Synthesis of tricyclic bioactive compounds

Reactivity of cyclopropanated 2-pyrones and 2-pyridinones

Dissertation

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Meiner Familie

“Die Definition von Wahnsinn ist, immer wieder das Gleiche zu tun und andere Ergebnisse zu erwarten.“

Albert Einstein

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Abbreviations

λ	wavelength	DABCO	1,4-diazabicyclo[2.2.2] octane
Ac	acetyl	dba	dibenzylideneacetone
Ac_2O	acetic anhydride	FVT	flash vacuum thermolysis
AcO	acetoxy	GC	gas chromatography
AIBN	azoisobutyronitrile	glyme	dimethoxyethane
Am	amyl	h	hour(s)
aq.	aqueous	Hept	heptyl
Ar	aryl	Hex	hexane
atm	atmosphere	HFIP	hexafluoroisopropanol
AZADOL	2-hydroxy-2-azaadamantane	HIV	human immunodeficiency viruses
BHT	butylated hydroxytoluene	HMPA	hexamethylphosphoramide
BINOL	1,1-binaphthol	HOMO	highest occupied molecular orbital
Bn	benzyl	HPLC	high-performance liquid chromatography
Boc	*tert*-butyloxycarbonyl	HRMS	high-resolution mass spectrometry
bpy	bipyridine	Hz	hertz
Bs	brosyl	hν	light
Bu	butyl	*i*-	*iso*-
Bz	benzoyl	iNOS	inducible nitric oxide synthase
cat.	catalyst	IR	infrared
CDI	1,1’-carbonyldiimidazole	L	undefined ligand
CFL	compact fluorescent lamp	LA	Lewis acid
COD	1,5-cyclooctadiene	LB	Lewis base
Cp*	pentamethylcyclopentadiene	LDA	lithium diisopropylamide
crm	complex reaction mixture	LED	light-emitting diode
CSA	camphor sulfonic acid	LiHMDS	lithium bis(trimethylsilyl) amide
Cy	cyclohexyl	LG	leaving group
4CzIPN	1,2,3,5-tetrakis(carbazole-9-yl)-4,6-dicyanobenzene	LUMO	lowes unoccupied molecular orbital
d	day(s)	M	molar or metal

*m*CPBA	*meta*-chloroperbenzoic acid	Py	pyridine
Me	methyl	Pr	propyl
MeCN	acetonitrile	quant.	quantitative
min	minute(s)	R	arbitrary rest
MOM	methoxymethyl	RCM	ring-closure metathesis
mp	melting point	R_f	retention factor
MS	mass spectrometry or molecular sieves	rt	room temperature
Ms	mesyl	s	second(s)
MW	microwave	*s*-	*sec*
m/z	mass-to-charge ratio	sat.	saturated
n-	normal	SET	single electron transfer
NBS	*N*-bromosuccinimide	SM	starting material
NHC	*N*-heterocyclic carbene	T	temperature
NMO	*N*-methylmorpholine-*N*-oxide	t	time
NMP	*N*-methyl-2-pyrrolidone	*t*-	*tert*
NMR	nuclear magnetic resonance	TBAF	Tetrabutyl ammonium fluoride
Ns	nosyl	TBS	*tert*-butyldimethylsilyl
n.r.	no reaction	TES	triethylsilyl
Nu	nucleophile	Tf	triflyl
Oct	octyl	TFA	trifluoroacetic acid
OTf	triflate	THF	tetrahydrofuran
ox.	oxidation	THP	tetrahydropyran
p	pressure	TIPS	triisopropylsilyl
p-	*para*	TLC	thin layer chromatography
Pent	pentyl	TMEDA	tetramethylethylenediamine
Ph	phenyl	TMS	trimethylsilyl
Phen	phenanthrene	Tol	toluene
Piv	pivalate	TPS	triphenylsilyl
PMB	*para*-methoxybenzyl	Tr	tritylium
ppy	2-phenylpyridine	TS	transition state
Ts	tosyl	Vis	visible

W	watt
X	arbitrary moiety

A Synthesis of tricyclic bioactive compounds

1. Introduction

1.1 Diterpenoid families and their biological activity

Natural products have played and still play an important role in the treatment and prevention of diseases. Especially the plant families of *Euphorbiaceae* and *Thymelaeaceae* contain a large number of biologically active compounds with a unique core framework, namely the diterpenoid structure.[1] The main structure skeletons such as ingenane, jatropholane, tigliane, abietane and daphnane[2] are shown in Figure 1 as well as the taxane diterpenoid structure which can be found in the compounds of the *Taxaceae* plant family.[3] All of them have a tricyclic core structure in common, mostly with 5-,6- and 7-membered rings. A part of them also contains a cyclopropane ring attached to the core structure, *e.g.* ingenane, jatropholane and tigliane diterpenes.

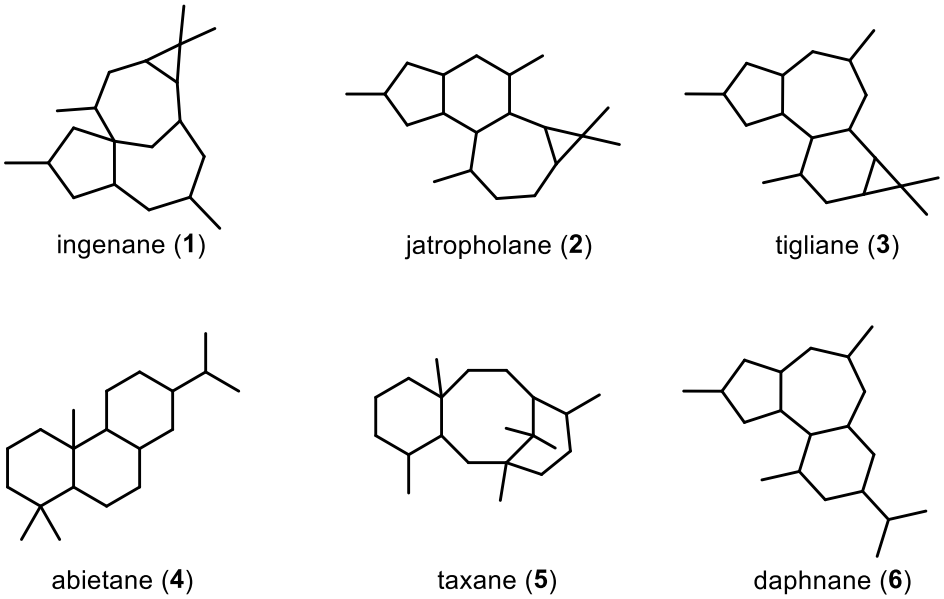
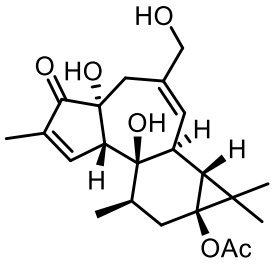


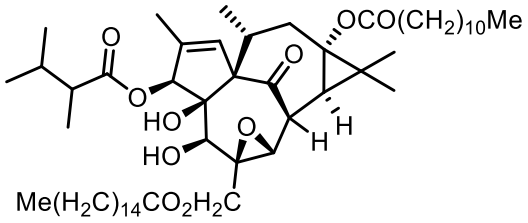
Figure 1. Diterpenoid structure skeletons found in the *Euphorbiaceae*, *Thymelaeaceae* as well as *Taxaceae* plant family.[1–3]

These compounds cover a vast range of biological activities including anti-HIV, anti-cancer, anti-leukaemia, insecticidal and cytotoxic effects.[4] Figure 2 shows some selected compounds, *e.g.* Prostratin (**7**), a tigliane diterpene, is a protein kinase C (PKC) activator which is responsible for many physiological functions and anti-HIV properties amongst others, since it affects viral reservoirs of $CD4^+$ T-cells. In addition, Prostratin (**7**) also exhibits analgesic and sedative effects.[2] The ingenane diterpene Kansuiphorin B (**8**) is

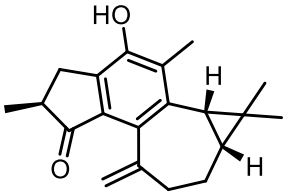
known for its cytotoxicity against various cancer cell lines and the jatropholane diterpenoid Jatropholone A (**9**) exhibits anti-plasmodial activity against the protozoan parasite *Plasmodium falciparum* which carries the Malaria disease as the most prevalent and fatal strain.[2] On the other hand, the taxane diterpene Taxol® (**10**) which was first isolated by Monroe Wall and Mansukh Wani is an effective anti-cancer drug for various human cancer cells.[3]



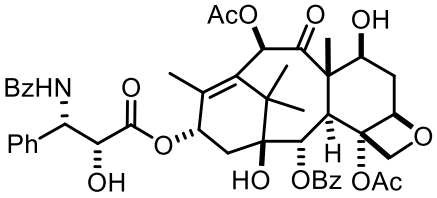
Prostratin (**7**)



Kansuiphorin B (**8**)



Jatropholone A (**9**)



Taxol® (**10**)

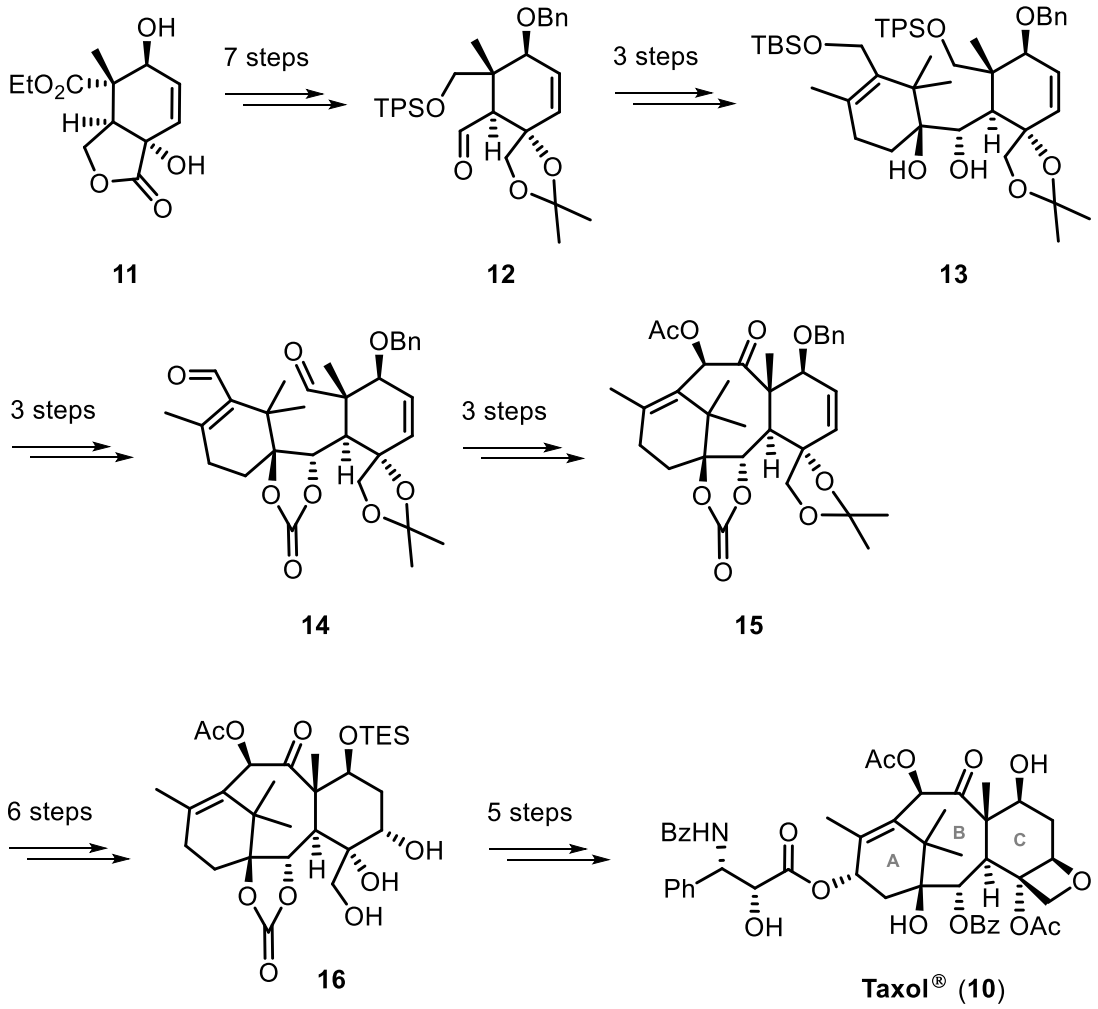
Figure 2. Some important diterpenoids.

Since this is just a small selection of the various compounds with a diterpenoid structure which possess outstanding physiological activities, it is not surprising that researchers see a big challenge in the synthesis of new derivatives which might show even better activities or improve already reported syntheses of some clinically used compounds. Because of this broad area, the focus will be mainly placed on the tigliane, daphnane and taxane diterpenoids which also play a role in this thesis.

1.2 Synthetical strategies towards diterpenoids

Because the extraction of biologically active compounds from plants is not very effective in the long run, researchers had to find ways to synthesize diterpenoids which are suitable for disease treatment in an inexpensive and up-scalable way. Therefore, some synthetical strategies towards the diterpenoid core structure and some successful total syntheses will be presented here. Starting with a very elegant synthesis from the perspective of an

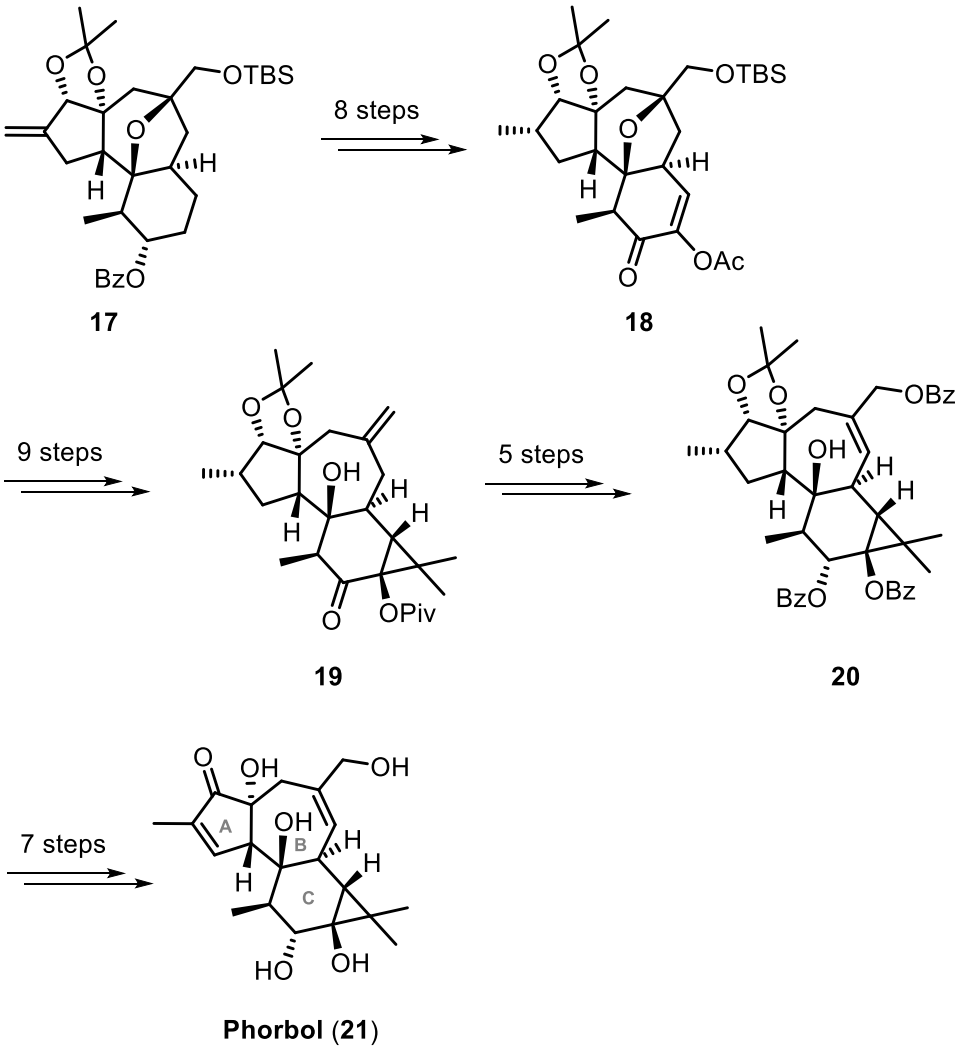
organic chemist, namely the total synthesis of Taxol® (**10**) first accomplished by the group of Nicolaou[5] in 1994 (Scheme 1). They solved the synthetical problem by first introducing the C-ring originating from compound **11** which, after several protection and deprotection steps as well as reduction of ester and opening of lactone followed by the oxidation to aldehyde **12**, was then coupled with the precursor of the A-ring resulting in product **13**. Further oxidation to aldehyde **14** and ring closure gave the tricyclic structure **15**. By treating **15** with hydrogen peroxide and cleavage of the acetal, triol **16** was obtained which was finally transformed to Taxol® (**10**) in a total of 27 steps.



Scheme 1. Total synthesis of Taxol® (**10**) by Nicolaou *et al.*[5]

A different synthesis of an important tigliane diterpene was reported by Wender and his group[6] in 1989. They were successful in synthesizing Phorbol (**21**) which belongs to a group of the most potent tumor promotors since it can activate PKC isozymes, which play an important role in cellular signal transduction, meaning that it can influence antitumor, anti-HIV and analgesic properties.[7] For the total synthesis (Scheme 2) the Wender group

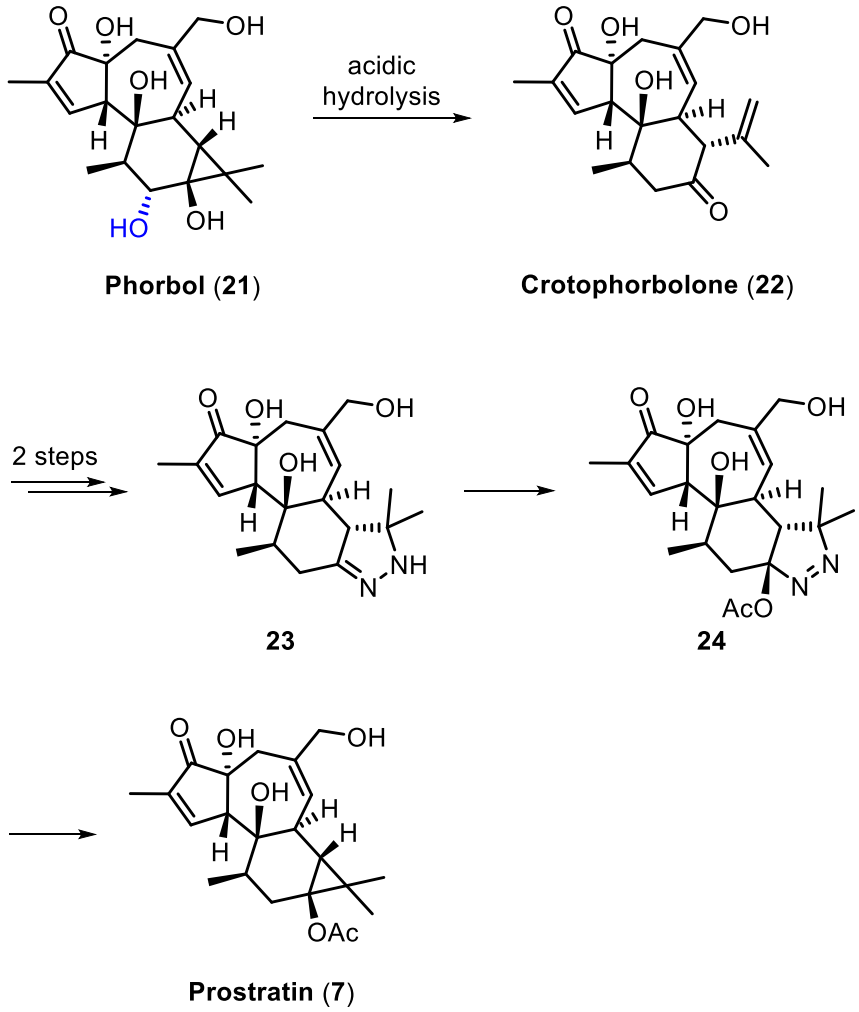
started with the core structure **17** whose synthesis was reported before[8] by first reducing the double bond with Wilkinson's catalyst and then oxidizing the benzylic alcohol followed by further oxidations to yield the acyloxy-enone **18**. In order to install the cyclopropane, enone **18** was reacted with an ylide and reduced to intermediate **19**. Introduction of the benzoate was accomplished by a two-step chlorination and substitution, and reduction of the ketone gave compound **20**. Finally, Phorbol (**21**) was obtained by functionalization of the A-ring, consisting of cleavage of the acetal, bromination and consecutive elimination to yield the enone moiety.



Scheme 2. Total synthesis of Phorbol (**21**) starting from compound **17** according to Wender *et al.*[6]

Starting from Phorbol (**21**), the synthesis of the biologically active natural product Prostratin (**7**) was also reported by the group of Wender[9] in 2008. In just five steps they were able to obtain the desired product with Crotophorbolone (**22**) as an important

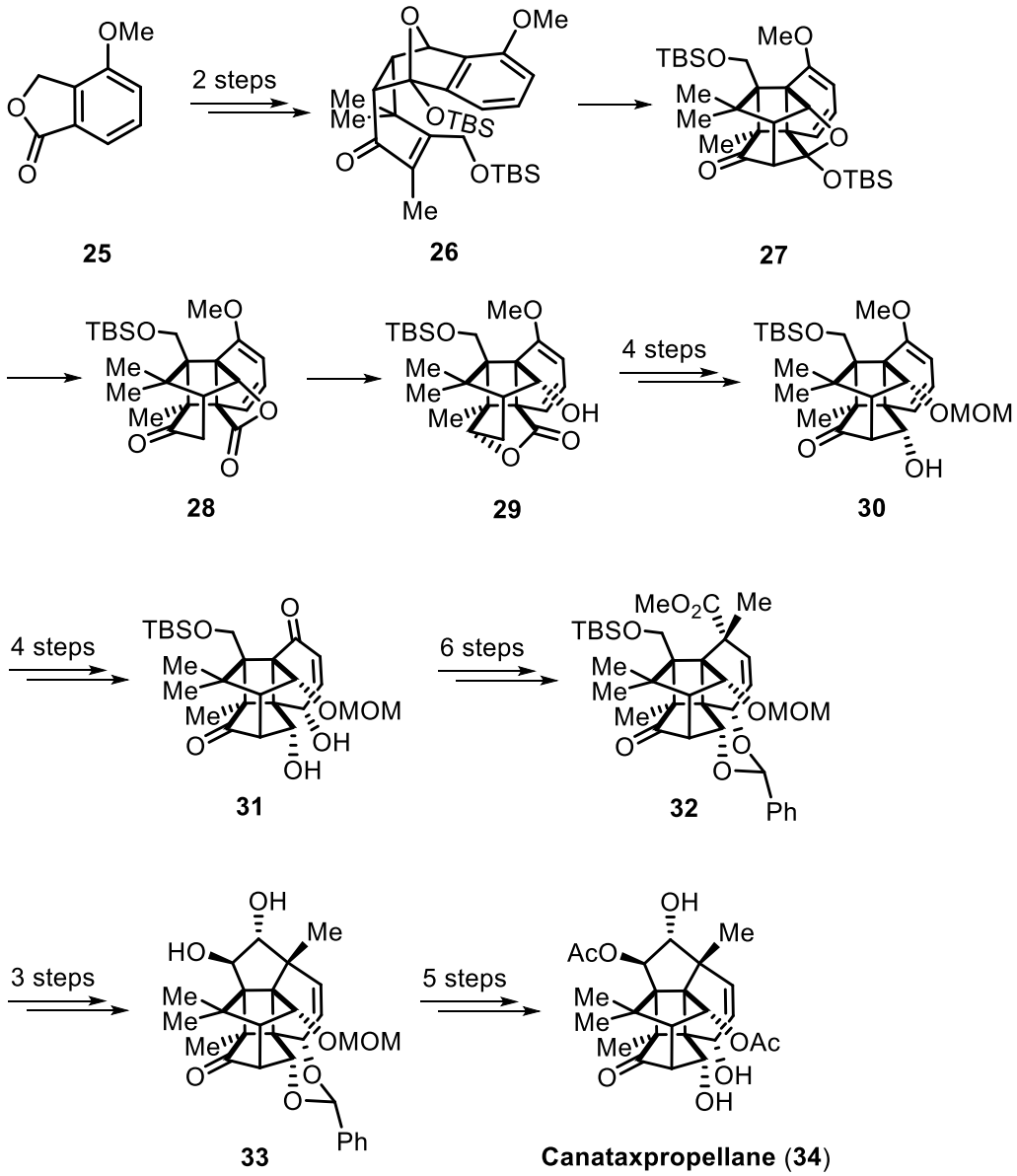
intermediate (Scheme 3). In this case the hydrolysis of Phorbol (**21**) to Crotophorbolone (**22**) was already reported by Thielmann *et al.*[10] in 1969. Since the main difference between Phorbol and Prostratin (**7**) is the absence of one alcohol (marked in blue) and hydrolysis to Crotophorbolone leads to the required precursor, the authors had just to re-establish the cyclopropane ring. Hence, treating Crotophorbolone with hydrazine gave pyrazoline **23** which was then oxidized and acylated to give the cyclic diazene **24**. Photolysis of the latter yielded Prostratin (**7**) by extrusion of nitrogen and thus formation of the cyclopropane ring.



Scheme 3. Synthesis of Prostratin (**7**) starting from Phorbol by Wender *et al.*[9]

Recently, the synthesis of the taxane diterpenoid Canataxpropellane (**34**), a highly oxygenated and most complex natural compound was reported by Gaich *et al.*[11] The challenge in synthesizing this molecule stems from the presence of two propellanes, 12 stereocenters and a mostly neopentylic backbone. Nonetheless, the authors found a way to synthesize this complex compound in 26 steps from lactone **25** (Scheme 4). A Diels-

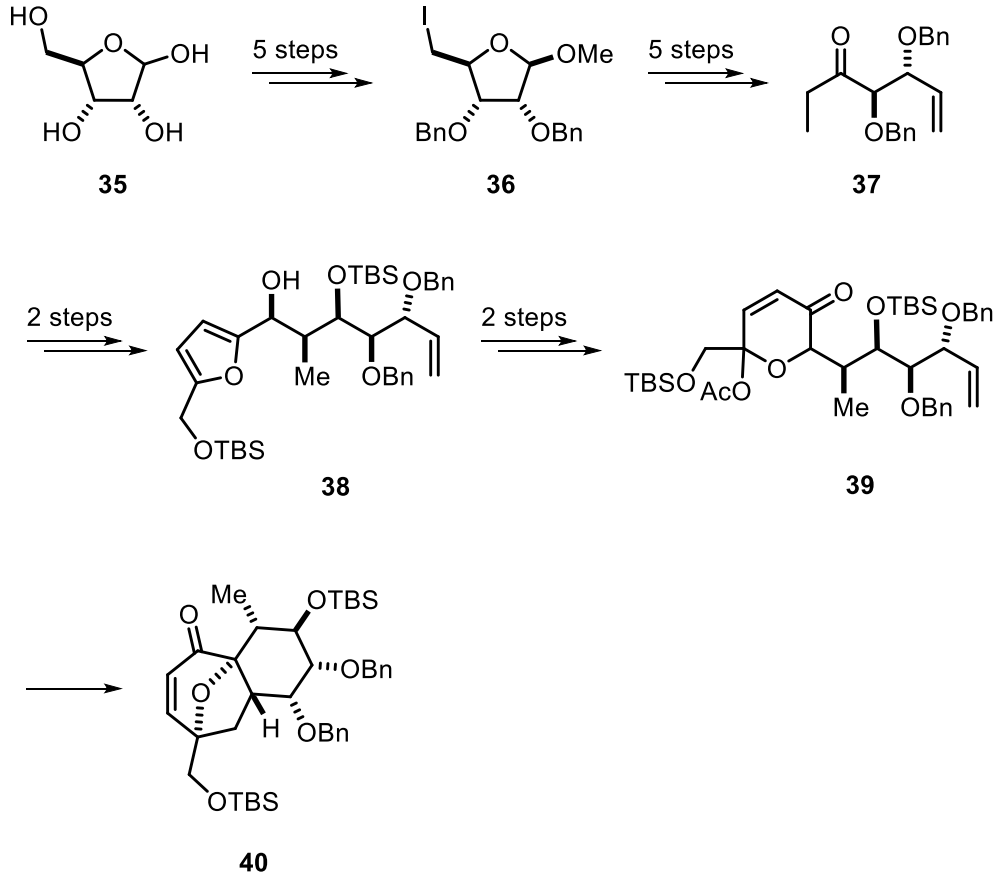
Alder reaction with a corresponding diene led to product **26** which underwent photocatalyzed cyclization to give the cage structure **27**. A trans lactonization from the retro-aldol intermediate **28** gave compound **29** which was further transformed to ketone **30** by Pinacol coupling. Then the six-membered ring was transformed *via* peroxide formation and cleavage into intermediate **31** whose ketone functionality was converted to an ester (**32**). Reduction to an alcohol and subsequent Swern oxidation gave the starting material for another Pinacol coupling to obtain the precursor **33**. Further protection and deprotection steps finally gave the desired Canataxpropellane (**34**).



Scheme 4. Total synthesis of Canataxpropellane (**34**) according to Gaich *et al.*[11]

As demonstrated by these examples, the synthesis of certain natural products requires a lot of reaction steps and costs a lot of time from organic chemists. Therefore, some

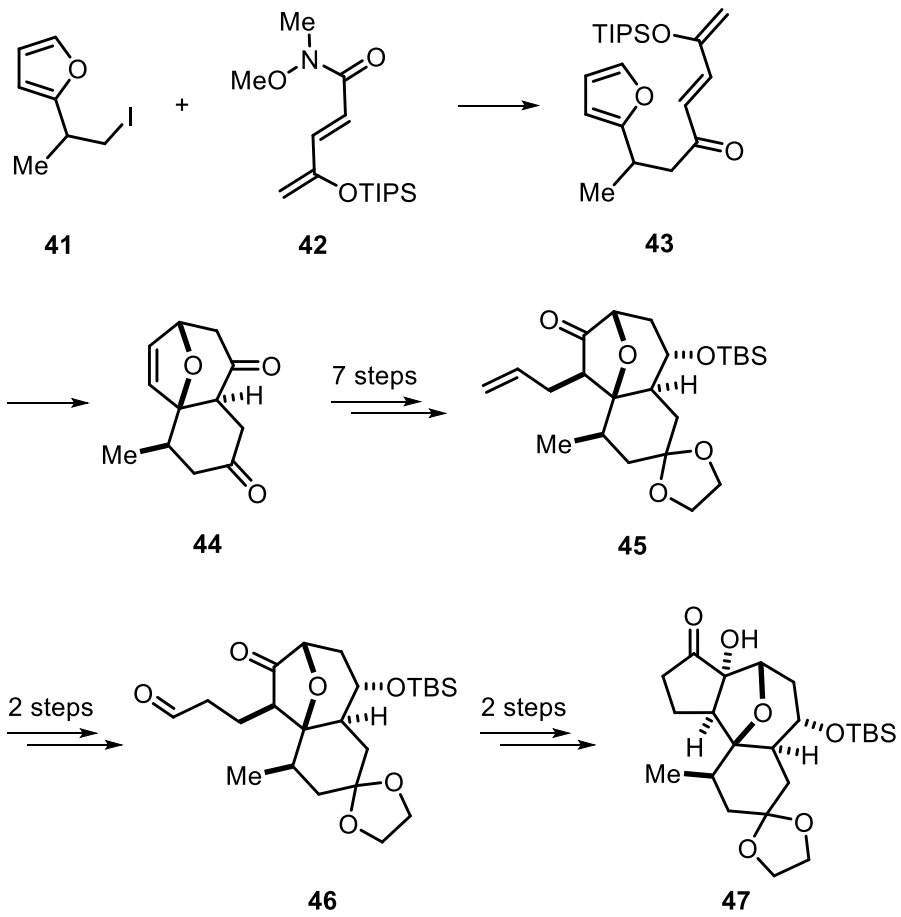
researchers also invented methods to synthesize just the core structure of specific diterpenoids in order to obtain complex compounds in a faster and easier way and test their biological activity. One of such synthetic strategies for daphnetoxins was reported by Wender and his group[12] in 2006. They started from the readily available D-ribose **35**, which after obtaining iodide **36** was transformed into ketone **37**. Aldol reaction with a furfuryl aldehyde gave intermediate **38** and oxidative ring expansion yielded compound **39**, which was then converted to the desired daphnetoxin structure **40** by a [5+2]-cycloaddition (Scheme 5).



Scheme 5. Synthesis of daphnetoxin structure **40** by a [5+2]-cycloaddition by Wender *et al.*[12]

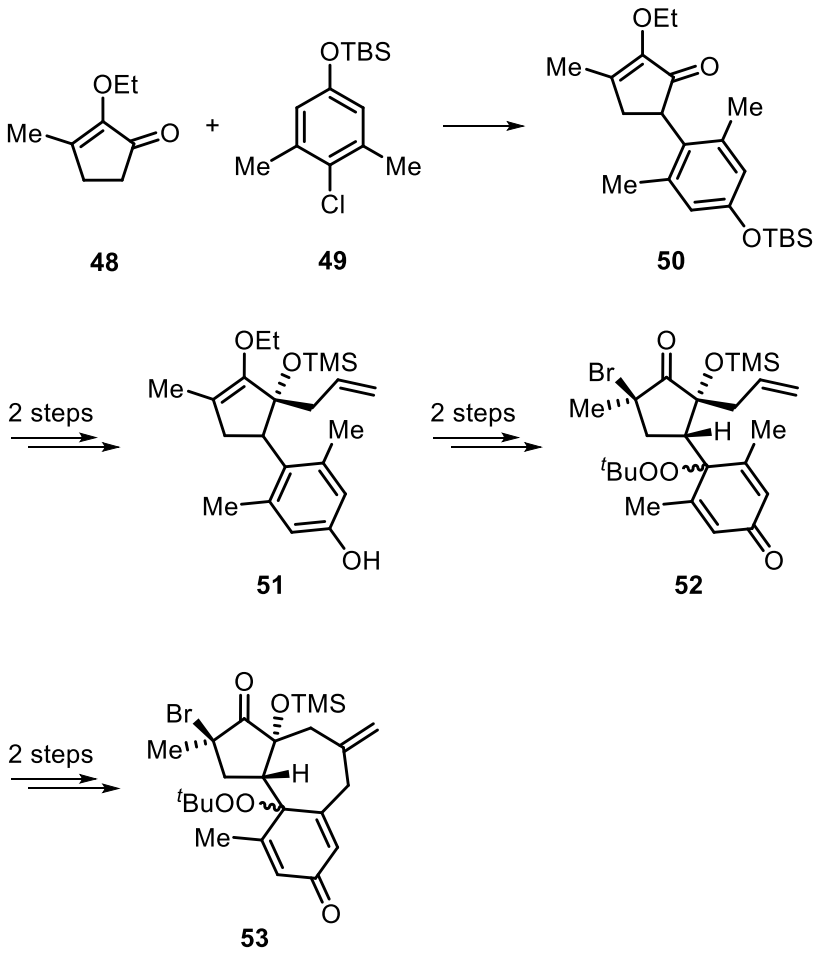
Some years later, in 2015, the group of Cho[13] reported a similar approach towards the core structure of daphnane diterpenoids (Scheme 6). A reaction between iodide **41**, readily available from furane, and Weinreb amide **42** gave the dienone **43**, which then underwent a [4+3]-cycloaddition to the bicycle **44**. Oxidation and allylation steps gave intermediate **45** which was oxidized *via* a Dess-Martin protocol (**46**). A Pinacol coupling

finally gave the tricyclic daphnane structure **47**, which may be derivatized in further reaction steps.



Scheme 6. Synthesis of daphnane core structure **47** by Cho *et al.*[13]

A slightly different approach was reported by Maimone *et al.*[14] in 2019 starting from aromatic precursors as shown in Scheme 7. After a Pd-catalyzed arylation of enolate **48** with aryl chloride **49**, the intermediate **50** was allylated which gave compound **51**. This was then subjected to a bromination and oxidative dearomatization which led to the stable peroxide **52**. Pd-catalyzed oxidative cyclization yielded the 5-, 7-, 6-membered ring structure **53** found in daphnane and tigliane diterpenoids.



Scheme 7. Synthesis of daphnane and tigliane core structure **53** from aromatic precursors according to Maimone *et al.*[14]

This is just a brief glimpse on synthetical strategies towards the complex tricyclic structures of daphnane, tigliane and taxane diterpenoids and many reviews already exist on this.[1,15]

1.3 Photocatalysis in natural product syntheses

One of the first radical reactions in organic synthesis were reported by Julia[16] and Barton *et al.*[17] though that time mostly toxic tin compounds and others were used. During the last two decades visible light photoredox catalysis gained more and more popularity in synthetic transformations because of its environmentally friendly, mild, clean and inexpensive reaction conditions. Pioneer reactions are already presented in several reviews from the last years[18] and are based on the fact that most of organic molecules do not absorb in the visible wavelength range (400 – 700 nm). Therefore, a catalyst is needed which upon oxidation can mediate single electron transfer (SET) processes via an oxidative or reductive pathway (Figure 3). Hence, after excitation of photocatalyst **PC** to **PC*** during the oxidative quenching cycle, the sacrificial electron acceptor **A** oxidizes the catalyst to $\mathbf{PC}^{\bullet+}$ which takes an electron from electron donor **D**, producing the ground state catalyst **PC** and the radical $\mathbf{D}^{\bullet+}$. For the reductive quenching cycle, a sacrificial donor **D** reduces the excited catalyst to $\mathbf{PC}^{\bullet-}$ which then reduces an electron acceptor **A** to $\mathbf{A}^{\bullet-}$ and regenerates the ground state **PC**. The generated radicals $\mathbf{D}^{\bullet+}$ and $\mathbf{A}^{\bullet-}$ follow well known reaction routes to obtain the desired products.[19]

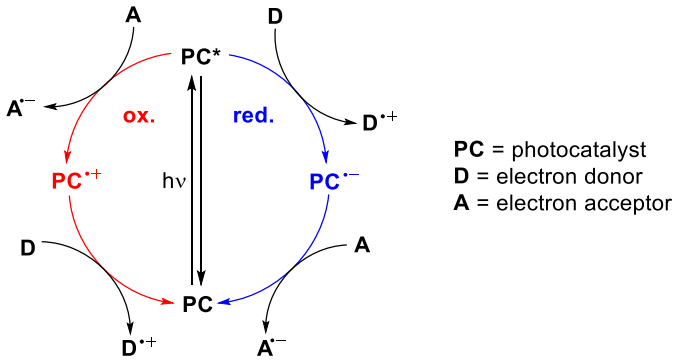


Figure 3. General photocatalyzed oxidative and reductive quenching cycle.

A small overview of frequently used photocatalysts is shown in Figure 4 where in the upper part transition metal-based catalyst like $[Ru(bpy)_3]^{2+}$ (**54**) and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$ (**55**) are shown and in the lower part the organo dyes Fukuzumi's catalyst (**56**) and Eosin Y (**57**). Those catalysts usually absorb in the blue (420 – 490 nm) and green (490 – 575 nm) light region.

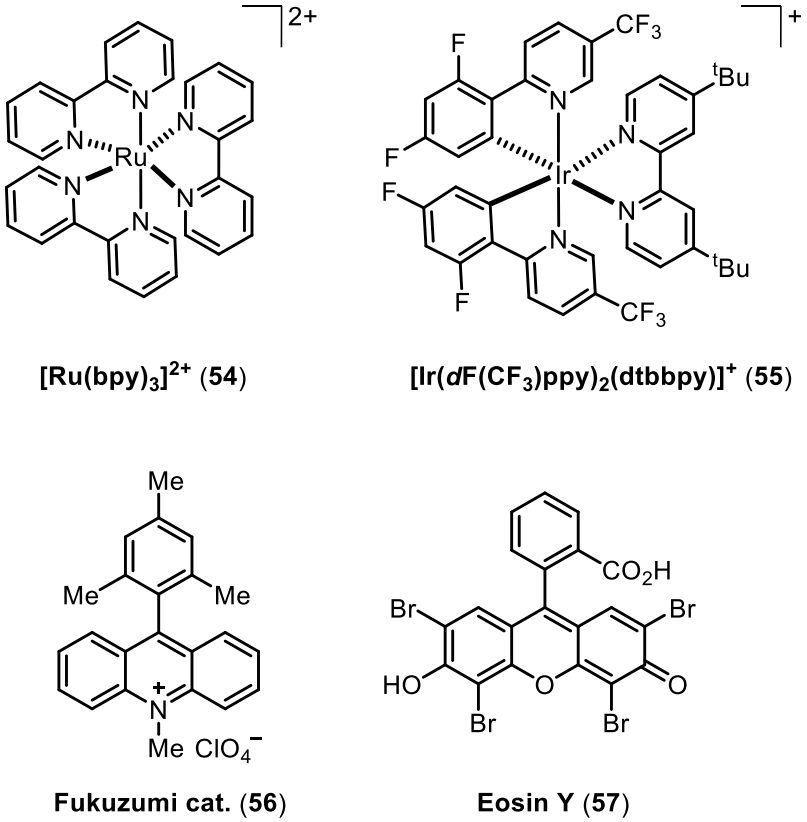
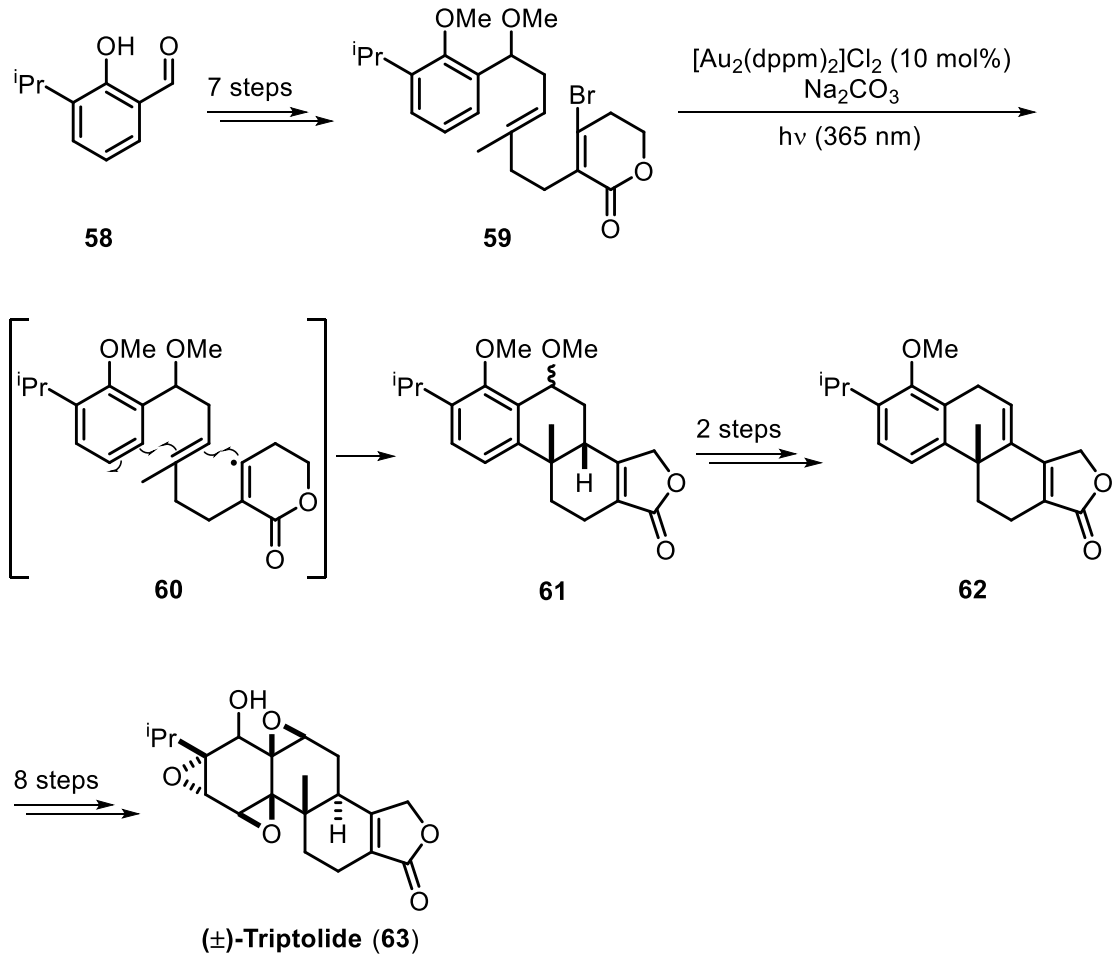


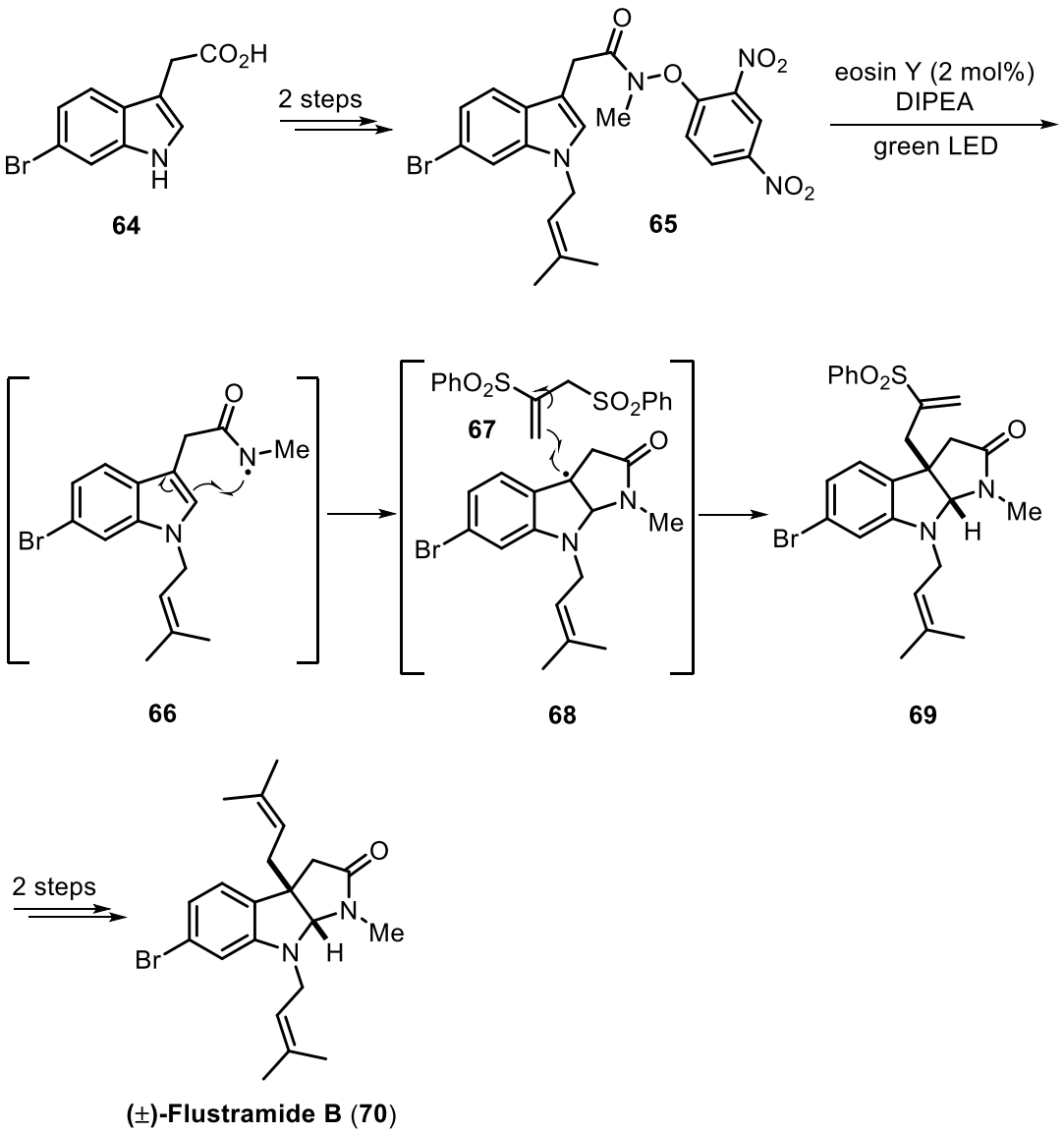
Figure 4. Transition metal-based and organocatalysts.

In natural product synthesis photocatalysis also started to play a more important role since controlled radical reactions became more widely employed and some unhealthy reaction conditions could be circumvented. In addition, interesting cascades and rearrangements were observed of which some will be presented in the following. For example, the group of Barriault[20] reported the total synthesis of (±)-Triptolide (**63**) which is known for its immunosuppressive, anti-inflammatory and anti-cancer effects[21] starting from aldehyde **58** (Scheme 8). After the formation of vinyl radical **60** with a dimeric gold complex under UV light irradiation, a 6-endo-trig/6-exo-trig radical cascade was triggered to give the tetracyclic lactone **61**. After further transformations, the natural product (±)-Triptolide (**63**) was obtained. Since not many examples for gold catalysis exists, this synthesis gives a good application for it.



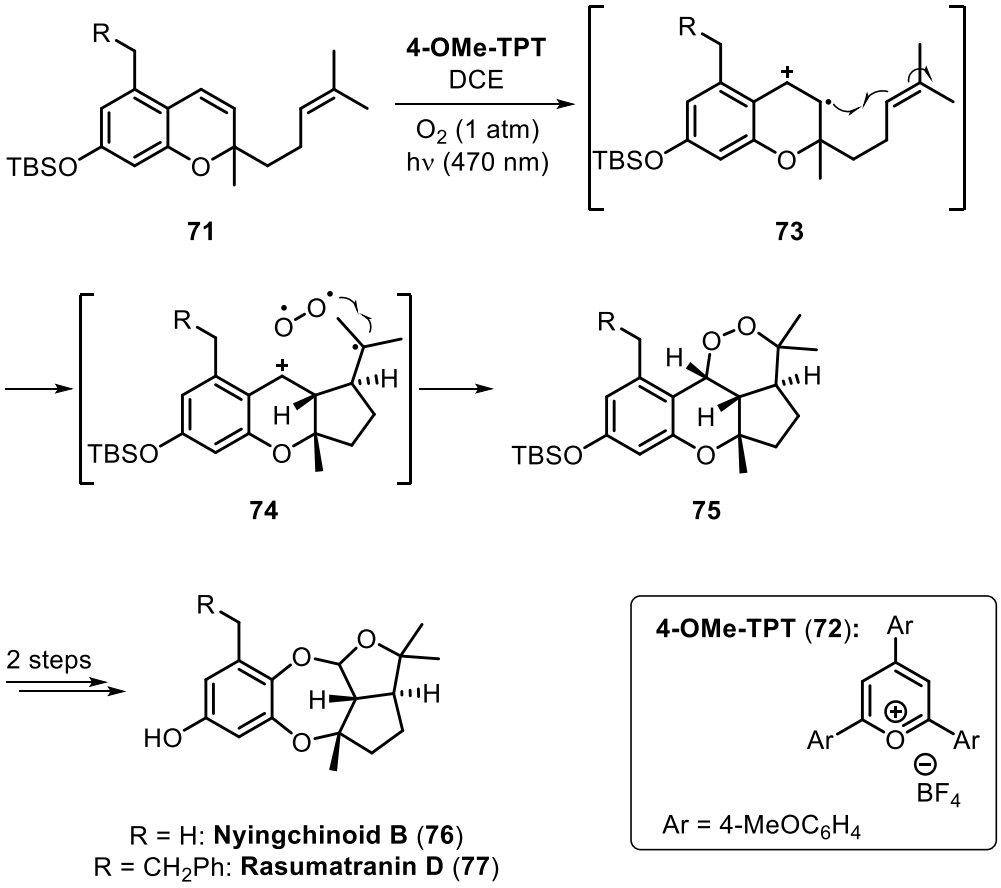
Scheme 8. Total synthesis of (±)-Triptolide (**63**) *via* a 6-endo-trig/6-exo-trig cyclisation catalyzed by Au-catalyst.

A metal free photocatalyzed synthesis of (±)-Flustramide B (**70**) – a marine alkaloid which could block voltage-activated potassium channels and exhibit skeletal and smooth muscle relaxation properties – was reported by Wang *et al.*[22] in 2017 (Scheme 9). Starting from the commercially available acid **64**, the amidyl radical precursor **65** was synthesized. After reduction with the organocatalyst Eosin Y the electrophilic radical **66** underwent a 5-endo-trig cyclization which itself gave the nucleophilic radical **68**. Following an addition-fragmentation reaction with vinyl sulfone **67**, the precursor **69** for the natural product was synthesized in just a few steps.



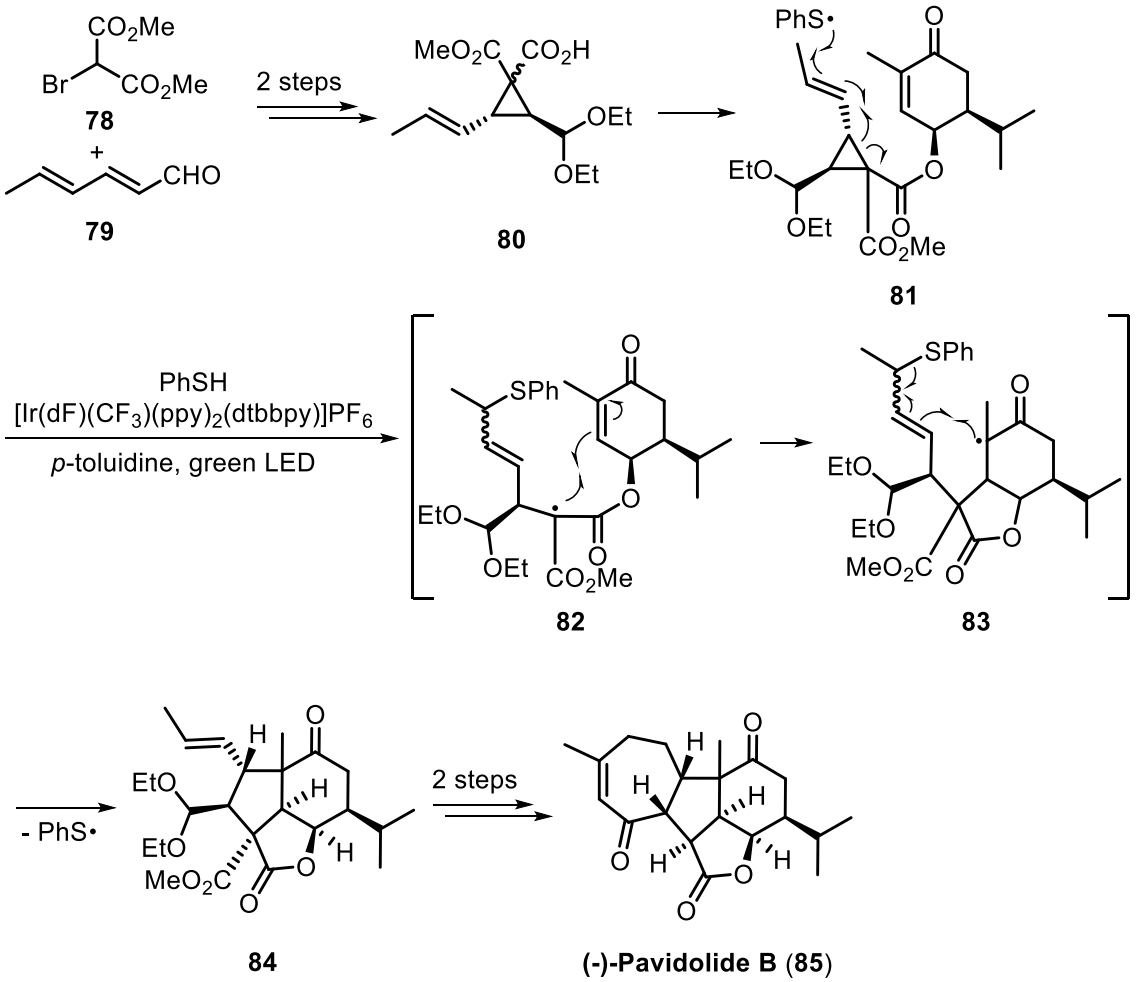
Scheme 9. Total synthesis of (±)-Flustramide B (**70**) with Eosin Y as photocatalyst.

Another organocatalyst, namely 4-OMe-TPT (**72**) – a triarylpyrylium salt – was applied by the group of George[23] for the cumulative synthesis of Nyingchinoids A, B and D and Rasumatranin D (Scheme 10). Starting with chromene **71**, oxidation by the excited photocatalyst gave radical **73** whose resulting radical **74**, after a 5-exo-trig cyclisation, was captured by oxygen to give the 1,2-dioxane **72** in a net [2+2+2]-cycloaddition. Rearrangement of the endoperoxide gave the desired natural products – Nyingchinoid B (**76**) and Rasumatranin D (**77**).



Scheme 10. Synthesis of Nyingchinoid B (**76**) and Rasumatranin D (**77**) by a [2+2+2]-cycloaddition.

Another interesting annulation cascade was presented by Yang and his group[24] who used a thiyl radical in order to start the cascade for the synthesis of (-)-Pavidolide B (**85**), a diterpenoid which shows high selective inhibitory activity against a number of human leukemic cell lines (Scheme 11). Starting with an enantioselective catalytic domino Michael/α-alkylation reaction to produce cyclopropane **80**, it was then coupled under Mitsunobu conditions to give precursor **81** for the photoreaction. When the thiyl radical was produced by irradiation with blue light under Ir-catalysis, it first added to the vinyl group causing the cyclopropane to open, forming radical **82**. This underwent a double 5-exo cyclization and elimination of thiyl radical to yield the tricycle **84**. After some more transformation, (-)-Pavidolide B (**85**) was obtained.



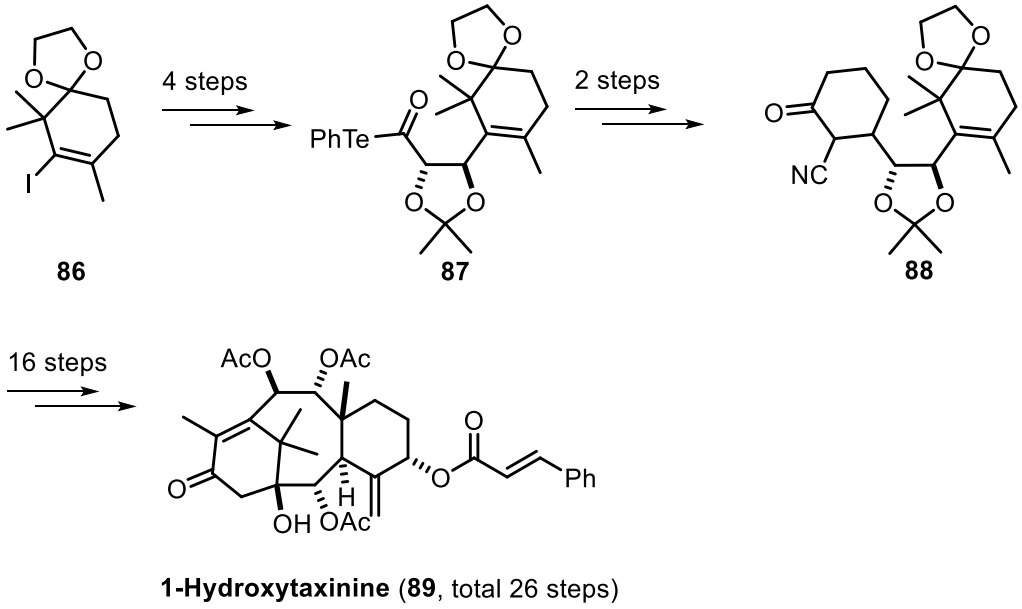
Scheme 11. Total synthesis of (-)-Pavidolide B (**85**).

These examples show that photocatalysis is a powerful tool that should not be neglected during the planning of synthetical routes. It poses a good as well as a cheap alternative for established procedures and can replace many unhealthy reagents. Therefore, in this work photochemistry will also play a big role towards the synthesis of known diterpenoid structures.

2. Decarboxylative α-alkoxy radical addition through photoredox catalysis

2.1 Investigation of reaction conditions

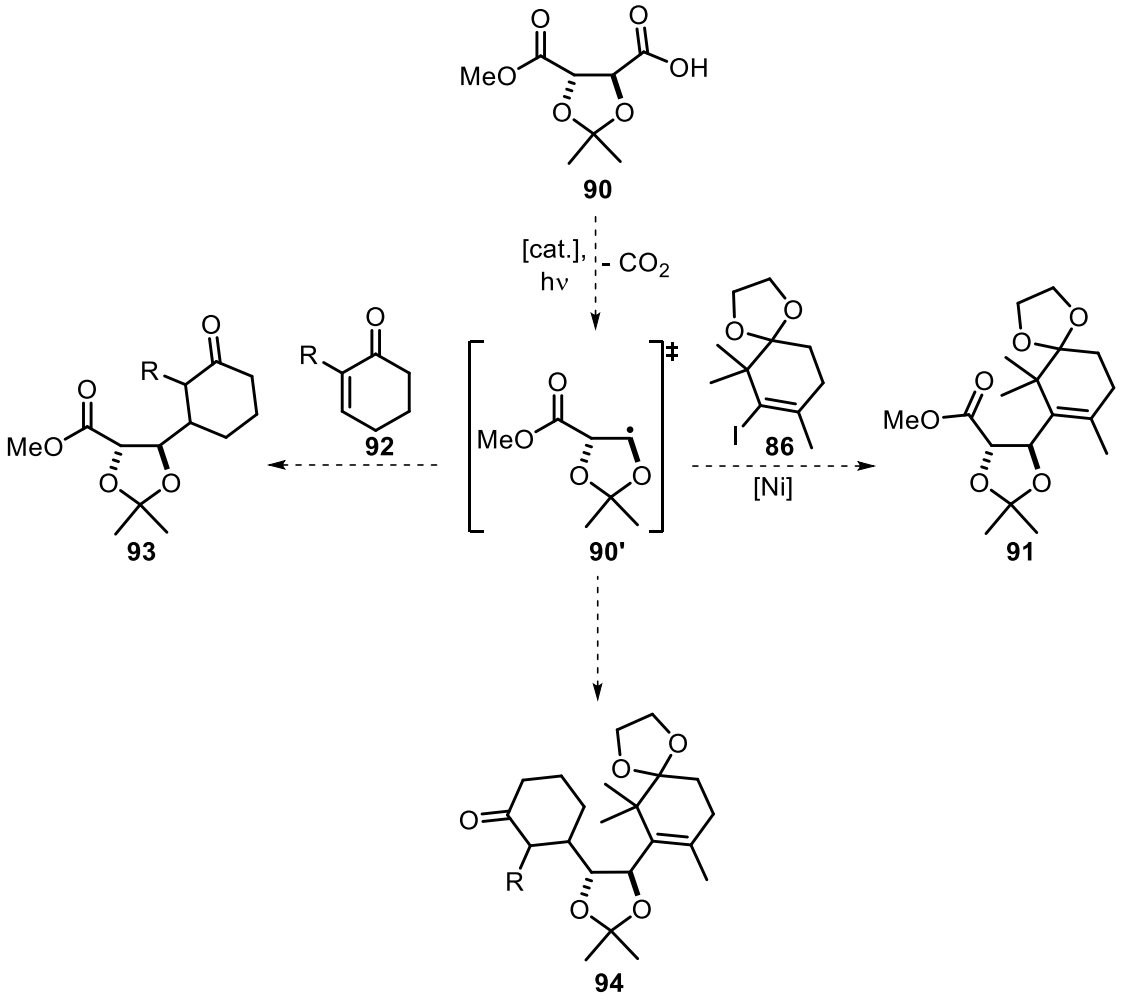
In 2019 Inoue *et al.*[25] managed to synthesise 1-Hydroxytaxinine (**89**) in 26 steps as shown in Scheme 12, which belongs to a family of taxane diterpenoids and is closely related to Taxol® (**10**), a highly bioactive anti-cancer drug. In this reaction sequence, starting from compound **86**, molecule **87** could be obtained in four steps and by applying the well-established telluride coupling chemistry in the working group, intermediate **88** was synthesized in two steps. Further transformation consisting of 16 steps lead to product **89**.



Scheme 12. Total synthesis of 1-Hydroxytaxinine (**89**) by Inoue *et al.*[25]

The main idea of this project was a synthesis towards 1-Hydroxytaxinine (**89**) in order to shorten the published synthesis shown above by at least four steps. The investigations were conducted during the six months of research stay in the group of Prof. Inoue at the University of Tokyo, Japan. As mentioned before, photochemical transformations present a useful tool which would allow avoiding the formation of tellurides, resulting in environmental friendlier reaction conditions as well as saving reaction steps. MacMillan and his group[26,27] have a leading role in this field and their strategies in the decarboxylative coupling using an Ir-complex as photocatalyst seemed to be promising in this project. Thus, it was suggested that after producing radical **90'** by light assisted

decarboxylation coupling with acceptor **92** or vinylation by iodide **86** by dual catalysis with a Ni-complex would lead to products **93** and **91** respectively. Combining both reactions should lead to intermediate **94** which is a key substrate in the synthesis of 1-Hydroxytaxinine (**89**) as shown in Scheme 13.

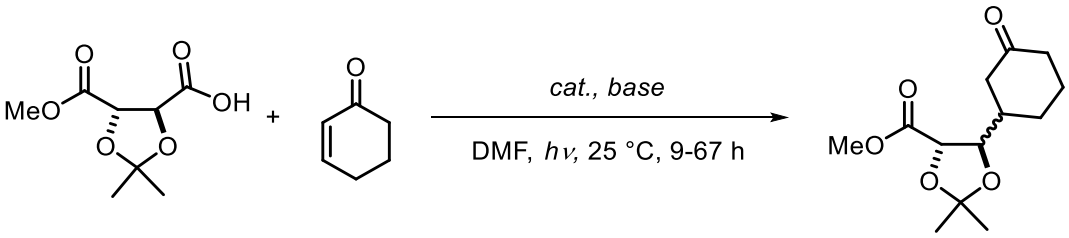


Scheme 13. Proposal for the synthesis of intermediate **94** towards the synthesis of 1-Hydroxytaxinine (**89**).

Based on previously reported results by the group of Inoue[25,28] where radical coupling reactions – *via* telluride and phenyl selenide chemistry – were successfully applied for the synthesis of natural products, it was decided to follow another approach through direct decarboxylative coupling according to the work of McMillan *et al.*[26].

Therefore, the study began by finding suitable reaction conditions for the decarboxylative coupling reaction with cyclohexenone **95** as the model acceptor shown in Table 1.

Table 1. Tested reaction conditions of acid **90** with cyclohexanone (**95**).



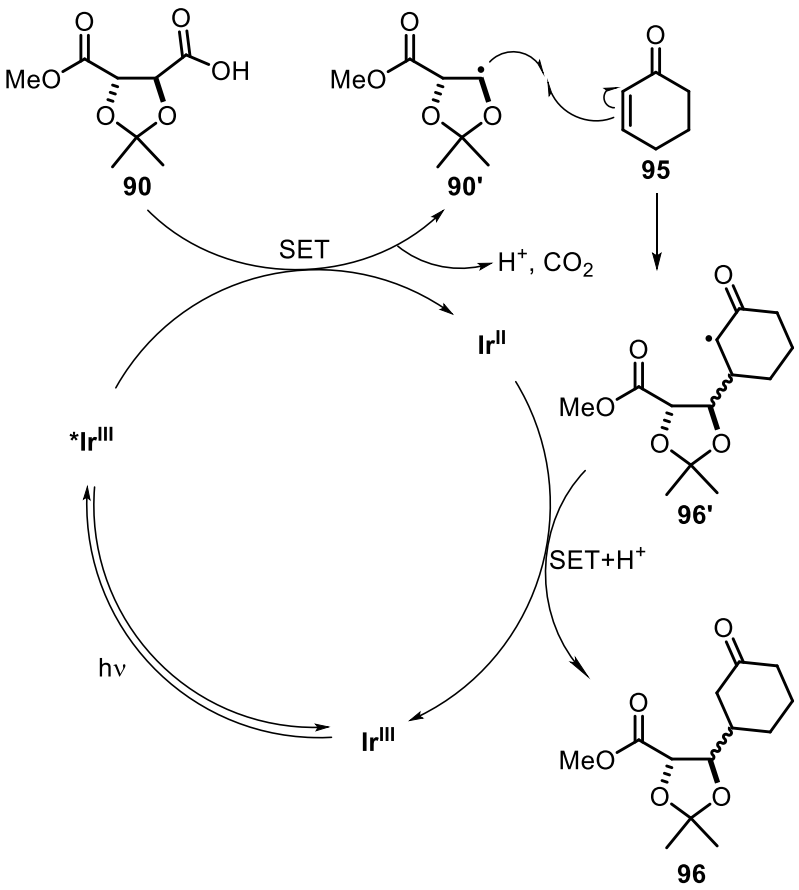
90 **95** (2.0 equiv) **96**

entry	conditions	base	hv	result
1[a)]	Phen (1.0 equiv), DCB (1.0 equiv),	NaOH (0.2 M, 1.0 equiv)	Hg light	n.r.
2[b)]	Mes-Acr-Ph$^+$BF$_4^-$ (10 mol%)	K_2HPO_4 (1.2 equiv)	455 nm	22% (**96**), d.r. 1:1.2,
3	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (10 mol%)	K_2HPO_4 (1.5 equiv)	**455 nm**	30% (**96**), d.r. 1:1.5
4	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (10 mol%)	K_2HPO_4 (1.5 equiv)	**448 nm**	36% (**96**), d.r. 1:1.3
5	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (10 mol%)	**Cs_2CO_3** (1.5equiv)	448 nm	16% (**96**), d.r. 1:1.5
6	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (10 mol%)	**K_2CO_3** (1.5 equiv)	448 nm	37% (**96**), d.r. 1:1
7	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (10 mol%)	**2,6-Lutidine** (1.5 equiv)	448 nm	15% (**96**), d.r. 1:1
8	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**5 mol%**)	K_2HPO_4 (1.5 equiv)	448 nm	50% (**96**), d.r. 1:1.2

9	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**2.5 mol%**)	K$_2$HPO$_4$ (1.5 equiv)	448 nm	50% (**96**), d.r. 1:1
10	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**1 mol%**)	K$_2$HPO$_4$ (1.5 equiv)	448 nm	47% (**96**), d.r. 1:1
11	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**1 mol%**)	K$_2$HPO$_4$ (1.5 equiv)	**dark**	n.r.
12	**none**	K$_2$HPO$_4$ (1.5 equiv)	448 nm	n.r.

a) MeCN/H$_2$O (9:1) was used as a solvent; b) MeCN was used as a solvent

At first, different photocatalytic systems were investigated (Table 1, entries 1 to 4). Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ showed the best result with 30% yield (entry 3) of desired product **96** compared to the Phen/DCB system which gave no reaction under Hg lamp irradiation (entry 1) and the Fukuzumi's catalyst (entry 2), where a yield of 22% was obtained after 9 h of irradiation with blue LED. In entry 4, it was investigated whether the change of the light source from a 455 nm light bulb, irradiating the reaction flask from the outside, to a 448 nm LED stick, placed inside the reaction mixture, would have an influence on the yield, which was not the case. Then different bases were screened (entries 5 to 7). In case of Cs$_2$CO$_3$ and 2,6-Lutidine (entries 5 and 7) the yield dropped by half to 16% and 15% respectively. With K$_2$CO$_3$ (entry 6) the yield remained constant as with the phosphate base (entry 4). It was decided to use K$_2$HPO$_4$ for further reactions since it is more established in photocatalyzed reactions. After that, the catalyst loading was examined (entries 8 to 10) which resulted in the finding that a loading of 2.5 mol% (entry 9) is sufficient and gives the best yield of 50% and d.r. of 1:1 of coupled product **96**. Raising the loading to 5% in entry 8 did not change the yield of 50% and lowering the loading to 1% slightly decreased the yield to 47% (entry 10). In conclusion, the reaction conditions applied in entry 9 are the best ones for this reaction and were used in all further transformations. Finally, entries 11 and 12 were control reactions in the dark and without catalyst to verify that this reaction is in fact a photocatalyzed decarboxylative coupling. The oxidative catalytic cycle is shown in Scheme 14.



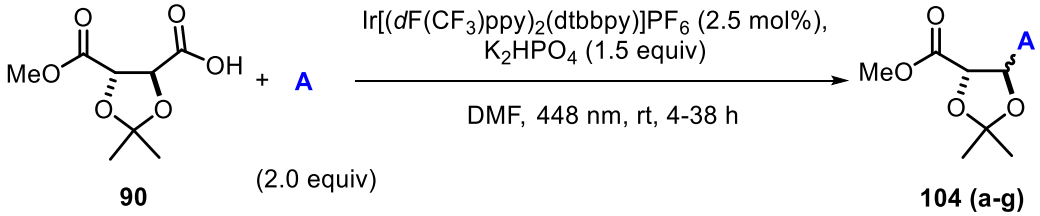
Scheme 14. Catalytic cycle for the decarboxylative coupling of acid **90** with acceptor **95**.

After excitation of $\mathbf{Ir^{III}}$ to $\mathbf{*Ir^{III}}$, decarboxylation by single electron transfer (SET) occurs to give radical **90'** with the simultaneous reduction of the catalyst to $\mathbf{Ir^{II}}$. Radical **90'** then undergoes a 1,4-coupling with acceptor **95** to yield intermediate **96'** which then is transformed to product **96** by another SET and the catalyst is reoxidized to $\mathbf{Ir^{III}}$, thus closing the catalytic cycle.

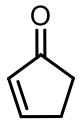
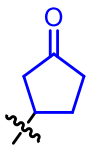
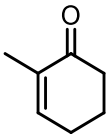
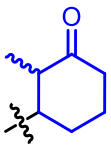
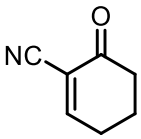
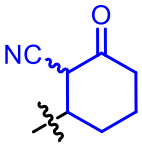
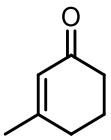
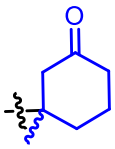
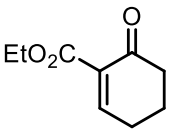
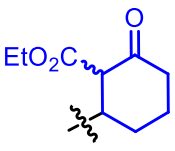
2.2 Decarboxylative coupling with different acceptors

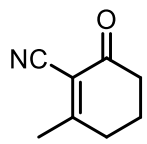
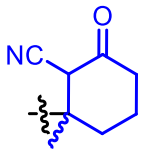
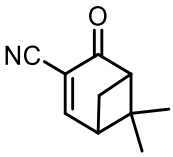
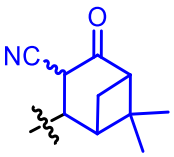
The focus was then moved to test different acceptors starting with tartaric acid **90**. Both, the applied acceptors as well as the results from the decarboxylative coupling are summarized in Table 2.

Table 2. Decarboxylative coupling of acid **90** with different acceptors.



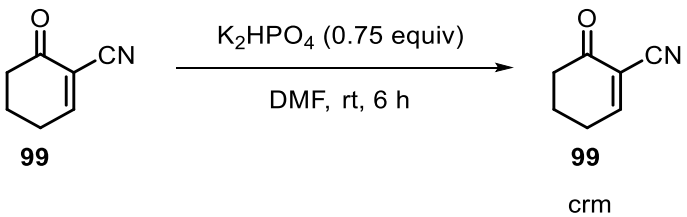
90 (2.0 equiv) **104 (a-g)**

entry	acceptor A	-A	result
1	 **97**	 **104 a**	65% (**104 a**), d.r. 5:2:1:1
2	 **98**	 **104 b**	34% (**104 b**), d.r. 1:1.7
3[a)]	 **99**	 **104 c**	n.r.
4	 **100**	 **104 d**	n.r.
5	 **101**	 **104 e**	24% (**104 e**)

6	 **102**	 **104 f**	n.r.
7	 **103**	 **104 g**	n.r.

a) compound **14** is not stable under basic conditions

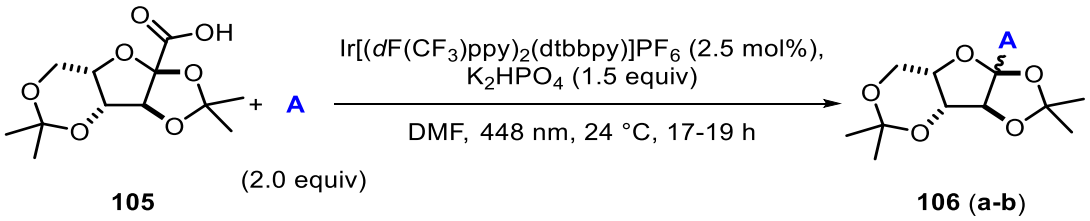
In case of cyclopentenone **97** product **104 a** could be obtained in 65% yield (entry 1), slightly higher compared to cyclohexanone **95**. When 2-methyl-cyclohexenone **98** was used, the decarboxylative coupling reaction gave low yield of the corresponding product **104 b** (entry 2). This could be expected because the Michael acceptor is disactivated by the methyl group, thus having a lower reactivity towards acid **90**. In case of 3-methyl-cyclohexenone **100** no reaction occurred, presumably because of steric hindrance (entry 4). By trying to increase the reactivity of the acceptor with a nitrile (entry 3) or an ester group (entry 5), no reaction occurred at all or the yield of the desired product was very low respectively. The reason for this is based on the fact, that compounds **99** and **101** are unstable under basic conditions. This was demonstrated on nitrile **99** by stirring it just with the base for some time (Scheme 15). All of it was consumed and a possible polymerisation seemed to occur. Likewise, ester **101** is also unstable under basic conditions but more stable than the nitrile which may explain why some coupling product **104 e** was formed. In entries 6 and 7, it was tried to increase the sterical hindrance of the acceptor, resulting in a better stability under basic conditions, but in both cases no coupling with acid **90** occurred. From this it was concluded that electron-withdrawing groups on cyclohexanone are not compatible with the applied basic conditions.

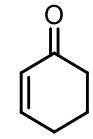
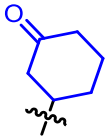
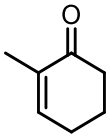
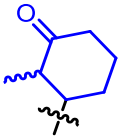


Scheme 15. Stability test of acceptor **99**.

Other acids which may be important building blocks in natural product synthesis were also applied for the decarboxylative coupling reaction with acceptors **95** and **98**. Table 3 summarizes the reaction of acid **105** with different acceptors.

Table 3. Decarboxylative coupling of acid **105** with different acceptors.

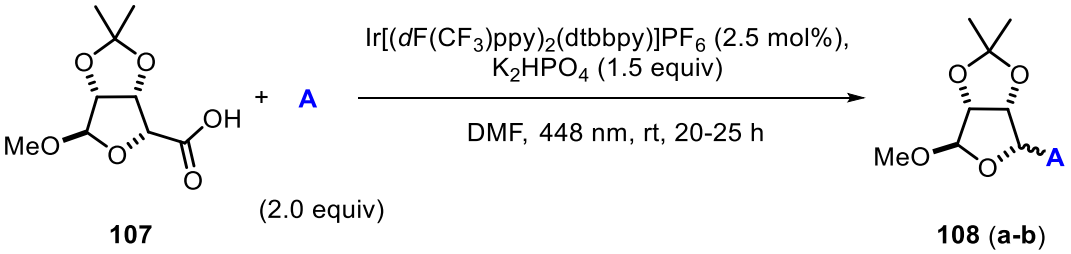


entry	acceptor A	-§-A	result
1	 **95**	 **106 a**	65% (**106 a**), d.r. 1:1.6
2	 **98**	 **106 b**	22% (**106 b**)

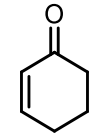
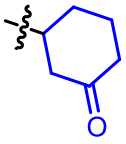
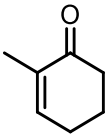
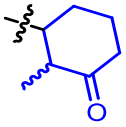
The coupling with cyclohexenone **95** gave corresponding product **106 a** in moderate yield (65%) and a d.r. of 1:1.6 (entry 1). The yield is higher compared to acid **90** (see Table 1), because the resulting tertiary radical formed in this case is more stable than the secondary one generated by acid **90**. Reaction with the disactivated acceptor **98** yielded product **106 b** in lower yield (22%), based on the slightly lower reactivity of acceptor **98** and increased sterical hindrance.

Acid **107** was as well subjected to decarboxylative coupling, yielding product **108**. The yields with the acceptors **95** and **98** are comparable to the reaction of tartaric acid **90** (Table 4). The desired products **108 a** and **108 b** were obtained in 55% and 34% yield respectively (entry 1 and 2).

Table 4. Decarboxylative coupling of acid **107** with different acceptors.



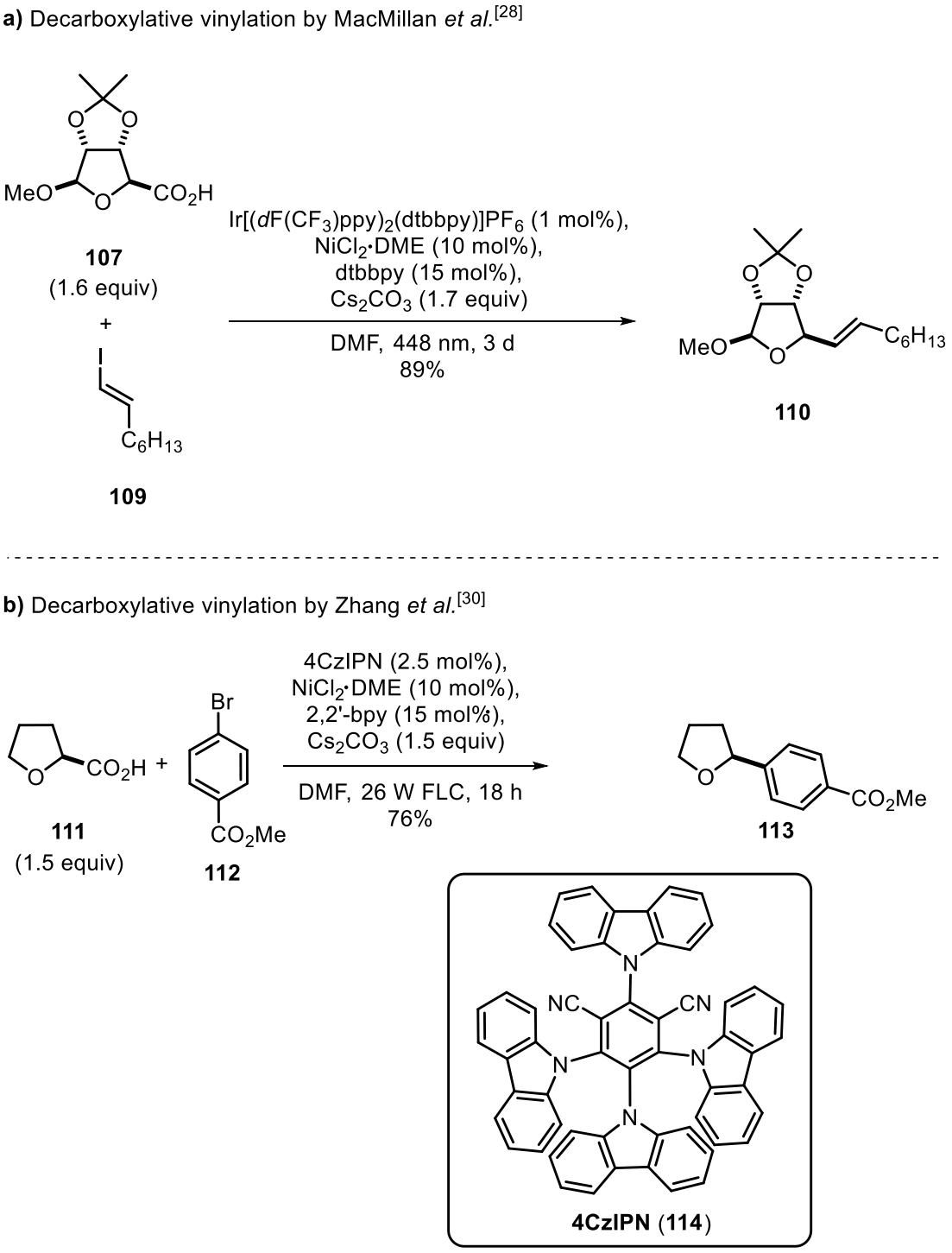
107 **108** (**a-b**)

entry	acceptor A	-§-A	result
1			55% (**108 a**), d.r. 1:3.8
	95	**108 a**	
2			34% (**108 b**)
	98	**108 b**	

With these results in hand, it was shown that the first step, namely the decarboxylative coupling, especially of acid **90** and cyclohexanone **95**, proposed for the synthesis towards the natural product **89** (see Scheme 13), was possible.

2.3 Decarboxylative vinylation

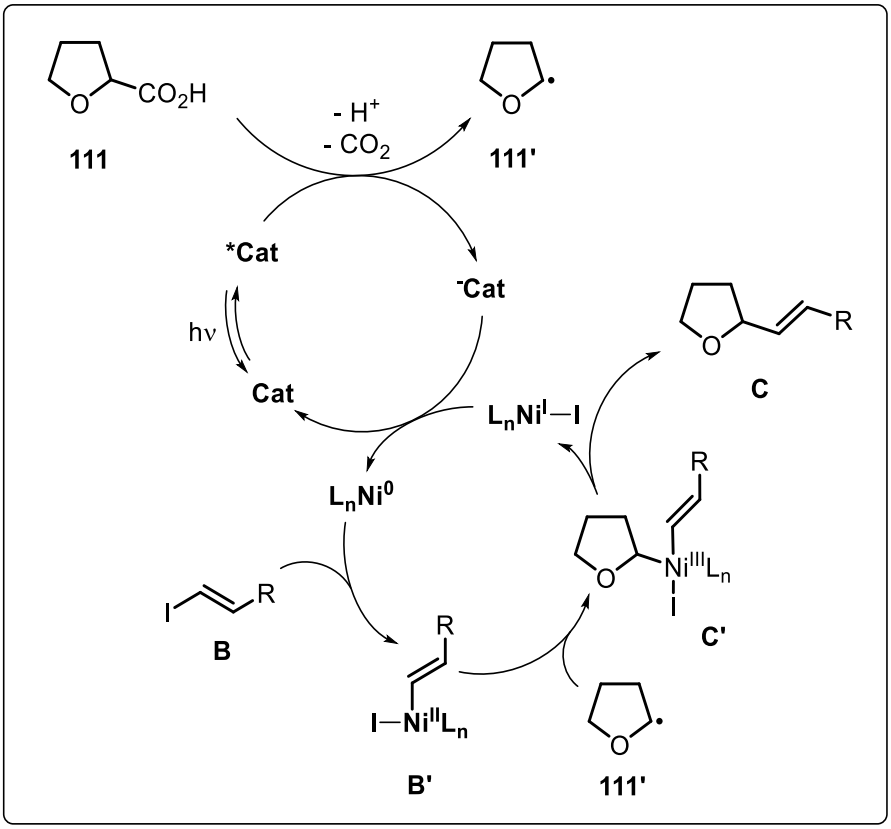
Considering the goal of this study to decrease the reaction steps on the way to intermediate **94**, a decarboxylative vinylation as reported by MacMillan *et al.*[27] seemed to be suitable (Scheme 16 a). A similar reaction was presented by Zhang and Luo in 2016 (Scheme 16 b)[29].



Scheme 16. Dual catalyst based decarboxylative vinylation by a) MacMillan *et al.*[27] and b) Zhang *et al.*[29]

The reaction procedures have a dual Ni-catalysis in common, differentiating in the second catalyst where MacMillan uses an Ir-photocatalyst and Zhang an organic one. In both cases the catalytic cycle is based on the same principle (Scheme 17) in which the catalyst is first excited by a light source, resulting in the oxidation of the acid **111**. As a result, the

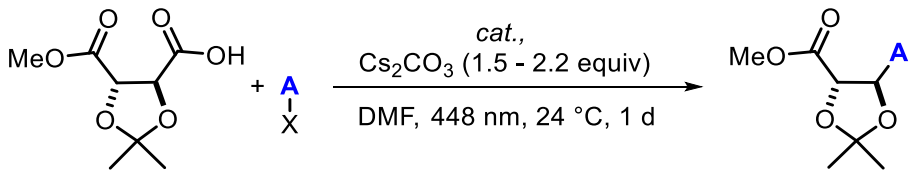
catalyst is reduced and needs to be oxidized by the Ni-source which itself is reduced to a Ni^0-species. Now oxidative addition of **B** as well as insertion of radical **111'** can take place and the product **C** is released by reductive elimination of **C'**, closing the catalytic cycle.



Scheme 17. Catalytic cycle of the dual decarboxylative vinylation with Ni.[27,29]

Before applying these reaction conditions on vinyliodide **86** shown in Scheme 13, test reactions of different vinyl halogens with acid **90** were conducted. Table 5 shows a summary of applied conditions and substrates. Substrate **116** (entry 1) was examined first to compare the yields between decarboxylative coupling and decarboxylative vinylation of acid **90** since nearly the same product would be obtained. In this case, no reaction between the two compounds happened and the desired product **115 a** was not obtained. In entry 2 and 3 iodide **117** was used as test substrate under two different conditions. The reaction condition reported by MacMillan with Ir-photocatalyst resulted in no formation of product **115 b** (entry 2). For this reason, the organocatalyst 4CzIPN (**114**) was tested with bpy as ligand, which was reported to have a better effect compared to dtbbpy for some substrates.[29,30] In this case, formation of product **115 b** was observed in traces (entry 3).

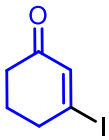
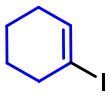
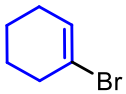
Table 5. Different conditions for the decarboxylative vinylation of acid **90** with different vinyl halogens.

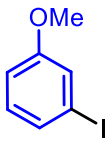
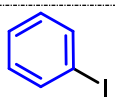
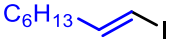


90

(1.6 equiv)

115 (**a-e**)

entry	A	cat.	results
1	 **116**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·glyme (10 mol%), dtbbpy (15 mol%)	n.r.
2	 **117**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·glyme (10 mol%), dtbbpy (15 mol%)	n.r.
3		**4CzIPN** (4 mol%), NiCl$_2$·glyme (14 mol%), **bpy** (22 mol%)	3% (**115 b**)
4		Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·glyme (10 mol%), dtbbpy (15 mol%)	n.r.
5[a)]	 **118**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·glyme (10 mol%), dtbbpy (15 mol%)	n.r.
6		Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·glyme (10 mol%), dtbbpy (15 mol%), ***N*-Boc-Benzylamine** (6 mol%)	n.r.

7		Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), **NiCl$_2$·dtbbpy** (10 mol%)	n.r.
8[b)]		Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%), **not degassed**	n.r.
9[b)]		Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%), **degassed**	n.r.
10		**4CzIPN** (2.5 mol%), NiCl$_2$·dtbbpy (10 mol%)	5% (**115 b**)
11		4CzIPN (2.5 mol%), NiCl$_2$·glyme (10 mol%), **bpy** (15 mol%)	n.r.
12		4CzIPN (**10 mol%**), NiCl$_2$·dtbbpy (10 mol%)	3% (**115 b**)
13	 **119**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·glyme (10 mol%), dtbbpy (15 mol%)	n.r.
14	 **120**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%)	5% (**115 d**)
15	 **109**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%)	n.r.

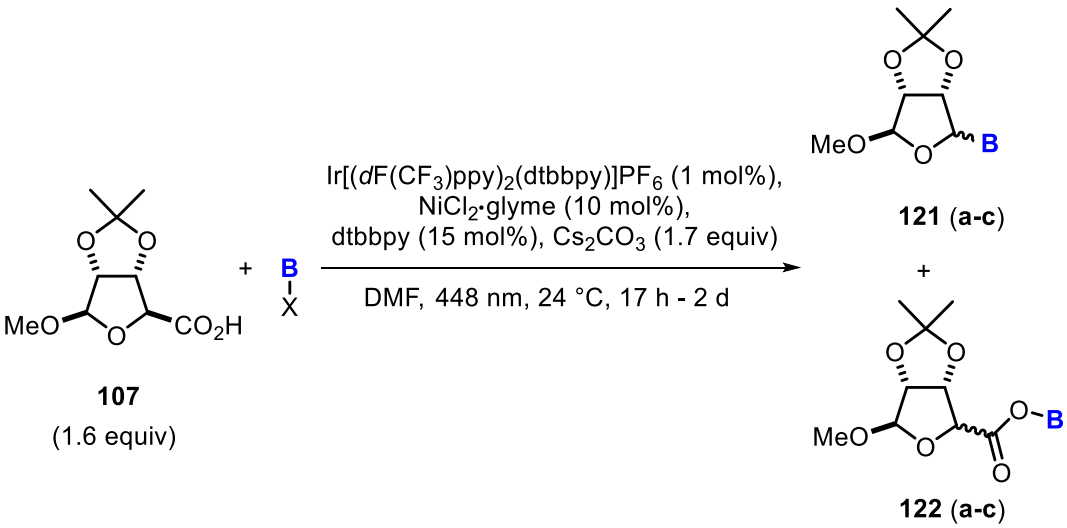
a) DBU (1.6 equiv) was used as a base; b) MeCN/DMF (4:1) was used as a solvent.

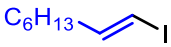
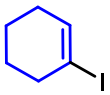
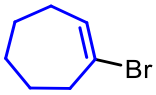
To examine if the halogen might play a role in this transformation, the corresponding bromide **118** was tested (entries 4 to 12). Entries 3 to 9 show the reaction with Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$. Modifications were made by using the better soluble base DBU (entry 5) or *N*-Boc-benzylamine (entry 6) as additive as well as commercially available Ni-catalyst (entry 7) instead of the in situ prepared one. Another solvent system

was also tested under degassed and ambient conditions (entries 8 and 9) as reported by the workers of Oderinde and Johannes[30] who showed that the presence of oxygen is in some cases favourable for this type of reactions. In the end, none of these changes led to the formation of desired product **115 b**. Therefore, the catalyst was changed to 4CzIPN (entries 10 to 12) which led to the formation of product **115 b** albeit in low yield (entry 10). Application of bpy as ligand instead of the dtbbpy ligand (entry 11) or increasing the catalyst loading to 10 mol% (entry 12) did not improve the yield. Seeing that these reactions gave no satisfying results, the substrate was changed to *m*-iodoanisol (**119**). If product **115 c** (entry 13) could be obtained, then the aromatic ring might be oxidized to give the desired intermediate. But in this case, the substrates did not react even after 2 days of irradiation. Therefore, in entries 14 and 15 control reactions were conducted with substrates **120** and **109** respectively, which are usually reported to give good results in decarboxylative vinylation reactions.[27,29] In case of iodobenzene (**120**), traces of desired product **115 d** were detected (entry 14) but no product formation was observed in case of primary vinyliodide **109** (entry 15). Another aspect to mention here is, that in all experiments acid **90** was partially consumed although no product was formed. The detectable byproducts are mainly the β-H elimination product **124** and traces of the homocoupling product **125**, whose possible formation is explained below (see Scheme 18).

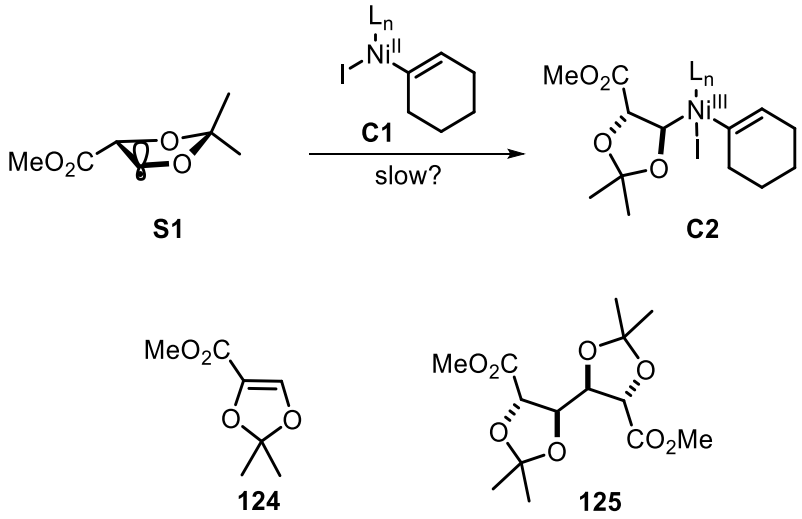
To find out why the decarboxylative vinylation did not work as expected with acid **90**, it was decided to conduct control experiments with acid **107** instead, which was reported to react under the described reaction conditions.[27] Subjecting substrate **109** to the conditions reported by MacMillan gave the desired product **121 a** in 75% yield (entry 1) – compared to a literature yield of 89% -, therefore demonstrating the reproducibility of this reaction. Hence, it was concluded, that no fundamental experimental error, *e.g.* from the light source, was imparting the reaction. The focus was then moved to substrate **117** which did not undergo radical coupling with acid **90** before. Although conversion of starting material was observed this time, instead of the desired product **121 b** the ester **122 b** was obtained (entry 2). As MacMillan never reported the usage of six-membered rings but just that of seven-membered bromide **123** in case of decarboxylative vinylations, the coupling was conducted with substrate **123** (entry 3). The result was the same as with substrate **117** where instead of the desired product **121 c** the corresponding ester **122 c** was obtained in good yield.

Table 6. Decarboxylative vinylation of acid **107** with different vinyl halogens.



entry	B	results
1	 **109**	75% (**121 a**, Lit. 89%)
2	 **117**	58% (**122 b**), d.r. 1:1.3
3	 **123**	91% (**122 c**)

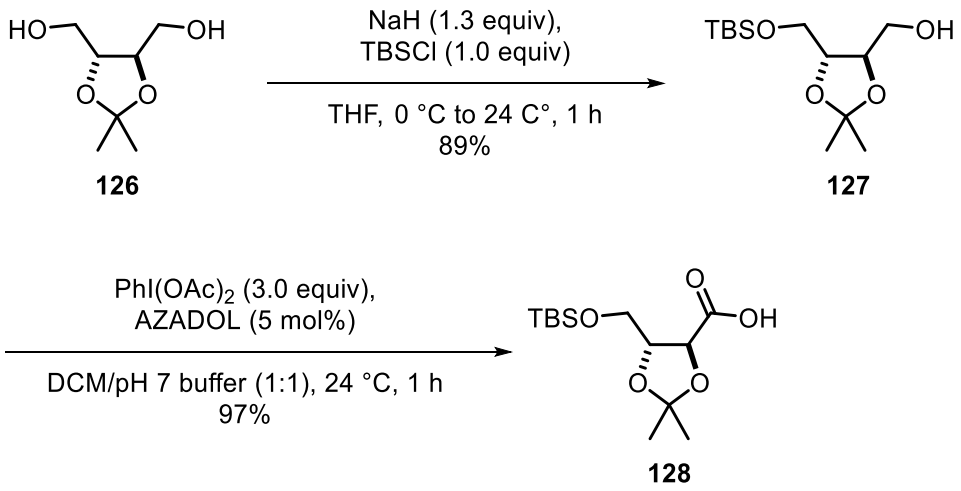
From the conducted reactions so far, it could be assumed that the problem lied within the acid **90** itself. Scheme 18 shows a simplified possible explanation for the failed coupling as well as the formation of byproducts **124** and **125** mentioned before.



Scheme 18. Possible explanation for the formation of byproducts **124** and **125** based on the reaction intermediates **S1** and **C2**.

Based on the decarboxylative coupling experiments shown above, it can be concluded that radical **S1** is indeed formed. Starting from this, several reasons are possible for the failed reaction. First reason might be, that the steric hindrance in intermediate **S1** is too large to react with the inserted vinyl halogen in complex **C2** or complex **C2** is not formed in general. And second, this sterical hindrance could also be responsible that β-H abstraction of **S1** is faster than the addition to catalyst species **C1**, or β-H elimination of **C2** is easier than coupling with vinyl halide originated from complex **C2**, thus leading to the byproducts **124** and **125** correspondingly.

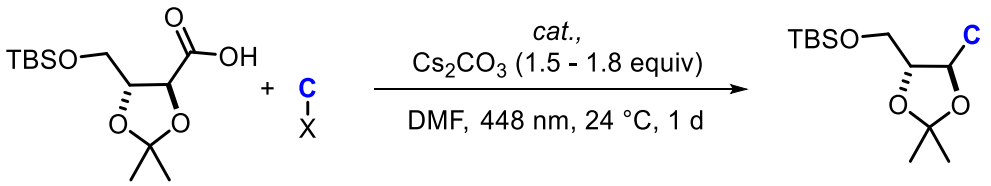
On that basis, it was attempted to change the structure of acid **90** so it could react with the Ni-complex to give the desired coupling product and avoid the β-H elimination to product **124**. Starting by examining the effect of the ester moiety, acid **128** was synthesized from diol **126**. In the first step, one alcohol was protected with TBSCl to give compound **127** which then was oxidized to yield the desired acid **128** (Scheme 19).[28]

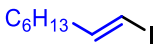
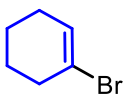


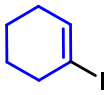
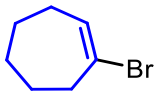
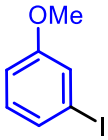
Scheme 19. Synthesis of acid **128**.

Then acid **128** was subjected to test reactions with different vinyl halogens. The summarized results are shown in Table 7 where it has to be said that in entries 1 to 3 the enantiomer **128'** of acid **128** was used.

Table 7. Decarboxylative vinylation of acid **128** with different vinyl halogens.



entry	C	conditions	results
1[a)]	 **109**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%),)	55% (**129' a**)
2[a)]	 **118**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%)	**130** and **131**
3[a)]		**4CzIPN** (2.5 mol%), NiCl$_2$·dtbbpy (10 mol%)	traces (**129' b**)

4	 **117**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%)	**130** and **131**
5	 **123**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%)	traces (**129 c**), rest **130** and **131**
6	 **119**	Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NiCl$_2$·dtbbpy (10 mol%)	14% (**129 d**), rest **130** and **131**

a) Enantiomer of acid **128** (= **128'**) was used

At first the decarboxylative vinylation was tested with primary vinyl halogen **109** (entry 1) under Ir-catalysed conditions, giving the desired product **129' a** in 55% yield. Then, encouraged by this positive result, the investigation was continued with cyclohexene bromide (**118**) but no formation of product **129' b** was observed (entry 2). Instead, the formation of byproducts **130** and **131** was noticed. By changing the catalyst to 4CzIPN, only traces of the desired product were detected (entry 3). Using the corresponding vinyl iodide **117** made no difference in the result (entry 4), the same as with cycloheptene **123** where just traces of product **129 c** were detected (entry 5). Finally, *m*-iodoanisol (**119**) was tried which gave the coupling product **129 d** in 14% yield (entry 6).

Seeing that changes to the ester group did not give the desired results and the homocoupling byproduct **130** as well as the β-H elimination product **131** still occurred (Figure 5) in cases where no or just a small amount of the vinylation product was formed, it was concluded that sterical issues might still play a big role in this reaction.

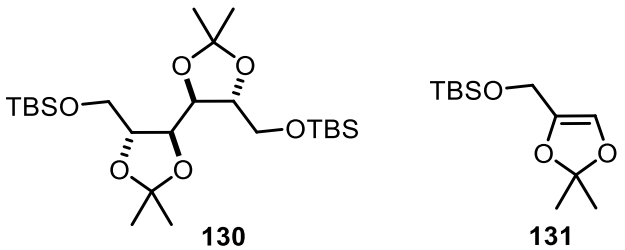
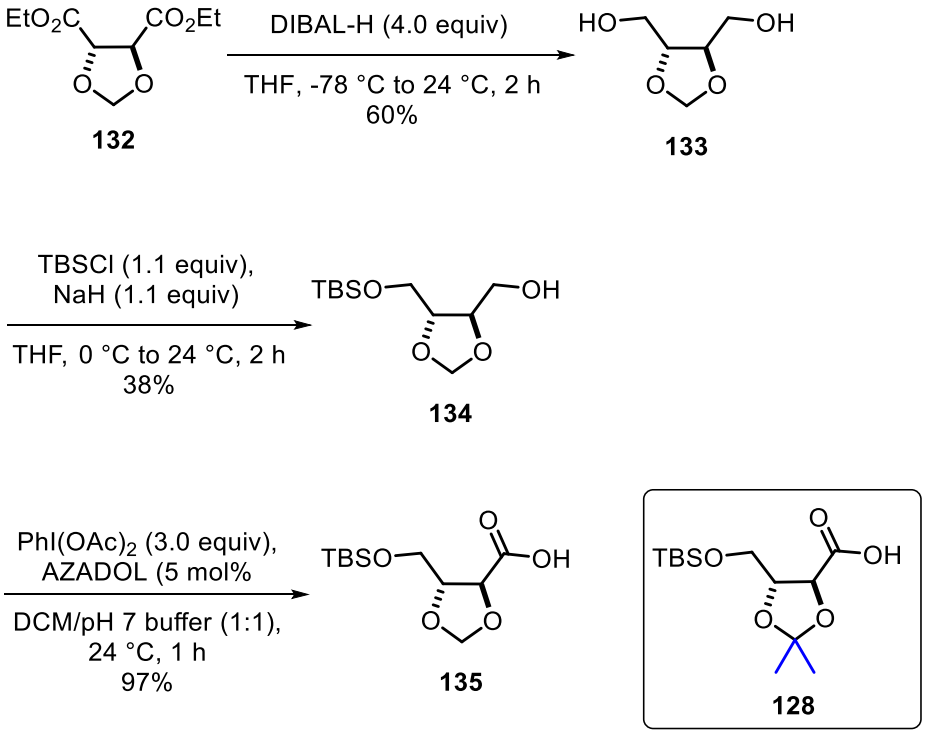


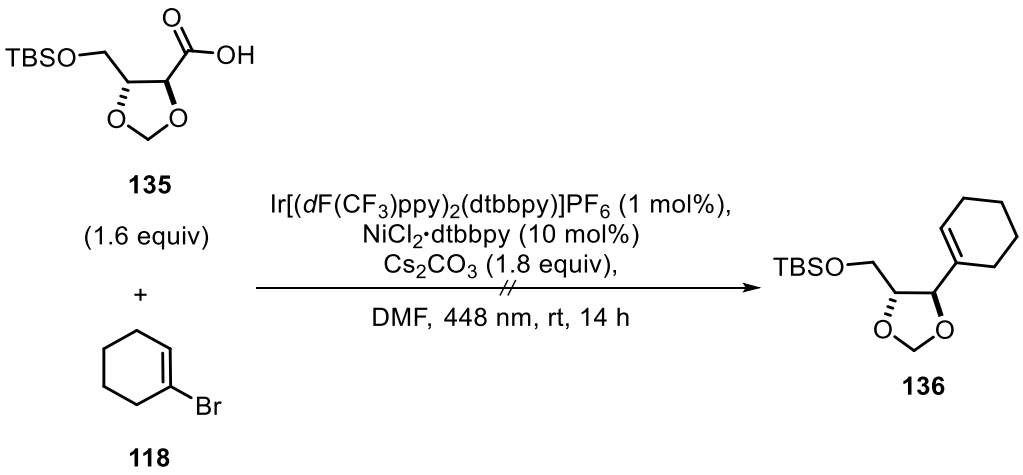
Figure 5. Formed byproducts **130** and **131** during the decarboxylative vinylation of acid **128**.

For this reason, further modifications of acid **128** were considered to reduce the steric effect. Thus, acid **135** was synthesized starting from diester **132** which was first reduced to diol **133** with DIBAL-H and then mono-protected with TBSCl to give compound **134**. This was finally oxidized to the corresponding acid **135** to see if the absence of the methyl groups from the acetal (marked in blue) compared to acid **128** would make a difference (Scheme 20).[28]



Scheme 20. Synthesis of acid **135**.

When performing the decarboxylative vinylation with model substrate **135**, no formation of product **136** was observed (Scheme 21).



Scheme 21. Decarboxylative vinylation of acid **135** with cyclohexene bromide (**118**).

Although, in this case different byproducts were formed, in particular the decarboxylated compound **137** and a proposed coupling product with DMF **138** (Figure 6), it became clear that the desired transformation was not compatible with the required substrates under the tested reaction conditions.

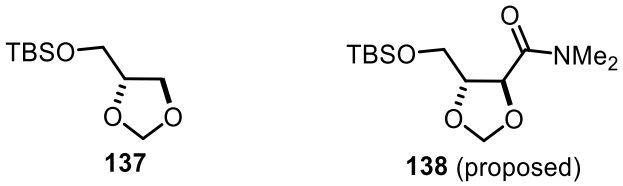
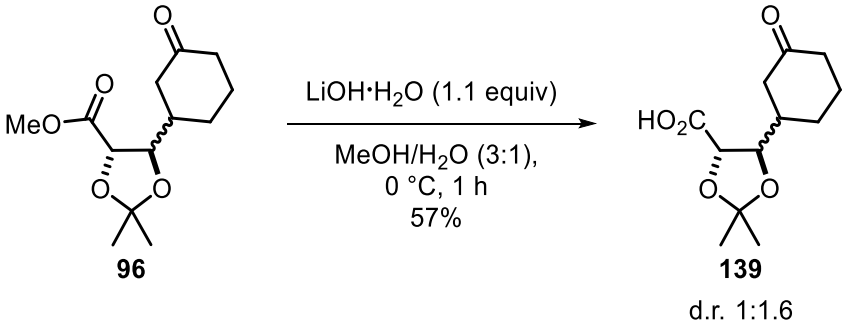


Figure 6. Formed byproducts **137** and proposed **138** during the decarboxylative vinylation of acid **135**.

The sterical hindrance or reactivity of the applied acids as well as the necessary cyclohexene halogen were not suited for this photocatalyzed decarboxylative vinylation, since either no reaction occurred or byproducts were formed (see Scheme 18 and Figure 5). Hence, a new approach was needed to accomplish the desired synthesis.

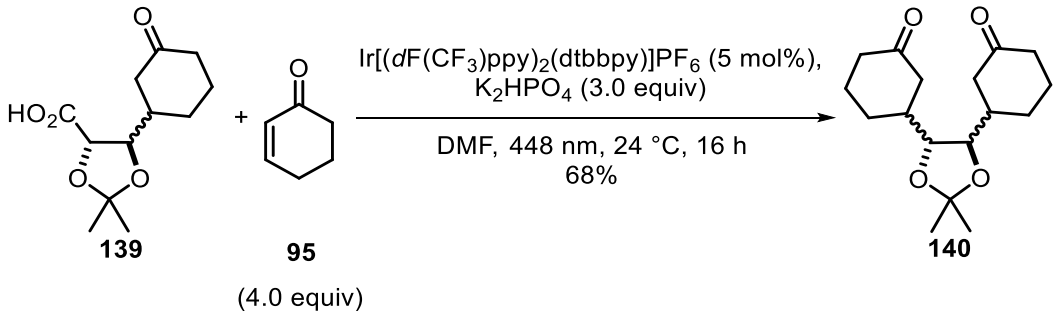
2.4 Dual decarboxylative coupling

Since the decarboxylative vinylation was not successful, the attention was again turned towards the decarboxylative coupling which gave the desired product in moderate yields before (see Table 1 entry 9). Therefore, the ester **96** was hydrolysed to give the corresponding acid **139** for further test reactions (Scheme 22).



Scheme 22. Hydrolysis of ester **96** to acid **139**.

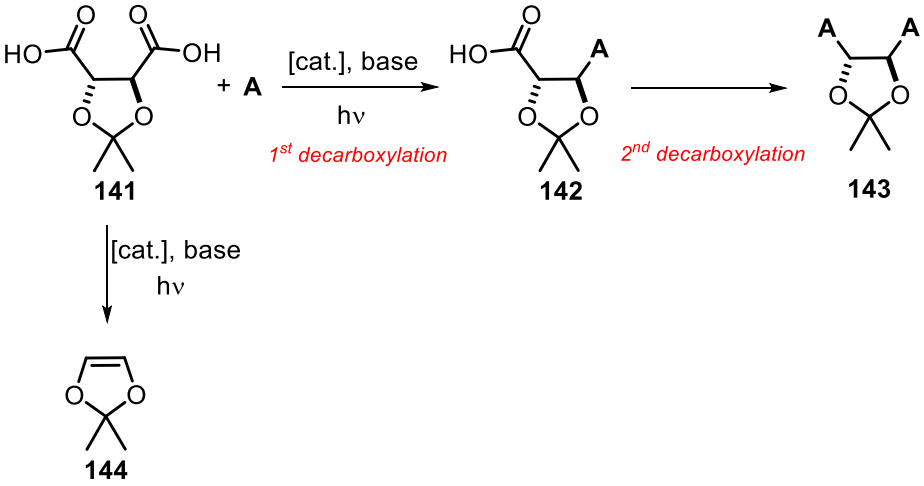
Subjecting acid **139** to the decarboxylative coupling with acceptor **95** gave the desired product in 68% yield (Scheme 23). Now, the sterical hindrance of acid **139** seemed not to play as big of a role as in the vinylation case, probably because no insertion into a complex was needed. Thus, allowing the reaction to be carried out despite of the rather bulky cyclohexanone group. Though four possible diastereomers were formed, it was not possible to adjust the diastereomeric ratio. On the other hand, the stereoselectivity was negligible in the first approach since the main concern was whether the reaction was feasible.



Scheme 23. Decarboxylative coupling of acid **139** with cyclohexenone (**95**).

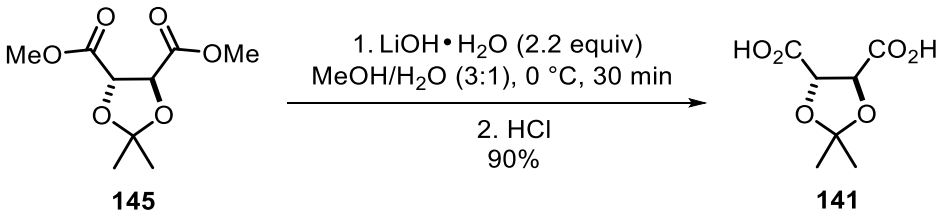
Considering that the second coupling was successful, the question arose if this reaction would also be realizable with the corresponding diacid **141** in one step. Although, it had to be considered in this case whether the decarboxylation step would occur consecutively

which would give the desired product. Otherwise, the possibility of a radical coupling after double decarboxylation of the diacid would lead to byproduct **144** (Scheme 24).



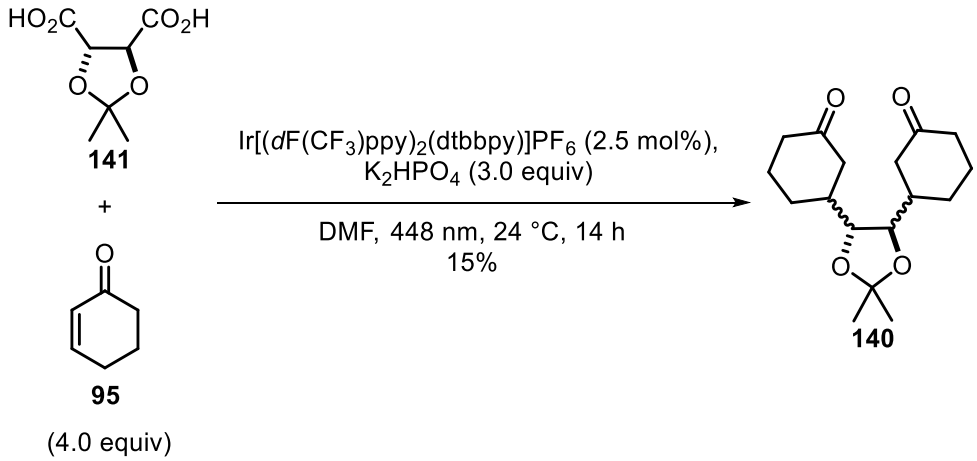
Scheme 24. Possible outcome during double decarboxylative coupling of acid **141**.

Therefore, diacid **141** was synthesized by simple hydrolysis (Scheme 25).



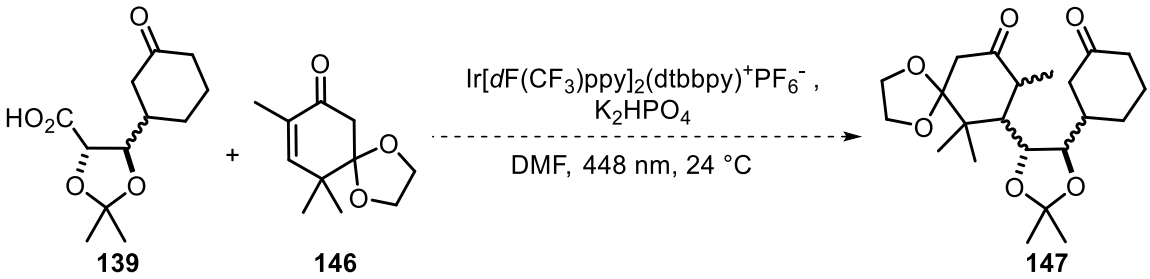
Scheme 25. Hydrolysis of ester **145** to diacid **141**.

After conducting the reaction (Scheme 26), product **140** was indeed obtained although in low yield. Most of the starting material was reisolated and the possible byproduct **144** was not detected, indicating that the decarboxylation step does not happen with both acids at the same time but consecutive. Still, two steps were necessary in order to form the desired product **140** since a one-pot reaction appeared to interfere with the catalytic cycle.



Scheme 26. Decarboxylative coupling of diacid **141** with cyclohexenone (**95**).

Thus, it would be better to run the coupling in two steps. To obtain the desired intermediate **147**, the following reaction (Scheme 27) still had to be conducted with acceptor **146**.



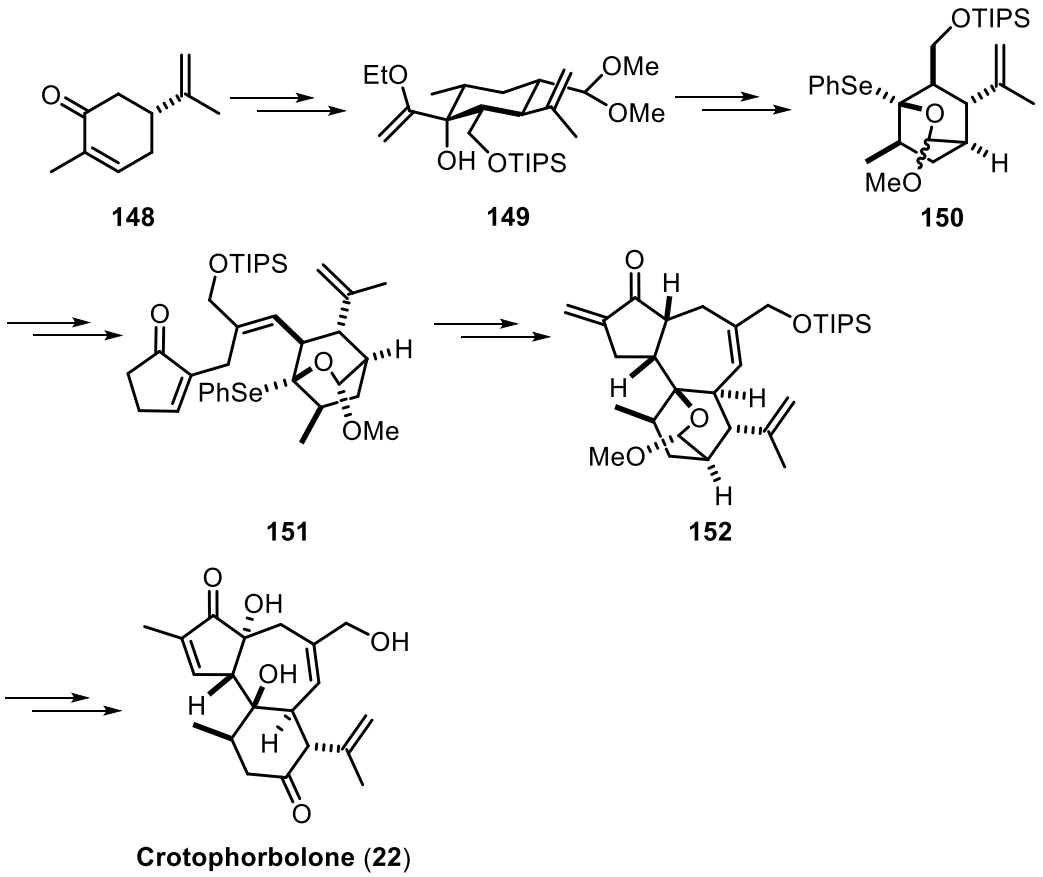
Scheme 27. Decarboxylative coupling of acid **139** with acceptor **146**.

