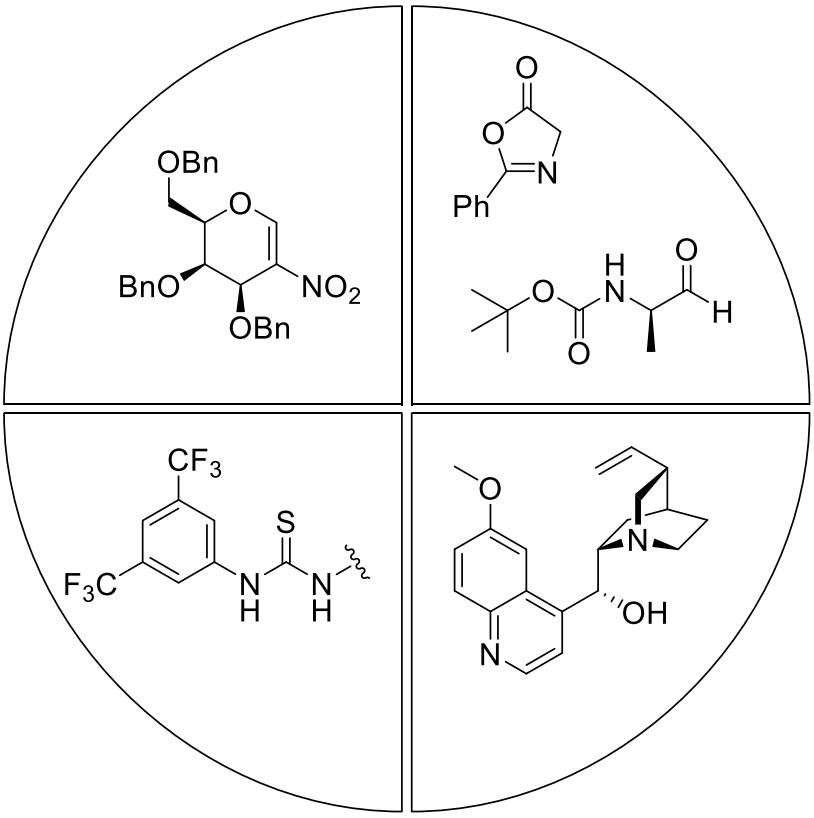
Organocatalytic *C*-Glycosylation of Amino Acids

Organokatalytische *C*-Glykosylierung von Aminosäuren

Master Thesis



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In this game that we're playing, we can't win.
Some kinds of failure are better than other kinds, that's all.

– George Orwell in 1984

The present work was made at the institute of organic chemistry of the Justus-Liebig-Universität in the group of Prof. Dr. Peter R. Schreiner under the shared supervision of Prof. Dr. Peter R. Schreiner and Dr. Manuel Orlandi from April 2022 to November 2022.

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Selbstständigkeitserklärung

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List of Abbreviations

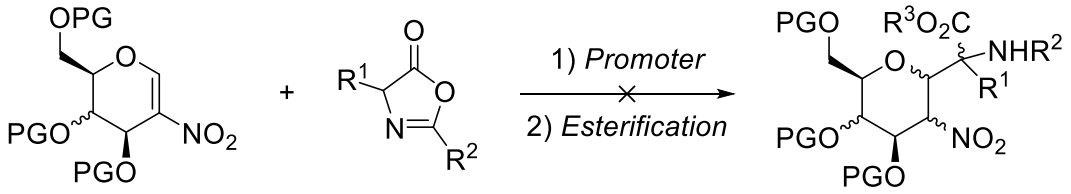
Ac	Acetyl
AcCl	Acetyl Chloride
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
CAM-stain	Cerium Ammonium Molybdate Stain / Hanessian's Stain
CGs	*C*-Glycosides
CGSAAs	*C*-Glycosidic Sugar Amino Acids
Conv.	Conversion
dba	Dibenzylideneacetone
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,2-DCE	1,2-Dichloroethane
Det.	Determined
dCGs	2-Deoxy-*C*-Glycosides
dCGSAAs	(2-Deoxy-)*C*-Glycosidic Sugar Amino Acids
dGs	2-Deoxy-Glycosides
DHP	3,4-Dihydropyran
DiAD	Diisopropyl Azodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMHA	N,O-Dimethylhydroxylamine
DPPA	Diphenylphosphoryl Azide
HOBt	1-Hydroxybenzotriazole
FMOA	Frontier Molecular Orbital Analysis
LAH	Lithium Aluminum Hydride
NIS	*N*-Iodosuccinimide
PG	Protecting Group
Reis.	Reisolated
SAAs	Sugar Amino Acids
SM	Starting Material
TBAN	Tetrabutyl Ammonium Nitrate

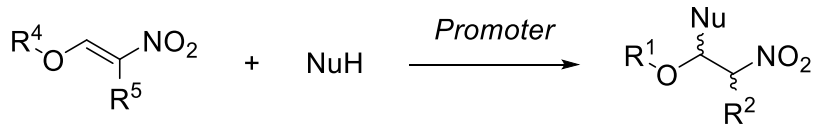
TFAA	Trifluoro Acetic Anhydride
TMSCl	Trimethylsilyl chloride
t_R	Retention Time
TS	Transition State
VAE	Vinylogous Anomeric Effect

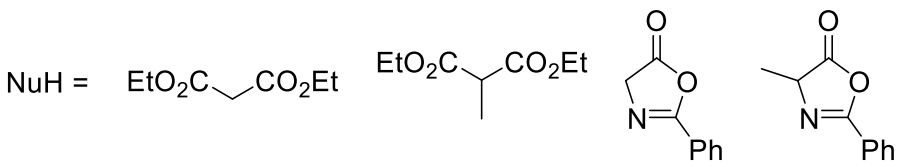
1 – Abstract

C-Glycoconjugates with amino acids (CGSAAs) constitute a class of potentially valuable precursors in pharmaceutical and biochemical research due to their increased stability towards enzymatic and acid catalyzed degradation and improved pharmacokinetic profiles compared to their *O*- and *N*-glycosidic counterparts. Despite this, only a limited number of reports on their stereoselective synthesis are available. Additionally, the deployment of potentially toxic or expensive reagents further impedes the exploration of their potential as elaborate purification processes become necessary. Therefore, new synthetic strategies that avoid potentially toxic reagents are highly desirable.

In the present work, the stereoselective organocatalyzed addition of oxazolones to 2-nitroglycals has been attempted as a means of achieving the stereoselective synthesis of 2-deoxy-*C*-glycosylated amino acid (dCGSAA) derivatives. As the initially envisioned strategy did not yield the anticipated results, several model compounds were synthesized to shed light on the factors governing the addition of nucleophiles to nitro-vinyl ethers. These reactions revealed a complex interplay of stereoelectronic and solvent effects. Furthermore, the products are highly unstable, precluding their isolation.





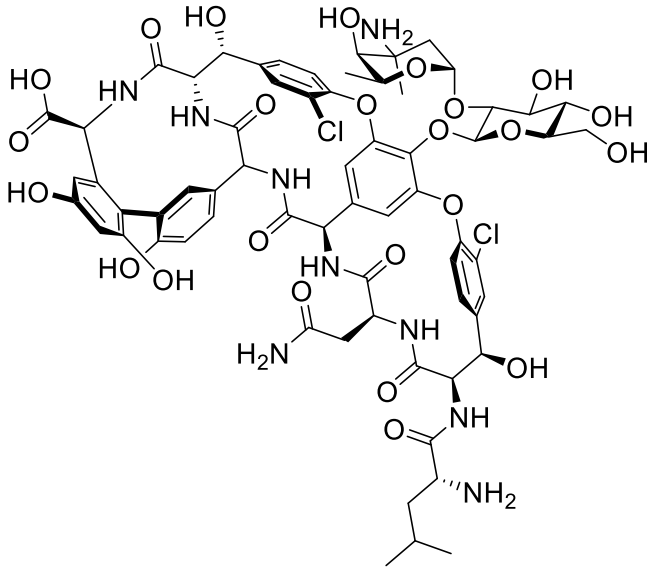


2 – Theory and Background

2.1 – Glycopeptide-Based Drugs

2.1.1 – Glycopeptides as Antibiotics

Glycopeptide antibiotics constitute an important class of medical agents used to treat bacterial infections. The oldest and most prominent member of this class is vancomycin **1**, an antibiotic discovered in 1952 and used in treating penicillin-resistant *staphylococcus aureus* and other Gram-positive bacteria since 1980.[1,2] Many new variants of glycopeptide antibiotics have been approved and introduced for treating bacterial infections. Still, the emergence of resistances and the need to find effective treatments against gram-negative bacteria necessitates the development of new and effective methods for synthesizing and modifying complex glycopeptide structures.[1]



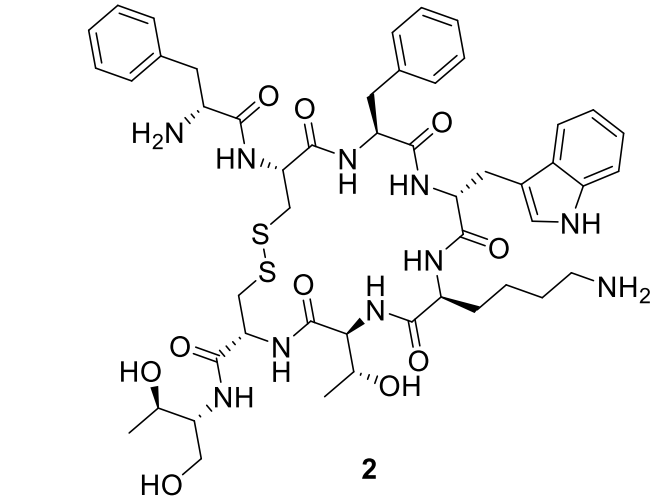
1

Scheme 1: Structure of vancomycin.

2.1.2 – Effects of Glycosylation on Peptide-Based Drugs

Many peptide-based agents often show a high receptor affinity in combination with low toxicity. Despite these advantages, the low bioavailability and pharmacokinetic profiles inferior to those found in “classic” small molecule drugs severely hamper the deployment of new agents. These drawbacks are caused by solubility issues, a low capability of crossing cellular membranes, and enzymatic degradation.[3] Throughout the years, many modifications have

been introduced to tackle the problem of stability of the peptide chain, e.g., the use of unnatural amino acids. Such changes rarely lead to an improvement in solubility or membrane permeation capability.[3,4] The glycosylation of these biologically active peptides profoundly impacts the properties of the peptides, ranging from improved stability, over an improved penetration capability, to enabling specific receptor binding.[3–5] An excellent example of such a pharmacokinetic improvement is SDZ CO 611 **3**,[6] a glycosylated analogue of octreotide **2** (Scheme 2).[7] The original drug, an analog of the naturally occurring peptide hormone somatostatin, is used in many treatments and has to be administered by injection. By performing an Amadori reaction[8] with the terminal phenylalanine, the group of Pless increased the bioavailability of the molecule, enabling the oral administration of **3** in trials with rhesus monkeys.[6]



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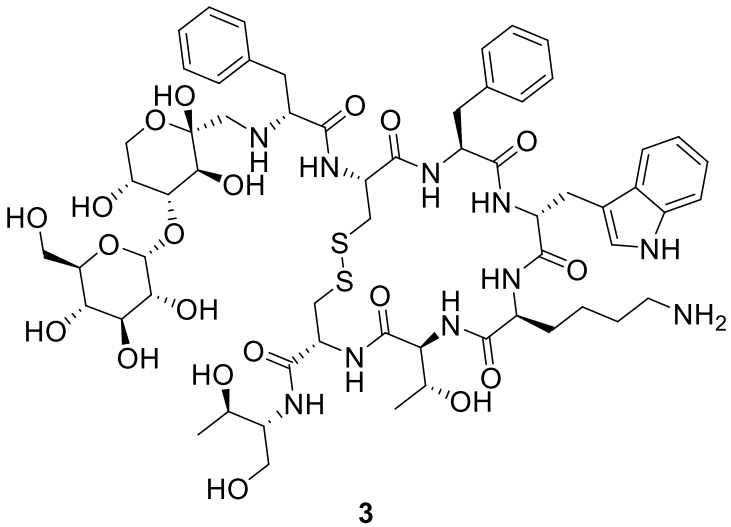
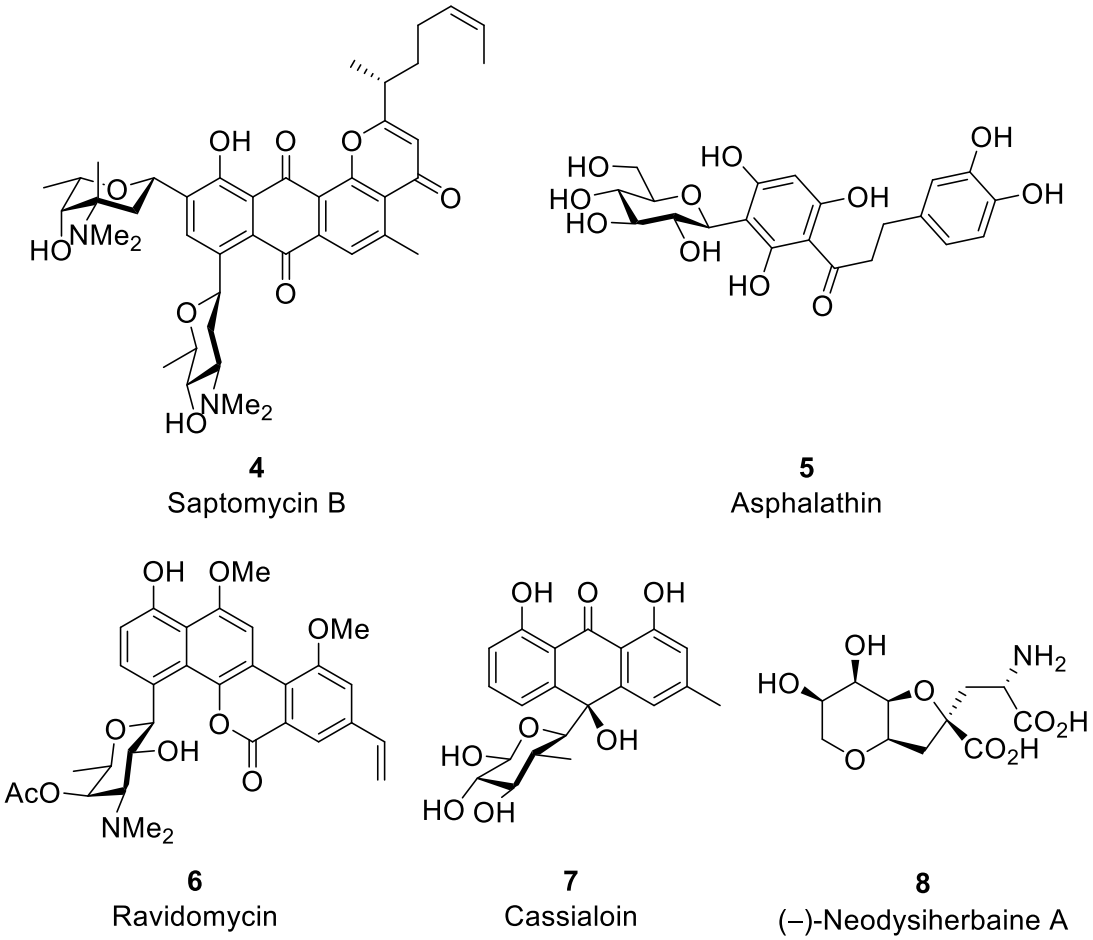


3

Scheme 2: Octreotide **aa** and its glycosylated analogon SDZ CO 611 **aa**, exhibiting an improved pharmacokinetic profile.[6]

2.2 – *C*-Glycosides

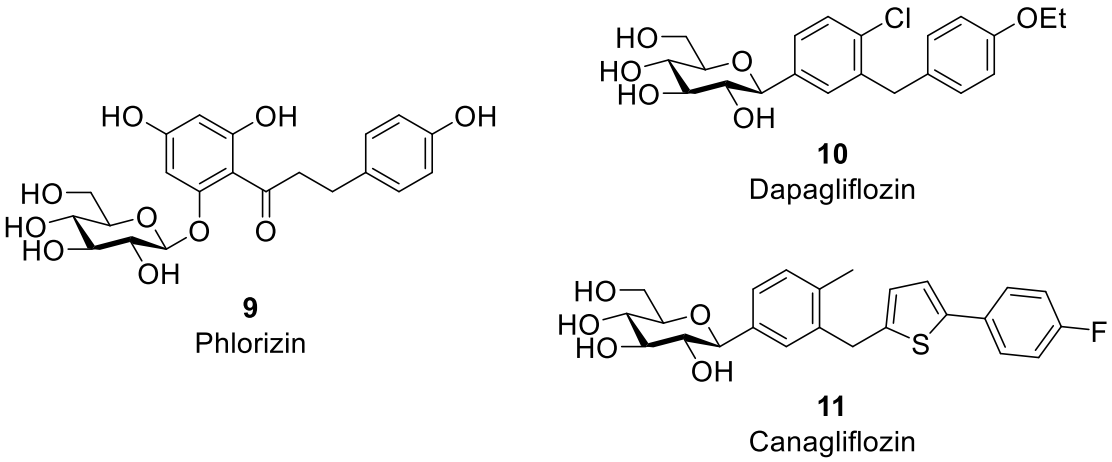
Within a *C*-glycoside, a C–C-bond links the carbohydrate scaffold to another carbohydrate or an aglycon. These *C*-glycosides (CGs) are found within an extensive array of natural products and are often associated with critical biological processes. Therefore, to understand their structure reactivity relationships and privileged role in nature, many of these CGs have been synthesized over the years. Some of which are depicted in Scheme 3.[9–13]



Scheme 3: Natural products containing CGs synthesized previously.[9–13]

Such a displacement of the anomeric oxygen by a carbon atom in therapeutic agents can improve pharmacokinetic profiles, making them attractive targets for discovering new and more potent drugs. The advantage of incorporating GCs has been shown in the case of dapagliflozin **10**[14] and canagliflozin **11**,[15] two synthetic analogs of phlorizin **9** (Scheme 4),[16] which are used as inhibitors of glucose transporters in the treatment of type II diabetes. While phlorizin suffered from enzymatic hydrolysis of the glycosidic linkage and therefore exhibited a poor bioavailability, canagliflozin and dapagliflozin, containing a CG-moiety, cannot be degraded

in this manner. Thereby, the drug can be administered orally without any modifications needed.[17]



Scheme 4: Parent compound Phlorizin and C-glycosidic synthetic analog Canagliflozin and Dapagliflozin exhibiting an improved pharmacokinetic profile.[14–16]

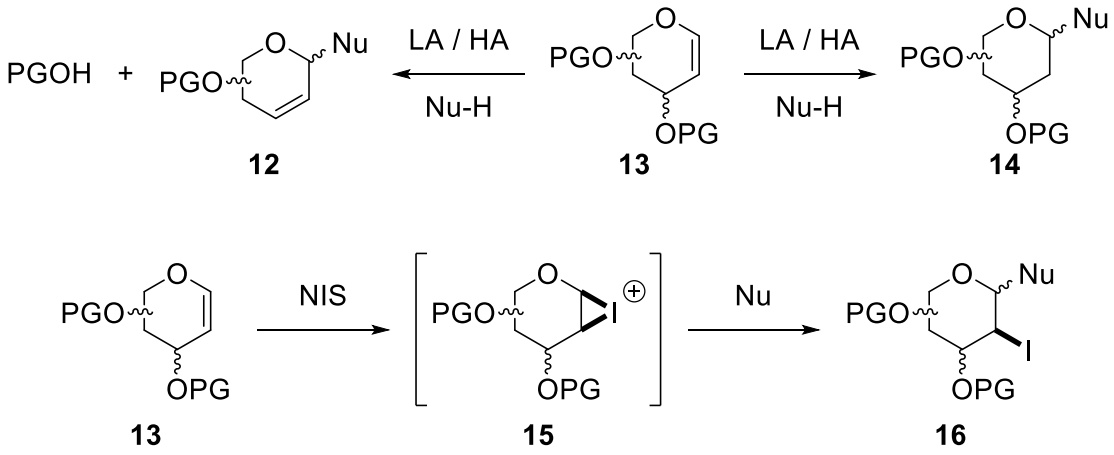
Although CGs are often incorporated solely to improve a compound's stability, such displacement can also be utilized to access unique conformers. This is due to the fact that GCs are not as susceptible to the anomeric effect as their *O*-based counterparts. Furthermore, they now lack the capability of forming hydrogen bonds at this position.[18] In order to allow the synthesis of such diverse structures, a large variety of synthetic protocols have been developed, but the stereoselective synthesis of CGs concerning the anomeric selectivity remains challenging. Most of the methods reported rely on the direct construction of the C–C-bond in an S_N2-type fashion, utilizing a carbohydrate derivative as a glycosyl donor. Thereby, the stereochemistry at the anomeric center is predefined. Furthermore, these protocols often involve anchimeric group assistance from other substituents on the carbohydrate backbone. A less utilized approach involves a *de novo* synthesis of the carbohydrate after the construction of the desired C–C-bond.[19]

2.3 – 2-Deoxy-Glycosides

2.3.1 – Synthetic Challenges and Glycals

2-Deoxy-glycosides (dGs) and especially 2-deoxy-*C*-glycosides (dCGs) provide a unique challenge from the synthetic point of view. Most of the glycosylation protocols used routinely rely upon some sort of, often indirect, anchimeric assistance of the oxygen function at the C2-position.[20] Glycals like **12** (Scheme 5) already possess the desired 2-deoxy-motif and could

therefore be considered to be privileged substrates in the synthesis of dGs and dCGs.[21] This, however, is debatable, as glycals naturally require activation by (Lewis) acids, often precluding the usage of anionic nucleophiles. Additionally, the activation by (Lewis) acids commonly results in the formation of Ferrier-rearranged products **12**,[22] leading to the loss of one stereogenic center on the carbohydrate scaffold. An alternative activation method widely used deploys *N*-iodosuccinimide (NIS),[23] which leads to the formation of a 2-iodo-carbohydrate species **16**. The iodine has to be removed either in a reductive fashion or functionalized to prevent hydrolysis, necessitating additional synthetic steps. Therefore, using other, more activated, glycal donors offers many advantages regarding nucleophile compatibility and reaction conditions.

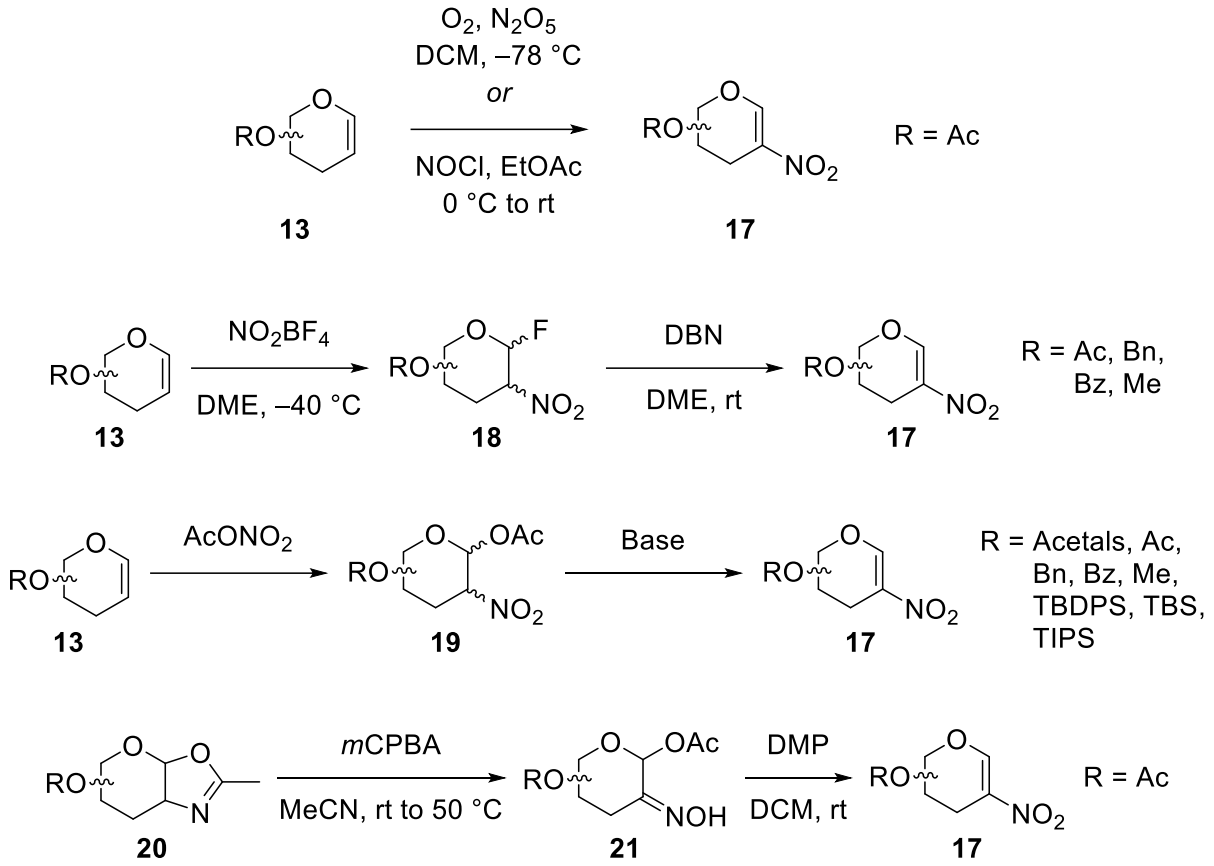


Scheme 5: Schematic representation of the standard activation methods for glycals.[23]

2.3.2 – 2-Nitroglycals as 2-Deoxy-Glycoside Donors

The need for more activated glycal analogs led to the introduction of 2-nitroglycals by the group of Lemieux in 1968.[24] The original synthesis relies on the reaction between dinitrogen pentoxide and glycals to obtain the corresponding 2-nitroglycals (Scheme 6). Various other nitration procedures of glycals have been developed over time, e.g., reaction with nitrosyl chloride or nitronium tetrafluoroborate with subsequent elimination of fluoride.[25,26] Later, protocols using acetyl nitrate as a nitrating agent became more popular, as these are far less laborious and do not require special laboratory equipment.[27–30] This allows for the synthesis of a large variety of different 2-nitroglycals concerning the protecting groups on the carbohydrate moiety, as the procedures involving acetyl nitrate are far milder than those

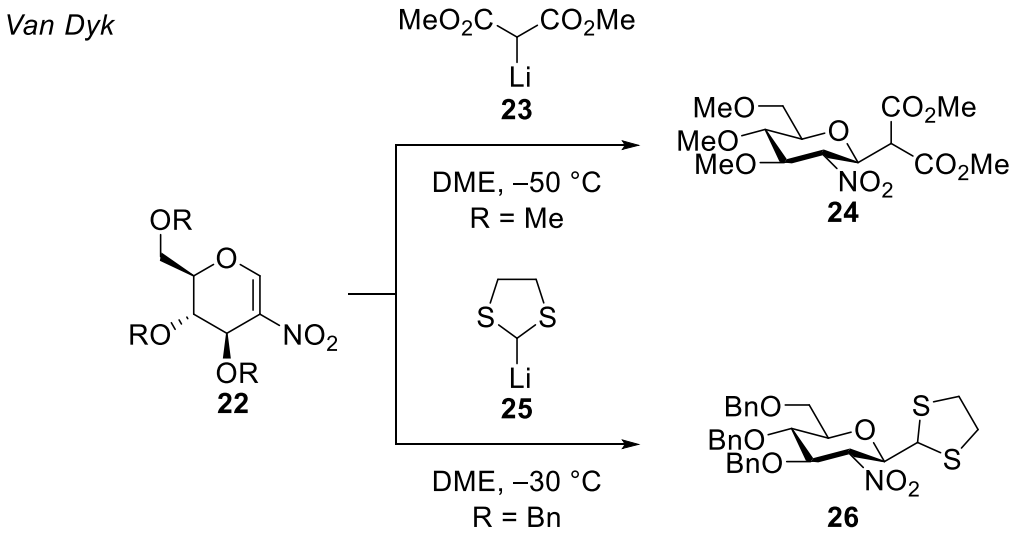
reported previously. The Ganem group has reported an alternative synthetic pathway starting from oxazolidine derivatives **20**, yielding the desired 2-nitroglycal only in moderate yield.[31]

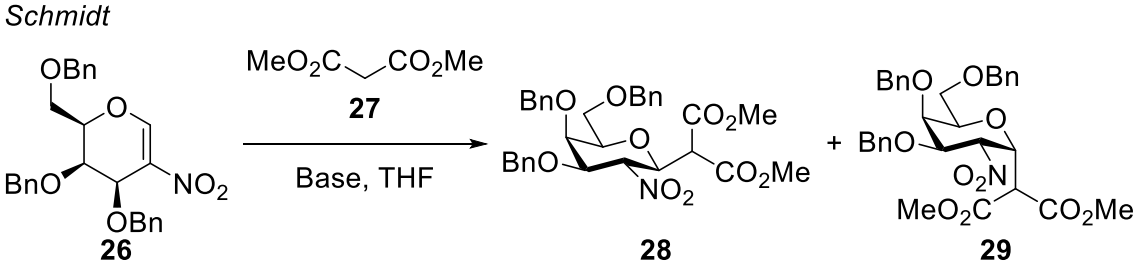


Scheme 6: Different synthetic routes towards 2-nitroglycals with their reported protecting group tolerance.

Early investigations in 1988 by the group of Van Dyk into the use of 2-nitroglycals revealed their versatility as glycoside donors for synthesizing dCGs.[25] They synthesized different dCGs, using 2-nitroglycals as Michael acceptors[32] and lithiated malonate **23** or dithiane **25** as nucleophiles to obtain the corresponding addition products shown in Scheme 7. Despite claiming complete conversion of the starting material and the formation of a *cis* β-addition product for both nucleophiles, the group reported no further information on the yield or the anomeric selectivity. Later, the group of Schmidt also investigated the addition of malonates to 2-nitroglycals.[33] During their investigation, they found a strong dependency of the anomeric selectivity on the base used. While KO^{t}Bu and DBU yield an absolute β-selectivity for the addition to 2-nitrogalactal **26**, KHMDS only gives a diminished selectivity. Bases such as NaHMDS and NaOMe show almost no anomeric selectivity, and NaH leads to no product at all. In the reactions where 2-nitroglucal **22** (R = Bn) is deployed as the glycoside donor, even the previously optimized conditions do not lead to an anomeric selectivity greater than 1:3 (β:α). Furthermore, the observed relationship between the bases used and the anomeric selectivity

completely contradicts a model proposed earlier by Schmidt.[27,34] The group of Schmidt used this model in a previous investigation to explain the dependency of the anomeric selectivity on the base for the addition reactions of alcohols. This breakdown underlines the difficulties associated with the construction of CGs and dCGs. With few exceptions,[35,36] further additions of carbon-based nucleophiles have only been accomplished so far by using either organometallic compounds[37,38] or under harsh conditions.[39]



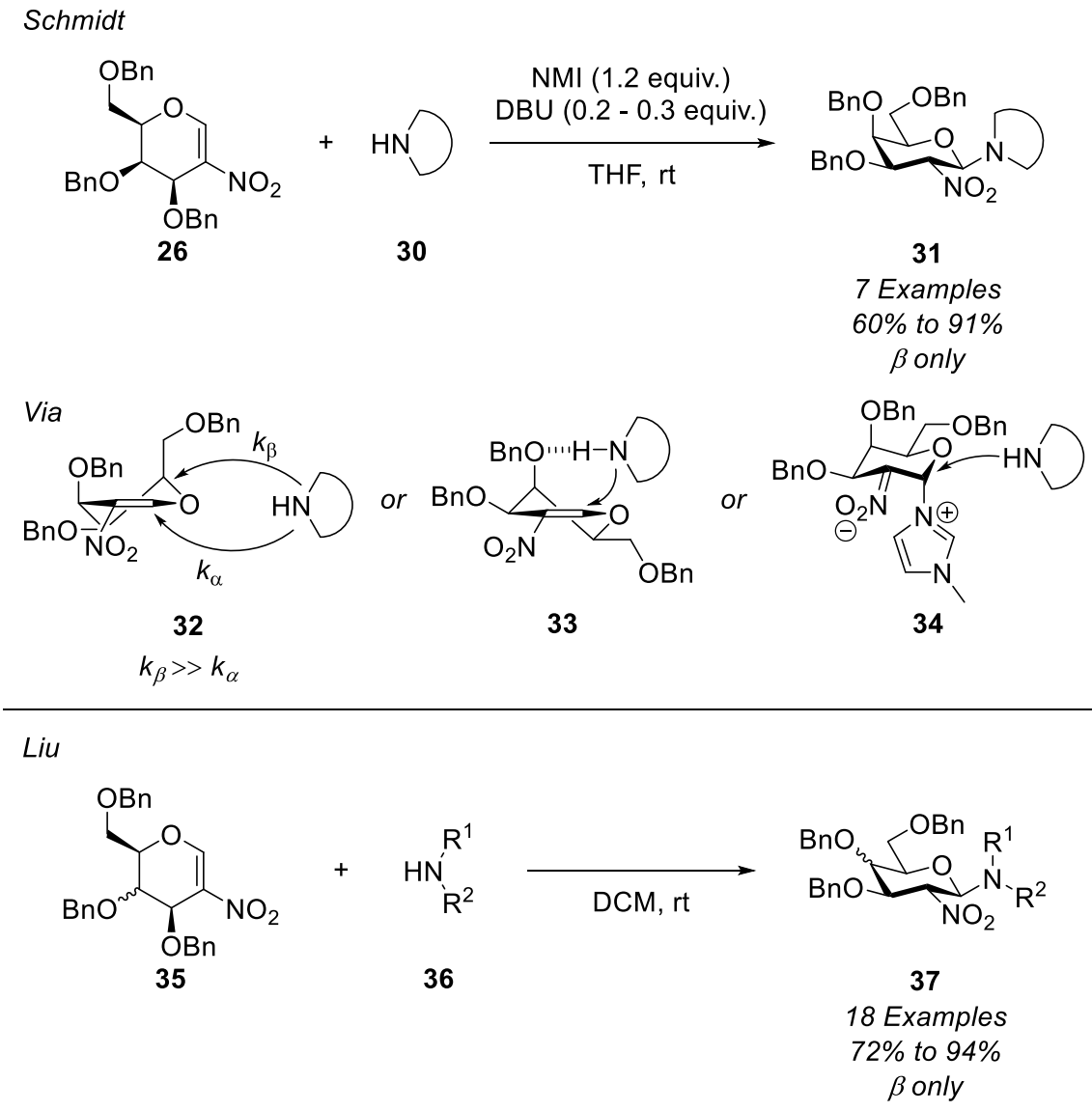


Entry	Base	Time / h	Temperature / °C	28/29	Yield / %
1	NaH	1	0 °C	–	–
2	DBU	3	0 °C to rt	**28** only	62
3	KO^{t}Bu	3	0 °C to rt	**28** only	80
4	KHMDS	3	–78 °C	1:15.2	81
5	NaOMe	48	–40 °C to rt	1:2.8	48
6	NaHMDS	5	–40 °C to rt	1:1.4	52

Scheme 7: Early investigations by Van Dyk into the addition of C-nucleophiles to 2-nitroglucals (no yields or selectivity reported) and a later study by Schmidt revealing the influence on the base in the anomeric selectivity.[25,33]

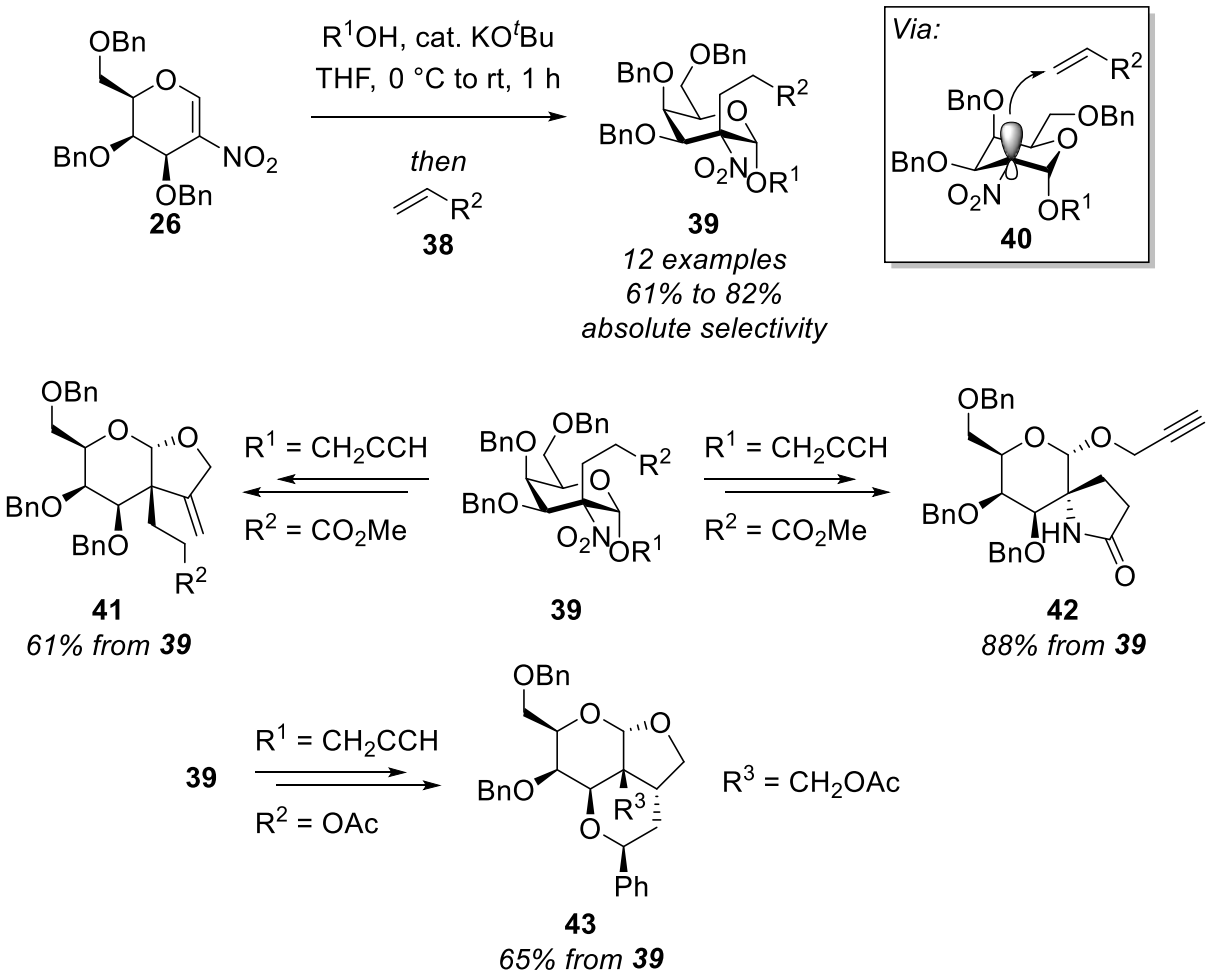
Investigations on the addition of nitrogen-based heterocyclic nucleophiles by Schmidt and coworkers (Scheme 8) revealed the criticality of a base-promoter in catalytic amounts to ensure

the formation of the desired product with absolute *β*-selectivity.[40] One explanation by the authors is the prior coordination of the amine to the oxygen on C4 in the case of the favored $^4H_5$-conformation **33** (*see Scheme 48 and associated text*) of the nitroglycal. Another rationalization is the proposed kinetic favoring of a *β*-attack in the $^5H_4$-conformation **32**. In the case of the reaction reported by Schmidt, a later investigation into DMAP-catalyzed addition reactions by Yu suggest the viability of a third option for the origin of the absolute *β*-selectivity, namely the nucleophilic addition of NMI prior to the attack of the nucleophile **34**.[41] A follow-up investigation by the group of Liu found that adding base is obsolete in the case of aliphatic nitrogen nucleophiles **36**.[42] Similar to the previous investigation by Schmidt, only the *β*-products **37** form. The high yields of this reaction preclude the use of enamine catalysis in combination with 2-nitroglycals, as the catalyst itself would irreversibly add to the nitroglycal.



