represents a form of Lewis acid assisted Lewis acid catalysis.



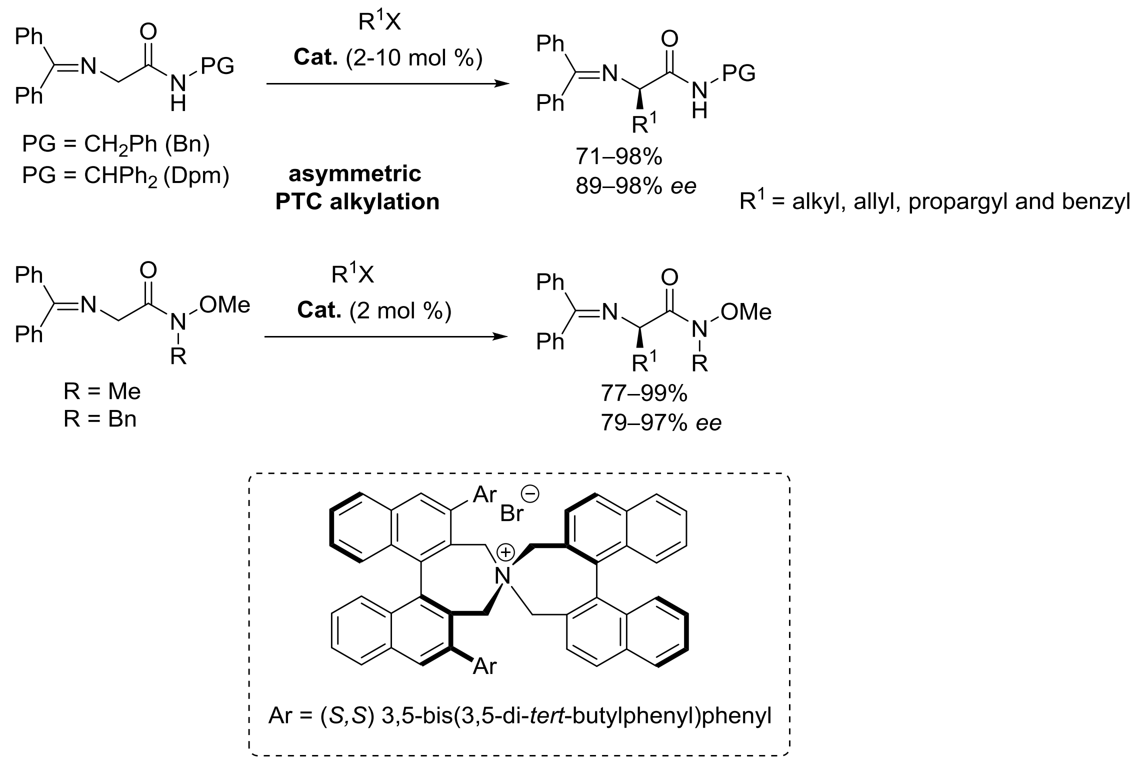
Scheme 8. Enantioselective Mukaiyama aldol reaction of silicon enolates of amides catalysed by a taddol derivative.

About the same time Maruoka and co-workers described a highly enantioselective alkylation of protected glycine amides under phase transfer conditions based on a designer chiral quaternary ammonium salt. They achieved the desired α-alkylated amide products with high efficiency and enantioselectivity (Scheme 9). [31]

---

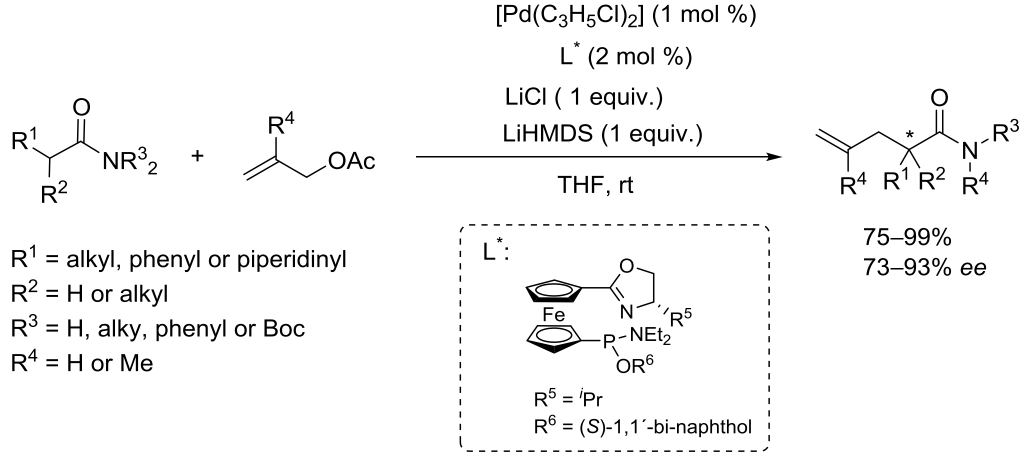
[30] McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130–6133.

[31] Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073–5083.


Ph
Ph
O
N
N
PG
H
R1X
Cat. (2-10 mol %)
PG = CH2Ph (Bn)
PG = CHPh2 (Dpm)
asymmetric
PTC alkylation
R1
71–98%
89–98% ee
R1 = alkyl, allyl, propargyl and benzyl
OMe
R
Cat. (2 mol %)
R = Me
R = Bn
77–99%
79–97% ee
Ar
Br
Ar = (S,S) 3,5-bis(3,5-di-tert-butylphenyl)phenyl

Scheme 9. Phase transfer catalyzed asymmetric alkylation of protected glycine amide.

In 2008, Wu and co-workers reported the first highly enantioselective palladium catalyzed alkylation of amides using 1 equiv. of LiCl and 1 equiv. of strong base in the presence of 1,1-P,N ferrocene ligands. In this way, they achieved the corresponding *γ*, *δ*-unsaturated amides with very high enantioselectivities (Scheme 10).[32]

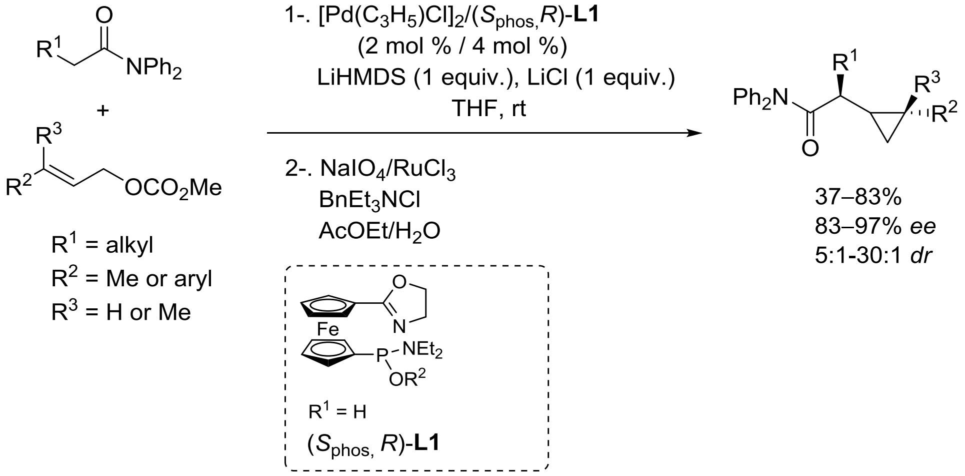

[Pd(C3H5Cl)2] (1 mol %)
L* (2 mol %)
LiCl (1 equiv.)
LiHMDS (1 equiv.)
THF, rt
R1
O
NR32
R2
+
R4
OAc
R1 = alkyl, phenyl or piperidinyl
R2 = H or alkyl
R3 = H, alky, phenyl or Boc
R4 = H or Me
L*:
Fe
O
N
R5
P
NEt2
OR6
R5 = iPr
R6 = (S)-1,1´-bi-naphthol
*
N
R3
R4 R1 R2 R4
75–99%
73–93% ee

Scheme 10. Pd-catalyzed AAA of acyclic amides.

---

[32] Zhang, K.; Peng, Q.; Hou, X. L.; Wu, Y. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 1741–1744.

One year later, the Pd-catalyzed asymmetric cyclopropanation reaction of acyclic amides with monosubstituted allylic reagents was reported by the Hou group. In this reaction cyclopropane derivatives with two chiral centers are obtained with high diastereo- and enantioselectivities (Scheme 11).[33]


R1
NPh2
O
+
R3
R2
OCO2Me
R1 = alkyl
R2 = Me or aryl
R3 = H or Me
1-. [Pd(C3H5)Cl]2/(Sphos,R)-L1
(2 mol % / 4 mol %)
LiHMDS (1 equiv.), LiCl (1 equiv.)
THF, rt
2-. NaIO4/RuCl3
BnEt3NCl
AcOEt/H2O
O
N
Fe
P
NEt2
OR2
R1 = H
(Sphos, R)-L1
Ph2N
R1
R3
R2
O
37–83%
83–97% ee
5:1-30:1 dr

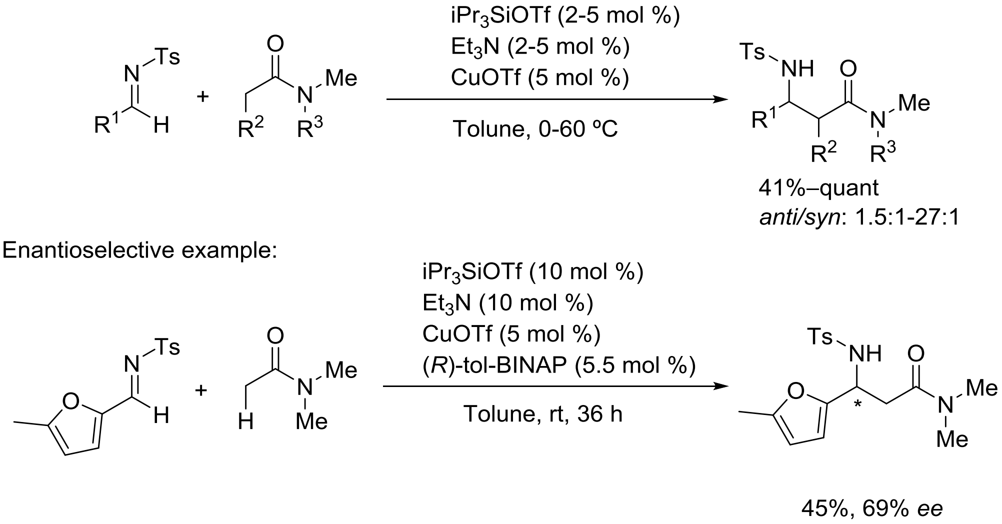
Scheme 11. Cyclopropanation of amides with substituted allyl carbonates.

Kobayashi´s group achieved the activation of simple alkyl amides through silicon-mediated catalysis in 2011 by using catalytic amounts of ^{i}Pr3SiOTf/Et3N for a direct Mannich-type reaction with *N*-Ts imines, leading to high yields and high *anti*/*syn* selectivities. Unfortunately, once again, it appears that development of an enantioselective variation is difficult as they described a single asymmetric entry using Cu^{I}/(*R*)-tol-BINAP affording a 69% *ee* (Scheme 12).[34]

---

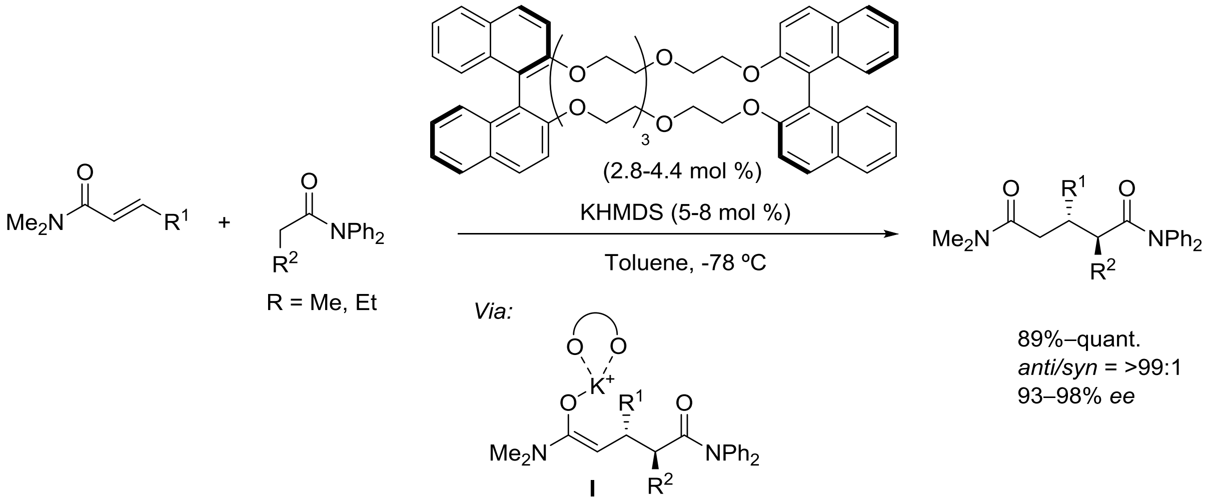
[33] Liu, W.; Chen, D.; Zhu, X. Z.; Wan, X. L.; Hou, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 8734–8735.

[34] Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708–711.


iPr3SiOTf (2-5 mol %)
Et3N (2-5 mol %)
CuOTf (5 mol %)
Tolune, 0-60 ºC
41%–quant
anti/syn: 1.5:1-27:1
Enantioselective example:
iPr3SiOTf (10 mol %)
Et3N (10 mol %)
CuOTf (5 mol %)
(R)-tol-BINAP (5.5 mol %)
Tolune, rt, 36 h
45%, 69% ee

Scheme 12. Catalytic direct-type addition of amides to imines promoted by $^{i}Pr_3SiOtf/Et_3N$ catalytic system, and its enantioselective variant using Cu^{I}/(*R*)-tol-binap.

Few years later, the same group described the asymmetric direct 1,4-addition reactions of simple amides with α,β-unsaturated carbonyl compounds using a catalytic amount of a novel chiral catalyst (Scheme 13).[35] The desired 1,5-dicarbonyl compounds were obtained in high yields with excellent diastereo- and enantioselectivities. In this reaction, the intermediate **I** possesses strong Brønsted basicity for deprotonation of the amides directly.

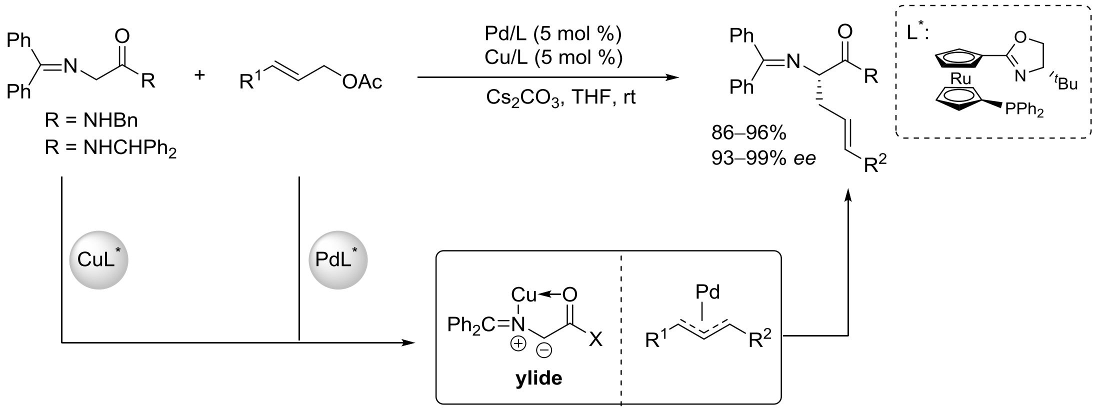

(2.8-4.4 mol %)
KHMDS (5-8 mol %)
Toluene, -78 ºC
R = Me, Et
Via:
I
89%–quant.
anti/syn = >99:1
93–98% ee

Scheme 13. Direct catalytic asymmetric conjugate addition of amides to α,β-unsaturated amides promoted by KHMDS/chiral crown ether.

---

[35] Suzuki, H.; Sato, I.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 4336–4339.

More recently, Zhang and co-workers reported the asymmetric alkylation of glycine iminoamides through a synergistic Pd/Cu catalyst system. A range of α-substituted α-amino acids are obtained in high yields and with excellent enantioselectivities (Scheme 14).[36]


Ph
Ph
N
O
R
R = NHBn
R = NHCHPh2
+
R1
OAc
Pd/L (5 mol %)
Cu/L (5 mol %)
Cs2CO3, THF, rt
86–96%
93–99% ee
R2
L*:
O
N
tBu
Ru
PPh2
CuL*
PdL*
Cu
Ph2C=N
X
ylide
Pd
R1
R2

Scheme 14. Alkylation of glycine amides.

.

---

[36] Huo, X. Fu, J.; He, X.; Chen, J.; Xien, F.; Zhang, W. *Chem. Commun*. **2018**, *54*, 599–602.

1.4. Objectives and working hypothesis

Precedents make clear the scarcity of strategies for the asymmetric α-functionalization of amides. In addition, the stereoselective creation of carbon atoms bonded to four different substituents (quaternary stereocenters), that are common motifs in complex molecules in nature, continues to be a challenge. [37] This realization presents two major problems. On the one hand, the formation of the fourth C-C bond must be performed on a central atom that it is already hindered for the presence of three preinstalled groups (steric congestion). On the other hand, the chiral catalyst substrate complex in the TS should impar enough stereoinduction as to differentiate the two faces of the prochiral reaction center.

The objective of this Ph. D. work has been the design of new methodologies for the enantioselective α-functionalization of amides, based on a Brønsted base/H-bonding catalysis approach as the main activation element.

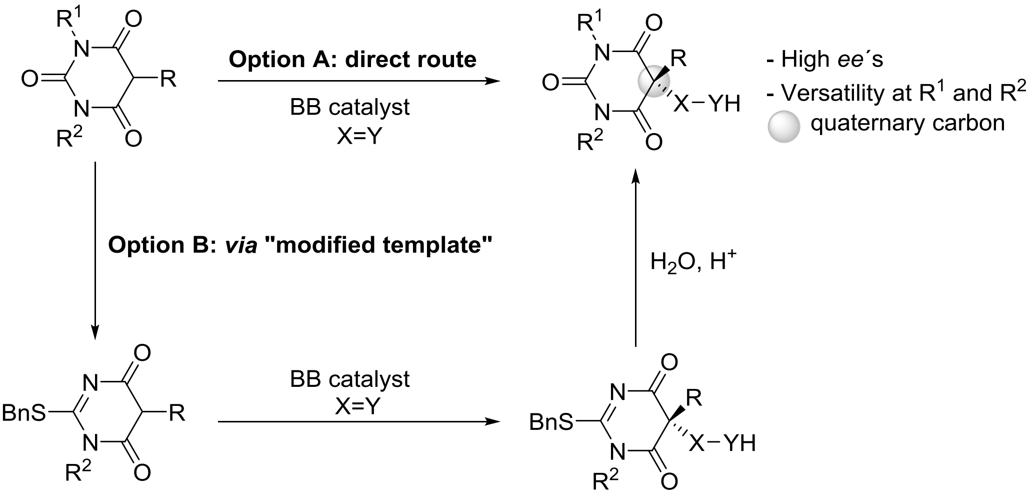
In this context, barbituric acids and derivatives are a particular type of (*pseudo*)symmetrical amides (imides) that have attracted great attention owing to their medical use as hypnotic agents, sedatives or anesthesic agents. Thus, the first goal of this work is focused on the development of a BB-catalyzed method for the enantioselective α-functionalization of barbituric acid templates to obtain the corresponding quaternary barbiturate. Quaternary stereocenters can be found in a wide range of important compounds in pharmaceutical and medical contexts including barbiturates, as well as in a large variety of natural products.[38]

Due to the (*pseudo*)symmetrical nature of barbiturates, two different routes were proposed to proceed with their desymmetrization, route A (Scheme 15), which was the most direct and route B (Scheme 15) that consisted of modifying the barbituric acid to break the initial symmetry of the compound. If the reaction proceeds in a satisfactory way, the obtained Michael adducts could be transformed easily into the corresponding optically active barbituric derivatives. So, a new method for the synthesis of a broad-scope of enantiopure barbituric acids could be obtained (Scheme 15).

---

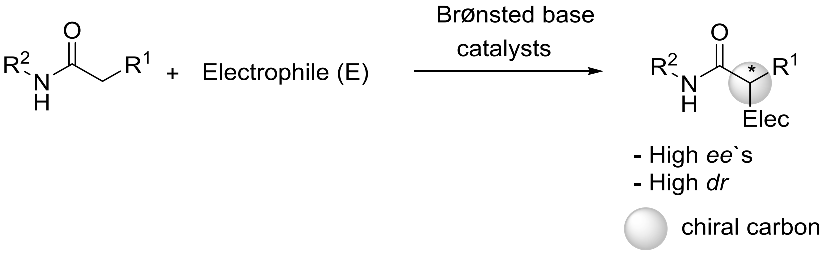
[37] a) Bella, M.; Caspery, T. *Synthsesis*, **2009**, 1583–1614. b) Das, J. P.; Marek, I. *Chem. Commun*. **2011**, *47*, 4593–4623. c) Hong, A. Y.; Stoltz, B. *Eur. J. Org. Chem*. **2013**, 2745–2759.

[38] Long, R.; Huang, J.; Gong, J.; Yang, Z. *Nat. Prod. Rep*. **2015**, *32*, 1584–1601.


Option A: direct route
BB catalyst
X=Y
- High ee´s
- Versatility at R1 and R2
quaternary carbon
Option B: via "modified template"
H2O, H+
BB catalyst
X=Y

Scheme 15.

In the second part of the work, we planned the design of a new amide pronucleophile suitable for smooth activation *via* proton transfer with common Brønsted base catalysts. This realization would led optically active α-functionalization amides using a methodology that have not been described previously (Scheme 16).


Brønsted base
catalysts
Electrophile (E)
Elec
- High ee`s
- High dr
chiral carbon

Scheme 16.

CHAPTER 2

BRØNSTED BASE-CATALYZED α-FUNCTIONALIZATION OF BARBITURIC ACIDS

2. BRØNSTED BASE-CATALYZED α-FUNCTIONALIZATION OF BARBITURIC ACIDS 45

2.1. INTRODUCTION 45
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2. Brønsted base-catalyzed *α*-functionalization of barbituric acids

2.1. Introduction

2.1.1. Working hypothesis and synthetic plan

As mentioned above, the amide group is very important for the synthesis of essential molecules in the pharmaceutical and chemical industry. Despite this, there are few methods to achieve these compounds asymmetrically. On the other hand, as far as we know, no example of asymmetric *α*-functionalization of amides using organocatalysis has been described. For these reasons, we proposed to evaluate the feasibility of a BB-catalyzed asymmetric *α*-functionalization of amides using suitable acceptors (electrophilic reagents) (Figure 7). One aspect to evaluate would be the nature of R^1 and R^2 groups in the amide and how they can modulate reactivity.

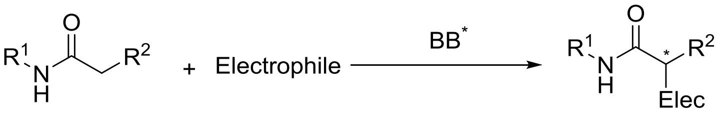


Figure 7. Research objective.

For this study, we selected two representative and accesible electrophiles, *trans-β*-nitrostyrene and 3-phenylpropanal.

2.1.2. First amides screening

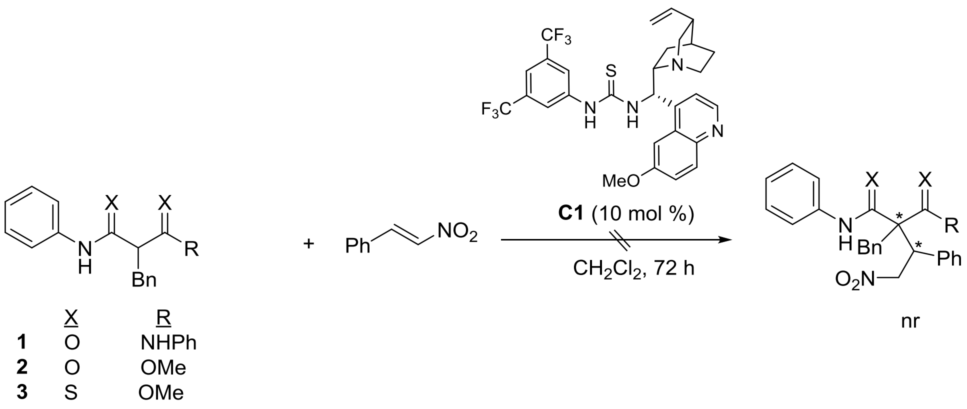
We began our study by checking several amides bearing an additional EWG at C*α* in the Michael addition to *trans-β*-nitrostyrene using 10 mol % of known thiourea organocatalyst **C1**.[39] As plausible substracts malonamides were initially selected given their relatively lower pKa.

In this context, several *α*-substituted (thio)malonamides derivatives namely 2-benzyl-*N*1,*N*3-diphenylmalonamide **1**, methyl 2-benzyl-3-oxo-3-(phenylamino)propanoate **2** and *O*-methyl 2-benzyl-3-(phenylamino)-3-

---

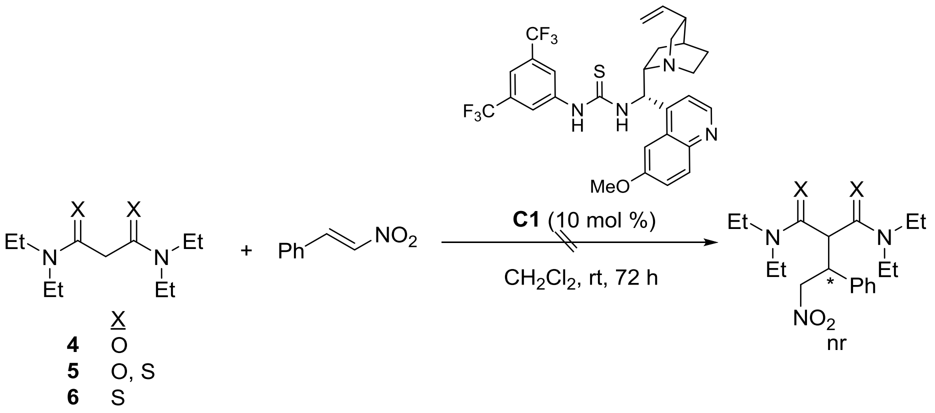
[39] a) Ono, N. *The nitro group in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**. b) Barrett, A. G.; Graboski, G.G. *Chem. Rev*. **1986**, *86*, 751–762. c) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev*. **2005**, *105*, 933 –971. d) Rosini, G.; Ballini, R. *Synthesis*, **1988**, 833–847. e) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis*, **1991**, 423–434.

thioxopropanethioate **3** were synthetized following standard procedures (Scheme 17). The experimental procedure for these catalytic reactions was the same in all cases. To a mixture of the corresponding starting (thio)malonamide (1 equiv., 0.2 mmol) in dichloromethane, catalyst **C1** (10 mol %) and nitrostyrene (1.5 equiv., 0.3 mmol) were added. Then, the reactions were stirred at rt for 72 h and monitored by NMR every 24 hours.We observed that in neither case the reactions did work. At this point, it reminded unclear whether these results can be explained by retroaddition reaction of the product under the reaction conditions.


CF3
S
F3C
N
H
N
H
N
N
MeO
X
X
N
H
R
Bn
+
Ph
NO2
C1 (10 mol %)
CH2Cl2, 72 h
X
X
N
H
Bn
*
*
R
Ph
O2N
nr
X R
1 O NHPh
2 O OMe
3 S OMe

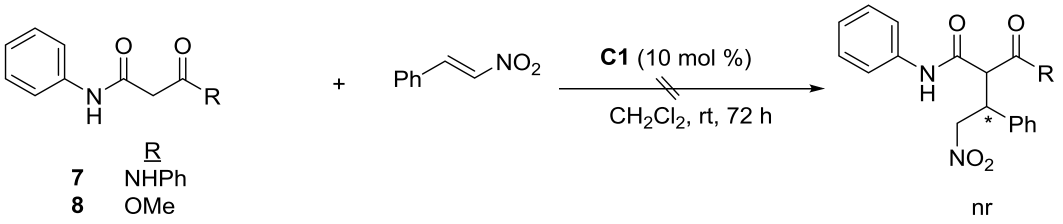
Scheme 17. Attempted catalytic reaction between α-substituted (thio)malonamides and nitrostyrene.

Then, we decided to test the corresponding (thio)malonamides **4-6** which lack any substitution at the methylene unit (Scheme 18). *N,N*-tetraethylmalonamide **4** was checked but the reaction did not work. We tried the thioamide derivative, **5** too but, unfortunately, the reaction did not give the desired product neither. Finally, we checked too dithiomalonamide **6**, but even so, the reaction did not work.


CF3
S
F3C
N
H
N
H
N
N
MeO
X
X
Et
N
Et
N
Et
Et
+
Ph
NO2
C1 (10 mol %)
CH2Cl2, rt, 72 h
X
X
Et
N
Et
N
Et
Et
*
Ph
NO2
nr
X
4 O
5 O, S
6 S

Scheme 18. Michael addition of malonamides to nitrostyrene.

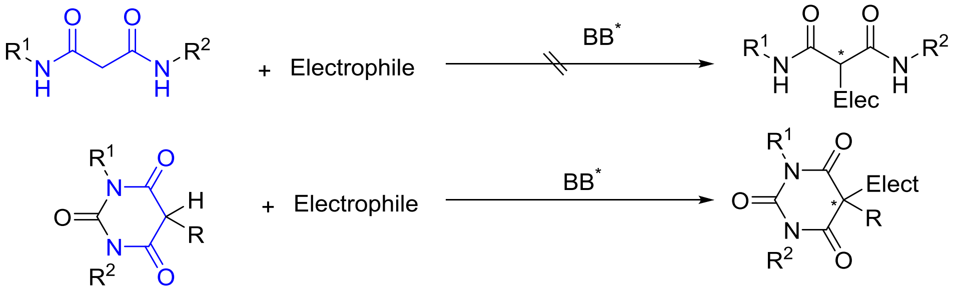
Following with our approach, we shifted from (thio)malonamides to β-ketoamide **7**, featurig a secondary amide, but it was not the solution for our problem (Scheme 19). Similarly, no reaction was observed with β-ketoester **8** (Scheme 19).


+
Ph
NO2
C1 (10 mol %)
CH2Cl2, rt, 72 h
O
N
H
R
*
Ph
NO2
nr

	R
7	NHPh
8	OMe

Scheme 19. The attempts with diphenyl amides and ester.

In view of these unsatisfactory results, we move from the acyclic to the cyclic congeneus with the hope that both acidy and nucleophilicity of the eventually formed enolates would get increased (Scheme 20). On the other hand, barbiturates are medically interesting compounds belong to this structural class of molecules.


R1
N
H
O
R2
+ Electrophile
BB*
Elec
*
O
H
R
Elect
+ Electrophile
BB*

Scheme 20.

2.1.3. **Barbituric acids**

The chemistry of barbituric acid and its derivatives has been studied for over 100 years. In 1864, *phenobarbital* (Figure 8), the parent compound of this class, was prepared by von Baeyer[40] and in 1873 was Muleder who confirmed its chemical structure. Barbituric acids and derivatives are very interesting 1,3-diamide scaffolds for the development of therapeutic agents and functional materials. In 1903 Fisher and von Mering[41] reported the therapeutic value of the 5,5-diethylbarbituric acid (*barbital*) as a hypnotic agent and since that time chemical and pharmacological studies on barbiturates has continued.

Nowadays, barbiturates are used in specific therapeutic applications. P*henobarbital* and *butabarbital* (Figure 8) are still used as sedatives in cases of gastrointestinal and asthmatic functional disorders. *Phenobarbital* is also used like hypnosedative agent. In the field of neurology, barbiturates are still employed, in the treatment of certain types of epilepsy and in the emergency treatment of some types of convulsions, such as those associated with tetanus, cerebral haemorrhage, status epilepticus, or different forms of poisoning. In addition, the barbiturates present other current uses; *phenobarbital* is capable of improving the hepatic transport of bilirubin in patients with haemolytic jaundice.[42] At a diagnostic level, *amobarbital* (Figure 8), in low doses, can be injected directly into the carotid artery prior to neurosurgency to identify the dominate cerebral hemisphere.[42] Finally, anesthetic doses of barbiturates can attenuate post-surgical cerebral enemas and have positive effects in case of cardiac and cerebral ischemia reducing the size of the infarcted region.[42]

Barbiturates were introduced into the clinical practice at the beginning of the 20th century and since then they are well positionated in the group of central nervous system agents. These drugs are highly addictive too and are often used as recreational drugs.[43] For example, the commercially available barbiturates *secobarbital*, *pentobarbital*, and *amobarbital* (Figure 8) are no longer routinely recommended for the treatment of insomnia because of their ability to cause dependence, tolerance, and withdrawal. In addition, they have significant secundary effects when taken in large doses and can cause respiratory failure and death.

---

[40] Von Baeyer, A. *Ann. Chem. Pharm*. **1864**, *130*, 129–175.

[41] Fisher, E.; Von Mering, J. R. *Ther. Ggw*. **1903**, *44*, 97–101.

[42] Muñoz, F.; Ucha-Udabe R.; Alamo, C. *Neuropsychiatr. Dis. and treat.* **2005**, *4*, 329–343.

[43] Dhiman, P. *Drug Discov and The*. **2013**, *8*, 15–22.

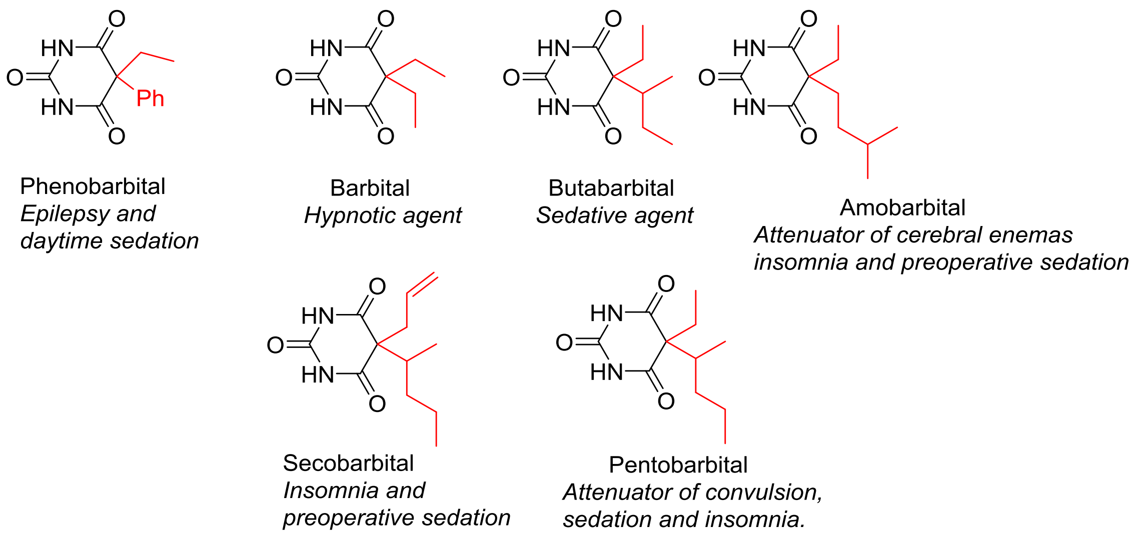

Phenobarbital
Epilepsy and daytime sedation
Barbital
Hypnotic agent
Butabarbital
Sedative agent
Amobarbital
Attenuator of cerebral enemas insomnia and preoperative sedation
Secobarbital
Insomnia and preoperative sedation
Pentobarbital
Attenuator of convulsion, sedation and insomnia.
HN
O
Ph

Figure 8. Examples of barbituric acids with therapeutic uses.

2.1.3.1. **Chemical properties of barbituric acids**

Most barbiturates used in medical application contain a “balance” of hydrophilic character, that depends on the ring structure, and lipophilic character, which depends on the nature of substituents at C5. The equilibrium between these properties allow them to go through the hematoencephalic membrane and interact with the central nervous system.

The lipophilic character could be tunned by changing the substituent at C5 position (Figure 9). Normally, with large aryl or aliphatic groups, the lipophilic character increases and the acidity decreases.

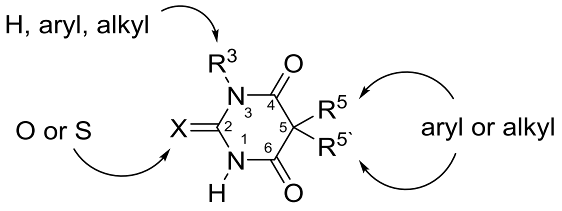

H, aryl, alkyl
R3
O or S
X
N
H
O
R5
R5`
aryl or alkyl
1
2
3
4
5
6

Figure 9. General structure of the barbituric acids.

If one of the amide nitrogens is substituted, the lipophilicity could be increased too. Finally, both the acidity and the lipophilicity increase upon shifting from barbituric to the corresponding thiobarbituric analogs.

On the other hand, the acid-base equilibria is strongly dependent on the site of substitution and the inductive effects of substituents (Figure 10). Acid strenght is almost independent of the length of the straight-chain alkyl groups attached to the C5 atom of the heterocyclic ring. Attachment of a phenyl group to C5 of barbituric acid decreases the pKa, whereas barbiturates with alkyl groups at that position have an increased pKa. On the other hand, the alkyl substitution of *N*3 causes a slight increase in the value of the pKa.[44]

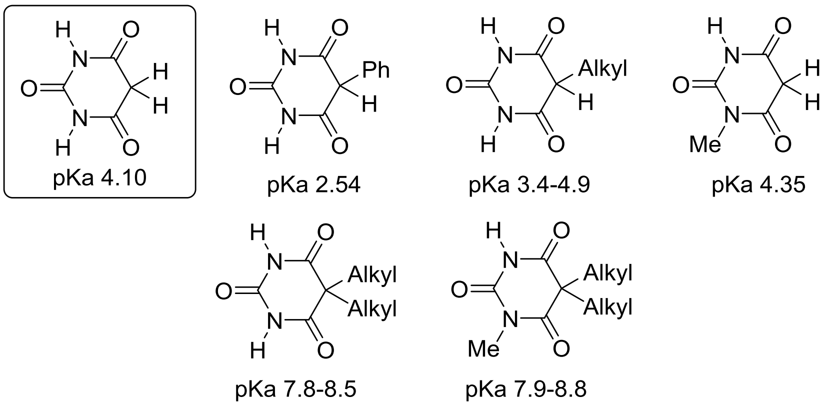


Figure 10. Relative acidity of different barbiturates.

In the solid state the parent barbituric acid exists as two anhydrous forms (polymorph **II** and **III**) (Figure 11a) and the dihydrate phase which differs mainly in the hydrogen pattern.[45] In the dihydrate structure (Figure 11b), the barbituric acid molecules form chains *via* hydrogen bonds involving the donor and the acceptor groups which are in 1 and 4 position, respectively. The barbituric acid molecules in the chain are related by screw axes, so that the CH_2 groups are in alternated positions. These chains are bridged by water molecules forming a 2-D netwoork.[46] In solution, the barbituric acid may exists as 11 possible tautomers. The tautomeric forms are very difficult to detect, but they are supposed important intermediates in many reactions (Figure 12).[47]

---

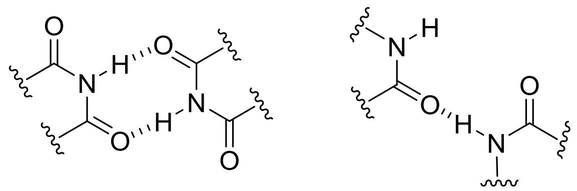
[44] Bojarski, J.; Mokrosz, J.; Barton, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229–297

[45] Jeffrey, G. A.; Ghose, S.; Warwicker, J. O. *Acta Crystallogr*. **1961**, *14*, 881–887.

[46] Braga, D.; Codoni, M.; Grepioni, F.; Maini, L.; Rubini, K. *Cryst. Eng. Commun.* **2006**, *8*, 756–763.

[47] Chierotti, M.; Gobetto, R.; Pellegrino, L.; Milone, L.; Venturello, P. *Cryst. Growth Des.* **2008**, *8*, 1454–1457.

a) Anhydrous forms



form **II** form **III**

b) Dihydrate form

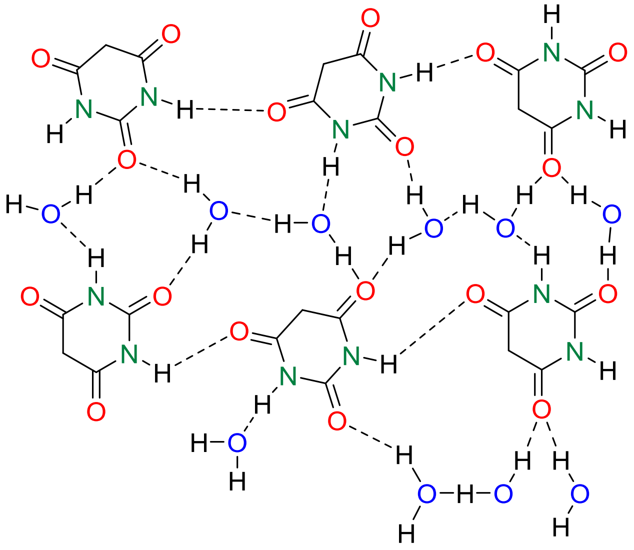


Figure 11. Hydrogen bond network in anhydrous forms **II** and **III** (a) and dihydrate form (b) of barbituric acid.

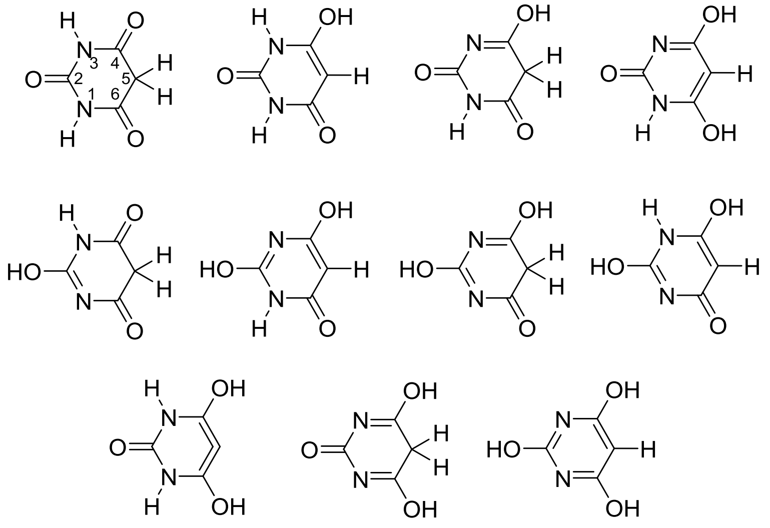
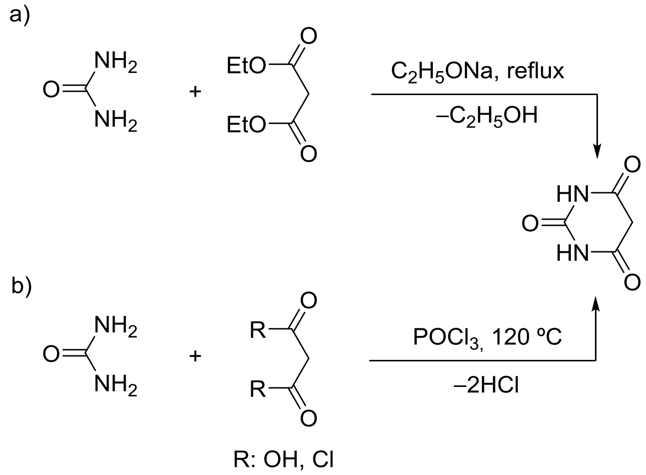


Figure 12. Eleven possible tautomers of the barbituric acid.

2.1.3.2. **Synthesis of barbituric acid derivatives**

2.1.3.2.1. Construction of the core structure

Since the first introduction of barbituric acids for medical use as early as 1900s, more than 2500 derivatives have been synthesized, and about 50 were marketed, mainly for pharmacological use. By far the most common procedure for the synthesis of barbituric acids is the condensation of urea with the appropiate diethyl malonate in the presence of sodium ethoxide in anhydrous alcohol (Scheme 21a). This method has been generally adopted for the industrial production of barbituric acids and represents the most common laboratory procedure as well. Another manner to access barbituric acid is the condensation between urea and the corresponding malonic acid or malonyl chloride (Scheme 21b). [48]



Scheme 21. Traditional synthesis of barbituric acids.

2.1.3.2.2. Modifications of the core structure

Barbituric acid and derivatives can be modified at the C5 and the two *N*-positions.

2.1.3.2.2.1. Achiral approaches

Non asymmetric modification of the barbituric acid core have been developed mainly through Mannich and Knoevenagel reactions. Alternatively, alkylation of barbiturics acids has been carried out based on metal catalyzed coupling procedures. Although many types of reactions have been described, only the ones with the most representative reaction conditions will be mentioned in the following sections.[49]

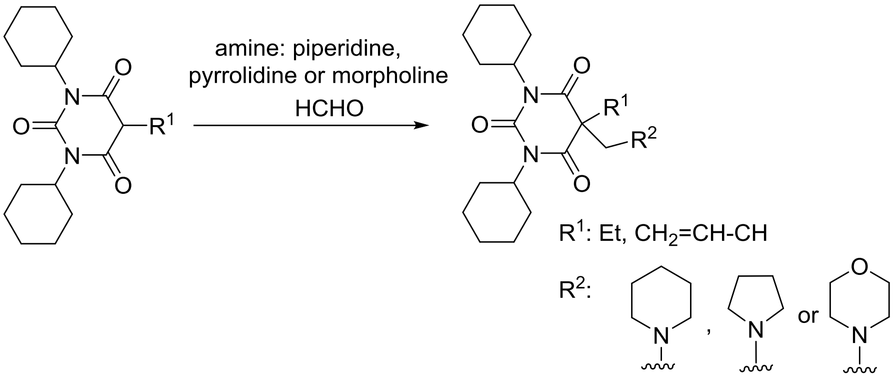
---

[48] Mahmudov, K. T.; Kopylovich, M. N.; Maharramov, A. M.; Kurbanova, M. M.; Gurbanov, A. V.; Pombeiro, J. L. *Coord. Chem. Rev.* **2014**, *265*, 1–37.

2.1.3.2.2.1.1. Mannich type reactions

The Mannich reaction is a powerful method for the preparation of *β*-amino carbonyl compounds, an important class of building blocks of pharmaceutically relevant compounds. Mannich-type transformations have been carried out at both C5 (Mannich reaction) and *N*-positions (*pseudo* Mannich or aza-Mannich).

Sladowska reported one of the first examples of Mannich reaction through C5 to obtain a series of 5-alkyl-5-aminomethyl-1,3-dicyclohexyl-barbituric acids (Scheme 22). Some of these compounds showed a strong anti-inflammatory activity in biological tests.[50]



Scheme 22. Mannich reaction at C5 position of barbituric acid derivatives.

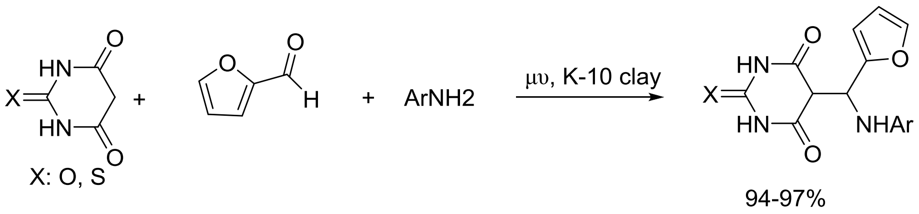
In 2005, Kidwai and coworkers described the one pot synthesis of substituted barbituric and thiobarbituric acids *via* the Mannich reaction of barbiturates and thiobarbiturates with furan-2-carbaldehyde and other heteroaromatic carbaldehydes (1*H*-indole-3-carbaldehyde) and aryl amines using montmotillonite clay in dry media under microwave irradiation. The same reaction under conventional heating conditions was complete in 10-12 hours, but led to moderate yields, whereas excellent yields were obtained within few minutes under MWI irradiation (Scheme 23).[51]

---

[49] a) Bojarski, J. T.; Mokrosz, J. L.; Barton, H. J.; Oaluchowska, M. H. *Adv. Heterocyclic Chem.* **1985**, *38*, 229–297. b) Ziarani, G. M.; Aleali, F.; Lashgari, N. *RSC Adv.* **2016**, *6*, 50895–50922.

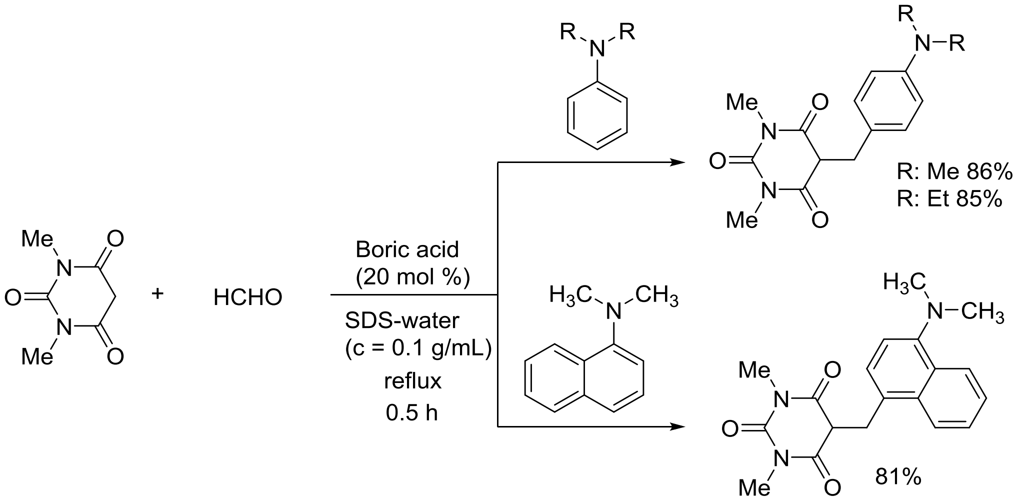
[50] Sladowska, H. *Farmac.* Ed. Sci. **1977**, *32*, 866–871.

[51] Kidway, M.; Thakur, R.; Mohan, R. *Acta. Chim. Slov*. **2005**, *52*, 88–92.


X: O, S
μυ, K-10 clay
ArNH2
NHAr
94-97%

Scheme 23. Microwave assisted C5-functionalization of thiobarbituric acid.

An unusual Mannich type reaction of tertiary aromatic amines, formaldehyde and *N,N′*-dimethylbarbituric acid was described to produce 5-dialkylaminoaryl-1,3-dimethyl-pyrimidine-2,4,6-triones in aqueous micelles catalyzed by boric acid. The reaction is highly regioselective, and *para* functionalized products are formed exclusively with high yields (Scheme 24).[52]

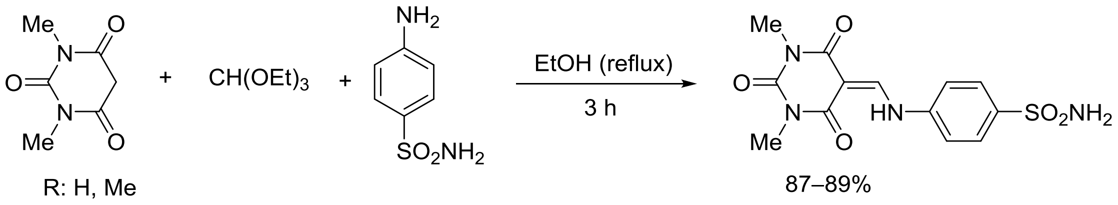

HCHO
Boric acid
(20 mol %)
SDS-water
(c = 0.1 g/mL)
reflux
0.5 h
R: Me 86%
R: Et 85%
81%

Scheme 24. Mannich reaction of *N,N*-dimethylbarbiturate catalyzed by boronic acid.

---

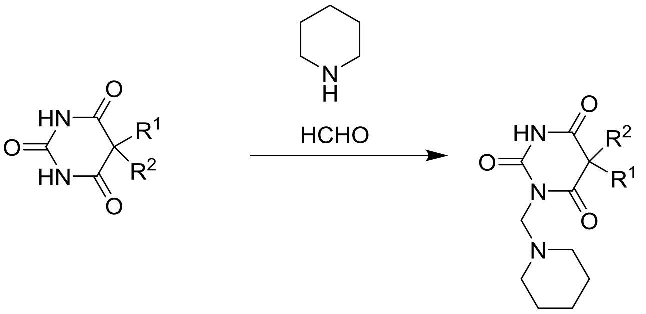
[52] Kumar, A.; Maurya, R. A. *Tetrahedron Lett.* **2008**, *49*, 5471–5474.

Recently, Arslan group described the synthesis of 1,3-dicarbonyl substituted sulfonamide derivatives using *N*,*N*-dimethylbarbiturate and triethyl(orthoformate) in refluxing ethanol (Scheme 25).[53]



Scheme 25. Synthesis of 1,3-dicarbonyl substituted sulphonamide derivatives.

On the other hand, Mannich-type reactions through *N*-1 of barbituric acids have also been developed. A classic example is the *N*-aminomethylations of 5,5-diethyl- and 5-ethyl-5-phenylbarbituric acids using formaldehyde and morpholine as reagents (Scheme 26).[54]



Scheme 26. Mannich reaction at the *N* of the barbituric acid.

More examples about the aminoamination at nitrogen have been described in the literature.[55]

---

[53] Demirci, T.; Arslan, M.; Bilen, C.; Demir, D.; Gencer, N.; Arslan, O. *J. Enz. Inhib. Med. Chem*. **2014**, *29*, 132–136.

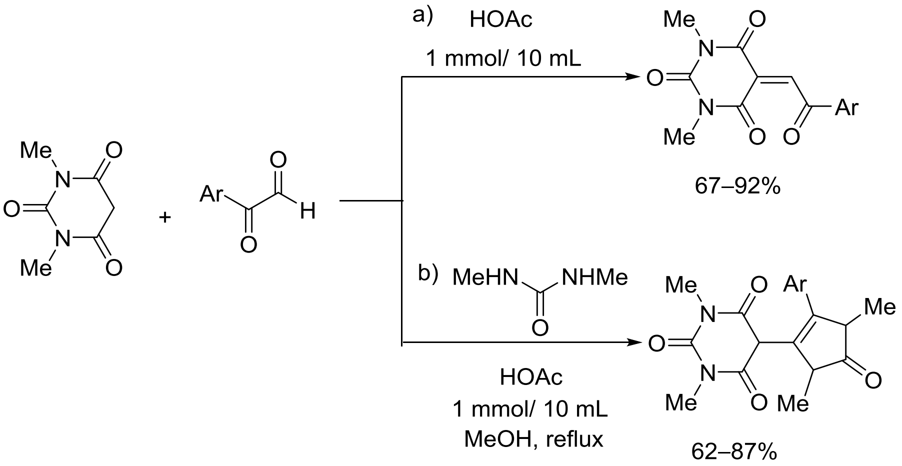
[54] Danielsson, B.; Dolby, J. *Acta Pharm. Suec*. **1964**, *1*, 233–236.

[55] Werner, W.; Frietzsche, H. *Arch. Pharm*. **1969**, *302*, 188–196.

2.1.3.2.2.1.2. Knoevenagel reactions

The Knoevenagel reaction consists of the condensation of aldehydes or ketones with active methylene compounds usually performed in a weakly basic medium. Some *N,N´*-dimethylbarbituric acid derivatives are interesting compounds for pharmacology, and this type of reaction has been used for their synthesis.

In 2008, Kolos and co-workers described the synthesis of 5,5-(2-arylethylidene-2-oxo)-1,3-dimethylpirimidine-2,4,6-triones obtained by Knoevenagel reaction of 1,3-dimethylbarbituric acid and arylglyoxals. The reaction was accomplished in glacial acetic acid at room temperature overnight (Scheme 27 path a).[56] In addition, the interaction of 1,3-dimethylbarbituric acid, with different glyoxals and dimethylurea in methanol with catalytic amounts of glacial acetic acid leads to the corresponding condensation products (Scheme 27 path b).



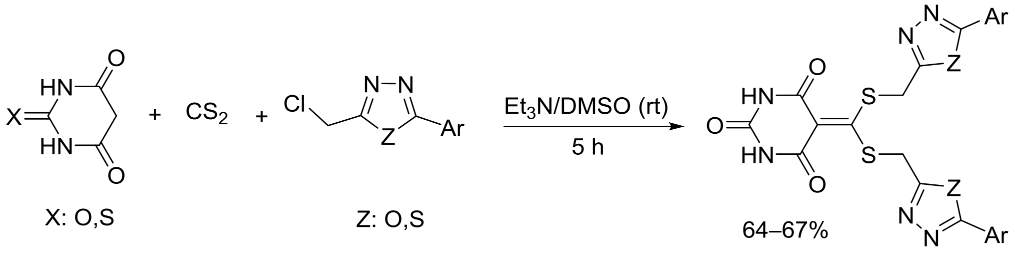
Scheme 27. Barbiturate C5-functionalization via Knoevenagel reaction.

In another example, the group of Padmaja and co-workers described a new class of tris-heterocyclic systems, that were prepared by the condensation of barbituric acid derivatives, carbon disulfide and 1,3,4-oxadiazole/thiadiazole under base catalyst (Scheme 28).[57]

---

[56] Gozalishvili, L.; Beryozkina, T. V.; Omelchenko, I. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kolos, N. N. *Tetrahedron* **2008**, *64*, 8759–8765.

[57] Padmavathi, V.; Reddy, G. D.; Venkatesh, B. C.; Padmaja, A. *Arch. Pharm.* **2011**, *344*, 165–169.



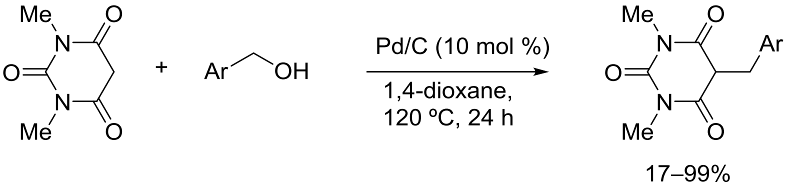
Scheme 28. Sythesis of tris-heterocyclic systems using a Knoevenagel reaction.

To date, the Knoevenagel reaction constitutes the most common method employed for the synthesis of barbituric acid derivatives.[58]

2.1.3.2.2.1.3. Methods based on metal catalyzed couplings

Alkylation of barbituric acids via traditional methods using alkyl halides are ineffective because of multiple alkylations occur at both C5 and *N*-1. The poly-alkylation problem on the synthesis of monoalkylated barbituric acids has been overcome by using metal-catalyzed approaches.

For example, in 2015, Ohta and co-workers described the Pd-catalyzed alkylation of heterocyclic compounds including barbituric acid derivatives using alcohols as the alkylating agents. This method gives the corresponding mono-alkylated heterocyclic compounds with yields from 17 to 99% (Scheme 29).[59]



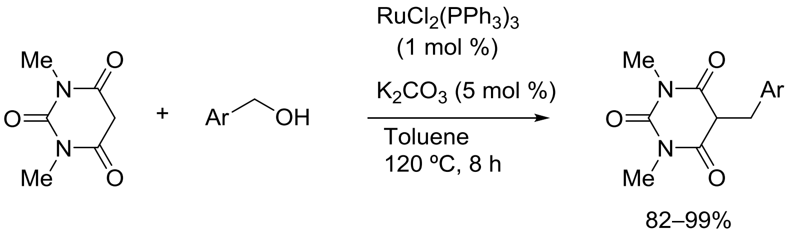
Scheme 29. *C*-alkylation of barbituric acid derivatives with alcohol using a Pd-catalyzed reaction.

---

[58] Moskvin, A. V.; Reznikova, N. R.; Ivin, B. A. *Russ. J. Org. Chem.* **2002**, *38*, 463–474.

[59] Putra, A. E.; Oe, Y.; Ohta, T. *Eur. J. Org. Chem.* **2015**, *35*, 7799–7805.

In 2017, the same group described the alkylation of barbituric acids with alcohols as electrophiles via ruthenium catalysis. The corresponding 5-(alkyl)barbituric acids were obtained in good to excellent yields with low catalyst loading (Scheme 30).[60]


Me
N
O
O
N
Me
O
+
Ar
OH
$RuCl_2(PPh_3)_3$
(1 mol %)
K_2CO_3 (5 mol %)
Toluene
120 °C, 8 h
Ar
82–99%

Scheme 30. Alkylation of babituric acid derivatives using a Ru-catalyzed reaction.

2.1.3.2.2.2. Asymmetric approaches

In contrast to the ample precedents concerning the synthesis of racemic barbituric acids and derivatives, very few approaches to construct chiral non-racemic barbiturates have been reported. Chiral barbituric acids can be grouped in two categories: (i) those in which the chirality is outside of the ring, that is, the synthesis of derivatives with a chiral substituent chain at either C5 or N and (ii) those in which the chirality resides in the ring (Figure 13). Whereas there are several methods to construct stereoselectively chiral compounds of type (i), only a few enantioselective approaches for the synthesis of compounds of type (ii) are known.

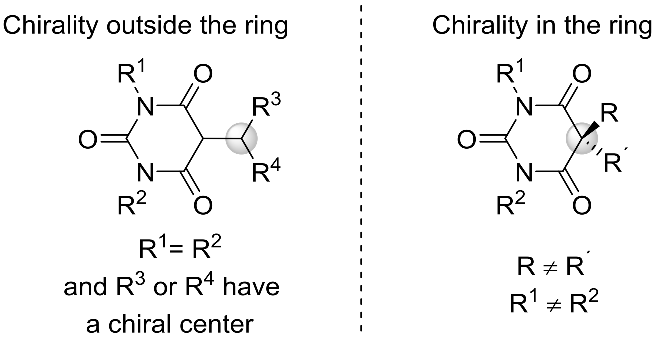

Chirality outside the ring
R^1
O
N
R^3
O
N
R^4
R^2
O
R^1= R^2
and R^3 or R^4 have
a chiral center
Chirality in the ring
R^1
O
N
R
O
R´
N
R^2
O
R ≠ R´
R^1 ≠ R^2

Figure 13. Two possibilities of chirality in barbituric acids.

In 2000, Trost and co-workers described the enantioselective Pd-catalyzed allylic alkylation of 5-allylpyrimidine and 5-ethyl pyrimidine with cyclopent-2-en-1-yl methyl carbonate and (*E*)-methyl pent-3-en-2-yl carbonate respectively, affording the quaternary adducts in good yield and 91% and 72% enantioseletivities (Scheme 31). The use of a C_2-

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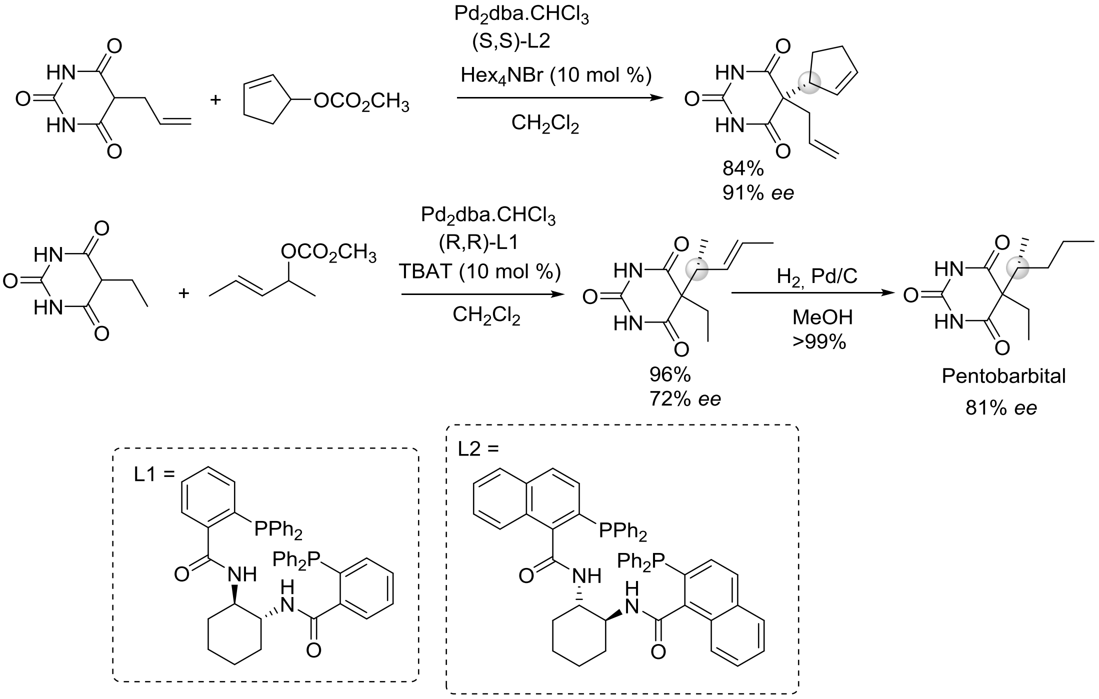
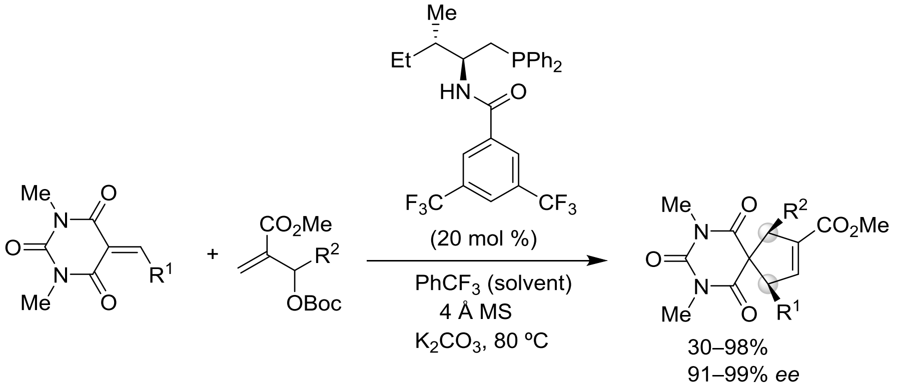
[60] Putra, A. E.; Oe,Y.; Ohta, T. *Tetrahedron Letters*, **2017**, *58*, 1098–1101.

symmetric diamide diphosphine chiral ligand was key.[61] Further reduction of the C=C with H_2/Pd/C afforded pentobarbital with a 81% *ee* after recrystallization.


Pd2dba.CHCl3
(S,S)-L2
Hex4NBr (10 mol %)
CH2Cl2
84%
91% ee
Pd2dba.CHCl3
(R,R)-L1
TBAT (10 mol %)
CH2Cl2
96%
72% ee
H2, Pd/C
MeOH
>99%
Pentobarbital
81% ee
L1 =
L2 =

Scheme 31. Trost asymmetric synthesis of pentobarbital.

Once our work was in progress a few novel organocatalytic protocols appeared. In 2016, Guo´s group described an enantioselective formal [3+2] annulation of alkyliden barbiturates with Morita-Baylis-Hillman carbonates catalyzed by a chiral phosphine-amide catalyst to afford a variety of chiral spirobarbiturate cyclopentenes (Scheme 32).[62]


(20 mol %)
PhCF3 (solvent)
4 Å MS
K2CO3, 80 ºC
30–98%
91–99% ee

Scheme 32. Synthesis of spirobarbiturate cyclopentenes catalyzed by a chiral phosphine amide.

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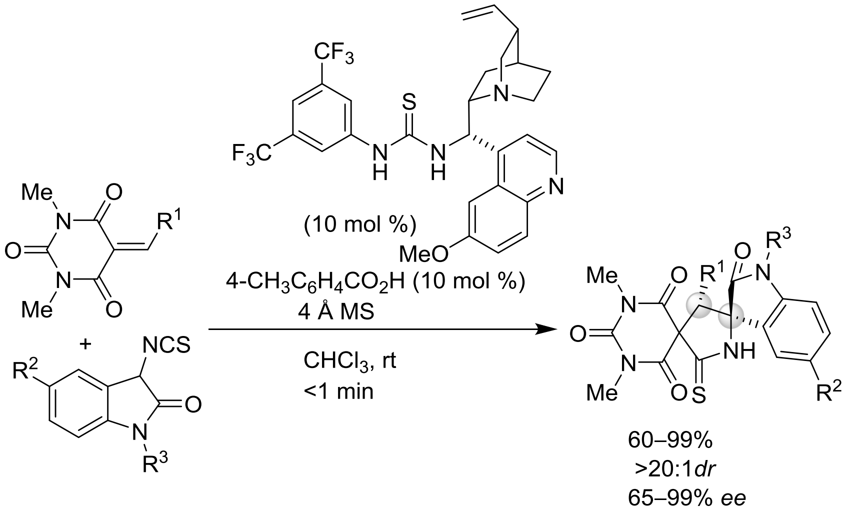
[61] Trost, B. M.; Getchen, M. S. *J. Org. Chem.* **2000**, *65*, 1569–1573.

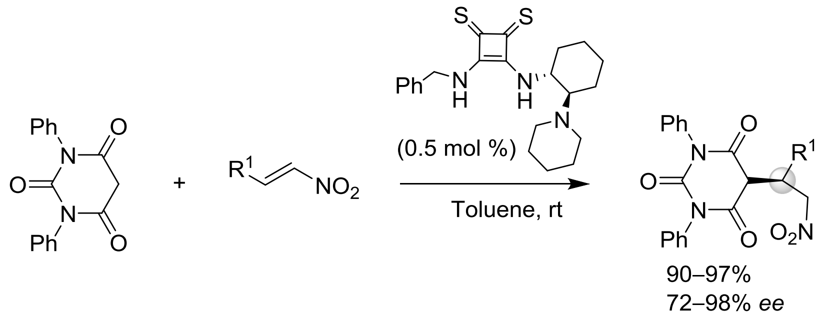
[62] Liu, Y.; Yang, W.; Wu, Y.; Mao, B.; Gao, X.; Liu, H.; Sun, Z.; Xiao, Y.; Guoa, H. *Adv. Synth. Catal.* **2016,** *358,* 2867–2872.

This same year Liu´s group described a novel formal [3+2] cycloaddition of the 5-alkylidenbarbiturate with 3-isothiocyanatooxindoles catalyzed by a thiourea catalyst and benzoic acid as additive. Generally, good yield and diastereo and enantioselectivities were obtained (Scheme 33).[63]



Scheme 33. Formal [3+2] cycloaddition reaction of 5-alkylidenbarbiturate and 3-isothiocyanatooxindoles.

More recently, Rawal and coworkers described the addition of barbituric acid derivatives to nitroolefins using a new class of bifunctional catalyst based on thiosquaramides (Scheme 34). They achieved a battery of asymmetric compounds with high yields and high enantioselectivities.[64]



Scheme 34. Bifunctional thiosquaramide/amine-catalyzed conjugate addition of barbituric acid derivatives to nitroolefins.

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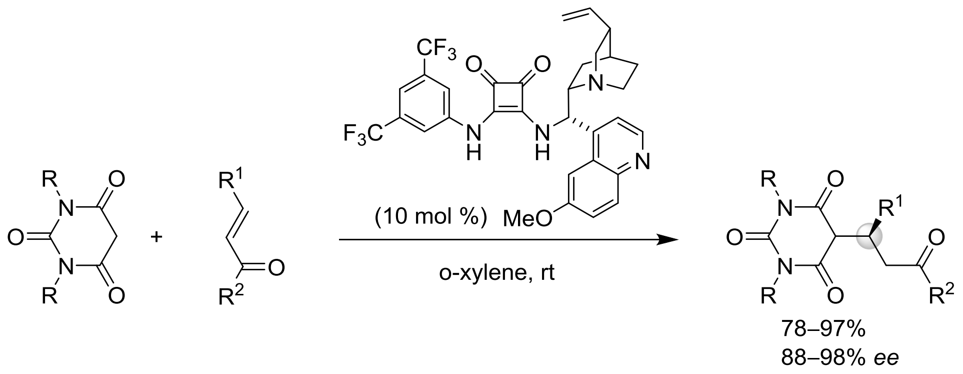
[63] Zhao, H. W.; Tian, T.; Pang, H. L.; Li, B.; Chen, X. Q.; Yang, Z.; Meng, W.; Song, X. Q.; Zhao, Y. D.; Liu, Y. Y. *Adv. Synth. Catal.* **2016**, *358*, 2619–2630.

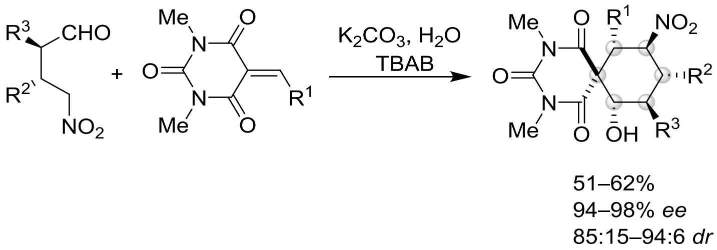
[64] Rombola, M.; Chintan, S. S.; Montgomery, T. D.; Rawal, V. H. *J. Am. Chem. Soc.* **2017**, *139*, 5297–5300.

Also very recently Wang and co-workers described an asymmetric Michael reaction of *N*,*N*-dialkylbarbiturates catalyzed by a cinchona alkaloid-based bifunctional squaramide with good yields and enantioselectivity (Scheme 35).[65]



Scheme 35. Catalytic asymmetric Michael reaction of *N*,*N*-dialkilbarbituric acids to enones.

On the other hand, Peng´s group described[66] an asymmetric three-component tandem organocatalytic Michael-Michael-aldol reaction involving alkyliden barbiturates. In this reaction, three new bonds are formed with excellent diastereo and enantioselectivity leading to spirobarbiturates, a type of barbiturates that also showed a range of pharmacological and physiological activities (Scheme 36).



Scheme 36. Synthesis of the spirocyclic compounds derived from barbituric acids.

All these examples imply the asymmetric synthesis of chiral barbiturates with chirality *outside* the ring. In contrast, the enantioselective synthesis of chiral barbiturates with *in-ring* chirality remains essentially unsolved, in spite of the fact that pharmacological activity of *R* and *S* enantiomers of the barbiturics acids can be different. Only a few examples have been published, all relying on metal catalysis.

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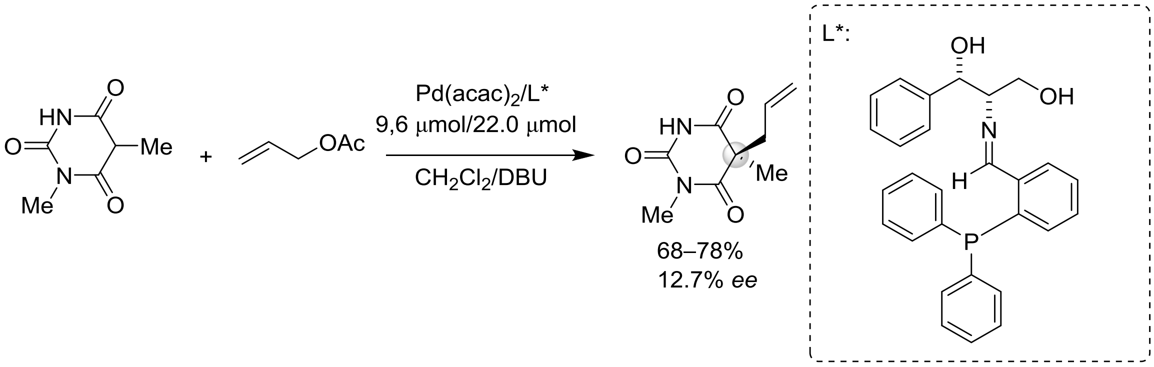
[65] Liu, Y.; Zhang, Y.; Duan, H. X.; Wanyan, D.; Wang, Y. Q. *Org. Biomol. Chem.* **2017**, *15*, 8669–8679.

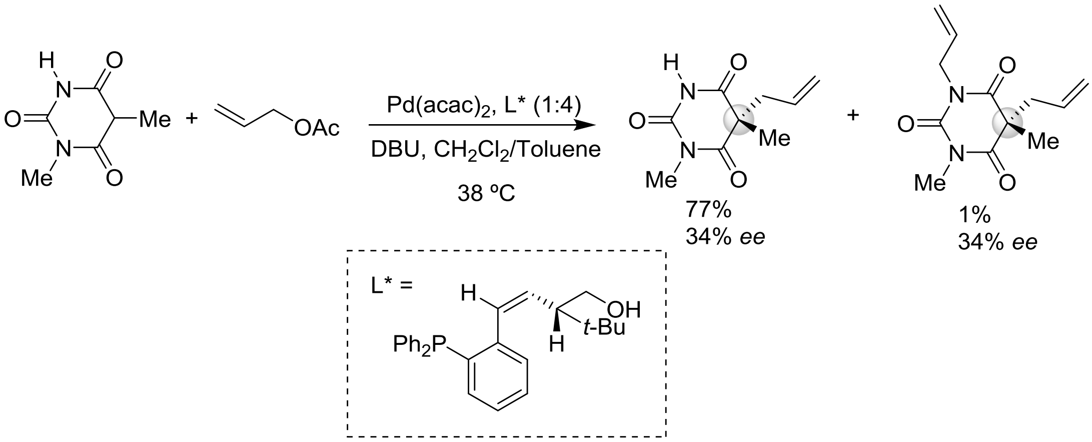
[66] Han, B.; Huang, W.; Ren, W.; He, G.; Wang, J.; Peng, C. *Adv. Synth. Catal.* **2015**, *357*, 561–568.

Brunner and coworkers in 1994 described the Pd-catalyzed asymmetric *α*-allylation of *N*-methyl barbituric acid based on a new chiral diphosphine-amide-ester ligand. Using this procedure yields between 68% and 78% are achieved and the highest enantiomeric excess was a 12.7% (Scheme 37).[67]


Pd(acac)2/L*
9,6 μmol/22.0 μmol
CH2Cl2/DBU
OAc
68–78%
12.7% ee
L*:

Scheme 37. Pd-catalyzed allylic alkylation of *N*-methyl barbituric acid.

Few years later, the same group described an improved variant that affords the quaternary barbituric acid derivatives with good yield, although still low *ee* (34%) (Scheme 38).[68]


Pd(acac)2, L* (1:4)
DBU, CH2Cl2/Toluene
38 °C
OAc
77%
34% ee
1%
34% ee
L* =
Ph2P
t-Bu

Scheme 38. Brunner 2nd generation allylic alkylation of 1,5-dimethylbarbituric acid.

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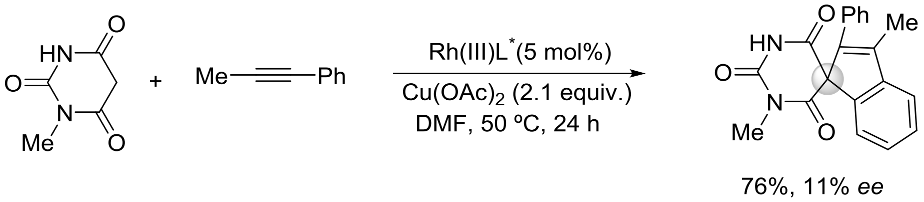
[67] Brunner, H.; Fürst, J. *Inorg. Chim. Acta*. **1994**, *220*, 63–66.

[68] Brunner, H.; Deml, I.; Dimberger, W.; Nuber, B.; Reiβer, W. *Eur. J. Inorg. Chem*. **1998**, 43–54.

In 2015, Lam´s group described the Rh (III)-catalyzed oxidative annulations of cyclic 1,3-dicarbonyl compounds with alkynes, including a single example involving barbiturates that yields the corresponding spiroindene adduct in 11% *ee* (Scheme 39).[69]


HN
O
O
N
Me
O
+
Me
Ph
Rh(III)L*(5 mol%)
Cu(OAc)2 (2.1 equiv.)
DMF, 50 °C, 24 h
O Ph
Me
HN
O
N
Me
O
76%, 11% ee

Scheme 39. Rh (III)-catalyzed oxidative annulations.

In spite of the importance of the asymmetric synthesis of barbituric acids with in-ring chirality, the realization of that goal *via* catalysis remained unsolved.

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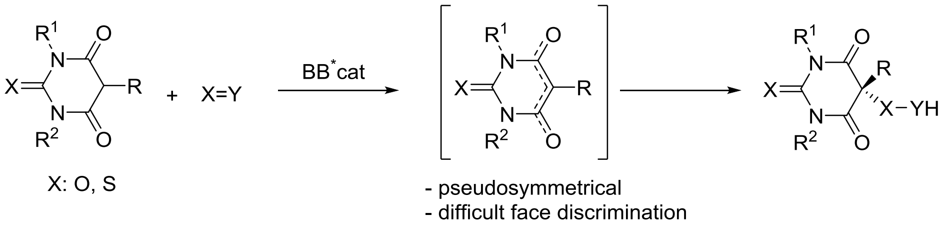
[69] Chidipudi, S. R.; Burns, D. J.; Khna, I.; Lam, H. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 13975–13979.

2.2. **Results and discussion**

As shown above, methods to generate barbituric acid derivatives enantioselectively with an *in-ring* stereogenic carbon were scarce. This is so probably because the intermediate enolate is *pseudo*-symmetric and therefore discrimination between both enantiotopic faces is challenging (Scheme 40).

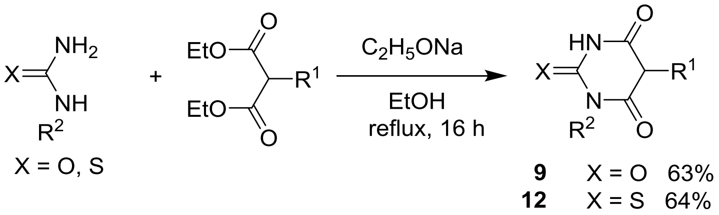


Scheme 40. Scheme option A.

For first assessment of the likelihood of the approach, we started by exploring the behaviour of several "conventional" barbituric and thiobarbituric acid derivatives in their Michael reaction with vinyl ketones in presence of a BB catalysts.

2.2.1. **Initial attempts with conventional (thio)barbituric acid derivatives**

(Thio)barbituric acid derivatives **9**/**12** were prepared by heating at reflux a mixture of (thio)urea and the corresponding ethyl malonate in ethanol during 16 hours, following the procedure described by Borrell and co-workers in 2015 (Scheme 41).[70]



Scheme 41. Synthesis of (thio)barbituric acid derivatives.

On the other hand, (thio)barbituric acid derivatives **10**/**11** were prepared by heating at reflux a mixture of corresponding (thio)urea and the diethyl 2-methylmalonate in isopropanol for 16 hours (Scheme 42). After the reaction was complete, aqueous hydrochloric acid was added to make the solution acidic. Then, the precipitate was washed with methanol and dried at vacuum (735 mmHg) in a bath at 80 °C affording the products as white solids.

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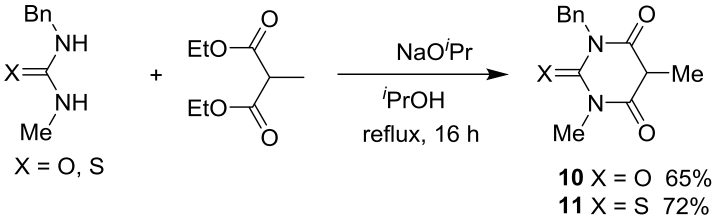
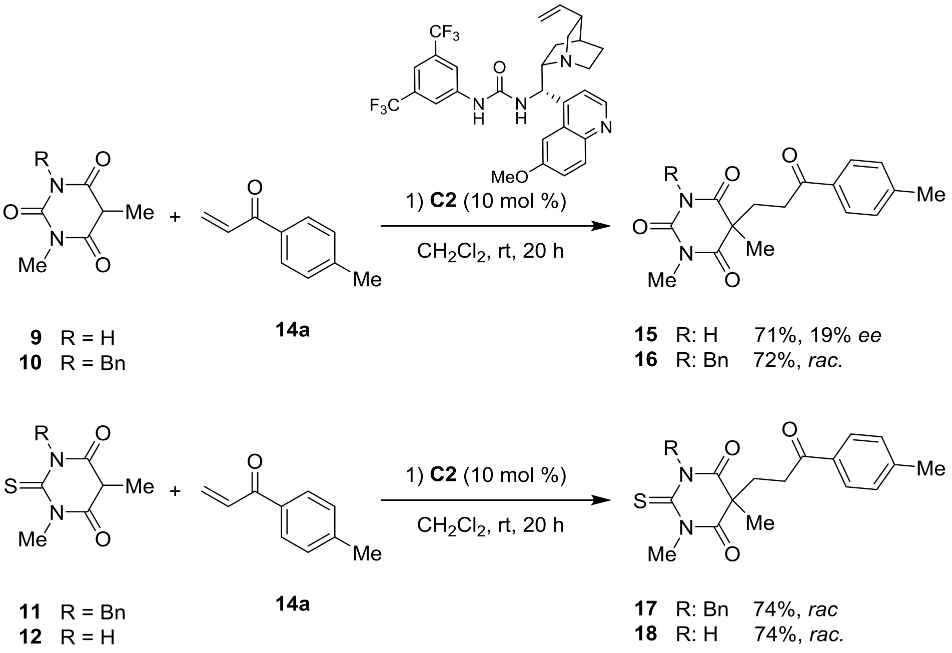
[70] Puig-de-la-Bellacasa, R.; Giménez, L.; Pettersson, S.; Gonzalo, P.; Esté, J. A.; Clotet, B.; Borrell, J. I. *Eur. J. Med. Chem.*, **2012**, *54*, 159-174.


Bn
NH
X
NH
Me
X = O, S
+
EtO
EtO
O
O
NaO^{i}Pr
^{i}PrOH
reflux, 16 h
Bn
N
O
X
Me
N
Me
O
10 X = O 65%
11 X = S 72%

Scheme 42. Synthesis of *N*,*N*-disubstituted barbiturates.

Firstly, barbiturates **9**/**10** as well as their thio-analogues **11**/**12** were treated with vinyl ketone **14a** in the presence of 10 mol % catalyst **C2** (Scheme 43). The corresponding adducts **15**-**18** were obtained as essentially racemic material (< 20% *ee* at best). Reaction reversibility (retro Michael process) as a cause of the low enantiocontrol could be discarded as no crossover products were detected when adducts **15** and **16** were admixed with vinyl ketone **14b** in the presence of a base catalyst. We thought, as in the previous section is explained, that the major problem of this type of structures is the *pseudo* symmetrical structure of 1,3-diamide moiety which makes enantioface discrimination complicated. In addition, the starting barbiturates exhibited very low solubility in CH_2Cl_2, which was also poor in THF.[71]


CF3
F3C
O
N
H
N
H
N
N
MeO
R
O
N
O
Me
N
Me
O
+
O
Me
1) C2 (10 mol %)
CH2Cl2, rt, 20 h
9 R = H
10 R = Bn
14a
15 R: H 71%, 19% ee
16 R: Bn 72%, rac.
S
11 R = Bn
12 R = H
17 R: Bn 74%, rac
18 R: H 74%, rac.

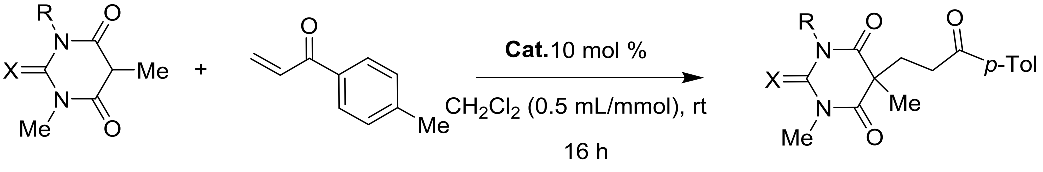
Scheme 43. First essays of the Michael addition of barbiturates to enone **14a**.

---

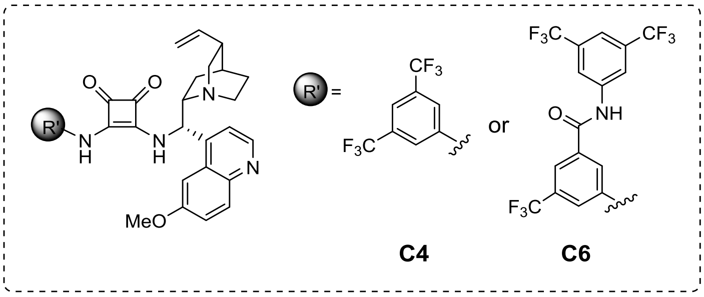
[71] Chidipudi, S. R.; Burns, D. J.; Khan, I.; Lam, H. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 13975–13979.

In order to assess whether the lack of selectivity in the above reactions was catalyst-dependent, additional bifunctional BB catalysts were also tested. As results in Table 1 show both **C4** and **C6** were checked but the obtained adducts were racemic in all the cases.

Table 1. Screening of donor barbiturates and BB catalysts for the Michael reaction with **14a**



Donor **14a** **Adduct**



R	X	Donor/adduct	Catalyst	Yield (%)	*ee* (%)
H	O	**9/15**	**C4**	63	0
			C6	64	0
H	S	**12Aa/18**	**C4**	67	0
			C6	69	0
$PhCH_2$	O	**10/16**	**C4**	70	0
			C6	74	0
$PhCH_2$	S	**11/17**	**C4**	75	0
			C6	79	0

Reaction conditions: **donor** (1 equiv., 0.2 mmol), **14a** (3 equiv., 0.6 mmol); yields of isolated product after column chromatography.

In view of these unsatisfactory results and taking into account our group precedent,[72] we designed another pronucleophile for solving the above mentioned problems. As part of their Doctoral Thesis in our laboratory, Etxabe, Izquierdo, et al. described the use of 2-(benzylthio)-1,5-dihydro-4*H*-imidazol-4-ones as synthetic equivalents of imidazolones in reactions that proceed under Brønsted base/H-bonding catalysis (Scheme 44).

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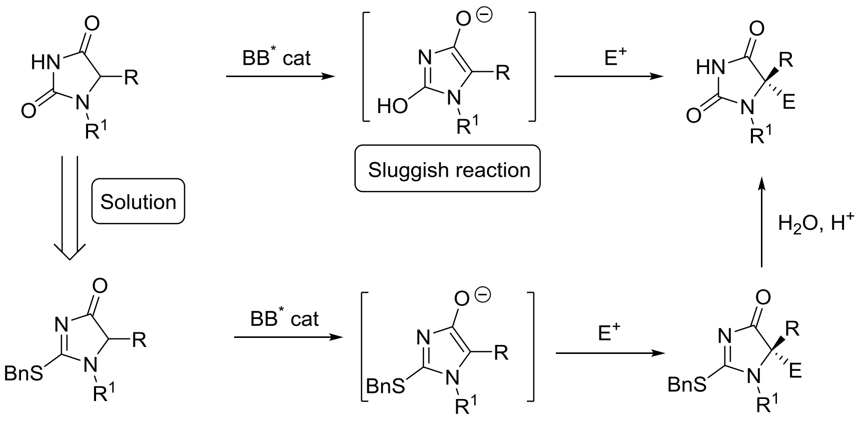
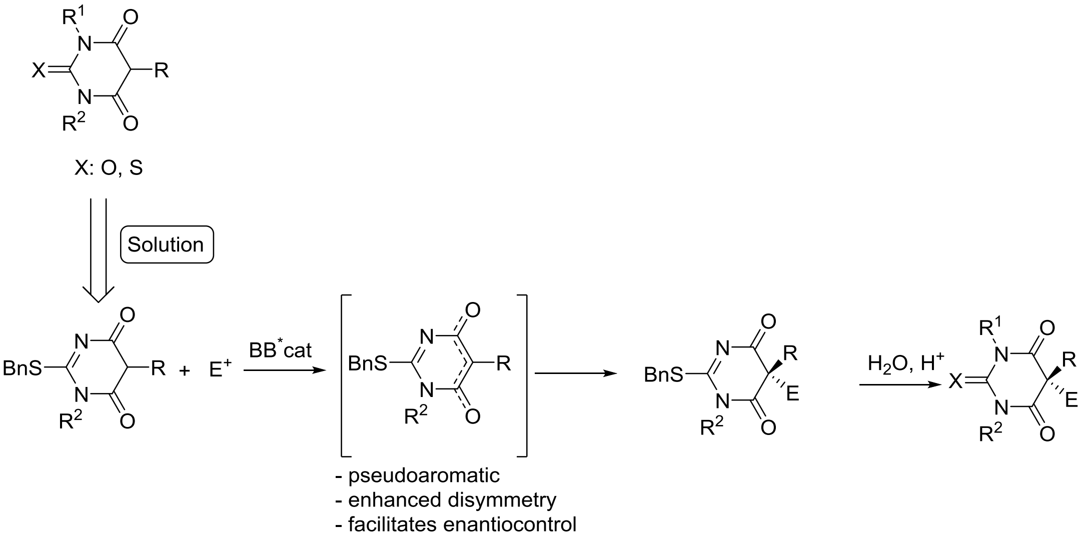
[72] Etxabe, J.; Izquierdo, J.; Aitor, l.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed*. **2015**, *54*, 6883–6886.


BB* cat
Sluggish reaction
Solution
E+
H2O, H+
BB* cat
E+

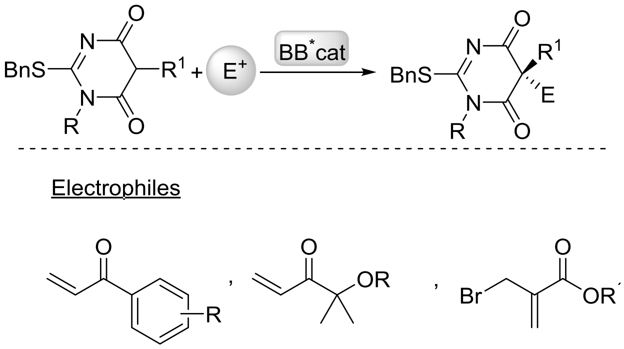
Scheme 44. Our laboratory precedents in the use of *S*-benzyl heterocycles as proNu in BB-cat additions.

Inspired by these precedents, we proposed a similar scheme to apply to our case. The 2-benzylthio-4,6-dioxopyrimidine structure would meet the following characteristics: (i) easy conversion into the barbituric acid via standard hydrolytic conditions, (ii) enhancement of structural dissymmetry as compared to the nearly symmetric starting diimides and (iii) suitability toward deprotonation promoted by a weak base, because the formed enolate would be *pseudo*aromatic (Scheme 45).


X: O, S
Solution
BB*cat
H2O, H+
- pseudoaromatic
- enhanced disymmetry
- facilitates enantiocontrol

Scheme 45. Similar strategy for the barbituric acids.

To validate our hypothesis we selected three different electrophiles for study, on the one hand, vinyl ketones and acrylates or acrylate equivalents as Michael acceptors and Morita-Baylis-Hillmann type allyl bromides as alkylating agents. To achieve our goal we chose different Brønsted bases and, at the same time, a new ones were synthetized for achieve this purpose (Scheme 46).



Scheme 46. General scheme.

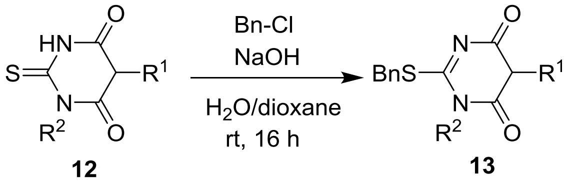
2.2.2. **Synthesis of 2-benzylthio-4,6-dioxopyrimidines 13**

The synthesis of the new BnS-derivatives **13** was carried out by treatment of thiobarbituric acids **12** with sodium hydroxide and benzyl chloride, in a mixture of dioxane/water.[73] When the reaction finished, the mixture was treated with hydrochloric acid to make the solution acidic, and the resulting precipitate was filtered and washed with methanol and dried (735 mmHg, 80 °C). In this way, products **13** were obtained as white, high melting point solids (above 180 °C) (Table 2) with yields from moderate to good.

---

[73] Rakhimov, A. I.; Avdeev, S. A.; Chang, L. T. D. *Russ. J. Gen. Chem*. **2009**, *79*, 338–339.

Table 2. Synthesis of 2-benzylthio-4.6-dioxopyrimidines.



Entry		R^1	R^2	Yield (%)
1	**13Aa**	Me	Me	91
2	**13Ab**	Me	Bn	48
3	**13Ac**	Me	Pent	51
4	**13Ad**	Me	Ph	46
5	**13Ae**	Me	3,5-bis(trifluoromethyl)phenyl	57
6	**13Ba**	Et	Me	58
7	**13Ca**	Bn	Me	68
8	**13Da**	^{i}But	Me	52
9	**13Ea**	^{i}Prop	Me	78
10	**13Fa**	Allyl	Me	57

As judged by the ^{1}H NMR of the crude sample (e.g. **13Aa**, Figure 14), it seems that the enolic form is predominant in $CDCl_3$ solution, as we can observe clearly a singlet signal for the Me at C5 position (1.97 ppm).

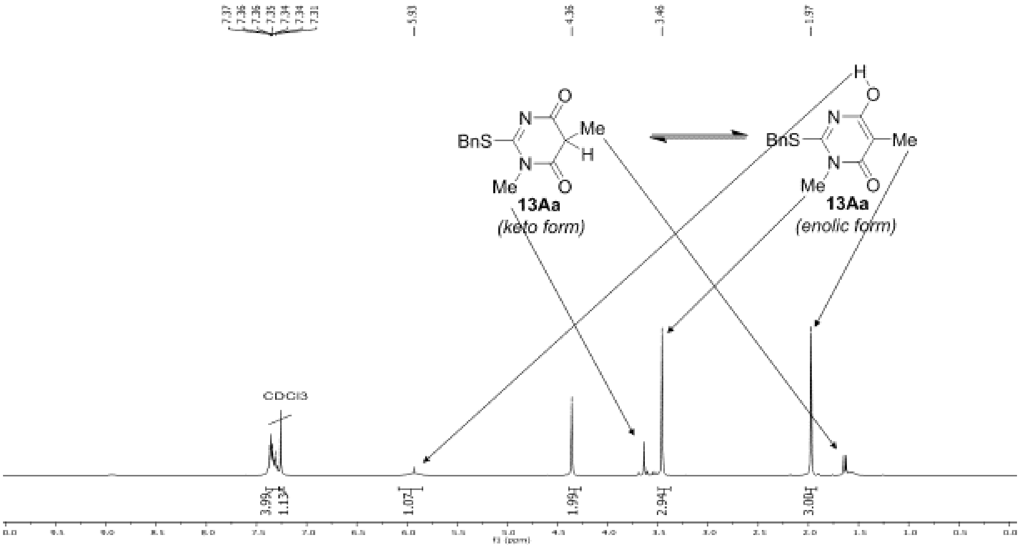


Figure 14. Sample NMR spectrum.

2.2.3. **Michael addition of 13 to enones**

With the new barbituric acid equivalents **13** in hand, their behaviour in the BB-catalyzed Michael reactions with enones was explored first. The study began with the evaluation of several Brønsted base catalysts for the addition reaction of 2-(benzylthio)-derivative **13Aa** to aryl vinyl ketone **14a**. It was gratifying to observe that the reaction in CH_2Cl_2 at rt for 16 h in the presence of known thiourea catalyst **C1** and urea catalyst **C2** (10 mol %), afforded product **19** in isolated yields of 71% and 67%, respectively, and 36% *ee* and 66% *ee*. In order to improve yield, but especially enantioselectivity, a set of additional bifunctional BB/H-bond catalysts were tried .Using as catalyst squaramide **C3**[74] the reaction showed very low reactivity, so, the *ee* was not determined, and with squaramide catalyst **C4**[75] the *ee* was 32%, yet unsatisfactory. In view of these results, we prepared and checked some catalysts with a modified aromatic moiety at the squaramide *N*-terminus. Thus the ester and amide bearing catalysts **C5–C9** all led to the desired addition adduct in selectivities in the range 54–75% *ee*´s. **C6** gives the lowest value of *ee* (54%).Then, cat **C10** and **C11** both with a polyaromatic congested group, and concomitantly developed in our group,[76] were evaluated. Catalyst **C10** provided product **19** in good yield (72%) and with 80% *ee* at room temperature (96% *ee* at 0 °C). The *O*-silyl analogue **C11** gave similar selectivity but the reaction was comparatively much slower (Table 3).

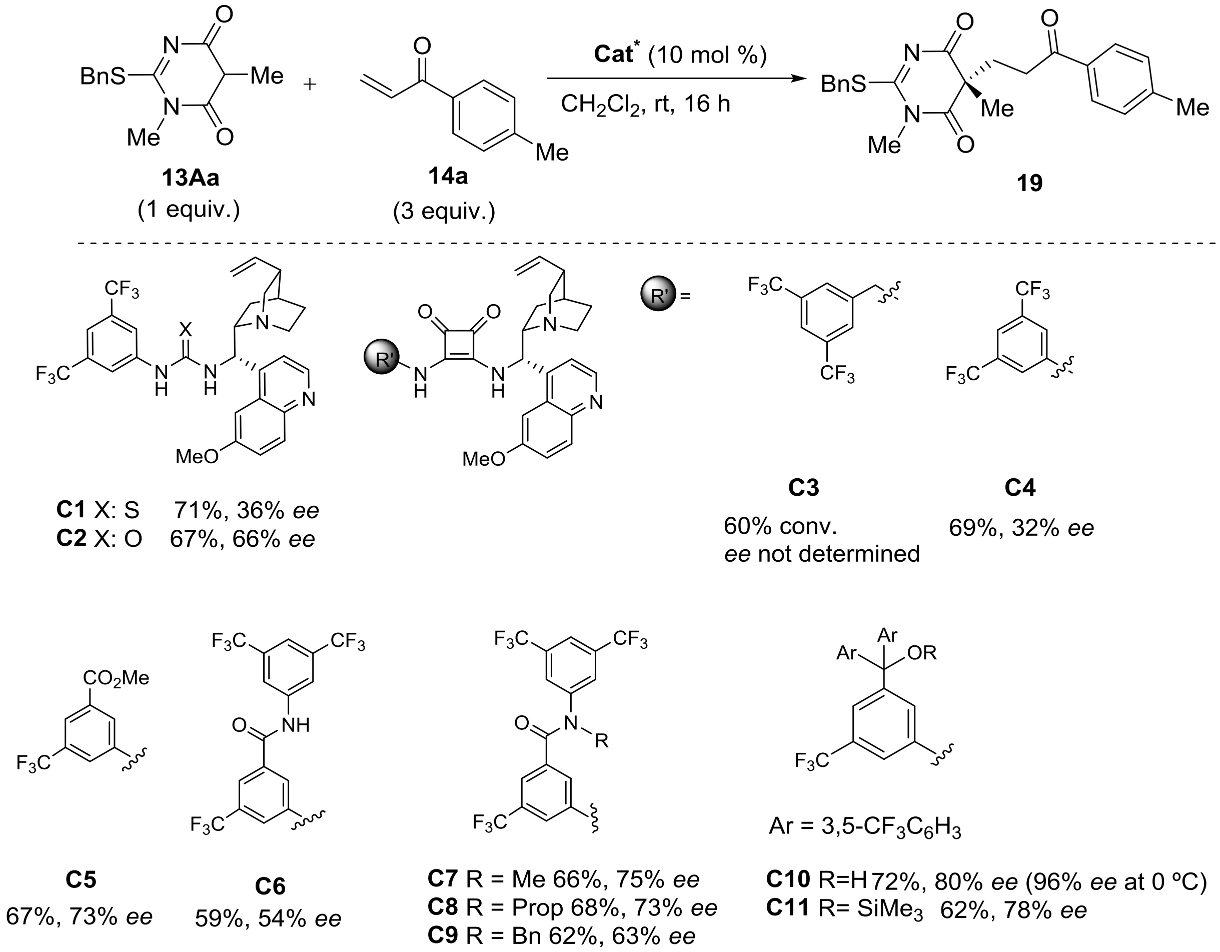
---

[74] a) Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2010**, *132*, 2775–2783. b) Malerich, J. P.; Hagihara, K.; Rawal, V. R. *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417.

75 a) Dai, L.; Wang, S. X.; Chen, F. E. *Adv. Synth. Catal*. **2010**, *352*, 2137–2141. b) Yang, W.; Du, D. M. *Org. Lett*. **2010**, *12*, 5450–5453.

[76] Odriozola, A.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 12758–12762.

Table 3. Catalyst screening for the reaction of **13Aa** with **14a** to give **19**.


BnS
Me
O
N
13Aa
(1 equiv.)
14a
(3 equiv.)
Cat* (10 mol %)
CH2Cl2, rt, 16 h
19
R' =
CF3
F3C
X
MeO
C1 X: S 71%, 36% ee
C2 X: O 67%, 66% ee
C3
60% conv.
ee not determined
C4
69%, 32% ee
CO2Me
NH
R
Ar
OR
Ar = 3,5-CF3C6H3
C5
67%, 73% ee
C6
59%, 54% ee
C7 R = Me 66%, 75% ee
C8 R = Prop 68%, 73% ee
C9 R = Bn 62%, 63% ee
C10 R=H 72%, 80% ee (96% ee at 0 ºC)
C11 R= SiMe3 62%, 78% ee

Reaction conditions: **13Aa** (1 equiv., 0.2 mmol), **14a** (3 equiv., 0.6 mmol); yields of isolated product after column chromatography; reaction time 16 h except for the catalyst **C3** (48 h); *ee*´s determinated by chiral HPLC column IA eluting with Hex/^{i}PrOH 80:20 f = 0.5 mL/min.

Figure 15 shows the ^{1}H NMR spectrum of the crude material for the **C10** catalyzed reaction between **13Aa** and aryl vinyl ketone **14a** after 16 h.

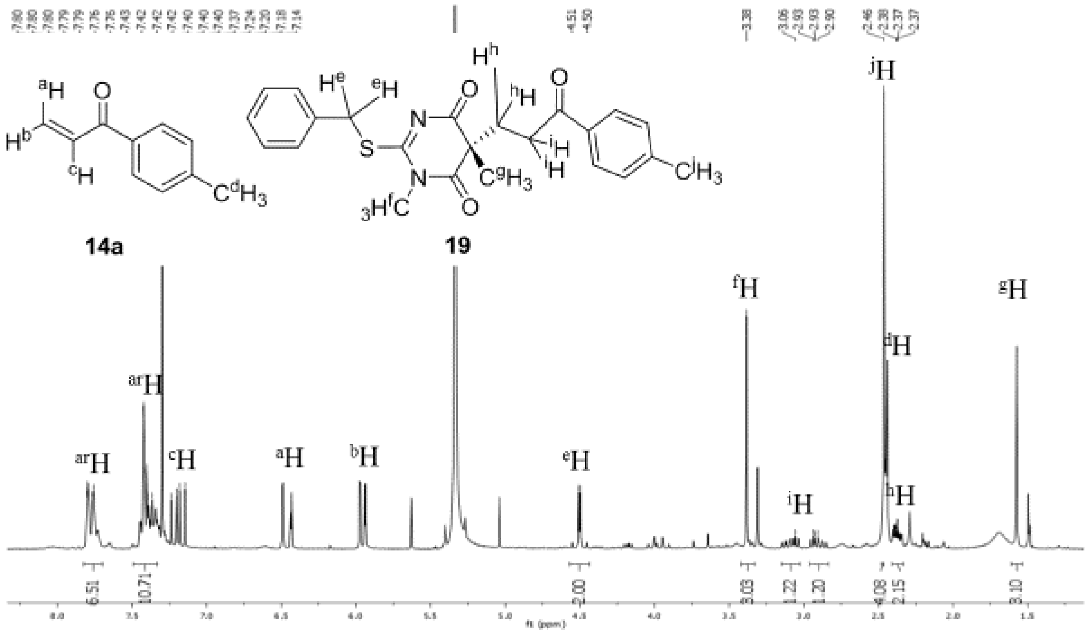
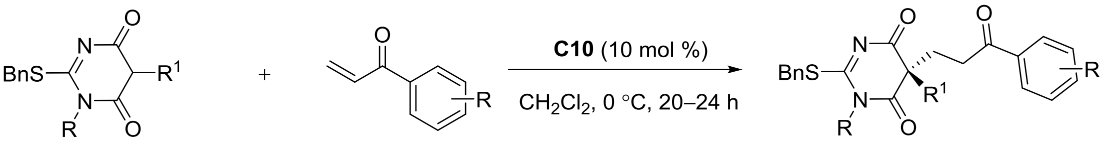


Figure 15. ^{1}H-NMR spectrum of crude reaction product between **14a** and **13Aa** catalyzed by **C10**.

2.2.3.1. **Reaction scope**

Once with the optimal conditions in hand, a range of dioxopyrimidines **13** were evaluated for the addition to several aryl vinyl ketones **14**. The catalytic reaction was robust with respect to the acceptor enone, and aryl vinyl ketone with either electron withdrawing (**14b**) or donor aryl groups (**14a**, **14c**, **14d** and **14e**) were well tolerated giving *ee*´s from 85% to 96%. As the data in Table 4 show, apart from the 5-Me substituted template, derivatives with a Et, Bn, and allyl R^1 group at C5, all worked well, affording the corresponding quaternary products in yields ranging from 65% to 75% and excellent *ee* for all the cases. We also checked the reaction of templates **13** with different substitution at *N* position. Thus, it was confirmed that the reaction worked very well with 2-benzylthio-4,6-dioxopyrimidines bearing Me, Bn, bis(trifluoromethyl)phenyl , and *n*-pentyl R groups affording products in 65–73% yield and with *ee*´s from 90% to 92% (Table 4).

Table 4. Scope of the reaction of 2-benzylthio-4,6-dioxopyrimidines **13** with aryl vinyl ketones **14**.


BnS
R¹
R
+
R
C10 (10 mol %)
CH$_2$Cl$_2$, 0 °C, 20–24 h
BnS
R¹
R
R

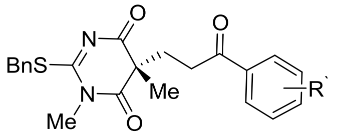
13

14a-14e
(3 equiv.)

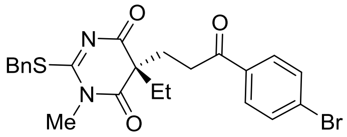
19–29

	R¹	R²
13Aa	Me	Me
13Ab	Me	Bn
13Ac	Me	Pen
13Ad	Me	Ph
13Ae	Me	3,5-bis (trifluoromethyl)phenyl
13Ba	Et	Me
13Ca	Bn	Me
13Da	^{i}But	Me
13Ea	^{i}Prop	Me
13Fa	Allyl	Me

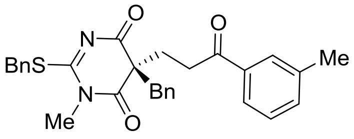
	R
14a	4-Me
14b	4-Br
14c	H
14d	2-Me
14e	3-Me



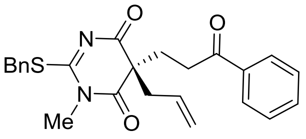
19	R′: 4-Me,	72%, 96% *ee*
20	R′: 4-Br,	63%, 95% *ee*
21	R′: H,	61%, 92% *ee*
22	R′: 2-Me,	72%, 85% *ee*
23	R′: 3-Me,	62%, 96% *ee*



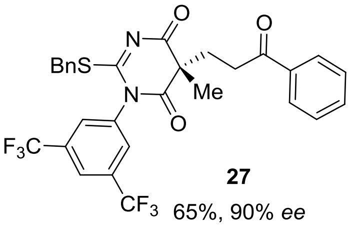
24
71%, 97% *ee*



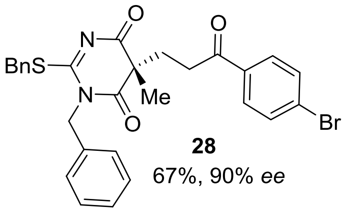
25
75%, 94% *ee*



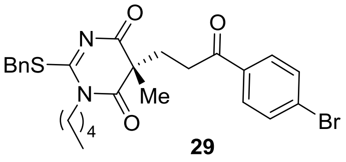
26
65%, 92% *ee*


BnS
Me
F$_3$C
CF$_3$

27
65%, 90% *ee*



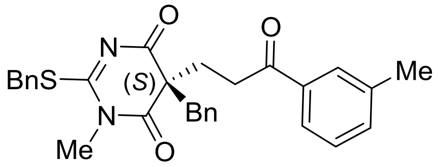
28
67%, 90% *ee*



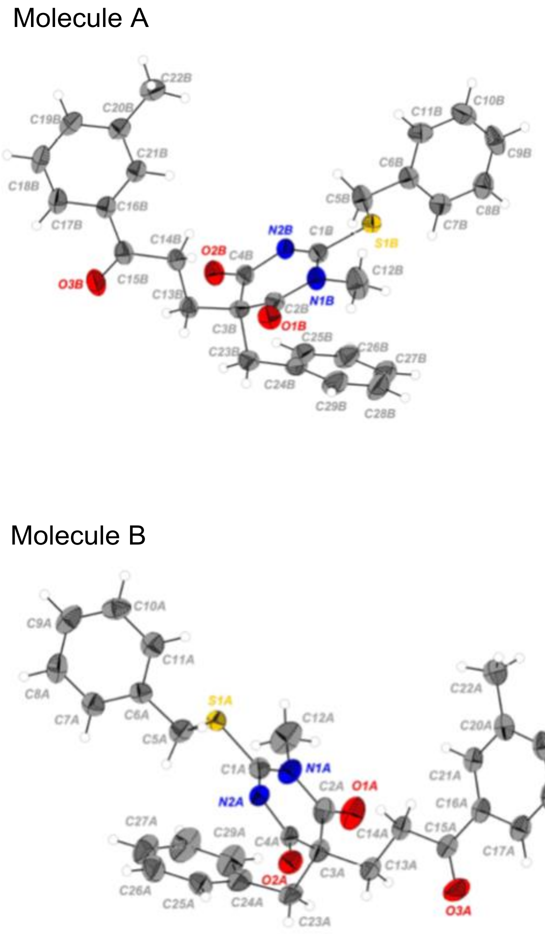
29
73%, 92% *ee*

Reaction conditions: **13** (1 equiv., 0.2 mmol), **14** (3 equiv., 0.6 mmol); yields of isolated product after column chromatography.

Crystallization of adduct **25**, obtained from the Michael addition of **13Ca** to enone **14e**, allowed to obtain a crystalline compound for X-ray structure analysis and unambiguous determination of its absolute configuration (Figure 16). Configuration of the remaining adducts was assigned by analogy and by assuming an uniform reaction mechanism.


O
N
O
BnS
(S)
Me
N
Bn
Me
O

25
75%, 94% *ee*

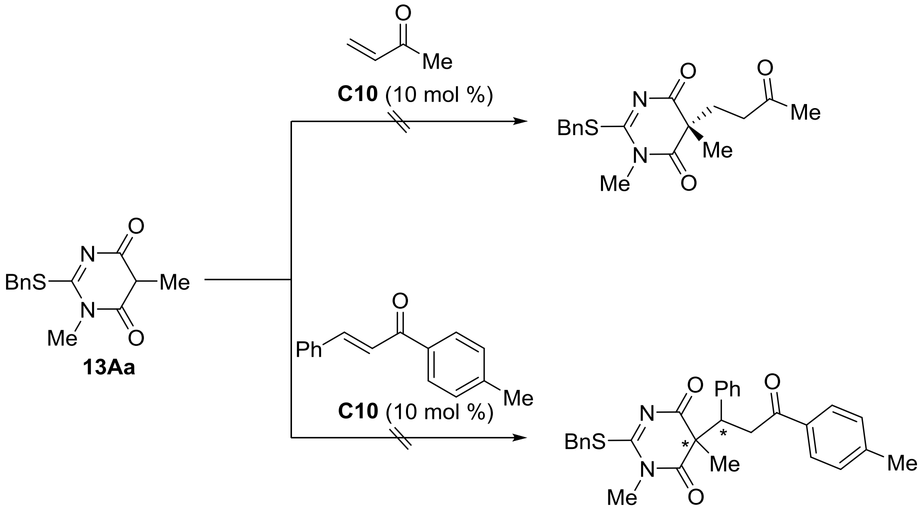

Molecule A

Molecule B
C22B
C19B
C20B
C21B
C18B
C16B
C17B
C14B
O2B
C4B
N2B
C1B
O3B
C15B
C13B
C3B
O1B
C2B
N1B
C23B
C24B
C25B
C26B
C27B
C29B
C28B
C11B
C10B
C6B
C9B
C5B
C8B
S1B
C7B
C12B
C10A
C9A
C11A
C8A
C7A
C6A
S1A
C5A
C12A
C1A
N1A
N2A
C2A
O1A
C27A
C29A
C4A
C14A
C26A
C25A
C24A
O2A
C3A
C13A
C23A
C22A
C20A
C19A
C21A
C16A
C15A
C18A
C17A
O3A

Figure 16. ORTEP diagram of compound **25**

As these results show the method is general for a range of aryl vinyl ketones as electrophiles. However, attempts to expand this protocol to different unsaturated ketones such as methyl vinyl ketone and β-substituted aryl vinyl ketones, failed. For example, the reaction of **13Aa** with methyl vinyl ketone using **C10** as catalyst did not work, probably because of the comparatively lower reactivity of this electrophile. Similarly, the attempted reaction of **13Aa** with β-substituted phenyl vinyl ketone using the same catalyst did not proceed and starting material was recovered unchanged. In this case, the lower reactivity could be due to steric reasons (Table 5).

Table 5. Different ketones.

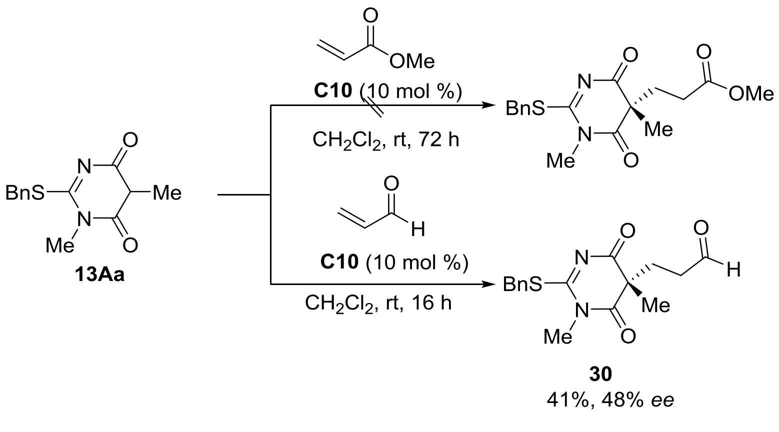

Me
C10 (10 mol %)
BnS
Me
13Aa
Ph
C10 (10 mol %)
Me
BnS
Me
Me
BnS
Ph
Me
Me
Me

Reaction conditions: **13Aa** (1 equiv., 0.2 mmol), but-3-en-2-one or (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (3 equiv., 0.6 mmol), catalyst **C10** (10 mol %) were stirred at room temperature for 72 h in CH_2Cl_2 (0.5 mL).

2.2.4. **Michael addition of 13 to α´-oxy enones as enabling acrylate ester equivalent.**

Similarly, attempts to apply the method to common Michael acceptors other than enones, such as unsaturated esters and aldehydes, were unfruitful too. For example, the reaction of **13Aa** with an *α,β*-unsaturated ester using **C10** as catalyst did not work. However, in opposite direction, the more reactive but less sterically demanding acrolein, upon reaction with **13Aa**, led to, after hydrolysis, adduct **30**, but with a poor 48% *ee* (Table 6).

Table 6. Different carbonylic Michael acceptors.


OMe
C10 (10 mol %)
CH2Cl2, rt, 72 h
BnS
OMe
Me
BnS
Me
13Aa
H
C10 (10 mol %)
CH2Cl2, rt, 16 h
BnS
H
Me
30
41%, 48% ee

Reaction conditions: **13Aa** (1 equiv., 0.2 mmol), methyl acrylate or acrolein (3 equiv., 0.6 mmol), catalyst **C10** (10 mol %) were stirred at room temperature for stated time in CH_2Cl_2 (0.5 mL); yields of isolated product after column chromatography.

To solve these limitations that hamper extension of the approach to the obtention of relevant ester and aldehyde products, we turned our attention to the use of α-silyloxy enone as an equivalent of either acrylates/acrolein/vinyl ketones (Figure 17). This type of bidentated acceptor has demonstrated to be very versatile for a number of BB-catalyzed asymmetric conjugate additions of C-centered soft nucleophiles,[77] by virtue of its ability for internal 1,4-H (or 1,4-metal) chelation and also H-bond networking with the catalyst.

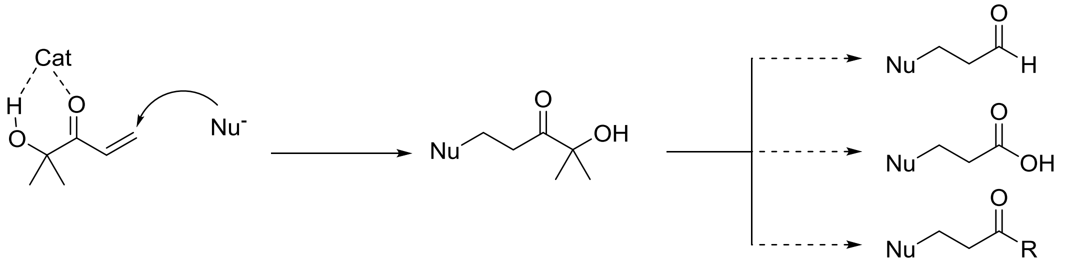


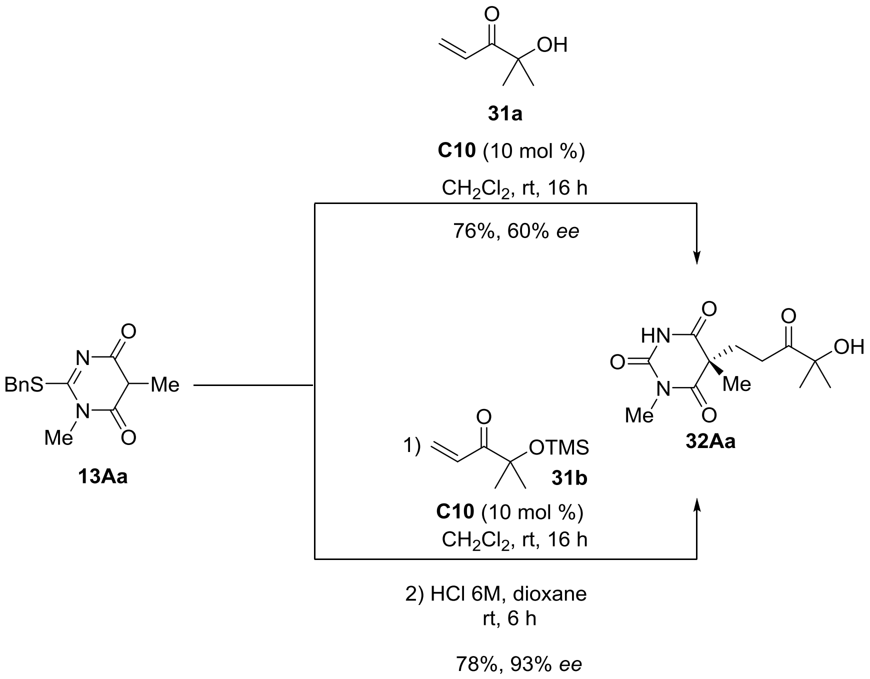
Figure 17. Synthetic equivalents of the ketol moiety.

In a first experiment, **13Aa** was reacted with **31a** giving the desired product (**32Aa**) in 76% yield and 60% *ee*, demonstrating that this type of enones are more active as it has been indicated above. Subsequently, the reaction with α′-silyloxy **31b** was checked. The crude reaction product in this case was treated with HCl 6M to deprotect the silyl ether, and same adduct **32Aa** was obtained in 78% yield after two steps and with 93% *ee* (Scheme 47).

These results encouraged us to explore the scope of the reaction for differently substituted **13** using silyloxy enone **31b**.

---

[77] For more information about α-hydroxyenone reactions: a) Sanchez-Duque, M. M.; Basle, O.; Isambert, N.; Gaudel, N.; Siri, A.; Genisson, Y.; Plaquevent, J. C.; Rodriguez, J.; Constantieux, T. *Org.Lett.* **2011**,*13*, 3296–3299. b) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. *J. Am. Chem.Soc.* **1979**, *101*, 7077–7079. c) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Lecumberri, A.; Linden, A. *J. Am.Chem. Soc.* **2002**, *124*, 10288–10289. d) Badiola, E.; Fiser, B.; Gomez-Bengoa, E.; Mielgo, A.; Olaizola, I; Urruzuno, I.; Garcia, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.

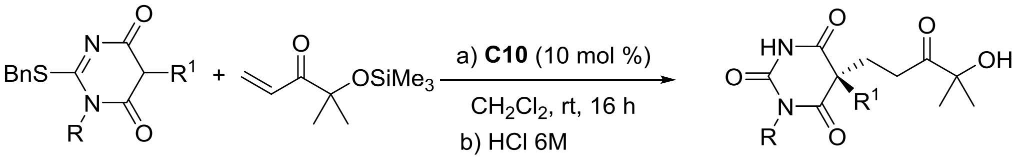

31a
C10 (10 mol %)
CH2Cl2, rt, 16 h
76%, 60% ee
13Aa
32Aa
1)
31b
C10 (10 mol %)
CH2Cl2, rt, 16 h
2) HCl 6M, dioxane
rt, 6 h
78%, 93% ee

Scheme 47. Michael addition of **13Aa** to *α*´-oxy enones.

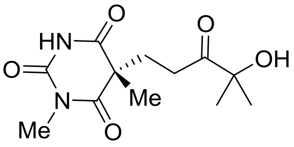
2.2.4.1. Reaction scope

Next, the generality of the reaction with respect to the 2-bezylthio-4,6-dioxopyrimidines templates was evaluated. Adducts from these reactions were isolated after acidic hydrolysis leading to barbituric acids **32**. As data in the Table 7 show, products **32** bearing linear/branched alkyl or allyl R^1 substituents are isolated in good yields and enantioselectivities typically above 90%, with isopropyl being an exception, probably due to steric reasons. Different R substitutions were checked too, with Me, Bn, Ph and pentyl groups, all leading to proceed in good yields and enantioselectivities above 90% (Table 7).

Table 7. Scope of the reaction of 2-benzylthio-4,6-dioxopyrimidines **13** with α′-silyloxy enone **31b**.

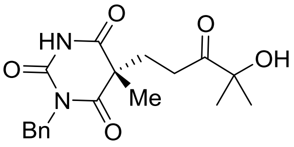

BnS
R^1
R
OSiMe$_3$
a) **C10** (10 mol %)
CH$_2$Cl$_2$, rt, 16 h
b) HCl 6M
dioxane, 6 h
OH
R^1
R

13 **31b** **32**



32Aa

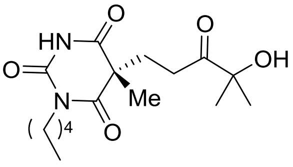
82%, 90% *ee*



32Ab

61%, 81% *ee*,

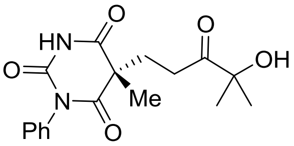
with **C9** 64%, 87% *ee*



32Ac

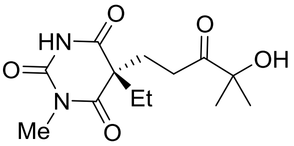
63%, 83% *ee*,

with **C9** 65%, 87% *ee*



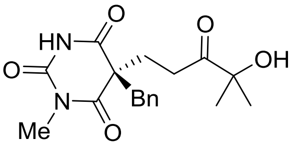
32Ad

62%, 90% *ee*



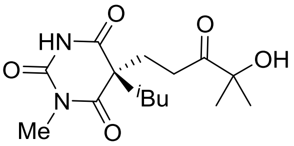
32Ba

71%, 94% *ee*



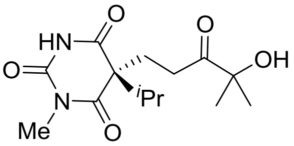
32Ca

70%, 92% *ee*



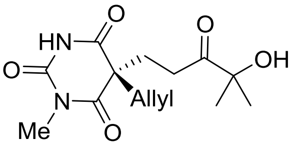
32Da

68%, 93% *ee*



32Ea

--, --



32Fa

72%, 92% *ee*

Reaction conditions: **13** (1 equiv, 0.2 mmol), **31b** (3 equiv, 0.6 mmol); yields of isolated product after column chromatography.

The absolute configuration of adduct **32Ad** was determined by a single-crystal X-ray analysis (Figure 18), it was the same as with previous enones and that of the remaining adducts was assumed based on a uniform reaction mechanism.

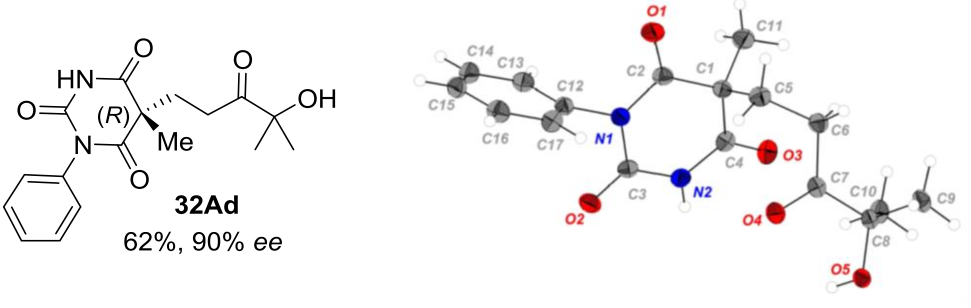
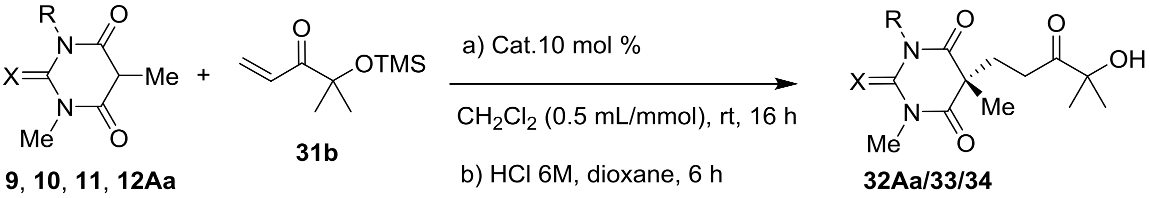

(R)
Me
OH
32Ad
62%, 90% ee
O1
C11
C14
C13
C2
C1
C5
C12
C15
N1
C6
C16
C17
O3
C4
N2
C7
C3
C10
C9
O2
O4
C8
O5

Figure 18. ORTEP diagram of compound **32Ad.**

Once again, we confirmed that designed 2-benzylthio-4,6-dioxopyrimidine reagent was essential for successful reactivity and selectivity. As data in Table 8 show, when (thio)barbituric acids **9** and **12Aa** were used instead, adduct **32Aa** was obtained with good yields (61–69%) but essentially racemic. Similarly, the *N*-Bn analogues **10** and **11** gave **33** and **34**, respectively, as racemic compounds too, irrespective of the catalyst employed.

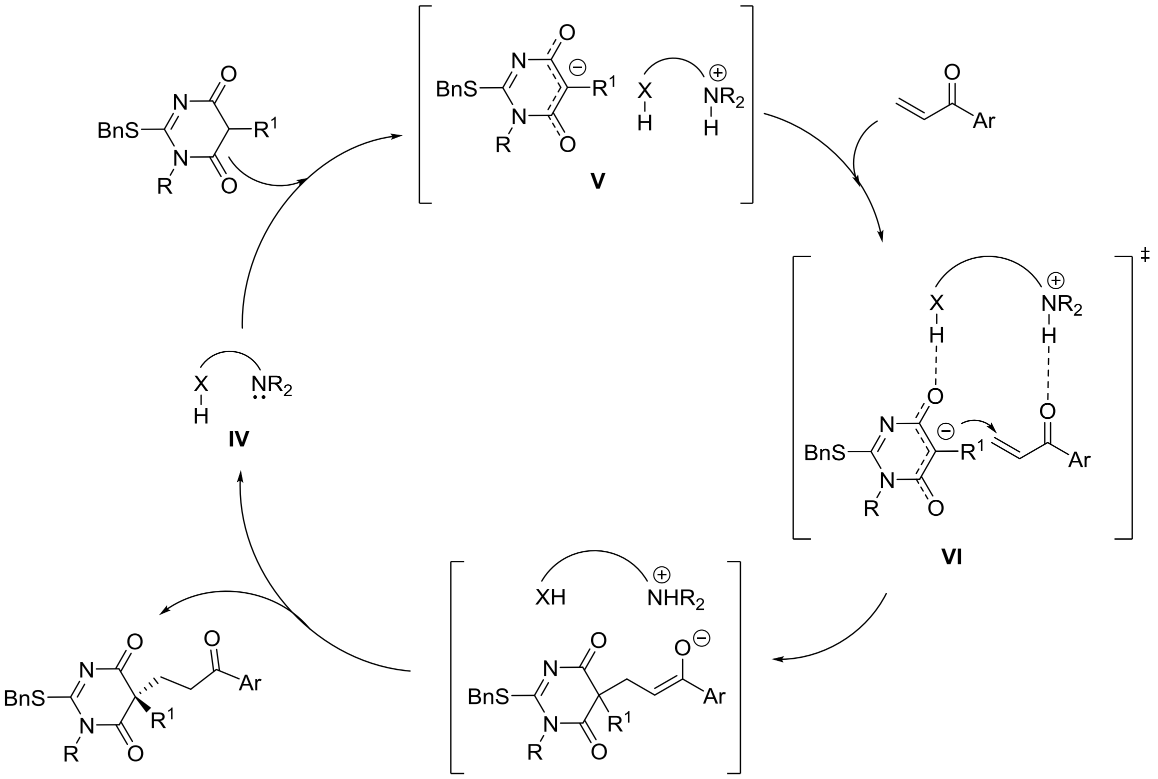
Table 8. Results using (thio)barbituric substrates **9**-**12**.


R
O
N
X
Me
+
N
Me
O
9, 10, 11, 12Aa
O
OTMS
31b
a) Cat.10 mol %
CH2Cl2 (0.5 mL/mmol), rt, 16 h
b) HCl 6M, dioxane, 6 h
R
O
O
N
OH
X
Me
N
Me
O
32Aa/33/34

R	X	Pro-Nu	Catalyst	Adduct	Yield (%)	*ee* (%)
H	O	**9**	**C2**	**32Aa**	62	0
			C4		61	0
			C6		61	0
H	S	**12Aa**	**C2**	**32Aa**	67	0
			C4		64	0
			C6		69	0
$PhCH_2$	O	**10**	**C2**	**33**	72	0
			C4		60	0
			C6		68	0
$PhCH_2$	S	**11**	**C2**	**34**	63	0
			C4		73	0
			C6		74	0

2.2.5. **Mechanistic proposal**

We assume that these catalytic reactions proceed along the generally accepted activation mechanisms for these types of bifunctional catalysts. First step would be deprotonation of the dihydropyrimidine by the tertiary amine group, forming a highly nucleophilic enolate specie (**V**). Then, the *C-C* bond forming approaching takes place wherein the electrophile interacts with the protonated amine moiety *via* H-bond, enhancing, this way, the electrophilic character of the reacting carbon center and the enolate coordinates to the other H-bond donor site of the catalyst (TS **VI**) (Scheme 48).



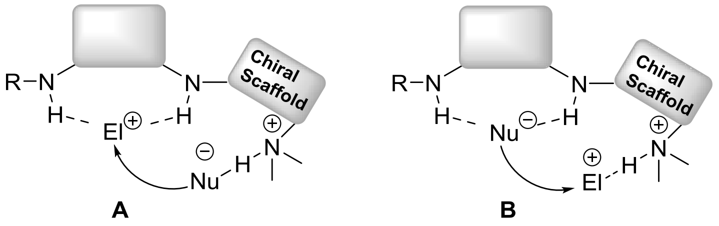
Scheme 48. Supposed global process

For the stereochemistry determining step, two different geometries can be envisaged for the Nu-cat-E ternary complex (Scheme 49): in (A) the electrophile (E^+) is H-bonded to the thiourea and the nucleophile (Nu^-) coordinates to the tertiary amine (Takemoto model),[78] while in (B), the electrophile and nucleophile reactants swicht their coordination position relative to the catalyst (Pápai model).[79] In model B, the thiourea, an efficient anion acceptor, binds the anionic nucleophile, while the protonated quinuclidine activates and positions the electrophile.

---

[78] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119–125.

[79] Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631–5639. For similar models, see: b) Almasi, D.; Alonso, D. A.; Gomez-Bengoa, E.; Nájera, C. *J. Org. Chem*. **2009**, *74*, 6163–6168. c) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *J. Org. Lett*. **2010**, *12*, 2682–2685. d) Han,


R−N
H
El⊕
H
N
Chiral Scaffold
⊕
N
⊖
Nu
H
A
R−N
H
Nu⊖
H
N
Chiral Scaffold
⊕
N
⊕
El
H
B

Scheme 49. Transition-state variants of the bifunctional mechanisms.

According to these premises, the two models in Figure 19 may account for the observed stereochemistry. However, we believed that model b is more favorable than a due to in model a steric interactions between R and the Nitrogen atom of quinuclidine ring, making more difficult the interactions between the nucleophile and the catalyst.

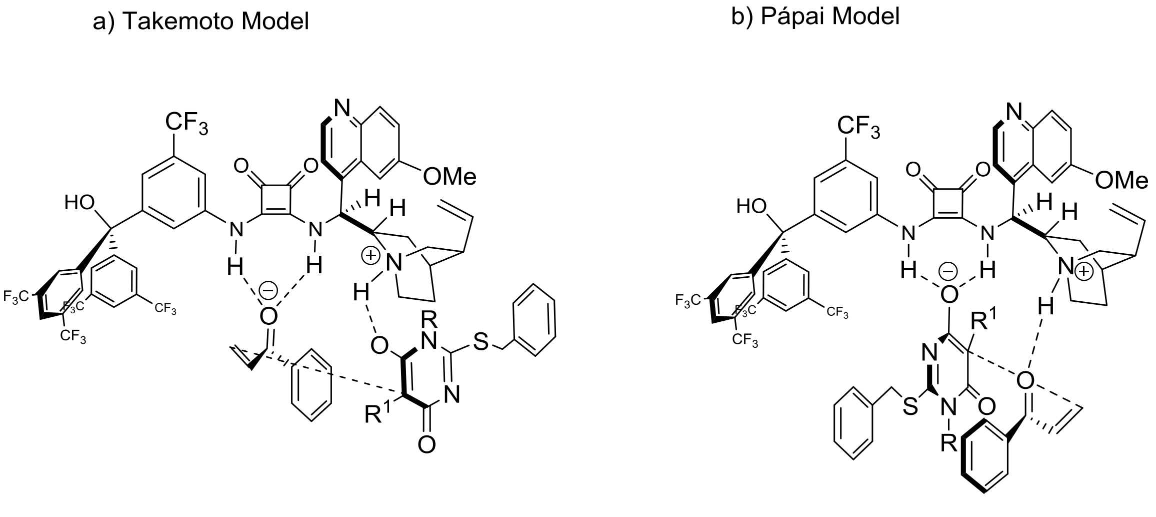

a) Takemoto Model
b) Pápai Model
CF3
HO
F3C
F3C
CF3
CF3
O
O
N
H
N
H
⊖
O
N
OMe
H
H
⊕
N
H
O
R
N
S
N
R1
O
CF3
HO
F3C
F3C
CF3
CF3
O
O
N
H
N
H
⊖
O
N
OMe
H
H
N⊕
H
R1
N
S
N
R
O
O

Figure 19. Plausible transition states.

X.; Lee, R.; Chen, T.; Luo, J.; Lu, Y.; Huang, K. W. *Sci. Rep.* **2013**, *3*, 2557–2563. e) Azuma, T.; Kobayashi, Y.; Sakata, K.; Sasamori, T.; Tokitoh, N.; Takemoto, Y. *J. Org. Chem.* **2014**, *79*, 1805–1817.

2.2.6. Extension to other acceptors: vinyl sulfones and azodicarboxylates

Vinyl sulfones:

As a logical continuation of the study, we set to validate this template-catalyst system against vinyl sulfones and azodicarboxylates as two additional examples of relevant electrophilic reagents. Since sulfone functionality can be removed by various desulfonylation methods, aryl sulfones have been employed as electron withdrawing groups to increase the electrophilicity or nucleophilicity of a parent reagent. Thus, subsequent desulfonation of adducts gives raise to a wide range of enantiomerically enriched building blocks.[80] We checked the reaction of 2-benzylthio-4,6-dioxopyrimidine **13Aa** with vinyl sulfone **35** bearing the 1*H*-tetrazole moiety, with different Brønsted bases (Table 9). The product **36** was afforded in yields ranging from 58%-73%. However, using the thiourea catalyst **C1**, the urea catalyst **C2** and the ureidopeptide catalyst **C16** the product was obtained racemic. By using the new squaramide Brønsted base catalysts **C10**, **C11** and **C20** product **36** was obtained, but with *ee* in the range from 20% to 40%, so, further optimization is necessary. This reaction is currently under further optimization atudies.

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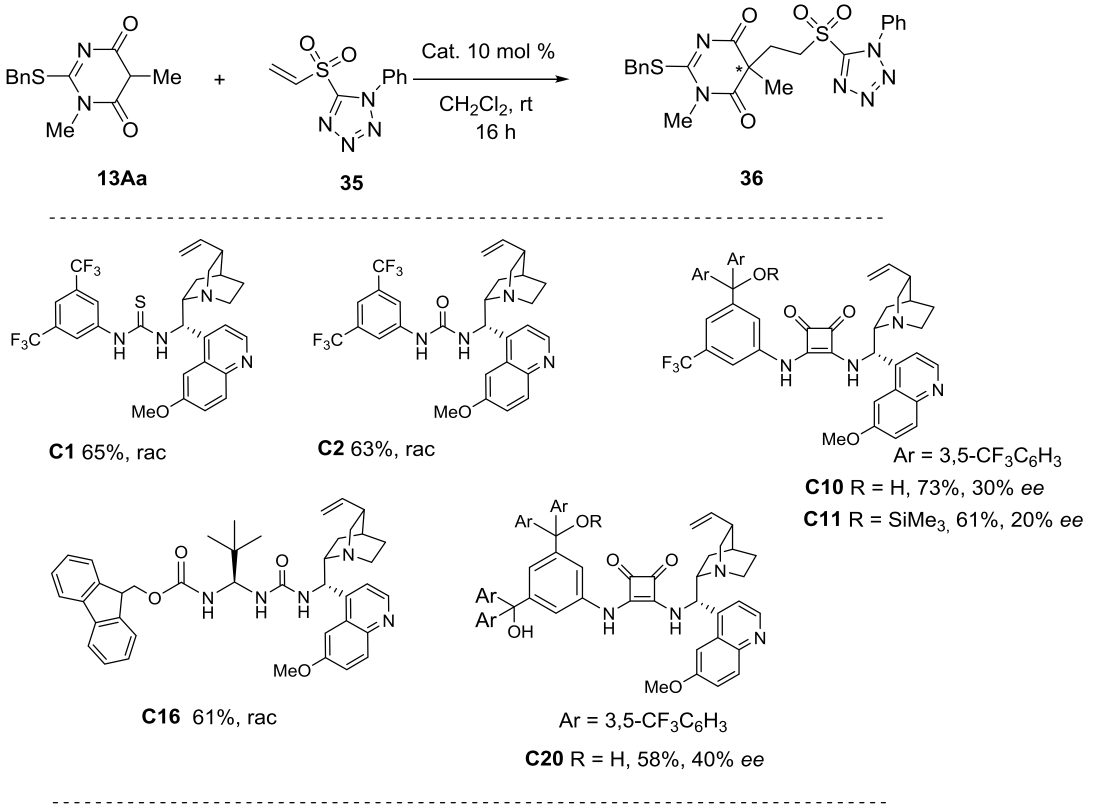
[80] Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2668–2679.