Since the research stay came to an end, it was not possible to pursue this project. Still, the photocatalyzed decarboxylative coupling may be a promising approach towards a faster synthesis of 1-Hydroxytaxinine (**89**) if compound **147** could be obtained, but further investigations are needed.

3. Enolate cascade towards the synthesis of Crotophorbolone derivatives

3.1 One-pot cascades by in-situ preparation of an enolate

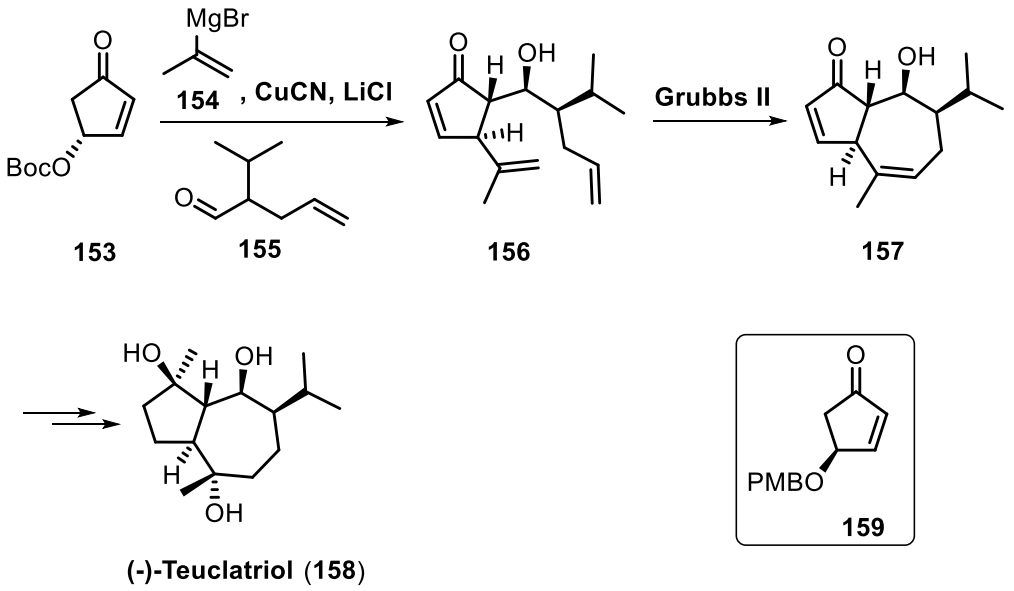
In 2015 Inoue *et al.*[31] presented the total synthesis of Crotophorbolone (**22**) in 33 linear steps (Scheme 28). Starting from (*R*)-Carvone (**148**), several transformations were conducted to obtain selenide **150**, subjecting it to a radical cyclization with controlled stereocenters to yield the tricyclic ring system **152**. Further functionalization finally gave the desired natural product **22** which structure was first determined in 1969 as a degradation product of phorbol[10], being related to the tigliane diterpenoid family with a typical 5/7/6-tricyclic skeleton. These compounds exhibit a wide range of biological activities, *e.g.* anti-HIV, anticancer as well as tumor promotional and proinflammatory activities, depending on the circumstances (*vide supra*, chapter A 1.1).[32]



Scheme 28. Total synthesis of Crotophorbolone (**22**) by Inoue *et al.*[28]

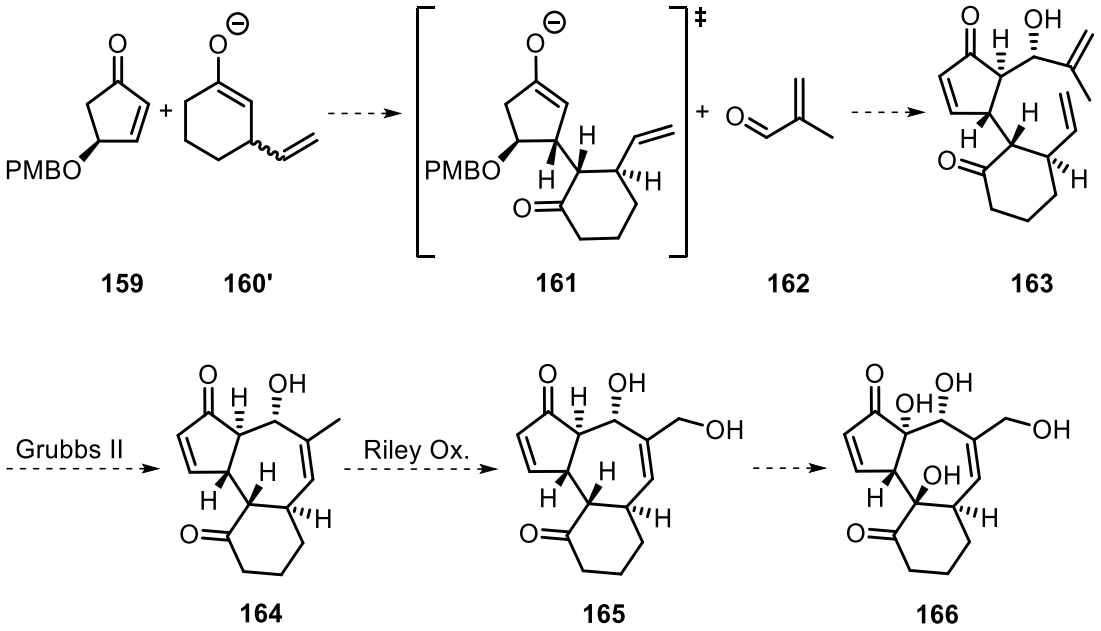
The same year, Reiser *et al.* presented a cascade reaction starting from cyclopentenone **153** which led to the synthesis of (-)-Teuclatriol (**158**).[33] A remarkable characteristic of

this reaction was the stereo control it allowed. When starting from the enantiomerically pure substrate **153**, a Michael addition with a cuprate from the Grignard reagent **154** and a subsequent aldol reaction with aldehyde **155** resulted in product **156** with five fixed stereocenters as shown in Scheme 29. The opposite stereochemistry would arise when the other enantiomer of protected hydroxy-cyclopentenone **159** was used.



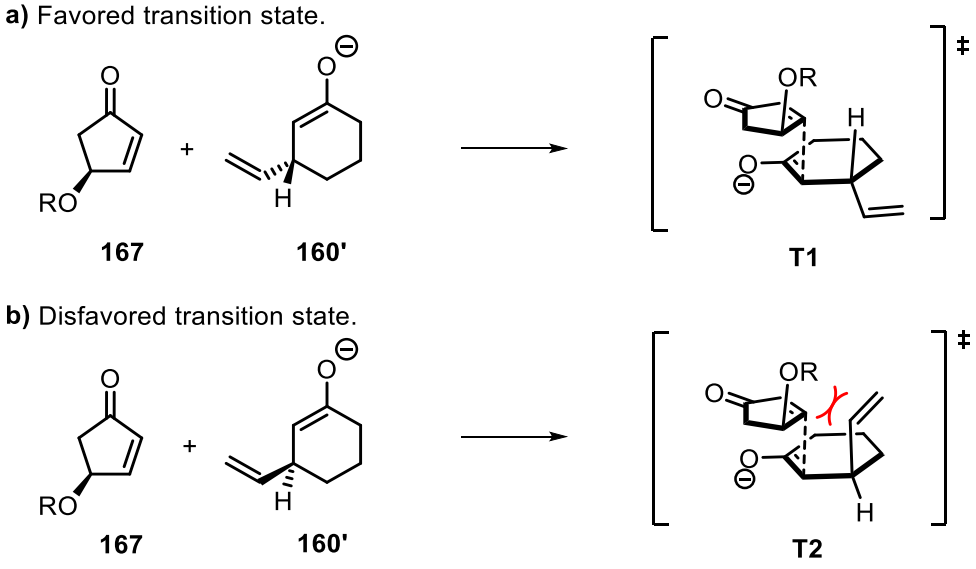
Scheme 29. Synthesis of (-)-Teuclatriol (**158**) through a ring closure metathesis of intermediate **156**.[33]

Based on these reported reactions, a new synthetical approach towards a Crotophorbolone derivative, with an enolate cascade playing the major role, was considered. Scheme 30 shows the main idea, where the enolate **160'** would undergo a Michael addition and the resulting enolate **161** would then be trapped with methacrolein (**162**). A consecutive Grubbs-metathesis would lead to the five-seven-six-ring structure **164** and further functionalization would yield Crotophorbolone derivative **166**.



Scheme 30. Possible new route to Crotophorbolone derivative **166**.

Even if enolate **160'** is a racemic mixture, facilitating its synthesis, the stereochemistry of the resulting product would be determined by a favored (Scheme 31 **a**) and a disfavored (Scheme 31 **b**) transition state (**T1** and **T2** respectively) during the Michael addition due to the repulsion between the protected hydroxy group and the vinyl group from the enolate.

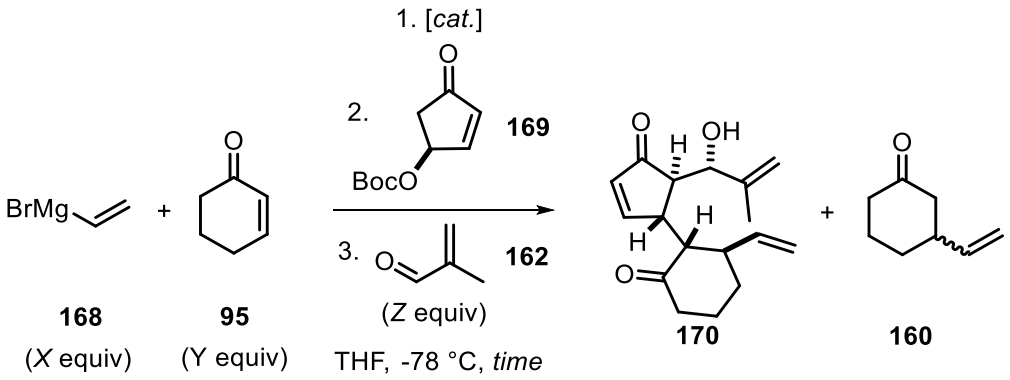


Scheme 31. Determination of stereochemistry of enolate addition by a favored (a) and disfavored (b) transition state.

In the first attempt, a one-pot enolate cascade was performed by creating the cuprate of vinyl magnesium bromide (**168**) and reacting it with cyclohexenone (**95**). To this resulting

enolate, racemic cyclopentenone (**169**) was added followed by methacrylaldehyde (**162**). Table 8 shows the different test reactions, where various copper sources as well as different ratios of the reagents were tested.

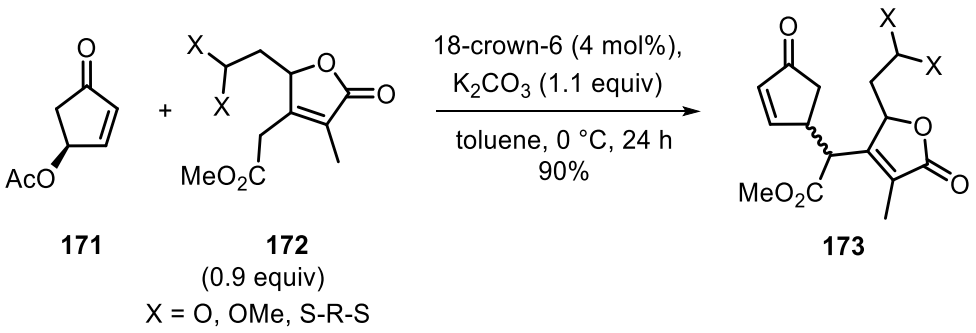
Table 8. Enolate cascade *via* Cu-enolate.



entry	X	Y	Z	cat.	time	result
1	6.0	3.0	1.7	CuI (3.3 equiv)	2 h	**160** (43%)
2	2.0	1.0	1.0	CuI (1.0 equiv)	3 h	**160** (32%)
3	6.0	3.0	1.7	CuCN (3.0 equiv), LiCl (6.0 equiv)	3 h	n. r.

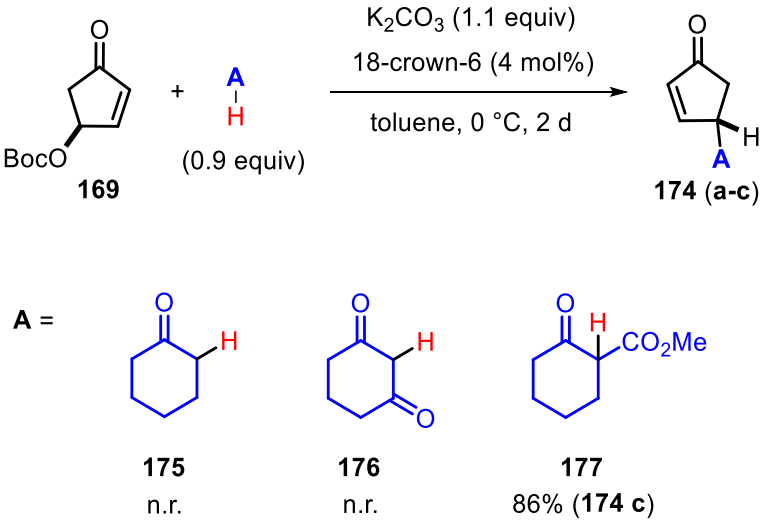
With CuI (entries 1 and 2) only the first 1,4-addition to cyclohexenone (**95**) occurred and no further reaction was observed. The reason might be, that the first formed enolate of **160** was protonated by one of the acidic protons of cyclohexenone (**95**) and thus was not available for further transformation, or the reactivity of the copper enolate intermediate was too low to react with cyclopentenone (**169**). In case of the CuCN/LiCl system (entry 3) no reaction of the starting materials was observed, which might have been caused by the lower reactivity of the cuprate.

Before conducting more test reactions on the one-pot enolate cascade, it was investigated whether a 1,4-addition to Boc-hydroxy-cyclopentenone (**169**) is in general possible. In this case, Winterfeldt and coworkers[34] reported a reaction where they used an acetate protected cyclopentenone (**171**) and β-keto ester **172** in a two-phase system which gave the 1,4-adduct **173** in excellent yield (Scheme 32).



Scheme 32. 1,4-addition of compound **172** to cyclopentenone **171** in a two-phase system by Winterfeldt *et al.* [34]

Applying these conditions to the reaction depicted in Scheme 33 with compound **169** gave the desired product **174 c** in 86% yield after a reaction time of two days. The only limitation seems to be, that a β-keto ester is necessary, otherwise the reaction would not work as was observed with the test substrates **175** and **176**. The reason for this is, that the proton in the β-keto ester (**177**) is acidic enough, compared to the other substrates, to be deprotonated by K_2CO_3.

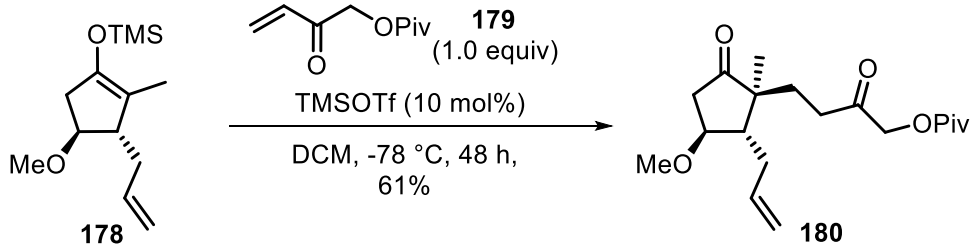


Scheme 33. 1,4-addition of different enolate precursors to cyclopentenone **169** in a two-phase system.

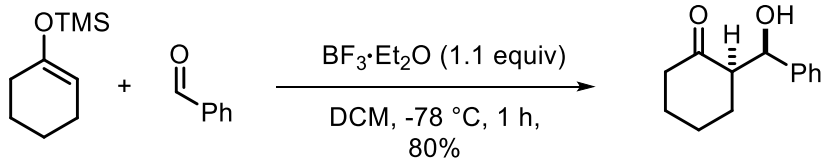
Though the Michael addition worked, it would not lead to the desired enolate cascade. Due to the existing proton in the reaction medium the resulting enolate would be protonated and thus could not undergo the following aldol reaction. For this reason, it is important to exclude a proton source by *e.g.* using a TMS-enol-ether. Similar reactions were already reported by several groups which are summarized in Scheme 34. For

example, 2014 the group of Wicha[35] reported a Michael addition of TMS-enolate **178** to an unsaturated ketone **179** by using TMSOTf as a Lewis acid (Scheme 34 **a**). Much earlier in 1974 Mukaiyama *et al.*[36] reported an aldol reaction of TMS-enol ether **181** with benzaldehyde **182** in the presence of $BF_3 \cdot Et_2O$ as a Lewis acid (Scheme 34 **b**). Other Lewis acids applied were SmI_2 by Collin *et al.*[37] (Scheme 34 **c**) and $Zn(OTf)_2$ by the group of Doyle[38] (Scheme 34 **d**). Different reaction conditions were presented by Prunet and coworkers[39] in 2008 (Scheme 34 **e**) with rather bulky substrates. They were first converting the TMS-enol ether **190** to a more reactive Li-enolate with ^{n}BuLi and reacted it with the activated cyclopentenone derivative **189** in the presence of $ZnCl_2$. The stereochemistry was controlled by the choice of solvent. The more unpolar the solvent was, the higher was the *syn*-selectivity of the enolate attack, regarding the TBS-protecting group.

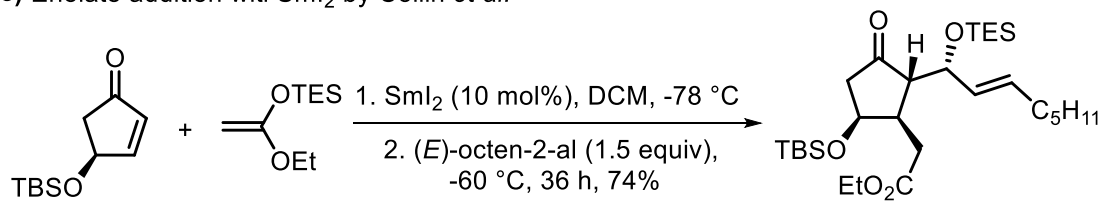
a) Enolate addition with TMSOTf by Wicha *et al.*[35]



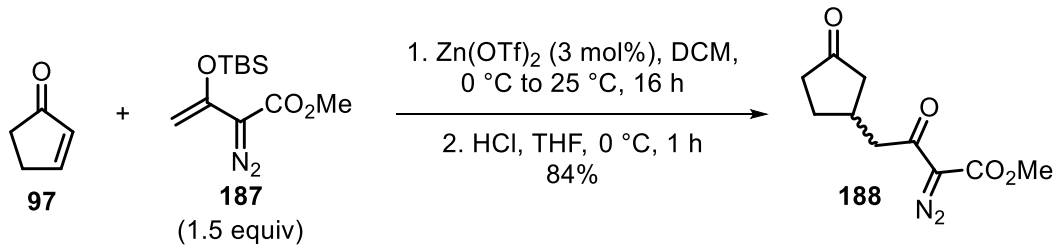
b) Enolate addition with $BF_3{\cdot}Et_2O$ by Mukaiyama *et al.*[36]



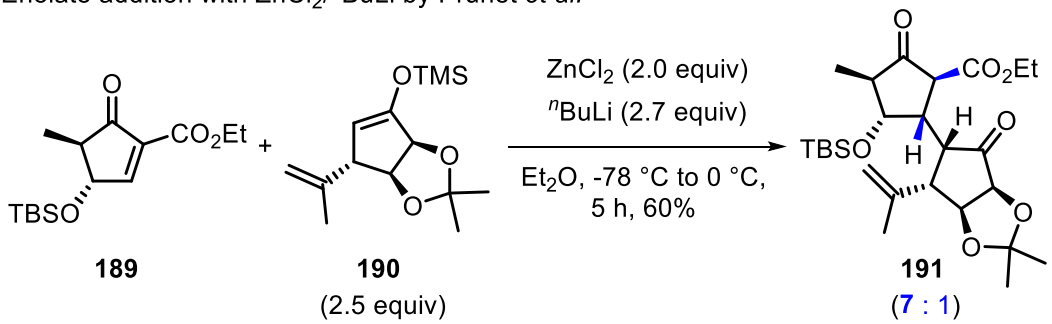
c) Enolate addition witi SmI_2 by Collin *et al.*[37]



d) Enolate addition with $Zn(OTf)_2$ by Doyle *et al.*[38]



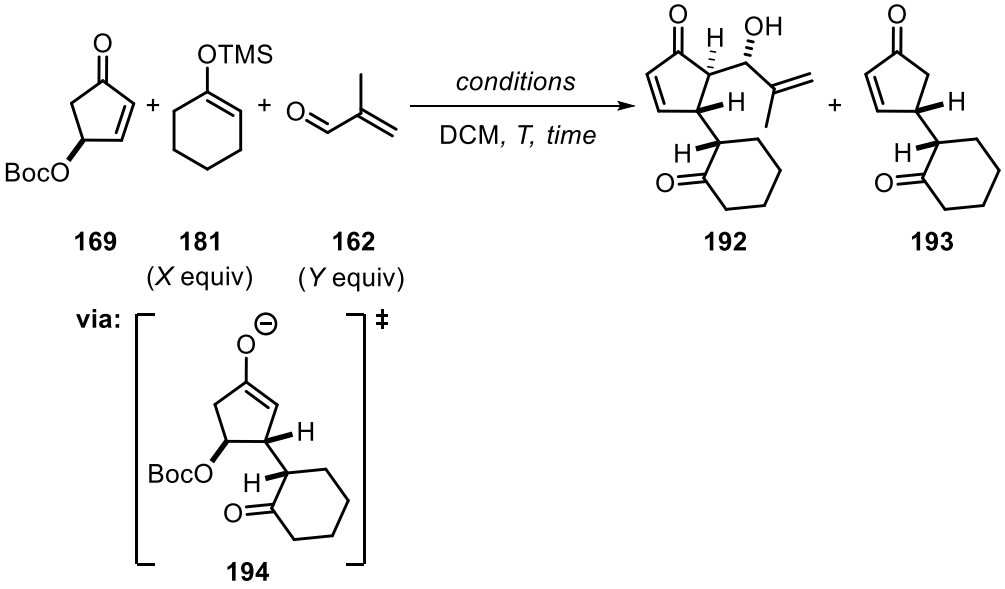
e) Enolate addition with $ZnCl_2/{}^n$BuLi by Prunet *et al.*[39]



Scheme 34. Overwiev of different 1,4-additions of enolates with diverse Lewis acids.[35–39]

The results of applying the different reaction protocols on the test substrates are shown in Table 9. By using TMSOTf (entry 1) or $BF_3 \cdot Et_2O$ (entry 2) as a Lewis acid, only the 1,4-adduct **193** was obtained in a low yield. In case of SmI_2 (entry 4) and $Zn(OTf)_2$ (entry 5) no reaction occurred at all. The problem here might be the low reactivity of the enolate **194**, resulting from the attack of enolate **181** on cyclopentenone **169**, which further hinders a reaction with methacrolein (**162**). Changing to $ZnCl_2$ and ^{n}BuLi (entry 3) for the formation of the more reactive Li-enolate resulted in the formation of byproduct **193**. In this case, a fast protonation of the Li-enolate **194** by an acidic proton blocks the reaction sequence. The same might be the case for the reactions reported in the other entries.

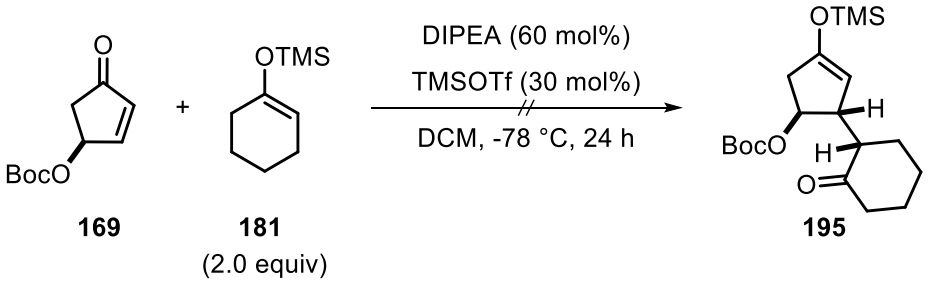
Table 9. Enolate cascade with different Lewis-acids.



entry	X	Y	conditions	T [°C]	time	result
1	2.0	2.0	TMSOTf (30 mol%)	-78	24 h	**193** (19%)
2	1.0	1.7	$BF_3 \cdot Et_2O$ (1.0 equiv)	-78	5 h	**193** (7%)
3[a)]	2.5	1.7	$ZnCl_2$ (2.0 equiv), ^{n}BuLi (2.7 equiv)	-78 to 0	6 h	**193** (43%)
4[b)]	1.0	1.5	SmI_2 (10 mol%)	-60	2 d	n.r.
5	1.5	2.0	$Zn(OTf)_2$ (10 mol%)	0 to 25	24 h	n.r.

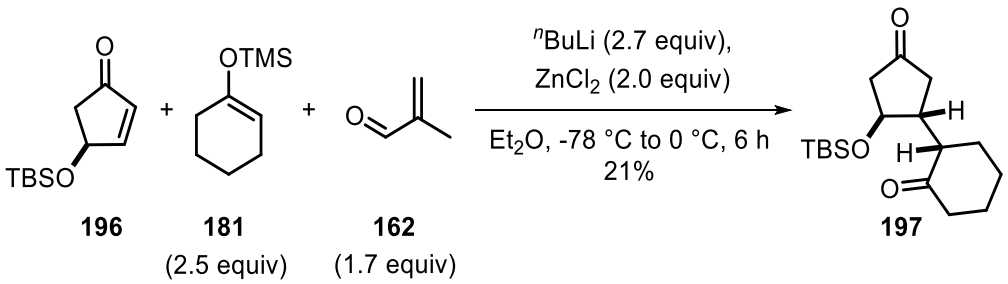
a) Et_2O was used as a solvent; b) THF was used as a solvent.

An effort to use a combination of DIPEA and TMSOTf, as reported by Downey *et al.*[40] to form the corresponding TMS-enolate **195** and react this further with methacrolein was unsuccessful. No formation of the 1,4-adduct **195** was observed in this case (Scheme 35).



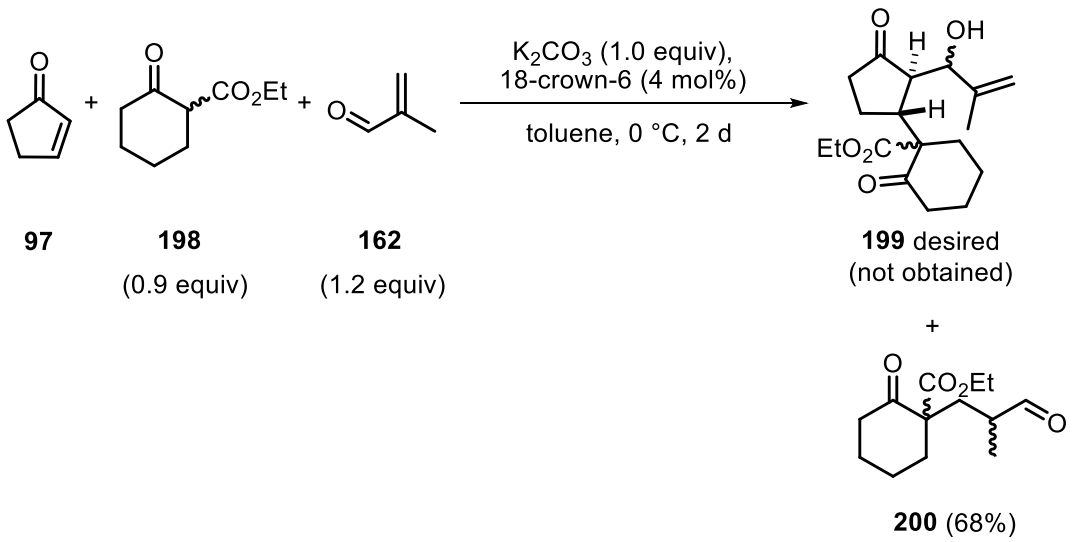
Scheme 35. Enolate addition implementing conditions by Downey *et al.*[40]

Furthermore, it was examined whether the protecting group might make a difference. Therefore, TBS-protected cyclopentenone **196**, which is not as labile as the Boc-group and should not undergo elimination after a Michael addition, was used under ^{n}BuLi/$ZnCl_2$ conditions (Scheme 36). Once more, just the 1,4-adduct **197** was obtained in a lower yield compared to the Boc-protected substrate **169** (see Table 9, entry 3) and no further reaction with methacrolein **162** was observed.



Scheme 36. Enolate cascade with TBS hydroxy-cyclopentenone (**196**) with $ZnCl_2$ as a Lewis acid.

Seeing that in all performed test reactions the 1,4-addition in the two-phase system worked the best, an attempt was made to find out, whether the enolate cascade would work when all three reaction components are subjected to the two-phase system at once (Scheme 37). This time, unsubstituted cyclopentenone (**97**) was used to reduce possible sterical hindrance. In this case, not the desired product **199** but the 1,4-adduct **200** between β-keto ester **198** and methacrolein (**162**) was obtained. The explanation for this outcome is, that methacrolein (**162**) is more reactive than cyclopentenone (**97**), therefore the resulting enolate from ester **198** reacts preferentially with enone **162**.

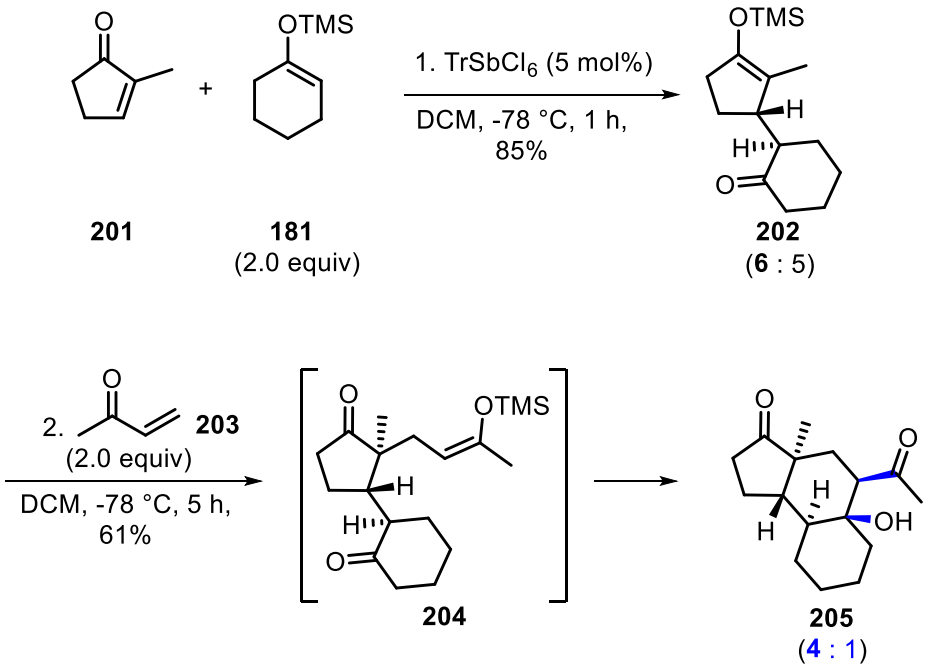


Scheme 37. One-pot enolate cascade with cyclopentenone (**97**) in a two-phase system.

Under these circumstances, the one-pot enolate cascade was not performed with Boc-cyclopentenone **169** since the outcome would be the same as shown in Scheme 37. This is due to the fact that, even though a carbamate is a little electron-withdrawing, thus activating the enone moiety, the reaction would have still happened with methacrolein (**162**), being the most reactive enone in this case because of its terminal double bond.

3.2 Application of preformed enolate

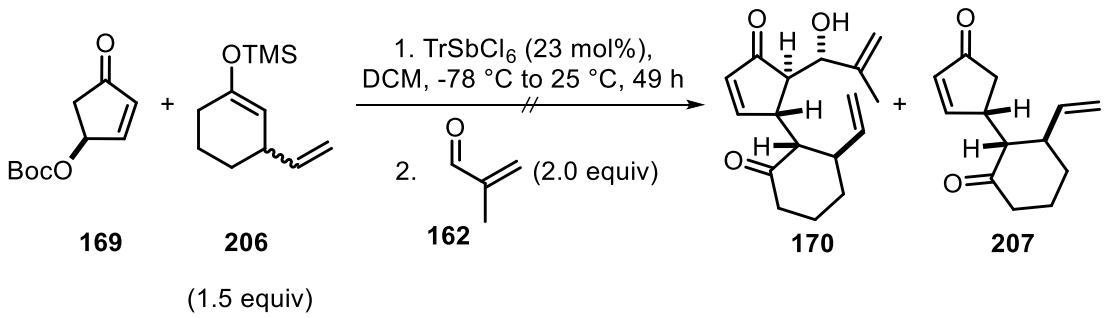
In 2006, De Groot *et al.*[41] reported an enolate cascade where they used triphenylcarbenium-hexachloroantimonate ($TrSbCl_6$) as a Lewis acid for the 1,4-addition of TMS-enolate **181** to cyclopentenone **201**, followed by a second Michael addition with acrylate **203** (Scheme 38).



Scheme 38. Enolate cascade with $TrSbCl_6$ as Lewis acid by De Groot *et al.*[41]

Seeing that the substrates did not differ much from the ones that are used in this study, the investigation of the cascade with the TMS-enolether **206** and $TrSbCl_6$ was continued.

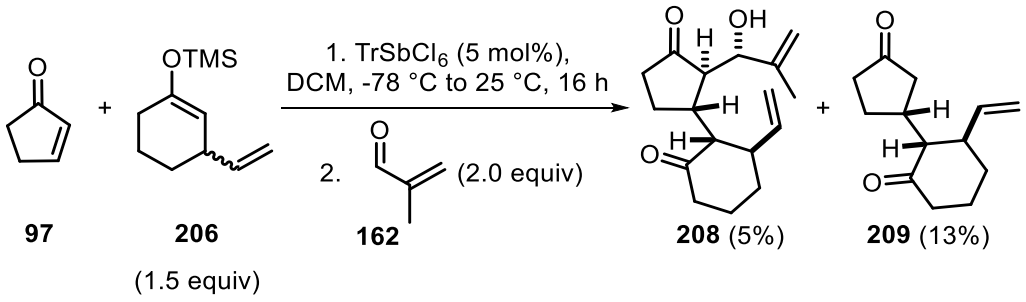
Scheme 39 shows the test reaction. At first, the catalyst loading was increased stepwise from 5 mol% to 23 mol%, keeping the reaction temperature constant at -78 °C. When no conversion of the starting materials **169** and **206** was observed, the temperature was increased stepwise to 25 °C over 49 h which did not result in any reaction.



Scheme 39. Enolate cascade with cyclopentenone **169** and TMS-enolether **206** catalyzed by $TrSbCl_6$.

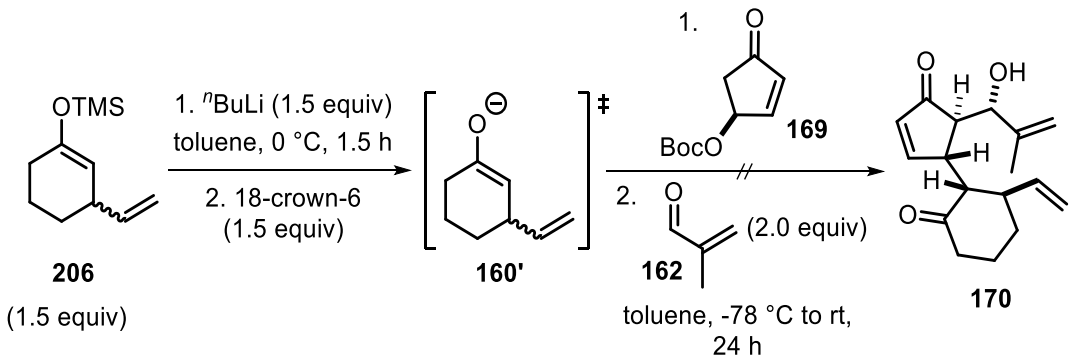
Considering, whether the sterical hindrance might be a problem compared to the literature reaction, where neither the enolate **181** nor the cyclopentenone **201** contained any bulky substituents, the reaction was repeated with the unsubstituted cyclopentenone **97** (Scheme 40).

This time, trace amounts of the desired product **208** were obtained as the minor product. Major product was the 1,4-addition compound **209** with 13% yield. From these experiments it could be assumed, that the sterical hindrance of the applied substrates may be too big or $TrSbCl_6$ as a Lewis acid is not strong enough for this reaction.



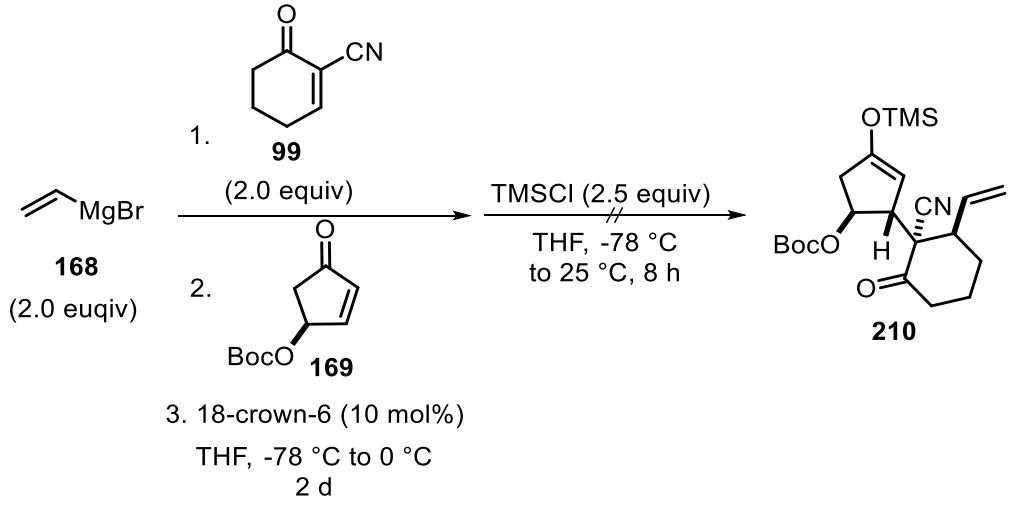
Scheme 40. Enolate cascade with unsubstituted cyclopentenone **97** and TMS-enolether **206** catalyzed by $TrSbCl_6$.

For this reason, an approach was made to increase the reactivity of enolate **206** by forming the corresponding Li-enolate and complexing the metal with 18-crown-6 to obtain a 'naked' enolate **160'** which should readily react with cyclopentenone **169** (Scheme 41). However, when adding enone **169** and after some time methacrolein (**162**) to the reaction mixture, no reaction was observed.



Scheme 41. Enolate cascade with more reactive enolate **160'**.

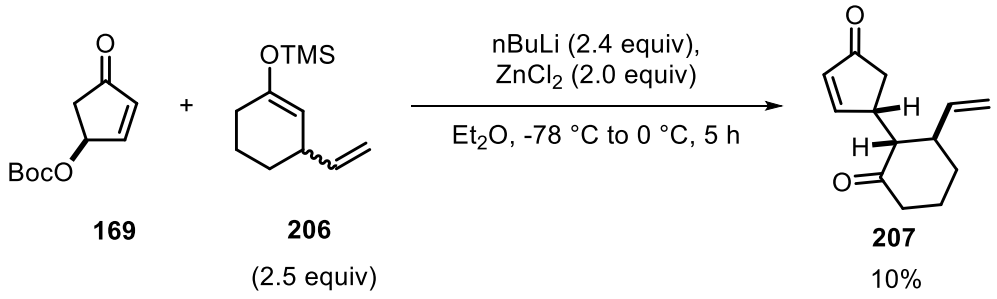
The reactivity of the enolate **160'** seemed to be too big, which is why the intramolecular protonation occurred faster than the reaction with enone **169**. Therefore, it was attempted to carry out a one-pot reaction with the more reactive cyclohexenone **99** (Scheme 42) by first reacting it with vinyl magnesium bromide (**168**) and then adding cyclopentenone **169** to the mixture.



Scheme 42. Enolate cascade with reactive enolate **99** and final trapping with TMSCl to obtain intermediate **210**.

When no conversion of the starting materials was observed, 18-crown-6 was added to complexate the Mg-ion, and TMSCl with the idea of trapping the formed enolate to obtain enolether **210**. Intermediate **210** then could be subjected to an aldol reaction in a separate step. However, no conversion was observed even after carefully raising the temperature.

Wondering, why even the 1,4-addition did not work, although the reactivity of enolate **206** or **99** was increased, a control reaction was performed (Scheme 43).

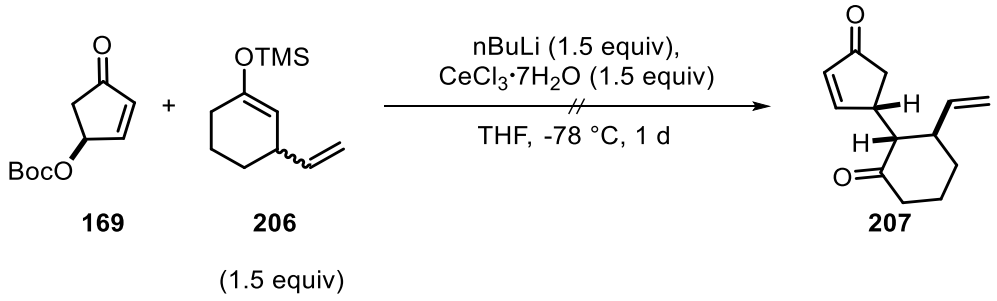


Scheme 43. Control reaction of cyclopentenone **169** with substituted enolate **206**.

Previously, the 1,4-addition between cyclopentenone **169** and unsubstituted cyclohexanone **181** proceeded with moderate yields under the reaction conditions shown above (see Table 9, entry 3). When subjecting enolether **206** to the same conditions, product **207** was obtained in just 10% yield. During this reaction it seemed that mainly polymerisation occurred. Based on this outcome, it could be concluded that the sterical hindrance of the vinyl group from enolate **206** is too big for the addition to enone **169**, therefore another approach is necessary.

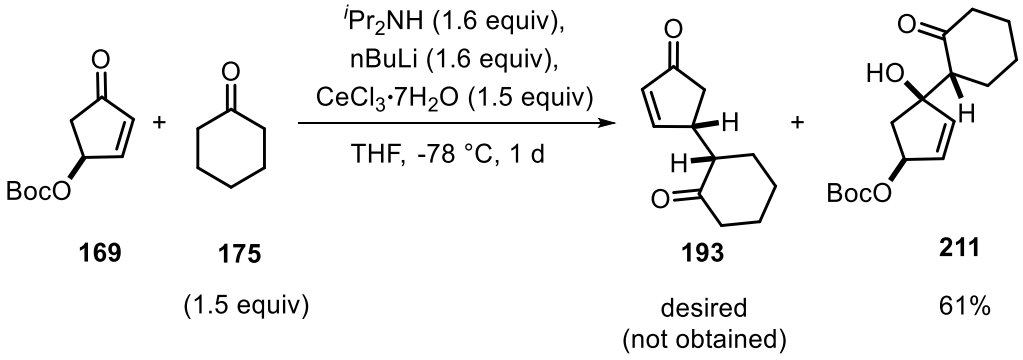
3.3 Enolate cascade *via* Ce-and K-enolate

To examine if the effect of sterical hindrance could be circumvented by further increasing the reactivity of the enolate, a Ce-enolate was prepared and reacted with cyclopentenone **169**, but no reaction occurred (Scheme 44).[42]



Scheme 44. Enolate cascade with *in situ* prepared Ce-enolate from substituted enolate **206**.

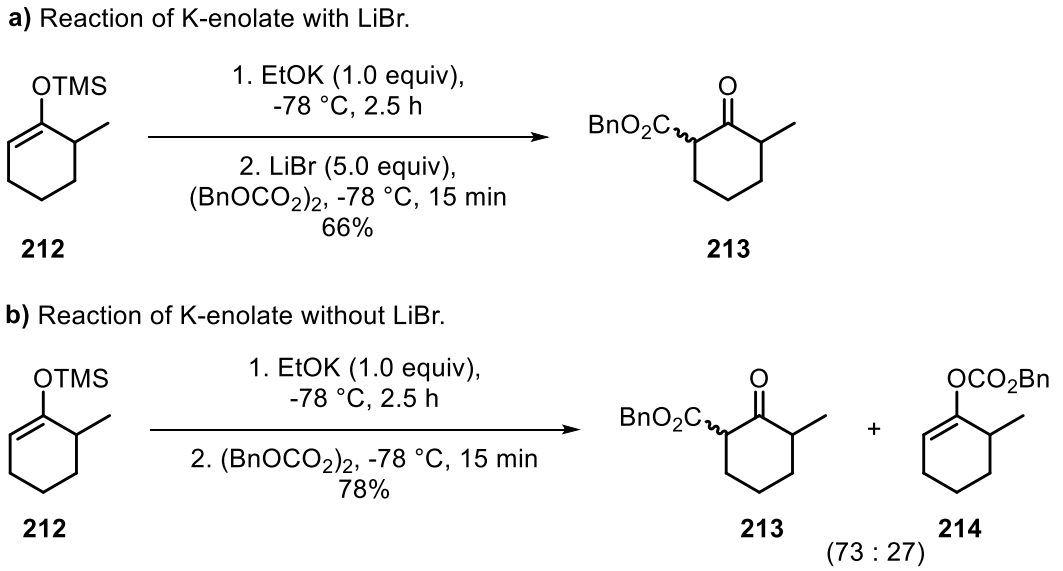
This result showed, that the sterical hindrance of the vinyl group of compound **206** was not compensated by a stronger nucleophilicity. Yet, another experiment was run with unsubstituted cyclohexanone (**175**) to exclude the possibility of the reactivity being too low. Scheme 45 shows the reaction between enone **169** and ketone **175** where the obtained product was not the 1,4-adduct **193** but the aldol product **211**, acquired in 61% yield.



Scheme 45. 1,4-addition to cyclopentenone **169** via Ce-enolate of compound **175**.

This outcome was expected because Ce-enolates are highly nucleophilic and usually react in 1,2-additions, strengthening the assumption of vinyl cyclohexanone **206** being too bulky for the reaction with enone **169** instead of insufficient reactivity.

A last attempt was made to react enolate **206** with cyclopentenone **169** and methacrolein (**162**) in a one-pot reaction by forming a potassium enolate. In 2001, Jin *et al.*[43] reported the formation of potassium enolates from EtOK or ^{t}BuOK and further reacting them with electrophiles (Scheme 46).



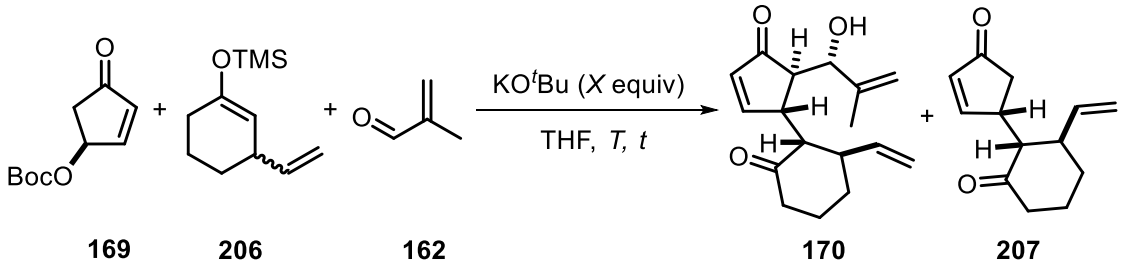
Scheme 46. Formation and reaction of a potassium enolate from **212**. a) With addition of LiBr; b) without addition of LiBr.[43]

The only difference between the potassium sources was, that with ^{t}BuOK the thermodynamic enolate was generated and a longer reaction time was required compared to EtOK. Additionally, in the literature LiBr was used to convert the potassium enolate to

the corresponding lithium enolate so that the reactive nucleophile was the carbon atom instead of the oxygen (Scheme 46 **b**).

Table 10 shows the test reactions. In this study ^{t}BuOK was used as potassium source and no LiBr was added because the reaction *via* lithium enolate was already performed above without the desired outcome. In entries 1 and 2, different addition orders were investigated. Addition of cyclopentenone **169** to the preformed enolate solution of compound **206** yielded only the 1,4-adduct **207** in 12% (entry 1). Reversing the addition order gave byproduct **207** in a better yield but again no formation of the desired product **170** was observed (entry 2). In both cases, only traces of the starting material **169** were reisolated, indicating unknown side reactions. Thus, in entry 3, the amount of the enolate was reduced, giving mostly the starting material.

Table 10. Enolate cascade *via* potassium enolate under different conditions.



169 **206** (*X* equiv) **162** (2.0 equiv) **170** **207**

entry	X	T [°C]	time [h]	result
1[a)]	2.0 equiv	0 to -78 to 0	3	12% (**207**)
2[b)]	2.0 equiv	0 to -78	1.5	31% (**207**)
3[b)]	1.1 equiv	0 to -78	1.5	traces (**207**)

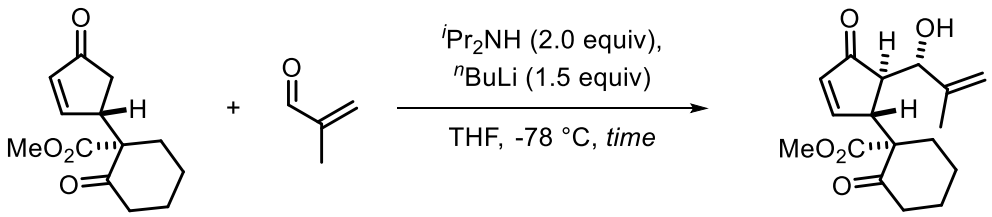
a) Enone **169** was added to the enolate-solution
b) Enolate-solution was added to enone **169**

Based on the results so far, it became clear that the enolate cascade was not feasible as planned. Either the sterical hindrance or the reactivity of the required substrates were not compatible with the desired reaction sequence. In addition, the existence of acidic protons in the reaction medium complicates the synthetical approach pursued in this work.

3.4 Aldol reaction of 1,4-adduct with LDA

According to the previous outcome, where the enolate cascade did not give the expected results, another method was attempted. In this case, the starting material was the 1,4-adduct **174 c** from the two-phase system reaction which was obtained in excellent yield. The idea was to see if a Li-enolate might be formed selectively on the cyclopentenone instead the cyclohexanone moiety. Table 11 shows the results of this approach.

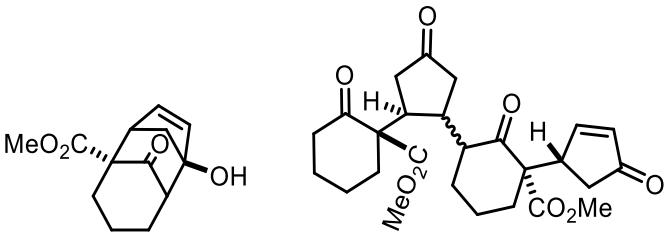
Table 11. Aldol reaction of compound **174 c** with methacrolein (**162**) under different conditions.



174 c **162** (1.4 equiv) **215**

entry	procedure	time	result
1	**162** was added to mixture of LDA and **174 c**	2 h	n.r.
2	**174 c** was added to mixture of LDA and **162**	1 h	37% (**216**) + traces (**217**)
3	LDA was added to mixture of **162** and **174 c**	19 h	15% (**216**) + traces (**217**)
4	mixture of **162** and **174 c** added to LDA	3 h	n.r.

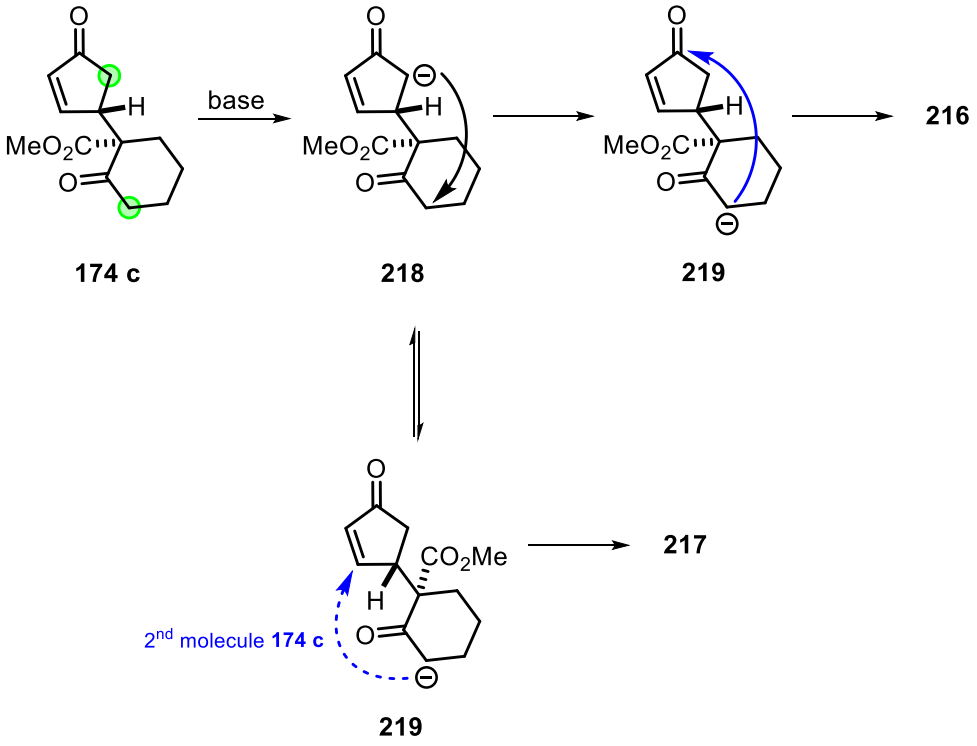
Different addition orders of the reactants were tested. In entry 1, aldehyde **162** was added to a mixture of enone **174 c** and LDA. No reaction occurred in this case, suggesting that the Li-enolate did not form in this step or was quenched before reacting with the aldehyde. In entries 2 and 3, enone **174 c** was added to a mixture of LDA and aldehyde **162** or LDA was added to a mixture of aldehyde **162** and enone **174 c**, respectively. In both reactions, byproduct **216** was obtained in a low yield as well as traces of the dimer **217** (Figure 7). In the case were a mixture of the aldehyde and enone was added to LDA no reaction occurred (entry 4).



216 (proposed) **217** (proposed)

Figure 7. Proposed structures of obtained byproducts **216** and **217** during the aldol reaction.

An explanation for the formation of byproduct **216** and dimer **217** is shown in Scheme 47. Due to the fact that two possible acidic protons exist in enone **174 c** (marked in green), either cyclopentenone is deprotonated first (**218**) and can be protonated by intra- or intermolecular H-abstraction to give intermediate **219**. Or the cyclohexanone moiety in **174 c** is deprotonated to also yield intermediate **219** which then can react in an intramolecular 1,2-addition to yield byproduct **216** (continuous blue arrow). Byproduct **217** is obtained when molecule **219** attacks the enone moiety in compound **174 c** (dashed blue arrow).



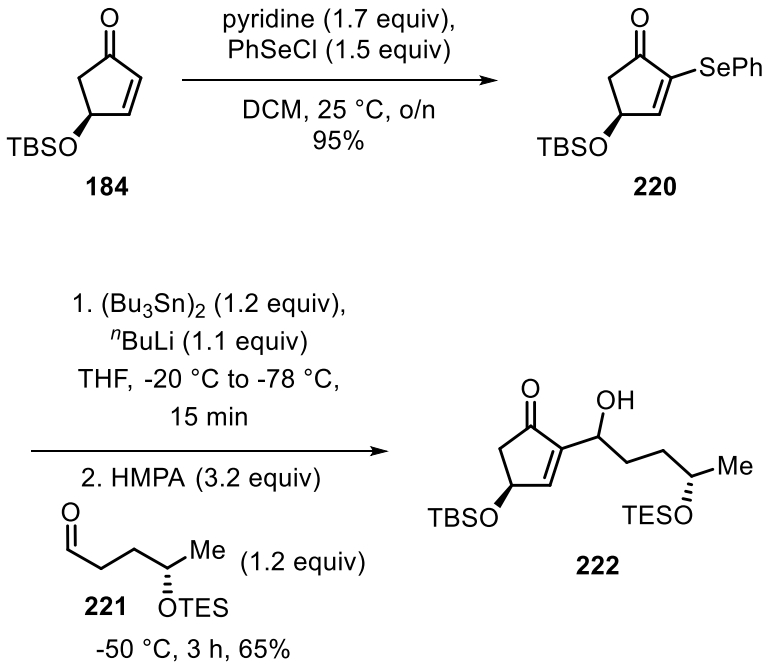
Scheme 47. Possible explanation for the formation of byproducts **216** and **217**.

Dimer **217** is formed in trace amount because of the reactivity of a Li-enolate which is a hard nucleophile, therefore not suitable for a 1,4-addtion. Probably, both deprotonations

happen in solution and there might be an equilibrium between both enolates but only intermediate **219** reacts further. Thus, this approach was also abandoned since it did not lead to the desired product.

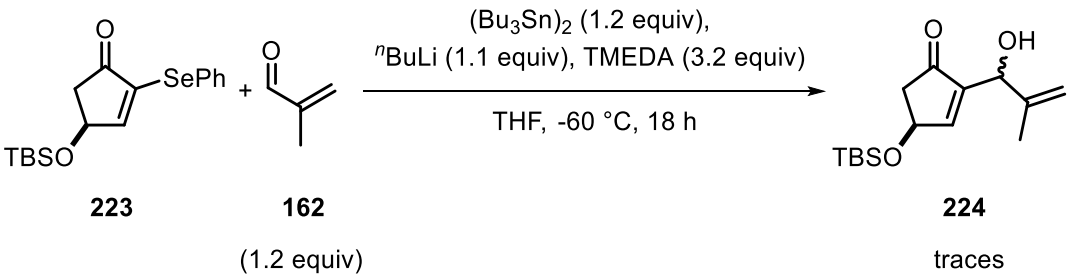
3.5 Approach through Stille coupling

Regarding the experiments reported above, it appeared that an enolate cascade as planned was not feasible. For this reason, the idea of a one-pot reaction was dismissed, and a new approach was tried. Since the Michael addition was possible but not the following aldol reaction, the decision was made to first introduce the allylic alcohol function and conduct the Michael addition in a second step. A very similar reaction was reported by Tong *et al.*[44] where a reductive deselenation aldol coupling was performed on the TBS-hydroxy cyclopentenone (**184**) with a different aldehyde **221** (Scheme 48). They also described, that neither a Morita-Baylis-Hillman nor a Nozaki-Hiyama-Kishi reaction was possible on cyclopentenone **184**. Therefore, these reactions were not tried in this study.



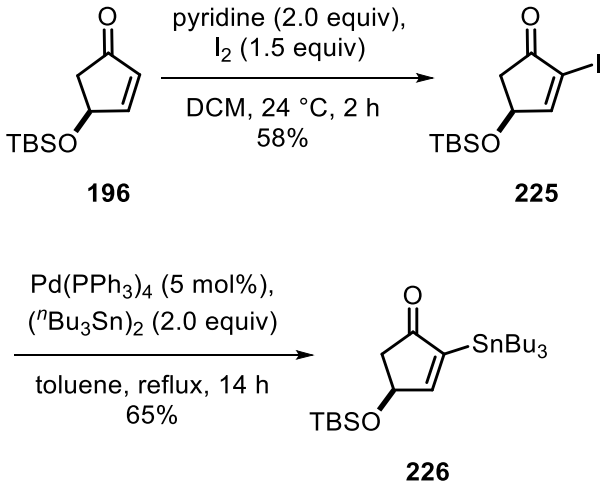
Scheme 48. Reductive deselenation aldol coupling of cyclopentenone **184** with aldehyde **221** by Tong *et al.*[44]

Performing the reaction with methacrolein under this conditions gave mostly the starting material and traces of the desired product **224** (Scheme 49). Maybe the use of the less toxic TMEDA instead of HMPA, which was applied in literature, played a decisive role in this outcome.



Scheme 49. Reductive deselenation aldol coupling of cyclopentenone **223** with methacrolein (**162**).

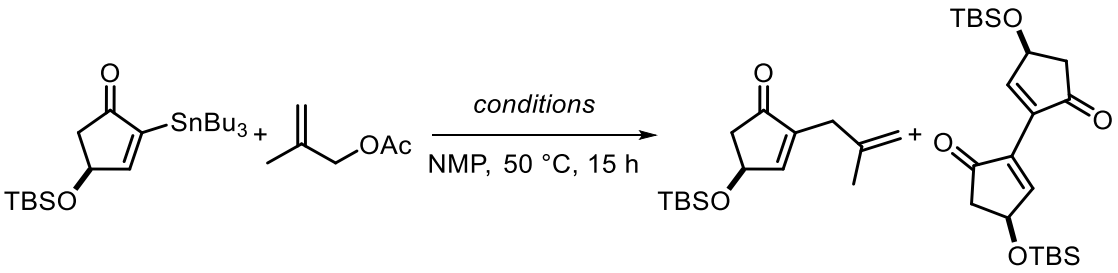
Thus, it was decided to leave out the alcohol functionality and conduct a Stille coupling. The synthesis for the corresponding tin substrate **226** proceeded without any problems in a good yield (Scheme 50).[31,44]



Scheme 50. Synthesis of tributyltin cyclopentenone **226**.

The next step was a Stille coupling with allyl acetate **227** under standard coupling conditions with LiCl and Pd_2dba_3 as catalyst which gave the desired product **228** in just 41% yield (Table 12). Using CuCl as an additive as described by Corey *et al.* in 1999[45] improved the yield to 96%. In both cases, the homocoupling product **229** was obtained in low amounts.

Table 12. Stille coupling between cyclopentenone **226** and acetate **227** under different conditions.

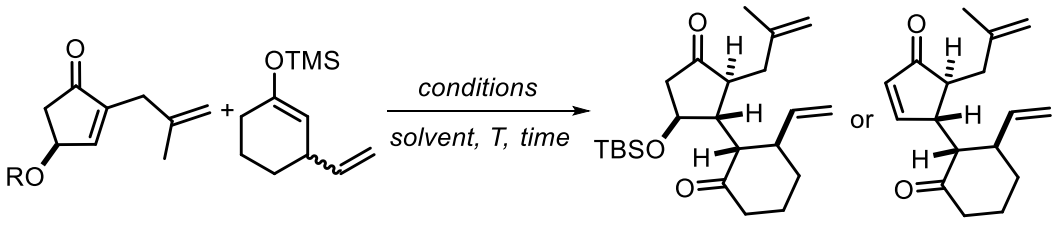


226 **227** (1.0 equiv) **228** **229**

entry	conditions	result
1	LiCl (4.0 equiv), Pd_2dba_3 (20 mol%)	41%, **228**:**229** (7.1:1)
2	LiCl (4.0 equiv), CuCl (3.3 equiv), Pd_2dba_3 (20 mol%)	96%, **228**:**229** (5.9:1)

With the coupling product **228** in hand, the Michael addition of enolate **206** was tried under the most promising conditions (Table 13).

Table 13. 1,4-addition of enolate **206** to cyclopentenone **228** or **230** under different conditions.

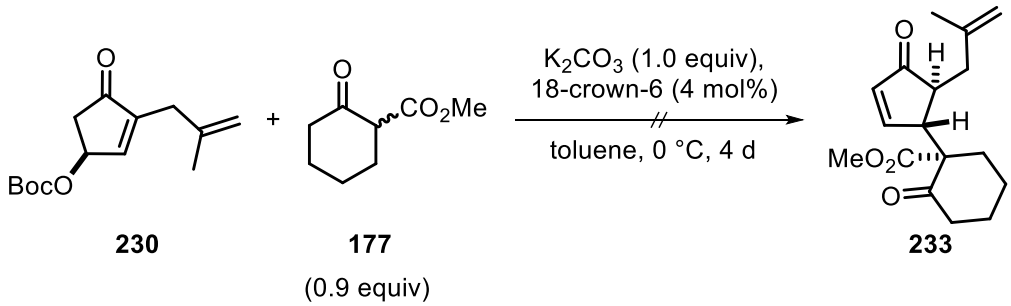


R = TBS: **228**
R = Boc: **230**
206 (*X* equiv)
231 **232**

entry	R	*X*	conditions	solvent	T [°C]	time	result
1	TBS	1.5	$TrSbCl_6$ (8 mol%)	DCM	-78	5 h	n.r.
2	TBS	2.5	$ZnCl_2$ (2.0 equiv), ^{n}BuLi (2.4 equiv)	Et_2O	-78 to 0	5 h	n.r.
3	Boc	2.0	KO^{t}Bu (2.0 equiv)	THF	-78	30 min	crm

But neither with $TrSbCl_6$ (entry 1) nor with $ZnCl_2$ (entry 2) as Lewis acids the desired product **231** was obtained. In both cases, only the starting material was reisolated. It seems that the reactivity of enolate **206** is too low or the sterical hindrance of both starting materials is too high. For the reaction with KO^{t}Bu (entry 3), Boc-protected enone **230**, which was obtained by basic deprotection-protection method, was applied since elimination after the reaction would occur, thus reducing sterical hindrance of product **232** compared to **231**. Although now decomposition of the starting material occurred, suggesting that the reactivity of the potassium enolate was too high in this case.

In Scheme 51 a last attempt was made to see, whether a 1,4-addtion of starting material **230** with β-keto ester **177** was possible, considering the good outcome shown before without the allyl group (see Scheme 33).



230 **177** (0.9 equiv) **233**

Scheme 51. 1,4-addition of compound **177** to cyclopentenone **230** in a two-phase system.

No product formation was observed under the shown conditions, underlining the hypothesis that the allylic group in compound **230** poses a sterical hindrance which cannot be overcome easily.

Therefore, it was concluded that the idea of an enolate cascade towards the synthesis of Crotophorbolone derivatives as planned might be impossible with the desired substrates and no further investigations were conducted.

B Reactivity of cyclopropanated 2-pyrones and 2-pyridinones

1. Introduction

1.1 2-Pyrone and 2-pyridinone moiety in natural products

The 2-pyrone moiety is present in a large number of natural products which exhibit a wide range of biological active properties, including antibiotic, antifungal, cytotoxic, neurotoxic and phytotoxic effects. Representatives can be isolated from a considerable range of natural sources, *e.g.* plants, animals and marine organisms. The 2-pyrone moiety serves as a versatile building block for syntheses in organic chemistry as well – due to the presence of functional groups such as conjugate diene and the lactone group which will be discussed further in chapter B 1.4.[46] Some natural products with a pyrone moiety are shown in Figure 8, of which Pyrenocine A (**234**) and Radicinin (**235**) belong to the category of phytotoxic compounds. Pyrenocine A prevents the germination of lettuce seed and inhibits the root elongation in seedlings similar to Radicinin, preventing the germination of cress (*Lepidum sativum*) seeds.[47] In contrast, Alternariol (**236**) shows cytotoxicity against mouse lymphoma cells and Aflatoxins are known for their poisonous and cancerogenic properties. Especially notable is Aflatoxin B_1 (**237**), which is the most poisonous member of the Aflatoxin family and can even permeate through the skin.[48]

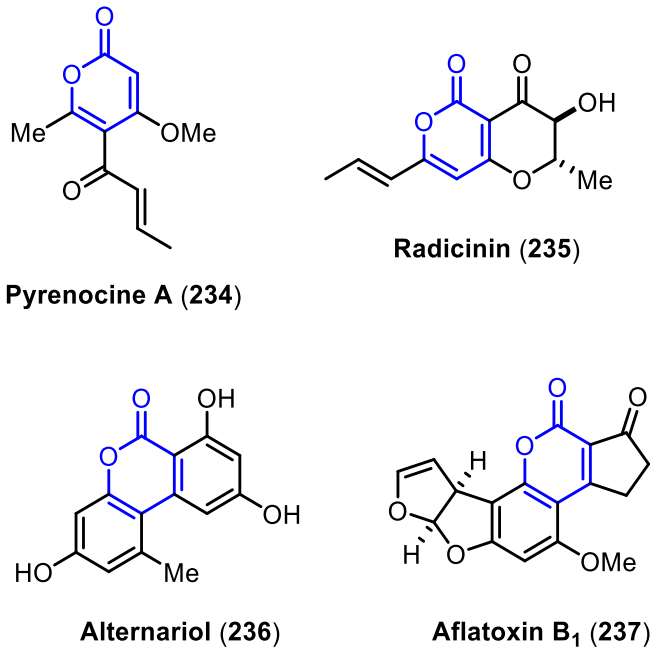


Figure 8. Naturally occurring biological active compounds with 2-pyrone moiety.

Similar to 2-pyrone is the 2-pyridinone moiety, which is as well present in many promising biological active compounds, some of them shown in Figure 9. The importance as an active component against many diseases like cancer[49] and as a building block in organic syntheses is comparable to that of 2-pyrone and its transformations will be discussed further in chapter B 1.5. Accordingly, it was reported that compounds **238** and **239** show potential activity against the Hepatitis B and C virus, which causes chronic liver disease with acute and chronic infections.[50] Whereas, compound **240** was shown to be a dengue virus inhibitor[51] and Ciclopirox (**241**) may be used for treatment for ischemic strokes.[52] In the course of the recent pandemic caused by the SARS-CoV-2 virus in 2019, resulting in respiratory problems with partially severe symptoms, a possible inhibitor of the SARS-CoV-2 main protease was found to be Leporin A (**242**) but further investigations are still necessary.[53]

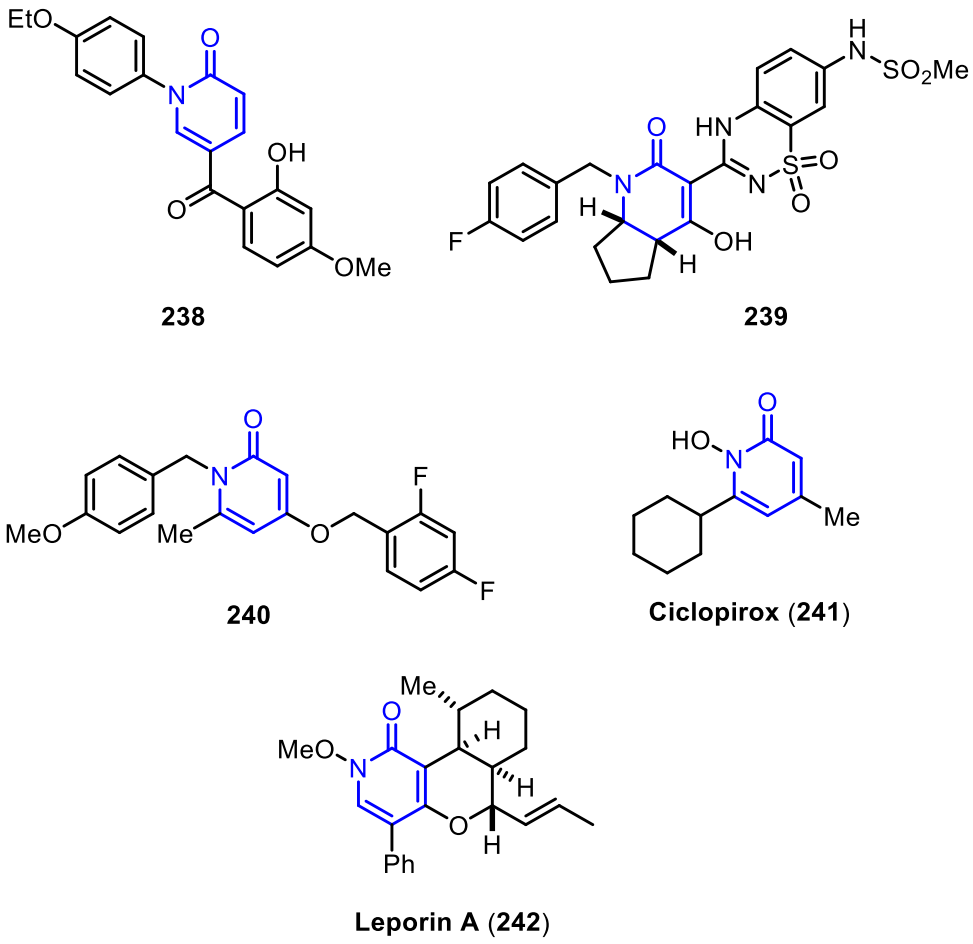
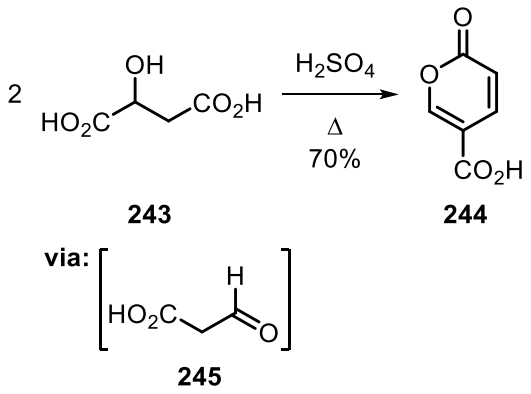


Figure 9. Biologically active compounds with a 2-pyridinone moiety.

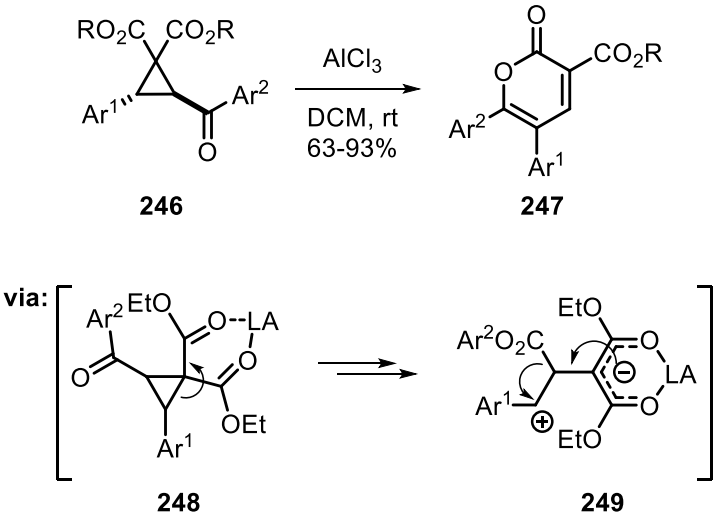
1.2 Synthesis of 2-pyrones

The synthesis of the pyrone moiety as a versatile building block was reported by many authors up to this date. In this chapter, just a selection of those is presented starting with one of the first published ones from 1891 by Pechmann[54] (Scheme 52). He observed that when malic acid (**243**), a compound derived from the fermentation of glucose, was heated in the presence of fuming H_2SO_4, coumalic acid (**244**) was obtained *via* self-condensation of the *in-situ* formed formyl acetic acid **245**.



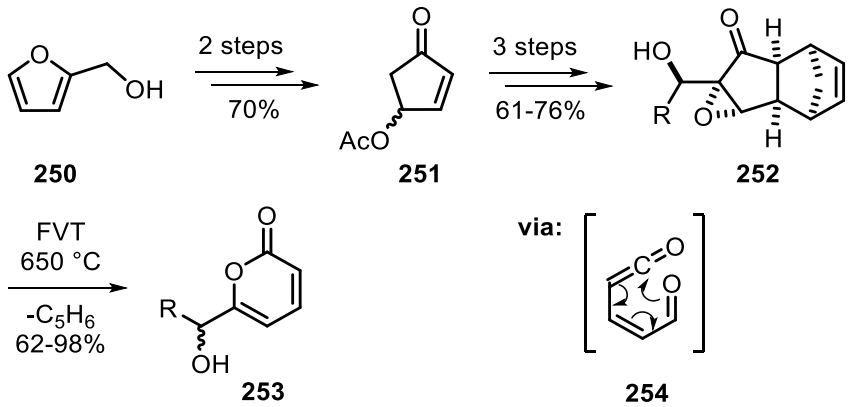
Scheme 52. Synthesis of coumalic acid (**244**) *via* formyl acetic acid (**245**) by acid catalysis.

Compared to this, in 2014, the group of Srinivasan[55] transformed donor-acceptor cyclopropanes **246** into substituted 2-pyrones **247** by a Lewis acid (LA) mediated ring opening (Scheme 53). After coordination of the LA to the malonyl unit **248**, the ring opens and the zwitterionic structure **249** undergoes recombination followed by lactonization, leading to the 2-pyrone structures **247**.



Scheme 53. Synthesis of 2-pyrones **247** by LA catalyzed opening of donor-acceptor substituted cyclopropanes **246**.

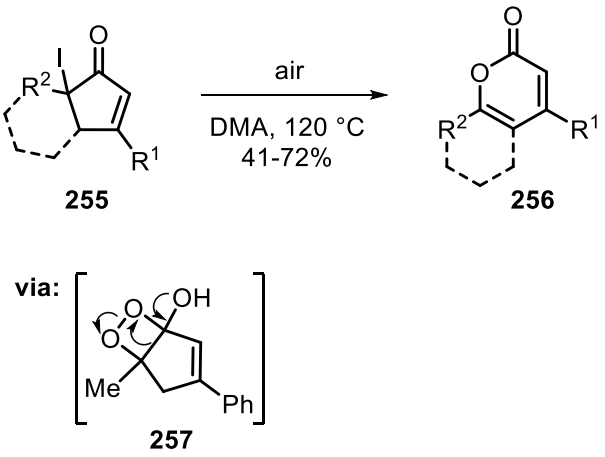
Another method was presented some years earlier by Reiser *et al.*[56] starting from the renewable furfuryl alcohol **250**, which can be obtained from agricultural waste products such as bran and bagasse (Scheme 54). After a Piancatelli rearrangement and acetylation, cyclopentenone **251** was obtained and subjected to a cycloaddition and Baylis-Hillman reaction with various aldehydes, followed by epoxidation to yield compound **252**. Latter then underwent a rearrangement under flash vacuum thermolysis-conditions (FVT) *via* intermediate **254**, giving the desired C6-substituted products **253**.



Scheme 54. Synthesis of 2-pyrones **253** from renewable furfuryl alcohol **250**.

Recently, Rao and coworkers[57] reported a catalyst-and additive-free synthesis of substituted 2-pyrones starting from iodo-cyclopentenones **255** *via* Baeyer-Villiger oxidation with molecular oxygen as oxidant (Scheme 55). In this procedure a wide range of functional groups were tolerated, and the mechanism was proposed to start with the

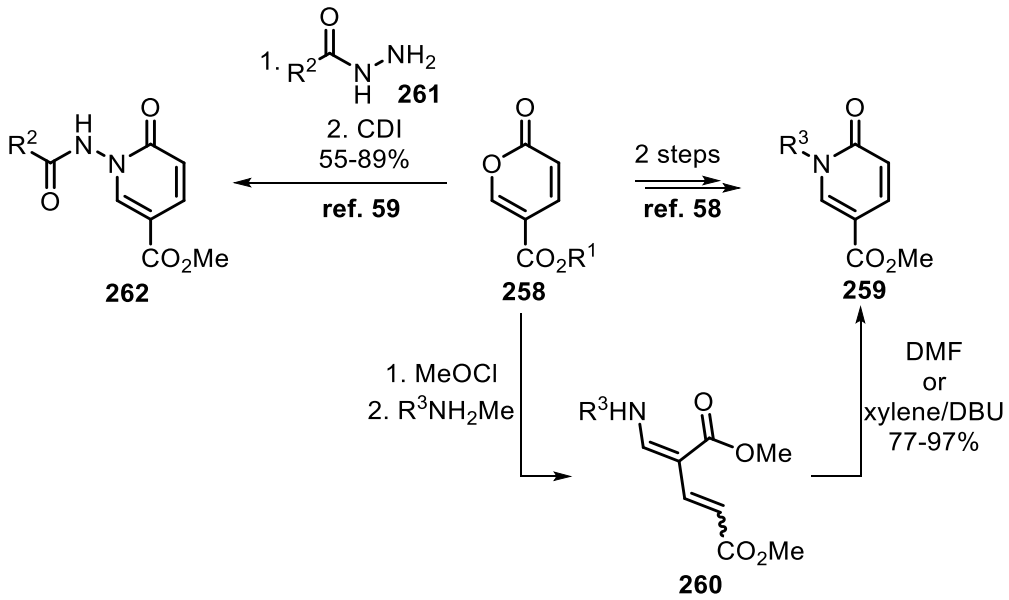
thermal homolysis of the C-I bond, resulting in a radical which was trapped by oxygen. Intramolecular attack on the carbonyl, leading to intermediate **257** and its rearrangement led to pyrone **256**.



Scheme 55. Baeyer-Villiger oxidation of iodo-cyclopentenones **255** for the synthesis of 2-pyrones **256**.

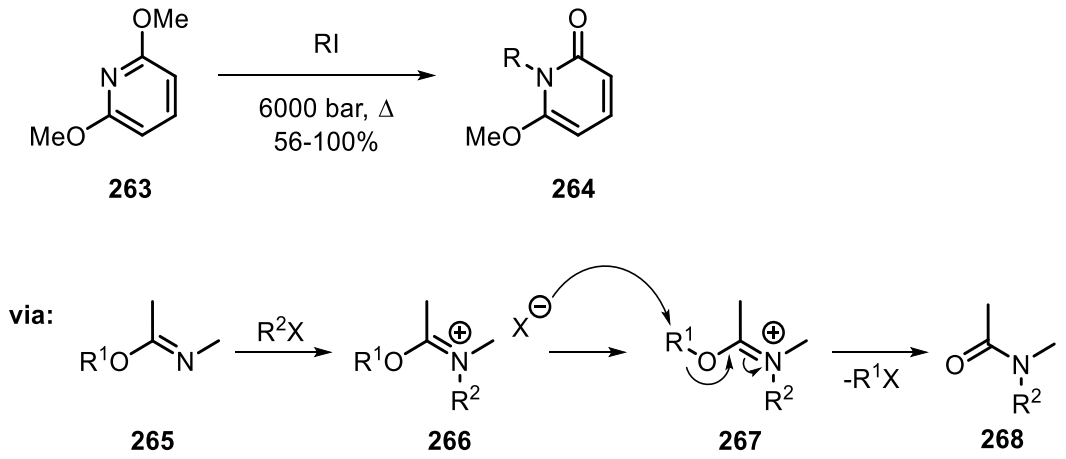
1.3 Synthesis of 2-pyridinones

A remarkable amount of syntheses for the 2-pyridinone moiety already exists and some selected examples are presented in this chapter. In 2001, Ko *et al.*[58] reported the reaction of coumalic acid **258** with different amines to give intermediate **260** which then was cyclized to give 2-pyridinone **259** in good yields shown in Scheme 56 (right part). A similar approach was made by the group of Moloney[59] in 2007 who used hydrazides **261** instead of amines to obtain 2-pyridinones **262** (left part).



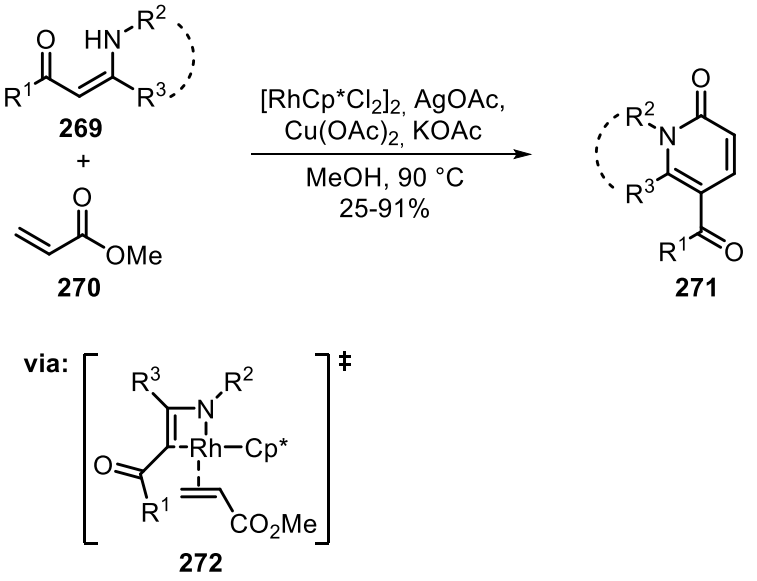
Scheme 56. Synthesis of 2-pyridinones **259** and **262** from coumalate **258**.

Another strategy is to begin with pyridines, as demonstrated by the groups of Anderson[60] and of Matsumoto[61]. The synthesis presented by the latter group can be seen in Scheme 57. Pyridine **263** was reacted with an iodide under high pressure to yield pyridinone **264** through a Hilbert-Johnson reaction. The postulated mechanism for this reaction is shown in the lower part and starts with a quaternization of the hetero cycle **265** followed by a lactim-lactam tautomerization to yield the desired product **268**.



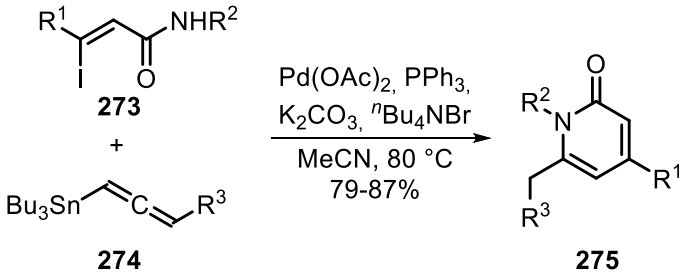
Scheme 57. Synthesis of pyridinone **264** by a Hilbert-Johnson reaction under high pressure according to Matsumoto *et al.*[61]

In contrast to this, Loh and his group[62] showed a different approach – a formal [3+3] annulation of enaminone **269** with acrylate **270** under ruthenium catalysis (Scheme 58). Deprotonation of the amine and CH-activation followed by coordination of acrylate **270** leads to intermediate **272** which then undergoes insertion, forming the six-membered ring **271**.



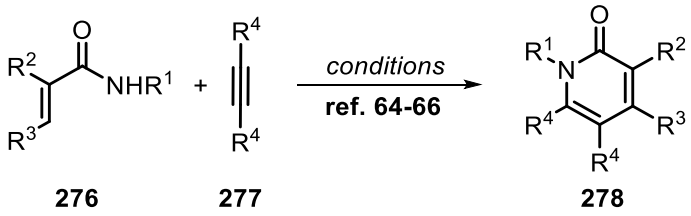
Scheme 58. Annulation of enaminone **269** with acrylate **270** under Rh^{III} catalysis.

Another catalyzed annulation with Pd^{II} was presented by Duchene *et al.*[63] who synthesized pyridinones **275** in good yields by a regio- and stereo controlled cross-coupling reaction with stannanes **274** and iodopropenamides **273** (Scheme 59).



Scheme 59. Pd^{II}-catalyzed cross-coupling reaction of stannanes **274** and iodopropenamides **273**.

A different kind of catalyzed reactions is the oxidative coupling of alkynes with acrylamides (Scheme 60). Several publications describe this transformation, mostly differing in the reaction procedure, *e.g.* the group of Song[64] reported the synthesis of substituted 2-pyridinones **278** with Rh^{III} as catalyst and $Cu(OAc)_2$ as the oxidant. Ackermann *et al.*[65] used a Ru^{III} catalyst instead, thus being able to conduct the annulation with electron-rich and electron-deficient acrylamides as well as using dialkyl substituted alkynes compared to the Song group. In contrast to this, Jiang and coworkers[66] applied $Pd(OAc)_2$ as catalyst and oxygen for the oxidative coupling, presenting an alternative synthesis under mild conditions and H_2O as the only byproduct. Other groups were also able to synthesize pyridinones through a reaction of different amides and alkynes under slightly modified conditions as shown below.[67]

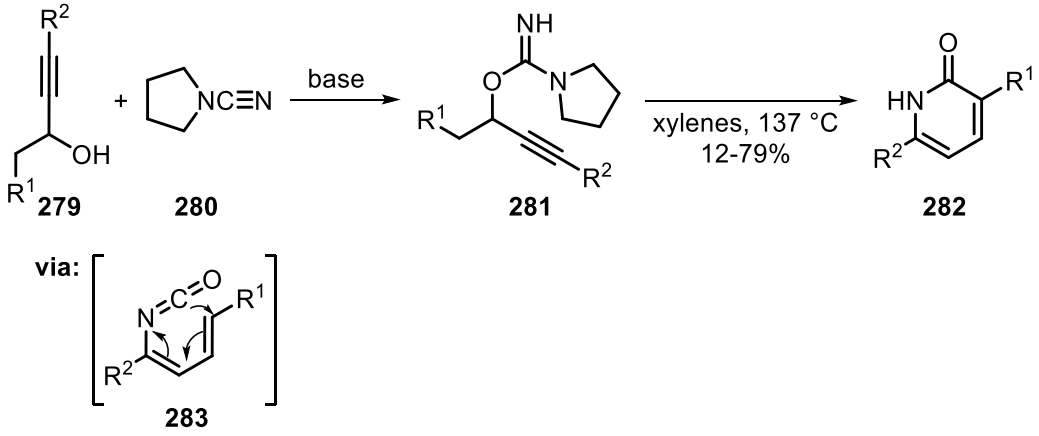


Song *et al.*[64]	**Ackermann *et al.*[65]**	**Jiang *et al.*[66]**
$[RhCp^*Cl_2]_2$, $Cu(OAc)_2$	$[RuCl_2(p\text{-cymene})]_2$, $Cu(OAc)_2 \cdot H_2O$	$Pd(OAc)_2$, $CuBr_2$, NEt_3, O_2
acetone, 100 °C	*t*-AmOH, 120 °C	AcOH/Ac_2O (1:3), 90 °C
48-94%	51-98%	67-94%

Scheme 60. Synthesis of substituted 2-pyridinones **278** by oxidative cross-coupling of amides **276** and alkynes **277**.

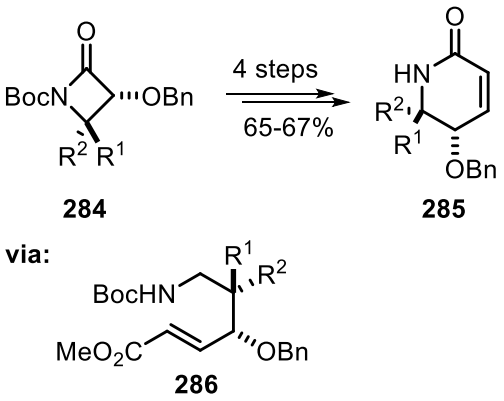
A slightly different approach was reported decades earlier by Overman *et al.*[68] who were able to form 2-pyridinones **282** by a base-catalyzed condensation of propargylic alcohols **279** and cyanopyrrolidine **280** (Scheme 61). The formation of the 6-membered ring **282** from the condensation product **281** was explained by an initial sigmatropic rearrangement

and consecutive tautomerizations as well as elimination of pyrrolidine, yielding the intermediate **283**. Latter then underwent an electrocyclic ring-closure, giving the desired product **282**.



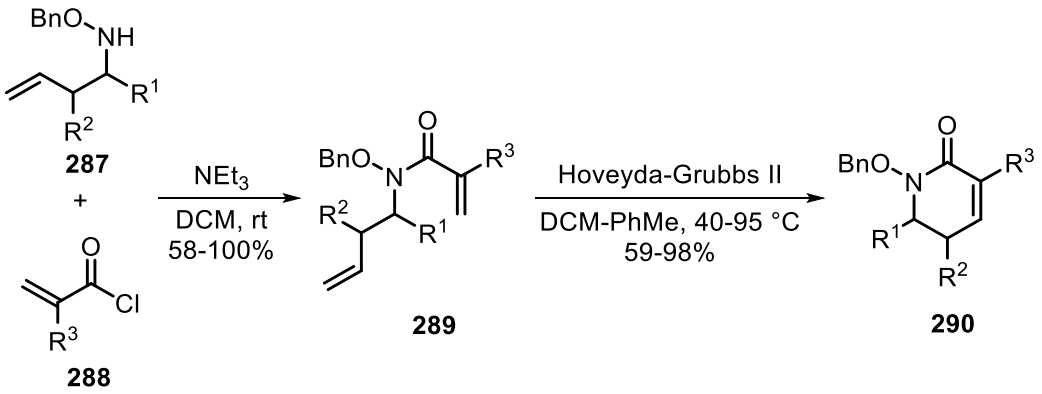
Scheme 61. Condensation between propargylic alcohols **279** and cyanopyrrolidine **280** to yield pyridinones **282** according to Overman *et al.*[68]

Another interesting approach towards the synthesis of pyridinones was presented by Lee and coworkers[69] in 2001, starting from azetidinones **284**. Reduction of the ring followed by elongation of the carbon chain gave intermediate **286** which was cyclized to the desired product (Scheme 62).



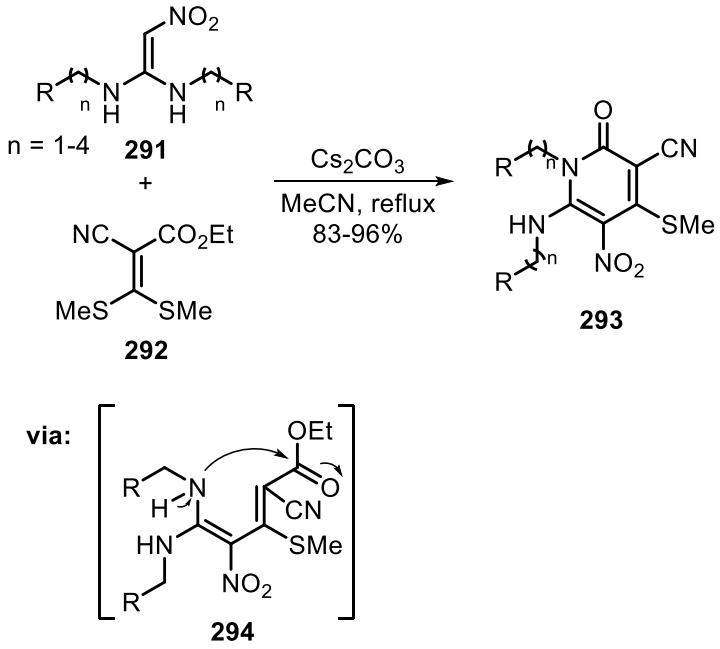
Scheme 62. Synthesis of pyridinone **285** from azetidinone **284**.

An alternative route with ring-closure metathesis (RCM) of acrylamides **289** as the key step was shown by Donohoe *et al.*[70] The starting material **289** for the RCM was easily prepared from an acid chloride **288** and an amine **287**, which then underwent RCM to form the desired 2-pyridinone **290** (Scheme 63). Because of its mild conditions, a wide range of functional groups is tolerated, thus allowing for different substituents on the 6-membered ring.



Scheme 63. RCM of acrylamide **289** for the synthesis of 2-pyridinones.

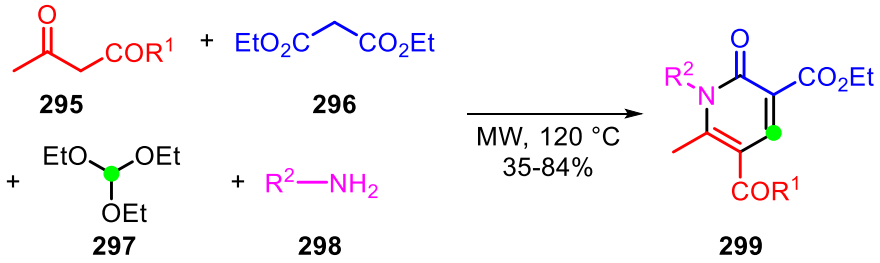
For fully substituted and arylated pyridinones the group of Yan[71] found a synthetical strategy, where the diamine **291** was reacted with compound **292** *via* a Michael addition followed by an elimination of one MeSH group and an imine-enamine tautomerization, yielding intermediate **294**. Intramolecular cyclization and EtOH elimination gave the desired product **293** (Scheme 64). Thus, different arylated substrates with potential antitumor activity were prepared.



Scheme 64. Synthesis of highly substituted 2-pyridinones **293** according to Yan *et al.*[71]

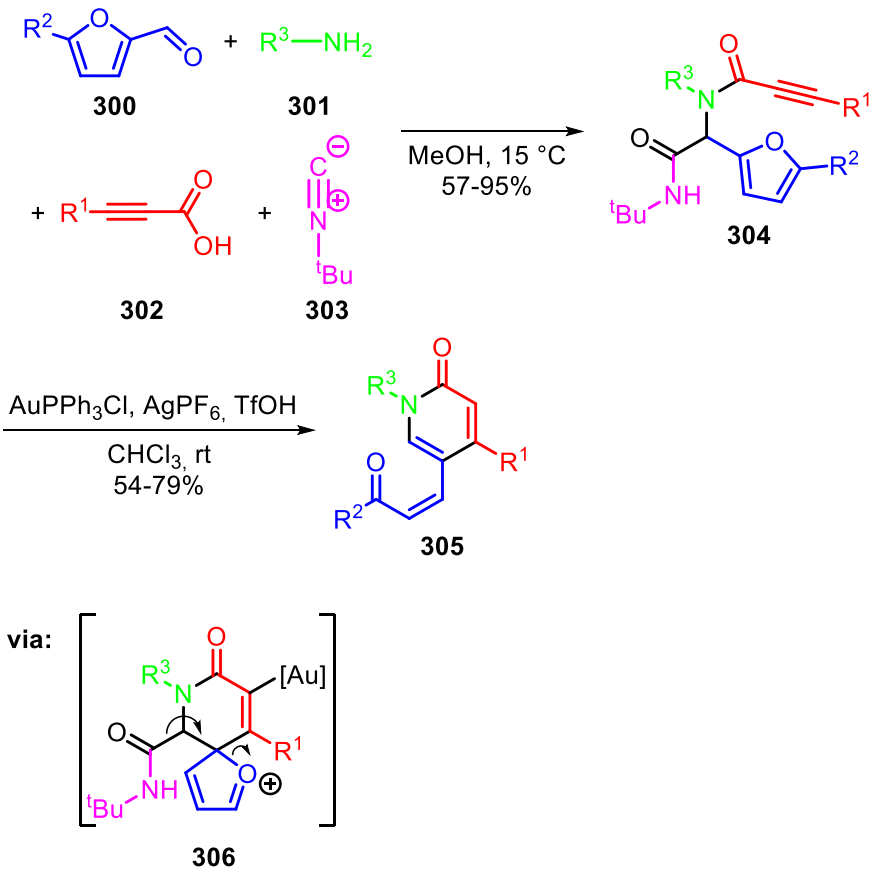
Compared to this, Chen and his group[72] also managed to prepare highly substituted pyridinones through a four component reaction of **295**, **296**, **297**, and **298** under microwave irradiation, fulfilling the concept of green chemistry. Different amines like

anilines and alkyl amines could be used and gave good to excellent yields of the corresponding product (Scheme 65).



Scheme 65. Formation of pyridinone **299** by a four-component reaction under microwave irradiation.

A last example for the pyridinone preparation in this chapter is a recent synthesis by Pereshivko and conworkers[73] who found a post-Ugi cascade transformation catalyzed by Au^{I} (Scheme 66). Therefore, the Ugi adduct **304** was synthesized in a one-pot procedure from furfural **300**, aniline **301**, propiolic acid **302** and isocyanide **303**, followed by a cyclization in presence of a gold-catalyst. Additionally, the authors found that a Brønsted acid, TfOH in this case, was necessary for the protonolysis of the formed vinyl-Au species **306** by the furane-alkyne cyclization. This intermediate then underwent a furane ring opening giving pyridinone **305** in moderate to good yields.

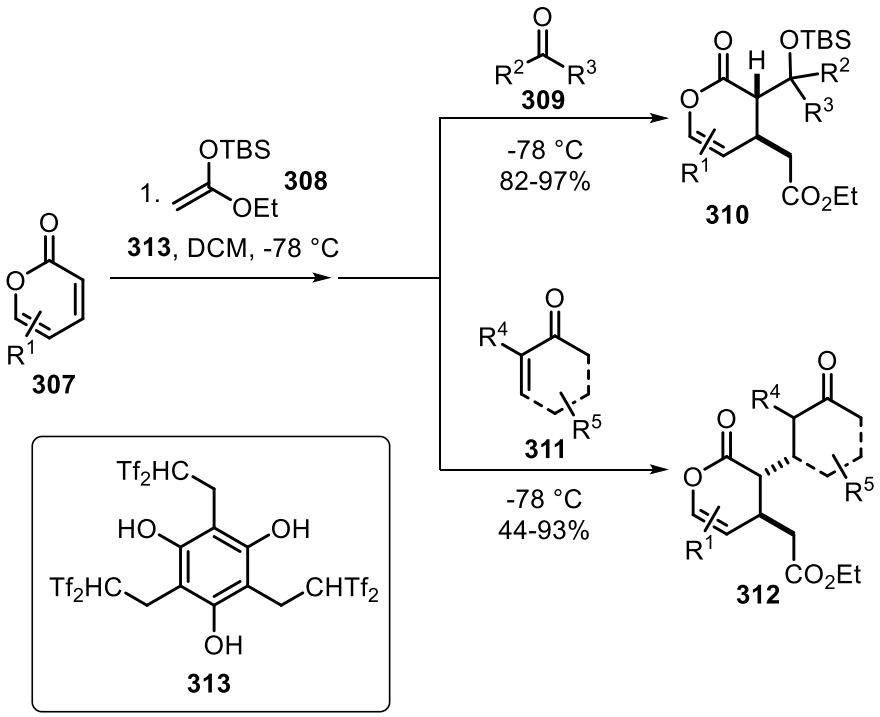


Scheme 66. 2-Pyridinone **305** synthesis by a Au^{I} catalyzed post-Ugi cascade transformation.

These examples underline the various possibilities for a 2-pyridinone synthesis with different substituents but are only a small glimpse of the possibilities. Other methods[74] differ mostly in minor variations like the use of other starting materials or reaction conditions and thus are not presented in this chapter.

1.4 Reactions of 2-pyrones

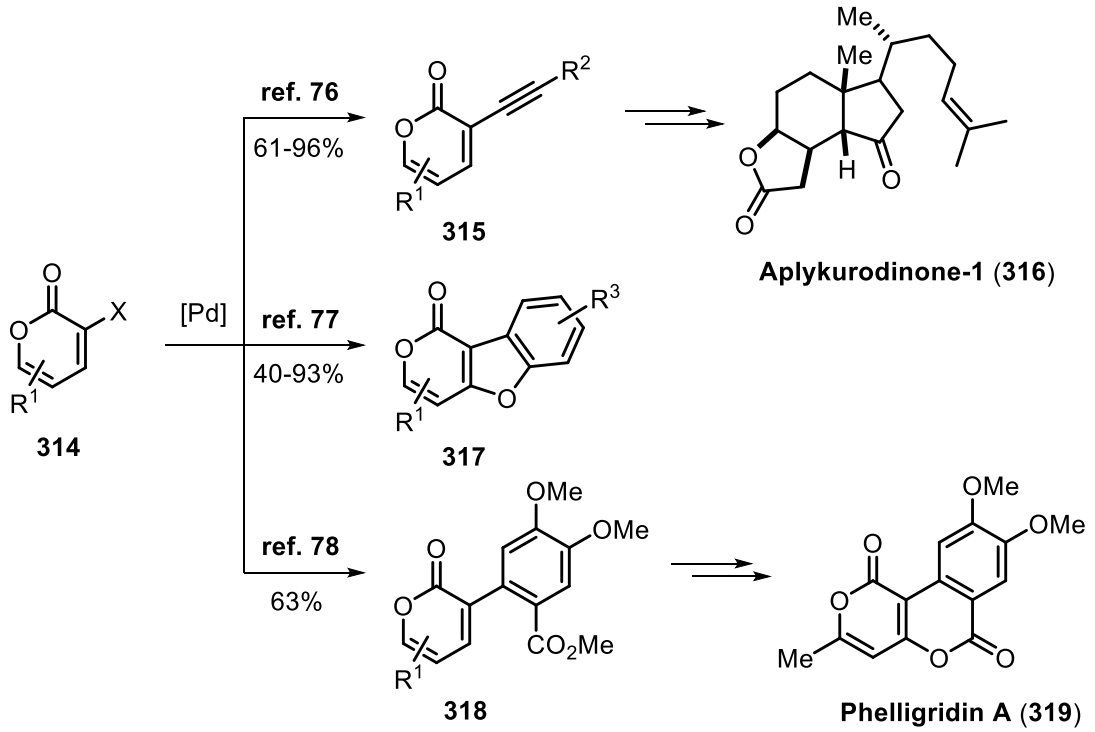
Before, in chapter B 1.2, it was shown that the 2-pyrone moiety is an important building block and several syntheses lead to this structure. In the following, a short overview of some interesting and useful transformations of 2-pyrone is presented, providing methods towards the synthesis of biologically active compounds. Due to the electronic properties of the pyrone, many different reaction types can be conducted, among others a conjugate addition. An intriguing example was shown by the group of Yanai[75] in 2016, presenting a sequential Mukaiyama-Michael reaction in the presence of a strong carbon acid **313** with perfect *anti*-selectivity of the products **310** and **312**, where ketones **309** (upper arrow), Michael acceptors **311** (lower arrow) and chromones were tolerated (Scheme 67).



Scheme 67. Sequential Mukaiyama-Michael reaction of 2-pyrone **307** with different acceptors.

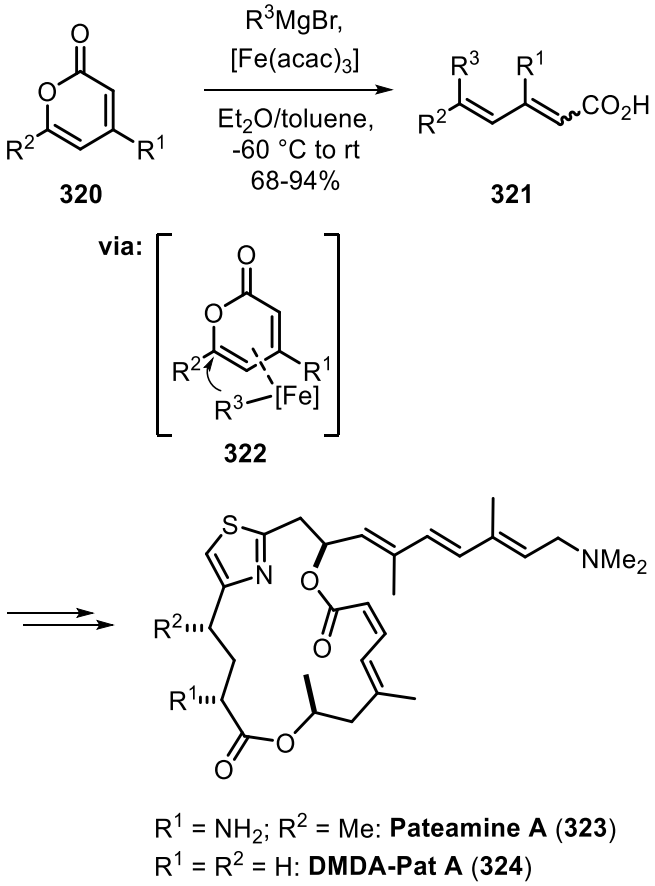
Further, coupling reactions proved to be a useful tool in the derivatization of 2-pyrones, opening a path for the synthesis of different natural products, *e.g* a Sonogashira coupling of pyrone **314** with alkynes according to Cho *et al.*[76] This led to intermediate **315**, which served as a precursor for the natural product Aplykurodinone-1 (**316**) whose analogues possess cytotoxic activity against various human cancer cells (Scheme 68 upper arrow). The key step in this reaction sequence was an *endo* selective intramolecular Diels-Alder cycloaddition. Another important transformation is the direct arylation (middle arrow)

which resulted in the tricycle **317**, an important structure due to the abundance of aryl-heteroaryl moieties in natural products.[77] Similar to this, Ohyoshi and his group[78] reported a Suzuki-Miyaura coupling of 2-pyrone **314** to form structures like **318**, which then was transformed to the natural product Phelligridin A (**319**), known for its inhibition of the cell growth of various cancer cell lines (lower arrow). It was also shown by the authors that different substituents R^1 could be installed on intermediate **318** by an aldol-type coupling, leading to analogues of the natural product **319**.



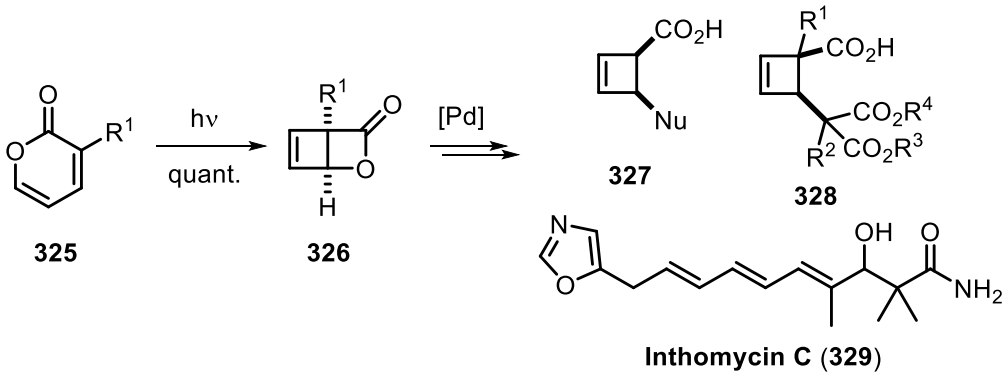
Scheme 68. Coupling reactions of 2-pyrone **314** under different conditions.

A further possible derivatization was reported by the group of Fürstner[79] during the last years by opening of the lactone ring (Scheme 69). This way, he was able to conduct a macrolactonization by an iron catalyzed ring opening/cross coupling reaction, in order to synthesize the macrolides Pateamine A (**323**) and DMDA-Pat A (**324**) which are known as anticancer agents. This reaction is realized *via* intermediate **322** where the pyrone serves as a η^4-bound diene ligand to the iron center and the nucleophile is delivered by an inner sphere mechanism.



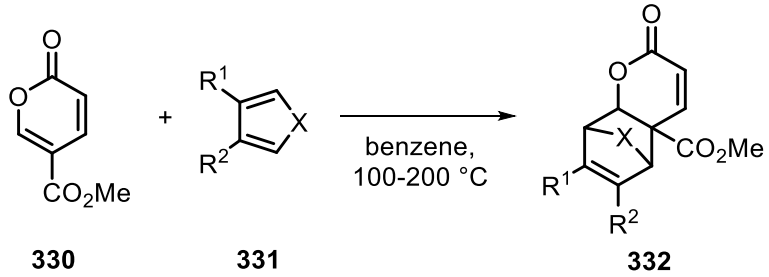
Scheme 69. Iron catalyzed ring opening/cross coupling of 2-pyrone **320** for the synthesis of macrolides **323** and **324**.

Since the pyrone moiety can act both as a diene and a dienophile, cycloadditions are an important category of transformations as well. One of the first [2+2]-photocycloadditions was reported by Corey *et al*.[80] in 1964, giving the bicycle **326** in nearly quantitative yield (Scheme 70). Latter then served as a versatile starting material for chemical derivatizations, *e.g.* for the synthesis of functionalized cyclobutanes **327** and **328** by palladium catalyzed allylic alkylation and allylation in high regio- and stereoselectivity which was widely explored by the group of Maulide[81]. Several nucleophiles like malonates, azlactones and allyl boronates were tolerated and opened a path towards the synthesis of polyene natural products like Inthomycin C (**329**) by 4π-electrocyclic ring-opening reactions of the corresponding cyclobutenes.



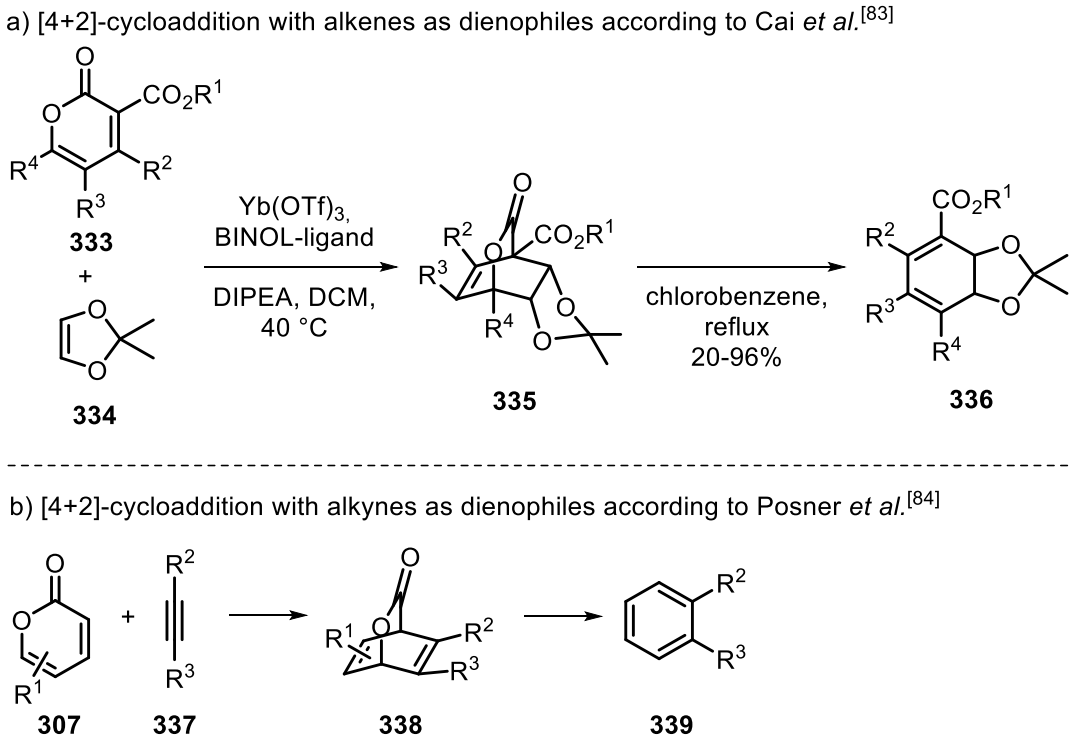
Scheme 70. [2+2]-photocycloaddition of 2-pyrone **325** and further transformation towards cyclobutenes **327** and **328** as well as Inthomycin C (**329**).

As mentioned above, the 2-pyrone structure can act as a dienophile in intermolecular cyclizations too, although not many reactions are reported so far. One of the first reactions is the cycloaddition of coumalic acid **330** with dienes **331** by Kawanisi *et al.*[82] shown in Scheme 71, where an electron-withdrawing substituent in C5 position is necessary in order to accomplish the cycloaddition.



Scheme 71. [4+2]-cycloaddition of coumalic acid **330** acting as a dienophile.

In contrast to this, more cycloaddition reactions are known with the 2-pyrone acting as the diene with alkenes and alkynes as dienophiles. One example is the recent work by Cai and coworkers[83] with compound **334** acting as dienophile to yield intermediate **335** which underwent a retro Diels-Alder reaction by extrusion of CO_2 to yield compound **336** (Scheme 72 a). In this case multi substituted pyrones were also tolerated. Regarding the use of alkynes **337** as dienophiles[84], a similar cycloadduct **338** was obtained, which readily underwent aromatization due to its highly strained core, giving aromatic compounds **339** as product (Scheme 72 b).

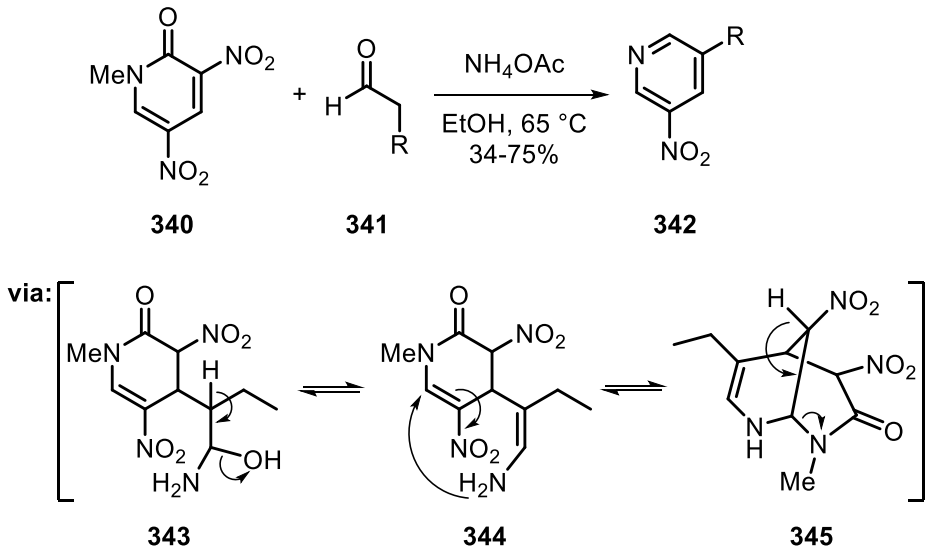


Scheme 72. [4+2]-cycloaddition of 2-pyrone with a) alkenes and b) alkynes as dienophiles.

This chapter only gave a short overview of the possible transformations of 2-pyrones since several reviews[46,47,84,85] already exist on this subject. Nevertheless, the versatility of different derivatizations on this compound is illustrated, acting as the basis for the research conducted in this thesis.

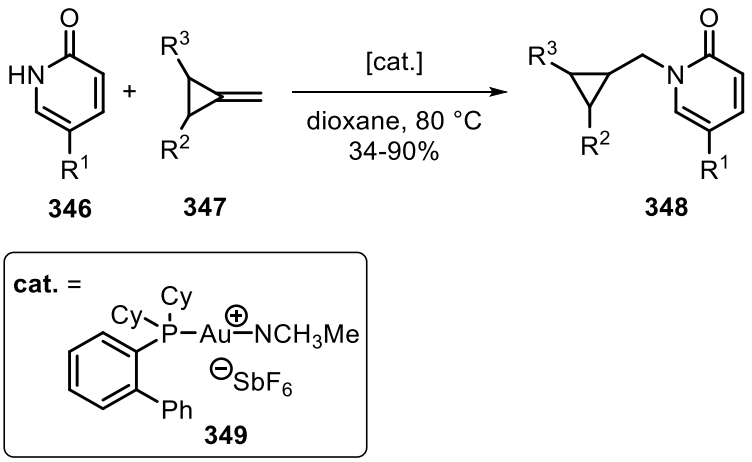
1.5 Reactions with 2-pyridinones

The 2-pyridinone moiety is an important building block for other useful and potentially biological active compounds. Several reviews[86,87] dealing with its transformation already exist and some interesting examples will be presented in this chapter. Before, in Scheme 57, it was shown that 2-pyridinone can be synthesized from pyridines by a Hilbert-Johnson reaction but this reaction is also possible the other way round, namely preparing pyridines from pyridinones by a three-component ring transformation as reported by Nishiwaki *et al.*[88] in 2015 (Scheme 73). In this case, pyridinone **340** reacted with aldehyde **341** and NH_4OAc to form intermediate **343** and then the enamine **344**. Latter undergoes nucleophilic ring closure, yielding the bicycle **345** followed by ring opening and aromatization to give 3-nitropyridine **342**, a synthetic intermediate for biologically active compounds.



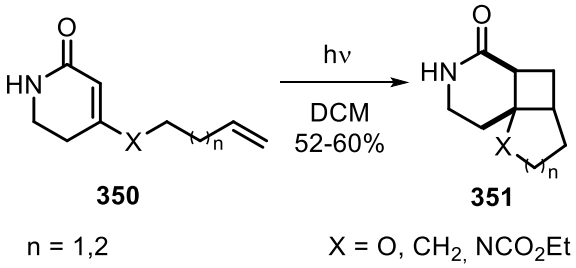
Scheme 73. 3-nitropyridine synthesis from 2-pyridinones **340** by a three-component transformation.

In the same year, a different kind of reaction was published by the group of Widehoefer[89], who reported a gold-catalyzed hydroamination of methylenecyclopropanes **347** with 2-pyridinones **346** (Scheme 74). This reaction protocol allows the preparation of *N*-alkylated pyridinones, owning biological activities, whose synthesis by different strategies is often limited.