Scheme 8: Investigation into the addition of nitrogen heterocycles and amines to 2-nitroglycals by Schmidt and Liu.[40,42]

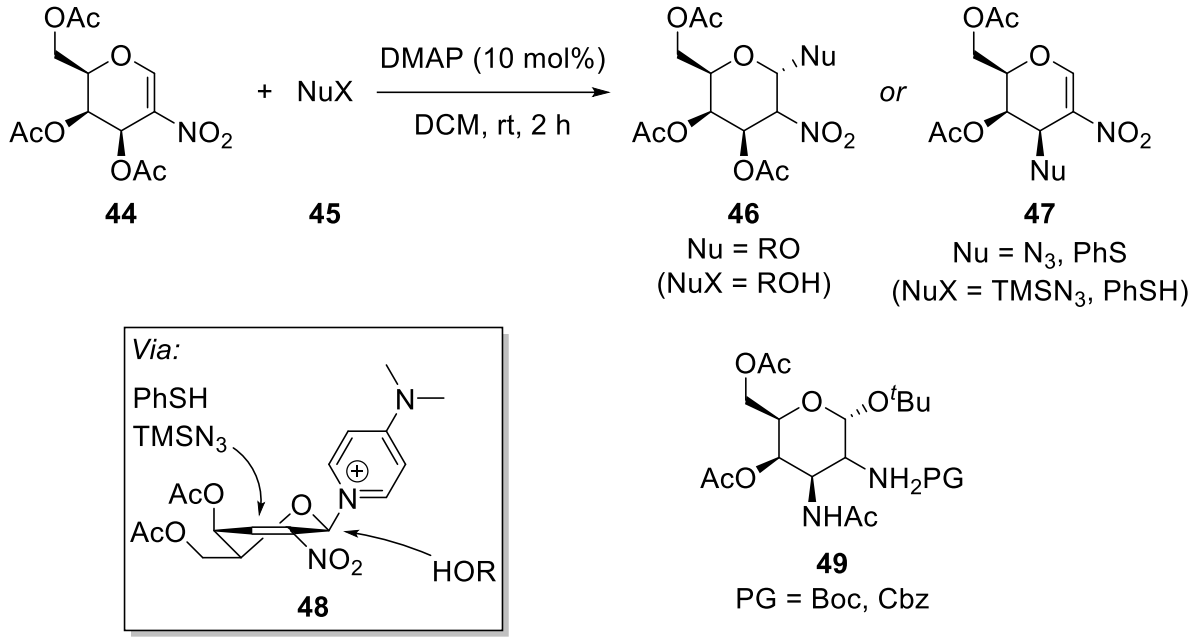
Two reports by the group of Vankar highlight the versatility and the high degree of functionalization achievable by using 2-nitroglycals as precursors.[28,43] Deploying the conditions previously reported by Schmidt[27] for the selective one-pot synthesis of *α*-*O*-galactosides, and by adding a Michael acceptor, they obtained the 2-*C*-branched *O*-galactosides **39** in good yield and absolute selectivity (Scheme 9). Further reactions lead to the formation of a spiro-GABA analogue **41** by reduction of the nitro group. Additionally, the authors synthesized bi- and tricyclic compounds (**42** and **43**) by a radical cyclization. This approach is, however, somewhat limited to the synthesis of galactosides, as experiments with 2-nitroglucal result in the unselective formation of the 2-*C*-branched *O*-galactosides. The difference in stereoselectivity is explained by the different conformational behavior of gluco- and galactosides, whereas in the latter the intermediate nitronate **40** will preferentially adopt a pseudoequatorial position due to the presence of an axial substituent on the C4 position.



Scheme 9: One-pot synthesis of 2-*C*-branched carbohydrate derivatives using 2-nitroglycals.[43]

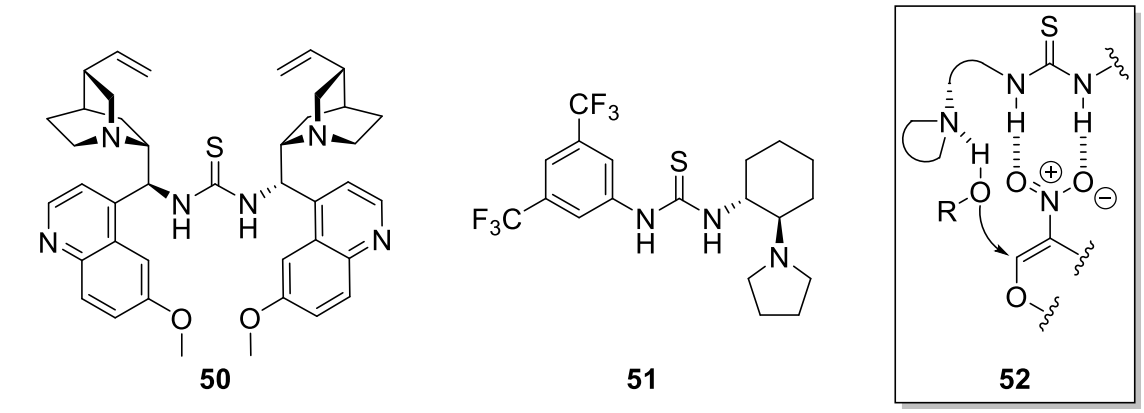
While investigating a DMAP-catalyzed Ferrier-glycosylation using acetyl-protected nitrogalactal **44**, the group of Vankar found that the electronic properties of the glycosyl-

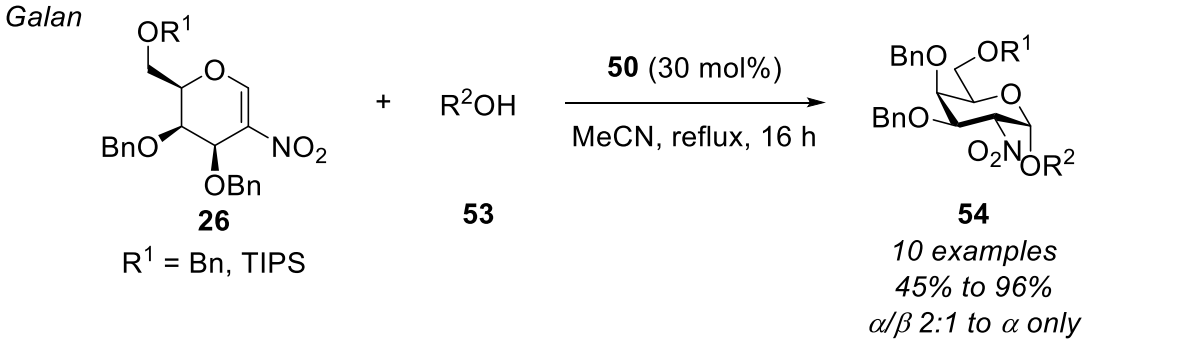
acceptor control the regioselectivity of the glycosylation (Scheme 10).[28] Soft acceptors like TMS-azide and thiophenol only attack at the C3-position, whereas alcohols only attack at the anomeric carbon. Furthermore, the additions in both positions are fully selective. To rationalize their findings, they proposed a mechanism in which DMAP adds from the *α*-side at the anomeric position in the $^5H_4$-conformer to extrude the allylic acetate, forming the intermediate **48**. The softer nucleophiles add to the C3-position in an S_N2'-type mechanism, whereas the harder nucleophiles directly displace DMAP on the anomeric position in an S_N2-type fashion. Using this approach, the authors obtained the differently protected 2,3-diaminogalactoside **49**.

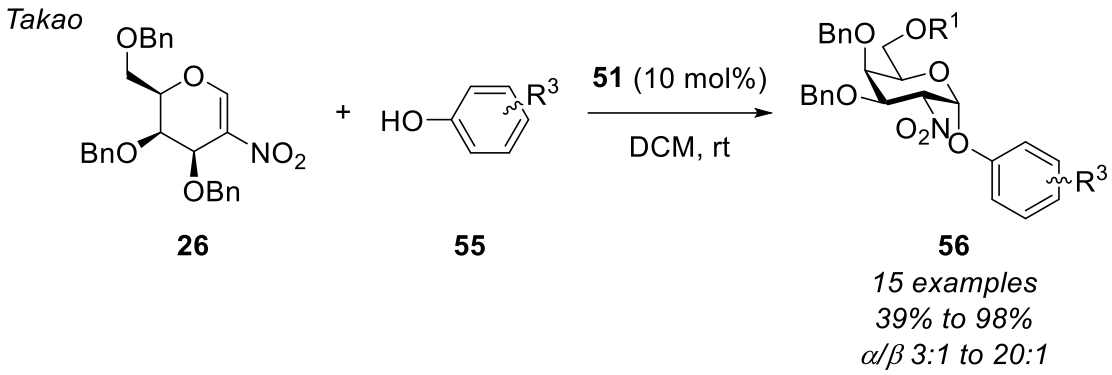


Scheme 10: DMAP-catalyzed Ferrier-glycosylation using 2-nitrogalactal.[28]

Furthermore, two studies by the groups of Galan and Takao in 2016 demonstrated the applicability of thiourea catalysis to 2-nitroglycals (Scheme 11).[44,45] Using the bifunctional thioureas **50** and **51**, they obtained various *O*-glycosides with moderate to absolute *α*-selectivity. Applying this approach to the construction of mucin-type core 6 and 7 enabled the group of Galan to avoid the use of protecting groups on the C2 amino function. By avoiding the extra step for removing this protecting group, they achieved a significantly higher yield in the later stages of the synthesis. Regarding mechanistic considerations, both groups independently proposed **52** to be the key intermediate in the reaction. Further experiments by the Takao group suggested a kinetic control for the anomeric selectivity and the chirality of the catalyst as being central to obtaining a high anomeric selectivity. These findings establish the catalyst configuration as one additional factor for controlling the anomeric selectivity of a glycosylation reaction besides solvent effects and the glycosyl donor and acceptor properties.







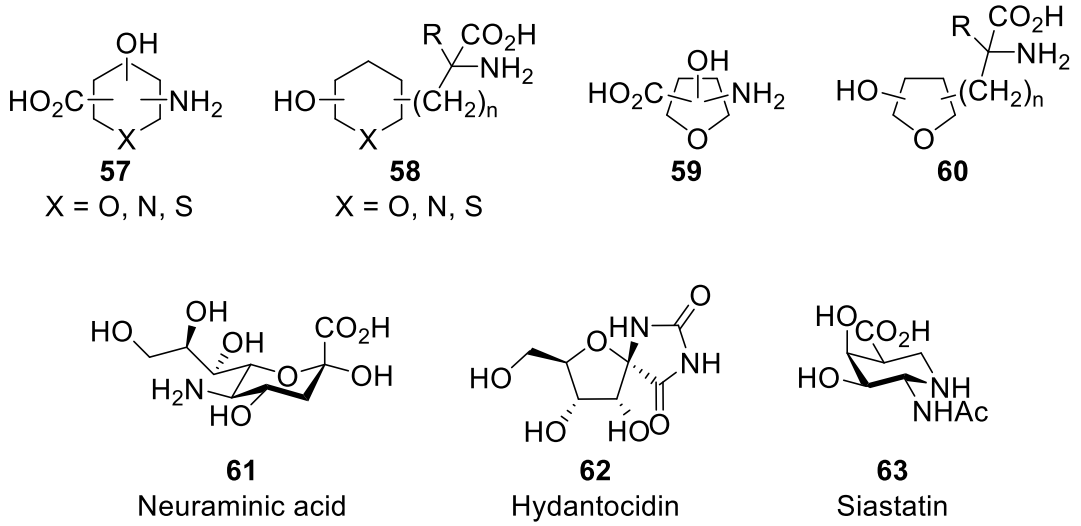
Scheme 11: Organocatalytic glycosylation of alcohols using thiourea catalysts and nitroglycals.[44,45]

2.4 – Sugar Amino Acids

2.4.1 – General Remarks

Sugar amino acids (SAAs) are compounds in which a carbohydrate motif contains an additional carboxylic and amino function. These can be either located on the same or a different carbon atom within the carbohydrate ring. Additionally, *C*-glycosylated amino acids in which the carboxylic and amino functions are located outside the ring can also be considered SAAs. Numerous examples of naturally occurring SAAs are known. Due to this high density of

functional groups, SAAs can be considered privileged substrates for synthesizing glycopeptides and glycopeptide-based drugs, as well as demanding targets to synthesize.[46,47]

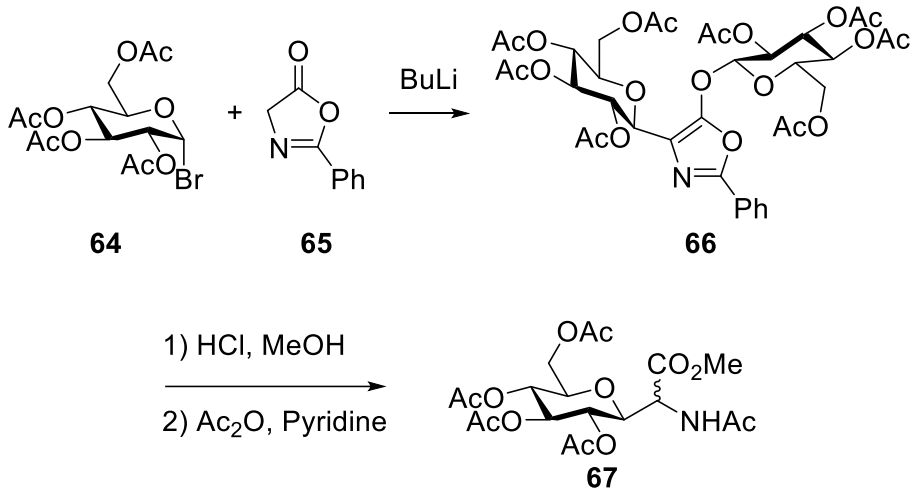


Scheme 12: Generic structures of pyranoid and furanoid SAAs and examples for naturally occurring SAAs.

2.4.2 – Selected Synthesis of *C*-Glycosidic-SAAs

One of the first examples of the synthesis of a glycine-based *C*-glycosidic SAAS (CGSAAs) has been reported by Brink and Rosenthal (Scheme 13).[48] Although there are reports dating back to 1949[49] and 1951[50] for the synthesis of *C*-glycosyl glycine, later attempts to reproduce these reactions only led to the formation of complex mixtures.[51] In their report, Brink and Rosenthal synthesized a *C*-glycosyl glycine **67** by the reaction between peracylated *α*-bromoglucose **64** and oxazolone **65**. After an acidic workup of the bis-glycosylated intermediate **66** and acetylation, they isolated the desired product **67**. Although only the *β*-anomer was detected, both epimers concerning the stereogenic center at the glycine moiety form in a racemic fashion.

Later, the group of Dondoni developed a divergent method to access either the (*R*)- or (*S*)-glycine isomer of *β*-mannofuransoyl glycines selectively using a reagent-controlled approach (Scheme 14).[52] The configuration of the anomeric center is predefined by utilizing the formyl *C*-glycoside aa as a precursor. The addition of *N*-benzylhydroxylamine yields the *N*-benzyl nitrone **69** as the key intermediate, which can either be first treated with diethyl aluminum chloride or directly reacted with the lithiated 2-lithiothiazole **70**. The addition to the nitronate treated with diethyl aluminum chloride preferentially forms the (*R*)-epimer **73** in a d.r. of 4:1.

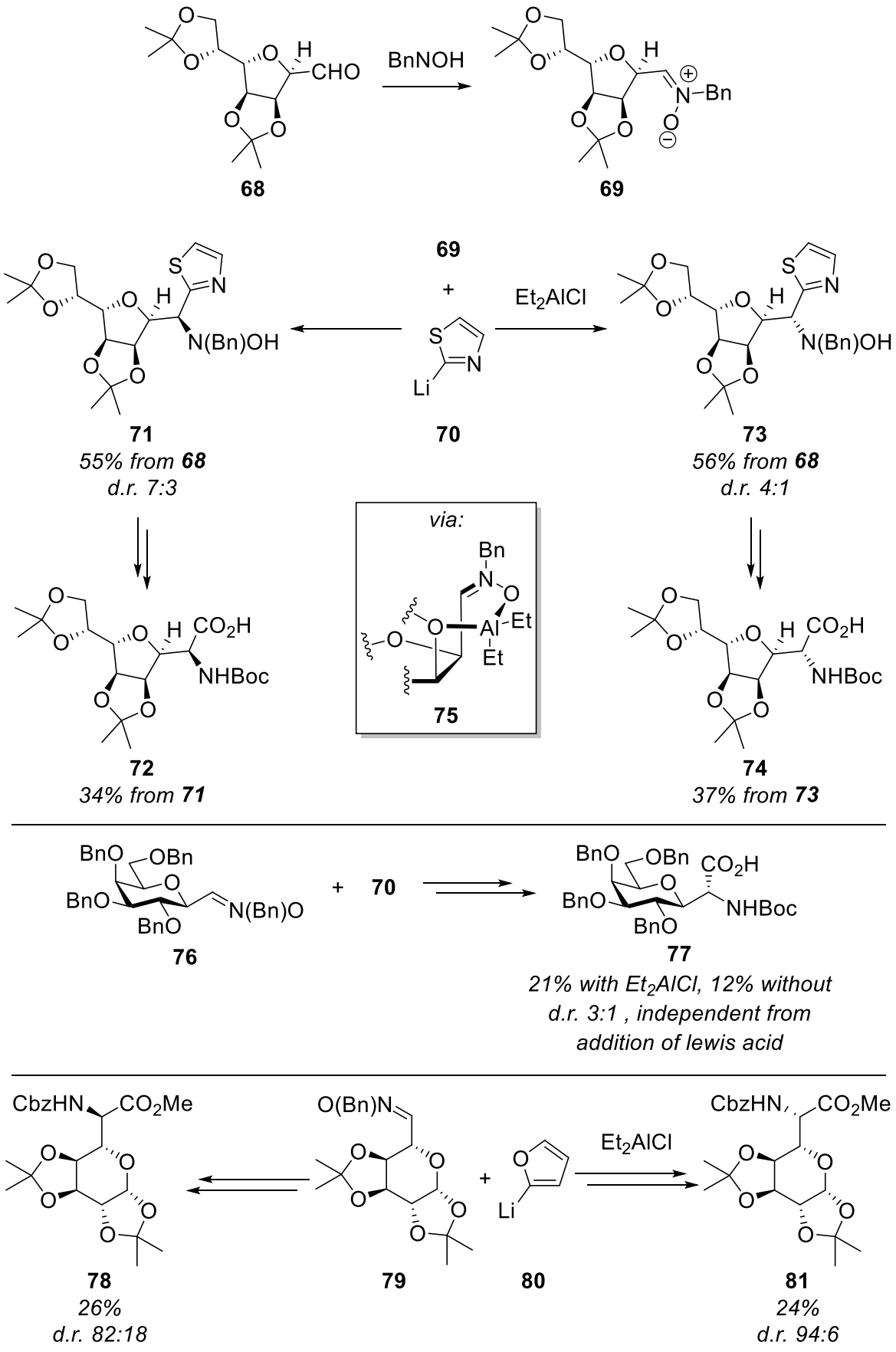


64 **65** **66** **67**

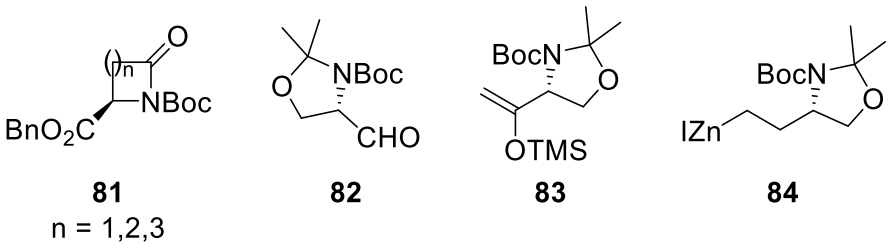
Scheme 13: Unselective synthesis of *β*-glucopyranosyl glycinate.

Direct addition to the nitronate, on the other hand, leads to the (*S*)-epimer **71** preferentially forming in a dr. of 7:3. This inversion of the selectivity is explained with the complexation of the nitronate by the diethyl aluminum, leading to the exposure of the *Si*-side (**75**). In the uncomplexed nitronate, the attack on the *Re*-side is preferred due to the nitronate adopting the opposite conformation. This conformational change leads to the reduction of unfavorable interactions between the nitronate and the furanoside ring. The authors also observed a strong dependency on the carbohydrate scaffold, the site of the substitution, and the nucleophile used. In an attempt to prepare the corresponding galactopyranosyl glycine **77** using the same methodology, the previous inversion of the stereochemistry did not occur. Furthermore, using a galactose scaffold **79** with the nitronate on the C6 and 2-lithiofuran **80** as a nucleophile, the authors obtained an even higher degree of stereocontrol than in the additions to furanoses. However, despite the advantage inherent to a divergent approach, the method suffers from an overall low yield of the final products. Using 2-lithiofuran and 2-lithiothiazole as precursors for the carboxylic acid function makes additional steps for its liberation inevitable, diminishing the final yield.

A standard method used in the synthesis of CGSAAs is the introduction of aliphatic spacers between the carbohydrate moiety and the amino acid moiety.[53] This strategy offers two main advantages. First, the amino acid moiety's stereocenter is often pre-determined, simplifying the issue of stereocontrol and subsequently limiting the number of possible products that could form during the reaction. Second, numerous methods have been developed for the stereoselective construction of anomeric C–C-bonds involving aliphatic substrates.[19,53] Examples of the synthons used in literature to construct such “spaced” CGSAAS are depicted in Scheme 15.

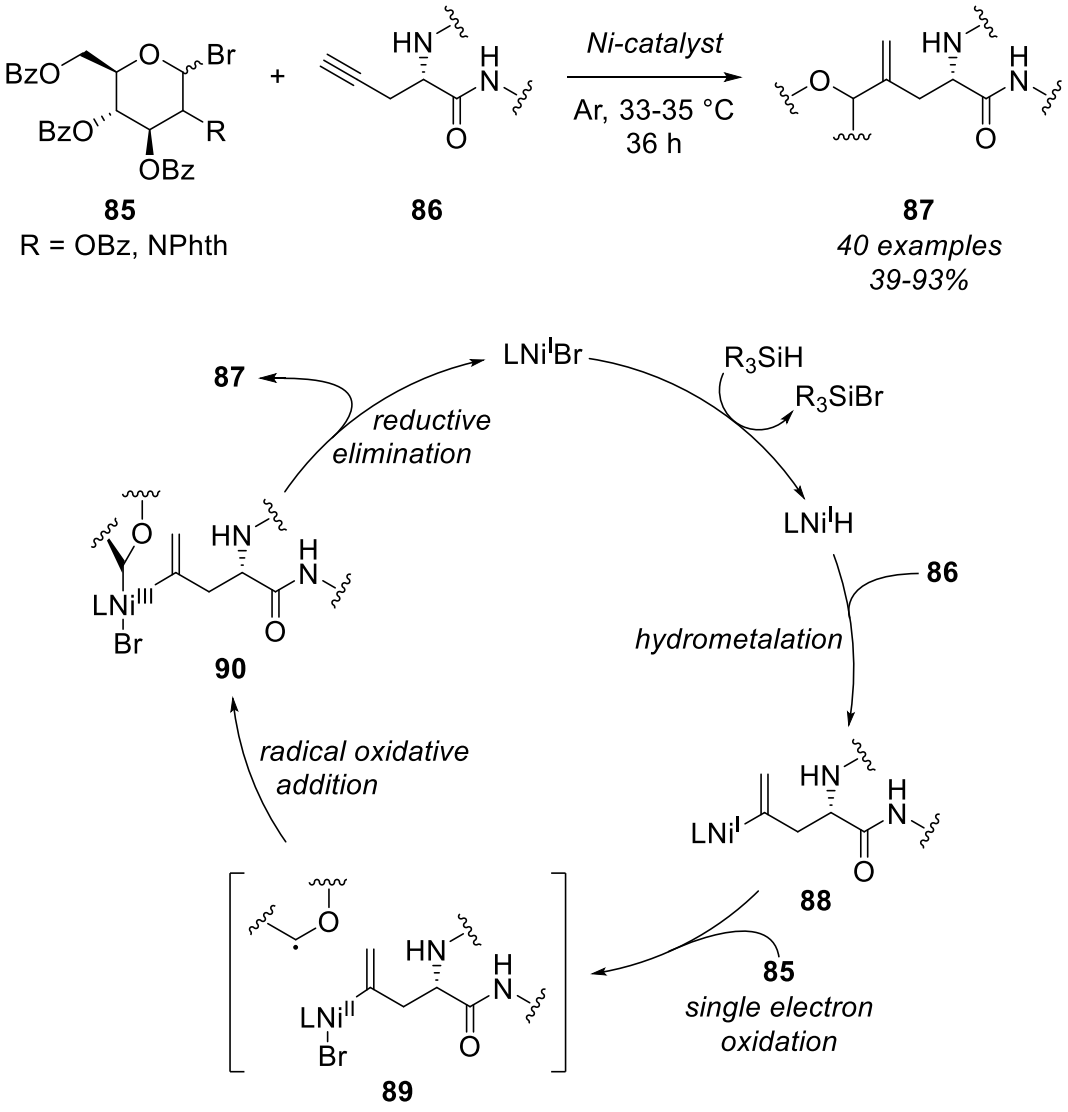


Scheme 14: Stereodivergent approach for synthesizing various *C*-glycosyl glycines reported by the Dondoni group.[52]



Scheme 15: Synthons used for the construction of alanine and serine glycosides.[53]

The group of Yu recently reported an example for the synthesis of complex CGSAAs and dCGSAAs (Scheme 16).[54] Their approach relies on a nickel-catalyzed reductive hydroglycosylation of alkyne precursors similar to **86**. One advantage of this method is that it allows the coupling of complex peptide or glycoside chains in moderate to good yields and gram-scale experiments.

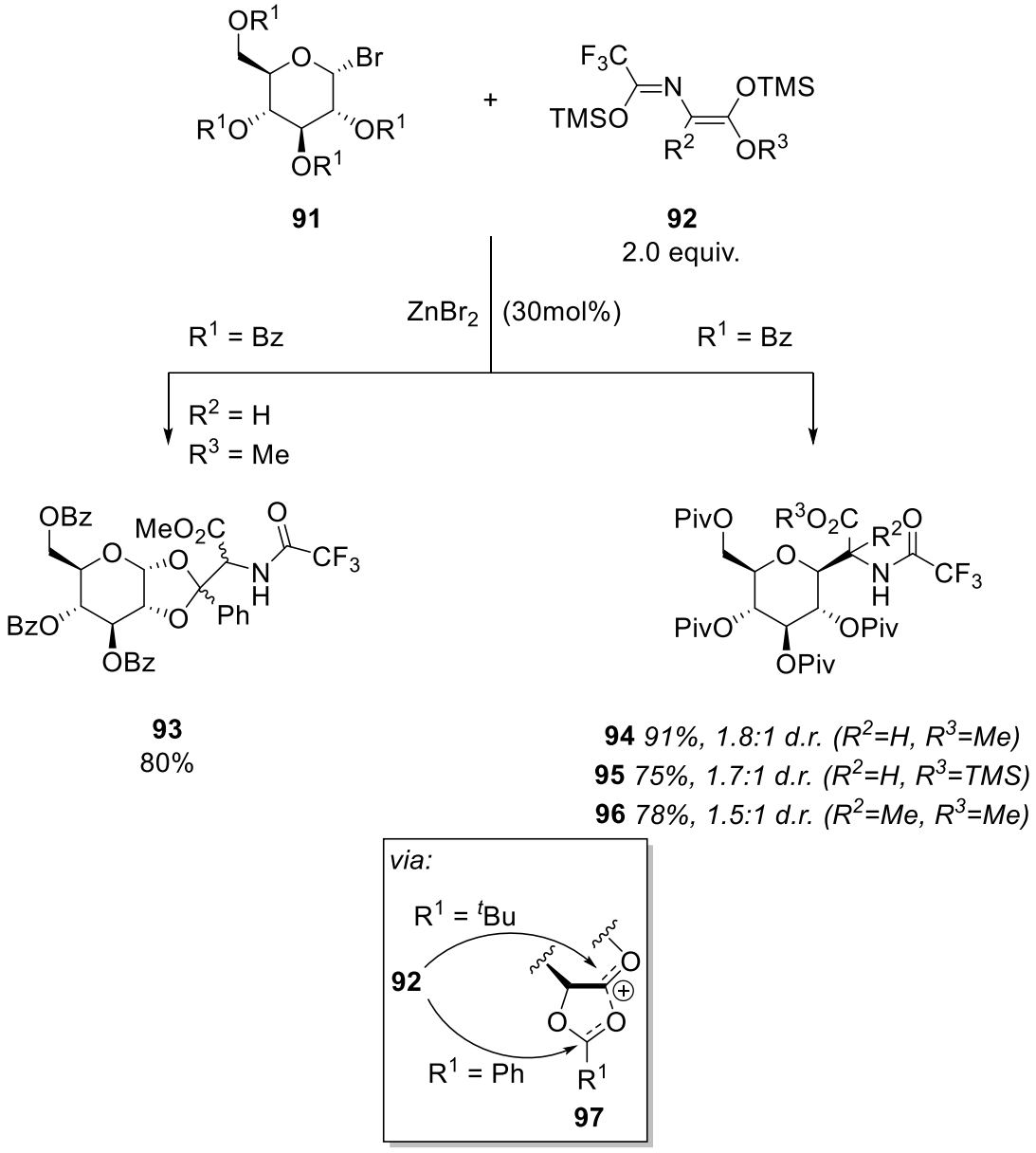


Scheme 16: Overview and proposed mechanism of the glycosylation reported by the Yu group.[54]

A significant drawback of the approach is the need for 2.5 equivalents of base, and a silane needs to be deployed as promoter, generating a large amount of waste. Furthermore, the reaction needs strict exclusion of air and moisture as the reaction otherwise ceases to proceed. Lastly, the protecting group of the amino function on the carbohydrate used under the reaction conditions reported is phthalimide, which requires harsh conditions to be removed, excluding the introduction of sensitive functional groups.

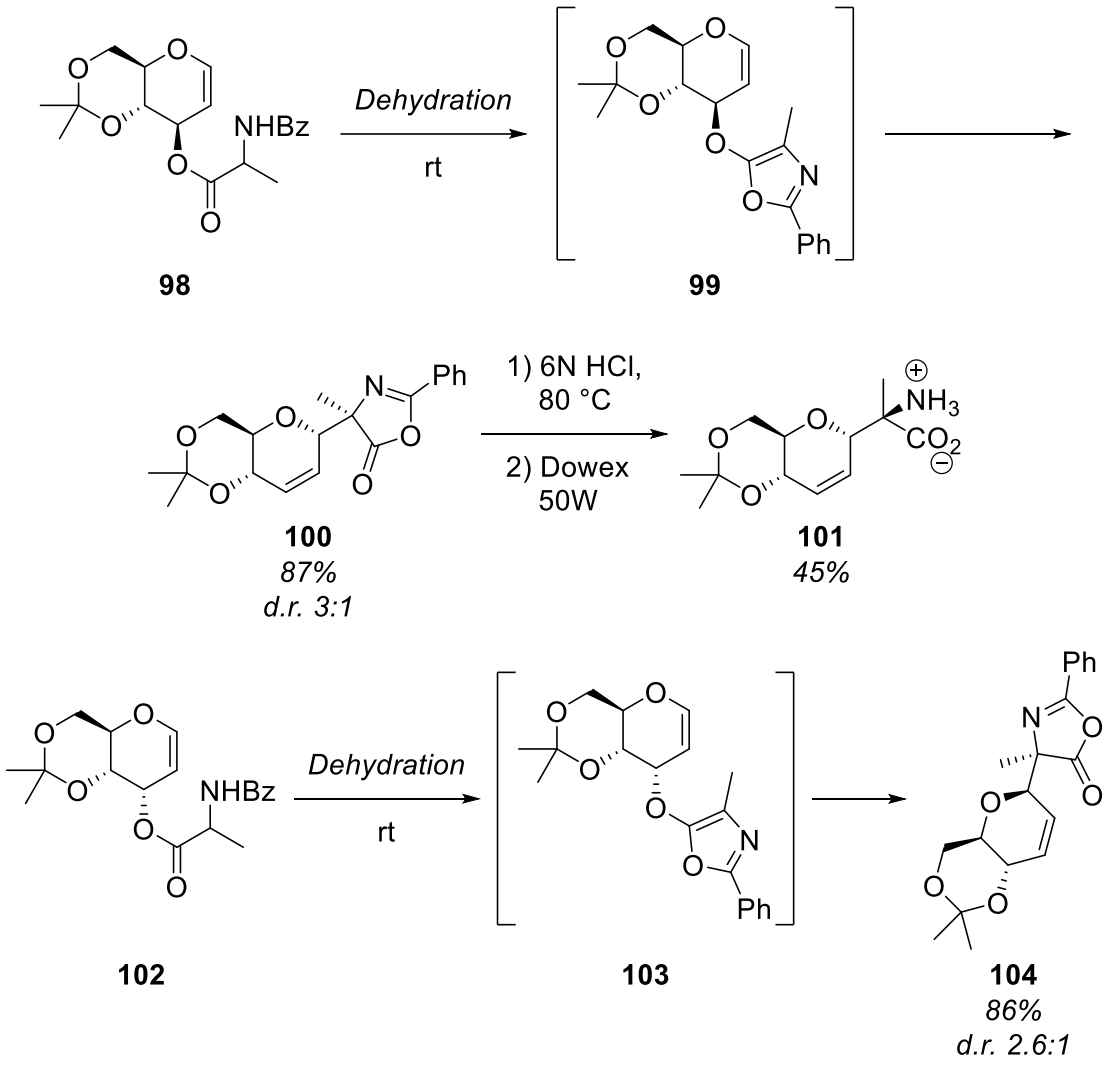
The number of reported synthetic routes leading to CGSAAs with the amino acid bearing a quaternary stereocenter next to the anomeric carbon is very limited. To the best of our knowledge, only six reports for the synthesis of this scaffold exist so far.[55–60] The synthesis of Simchen and Pürkner (Scheme 17),[57] while not being selective with respect to the newly formed quaternary stereocenter, highlights the strong influence the protecting groups on the carbohydrate can have. Only the undesired product **93** forms when the silyl-enol ether **93** and the benzoyl-protected *α*-glycosyl bromide **91** are used under zinc catalysis. By changing the protecting groups from benzoyl to pivaloyl, the desired addition products **94-96** form exclusively. This change in selectivity is rationalized by the formation of an intermediary oxonium ion **97** with the neighboring ester function. This oxonium ion stabilizes the oxocarbenium ion and assists in the determination of the anomeric stereocenter by blocking the attack of the nucleophile from the *α*-side. In the case of the benzoyl-protected glycosyl bromide, this results in an attack on the protecting group. In contrast, the steric demand of the *tert*-butyl group in the pivaloyl-protected glucoside precludes such a reaction pathway.

Less than one year later, Colombo and coworkers reported an approach utilizing an intramolecular Steglich-variant[61] of the Claisen-rearrangement[62] of the *in situ* created oxazolone bound to glucal **98** on the C3 position (Scheme 18).[58] Interestingly, the reaction proceeded at room temperature without needing prolonged heating, usually required for Claisen rearrangements in carbohydrates.[63] Furthermore, the authors isolated the rearrangement product **100** in high yield and with absolute *β*-anomeric selectivity. The relative position of the hydroxyl group on C3 determined the anomeric selectivity during the rearrangement. Despite the high anomeric selectivity, the approach suffers from several drawbacks. First, one stereogenic center on the carbohydrate is depleted during the rearrangement, necessitating additional steps for reconstructing these stereogenic centers.



Scheme 17: First reported synthesis of a CGSAAs containing a quaternary stereocenter next to the anomeric carbon.[57]

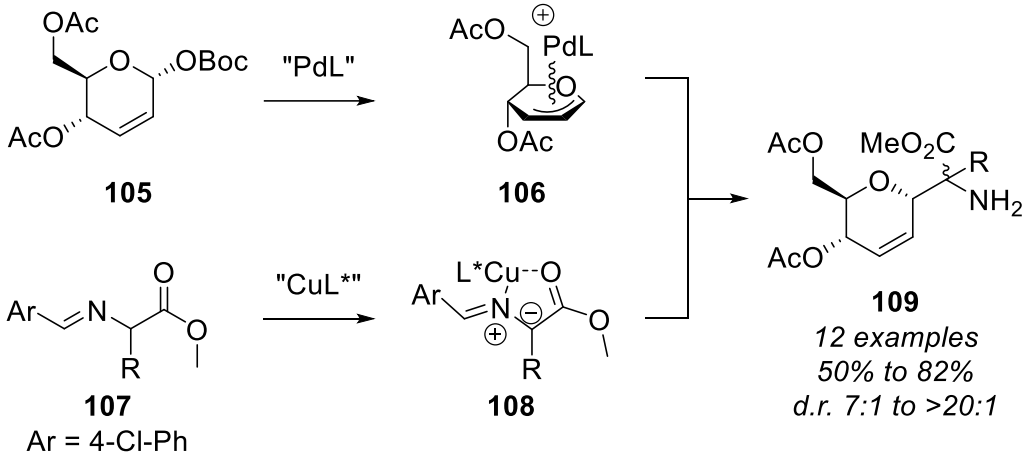
Secondly, the opening of the azlactone and deprotection of the carbohydrate only proceeds in moderate yield. Lastly, the diastereoselectivity concerning the quaternary stereocenter does not exceed a 3:1 ratio due to the high degree of flexibility of the system. This allows the intermediary formed oxazolone to rotate around the C–O-bond before undergoing the rearrangement. In a follow-up publication the group repeated the oxazolone rearrangement on allal **102** leading to an even lower diastereomeric selectivity.[59] Additionally, the dehydration step for the azlactone synthesis requires a two-fold excess of toxic and expensive CCl_4, precluding the application on a larger scale.



Scheme 18: Claisen-rearrangement-based synthesis of CGSAAs reported by Colombo and coworkers. The azlactones are synthesized by dehydration with a mixture of PPh_3, CCl_4, and Et_3N.[58,59]

Recently, the group of Wang reported a stereodivergent glycosylation method relying on a dual catalytic system (Scheme 20).[55] Using the Boc-glycoside precursor **105** enabled them to obtain an allyl-palladium species **106**, similar to a previously reported example (Scheme 19).[56] The facial selectivity in the generation of the allyl-palladium species **106** controls the anomeric selectivity. In parallel, an azomethine-ylide **108** is generated from the imine **107** using a copper catalyst, with the chiral ligand on the copper controlling the stereoselectivity in the formation of the quaternary stereogenic center. In contrast to all previous reports, when the authors changed to the opposite enantiomer of the chiral ligand on the copper, the opposite diastereomer of the quaternary stereogenic center forms, albeit the d.r. is cut in half by this. Similar to the previous example of Yu, scale-up experiments were conducted without encountering any problems, but the use of an allyl-palladium species necessitates subsequent steps to re-built the stereogenic centers on C2 and C3, similar to the rearrangement-based approaches described

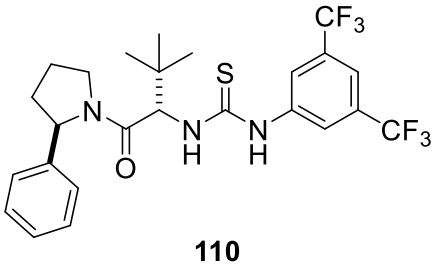
earlier.[58,59] Furthermore, the reaction needs to be run under the strict exclusion of oxygen or moisture, and only the acetyl-protected glycoside donor **105** is compatible with this approach.



Scheme 20: Stereodivergent system for the synthesis of CGSAAs.[55]

2.3 – Thiourea Catalysis and Carbohydrate Chemistry

Since the cyanide catalyzed benzoin condensation was discovered by Liebig and Wöhler in 1832[64] as the first example of an organocatalyzed reaction, many breakthroughs were achieved, finally culminating in the Nobel Prize of 2021 being awarded to List and MacMillan "for the development of asymmetric organocatalysis".[65] Offering a mild and environmentally friendly alternative to the established glycosylation reactions, which often rely on the stochiometric use of potentially hazardous reagents or expensive transition metal catalysts, the concept of organocatalysis has attracted ever more attention over the years.[66,67] Among the numerous organocatalysts used for glycosylation reactions, thiourea catalysts are commonly used owing to their stability, good synthetic availability, and diversity. The first investigation into thiourea-catalyzed glycosylation reactions dates back to a study conducted by the Jacobsen group in 2008 (Scheme 21).[68] They observed a significant rate acceleration for the addition of methanol to glycosyl acetate **111**, when thiourea **110** was added to the reaction. This increases the conversion of **111** from 19% to 94% within the same reaction time. Additionally, by using the opposite enantiomer of catalyst **110**, an inversion of the previous, albeit small, anomeric selectivity was observed. Furthermore, a change in the original diastereomeric ratio was found when they re-isolated the remaining starting material. This, according to the authors, suggested a certain degree of stereocontrol being exerted by the catalyst, therefore proving the possibility of catalyst-controlled stereoselective glycosylations with thioureas.