Table 9. Screening of catalyst.


BnS
Me
13Aa
35
Ph
Cat. 10 mol %
CH2Cl2, rt
16 h
36
C1 65%, rac
C2 63%, rac
Ar = 3,5-CF3C6H3
C10 R = H, 73%, 30% ee
C11 R = SiMe3, 61%, 20% ee
C16 61%, rac
Ar = 3,5-CF3C6H3
C20 R = H, 58%, 40% ee

Reaction conditions: **13Aa** (1 equiv, 0.2 mmol), **35** (1.2 equiv, 0.24 mmol); yields of isolated product after column chromatography; *ee*´s determinated by chiral HPLC: column IC eluting with Hex/^{i}PrOH 50:50 f = 1.0 mL/min.

Azadicarboxylates:

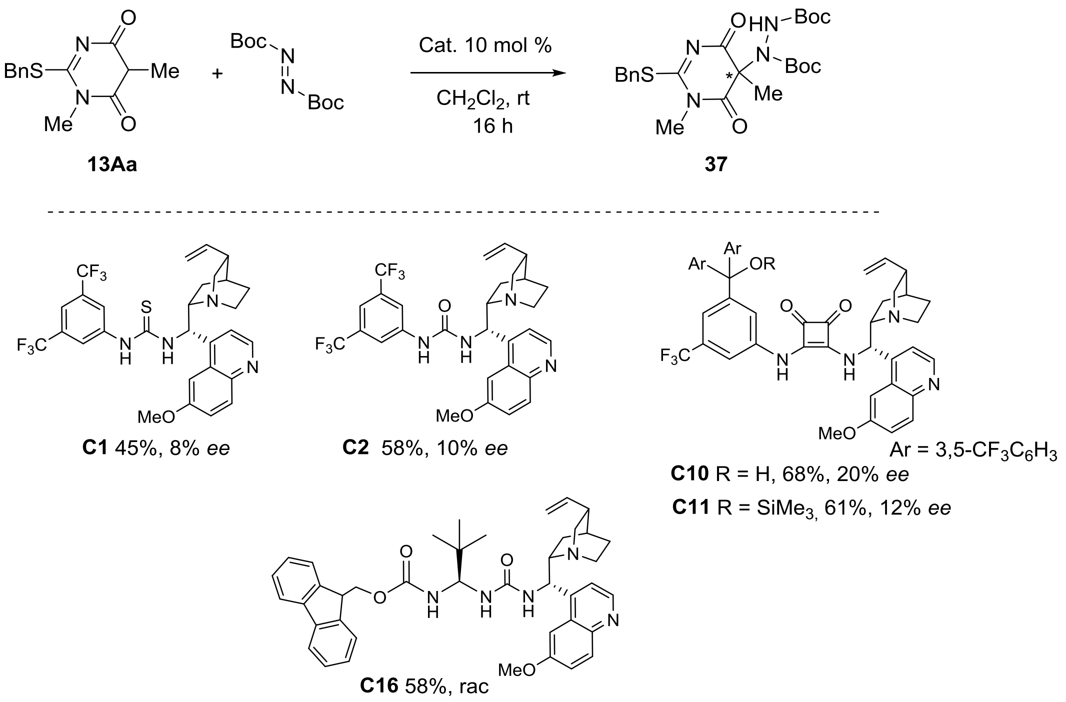
Besides C-alkylation reactions that afford quaternary all carbon stereocenters at C5 of the barbituric system, C-amination reactions are an interesting entry to tetrasubstituted C-N systems.[81]

We decided to test the reaction with 2-benzylthio-4,6-dioxopyrimidines **13Aa** and the commercially available *di*-*tert*-butyl (*E*)-azo-1,2-dicarboxylate in CH_2Cl_2 at rt using a 10 mol % of different catalysts (Table 10). Using thiourea catalyst **C1** and urea catalyst **C2** in 10 mol % catalytic loading, afforded the product **37** in moderate yields (45% and 58% respectively) but very low *ee*´s, 8% and 10% respectively. Then, the squaramide-based bifunctional catalysts **C10** and **C11** were tested. With **C10** the yield was improved up to 68% but the *ee*´s did not improve, 20% and 12% respectively. Finally, an ureidopeptide type catalyst **C16** was checked and we obtained the product with 58% yield but 0% *ee* was achieved. As in the previous case, further optimization is needed and other type of catalysts are currently being analyzed with the hope to obtain useful results.

---

[81] a) Suri, J. T.; Steiner, D. D.; Barbas, C. F. *Org. Lett.* **2005**, *18*, 3885–1888. b) Dalko, P.; Moisan, L. *Angew. Int. Ed.* **2004**, *43*, 5138–5175.

Table 10. Catalyst screening for the reaction of **13Aa** with *di*-*tert*-butyl (*E*)-azo-1,2-dicarboxylate .



13Aa

37

C1 45%, 8% *ee*

C2 58%, 10% *ee*

C10 R = H, 68%, 20% *ee*

C11 R = SiMe$_3$, 61%, 12% *ee*

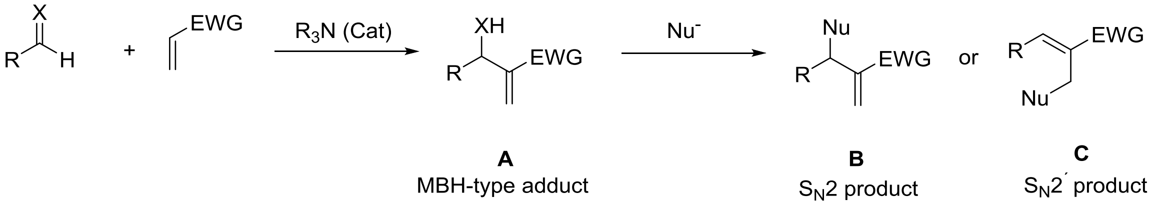
C16 58%, rac

Reaction conditions: **13Aa** (1 equiv, 0.2 mmol), *di*-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (1.2 equiv, 0.24 mmol); yields of isolated product after column chromatography; *ee*´s determinated by chiral HPLC: column IC eluting with Hex/^{i}PrOH 80:20 f = 0.5 mL/min.

2.2.7. Extension to allylic alkylation with Morita-Baylis-Hillmann type (pseudo)halogenides.

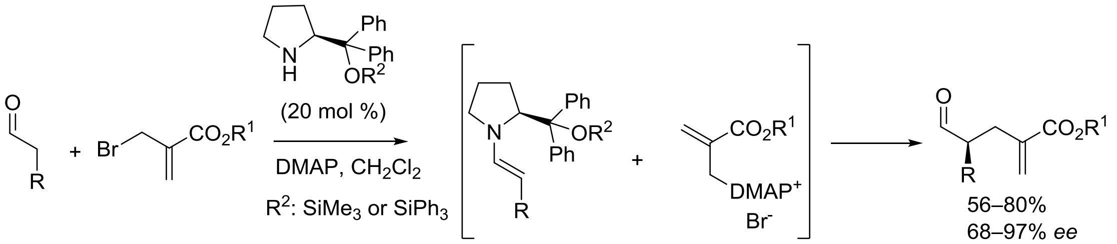
2.2.7.1. Initial experiments

MBH-type (*pseudo*)halides (A, Scheme 50) are synthetically useful electrophilic reactants because the adducts resulting from a nucleophilic displacement (B or C, Scheme 50) display a densely functionalized architecture amenable for further organic transformations.[82]


X
R
H
+
EWG
R_3N (Cat)
XH
R
EWG
Nu^-
Nu
R
EWG
or
R
EWG
Nu
A
MBH-type adduct
B
S_N2 product
C
S_N2' product

Scheme 50. S_N2 and S_N2'reaction pathways of MBH-type adducts.

In our own research group MBH type allylic bromides were employed in the first enamine-mediated direct asymmetric α-alkylation of aldehydes, in which the reaction is believed to proceed through a double S_N2`-type addition-elimination mechanism (Scheme 51).[83]


O
R
+ Br
CO_2R^1
N
H
Ph
Ph
OR^2
(20 mol %)
DMAP, CH_2Cl_2
R^2: $SiMe_3$ or $SiPh_3$
N
R
Ph
OR^2
Ph
+
CO_2R^1
$DMAP^+$
Br^-
O
R
CO_2R^1
56–80%
68–97% *ee*

Scheme 51. Amine-catalyzed α-alkylation of aldehydes with allyl halides.

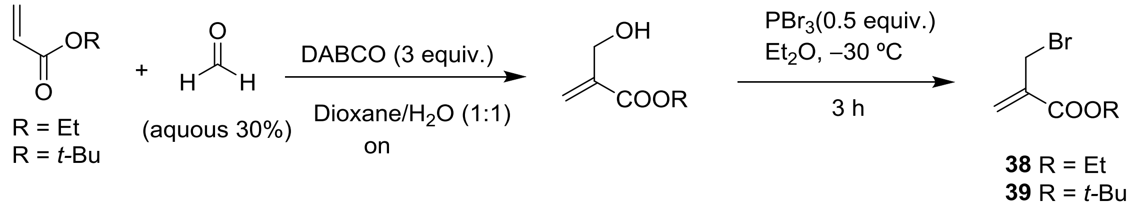
Once the BB-catalyzed conjugate additions of barbituric acid equivalents **13** to enones was demonstrated, we decided to test a slightly different type of reactivity with the same nucleophilic templates, in order to open a synthetic route to a broader range of quaternary barbituric acid derivatives. Specifically, we envisaged the use of allylic reagents **38**/**39** (MBH type (*pseudo*)halogenides), electrophilic reagents amenable to undergo a sequential addition/elimination pathway.

---

[82] For general reviews: a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659–6690. b) Liu, T. Y.; Xie, M.; Chen, Y. C. *Chem. Soc. Rev.* **2012**, *41*, 4101–4112.

[83] Gómez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353–357.

Allyl bromides were synthetized in two steps according to the procedure of Zhang[84] which involves Baylis-Hillman reaction of acrylate ester with formaldehyde followed by transformation of the resulting hydroxy ester into the corresponding bromide under usual conditions (Scheme 52).



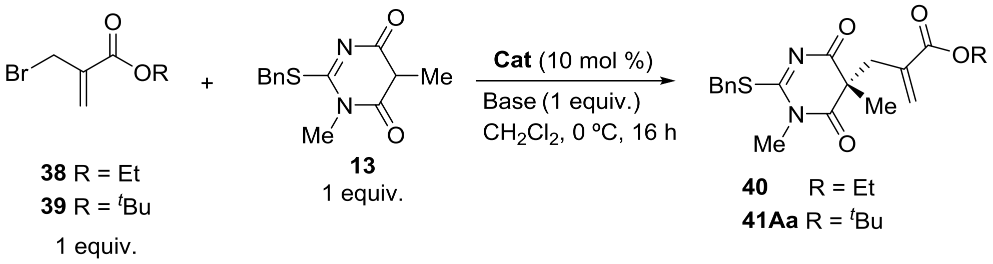
Scheme 52. Shyntesis of allyl bromides **38** and **39**.

For initial evaluation, bromide **38** was selected and the reaction with **13Aa** was carried out in the presence of 10 mol % catalyst **C10** and 1 equiv. of K_2CO_3, giving rise product **40** in 62% yield and 54% *ee* (Table 11, entry 1). We decided to increase the steric impediment in the electrophile, so, the ^{t}Bu ester derivative **39** was applied leading to product **41Aa** with a significant increase in *ee* (entry 2, Table 11, 99% *ee*). The reaction in the absence of catalyst at rt after 72 h, also yielded **41** with similar yield and obviously in racemic form (entry 3, Table 11). However, lowering the temperature to 0 °C, < 5% of conversion was observed indicating that background reaction is cancelled at this temperature (entry 4). Among the bases examined, K_3PO_4 also provided a good *ee* (97% *ee*, entry 5), whereas Cs_2CO_3 led to a reduced 77% *ee* and tertiary amines were completely ineffective in terms of enantioselectivity (entry 7 and 8). On the contrary, it was demonstrated that the reaction without base do not work (entry 9). This result is consistent with catalyst reaction through either: (i) acid-base neutralization by the evolving HBr, or (ii) competitive irreversible *N*-alkylation of the catalyst by the allylic halide.

---

[84] Pautigny, C.; Séverine Jeulin, T.; Ayad, Z.; Zhang, J.; Genêt, V.; Vidal, R. *Adv. Synth. Catal.* **2008**, *350*, 2525–2532

Table 11. Screening of bases for the allylic alkylation with MBH bromide [a].



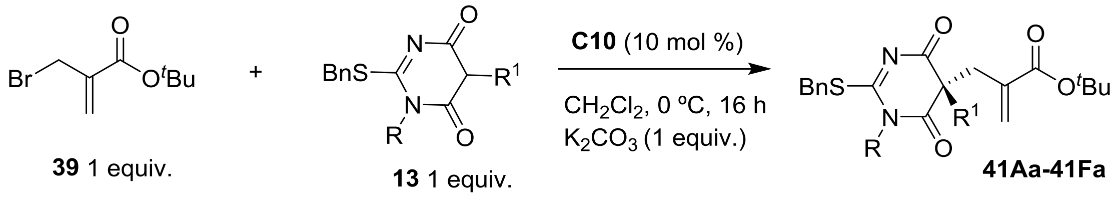
Entry	R	Cat.	Base	Yield (%)	*ee* (%)
1	Et	**C10**	K_2CO_3	62	54
2	^{t}Bu	**C10**	K_2CO_3	63	99
3[b]	^{t}Bu	--	K_2CO_3	62	0
4[c]	^{t}Bu	--	K_2CO_3	--	--
5	^{t}Bu	**C10**	K_3PO_4	61	97
6	^{t}Bu	**C10**	Cs_2CO_3	65	77
7	^{t}Bu	**C10**	Et_3N	71	10
8	^{t}Bu	**C10**	DMAP	68	24
9	^{t}Bu	**C10**	--	--	--

[a] Reaction conditions: **38/39** (1 equiv., 0.2 mmol), **13** (1 equiv., 0.2 mmol), catalyst (10 mol %) and base (1 equiv., 0.2 mmol) were stirred at 0 ºC for 16 h in CH_2Cl_2 (0.5 mL); yields of isolated product after column chromatography; *ee*´s determined by chiral HPLC: column IA eluting with Hex/^{i}PrOH 80:20 f = 0.5 mL/min. [b] Reaction carried out at rt for 72 h. [c] Reaction carried out at 0 °C for 72 h.

2.2.7.2. **Scope of the reaction regarding the nucleophilic template**

With 10 mol % catalyst **C10** and 1 equiv of K_2CO_3 at 0 °C selected as the best conditions, the reaction of bromide **39** with a series of 2-benzylthio-4,6-dioxopyrimidines **13** was screened. As the data in Table 12 show, the reaction with 5-methyl templates **13Aa-c** all afforded the corresponding adducts in yields ranging from 61 to 77% and high *ee* (99, 90 and 99%, respectively). On the other hand, the reaction tolerates well barbiturate templates with C5 substituents other than Me. For example, with Et, Bn and Allyl groups at C5 position the corresponding quaternary adducts **41Ba**, **41Ca** and **41Fa** were synthetized with good yields and enantioselectivities up to 96%.

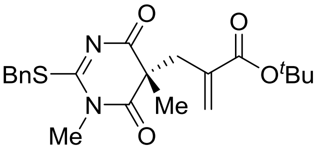
Table 12. Scope of the allylic alkylation of barbituric template **13**.


Br
O
O^{t}Bu
+
BnS
N
N
R
O
O
R^1
C10 (10 mol %)
CH_2Cl_2, 0 ºC, 16 h
K_2CO_3 (1 equiv.)
BnS
N
N
R
O
O
R^1
O
O^{t}Bu

39 1 equiv.

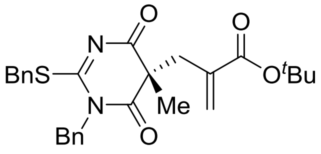
13 1 equiv.

41Aa-41Fa


O
N
BnS
N
Me
Me
O
O
O^{t}Bu

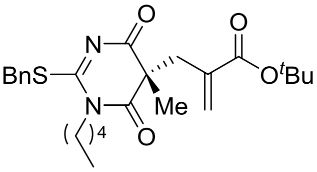
41Aa

63%, 99% *ee*


O
N
BnS
N
Bn
Me
O
O
O^{t}Bu

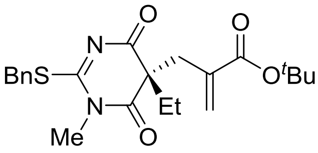
41Ab

61%, 90% *ee*


O
N
BnS
N
( )4
Me
O
O
O^{t}Bu

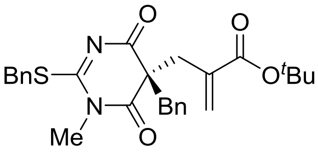
41Ac

77%, 99% *ee*


O
N
BnS
N
Me
Et
O
O
O^{t}Bu

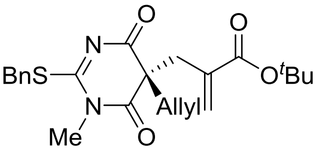
41Ba

67%, 96% *ee*


O
N
BnS
N
Me
Bn
O
O
O^{t}Bu

41Ca

63%, 86% *ee*


O
N
BnS
N
Me
Allyl
O
O
O^{t}Bu

41Fa

65%, 92% *ee*

Reaction conditions: **39** (1 equiv., 0.2 mmol), **13** (1 equiv., 0.2 mmol; yields of isolated product after column chromatography; *ee*´s determinated by chiral HPLC.

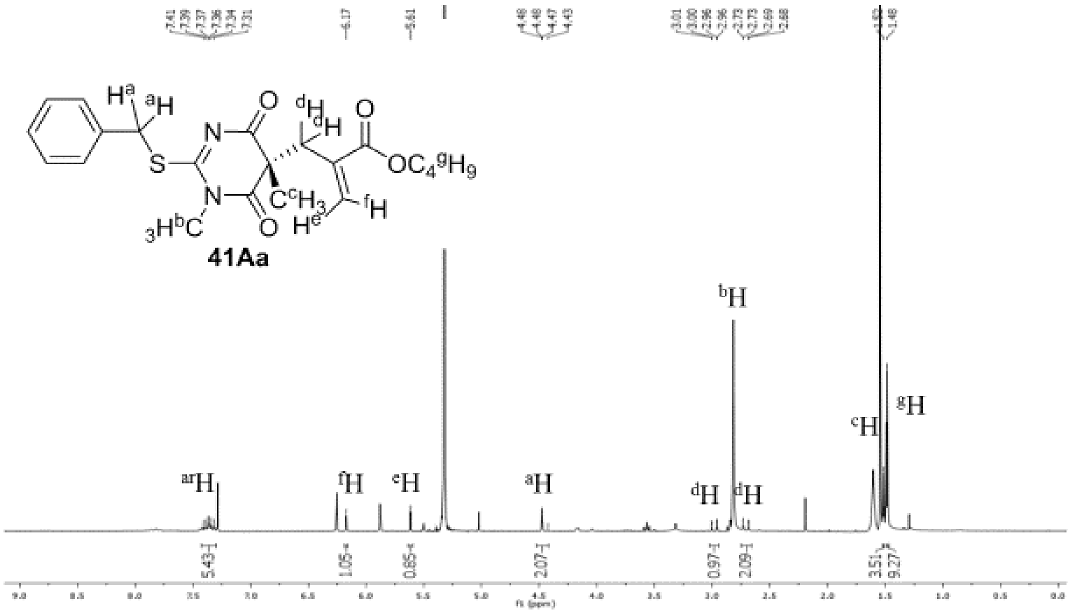
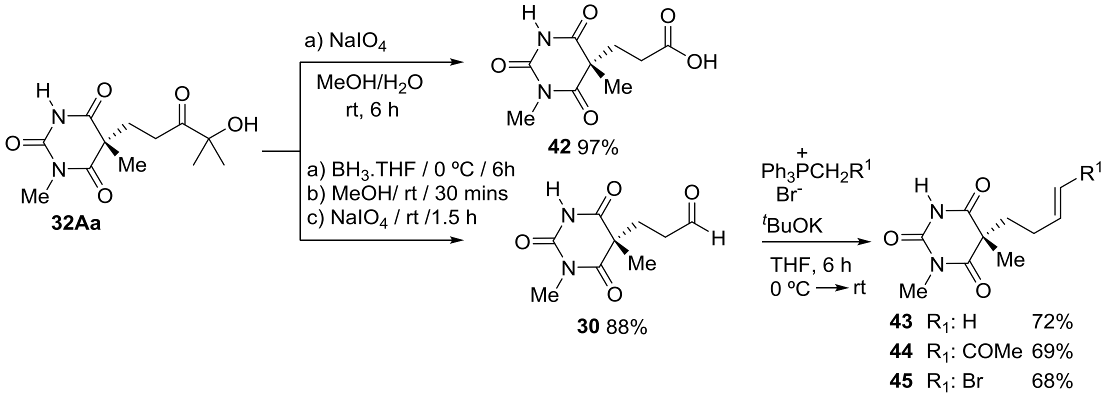


Figure 20. ^{1}H-NMR spectrum of the reaction crude for adduct **41Aa**.

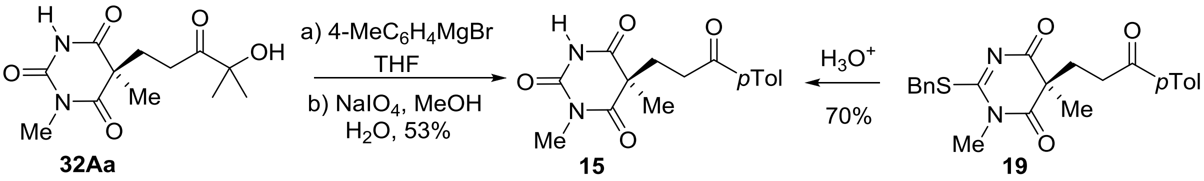
2.2.8. **Elaboration of the adducts**

In order to illustrate the potential of the present catalytic method for the C5-functionalization of barbiturate surrogates **13**, some selected transformations of adducts were carried out. For example, adduct **32Aa** was transformed quantitatively into the carboxylic acid **42** through oxidative treatment with $NaIO_4$ in a mixture of $MeOH/H_2O$ (2:1). In its turn, applying a reduction /1,2-diol cleavage sequence, aldehyde **30** was produced in 88% overall yield. Then, Wittig reaction of aldehyde **30** with the corresponding triphenylphosphonium bromide and ^{t}BuOK gave rise the quaternary barbiturates **43**, **44** and **45** with an elonged carbon chain in yields of 72%, 69% and 68%, respectively (Scheme 53).


32Aa
a) $NaIO_4$
$MeOH/H_2O$
rt, 6 h
42 97%
a) BH_3.THF / 0 ºC / 6h
b) MeOH/ rt / 30 mins
c) $NaIO_4$ / rt /1.5 h
30 88%
$Ph_3\overset{+}{P}CH_2R^1$
Br^-
^{t}BuOK
THF, 6 h
0 ºC → rt
43 R_1: H 72%
44 R_1: COMe 69%
45 R_1: Br 68%

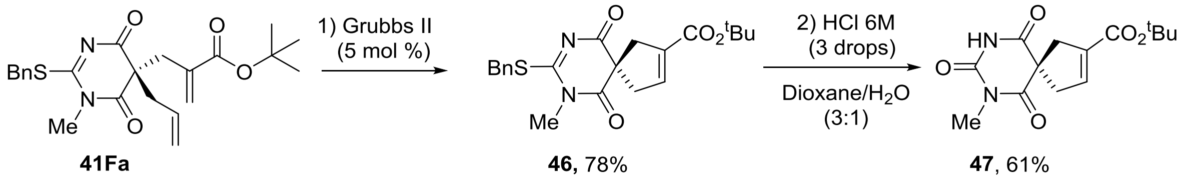
Scheme 53. Several possibilities for elaboration of the ketol moiety in adducts.

On the other hand, Grignard reaction of adduct **32Aa** with *p*-tolylmagnesium bromide followed by an oxidation process with $NaIO_4$ of the resulting 1,2-diol afforded adduct **15**. Same compound was obtained through hydrolysis of previously prepared **19**, which served to confirm the assigned configuration of adducts (Scheme 54).


32Aa
a) $4\text{-}MeC_6H_4MgBr$
THF
b) $NaIO_4$, MeOH
H_2O, 53%
15
H_3O^+
70%
19

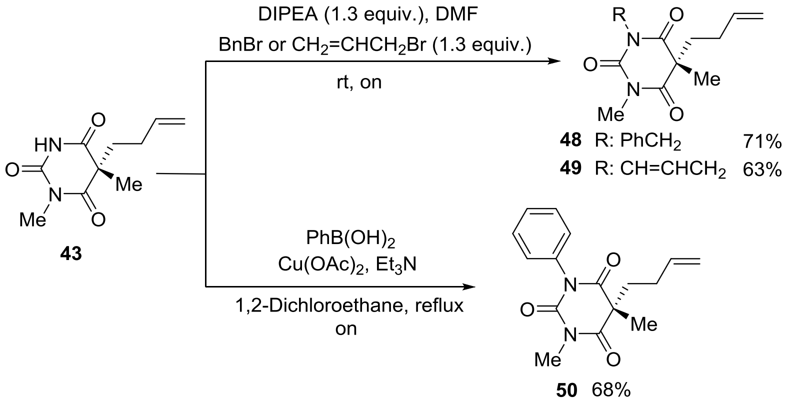
Scheme 54. Chemical correlation between adducts **32Aa** and **19**.

Regarding adducts obtained through catalytic allylic alkylation reaction, adduct **41Fa** was transformed into spiranic compound **46** through ring-closing metathesis reaction with Grubbs 2nd generation catalyst in good yield. Subsequent, acid hydrolysis afforded spiranic barbituric acid **47** in 61% (Scheme 55). Spirobarbiturates represent a family of structurally unique spiroheterocycles and possess a wide range of biological and pharmacological activities.[85]


1) Grubbs II
(5 mol %)
2) HCl 6M
(3 drops)
Dioxane/H2O
(3:1)
BnS
Me
CO2tBu
HN
41Fa
46, 78%
47, 61%

Scheme 55. Synthesis of spiranic compound.

On the other hand, *N*-arylation and *N*-alkylation protocols were also evaluated in order to demonstrate how the method may combine with other intermediate transformations to obtain differently *N*-substituted derivatives. For instance, treatment of **43** with DIPEA and benzyl or allyl bromide allowed access to the desired *N*-alkylated products **48** and **49** in 71% and 63% yield (Scheme 56). In another instance, the *N*-arylated product **50** could be prepared with 68% yield by treatment of **43** with $Cu(OAc)_2$, Et_3N and phenylboronic acid in dichloroethane at reflux (Scheme 56).


DIPEA (1.3 equiv.), DMF
BnBr or CH2=CHCH2Br (1.3 equiv.)
rt, on
PhB(OH)2
Cu(OAc)2, Et3N
1,2-Dichloroethane, reflux
on
R
Me
43
48 R: PhCH2 71%
49 R: CH=CHCH2 63%
50 68%

Scheme 56. Alkylation and arylation of the amide.

---

[85] For selected examples: a) Barakat, A.; Islam, M. S.; Al-Majid, A. M. *Bioorg. Med. Chem.* **2015**, *23*, 6740–2748. b) Fessenden, R. J.; Larsen, J. G.; Coon, M. D.; Fessenden, J. S. *J. Med. Chem.* **1964**, *7*, 695–698. c) King, S. B.; Stratford, E. S.; Craig, C. R.; Fider, E. K. *Pharm. Res.* **1995**, *12*, 1240–1243. d) Galati, E. M.; Monforte, M. T.; Miceli, N.; Rameri, E. *Il farmaco*, **2001**, *56*, 459–461. e) Kim, S. H.; Pudzianowski. A. T.; Leavitt, K. J.; Barbosa, J.; Mcdonell, P. A.; Metzler, W. J.; Rankin, B. M.; Liu, R.; Vaccaro, W.; Pitts, W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1101–1106. f) Ingle, V. N.; Gaidhane, P. K.; Dutta, S. S.; Naha, P. P.; Sengupta, M. S. *J. Carbohydr. Chem.* **2006**, *25*, 661–671.

CHAPTER 3

BRØNSTED BASE-CATALYZED REACTIONS OF α-IMINOAMIDES

3. BRØNSTED BASE-CATALYZED REACTIONS OF α-IMINOAMIDES 95

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3.2.3. Reactivity of glycine benzophenone imine. 99

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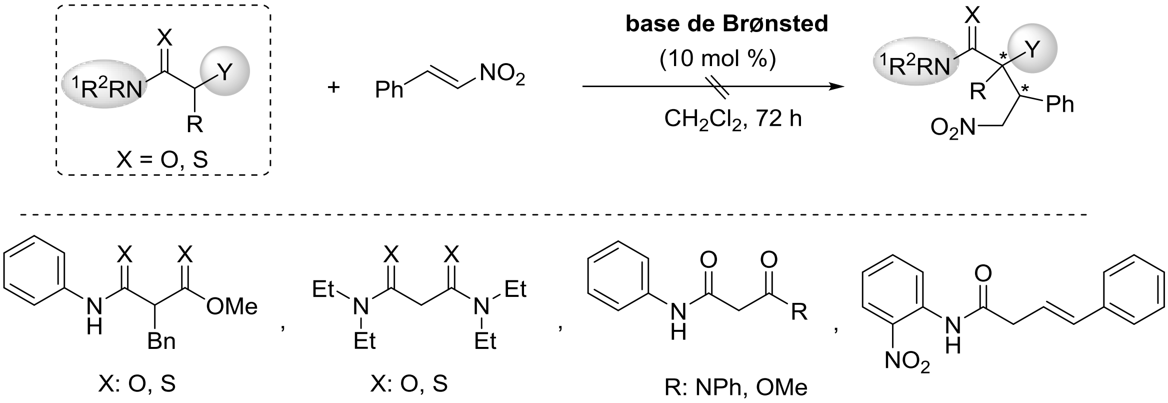
3. **Brønsted base-catalyzed reactions of *α*-iminoamides**

3.1. **Introduction**

As in the previous section is explained, the essays to achieve the desymmetrization of acyclic amides using Brønsted bases were unfruitful, so, the second part of this work is focused on getting the addition in *α* position to acyclic amides synthesizing a new pronucleofile modifying R^1, R^2 and Y (Scheme 57).



Scheme 57.

3.2. **Results and discussion**

3.2.1. **Design of a new amide-type nucleophile**

Due to our problems to achieve the Michael addition of acyclic amides to *trans-β*-nitrostyrene (Chapter 2, section 2.1.2 p. 45), we decided to explore new types of amide nucleophiles with adjacent activating elements. In the literature, we can find various examples in which intramolecular hydrogen bonds have been used as a preactivation element to make subsequent catalyst-assisted reaction acceleration plausible (Figure 21).[86]

---

[86] a) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2006**, *128*, 9413–9419. b) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed*. **2012**, *51,* 4104–4107. c) Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; Garcia, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc*. **2014**, *136,* 17869–17881. d) Jung, C. K.; Krische, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 17051–17056. e) Guerrero-Corella, A.; Esteban, F.; Iniesta, M.; Martín-Somer, A.; Parra, M.; Díaz-Tendero, S.; Fraile, A.; Alemán, J. *Angew. Int. Chem. Ed.* **2018**, *57*, 5350–5354.

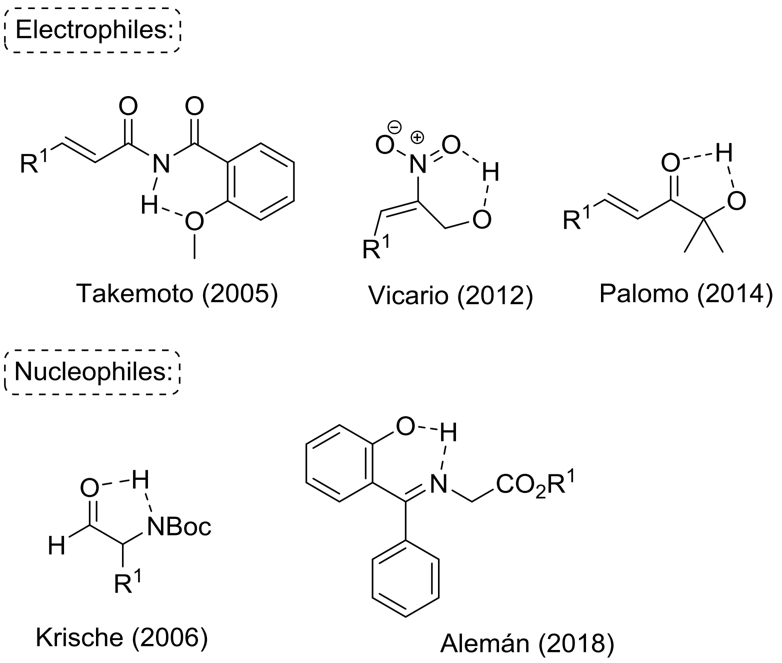
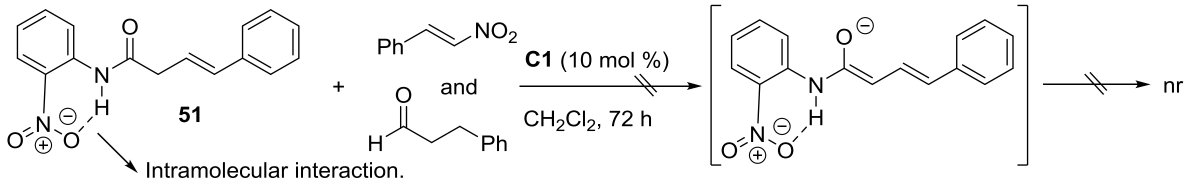

Electrophiles:
Takemoto (2005)
Vicario (2012)
Palomo (2014)
Nucleophiles:
Krische (2006)
Alemán (2018)

Figure 21. Previous examples of intramolecular hydrogen bond activated Elec/Nu in asymmetric (organo) catalysis.

Our plan was to evaluate the *β*,γ-unsaturated anilide **51** as a suitable donor amide reagent in BB-catalyzed addition reactions. This template should be easier to deprotonate due to the conjugate system that is formed upon deprotonation. However, the resulting dienolate (Scheme 58) presents two reactive carbons and there are two possible positions for the addition. In addition, a nitro group was inserted in *ortho* position in the *N*-aromatic ring could form an hydrogen bond with the NH amide and thus increase both the carbonyl electrophilicity[87] but also the *α* carbon acidity. Unfortunately, the reaction did not work.

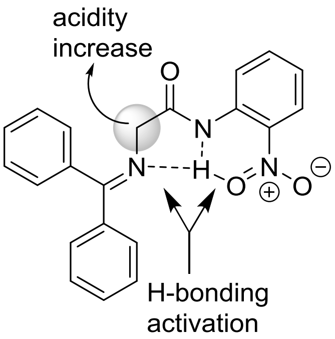

51
Intramolecular interaction.
+
and
C1 (10 mol %)
CH2Cl2, 72 h
nr

Scheme 58. Amide activated through a nitro group.

Based on our previous experiments, a new pronucleophile more prone to deprotonation was designed. A benzophenone imine group was included in the molecule, which could also form hydrogen bonds with the amidic NH and increase the acidity of the adjoining carbon (Scheme 59).

---

[87] Darvesh, S.; McDonald, R. S.; Darvesh, K.; Mataija, D.; Mothana, S.; Cook, H.; Carneiro, K.; Richard, N.; Walsh, R.; Martin, N. *Bioorg. Med. Chem.*, **2006**, *14*, 4586–4599.



56

Scheme 59.

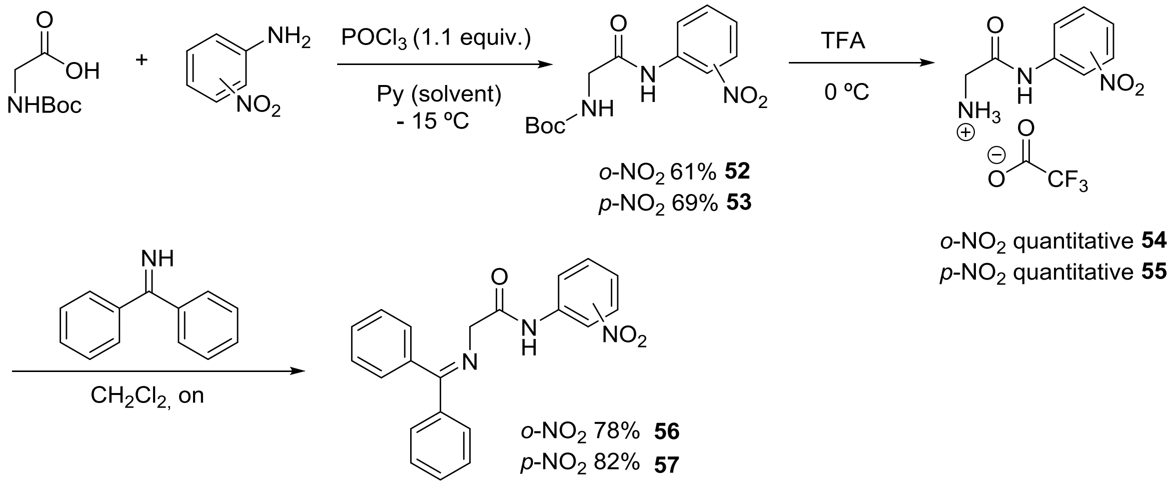
3.2.2. **Synthesis of 56**

Preparation of *α*-imino amides **56** (and **57**) was carried out by the coupling of *N*-(*tert*-butoxycarbonyl)glycine with the 2-nitroaniline, through initial attempts were unsuccessfull. Several standard procedures for the acid coupling were tried, including the transformation of the carboxylic acid into different leaving groups, but these procedures did not work. Finally, the procedure reported by Tesser and co-workers using pyridine as solvent and phosphorous oxychloride as the condensing agent worked well, affording **52** in 61% yield. The *p*-nitroanilide **53** was also prepared in 69% yield for comparative purposes.[88] Removal of the BOC group and condensation with the benzophenone imine in dichloromethane,[89] led to the *o*-nitroanilide **56** and the *p*-nitroanilide derivatives **57** in good yields (Scheme 60).

---

[88] Rijkers, D. T. S.; Adams, H.; Hemker, C.; Tesser, G. I. *Tetrahedron*, **1995**, *51*, 11235–11250.

[89] Abaskharon, R. M.; Brown, S. P.; Zhang, W.; Chen, J.; Smith, A. B.; Gai, F. *Chemical Physics Letters*, **2017**, *683*, 193–198.


OH
NHBoc
+
NH2
NO2
POCl3 (1.1 equiv.)
Py (solvent)
- 15 ºC
Boc
NH
N
H
NO2
o-NO2 61% 52
p-NO2 69% 53
TFA
0 ºC
NH3
O
CF3
NO2
o-NO2 quantitative 54
p-NO2 quantitative 55
NH
CH2Cl2, on
N
o-NO2 78% 56
p-NO2 82% 57

Scheme 60. Synthesis of the starting materials.

These intramolecular interactions could be confirmed in the X-ray structure analysis of compound **56** (Figure 22).

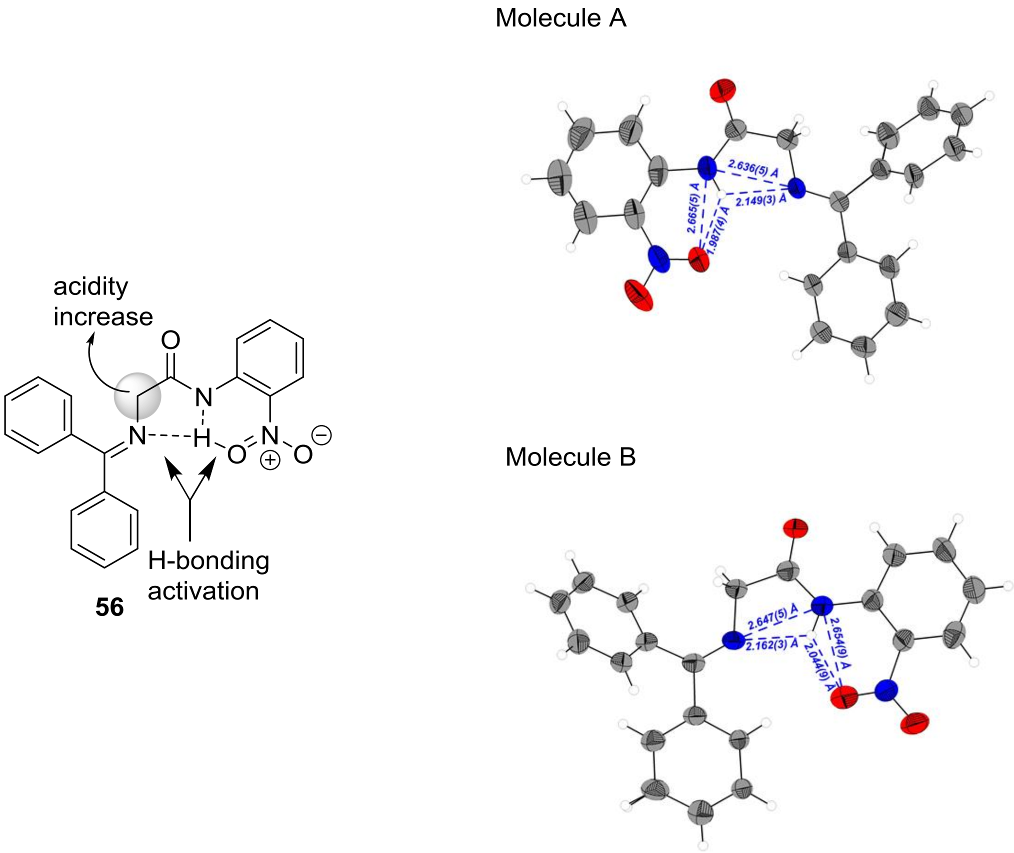
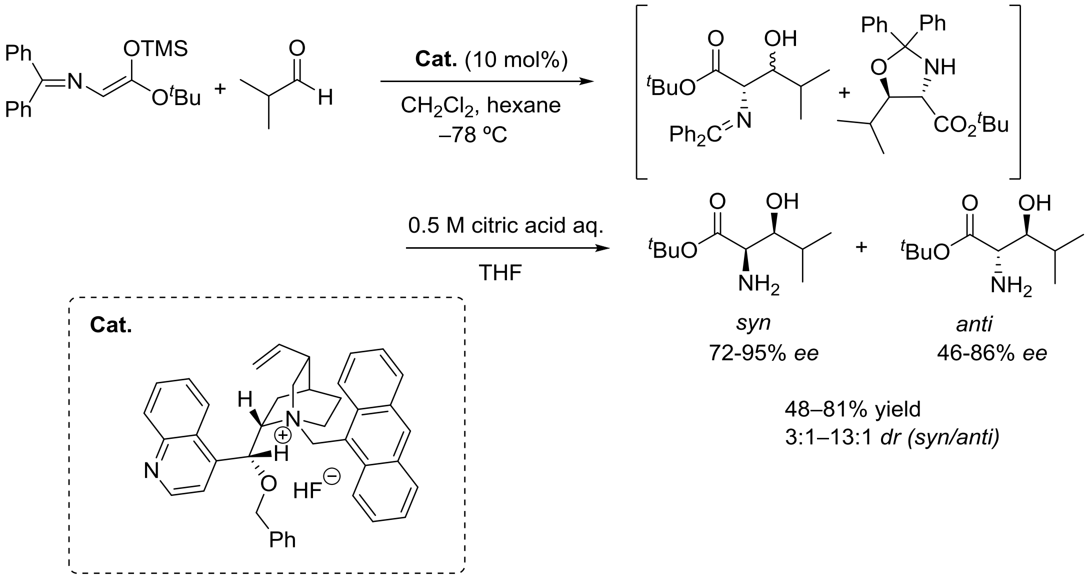

Molecule A
2.636(5) Å
2.149(3) Å
2.665(5) Å
1.987(4) Å
acidity increase
H-bonding activation
56
Molecule B
2.647(5) Å
2.162(3) Å
2.654(9) Å
2.044(9) Å

Figure 22. ORTEP diagram of compound **56**.

Once with the substrates in hand, we proceeded to study the behaviour of these amides in the aldol reaction promoted by several BB catalysts.

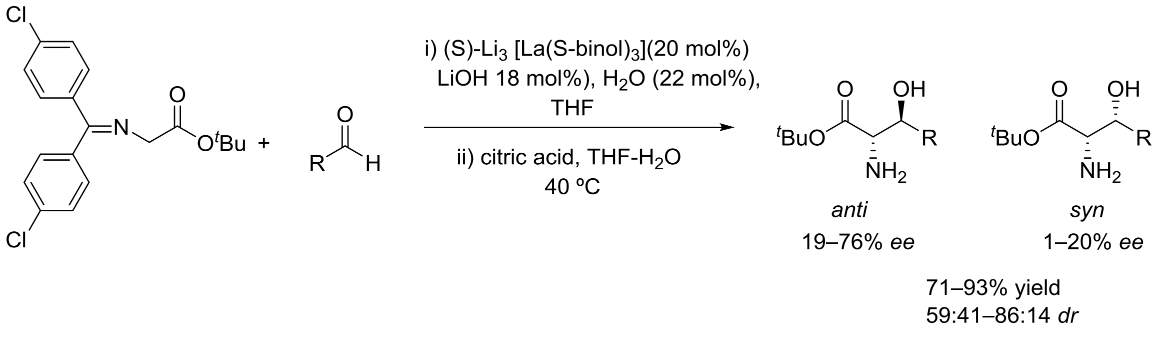
3.2.3. **Reactivity of glycine benzophenone imine.**

Corey and coworkers reported the synthesis of chiral *β*-hydroxy-*α*-amino acids by aldol coupling of aldehydes with the trimethylsilyl enol ether derivative of *tert* butylglycinate benzophenone Schiff base, using the chinchonidine derived quaternary ammonium salt as catalyst (Scheme 61).[90]


Ph
Ph
N
OTMS
O^{t}Bu
+
O
H
Cat. (10 mol%)
CH$_2$Cl$_2$, hexane
−78 °C
^{t}BuO
O
OH
Ph$_2$C=N
+
Ph
Ph
O
NH
CO$_2$^{t}Bu
0.5 M citric acid aq.
THF
^{t}BuO
O
OH
NH$_2$
+
^{t}BuO
O
OH
NH$_2$
syn
72-95% ee
anti
46-86% ee
48–81% yield
3:1–13:1 dr (syn/anti)
Cat.
H
N
H
N
O
HF
Ph

Scheme 61.

Shibasaki and coworkers described in 2002 a direct aldol reaction of gycinate Schiff bases with aldehydes using heteroarobimetallic asymmetric complexes as a catalyst. In this way, *anti*-*β*-hydroxy-*α*-amino acid esters were obtained as the major diastereomers with generally low *ee* (Scheme 62).[91]


Cl
Cl
N
O
O^{t}Bu +
O
R
H
i) (S)-Li$_3$ [La(S-binol)$_3$](20 mol%)
LiOH 18 mol%), H$_2$O (22 mol%),
THF
ii) citric acid, THF-H$_2$O
40 °C
^{t}BuO
O
OH
R
NH$_2$
^{t}BuO
O
OH
R
NH$_2$
anti
19–76% ee
syn
1–20% ee
71–93% yield
59:41–86:14 dr

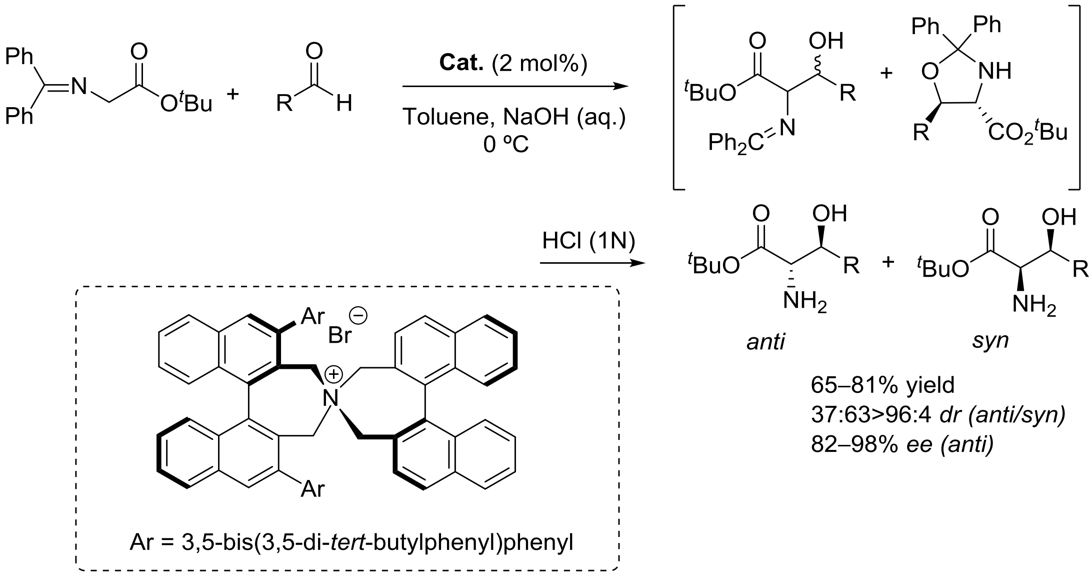
Scheme 62.

---

[90] Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843–3846.

[91] Yoshikawa, N.; Shibasaki, M. *Tetrahedron*, **2002**, *58*, 8289–8298.

In 2004, Maruoka and coworkers described an asymmetric aldol reaction of glycine benzophenone imine with aldehydes using chiral quaternary ammonium salts as a phase-transfer catalysts affording the corresponding *anti*-*β*-hydroxy-*α*-amino esters with good stereochemical control and *ee´*s up to 98% (Scheme 63).[92]

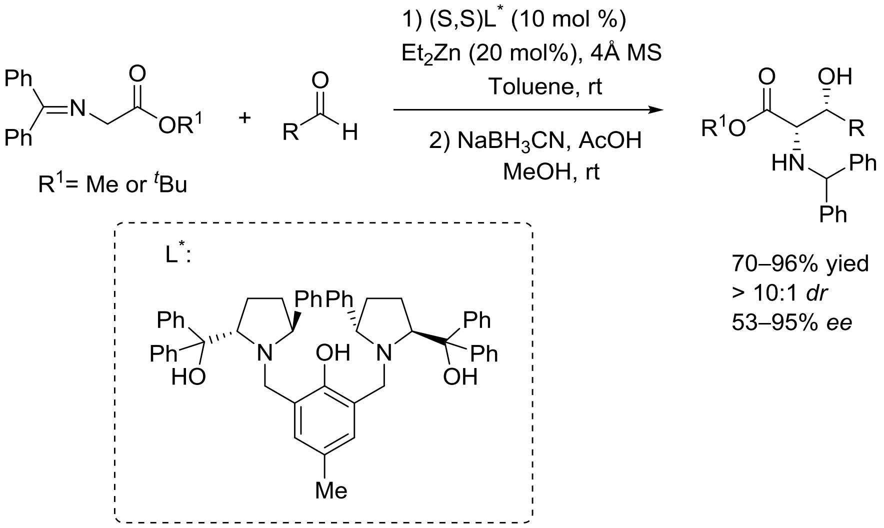

Ph
Ph
N
O
O^{t}Bu
+
R
H
O
Cat. (2 mol%)
Toluene, NaOH (aq.)
0 ºC
^{t}BuO
O
OH
R
Ph$_2$C=N
+
Ph
Ph
O
NH
R
CO$_2$^{t}Bu
HCl (1N)
^{t}BuO
O
OH
R
NH$_2$
anti
+
^{t}BuO
O
OH
R
NH$_2$
syn
Ar
Br
N
Ar
Ar = 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl
65–81% yield
37:63>96:4 *dr (anti/syn)*
82–98% *ee (anti)*

Scheme 63. Aldol reaction using phase-transfer catalysis.

---

[92] Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685–9694.

Ten years later, Trost described an asymmetric aldol reaction between glycine Schiff base derivatives and different aldehydes using a zinc-prophenol catalyst, in this way, s*yn* *β*-hydroxy-*α*-amino esters were obtained with good diastereo and enantioselectivities (Scheme 64).[93] Obtention of *syn* diastereomer proved problematic[94] and, as far as we know, this is the only example in the literature.



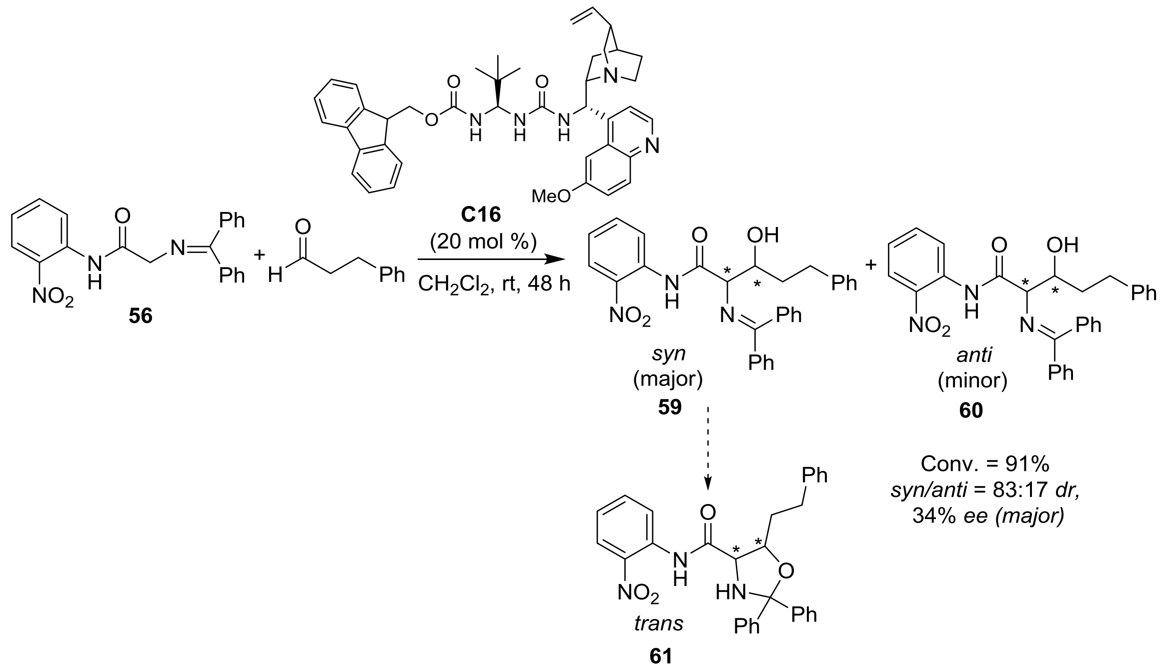
Scheme 64. Aldol reaction using a dinuclear zinc complex as catalyst.

We started our study exploring the aldol addition of iminoacetamides **56** with 3-phenylpropanal using different bifunctional BB catalysts. First experiment carried out in CH_2Cl_2 using 20 mol % of ureidopeptide catalyst **C16** developed in our group gave the desired aldol products **59**/**60** with 61% yield, 83:17 *dr* but with a low *ee* (Scheme 65). However, a second product was also formed which was identified as the cyclic oxazolidine compound **61** which may arise from an intramolecular cyclization of **59**. NMR monitoring of the reaction progress showed that the amount of oxazolidine **61** increases over time. Thus, while after 48 h at r.t. the ratio of **59** + **60**/**61** is 93:7, after 5 days changed to 22:78 (Figure 23).

---

[93] Trost, B. M.; Miege, F. *J. Am. Chem. Soc.* **2014**, *136*, 3016–3019.

[94] a) Kano, T.; Lan, Q.; Wang, X.; Maruoka, K. *Adv. Synth. Catal.* **2007**, *349*, 556–560. b) Kitamura, M.; Shirakawa, S.; Arimura, Y.; Wang, X.; Maruoka, K. *Chem. Asian, J.* **2008**, *3*, 1702–1714.


C16
(20 mol %)
CH2Cl2, rt, 48 h
56
syn
(major)
59
anti
(minor)
60
trans
61
Conv. = 91%
syn/anti = 83:17 dr,
34% ee (major)

Scheme 65.

In addition, it is appreciated that while the amount of diastereomer **60** remains constant, the amount of initially major diastereomer **59** varies drastically from 82% at 48 h to 11% after 5 days. According to literature precedents, *syn* imine aldol adduct seems to cyclize faster.[92] Therefore, we assume that the initially major diastereomer in the reaction was the *syn* diasteroisomer.

	Syn **(59)**	*Anti* **(60)**	*Trans* **(61)**
48h	82%	11%	7%
5 days	11%	11%	78%

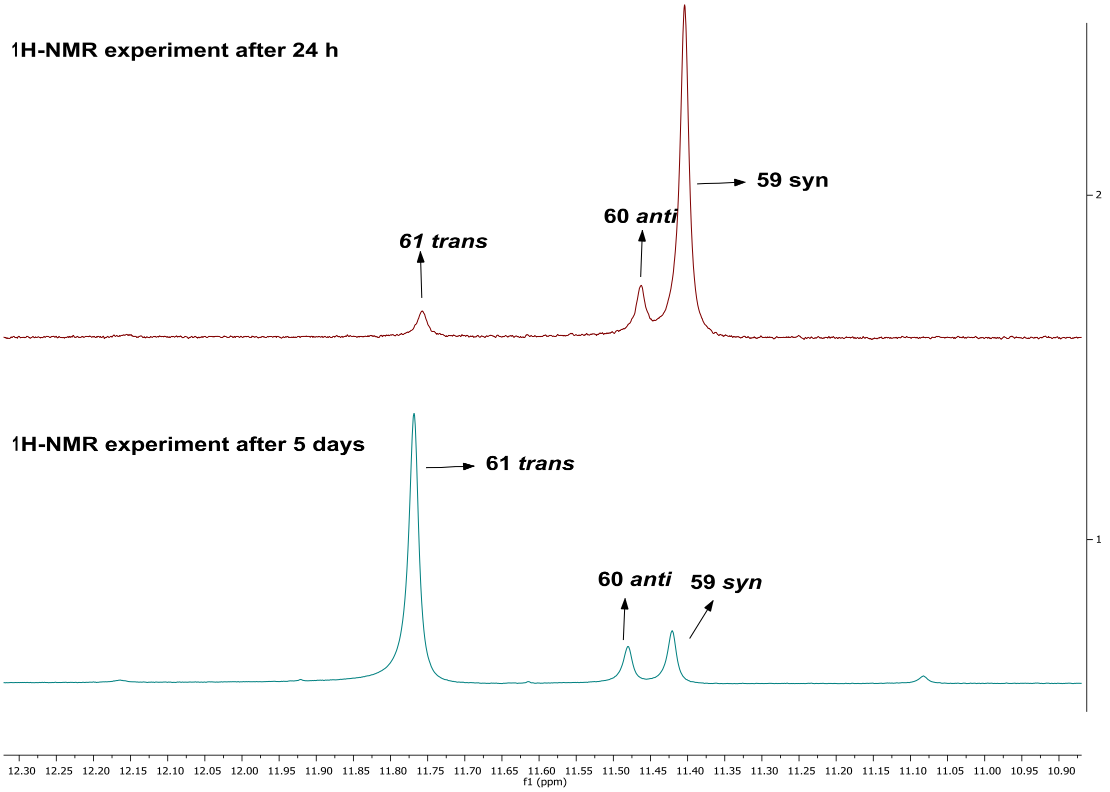
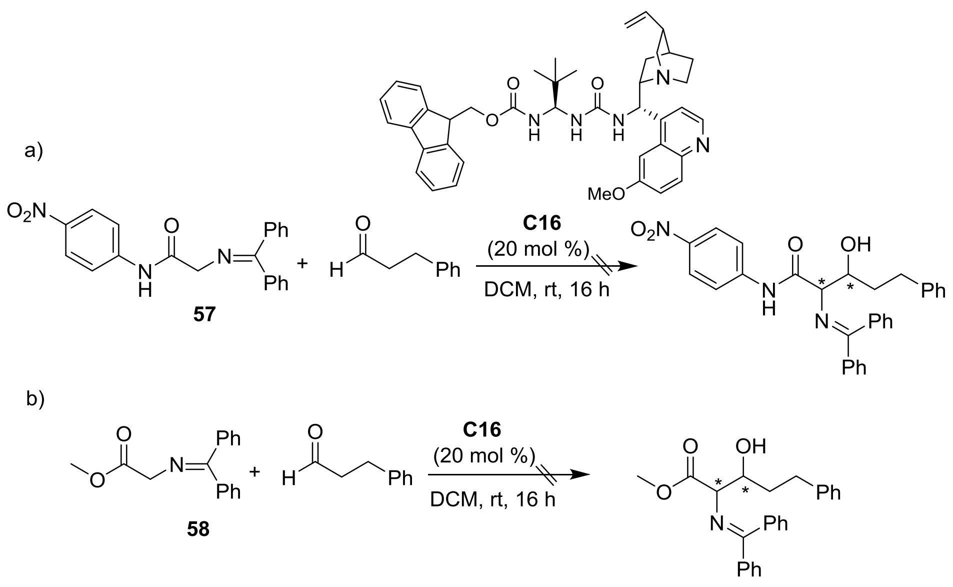


Figure 23. ^{1}H-NMR monitoring of **59**, **60** and **61** after 5 days.

When the same aldol reaction was attempted under otherwise identical conditions (in CH_2Cl_2 and 20 mol % of catalyst **C16**), but using the *p*-nitrophenyl amide **57** instead, no reaction was observed. This observation could be attributed to the inability of the NO_2 group in *para* to participate in internal *H*-bond, thus supporting the importance of the amide design (Scheme 66a). Similarly, the reaction using the *α*-imino ester **58** neither worked under the described conditions. This result seems to indicate that the amide NH group is essentially for carrying out the reaction (Scheme 66b).

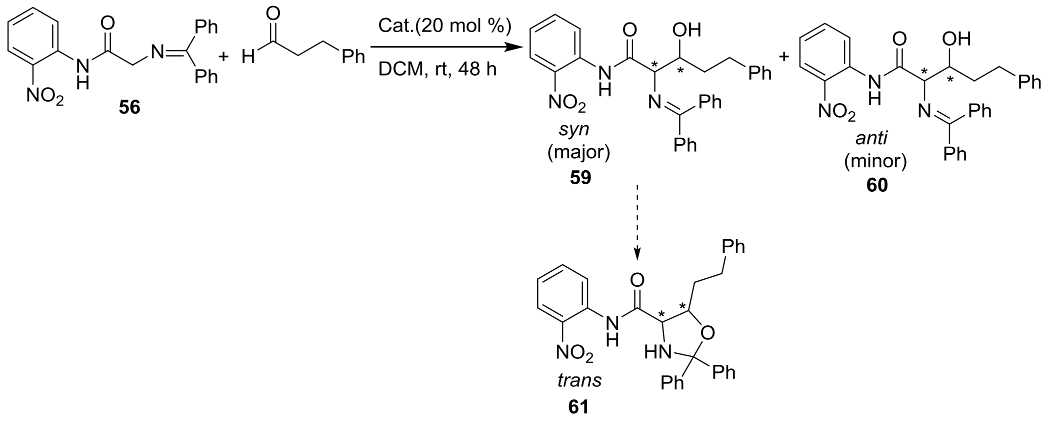

a)
O₂N
O
N
H
N
Ph
Ph
57
+
O
H
Ph
C16
(20 mol %)
DCM, rt, 16 h
MeO
N
O
O
O
N
H
N
H
N
H
N
OH
*
*
Ph
b)
58

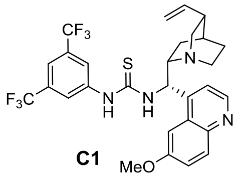
Scheme 66.

3.2.3.1. **Catalyst screening**

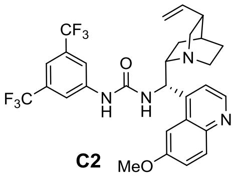
Once the feasibility of the aldol reaction between *α*-iminoamide **56** with 3-phenylpropanal in CH_2Cl_2 was confirmed, a range of bifunctional BB-catalysts were tested in order to improve the reaction outcome. As the data in Table 13 show using known thiourea catalyst **C1** and urea catalyst **C2** moderate conversions were obtained (48% and 66% respectively), a *syn*/*anti* ratios above 85:15, and, essentially racemic product.

Table 13. Screening of catalysts for the aldol reaction between **56** and hydrocinamaldehyde.

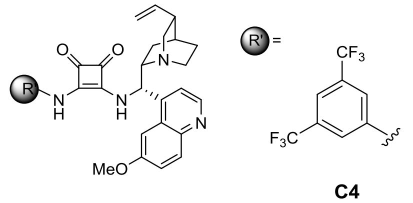



C1

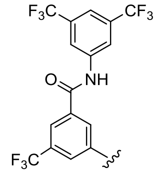
Conv. = 48%
syn/anti = 86:14 *dr*,
racemic


C2

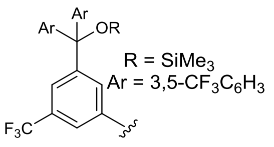
Conv. = 66%
syn/anti = 87:13 *dr*,
racemic


C4

Conv. = 90%
syn/anti = 70:30 *dr*,
70% *ee*

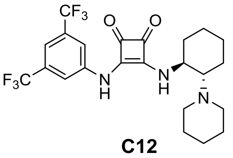

C6

Conv. = 27%
syn/anti = 63:37 *dr*,
70% *ee*

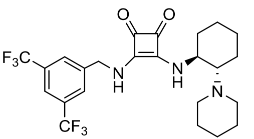

R = $SiMe_3$
Ar = 3,5-$CF_3C_6H_3$

C11

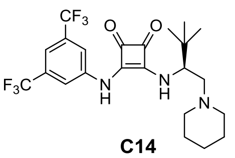
Conv. = 39%
syn/anti = 80:20 *dr*
56% *ee*


C12

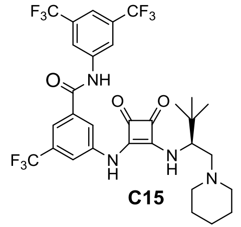
Conv. = 92%
syn/anti = 73:27 *dr*,
83% *ee*


C13

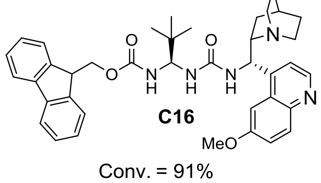
Conv. = 55%
syn/anti = 87:13 *dr*,
45% *ee*


C14

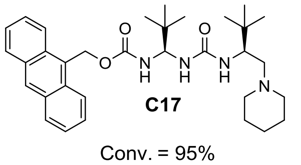
Conv. = 90%
syn/anti = 75:25 *dr*,
93% *ee*


C15

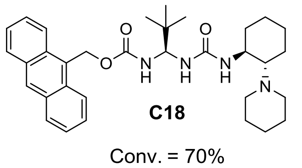
Conv. = 80%
syn/anti = 68:32 *dr*,
92% *ee*


C16

Conv. = 91%
syn/anti = 90:10 *dr*,
34% *ee*


C17

Conv. = 95%
syn/ anti = >98:2 *dr*,
80% *ee*


C18

Conv. = 70%
syn/anti = >98:2 *dr*,
80% *ee*

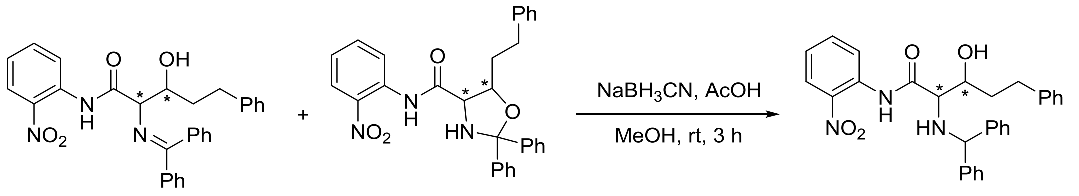
Reaction conditions: **56** (1 equiv., 0.2 mmol), phenylpropanal (3 equiv., 0.6 mmol) and 0.2 mL of CH_2Cl_2; Reaction time 48 h; *dr* refers to the ratio of **59**+**61**/**60**; *ee*´s are determinated for the major diastereoisomer (**59**) by chiral HPLC, column IC eluting with Hex/*Et*OH 90:10 f = 0.5 mL/min.

Further catlyst screening revealed that the best conversion was obtained with **C4** (90%) whereas **C6** and **C11** gave low conversions after 48 h (39% and 27% respectively). The *ee´*s were moderate in all of cases, (56%, 70%) and *dr* varies from 70:30 (**C4**) and 63:37 (**C6**) to 80:20 with **C11**.

Then, squaramide type catalyst **C12**, **C13**, **C14**, and **C15** were checked, but the results were still unsatisfactory.

Finally, ureidopeptide type catalysts **C16**, **C17** and **C18** were screened. Both **C16** and **C17** afforded good conversion (91% and 95% respectively) but **C17** was the best in terms of stereocontrol (*dr* >98:2 and 80% of *ee*).

The treatment of a mixture of **59** and **61** with $NaBH_3CN$ in AcOH/MeOH gave rise to amino alcohol product **62** in 86% yield and 80% *ee* (Scheme 67).



syn
59

trans
61

86% yield
80% *ee*
62

Scheme 67.

The scope of this catalytic and enantioselective aldol reaction of α-imino amide **56** is currently being investigated in own laboratory.

CHAPTER 4

CONCLUSIONS

4. Conclusions

We have investigated α-functionalization reactions of a set of amides promoted by chiral Brønsted base catalysts.

In one set, the reactions of barbituric acid and derivatives were evaluated. Attempts with barbituric acids and thiobarbituric acids led to the corresponding C5-quaternary derivatives in good yields but racemic products were obtained. Therefore, desymmetrization of these substrates relying in BB-H-bond cat seems unsuitable.

As a solution to this defficiency, 2-benzylthio-4,6-dioxopyridines were design as a new barbiturate template. The BB-catalyzed addition of these templates to enones, particularly aryl vinyl ketones proceeds effiently and with high enantioselectivity. Best selectivities (up to 97% *ee*) were obtain with catalyst **C10**. On the other hand, using α´-silyloxy enone, products were obtained in good yields and good enantioselectivities too (up to 93% *ee*). Finally, the allylic alkylation with Morita-Baylis Hillmann type (*pseudo*)halogenides allowed to obtain the synthesis of the corresponding barbiturates derivatives with good yields and good *ee*´s (up to 99%).

On the other hand, we have developed the α-desymmetrization of acyclic amides using a new designed amide-type nucleophile based on a glycine benzophenone imine derivative, in an aldol reaction. In this way, the product was obtained with good yield and good enantio and diastero ratio using an ureidopeptide type catalyst **C16**.

CHAPTER 5

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5. *Experimental section*

5.1. Materials and Generals Techniques

5.1.1. Reagents and solvents

Reagents were purchased from commercial suppliers (Aldrich, Across, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated.

Triethylamine, DBU, DIPA and DIPEA were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at –30 °C under nitrogen.

When anhydrous solvents were required, they were dried following established procedures.[95] Dichloromethane was dried over CaH, diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder 150 mesh, pore size 58 Å, basic Sigma Aldrich) columns.

5.1.2. General experimental

All non-aqueous reactions were performed under inert atmosphere using oven-dried glassware and were magnetically stirred. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Heat requiring reactions were performed using a hotplate with a sand bath and a condenser. Reactions requiring low temperatures were performed using cooling bath circulators *Huber* T100E and acetone or isopropanol baths.

Organic layers washed with aqueous phases were dried over $MgSO_4$ or Na_2SO_4 and filtered through cotton.

Organic solvents were evaporated under reduced pressure using rotary evaporator Büchi R-100, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (≈ 0.5 mmHg) was employed.

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[95] Armanego, W. L. F.; Perrin, D. D. *Purification of laboratory Chemicals*, 3rd Edition Butterworth-Heinemann, Oxford, **1988**.

5.1.3. **Chromatography**

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Biolock lamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1g) in 100 ml of water (limited lifetime), followed by heating.

Chromatographic purification was performed on Merck ROCC 60 silica gel 40-63 µm as stationary phase and a suitable mixture of solvents (typically hexane: ethyl acetate, pentane: diethyl ether or dichloromethane: methanol) as eluent.

5.1.4. **Optical rotation**

Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg.cm^2.g^{-1}; concentrations (*c*) are quoted in g/100 mL; $_D$ refers to the D-line of sodium (589 nm); temperatures (T) are given in degree Celsius (°C).

5.1.5. **Melting points**

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected.

5.1.6. **NMR spectra**

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer, Bruker 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) Varian 400 MR (400 MHz for ^{1}H, 100 MHz for ^{13}C) or Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (HZ).

MestrReNova Mnova 8.1 program was used to process and edit the registered spectra.

5.1.7. **Mass spectra**

Ms spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model) on a UPLC-DAD-QTOF, Ultra High Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU).

5.1.8. **Infrared spectra**

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film.

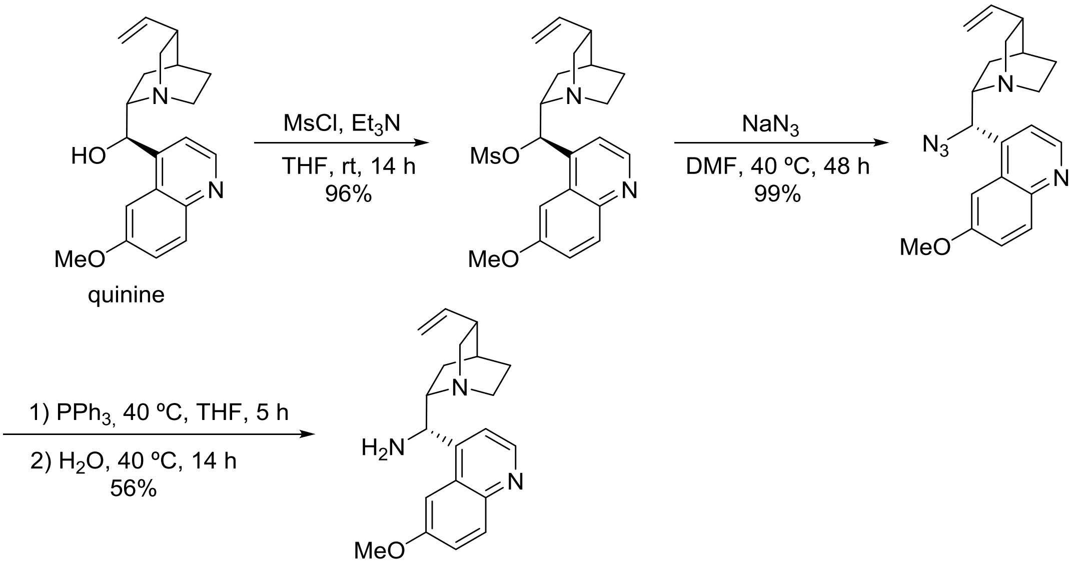
5.1.9. **X-Ray diffraction analysis**

The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using difractometers for monocrystals.

5.2. **Preparation of catalysts**

5.2.1. **Preparation of catalysts C1-C9**

5.2.1.1. **Preparation of 9-amino-(9-deoxy)epiquinine**[96]



Step 1: A mixture of quinine (16.2 g, 50 mmol, 1 equiv.) and triethylamine (25.1 mL, 180 mmol, 3.6 equiv.) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (7.0 mL, 90 mmol, 1.8 equiv.) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford the crude product in 96 % yield, which was used in the next step without further purification.

Step 2: The crude product (19.3 g, 48 mmol, 1 equiv.) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and NaN_3 (6.2 g, 96 mmol, 2 equiv.) was added portionwise. The mixture was stirred at 40 ºC for 48 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield, which was used in the next step without further purification.

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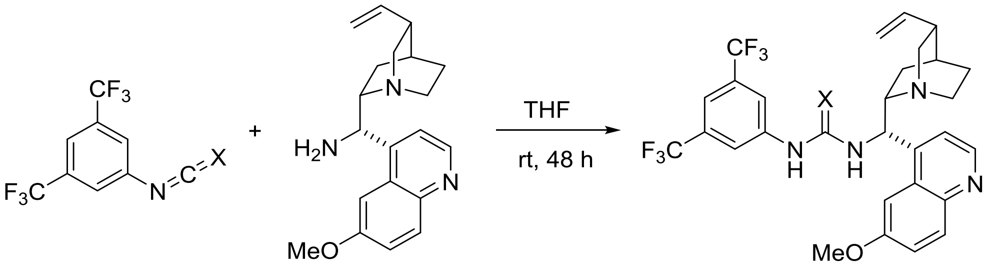
[96] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

Step 3: The crude product was dissolved in THF (250 mL) and PPh_3 (12.6 g, 48 mmol, 1 equiv.) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (150 mL). HCl 6 M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 8.7 g, 26.9 mmol, 56 %. All data were consistent with those previously reported.[96] ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36 – 8.05 (m, 4H), 5.79 – 5.75 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02 – 3.34 (m, 3H), 2.75 – 2.77 (m, 2H), 2.27 – 2.24 (m, 1H), 2.08 (s, 2H), 1.26 – 1.63 (m, 4H), 0.80 – 0.78 (m, 1H).

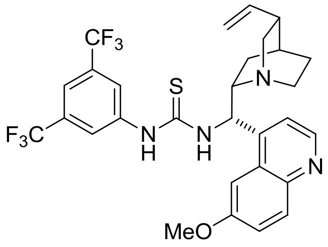
5.2.1.2. **Preparation of catalysts C1[97]and C2[98]**



C1 X = S
C2 X = O

To a solution of 9-amino-(9-deoxy)*epi*quinine (1.6 g, 5 mmol, 1 equiv.) in dry THF (7.5 mL) at 0 °C, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.5 g, 5.5 mmol, 1.1 equiv.) or bis(trifluomethyl)phenyl isocyanate (0.6 mL, 5.5 mmol, 1.1 equiv.) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on non acid silica gel (eluent with hexane: ethyl acetate, 80:20 → ethyl acetate).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea C1



White solid. Yield: 2.6 g, 4.4 mmol, 88 %. M. p. = 123 – 125 °C. All data were consistent with those previously reported.[97] ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (brs, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56 – 3.53 (m, 1H), 3.39 – 3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38 – 2.35 (m, 1H), 1.71 – 1.68 (m, 2H), 1.64 – 1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

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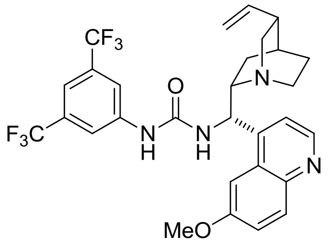
[97] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

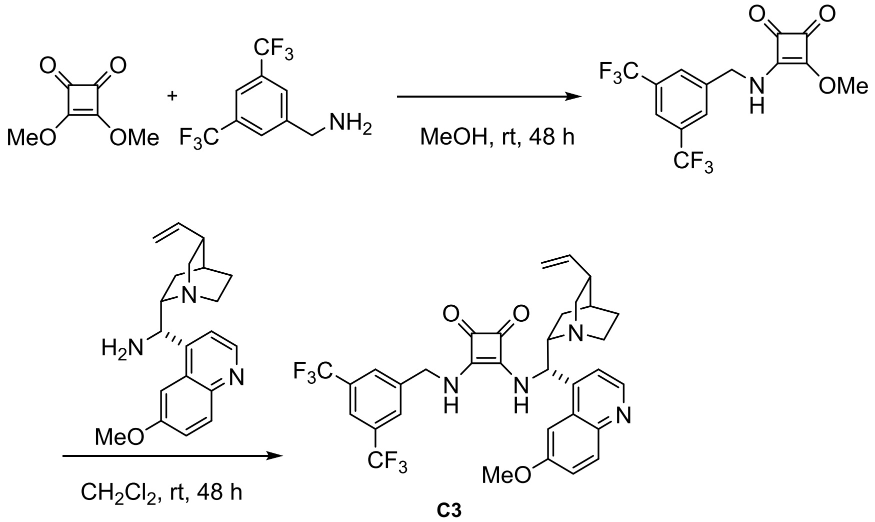
[98] Greenaway, K.; Dambruoso, P.; Ferrali, A.; Hazelwood, A. J.; Sladojevich, F.; Dixon, D. J. *Synthesis*, **2011**, *12*, 1880–1886.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea C2



White solid. Yield: 2.4 g, 4.1 mmol, 82 %. M. p. = 132 – 134 °C. All data were consistent with those previously reported.[98] ^{1}H NMR (300 MHz, CD_3OD) δ 8.58 (d, *J* = 4.5 Hz, 1H), 7.90 – 7.88 (m, 3H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 5.83 – 5.89 (m, 1H), 5.65 (brs, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.91 (s, 3H), 3.47 – 3.52 (m, 1H), 3.35 – 3.41 (m, 1H), 3.03 – 3.15 (m, 4H), 2.41 – 2.43 (m, 1H), 1.40 – 1.73 (m, 3H), 1.17 – 1.25 (m, 3H).

5.2.1.3. **Preparation of catalyst C3**[99]



Step 1: synthesis of squaric ester monoamide intermediate

To a solution of dimethyl squarate (142 mg, 1.0 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) was added a solution of 3,5-bis(trifluoromethyl)benzylamine (255 mg, 1.1 mmol, 1.1 equiv.) in CH_2Cl_2 (1 mL) and the mixture was stirred at room temperature for 48 h. The reaction mixture was filtered, and the filtrate was washed with (aq) 1 M HCl (10 mL), dried with Na_2SO_4, filtered again, and concentrated to afford 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione as a white solid. Yield: 309 mg, 0.87 mmol, 87%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.77 (s, 2H), 4.78 (bs, 1H), 4.41 (s, 3H).

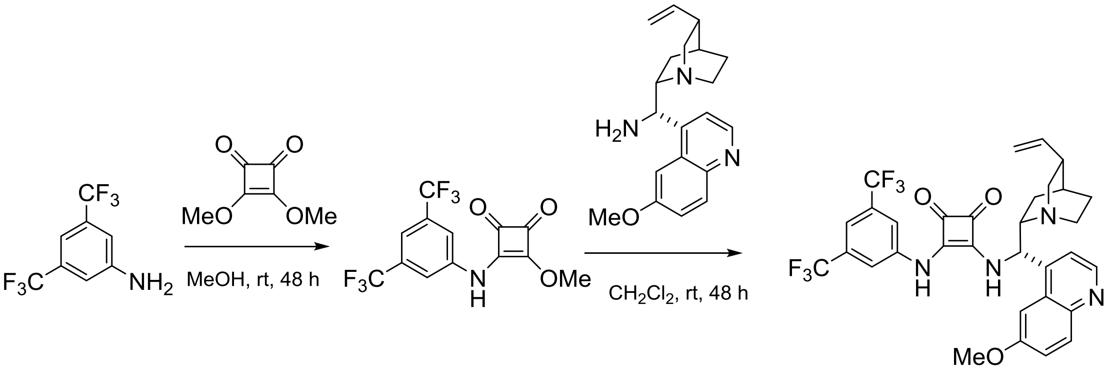
Step 2: coupling to final squaramide **C3**

To a solution of previously obtained material (309 mg, 0.87 mmol, 1.2 equiv.) in MeOH (10 mL) at room temperature was added a solution of 9-amino-(9-deoxy)*epi*quinine (236 mg, 0.73 mmol, 1 equiv.) in MeOH (3 mL). After stirring the mixture for 24 h, the solvent was evaporated under reduced pressure and the residue was purified by non acid column chromatography (Hex: EtOAc, 50:50) to afford the desired squaramide **C3** as a white solid. Yield: 227 mg, 0.35 mmol, 50 %. All spectroscopic data were identical to those reported in the literature.[99] ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.91 – 7.94 (m, 1H), 7.77 (s, 1H), 7.51 – 7.34 (m, 5H), 5.74 – 5.68 (m, 1H), 5.00 – 4.91 (m, 2H), 4.52 (bs, 2H), 3.88 (s, 3H), 3.24 – 3.19 (m, 3H), 2.77 – 2.68 (m, 1H), 2.31 (bs, 1H), 1.69 – 1.43 (m, 5H), 0.88 (bs, 1H).

---

[99] Reproduced from: Malerich, J.; Hagihara, K.; Rawal, H. *J. Am. Chem. Soc.* **2008**, *130,* 14416–14417.

5.2.1.4. **Preparation of catalyst C4**[100]



C4

Step 1: preparation of squaric ester monoamide intermediate

To a solution of dimethyl squarate (1.42 g, 10 mmol, 1 equiv.) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1.56 mL, 10 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give the desired product. Yield: 2.25 g, 6.6 mmol, 66 %. M.p. = 179 – 181 °C. All spectroscopic data where consistent with those reported in literature.[100] ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

Step 2: coupling to final squaramide **C4**

To a solution of the above obtained material (339 mg, 1.0 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) 9-amino-(9-deoxy)*epi*quinine (323 mg, 1.0 mmol, 1 equiv.), was added. The reaction mixture was stirred at room temperature for 48 h. Then the solvent was evaporated, and the product submitted to purification by silica gel column chromatography (eluent dichloromethane: methanol, 98:2). White solid. Yield: 441 mg, 0.7 mmol, 70%. M.p. = 224 – 225 °C. All spectroscopic data were identical to those reported in the literature.[100] ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (brs, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (brs, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s, 3H), 3.52 – 3.42 (m, 1H), 3.30 – 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H).

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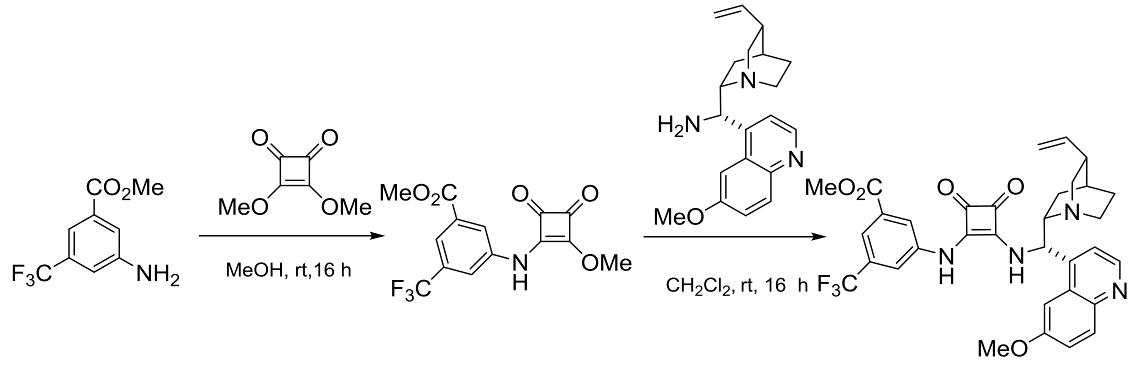
[100] Reproduced from: Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

5.2.1.5. **Preparation of catalyst C5**



C5

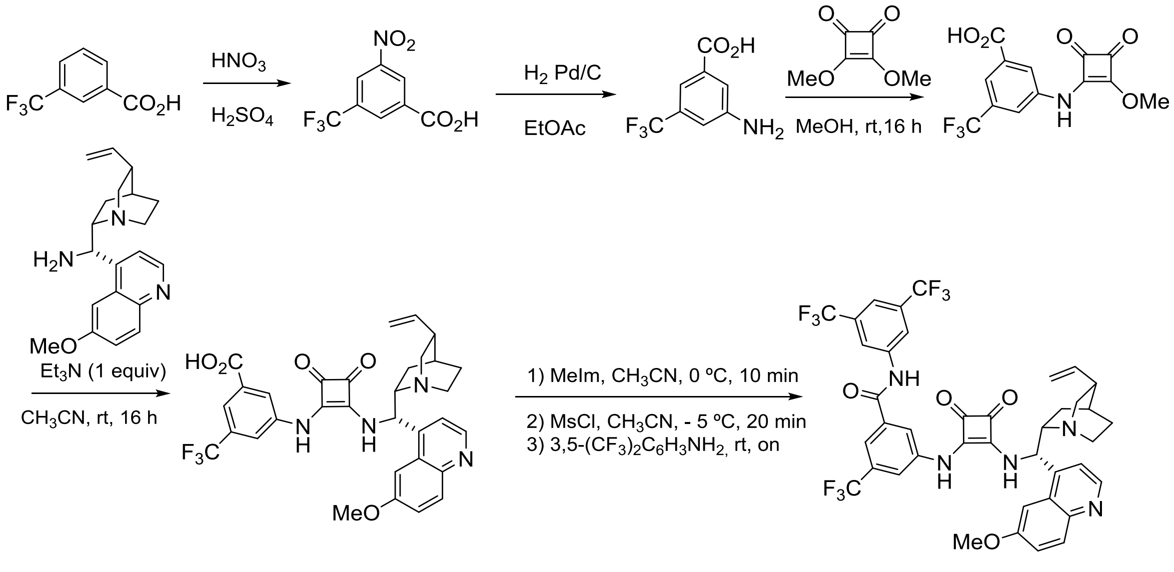
Step 1: preparation of ester monoamide intermediate

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (147 mg, 1.0 mmol, 1 equiv.) in MeOH (5 mL) the methyl 3-amino-5-(trifluoromethyl)benzoate (227 mg, 1.0 mmol, 1 equiv.) was added at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtered and washed with MeOH. The obtained white solid was dried *in vacuo* to give the title product as a white solid. Yield: 403 mg, 0.65 mmol, 65 %. M.p. = 219 – 221 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 15.0 Hz, 2H), 7.83 (d, J = 2.4 Hz, 1H), 4.58 (s, 3H), 4.02 (s, 3H). UPLC-DAD-QTOF: $C_{14}H_{10}F_3NO_5$ $[M+H]^+$ calcd.: 330.0511, found: 330.0411.

Step 2: coupling to final squaramide **C5**

To a solution of the above obtained material (150 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2.5mL) 9-amino-(9-deoxy)*epi*quinine (180 mg, 0.5 mmol, 1 equiv.) was added and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was submitted to purification by silica gel column chromatography (eluent dichloromethane: methanol, 98:2). White solid. Yield: 441 mg, 0.34 mmol, 67 %. M.p. = 184 – 187 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 4.4 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.88 (s, 1H), 7.74 (d, J = 23.1 Hz, 2H), 7.62 (s, 2H), 7.38 – 7.32 (m, 1H), 6.28 (s, 1H), 5.93 – 5.72 (m, 1H), 5.12 – 4.87 (m, 2H), 3.94 (s, 3H), 3.70 (s, 3H), 3.47 (dd, J = 11.4, 5.7 Hz, 1H), 3.20 (q, J = 9.4 Hz, 1H), 3.00 – 2.62 (m, 2H), 2.40 – 2.23 (m, 1H), 1.75 – 1.52 (m, 4H), 0.82 (d, J = 11.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 184.3, 181.8, 170.2, 165.5, 163.6, 159.3, 148.2, 145.3, 143.5, 141.35, 139.9, 132.5, 132.4, 132.3, 132.1, 128.5, 123.1, 122.1, 121.9, 121.1, 119.9, 115.7, 102.0, 60.9, 56.5, 56.4, 54.5, 53.1, 41.1, 39.9, 28.1, 28.0, 26.5. UPLC-DAD-QTOF: $C_{33}H_{31}F_3N_4O_5$ $[M+H]^+$ calcd.: 620.2247, found: 620.2330.

5.2.1.6. **Preparation of catalyst C6**[101]


F3C
CO2H
HNO3
H2SO4
NO2
H2 Pd/C
EtOAc
NH2
MeO
OMe
MeOH, rt,16 h
HO2C
N
H
H2N
MeO
Et3N (1 equiv)
CH3CN, rt, 16 h
1) MeIm, CH3CN, 0 °C, 10 min
2) MsCl, CH3CN, - 5 °C, 20 min
3) 3,5-(CF3)2C6H3NH2, rt, on
CF3
NH
O

C6

Step 1: preparation of 3-nitro-5-(trifluoromethyl)benzoic acid

To a solution of 3- trifluoromethylbenzoic acid (2 g, 10 mmol) in concentrated sulphuric acid (10 mL) was added nitric acid (2 mL) at 0 °C over 15 min. The mixture was stirred at 35 °C for 3 h, and slowly poured onto ice. The precipitate was filtered and dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to give 3- nitro-5-(trifluoromethyl) benzoic acid as a white powder. Yield: 2,16 g, 9.2 mmol, 92 %. All spectroscopic data were identical to those reported in the literature.[101] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.74 (s, 1H), 9.1 (s, 1H).

Step 2: preparation of 3-amino-5-(trifluoromethyl)benzoic acid

To a solution of the nitrocompound (1.56 g, 6.68 mmol) in EtOAc (15 mL) under inert atmosphere, Pd/C (Pd 10% in activated carbon, 10 % in weight) was added and the reaction mixture was stirred under H_2 atmosphere (1 atm.) at room temperature for 20 h. The solution was filtered over celite and the filtrate was concentrated under reduced pressure to 3-amino-5-(trifluoromethyl)benzoic acid as a white solid. Yield: 1.08 g, 5.3 mmol, 79 %. All spectroscopic data were identical to those reported in the literature.[101] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (s, 1H), 7.53 (s, 1H), 7.72 (s, 1H).

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[101] Reproduced from: Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185–8195.

Step 3: preparation of 3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (710 mg, 5.0 mmol, 1 equiv.) in MeOH (5 mL) at room temperature the 3-amino-5-(trifluoromethyl)benzoic acid (685 mg , 5.0 mmol, 1 equiv.) was added. The mixture was stirred at the same temperature for 15 h. The white precipitate was filteredand washed with MeOH. The obtained yellow solid was dried *in vacuo*. Yield: 1.5 g, 4.8 mmol, 96 %. All spectroscopic data were identical to those reported in the literature.[101] ^{1}H NMR (300 MHz, Acetone-*d6*) δ 9.88 (s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 4.50 (s, 3H).

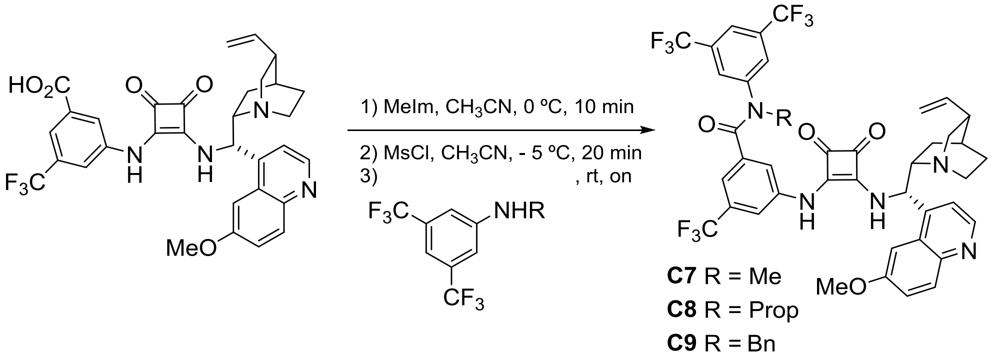
Step 4: preparation of 3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid

To a suspension of the above obtained material (630 mg, 2.0 mmol, 1 equiv.) in CH_3CN (2 mL) at room temperature, Et_3N (0.3 mL, 2.0 mmol, 1 equiv.) and (*R*,*R*)-9-deoxy-9-*epi*aminoquinine (646 mg, 2.0 mmol, 1 equiv.) was added. The reaction mixture was stirred vigorously at room temperature for 16 h. The reaction mixture was directly submitted to purification by purified by flash column chromatography (CH_2Cl_2: MeOH, 99:1). The obtained yellow solid was dried *in vacuo*. Yield: 570 mg, 0.94 mmol, 47 %. All spectroscopic data were identical to those reported in the literature.[101] ^{1}H NMR (300 MHz, Acetonitrile-*d*3) δ 11.51 (brs, 1H), 10.17 (bs, 1H), 8.85 (d, *J* = 4.5 Hz, 1H), 8.38 (s, 1H), 8.07 – 7.56 (m, 5H), 7.32 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.40 (bs, 1H), 5.86 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.32 – 4.97 (m, 2H), 4.50 (s, 1H), 4.05 – 3.53 (m, 5H), 3.51 – 3.11 (m, 2H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.25 – 1.97 (m, 4H), 1.78 (t, *J* = 12.4 Hz, 1H), 1.22 (d, *J* = 13.9 Hz, 1H).

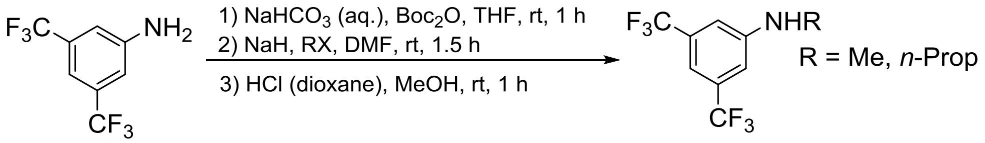
Step 5: preparation of *N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide **C6**

1-Methylimidazole (0.2 mL, 2.5 mmol, 2.5 equiv.) was added to a slurry of the above obtained material (570 mg, 1.0 mmol, 1 equiv.) in CH_3CN (2.5 mL) at 0 °C, and the mixture was stirred for 10 min then a solution of MsCl (0.17 mL, 1.5 mmol, 1.5 equiv.) in CH_3CN (0.1 mL) was added. After the mixture was stirred at 0 °C for 20 min, 3,5-bis(trifluoromethyl)aniline (0.15 mL, 1.0 mmol, 1 equiv.) was added and the mixture was stirred at room temperature over night. H_2O (10 mL) was added to the mixture causing a precipitate, which upon addition of EtOAc (10 mL) redissolved. The layers were separated and the organic layer was washed with brine (3 x 50 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the compound **C6** as a yellow solid. Yield: 556 mg, 6.8 mmol, 68 %. All spectroscopic data were identical to those reported in the literature.[101] $[\alpha]_D^{25} = -52.7$ °(C = 0.5, MeOH). M.p. = 195.6 – 197.2 °C. ^{1}H NMR (300 MHz, DMSO-*d*6) 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, *J* = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.22 – 5.82 (m, 2H), 5.30 – 4.81 (m, 2H), 3.96 (s, 3H), 3.56 – 3.06 (m, 4H), 2.85 – 2.55 (m, 2H), 2.28 (q, *J* = 8.0, 7.2 Hz, 1H), 1.84 – 1.34 (m, 4H), 0.68 (s, 1H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 184.6, 180.1, 168.5, 164.4, 163.0, 157.9, 147.8, 144.3, 143.1, 142.1, 140.7, 140.3, 136.0, 131.5, 130.9, 130.5, 127.5, 125.1, 121.2, 120.0, 118.0, 117.5, 116.8, 114.3, 101.5, 58.9, 55.7, 27.3, 26.0. UPLC-DAD-QTOF: $C_{40}H_{33}N_5O_4F_9$ $[M+H]^+$ calcd.: 818.2389, found: 818.2398.

5.2.1.7. **Preparation of catalyst C7[102], C8 and C9**


1) MeIm, CH$_3$CN, 0 ºC, 10 min
2) MsCl, CH$_3$CN, - 5 ºC, 20 min
3) , rt, on
C7 R = Me
C8 R = Prop
C9 R = Bn

5.2.1.7.1. Preparation of N-alkyl benzylamines[103]


1) NaHCO$_3$ (aq.), Boc$_2$O, THF, rt, 1 h
2) NaH, RX, DMF, rt, 1.5 h
3) HCl (dioxane), MeOH, rt, 1 h
R = Me, *n*-Prop

To a stirred solution of 3,5-bistrifluoromethylbenzylmine (1.22 g, 5.0 mmol, 1 equiv.) in THF (15 mL) Boc$_2$O (1.30 g, 6.0 mmol, 1.2 equiv.) was added and an aqueous saturated solution of NaHCO$_3$ (15 mL) were successively added. The resulting mixture was stirred at room temperature for 1 h, quenched with water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$ and the solvent was eliminated under reduced pressure. The product obtained was dissolved in DMF (15 mL) and cooled to 0 °C. NaH (60 % in oil) previously washed with hexane (383 mg, 10 mmol, 2 equiv.) was slowly added to the solution and the resulting mixture was allowed to stir at room temperature for 20 min. Then methyl or *n*-propyl iodide (5.0 mmol, 1 equiv.) was added and the mixture was allowed to stir for a further 1.5 h. The reaction was stopped by adding water (15 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (5 x 15 mL), dried over MgSO$_4$, filtered, and the solvent was eliminated under reduced pressure. The crude obtained was then dissolved in MeOH (7.5 mL) and 4 M HCl solution was added and the resulting solution was stirred at room temperature for 3 h. The reaction was slowly quenched with a saturated aqueous solution of NaHCO$_3$ (3 x 15 mL). The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with brine (3 x 15 mL), dried over MgSO$_4$, filtrate, and the solvent was eliminated under reduced pressure. The product obtained was used without further purification. All spectroscopic data were identical to those reported in the literature.

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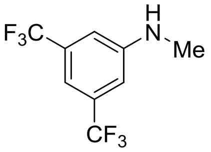
[102] Reproduced from: Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185–8195.

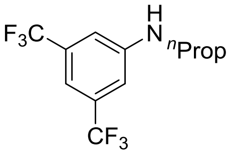
[103] Kataja, O. A.; Koskinen, A. M. P. *ARKIVOK*, **2010**, 205–223.

1-(3,5-bis(trifluoromethyl)phenyl)-*N*-methylmethanamine



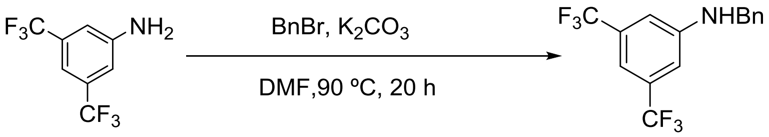
The title compound was prepared from methyl iodide (0.93 mL, 15 mmol, 3 equiv.) according to the general procedure. Yellow oil. Yield: 1.03 g, 4.3 mmol, 85%. All data were consistent with those previously reported.[103] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.77 (s, 1H), 3.89 (s, 2H), 2.48 (s, 3H), 1.47 (s, 1H).

***N*-propyl-1-(3,5-bis(trifluoromethyl)benzyl)methanamine**



The title compound was prepared from *n*-propyl iodide (2.44 mL, 25 mmol, 5 equiv.) according to the general procedure. Yellow oil. Yield: 1.06 g, 3.9 mmol, 79%. All data were consistent with those previously reported.[103] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 2H), 6.92 (s, 2H), 4.07 (s, 1H), 3.13 (td, *J* = 7.0, 5.5 Hz, 2H), 1.76 – 1.60 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).

***N*-Benzyl-3,5-bis(trifluoromethyl)aniline**



A solution of 3,5-bis(trifluoromethyl)phenyl aniline (2.4 g, 10 mmol, 1 equiv.), benzyl bromide (1.18 mL, 10 mmol, 1 equiv.) and potassium carbonate (1.38 g, 10 mmol, 1 equiv.) in DMF (10 mL) was stirred at 90 °C. After 20 h the mixture was cool at room temperature, the mixture was diluted with EtOAc and the organic phase was washed with brine (6 x 40 mL). Drying $MgSO_4$ filtration and evaporation gave the corresponding crude that was purified by flash column chromatography on silica gel (hexane: EtOAc, 99:1-95:5) to afford the desired product as a yellow pale oil. Yield: 1.13 g, 7.1 mmol, 71%. All data were consistent with those previously reported.[104] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 6.98 (s, 2H), 4.45 (d, *J* = 4.3 Hz, 1H), 4.38 (d, *J* = 5.3 Hz, 2H).

5.2.1.7.2. Coupling of acids with anilines to benzamides

1-Methylimidazole (0.2 mL, 2.5 mmol, 2.5 equiv) was added to a slurry of previously prepared 3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid (606 g, 1.0 mmol, 1 equiv.) in CH_3CN (2.5 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (0.17 mL, 1.5 mmol, 1.5 equiv.) in CH_3CN (0.1 mL) was added at the same temperature, and the mixture was stirred for 20 min. the correspondent benzamide (1.0 mmol, 1 equiv.) was then added and the mixture was stirred at room temperature over night. H_2O (10 mL) was added to the mixture, causing a precipitate, which upon addition of EtOAc (10 mL) redissolved. The organic layer was washed with brine (3 x 50 mL), dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether.

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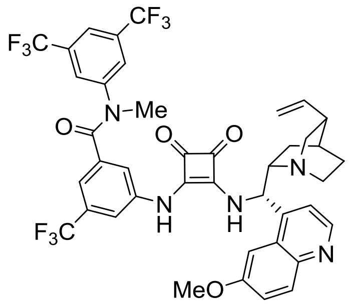
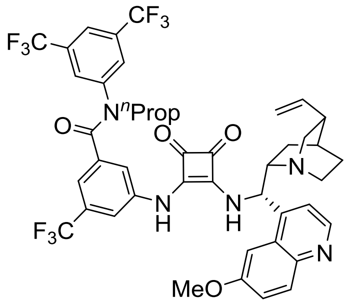
[104] Matsumura, T.; Nakada, M. *Tetrahedron Lett.* **2014**, *55*, 1829–1834.

_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-_N_-methyl-5-(trifluoromethyl)benzamide C7



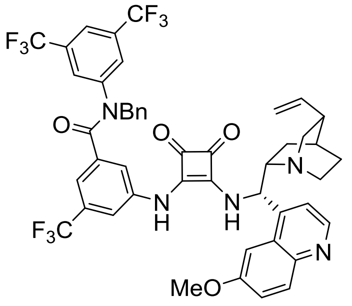
The title compound was prepared from 1-(3,5-bis(trifluoromethyl)phenyl)-*N*-methylmethanamine according to the general procedure. Yellow solid. Yield: 639 mg, 0.7 mmol, 77%. M.p. = 165 – 170 °C. $[\alpha]_D$ = – 115.9 (c = 1, CH_2Cl_2). ^1H NMR (300, $CDCl_3$) δ 8.59 (s, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.87 – 7.16 (m, 8H), 6.90 (s, 1H), 6.19 (s, 1H), 5.87 – 5.66 (m, 1H), 5.15 – 4.82 (m, 2H), 3.96 (s, 3H), 3.45 (s, 4H), 3.21 (d, *J* = 19.8 Hz, 2H), 2.73 (s, 2H), 2.31 (s, 1H), 1.75 – 1.36 (m, 4H), 0.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 181.2, 169.0, 163.5, 159.1, 147.6, 145.2, 144.9, 143.2, 140.6, 140.1, 137.0, 133.1, 133.1, 132.7, 132.0, 131.8, 128.1, 127.1, 124.9, 124.5, 123.0, 121.2, 120.9, 118.9, 117.3, 116.6, 115.4, 101.2, 77.6, 77.4, 77.2, 76.8, 60.2, 56.2, 55.8, 53.9, 41.1, 39.2, 38.6, 27.4, 26.0. UPLC DAD – QTOF: $C_{41}H_{38}N_5O_4F_6$ $[M+H]^+$ calcd.: 831.2593, found: 831.2596.

_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-_N_-propyl-5-(trifluoromethyl)benzamide C8



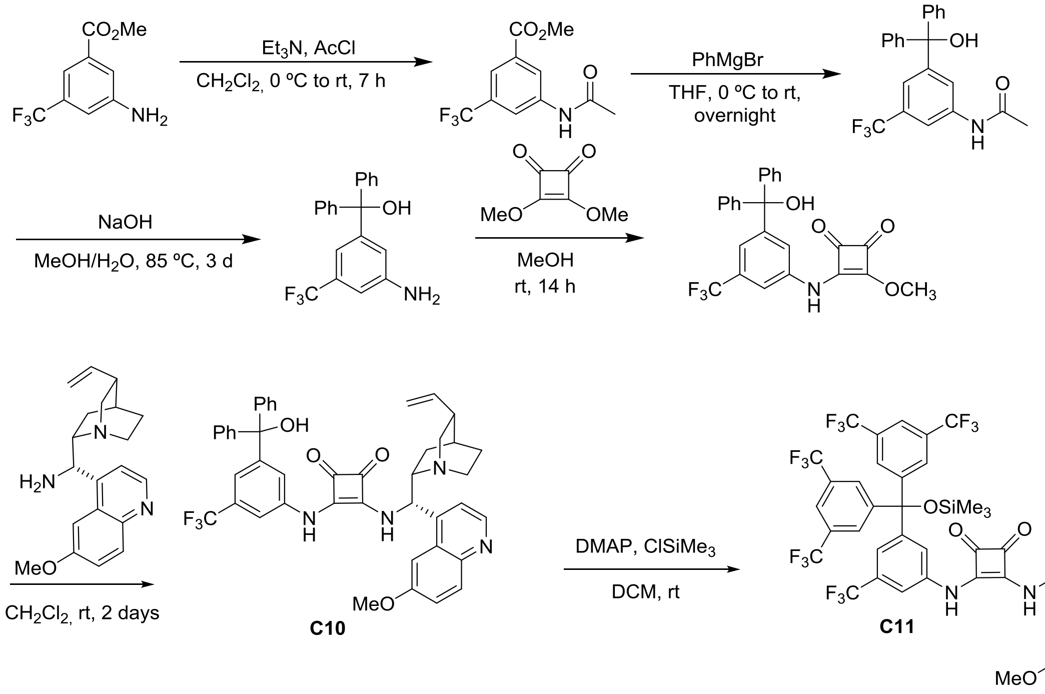
The title compound was prepared from *N*-propyl-1-(3,5-bis(trifluoromethyl)benzyl)methanamine according to the general procedure. Yellow pale solid. Yield: 610 mg, 0.71 mmol, 71%. M.p. = 168 – 173 °C. $[\alpha]_D^{25}$ = – 48.2 (c = 1, CH_2Cl_2). ^1H NMR (300, $CDCl_3$) δ 8.57 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.73 (s, 1H), 7.66 (s, 2H), 7.52 (s, 2H), 7.36 (d, *J* = 8.9 Hz, 2H), 7.18 (s, 1H), 6.85 (s, 1H), 6.17 (s, 1H), 5.90 – 5.68 (m, 1H), 5.18 – 4.89 (m, 2H), 3.94 (d, *J* = 10.7 Hz, 3H), 3.92 – 3.72 (m, 2H), 3.44 (d, *J* = 6.9 Hz, 2H), 3.16 (d, *J* = 10.2 Hz, 1H), 2.92 – 2.60 (m, 2H), 2.33 (s, 1H), 1.89 – 1.42 (m, 5H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 181.1, 169.1, 168.8, 159.1, 147.5, 144.8, 144.0, 139.9, 137.5, 133.2, 132.8, 131.6, 128.2, 124.8, 124.4, 122.9, 121.5, 121.1, 120.8, 119.1, 117.2, 116.5, 115.0, 101.4, 60.2, 56.1, 52.3, 41.0, 39.6, 27.6, 26.2, 21.2, 11.2. UPLC-DAD-QTOF: $C_{34}H_{39}N_5O_4F_9$ [M+H]$^+$ calcd.: 860.2858, found: 860.2842.

***N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide C9**



The title compound was prepared from *N*-Benzyl-3,5-bis(trifluoromethyl)aniline according to the general procedure. Yellow pale solid. Yield: 708 mg, 0.8 mmol, 78%. M.p. = 155 – 168 °C. $[\alpha]_D^{25}$ = – 47.2 (c = 1, CH_2Cl_2). ^{1}H NMR (300, $CDCl_3$) δ 8.56 (s, 1H), 8.02 – 7.66 (m, 3H), 7.57 (s, 1H), 7.43 – 7.02 (m, 10H), 6.85 (s, 1H), 6.17 (s, 1H), 5.81 – 5.62 (m, 1H), 5.05 – 4.91 (m, 4H), 3.93 (s, 3H), 3.63 – 3.30 (m, 2H), 3.13 (s, 1H), 2.78 (s, 1H), 2.66 (s, 1H), 2.30 (s, 1H), 1.63 (brs, 4H), 0.84 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 181.1, 168.9, 163.5, 159.0, 147.6, 144.8, 143.8, 137.0, 135.7, 129.1, 128.4, 122.8, 121.6, 121.1, 120.7, 119.2, 117.1, 116.5, 115.2, 101.4, 60.6, 56.1, 55.9, 54.2, 41.1, 39.3, 27.4, 26.0. UPLC-DAD-QTOF: $C_{47}H_{39}N_5O_4F_9$ [M+H]$^+$ calcd.: 908.2858, found: 908.2855.

5.2.1.8. **Preparation of catalysts C10 and C11**[105]


CO2Me
F3C
NH2
Et3N, AcCl
CH2Cl2, 0 °C to rt, 7 h
PhMgBr
THF, 0 °C to rt, overnight
NaOH
MeOH/H2O, 85 °C, 3 d
MeO
OMe
MeOH
rt, 14 h
Ph
OH
OCH3
H2N
N
CH2Cl2, rt, 2 days
C10
DMAP, ClSiMe3
DCM, rt
CF3
OSiMe3
C11

Step 1: preparation of methyl 3-acetamido-5-(trifluoromethyl)benzoate[106]

To a solution of the obtained methyl 3-amino-5-(trifluoromethyl)benzoate (2.192 g, 10 mmol, 1 equiv.) and Et_3N (1.40 mL, 10 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) acetyl chloride (0.757 mL, 10.5 mmol, 1.5 equiv.) was added dropwise at 0 °C. After 7 hours at room temperature, the reaction mixture was washed with water and brine, dried over $MgSO_4$ and concentrated to provide the title compound as white solid. Yield: 2.534 g, 9.7 mmol, 97%.Which was used in the next step without further purification. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.20 (d, J = 5.4 Hz, 2H), 8.03 (s, 1H), 7.44 (s, 1H), 3.95 (s, 3H), 2.23 (s, 3H).

Step 2: preparation of *N*-(3-(hydroxydiphenylmethyl)-5-(trifluoromethyl)phenyl)acetamide[106]

A solution of the crude material of the previous reaction (1.31 g, 5.0 mmol, 1 equiv.) in THF (10 mL) was added dropwise at 0 °C to a solution of phenyl magnesium bromide (0.5 M in THF, 15 mmol, 3 equiv.). The mixture was stirred at room temperature overnight. The reaction was quenched with NH_4Cl saturated solution, the solvent was evaporated under reduced pressure and diluted with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane: ethyl acetate, 7: 3) to give the title compound as a yellow solid. Yield: 1.67 g, 4.3 mmol, 86%. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.39 (d, *J* = 1.8 Hz, 2H), 7.36 – 7.30 (m, 5H), 7.27 – 7.21 (m, 5H), 2.87 (s, 1H), 2.13 (s, 3H).

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[105] Reproduced from: Odriozola, A.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 12758–12762.

[106] Adapted from: Yang, H.; Zhou, L.; Wang, P. *Photochem. Photobiol. Sci.* **2012**, *11*, 514–517.

Step 3: preparation of (3-amino-5-(trifluoromethyl)phenyl)diphenylmethanol[106]

To a solution of the acetamide obtained above (770 mg, 2.0 mmol, 1 equiv.) in MeOH (15 mL), H_2O (2 mL) and NaOH (1.60 g, 40 mmol, 20 equiv.) was added and the mixture was heated at 85 °C for 3 d. The reaction mixture was neutralized with HCl 1M until pH 7, extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a yellow solid. Yield: 651 mg, 1.9 mmol, 95%. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 10H), 6.97 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.81 (s, 1H), 6.76 (s, 1H), 3.87 (s, 3H).

Step 4: preparation of 3-((3-(hydroxydiphenylmethyl)-5-(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione[107]

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (142 mg, 1.0 mmol, 1 equiv.) in MeOH (4 mL) was added the free aniline obtained above (343 mg, 1.0 mmol, 1 equiv.) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluting with Hexane: ethyl acetate, 7:3) to give the title compound as a yellow solid. Yield: 316 mg, 0.7 mmol, 70%. M.p. = 100 – 110 °C. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.48 (s, 2H), 7.39 – 7.32 (m, 5H), 7.27 – 7.23 (m, 5H), 4.37 (s, 3H), 2.89 (s, 1H). UPLC-DAD-QTOF: $C_{25}H_{19}NO_4F_3$ $[M+H]^+$ calcd.: 454.1266, found: 454.1260.

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[107] Adapted from: Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 3004–3006.

Step 5: preparation of 3-((3-(Hydroxydiphenylmethyl)-5-(trifluoromethyl)phenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione **C10**

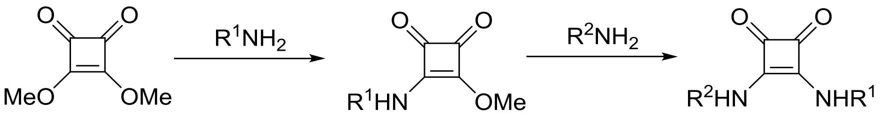
To a suspension of the hemisquaramide obtained above (227 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added (*R*,*R*)-9-deoxy-9-*epi*aminoquinine (162 mg, 0.5 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature for 2 days. The solvent was evaporated in the rotary evaporator and the oil residue was submitted to purification by silica gel column chromatography (CH_2Cl_2: MeOH, 98:2) to give the pure **C10** catalyst as a yellow solid. Yield: 253 mg, 0.34 mmol, 68%. All spectroscopic data were identical to those reported in the literature.[105] M.p.= 185 – 198 °C.^{1}H NMR (300 MHz, MeOD) δ 8.63 (d, *J* = 4.7 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.82 – 7.71 (m, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.29 – 7.10 (m, 10H), 6.20 (d, *J* = 11.1 Hz, 1H), 5.84 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 5.09 – 4.93 (m, 2H), 3.93 (s, 3H), 3.54 (ddd, *J* = 21.8, 17.1, 8.7 Hz, 2H), 3.29 – 3.26 (m, 1H), 3.26 – 3.19 (m, 1H), 2.91 – 2.67 (m, 2H), 2.43 – 2.26 (m, 1H), 1.71 – 1.50 (m, 4H), 0.77 – 0.63 (m, 1H). ^{13}C NMR (75 MHz, MeOD) δ 185.3, 181.9, 169.6, 165.5, 160.4, 152.1, 148.3, 147.8, 145.4, 145.0, 141.9, 140.1, 131.7, 129.3, 129.1, 128.9, 128.3, 124.4, 122.8, 120.4, 120.3, 115.5, 114.9, 102.0, 82.3, 61.1, 56.7, 54.7, 41.8, 40.2, 28.6, 27.9, 27.0. UPLC-DAD-QTOF: $C_{44}H_{40}N_4O_4F_3$ $[M+H]^+$ calcd.: 745.3002, found: 745.2998.

Step 6: preparation of 3-((3-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-5-(trifluoromethyl) phenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) amino)cyclobut-3-ene-1,2-dione **C11**

To a suspension of catalyst **C10** (102 mg, 0.1 mmol, 1 equiv.) and DMAP (20 mg, 0.15 mmol, 1.5 equiv.) in CH_2Cl_2 (0.2 mL) was added dropwise chlorotrimethylsilane (20 μL, 0.15 mmol, 1.5 equiv.) and the reaction mixture was stirred for 14 h at room temperature. Then, CH_2Cl_2 (2 mL) was added and the organic layer was washed twice with water and HCl 1 M, dried over $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography on silica gel (CH_2Cl_2: MeOH, 98:2) to give pure catalyst **C11** as a yellow solid. Yield: 93.6 mg, 0.086 mmol, 86%. All spectroscopic data were identical to those reported in the literature.[105] M.p. = 160 – 165 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.74 (d, *J* = 4.6 Hz, 1H), 8.07 (t, *J* = 1.8 Hz, 1H), 8.00 (s, 6H), 7.98 – 7.92 (m, 2H), 7.76 (d, *J* = 2.6 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.41 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.32 (s, 1H), 6.34 (d, *J* = 11.4 Hz, 1H), 5.96 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.04 (d, *J* = 10.3 Hz, 1H), 3.97 (s, 3H), 3.82 – 3.67 (m, 1H), 3.52 (dd, *J* = 13.4, 10.2 Hz, 1H), 3.25 – 2.98 (m, 2H), 2.7 – 2.57(m, 1H), 1.37 – 1.11 (m, 2H), 1.02 – 0.87 (m, 1H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, MeOD) δ 185.8, 181.3, 169.5, 166.0, 160.7, 149.1, 148.4, 145.5, 143.8, 141.6, 140.7, 133.3, 132.8, 131.8, 129.4, 129.1, 126.3, 124.6, 123.3, 122.7, 122.3, 120.4, 119.6, 119.1, 116.4, 115.9, 115.9, 101.7, 84.6, 61.2, 56.7, 56.1, 42.2, 39.4, 28.4, 26.8, 26.3, 1.4. UPLC-DAD-QTOF: $C_{42}H_{22}NO_3F_{24}$ $[M+H]^+$ calcd.: 1044.1216, found: 1044.1239.

5.2.1.9. **Preparation of catalysts C12[108] and C13[108]**

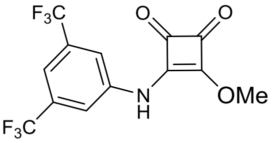
These catalysts were prepared according to the following two-step sequence that involves a squaric ester monoamide intermediate.



5.2.1.9.1. Preparation of common squaric ester monoamide intermediate[109]

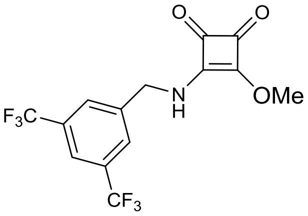
To a solution of 3,4-dimethoxy-3-cyclobute-1,2-dione (1.42 g, 10.0 mmol, 1 equiv.) in MeOH was added the corresponding aniline or benzyl amine (10 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried *in vacuo* to give the desired products.

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione



The title compound was prepared from 3,5-bis(trifluoromethyl)aniline. White solid. Yield: 2.23 g, 6.6 mmol, 66%. All spectroscopic data were identical to those reported in literature.[110] ^{1}H NMR (300, DMSO-*d6*) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione



The title compound was prepared from (3,5-bis(trifluoromethyl)phenyl)methanamine. White solid. Yield: 2.68 g, 7.6 mmol, 76%. All spectroscopic data were identical to those reported in literature.[110] ^{1}H NMR (300, DMSO-*d6*) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

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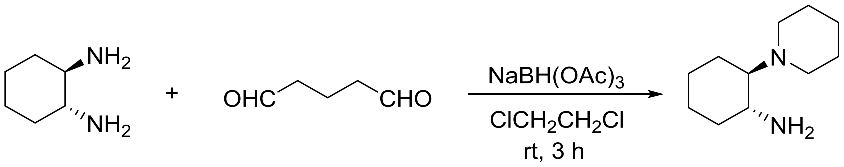
[108] Alegre-Requena, J. V.; Marqués-López, E.; Herrera, R. P. *RSC Adv.* **2015**, *5*, 33450–33462.

[109] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

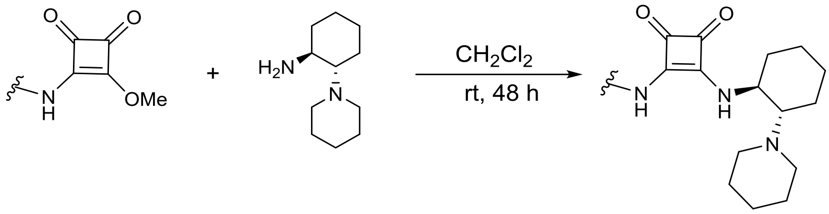
[110] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.

5.2.1.9.2. Synthesis of the (1R,2R)-2-(piperidin-1-yl)cyclohexan-1-amine[111]



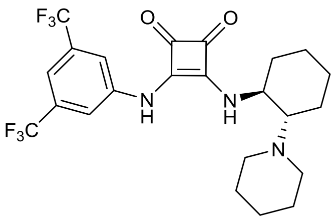
Glutaraldehyde (50 wt % in H_2O, 1.90 mL, 10.4 mmol, 1.04 equiv.) was added dropwise into a mixture of diamine (1.140 g, 10 mmol, 1 equiv.), and $NaBH(OAc)_3$ (8.5 g, 40 mmol, 4 equiv.), in $ClCH_2CH_2Cl$ (60 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 hours, and quenched with NaOH aq solution (6 M, 30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated. The residue was dissolved in 50 mL CH_2Cl_2, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrate to give 1.6 g product as a yellow liquid. Yield: 1.61 g, 8.9 mmol, 89%. All spectroscopy data were identical to those reported in the literature. ^1H NMR (300, $CDCl_3$) δ 2.87 – 2.68 (m, 1H), 2.67 – 2.49 (m, 3H), 2.41 – 2.19 (m, 2H), 2.16 – 1.92 (m, 2H), 1.88 – 1.34 (m, 8H), 1.31 – 0.97 (m, 4H).

5.2.1.9.3. Coupling to final squaramide



To a solution of squaric ester monoamide (1.0 mmol, 1 equiv.) in 5 mL of CH_2Cl_2 was added 2-(piperidin-1-yl)ciclohexanamine (379 mg, 1.0 mmol, 1 equiv.). The reaction mixture was stirred for 48 hours at room temperature. After solvent evaporation the crude material was subjected to silica gel column chromatography (eluent CH_2Cl_2: MeOH, 98:2).

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione C12



The title compound was prepared from 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione. White solid. Yield: 347 mg, 0.7 mmol, 71%. All spectroscopic data were identical to those reported in literature.[108] ^1H NMR (300, $CDCl_3$) δ 7.88 (s, 2H), 7.43 (s, 1H), 4.00 – 3.80

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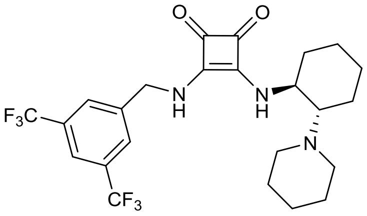
[111] Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

(m, 1H), 2.66 – 2.49 (m, 2H), 2.39 – 2.14 (m, 3H), 1.93 – 1.59 (m, 4H), 1.48 – 0.98 (m, 10H).

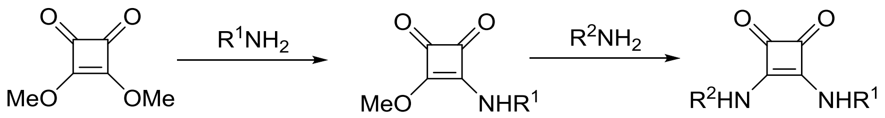
3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione C13



The title compound was prepared from 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione. White solid. Yield: 301 mg, 0.6 mmol, 60%. All spectroscopic data were identical to those reported in literature.[107] ^{1}H NMR (300, $CDCl_3$) δ 7.91 (s, 2H), 7.40 (s, 1H), 4.82 – 4.78 (m, 2H), 4.00 – 3.80 (m, 1H), 2.69 – 2.59 (m, 2H), 2.49 - 2.24 – 2.20 (m, 3H), 1.90 – 1.58 (m, 4H), 1.45 – 0.98 (m, 10H).

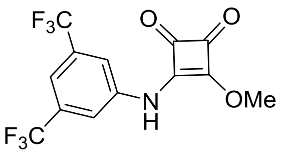
5.2.1.10. Preparation of catalysts C14[112] and C15[112]

These catalysts were prepared according to the following two-step sequence that involves a squaric ester monoamide intermediate.



5.2.1.10.1. Preparation of common squaric ester monoamide intermediate[113]

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione



To a solution of 3,4-dimethoxy-3-cyclobute-1,2-dione (1.42 g, 10.0 mmol, 1 equiv.) in MeOH was added 3,5-bis(trifluoromethyl)aniline (2.29 g, 10 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried *in vacuo* to give the desired product as a white solid. Yield: 2.23 g, 6.6 mmol, 66%. All spectroscopic data were identical to those reported in literature. ^{1}H NMR (300, DMSO-*d6*) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

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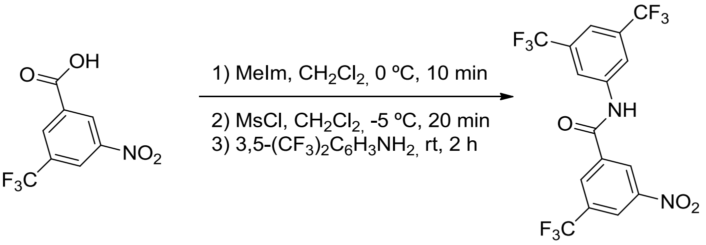
[112] Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185–8195.

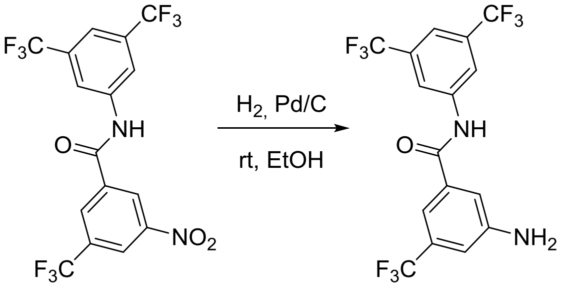
[113] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

N-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide[114]


1) MeIm, CH2Cl2, 0 °C, 10 min
2) MsCl, CH2Cl2, -5 °C, 20 min
3) 3,5-(CF3)2C6H3NH2, rt, 2 h

1-Methylimidazole (1.99 mL, 25 mmol, 2.5 equiv.) was added to a slurry of the 3-nitro-5-(trifluoromethyl)benzoic acid (2.3 g, 10 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.16 mL, 15 mmol, 1.5 equiv.) in CH_2CL_2 (1 mL) was added to the mixture under – 5 °C. After the mixture was stirred under that temperature for 20 min, 3,5-bis(trifluoromethyl)aniline (1.56 mL, 10 mmol, 1 equiv) was added. Then the mixture was stirred at room temperature for 2 hours. H_2O (100 mL) was added to the mixture and a solid precipitated, which was solved with EtOAc (100 mL). The organic layer was washed with brine (3 x 50 mL) and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the title product as a white solid. Yield: 4.5 g, 10 mmol, > 99%. ^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (s, 1H), 8.72 (s, 2H), 8.43 (s, 2H), 7.72 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 164.9, 150.3, 141.9, 138.7, 134.3, 133.3, 131.6, 131.5, 127.5, 124.8, 124.7, 121.7, 121.6, 118.7. UPLC-DAD-QTOF: $C_{16}H_6F_9N_2O_3$ $[M+H]^+$ calcd.: 445.0235, found: 445.0233.

3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide



To a solution of the protected aniline (4.5 g, 10 mmol) in EtOH (20 mL) and EtOAc (2 mL) under inert atmosphere, Pd/C was added (450 mg, Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. After the solution was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product. Yield: 4.2 g, 10 mmol, > 99%. ^{1}H NMR (300 MHz, CD_3OD) 8.40 (s, 2H), 7.77 (s, 1H), 7.68 (s, 1H), 7.49 – 7.42 (m, 1H), 7.42 – 7.38 (m, 1H), 7.12 (s, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 168.4, 151.1, 142.3,

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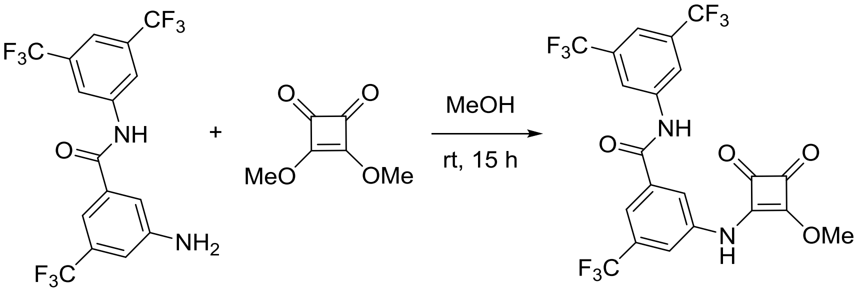
[114] Adapted from: Mao, L.; Wang, Z.; Li, Y.; Han, X.; Zhou, W. *Synlett* **2011**, *1*, 129–133.

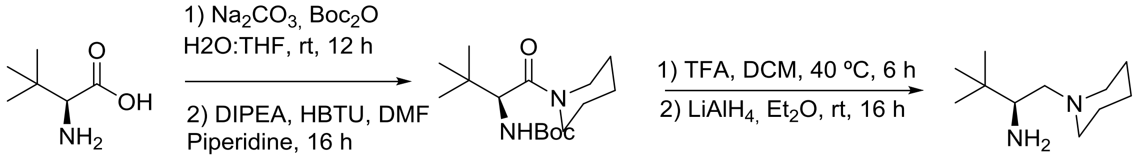
137.4, 133.3 (q), 132.4 (q), 121.5, 118.2, 117.8, 115.0, 115.0, 113.1, 113.1. UPLC-DAD-QTOF: $C_{16}H_{10}N_2OF_9$ $[M+H]^+$ calcd.: 417.0649, found: 417.0638.

N-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide



To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (711 mg, 5.0 mmol, 1 equiv.) in MeOH (10 mL) was added the free aniline (2.29 g, 5.5 mmol, 1.1 equiv.) at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtrated and washed with MeOH. Obtained white solid was dried *in vacuo* to give the title product as a white solid. Yield: 2.31 g, 4.4 mmol, 88%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.71 (s, 1H), 10.52 (s, 1H), 8.03 (s, 2H), 7.73 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.39 (s, 1H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 187.5, 184.4, 179.6, 169.2, 164.2, 140.7, 139.5, 136.0, 130.5 (q), 129.5 (q), 125.0, 122.6, 121.4, 120.1, 119.1, 118.7, 116.8, 60.8. UPLC-DAD-QTOF: $C_{21}H_{12}F_6N_2O_4F_9$ $[M+H]^+$ calcd.: 527.0653, found: 527.0655.

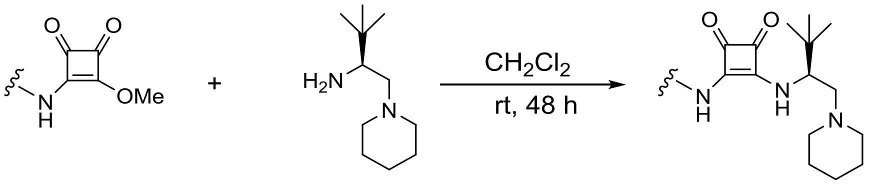
5.2.1.10.2. Synthesis of the (S)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine[110]



Na_2CO_3 (2.12 g, 20 mmol, 2 equiv.) and Boc_2O (3.3 g, 15 mmol, 1.5 equiv.) were added to a solution of *tert*-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL) an THF (5 mL) at 0 °C. After stirring for 12 h at room temperature HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The aquous phases were combined, washed with brine (50 mL) and dried over $MgSO_4$. After removing the solvent under reduced pressure, the resulting residue was redissolved in dry DMF (20 mL) and DIPEA (2.6 g, 20 mmol, 2 equiv.) and HBTU (5.7 g, 15 mmol, 1.5 equiv.) were added. After stirring for 1 h piperidine (0.94 g, 11 mmol, 1.1 equiv.) was added and the mixture was stirred for further 16 h. The reaction was quenched adding HCl 1 M (20 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were combined and washed with HCl 1 M and brine (20 mL). The solvent was then removed under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluting with hexane: EtOAc, 85:15) to afford *tert*-butyl (*S*)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate as a white solid. Yield: 1.6 g, 8.3 mmol, 83%. All spectroscopy data were identical to those reported in the literature.[110] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.43 (s, 9H), 1.52 – 1.62(m, 6H), 3.46 – 3.69 (m, 4H), 4.54 (d, *J* = 9.7 Hz, 1H), 5.38 (d, *J* = 9.6 Hz, 1H).

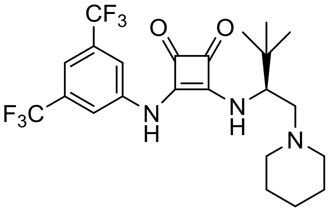
The previously obtained amide (1.6 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 °C until no more starting material was observed by TLC (eluting with hexane: EtOAc, 70:30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40 %), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afferd the aminoamide as a yellow oil. The aminoamide was then dissolved in dry diethyl ether (10 mL) and was added dropwise over a suspension of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 h. The reaction was quenched by the addition of water (5 mL) and NaOH 15 % (1.2 mL) al 0 °C. The resulting mixture was filtered and the filtrate was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane: EtOAc, 1:1) to afford (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine as yellow oil. Yield: 1.4 g, 7.4 mmol, 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.52 (d, *J* = 12.3 Hz, 4H), 2.28 (dd, *J* = 12.3, 2.8 Hz, 3H), 2.13 (dd, *J* = 12.1, 11.2 Hz, 1H), 1.61 – 1.53 (m, 4H), 1.44 – 1.42 (m, 2H), 0.90 (s, 9H).

5.2.1.10.3. Coupling to final squaramide



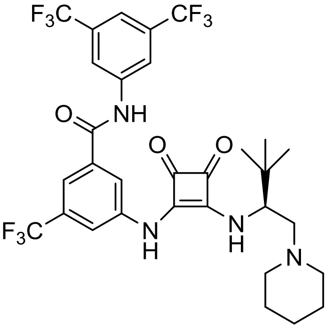
To a solution of squaric ester monoamide (1.0 mmol, 1 equiv.) in 5 mL of MeOH was added (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine (169 mg, 1.0 mmol, 1 equiv.). The reaction mixture was stirred for 48 hours at room temperature. The formed white precipitate was filtered and washed with CH_2Cl_2 to afford essentially pure the desired compounds.

(*S*)-3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)amino)cyclobut-3-ene-1,2-dione C14



The title compound was prepared from 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione. White solid. Yield: 289 mg, 0.59 mmol, 59%. All spectroscopic data were identical to those reported in literature.[110] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.08 (s, 2H), 7.64 (s, 1H), 4.07 – 3.93 (m, 1H), 2.49 – 2.04 (m, 5H), 1.51 – 1.22 (m, 6H), 0.93 (s, 9H).

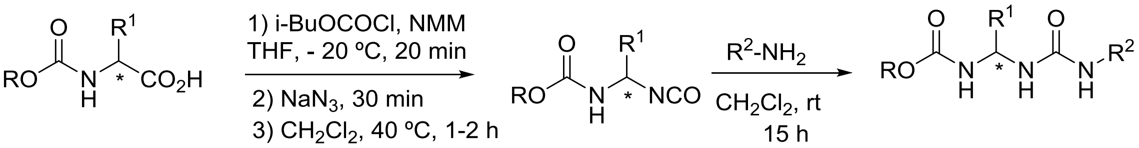
(*S*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-((3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide C15



The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide. White solid. Yield: 440 mg, 0.65 mmol, 65%. All spectroscopic data were identical to those reported in literature.[112] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1H), 10.01 (s, 1H), 8.61 (s, 2H), 8.46 (s, 1H), 8.01 (s, 1H), 8.00 (s, 1H), 7.61 (s, 1H), 7.56 (s, 1H), 4.02 – 3.98 (m, 1H), 2.51 – 2.47 (m, 2H), 2.48 – 2.44 (m, 1H), 2.36 – 2.33 (m, 2H), 1.49 – 1.40 (m, 6H), 0.98 (s, 9H).

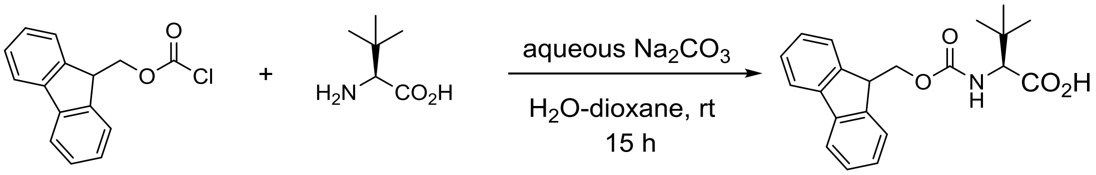
5.2.1.11. **Preparation of ureidopeptide-based Brønsted base catalysts C16[115], C17 and C18**

Ureidopeptide-based Brønsted base catalysts were prepared according to the following general scheme:



5.2.1.11.1. Preparation of carbamate N-protected α-amino acids

(*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3,3-dimethylbutanoic acid[116]



To a stirred solution of *L-tert*-leucine (1.31 g, 10 mmol, 1 equiv.) in 10% aqueous Na_2CO_3 (26 mL) and dioxane (10 mL), was slowly added at 0 °C a solution of the chloroformiate (1.26 mL, 10 mmol, 1 equiv.) in dioxane (30 mL). The mixture was stirred in an ice bath for 1 hour and the allowed to warm to room temperature and subsequently stirred at the same temperature for 15 hours, poured into water (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated to afford the product as a white solid. Yield: 3.53 g, 9.5 mmol, 95%. ^1H NMR (300 MHz, CD_3OD) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 6.7 Hz, 2H), 7.39 (t, *J* = 7.5, 2H), 7.30 (dt, *J* = 7.5 Hz, 1.0, 2H), 4.50 (s, 2H), 4.39 - 4.33 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.05 (d, brs, 1H), 3.66 (s, 1H), 1.03 (s, 9H).

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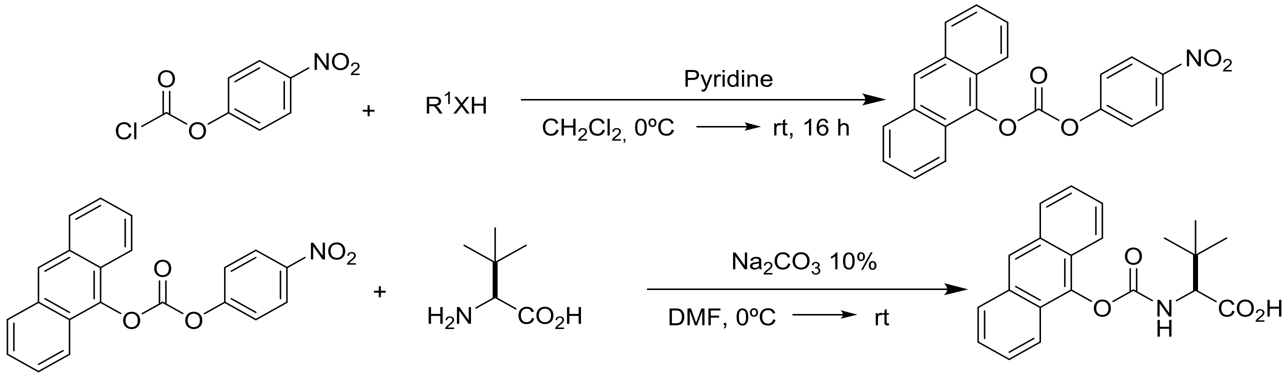
[115] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

[116] Bain, J. D.; Wacker, D. A.; Kuo, E. E.; Chamberlin, A. R. *Tetrahedron*, **1991**, *47*, 2389–2400.