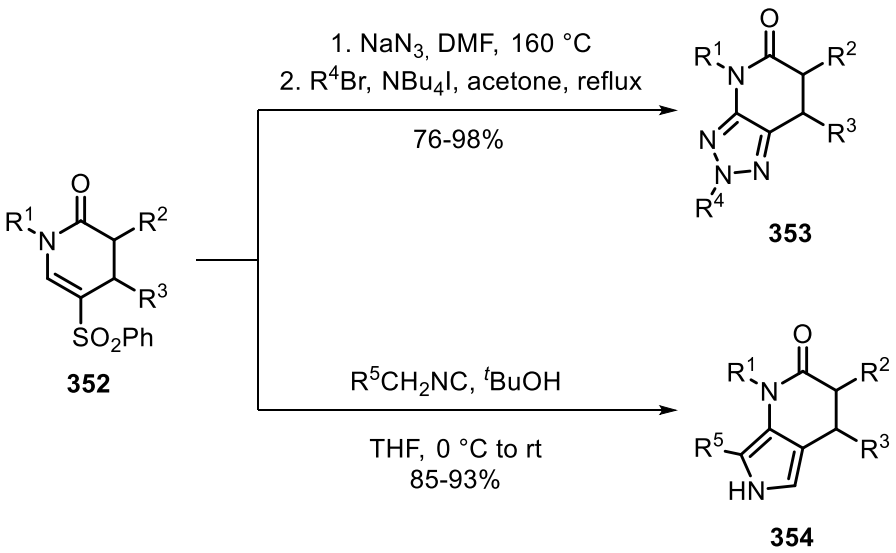
Scheme 74. *N*-alkylation of 2-pyridinones *via* gold-catalysis according to Widehoefer *et al.*[89]

Along the same lines as the previously discussed 2-pyrones, 2-pyridinones can undergo photochemical transformations, *e.g.* an intramolecular [2+2] cycloaddition, or act as a diene for other photocyclizations, *e.g* [4+2] or [4+4] cycloadditions.[90] This opens up more opportunities for the functionalization of 2-pyridinones, leading to interesting ring systems such as **351** reported by Bach *et al.*[91] (Scheme 75). Thus, an intramolecular [2+2] photocycloaddition of compound **350** led to tricyclic structures **351** which are otherwise not so easy to obtain.



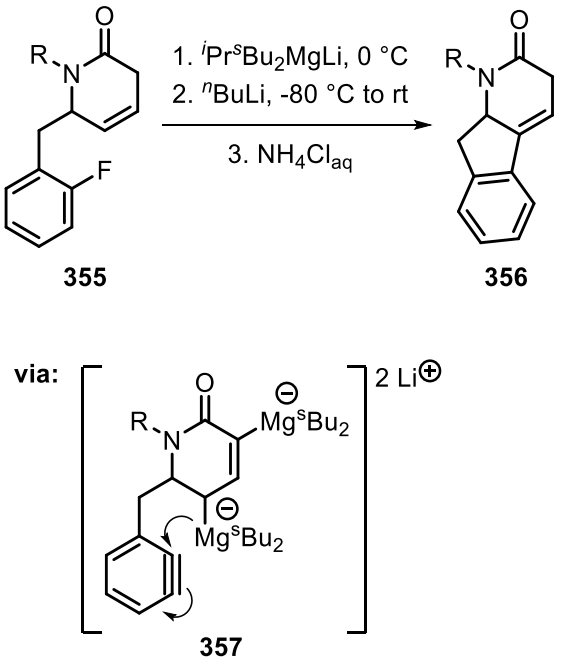
Scheme 75. Intramolecular [2+2] photocycloaddition of compound **350**.

Another kind of cycloaddition, namely a [3+2] cycloaddition was found by the group of Lam[92] in 2008 which results are shown in Scheme 76. They were able to synthesize two kinds of different structures, triazoles **353** and pyrroles **354**, either by cycloaddition with sodium azide and an alkyl bromide (upper arrow) or isocyanides (lower arrow).



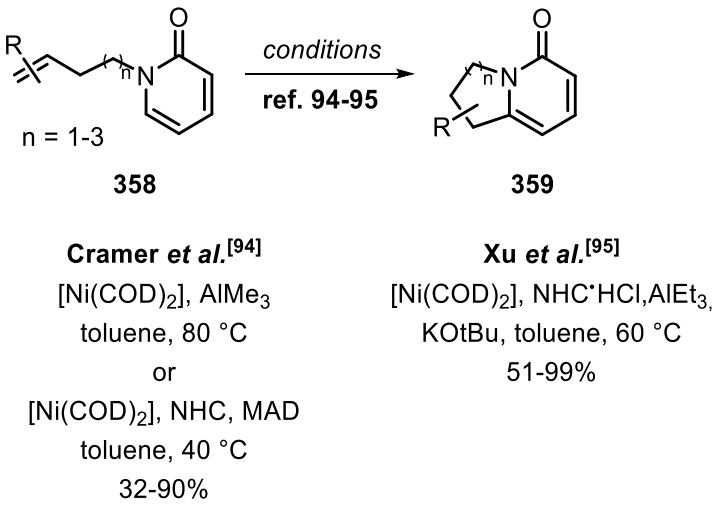
Scheme 76. [3+2] cycloaddition of pyridinone **352** with sodium azide (upper arrow) or isocyanide (lower arrow).

A method for preparation of idenopyridin-2-ones, occurring in a wide range of bioactive compounds, including anticancer agents and antispermatogenic compounds, was reported by Sośnicki and his coworkers[93]. The cyclization of starting material **355** was achieved thorough intermediate **357**, formed by deprotection with lithium magnesiate and elimination of LiF to generate the benzyne moiety **357**. This allowed then for a nucleophilic attack of the metalated lactam, forming product **356** (Scheme 77).



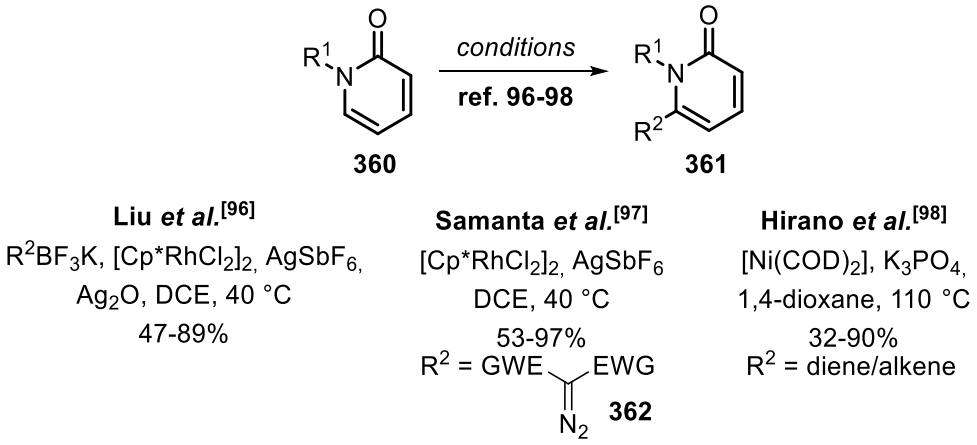
Scheme 77. Annulation of compound **355** according to Sośnicki *et al.*[93]

A different annulation type of 2-pyridinones is shown in Scheme 78. This 1,6-annulation is found in many biologically active compounds and can be achieved by CH-functionalization *via* nickel catalysis as reported by Cramer and his group[94] and lately also by Xu *et al.*[95] with slightly altered conditions. In order to induce enantioselectivity, *N*-heterocyclic carbene (NHC) ligands can be employed.



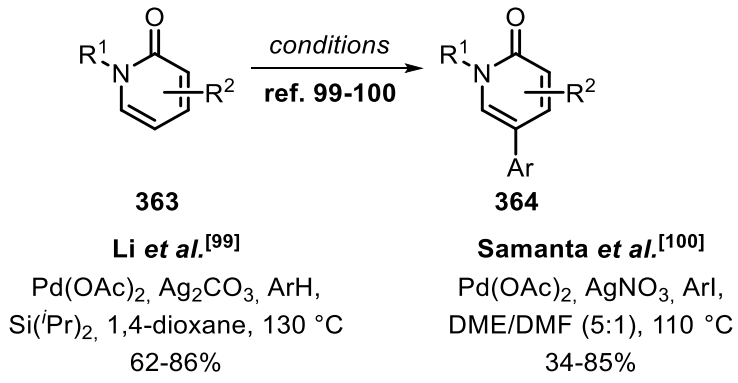
Scheme 78. 1,6-annulatio of 2-pyridinons **358** by CH-functionalization.

Further CH-functionalization focus on the C6-selective transformation, of which a large number of protocols exist in literature. A limited number is shown in Scheme 79, *e.g.* the group of Liu[96] applied organoboron reagents in combination with Rh^{III} catalysis to obtain substituted pyridinones **361** in moderate to good yields. In comparison, Samanta *et al.*[97] used diazo compounds **362**, which gave a high regioselectivity and allowed the use of a broad range of substrate scope. Contrary to this, Hirano and coworkers[98] applied $[Ni(COD)_2]$ as the catalyst for the CH activation, and different dienes and alkenes for the C6 functionalization with K_3PO_4 as accelerator for the reaction.



Scheme 79. C6-selective transformation of 2-pyridinone **361** under different conditions.

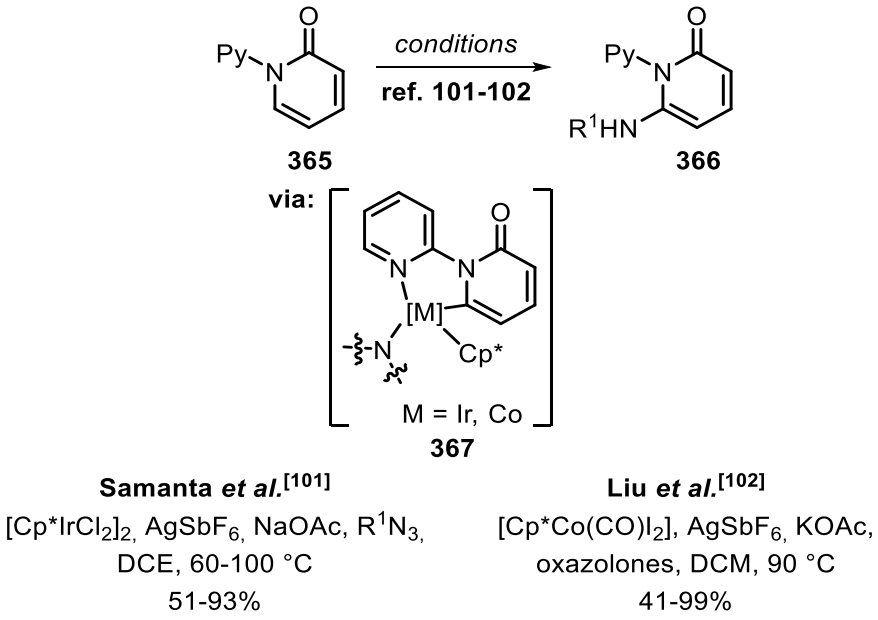
Another important transformation is the C5 arylation under Pd^{II} catalysis with ArH as substrate according to Li and his group[99] on the one hand, and on the other hand with aryl iodides according to Samanta *et al.*[100]. In both cases, moderate to good yields of the product **364** were obtained (Scheme 80).



Scheme 80. C5 arylation of 2-pyridinones under different reaction conditions.

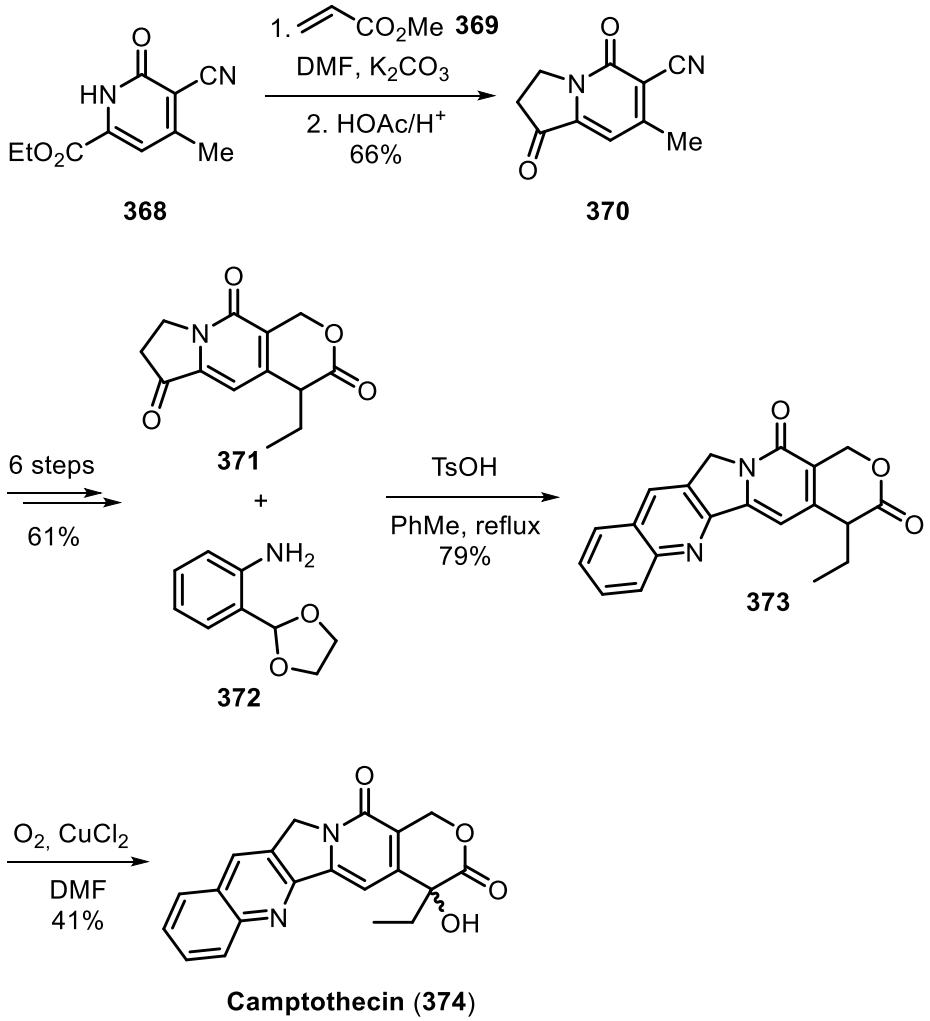
Site-selective amidation poses an additional important transformation, since nitrogen containing functional groups often play an important role during the synthesis or in the activity of biologically active compounds. Therefore, successful amidation reactions were performed on the 2-pyridinone moiety under various conditions (Scheme 81). For example, Samanta and coworkers[101] reported the formation of **366** from **365** with the help of $[Cp^*IrCl_2]_2$ and azides, which allowed the generation of a wide range of amides in excellent yields. A different method was presented by Liu *et al.*[102] who used a Co^{III} catalyst instead together with different oxazolones as the amide source. This allowed for mild conditions and a good tolerance for functional groups on the pyridinone moiety. In

both cases the amidation was accomplished by the transition state **367**, where the catalyst coordinated to the pyridine ring, resulting in the site-selective reaction.



Scheme 81. Site-selective amidation of 2-pyridinone **365** under different conditions.

A direct example for a synthesis of a naturally occurring biologically active compound starting from pyridinone is shown in Scheme 82. Camptothecin (**374**) is a pentacyclic alkaloid from the wood and bark of *Camptotheca acuminata* and displayed excellent antitumor activity in animal testing. One of the syntheses was reported by Wani and his group[103] in 1980, starting from pyridinone **368**, which was first converted to the bicyclic structure **370** followed by further transformation to yield lactone **371**. Then Friedlander condensation with toluidine **372** gave compound **373** and after oxidation Camptothecin (**374**) was obtained.



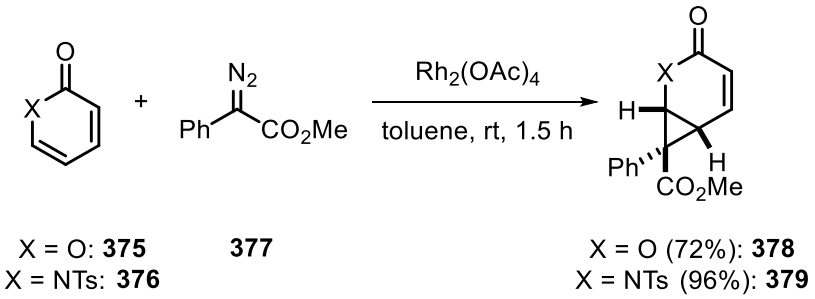
Scheme 82. Total synthesis of Camptothecin (**374**) starting from pyridinone **368**.

More transformations and synthetical strategies towards important biological molecules are summarized in several reviews as well as the synthesis of analogues of Camptothecin, since they also might possess considerable biological activity.[87,104] Based on these examples, it becomes clear that the pyridinone moiety is an important precursor for further syntheses and shows interesting chemistry, still not fully examined. This part of the thesis will therefore focus on this compound and its reactivity beside the pyrone structure.

2. Main part

2.1 Preliminary work

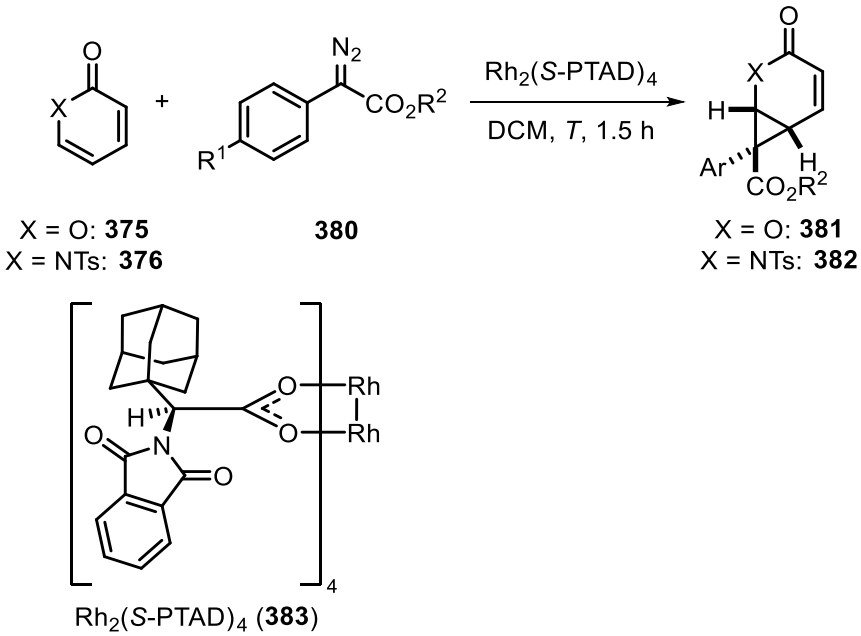
Part of this thesis is a continuation of the work by Dr. Michael Leitner, a member of this working group. He was able to successfully cyclopropanate 2-pyrone **375** and 2-pyridinone **376** with diazo ester **377** in the presence of $Rh_2(OAc)_4$ as the best catalyst (Scheme 83).



Scheme 83. Cyclopropanation of 2-pyrone and 2-pyridinone with diazo ester **377**.

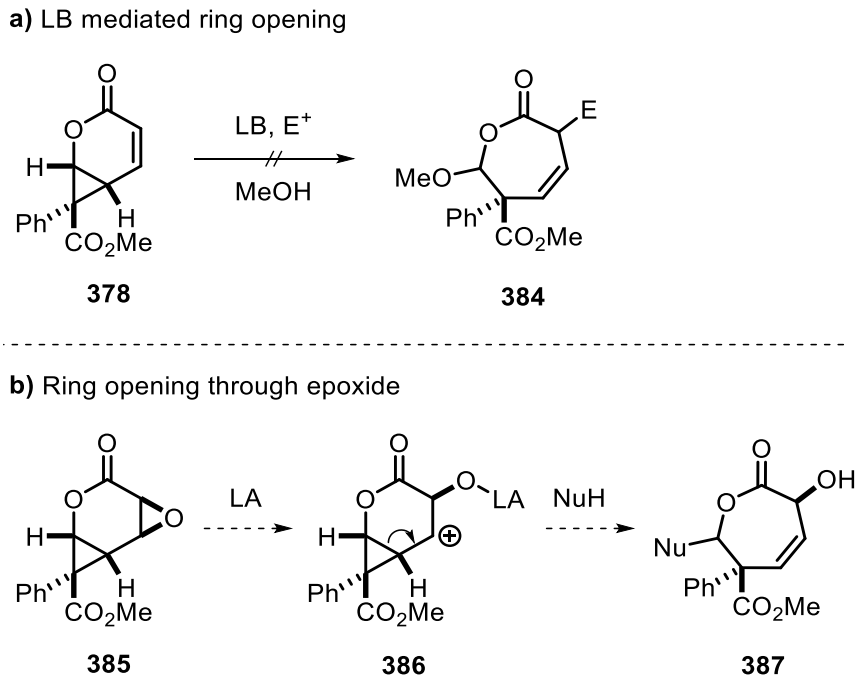
Further, the enantioselective cyclopropanation was accomplished with Rh_2(*S*-PTAD)$_4$ (**383**) as catalyst and gave the products **381** and **382** in excellent yields and *ee* values as shown in Table 14. In addition, different substituents on the diazo ester **380** were as well tolerated (entries 2 and 3).

Table 14. Enantioselective cyclopropanation with Rh_4(*S*-PTAD)$_4$.



entry	X	R^1	R^2	T [° C]	yield [%]	*ee* [%]
1	O	H	Me	rt	94	87
2	O	Br	CH_2CCl_3	0	98	93
3	NTs	Br	CH_2CCl_3	0	99	95

Moreover, he started to examine the reactivity of the cyclopropanated compounds, especially the ring opening of the cyclopropane moiety, in order to obtain a seven-membered ring. Although neither the Lewis base (LB) mediated *endo* cyclic ring opening (Scheme 84 a) nor the path through an epoxide **385** (Scheme 84 b) were successful. In the upper case a), DABCO and Bu_3Ph were used as LB with or without benzaldehyde as electrophile but just decomposition of the pyrone **378** occurred. In case of b), the epoxidation of pyrone **378** in order to obtain epoxide **385** was not possible – as discussed more in detail in chapter B 2.7, Table 32 – , thus not allowing for the proposed reaction path.

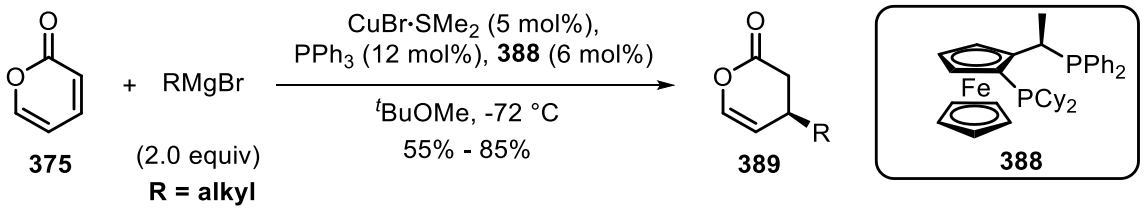


Scheme 84. *Endo*-cyclic ring opening of pyrone **378** a) with the help of a LB or b) through the epoxide **385**.

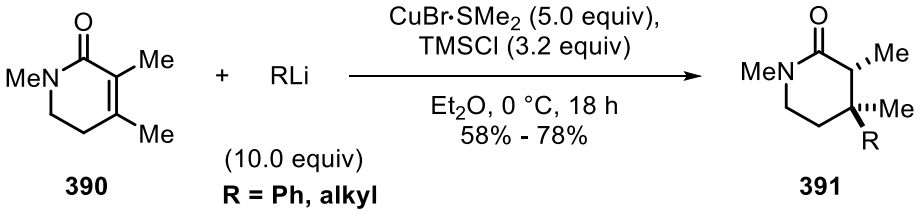
2.2 Grignard additions

Continuing Dr. Michael Leitner's work in our research group of exploring the reactivity of cyclopropanated pyrones and pyridinones, the investigation started with Grignard reactions. According to literature, most of the additions involving enones were performed using a copper salt with different additives which are suited for 1,4-additions to α-,β-unsaturated carbonyls, *e.g.* PPh_3 and ligand **388** (Scheme 85 a) by Feringa and his group[105] or TMSCl (Scheme 85 b) as reported by Perrio *et al.*[106]

a) Grignard addition by Feringa *et al.*[105]



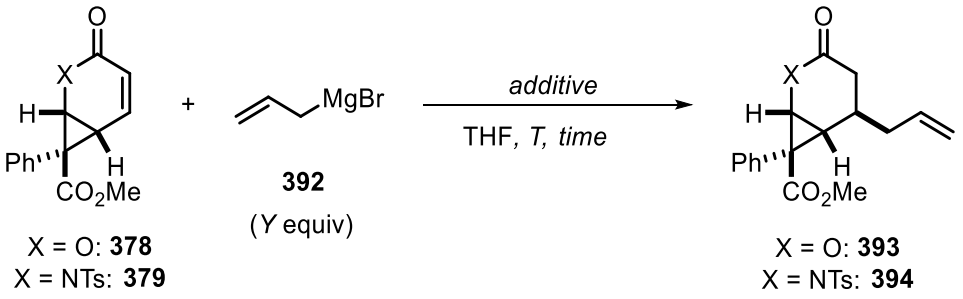
b) Grignard addition by Perrio *et al.*[106]



Scheme 85. Reported Grignard additions by a) Feringa *et al.*[105] and b) Perrio *et al.*[106]

The outcome of applying various conditions for the reaction of pyrone **378** or pyridinone **379** with vinyl magnesium bromide is shown in Table 15.

Table 15. Grignard addition under different conditions.



X = O: **378**
X = NTs: **379**

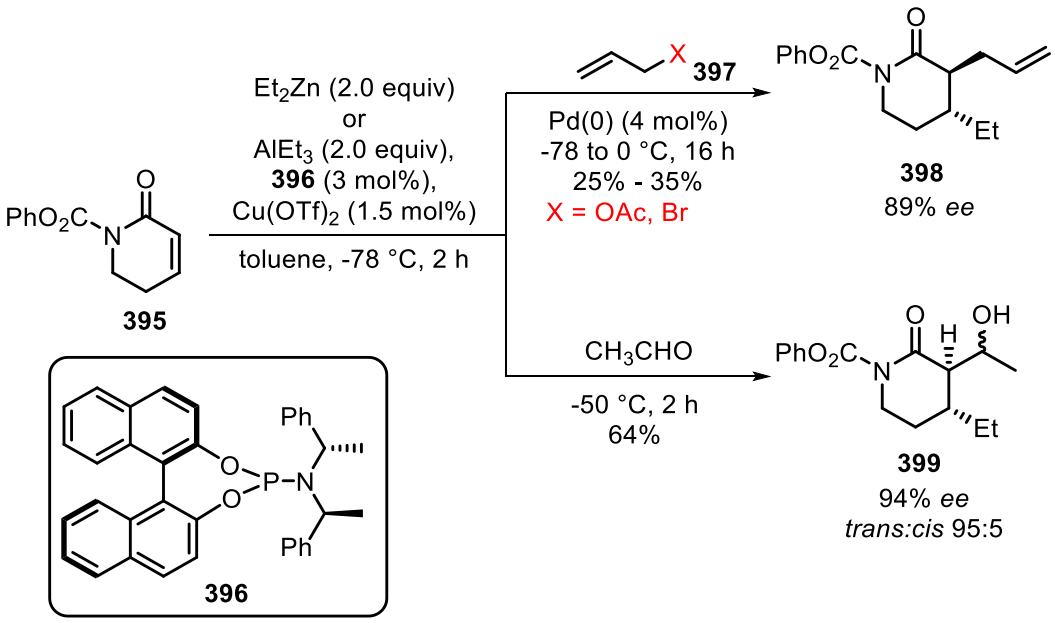
X = O: **393**
X = NTs: **394**

entry	X	Y	additive	T [°C]	time [h]	result
1[a)]	**NTs**	2.0	CuBr·SMe_2 (5 mol%), PPh_3 (12 mol%)	-78 to 25	15	n.r.
2[b)]	**NTs**	2.0	CuBr·SMe_2 (1.0 equiv), TMSCl (1.0 equiv)	-78 to 0	3	n.r.
3	**NTs**	3.0	LiCl (6.0 equiv), CuCN (3.0 equiv)	-78 to 25	19	n.r.
4	**NTs**	2.0	none	-78 to 25	19	crm
5[a)]	**O**	2.0	CuBr·SMe_2 (5 mol%), PPh_3 (12 mol%)	-78 to 25	18	n.r.
6[b)]	**O**	2.0	CuBr·SMe_2 (1.0 equiv), TMSCl (1.0 equiv)	-78 to 0	2	crm
7	**O**	3.3	LiCl (6.5 equiv), CuCN (3.3 equiv)	-78	1.5	crm
8	**O**	2.0	CuI (1.0 equiv)	-78 to 25	5	n.r.

a) ^{t}BuOMe was used as a solvent. b) Et_2O/THF was used as a solvent.

From entries 1 to 4, pyridinone **379** was used as test substrate and in the remaining entries pyrone **378**. At first, CuBr·SMe_2 with PPh_3 was applied in catalytical amounts (entry 1) but resulted in no reaction of the starting material. Changing to TMSCl as an additive (entry 2) did not change the outcome. Therefore, another copper source, CuCN/LiCl, was applied (entry 3) but this also did not give any reaction. Then it was decided to try reacting the Grignard reagent directly with pyridinone **379**, which gave a complex reaction mixture based on the higher reactivity of the metal organyl (entry 4). These reactions were then performed with pyrone **378** in a similar manner but with slightly different outcomes. In entries 5 and 6, again CuBr·SMe_2 was applied. In the case of PPh_3 as an additive (entry

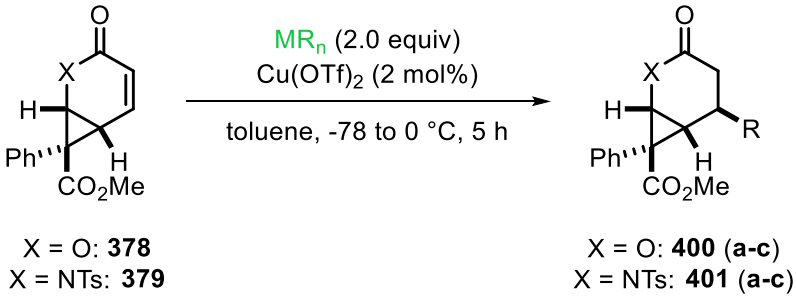
5) no reaction was observed, but with TMSCl (entry 6) a complex reaction mixture was obtained. The same result was seen with CuCN/LiCl (entry 7) which may indicate that the nucleophile was too reactive for the pyrone. When only CuI was used (entry 8), no reaction was observed. Based on these results, it became clear that the traditional 1,4-Grignard addition with vinyl magnesium bromide was not as straightforward as assumed. Organomagnesium compounds were too reactive and copper nucleophiles seemed to be not reactive enough. Therefore, an intermediate reactivity was needed, which led to the idea of applying zinc or aluminum compounds as reported by Pineschi *et al.*[107] (Scheme 86). They described the enantioselective 1,4-addition of aluminum or zinc nucleophiles under copper catalysis to pyridinone **395** which would react further with an aldehyde (lower arrow) or allylbromide **397** under palladium catalysis (upper arrow) to give products **399** and **398**. In order to obtain enantioselective products, he also used a chiral ligand **396** which should not be necessary in the reaction with compounds **378** and **379**, since the cyclopropane ring already determines the stereoselectivity.



Scheme 86. 1,4-addition of aluminum and zinc nucleophiles with pyridinone and further reactions to products **398** or **399**.

Table 16 shows the different test reactions with pyridinone **379** and pyrone **378**.

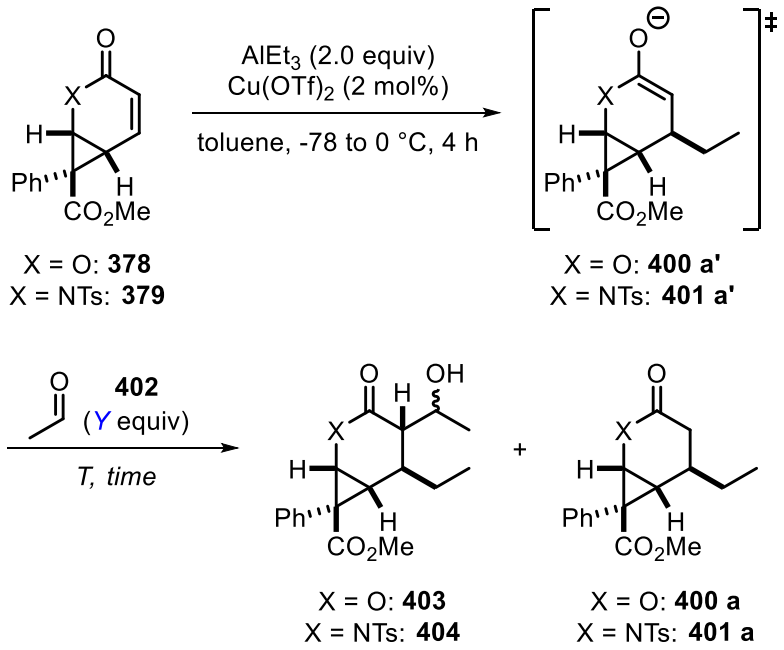
Table 16. Test reactions of pyridinone **379** and pyrone **378** with organozinc and organoaluminum compounds.



entry	X	MR_n	R	results
1	**NTs**	$AlEt_3$	Et (**401 a**)	95%
2	**NTs**	$ZnMe_2$	Me (**401 b**)	n.r.
3	**NTs**	$ZnPh_2$	Ph (**401 c**)	n.r.
4	**O**	$AlEt_3$	Et (**400 a**)	57%
5	**O**	$ZnMe_2$	Me (**400 b**)	n.r.
6	**O**	$ZnPh_2$	Ph (**400 c**)	n.r.

This time, the reactivity of $AlEt_3$ with pyridinone (entry 1) seemed to be suitable and gave the desired product **401 a** in 95% yield as one diastereomer due to the cyclopropane ring. With pyrone, the 1,4-addition also proceeded well and gave the product **400 a** in 57% yield (entry 4). In the case of zinc nucleophiles which were described by Pineschi and coworkers[107] to not make a significant difference in the yield compared to aluminum nucleophiles, neither with pyridinone substrate (entries 2 and 3) nor with pyrone substrate (entries 5 and 6) product formation was observed. Additionally, it was tested whether a consecutive reaction with an aldehyde was possible. The results are summarized in Table 17.

Table 17. 1,4-addition with $AlEt_3$ and consecutive reaction with an aldehyde.



entry	X	Y	T [°C]	time [h]	results[b)]
1	**NTs**	2.0	-78 to 0	2 h	**404** (20%), d.r. 1:3:5.6 + **401 a** (65%)
2[a)]	**NTs**	2.0	-78 to 25	23 h	**404** (42%), d.r. 1:1.4 + **401 a** (36%)
3[a)]	**NTs**	6.0	-78 to 25	24 h	**404** (37%), d.r. 1:1.4 + **401 a** (39%)
4[a)]	**O**	2.0	-78 to 0	6 h	**403** (traces) + **400 a** (53%)
5[a)]	**O**	6.0	-78 to 25	24 h	**403** (31%), d.r. 1:4 + **400 a** (36%)

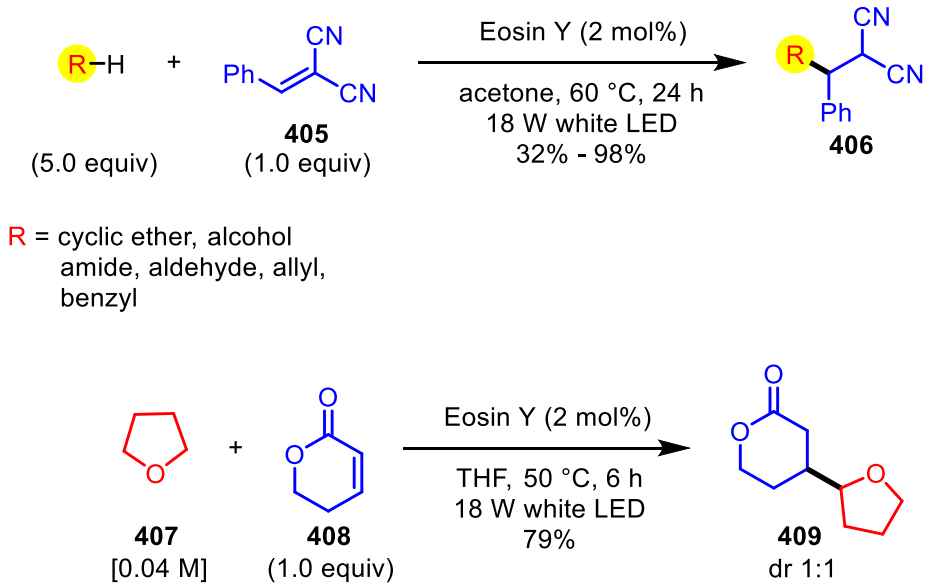
a) Aldehyde **402** was added in portions over 35 min.; b) D.r. was determined from ^{1}H-NMR spectra.

In entry 1, pyridinone **379** was reacted with $AlEt_3$ followed by the addition of acetaldehyde (**402**) after the starting material was completely consumed. The desired alcohol **404** was obtained in 20% yield and the 1,4-adduct **401 a** was isolated in 65%. The attempt to raise the yield of the alcohol started with the slower addition of the aldehyde in entry 2, which was successful and gave the product in 42% yield. Adding more equivalents of the aldehyde (entry 3) did not change the yield. In the case of pyrone **378**, when only two equivalents of the aldehyde were used (entry 4), traces of the product **403** were observed. In contrast, by using more equivalents (entry 5), the yield was raised to 31%. In all cases a good amount of the 1,4-adduct **400 a** was still isolated, which did not react further to the alcohol. More investigations might be useful for this reaction type, *e.g.* whether other organoaluminum compounds might also work or the reaction with different

aldehydes to give a larger substrate scope, but were not further pursued during this work, since other reaction types were thought to give more desirable results.

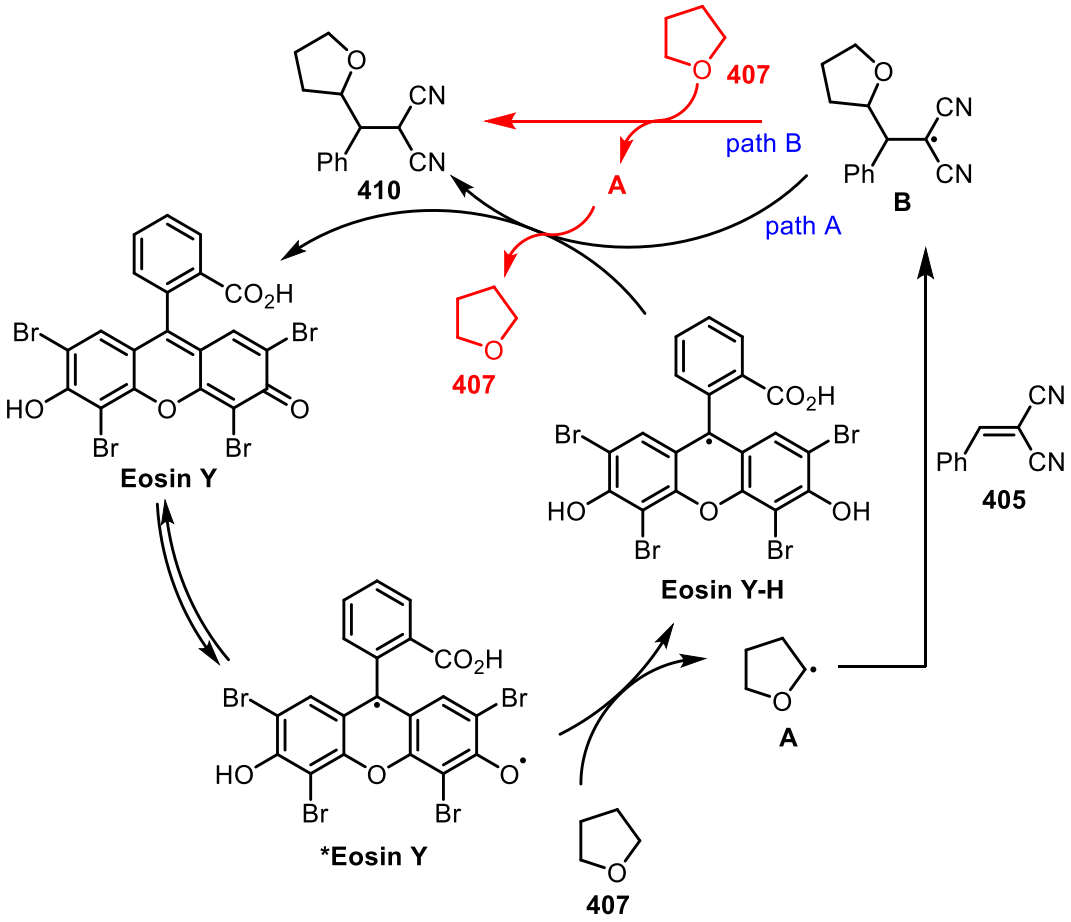
2.3 CH-activation

The next reaction type was inspired by the work of Wu *et al.*[108] In 2018 they reported a CH-activation with consecutive radical addition to an activated double bond, photocatalyzed by Eosin Y (Scheme 87). This kind of conversion sparked interest because of a reaction between pyrone **408** and THF (**407**), which would open a number of functionalization possibilities in the 1,4-position of the cyclopropanated substrates described in this work. Due to the fact, that the Grignard addition was limited – as shown above – this CH-activation would provide an alternative route for similar products.



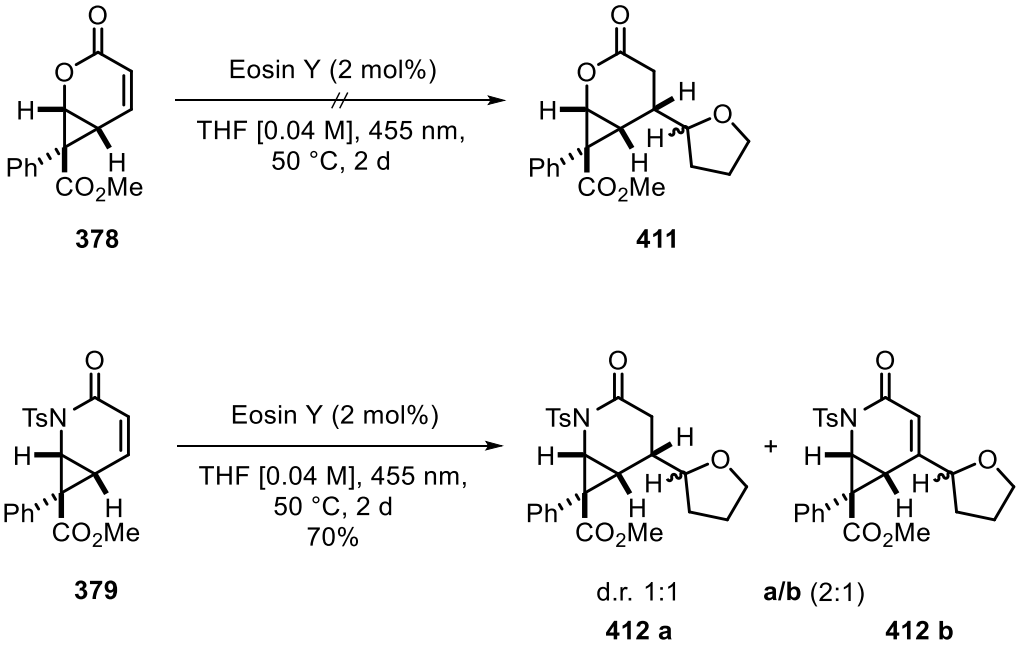
Scheme 87. CH-bond functionalization under Eosin Y catalysis described by Wu *et al.*[108]

The mechanism for this reaction is shown in Scheme 88. As proposed by the authors, after the excitation of Eosin Y by light from a white LED, a hydrogen radical is abstracted from the substrate **407**, giving rise to the corresponding radical **A**. This radical can then undergo addition to a double bond (**405**), which results in radical **B**. For the closure of the catalytic cycle, the authors propose two paths: Either radical **B** abstracts a hydrogen radical from the catalyst **Eosin Y-H** (path A) or radical **B** abstracts a hydrogen radical from the substrate **407**, which results in radical **A**, and this radical **A** then abstracts a hydrogen radical from **Eosin Y-H** (path B).



Scheme 88. Catalytic cycle for the CH-bond activation proposed by Wu *et al.*[108]

When these reaction conditions were applied to pyrone **378** and pyridinone **379**, an interesting outcome was observed. In the case of pyrone **378** with THF no reaction occurred at all (Scheme 89 upper part), even though in the literature procedure it worked pretty well with the non-cyclopropanated pyrone (see Scheme 87). In contrast to this, switching to pyridinone **379** gave the product **412 a** in 70% as well as a byproduct **412 b** in a ratio of **a**/**b** 2:1 (Scheme 89 lower part). The formation of byproduct **412 b** implies a reductive or an additional pathway during the reaction, closing the catalytic cycle, which was not observed by the group of Wu.



Scheme 89. CH-bond activation of THF and reaction with pyrone **378** (upper image) and pyridinone **379** (lower image).

Figure 10 shows the X-ray structure of product **412 a**.

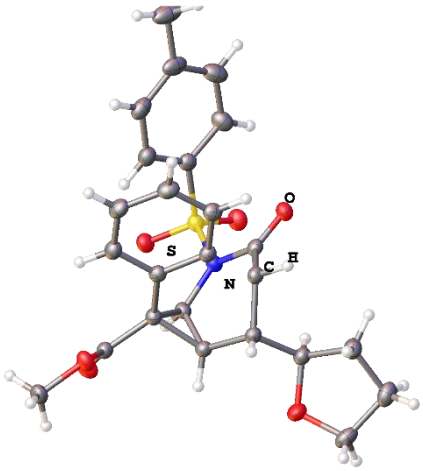
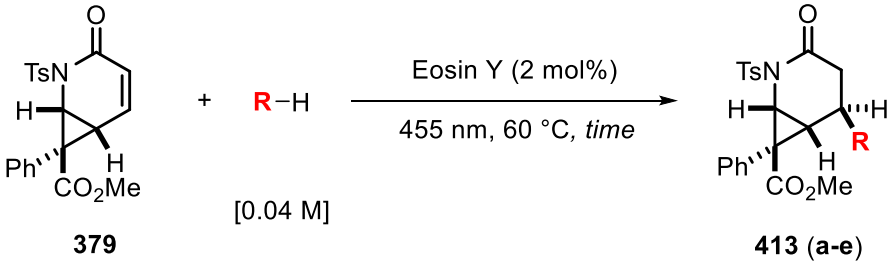


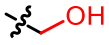
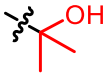
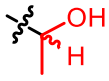
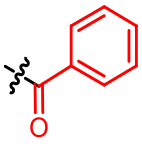
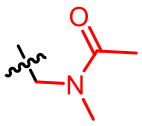
Figure 10. X-ray structure of product **412 a**.

Motivated by the promising result with pyridinone **379**, it was decided to screen different substrates in order to obtain more interesting products. Table 18 summarizes the results.

Table 18. Screening of different substrates for CH-bond activation with pyridinone **379**.



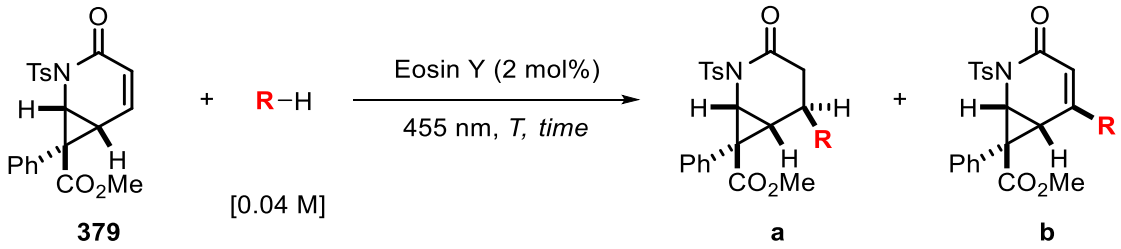
379 **413 (a-e)**

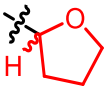
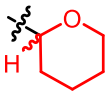
entry	R-H	time	-R	results
1[a)]	MeOH	19 h	 (**413 a**)	n.r.
2	MeOH	5 d		n.r.
3	^{i}PrOH	4 d	 (**413 b**)	traces
4	EtOH	3 d	 (**413 c**)	traces
5[a)]	benzaldehyde	19 h	 (**413 d**)	n.r.
6	benzaldehyde	4 d		n.r.
7[a)]	DMAC	16 h	 (**413 e**)	n.r.
8	DMAC	4 d		n.r.

a) R-H (5.0 equiv), acetone as solvent.

In entry 1, CH-activation of MeOH was attempted by using 5 equivalents of methanol in acetone as a solvent, according to the reaction protocol by Wu *et al.*[108] When no reaction was observed, it was decided to use pure methanol as a solvent (entry 2) but this was unsuccessful. Switching to isopropanol and ethanol as alcohol component (entries 3 and 4 respectively) did not yield the desired product. Assuming that the problem might be the alcohol, benzaldehyde and DMAC were tested. However, neither the reaction in acetone (entries 5 and 7) nor the solvent-free reactions (entries 6 and 8) led to the desired products. Therefore, it was decided to try a substrate similar to THF, namely THP, to see if the reaction might be limited to a certain substrate type (Table 19).

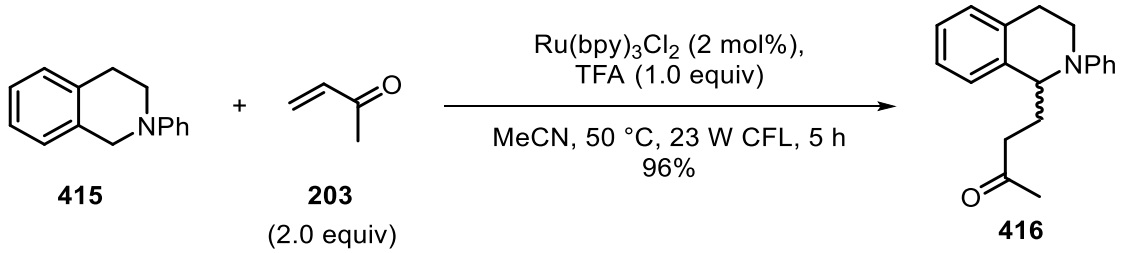
Table 19. Comparison of THF and THP of CH-bond activation.



entry	R-H	T [°C]	time	–R	results
1	THF (anh.)		27 h		36% (**a/b** 1:1), d.r. 1:1
2	THF (non anh.)	50	2 d	 (**412**)	70% (**a/b** 2:1), d.r. 1:1
3[a)]	THP		19 h		n.r.
4	THP	60	5 d	 (**414**)	52% (**a/b** 1.4:1), d.r. 1:1

a) THP (5.0 equiv), acetone as solvent. Only anh. THP available.

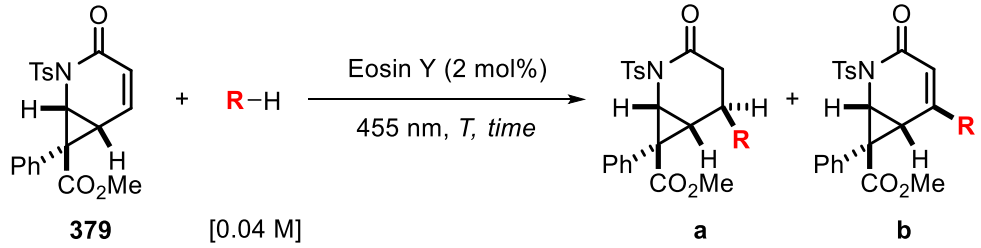
Entries 1 and 2 again show the reaction with THF and in entries 3 and 4 the reaction with THP is shown. Interestingly, when THP was used in acetone as a solvent (entry 3), no reaction occurred. Compared to when pure THP was used as a solvent (entry 4) and the product **414 a** as well as byproduct **414 b** were obtained in 52% combined yield. From this it can be concluded that the substrate has to be used as a solvent, otherwise the reaction will not work. Another thing which was found out by mistake was, that it made a difference whether anhydrous or wet solvent was used. In the case of THF, when anhydrous THF was applied in entry 1, the yield of **412 a** and **412 b** dropped to 36% compared to the wet THF with a yield of 70% (entry 2). Also, the ratio of product **412 a** and byproduct **412 b** became worse for the anhydrous reaction. Therefore, suitable reaction conditions were examined in the next step. On the one hand the focus laid on the amount of water, required in the reaction medium and, on the other hand, whether acid presence would affect the reaction outcome, since it was reported by Yoon *et al.*[109] in 2013 that the addition of TFA to a CH-bond activation reaction was beneficial. Even though their reaction conditions differed with respect to the catalyst, as $Ru(bpy)_3Cl_2$ was used, the principle of the mechanism remained similar (Scheme 90).

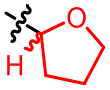
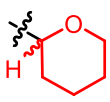


Scheme 90. CH-bond activation with $Ru(bpy)_3Cl_2$ as a catalyst and TFA as an additive reported by Yoon *et al.*[109]

The results of this investigation are shown in Table 20.

Table 20. Investigation on reaction conditions with water and TFA as additives.



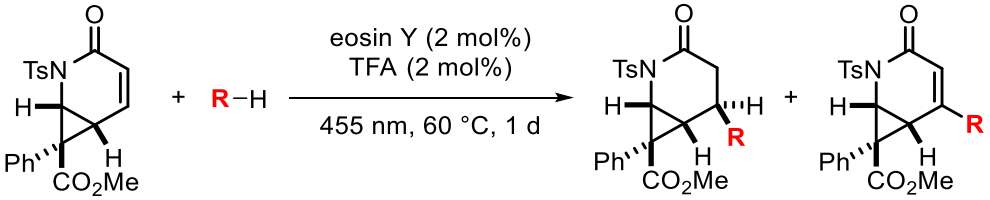
entry	R-H	additive	T [°C]	time	-§-R	results
1	THF	H_2O (0.4 v%)		3 d		70% (**a**/**b** 1:1.1), d.r. 1:1
2	THF	H_2O (1 v%)		4 d		61% (**a**/**b** 1:1), d.r. 1:1
3	THF	TFA (2 mol%)	50	18 h	(**412**)	90% (**a**/**b** 2:1), d.r. 1:1.3
4[a)]	THF	TFA (2 mol%)		18 h		13% (**a**/**b** 1:1), d.r. 1:1
5	THP	H_2O (0.2 v%)	60	1 d	 (**414**)	59% (**a**/**b** 9.4:1), d.r. 1:1

6	THP	H_2O (0.4 v%)	3 d	25% (**a/b** 1:1), d.r. 1:1
7	THP	H_2O (1 v%)	4 d	38% (**a/b** 1:1), d.r. 1:1

a) Wet THF was used.

From entries 1 to 4, the reaction was performed with anhydrous THF and it was shown that 0.4 v% of water was ideal, giving the products **412 a** and **412 b** in 70% yield (entry 1). More water (1 v% in entry 2) reduced the yield to 61%. In the case of THP, even 0.2 v% of water was enough to give the best yield of 59% and the best product **414 a** to byproduct **414 b** ratio of 9.4:1 (entry 5). Adding more water to the reaction mixture, namely 0.4 v% and 1 v% in entries 6 and 7 respectively, led to a decrease in yield to 25% and 38% correspondingly. Furthermore, the yield was again increased with 1 v% water (entry 7), although still lower compared to entry 5. Then the impact of the presence of TFA was examined, but only for the reaction with THF. To our delight the yield of **412 a** and **412 b** could be improved to 90% with just 2 mol% of TFA, while simultaneously the reaction time was decreased to 18 h (entry 3), compared to 3 days or 4 days (entries 1 and 2 respectively) without acid. Entry 4 was a control experiment to examine, whether TFA in the presence of small amounts of water would also give a good outcome by using wet THF, but in this case the yield was very low (13%) after 18 h. For this reason, it was decided, that the best reaction conditions would be in an anhydrous medium with 2 mol% of TFA as an additive. With this knowledge in hand, the investigation moved on to different substrates which might give interesting products for further transformations (Table 21).

Table 21. Substrate scope for CH-bond activation reaction.

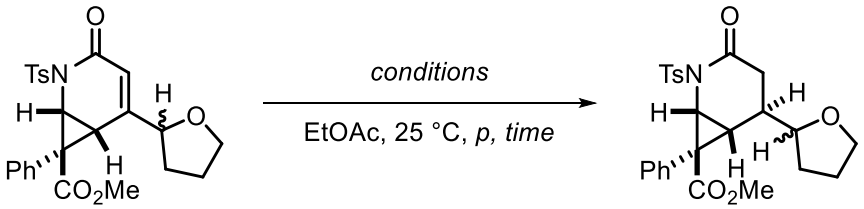


379 [0.04 M] **417-419 a** **417-419 b**

entry	R-H	-R	results
1	(**420**)	(**417**)	21% (**a**/**b** 3:1)
2	(**421**)	(**418**)	traces
3	(**422**)	(**419**)	traces

The reaction with acetal **420** gave the desired product in 21% and a ratio of product **417 a** and byproduct **417 b** of 3:1 (entry 1). For the reactions with lactone **421** and lactam **422**, only traces of product formation were observed and mainly the starting material **379** was reisolated (entries 2 and 3). Based on these results, it was concluded that this reaction is limited to THF and substrates with similar electronic properties, at least for the applied reaction conditions. Still, one last thing was examined, particularly whether it was possible to hydrogenate the byproduct **412 b** to obtain just product **412 a** instead of an inseparable mixture. The attempts are summarized in Table 22. It was impossible to reduce the double bond, neither with palladium nor with rhodium on charcoal as catalyst (entries 1 and 2 respectively). Probably the sterical hindrance of the double bond is too high for the hydrogenation reaction with the cyclopropane ring shielding it from one side and the THF moiety from the other.

Table 22. Hydrogenation reactions of byproduct **412 b**.



412 b **412 a**

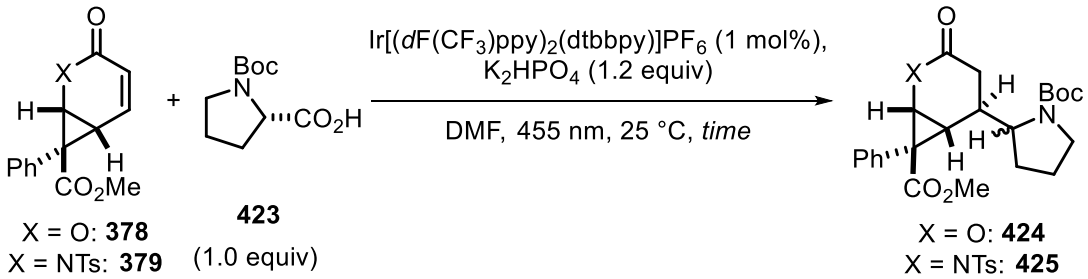
entry	catalyst	p [H_2]	time	results
1	Pd/C (10 mol%)	atm	24 h	n.r.
2	Rh/C (10 mol%)	40 bar	4.5 h	n.r.

Due to this outcome, the future of this CH-bond activation reaction was questionable. Further investigations on different catalyst and substrates might lead to better results with a larger substrate scope but were not pursued any longer for this thesis.

2.4 Decarboxylative coupling

Moving on to the next reaction type, namely the decarboxylative coupling which was already discussed in depth in chapter A, it was interesting to see that, this time, no reaction occurred with pyridinone **379** (Table 23 entry 1). Compared to this, the reaction of pyrone **378** and Boc-proline **423** gave the desired product **424** in 72% yield (Table 23 entry 2) by applying the photocatalytic conditions reported by the group of MacMillan[110].

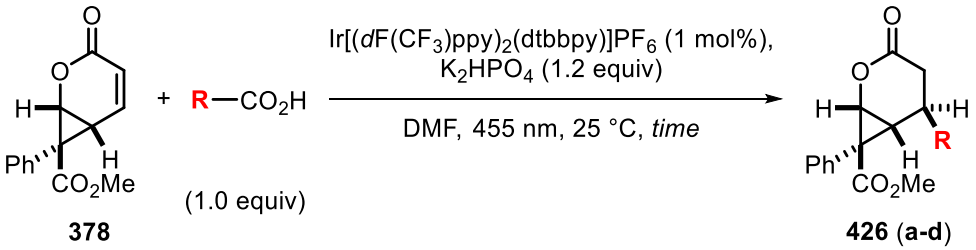
Table 23. Decarboxylative coupling with Boc-proline **423** under photocatalytic conditions.

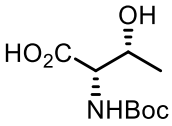
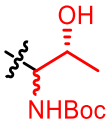
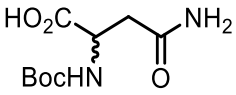
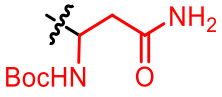
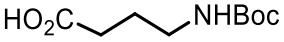
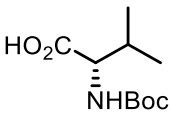
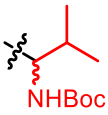


entry	X	time	results
1	**NTs**	2 d	n.r.
2	**O**	1 d	72% (**424**), d.r. 1:1.4

After that, the substrate scope was investigated with different acids (Table 24). In the case of Boc-protected threonine **427**, exhibiting an electron withdrawing hydroxy group (entry 1), and butanoic acid **429** (entry 3), which would produce a barely stabilized primary radical after decarboxylation, no reaction with pyrone **378** occurred. In contrast to this, Boc-protected asparagine **428** (entry 2) and valine **430** (entry 4) gave moderate yields of 55% and 41% after a prolonged reaction time of six and four days, respectively.

Table 24. Substrate scope for decarboxylative coupling reaction.

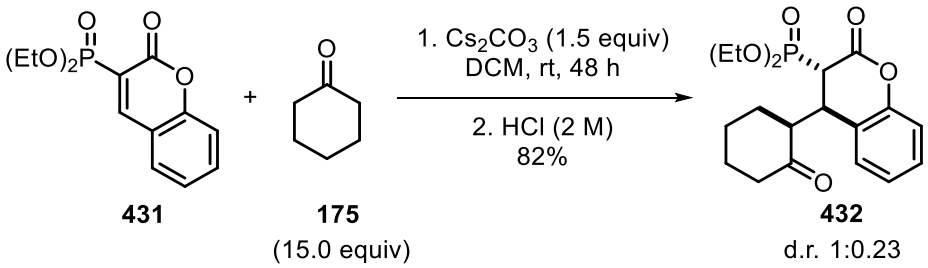


entry	R-CO_2H	time	-R	results
1	 (**427**)	6 d	 (**426 a**)	n.r.
2	 (**428**)	6 d	 (**426 b**)	55%, d.r. 1:4.3
3	 (**429**)	6 d	 (**246 c**)	n.r.
4	 (**430**)	4 d	 (**426 d**)	41%, d.r. 1:1.7

Summarizing these results, the substrate scope seems to be limited to secondary acids with electron rich properties. Therefore, further investigations were not conducted with this reaction.

2.5 Enolate additions

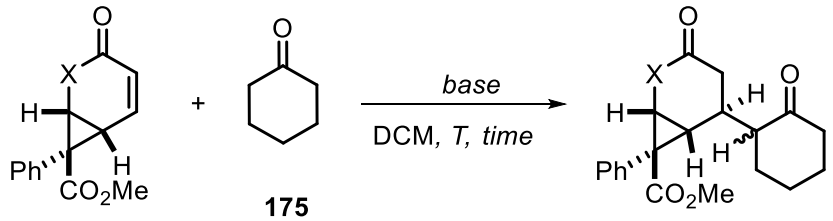
Another kind of reaction presented in detail in chapter A, which might be interesting for the transformation of cyclopropanated pyrone **378** and pyridinone **379**, was the Michael addition. As a good overview of previous work on this topic was already presented in the previous chapter A, just one additional example with particular importance to pyrones' reactivity is shown in Scheme 91. Krawczyk and co-workers reported that a formation of cyclohexanone enolate with Cs_2CO_3 as a base and the following Michael addition to the activated pyrone **431** is possible, and gave product **432** in a good yield of 82%.[111]



Scheme 91. Enolate addition of cyclohexanone to activated pyrone **431** with Cs_2CO_3 according to Krawczyk *et al.*[111]

Impressed by these mild conditions, the same reaction was performed with cyclopropanated pyrone **378** and pyridinone **379** (Table 25).

Table 25. Michael addition of cyclohexanone with different bases.

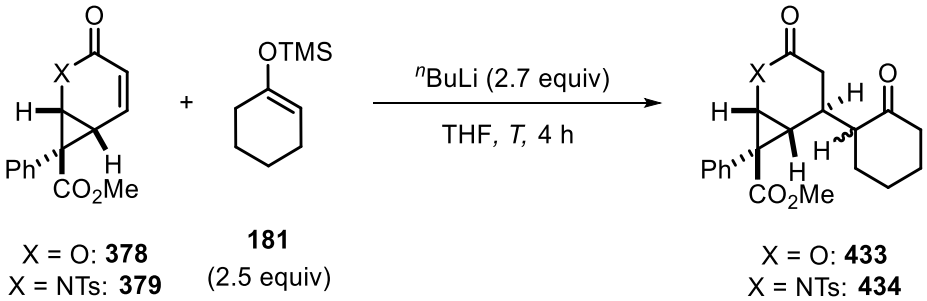


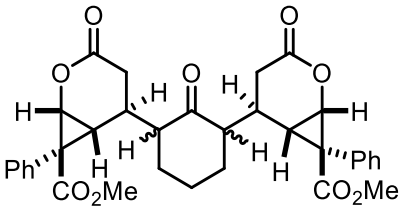
entry	X	Y	base	T [°C]	time	reuslts
1	**NTs**	15.0	Cs_2CO_3 (1.5 equiv)	25	2 d	n.r.
2[a)]	**NTs**	1.2	$^{i}Pr_2NH$ (1.3 euqiv), $^{n}BuLi$ (1.3 equiv)	-78 to 0	2.5 h	8% (**434**)
3	**O**	15.0	Cs_2CO_3 (1.5 equiv)	25	2 d	n.r.

a) THF was used as a solvent.

Entries 1 and 3 show the reaction of pyridinone **379** and pyrone **378** with cyclohexanone (**175**) and Cs_2CO_3 as a base, but even after two days of stirring, no conversion of the starting material was observed. This can be explained by the fact that the Michael system was activated by ethyl phosphate in the literature reaction compared to the less reactive double bond of the cyclopropanated substrates **378** and **379**. For this reason, LDA was used as a base (entry 2) during the reaction of pyridinone **379** with cyclohexane, which gave the desired product **434** in low yield with mostly unreacted starting material. This outcome indicates that there might be a problem with the enolate formation. Therefore, in the next step, the preformed TMS-enol ether **181** was used with ^{n}BuLi to convert the less reactive TMS-enolate to a more reactive Li-enolate (Table 26).

Table 26. Enolate addition with TMS-enolate **181** and ^{n}BuLi.





435

entry	X	T [°C]	results
1	**NTs**	-78 to 0	34% (**434**), d.r. 1:1
2	**O**	-78 to 25	traces (**433**), 8% (**435**)

In the case of pyridinone **379**, the desired product **434** was obtained in 34% yield, consisting of two diastereomers (entry 1). Compared to this, the reaction with pyrone gave the double addition product **435** in low yield and only traces of product **433** were observed (entry 2). Also, no starting material was reisolated, indicating that a decomposition reaction took place. Hence, it was decided that a Michael addition might not be suitable for these cyclopropanated compounds.

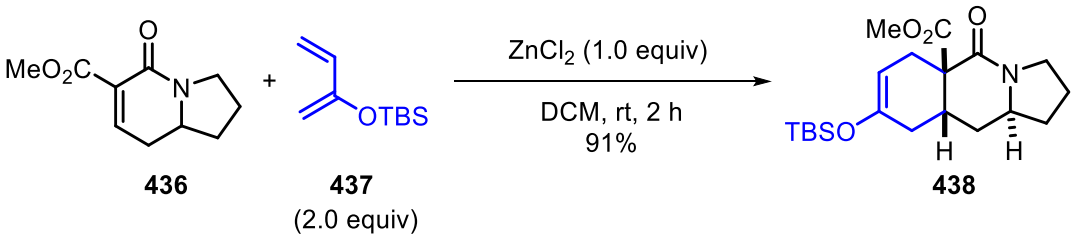
2.6 Cycloaddition reactions

Cycloaddition reactions are an important tool for building up cyclic systems during a synthesis. One of the most popular is the Diels-Alder reaction, a [4+2]-cycloaddition found by Otto Diels and Kurt Alder in the early 20th century, earning them the Nobel prize in 1950[112]. The driving force for such cyclizations is the reaction between a diene and a dienophile, where a π-bond is converted to a more stable σ-bond. Some years later, Woodward and Hoffmann established rules for the cyclization, where the outcome of the reaction could be predicted, with the orbital symmetry playing a major role. For a successful reaction, it is required that the highest occupied molecular orbital (HOMO) of the diene is overlapping with the lowest unoccupied molecular orbital (LUMO) of the dienophile. Also, regarding the sterical aspect especially in electrocyclic reactions, a distinction between a conrotatory and a disrotatory pathway was made. The authors showed that when (4n)π-electrons are present, the reaction is thermally conrotatory and photochemically disrotatory. And when (4n+2)π-electrons are present, it is the other way round – thermally disrotatory and photochemically conrotatory[113]. Of course, more electrocyclic and cycloaddition reactions are possible and widely applied, *e.g.* the Nazarov cyclization or Staudinger reaction as well as [2+2]-, [3+2], [5+2] *etc*. Several reviews on this field cover the use of cyclization reactions in natural product synthesis[114].

Since the cycloaddition is a mighty tool for building up more complex molecular structures and the cyclopropanated pyrone **378** and pyridinone **379** are potential dienophiles, it would have made an incomplete study to leave out this reaction type. A look into existing literature showed, that similar compounds had been successfully employed in Diels-Alder reactions before under various conditions. Starting with the group of Levinson[115], who showed that the cyclization worked with $ZnCl_2$ as Lewis acid under mild conditions (Scheme 92 a) compared to Dias *et al.*[116], who presented the reaction with Danishefsky's diene **440** under relatively neutral conditions by using butylated hydroxytoluene (BHT) (Scheme 92 b). The same diene was applied by Casamitjana and his group[117] in 2000 and Simpkins *et al.*[118] in 1989, where the authors eliminated the methoxy group after cyclization, by addition of camphor sulfonic acid (CSA). The biggest difference during the reaction procedure of both groups is that Casamitjana used *p*-cymene and Simpkins benzene as a solvent, although they also

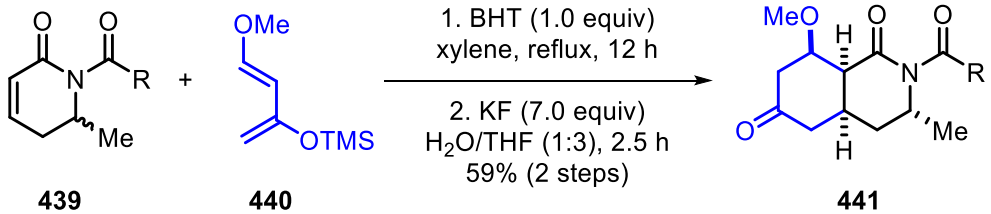
mentioned that when a less reactive diene was transformed, it was necessary to add a Lewis acid such as $ZnBr_2$ to the reaction (Scheme 92 c).

a) Diels-Alder reaction with $ZnCl_2$ according to Levinson *et al.*[115]



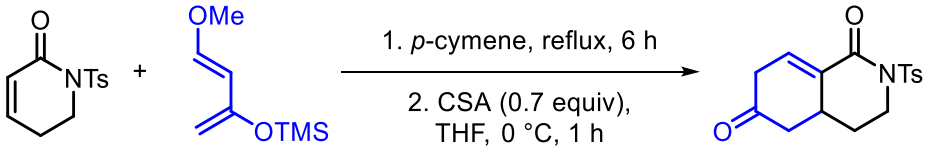
436 **437** (2.0 equiv) **438**

b) Diels-Alder reaction with BHT according to Dias *et al.*[116]



439 **440** (10.0 equiv) **441**

c) Diels-Alder reaction and following OMe-elimination with CSA according to Casamitjana *et al.*[117]

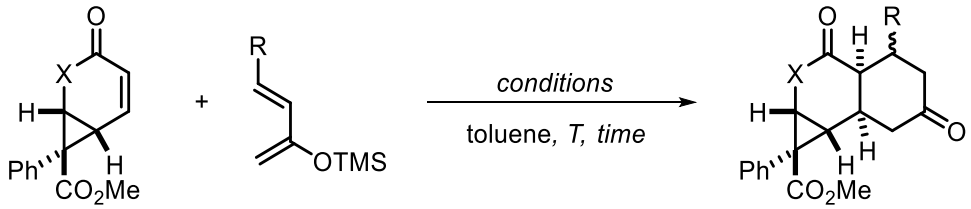


442 **440** (3.5 equiv) **443**

Scheme 92. Overview of different conditions for the Diels-Alder reaction with pyridinones as dienophiles.

Encouraged by these reports and their promising outcomes, it was decided to investigate, which conditions worked best for the starting materials examined in this work. Table 27 shows the conducted reactions and their outcome.

Table 27. Screening of reaction conditions for the Diels-Alder reaction.



X = O: **378**
X = NTs: **379**

R = OMe: **440**
R = H: **444**

X = O: **445** (**a**: R = OMe, **b**: R = H)
X = NTs: **446** (**a**: R = OMe, **b**: R = H)

entry	X	R	diene (equiv)	additive (1.0 equiv)	T [°C]	time [h]	results
1[a)]	**NTs**	OMe	2.5	$ZnCl_2$	25	2.5	n.r.
2[a)]	**NTs**	OMe	2.5	$ZnCl_2$	0 to 25	18	n.r.
3[a)]	**NTs**	OMe	2.5	$BF_3{\cdot}Et_2O$	25	19	n.r.
4	**NTs**	OMe	10.0	BHT	130	22	40% (**446 a**), d.r. 1:1
5	**NTs**	OMe	2.6	BHT	130	17	18% (**446 a**), d.r. 1:1
6	**NTs**	OMe	15.0	BHT	130	17	64% (**446 a**), d.r. 1:1
7	**NTs**	H	10.0	BHT	130	17	n.r.
8[a)]	**NTs**	H	2.0	$ZnBr_2$	0 to 25	24	n.r.
9[b)]	**O**	OMe	15.0	BHT	130	22	26% (**445 a**)
10	**O**	H	10.0	BHT	130	48	n.r.
11[a)]	**O**	H	2.5	$ZnBr_2$	0 to 25	24	n.r.

a) DCM was used as a solvent. b) Only one diastereomer was isolated.

From entries 1 to 8, the reaction was run with pyridinone **379** and from entries 9 to 11 with pyrone **378**. It was decided, to use the Danishefsky's diene **440** as it is known for

being very reactive and at first, $ZnCl_2$ was used as a Lewis acid (entry 1), resulting in no conversion of the starting material. Therefore, in entry 2, the temperature was lowered to 0 °C, as described by Simpkins *et al.*[118] in some cases, and slowly raised to rt when no reaction was observed. But even with a prolonged reaction time of 18 h no conversion of the starting material was observed. For this reason, a different Lewis acid was applied in entry 3, namely $BF_3 \cdot Et_2O$ which only allowed for reisolation of the starting material. When BHT was used (entry 4), finally the desired product **446 a** was obtained in 40% yield and a dr of 1:1. Since it was desirable to lower the amount of diene, in entry 5, only 2.6 equivalents were used, which drastically diminished the yield to 18%. When the amount was raised to 15 equivalents (entry 6) the yield improved to 64%. Satisfied with this outcome a different, less reactive diene **444** was tested in entry 7, but this resulted in the unreacted starting material. Attempting to enhance the conditions by using $ZnBr_2$ as a Lewis acid instead of BHT (entry 8) did not improve the result. Hence, the attention was moved to pyrone **378**, which was reacted with Danishefsky's diene **440** under the best conditions given in entry 9. This led to the desired product **445 a** in 26% yield and just one diastereomer was isolated. As there were two diastereomers observed in the crude NMR spectra, but only one after column chromatography, it is assumed that the product decomposes during purification. Not only did it decompose on the column, but also in the crude mixture after longer standing before column chromatography. Unfortunately, it was not possible to determine the decomposition products since they could not be isolated. When the less reactive diene **444** was used with pyrone in entry 10, no reaction occurred and the replacement with $ZnBr_2$ as a Lewis acid did not change the outcome (entry 11).

The structure of one of the diastereomers of product **446 a** was shown by X-ray measurements which can be seen in Figure 11. Unfortunately, it was not possible to crystallize the other diastereomer.

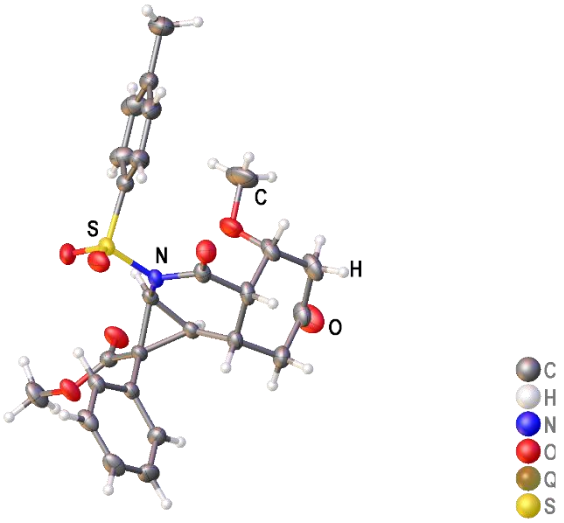
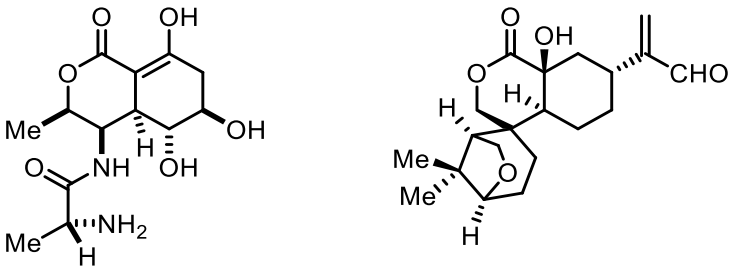


Figure 11. X-ray structure of Diels-Alder product **446 a**.

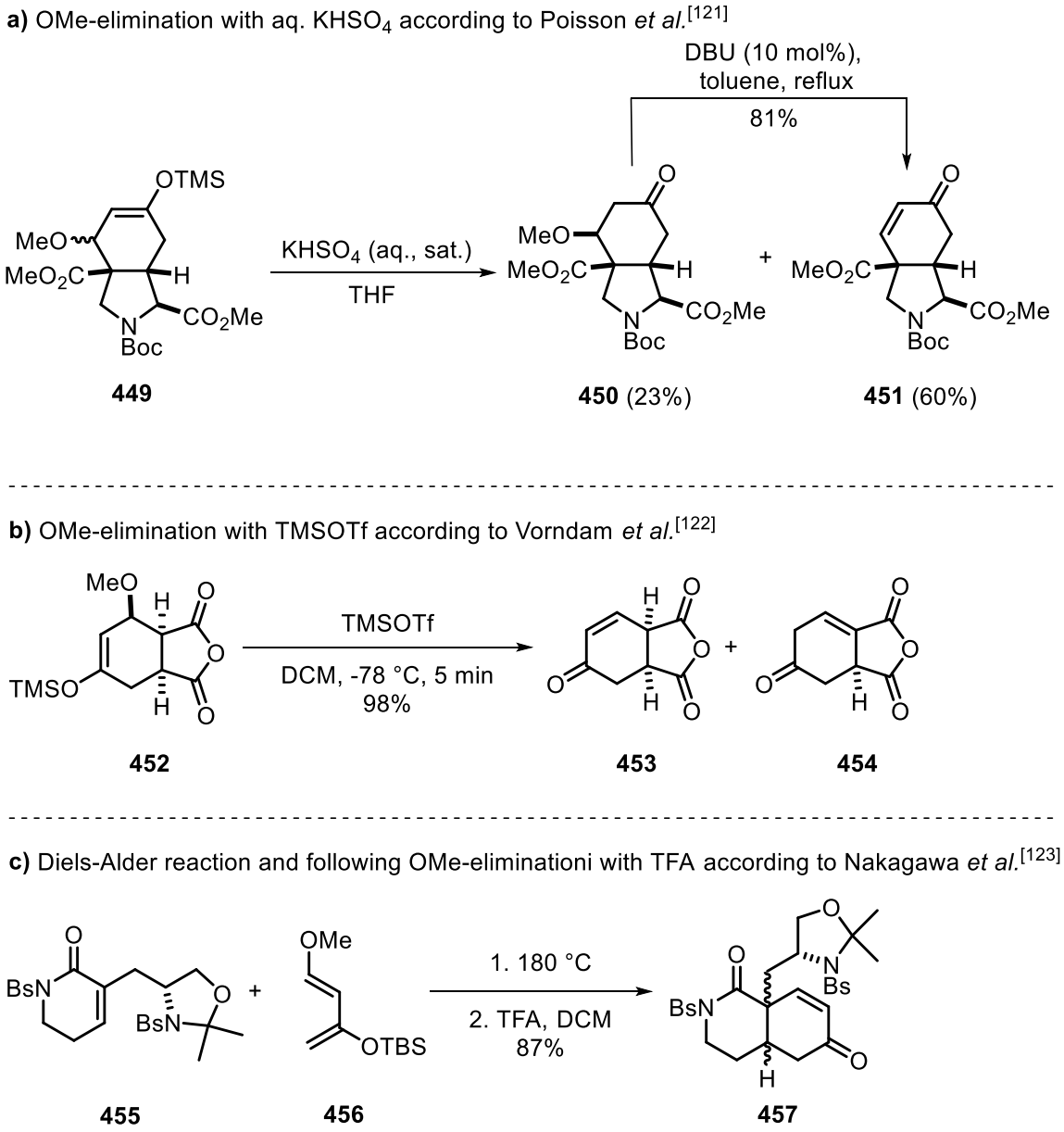
Another interesting aspect of these cycloadducts is the similarity to some natural products, which are shown in Figure 12. For example Actinobolin (**447**) is known for its antileukemic and antibacterial activity, since it can inhibit the growth of gram-positive and gram-negative bacteria.[119] On the other hand, the more complex Laxiflorolide C (**448**) is a potent inhibitor against NO production and has a selective cytotoxic activity against some specific human tumor cell lines.[120]



Actinobolin (447) **Laxiflorolide C (448)**

Figure 12. Naturally occurring compounds Actinobolin (**447**) and Laxiflorolide C (**448**).

Since in the previously described Diels-Alder reaction a mixture of diastereomers was obtained, even though they could be separated in the case of cyclization product **446 a**, the question arose, whether the formation could be circumvented by the elimination of the methoxy group after the cycloaddition reaction with Danishefsky's diene. In fact, one possible way was already presented in Scheme 92 c), where CSA was used for the elimination. Other methods are shown in Scheme 93, *e.g.* the group of Poisson[121] reported that they applied aqueous $KHSO_4$ directly after the initial reaction.



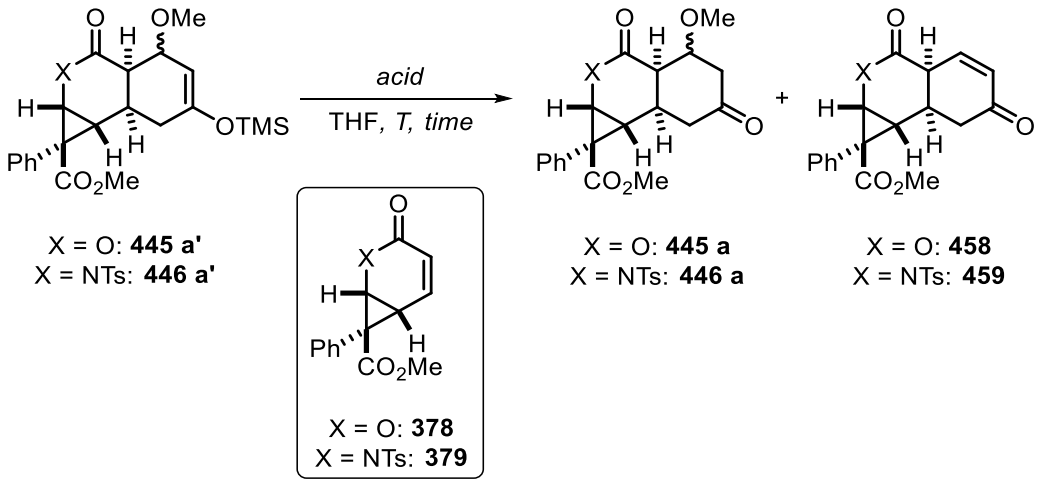
Scheme 93. Different methoxy-elimination methods with a) aq. $KHSO_4$, b) TMSOTf and c) TFA.

Even though they still obtained some of the methoxy product **450**, they were able to transform it into the unsaturated compound **451** by refluxing it with catalytical amounts of DBU (Scheme 93 a). A milder approach was shown by Vorndam *et al.*[122] who just stirred the methoxy compound **452** with TMSOTf at low temperature and got an inseparable mixture of two unsaturated products **453** and **454**, since two possible protons were available for the elimination (Scheme 93 b). An additional method is the use of TFA as reported by Nakagawa and his group[123], who also obtained the desired unsaturated product **457** in good yield (Scheme 93 c). A similar outcome was reported by Laschat *et*

al.[124] who instead used aqueous HCl but due to the similarity of the procedures the reaction is not shown here.

Continuing the research, various reaction conditions were tested in order to eliminate the methoxy group. For this reason, directly after the cyclization reaction was finished, different acids were added and the results are summarized in Table 28.

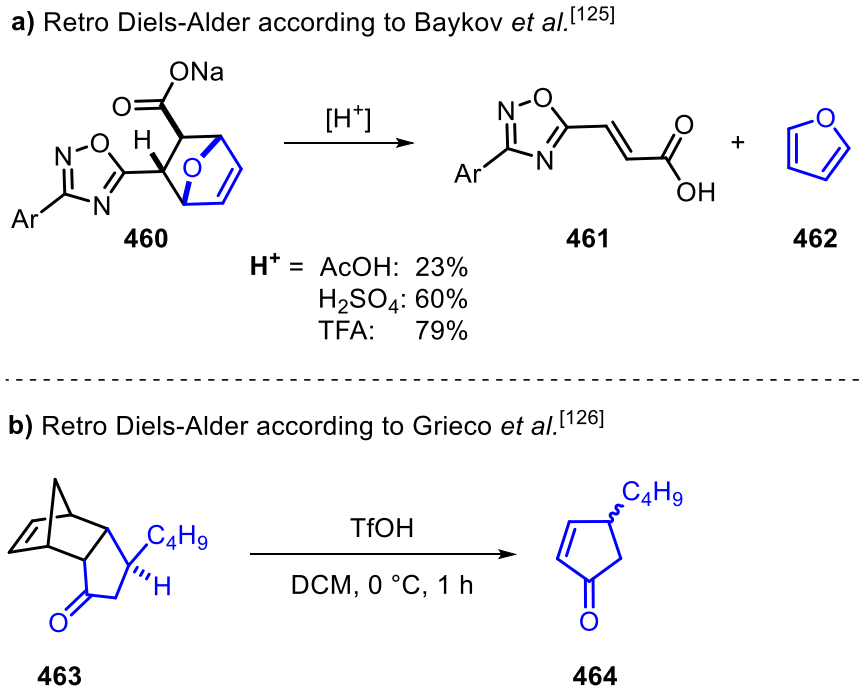
Table 28. Screening of different acids for the methoxy-elimination.



entry	X	acid	T [°C]	time	results
1	**NTs**	CSA (1.0 equiv)	0 to 25	5 h	**446 a** (52%, d.r. 1:3) + **459** (traces)
2[a)]	**NTs**	$KHSO_4$ aq, sat.	0	30 min	**446 a** (32%, d.r. 1:7) + **459** (24%)
3[b)]	**NTs**	TMSOTf (6 mol%)	-78	5 min	**459** (traces) + **379**
4[b)]	**NTs**	TMSOTf (5 mol%), collidine (10 mol%)	-78 to 0	2.5 h	**379**
5[b)]	**NTs**	TFA (3.0 equiv)	25	2.5 h	**379**
6[b)]	**NTs**	HCl (1 M)	0 to 25	1.5 h	**379**
7	**O**	CSA (1.0 equiv)	0 to 25	5 h	**445 a** (17%, d.r. 1:4) + **458** (traces)
8	**O**	$KHSO_4$ aq, sat.	0	45 min	crm

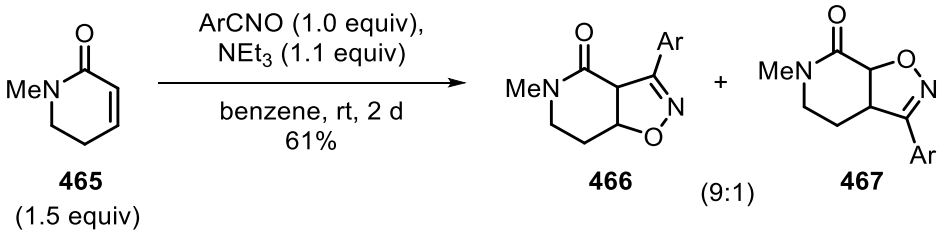
a) Refluxing of **A** with DBU (10 mol%) led to decomposition. b) DCM was used as a solvent.

In entry 1, CSA was added after the Diels-Alder reaction was complete, giving traces of the desired product **459** and 52% of the methoxy product **446 a**. Therefore, in entry 2, the acid was changed to aq. sat. $KHSO_4$ which resulted in 24% of product **459**, but still 32% of uneliminated compound **446 a** were obtained. Stirring of product **446 a** with catalytical amounts of DBU, following the procedure reported by Poisson *et al.*[121], led to the decomposition of the compound. In the next try (entry 3), TMSOTf was used as a Lewis acid in catalytical amount, which gave the product **459** in trace amounts and seemed to mostly result in retro Diels-Alder reaction since starting material **379** was the major product and no compound **446 a** was isolated. Because of this, collidine was added to TMSOTf as a proton scavenger, which was also reported by Vorndam *et al.*[122] in one of his procedures, but this resulted only in the retro Diels-Alder product **379**. Then, in entries 5 and 6, TFA and HCl were used correspondingly but did not change the outcome – only the formation of cyclopropane **379** was observed. From these results it can be concluded that the conditions in entry 2 gave the best yield of 24% and that this approach might not be as promising as expected since the diastereomers from the cyclic reaction, in case of pyridinone **379**, can be separated and elimination of the methoxy group only decreases the overall yield. In entries 7 and 8, the reaction was run with pyrone cycloadduct **445 a'** at first with CSA as an acid (entry 7), which also gave traces of desired product **458** and mainly compound **445 a** was isolated in 17%. When the acid was changed to aq, sat. $KHSO_4$ after the consumption of compound **445 a'**, only a complex reaction mixture was obtained. Based on these results it seems that molecule **445 a** is not stable under acidic conditions. In addition, because a retro Diels-Alder reaction occurred in entries 3 to 6, which did not seem to take place in the reported literature presented in Scheme 93, the question arose whether this really was possible. In fact, two reports were found which described this phenomenon. A recent paper was published in 2020 by the group of Baykov[125] who described a retro Diels-Alder reaction with furane, induced by different acids such as H_2SO_4 or TFA (Scheme 94 a). Several years earlier in 1989 Grieco *et al.*[126] also observed a similar reaction with cyclopentenone under the influence of TfOH (Scheme 94 b). Even though the shown examples' chemical and electronic structure is different from the compounds this work is focused on, it was shown that the retro Diels-Alder reaction is in principle possible. Since the main difference between the compounds in the reported literature is either the amide moiety or the cyclopropane ring (see Scheme 92 c and Scheme 93), it may be possible that these play an important role in the reaction outcome.



Scheme 94. Retro Diels-Alder reaction enabled by acids with a) furane and different acids and b) cyclopentane and TfOH.

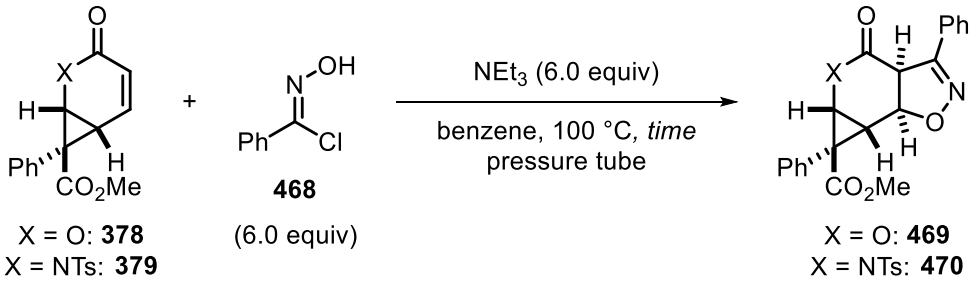
In order to increase the scope of cycloaddition reactions, the next idea was to test a [3+2]-cycloaddition, inspired by the work of Caramella *et al.*[127], who conducted a reaction of pyridinone **465** and aryl nitrile oxide under basic conditions to obtain a mixture of two-cyclic products **466** and **467** in 61% yield and a ratio of 9:1 (Scheme 95).

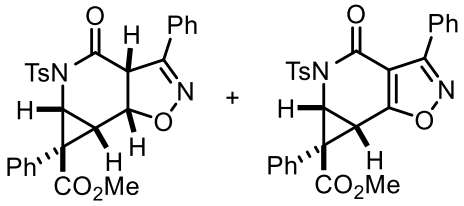


Scheme 95. [3+2] – cycloaddition of pyridinone **465** and aryl nitrile oxide according to Caramella *et al.*[127]

Under the sterical influence of the cyclopropane ring in compounds **378** and **379** at one side, it was expected that the cycloaddition would lead to only one product, compared to the product mixture shown in Scheme 95. The realization of the reaction is described in Table 29

Table 29. [3+2]-cycloaddition with PhCNO.





471 472

entry	X	time	results
1	**NTs**	18 h	56% (**470**)
2[a)]	**NTs**	6 h	30% (**470**)
3[b)]	**NTs**	18 h	58% (**470**)
4[b)]	**NTs**	2 d	46% (**470**+**471**+**472**)
5	**O**	20 h	crm
6[a)]	**O**	3.5 h	crm
7[b)]	**O**	2 d	17% (**469**)

a) Toluene was used as a solvent at 120 °C. b) Preparation of dipole PhCNO beforehand[128] and portion wise addition over 5 h to **378** or **379**.

From entries 1 to 4, the reactions were performed with pyridinone **379**, and from entries 5 to 7 with pyrone **378**. When the reaction was performed with cyclopropane **379** in benzene under reflux conditions (entry 1), the desired product **470** was obtained in 56% yield as one diastereomer – as expected based on the sterical hindrance from the cyclopropane ring, and 40% of unreacted starting material were reisolated. In entry 2, the

solvent was changed to the less carcinogenic toluene, resulting in lower product formation of 30%, indicating that benzene is considerably better in this case. In an attempt to increase the yield further by adding the dipole in portions to the reaction mixture, PhCNO was prepared beforehand from **468** and added portion wise to the reaction over 5 h, which did not improve the yield (entry 3) and gave 58% of compound **470**. Also, running the reaction for a longer time of 2 days decreased the yield to 46% and a mixture of inseparable byproducts, namely the isomerized product **471** and the elimination product **472** were obtained (entry 4). Seeing that the yield could not be significantly improved, the investigation was continued with pyrone **378**. In this case, when the reaction was performed in benzene, a complex mixture was obtained (entry 5). Changing to toluene (entry 6) led to similar results. When the dipole was prepared in advance in entry 7, the desired product **469** was isolated in only 17% yield after 2 days, but without other byproducts compared to the outcome of pyridinone **379** in entry 4. From these results it can be concluded, that pyrone **378** seems to be unstable under basic conditions which will be explained later (see Table 31).

The structure of oxazole **470** was unmistakably proofed by X-ray measurements (Figure 13).

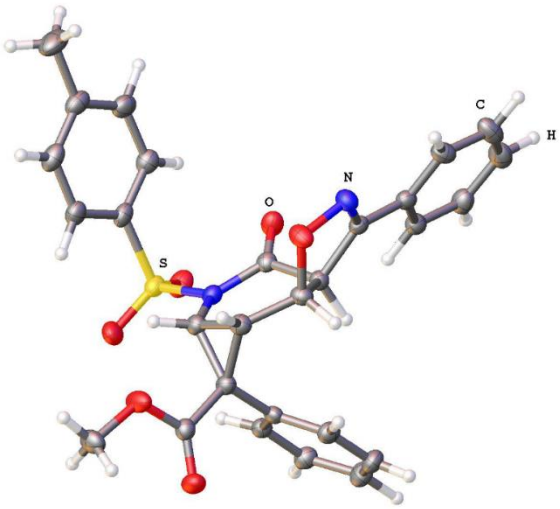
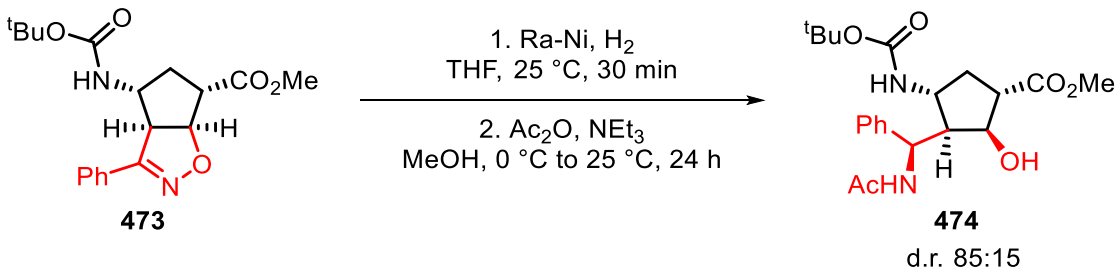


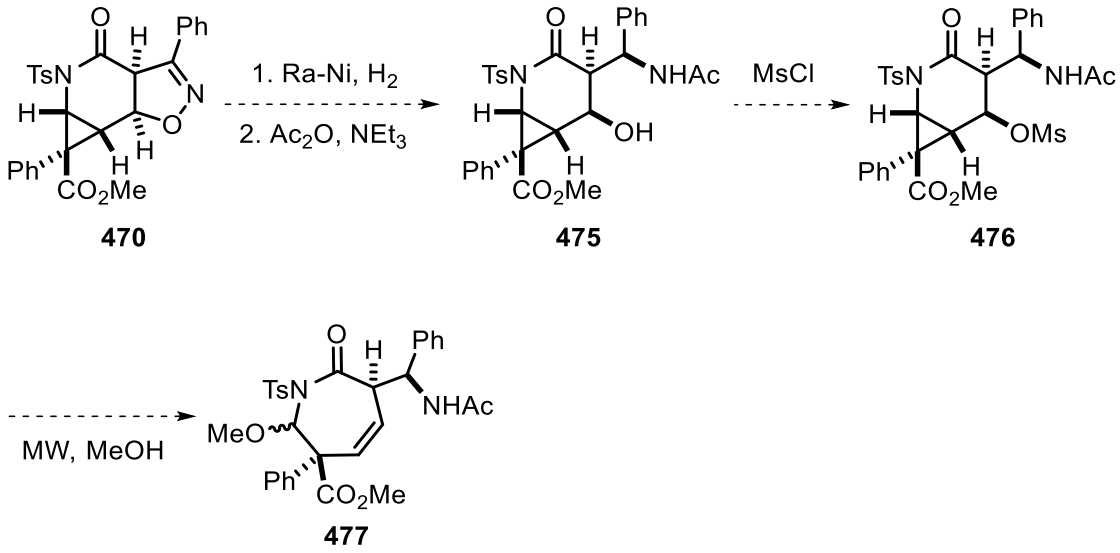
Figure 13. X-ray structure of bicyclic compound **470**.

An interesting aspect of the bicyclic compound **470** is, that it might be possible to open the isoxazole bond. This kind of reaction was recently reported by the group of Fang[129] who used Raney nickel to open the N-O bond of **473** and protected the resulting amine as an acetamide **474** (Scheme 96).



Scheme 96. Opening of isoxazole **473** and protection of amine with Ac_2O according to Fang *et al.*[129]

The main idea of this reaction was, that if it was possible to open the isoxazole **470**, the next step would be the protection of the free alcohol **475** with MsCl to yield product **476**. This could be subjected to ring opening of the cyclopropane moiety under microwave conditions in the presence of a nucleophile to yield the 7-membered ring **477** (Scheme 97).[1]

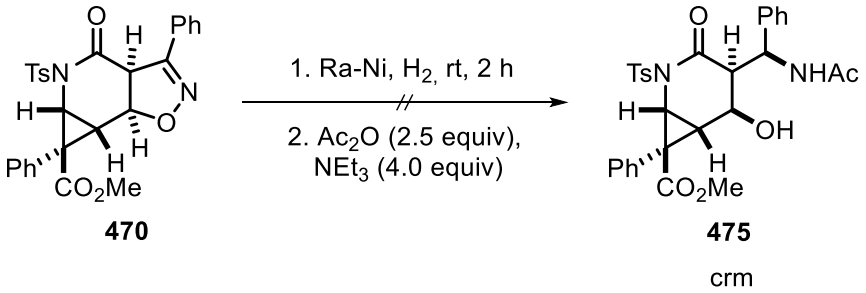


Scheme 97. Synthesis plan for the opening of isoxazole **470** and cyclopropane **476** to obtain the 7-membered ring **477**.

Unfortunately, the first step of reacting isoxazole **470** with Raney nickel, shown in Scheme 98, led to a complex reaction mixture. A possible explanation for this different outcome, compared to the literature reaction presented in Scheme 96, might be the existence of an amide, which was probably also reduced in addition to the oxazole bond

[1] The cyclopropane opening reaction under microwave conditions with neighboring mesylate was Robert Eckl's project during his PhD thesis (2021) and was not yet published to this date (Working group of Prof. Reiser, University of Regensburg).

and then underwent further reactions, leading to the complex reaction mixture. Therefore, the approach towards the 7-membered ring, starting from oxazole **470** was not pursued any further.



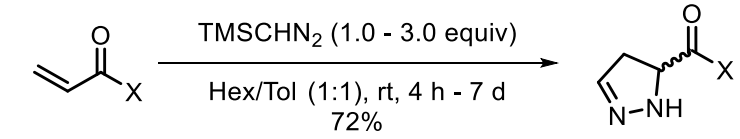
470 **475**

crm

Scheme 98. Reduction of isoxazole **470** with Raney nickel and H_2.

Expanding the reaction scope further, other cycloaddition reactions were envisaged inspired by the publications summarized in Scheme 99. Starting with a reaction, reported by Carreira and his group[130] in 1997, who were able to synthesize a pyrazole **479** by the cycloaddition of an unsaturated carbonyl **478** with trimethylsilyl diazomethane as a dipole in good yields (Scheme 99 a). A similar reaction was reported years later by Maruoka *et al.*[131], who used a less toxic diazo ester **482** and Ti-catalyst in order to obtain the substituted pyrazole **483** with good enantioselectivity (Scheme 99 c). Another approach was made by the Takai group[132] who applied dipoles like triethyl iodoethoxysilane **480**, synthesizing the tetrahydrofuran structures **481** with a catalytical amount of $PbCl_2$ and an excess of manganese (Scheme 99 b).

a) Cycloaddition with $TMSCHN_2$ as dipole according to Carreira *et al.*[130]



478 **479**

X = (1*R*)-(+)-2,10-camphorsultam dr 9:1

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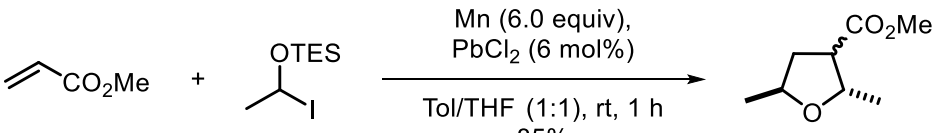
b) Cycloaddition of dipole **480** with $Mn/PbCl_2$ according to Takai *et al.*[132]



369 **480** (4.0 equiv) **481** dr 1:4.9

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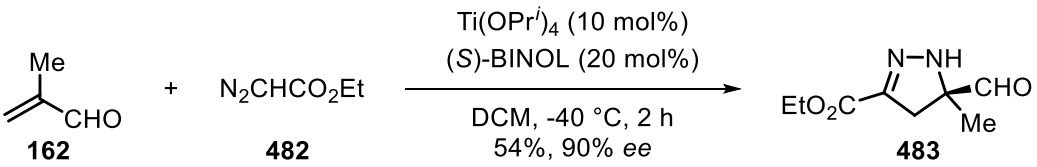
c) Cycloaddition with diazoester **483** as dipole according to Maruoka *et al.*[131]

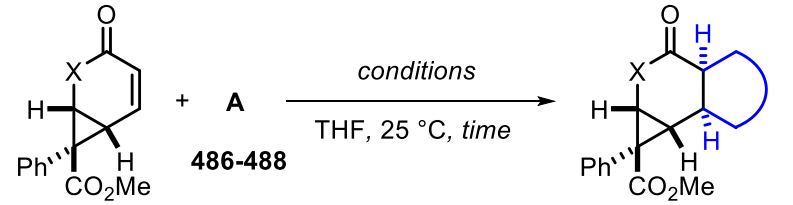


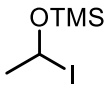
162 **482** (1.5 equiv) **483**

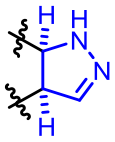
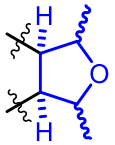
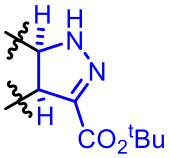
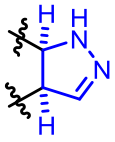
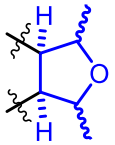
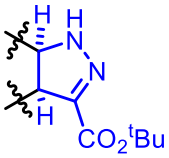
Scheme 99. Different cycloaddition reaction conditions with a) $TMSCHN_2$, b) triethyl iodoethoxysilane **480** and c) diazo ester **482** as a dipole.

The results from the reaction of cyclopropanes **378** and **379** under the different cyclization conditions are shown in Table 30.

Table 30. Different cycloadditions with compounds **378** and **379**.



A = $TMSCHN_2$ **486** (3.0 equiv);  **487** (4.0 equiv); $^tBuCO_2CHN_2$ **488** (1.5 equiv)

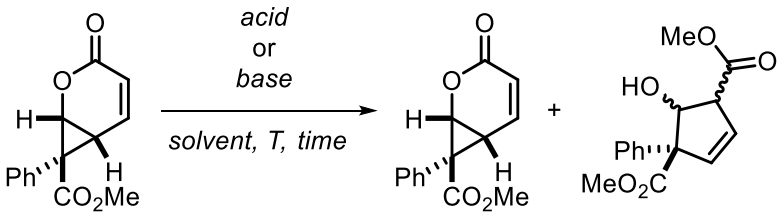
entry	X	A + conditions	time	product	results
1[a)]	**NTs**	**486**	7 d	 **(485 a)**	n.r.
2	**NTs**	**487**, Mn (6.0 equiv), $PbCl_2$ (6 mol%)	5 h	 **(485 b)**	n.r.
3[b), c)]	**NTs**	**488**, $Ti(OPr^i)_4$ (10 mol%)	1 d	 **(485 c)**	n.r.
4[a)]	**O**	**486**	7 d	 **(484 a)**	n.r.
5	**O**	**487**, Mn (6.0 equiv), $PbCl_2$ (6 mol%)	5 h	 **(484 b)**	n.r.
6[b), c)]	**O**	**488**, $Ti(OPr^i)_4$ (10 mol%)	1 d	 **(484 c)**	n.r.

a) Toluene/Et_2O was used as a solvent. b) DCM was used as a solvent. c) Temperature was increased from -40 °C to 25 °C during the reaction time.

In entry 1, pyridinone **379** was reacted with dipole **486**, but no conversion of the starting material was observed even after seven days. The same result was obtained, when changing the conditions to dipole **487** with the addition of manganese and $PbCl_2$ in entry 2, as well as with dipole **488** under $Ti(OPr^i)_4$ catalysis (entry 3). Replacing the starting material with pyrone **378** did not change the outcome. Again, neither with dipole **486** (entry 4) nor under the conditions shown in entries 5 and 6, the desired product was obtained. Only starting material **378** was reisolated. Even increasing the temperature during the reaction in entries 3 and 6 did not help to form the desired product. Therefore, it was concluded that the reactivity of the chosen dipoles was not high enough for the dipolarophiles **378** and **379** and further investigations on cycloaddition reactions might be necessary.

As already mentioned before, after conducting all the different reaction types so far, it seemed that the cyclopropanated pyrone **378** was not stable under certain conditions. For this reason, small scale reactions in three different solvents – polar, polar aprotic and unipolar – under neutral, acidic and basic conditions were conducted with pyrone **378**. The results are summarized in Table 31.

Table 31. Stability test of pyrone **378** under different conditions.

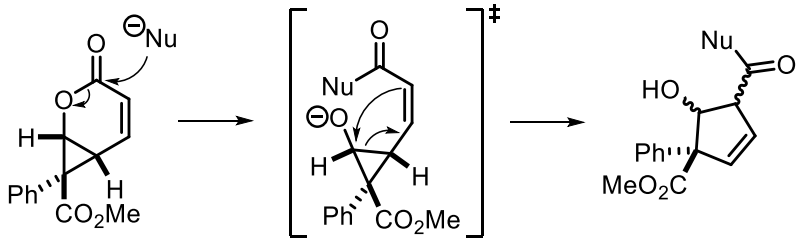


378 **378** **489**

entry	solvent	acid/base	T [°C]	time	result
1	MeOH	none	80	3 h	**378**
2		TFA (1.0 equiv)	25	1.5 h	**378**
3			80	2.5 d	**489**
4		NEt_3 (1.0 equiv)	25	1.5 h	**378**
5			80	2.5 d	**489**
6	toluene	none	120	3 h	**378**
7		TFA (1.0 equiv)	25	1.5 h	**378**
8			120	2.5 d	**378**

9		NEt_3 (1.0 equiv)	25	1.5 h	**378**
10			120	2.5 d	crm
11		none	60	3 h	**378**
12		TFA (1.0 equiv)	25	1.5 h	**378**
13	THF		60	2.5 d	**378**
14		NEt_3 (1.0 equiv)	25	1.5 h	**378**
15			60	2.5 d	**378**

In entries 1 to 5, methanol was used as a polar solvent. First, pyrone **378** was refluxed under neutral conditions in entry 1 where it proved to be stable. Then one sample was stirred at room temperature with TFA as an acid (entry 2) and another one with NEt_3 as a base (entry 4). Both were stable under these conditions but when they were refluxed (entries 3 and 5), the formation of compound **489** was observed and all of pyrone **378** was consumed. Product **489** is a proposed structure since the reactions were run on a 10 mg scale and analysed using proton NMR spectra. Also, because of two stereocenters, a mixture of four diastereomers was obtained. The same reactions were conducted with unpolar toluene (entries 6 to 10) and polar aprotic THF (entries 11 to 15) as solvents, at room temperature and under reflux conditions. In these cases, only pyrone **378** was reisolated with the only exception in entry 10, where under reflux conditions in toluene with NEt_3 a decomposition of the starting material occurred. From this investigation, it can be concluded that pyrone **378** is not stable when a nucleophile is present under acid or base catalyzed conditions. The formation of product **489** is explained in Scheme 100. After the nucleophilic opening of lactone **378**, the formed intermediate **490** can rearrange to cyclopentene **491** with two stereocenters.



378 **490** **491**

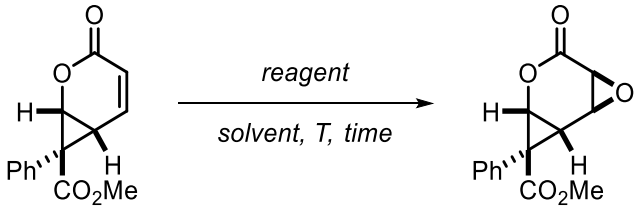
Scheme 100. Proposed mechanism for the rearrangement of pyrone **378** to cyclopentene **491**.

Since the control of the stereocenters is not possible in this step, this rearrangement was not pursued any further and due to the side reaction of pyrone **378**, the chemistry in the next chapters is mainly focused on pyridinone **379**.

2.7 Epoxidation

In the case of the epoxidation reaction, some investigations were already done by Dr. Michael Leitner.[133] During his work, he mostly concentrated on the epoxidation of cyclopropanated 2-pyrone **378**. His results are taken from his PhD thesis and are summarized in Table 32.

Table 32. Epoxidation reactions on pyrone **378** performed by Dr. Michael Leitner.[133]

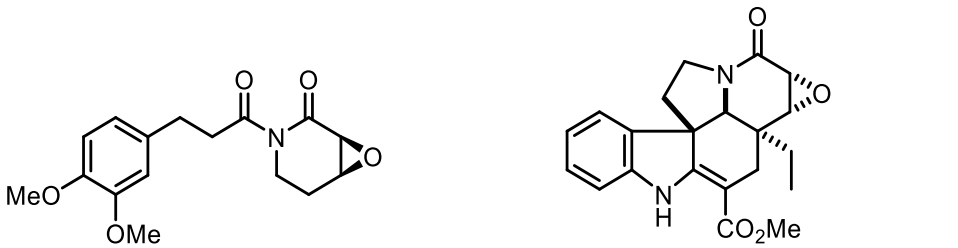


378 **385**

entry	reagent	solvent	T [°C]	time [h]	results
1	H_2O_2/NaOH	DCM/MeOH	25	24	crm
2	DMDO	Acetone/H_2O	0 to 25	72	n.r.
3	*m*CPBA	DCM	25	72	n.r.
4	*m*CPBA, $NaHCO_3$	DCM	25	24	crm
5	^{t}BuOOH, DBU	DCM	25	24	crm

According to his studies, none of the tested reaction conditions led to the desired epoxide **385**. Either, it led to decomposition under basic conditions (entries 1, 4 and 5), or no reaction occurred using milder reagents as shown in entries 2 and 3. Taking into consideration the stability test conducted in the previous chapter (see Table 31), it can be explained why this reaction was not going as expected and the pyrone ring always rearranged, as long as there was a nucleophile present. Therefore, in this chapter, the focus was placed on the epoxidation of pyridinone **379**, leading to interesting structures similar

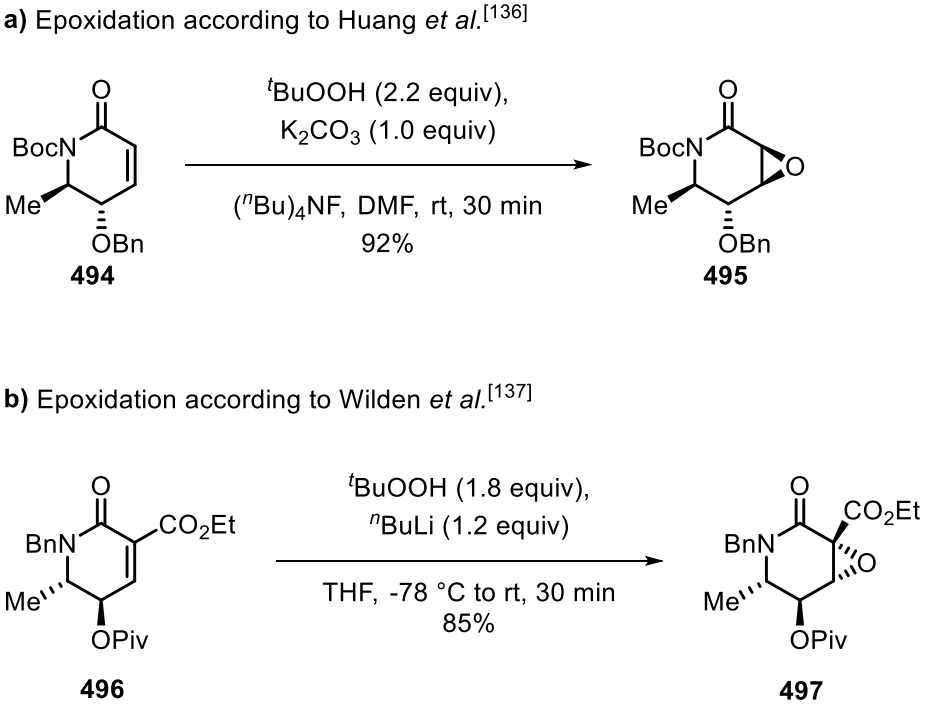
to the natural products shown in Figure 14. For example, it is known that Piplaroxide (**492**) shows repellent activity against the leafcutter ant *Atta cephalotes*[134] and the more complex 6,7-epoxy-8-oxo-vincadifformine (**493**) exhibited significant cytotoxicity against some cell lines of the head and neck squamous cell carcinoma, as well as significant antimicrobial activities against the fungi *A. alternata* and *P. capsici*.[135]



(+)-Piplaroxide (**492**) **6,7-epoxy-8-oxo-vincadifformine** (**493**)

Figure 14. Biologically active 2-pyridinone epoxides found in nature.

Searching for similar reactions in the literature showed that commonly ^{t}BuOOH with different bases was used as the epoxidizing agent (Scheme 101).

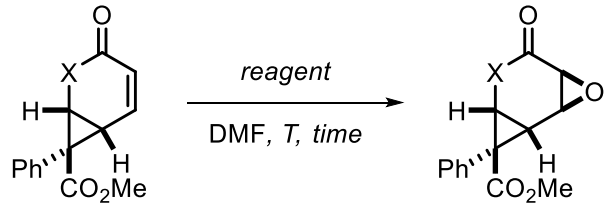


Scheme 101. Epoxidation of substituted pyridinones with ^{t}BuOOH and a) K_2CO_3 or b) ^{n}BuLi as bases.

For example, Huang and his group[136] used K_2CO_3 as a base followed by the addition of TBAF (Scheme 101 a) when Wilden and coworkers[137] decided to use ^{n}BuLi (Scheme 101 b). In both cases the product was obtained in good yield after a short reaction time.

Table 33 shows the different epoxidation conditions. In entry 1, usually applied epoxidation conditions with H_2O_2 and NaOH were employed but led to no conversion of the starting material. When trying the conditions with ^{t}BuOOH and K_2CO_3 in entry 2, the desired product **498** was obtained in 93% yield. Using the same conditions for pyrone **378** in entry 3, in the hope of obtaining the epoxide **385**, led to a complex reaction mixture.

Table 33. Epoxidation under different conditions.



X = O: **378**
X = NTs: **379**

X = O: **385**
X = NTs: **498**

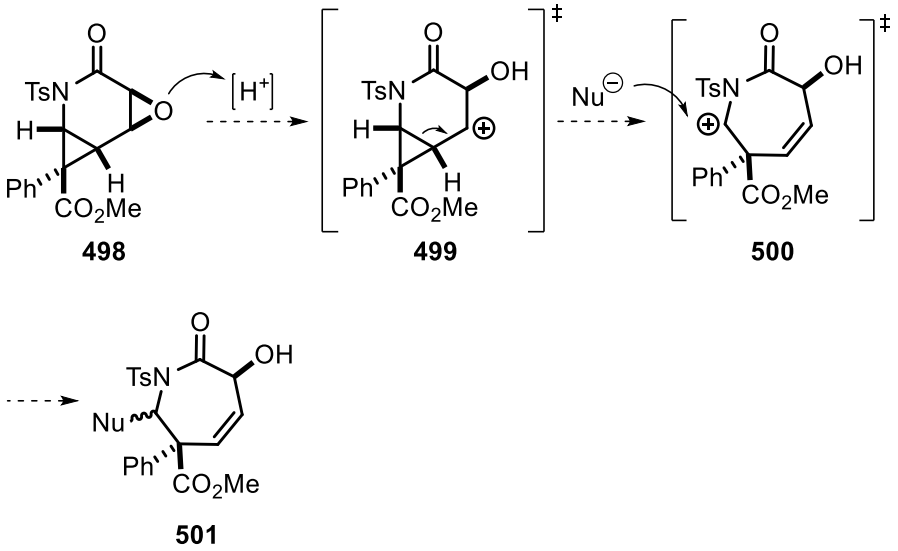
entry	X	reagent	T [°C]	time	results
1[a)]	**NTs**	H_2O_2 (3.4 equiv), NaOH (0.6 equiv)	0 to 25	1 d	n.r.
2	**NTs**	^{t}BuOOH (2.2 equiv), K_2CO_3 (1.0 equiv), TBAF (1.0 equiv)	25	1 h	93% (**498**)
3	**O**	^{t}BuOOH (2.2 equiv), K_2CO_3 (1.0 equiv), TBAF (1.0 equiv)	25	1 h	crm

a) DCM/MeOH was used as a solvent.