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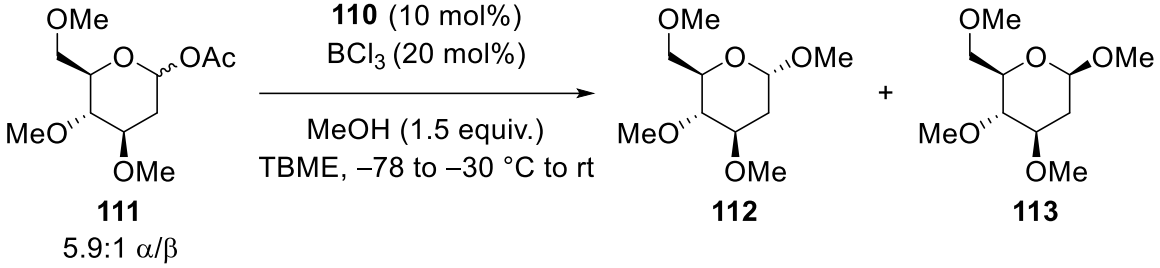
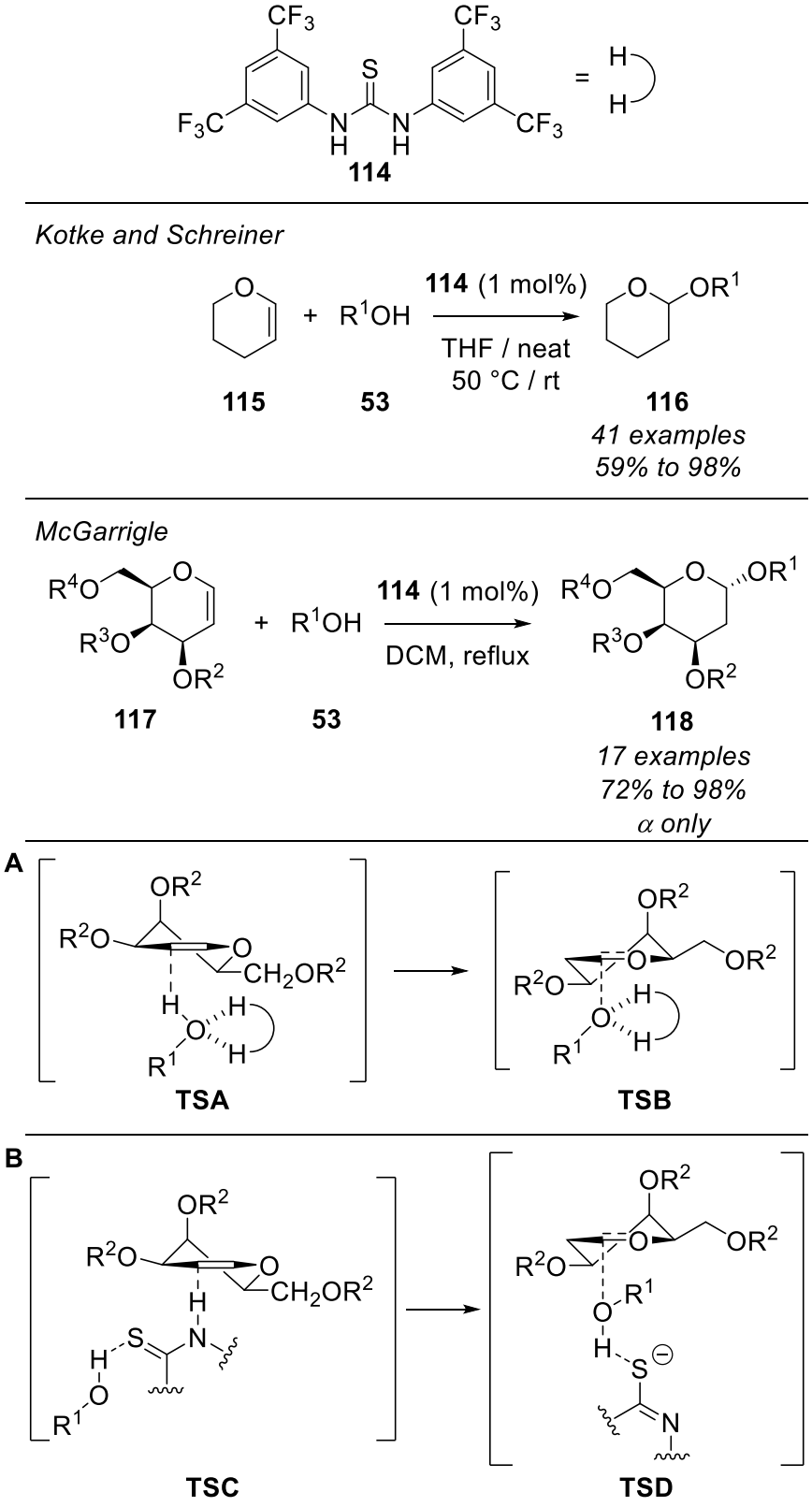


Entry	Catalyst	Conv. / %	112 / 113	111 reis. / *α*/*β*
1	–	19	1:1.1	>15:1
2	(*R*,*S*)-**110**	94	1:1.7	>15:1
3	(*S*,*R*)-**110**	56	1.4:1	8.9:1

Scheme 21: Results reported by the Jacobsen group of their preliminary investigation (reis. = reisolated).[68]

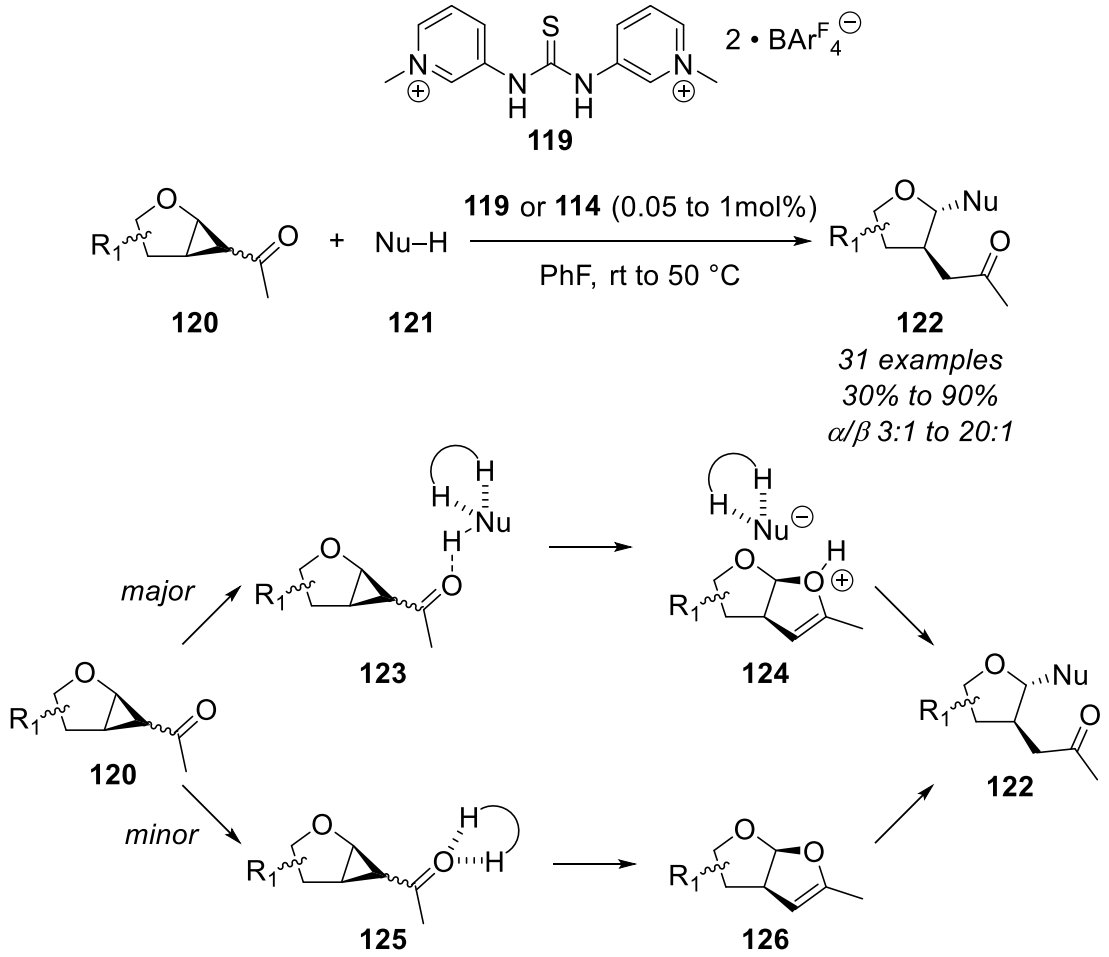
Four years later, inspired by the work of Kotke and Schreiner,[69] the group of McGarrigle reported highly *α*-selective glycosylation of galactals (Scheme 22).[70] Using the previously introduced thiourea **114**, also known as T1, enables the synthesis of 17 2-deoxygalactosides in good to excellent yield. Currently, there are two mechanistic proposals explaining the high degree of selectivity. The group of McGarrigle used an adapted version of the initially proposed oxyanion mechanism (**A**) of Kotke and Schreiner to explain the observed selectivity. In this mechanism, the thiourea coordinates the alcohol, increasing its acidity. This activation, in turn, leads to the protonation of the glycal by the alcohol, and an oxocarbenium-ion forms (**TSA**). The adjacent oxyanion then stabilizes this intermediary oxocarbenium ion (**TSB**). The preferential adoption of the $^4H_5$-conformation of the galactal used can explain the facial selectivity, as the protonation will proceed from the less hindered face, i.e., from the lower side. The following addition of the oxyanion is then mainly governed by the resulting anomeric effect, the favored chair-like transition state, and sterical factors.[69,70] Overall, this pathway for a formal [2+2]-addition of the alcohol leads to the observed *α*-product. Later, a computational study by Pápai and coworkers challenged this model, proposing a Brønsted acid activation of the glycal by the thiourea (mechanism **B**).[71] During this mechanism, the sulfur atom is coordinated by the alcohol, leading to an increase in acidity of the amide protons. Next, the

amide of the thiourea protonates the glycal (**TSC**), and in a subsequent step, the alcohol adds to the oxocarbenium resulting from the previous protonation (**TSD**). The stereochemical reasoning for the exclusive addition to the α-side of the glycal remains the same.



Scheme 22: Thiourea catalyzed addition of alcohols to DHP and Galactal with the proposed mechanisms.[69–71]

A recent example by the group of Loh[72] used the electronically enhanced thiourea **119** developed by the Kass group[73] or **114** for a strain-release glycosylation of furanosides and pyranosides (Scheme 23). This approach leads to the formation of 2-deoxy-glycosides with an almost exclusive *α*-selectivity. Furthermore, various *O*-, *N*-, *S*-, and even *C*-based nucleophiles are compatible with this approach. Additionally, catalyst loadings of 0.05 mol% are feasible in a gram-scale experiment, and one-pot multicatalytic diversifications were carried out, further expanding the scope. Dedicated mechanistic studies revealed two competing pathways for the addition to the cyclopropanated carbohydrate **120**.



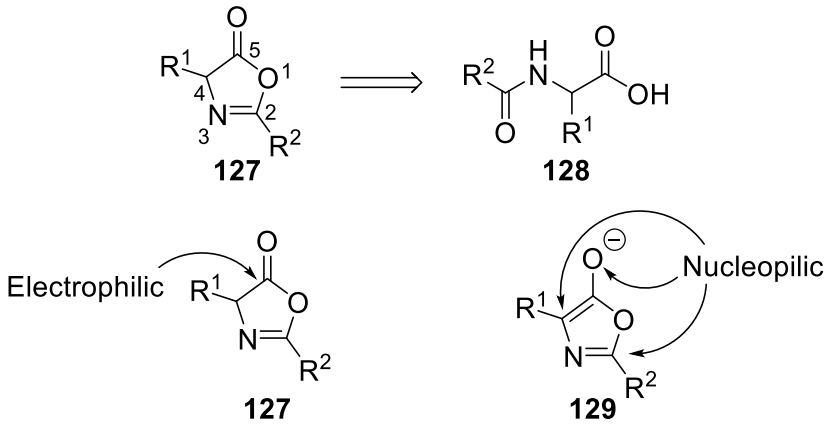
Scheme 24: Thiourea catalyzed train release glycosylation and proposed mechanism reported by the Loh group.[72]

In the major reaction pathway, the thiourea first coordinates the nucleophile before it protonates the ketone adjacent to the cyclopropane (**123**). This leads to the opening of the cyclopropane ring, the formation of an enolate, and the subsequent attack by the oxygen of the enolate at the newly formed oxocarbenium ion. The anomeric stereocenter retains its configuration during this reaction sequence, forming the intermediate **124**. During the minor pathway, the thiourea directly coordinates to the ketone (**125**) and initiates the formation of the bicyclic intermediate

126. The nucleophile then opens up both intermediates **124** and **126** from the unshielded side in an S_N2-like fashion forming the product **122**.

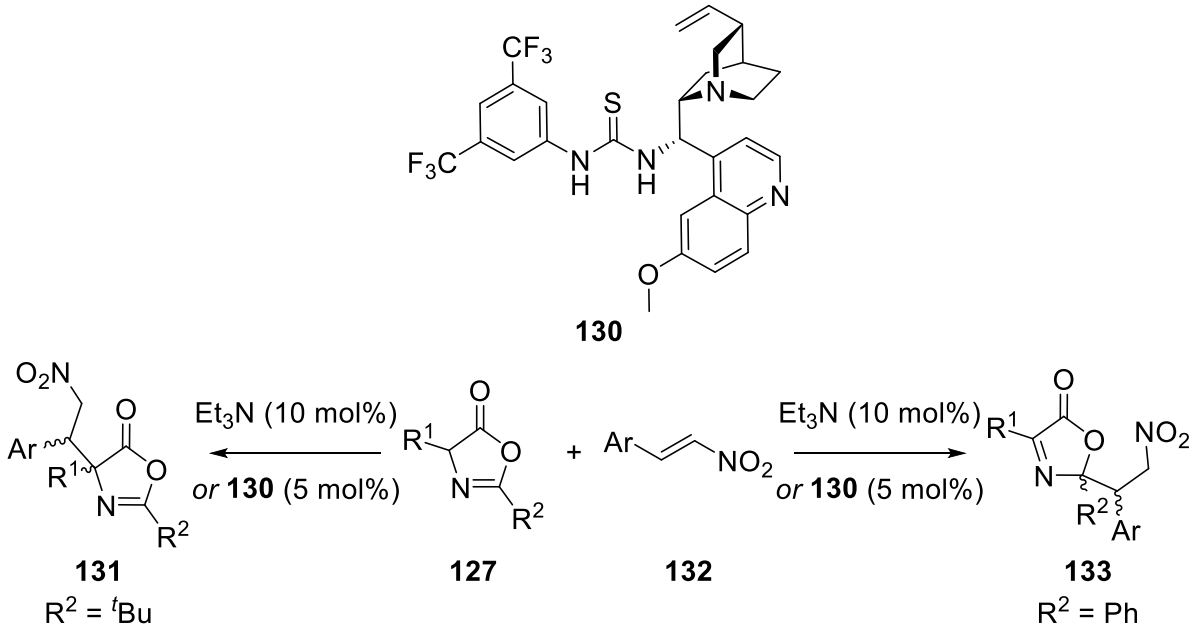
2.5 – Azlactones

1,3-Oxazol-5(4*H*)-ones **127**, commonly called oxazolones or azlactones, are widely recognized as valuable scaffolds for the synthesis of substituted amino acids[74,75] and dipeptides[76]. The density of reactive sites within azlactones, in combination with the high acidity of the C4-hydrogen ($pK_a \approx 9$)[77,78] caused by the aromatic character of the corresponding enolate, makes them privileged scaffolds to be deployed as masked amino acid equivalents under mild conditions.



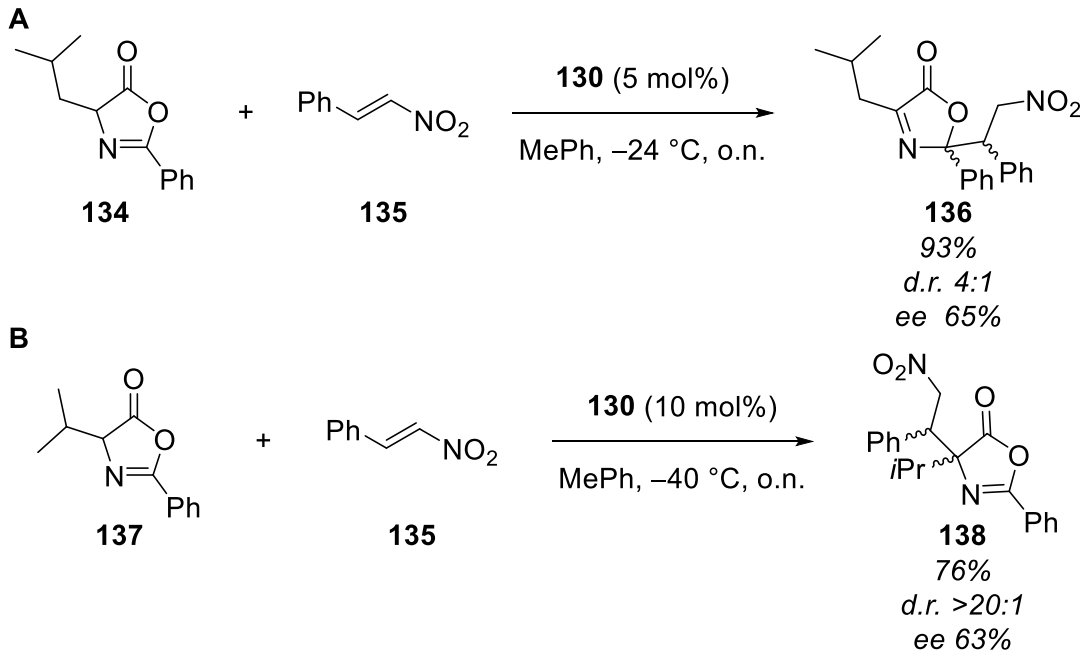
Scheme 25: General structure of azlactones and reactive sites.

Due to these advantages, numerous reports have been published for the asymmetric synthesis of quaternary amino acids, using azlactones as key intermediates.[79,80] However, in the organocatalytic Michael-addition of azlactones, the regioselectivity of the nucleophilic attack of oxazolones has been a known issue, as it can either occur from the C2 or C4 carbon. During an investigation into the addition of various azlactones to nitrostyrenes, the groups of Jørgensen[81] and Rios[82] found an inherent selectivity for the formation of the C2-regioisomer **133** (Scheme 26). The group of Jørgensen was able to override this selectivity by using azlactones derived from *N*-pivaloyl-protected amino acids, concluding that the steric bulk of the *tert*-butyl group at the C2-position leads to the inverted regioselectivity and the formation of the C4-regioisomer **131**.[81]



Scheme 26: Dependency of the regioselectivity on the substitution pattern as reported by Rios and Jørgensen.[81,82]

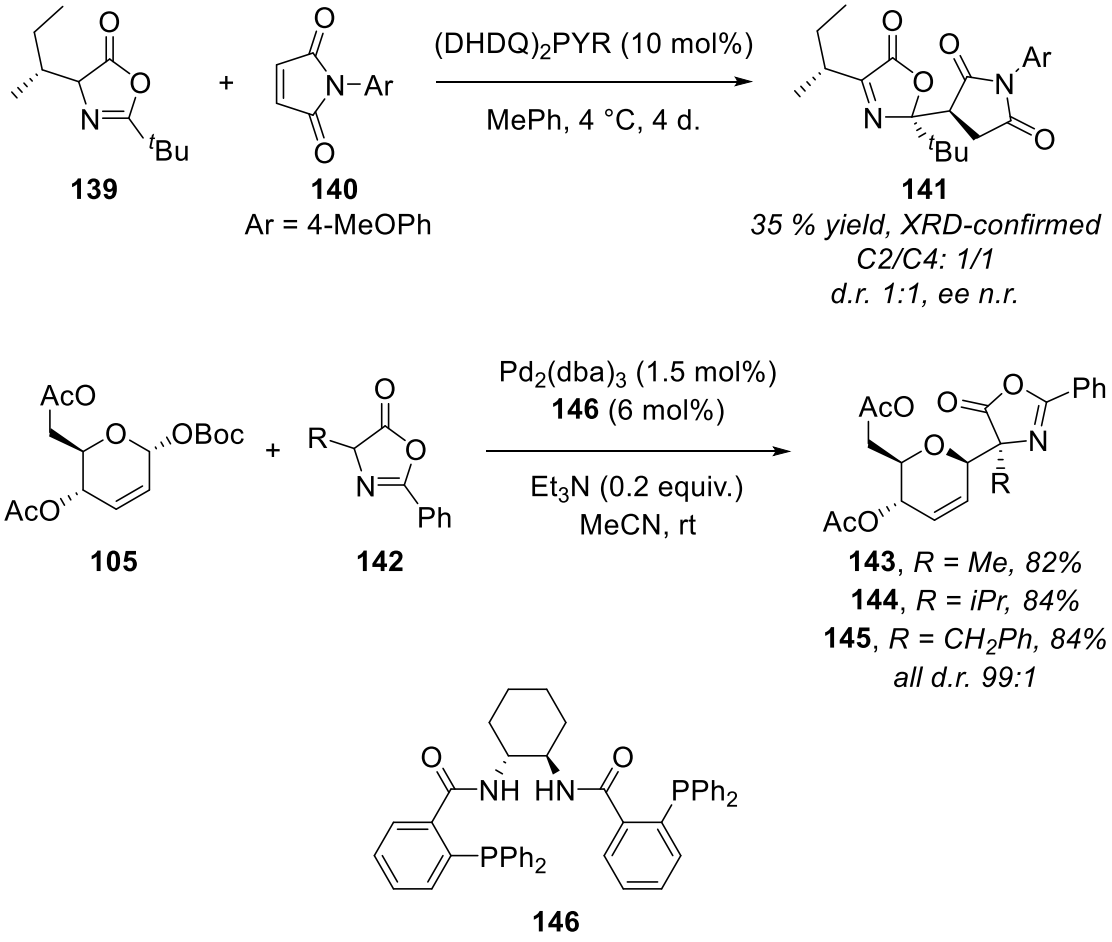
Results from an investigation conducted by Wang (**B**) and coworkers question the general reactivity towards the C2-selective addition of azlactones to nitrostyrenes.[83] Despite using an azlactone and conditions comparable to the ones reported by Jørgensen (**A**) in combination with the same catalyst, the C4 regioisomer **139** forms instead of the expected C2 isomer.



Scheme 27: Regioselectivity reported by Jørgensen (**A**) and Wang (**B**).[81,83]

Additionally, it is well established that the regioselectivity also strongly depends on the acceptor's nature. For example, reactions with *α,β*-unsaturated aldehydes, and ketones generally

favor the formation of the C4 regioisomer. [79,80,84] The addition to maleimides, on the other hand, prefers the addition to the C2-position to such a degree that, in some cases the previously mentioned strategy of Jørgensen to suppress this reactivity by introducing a *tert*-butyl group at C2 is unable to prevent the formation of the C2 regioisomer **142**.[85] Despite these drawbacks regarding the regioselectivity, azlactones have previously been successfully deployed in one of the few reported examples for the stereoselective formation of GCSAAs with the amino acid bearing a quaternary stereocenter next to the anomeric position.[56] This allowed the authors to access a set of three different mannosylated amino acids (**144**) with an inverted, absolute, anomeric selectivity compared to the previous example and without the need for a dual catalytic system.[55]

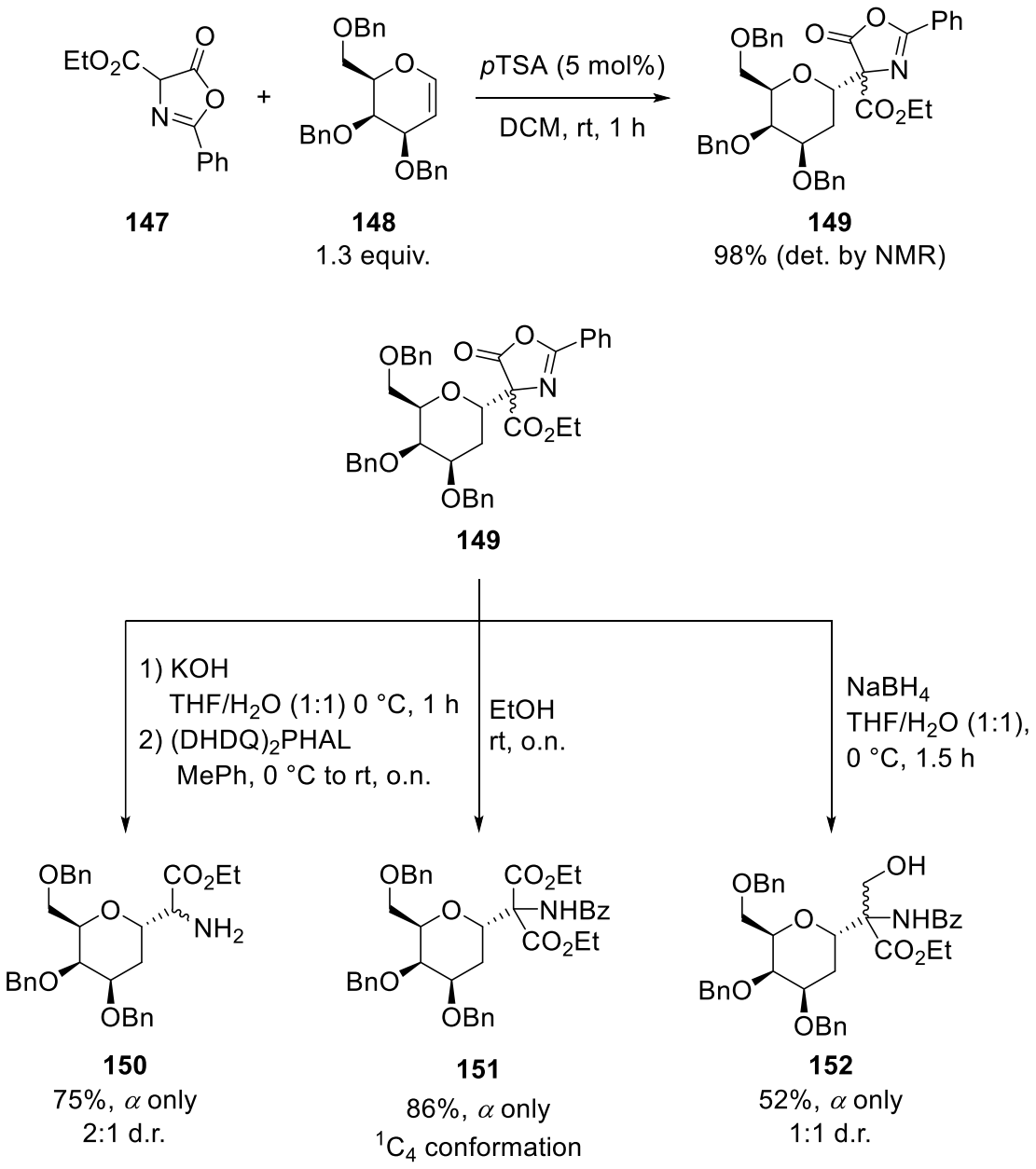


Scheme 28: Unusual regioselectivity observed for the addition of azlactones to maleimides and stereoselective glycosylation of azlactones using Pd-catalysis (n.r. = not reported).[56,85]

3 – Objective and Background

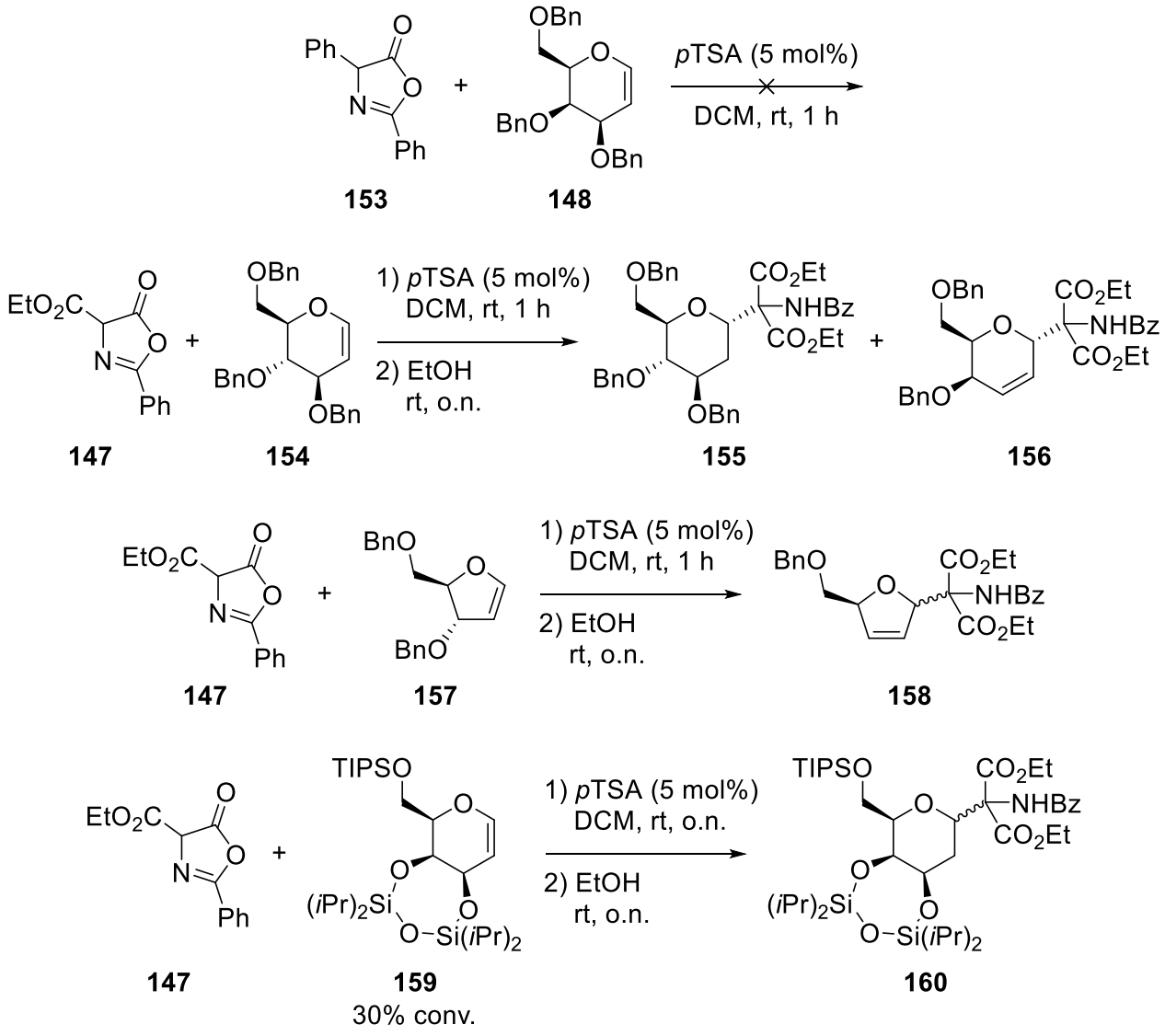
3.1 – Previous Investigations

A previous investigation on the organocatalytic synthesis of 2-deoxy-*C*-glycoside amino acids yielded a divergent strategy to synthesize 2-deoxy-*C*-galactosyl serine **152** and the corresponding glycine analog **150** (Scheme 29).[86] Albeit the attractivity of this approach due to its high atom economy and short reaction times, several limitations were encountered. As it turned out, the azlactone **147** was the only one compatible with the reaction conditions employed.



Scheme 29: Overview of the results of the previous investigations.[86]

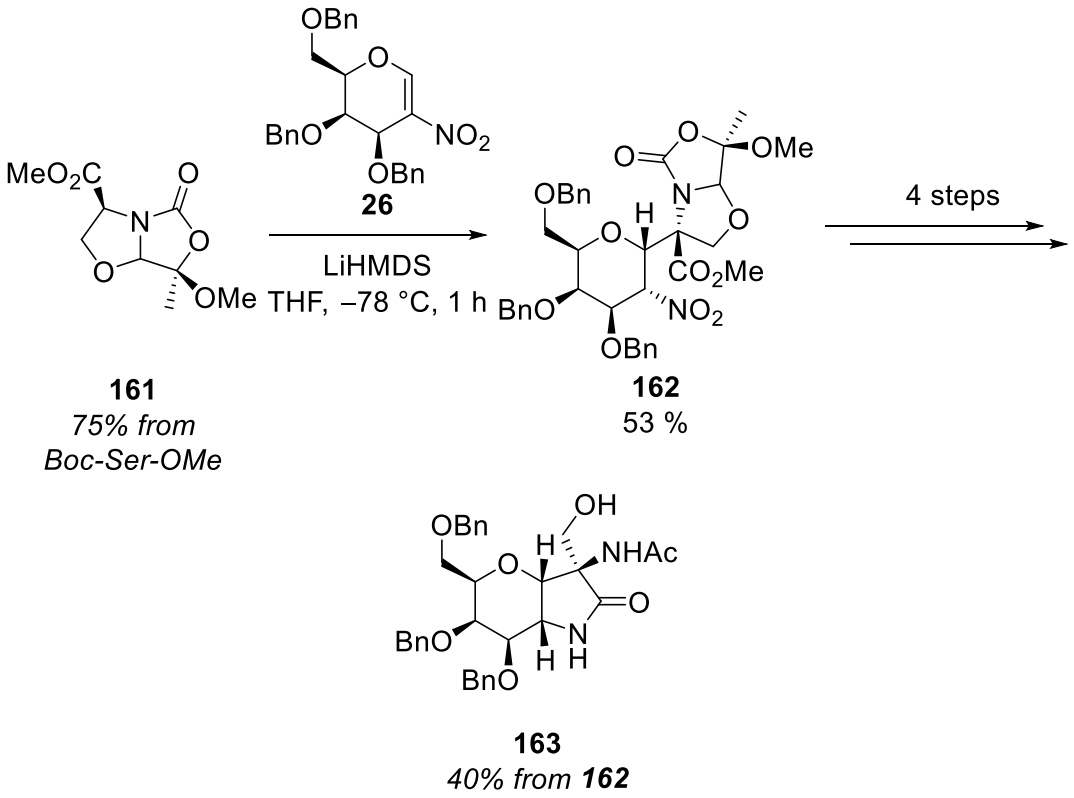
Using other azlactones like **153** gave no conversion, therefore limiting this approach to the synthesis of serine and glycine analogs. Furthermore, no satisfying diastereoselectivity could be achieved despite using stochiometric amounts of $(DHDQ)_2PHAL$ in the decarboxylation step for the glycine analogue. Moreover, it was found that the initially used benzylated galactal **148** was the only glycosyl donor that provided the desired products. Using ribal **157** under the reaction conditions described above with subsequent ethanolysis gave low conversion of the starting material and exclusively the Ferrier-rearrangement product **158**. With glucal **154** formation of an inseparable mixture of the desired *C*-glycoside **155** and the Ferrier side product **156** in a 1:1 ratio with 60% overall yield was observed (Scheme 30). Attempts to suppress the formation of the Ferrier side product **156** by employing a *trans*-fused protected glucal **159** led to the exclusive formation of the desired product **160** but considerably lower conversion despite prolonged reaction times (Scheme 30).



Scheme 30: Limitations of the substrate scope and use of the *trans*-fused glucal **160**.[86]

3.2 – Synthetic Overview

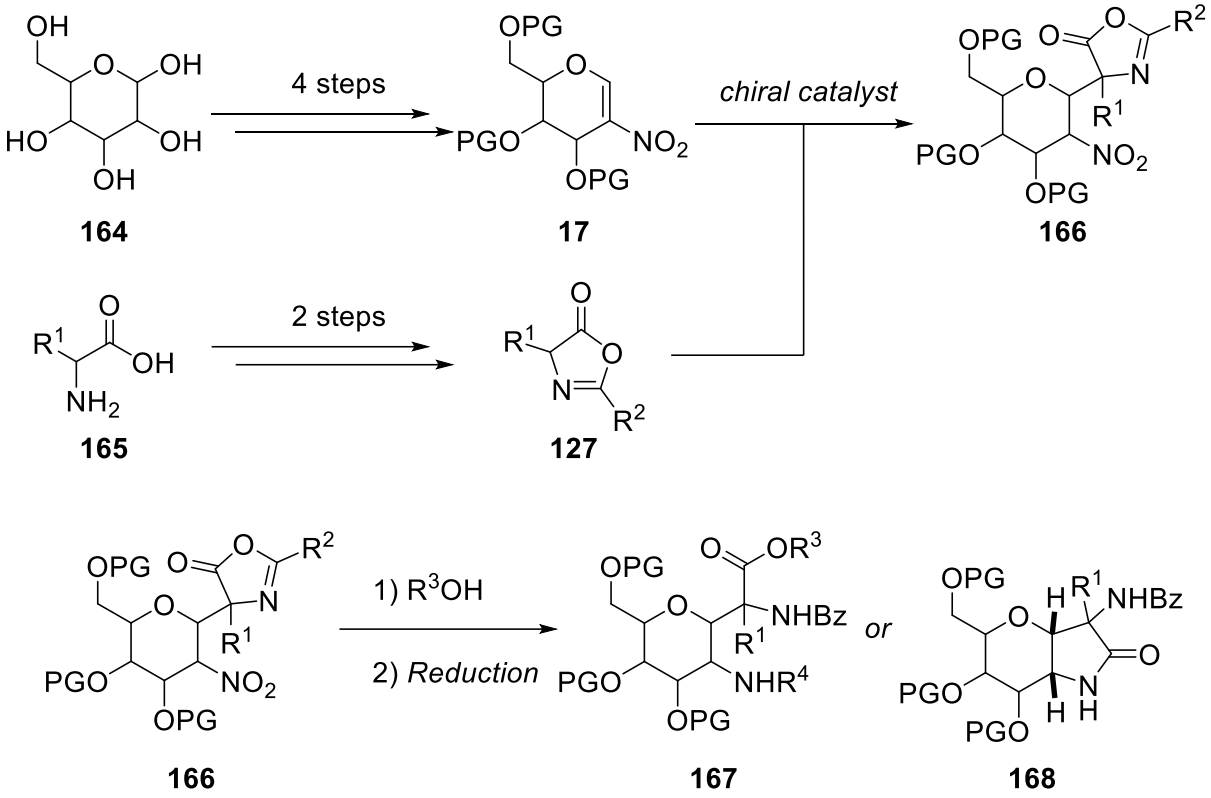
Inspired by the work of the Peregrina group[60] (Scheme 31), we envisioned an organocatalytic, divergent approach that would enable the synthesis of a large variety of 2-deoxy-2-amino-*C*-glycoside amino acids. During their studies, the group of Peregrina utilized the bicycle **161**, derived from *N*-Boc-protected serine methyl ester in a double diastereoselective Michael-type addition to 2-nitrogalactal **26**. Using LiHMDS as base, they obtained the desired product **162** in 53% yield as a single diastereomer. Further modifications led to the formation of the T_n-antigen mimic **163**, evaluated for its lectin-blocking properties.



Scheme 31: Excerpt from the T_n-antigen mimic synthesis reported by the Peregrina group[60,87]

By using 2-nitroglycal **17** and azlactone **127** as established precursors in combination with a chiral organocatalyst, we envisioned that a reasonable degree of stereocontrol over the newly formed quaternary stereogenic center might be achieved. The stereogenic centers created on the carbohydrate moiety will most likely be controlled by a multitude of factors, like the other existing stereogenic centers on the carbohydrate, solvent effects, or the choice of the protecting groups. Therefore, the focus will be on the newly formed quaternary stereogenic center. Alcoholysis of the azlactone scaffold in **166**, followed by a reduction of the nitro group on the carbohydrate moiety, should yield the desired 2-deoxy-2-amino-*C*-glycoside amino acid **167** or the five-membered lactam **168** as a result of subsequent cyclization. These products represent

highly interesting synthetic targets due to them being T_n-antigen analogs, which are investigated for the development of new cancer immunotherapies.[88] Furthermore, previous works revealed the glycosidase inhibiting properties of such frameworks, making them potential candidates for the treatment of Gaucher's disease.[89] Despite the potential usefulness of such scaffolds, no simple and divergent synthesis allowing the screening of a large number of structural variants has been reported so far.

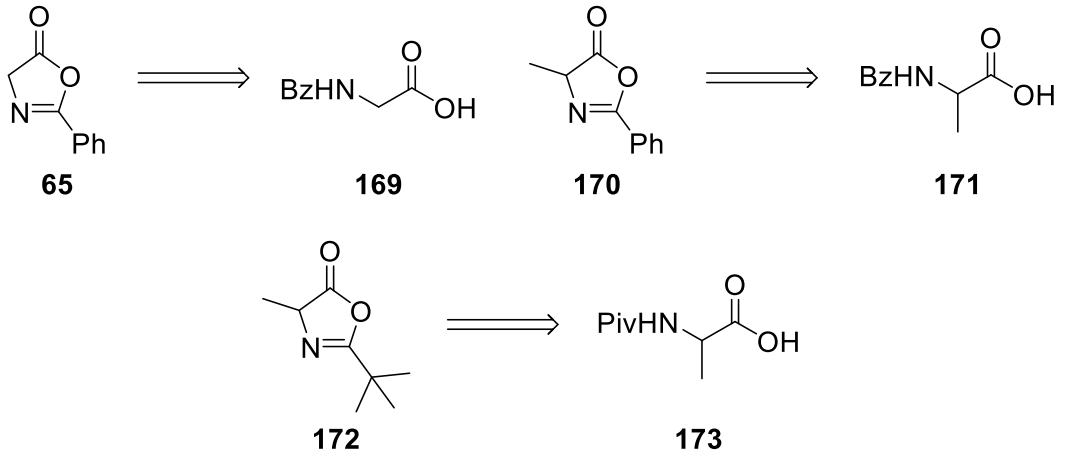


Scheme 32: Overview of the divergent strategy for the synthesis of 2-deoxy-2-amino-*C*-glycoside amino acids.