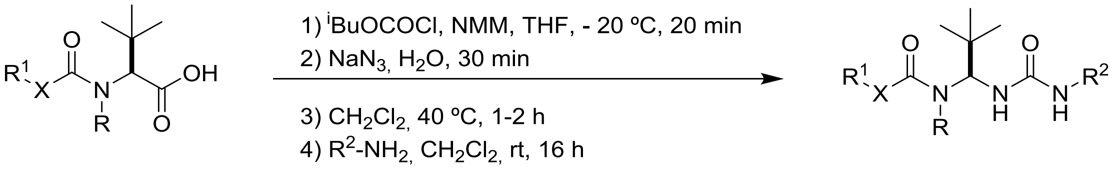
(*S*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid[115]



Step 1: To a stirred solution of *p*-nitrophenylchloroformate (2.2 g, 11 mmol, 1.1 equiv.) in dichloromethane (13.6 mL) was added pyridine (0.9 mL, 11 mmol, 1.1 equiv.). The white slurry was cooled to 0 °C, and alcohol (10 mmol, 1 equiv.) was added in several portions to keep the temperature at 0 °C. After completion of the addition, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and subsequently washed with 1 M HCl (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under reduced pressure. The residue was used in the next step without further purification, 3.6 g, 10 mmol, 91% yield.

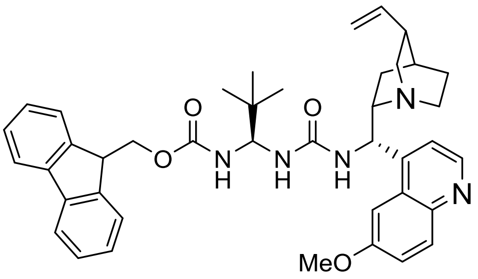
Step 2: To a stirred solution of *L*-*tert*-leucine (1.31 g, 10 mmol, 1 equiv.) in 10 % aqueous Na_2CO_3 (26 mL), and dimethylformamide (10 mL) was slowly added at 0 °C solution of the 4-nitrophenyl carbonate (3.6 g, 10 mmol, 1 equiv.) in dimethylformamide (30 mL). The mixture was stirred in an ice bath for 1 h and then allowed to warm to room temperature and subsequently stirred at the same temperature overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane: ethyl acetate, 80:20) to afford the (*S*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid, 2.5 g, 7.2 mmol, 72% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.38 (d, *J* = 8.9 Hz,2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.65 – 7.54 (m, 2H), 7.53 – 7.46 (m, 2H), 6.18 (q, *J* = 12.1 Hz, 2H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.28 (d, *J* = 10.2 Hz, 1H), 1.01 (s, 9H).

5.2.1.11.2. Preparation of α-amino acid derived isocyanates and coupling with amines[117]


1) ^{i}BuOCOCl, NMM, THF, - 20 °C, 20 min
2) NaN$_3$, H$_2$O, 30 min
3) CH$_2$Cl$_2$, 40 °C, 1-2 h
4) R^2-NH$_2$, CH$_2$Cl$_2$, rt, 16 h
R^1
X
N
R
O
OH
O
R^2
H
H

To a cooled solution of the corresponding *N*-protected dipeptide (5.0 mmol, 1 equiv.) in dry THF (20 mL) were added isobutyl chloroformate (0.65 mL, 5.0 mmol, 1.equiv.), and *N*-methylmorpholine (0.6 mL, 5.0 mmol, 1 equiv.) and the mixture was stirred at – 20 °C for 20 min. Then, a suspension of NaN_3 (0.48 g in 5 mL of H_2O, 7.5 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at the same temperature. After 30 min, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil which was dissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 °C under nitrogen for 1-2 h. The reaction was monitored by IR analysis until disappearance of the azide band. After completion, the chiral amine was added (3.5 mmol, 0.7 equiv.) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2: MeOH, 95:5).

(9*H*-fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate C16:



The title compound was prepared from (*s*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3,3-dimethylbutanoic acid and 9-amino-(9-deoxy)*epi*hydroquinine according to the general procedure. White solid. Yield 1.9 g., 2.9 mmol, 58%. All data were consisted with those previously reported.[115] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.0 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.55 (t, *J* = 8.1 Hz, 2H), 7.43 – 7.24 (m, 6H), 6.35 (s, 1H), 5.25 (s, 1H), 5.17 – 4.90 (m, 3H), 4.40 (dd, *J* = 10.5, 7.2 Hz, 1H), 4.30 (dd, *J* = 10.5, 6.8 Hz, 1H), 4.18 (d, *J* = 6.5 Hz, 1H), 3.93 (s, 3H), 3.21 (dd, *J* = 16.5, 6.7 Hz, 2H), 3.03 (s, 1H), 2.76 – 2.59 (m, 1H), 2.44 (d, *J* = 11.5, 1H), 1.64 – 1.15 (m, 8H), 0.86 (s, 9H), 0.78 (t, *J* = 7.3, 3H).

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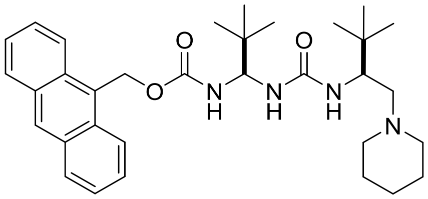
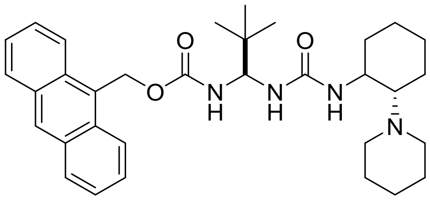
[117] Procedure adapted from: Suresh Babu, V. V.; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705.

Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)ureido)-2,2-dimethylpropyl)carbamate C17:



The title compound was prepared from (*S*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid and (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine according to the general procedure. The catalyst was purified by filtration affording a white solid. Yield: 1.6 g., 3.0 mmol, 61%. M.p. = 146 – 148 °C. $[\alpha]_D^{25}$ = – 57.2° (c = 1, CH_2Cl_2). ^1H NMR (300 MHz, DMSO-*d6*) δ 8.67 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 2H), 8.12 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.65 – 7.43 (m, 4H), 7.28 (d, *J* = 9.2 Hz, 1H), 6.05 (q, *J* = 12.3 Hz, 2H), 5.87 (dd, *J* = 13.3, 9.6 Hz, 1H), 5.20 (t, *J* = 9.3 Hz, 1H), 3.54 (td, *J* = 9.2, 3.7 Hz, 1H), 2.42 – 1.93 (m, 6H), 1.40 (t, *J* = 5.7 Hz, 4H), 1.33 – 1.26 (m, 2H), 0.81 (s, 18H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 157.1, 155.6, 130.9, 130.5, 128.9, 128.5, 127.4, 126.5, 125.2, 124.1, 64.9, 60.1, 57.7, 54.2, 53.7, 36.2, 34.6, 26.4, 25.5, 24.1. UPLC-DAD-QTOF: $C_{33}H_{46}NO_4O_3$ $[M+H]^+$ calcd.: 546.3570, found: 546.3583.

Anthracen-9-ylmethyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate C18:

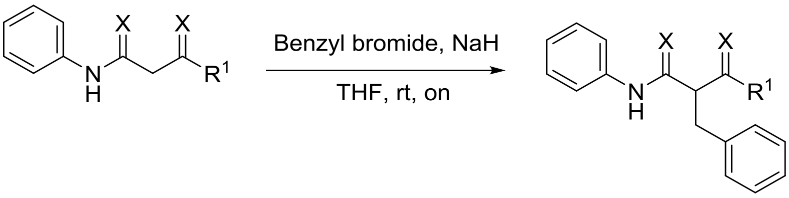


The title compound was prepared from (*S*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid and (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexan-1-amine according to the general procedure. The catalyst was purified by filtration affording a white solid. Yield: 1.7 g., 3.1 mmol, 63%. M.p. = 146 – 148 °C. $[\alpha]_D^{25}$ = + 65.5 (c = 1, CH_2Cl_2). ^1H NMR (300 MHz, DMSO-*d6*) δ 8.69 (s, 1H), 8.33 (d, *J* = 8.5 Hz, 2H), 8.13 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.66 – 7.44 (m, 4H), 7.28 (d, *J* = 9.2 Hz, 1H), 6.10 (q, *J* = 12.3 Hz, 2H), 5.97 – 5.89 (m, 1H), 5.20 (t, *J* = 9.3 Hz, 1H), 3.56 (td, *J* = 9.2, 3.7 Hz, 1H), 2.45 – 1.98 (m, 6H), 1.47-1.49 (m, 4H), 1.33 – 1.26 (m, 1H), 0.81 (s, 18H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 157.43, 155.81, 130.94, 130.50, 128.91, 128.55, 127.42, 126.53, 125.24, 124.15, 67.14, 65.98, 57.84, 54.97, 49.16, 48.64, 35.80, 33.18, 25.99, 25.41, 24.96, 24.67, 24.37, 24.25, 24.01, 23.84, 22.89.UPLC-DAD-QTOF: $C_{33}H_{44}N_4O_3$ $[M+H]^+$ calcd.: 544.3413, found: 544.3333.

5.3. **Experimental section of Chapter 3**

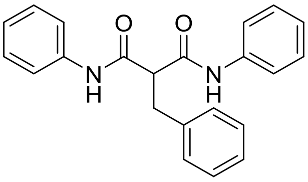
5.3.1. **Synthesis of maloimides**

5.3.1.1. **Synthesis of 1, 2 and 3**



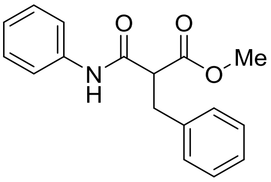
A solution of the corresponding (thio)malonate or (thio)malonamide(3 mmol, 1 equiv.), benzyl bromide (0.35 mL, 3 mmol, 1 equiv.) and sodium hydride (72 mg, 3.6 mmol, 1.2 equiv.) in THF (10 mL) were added and the mixture was stirred at room temperature for 20 h. Then, the mixture was cooled at room temperature, diluted with EtOAc and washed with brine (6 x 40 mL). Drying with $MgSO_4$ filtration and evaporation gave the corresponding crude product that was purified by flash column chromatography.

2-Benzyl-*N*1,*N*3-diphenylmalonamide 1:



The title compound was prepared from *N*1,*N*3-diphenylmalonamide. The product was purified by flash column chromatography on silica gel (hexane: EtOAc, 6:1) and obtained as a white foam. Yield: 774 mg. 2.2 mmol, 75%. All data were consistent with those previously reported.[118] ^1H NMR (300 MHz, DMSO-*d6*) δ 9.97 (brs, 2H), 7.65 – 7.47 (m, 4H), 7.37 – 7.24 (m, 8H), 7.19 (d, *J* = 6.9 Hz, 1H), 7.10 – 6.95 (m, 2H), 3.85 (t, *J* = 7.5 Hz, 1H), 3.25 (d, *J* = 7.6 Hz, 2H).UPLC-DAD-QTOF: $C_{22}H_{20}N_2O_2$ $[M+H]^+$ calcd.: 344.1525, found: 344.1672.

Methyl 2-benzyl-3-oxo-3-(phenylamino)propanoate 2:



The title compound was prepared from methyl 3-oxo-3-(phenylamino)propanoate. The product was purified by flash column chromatography on silica gel (hexane: EtOAc, 10:1) and was obtained as a yellow oil. Yield: 594 mg, 2.1 mmol, 71%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (brs, 1H), 7.55 – 7.44 (m, 2H), 7.39 – 7.10 (m, 8H), 3.69 (s, 3H), 3.70 – 3.58 (m, 1H), 3.47 – 3.20 (m, 2H). ^{13}C NMR (75

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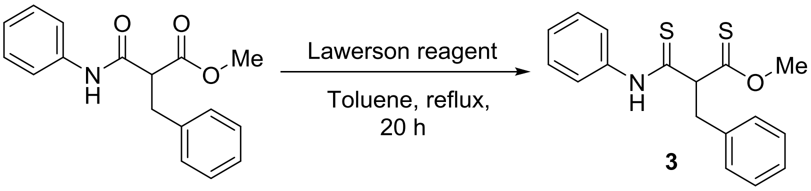
[118] Kappe, T.; Karem, A. S.; Stadlbauer, W. *J. Heterocyclic Chem.* **1988**, *25*, 857–862.

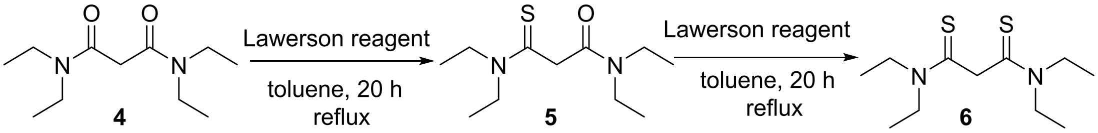
MHz, CDCl3) δ 165.2, 162.4, 136.0, 135.9, 129.8, 129.4, 129.2, 128.5, 128.4, 67.8, 48.3, 37.3. UPLC-DAD-QTOF: $C_{17}H_{17}NO_3$ $[M+H]^+$ calcd.: 283.1208, found: 283.1467.

*5.3.1.1.1. Synthesis of o-methyl 2-benzyl-3-(phenylamino)-3-thioxopropanethioate **3**:*



A solution of methyl 2-benzyl-3-oxo-3-(phenylamino)propanoate **2** (283 mg, 1 mmol, 1 equiv.) and Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulphide] (176 mg, 4 mmol, 4 equiv.) in anhydrous toluene (10 mL) were heated at reflux under nitrogen for 20 h. After completion, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane: EtOAc, 3:1) to afford the *O*-methyl 2-benzyl-3-(phenylamino)-3-thioxopropanethioate **3** as a yellow foam, 94 mg, 0.3 mmol, 31% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (brs, 1H), 7.69 – 7.51 (m, 2H), 7.50 – 7.13 (m, 8H), 4.26 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.68 (s, 3H), 3.44 (dd, *J* = 18.4, 7.2 Hz, 2H).^{13}C NMR (75 MHz, CDCl3) δ 171.6, 166.8, 129.5, 129.4, 125.6, 125.5, 125.3, 119.7, 119.6, 119.4, 74.1, 56.6, 22.6. UPLC-DAD-QTOF: $C_{17}H_{17}NOS_2$ $[M+H]^+$ calcd.:315.0752, found:315.1179.

5.3.1.2. **Synthesis of 4, 5 and 6**



Step 1:

*N*1,*N*1,*N*3,*N*3-tetraethylmalonamide **4** (0.21 mL, 1 mmol, 1 equiv.) and Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulphide] (484 mg, 1.2 mmol, 1.2 equiv.) in anhydrous toluene (10 mL) were heated at reflux under nitrogen for 20 h. After completion, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane: EtOAc, 3:1) to afford the 3-(diethylamino)-*N*,*N*-diethyl-3-thioxopropanamide **5** as a yellow foam, 78 mg, 0.7 mmol, 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 – 3.72 (m, 4H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 1.34 – 1.22 (m, 9H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.10, 53.65, 48.19, 47.36, 13.81, 11.08. UPLC-DAD-QTOF: $C_7H_{14}N_2O_S$ $[M+H]^+$ calcd.: 174.0827, found: 174.1727.

Step 2:

To a solution of **5** (87 mg, 0.5 mmol, 1 equiv.) in anhydrous toluene (5 mL) Lawesson's reagent (808 mg, 2 mmol, 4 equiv.) was added. The reaction was heated at reflux under nitrogen for 20 h. After completion, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1) to afford the *N*1,*N*1,*N*3,*N*3-tetraethylpropanebis(thioamide) **6** as a yellow oil, 122 mg, 0.41 mmol, 82% yield. All data were consistent with those previously reported.[119] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 4H), 3.90 – 3.81 (m, 4H), 1.33 (td, *J* = 7.2, 1.6 Hz, 12H).

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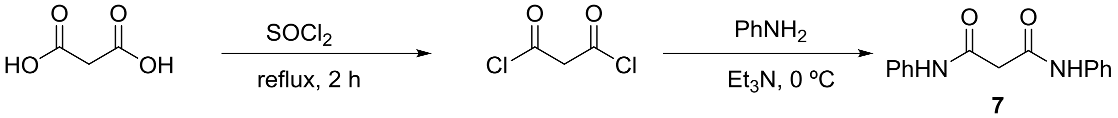
[119] Hartke, K.; Heinz-Georg, M. *Arch. Pharm.* **1988**, *321*,863–871.

5.3.1.3. **Synthesis of 7 and 8**

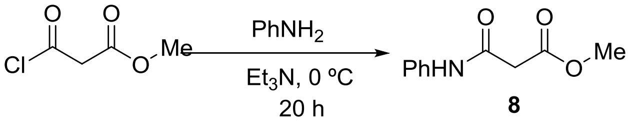
*5.3.1.3.1. Synthesis of **7***



7

To a solution of malonic acid (2.1 g, 20 mmol, 1 equiv.) $SOCl_2$ was added (3 mL, 40 mmol, 2 equiv.) and the mixture was heated at reflux under nitrogen for 2 h. After completion the excess $SOCl_2$ was evaporated under reduced pressure and the residue was dissolved in Et_3N (7 mL, 50 mmol, 2.5 equiv.) and phenyl amine (5.5 mL, 60 mmol, 3 equiv.) was added dropwise at 0 °C. After completion of coupling reaction, the mixture was diluted in DCM (15 mL) and acidified with HCl 3 M to pH 2, the aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The solid obtained was filtered and the filtrate was washed with diethyl ether. *N*1,*N*3-diphenylmalonamide **7** was obtained as a white foam. Yield: 3.0 g, 11.8 mmol, 59 %. All data were consistent with those previously reported.[120] ^1H NMR (300 MHz, DMSO-*d6*) δ 10.19 (brs, 2H), 7.69 – 7.54 (m, 4H), 7.32 (dd, *J* = 8.5, 7.3 Hz, 4H), 7.08 (d, *J* = 7.3 Hz, 2H), 3.49 (s, 2H).

*5.3.1.3.2. Synthesis of **8***



8

To a solution of commercially available methyl 3-chloro-3-oxopropanoate (1.18 mL, 11 mmol, 1.1 equiv.) in DCM (30 mL), Et_3N (2.8 mL, 20 mmol, 2 equiv.) and phenyl amine (0.9 mL, 10 mmol, 1 equiv.) were added at 0 °C and the mixture was stirred for 20 h. After reaction completion, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane: EtOAc, 5:1) to afford methyl 3-oxo-3-(phenylamino)propanoate **8** as a yellow foam. Yield: 1.9 g, 9.8 mmol, 98% yield. All data were consistent with those previously reported.[121] ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (brs, 1H), 7.66 – 7.47 (m, 2H), 7.39 – 7.23 (m, 2H), 7.13 (dd, *J* = 7.5, 1.4 Hz, 1H), 3.83 – 3.73 (m, 3H), 3.48 (s, 2H).

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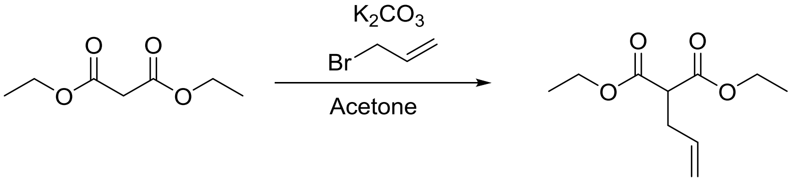
[120] Echi, M.; Azzena, U.; Delussu, M. P.; Dalloccio, R.; Dessi, A.; Cosseddu, A.; Pala, N.; Neamati, N. *Molecules*, **2008**, *13*, 2442–2461.

[121] Abas, H.; Frampton, C. S.; Spivey, A. C. *J. Org. Chem*. **2016**, *81*, 9947–9956.

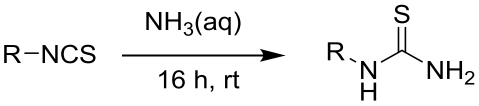
5.3.2. **Synthesis of barbituric acid derivative 9 and 12:**

5.3.2.1. **Synthesis of diethyl 2-allylmalonate**



Diethyl malonate (5.9 mL, 37.5 mmol, 1.5 equiv.) and allyl bromide (2.16 mL, 25 mmol, 1 equiv.) were added to a solution of potassium carbonate (17.27 g, 75 mmol, 3 equiv.) in acetone (124 mL) and the mixture was stirred for 24 h at 23 °C. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride solution (200 mL) and extracted with methylene chloride (3 x 100 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed under reduced pressure. The oily residue was purified by flash-chromatography through silica gel (Hexane: ethyl acetate 99:1). The product containing fractions were evaporated and the oily residue was distillated under reduced pressure (2 mbar, 45 °C, rotary evaporator/heat gun) to remove the excess of diethyl malonate. Diethyl 2-allylmalonate was obtained as a colorless oil (6.8 g, 24.0 mmol, 90%). All the analytical data are consistent with the previously published data.[122] ^{1}H NMR (300 MHz, $CDCl_3$) 5.78 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.15 – 5.03 (m, 2H), 4.19 (dd, *J* = 7.2, 1.0 Hz, 4H), 3.45 – 3.34 (m, 1H), 2.71 – 2.56 (m, 3H), 1.27 (d, *J* = 7.2Hz, 6 H).

5.3.2.2. **Synthesis of monosustituted thioureas**



To a solution of 30% aqueous ammonium (6 mL) was added the corresponding isocyanate (6 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. The product precipitated as a white solid which was filtrated and the filtrate was washed with MeOH and the solid residue was dried *in vacuo*.

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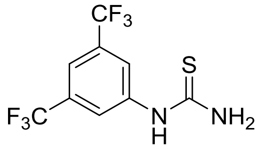
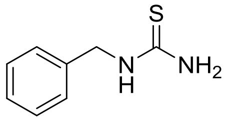
[122] Reproduced of: Klahn, P.; Erhardt, H.; Kotthaus, A.; Kirsch, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 7913–7917.

1-(3,5-Bis(trifluoromethyl)phenyl)thiourea



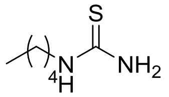
Prepared according to the general procedure starting from bis(3,5-trifluoro-methyl)phenylisothiocyanate. M.p: 180 – 185 °C. Yield: 1.7 g, 5.8 mmol, 98%. ^{1}H NMR (300 MHz, acetone) δ 9.67 (s, 1H), 8.41 (s, 2H), 7.77 (s, 1H), 7.38 (bs, 2H).^{13}C NMR (75 MHz, acetone) δ 184.3, 143.2, 132.2, 126.6, 124.0, 123.9, 122.9, 118.3, 118.3. UPLC-DAD-QTOF: calcd. for $C_9H_7N_2SF_6$ $[M+H]^+$, 289.0243; found ,289.0234.

1-Benzylthiourea



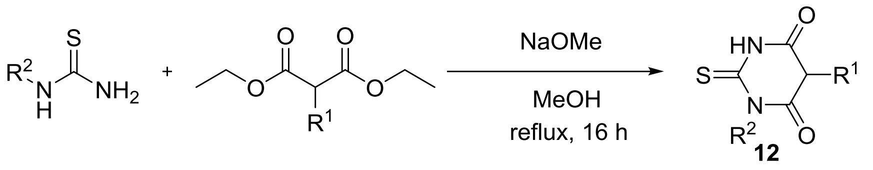
Prepared according to the general procedure starting from benzylisothiocyanato. M.p: 217 – 220 °C. Yield: 6.0 g, 6 mmol, > 99%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (m, 5H), 5.67 (bs, 1H), 4.72 (s, 2H). UPLC-DAD-QTOF: calcd for $C_8H_{11}N_2S$ (M, H$^+$), 167.0641; found, 167.0643.

1-Pentylthiourea



Prepared according to the general procedure starting from pentylisothiocyanato. M.p: 234 – 236 °C. Yield: 790 mg, 6 mmol, > 99%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.16 (t, 2H), 1.61 (m, 2H), 1.35 – 1.30 (m, 4H), 0.95 (t, 3H).MS (ESI, *m*/*z*): calcd for $C_6H_{11}N_2S$ (M, H$^+$), 129.0612; found, 129.17413.

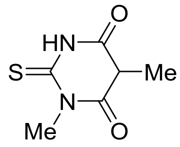
5.3.2.3. Coupling of thioureas with malonic esters (synthesis of 12)



In a 250 mL round-bottom flask fitted with a reflux condenser protected with a calcium chloride tube, sodium metal was placed 1.150 g (50 mmol, 1 equiv.) and 20 mL of anhydrous MeOH. The mixture was stirred until all the sodium disappeared. Then a solution of the respective *N*-alkyl or *N*-aryl thiourea (50 mmol, 1 equiv.) in 20 mL of anhydrous MeOH,(warming was required in order to set thioureas completly dissolved) was added, followed by a dropwise addition of the corresponding malonate (50 mmol, 1 equiv.). The mixture was refluxed for 16 h. A white solid formed rapidly. After the reaction was completed, 100 mL of hot (50 °C) water was added and then enough hydrochloric acid

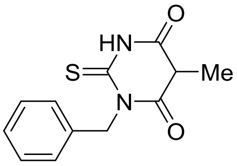
(2 M) to make the solution acidic. The precipitate was washed with MeOH and dried at vacuum (735 mmHg) in a bath at 80 °C.[123]

1, 5-Dimethyl-2-thioxodihydropyrimidine-4,6 (1*H,5H)*-dione (12Aa)



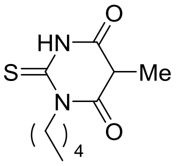
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-methylmalonate. The title compound was obtained as a white solid. M.p: 211 – 212 °C. Yield: 5.5 g, 32 mmol, 64%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 12.78 (s, 1H), 3.91 (s, 3H), 2.92 (p, *J* = 1.8 Hz, 1H), 2.18 (s, 3H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 173.4, 162.7, 155.9, 89.6, 33.2, 8.3. UPLC-DAD-QTOF: calcd for $C_6H_9N_2O_2S$ (M, H$^+$), 173.0385; found, 173.0387.

1-Benzyl-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*) (12Ab)



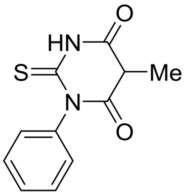
Prepared according to the general procedure starting from 1-benzylthiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 148 – 151 °C. Yield: 10.5 g, 42.5 mmol, 85%. ^{1}H NMR (300 MHz, MeOD) δ 7.29 – 7.26 (m, 5H), 5.65 (s, 2H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ 175.9, 165.4, 158.1, 138.1, 129.1, 129.1, 128.7, 128.7, 128.0, 91.4, 50.3, 8.01. UPLC-DAD-QTOF: calcd for $C_{12}H_{13}N_2O_2S$: 249.0698; found, 249.0702.

5-Metil-1-pentil-2-tioxodihidropirimidin-4,6(1*H*,5*H*)-diona (12Ac)



Prepared according to the general procedure from the 1-pentylthiourea and diethyl 2-methylmalonate. The title compound was obtained as a white solid. M.p: 176 – 177 °C. Yield: 9.5 g, 41.5 mmol, 83%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.29 (s, 1H), 4.59 (m, 2H), 3.52 (q, 1H), 1.66 (m, 2H), 1.62 (d, 3H), 1.34 (m, 4H), 0.90 (t, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 178.6, 167.8, 166.1, 47.2, 44.9, 28.9, 26.8, 22.4, 14.1, 13.6. UPLC-DAD-QTOF: calcd for $C_{10}H_{17}N_2O_2S$: 229.1011; found, 229.1012.

5-Methyl-1-phenyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (12Ad)



Prepared according to the general procedure starting from 1-phenylthiourea and diethyl 2-methylmalonate. The title compound was obtained as a white solid. M.p: 173 – 175 °C. Yield: 8.5 g, 36.5 mmol, 73%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 12.37 (s, 1H), 7.47 – 7.33 (m, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 3.17 (s, 3H). ^{13}C NMR (75 MHz, DMSO-

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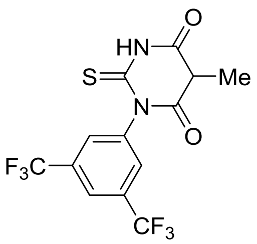
[123] Addapted from: Puig-de-la-Bellacasa, R.; Giménez , G.; Pettersson , S.; Gonzalo, P.; Esté , J. A.; Clotet , B.; Borrell, J. I. *Eur. J. Med. Chem.*, **2012**, *54*, 159–174.

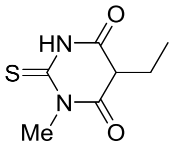
d6) δ 174.21, 162.91, 156.66, 139.77, 128.88, 128.76, 127.78, 89.97, 48.59, 8.14.UPLC (DAD-QTOF $[M+H]^+$) MS (ESI, *m*/*z*): calcd for $C_{10}H_{10}N_2O_2S$: 234.0463; found, 234.0476.

1-(3,5-Bis(trifluoromethyl)phenyl)-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (12Ae)



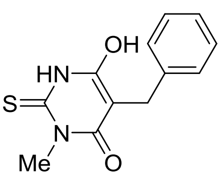
Prepared according to the general procedure starting from 1-(3,5-bis(trifluoromethyl)phenyl)thiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 165 – 170 °C Yield: 13.1 g, 35.5 mmol, 71%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 12.66 (s, 1H), 8.13 (s, 1H), 8.04 (d, *J* = 1.6 Hz, 2H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 174.2, 162.8, 157.3, 141.9, 131.0, 130.9, 130.6, 124.9, 121.8, 121.3, 90.0, 8.2 .UPLC-DAD-QTOF: calcd for $C_{13}H_9N_2O_2SF_6$: 371.0289; found, 371.0284.

5-Ethyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (12Ba)



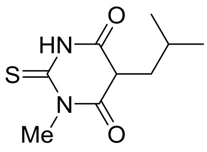
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-ethylmalonate**.** The title compound was obtained as a white solid. M.p: 164 – 165 °C. Yield: 10.3 g, 50 mmol, > 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 3.64 (s, 3H), 3.51 (t, *J* = 5.3 Hz, 1H), 2.22 (qd, *J* = 7.4, 5.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 173.6, 162.4, 155.6, 96.1, 33.3, 15.8, 13.2. UPLC-DAD-QTO: calcd for $C_7H_{11}N_2O_2S$ (M, H^+), 187.0541; found, 187.0539.

5-Benzyl-1-methyl-2-thoxodihydropyrimidine-4,6(1*H*,5*H*)-dione (12Ca)



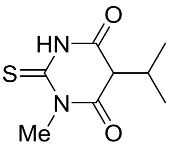
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-benzylmalonate**.** The title compound was obtained as a white solid. M.p: 163 – 164 °C. Yield: 4.3 g, 36.5 mmol, 73%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 12.17 (s, 1H), 7.34 – 7.00 (m, 5H), 3.64 (s, 2H), 3.49 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 173.71, 162.32, 156.74, 140.5 127.99, 127.92, 125.58, 93.35, 33.17, 27.88. UPLC-DAD-QTOF: calcd for $C_{12}H_{13}N_2O_2S$ (M, H^+), 249.0698; found, 249.0694.

5-Isobutyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (12Da)



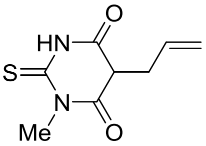
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-isobutylmalonate**.** The title compound was obtained as a white solid. M.p: 107 – 111 °C. 5.2 g, 48.5 mmol, 97%.^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 3.50 (s, 3H), 2.20 (d, *J* = 7.3 Hz, 2H), 1.84 – 1.71 (m, 1H), 0.83 (d, *J* = 6.6 Hz, 6H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 12.34, 7.37, 7.36, 7.34, 7.29, 7.29, 7.29, 7.28, 3.56.UPLC-DAD-QTOF: calcd for $C_9H_{15}N_2O_2S$ (M, H$^+$),215.0854; found, 215.0857.

5-Isopropyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (12Ea)



Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-isopropylmalonate**.** The title compound was obtained as a white solid. M.p: 94 – 95 °C. Yield: 2.3 g, 45 mmol, 90%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.43 (s, 1H), 3.65 (s, 3H), 3.42 (d, *J* = 4.1 Hz, 1H), 2.65 (qt, *J* = 7.0, 3.5 Hz, 1H), 1.14 (dd, *J* = 7.0, 3.0 Hz, 6H).^{13}C NMR (75 MHz, CDCl$_3$) δ 179.09, 167.64, 165.67, 55.76, 34.68, 33.53, 19.60, 19.47.UPLC-DAD-QTOF: calcd for $C_8H_{13}O_2S$ (M, H$^+$), 201.0698; found, 201.0700.

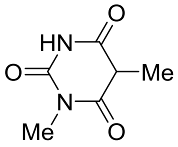
5-Allyl-1-methyl-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione (12Fa)



Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-allylmalonate**.** The title compound was obtained as a white solid. M.p: 171 – 173 °C. Yield: 3.3 g, 35 mmol, 71%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.15 (s, 1H), 5.70 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.23 – 5.11 (m, 2H), 3.62 (s, 4H), 2.95 – 2.89 (m, 2H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 173.7, 162.1, 156.1, 135.4, 114.5, 92.0, 33.2, 26.1. UPLC-DAD-QTOF: calcd for $C_8H_{11}N_2O_2S$ (M, H$^+$), 199.0542; found, 199.0542.

5.3.2.4. **Synthesis of barbituric acid 9**

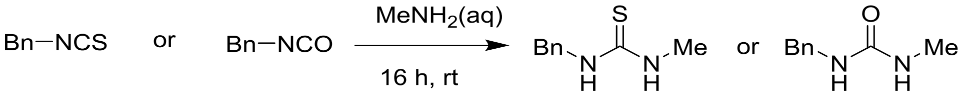
1,5-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (9)



The same procedure employed for the synthesis of thiobarbiturates was used except that *N*-methyl urea (450 mg, 5 mmol) was used as the coupling partner with diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 213 – 216 °C. Yield: 500 mg, 3.2 mmol, 63%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.92 (s, 1H), 3.48 (q, *J* = 7.5 Hz, 1H), 3.29 (s, 3H), 1.63 (d, *J* = 7.5 Hz, 3H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 171.2, 170.3, 152.3, 44.7, 28.2, 13.1. UPLC-DAD-QTOF: calcd for $C_6H_9N_2O_3$ (M, H$^+$), 157.0613; found, 157.0614.

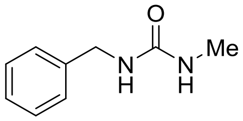
5.3.3. **Synthesis of *N*,*N*`-disubstituted (thio)barbituric acid derivatives 10 and 11**

5.3.3.1. **Synthesis of *N*-benzyl-*N*-methyl urea and thiourea**



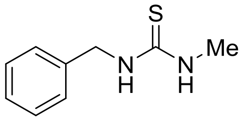
To a solution of aqueous methyl amine (6 mL) was added the corresponding *N*-benzyl isocyanate or thioisocyanate (6 mmol) at room temperature, and the mixture was stirred for 15 h. The white precipitate was filtered and washed with MeOH. The solid was dried *in vacuo* and the products used in the next step without further purification.[124]

1-Benzyl-3-methylurea



White solid. M.p: 72 – 74 °C. Yield: 0.95 g, 5.8 mmol, 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 5H), 5.38 (brs, 1H), 5.02 (bs, 1H), 4.32 (s, 2H), 2.70 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 139.4, 128.5, 127.7, 127.1, 44.3, 27.0. MS (ESI, m/z): calcd for $C_9H_{13}N_2O$ (M, H+), 165.1030; found, 165.1028.

1-Benzyl-3-methylthiourea



Yellow solid. M.p: 67 – 68 °C. Yield: 1.08 g, 6 mmol, > 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 5 H), 7.30 (brs, 1 H), 4.82 (d, J = 5.0 Hz, 2H), 2.59 (s, 3 H). MS (ESI, m/z): calcd for $C_9H_{13}N_2S$ (M, H+), 181.0800; found, 181.0799.

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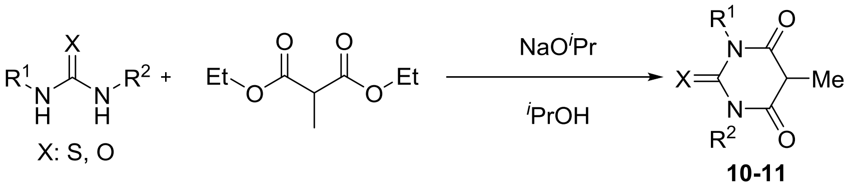
[124] Reproduced from: Klahn, P.; Erhardt, H.; Kotthaus, A.; Kirsch, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 7913–7917.

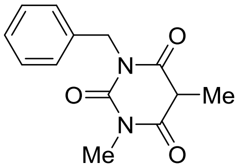
5.3.3.2. **Condensation of *N*,*N*´disustituted (thio)ureas with diethyl methylmalonate**



10-11

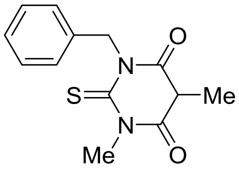
In a 250 mL round-bottom flask fitted with a reflux condenser and protected with a calcium chloride tube, sodium metal was placed (1.2 g, 50 mmol, 1 equiv.) and then 20 mL of anhydrous ^{i}PrOH. The mixture was stirred until all the solid sodium disappeared. Then a solution of N-benzyl-N´-methyl (thio)urea (50 mmol, 1 equiv.) in 20 mL of anhydrous ^{i}PrOH, (warming was required in order the (thio)urea to get completely dissolved) was added followed by a dropwise addition of diethyl methylmalonate (50 mmol, 1 equiv.). The mixture was refluxed for 16 h, and a white solid formed rapidly. After the reaction was completed, 100 mL of hot (50 °C) water was added and then enough hydrochloric acid (2 M) to make the solution acidic. The precipitate was washed with MeOH and dried *in vacuum* (735 mmHg) at 80 °C.

1-benzyl-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10)



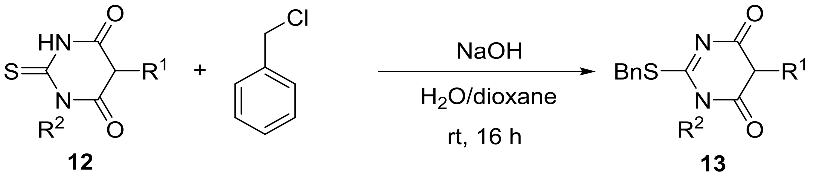
White solid. M.p: 97 – 98 °C. Yield: 8.0 g, 32.5 mmol, 65%. ^{1}H NMR (300 MHz, acetone) (enolic form) δ 7.59 – 7.19 (m, 5H), 5.03 (d, *J* = 3.8 Hz, 2H), 3.22 (s, 3H), 1.55 (s, 3H).^{13}C NMR (75 MHz, acetone) δ 170.5, 170.3, 153.2, 138.5, 129.5, 128.5, 45.9, 13.6. UPLC-DAD-QTOF: calcd for $C_{13}H_{15}N_2O_3$ (M, H+), 247.1083; found, 247.1082.

1-Benzyl-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (11)



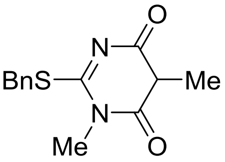
White solid. M.p: 109 – 110 °C. Yield: 72%. ^{1}H NMR (300 MHz, acetone) (enolic form) δ 7.41 – 7.20 (m, 4H), 5.62 (s, 2H), 3.62 (s, 3H), 1.58 (s, 3H).^{13}C NMR (75 MHz, acetone) δ: 205.7, 138.1, 129.4, 128.8, 128.2, 51.8, 36.3, 12.6. UPLC-DAD-QTOF : calcd for $C_{13}H_{15}N_2O_2S$ (M, H+),263.0851; found, 263.0854.

5.3.4. **Synthesis of 2-pyrimidine-4,6(1*H*,5*H*)-diones 13**



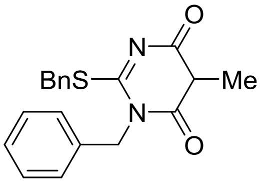
To a suspension of the corresponding thiobarbituric acid derivative **12** (10 mmol, 1 equiv.) in a mixture of water (10 mL) and dioxane (26 mL) a solution of sodium hydroxide (813 mg, 20 mmol, 2 equiv.) in 15 mL of water was added dropwise. The mixture was stirred until the mixture became completly homogeneous. Then, a solution of benzyl chloride (3.45 mL, 30 mmol, 3 equiv.) in dioxane 5 mL was added. The mixture was stirred at room temperature for 16 h. After the reaction was completed, enough hydrochloric acid (4 M) to make the solution acidic was added and the precipitate was filtered and washed with MeOH and dried *in vacuum* (735 mmHg) at 80 °C. [125]

2-(Benzylthio)-6-hydroxy-3,5-dimethylpyrimidin-4(3*H*)-one 13Aa



Prepared according to the general procedure starting from 1,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Aa**. The title compound was obtained as a white solid. M.p.: 175 – 176 °C. Yield: 1.8 g, 9.1 mmol, 91%.^{1}H NMR (300 MHz, $CDCl_3$) (enolic form) δ 7.41 – 7.28 (m, 5H), 4.36 (s, 2H), 3.46 (s, 3H), 1.97 (s, 3H).13C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.9, 157.6, 136.8, 129.3, 128.5, 127.4, 92.5, 34.8, 33.2, 29.9, 8.4. UPLC-DAD-QTOF: calcd for $C_{13}H_{15}N_2O_2S$ (M, H+), 263.854; found, 263.858.

3-Benzyl-2-(benzylthio)-6-hydroxy-5-methylpyrimidin-4(3*H*)-one 13Ab



Prepared according to the general procedure starting from 1-benzyl-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ab**. The title compound was obtained as a white solid. M.p: 186 – 188 °C. Yield: 1.6 g, 4.8 mmol, 48%. ^{1}H NMR (300 MHz, $CDCl_3$) (enolic form) δ 7.40 – 7.21 (m, 8H), 5.26 (s, 2H), 4.33 (s, 2H), 3.73 (s, 1H), 2.02 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 162.4, 159.5, 136.0, 135.9, 129.8, 129.4, 129.21, 128.5, 128.4, 67.8, 48.3, 37.3, 8.9. UPLC-DAD-QTOF: calcd for $C_{19}H_{19}N_2O_2S$ (M, H+),339.1167; found, 339.1175.

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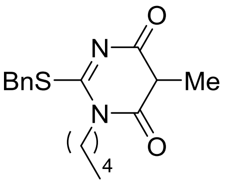
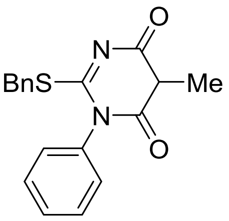
[125] Rakhimov, A. I.; Avdeev, S. A.; Chang, D. *Org. Lett.* **2009**, *79*, 348–349.

2-(Benzylthio)-3-pentyl-6-hydroxy-5-methylpyrimidin-4(3H)-one 13Ac



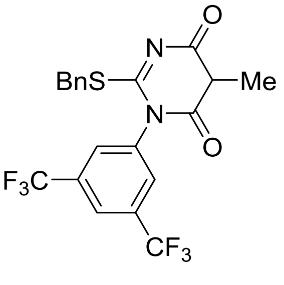
Prepared according to the general procedure starting from 5-methyl-1-pentyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ac**. The title compound was obtained as a white solid. M.p: 174 – 176 °C. Yield: 1.8 g, 5 mmol, 51%. ^{1}H NMR (300 MHz, $CDCl_3$) (enolic form) 7.42 – 7.28 (m, 5H), 5.93 (s, 1H), 4.34 (s, 2H), 3.95 – 3.90 (m, 2H), 1.96 (s, 3H), 1.68 – 1.65 (m, 2H), 1.32 – 1.28 (m, 4H), 0.88 (t, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 162.1, 158.1, 135.6, 129.3, 129.3, 128.9, 128.9, 128.0, 95.3, 45.2, 36.4, 29.1, 27.5, 22.4, 14.1, 8.3. UPLC-DAD-QTOF : calcd for $C_{17}H_{23}N_2O_2S$ (M, H+), 319.1480; found, 319.1482.

2-(Benzylthio)-5-methyl-1-phenylpyrimidine-4,6(1*H*,5*H*)-dione 13Ad



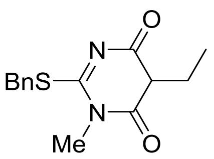
Prepared according to the general procedure starting from 5-methyl-1-phenyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ad**. The title compound was obtained as a white solid. M.p: 189 – 192 °C. Yield: 1.8 g, 5.7 mmol, 57%. ^{1}H NMR (300 MHz, DMSO-*d6*) (enolic form) δ 7.49 (dd, *J* = 5.3, 1.8 Hz, 3H), 7.41 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.33 – 7.21 (m, 5H), 4.33 (s, 2H), 1.80 (s, 3H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 163.5, 163.4, 158.18, 136.7, 136.2, 129.5, 129.3, 129.2, 129.0, 128.4, 127.3, 93.1, 35.3, 8.2. MS (ESI, m/z): calcd for $C_{18}H_{16}N_2O_2S$ (M, H+), 324.0932; found, 324.0740.

2-(Benzylthio)-1-(3,5-bis(trifluoromethyl)phenyl)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione 13Ae



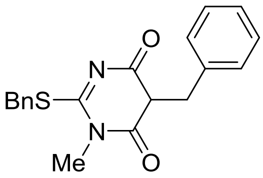
Prepared according to the general procedure starting from 1-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ae**. The title compound was obtained as a yellow solid. M.p: 192 – 194 °C. Yield: 2.1 g, 4.6 mmol, 46%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.72 (s, 2H), 7.30 – 7.28 (m, 3H), 6.05 (s, 1H), 4.28 (s, 2H), 1.98 (s, 3H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 164.7, 163.4, 158.5, 137.4, 135.0, 134.1, 133.6, 133.2, 132.7, 129.9, 129.2, 129.2, 128.9, 128.9, 128.1, 124.5, 124.2, 95.7,37.0, 8.0. UPLC-DAD-QTOF: calcd for $C_{20}H_{15}N_2O_2SF_6$ (M, H^+), 461.0758; found, 461.0759.

2-(Benzylthio)-5-ethyl-6-hydroxy-3-methylpyrimidin-4(3*H*)-one 13Ba



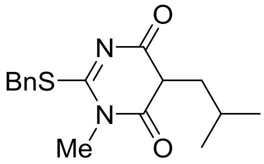
Prepared according to the general procedure starting from 5-ethyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ba**. The title compound was obtained as a white solid. M.p: 186 – 188 °C. Yield: 1.6 g, 5.8 mmol, 58%. ^{1}H NMR (300 MHz, CDCl$_3$) (enolic form) δ 7.54 – 7.50 (m, 2H), 7.37 – 7.28 (m, 3H), 4.49 (s, 2H), 3.33 (s, 3H), 2.33 (q, *J* = 9, 6 Hz, 2H), 0.99 (t, *J* = 6Hz, 3H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 162.8, 162.7, 157.8, 136.8, 129.2, 128.4, 127.4, 98.7, 34.8, 29.8, 16.1, 12.6. UPLC-DAD-QTOF : calcd for $C_{14}H_{17}N_2O_2S$ (M, H$^+$), 277.1011; found, 277.1015.

5-Benzyl-2-(benzylthio)-6-hydroxy-3-methylpyrimidin-4(3*H*)-one 13Ca



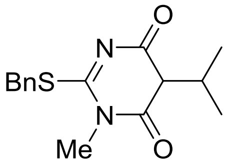
Prepared according to the general procedure starting from 5-benzyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ca**. The title compound was obtained as a white solid. M.p: 209 – 211 °C. Yield: 1.9 g, 6.8 mmol, 68%.^{1}H NMR (300 MHz, DMSO-*d6*) (enolic form) δ 7.44 – 7.10 (m, 10H), 4.35 (s, 2H), 3.80 (s, 2H), 3.44 (s, 3H).^{13}C NMR (75 MHz, DMSO-*d6*) δ 163.1, 158.7, 141.0, 136.7, 129.3, 128.5, 128.2, 128.0, 127.5, 125.5, 96.8, 34.9, 30.0, 28.6. UPLC-DAD-QTOF: calcd for $C_{19}H_{19}N_2O_2S$ (M, H$^+$), 339.1167; found, 339.1166.

2-(Benzylthio)-6-hydroxy-5-isobutyl-3-methylpyrimidin-4(3*H*)-one 13Da



Prepared according to the general procedure starting from 5-isobutyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Da.** The title compound was obtained as a white solid. M.p: 176 – 177 °C. Yield: 1.5 g, 5.2 mmol, 52%. ^{1}H NMR (300 MHz, CDCl$_3$) (enolic form) δ 7.43 – 7.27 (m, 5H), 4.37 (s, 2H), 3.45 (s, 3H), 2.34 (d, *J* = 7.3 Hz, 2H), 2.06 – 1.89 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 6H).^{13}C NMR (75 MHz, DMSO) δ 163.3, 163.2, 157.9, 136.7, 129.3, 128.4, 127.4, 96.4, 34.9, 31.9, 29.8, 27.0, 22.4, 22.4. UPLC-DAD-QTOF: calcd for $C_{16}H_{21}N_2O_2S$ (M, H$^+$), 305.1324; found, 305.1325.

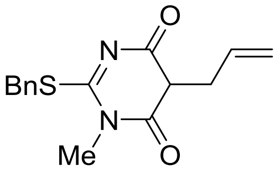
2-(Benzylthio)-6-hydroxy-5-isopropyl-3-methylpyrimidin-4(3*H*)-one 13Ea



Prepared according to the general procedure starting from 5-isopropyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Ea**. The title compound was obtained as a white solid. M.p: 196 – 197 °C. Yield: 2.3 g, 8.7 mmol, 87%. ^{1}H NMR (300 MHz, DMSO-*d6*) (enolic form) δ 7.41 – 7.27 (m, 5H), 4.35 (s, 2H), 3.41 (s, 3H), 3.25 (p, *J* = 7.1 Hz, 1H), 1.25 (d, *J* = 7.1 Hz, 6H).^{13}C

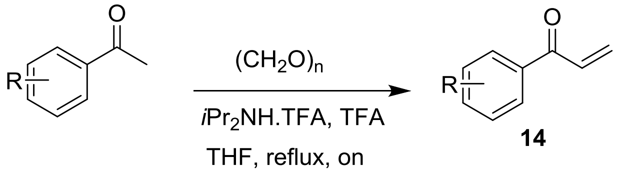
NMR (75 MHz, DMSO-*d6*) δ 179.09, 167.64, 165.67, 55.76, 34.68, 33.53, 19.60, 19.47. UPLC-DAD-QTOF: calcd for $C_{15}H_{19}N_2O_2S$ (M, H+), 291.1167; found, 291.1171.

5-Allyl-2-(benzylthio)-6-hydroxy-3-methylpyrimidin-4(3*H*)-one 13Fa



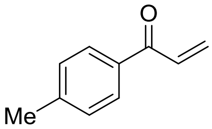
Prepared according to the general procedure starting from 5-allyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **12Fa**. The title compound was obtained as a white solid. M.p: 143 – 144 °C. Yield: 1.6 g, 5.7 mmol, 57%. ^{1}H NMR (300 MHz, $CDCl_3$) (enolic form) δ 7.42 – 7.32 (m, 5H), 5.96 (ddt, *J* = 17.1, 10.0, 6.4 Hz, 1H), 5.20 – 5.02 (m, 2H), 4.36 (s, 2H), 3.47 (s, 3H), 3.29 – 3.26 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 162.6, 159.1, 135.3, 135.1, 129.5, 129.1, 128.7, 128.1, 127.8, 115.1, 97.0, 36.3, 30.6, 27.4. UPLC-DAD-QTOF: calcd for $C_{15}H_{17}N_2O_2S$ (M, H+), 289.1011; found, 289.1014.

5.3.5. **Synthesis of vinyl aryl ketones 14:**



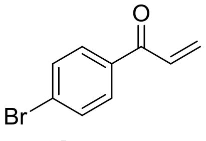
To a solution of the corresponding acetophenone (10.0 mmol, 1 equiv.) and paraformaldehyde (606 mg, 20.0 mmol, 2 equiv.) in dry THF (10.0 mL) was added diisopropylammonium trifluoroacetate (2.05 g, 10.0 mmol, 1 equiv.) and trifluoroacetic acid (0.08 mL, 1 mmol, 10 mol %). The reaction mixture was stirred at reflux for 2 h, then cooled down to room temperature and a second portion of paraformaldehyde (606 mg, 20 mmol, 2 equiv.) was added. Next, the reaction mixture was stirred at reflux overnight. Then the mixture was cooled down and the solvent was removed under reduced pressure. The residue was dissolved in Et$_2$O and washed with 1N HCl (3 x 10 mL), 1N NaOH (3 x 10 mL), and brine (3 x 10 mL). The resulting solution was dried over Na$_2$SO$_4$, filtered and concentrated under *vacuum*. The crude product was purified by silica gel column chromatography (eluent hexane: ethyl acetate, 99:1). [126]

1-(*p*-Tolyl)prop-2-en-1-one) (14a)



Prepared according to the general procedure starting from 1-(*p*-tolyl)ethan-1-one. The title compound was obtained as a yellow oil. Yield: 723.9 mg, 5.4 mmol, 54%. ^{1}H NMR (300 MHz, CDCl$_3$ δ 7.93 – 7.77 (m, 2H), 7.31 – 7.05 (m, 3H), 6.42 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.87 (d, *J* = 10.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ = 190.3, 143.8, 134.7, 132.3, 129.5, 129.3, 128.8, 21.6. UPLC-DAD-QTOF : calcd for $C_{10}H_{10}O$ (M, H+), 146.0810; found, 147.0811.

1-(4-Bromophenyl)prop-2-en-1-one (14b)



Prepared according to the general procedure starting from 1-(4-bromophenyl)ethan-1-one. The title compound was obtained as a yellow oil. Yield: 1.1 g, 5.1 mmol, 51%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.10 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.43 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.93 (dd, *J* = 10.6, 1.6 Hz, 1H).^{13}C NMR (75 MHz, CDCl$_3$) δ =

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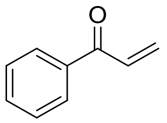
[126] Reproduced from: Guo, S. H.; Xing, S. Z.; Mao, S.; Gao, Y. R.; Chen, W. L.; Wang, Y. Q. *Tetrahedron lett.* **2014**, *23*, 6718–6720.

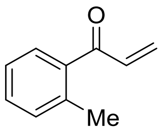
189.9, 135.8, 131.7, 131.6, 130.5, 130.0, 128.0, 125.8, 98.2. UPLC-DAD-QTOF : calcd for C_9H_7BrO (M, H+), 209.9680; found, 209.9781.

1-Phenylprop-2-en-1-one (14c)



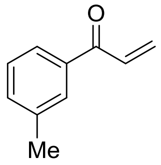
Prepared according to the general procedure starting from acetophenone. The title compound was obtained as a yellow oil. Yield: 765.9 mg, 5.8 mmol, 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.84 (m, 2H), 7.61 – 7.37 (m, 3H), 7.21 – 7.04 (m, 1H), 6.42 (dt, *J* = 17.1, 1.8 Hz, 1H), 5.93 – 5.83 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 137.4, 133.2, 132.5, 130.2, 128.8, 128.8, 128.4. UPLC-DAD-QTOF : calcd for C_9H_8O (M, H+), 132.0575; found, 132.0508.

1-(*o*-Tolyl)prop-2-en-1-one (14d)



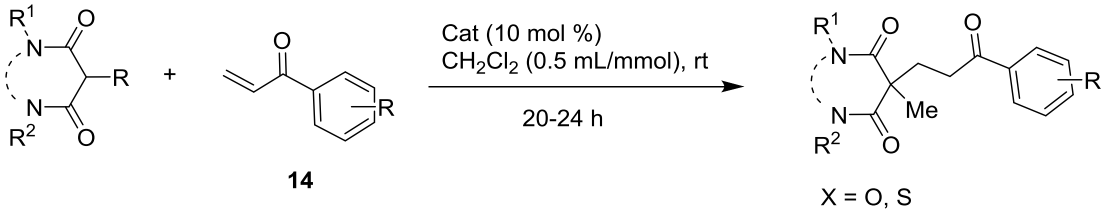
Prepared according to the general procedure starting from 1-(*o*-tolyl)ethan-1-one. The title compound was obtained as a yellow oil. Yield: 838.3 mg, 5.7 mmol, 57%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 1H), 7.42 – 7.28 (m, 1H), 7.29 – 7.17 (m, 2H), 6.87 – 6.71 (m, 1H), 6.21 – 6.08 (m, 1H), 6.03 – 5.91 (m, 1H), 2.42 (d, *J* = 1.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 138.1, 137.5, 136.7, 131.6, 131.3, 130.9, 128.6, 125.6, 20.5. UPLC-DAD-QTOF : calcd for $C_{10}H_{10}O$ (M, H+), 146.0810; found, 147.0807.

1-(*m*-Tolyl)prop-2-en-1-one(14e)



Prepared according to the general procedure starting from 1-(*m*-tolyl)ethan-1-one. The title compound was obtained as a yellow oil. Yield: 818 mg, 5.6 mmol, 56%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.67 (m, 2H), 7.36 (dd, *J* = 4.4, 2.6 Hz, 2H), 7.15 (ddd, *J* = 17.1, 10.5, 1.3 Hz, 1H), 6.43 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.94 – 5.83 (m, 1H), 2.40 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 138.4, 137.3, 133.7, 132.5, 129.8, 129.2, 128.4, 125.8, 21.3. UPLC-DAD-QTOF: calcd for $C_{10}H_{10}O$ (M, H+), 146.0810; found, 147.0804.

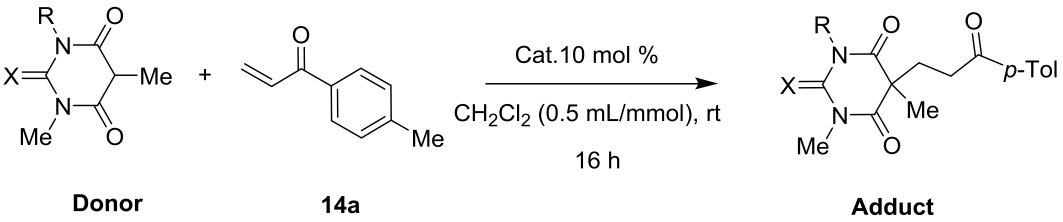
5.3.6. **Catalytic reactions of barbituric acid derivatives with vinyl aryl ketones 14.**


R1
O
N
R
+
N
R2
O
O
R
14
Cat (10 mol %)
CH2Cl2 (0.5 mL/mmol), rt
20-24 h
R1
O
O
N
R
N
Me
R2
O
X = O, S

5.3.6.1. **General procedure**

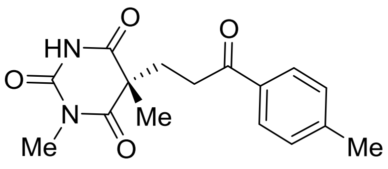
To a mixture of the corresponding barbituric acid or equivalent (0.2 mmol, 1 equiv.) and vinyl aryl ketone **14** (0.6 mmol, 3 equiv.) in CH_2Cl_2 (1 mL), was added the catalyst (10 mol %) and the resulting mixture was stirred at room temperature for 20 – 24 h. Then the mixture was quenched with HCl 0.1 M and the organic layer was washed with water (0.7 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane: ethyl acetate, 3:1).

5.3.6.2. **Screening of donor barbituric substrates (Scheme 1)**


R
O
N
X
Me
+
N
Me
O
O
Me
Donor
14a
Cat.10 mol %
CH2Cl2 (0.5 mL/mmol), rt
16 h
R
O
O
N
p-Tol
X
N
Me
Me
O
Adduct

R	X	Donor/adduct	Catalyst	Yield (%)	*ee* (%)
H	O	**9/15**	**C4**	63	0
			C6	64	0
H	S	**12Aa/18**	**C4**	67	0
			C6	69	0
$PhCH_2$	O	**10/16**	**C4**	70	0
			C6	74	0
$PhCH_2$	S	**11/17**	**C4**	75	0
			C6	79	0

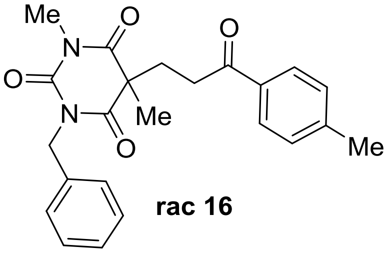
(*R*)-1,5-Dimethyl-5-(3-oxo-3-(*p*-tolyl)propyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (15)



15

Prepared according to the general procedure starting from 1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **9** and 1-(*p*-tolyl)prop-2-en-1-one **14a**. The title compound was obtained as a white oil. Data for the product obtained with catalyst **C10** and **13** as donor at 0ºC: Yield: 41 mg, 0.14 mmol, 71 %. $[\alpha]_D^{23}$= − 54.32 (c= 0.29, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 3.28 (d, *J* = 1.0 Hz, 3H), 2.93 (dt, *J* = 10.0, 7.5 Hz, 2H), 2.40 (d, *J* = 11.1 Hz, 5H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 172.5, 171.8, 150.0, 144.1, 133.8, 129.3, 128.1, 50.7, 33.4, 32.4, 28.1, 24.3, 21.6. UPLC-DAD-QTOF: calcd for $C_{16}H_{18}N_2O_4$ (M, H+), 303.1345; found, 303.1353.

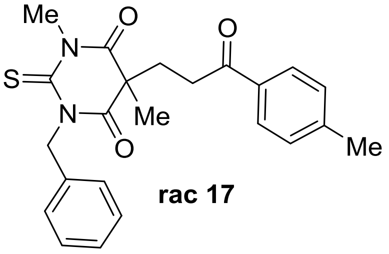
Rac-1-Benzyl-3,5-dimethyl-5-(3-oxo-3-(*p*-tolyl)propyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (16)



rac 16

Prepared according to the general procedure starting from 1-benzyl-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**10**) and 1-(*p*-tolyl)prop-2-en-1-one (**14a**). The title compound was obtained as a white oil. Data for the product obtained with catalyst **C4**: Yield: 58.8 mg, 0.15 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.48 (m, 2H), 7.52 – 7.22 (m, 7H), 5.11 (s, 2H), 3.35 (s, 3H), 2.97 – 2.67 (m, 2H), 2.43 (s, 5H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 171.8, 171.7, 150.9, 138.4, 136.4, 134.0, 128.8, 128.7, 128.6, 128.4, 127.9, 125.2, 50.7, 45.2, 33.5, 33.2, 28.8, 24.4, 21.3. UPLC-DAD-QTOF : calcd for $C_{23}H_{25}N_2O_4$ (M, H+), 393.1814; found, 393.1818.

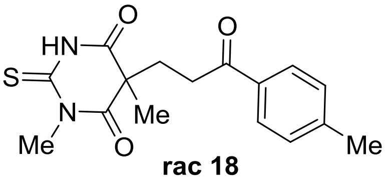
Rac-1-benzyl-3,5-dimethyl-5-(3-oxo-3-(*p*-tolyl)propyl)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione(17)



rac 17

Prepared according to the general procedure starting from 1-benzyl-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**11**) and 1-(*p*-tolyl)prop-2-en-1-one (**14a**). The title compound was obtained as a white oil. Data for the product obtained with catalyst **C4**: Yield: 64.4 mg, 0.15 mmol, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H), 7.48 – 7.16 (m, 7H), 5.81 – 5.56 (m, 2H), 3.73 (s, 3H), 3.02 – 2.71 (m, 2H), 2.49 – 2.39 (m, 5H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 180.2, 170.3, 170.3, 138.4, 136.4, 136.1, 134.0, 128.4, 128.4, 128.2, 127.6, 125.2, 51.6, 50.8, 36.0, 33.3, 32.8, 23.5, 21.3. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}N_2O_3S$ (M, H^+), 409.1592; found, 405.1586.

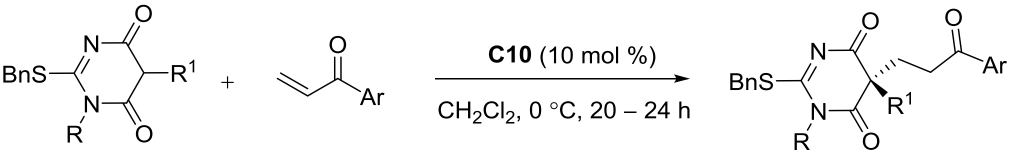
Rac-1,5-Dimethyl-5-(3-oxo-3-(p-tolyl)propyl)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (18)



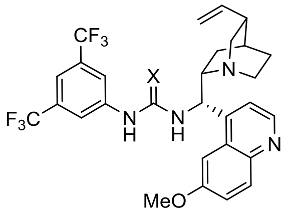
rac 18

Prepared according to the general procedure starting from 1-(*p*-tolyl)prop-2-en-1-one and 1-(*p*-tolyl)prop-2-en-1-one **12Aa** and 1-(*p*-tolyl)prop-2-en-1-one **14a**. The title compound was obtained as a white oil. Data for the product obtained with catalyst **C4**: Yield: 45 mg, 0.15 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.24 (m, 2H), 3.67 (s, 3H), 2.99 (dt, *J* = 9.2, 7.4 Hz, 2H), 2.51 – 2.42 (m, 5H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 178.6, 171.3, 169.2, 144.7, 134.3, 129.7, 129.7, 128.6, 51.9, 34.6, 33.7, 32.8, 24.4, 22.1. UPLC-DAD-QTOF: calcd for $C_{16}H_{18}N_2O_3S$ (M, H+), 319.1116; found, 319.1116.

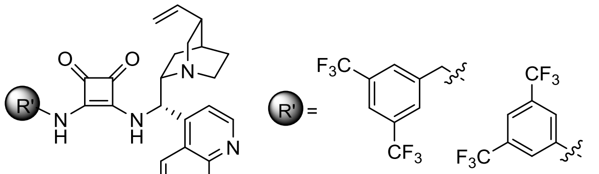
5.3.6.3. **Catalyst screening for the reaction of 13Aa with 14a**[a]


BnS
N
N
R
O
O
R^1
+
O
Ar
C10 (10 mol %)
CH$_2$Cl$_2$, 0 °C, 20 – 24 h
BnS
N
N
R
O
O
R^1
O
Ar

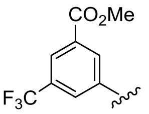
13 **14** (3 equiv.) **19-29**


CF$_3$
F$_3$C
X
N
H
N
H
N
N
MeO

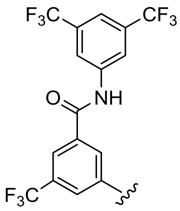
C1 X: S 71%, 36% *ee*
C2 X: O 67%,66% *ee*


O
O
R'
N
H
N
H
N
N
MeO
R' =
F$_3$C
CF$_3$
CF$_3$
F$_3$C

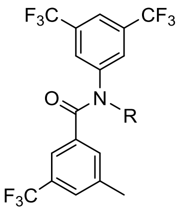
C3 --,--
C4 69%, 32% *ee*



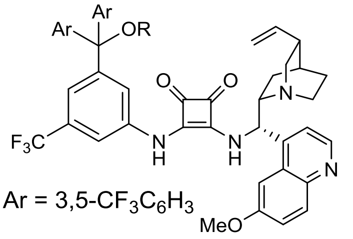
C5
67%, 73% *ee*


F$_3$C
CF$_3$
O
NH
F$_3$C

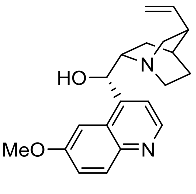
C6
59%, 54% *ee*


F$_3$C
CF$_3$
O
N
R
F$_3$C

C7 R = Me 66%, 75% *ee*
C8 R = Prop 68%, 73% *ee*
C9 R = Bn 62%, 63% *ee*


Ar
Ar
OR
O
O
F$_3$C
N
H
N
H
N
N
Ar = 3,5-CF$_3$C$_6$H$_3$
MeO

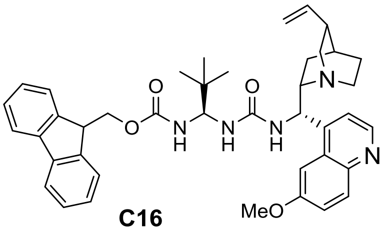
C10 R= H, 72%, 80% *ee* (96% *ee*)[c]
C11 R= SiMe$_3$, 62%, 78% *ee*



C21
36%, 15% *ee*

(DHQD)$_2$PyR

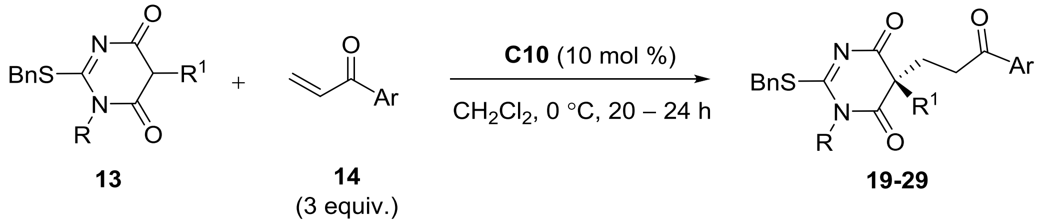
C22
--,--


O
O
O
N
H
N
H
N
H
N
N
MeO

C16
63%, 40% *ee*

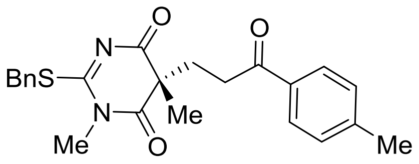
[a] Reactions carried out at room temperature using 0.2 mmol of **13Aa**, 0.6 mmol of enone **14a** and 10 mol % catalyst in 0.2 mL of CH$_2$Cl$_2$. Reaction time 16 h. [b] *ee* determined by chiral HPLC [c] Reaction carried out at 0 °C.

5.3.6.4. **Data for the reaction of templates 13 with enones 14**



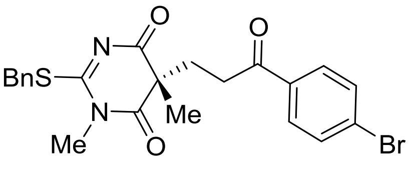
The same general procedure described in section 5.3.6 (pag. 166) was employed using catalyst **C10** and the specified temperature and time.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-(*p*-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*)-dione (19)



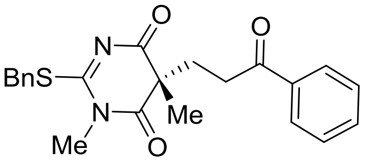
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **13Aa** and 1-(*p*-tolyl)prop-2-en-1-one **14a.** The title compound was obtained as a white oil. Yield: 55 mg, 0.15 mmol, 72%. $[\alpha]_D^{23}= -67.7°$ (c= 0.23, 96 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.44 – 7.20 (m, 7H), 4.47 (d, J = 2.0 Hz, 2H), 3.35 (s, 3H), 3.11 – 2.98 (m, 1H), 2.92 – 2.80 (m, 1H), 2.47 – 2.28 (m, 5H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 179.5, 174.0, 173.3, 144.4, 134.9, 134.4, 129.8, 129.6, 129.3, 129.2, 128.9, 128.5, 128.4, 53.5, 37.8, 34.0, 32.9, 30.4, 22.6, 22.0 UPLC-DAD-QTOF: calcd for $C_{23}H_{24}N_2O_3S$ (M, H^+), 409.1586; found, 409.1589.

(*R*)-2-(Benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (20)



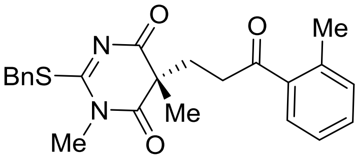
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **13Aa** and 1-(4-bromophenyl)prop-2-en-1-one **14b**. The title compound was obtained as a white oil. Yield: 59 mg, 0.13 mmol, 63%. $[\alpha]_D^{23} = -63.2°$ (c= 0.34, 95 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 7.47 – 7.27 (m, 5H), 4.50 (s, 2H), 3.38 (s, 3H), 3.13 – 2.98 (m, 1H), 2.93 – 2.79 (m, 1H), 2.38 (td, J = 6.3, 3.0 Hz, 2H), 1.57 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 179.0, 173.5, 172.9, 135.2, 134.5, 131.9, 129.6, 129.4, 128.8, 128.4, 128.1, 53.1, 37.4, 33.8, 31.8, 30.0, 22.9. UPLC-DAD-QTOF: calcd for $C_{22}H_{21}BrN_2O_3S$ (M, H+), 473.0535; found, 473.0529.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-phenylpropyl)pyrimidine-4,6(1*H*,5*H*)-dione (21)



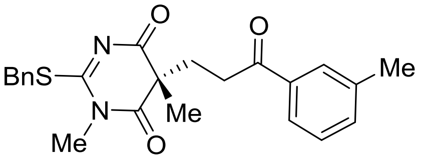
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **13Aa** and 1-phenylprop-2-en-1-one **14c**. The title compound was obtained as a white oil. Yield: 48 mg, 0.12 mmol, 61%. $[\alpha]_D^{23}$= − 64.3° (*c*= 0.27, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.69 – 7.25 (m, 8H), 4.50 (s, 2H), 3.38 (d, *J* = 2.9 Hz, 3H), 3.10 (ddd, *J* = 17.1, 9.1, 6.4 Hz, 1H), 2.93 (td, *J* = 9.1, 6.8 Hz, 1H), 2.47 – 2.32 (m, 2H), 1.57 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 179.1, 173.6, 172.9, 136.5, 134.5, 133.2, 129.4, 128.8, 128.6, 128.1, 128.0, 53.1, 37.4, 33.7, 32.2, 30.0, 22.3. UPLC-DAD-QTOF: calcd for $C_{22}H_{22}N_2O_3S$ (M, H$^+$), 395.1429; found, 395.1433.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-(*o*-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*) (22)



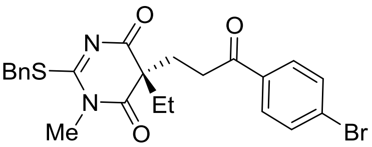
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**13Aa**) and 1-(*o*-tolyl)prop-2-en-1-one (**14d**). The title compound was obtained as a white oil. Yield: 58 mg, 14 mmol, 72%. $[\alpha]_D^{23}$= − 70.3° (c= 0.28, 85 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 6.9 Hz, 1H), 7.51 – 7.18 (m, 8H), 4.51 (s, 2H), 3.38 (s, 3H), 2.99 (dd, *J* = 9.2, 5.9 Hz, 1H), 2.91 – 2.78 (m, 1H), 2.50 (s, 3H), 2.36 (dt, *J* = 9.0, 5.9 Hz, 2H), 1.56 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 174.2, 168.8, 168.0, 133.3, 132.5, 129.6, 127.1, 126.5, 124.5, 124.0, 123.7, 23.2, 120.8, 48.2, 32.5, 31.5, 27.4, 25.1, 17.6, 16.4. UPLC-DAD-QTOF: calcd for $C_{23}H_{24}N_2O_3S$ (M, H+),409.1586; found, 409.1587.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-(*m*-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*)-dione (23)



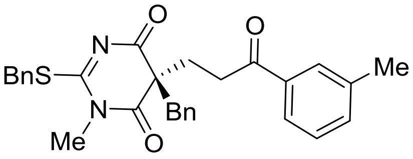
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**13Aa**) and 1-(*m*-tolyl)prop-2-en-1-one (**14e**). The title compound was obtained as a white oil. Yield: 50 mg, 0.12 mmol, 62%. $[\alpha]_D^{23}$= − 69.2° (c= 0.24, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.0 Hz, 2H), 7.54 – 7.17 (m, 7H), 4.50 (d, *J* = 3.0 Hz, 2H), 3.38 (s, 3H), 3.09 (ddd, *J* = 17.0, 9.0, 6.2 Hz, 1H), 3.02 – 2.80 (m, 1H), 2.44 (s, 3H), 2.43 – 2.24 (m, 2H), 1.57 (s, 3H).^{13}C NMR (75 MHz, CDCl$_3$) δ 198.7, 179.1, 173.6, 172.8, 138.3, 136.6, 134.5, 133.9, 129.4, 128.8, 128.5, 128.4, 128.0, 125.2, 53.1, 37.4, 33.7, 32.3, 30.0, 22.2, 21.3. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}N_2O_3S$ (M, H+), 409.1586; found, 409.1587.

(*R*)-2-(Benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (24)



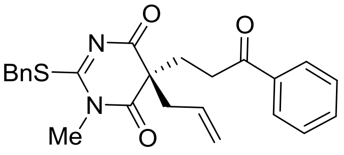
Prepared according to the general procedure starting from 2-(benzylthio)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ba**) and 1-(4-bromophenyl)prop-2-en-1-one (**14b**). The title compound was obtained as a white oil. Yield: 69 mg, 0.14, 71%. $[\alpha]_D^{23}$= − 64.2° (c= 0.42, 97 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.49 – 7.21 (m, 5H), 4.51 (t, *J* = 5.8 Hz, 2H), 3.39 (s, 3H), 3.11 – 2.95 (m, 1H), 2.95 – 2.72 (m, 1H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.02 (dd, *J* = 7.5, 1.6 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 197.7, 178.3, 173.4, 173.1, 135.2, 134.4, 131.8, 129.6, 129.4, 128.8, 128.2, 128.1, 127.7, 127.5, 121.3, 110.4, 58.4, 37.4, 34.0, 33.0, 9.26. UPLC-DAD-QTOF: calcd for $C_{23}H_{23}BrN_2O_3S$ (M, H+), 487.0691; found, 487.0698.

(*S*)-5-Benzyl-2-(benzylthio)-1-methyl-5-(3-oxo-3-(*m*-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*)-dione (25)



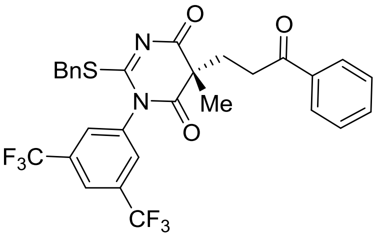
Prepared according to the general procedure starting from 5-benzyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ca**) and 1-(*m*-tolyl)prop-2-en-1-one (**14e**). The title compound was obtained as a white oil. Yield: 80 mg, 0.15 mmol, 75%. $[\alpha]_D^{22}$= − 71.2° (*c*= 0.22, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.82 – 7.70 (m, 2H), 7.44 – 7.16 (m, 10H), 7.14 – 7.04 (m, 2H), 4.27 (d, *J* = 3.4 Hz, 2H), 3.29 – 3.03 (m, 6H), 2.88 – 2.77 (m, 1H), 2.64 (ddd, *J* = 9.6, 5.6, 2.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 198.9, 177.7, 173.6, 172.6, 138.3, 136.5, 134.5, 134.3, 133.8, 129.4, 129.4, 128.7, 128.5, 128.4, 128.1, 128.0, 127.5, 125.3, 59.9, 48.2, 37.3, 34.4, 31.3, 29.6, 21.3. UPLC-DAD-QTOF: calcd for $C_{29}H_{28}N_2O_3S$ (M, H$^+$), 485.1899; found, 485.1901.

(*S*)-5-Allyl-2-(benzylthio)-1-methyl-5-(3-oxo-3-phenylpropyl)pyrimidine-4,6(1*H*,5*H*)-dione (26)



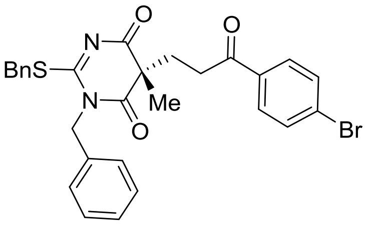
Prepared according to the general procedure starting from 5-allyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Fa**) and 1-phenylprop-2-en-1-one (**14c**). The title compound was obtained as a white oil. Yield: 54 mg, 0.13 mmol, 65%. $[\alpha]_D^{23} = -62.8°$ (*c*= 0.25, 92 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H), 7.64 – 7.53 (m, 1H), 7.52 – 7.29 (m, 7H), 5.64 (dddd, *J* = 17.0, 10.1, 7.9, 6.8 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.58 – 4.41 (m, 2H), 3.37 (s, 3H), 3.15 – 3.02 (m, 1H), 2.91 – 2.78 (m, 1H), 2.78 – 2.63 (m, 2H), 2.50 – 2.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 177.8, 173.6, 172.7, 136.5, 134.6, 133.1, 131.1, 129.4, 128.8, 128.7, 128.5, 128.0, 120.2, 58.0, 43.6, 37.4, 34.0, 31.1, 29.8. UPLC-DAD-QTOF: calcd for $C_{24}H_{24}N_2O_3S$ (M, H^+), 421.1586; found, 421.1593.

(*R*)-2-(Benzylthio)-1-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-5-(3-oxo-3-phenylpropyl)pyrimidine-4,6(1*H*,5*H*)-dione (27)



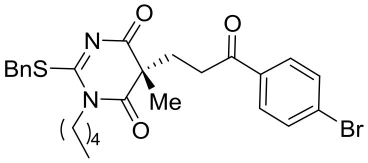
Prepared according to the general procedure starting from 2-(benzylthio)-1-(3,5-bis(trifluoromethyl)phenyl)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ae**) and 1-phenylprop-2-en-1-one (**14c**). The title compound was obtained as a white oil. Yield: 77 mg, 0.13 mmol, 65%. $[\alpha]_D^{23} = -63.02°$ (*c*= 1.4, 90 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.07 – 7.92 (m, 3H), 7.71 (s, 1H), 7.68 – 7.57 (m, 1H), 7.50 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.38 – 7.24 (m, 4H), 4.44 (t, *J* = 6.9 Hz, 2H), 3.32 (dt, *J* = 17.4, 6.2 Hz, 1H), 3.17 – 3.00 (m, 1H), 2.62 (dt, *J* = 13.8, 6.4 Hz, 1H), 2.53 – 2.40 (m, 1H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 178.6, 173.1, 171.4, 136.3, 136.2, 133.9, 133.5, 130.8, 130.1, 130.0, 129.4, 128.8, 128.7, 128.1, 128.0, 124.3, 124.3, 124.2, 53.2, 38.2, 33.1, 32.2, 22.5. UPLC-DAD-QTOF: calcd for $C_{29}H_{22}F_6N_2O_3S$ (M, H^+), 593.1334; found, 593.1337.

(*R*)-1-Benzyl-2-(benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (28)



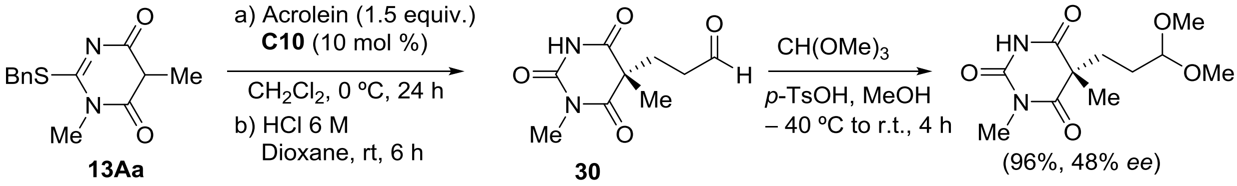
Prepared according to the general procedure starting from 1-benzyl-2-(benzylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ab**) and 1-(4-bromophenyl)prop-2-en-1-one (**14b**). The title compound was obtained as a white oil. Yield: 74 mg, 0.13 mmol, 67%. $[\alpha]_D^{22} = -70.02°$ (*c* = 0.22, 90 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.20 (m, 8H), 5.23 – 4.99 (m, 2H), 4.49 (s, 2H), 3.07 – 2.74 (m, 2H), 2.50 – 2.30 (m, 2H), 1.59 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 178.8, 173.7, 172.4, 134.88, 131.9, 129.4, 128.8, 128.3, 128.1, 128.1, 127.5, 53.3, 47.1, 37.8, 33.7, 31.7, 22.9. UPLC-DAD-QTOF: calcd for $C_{28}H_{25}BrN_2O_3S$ (M, H^+), 549.0848; found, 549.0855.

(*R*)-2-(Benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-5-methyl-1-pentylpyrimidine-4,6(1*H*,5*H*)-dione(29)



Prepared according to the general procedure starting from 2-(benzylthio)-5-methyl-1-pentylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ac**) and 1-(4-bromophenyl)prop-2-en-1-one (**14b**). The title compound was obtained as a white oil. Yield: 78 mg, 0.15 mmol, 73%. $[\alpha]_D^{22}$= − 73.13 °(*c*= 0.23, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.45 – 7.26 (m, 4H), 4.48 (s, 2H), 3.93 – 3.75 (m, 2H), 3.11 – 2.94 (m, 1H), 2.94 – 2.75 (m, 1H), 2.44 – 2.28 (m, 2H), 1.75 – 1.59 (m, 3H), 1.60 – 1.51 (m, 3H), 1.33 (dd, *J* = 6.9, 3.5 Hz, 5H), 0.97 – 0.84 (m, 3H).^{13}C NMR (300 MHz, $CDCl_3$) δ 198.7, 180.2, 174.5, 173.6, 136.4, 135.6, 133.0, 130.7, 130.6, 130.0, 129.5, 129.2, 54.2, 45.4, 38.6, 34.9, 32.7, 29.9, 29.1, 24.0, 23.3, 15.0. UPLC-DAD-QTOF: calcd for $C_{26}H_{30}N_2O_3SBr$ (M, H^+), 529.1161; found, 529.1165.

5.3.6.5. **C10-catalyzed reaction of 13Aa with acrolein**



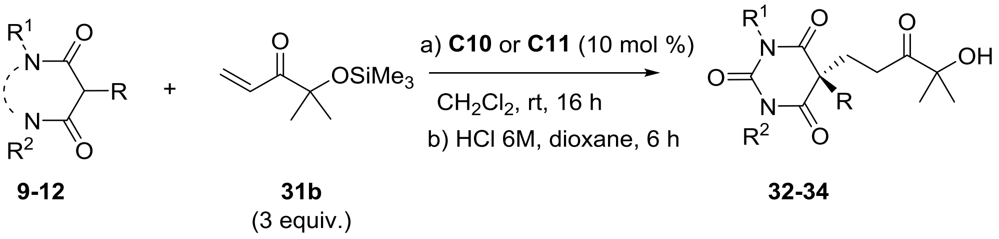
To a mixture of **13Aa** (52.4 mg, 0.2 mmol, 1equiv.) and acrolein (0.02 mL, 0.3 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL), catalyst **C10** (10 mol %) was added and the resulting mixture was stirred at 0 °C for 24 h. Then the reaction mixture was concentrated in the rotary evaporator, the residue was dissolved in dioxane/ HCl 6M (0.5ml/ 0.5mL), and the resulting mixture was stirred at room temperature for 6 h. Then, it was quenched with an aqueous solution of $NaHCO_3$ (1 mL), diluted with water (1 mL) and the mixture extracted with EtOAc (3 x 3 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate, 1/1) to give aldehyde **30** as a colorless oil. Yield: 17.3 mg, 0.082 mmol, 41%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.92 (s, 1H), 3.27 (s, 3H), 2.48 – 2.33 (m, 2H), 2.31 – 2.28 (m, 2H), 1.56 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.0, 172.3, 171.5, 149.8, 50.5, 39.1, 30.0, 28.1, 24.5. MS (ESI, *m*/*z*): calcd for $C_9H_{12}N_2O_4Na$ (M, +Na), 235.0695; found, 235.0683.

The enantiomeric purity of this material was determined by chiral HPLC analysis after derivatisation into the corresponding dimethyl acetal, as follow:

Derivatization of **30** onto the corresponding dimethyl acetal: To a solution of aldehyde **30** (31.6 mg, 0.15 mmol, 1 equiv.) in MeOH (0.6 mL) at – 40 °C trimethyl orthoformate (0.03 mL, 0.15 mmol, 1 equiv.) and *p*-toluensulfonic acid (5 mg, 20 mol %) were added. The resulting mixture was allowed to reach the room temperature and stirred for 4 h at that temperature. Water (3 mL) was added to the reaction flask and the resulting mixture was extracted with EtOAc (3 x 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Thus, obtained product was essentially pure (yellow oil) and submitted to HPLC analysis. Yield: 38.7 mg, 0.15 mmol, > 99%. $[\alpha]_D^{22} = -3.6^o$ (c = 0.1, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CDC13) 3.28 (s, 3H), 3.22 (d, *J* = 1.8 Hz, 6H), 2.09 (t, *J* = 7.8 Hz, 2H), 1.58 – 1.50 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 173.1, 172.1, 150.3, 103.8, 53.0, 52.9, 51.4, 33.1, 28.6, 28.4, 26.4. MS (ESI, m/z): calcd for $C_{11}H_{18}N_2O_5Na$ (M, Na+), 281.1113; found, 281.1118.

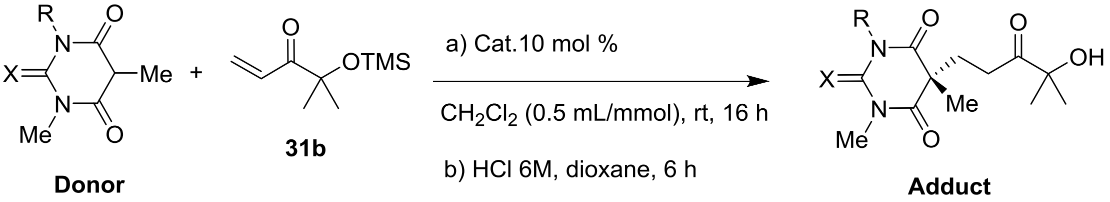
5.3.7. **Catalytic reactions with vinyl ketone 31b**

5.3.7.1. **General procedure**



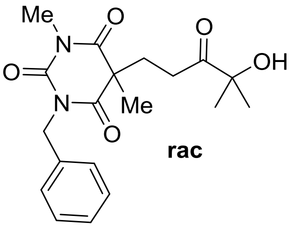
To a suspension of the corresponding barbituric acid derivative **9-12** (0.2 mmol, 1 equiv.) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **31b** (110 mg, 0.6 mmol, 3 equiv.) in CH_2Cl_2 (1 mL), was added catalyst **C10** or **C11** (10 mol %) and the reaction was stirred at rt for 16 h. Then the mixture was quenched with HCl 0.1 M and the organic layer was washed with water (0.7 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was dissolved in dioxane/ HCl 6 M (0.5 ml/0.5 mL), and the resulting mixture was stirred for 6 h (until consumption of the silyl ether compound). The mixture was quenched with an aqueous solution of $NaHCO_3$, diluted with water and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

5.3.7.2. **Screening of donor barbiturates**


R
O
N
X
Me
N
Me
O
+
O
OTMS
31b
Donor
a) Cat.10 mol %
CH2Cl2 (0.5 mL/mmol), rt, 16 h
b) HCl 6M, dioxane, 6 h
R
O
O
N
OH
X
N
Me
Me
O
Adduct

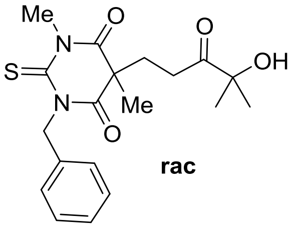
R	X	Donor	Catalyst	Adduct	Yield (%)	*ee* (%)
H	O	**9**	**C2**	**32Aa**	62	0
			C4		61	0
			C6		61	0
H	S	**12Aa**	**C2**	**32Aa**	67	0
			C4		64	0
			C6		69	0
$PhCH_2$	O	**10**	**C2**	**33**	72	0
			C4		60	0
			C6		68	0
$PhCH_2$	S	**11**	**C2**	**34**	63	0
			C4		73	0
			C6		74	0

1-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (33)


Me
O
O
N
OH
O
N
Me
O
rac

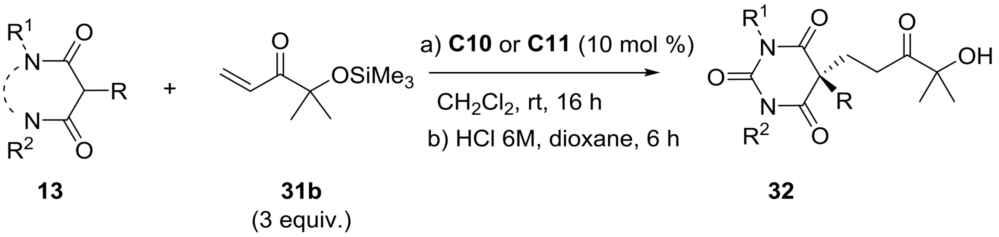
Prepared according to the general procedure section 5.3.7.1 starting from 1-benzyl-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**10**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 4:1) to give the title compound as a white oil. Yield: 48.9 mg, 0.14 mmol, 68%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.24 (m, 5H), 5.20 – 4.98 (m, 2H), 3.34 (s, 3H), 2.54 – 2.41 (m, 2H), 2.32 (d, *J* = 6.9 Hz, 2H), 1.56 (s, 3H), 1.29 (d, *J* = 1.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 172.1, 172.0, 151.3, 136.7, 129.3, 129.0, 128.4, 51.0, 45.7, 32.7, 31.0, 30.1, 29.3, 28.7, 26.8, 25.2. UPLC-DAD-QTOF: calcd for $C_{19}H_{24}N_2O_5$ (M, H$^+$), 360.1685; found, 360.1682.

1-benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (34)



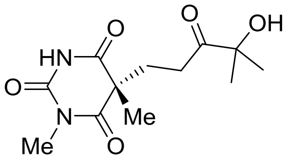
Prepared according to the general procedure section 5.3.7.1 starting from 1-benzyl-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**11**). The title compound was obtained as a white oil. The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 4:1) to give the title compound as a white oil. Yield: 52.7 mg, 0.15 mmol, 74%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.22 (m, 5H), 5.79 – 5.54 (m, 2H), 3.71 (s, 3H), 2.64 – 2.40 (m, 2H), 2.40 – 2.25 (m, 2H), 1.58 (s, 3H), 1.32 (d, *J* = 3.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.0, 180.1, 170.1, 136.0, 128.4, 128.2, 127.7, 51.4, 50.8, 36.0, 31.7, 30.5, 26.4, 24.1. UPLC-DAD-QTOF: calcd for $C_{19}H_{24}N_2O_4S$ (M, H$^+$), 376.1457; found, 376.1456.

5.3.7.3. **General procedure for the reaction of templates 13 with enone 31b**



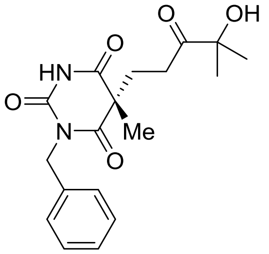
To a suspension of the corresponding barbituric acid derivative **13** (0.2 mmol, 1 equiv.) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **31b** (110 mg, 0.6 mmol, 3 equiv.) in CH_2Cl_2 (1 mL), was added catalyst **C10** or **C11** (10 mol %) and the reaction was stirred at rt for 16 h. Then the mixture was quenched with HCl 0.1 M and the organic layer was washed with water (0.7 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was dissolved in dioxane/ HCl 6 M (0.5 ml/0.5 mL), and the resulting mixture was stirred for 6 h (until consumption of the silyl ether compound). The mixture was quenched with an aqueous solution of $NaHCO_3$, diluted with water and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*) (32Aa)



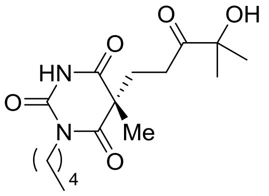
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**13Aa**). The crude material was purified by flash column chromatography on silica gel (elutent with hexane: ethyl acetate, 1:1) to give the title compound as colourless oil. Yield: 43 mg, 0.16 mmol, 82%. $[\alpha]_D^{23}$= +0.76° (*c*= 0.97, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 2.56 (q, *J* = 7.5, 7.1 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 173.5, 172.7, 151.0, 51.6, 32.6, 31.8, 29.2, 27.5, 25.9. UPLC-DAD-QTOF: calcd for $C_{12}H_{19}N_2O_5$ (M, H$^+$), 271.1294; found, 271.1301.

(*R*)-1-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (32Ab)



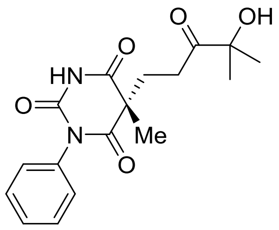
Prepared according to the general procedure starting from 1-benzyl-2-(benzylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ab**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 1:1) to give the title compound as a colorless oil. Yield: 47.2 mg, 0.12 mmol, 61%. $[\alpha]_D^{23}$= −3.8° (*c*= 0.73, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.47 – 7.38 (m, 2H), 7.38 – 7.26 (m, 3H), 5.14 – 4.93 (m, 2H), 2.56 – 2.38 (m, 2H), 2.29 (d, *J* = 7.0 Hz, 2H), 1.55 (s, 3H), 1.26 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 173.2, 172.8, 150.9, 137.1, 129.9, 129.8, 129.7, 129.2, 51.6, 45.7, 32.9, 31.7, 27.4, 27.3, 25.7. UPLC-DAD-QTOF: calcd for $C_{18}H_{22}N_2O_5Na$ (M, Na$^+$), 369.1426; found, 369.1433.

(*R*)-1-Pentyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (32Ac)



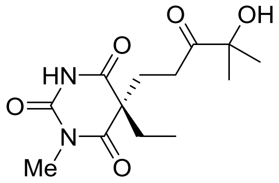
Prepared according to the general procedure starting from 2-(benzylthio)-5-methyl-1-pentylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ac**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 1:1) to give the title compound as a colorless oil. Yield: 42 mg, 0.13 mmol, 63%. $[\alpha]_D^{23}$= −0.21° (*c*= 0.45, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 – 3.94 (m, 1H), 3.85 – 3.76 (m, 1H), 2.65 – 2.49 (m, 1H), 2.25 (t, *J* = 7.4 Hz, 2H), 1.53 (s, 3H), 1.41 – 1.25 (m, 6H), 1.19 (d, *J* = 6.1 Hz, 8H), 0.88 (t, *J* = 6.9 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 172.5, 172.3, 150.1, 64.4, 50.6, 41.6, 31.5, 30.9, 28.9, 27.6, 26.4, 25.3, 24.9, 22.3, 14.0. UPLC-DAD-QTOF: calcd for $C_{16}H_{26}N_2O_5Na$ (M, Na^+), 349.1739; found, 349.1739.

(R)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1-phenylpyrimidine-2,4,6(*1H,3H,5H)*-trione (32Ad)



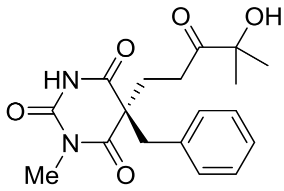
Prepared according to the general procedure starting from 2-(benzylthio)-5-methyl-1-phenylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ad**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 1:1) to give the title compound as a colorless oil. Yield: 42 mg, 0.12 mmol, 62%. $[\alpha]_D^{23}= -0.21°$ (*c*= 0.45, 90% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (brs, 1H), 7.38 (m, 2H), 7.28 (m, 3H), 5.00 (m, 2H), 3.45 (s, 1H), 2.43 (m, 2H), 2.29 (m, 2H), 1.50 (s, 3H), 1.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ UPLC-DAD-QTOF : calcd for $C_{18}H_{22}N_2O_5Na$, 369.1426; found, 369.1433.

(*R*)-5-Ethyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (32Ba)



Prepared according to the general procedure starting from 2-(benzylthio)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ba**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 2:1) to give the title compound as a yellow oil. Yield: 40 mg, 1.14 mmol, 71%. $[\alpha]_D^{23}= -2.8$ °(*c*= 1, 94 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 3.29 (s, 3H), 2.63 – 2.51 (m, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.01 (q, J = 7.4 Hz, 2H), 1.32 (d, J = 1.0 Hz, 6H), 0.86 (t, J = 7.4 Hz, 3H).^{13}C NMR (300 MHz, $CDCl_3$) δ 213.7, 172.4, 171.5, 150.2, 77.0, 56.3, 33.8, 31.5, 31.3, 28.3, 26.9, 9.7. UPLC-DAD-QTOF: calcd for $C_{13}H_{21}N_2O_5$ (M, H^+), 285.1450; found, 285.1451.

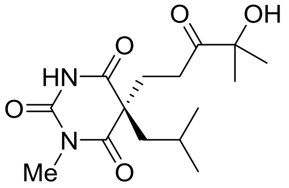
(*S*)-5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*) (32Ca)



Prepared according to the general procedure starting from 5-benzyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ca**). The crude material was diluted with 0.2 mL of water and 0.3 mL of acetone and oxone (92 mg, 0.3 mmol, 1.5 equiv.) in 0.1 mL of water was added and the reaction mixture was stirred 24 h at room temperature. The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 2:1) to give the title compound as a white solid. M.p: 227 – 230 °C. Yield: 48 mg, 0.14 mmol, 70%. $[\alpha]_D^{22}= -1.72°$ (*c*= 0.84, 92% *ee*,

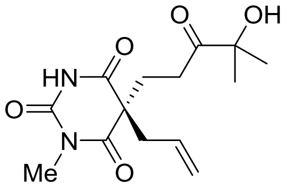
CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.33 – 7.25 (m, 3H), 7.08 – 7.03 (m, 2H), 3.27 (s, 2H), 3.09 (s, 3H), 2.70 – 2.43 (m, 4H), 1.38 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 171.8, 170.8, 149.2, 134.2, 129.5, 129.2, 129.1, 128.6, 57.9, 47.4, 31.8, 31.7, 31.5, 28.0, 26.9. UPLC-DAD-QTOF: calcd for $C_{18}H_{23}N_2O_5$ (M, H^+), 347.1607; found, 347.1606.

(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (32Da)



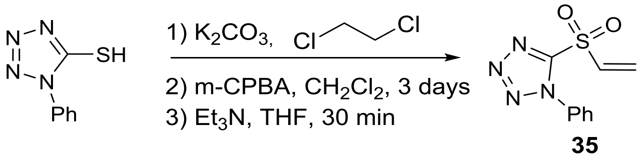
Prepared according to the general procedure starting from 2-(benzylthio)-5-isobutyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Da**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 3:1) to give the title compound as a yellow oil. Yield: 42 mg, 0.14 mmol, 68%. $[\alpha]_D^{22}$= −1.25° (*c*= 0.27, 93 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 3.34 – 3.23 (m, 3H), 2.66 – 2.41 (m, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 1.95 (d, *J* = 6.6 Hz, 2H), 1.62 – 1.56 (m, 1H), 1.31 (s, 6H), 0.80 (dd, *J* = 12.2, 6.6 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 172.5, 171.6, 150.1, 54.6, 47.7, 34.2, 30.9, 30.1, 28.4, 27.0, 25.8, 23.8, 23.5, 1.4. UPLC-DAD-QTOF : calcd for $C_{15}H_{25}N_2O_5$ (M, H^+), 313.1763; found, 313.1769.

(*S*)-5-Allyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione(32Fa)



Prepared according to the general procedure starting from 5-allyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Fa**). The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate, 2:1) to give the title compound as a colourless oil. Yield: 42 mg, 0.14 mmol, 72%. $[\alpha]_D^{23}$= −4.84° (*c*= 0.75, 92 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 5.63 – 5.46 (m, 1H), 5.16 – 5.06 (m, 2H), 3.23 (s, 3H), 2.66 – 2.49 (m, 4H), 2.34 – 2.26 (m, 2H), 1.30 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 171.9, 170.99, 150.1, 130.4, 121.7, 56.0, 44.5, 31.3, 31.2, 28.2, 26.8. UPLC-DAD-QTOF: calcd for $C_{14}H_{21}N_2O_5$ (M, H^+), 297.1450; found, 297.1455.

5.3.8. **Synthesis of heteroaryl vinylsulfone 35**



Step 1: 1-Phenyl-1*H*-tetrazole-5-thiol (10.7 g, 60 mmol, 1 equiv.) was placed in a 500 ml flask equipped with a magnetic stirring bar and 1,2-dichloroethane (250 ml) followed by K_2CO_3 (20.1 g, 150 mmol, 2.5 equiv.) were added. The suspension was stirred and heated under reflux during 2 days. After cooling to room temperature, 200 ml of water were added and the mixture was extracted with CH_2Cl_2 (2 x 100 ml). The organic layers were combined, washed with water (200 ml) ad brine (200 ml), dried over $MgSO_4$, filters and concentrated under reduced pressure to afford 13.9 g (58.2 mmol, 97%) of 5-(2-chloroethylthio)-1-phenyl-1*H*-tetrazole as a pale yellow solid that was used in the next step without further purification. All data were consistent with those previously reported.[127] ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.72 (brs, 5H), 3.90 (t, *J* = 6.9 Hz, 2H), 3.67 (t, *J* = 6.9 Hz, 2H).

Step 2: The crude compound (4.8 g, 20 mmol, 1 equiv.) was placed in a 500 ml flask equipped with a magnetic stirring bar and dissolved in CH_2Cl_2 (50 ml). A solution of m-chloroperbenzoic acid (17.2 g, 100 mmol, 5 equiv.) in CH_2Cl_2 (200 ml) was added and the reaction mixture was stirred at room temperature for 3 days, whereupon it was filtered. The filtrate was transferred into a separatory funnel, washed with 150 ml of a $NaHSO_3$ solution 40% w/v, a sat. aq. $NaHCO_3$ solution (2 x 150 ml) and brine (150 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. The obtained crude was dissolved in THF (100 mL) in a 250 mL flask equipped with a magnetic bar and triethylamine (4.1 mL, 30 mmol, 1.5 equiv.) was added dropwise. The clear solution turned to a clouded suspension which was stirred for 30 min. Solid triethylamine chloride was filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexane: EtOAc, 4: 1) to afford 4.53 g (19.2 mmol, 96%) of vinyl sulfone **35** as a white solid. All data were consistent with those previously reported.[127] ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.72 – 7.57 (m, 5H), 7.14 (dd, *J* = 10.0, 16.5 Hz, 1H), 6.67 (d, *J* = 16.5, 1H), 6.49 (d, *J* = 10 Hz, 1H).

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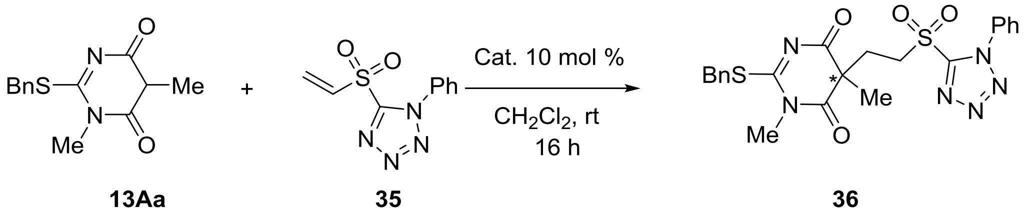
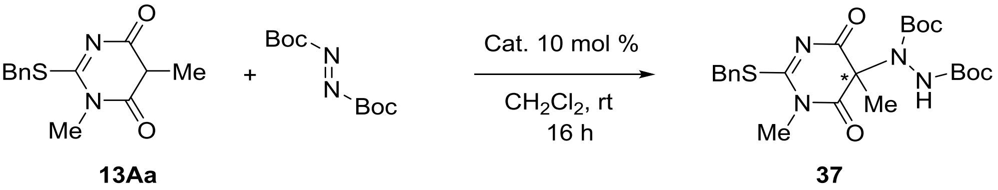
[127] Rodrigo, E.; Morales, S.; Duce, S.; García Ruano, J. L. *Chem. Commun.* **2011**, *47*, 11267–11269.

5.3.9. **Addition of 2-benzylthio-4,6-dioxopyrimidines to heteroaryl vinyl sufone 35**



To a mixture of 2-(benzylthio)-1,5-dimethyldihydropyrimidine-4,6(1*H*,5*H*)-dione **13Aa** (52.8 mg, 0.2 mmol, 1 equiv.) and heteroaryl vinyl sulfone **35** (56.7 mg, 0.24 mmol, 1.2 equiv.) in CH_2Cl_2 (0.2 mL), was added the catalyst **C10** (10 mol %) and the resulting mixture was stirred at room temperature for 16 h. Then the mixture was washed with water (0.4 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane: ethyl acetate, 1:1) to afford the 2-(benzylthio)-1,5-dimethyl-5-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)dihydropyrimidine-4,6(1*H*,5*H*)-dione **36** as a yellow foam, 65 mg, 0.13 mmol, 65% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.53 (m, 5H), 7.52 – 7.28 (m, 4H), 4.48 (d, *J* = 1.7 Hz, 2H), 3.99 – 3.69 (m, 2H), 3.30 (s, 3H), 2.61 (ddd, *J* = 10.2, 9.0, 5.8 Hz, 2H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 178.14, 173.53, 173.03, 153.31, 134.66, 133.37, 131.79, 130.59, 130.43, 130.00, 129.81, 129.46, 129.30, 128.56, 125.63, 121.61, 52.60, 52.44, 37.95, 31.30, 30.46, 27.92, 25.96. UPLC-DAD-QTOF: $C_{22}H_{24}N_6O_4S_2$ $[M+H]^+$ calcd.:500.1300, found: 500.1702.

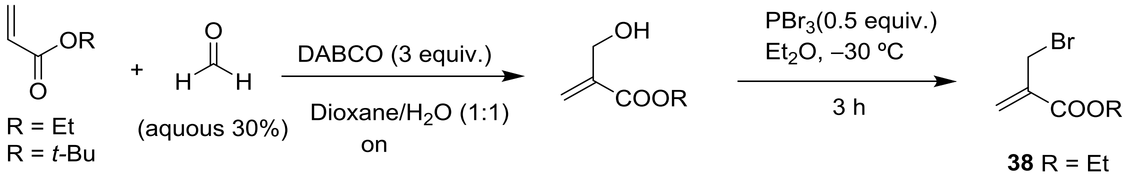
5.3.10. *α*-Amination reaction of 2-benzylthio-4,6-dioxopyrimidines



To a mixture of 2-(benzylthio)-1,5-dimethyldihydropyrimidine-4,6(1*H*,5*H*)-dione **13Aa** (52.8 mg, 0.2 mmol, 1 equiv.) and commercially available di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (55.2 mg, 0.24 mmol, 1.2 equiv.) in CH_2Cl_2 (0.2 mL), was added the catalyst **C10** (10 mol %) and the resulting mixture was stirred at room temperature for 16 h. Then the mixture was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane: ethyl acetate, 2:1) to afford di-*tert*-butyl 1-((2-(benzylthio)-1,5-dimethyl-4,6-dioxohexahydropyrimidin-5-yl)methyl)hydrazine-1,2-dicarboxylate **37** as a yellow foam, 71.1 mg, 0.14 mmol, 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, *J* = 1.8 Hz, 3H), 7.29 – 7.28 (m, 1H), 7.20 (s, 1H), 4.40 (d, *J* = 2.2 Hz, 3H), 3.25 (s, 4H), 1.40 (s, 18H), 1.15 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 178.43, 173.10, 172.89, 170.15, 154.54, 129.38, 128.86, 128.43, 128.19, 128.09, 127.69, 82.73, 64.37, 54.29, 52.80, 37.44, 31.62, 29.97, 28.06, 27.22, 25.32, 23.28.UPLC-DAD-QTOF: $C_{23}H_{34}N_4O_6S$ $[M+H]^+$ calcd.: 494.2199, found: 494.2274.

5.3.11. Catalytic reactions of barbituric acid derivatives with allyl bromides 38 and 39.

5.3.11.1. Synthesis of 2-(bromomethyl)acrylates 38 and 39



38 R = Et
39 R = *t*-Bu

Step 1: A solution of formaldehyde (30% aqueous, 2.5 mL, 30 mmol, 1.0 equiv.) and *tert*-butyl or ethyl acrylate (90 mmol, 3.0 equiv.) in 200 mL of a mixture of 1,4-dioxane water (1:1, v/v) was stirred at room temperature over night. Then DABCO (10 g, 90 mmol, 3 equiv.) was added and the mixture was stirred until the starting acrylate disappeared (monitored by TLC). The reaction mixture was then partitioned with ether (100 mL) and water (80 ml). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give *tert*-butyl 2-(hydroxymethyl)acrylateas and the ethyl 2-(hydroxymethyl)acrylate, respectively, as a yellow oil.

Step 2: The material obtained in the previous step (5 mmol, 1 equiv.), was dissolved in ether (5 mL) and cooled down in an ice/salt bath to – 30 °C. A solution of PBr_3 (1.24 mL, 2.5 mmol, 0.5 equiv.) in ether (7 mL) and added dropwise over a period of 5 min to the chilled reaction mixture, and the mixture was allowed to stir at 0 °C for 3 h. The reaction flask was cooled to – 10 °C, and H_2O (5 mL) was added slowly with stirring. The mixture was then diluted with hexane (15 mL) and washed with H_2O (20 mL). The organic layer was separated, dried, filtered, and the solvent evaporated to afford an oil product wich was purified by flash column chromatography (eluent hexane ethyl acetate, 10:1). Physical and spectroscopic data of that obtained products **38**[128] and **39**[129] were identical to those reported in the literature. Compound **38**, yield: 599 mg, 18.6 mmol, 62%;^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, J = 1.0, 0.8 Hz, 1H), 5.85 (q, J = 1.1 Hz, 1H), 4.35 (d, J = 1.1 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). Compound **39**, yield: 545 mg, 18.9 mmol, 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J = 1.0 Hz, 1H), 5.88 (q, J = 0.9 Hz, 1H), 4.17 (d, J = 0.9 Hz, 2H), 1.55 (s, 9H).

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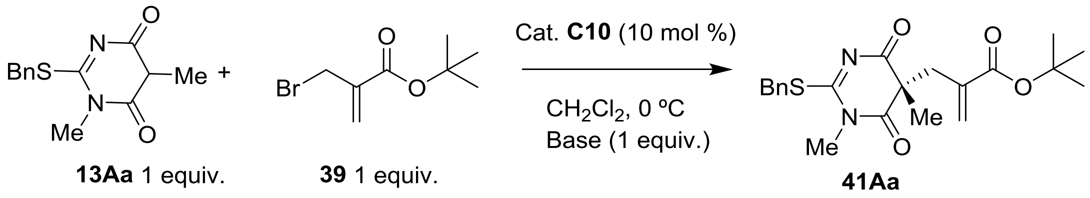
[128] Reproduced from: Pautigny, C.; Séverine Jeulin, T.; Ayad, Z.; Zhang, J.; Genêt, V.; Vidal, R. *Adv. Synth. Catal.* **2008**, *350*, 2525–2532.

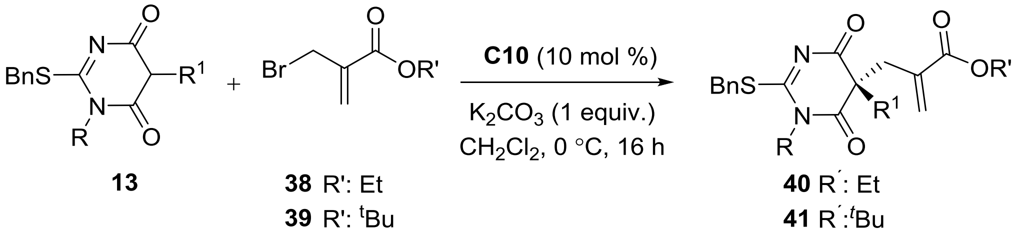
[129] Reproduced from: Rüping, F.; Maison, C.H. K., W. *ARKIVOC*, **2015**, *(ii)*, 93–108.

5.3.11.2. Screening of bases for the reaction of 13Aa with 39 using catalyst C10


BnS
N
O
Me
+
Me
O
13Aa 1 equiv.
Br
O
O
39 1 equiv.
Cat. **C10** (10 mol %)
CH2Cl2, 0 °C
Base (1 equiv.)
BnS
Me
Me
41Aa

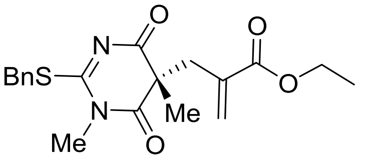
Base	Conversion (%, overnight)	Yield (%)	*ee* (%)
K_2CO_3	100	63	99
K_3PO_4	100	61	97
Cs_2CO_3	100	65	77
Et_3N	100	71	10
DMAP	100	68	24
Without base	0	--	--

5.3.11.3. General procedure and data of adducts


BnS
N
O
R¹
+
R
O
13
Br
O
OR'
38 R': Et
39 R': ᵗBu
C10 (10 mol %)
K2CO3 (1 equiv.)
CH2Cl2, 0 °C, 16 h
BnS
R¹
OR'
R
40 R': Et
41 R': ᵗBu

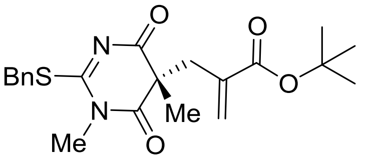
To a mixture of the corresponding template **13** (0.2 mmol, 1.0 equiv.) and allylic bromide **38** or **39** (0.20 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL), catalyst **C10** (10 mol %) and K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv.) were added and the reaction was stirred at 0 °C for 16 h. Then the mixture was quenched with HCl 1 M and extracted with CH_2Cl_2 (3 x 2 mL). The organic layer was washed with water (3 x 2 mL), dried over $MgSO_4$, filtered, and solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ ethyl acetate, 4:1).

(*R*)-2-((2-(Benzylthio)-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (40)



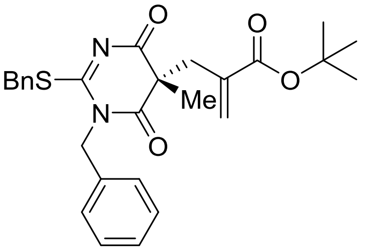
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**13Aa**) and ethyl 2-(bromomethyl)acrylate (**38**). The title compound was obtained as a yellow oil. Yield: 45.6 mg, 0.12 mmol, 62%. $[\alpha]_D^{23}$= +81.25 ° (*c* = 0.24, 48 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 5H), 6.25 (s, 1H), 5.55 (s, 1H), 4.47 (d, *J* = 1.5 Hz, 2H), 4.17 (dd, *J* = 7, 1Hz, 2 H), 3.31 (s, 3H), 3.01 (dd, *J* = 13, 1 Hz, 1 H), 2.79 (dd, *J* = 13,1 Hz, 1H), 1.52 (s, 3H), 1.30 (t, *J* = 7 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 173.3, 173.2, 166.6, 135.3, 134.8, 129.7, 129.3, 129.1, 128.2, 125.6, 61.3, 53.8, 44.6, 41.6, 37.6, 30.2, 21.2, 14.3. MS (ESI, *m*/*z*): calcd for $C_{19}H_{22}N_2O_4S$ (M, H^+), 375.1300; found, 375.1400.

tert-Butyl (*R*)-2-((2-(benzylthio)-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (41Aa)



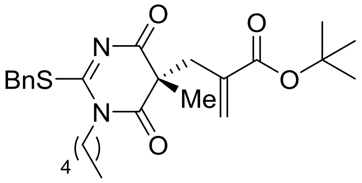
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**13Aa**) and *tert*-butyl 2-(bromomethyl)acrylate (**39**). The title compound was obtained as a yellow oil. Yield: 50.7 mg, 0.13 mmol, 63%. $[\alpha]_D^{22}$= +45.47° (*c* = 0.17, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.25 (m, 5H), 6.17 (d, *J* = 1.3 Hz, 1H), 5.50 (d, *J* = 1.2 Hz, 1H), 4.48 (s, 2H), 3.31 (s, 3H), 2.98 (dd, *J* = 13.5, 0.9 Hz, 1H), 2.71 (dd, *J* = 13.6, 0.9 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 173.7, 166.3, 136.9, 135.3, 130.2, 129.5, 129.3, 129.1, 128.7, 81.9, 67.8, 54.3, 42.4, 38.0, 30.7, 30.4, 28.6, 28.6, 21.3. MS (ESI, *m*/*z*): calcd for $C_{21}H_{26}N_2O_4S$ (M, H^+), 403.1613; found, 143.1614.

tert-Butyl (*R*)-2-((1-benzyl-2-(benzylthio)-5-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (41Ab)



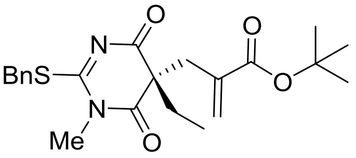
Prepared according to the general procedure starting from 1-benzyl-2-(benzylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ab**) and *tert*-butyl 2-(bromomethyl)acrylate (**39**). The title compound was obtained as a yellow oil. Yield: 65.1 mg, 0.14 mmol, 68%. $[\alpha]_D^{22}$= +36.45° (*c*= 0.27, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.19 (m, 12H), 6.13 (d, *J* = 1.1 Hz, 1H), 5.40 (q, *J* = 1.0 Hz, 1H), 5.18 (d, *J* = 16.1 Hz, 1H), 4.90 (d, *J* = 16.1 Hz, 1H), 4.53 – 4.38 (m, 2H), 3.01 (dd, *J* = 13.9, 1.0 Hz, 1H), 2.82 (dd, *J* = 13.9, 1.0 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.51, 174.47, 173.51, 166.77, 137.43, 136.14, 135.64, 130.54, 129.86, 129.74, 129.15, 129.04, 128.76, 82.26, 54.82, 48.27, 41.78, 38.71, 29.03, 28.96, 22.66.MS (ESI, *m*/*z*): calcd for $C_{27}H_{30}N_2O_4S$ (M, H^+), 479.1926; found, 479.18263.

tert-Butyl (*R*)-2-((2-(benzylthio)-1-pentyl-5-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate(41Ac)



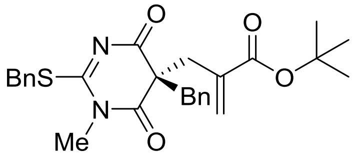
Prepared according to the general procedure starting from 1-benzyl-2-(pentylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ac**) and *tert*-butyl 2-(bromomethyl)acrylate (**39**). The title compound was obtained as colorless oil. Yield: 68.6 mg, 0.15 mmol, 73%. $[\alpha]_D^{22}$= +77.65° (*c* = 0.25, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.22 (m, 5H), 6.15 (d, *J* = 1.2 Hz, 1H), 5.43 (d, *J* = 1.1 Hz, 1H), 4.47 (s, 2H), 3.91 – 3.63 (m, 2H), 2.97 (dd, *J* = 13.9, 1.0 Hz, 1H), 2.77 (dd, *J* = 13.9, 1.0 Hz, 1H), 1.67 – 1.61 (m, 3H), 1.50 (d, *J* = 5.5 Hz, 12H), 1.32 (ddd, *J* = 9.3, 7.7, 5.5 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.42, 173.73, 173.10, 166.25, 137.16, 135.32, 130.18, 129.50, 128.66, 128.58, 81.80, 54.13, 45.14, 41.59, 38.01, 29.50, 28.61, 28.52, 22.80, 22.27, 14.56. MS (ESI, *m*/*z*): calcd for $C_{25}H_{34}N_2O_4S$ (M, H^+), 459.2239; found, 459.2240.

tert-Butyl (*R*)-2-((2-(benzylthio)-5-ethyl-1-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylatetert-butyl (41Ba)



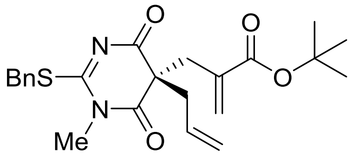
Prepared according to the general procedure from 2-(benzylthio)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ba**) and *tert*-butyl 2-(bromomethyl)acrylate (**39**). The title compound was obtained as a yellow oil. Yield: 54.1 mg, 0.13 mmol, 67%. $[\alpha]_D^{22}$= −55.63°(*c* = 0.19, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.24 (m, 5H), 6.12 (d, *J* = 1.3 Hz, 1H), 5.49 (d, *J* = 1.2 Hz, 1H), 4.47 (s, 2H), 3.33 (s, 3H), 3.04 – 2.77 (m, 2H), 2.09 (q, *J* = 7.4 Hz, 2H), 1.47 (s, 10H), 0.83 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 174.2, 173.4, 166.4, 137.3, 135.3, 130.1, 129.5, 128.9, 128.7, 81.8, 59.9, 42.1, 38.0, 31.6, 30.5, 28.6, 10.3.MS (ESI, *m*/*z*): calcd for $C_{22}H_{28}N_2O_4S$ (M, H^+), 417.1770; found, 417.1774.

***tert*-Butyl (*R*)-2-((5-benzyl-2-(benzylthio)-1-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (41Ca)**



Prepared according to the general procedure starting from 5-benzyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Ca**) and *tert*-butyl 2-(bromomethyl)acrylate (**39**). The title compound was obtained as a yellow oil. Yield: 60.2 mg, 0.13 mmol, 63%. $[\alpha]_D^{22}$= +70.30° (*c*= 0.20, 86 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.01 (m, 10H), 6.11 (d, *J* = 1.0 Hz, 1H), 5.43 (d, *J* = 1.1 Hz, 1H), 4.28 (d, *J* = 1.9 Hz, 2H), 3.44 – 3.20 (m, 2H), 3.13 (d, *J* = 9.5 Hz, 5H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 174.6, 173.4, 166.9, 138.2, 136.3, 135.7, 130.9, 130.5, 129.9, 129.2, 129.0, 128.3, 128.3, 82.19, 61.1, 46.9, 41.4, 38.3, 30.7, 29.0.MS (ESI, *m*/*z*): calcd for $C_{27}H_{30}N_2O_4S$ (M, H^+), 479.1926; found, 479.19263.

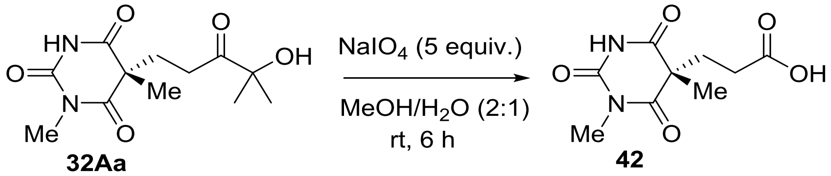
***tert*-Butyl (*R*)-2-((5-allyl-2-(benzylthio)-1-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (41Fa)**



Prepared according to the general procedure starting from 5-allyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (**13Fa**) and *tert*-butyl 2-(bromomethyl)acrylate (**39**). The title compound was obtained as a yellow oil. Yield: 54.8 mg, 0.13 mmol, 65%. $[\alpha]_D^{22}$= +69.68° (*c*= 0.25, 92 % *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 4H), 6.14 (s, 1H), 5.72 – 5.54 (m, 1H), 5.49 (d, *J* = 1.2 Hz, 1H), 5.19 – 5.00 (m, 2H), 4.46 (s, 2H), 3.31 (s, 3H), 3.02 – 2.83 (m, 2H), 2.81 – 2.66 (m, 2H), 1.47 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 174.3, 172.9, 166.3, 137.2, 135.3, 132.5, 130.5, 130.1, 129.5, 128.9, 128.8, 128.7, 120.6, 81.8, 59.1, 42.3, 41.6, 38.0, 30.47, 28.6. MS (ESI, *m*/*z*): calcd for $C_{23}H_{18}N_2O_4S$ (M, H^+), 429.1770; found, 429.1870.

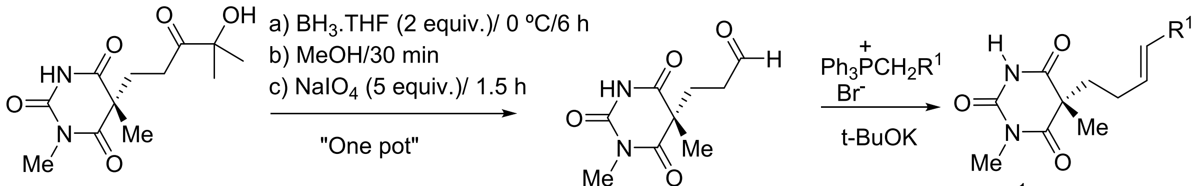
5.3.12. Elaborations of Adducts

5.3.12.1. . Synthesis of carboxylic acid 42



Adduct **32Aa** (54 mg, 0.2 mmol, 1 equiv.) was dissolved in 2 mL of methanol, and to this solution a suspension of sodium periodate (200 mg, 1.0 mmol, 5 equiv.) in water (1.0 mL) was added. The reaction mixture was stirred at room temperature, until disappearance of starting material as monitored by TLC (6 h). Then the solvent was evaporated under reduced pressure. The residue was partitioned between water (3 mL) and EtOAc (6 mL) and the aqueous phase was extracted with EtOAc (3 x 6 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure, to afford essentially pure (*R*)-3-(1,5-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)propanoic acid **42**. Yellow oil. Yield: 43.3 mg, 0.19 mmol, 97%. $[\alpha]_D^{22}$= +2.1° (*c*= 0.18, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 3.30 (s, 3H), 2.49 – 2.24 (m, 4H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 173.0, 172.6, 150.6, 50.8, 32.8, 30.2, 28.5, 25.8. UPLC-DAD-QTOF: calcd for $C_9H_{13}N_2O_2$ (M, H^+), 229.0824; found, 229.0822.

5.3.12.2. Conversion of 45Aa into alkenes 56-58



32Aa **30**

43 R1: H 72%
44 R1: COMe 69%
45 R1: Br 68%

Step 1: BH_3.THF complex (1 M in THF, 0.4 mL, 0.4 mmol, 2 equiv.) was added to a solution of adduct **32Aa** (54 mg, 0.2 mmol, 1 equiv.) in dry THF (0.8 mL) at 0 °C and the resulting solution was stirred at the same temperature until the starting material disappeared (6 h). MeOH (0.4 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were evaporated under reduced pressure and the residue thus obtained was dissolved in MeOH (0.4 mL) and a suspension of sodium periodate (107 mg, 1 mmol, 5 equiv.) in water (0.5 mL) was added to the solution at room temperature. The reaction mixture was stirred at the same temperature for 1.5 h and solvents were evaporated under reduced pressure. Water 3 mL was added to the crude product and the resulting mixture was extracted with EtOAc (3 X 3 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure, affording the aldehyde **30** as essentially pure compound. Yellow oil. Yield: 41.3 mg, 0.18 mmol, 88%. $[\alpha]_D^{23}$= +0.84° (*c* = 0.34, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.92 (s, 1H), 3.27 (s, 3H), 2.49 – 2.41 (m, 2H), 2.30 (dd, *J* = 7.7, 6.3 Hz, 2H), 1.56 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 172.3, 171.5, 149.8, 50.5, 39.1, 30.0, 28.1, 24.5. UPLC-DAD-QTOF: calcd for $C_9H_{12}N_2O_4Na$ (M, +Na), 235.0695; found, 235.0683.

Step 2:

(Method A) [130] Synthesis of (*R*)-5-(but-3-en-1-yl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 43

Methyltriphenylphosphonium bromide (142.8 mg, 0.4 mmol, 2 equiv.) was dissolved in THF (0.5 mL). Then *t*-BuOK (67.2 mg, 0.6 mmol, 3 equiv.) was added and the yellow suspension was stirred at 0 °C for 45 min. To this suspension a solution of the aldehyde (**30**) (42 mg, 0.2 mmol, 1 equiv.) in THF (0.3 mL) was added dropwise and the resulting mixture was stirred at room temperature for 6 h. Then, the solvents were evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent hexane: ethyl acetate, 4:1) to give the title compound as a white oil. Yield: 26 mg, 1.14 mmol, 72%. $[\alpha]_D^{23}$= +1.34 °(*c* = 0.88, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93

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[130] Yang, N. Y.; Li, Z. L.; Ye, L.; Tan, B.; Liu, X. Y. *Chem. Commun.* **2016**, *52*, 9052–9055.

(s, 1H), 5.77 – 5.62 (m, 1H), 5.05 – 4.92 (m, 2H), 3.30 (s, 3H), 2.16 (dd, $J = 8.2, 1.2$ Hz, 2H), 2.08 – 1.97 (m, 2H), 1.58 (s, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 171.5, 149.5, 136.4, 116.1, 51.1, 37.9, 29.9, 29.7, 25.1. UPLC-DAD-QTOF: calcd for $C_{10}H_{13}N_2O_3$ (M, H^+), 209.0926; found, 209.0949.

(Method B) Synthesis of (*R*,*E*)-1,5-dimethyl-5-(5-oxohex-3-en-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 44

1-(Triphenylphosphoranylidene)-2-propanone (127.3 mg, 0.4 mmol, 2 equiv.) was dissolved in THF (0.5 mL). Then *t*-BuOK (33.6 mg, 0.6 mmol, 3 equiv.) was added and the yellow suspension was stirred at 0 °C for 45 min. To this suspension a solution of aldehyde **30** (42 mg, 0.2mmol, 1 equiv.) in THF (0.3 mL) was added dropwise and the resulting mixture was stirred at room temperature for 6 h. After reaction completion the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent with hexane: ethyl acetate 4:1) to give the title compound as a single diastereomer as a white oil. Yield: 55.7 mg, 0.14 mmol, 69%. $[\alpha]_D^{23}$= +0.87°($c = 0.47$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 6.68 (d, $J = 16.0$ Hz, 1H), 6.05 (d, $J = 16.2$ Hz, 1H), 3.31 (s, 3H), 2.28 – 2.12 (m, 7H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 173.0, 172.0, 150.2, 145.7, 132.6, 51.9, 36.9, 29.0, 28.8, 27.8, 26.2. UPLC-DAD-QTOF: calcd for $C_{12}H_{17}N_2O_4$ (M, H^+), 253.1188; found, 253.1197.

(Method C) [131] Synthesis of (*R*,*E*)-5-(4-bromobut-3-en-1-yl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 45

To a solution of bromomethyl triphenylphosphonium bromide (95.8 mg, 0.22 mmol, 1.1 equiv.) in anhydrous THF (1 mL), at – 78 °C, *t*-BuOK (26.6 mg, 0.22 mmol, 1.1 equiv.) was added. After stirring the mixture for 1 h at – 78 °C, a solution of aldehyde **30** (42 mg, 0.2 mmol, 1 equiv.) in anhydrous THF (0.2 mL) was added dropwise and the reaction mixture was stirred for a further 1 h at – 78 °C. The reaction was then warmed to room temperature over 1 h. The solvents were evaporated under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 2:1) to give the title compound as a mixture of diastereomers (*dr* 17:3) as a white oil. Yield: 34.4 mg, 0.14 mmol, 68%. $[\alpha]_D^{23}$= +1.34 ° ($c = 0.52$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 6.19 (d, $J = 6.9$ Hz, 1H), 6.07 – 5.93 (m, 1H), 3.32 (s, 3H), 2.24 – 2.19 (m, 4H), 1.59 (s, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.2, 150.2, 133.3, 110.1, 51.7, 37.2, 28.8, 26.8, 26.2. UPLC-DAD-QTOF: calcd for $C_9H_{13}N_2O_2$ (M, H^+), 287.0031; found, 207.0034.

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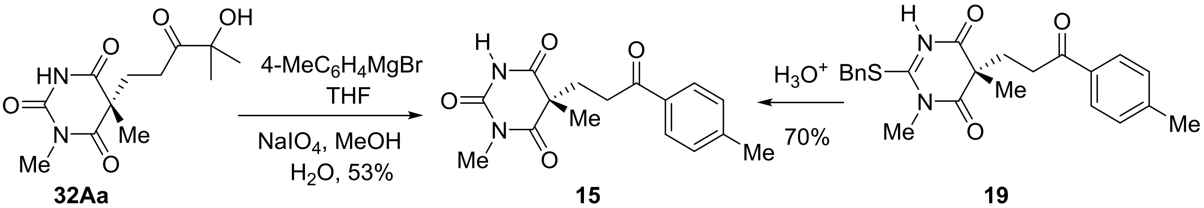
[131] Tofi, M.; Georgiou, T.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2005**, *15*, 3347–3350.

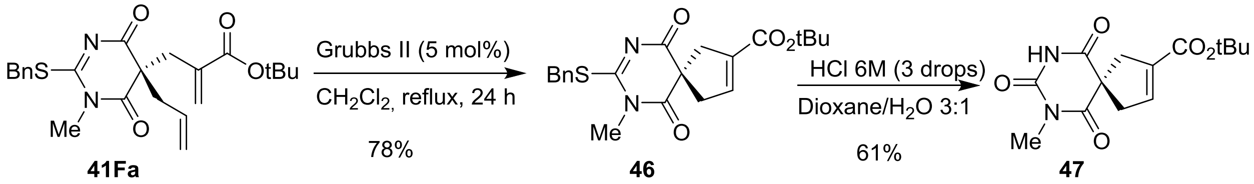
5.3.12.3. Conversion of 32Aa into ketone 15 (chemical correlation to 19)



p-Tolylmagnesium bromide (5 M in THF, 1 mmol, 5 equiv.) was added to a solution of **32Aa** (54 mg, 0.2 mmol, 1 equiv.) in dry THF (1 mL) at 0 ^{o}C and the resulting solution was stirred at the same temperature until the reaction was finished (monitored by TLC). Then a saturated aqueous solution of NH_4Cl (2 mL) was added at 0 ^{o}C and the resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL). The solvents were evaporated under reduced pressure and the residue thus obtained was dissolved in MeOH (1 mL). A suspension of $NaIO_4$ (214 mg, 1 mmol, 5 equiv.) in water (0.4 mL) was added to the solution at room temperature and the resulting mixture was stirred at the same temperature for 1 h. Then solvents were evaporated under reduced pressure, water (2 mL) was added to the residue and the resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 3:1) to give ketone **15** as a white oil. Yield: 32 mg, 0.12 mmol, 53%. $[\alpha]_D^{24}$= –58.70° (*c*= 0.27, CH_2Cl_2, 90 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.77 (d, *J* = 9 Hz, 2H), 7.22 (d, *J* = 9 Hz, 2H), 3.28 (s, 3H), 2.97 – 2.80 (m, 2H), 2.44 – 2.38 – 2.35 (m, 5H), 1.58 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.0, 172.5, 171.8, 150.0, 144.2, 133.8, 129.26, 128.1, 50.7, 33.4, 32.4, 28.1, 24.3, 21.6. MS (ESI, *m*/*z*): calcd for $C_{16}H_{18}N_2O_4$ (M, H$^+$), 303.1345; found, 303.1353.

On the other hand, adduct **19** (60.6 mg, 0.2 mmol, 1 equiv.) was dissolved in dioxane/6 M HCl (0.5 ml/ 0.5 mL), and the resulting mixture was stirred at r.t. for 6 h. Then the mixture was quenched with an aqueous solution of $NaHCO_3$ (2 mL), diluted with water (2 mL) and extracted with EtOAc (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 3:1) to give ketone **15** as a white oil. Yied 45 mg, 0.14 mmol, 70%. $[\alpha]_D^{23}$= – 54.32° (*c*= 0.29, CH_2Cl_2).

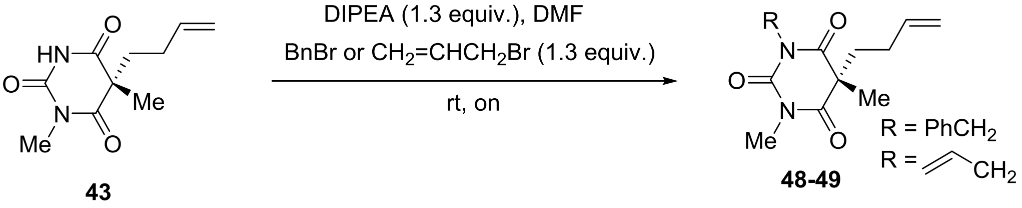
5.3.12.4. Conversion of adduct 41Fa into spiranic compounds 46 and 47



Step 1: To a solution of **41Fa** (85.7 mg, 0.2 mmol, 1 equiv.) in CH_2Cl_2 (8 mL) was added Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)(tricyclohexylphosphine)ruthenium(II) (2nd generation Grubbs Catalyst) (6.4 mg, 5 mol %) and the reaction was stirred a reflux for 24 h. The resulting mixture was directly submitted to a flash column chromatography on silica gel (eluent hexane: ethyl acetate, 8:1) to give the title compound **46** as a red oil. Yield: 63.1 mg, 0.16 mmol, 78%. $[\alpha]_D^{22}$= +5.07° (*c*= 0.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.31 (m, 4H), 6.61 (d, *J* = 2.4 Hz, 1H), 4.50 (s, 2H), 3.38 (s, 3H), 3.34 – 3.02 (m, 4H), 1.49 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 173.7, 173.5, 163.7, 139.6, 135.2, 134.2, 130.1, 129.6, 128.8, 81.5, 58.2, 43.9, 41.7, 38.1, 30.9, 28.8, 28.6. UPLC-DAD-QTOF: calcd for $C_{21}H_{24}N_2O_4S$ (M^+), 400.1457; found, 400.1455.

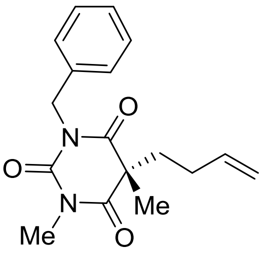
Step 2: To a solution of spiranic compound **46** (40.1 mg, 0.1 mmol, 1 equiv.) in a mixture of dioxane/ H_2O (3:1, 0.4 mL) was added HCl 6 M (3 drops). The reaction was stirred at room temperature for 1 h. Then the mixture was directly submitted to a column chromatography on silica gel (eluent hexane: ethyl acetate, 2:1) to give the title compound **47** as a red oil. Yield: 17.9 mg, 0.06 mmol, 61%. $[\alpha]_D^{22}$= +3.05° (*c*= 0.07, CH_2Cl_2).^1H NMR (300 MHz, $CDCl_3$) δ 6.65 – 6.57 (m, 1H), 3.33 (s, 3H), 3.21 (s, 4H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 170.9, 162.7, 149.5, 138.2, 134.3, 81.1, 54.5, 44.9, 43.3, 28.5, 28.1.UPLC-DAD-QTOF: calcd for $C_{14}H_{18}N_2O_5$ (M^+), 294.1216; found, 294.1214.

5.3.12.5. *N*-Alkylation of adduct 43



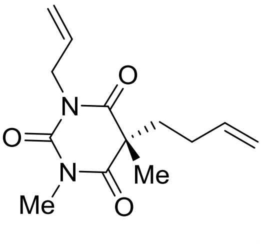
To a solution of adduct **43** (54 mg, 0.2 mmol, 1 equiv.) in DMF (0.4 mL) was added DIPEA (44 µL, 0.26 mmol, 1.3 equiv.) and after stirring for 5 minutes at room temperature benzyl or allyl bromide was added (0.26 mmol, 1.3 equiv.). The resulting solution was stirred at the same temperature until disappearance of starting material as monitored by ^{1}H NMR. Water (1 mL) was added and the resulting mixture was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (10 x 3 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane: ethyl acetate, 6:1)

(*R*)-1-Benzyl-5-(but-3-en-1-yl)-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (48)



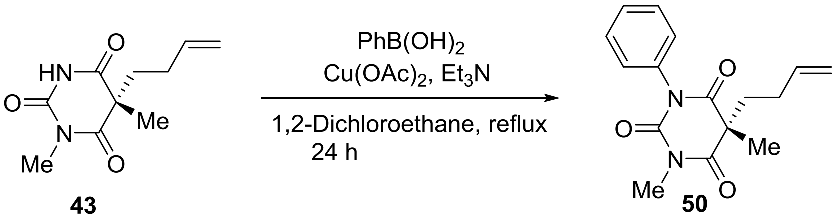
Prepared according to the general procedure using benzyl bromide**.** Colorless oil. Yield: 42.6 mg, 0.14 mmol, 71%. $[\alpha]_D^{23}$= +1.23° (*c* = 0.23, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.23 (m, 5H), 5.70 – 5.45 (m, 1H), 5.08 (d, *J* = 1.4 Hz, 2H), 4.84 – 4.67 (m, 2H), 3.30 (s, 3H), 2.18 – 2.09 (m, 2H), 1.94 – 1.81 (m, 2H), 1.54 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.7, 151.6, 137.2, 129.8, 129.2, 128.7, 116.5, 51.8, 45.8, 39.4, 30.5, 29.3, 26.0. UPLC-DAD-QTOF: calcd for $C_{17}H_{20}N_2O_3$ (M, H$^+$), 301.1474; found, 301.1476.