With epoxide **498** in hand, the next step would be to try and open the cyclopropane ring. These approaches are discussed in the next chapter.

2.8 Ring-opening of cyclopropane

To open the cyclopropane ring with help of the epoxide, a positive charge is necessary adjacent to the cyclopropane. Thus, the epoxide had to be opened by an acidic path, which would give the carbocation **499** and the cyclopropane would open endocyclic to give a seven-membered ring **500**. A present nucleophile, *e.g.* from the solvent or another additive could attack at the positive position next to the lactam, resulting in the desired product **501** (Scheme 102).



Scheme 102. Mechanistic proposal for the opening of the cyclopropane ring through the epoxide **498**.

These 7-membered lactams, like **502** and **503**, do not fit a specific category, but are known to affect the central nervous system for their potent depressant and high convulsant properties depending on the substituents[138] as shown in Figure 15. Another more complex structure of a lactone is Aphanamixoid A (**504**), known for its antifeedant activity against the larvae of the beet armyworm *Spodoptera exigua* and the cotton bollworm *Helicoverpa armigera*[139].

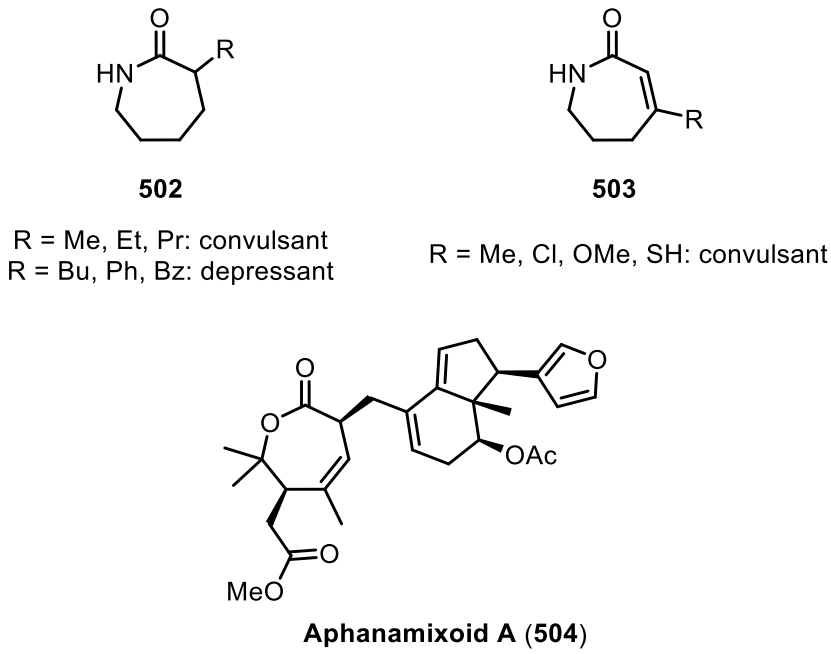
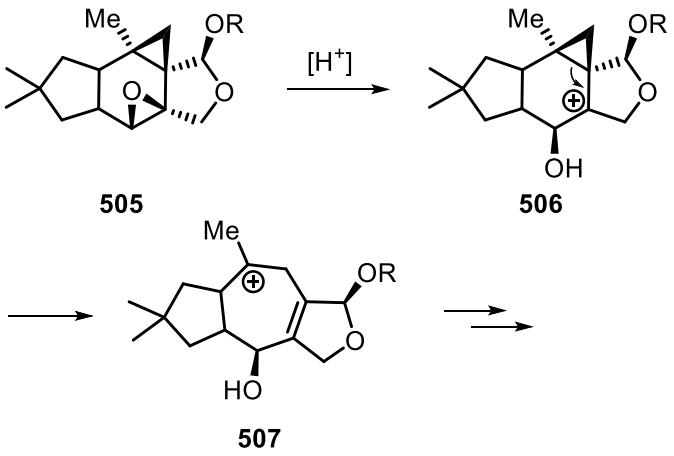


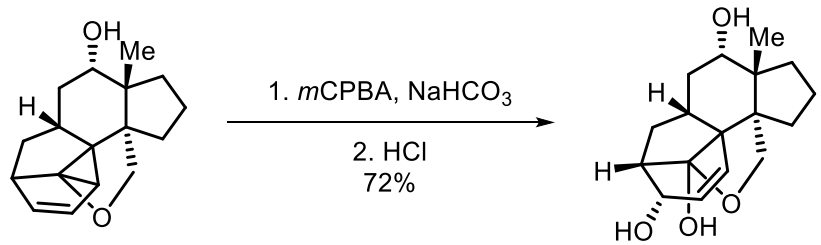
Figure 15. Bioactive 7-membered lactams **502** and **503** and the lactone Aphanamixoid A (**504**).

Such cyclopropane ring openings through an epoxide are not commonly encountered and just a few reports on this chemistry exists. Scheme 103 shows two useful approaches for the desired transformation. In 1985, Wickberg *et al.*[140] reported that the cyclopropanated compound **505** was opened by the acidic nature of SiO_2 by first forming the alcohol **506** with a positive charge in the neighborhood, leading to ring expansion in the next step (Scheme 103 a). A more recent reaction was presented in 2015 by the Chen group[141] who, after the epoxidation of the double bond of compound **508**, used HCl to open the epoxide and the cyclopropane ring in order to obtain product **509** in good yields (Scheme 103 b).

a) Cyclopropane opening through epoxide according to Wickberg *et al.*[140]



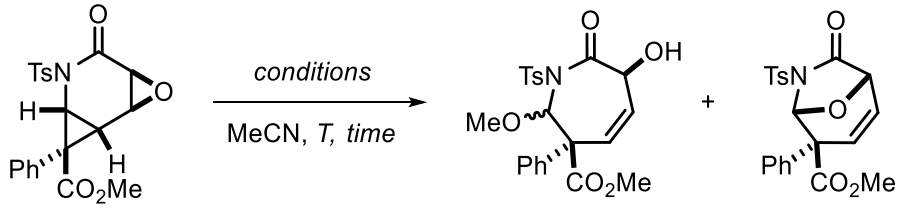
b) Cyclopropane opening through epoxide according to Chen *et al.*[141]



Scheme 103. Cyclopropane ring-opening through an epoxide induced by an acid. a) With H^+ of SiO_2 and b) with HCl.

Seeing that the strategy of cationic opening might be possible, it was proceeded to try different conditions for this reaction, shown in Table 34.

Table 34. Different condition for opening the epoxide **498**.



498 **510** **511**

entry	H^+	additive	T [°C]	time	results
1[a)]	Amberlyst 15 (20 mol%)		25 to 40 to 130	2 d	n.r.
2[a)]	TFA (1.0 equiv)		25 to 120	3 d	n.r.
3	TMSOTf (1.1 equiv)	Et_3SiH (5.0 equiv)	0 to 25 to 60	19 h	27% (**511**)
4	TMSOTf (1.3 equiv)		60	1 h	50% (**511**)
5	TMSOTf (1.1 equiv)		60	0.5 h	85% (**511**)
6	TMSOTf (1.1 equiv)	MeOH (5.0 equiv)	60	1 h	**498** + 27% (**511**)
7[a)]	TMSOTf (1.1 equiv)		60	1 h	**498** + **511** (traces)

a) MeOH was used as a solvent.

First, the opening was conducted with Amberlyst 15 (entry 1) in MeOH. However, even after increasing the temperature to 130 °C, no consumption of starting material was observed. For this reason, the acid source was changed to TFA, which also resulted in no reaction even after heating to reflux (entry 2). Seeing that Brønsted acids did not lead to any reaction of the epoxide **498**, it was decided to use a Lewis acid instead, namely TMSOTf. In entry 3, TMSOTf was used with Et_3SiH as a nucleophile and after heating

the reaction mixture to 60 °C, conversion of the starting material was observed, albeit not producing the desired product **510**, but surprisingly the bridged 7-membered ring **511** in 27% yield. Formation of product **511** was not expected as the ring system is already pretty strained due to the sp^2 centers, and thus a bridged oxide would even increase the strain. Still, it was attempted to increase the yield of the product by first leaving out the nucleophile source in entry 4, which indeed gave the compound **511** in 50% yield and this was even raised to 85% by decreasing the amount of TMSOTf to 1.1 equivalents and the reaction time to 30 min (entry 5). Another attempt to obtain the opened ring **510** by using MeOH as nucleophile resulted again in the bridged product **511** in 27% and unreacted starting material (entry 6). Also, changing the solvent to MeOH gave mostly unreacted starting material instead (entry 7). From this it seems that a nucleophilic source interrupts the ring-opening and the best conditions for the cyclopropane opening are those applied in entry 5.

The structure of 7-membered ring **511** was confirmed by X-Ray measurements (Figure 16).

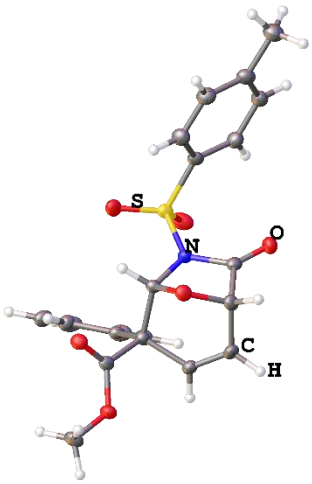
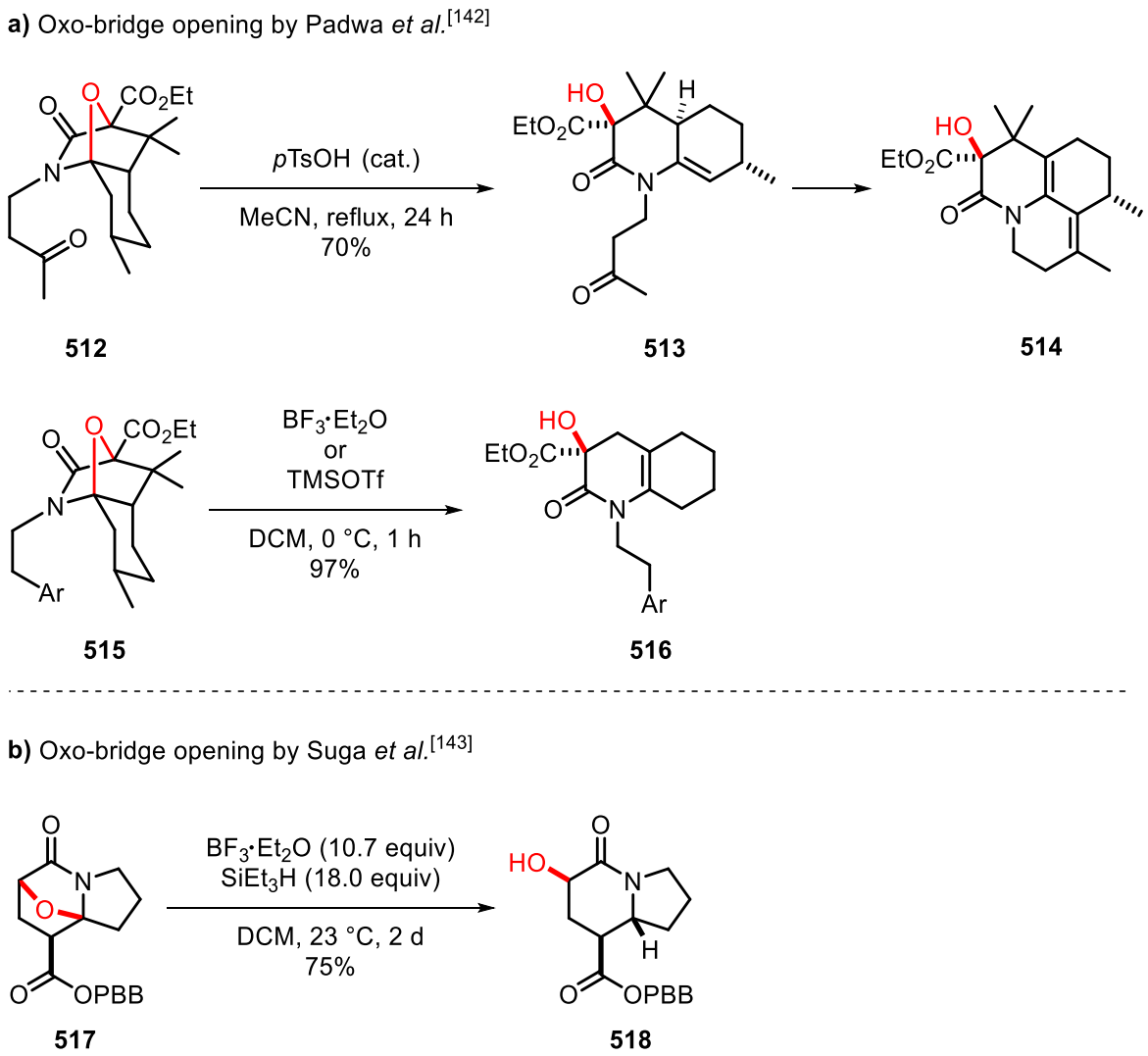


Figure 16. X-Ray structure of 7-membered ring **511**.

2.9 Ring-opening of acetal

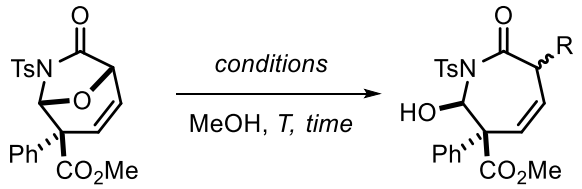
Despite of the excellent result for the ring-opening described above, the opening of the oxo-bridge was pursued further to get closer to the natural products shown in Figure 15. Some representative examples were found in literature, *e.g.* by Padwa and coworkers[142], who used Lewis acids like *p*TsOH or $BF_3 \cdot Et_2O$ to open the acetal on a 6-membered ring **512** or **515** (Scheme 104 a) as well as the group of Suga[143], who used Et_3SiH in addition as a hydride donor (Scheme 104 b). Both openings worked in comparably good yields and seemed to be a promising approach in this work.



Scheme 104. Opening of oxo-bridge with different Lewis acids by a) Padwa *et al.*[142] and b) Suga *et al.*[143]

Table 35 shows the attempts of ring-opening under different conditions.

Table 35. Screening of conditions for the oxo-bridge opening.



511

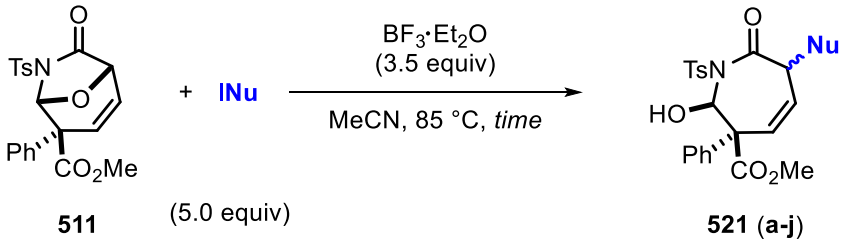
R = H: **519**
R = OMe: **520**

entry	LA	additive	T [°C]	time	R	results
1[a)]	$BF_3 \cdot Et_2O$ (10.7 equiv)	Et_3SiH (18.0 equiv)	25	5 d	H	traces
2[a)]	$BF_3 \cdot Et_2O$ (5.2 equiv)	MeOH (2.0 equiv)	60	18 h	OMe	n.r.
3	$BF_3 \cdot Et_2O$ (5.2 equiv)		70	2.5 h	OMe	30% (**520**), d.r. 1:4
4	$BF_3 \cdot Et_2O$ (2.0 equiv)		70	3 h	OMe	35% (**520**) + 50% (**511**)
5	$BF_3 \cdot Et_2O$ (3.5 equiv)		70	3 h	OMe	43% (**520**)
6[b)]	$BF_3 \cdot Et_2O$ (3.5 equiv)		70	3 h	OMe	43% (**520**)
7	TMSOTf (1.1 equiv)		70	3 h	OMe	45% (**520**)
8	*p*TsOH (0.7 equiv)		70	20 h	OMe	44% (**520**)

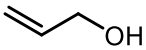
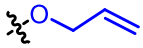
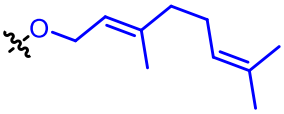
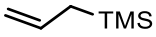
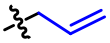
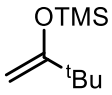
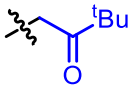
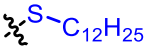
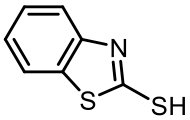
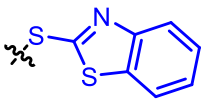
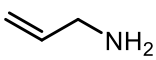
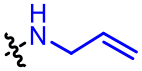
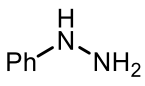
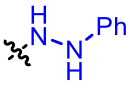
a) DCM was used as a solvent. b) Quenched with NH_4Cl (aq., sat.) instead of $NaHCO_3$ (aq., sat.).

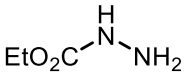
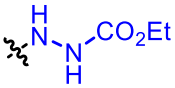
It was decided to investigate the oxo-bridge opening by using $BF_3 \cdot Et_2O$ as a Lewis acid with Et_3SiH as a hydrogen donor first (entry 1), which gave traces of the desired product **519**, but consumption of the starting material **511**. Based on this result, and taking into account the epoxide opening (see Table 34 entry 3), it was concluded that hydride sources are too reactive for the 7-membered ring **511** and should be avoided. Therefore, in entry 2, MeOH was chosen as the nucleophile and DCM as a solvent. The reaction mixture was heated to reflux but still no conversion of the starting material was observed. Though when MeOH itself was used as a solvent, the product **520** was obtained in 30% yield and a d.r. of 1:4 (entry 3). In an attempt to raise the yield, first the amount of the necessary Lewis acid was examined. When using just 2.0 equivalents of $BF_3 \cdot Et_2O$, the yield increased to 35% but still 50% of unreacted starting material were reisolated (entry 4), compared to applying 3.5 equivalents and a resulting yield of 43% (entry 5). Since the starting material was entirely consumed, the question arose whether the basic workup might be crucial. Hence, in entry 6, only the workup was changed to aq. sat. NH_4Cl instead of the previous aq. sat. $NaHCO_3$, but this made no difference in the outcome of the reaction. In entries 7 and 8 different Lewis acids were screened, namely TMSOTf and *p*TsOH, but gave comparable yields to the use of $BF_3 \cdot Et_2O$ with 45% and 44% respectively. It has to be mentioned here, that it was surprising that TMSOTf was also working since it was used for the opening of the cyclopropane ring *via* the epoxide before (see Table 34 entry 5). However, it seems impossible to go from the epoxide to the opened 7-membered ring **520** in one step because during the reaction with MeOH, mostly unreacted epoxide **498** was reisolated (see Table 34 entries 6 and 7). This result leads to the conclusion that the formation of bridged ring **511** is more favourable than the less strained compound **510**, which might be due to the fact that intramolecular reactions are in general faster than intermolecular ones. Thus, entry 5 was judged to be the best conditions for the opening reaction. Keeping in mind, that the moderate yield of the opening with MeOH might be because of the nucleophile's nature, different nucleophiles were screened in MeCN as solvent (Table 36).

Table 36. Nucleophile screening for acetal opening.



511 **521** (**a-j**)

entry	Nu	time	-Nu	results
1	 (**522**)	21 h	 (**521 a**)	n.r.
2[a)]	Geraniol (**523**)	3.5 h	 (**521 b**)	n.r.
3	 (**524**)	19 h	 (**521 c**)	n.r.
4	NC−TMS (**525**)	19 h	 (**521 d**)	n.r.
5	 (**526**)	21 h	 (**521 e**)	n.r.
6	$C_{12}H_{25}$−SH (**527**)	20 h	 (**521 f**)	n.r.
7	 (**258**)	20 h	 (**521 g**)	n.r.
8	 (**259**)	1 h	 (**521 h**)	29%, d.r. 1:7.5
9	 (**530**)	3.5 h	 (**521 i**)	48%, d.r. 1:5.1

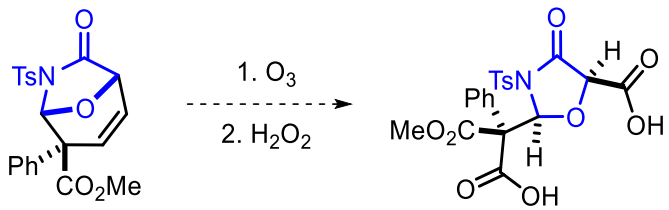
10	 (**531**)	3.5 h	 (**521 j**)	47%, d.r. 1:7.7

a) Addition of 5.0 equiv. after 4 h

In entries 1 and 2, oxygen nucleophiles were tested. Nevertheless, neither allylic alcohol **522** (entry 1) nor geraniol **523** (entry 2) gave the desired products **521 a** or **521 b**. Even after adding more geraniol after 4 h the reaction did not proceed. The next group were TMS-nucleophiles, represented by **524** and **525**, which also did not react with the bridged ring **511** (entries 3 and 4). A similar outcome was observed for enolate **526** in entry 5 and the thiols **527** and **528** in entries 6 and 7 respectively. A plausible explanation for this might be the lower nucleophilicity compared to MeOH. When using allylamine **529**, the product **521 h** was obtained in 29% yield (entry 8) and a d.r. of 1:7.5. Switching to the more nucleophilic hydrazines **530** and **531**, gave the products **521 i** and **521 j** in moderate yields of 48% and 47% with a d.r. of 1:5.1 and 1:7.7 (entries 9 and 10 respectively). These results show that nitrogen nucleophiles with different steric properties seem to have the right reactivity for the opening.

2.10 Derivatization of the 7-membered ring

Wondering, if other transformations might be possible with the bridged substrate **511**, the focus in this chapter was laid on the double bond. First, it was investigated whether an ozonolysis would give the interesting oxazolidinone structure **532** (marked in blue) (Scheme 105).

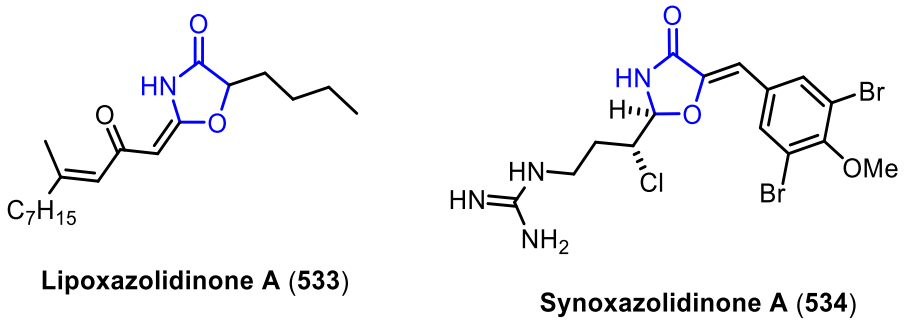


511 **532**

Scheme 105. Possible ozonolysis reaction of compound **511** to obtain the oxazolidinone structure **532**.

This structure is interesting because of some natural products, such as Lipoxazolidinone A (**533**) and Synoxazolidinone A (**534**) (Figure 17). The first one was isolated from

marine sediments on the coast of Guam and the second one from the subarctic ascidian *Synoicum pulmonaria*, found at the Norwegian coast. These compounds are known for their antimicrobial properties, as they can inhibit the cell-wall and protein synthesis of some bacteria strains.[144,145]

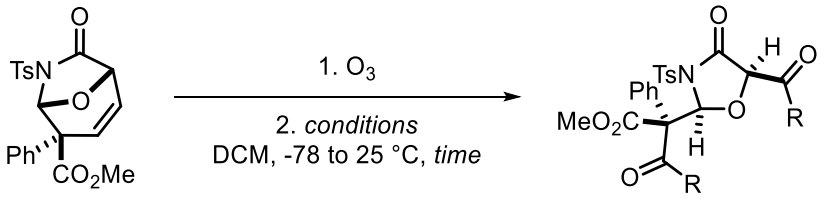


Lipoxazolidinone A (**533**) **Synoxazolidinone A** (**534**)

Figure 17. Naturally occurring compounds **533** and **534** with an oxazolidinone structure.[144,145]

Depending on the workup, an acid, aldehyde or an alcohol may be obtained. It was decided to apply H_2O_2 as a workup reagent first, which should give an acid and facilitate the purification step. Table 37 shows the summarized results.

Table 37. Ozonolysis reaction of **511** under different conditions.



511 R = OH: **532** R = H: **535**

entry	conditions	time	R	results
1[a)]	H_2O_2 (5.0 equiv)	17 h	OH	crm
2[b)]	H_2O_2 (5.0 equiv)	20 h	OH	crm
3[b)]	DMS (5.0 equiv)	21 h	H	crm

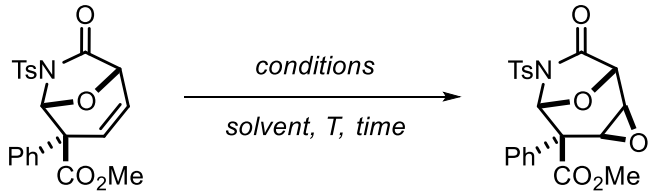
a) O_3 was bubbled through for 2 h. b) O_3 was bubbled through for 10 min.

In entry 1, O_3 was bubbled through the solution of **511** for 2 h, expecting the reaction solution to turn blue, indicating an excess of ozone and therefore completion of the reaction. Since this was not the case after 2 h, it was proceeded with the workup with

H_2O_2. This gave only a complex reaction mixture and decomposed starting material. Therefore, in entry 2, to exclude the possibility that an excess of ozone might be unfavourable, O_3 was bubbled through for only 10 minutes, giving the same outcome as in entry 1. Considering the problem might be with the chosen workup, DMS was applied after the ozonolysis which would give the aldehyde **535** instead of acid **532**. However, this attempt failed and again a complex reaction was obtained (entry 3). Based on these results, the 7-membered ring **511** might be too reactive for an ozonolysis reaction.

Another possible derivatization of the double bond is an epoxidation. Thus, the formed epoxide **536** might be opened in the next step to yield an alcohol, or in the case of nucleophilic opening, further functionalize the 7-membered ring. Table 38 shows the attempts of this derivatization reaction.

Table 38. Derivatization of 7-membered ring **511** by epoxidation.



511 **536**

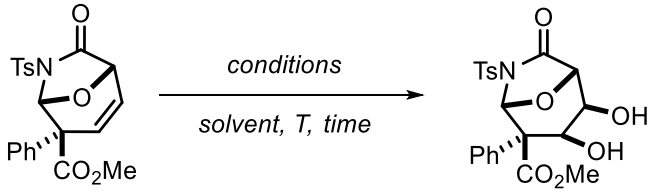
entry	conditions	solvent	T [°C]	time	results
1	*m*CPBA (4.0 equiv)	DCM	25 to 50	3 d	n.r.
2	^{t}BuOOH (2.2 equiv), K_2CO_3 (1.0 equiv), TBAF (2.0 equiv)	DMF	25	2 h	crm
3	^{t}BuOOH (2.0 equiv), Na_2CO_3 (aq., sat., 0.7 M)	MeOH/H_2O	0	1 h	crm

At first, standard epoxidation conditions with *m*CPBA were applied, without any reaction of the starting material as an outcome (entry 1). Thus, in entry 2, the successfully applied conditions with ^{t}BuOOH were examined, which gave good results during the epoxidation of the cyclopropanated pyridinone **379** before (see Table 33 entry 2). In this case, even though the starting material was consumed, a mixture of different unidentifiable products was obtained. In entry 3, slightly modified conditions with ^{t}BuOOH, following a report by Trivedi *et al.*[146] in the aqueous medium were applied, but gave the same result of a

complex reaction mixture as in entry 2. The problem here might be that the formed epoxide **536** is opened during the aqueous workup, to either give an alcohol or when water acts as nucleophile a diol and other byproducts, which were not possible to characterize.

This said, another reaction type, namely a dihydroxylation, might circumvent the unwanted epoxide opening and give the diol **537** right away, which could be transformed afterwards. Hence, in Table 39 different dihydroxylation methods were tested on compound **511**.

Table 39. Dihydroxylation reactions of compound **511**.

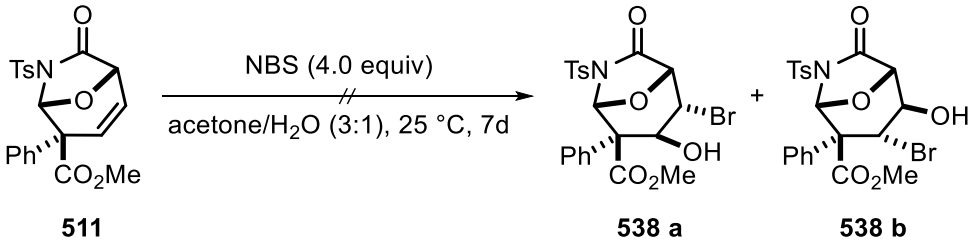


511 **537**

entry	conditions	solvent	T [°C]	time	results
1	$RuCl_3 \cdot 3H_2O$ (6 mol%), $NaIO_4$ (1.6 equiv)	MeCN/H_2O	25	30 min	crm
2	$RuCl_3 \cdot 3H_2O$ (6 mol%), $NaIO_4$ (1.6 equiv)	MeCN/H_2O	0	20 min	crm
3	$K_2OsO_4 \cdot 2H_2O$ (5 mol%), NMO (2.0 equiv)	acetone/H_2O	25	22 h	n.r.

The first attempts for dihydroxylation were made with $RuCl_3$ and $NaIO_4$ as reagents (entries 1 and 2). In entry 1, the reaction was conducted at room temperature, and although after 30 minutes no starting material was left, the outcome was a complex reaction mixture. Based on this, in entry 2, the reaction temperature was lowered to 0 °C, though with the same outcome. Thus, in entry 3, a combination of K_2OsO_4 and NMO was tested since the reactivity of the $RuCl_3$ reagent might be too high. In contrast to the first two entries, no conversion of the starting material occurred with K_2OsO_4. Due to this, more investigation on the reaction conditions might be necessary.

The last approach for derivatization was made by performing a halohydrin reaction of bridged ring **511** with NBS[147] (Scheme 106). In this case, even after adding more NBS over time, which resulted in a total of 4.0 equivalents, and stirring the reaction for seven days, no conversion of starting material **511** was observed.



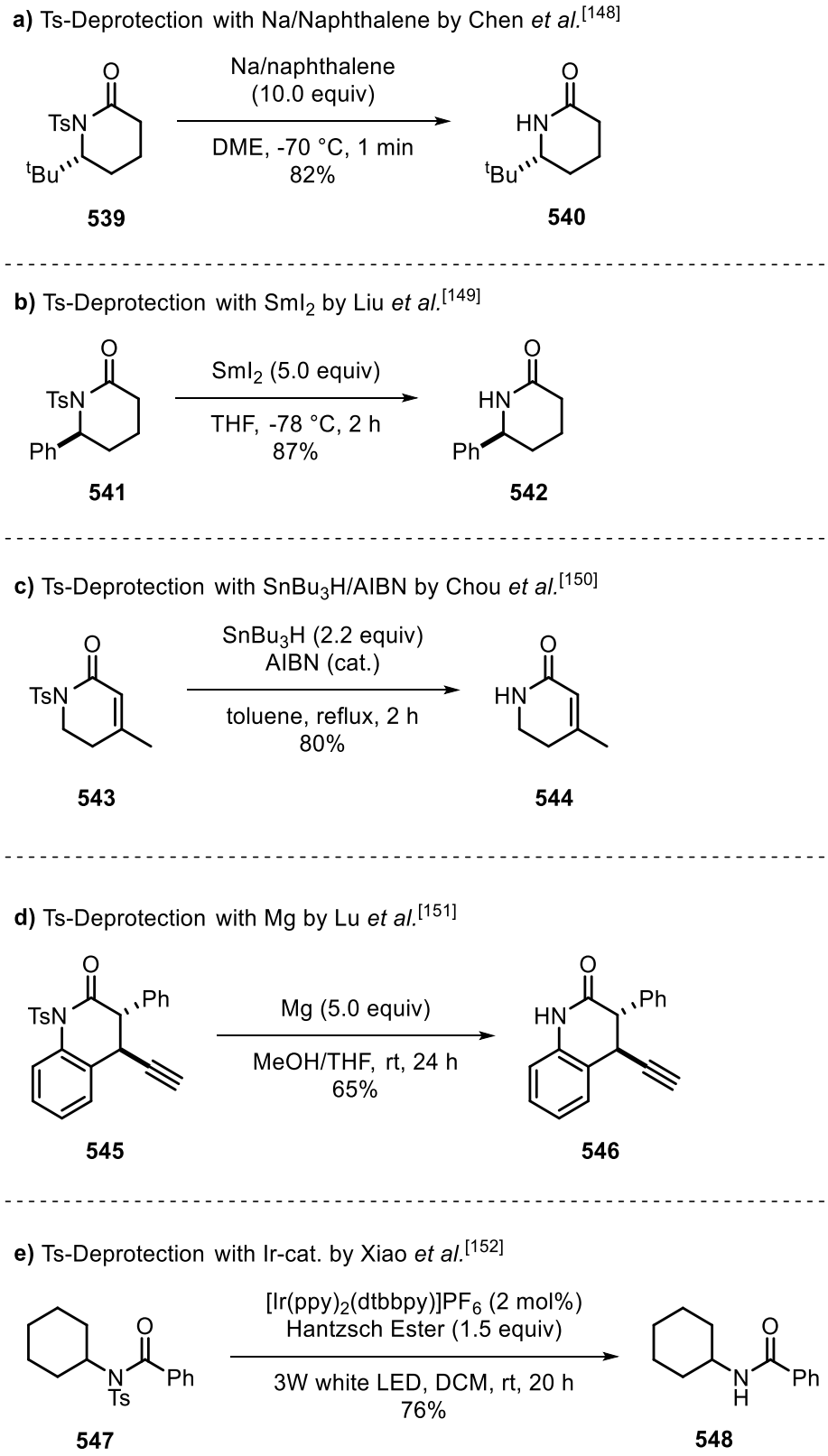
511 **538 a** **538 b**

Scheme 106. Halohydrin reaction of compound **511** with NBS.

Based on these results, more investigations are necessary, to obtain interesting derivatives of compound **511** as well as insight into its reactivity.

2.11 Deprotection of Ts-protecting group

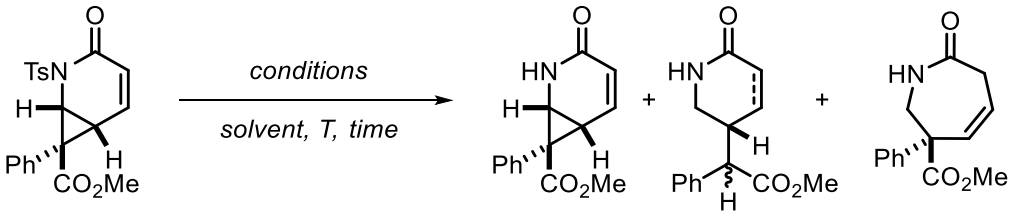
Protecting groups play an important role during natural product synthesis and it lies within the consideration of the researcher to choose the right protecting group, depending on the reaction sequence and the stability requirements. During this work, the tosyl group was selected as the protecting group, based on its stability towards many reagents and reaction conditions, *e.g.* basic, acidic, oxidative *etc*. The downside of these beneficial properties is the difficulty of removing the tosyl group. For this step, relatively harsh reductive conditions are usually necessary. Scheme 107 gives an overview of popular approaches towards a deprotection of this group. The most common choice is by using sodium and naphthalene as reported by the group of Chen[148] (Scheme 107 a) as well as SmI_2 as shown by Liu *et al*.[149] Alternatively, the more unhealthy $SnBu_3H$/AIBN system was published by Chou and co-workers[150] (Scheme 107 b and c respectively). Other methods are the use of Mg in combination with methanol[151] (Scheme 107 d) instead of sodium, as well as a photocatalytic pathway with an Ir-catalyst, which was introduced by the group of Xiao[152] (Scheme 107 e).



Scheme 107. Overview of different Ts-deprotection methods.

Based on these literature reports, the deprotection of the cyclopropanated pyridinone **379** was first investigated. The results are summarized in Table 40.

Table 40. Ts-deprotection of cyclopropanated pyridinone **379**.



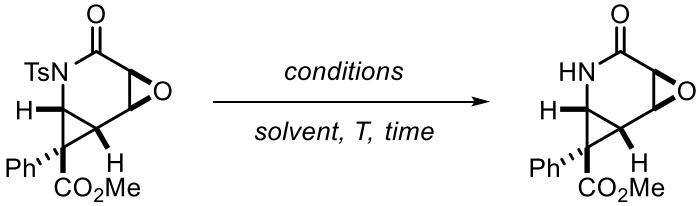
379 **549 a** **549 b** (proposed) **549 c** (proposed)

entry	conditions	solvent	T [°C]	time	results
1	Na/naphthalene (5.0 equiv)	THF	-78	15 min	**549 b** (38%)
2	Na/naphthalene (3.0 equiv)	THF	-78 to 25	17 h	n.r.
3	$SnBu_3H$ (2.2 equiv), AIBN	toluene	reflux	3 h	**549 b**+**549 c** (25%)
4	$Ir[(ppy)_2dtbbpy]PF_6$ (2 mol%), Hantzsch Ester (1.5 equiv)	DCM	25	2 d	decomposition

In the first two entries, the deprotection was examined with sodium and naphthalene. When 5.0 equivalents of sodium naphthalenide were used, an exocyclic opening occurred, and a mixture of saturated and unsaturated product **549 b** was obtained in 38% as well as some undefined byproducts (entry 1). This is just a proposed structure, based on analysis of the crude NMR and mass spectrometry since a successful purification as well as the separation of the different products was not possible. Lowering the amount of sodium naphthalenide to 3.0 equivalents in entry 2, in order to check whether a too large excess might cause an increased byproduct formation, led to no conversion of the starting material. Even letting the reaction stir for 17 h and warming it to room temperature did not give comparable results to entry 1, where already after 15 minutes all starting material **379** was consumed. Not understanding, why with less amount, but still an excess of the reductant nothing happened, a different method was employed for the deprotection, namely $SnBu_3H$ and AIBN as a radical starter in entry 3. In this case, the proposed

exocyclic opened product **549 b** as well as the proposed endocyclic opened product **549 c** were obtained in low yield with other undefinable byproducts. Again, no clear statement could be made about the structure since the purification and clean separation of the obtained compounds was not possible. Finally, the photocatalytic pathway with $Ir[(ppy)_2dtbbpy]PF_6$ as a catalyst and Hantzsch Ester was tested in entry 4, resulting in decomposition of the starting material. From these results it can be concluded that the cyclopropane ring and the Michael system in compound **379** are prone to react under reductive conditions, and thus a deprotection at this stage might not be possible. Hence, the deprotection was examined on the epoxide **498** in the next step. Even though the cyclopropane moiety is still present and might cause problems, the unsaturated system vanished in this case. In addition, a possible opening of the cyclopropane ring would be favourable since it could be done in one step during the deprotection. Table 41 shows the different Ts-deprotection methods.

Table 41. Ts-deprotection of epoxide **498** with different methods.

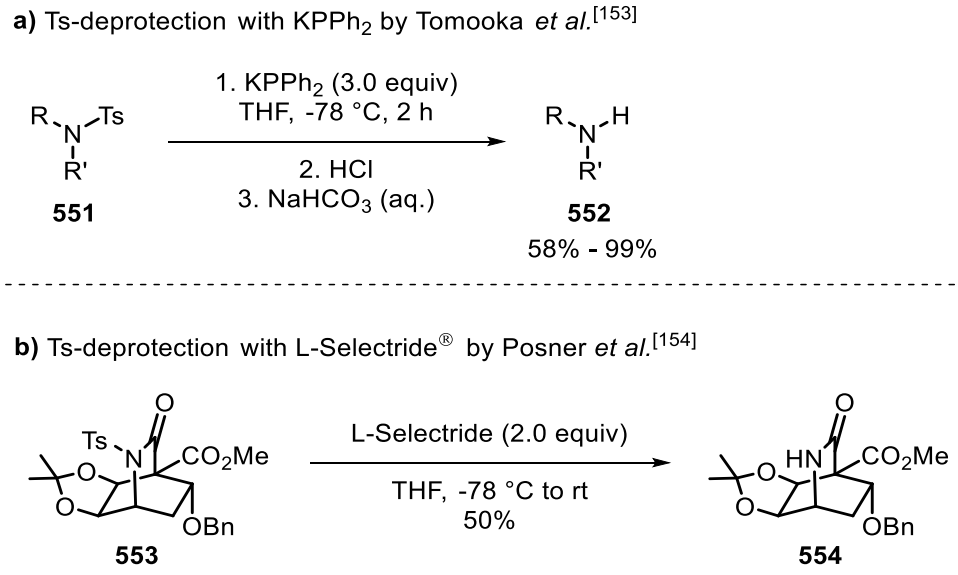


498 **550**

entry	conditions	solvent	T [°C]	time	results
1	Na/naphthalene (2.0 equiv)	THF	-78 to 25	18 h	n.r.
2	$SnBu_3H$ (2.2 equiv), AIBN	toluene	reflux	20 h	n.r.
3	SmI_2 (5.0 equiv)	THF	-78 to 25	20 h	n.r.
4	$Ir[(ppy)_2dtbbpy]PF_6$ (2 mol%), Hantzsch Ester (1.5 equiv)	DCM	25	3 d	n.r.

5	$KPPh_2$ (3.0 equiv)	THF	-78	30 min	crm
6	L-Selectride® (2.0 equiv)	THF	-78 to 25	18 h	crm

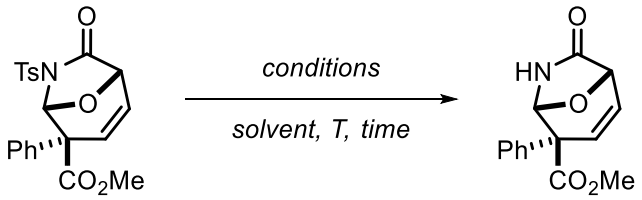
The first investigations towards the deprotection of the tosyl group were conducted with sodium naphthalenide (entry 1), $SnBu_3H$/AIBN (entry 2), SmI_2 (entry 3) and photocatalytic in entry 4, but in all cases no conversion of the epoxide **498** was observed. From these outcomes, it can be concluded that reductive cleavage of the protecting group through a radical mechanism is not possible. The radical species' reactivity is probably too low because of the changed electronic properties of the epoxide **498** compared to the unsaturated pyridinone **379**. For this reason, other nucleophilic methods were applied, *e.g.* in entry 5, $KPPh_2$ was used as described by Tomooka *et al.*[153] in 2012, who successfully deprotected especially tosylated amines **551** by this method. Another approach was using L-Selectride® (entry 6) as reported by the group of Posner[154] in 2016, who were able to deprotect the amide **553** without reducing the ester and amide bond (Scheme 108). However, in this case only a complex reaction mixture was obtained, based on the reactivity of epoxide **498** towards relatively strong nucleophiles.



Scheme 108. Ts-deprotection under nucleophilic conditions with a) $KPPh_2$ and b) L-Selectride®.

Seeing that the deprotection was not successful with the epoxide, the last trial was made to cleave the tosyl group within the bridged 7-membered ring **511** (Table 42).

Table 42. Ts-deprotection of compound **511** with different conditions.

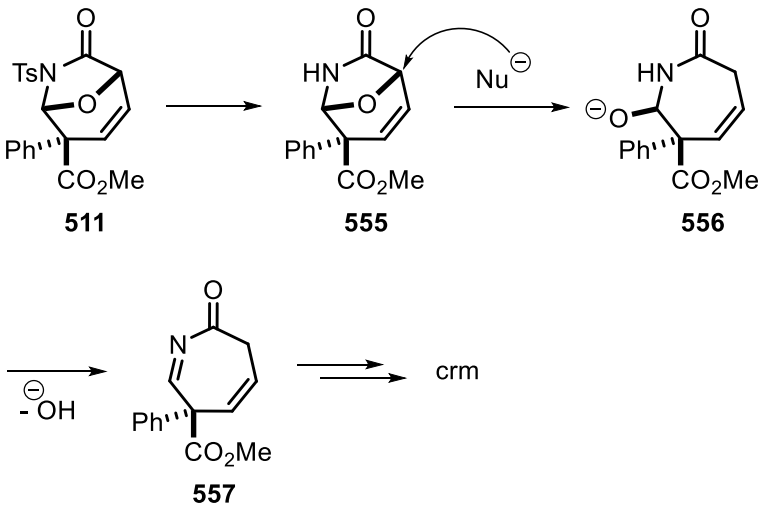


511 **555**

entry	conditions	solvent	T [°C]	time	results
1	Na/naphthalene (3.0 equiv)	THF	-78 to 25	5 h	25%
2	Na/naphthalene (3.0 equiv)	THF	**-50**	2.5 h	22%
3	PhOH (3.2 equiv)	HBr/HOAc	80	19 h	crm
4	SmI_2 (5.0 equiv)	THF	-78	1 h	10%
5	$KPPh_2$ (3.0 equiv)	THF	-78	1 h	5%
6	$Ir[(ppy)_2dtbbpy]PF_6$ (2 mol%), Hantzsch Ester (1.5 equiv)	DCM	25	5 d	n.r.
7	Mg (5.0 equiv)	MeOH/THF	25	2.5 h	crm
8	Mg (5.0 equiv)	MeOH/THF	-78 to 25	7 h	crm
9	TBAF (6.0 equiv)	THF	25	1 d	crm
10	NaI/TMSCl (1.5 equiv)	MeCN	85	19 h	n.r.

11	L-Selectride® (2.0 equiv)	THF	-78 to 25	18 h	crm
12	Na/naphthalene (3.0 equiv)	THF	-70	3 min	45%
13	Na/naphthalene (3.0 equiv)	THF	-70	5 min	36%
14	Na/naphthalene (3.0 equiv)	THF	-70	1 min	18%
15	Na/naphthalene (3.0 equiv)	THF	-70	2 min	27%

In entry 1, the reaction with sodium naphthalenide was investigated, which gave the desired product **555** in 25% yield after the starting material was completely consumed after 5 h and increasing the temperature to rt. Next, it was tested whether the yield could be raised, when the temperature was closely controlled (entry 2). Still, the yield was 22% after running the reaction at -50 °C. For this reason, other reagents were applied (entries 3 to 11). Starting with phenol under acidic conditions[155] (entry 3), a complex reaction mixture was obtained, because the conditions might be too harsh for compound **511**. With SmI_2 and $KPPh_2$ just low yields of product **555** were obtained (entries 4 and 5 respectively), whereas under photocatalytic reaction conditions no conversion of starting material was observed (entry 6). A complex reaction mixture was seen with magnesium, when it was performed at ambient temperature (entry 7), as well as when the temperature was monitored carefully starting from -78 °C (entry 8). The deprotection reactions with TBAF[156] (entry 9) and L-Selectride® (entry 11) gave a complex reaction mixture and with NaI/TMSCl[157] (entry 10), no reaction was observed. From this outcome it became clear that compound **555** is not stable in a nucleophilic reaction environment. The oxo-ring is probably opened by nucleophilic attack after the deprotection of the tosyl group occurs, and the resulting hemiaminal **556** is an unstable species, readily undergoing water elimination and forming an imine **557**, which then reacts further (Scheme 109).



Scheme 109. Explanation for the instability of compound **555** under nucleophilic conditions.

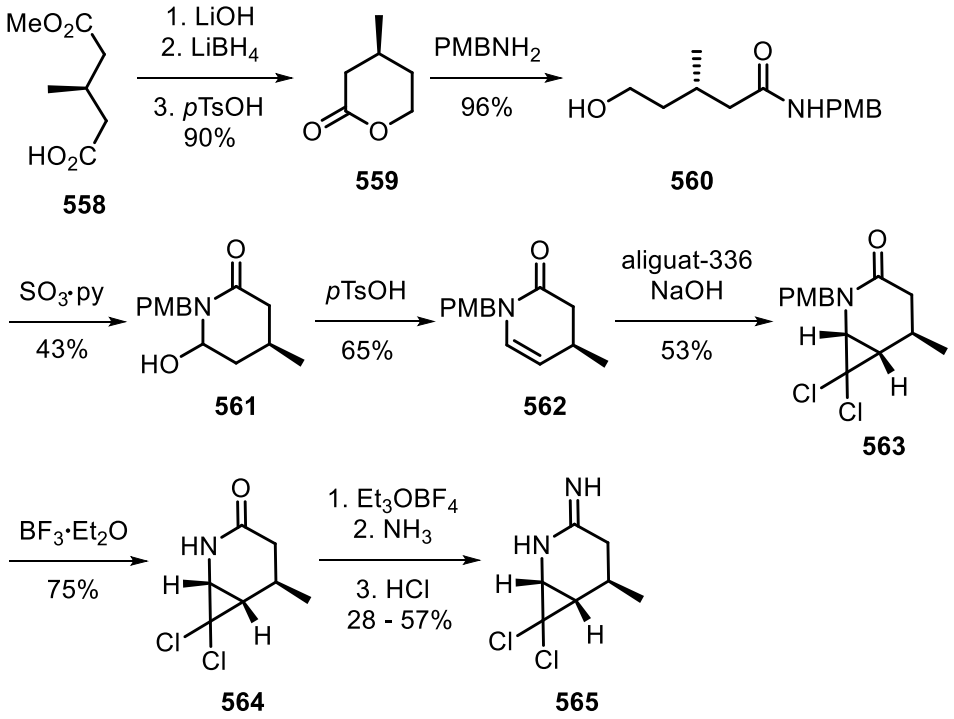
Therefore, the focus was again laid on the deprotection with sodium naphthalenide since it gave the best results before (see Table 42 entry 1). This time, it was decided to closely investigate the reaction time since it might be important to stop the reaction before the product might undergo decomposition as explained in Scheme 109. Hence, in entry 12 (Table 42) the reaction was quenched after 3 minutes and this gave the desired product in 45% yield. Attempting to increase the yield by running the reaction for 5 minutes (entry 13), reduced the yield to 36%. Shorter reaction times of 1 minute and 2 minutes did not result in an improved outcome, with 18% and 27% of product **555** (entries 14 and 15 respectively). In all these cases (entries 12 – 15), still some unreacted starting material was reisolated, which strengthens the idea, that the formed product **555** is reacting further with time, resulting in the low yields observed.

2.12 Synthesis of iNOS inhibitor

2.12.1 Synthetical approach

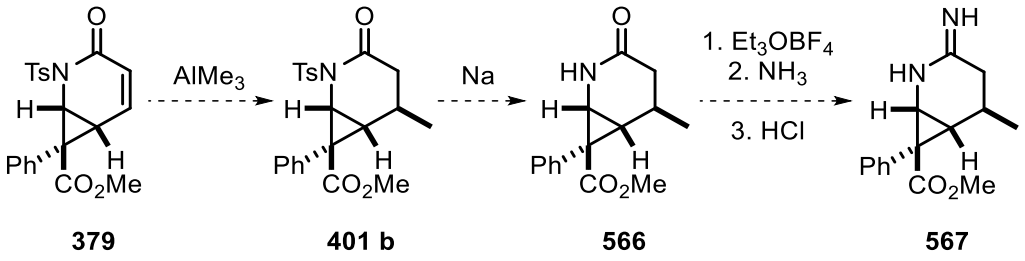
Nitric oxide (NO), as a chemical mediator, is responsible for many physiological transmissions, *e.g*. neuronal transmission, cardiovascular, gastrointestinal, genitourinary, respiratory, antipathogenic and antitumor responses. It is produced, *inter alia*, by the inducible nitric oxide synthase (iNOS), which itself is responsible for immune response. However, when iNOS is overexpressed, an excess of NO is produced, reacting with a superoxide radical, generated during cellular metabolism, to produce reactive nitrogen species. These cause oxidative stress and inflammations in the body, leading to diseases such as Parkinson's, Alzheimer's, multiple sclerosis, stroke, diabetes mellitus and different cancer concerning breast, lung, colon and melanoma. Therefore, selective inhibition of iNOS might help treat certain diseases caused by the overproduction of NO.[158,159]

In 2003, the group of Kawanaka presented a total synthesis of the iNOS inhibitor **565**, starting from compound **558**, which after several transformations gave the cyclopropanated pyridinone **563**. Cleavage of the protecting group and formation of amidine **565** finished the synthesis (Scheme 110), yielding iNOS inhibitor **565** with an IC_{50} value of 0.02 µM. Especially the substituents on the cyclopropane ring seem to play a role in the compound's activity, with chloride being the best one so far.[159]



Scheme 110. Total synthesis of iNOS inhibitor **565** according to Kawanaka *et al.*[159]

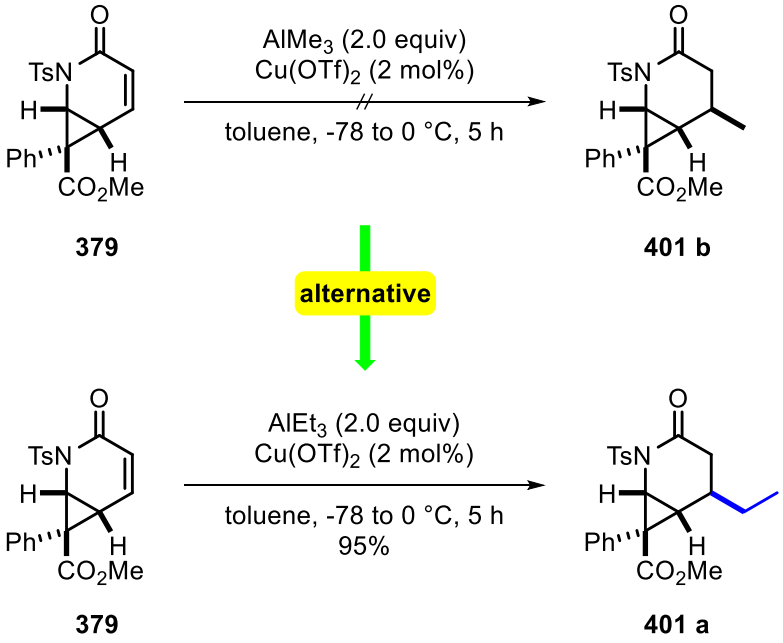
Looking closely at the structure of amidine **565**, a great similarity can be found with the cyclopropanated pyridinone **379**, that the work of this chapter is focused on. Thus, the idea arose, that the transformation of amide **379** into amidine **567** might be possible in just three steps, as proposed in Scheme 111. After methylation and deprotection of the tosyl group, amide **566** could be transformed to a possibly potent iNOS inhibitor **567**.



Scheme 111. Synthetic strategy for the formation of a possible iNOS inhibitor **567** in three steps form pyridinone **379**.

The investigation started by methylation of cyclopropanated pyridinone **379** with $AlMe_3$ since the same reaction with $AlEt_3$ gave outstanding results (see Table 16 entry 1). Though in this case, no reaction occurred with $AlMe_3$ and just the starting material **379** was reisolated (Scheme 112). Not being demotivated by this outcome, it was decided to

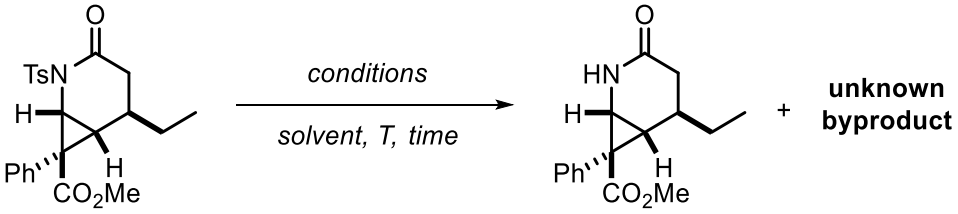
continue the synthesis with the ethyl product **401 a** since it was assumed that the change from methyl to ethyl group would not pose a big difference.



Scheme 112. Attempt of methylating compound **379** with $AlMe_3$ (upper image) and use of successfully ethylated product **401 a** as an alternative (lower image).

In the second step, various methods for deprotection of the tosyl group were applied (Table 43). Since the several approaches were already discussed in the previous chapter B 2.11, only the results will be presented in this case.

Table 43. Screening of different Ts-deprotection methods with compound **401 a**.



401 a **568**

entry	conditions	solvent	T [°C]	time	results
1	Na/naphthalene (3.0 equiv)	THF	-78	20 min	38%
2[a)]	Na/naphthalene (3.0 equiv)	THF	-78 to 25	5.5 h	32% + bp
3[b)]	Na/naphthalene (3.0 equiv)	THF	-78 to 25	4 h	bp
4[c)]	Na/naphthalene (3.0 equiv)	THF	-78 to 25	3.5 h	bp
5	$SnBu_3H$ (2.2 equiv), AIBN	toluene	reflux	20 h	n.r.
6	SmI_2 (5.0 equiv)	THF	-78 to 25	23 h	n.r.
7	Mg (5.0 equiv)	MeOH/THF	25	2 d	n.r.
8	$Ir[(ppy)_2dtbbpy]PF_6$ (2 mol%), Hantzsch Ester (1.5 equiv)	DCM	25	2 d	n.r.

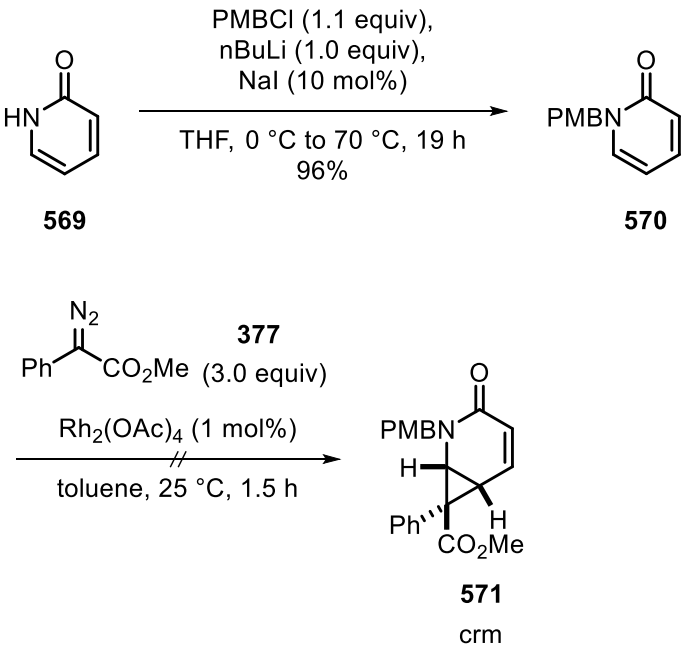
a) Larger scale. b) Same scale as entry 1. c) Longer stirring of Na with naphthalene.

Entry 1 shows the deprotection with sodium naphthalenide, which gave the desired product **568** in 38% after 20 min. Repeating the same reaction in entry 2 on a bigger scale gave the product in 32% yield as well as an unknown byproduct (bp). The reaction took much longer – only after 5.5 hours all the starting material **401 a** was consumed. Therefore, in entry 3, the deprotection was repeated on the same small scale as in entry 1, because of the possibility that this reaction might only work on smaller scale, but this only gave the byproduct this time. The last attempt was made to reproduce the first outcome by stirring sodium and naphthalene for a longer time, before adding pyridinone

401 a compared to entry 1. The idea of this step was that maybe not all the sodium was dissolved to form sodium naphthalenide, and thus side reactions happened. Though again, just the byproduct was obtained. Due to difficulties in purification and isolation it was impossible to find out the byproducts' structure. Thus, from entries 5 to 8, different deprotection methods were examined. Alas, neither the reduction with $SnBu_3H$/AIBN (entry 5) or SmI_2 (entry 6) or Mg in MeOH (entry 7), nor the photocatalytic pathway (entry 8) showed any conversion of starting material. Only compound **401 a** was reisolated in all cases. It cannot be explained, why no reaction happened in these cases, but it probably has to be the same electronical reason as with epoxide **498** (see Table 41) that a reduction *via* a radical path is not possible. Due to this outcome, a different approach was necessary to circumvent the use of the tosyl protecting group.

2.12.2 Use of different protecting groups

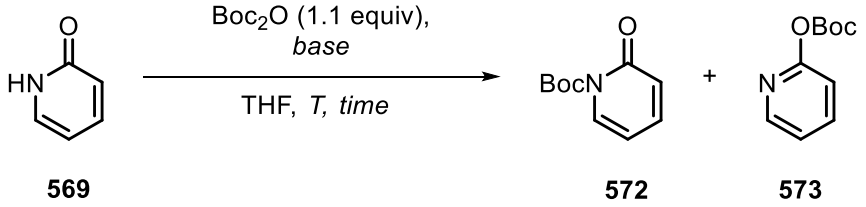
Another attempt to synthesize an iNOS inhibitor was to change the protecting group to an easier cleavable one. The first choice fell upon the *para*-methoxybenzyl (PMB) protecting group, as it was also used during the synthesis reported by Kawanaka *et al.*[159] (see Scheme 110). Protection of pyridinone **569** was already reported in the literature by Sośnicki and his group[93] in 2019 and could be reproduced without any problems to give compound **570** in 96% yield. In the next cyclopropanation step, only a complex reaction mixture was obtained, where among other byproducts, a mono and double cyclopropanated compound were identified (Scheme 113). This low regioselectivity, compared to the tosyl group, can be explained, because the PMB group is less electron-withdrawing, resulting in a mixture of different products, since the desired double bond for cyclopropanation was less or not activated at all.



Scheme 113. PMB-protection of pyridinone **569** and following cyclopropanation.

Since an electron-withdrawing group was necessary, it was decided to investigate the Boc-protecting group. The first problem arose during the protection of pyridinone **569** when two products, **572** and **573**, were formed. Therefore, some reaction conditions were screened, in order to obtain the desired product **572** in a better ratio (Table 44).

Table 44. Screening of conditions for Boc-protection of pyridinone **569**.



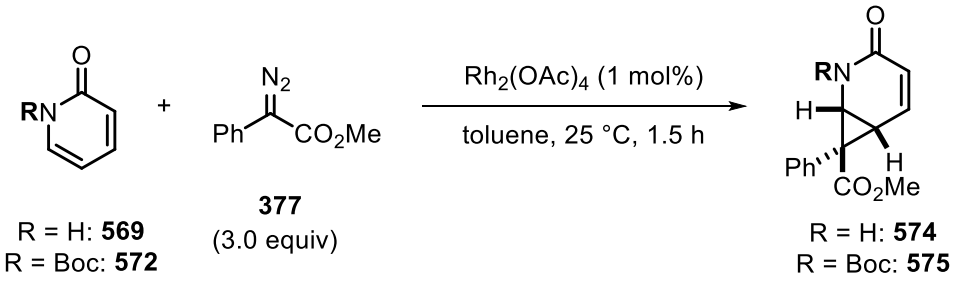
entry	base	time	T [°C]	results
1	DMAP (10 mol%)	2 h	0 to 25	**572** (27%) + **573** (16%)
2	DMAP (10 mol%)	45 min	0	*crude* **572**/**573** 1:1.9
3[a)]	^{n}BuLi (1.14 equiv)	1 h	0	**572** (21%) + **573** (42%)

a) 1% NEt_3 was used in solvent mixture during column chromatography.

Entry 1 shows the first approach according to the patent of Haydon and Czaplewski[160] with DMAP as a base, which gave a mixture of two products **572** and **573** in low yield.

For this reason, in entry 2, it was attempted to stay low with the temperature, which gave the opposite ratio of **572**/**573**. In this case, the crude mixture was not purified since it will be used in the next step as explained below. The last try was made with ^{n}BuLi as a base[161] (entry 3), which gave the two products in better yield compared to entry 1 but less favourable ratio of **572**/**573** 1:2. Additionally, during column chromatography, 1% NEt_3 was added to the eluent in order to test, whether the silica gel might be too acidic, and thus a partial cleavage of the Boc-group occurred. This test also did not give satisfactory results. For this reason, it was decided to move on to the cyclopropanation step to see if this would give good results, before optimization of the protection step. The results for the cyclopropanation are summarized in Table 45.

Table 45. Cyclopropanation reactions of compounds **569** and **572**.



R = H: **569**
R = Boc: **572**

377
(3.0 equiv)

R = H: **574**
R = Boc: **575**

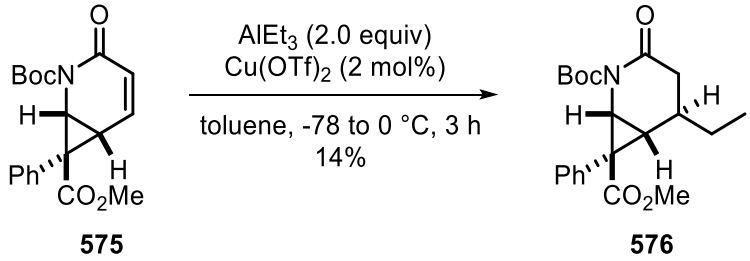
entry	R	results
1	Boc	51% (**575**)
2[a)]	Boc	traces
3	H	n.r.

a) Crude mixture from the previous step was used.

First, the clean compound **572** was cyclopropanated, yielding the desired product **575** in 51% (entry 1). In entry 2, it was then tried to conduct this reaction with the crude mixture from Table 44 entry 2. The idea was, that an equilibrium between product **572** and **573** might be present, and since only compound **572** is cyclopropanated, the equilibrium should be shifted and thus better yields of product **575** could be obtained, as well as resolving the problem of byproduct formation from the protection step. Alas, just traces of cyclopropane **575** was observed. After that, it was attempted to cyclopropanate the unprotected pyridinone **569** (entry 3), but in this case no reaction occurred. Here, the

catalyst was probably poisoned by the free amide because the initially green colour turned purple, which is usually an indicator for $Rh_2(OAc)_4$ poisoning.[162]

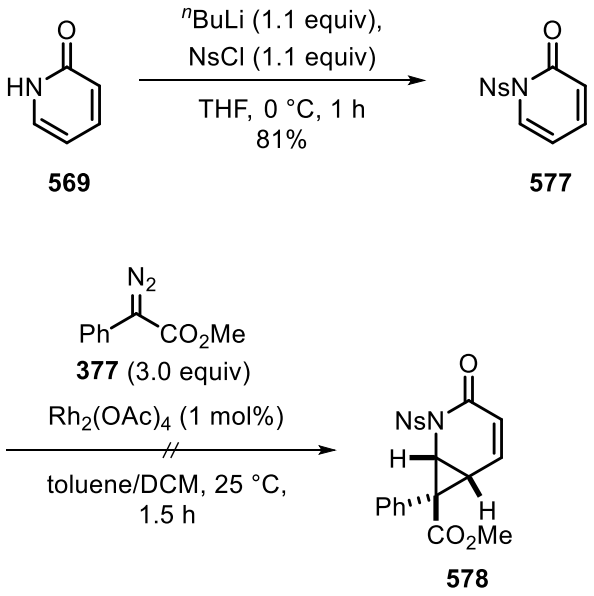
In the next step, cyclopropane **575** was ethylated with $AlEt_3$ (Scheme 114), which gave the product **576** in just 14% yield. From this outcome, it was clear that the reactions with Boc-protected pyridinone **575** were inferior to the tosyl-protected one, and thus were not pursued further.



575 **576**

Scheme 114. 1,4-addition with $AlEt_3$ to Boc-protected pyridinone **575**.

The last approach, in order to synthesize the natural product **567**, was made by using the nosyl protecting group. It is even more electron-withdrawing then the tosyl group because of a nitro-group, but easier to remove. As shown in Scheme 115, protection of pyridinone **569** according to the literature[161] worked without any problem and gave the desired product **577** in 81% yield. However, the cyclopropanation step was problematic since compound **577** was not soluble in toluene or DCM due to its high polarity. Even after warming the reaction mixture to 30 °C and subjecting it to ultra sound for nearly one hour did not help in dissolving the starting material. A solubility test showed that compound **577** is only soluble in DMSO and plenty of MeOH, both of which solvents cannot be used in the presence of $Rh_2(OAc)_4$ since the catalyst is then coordinating to the solvent and facilitating a reaction with the diazo ester instead of starting material **577**.[163]

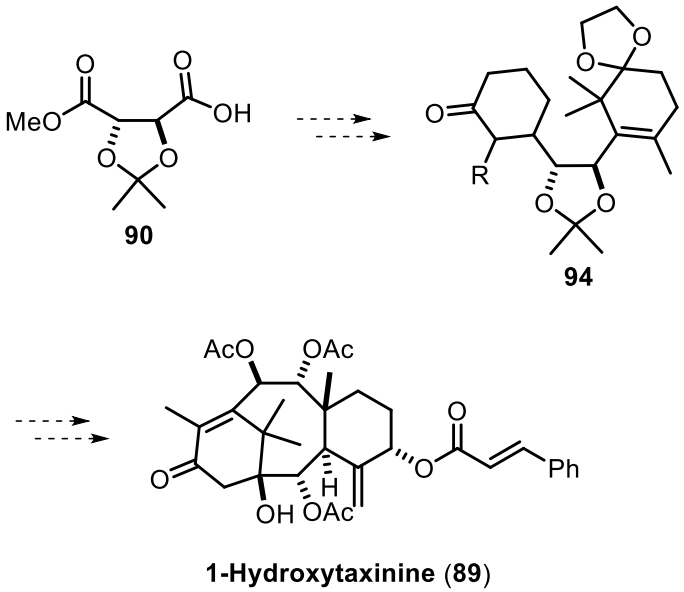


Scheme 115. Nosyl-protection of pyridinone **569** and cyclopropanation attempt.

Seeing that screening of different protecting groups, being worth considering due to their stability and electronic effects, did not lead to the desired results, it was decided to give up the synthesis of the iNOS inhibitor.

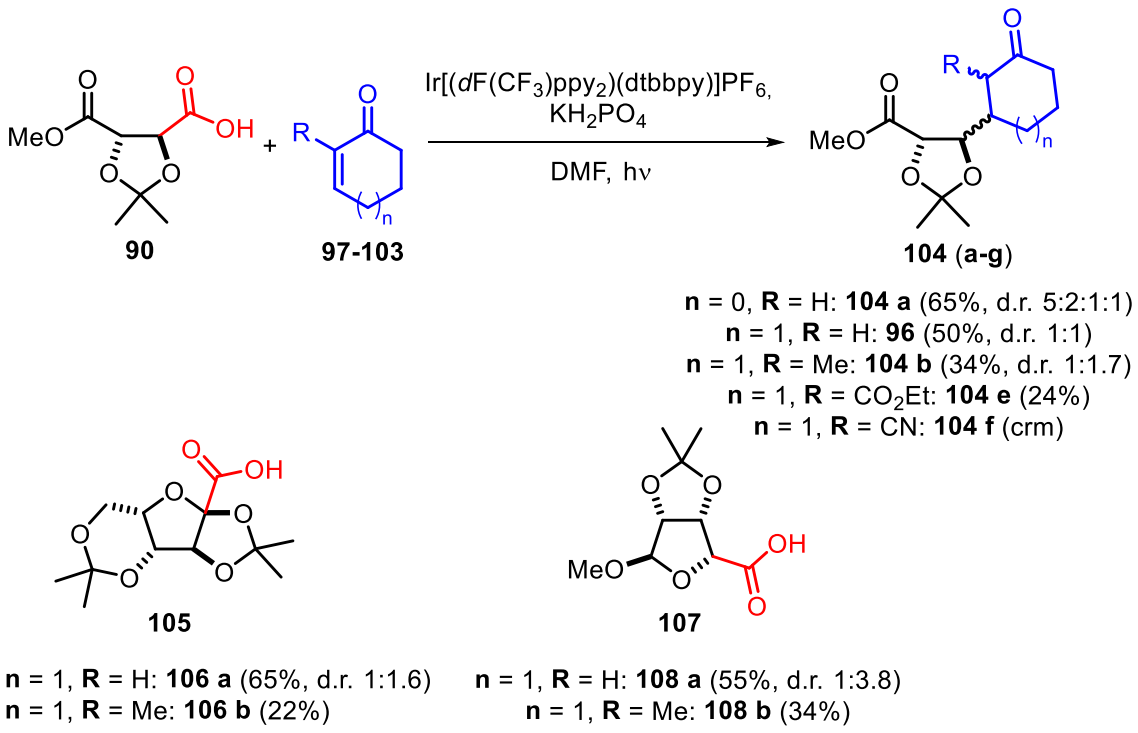
C Summary

One part of this thesis was partially performed at the University of Tokyo in the group of professor Masayuki Inoue and focused on the synthesis of bioactive tricyclic compounds like the synthesis towards 1-Hydroxytaxinine (**89**) *via* photocatalyzed decarboxylative coupling of acid **90** (Scheme 116). The idea of this approach was the consecutive coupling of suitable acceptors with acid **90** in order to obtain compound **94** which then could be transformed to the desired natural product **89**, thus reducing the already reported synthesis[25] by at least four steps.



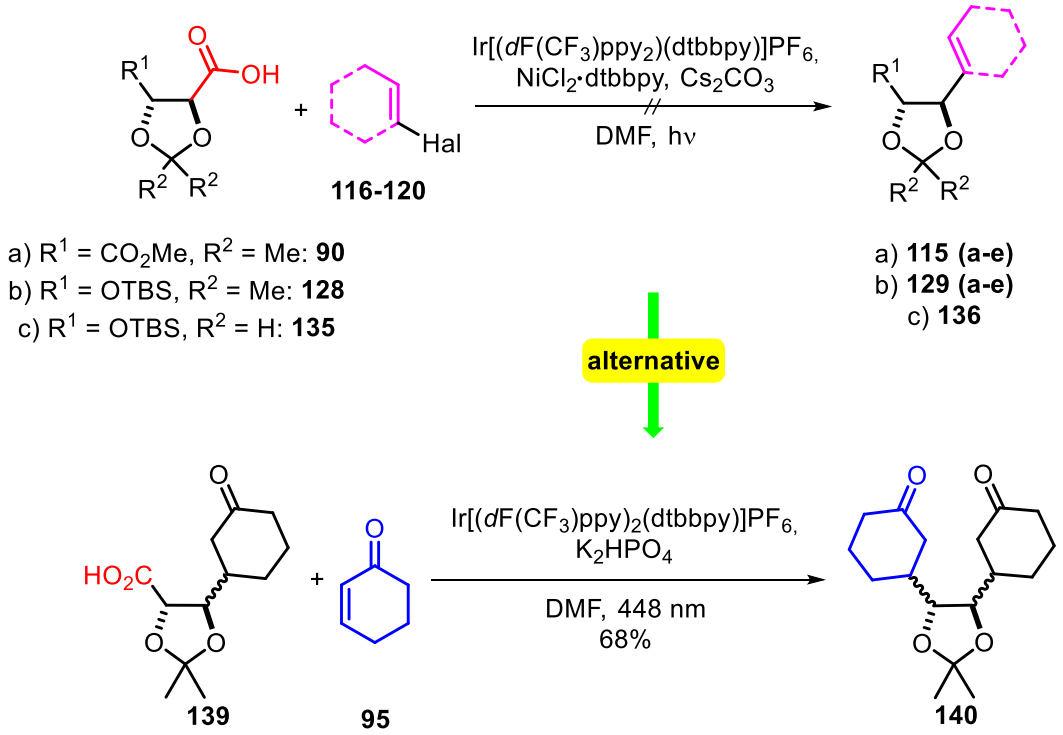
Scheme 116. Synthetical approach for the decarboxylative coupling of acid **90** towards the preparation of 1-Hydroxytaxinine (**89**).

The investigation started with the decarboxylative coupling of the acids **90**, **105** and **107** with different acceptors **97-103**, giving the desired products **104 a-g**, **106 a-b** and **108 a-b** without major problems in moderate yields (Scheme 117). The only limitation of this reaction was that electron-withdrawing groups R (*e.g.* CO_2Et, CN) could not be used since the corresponding acceptors **99** and **101** became labile under basic conditions, thus resulting in a lower yield or a complex reaction mixture.



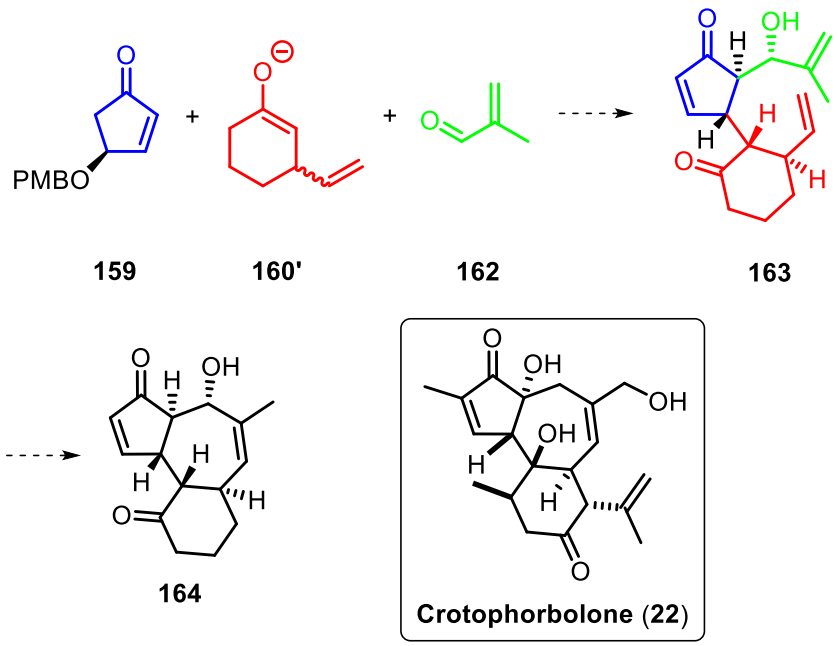
Scheme 117. Decarboxylative coupling of acids **90**, **105** and **107** with different acceptors **97-103**.

Further, it was examined whether a decarboxylative coupling with vinyl halogens **116-120** was possible under double catalysis but it turned out to be impossible (Scheme 118, upper part). Even after the sterical hindrance of the acid **90** was reduced step by step – first by reducing the ester group in case b) and then by omitting the methyl groups of the acetal moiety in case c) –, no reaction between the starting material or only the formation of byproducts in small amounts was observed. Therefore, it was concluded that these substrates were not compatible with the applied reaction conditions. An alternative reaction was a second decarboxylative coupling with acceptor **95**, giving the desired product **140** in good yield (Scheme 118, lower part). Since the research stay came to an end, more investigations on this transformation were not conducted, but provided the basis for further examinations.



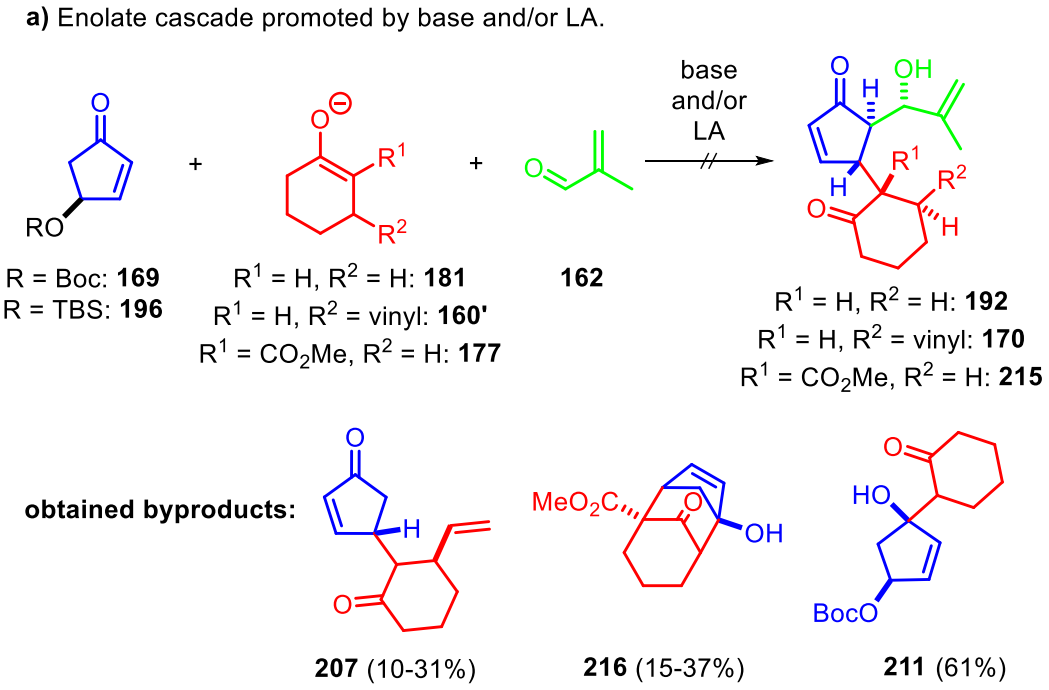
Scheme 118. Decarboxylative coupling with vinyl halogens **116-120** under double catalysis (upper part) or with acceptor **95** (lower part).

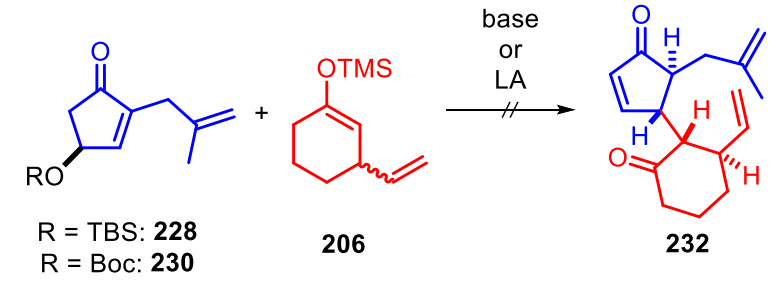
Another tricyclic structure, which synthesis was pursued was compound **164**, a derivative of the bioactive Crotophorbolone (**22**). The synthesis focused on an enolate cascade between the substrates **159**, **160'** and **162** which should give intermediate **163** with set stereocenters based on the enantiomerically pure cyclopentenone **159**, followed by an RCM to yield the product **164** (Scheme 119).



Scheme 119. Synthetical strategy for the synthesis of tricycle **164** *via* an enolate cascade.

Unfortunately, none of the applied reactions led to the desired compound **163**. In the case of the enolate cascade promoted by different bases or Lewis acids or the combination of both of them, only byproducts (**207**, **216** and **211**) were obtained in low to moderate yields (Scheme 120 a). When it was decided to conduct a single 1,4-addition of enolate **206** with the Stille coupling product **228** or **230**, no reaction occurred (Scheme 120 b). There are several possible explanations for these outcomes: First, the TMS-enolether **206** possess acidic protons which might either protonate the corresponding enolate anion of **206** or the resulting enolate from the enolate addition with cyclopentenone, thus not allowing for further reaction with methacrolein (**162**). The second reason concerns the sterical hindrance of the substrates as the protecting group of the cyclopentenone and the vinyl moiety of **206** or **160'** can be considered as bulky groups as well as the allylic moiety of compound **228** or **230**, hence hindering the addition of the substrates and/or favor the inter-and intramolecular protonation of the formed enolate.

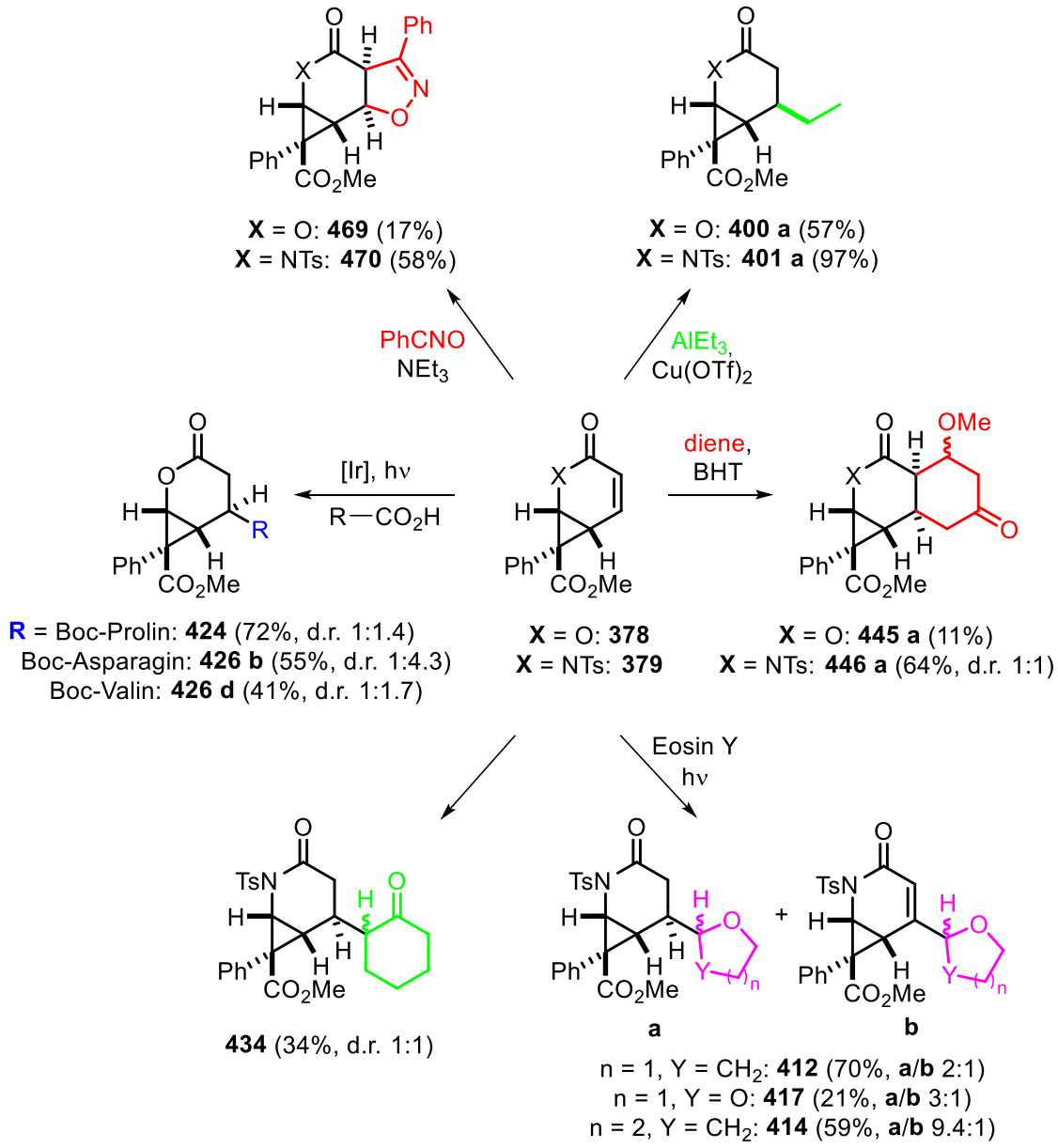




Scheme 120. Intended enolate cascade (a) or enolate addition (b) towards the products **192**, **170**, **215** or **232** under basic or LA conditions.

The other part of the thesis was a continuation of Dr. Michael Leitners' work from this group and focused on the reactivity of cyclopropanated 2-pyrone **378** and 2-pyridinone **379**. At first, different reaction types were applied to figure out the most promising ones and which are summarized in Scheme 121. Thus, 1,4-addition (green) of $AlEt_3$ (**400 a** and **401 a**) gave good results but was just limited to this organoaluminum compound and enolate addition (**434**) was only possible with 2-pyridinone – since 2-pyrone is not stable under basic or nucleophilic conditions – and was not pursued any further. Photocatalyzed decarboxylative coupling only worked with 2-pyrone (**424**, **426 b** and **426 d**) and secondary amino acids in moderate to good yields (blue). Compared to this, CH-activation with Eosyn Y as photocatalyst only performed with 2-pyridinone (**412**, **414** and **417**), though it was limited to cyclic substrates with electronic properties like THF

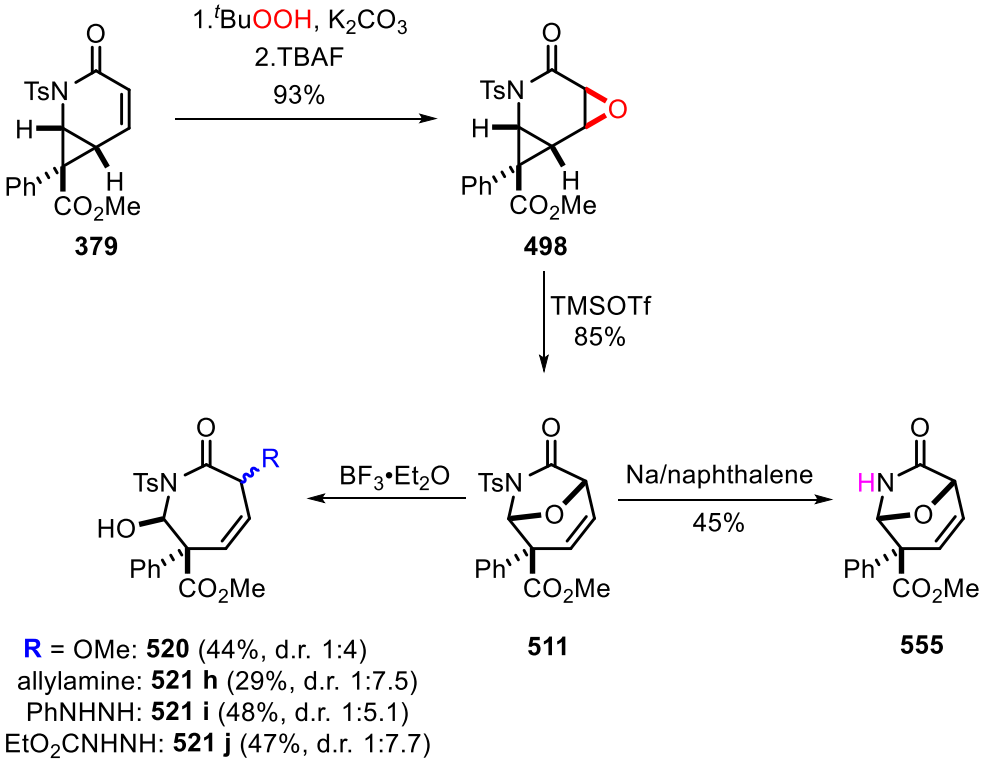
(purple) and in all cases the reduced byproduct **b** was obtained. Concerning the cycloadditions (red), the Diels-Alder reaction was limited to the Danishefsky's diene (**445 a** and **446 a**) and the [3+2]-cycloaddition gave the interesting tricycles **469** and **470**. Both reactions gave the products in good yields when 2-pyridinone was applied and in low yields in case of the 2-pyrone.



Scheme 121. Overview of the different reaction types with cyclopropanated 2-pyrone **378** and 2-pyridinone **379** and their outcome.

An additional reaction type, namely the epoxidation of 2-pyridinone, gave the desired epoxide **498** in an excellent yield and was pursued further in order to open the cyclopropane ring, giving the bridged 7-membered ring **511** in excellent yield as well

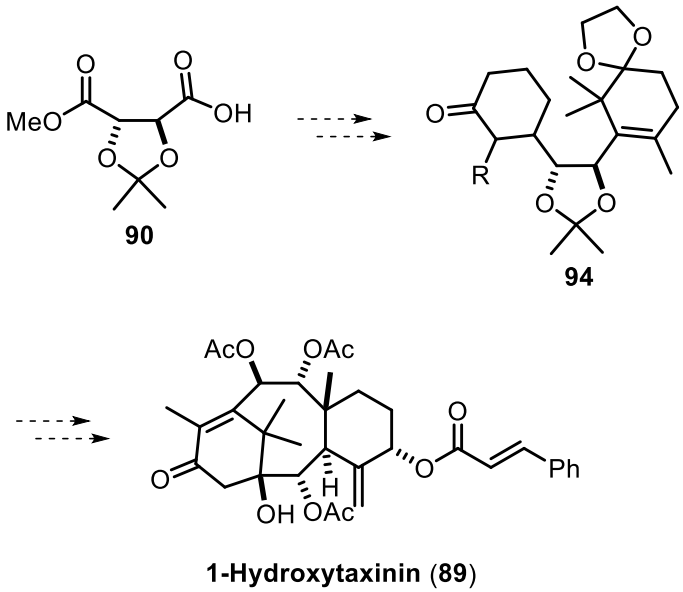
(Scheme 122). This interesting compound, on the one hand, was deprotected to the amide **555** in moderate yield. On the other hand, the oxo-bridge was opened with different nucleophiles in moderate yields (**520** and **521 h-j**), although this reaction is basically limited to amine-nucleophiles. With this, a reaction scope of interesting compounds was accomplished and further investigations, especially on the reactivity of the 7-membered ring **511**, may be promising.



Scheme 122. Epoxidation of 2-pyridinone **379** and cyclopropane ring-opening, followed by functionalization reactions of compound **511**.

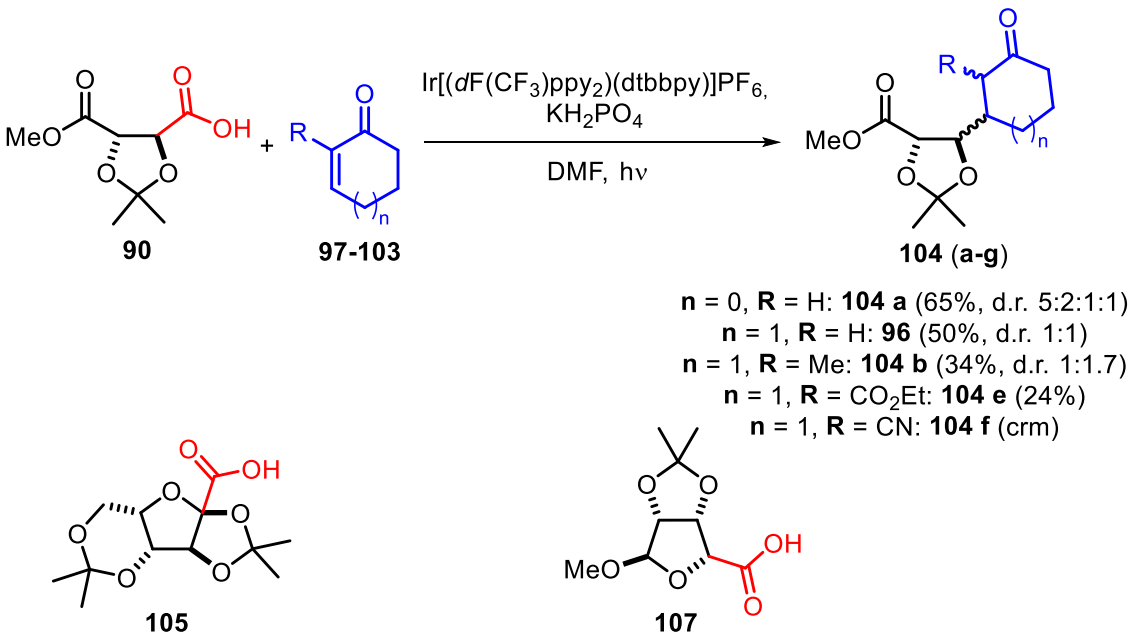
D Zusammenfassung

Ein Teil dieser Arbeit wurde am Arbeitskreis von Prof. Masayuki Inoue an der Tokio Universität durchgeführt und konzentriert sich auf die Synthese von bioaktiven, trizyklischen Verbindungen wie 1-Hydroxytaxinin (**89**) mittels photokatalytischer decarboxylativen Kupplung von Säure **90** (Schema 123). Die Idee war, geeignete Akzeptoren nacheinander mit Säure **90** zu koppeln, um Verbindung **94** zu erhalten. Diese könnte dann in den Naturstoff **89** umgewandelt werden und somit die schon dafür vorhandene Synthese[25] um mindestens vier Schritte verkürzen.



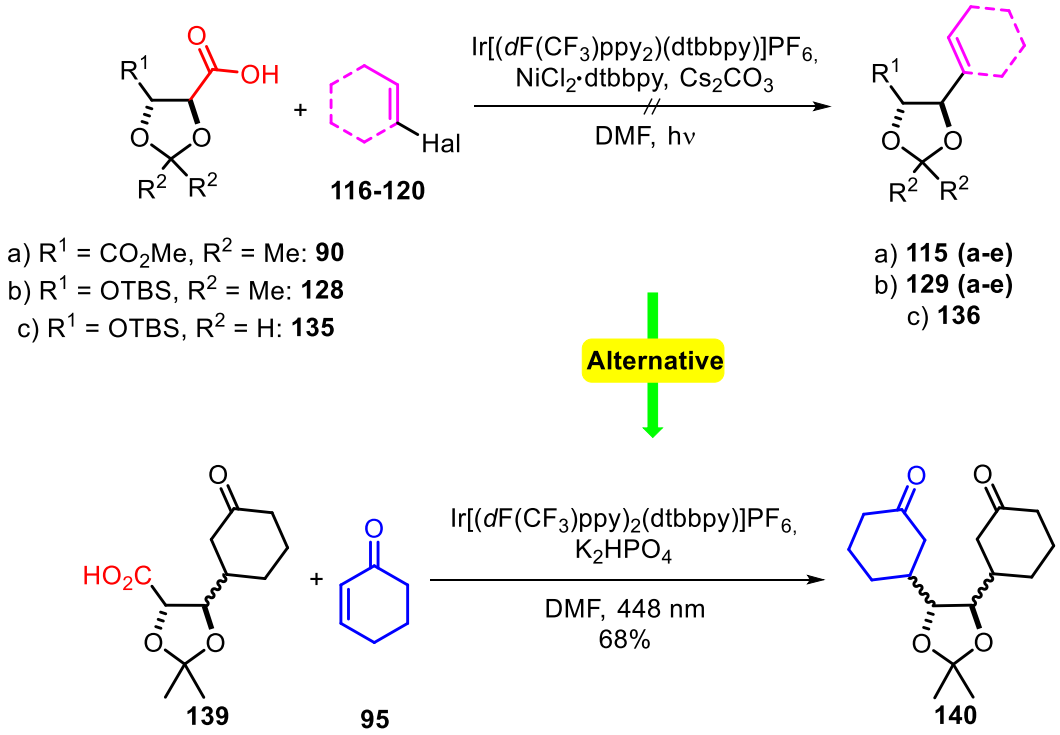
Schema 123. Synthesevorschlag für die decarboxylative Kupplung von Säure **90**, um 1-Hydroxytaxinin (**89**) herzustellen.

Die Untersuchung fing mit der decarboxylativen Kupplung der Säuren **90**, **105** und **107** mit unterschiedlichen Akzeptoren **97-103** an, die die gewünschten Produkte **104 a-g**, **106 a-b** und **108 a-b** in mäßiger Ausbeute ergab (Schema). Der limitierende Faktor dieser Reaktion ist die Zersetzung der Akzeptoren **99** und **101** mit elektronen-ziehenden Gruppen R (z.B. CO_2Et, CN), da diese unter den basischen Reaktionsbedingungen instabil sind. Mit solchen Substituenten lief die Reaktion schlecht ab oder führte zu Zersetzungsreaktionen.



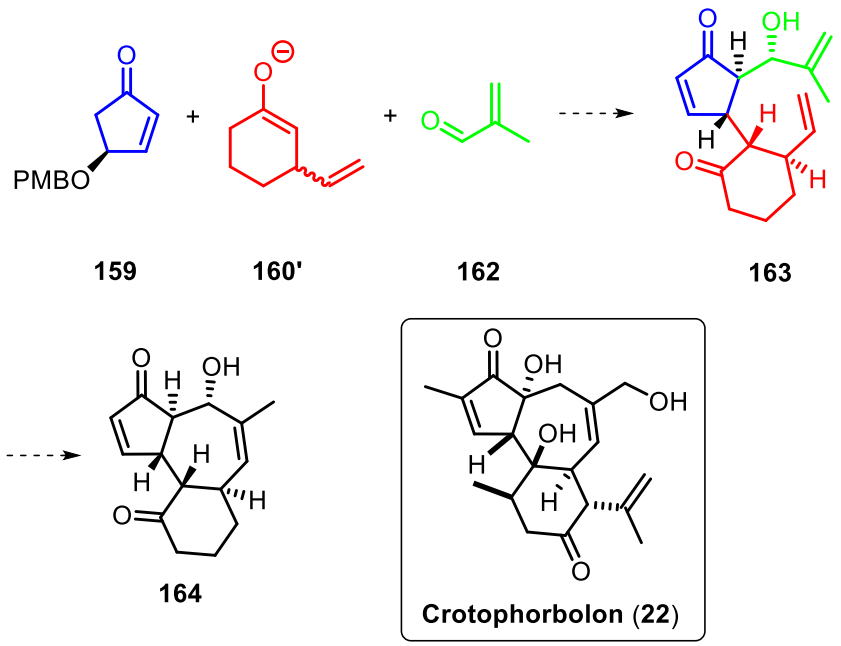
Schema 124. Decarboxylative Kupplung der Säuren **90**, **105** und **107** mit unterschiedlichen Akzeptoren **97-103**.

Weiterhin wurde untersucht, ob eine decarboxylative Kupplung mit Vinylhalogenen **116-120** unter doppelter Katalyse möglich sei. Dies war jedoch nicht der Fall (Schema , oberer Teil). Auch, nachdem die sterische Hinderung von Säure **90** Schritt für Schritt verringert wurde – zuerst durch die Reduktion der Estergruppen im Fall b) und dann bei der Vermeidung der Methylgruppen im Fall c) –, konnte keine Reaktion oder nur die Entstehung von Zersetzungsprodukten in geringen Mengen beobachtet werden. Daraus konnte gefolgert werden, dass diese Substrate nicht kompatibel mit den hier verwendeten Reaktionsbedingungen sind. Als Alternative diente eine zweite decarboxylative Kupplung mit Akzeptor **95**, welche das gewünschte Produkt **140** in guter Ausbeute ergab (Schema , unterer Teil). Da der Auslandsaufenthalt zu Ende ging, wurden keine weiteren Untersuchungen dieser Reaktion durchgeführt. Allerdings wurde das Fundament für weitere Versuche geschaffen.



Schema 125. Decarboxylative Kupplung mit Vinylhalogenen **116-120** mittels doppelter Katalyse (oberer Teil) oder mit Akzeptor **95** (unterer Teil).

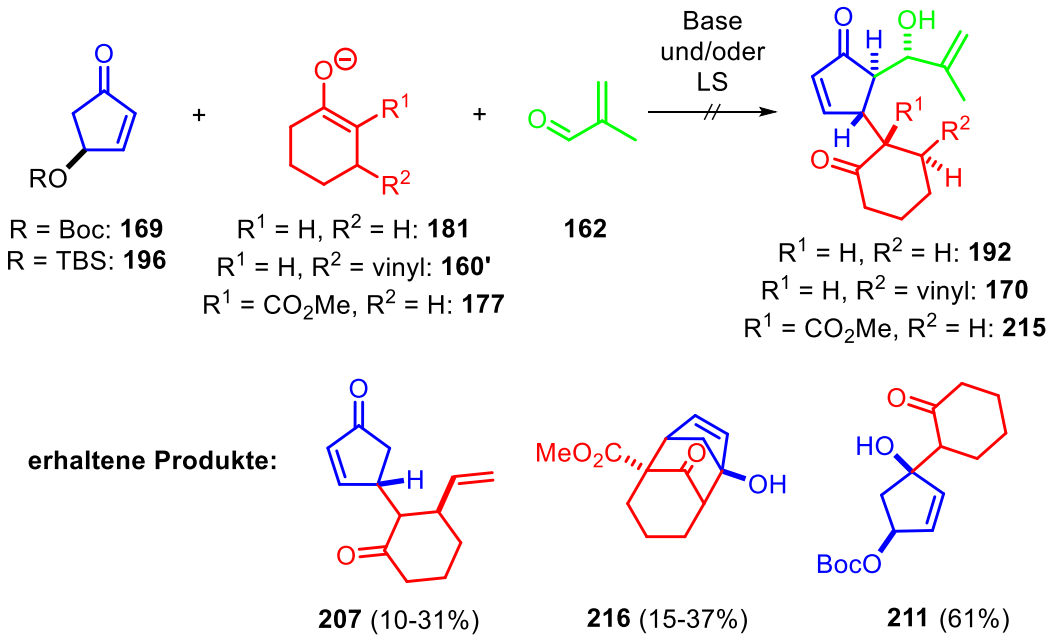
Eine andere trizyklische Struktur, deren Synthese verfolgt wurde, ist die Verbindung **164** – ein Derivat vom bioaktiven Crotophorbolon (**22**). Der Schwerpunkt der Synthese ist eine Enolatkaskade der Edukte **159**, **160'** und **162**, welche das Zwischenprodukt **163** ergibt, dessen Stereozentren durch das enantiomerenreine Cyclopentenon **159** bestimmt werden sollten. Eine Ringschlussmetathese würde dann das gewünschte Produkt **164** ergeben (**Schema**).



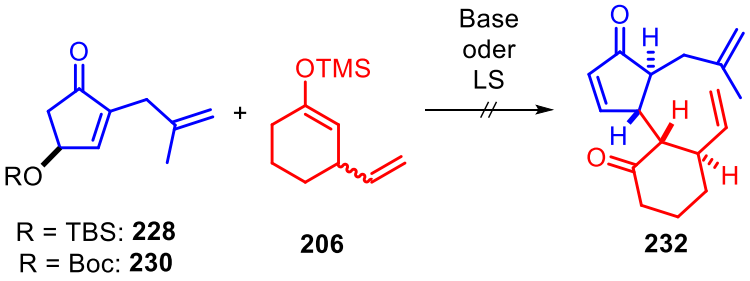
Schema 126. Synthesestrategie für den Trizyklus **164** mittels einer Enolatkaskade.

Leider führten keine der durchgeführten Reaktionen zum gewünschten Produkt **164**. Im Falle der Enolatkaskade, die mit unterschiedlichen Basen oder Lewis Säuren oder einer Kombination der Beiden durchgeführt wurde, wurden nur andere Produkte (**207**, **216** und **211**) erhalten (Schema a). Als eine einfache 1,4-Addition von Enolat **206** an das Stille-Produkt **228** oder **230** durchgeführt wurde, konnte keine Reaktion beobachtet werden (Schema b). Es gibt mehrere mögliche Erklärungen für diese Ergebnisse: Erstens enthält der TMS-Enolether **206** acide Protonen, welche das jeweilige Enolatanion von **206**, oder das resultierende Enolat aus der Enolatreaktion mit Cyclopentenon protonieren können. Dadurch wird die Reaktion mit Methacrolein (**162**) nicht möglich. Der zweite Grund betrifft die sterische Hinderung der Edukte, da die Schutzgruppe am Cyclopentenon und die Vinylgruppe von **160'** oder **206** als sterisch anspruchsvoll angesehen werden können. Das gleiche gilt auch für die Alkylgruppe von **228** oder **230**, was die Addition der anderen Substrate behindert und/oder eine inter- und intramolekulare Protonierung des entstandenen Enolatanions begünstigt.

a) Enolatkaskade mittels Base und/oder Lewis Säure.



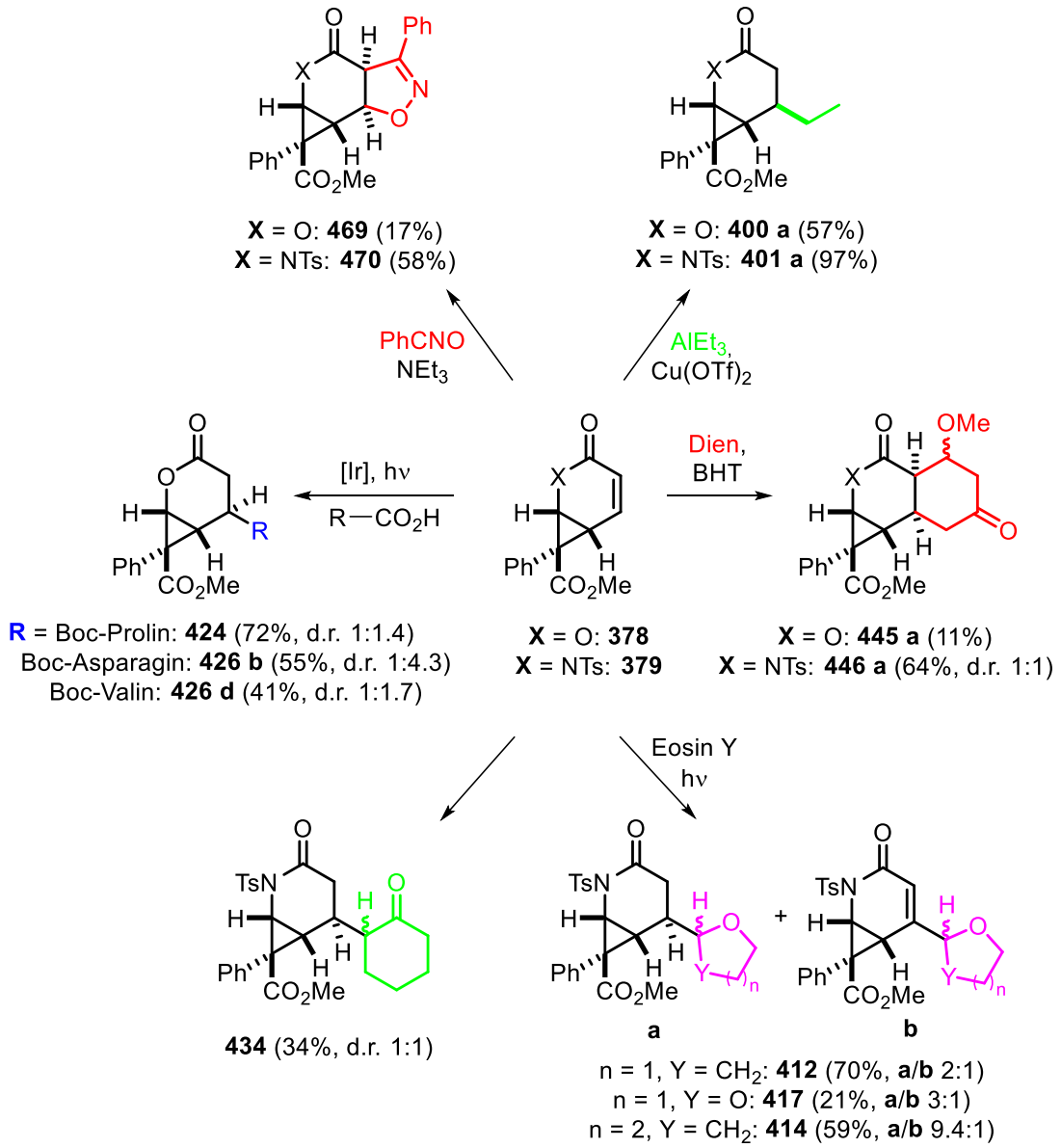
b) Enolataddition mittels Base oder Lewis Säure.



Schema 127. Geplante Enolatkaskade (a) oder Enolataddition (b), um die Produkte **192**, **170**, **215** oder **232** unter basischen oder Lewis Säure Bedingungen zu erhalten.

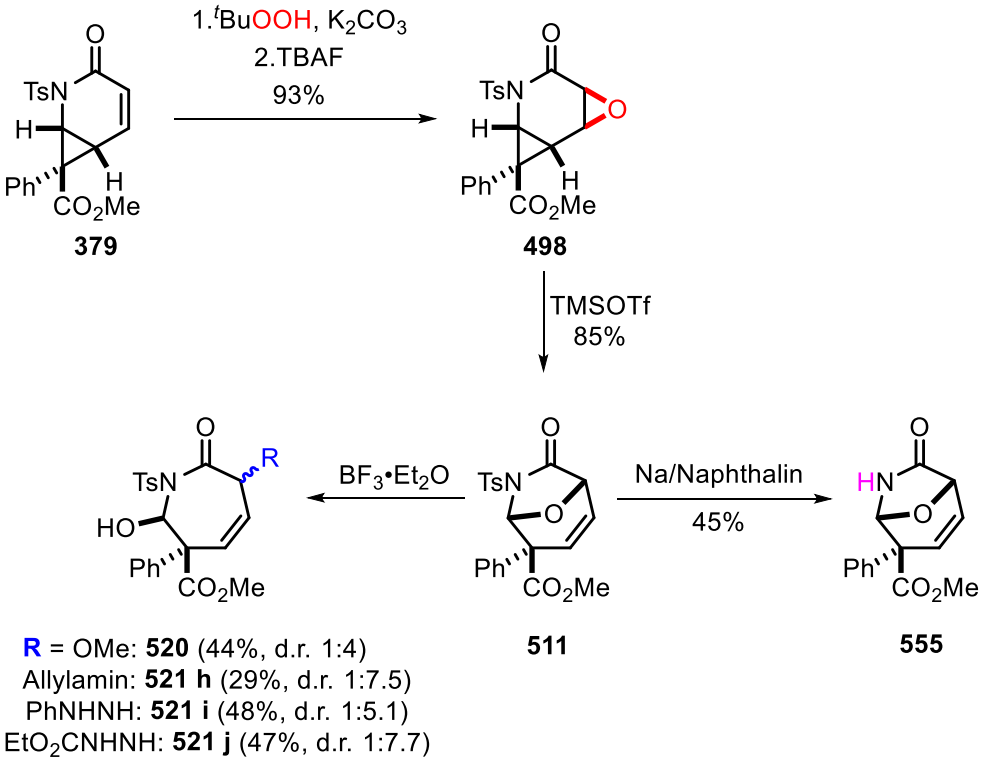
Der andere Teil dieser Arbeit beruhte auf den Vorarbeiten von Dr. Michael Leiter[133] aus diesem Arbeitskreis und betraf die Untersuchung der Reaktivität vom cyclopropanierten 2-Pyron **378** und 2-Pyridinon **379**. Zuerst wurden verschiedene Reaktionsarten durchgeführt, um herauszufinden, welche von ihnen am vielversprechendsten sind. Diese sind in **Schema** zusammengefasst. 1,4-Additionen (grün) mit $AlEt_3$ (**400 a** und **401 a**) ergaben zwar gute Resultate, waren aber nur auf $AlEt_3$ limitiert. Die Enolataddition (**434**) war nur mit 2-Pyridinon möglich – da 2-Pyron unter basischen oder nukleophilen Bedingungen instabil ist – und wurde nicht weiterverfolgt. Die photokatalytische decarboxylative Kupplung funktionierte nur mit 2-Pyron (**424**, **426 b** und **426 d**) und sekundären Aminosäuren in mäßigen bis guten Ausbeuten (blau). Im Vergleich dazu konnte die CH-Aktivierung mit Eosin Y als Photokatalysator nur mit 2-Pyridinon (**412**,

414 und **417**) durchgeführt werden (lila). Jedoch funktionierte diese Reaktion nur mit cyclischen Substraten, deren elektronische Eigenschaften ähnlich zu THF sind. In allen Fällen wurde ebenfalls das reduzierte Nebenprodukt **b** erhalten. Was die Cycloadditionen betrifft (rot), so war die Diels-Alder Reaktion nur mit dem Danishefsky Dien möglich (**445 a** und **446 a**) und die [3+2]-Cycloaddition resultierte in den interessanten Trizyklen **469** und **470**. In beiden Reaktionen wurden für das 2-Pyridinon gute und für das 2-Pyron niedrige Ausbeuten erhalten.



Schema 128. Übersicht über die verschiedenen Reaktionsarten mit cyclopropaniertem 2-Pyron **378** oder 2-Pyridinon **379** und deren Ergebnisse.

Als weitere Reaktionsart am 2-Pyridinon wurde die Epoxidierung mit einem ausgezeichneten Ergebnis durchgeführt. Der Cyclopropanring von diesem Epoxid **498** wurde im weiteren Verlauf erfolgreich zum überbrückten 7-Ring **511** geöffnet (Schema). Die interessante Verbindung konnte einerseits zum Amid **555** entschützt werden und andererseits war es möglich, die Oxobrücke mit unterschiedlichen Nukleophilen zu öffnen (**520** und **521 h-j**). Dabei ist diese Reaktion hauptsächlich auf Amin-Nukleophile beschränkt. Es wurde somit eine vielversprechende Substratbreite erhalten und weitere Untersuchungen, v.a. die Reaktivität des 7-Rings **511** könnten interessant sein.



Schema 129. Epoxidierung von 2-Pyridinon **379** und Ringöffnung des Cyclopropans mit nachfolgenden Funktionalisierungen von Verbindung **511**.

E Experimental part

1. General information

Solvents and chemicals

All commercially available compounds were used as received. Anhydrous solvents were prepared by established laboratory procedures[164] or taken from a Glass Contour solvent dispensing system (Nikko Hansen & Co., Ltd.). Hexanes and EtOAc were distilled prior to use in column chromatography.

The following substrates were prepared according to literature procedures and the spectroscopic data were in accordance with those reported in literature:

6-oxocyclohex-1-ene-1-carbonitrile (**99**)[165], 2-methyl-6-oxocyclohex-1-ene-1-carbonitrile (**102**)[166], ethyl 6-oxocyclohex-1-ene-1-carboxylate (**101**)[167], 3-iodocyclohex-2-en-1-one (**116**)[168], 1-iodocyclohex-1-ene (**117**)[169], 1-bromocyclohex-1-ene (**118**)[170], 1-bromocyclohept-1-ene (**123**)[170], Ir[$(CF_3)(ppy)_2$](dtbbpy)PF_6 (**55**)[172], 4CzIPN (**114**)[173], (cyclohex-1-en-1-yloxy)trimethylsilane (**181**)[174], methyl 2-oxocyclohexane-1-carboxylate (**177**)[175], trimethyl((3-vinylcyclohex-1-en-1-yl)oxy)silane (**206**)[177], 2-methylallyl acetate (**227**)[178], (*Z*)-*N*-hydroxybenzimidoyl chloride (**468**)[179].

Light source

For irradiation in photoreactions, CREE XLamp XP-E D5-15, OSLON SSL 80 LED or Nichia NVSU233A LED (λ_{max} = 455 nm, λ_{max} = 405 nm) light emitting diodes were employed.

NMR spectroscopy

^{1}H and ^{13}C spectra were recorded on BRUKER Avance 300, BRUKER Avance III 400 "Nanobay" spectrometer or JNM-ECX-500, JNM-ECZ-500 or JNM-ECS-400 spectrometer. The spectra were recorded in $CDCl_3$ unless otherwise noted. The chemical shifts are reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^{1}H-NMR) and $CDCl_3$ (δ = 77.0 for ^{13}C-NMR). Coupling constants *J* are given in Hertz (Hz) and signal patterns are indicated as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublet, ddd = doublet of douplet of doublet, dt = doublet of triplet, m = multiplet.

Chromatography

For column chromatography silica gel 60 (Merck-Geduran, 0.063-0.200 mm particle size) or flash silica gel Si 60 (Merck-Geduran, 0.040-0.063 mm particle size) or silica gel 60N (Kanto Chemical Co., Inc., 0.040-0.050 mm particle size) was used. Purification by flash system was performed with silica gel (Merck, 0.040-0.063 mm particle size) on a Reveleris® X2 Flash System (Büchi). Thin layer chromatography (TLC) was performed on silica gel 60 F254 coated aluminum sheets (Merck) or silica gel 60 F254 coated plates (Merck, 0.25 mm) and visualized with UV and vanillin, ninhydrin, $KMnO_4$ or anisaldehyde.

Melting points

Melting points were measured on Stanford Research System OptiMelt MPA 100 Automated melting point system using a ramp rate of 5 °C/min.

IR spectroscopy

IR-spectra were measured on an Agilent Technologies Cary 680 FTIR machine with diamond single reflection accessory or on JASCO FT/IR-4100 spectrometer on an NaCl plate.

Mass spectroscopy

High resolution mass spectra were recorded by the Central Analytical Laboratory (University of Regensburg) using JEOL AccuTOF GCX and Agilent Q-TOF 6540 UHD or were measured on JEOL JMS-T100LP.

X-ray crystallography

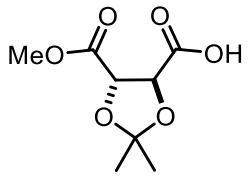
X-ray crystallography was performed on Agilent Technologies SuperNova, Single source at offset/far, Atlas diffractometer or a GV1000, TitanS2 diffractometer at $T = 123$ K during data collection.