3.2 – Synthetic Considerations

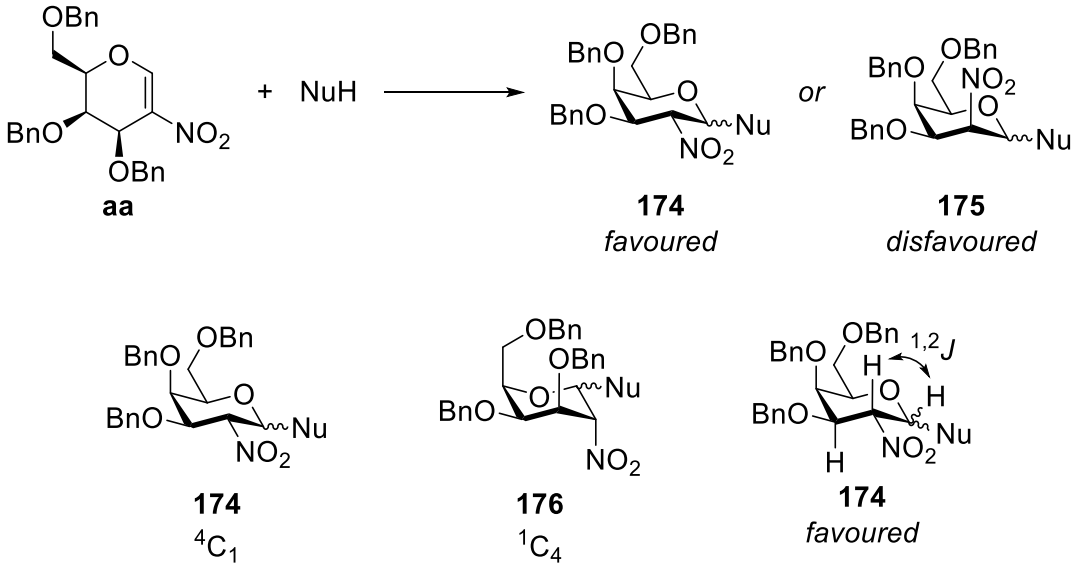
Given the previously mentioned factors governing the regioselectivity of nucleophilic attacks of azlactones in combination with the conflicting reports in the literature, differently protected amino acids must be synthesized to ensure the formation of the correct regioisomer. Therefore, three different azlactones were chosen (Scheme 33). The azlactone **65** derived from hippuric acid **169** can be used to evaluate the general feasibility of the envisioned synthetic route, as there are only reports on the formation of the C2-regioisomer when the azlactone is used as a nucleophile. Additionally, hippuric acid **169** is a readily available and cheap starting material. Furthermore, azlactone **170** derived from benzoyl-protected alanine **171** should be used initially

as it is considerably more stable than differently protected azlactones. If the formation of the undesired C2-regioisomer is observed, the azlactone **172** derived from pivaloyl-protected alanine **173** should be deployed, as the steric bulk of the *tert*-butyl group typically suppresses any reactivity at the C2 position.



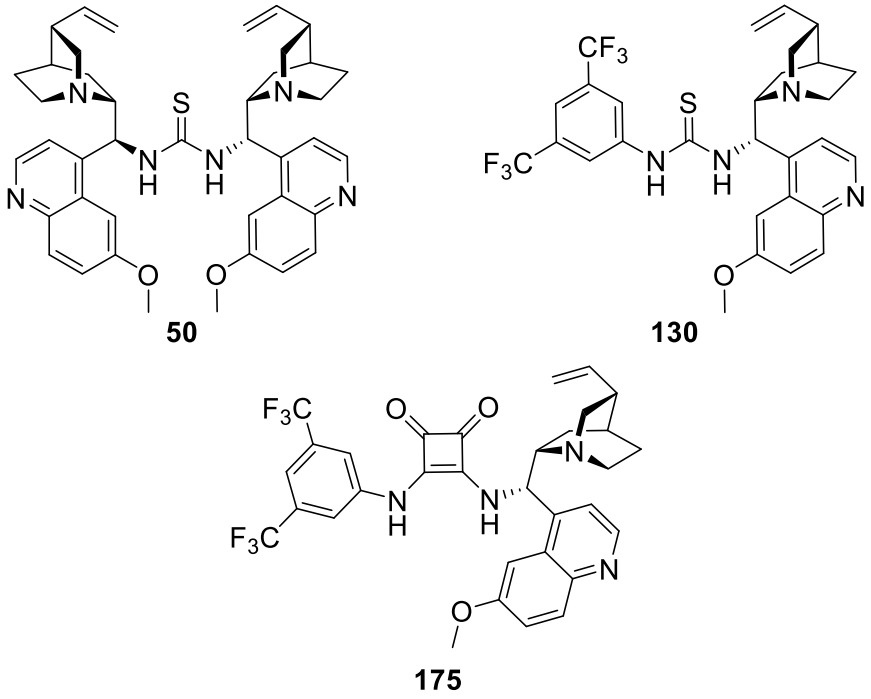
Scheme 33: Azlactone candidates and the precursors for their synthesis.

Concerning the choice of the nitroglycal, the use of benzyl-protected nitro galactal **26** might be the best choice for the initial screening reactions. As in the literature, the highest anomeric selectivities for the addition of nucleophiles to nitroglycals were obtained by deploying a nitro-galactal derivative. A high or even absolute anomeric selectivity is desirable as the effort needed for the analysis and purification of addition products would be significantly reduced. Furthermore, in the addition reactions reported in the literature, the nitro group almost exclusively adopts the equatorial position to give the galacto-product **174** instead of the corresponding talo-isomer **175**. This, in combination with a preference for the $^{4}C_{1}$-conformation of the resulting addition product due to 1,3-diaxial strain between the benzyl groups in **176**, allows the determination of the anomeric selectivity by evaluation of the coupling constants between the hydrogen atom at the anomeric carbon and the hydrogen atom next to the nitro group. The stability of the benzyl groups suppresses any premature cleavage of the protecting groups or substitution due to their poor leaving group ability.



Scheme 34: Addition to 2-nitrogalactal and preferred conformations reported in the literature.

Based on the reports by the Jørgensen and Galan groups,[44,81] catalyst **130** might be a promising choice. If higher catalyst loadings become necessary, a catalyst similar to the one deployed by the Galan group (i.e., **50**) might become more feasible as it was explicitly designed to suppress the dimerization. In addition to the thiourea catalyst, a squaramide-derived catalyst like **175** could also be tested, as these are known to form generally stronger hydrogen bonds than their thiourea counterparts, which should lead to more favorable interactions.



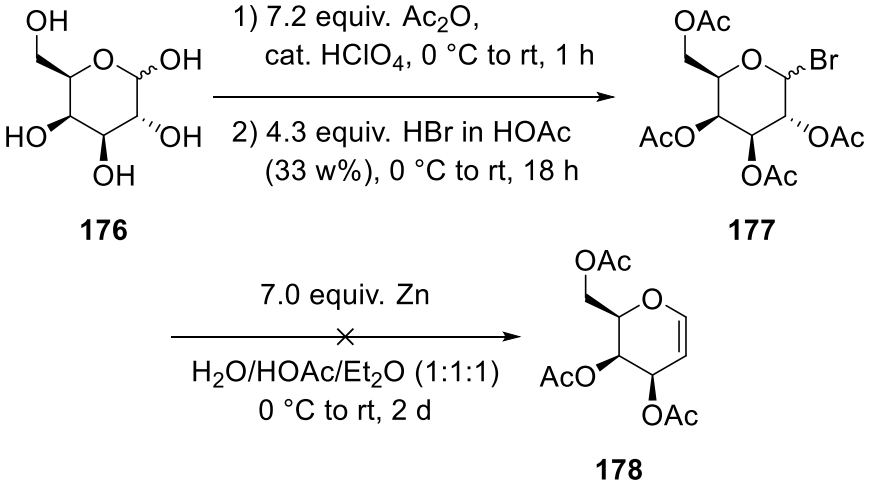
Scheme 35: Possible catalyst candidates for the glycosylation reaction.

4 – Results and Discussion

4.1 – Addition to 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal

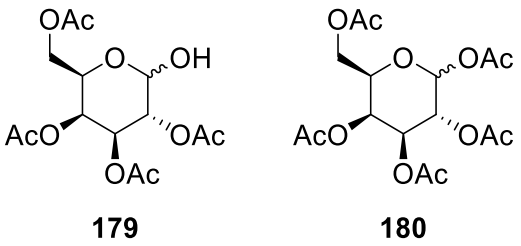
4.1.1 – Synthesis of 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal

Using the methods for the galactal synthesis used in the previous investigation (Scheme 36),[86] it was impossible to obtain the desired galactal **178** in satisfactory yields. The synthesis consists of a three-step-two-pot procedure. In the first step, the corresponding carbohydrate **176** is peracylated using acetic anhydride and an acid catalyst. Subsequent substitution of the anomeric acetate leads to the formation of the bromo-pyranoside **177**, which is then quickly reduced, to avoid its hydrolysis.



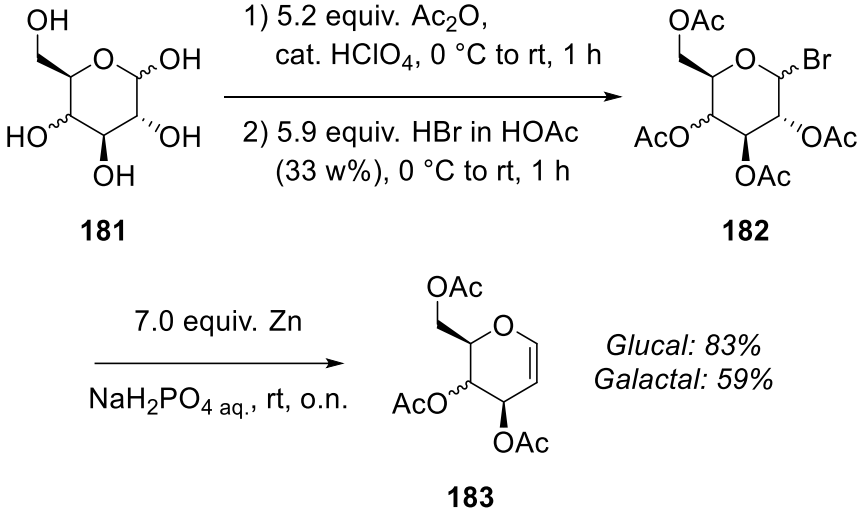
Scheme 36: Previously utilized synthetic route for galactal **178**.[86]

Analysis of the crude reaction mixture after the bromination step revealed that only a minimal amount of the pyranosyl bromide **177**, needed for the subsequent reduction, formed. Instead, a large amount of the corresponding hydrolysis product **179** and starting material **180** shown in Scheme 37 was detected. This indicated an *in situ* hydrolysis of the pyranosylbromide **177**, most likely from water present in the hydrobromic acid due to improper storage. Additionally, by using freshly distilled acetic anhydride, the equivalents of acetic anhydride used for the acetylation were lowered from 7.2 equivalents to 5.2 equivalents. With a simultaneous increase in the equivalents of hydrobromic acid, the reaction time of the bromination was reduced to 1.5 h, and the purity of the pyranosyl bromide **177** increased.[90]



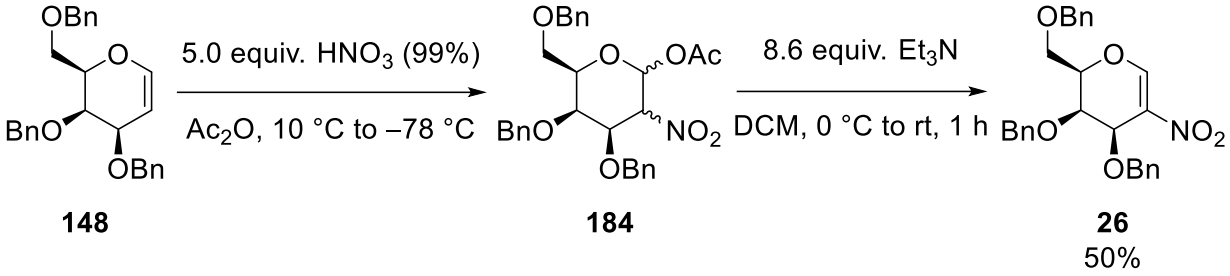
Scheme 37: Compounds detected after bromination of the peracylated carbohydrate.

When almost pure pyranosyl bromide **177** was subjected to the reduction conditions, again, no satisfying amount of the corresponding glycal was obtained. By testing different batches of zinc for the reduction, the batch initially used displayed an inferior reactivity compared to the other batches tested. Furthermore, by changing the reduction procedure, the reduction time was decreased significantly, without any significant decrease in yield.[91]



Scheme 38: Optimized reaction conditions used for the synthesis of glycals.

The benzyl protection of galactal **178** was carried out according to the procedure used before without encountering any problems.[86] Upon conducting multiple nitrations following the method by Schmidt and Das[27] and developed by Kogan and Gaeta[92] on DHP as a model substrate as well as tri-*O*-benzyl galactal **148**, it was found that the use of 99% nitric acid in at least 5.0 equivalents, as well as the deployment of freshly distilled acetic anhydride, were crucial for a successful nitration. Additionally, despite multiple co-evaporations with toluene for the removal of the remaining acetic acid prior to the elimination step, triethylamine still needed to be used in excess for a quantitative elimination to take place.



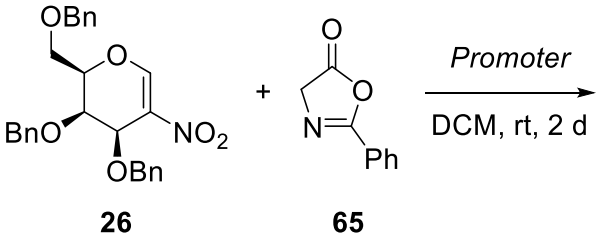
148 **184** **26** 50%

Scheme 39: Optimized procedure for the synthesis of 2-nitrogalactal.

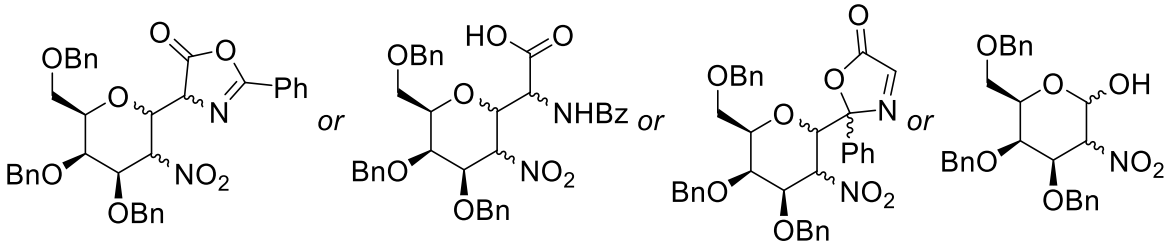
4.1.2 – Addition of 2-Phenyl-5(4*H*)-Oxazolone

To evaluate the feasibility of the envisioned approach, we carried out a series of trial reactions on a 0.1 mmol scale using **26** as the glycoside donor and **65** as the acceptor. A set of different bases was chosen as promotors for the reaction to identify a suitable candidate for the synthesis of a racemic standard.

Table 1: Initially screened conditions for the addition of **65** to **26**.



26 **65**



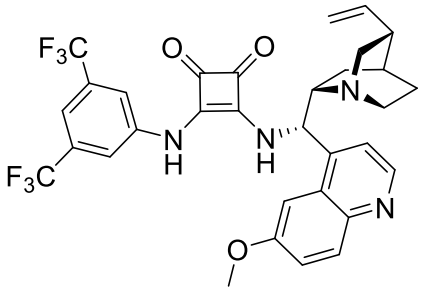
185 **186** **187** **188**

Entry[a]	Promoter	Loading / equiv.	Product detected[b,c]	Full Conv.[b]
1	–	–	No	No
2	Et_3N	1.3	Yes	Yes
3	DBU	1.3	Yes	Yes
4	KO^tBu	1.6	Yes	Yes
5	**175**	0.1	Yes	No

[a]Reactions were carried out in dry solvents on a 0.1 mmol scale and in 0.2 mmol concentration. **65** used in 1.2-fold excess to glycoside donor **26**. [b]Analyzed by ESI-MS after washing with 1 N HCl. [c]**185** and **186** are defined as products.

As the crude reaction mixtures are too complex for NMR analysis and GC-MS analysis is not possible with the glycoside donor used, the reactions were analyzed by ESI-MS to determine if the desired product was formed and if a complete conversion of the starting material occurred. Omitting the use of a promoter gave no result, and only starting material and **188** were detected (Table 1, entry 1). The reaction with triethylamine yielded the complete conversion of **26**, and no masses corresponding to hydrolysis or degradation products of **188** were detected. Next to the masses of various species that could not be linked to either the products or the starting materials, i.e., unidentified side products, signals corresponding to the desired product **185** were detected. Furthermore, when measured in negative mode, besides the mass of the desired product **185** a signal with the corresponding mass of the acid **186** was detected, pointing towards the formation of the desired C4 regioisomer instead of the undesired C2 isomer **187**. DBU also yielded the full conversion of **26**, although the number of side products increased when compared to the reaction with Et_3N, and according to the ESI-MS analysis, far less product formed when compared to the reaction with Et_3N. Using KO^{t}Bu as promoter yielded almost exclusively signals with masses corresponding to the opened azlactone **186**. Additionally, masses corresponding to hydrolysis product **188** were detected, but only in trace amounts. This is most likely due to water accumulated in the batch of KO^{t}Bu used for the reactions. Catalyst **175** showed a lower reactivity compared to the promoters discussed above, as according to ESI-MS analysis, large quantities of **26** could still be detected. This indicates that the reaction is significantly slowed down if only catalytic amounts of a promoter are used. Later experiments using only catalytic amounts (14 mol%) of triethylamine confirmed this hypothesis, as only trace amounts of product were detected after two days reaction time.

For the reactions yielding the desired product, a characteristic and often dark red coloration of the reaction mixture was observed. The coloration always appeared directly after the addition of the promoter to the reaction mixture, and we were unable to obtain a similar coloration in control experiments where only the azlactone **65** or **26** neat or in DCM were exposed to a promoter. Furthermore, an acidic workup with 1 N HCl did not lead to discoloration of the reaction mixture. The coloration seems to be linked to the formation of the product **185**, as it only appeared when the desired product was formed. In the reaction where catalyst **175** was used (Table 1, entry 5), the resulting mixture was pale orange, which substantiates this assumption.

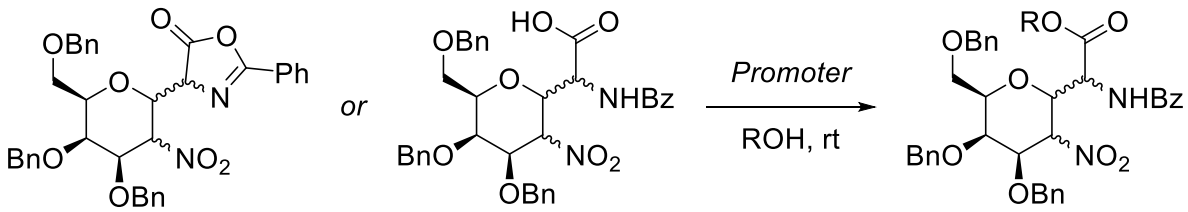


175

Scheme 40: Catalyst **175** used for the initial screening reactions.

After finding conditions that, according to ESI-MS analysis, led to the formation of the desired C4 addition product **185**, multiple attempts to isolate it were made. The attempt to isolate the product from a reaction where Et_3N was used as a promoter did not lead to any product being isolated after column chromatography. It is reasonable to assume that during column chromatography, the oxazolone moiety in **185** has opened to the acid **186** and thus resists elution. Therefore we decided to derivatize the product *in situ* to the corresponding ester before isolating it. Multiple conditions reported in literature for the esterification of oxazolones listed in Table 2 were tested.

Table 2: Conditions tested for the alcoholysis/esterification of **185** or **186**.



185 **186** **189**

Entry	SM[a]	ROH	Additive	Product detected[b]	Full Conv.[b]
1	**185**	EtOH	–	No	No
2	**185**	EtOH	DMAP	No	No
3	**185**	MeOH	pTSA	Yes	Yes
4	**185 + 186**	MeOH	TMSCl	Yes	Yes

Reactions were carried out at room temperature using the corresponding alcohol as the solvent (SM = starting material). [a]Obtained by repeating the reactions under the conditions given in Table 1. [b]Determined by ESI-MS.

Attempting to reproduce the esterification method used in the previous studies,[86] an excess of ethanol was added to the reaction mixture after completion of the first reaction step. As no ester formed after 24 h, 20 mol% of DMAP was added to the reaction, and stirring was continued for another 48 h. ESI-MS analysis of the reaction mixture revealed that no esterification occured, but a portion of the azlactone **185** had opened up to the corresponding acid **186** instead. An attempt to isolate either the acid **186** or the closed oxazolone **185** by using neutral aluminum oxide instead of silica as the stationary phase during column chromatography did not lead to any product being isolated.

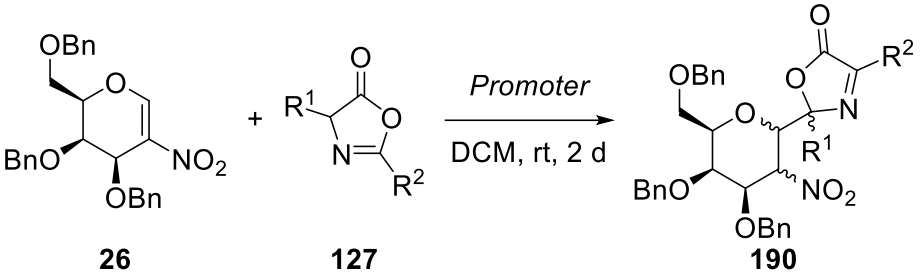
To achieve a quantitative conversion of both the closed azlactone as well as the corresponding acid into the desired ester, a Fischer-Speier esterification[93] was attempted. After 24 h, the originally dark red color of the mixture changed into a light orange. Column chromatography and subsequent analysis revealed a complex mixture with only trace amounts of product being formed.

Lastly, a protocol developed by Trost[94] was tested to achieve a quantitative methanolysis of the addition product. ESI-MS analysis of the crude product revealed a highly complex mixture but also the presence of the desired ester **189**. Using preparative HPLC, multiple fractions could be obtained, but none contained the desired product or any other identifiable substance. To rule out that the problems encountered are caused by the specific oxazolone **65** or reaction conditions used, we decided to screen a different set of nucleophiles and conditions.

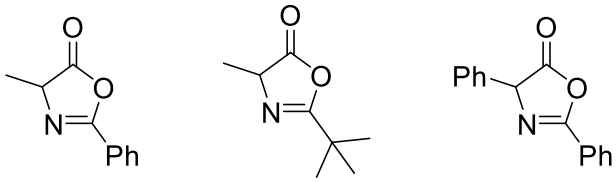
4.1.3 – Nucleophile screening

For further investigation into the addition reactions of oxazolones to **26**, three different oxazolones were selected and subjected to the reaction conditions shown below. The azlactones **170** and **172** were chosen due to the previous publications discussed above and **153** for its different electronic properties when compared to the other azlactones.

Table 3: Initially screened conditions for the addition of different oxazolones to **26**.



26 **127** **190**



170 **172** **153**

Entry	Oxazolone[a]	Promoter	Solvent	Product detected[b]
1	**153**	Et_3N (1.2 equiv.)	DCM	No
2	**153**	130 (20 mol%)	DCM	Trace
3	**172**	Et_3N (1.2 equiv.)	DCM	No
4	**172**	KO^tBu (6.0 equiv.)	DCM	No
5	**172**	Quinine (1.8 equiv.)	DCM	No
6	**170**	Et_3N (1.2 equiv.)	DCM	No
7	**170**	130 (20 mol%)	DCM	Trace
8	**170**	*p*TSA (20 mol%)	DCM	No
9	**170**	–	Pyridine	Trace
10[c]	**170**	LiHMDS (4.8 equiv.)	THF	No

Reactions were carried out in dry solvents on a 0.1 mmol scale in 0.2 mmol concentration by stirring for 2 days at room temperature. [a]Used in 1.2-fold excess to glycoside donor. [b]Determined by ESI-MS after workup using 1 N HCl. [c]Carried out according to the procedure reported in ref. [60].

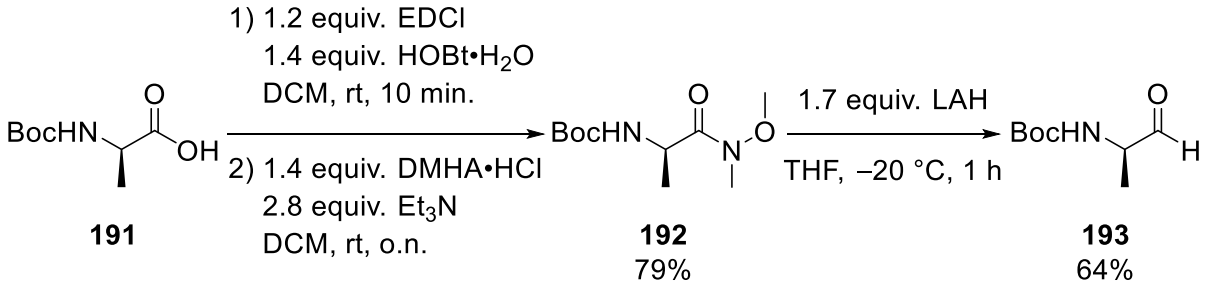
Although the addition of **65** using Et_3N as a promoter has previously resulted in the complete conversion of **26** and the formation of the desired product **185**, no product formed under the same conditions with the oxazolones shown in Table 3.

Using thiourea **130** in combination with oxazolone **153** only resulted in the formation of a complex mixture without any traces of product detectable. Employing oxazolone **170** under the same conditions, on the other hand, resulted in the formation of trace amounts of the desired product. The reaction of **172** with quinine also did not afford any product formation.

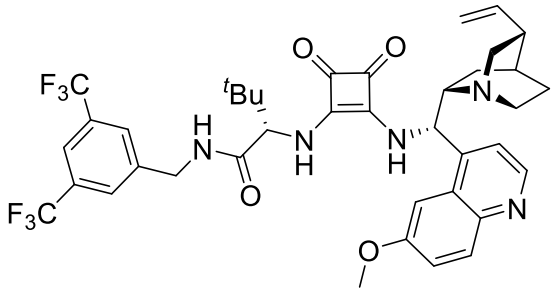
To rule out the possibility that quantitative deprotonation of the nucleophile is needed for the reaction to proceed, the oxazolone **172** was treated with KO^{t}Bu, but this also did not yield any product. Instead, the oxazolone degraded under the reaction conditions and additionally underwent a self-acylation reaction (*see Scheme 65*). In an attempt to utilize the reaction conditions deployed by Peregrina and coworkers,[60] oxazolone **170** was treated with an excess of LiHMDS in THF. Like in the previous reactions, no product could be detected after workup. Subjecting the oxazolone **170** to conditions similar to those successfully deployed during the previous investigation[86] did not yield any product.

Interestingly when pyridine was used as a solvent in combination with oxazolone **170**, ESI-MS analysis of the reaction mixture revealed a signal with the m/z corresponding to the desired addition product. An attempt to isolate and purify the product was undertaken, but like before, no product could be obtained after column chromatography.

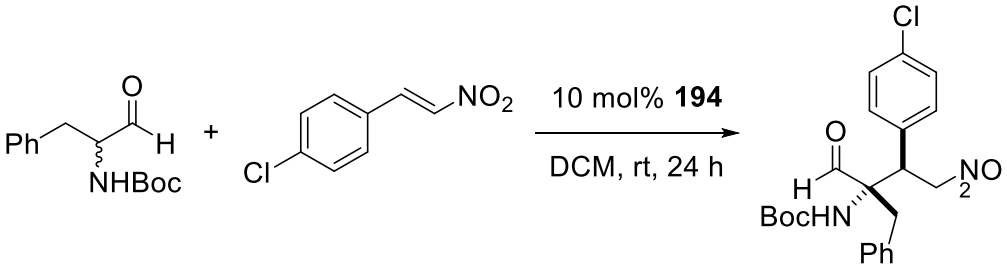
Inspired by the work of the Palomo group (Scheme 42),[95] we envisioned that a change in the electronic nature of the nucleophile might lead to a more favorable interaction with the glycoside donor **26**. Therefore, a small set of test reactions was performed, using the Boc-protected alanine-derived aldehyde **193** as a nucleophile. The aldehyde was synthesized as shown in Scheme 41 in two steps from Boc-protected alanine following the procedure reported by Palomo and coworkers.



Scheme 41: Two-step synthesis of the Boc-protected alanine-derived aldehyde **193**.



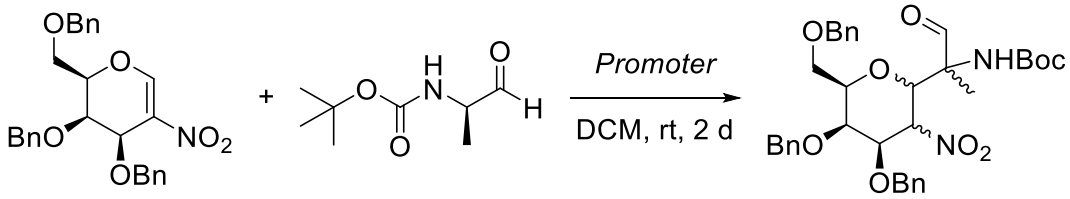
194



195 **196** **197**
91%
80% *de*., 98% *ee*.

Scheme 42: Reaction developed by the Palomo group for the synthesis of quaternary α-amino acids.[95]

Table 4: Screened conditions for the addition of **193** to **26**.



26 **193** **198**

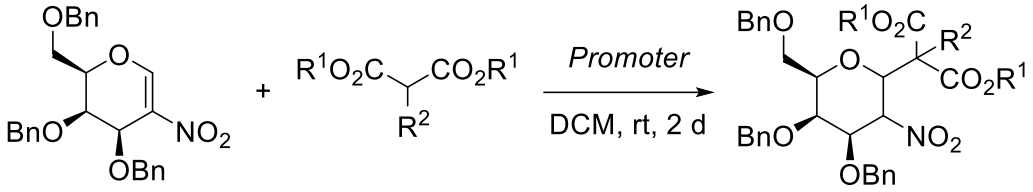
Entry	Promoter 1	Promoter 2	Solvent	Product formed[a]	Conversion of SM[b]
1	–	–	DCM	No	< 10%
2	T1 (20 mol%)	–	DCM	No	< 10%
3	Et_3N (1.2 equiv.)	–	DCM	No	< 10%
4	T1 (20 mol%)	Et_3N (1.2 equiv.)	DCM	No	< 10%
5	Thiourea 041 (20 mol%)	–	DCM	No	< 10%

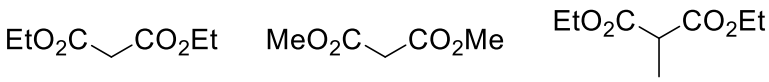
Reactions were carried out in dry solvents on a 0.1 mmol scale in 0.2 mmol concentration, using **193** in 1.2-fold excess with respect to **26** and by stirring for 2 days at room temperature. [a]Determined by ESI-MS after workup using 1 N HCl. [b]Determined by ^{1}H NMR using *para*-nitro benzaldehyde as internal standard.

Similar to the previous attempts, only traces of the product were detected, and no conversion of the starting material **193** greater than 10% occurred.

Attempting to identify the reason for the apparent degradation of the products, the addition of derivatives of malonic acid using different promoters has been tested. The addition of **201** to **26** is known to work well in combination with strong bases, and the resulting products are stable towards acidic workup and column chromatography.[25,27,41]

Table 5: Conditions screened for the addition of different malonates to **26**.





201 **27** **202**

Entry	NuH[a]	Promoter	Solvent	Product detected[b]
1	**201**	Et_3N (1.2 equiv.)	DCM	Traces
2	**201**	Et_3N (2.1 equiv.)	DCM	Yes
3	**201**	Et_3N (2.1 equiv.)	THF	Traces
4	**201**	DABCO (1.6 equiv.)	DCM	Yes
5	**201**	*p*TSA (20 mol%)	DCM	No
6	**27**	Et_3N (1.2 equiv.)	DCM	Yes
7	**202**	Et_3N (2.0 equiv.)	DCM	No
8	**202**	pTSA (20 mol%)	DCM	No

Reactions were carried out in dry solvents on a 0.1 mmol scale in 0.2 mmol concentration by stirring for 2 days at room temperature. [a]Used in 1.2-fold excess to glycoside donor. [b]Determined by ESI-MS after workup using 1 N HCl.

Using 1.2 equivalents of Et_3N for the reaction between **201** and **26**, only trace amounts of product **203** were detected (Table 5). However, with 2.1 equivalents Et_3N, **26** has been completely consumed, and the desired product **203** was detected via ESI-MS. After the acidic workup, only **201** and the corresponding addition product **203** have been present in the NMR. Isolating the pure product by column chromatography was possible, although no absolute yield could be determined due to complications during the purification process (*see spectra addendum*). As the product **203** and the starting material **201** were the only species present in

the crude NMR mentioned above, it is reasonable to assume the desired product formed quantitatively. Furthermore, a comparison of the NMR of the isolated product to literature data revealed that the product was exclusive β-configured (Scheme 43). The same result was obtained when **27** was used as a nucleophile. Again, problems during purification precluded the determination of the absolute yield.

Repeating the addition of **201** using DABCO as a promoter also yielded the desired product, although no complete conversion of **26** was observed, and the resulting reaction mixture was far more complex than in the previous examples. Therefore, an isolation attempt was not further pursued.

203 **28**

Scheme 43: Products formed after the Et_3N promoted addition of malonates **201** and **27** to **26**.

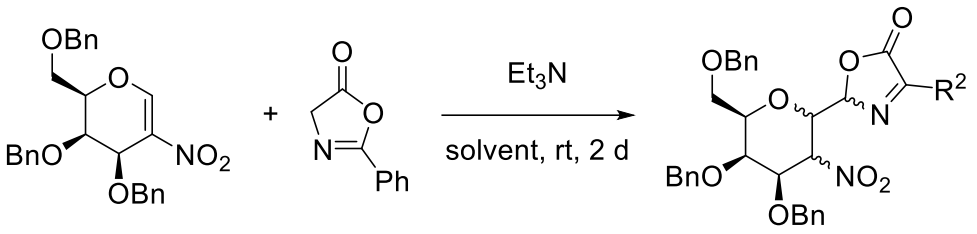
Using THF as the solvent seemed to strongly inhibit the reaction, as only traces of the product **203** could be detected by ESI-MS. This observation is consistent with previously reported results.[96] Furthermore, this result suggests that solvent effects also need to be carefully considered.

Next, encouraged by the previous success in the addition of malonates, an attempt was made to obtain an addition product bearing a quaternary center using **202** as nucleophile. Like in previous experiments where a quaternary center would be formed, the reaction did not lead to any product formation. Lastly, we decided to test the reaction conditions from the previous study[86] in the addition reaction of malonates, but again no product formed.

4.1.4 – Solvent Screening

Intrigued by the findings made during the investigation of the addition of malonates to **26**, we decided to carry out a solvent screening. The four different solvents shown in Table 6 were selected to evaluate the influence of an increase in solvent polarity on the reaction.

Table 6: Evaluation of different solvents for the addition of **65** to **26**.



26 **65** **185**

Entry	Solvent	Product detected[a]
1	MePh	Yes
2	1,2-DCE	Yes
3	THF	Yes
4	EtOAc	No

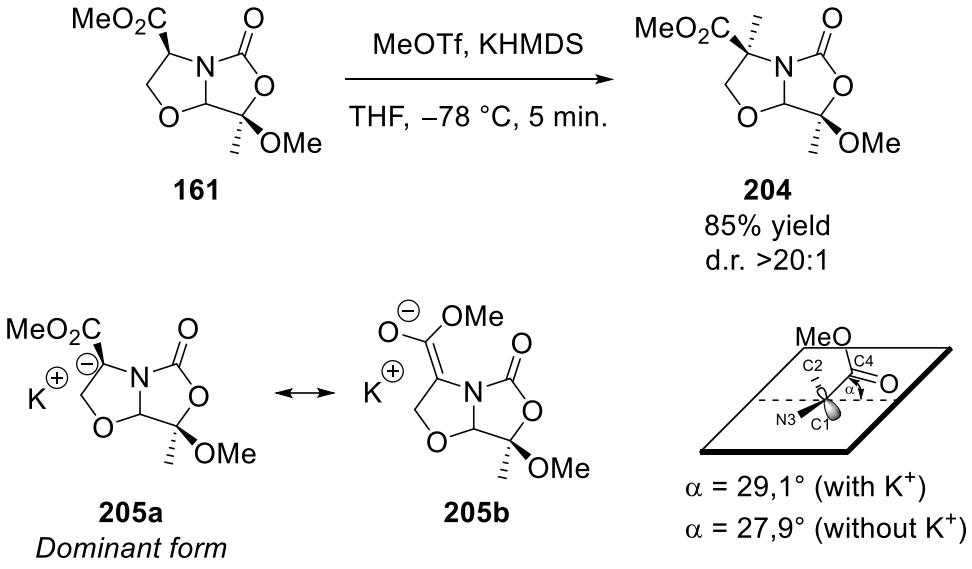
Reactions were carried out in dry solvents on a 0.1 mmol scale in 0.2 mmol concentration by stirring for 2 days at room temperature. **65** and Et_3N were used in 1.2-fold excess to glycoside donor **26**. [a]Determined by ESI-MS after workup using 1 N HCl.

Interestingly in all cases except where ethyl acetate was used as a solvent, no **26** could be detected after the reaction. Furthermore, in all these cases, no product could be detected if the mass spectra were recorded in positive mode. Switching to negative mode, in all cases, the clean formation of the product **185** has been observed. If this phenomenon is due to signal suppression or another reason remains unclear as the isolation of the addition products remains elusive.

4.1.5 – Conclusions

Although the addition of **65** succeeded, isolation or derivatization could not be carried out as only complex mixtures are obtained. Experiments dedicated to the addition of different oxazolones that would yield a product bearing a quaternary stereocenter were futile. Based on the observation that even with strong bases, no product has been formed, it is reasonable to assume that the limiting factor is associated with the acid-base chemistry involved. Given the fact that the reaction reported by Peregrina and coworkers did indeed yield a product bearing a quaternary stereogenic center that was stable enough for isolation, it seems unreasonable to attribute the problem encountered solely to steric factors.[60] It is worth noting that in an earlier publication on the alkylation of the *N,O*-acetal derived from serine, the authors proposed that the enolates of these serine-acetals are strongly distorted into a pyramidal shape.[87] This significantly changes not only the geometric properties but also the electronic nature of the

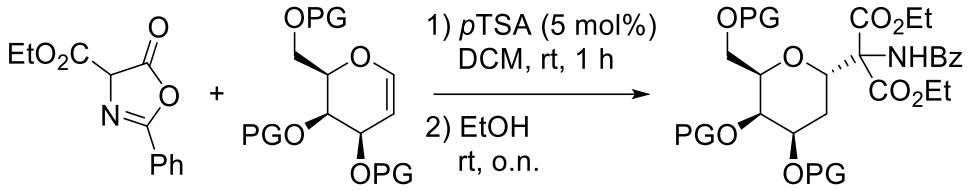
enolate **205**, pronouncing the carbanionic character on C1. Furthermore, this pyramidalization is used to explain the diastereoselectivity of the alkylation, as the carbanion retains its conformation due to a high inversion barrier. Therefore, it seems that the problems encountered result from a complex interplay of sterical and electronic factors, complicated further by pronounced solvent effects.



Scheme 44: Alkylation of the serine-*N*,*O*-acetal **161** and pyramidal geometry of the enolate with and without potassium counterion included in the calculation on a B3LYP/6-31+G(d) level of theory as reported in the literature.[87]

As the use of azlactones as masked amino acid equivalents is essential for the divergence of the envisioned approach, we opted to find a more feasible glycoside donor by changing the stereoelectronic properties of the nitroglycal, instead of changing the amino acid precursor in order to maintain the synthetic simplicity associated with azlactones. One way to reduce the steric demand of the glycoside donor and simultaneously retaining roughly its electronic properties would be to change the protecting groups of the acceptor from benzyl to methoxy. The previous investigation showed that such a change could significantly accelerate the acid-catalyzed addition of oxazolones to glycals, whilst at the same time, no significant deterioration in yield or selectivity of the product is observed.[86]

Table 7: Influence of the protecting groups on the addition reaction from a previous investigation.[86]



147 **206** **207**

Entry	PG	Reaction time	Yield
1	Bn	1 h	86 %
2	Me	0.25 h	80 %
3	Ac	24 h	–

One should note that the reaction shown above is acid-catalyzed and most likely proceeds via a cationic intermediate, i.e., an oxocarbenium ion. This oxocarbenium ion requires a certain degree of stabilization by electron-donating protecting groups. Therefore, it appears reasonable that a base-promoted pathway demands a more electron-deficient acceptor.