(*R*)-1-Allyl-5-(but-3-en-1-yl)-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (49)



Prepared according to the general procedure using allyl bromide. Colorless oil. Yield: 31.5 mg, 0.13 mmol, 63%. $[\alpha]_D^{23}$= +0.87° (*c*= 0.27, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.75 – 5.58 (m, 1H), 5.39 – 5.19 (m, 2H), 5.04 – 4.83 (m, 2H), 4.50 (dd, *J* = 6.1, 1.3 Hz, 2H), 3.31 (d, *J* = 0.7 Hz, 3H), 2.16 (dd, *J* = 9.2, 6.5 Hz, 2H), 2.05 – 1.88 (m, 2H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 172.33, 151.3, 137.3, 132.0, 119.6, 116.6, 51.8, 44.7, 39.2, 30.6, 29.3, 26.2.UPLC-DAD-QTOF: calcd for $C_{13}H_{18}N_2O_3$ (M, H$^+$), 251.1317; found, 251.1319.

5.3.12.6. Arylation of adduct 43[132]



A slurry of adduct **43** (42 mg, 0.2 mmol, 1 equiv.), phenylboronic acid (73.0 mg, 0.6 mmol, 3 equiv.), anhydrous Cu(OAc)$_2$ (72.6 mg, 0.4 mmol, 2 equiv.), and triethylamine (80 µL, 0.6 mmol, 3 equiv.) in ethylene chloride (0.2 mL) was stirred a reflux for 24 h. Then the mixture was directly submitted to a flash column chromatography on silica gel (eluent hexane: ethyl acetate, 8:1) to give the title compound as a yellow oil. Yield: 38.9 mg, 0.14 mmol, 68%. $[\alpha]_D^{22}$= +0.34° (*c*= 0.12, CH$_2$Cl$_2$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 – 7.43 (m, 3H), 7.21 – 7.17 (m, 2H), 5.86 – 5.65 (m, 1H), 5.12 – 4.97 (m, 2H), 3.37 (s, 3H), 2.30 – 2.21 (m, 2H), 2.17 – 2.07 (m, 2H), 1.66 (s, 3H).^{13}C NMR (75 MHz, CDCl$_3$) δ 172.1, 171.9, 150.8, 136.7, 134.5, 129.4, 129.1, 128.2, 116.1, 51.5, 38.5, 30.1, 28.7, 25.6. UPLC-DAD-QTOF: calcd for C$_{16}$H$_{18}$N$_2$O$_3$ (M, H$^+$), 286.1317; found, 286.1315.

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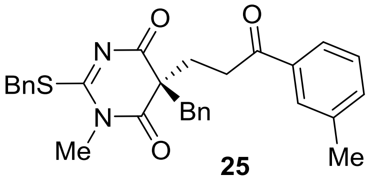
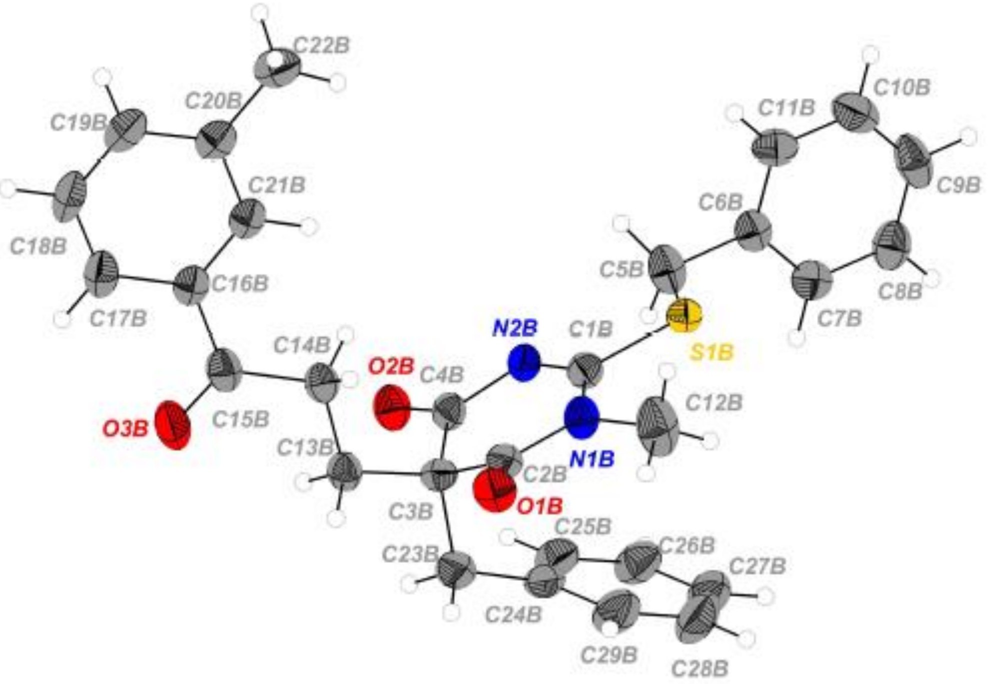
[132] Addapted from: Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.

5.3.12.7. X-ray analysis: ORTEP diagrams of compounds 25 and 32Ad

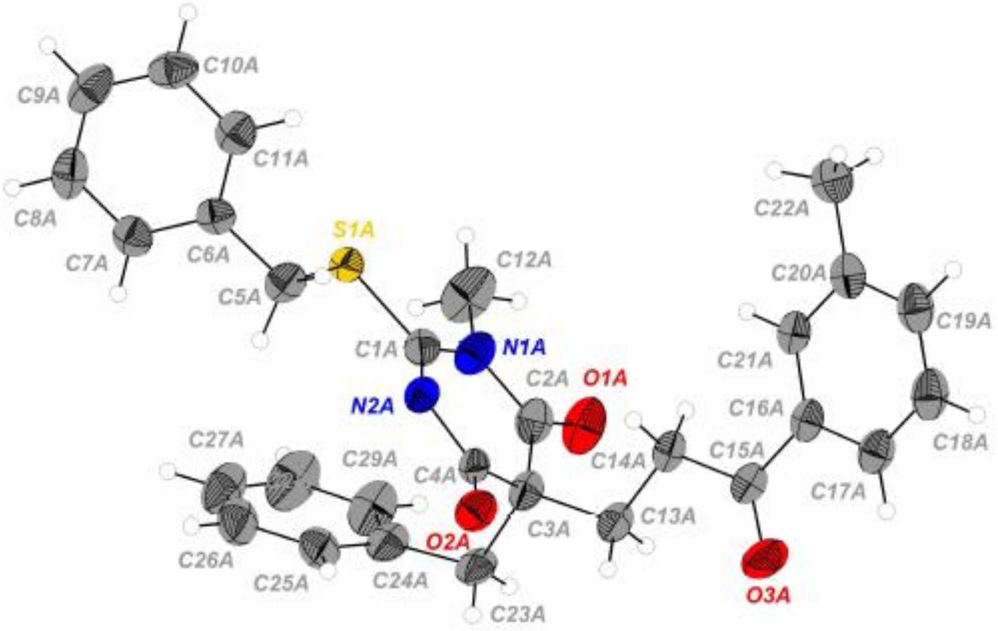

O
O
N
BnS
N
Me
Bn
O
Me

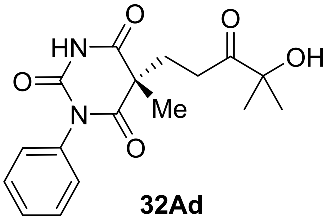
25

Molecule A

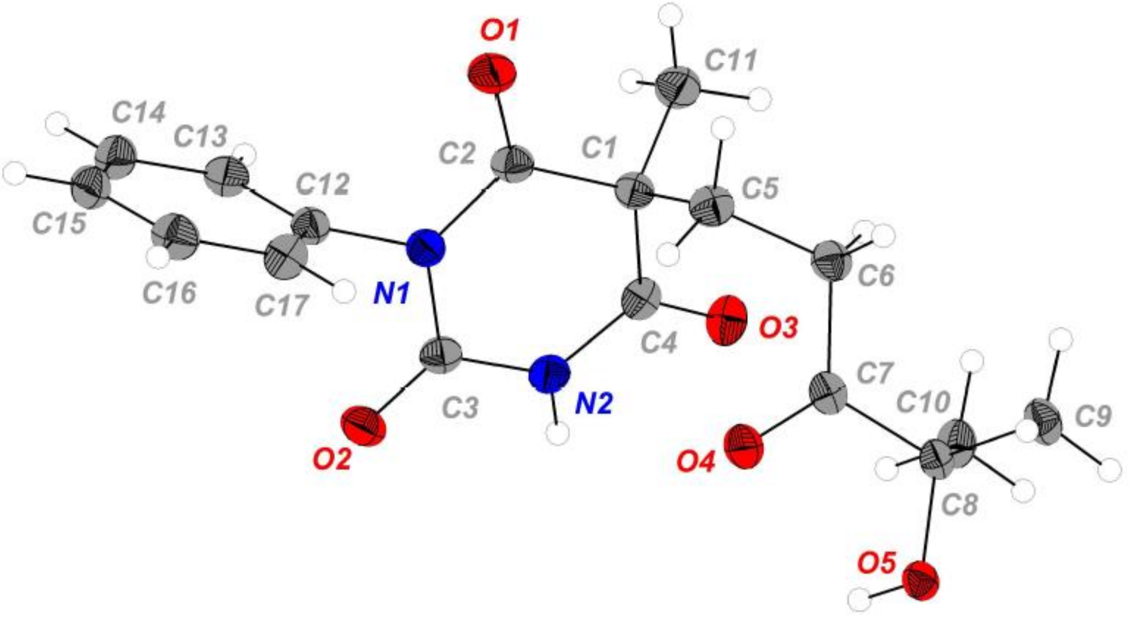

C22B
C20B
C19B
C21B
C18B
C16B
C17B
C14B
O2B
C4B
N2B
C1B
S1B
C11B
C10B
C9B
C6B
C5B
C8B
C7B
O3B
C15B
C13B
C12B
N1B
C2B
O1B
C3B
C23B
C25B
C26B
C27B
C24B
C29B
C28B

Molecule B

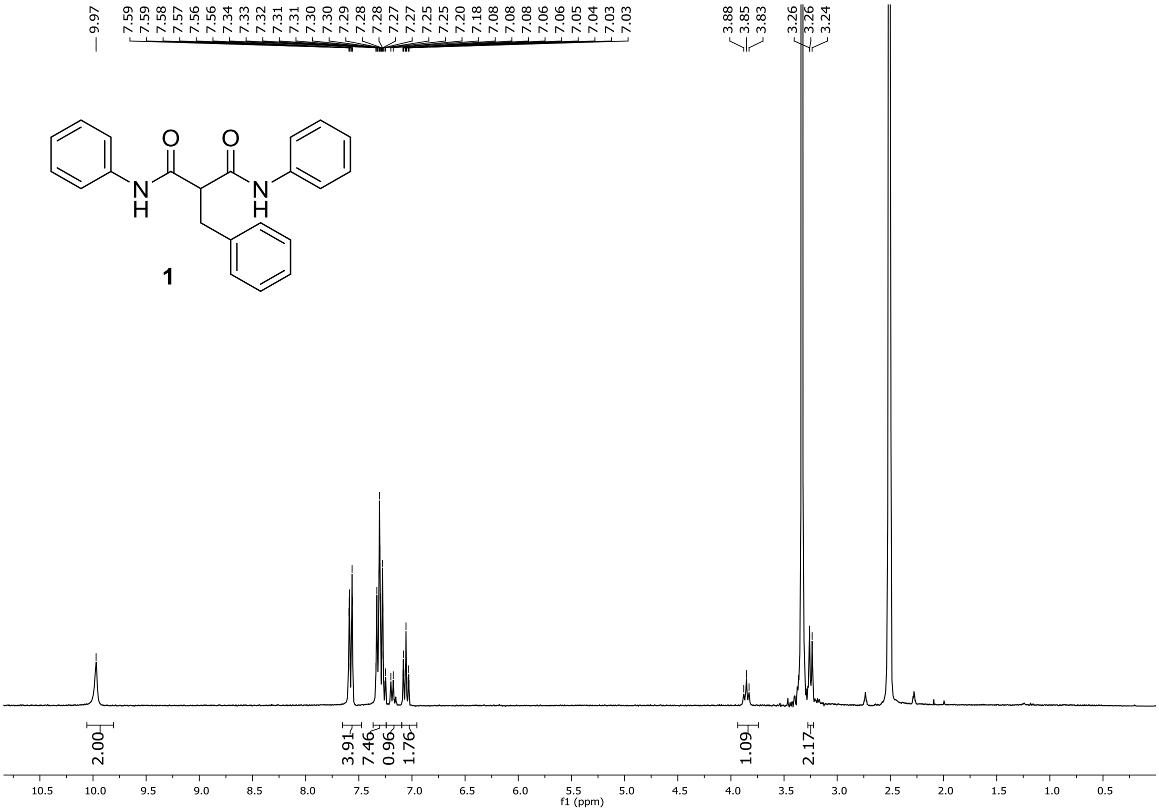

C10A
C9A
C11A
C8A
C7A
C6A
S1A
C5A
C12A
C22A
C20A
C19A
C1A
N1A
C21A
C2A
O1A
N2A
C16A
C18A
C27A
C29A
C4A
C14A
C15A
C17A
C3A
C13A
O2A
C26A
C25A
C24A
C23A
O3A


O
HN
O
OH
O
N
Me
O

32Ad

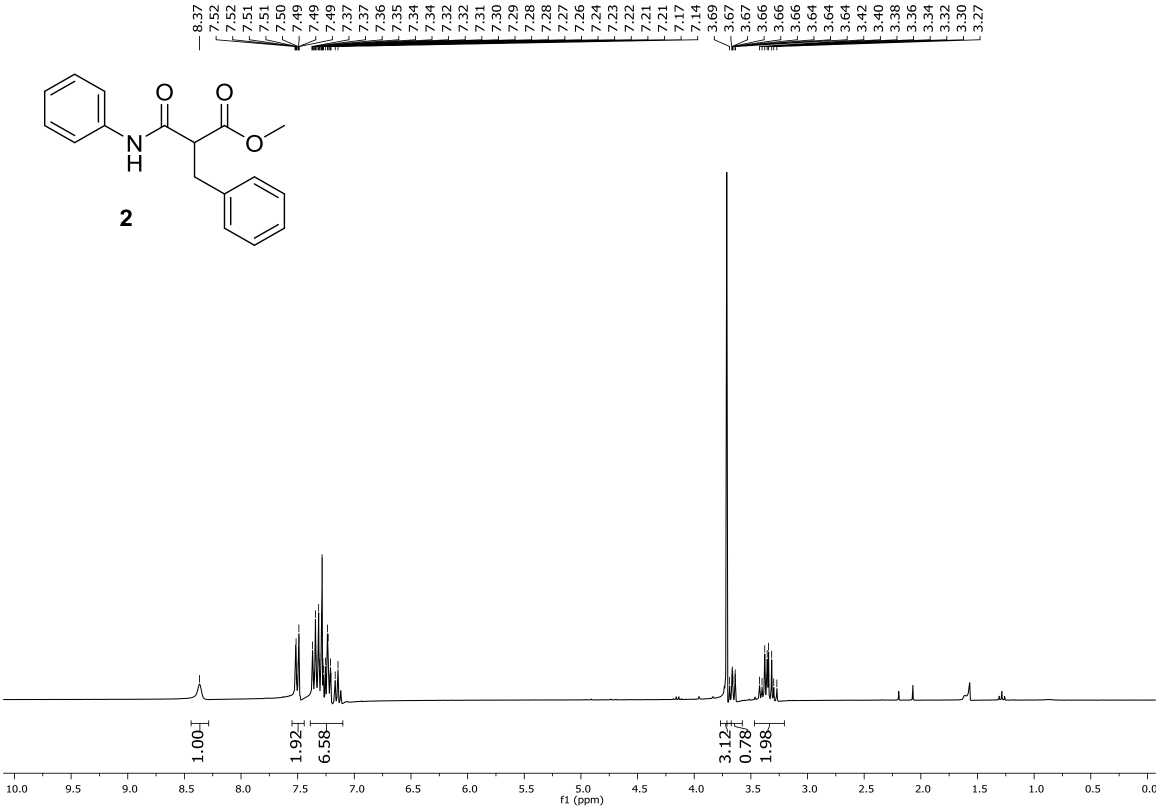

O1
C11
C14
C13
C2
C1
C12
C5
C15
C16
C17
N1
C6
C4
O3
C7
C10
C3
N2
C9
O2
O4
C8
O5

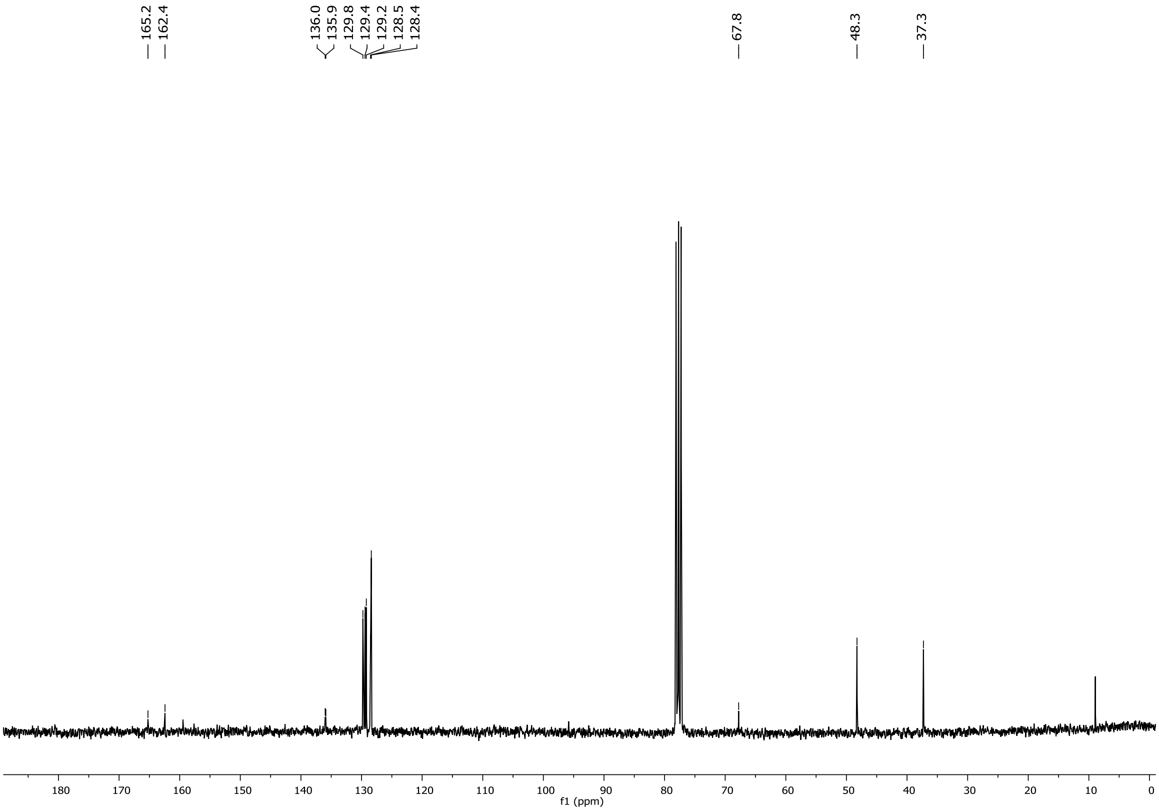
5.3.13. **Representative NMR spectra**

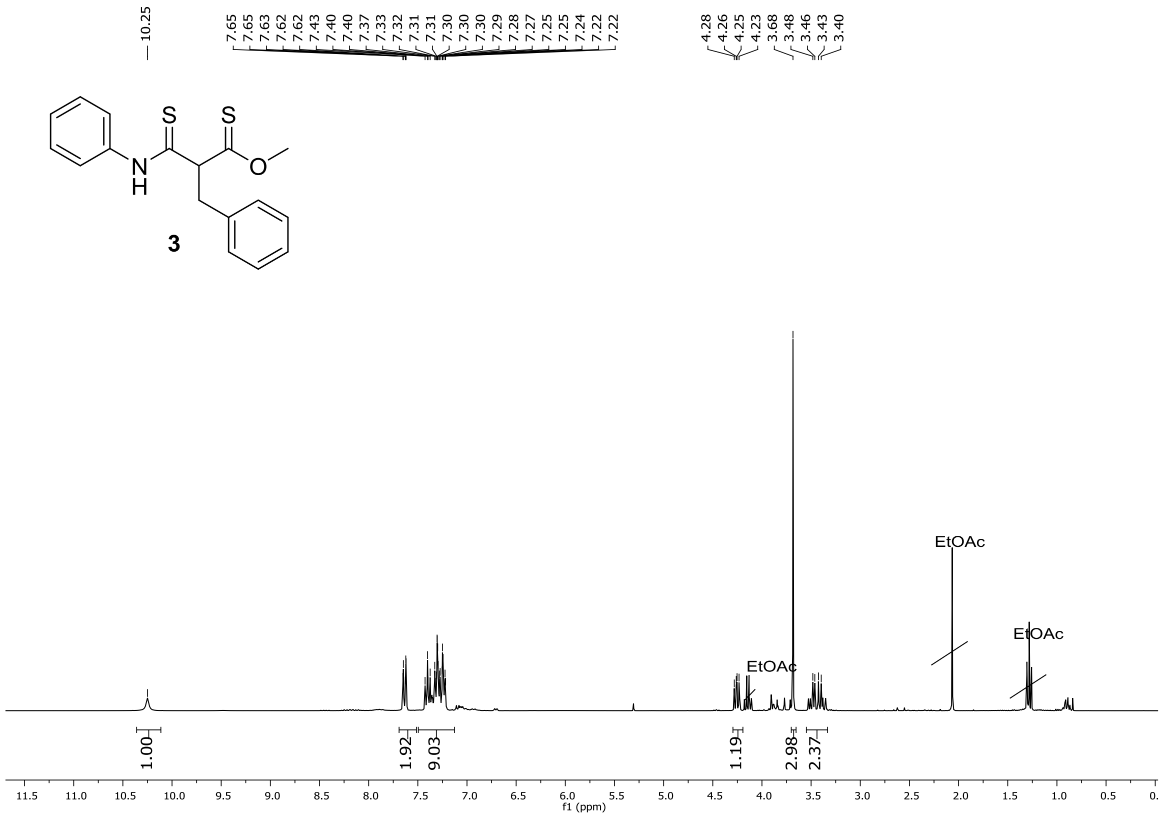


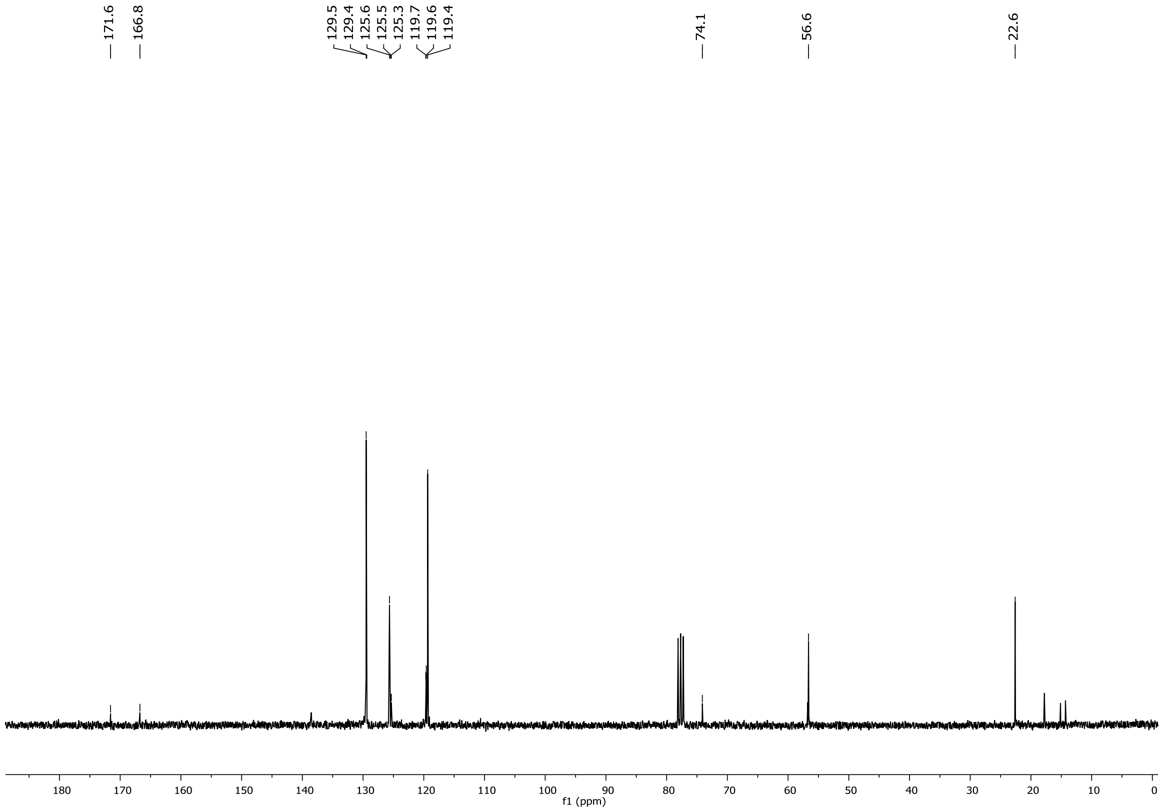
O
O
N
H
O

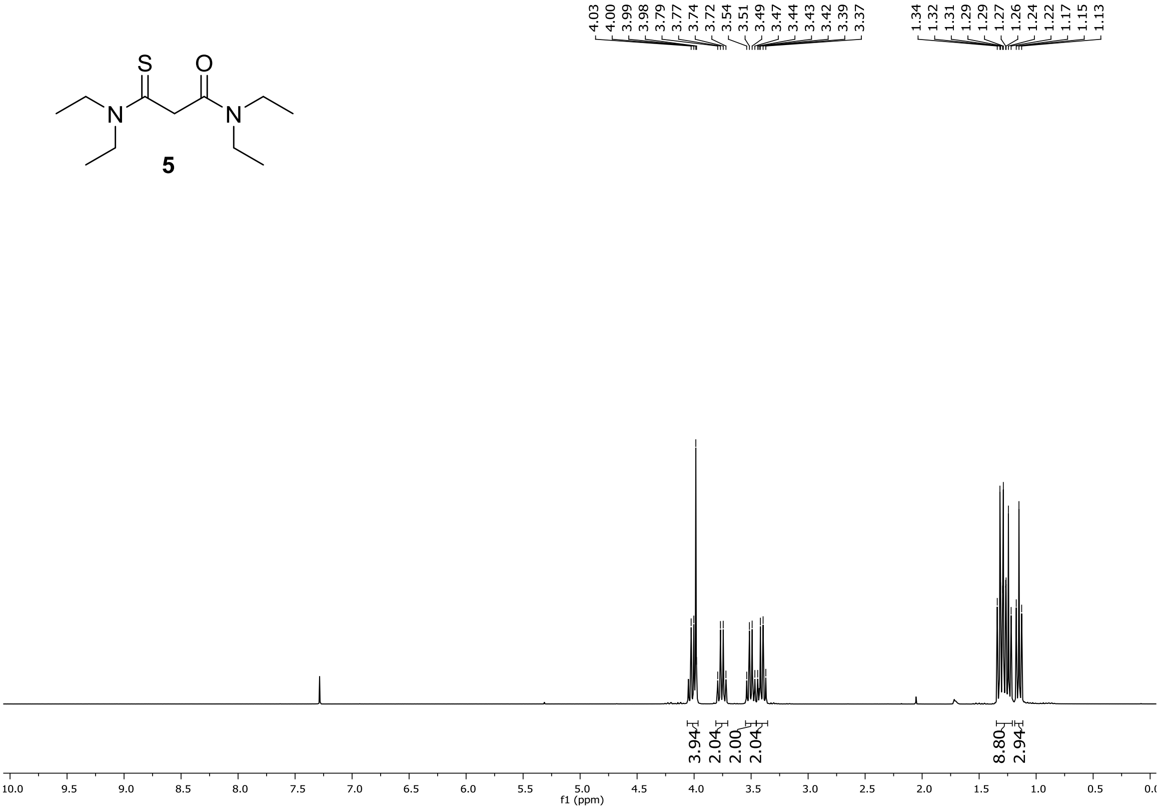
2


8.37
7.52
7.52
7.51
7.51
7.50
7.49
7.49
7.49
7.37
7.37
7.36
7.35
7.34
7.34
7.32
7.32
7.31
7.30
7.29
7.28
7.28
7.27
7.26
7.24
7.23
7.22
7.21
7.21
7.17
7.14
3.69
3.67
3.67
3.66
3.66
3.66
3.64
3.64
3.64
3.42
3.40
3.38
3.36
3.34
3.32
3.30
3.27
1.00
1.92
6.58
3.12
0.78
1.98
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
f1 (ppm)


165.2
162.4
136.0
135.9
129.8
129.4
129.2
128.5
128.4
67.8
48.3
37.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

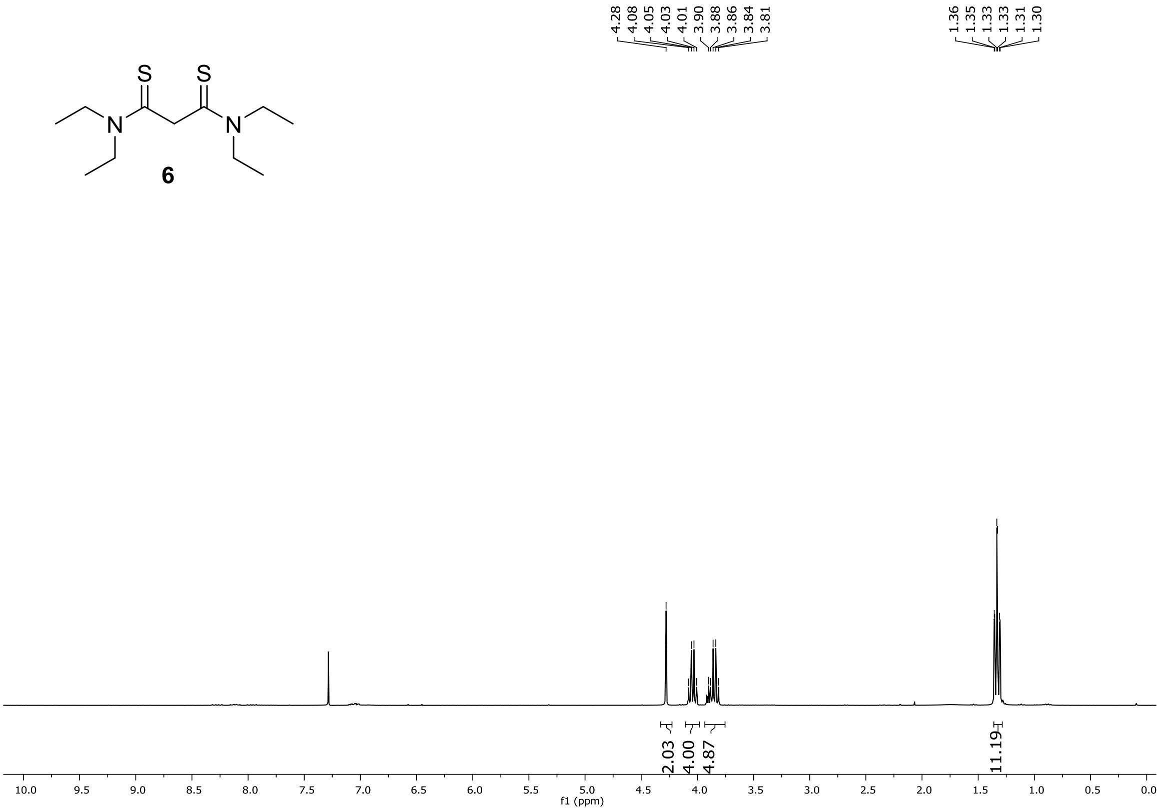

10.25
7.65 7.65 7.63 7.62 7.43 7.40 7.37 7.33 7.32 7.31 7.30 7.30 7.30 7.29 7.28 7.27 7.25 7.25 7.24 7.22 7.22
4.28 4.26 4.25 4.23 3.68 3.48 3.46 3.43 3.40
S
S
N
H
O
3
EtOAc
EtOAc
EtOAc
1.00
1.92
9.03
1.19
2.98
2.37
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)


171.6
166.8
129.5 129.4 125.6 125.5 125.3 119.7 119.6 119.4
74.1
56.6
22.6
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



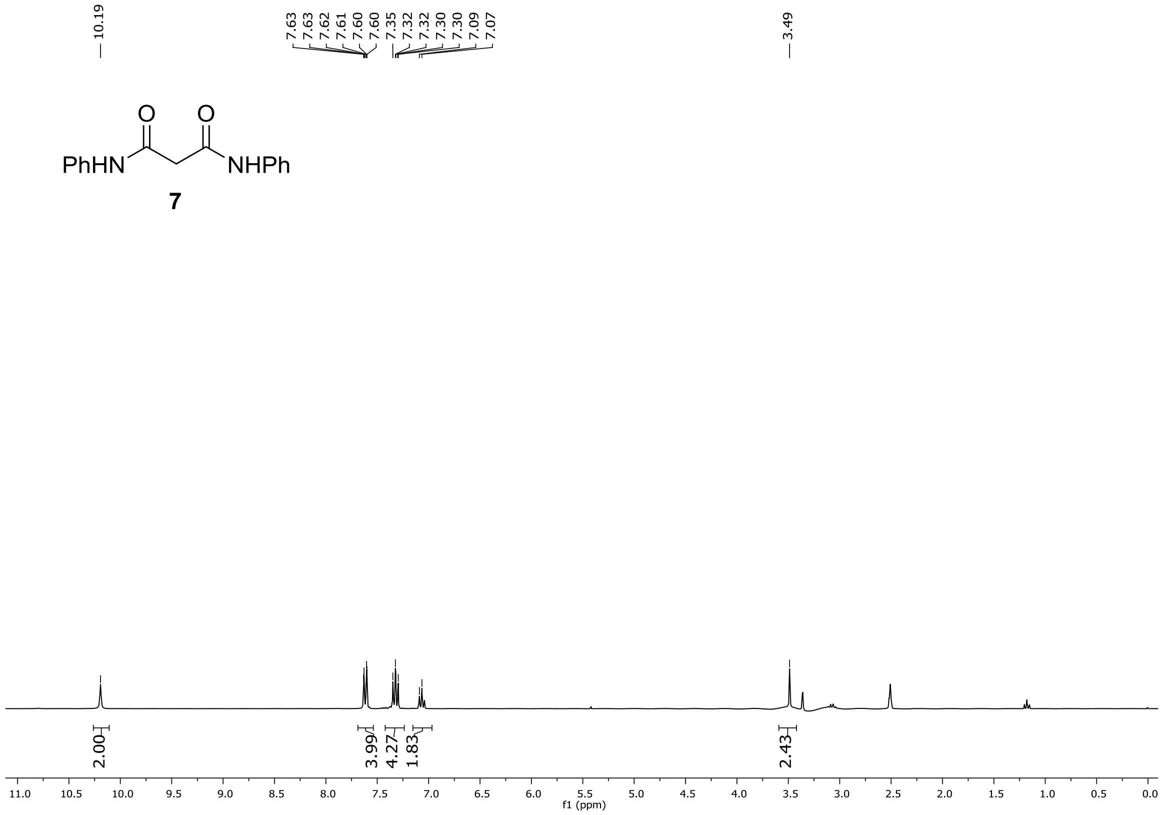
5

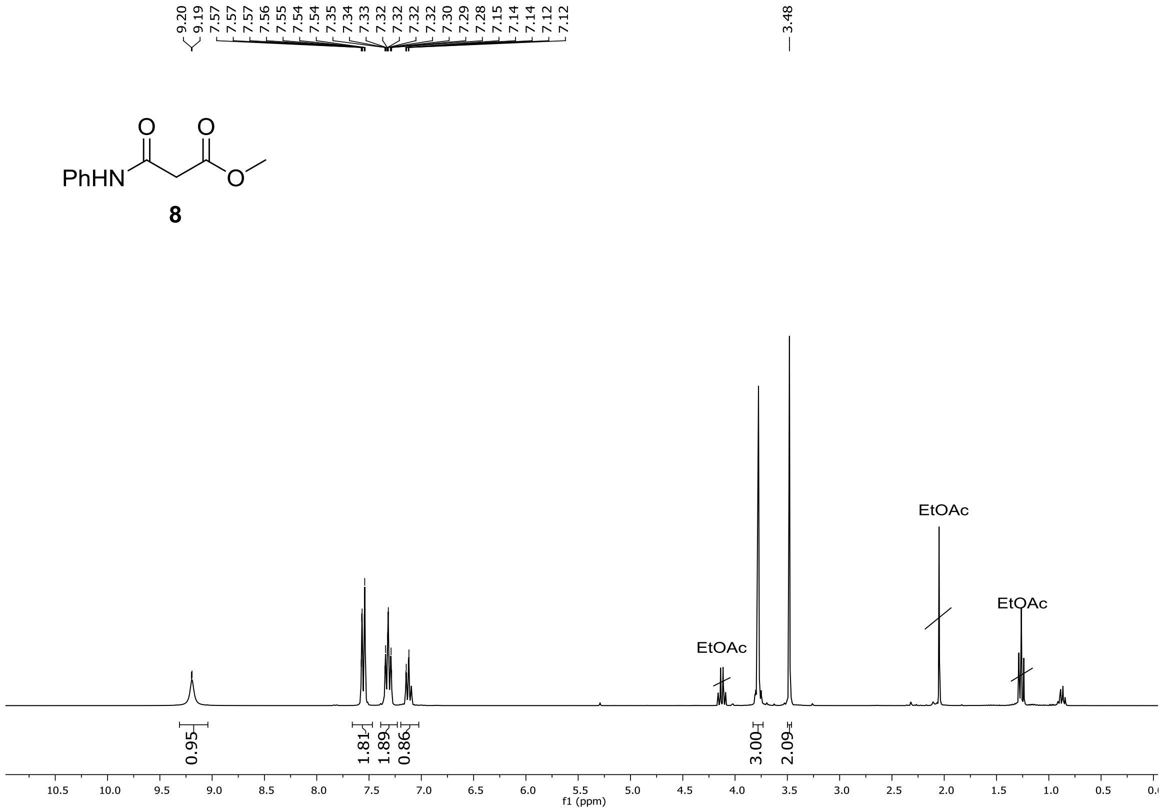
4.03
4.00
3.99
3.98
3.79
3.77
3.74
3.72
3.54
3.51
3.49
3.47
3.44
3.43
3.42
3.39
3.37
1.34
1.32
1.31
1.29
1.29
1.27
1.26
1.24
1.22
1.17
1.15
1.13
3.94
2.04
2.00
2.04
8.80
2.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

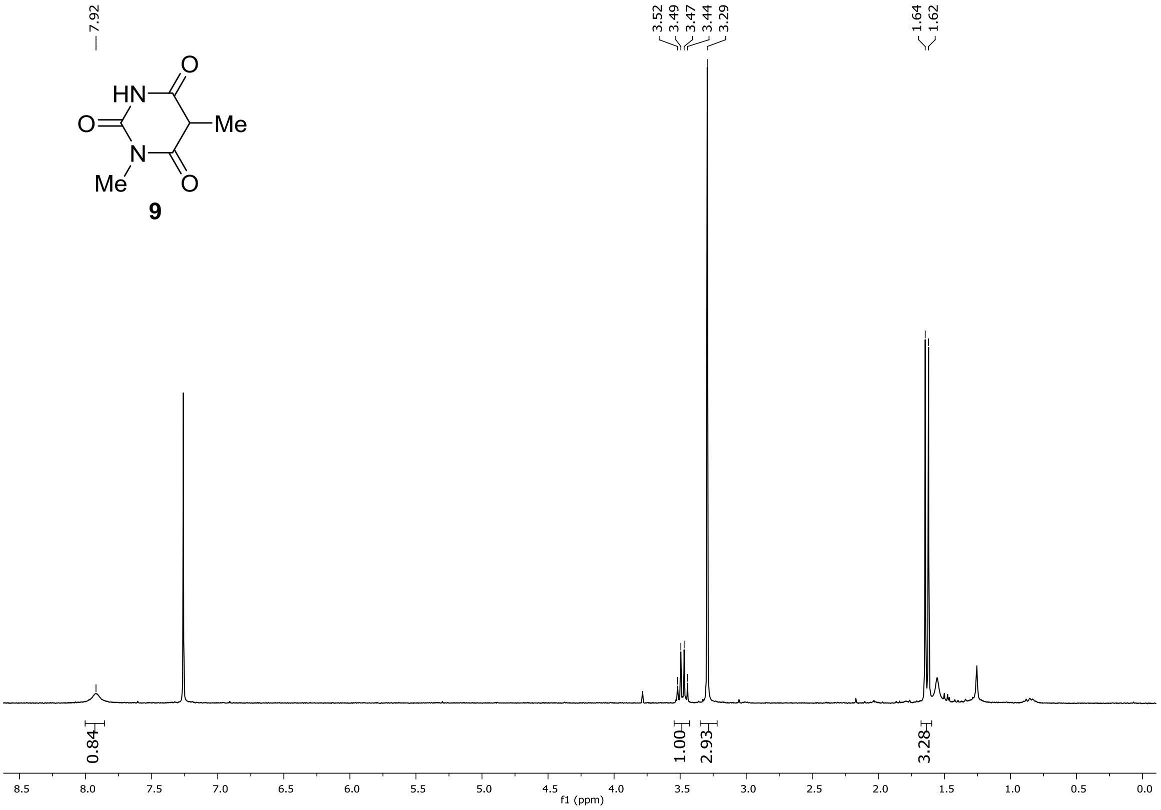


6

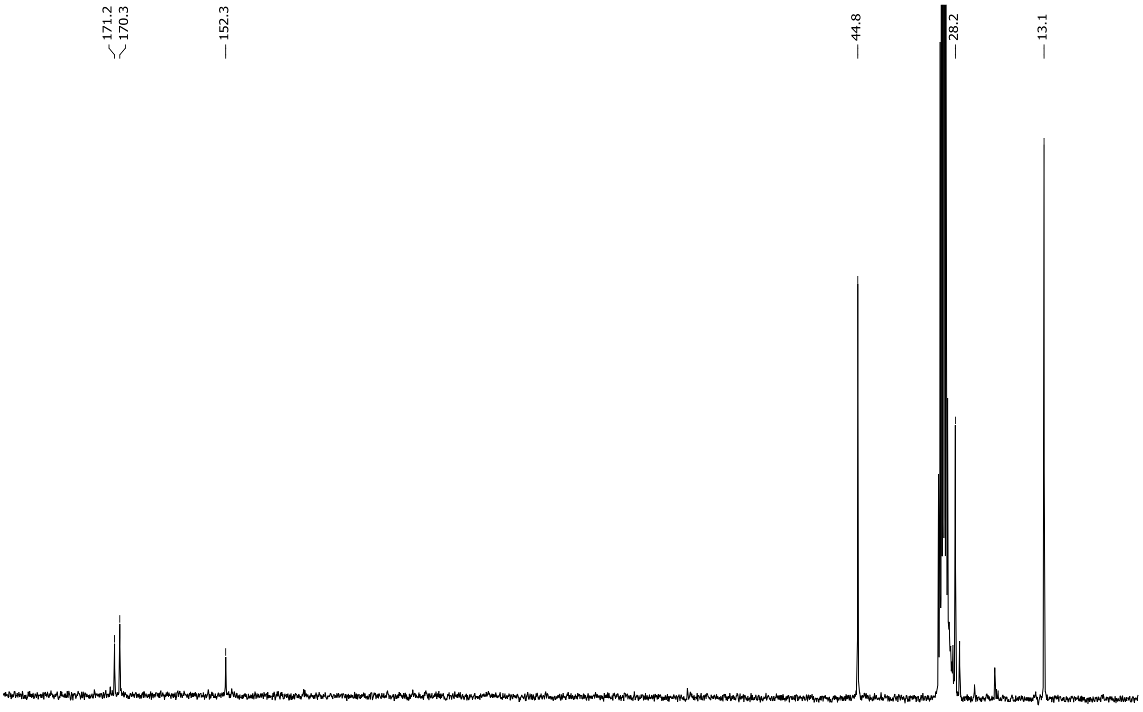
4.28
4.08
4.05
4.03
4.01
3.90
3.88
3.86
3.84
3.81
1.36
1.35
1.33
1.33
1.31
1.30
2.03
4.00
4.87
11.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7
10.19
7.63
7.63
7.62
7.61
7.60
7.60
7.35
7.32
7.32
7.30
7.30
7.09
7.07
3.49
PhHN
NHPh
O
O
2.00
3.99
4.27
1.83
2.43
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
f1 (ppm)

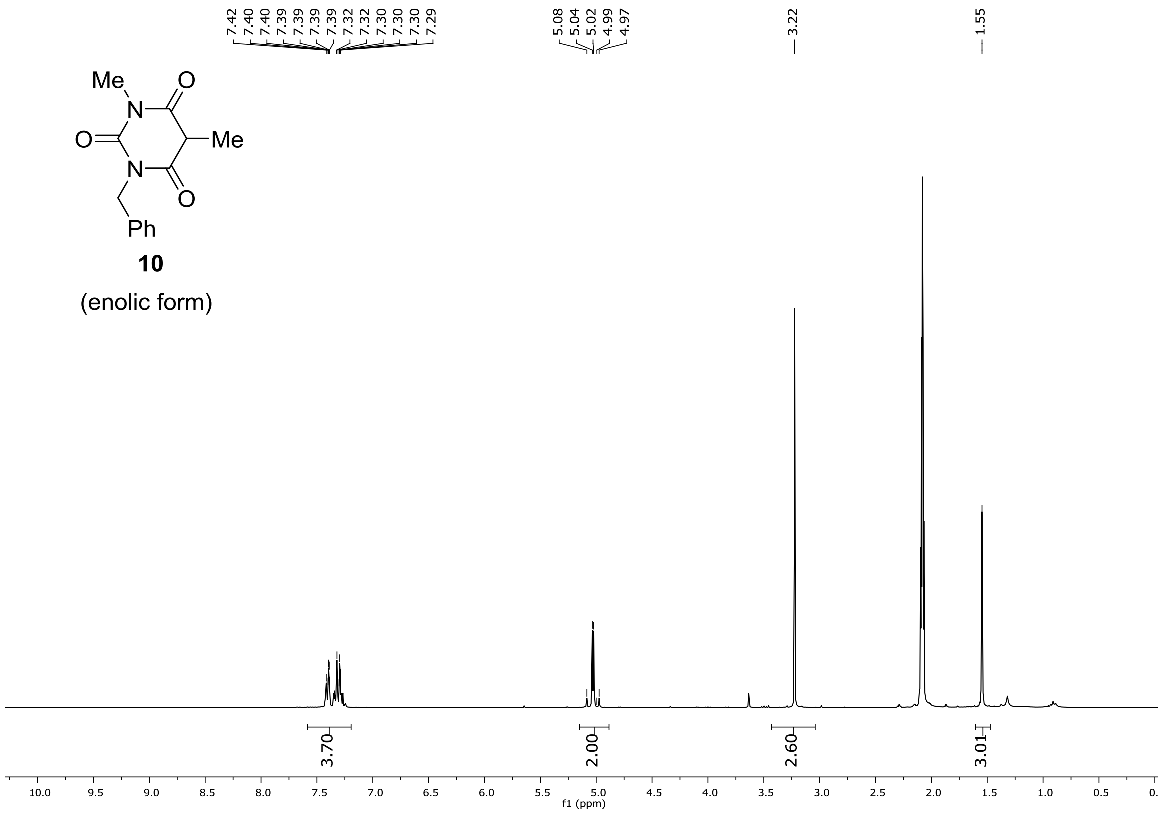

8
9.20
9.19
7.57
7.57
7.56
7.55
7.54
7.35
7.34
7.33
7.32
7.32
7.32
7.32
7.30
7.29
7.28
7.15
7.14
7.14
7.12
7.12
3.48
PhHN
O
O
O
EtOAc
EtOAc
EtOAc
0.95
1.81
1.89
0.86
3.00
2.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



7.92
3.52
3.49
3.47
3.44
3.29
1.64
1.62
HN
O
O
Me
N
Me
O
9
0.84
1.00
2.93
3.28
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
f1 (ppm)

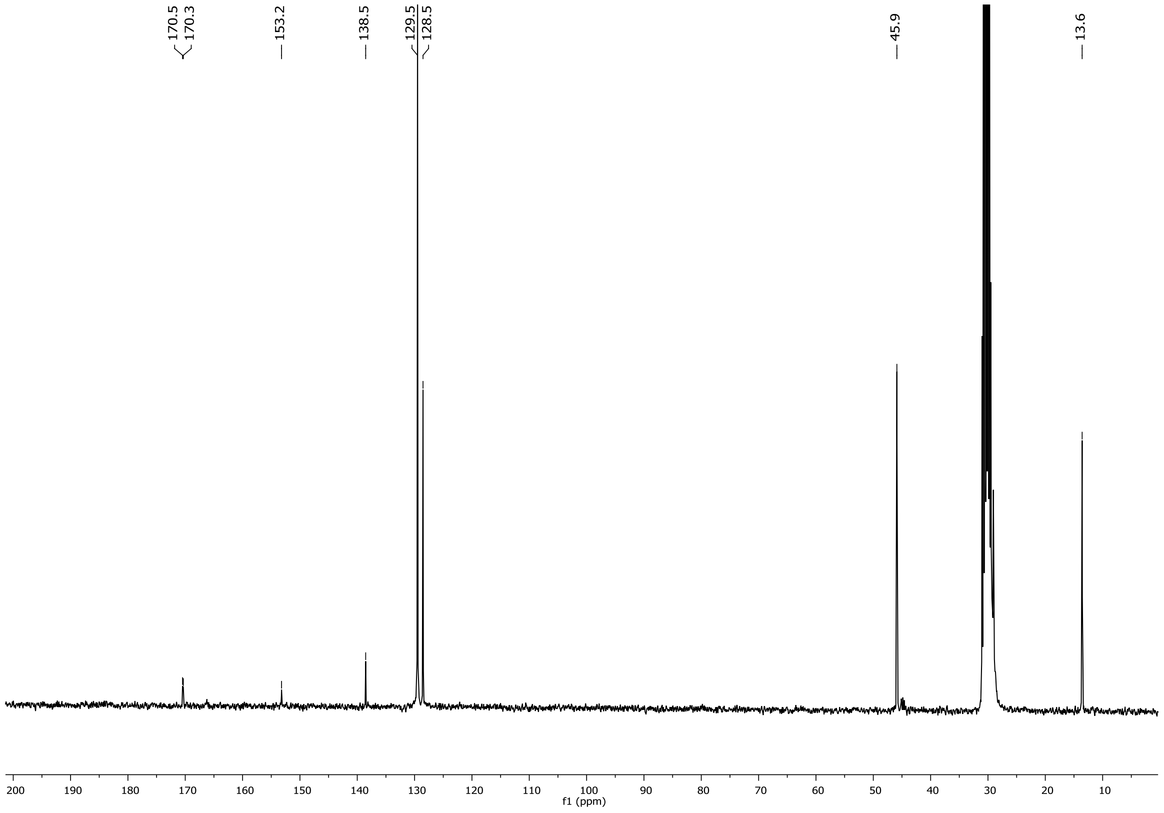


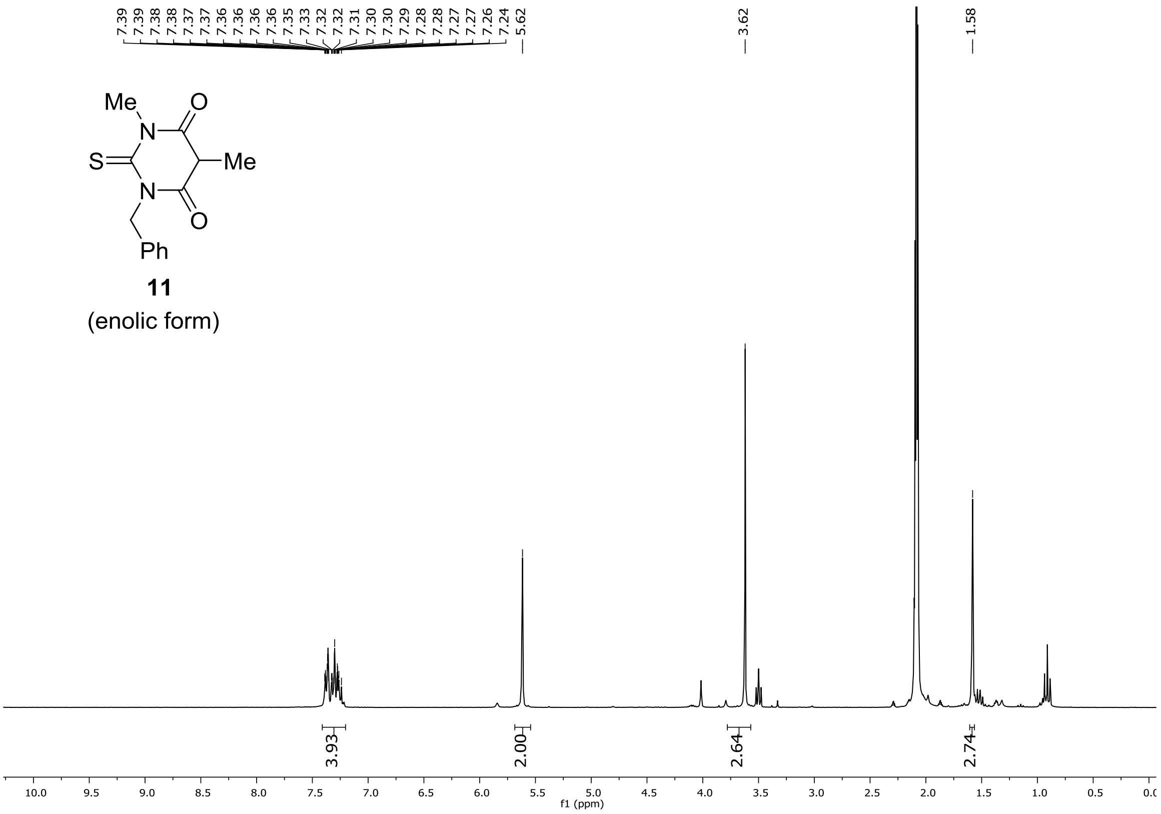
171.2
170.3
152.3
44.8
28.2
13.1
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



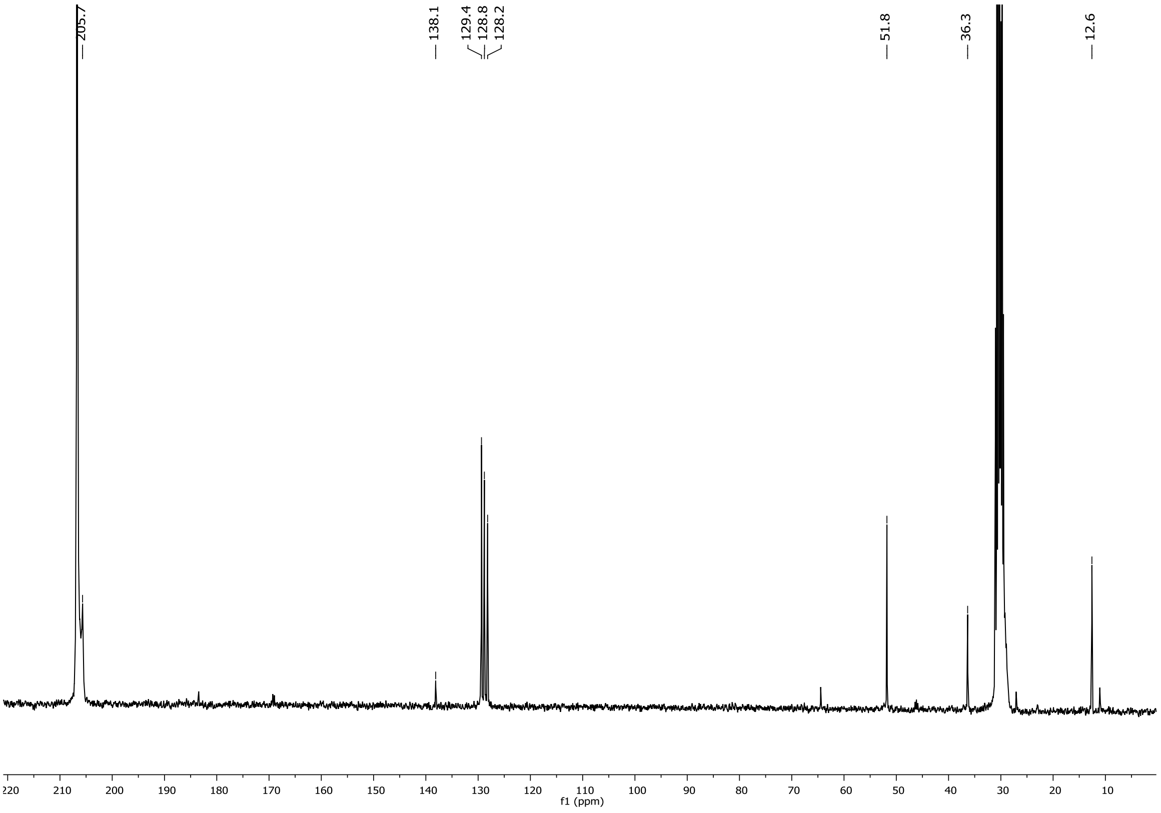
10

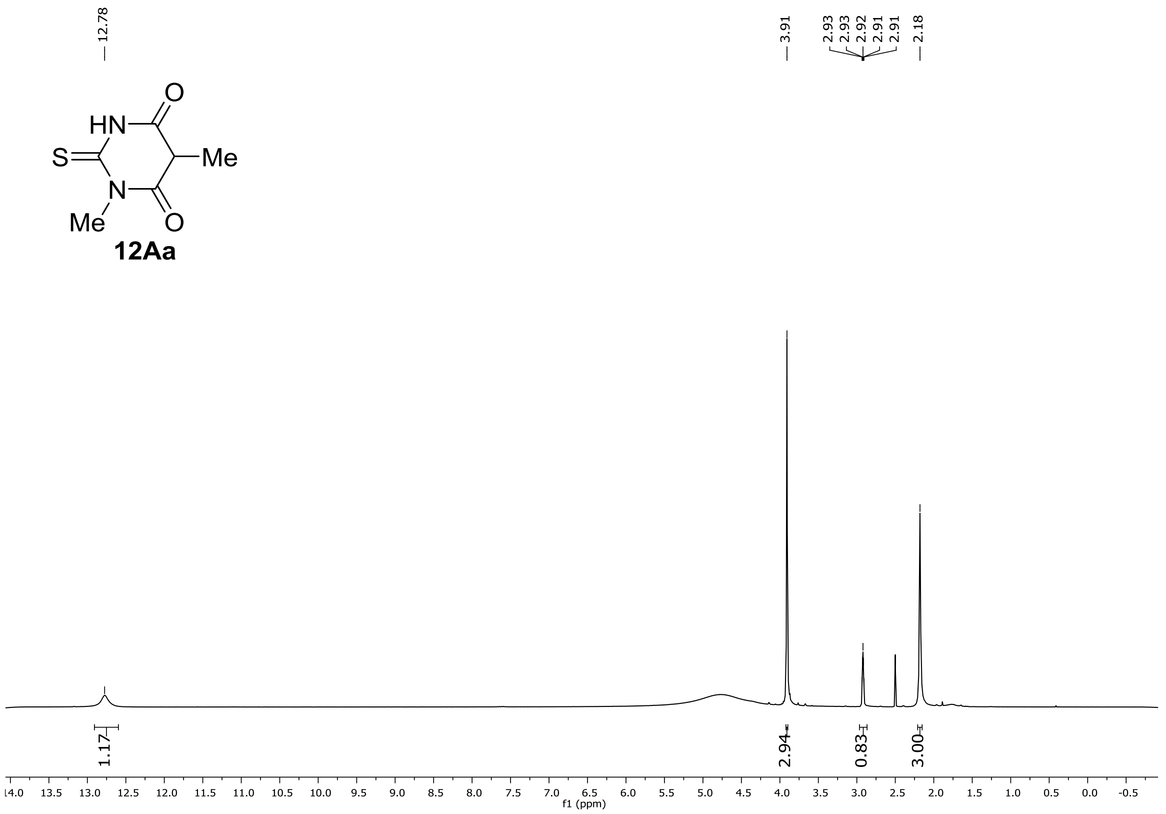
(enolic form)





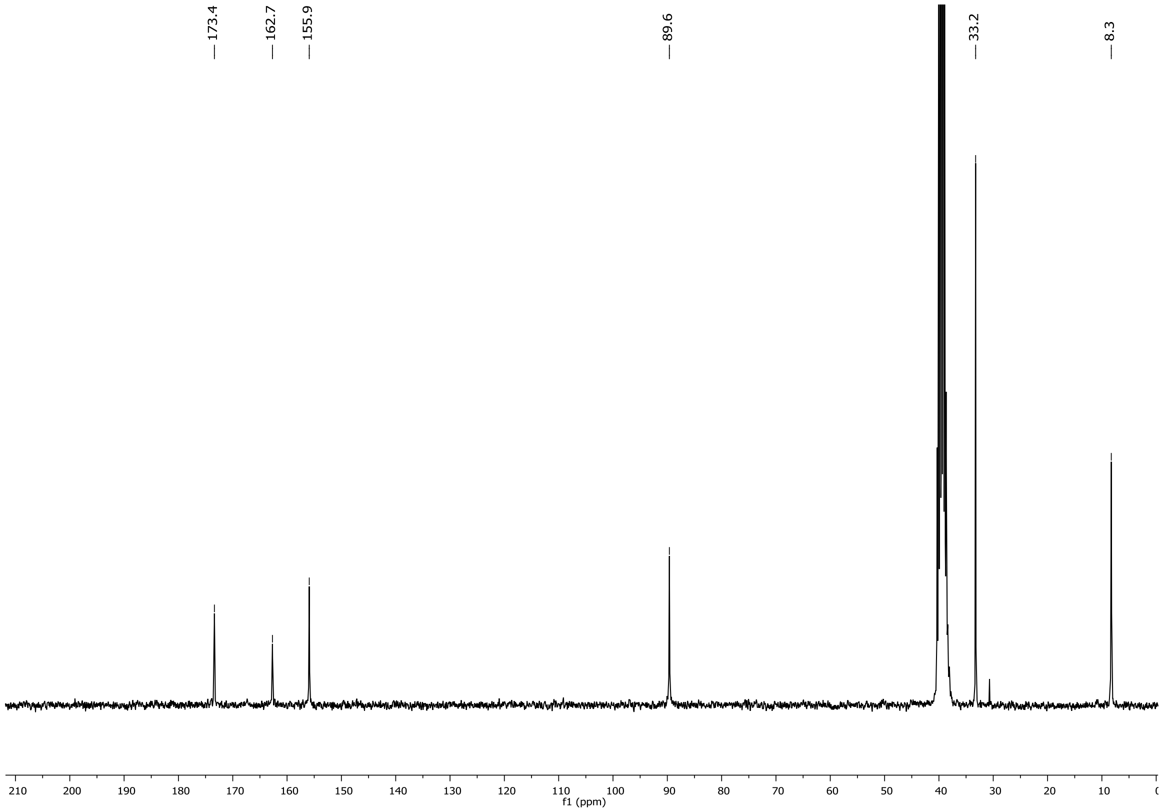
11
(enolic form)



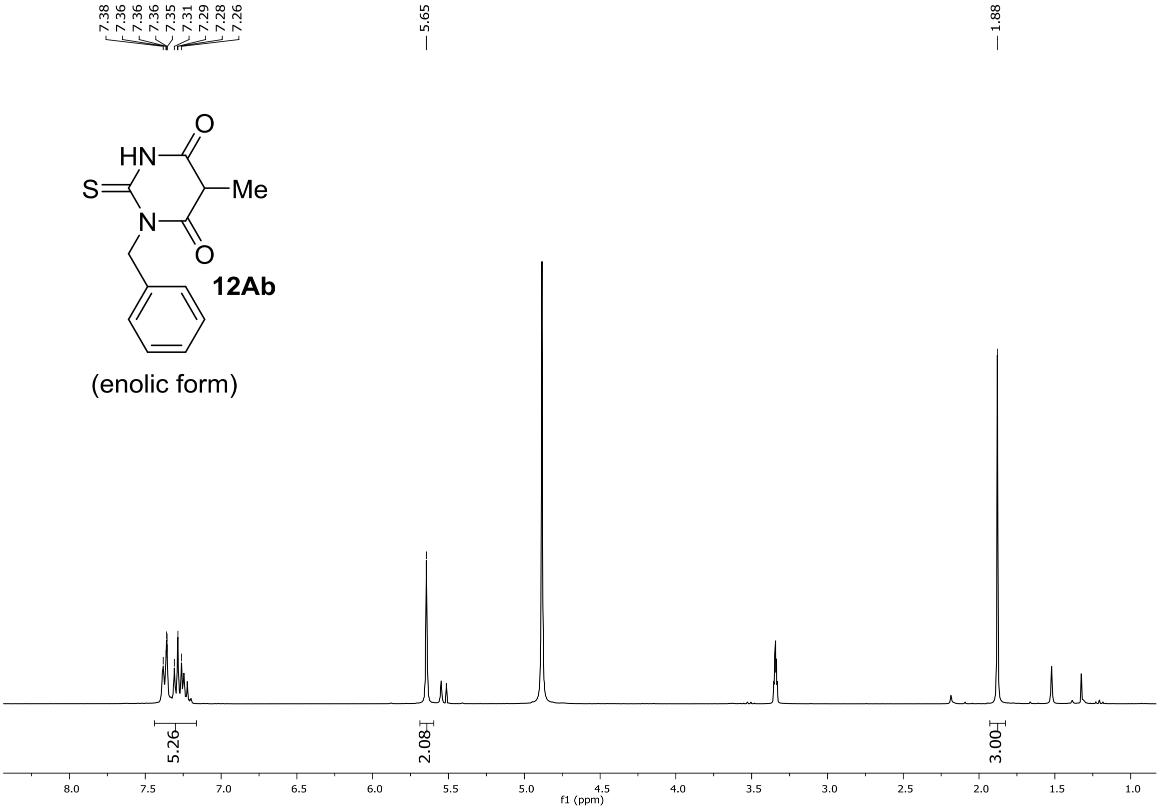


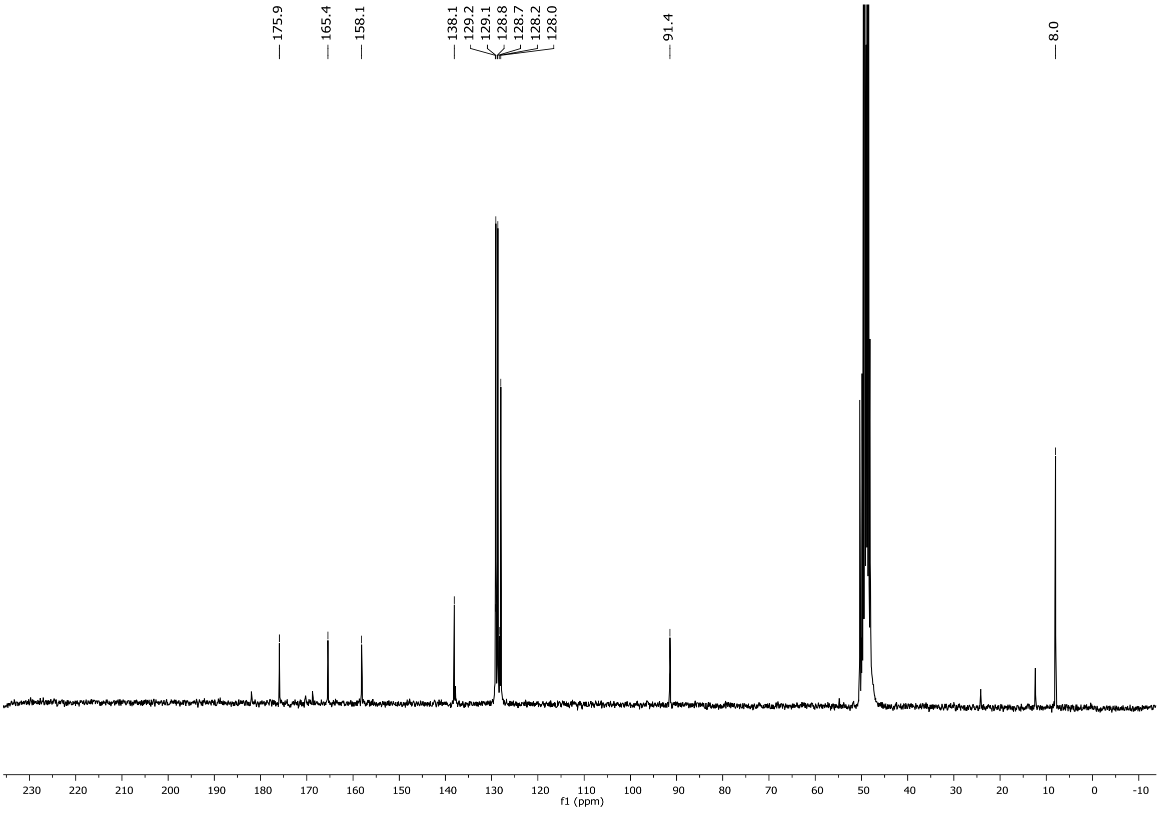
12Aa

12.78
3.91
2.93
2.93
2.92
2.91
2.91
2.18
HN
O
S
Me
N
Me
O
1.17
2.94
0.83
3.00
14.0 13.5 13.0 12.5 12.0 11.5 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)



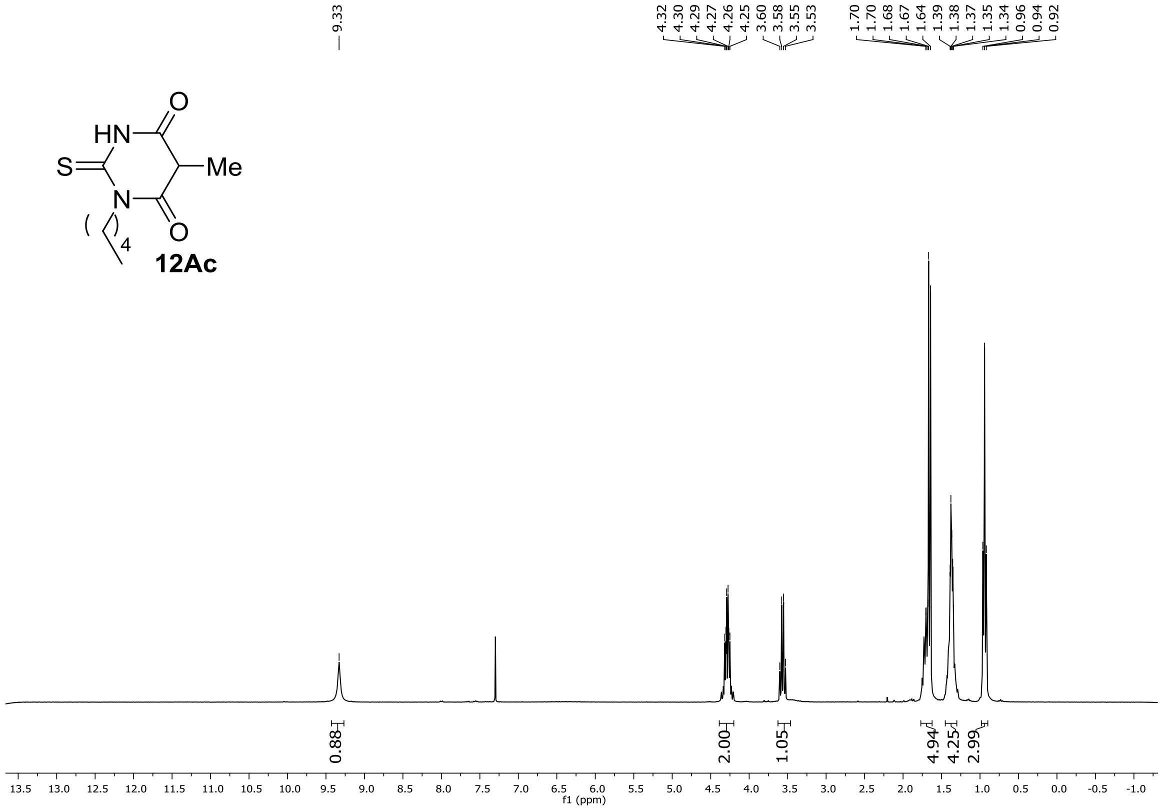
173.4
162.7
155.9
89.6
33.2
8.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

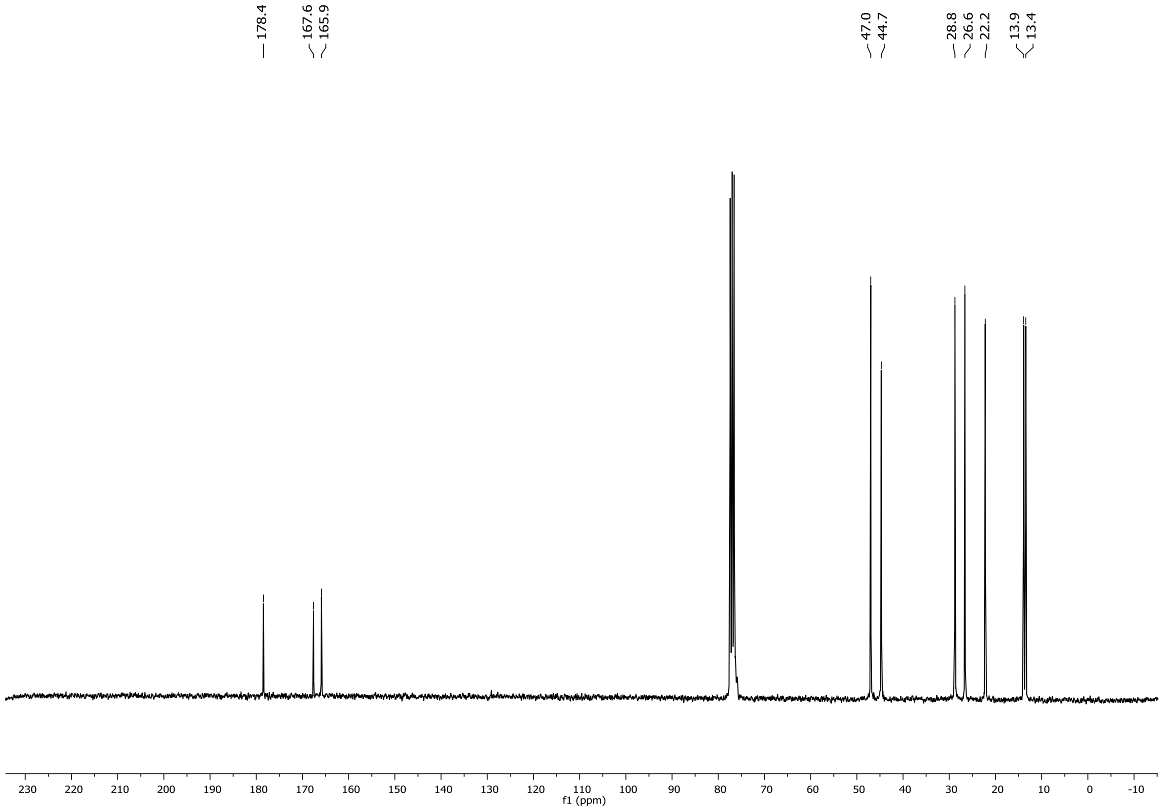

7.38
7.36
7.36
7.36
7.35
7.31
7.29
7.28
7.26
5.65
1.88
HN
O
S
N
Me
O
12Ab
(enolic form)
5.26
2.08
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

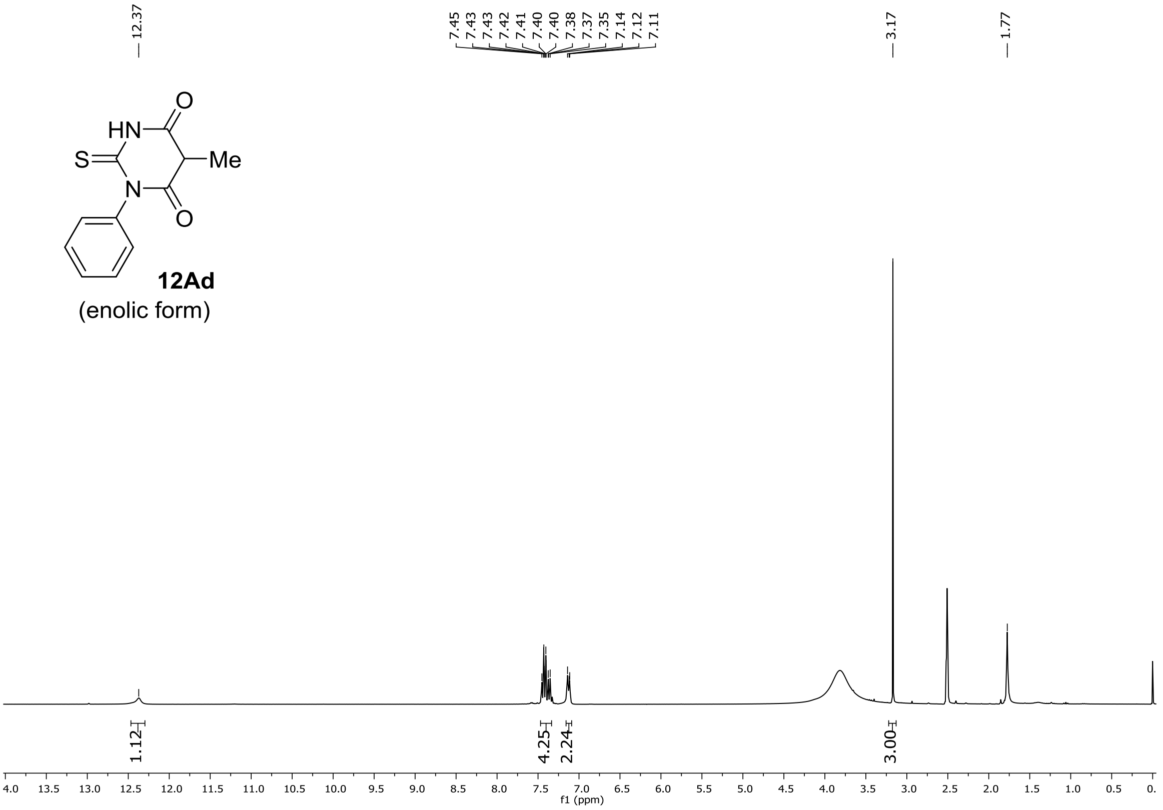

175.9
165.4
158.1
138.1
129.2
129.1
128.8
128.7
128.2
128.0
91.4
8.0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

HN
O
S
Me
N
O
( )4

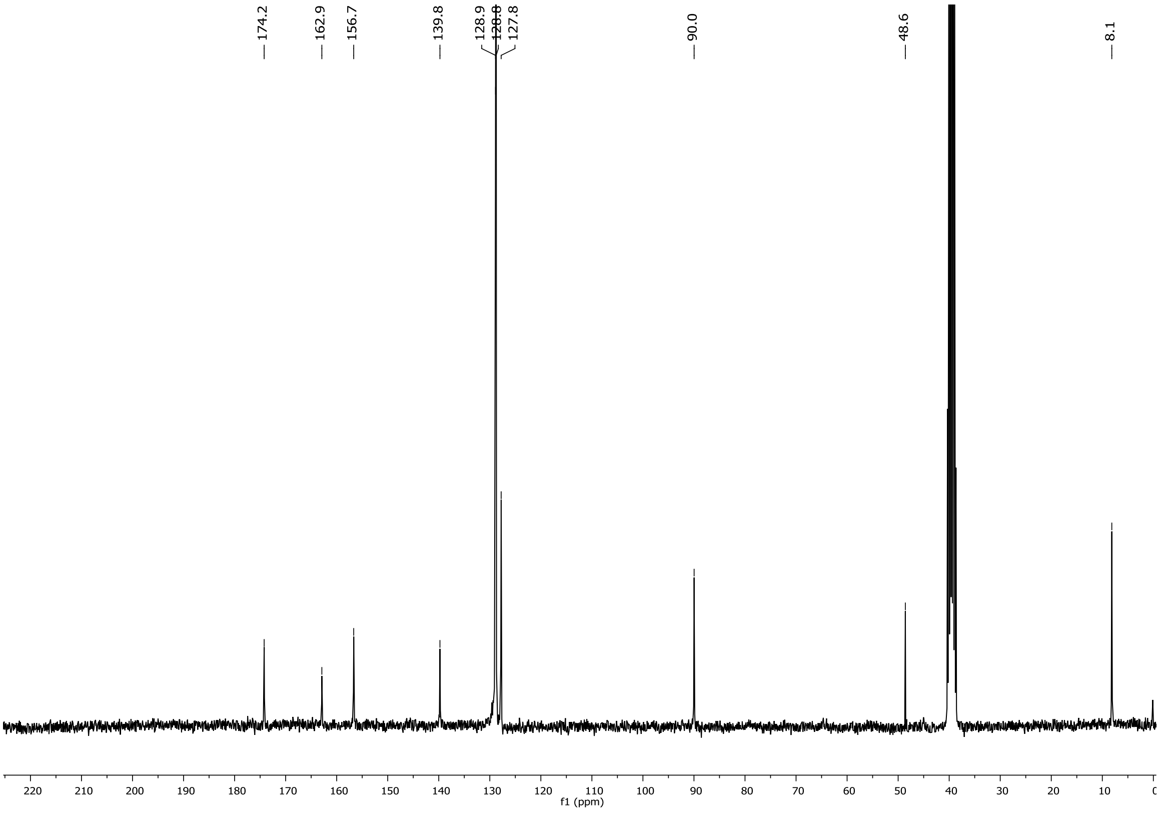
12Ac

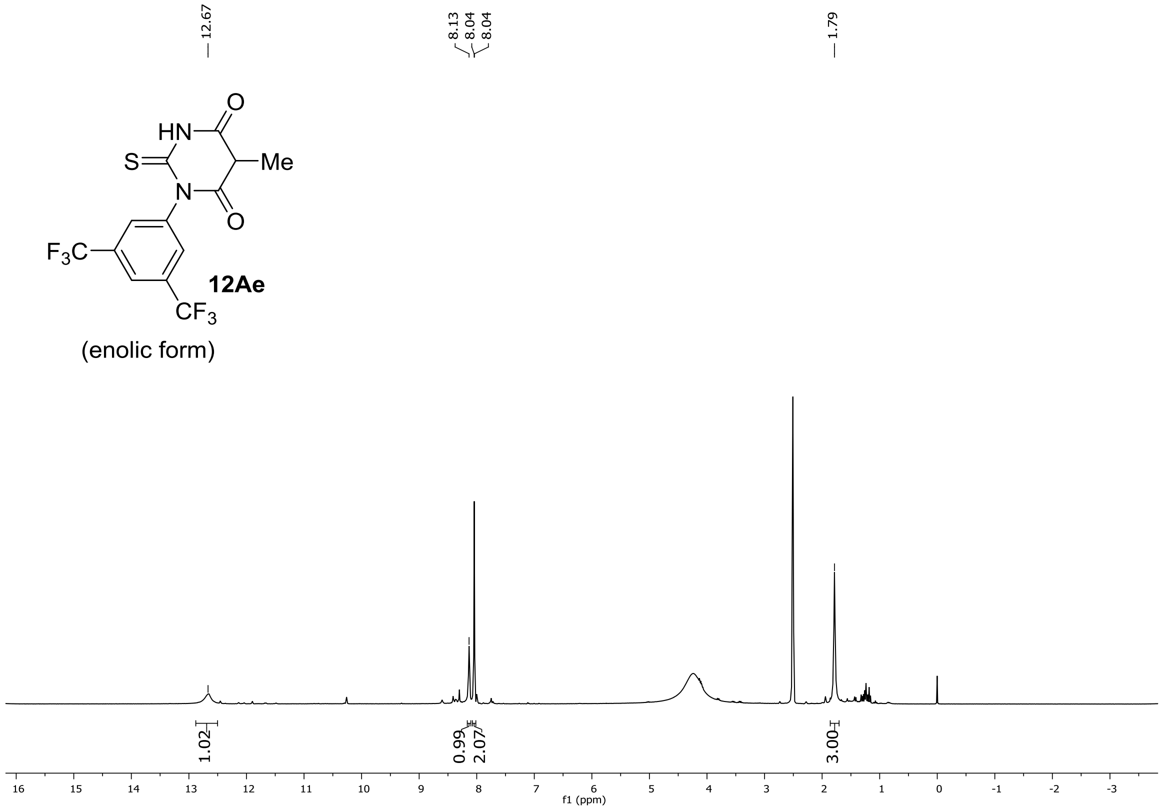

9.33
4.32
4.30
4.29
4.27
4.26
4.25
3.60
3.58
3.55
3.53
1.70
1.70
1.68
1.67
1.64
1.39
1.38
1.37
1.35
1.34
0.96
0.94
0.92
0.88
2.00
1.05
4.94
4.25
2.99
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

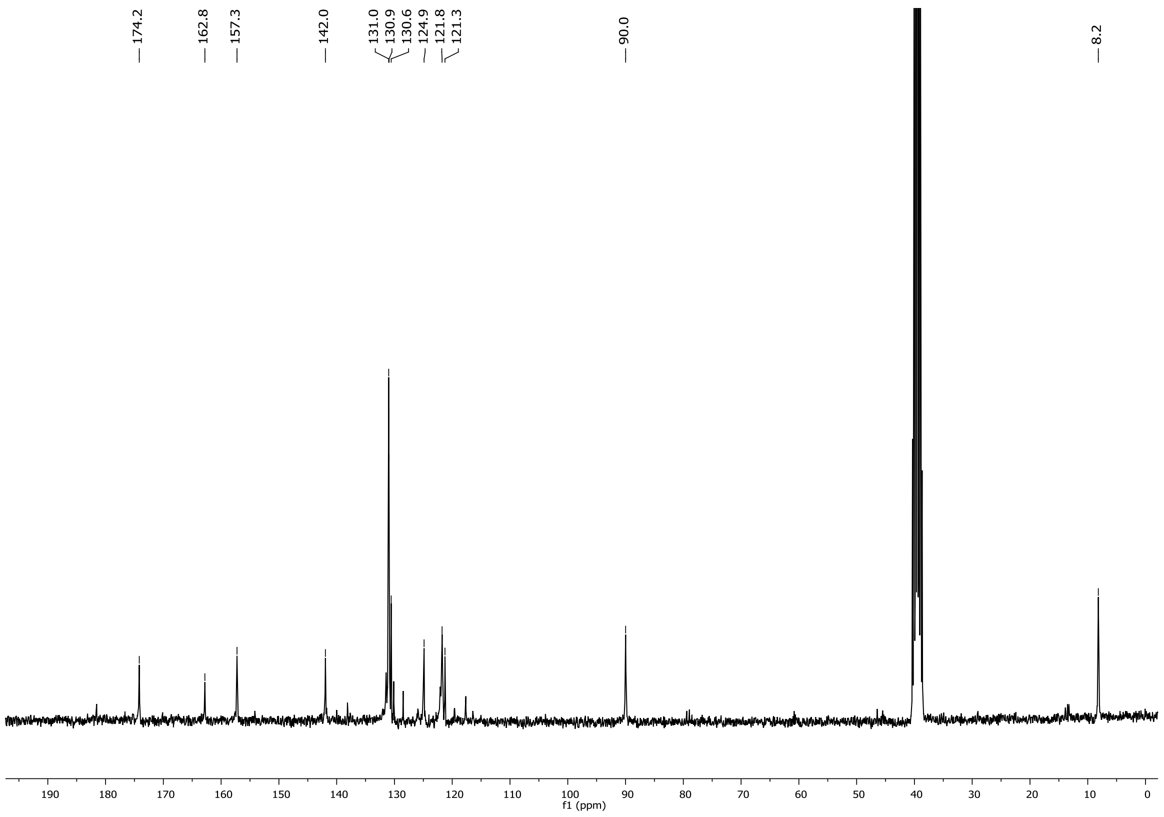

178.4
167.6
165.9
47.0
44.7
28.8
26.6
22.2
13.9
13.4
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

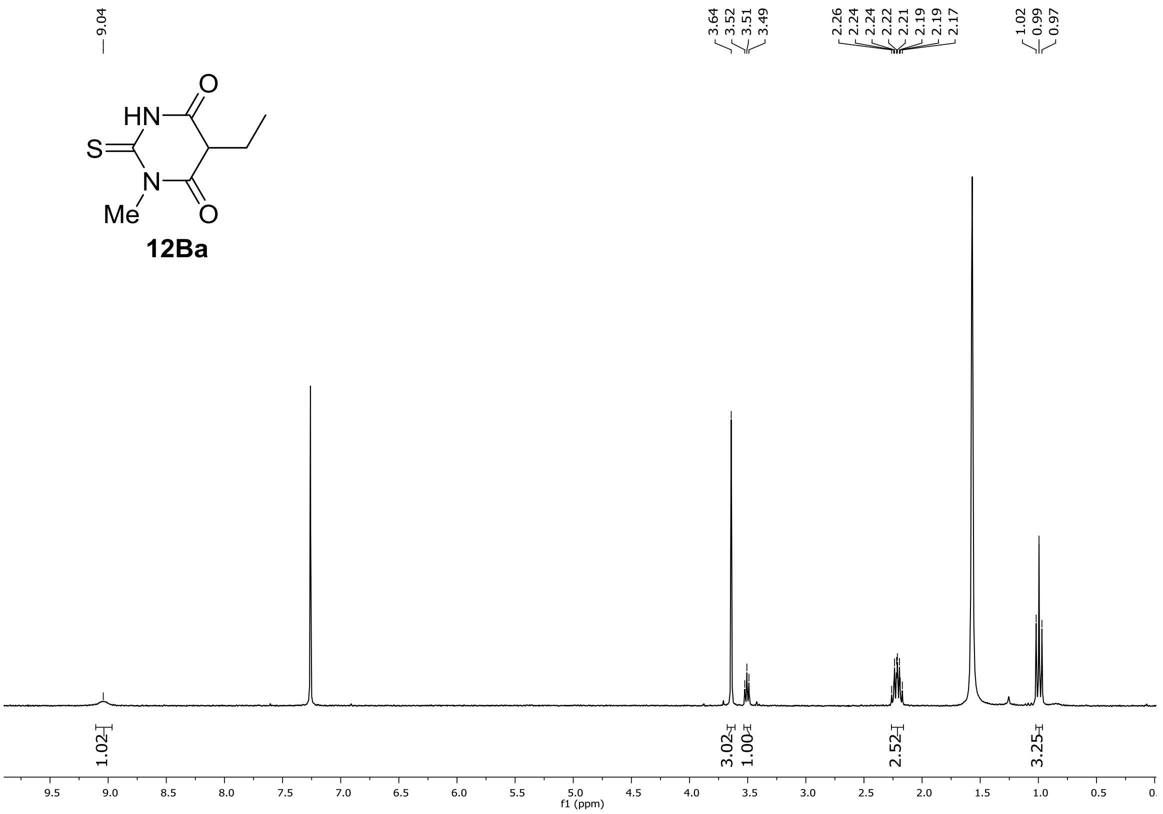


12Ad
(enolic form)

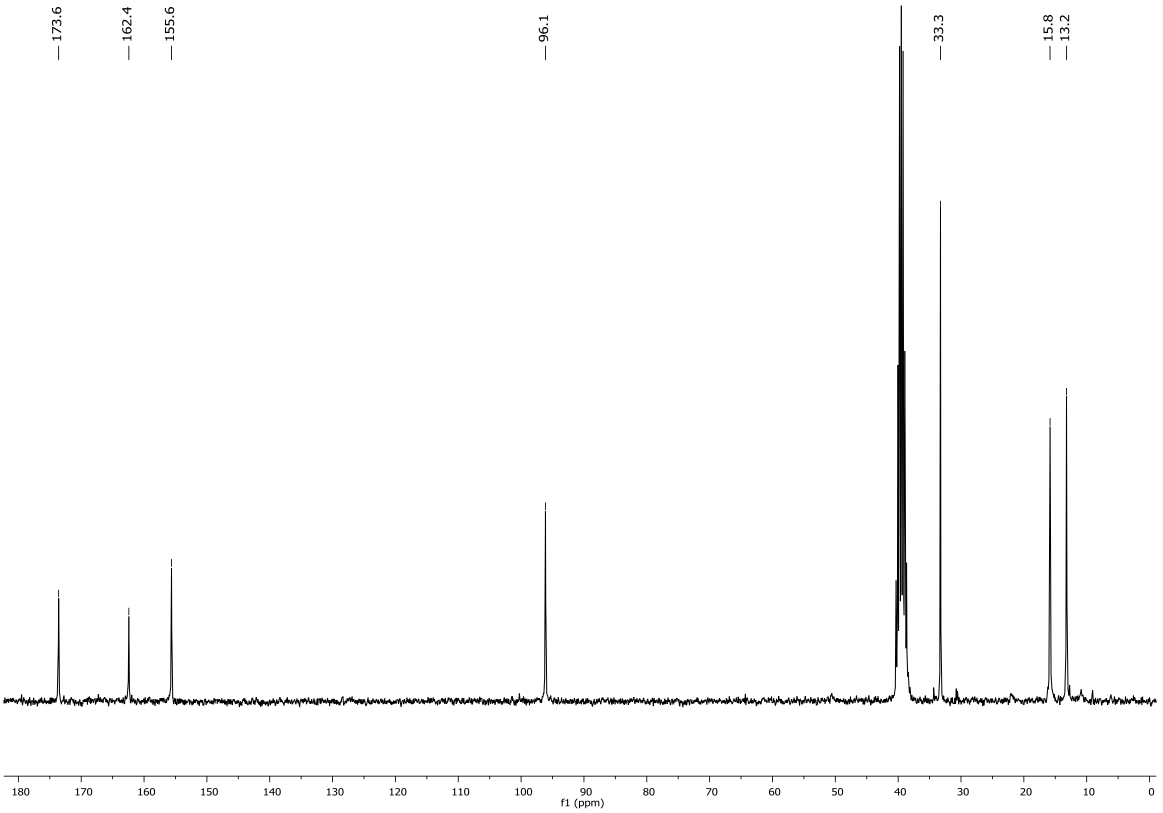


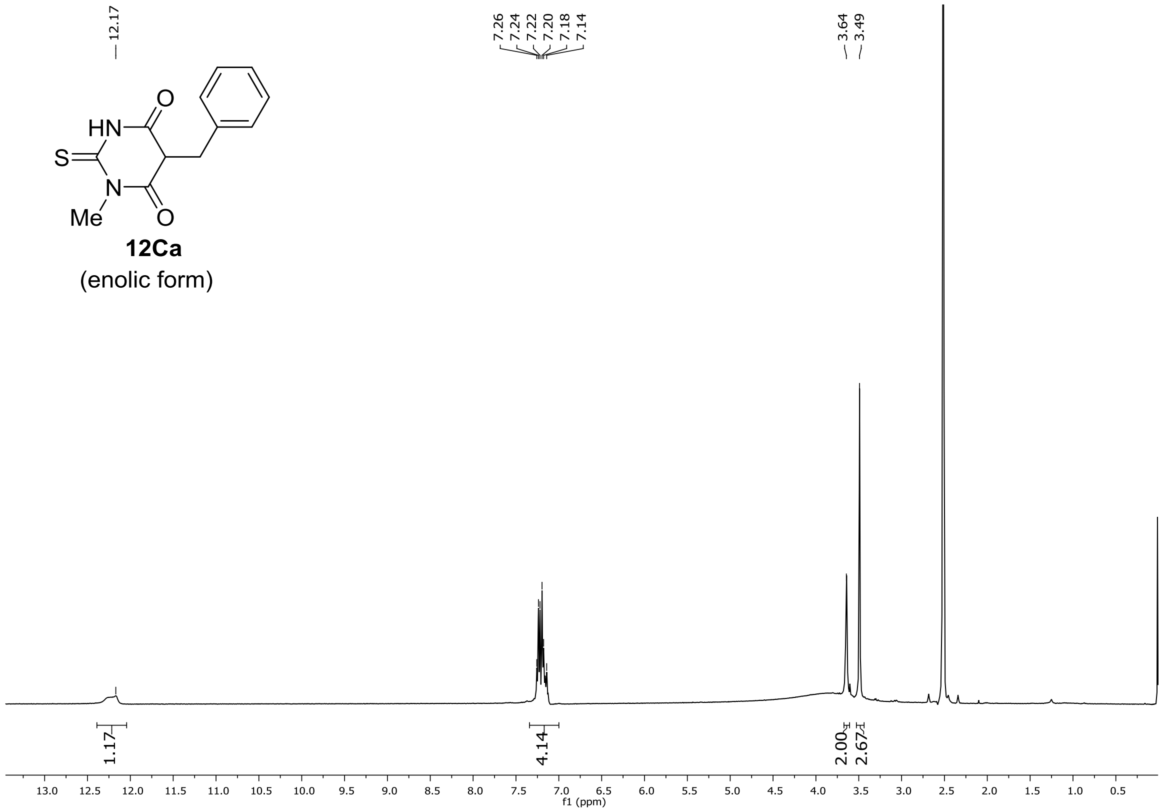

12.67
8.13
8.04
8.04
1.79
HN
O
S
Me
N
O
F3C
CF3
12Ae
(enolic form)
1.02
0.99
2.07
3.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


174.2
162.8
157.3
142.0
131.0
130.9
130.6
124.9
121.8
121.3
90.0
8.2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


12Ba

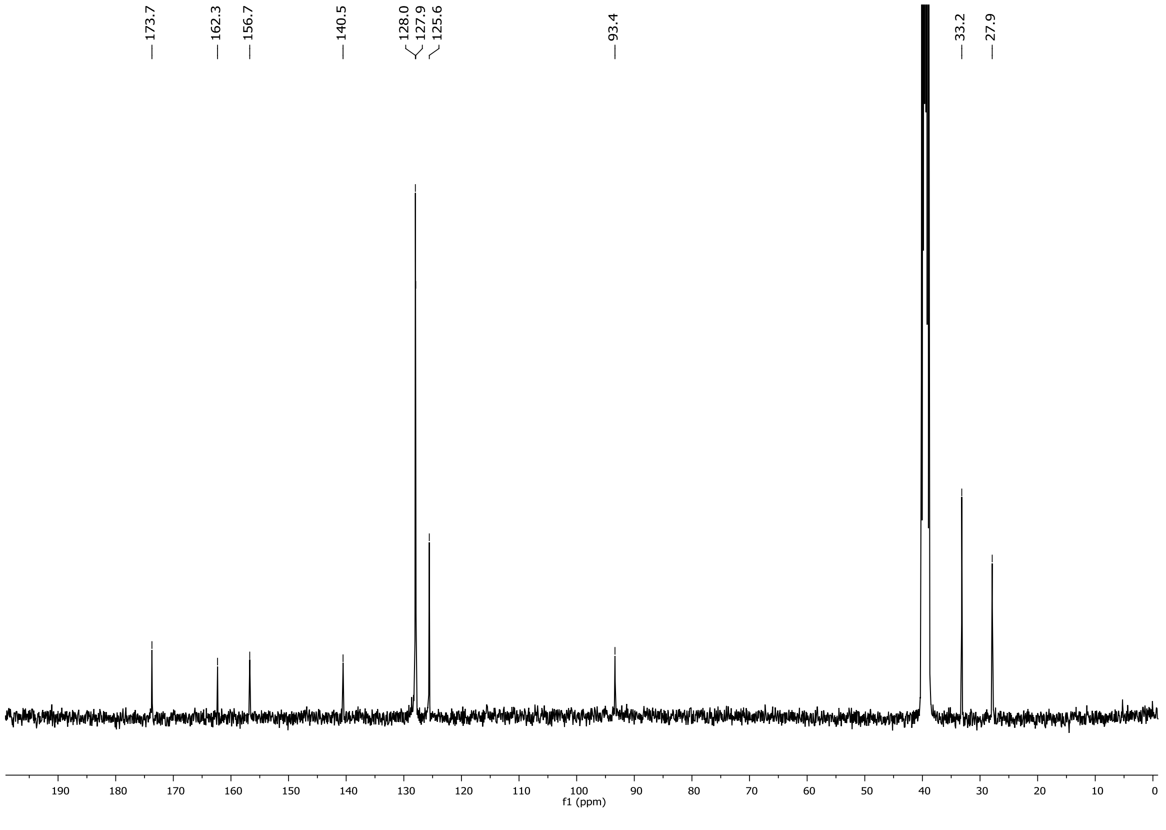
9.04
3.64
3.52
3.51
3.49
2.26
2.24
2.24
2.22
2.21
2.19
2.19
2.17
1.02
0.99
0.97
HN
O
S
N
Me
O
1.02
3.02
1.00
2.52
3.25
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

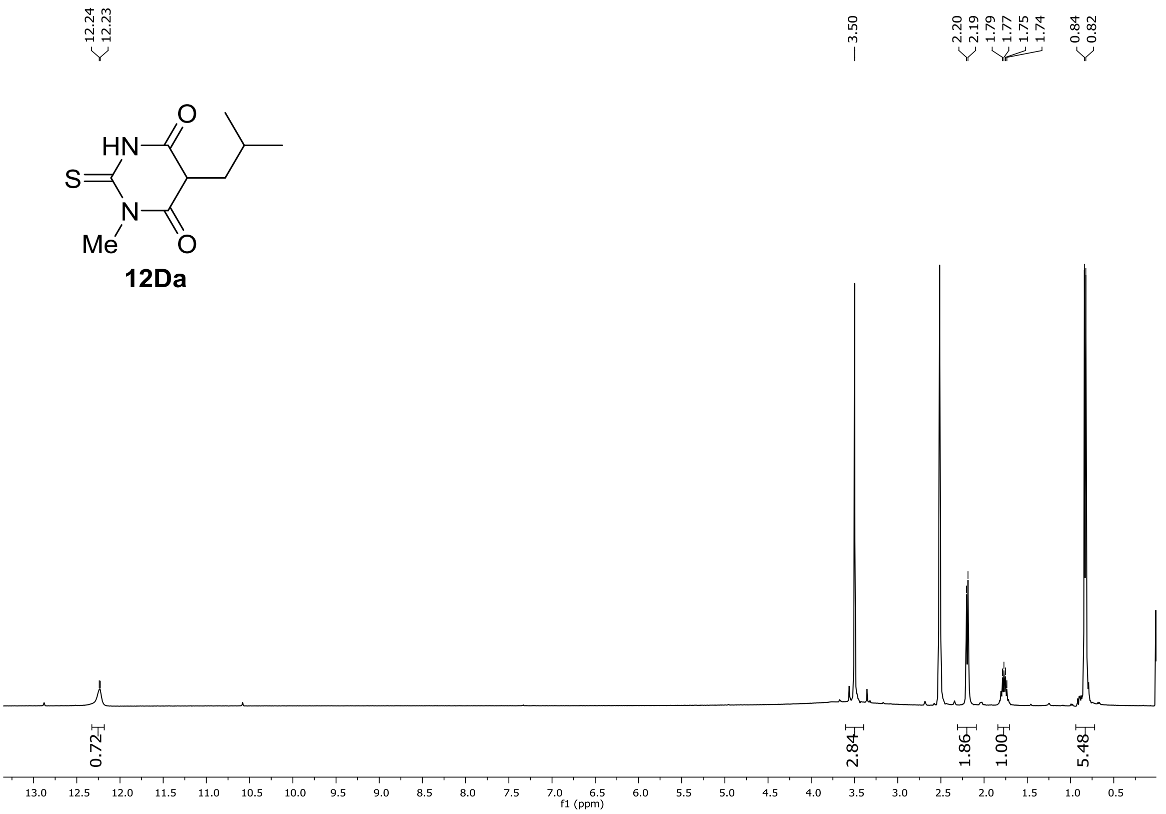

173.6
162.4
155.6
96.1
33.3
15.8
13.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

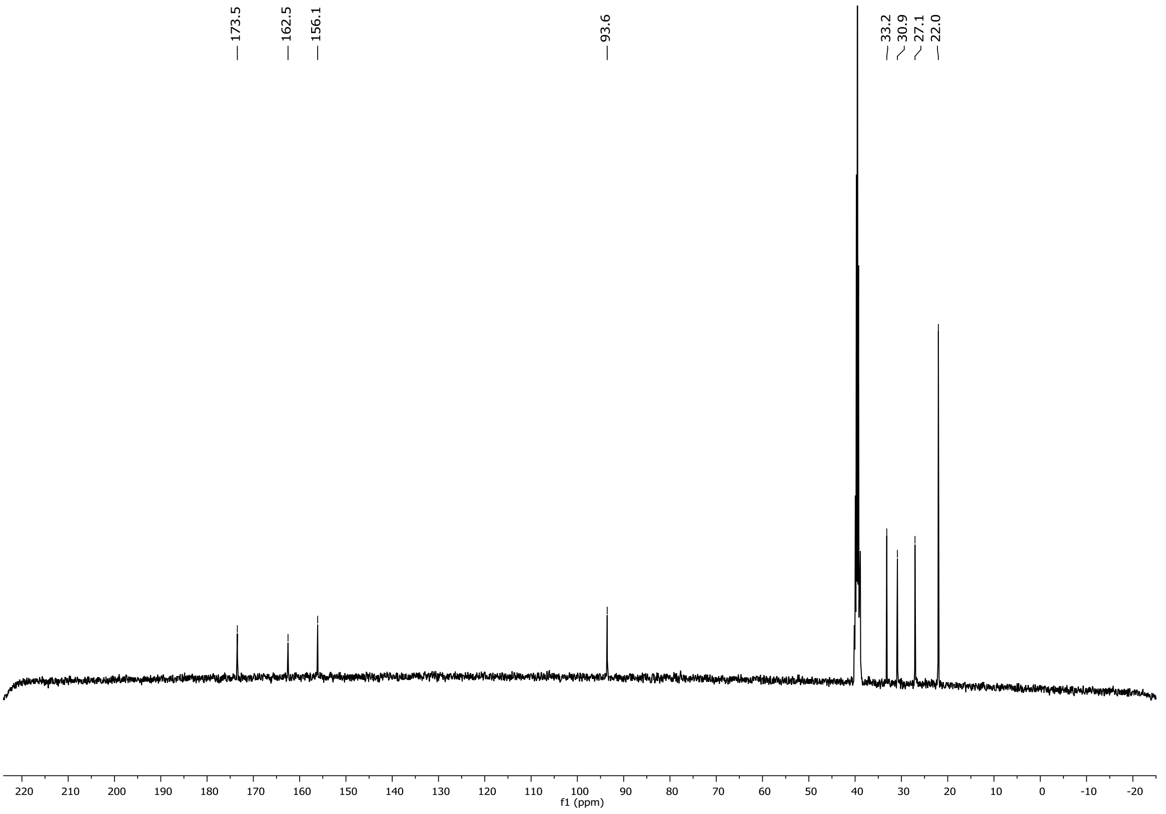


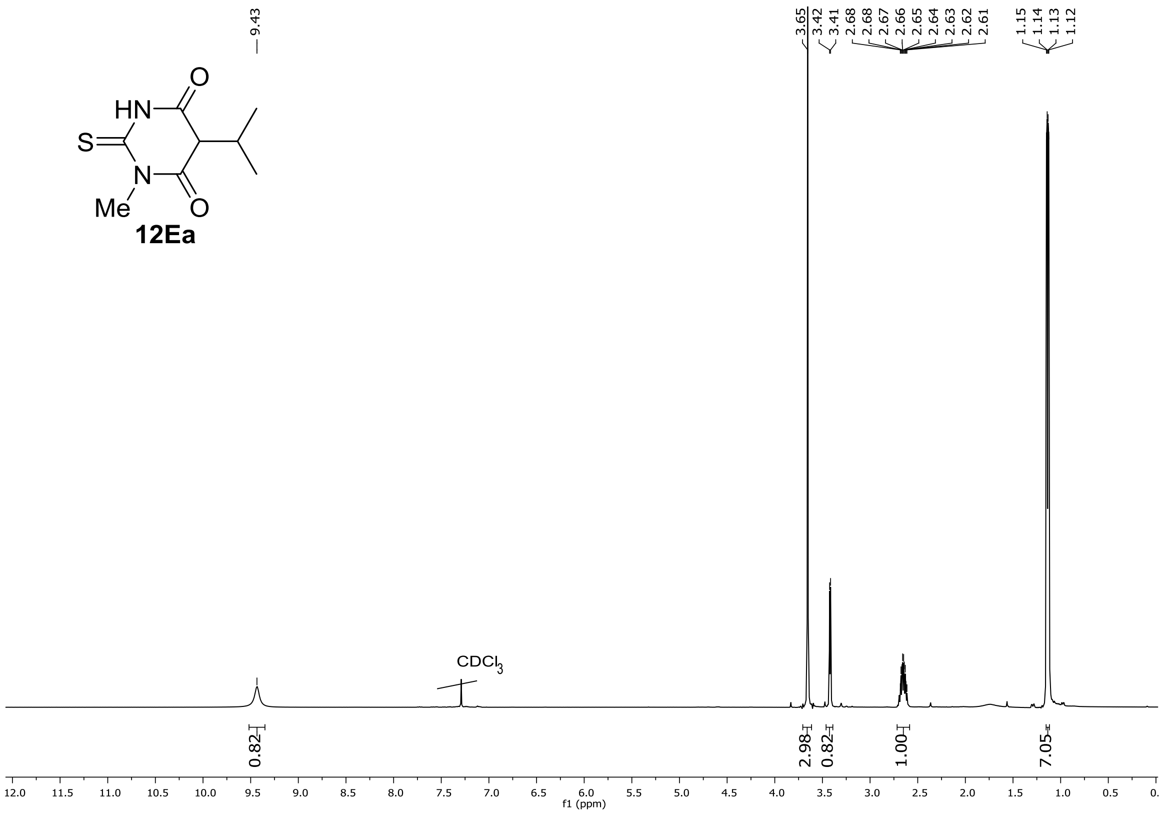
12Ca

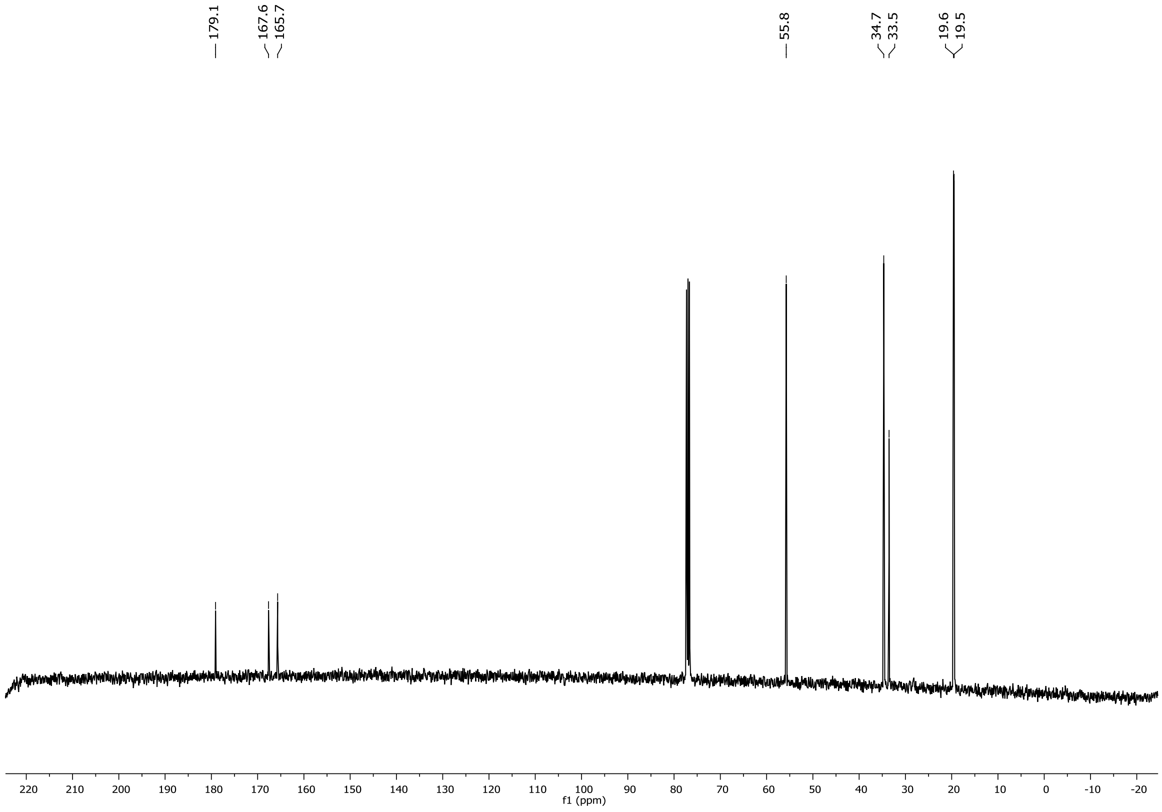
(enolic form)

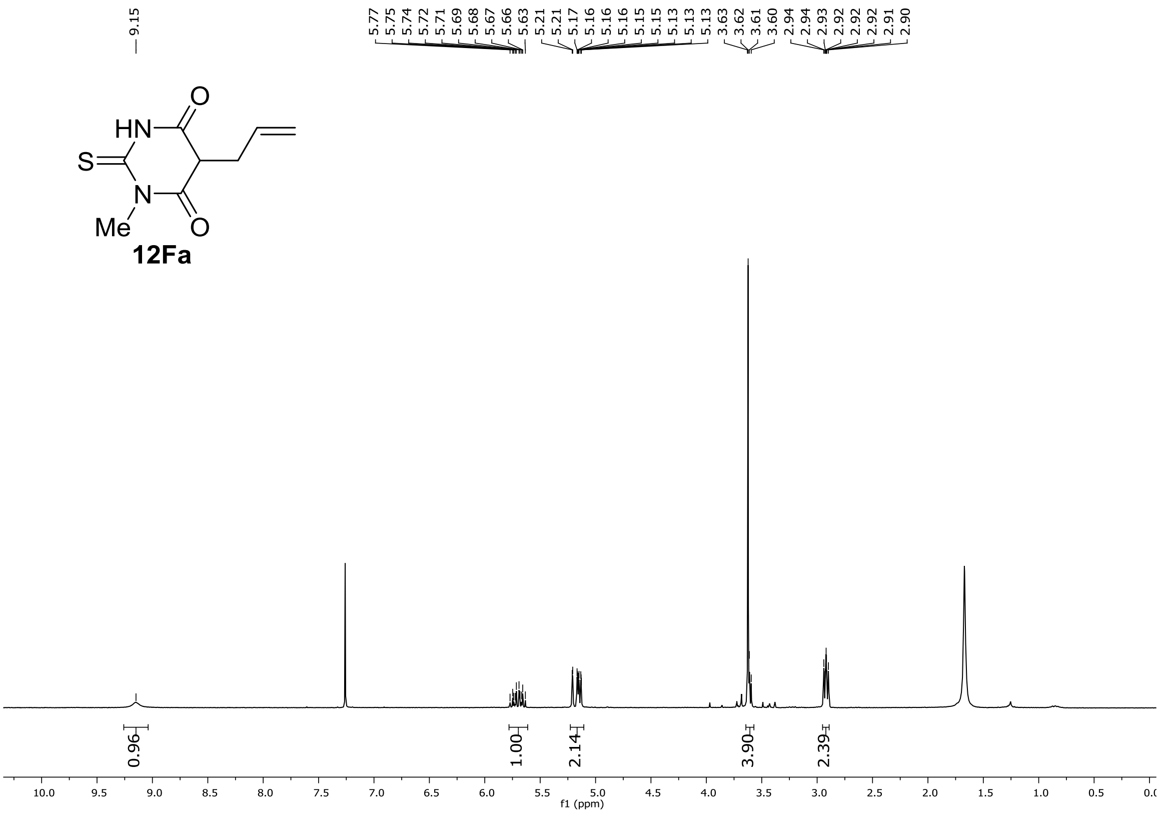



12.24
12.23
3.50
2.20
2.19
1.79
1.77
1.75
1.74
0.84
0.82
HN
O
S
N
Me
O
12Da
0.72
2.84
1.86
1.00
5.48
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


173.5
162.5
156.1
93.6
33.2
30.9
27.1
22.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

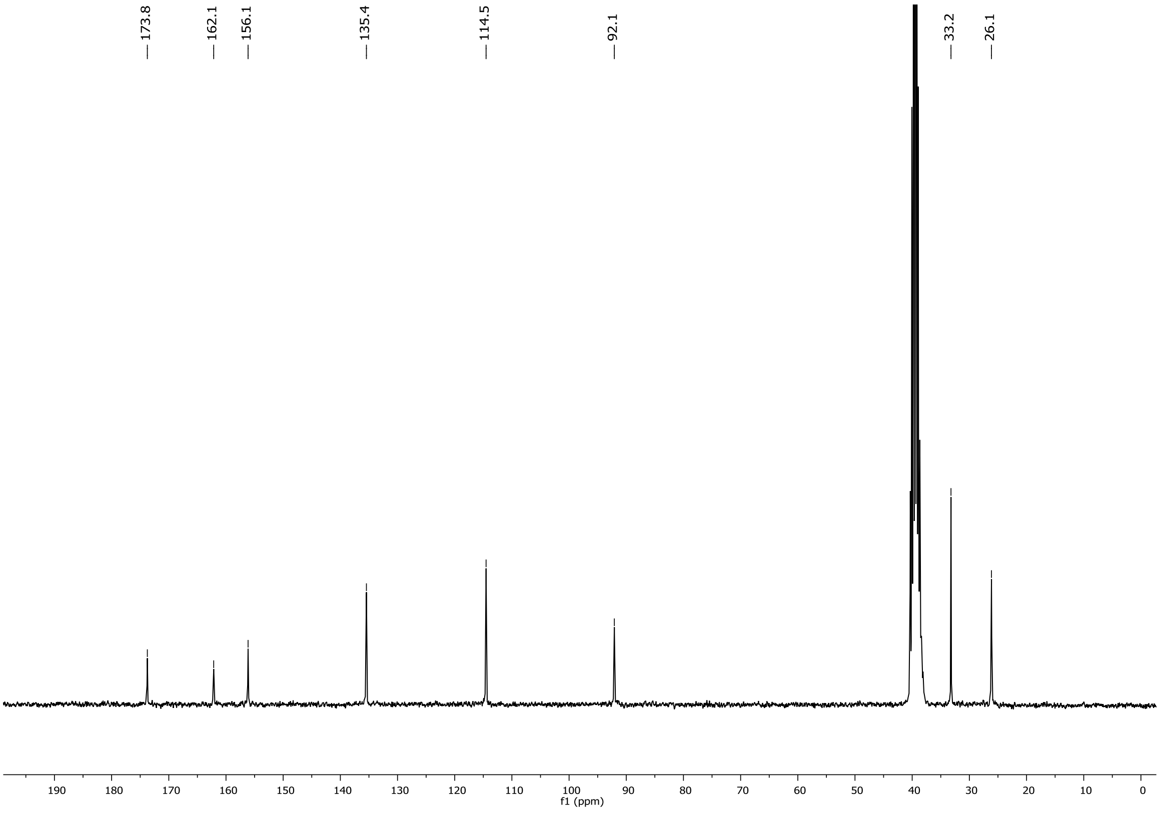

12Ea
HN
S
N
Me
O
O
9.43
3.65
3.42
3.41
2.68
2.68
2.67
2.66
2.65
2.64
2.63
2.62
2.61
1.15
1.14
1.13
1.12
CDCl3
0.82
2.98
0.82
1.00
7.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)


179.1
167.6
165.7
55.8
34.7
33.5
19.6
19.5
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

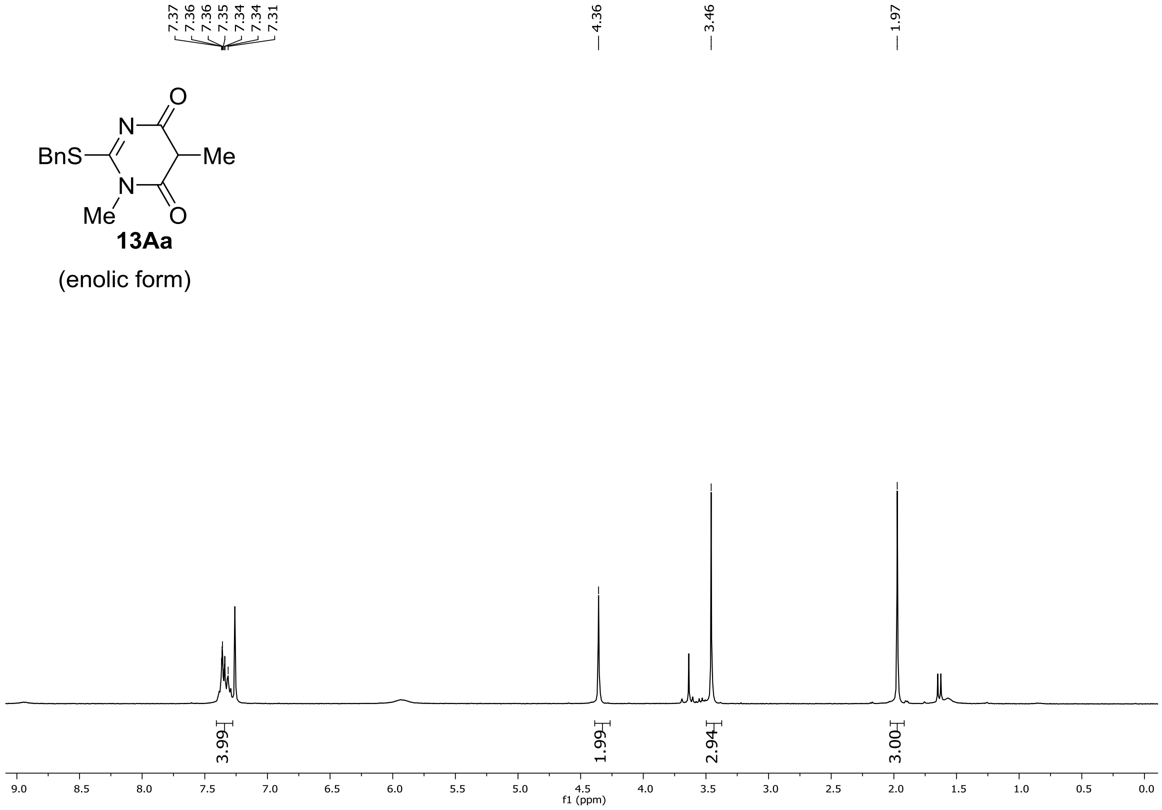


12Fa

HN
S
N
Me
O
O
9.15
5.77
5.75
5.74
5.72
5.71
5.69
5.68
5.67
5.66
5.63
5.21
5.21
5.17
5.16
5.16
5.16
5.15
5.15
5.13
5.13
5.13
3.63
3.62
3.61
3.60
2.94
2.94
2.93
2.92
2.92
2.92
2.91
2.90
0.96
1.00
2.14
3.90
2.39
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
f1 (ppm)

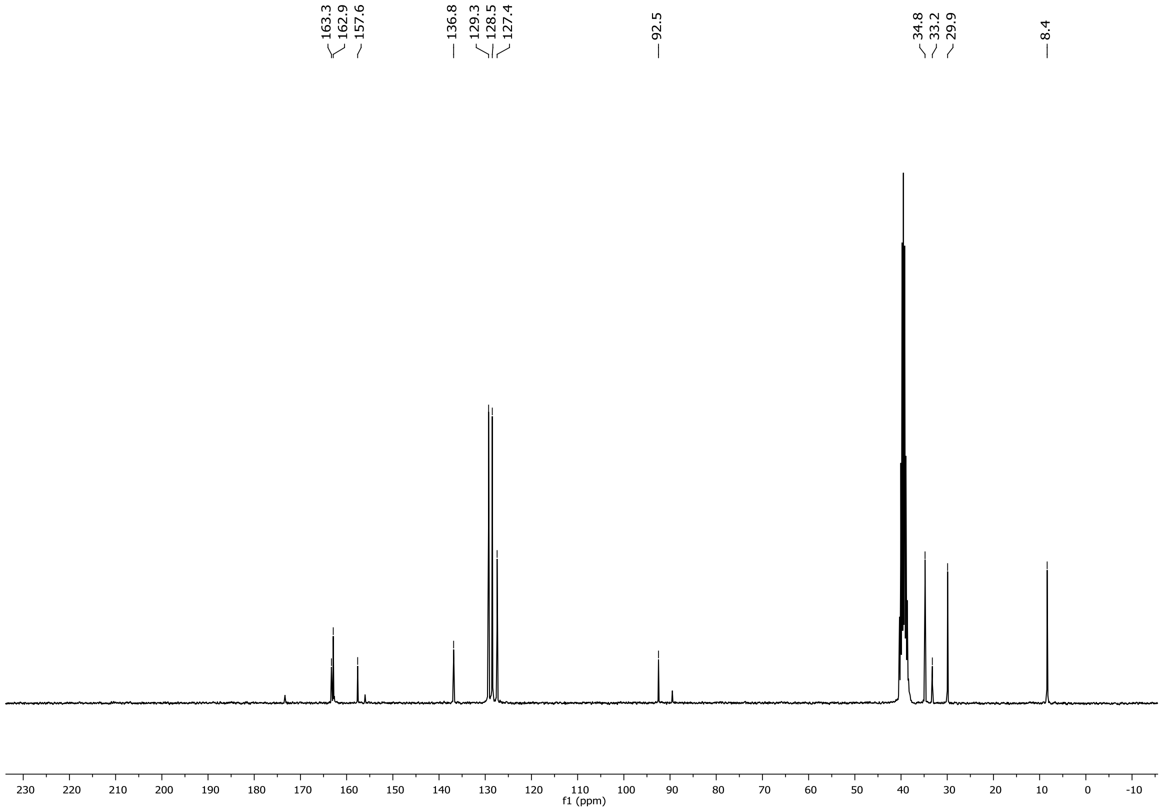


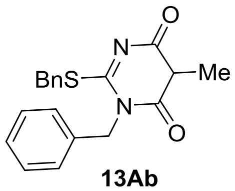
173.8
162.1
156.1
135.4
114.5
92.1
33.2
26.1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



13Aa

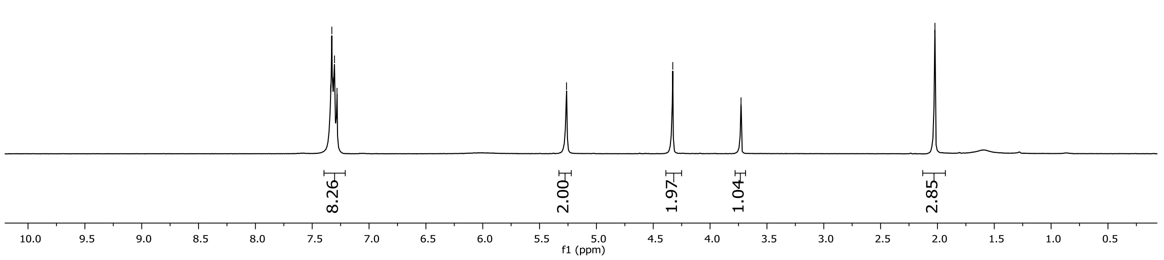
(enolic form)

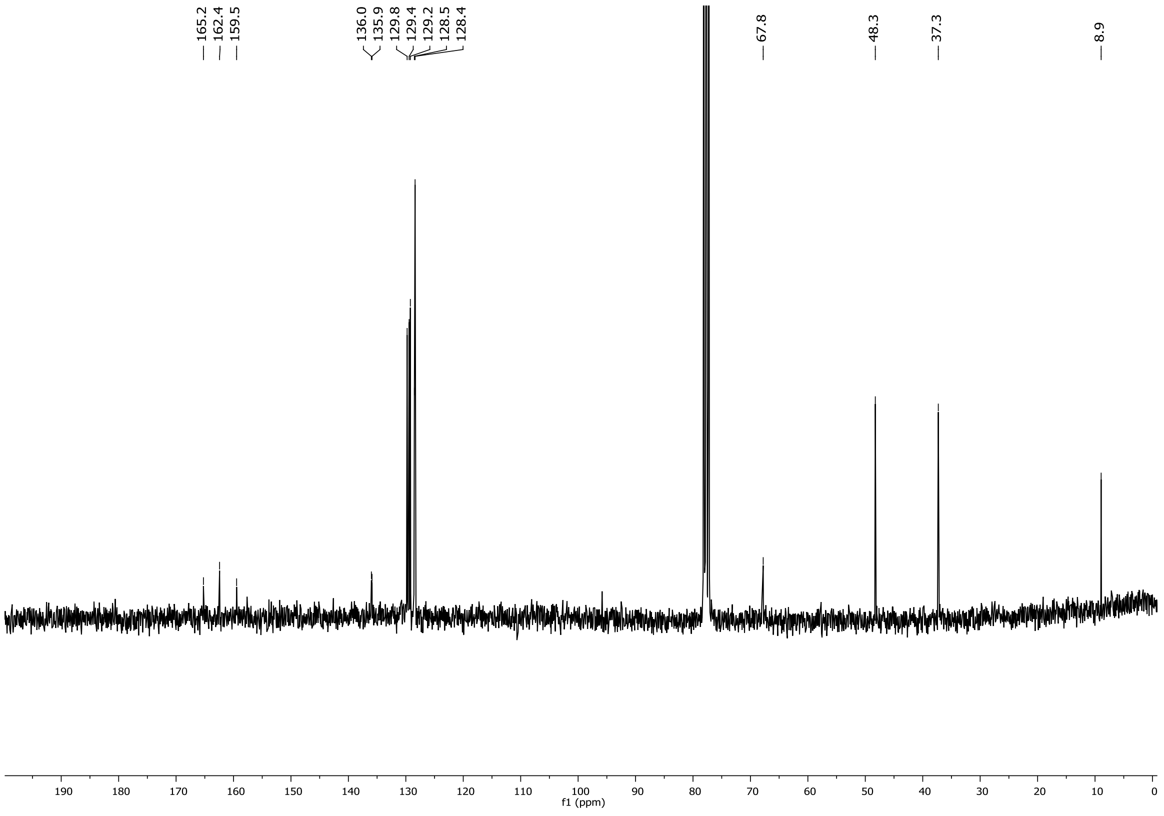


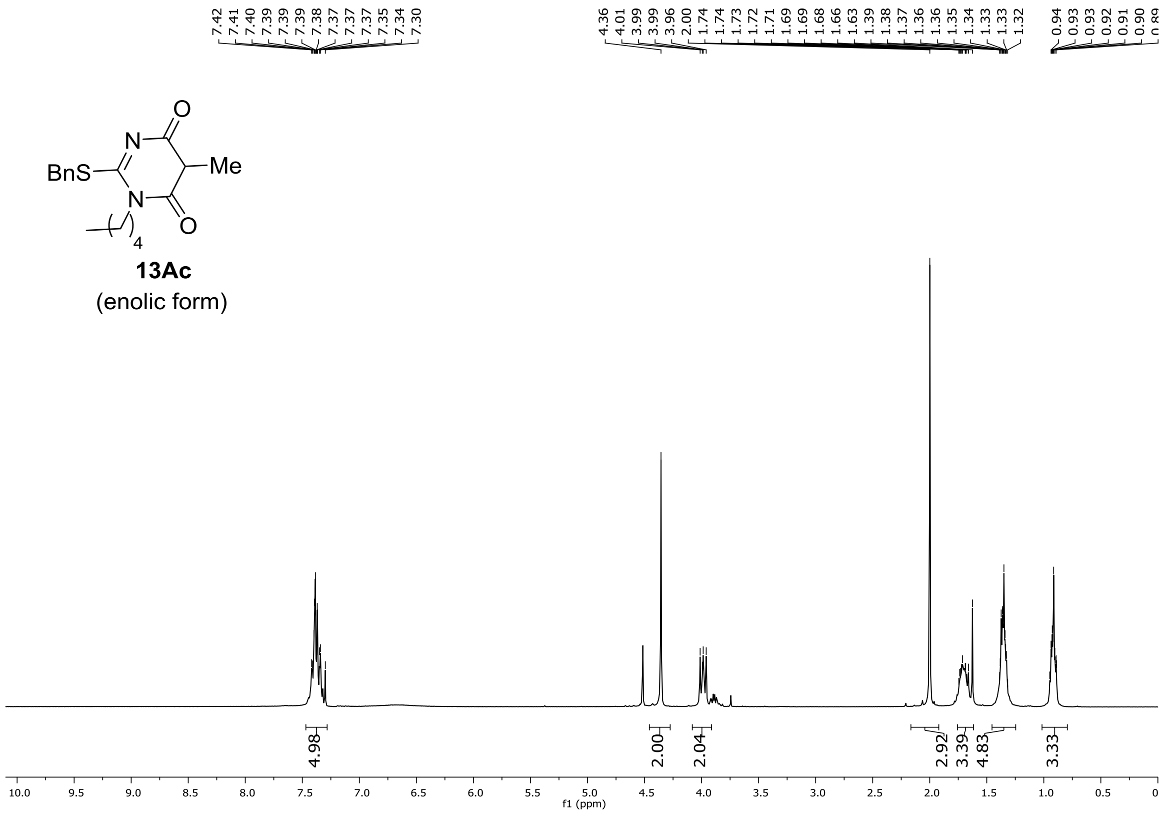


13Ab

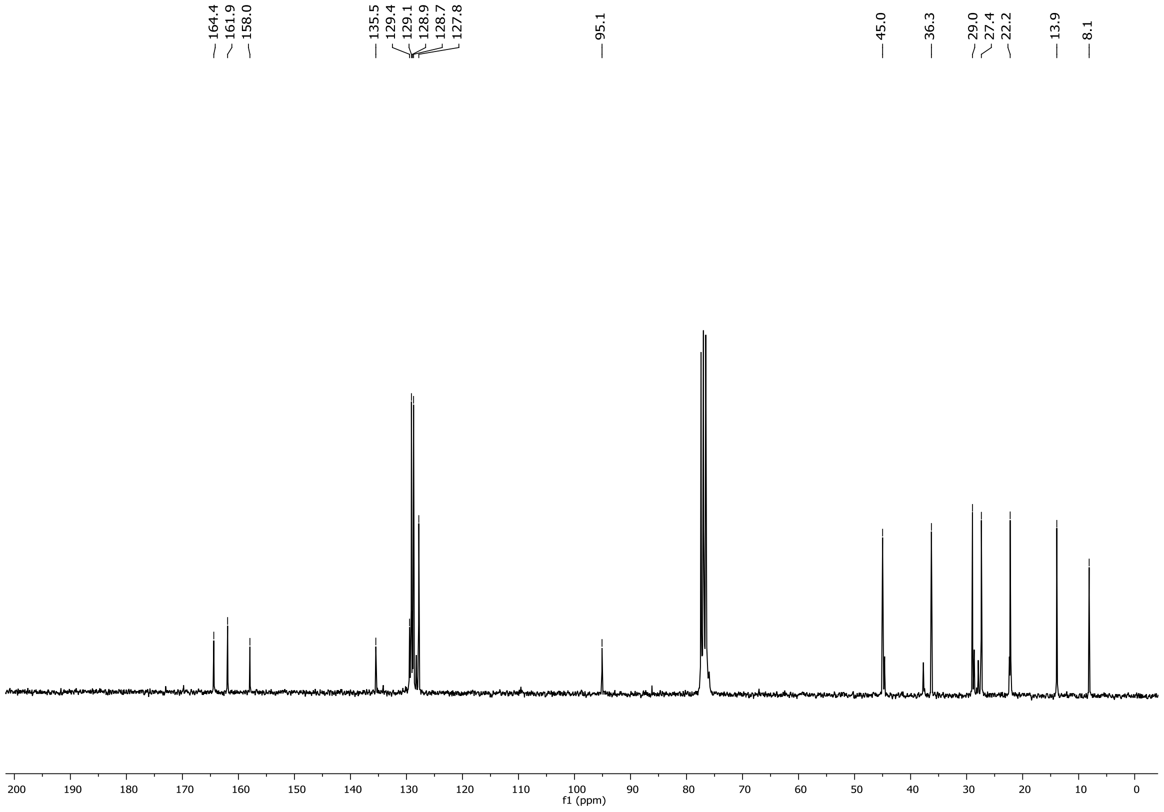
(enolic form)