2. Experimental procedures for chapter A

2.1 Experimental procedures for decarboxylative α-alkoxy radical addition

2.1.1 Synthesis of starting materials

(4*S*,5*S*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (90)



A 300 mL round bottom flask was charged with dimethyl (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (3.1 mL, 16.91 mmol, 1.0 equiv) solved in MeOH/H_2O (3:1, 148 mL). The solution was cooled to 0 °C and LiOH·H_2O (780.6 mg, 18.6 mmol, 1.1 equiv) was added portion wise over 7 min. After stirring for 30 min at 0 °C the reaction mixture was acidified to pH 3 with Amberlyst 15 followed by filtration over Celite and evaporation. Column chromatography ($CHCl_3$/HOAc, 20:1 to 10:1, stain Anisaldehyde) gave the title product **90** as an orange oil in 82% yield (2.84 g, 13.92 mmol).

R_f (DCM/EA = 1:1) = 0.00; red with anisaldehyde.

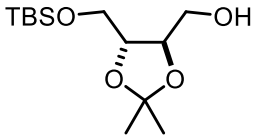
^{1}H-NMR (396 MHz, $CDCl_3$) δ 4.89 (dd, *J* = 5.4, 1.7 Hz, 1H), 4.83 (dd, *J* = 5.4, 1.2 Hz, 1H), 3.85 (d, *J* = 1.9 Hz, 3H), 1.53 – 1.48 (d, *J* = 11.9 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.6, 170.1, 114.4, 100.0, 77.1, 76.6, 53.1, 26.4.

IR (neat) (cm^{-1}) ν_{max}: 3553, 3225, 2996, 2952, 2606, 1981, 1740, 1635, 1445, 1382, 1217, 1107.

HRMS (ESI)(m/z): calculated for $C_8H_{12}O_6$ $[M+Na]^+$ 227.0532, found 227.1299.

((4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (127)

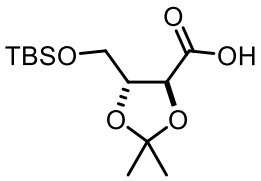


A 50 mL two necked flask was charged with NaH (123.3 mg, 3.08 mmol, 1.3 equiv, 60 w%) and dry THF (8 mL) under Ar. Then a solution of ((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (380.0 mg, 2.34 mmol, 1.0 equiv) in dry THF (8 mL) was added dropwise at 0 °C and the reaction mixture was stirred for 30 min followed by the addition of TBSCl (360.2 mg, 2.39 mmol, 1.0 equiv). After stirring for 1 h the reaction was quenched with sat. aq. NH_4Cl and extracted with EA (3x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 10:1 to 5:1 to 3:1) gave the title product **127** as colourless oil in 89% yield (573.9 mg, 2.08 mmol). Analytical data are according to literature.[180]

^{1}H NMR (396 MHz, $CDCl_3$) δ 3.99 (dt, *J* = 7.6, 4.6 Hz, 1H), 3.92 – 3.84 (m, 2H), 3.81 – 3.63 (m, 3H), 2.38 (dd, *J* = 8.2, 4.3 Hz, 1H), 1.41 (d, *J* = 6.1 Hz, 5H), 0.90 (s, 6H), 0.09 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3, 80.3, 78.3, 63.8, 62.9, 27.2, 27.0, 25.9, 18.5, -5.4, -7.1.

(4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (128)



A 50 mL round bottom flask was charged with ((4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (570.0 mg, 2.06 mmol, 1.0 equiv) solved in dry DCM (10.5 mL) and pH 7 buffer (10.5 mL) followed by addition of $PhI(OAc)_2$ (1.99 g, 6.19 mmol, 3.0 equiv) and AZADOL (15.8 mg,

5 mol%). The resulting reaction mixture was stirred at rt for 1 h before sat. aq. $Na_2S_2O_3$ (10 mL) was added and the solution was stirred for another 30 min. Afterwards, the reaction mixture was extracted with DCM (3x 20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 4:1 with 0.5% HOAc) gave the title product **128** as a pale yellow oil in 97% yield (578.9 mg, 2.00 mmol).

R_f (Hexane/EA = 1:1+0.5% HOAc) = 0.80; red with anisaldehyde.

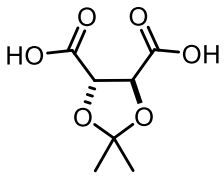
^{1}H NMR (396 MHz, $CDCl_3$) δ 4.52 (d, *J* = 7.7 Hz, 1H), 4.25 – 4.19 (m, 1H), 3.94 – 3.84 (m, 2H), 1.47 (d, *J* = 7.4 Hz, 6H), 0.91 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 111.9, 79.4, 75.1, 62.8, 26.9, 25.9, 25.9, 18.5, -5.2, -5.4.

IR (neat) (cm^{-1}) ν_{max}: 3487, 3197, 2996, 2946, 2896, 2863, 2651, 1736, 1463, 1385, 1256, 1218, 1145, 1100.

HRMS (ESI) (m/z): calculated for $C_{13}H_{26}O_5Si$ $[M+Na]^+$ 313.1447, found 313.2402.

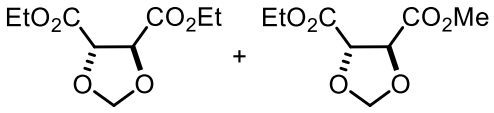
(4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid (141)



A 30 mL round bottom flask was charged with dimethyl (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (358.2 mg, 1.75 mmol, 1.0 equiv) solved in MeOH/H_2O (3:1, 16 mL). The solution was cooled to 0 °C and $LiOH \cdot H_2O$ (147.2 mg, 3.51 mmol, 2.0 equiv) was added portion wise over 9 min. After stirring for 45 min at 0 °C the reaction mixture was concentrated in vacuo and the residue dissolved in H_2O (3 mL). The solution was acidified with HCl (1 M) to pH 2 and extracted with EA (6x 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to yield the title product **141** in 90% (300.0 mg, 1.58 mmol). Analytical data are according to literature.[181]

^{1}H NMR (396 MHz, $CDCl_3$) δ 4.90 (d, *J* = 0.6 Hz, 2H), 1.54 (s, 6H).

diethyl (4*S*,5*S*)-1,3-dioxolane-4,5-dicarboxylate (132 a) and **4-ethyl 5-methyl (4*S*,5*S*)-1,3-dioxolane-4,5-dicarboxylate (132 b)**



A 20 mL two necked tube equipped with a reflux condenser was charged with dimethyl (2*S*,3*S*)-2,3-dihydroxysuccinate (300.0 mg, 1.68 mmol, 1.0 equiv) solved in dry EA (2.8 mL) followed by the dropwise addition of dimethoxymethane (180 µL, 2.02 mmol, 1.2 equiv) and $BF_3 \cdot Et_2O$ (530 µL, 4.21 mmol, 2.5 equiv) under Ar atmosphere. The resulting mixture was heated under reflux for 17 h before cooling to rt and slowly quenching with sat. aq. $NaHCO_3$ until no gas evolution was observed. The aqueous layer was extracted with EA (3x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 4:1) gave a mixture of the diethylester-product **132 a** and mono-ethyl-mono-methyl-ester-product **132 b** in combined yield of 67% (247.5 mg, 1.13 mmol) as a colourless oil.

R_f (Hexane/EA = 5:1) = 0.21; stained with ceric ammonium molybdate.

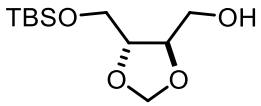
^{1}H NMR (396 MHz, $CDCl_3$) δ 5.23 (d, *J* = 2.1 Hz, 4H), 4.73 (qd, *J* = 3.7, 2.2 Hz, 2H), 4.70 (d, *J* = 2.0 Hz, 2H), 4.26 (dq, *J* = 7.1, 2.1 Hz, 6H), 3.80 (d, *J* = 2.1 Hz, 3H), 1.30 (dt, *J* = 7.1, 2.1 Hz, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 169.3, 169.2, 100.0, 97.5, 76.9, 76.9, 76.8, 76.8, 62.2, 62.1, 52.9, 52.9, 14.2.

IR (neat) (cm^{-1}) ν_{max}: 2985, 2901, 1753, 1441, 1374, 1273, 1218, 1112, 1028.

HRMS (ESI) (m/z): calculated for $C_9H_{14}O_6$ $[M+Na]^+$ 241.0688, found 241.1016.

((4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)methanol (134)



A 30 mL two-necked flask was charged with diethyl (4*S*,5*S*)-1,3-dioxolane-4,5-dicarboxylate (120.0 mg, 0.55 mmol, 1.0 equiv) solved in dry THF (5.5 mL) and cooled to -78 °C. DIBAL-H (2.25 mL, 2.25 mmol, 4.1 equiv, 1.0 M in hexane) was added dropwise and the resulting solution was warmed up to 0 °C over 30 min. After 1.5 h of stirring ^{i}PrOH (2 mL) and H_2O (2 mL) were added and the solution was allowed to warm to rt. Then SiO_2 (acidic) and EA (2 mL) were added and stirring was continued for another 30 min before $MgSO_4$ was added. After stirring the reaction for another 30 min, the mixture was filtered through a plug of Celite, concentrated in vacuo and washed with $CHCl_3$ (3x 5 mL). The crude mixture was used as such in the next step with some residual ^{i}PrOH.

A 50 mL two necked flask was charged with NaH (13.5 mg, 0.34 mmol, 1.1 equiv, 60 w%) and dry THF (0.8 mL) under Ar. Then a solution of the crude ((4*R*,5*R*)-1,3-dioxolane-4,5-diyl)dimethanol (41.0 mg, 0.31 mmol, 1.0 equiv) in dry THF (0.8 mL) was added dropwise at 0 °C and the reaction mixture was stirred for 30 min followed by the addition of TBSCl (50.7 mg, 0.34 mmol, 1.1 equiv). After stirring for 1.5 h the reaction was quenched with aq. sat. NH_4Cl and extracted with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 1:1) gave the title product **134** as yellow oil in 23% yield (17.5 mg, 70.5 µmol).

R_f (Hexanes/EA = 1:1) = 0.86; blue with vanillin.

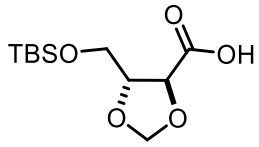
^{1}H NMR (396 MHz, $CDCl_3$) δ 5.02 (d, *J* = 19.8 Hz, 2H), 4.03 – 3.93 (m, 1H), 3.93 – 3.76 (m, 3H), 3.76 – 3.64 (m, 2H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 95.4, 79.6, 77.8, 63.4, 62.8, 25.9, 18.4, -5.3.

IR (neat) (cm^{-1}) ν_{max}: 3470, 2930, 2859, 1465, 1390, 1364, 1252, 1088, 1006, 977, 834, 775, 671.

HRMS (APCI) (m/z): calculated for $C_{11}H_{24}O_4Si$ $[M+H]^+$ 249.1517, found 249.1518.

(4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dioxolane-4-carboxylic acid (135)



A 30 mL round bottom flask was charged with ((4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)methanol (17.5 mg, 70.5 µmol, 1.0 equiv) solved in dry DCM (353 µL) and pH 7 buffer (353 µL) followed by addition of $PhI(OAc)_2$ (68.1 mg, 0.21 mmol, 3.0 equiv) and AZADOL (0.5 mg, 5 mol%). The resulting reaction mixture was stirred at rt for 1 h before sat. aq. $Na_2S_2O_3$ (2 mL) was added and the solution was stirred for another 30 min. The reaction mixture was extracted with DCM (3x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 1:1 with 0.5% HOAc) gave the title product **135** as yellow oil in 97% yield (18.0 mg, 68.4 µmol, d.r. 1:4.3).

R_f (Hexanes/EA = 1:1 + 0.5% HOAc) = 0.70; yellow with vanillin.

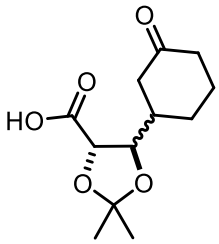
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 – 5.16 (m, 1H), 5.12 – 5.03 (m, 1H), 4.52 – 4.44 (m, 1H), 4.22 – 4.14 (m, 1H), 3.91 – 3.79 (m, 2H), 0.93 – 0.87 (m, 9H), 0.11 – 0.07 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$,) δ 174.6, 96.9, 96.5, 80.1, 80.0, 74.6, 63.2, 62.2, 25.9, 25.8, 18.4, 18.1, -3.5, -5.3, -5.3.

IR (neat) (cm^{-1}) ν_{max}: 3403, 2930, 2885, 2859, 1759, 1539, 1469, 1390, 1252, 1170, 1137, 1096, 1047, 969, 939, 835, 775, 716, 682.

HRMS (APCI) (m/z): calculated for $C_{11}H_{22}O_5Si$ $[M+H]^+$ 263.1309 found 263.1315.

(*S*)-2,2-dimethyl-5-(3-oxocyclohexyl)-1,3-dioxolane-4-carboxylic acid (139)



A 20 mL round bottom flask was charged with methyl (4*S*,5*R*)-2,2-dimethyl-5-(3-oxocyclohexyl)-1,3-dioxolane-4-carboxylate (100.0 mg, 0.39 mmol, 1.0 equiv) solved in MeOH/H_2O (3:1, 3.6 mL). The solution was cooled to 0 °C and LiOH·H_2O (18.0 mg, 0.43 mmol, 1.1 equiv) was added portion wise over 10 min. After stirring for 1 h at 0 °C the reaction mixture was acidified to pH = 3 with Amberlyst 15 followed by filtration over Celite and evaporation under reduced pressure. Column chromatography (Hex/EA, 1:1) gave the title product **139** as an orange oil in 57% yield (54.3 mg, 0.22 mmol) and a d.r. of 1:1.6.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexane/EA = 1:1 + 0.5% HOAc) = 0.13; red with anisaldehyde.

^{1}H-NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.33 – 4.25 (m, 1H), 4.18 – 4.06 (m, 1H), 2.53 – 2.24 (m, 4H), 2.19 – 1.90 (m, 3H), 1.71 – 1.53 (m, 2H), 1.49 – 1.40 (m, 6H).

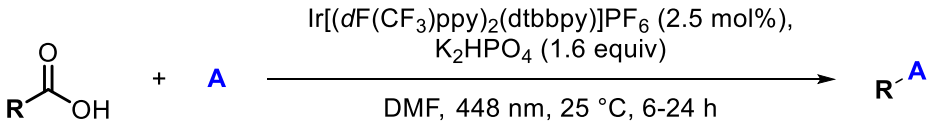
^{13}C-NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 211.7, 211.4, 174.93, 174.92, 111.8, 111.7, 81.9, 76.3, 76.2, 44.7, 42.1, 41.7, 41.34, 41.30, 40.9, 28.5, 26.9, 26.87, 25.9, 25.7, 25.6, 24.8, 21.2, 14.3.

IR (neat) (cm^{-1}) ν_{max}: 3498, 3202, 2985, 2941, 2879, 2617, 2360, 2327, 1709, 1452, 1424, 1379, 1251, 1218, 1168, 1094.

HRMS (ESI) (m/z): calculated for $C_{12}H_{18}O_5$ $[M+Na]^+$ 265.1052, found 265.1866.

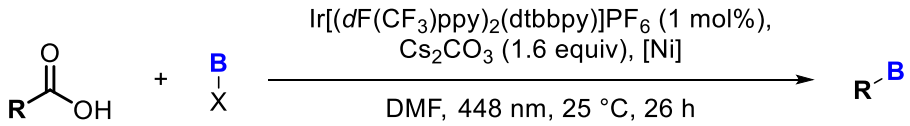
2.1.2 Photoreactions

Decarboxylative coupling general procedure A (GP A):



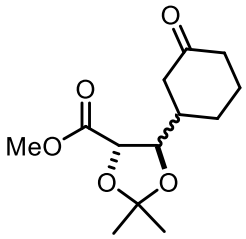
A 10 mL two necked tube was charged with acid (1.0 equiv), base (1.6 equiv), acceptor (2.0 equiv) and Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (2.5 mol%) solved in dry DMF (2 mL). The yellow reaction mixture was degassed by three cycles of freeze-pump-thaw under Ar atmosphere followed by irradiation with a blue LED lamp (455 nm). After 6 – 24 h sat. aq. NaHCO$_3$ (2 mL) was added and the mixture was extracted with Et$_2$O (3x 5 mL). The combined organic layers were washed with H$_2$O (2x 5 mL) and brine (5 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Flash chromatography (Hex/EA, 2:1) gave the product.

Decarboxylative vinylation general procedure B (GP B):



A 10 mL two necked tube was charged with acid (1.6 equiv), base (1.8 equiv) and Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.0 mol%). The flask was back filled with Argon three times before dry DMF (4 mL) and vinyl halogen (1.0 equiv.) were added as well as a 0.01 M solution of NiCl$_2$·glyme (10 mol%) and dtbbpy (15 mol%) or NiCl$_2$·dtbbpy (10 mol%). The solution was degassed by three cycles of freeze-pump-thaw and irradiated with a 448 nm LED stick. After 26 h the reaction was diluted with H$_2$O (5 mL) and brine (2 mL) and extracted with Et$_2$O (3x 5 mL). The combined organic layers were washed with H$_2$O (2x 10 mL) and brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography (Hex/EA, 5:1) gave the product.

methyl 2,2-dimethyl-5-(3-oxocyclohexyl)-1,3-dioxolane-4-carboxylate (96)



According to GP A, (4*S*,5*S*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (41.0 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (53.1 mg, 0.30 mmol, 1.5 equiv), cyclohex-2-en-1-one (39 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 22 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **96** as an orange oil (25.9 mg, 0.15 mmol, 50%, d.r. 1:1).

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexane/EA = 1:1) = 0.56; red-blue with anisaldehyde.

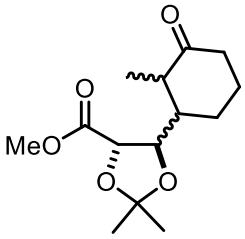
^{1}H-NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.29 – 4.23 (m, 1H), 4.16 – 4.04 (m, 1H), 3.80 – 3.76 (m, 3H), 2.56 – 2.35 (m, 2H), 2.35 – 2.22 (m, 2H), 2.19 – 1.99 (m, 3H), 1.73 – 1.59 (m, 2H), 1.48 – 1.39 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 210.9, 210.5, 171.6, 111.5, 111.4, 81.9, 76.8, 76.6, 52.7, 52.7, 44.7, 42.3, 41.7, 41.4, 41.4, 41.0, 28.5, 27.0, 26.9, 26.1, 25.8, 25.7, 24.9, 24.9.

IR (neat) (cm^{-1}) ν_{max}: 2946, 1750, 1713, 1442, 1377, 1258, 1212, 1097, 866, 755.

HRMS (ESI) (m/z): calculated for $C_{13}H_{20}O_5$ $[M+Na]^+$ 279.1208, found 279.2123.

methyl 2,2-dimethyl-5-(2-methyl-3-oxocyclohexyl)-1,3-dioxolane-4-carboxylate (104 b)



According to GP A, (4*S*,5*S*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (41.0 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.5 mg, 0.30 mmol, 1.5 equiv), 2-methylcyclohex-2-en-1-one (46 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 38 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **104 b** as an orange oil (18.2 mg, 0.07 mmol, 34%, d.r. 1:2.6:5:10.5).

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (Hexane/EA = 1:1 +0.5% HOAc) = 0.58; blue with anisaldehyde.

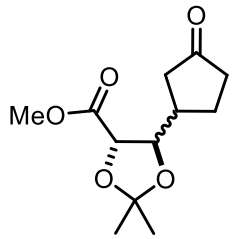
^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.80 – 4.13 (m, 2H), 3.82 – 3.74 (m, 3H), 2.82 – 2.34 (m, 2H), 2.34 – 1.92 (m, 3H), 1.90 – 1.57 (m, 3H), 1.49 – 1.36 (m, 6H), 1.20 – 1.05 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 214.3, 213.7, 213.3, 212.6, 212.4, 172.1, 171.9, 171.6, 170.2, 113.9, 111.5, 111.4, 111.3, 111.1, 80.7, 79.7, 79.6, 78.9, 78.4, 77.2, 77.1, 76.1, 75.9, 52.9, 52.7, 52.6, 52.6, 52.6, 47.6, 47.2, 46.2, 46.2, 46.1, 45.9, 45.5, 43.4, 41.3, 40.5, 38.3, 37.8, 27.3, 27.1, 26.8, 26.7, 26.4, 25.8, 25.6, 25.5, 25.4, 25.1, 25.0, 24.5, 24.4, 23.5, 23.0, 21.7, 13.8, 12.3, 11.8, 11.6.

IR (neat) (cm^{-1}) ν_{max}: 3626, 2979, 2946, 2868, 2372, 1759, 1709, 1446, 1374, 1256, 1218, 1100.

HRMS (ESI) (m/z): calculated for $C_{14}H_{22}O_5$ $[M+Na]^+$ 293.1365, found 293.1454.

methyl 2,2-dimethyl-5-(3-oxocyclopentyl)-1,3-dioxolane-4-carboxylate (104 a)

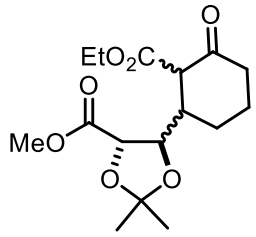


According to GP A, (4*S*,5*S*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (41.0 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.5 mg, 0.30 mmol, 1.5 equiv), cyclopent-2-en-1-one (34 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 6 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **104 a** as a yellow oil (31.7 mg, 0.13 mmol, 65%, d.r. 1:1.7:8:8.9). Analytical data are according to literature.[182]

In the proton and carbon NMR the signals of both diastereomers are overlapping.

^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.67 – 4.15 (m, 2H), 3.81 – 3.74 (m, 3H), 2.64 – 2.47 (m, 1H), 2.44 – 2.28 (m, 2H), 2.28 – 2.07 (m, 3H), 1.94 – 1.59 (m, 2H), 1.48 – 1.35 (m, 6H).

methyl 5-(2-(ethoxycarbonyl)-3-oxocyclohexyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (104 e)



According to GP A, (4*S*,5*S*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (41.0 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.5 mg, 0.30 mmol, 1.5 equiv), cyclopent-2-en-1-one (34 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 6 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **104 e** as a yellow oil (31.7 mg, 0.13 mmol, 65%, d.r. 1:1.2).

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexane/EA = 1:1 +0.5% HOAc) = 0.61; blue with anisaldehyde.

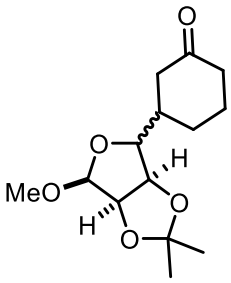
^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 5.98 – 5.91 (m, 1H), 5.74 – 5.68 (m, 1H), 5.04 (d, *J* = 1.1 Hz, 1H), 4.45 – 4.06 (m, 5H), 3.05 (dd, *J* = 7.6, 2.6 Hz, 1H), 2.45 – 2.08 (m, 6H), 1.96 – 1.71 (m, 4H), 1.54 – 1.23 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 205.9, 173.8, 167.5, 131.9, 124.3, 77.9, 77.3, 67.3, 61.9, 61.3, 53.1, 43.0, 39.6, 29.1, 25.5, 24.3, 19.2, 14.3, 14.0.

IR (neat) (cm^{-1}) ν_{max}: 3442, 2985, 2935, 2350, 1713, 1452, 1368, 1296, 1246, 1173, 1106, 1039.

HRMS (ESI) (m/z): calculated for $C_{16}H_{24}O_7$ $[M+Na]^+$ 351.1420, found 351.1205.

3-((3a*R*,6*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)cyclohexan-1-one (108 a)



According to GP A, (3a*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (43.7 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.3 mg, 0.30 mmol, 1.5 equiv), cyclohex-2-en-1-one (39 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 25 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **108 a** as an orange oil (30.0 mg, 0.11 mmol, 55%, d.r. 1:3).

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexane/EA = 1:1 +0.5% HOAc) = 0.60; red with anisaldehyde.

^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.94 (d, *J* = 4.1 Hz, 1H), 4.66 – 4.49 (m, 2H), 3.92 – 3.85 (m, 1H), 3.43 – 3.34 (m, 3H), 2.68 – 2.01 (m, 6H),

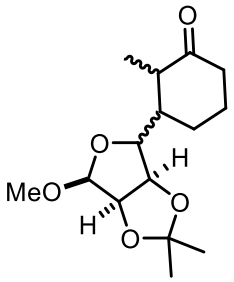
2.00 – 1.80 (m, 1H), 1.69 – 1.55 (m, 1H), 1.47 (d, *J* = 3.0 Hz, 3H), 1.45 – 1.34 (m, 1H), 1.30 (d, *J* = 4.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 210.9, 210.3, 112.7, 109.5, 109.4, 100.0, 91.0, 90.8, 85.4, 85.4, 82.3, 81.8, 77.4, 55.9, 55.6, 45.2, 44.7, 42.9, 41.6, 41.3, 28.4, 28.0, 26.7, 26.7, 25.2, 25.1, 24.9, 24.9.

IR (neat) (cm^{-1}) ν_{max}: 2985, 2941, 2327, 2366, 1747, 1452, 1379, 1218, 1100, 1022.

HRMS (ESI) (m/z): calculated for $C_{14}H_{22}O_5$ $[M+Na]^+$ 293.1365, found 293.2362.

3-((3a*R*,6*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2-methylcyclohexan-1-one (108 b)



According to GP A, (3a*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (43.7 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.3 mg, 0.30 mmol, 1.5 equiv), 2-methylcyclohex-2-en-1-one (45 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 20 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **108 b** as an orange oil (19.6 mg, 0.07 mmol, 34%, d.r. 1:1.1:1.6:2.3).

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (Hexane/EA = 1:1 +0.5% HOAc) = 0.70; brown with anisaldehyde.

^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.97 – 4.91 (m, 1H), 4.69 – 4.49 (m, 2H), 4.34 – 3.99 (m, 1H), 3.41 – 3.32 (m, 3H), 2.79 – 2.19 (m, 3H), 2.12 – 1.53 (m, 5H), 1.51 – 1.27 (m, 6H), 1.26 – 1.08 (m, 3H).

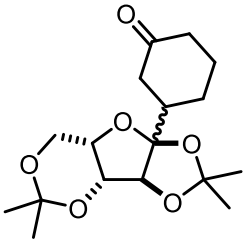
^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 215.2, 214.3, 213.6, 213.3, 113.2, 112.8, 112.7, 112.6, 110.2, 109.5, 109.3, 109.0, 100.1, 99.7, 88.3, 87.9, 87.6, 87.5, 85.7, 85.6, 85.5, 85.4, 83.3, 82.9, 82.1, 81.1, 80.9, 56.3, 55.9, 55.8, 55.5, 48.1, 47.5,

47.2, 47.0, 46.9, 46.2, 44.9, 44.7, 40.8, 40.0, 37.9, 37.5, 27.0, 26.9, 26.7, 26.7, 25.4, 25.2, 25.1, 25.1, 24.7, 24.6, 24.0, 23.9, 23.3, 22.3, 14.7, 13.3, 11.5, 11.4.

IR (neat) (cm^{-1}) ν_{max}: 2935, 2366, 2327, 1709, 1457, 1374, 1273, 1206, 1162, 1100.

HRMS (ESI) (m/z): calculated for $C_{15}H_{24}O_5$ $[M+Na]^+$ 307.1521, found 307.1800.

3-((3a*S*,3b*R*,7a*S*,8a*S*)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)cyclohexan-1-one (106 a)



According to GP A, (3a*S*,3b*R*,7a*S*,8a*R*)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylic acid (55.0 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.4 mg, 0.30 mmol, 1.5 equiv), cyclohex-2-en-1-one (39 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 20 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **106 a** as a yellow oil (42.2 mg, 0.13 mmol, 65%) with an undeterminable d.r.

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (Hexane/EA = 1:1 +0.5% HOAc) = 0.64; blue with anisaldehyde.

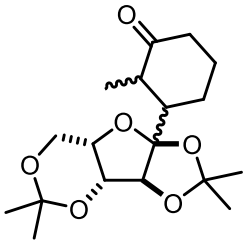
^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.33 (d, *J* = 4.5 Hz, 1H), 4.23 (dd, *J* = 15.0, 1.8 Hz, 1H), 4.13 – 4.00 (m, 3H), 2.71 – 2.60 (m, 1H), 2.56 – 2.09 (m, 6H), 1.85 – 1.64 (m, 2H), 1.52 – 1.30 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 212.0, 211.9, 116.0, 115.9, 111.2, 110.9, 97.5, 97.4, 86.0, 85.8, 77.4, 73.7, 71.9, 71.9, 60.5, 60.4, 46.4, 45.9, 43.7, 43.2, 41.5, 41.4, 28.9, 28.8, 27.7, 27.6, 27.1, 26.9, 25.9, 25.7, 25.3, 25.1, 18.8, 18.8.

IR (neat) (cm^{-1}) ν_{max}: 3599, 3520, 3409, 2991, 2935, 2372, 2311, 1713, 1452, 1374, 1246, 1178, 1122, 1078.

HRMS (ESI) (m/z): calculated for $C_{17}H_{26}O_6$ $[M+Na]^+$ 349.1627, found 349.2352.

2-methyl-3-((3a*S*,3b*R*,7a*S*,8a*S*)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)cyclohexan-1-one (106 b)



According to GP A, (3a*S*,3b*R*,7a*S*,8a*R*)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylic acid (55.0 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (52.4 mg, 0.30 mmol, 1.5 equiv), 2-methylcyclohex-2-en-1-one (46 µL, 0.40 mmol, 2.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 17 h the crude mixture was purified by flash column chromatography (Hex/EA, 2:1) to give the title product **106 b** as a yellow oil (15.3 mg, 0.04 mmol, 22%) with an undeterminable d.r.

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (Hexane/EA = 1:1 +0.5% HOAc) = 0.69; blue with anisaldehyde.

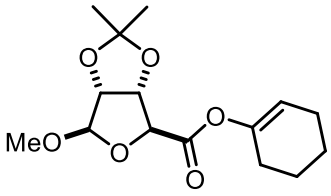
^{1}H NMR (495 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 4.53 – 3.91 (m, 5H), 3.04 – 2.70 (m, 1H), 2.60 – 1.69 (m, 6H), 1.62 – 1.50 (m, 1H), 1.50 – 1.29 (m, 12H), 1.29 – 1.21 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 116.6, 116.2, 112.2, 110.9, 97.5, 97.4, 89.4, 86.4, 73.7, 73.6, 72.6, 72.3, 60.7, 60.6, 49.2, 46.9, 46.8, 45.9, 37.9, 37.4, 28.9, 28.7, 28.2, 27.7, 27.6, 27.1, 25.0, 25.0, 24.2, 21.9, 21.5, 19.1, 18.9, 14.2, 13.9, -19.1.

IR (neat) (cm^{-1}) ν_{max}: 3610, 3532, 3392, 2985, 2941, 2885, 2367, 2327, 1709, 1452, 1379, 1240, 1196, 1118, 1084.

HRMS (ESI) (m/z): calculated for $C_{18}H_{28}O_6$ $[M+Na]^+$ 363.1784, found 363.2799.

cyclohex-1-en-1-yl (3a*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (122 b)



According to GP B, (3a*S*,4*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (35.2 mg, 0.16 mmol, 1.6 equiv), Cs_2CO_3 (59.2 mg, 0.18 mmol, 1.8 equiv), 1-iodocyclohex-1-ene (21.0 mg, 0.10 mmol, 1.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (1.1 mg, 1 mol%), 1 mL of a 0.01 M solution of $NiCl_2$·glyme (2.2 mg, 10 mol%) and dtbbpy (4.1 mg, 15 mol%) in DMF and dry DMF (4 mL) were used. After 26 h the crude mixture was purified by flash column chromatography (Hex/EA, 5:1) to give the title product **122 b** as a colourless oil (17.6 mg, 0.09 mmol, 58%).

R_f (Hexane/EA = 5:1) = 0.58; red with anisaldehyde.

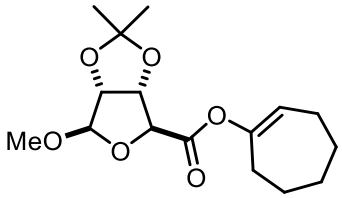
^{1}H-NMR (396 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.23 (d, *J* = 5.9 Hz, 1H), 5.05 (s, 1H), 4.66 (s, 1H), 4.56 (d, *J* = 5.9 Hz, 1H), 3.41 (s, 3H), 2.18 - 2.07 (m, 4H), 1.78 - 1.70 (m, 2H), 1.65 - 1.58 (m, 2H), 1.49 (s, 3H), 1.33 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.8, 148.3, 114.5, 112.9, 109.6, 84.5, 83.9, 82.3, 55.8, 26.7, 26.5, 25.2, 23.7, 22.7, 21.7.

IR (neat) (cm^{-1}) ν_{max}: 2937, 2851, 1755, 1695, 1456, 1376, 1256, 1197, 1111, 1058, 958, 865.

HRMS (ESI)(m/z): calculated for $C_{15}H_{22}O_6$ $[M+Na]^+$ 321.1314, found 321.2049.

cyclohept-1-en-1-yl (3a*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (122 c)



According to GP B, (3a*S*,4*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (35.6 mg, 0.16 mmol, 1.6 equiv), Cs_2CO_3 (59.8 mg, 0.18 mmol, 1.8 equiv), 1-bromocyclohept-1-ene (21.0 mg, 0.10 mmol, 1.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (1.1 mg, 1 mol%), $NiCl_2$·dtbbpy (4.1 mg, 10 mol%)and dry DMF (5 mL) were used. After 17 h the crude mixture was purified by flash column chromatography (Hex/EA, 5:1) to give the title product **122 c** a colourless oil (29.0 mg, 0.15 mmol, 91%).

R_f (Hexane/EA = 5:1) = 0.67; red with anisaldehyde.

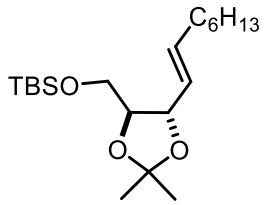
^{1}H NMR (396 MHz, $CDCl_3$) δ 5.50 (t, *J* = 6.5 Hz, 1H), 5.23 (d, *J* = 5.9 Hz, 1H), 5.04 (s, 1H), 4.66 – 4.63 (m, 1H), 4.55 (d, *J* = 5.9 Hz, 1H), 3.40 (d, *J* = 0.7 Hz, 3H), 2.33 – 2.26 (m, 2H), 2.14 – 2.05 (m, 2H), 1.77 – 160 (m, 4H), 1.62 – 1.54 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 152.9, 118.5, 112.8, 109.6, 84.4, 83.8, 82.2, 55.8, 32.8, 31.0, 27.0, 26.5, 25.4, 25.3, 25.1.

IR (neat) (cm^{-1}) ν_{max}: 2985, 2924, 2846, 1741, 1691, 1446, 1379, 1256, 1206, 1100, 1062.

HRMS (ESI)(m/z): calculated for $C_{16}H_{24}O_6$ $[M+Na]^+$ 335.1471, found 335.2299.

***tert*-butyl(((4*S*,5*S*)-2,2-dimethyl-5-((*E*)-oct-1-en-1-yl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane (129' a)**



According to GP B, (4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (48.8 mg, 0.17 mmol, 1.6 equiv), Cs_2CO_3 (61.6 mg, 0.19 mmol, 1.8 equiv), (*E*)-1-iodooct-1-ene (19 µL, 0.11 mmol, 1.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (1.2 mg, 1 mol%), $NiCl_2$·dtbbpy (4.2 mg, 10 mol%)and dry DMF (5 mL) were used. After 23 h the crude mixture was purified by flash column chromatography (Hex/EA, 5:1) to give the title product **129' a** as a yellow oil (20.4 mg, 0.09 mmol, 55%).

R_f (Hexane/EA = 5:1) = 0.86; blue with anisaldehyde.

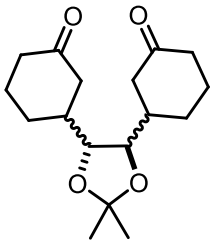
^{1}H NMR (396 MHz, $CDCl_3$) δ 5.87 – 5.71 (m, 1H), 5.55 – 5.39 (m, 1H), 4.28 (t, *J* = 7.7 Hz, 1H), 3.82 – 3.64 (m, 2H), 2.13 – 1.96 (m, 2H), 1.61 – 1.51 (m, 1H), 1.51 – 1.19 (m, 14H), 0.90 (s, 9H), 0.07 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 127.1, 108.8, 81.6, 79.2, 78.9, 77.4, 62.5, 32.5, 31.8, 29.0, 28.9, 27.3, 27.0, 26.1, 26.0, 25.9, 22.7, 18.5, 14.2, -5.2, -5.3, -5.3.

IR (neat) (cm^{-1}) ν_{max}: 2935, 2857, 2355, 1797, 1741, 1463, 1379, 1251, 1145, 1094.

HRMS (ESI) (m/z): calculated for $C_{20}H_{40}O_3Si$ $[M+Na]^+$ 379.2644, found 379.3324.

3,3'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(cyclohexan-1-one) (140)



According to GP A, (4*S*,5*R*)-2,2-dimethyl-5-(3-oxocyclohexyl)-1,3-dioxolane-4-carboxylic acid (24.8 mg, 0.10 mmol, 1.0 equiv), K_2HPO_4 (52.3 mg, 0.30 mmol, 3.0 equiv), cyclohex-2-en-1-one (39 µL, 0.40 mmol, 4.0 equiv), Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5.6 mg, 2.5 mol%) and dry DMF (2 mL) were used. After 16 h the crude mixture was purified by flash column chromatography (Hex/EA, 3:1 to 1:1) to give the title product **140** as a yellow oil (20.6 mg, 68.0 µmol, 68%) with an undeterminable d.r.

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (Hexane/EA = 5:1) = 0.09; brown with anisaldehyde.

^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 3.83 – 3.57 (m, 2H), 2.49 – 2.19 (m, 8H), 2.19 – 1.83 (m, 5H), 1.83 – 1.48 (m, 5H), 1.35 (dd, *J* = 10.5, 2.8 Hz, 6H).

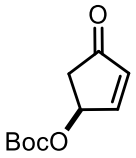
^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 211.4, 211.3, 210.7, 210.7, 109.2, 109.0, 81.9, 81.3, 81.2, 81.1, 45.5, 45.2, 42.5, 42.4, 42.3, 41.9, 41.5, 41.5, 41.4, 41.3, 41.3, 40.9, 29.4, 29.4, 27.5, 27.4, 26.6, 25.9, 25.2, 25.1, 25.0, 24.9.

IR (neat) (cm^{-1}) ν_{max}: 2941, 2873, 1713, 1446, 1374, 1312, 1228, 1173, 1039.

HRMS (ESI) (m/z): calculated for $C_{17}H_{26}O_4$ $[M+Na]^+$ 317.1729, found 317.3098.

2.2 Experimental procedures for enolate cascades

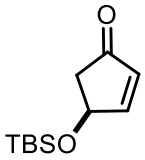
tert-butyl (4-oxocyclopent-2-en-1-yl) carbonate (169)



A 100 mL round bottom flask was charged with 4-hydroxy-2-cyclopentenone (3.00 g, 30.58 mmol, 1.0 equiv) and Boc_2O (8.01 g, 36.70 mmol, 1.2 equiv) solved in THF (30 mL). Then NEt_3 (5.1 mL, 36.70 mmol, 1.2 equiv) and DMAP (74.7 mg, 0.61 mmol, 2 mol%) were added. After the reaction mixture was stirred at rt for 45 min, the solvent was removed under reduced pressure. Purification by column chromatography (hexanes/EA, 5:1) gave the title product **169** as a light yellow oil in 84% yield (5.10 g, 25.69 mmol). Analytical data are according to literature.[33]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.32 (dd, *J* = 5.7, 1.3 Hz, 1H), 5.71 (dtd, *J* = 6.1, 2.3, 1.3 Hz, 1H), 2.83 (dd, *J* = 18.7, 6.3 Hz, 1H), 2.39 (dd, *J* = 18.7, 2.3 Hz, 1H), 1.50 (s, 9H).

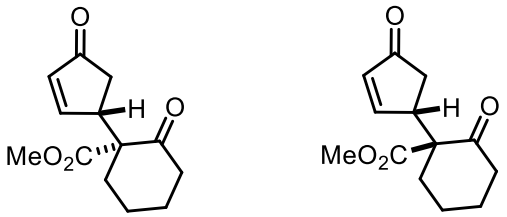
4-((_tert_-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (196)



A 100 mL round bottom Schlenk flask was charged with 4-hydroxycyclopent-2-en-1-one (1.0 g, 10.19 mmol, 1.0 equiv) solved in pyridine (45 mL) and DMAP (249.1 mg, 20 mol%) followed by TBDMSCl (3.07 g, 20.39 mmol, 2.0 equiv) were added. The resulting solution was stirred for 24 h at rt, filtered and the solvent was evaporated under reduced pressure. Column chromatography (hexanes/EA, 5:1) gave the title product **196** as a clear oil in 78% yield (1.70 g, 7.95 mmol). Analytical data are according to literature.[183]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 5.7, 2.3 Hz, 1H), 6.18 (dd, *J* = 5.7, 1.3 Hz, 1H), 4.98 (dtd, *J* = 5.9, 2.3, 1.3 Hz, 1H), 2.71 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.24 (dd, *J* = 18.2, 2.2 Hz, 1H), 0.91 (s, 9H), 0.13 (d, *J* = 3.6 Hz, 6H).

methyl 2-oxo-1-(4-oxocyclopent-2-en-1-yl)cyclohexane-1-carboxylate (174 c)



major **minor**

A 100 mL round bottom Schlenk flask was charged with *tert*-butyl (4-oxocyclopent-2-en-1-yl) carbonate (500.0 mg, 2.52 mmol, 1.0 equiv) and methyl 2-oxocyclohexane-1-carboxylate (457.6 mg, 2.27 mmol, 0.9 equiv) solved in dry toluene (50 mL) and cooled to 0 °C. Then K_2CO_3 (362.6 mg, 2.62 mmol, 1.0 equiv) and 18-crown-6 (26.7 mg, 4 mol%) were added and the reaction was stirred for 2 d at 0 °C. The reaction mixture was washed with H_2O (2x 10 mL) and brine (1x 10 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification by automation flash column chromatography (hexanes/EA) gave the title product **174 c** as white oil in 86% yield (515.0 mg, 2.17 mmol) and a d.r. of 1:6.8.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 5:1) = 0.09; brown with vanillin.

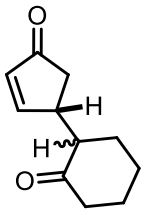
^{1}H NMR (300 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.66 – 7.51 (m, 1H), 6.21 – 6.09 (m, 1H), 3.72 – 3.66 (m, 3H), 3.65 – 3.48 (m, 1H), 2.50 – 2.32 (m, 4H), 2.25 – 2.13 (m, 1H), 2.08 – 1.97 (m, 1H), 1.87 – 1.56 (m, 3H), 1.43 – 1.29 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 208.3, 208.2, 206.6, 206.3, 170.6, 170.4, 165.2, 164.2, 135.4, 134.7, 62.8, 62.5, 52.9, 52.6, 45.1, 44.7, 41.5, 41.4, 36.8, 36.7, 34.2, 32.3, 27.3, 27.2, 22.6, 22.3.

IR (neat) (cm^{-1}) ν_{max}: 2948, 2871, 1707, 1588, 1435, 1346, 1312, 1234, 1129, 1088, 992, 954, 887, 839, 779, 753, 686.

HRMS (APCI) (m/z): **major diastereomer** (acquisition time 7.418 – 7.481 min): calculated for $C_{13}H_{16}O_4$ $[M+H]^+$ 237.1121, found 237.1127; **minor diastereomer** (acquisition time 7.328 – 7.345 min) calculated for $C_{13}H_{16}O_4$ $[M+H]^+$ 237.1121, found 237.1127.

2-(4-oxocyclopent-2-en-1-yl)cyclohexan-1-one (193)



A 10 mL round bottom Schlenk flask was charged with (cyclohex-1-en-1-yloxy)trimethylsilane (107.4 mg, 0.63 mmol, 2.5 equiv) solved in dry Et_2O (1 mL). ^{n}BuLi (426 µL, 0.68 mmol, 2.7 equiv, 1.6 M in hexane) was added dropwise at 0 °C and the resulting solution was stirred for 1.5 h at 0 °C. Afterwards this solution was added dropwise to a mixture of *tert*-butyl (4-oxocyclopent-2-en-1-yl) carbonate (50.0 mg, 0.25 mmol, 1.0 equiv) and $ZnCl_2$ (63.0 mg, 0.46 mmol, 1.8 equiv) in dry Et_2O (1 mL) at -78 °C. The flask was rinsed with Et_2O. After 1 h of stirring the reaction mixture was allowed to warm to 0 °C over 3 h and stirred at this temperature for 1 h. Then methacrylaldehyde (36 µL, 0.43 mmol, 1.7 equiv) was added. After 40 min the reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Automation flash column chromatography (hexanes/EA) gave the title product **193** as yellow oil in 47% yield (21.0 mg, 0.12 mmol) and a d.r. of 1:2.5:5.

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (DMC/MeOH = 95:5) = 0.60; brown with vanillin.

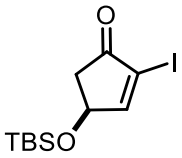
^{1}H NMR (300 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.79 – 7.63 (m, 1H), 6.23 – 6.11 (m, 1H), 3.55 – 3.26 (m, 1H), 2.68 – 2.50 (m, 1H), 2.49 – 2.29 (m, 3H), 2.15 – 1.95 (m, 3H), 1.71 – 1.63 (m, 2H), 1.50 – 1.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 211.4, 211.3, 210.2, 209.6, 167.4, 167.3, 166.2, 135.2, 134.9, 134.5, 134.3, 134.29, 134.2, 54.1, 53.8, 53.7, 43.03, 43.01, 42.6, 42.5, 42.3, 41.1, 40.4, 40.1, 38.5, 36.0, 35.8, 31.2, 30.4, 28.9, 28.0, 27.98, 27.91, 27.8, 27.7, 25.3, 25.26, 25.2, 21.5, 21.3, 21.2.

IR (neat) (cm^{-1}) ν_{max}: 3452, 3079, 2937, 2862, 2363, 1707, 1588, 1450, 1409, 1349, 1282, 1163, 1133, 1103, 969, 947, 891, 839, 790, 753, 671.

HRMS (EI) (m/z): **major diastereomer** (acquisition time 7.2046 – 7.2345 min): calculated for $C_{11}H_{14}O_2$ $[M]^{+\cdot}$ 178.09883, found 178.09926; **minor diastereomer** (acquisition time 7.1746 – 7.1913 min): calculated for $C_{11}H_{14}O_2$ $[M]^{+\cdot}$ 178.09883, found 178.09914.

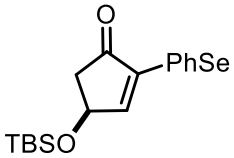
4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (225)



A 10 mL two necked tube was charged with 4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (215.0 mg, 1.01 mmol, 1.0 equiv) solved in dry DCM (2.5 mL) under Ar followed by the addition of pyridine (163 µL, 2.02 mmol, 2.0 equiv) and I_2 (385.4 mg, 1.52 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 2 h before being diluted with DCM and washed with sat. aq. Na_2SO_3 (2x 10 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 50:1) gave the title product **225** as a light yellow oil in 58% yield (200.0 mg, 0.59 mmol). Analytical data are according to literature.[44]

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.5 Hz, 1H), 4.95 (dt, *J* = 5.9, 2.2 Hz, 1H), 2.87 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.35 (dd, *J* = 18.2, 2.1 Hz, 1H), 0.91 (s, 9H), 0.13 (d, *J* = 5.3 Hz, 6H).

4-((*tert*-butyldimethylsilyl)oxy)-2-(phenylselanyl)cyclopent-2-en-1-one (223)

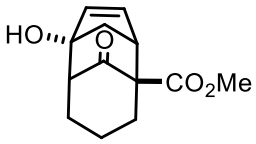


A 20 mL Schlenk tube was charged with PhSeCl (290.9 mg, 1.52 mmol, 1.5 equiv) solved in dry DCM (2.8 mL) under Ar. Pyridine (139 µL, 1.72 mmol, 1.7 equiv) was added and the resulting solution was stirred for 15 min at rt before a solution of 4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (215.0 mg, 1.01 mmol, 1.0 equiv) in dry DCM (1.4 mL) was added in one portion. After 15 h of stirring the mixture was diluted

with DCM and the organic layer was washed with H_2O, citric acid (1 M, aq.), aq. sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 100:1 to 20:1 to 10:1) yielded the title product **223** as a yellow solid in 73% yield (272.9 mg, 0.74 mmol). Analytical data are according to literature.[44]

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.43 – 7.34 (m, 3H), 6.72 (d, *J* = 2.6 Hz, 1H), 4.86 (dt, *J* = 5.8, 2.3 Hz, 1H), 2.87 (dd, *J* = 18.3, 5.9 Hz, 1H), 2.39 (dd, *J* = 18.3, 2.0 Hz, 1H), 0.85 (s, 9H), 0.04 (d, *J* = 6.0 Hz, 6H).

methyl 5-hydroxy-10-oxotricyclo[4.3.1.12,5]undec-3-ene-1-carboxylate (216)



A 10 mL flame dried Schlenk tube was charged with ^{i}Pr$_2$NH (29 µL, 0.20 mmol, 2.0 equiv) solved in dry THF (1.5 mL) and cooled to 0 °C. ^{n}BuLi (95 µL, 0.15 mmol, 1.5 equiv, 1.6 M in hexane) was added dropwise and the resulting solution was stirred for 15 min before cooling to -78 °C. Methacrylaldehyde (12 µL, 0.14 mmol, 1.4 equiv) in dry THF (180 µL) was added followed by the dropwise addition of enone **174 C** (24.0 mg, 0.10 mmol, 1.0 equiv) in dry THF (357 µL). After 1 h of stirring at -78 °C the solution was poured onto a cold mixture of Et_2O and sat. aq. NH_4Cl. The aqueous phase was extracted with Et_2O (2x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 5:1 to 2:1) gave mostly the by-product **216** in 37% yield (8.8 mg, 37.0 µmol, d.r. 1:4).

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexane/EA = 5:1) = 0.03; brown with anisaldehyde.

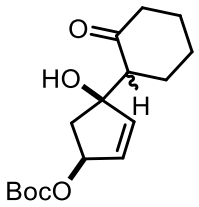
^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 6.12 – 6.01 (m, 1H), 5.95 – 5.84 (m, 1H), 3.80 – 3.73 (m, 3H), 3.50 – 3.36 (m, 1H), 2.88 – 2.70 (m, 1H), 2.61 – 2.53 (m, 1H), 2.51 – 2.42 (m, 2H), 2.10 – 1.99 (m, 1H), 1.95 (dd, *J* = 19.2 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.73 – 1.60 (m, 2H), 1.52 – 1.43 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 207.4, 171.2, 146.7, 139.3, 131.7, 95.4, 64.2, 63.4, 52.8, 49.4, 41.7, 37.5, 37.1, 33.7, 27.9, 27.6, 22.6.

IR (neat) (cm^{-1}) ν_{max}: 3465, 2952, 2868, 2360, 2338, 1713, 1603, 1441, 1363, 1246, 1218, 1140, 1090.

HRMS (ESI) (m/z): calculated for $C_{13}H_{16}O_4$ $[M+Na]^+$ 259.0946, found 259.1290.

***tert*-butyl (4-hydroxy-4-(2-oxocyclohexyl)cyclopent-2-en-1-yl) carbonate (211)**



A 20 mL two-necked flask was charged with previously grounded $CeCl_3 \cdot 7H_2O$ (141.0 mg, 0.38 mmol, 1.5 equiv) and heated to 140 °C under vacuo. A stirring bar was added and heating at 140 °C while stirring continued for 1 h under vacuo. The hot flask was filled with Ar, cooled with an ice bath to rt and dry THF (1.3 mL) was added. The milky suspension was stirred at rt for 3 h. Another 10 mL two-necked tube was filled with $^{i}Pr_2NH$ (57 µL, 0.40 mmol, 1.6 equiv) and cooled to -78 °C. Then ^{n}BuLi (252 µL, 0.40 mmol, 1.6 equiv, 1.6 M in hexane) was added dropwise and stirred for 30 min at -78 °C before cyclohexanone (39 µL, 0.38 mmol, 1.5 equiv) was added over 20 min and stirring was continued for another 30 min. The Ce-solution was cooled to -78 °C and the Li-solution was added dropwise during which the reaction mixture turned orange. After stirring for 30 min a solution of *tert*-butyl (4-oxocyclopent-2-en-1-yl) carbonate (50.0 mg, 0.25 mmol, 1.0 equiv) in dry THF (0.5 mL) was added dropwise and stirring continued for 1.5 h at -78 °C. H_2O containing 0.3% of HOAc was added and the aqueous layer extracted with Et_2O (3x 5 mL). The combined organic layers were washed with brine, aq. sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex/EA, 5:1 to 1:1) gave the title product **211** in 61% yield as colourless oil (45.3 mg, 0.15 mmol) with an undeterminable d.r.

In the proton and carbon NMR the signals of the diastereomers are overlapping.

R_f (Hexane/EA = 5:1) = 0.07; brown with anisaldehyde.

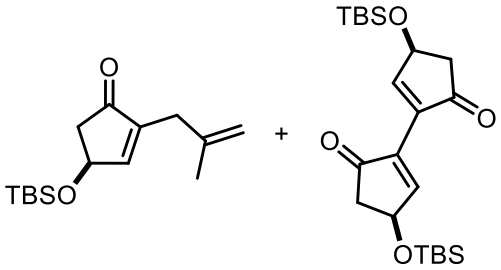
^{1}H NMR (396 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 6.09 – 5.93 (m, 2H), 5.34 (dd, *J* = 7.3, 4.0 Hz, 1H), 2.70 – 2.50 (m, 2H), 2.49 – 2.39 (m, 1H), 2.38 – 2.25 (m, 1H), 2.16 – 2.06 (m, 1H), 2.06 – 1.96 (m, 2H), 1.96 – 1.85 (m, 1H), 1.73 – 1.58 (m, 3H), 1.48 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 215.2, 214.9, 153.4, 140.1, 138.8, 132.2, 132.0, 83.9, 82.3, 82.2, 80.1, 79.5, 58.8, 57.9, 53.6, 44.8, 44.6, 44.5, 43.1, 43.1, 42.8, 40.9, 29.4, 27.9, 27.7, 25.3, 25.2, 25.1, 25.0.

IR (neat) (cm^{-1}) ν_{max}: 3515, 3063, 2946, 2863, 1731, 1703, 1457, 1368, 1340, 1284, 1168, 1118.

HRMS (ESI) (m/z): calculated for $C_{16}H_{24}O_5$ $[M+Na]^+$ 319.1521, found 319.2333.

4-((*tert*-butyldimethylsilyl)oxy)-2-(2-methylallyl)cyclopent-2-en-1-one (228) and **4,4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclopentane)]-5,5'-diene-2,2'-dione (229)**



A 50 mL flame dried two necked flask equipped with a reflux condenser was charged with 4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (1.18 g, 3.50 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (202.3 mg, 5 mol%) solved in dry toluene (17.5 mL). ($^{n}Bu_3Sn)_2$ (3.5 mL, 7.00 mmol, 2.0 equiv) was added at rt and the resulting reaction mixture heated to reflux for 14 h. After cooling to rt a solution of KF (10%, aq.) and sat., aq. NH_4Cl were added followed by filtration and extraction with hexane (3x 30 mL). The combined organic layers were washed with sat., aq. $Na_2S_2O_3$, KF (10%, aq.) and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (Hex to Hex/EA, 9:1) gave the tin compound (**226**) as light yellow oil in 86% yield (1.68 g, 3.35 mmol).

A 100 mL two necked flask was charged with LiCl (568.1 mg, 13.40 mmol, 4.0 equiv) and flame dried. Then Pd_2dba_3 (613.6 mg, 20 mol%) and CuCl (1.1 g, 11.06 mmol, 3.3 equiv) as well as a solution of 2-methylallyl acetate (420.7 mg, 3.69 mmol, 1.1 equiv) in dry NMP (16 mL) were added. After stirring for 10 min at rt a solution of **226** (1.68 g, 3.35 mmol, 1.0 equiv) in dry NMP (17 mL) was added. The resulting reaction mixture was stirred at 50 °C for 15 h before cooling to rt. H_2O (5 mL) was added and the aqueous layer extracted with Et_2O (4x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Two flash column chromatographies (Hex to Hex/EA, 9:1) gave the title product **228** in 63% yield over two steps (650.0 mg, 2.11 mmol) together with the homocoupling product **229** in a ratio of 4.6:1.

In the proton and carbon NMR the signals of the product and homocoupling product are overlapping. Characteristic signals of the homocoupling product are marked with *bp*.

R_f (Hexane/EA = 5:1) = 0.75; blue with anisaldehyde.

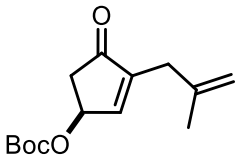
^{1}H NMR (396 MHz, $CDCl_3$) δ 8.30 – 8.20 (m, 0.3H)^{bp}, 7.09 – 7.05 (m, 1H), 7.05 – 7.02 (m, 0.2H)^{bp}, 5.01 – 4.97 (m, 0.3H) ^{bp}, 4.93 – 4.89 (m, 1H), 4.89 – 4.86 (m, 0.2H) ^{bp}, 4.84 – 4.81 (m, 1H), 4.75 – 4.72 (m, 1H), 2.89 (s, 2H), 2.81 – 2.71 (m, 1.6H), 2.34 – 2.25 (m, 1.6H), 1.72 (s, 3H), 0.91 (s, 17H), 0.17 – 0.09 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 204.8^{bp}, 161.5 ^{bp}, 158.3, 156.7 ^{bp}, 150.6 ^{bp}, 147.4 ^{bp}, 144.9, 142.1, 134.6 ^{bp}, 133.4 ^{bp}, 112.8, 69.3 ^{bp}, 69.1 ^{bp}, 69.0, 45.7 ^{bp}, 45.6, 45.3 ^{bp}, 32.7, 29.7 ^{bp}, 27.9 ^{bp}, 26.9 ^{bp}, 25.94 ^{bp}, 25.91, 25.89 ^{bp}, 24.3 ^{bp}, 22.6 ^{bp}, 22.5, 18.3 ^{bp}, 17.7 ^{bp}, 13.9 ^{bp}, 13.7 ^{bp}, -4.5.

IR (neat) (cm^{-1}) ν_{max}: 2946, 2896, 2863, 1713, 1653, 1463, 1401, 1357, 1256, 1168, 1090.

HRMS (ESI) (m/z): calculated for $C_{16}H_{24}O_5$ $[M+Na]^+$ 289.1600, found 289.2143.

***tert*-butyl (3-(2-methylallyl)-4-oxocyclopent-2-en-1-yl) carbonate (230)**



A 50 mL Schlenk flask was charged with AcCl (273 µL, 3.83 mmol, 5.1 equiv) solved in dry MeOH (10.9 mL) under Ar and cooled to 0 °C. A solution of 4-((*tert*-butyldimethylsilyl)oxy)-2-(2-methylallyl)cyclopent-2-en-1-one (200.0 mg, 0.75 mmol, 1.0 equiv) in dry MeOH (2.1 mL) was added. The reaction mixture was stirred for 30 min at 0 °C before brine and EA were added. The aqueous layer was extracted with EA (2x 5 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was azeotroped with toluene (3x 5 mL) to remove the remained TBSOH which yielded the crude product **x** as a light yellow oil (109.2 mg).

To a solution of crude 4-hydroxy-2-(2-methylallyl)cyclopent-2-en-1-one (109.2 mg) and Boc_2O (187.9 mg, 0.86 mmol, 1.2 equiv) in THF (1.5 mL) were added NEt_3 (120 µL, 0.86 mmol, 1.2 equiv) and DMAP (1.8 mg, 2 mol%). After the reaction mixture was stirred at 25 °C for 1 h, the solvent was removed under reduced pressure. Purification by column chromatography (hexanes/EA, 4:1) gave the title product **230** as a colourless oil in 64% yield over two steps (133.2 mg, 0.48 mmol).

R_f (Hexane/EA = 5:1) = 0.48; blue with anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$, signal broadening due to rotamers) δ 7.19 – 7.13 (m, 1H), 5.63 – 5.59 (m, 1H), 4.82 – 4.78 (m, 1H), 4.72 – 4.66 (m, 1H), 2.88 (s, 2H), 2.81 (ddd, *J* = 14.2, 6.3, 1.3 Hz, 1H), 2.46 – 2.35 (m, 1H), 1.67 (s, 3H), 1.46 (s, 9H).

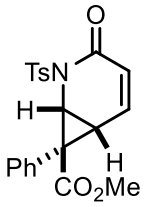
^{13}C NMR (101 MHz, $CDCl_3$, signal splitting due to rotamers) δ 204.5, 203.9, 152.98, 152.94, 152.7, 151.2, 150.3, 147.9, 141.4, 113.2, 83.0, 82.9, 72.8, 72.6, 41.5, 32.8, 29.5, 27.8, 24.3, 22.5, 22.4, 13.8.

IR (neat) (cm^{-1}) ν_{max}: 3079, 2978, 2937, 2356, 1718, 1655, 1457, 1394, 1371, 1275, 1152, 1088, 1036, 992, 958, 891, 842, 794, 727.

HRMS (ESI) (m/z): calculated for $C_{14}H_{20}O_4$ $[M+Na]^+$ 275.1254, found 275.1250.

3. Experimental procedures for chapter C

methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (379)

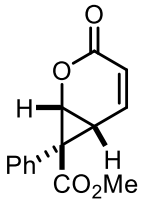


A 100 mL flame dried Schlenk flask was charged with 1-tosylpyridin-2(1H)-one (3.50 g, 14.04 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (62.1 mg, 1 mol%) solved in dry toluene (28 mL). A solution of methyl 2-diazo-2-phenylacetate (7.42 g, 42.12 mmol, 3.0 equiv) in dry toluene (38 mL) was added via syringe pump over 1.5 h at rt. Then the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes/EA, 3:1 to 1:1, column packed with 4:1) gave the title product **379** as a light yellow solid in 98% yield (5.48 g, 13.76 mmol). Analytical data are according to literature.[133]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.94 (m, 2H), 7.37 – 7.27 (m, 5H), 7.25 – 7.19 (m, 2H), 6.80 (ddd, *J* = 9.9, 5.3, 0.7 Hz, 1H), 5.52 (d, *J* = 9.9 Hz, 1H), 4.81 (dd, *J* = 8.9, 0.7 Hz, 1H), 3.70 (s, 3H), 3.00 (dd, *J* = 9.0, 5.3 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 159.5, 145.5, 139.9, 135.8, 133.8, 129.6, 129.1, 128.6, 128.4, 125.8, 53.5, 46.8, 35.4, 26.9, 21.9.

methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (378)



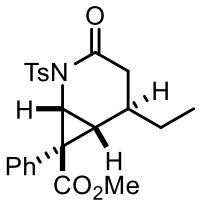
A 50 mL flame dried Schlenk flask was charged with 2H-pyran-2-one (500.0 mg, 5.20 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (57.5 mg, 3 mol%) solved in dry toluene (10.4 mL). A solution of methyl 2-diazo-2-phenylacetate (2.75 g, 15.61 mmol, 3.0 equiv) in dry toluene (12 mL) was added via syringe pump over 1.5 h at rt. Then the solvent was removed under reduced pressure. Purification by flash column chromatography

(hexanes/EA, 4:1 to 1:1) gave the title product **378** as a yellow solid in 76% yield (966.0 mg, 3.95 mmol). Analytical data are according to literature.[133]

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3H), 7.24 – 7.10 (m, 2H), 6.91 (ddd, *J* = 10.0, 5.6, 1.0 Hz, 1H), 5.61 (d, *J* = 10.0 Hz, 1H), 5.00 (dd, *J* = 7.0, 1.0 Hz, 1H), 3.67 (s, 3H), 2.84 (dd, *J* = 7.1, 5.5 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.9, 141.9, 133.9, 128.7, 128.5, 127.9, 121.1, 65.3, 53.4, 36.9, 25.5.

methyl 5-ethyl-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (401 a)



A 20 mL Schlenk tube was charged with $Cu(OTf)_2$ (3.6 mg, 2 mol%) solved in dry toluene (2.5 mL) and cooled to -78 °C. Then a solution of methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (200.0 mg, 0.50 mmol, 1.0 equiv) in dry DCM (1.2 mL) followed by $AlEt_3$ (540 µL, 1.01 mmol, 2.0 equiv, 25 w% in toluene) were slowly added and the reaction mixture stirred for 2.5 h at -78 °C. Then the reaction was gradually warmed to 0 °C and after 3 h additional $AlEt_3$ (540 µL, 2.0 equiv) was added. After another 1.5 h the reaction mixture was quenched with sat. aq. NH_4Cl, extracted with Et_2O (4x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was filtrated over Celite and washed with $CHCl_3$ to give the title product **401 a** as a light yellow solid in 95% yield (204.0 mg, 0.48 mmol).

R_f (Hexanes/EA = 1:1) = 0.62.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.58 – 7.49 (m, 2H), 7.46 – 7.30 (m, 5H), 4.10 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 2.44 (s, 3H), 2.25 – 2.16 (m, 1H), 2.06 – 1.92 (m, 2H), 1.91 – 1.76 (m, 1H), 1.70 – 1.41 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

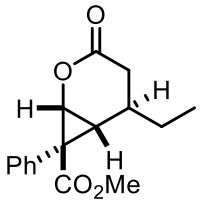
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 170.5, 145.4, 135.7, 132.5, 130.9, 129.5, 129.1, 128.9, 128.3, 53.2, 45.3, 38.8, 38.2, 31.3, 29.6, 28.9, 21.8, 11.2.

IR (neat) (cm^{-1}) ν_{max}: 3030, 2960, 1707, 1595, 1498, 1435, 1357, 1241, 1170, 1088, 977, 913, 813, 731, 705.

HRMS (ESI) (m/z): calculated for $C_{23}H_{25}NO_5S$ $[M+H]^+$ 428.1526, found 428.1535.

mp: 133.2 °C

methyl 5-ethyl-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (400 a)



A 10 mL Schlenk tube was charged with $Cu(OTf)_2$ (1.5 mg, 2 mol%) solved in dry toluene (1 mL) and cooled to -78 °C. Then methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.20 mmol, 1.0 equiv) solved in dry DCM (0.5 mL) was added followed by $AlEt_3$ (220 µL, 0.41 mmol, 2.0 equiv, 25 w% in toluene) and the mixture was stirred for 1 h at -78 °C. Then the reaction was gradually warmed to -30 °C over 2.5 h before being stirred at 0 °C. After 1 h the reaction mixture was quenched with sat. aq. NH_4Cl, extracted with Et_2O (4x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 3:1 to 1:1) gave the title product **400 a** as white solid in 57% yield (32.0 mg, 0.11 mmol).

R_f (Hexanes/EA = 1:1) = 0.70.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 3H), 7.30 – 7.27 (m, 1H), 7.27 – 7.23 (m, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 3.62 (s, 3H), 2.20 – 2.00 (m, 3H), 1.69 – 1.50 (m, 3H), 1.05 (t, *J* = 7.1 Hz, 3H).

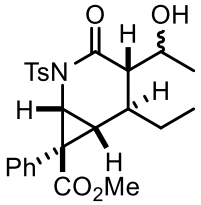
^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.5, 171.1, 132.7, 130.2, 128.8, 128.1, 62.9, 53.1, 37.5, 34.4, 31.7, 30.1, 29.0, 11.3.

IR (neat) (cm^{-1}) ν_{max}: 3064, 3030, 2967, 1767, 1711, 1602, 1435, 1394, 1353, 1256, 1170, 1115, 1074, 1033, 980, 921, 824, 787, 701.

HRMS (APCI) (m/z): calculated for $C_{16}H_{18}O_4$ $[M+H]^+$ 275.1278, found 275.1280.

mp: 82 °C

methyl 5-ethyl-4-(1-hydroxyethyl)-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (404)



A 10 mL Schlenk tube was charged with $Cu(OTf)_2$ (1.2 mg, 3 mol%) and methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv) solved in dry toluene (0.5 mL) and dry DCM (0.1 mL) and cooled to -78 °C. Then $AlEt_3$ (110 µL, 0.20 mmol, 2.0 equiv, 25 w% in toluene) was added and the reaction mixture was stirred for 2 h and gradually warmed to -30 °C. Then the reaction was warmed to 0 °C. After 2 h the reaction was cooled to -78 °C and additional $AlEt_3$ (110 µL, 0.20 mmol, 2.0 equiv, 25 w% in toluene) was added and the reaction mixture stirred for 1 h at 0 °C before being cooled to -78 °C and acetaldehyde (12 µL, 0.20 mmol, 2.0 equiv) in dry toluene (0.4 mL) was added over 35 min. Stirring was continued at -78 °C for 1 h and then for 23 h where the reaction gradually warmed to rt before being quenched with sat. aq. NH_4Cl, extracted with Et_2O (4x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 2:1 to EA) gave the title product **404** as white solid in 42% yield (20.0 mg, 42.0 µmol) and a d.r. 1:1.2.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.45.

^{1}H-NMR (400 MHz, $CDCl_3$) (signal splitting due to diastereomers) δ 7.96 – 7.87 (m, 2H), 7.58 – 7.51 (m, 2H), 7.46 – 7.38 (m, 2H), 7.37 – 7.30 (m, 3H), 4.02 – 3.95 (m, 1H), 3.68 – 3.64 (m, 3H), 2.48 – 2.44 (m, 3H), 2.35 – 2.23 (m, 1H), 2.12 – 2.02 (m, 1H), 2.02 – 1.85 (m, 1H), 1.81 – 1.66 (m, 1H), 1.64 – 1.50 (m, 1H), 1.49 – 1.30 (m, 1H), 1.14 – 1.11 (m, 1H), 1.12 – 1.05 (m, 3H), 0.95 – 0.84 (m, 1H), 0.79 – 0.70 (m, 2H).

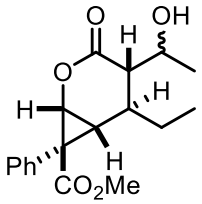
^{13}C-NMR (101 MHz, $CDCl_3$) (signal splitting due to diastereomers) δ 173.9, 173.1, 172.9, 172.7, 145.8, 145.4, 135.7, 135.2, 132.9, 132.8, 130.2, 129.7, 129.6, 129.2, 129.0, 128.9, 128.8, 128.4, 128.3, 66.5, 65.1, 53.3, 53.2, 51.3, 50.1, 44.2, 43.8, 39.5, 38.9, 32.6, 32.5, 29.4, 27.9, 25.6, 25.0, 22.3, 21.9, 9.8, 9.7.

IR (neat) (cm^{-1}) ν_{max}: 3526, 3030, 2967, 2877, 2363, 2251, 1711, 1595, 1498, 1435, 1402, 1361, 1244, 1170, 1118, 1032, 973, 910, 813, 731, 664.

HRMS (ESI) (m/z): **major diastereomer** (acquisition time 2.916 – 2.920 min): calculated for $C_{25}H_{29}NO_6S$ $[M+H]^+$ 472.1788, found 472.1796; **minor diastereomer** (acquisition time 2.849 min): calculated for $C_{25}H_{29}NO_6S$ $[M+H]^+$ 472.1788, found 472.1797.

mp: 76.7 °C

methyl 5-ethyl-4-(1-hydroxyethyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (403)



A 10 mL Schlenk tube was charged with $Cu(OTf)_2$ (3.4 mg, 5 mol%)solved in dry toluene (1 mL) and cooled to -78 °C. Then a solution of methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.20 mmol, 1.0 equiv) in dry DCM (0.2 mL) followed by $AlEt_3$ (220 µL, 0.41 mmol, 2.0 equiv, 25 w% in toluene) were added and the reaction mixture stirred for 2 h and gradually warmed to 0 °C. After 2 h the reaction was cooled to -78 °C and acetaldehyde (69 µL, 1.23 mmol, 6.0 equiv) in dry toluene (1 mL) was added over 1.5 h. Stirring was continued at -78 °C for 1 h and then the reaction mixture was allowed to warm to rt for another 17 h before being quenched with sat. aq. NH_4Cl, extracted with Et_2O (4x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 2:1 to EA) gave the title product **403** as colourless oil in 31% yield (20.0 mg, 62.0 µmol) and a d.r. of 1:7.6.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.22, blue with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.43 – 7.27 (m, 5H), 4.69 – 4.55 (m, 1H), 4.23 – 4.09 (m, 1H), 3.89 – 3.78 (m, 1H), 3.67 – 3.59 (m, 3H), 2.20

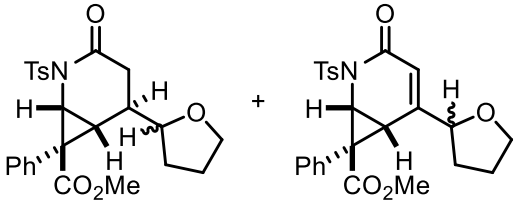
– 2.10 (m, 1H), 2.06 – 2.01 (m, 1H), 1.37 – 1.27 (m, 3H), 1.21 – 1.08 (m, 3H), 1.08 – 0.99 (m, 1H), 0.92 – 0.65 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, minor diastereomer weakly distinctive) δ 173.2, 172.3, 132.8, 132.7, 128.8, 128.2, 65.6, 61.7, 53.1, 47.5, 37.1, 33.2, 29.2, 25.3, 16.9, 10.6.

IR (neat) (cm^{-1}) ν_{max}: 3504, 3060, 3030, 2960, 2930, 2359, 1718, 1498, 1435, 1379, 1245, 1178, 1103, 1066, 980, 917, 891, 734, 701.

HRMS (APCI) (m/z): **major diastereomer** (acquisition time 7.089 – 7.097 min): calculated for $C_{18}H_{22}O_5$ $[M+H]^+$ 319.1540, found 319.1543; **minor diastereomer** (acquisition time 7.320 – 7.348 min): calculated for $C_{18}H_{22}O_5$ $[M+H]^+$ 319.1540, found 319.1542.

methyl 3-oxo-7-phenyl-5-(tetrahydrofuran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (412 a) and **methyl 3-oxo-7-phenyl-5-(tetrahydrofuran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (412 b)**



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv) and eosin Y (1.3 mg, 2 mol%) and backfilled with N_2 three times. Then THF (2.5 mL) was added and the resulting solution degassed by three cycles of freeze-pump-thaw. Irradiation for 2 d with a 455 nm LED at 50 °C followed by evaporation of the solvent and flash column chromatography (hexanes/EA, 3:1 to 1:1) gave the product **412 a** and byproduct **412 b** as a white solid in a ratio of 2:1 in 70% combined yield (33.0 mg, 70.0 µmol) and a d.r. of 1:1.3.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the byproduct are marked.

R_f (Hexanes/EA = 1:1) = 0.36 and 0.62.

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer A) δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.29 (m, 4H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 7.05 – 6.90 (m, 3H), 5.09 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.85 – 3.71 (m, 3H), 3.47 (t, *J* = 2.5 Hz, 1H), 2.82 (dt, *J* = 8.7, 2.2 Hz, 1H), 2.31 (s, 3H), 2.14 (tdd, *J* = 7.8, 6.7, 4.7 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.98 – 1.86 (m, 2H), 1.67 – 1.55 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, diatereomer A) δ 169.9, 165.9, 144.8, 134.2, 130.1, 129.2, 129.1, 129.0, 128.5, 128.0, 127.6, 127.5, 79.8, 68.5, 52.8, 51.8, 43.4, 36.2, 32.2, 30.2, 25.9, 25.6, 21.7.

^{1}H NMR (400 MHz, $CDCl_3$, diatereomer B + byproduct **412 b**) δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.95 (dd, *J* = 8.4, 1.8 Hz, 0.4H)^{bp}, 7.62 – 7.50 (m, 0.5H)^{bp}, 7.49 – 7.28 (m, 4H), 7.13 (td, *J* = 7.5, 1.3 Hz, 1H), 7.07 – 6.96 (m, 3H), 5.09 (d, *J* = 8.7 Hz, 1H), 4.21 (dd, *J* = 59.4, 9.6 Hz, 0.3H)^{bp}, 3.97 (ddd, *J* = 7.9, 6.7, 5.1 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.66 (m, 1H), 3.67 – 3.64 (m, 1.4H)^{bp}, 3.62 – 3.51 (m, 2H), 2.52 (dt, *J* = 8.7, 2.2 Hz, 1H), 2.43 (s, 0.8H)^{bp}, 2.32 (s, 3H), 2.12 (dt, *J* = 4.8, 2.2 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.93 – 1.83 (m, 3H), 1.73 – 1.64 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer B + byproduct **412 b**) δ 172.7^{bp}, 169.9, 169.5^{bp}, 166.2, 144.6, 134.6, 132.9^{bp}, 132.1^{bp}, 130.6, 129.5^{bp}, 129.4^{bp}, 129.14, 129.09, 129.06^{bp}, 128.95, 128.91^{bp}, 128.4, 128.2, 127.9^{bp}, 127.8, 127.5, 125.3^{bp}, 81.5^{bp}, 81.4^{bp}, 79.8^{bp}, 79.4^{bp}, 68.4^{bp}, 68.37, 53.2^{bp}, 52.8, 51.8^{bp}, 49.7, 45.23^{bp}, 45.20^{bp}, 43.8, 40.6^{bp}, 37.4^{bp}, 35.9, 35.1^{bp}, 34.3^{bp}, 33.4^{bp}, 32.4, 29.6, 28.3^{bp}, 27.2^{bp}, 26.9, 26.2^{bp}, 26.1, 21.8^{bp}, 21.7.

IR (neat) (cm^{-1}) ν_{max} (diastereomer A): 3068, 2956, 2874, 2259, 1715, 1595, 1490, 1439, 1402, 1357, 1252, 1170, 1092, 1058, 1021, 991, 910, 842, 813, 731.

IR (neat) (cm^{-1}) ν_{max} (diastereomer B + byproduct **412 b**): 3068, 2956, 2878, 2259, 1715, 1595, 1490, 1439, 1405, 1357, 1290, 1252, 1219, 1170, 1118, 1088, 1059, 992, 910, 842, 812, 734.

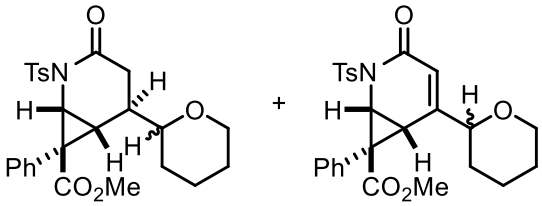
HRMS (ESI) (m/z): calculated for $C_{25}H_{27}NO_6S$ $[M+H]^+$ 470.1637, found 470.1633.

HRMS (ESI) (m/z): calculated for $C_{25}H_{25}NO_6S$ $[M+H]^+$ 468.1481, found 468.1474.

mp (diastereomer A): 136.9 °C

mp (diastereomer B + byproduct **412 b**): 162.1 °C

methyl 3-oxo-7-phenyl-5-(tetrahydro-2H-pyran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (414 a) and **methyl 3-oxo-7-phenyl-5-(tetrahydro-2H-pyran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (414 b)**



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv), eosin Y (1.3 mg, 2 mol%) solved dry tetrahydro-2H-pyran (2.5 mL). Then H_2O (0.5 µL) was added and the resulting solution was degassed by three cycles of freeze-pump-thaw. Irradiation for 1 d at 60 °C with a 455 nm LED was followed by evaporation of the solvent and purification by flash column chromatography (hexanes/ EA, 4:1 to 2:1) gave an unseparable mixture of the product **414 a** and byproduct **414 b** as a white solid in a ratio of 9.4:1 in 59% combined yield (28.8 mg, 59.0 µmol) and a d.r. of 1:1.7 (**414 a**) and d.r. 1:1.2 (**414 b**).

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the byproduct are marked.

R_f (Hexanes/EA = 1:1) = 0.52.

^{1}H-NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 8.14 – 8.06 (m, 1H), 7.96 – 7.78 (m, 0.3H)^{bp}, 7.60 – 7.48 (m, 0.3H)^{bp}, 7.44 – 7.36 (m, 2H), 7.36 – 7.27 (m, 2H), 7.14 – 7.06 (m, 1H), 7.04 – 6.93 (m, 3H), 5.11 – 5.03 (m, 1H), 4.24 – 4.05 (m, 0.2H)^{bp}, 3.89 – 3.85 (m, 3H), 3.85 – 3.83 (m, 0.3H)^{bp}, 3.83 – 3.80 + 3.53 – 3.49 (m, 1H), 3.78 – 3.72 (m, 0.6H)^{bp}, 3.67 – 3.65 (m, 0.3H)^{bp}, 3.38 – 3.28 (m, 2H), 2.80 – 2.50 (m, 1H), 2.44 – 2.40 (m, 0.4H)^{bp}, 2.33 – 2.28 (m, 3H), 2.07 – 1.98 (m, 1H), 1.91 – 1.82 (m, 1H), 1.75 – 1.64 (m, 1H), 1.60 – 1.33 (m, 5H), 0.96 – 0.84 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 170.1, 170.0, 166.2, 166.0, 144.7, 144.6, 134.5, 134.3, 132.7^{bp}, 132.3^{bp}, 130.66, 130.64, 129.45^{bp}, 129.43^{bp}, 129.18, 129.15, 129.09^{bp}, 129.01, 128.97, 128.96, 128.92^{bp}, 128.4, 128.3, 128.2^{bp}, 128.03, 128.00, 127.9, 127.7, 127.5, 127.4, 78.5, 77.9, 77.4, 68.9, 68.8, 53.19^{bp}, 53.16^{bp}, 52.8,

52.7, 51.5, 49.7, 43.9, 43.7, 40.9^{bp}, 40.6^{bp}, 36.5, 36.3, 32.32, 32.30, 29.6, 29.4, 25.9, 25.9, 25.2, 23.9^{bp}, 23.3, 21.8^{bp}, 21.7, 20.9^{bp}.

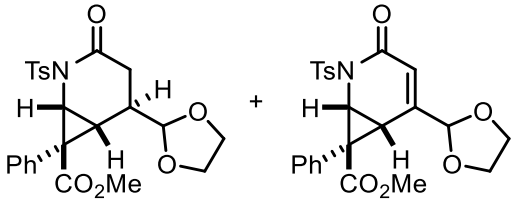
IR (neat) (cm^{-1}) ν_{max}: 3068, 2941, 2848, 2259, 1715, 1595, 1491, 1439, 1405, 1357, 1252, 1208, 1170, 1088, 1044, 992, 910, 842, 813, 731.

HRMS (ESI) (m/z): **major diastereomer** (acquisition time 3.231 – 3.252 min): calculated for $C_{26}H_{29}NO_6S$ $[M+H]^+$ 484.1788, found: 484.1799; **minor diastereomer** (acquisition time 3.173 – 3.181 min): calculated for $C_{26}H_{29}NO_6S$ $[M+H]^+$ 484.1788, found: 484.1776.

HRMS (ESI) (m/z): calculated for $C_{26}H_{27}NO_6S$ $[M+H]^+$ 482.1637, found: 482.1638.

mp: 69.5 °C

methyl 5-(1,3-dioxolan-2-yl)-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (417 a) and **methyl 5-(1,3-dioxolan-2-yl)-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (417 b)**



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv) and eosin Y (1.3 mg, 2 mol%) and backfilled with N_2 three times. Then dry 1,3-dioxolane (2.5 mL) and TFA (0.2 µL, 2 mol%) were added and the resulting solution was degassed by three cycles of freeze-pump-thaw. Irradiation for 19 h with a 455 nm LED at 60 °C followed by evaporation of the solvent and flash column chromatography (hexanes/EA, 2:1 to 1:1) gave the product **417 a** and byproduct **417 b** as a colourless oil in 25% (12.0 mg, 25.0 µmol) combined yield and a ratio of 3:1.

In the proton and carbon NMR the signals of product and byproduct are overlapping. Characteristic signals of the byproduct are marked.

R_f (Hexanes/EA = 1:1) = 0.40, red with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 0.3H)^{bp}, 7.95 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.53 (m, 2H), 7.52 – 7.47 (m, 1H), 7.45 – 7.38 (m, 2H), 7.38 – 7.30 (m, 3H), 7.15 (td, *J* = 7.5, 1.3 Hz, 0.4H)^{bp}, 7.08 – 6.98 (m, 1H), 5.12 – 5.07 (m, 1H), 4.89 (d, *J* = 2.8 Hz, 1H), 4.28 (d, *J* = 9.6 Hz, 1H), 4.00 – 3.91 (m, 0.6H)^{bp}, 3.89 (s, 1.3H)^{bp}, 3.87 – 3.76 (m, 3H), 3.66 (s, 3H), 2.65 (dt, *J* = 8.7, 2.1 Hz, 0.4H)^{bp}, 2.51 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.43 (s, 3H), 2.36 (d, *J* = 2.4 Hz, 1H), 2.34 (s, 1H)^{bp}, 2.11 (dd, *J* = 16.8, 7.6 Hz, 1H), 1.56 (dd, *J* = 16.8, 5.8 Hz, 1H).

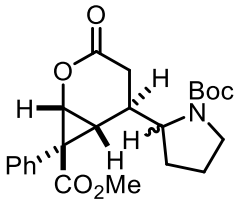
^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.7, 169.9^{bp}, 169.1, 166.2^{bp}, 145.1, 144.6^{bp}, 136.0, 134.8^{bp}, 132.2, 131.0^{bp}, 130.4^{bp}, 129.4, 129.2, 128.95^{bp}, 128.92, 128.5^{bp}, 128.4, 128.3, 127.9^{bp}, 127.6^{bp}, 104.8, 103.7^{bp}, 65.8^{bp}, 65.5, 65.4^{bp}, 65.3, 53.3, 52.9^{bp}, 48.2^{bp}, 45.1, 43.7^{bp}, 37.3, 35.5^{bp}, 34.2, 32.6, 32.5^{bp}, 24.8^{bp}, 24.7, 21.8, 21.7^{bp}.

IR (neat) (cm^{-1}) ν_{max}: 3064, 3030, 2956, 2892, 2269, 1715, 1595, 1495, 1435, 1401, 1361, 1252, 1170, 1126, 1032, 910, 813, 731.

HRMS (ESI) (m/z): calculated for $C_{24}H_{25}NO_7S$ $[M+H]^+$ 472.1424, found: 472.1431.

HRMS (ESI) (m/z): calculated for $C_{24}H_{23}NO_7S$ $[M+H]^+$ 470.1268, found: 470.1274.

tert-butyl 2-(7-(methoxycarbonyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptan-5-yl)pyrrolidine-1-carboxylate (424)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.20 mmol, 1.0 equiv), (*tert*-butoxycarbonyl)-*L*-proline (44.1 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (42.8 mg, 0.25 mmol, 1.2 equiv) and Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (4.6 mg, 2 mol%) solved in dry DMF (1 mL). The resulting solution was degassed by three cycles of freeze-pump-thaw and irradiated with 455 nm LED for 1 d. Then sat. aq. $NaHCO_3$ was added followed by extraction with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 2:1 to

1:1) gave the title product **424** as a colourless oil in 72% yield (61.3 mg, 0.14 mmol) and a d.r. of 1:1.4.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.65; yellow with ninhydrin.

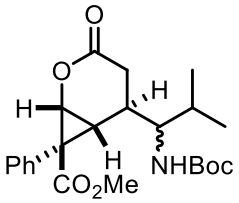
^{1}H-NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.40 – 7.28 (m, 3H), 7.25 – 7.16 (m, 2H), 4.70 – 4.60 (m, 1H), 4.17 – 3.92 (m, 1H), 3.87 – 3.65 (m, 1H), 3.63 – 3.54 (m, 3H), 3.46 – 3.28 (m, 1H), 3.26 – 2.80 (m, 1H), 2.76 – 2.25 (m, 1H), 2.21 – 2.13 (m, 1H), 2.10 – 2.01 (m, 1H), 2.01 – 1.95 (m, 1H), 1.89 – 1.78 (m, 2H), 1.75 – 1.59 (m, 1H), 1.48 – 1.39 (m, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 172.3, 132.8, 132.6, 130.0, 128.9, 128.8, 128.3, 128.2, 127.5, 77.5, 62.9, 53.2, 47.2, 37.0, 34.4, 32.4, 32.2, 28.6, 28.5, 28.5, 27.9, 27.8, 23.8.

IR (neat) (cm^{-1}) ν_{max}: 2974, 2889, 2251, 1759, 1718, 1685, 1476, 1435, 1387, 1252, 1230, 1167, 1103, 1074, 973, 910, 727.

HRMS (ESI) (m/z): calculated for $C_{23}H_{29}NO_6$ $[M+H]^+$ 416.2068, found: 416.2069.

methyl 5-(1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (426 d)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.20 mmol, 1.0 equiv), (*tert*-butoxycarbonyl)-*L*-valine (44.5 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (42.8 mg, 0.25 mmol, 1.2 equiv) and Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (4.6 mg, 2 mol%) solved in dry DMF (1 mL). The resulting solution was degassed by three cycles of freeze-pump-thaw and irradiated with 455 nm LED for 4 d. The solvent was evaporated under reduced pressure and flash column chromatography (hexanes/EA, 3:1 to EA) gave the title product **426 d** as a yellow oil in 41% yield (34.7 mg, 82.0 µmol) and a d.r. of 1:2.5.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.50; yellow with ninhydrin.

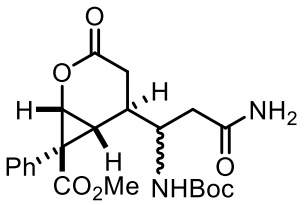
^{1}H-NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.43 – 7.28 (m, 5H), 4.72 – 4.60 (m, 1H), 4.59 – 4.27 (m, 1H), 3.75 – 3.65 (m, 1H), 3.64 – 3.57 (m, 3H), 2.38 – 2.22 (m, 1H), 2.20 – 2.08 (m, 1H), 1.83 – 1.74 (m, 1H), 1.57 – 1.49 (m, 1H), 1.48 – 1.37 (m, 9H), 1.01 – 0.90 (m, 3H), 0.90 – 0.73 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 172.1, 172.0, 171.0, 170.4, 156.4, 156.3, 132.6, 132.5, 130.2, 130.1, 128.8, 128.7, 128.3, 128.2, 80.0, 79.9, 77.4, 62.97, 62.93, 59.4, 59.1, 53.1, 52.9, 40.9, 37.4, 36.9, 34.3, 33.9, 32.8, 32.5, 30.2, 29.5, 28.9, 28.8, 28.4, 28.3, 27.4, 23.9, 20.7, 20.6, 18.1, 17.6, 17.4, 16.2.

IR (neat) (cm^{-1}) ν_{max}: 3370, 2967, 2359, 2117, 1715, 1498, 1435, 1368, 1249, 1170, 1077, 1021, 917, 753, 705.

HRMS (ESI) (m/z): **major diastereomer** (acquisition time 2.944 – 3.011 min):calculated for $C_{23}H_{31}NO_6$ $[M+Na]^+$ 440.2044, found: 440.2051; **minor diastereomer** (acquisition time 2.899 – 2.944 min): calculated for $C_{23}H_{31}NO_6$ $[M+Na]^+$ 440.2044, found: 440.2046.

methyl 5-(3-amino-1-((*tert*-butoxycarbonyl)amino)-3-oxopropyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (426 b)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.20 mmol, 1.0 equiv), (*tert*-butoxycarbonyl)asparagine (47.5 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (42.8 mg, 0.25 mmol, 1.2 equiv) and Ir[(*d*F(CF_3)ppy)$_2$(dtbbpy)]PF_6 (4.6 mg, 2 mol%) solved in dry DMF (1 mL). The resulting solution was degassed by three cycles of freeze-pump-thaw and irradiated with 455 nm LED for 1 week. Then sat. aq. $NaHCO_3$ was added followed by extraction with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (DCM/MeOH, 9:1)

followed by crystallisation by vapor diffusion ($CHCl_3$/pentane) gave the title product **426 b** as a light yellow solid in 55% yield (48.9 mg, 0.11 mmol) and a d.r. of 1:4.3.

In the proton NMR the signals of both diastereomers are overlapping and in the carbon NMR the signals of the minor diastereomer are not visible.

R_f (DCM/MeOH = 9:1) = 0.50; yellow with ninhydrin.

^{1}H-NMR (300 MHz, $CDCl_3$, signal splitting and broadening due to diastereomers and rotamers) δ 7.44 – 7.29 (m, 5H), 5.97 (s, 1H), 5.54 (s, 1H), 5.26 (d, *J* = 9.4 Hz, 1H), 4.65 (d, *J* = 7.7 Hz, 1H), 4.09 (s, 1H), 3.63 (s, 3H), 2.78 – 2.54 (m, 2H), 2.30 – 2.14 (m, 3H), 1.94 (s, 1H), 1.42 (s, 9H).

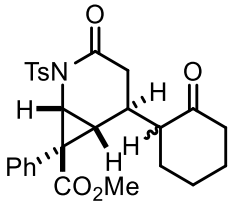
^{13}C-NMR (101 MHz, $CDCl_3$, signal splitting due to rotamers) δ 172.3, 172.1, 170.2, 155.9, 132.6, 129.6, 129.0, 128.4, 80.5, 62.7, 53.2, 51.7, 37.8, 37.4, 34.7, 31.4, 28.4, 27.6.

IR (neat) (cm^{-1}) ν_{max}: 3355, 2978, 2363, 2259, 1759, 1715, 1614, 1521, 1435, 1394, 1368, 1338, 1252, 1170, 1070, 1029, 917, 887, 850, 734.

HRMS (ESI) (m/z): calculated for $C_{22}H_{28}N_2O_7$ $[M+H]^+$ 433.1969, found: 433.1969.

mp: 173.8 °C

methyl 3-oxo-5-(2-oxocyclohexyl)-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (434)



A 10 mL Schlenk tube was charged with (cyclohex-1-en-1-yloxy)trimethylsilane (42.9 mg, 0.25 mmol, 2.5 equiv) solved in dry THF (1 mL) and cooled to 0 °C. To the resulting solution, ^{n}BuLi (170 µL, 0.27 mmol, 2.7 equiv, 1.6 M in hexane) was added dropwise and the resulting mixture was stirred for 1.5 h at 0 °C. Then the mixture was added dropwise to a solution of methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv) in dry THF (1 mL) at -78 °C and rinsed with dry THF (1 mL). After stirring at -78 °C for 3 h the reaction mixture was

warmed to 0 °C and after one more hour quenched with sat. aq. NH_4Cl, extracted with Et_2O (3x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 3:1 to 1:1) gave the title product **434** as colourless solid in 34% yield (17.0 mg, 34.0 µmol) and a d.r. of 1:1.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.51.

^{1}H NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.40 (ddd, *J* = 7.8, 6.4, 2.0 Hz, 2H), 7.37 – 7.30 (m, 3H), 4.31 - 4.22 (m, 1H), 3.67 - 3.62 (m, 3H), 2.61 – 2.45 (m, 1H), 2.46 – 2.41 (m, 3H), 2.41 – 2.15 (m, 4H), 2.14 – 1.98 (m, 2H), 1.91 – 1.76 (m, 2H), 1.73 – 1.47 (m, 4H).

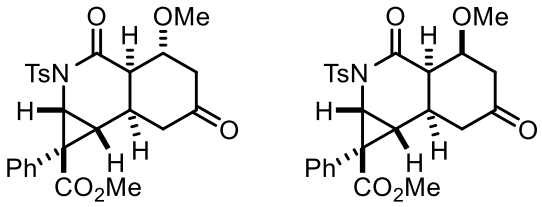
^{13}C NMR (101 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 210.5, 209.9, 172.9, 172.7, 169.7, 169.6, 145.3, 135.8, 135.8, 132.1, 132.0, 131.0, 130.7, 129.5, 129.2, 129.1, 129.1, 128.4, 128.4, 77.4, 55.3, 55.2, 53.3, 53.2, 45.4, 45.4, 42.7, 42.4, 37.7, 37.3, 35.5, 35.3, 30.9, 30.3, 29.5, 29.1, 27.8, 27.6, 27.5, 27.2, 25.4, 25.3, 21.8.

IR (neat) (cm^{-1}) ν_{max}: 2926, 2859, 1707, 1595, 1498, 1435, 1357, 1312, 1252, 1163, 1085, 977, 895, 816, 746, 705.

HRMS (ESI) (m/z): calculated for $C_{27}H_{29}NO_6S$ $[M+H]^+$ 496.1788, found: 496.1795.

mp: 186.5 °C

methyl 4-methoxy-3,6-dioxo-1-phenyl-2-tosyldecahydro-1H-cyclopropa[c]isoquinoline-1-carboxylate (446 a)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.13 mmol, 1.0 equiv) and BHT (27.7 mg, 0.13 mmol, 1.0 equiv) solved in dry toluene (2.2 mL) and degassed by two cycles of freeze-pump-thaw. Then Danishefsky diene (370 µL, 1.89 mmol, 15.0 equiv) was added and the solution degassed by another cycle of freeze-pump thaw. Afterwards, the resulting solution was stirred at 130 °C for 22 h. The solvent was evaporated under reduced pressure and the residue dissolved in THF (2 mL) and H_2O (0.7 mL) followed by addition of KF (30 mg). After 3 h of stirring at rt the solution was extracted with EA (3x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **446 a** as a white solid in 64% yield (80.5 mg, 80.9 µmol) and a d.r. of 1:1.

R_{fA} (Hexanes/EA = 1:1) = 0.22; red with vanillin.

R_{fB} (Hexanes/EA = 1:1) = 0.12.

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer A) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.52 – 7.41 (m, 4H), 7.41 – 7.34 (m, 3H), 4.45 (d, *J* = 9.5 Hz, 1H), 3.80 (q, *J* = 3.9 Hz, 1H), 3.67 (s, 3H), 3.03 – 2.95 (m, 1H), 2.84 (s, 3H), 2.54 – 2.47 (m, 1H), 2.46 (s, 3H), 2.37 – 2.30 (m, 1H), 2.30 – 2.22 (m, 2H), 1.96 (dd, *J* = 14.5, 11.8 Hz, 1H), 1.85 – 1.81 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer A) δ 206.0, 205.8, 172.2, 168.4, 145.8, 135.8, 131.5, 130.9, 129.9, 129.7, 128.8, 77.4, 76.5, 56.5, 53.5, 45.8, 44.3, 43.7, 42.8, 36.3, 29.5, 28.2, 21.9, 1.2.

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer B) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.40 (m, 4H), 7.39 – 7.31 (m, 3H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.90 – 3.86 (m, 1H), 3.65 (s, 3H), 2.81 (s, 3H), 2.75 – 2.69 (m, 1H), 2.61 – 2.55 (m, 2H), 2.55 – 2.45 (m, 2H), 2.43 (s, 3H), 2.37 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.18 (dd, *J* = 9.7, 7.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer B) δ 205.9, 172.5, 171.7, 145.3, 135.5, 132.8, 130.4, 129.3, 129.2, 129.1, 128.3, 81.9, 77.4, 57.2, 53.2, 47.1, 46.9, 43.7, 43.5, 41.1, 30.8, 27.3, 21.8, 1.2.

IR (neat) (cm^{-1}) ν_{max} (diastereomer A): 3064, 3030, 2952, 2930, 2363, 2255, 2136, 1718, 1595, 1498, 1435, 1368, 1252, 1174, 1088, 977, 816, 731, 667.

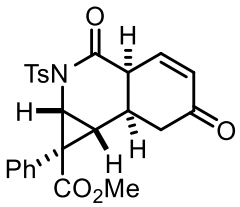
IR (neat) (cm^{-1}) ν_{max} (diastereomer B): 3030, 2952, 2356, 2259, 2147, 1715, 1599, 1498, 1435, 1364, 1245, 1170, 1088, 992, 913, 813, 731, 671.

HRMS (ESI) (m/z): calculated for $C_{26}H_{27}NO_7S$ $[M+H]^+$ 498.1586, found: 498.1585.

mp (diastereomer A): 170.3 °C

mp (diastereomer B): 163.5 °C

methyl 3,6-dioxo-1-phenyl-2-tosyl-1a,2,3,3a,6,7,7a,7b-octahydro-1*H*-cyclopropa[c]isoquinoline-1-carboxylate (459)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv) and BHT (22.2 mg, 0.10 mmol, 1.0 equiv) solved in dry toluene (1.7 mL) and degassed by two cycles of freeze-pump-thaw. Then Danishefsky diene (340 µL, 1.51 mmol, 15.0 equiv, 86 w%) was added and the solution degassed by another cycle of freeze-pump-thaw and then stirred at 130 °C for 24 h. The solvent was evaporated under reduced pressure and the residue dissolved in THF (2.0 mL) followed by addition of sat. aq. $KHSO_4$ (1 mL) at 0 °C. After 30 min the solution was extracted with Et_2O (3x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 3:1 to 1:1) gave the product **459** in 24% yield (11.3 mg, 24.0 µmol) as well as the not eliminated product **446 a** in 32% yield (16.0 mg, 32.0 µmol) as a yellow solid.

R_f (Hexanes/EA = 1:1) = 0.22; yellow with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.35 (m, 7H), 7.19 (d, *J* = 10.2 Hz, 1H), 6.00 (d, *J* = 10.2 Hz, 1H), 4.17 (d, *J* = 9.4 Hz, 1H), 3.68 (s, 3H), 2.92 (dd, *J* = 17.0, 12.7 Hz, 1H), 2.79 (dd, *J* = 17.0, 4.8 Hz, 1H), 2.46 (s, 3H), 2.36 (dd, *J* = 9.5, 7.8 Hz, 1H), 2.27 – 2.07 (m, 2H).

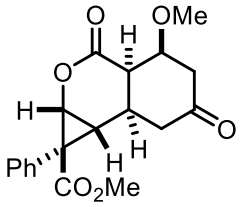
^{13}C-NMR (101 MHz, $CDCl_3$) δ 196.3, 172.5, 168.3, 145.9, 142.6, 134.9, 132.4, 131.9, 130.1, 129.8, 129.4, 129.2, 128.8, 67.9, 53.4, 44.4, 40.3, 38.1, 35.9, 26.6, 21.9.

IR (neat) (cm^{-1}) ν_{max}: 3414, 3060, 2955, 2926, 2855, 2333, 2259, 1715, 1595, 1498, 1435, 1405, 1364, 1312, 1260, 1170, 1088, 1013, 939, 909, 812, 730.

HRMS (ESI) (m/z): calculated for $C_{25}H_{23}NO_6S$ $[M+H]^+$ 466.1391, found: 466.1323.

mp: 204.2 °C

methyl 4-methoxy-3,6-dioxo-1-phenyldecahydrocyclopropa[c]isochromene-1-carboxylate (445 a)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (50.0 mg, 0.20 mmol, 1.0 equiv) and BHT (45.1 mg, 0.20 mmol, 1.0 equiv) solved in dry toluene (3.3 mL) and degassed by two cycles of freeze-pump-thaw. Then Danishefsky diene (600 µL, 3.07 mmol, 15.0 equiv) was added and the solution degassed by another cycle of freeze-pump thaw. Afterwards, the resulting solution was stirred at 130 °C for 22 h. Then the solvent was evaporated under reduced pressure and the residue dissolved in THF (3 mL) and H_2O (1 mL) followed by addition of KF (46 mg). The mixture was stirred at rt for 3 h before being extracted with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **445 a** in 26% yield (18.1 mg, 52.0 µmol) as a yellow solid.

R_f (Hexanes/EA = 1:1) = 0.39; grey with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 3H), 7.22 – 7.18 (m, 2H), 4.57 (d, *J* = 7.8 Hz, 1H), 4.23 (qd, *J* = 3.5, 1.0 Hz, 1H), 3.62 (s, 3H), 3.35 (s, 3H), 2.88 (dt, *J* = 14.8, 2.4 Hz, 1H), 2.66 (dd, *J* = 5.9, 3.4 Hz, 1H), 2.64 – 2.56 (m, 2H), 2.47 (dd, *J* = 14.7, 3.4 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.10 (dd, *J* = 7.8, 6.6 Hz, 1H).

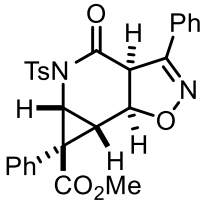
^{13}C-NMR (101 MHz, $CDCl_3$) δ 205.9, 171.9, 171.3, 132.7, 129.8, 129.1, 128.3, 81.5, 64.2, 57.6, 53.0, 43.7, 43.4, 43.0, 39.3, 30.7, 27.2.

IR (neat) (cm^{-1}) ν_{max}: 3030, 2952, 2837, 2363, 2255, 1718, 1498, 1435, 1364, 1342, 1226, 1778, 1126, 1088, 1033, 910, 876, 790, 731, 705, 678.

HRMS (ESI) (m/z): calculated for $C_{19}H_{20}O_6$ $[M+H]^+$ 345.1333, found: 345.1341.

mp: 173.8 °C

methyl 4-oxo-3,6-diphenyl-5-tosyl-3a,5,5a,6,6a,6b-hexahydro-4H-cyclopropa[b]isoxazolo[5,4-d]pyridine-6-carboxylate (470)



A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (40.0 mg, 0.10 mmol, 1.0 equiv) and *N*-hydroxybenzimidoyl chloride (99.0 mg, 0.64 mmol, 6.3 equiv) solved in dry benzene (1.2 mL). Then a solution of NEt_3 (84 µL, 0.60 mmol, 6.0 equiv) in dry benzene (0.3 mL) was added over 20 min. The resulting yellow solution was stirred at 100 °C for 18 h. The reaction was monitored by TLC. Afterwards, the resulting mixture was washed with H_2O (3x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (hexanes/EA, 9:1 to 1:1) gave the title product **470** as a white solid in 56% yield (29.3 mg, 56.0 µmol).

R_f (Hexanes/EA = 1:1) = 0.71.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H), 7.32 – 7.22 (m, 7H), 7.13 – 7.02 (m, 5H), 4.85 (d, *J* = 8.5 Hz, 1H), 4.42 (d, *J* = 9.3 Hz, 1H), 3.52 (s, 3H), 2.84 (d, *J* = 9.3 Hz, 1H), 2.51 (d, *J* = 8.5 Hz, 1H), 2.19 (s, 3H).

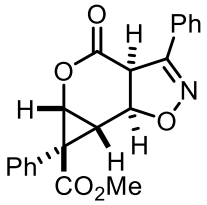
^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.4, 162.6, 157.5, 145.8, 134.8, 131.9, 130.5, 129.8, 129.6, 129.1, 128.9, 128.4, 128.1, 78.9, 53.5, 51.6, 44.7, 35.6, 23.3, 21.8.

IR (neat) (cm^{-1}) ν_{max}: 3064, 2956, 2363, 2259, 1703, 1595, 1498, 1446, 1360, 1256, 1170, 1081, 1014, 958, 910, 812, 760, 731, 708.

HRMS (ESI) (m/z): calculated for $C_{28}H_{24}N_2O_6S$ $[M+H]^+$ 517.1428, found: 517.1434.

mp: 206.6 °C

methyl 4-oxo-3,6-diphenyl-3a,4,5a,6,6a,6b-hexahydrocyclopropa[5,6]pyrano[3,4-d]isoxazole-6-carboxylate (469)



The dipole was prepared beforehand by the dropwise addition of NEt_3 (230 µL, 1.66 mmol, 5.1 equiv) to a solution of *N*-hydroxybenzimidoyl chloride **468** (258.0 mg, 1.66 mmol, 5.1 equiv) in dry benzene (3 mL) at 0 °C. The mixture was stirred for 5 min before being washed with H_2O (2x 2 mL) and dried over $MgSO_4$. The resulting solution of dipole in benzene was kept at 0 °C.

A 10 mL pressure tube was charged with methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (80.0 mg, 0.33 mmol, 1.0 equiv) solved in dry benzene (3.3 mL) and the dipole solution was added. The resulting yellow reaction mixture was stirred at 100 °C for 2 d followed by evaporation of the solvent under reduced pressure. Automation flash column chromatography (hexanes/EA) gave the title product **469** in 18% yield (21.0 mg, 59.4 µmol) as brown crystals.

R_f (Hexanes/EA = 5:1) = 0.16.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.29 – 7.26 (m, 2H), 7.19 – 7.09 (m, 6H), 4.87 (dt, *J* = 9.3, 1.3 Hz, 1H), 4.75 (dd, *J* = 7.6, 1.1 Hz, 1H), 3.49 (s, 3H), 2.67 (dd, *J* = 7.7, 1.5 Hz, 1H), 2.59 (d, *J* = 9.3 Hz, 1H).

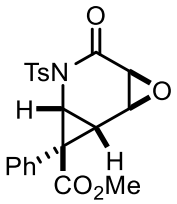
^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.9, 161.2, 156.1, 132.2, 130.8, 129.7, 129.3, 129.1, 128.6, 128.1, 127.9, 78.2, 63.7, 53.4, 48.3, 35.2, 22.4.

IR (neat) (cm^{-1}) ν_{max}: 3064, 2952, 2848, 2359, 2255, 1752, 1722, 1599, 1558, 1498, 1446, 1375, 1331, 1252, 1182, 1141, 1077, 1003, 913, 880, 768, 731, 705.

HRMS (ESI) (m/z) calculated for $C_{21}H_{17}NO_5$ $[M+H]^+$ 364.1179, found: 364.1187.

mp: 193.8 °C

methyl 5-oxo-8-phenyl-6-tosyl-3-oxa-6-azatricyclo[5.1.0.02,4]octane-8-carboxylate (498)



A 100 mL Schlenk flask was charged with methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (1.00 g, 2.52 mmol, 1.0 equiv) solved in dry DMF (25 mL). Then K_2CO_3 (347.7 mg, 2.52 mmol, 1.0 equiv) and ^{t}BuOOH (1.0 mL, 5.54 mmol, 2.2 equiv, 5.5 M in pentane) were added and the resulting reaction mixture was stirred for 30 min. Then TBAF (2.5 mL, 1.0 equiv, 1 M in THF) was added and stirring was continued for another 30 min at rt before the reaction was quenched with sat. aq. NH_4Cl, extracted with Et_2O (4x 20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Remaining DMF was azeotroped with xylene (3x 5 mL) and the epoxide **498** was obtained in 93% yield as a beige solid (963.5 mg, 2.34 mmol) with sufficient purity. A cleaner product was obtained by crystallization from Et_2O which gave a white solid.

R_f (Hexanes/EA = 1:1) = 0.59; yellow with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.39 – 7.31 (m, 7H), 4.43 (dd, *J* = 9.4, 0.7 Hz, 1H), 3.78 (ddd, *J* = 3.8, 2.0, 0.7 Hz, 1H), 3.69 (s, 3H), 3.00 (ddd, *J* = 9.4, 2.0, 1.0 Hz, 1H), 2.74 (dd, *J* = 3.8, 1.0 Hz, 1H), 2.44 (s, 3H).

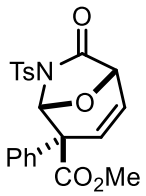
^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.5, 163.6, 145.9, 134.8, 132.7, 129.7, 129.2, 129.1, 129.03, 129.02, 54.9, 53.4, 51.6, 43.3, 38.1, 24.5, 21.9.

IR (neat) (cm^{-1}) ν_{max}: 3064, 2960, 2359, 1715, 1595, 1498, 1435, 1364, 1260, 1207, 1174, 1088, 1054, 1021, 969, 910, 880, 813, 783, 734, 671.

HRMS (ESI) (m/z): calculated for $C_{21}H_{19}NO_6S$ $[M+H]^+$ 414.1006, found: 414.1014.

mp: 120.4 °C

methyl 7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (511)



A 100 mL two necked round bottom Schlenk flask equipped with a reflux condenser was charged with methyl 5-oxo-8-phenyl-6-tosyl-3-oxa-6-azatricyclo[5.1.0.02,4]octane-8-carboxylate (500.0 mg, 1.21 mmol, 1.0 equiv) under N_2 solved in dry MeCN (24 mL). Then TMSOTf (240 µL, 1.33 mmol, 1.1 equiv) was added and the orange reaction mixture was stirred at 65 °C for 30 min before cooling down to rt and quenching with H_2O. The solution was extracted with EA (3x 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The title product **511** was obtained in 85% yield (425.0 mg, 1.03 mmol) as an orange solid with sufficient purity. A clean product was obtained by vapour diffusion (acetone/pentane) which gave colourless crystals.

R_f (Hexanes/EA = 1:1) = 0.74; orange with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.42 – 7.37 (m, 3H), 7.32 – 7.28 (m, 2H), 7.25 – 7.19 (m, 2H), 6.63 (d, *J* = 1.9 Hz, 1H), 6.41 (dd, *J* = 9.8, 4.5 Hz, 1H), 6.34 (dd, *J* = 9.8, 1.9 Hz, 1H), 4.48 (d, *J* = 4.5 Hz, 1H), 3.80 (s, 3H), 2.40 (s, 3H).

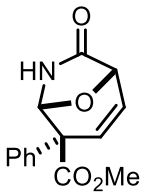
^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.2, 170.8, 145.4, 135.4, 134.1, 130.9, 129.7, 129.2, 129.1, 128.2, 127.5, 125.5, 92.7, 77.5, 73.1, 56.1, 53.2, 21.8.

IR (neat) (cm^{-1}) ν_{max}: 3064, 2956, 2359, 2259, 1767, 1733, 1595, 1495, 1435, 1368, 1327, 1249, 1170, 1088, 1040, 969, 935, 816, 764, 734, 701, 664.

HRMS (ESI) (m/z): calculated for $C_{21}H_{19}NO_6S$ $[M+H]^+$ 414.1006, found: 414.1014.

mp: 188.7 °C

methyl 7-oxo-4-phenyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (555)



A 10 mL flame dried Schlenk tube was charged with naphthalene (55.8 mg, 0.44 mmol, 3.0 equiv) solved in dry THF (2 mL) and Na (10.0 mg, 0.44 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 45 min at rt before the resulting dark green solution was cooled to -70 °C and methyl 7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (60.0 mg, 0.15 mmol, 1.0 equiv) solved in dry THF (0.6 ml) was added. After 3 min the brown mixture was quenched with sat. aq. NH_4Cl and extracted with DCM (4x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **555** as a yellow oil in 45% yield (17.0 mg, 67.5 µmol).

R_f (Hexanes/EA = 1:1) = 0.41.

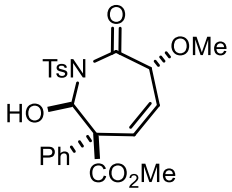
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H), 6.52 (ddd, *J* = 9.9, 4.5, 1.3 Hz, 1H), 6.29 (ddd, *J* = 9.9, 2.2, 0.9 Hz, 1H), 5.97 (d, *J* = 1.1 Hz, 1H), 5.66 (s, 1H), 4.40 (d, *J* = 4.6 Hz, 1H), 3.77 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 175.3, 171.4, 134.6, 129.6, 129.2, 128.8, 128.4, 126.3, 88.2, 71.5, 54.5, 53.1.

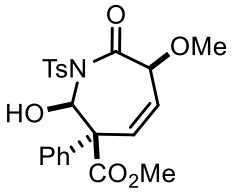
IR (neat) (cm^{-1}) ν_{max}: 3280, 3064, 2926, 2855, 2363, 2251, 1722, 1599, 1435, 1439, 1338, 1245, 1163, 1088, 1036, 965, 910, 816, 734, 701, 667.

HRMS (ESI) (m/z): calculated for $C_{14}H_{13}NO_4$ $[M+H]^+$ 260.0917, found: 260.0922.

methyl 2-hydroxy-6-methoxy-7-oxo-3-phenyl-1-tosyl-2,3,6,7-tetrahydro-1H-azepine-3-carboxylate (520)



major



minor

A 10 mL pressure tube was charged with methyl-7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (41.0 mg, 0.10 mmol, 1.0 equiv) solved in dry MeOH (3.3 mL). Then $BF_3 \cdot Et_2O$ (44 µL, 0.35 mmol, 3.5 equiv) was added and the reaction mixture was stirred at 70 °C for 3 h before being quenched with sat. aq. $NaHCO_3$ and extracted with EA (5x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product (d.r. 1:4.5) was purified by flash column chromatography (hexanes/EA, 2:1 to EA) and gave the major diastereomer **520** as a light yellow solid in 44% yield (19.5 mg, 44.0 µmol).

R_f (Hexanes/EA = 1:1) = 0.67; yellow with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 2H), 7.34 – 7.28 (m, 3H), 7.17 – 7.11 (m, 4H), 7.09 (d, *J* = 10.5 Hz, 1H), 6.22 (dd, *J* = 10.1, 2.2 Hz, 1H), 6.14 (dd, *J* = 10.1, 3.2 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.84 (t, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.37 (s, 3H).

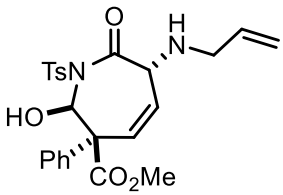
^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.2, 169.7, 142.9, 138.7, 137.2, 130.3, 129.3, 128.9, 128.2, 127.2, 127.1, 125.2, 83.7, 74.1, 54.4, 52.9, 52.6, 21.6.

IR (neat) (cm^{-1}) ν_{max}: 3332, 3064, 3030, 2956, 2363, 2259, 1726, 1599, 1495, 1435, 1342, 1293, 1252, 1219, 1140, 1077, 998, 965, 910, 850, 794, 671.

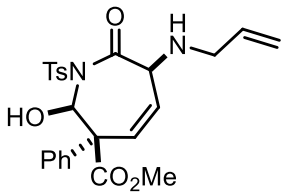
HRMS (ESI) (m/z): calculated for $C_{22}H_{23}NO_7S$ $[M+H]^+$ 446.1273, found: 496.1268.

mp: 55 °C

methyl 6-(allylamino)-2-hydroxy-7-oxo-3-phenyl-1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (521 h)



major



minor

A 10 mL pressure tube was charged with methyl-7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (41.0 mg, 0.10 mmol, 1.0 equiv) solved in dry MeCN (3.3 mL). Then $BF_3 \cdot Et_2O$ (44 µL, 0.35 mmol, 3.5 equiv) and allylamine (37 µL, 0.50 mmol, 5.0 equiv) were added and the reaction mixture was stirred at 85 °C for 1 h before being quenched with sat. aq. $NaHCO_3$ and extracted with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **521 h** as a yellow oil in 29% yield (13.6 mg, 29.0 µmol) and a d.r. of 1:7.5.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.47.

^{1}H-NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 7.91 – 7.70 (m, 1H), 7.60 – 7.29 (m, 2H), 7.24 – 7.09 (m, 5H), 6.99 – 6.87 (m, 3H), 6.55 – 6.39 (m, 1H), 6.15 – 6.00 (m, 1H), 5.94 – 5.72 (m, 1H), 5.26 – 5.01 (m, 2H), 4.96 – 4.72 (m, 1H), 4.63 – 4.54 (m, 1H), 4.07 – 3.92 (m, 1H), 3.91 – 3.79 (m, 1H), 3.79 – 3.71 (m, 3H), 2.42 – 2.31 (m, 3H).

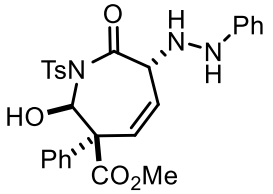
^{13}C-NMR (101 MHz, $CDCl_3$, minor diastereomer not seen) δ 171.9, 168.7, 143.3, 137.1, 136.3, 133.9, 129.5, 128.9, 128.0, 127.9, 127.0, 126.9, 126.7, 116.6, 84.1, 75.7, 53.9, 53.0, 41.9, 21.6.

IR (neat) (cm^{-1}) ν_{max}: 3358, 3064, 2956, 2926, 2359, 2251, 2132, 1733, 1670, 1599, 1528, 1435, 1342, 1256, 1167, 1092, 999, 965, 928, 854, 813, 734, 701, 667.