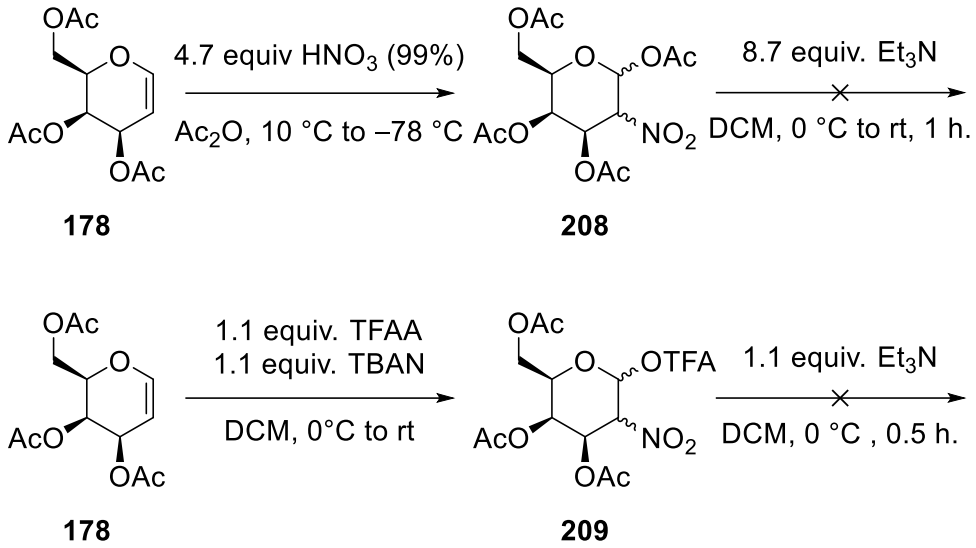
Using the well-established concept of electronically armed and disarmed saccharides[97] as an orientation guideline, we decided to opt for the synthesis of a tri-*O*-acetyl-protected nitroglycal **44**. These should be more electron deficient and less sterically demanding and therefore more reactive in the base-promoted addition of oxazolones compared to their benzyl-protected counterparts.

4.2 – Addition to 3,4,6-Tri-*O*-acetyl-2-nitro-D-glucal

4.2.1 – Synthesis of Tri-*O*-acetyl-2-nitroglycals

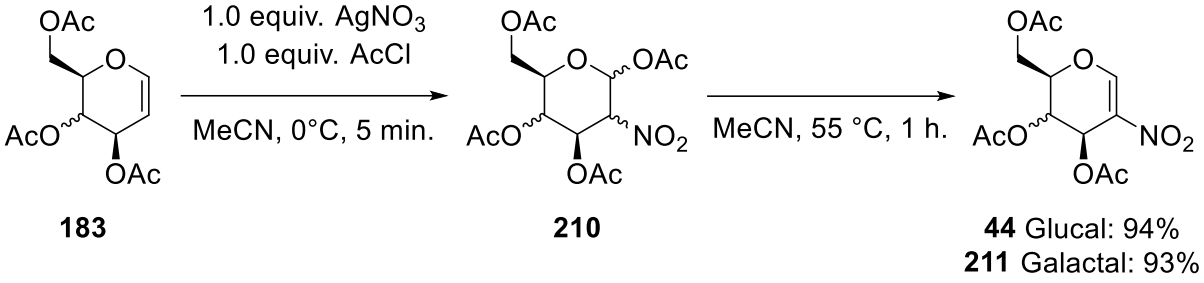
Attempting to utilize the synthesis shown in Scheme 45 for 3,4,6-Tri-*O*-acetyl-2-nitro-D-glucal, previously deployed for the synthesis of its benzyl-protected counterpart, did not lead to the product being isolated. Although the nitration with *in situ* generated acetyl nitrate proceeded smoothly, the subsequent elimination using Et_3N only led to a black, tar-like substance being formed. Additionally, the procedure reported by the Vankar group was deployed. [28] By using tertbutyl ammonium nitrate (TBAN) in combination with trifluoroacetic anhydride (TFAA), trifluoro acetyl nitrate was formed in an almost equimolar amount for the nitration. The

subsequent addition of only 1.1 equivalents Et_3N again led to the reaction mixture rapidly darkening before a black tar-like substance precipitated.



Scheme 45: Failed attempts to synthesize 3,4,6-tri-*O*-2-nitrogalactal.

According to literature reports, the desired product is highly reactive,[24,25,29] and even if it forms, the subsequent aqueous workup might lead to decomposition. Additionally, the reported difficulties associated with the purification of the product indicated that even a standard purification like column chromatography or crystallization could pose a significant challenge.[24,25] Therefore, a one-step procedure, yielding a pure product that eliminates the need for an elaborate workup, would be very beneficial. The method also developed in the Vankar group[29] using acetyl chloride and silver nitrate as a reagent system for the nitration seemed quite attractive. All by-products resulting from the nitration may potentially be either filtered off or removed under reduced pressure. Moreover, the elimination of the acetoxy adduct **20** is carried out by simply heating the reaction mixture, thereby avoiding the use of base otherwise needed for this step. Lastly, the authors reported almost quantitative yields for the nitrogalactal **211** as well as nitroglucal **44** and state that these products did not require any futher purification.



Scheme 46: Synthesis of 3,4,6-tri-*O*-acetyl protected nitroglycals as reported by the Vankar group.[29]

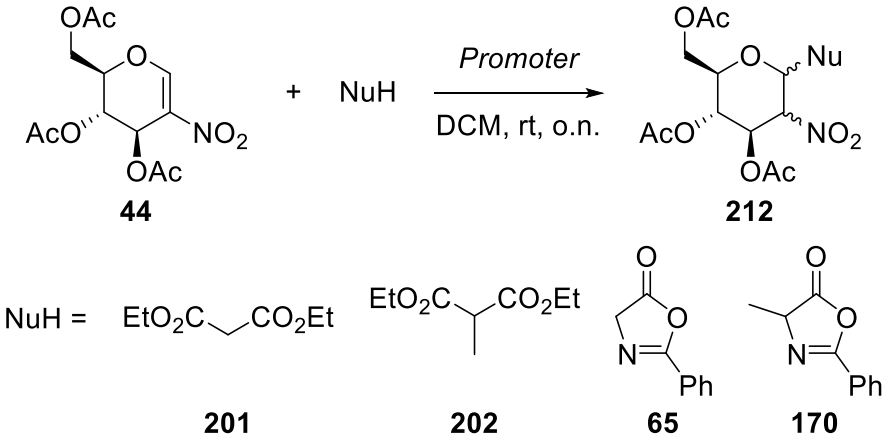
Carrying out the synthesis with 3,4,6-tri-*O*-acetyl-galactal **178** as starting material resulted in multiple olefinic species being detected in an NMR of the crude reaction mixture. Subjecting the crude product **211** to flash column chromatography only led to its decomposition. Repetition of the synthesis and employing higher purity reagents led to the same result. Subjecting 3,4,6-tri-*O*-acetyl-glucal **213** to the same reaction conditions, the almost pure product **44** formed.

4.2.2 – Nucleophile Screening

One advantage of the use of **44** over **26** is its compatibility with GC-MS analysis. A small set of nucleophiles and promoters previously used in combination with **26** were chosen to evaluate the reactivity of **44**.

All of the above-mentioned reactions yielded a complete consumption of **44**. Furthermore, in all cases, highly complex reaction mixtures were obtained. Although a higher reactivity of the acceptor was anticipated by the use of **44**, it is likely too reactive and numerous side products formed. Additionally, reactions dedicated to evaluating the stability of **44** against various promoters used so far revealed that **44** itself is degraded by all the promoters tested, even by thiourea **130**, further complicating the situation. This drastic change in reactivity can, in addition to the shift in electronics and sterics of the protecting groups, most likely be attributed to the difference in conformational behavior of glucals compared to galactals. Glycals are, in general, able to adopt two different half-chair conformers, $^{5}H_{4}$ and $^{4}H_{5,}$ resulting from the relative position of the hydrogen atoms on C4 and C5 to the axis when placing the double bond horizontally as depicted in Scheme 47. The exact population of each conformer is dependent on a multitude of factors, including the vinylogous anomeric effect (VAE).[98] The VAE, originally called the allylic effect by Ferrier and Sankey,[99] results from a hyperconjugative interaction between the lone pair of the *endo* oxygen and the antibonding orbital of the C3-substituent through the intermediate double bond.

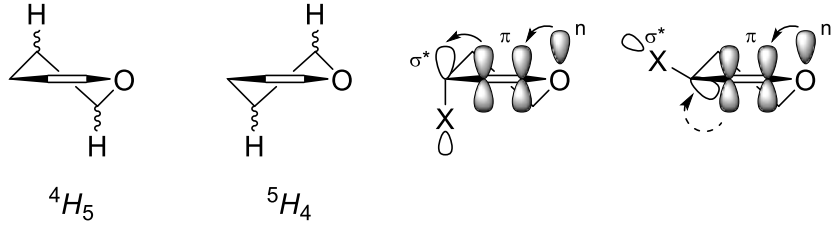
Table 8: Screened conditions for the addition of different nucleophiles to **44**.



Entry	Nucleophile[a]	Promoter[a]	Result[b]
1	**201**	Et_3N	Degradation
2	**201**	Quinine	Degradation
3	**202**	Et_3N	Degradation
4	**202**	Quinine	Degradation
5	**65**	Et_3N	Degradation
6	**65**	Quinine	Degradation
7	**170**	Et_3N	Degradation
8	**170**	Quinine	Degradation
9	**170**	KO^tBu	Degradation

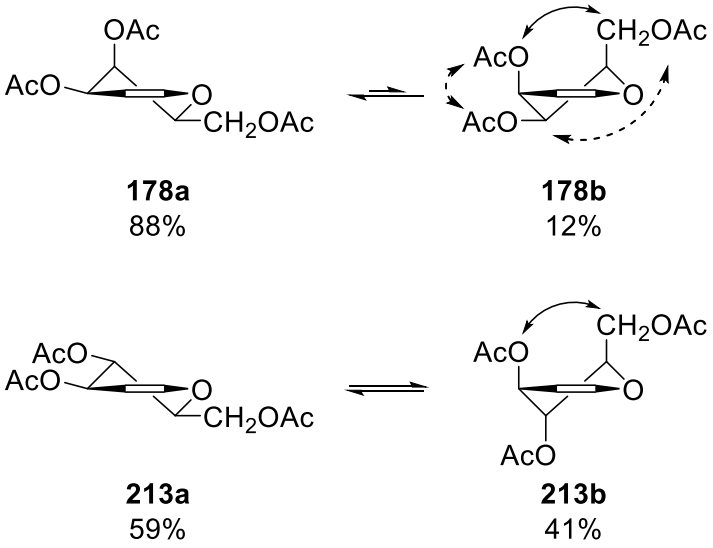
Reactions were carried out in dry solvents on a 0.1 mmol scale in 0.2 mmol concentration by stirring over night at room temperature. [a]Used in 1.2 equiv. with respect to **44**. [b]Obtained by GC-MS analysis of the crude reaction mixture.

It should be noted that the effect is only present when the substituent at C3 is positioned in a pseudo axial fashion, as a semi-equatorial placement of the substituent would only lead to a neglectable orbital overlap between the antibonding orbital of the substituent and the double bond. As a result of this interaction, the bond between the substituent and C3 is elongated and the tendency of the substituent to function as a leaving group increases.



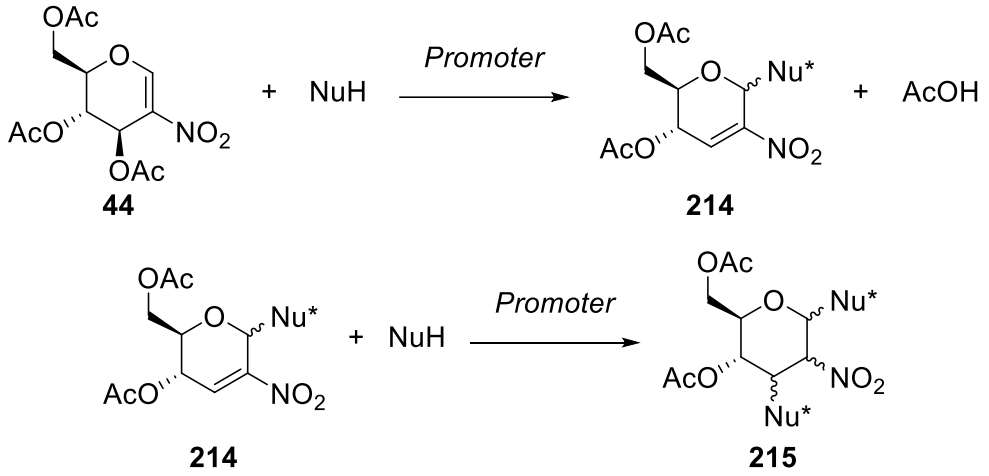
Scheme 47: Possible conformations in glycals and the origin of the VAE.

In the case of peracylated galactal **178**, despite the VAE favoring the $^{5}H_{4}$ conformer **178b**, the 1,3-diaxial strain induced by the interaction of the substituent at C3 and C5 leads to a preference towards the $^{4}H_{5}$ conformer **178a**. Additionally, the 1,3-diaxial strain is more pronounced in glycals where the C3-C4-C6 substituents are positioned in an axial-equatorial-axial fashion, giving rise to the "wedge-effect".[100] This effect results from the C4 group being pushed between the pseudo axial C3 and C5 substituents like a wedge, as the system tries to minimize the 1,3-diaxial strain by a distortion of the ring geometry. Therefore, the ring cannot distort, like in other glycals, to reduce the 1,3-diaxial strain. In peracylated glucal **213** the pseudo axial positioning of the C4 substituent leads to a decrease in the 1,3-diaxial strain as the ring can be distorted slightly without giving rise to the wedge-effect. In sum, this causes an almost equal population of both conformers in the case of glucal.



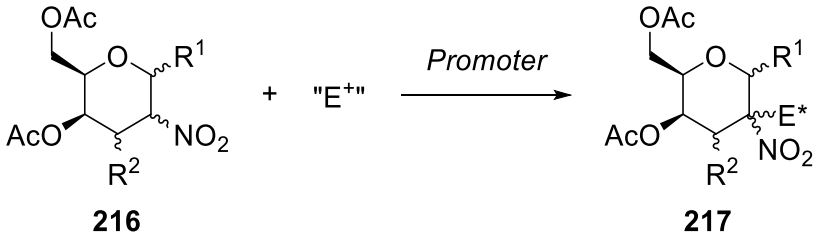
Scheme 48: Conformer population of peracylated galactal **178** and glucal **213** in acetone-d_6 at 299.15 K at 0.4 M concentration. 1,3-Axial strain highlighted by the bold arrow, wedge effect with the dotted arrow.[100,101]

Because of this and the fact that acetoxy groups are superior leaving groups than benzyl alcohols, **44** should possess a stronger preference for undergoing a Ferrier rearrangement than **26**. This would open up the possibility of a second attack of a nucleophile, this time on C3, and the formation of another set of diastereomeric species, further complicating the analysis of the crude reaction mixture (Scheme 49). Such side reactions have also been observed and even utilized previously.[28]



Scheme 49: Ferrier sideproduct formation of **44** and follow-up reactivity of it.

Although overall less likely to occur, the superior stabilization of the negative charge intermediary formed adjacent to the nitro group in **44** compared to **26** could lead to an additional reaction of **44** with an electrophile (Scheme 50). Furthermore, depending on the nature of the electrophile, an additional stereogenic center might be formed at the electrophile. Such reactions have also been reported previously.[28,43]



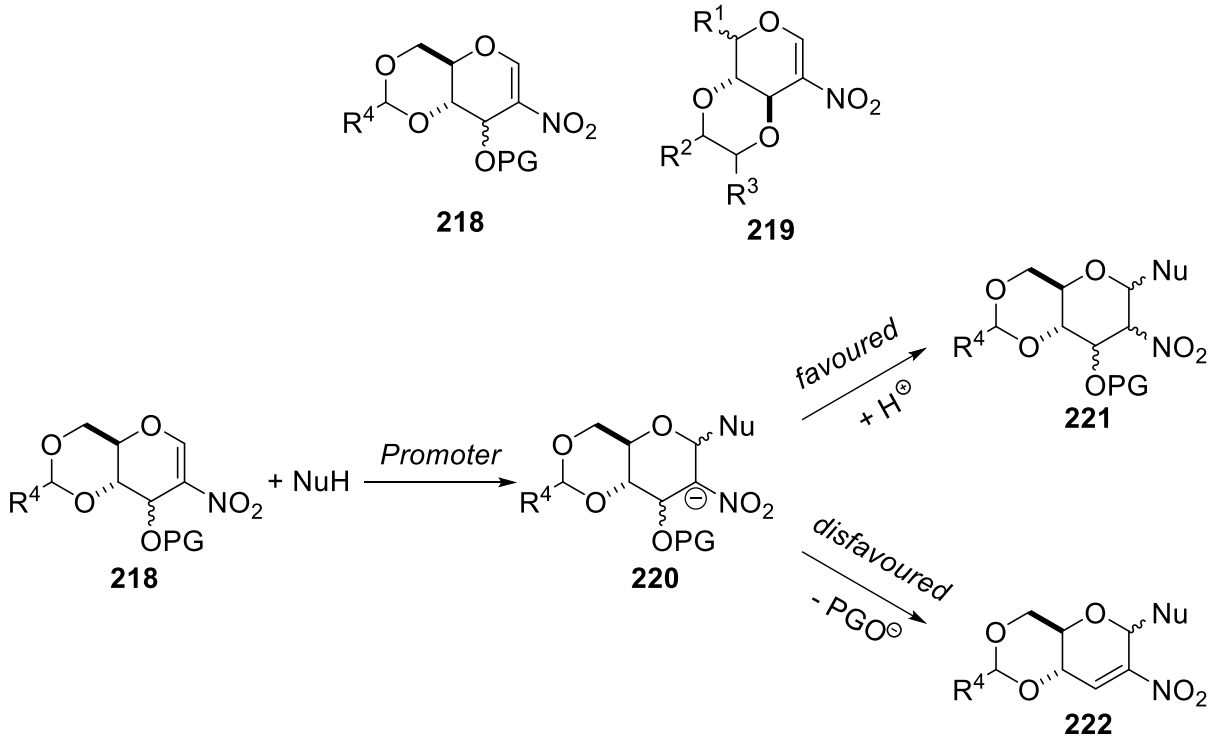
Scheme 50: Possible reaction of a 2-nitro-carbohydrate **216** with electrophiles.

4.2.3 – Conclusions

Given the apparent overreactions encountered when using **44**, it seems a finely tuned acceptor is required to ensure an efficient proceeding of the reaction whilst at the same time suppressing side reactions. One way to ensure the suppression of side reactions would be the utilization of protecting groups yielding a 4,6-*trans*-fused bicyclic system, a commonly used strategy for the torsional disarming of saccharides.[102] Such a *trans*-fusion would significantly diminish the tendency of the system to yield a Ferrier-rearranged product, like **222**, by raising the activation barrier for the elimination as the rehybridization on C3 from sp^3 to sp^2 and subsequent planarization would result in significant strain. Although the electronics of such protecting groups might yield a deactivated acceptor, when compared to **44**, the strain release from the

de-planarization from **220** to **221** could provide a reasonable compensation. However, it should be noted that such an approach would only apply to 2-nitroglycals where the substituent on C4 is in a *trans*-relationship with either the substituent on C3 or the substituent on C5.

Such a process of fine-tuning the glycoside donor by the manipulation of the protecting groups is a very laborious process. This is especially true in the case of 2-nitroglycals as the protecting groups have to be placed on the glycal before the nitration as the introduction of any nucleophile or liberation of the hydroxy function of the carbohydrate backbone would likely lead to an attack on the nitroglycal. Thus, any late-stage functionalization of the nitroglycal is precluded. Due to these limitations and the short amount of time left, we instead decided to opt for the synthesis of various model nitro-vinyl ethers with the goal of better understanding the factors governing the addition to these acceptor moieties and thereby finding a way to avoid the time-consuming process of fine-tuning the glycoside donor by protecting group manipulation.



Scheme 51: Generic *trans*-fused 2-nitroglycals **218** and **219**. Schematic representation of the suppression of the Ferrier-rearrangement by the introduction of *trans*-fused protecting groups.

4.3 – Addition to Nitro-vinyl Ethers

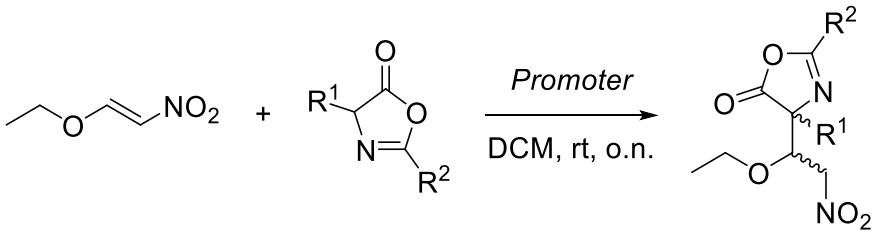
As described above, a series of model acceptors were synthesized to elucidate the main factors governing the addition of azlactones and malonates to nitro-vinyl ethers. These were specifically chosen to evaluate the effect of the substitution pattern of the acceptor on the

efficacy of the reaction. A set of four different nucleophiles shown below and five different promoters were initially chosen for this investigation. As it turned out, DBU led to the complete degradation of the acceptors **223**, **249**, and **256** in the test reactions and is therefore excluded during the course of this discussion, leaving only four different promoters to be tested with each nucleophile, listed in Table 10. This degradation can likely be attributed to the nucleophilic properties of DBU, as a test reaction between **223** and malonate **201** with DMAP as promoter resulted in the complete degradation of **223** without any product formation.

4.3.1 – Addition to (1*E*)-1-Ethoxy-2-nitroethene

To better understand the general reactivity of nitro-vinyl ethers, **223** was chosen as a model substrate. Although addition reactions of *C*-nucleophiles to **223** are known in the literature, they involve the use of organo-aluminum compounds.[103] Therefore, it seems unlikely that the reactions reported so far reflect the system used in this work, giving rise to the necessity of such an investigation.

Table 9: Additional reactions tested with **223**.

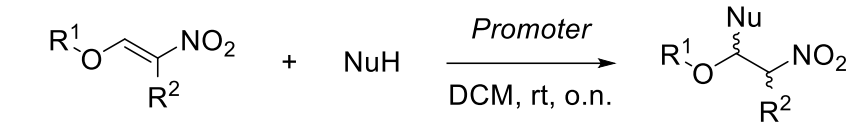


223 **170** R^1 = Me, R^2 = Ph; **172** R^1 = Me, R^2 = ^{t}Bu; **224**

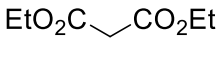
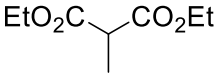
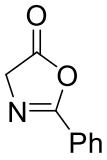
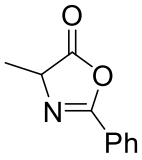
Entry	Nucleophile	Promoter	Product detected
1	**170**	$(DHQ)_2PHAL$	Yes
2	**170**	LiHMDS	No
3	**172**	Et_3N	Yes
4	**172**	Quinine	Yes
5	**172**	KO^{t}Bu	Trace
6	**172**	**130** (20 mol%)	Trace

Reactions were carried out on a 0.1 mmol scale in 0.2 mmol concentration using 1.2 equiv. of promoter and nucleophile compared to the acceptor **223** and stirring overnight. Reaction mixtures analyzed by GC-MS and ESI-MS (workup with 1 N HCl), where stated.

Table 10: Standard addition reactions of various nucleophiles to the selected vinyl ethers.



225 **226**

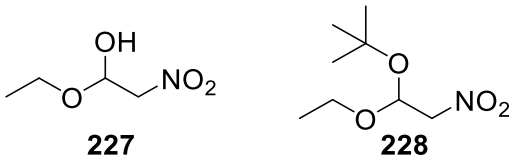
NuH =    

201 **202** **65** **170**

Entry	Nucleophile	Promoter
1	–	Et_3N
2	–	Quinine
3	–	KO^{t}Bu
4	–	**130** (20 mol%)
5	**201**	Et_3N
6	**201**	Quinine
7	**201**	KO^{t}Bu
8	**201**	**130** (20 mol%)
9	**202**	Et_3N
10	**202**	Quinine
11	**202**	KO^{t}Bu
12	**202**	**130** (20 mol%)
13	**65**	Et_3N
14	**65**	Quinine
15	**65**	KO^{t}Bu
16	**65**	**130** (20 mol%)
17	**170**	Et_3N
18	**170**	Quinine
19	**170**	KO^{t}Bu
20	**170**	**130** (20 mol%)

Reactions were carried out on a 0.1 mmol scale in 0.2 mmol concentration using 1.2 equiv. of promoter and nucleophile compared to the acceptor (unless stated otherwise) and stirring overnight. Reaction mixtures analyzed by GC-MS and ESI-MS (workup with 1 N HCl), where stated.

Analysis of the chromatograms of the background reactions (Table 10, entries 1-4) revealed that in all cases, a new peak next to the original residual peak of **223** occurred. This can be attributed to the presence of traces of water in the reaction mixture, leading to the formation of a water adduct **227**, shown in Scheme 52. The fragments detected for the newly detected peak support the hypothesis that compound **227** forms (*see spectra addendum*). Additionally, in the blind reaction involving KO^{t}Bu, the addition product with *tert*-butanolate **228** forms.

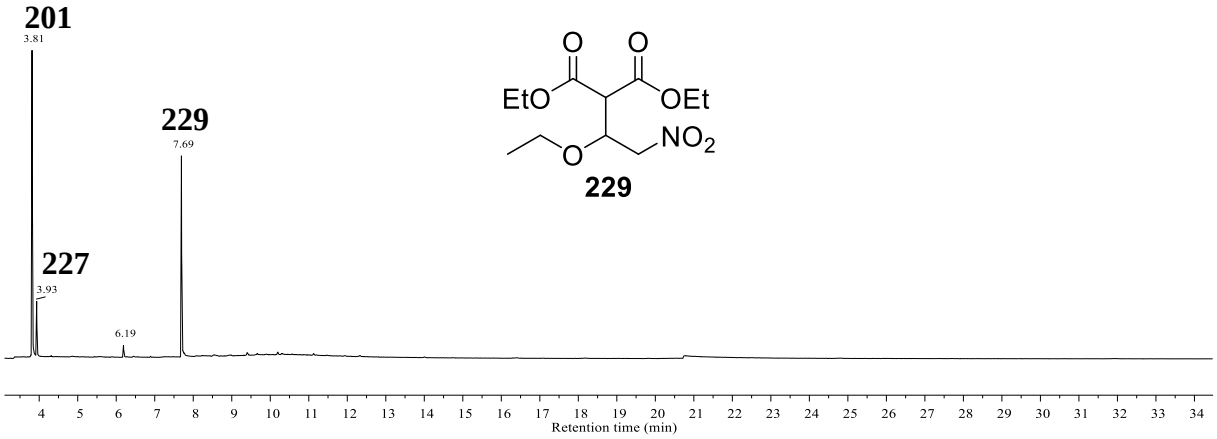


227 **228**

Scheme 53: Water and *tert*-butanol addition product detected in blind probes.

Changing to the reactions involving diethyl malonate as a nucleophile (Table 10, entry 5-8) yielded inconsistent results. While the use of KO^{t}Bu delivered no addition product. Interestingly the previously encountered addition product of *tert*-butanol was not formed according to GC-MS analysis. This can be explained by the fact that after the full deprotonation of malonate **201**, no KO^{t}Bu remained for the addition to **223**. However, this does not explain the absence of the desired addition product **229**. Using Et_3N yielded trace amounts of a new species detected by GC-MS at a retention time of t_R = 7.69 min. Thiourea **130** led even more of the new compound being formed. The use of Quinine as promoter resulted in the largest amount of the desired product being formed. Analysis of the fragmentation pattern revealed signals consistent with the expected addition product **229**. Additionally, a second and unknown species formed in trace amounts with a retention time of t_R = 6.19 min. Analysis of the fragmentation pattern and ESI-MS analysis of the reaction mixture did not provide any information as to the structure of this compound. Furthermore, in all cases, the formation of the water addition product **227** could be observed.

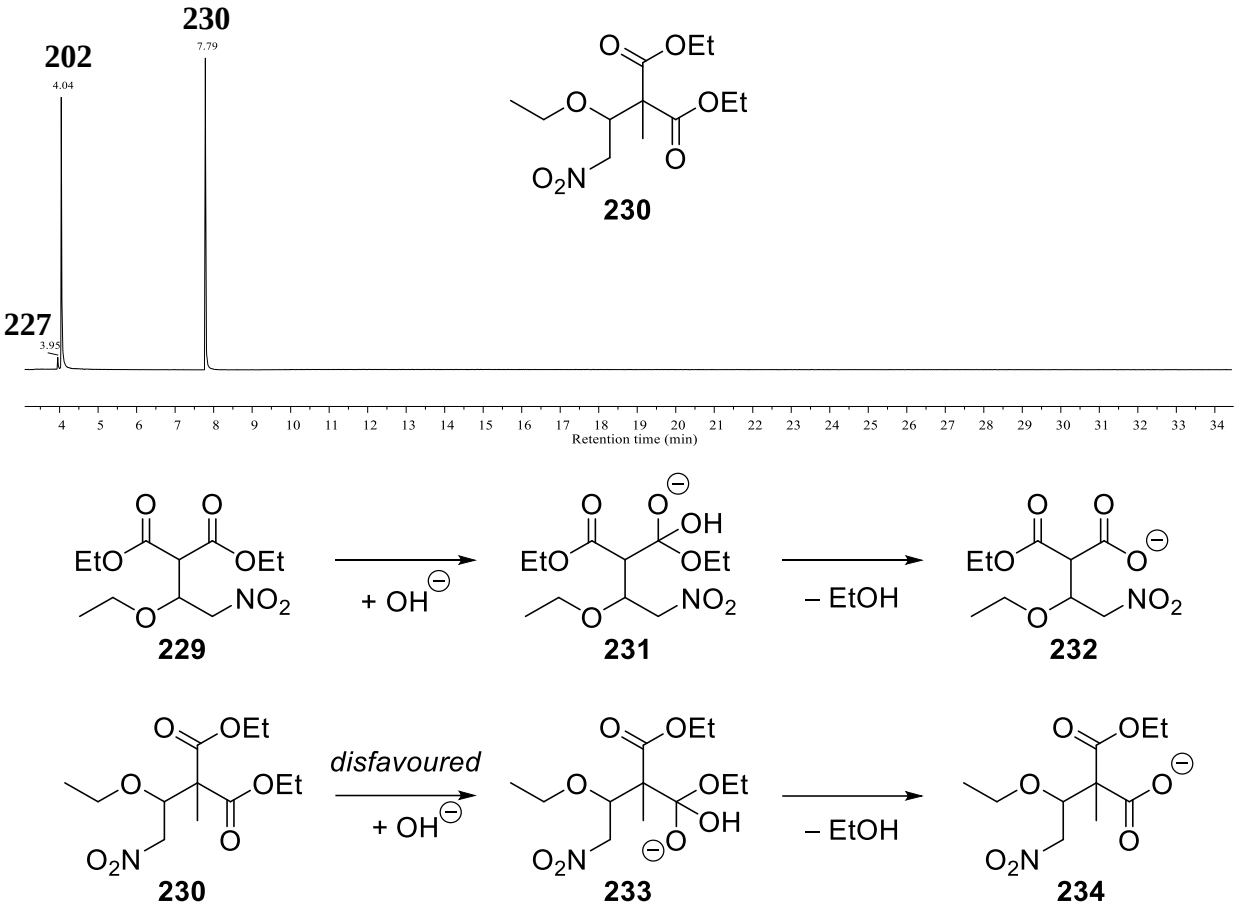
With MeEtO2Mal **202** as a nucleophile (Table 10, entry 9-12), the use of Et_3N, quinine, and thiourea **130** showed no product formation besides the previously encountered water adduct **227**. When KO^{t}Bu was deployed as a promoter, the desired addition product formed along with **230**. This contrast compared to the previous results obtained for diethyl malonate could be explained by the circumstance that the proton at C2 in the diethyl-methylmalonate **202** is far less acidic than in the simple malonate **201** (pK_a = 15.88 vs. pK_a = 18.04 for the dimethoxy malonates respectively, measured in DMSO at 25 °C).[104]



Scheme 54: Chromatogram of the crude reaction mixture of the addition of malonate **201** to **223** promoted by Quinine. Starting materials are at t_R = 3.81 (**223**) and 3.93 min. (**227** *water*) respectively. **229** can be seen at t_R = 7.69, and the unknown compound at t_R = 6.19 min.

Although this explains the exclusive product formation for entry 11, it does not explain the apparent absence of the desired addition product for entry 7. One explanation could be that the water accumulated in the KO^{t}Bu batch used, present as KOH, led to the saponification of at least one ester in the addition product **229**. The resulting anionic species/carboxylic acid product **232** might not be stable under GC-MS conditions and degrade upon injection via decarboxylation or fragmentation. If and why such a saponification process should take place preferably on **229** could be explained through the presence of the quaternary stereogenic center in **230** in direct proximity to the ester group. If an attack of a hydroxide ion were to occur on the ester group of **230,** the resulting tetrahedral intermediate **233** would contain two quaternary centers adjacent to each other. This might lead to considerable strain, exacerbated by the fact that the oxyanion formed can, therefore, most likely not lower repulsive interactions by distortion of the tetrahedral geometry (Scheme 55). This is underlined by the increased stability of pivalic esters when compared to isobutyric acid esters. Attempts to isolate the desired product were unsuccessful as no product eluated during the column chromatographic purification process.

The use of **65** as a nucleophile (Table 10, entry 13–16) yielded a highly complex mixture of species when Et_3N was used as a promoter. Quinine and KO^{t}Bu showed only minor formation of the desired product **235** shown in Scheme 56, but interestingly the signals corresponding to the starting material **65** also disappeared, indicating its complete conversion. This could be an indication of degradation of the starting material or transformation into a derivative not measurable by GC-MS.



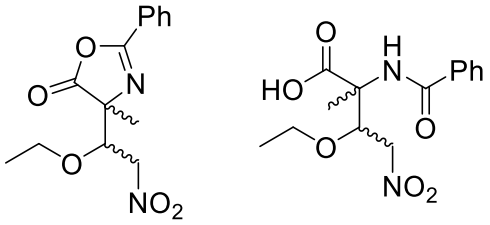
Scheme 55: Chromatogram of the crude reaction mixture of the addition of malonate **202** to **223** promoted by KO^{t}Bu showing the exclusive formation of the desired addition product **230** at t_R = 7.79. Starting materials are at t_R = 4.04 and 3.95 min. respectively. Below, the addition product of diethyl methylmalonate **202** and the schematic explanation for the observation of **230** instead of **229** is shown.

Thiourea **130** showed almost no conversion of the starting material, although a minor signal belonging to the product was detected, no second peak in the same region appeared, which is usually the case when diastereomers are formed. Due to the lack of characteristic fragments belonging to the nitro-vinyl ether, it remains unclear if the compound detected is the desired addition product, although a species with the same m/z-value have been detected using ESI-MS.

Scheme 56: Product from the addition of **65** to **223**.

By using **170** in combination with Et_3N for the addition reaction (Table 10, entry 17–20), a complex mixture formed while at the same time, complete consumption of the nitro-vinyl ether

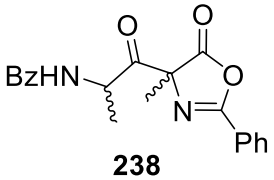
and no formation of the corresponding water addition product **227** has been observed. When quinine was used as a promoter, a clean spectrum was obtained, with only two signals occurring besides the azlactone and quinine signals. As shown below, the compounds detected show an almost similar fragmentation pattern in GC-MS, which would be consistent with the formation of a pair of diastereomers. Analysis of the fragmentation pattern and HRMS measurements of the crude mixture confirmed the presence of the desired addition product **236** as well as the presence of traces of the acid **237** resulting from an opening of the azlactone moiety. Deployment of thiourea **130** yielded a comparable result, although the formation of the water adduct has been observed again. $(DHQ)_2PHAL$ (Table 9, entry 1) also yielded the formation of the pair of diastereomers, although the chromatogram revealed that various other unknown species, as well as a considerable amount of the water addition product **227** formed.



236 **237**

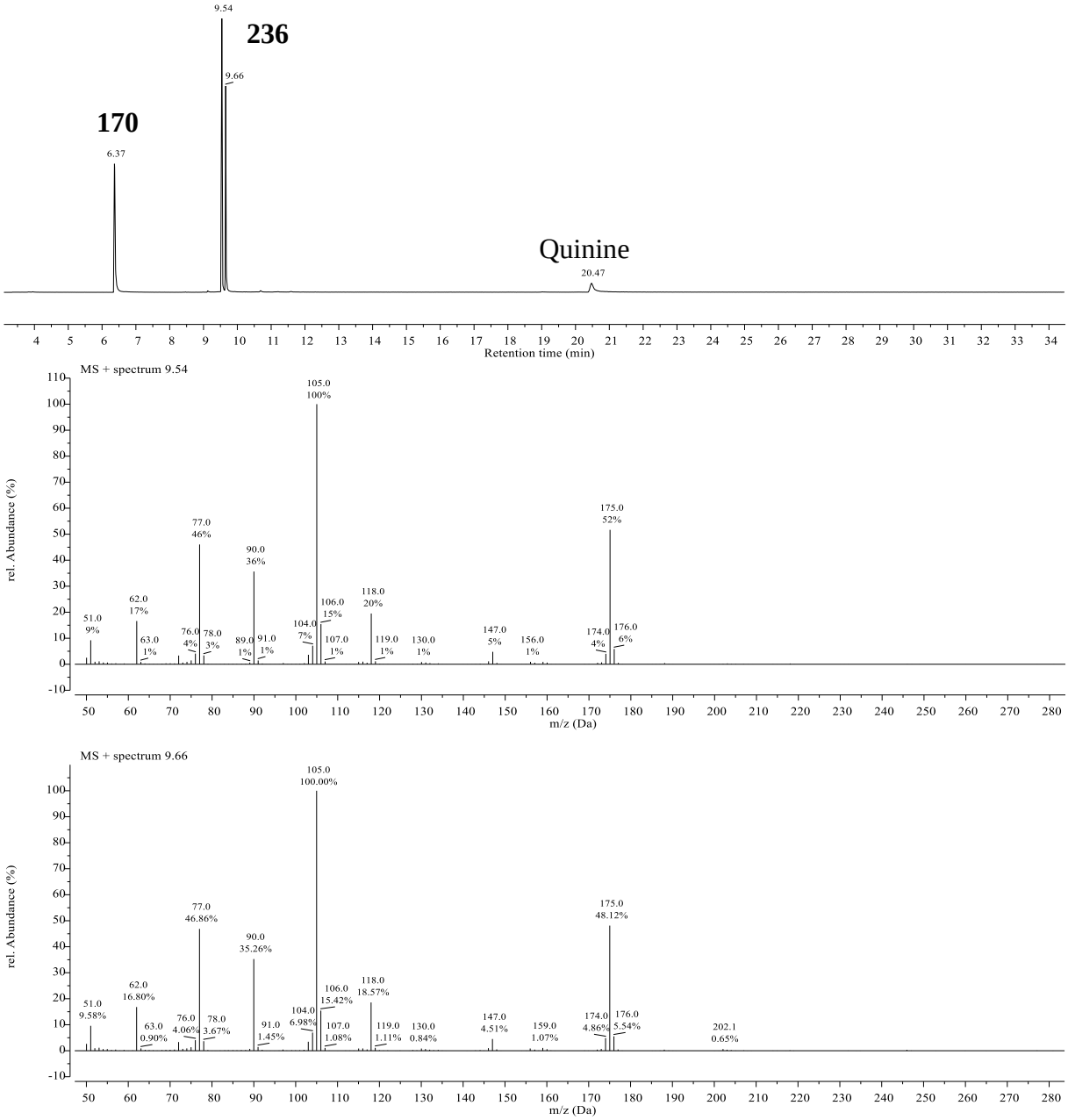
Scheme 57: Addition products detected after the reaction of **170** with **223**.

Furthermore, prolonged reaction times with quinine as a promoter lead to the degradation of the diastereomer with t_R = 9.54 min. and the formation of a new compound with an unknown structural formula. The usage of KO^{t}Bu as promoter yielded a complex mixture of compounds. Interestingly, the previously observed *tert*-butanol addition product **228** formed again in this reaction. Furthermore, the desired addition product **236** did not form. Instead, the self-acylation product of the azlactone **238** formed. This indicates that the use of strong bases results in the self-acylation side reaction outperforming the desired addition reaction. Such self-acylation reactions of azlactones have been reported previously, but usually, higher temperatures are required to promote the dimerization, and the overall number of literature accounts on these reactions is limited.[105–109]



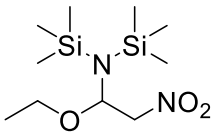
238

Scheme 58: Azlactone dimer detected after the reaction with KO^{t}Bu.