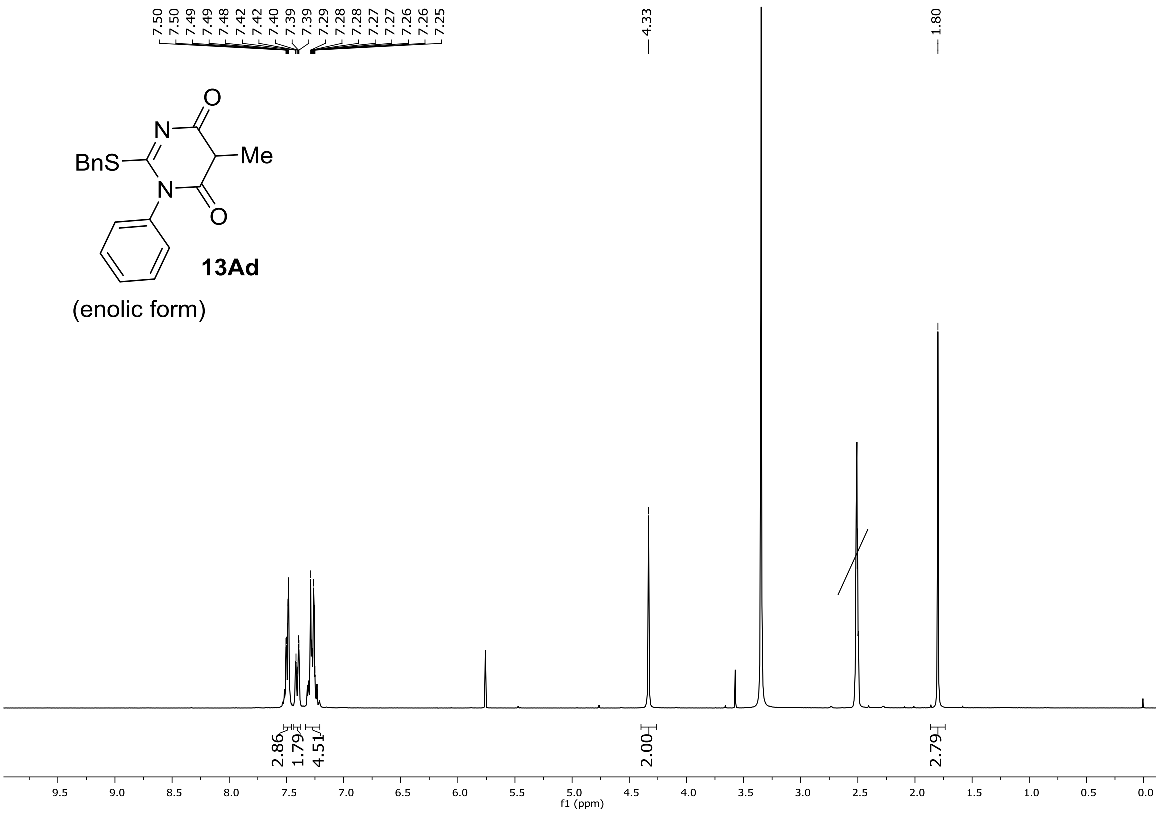


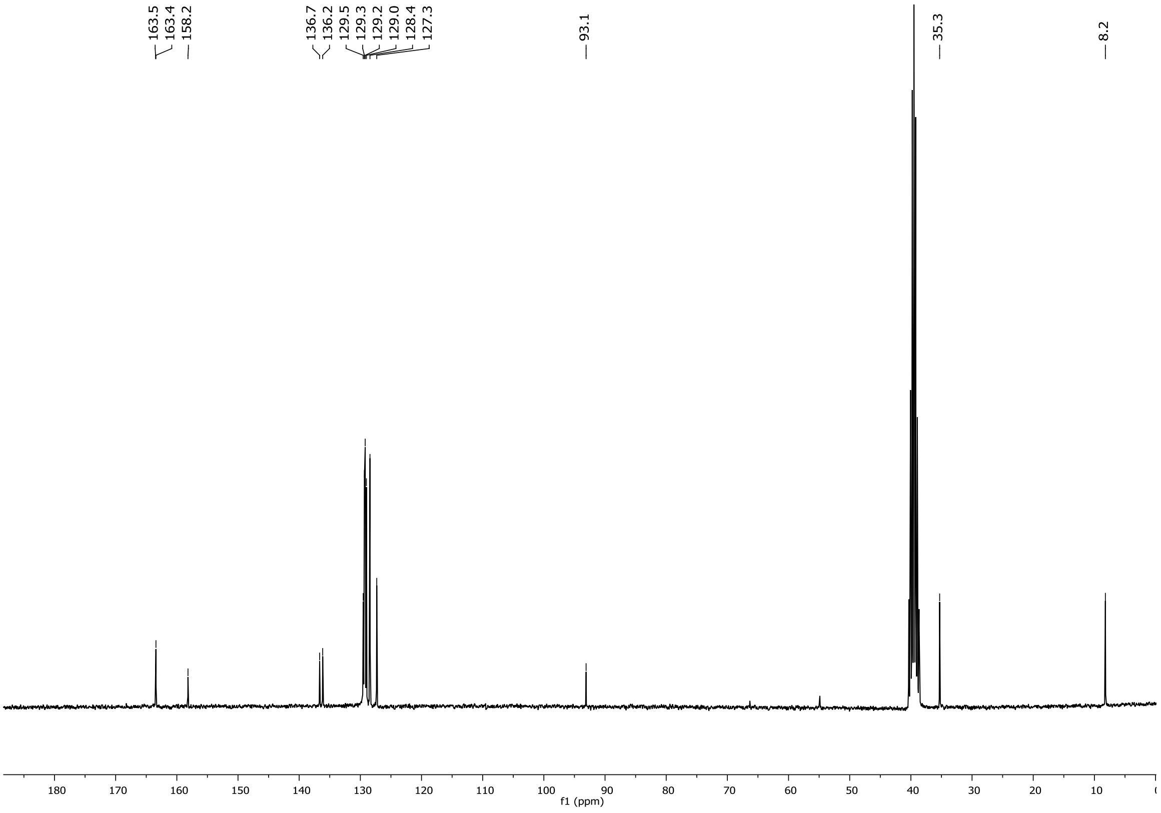


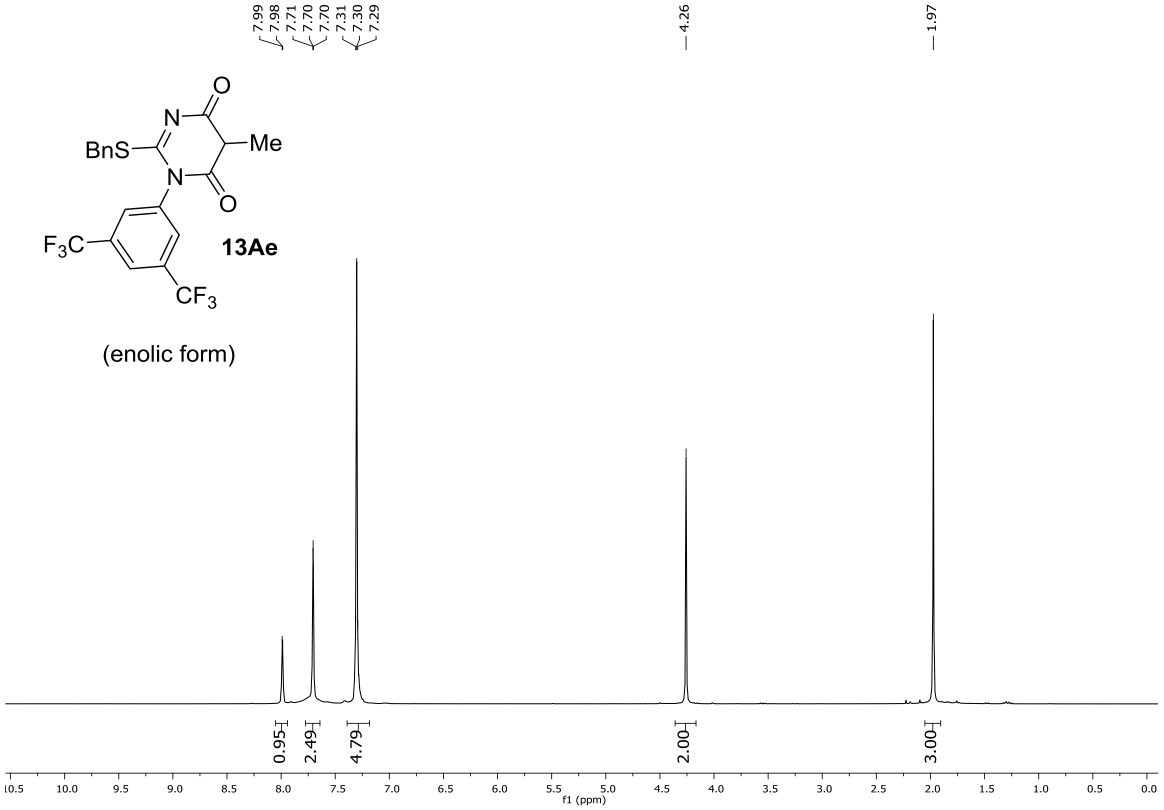


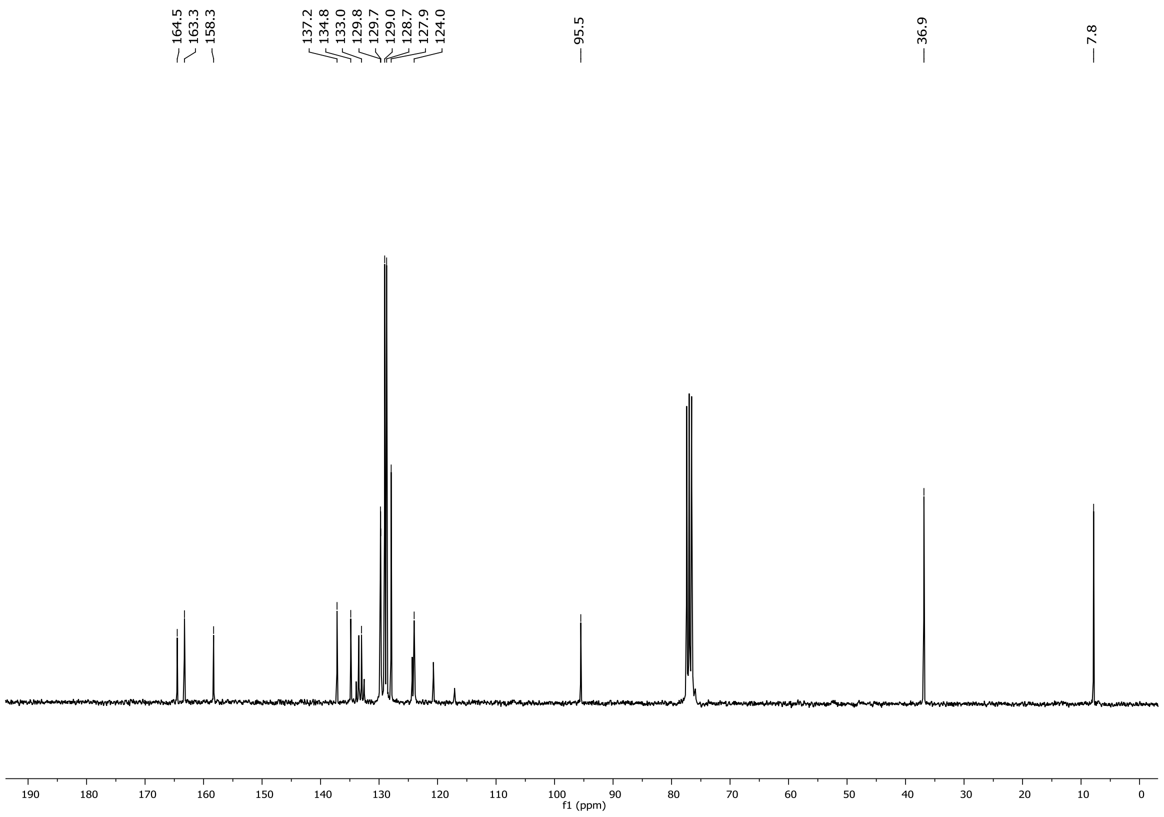
13Ac
(enolic form)

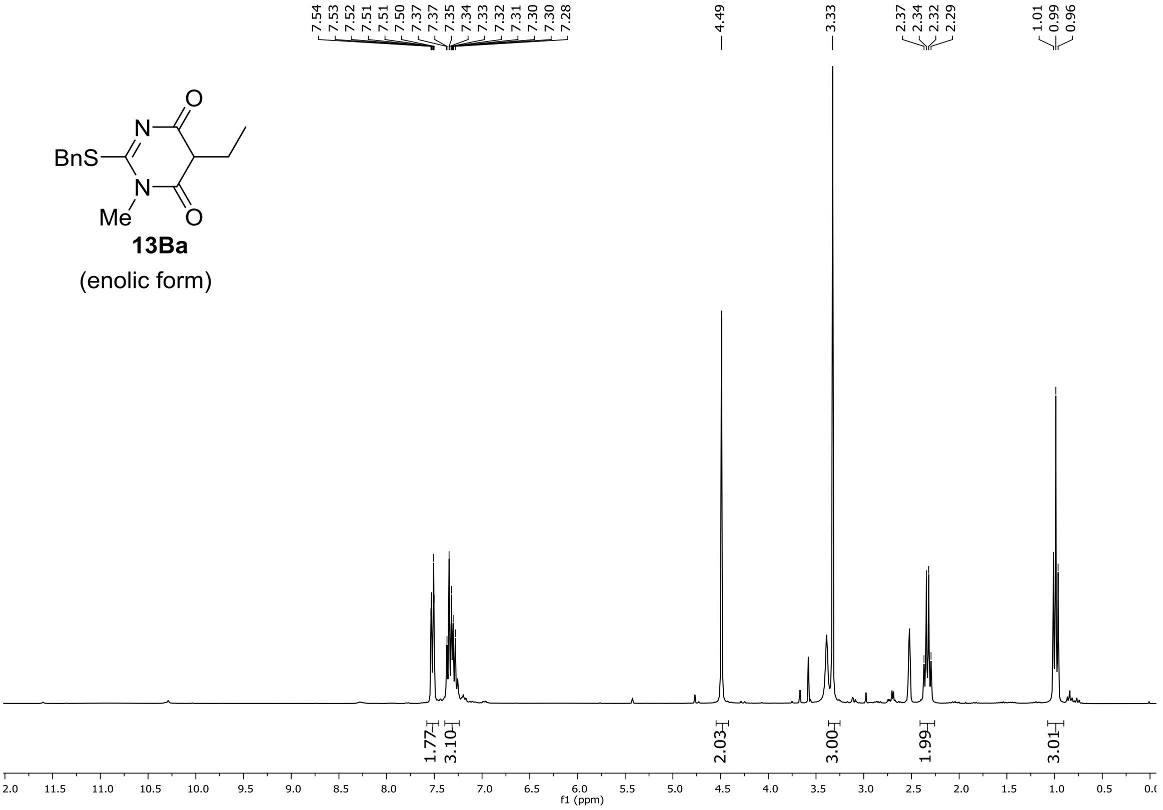



7.50
7.50
7.49
7.49
7.48
7.42
7.42
7.40
7.39
7.39
7.39
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.25
4.33
1.80
O
N
BnS
Me
N
O
13Ad
(enolic form)
2.86
1.79
4.51
2.00
2.79
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


163.5
163.4
158.2
136.7
136.2
129.5
129.3
129.2
129.0
128.4
127.3
93.1
35.3
8.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

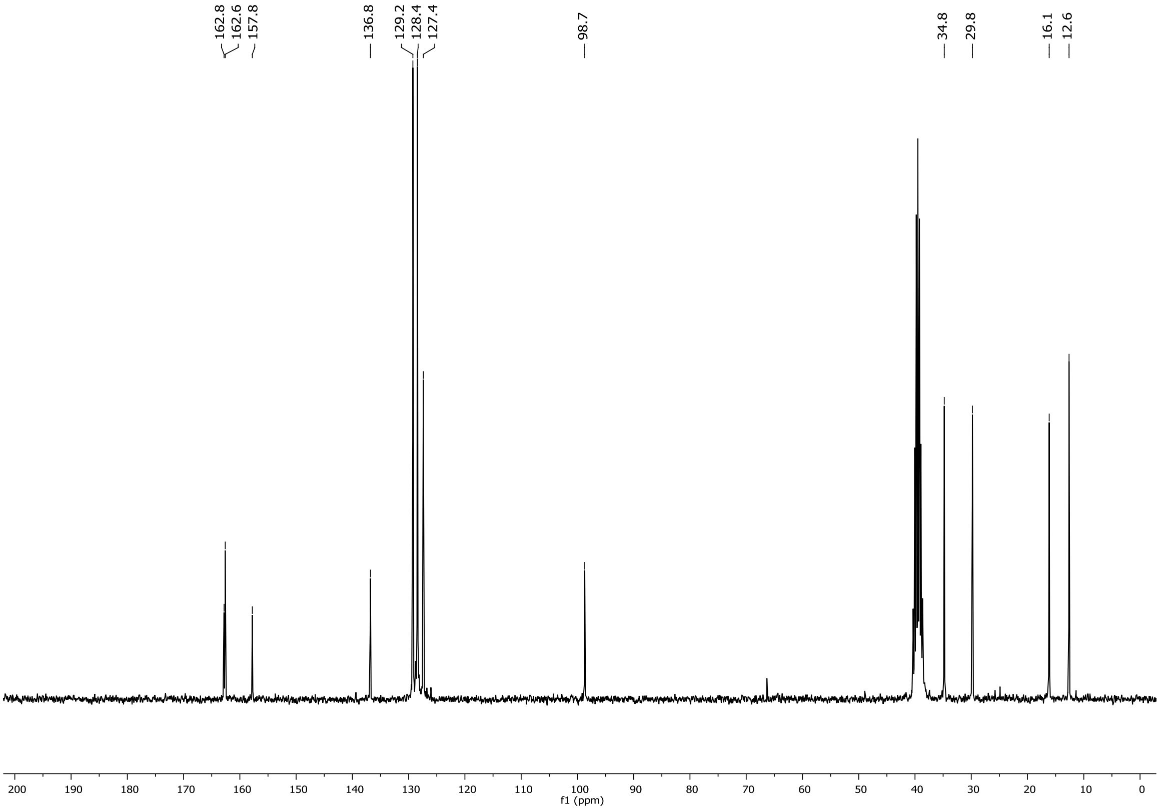

7.99
7.98
7.71
7.70
7.70
7.31
7.30
7.29
4.26
1.97
BnS
N
O
Me
F$_3$C
CF$_3$
13Ae
(enolic form)
0.95
2.49
4.79
2.00
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

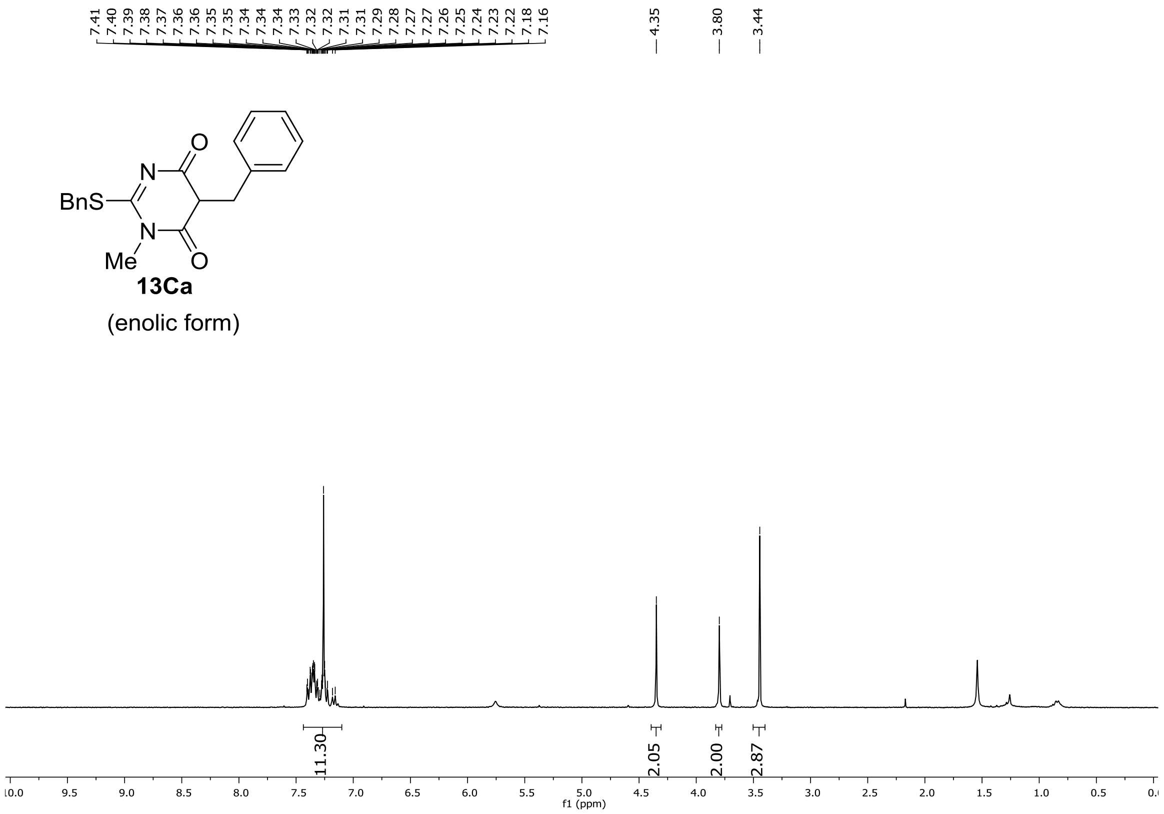

164.5
163.3
158.3
137.2
134.8
133.0
129.8
129.7
129.0
128.7
127.9
124.0
95.5
36.9
7.8
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



13Ba

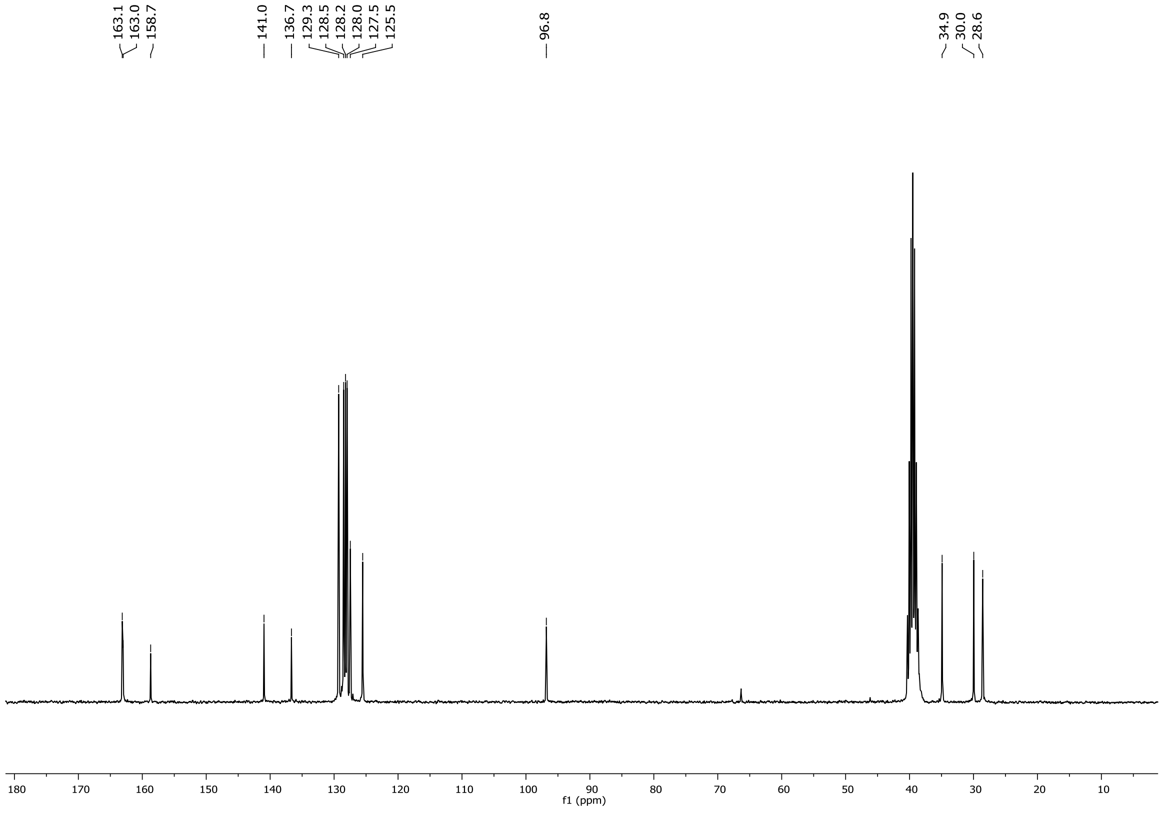
(enolic form)

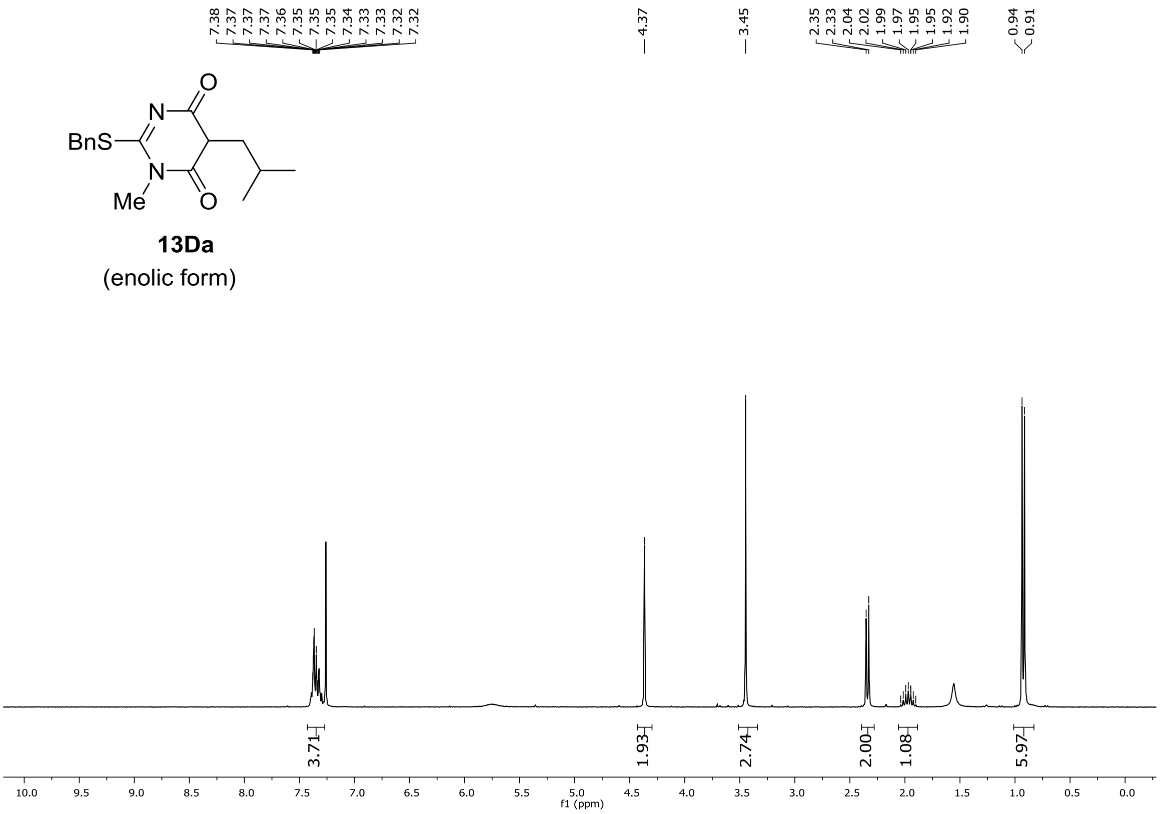




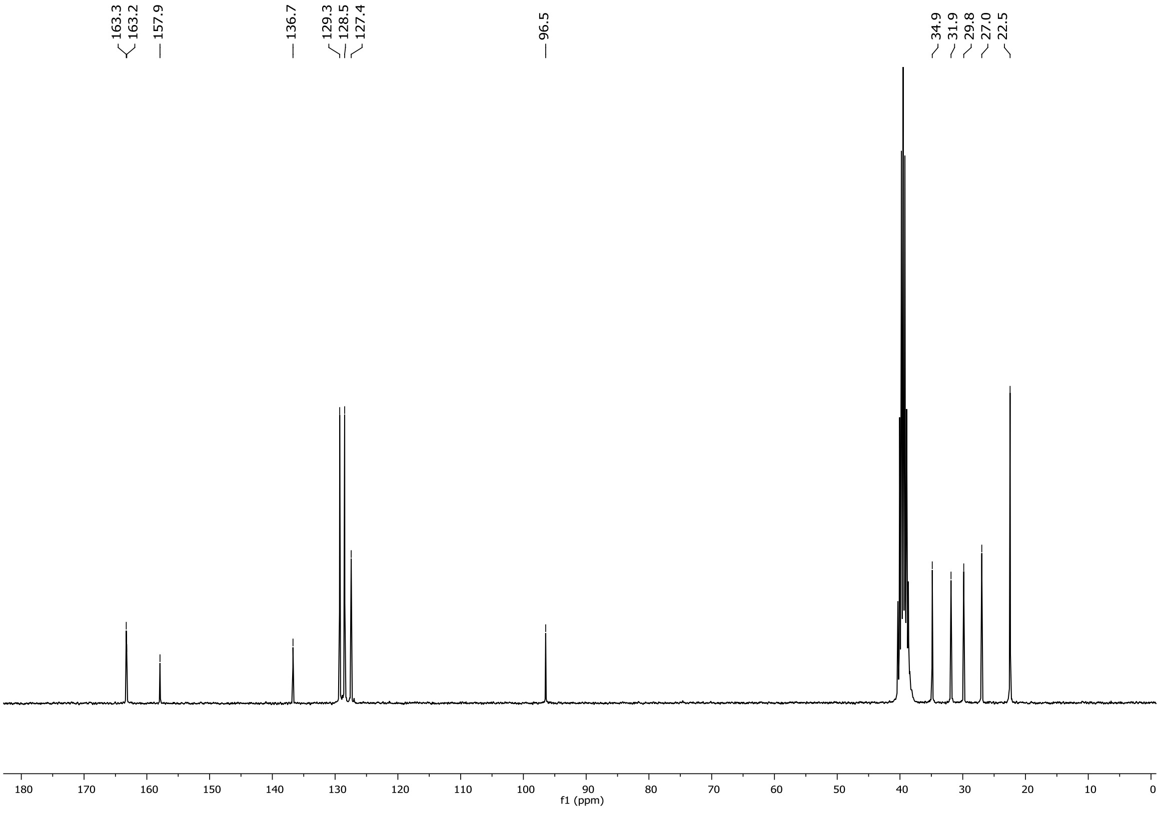
13Ca

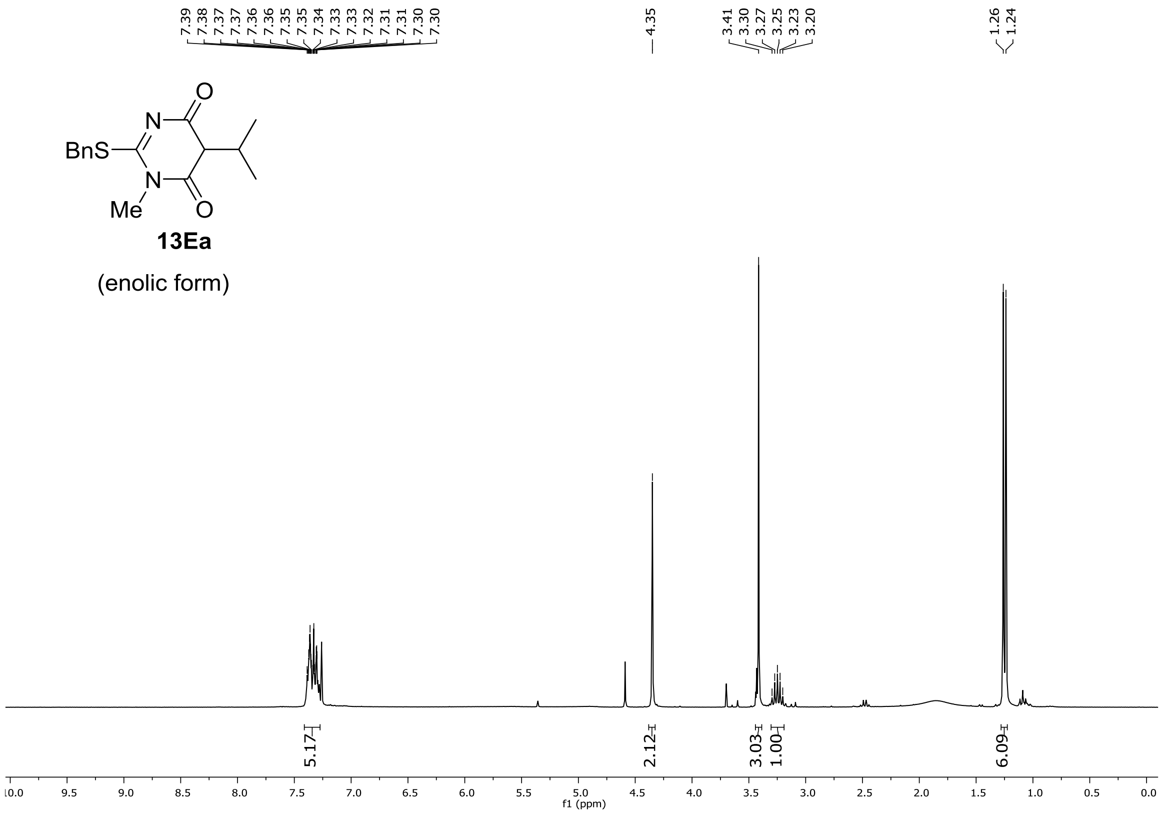
(enolic form)





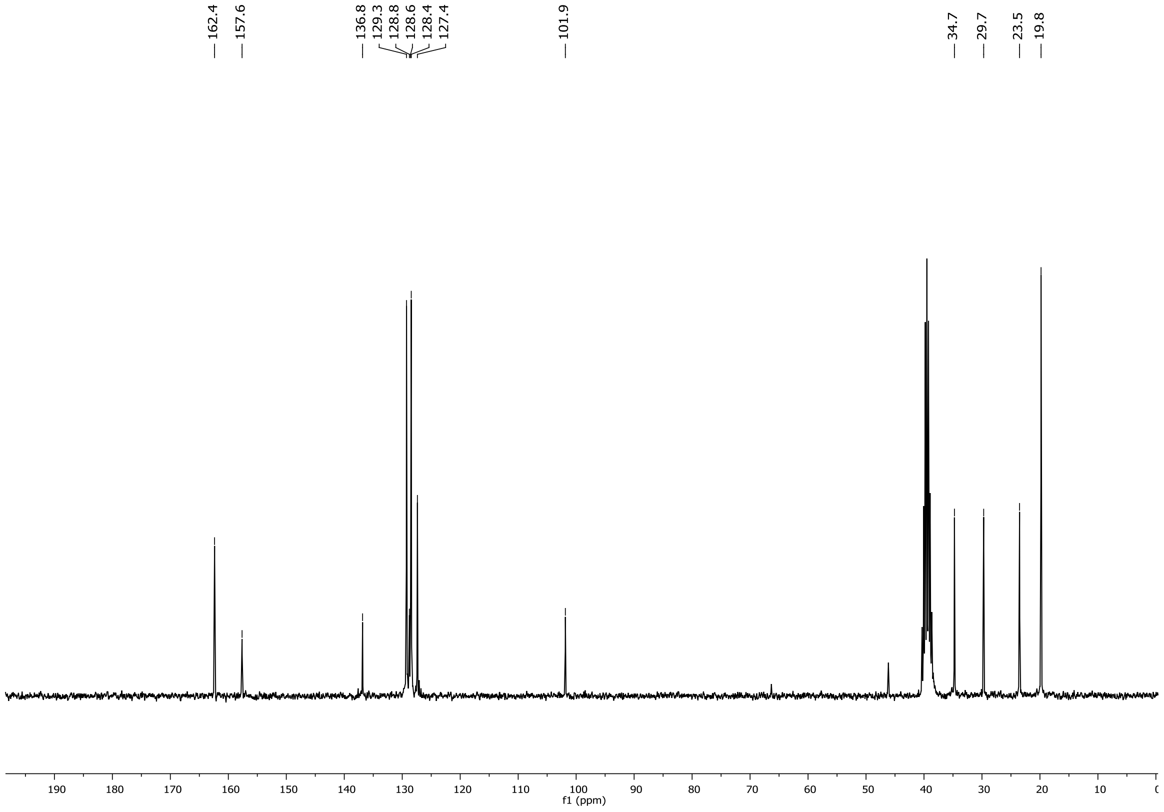
13Da
(enolic form)

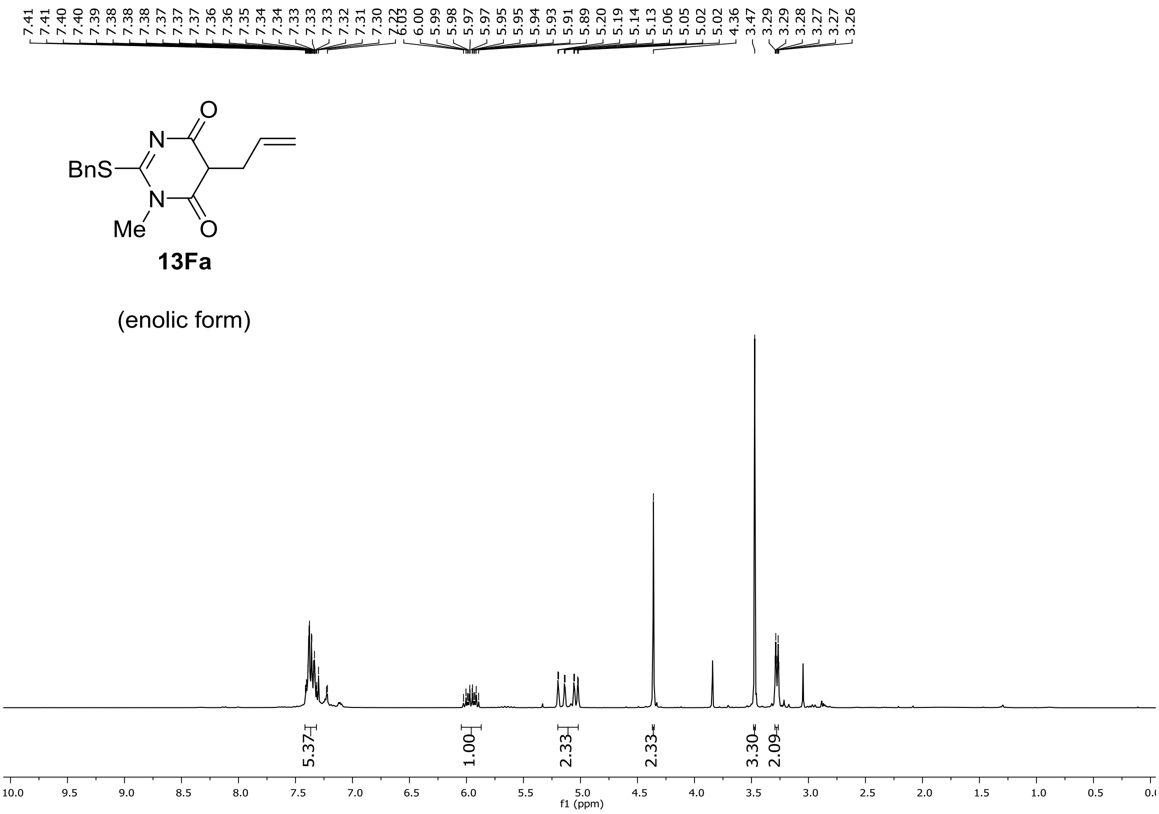




13Ea

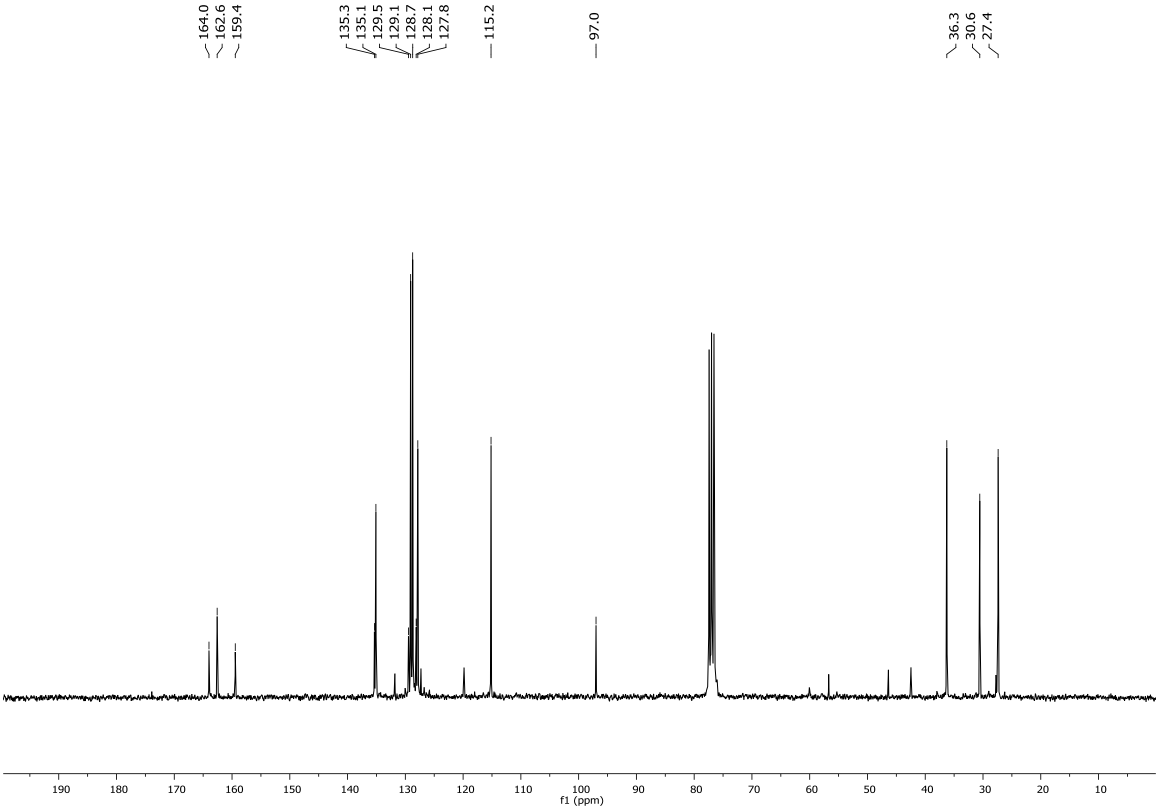
(enolic form)

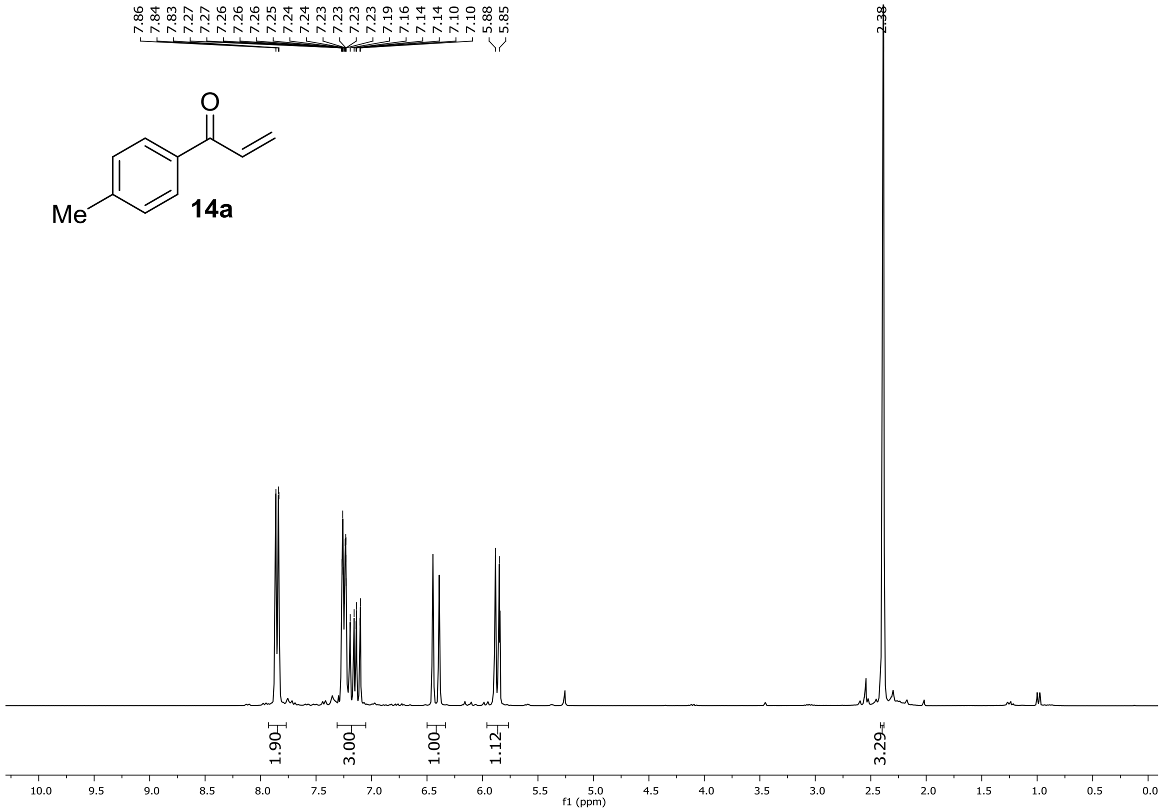


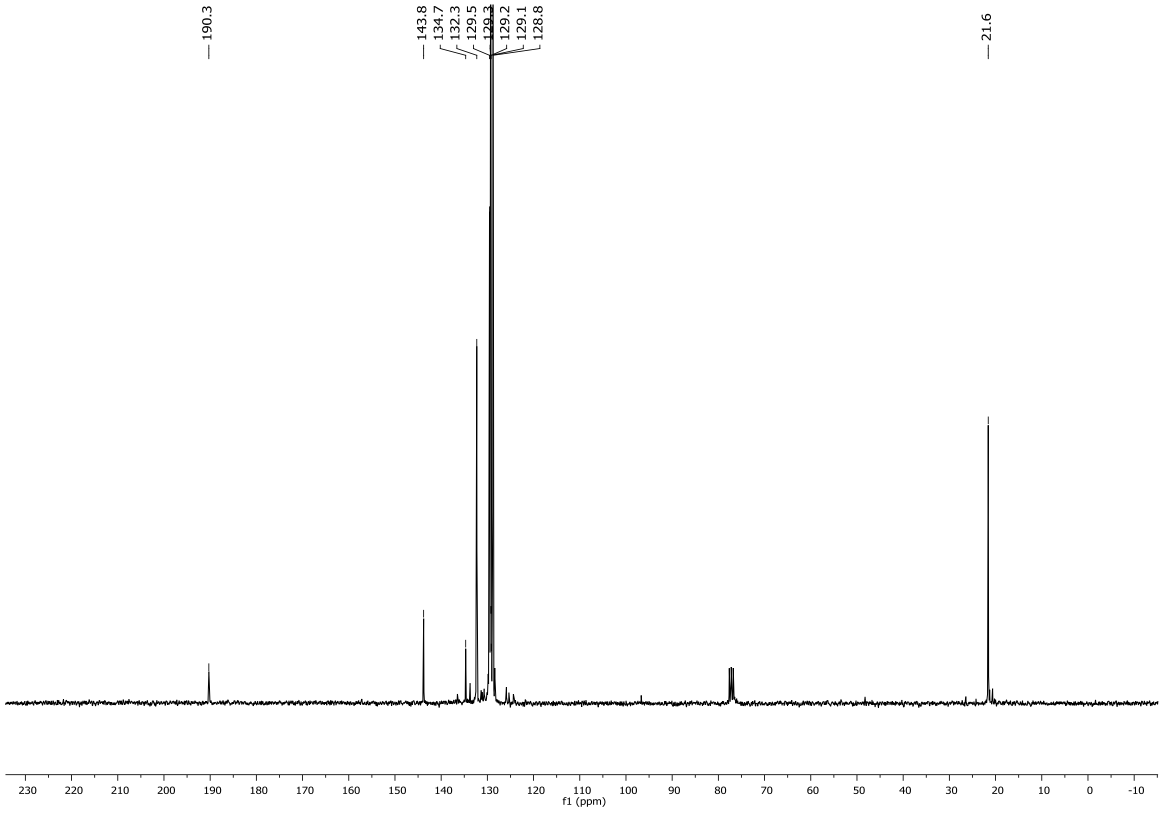


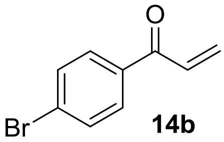
13Fa

(enolic form)

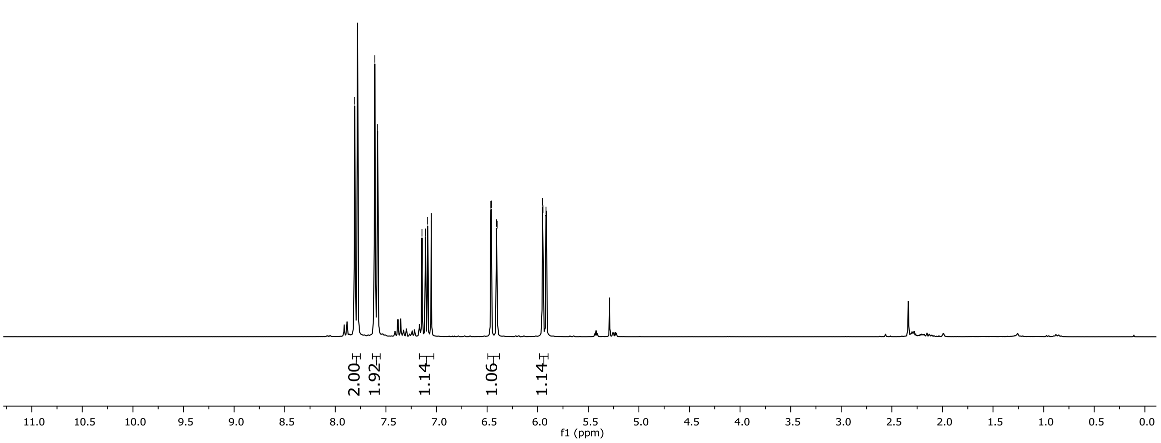


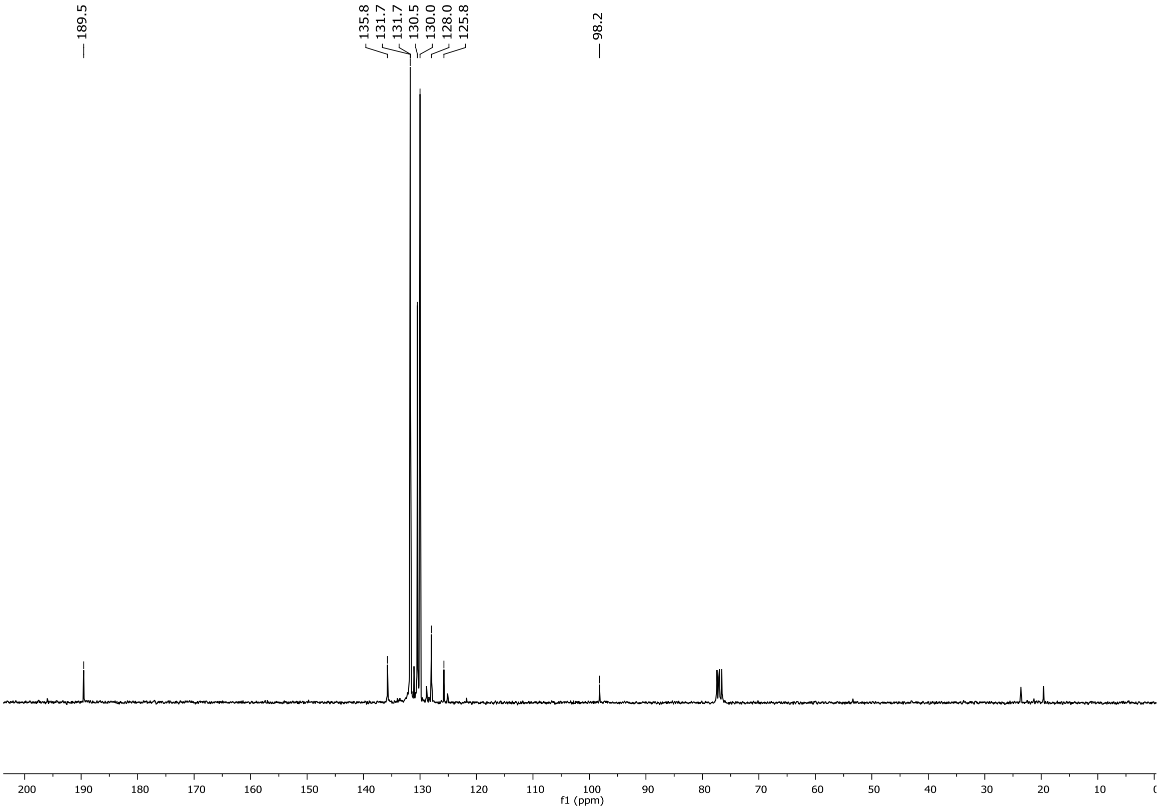

7.86
7.84
7.83
7.27
7.27
7.26
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.23
7.23
7.23
7.19
7.16
7.14
7.14
7.10
7.10
5.88
5.85
2.38
O
Me
14a
1.90
3.00
1.00
1.12
3.29
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

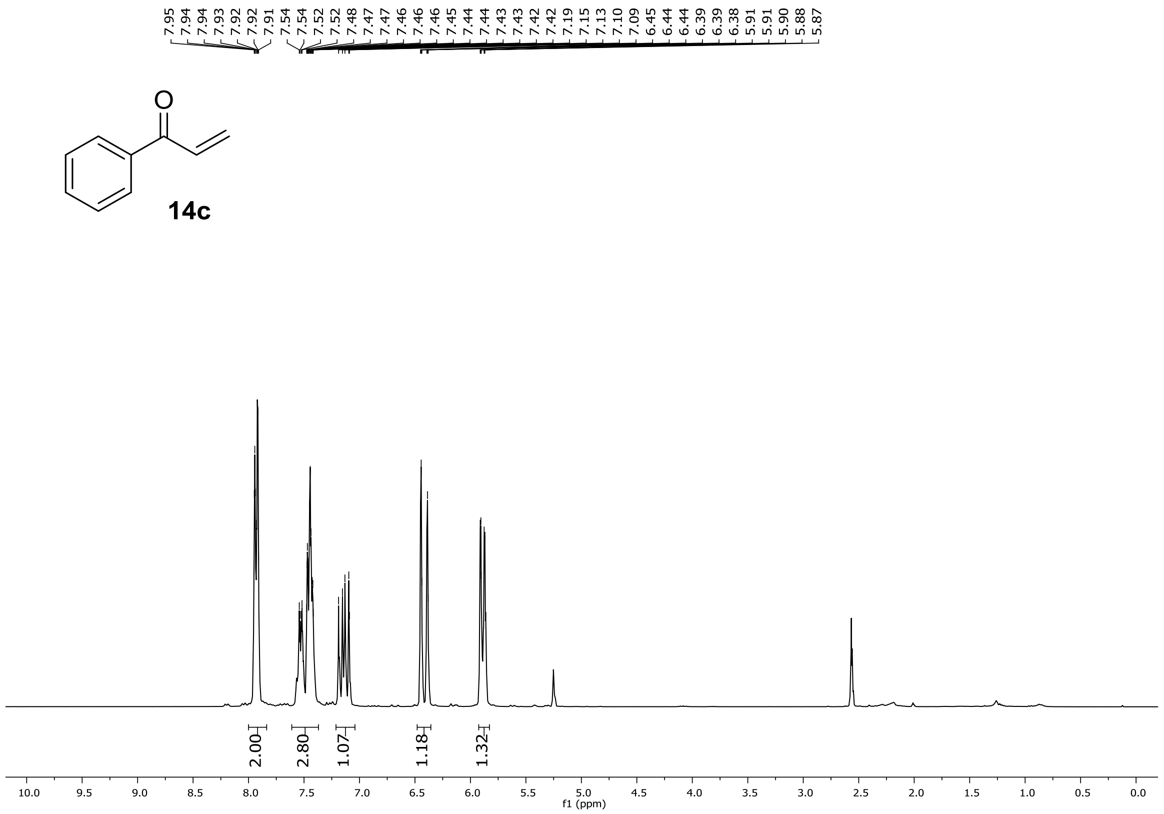

190.3
143.8
134.7
132.3
129.5
129.3
129.2
129.1
128.8
21.6
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
Br

14b

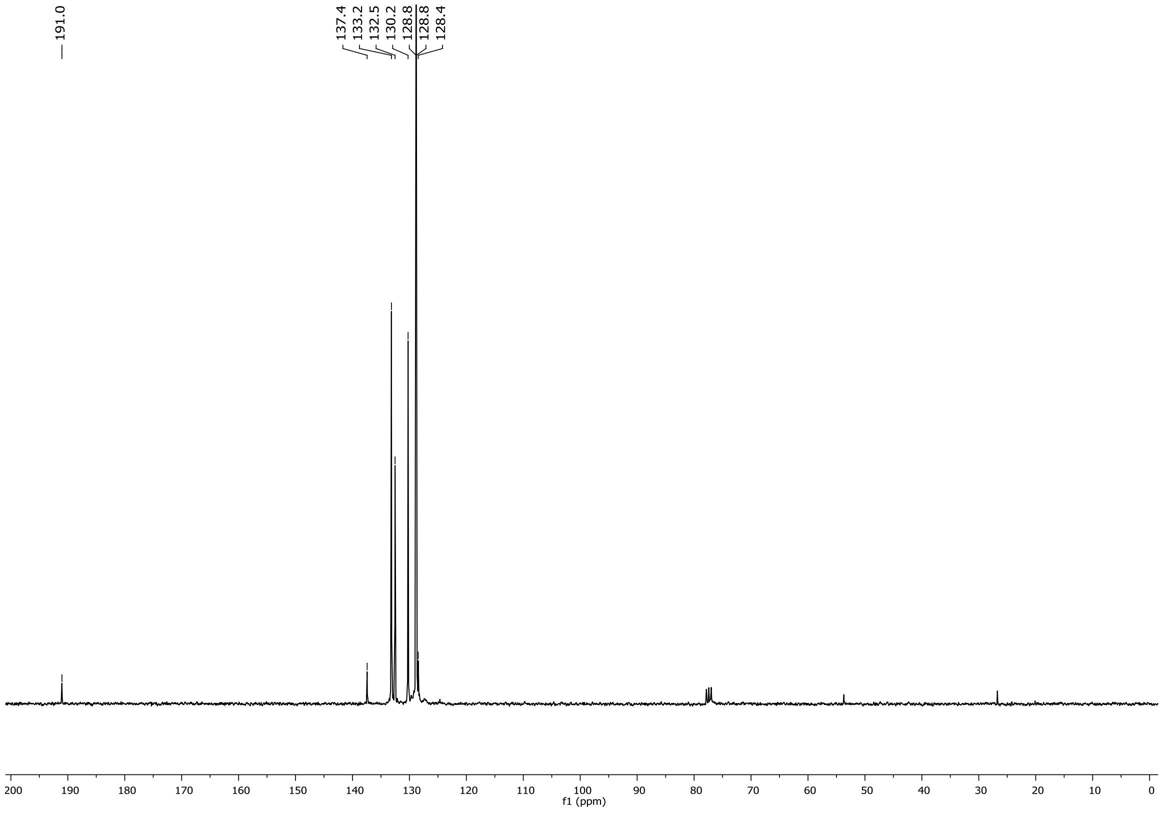

7.81
7.78
7.61
7.58
7.14
7.11
7.09
7.05
6.46
6.46
6.41
6.40
5.95
5.95
5.92
5.91
2.00
1.92
1.14
1.06
1.14
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


189.5
135.8
131.7
131.7
130.5
130.0
128.0
125.8
98.2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

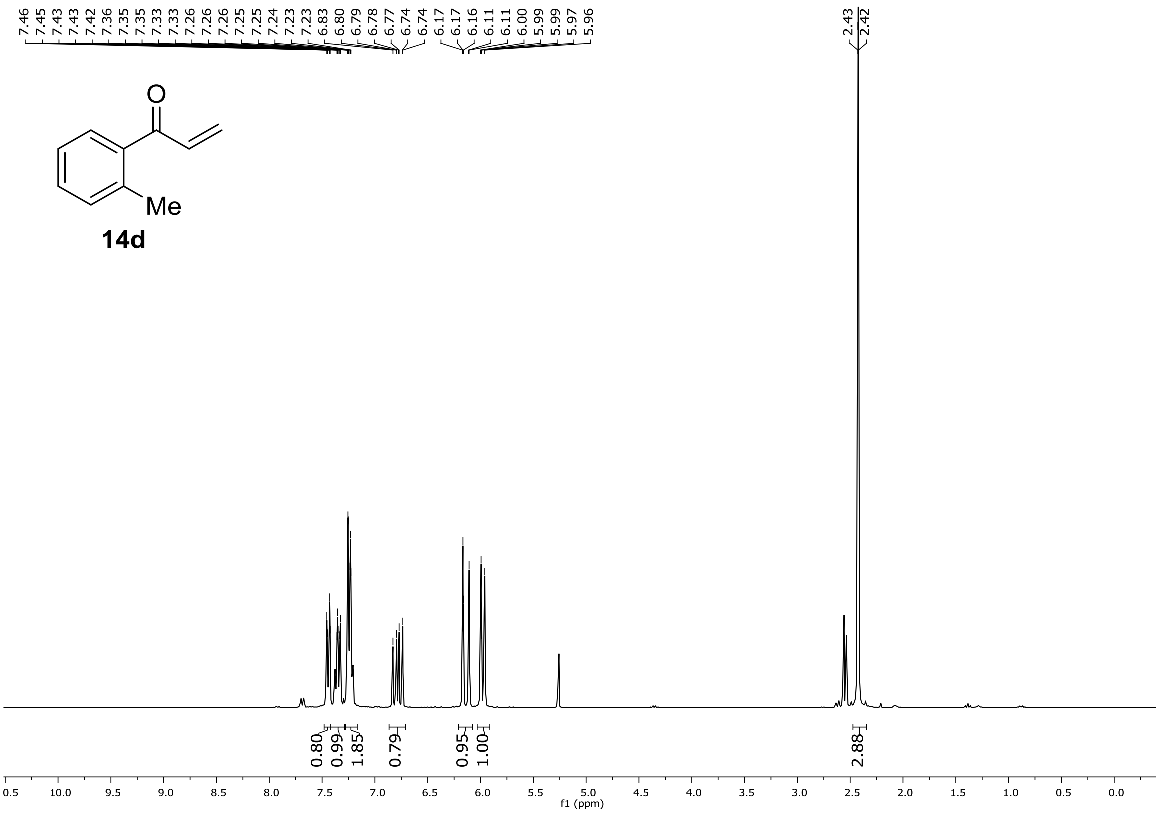


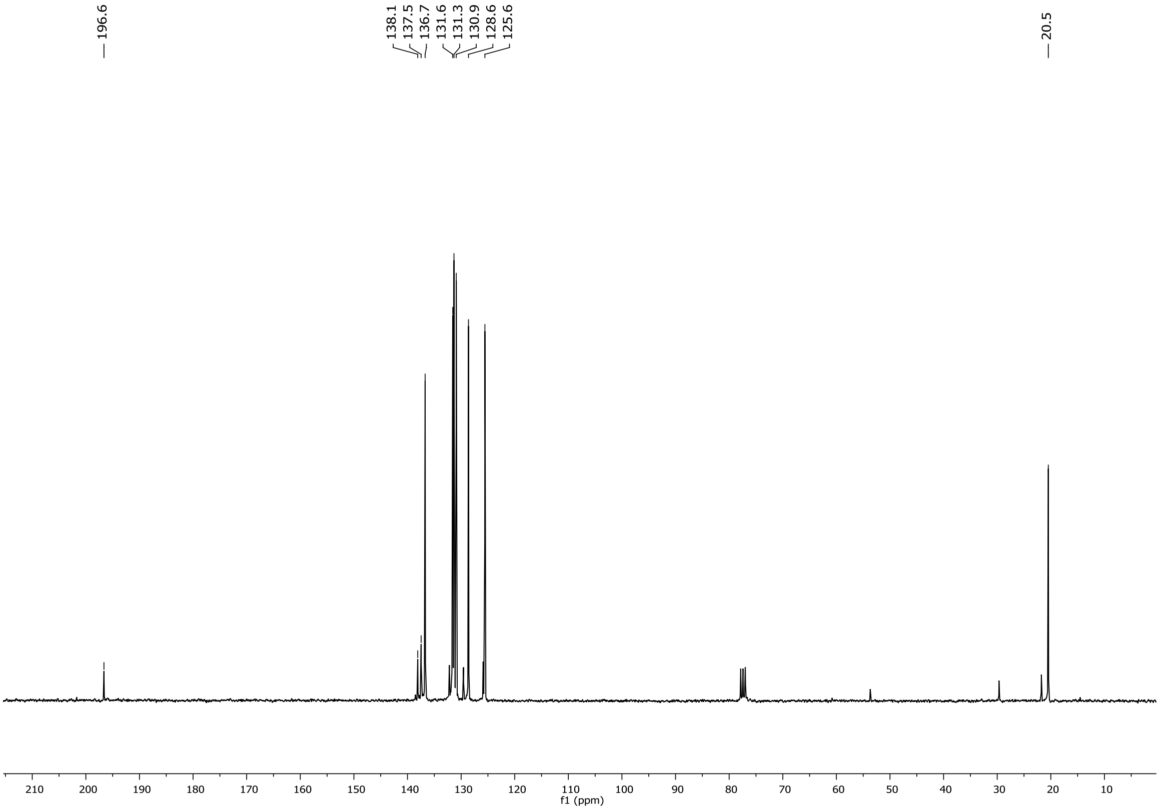
14c

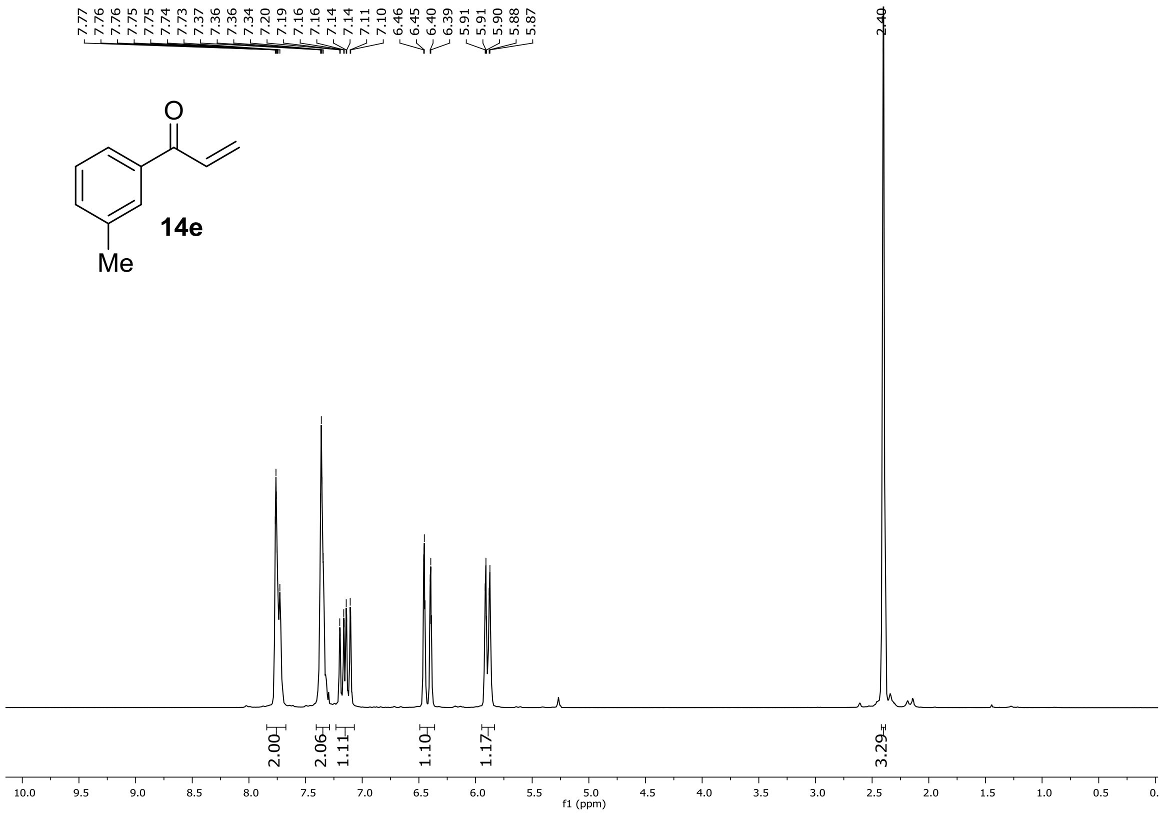
7.95
7.94
7.94
7.93
7.92
7.92
7.91
7.54
7.54
7.52
7.52
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.19
7.15
7.13
7.10
7.09
6.45
6.44
6.39
6.38
5.91
5.91
5.90
5.88
5.87
O
2.00
2.80
1.07
1.18
1.32
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

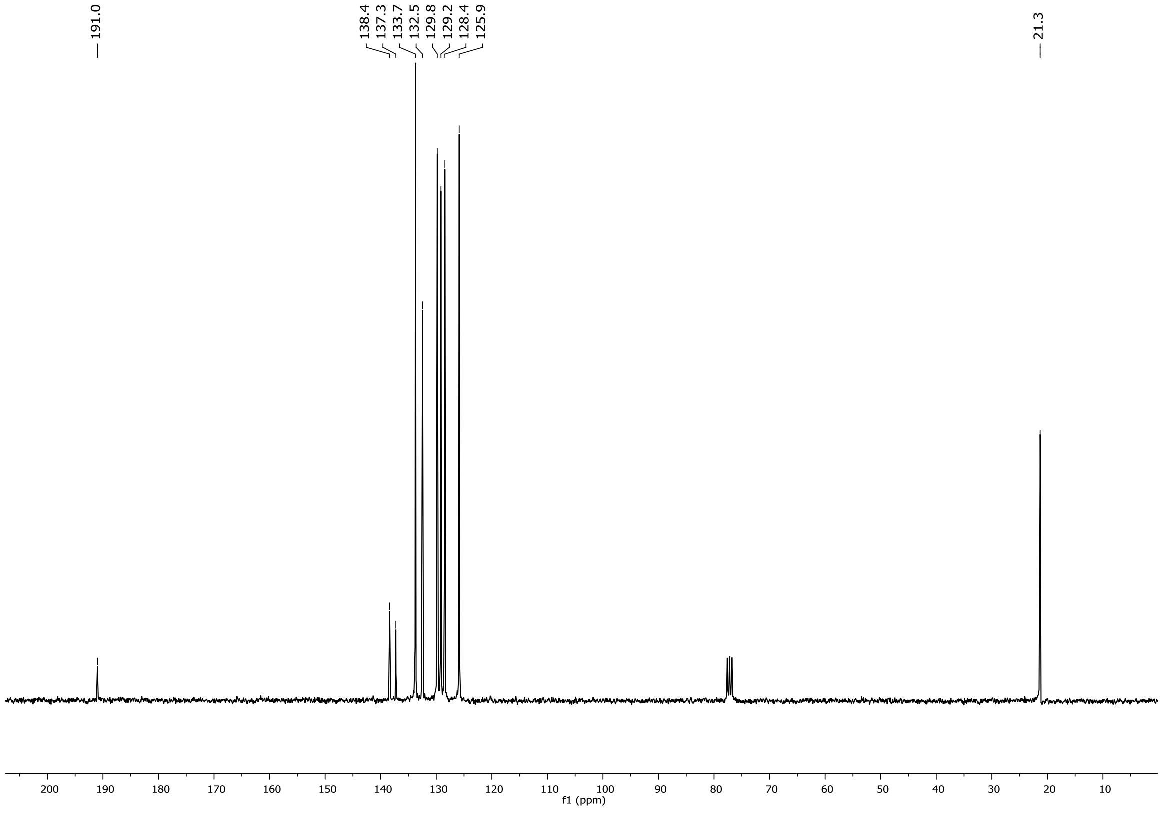


191.0
137.4
133.2
132.5
130.2
128.8
128.8
128.4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.46
7.45
7.43
7.43
7.42
7.36
7.35
7.35
7.33
7.33
7.26
7.26
7.26
7.25
7.25
7.24
7.23
7.23
7.23
6.83
6.80
6.79
6.78
6.77
6.74
6.74
6.17
6.17
6.16
6.11
6.11
6.00
5.99
5.99
5.97
5.96
2.43
2.42
O
Me
14d
0.80
0.99
1.85
0.79
0.95
1.00
2.88
0.5
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
f1 (ppm)


196.6
138.1
137.5
136.7
131.6
131.3
130.9
128.6
125.6
20.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


14e
7.77
7.76
7.76
7.75
7.75
7.74
7.73
7.37
7.36
7.36
7.34
7.20
7.19
7.16
7.16
7.14
7.14
7.11
7.10
6.46
6.45
6.40
6.39
5.91
5.91
5.90
5.88
5.87
2.40
O
Me
2.00
2.06
1.11
1.10
1.17
3.29
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.
f1 (ppm)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133.7
132.5
129.8
129.2
128.4
125.9
21.3
200
190
180
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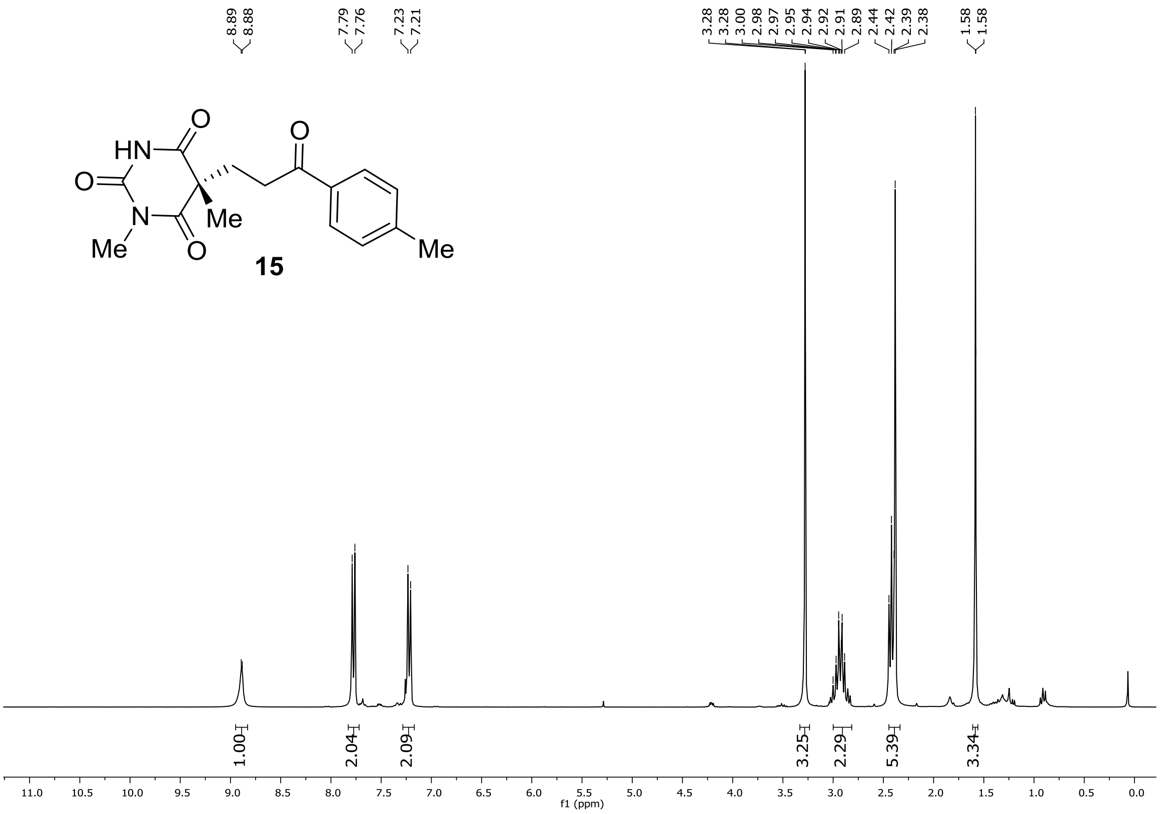
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



15

8.89
8.88
7.79
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7.23
7.21
3.28
3.28
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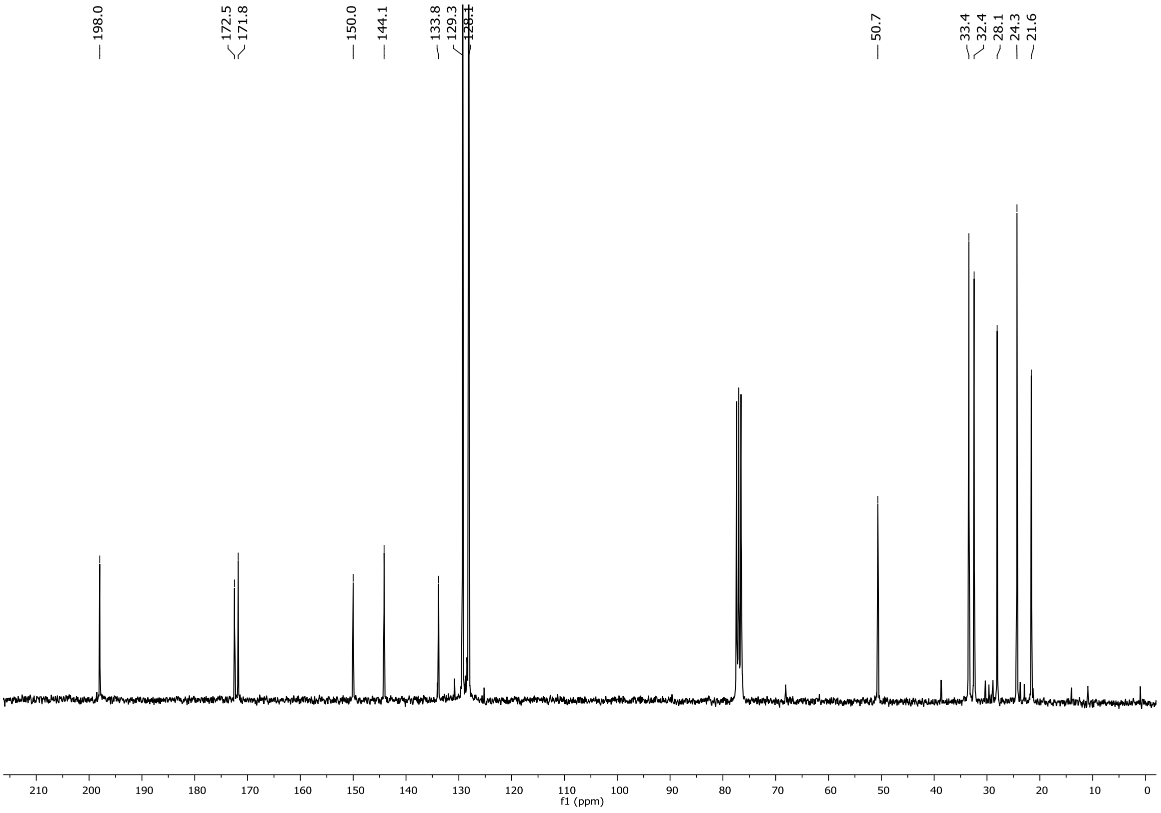
2.98
2.97
2.95
2.94
2.92
2.91
2.89
2.44
2.42
2.39
2.38
1.58
1.58
HN
O
O
N
Me
Me
O
O
Me
1.00
2.04
2.09
3.25
2.29
5.39
3.34
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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172.5
171.8
150.0
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133.8
129.3
128.1
50.7
33.4
32.4
28.1
24.3
21.6
210
200
190
180
170
160
150
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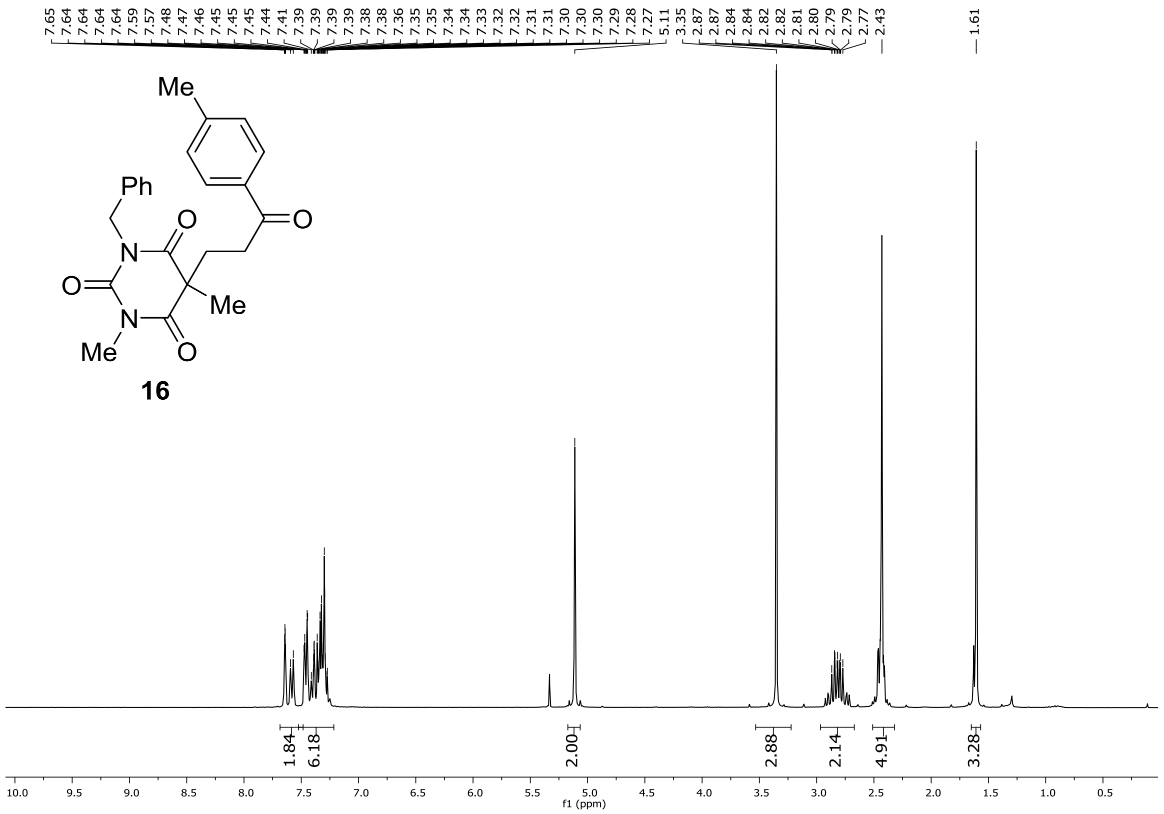
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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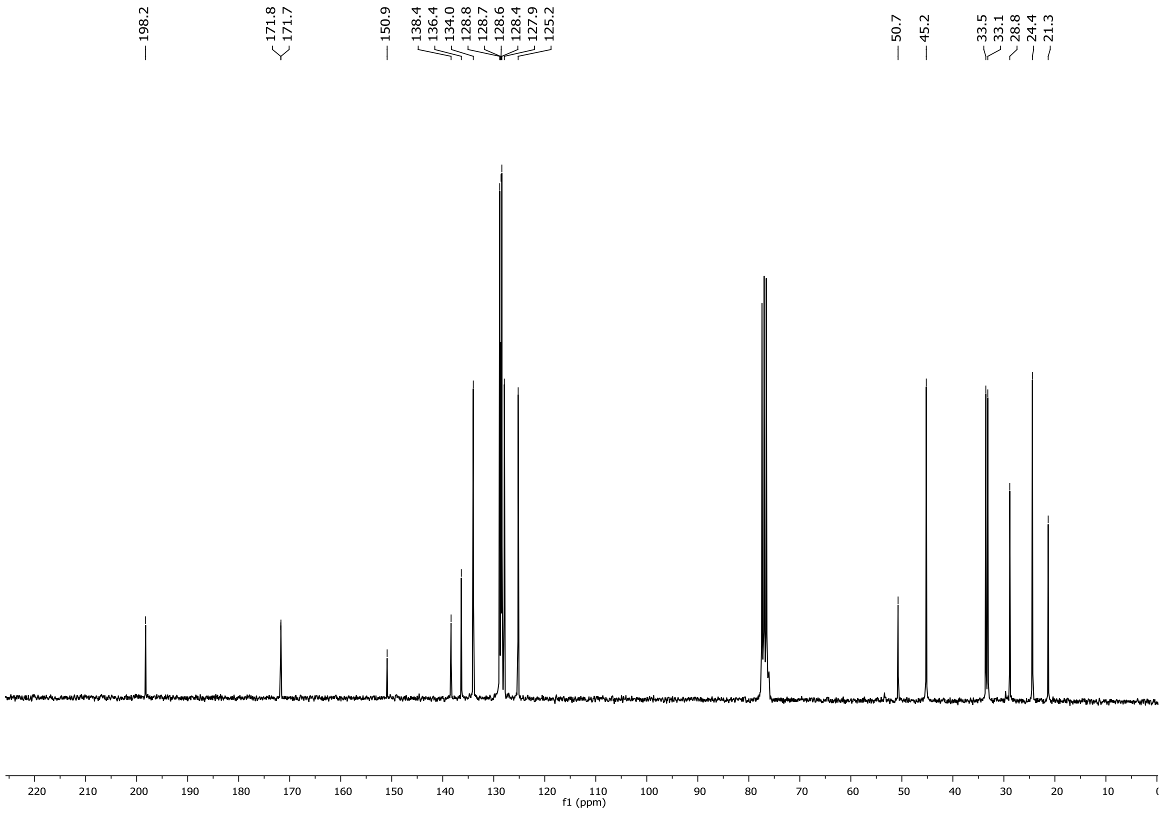
7.46
7.45
7.45
7.45
7.44
7.41
7.39
7.39
7.39
7.39
7.38
7.38
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.29
7.28
7.27
5.11
3.35
2.87
2.87
2.84
2.84
2.82
2.82
2.81
2.80
2.79
2.79
2.77
2.43
1.61
Me
Ph
O
N
O
O
N
Me
Me
O
1.84
6.18
2.00
2.88
2.14
4.91
3.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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
f1 (ppm)

16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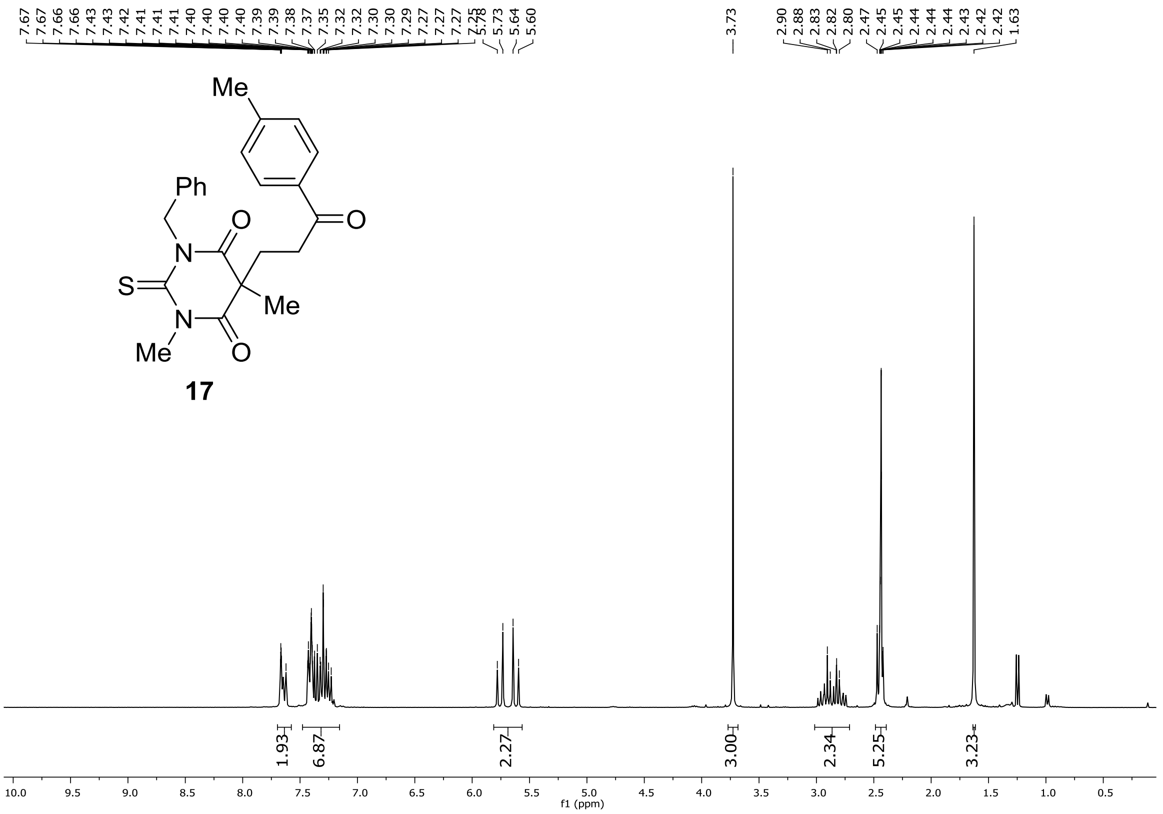
171.8
171.7
150.9
138.4
136.4
134.0
128.8
128.7
128.6
128.4
127.9
125.2
50.7
45.2
33.5
33.1
28.8
24.4
21.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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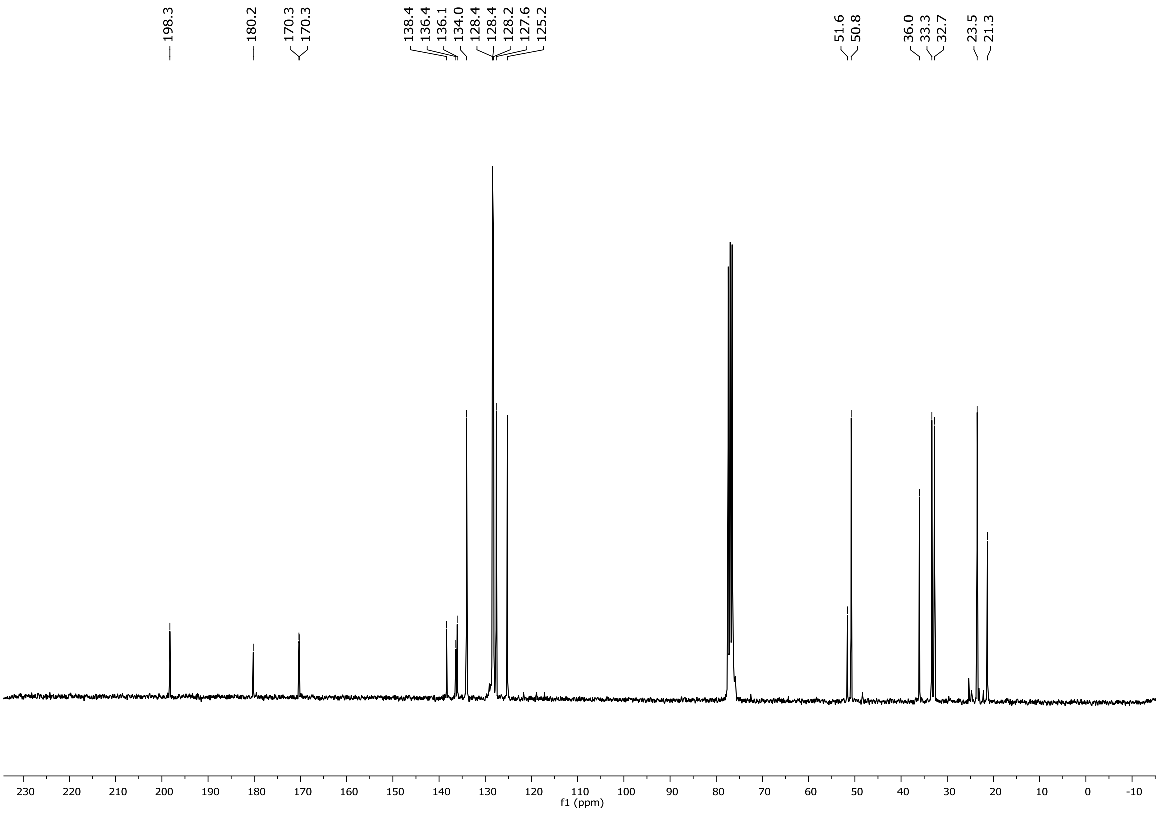
7.39
7.39
7.38
7.37
7.35
7.32
7.32
7.30
7.30
7.29
7.27
7.27
7.27
7.25
5.78
5.73
5.64
5.60
3.73
2.90
2.88
2.83
2.82
2.80
2.47
2.45
2.45
2.44
2.44
2.44
2.43
2.42
2.42
1.63
Me
Ph
O
N
O
S
N
Me
Me
O
1.93
6.87
2.27
3.00
2.34
5.25
3.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

17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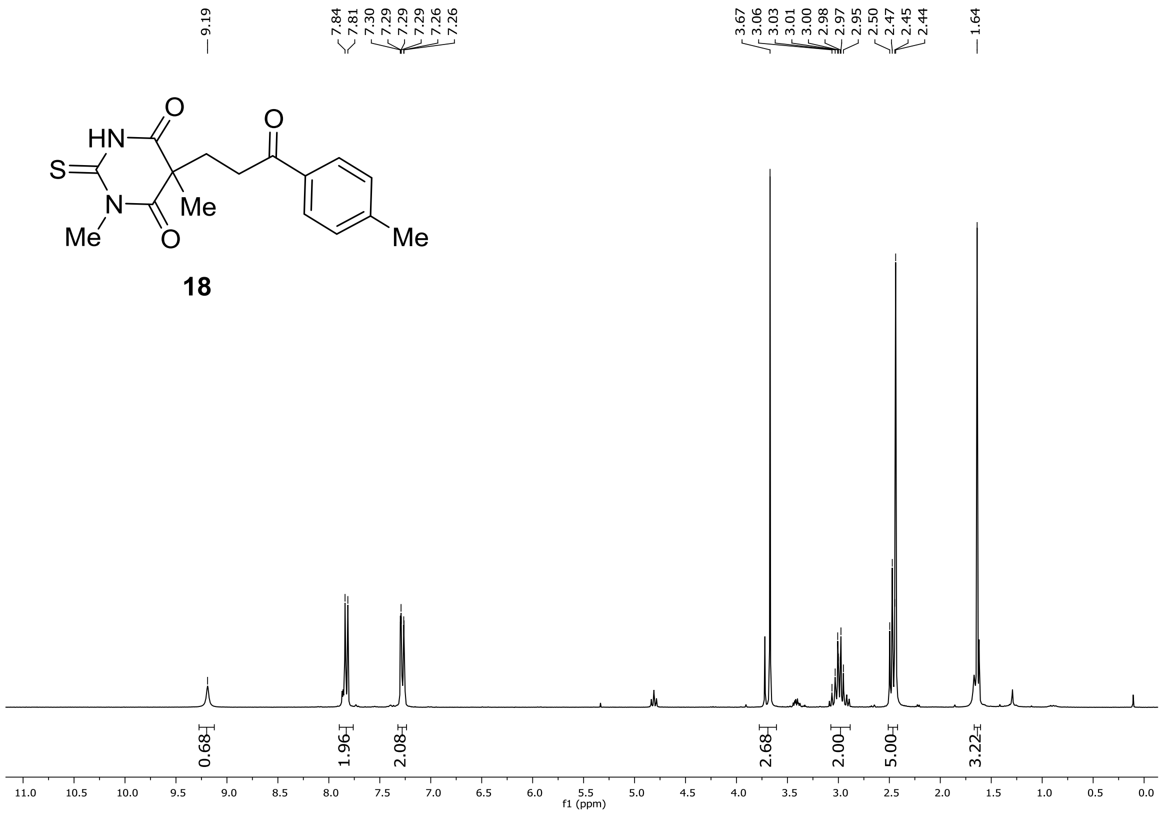
180.2
170.3
170.3
138.4
136.4
136.1
134.0
128.4
128.4
128.2
127.6
125.2
51.6
50.8
36.0
33.3
32.7
23.5
21.3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


9.19
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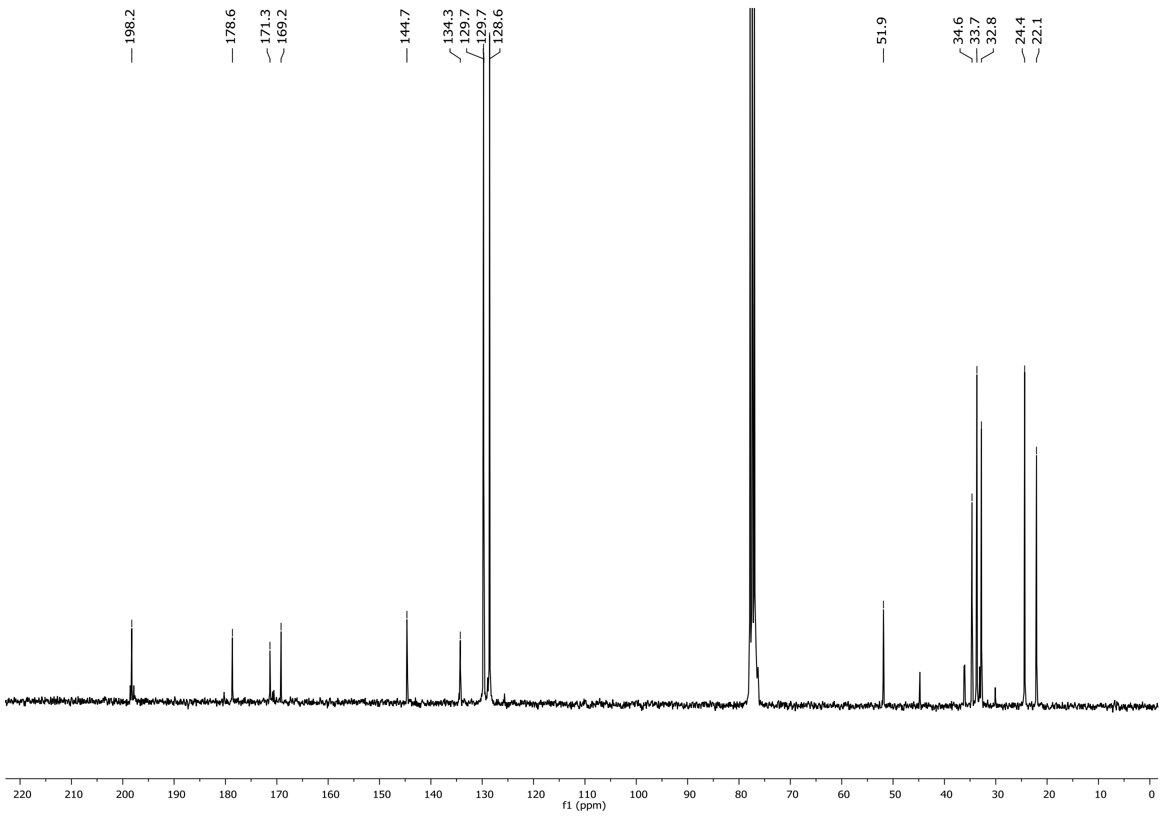
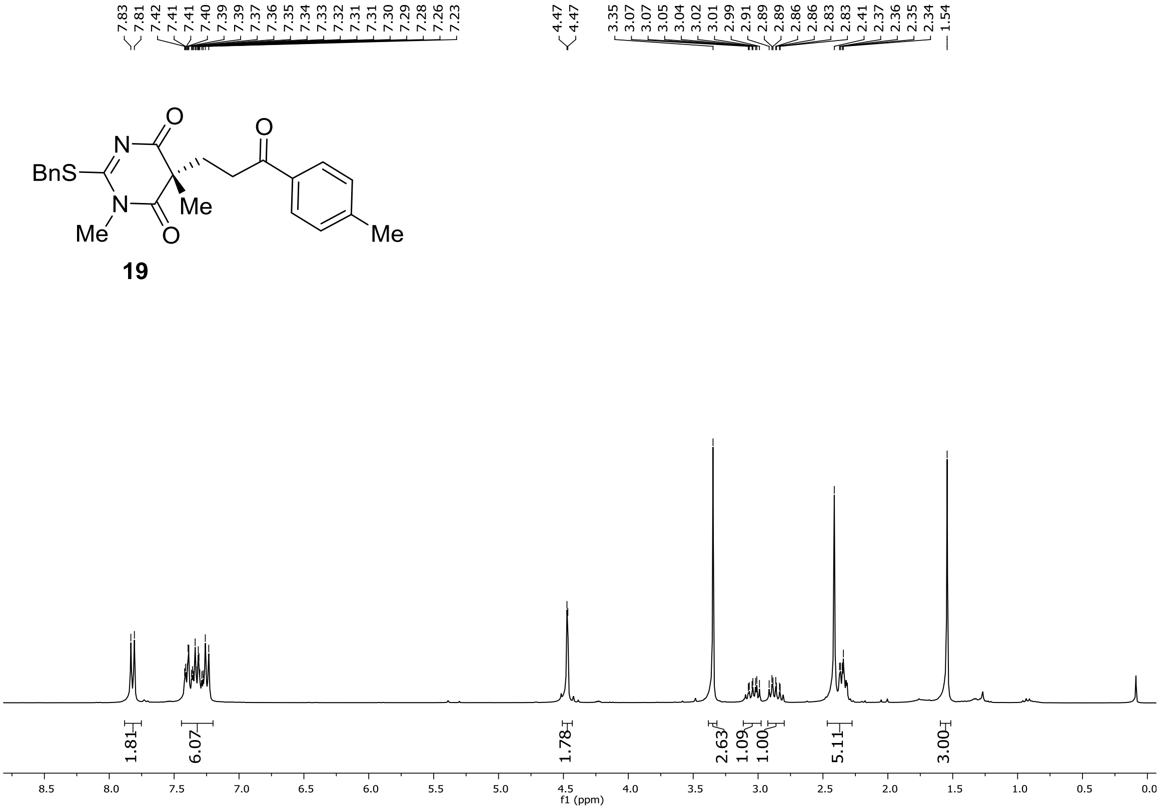
7.81
7.30
7.29
7.29
7.29
7.26
7.26
3.67
3.06
3.03
3.01
3.00
2.98
2.97
2.95
2.50
2.47
2.45
2.44
1.64
HN
S
N
Me
O
O
Me
O
Me
0.68
1.96
2.08
2.68
2.00
5.00
3.22
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

18


198.2
178.6
171.3
169.2
144.7
134.3
129.7
129.7
128.6
51.9
34.6
33.7
32.8
24.4
22.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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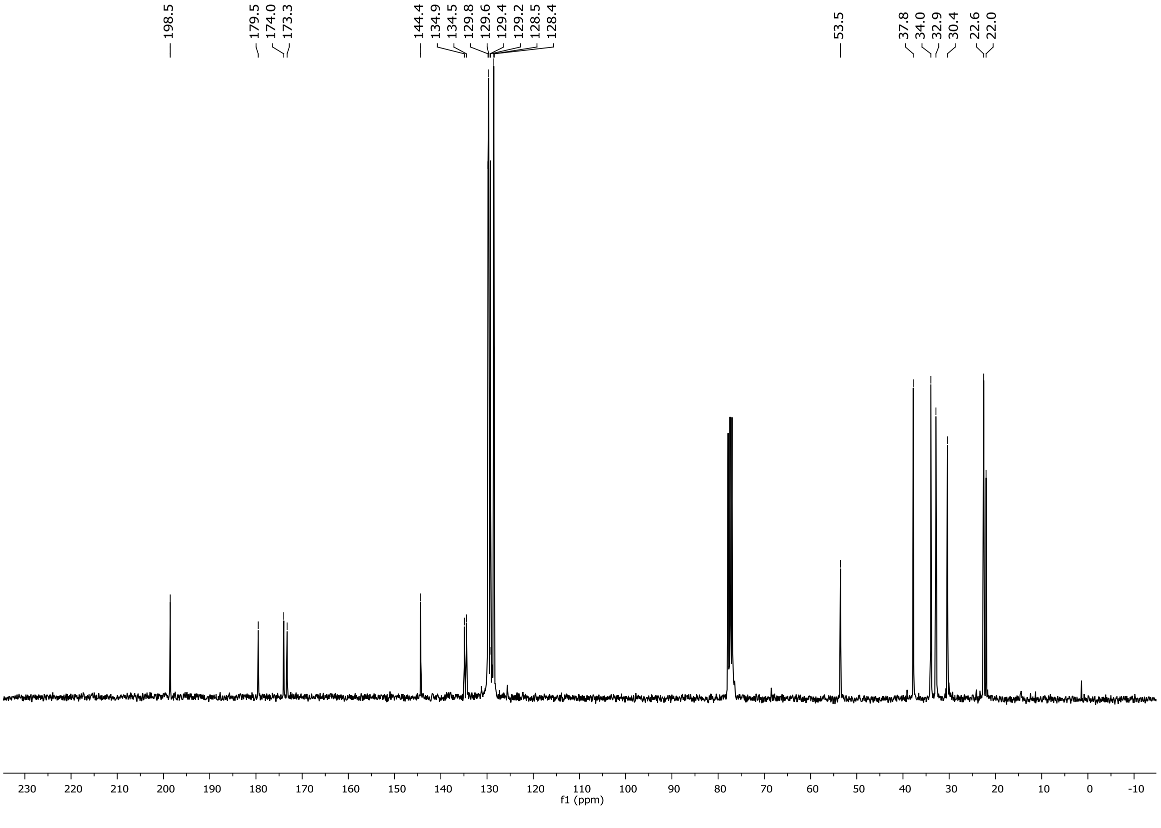
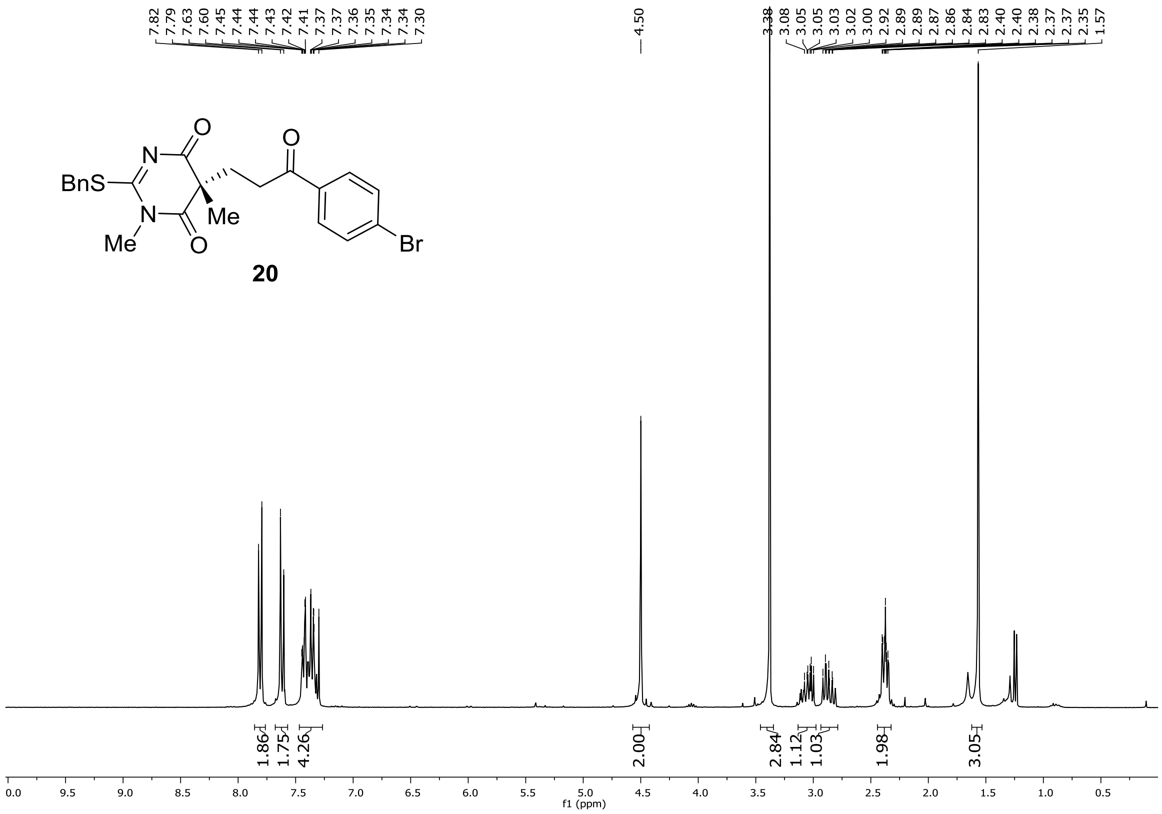
7.42
7.41
7.41
7.40
7.39
7.39
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.26
7.23
4.47
4.47
3.35
3.07
3.07
3.05
3.04
3.02
3.01
2.99
2.91
2.89
2.89
2.86
2.86
2.83
2.83
2.41
2.37
2.36
2.35
2.34
1.54
BnS
N
N
O
O
O
Me
Me
Me
1.81
6.07
1.78
2.63
1.09
1.00
5.11
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

19


198.5
179.5
174.0
173.3
144.4
134.9
134.5
129.8
129.6
129.4
129.2
128.5
128.4
53.5
37.8
34.0
32.9
30.4
22.6
22.0
230
220
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)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7.63
7.60
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7.44
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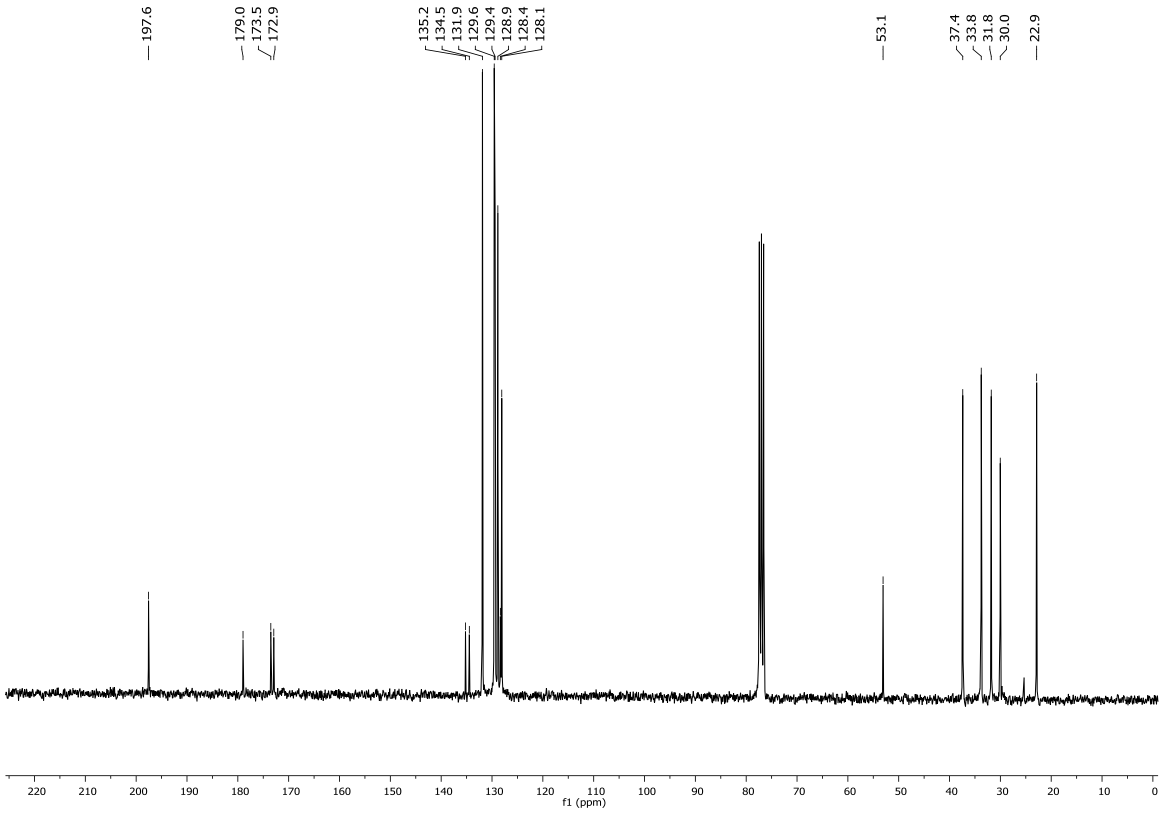
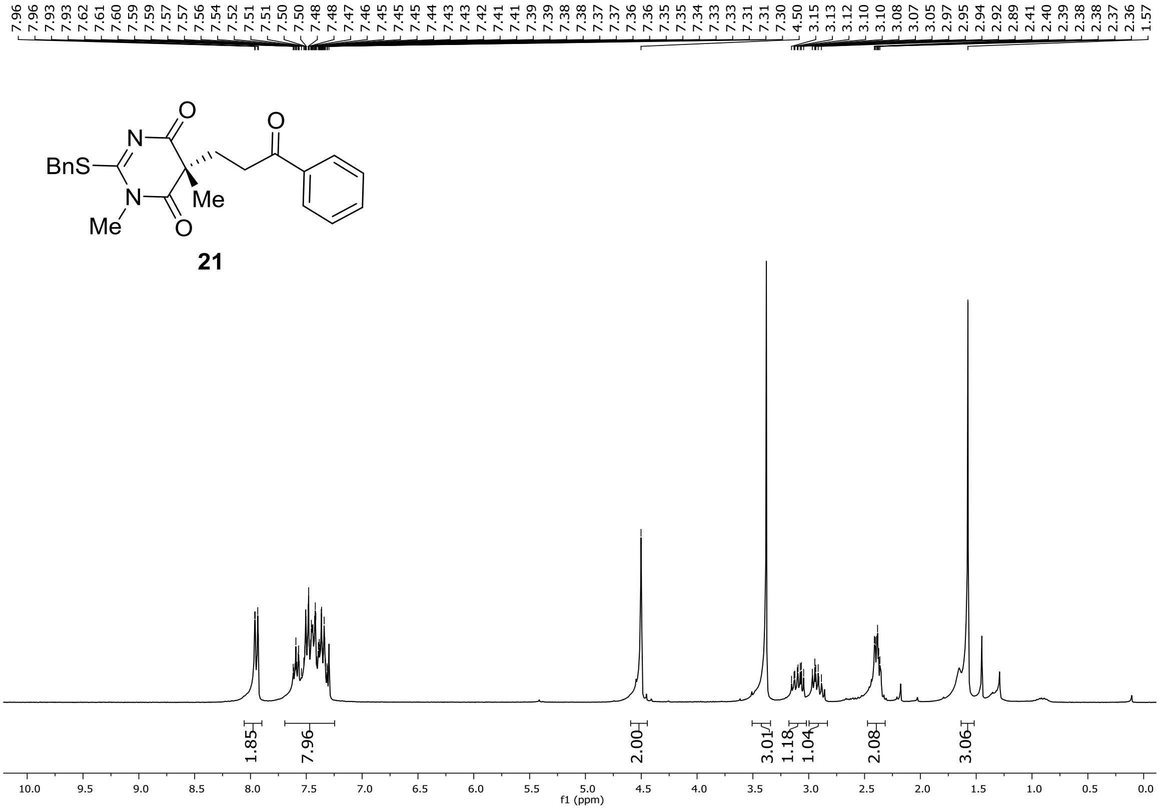
7.43
7.42
7.41
7.37
7.37
7.36
7.35
7.34
7.34
7.30
4.50
3.38
3.08
3.05
3.05
3.03
3.02
3.00
2.92
2.89
2.89
2.87
2.86
2.84
2.83
2.40
2.38
2.37
2.37
2.35
1.57
BnS
N
O
O
Me
Me
O
Br
20
1.86
1.75
4.26
2.00
2.84
1.12
1.03
1.98
3.05
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


197.6
179.0
173.5
172.9
135.2
134.5
131.9
129.6
129.4
128.9
128.4
128.1
53.1
37.4
33.8
31.8
30.0
22.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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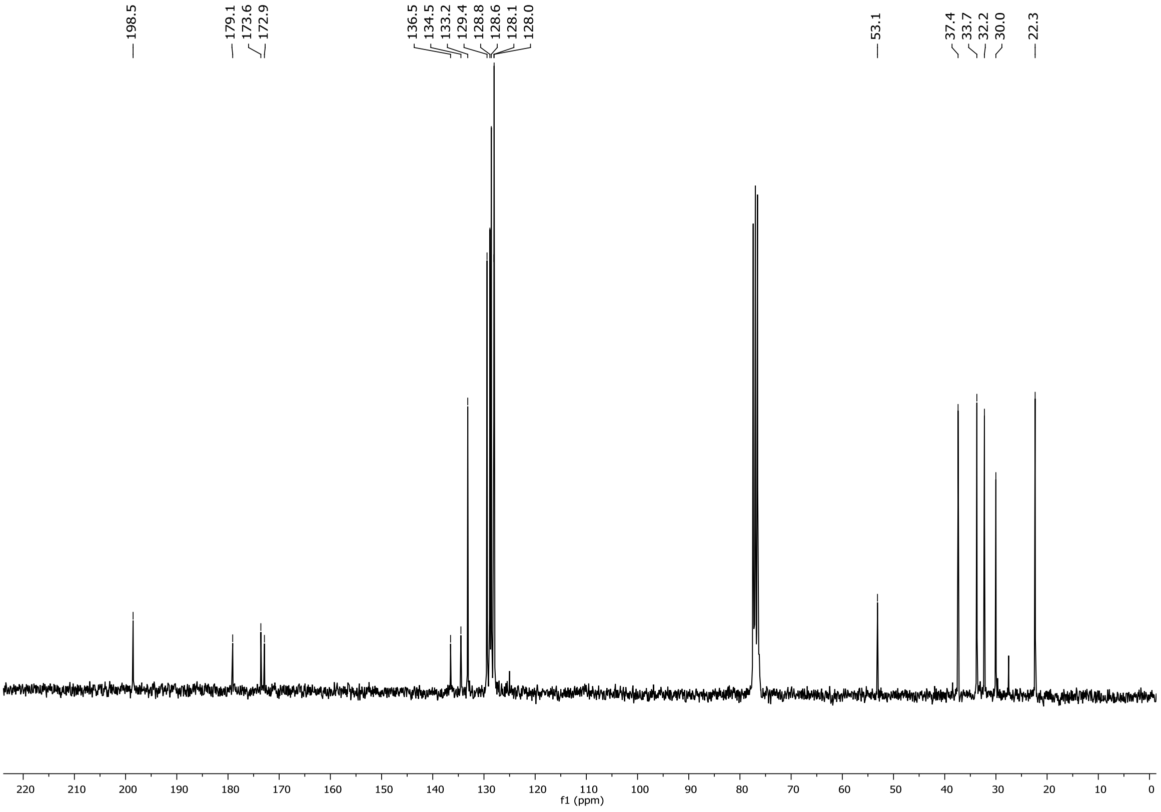
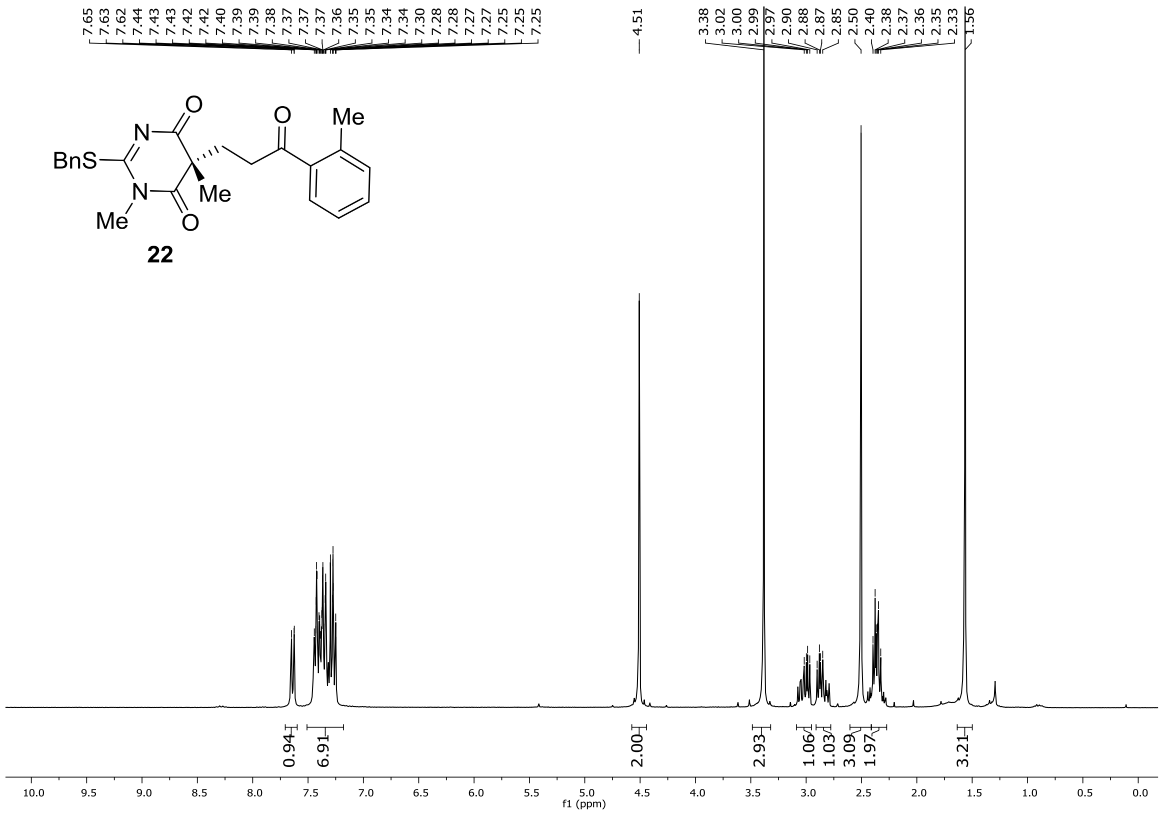
BnS
N
N
O
O
O
Me
Me
1.85
7.96
2.00
3.01
1.18
1.04
2.08
3.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

21


198.5
179.1 173.6 172.9
136.5 134.5 133.2 129.4 128.8 128.6 128.1 128.0
53.1
37.4 33.7 32.2 30.0
22.3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



22

7.65
7.63
7.62
7.44
7.43
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7.42
7.42
7.40
7.39
7.39
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.30
7.28
7.28
7.27
7.27
7.25
7.25
7.25
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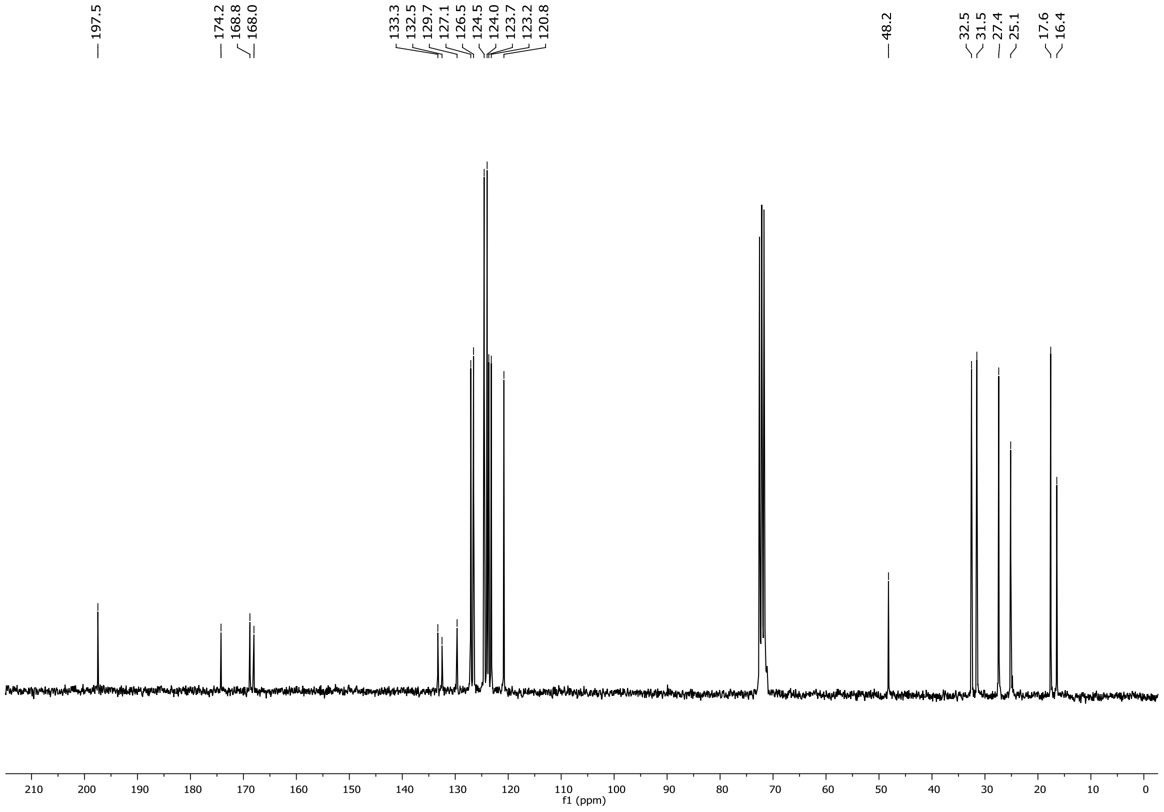
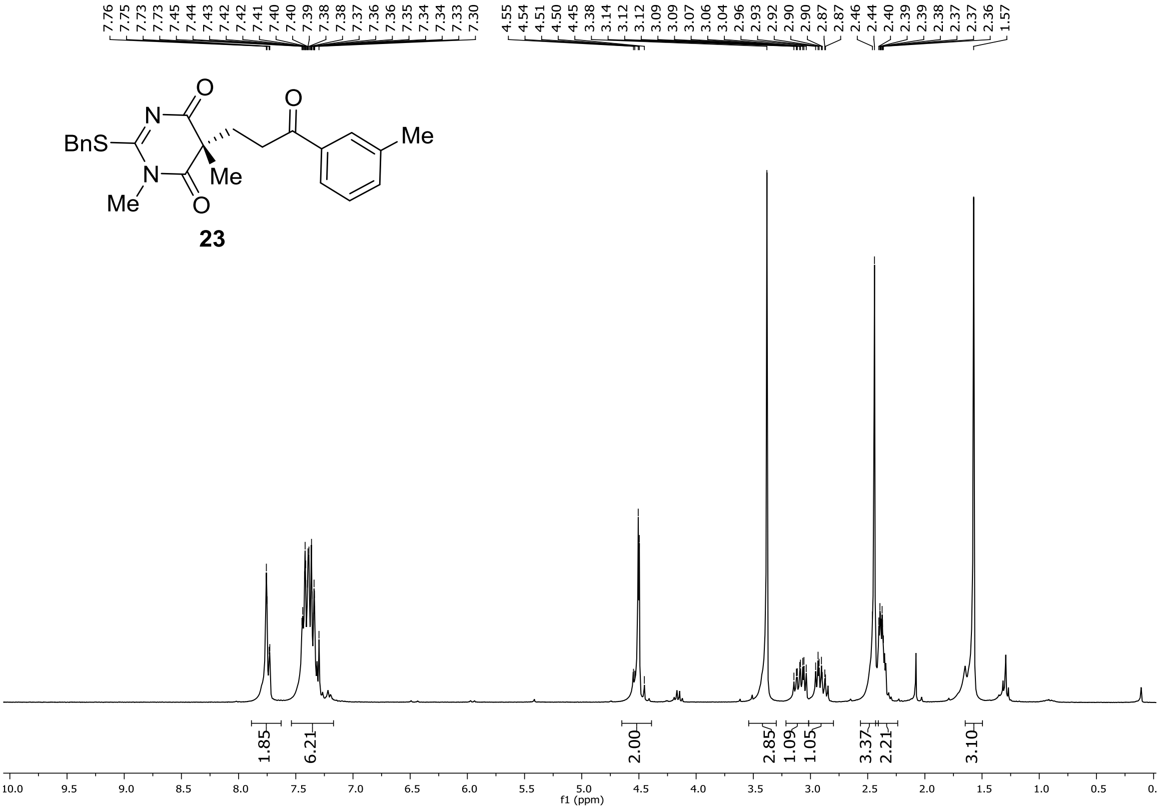
2.90
2.88
2.87
2.85
2.50
2.40
2.38
2.37
2.36
2.35
2.33
1.56
BnS
N
N
O
O
O
Me
Me
Me
0.94
6.91
2.00
2.93
1.06
1.03
3.09
1.97
3.21
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



197.5
174.2
168.8
168.0
133.3
132.5
129.7
127.1
126.5
124.5
124.0
123.7
123.2
120.8
48.2
32.5
31.5
27.4
25.1
17.6
16.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.38
7.38
7.37
7.36
7.36
7.35
7.34
7.34
7.33
7.30
4.55
4.54
4.51
4.50
4.45
3.38
3.14
3.12
3.12
3.09
3.09
3.07
3.06
3.04
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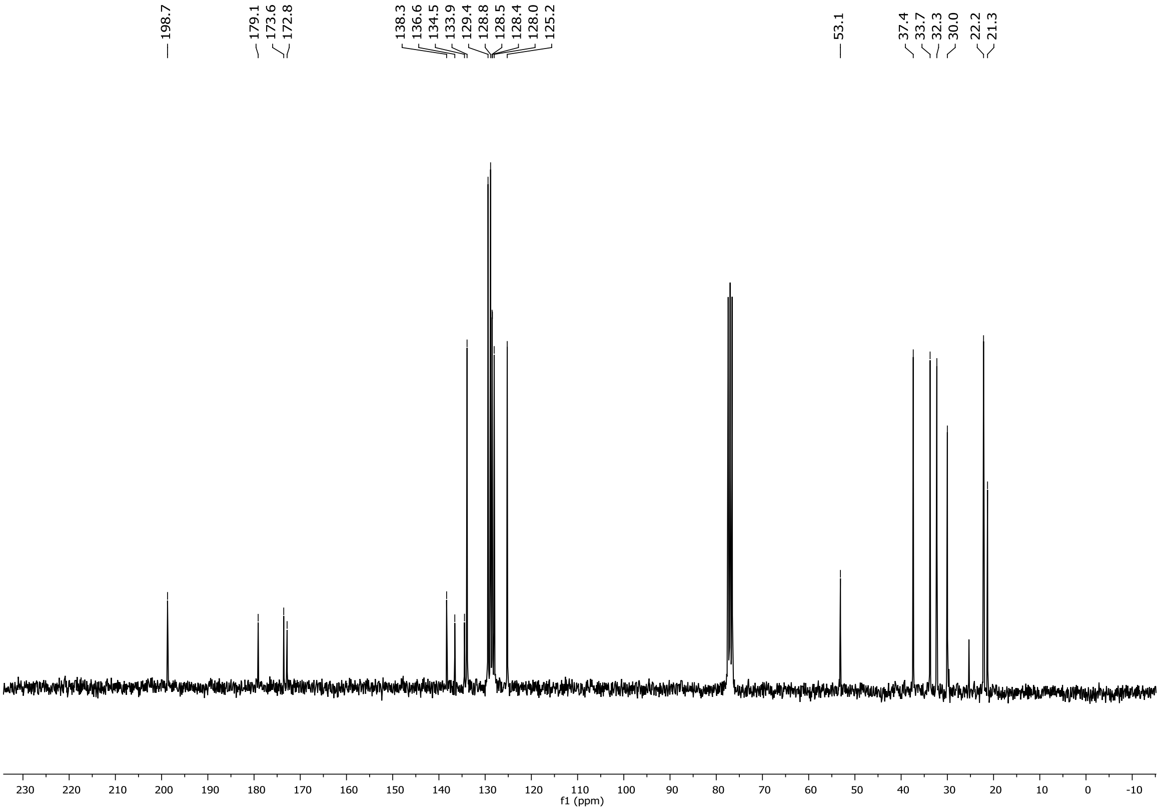
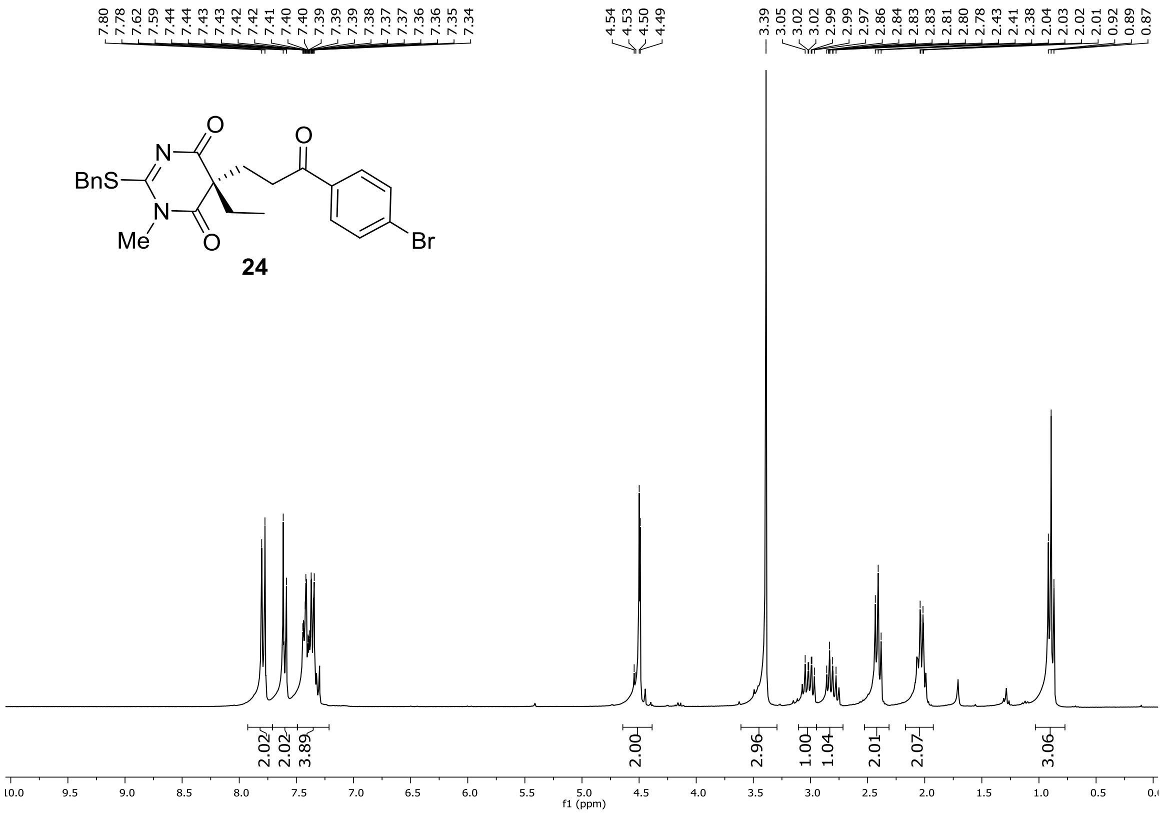
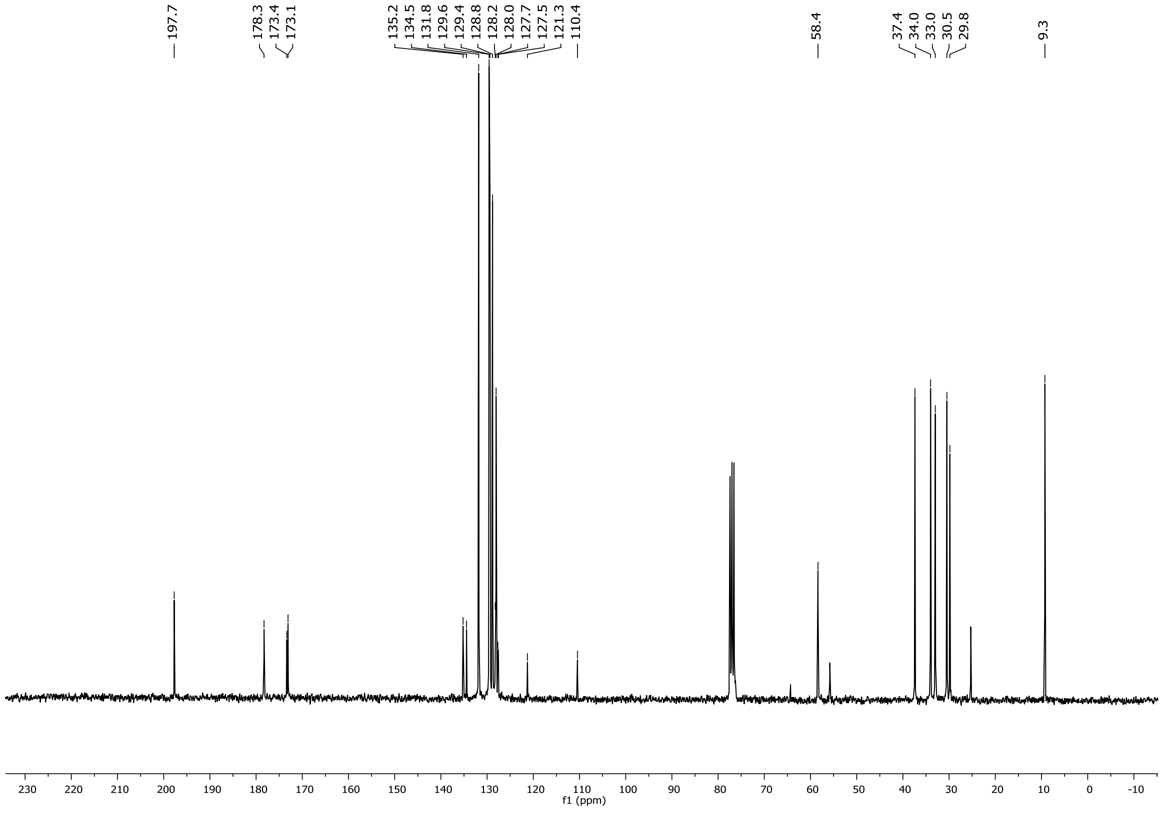
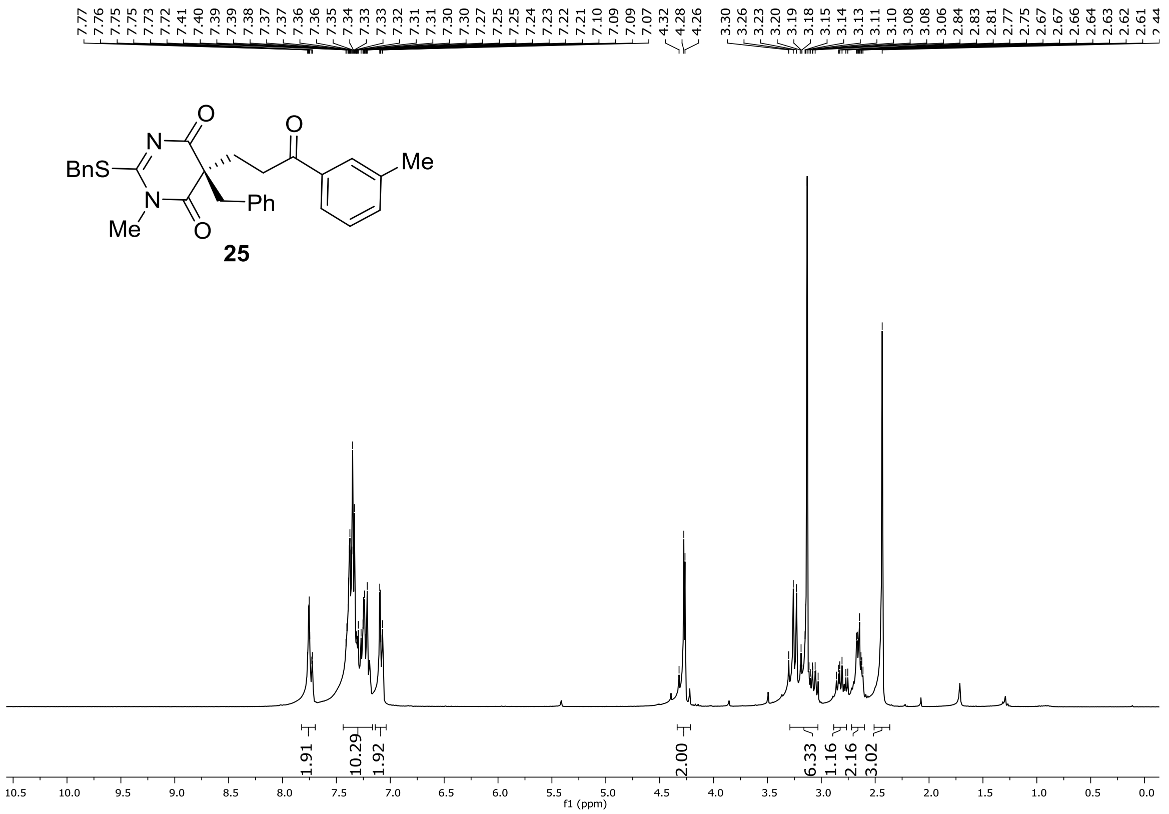
2.87
2.46
2.44
2.40
2.39
2.39
2.38
2.37
2.37
2.36
1.57
O
N
BnS
N
Me
Me
O
O
Me
1.85
6.21
2.00
2.85
1.09
1.05
3.37
2.21
3.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

23


198.7
179.1
173.6
172.8
138.3
136.6
134.5
133.9
129.4
128.8
128.5
128.4
128.0
125.2
53.1
37.4
33.7
32.3
30.0
22.2
21.3
230
220
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)


7.80 7.78 7.62 7.59 7.44 7.44 7.43 7.43 7.42 7.42 7.41 7.40 7.40 7.39 7.39 7.39 7.38 7.37 7.37 7.36 7.36 7.35 7.34
4.54 4.53 4.50 4.49
3.39 3.05 3.02 3.02 2.99 2.99 2.97 2.86 2.84 2.83 2.83 2.81 2.80 2.78 2.43 2.41 2.38 2.04 2.03 2.02 2.01 0.92 0.89 0.87
BnS
N
O
N
Me
O
O
Br
24
2.02 2.02 3.89
2.00
2.96
1.00 1.04
2.01
2.07
3.06
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
f1 (ppm)


197.7
178.3 173.4 173.1
135.2 134.5 131.8 129.6 129.4 128.8 128.2 128.0 127.7 127.5 121.3 110.4
58.4
37.4 34.0 33.0 30.5 29.8
9.3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
7.27
7.25
7.25
7.24
7.23
7.22
7.21
7.10
7.09
7.09
7.07
4.32
4.28
4.26
3.30
3.26
3.23
3.20
3.19
3.18
3.15
3.14
3.13
3.11
3.10
3.08
3.08
3.06
2.84
2.83
2.81
2.77
2.75
2.67
2.67
2.66
2.64
2.63
2.62
2.61
2.44
O
N
BnS
N
Me
O
Ph
O
Me
25
1.91
10.29
1.92
2.00
6.33
1.16
2.16
3.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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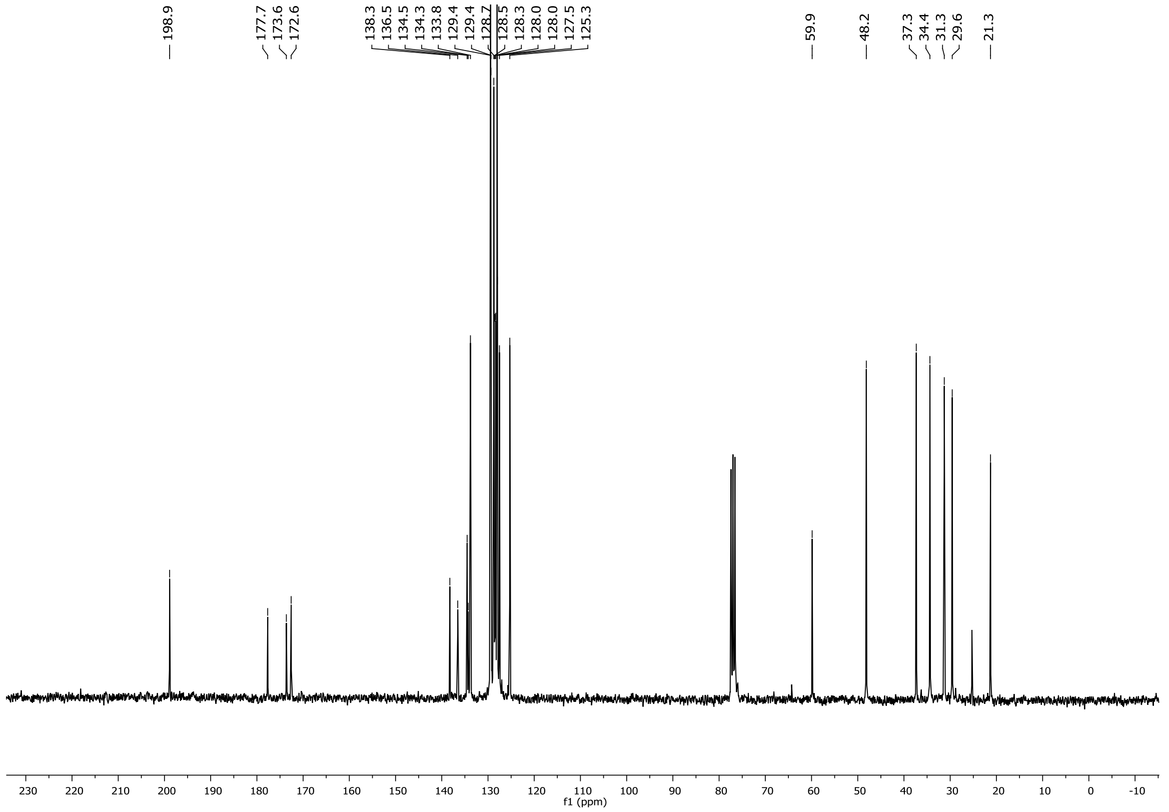
0.0
f1 (ppm)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172.6
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136.5
134.5
134.3
133.8
129.4
129.4
128.7
128.5
128.3
128.0
128.0
127.5
125.3
59.9
48.2
37.3
34.4
31.3
29.6
21.3
230
220
210
200
190
180
170
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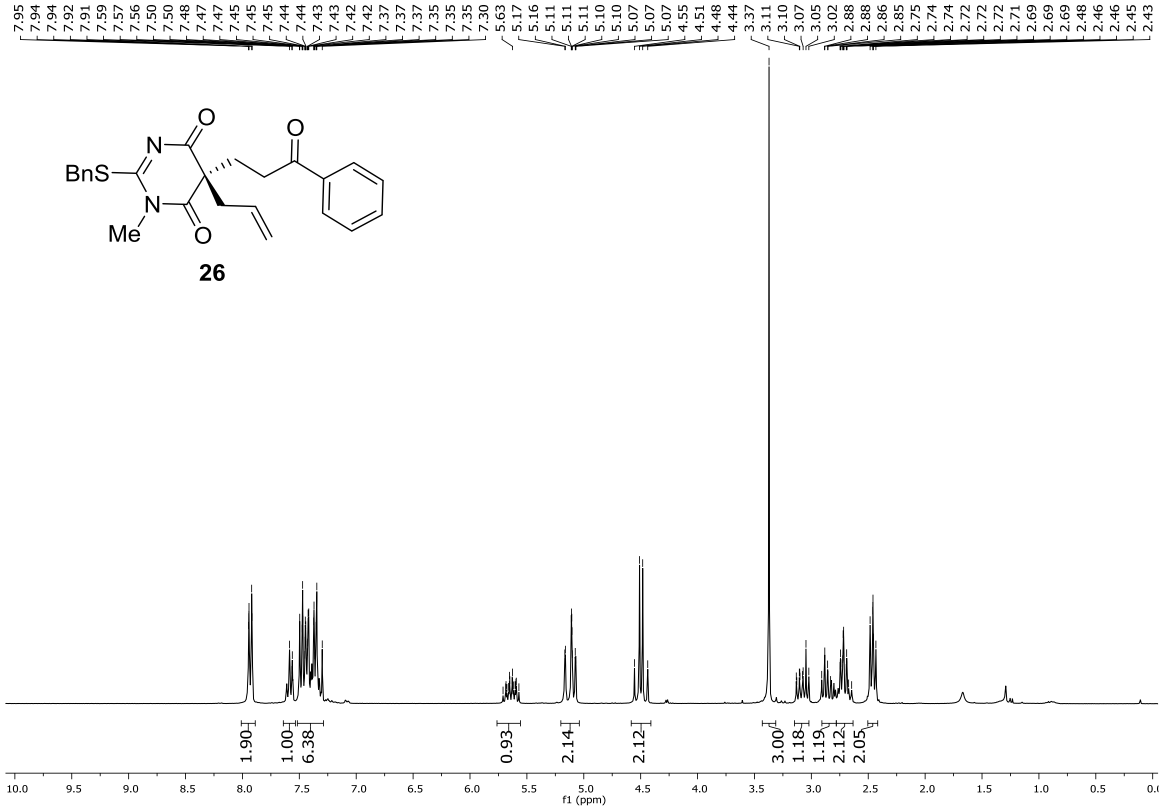
f1 (ppm)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7.56
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7.50
7.48
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7.45
7.45
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.37
7.37
7.37
7.35
7.35
7.35
7.30
5.63
5.17
5.16
5.11
5.11
5.11
5.10
5.10
5.07
5.07
5.07
4.55
4.51
4.48
4.44
3.37
3.11
3.10
3.07
3.05
3.02
2.88
2.88
2.86
2.85
2.75
2.74
2.74
2.72
2.72
2.72
2.71
2.69
2.69
2.69
2.48
2.46
2.45
2.43
O
O
N
BnS
N
Me
O
1.90
1.00
6.38
0.93
2.14
2.12
3.00
1.18
1.19
2.12
2.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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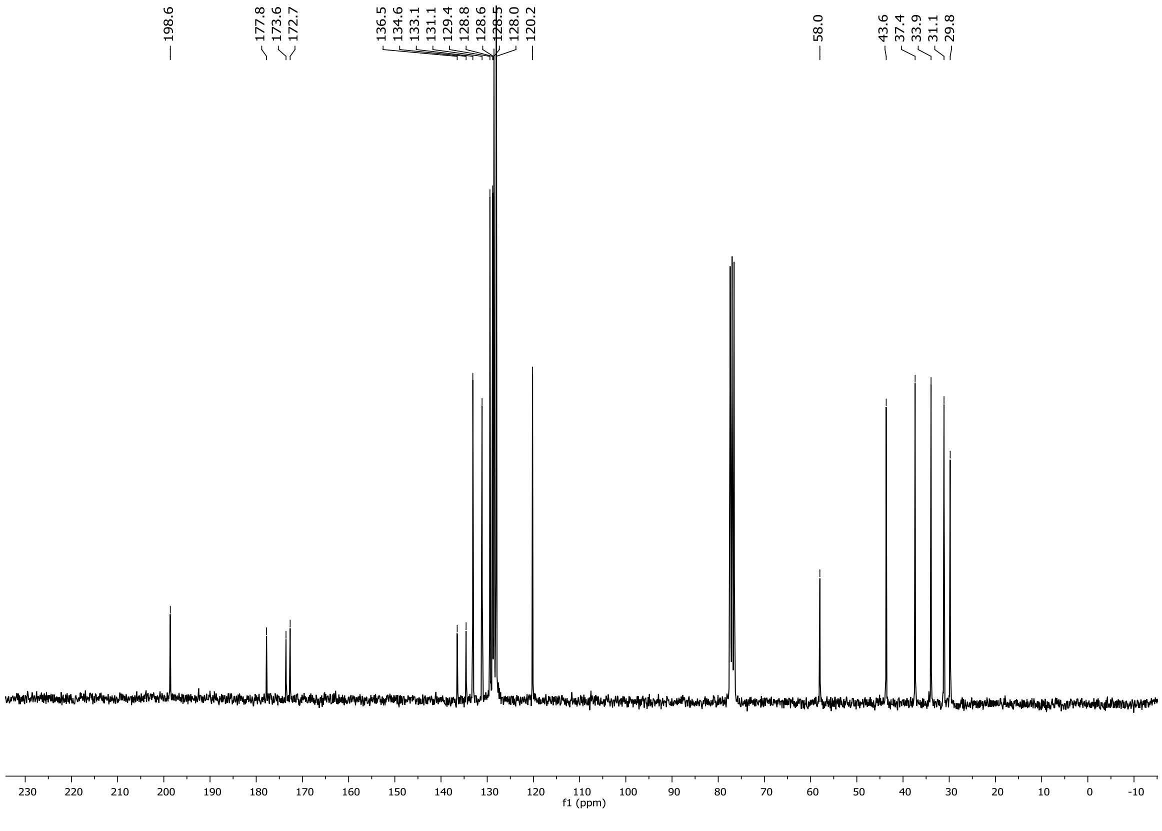
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