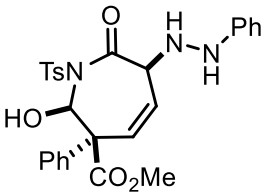
HRMS (ESI) (m/z): **major diastereomer** (acquisition time 2.737 – 2.812 min): calculated for $C_{24}H_{26}N_2O_6S$ $[M+H]^+$ 471.1584, found: 471.1589; **minor diastereomer**

(acquisition time 2.621 – 2.692 min): calculated for $C_{24}H_{26}N_2O_6S$ $[M+H]^+$ 471.1584, found: 471.1583.

methyl 2-hydroxy-7-oxo-3-phenyl-6-(2-phenylhydrazineyl)-1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (521 i)



major



minor

A 10 mL pressure tube was charged with methyl-7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (41.0 mg, 0.10 mmol, 1.0 equiv) solved in dry MeCN (3.3 mL). Then $BF_3 \cdot Et_2O$ (44 µL, 0.35 mmol, 3.5 equiv) and phenylhydrazine (49 µL, 0.50 mmol, 5.0 equiv) were added and the reaction mixture was stirred at 85 °C for 3.5 h before being quenched with sat. aq. $NaHCO_3$ and extracted with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **521 i** as a brown oil in 48% yield (24.6 mg, 48.0 µmol) and a d.r. of 1:5.1.

In the proton and carbon NMR the signals of both diastereomers are overlapping.

R_f (Hexanes/EA = 1:1) = 0.45; orange with vanillin.

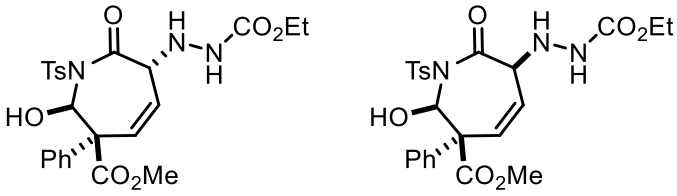
^{1}H-NMR (400 MHz, $CDCl_3$, signal splitting due to diastereomers) δ 9.60 – 9.43 (m, 1H), 7.82 – 7.29 (m, 4H), 7.24 – 7.12 (m, 6H), 7.08 – 6.60 (m, 6H), 6.50 – 6.40 (m, 1H), 6.22 – 6.06 (m, 1H), 5.10 – 4.87 (m, 1H), 4.81 – 4.72 (m, 1H), 3.86 – 3.67 (m, 3H), 2.45 – 2.29 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, minor diastereomer not seen) δ 171.7, 168.4, 147.9, 143.5, 137.1, 136.1, 129.6, 129.2, 129.0, 128.6, 128.1, 126.8, 126.7, 126.3, 121.5, 114.3, 113.7, 84.3, 75.2, 53.9, 53.1, 21.6.

IR (neat) (cm^{-1}) ν_{max}: 3321, 3060, 2952, 2926, 2251, 1722, 1685, 1602, 1495, 1435, 1334, 1252, 1152, 1074, 999, 962, 910, 854, 813, 731, 697, 664.

HRMS (ESI) (m/z): **major diastereomer** (acquisition time 2.806 – 2.910 min) calculated for $C_{27}H_{27}N_3O_6S$ $[M+H]^+$ 522.1693, found: 522.1699; **minor diastereomer** (acquisition time 2.757 – 2.806 min): calculated for $C_{27}H_{27}N_3O_6S$ $[M+H]^+$ 522.1693, found: 522.1701.

methyl 6-(2-(ethoxycarbonyl)hydrazineyl)-2-hydroxy-7-oxo-3-phenyl-1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (521 j)



A 10 mL pressure tube was charged with methyl-7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (41.0 mg, 0.10 mmol, 1.0 equiv) solved in dry MeCN (3.3 mL). Then $BF_3{\cdot}Et_2O$ (44 µL, 0.35 mmol, 3.5 equiv) and ethyl hydrazinecarboxylate (51.6 mg, 0.50 mmol, 5.0 equiv) were added and the reaction mixture was stirred at 85 °C for 3.5 h before being quenched with sat. aq. $NaHCO_3$ and extracted with EA (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **521 j** as a brown oil in 47% yield (24.3 mg, 47.0 µmol) and a d.r. of 1:7.7.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic sigals of the minor diastereomer are marked.

R_f (Hexanes/EA = 1:1) = 0.26; orange with vanillin.

^{1}H-NMR (400 MHz, $CDCl_3$, **major**) δ 9.53 (d, *J* = 2.2 Hz, 1H), 7.44 – 7.26 (m, 2H), 7.25 – 7.06 (m, 5H), 6.94 – 6.90 (m, 3H), 6.44 (dd, *J* = 10.2, 3.4 Hz, 1H), 6.39 (s, 1H), 6.11 (dd, *J* = 10.1, 2.7 Hz, 1H), 5.07 (t, *J* = 3.0 Hz, 1H), 4.71 (d, *J* = 10.7 Hz, 1H), 4.27 – 4.16 (m, 2H), 3.78 (s, 3H), 2.32 (s, 3H), 1.31 – 1.24 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, **major**) δ 171.8, 156.1, 143.3, 136.8, 135.9, 129.5, 128.9, 127.9, 126.9, 126.8, 125.9, 84.1, 75.3, 62.3, 53.8, 53.1, 32.7, 31.9, 21.6, 14.6.

^{1}H NMR (400 MHz, $CDCl_3$, **mixed fraction**) δ 9.53 (d, *J* = 2.3 Hz, 0.7H), 7.65 (s, 0.3H)^{minor}, 7.57 – 7.47 (m, 1H), 7.39 – 7.27 (m, 2H), 7.25 – 7.04 (m, 5H), 7.04 – 6.82 (m, 3H), 6.48 – 6.08 (m, 3H), 5.10 – 4.94 (m, 1H), 4.94 – 4.89 (m, 0.4H)^{minor}, 4.76 – 4.56 (m, 1H), 4.28 – 4.14 (m, 2H), 3.80 – 3.71 (m, 3H), 2.41 – 2.30 (m, 3H), 1.31 – 1.25 (m, 3H).

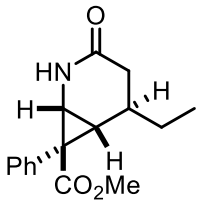
^{13}C-NMR of mixed fraction same as major, signals of minor diastereomer are not seen.

IR*$_{major}$* (neat) (cm^{-1}) ν_{max}: 3332, 3064, 2982, 2930, 2359, 2255, 1722, 1599, 1498, 1435, 1338, 1256, 1148, 1074, 999, 962, 917, 798, 764, 734, 663.

IR*$_{mix}$* (neat) (cm^{-1}) ν_{max}: 3340, 3064, 2982, 2960, 2926, 2363, 2251, 1730, 1599, 1498, 1435, 1338, 1252, 1152, 1074, 999, 962, 917, 798, 764, 734, 664.

HRMS (ESI) (m/z): **major diastereomer** (acquisition time 2.554 – 2.633 min): calculated for $C_{24}H_{27}N_3O_8S$ $[M+H]^+$ 518.1592, found: 518.1598; **minor diastereomer** (acquisition time 2.430 – 2.508 min): calculated for $C_{24}H_{27}N_3O_8S$ $[M+H]^+$ 518.1592, found: 518.1594.

methyl 5-ethyl-3-oxo-7-phenyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (568)



A 10 mL flame dried Schlenk tube was charged with naphthalene (37.8 mg, 0.30 mmol, 3.0 equiv) solved in dry THF (1.4 mL) and Na (6.8 mg, 0.30 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 45 min at rt before the resulting dark green solution was cooled to -78 °C and methyl 5-ethyl-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (42.0 mg, 0.10 mmol, 1.0 equiv) solved in dry THF (0.5 ml) was added. After 20 min the brown mixture was quenched with sat. aq. NH_4Cl and extracted with DCM (4x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Automation flash column chromatography (hexanes/EA) gave the title product **568** as a colourless oil in 45% yield (12.1 mg, 45.0 µmol).

R*$_f$* (Hexanes/EA = 1:1) = 0.18.

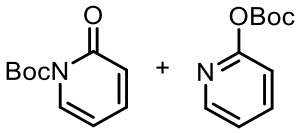
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3H), 7.18 – 7.11 (m, 2H), 6.97 (s, 1H), 3.58 (s, 3H), 3.52 (dd, *J* = 9.0, 1.7 Hz, 1H), 2.15 (dd, *J* = 9.0, 5.1 Hz, 1H), 2.04 (dd, *J* = 15.8, 10.8 Hz, 1H), 1.91 (dd, *J* = 15.8, 4.0 Hz, 1H), 1.69 – 1.52 (m, 3H), 1.05 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 174.2, 172.9, 132.7, 131.5, 128.9, 127.9, 52.9, 40.3, 39.6, 36.0, 32.3, 30.2, 29.3, 11.5.

IR (neat) (cm^{-1}) ν_{max}: 3220, 3030, 2960, 2926, 2855, 2363, 2251, 2125, 1715, 1666, 1435, 1379, 1334, 1241, 1189, 1088, 973, 913, 883, 813, 787, 731, 705.

HRMS (ESI) (m/z): calculated for $C_{16}H_{19}NO_3$ $[M+H]^+$ 274.1438, found: 274.1442.

***tert*-butyl 2-oxopyridine-1(2*H*)-carboxylate (572)** and ***tert*-butyl pyridin-2-yl carbonate (573)**



A 25 mL Schlenk flask was charged with pyridin-2(1*H*)-one (300.0 mg, 3.15 mmol, 1.0 equiv) suspended in dry THF (2.4 mL) and cooled to 0 °C. Then ^{n}BuLi (2.3 mL, 3.60 mmol, 1.14 equiv, 1.6 M in hexane) was added dropwise and the resulting solution was stirred for another 20 min at 0 °C. After that a solution of Boc_2O (757.3 mg, 3.47 mmol, 1.1 equiv) in dry THF (1.5 mL) was added dropwise followed by stirring for 1 h at 0 °C. Then a mixture of THF (2 mL) and H_2O (0.5 mL) was added dropwise followed by extraction with EA (3x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography (hexanes/EA + 1% NEt_3 3:1 to 1:1) gave the product **572** in 21% yield (130.0 mg, 0.66 mmol) and the byproduct **573** in 42% yield (261.2 mg, 1.32 mmol). Analytical data for byproduct **x** are according to literature.[184]

R_f (Hexanes/EA = 1:1) = 0.44.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (ddd, *J* = 7.4, 2.1, 0.9 Hz, 1H), 7.21 (ddt, *J* = 9.3, 6.3, 1.6 Hz, 1H), 6.46 (dd, *J* = 9.4, 1.2 Hz, 1H), 6.07 (ddd, *J* = 7.5, 6.4, 1.3 Hz, 1H), 1.57 (s, 9H).

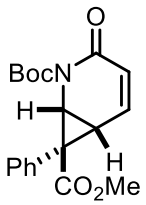
^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.9, 150.8, 139.9, 133.3, 123.6, 105.7, 86.2, 27.8.

IR (neat) (cm^{-1}) ν_{max}: 2982, 2937, 2356, 2132, 2002, 1782, 1752, 1674, 1603, 1536, 1461, 1394, 1252, 1133, 1092, 1039, 1006, 924, 883, 842, 757.

HRMS (ESI) (m/z): calculated for $C_{10}H_{13}NO_3$ $[M+H]^+$ 196.0968, found: 196.0978.

mp: 190.1 °C

2-(*tert*-butyl) 7-methyl 3-oxo-7-phenyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (575)



A 50 mL flame dried Schlenk flask was charged with *tert*-butyl 2-oxopyridine-1(2*H*)-carboxylate (550.0 mg, 2.82 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (12.5 mg, 1 mol%) solved in dry toluene (5.6 mL). A solution of methyl 2-diazo-2-phenylacetate (1.49 g, 8.45 mmol, 3.0 equiv) in dry toluene (7.7 mL) was added via syringe pump over 1.5 h at rt. Then the solvent was removed under reduced pressure. Purification by automation flash column chromatography (hexanes/EA) gave the title product **575** as a light yellow solid in 52% yield (500.0 mg, 1.47 mmol).

R_f (Hexanes/EA = 1:1) = 0.53.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 3H), 7.12 – 7.03 (m, 2H), 6.76 (ddd, *J* = 9.8, 5.2, 0.8 Hz, 1H), 5.62 (d, *J* = 9.8 Hz, 1H), 4.41 (dd, *J* = 8.8, 0.8 Hz, 1H), 3.66 (s, 3H), 2.93 (dd, *J* = 8.9, 5.2 Hz, 1H), 1.60 (s, 9H).

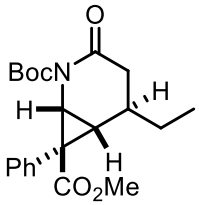
^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.7, 160.2, 152.3, 137.9, 133.3, 129.2, 128.6, 128.3, 127.2, 84.2, 53.3, 46.2, 35.5, 28.1, 26.5.

IR (neat) (cm^{-1}) ν_{max}: 3056, 2982, 2359, 1774, 1718, 1607, 1498, 1435, 1372, 1305, 1252, 1156, 1074, 1033, 965, 850, 824, 746, 705.

HRMS (ESI) (m/z): calculated for $C_{19}H_{21}NO_5$ $[M+H]^+$ 344.1492, found: 344.1494.

mp: 126.4 °C

2-(*tert*-butyl) 7-methyl 5-ethyl-3-oxo-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (576)



A 20 mL Schlenk tube was charged with $Cu(OTf)_2$ (9.1 mg, 3 mol%) solved in dry toluene (4.2 mL) and cooled to -78 °C. Then a solution of 2-(*tert*-butyl) 7-methyl 3-oxo-7-phenyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (289.0 mg, 0.84 mmol, 1.0 equiv) in dry DCM (2 mL) followed by $AlEt_3$ (910 µL, 1.82 mmol, 2.0 equiv, 25 w% in toluene) were slowly added and the reaction mixture stirred for 2 h at -78 °C. Then the reaction was gradually warmed to 0 °C and after 3 h the reaction mixture was quenched with sat. aq. NH_4Cl, extracted with Et_2O (4x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was filtrated over Celite and washed with $CHCl_3$. Automation flash column chromatography (hexanes/EA) gave the title product **576** as a yellow solid in 14% yield (44.8 mg, 0.12 mmol).

R_f (Hexanes/EA = 1:1) = 0.66.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 3H), 7.23 – 7.16 (m, 2H), 3.87 (d, *J* = 9.3 Hz, 1H), 3.61 (s, 3H), 2.30 – 2.15 (m, 3H), 1.81 – 1.61 (m, 3H), 1.60 (s, 9H), 1.02 (t, *J* = 7.2 Hz, 3H).

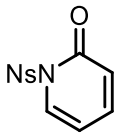
^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.9, 171.4, 152.7, 132.0, 131.6, 128.9, 128.1, 83.8, 52.9, 44.1, 39.8, 38.9, 31.5, 30.7, 28.8, 28.1, 11.4.

IR (neat) (cm^{-1}) ν_{max}: 2967, 2930, 2359, 2255, 1778, 1715, 1498, 1461, 1368, 1305, 1241, 1193, 1152, 1081, 1055, 978, 913, 850, 783, 731.

HRMS (ESI) (m/z): calculated for $C_{21}H_{27}NO_5$ $[M+H]^+$ 374.1962, found: 374.1969.

mp: 97.5 °C

1-((4-nitrophenyl)sulfonyl)pyridin-2(1*H*)-one (577)



A 100 mL Schlenk flask was charged with pyridin-2(1*H*)-one (1.00 g, 10.52 mmol, 1.0 equiv) suspended in dry THF (25 mL) and cooled to 0 °C. Then ^{n}BuLi (7.5 mL, 12.00 mmol, 1.14 equiv, 1.6 M in hexane) was added dropwise and the resulting solution was stirred for another 20 min at 0 °C. Afterwards, a solution of NsCl (2.59 g, 11.67 mmol, 1.1 equiv) in dry THF (25 mL) was added dropwise followed by stirring for 1 h at 0 °C. After that a mixture of THF (12 mL) and H_2O (3 mL) was added dropwise and THF was evaporated under reduced pressure. The residue was washed with EA (100 mL) and the washing was washed with H_2O. The aq. layer was extracted with EA (2x 50 mL) and the combined org. layers washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The title product **577** was obtained as a beige solid in 81% yield (2.4 g, 8.52 mmol).

R_f (Hexanes/EA = 1:1) = 0.30.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.51 – 8.43 (m, 1H), 8.17 – 8.00 (m, 3H), 7.91 (ddd, *J* = 7.5, 1.9, 0.8 Hz, 1H), 7.63 (ddd, *J* = 9.3, 6.5, 1.9 Hz, 1H), 6.53 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 6.47 (dt, *J* = 9.4, 1.0 Hz, 1H).

^{13}C-NMR (101 MHz, DMSO-d_6) δ 159.7, 148.0, 143.8, 137.6, 135.6, 133.4, 132.5, 129.0, 125.9, 122.3, 107.5.

IR (neat) (cm^{-1}) ν_{max}: 3109, 3027, 2359, 1677, 1610, 1539, 1443, 1368, 1256, 1185, 1126, 1059, 1021, 910, 854, 824, 742, 701.

HRMS (ESI) (m/z): calculated for $C_{11}H_8N_2O_5S$ $[M+H]^+$ 281.0227, found: 281.0228.

mp: 184.0 °C

F Appendix

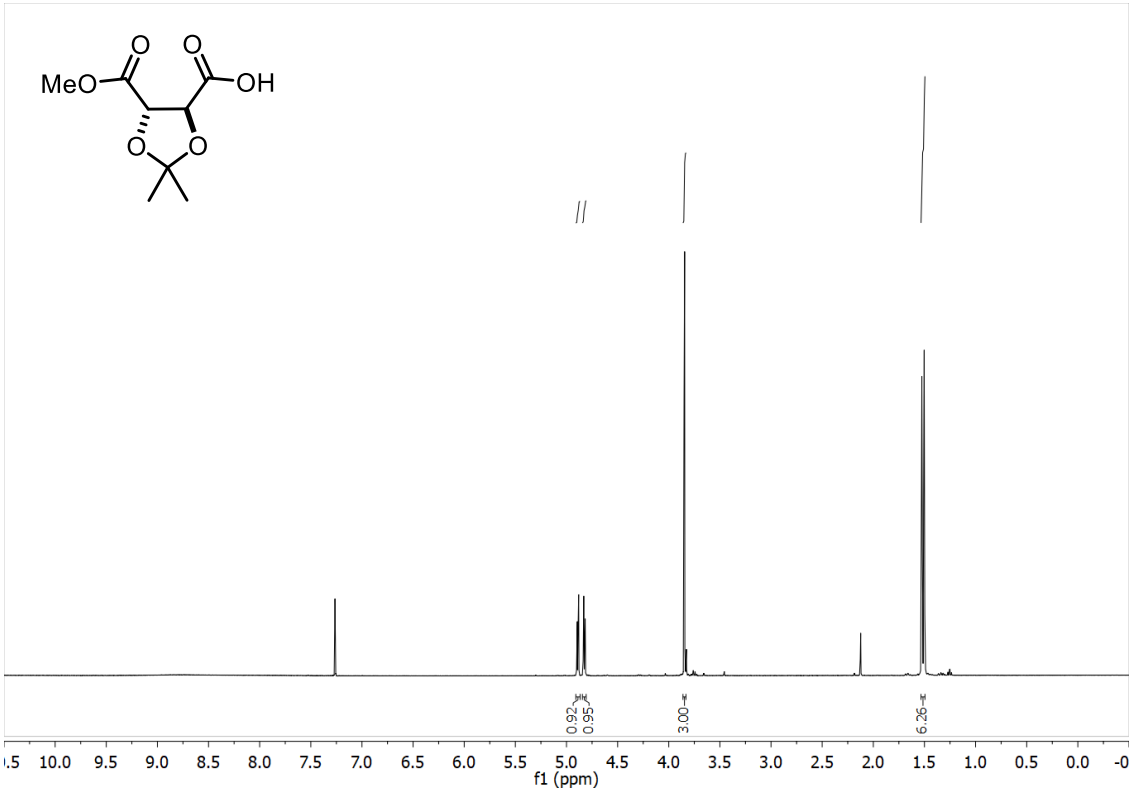
1. NMR Spectra

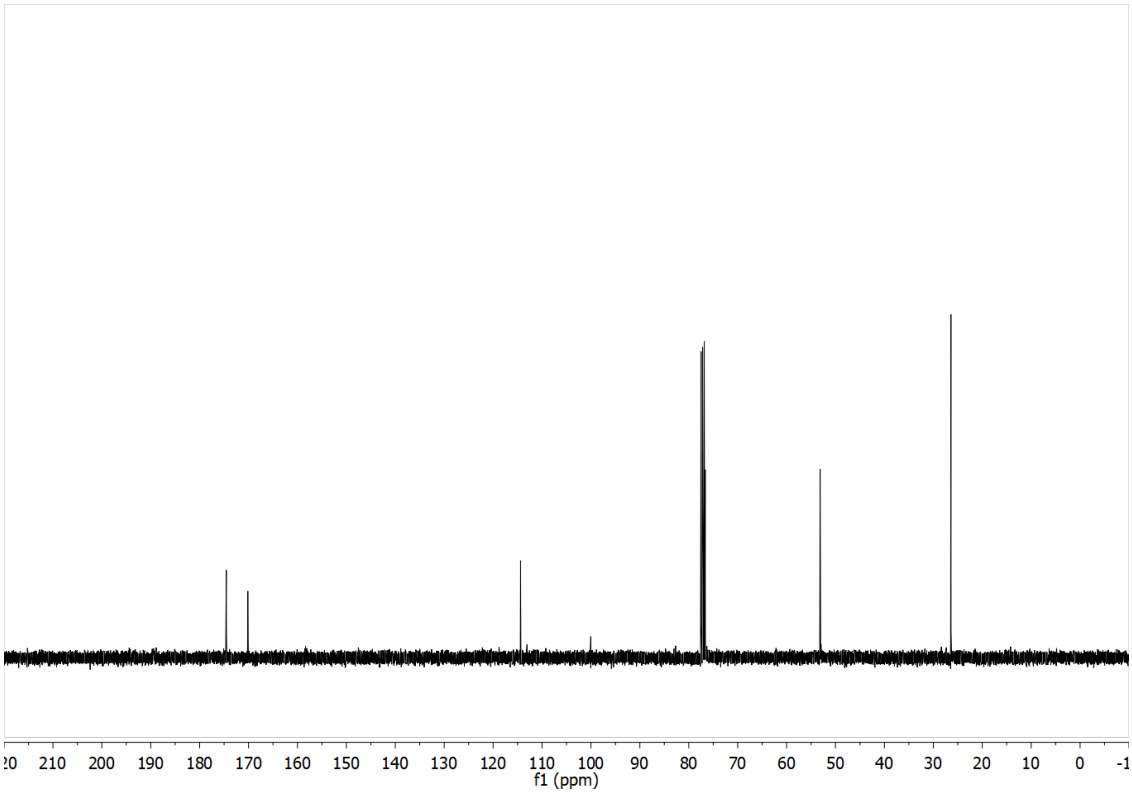
^{1}H-NMR spectra upper image

^{13}C-NMR spectra lower image

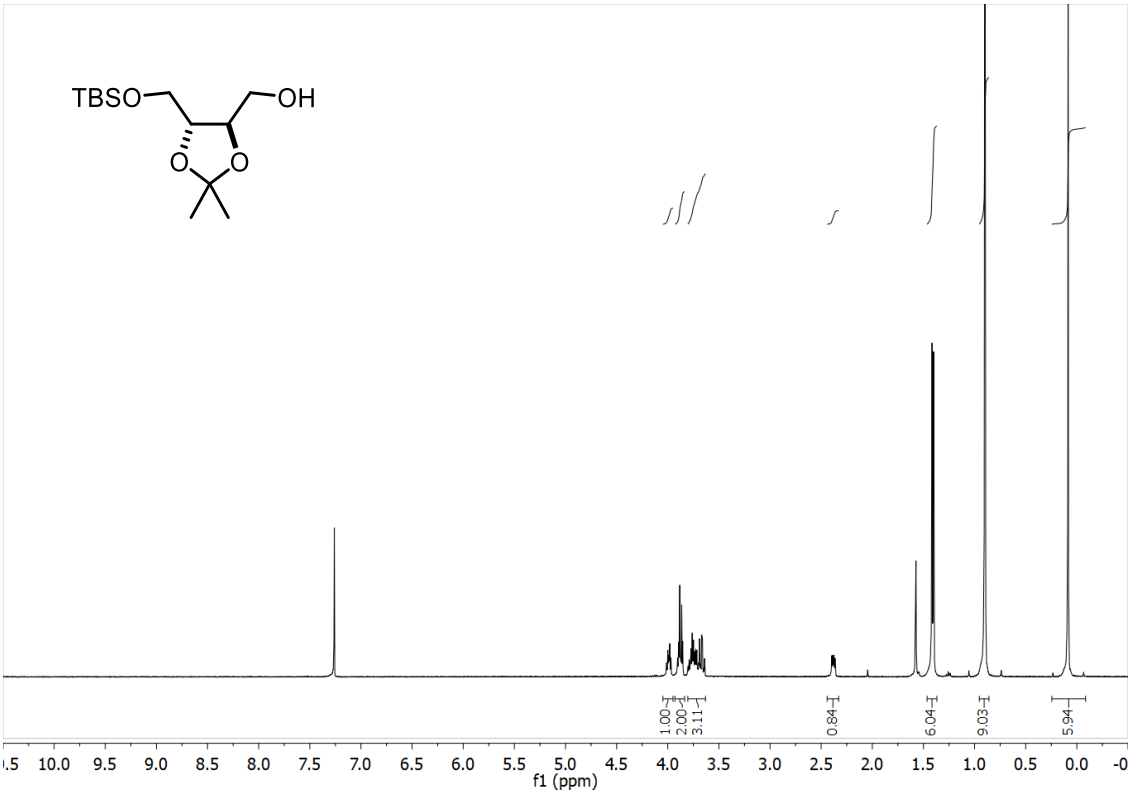
Solvent and frequency are given in the experimental part.

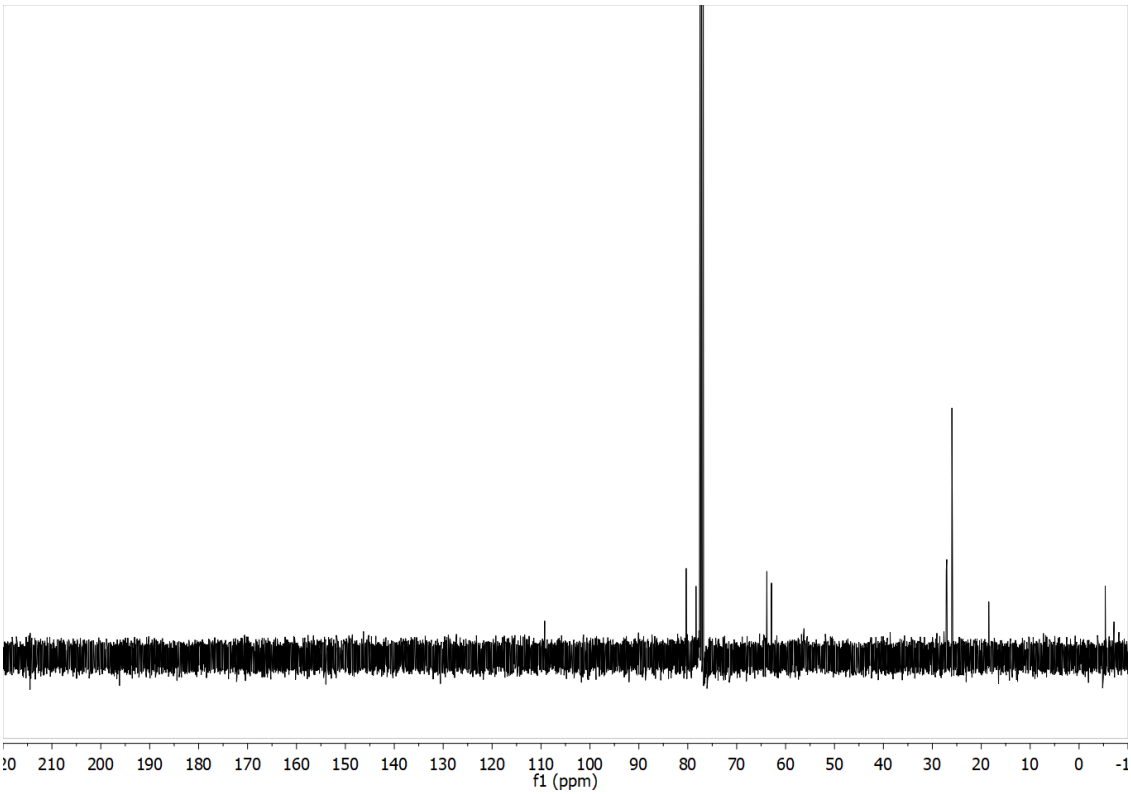
(4*S*,5*S*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (90)



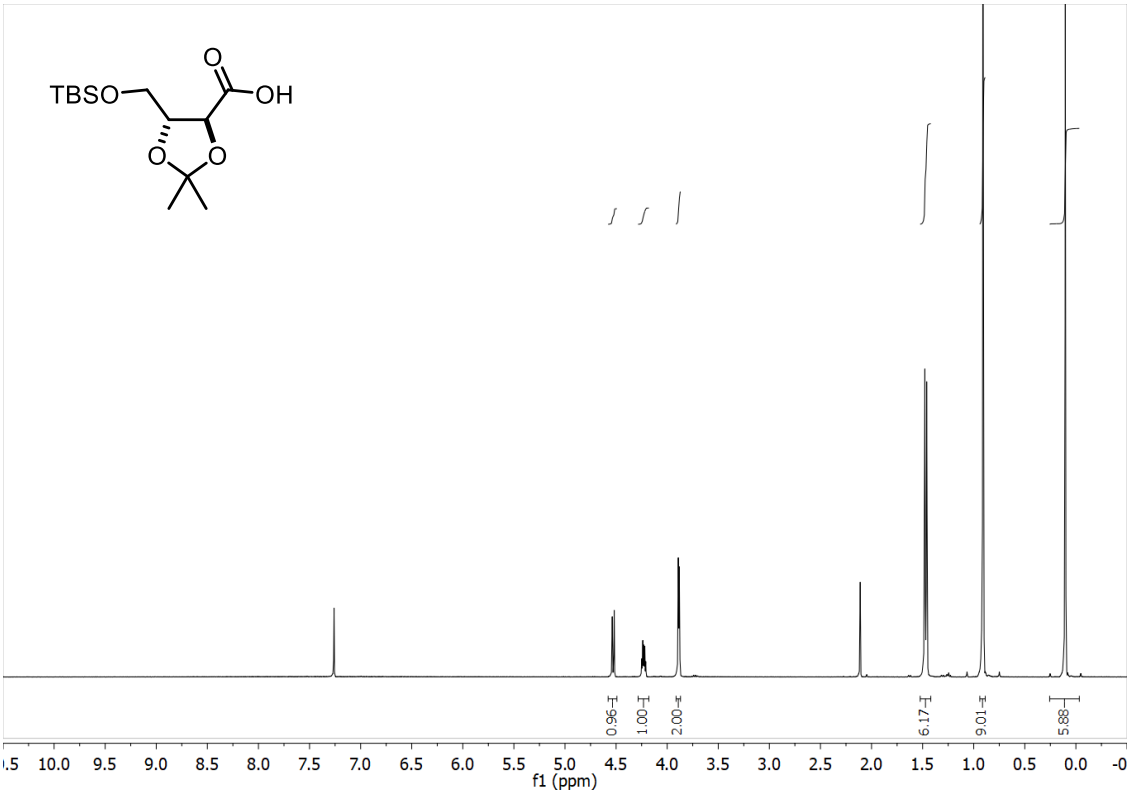


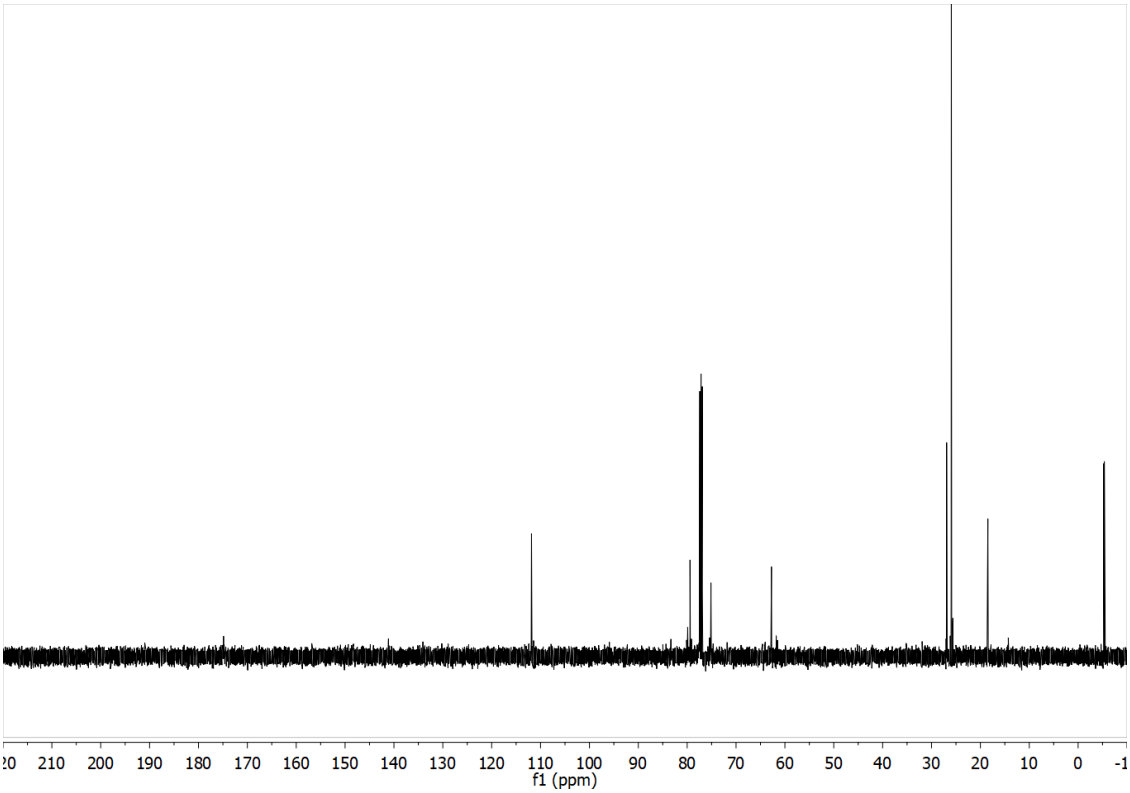
((4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (127)



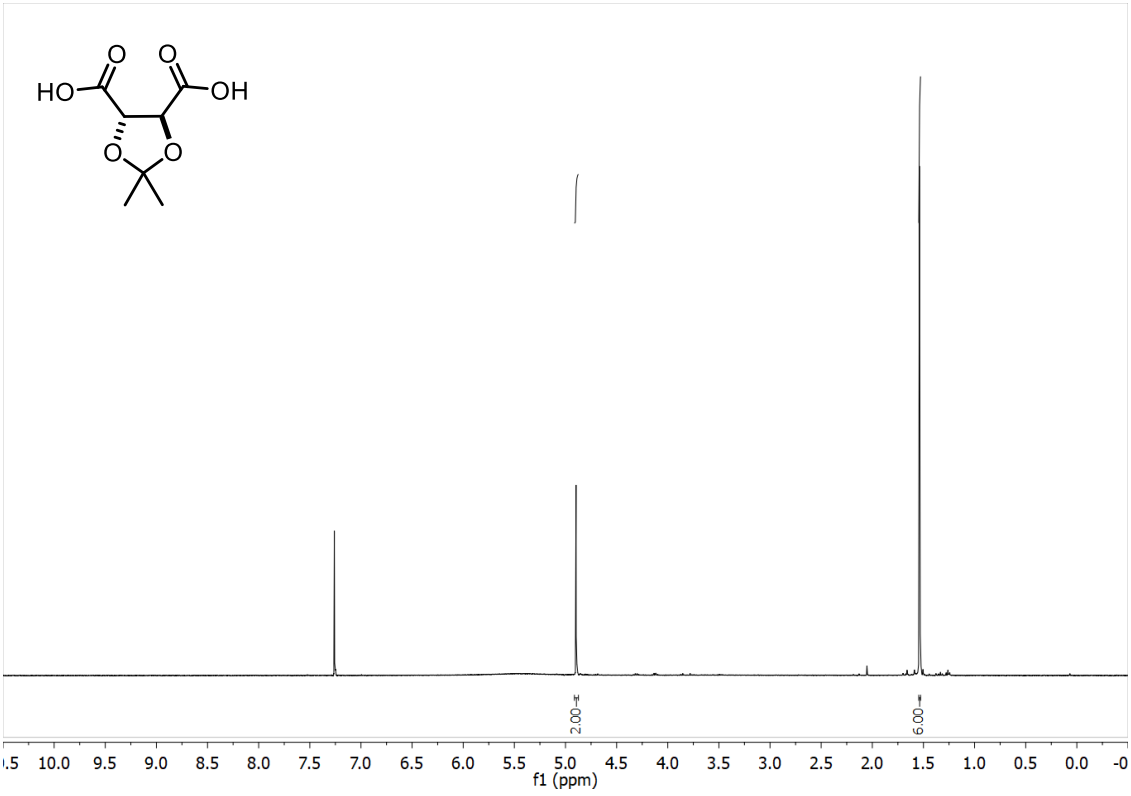


(4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (128)

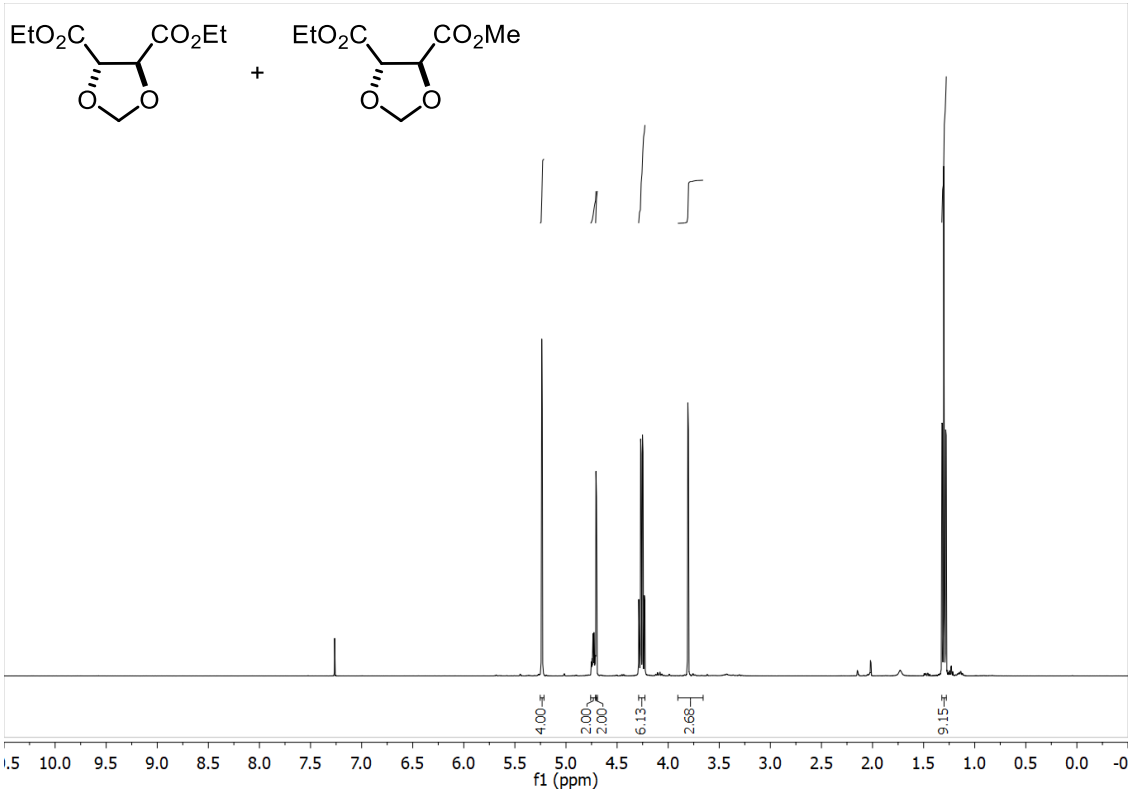


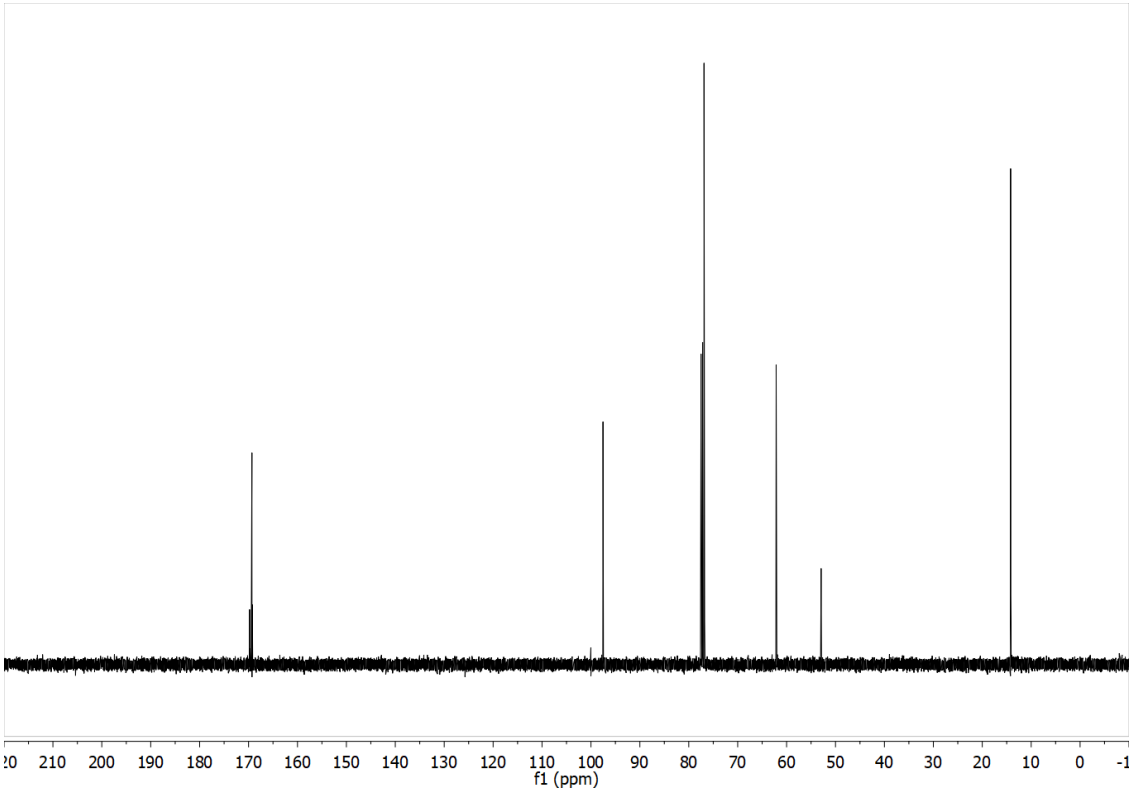


(4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid (141)

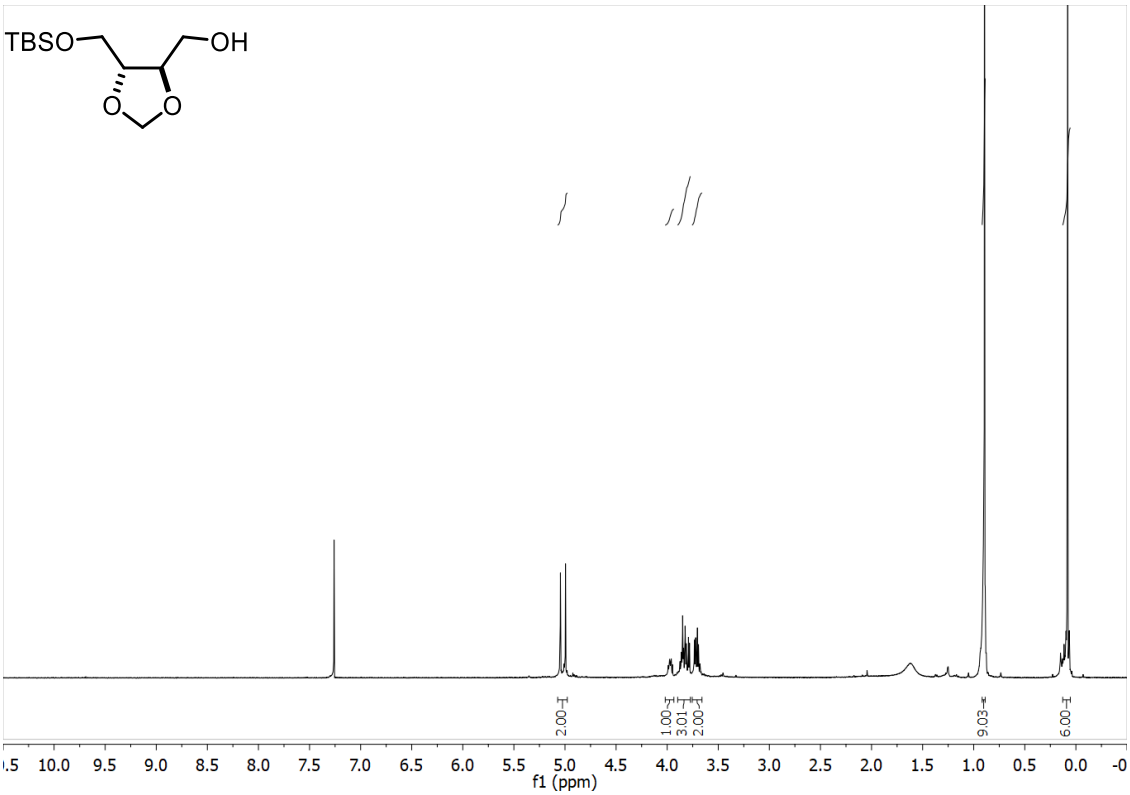


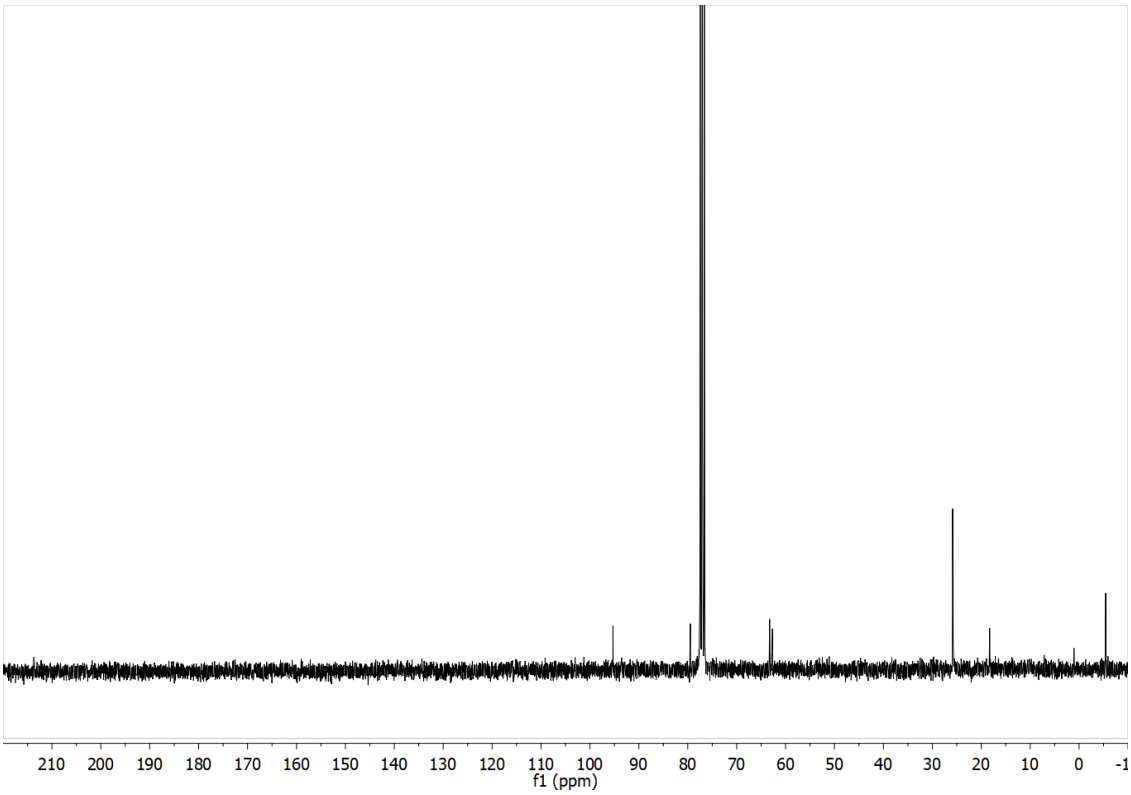
diethyl (4*S*,5*S*)-1,3-dioxolane-4,5-dicarboxylate (132 a) and **4-ethyl 5-methyl (4*S*,5*S*)-1,3-dioxolane-4,5-dicarboxylate (132 b)**



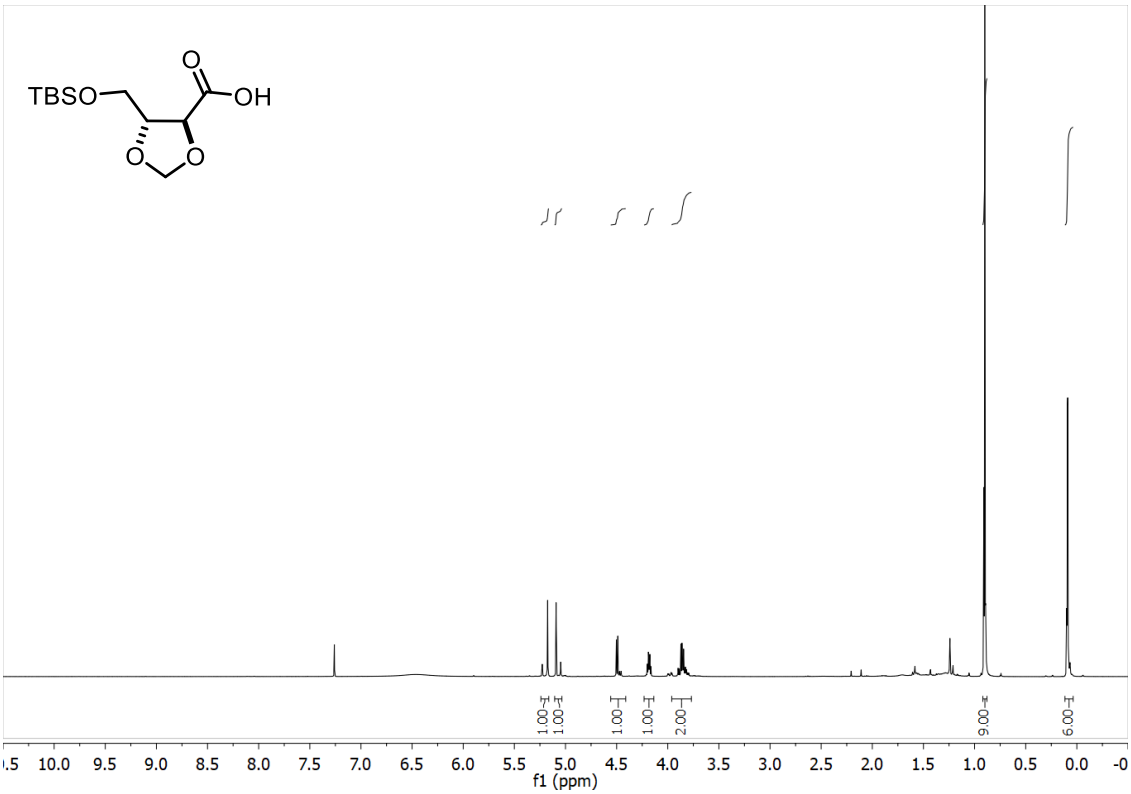


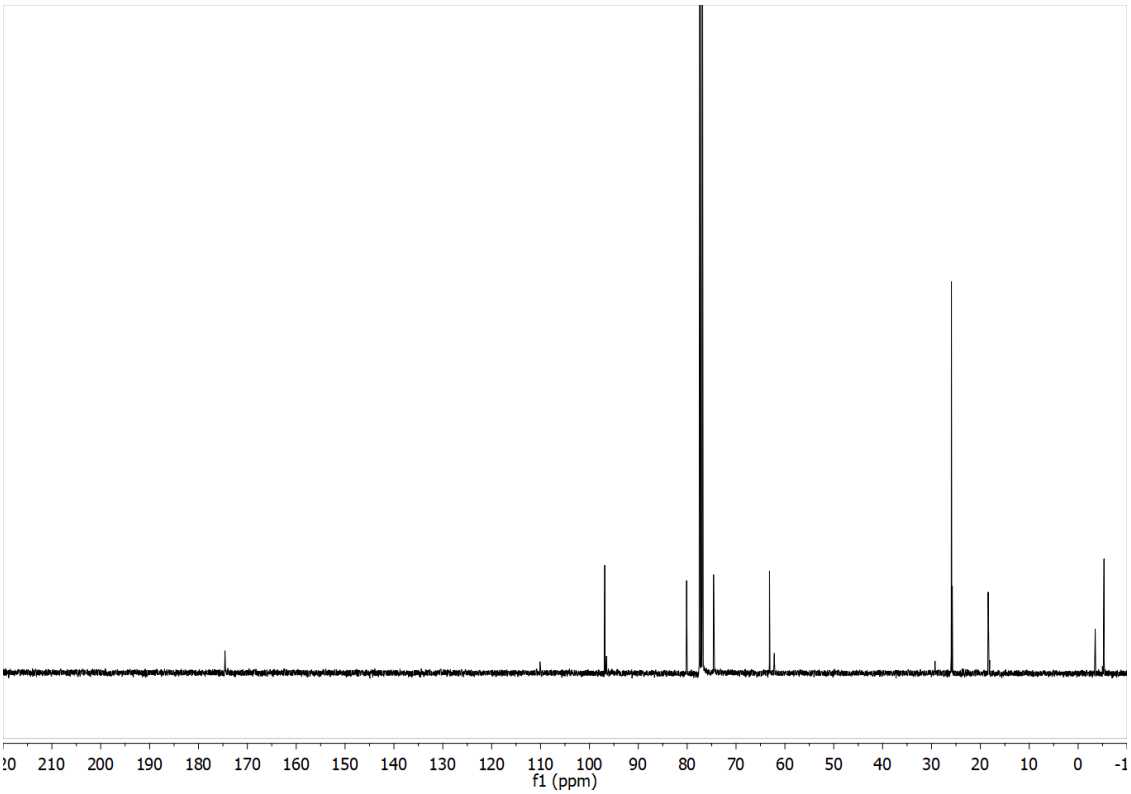
((4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)methanol (134)



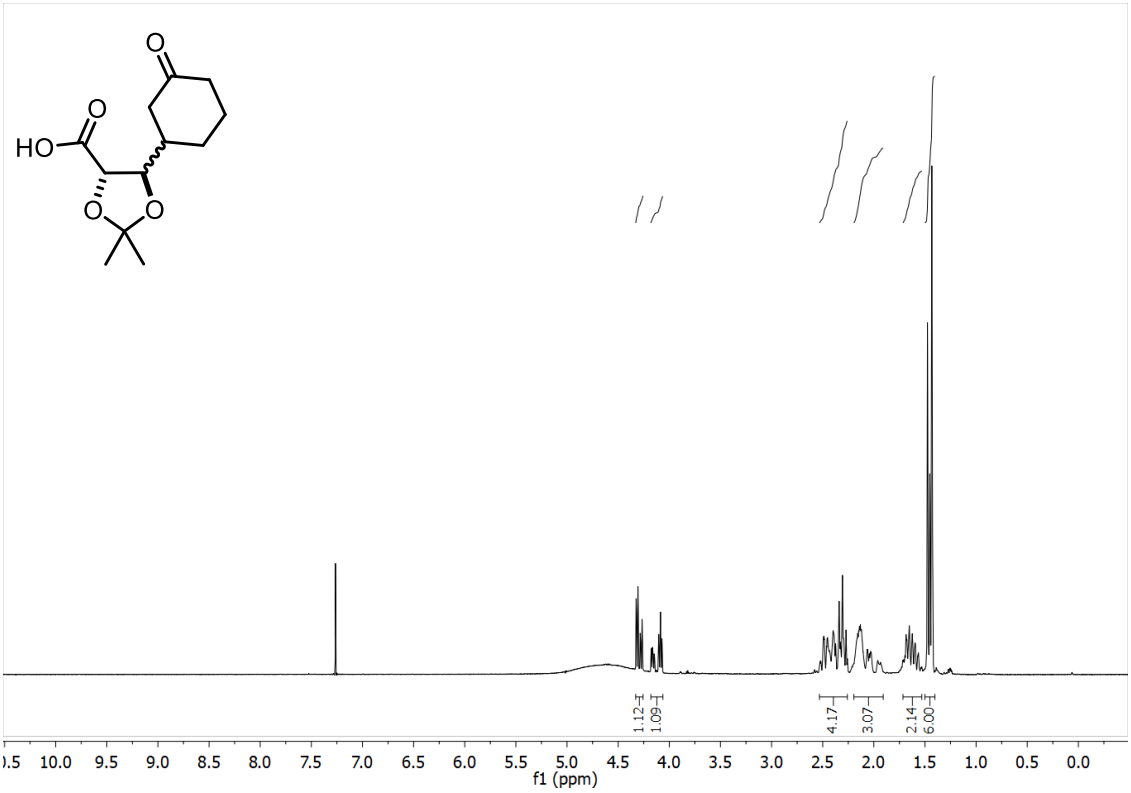


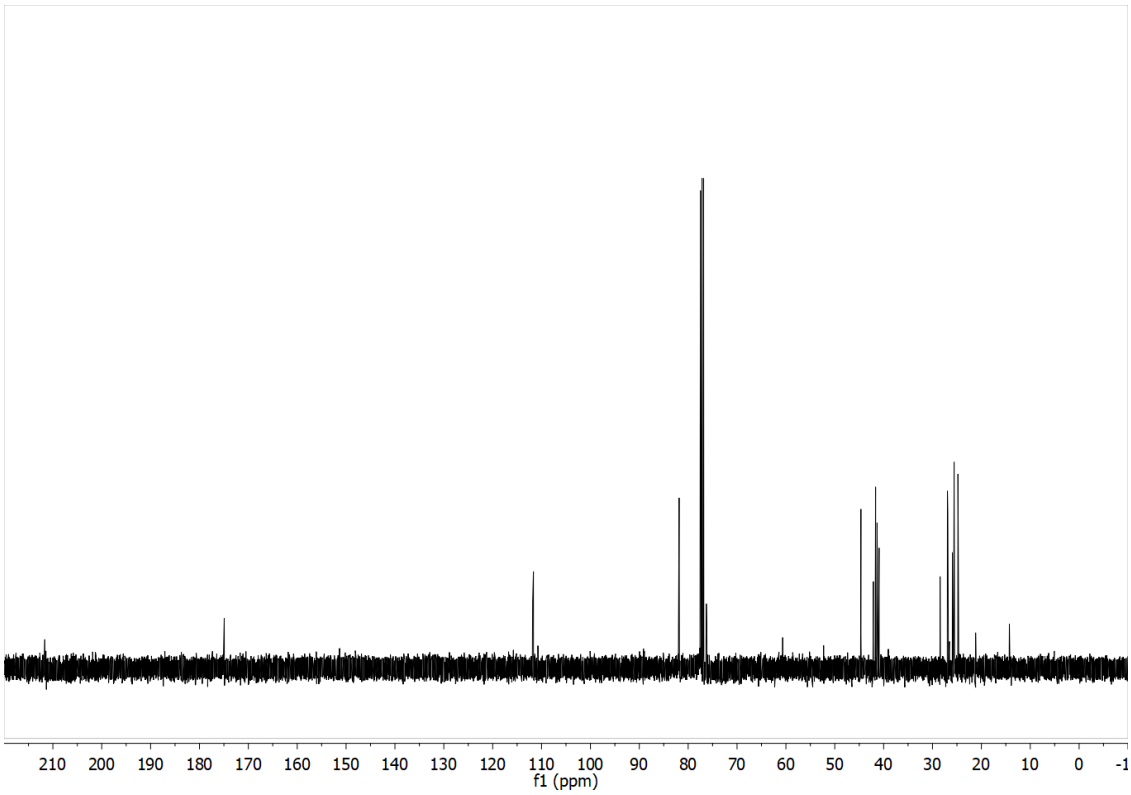
(4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dioxolane-4-carboxylic acid (135)



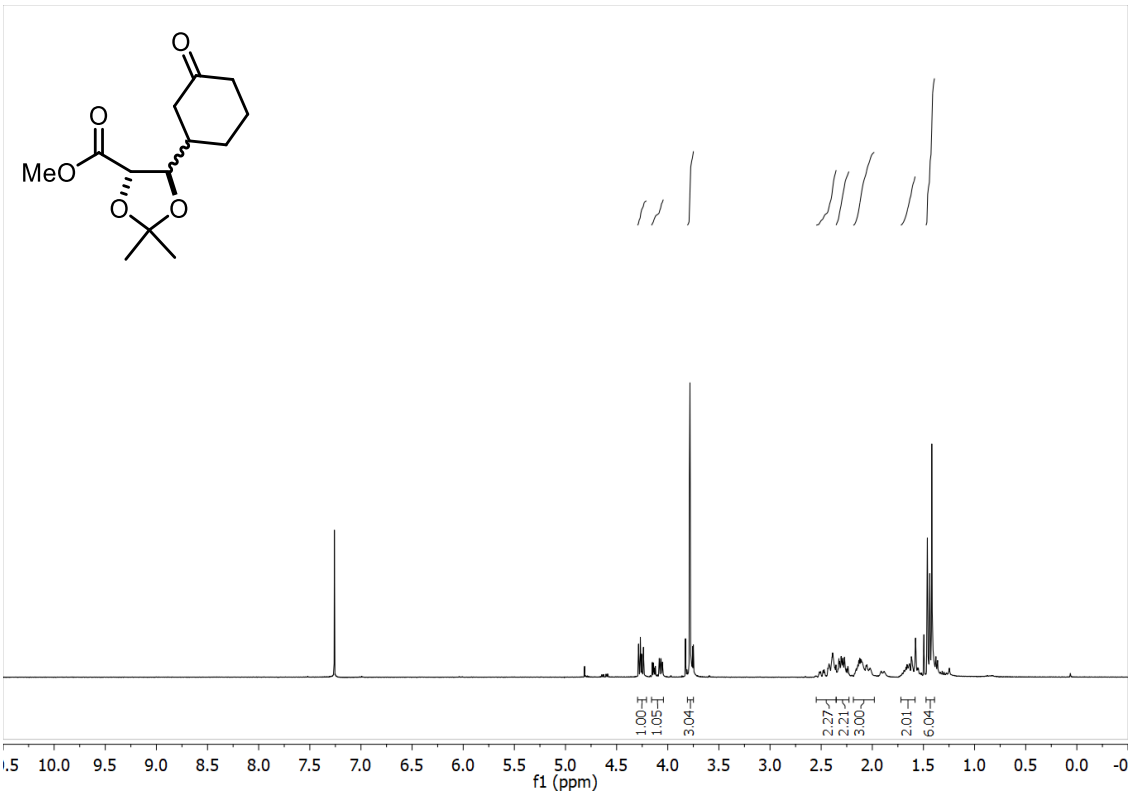


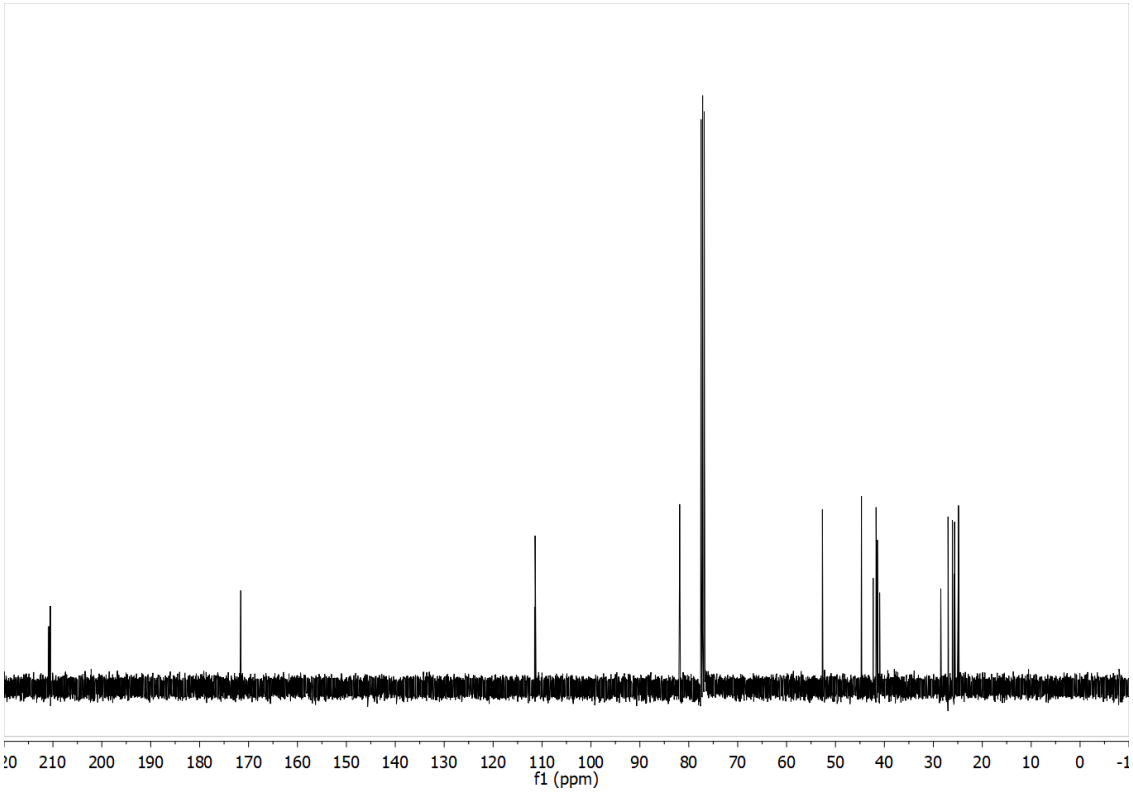
(*S*)-2,2-dimethyl-5-(3-oxocyclohexyl)-1,3-dioxolane-4-carboxylic acid (139)



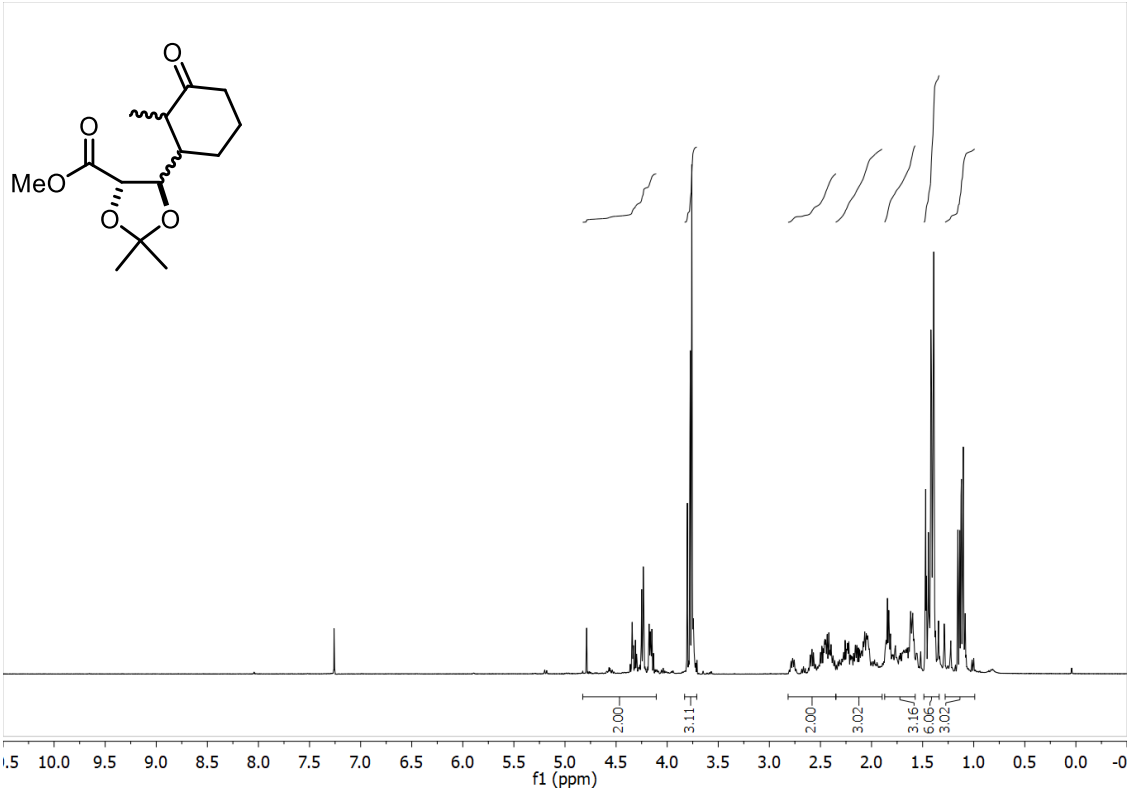


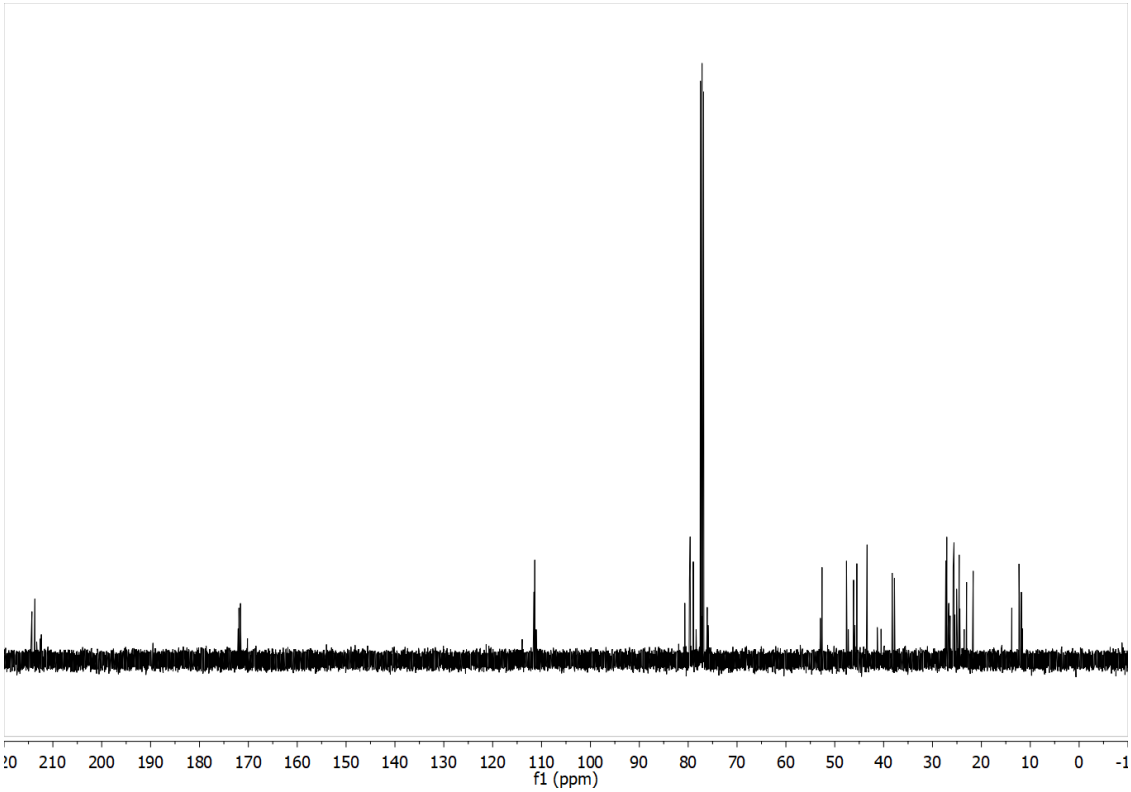
methyl 2,2-dimethyl-5-(3-oxocyclohexyl)-1,3-dioxolane-4-carboxylate (96)



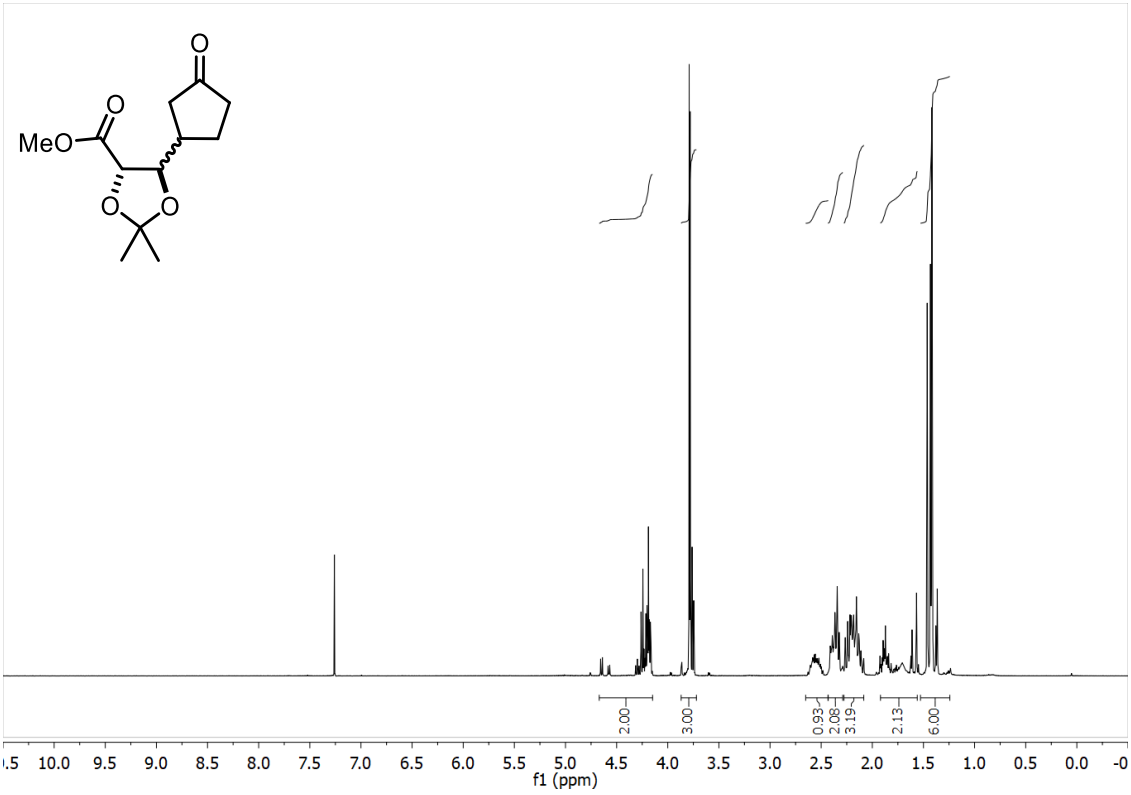


methyl 2,2-dimethyl-5-(2-methyl-3-oxocyclohexyl)-1,3-dioxolane-4-carboxylate (104 b)

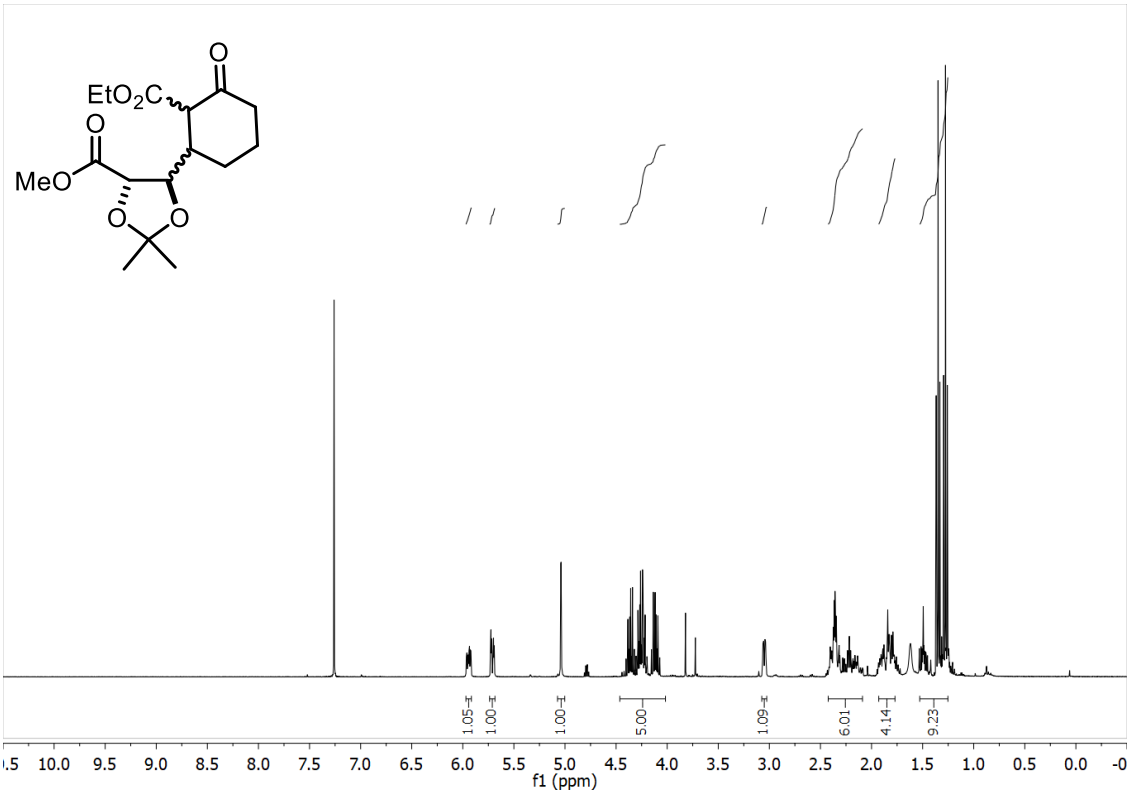


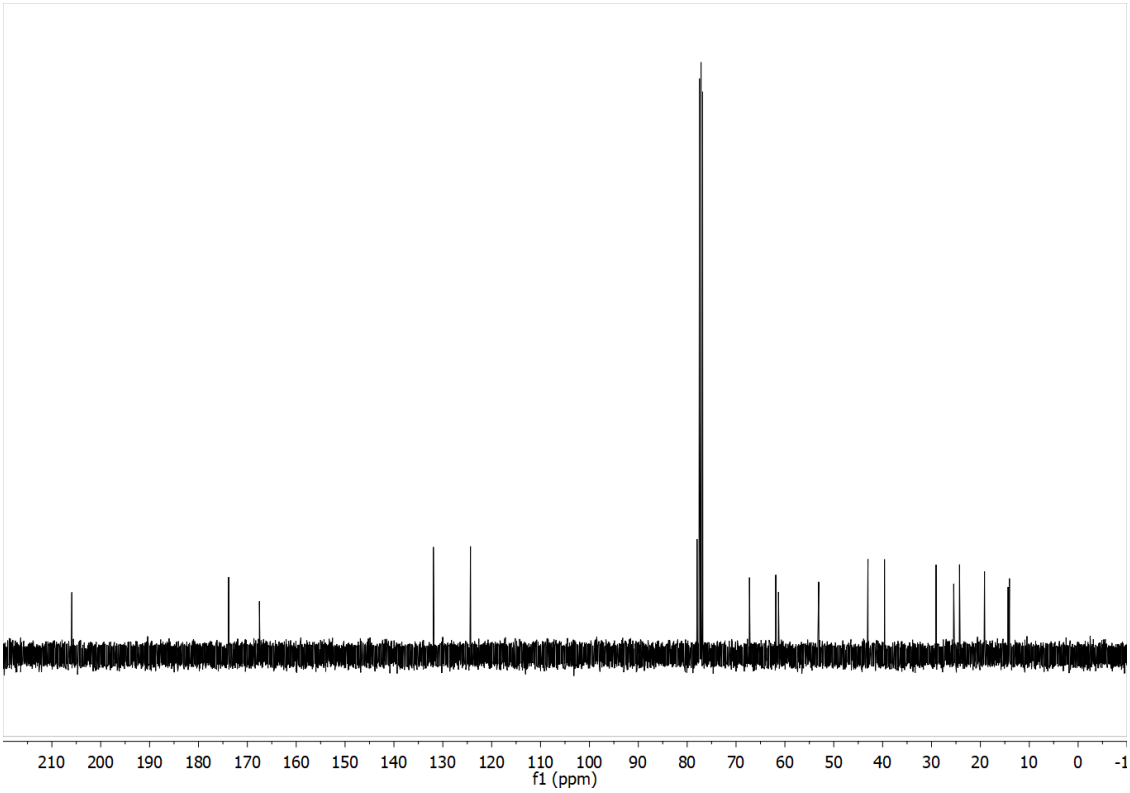


methyl 2,2-dimethyl-5-(3-oxocyclopentyl)-1,3-dioxolane-4-carboxylate (104 a)

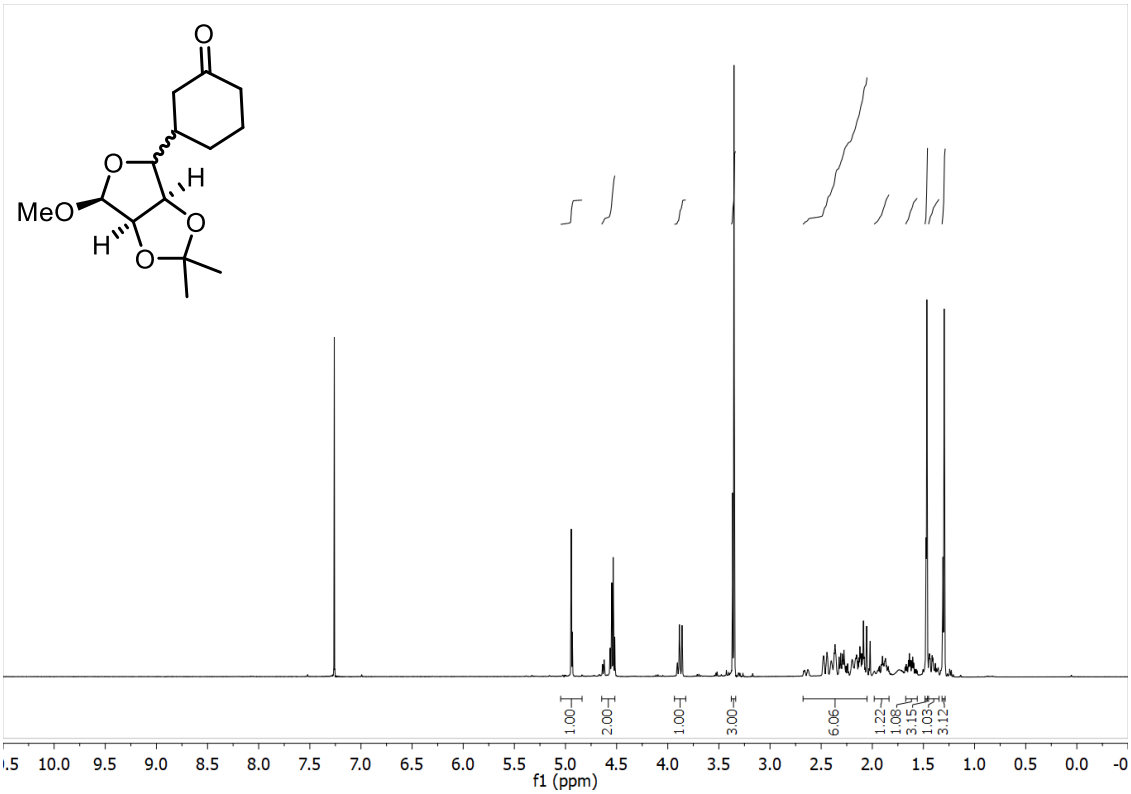


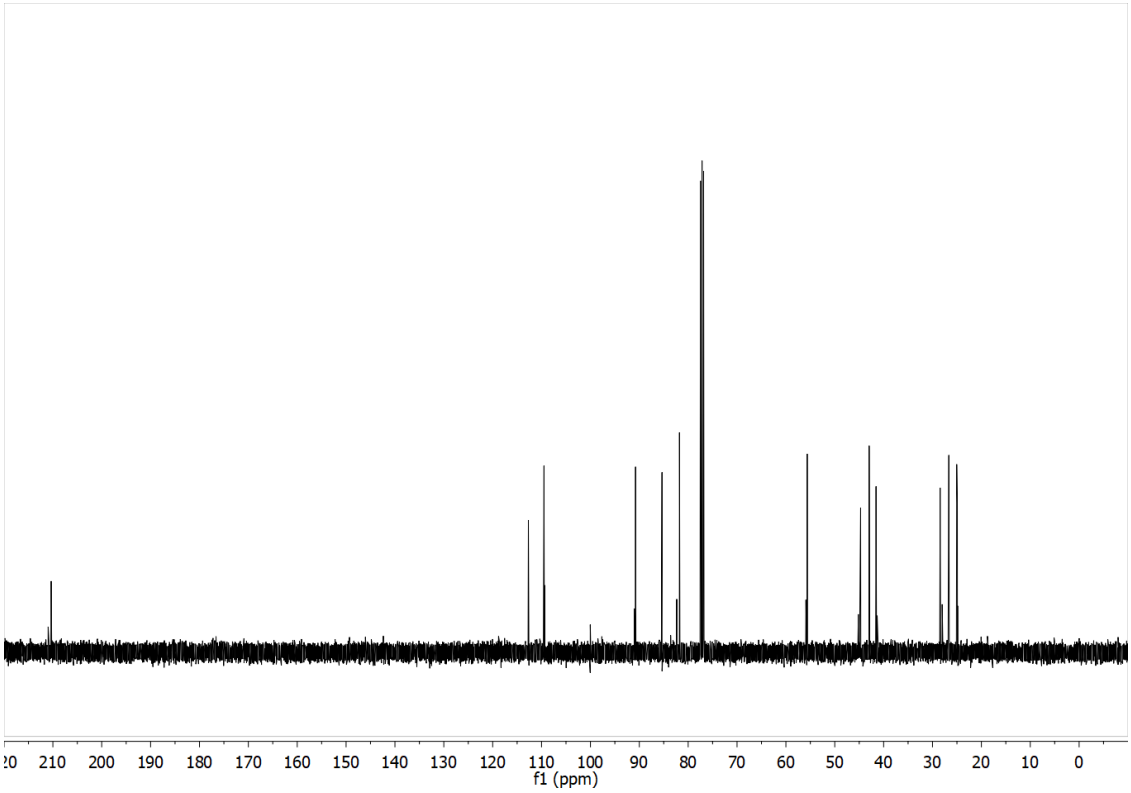
methyl 5-(2-(ethoxycarbonyl)-3-oxocyclohexyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (104 e)



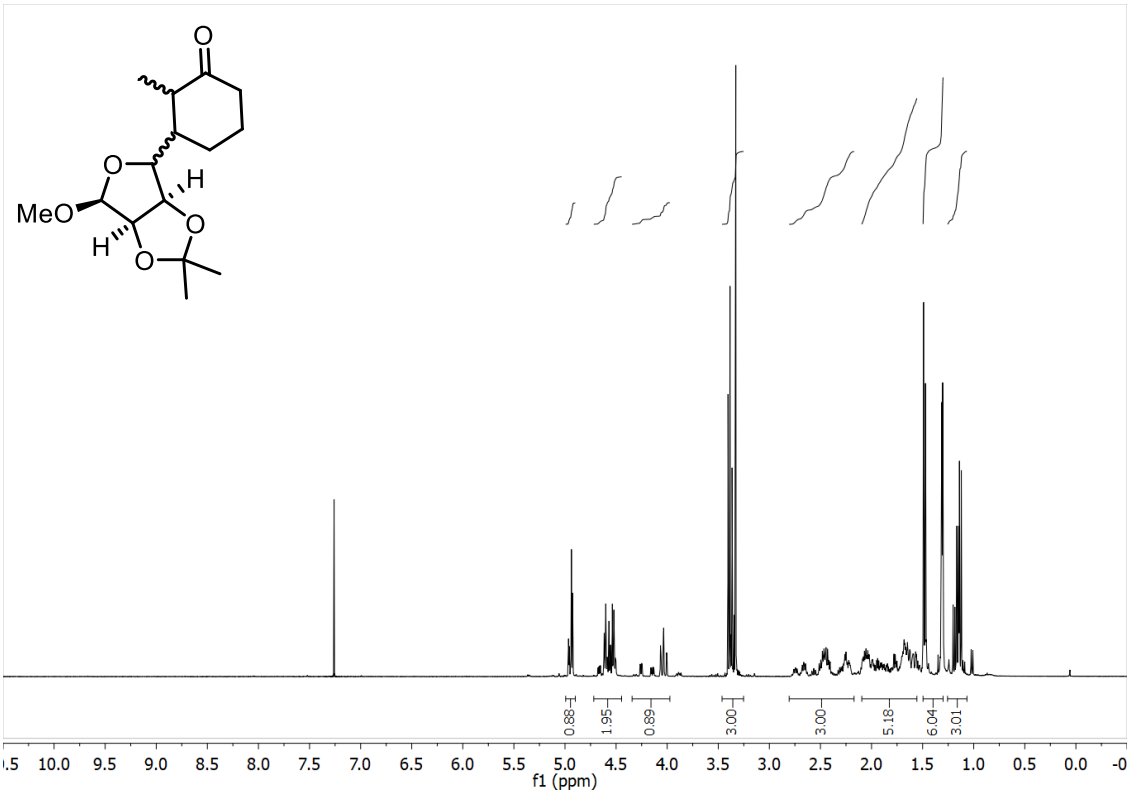


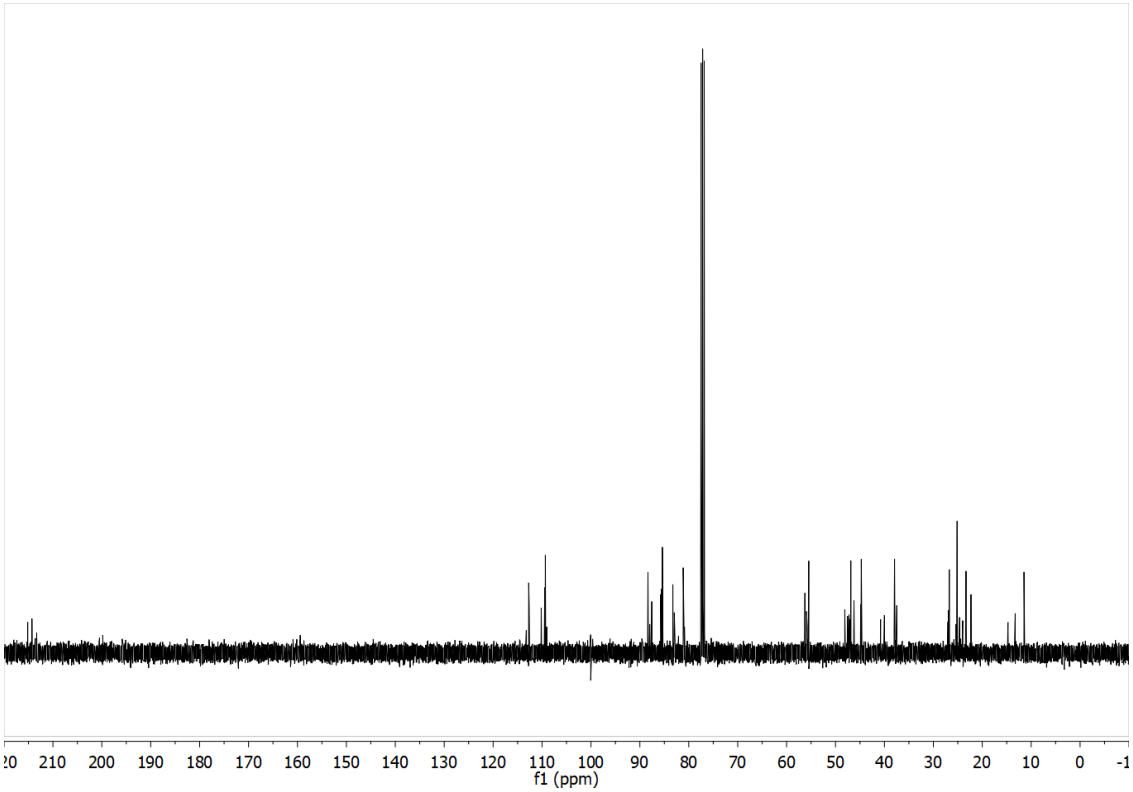
3-((3a*R*,6*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)cyclohexan-1-one (108 a)



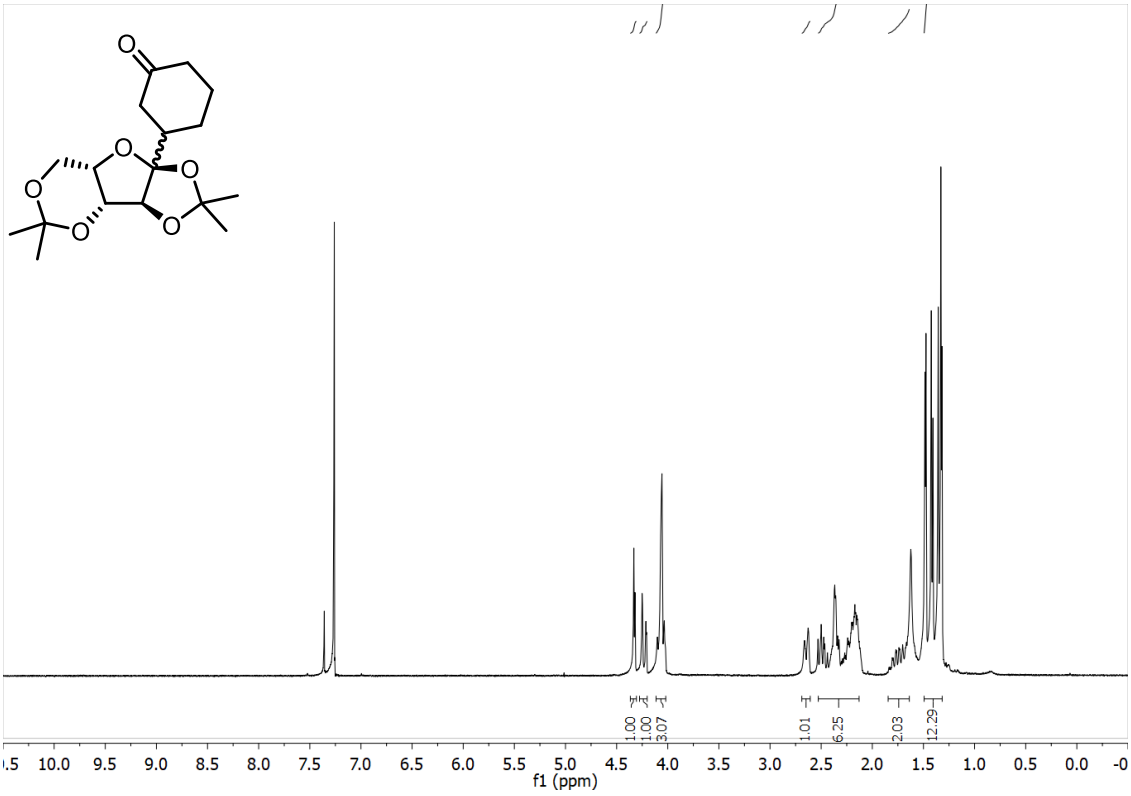


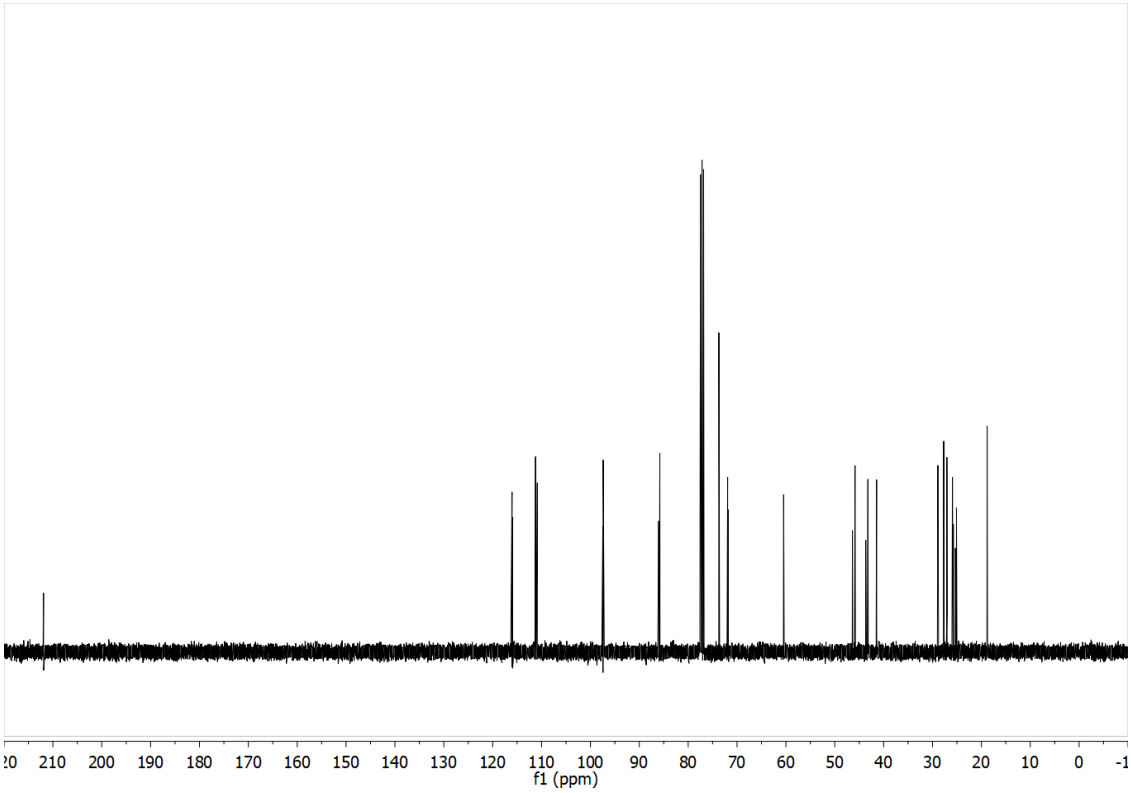
3-((3a*R*,6*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2-methylcyclohexan-1-one (108 b)



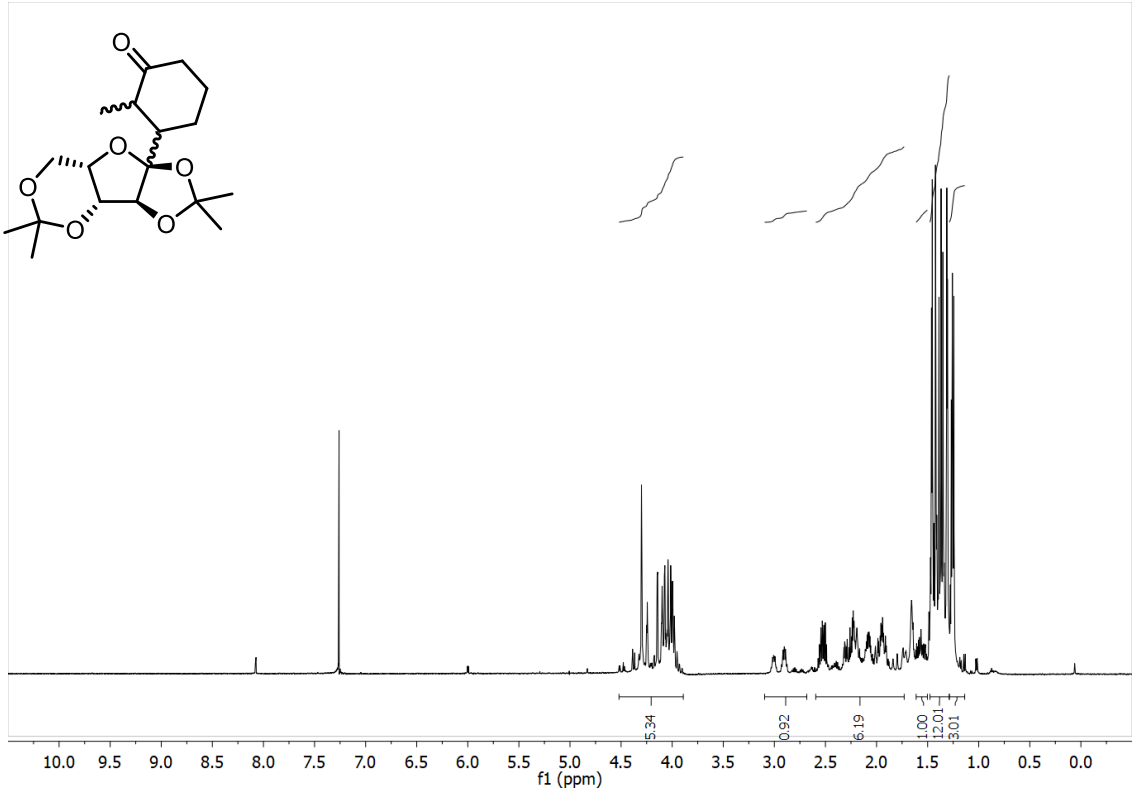


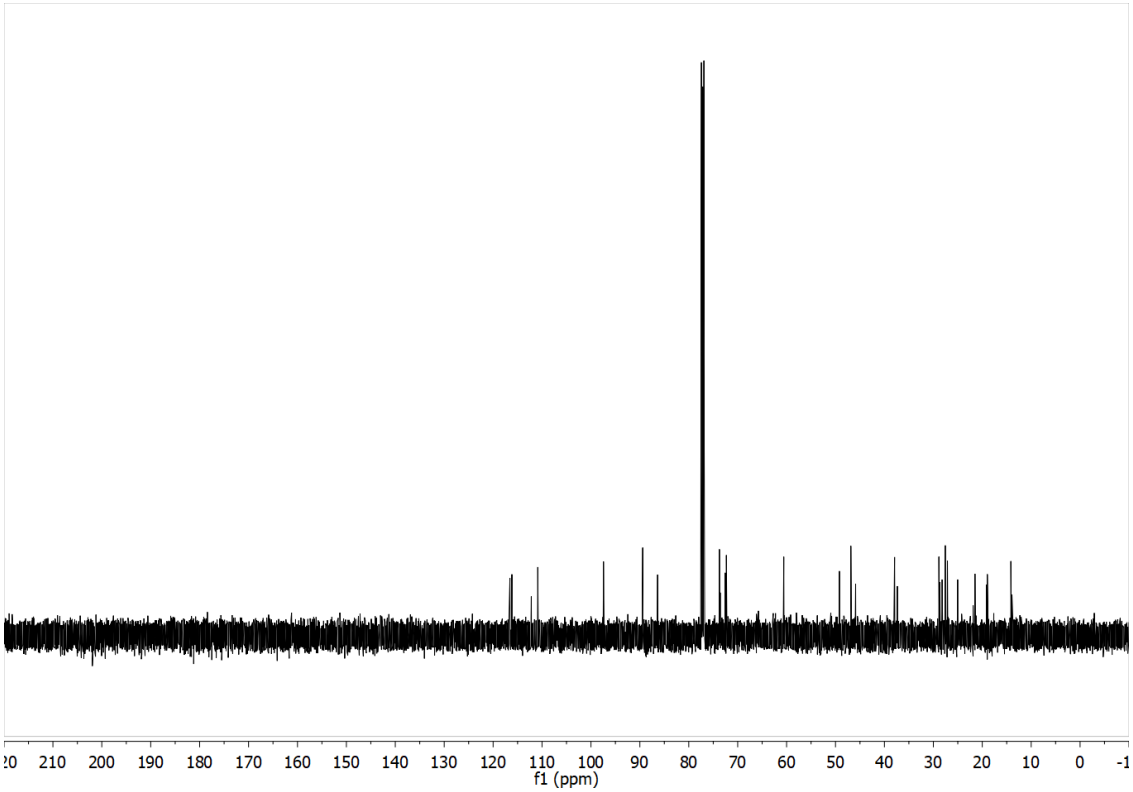
3-((3a*S*,3b*R*,7a*S*,8a*S*)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)cyclohexan-1-one (106 a)



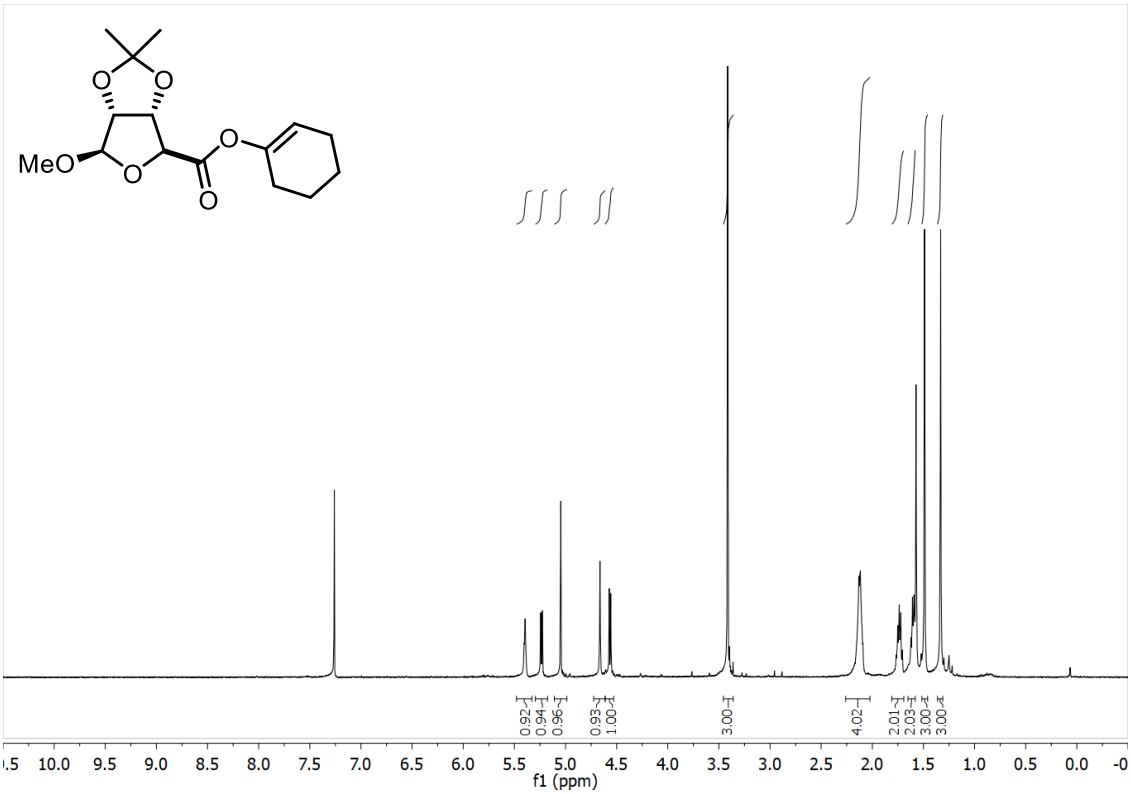


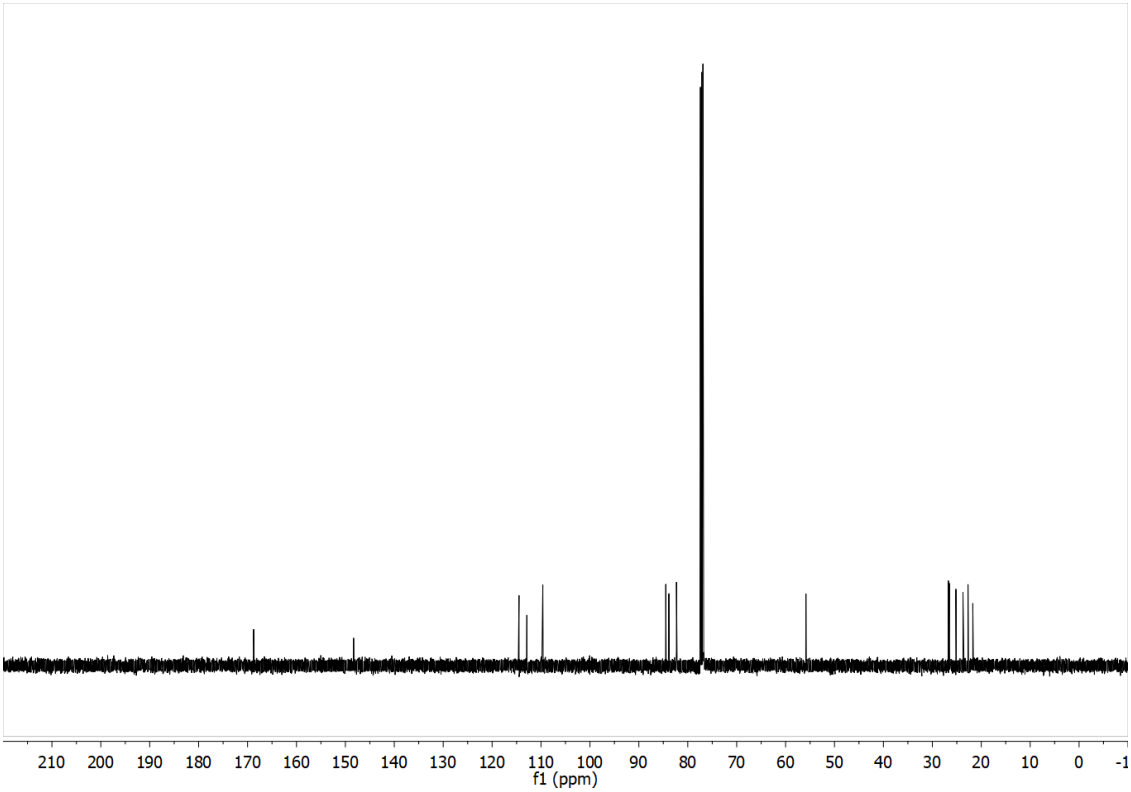
2-methyl-3-((3a*S*,3b*R*,7a*S*,8a*S*)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)cyclohexan-1-one (106 b)



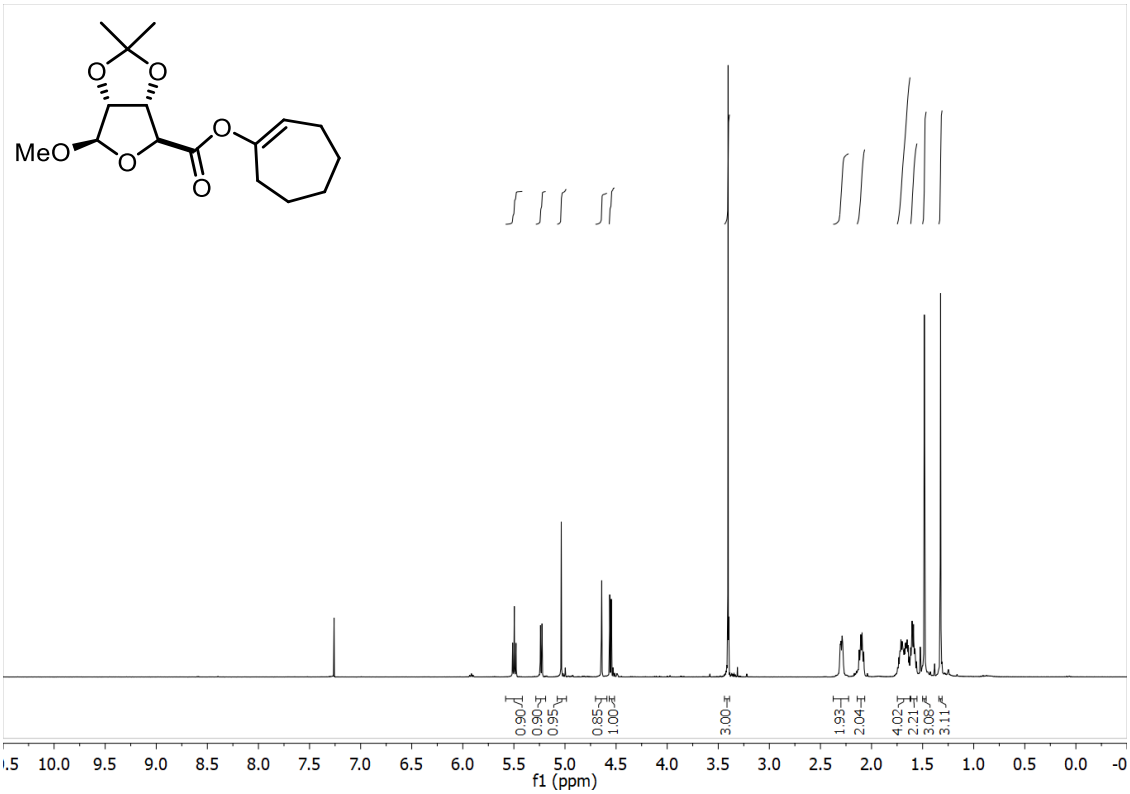


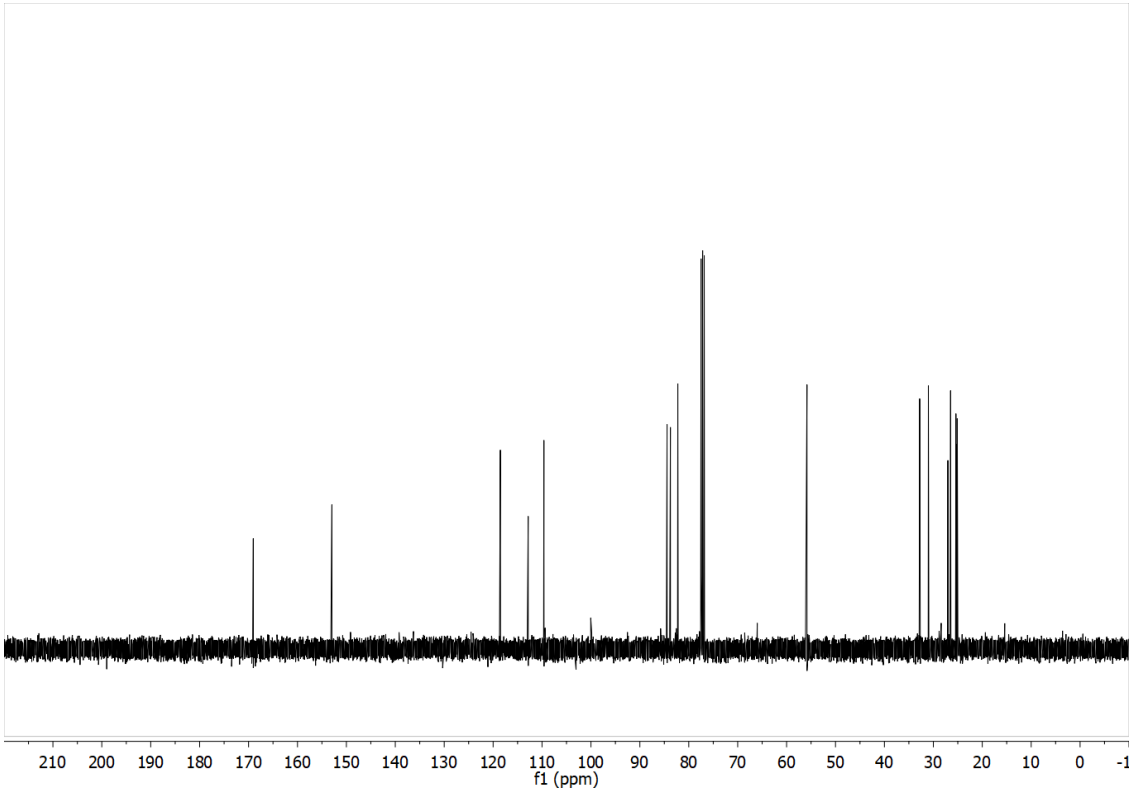
cyclohex-1-en-1-yl (3a*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (122 b)



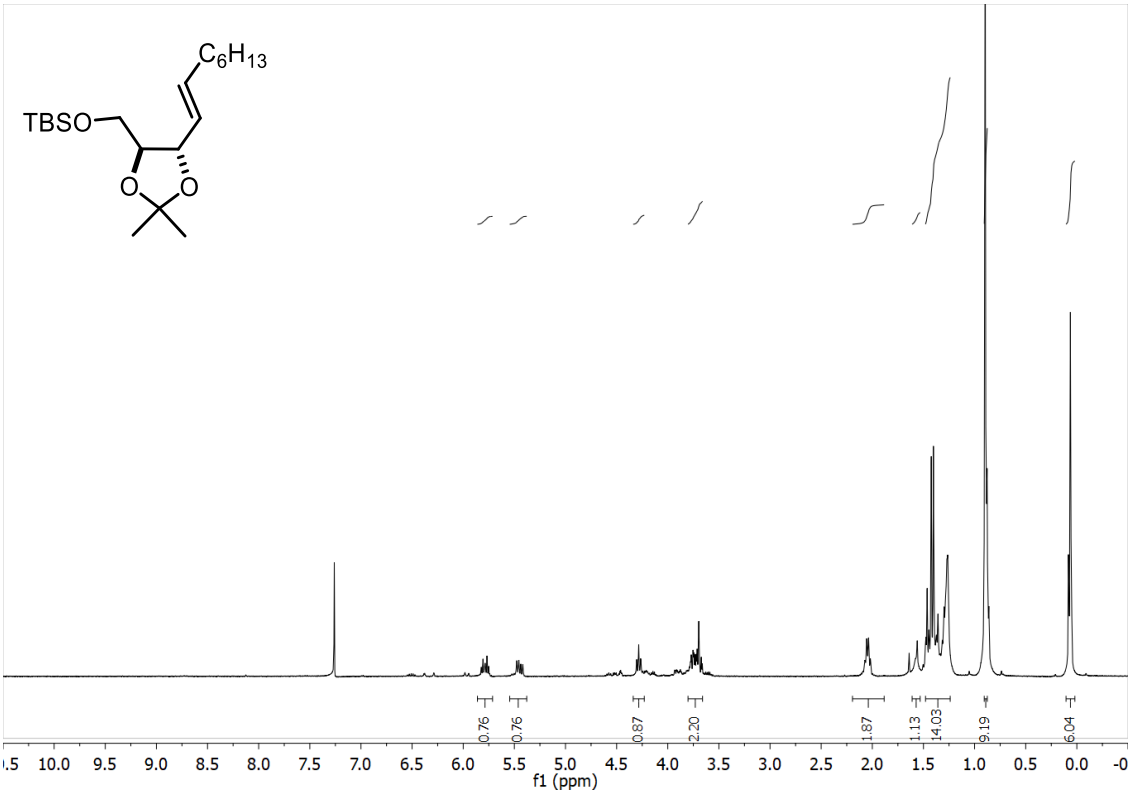


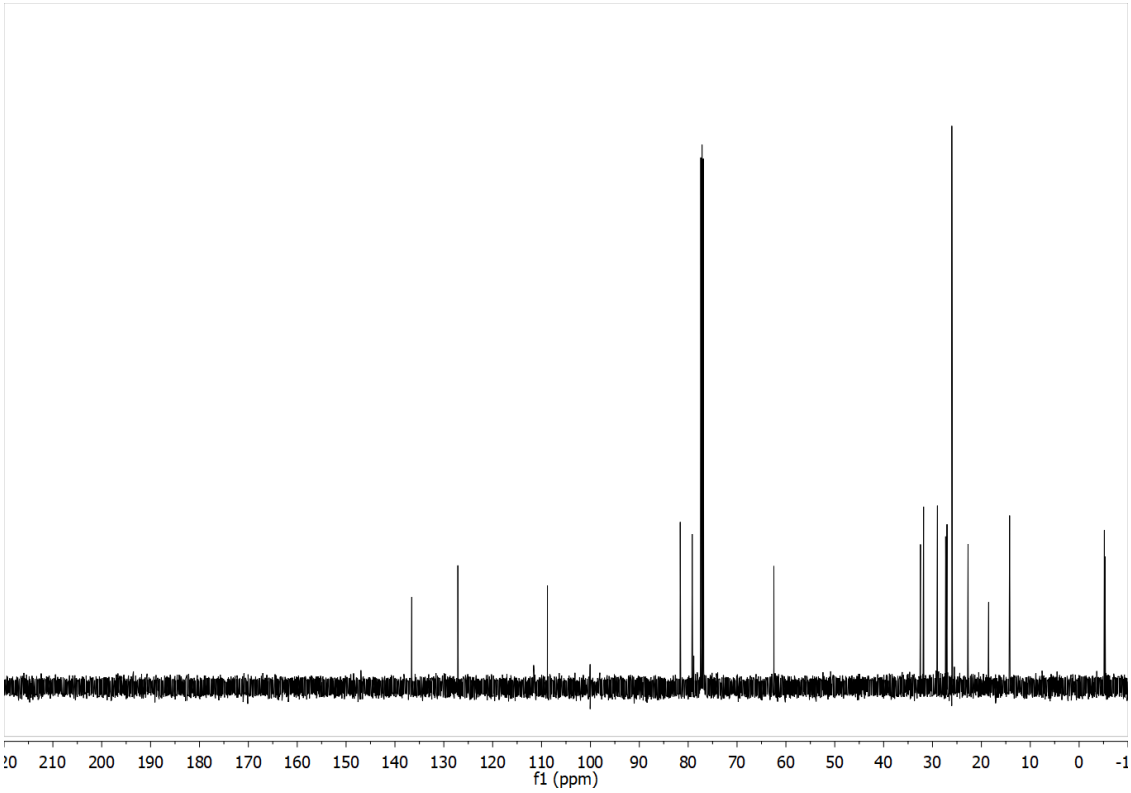
cyclohept-1-en-1-yl (3a*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (122 c)