Scheme 59: Chromatogram of the reaction mixture of the addition of **170** to **223** using quinine as promoter. The almost identical fragmentation pattern of the compounds at t_R = 9.54 and 9.66 min. indicate a diastereomeric relationship. Starting material **170** and quinine are at t_R = 6.37 and 20.47 min. respectively.

When LiHMDS was used as a promoter (Table 9, entry 2) in an attempt to apply the reaction conditions reported by the Peregrina group[60], no product formed. Again, the formation of an addition product between HMDS and **223** was apparent by GC-MS analysis. Furthermore, no starting material could be detected, indicating a complete decomposition.



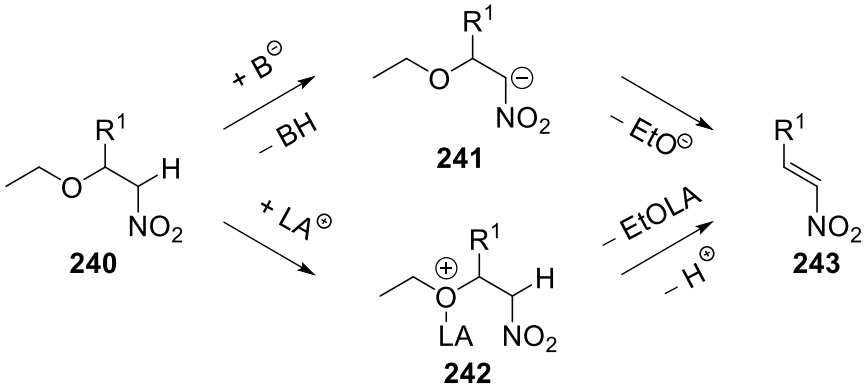
239

Scheme 60: LiHMDS addition product detected via GC-MS analysis.

The isolation of the diastereomers of **236** was attempted, but no the product could be isolated, most likely due to degradation during the purification process. Studies dedicated to evaluating the stability of the addition products against several workup and purification conditions were thus conducted. Subjecting the reaction mixture to acidic workup with 1 N HCl or saturated NH_4Cl solution, as well as prolonged exposure to moderate heat and reduced pressure, was overall tolerated by the addition product. Furthermore, during these studies, the addition product was exposed to silica, which led to its decomposition. Interestingly, it tolerated alumina in acidic, basic, and neutral grades. Due to these results, an attempt to isolate the diastereomers of **236** was made using neutral alumina as a stationary phase for column chromatography, but no product was isolated.

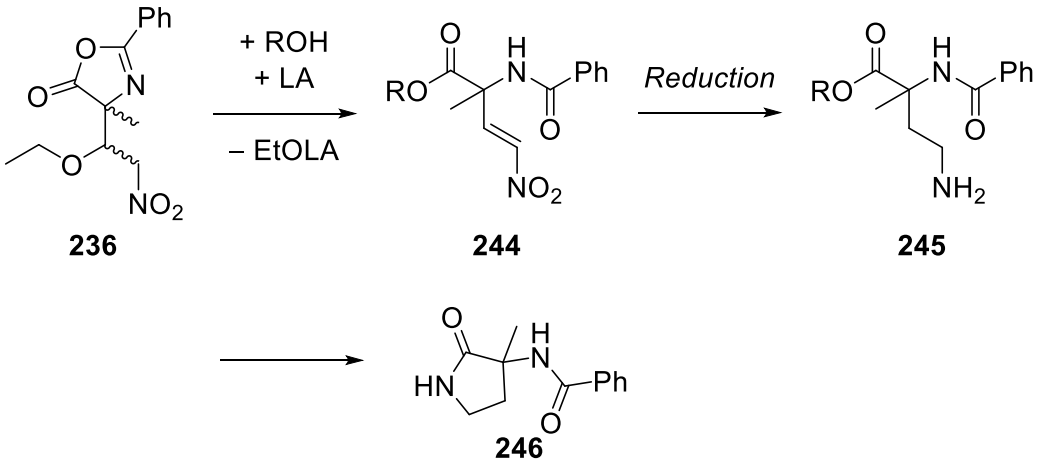
Attempts to form the ethoxy ester by *in situ* alcoholyses of the azlactone with or without the addition of different additives (TMSCl and $LiClO_4$) for the isolation of the product were performed. GC-MS analyses of all reaction mixtures only revealed highly complex mixtures. In the case of the ethanolysis, one diastereomer was consumed entirely, but the previously encountered side product now posed as the major constituent of the reaction mixture due to the degradation process mentioned earlier. If a Lewis acid was added, both diastereomers were wholly consumed, and various side products were also formed. Another experiment to reduce the azlactone using $NaBH_4$ in methanol also only resulted in the formation of a highly complex mixture.

Given the results of the experiments mentioned above and the sensitivity of **223** addition products towards the workup conditions reported in literature,[103] it seems reasonable that the side product encountered might be the result of an elimination reaction. Two possible pathways leading to this side product **243** are shown below in Scheme 61.



Scheme 62: Possible pathways leading to the elimination product **243**, LA either being a lewis acid or a proton.

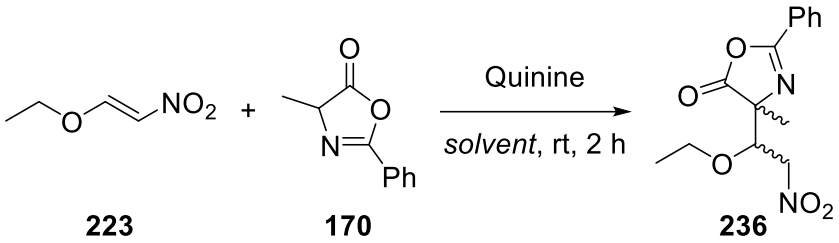
One way to prove these observations could be to form the nitroolefin **244** by first eliminating ethanol quantitatively and forming the ester by adding a lewis acid and an alcohol, followed by a reduction of both the nitro group and the newly formed olefinic bond. The resulting alkyl-amine **245** should cyclize to the corresponding lactam **246** leading to a mixture of only two enantiomers which should be stable enough for isolation. It should be noted that each of the steps might lead to the formation of various side products and result in the overall mixture becoming too complex for an adequate purification of the desired product.



Scheme 63: Possible reaction sequence allowing the isolation of the derivative **246** of the addition product **236**.

In addition to the screening of various nucleophiles and promoters, a short investigation into the effect of the solvent was conducted in order to verify that the results obtained earlier using **26** are reflected in the reactions using **223**. This time, a larger spectra of solvents was screened as after the screening some of the initially used solvents in Table 6 no trend became apparent.

Table 11: Solvent screening for the addition of **170** to **223**.



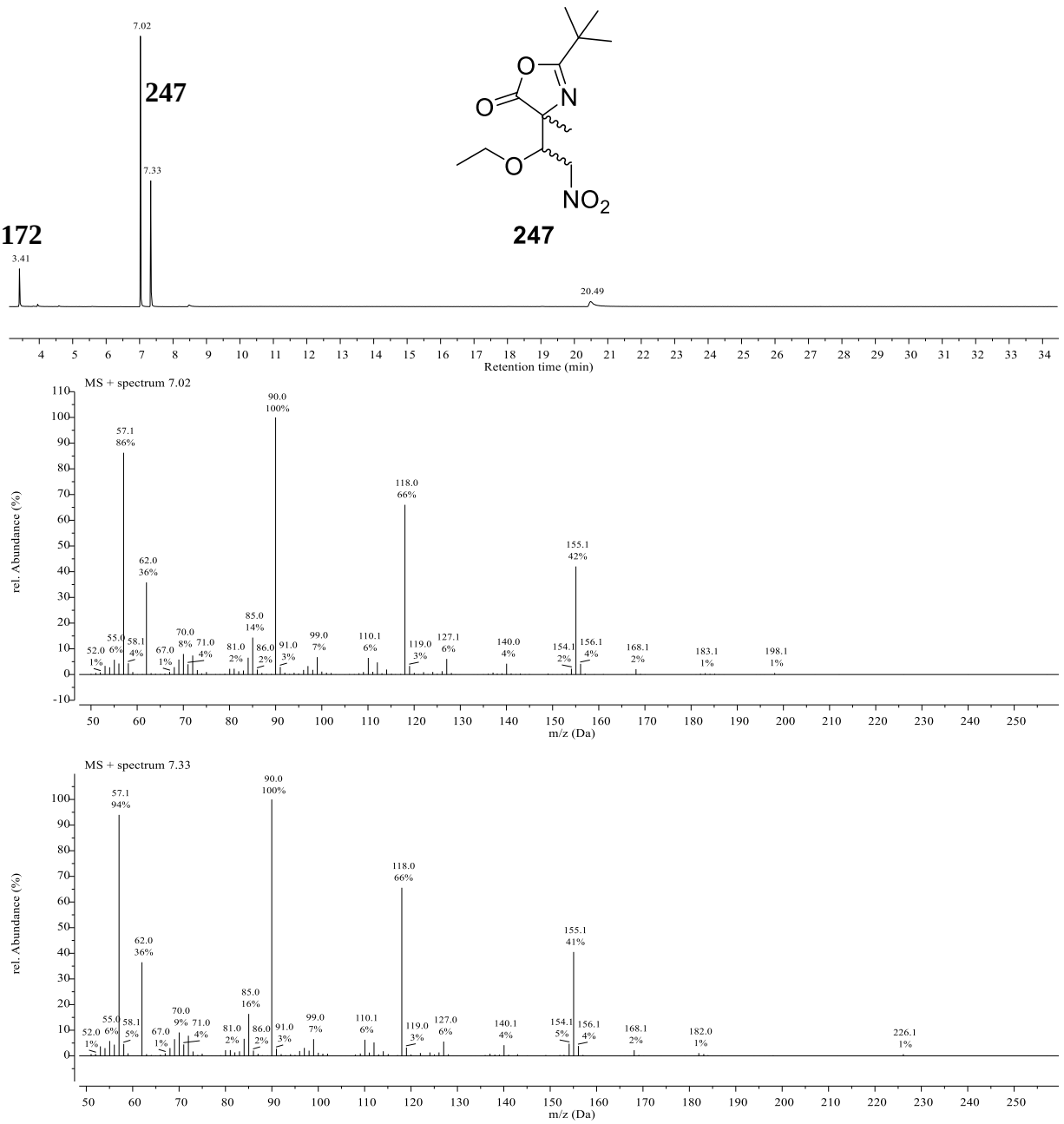
223 **170** **236**

Entry	Solvent	Product formed
1	Ethyl acetate	Yes
2	Diethyl ether	Yes
3	Tetrahydrofuran	Yes
4	Toluene	Yes
5	Dimethoxyethane	Yes
6	*n*-Hexane	Yes
7	Propylene carbonate	Yes
8	Acetonitrile	Yes

Reactions were carried out on a 0.1 mmol scale in 0.2 mmol concentration using 1.2 equiv. of Quinine and **170** compared to the acceptor and stirring for two hours at room temperature. Reaction mixtures were analyzed by GC-MS.

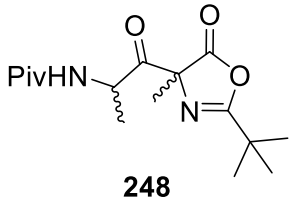
Surprisingly, in all cases the desired product **236** formed according to GC-MS analysis. Despite the low solubility of quinine in hexane, after 2 h, the desired product could be detected. This contradicts the previously solvent effect found for the addition of **65** to **26**, shown in Table 6. Additional control experiments were carried out to exclude the possibility of a background reaction between **223** and **170**, but background reactions occured.

Lastly, a set of experiments was conducted using **172** as a nucleophile. In the case of Et_3N and quinine, a full conversion of **223** occurred. Judging by the fragmentation pattern of the two species shown below, again, a set of diastereomers formed. As before, quinine yielded cleaner reactions compared to Et_3N. Using thiourea **130,** the desired addition product **247** formed, although in trace amounts when compared to the reactions with quinine and Et_3N. Comparing the chromatogram to the one obtained from the addition of **170** to **223**, a higher degree of diastereoselectivity is obtained when **172** is used as a nucleophile.



Scheme 64: Product detected after the addition of **172** to **223** using quinine as a promoter with the corresponding chromatogram and spectra of the diastereomers.

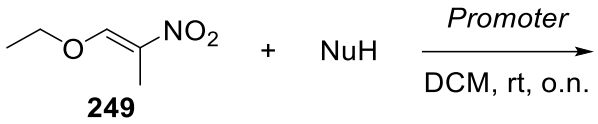
Upon repeating the reaction with KO^{t}Bu as promoter, the self-acylation product **248**, similar to the reaction with **170**, formed as the primary reaction product. Interestingly, traces of the desired addition product also formed in contrast to the reaction using **170**.



248

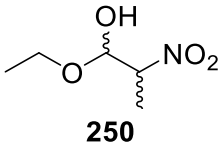
Scheme 65: Main product detected after the reaction between **172** and **223** promoted by KOtBu.

4.3.2 – Addition to (1*E*)-1-Ethoxy-2-nitropropane



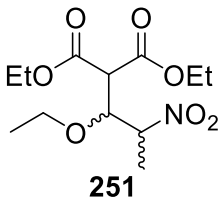
Scheme 66: Generalized scheme for the addition of nucleophiles to **249**.

To evaluate the effect a substituent next to the nitro group would have on the addition reaction, **249** was chosen as a substrate for the test reactions. Like in the previous experiments with **223**, the water addition product **250** formed in all of the control experiments (Table 10, entries 1-4). In the case of Et_3N and quinine, the formation of the addition product is only marginal, whereas, in the case of thiourea **130**, an almost equimolar amount of the addition product forms. The use of KO^{t}Bu led to a highly complex mixture of different species in the GC-MS spectra in contrast to the previous experiments, indicating degradation of **249** under the reaction conditions.



Scheme 67: Water addition product detected via GC-MS.

In contrast to the experiments with **223**, only the use of quinine in combination with **201** (Table 10, entry 5-8) yielded traces of the desired addition product **251**, shown below in Scheme 68. Interestingly, the reaction involving KO^{t}Bu exhibited no signs of the degradation encountered in the control experiment. The fact that neither Et_3N nor KO^{t}Bu nor thiourea **130** yielded any product indicates that the reaction is probably slowed down significantly. Additionally, a change in the activation mode or mechanism might have occurred since a simple reduction of the reaction rate cannot explain why the formation of the product is only detectable with quinine and not with Et_3N. However, the exact nature of this change remains elusive.

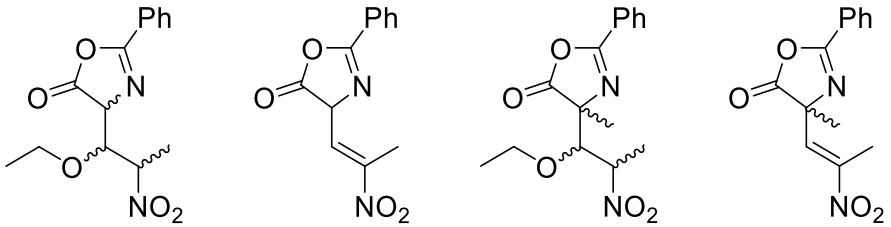


Scheme 68: Generic structure of the product detected via GC-MS after the reaction of **201** with **249**.

In the experiments where **202** (Table 10, entry 9-12) was used as a nucleophile, no addition product besides the water addition product formed. The use of **65** (Table 10, entry 13-16) in

combination with Et_3N and quinine as promoters led to the formation of complex reaction mixtures. It should be noted that no full conversion of the acceptor occurred in all of these cases, supporting the theory of a significant reduction of the reaction rate for the addition to **249**. The complexity of the reaction mixtures can be attributed to the fact that one additional stereogenic center is formed if compared to **223**. Upon including the elimination products **253** and **255** from the proposed elimination/degradation pathway shown in Scheme 62, the number of possible products that could theoretically form just from the desired addition and that would be detectable by GC-MS is further increased. In the cases where thiourea **130** and KO^{t}Bu were used, no product formed according to GC-MS analysis.

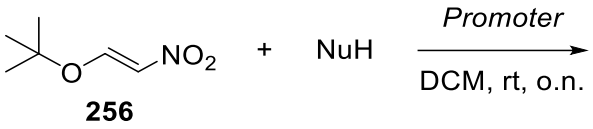
Deploying **170** (Table 10, entry 17-20) as a nucleophile led to a similar situation as with **65**. Et_3N and quinine gave complex mixtures. Only in the case where quinine was used as a promoter an almost quantitative consumption of **249** could be observed. The use of KO^{t}Bu gave no apparent formation of any of the desired products.



Scheme 69: Generic structure of the products detected via GC-MS after the reaction of **249** with azlactones **65** and **170**.

Given the results mentioned above, it is reasonable to conclude that the introduction of a substituent next to the nitro group significantly slows down the addition reactions. Additionally, the addition of malonates almost ceased to work entirely, while the addition of azlactones **65** and **170** still worked, albeit at a reduced rate. Furthermore, KO^{t}Bu and thiourea **130** proved to be ineffective as promoters. In the case of the thiourea catalyst **130**, this apparent ineffectiveness can be attributed to the reduced reaction rate in combination with the lower loading. For KO^{t}Bu, this observation can, at least in part, be attributed to the degradation of **249** observed in the control experiments. The fact that in the reaction with **170** and KO^{t}Bu, no formation of the self-acylation product **238** occurred could hint toward the contribution of other factors in the self-acylation process not accounted for in these test reactions or the presence of impurities. Overall, the steric factor only seems to influence the rate of addition, while the electronics of the nucleophile, in combination with the nature of the promoter, appear to govern the general feasibility of the addition to nitro-vinyl ethers.

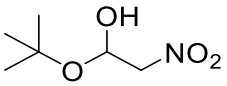
4.3.3 – Addition to (1*E*)-1-*tert*-Butoxy-2-nitroethene



256

Scheme 70: Generalized scheme for the addition of nucleophiles to **256**.

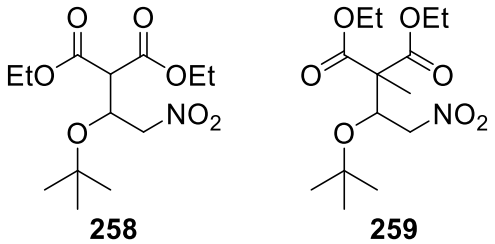
To test the sensitivity of the addition reactions to nitro-vinyl ethers towards the substitution on the ether function, **256** was chosen as a substrate. Like with **249** before, only traces of the water addition product **257** formed in the control experiments (Table 10, entry 1-4) involving Et_3N and quinine as promoters. The reaction with KO^{t}Bu resulted in the quantitative consumption of the vinyl ether and its conversion into the water addition product **257**.



257

Scheme 71: Water addition product detected via GC-MS after the blind reactions of **257** with the promoters.

The addition of **201** to **256** (Table 10, entry 5-8) led to no product forming with any of the promoters tested. Only the quantitative consumption of **256** in the reaction with KO^{t}Bu could be observed again in combination with the formation of the water addition product **257**. Although the same result was expected for the reactions with **202** (Table 10, entry 9-12), the reaction deploying KO^{t}Bu as promoter yielded traces of the desired product **259,** and no signs of the previously encountered water addition product were detected. This surprising result could be caused by the degradation of the addition product **258** under GC-MS conditions, as mentioned earlier. To rule out this possibility, several reaction mixtures were analyzed using ESI-MS, but no signs of the corresponding addition products **258** could be detected.

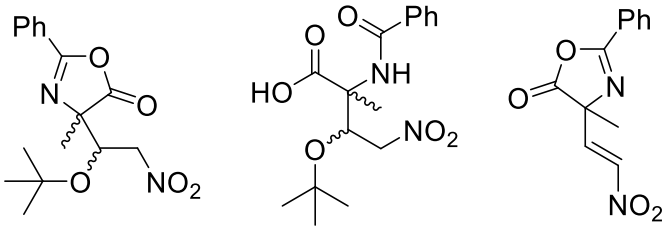


258 **259**

Scheme 72: Addition product of malonate **201** to **256** (undetected) and detected addition product **259** from the addition of malonate **202.**

For the addition of azlactone **65** (Table 10, entry 13-16) in all cases except where thiourea **130** was used, the azlactone got consumed quantitatively. Furthermore, in these cases, only traces of the desired addition product formed, indicating the degradation of the starting material.

Using azlactone **170** (Table 10, entry 17-20) in combination with Et_3N yielded a complex mixture but also an almost complete consumption of **256**. Analysis of the reaction mixture revealed that the desired addition product and its degradation product are most likely present in the reaction mixture. The addition reaction using quinine yielded a similar picture, although a smaller amount of side products was formed. Additionally, the formation of the self-acylation products **238** could be observed again in these reactions. When KO^{t}Bu was used as a promoter, the formation of diastereomeric compounds could be observed. Judging by the fragments observed in the GC-MS spectra, these compounds contain an azlactone moiety. Further information on the structure of these compounds could not be obtained. The deployment of thiourea **130** led to smaller amounts of product being present in the reaction mixture.

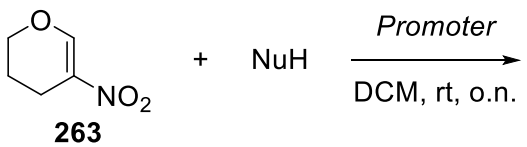


260 **261** **262**

Scheme 73: Plausible structures for the products detected after the reaction of **256** with azlactone **170**.

Overall it seems as if the introduction of a sterically demanding group next to the ether oxygen also strongly influences the reactivity of the corresponding nitro-vinyl ether. Like with **249** before, the addition of malonates seemingly ceases to function, while the addition of azlactones still proceeds, although at a reduced rate.

4.3.4 – Addition to 3,4-Dihydro-5-nitro-2*H*-pyran

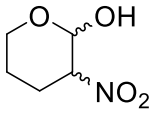


263

Scheme 74: Generalized scheme for the addition of nucleophiles to **263**.

Acceptor **263** was synthesized to evaluate the influence of a six-membered ring on the nitro-vinyl ether system, and at the same time, **263** allows for the exclusion of the effect of the

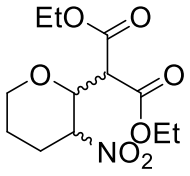
protecting groups and hydroxy functions on a nitroglycal. Except for the reaction where KO^{t}Bu was used, the use of **263** in the control experiments (Table 10, entry 1-4) did not yield the formation of water addition products encountered with other nitro-vinyl ethers. When KO^{t}Bu was deployed, unidentified side products formed next to the water addition product **264**.



264

Scheme 75: Structure of the water addition product detected via GC-MS after the blind reactions.

Using malonate **201** as a nucleophile (Table 10, entry 5-8), Et_3N and quinine gave trace amounts of the desired addition product. KO^{t}Bu and thiourea **130** failed to deliver the desired product **265**. This can again be attributed to a decreased reaction rate in the case of the thiourea **130**. Interestingly, like in the previous cases, no water addition product **264** formed in the KO^{t}Bu promoted reaction as soon as a nucleophile was added to the reaction mixture prior to the vinyl ether.



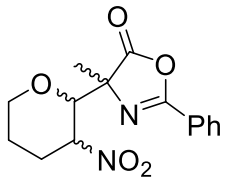
265

Scheme 76: Generic structure for the product detected by GC-MS after the reaction of malonate **201** with **263**.

For the reactions where **202** was used as a nucleophile (Table 10, entry 9-12), no product formation could be observed. Although in the case of the KO^{t}Bu promoted reaction, the water addition products formed again.

When azlactone **65** was used (Table 10, entry 13-16), in all cases except for the reaction with thiourea **130**, the almost complete degradation of the azlactone occurred. Only in the case of Et_3N the desired addition product formed, albeit in trace amounts.

Lastly, the deployment of **170** (Table 10, entry 17-20) resulted in complex mixtures in all reactions with the desired product **266** present except for the one where thiourea **130** was used. In the latter case, only traces of the desired addition product could be detected. If any sort of elimination product formed could not be determined.



266

Scheme 77: Plausible structure of the product detected after the reaction of azlactone **170** with **263**.

4.3.5 – Conclusions

Altogether, the addition of azlactone **170** to the chosen acceptors is observed in almost all cases, although a strong dependency on the promoter is observed in combination with the substitution pattern of the acceptor. The addition of azlactone **65** results in the preferential degradation of the azlactone instead of the desired addition. This is supported by the fact that the corresponding vinyl ether is still detectable after the reaction, despite being used as the deficit component. The possibility of the addition product of **65** being unstable under GC-MS conditions can be ruled out by the fact that the addition products of **170** can indeed be detected. Furthermore, the formation of self-acylation products of the azlactones **170** and **172** under varying conditions highlights the problems associated with the use of azlactone as amino acid precursors. As no clear trend is apparent in the conditions leading to the formation of these products, the suppression of such side reactions might be impossible if they are encountered in the synthesis of the initially desired compound **167**. (Zucker)

The addition of the chosen malonates yielded no apparent trend. Only a strong inhibition of the reaction was evident as the substitution pattern was slightly changed. In sum, the data suggest that the conditions chosen might be insufficient for investigating and gaining an in-depth understanding of the factors governing the addition reactions to nitro-vinyl ethers with the aim of realizing the addition of azlactones to 2-nitroglycals.

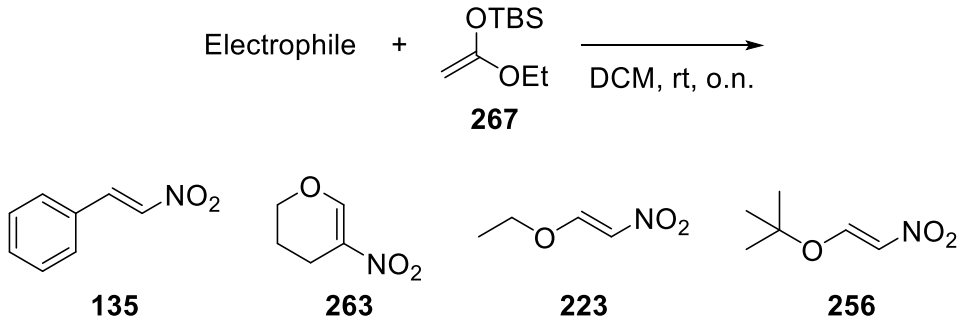
Neither the solvent effect nor the reactivity towards the nucleophiles chosen seems overall comparable to the trends observed for the addition to **26**. The addition of malonates to nitro-vinyl ethers, for example, appears to be much slower than to **26**, while the addition of azlactone **170** proceeds even to **263**. Furthermore, the fast degradation of the products due to their high inherent reactivity precludes their isolation and an investigation into the stereoselectivity of the addition reaction.

It is likely that the combined influence of the protecting groups and configuration of the stereogenic centers on the carbohydrates on the reactivity of nitroglycals is too pronounced for carrying out a reasonable simplification of the acceptor without diminishing the validity of the results obtained. Therefore, investigations on the behavior of 2-nitroglycals and the factors governing their reactivity might only be conclusive if they are carried out on the substrates themselves. Although the synthesis of various 2-nitroglycal derivatives is quite laborious compared to the synthesis of the model acceptors chosen in this work, an appropriate alternative may not exist.

4.4 – Miscellaneous

4.4.1 – Addition of Silyl Enol Ethers

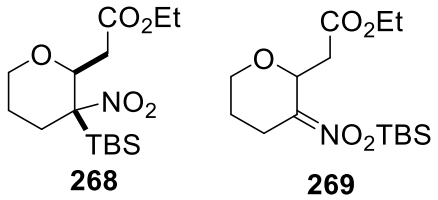
During the investigation of the behavior of nitro-vinyl ethers, various test reactions were carried out to evaluate the reactivity of silyl enol ethers towards nitro-vinyl ethers and nitro Michael acceptors. Therefore, a small set of nitro-vinyl ethers, as well as *β*-nitrostyrene, were stirred with the TBS-enol **267** without the presence of any promoter. Unexpectedly, GC-MS analysis of the mixture revealed the complete consumption of the acceptors as well as the formation of a new compound, interestingly without any signs of a diastereomeric mixture in the case of **263**. ESI-MS analysis of the crude reaction mixture revealed the presence of a compound with the m/z value corresponding to an addition product still bearing the TBS moiety.



Scheme 78: Reaction conditions and electrophiles used in the investigation of the addition of silyl enol ethers to various nitro Michael acceptors. Reactions were carried out in dry solvents in a 0.2 mmol concentration on a 0.1 mmol scale with 1.2 equiv. TBS enol protected from ambient light.

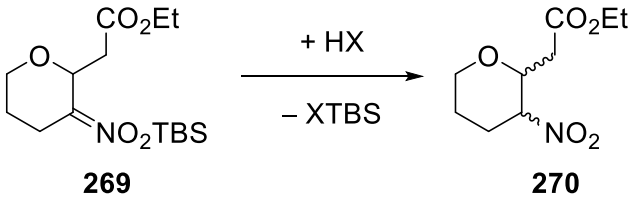
It is well known that the addition of silyl enol ethers to nitro-Michael acceptors can be accomplished under Lewis acid catalysis,[110,111] irradiation,[112] or by utilizing other promoters,[113] but to the best of our knowledge, only very few examples exist reporting a promoter-free Mukaiyama-nitro Michael reaction.[114] The formation of an addition product without the presence of a catalyst was therefore unexpected. Given the compound detected still

had the TBS-group attached, this gives rise to two different regioisomers of the addition product, whereas the TBS-group can either be located on the oxygen of the nitro group or the carbon adjacent to it.



Scheme 79: Possible structures for the detected addition product.

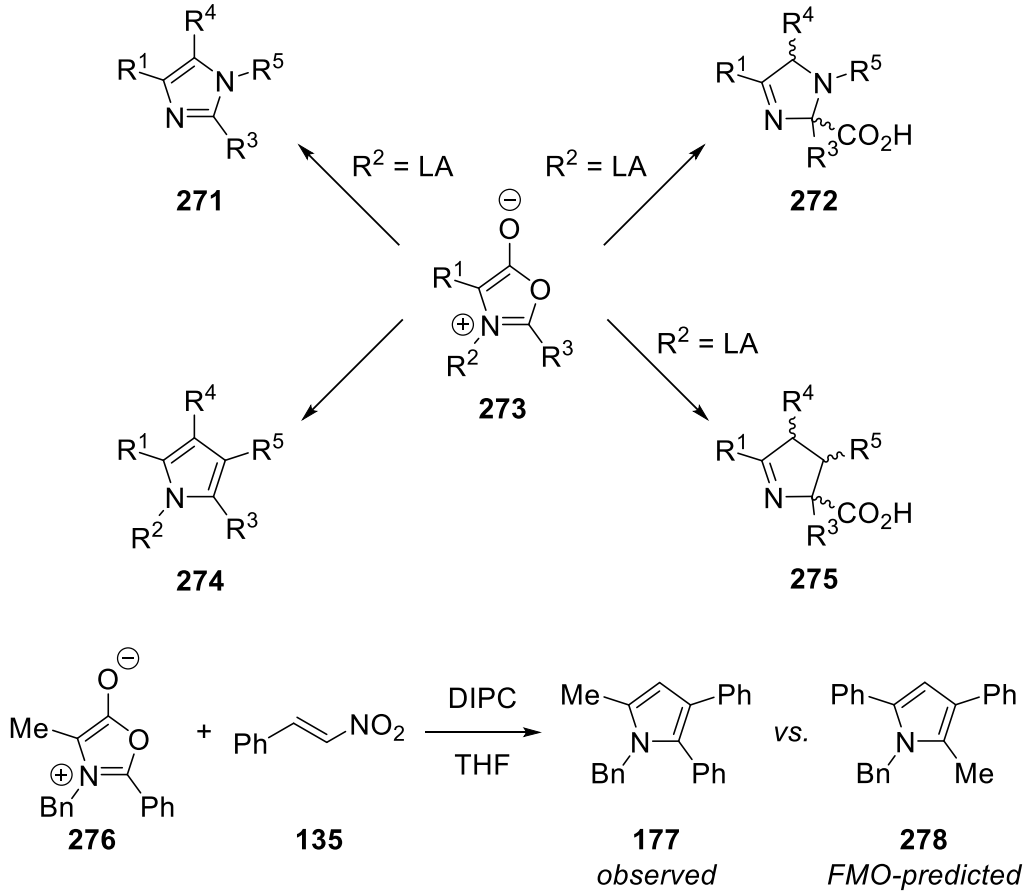
If the structure was to be **268**, the observation of only one of the two possible diastereomers could be explained by a mechanism exhibiting a highly concerted character, similar to an ene reaction.[115] On the other hand, structure **269** could also explain the occurrence of only one diastereomer, as in this structure, the second stereogenic center formed in **268** does not exist due to the sp^2 hybridization of the carbon atom adjacent to the nitro group. The mechanism leading to the formation of such an addition product would be less concerted compared to the one shown above. Upon cleavage of the TBS group, the formation of a diastereomeric mixture should be observed. Given the reports in the literature,[110,114] the latter mechanism seems more plausible.



Scheme 80: Cleavage of the TBS group resulting in the formation of a diastereomeric pair.

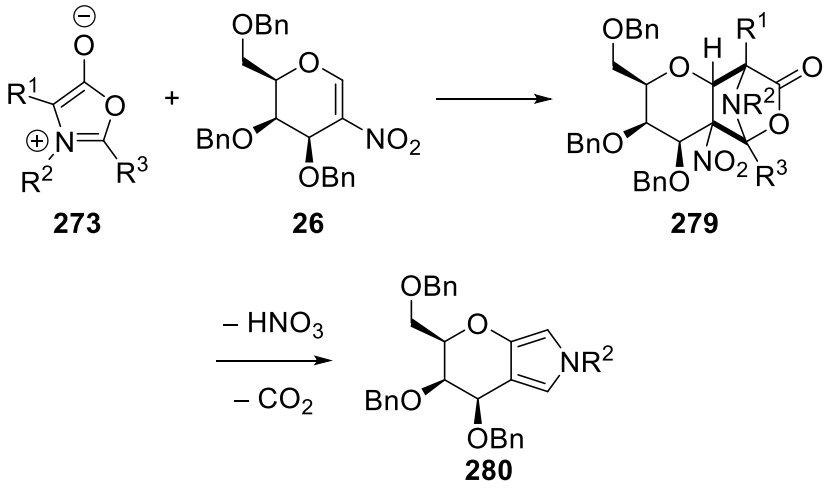
4.4.2 – Attempts towards the Addition of Münchnones

Münchnones[116] are mesoionic 1,3-dipolarophiles, used in addition reactions to electron-deficient alkenes and alkynes. Previously, münchnones have been extensively used in the (asymmetric) synthesis of pyrroles, pyrrolins, imidazoles, and imidazolines.[117,118] Although the regioselectivity of the addition can be difficult to predict since frontier molecular orbital analysis (FMOA) has been shown regularly to break down.[119,120] In case of a favorable regioselectivity, the addition of münchnones to electron-deficient glycals might yield valuable precursors for the synthesis of 2-deoxy-*C*-glycosidic amino acids.



Scheme 81: Targets synthesized using münchnones and FMOA breakdown observed by the Gribble group.[117,118,120]

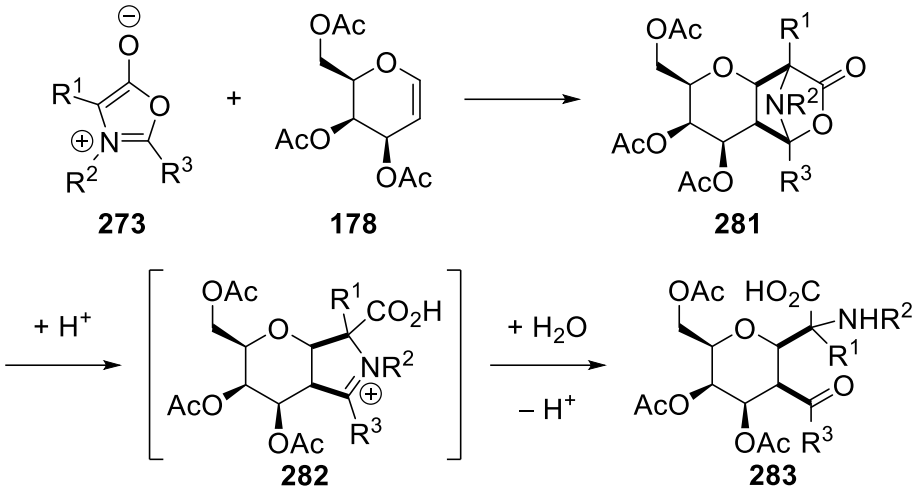
The addition of münchnones to 2-nitroglycals might initially lead to the desired structural motif, but an *in situ* elimination of HNO_3 and decarboxylation from the intermediate **279** would most likely lead to the pyrrole product **280**.[121]



Scheme 82: Probable formation of the pyrrole product **280** if the addition is conducted with **26**.

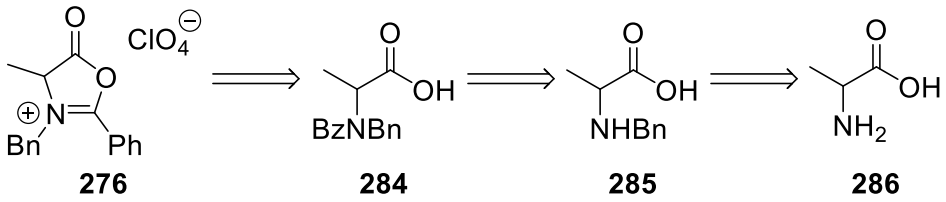
Therefore, to preclude the elimination of the nitro group, tri-*O*-acetyl glycals could be utilized as precursors, as the double bond should still be electron deficient enough to enable the reaction

to proceed. By using a tertiary amide as the starting material for the münchnone synthesis, the cleavage of the C–O-bond in intermediate **281** would yield an iminium ion **282**, which could easily be hydrolyzed to liberate the amine **283**, i.e., the desired structural motif.



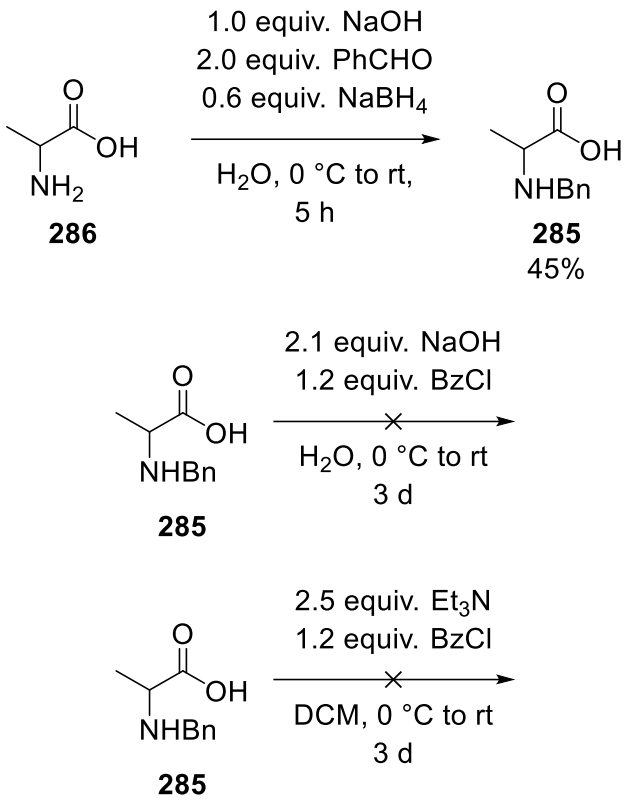
Scheme 83: Overview of the reaction sequence for the synthesis of 2-deoxy-*C*-glycosidic amino acids using münchnones.

In order to synthesize the desired münchnone **276**, a three-step synthesis starting from D,L-alanine was devised. The intermediate **284** could either be cyclized using the method developed by the Heider group and adapted by Trujillo,[122,123] or transformed into the corresponding perchlorate salt,[124] which would enable the synthesis of larger amounts of the münchnone as the perchlorate salts are stable. Additionally, when the corresponding perchlorate salts would be used, the reactions could be carried out under milder conditions, as the synthesis of the münchnones using the method of Trujillo requires elevated temperatures.



Scheme 84: Retrosynthetic analysis of münchnone **276**.

Although the benzyl protection of alanine **286** proceeded in moderate yield, the benzoyl protection of the amino acid, using the standard method utilized in the synthesis for the azlactone precursors, did not yield any of the desired product. Changing to prolonged reaction times and even a change in the procedure did not result in the formation of the desired product, as only highly complex mixtures could be obtained.



Scheme 85: Synthesis of *N*-benzylalanine **285** and failed attempts of the *N*-benzoyl protection of *N*-benzylalanine.