26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131.1
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128.6
128.5
128.0
120.2
58.0
43.6
37.4
33.9
31.1
29.8
230
220
210
200
190
180
170
160
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140
130
120
110
100
90
80
70
60
50
40
30
20
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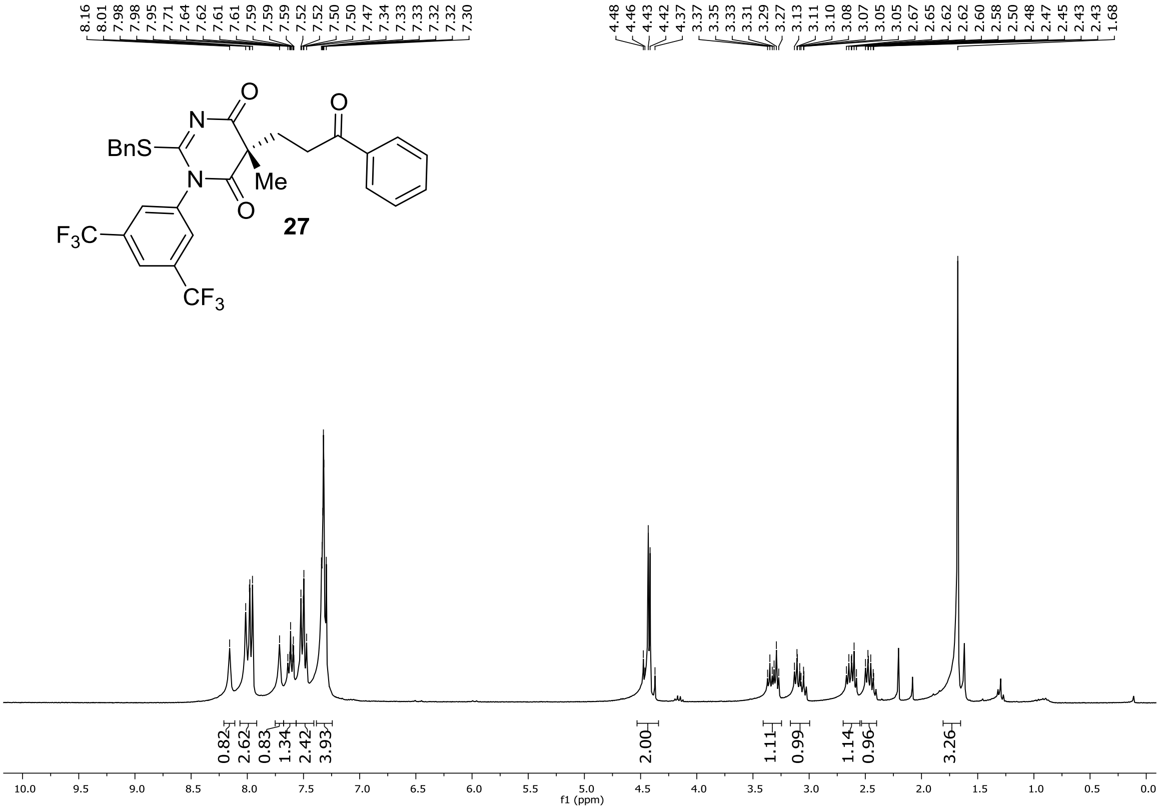
-10
f1 (ppm)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7.61
7.59
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7.59
7.52
7.52
7.50
7.50
7.47
7.34
7.33
7.33
7.32
7.32
7.30
4.48
4.46
4.43
4.42
4.37
3.37
3.35
3.33
3.31
3.29
3.27
3.13
3.11
3.10
3.08
3.07
3.05
3.05
2.67
2.65
2.62
2.62
2.60
2.58
2.50
2.48
2.47
2.45
2.43
2.43
1.68
BnS
N
N
O
O
O
Me
F3C
CF3
0.82
2.62
0.83
1.34
2.42
3.93
2.00
1.11
0.99
1.14
0.96
3.26
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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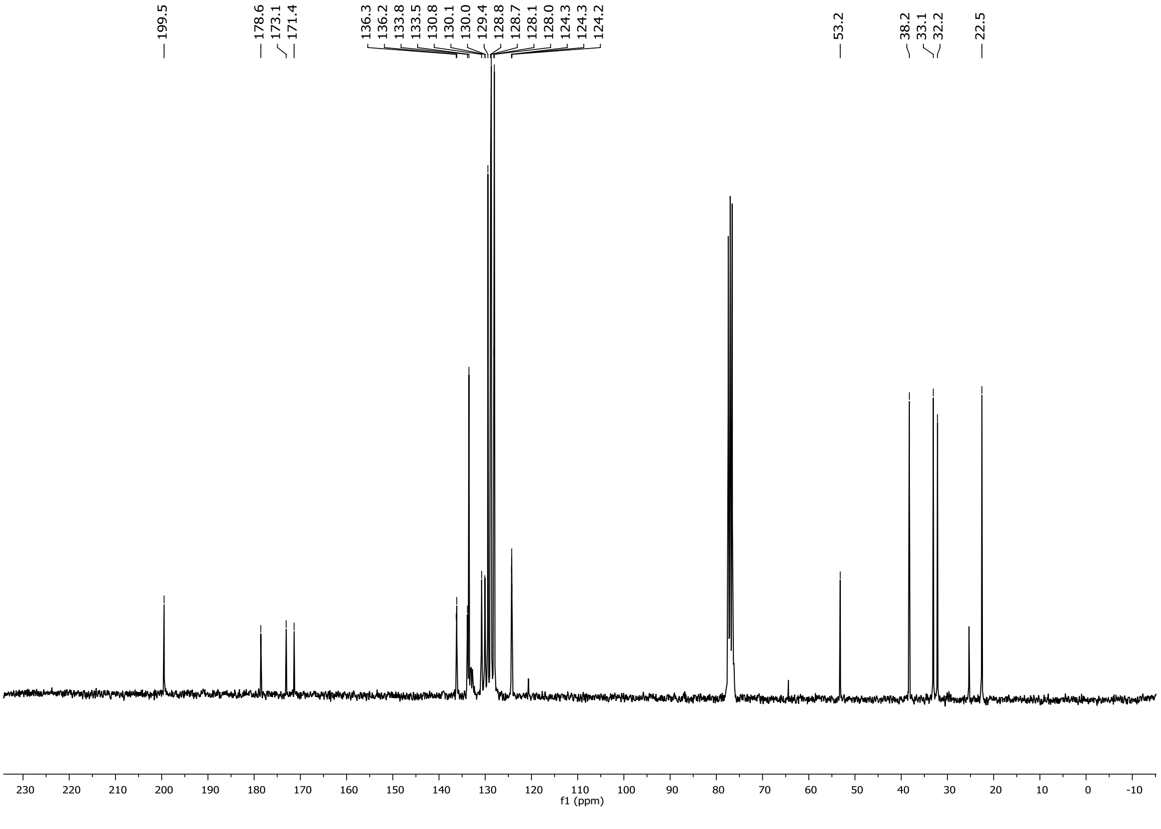
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

27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171.4
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133.8
133.5
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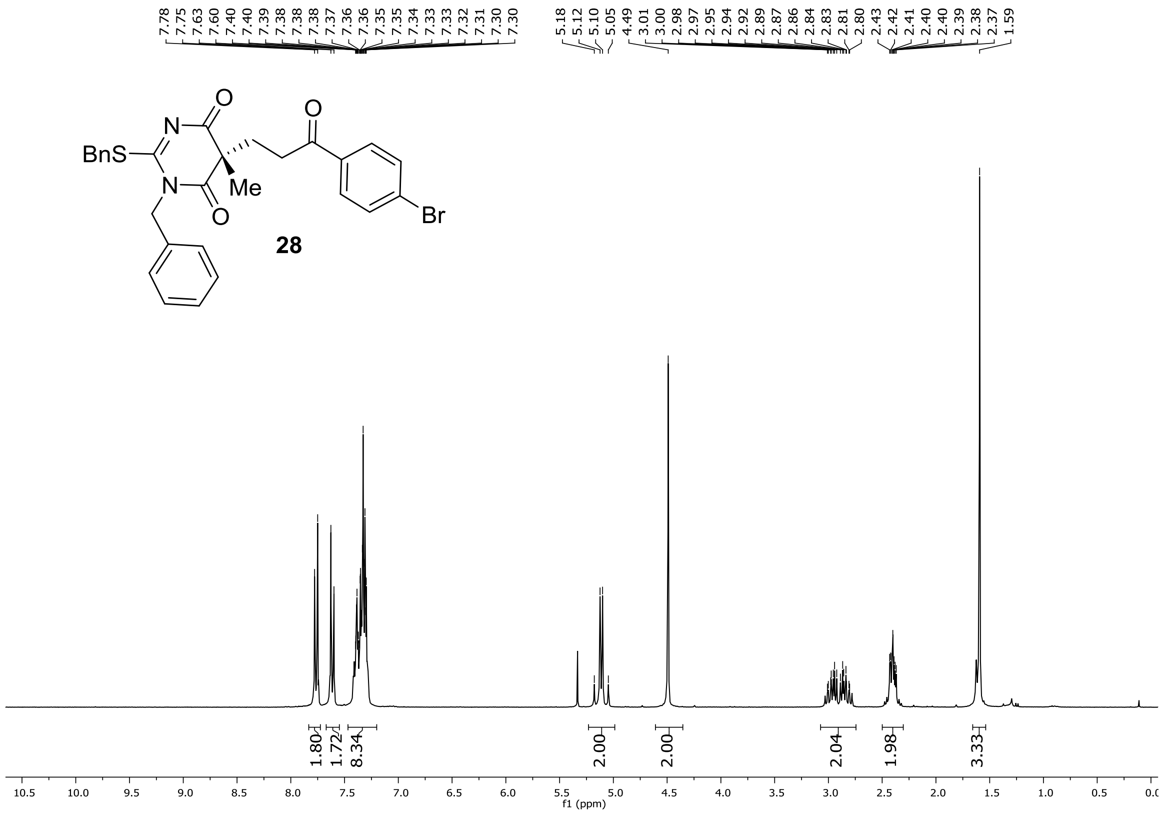
130.1
130.0
129.4
128.8
128.7
128.1
128.0
124.3
124.3
124.2
53.2
38.2
33.1
32.2
22.5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.39
7.38
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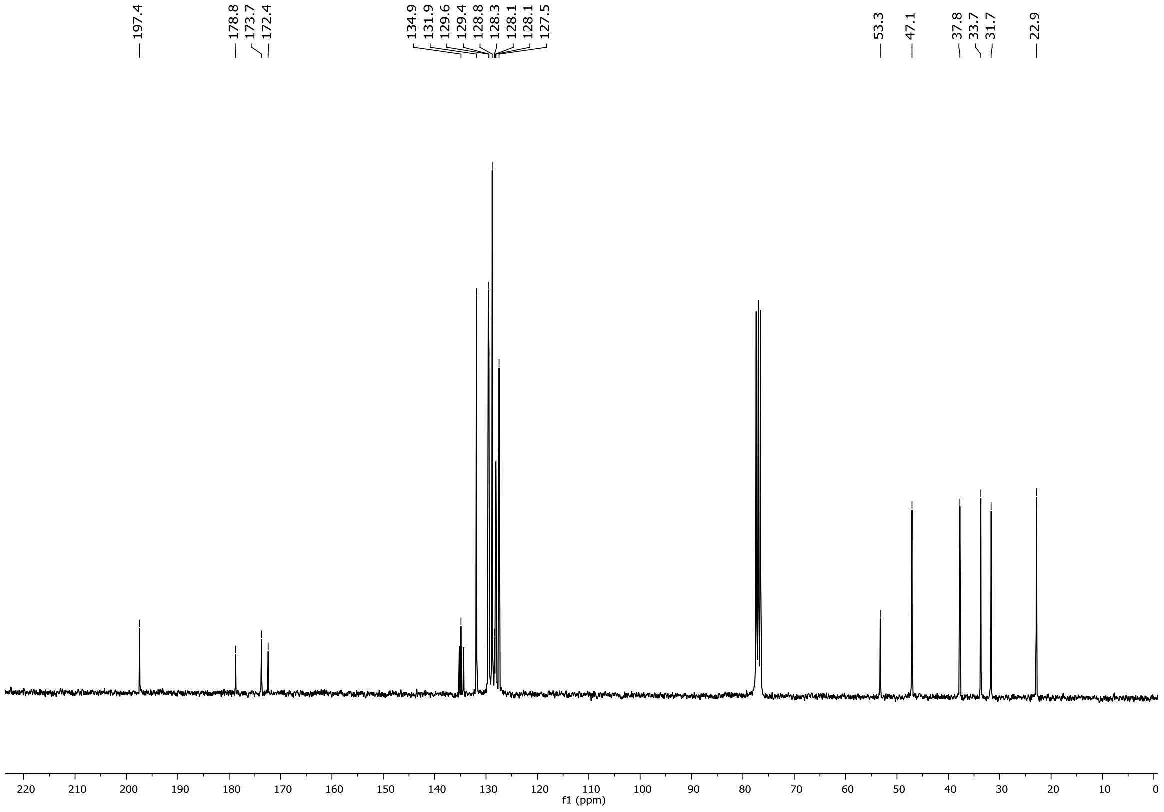
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.30
7.30
5.18
5.12
5.10
5.05
4.49
3.01
3.00
2.98
2.97
2.95
2.94
2.92
2.89
2.87
2.86
2.84
2.83
2.81
2.80
2.43
2.42
2.41
2.40
2.40
2.39
2.38
2.37
1.59
BnS
N
N
O
O
O
Me
Br
28
1.80
1.72
8.34
2.00
2.00
2.04
1.98
3.33
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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
f1 (ppm)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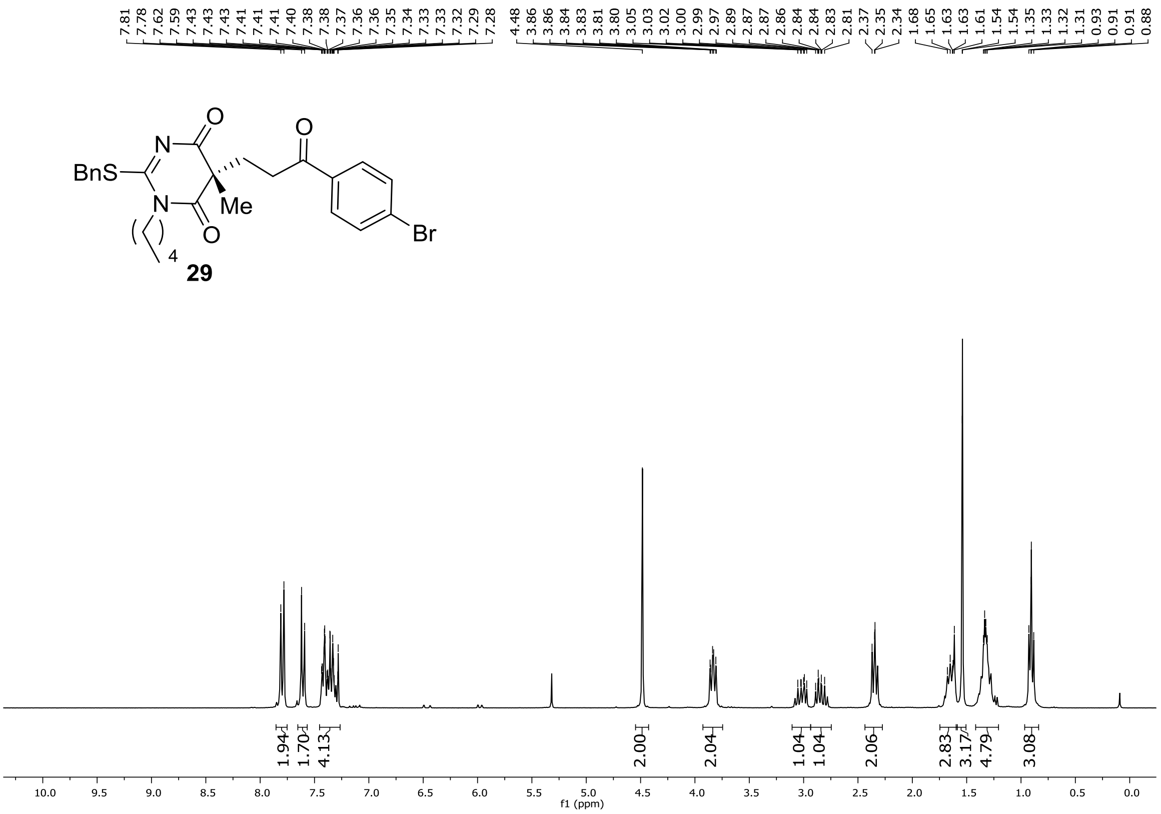
172.4
134.9
131.9
129.6
129.4
128.8
128.3
128.1
128.1
127.5
53.3
47.1
37.8
33.7
31.7
22.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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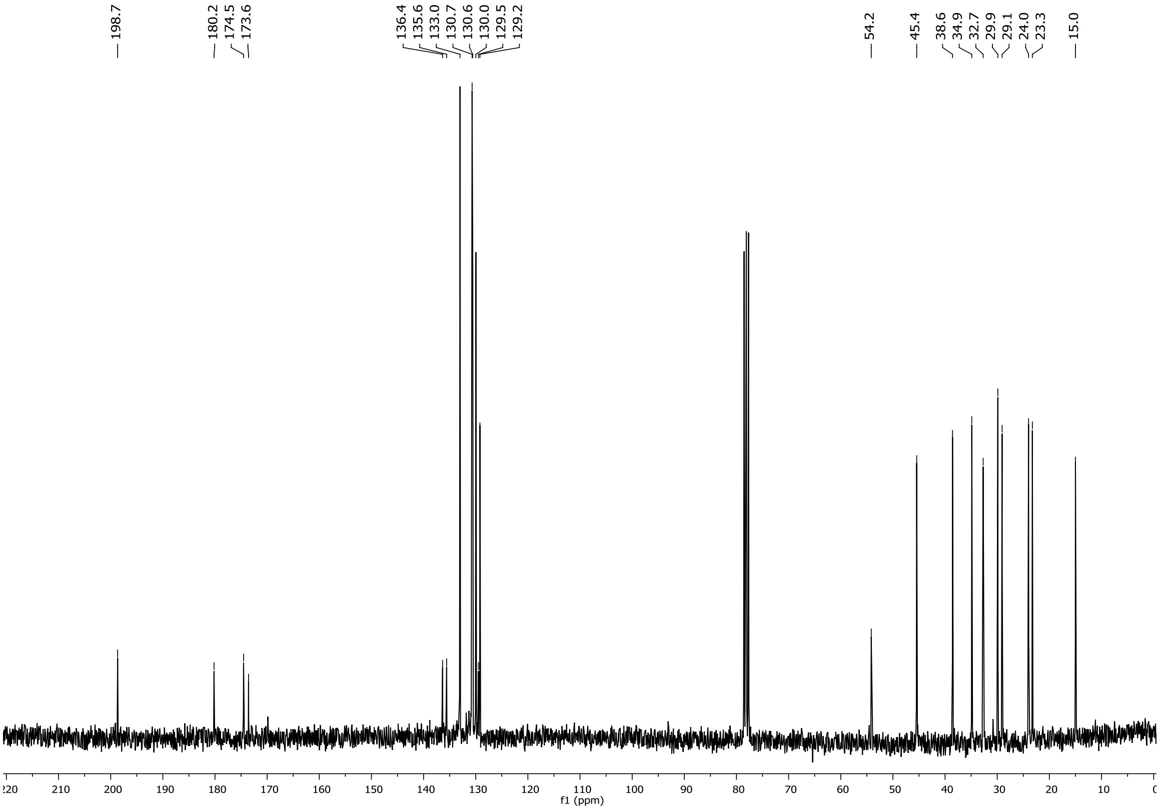
7.43
7.43
7.41
7.41
7.40
7.38
7.38
7.37
7.36
7.36
7.35
7.34
7.33
7.33
7.32
7.29
7.28
4.48
3.86
3.86
3.84
3.83
3.81
3.80
3.05
3.03
3.02
3.00
2.99
2.97
2.89
2.87
2.87
2.86
2.84
2.84
2.83
2.81
2.37
2.35
2.34
1.68
1.65
1.63
1.63
1.61
1.54
1.54
1.35
1.33
1.32
1.31
0.93
0.91
0.91
0.88
BnS
N
N
O
O
O
Me
Br
4
29
1.94
1.70
4.13
2.00
2.04
1.04
1.04
2.06
2.83
3.17
4.79
3.08
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
f1 (ppm)


198.7
180.2
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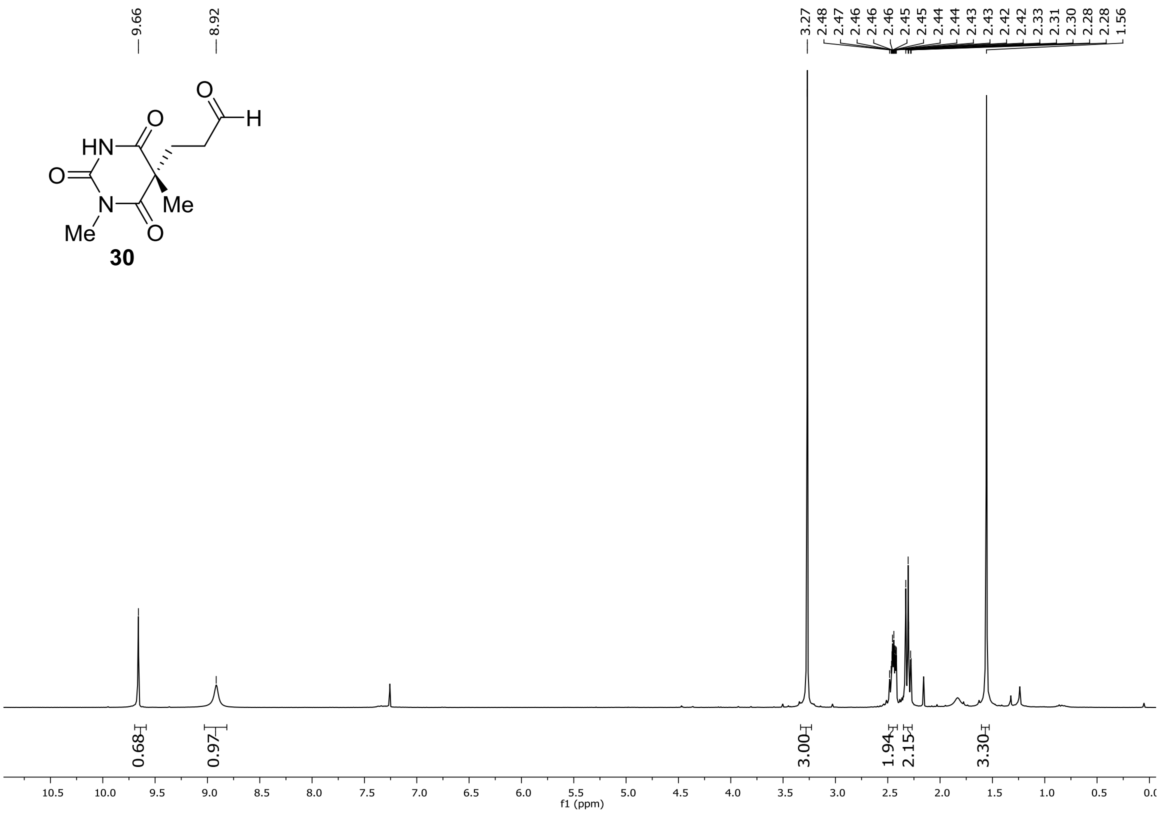
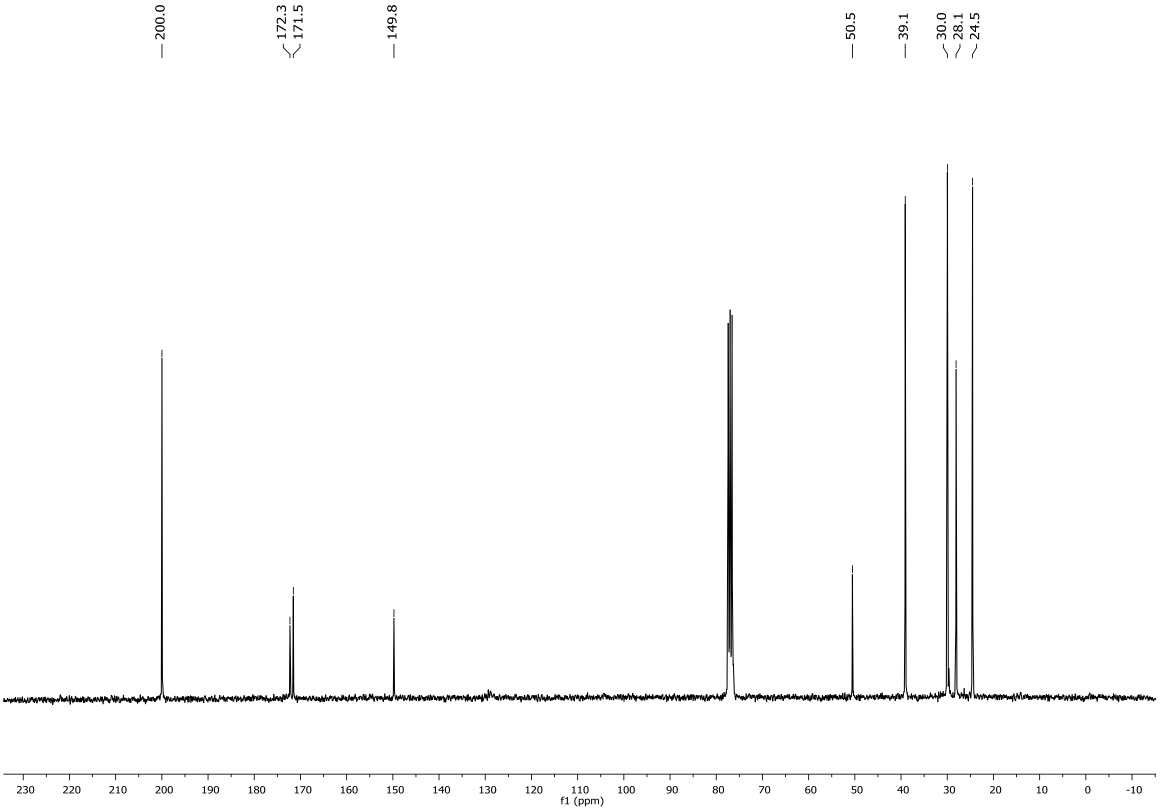
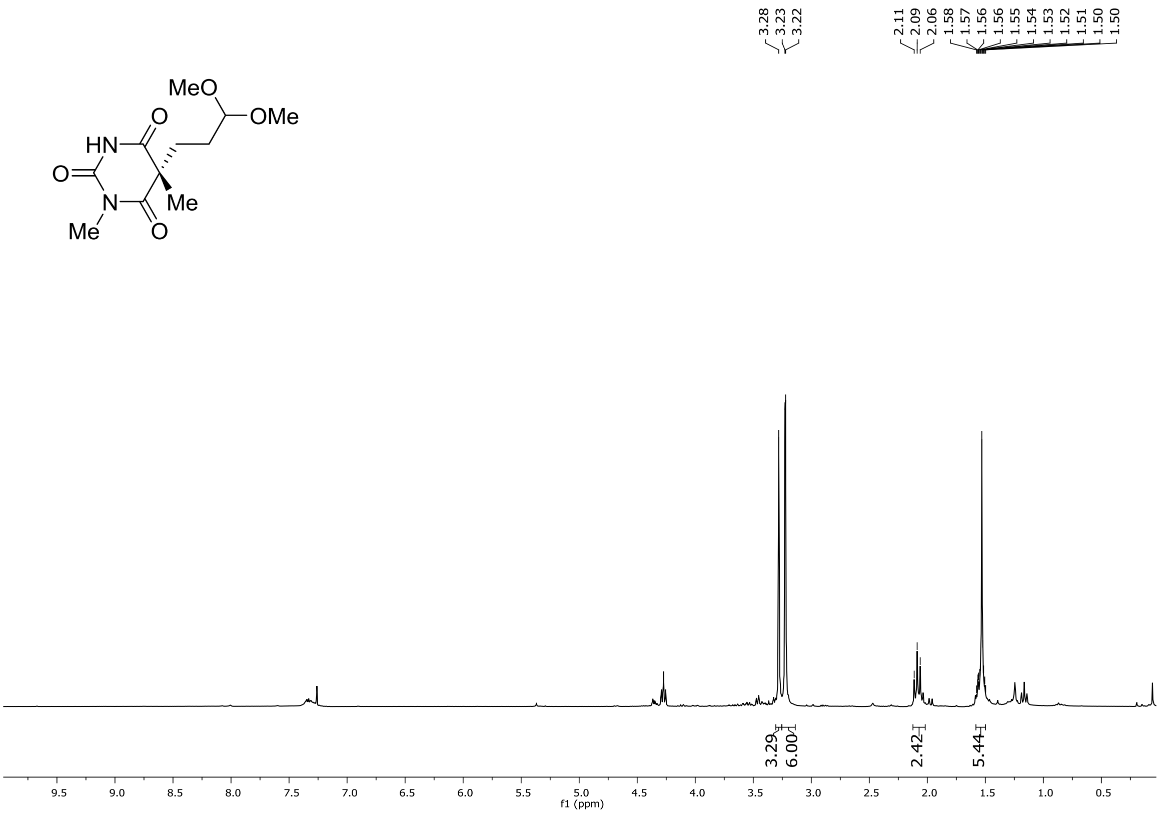
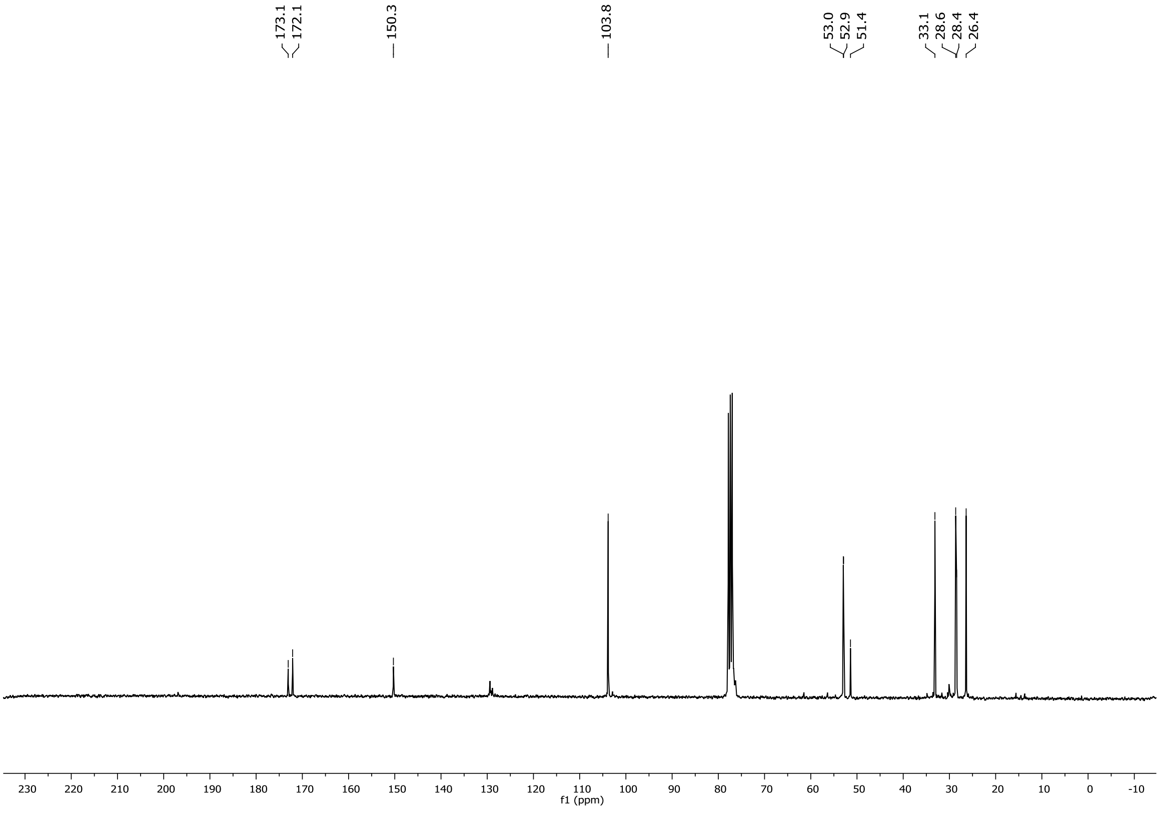
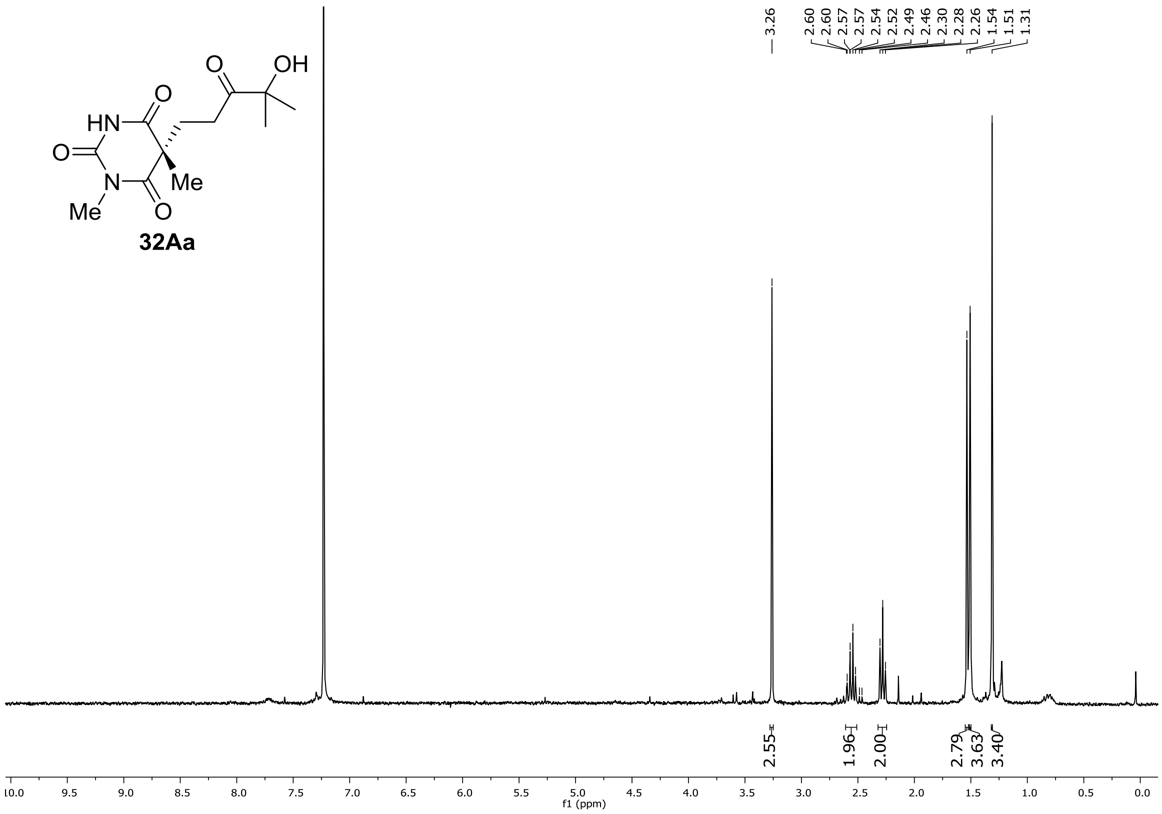
173.6
136.4
135.6
133.0
130.7
130.6
130.0
129.5
129.2
54.2
45.4
38.6
34.9
32.7
29.9
29.1
24.0
23.3
15.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


30
9.66
8.92
3.27
2.48
2.47
2.46
2.46
2.46
2.45
2.45
2.44
2.44
2.43
2.43
2.42
2.42
2.33
2.31
2.30
2.28
2.28
1.56
0.68
0.97
3.00
1.94
2.15
3.30
f1 (ppm)


200.0
172.3
171.5
149.8
50.5
39.1
30.0
28.1
24.5
f1 (ppm)


MeO
OMe
HN
O
O
N
Me
Me
O
3.28
3.23
3.22
2.11
2.09
2.06
1.58
1.57
1.56
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.50
3.29
6.00
2.42
5.44
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
f1 (ppm)


173.1
172.1
150.3
103.8
53.0
52.9
51.4
33.1
28.6
28.4
26.4
230
220
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)


32Aa
HN
O
O
OH
O
N
Me
Me
O
3.26
2.60
2.60
2.57
2.57
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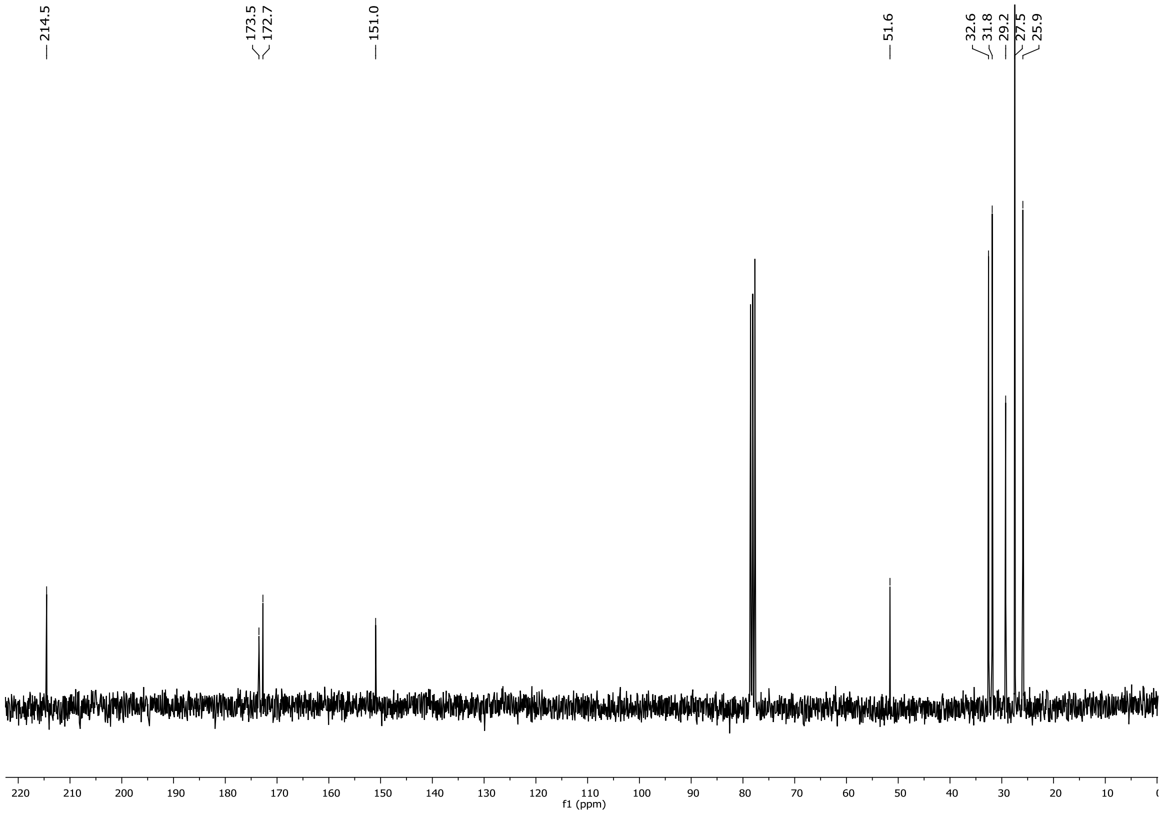
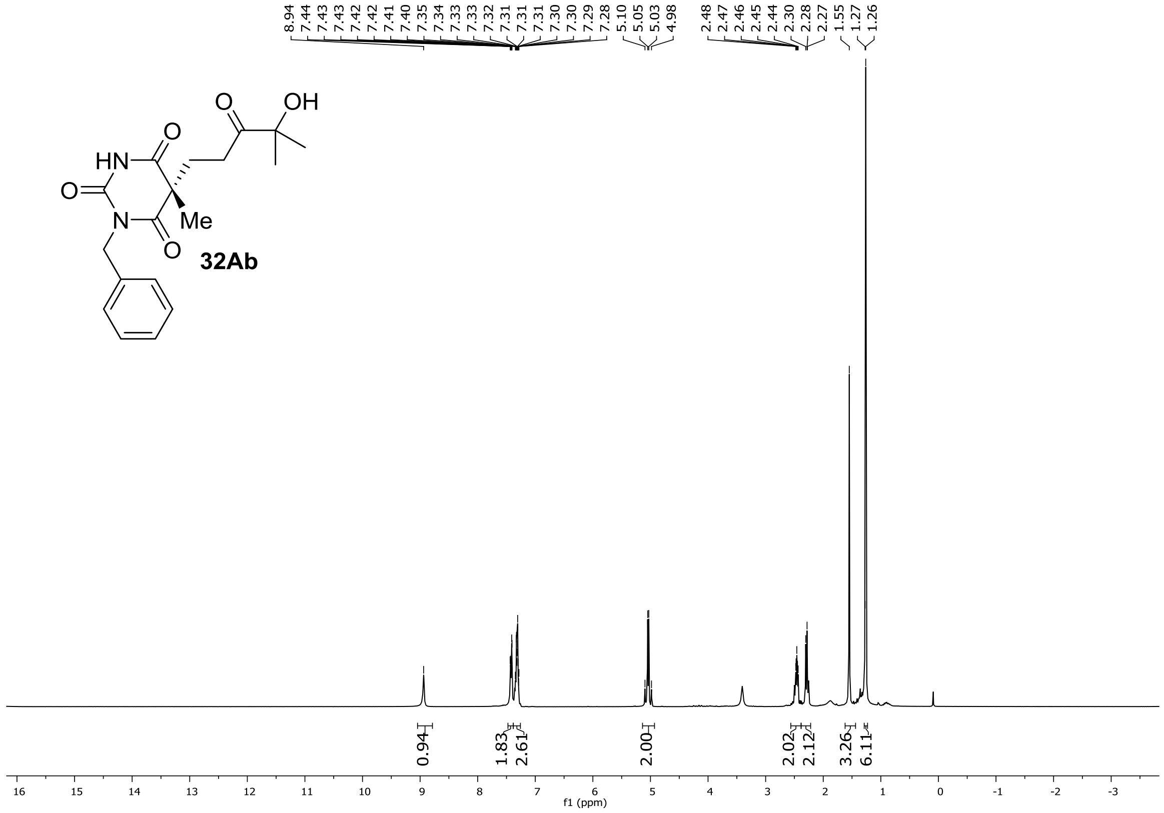
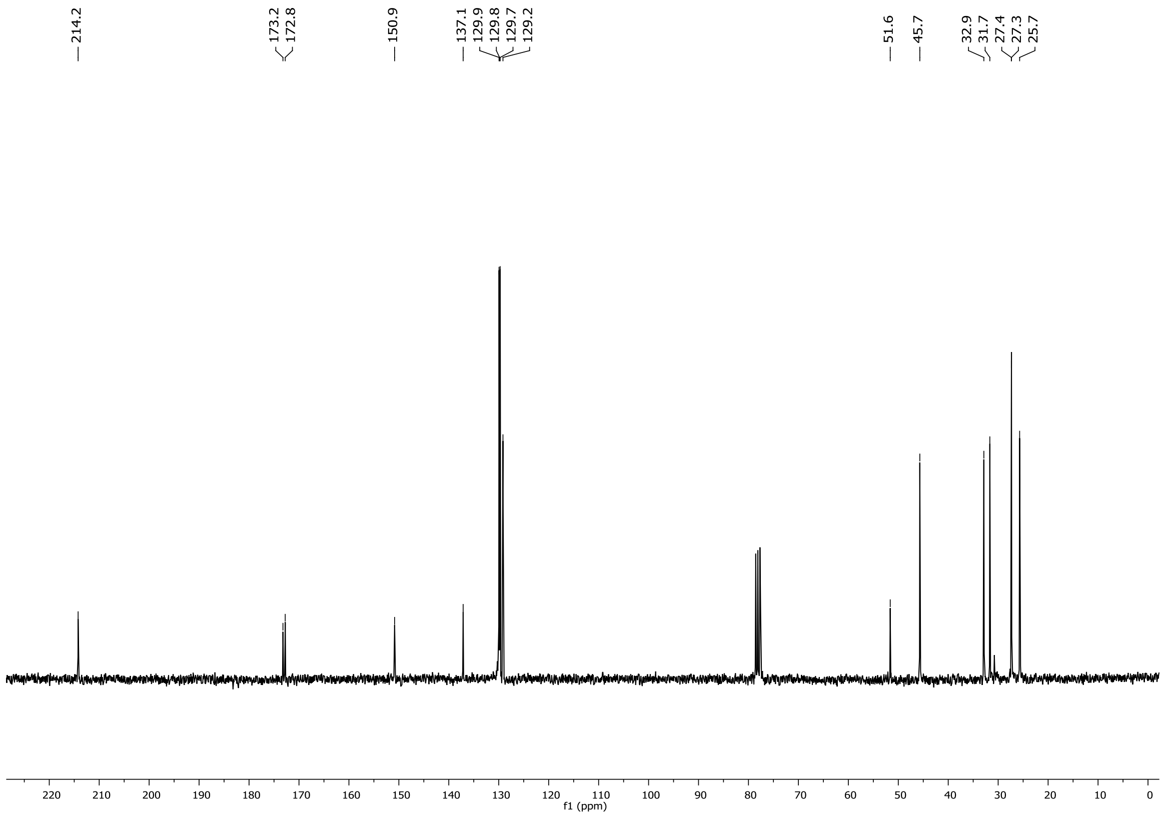
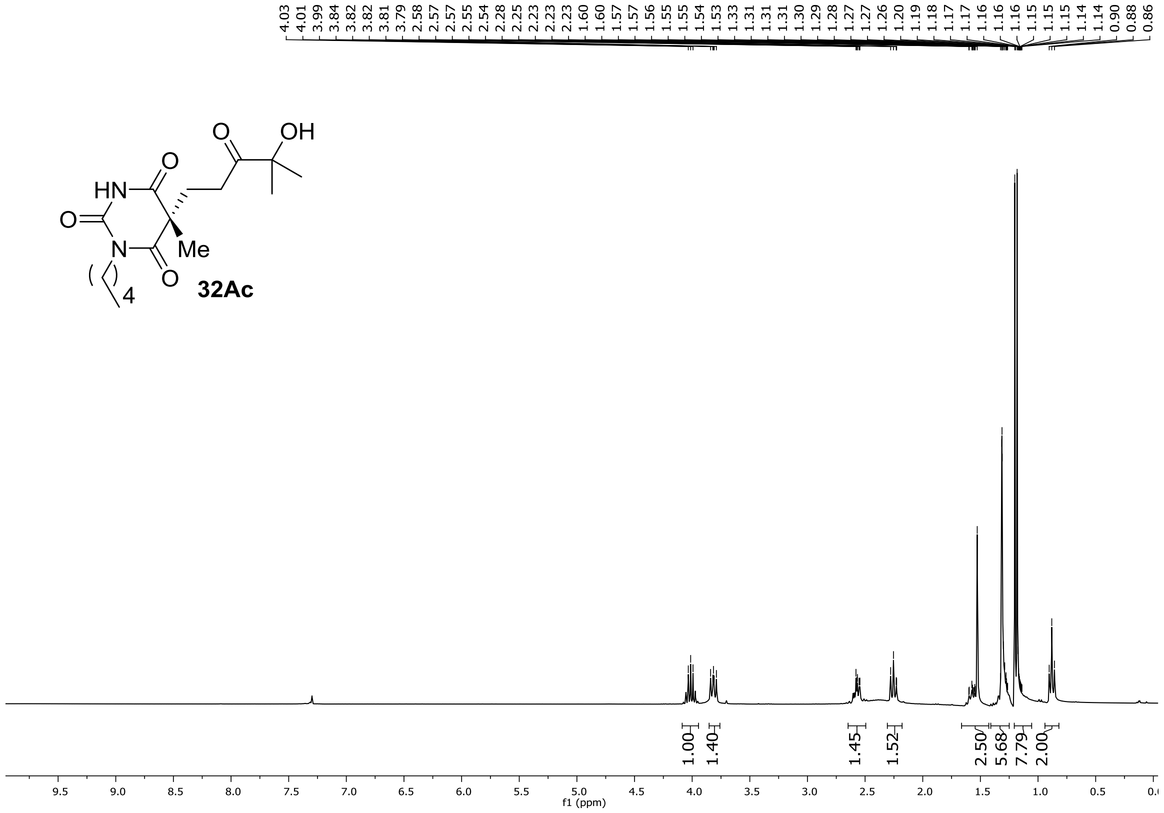
2.52
2.49
2.46
2.30
2.28
2.26
1.54
1.51
1.31
2.55
1.96
2.00
2.79
3.63
3.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


214.5
173.5
172.7
151.0
51.6
32.6
31.8
29.2
27.5
25.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.94 7.44 7.43 7.43 7.42 7.42 7.41 7.40 7.35 7.34 7.33 7.33 7.32 7.31 7.31 7.31 7.30 7.30 7.29 7.28 5.10 5.05 5.03 4.98 2.48 2.47 2.46 2.45 2.44 2.30 2.28 2.27 1.55 1.27 1.26
O
OH
HN
O
O
N
Me
O
32Ab
0.94
1.83
2.61
2.00
2.02
2.12
3.26
6.11
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


214.2
173.2 172.8
150.9
137.1 129.9 129.8 129.7 129.2
51.6
45.7
32.9 31.7 27.4 27.3 25.7
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


4.03
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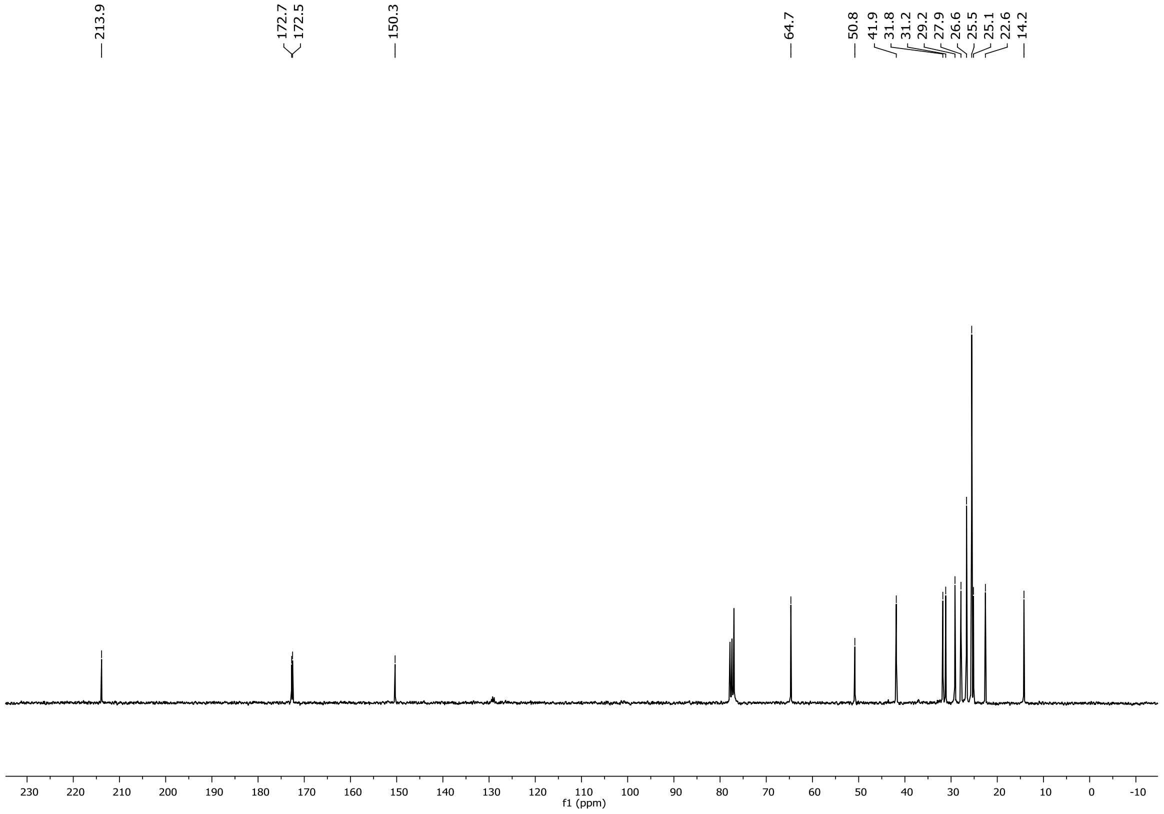
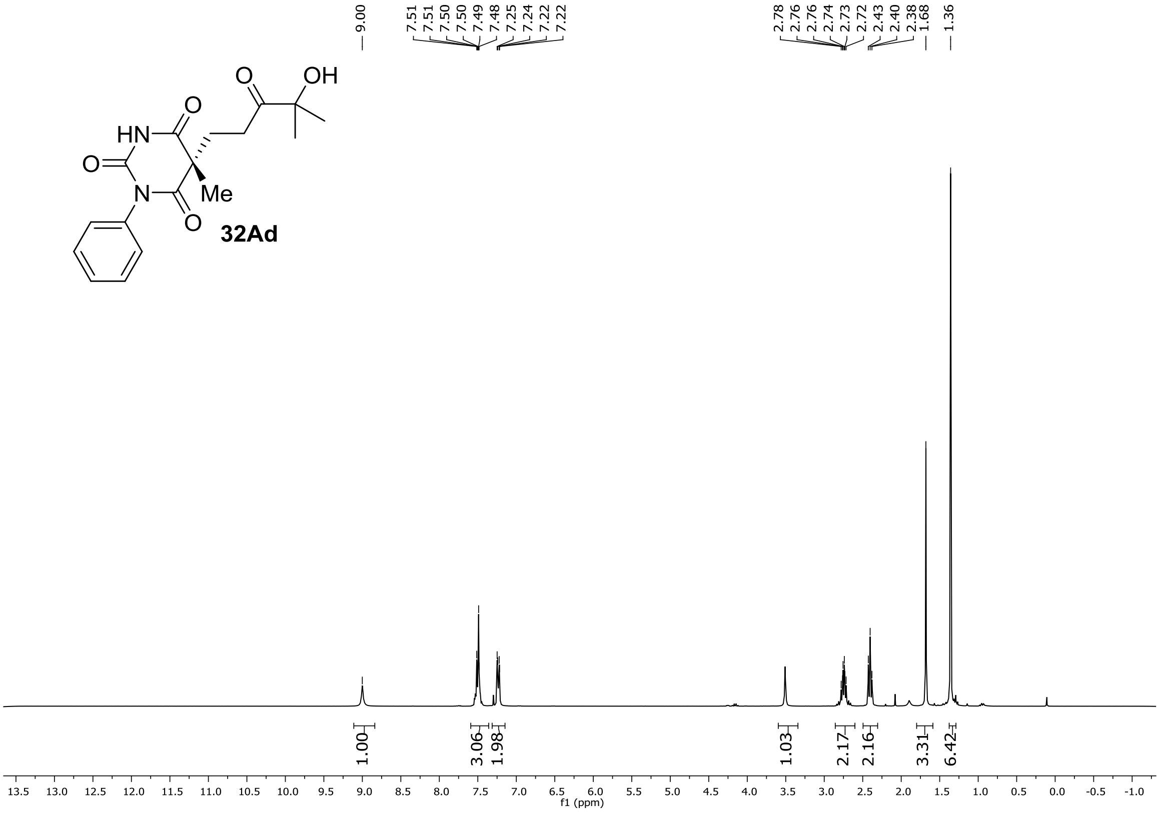
3.82
3.81
3.79
2.58
2.57
2.57
2.55
2.54
2.28
2.25
2.23
2.23
2.23
1.60
1.60
1.57
1.57
1.56
1.55
1.55
1.54
1.53
1.33
1.31
1.31
1.31
1.30
1.29
1.28
1.27
1.27
1.26
1.20
1.19
1.18
1.17
1.17
1.16
1.16
1.16
1.15
1.15
1.15
1.14
1.14
0.90
0.88
0.86
O
OH
O
HN
O
N
Me
O
4
1.00
1.40
1.45
1.52
2.50
5.68
7.79
2.00
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
f1 (ppm)

32Ac


213.9
172.7
172.5
150.3
64.7
50.8
41.9
31.8
31.2
29.2
27.9
26.6
25.5
25.1
22.6
14.2
230
220
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)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OH
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HN
O
N
Me
O
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7.51
7.51
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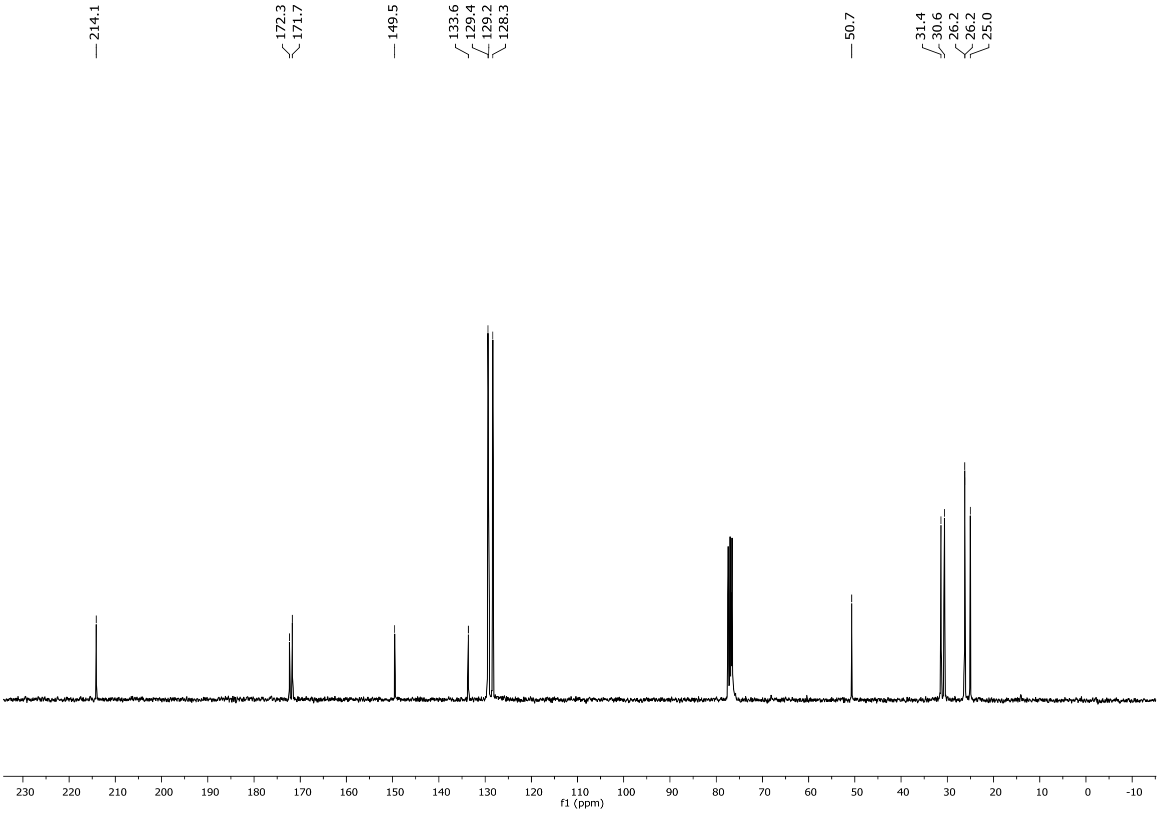
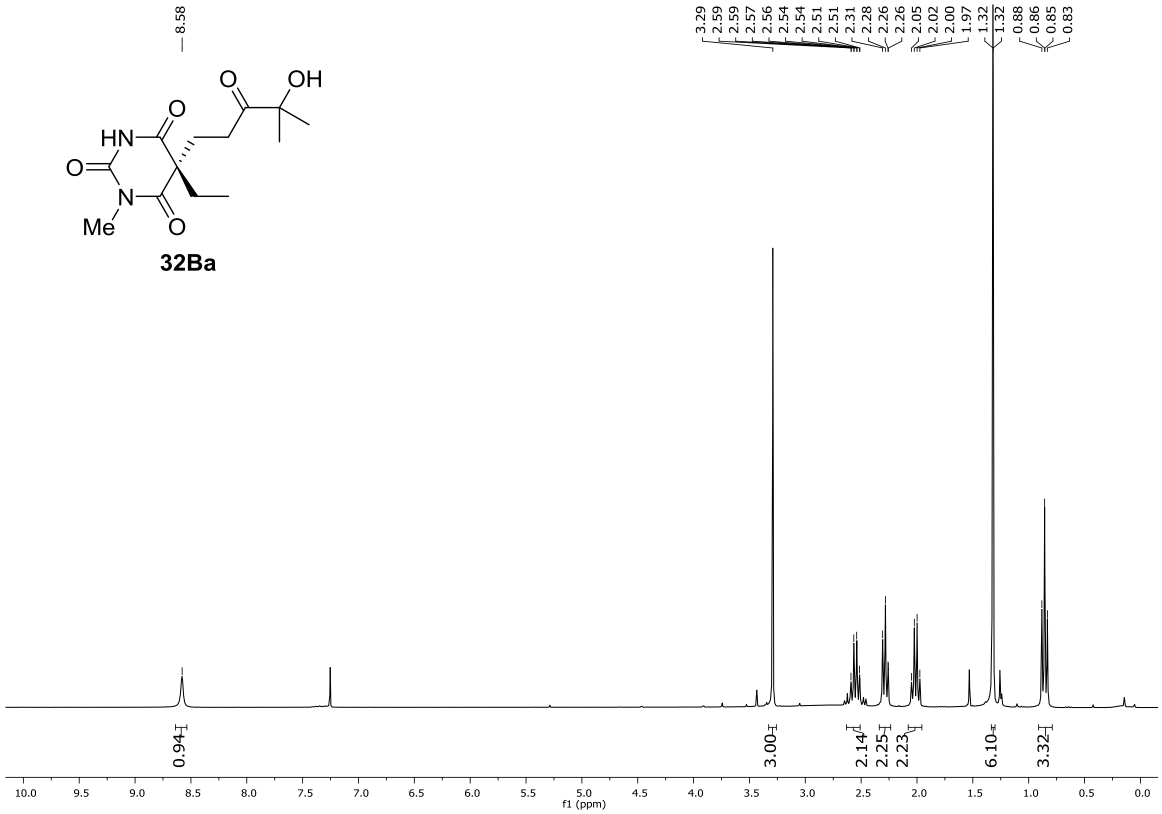
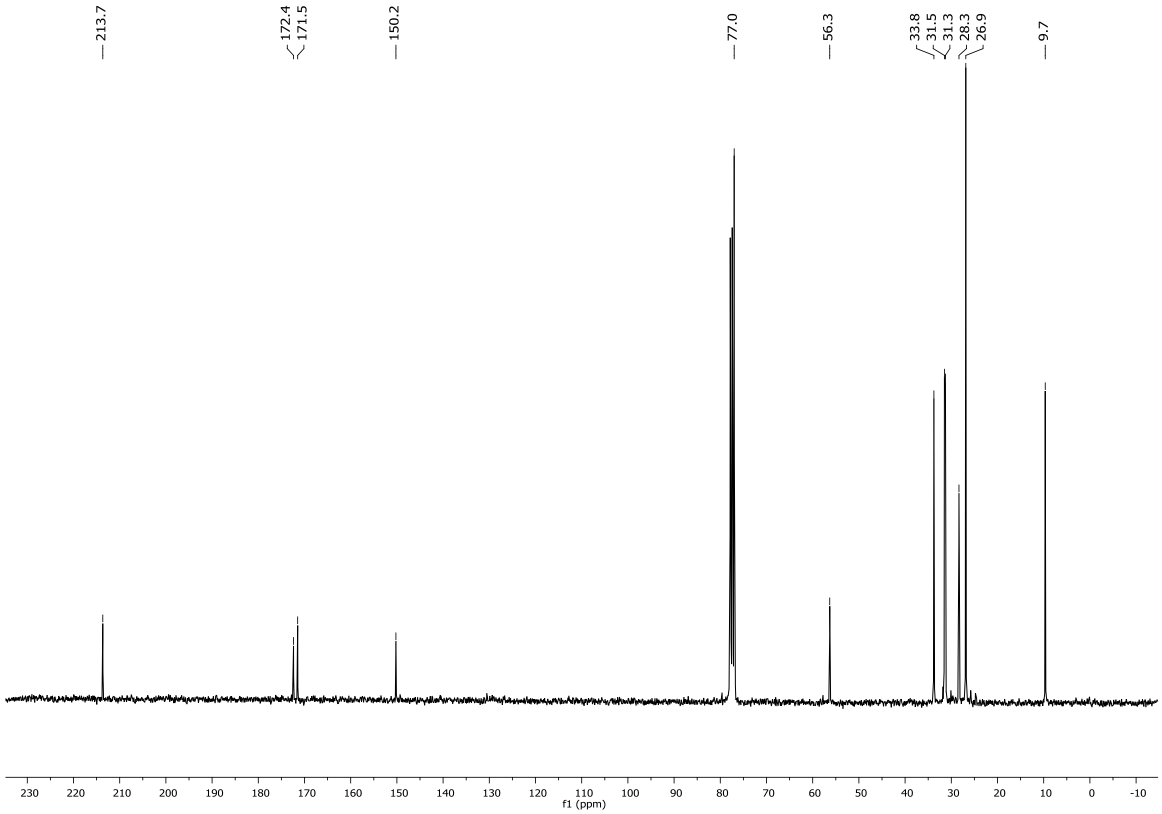
7.50
7.49
7.48
7.25
7.24
7.22
7.22
2.78
2.76
2.76
2.74
2.73
2.72
2.43
2.40
2.38
1.68
1.36
1.00
3.06
1.98
1.03
2.17
2.16
3.31
6.42
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


214.1
172.3
171.7
149.5
133.6
129.4
129.2
128.3
50.7
31.4
30.6
26.2
26.2
25.0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OH
O
HN
O
N
Me
O

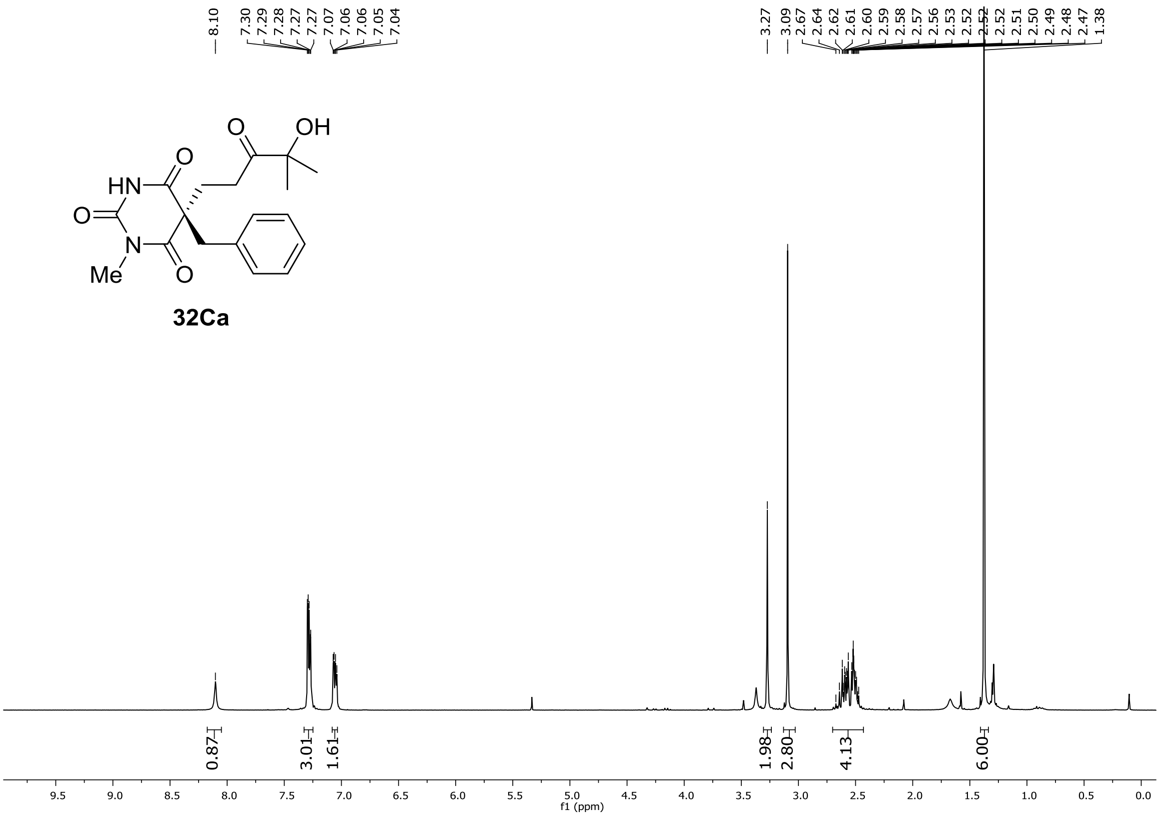
32Ba

8.58
3.29
2.59
2.59
2.57
2.56
2.54
2.54
2.51
2.51
2.31
2.28
2.26
2.26
2.05
2.02
2.00
1.97
1.32
1.32
0.88
0.86
0.85
0.83
0.94
3.00
2.14
2.25
2.23
6.10
3.32
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
f1 (ppm)


213.7
172.4
171.5
150.2
77.0
56.3
33.8
31.5
31.3
28.3
26.9
9.7
230
220
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)

O
OH
HN
O
O
N
Me
O

32Ca


8.10
7.30
7.29
7.28
7.27
7.27
7.07
7.06
7.06
7.05
7.04
3.27
3.09
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2.60
2.59
2.58
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2.56
2.53
2.52
2.52
2.52
2.51
2.50
2.49
2.48
2.47
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3.01
1.61
1.98
2.80
4.13
6.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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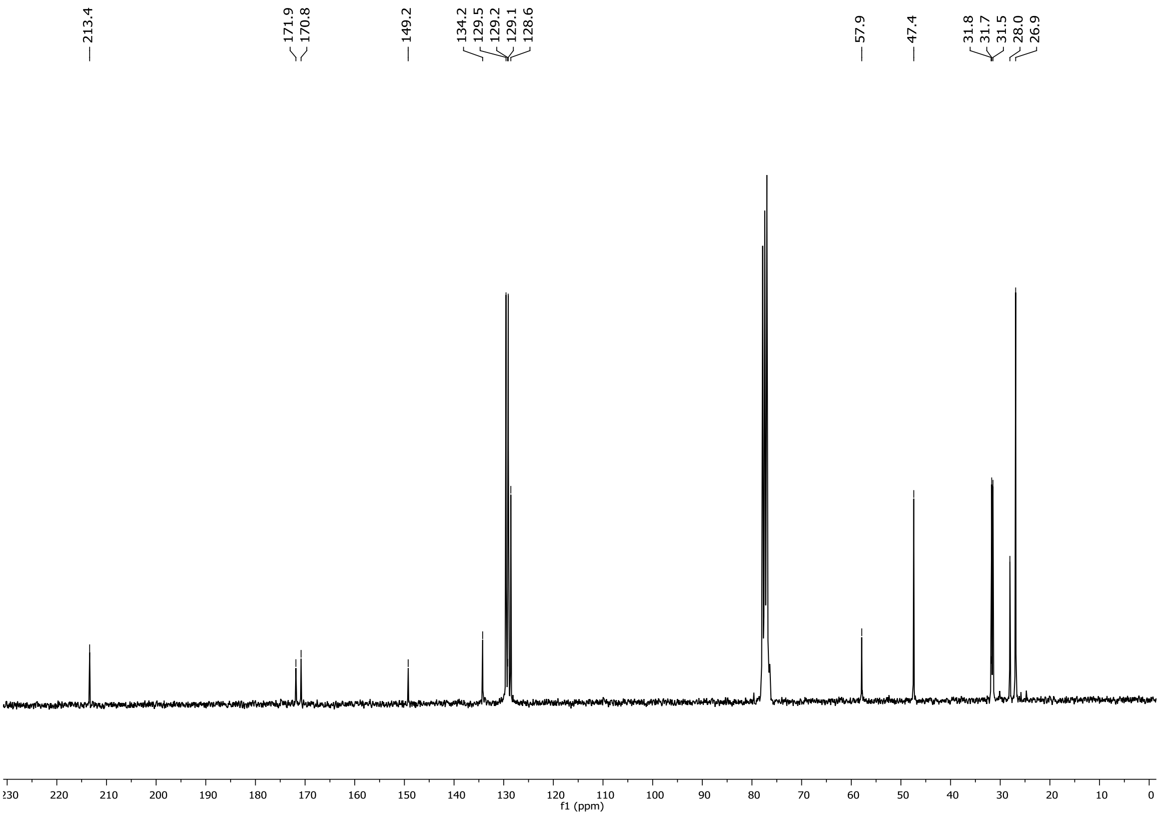
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31.5
28.0
26.9
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220
210
200
190
180
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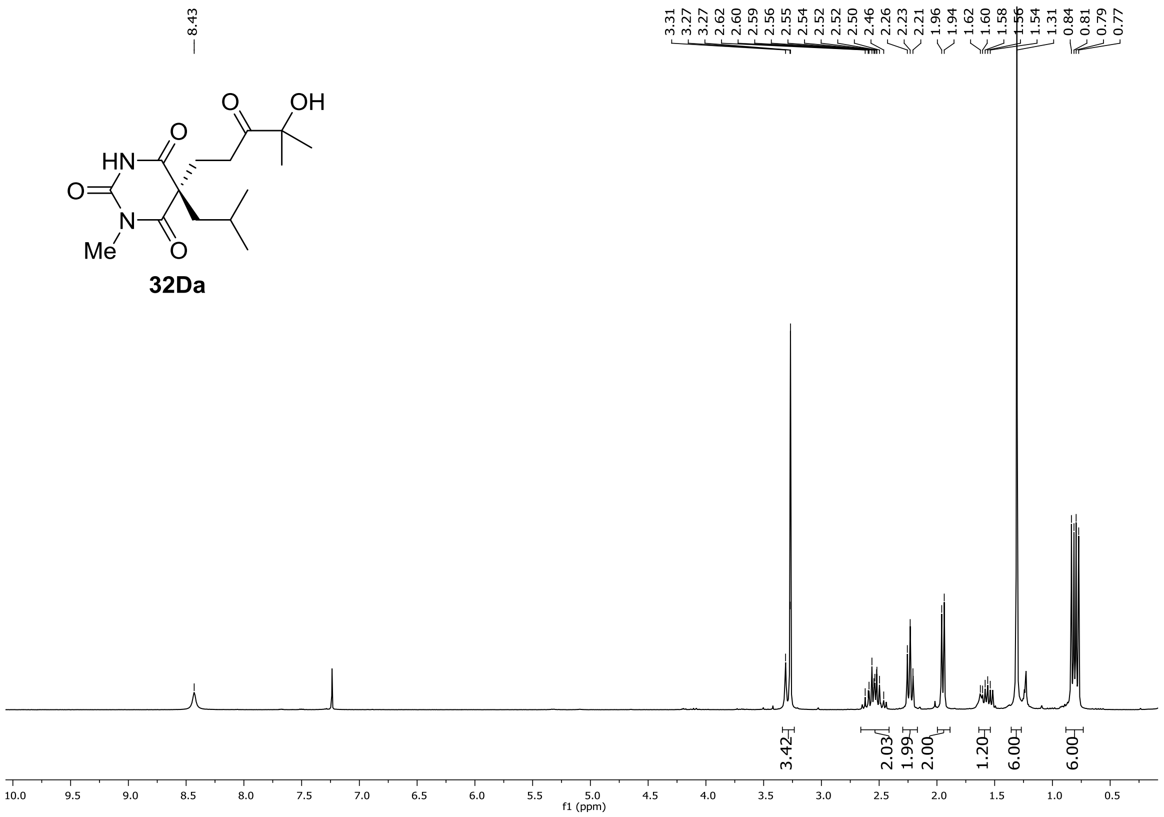
f1 (ppm)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2.26
2.23
2.21
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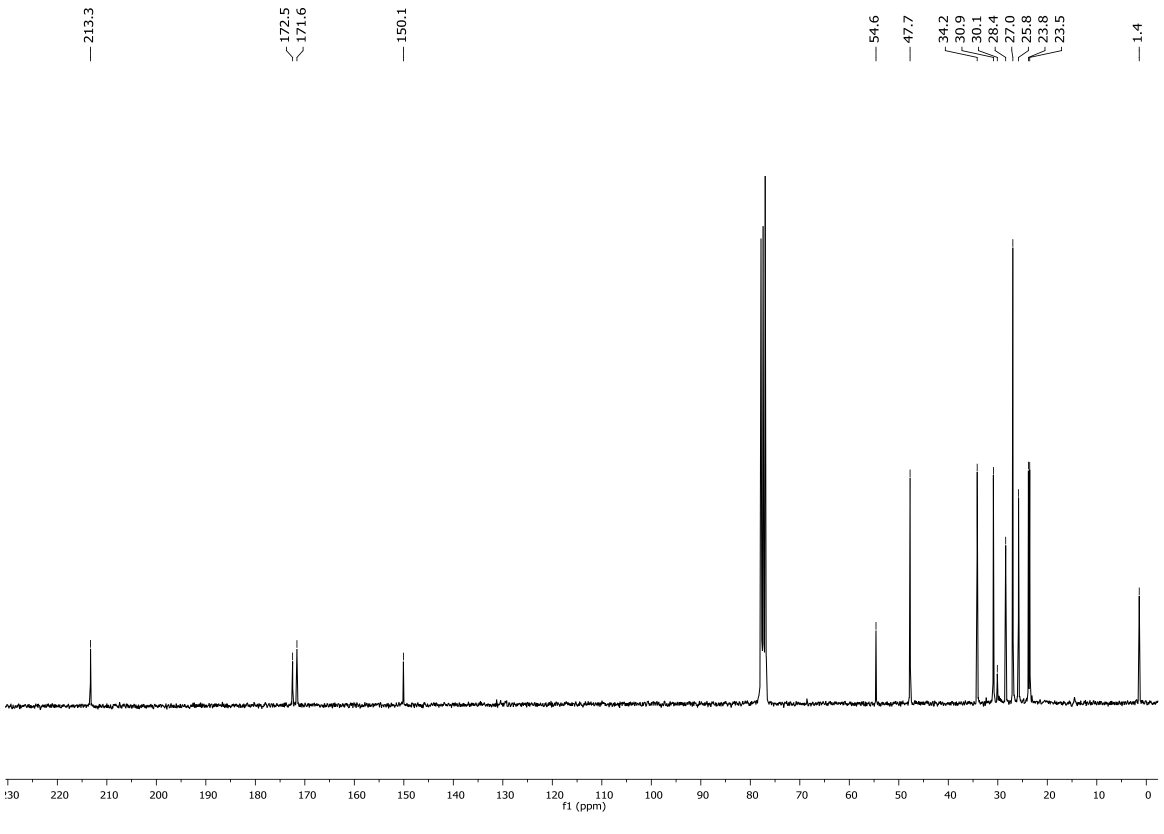
1.94
1.62
1.60
1.58
1.56
1.54
1.31
0.84
0.81
0.79
0.77
3.42
2.03
1.99
2.00
1.20
6.00
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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23.8
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1.4
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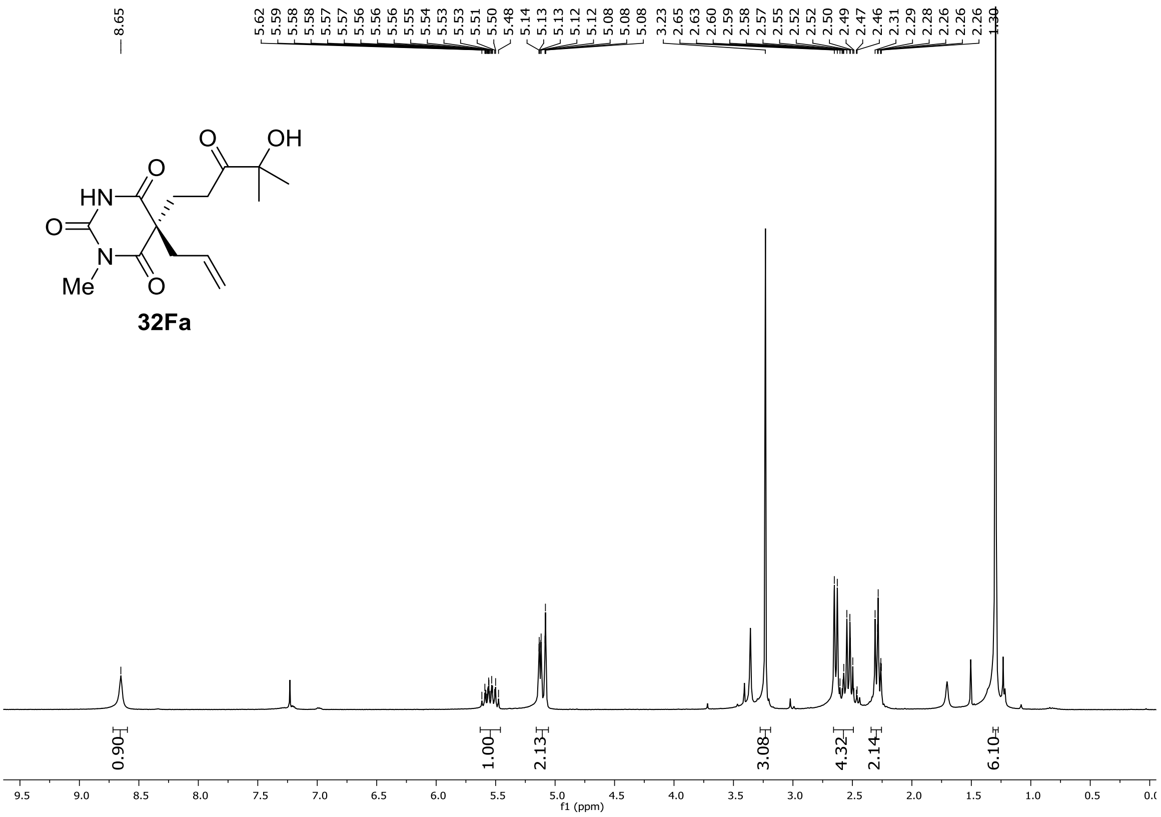
f1 (ppm)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5.08
5.08
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2.29
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2.26
2.26
2.26
1.30
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O
HN
O
N
Me
O
32Fa
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1.00
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3.08
4.32
2.14
6.10
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8.5
8.0
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6.0
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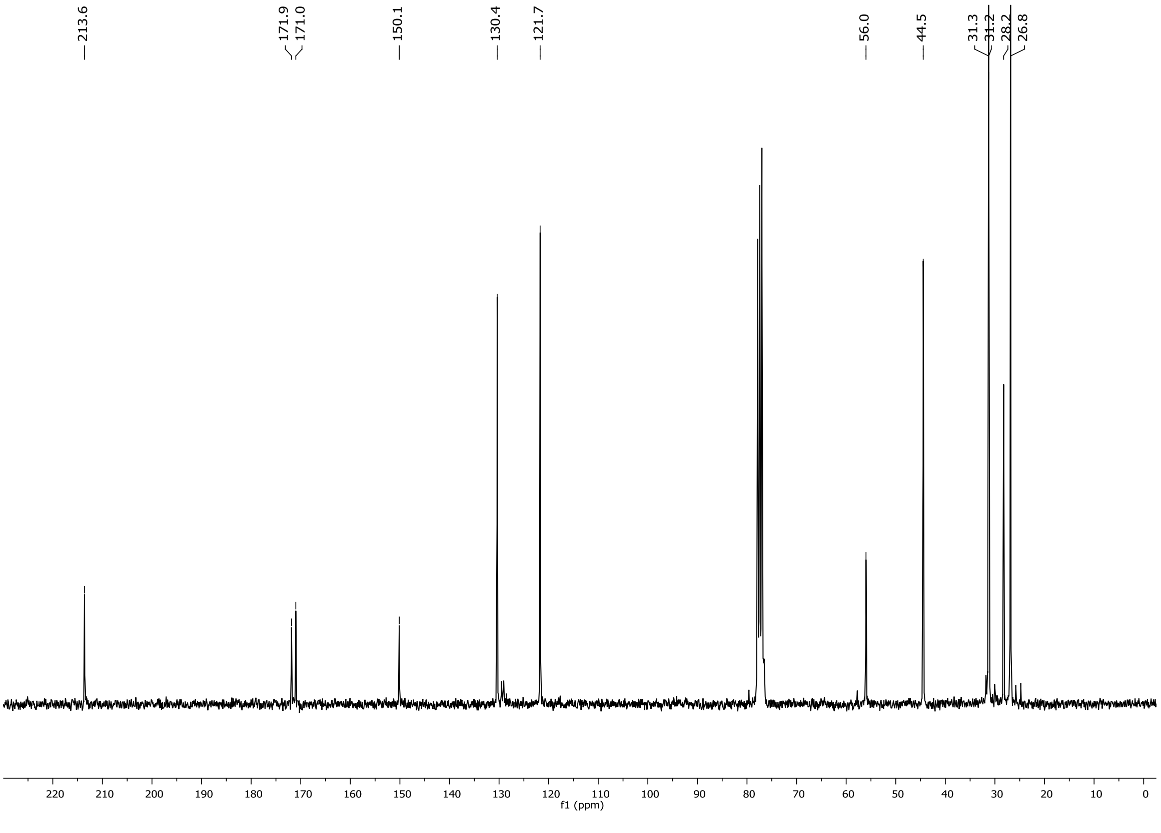
0.0
f1 (ppm)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200
190
180
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90
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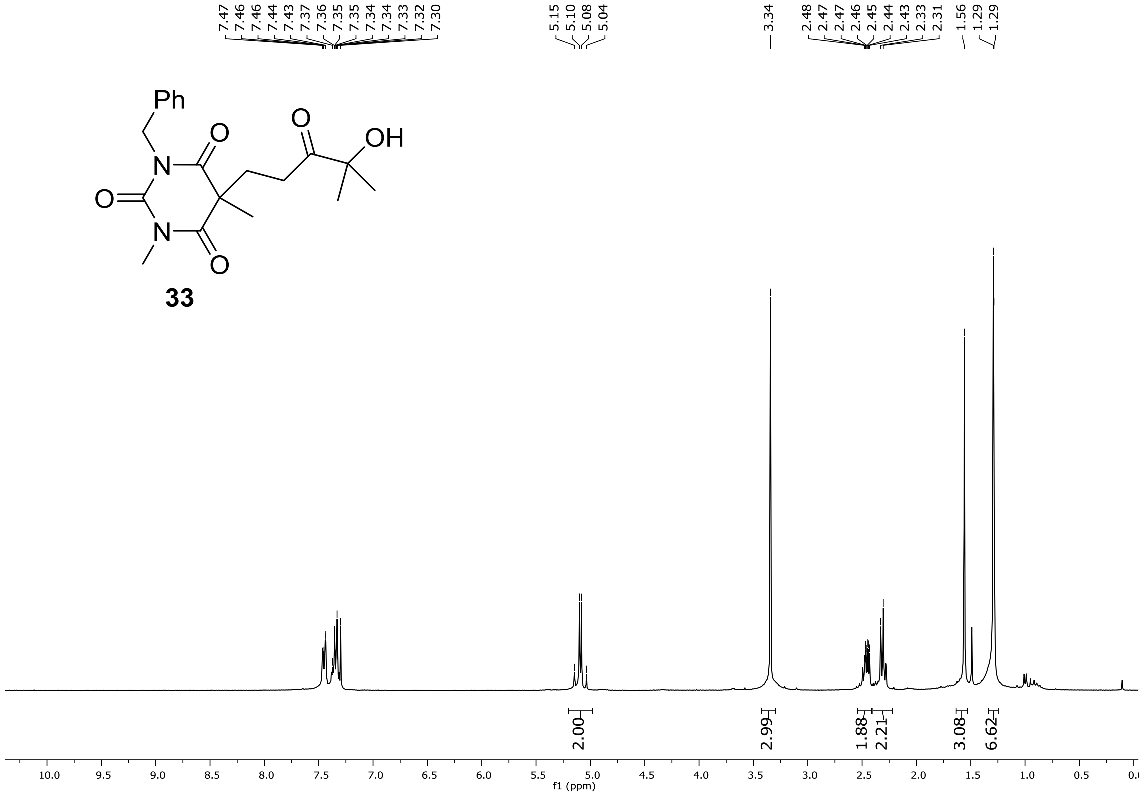
f1 (ppm)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2.31
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1.29
1.29
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O
OH
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O
N
O
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2.99
1.88
2.21
3.08
6.62
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9.0
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
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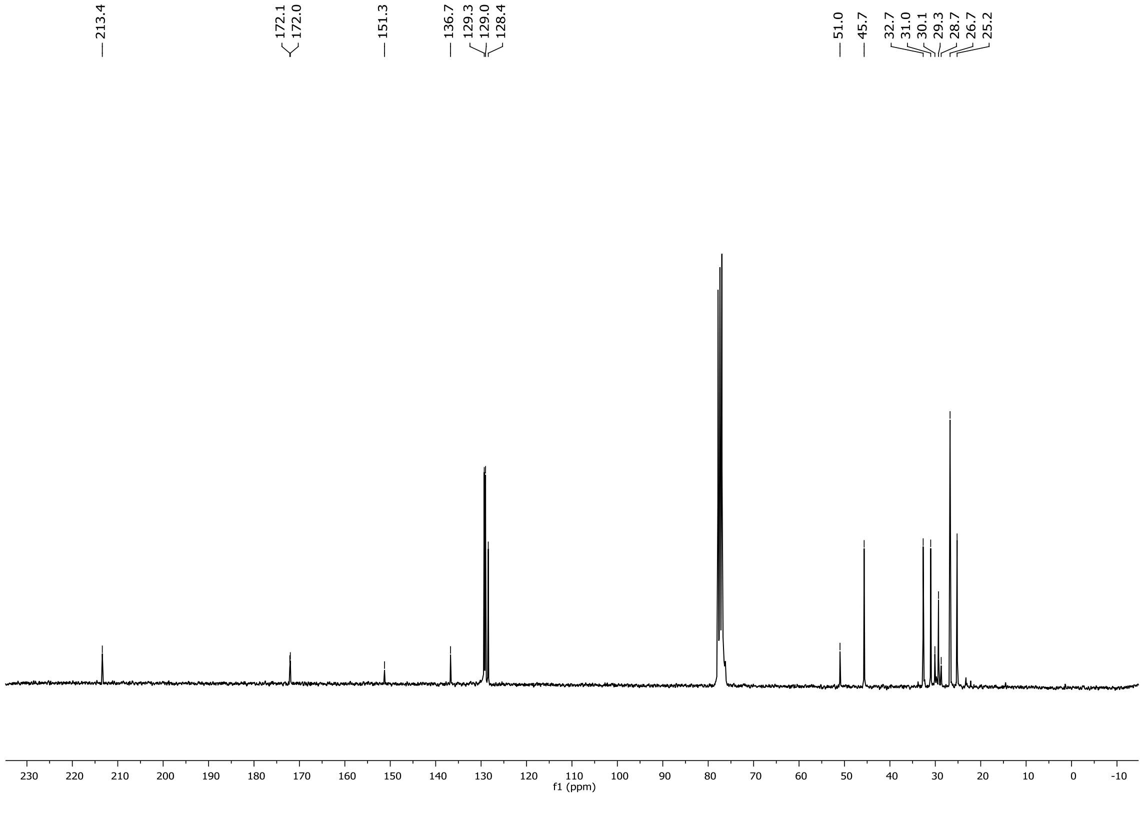
f1 (ppm)

33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29.3
28.7
26.7
25.2
230
220
210
200
190
180
170
160
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140
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120
110
100
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80
70
60
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40
30
20
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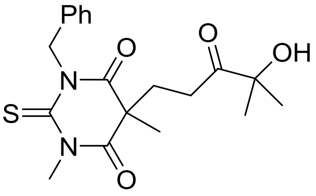
0
-10
f1 (ppm)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S
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O

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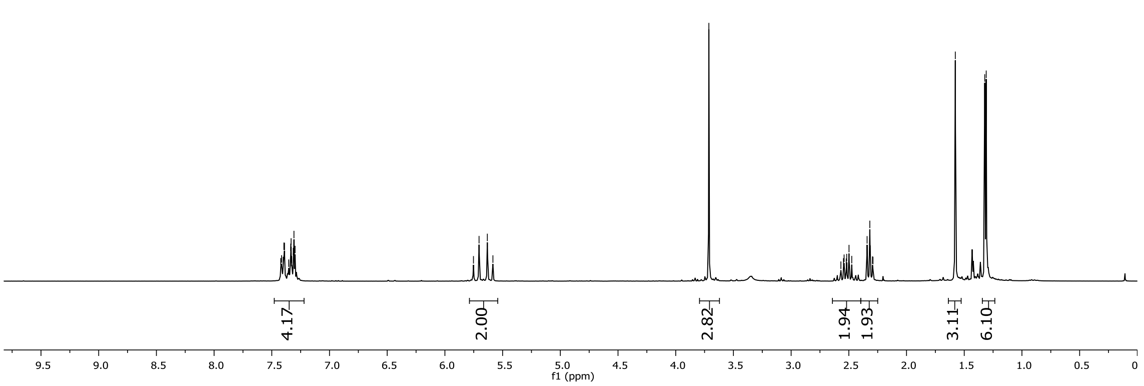
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2.31
2.29
2.29
1.58
1.32
1.31
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1.93
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8.0
7.5
7.0
6.5
6.0
5.5
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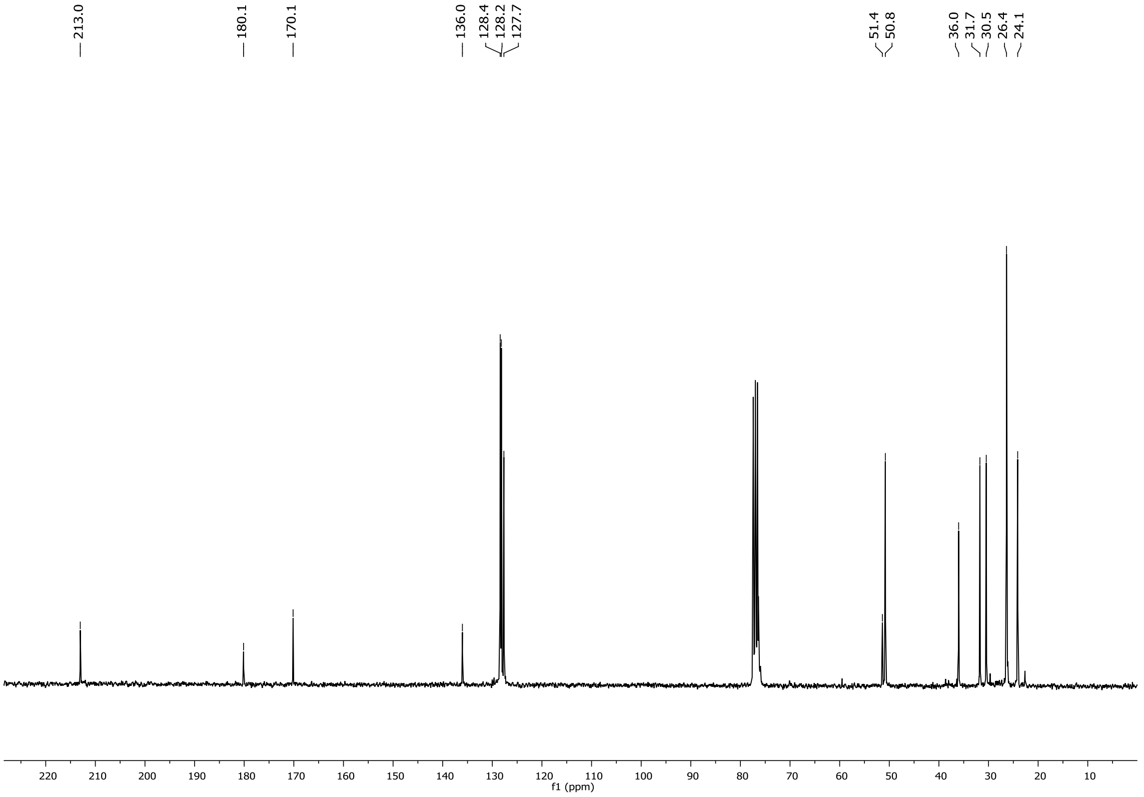
f1 (ppm)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127.7
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36.0
31.7
30.5
26.4
24.1
220
210
200
190
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120
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100
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80
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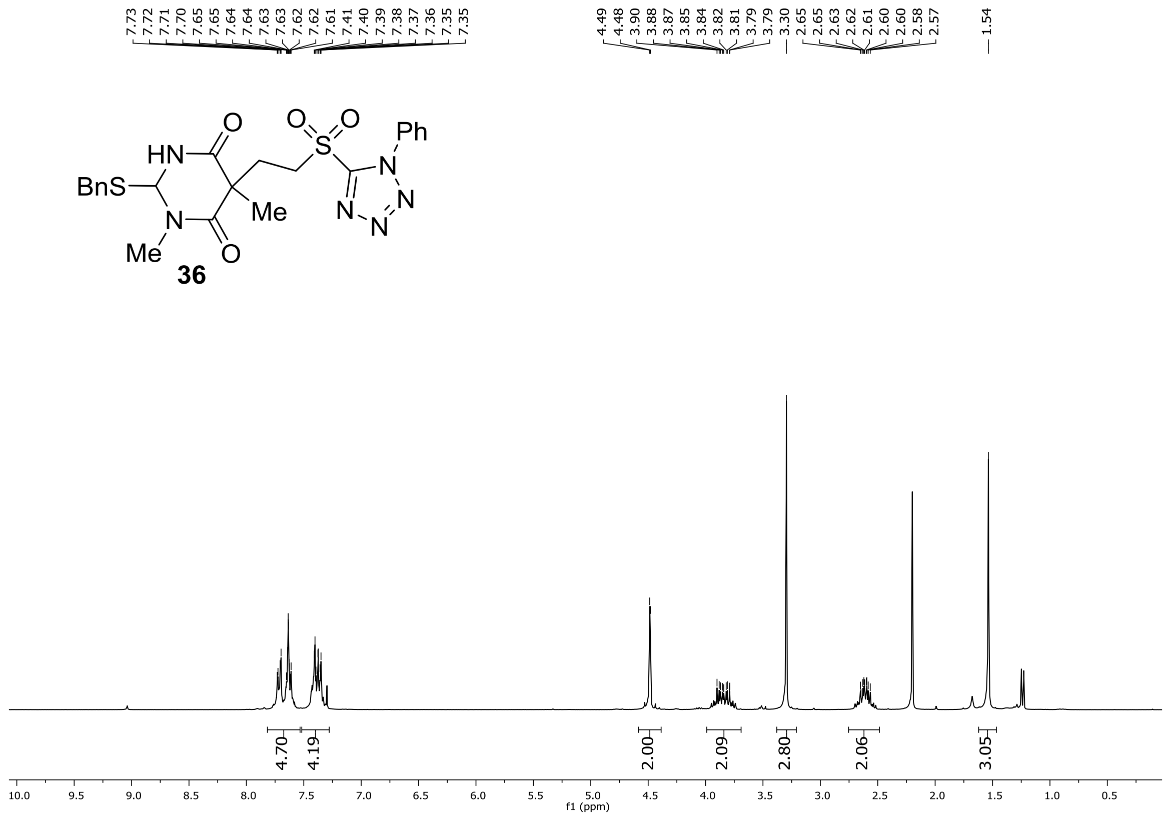
30
20
10
f1 (ppm)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3.82
3.81
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Ph
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BnS
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N
Me
N
Me
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2.06
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6.5
6.0
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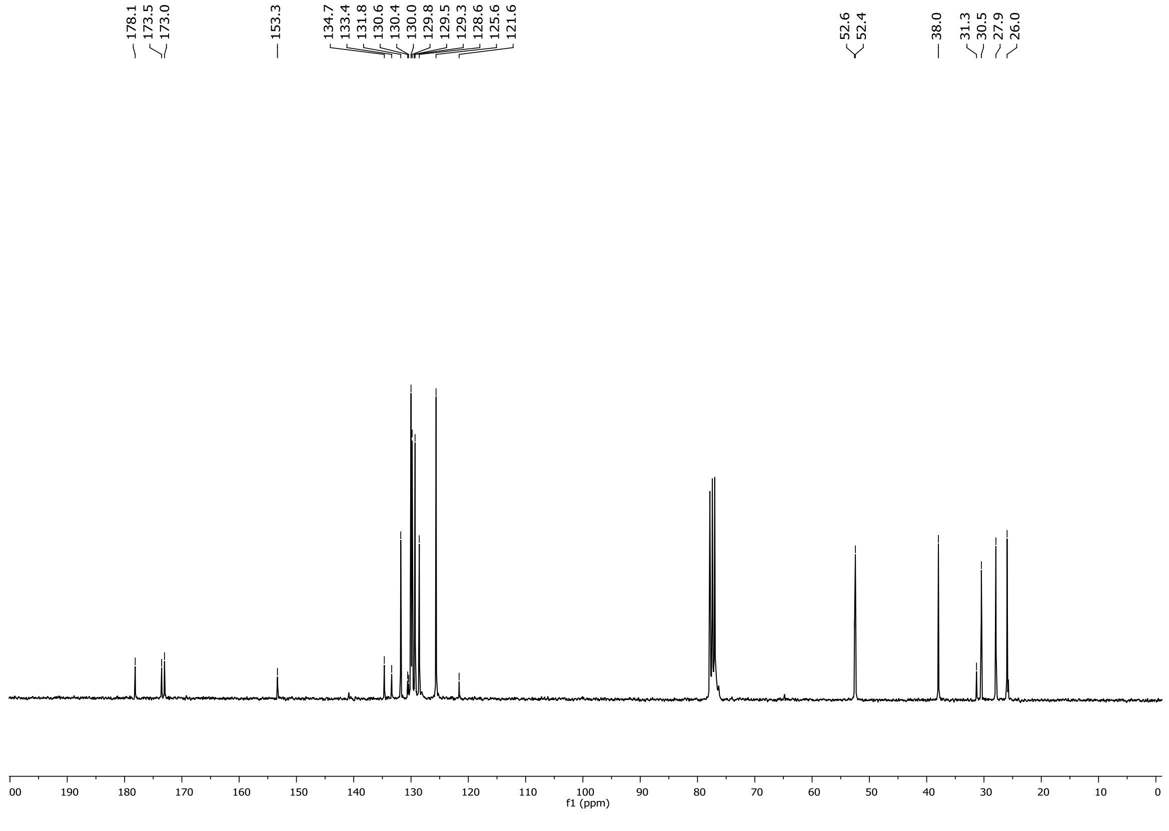
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125.6
121.6
52.6
52.4
38.0
31.3
30.5
27.9
26.0
00
190
180
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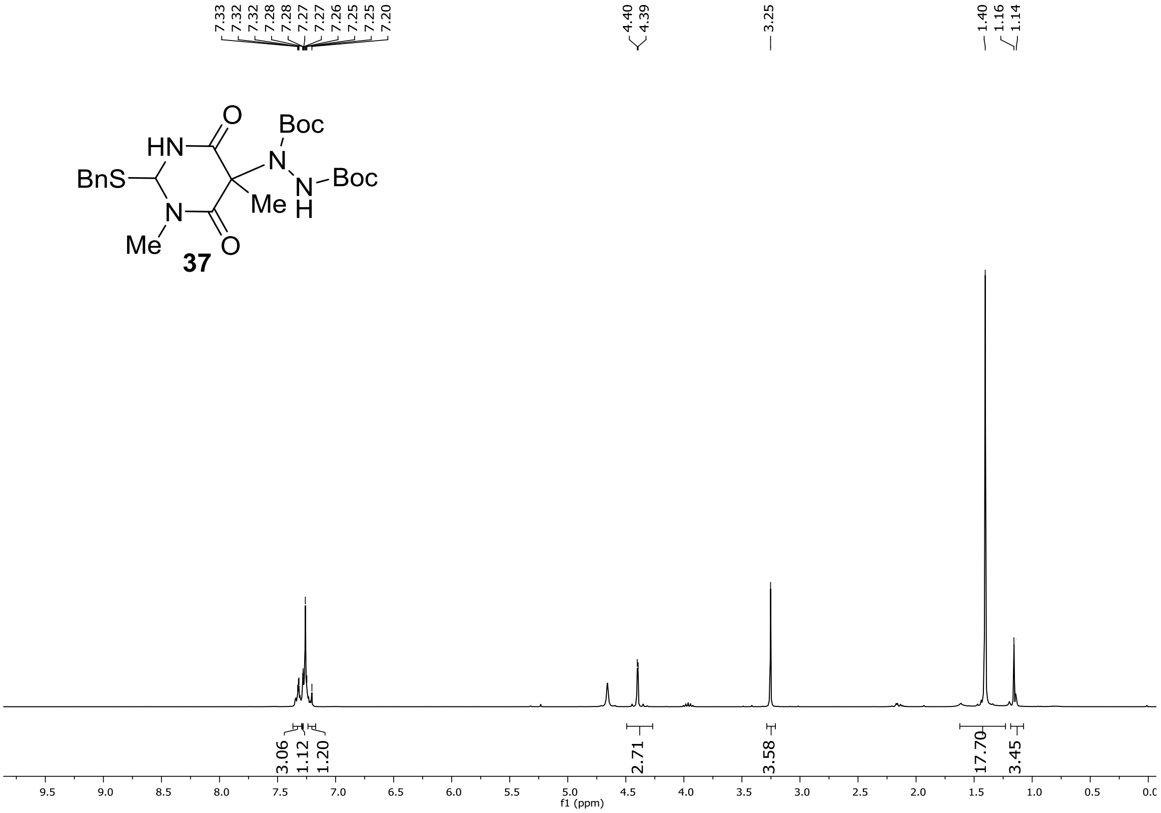
f1 (ppm)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4.39
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1.40
1.16
1.14
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O
Boc
BnS
N
N
N
Boc
Me
H
Me
O
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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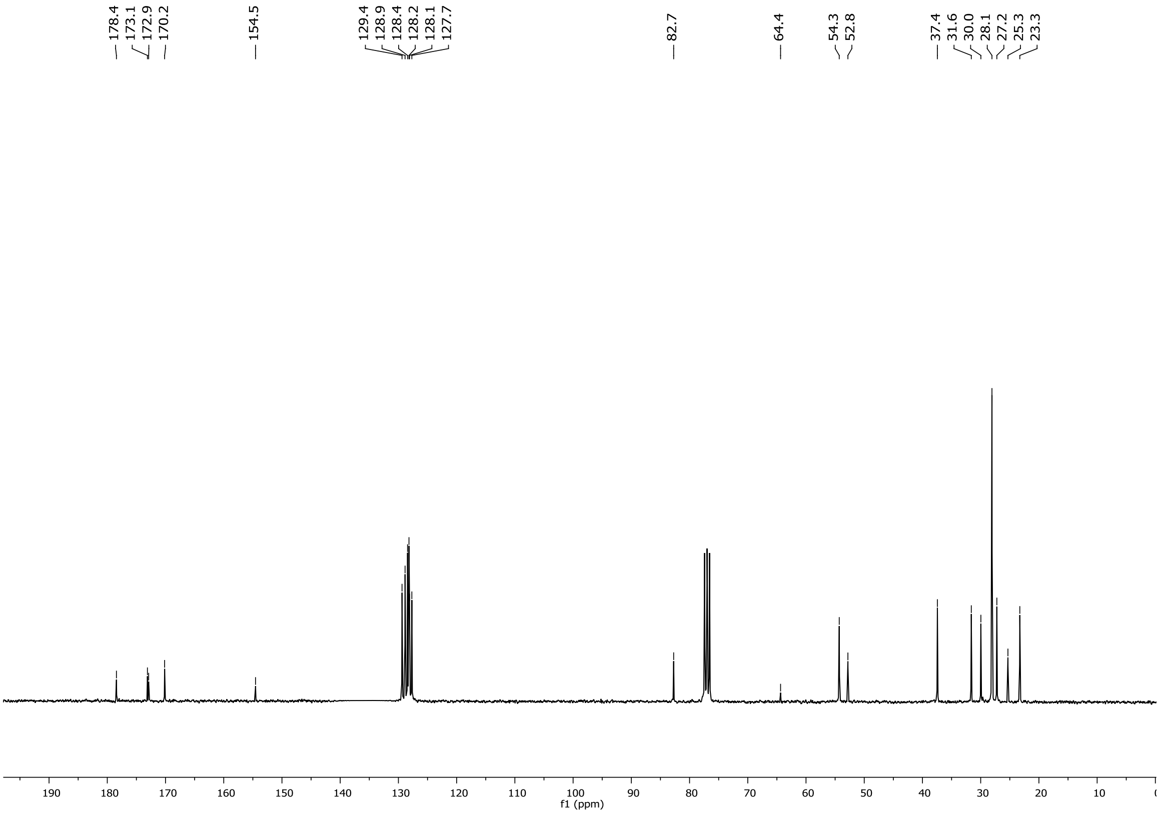
f1 (ppm)

37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128.4
128.2
128.1
127.7
82.7
64.4
54.3
52.8
37.4
31.6
30.0
28.1
27.2
25.3
23.3
190
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140
130
120
110
100
90
80
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20
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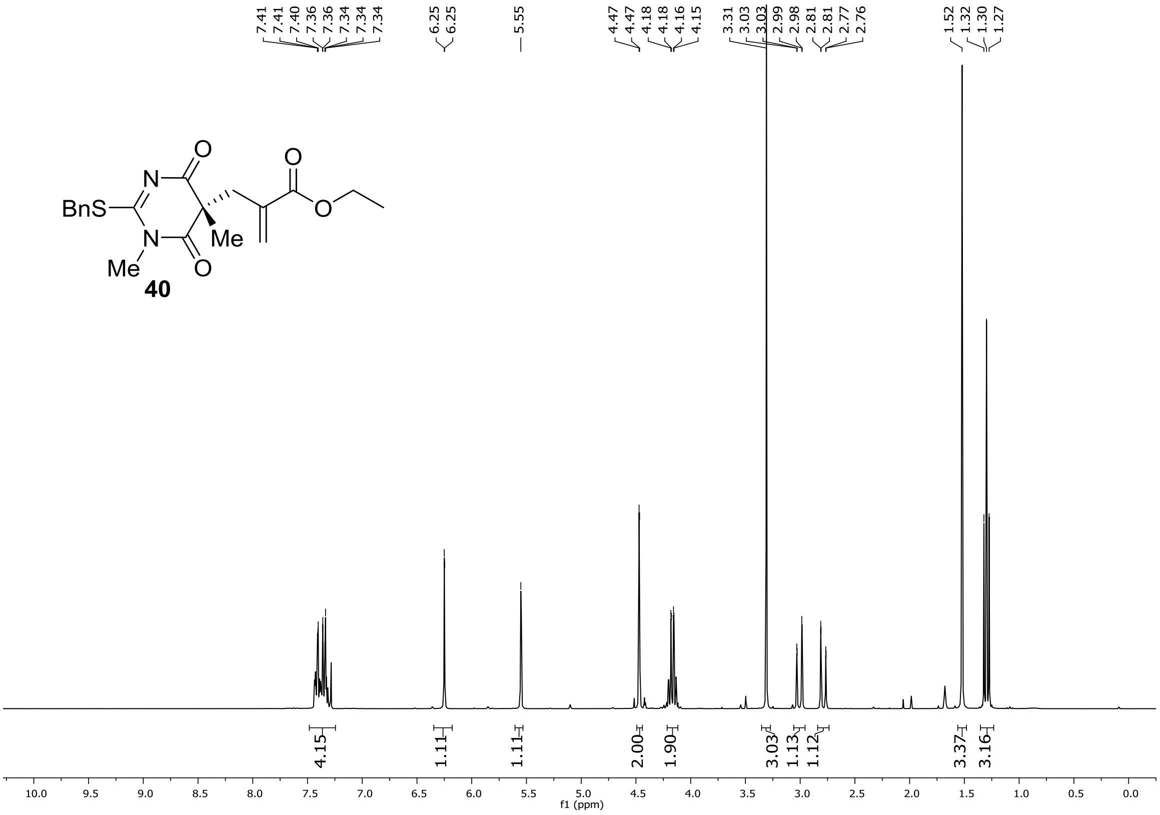
f1 (ppm)



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4.18
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4.15
3.31
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3.02
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2.98
2.81
2.81
2.77
2.76
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1.30
1.27
BnS
N
N
O
O
O
O
Me
Me
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1.11
2.00
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1.13
1.12
3.37
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9.0
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8.0
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7.0
6.5
6.0
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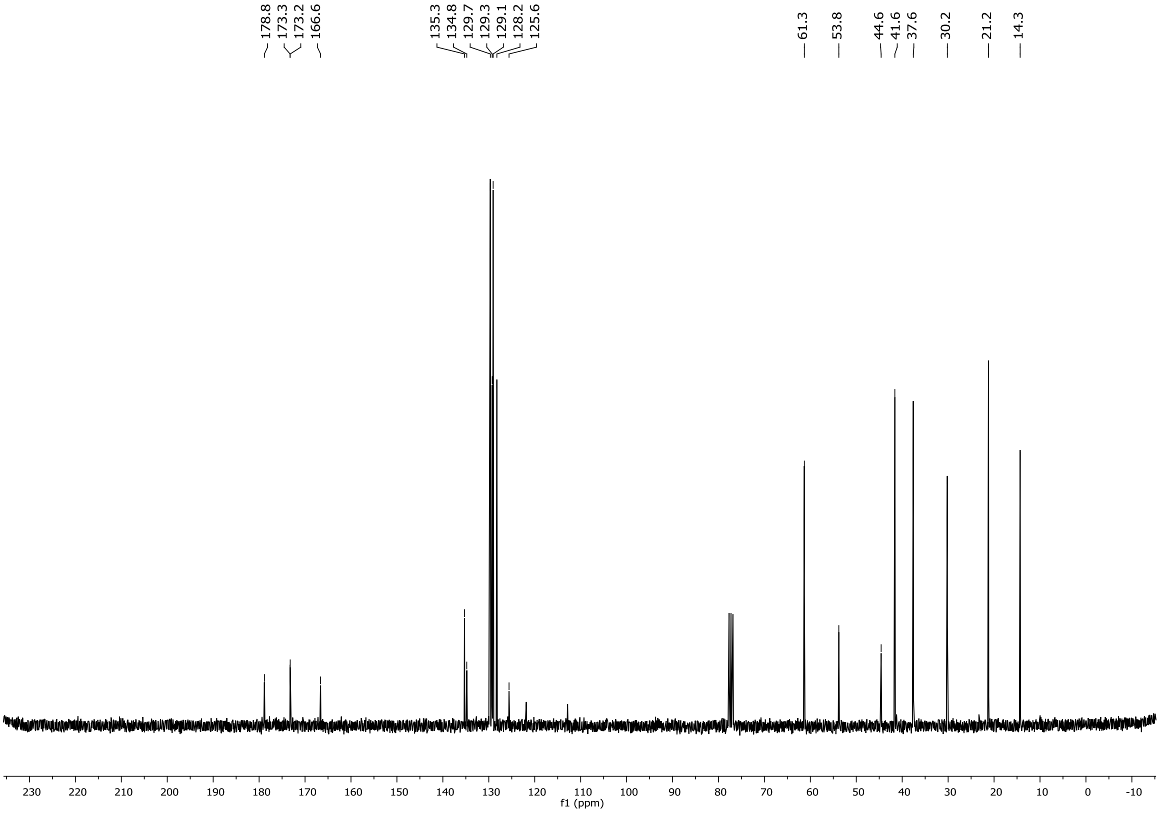

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200
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180
170
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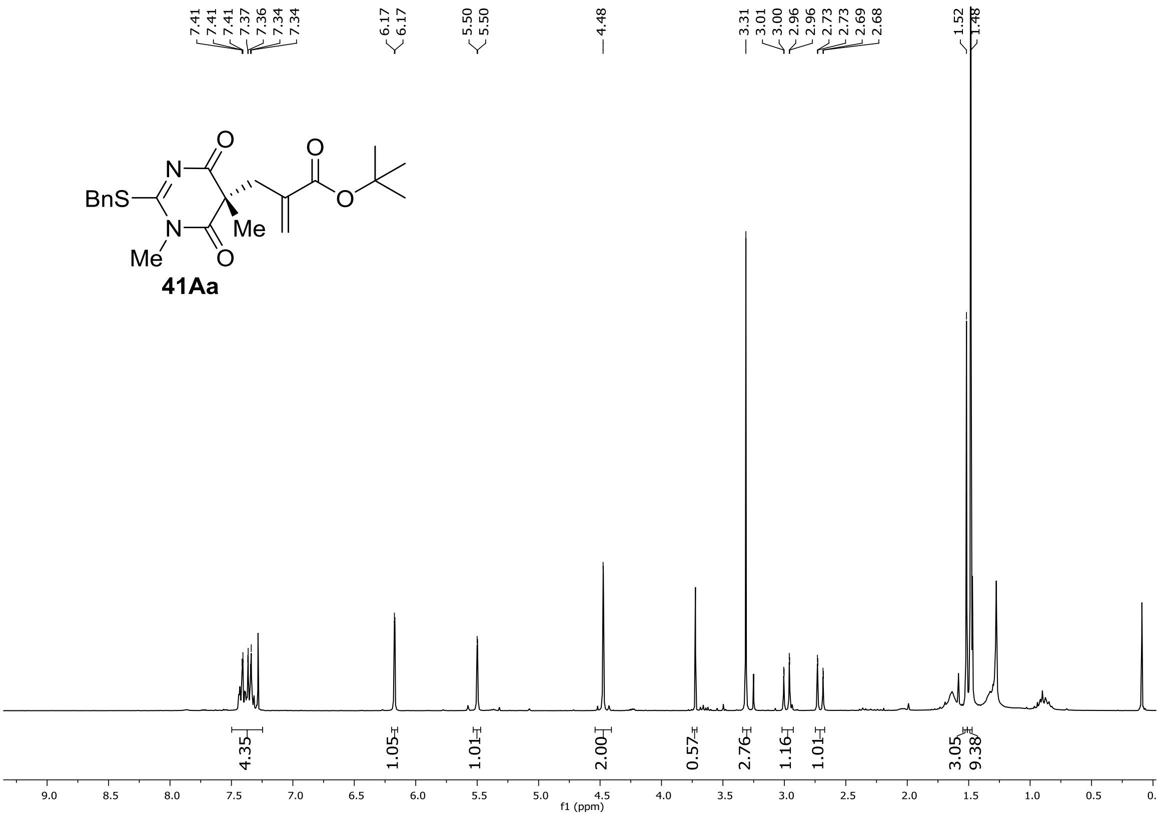
f1 (ppm)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1.52
1.48
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N
BnS
N
Me
Me
O
O
O
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6.0
5.5
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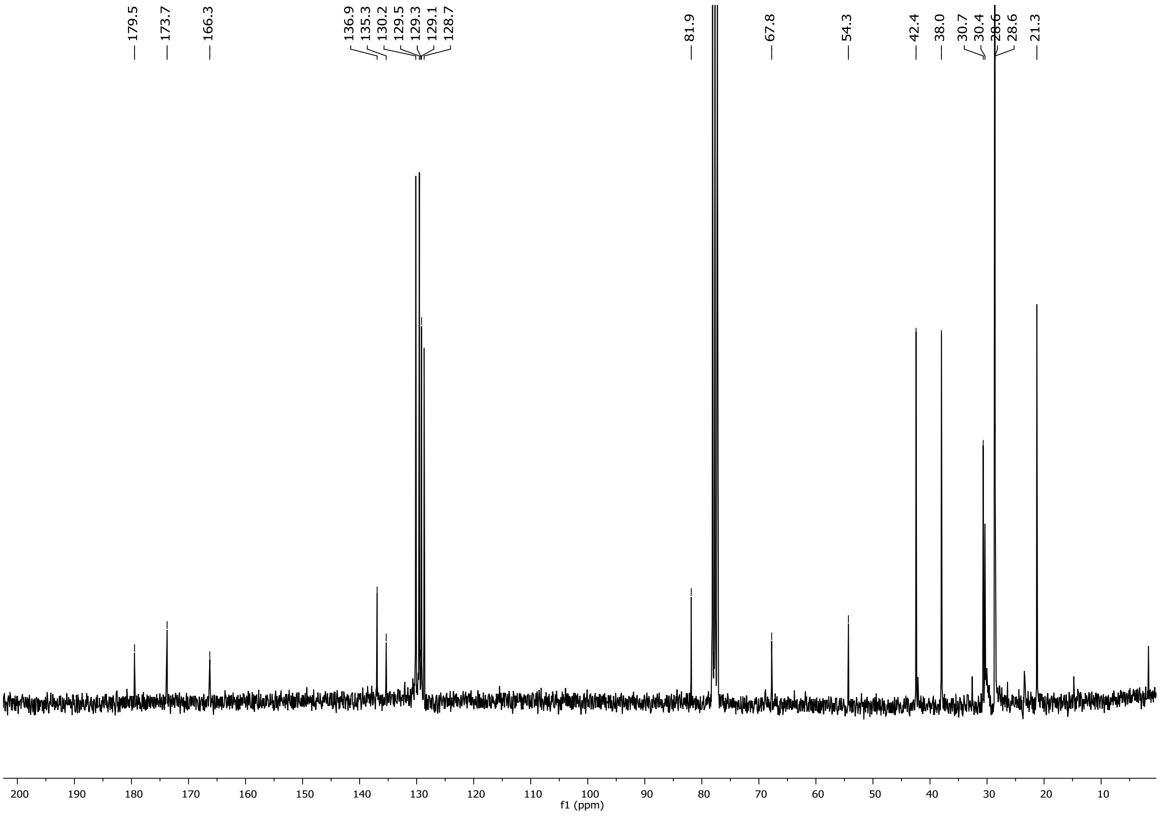
f1 (ppm)

41Aa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30.4
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28.6
21.3
200
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100
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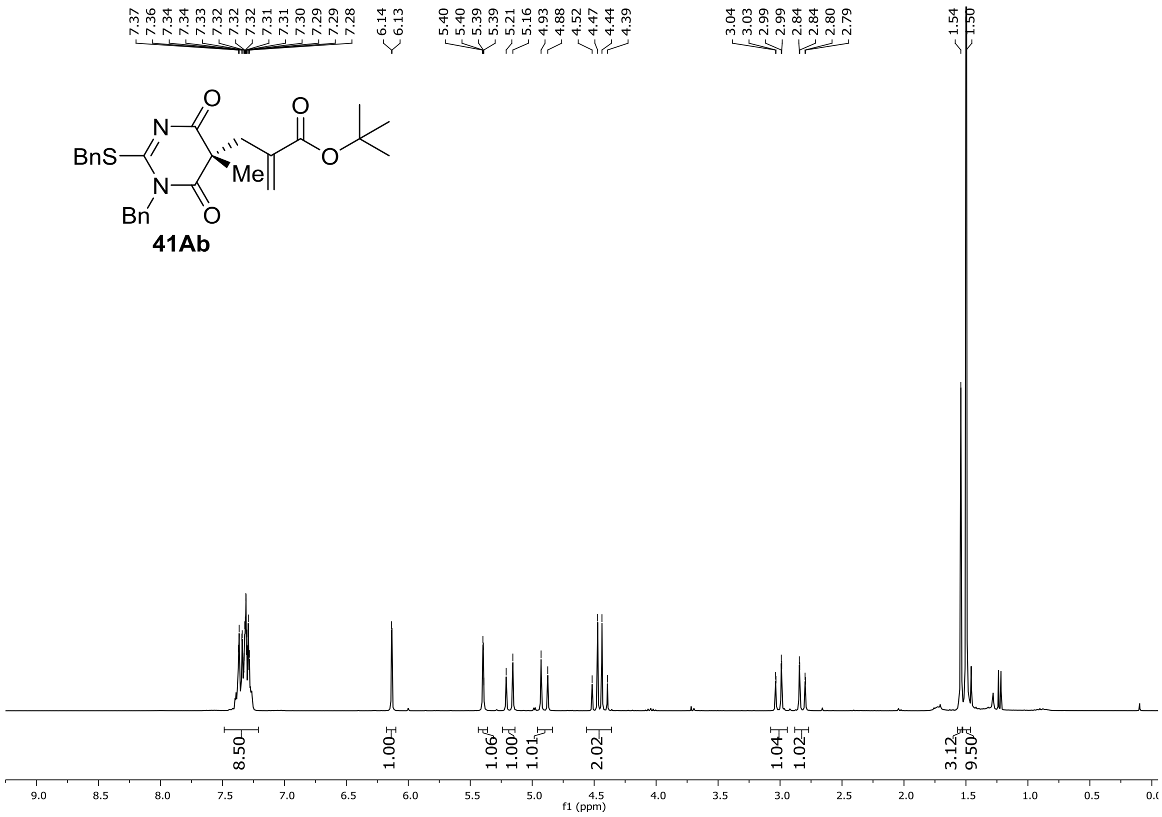
f1 (ppm)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1.50
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N
BnS
N
Bn
O
Me
O
O
41Ab
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2.02
1.04
1.02
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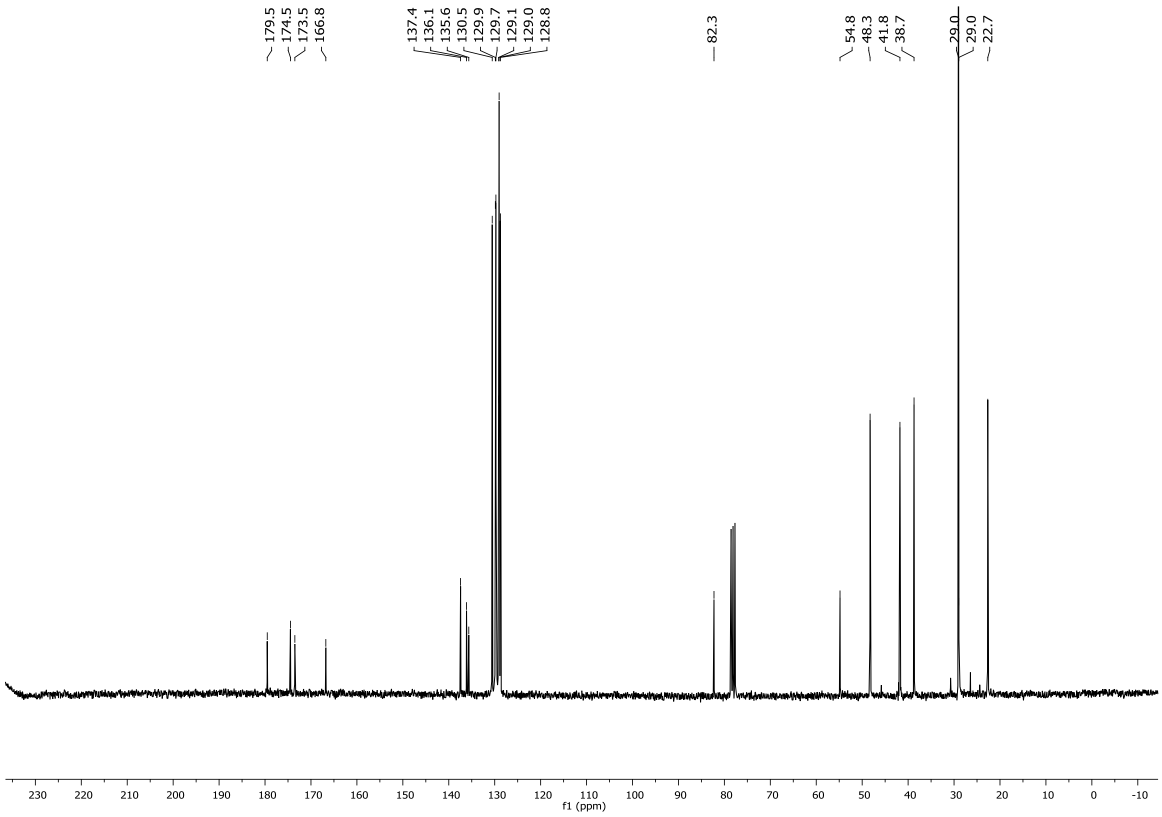
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128.8
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54.8
48.3
41.8
38.7
29.0
29.0
22.7
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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0
-10
f1 (ppm)

BnS
N
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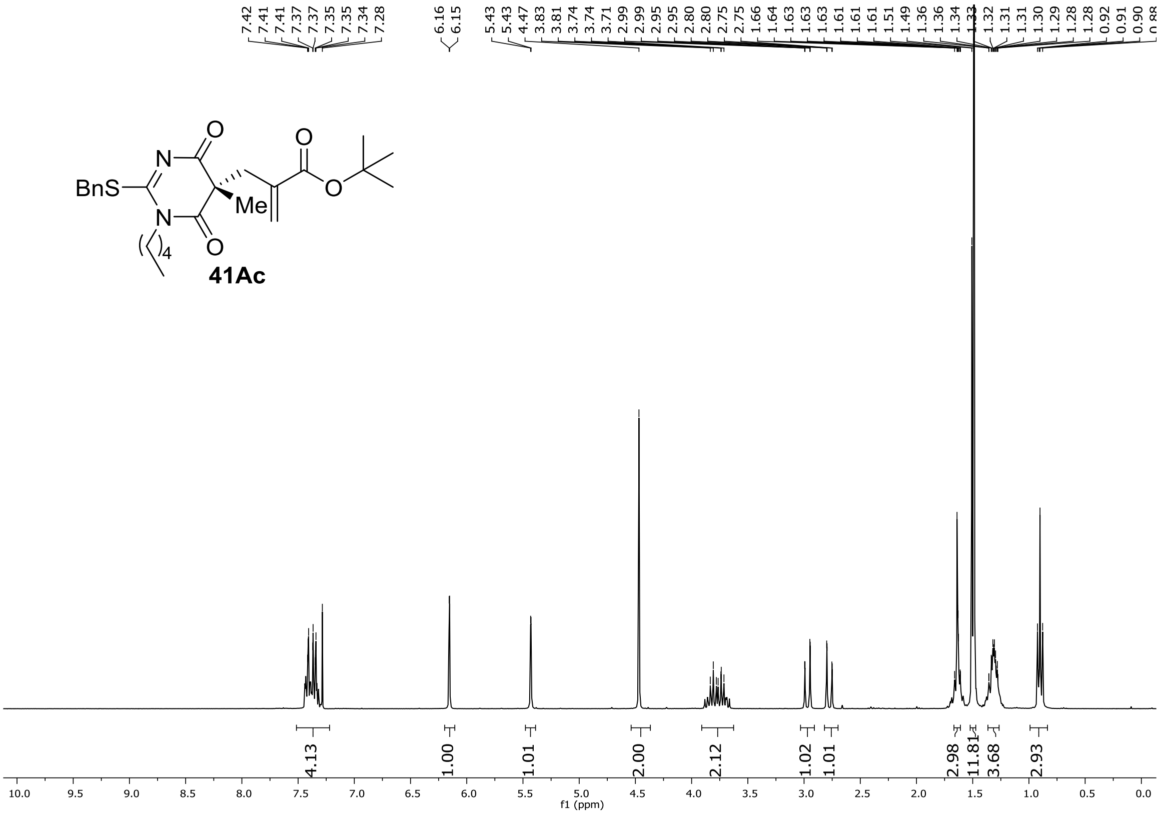
O
O
Me
O
O
( )4