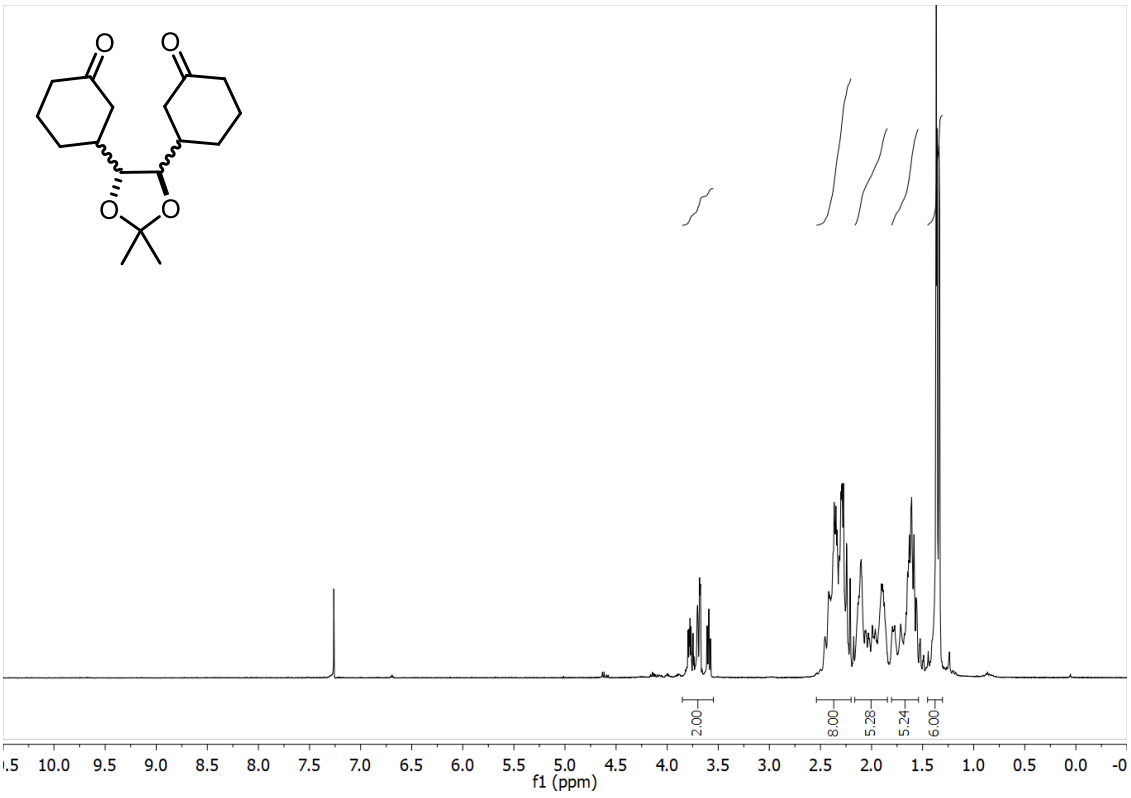


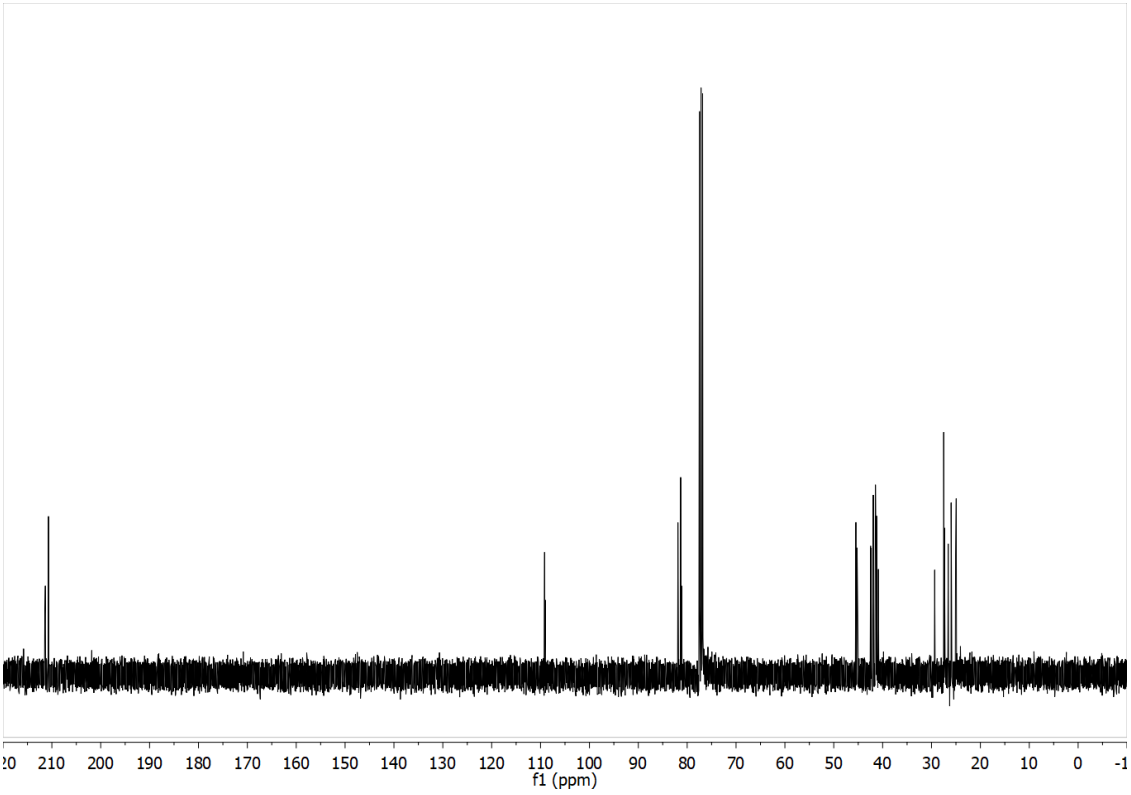
***tert*-butyl(((4*S*,5*S*)-2,2-dimethyl-5-((*E*)-oct-1-en-1-yl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane (129' a)**



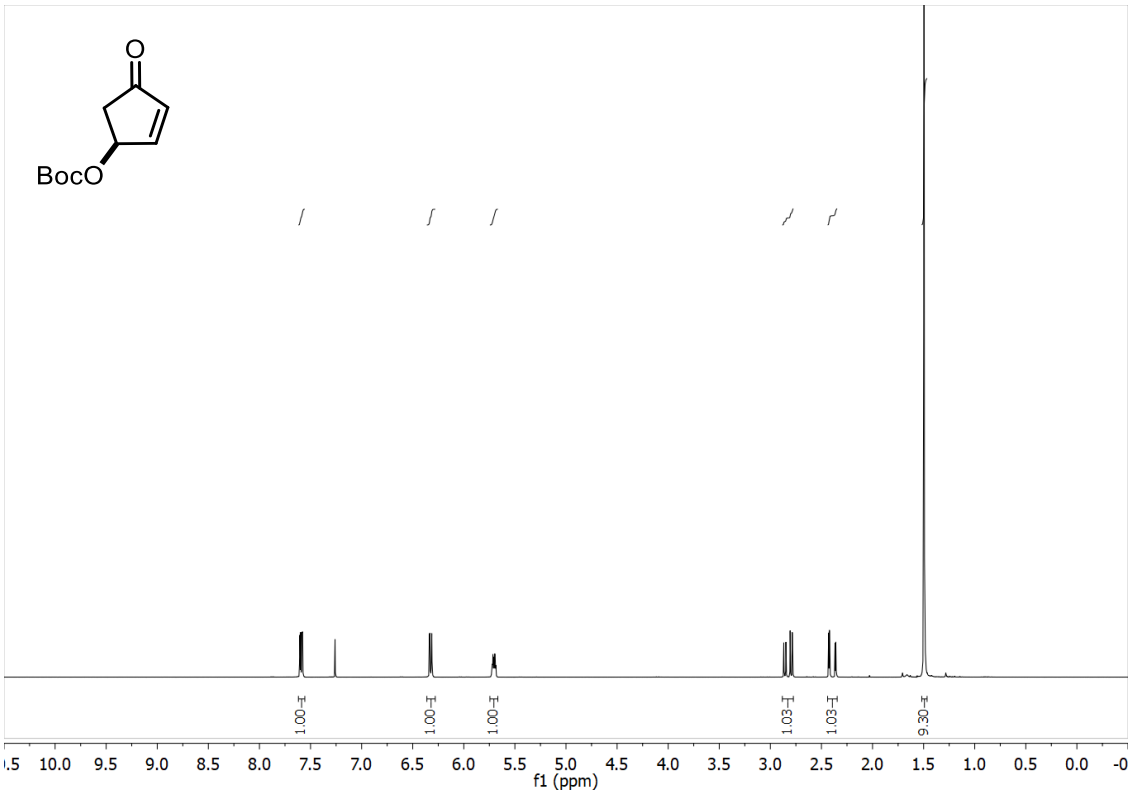


3,3'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(cyclohexan-1-one) (140)

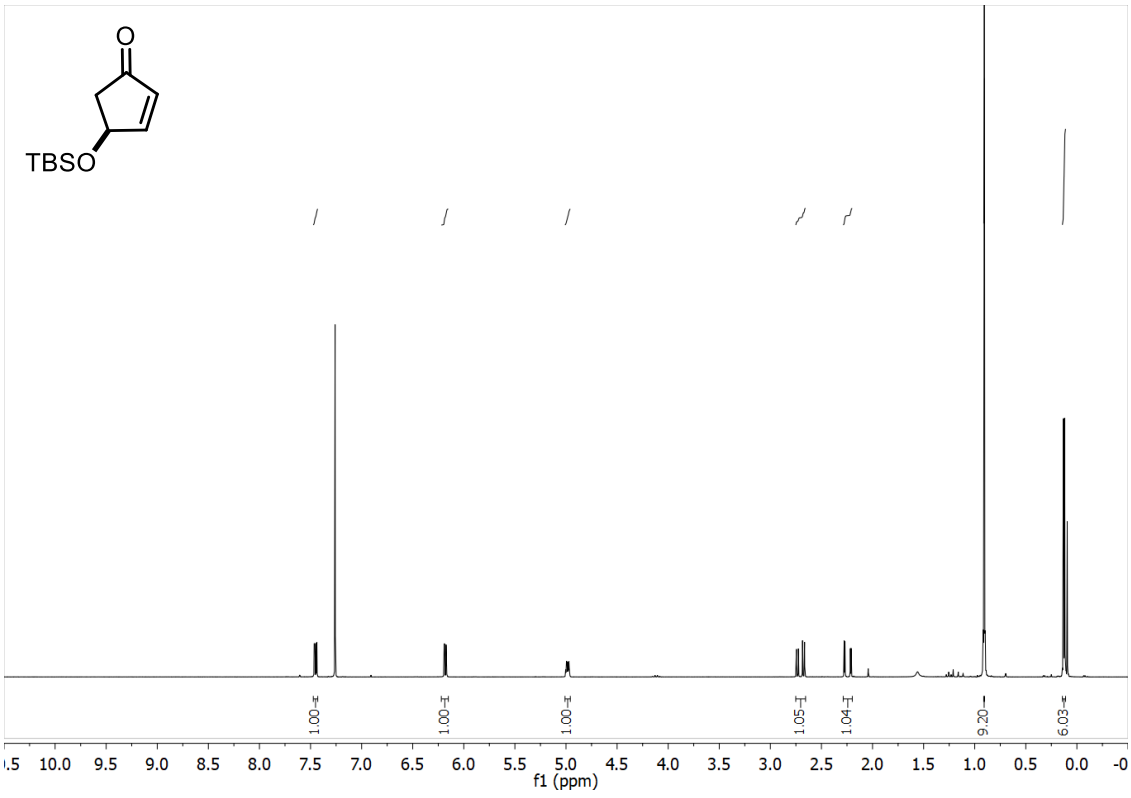




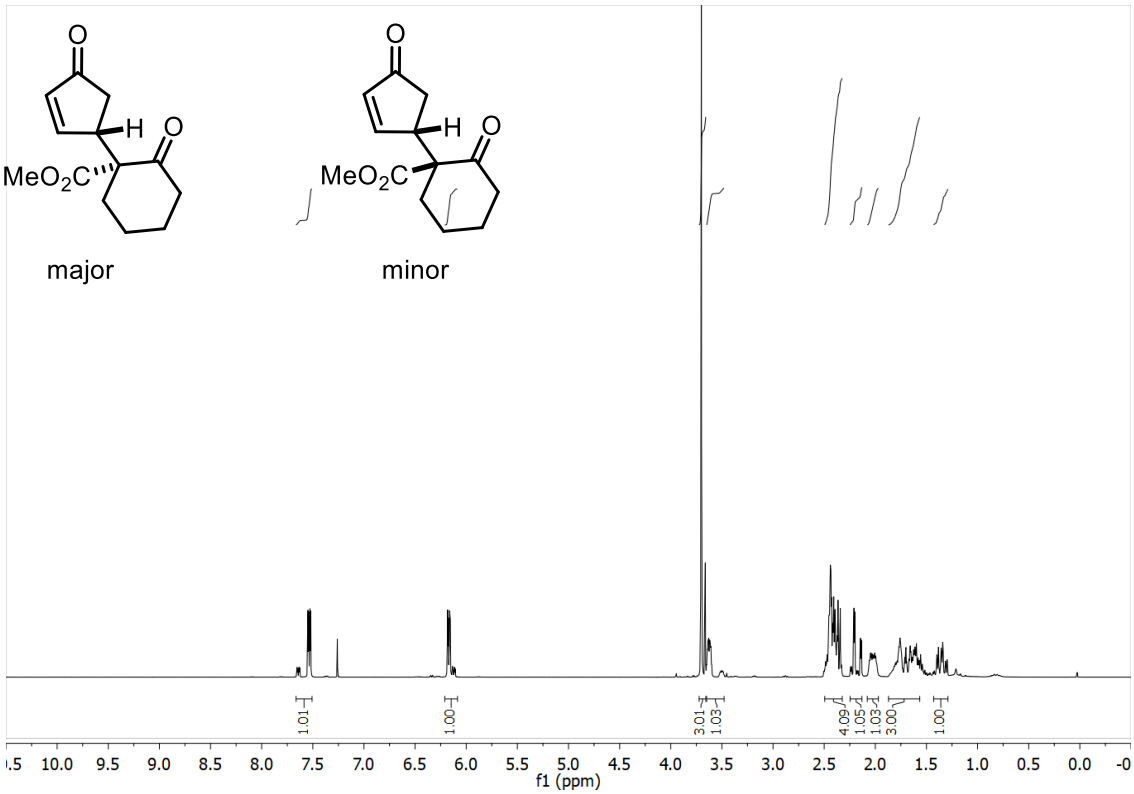
tert-butyl (4-oxocyclopent-2-en-1-yl) carbonate (169)

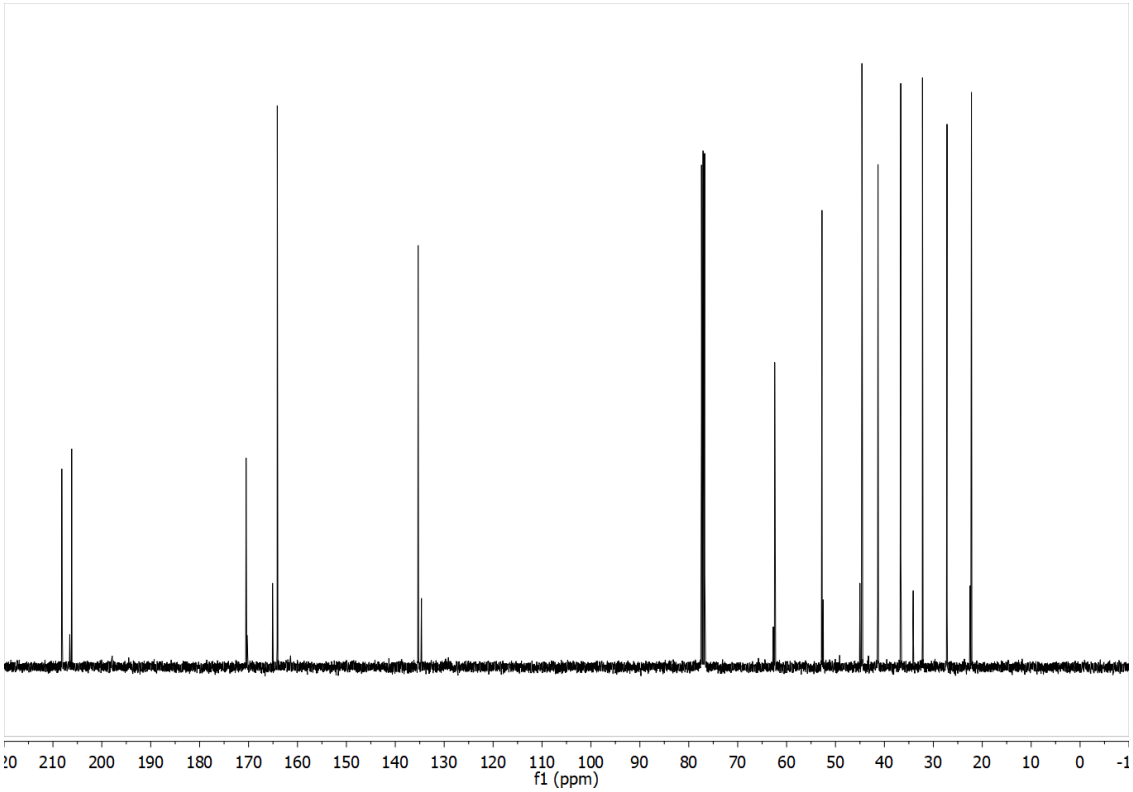


4-((_tert_-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (196)

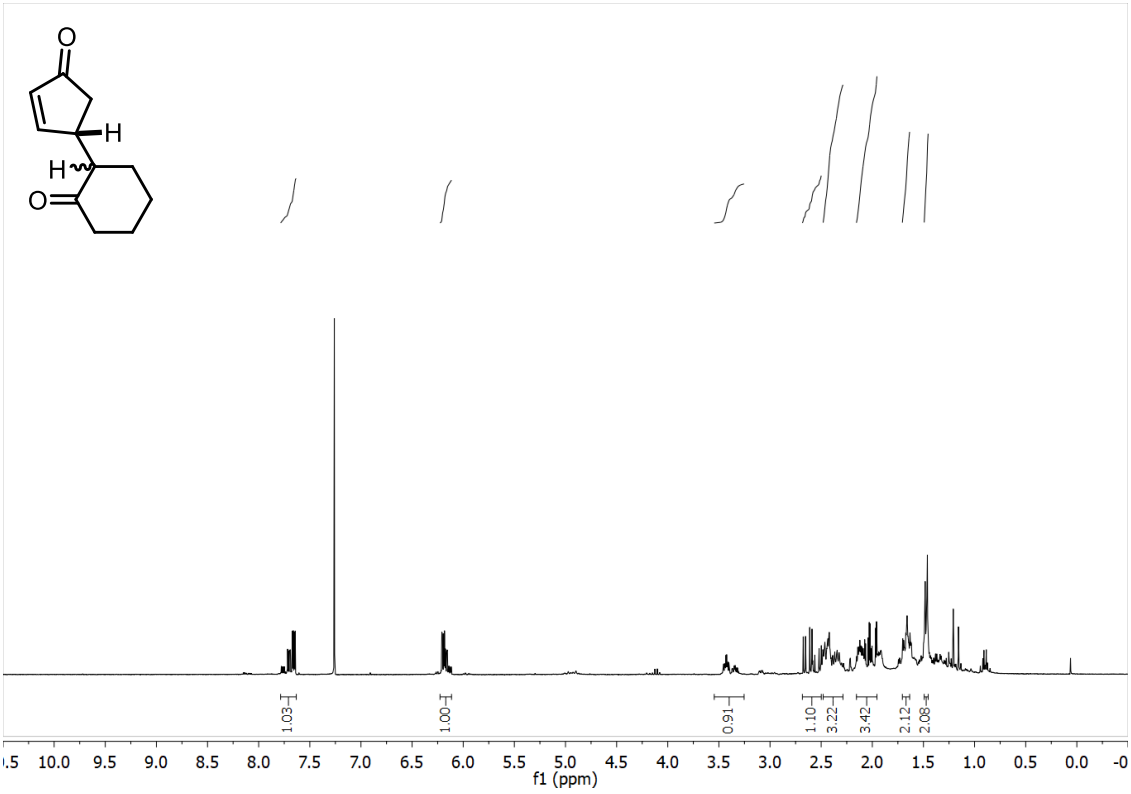


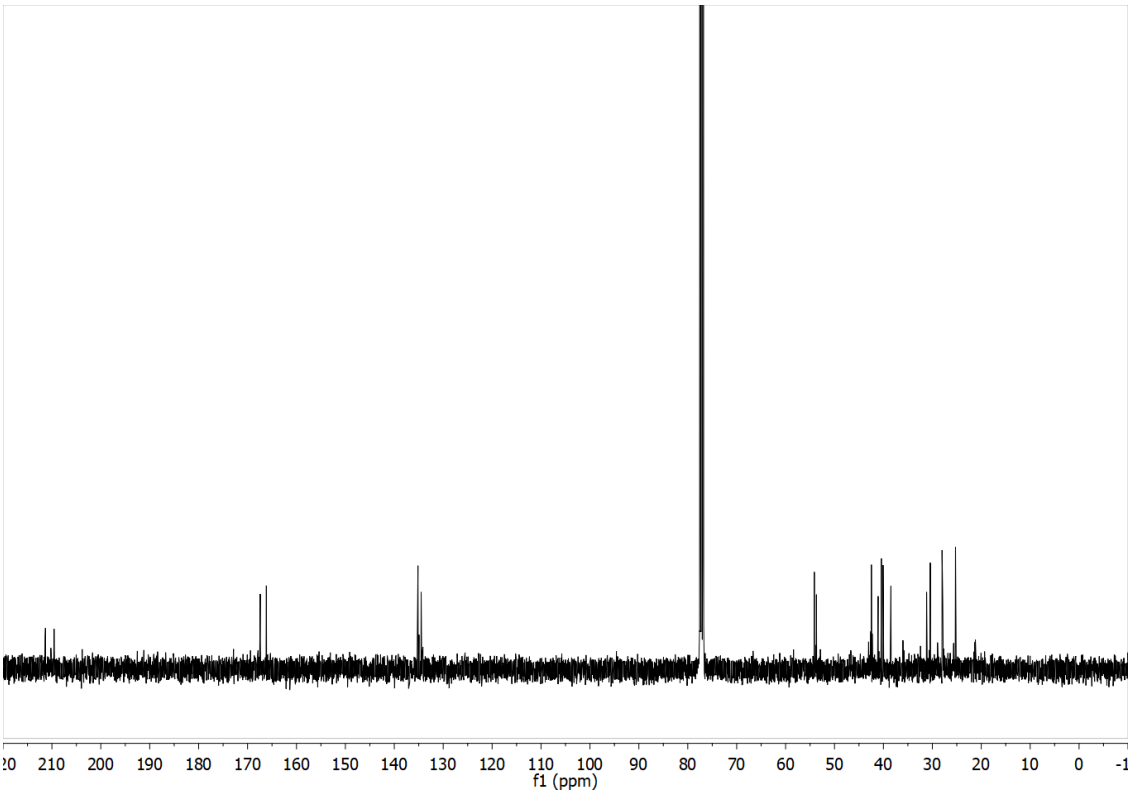
methyl 2-oxo-1-(4-oxocyclopent-2-en-1-yl)cyclohexane-1-carboxylate (174 c)



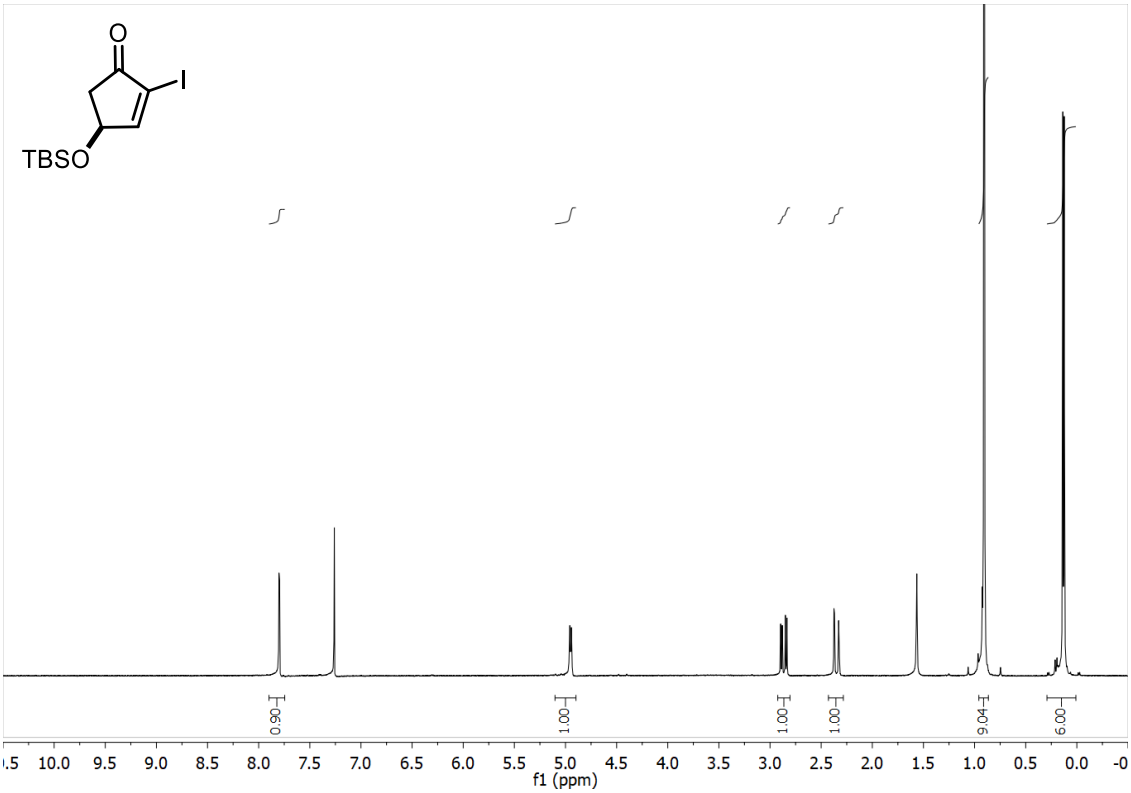


2-(4-oxocyclopent-2-en-1-yl)cyclohexan-1-one (193)

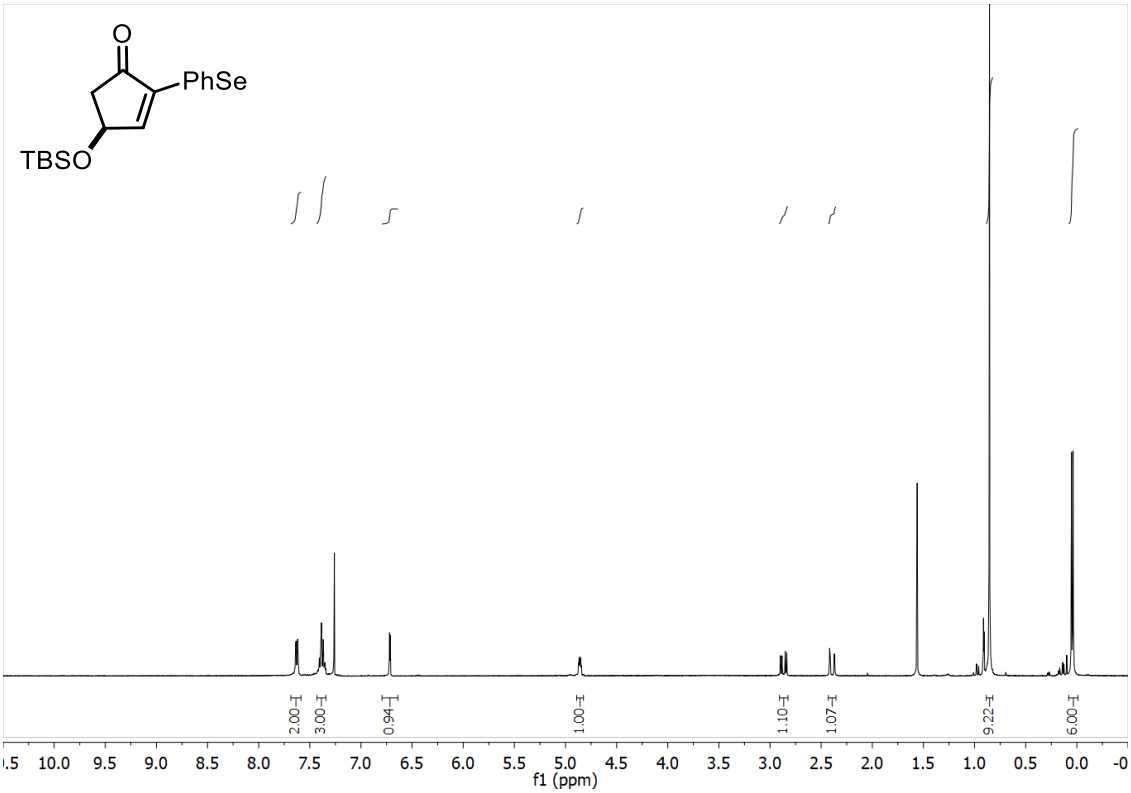




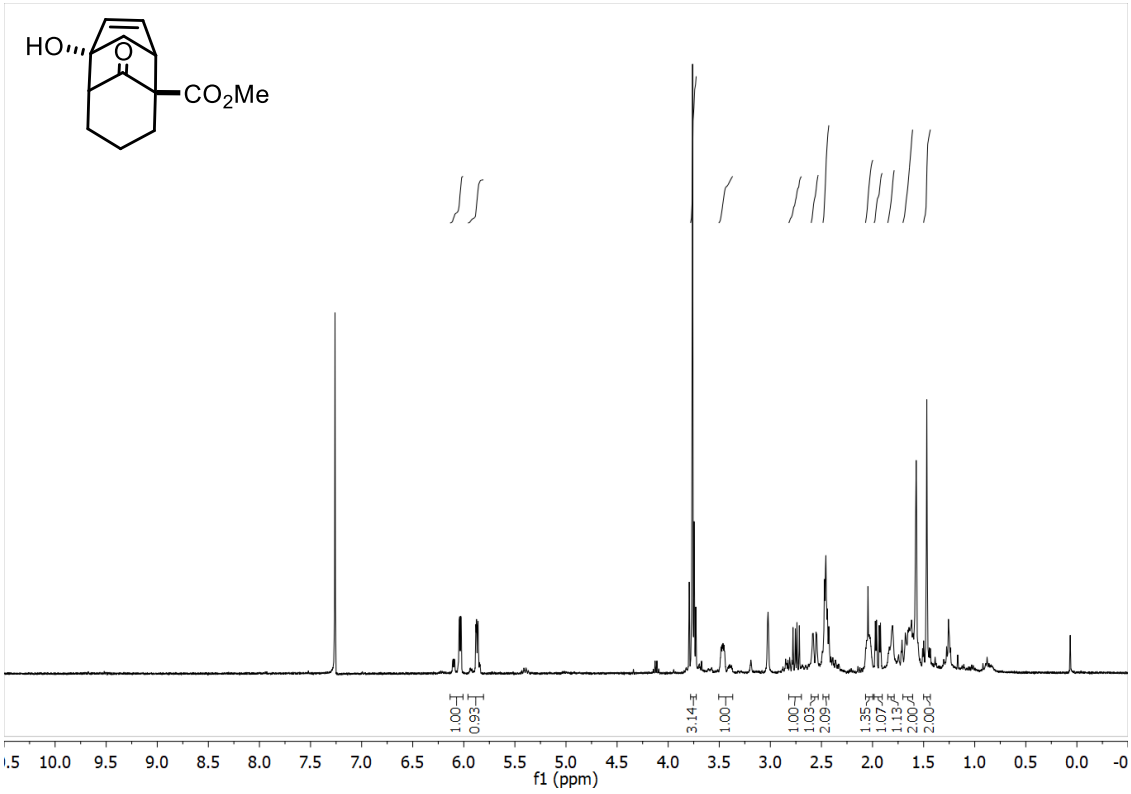
4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (225)

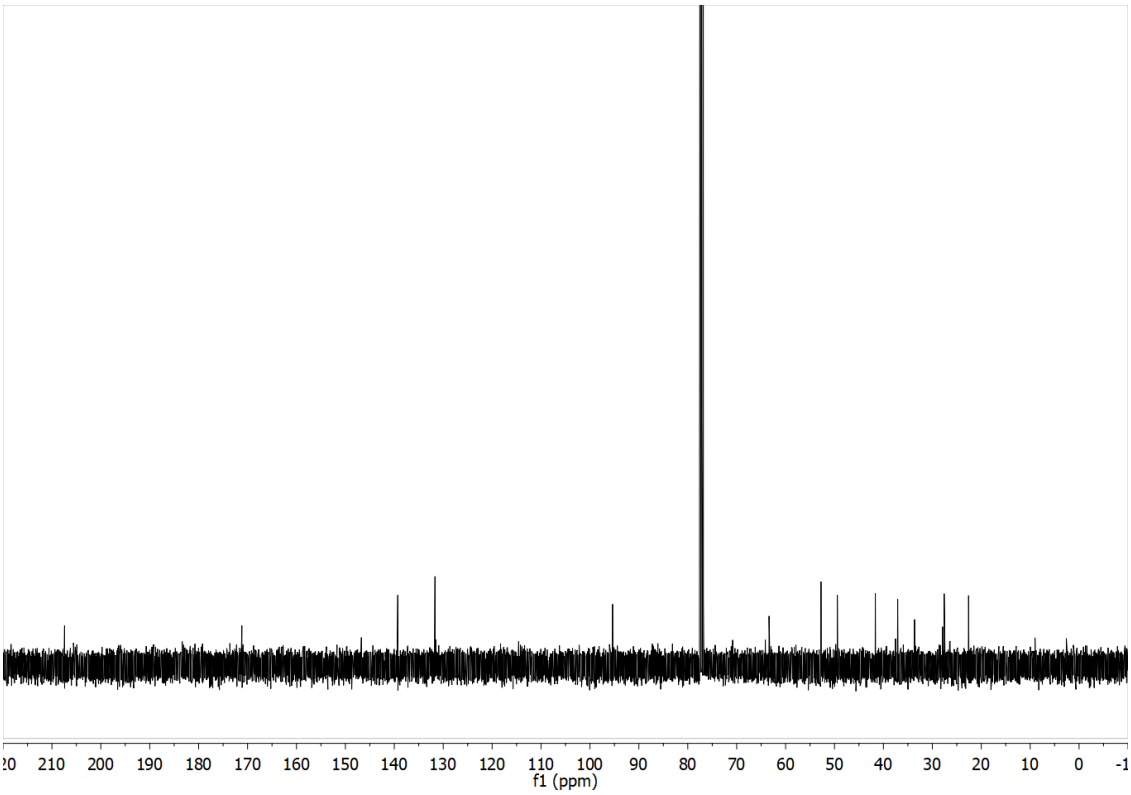


4-((*tert*-butyldimethylsilyl)oxy)-2-(phenylselanyl)cyclopent-2-en-1-one (223)

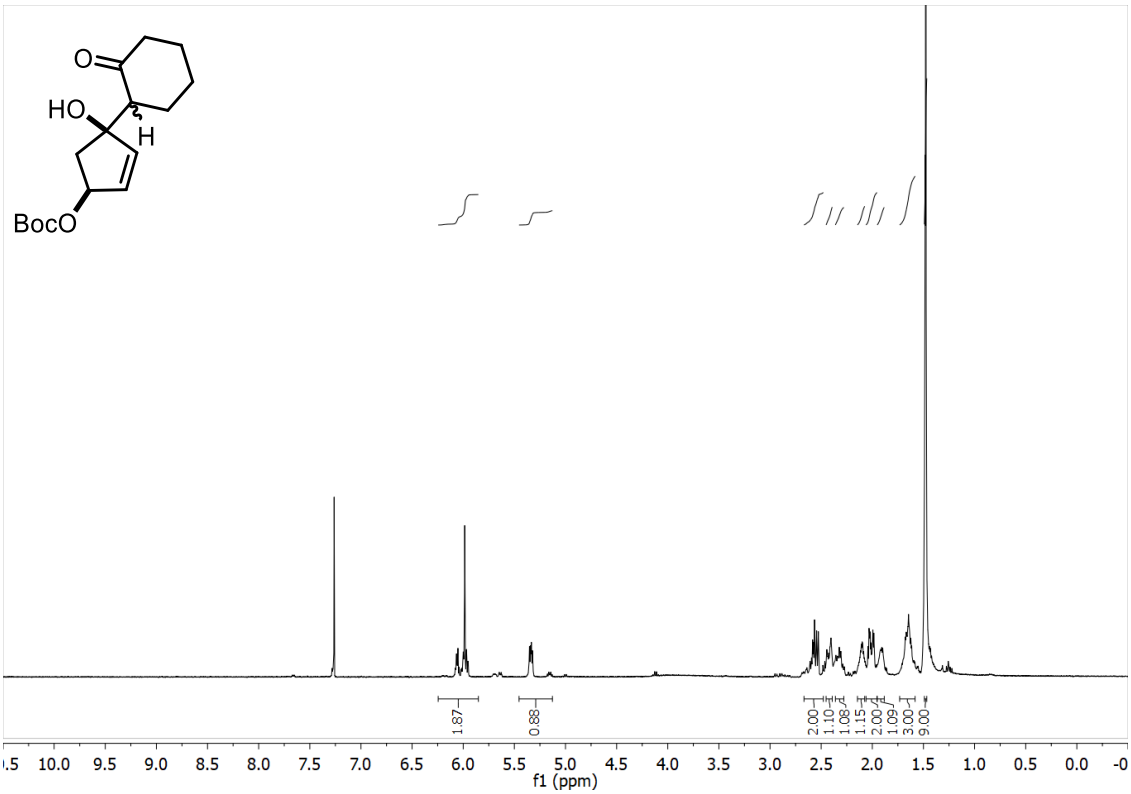


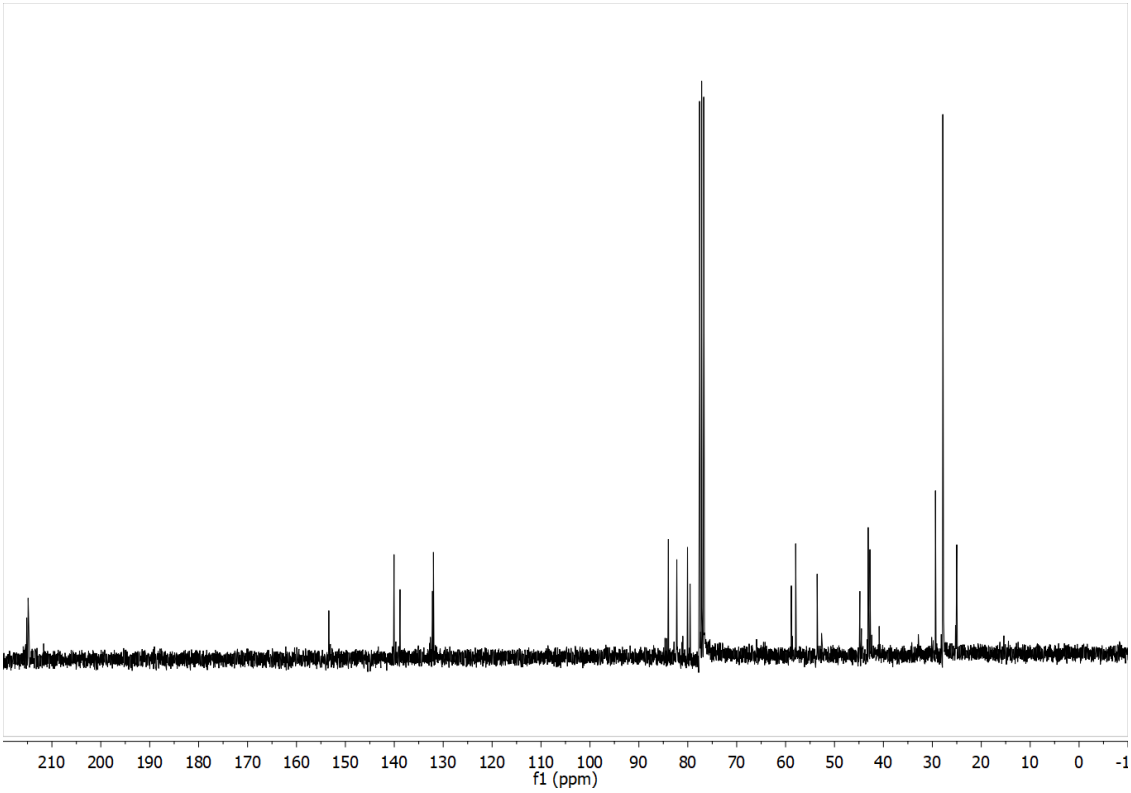
methyl 5-hydroxy-10-oxotricyclo[4.3.1.12,5]undec-3-ene-1-carboxylate (216)



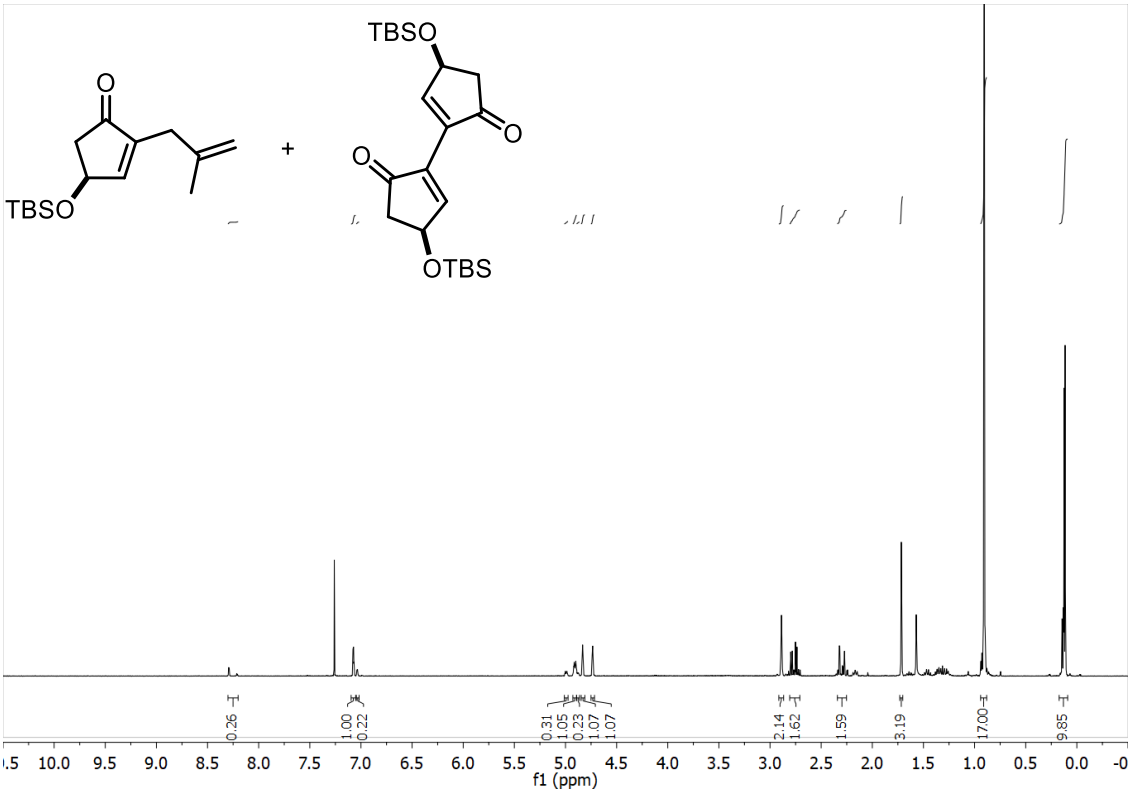


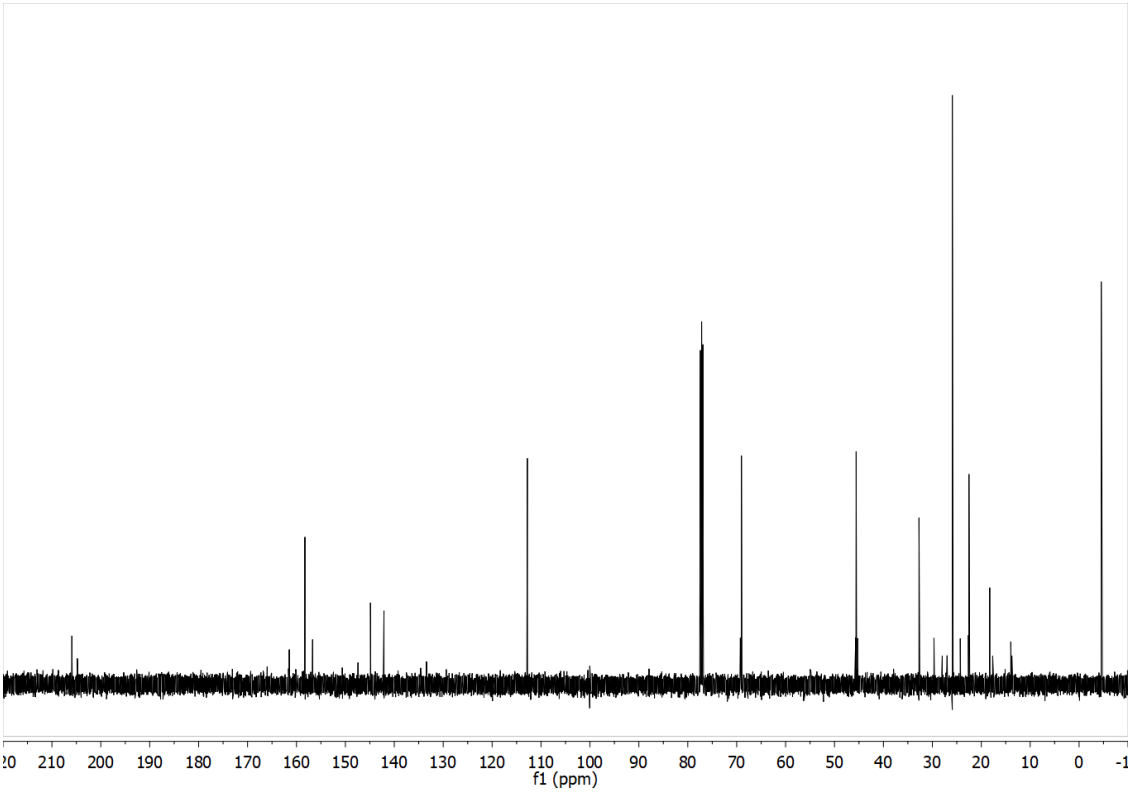
***tert*-butyl (4-hydroxy-4-(2-oxocyclohexyl)cyclopent-2-en-1-yl) carbonate (211)**



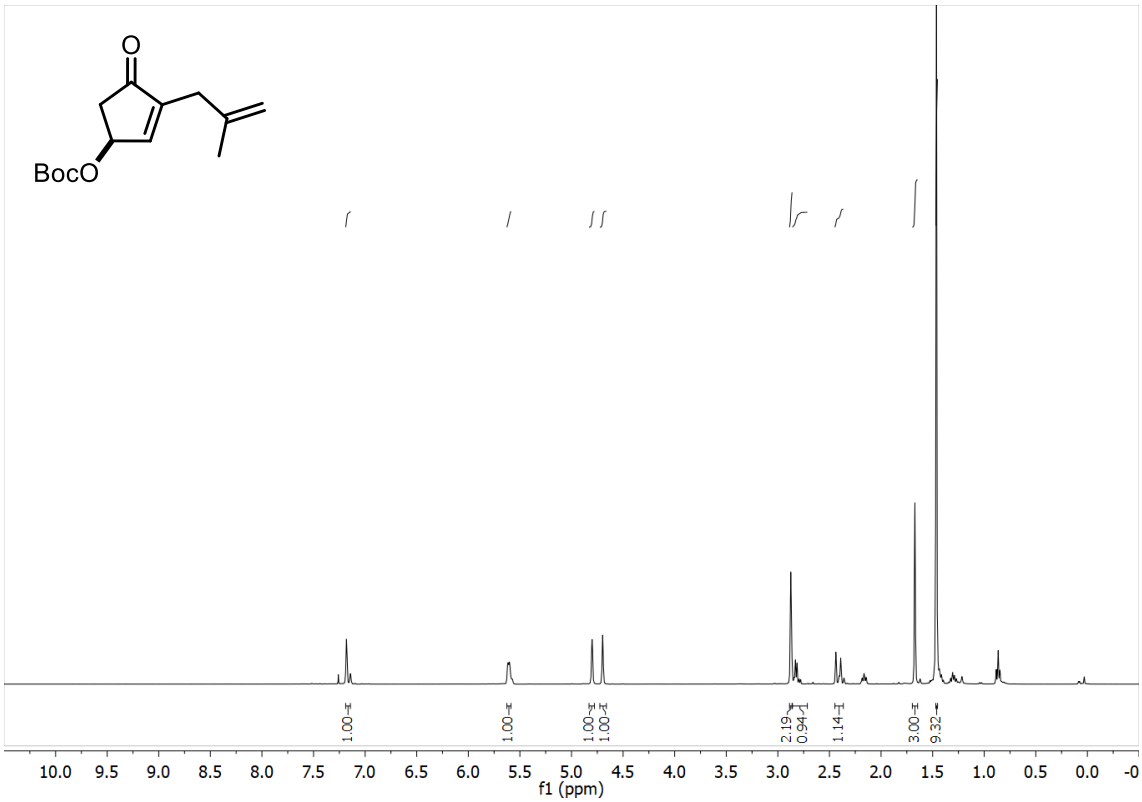


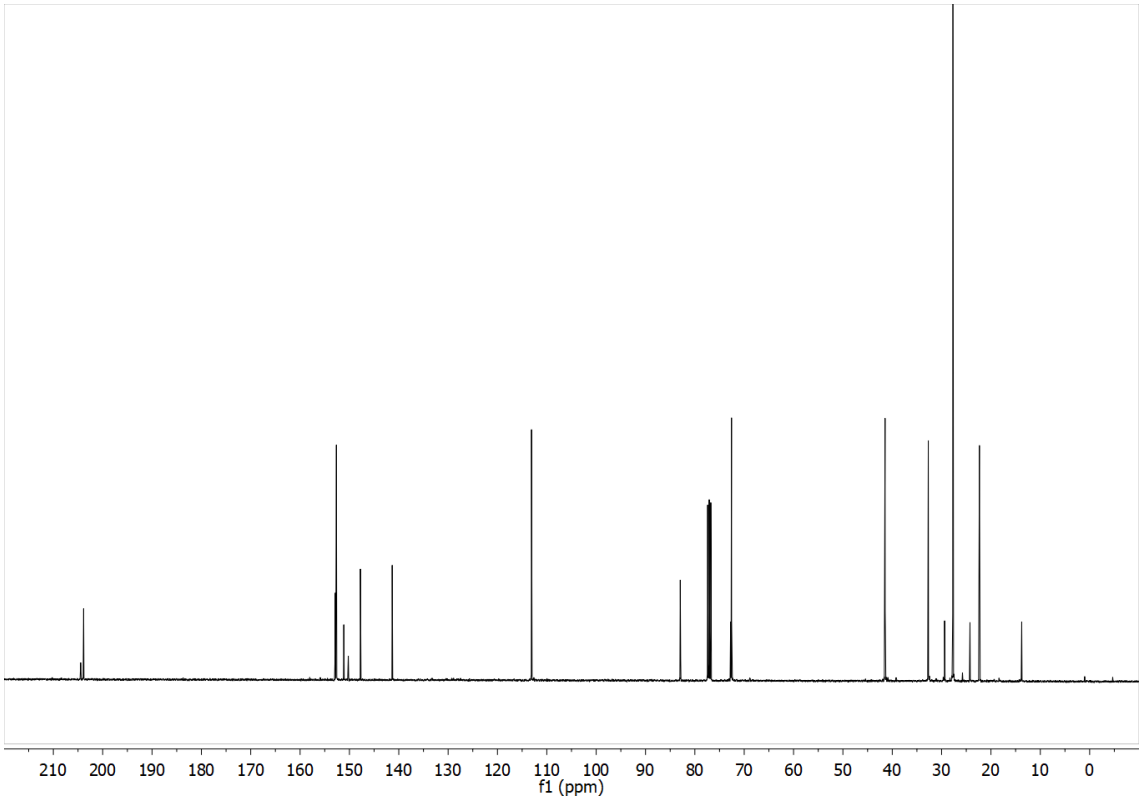
4-((*tert*-butyldimethylsilyl)oxy)-2-(2-methylallyl)cyclopent-2-en-1-one (228) and **4,4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclopentane)]-5,5'-diene-2,2'-dione (229)**



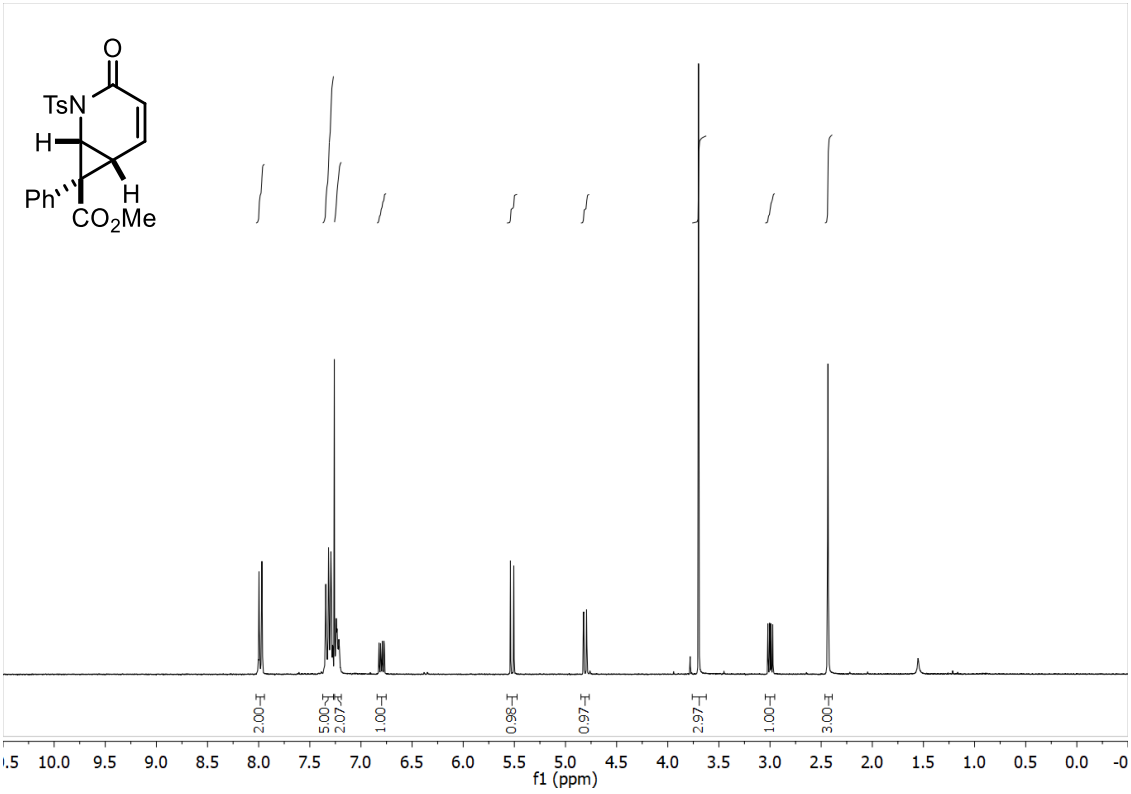


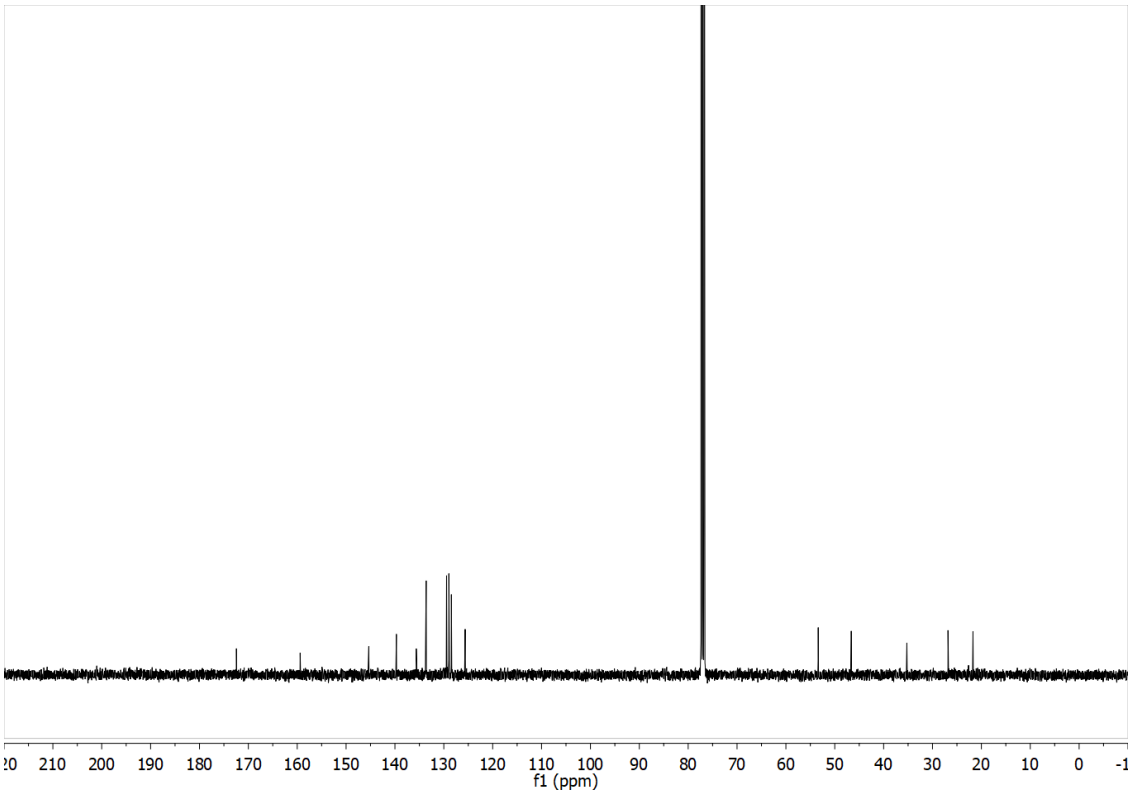
tert-butyl (3-(2-methylallyl)-4-oxocyclopent-2-en-1-yl) carbonate (230)



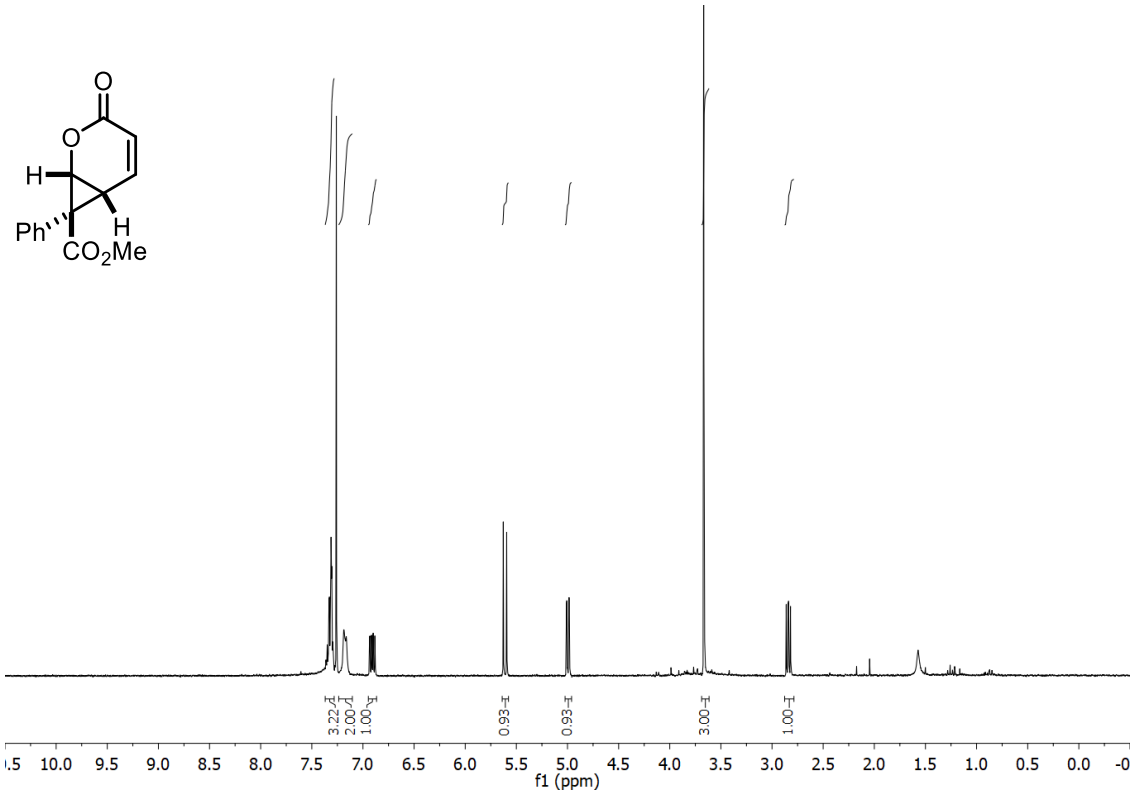


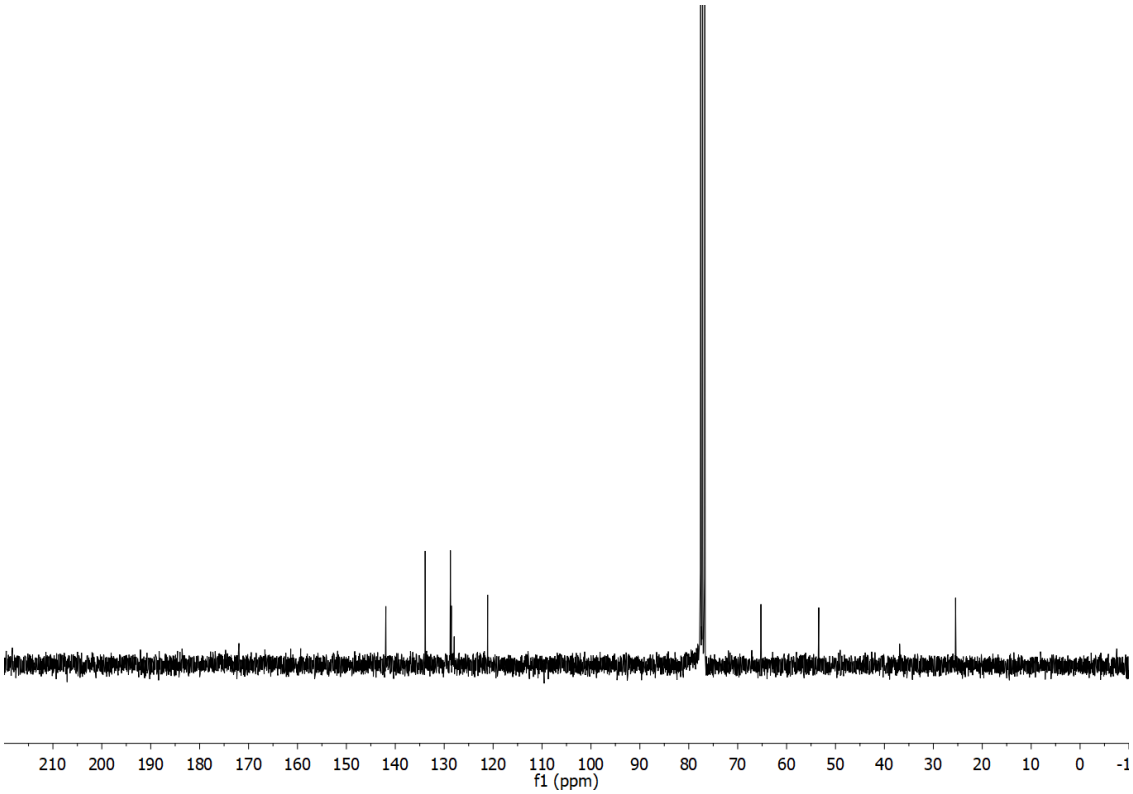
methyl 3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (379)



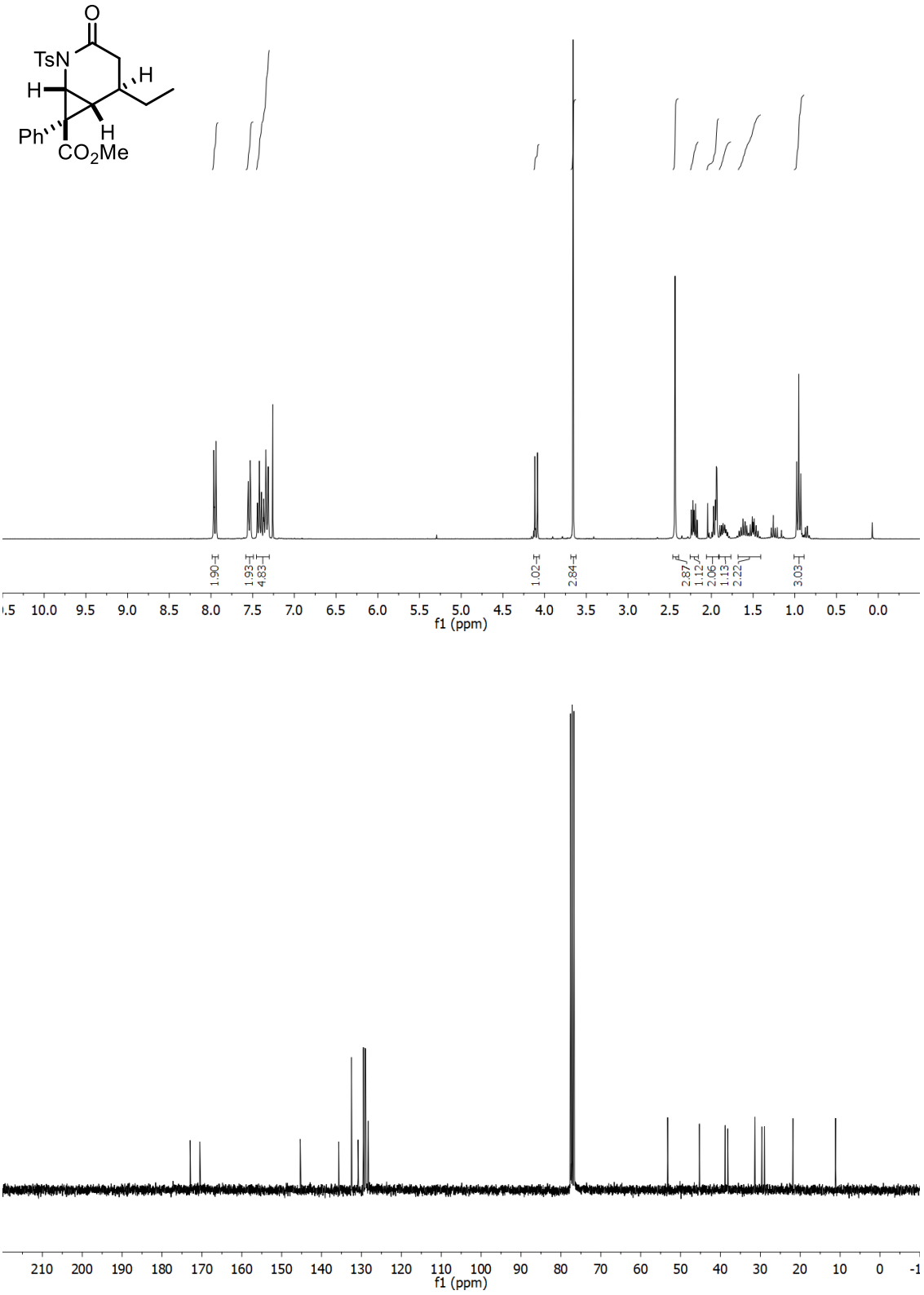


methyl 3-oxo-7-phenyl-2-oxabicyclo[4.1.0]hept-4-ene-7-carboxylate (378)

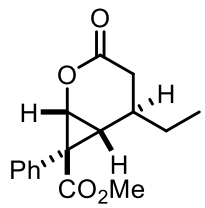


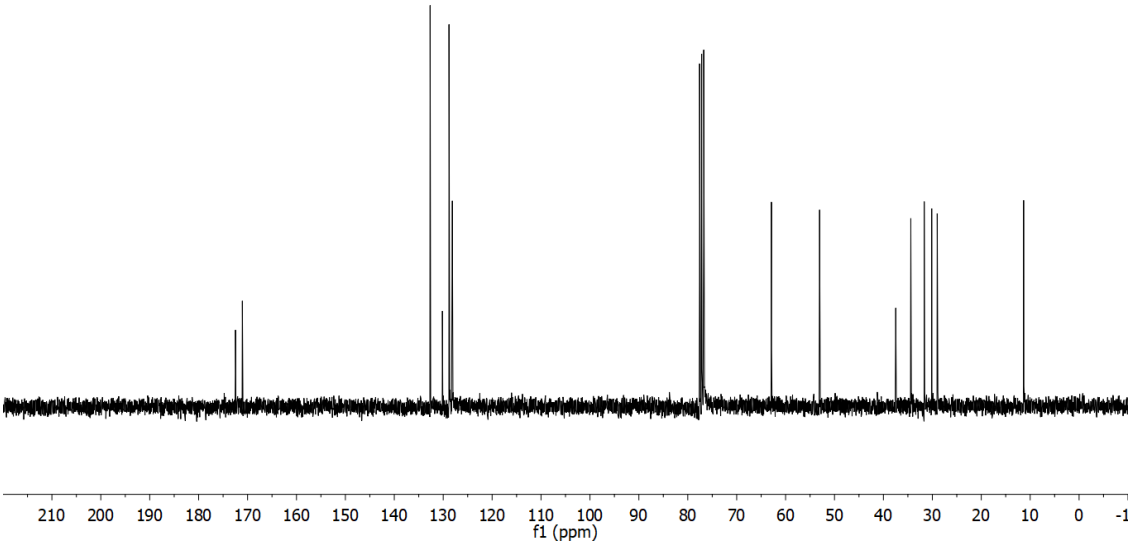


methyl 5-ethyl-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (401 a)

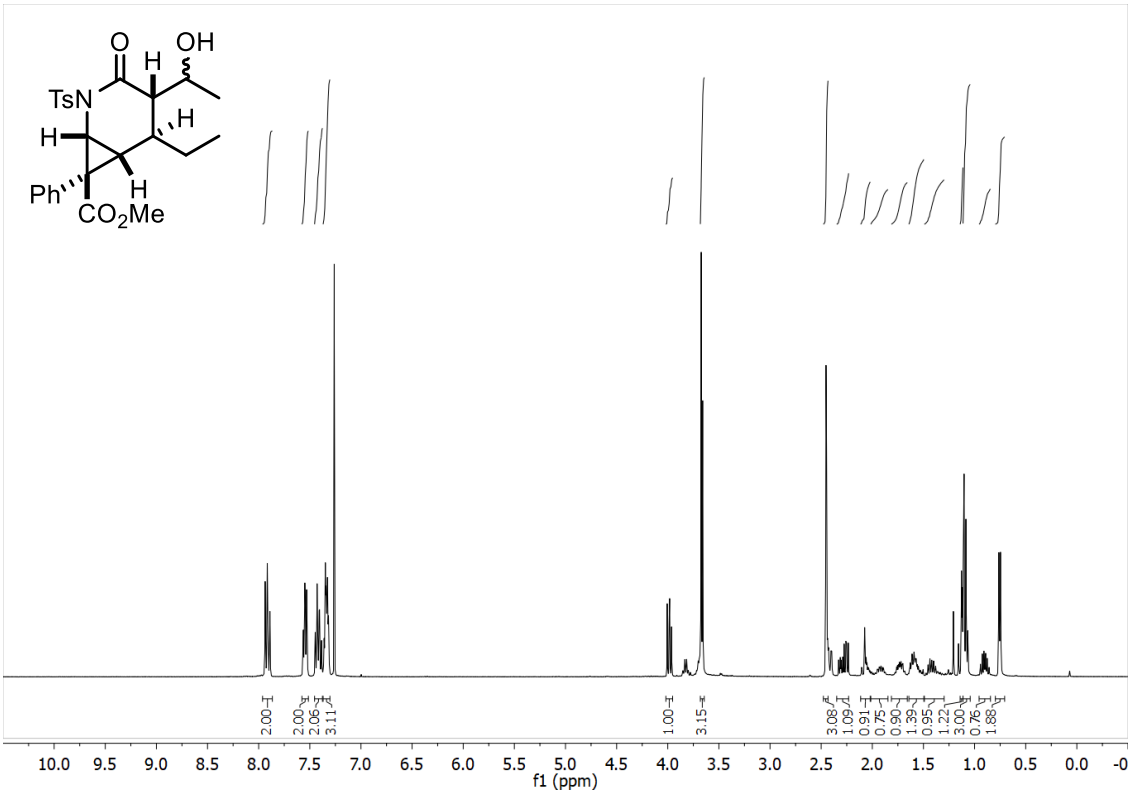


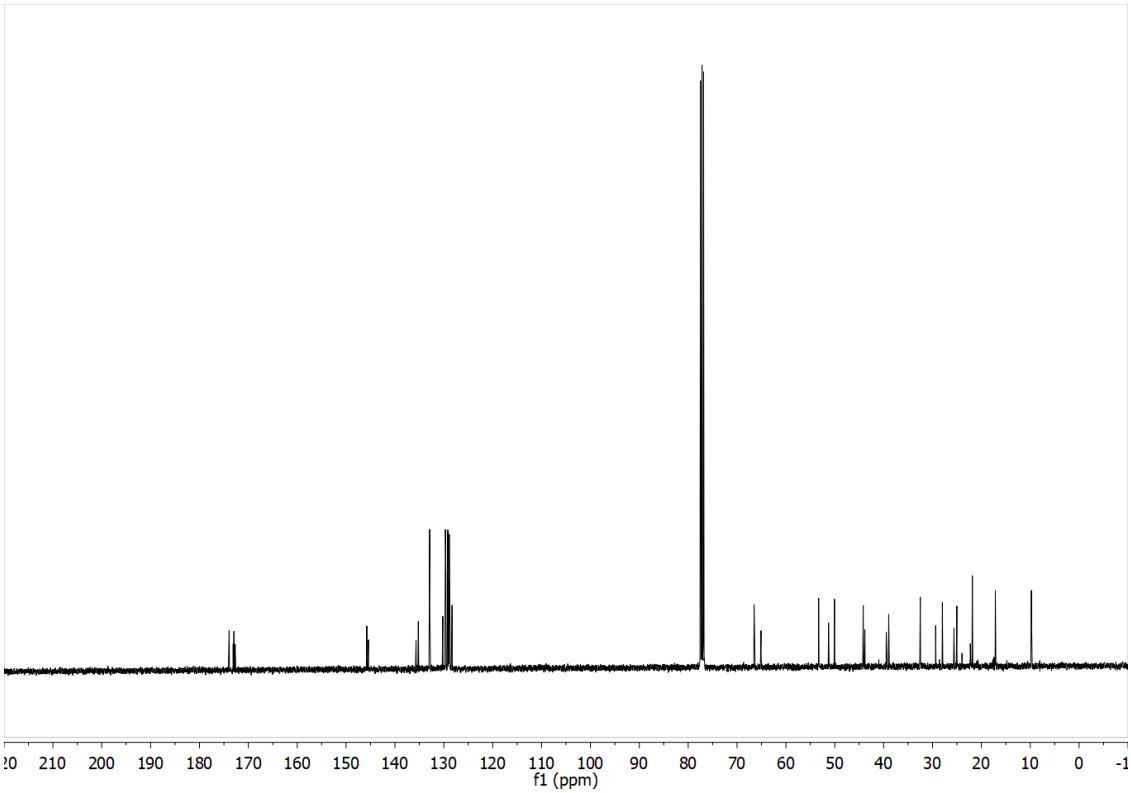
methyl 5-ethyl-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (400 a)



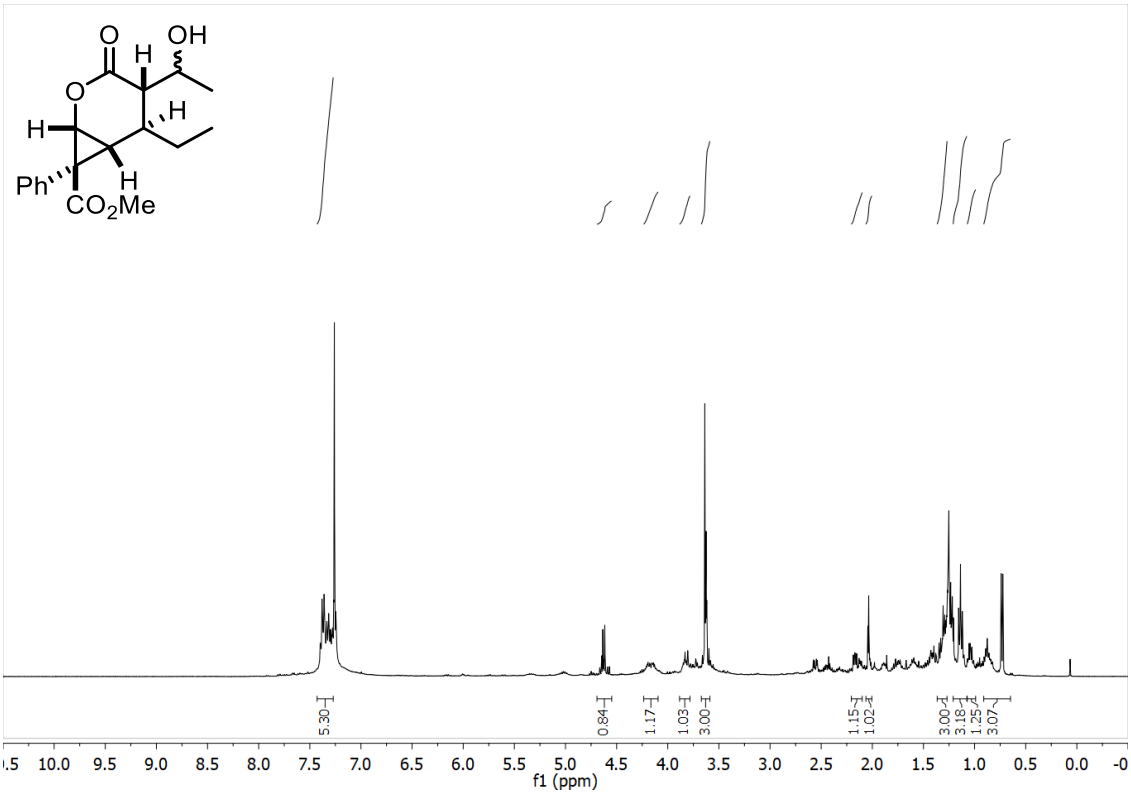


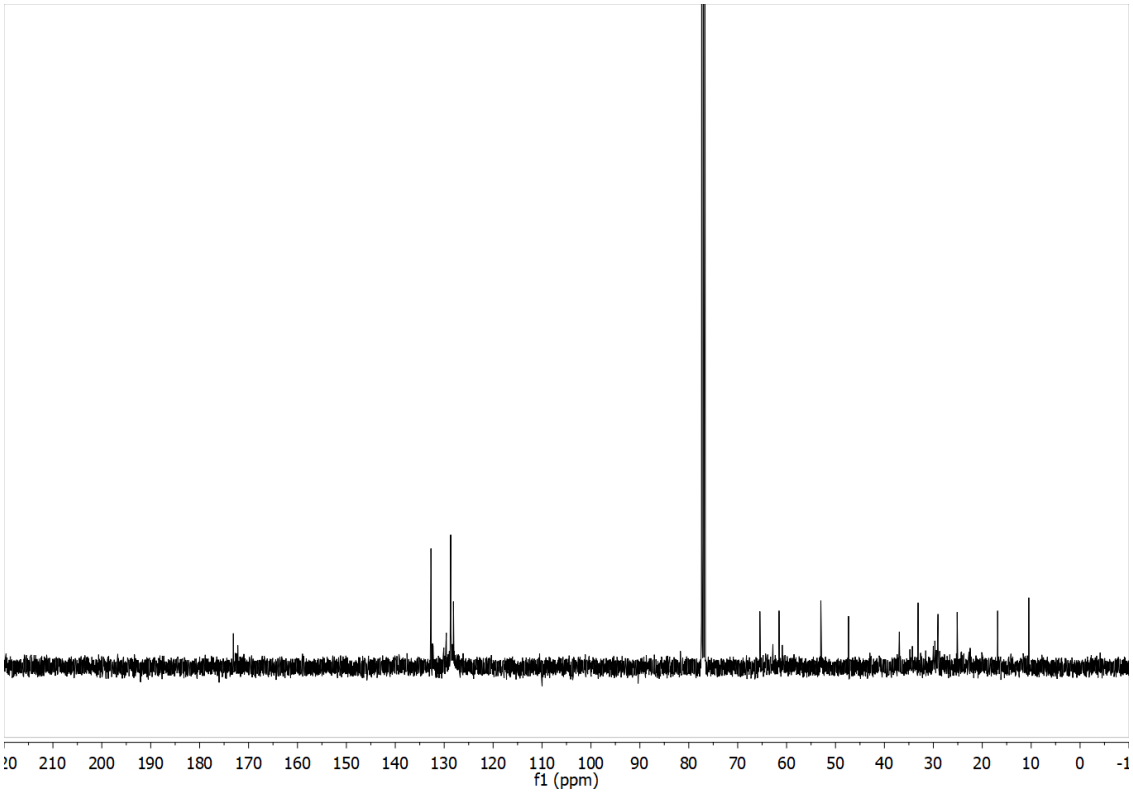
methyl 5-ethyl-4-(1-hydroxyethyl)-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (404)



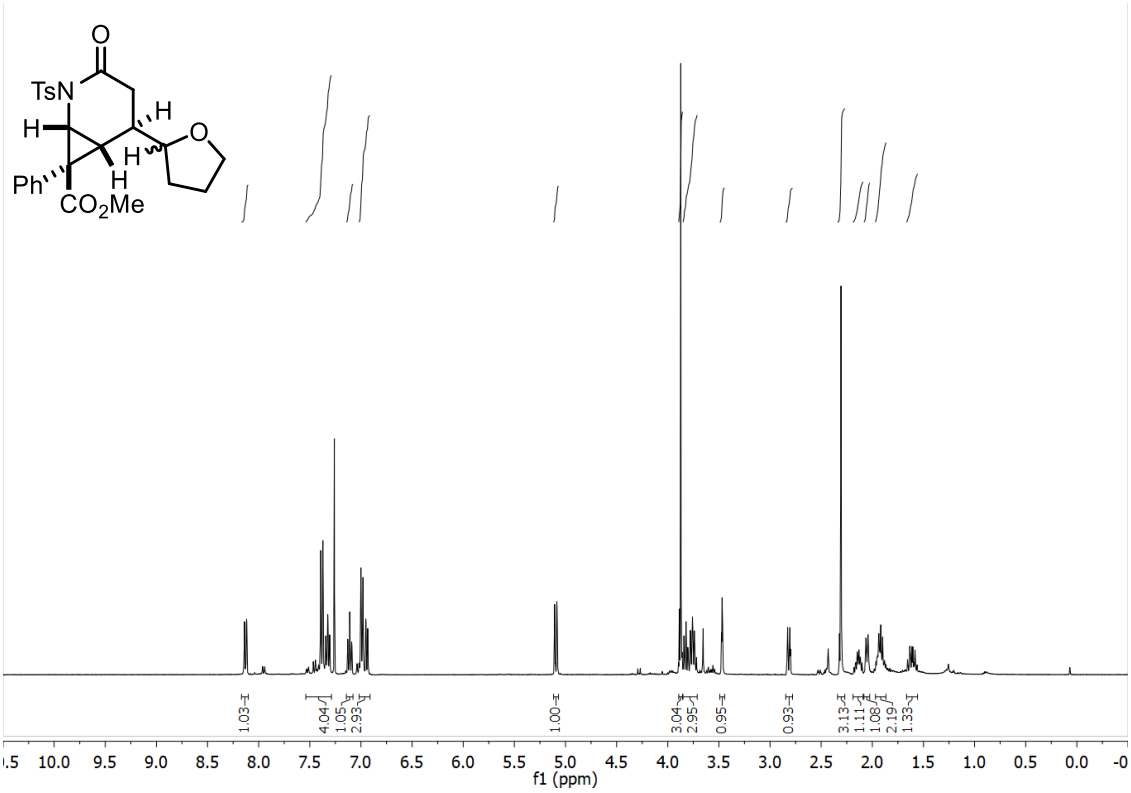


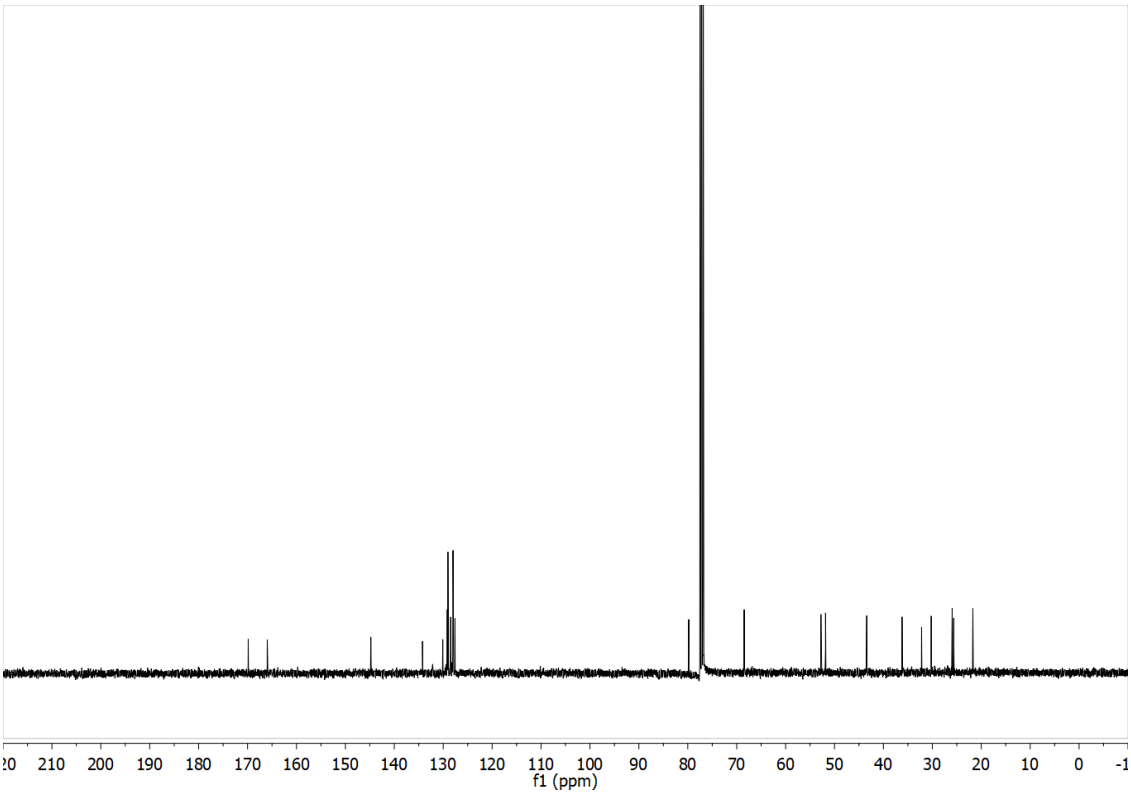
methyl 5-ethyl-4-(1-hydroxyethyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (403)



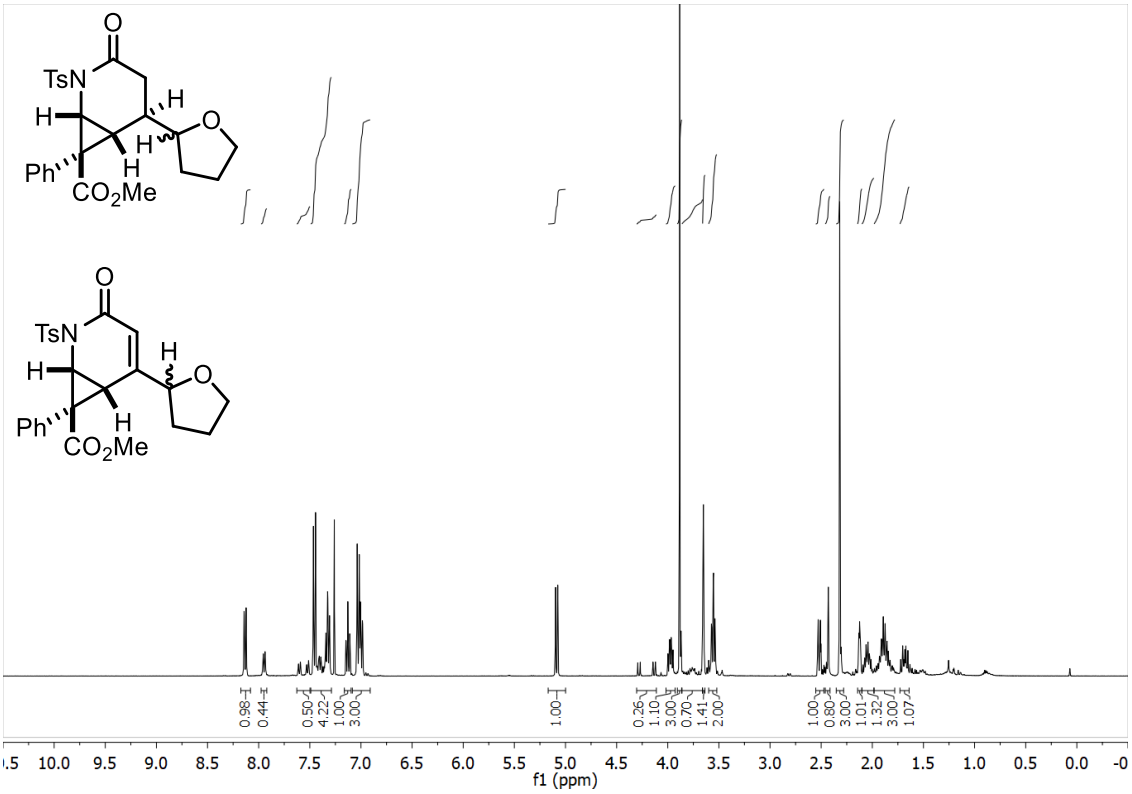


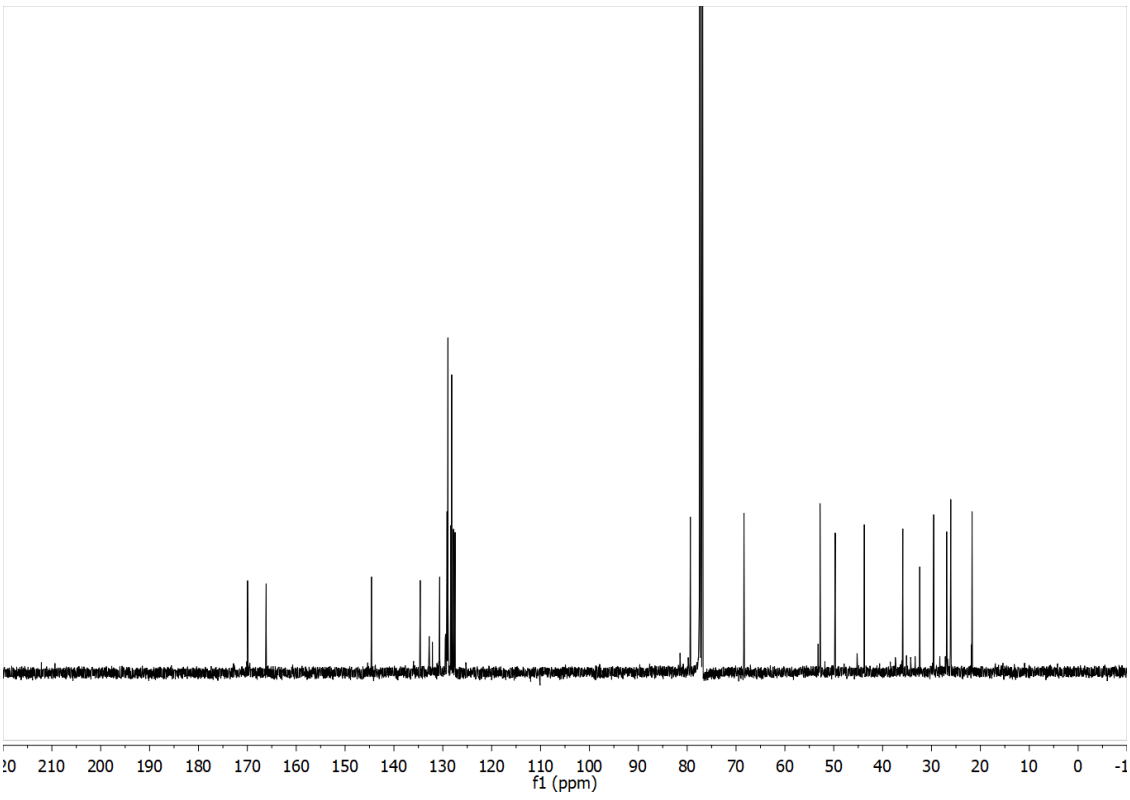
methyl 3-oxo-7-phenyl-5-(tetrahydrofuran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (412 a)



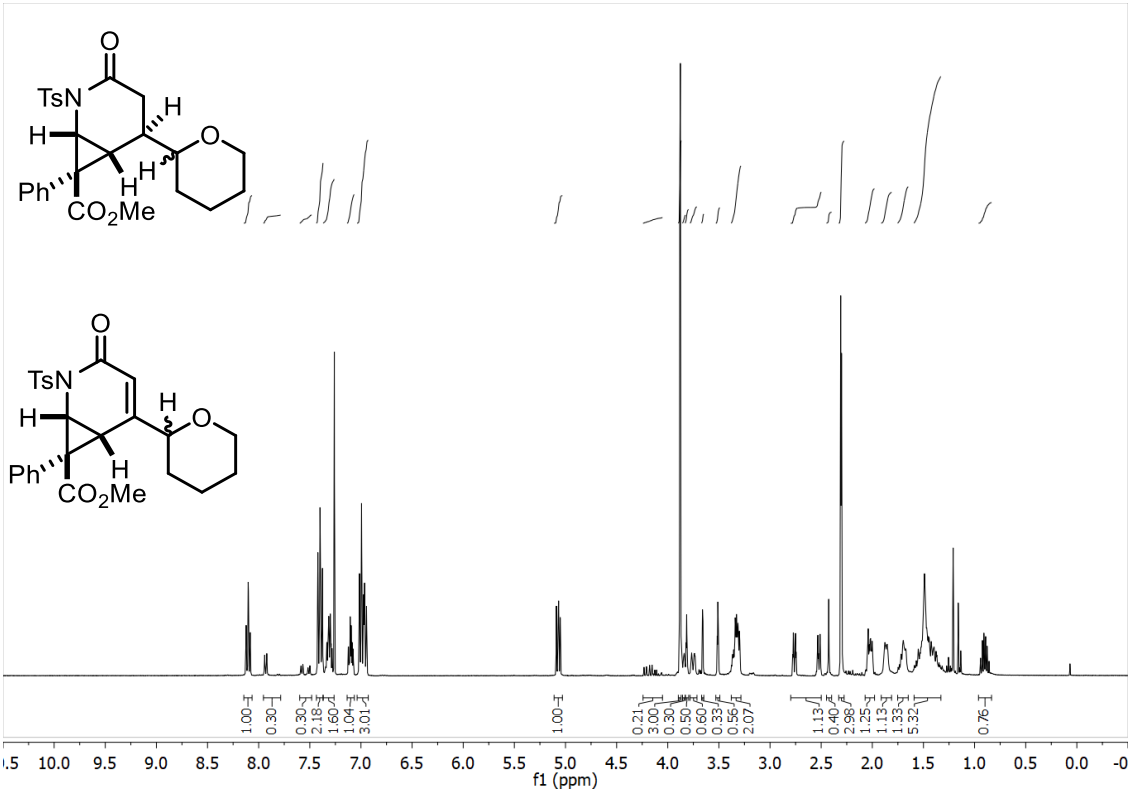


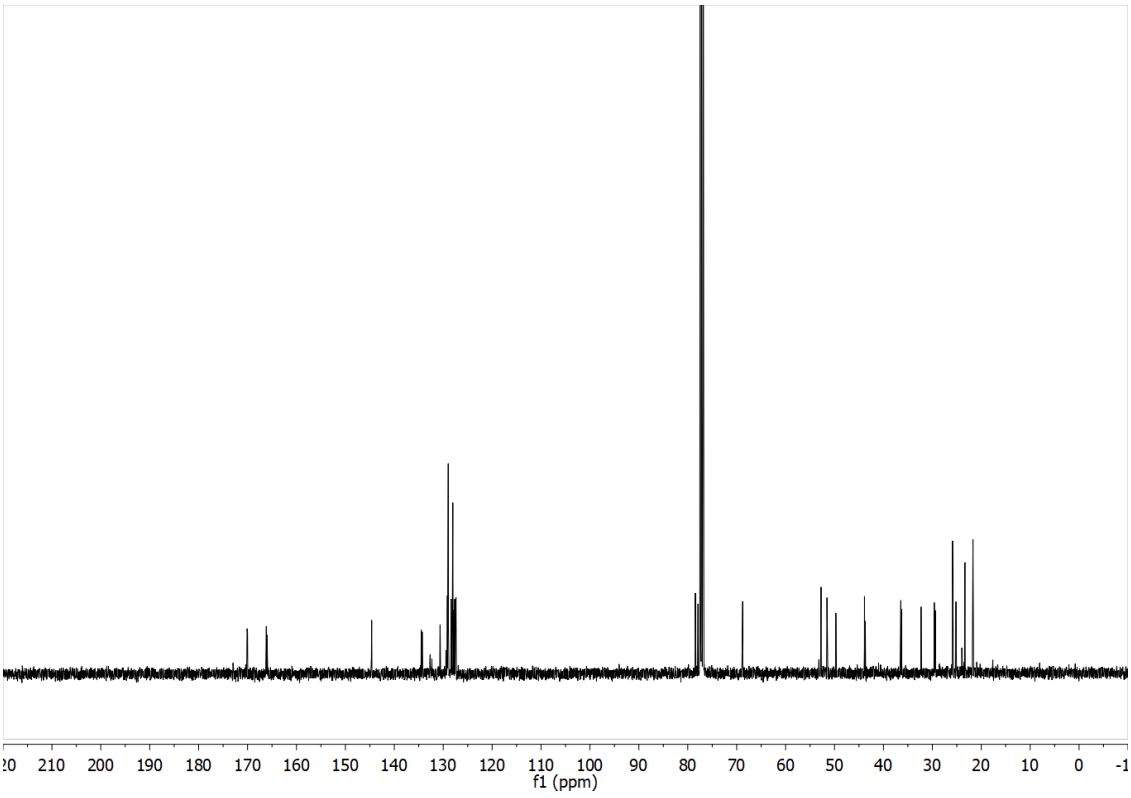
methyl 3-oxo-7-phenyl-5-(tetrahydrofuran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (412 a) and **methyl 3-oxo-7-phenyl-5-(tetrahydrofuran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (412 b)**



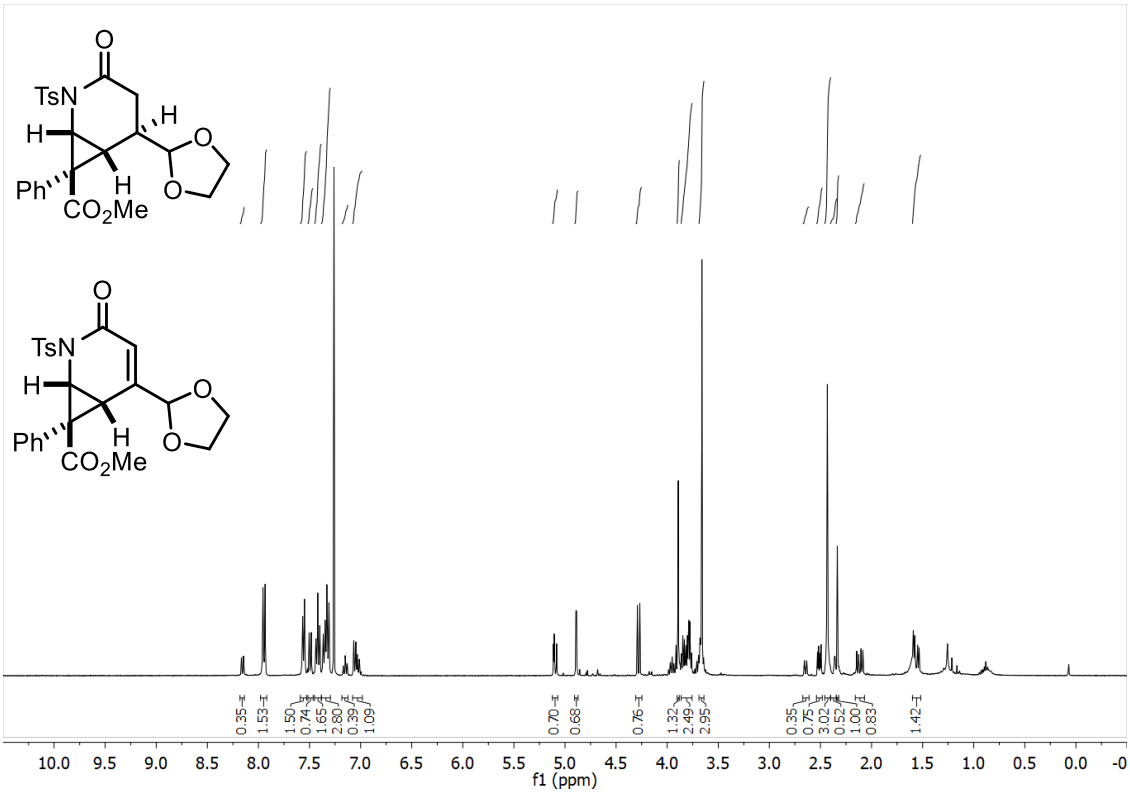


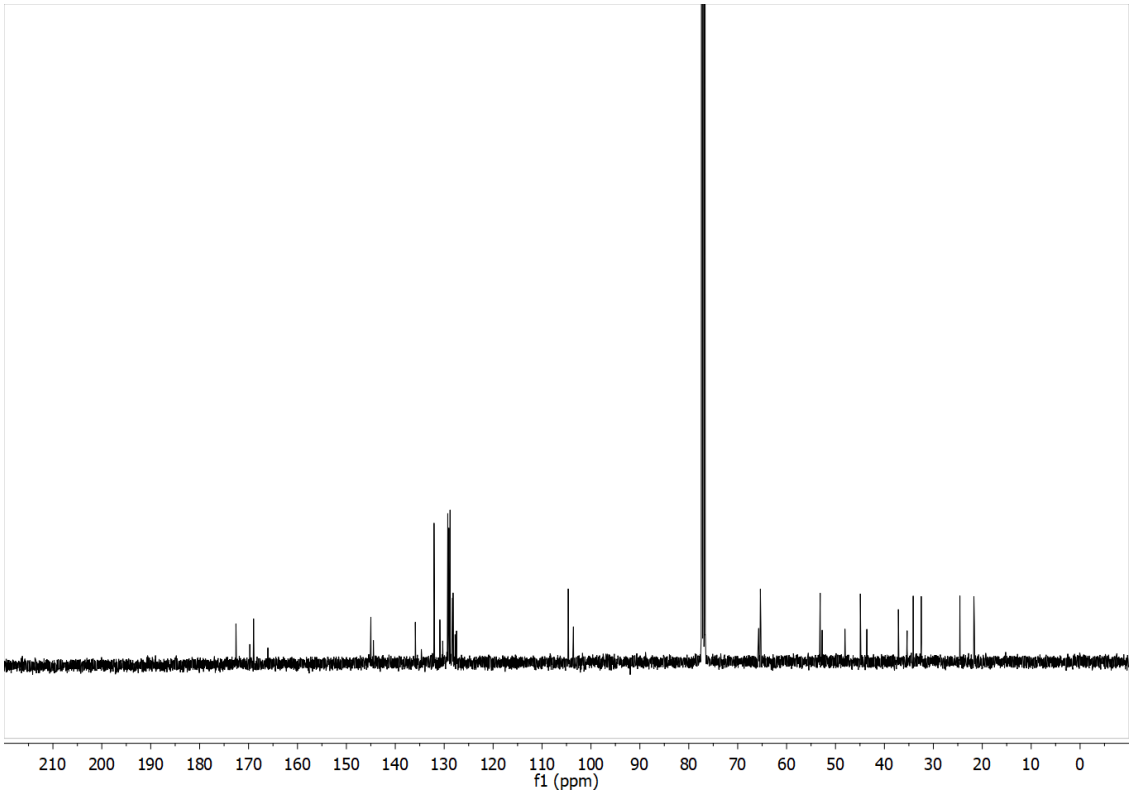
methyl 3-oxo-7-phenyl-5-(tetrahydro-2H-pyran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (414 a) and **methyl 3-oxo-7-phenyl-5-(tetrahydro-2H-pyran-2-yl)-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (414 b)**



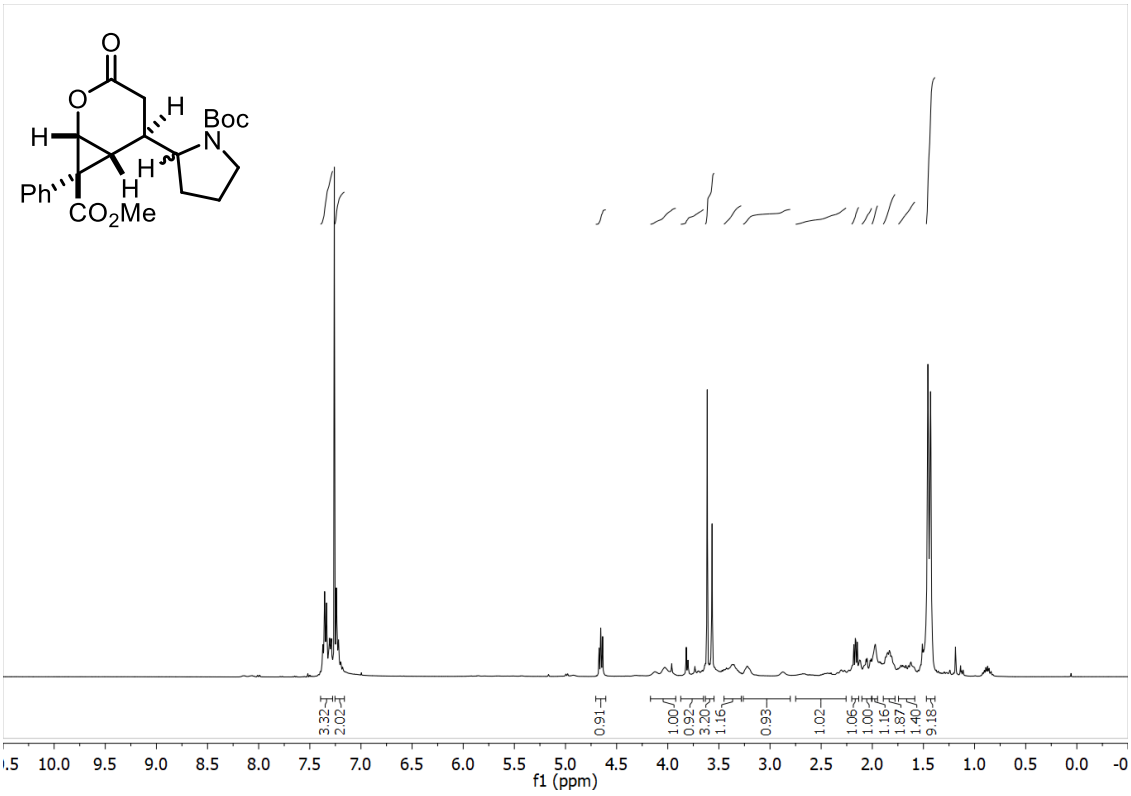


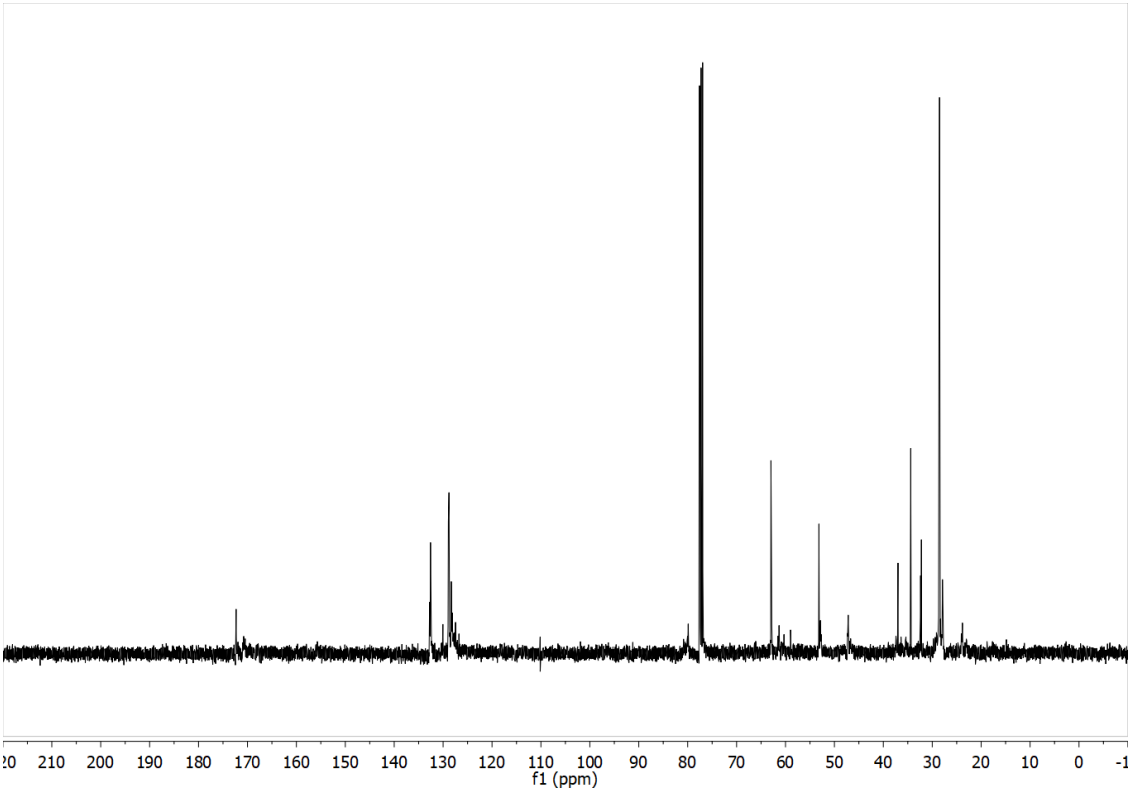
methyl 5-(1,3-dioxolan-2-yl)-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (417 a) and **methyl 5-(1,3-dioxolan-2-yl)-3-oxo-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]hept-4-ene-7-carboxylate (417 b)**



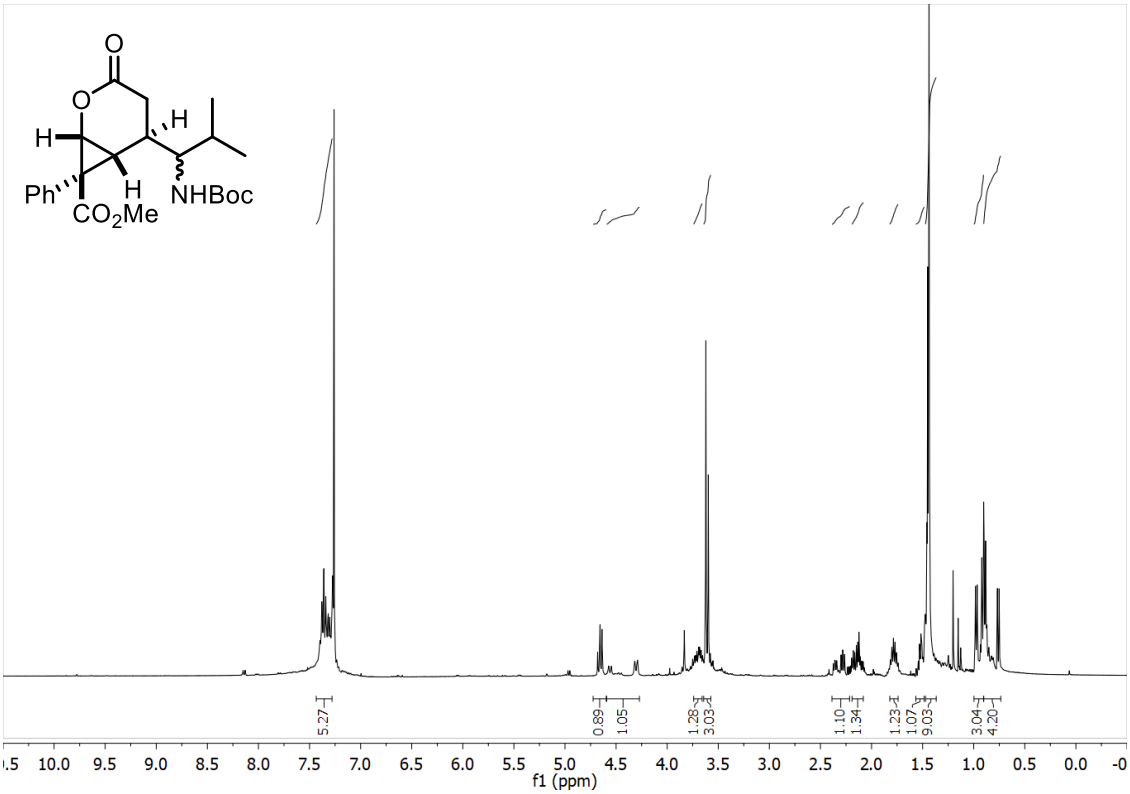


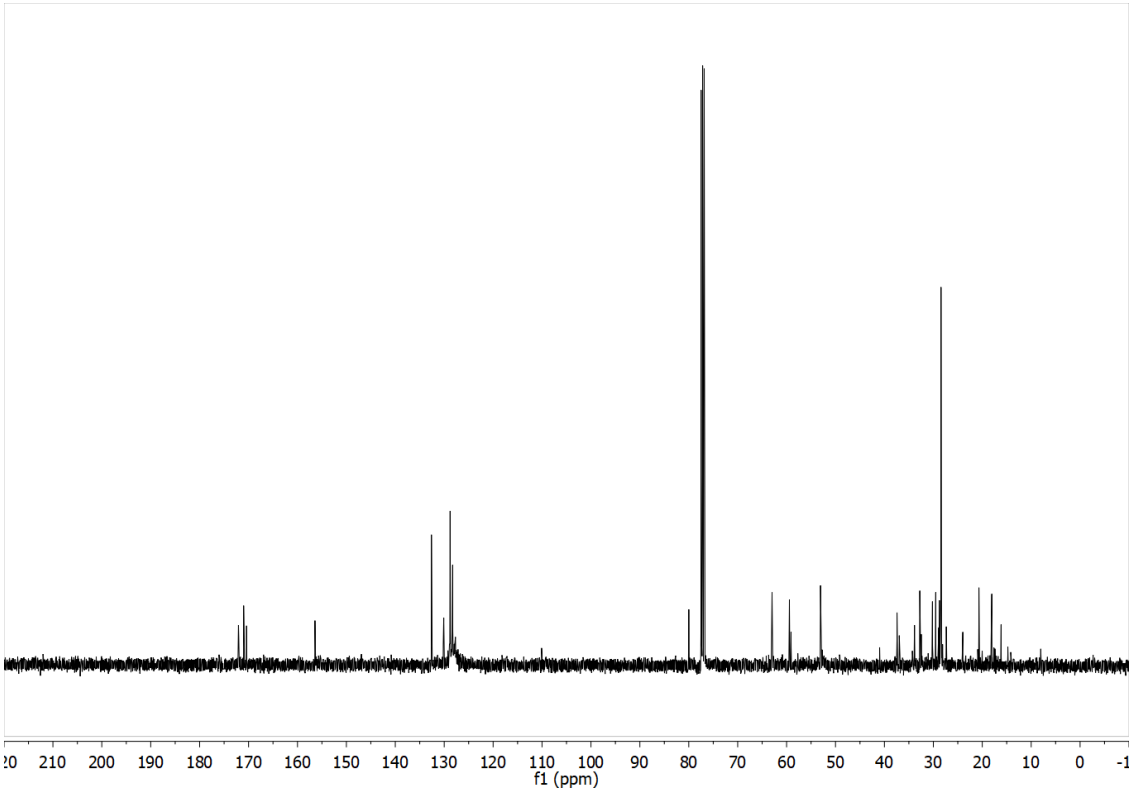
***tert*-butyl 2-(7-(methoxycarbonyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptan-5-yl)pyrrolidine-1-carboxylate (424)**