4 – Conclusion

In this work, various nitro-vinyl ethers and nitroglycals were synthesized to test their feasibility in addition to reactions with azlactones and malonates.The attempted (organocatalytic) synthesis of 2-deoxy-2-amino-*C*-glycoside amino acids using azlactones and 2-nitroglycals as precursors could not be accomplished. Despite the fact that the addition-product of azlactone **65** to **26** could be detected and quantitative conversion of the nitroglycal occurred, the direct isolation of the product **185** or esterification proved impossible due to degradation of the product under the conditions tested. The reaction with malonates **201** and **27** also yielded a quantitative conversion of nitroglycal **26**, but the isolation of the product proved challenging, leading to a loss of large amounts of product. The addition of azlactones different from **65** or malonates such as **202** proved to be unfeasible under the tested conditions. Investigations into the solvent effect led to inconsistent results, as the addition of malonate **201** ceased to work in THF, whilst the addition of **65** still proceeded.

The synthesis of a more activated nitroglycal proved to be demanding and could only be accomplished for **44**. In reactions involving the activated nitroglucal **44**, no formation of the desired product occurred, most likely due to many side and follow-up reactions. Additionally, the activated nitroglucal **44** decomposed when exposed to the promoters within a short amount of time. Further investigations into optimizing the properties of the acceptor were not conducted due to the laborious and complex nature of such an investigation.

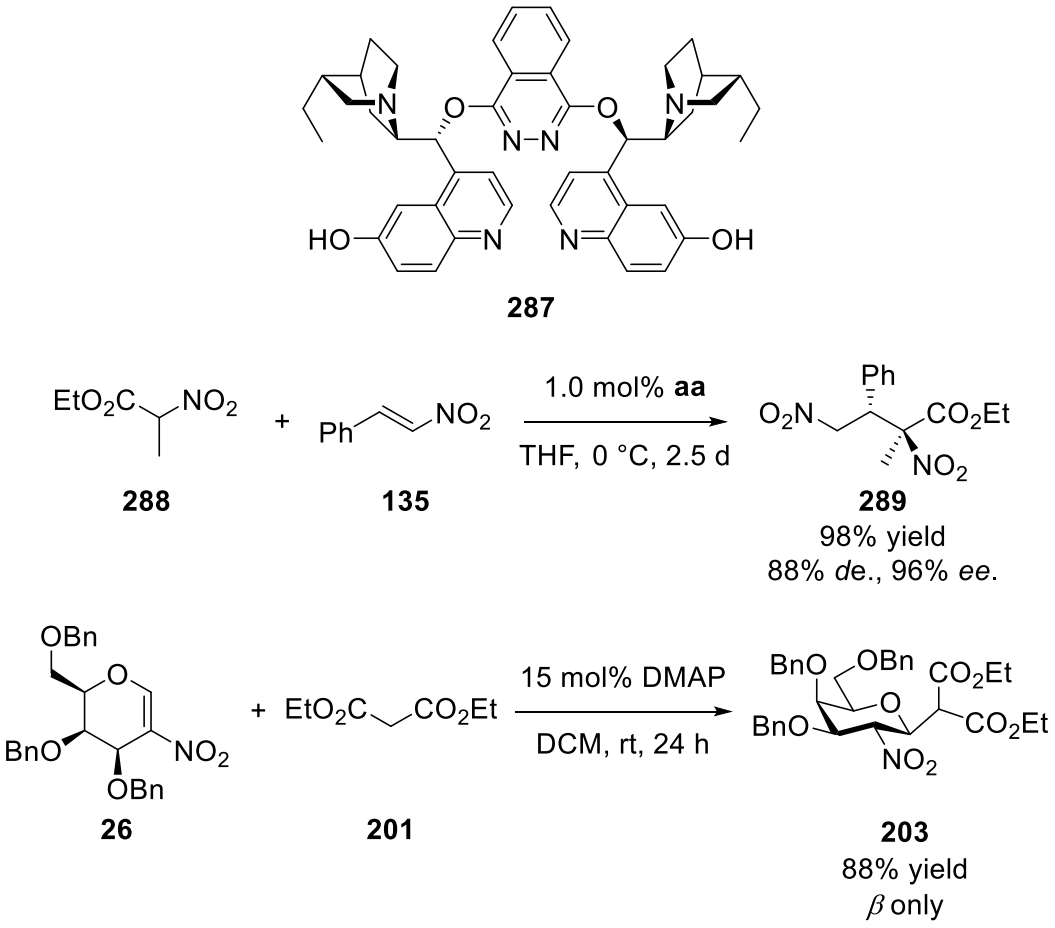
An investigation into the behavior of nitro-vinyl ethers as acceptors using four different model acceptors (**223**, **249**, **256**, and **263**) revealed a strong dependency on the substitution pattern of the acceptor with a slight increase in substitution, leading to an almost complete suppression of reactivity in some cases. The nature of the nucleophile also seems to play a vital role as with substituted acceptors, the addition of malonates ceases to function, while the addition of azlactone **170** still proceeds, sometimes even in a quantitative fashion. Furthermore, the choice of the promoter influences the reaction. Unfortunately, the products formed could not be isolated as these got most likely consumed, sometimes quantitatively, in follow-up reactions like the one shown in Scheme 62. Furthermore, the azlactones **170** and **172** underwent a self-acylation reaction in some reactions.

Altogether it seems unlikely that the organocatalytic synthesis of 2-deoxy-2-amino-*C*-glycoside amino acids can be achieved within a reasonable amount of time by using unmodified azlactones and 2-nitroglycals as synthons. The complex interplay of the effects of solvent, promoter, electronic properties as well as protecting groups on both the nitroglycal and azlactone have to be carefully evaluated and considered, as even slight deviations lead to overreactions or complete suppression of reactivity. Therefore, a change in at least one precursor seems to be necessary to achieve the synthesis of 2-deoxy-2-amino-*C*-glycoside amino acids to preclude the necessity of going through a cumbersome process without any guarantee of success.

5 – Outlook

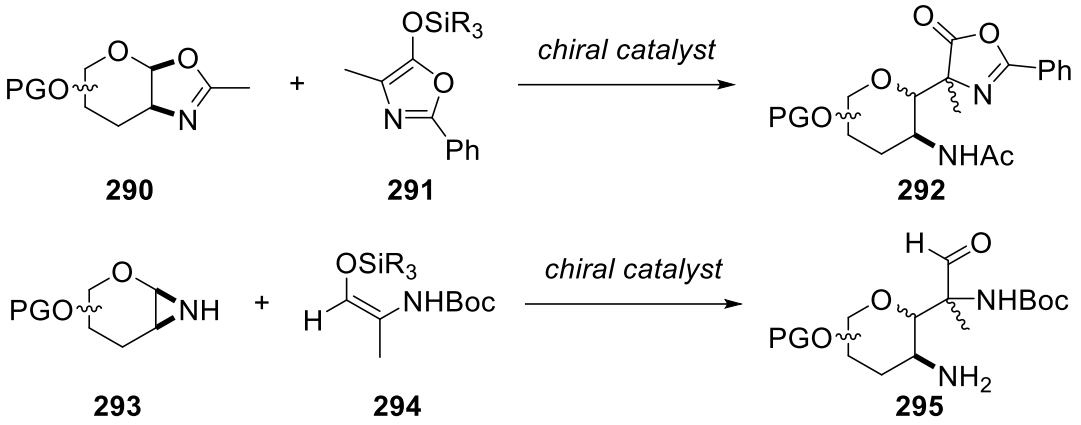
5.1 – Reactions yielding 2-Deoxy-2-aminoglycosides

Due to the fact that the addition of azlactones to 2-nitroglycals seems unlikely to be viable without the dedication of large amounts of resources, a change in the amino acid precursor might be more reasonable. As azlactones are themselves quite sensitive, thereby precluding, for example, the use of a nucleophilic (co-)catalyst like DMAP. Changing to different amino acid precursors like amino aldehydes **193** or nitro acetates **288** could solve the problems encountered during his project. Additionally, these precursors have previously been used in combination with organocatalysts to synthesize quaternary a-amino acids in a stereoselective fashion. Combining these precursors with the previously reported DMAP-mediated glycosylations involving 2-nitroglycals may circumvent a possibly long process of adjusting the reactivity of the glycosidic donor to the acceptor.



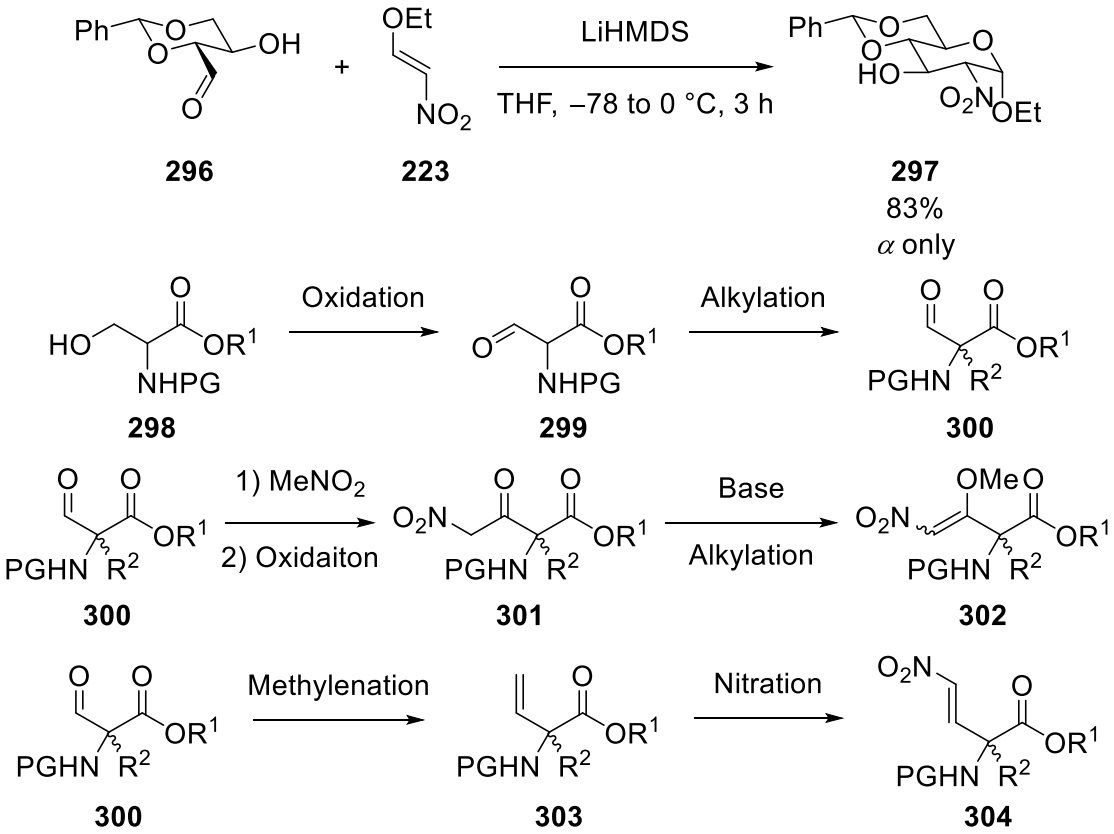
Scheme 86: Alternative synthons used in literature for the synthesis of quaternary a-amino acids and DMAP catalyzed glycosylation of diethyl malonate.[41,125]

Alternatively, the structural motif of 2-deoxy-2-aminoglyco-amino-acids could be accessed by using (ox-)aziridines **290** in combination with the deployment of a chiral (Lewis-)acid catalyst. The amino acid precursor used in this approach could be a silyl-protected enol of the alternative precursors mentioned above or a silyl-protected azlactone.



Scheme 87: Alternative glycosylations involving (ox)aziridines for the synthesis of 2-deoxy-2-amino-CGSAAs.

Another possibility for the synthesis of the desired structural motif would be the use of a semi-de novo synthesis. One starting point for this could be the work published by the Seeberger group.[126] By modifying the nitro-vinyl ether moiety, the desired structural motif should be accessible.



Scheme 88: De-novo synthesis reported by the Seeberger group and synthetic pathways for different synthons yielding 2-deoxy-2-amino-CGSAAs.[126]

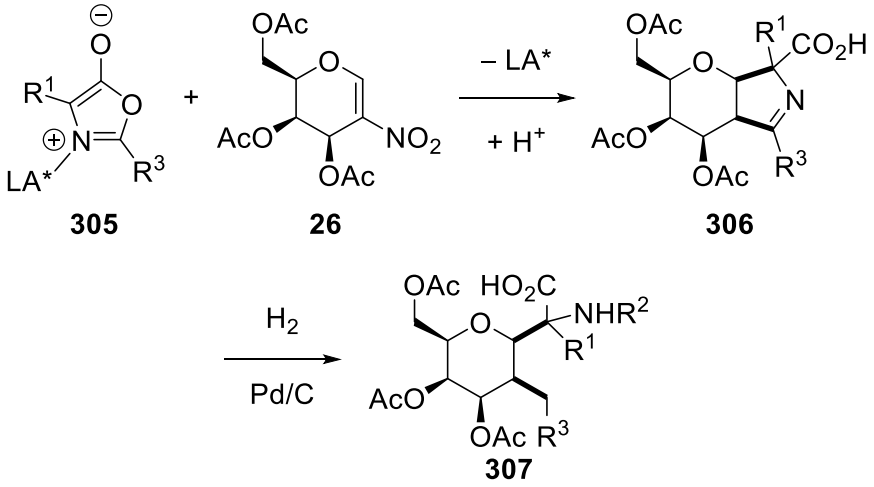
5.2 – Miscellaneous

5.2.1 – Mukaiyama-Nitro-Michael Reaction

For the reactions involving the use of TBS-enol **267**, the addition product needs to be isolated to determine the regioselectivity of the TBS-addition and thereby confirming one of the proposed structures shown in Scheme 79. Further experiments dedicated to ensuring the reproducibility of the reactions as well as excluding the possibility of an unknown impurity catalyzing the reaction. Furthermore, the reactivity of silyl-protected azlactones, similar to **291**, towards nitroglycals should be evaluated. Additionally, these azlactones should be compatible with nucleophilic catalysts. Thereby reaction conditions comparable to the ones described earlier could be utilized to promote the addition of **291** to **26**. If no diastereoselectivity in the newly formed quaternary stereogenic center is observed, the addition of chiral Lewis acid catalysts might lead to stereoinduction at this center.

5.2.2 – Reactions Involving Münchnones

Concerning the synthesis of 2-deoxy-CGAAs using münchnones as precursors, a change to a different synthetic route for the synthesis of *N*-benzyl-*N*-benzoyl alanine could prove vital. In addition to *N*-substituted münchnones, azlactones like **273** could be tested in combination with Lewis acids like TMSCl or silver acetate to promote the addition to glycals, as these Lewis acids might provide an additional activation of the glycal moiety.[127,128] Although the use of these azlactones will lead to the formation of relatively stable pyrrolines, these can be opened by hydrogenation using Pd/C.[129]

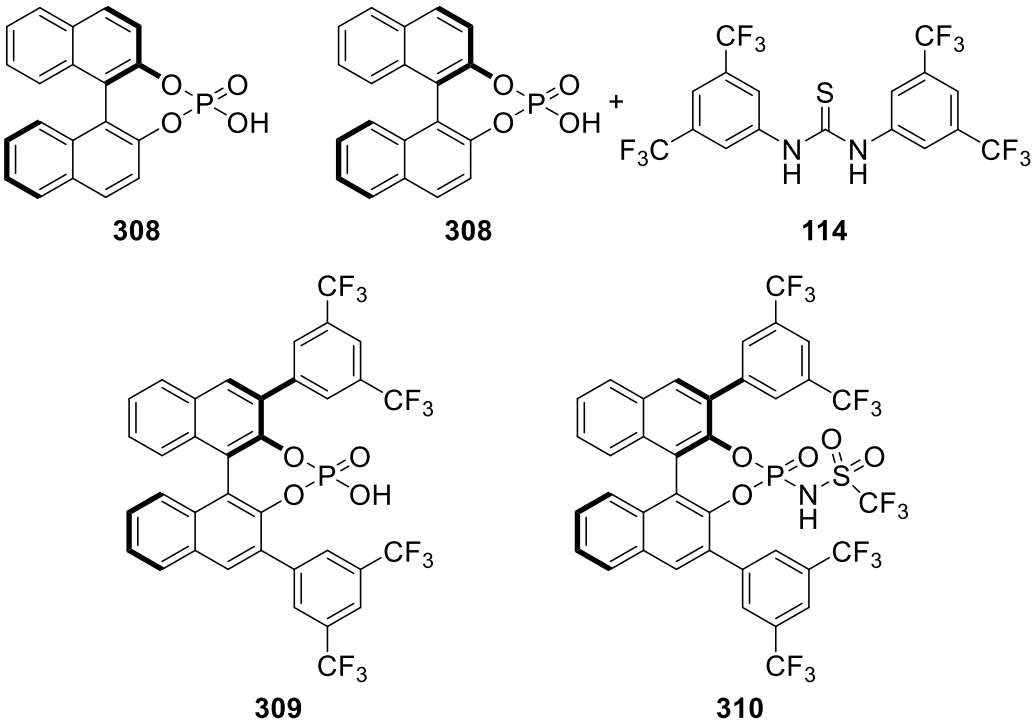


305 **26** **306** **307**

Scheme 89: Alternative synthesis of 2-deoxy-CGGAs using münchnones and chiral lewis acids.

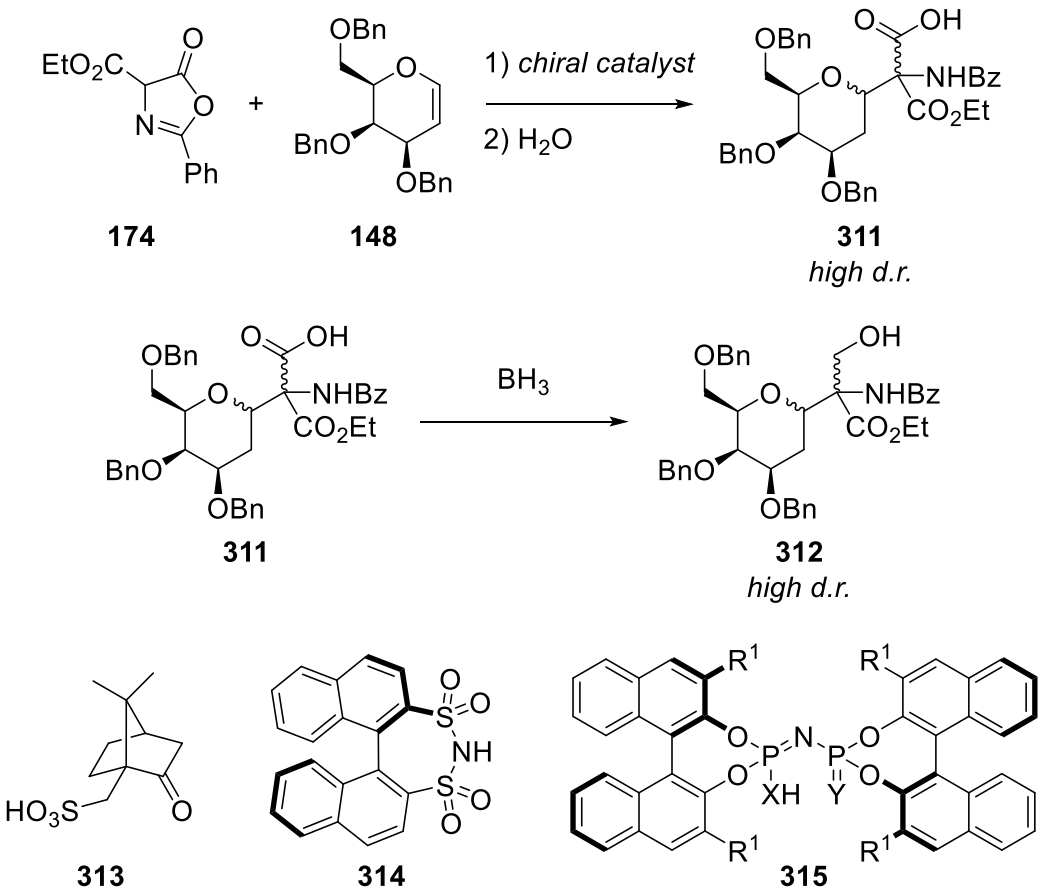
5.3 – Continuation of the Previous Project

In addition to the suggestions made earlier,[86] one way to expand the scope of the glycosylation reaction established prior to this investigation would be the use of a strong and chiral Brønsted acid in combination with modifications of the azlactone used. Despite the fact that chiral Brøensted acids (**308** with and without **114**, **309**, and **310**) have been deployed previously as promoters, so far, no thorough investigation has been carried out to maximize the stereoselectivity of the addition step concerning the newly formed stereogenic center on the azlactone moiety.



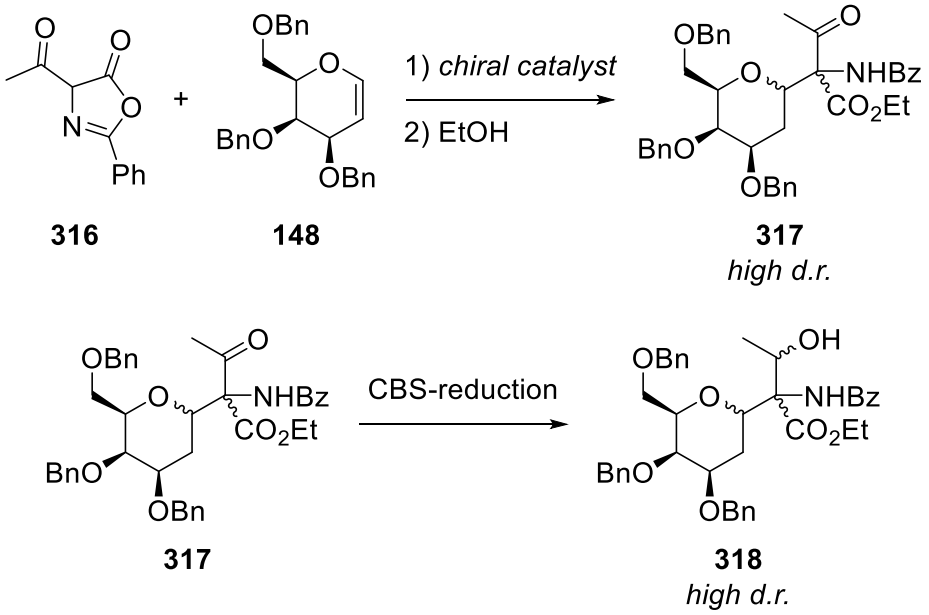
Scheme 90: Chiral catalysts deployed in the previous work.[86]

If the use of a chiral catalyst, e.g., camphor sulfonic acid (CSA) **313** or a catalyst similar to the ones developed by the List group (**314** or **315**) results in the addition of the azlactone in a non-racemic fashion (with respect to the stereogenic center formed on the azlactone), subsequent hydrolysis of the azlactone will lead to a chiral precursor **311** that can be reduced to the serine equivalent **312** (Scheme 91). In total, this would be a pathway to synthesize the previously racemic serine analog **152** in a stereoselective fashion.

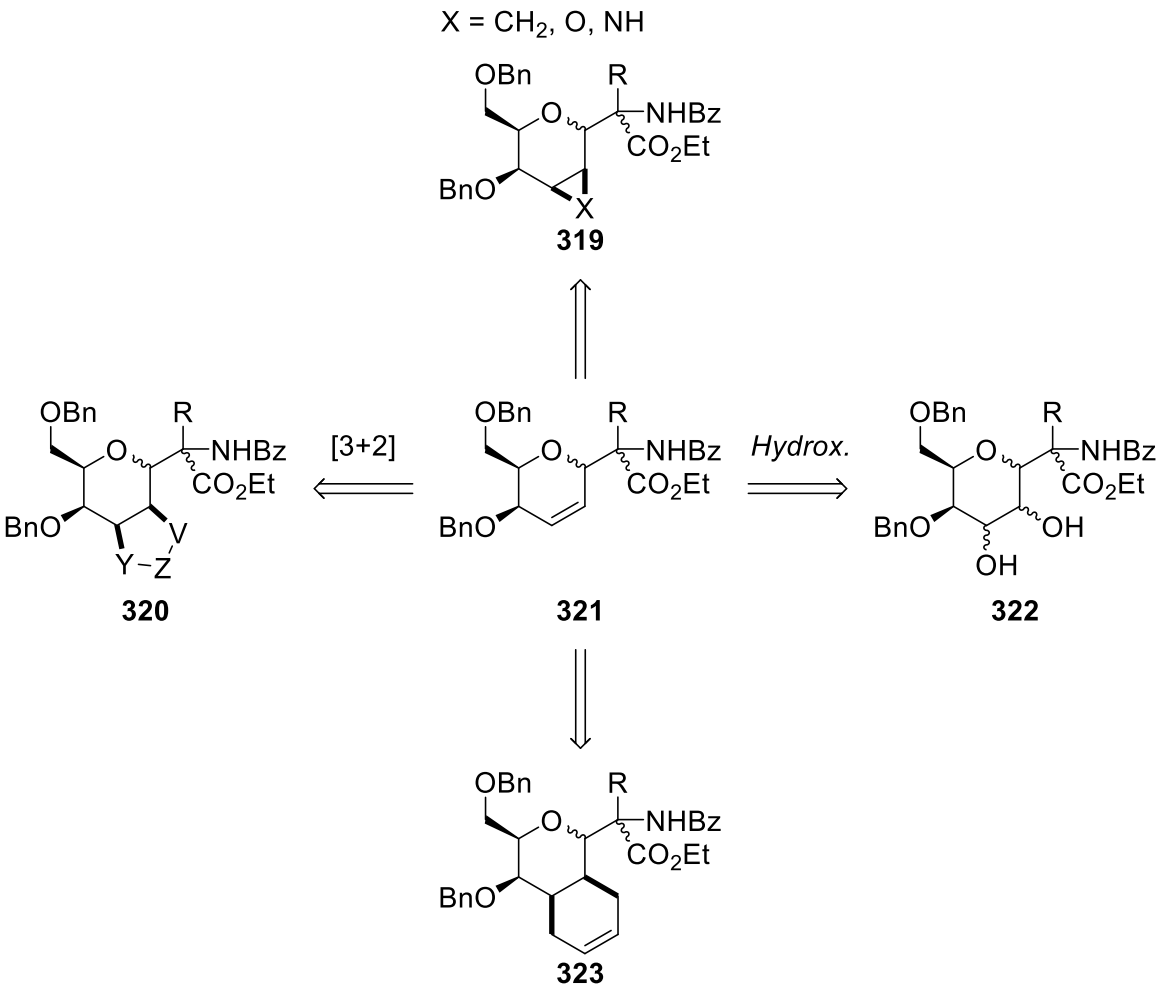


Scheme 92: Synthetic strategy towards the stereoselective synthesis of the serine analog **312** utilizing chiral catalysts **313**, **314**, or **315**.

Furthermore, by using the comparably activated azlactone-derivative **316** in combination with the approach mentioned above, a threonine derivative **318** could be accessed (Scheme 93). Hydrolyzing the addition product to **317** and subsequently reducing the ketone in a stereoselective fashion, for example, using a CBS-catalyst,[130] one should be able to obtain the desired product **318**. Additionally, optimizing the reaction towards the Ferrier-products obtained by the addition to glucal **321** and subsequent functionalized by hydroxylation, epoxidation, aziridination, or variants thereof, would enable access to various highly functionalized carbohydrate-derived scaffolds, similar to those shown in Scheme 94.



Scheme 95: Synthetic strategy towards the stereoselective synthesis of the threonine analog **318**.



Scheme 96: Possible functionalizations of the Ferrier-product **321**.

6 – Experimental Section

General Remarks

Unless stated otherwise, all chemicals were purchased from commercial suppliers in reagent grade. All solvents used were distilled prior to use. Dry solvents were bought from Acros Organics and used without further purification.

Column chromatography was performed using Machery-Nagel Silica gel 60 M (0.040 – 0.063 mm; 230 – 400 mesh) or Acros Organics aluminum oxide 50-200 micron in neutral grade. Thin layer chromatography was performed using Machery-Nagel Polygram® SIL G/UV254.

NMR spectra were recorded using a Bruker Avance II 400 MHz, Bruker Avance III HD 400 MHz, Bruker Avance III 600 MHz, or Bruker Avance III HD 700 MHz.

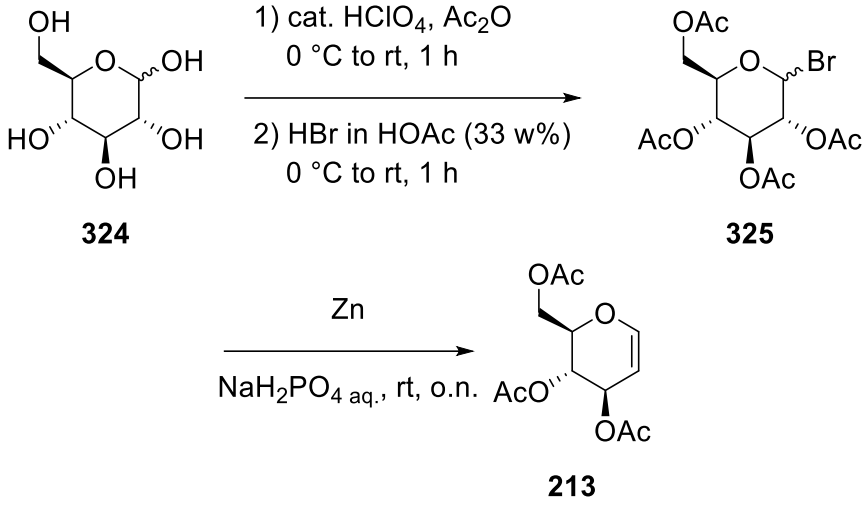
Reactions demanding inert conditions were carried out under an atmosphere of dry nitrogen, using glassware and stir bars dried overnight at 120 °C, heated and evacuated in high vacuum, and flushed at least three times prior to reaction.

IR spectra were measured using a Bruker ALPHA in combination with a diamond ATR cell.

GC-MS spectra were recorded using an Agilent 8860 GC-System in combination with an Agilent 5977B GC/MSD and a J&W HP-5ms (5%-phenyl)-methylpolysiloxane column (30 m x 250 µm x 0.25 µm). Helium was used as a carrier gas. The inlet temperature was set to 250 °C. The helium flow in the column was kept constant at 1.2 mL/min, while the oven temperature was increased from 60 °C to 250 °C within 10 min. before being kept isothermal for 25 min.

Catalyst **175** and TBS-enol **267** were provided by a coworker working on a different project and used without further purification.

3,4,6-Tri-*O*-acetyl-D-glucal



324 **325** **213**

At 0 °C, 100 mg glucose was suspended in 9.0 mL Ac_2O (95.37 mmol, 5.3 equiv.), and 2 drops of $HClO_4$ were added. Throughout 1 h, the remaining 3.133 g glucose (17.95 mmol, 1.0 equiv.) were added whilst maintaining the temperature at 0 °C. Following the last addition of glucose, the ice bath was removed, and the reaction mixture was allowed to reach room temperature. After stirring for 1 h at room temperature, the solution became completely clear and was subsequently cooled to 0 °C. 18 mL of HBr in HOAc (33 w%, 92.16 mmol, 5.1 equiv.) were added dropwise. After 30 min. of stirring at 0 °C, the ice bath was removed, and the reaction mixture was stirred for 1 h at room temperature before being slowly poured into a mixture of 100 mL DCM and 100 mL ice water. The organic phase was washed with 2×150 mL saturated $NaHCO_3$ solution and dried over $MgSO_4$. All volatiles were removed under reduced pressure yielding a rosé-brown colored resin. After dissolving the resin in 8 mL acetone, 40 mL saturated NaH_2PO_4, and 8.200 g zinc dust (<63 µm, 125.4 mmol, 7.0 equiv.) were added, and the reaction mixture was stirred vigorously overnight. The suspension was filtered over a pad of celite and washed with water and DCM. After extraction of the filtrate with 3×25 mL DCM, the combined organic phases were washed with 2×100 mL saturated $NaHCO_3$ solution and dried over $MgSO_4$. All volatiles were removed under reduced pressure and the resulting crude product was purified via column chromatography (silica, *n*Hex/EtOAc, 1/1, v/v). The product was obtained as 4.091 g (15.03 mmol) of a colorless viscous oil.

Yield: 83%

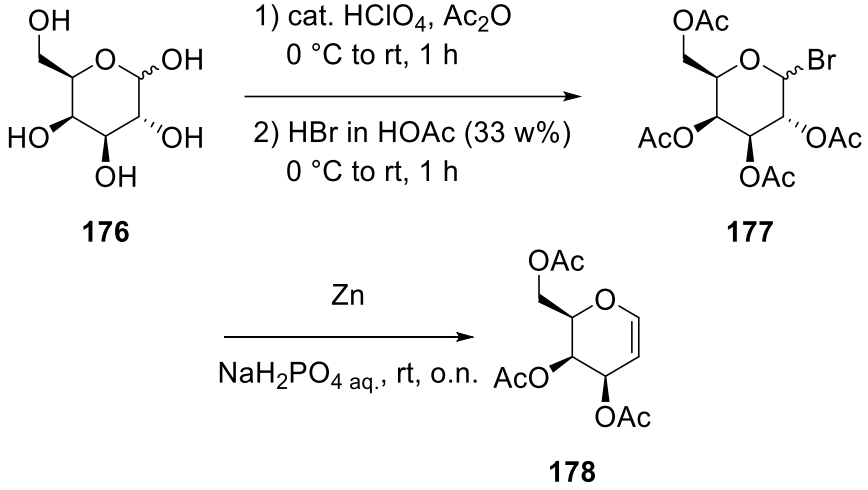
***R*f:** 0.41 (*n*Hex/EtOAc, 1:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (dd, *J* = 6.1, 1.4 Hz, 1H), 5.35 – 5.32 (m, 1H), 5.22 (dd, *J* = 7.6, 5.6 Hz, 1H), 4.84 (dd, *J* = 6.2, 3.2 Hz, 1H), 4.40 (dd, *J* = 12.0, 5.7 Hz, 1H), 4.25 (m, 1H), 4.19 (dd, *J* = 12.0, 3.1 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.74, 170.55, 169.72, 145.78, 99.15, 74.10, 67.58, 67.33, 61.53, 21.15, 20.95, 20.87 ppm.

The NMR data are consistent with those reported in the literature.[91]

3,4,6-Tri-*O*-acetyl-D-galactal



176 **177** **178**

At 0 °C, 100 mg galactose was suspended in 19.5 mL Ac_2O (206.3 mmol, 5.6equiv.), and 4 drops of $HClO_4$ were added. For 1 h the remaining 6.673 g galactose (37.04 mmol, 1.0 equiv.) were added whilst maintaining the temperature at 0 °C. Following the last addition of glucose, the ice bath was removed, and the reaction mixture was allowed to reach room temperature. After stirring for 1 h at room temperature, the solution became completely clear and was subsequently cooled to 0 °C. 42 mL of HBr in HOAc (33 w%, 217.6 mmol, 5.9 equiv.) were added dropwise. After 30 min. of stirring at 0 °C, the ice bath was removed, and the reaction mixture was stirred for 1 h at room temperature before being slowly poured into a mixture of 100 mL DCM and 200 mL ice water. The organic phase was washed with 2×200 mL saturated $NaHCO_3$ solution and dried over $MgSO_4$. All volatiles were removed under reduced pressure yielding a rosé-colored resin. After dissolving the resin in 30 mL acetone, 70 mL saturated NaH_2PO_4, and 18.358 g zinc dust (<63 µm, 280.8 mmol, 7.6 equiv.) were added, and the

reaction mixture was stirred vigorously overnight. The suspension was filtered over a pad of celite and washed with water and DCM. After extraction of the filtrate with 3×50 mL DCM, the combined organic phases were washed with 2×200 mL saturated $NaHCO_3$ solution and dried over $MgSO_4$. All volatiles were removed under reduced pressure and the resulting crude product was purified via column chromatography (silica, *n*Hex/EtOAc, 1/1, v/v). The product was obtained as 5.685 g (21.98 mmol) of a colorless viscous oil.

Yield: 59%

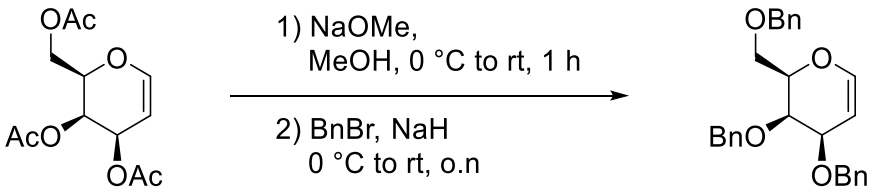
***R*f:** 0.43 (*n*Hex/EtOAc, 1:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (dd, *J* = 6.3, 1.8 Hz, 1H), 5.54 – 5.52 (m, 1H), 5.41 – 5.39 (m, 1H), 4.70 (ddd, *J* = 6.3, 2.7, 1.4 Hz, 1H), 4.32 – 4.28 (m, 1H), 4.27 – 4.17 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 170.3, 170.2, 145.5, 98.9, 72.9, 64.0, 63.8, 62.0, 20.9, 20.8, 20.7 ppm.

The NMR data are consistent with those reported in the literature.[91]

3,4,6-Tri-*O*-benzyl-D-galactal



178 **148**

A solution of 1.586 g 3,4,6-tri-*O*-acetyl-D-galactal (5.82 mmol, 1.0 equiv.) in 5.0 mL methanol was added in one portion to a solution of 0.126 g sodium methoxide (2.33 mmol, 0.4 equiv.) in 5.0 mL methanol at 0 °C. The mixture was stirred for 1 h, upon which it was allowed to reach room temperature. Subsequently, all volatiles were removed under reduced pressure, and the residue was suspended in 10.0 mL dry dimethylformamide under a nitrogen atmosphere. The suspension was cooled to 0 °C before 2.018 g sodium hydride (60w%, 50.45 mmol, 9.5 equiv.) were added portion-wise over 10 minutes. After the addition was complete, 3.20 mL benzyl

bromide (26.94 mmol, 5.1 equiv.) were added dropwise. The reaction mixture was stirred overnight upon warming to room temperature. The reaction was quenched by adding 10 mL of water and pouring it onto 300 mL of a 5 w% LiCl solution. The aqueous solution was extracted four times using 40 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$, and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography silica, *n*Hex/EtOAc, 10/1, v/v). The desired product was obtained as 1.807 g (4.34 mmol) of a colorless oil that solidified upon standing.

Yield: 75%

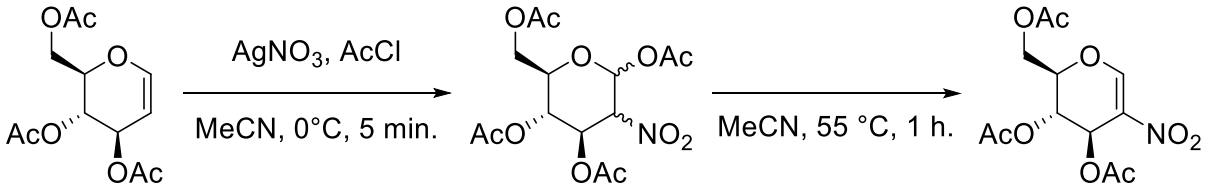
***R*f:** 0.22 (*n*Hex/EtOAc, 10:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.27 (m, 15H), 6.37 (dd, *J* = 6.3, 1.5 Hz, 1H), 4.89 – 4.85 (m, 2H), 4.67 – 4.61 (m, 3H), 4.52 – 4.42 (m, 2H), 4.20 – 4.18 (m, 2H), 3.96 – 3.95 (m, 1H), 3.79 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.65 (dd, *J* = 10.1, 5.0 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.3, 138.6, 138.5, 138.1, 128.5, 128.5, 128.3, 128.0, 127.8, 127.7, 127.6, 100.1, 75.8, 73.6, 73.5, 71.4, 71.0, 70.9, 68.6 ppm.

The NMR data are consistent with those reported in the literature.[86]

2-Nitro-3,4,6-Tri-*O*-acetyl-D-glucal



213 **326** **44**

To a vigorously stirred solution of 2.986 g 3,4,6-tri-*O*-acetyl-D-glucal (10.90 mmol, 1.0 equiv.) in 135 mL dry acetonitrile at 0 °C, 2.338 g silver nitrate (13.17 mmol, 1.2 equiv.) were added in one portion. After the silver nitrate dissolved completely, 1.00 mL acetyl chloride (14.01 mmol, 1.3 equiv.) was added dropwise and a white precipitate formed. The solution was allowed to reach room temperature before it was heated to 50 °C and checked regularly by TLC.

After 3 h, only one spot remained on the TLC, and the reaction mixture was cooled to room temperature and filtered through a sintered funnel under reduced pressure. All volatiles were removed under reduced pressure, and the crude product was obtained as a green syrup. The residue was dissolved in 100 mL dry diethyl ether and filtered through a syringe filter. All volatiles were removed again under reduced pressure, and the desired product was obtained as 3.450 g of a glassy solid. No further purification was attempted as the product resisted crystallization and decomposed during column chromatography.

Yield: quant.