41Ac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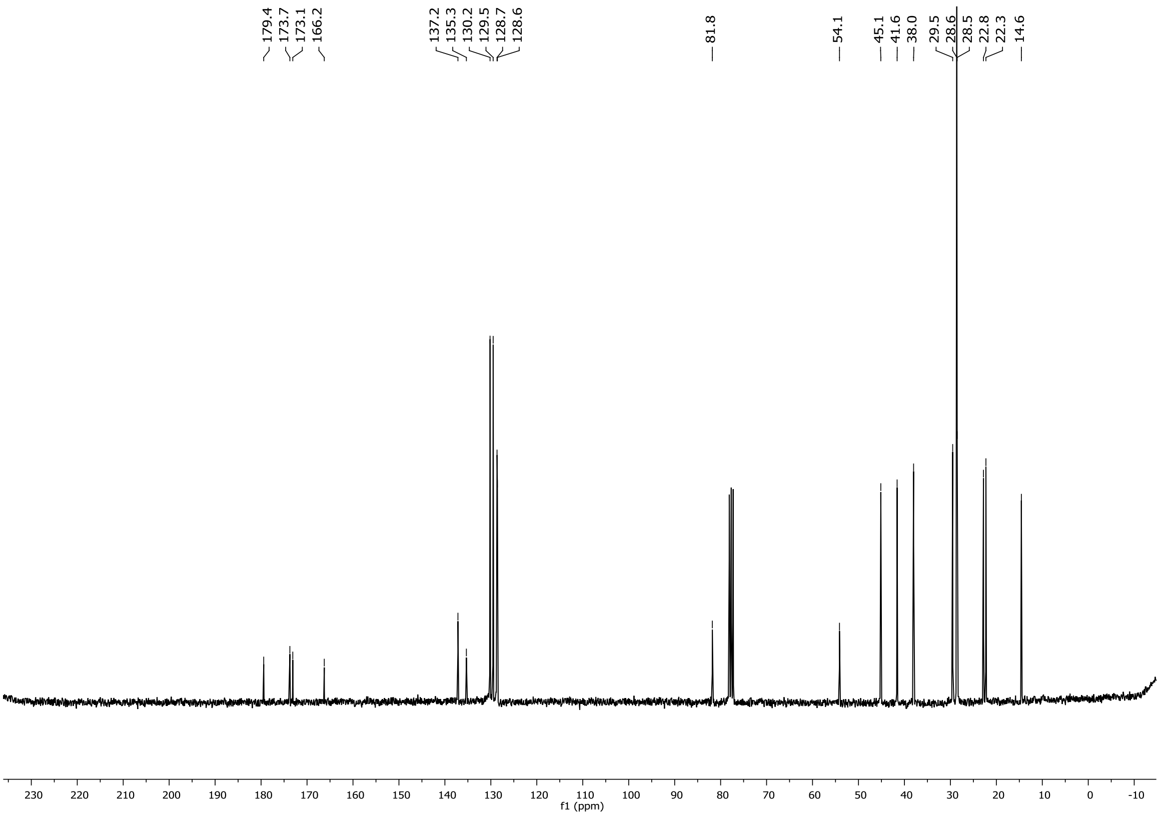
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14.6
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200
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180
170
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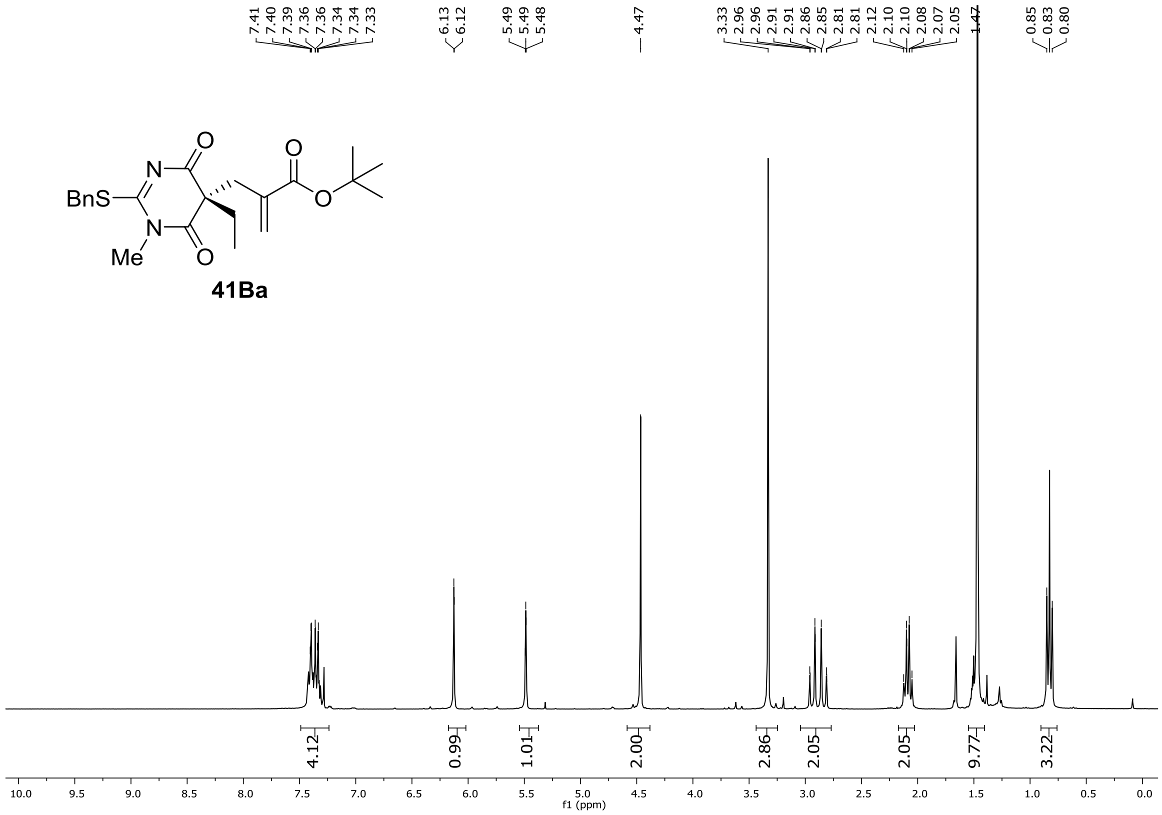
-10
f1 (ppm)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5.48
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2.81
2.12
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2.07
2.05
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0.80
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N
Me
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O
O
O
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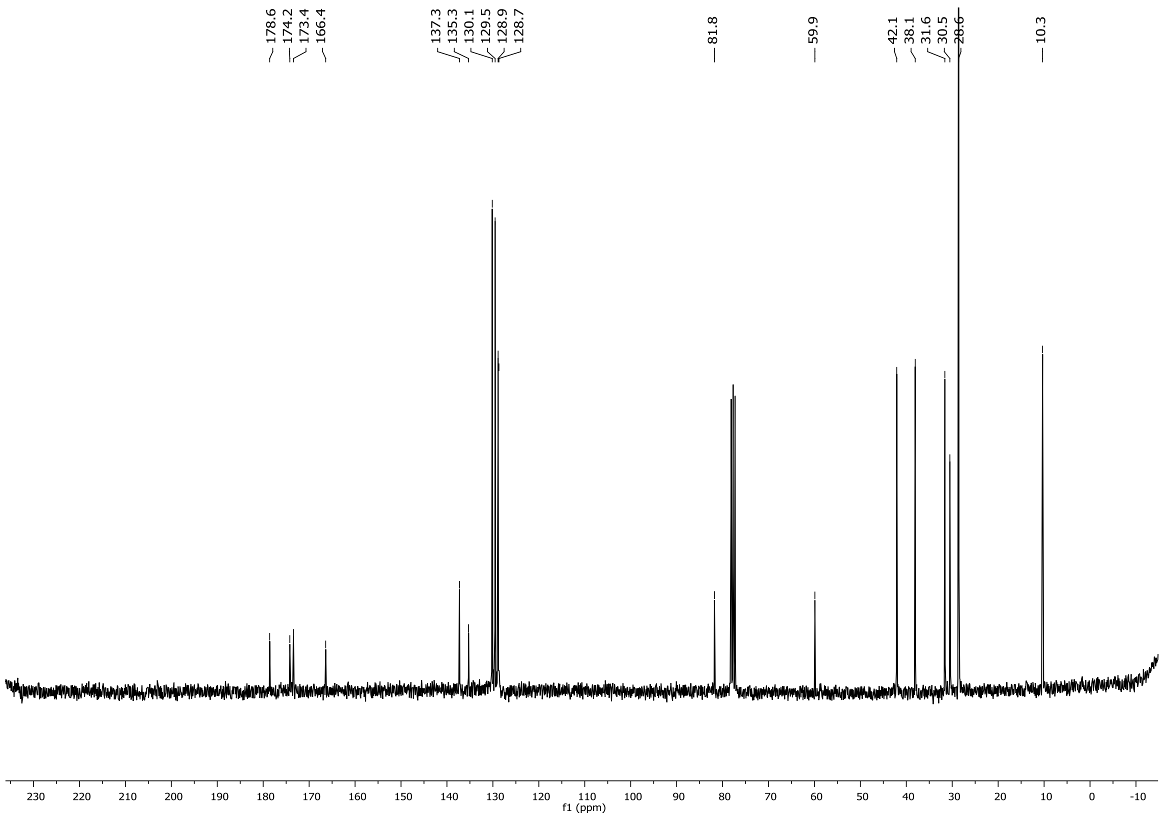
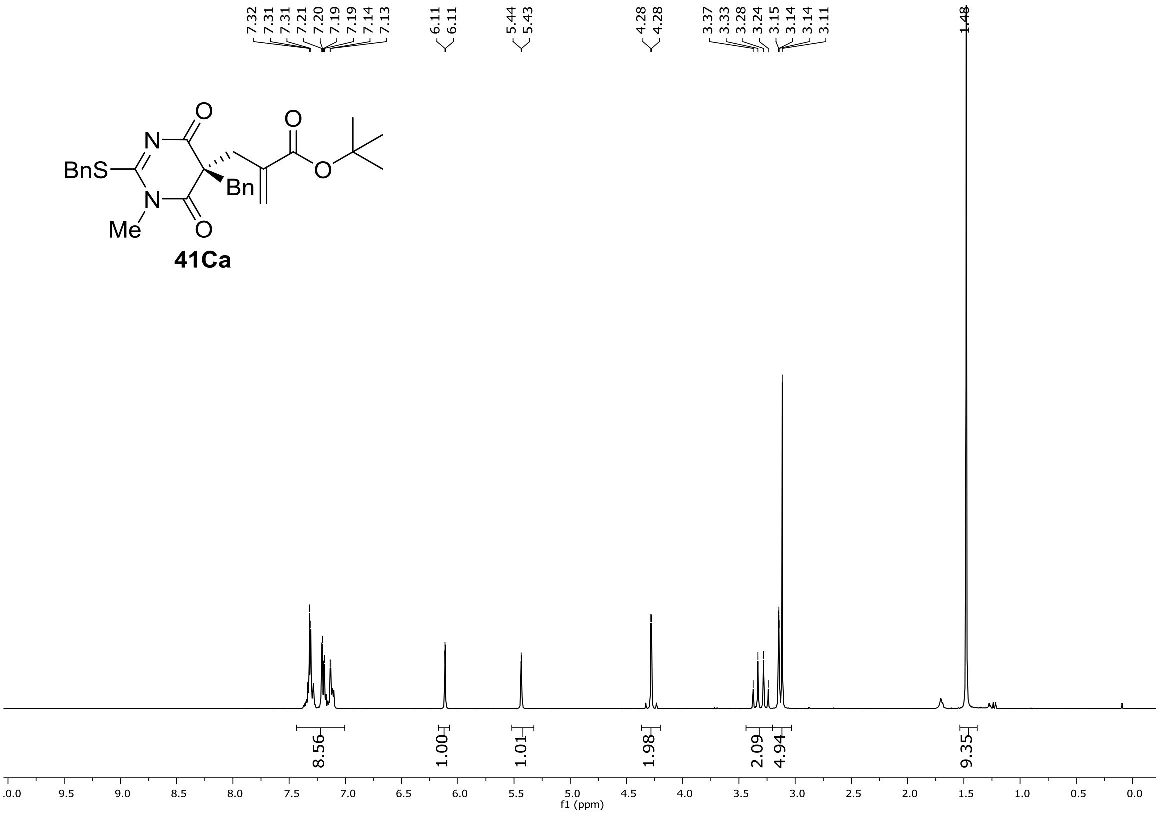
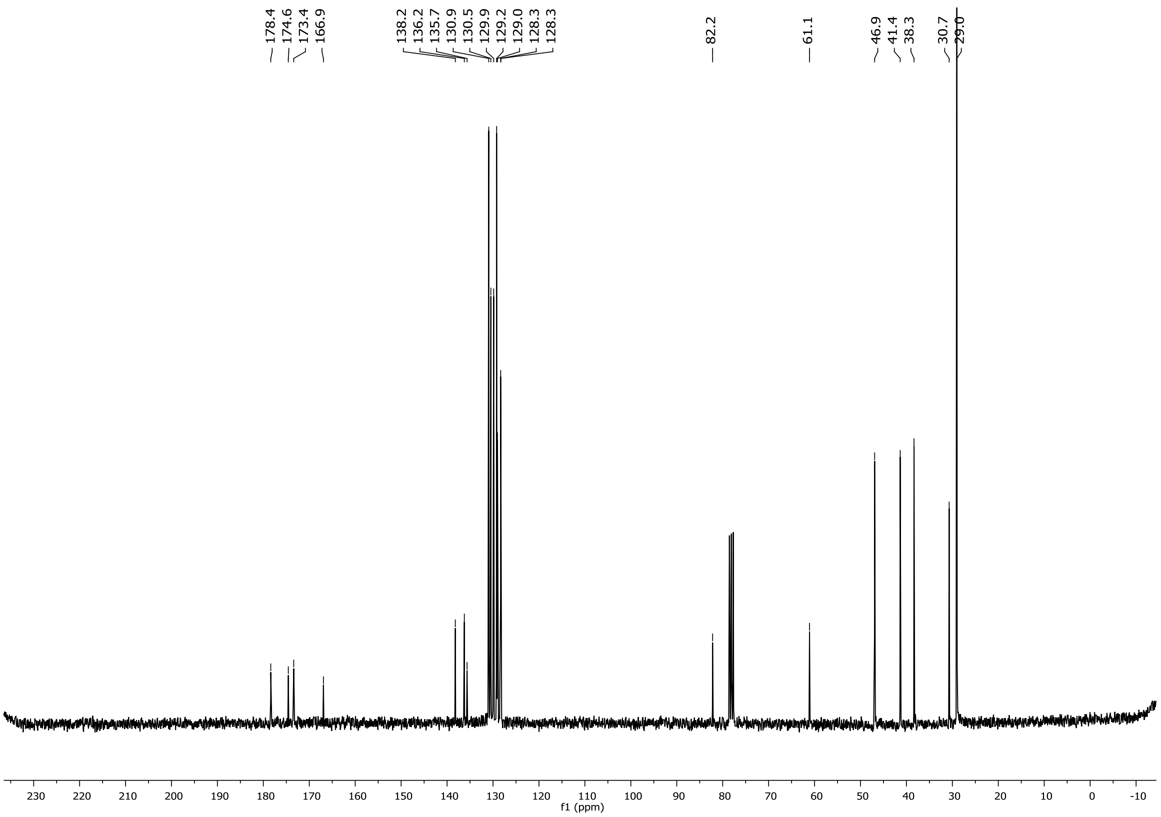
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

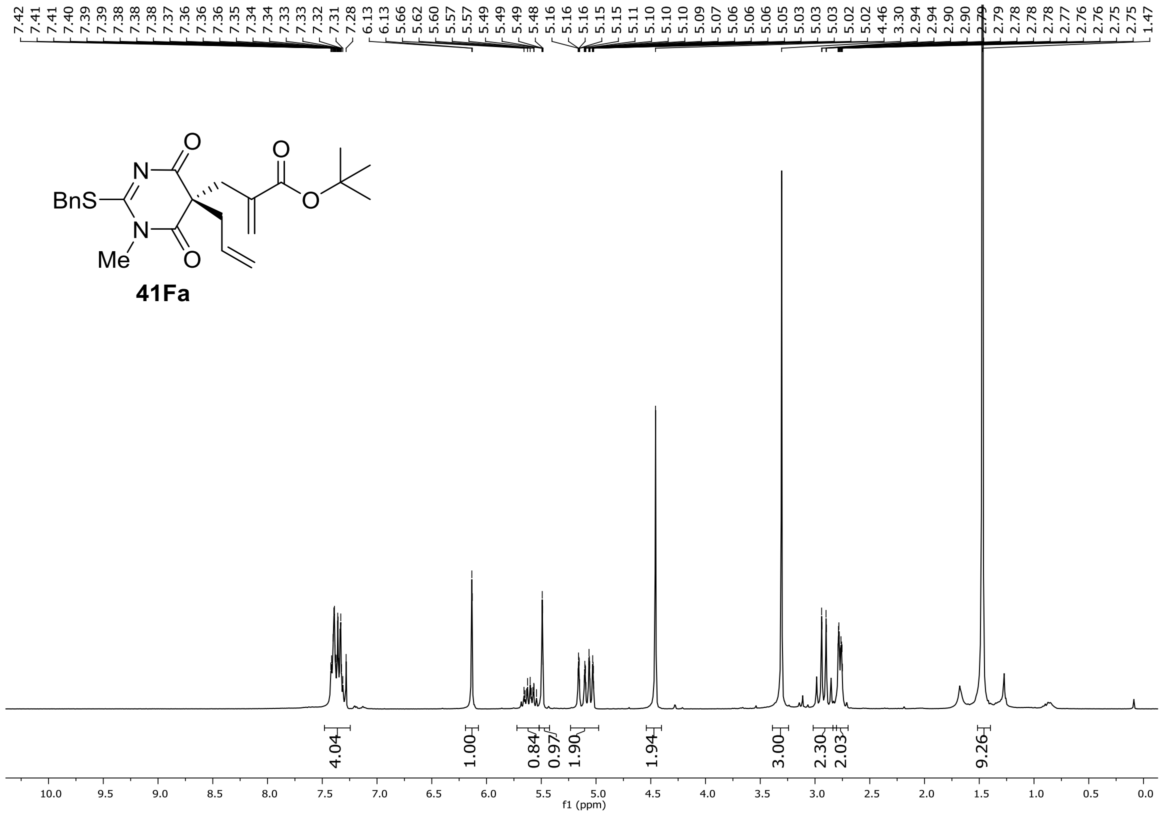
41Ba


178.6
174.2
173.4
166.4
137.3
135.3
130.1
129.5
128.9
128.7
81.8
59.9
42.1
38.1
31.6
30.5
28.6
10.3
230
220
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)

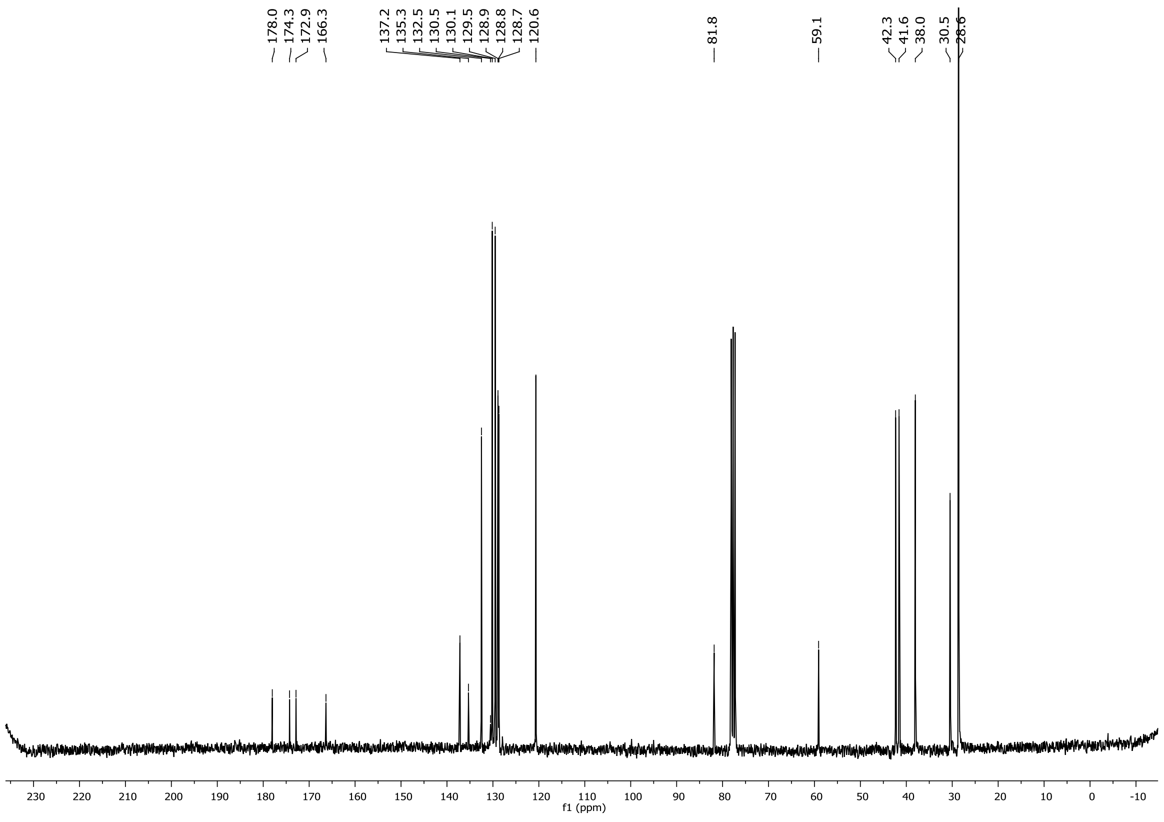

7.32
7.31
7.31
7.21
7.20
7.19
7.19
7.14
7.13
6.11
6.11
5.44
5.43
4.28
4.28
3.37
3.33
3.28
3.24
3.15
3.14
3.14
3.11
1.48
O
N
BnS
N
Me
O
Bn
O
O
8.56
1.00
1.01
1.98
2.09
4.94
9.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

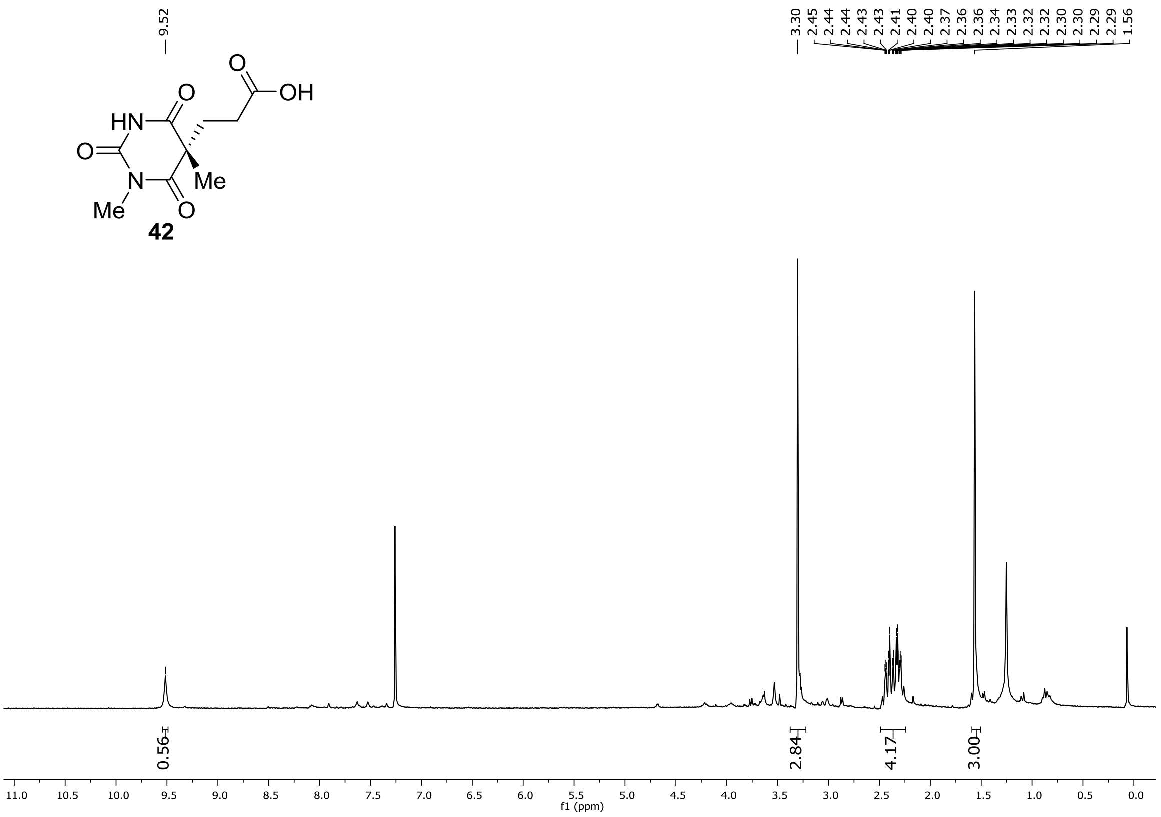
41Ca

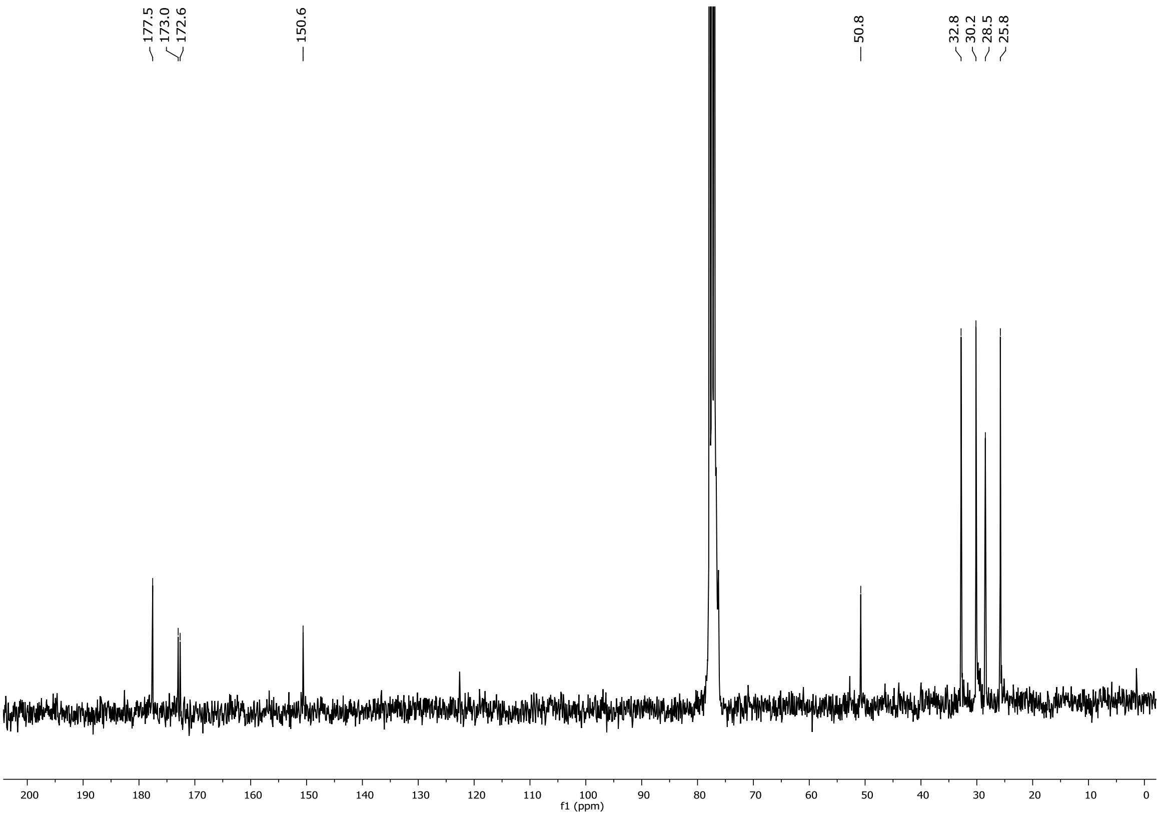

178.4
174.6
173.4
166.9
138.2
136.2
135.7
130.9
130.5
129.9
129.2
129.0
128.3
128.3
82.2
61.1
46.9
41.4
38.3
30.7
29.0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

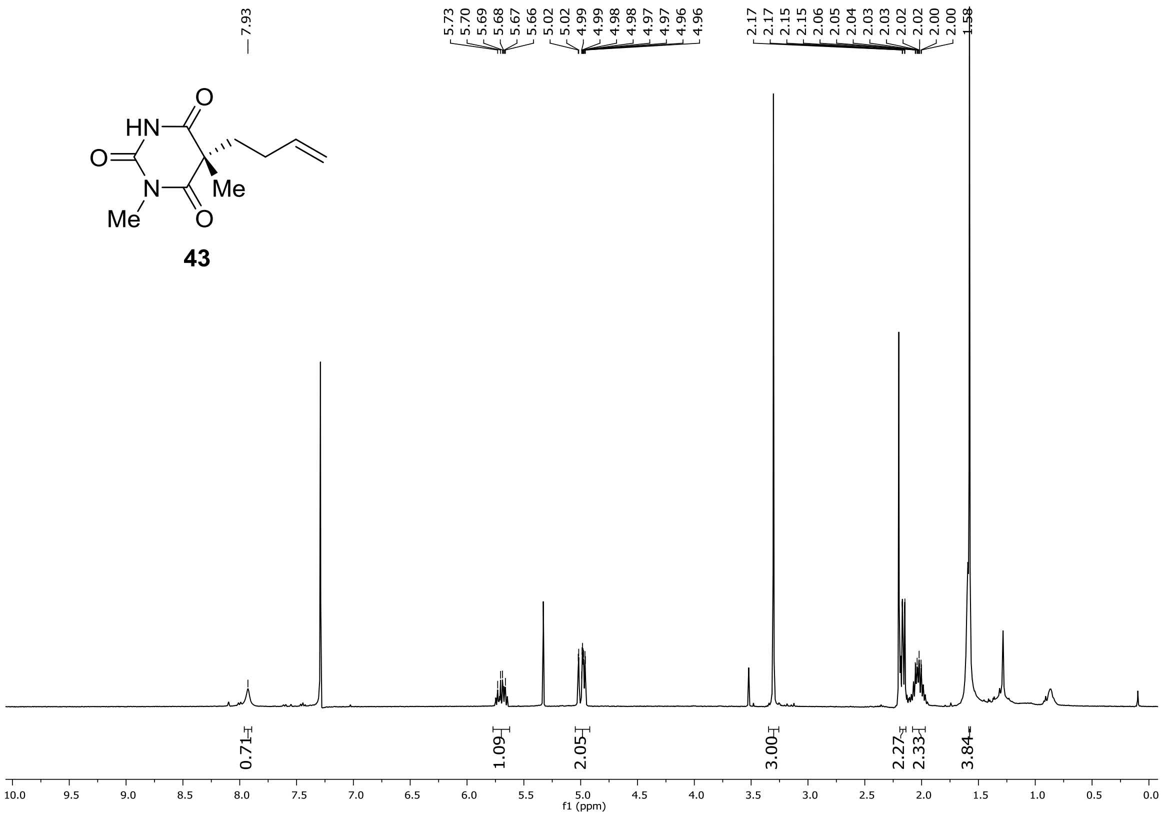

7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.38
7.37
7.36
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.28
6.13
6.13
5.66
5.62
5.60
5.57
5.57
5.49
5.49
5.49
5.48
5.16
5.16
5.16
5.15
5.15
5.11
5.10
5.10
5.10
5.09
5.07
5.06
5.06
5.06
5.05
5.03
5.03
5.03
5.02
5.02
4.46
3.30
2.94
2.94
2.90
2.90
2.79
2.79
2.78
2.78
2.77
2.76
2.76
2.75
2.75
1.47
O
N
O
BnS
N
O
Me
O
4.04
1.00
0.84
0.97
1.90
1.94
3.00
2.30
2.03
9.26
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
f1 (ppm)

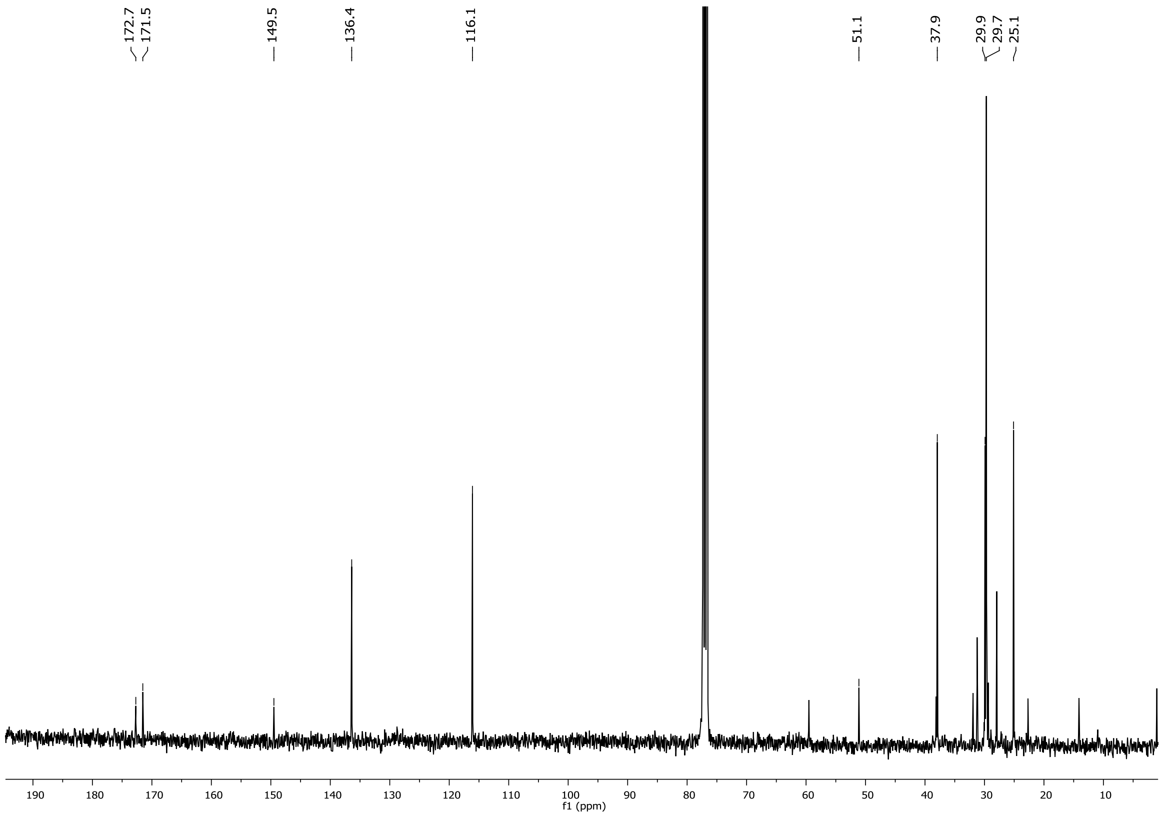
41Fa

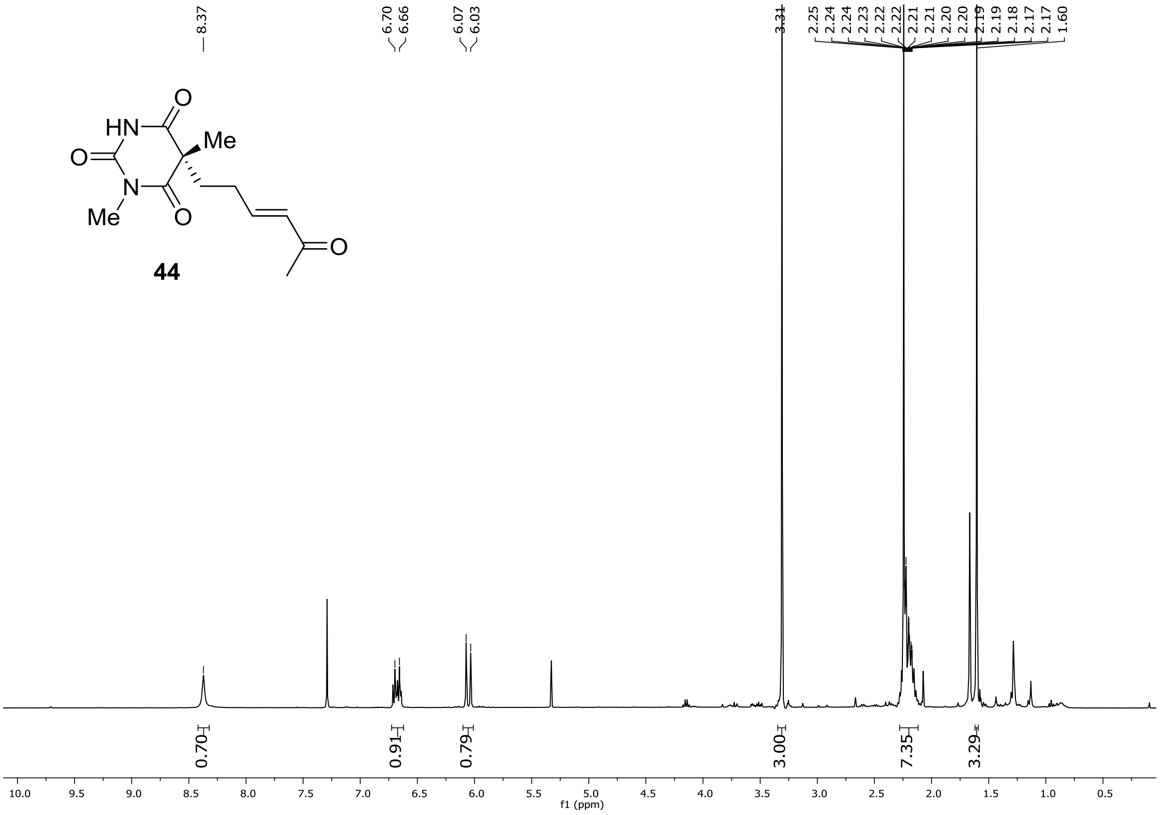

178.0
174.3
172.9
166.3
137.2
135.3
132.5
130.5
130.1
129.5
128.9
128.8
128.7
120.6
81.8
59.1
42.3
41.6
38.0
30.5
28.6
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


9.52
3.30
2.45
2.44
2.44
2.43
2.43
2.41
2.40
2.40
2.37
2.36
2.36
2.34
2.33
2.32
2.32
2.30
2.30
2.29
2.29
1.56
O
OH
HN
O
O
N
Me
Me
O
42
0.56
2.84
4.17
3.00
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
f1 (ppm)


177.5
173.0
172.6
150.6
50.8
32.8
30.2
28.5
25.8
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

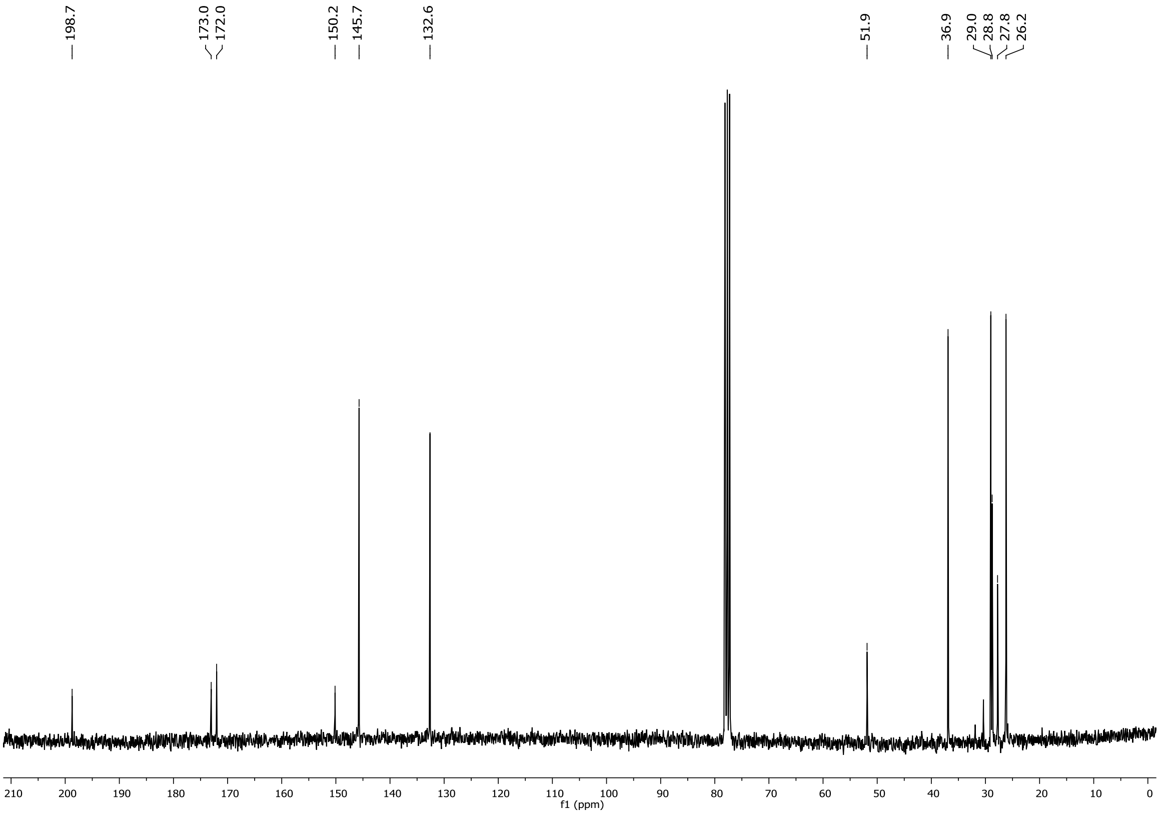

43
HN
O
O
N
Me
Me
O
7.93
5.73
5.70
5.69
5.68
5.67
5.66
5.02
5.02
4.99
4.99
4.98
4.98
4.97
4.97
4.96
4.96
2.17
2.17
2.15
2.15
2.06
2.05
2.04
2.03
2.03
2.02
2.02
2.02
2.00
2.00
1.58
0.71
1.09
2.05
3.00
2.27
2.33
3.84
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.7
171.5
149.5
136.4
116.1
51.1
37.9
29.9
29.7
25.1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

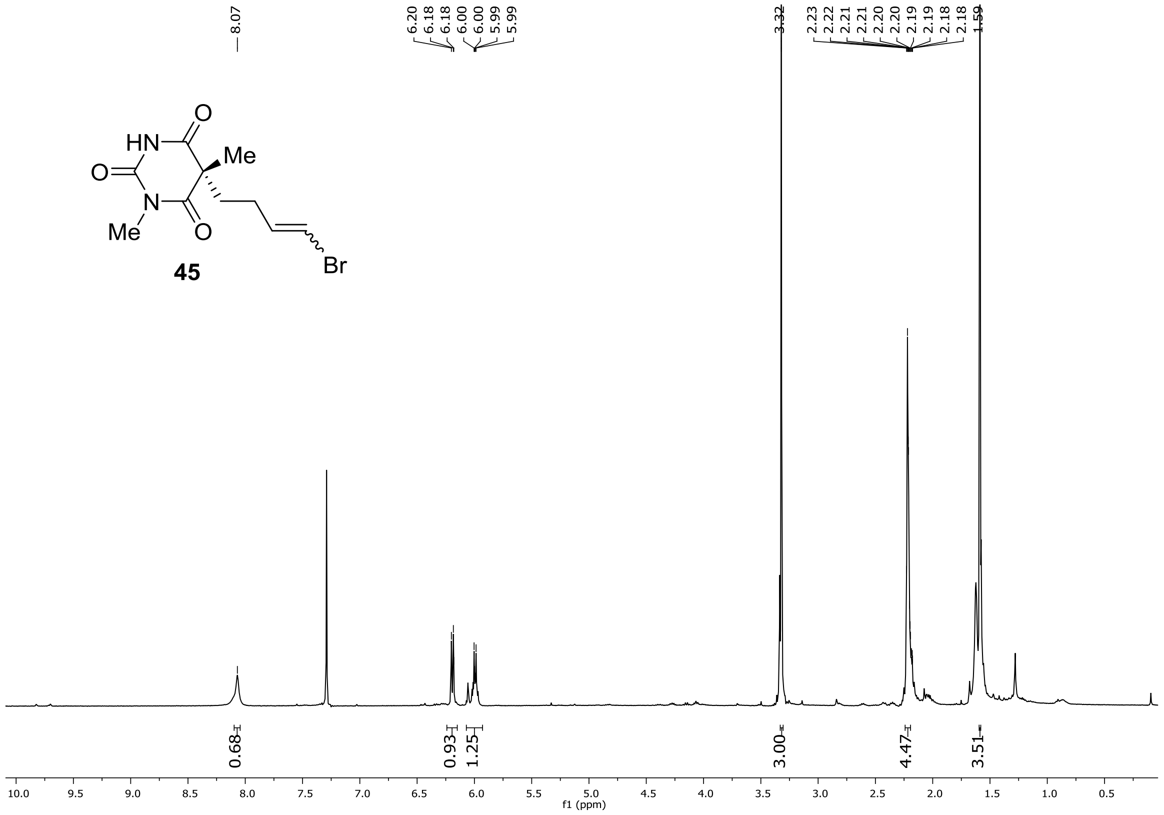


44

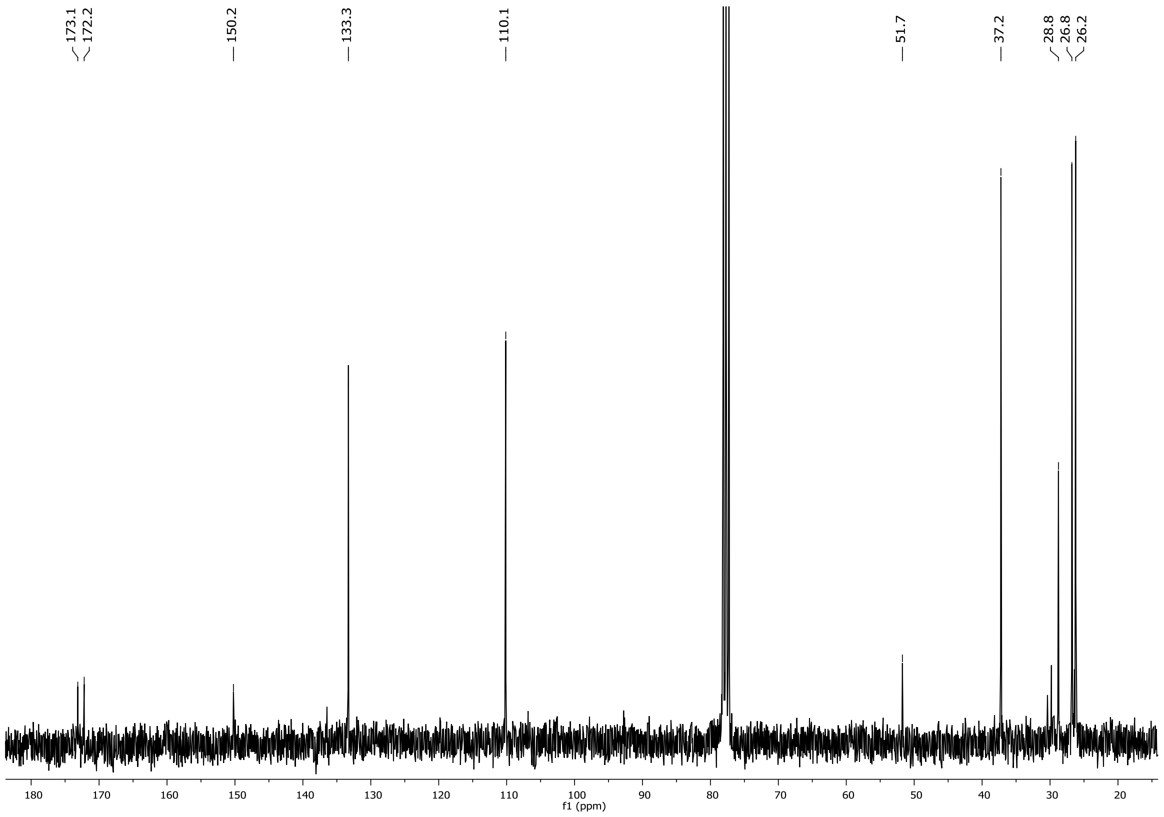
8.37
6.70
6.66
6.07
6.03
3.31
2.25
2.24
2.24
2.23
2.22
2.22
2.22
2.21
2.21
2.20
2.20
2.19
2.19
2.18
2.17
2.17
1.60
HN
O
Me
O
N
Me
O
O
0.70
0.91
0.79
3.00
7.35
3.29
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

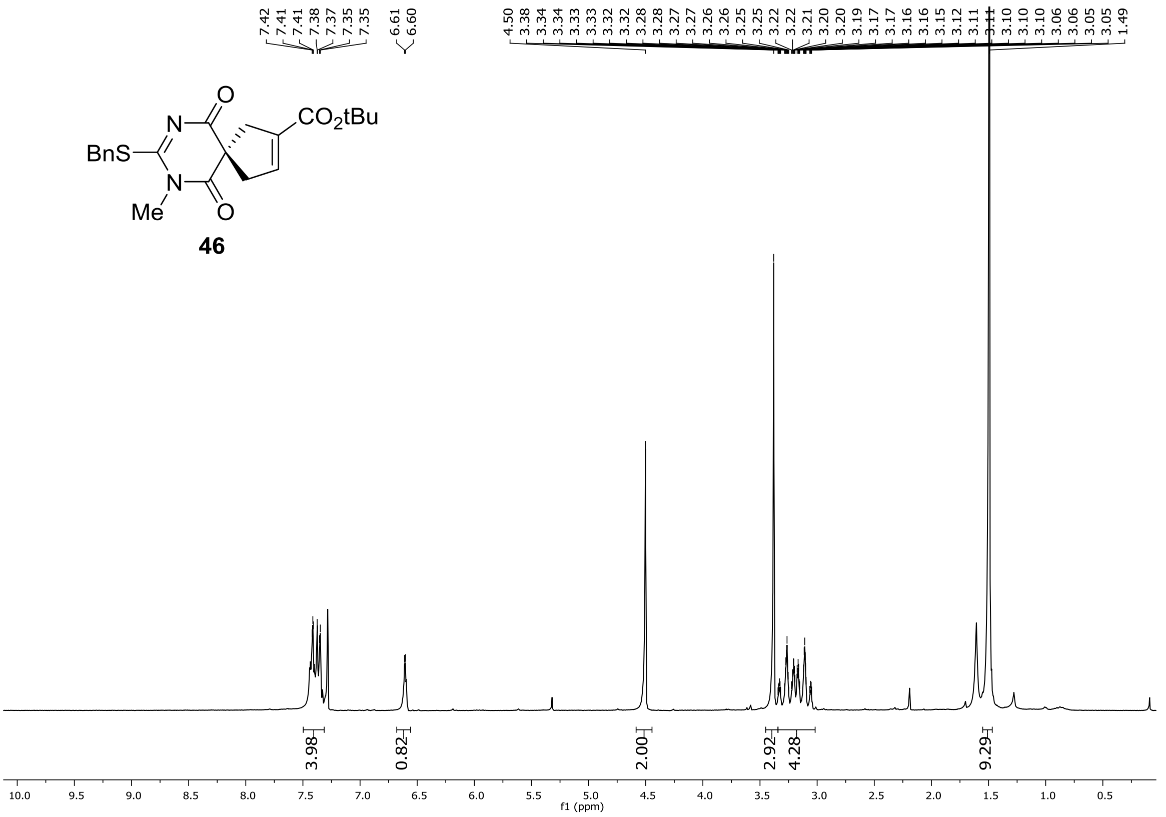


198.7
173.0
172.0
150.2
145.7
132.6
51.9
36.9
29.0
28.8
27.8
26.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

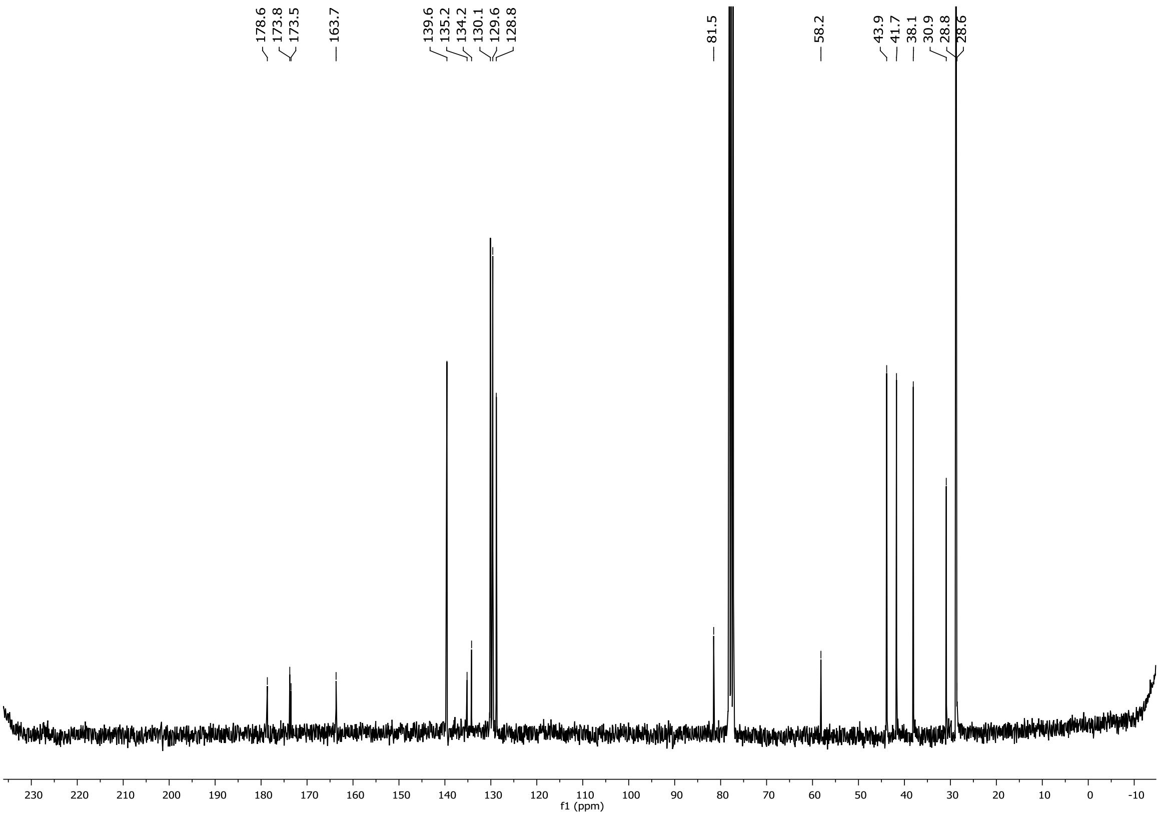

O
HN
Me
O
N
Me
O
Br
8.07
6.20
6.18
6.18
6.00
6.00
5.99
5.99
3.32
2.23
2.22
2.21
2.21
2.20
2.20
2.19
2.19
2.18
2.18
1.59
0.68
0.93
1.25
3.00
4.47
3.51
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

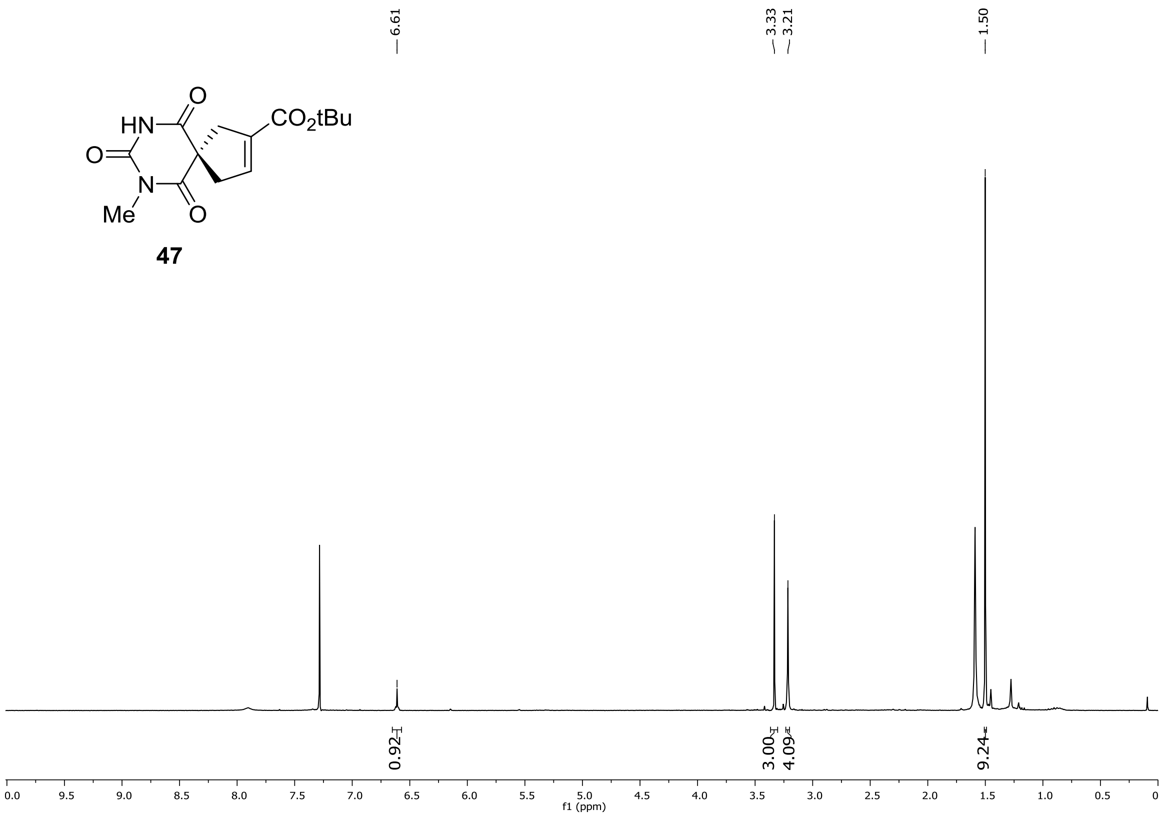
45


173.1
172.2
150.2
133.3
110.1
51.7
37.2
28.8
26.8
26.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

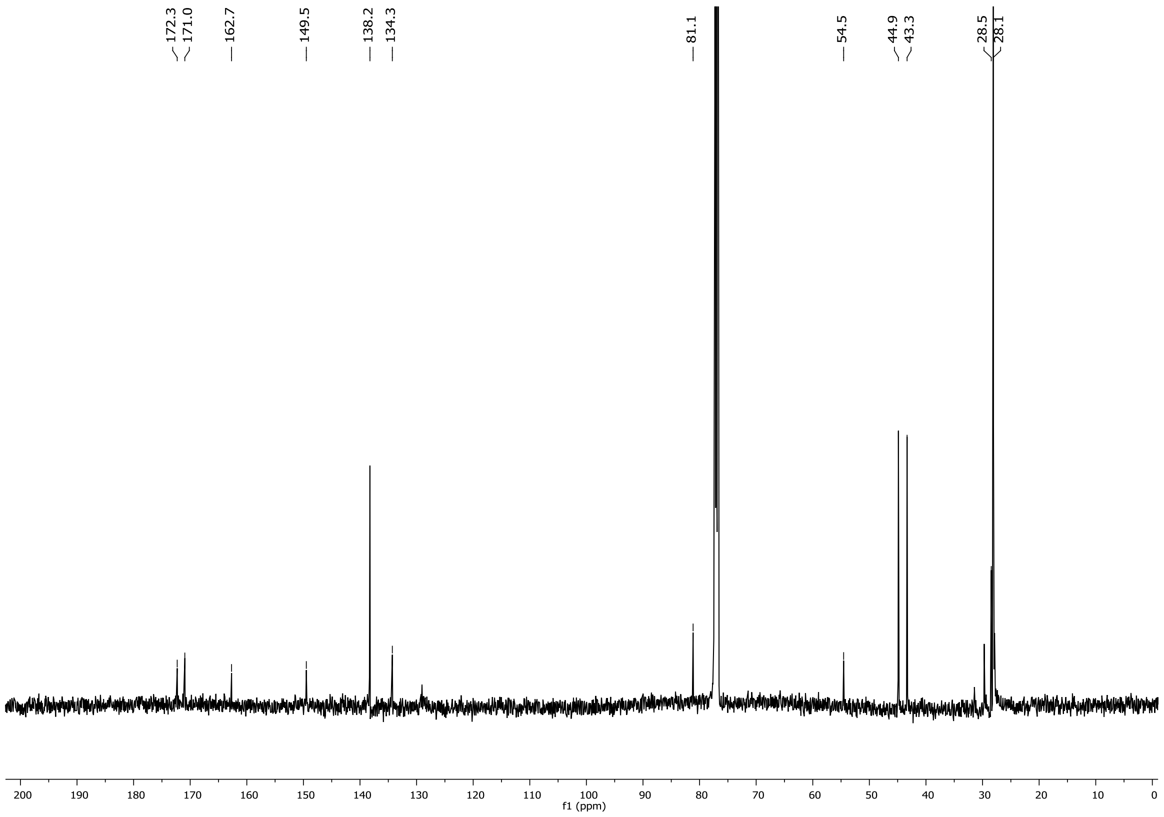

7.42
7.41
7.41
7.38
7.37
7.35
7.35
6.61
6.60
4.50
3.38
3.34
3.34
3.33
3.33
3.32
3.32
3.28
3.28
3.27
3.27
3.26
3.26
3.25
3.25
3.22
3.22
3.21
3.20
3.20
3.19
3.17
3.17
3.16
3.16
3.15
3.12
3.11
3.11
3.10
3.10
3.06
3.06
3.05
3.05
1.49
O
N
CO$_2$tBu
BnS
N
Me
O
3.98
0.82
2.00
2.92
4.28
9.29
10.0
9.5
9.0
8.5
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
f1 (ppm)

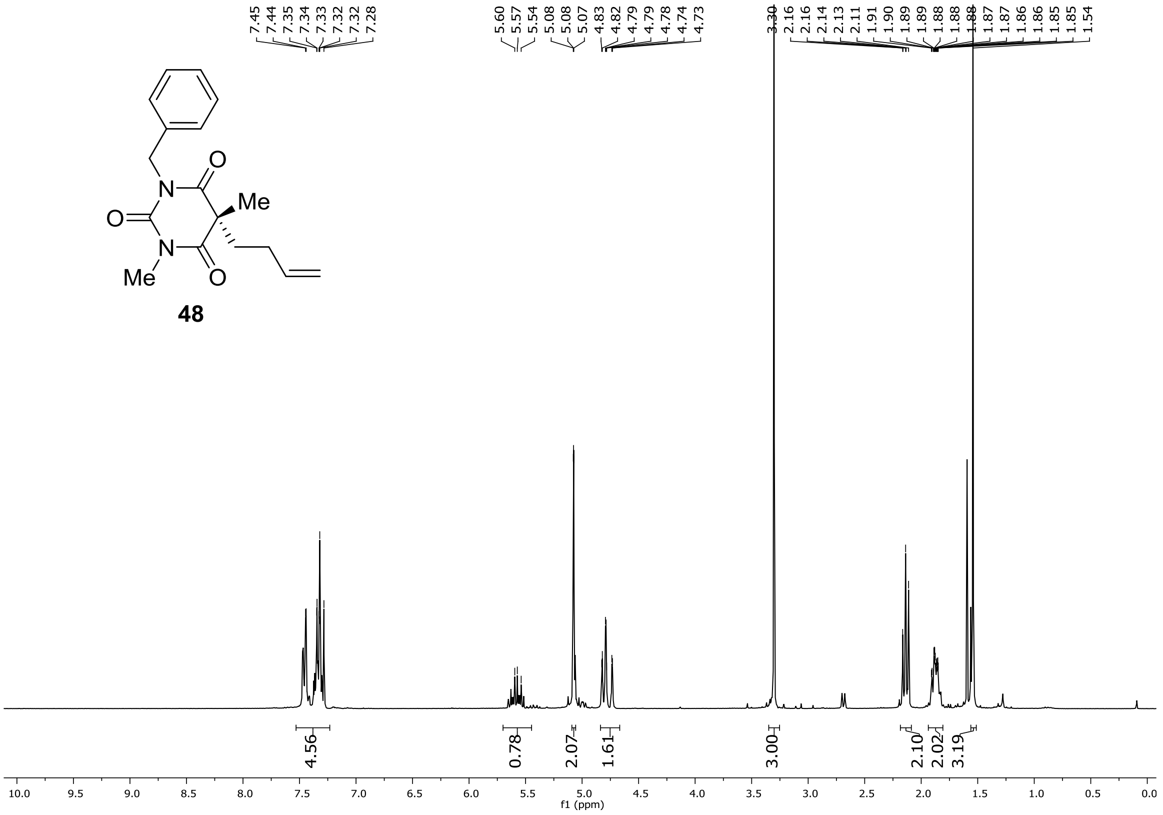
46


178.6
173.8
173.5
163.7
139.6
135.2
134.2
130.1
129.6
128.8
81.5
58.2
43.9
41.7
38.1
30.9
28.8
28.6
230
220
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)

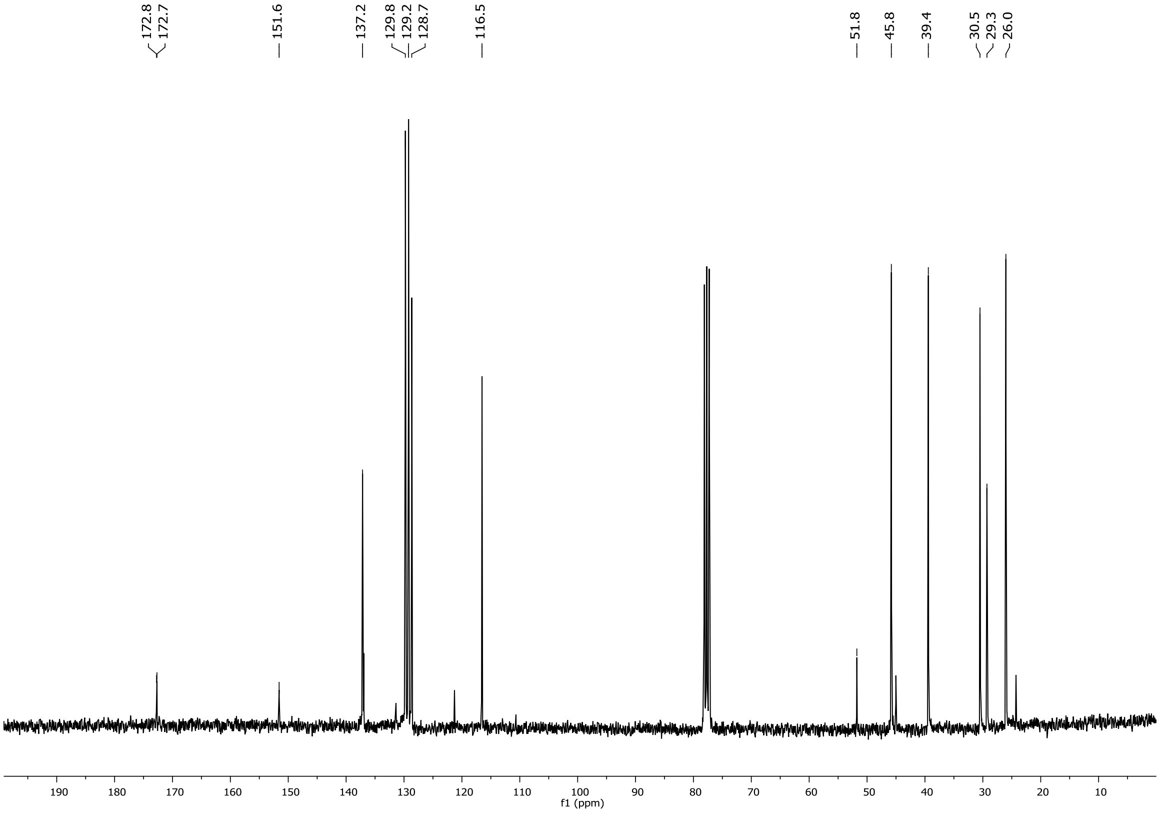

6.61
3.33
3.21
1.50
HN
O
CO2tBu
N
Me
0.92
3.00
4.09
9.24
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

47


172.3
171.0
162.7
149.5
138.2
134.3
81.1
54.5
44.9
43.3
28.5
28.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


48

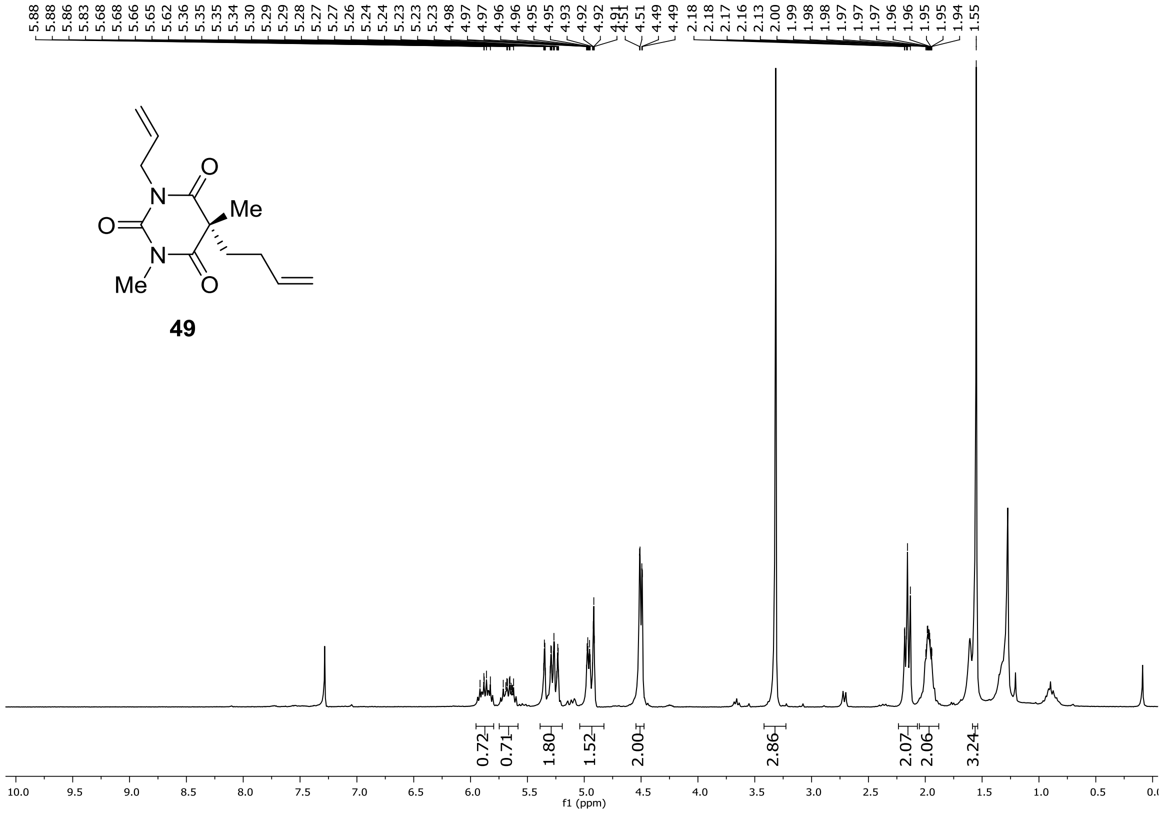
Me
O
N
O
N
Me
O
7.45 7.44 7.35 7.34 7.33 7.32 7.32 7.28
5.60 5.57 5.54 5.08 5.08 5.07 4.83 4.82 4.79 4.79 4.78 4.74 4.73
3.30 2.16 2.16 2.14 2.13 2.11 1.91 1.90 1.89 1.89 1.88 1.88 1.88 1.87 1.87 1.86 1.86 1.85 1.85 1.54
4.56
0.78
2.07
1.61
3.00
2.10
2.02
3.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

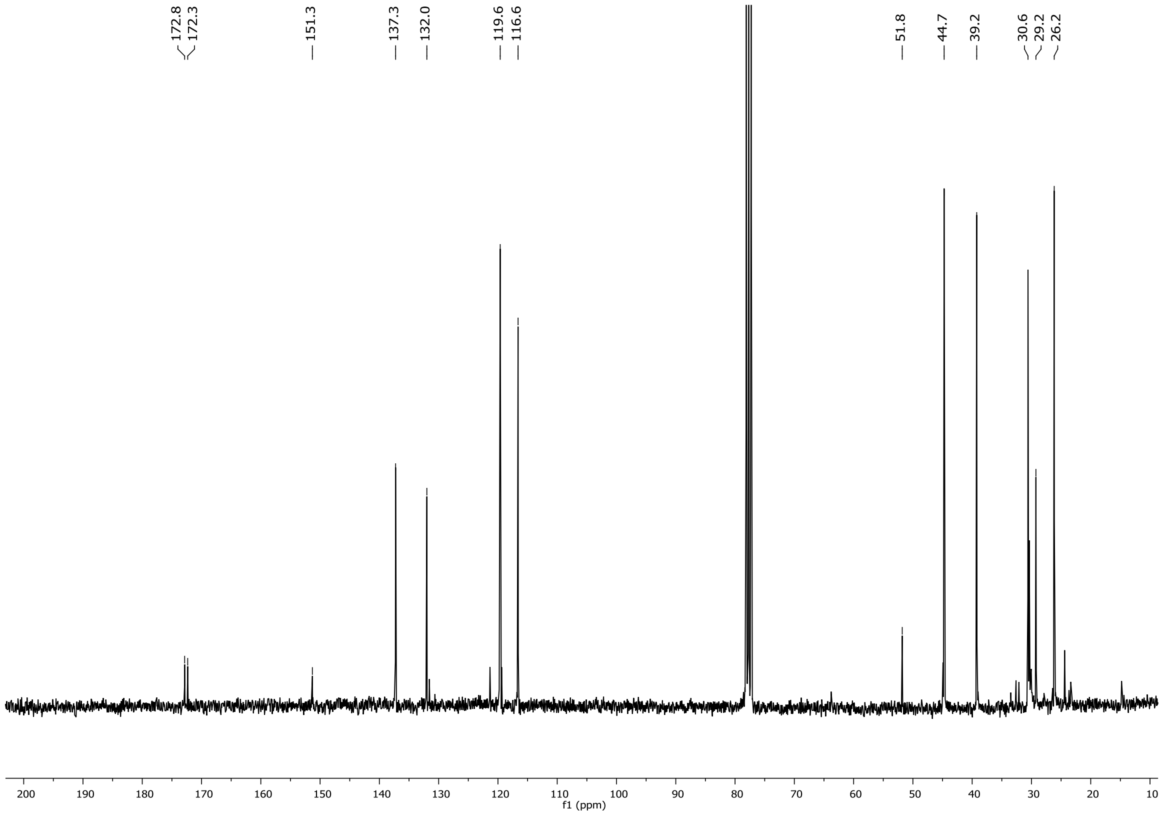


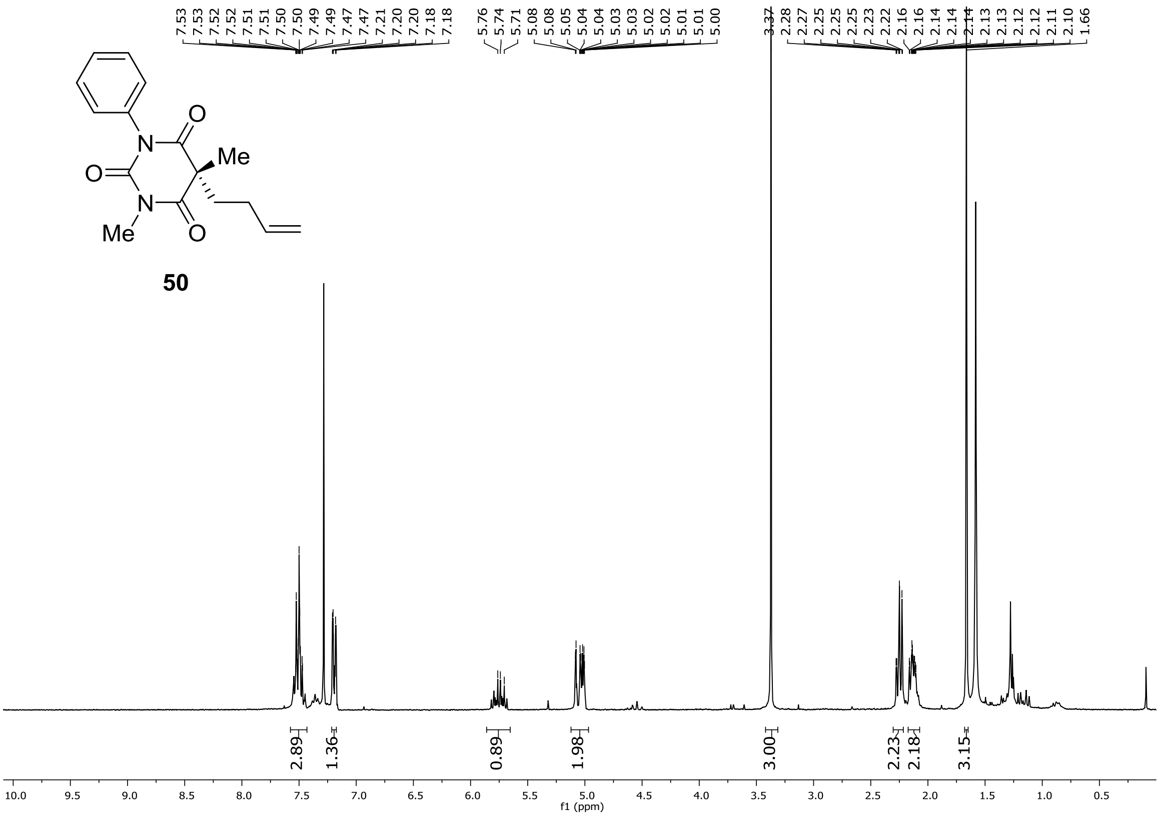
172.8 172.7
151.6
137.2
129.8 129.2 128.7
116.5
51.8
45.8
39.4
30.5 29.3 26.0
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

O
N
Me
O
N
Me
O

49

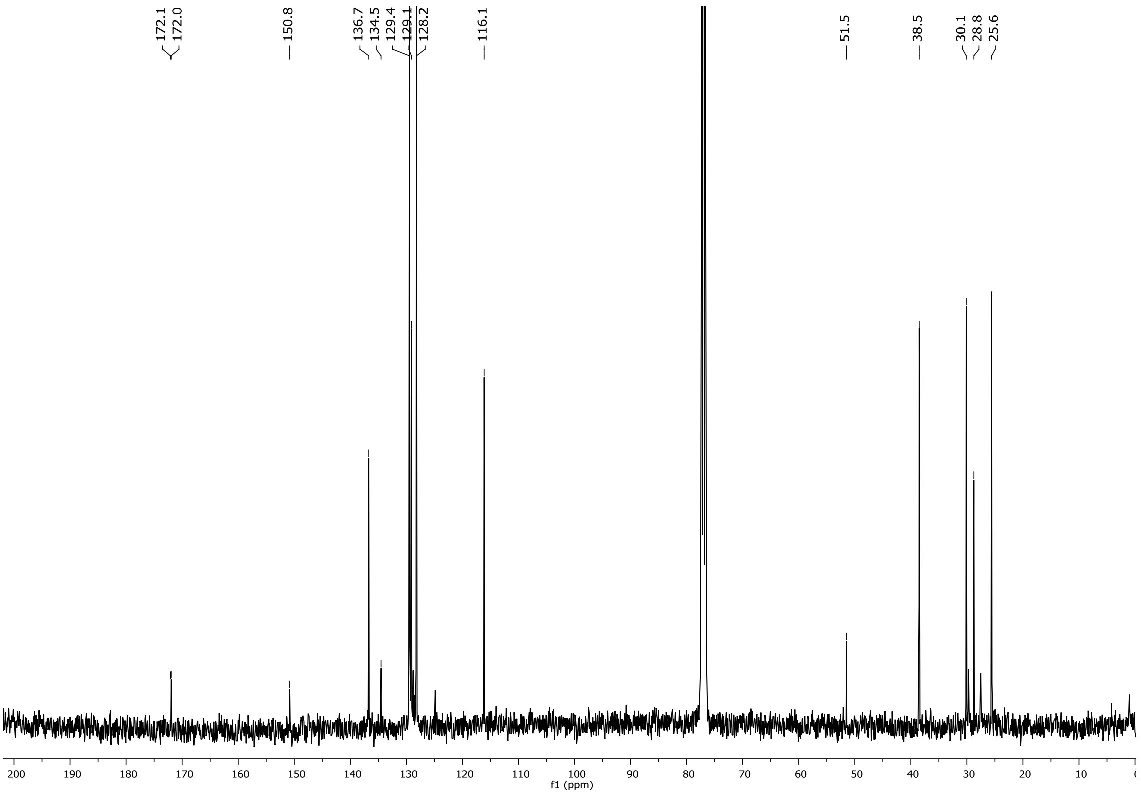

5.88
5.88
5.86
5.83
5.68
5.66
5.65
5.62
5.36
5.35
5.34
5.30
5.29
5.29
5.28
5.27
5.27
5.26
5.24
5.24
5.23
5.23
5.23
4.98
4.97
4.97
4.96
4.96
4.95
4.95
4.93
4.92
4.92
4.91
4.51
4.51
4.49
4.49
2.18
2.18
2.17
2.16
2.13
2.00
1.99
1.98
1.98
1.97
1.97
1.97
1.96
1.96
1.95
1.95
1.94
1.55
0.72
0.71
1.80
1.52
2.00
2.86
2.07
2.06
3.24
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
f1 (ppm)


172.8
172.3
151.3
137.3
132.0
119.6
116.6
51.8
44.7
39.2
30.6
29.2
26.2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



50

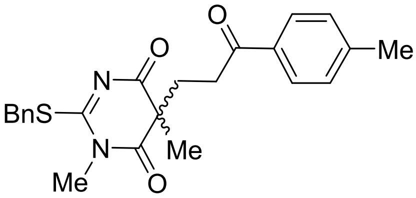
7.53
7.53
7.52
7.52
7.51
7.51
7.50
7.50
7.49
7.49
7.47
7.47
7.21
7.20
7.20
7.18
7.18
5.76
5.74
5.71
5.08
5.08
5.05
5.04
5.04
5.03
5.03
5.02
5.02
5.01
5.01
5.00
3.37
2.28
2.27
2.25
2.25
2.25
2.23
2.22
2.16
2.16
2.14
2.14
2.14
2.13
2.13
2.12
2.12
2.11
2.10
1.66
O
N
Me
O
N
Me
O
2.89
1.36
0.89
1.98
3.00
2.23
2.18
3.15
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
f1 (ppm)



172.1
172.0
150.8
136.7
134.5
129.4
129.1
128.2
116.1
51.5
38.5
30.1
28.8
25.6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

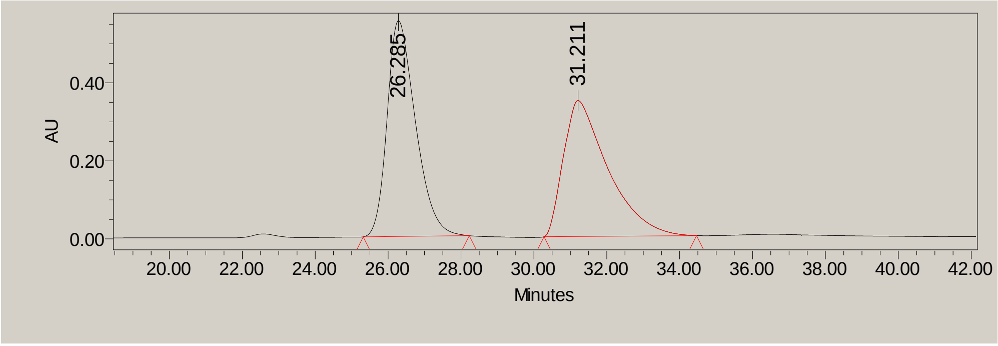
5.3.14. HPLC chromatograms

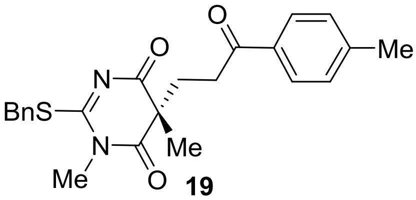
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
O
Me
N
BnS
N
Me
Me
O

19

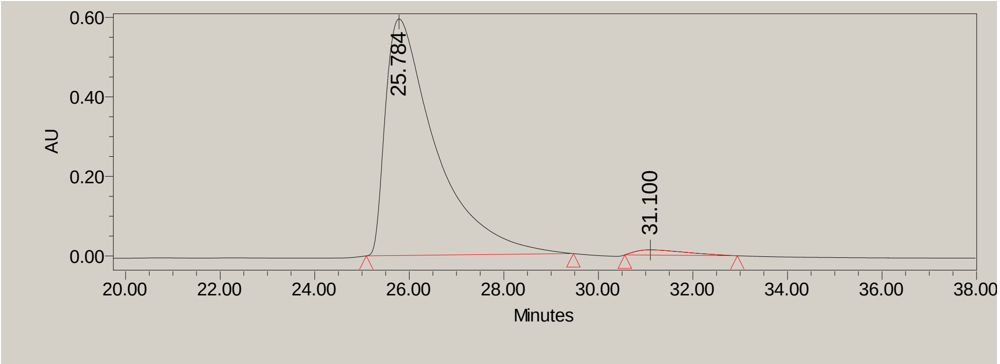
	Retention Time	% Area
	26.285	50.43
	31.211	49.57



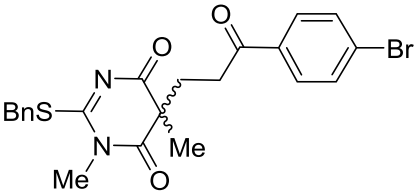

O
O
Me
N
BnS
N
Me
Me
O

19

	Retention Time	% Area
	25.784	97.81
	31.100	2.19

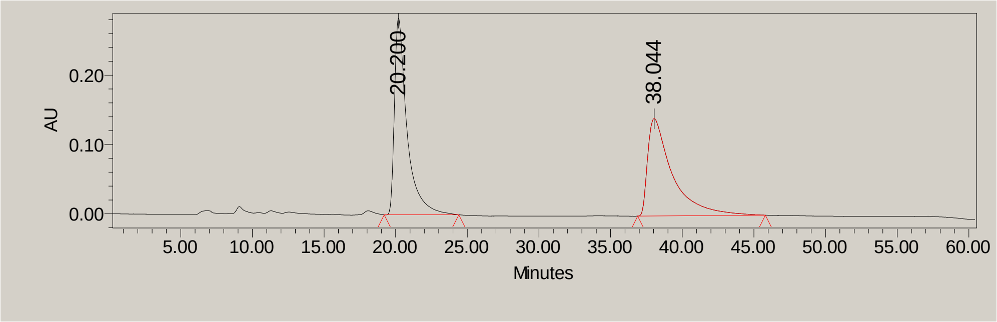


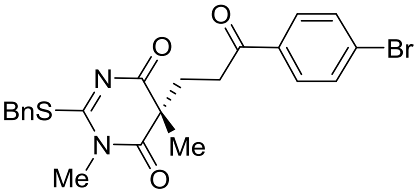
Chiralpack IA 0.5 mL/min, hexano:isopropanol 50:50, λ = 210 nm


O
O
Br
N
BnS
N
Me
Me
O

20

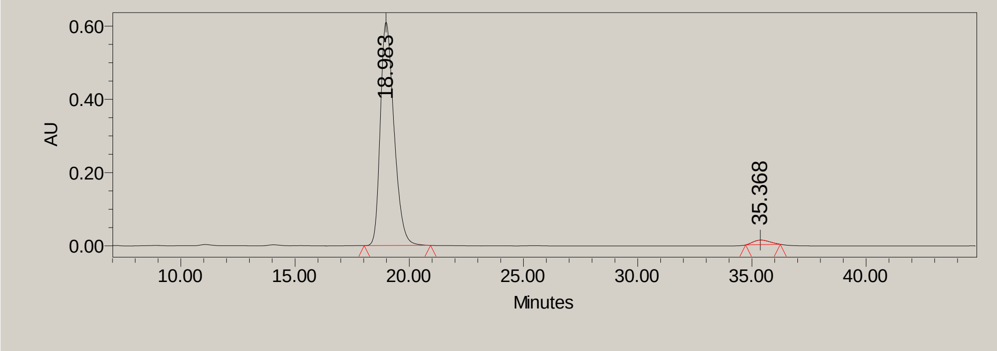
	Retention Time	% Area
	20.200	50.54
	38.044	49.46



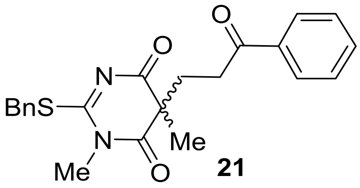

O
O
Br
N
BnS
N
Me
Me
O

20

	Retention Time	% Area
	18.983	97.58
	35.368	2.42

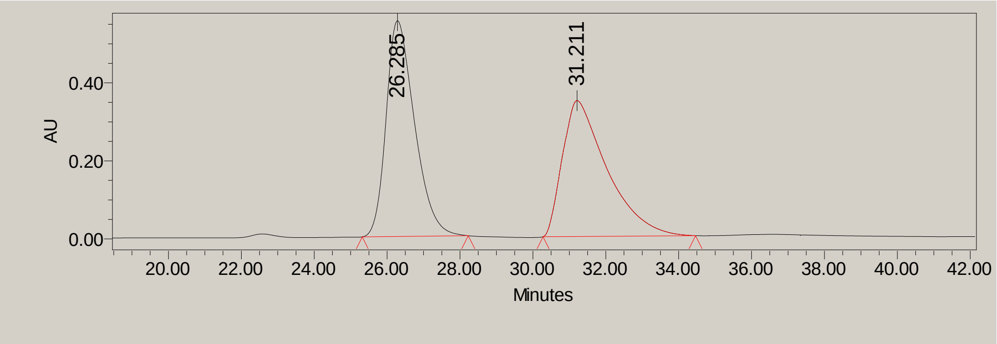


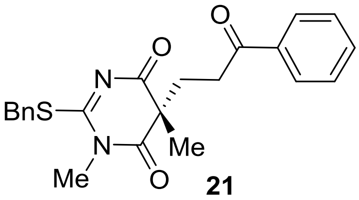
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
O
N
BnS
N
Me
O
Me

21

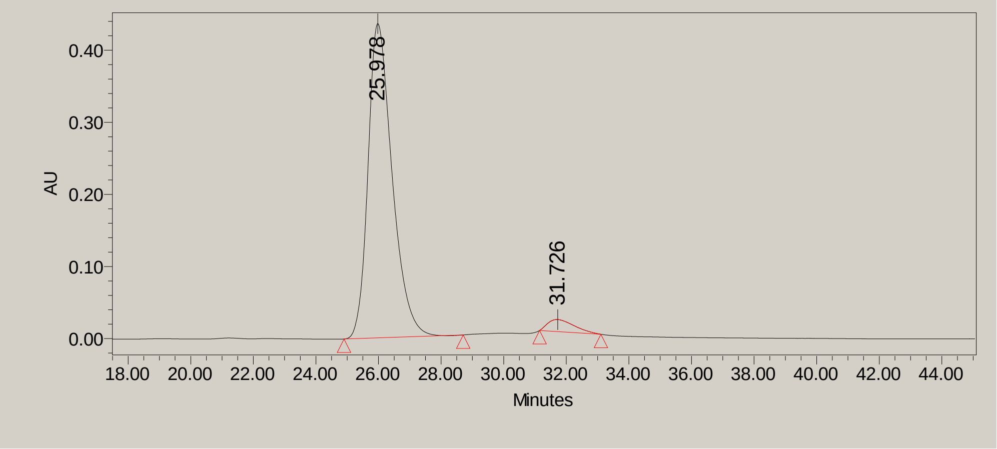
	Retention Time	% Area
	26.285	50.43
	31.211	49.57



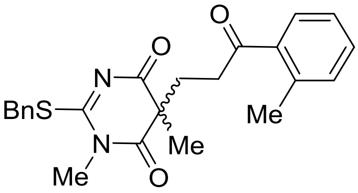

O
O
N
BnS
N
Me
O
Me

21

	Retention Time	% Area
	25.978	95.92
	31.726	4.08

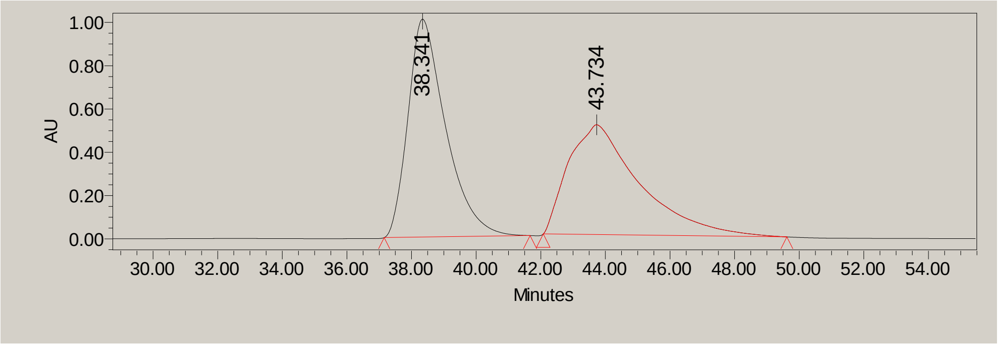


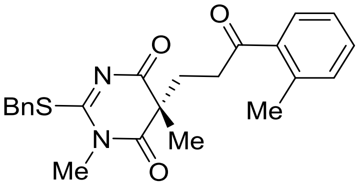
Chiralpack IA 0.5 mL/min, hexano:isopropanol 90:10, λ = 210 nm


O
O
N
BnS
N
Me
Me
O
Me

22

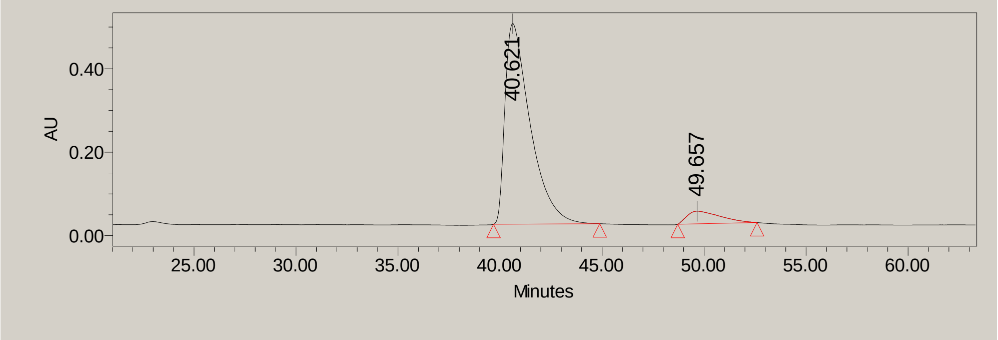
	Retention Time	% Area
	38.341	51.22
	43.734	48.78



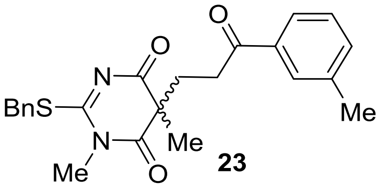

O
O
N
BnS
N
Me
Me
O
Me

22

	Retention Time	% Area
	40.621	92.32
	49.657	7.68

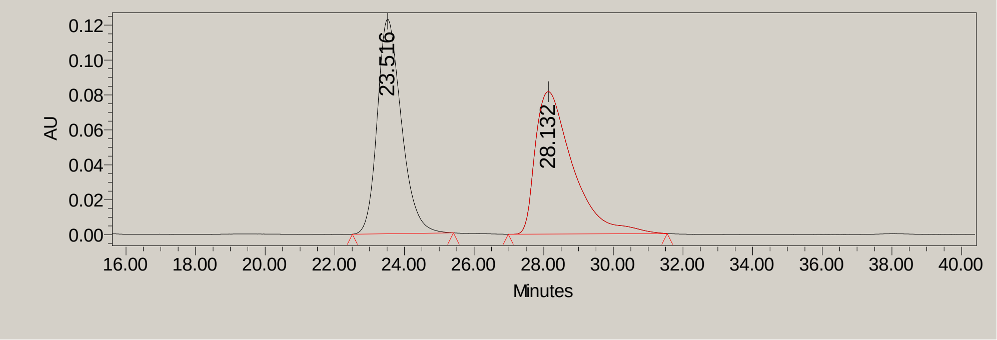


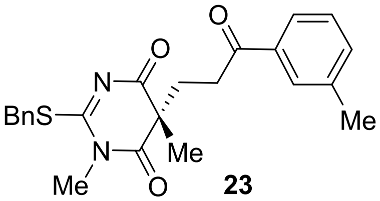
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
O
N
BnS
N
Me
Me
O
Me

23

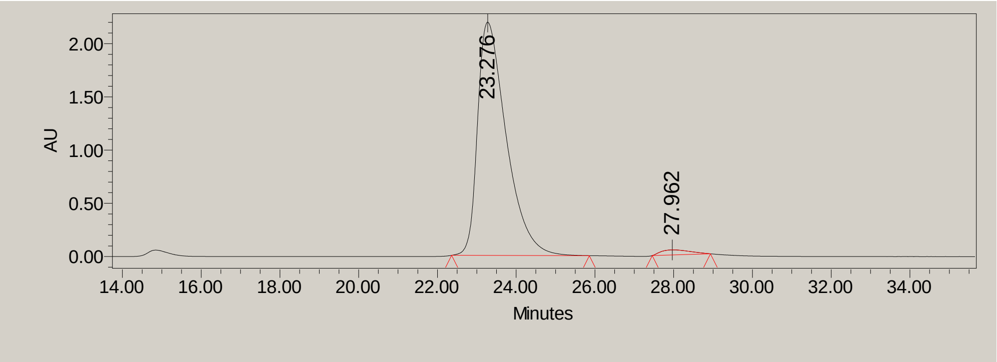
	Retention Time	% Area
	23.516	49.20
	28.132	50.80



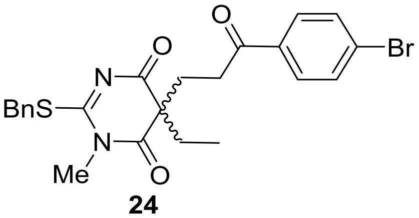

O
O
N
BnS
N
Me
Me
O
Me

23

	Retention Time	% Area
	23.276	97.83
	27.962	2.17

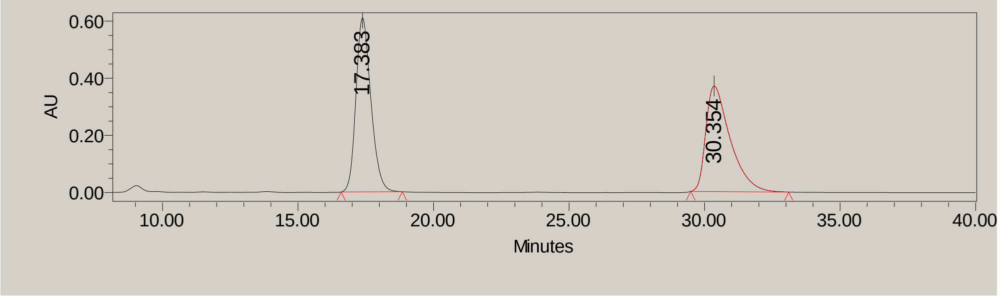


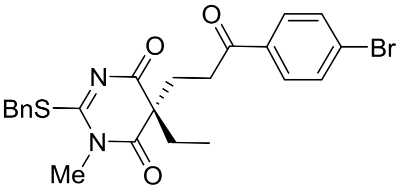
Chiralpack IA 0.5 mL/min, hexano:isopropanol 50:50, λ = 210 nm


O
Br
O
N
BnS
N
Me
O

24

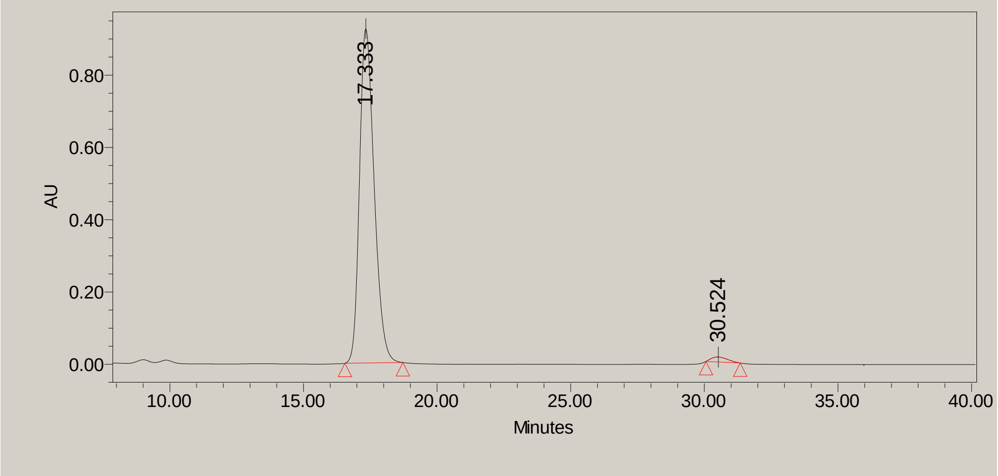
Retention Time	% Area
17.383	50.34
30.354	49.66



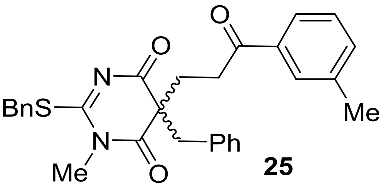

O
Br
O
N
BnS
N
Me
O

24

Retention Time	% Area
17.333	98.35
30.524	1.65

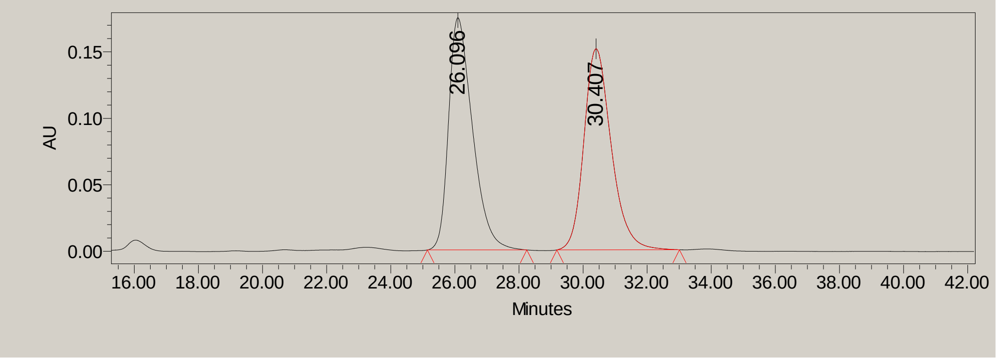


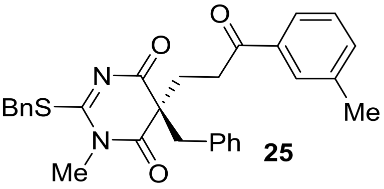
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
O
N
BnS
N
Me
O
Ph
Me

25

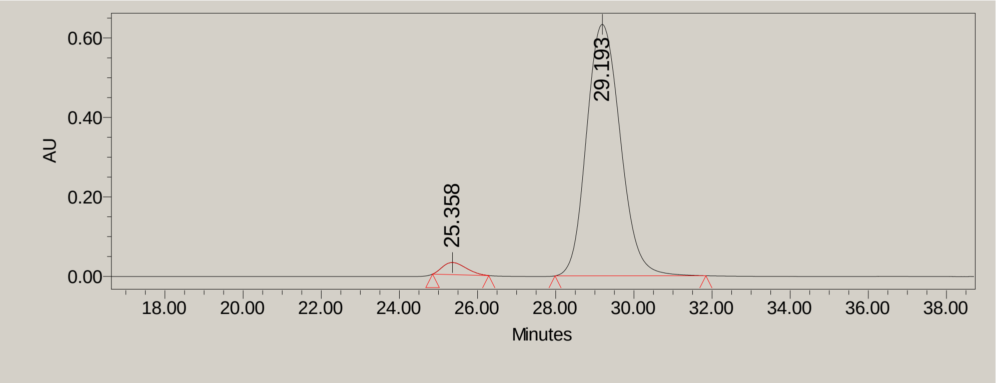
	Retention Time	% Area
	26.096	50.26
	30.407	49.74



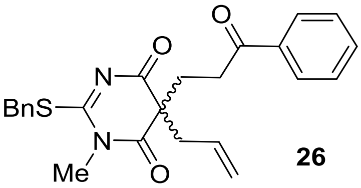

O
O
N
BnS
N
Me
O
Ph
Me

25

	Retention Time	% Area
	25.358	3.26
	29.193	96.74

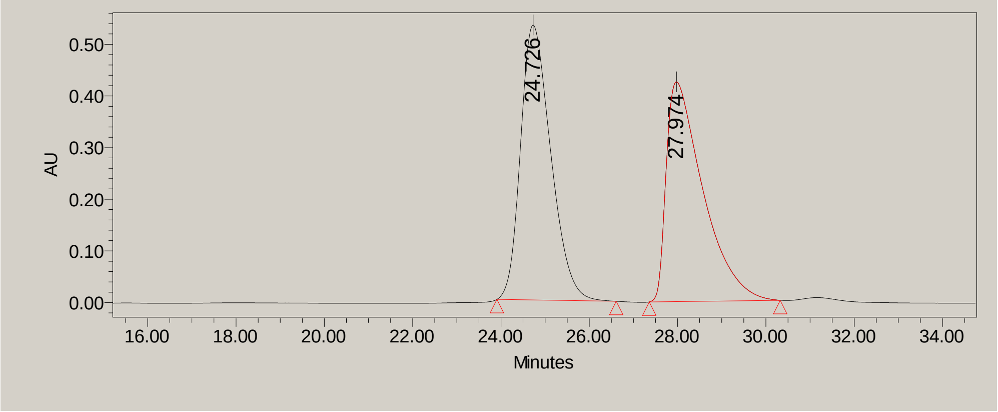


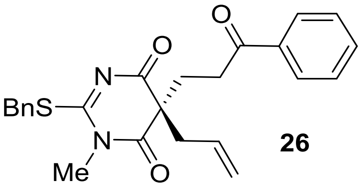
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
O
N
BnS
N
Me
O

26

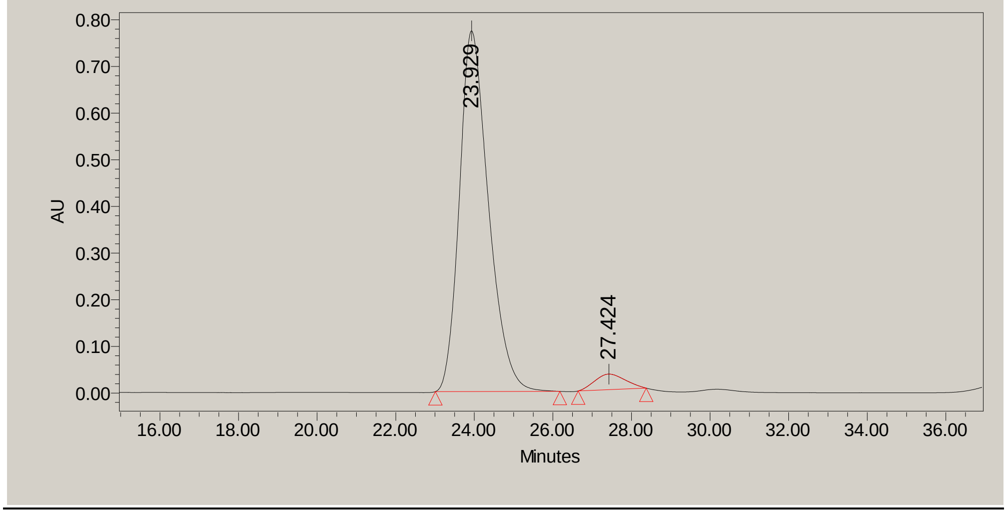
	Retention Time	% Area
	24.726	50.79
	27.974	49.21



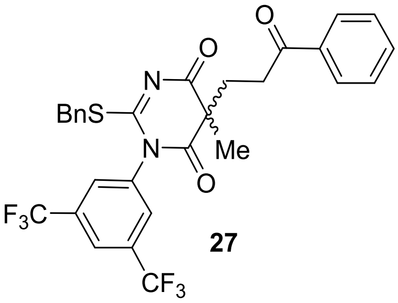

O
O
N
BnS
N
Me
O

26

	Retention Time	% Area
	23.929	95.67
	27.424	4.33

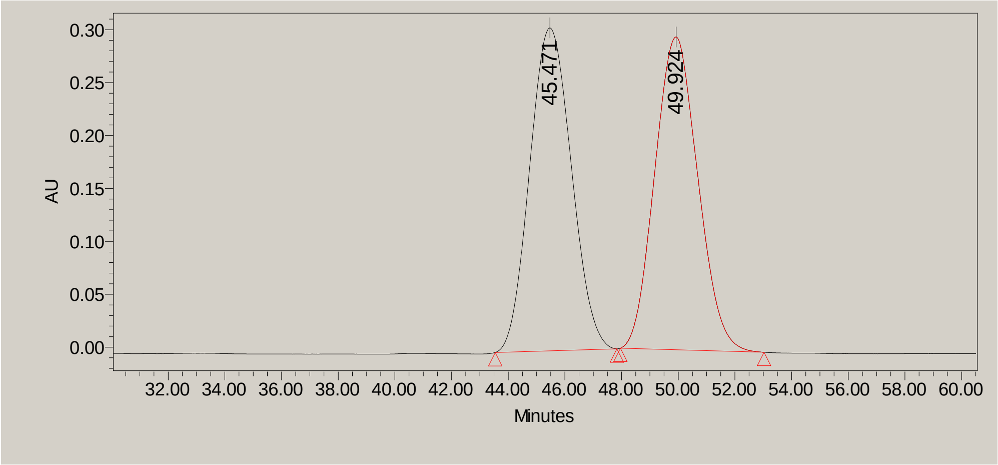


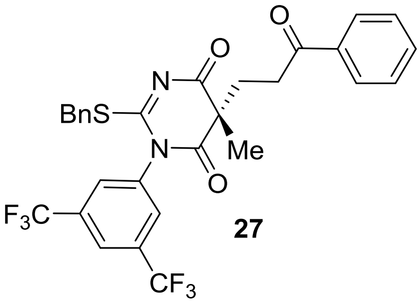
Chiralpack IC 0.5 mL/min, hexano:isopropanol 95:5, λ = 210 nm


O
O
N
BnS
N
Me
O
F3C
CF3

27

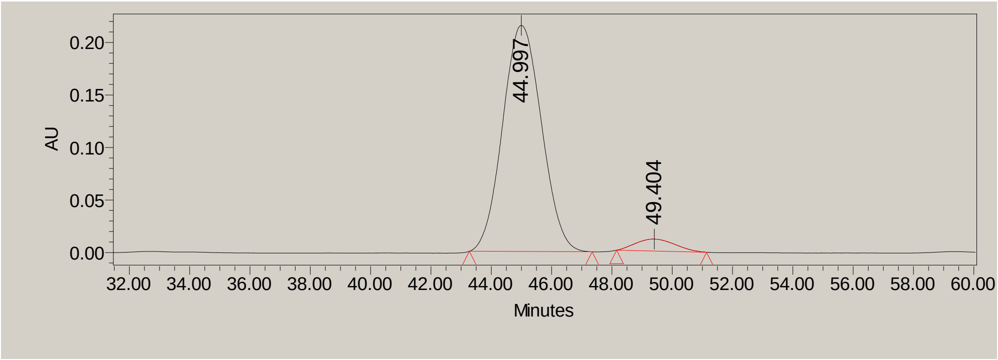
	Retention Time	% Area
	45.471	49.98
	49.924	50.02



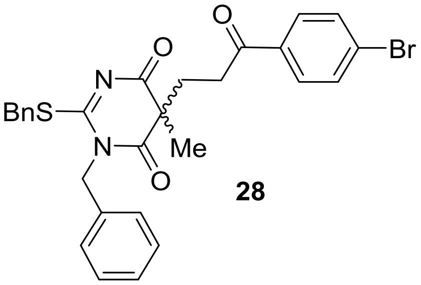

O
O
N
BnS
N
Me
O
F3C
CF3

27

	Retention Time	% Area
	44.997	94.93
	49.404	5.07

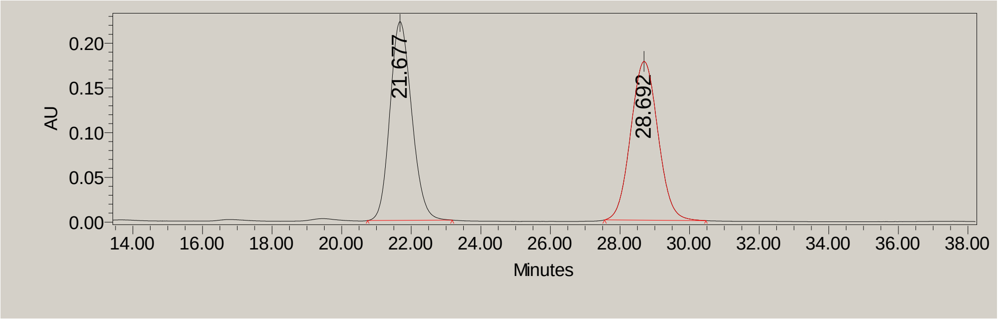


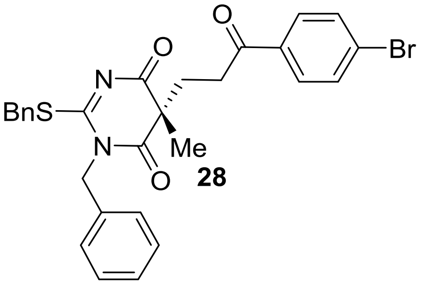
Chiralpack IA 0.5 mL/min, hexano:isopropanol 50:50, λ = 210 nm


BnS
N
N
O
O
O
Br
Me

28

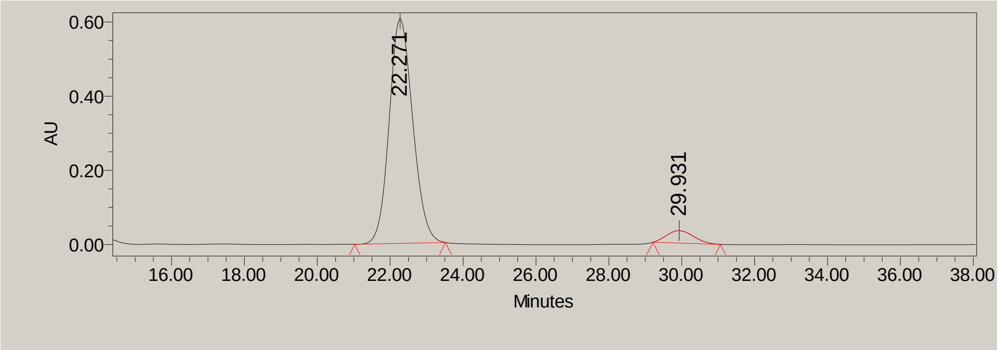
	Retention Time	% Area
	21.677	50.01
	28.692	49.99



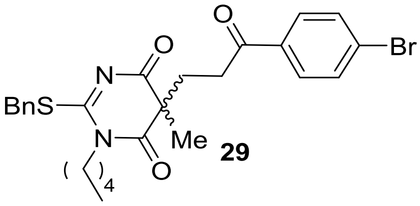

BnS
N
N
O
O
O
Br
Me

28

	Retention Time	% Area
	22.271	94.96
	29.912	5.04

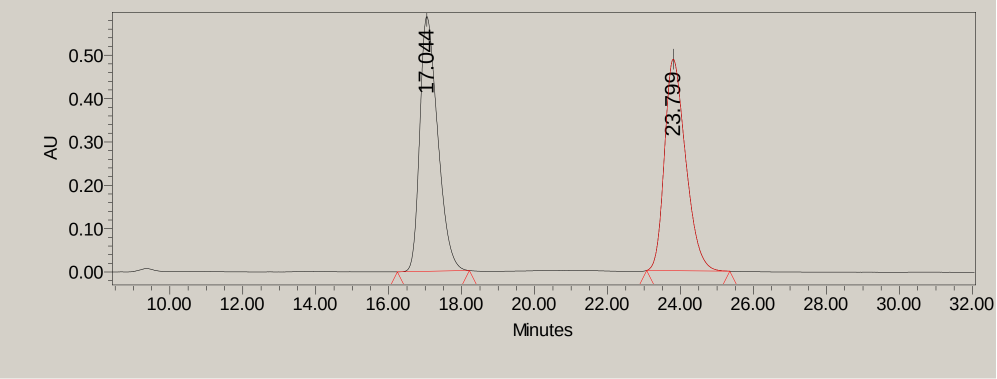


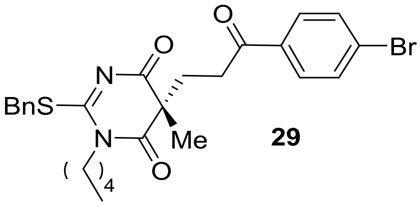
Chiralpack IB 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
O
Br
N
BnS
N
Me
O
( )4

29

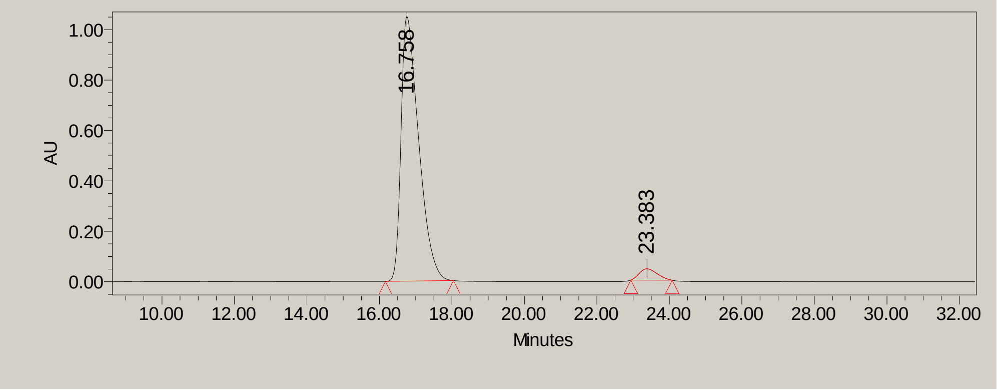
	Retention Time	% Area
	17.044	50.50
	23.799	49.50




O
O
Br
N
BnS
N
Me
O
( )4

29

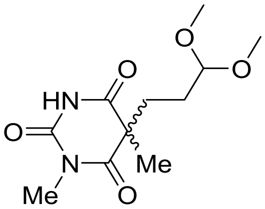
	Retention Time	% Area
	16.758	95.83
	23.383	4.17



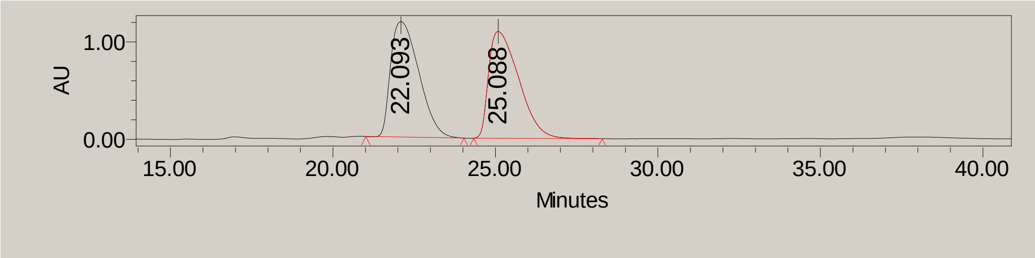
HPLC analyses of aldehyde **30** were carried out after derivatization of **30** onto the corresponding dimethyl acetal.

Chiralpack IB 0.5 mL/min, hexano:isopropanol 80:20, λ= 210 nm

(from rac **30**)

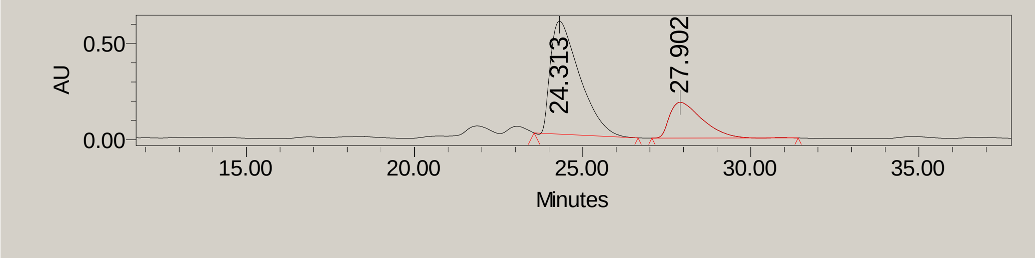


	Retention Time	% Area
	22.093	50.38
	25.088	49.62



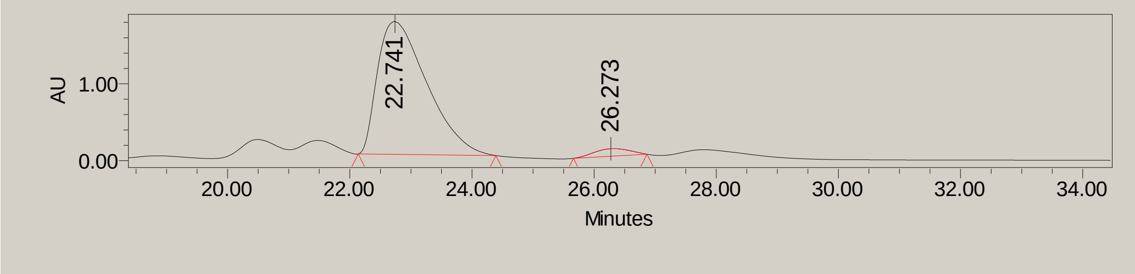
a) Obtained from the conjugate addition to acrolein and derivatization (Section 5.3.6.5 p. 175)

	Retention Time	% Area
	24.313	73.77
	27.902	26.23

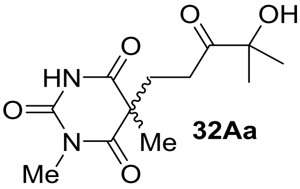


b) Obtained from the oxidative scission of adduct **32Aa** and derivatization (Section 5.3.12.3, p 191)

	Retention Time	% Area
	22.741	96.07
	26.273	3.93

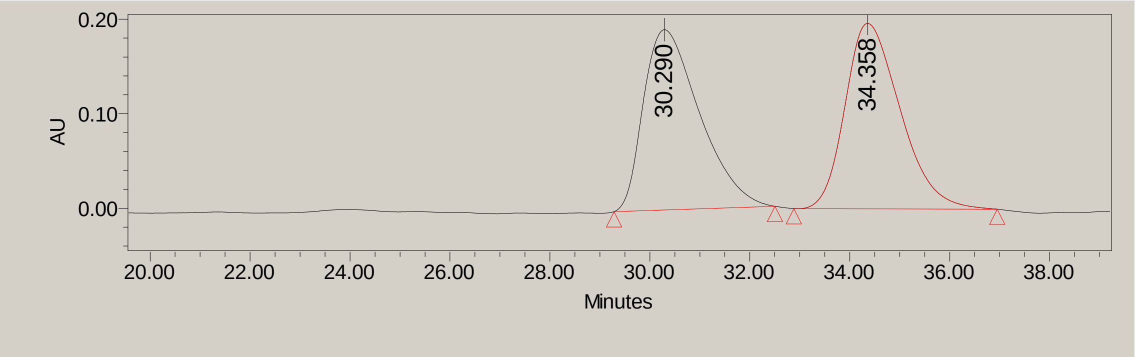


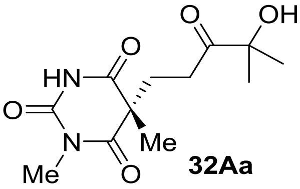
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
OH
O
HN
O
N
Me
Me
O

32Aa

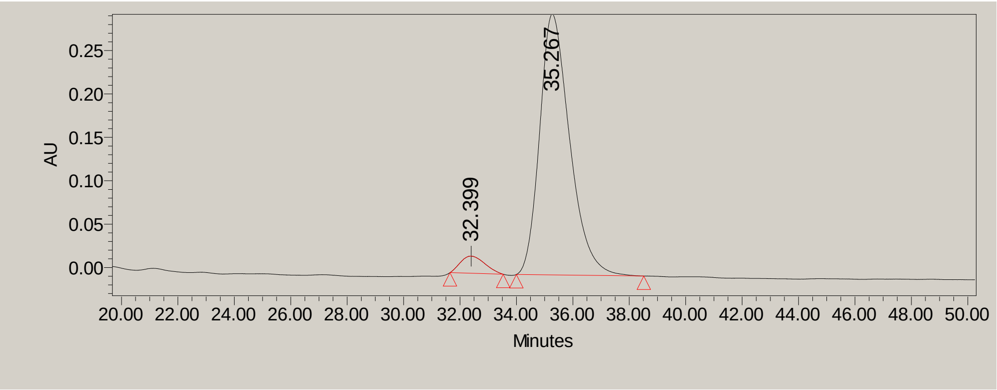
	Retention Time	% Area
	30.290	49.78
	34.358	50.22



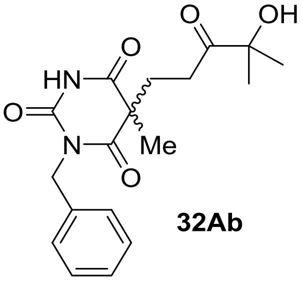

O
OH
O
HN
O
N
Me
Me
O

32Aa

	Retention Time	% Area
	32.399	5.05
	35.267	94.95

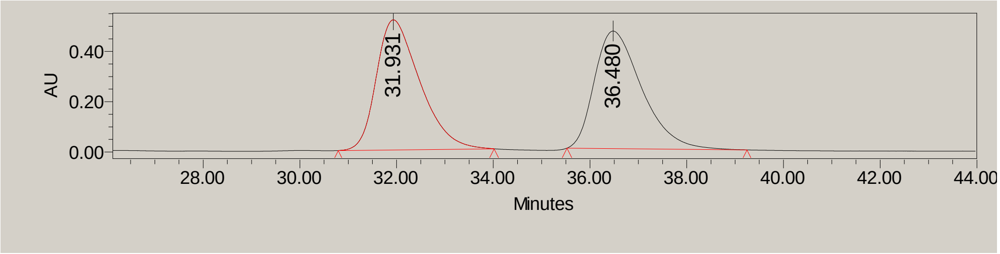


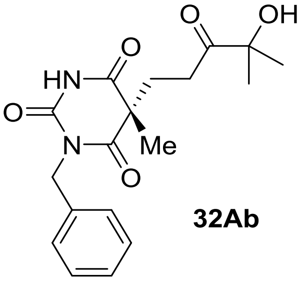
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
OH
HN
O
O
N
Me
O

32Ab

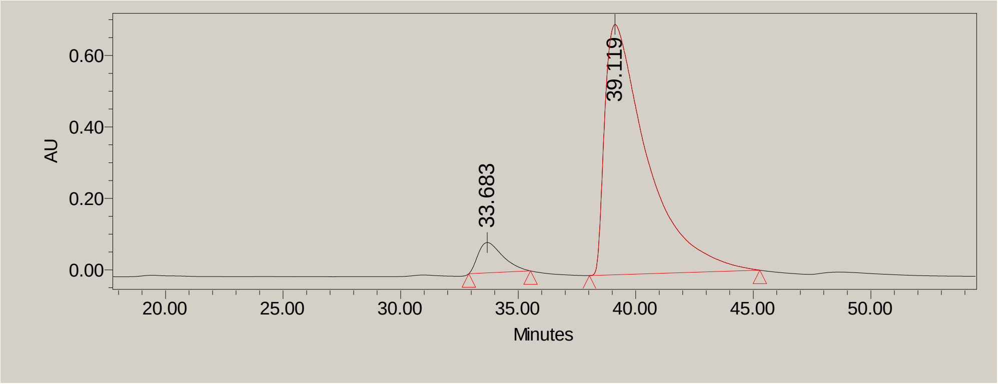
	Retention Time	% Area
	31.931	50.41
	36.480	49.59



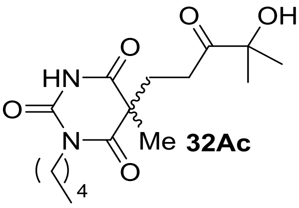

O
OH
HN
O
O
N
Me
O

32Ab

	Retention Time	% Area
	33.683	6.57
	39.119	93.43

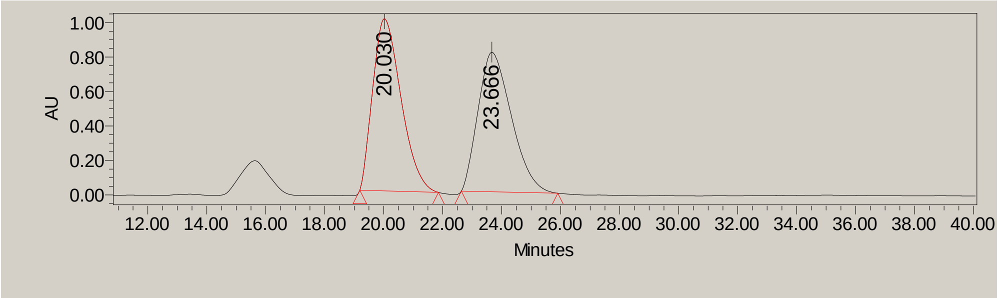


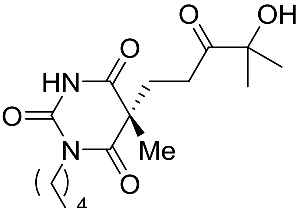
Chiralpack IB 0.5 mL/min, hexano:isopropanol 90:10, λ = 210 nm


O
OH
O
HN
O
N
Me
O
4

32Ac

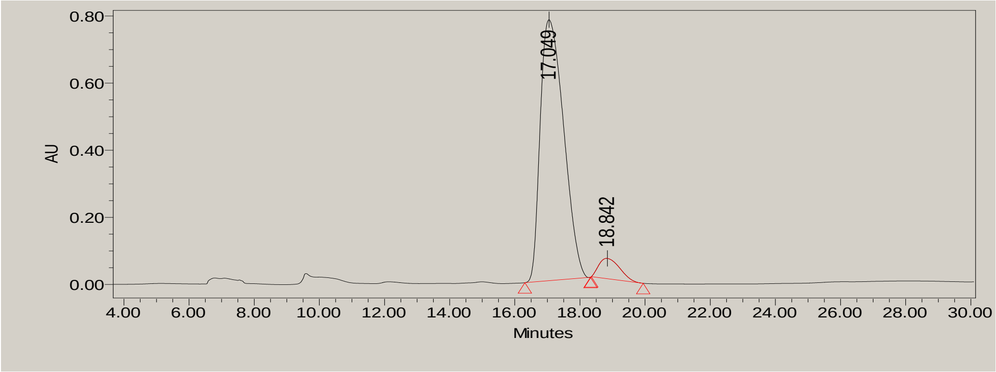
	Retention Time	% Area
	20.030	51.17
	23.666	48.83



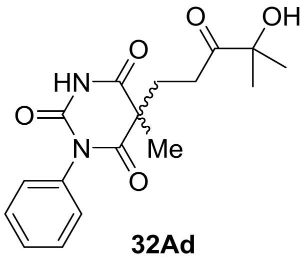

O
OH
O
HN
O
N
Me
O
4

32Ac

	Retention Time	% Area
	17.049	93.48
	18.842	6.52



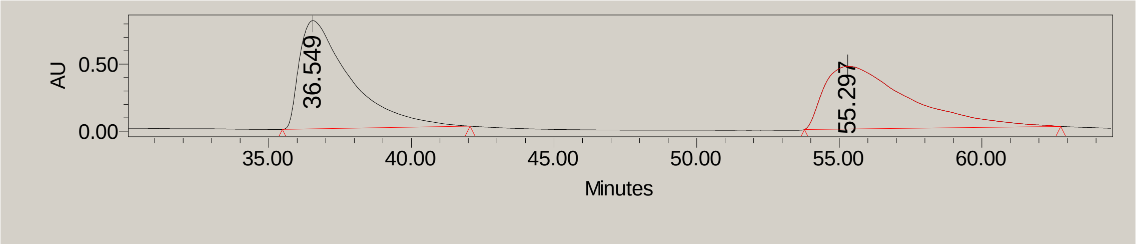
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm

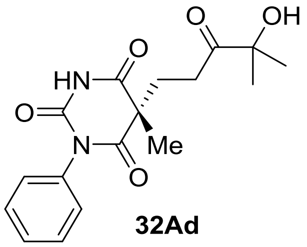


O
OH
O
HN
O
N
Me
O

32Ad

	Retention Time	% Area
	36.549	50.83
	55.297	49.17

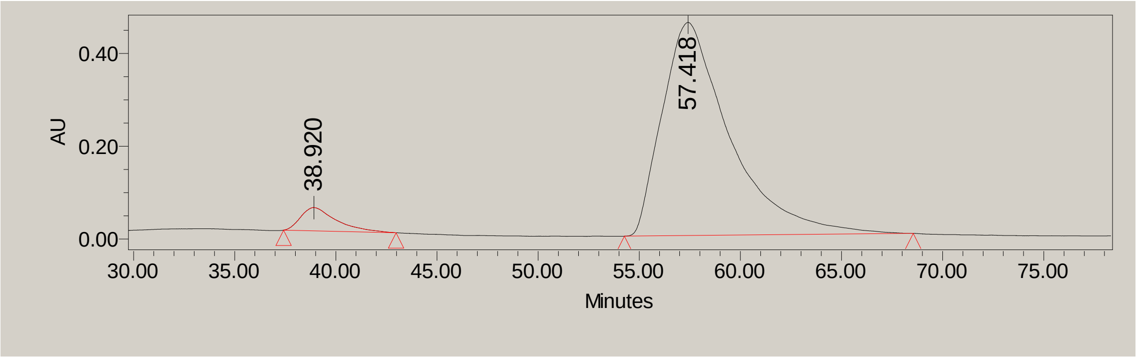




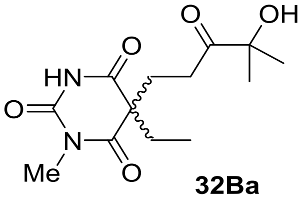
O
OH
O
HN
O
N
Me
O

32Ad

	Retention Time	% Area
	38.920	5.42
	57.418	94.58

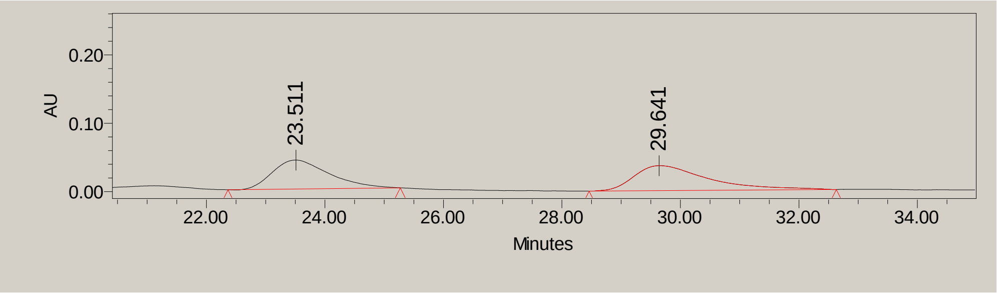


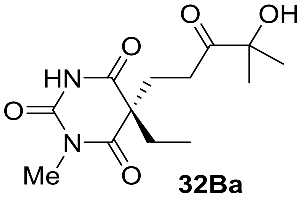
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
OH
HN
O
O
N
Me
O

32Ba

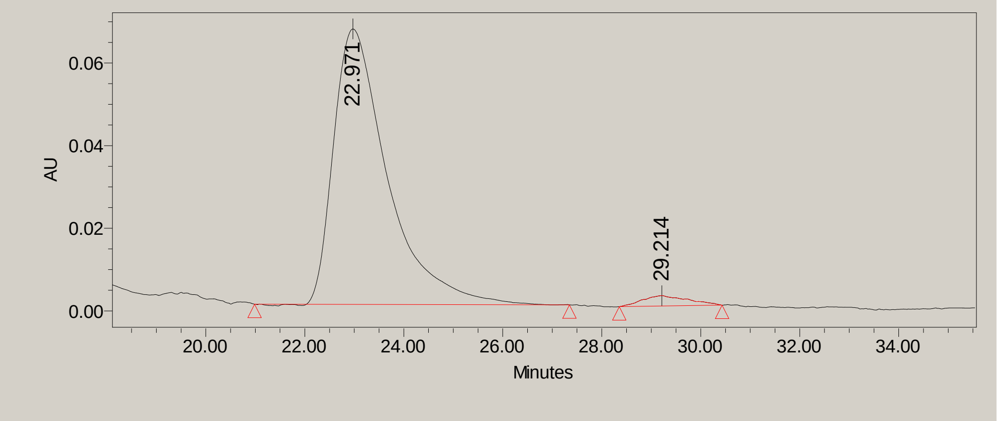
	Retention Time	% Area
	23.511	46.97
	29.641	53.03



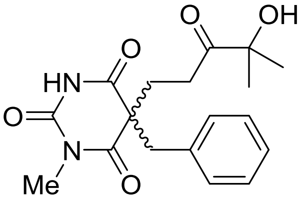

O
OH
HN
O
O
N
Me
O

32Ba

	Retention Time	% Area
	22.971	96.92
	29.214	3.08

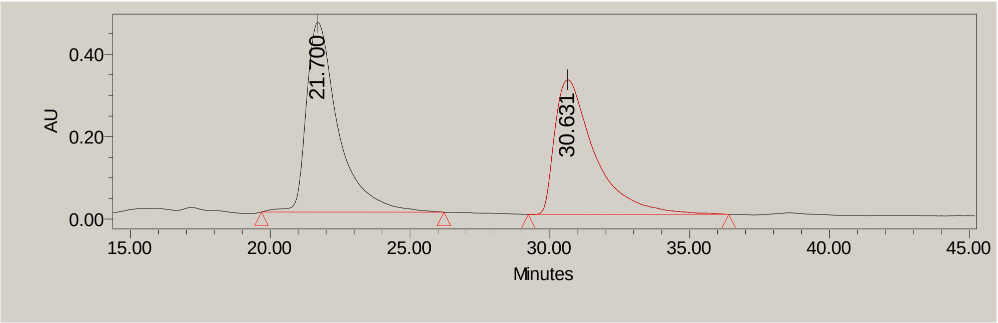


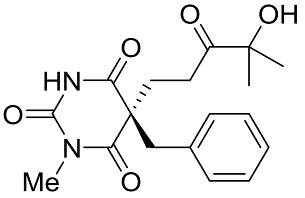
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
OH
O
HN
O
N
Me
O

32Ca

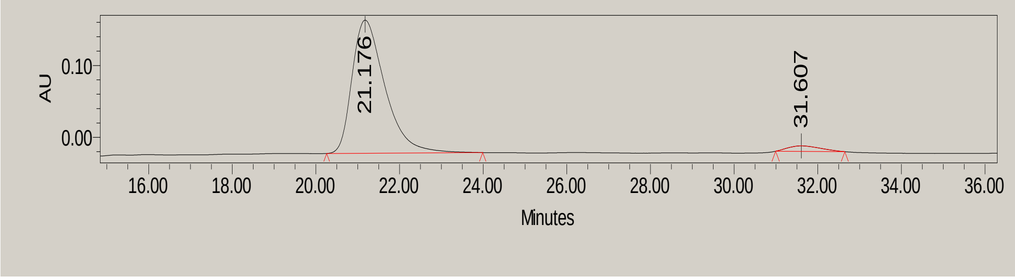
	Retention Time	% Area
	21.700	53.82
	30.631	46.18



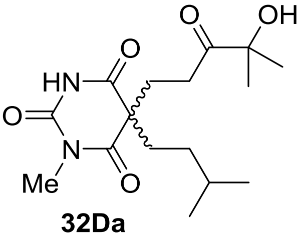

O
OH
O
HN
O
N
Me
O

32Ca

	Retention Time	% Area
	21.176	96.02
	31.607	3.98

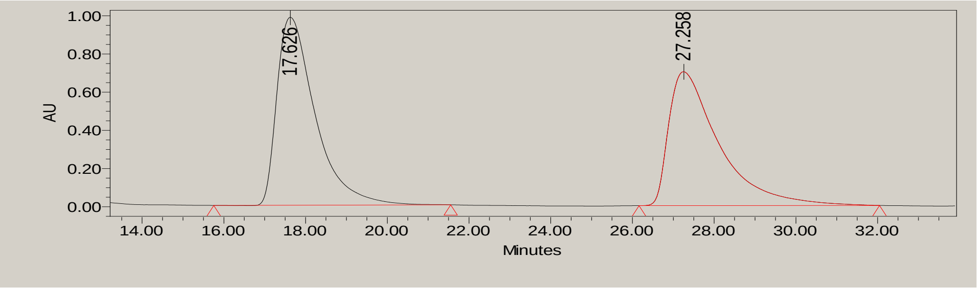


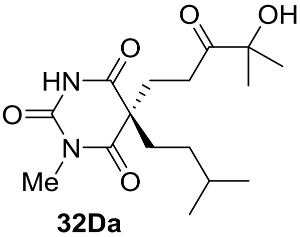
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
OH
O
HN
O
N
Me
O

32Da

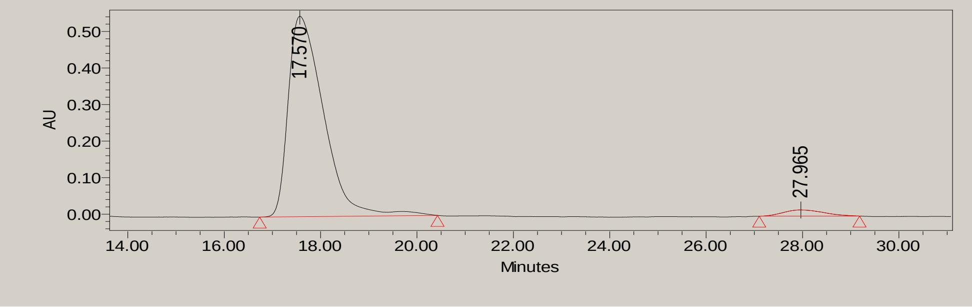
	Retention Time	% Area
	17.626	51.71
	27.258	48.29



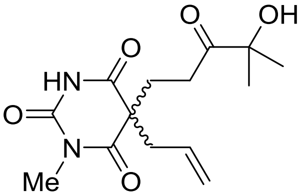

O
OH
O
HN
O
N
Me
O

32Da

	Retention Time	% Area
	17.570	96.59
	27.965	3.41

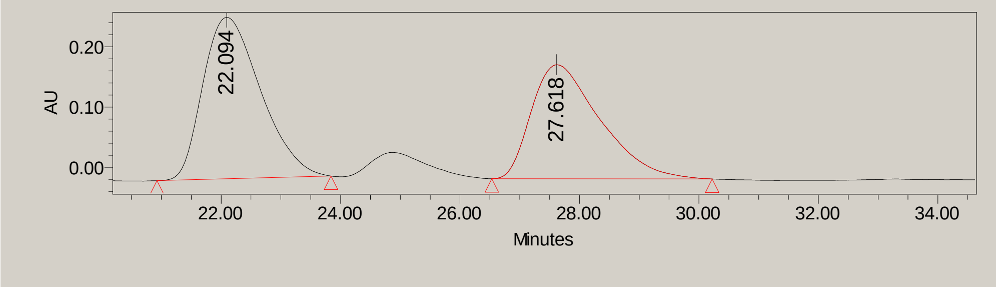


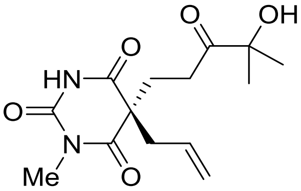
Chiralpack ADH 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm


O
OH
O
HN
O
N
Me
O

32Fa

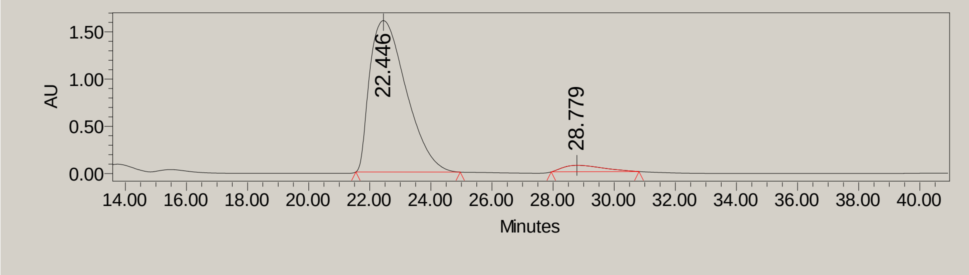
	Retention Time	% Area
	22.094	54.40
	27.618	45.60



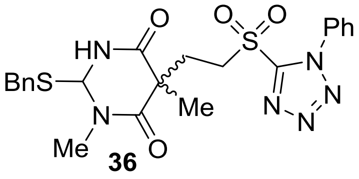

O
OH
O
HN
O
N
Me
O

32Fa

	Retention Time	% Area
	22.446	95.51
	28.779	4.49

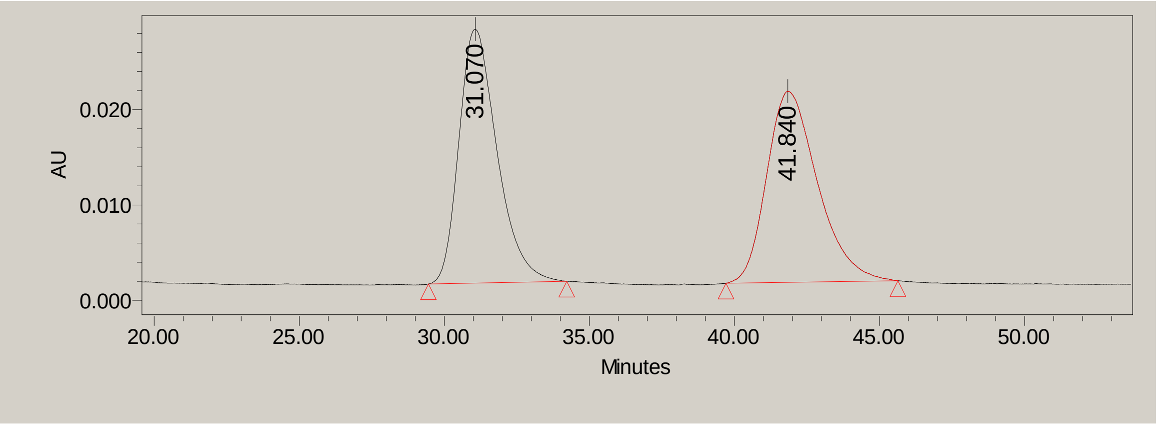


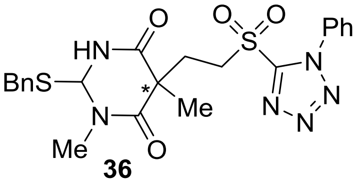
Chiralpak IC, 50:50 Hexano:^{i}PrOH, 1.0 mL/min, λ=210 nm


HN
BnS
N
Me
O
O
Me
O
S
O
Ph
N
N
N
N

36

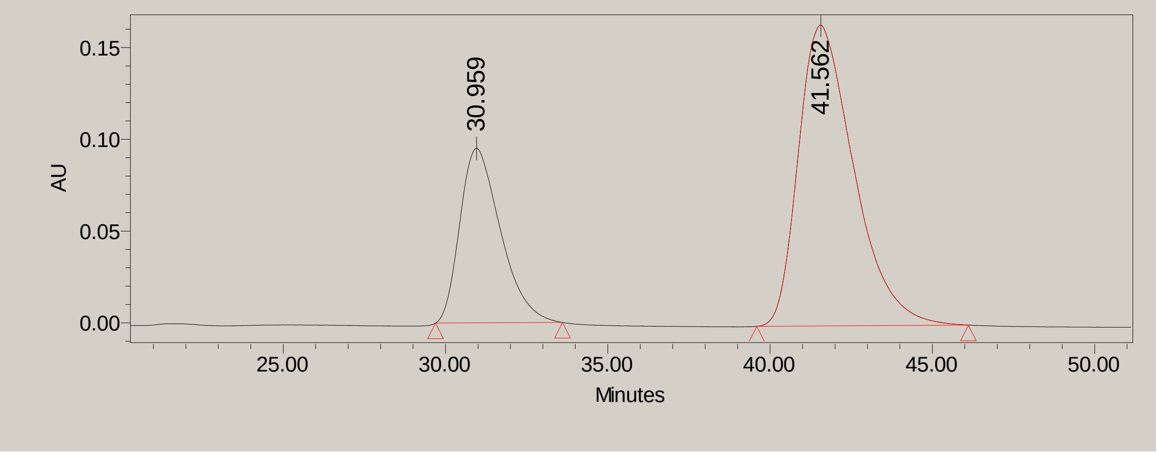
	RetentionTime	% Area
	31.070	49.93
	41.840	50.07