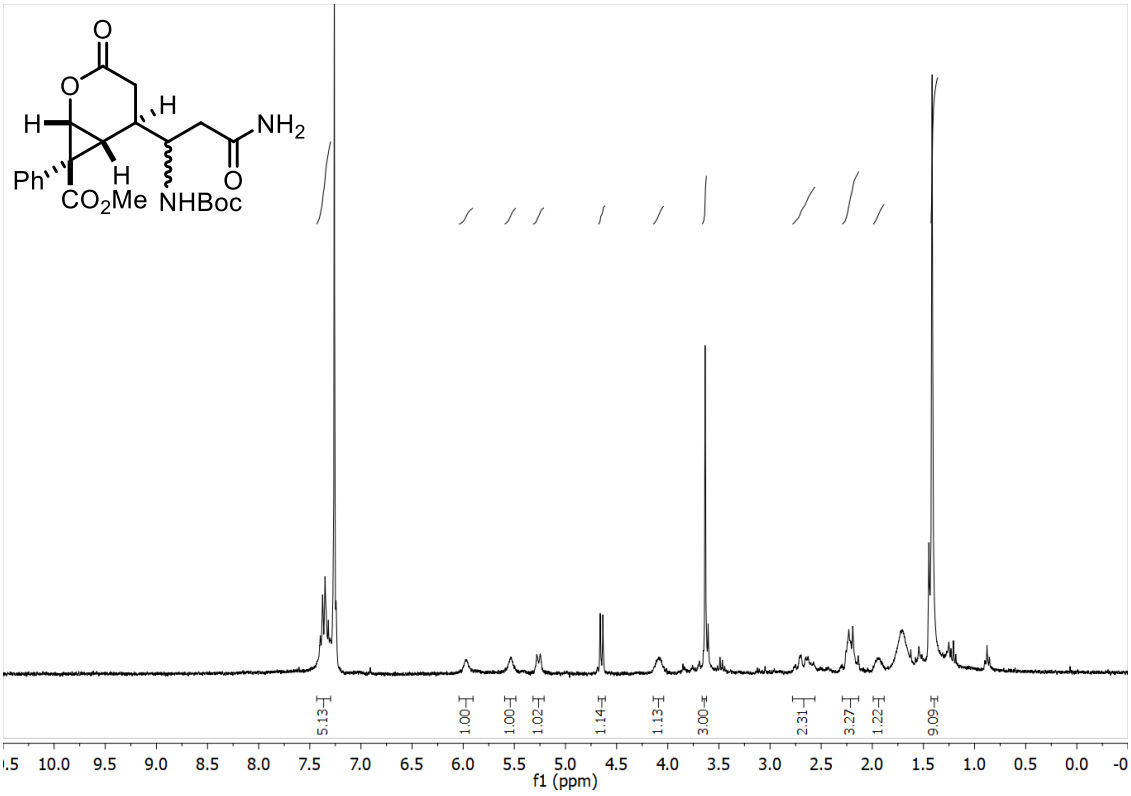


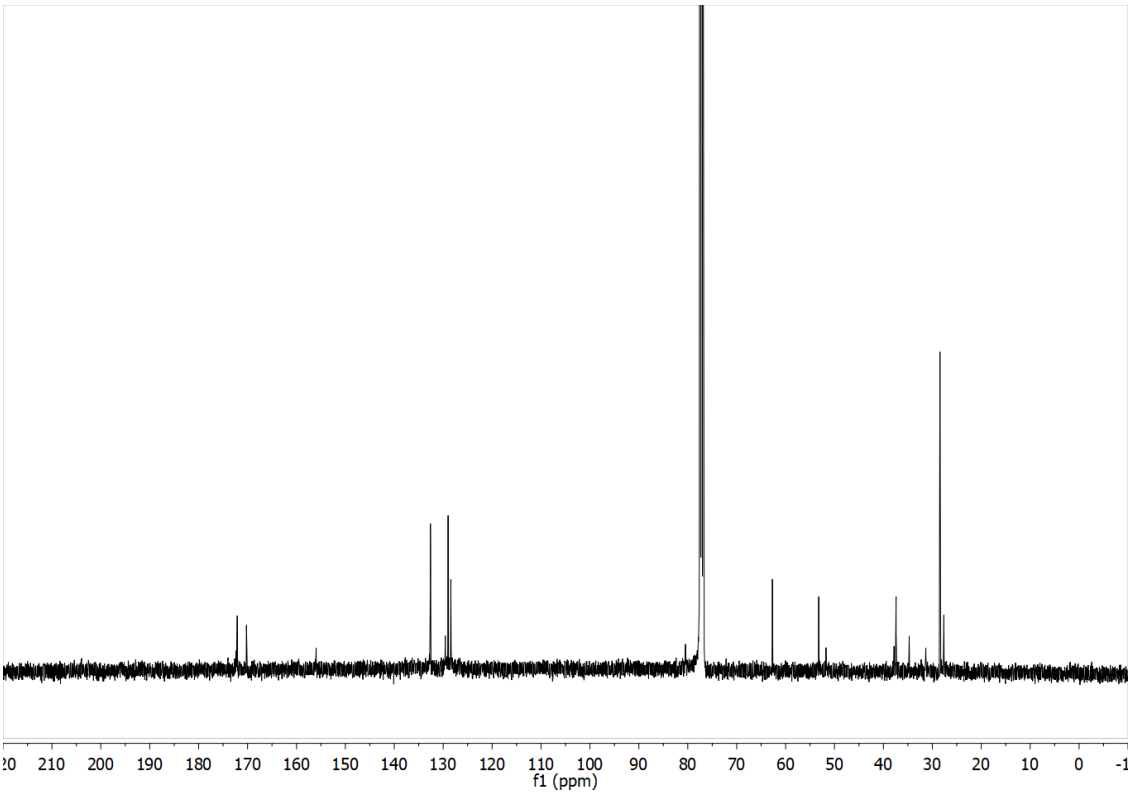
methyl 5-(1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (426 d)



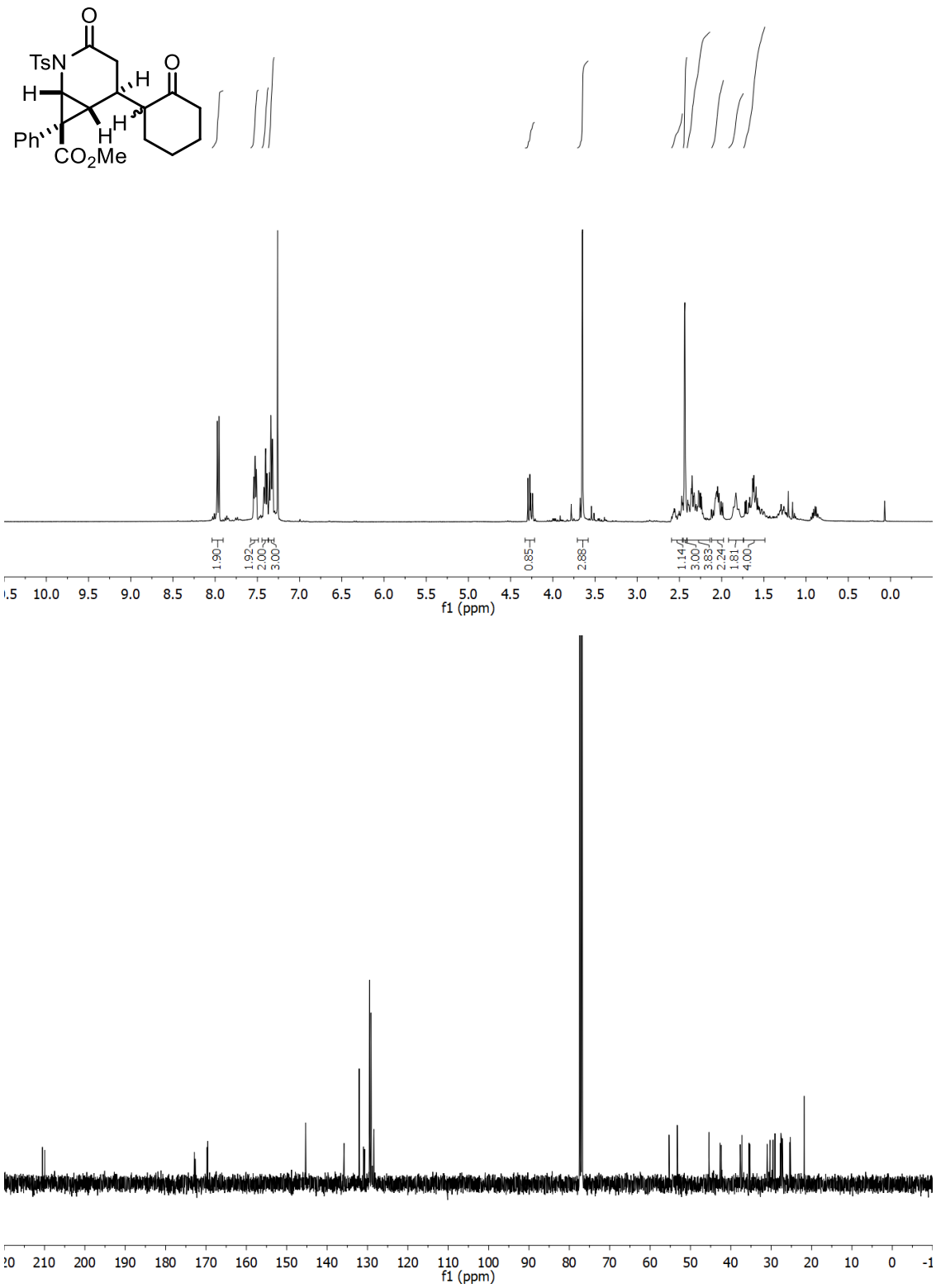


methyl 5-(3-amino-1-((*tert*-butoxycarbonyl)amino)-3-oxopropyl)-3-oxo-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate (426 b)

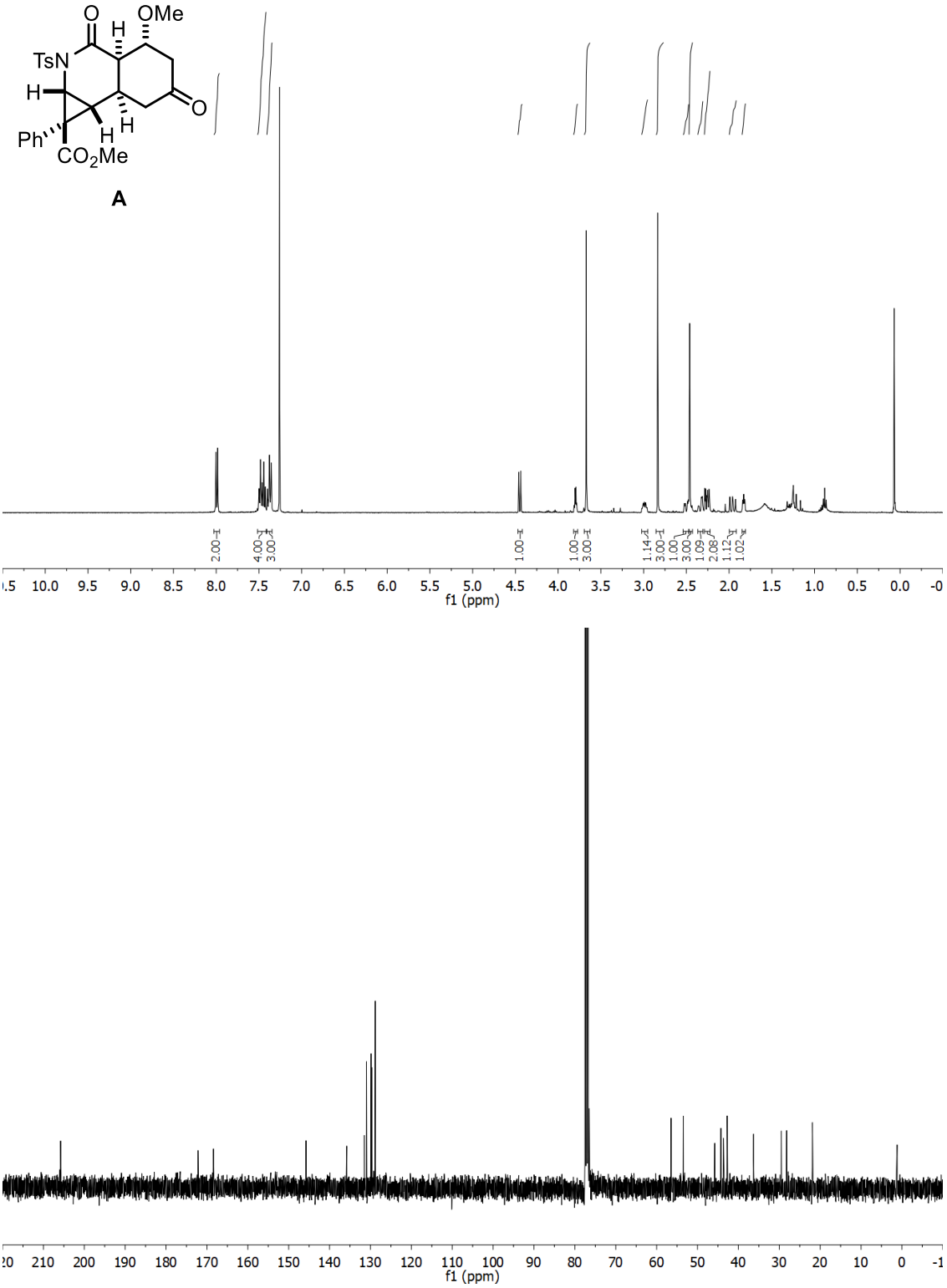




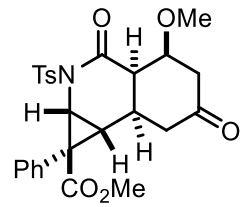
methyl 3-oxo-5-(2-oxocyclohexyl)-7-phenyl-2-tosyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (434)



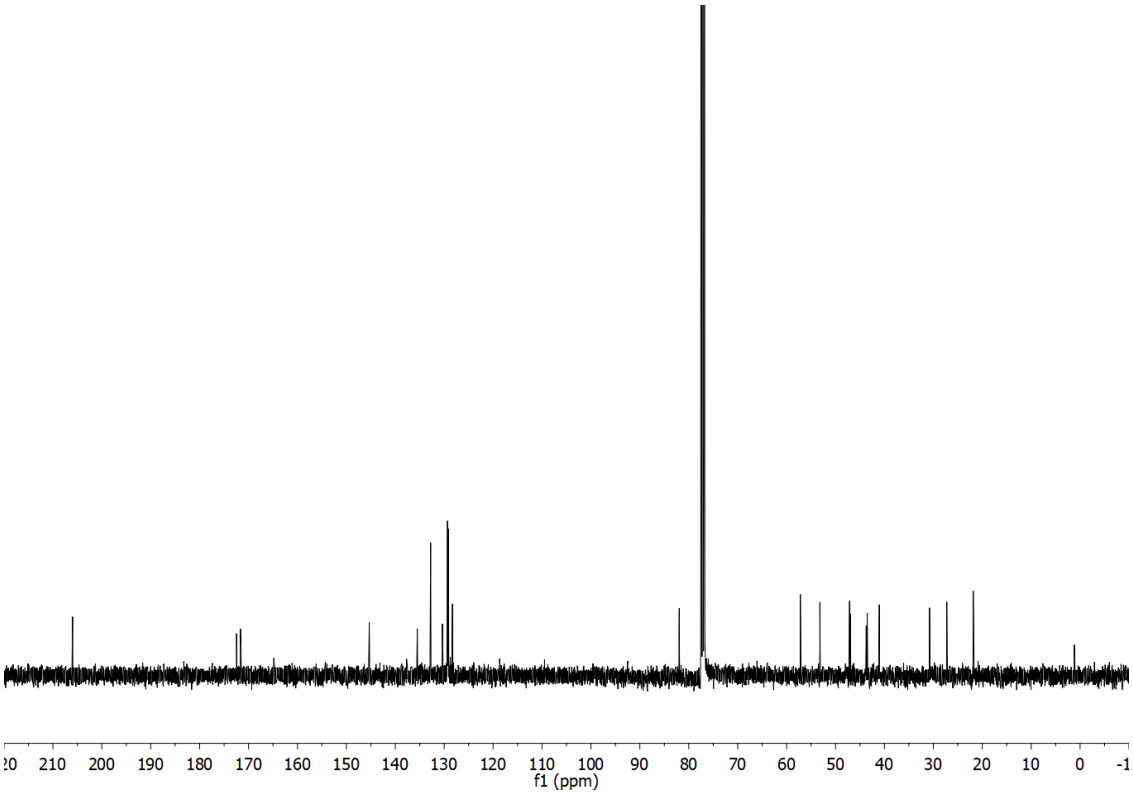
methyl 4-methoxy-3,6-dioxo-1-phenyl-2-tosyldecahydro-1H-cyclopropa[c]isoquinoline-1-carboxylate (446 a A)



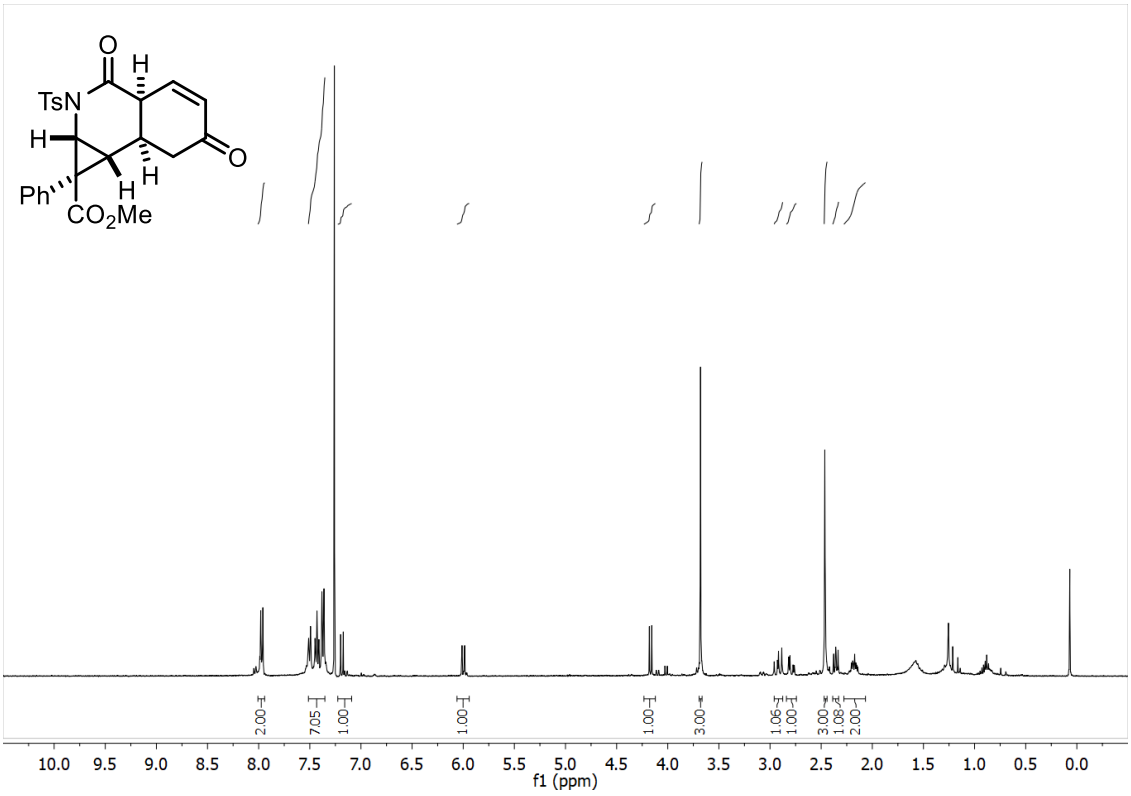
methyl 4-methoxy-3,6-dioxo-1-phenyl-2-tosyldecahydro-1H-cyclopropa[c]isoquinoline-1-carboxylate (446 a B)

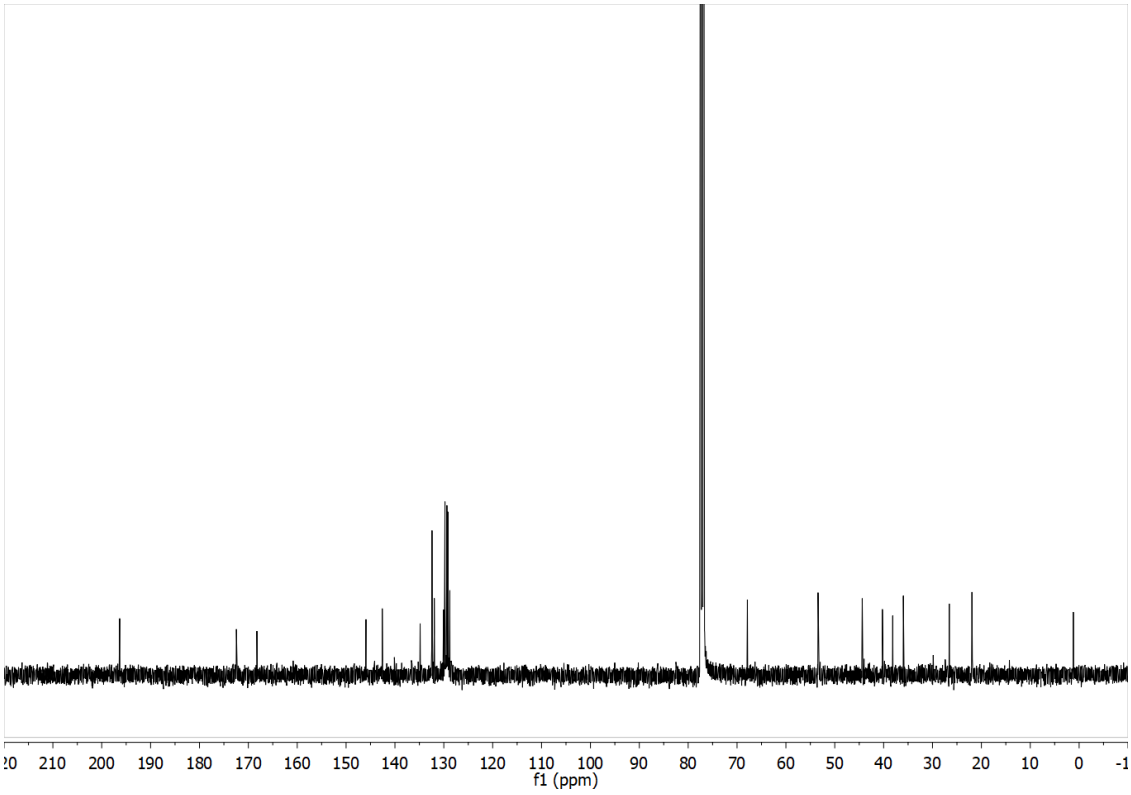


B

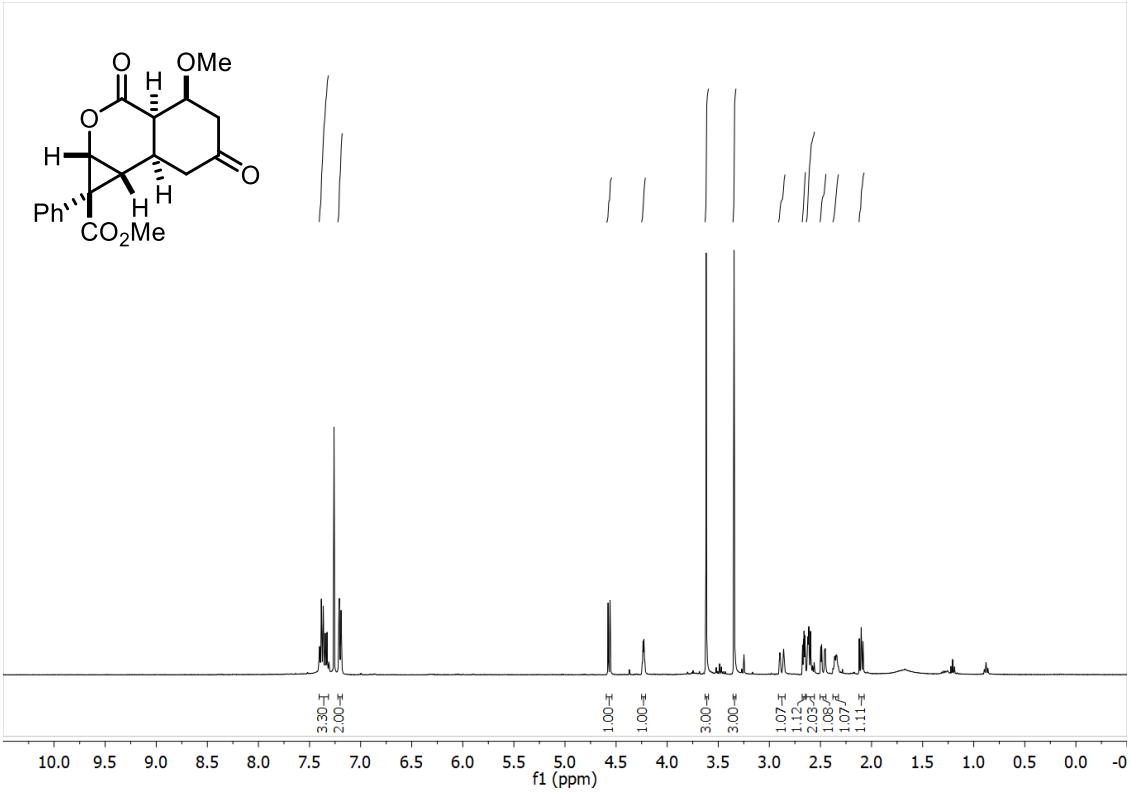


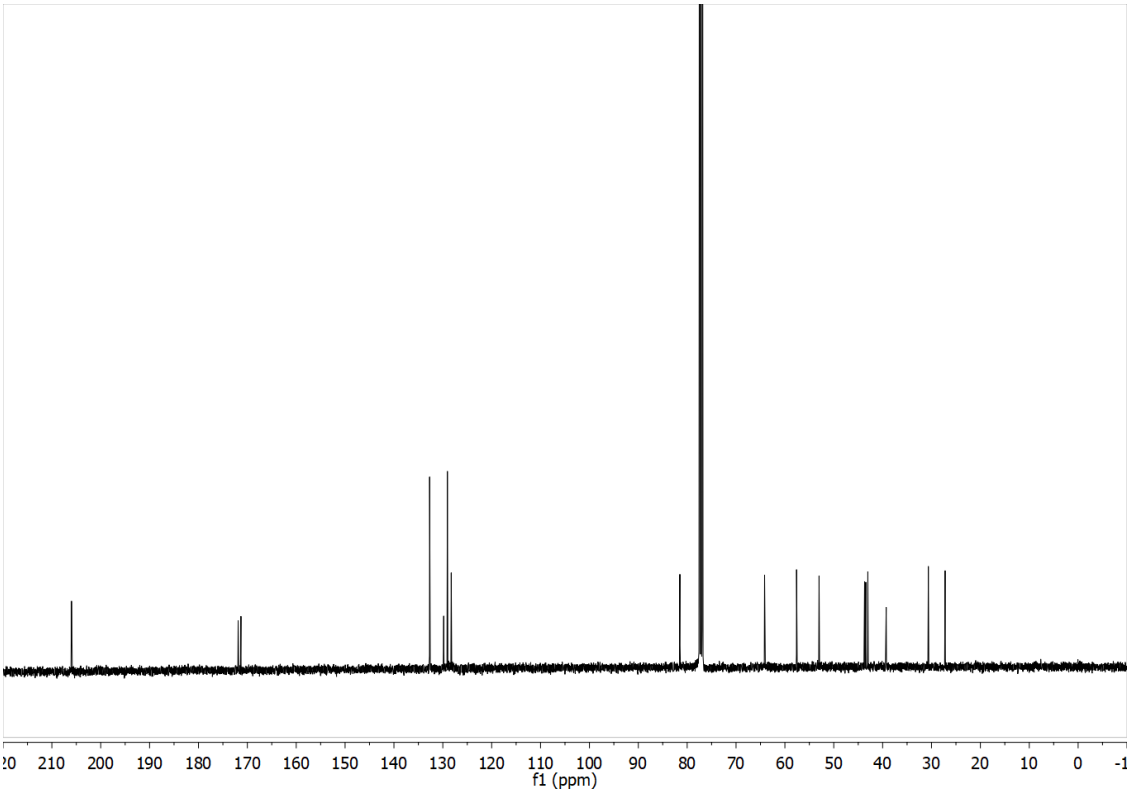
methyl 3,6-dioxo-1-phenyl-2-tosyl-1a,2,3,3a,6,7,7a,7b-octahydro-1*H*-cyclopropa[c]isoquinoline-1-carboxylate (459)



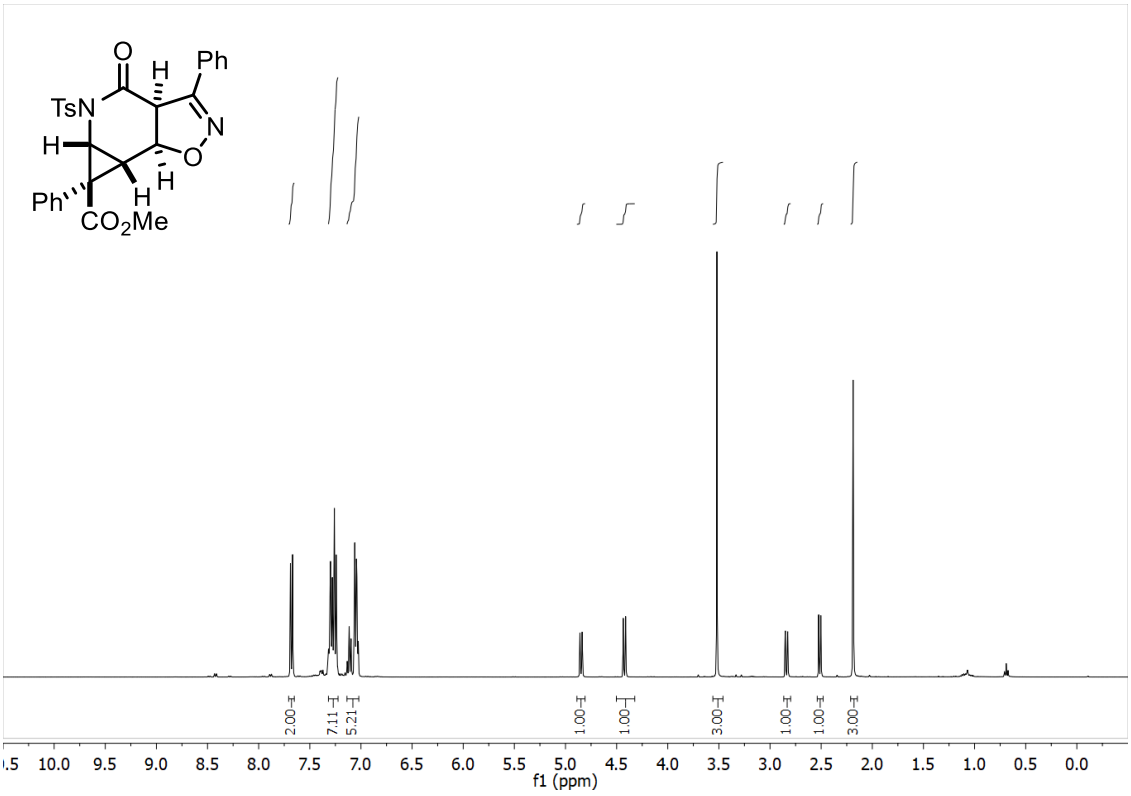


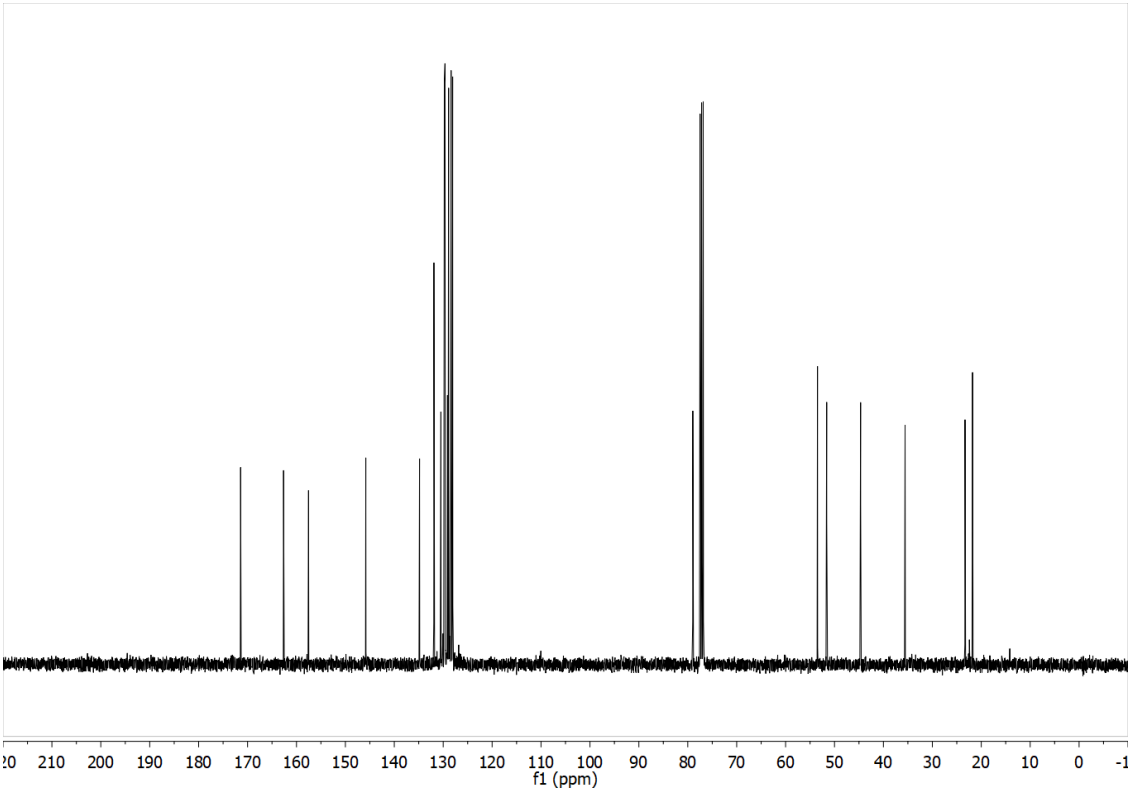
methyl 4-methoxy-3,6-dioxo-1-phenyldecahydrocyclopropa[c]isochromene-1-carboxylate (445 a)



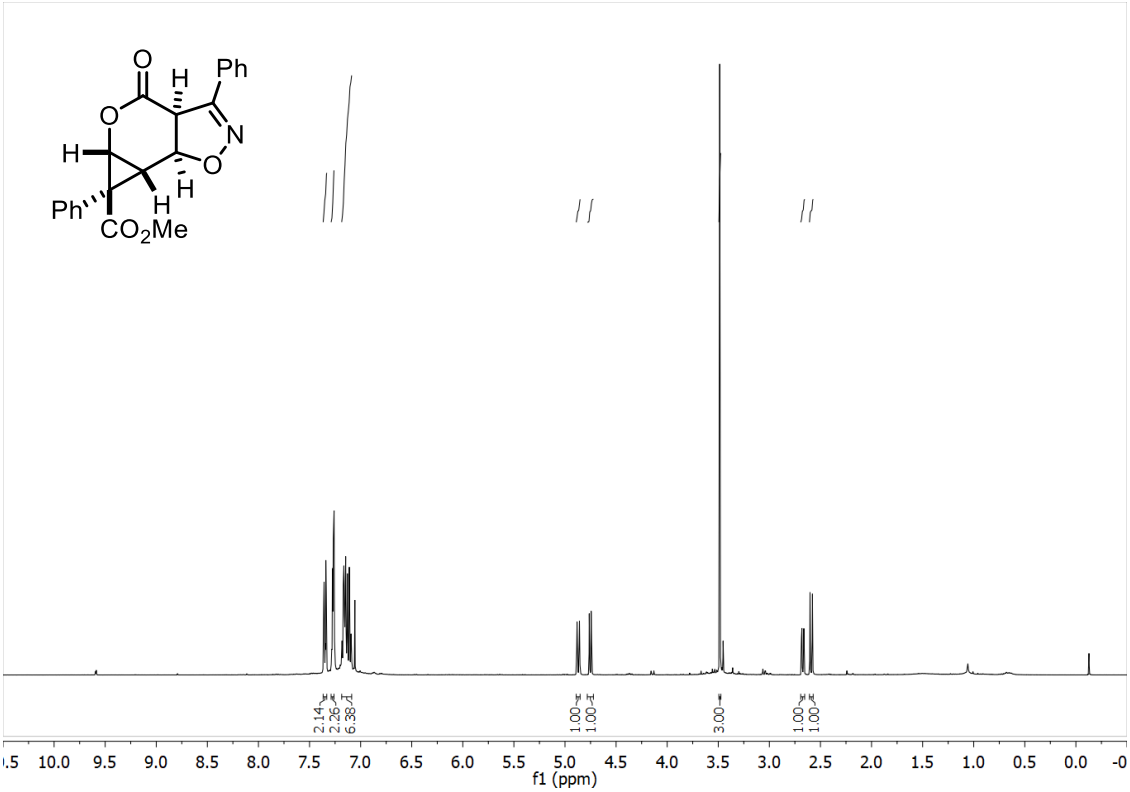


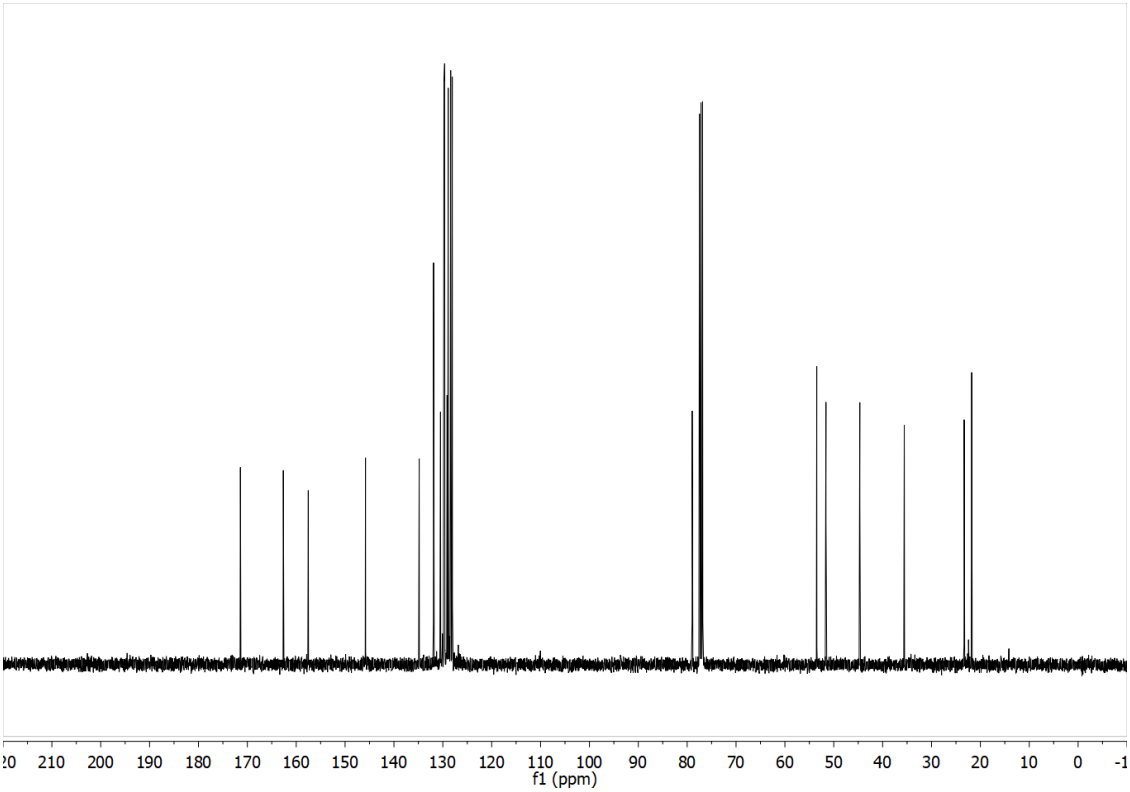
methyl 4-oxo-3,6-diphenyl-5-tosyl-3a,5,5a,6,6a,6b-hexahydro-4H-cyclopropa[b]isoxazolo[5,4-d]pyridine-6-carboxylate (470)



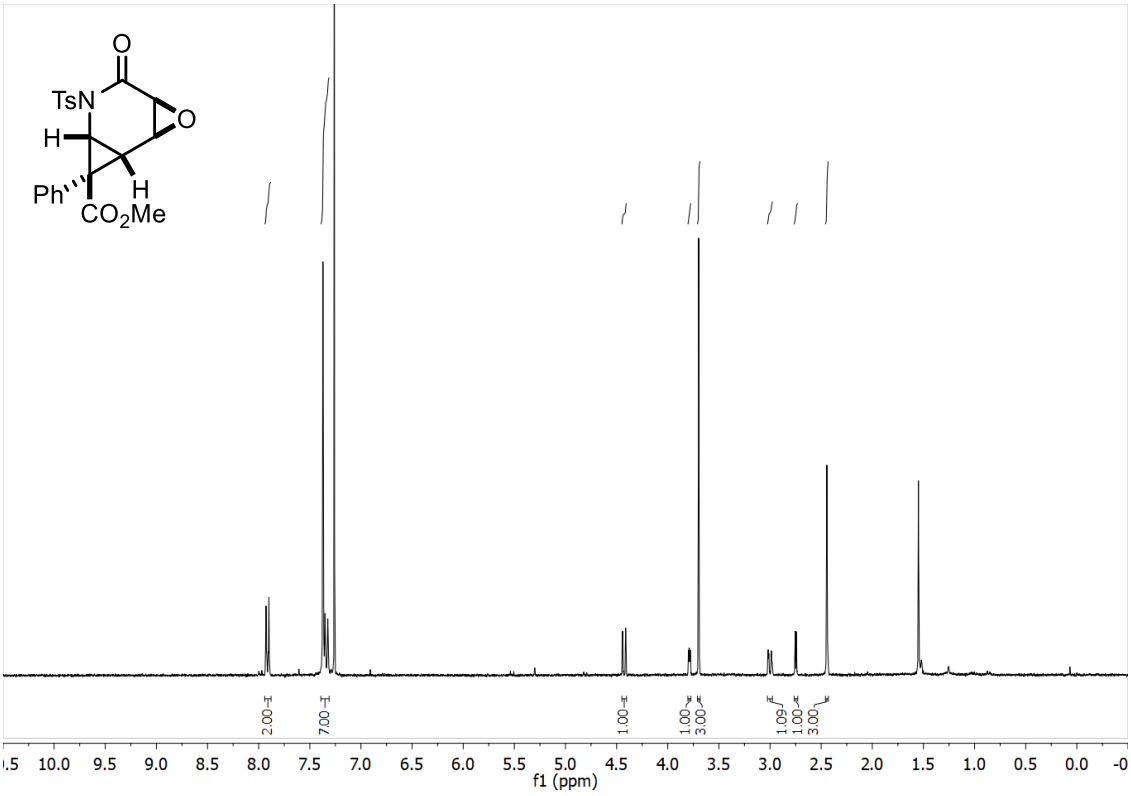


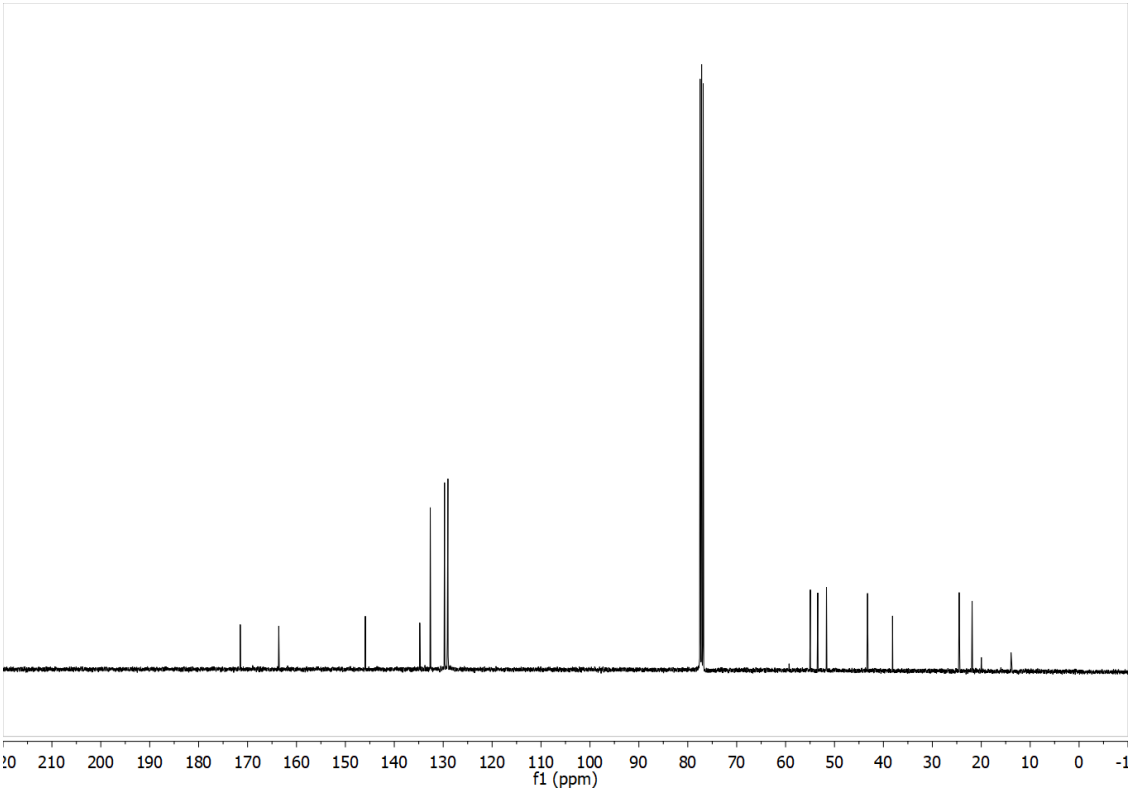
methyl 4-oxo-3,6-diphenyl-3a,4,5a,6,6a,6b-hexahydrocyclopropa[5,6]pyrano[3,4-d]isoxazole-6-carboxylate (469)



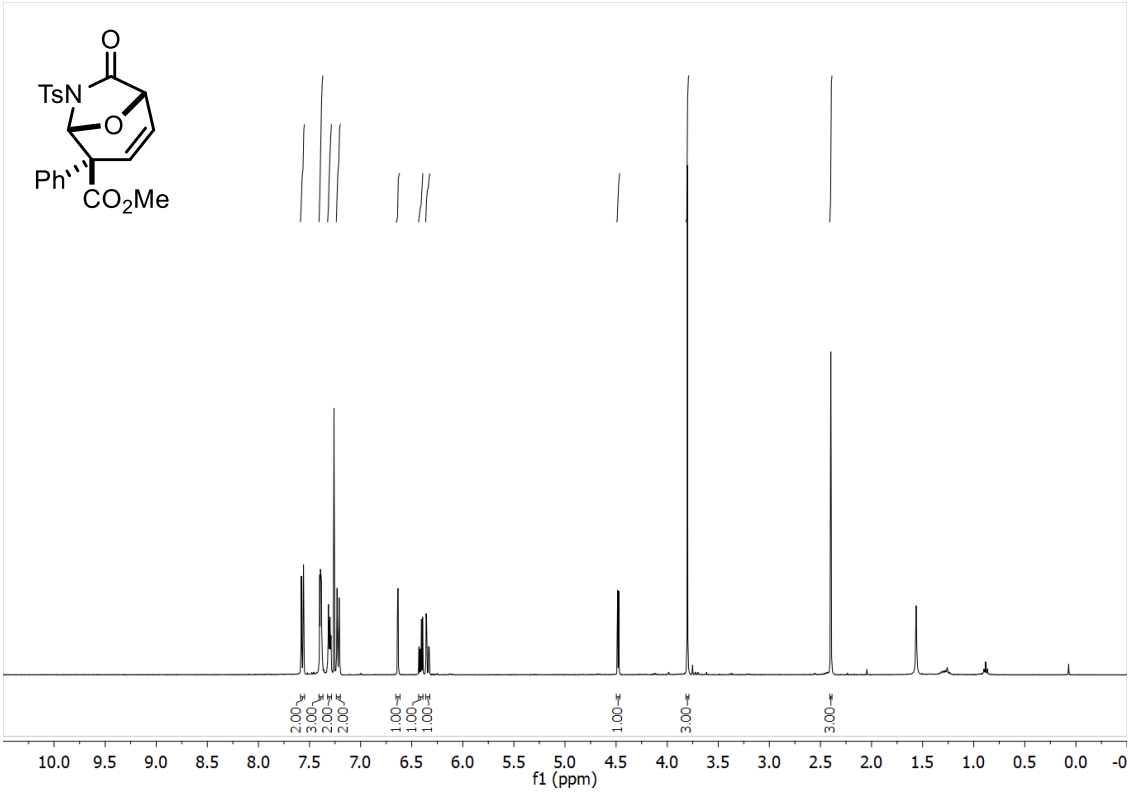


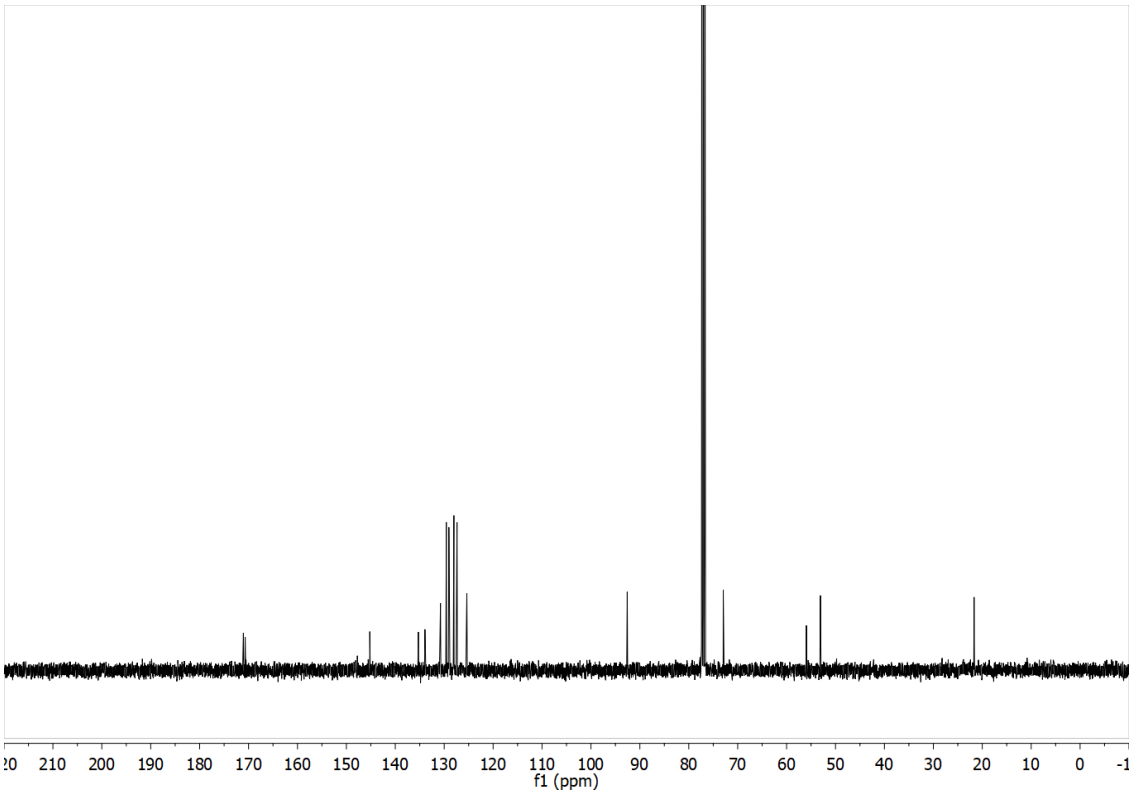
methyl 5-oxo-8-phenyl-6-tosyl-3-oxa-6-azatricyclo[5.1.0.02,4]octane-8-carboxylate (498)



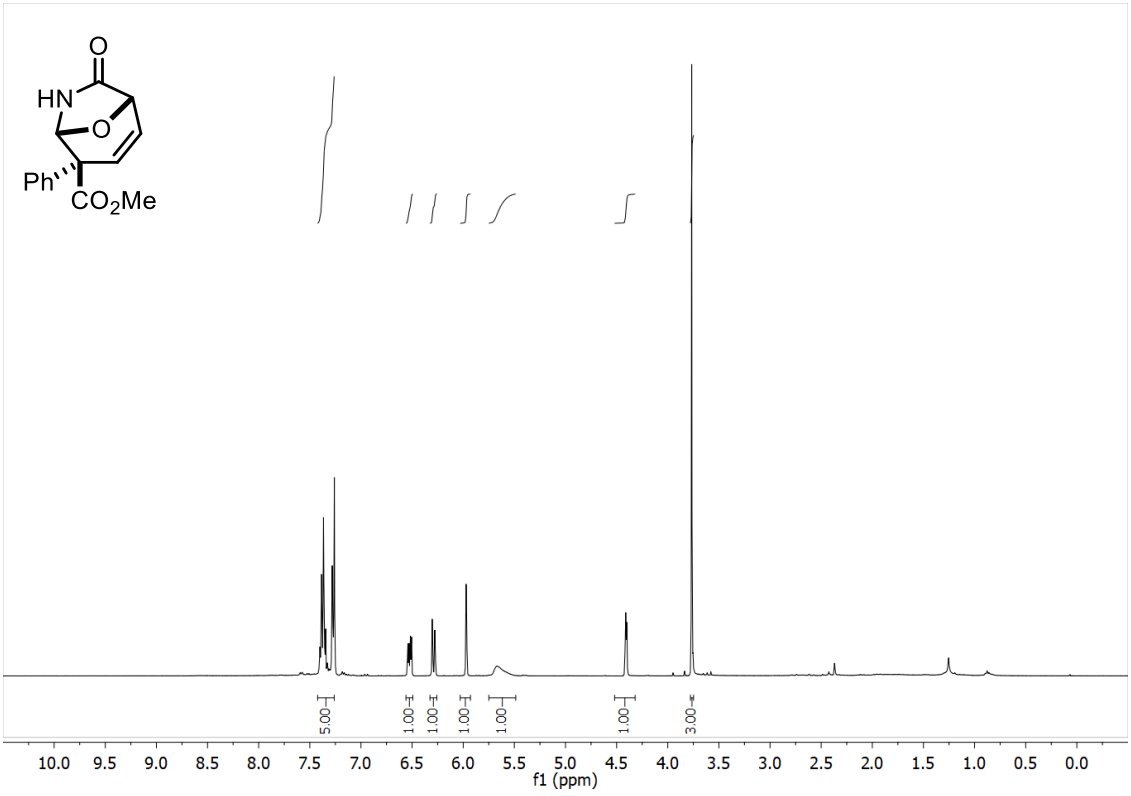


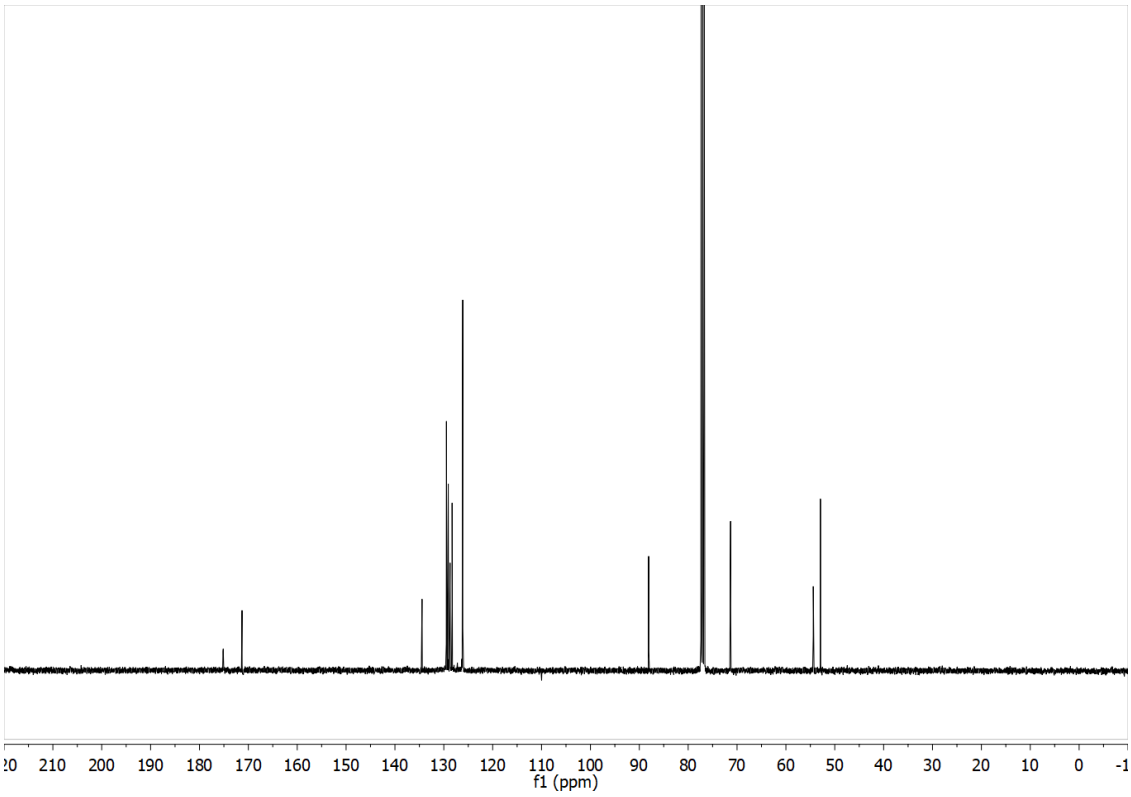
methyl 7-oxo-4-phenyl-6-tosyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (511)



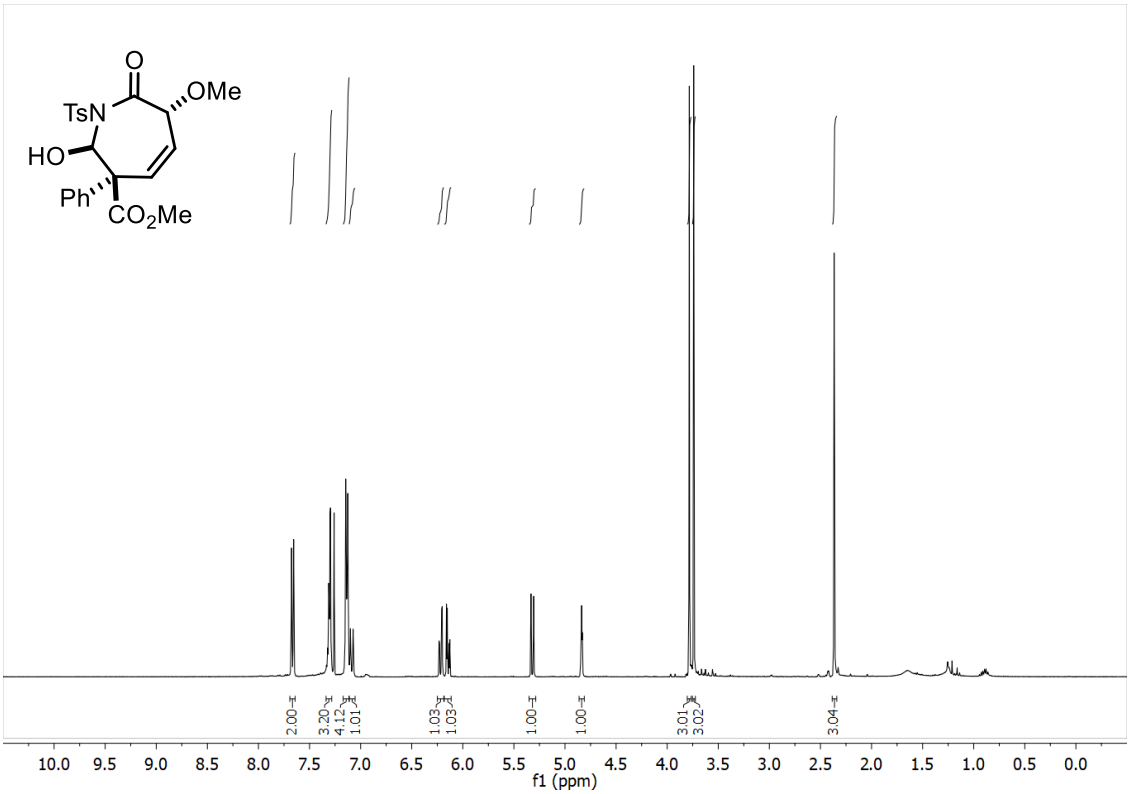


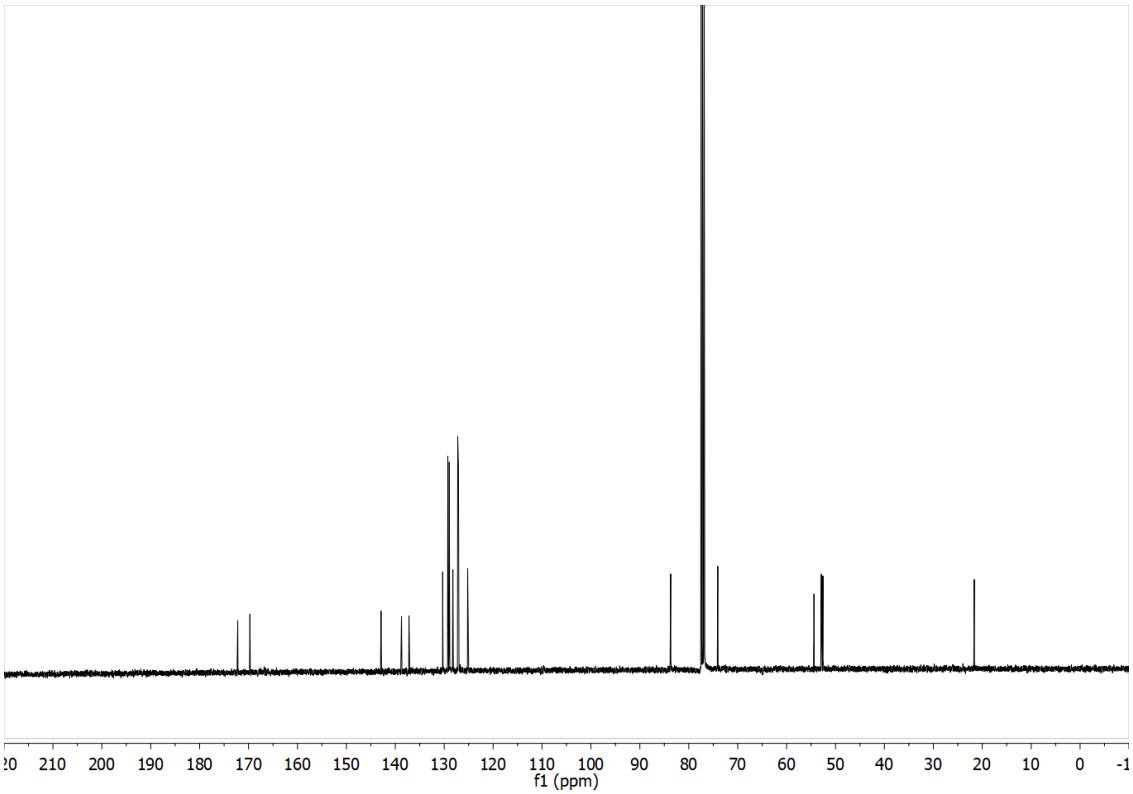
methyl 7-oxo-4-phenyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4-carboxylate (555)



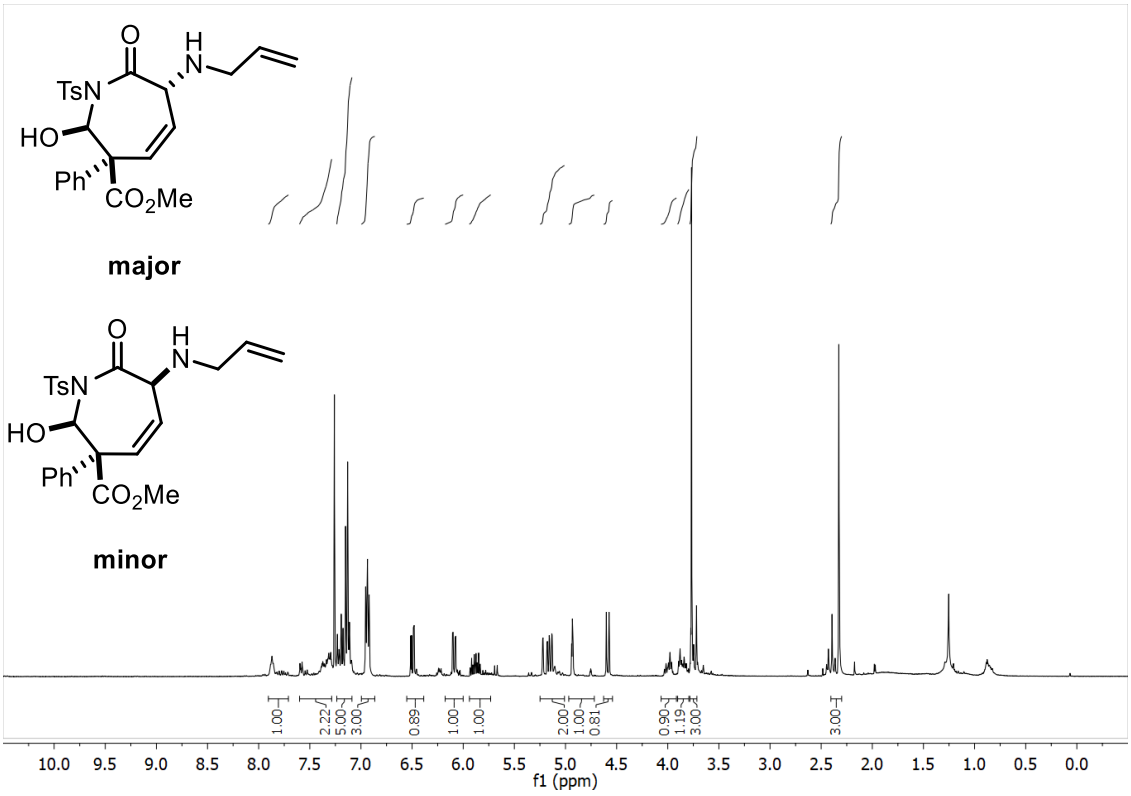


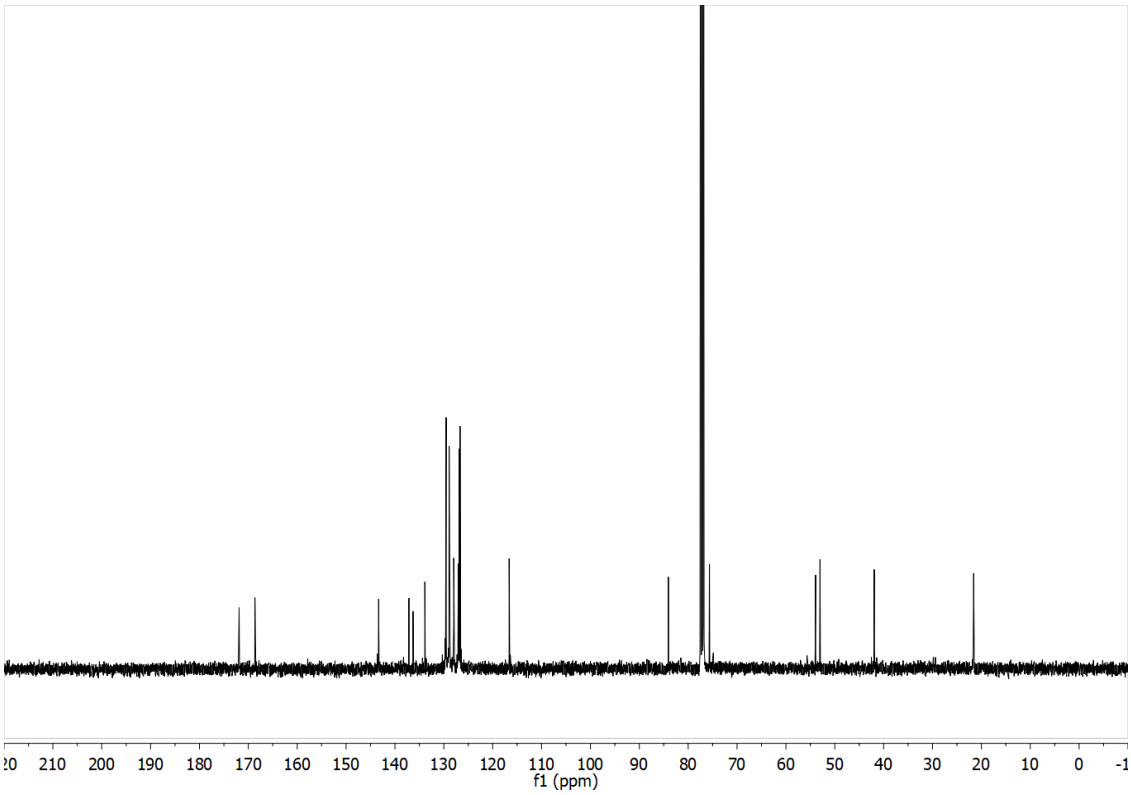
methyl 2-hydroxy-6-methoxy-7-oxo-3-phenyl-1-tosyl-2,3,6,7-tetrahydro-1H-azepine-3-carboxylate (520)



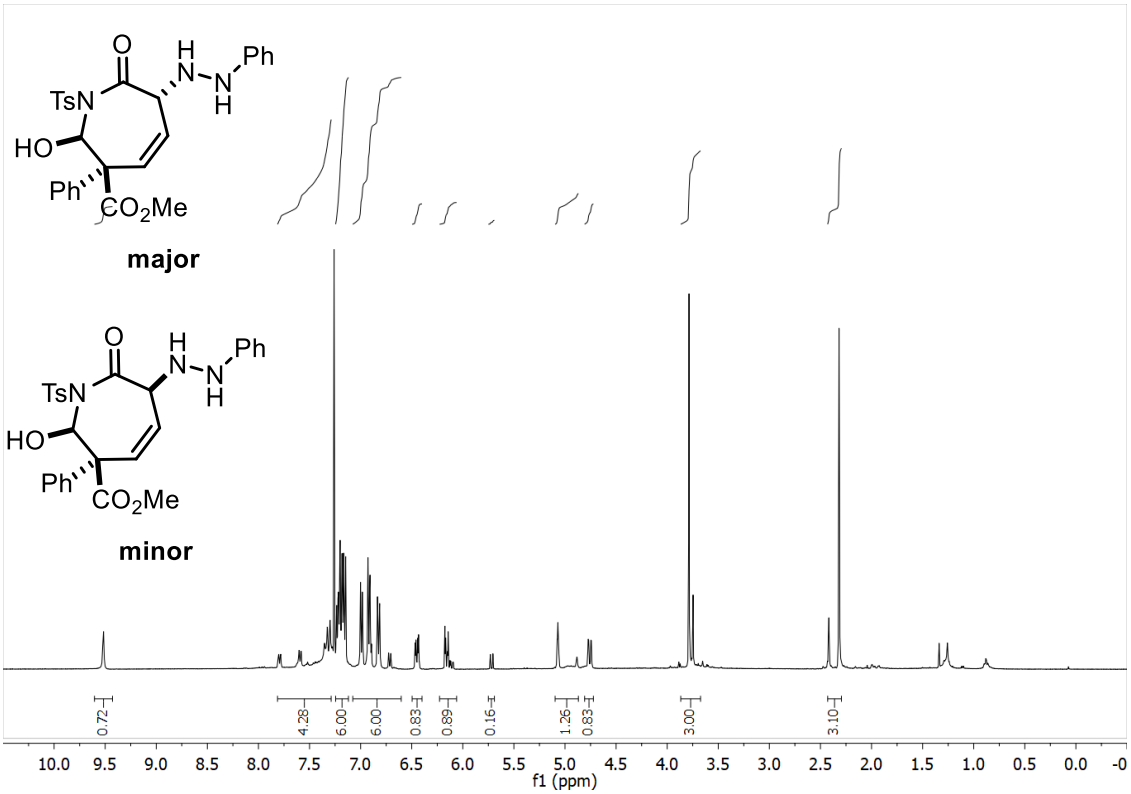


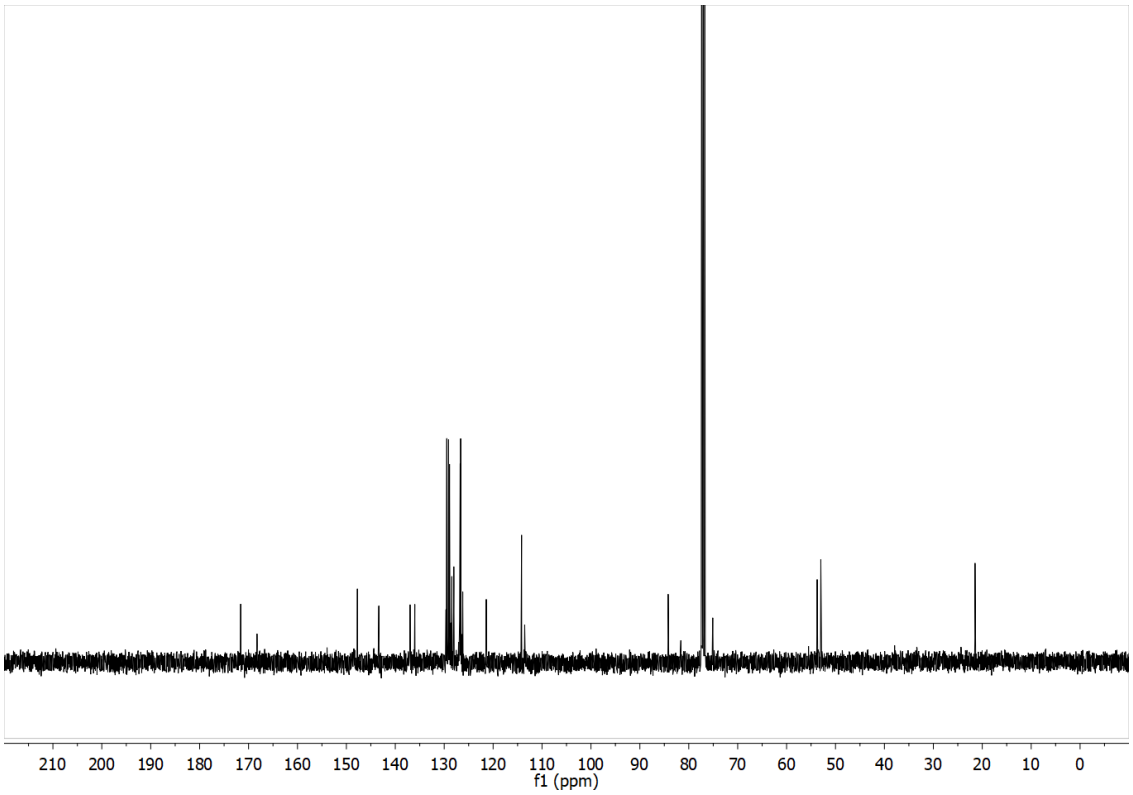
methyl 6-(allylamino)-2-hydroxy-7-oxo-3-phenyl-1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (521 h)



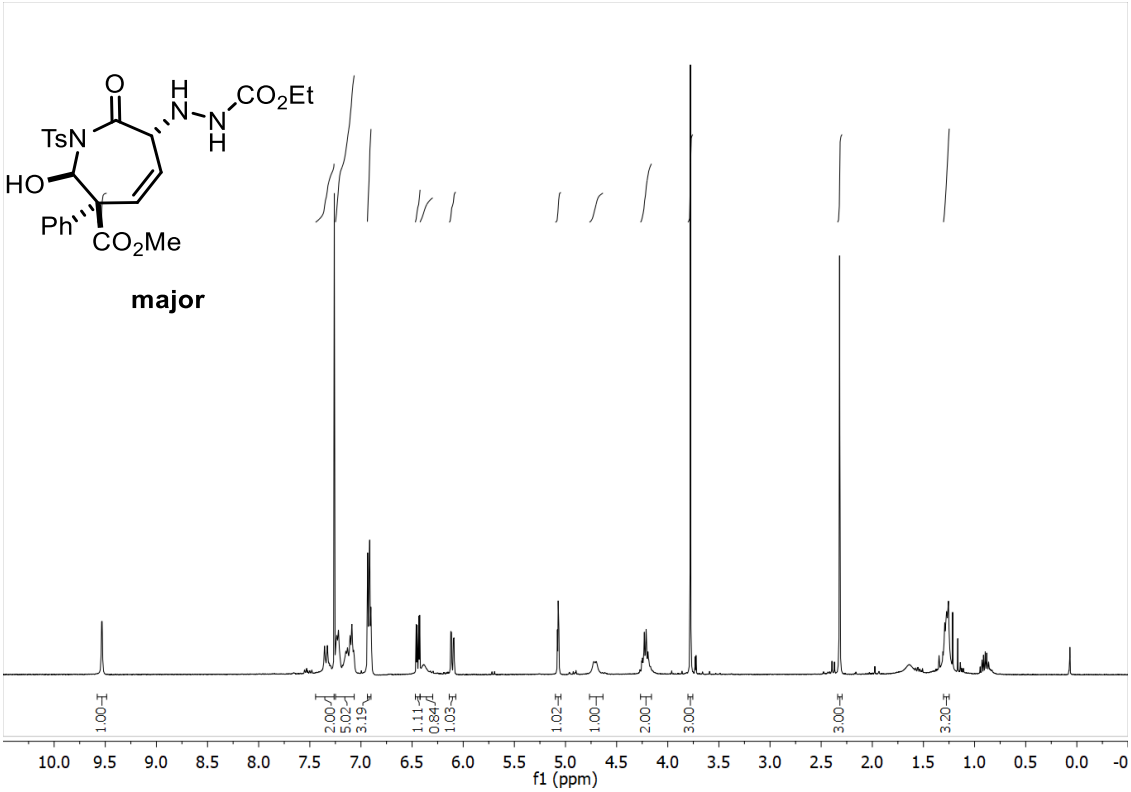


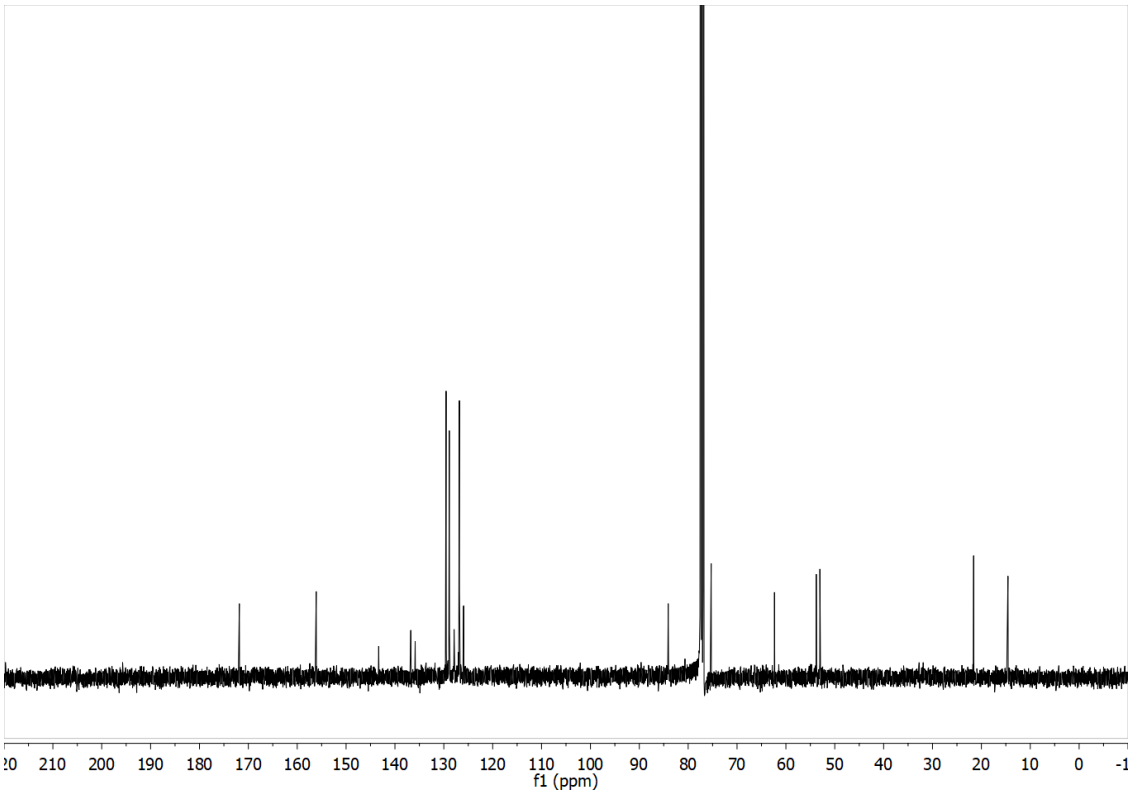
methyl 2-hydroxy-7-oxo-3-phenyl-6-(2-phenylhydrazineyl)-1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (521 i)

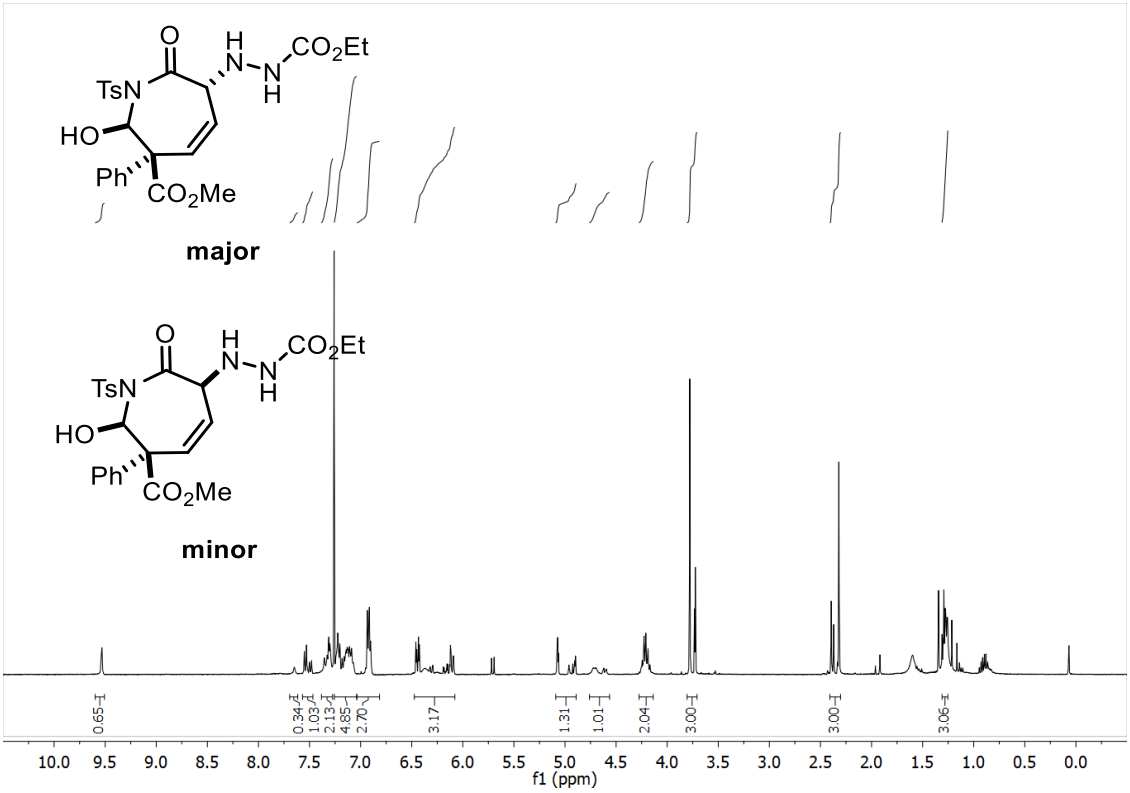




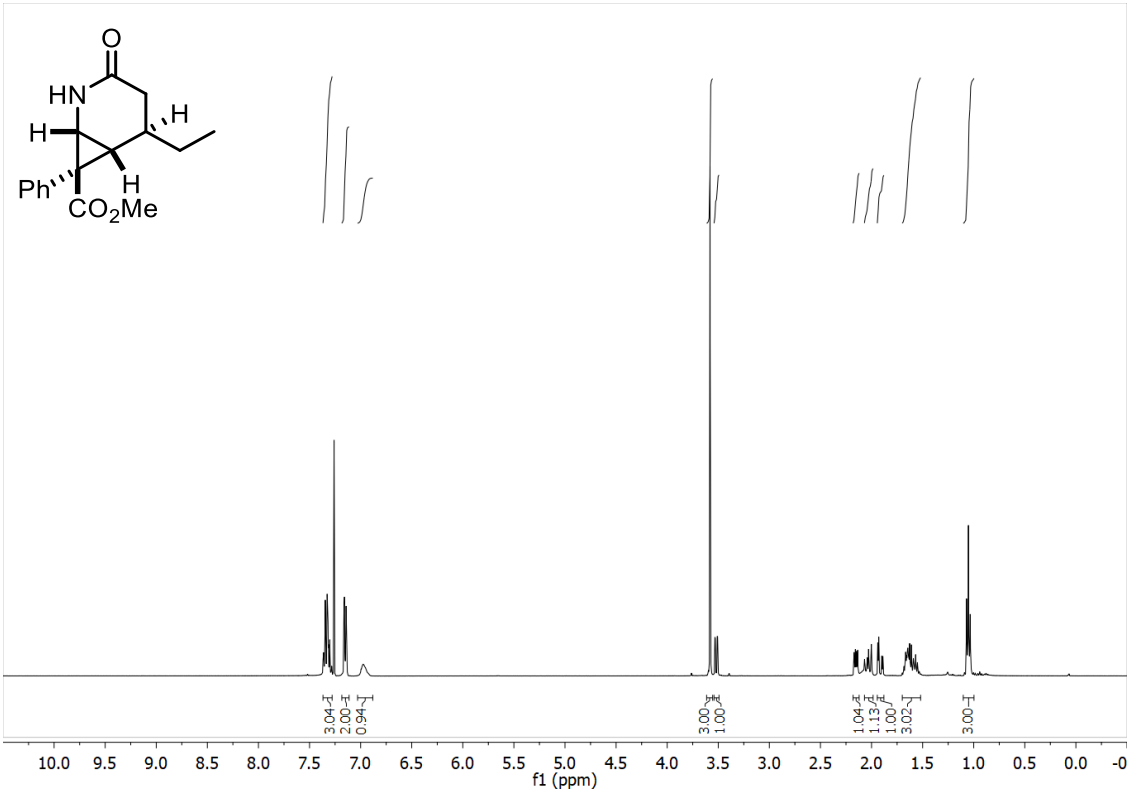
methyl 6-(2-(ethoxycarbonyl)hydrazineyl)-2-hydroxy-7-oxo-3-phenyl-1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (521 j)

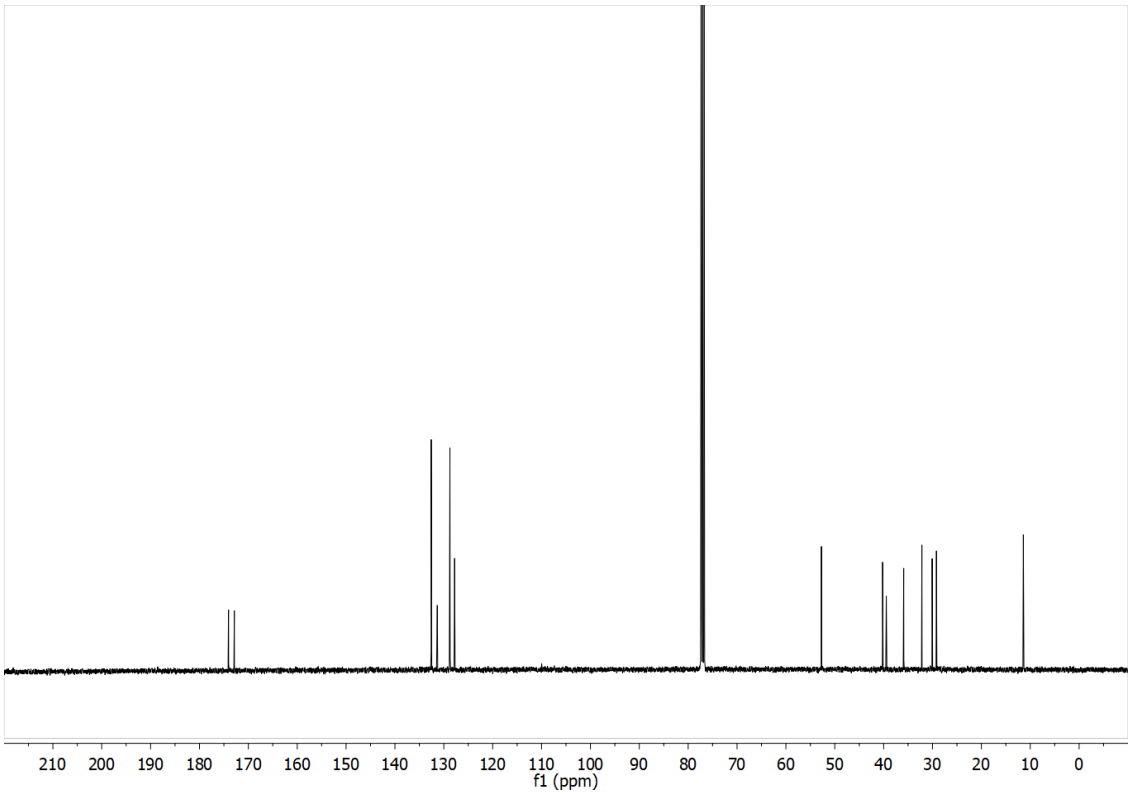




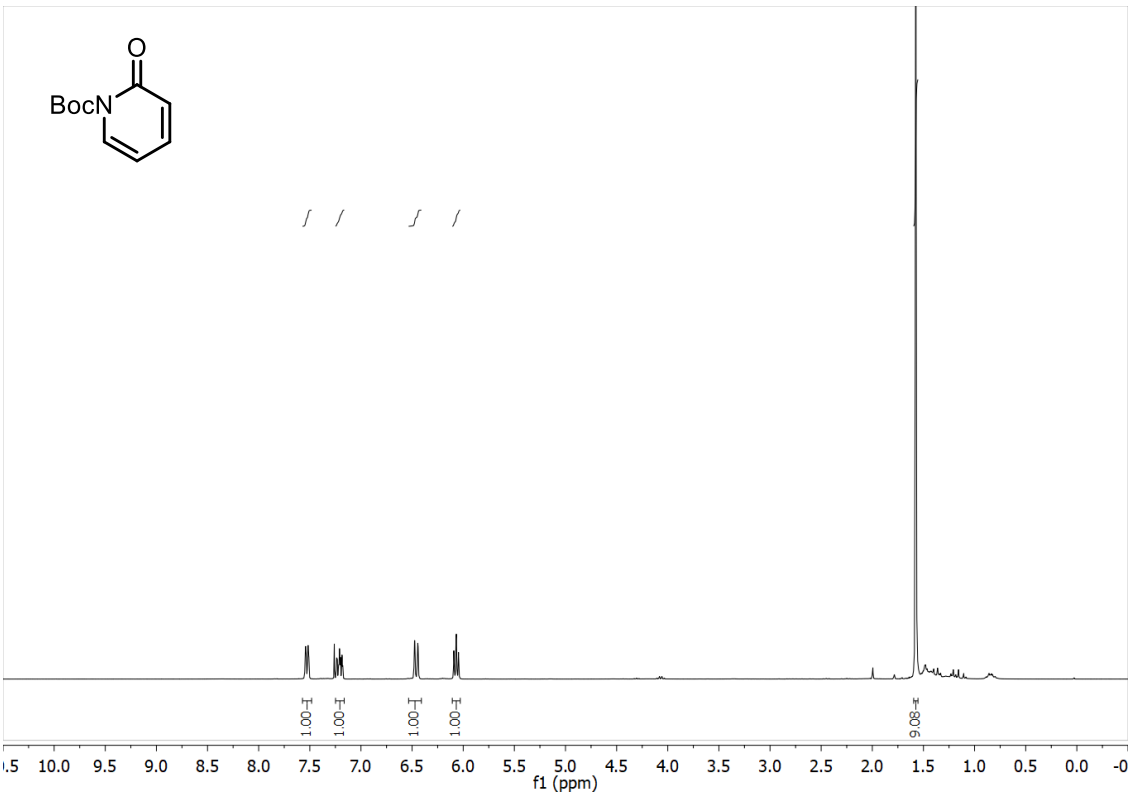


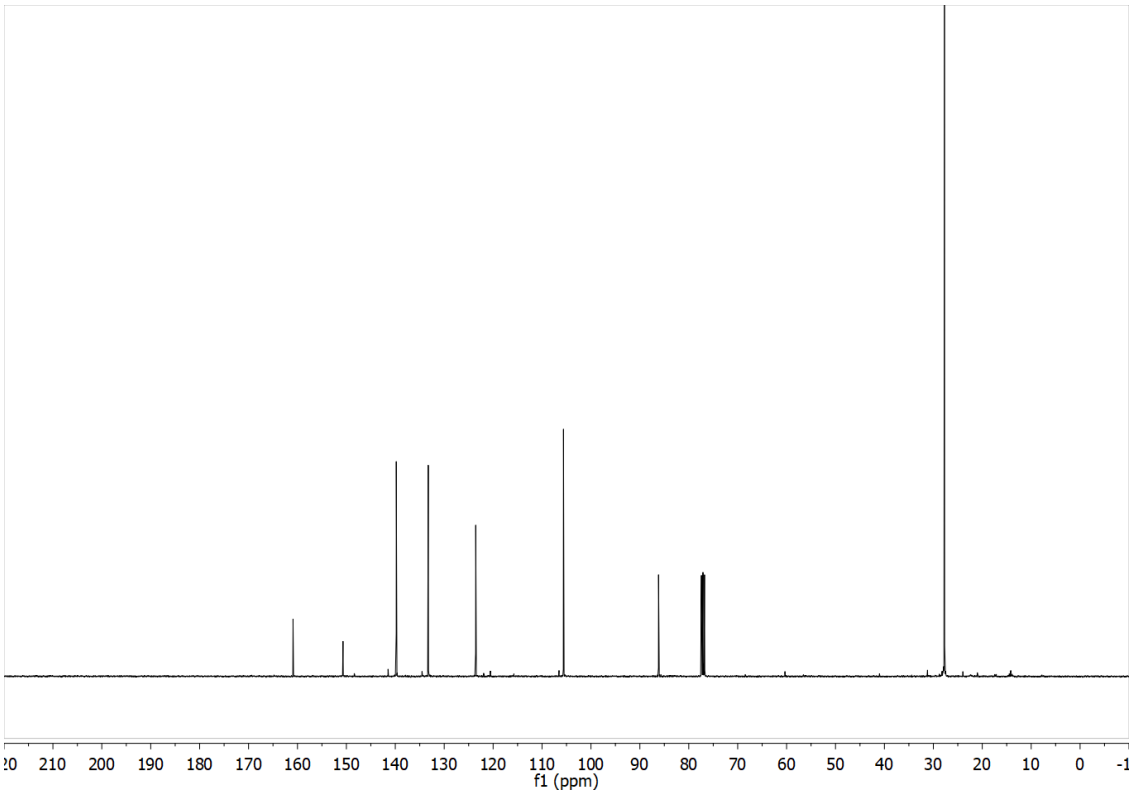
methyl 5-ethyl-3-oxo-7-phenyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (568)



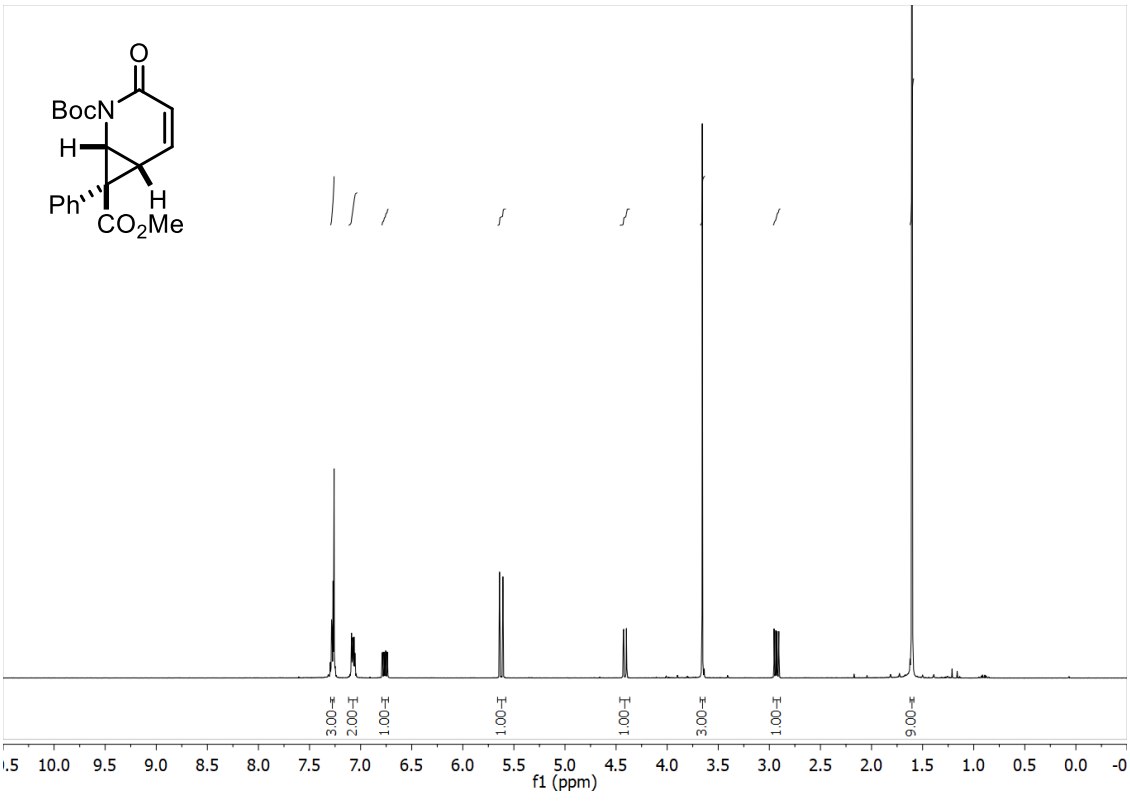


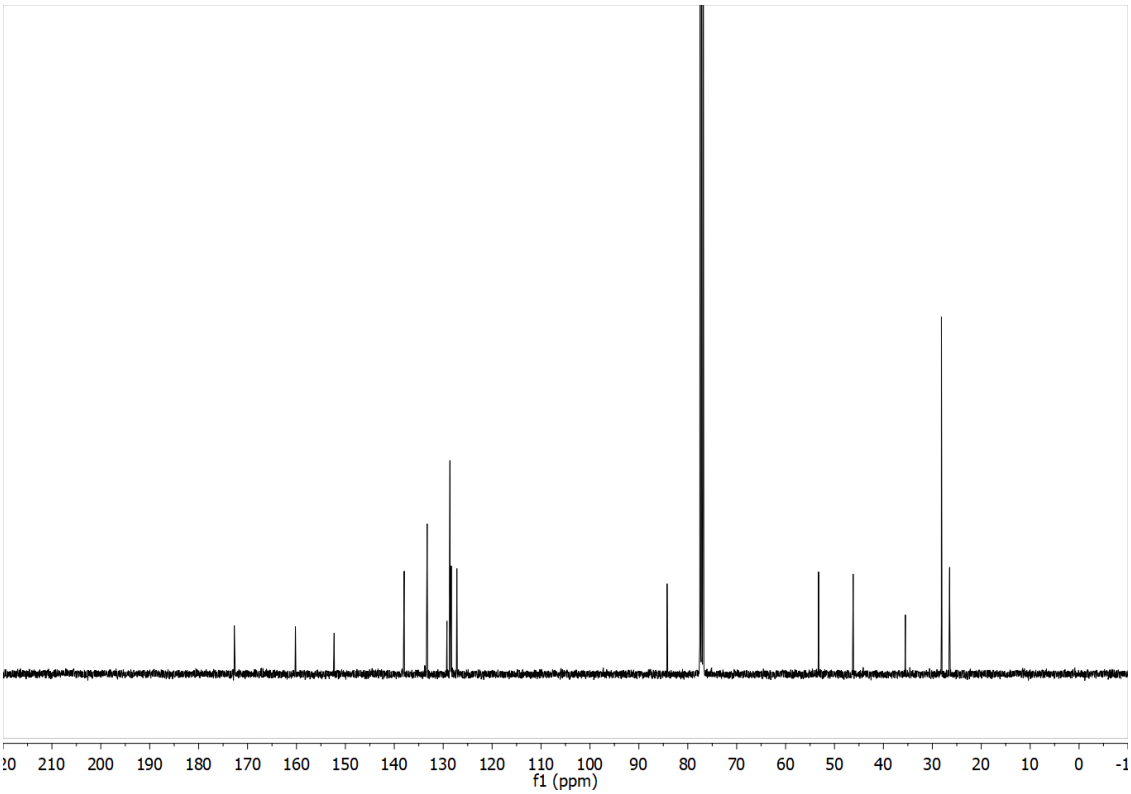
tert-butyl 2-oxopyridine-1(2*H*)-carboxylate (572)



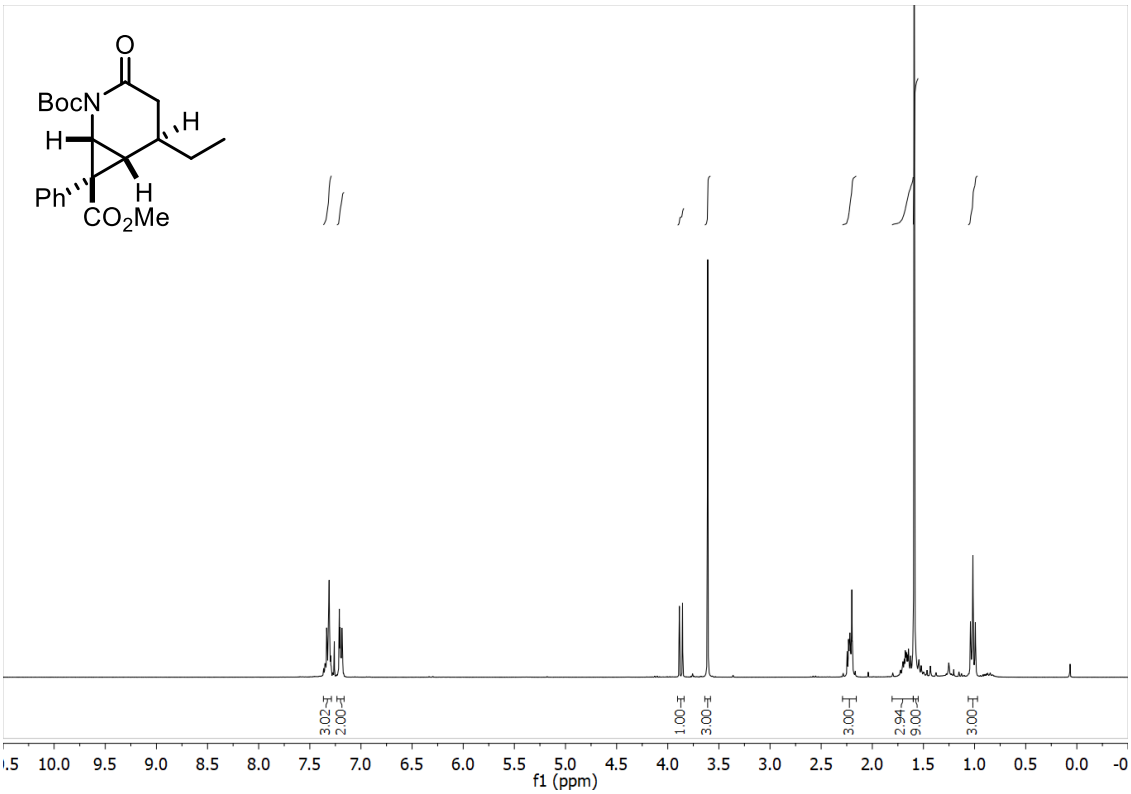


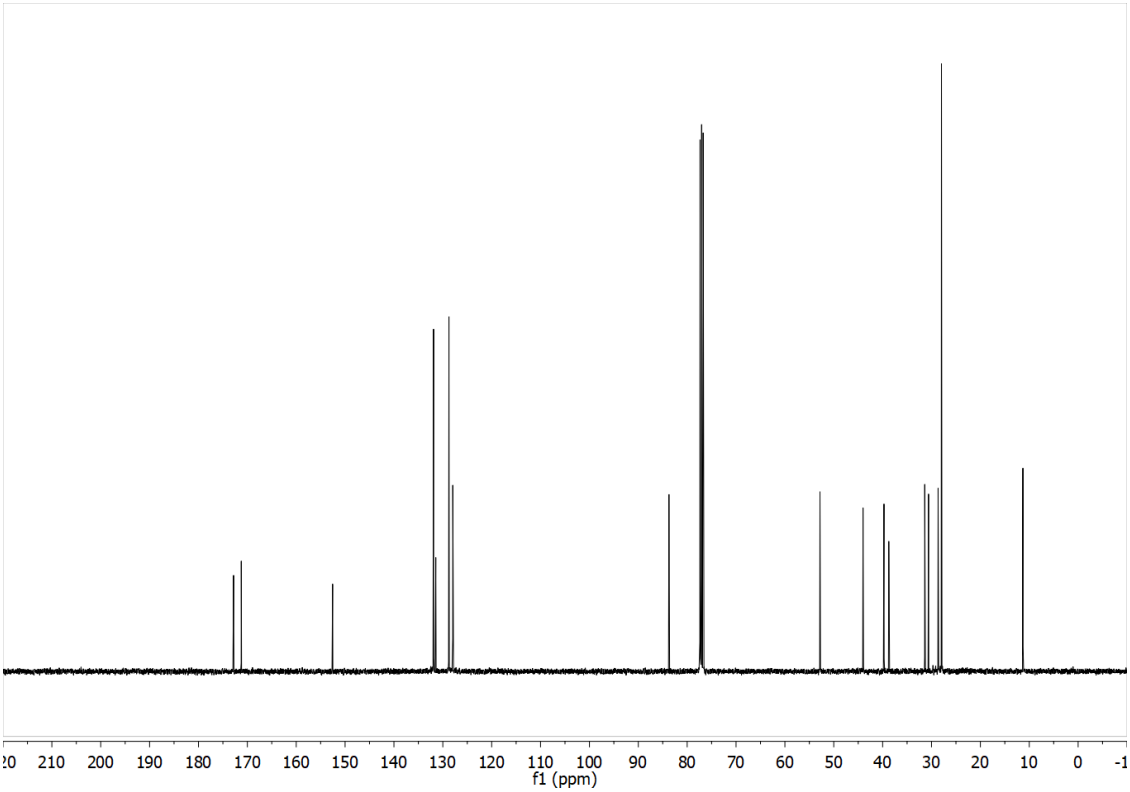
2-(*tert*-butyl) 7-methyl 3-oxo-7-phenyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (575)



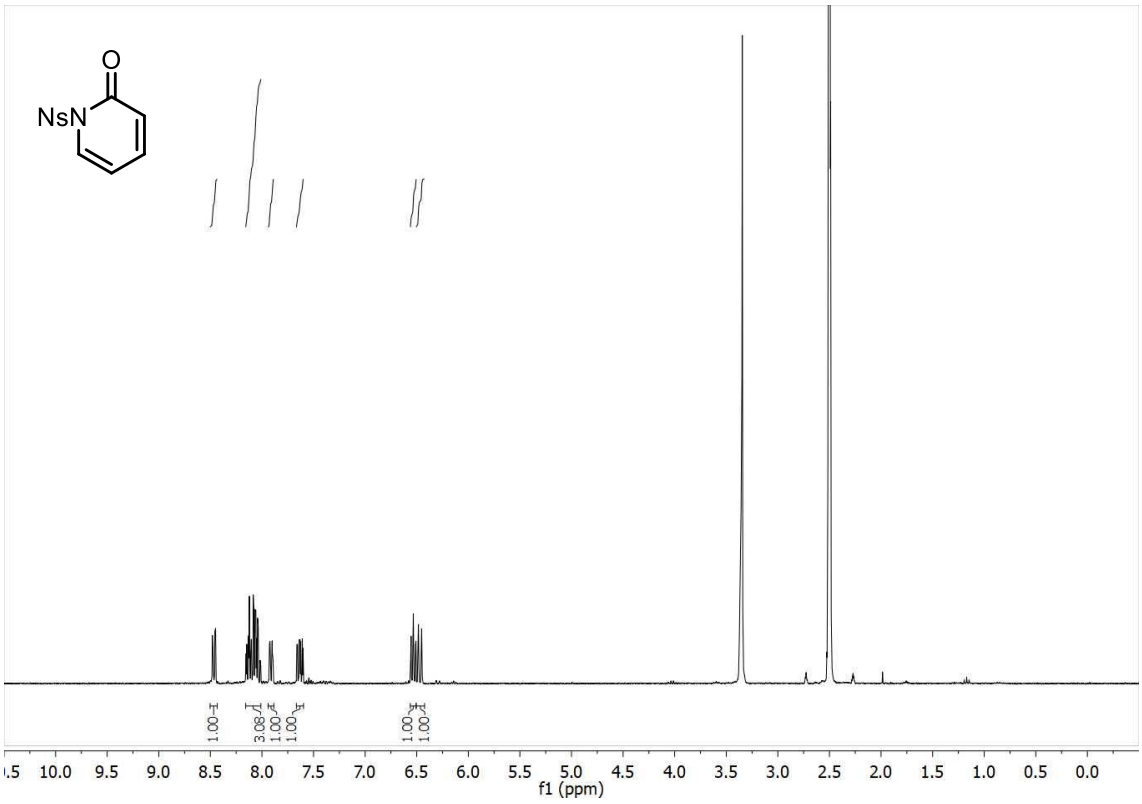


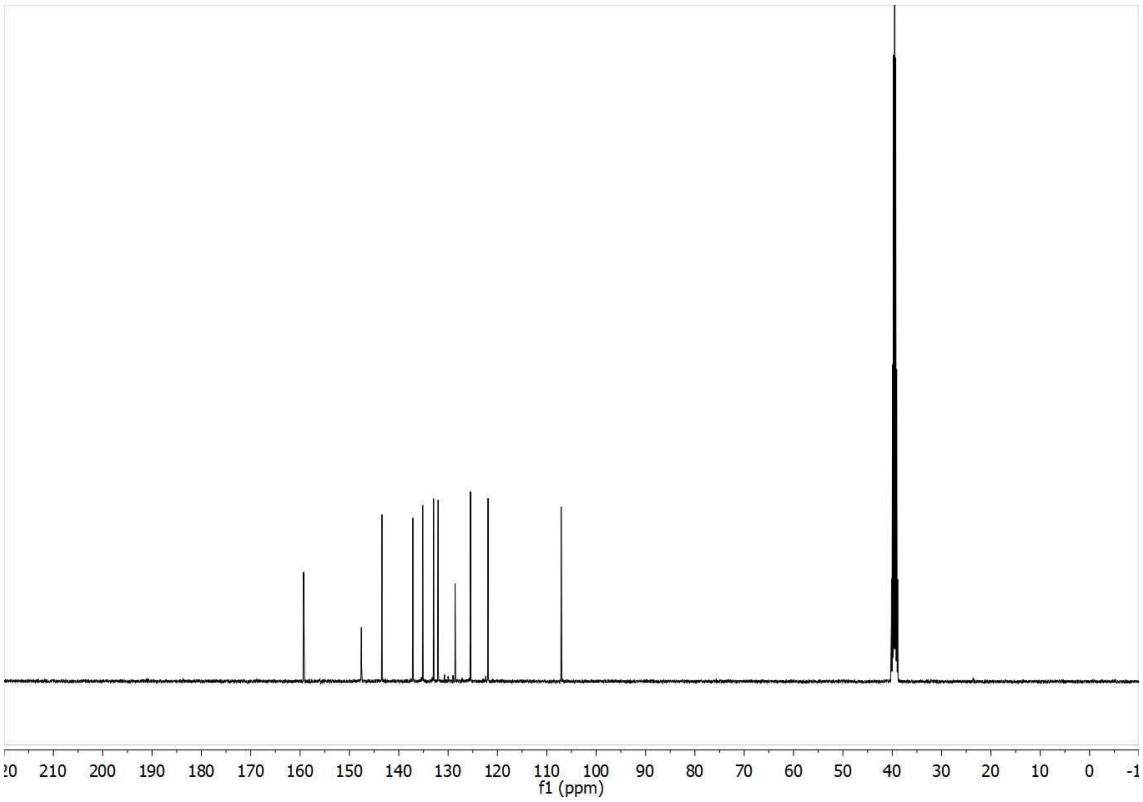
2-(*tert*-butyl) 7-methyl 5-ethyl-3-oxo-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (576)



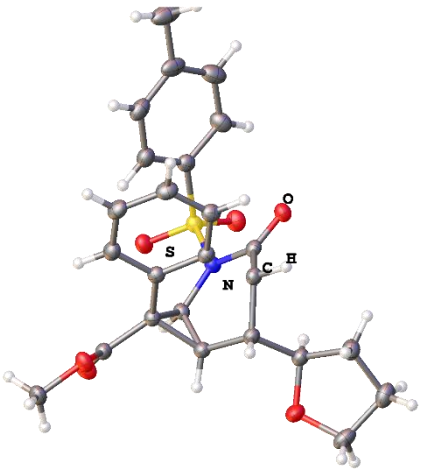


1-((4-nitrophenyl)sulfonyl)pyridin-2(1*H*)-one (577)

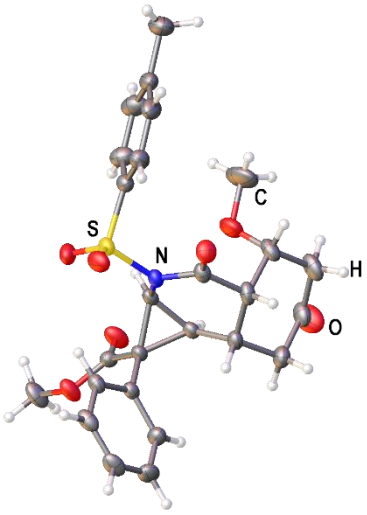



210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

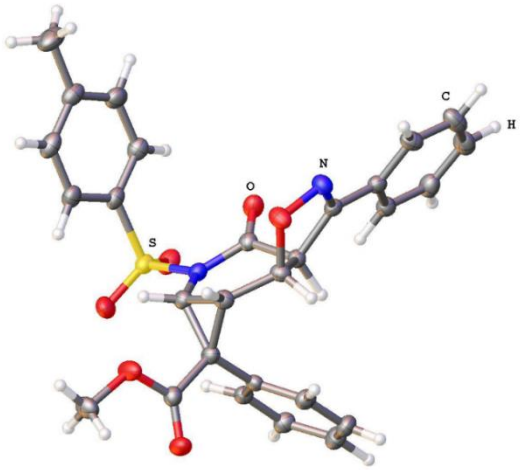
2. X-Ray structures



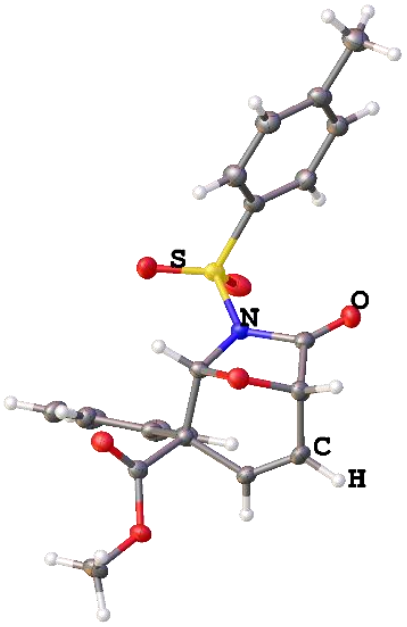
Compound	**412 a**
Formula	$C_{25}H_{25}NO_6S$
$D_{calc.}$/ g cm^{-3}	1.432
μ/mm^{-1}	1.243
Formula Weight	467.52
Colour	clear colourless
Shape	prism
Size/mm^3	0.22×0.16×0.13
T/K	122.99(10)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	11.8560(2)
b/Å	12.38357(19)
c/Å	14.9573(2)
α/°	90
β/°	99.1594(15)
γ/°	90
V/Å^3	2168.02(6)
Z	4
Z'	1
Wavelength/Å	1.39222
Radiation type	Cu K
Θ_{min}/°	4.000
Θ_{max}/°	65.758
Measured Refl's.	14648
Ind't Refl's	5011
Refl's with I > 2(I)	4462
R_{int}	0.0188
Parameters	300
Restraints	0
Largest Peak	0.393
Deepest Hole	-0.349
GooF	1.018
wR_2 (all data)	0.0978
wR_2	0.0944
R_1 (all data)	0.0415
R_1	0.0362



Compound	**446 a B**
Formula	$C_{26}H_{27}NO_7S$
$D_{calc.}$/ g cm^{-3}	1.288
μ/mm^{-1}	0.171
Formula Weight	497.54
Colour	clear colourless
Shape	prism
Size/mm^3	0.18×0.17×0.09
T/K	122.99(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	8.4676(4)
b/Å	13.3788(5)
c/Å	22.7311(10)
α/°	90
β/°	94.832(4)
γ/°	90
V/Å^3	2565.97(19)
Z	4
Z'	1
Wavelength/Å	0.71073
Radiation type	Mo K_α
Θ_{min}/°	3.045
Θ_{max}/°	29.065
Measured Refl's.	17068
Ind't Refl's	5938
Refl's with I > 2(I)	4522
R_{int}	0.0299
Parameters	319
Restraints	0
Largest Peak	0.476
Deepest Hole	-0.316
GooF	1.041
wR_2 (all data)	0.1489
wR_2	0.1383
R_1 (all data)	0.0778
R_1	0.0584



Compound	**470**
Formula	$C_{28}H_{24}N_2O_6S$
$D_{calc.}$/ g cm^{-3}	1.364
μ/mm^{-1}	1.538
Formula Weight	516.55
Colour	clear colourless
Shape	prism
Size/mm^3	0.18×0.10×0.06
T/K	123.00(10)
Crystal System	monoclinic
Flack Parameter	0.037(8)
Hooft Parameter	0.030(8)
Space Group	*Pn*
a/Å	14.8464(2)
b/Å	16.0517(2)
c/Å	21.8394(3)
α/°	90
β/°	104.7900(10)
γ/°	90
V/Å^3	5032.11(12)
Z	8
Z'	4
Wavelength/Å	1.54184
Radiation type	Cu K$_\alpha$
Θ_{min}/°	3.459
Θ_{max}/°	73.278
Measured Refl's.	28840
Indep't Refl's	15401
Refl's I≥2 σ(I)	14729
R_{int}	0.0294
Parameters	1686
Restraints	20
Largest Peak	0.263
Deepest Hole	-0.402
GooF	1.053
wR_2 (all data)	0.0904
wR_2	0.0889
R_1 (all data)	0.0394
R_1	0.0372



Compound	**511**
Formula	$C_{21}H_{19}NO_6S$
$D_{calc.}$/ g cm^{-3}	1.410
μ/mm^{-1}	1.821
Formula Weight	413.43
Colour	clear colourless
Shape	plate
Size/mm^3	0.19×0.12×0.09
T/K	100.01(10)
Crystal System	triclinic
Space Group	P-1
a/Å	6.32720(10)
b/Å	7.92280(10)
c/Å	40.2966(8)
α/°	91.560(2)
β/°	93.790(2)
γ/°	104.714(2)
V/Å^3	1947.49(6)
Z	4
Z'	2
Wavelength/Å	1.54184
Radiation type	Cu K_α
Θ_{min}/°	2.200
Θ_{max}/°	73.295
Measured Refl's.	25881
Indep't Refl's	7504
Refl's I≥2 σ(I)	5944
R_{int}	0.0254
Parameters	527
Restraints	0
Largest Peak	0.514
Deepest Hole	-0.352
GooF	1.058
wR_2 (all data)	0.1305
wR_2	0.1247
R_1 (all data)	0.0570
R_1	0.0459

3. Curriculum Vitae

Persönliche Daten

Name	Natalija Moor
Geburtstag & -ort	30.01.1993 in Ujar, Russland (12/2000 Umzug nach Deutschland)
Staatsangehörigkeit	deutsch & russisch
Mail	Natalija.Moor@chemie.uni-regensburg.de

Ausbildung

10/2017 – jetzt	Doktorandin am Institut für Organische Chemie Universität Regensburg, Prof. Dr. Oliver Reiser
03/2019 – 08/2019	Forschungsaufenthalt als JSPS-Stipendiatin Universität Tokio, Prof. Dr. Masayuki Inoue
10/2015 – 09/2017	Master of Science (M.Sc.), Chemie Universität Regensburg
10/2012 – 09/2015	Bachelor of Science (B.Sc.), Chemie Universität Regensburg
09/2004 – 06/2012	Abitur Gregor-Mendel-Gymnasium, Amberg

Engagement

03/2018 – 03/2020	Sprecherin für Organische Chemie Graduiertenschule ChemPharm, Universität Regensburg

Kenntnisse

Weiterbildung	Qualitätssicherungsmanagementkurs Kurs mit Abschlussvortrag am Laboratorium für Umweltradioaktivität der Universität Regensburg
	Ausbildung zum Brandschutz-und Ersthelfer

Sprachen	Deutsch und Russisch Muttersprache Englisch fließend Japanisch vertiefte Kenntnisse (JLPT N3) Französisch Grundkenntnisse
IT	MS Office, Powerpoint, ChemDraw, MesReNova, SciFinder

Konferenzteilnahmen

26. ISHC-congress (03.09 – 08.09.2017), Regensburg

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I Declaration

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from others are involved, all of them are marked clearly, with reference to the literature, license, and acknowledgment of collaborative research.

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