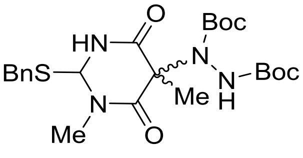

HN
BnS
N
Me
*
O
O
Me
O
S
O
Ph
N
N
N
N

36

	Retention Time	% Area
	30.959	29.82
	41.562	70.18

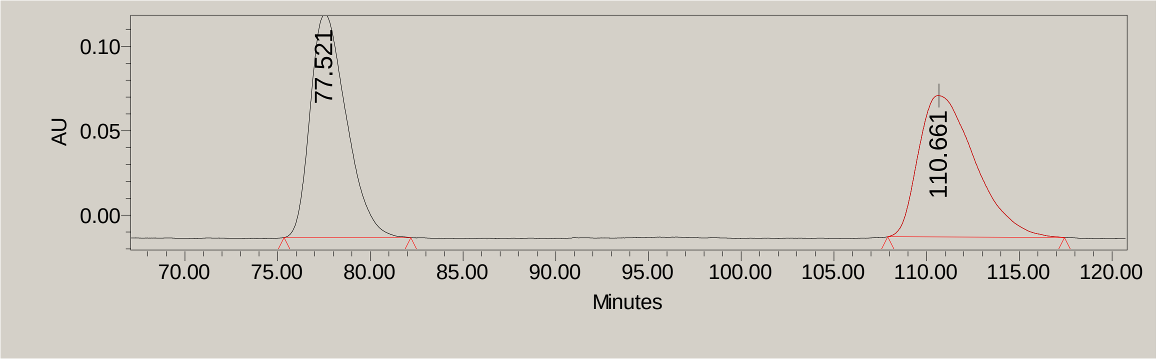


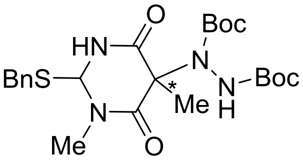
Chiralpack IC 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



37

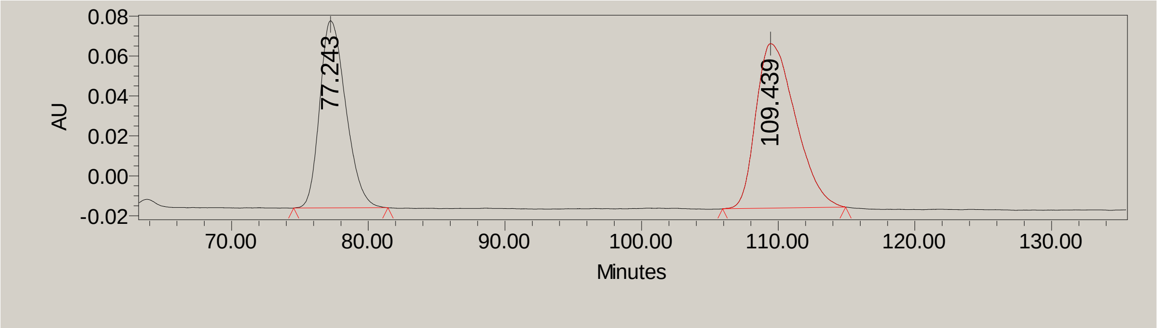
	Retention Time	% Area
	77.521	50.31
	110.661	49.69



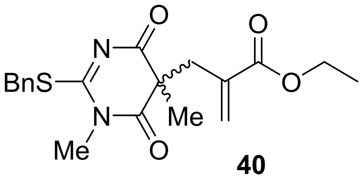


37

	Retention Time	% Area
	77.243	61.49
	109.439	38.51

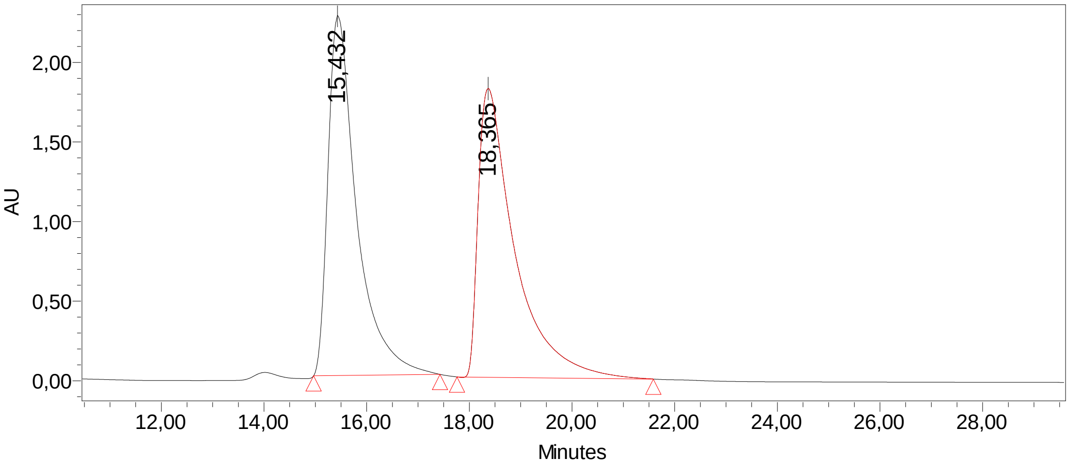


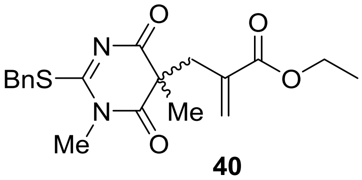
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm


BnS
N
N
Me
O
O
Me
O
O

40

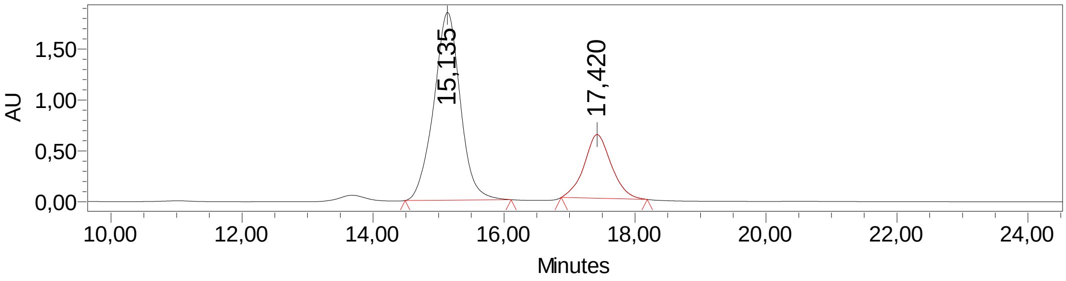
Migration Time	% Area
15,432	49,46
18,365	50,54



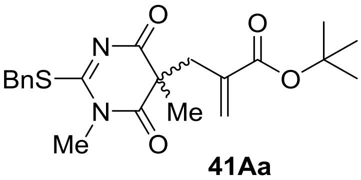

BnS
N
N
Me
O
O
Me
O
O

40

Migration Time	% Area
15,135	74,15
17,420	25,85

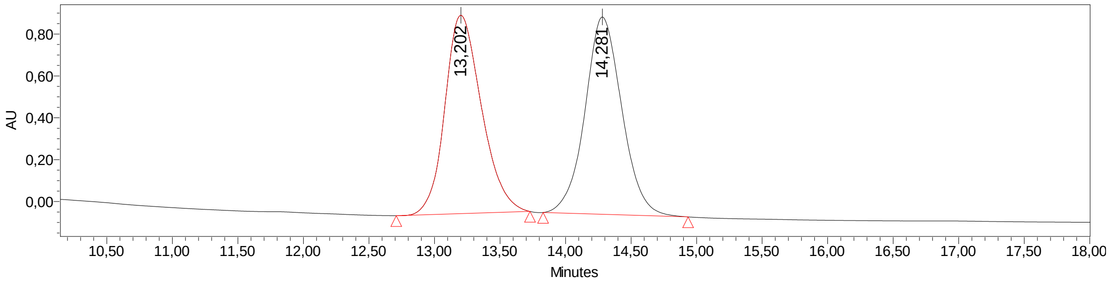


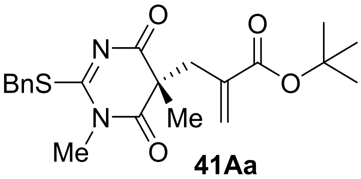
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm


BnS
N
N
Me
O
O
Me
O
O

41Aa

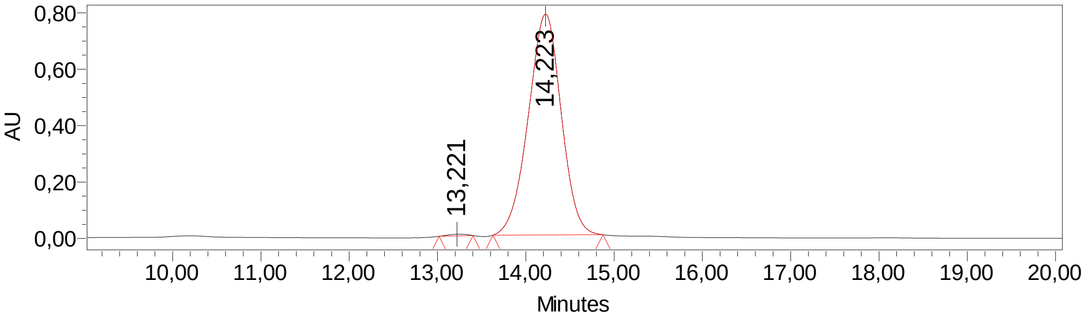
	Migration Time	% Area
	13,202	49,93
	14,281	50,07



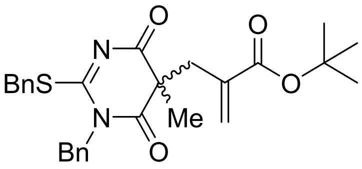

BnS
N
N
Me
O
O
Me
O
O

41Aa

	Migration Time	% Area
	13,221	0,42
	14,223	99,58

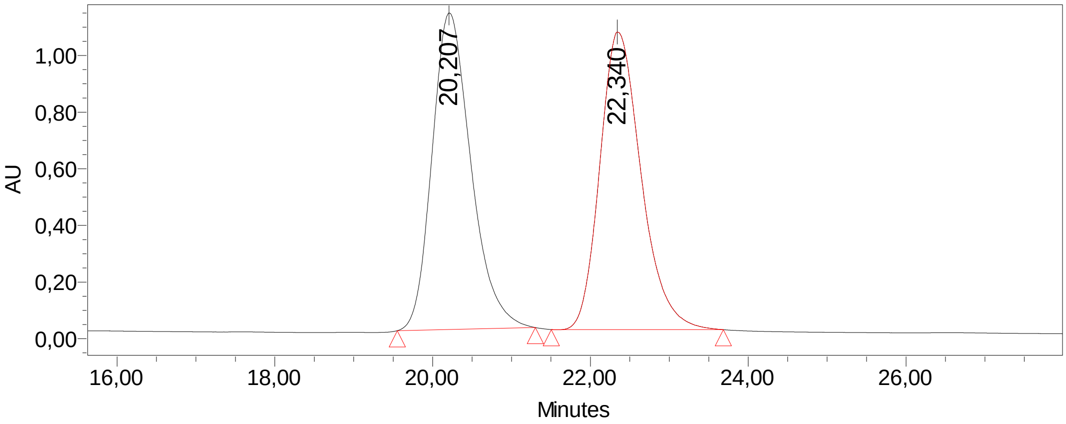


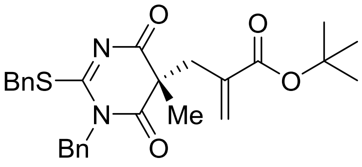
Chiralpak IC, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm


O
N
O
BnS
O
N
Me
Bn
O

41Ab

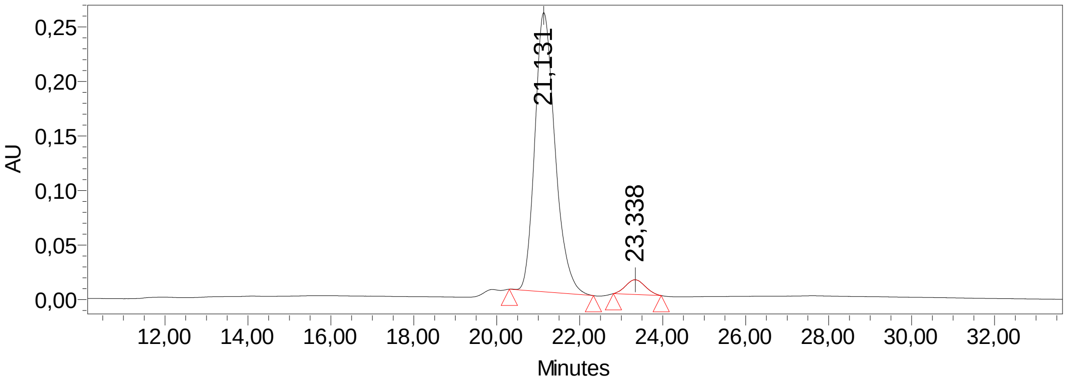
	Migration Time	% Area
	20,207	50,03
	22,340	49,97



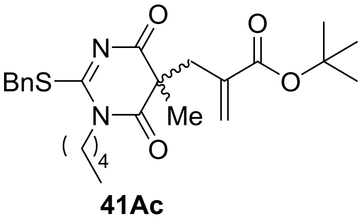

O
N
O
BnS
O
N
Me
Bn
O

41Ab

	Migration Time	% Area
	21,131	95,13
	23,338	4,87

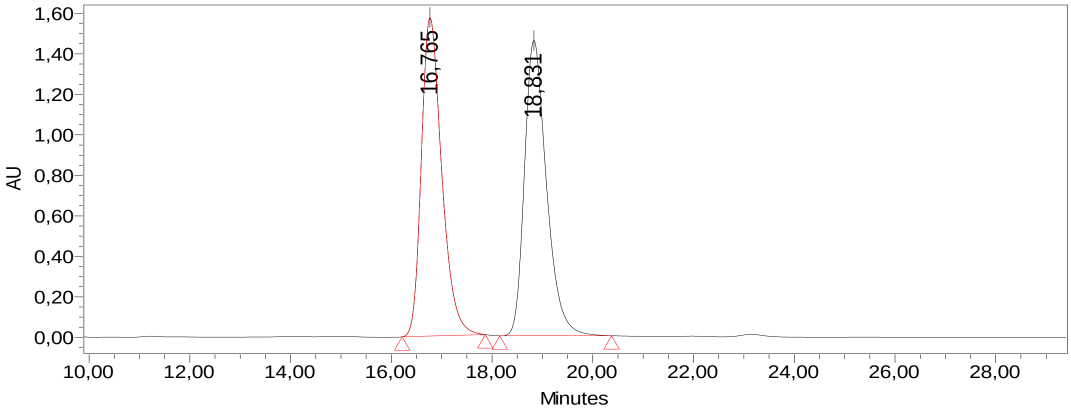


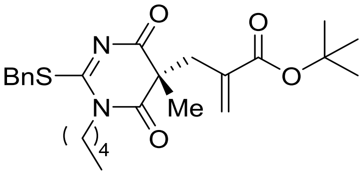
Chiralpak IC, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm


O
N
BnS
N
Me
O
O
O
4

41Ac

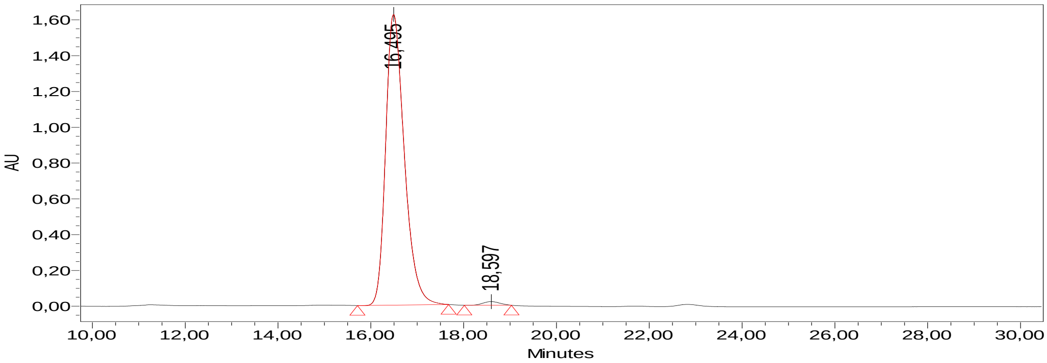
	Migration Time	% Area
	16,765	49,94
	18,831	50,06



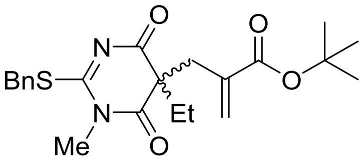

O
N
BnS
N
Me
O
O
O
4

41Ac

	Migration Time	% Area
	16,495	98,89
	18,597	1,11

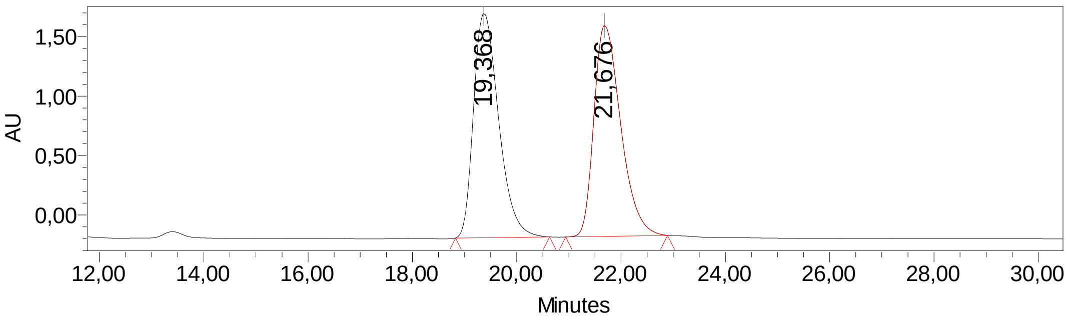


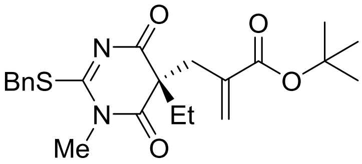
Chiralpak IC, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm


O
N
BnS
N
Me
O
Et
O
O

41Ba

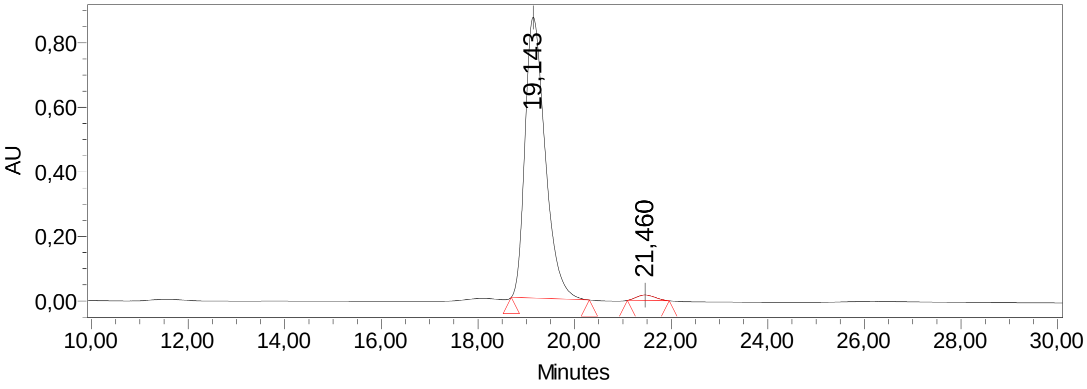
	Migration Time	% Area
	19,368	49,89
	21,676	50,11



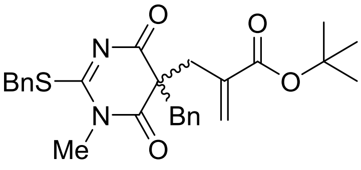

O
N
BnS
N
Me
O
Et
O
O

41Ba

	Migration Time	% Area
	19,143	98,23
	21,460	1,77

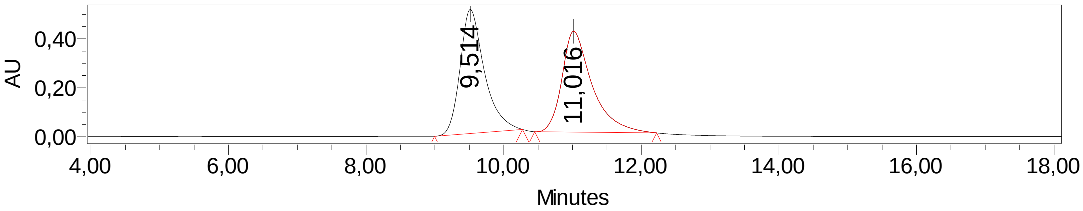


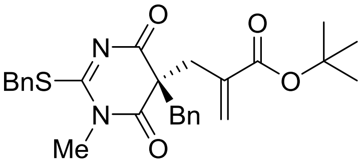
Chiralpak IA, 90:10 Hexano:*i*-PrOH, 1.0 mL/min, λ=210 nm


O
N
O
BnS
O
N
Bn
Me
O

41Ca

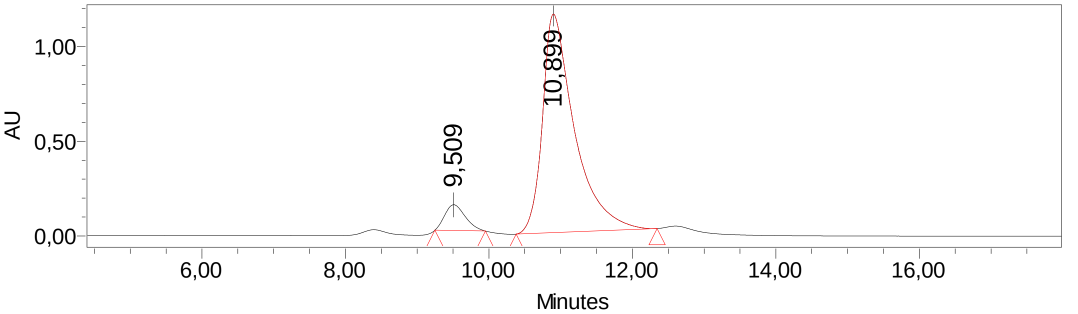
	Migration Time	% Area
	9,514	49,81
	11,016	50,19



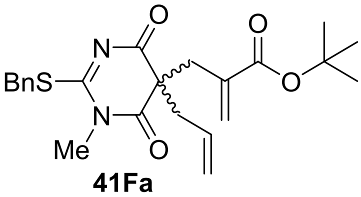

O
N
O
BnS
O
N
Bn
Me
O

41Ca

	Migration Time	% Area
	9,509	7,02
	10,899	92,98

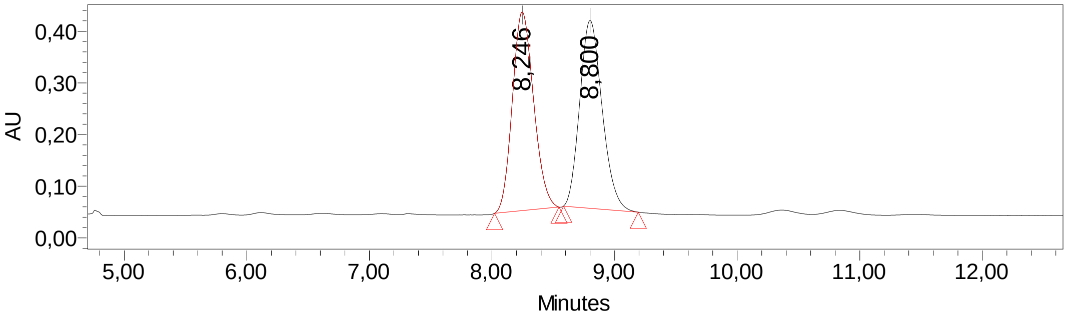


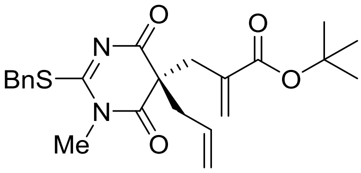
Chiralpak IC, 90:10 Hexano:EtOH, 1.0 mL/min, λ=210 nm


BnS
N
N
Me
O
O
O
O

41Fa

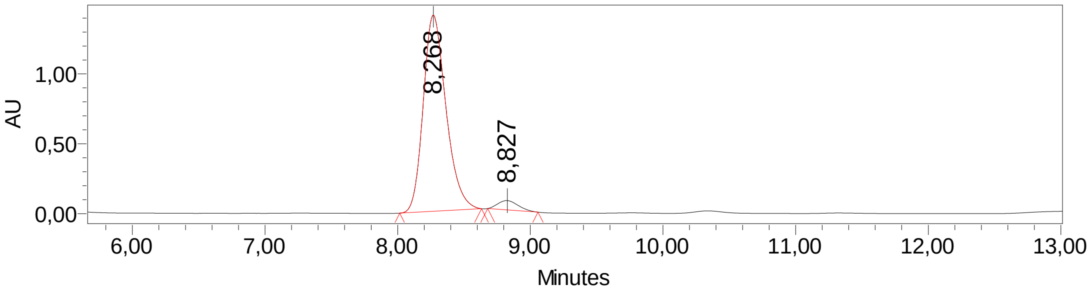
	Migration Time	% Area
	8,246	50,13
	8,800	49,87




BnS
N
N
Me
O
O
O
O

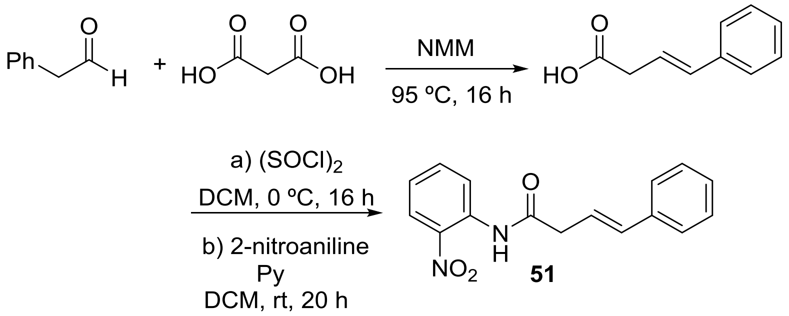
41Fa

	Migration Time	% Area
	8,268	95,91
	8,827	4,09



5.4. **Experimental section of Chapter 4**

5.4.1. **Synthesis of (*E*)-*N*-(2-nitrophenyl)-4-phenylbut-3-enamide 51**



Step 1: Preparation of allyl carboxylic acid:[133]

Phenylacetaldehyde (5.80 ml, 50.0 mmol, 1.0 equiv.) was added to a mixture of malonic acid (5.7 g, 55.0 mmol, 1.1 equiv.) and *N*-methylmorpholine (5.6 g, 55.0 mmol, 1.1. equiv.). The reaction mixture was heated at 95 ^{o}C for 16 h. Then, the mixture was cooled to room temperature, and 11 % H_2SO_4 (25.0 mL) was added with continuous stirring for 30 min. The mixture was extracted with CH_2Cl_2 (2 x 20 mL), washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified via silica gel chromatography (Hexane: EtOAc 60: 40) to obtain the acid as a yellow oil (2.9 g, 42.5 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.18 (m, 5H), 6.61 – 6.48 (m, 1H), 6.32 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.33 (dd, *J* = 7.1, 1.4 Hz, 2H).

Step 2: Preparation of **51**

To a solution of allyl carboxylic acid (3.6 g, 20 mmol, 1 equiv.) $SOCl_2$ is added (3 mL, 40 mmol, 2 equiv.) at 0 °C and stirred at room temperature under nitrogen for 16 h. After completion the $SOCl_2$ was evaporated under reduced pressure and the residue was dissolved in pyridine (5.2 g., 66 mmol, 3.3 equiv.) and *o*-nitrophenyl amine (2.4 g, 20 mmol, 1 equiv.) was added dropwise at 0 °C. After completion, the reaction was diluted in DCM (20 mL) and acidified with HCl 1 M, the aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified via silica gel chromatography (Hexane: EtOAc, 3:1) to obtain **51** as a yellow oil (6.9 g, 10.6 mmol, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (brs, 1H), 8.83 (dd, *J* = 8.6, 1.3 Hz, 1H), 8.23 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.67 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.43 – 7.24 (m, 3H), 7.20 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H), 6.73 (dt, *J* = 15.7, 1.3 Hz, 1H), 6.41 (dt, *J* = 15.7, 7.4 Hz, 1H), 3.45 (dd, *J* = 7.4, 1.3 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 135.3, 135.1, 134.84, 134.7, 134.6, 129.8,

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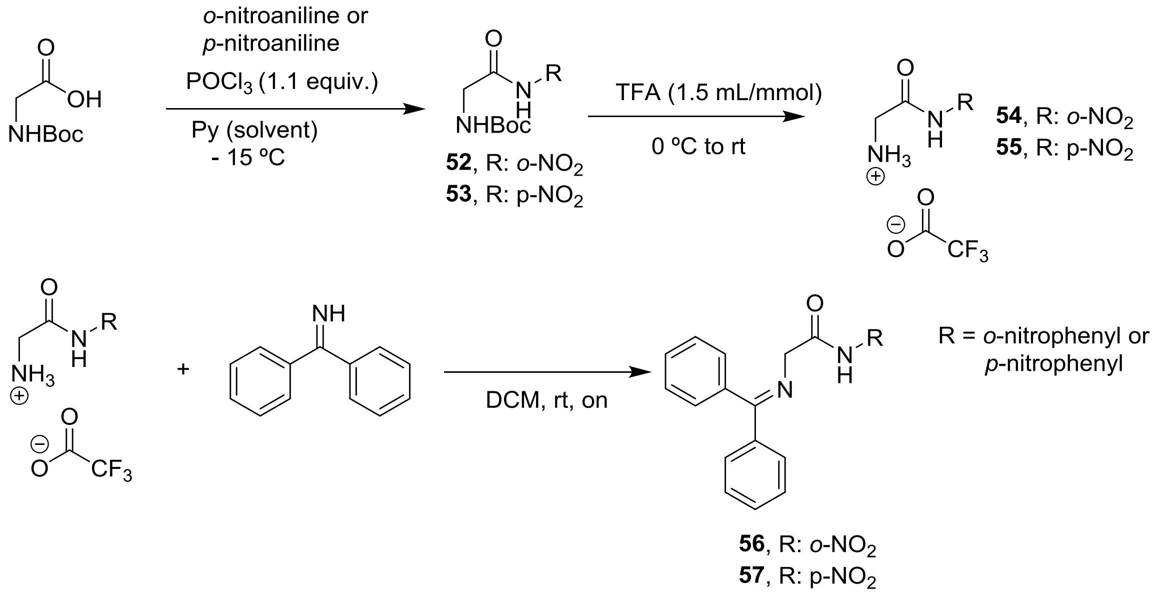
[133] Zhang, S. J.; Hu, W. X. *Synth. Commun.* **2010**, *40*, 3093–3100.

129.5, 126.2, 114.9, 114.9, 114.8, 114.7, 114.7, 56.2. UPLC-DAD-QTOF: $C_{16}H_{14}N_2O_3$ $[M+H]^+$ calcd.: 282.1004, found: 282.1107.

5.4.1.1. **Synthesis of iminoamides 56 and 57**


o-nitroaniline or
p-nitroaniline
POCl3 (1.1 equiv.)
Py (solvent)
- 15 °C
O
OH
NHBoc
N
H
R
52, R: o-NO2
53, R: p-NO2
TFA (1.5 mL/mmol)
0 °C to rt
NH3
CF3
54, R: o-NO2
55, R: p-NO2
+
NH
DCM, rt, on
N
R = o-nitrophenyl or
p-nitrophenyl
56, R: o-NO2
57, R: p-NO2

Step 1:[134]

A protected amino acid (997 mg, 5.7 mmol, 1 equiv.) and nitroaniline (780 mg, 5.7 mmol, 1 equiv.) were dissolved in dry pyridine (30 mL). The clear yellow solution was cooled to – 15 °C and recently distilled phosphorus oxychloride (0.6 mL, 6.3 mmol, 1.1 equiv.) was added dropwise with vigorous stirring. During the addition, the reaction mixture coloured deeply red and became turbid in the course of 5 to 20 minutes. The colour of the suspension slowly changed to brown and the reaction was complete after 30 minutes (monitored by TLC). The reaction mixture was then quenched with crushed ice water (100 mL) and extracted into EtOAc (once 50 mL and three times 30 mL). After drying on Na_2SO_4 filtered and evaporated *in vacuo*. The residue was co-evaporated successively with hexane and diethyl ether. The solid was recristalizated with a mixture of ether and hexane (1:1). The resulting yellow foam was used in the next step without further purification.

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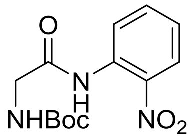
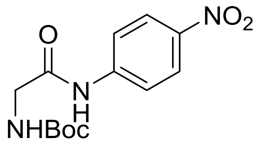
[134] Rijkers, D. T. S.; Adams, H.; Hemker, C.; Tesser, G. I. *Tetrahedron*, **1995**, *51*, 11235–11250.

Tert-butyl (2-((2-nitrophenyl)amino)-2-oxoethyl)carbamate 52



The title compound was prepared from *o*-nitroaniline. The product was purified by recrystallization as a yellow foam. Yield: 1.14 g, 3.5 mmol, 61%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.02 (brs, 1H), 8.84 (dd, *J* = 8.6, 1.3 Hz, 1H), 8.25 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.69 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.26 – 7.10 (m, 1H), 5.19 (brs, 1H), 4.05 (d, *J* = 6.1 Hz, 2H), 1.57 (s, 3H), 1.53 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 136.6, 134.9, 127.0, 126.5, 124.2, 122.7, 81.8, 46.4, 28.9.UPLC-DAD-QTOF: $C_{13}H_{17}N_3O_5$ $[M+H]^+$ calcd.: 295.1168, found: 295.1274.

***tert*-butyl (2-((4-nitrophenyl)amino)-2-oxoethyl)carbamate 53**

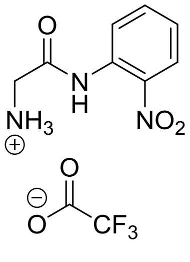


The title compound was prepared from *p*-nitroaniline. The product was purified by recrystallization as a yellow foam. Yield: 1.27 g, 3.9 mmol, 69 %. All data were consistent with those previously reported.[27]

Step 2:

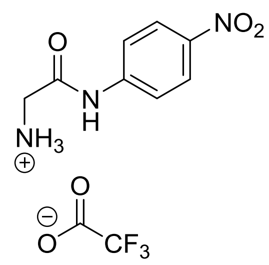
To a solution of carbamate (3 mmol, 880 mg, 1 equiv.) in CH_2Cl_2 (12 mL) trifluoroacetic acid (4.5 mL) was added at 0 °C and then warmed to room temperature during 30 min. The reaction was monitored by TLC and when the reactant was disappeared the reaction was evaporated *in vacuo*, washed with a mixture of ether and pentane (1:1) and finally was dried *in vacuo*. The resulting yellow salt was used in the next step without further purification.

2-((2-nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate 54



The title compound was prepared from *tert*-butyl (2-((2-nitrophenyl)amino)-2-oxoethyl)carbamate. Yield: 3 mmol, 929 mg, > 99%. ^{1}H NMR (300 MHz, D_2O) δ 8.15 – 7.93 (m, 1H), 7.84 – 7.59 (m, 2H), 7.41 (ddd, *J* = 8.6, 6.6, 2.3 Hz, 1H), 4.03 (s, 3H).^{13}C NMR (75 MHz, D_2O) δ 166.4, 135.1, 129.6, 127.1, 126.4, 125.6, 41.2. UPLC-DAD-QTOF: $C_{10}H_{10}F_3N_3O_5$ $[M+H]^+$ calcd.: 309.0573, found: 309.0574.

2-((4-nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate 55

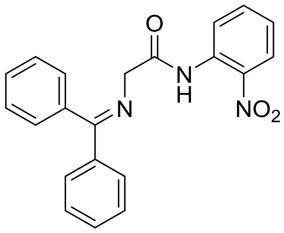


The title compound was prepared from *tert*-butyl (2-((4-nitrophenyl)amino)-2-oxoethyl)carbamate. Yield: 3 mmol, 929 mg, > 99%. ^{1}H NMR (300 MHz, D_2O) δ 8.15 (d, *J* = 9.2 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 2H), 3.97 (s, 2H). ^{13}C NMR (75 MHz, D_2O) δ 165.8, 143.7, 142.9, 127.4, 125.1, 120.1, 114.4, 41.2. UPLC-DAD-QTOF: $C_{10}H_{10}F_3N_3O_5$ $[M+H]^+$ calcd.: 309.0573, found: 309.1526.

Step 3:[135]

To a suspension of the trifluoroacetic salt (927 mg, 3 mmol, 1 equiv.) in CH_2Cl_2 (11 mL) benzophenone imine (0.5 mL, 3 mmol, 1 equiv.) and Na_2CO_3 anhydrous (630 mg, 7.5 mmol, 2.5 equiv.) was added. The reaction was stirred at room temperature for 24 h. Then the reaction was filtered to remove the salt that was formed and then evaporated to dryness *in vacuo*. The crude was purificated by recrystallization in ether: hexane (1:1).The solid was diluted in DCM (10 mL) and washed with a saturated aqueous sodium bicarbonate solution (3 x 10 mL) and dried *in vacuo*.

2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide 56



The title compound was prepared from 2-((2-nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate. The product was purified as a yellow foam. Yield: 606 mg, 2.3 mmol, 78 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.16 (brs, 1H), 9.09 – 8.75 (m, 1H), 8.29 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.03 – 7.79 (m, 2H), 7.79 – 7.64 (m, 1H), 7.64 – 7.37 (m, 6H), 7.37 – 7.06 (m, 3H), 4.17 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.6, 139.4, 138.1, 137.4, 136.7, 135.5, 132.1, 130.2, 130.1, 129.9, 129.5, 128.2, 126.9, 124.5, 123.5, 58.6. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3$ $[M+H]^+$ calcd.: 359.1270, found: 359.1274.

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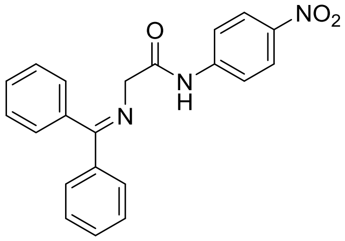
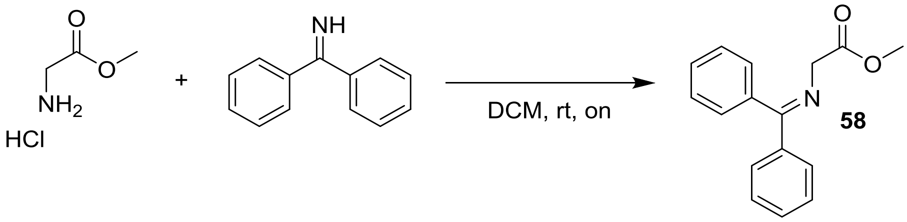
[135] Abaskharon, R. M.; Brown, S. P.; Zhang, W.; Chen, J.; Smith, A. B.; Gai, F. *Chemical Physics Letters*, **2017**, *683*, 193–198.

2-((diphenylmethylene)amino)-*N*-(4-nitrophenyl)acetamide 57



The title compound was prepared from 2-((4-nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate. The product was purified as a yellow foam. Yield: 883 mg, 2.5 mmol, 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 8.43 – 8.15 (m, 2H), 7.96 – 7.81 (m, 2H), 7.71 (dd, J = 8.2, 1.5 Hz, 2H), 7.61 – 7.39 (m, 5H), 7.39 – 7.08 (m, 3H), 4.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.0, 144.3, 144.0, 139.0, 136.5, 131.9, 130.1, 129.8, 129.2, 127.8, 125.9, 119.8, 57.4. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3$ [M+H]$^+$ calcd.: 359.1270, found: 359.1372.

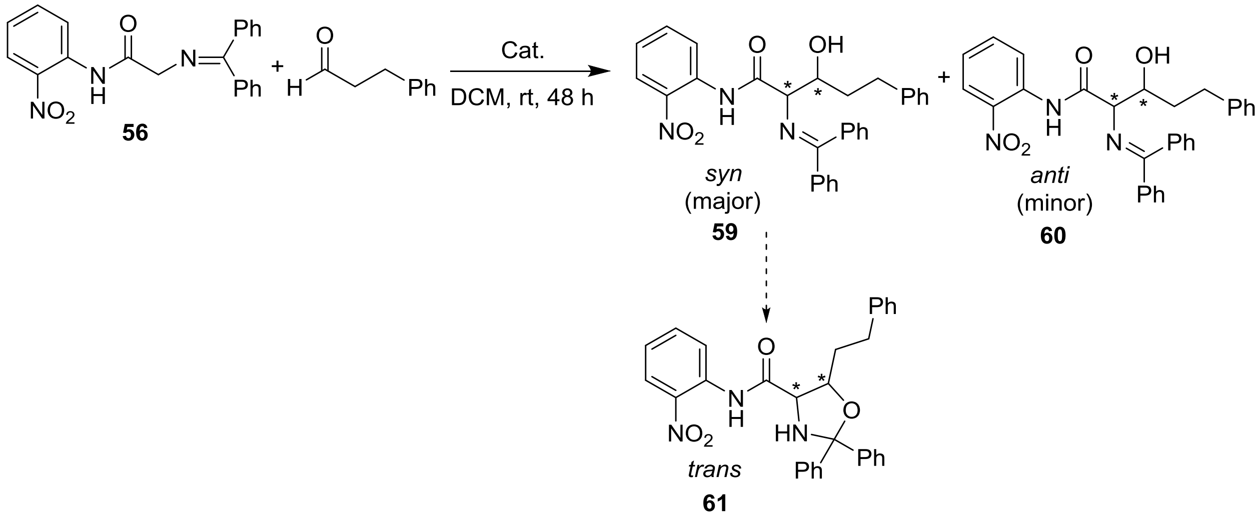
5.4.1.2. **Synthesis of iminoester 58**



58

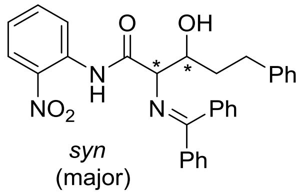
To a suspension of glycine methyl ester hydrochloride (1.4 g, 11 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) benzophenone imine (1.8 mL, 11 mmol, 1 equiv.) was added. The reaction was stirred at room temperature for 24 h. Then the reaction was filtered to remove the salt that was formed and then evaporated to dryness *in vacuo*. The crude was purificated by recrystallization in ether: hexane (1:1).The solid was diluted in DCM (10 mL) and washed with a saturated aqueous sodium bicarbonate solution (3 x 10 mL) and dried *in vacuo* to afford the methyl 2-((diphenylmethylene)amino)acetate as a white oil 2.8 g, 11 mmol, > 99% yield. All data were consistent with those previously reported.[135] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.61 (m, 2H), 7.56 – 7.42 (m, 4H), 7.43 – 7.29 (m, 3H), 7.25 – 7.14 (m, 1H), 4.25 (s, 2H), 3.77 (s, 3H).

5.4.2. **Aldol reaction of 56 with phenylpropanal**



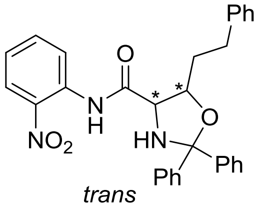
To a mixture of the 2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **56** (71.8, 0.2 mmol, 1 equiv.) and 3-phenylpropanal (80.4 mg, 0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.2 mL), was added the catalyst **C17** (20 mol %) and the resulting mixture was stirred at room temperature for 48 h. After that time, two products were formed, the desired product **60**/**61** and the cycled product **61**. Then, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane: EtOAc, 10:1) to afford the adduct **59** and **60** and the cycled product **61** as a yellow oil.

(2*R*,3*S*)-2-((diphenylmethylene)amino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 59



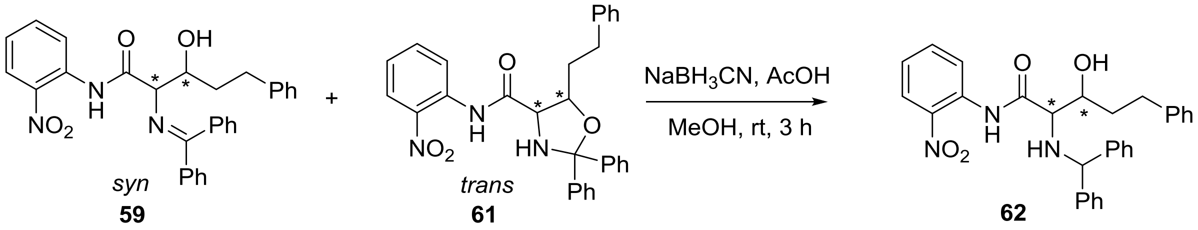
The product was purified as a yellow oil. Yield: 74 mg, 0.15 mmol, 72 %. $[\alpha]_D^{22}$= −64.17 °(*c*= 0.08, 80 % *ee,* CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 11.43 (s, 1H), 8.32 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.05 – 7.77 (m, 1H), 7.42 (dd, *J* = 7.1, 1.9 Hz, 2H), 7.37 – 7.20 (m, 3H), 7.15 (dd, *J* = 4.0, 2.3 Hz, 2H), 7.09 – 6.73 (m, 14H), 4.00 – 3.86 (m, 1H), 3.58 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.23 (d, *J* = 10.3 Hz, 1H), 2.76 – 2.53 (m, 2H), 2.09 (dp, *J* = 10.2, 3.2 Hz, 1H), 1.99 – 1.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.45, 171.98, 144.63, 143.22, 142.31, 136.23, 129.75, 129.58, 129.19, 129.05, 129.01, 128.82, 128.69, 128.31, 128.02, 127.66, 126.57, 126.32, 125.86, 123.97, 122.40, 79.34, 67.21, 37.49, 33.23.UPLC-DAD-QTOF: $C_{30}H_{27}N_3O_4$ $[M+H]^+$ calcd.: 493.2002, found: 493.20176.

(*4S*,*5R*)-*N*-(2-nitrophenyl)-5-phenethyl-2,2-diphenyloxazolidine-4-carboxamide 61



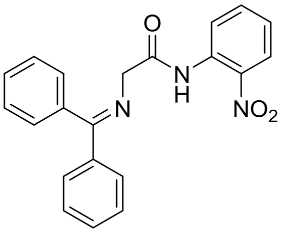
The product was purified as a yellow oil. Yield: 0.1 mg, 0.02 mmol, 10%. [*α*]$_D^{22}$= $-+$ 13.73 °(*c* = 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (brs, 1H), 8.66 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.22 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.95 – 7.84 (m, 1H), 7.84 – 7.69 (m, 2H), 7.69 – 7.52 (m, 3H), 7.49 (dd, *J* = 4.4, 2.1 Hz, 2H), 7.31 – 6.91 (m, 9H), 4.34 – 4.23 (m, 1H), 3.91 (dd, *J* = 10.4, J_{trans} = 7.0 Hz, 1H), 3.57 (d, *J* = 10.5 Hz, 1H), 3.15 – 3.03 (m, 1H), 2.95 (ddd, *J* = 13.8, 9.9, 6.4 Hz, 1H), 2.42 (ddd, *J* = 10.2, 6.7, 3.2 Hz, 1H), 2.33 – 2.12 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 144.6, 143.2, 142.3, 136.2, 129.8, 129.6, 129.2, 129.1, 129.0, 128.8, 128.7, 128.3, 128.0, 127.7, 126.6, 126.3, 125.9, 124.0, 122.4, 99.8, 79.3, 67.2, 37.5, 33.2. UPLC-DAD-QTOF: $C_{30}H_{27}N_3O_4$ [M+H]$^+$ calcd.: 493.2002, found: 493.2003.

Reduction reaction to afford 63



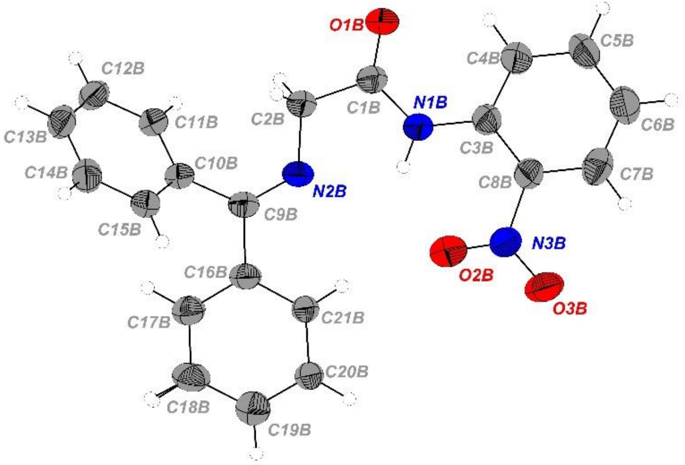
To a crude aldol reaction obtained in the previous step after 48 h, methanol (0.4 mL), $NaBH_3CN$ (32 mg, 0.5 mmol, 2.5 equiv.) and AcOH (24 µL, 0.4 mmol, 2 equiv.) were added and it stirred for 3 h. The solvents were evaporated, the residue was redissolved in dichloromethane, washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (Hx/EtOAc 90/10) to afford the reduced adduct **62** as a yellow foam in 86% of yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 7.60 (t, *J* = 8.6 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.46 – 7.31 (m, 4H), 7.31 – 7.05 (m, 9H)., 4.91 (s, 12H), 4.07 (m, 1H), 3.32 (d, *J* = 3.9 Hz, 1H), 2.86 (m, 1H), 2.67 (m, 1H), 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 , 143.0 , 142.4 , 141.4 , 137.1 , 135.7 , 134.0 , 129.0 , 128.8 , 128.7 , 128.6 , 127.8 , 127.6 , 127.4 , 126.2 , 125.9 , 123.7 , 122.2 , 72.1 , 66.8 , 65.0 , 35.4 , 32.4. UPLC-DAD-QTOF: $C_{30}H_{30}N_3O_4$ [M+H]$^+$ calcd.: 495.2158, found: 495.2267.

5.4.3. **X-ray analysis: ORTEP diagram of compound 56**



56

Molecule A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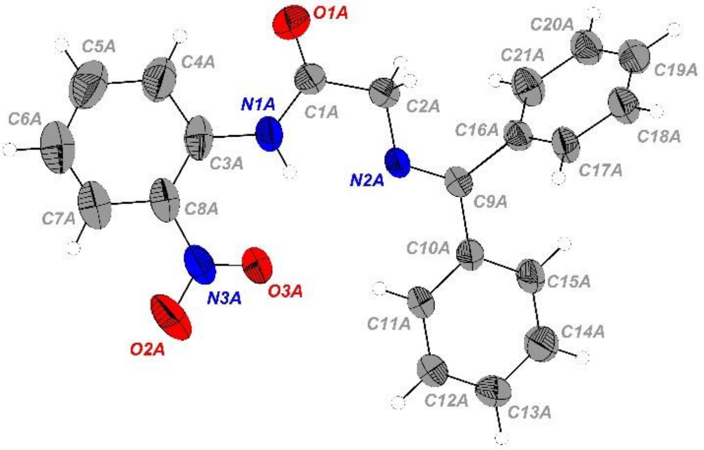
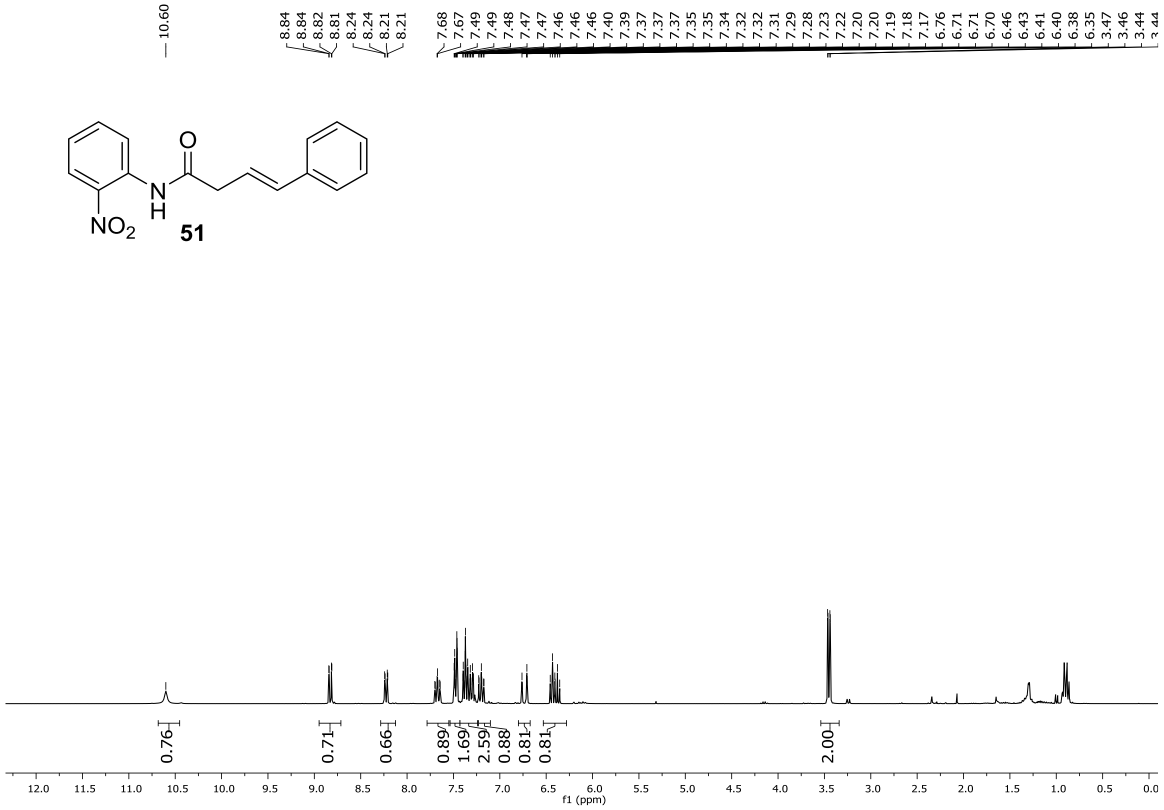
C12B
C4B
C5B
C2B
C1B
N1B
C13B
C11B
C6B
C10B
C3B
C14B
C8B
C7B
N2B
C15B
C9B
N3B
C16B
O2B
O3B
C21B
C17B
C20B
C18B
C19B

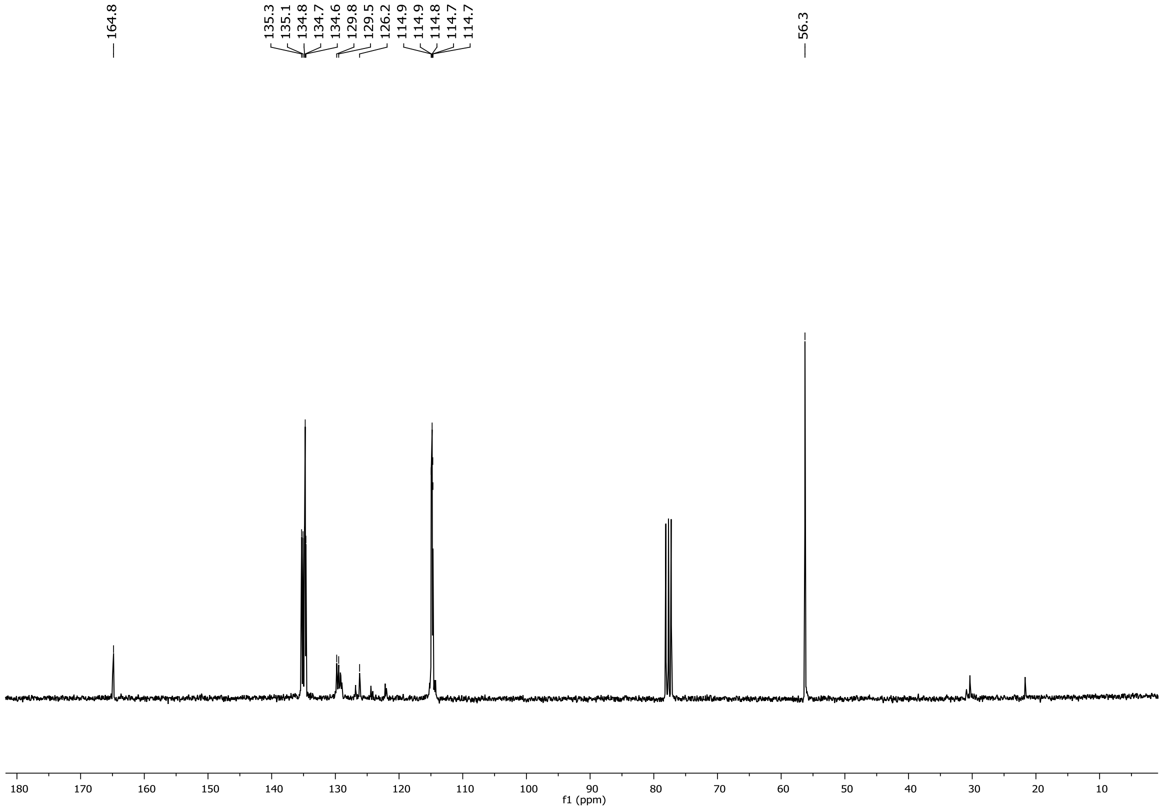
Molecule B

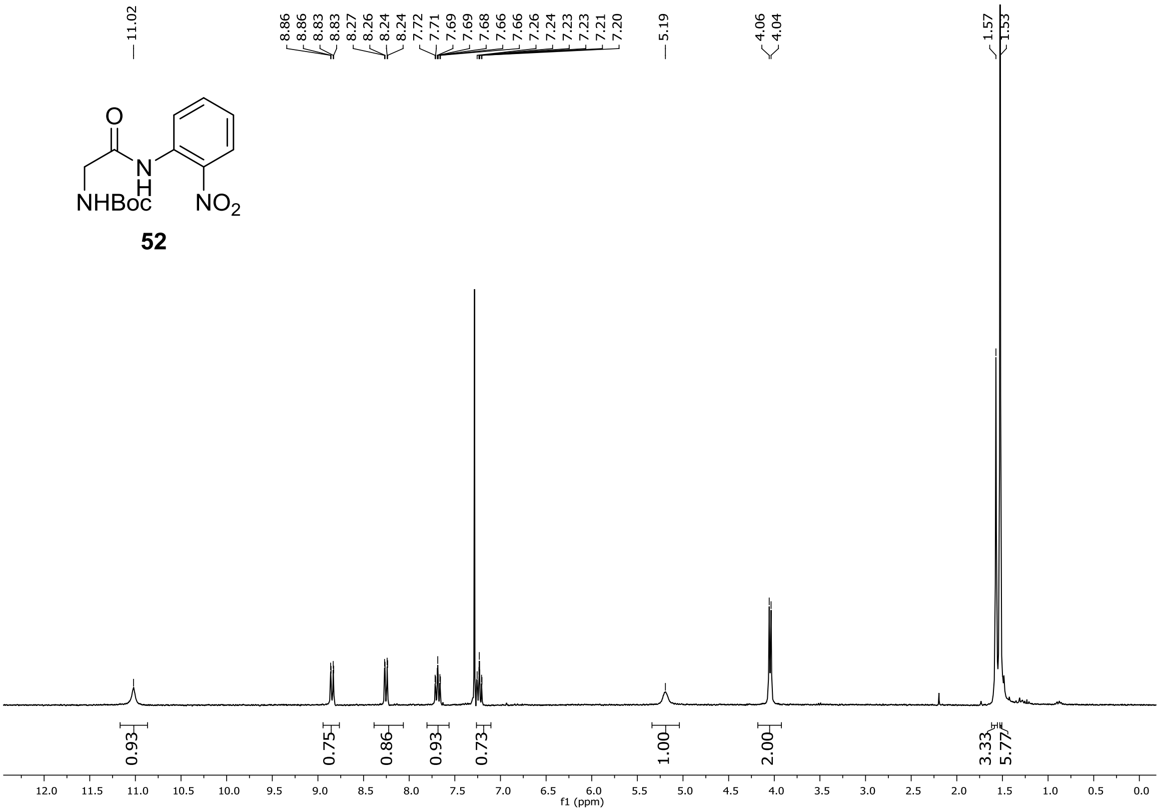

O1A
C20A
C5A
C4A
C21A
C19A
N1A
C1A
C2A
C6A
C16A
C18A
C3A
N2A
C17A
C9A
C7A
C8A
C10A
C15A
N3A
O3A
O2A
C11A
C14A
C12A
C13A

5.4.4. **Representative NMR spectra**



51

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8.86
8.83
8.83
8.27
8.26
8.24
8.24
7.72
7.71
7.69
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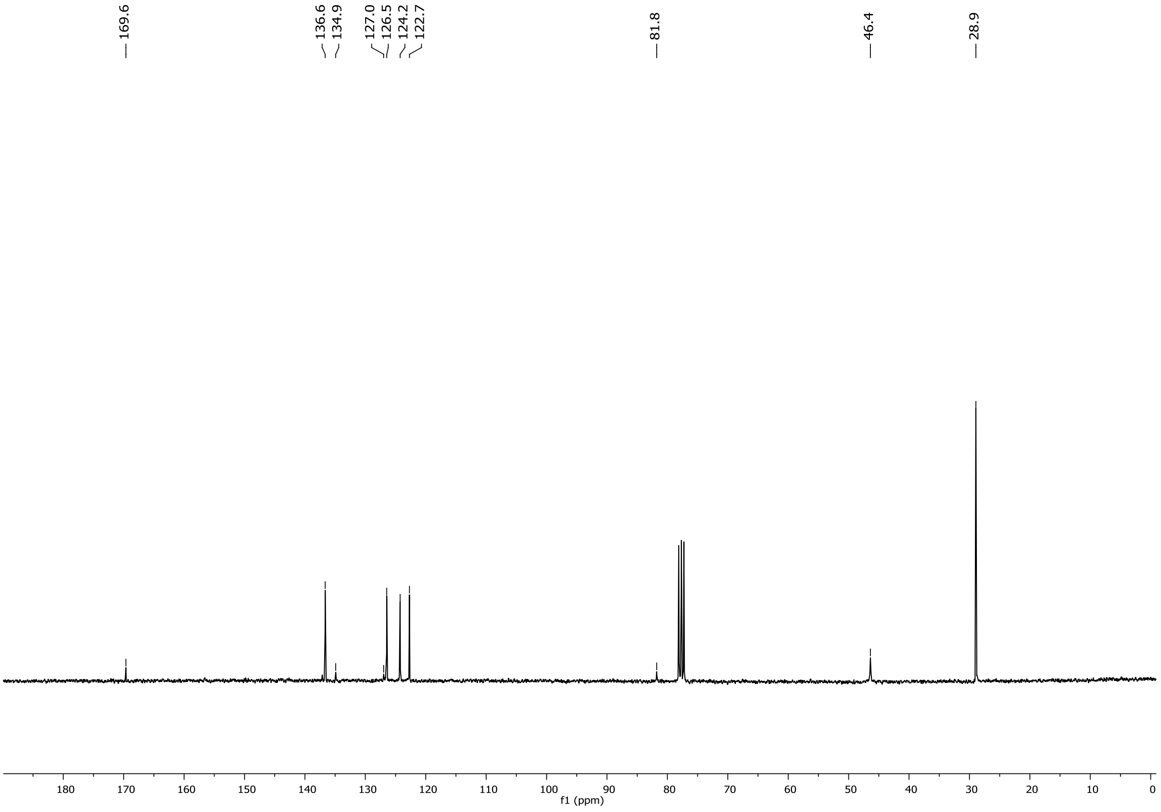
7.68
7.66
7.66
7.26
7.24
7.23
7.23
7.21
7.20
5.19
4.06
4.04
1.57
1.53
O
N
H
NHBoc
NO2
52
0.93
0.75
0.86
0.93
0.73
1.00
2.00
3.33
5.77
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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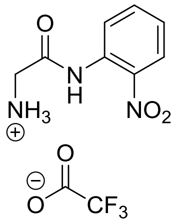
134.9
127.0
126.5
124.2
122.7
81.8
46.4
28.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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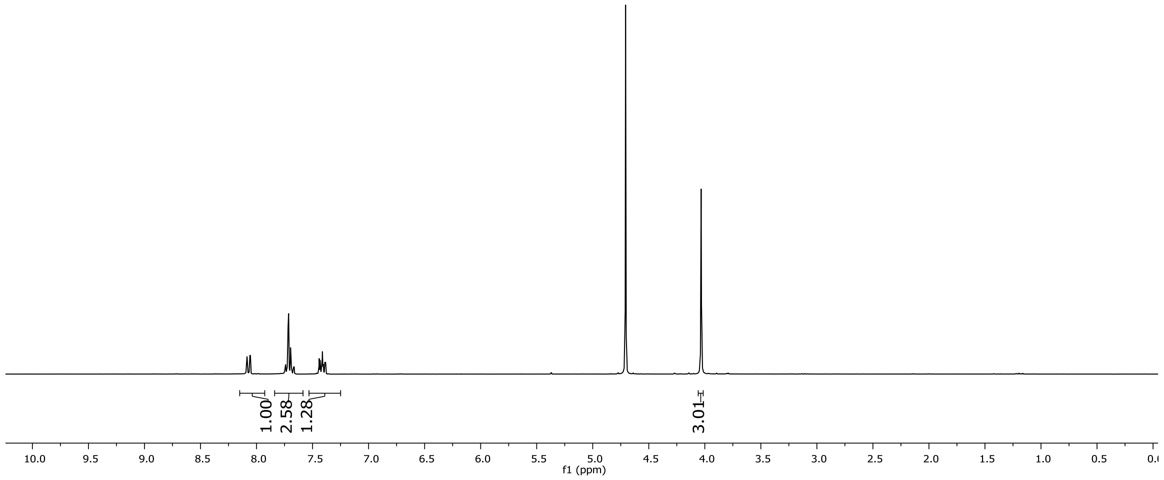
N
H
NH3
⊕
NO2
O
⊖
O
CF3

54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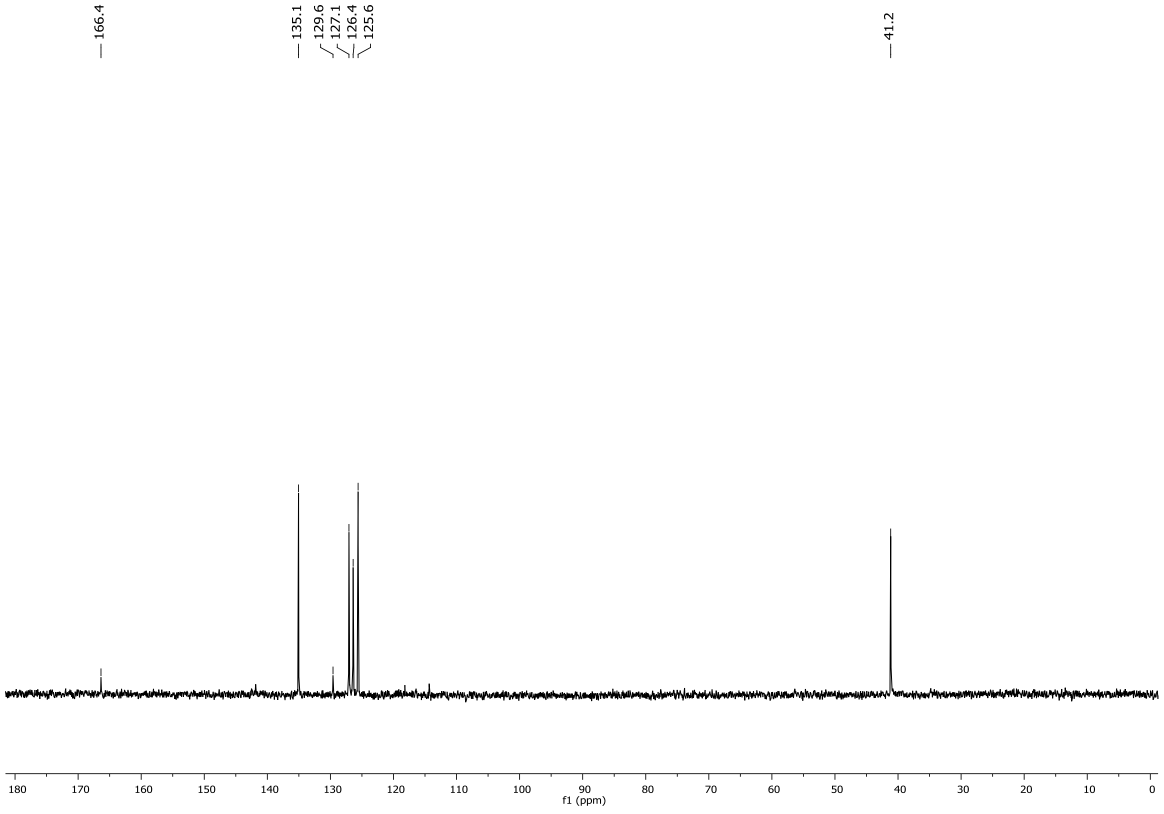
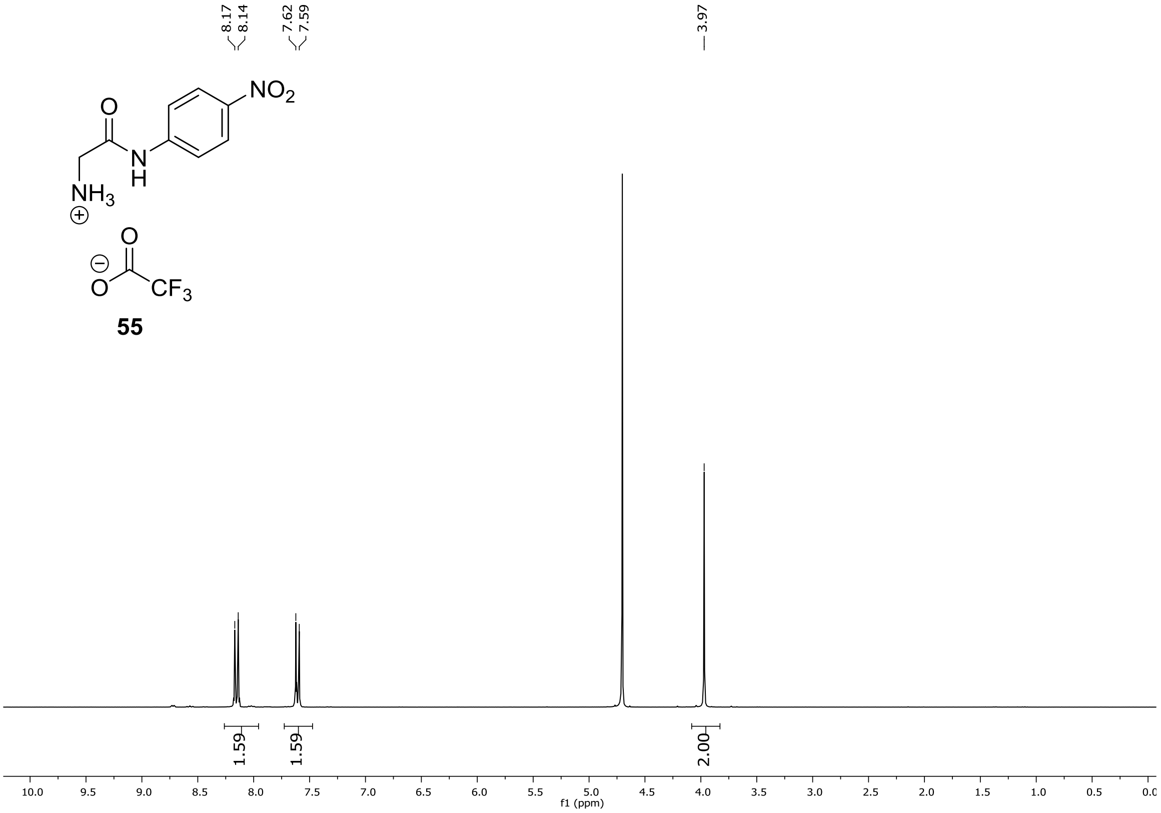
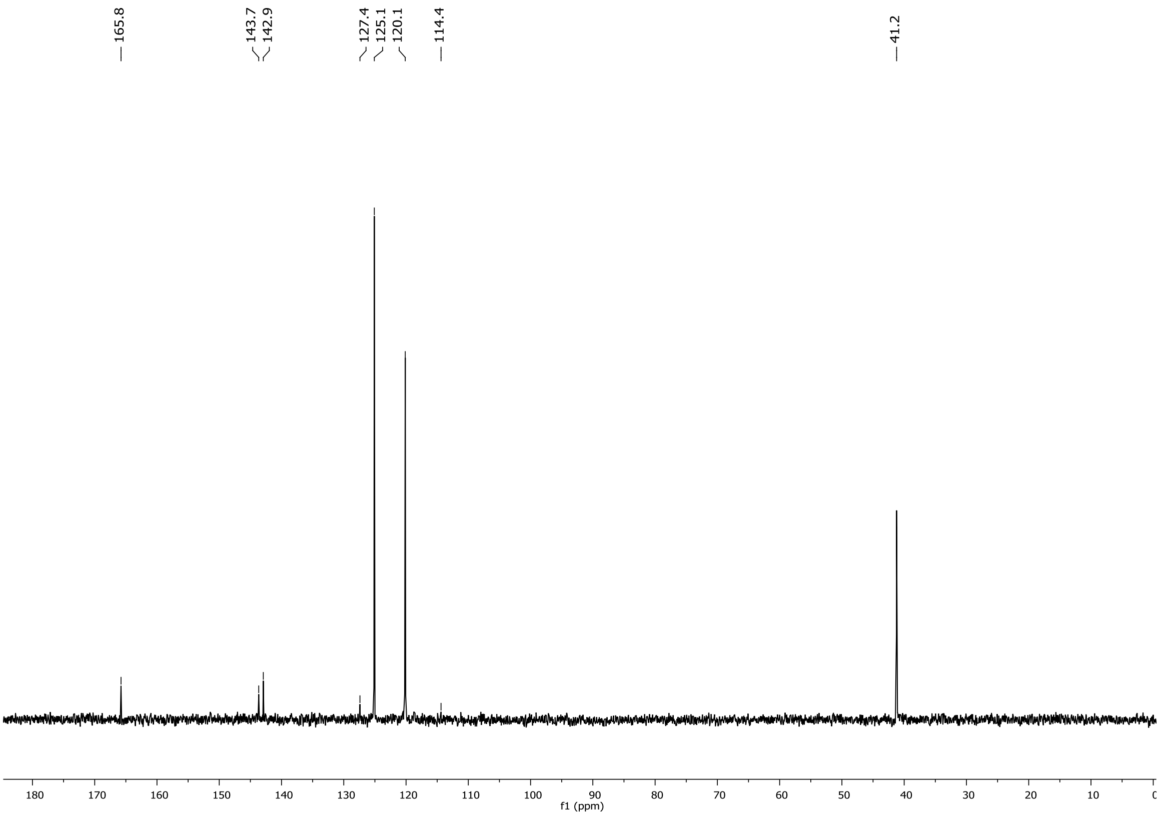
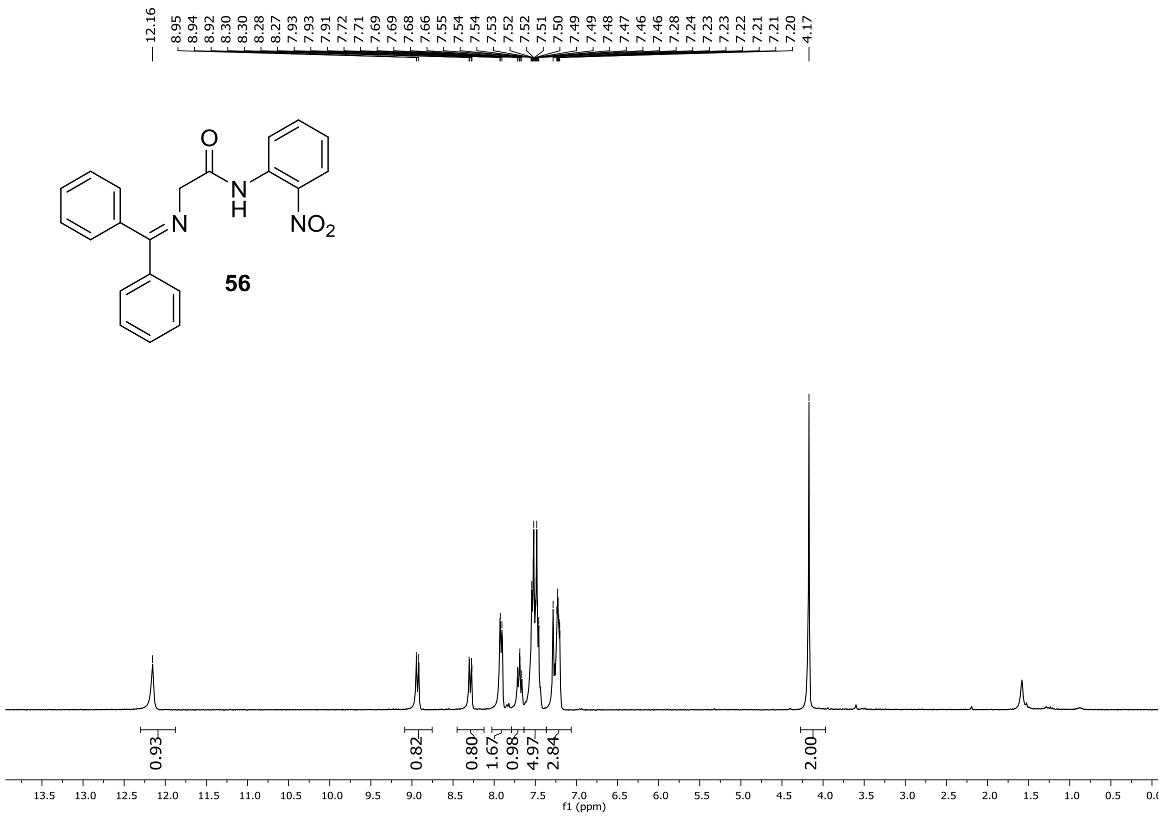
2.58
1.28
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


166.4
135.1
129.6
127.1
126.4
125.6
41.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.17
8.14
7.62
7.59
3.97
NO2
O
N
H
NH3
O
O
CF3
1.59
1.59
2.00
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
f1 (ppm)

55


165.8
143.7
142.9
127.4
125.1
120.1
114.4
41.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



56

12.16
8.95
8.94
8.92
8.30
8.28
8.27
7.93
7.93
7.91
7.72
7.71
7.69
7.69
7.68
7.66
7.55
7.54
7.54
7.53
7.52
7.52
7.51
7.50
7.49
7.49
7.48
7.47
7.46
7.46
7.28
7.24
7.23
7.23
7.22
7.21
7.21
7.20
4.17
O
N
H
N
NO2
0.93
0.82
0.80
1.67
0.98
4.97
2.84
2.00
13.5
13.0
12.5
12.0
11.5
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
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3.5
3.0
2.5
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1.5
1.0
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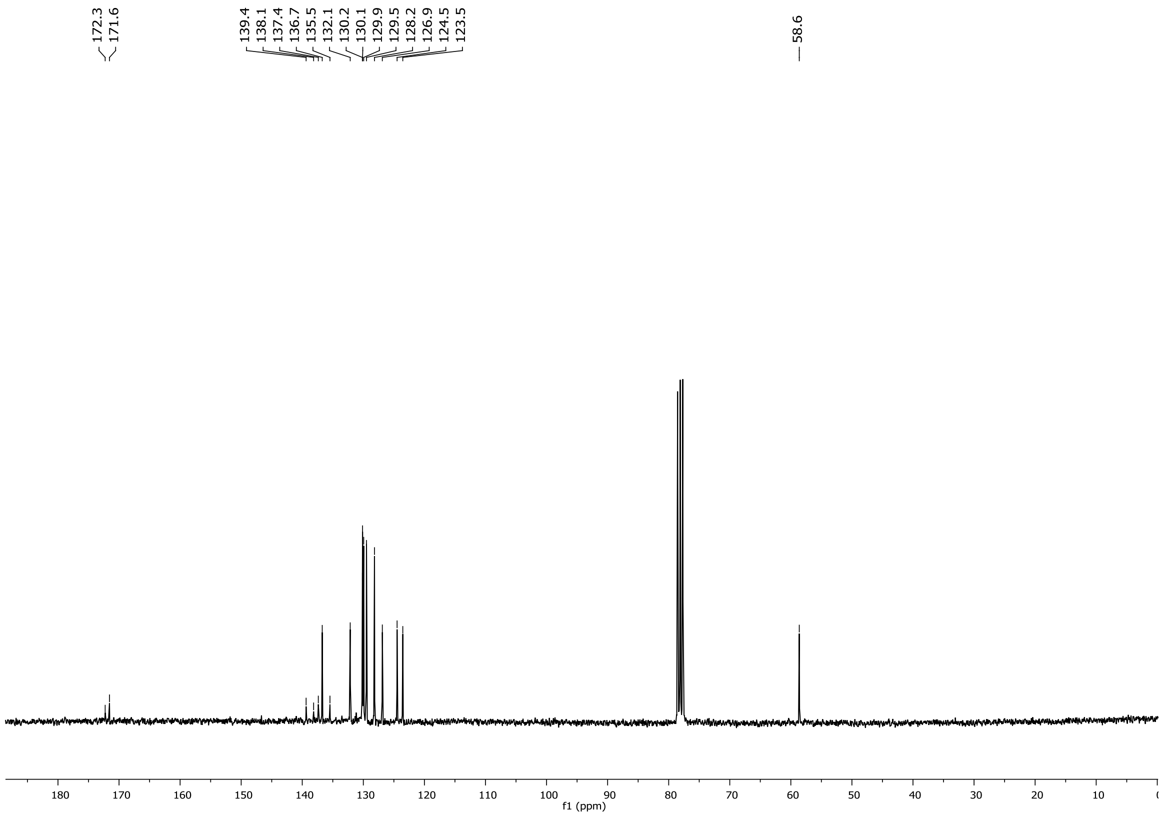
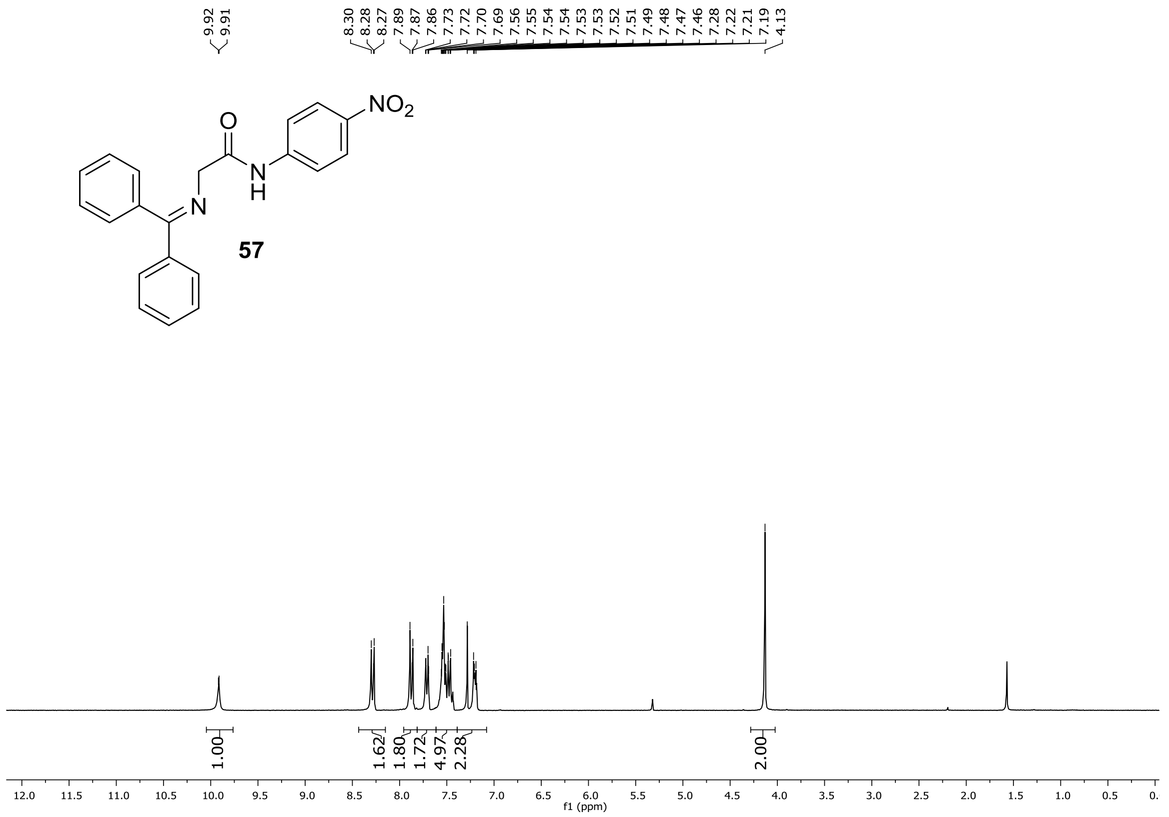
f1 (ppm)

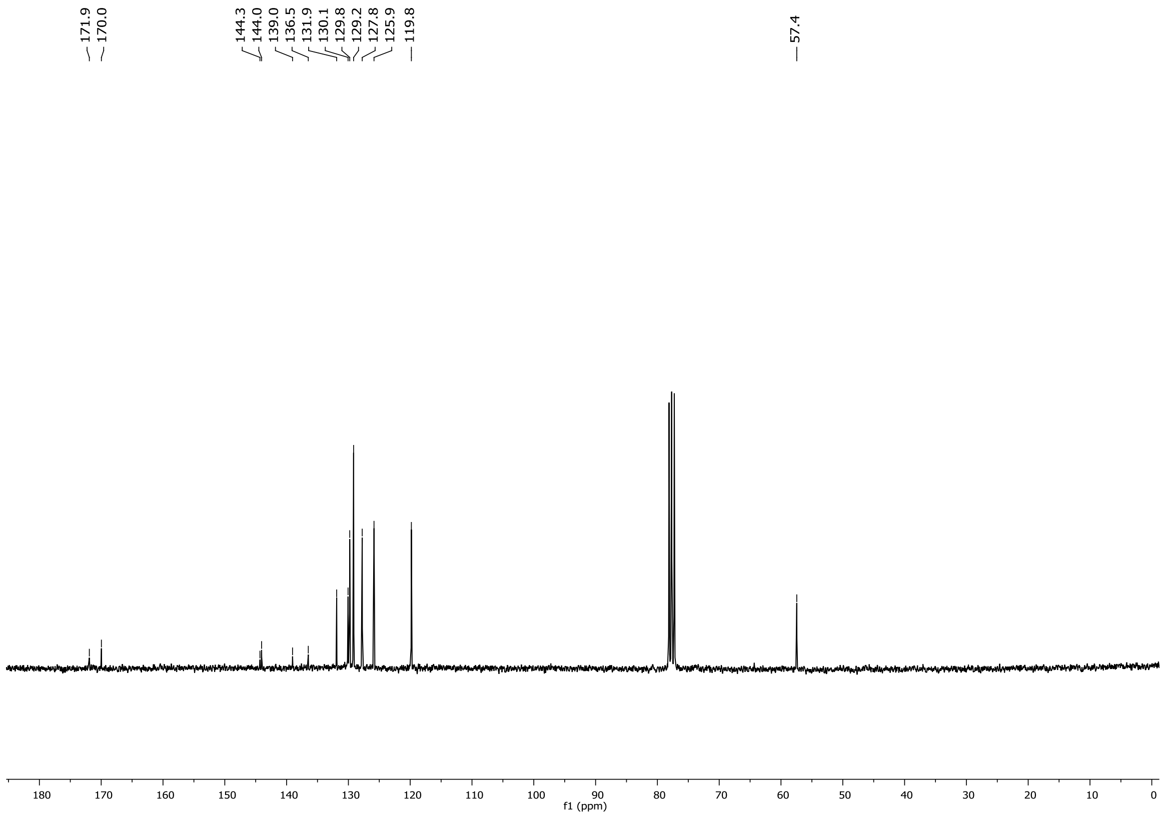


172.3
171.6
139.4
138.1
137.4
136.7
135.5
132.1
130.2
130.1
129.9
129.5
128.2
126.9
124.5
123.5
58.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



57

9.92
9.91
8.30
8.28
8.27
7.89
7.87
7.86
7.73
7.72
7.70
7.69
7.56
7.55
7.54
7.54
7.53
7.53
7.52
7.51
7.49
7.48
7.47
7.46
7.28
7.22
7.21
7.19
4.13
NO2
O
N
H
N
1.00
1.62
1.80
1.72
4.97
2.28
2.00
12.0
11.5
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.
f1 (ppm)



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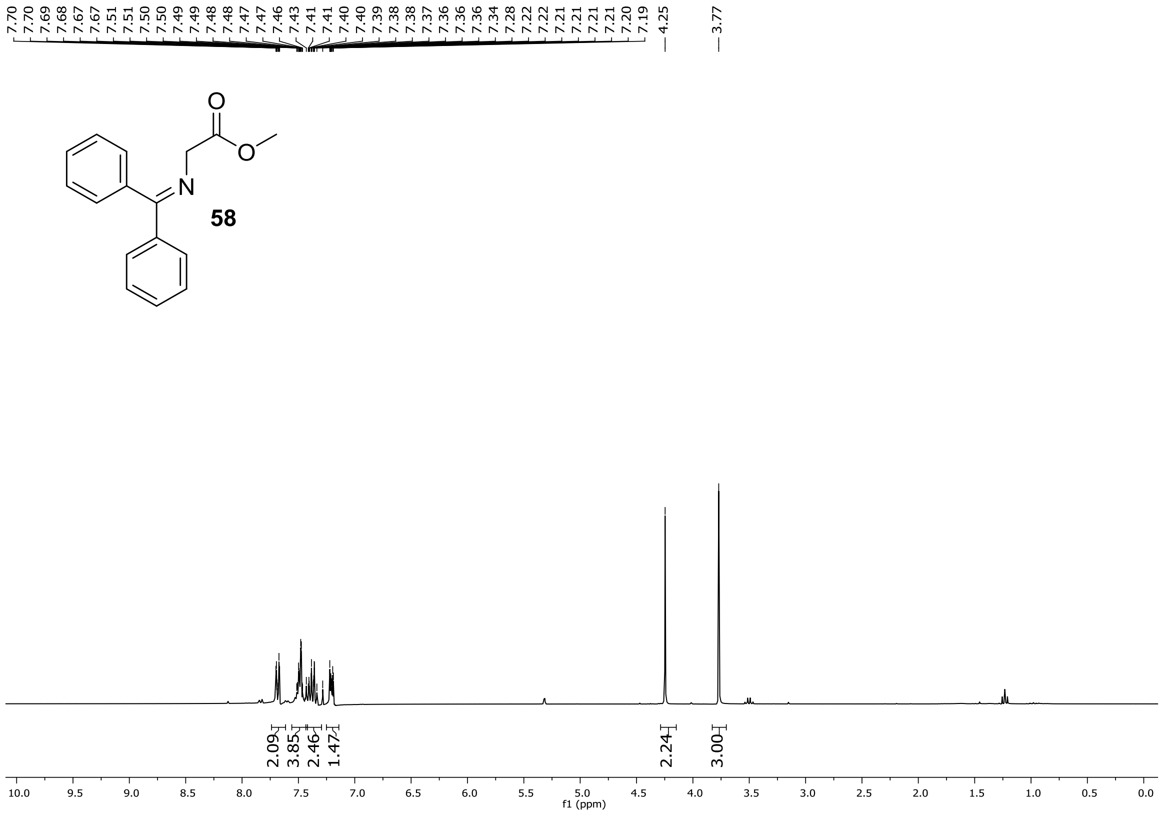
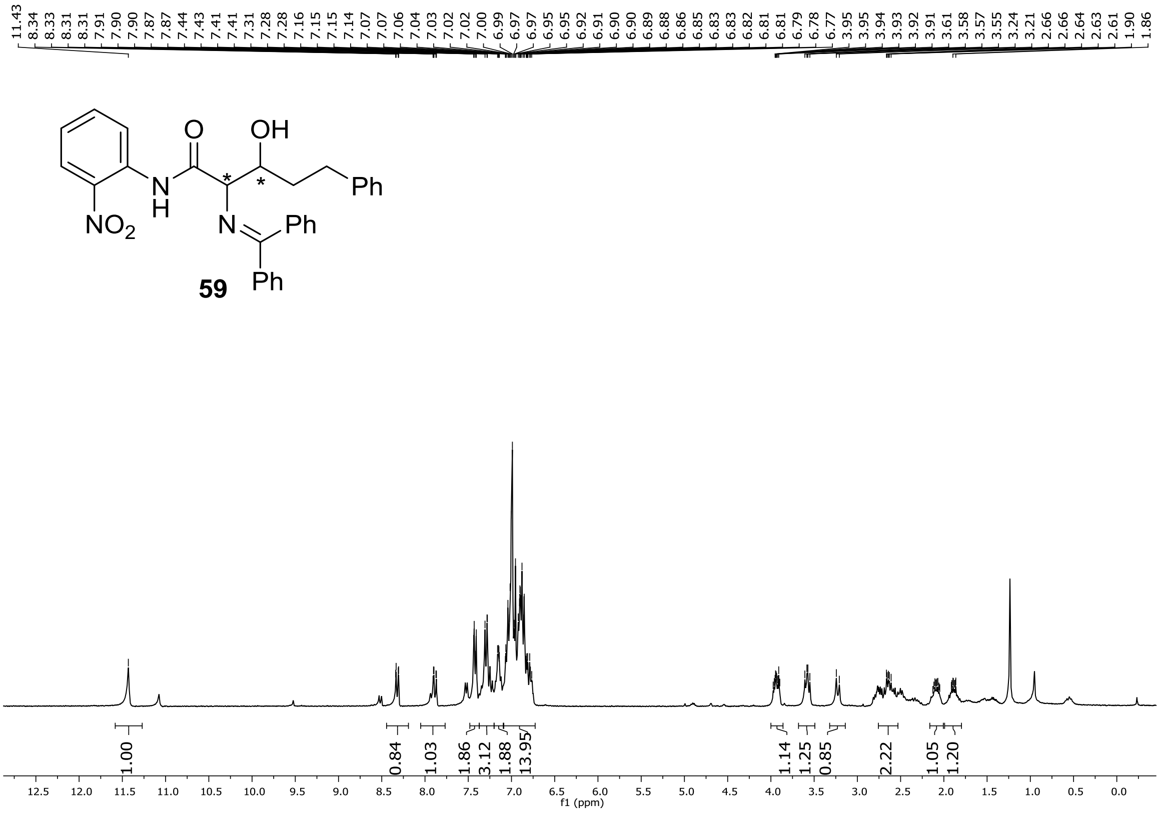
144.3
144.0
139.0
136.5
131.9
130.1
129.8
129.2
127.8
125.9
119.8
57.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



58

7.70
7.70
7.69
7.68
7.67
7.67
7.51
7.51
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.43
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.36
7.36
7.36
7.34
7.28
7.22
7.22
7.21
7.21
7.21
7.21
7.20
7.19
4.25
3.77
O
O
N
2.09
3.85
2.46
1.47
2.24
3.00
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
f1 (ppm)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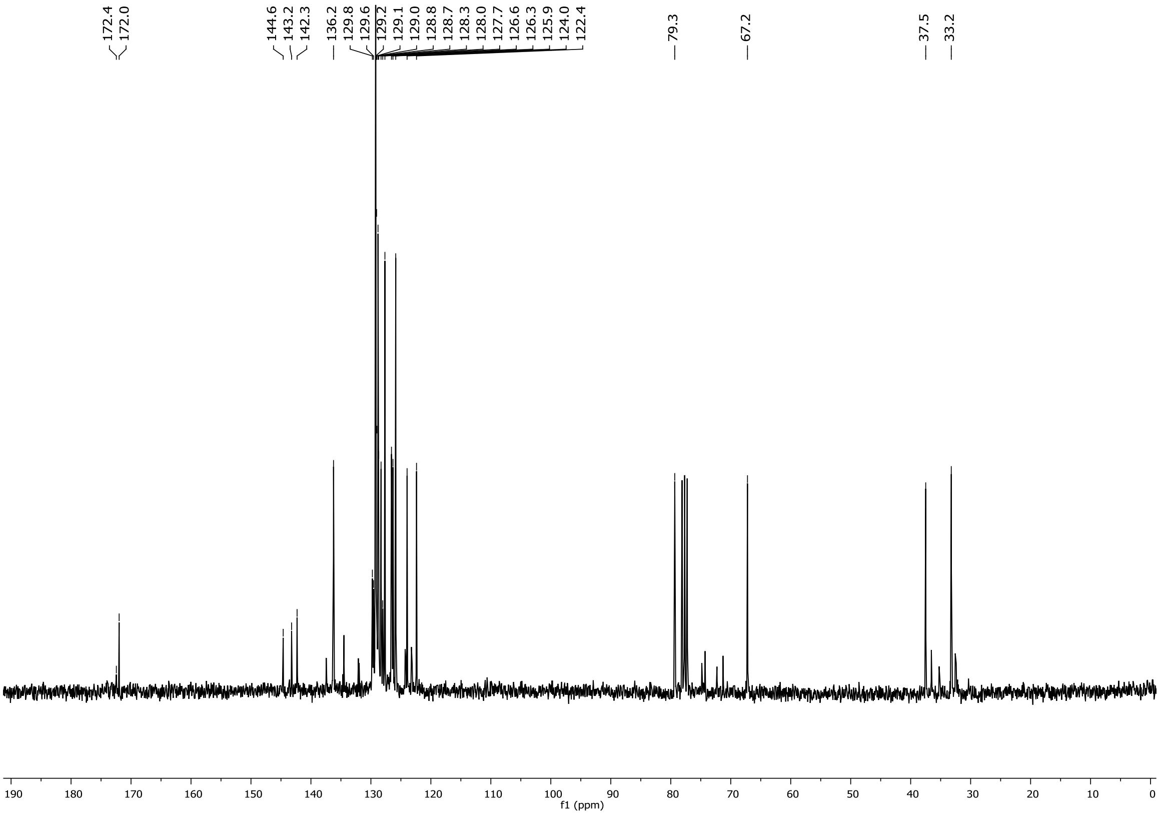
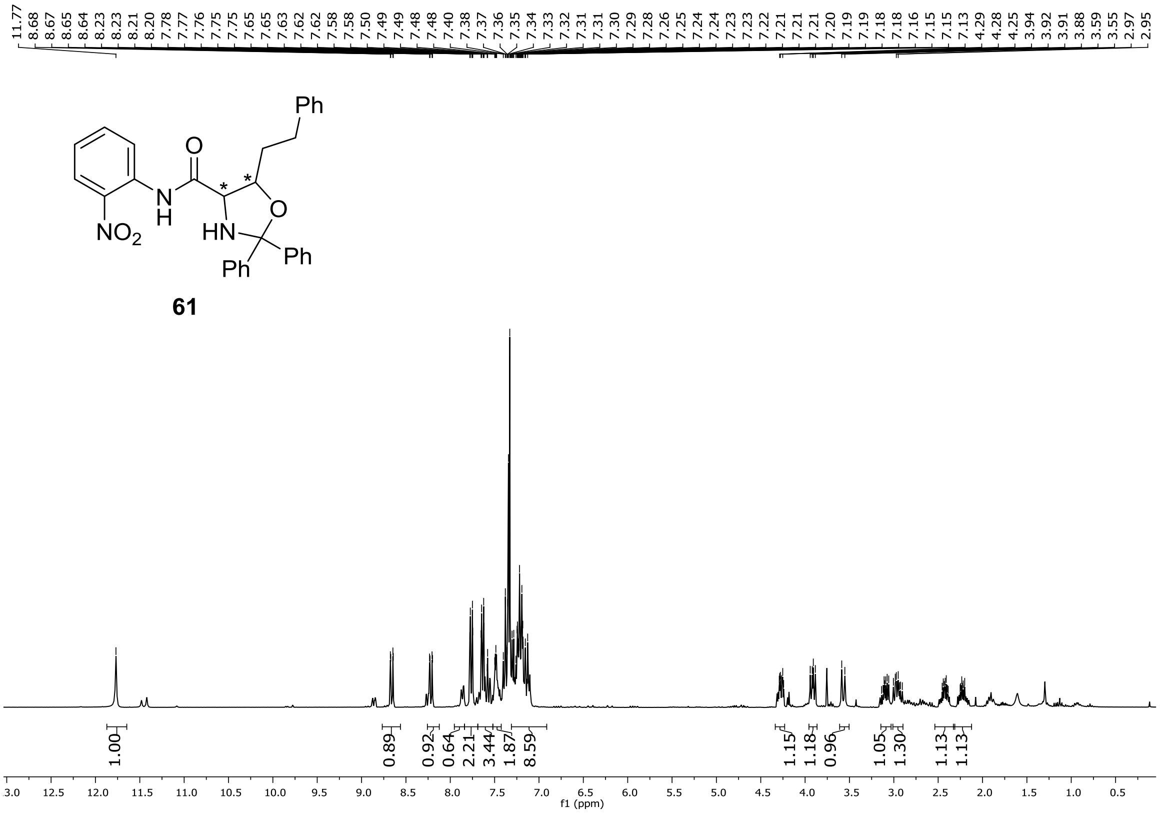
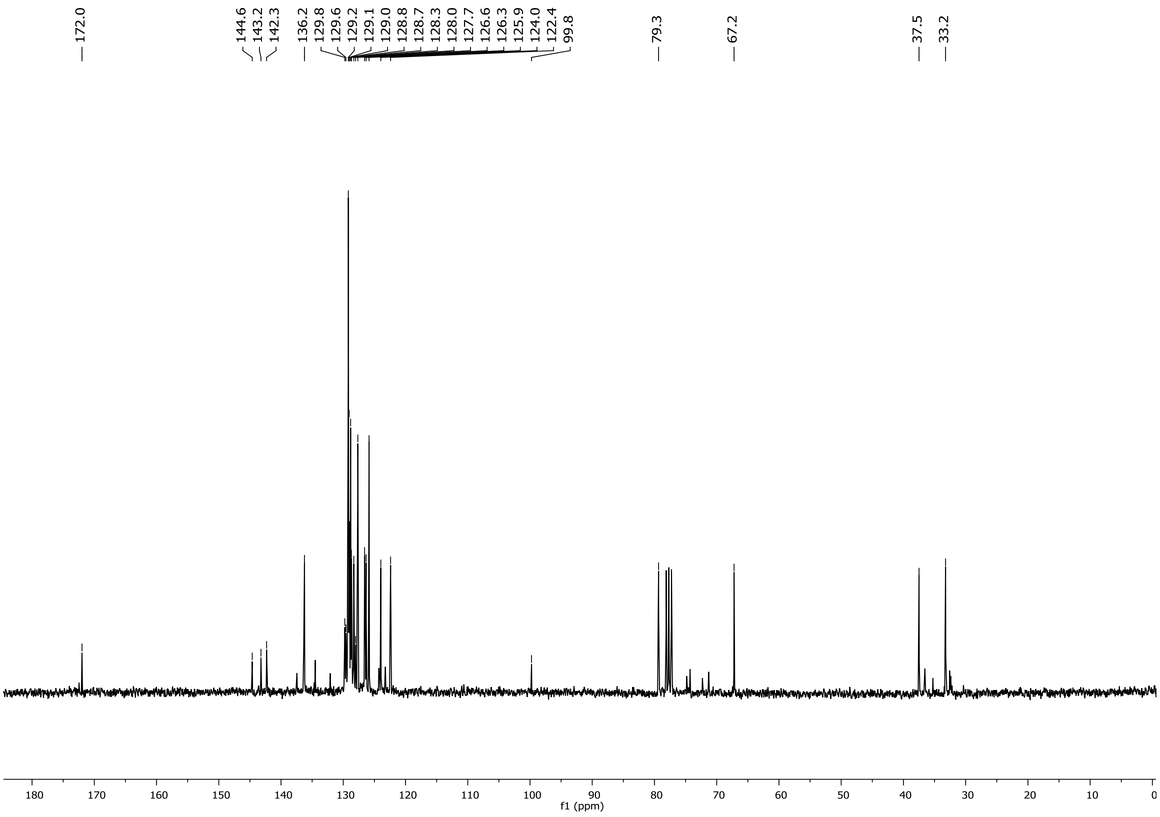
8.31
7.91
7.90
7.87
7.44
7.43
7.41
7.41
7.31
7.28
7.28
7.16
7.15
7.15
7.14
7.07
7.07
7.06
7.04
7.03
7.02
7.02
7.00
6.99
6.97
6.97
6.95
6.95
6.92
6.91
6.90
6.90
6.89
6.88
6.86
6.85
6.83
6.83
6.82
6.81
6.81
6.79
6.78
6.77
3.95
3.95
3.94
3.93
3.93
3.92
3.91
3.61
3.58
3.57
3.55
3.24
3.21
2.66
2.64
2.63
2.61
1.90
1.86
O
OH
N
H
NO2
*
*
Ph
N
Ph
Ph
1.00
0.84
1.03
1.86
3.12
1.88
13.95
1.14
1.25
0.85
2.22
1.05
1.20
12.5
12.0
11.5
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
f1 (ppm)

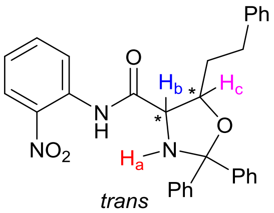
59


172.4
172.0
144.6
143.2
142.3
136.2
129.8
129.6
129.2
129.1
129.0
128.8
128.7
128.3
128.0
127.7
126.6
126.3
125.9
124.0
122.4
79.3
67.2
37.5
33.2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


11.77
8.68
8.67
8.65
8.64
8.23
8.23
8.21
8.20
7.78
7.77
7.76
7.75
7.75
7.65
7.65
7.63
7.62
7.62
7.58
7.58
7.50
7.49
7.49
7.48
7.40
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.21
7.21
7.21
7.20
7.19
7.19
7.18
7.18
7.16
7.15
7.15
7.13
4.29
4.28
4.25
3.94
3.92
3.91
3.88
3.59
3.55
2.97
2.95
Ph
O
N
H
NO2
*
*
O
HN
Ph
Ph
1.00
0.89
0.92
0.64
2.21
3.44
1.87
8.59
1.15
1.18
0.96
1.05
1.30
1.13
1.13
3.0
12.5
12.0
11.5
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
f1 (ppm)

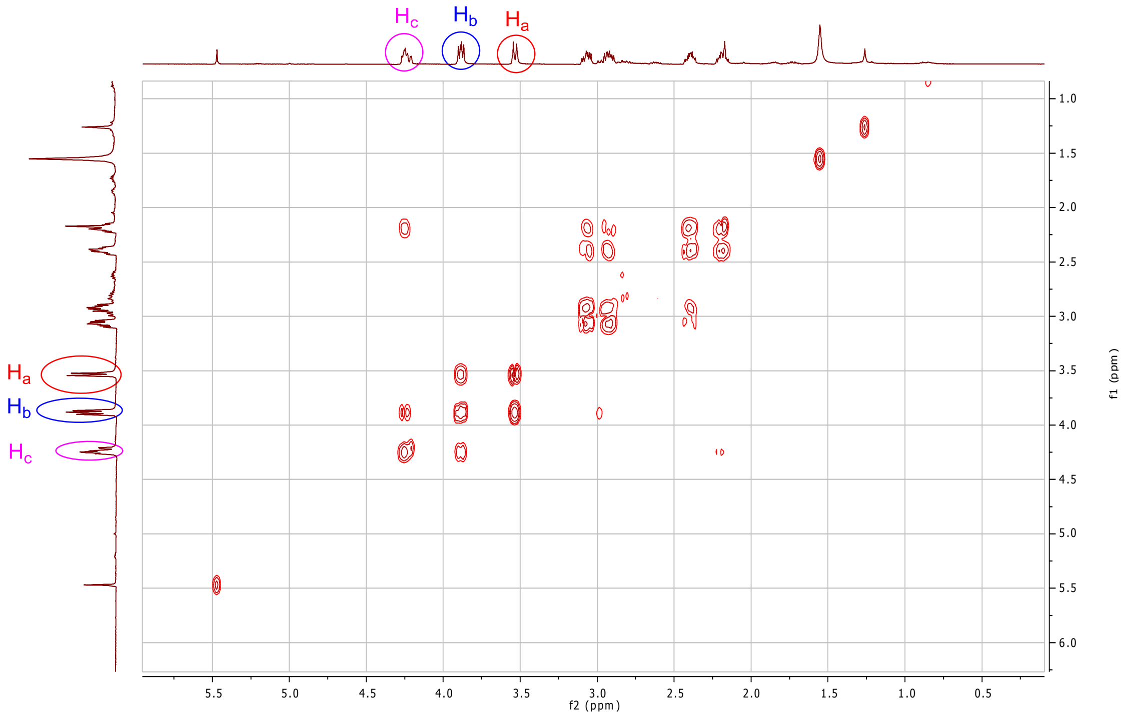
61


172.0
144.6
143.2
142.3
136.2
129.8
129.6
129.2
129.1
129.0
128.8
128.7
128.3
128.0
127.7
126.6
126.3
125.9
124.0
122.4
99.8
79.3
67.2
37.5
33.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

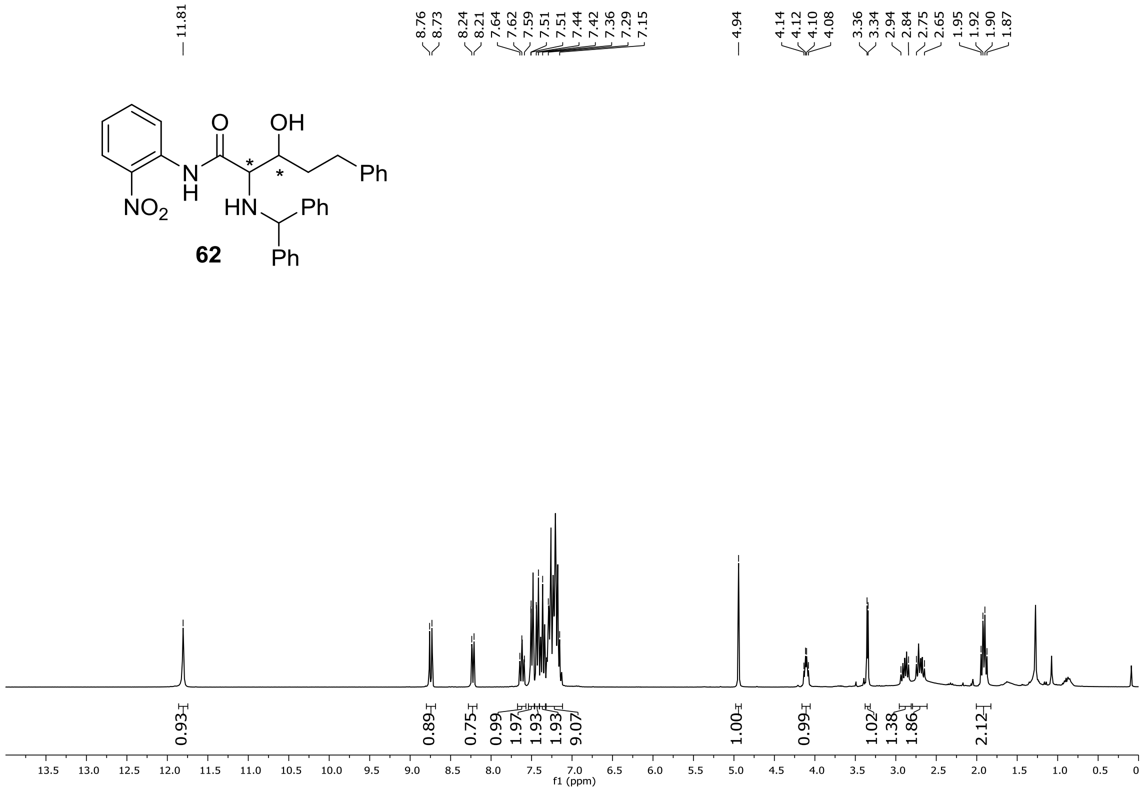

Ph
O
H_b
*
H_c
N
H
*
O
NO_2
H_a
N
Ph
Ph

trans

61

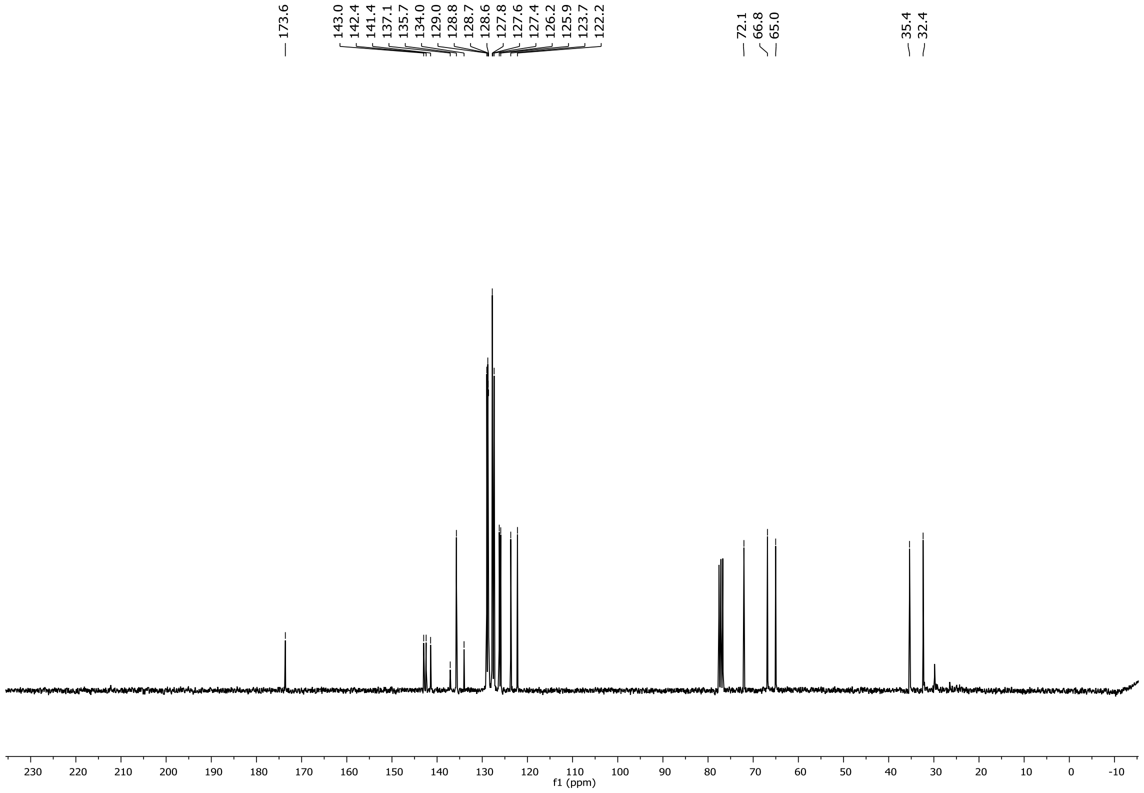


	H_a	H_b	H_c
H_a		J_{ba} = 10.5 Hz	
H_b	J_{ab} = 10.5 Hz		
H_c		J_{bc} = 7.0 Hz	J_{bc} = 7.0 Hz


O
OH
N
H
Ph
NO2
HN
Ph
Ph
*
*

62

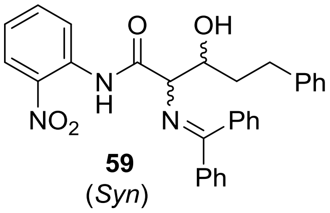
11.81
8.76
8.73
8.24
8.21
7.64
7.62
7.59
7.51
7.51
7.44
7.42
7.36
7.29
7.15
4.94
4.14
4.12
4.10
4.08
3.36
3.34
2.94
2.84
2.75
2.65
1.95
1.92
1.90
1.87
0.93
0.89
0.75
0.99
1.97
1.93
1.93
9.07
1.00
0.99
1.02
1.38
1.86
2.12
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


173.6
143.0
142.4
141.4
137.1
135.7
134.0
129.0
128.8
128.7
128.6
127.8
127.6
127.4
126.2
125.9
123.7
122.2
72.1
66.8
65.0
35.4
32.4
230
220
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)

5.4.5. **HPLC chromatograms**

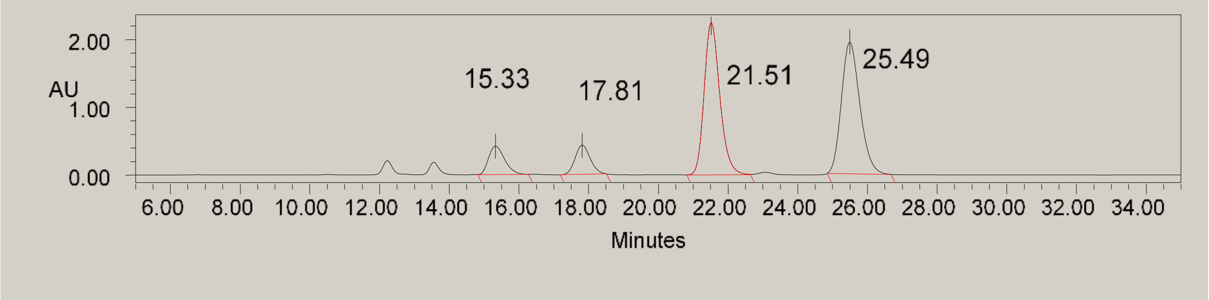
5.4.5.1. **Aldol reaction**

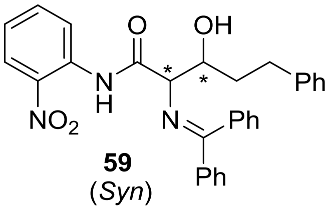
Chiralpak IC, 90:10 Hexano: EtOH, 0.5 mL/min, λ=210 nm


O
OH
N
H
Ph
NO2
N
Ph
Ph

59
(*Syn*)

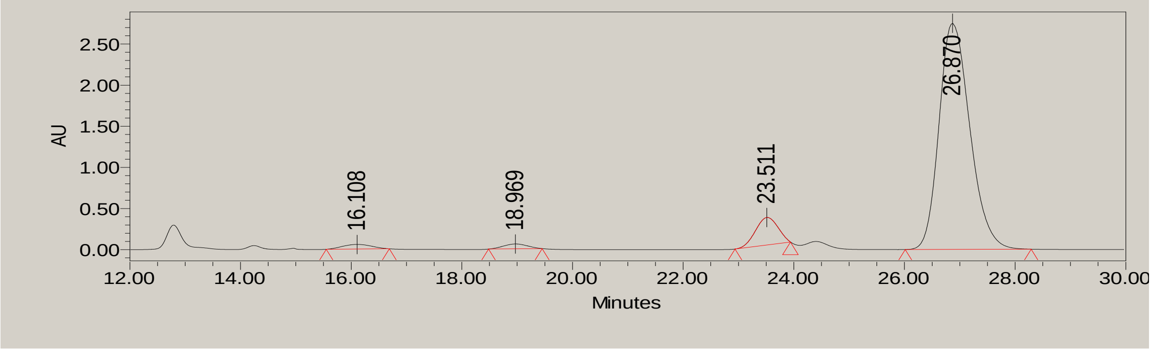
	Retention Time	% Area
1	15.331	7.89
2	17.814	7.75
3	21.516	41.73
4	25.492	42.63




O
OH
N
H
*
*
Ph
NO2
N
Ph
Ph

59
(*Syn*)

	Retention Time	% Area
1	16.108	1.70
2	18.969	1.48
3	23.511	7.86
4	26.870	88.96



PUBLICATION

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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pubs.acs.org/JACS

Catalytic Asymmetric Synthesis of Quaternary Barbituric Acids

Sandra del Pozo, Silvia Vera, Mikel Oiarbide,* and Claudio Palomo*

Departamento de Química Orgánica I, Universidad del País Vasco, Manuel de Lardizabal 3, 2018 San Sebastián, Spain

Supporting Information

ABSTRACT: The catalytic asymmetric α-functionalization of prochiral barbituric acids, a subtype of pseudosymmetric 1,3-diamides, to yield the corresponding 5,5-disubstituted (quaternary) derivatives remains essentially unsolved. In this study 2-alkylthio-4,6-dioxopirimidines are designed as key 1,3-diamide surrogates that perform exceedingly in amine-squaramide catalyzed C−C bond forming reactions with vinyl ketones or Morita−Baylis−Hillmann-type allyl bromides as electrophiles. Mild acid hydrolysis of adducts affords barbituric acid derivatives with an in-ring quaternary carbon in unprecedented enantioselectivity, offering valuable materials for biological evaluations.

Barbituric acids and derivatives are very interesting 1,3-diamide scaffolds for the development of therapeutic agents and functional materials.[1] Several approaches for the asymmetric synthesis of chiral barbiturates in which chirality resides outside of the ring (**I**, $R^1 = R^2$) are reported.[2] In contrast, the enantioselective synthesis of chiral barbiturates with in-ring chirality remains unsolved (Figure 1a). The groups of Brunner[3] and Trost,[4] independently, described palladium-catalyzed asymmetric allylic alkylation reactions of **I** (R^1 = H, R^2 = Me, R^3 = alkyl) with allyl acetates or carbonates to proceed with enantioselectivities from poor to modest. Lam's group has described the Rh(III)-catalyzed oxidative annulations of cyclic 1,3-dicarbonyl compounds with alkynes,[5] including a single example involving nonsymmetric barbiturates **I** (R^1 = H, R^2 = Me, R^3 = Ph) that yields the corresponding spiroindene adduct in 11% *ee*. It is thus not surprising that, among the thousands of 5,5-disubstituted barbiturates synthesized and selected for clinical trials, the great majority are racemic,[6] even though pharmacological profile may be configuration-dependent.[7] Here we describe a catalytic highly enantioselective route to barbiturates with an in-ring all-carbon quaternary stereocenter for the first time. For this realization 2-alkylthio-4,6-dioxopyrimidines **III** are designed as key barbituric acid equivalents that perform exceedingly under bifunctional Brønsted base/H-bond activation (Figure 1c).

Chiral organobase catalysis is recognized as one of the operationally simplest approach for the enantioselective functionalization of acidic CH pro-nucleophiles.[8] Recently, while our work was in progress, Rawal and co-workers reported the enantioselective conjugate addition of symmetrically *N*,*N*′-disubstituted barbituric acids to prochiral nitroalkenes triggered by a bifunctional amine-thiosquaramide organocatalyst.[2d] Whereas *N*,*N*′-disubstituted barbituric acids thus seems to be suitable for a mild Brønsted base deprotonation,[9] the asymmetric organocatalytic C(5)-functionalization of prochiral barbiturates of general structure **II** ($R^1 \neq R^2$, Figure 1b) has not yet been realized. A major problem concerns the pseudosymmetrical structure of the 1,3-diamide moiety (Figure 1b) which makes enantioface discrimination complicated,[10] a situation that would be critical during generation of a quaternary stereocenter.[11] For example (Scheme 1), at the outset of our investigation barbiturates **1** and **2**, as well as their thio-

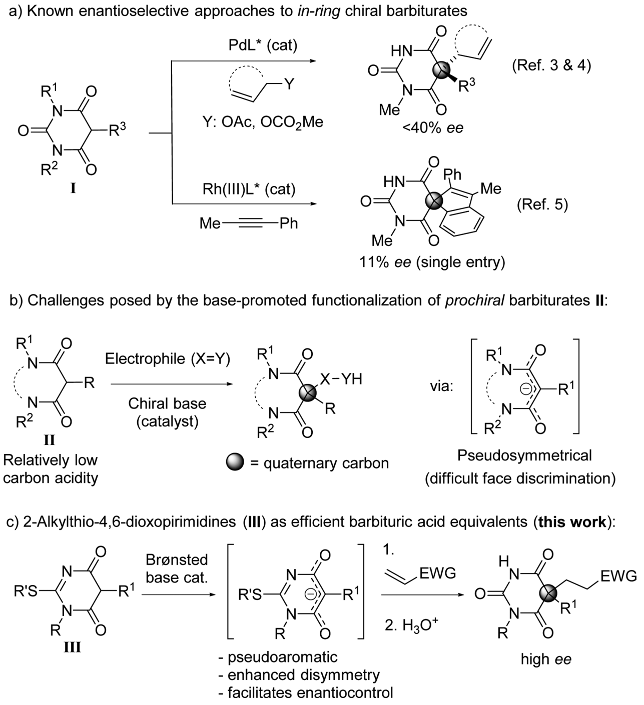
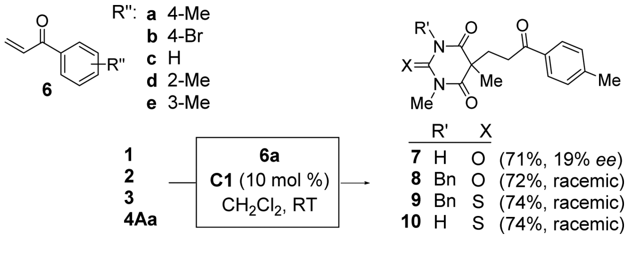

a) Known enantioselective approaches to *in-ring* chiral barbiturates
I
PdL* (cat)
Y: OAc, OCO2Me
(Ref. 3 & 4)
<40% ee
Rh(III)L* (cat)
Me—≡—Ph
(Ref. 5)
11% ee (single entry)
b) Challenges posed by the base-promoted functionalization of *prochiral* barbiturates II:
II
Relatively low carbon acidity
Electrophile (X=Y)
Chiral base (catalyst)
= quaternary carbon
via:
Pseudosymmetrical (difficult face discrimination)
c) 2-Alkylthio-4,6-dioxopirimidines (III) as efficient barbituric acid equivalents (this work):
III
Brønsted base cat.
- pseudoaromatic
- enhanced disymmetry
- facilitates enantiocontrol
1. EWG
2. H3O+
high ee

Figure 1. Asymmetric α-functionalization of 1,3-diamides toward barbituric acid derivatives with an in-ring stereogenic carbon.

Scheme 1. Initial Experiments with (Thio)Barbiturates 1−4


R'': a 4-Me
b 4-Br
c H
d 2-Me
e 3-Me
6
1
2
3
4Aa
6a
C1 (10 mol %)
CH2Cl2, RT
R' X
7 H O (71%, 19% ee)
8 Bn O (72%, racemic)
9 Bn S (74%, racemic)
10 H S (74%, racemic)

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analogues **3**/**4Aa**, were treated with vinyl ketone **6a** in the presence of 10 mol % catalyst **C1** (Figure 2) to give, respectively, adducts **7**–**10** as essentially racemic material (<20% *ee* at best).[12] Reaction reversibility (retro-Michael process)[2d,9] as a cause of the low enantiocontrol could be discarded as no crossover products were detected when adducts **7** and **8** were admixed with vinyl ketone **6b** in the presence of a base catalyst.[12] We then questioned whether 2-benzylthio-4,6-dioxopyrimidines **5** (Figure 2), which as far as we know have never been employed in asymmetric catalysis, could be used to solve this problem, considering: (i) the ready conversion into the target barbituric acids upon standard hydrolytic conditions, (ii) the enhancement of structural dissymmetry as compared to the nearly symmetric diamides **1**–**4**, and (iii) the suitability toward deprotonation (pseudoaromatic enolate would be formed) promoted by a weak base.

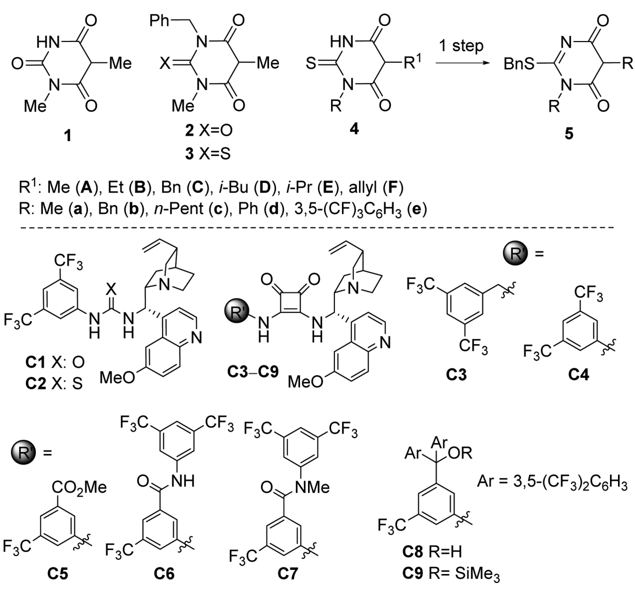

1
2 X=O
3 X=S
4
1 step
BnS
5
R^1: Me (**A**), Et (**B**), Bn (**C**), *i*-Bu (**D**), *i*-Pr (**E**), allyl (**F**)
R: Me (**a**), Bn (**b**), *n*-Pent (**c**), Ph (**d**), 3,5-(CF$_3$)$_3$C$_6$H$_3$ (**e**)
C1 X: O
C2 X: S
C3–C9
C3
C4
R =
C5
C6
C7
Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
C8 R=H
C9 R= SiMe$_3$

Figure 2. Barbituric substrates and catalysts used in this study.

The preparation of compounds **5** was afforded in one benzylation step from the easily available thiobarbiturates **4** (Figure 2).[12,13] Initial assessment of the behavior of these compounds in conjugate additions was gratifying as the reaction of **5Aa** with enone **6a** under the catalytic conditions of Scheme 1 afforded adduct **11** with a promising 66% *ee* (Table 1, entry 1). The enantioselectivity could not be improved when other known catalysts, such as bifunctional thiourea **C2**[14] or squaramides **C3**[15] and **C4**[16] (entries 2–4), or modified analogues **C5**, **C6** and **C7**[17] (entries 5–7) were employed. Eventually, the sterically more congested catalysts **C8** and **C9**, which can be prepared easily through Grignard technology, performed the best.[12] Thus, catalyst **C8** provided product **11** with 80% *ee* at room temperature and a remarkable 96% *ee* by running the reaction at 0 °C (entries 8, 9). The silyl analogue **C9** provided similar selectivities, but slower reaction. To the best of our knowledge, this realization constitutes the first catalytic asymmetric Michael reaction of α-branched 1,3-diamides.[18]

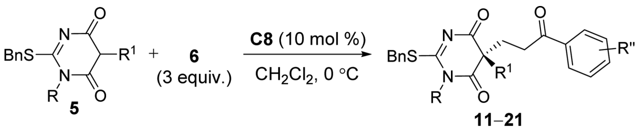
As the results in Table 2 show, several aryl vinyl ketones with electron donating (Me) or withdrawing (Br) substituents on the aromatic ring were equally competent reaction partners, apparently irrespective of the *o*-, *m*-, or *p*- substitution pattern (compounds **11**–**15**). Also, the method tolerates substrates **5** with a range of substituents at both the N(3) (methyl, pentyl, benzyl, aryl) and the C(5) (methyl, ethyl, benzyl, allyl) position of the heterocycle to give the respective adducts **11**–**21** in *ee*'s generally above 90%. However, intrinsically less reactive Michael acceptors, such as acrylates and, by extension, α,β-unsaturated esters, were not competent reaction partners. In the opposite direction, the more reactive but less sterically demanding acrolein, upon reaction with **5Aa**, led, after hydrolysis, to adduct **22**, but with a poor 48% *ee*. In order to surmount these difficulties, we next examined the reactions with α-silyloxy enone **23**, an acrylate and acrolein equivalent very easy to prepare from acetone.[19] As before, initial experiments using enone **23** in combination with (thio)-barbiturates **1** and **4** provided the corresponding addition adduct as essentially racemic material independently of the catalyst employed.[12] Gratifyingly, however, the reaction of **23** with various 2-benzylthio-4,6-dioxopyrimidines **5** proceeded smoothly and with very high enantioselectivity (Table 3). Adducts from these reactions were isolated after acidic hydrolysis leading to barbituric acids **24**. As data in the table show, products **24** bearing linear/branched alkyl or allyl R^1

Table 1. Catalyst Screening for the Reaction of 5Aa with 6a To Give 11[a]

entry	catalyst	yield (%)	*ee* (%)
1	**C1**	67	66
2	**C2**	71	36
3	**C3**	60[b]	n.d.
4	**C4**	69	32
5	**C5**	67	73
6	**C6**	59	54
7	**C7**	66	75
8	**C8**	72	80
9	**C8**[c]	60	96
10	**C9**	62	78

[a] Reactions carried out at r.t. using 0.2 mmol of **5Aa**, 0.6 mmol of enone **6a** and 10 mol % catalyst in 0.5 mL of CH$_2$Cl$_2$; yields of isolated product after chromatography; *ee* determined by chiral HPLC. [b] Conversion. [c] Reaction run at 0 °C.

Table 2. Scope of the Reaction of 2-Benzylthio-4,6-dioxopyrimidines 5 with Aryl Vinyl Ketones 6[a]



entry	R	R^1	R''	product	yield (%)[b]	ee (%)[c]
1	Me	Me	4-Me	**11**	72	96
2	Me	Me	4-Br	**12**	63	95
3	Me	Me	H	**13**	61	92
4	Me	Me	2-Me	**14**	72	85
5	Me	Me	3-Me	**15**	62	96
6	Me	Et	4-Br	**16**	71	97
7	Me	Bn	3-Me	**17**[d]	75	94
8	Me	Allyl	H	**18**	65	92
9	Ar[e]	Me	H	**19**	65	90
10	Bn	Me	4-Br	**20**	67	90
11	*n*Pent	Me	4-Br	**21**	73	92

[a] Reactions carried out at 0.2 mmol scale in 0.5 mL of CH$_2$Cl$_2$. [b] Yields of isolated product after chromatography. [c] *ee* determined by chiral HPLC. [d] X-ray. [e] Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$.

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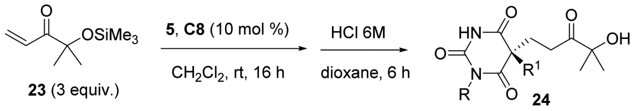
Table 3. Scope of Nucleophiles for the Reaction with Acrylate Equivalent 23[a]

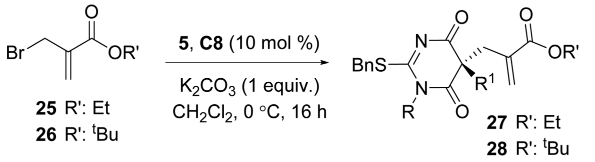

OSiMe3
23 (3 equiv.)
5, C8 (10 mol %)
CH2Cl2, rt, 16 h
HCl 6M
dioxane, 6 h
HN
O
N
R
R1
OH
24

entry	R^1	R	product	yield (%)	ee (%)
1	Me	Me	**24Aa**	82	90
2	Me	Bn	**24Ab**	61	81(87)[b]
3	Me	*n*Pent	**24Ac**	63	83(87)[b]
4	Me	Ph	**24Ad**[c]	62	90
5	Et	Me	**24Ba**	71	94
6	Bn	Me	**24Ca**	70	92
7	*i*Bu	Me	**24Da**	68	93
8	*i*Pr	Me	**24Ea**	–	–
9	Allyl	Me	**24Fa**	72	92

[a] Reactions carried out at 0.2 mmol scale in 0.5 mL of CH_2Cl_2. [b] Reactions run at room temperature using 10 mol % **C9**. [c] X-ray.

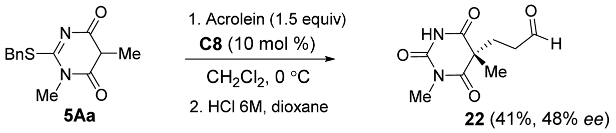
substituents are produced in good yields and enantioselectivities typically above 90%, with isopropyl being an exception (entry 8). The absolute configuration of adduct **24Ad** was established by single crystal X-ray structural analysis[20] and that of the remaining adducts by analogy and by assuming a uniform reaction mechanism. To further illustrate the potential of templates **5** to build-up quaternary barbiturates through modification at C(5), the alkylation reaction with allyl bromides derived from Morita–Baylis–Hillmann adducts was examined. It was found that the reaction of **5** with allyl bromides **25**/**26** in the presence of 1 equiv of K_2CO_3 and 10 mol % catalyst **C8** proceeded smoothly at 0 °C (Table 4).[21] Curiously, these reactions were sensitive to both the nature of the ester group and the base employed. For example, while ethyl ester **25** led to adduct **27Aa** using K_2CO_3 as base with moderate enantioselectivity (entry 1, 54% *ee*), the *tert*-butyl congener **25** afforded **28Aa** in a remarkable 99% *ee* under the same conditions (entry 2). Among the bases examined, K_3PO_4 provided a similar (97% *ee*) selectivity, whereas Cs_2CO_3 led to a reduced 77% *ee* and tertiary amines were completely ineffective in terms of enantioselectivity.[12] As data in Table 4 show, the allylic alkylation with **25** resulted suitable for a variety of substrates **5**, affording adducts **28** with short and long alkyl, allyl or aryl groups installed at the C(5) and N(1) positions in generally good yields and selectivities of 89% *ee* or higher.

Table 4. Allylic Alkylation with MBH Bromides 25/26[a]


Br
OR'
25 R': Et
26 R': tBu
5, C8 (10 mol %)
K2CO3 (1 equiv.)
CH2Cl2, 0 °C, 16 h
BnS
N
R
R1
OR'
27 R': Et
28 R': tBu

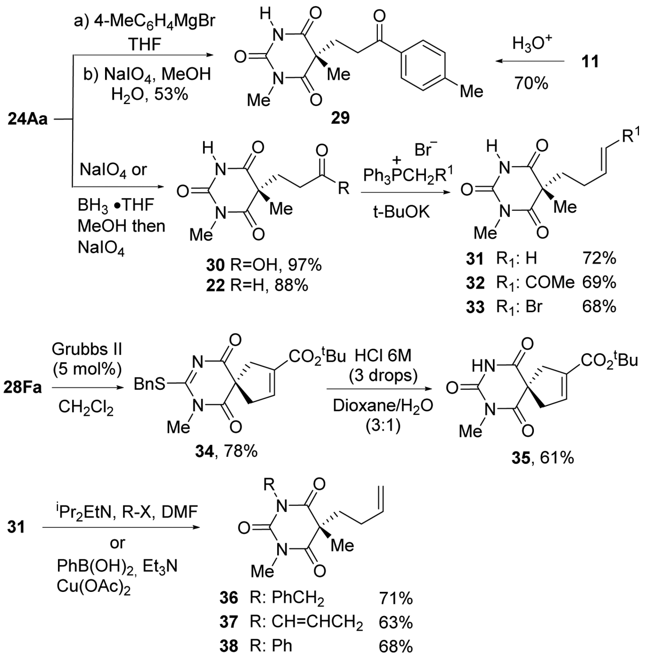
entry	R^1	R	product	yield (%)	ee (%)
1	Me	Me	**27Aa**	62	54
2	Me	Me	**28Aa**	63	99
3	Me	Bn	**28Ab**	61	90
4	Me	*n*Pent	**28Ac**	73	99
5	Et	Me	**28Ba**	67	96
6	Bn	Me	**28Ca**	63	86
7	Allyl	Me	**28Fa**	65	92

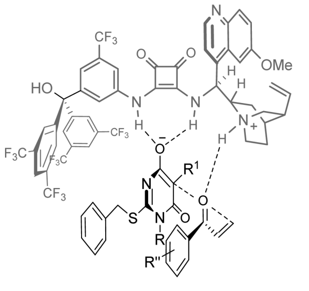
[a] Reactions carried out using 0.2 mmol of **5** and 1 equiv of each bromide **25**/**26** and K_2CO_3 in 0.5 mL of CH_2Cl_2.


BnS
N
Me
5Aa
1. Acrolein (1.5 equiv)
C8 (10 mol %)
CH2Cl2, 0 °C
2. HCl 6M, dioxane
HN
H
22 (41%, 48% ee)

Transformations in Scheme 2 give an idea of the versatility of the present method for the preparation of 5,5-disubstituted chiral barbituric acid derivatives. Thus oxidative ketol cleavage in **24Aa** furnished the acid **30** almost quantitatively, while applying a reduction/1,2-diol cleavage sequence, aldehyde **22** was produced in 88% overall yield. Subsequent Wittig olefination gave rise to elongated barbiturates **31**−**33**. Eventually, conversion of both **24Aa** and **11** into the same ketone **29** served to further corroborate the stereochemical assignments. On the other hand, ring closing metathesis of tethered diene **28Fa** and subsequent hydrolysis of the resulting adduct **34** provided spiranic barbiturate **35** as essentially enantiopure compound. Finally, N-alkylation/arylation of imide **31** using standard protocols gave rise fully substituted barbiturates **36**, **37** and **38**, which are products otherwise difficult to obtain in enantioenriched form.

Scheme 2. Elaboration of Adducts


24Aa
a) 4-MeC6H4MgBr
THF
b) NaIO4, MeOH
H2O, 53%
29
H3O+
70%
11
NaIO4 or
BH3 •THF
MeOH then
NaIO4
30 R=OH, 97%
22 R=H, 88%
Br−
Ph3PCH2R1
t-BuOK
31 R1: H 72%
32 R1: COMe 69%
33 R1: Br 68%
28Fa
Grubbs II
(5 mol%)
CH2Cl2
BnS
CO2tBu
34, 78%
HCl 6M
(3 drops)
Dioxane/H2O
(3:1)
35, 61%
31
iPr2EtN, R-X, DMF
or
PhB(OH)2, Et3N
Cu(OAc)2
36 R: PhCH2 71%
37 R: CH=CHCH2 63%
38 R: Ph 68%


CF3
HO
F3C
OMe
N
H
R1
R
R''
S

(**A**)

On the other hand, according to recent proposals for this type of catalysis where the squaramide is doubly H-bonded to the nuclephilic component (enolate) and the protonated quinuclidine activates the electrophile,[22] model **A** could be invoked, which would correctly explain the observed stereochemistry.

In summary, we report here the first highly enantioselective construction of chiral barbiturates with an in-ring quaternary stereogenic center, based on the catalytic α-functionalization of 2-alkylthio 4,6-dioxopyrimidines as key barbituric acid equivalents. Squaramide-tertiary amine bifunctional catalysts are able to trigger the reaction of these templates with Michael acceptors efficiently, being the highest selectivities attained with the new bulky catalyst **C8**. While extension of this approach (i.e., using different acceptors) can be foreseen, chemical elaboration of adducts provides a route to structurally diverse, quaternary barbituric acid derivatives hitherto inaccessible in optically active form.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09124.

Experimental details, NMR spectra, HPLC chromatograms (PDF)
Crystallographic data for **17** (CIF)
Crystallographic data for **24Ad** (CIF)

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Notes

The authors declare no competing financial interest.

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