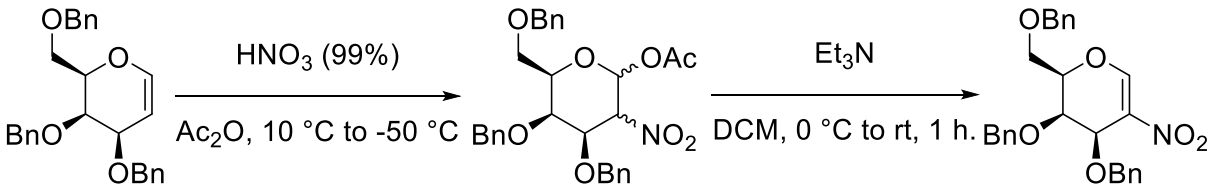
***R*f:** 0.44 (*n*Hex/EtOAc, 1:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 5.98 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.24 – 5.23 (m, 1H), 4.74 – 4.70 (m, 1H), 4.45 (dd, *J* = 12.3, 8.3 Hz, 1H), 4.17 (dd, *J* = 12.3, 4.7 Hz, 1H), 2.10 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H).ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 169.0, 155.4, 128.2, 76.2, 65.5, 61.4, 60.4, 20.8, 20.7, 20.6 ppm.

The NMR data are consistent with those reported in the literature.[25]

2-Nitro-3,4,6-Tri-*O*-benzyl-D-galactal



148 **184** **26**

To 40 mL of distilled acetic anhydride at 10 °C, 4.0 mL of 99% nitric acid (94.8 mmol, 5.7 equiv.) were added dropwise while the temperature was maintained between 10 °C and 15 °C. The solution was cooled to –50 °C, where a white precipitate formed. While maintaining the temperature between –50 °C and –60 °C, a solution of 6.968 g 3,4,6-tri-*O*-benzyl-D-galactal (16.73 mmol, 1.0 equiv.) in 16 mL distilled acetic anhydride was added dropwise. After the addition was complete, the solution was stirred for 30 minutes at –50 °C before being slowly warmed to 0 °C. Upon reaching 0 °C, the solution was poured on a mixture of 100 g ice and

100 mL brine. The mixture was extracted with 3×100 mL of diethyl ether, and the combined organic layers were washed with 3×100 mL of water. The organic phase was dried over $MgSO_4$, and all volatiles were removed under reduced pressure before the residue was co-evaporated with 3x100 mL of toluene. The resulting oil was dissolved in 40 mL of DCM before 20.0 mL of dry triethylamine (143.5 mmol, 8.6 equiv.) were added at 0 °C. The mixture was brought to room temperature during one hour of stirring. It was subsequently diluted with 100 mL of DCM and washed with 3×150 mL 1 N HCl. The organic phase was dried over $MgSO_4$, and all volatiles were removed under reduced pressure. The crude product was subjected to column chromatography (silica, *n*Hex/EtOAc, 2/1, v/v). The product was obtained as 3.826 g (8.29 mmol) of a pale yellow oil.

Yield: 50%

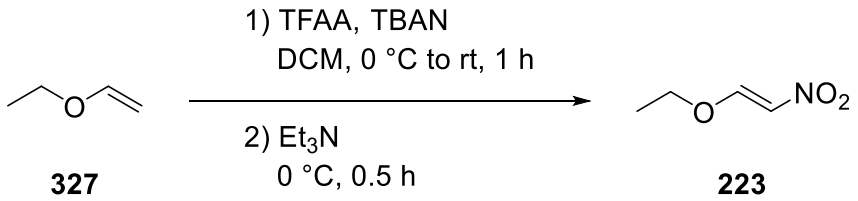
***R*f:** 0.45 (*n*Hex/EtOAc, 2:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H), 7.38 – 7.28 (m, 15H), 4.90 (dd, *J* = 3.8, 1.4 Hz, 1H), 4.88 – 4.78 (m, 2H), 4.73 – 4.61 (m, 3H), 4.58 – 4.45 (m, 2H), 3.96 – 3.91 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 138.2, 137.8, 137.0, 131.7, 128.8, 128.6, 128.5, 128.4, 128.0, 12128.0, 128.0, 127.8, 127.8, 78.2, 75.1, 73.6, 73.2, 72.3, 67.7, 67.7 ppm.

The NMR data are consistent with those reported in the literature.[27]

(1*E*)-1-Ethoxy-2-nitroethene



327 **223**

At 0 °C, 2.30 mL trifluoroacetic anhydride (16.54 mmol, 1.0 equiv.) were added dropwise to a solution of 5,029 g tetrabutylammonium nitrate (16.52 mmol, 1.0 equiv.) and 1.60 mL ethyl vinyl ether (16.64 mmol, 1.0 equiv.) in 165 mL dry DCM under a nitrogen atmosphere. After the addition was complete, the mixture was allowed to reach room temperature. Upon reaching

room temperature, the mixture was stirred for one hour before being cooled to 0 °C. At 0° C, 2.30 mL of dry triethylamine (16.50 mmol, 1.0 equiv.) were added, and the mixture was stirred for 30 min. The reaction mixture was poured into 200 mL of water. The aqueous layer was separated and discarded. Afterward, the organic phase was rewashed with 200 mL of water. After drying the organic phase over $MgSO_4$ and removal of all volatiles under reduced pressure, the crude product was purified via column chromatography (silica, *n*Hex/EtOAc, 2/1, v/v). The product was obtained as 0.934 g (7.976 mmol) of a golden oil.

Yield: 48%

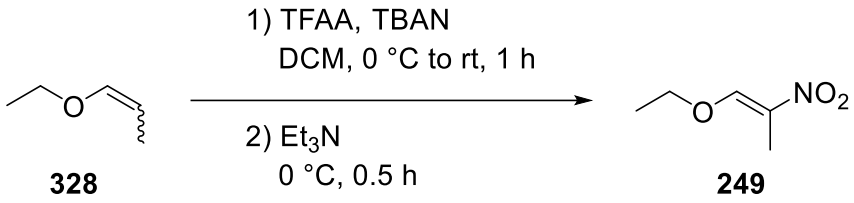
***R*f:** 0.60 (*n*Hex/EtOAc, 2:1, v/v, $KMnO_4$-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 11.0 Hz, 1H), 6.93 (d, *J* = 11.0 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2, 123.2, 69.6, 14.6 ppm.

The NMR data are consistent with those reported in the literature.[92]

(1*E*)-1-Ethoxy-2-nitropropane



328 **249**

At 0 °C, 3.80 mL trifluoroacetic anhydride (27.32 mmol, 1.1 equiv.) were added dropwise to a solution of 8.236 g tetrabutylammonium nitrate (27.05 mmol, 1.1 equiv.) and 2.80 mL ethyl 1-propen-1-yl ether (25.21 mmol, 1.0 equiv.) in 180 mL dry DCM under a nitrogen atmosphere. After the addition was complete, the mixture was allowed to reach room temperature. Upon reaching room temperature, the mixture was stirred for one hour before being cooled to 0 °C. At 0° C, 3.80 mL of dry triethylamine (27.27 mmol, 1.1 equiv.) were added, and the mixture was stirred for 30 min. The reaction mixture was poured into 200 mL of water. The aqueous layer was separated and discarded. The organic phase was washed again with 200 mL of water.

After drying the organic phase over $MgSO_4$ and removal of all volatiles under reduced pressure, the crude product was purified via flash column chromatography (silica, *n*Hex/EtOAc, 9/1 to 8/2, v/v). The product was obtained as 1.983 g (15.12 mmol) of a golden oil.

Yield: 60%

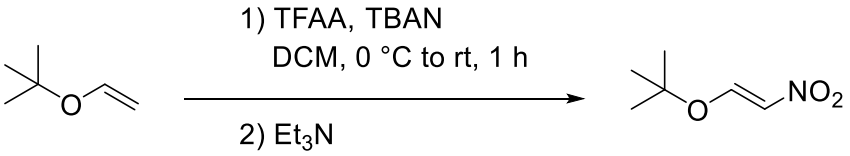
***R*f:** 0.57 (*n*Hex/EtOAc, 2:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (q, *J* = 1.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.07 (d, *J* = 1.0 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.0, 132.2, 72.0, 15.5, 10.3 ppm.

The NMR data are consistent with those reported in the literature.[131]

(1*E*)-1-*tert*-Butoxy-2-nitroethene



329 **256**

At 0 °C, 2.30 mL trifluoroacetic anhydride (16.53 mmol, 1.1 equiv.) were added dropwise to a solution of 5.042 g tetrabutylammonium nitrate (16.55 mmol, 1.1 equiv.) and 2.00 mL ethyl 1-propen-1-yl ether (15.22 mmol, 1.0 equiv.) in 150 mL dry DCM under a nitrogen atmosphere. After the addition was complete, the mixture was allowed to reach room temperature. Upon reaching room temperature, the mixture was stirred for one hour before being cooled to 0 °C. At 0° C, 2.30 mL of dry triethylamine (16.50 mmol, 1.1 equiv.) were added, and the mixture was stirred for 30 min. The reaction mixture was poured into 200 mL of water. The aqueous layer was separated and discarded. Afterward, the organic phase was rewashed with 200 mL of water. After drying the organic phase over $MgSO_4$ and removal of all volatiles under reduced pressure, the crude product was purified via flash column chromatography (silica, *n*Hex/EtOAc, 9/1 to 8/2, v/v). The product was obtained as 1.564 g (10.77 mmol) of a golden oil.

Yield: 71%

***R*f:** 0.59 (*n*Hex/EtOAc, 2:1, v/v, CAM-stain)

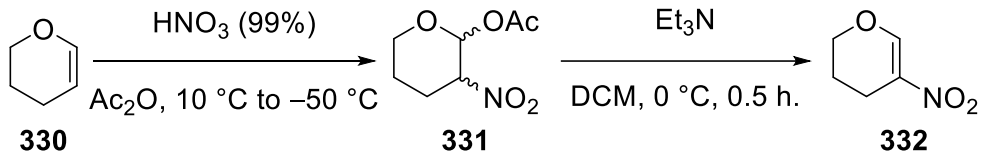
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 10.4 Hz, 1H, OC*H*$_2$), 6.97 (d, *J* = 10.4 Hz, 1H, O_2NCH_2), 1.41 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.7 (OCH_2), 124.6 (O_2NCH_2), 83.4 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$) ppm.

IR (ATR): $\tilde{\nu}$ = 29982, 1635, 1357, 1273, 1146, 855 cm^{-1}.

HRMS (ESI): *m*/*z* = found: 168.0630; calc.: 168.0631 $[M + Na]^+$.

3,4-Dihydro-5-nitro-2*H*-pyran



330 **331** **332**

At 10 °C, 10.0 mL of 99% nitric acid (237 mmol, 4.3 equiv.) were added to 60 mL distilled acetic anhydride under a nitrogen atmosphere. During the addition, a golden coloration of the solution was observed, and the internal temperature was maintained between 10 °C and 15 °C. After the addition was complete, the solution was cooled to –50 °C, where a white precipitate formed and the discoloration of the solution could be observed. Next, 5 mL of dihydropyran (55.10 mmol, 1.0 equiv.) were added carefully over 30 min. whilst the internal temperature was maintained at –50 °C. Afterward, the solution was stirred for 30 min at –50 °C before being slowly warmed to 0 °C. Upon reaching 0 °C, the solution was poured on a mixture consisting of 200 g ice and 100 mL brine. The resulting mixture was extracted three times with 100 mL ether and dried over $MgSO_4$. All volatiles were removed under reduced pressure, and the remaining oil was co-evaporated three times with 100 mL of toluene. Next, 45 mL of dry DCM were added, and the solution was cooled down to 0 °C. After the addition of 20,0 mL of dry triethylamine (143.5 mmol, 2.6 equiv.), the solution was stirred for 30 min at 0 °C before being diluted with 50 mL DCM and washed three times with 100 mL of 1 N HCl. The organic phase was dried over $MgSO_4$, and all volatiles were removed under reduced pressure to yield 5,923 g

of a brown liquid. The crude product was purified via column chromatography (silica, *n*Hex/EtOAc, 2/1, v/v) to yield 4,802 g (31.16 mmol) of a pale yellow oil, which solidified upon storage in the fridge.

Yield: 57%

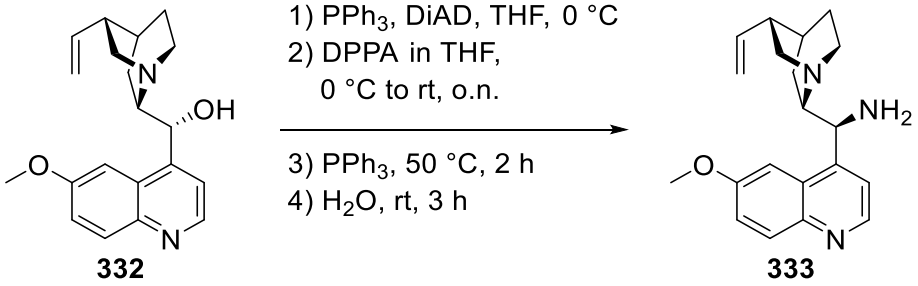
***R*f:** 0.50 (*n*Hex/EtOAc, 2:1, v/v, $KMnO_4$-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1H), 4.12 (d, J = 5.3 Hz, 2H), 2.65 (t, J = 6.4 Hz, 2H), 2.02 – 1.96 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 131.4, 67.5, 20.4, 20.3 ppm.

The NMR data are consistent with those reported in the literature.[132]

9-amino(9-deoxy)epiquinine



332 **333**

A solution of 3.265 g anhydrous quinine (10.06 mmol, 1.0 equiv.) and 3.319 g triphenylphosphine (12.65 mmol, 1.3 equiv.) in 70 mL dry THF was cooled to 0 °C before 2.4 mL diisopropyl azodicarboxylate (12.23 mmol, 1.2 equiv.) were added dropwise. After the addition was complete, a solution of 2.6 mL diphenylphosphoryl azide (12.05 mmol, 1.2 equiv.) in 17 mL dry THF were added dropwise. The mixture was stirred overnight upon warming to room temperature. After being heated to 50 °C for 2 hours, 3.540 g triphenylphosphine (13.50 mmol, 1.3 equiv.) were added, and the mixture was stirred for two additional hours at 50 °C. Next, 1.0 mL of water was added, and the mixture was stirred for 3 hours at room temperature. The reaction mixture was poured on 200 mL of a 1:1 mix of DCM and 1 N HCl before being extracted with 4×50 mL of DCM. The organic phases were discarded, and the aqueous layer was basified with concentrated aqueous ammonia. The resulting solution

was extracted with 4×50 mL DCM. The combined organic layers were dried over Na_2SO_4, and all volatiles were subsequently removed under reduced pressure. The resulting crude product was purified via column chromatography (silica, EtOAc/MeOH/Et_3N, 50/50/1, v/v/v). The product was obtained as 1,194 g (3.69 mmol) of a pale yellow oil.

Yield: 37%

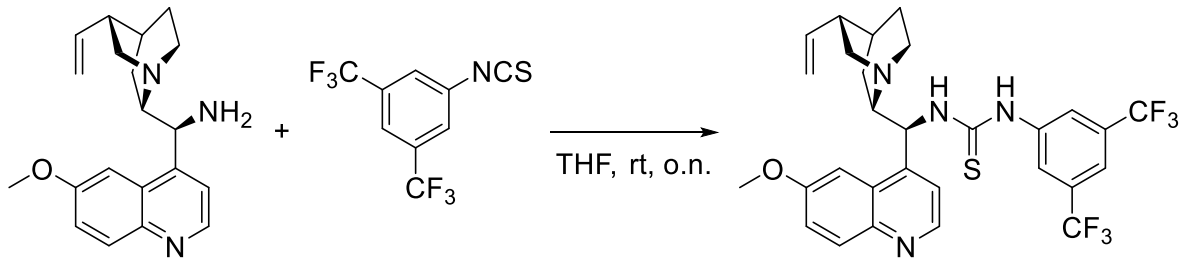
***R*f:** 0.15 (EtOAc/MeOH/Et_3N, 50:50:1, v/v/v, Ninhydrin-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.40 (d, *J* = 3.7 Hz, 2H), 7.33 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.74 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 4.97 – 4.90 (m, 2H), 4.54 (d, *J* = 10.1 Hz, 1H), 3.91 (s, 3H), 3.25 – 3.12 (m, 2H), 3.07 – 3.00 (m, 1H), 2.78 – 2.71 (m, 2H), 2.28 – 2.19 (m, 3H), 1.59 – 1.47 (m, 3H), 1.41 – 1.34 (m, 1H), 0.72 (ddt, *J* = 13.7, 7.5, 1.8 Hz, 1H) ppm.

^{13}C NMR (101 MHz, CD_3OD): δ = 160.0, 148.3, 145.5, 143.2, 142.5, 131.8, 129.4, 123.8, 122.6, 115.1, 103.1, 60.3, 56.6, 56.4, 49.9, 41.7, 40.6, 28.7, 28.4, 26.8 ppm.

The NMR data are consistent with those reported in the literature.[133,134]

9-amino(9-deoxy)epiquinine Thiourea



333 **334** **130**

To a solution of 1.194 g 9-amino(9-deoxy)epiquinine (3.69 mmol, 1.0 equiv.) in 10 mL dry THF, a mixture of 0.68 mL 3,5-bis(trifluoromethyl)phenyl in 0.7 mL dry THF was added dropwise. The mixture was stirred overnight at room temperature before all volatiles were removed under reduced pressure. The resulting crude product was first subjected to column chromatography (silica, DCM/MeOH, 90/10) before being recrystallized from boiling ethyl

acetate in heptane. The product was obtained as 1.032 g (1.74 mmol) of a white amorphous solid.

Yield: 48%

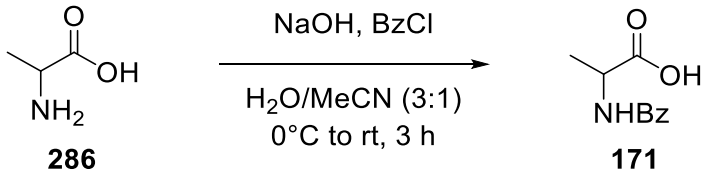
***R*f:** 0.18 (DCM/MeOH, 90:10, v/v, CAM-stain)

^{1}H NMR (400 MHz, CD_3OD): δ = 8.68 (d, *J* = 4.7 Hz, 1H), 8.10 – 8.08 (m, 3H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.43 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.39 (d, *J* = 11.1 Hz, 1H), 5.84 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1H), 5.06 – 4.97 (m, 2H), 4.01 (s, 3H), 3.69 – 3.62 (m, 1H), 3.49 (app. q, *J* = 9.8 Hz, 1H), 3.34 – 3.29 (m, 1H), 2.90 – 2.82 (m, 2H), 2.41 –2.36 (m, 1H), 1.74 – 1.63 (m, 3H), 1.53 – 1.45 (m, 1H), 0.92 – 0.83 (m, 1H) ppm.

^{13}C NMR (101 MHz, CD_3OD): δ = 181.6, 158.8, 147.3, 146.3, 144.23, 142.03, 141.3, 131.7 (q, *J* = 33.2 Hz), 130.3, 129.2, 123.7 (q, *J* = 271.9 Hz), 122.9, 122.7 (q, *J* = 3.9 Hz), 120.3, 117.1, 117.0 (sept., *J* = 3.9 Hz), 114.3, 103.2, 60.6, 55.7, 55.6, 55.0, 48.7, 48.5, 42.1, 39.5, 27.7, 27.4, 25.9 ppm.

The NMR data are consistent with those reported in the literature.[134]

N-Benzoyl-(D,L)-alanine



286 **171**

To a solution of 7.00 g (D,L)-alanine (78.56 mmol, 1.0 equiv.) and 12.50 g NaOH (312.5 mmol, 4.0 equiv.) in 185 mL of a 3:1 mixture of water and acetonitrile at 0 °C, 8.61 mL of benzoyl chloride (86.1 mmol, 1.1 equiv.) were added dropwise. The reaction mixture was stirred at 0 °C for 2 h and 1 h at room temperature. Subsequently, all volatiles were removed under reduced pressure, and 120 mL of conc. HCl was added to precipitate the product. The resulting solid was filtered off and washed with a minimal amount of cold diethyl ether. The remaining solid

was dried in high vacuum overnight. The product was obtained as 8.513 g (44.06 mmol) of a white fluffy solid.

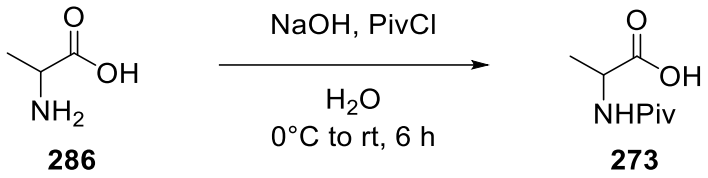
Yield: 56%

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.67 (d, J = 7.3 Hz, 1H), 7.90 – 7.87 (m, 2H), 7.56 – 7.52 (m, 1H), 7.49 – 7.45 (m, 2H), 4.42 (p, J = 7.3 Hz, 1H), 1.39 (d, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ =174.2, 166.2, 134.0, 131.4, 128.3, 127.5, 48.2, 17.0 ppm.

The NMR data are consistent with those reported in the literature.[135]

N-pivaloyl-(D,L)-alanine



286 **273**

To a solution of 5.834 g (D,L)-alanine and 5.260 g sodium hydroxide (131.5 mmol, 2.0 equiv.) in 150 mL of a 1:1 mixture of water and methanol at 0 °C, 9.0 mL pivaloyl chloride (73,07 mmol, 1.1 equiv.) was added dropwise. The mixture was allowed to reach room temperature before it was stirred for 6 hours. The Reaction mixture was acidified to pH 2-3 using concentrated HCl before being extracted with 3×100 mL of ethyl acetate. The combined organic layers were washed with 5×100 mL of water and 3×100 mL brine. The organic layer was dried with Na_2SO_4, and all volatiles were removed under reduced pressure. The residue was dried in high vacuum overnight to give the desired product as 4.236 g (24.49 mmol) of a white solid.

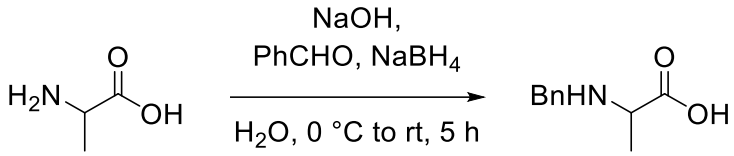
Yield: 37%

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54 (d, J = 7.3 Hz, 1H), 4.19 (p, J = 7.3 Hz, 1H), 1.27 (d, J = 7.3 Hz, 3H), 1.10 (s, 9H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 177.3, 174.4, 47.6, 37.8, 27.3, 16.9 ppm.

The NMR data are consistent with those reported in the literature.[135]

N-Benzyl-(D,L)-alanine



286 **285**

A solution of 8.900 g (D,L)-alanine (100.00 mmol, 1.0 equiv.), 4.102 g sodium hydroxide (102.55 mmol, 1.0 equiv.), and 10.20 mL benzaldehyde (99.96 mmol, 1.0 equiv.) in 50 mL of water were stirred for 30 min. at room temperature. Afterward, the solution was cooled to 0 °C, and 1.203 g sodium borohydride (31.80 mmol, 0.3 equiv.) was added portionwise. After the addition was complete, the mixture was stirred for 30 min at 0 °C before being warmed to room temperature for an additional hour of stirring. Next, another portion of 10.20 mL of benzaldehyde (99.96 mmol, 1.0 equiv.) was added, and the mixture was stirred for 30 min. at room temperature before being cooled to 0 °C. Upon reaching 0 °C, 1.093 g of sodium borohydride (28.89 mmol, 0.3 equiv.) were added, and the mixture was stirred for 30 min at 0 °C before being warmed to room temperature for two additional hours of stirring. The resulting mixture was washed twice with DCM and acidified to pH 7 using concentrated HCl. As no precipitate formed, the solvent was gradually evaporated under reduced pressure until the formation of a white precipitate could be observed. The precipitate was filtered off and dried in high vacuum. The product was obtained as 8.048 g (44.91 mmol) of a fine white powder.

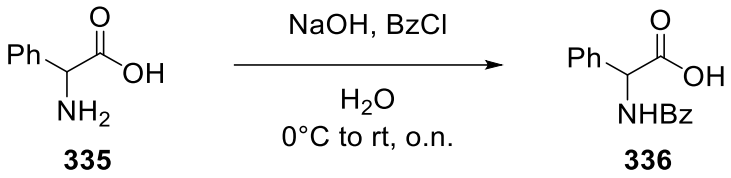
Yield: 45%

^{1}H NMR (400 MHz, D_2O): δ = 7.52 – 7.47 (m, 4H), 4.28 – 4.15 (m, 2H), 3.69 (q, *J* = 7.2 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (101 MHz, D_2O): δ = 175.0, 131.2, 129.8, 129.5, 129.2, 57.4, 49.8, 15.4 ppm.

The NMR data are consistent with those reported in the literature.[136]

N-Benzoyl-(D,L)-phenyl glycine



335 **336**

To a solution of 3.02 g (D,L)-phenylglycine (19.98 mmol, 1.0 equiv.) in 50 mL of a 2 M sodium hydroxide solution was added 2.55 mL benzoyl chloride (22.13 mmol, 1.1 equiv.) dropwise at 0 °C. The reaction mixture was stirred overnight upon warming to ambient temperature. Next, the solution was acidified to pH 5 using concentrated HCl before being extracted with 4×50 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$, and all volatiles were removed under reduced pressure. The crude product was recrystallized from a mixture of boiling hexane/ethyl acetate (1:1, v/v) to obtain the product as 3.543 g of a white powder.

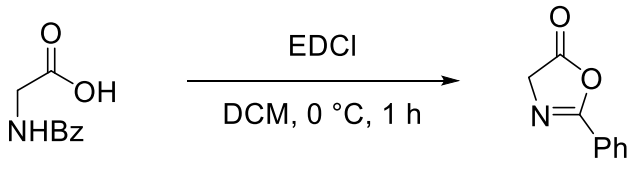
Yield: 70%

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 12.92 (br s, 1H), 9.04 (d, *J* = 7.5 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.57 – 7.44 (m, 5H), 7.41 – 7.31 (m, 3H), 5.61 (d, *J* = 7.5 Hz, 1H)ppm.

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ = 171.9, 166.3, 137.1, 133.7, 131.5, 128.4, 128.2, 128.2, 127.9, 127.7, 56.8 ppm.

The NMR data are consistent with those reported in the literature.[137]

2-Phenyl-5(4*H*)-oxazolone



169 **65**

At 0 °C, 2.466 g hippuric acid (13.77 mmol, 1.0 equiv.) was suspended in 40 mL DCM. Over 5 min. 2.601 g EDC·HCl (16.78 mmol, 1.2 equiv.) were added, and the reaction mixture was stirred for 1 h at 0 °C. Afterward, the mixture was diluted with 40 mL DCM and washed with 6×100 mL water, and the organic phase was dried over $MgSO_4$. All volatiles were removed under reduced pressure, and the product was obtained as 1.983 g (12.30 mmol) of a beige solid.

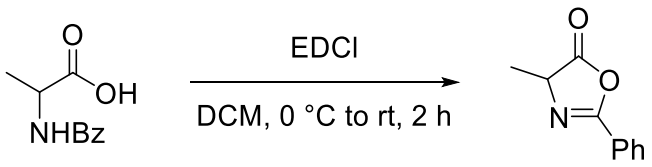
Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 4.42 (s, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.1, 163.6, 133.0, 129.0, 128.0, 126.0, 55.2 ppm.

The NMR data are consistent with those reported in the literature.[137]

2-Phenyl-4-methyl-5(4*H*)-oxazolone



171 **170**

At 0 °C, 0.340 g *N*-benzoyl-(D,L)-alanine (1.76 mmol, 1.0 equiv.) was suspended in 30 mL DCM. For 5 min. 0.336 g EDC·HCl (2.17 mmol, 1.2 equiv.) were added, and the reaction mixture was stirred for 1 h at 0 °C before the ice bath was removed for another hour of stirring at room temperature. Afterward, the mixture was diluted with 30 mL DCM and washed with 20 mL water, 2×20 mL saturated $NaHCO_3$ solution, and 20 mL water before the organic phase was dried over Na_2SO_4. All volatiles were removed under reduced pressure, and the product was obtained as 0.300 g (1.69 mmol) of a colorless oil that solidified upon standing.

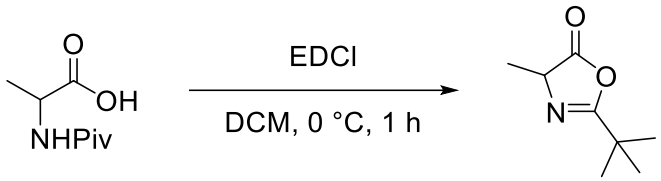
Yield: 96%

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.98 (m, 2H), 7.60 – 7.56 (m, 1H), 7.51 – 7.47 (m, 2H), 4.45 (q, *J* = 7.6 Hz, 1H), 1.59 (d, *J* = 7.6 Hz, 3H). ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.2, 161.7, 132.9, 129.0, 128.0, 126.0, 61.2, 17.1 ppm.

The NMR data are consistent with those reported in the literature.[137]

2-*tert*-Butyl-4-methyl-5(4*H*)-oxazolone



173 **172**

To a suspension of 0.620 g *N*-pivaloyl-(D,L)-alanine (3.60 mmol, 1.0 equiv.) in 25 mL of DCM at 0 °C, 0.861 g EDCl (4.48 mmol, 1.2 equiv.) was added in one portion. The solution was stirred for one hour at 0 °C before being diluted with 25 mL DCM and washed with 50 mL water, 50 mL sat. $NaHCO_3$, and 50 mL brine. The organic phase was dried over $MgSO_4$, and all volatiles were removed under reduced pressure. The product was obtained as 0.300 g (1.93 mmol) of a colorless oil.

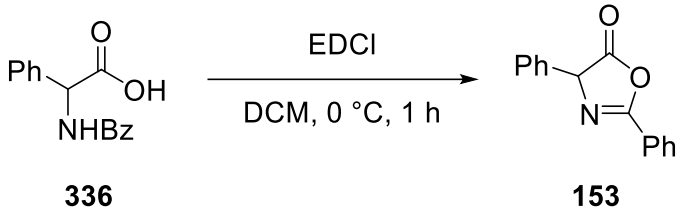
Yield: 48%

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (q, *J* = 7.6 Hz, 1H), 1.47 (d, *J* = 7.6 Hz, 3H), 1.29 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.9, 171.8, 60.7, 34.3, 26.9, 17.0 ppm.

The NMR data are consistent with those reported in the literature.[135]

2,4-Phenyl-5(4*H*)-oxazolone



336 **153**

To a suspension of 0.854 g *N*-benzoyl-(D,L)-phenylglycine (3.35 mmol, 1.0 equiv.) in 15 mL of DCM at 0 °C, 0.771 g EDCl (4.02 mmol, 1.2 equiv.) was added in one portion. The solution was stirred for one hour at 0 °C before being diluted with 20 mL DCM and washed with 50 mL water, 50 mL sat. $NaHCO_3$, and 50 mL brine. The organic phase was dried over $MgSO_4$, and all volatiles were removed under reduced pressure. The product was obtained as 0.591 g (2.49 mmol) of a yellow solid.

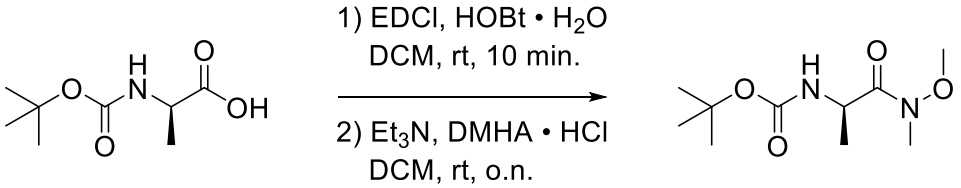
Yield: 48%

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 – 8.09 (m, 2H), 7.55 – 7.51 (m, 2H), 7.47 – 7.35 (m, 5H), 5.53 (s, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.4, 162.8, 133.6, 133.2, 129.2, 129.0, 128.9, 128.3, 127.0, 68.3 ppm.

The NMR data are consistent with those reported in the literature.[137]

tert-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate



191 **192**

A mixture of 3.054 g *N*-boc-L-alanine (16.14 mmol, 1.0 equiv.), 3.347 g EDCl (19.02 mmol, 1.2 equiv.), and 3.031 g HOBt hydrate (22.43 mmol, 1.4 equiv.) in 20 mL DCM was stirred for 10 minutes at room temperature. Subsequently, 2.223 g *N*,*O*-dimethylhydroxylamine

hydrochloride (22.79 mmol, 1.4 equiv.) were added together with 6.5 mL triethylamine (46.65 mmol, 2.8 equiv.). The mixture was stirred overnight at room temperature. Afterward, it was diluted with 100 mL ethyl acetate and washed with 3×100 mL 1 N HCl, 2×100 mL 10w% $NaHCO_3$ solution, and 2×100 mL brine. The organic phase was dried over $MgSO_4$, and all volatiles were removed under reduced pressure to yield the product as 2.954 g (12.72 mmol) of a white crystalline solid.

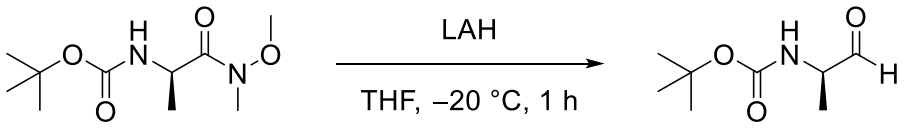
Yield: 79%

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (d, J = 8.7 Hz, 1H), 4.70 – 4.60 (m, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 1.43 (s, 9H), 1.30 (d, J = 6.9 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 79.7, 61.8, 46.7, 32.3, 28.5, 18.8 ppm.

The NMR data are consistent with those reported in the literature.[95]

tert-Butyl (*S*)-(1-oxopropan-2-yl)carbamate



192 **193**

To a solution of 2.954 g *tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (12.72 mmol, 1.0 equiv.) in 100 mL dry THF 0.831 g $LiAlH_4$ (21.89 mmol, 1.7 equiv.) was added portionwise at –20 °C. The resulting suspension was stirred for one hour at –20 °C before 2-propanol was added until no further gas development could be detected. Subsequently, 10 mL of water and 10 mL of 1 N HCl were added to ensure the complete consumption of LAH. The mixture was filtered over a short pad of celite and washed with ethyl acetate, and the aqueous phase was extracted with 3×25 mL ethyl acetate. The combined organic layers were washed with 3×100 mL of ethyl acetate and dried over $MgSO_4$. All volatiles were evaporated under reduced pressure and the residue was subjected to column chromatography (silica, *n*Hex/EtOAc, 2/1, v/v). The product was obtained as 1.403 g (8.10 mmol) of a white solid.

Yield: 64%

***R*f:** 0.36 (*n*Hex/EtOAc, 2:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1H), 5.10 (s, 1H), 4.28 – 4.18 (m, 1H), 1.45 (s, 9H), 1.33 (d, *J* = 7.4 Hz, 3H) ppm.

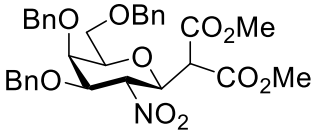
^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.8, 155.4, 80.2, 55.7, 28.4, 15.0 ppm.

The NMR data are consistent with those reported in the literature.[95]

General Procedure for the Addition Reactions

A fresh glass vial was charged with the nucleophile and promoter. Fresh stock solutions were used. Liquids were transferred using Eppendorf pipets and single-use epT.I.P.S. Next, a stir bar (cleaned for 2 d in conc. H_2SO_4, washed twice in $H_2O_{demin.}$ and dried overnight at 120 °C prior to its use) and the dry solvent was added. Lastly, the acceptor was added, and the vial was sealed using parafilm before the vial was placed in the dark for the indicated reaction time. The workup consisted of washing the reaction mixture twice, using a 1 N HCl solution, and drying over $MgSO_4$.

Dimethyl-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-*β*-D-galactopyranosyl)-malonate



28

Isolated by preparative TLC, eluent *n*Hex/EtOAc (1:1; v/v), colorless oil.

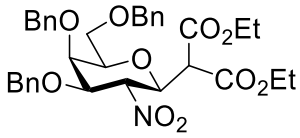
***R*f:** 0.56 (*n*Hex/EtOAc, 2:1, v/v, CAM-stain)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.23 (m, 15H), 5.22 (t, *J* = 10.1 Hz, 1H), 4.75 (m, 2H), 4.53 – 4.39 (m, 5H), 4.17 (dd, *J* = 10.3, 2.7 Hz, 1H), 4.05 (d, *J* = 2.1 Hz, 1H), 3.74 – 3.69 (m, 4H), 3.65 – 3.63 (m, 4H), 3.57 – 3.54 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 165.9, 138.2, 137.8, 136.8, 128.7, 128.6, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 85.8, 80.3, 77.4, 74.9, 74.8, 73.7, 72.6, 72.1, 68.0, 53.9, 53.0, 52.8. ppm.

The analytical data are consistent with the ones reported in the literature.[33]

Diethyl-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)-malonate



203

Isolated by column chromatography (silica), eluent *n*Hex/EtOAc (2:1; v/v), colorless oil.

***R*$_f$:** 0.39 (*n*Hex/EtOAc, 2:1, v/v, CAM-stain)

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.36 – 7.24 (m, 15H), 5.24 (t, *J* = 10.1 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.52 (dd, *J* = 11.2, 3.5 Hz, 2H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (dd, *J* = 10.0, 4.3 Hz, 1H), 4.19 – 4.11 (m, 5H), 4.05 (dd, *J* = 2.9, 1.1 Hz, 1H), 3.74 – 3.72 (m, 1H), 3.60 – 3.55 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.2, 165.4, 138.2, 137.9, 136.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 85.7, 80.4, 77.6, 75.0, 75.0, 73.7, 72.6, 72.2, 68.0, 62.1, 62.1, 54.0, 14.0, 14.0. ppm.

The analytical data are consistent with the ones reported in the literature.[41]

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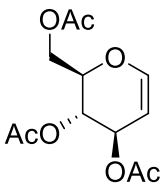
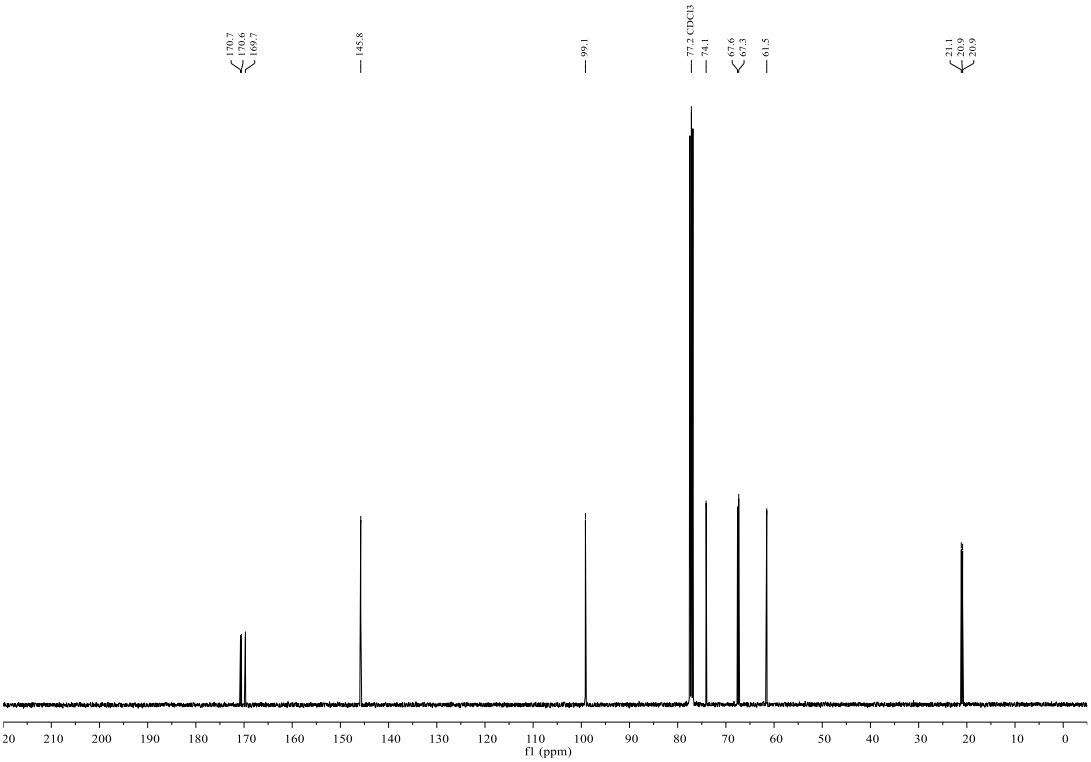
8 – Spectra

8.1 – NMR-Spectra

3,4,6-Tri-*O*-acetyl-D-glucal





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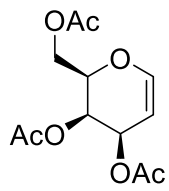

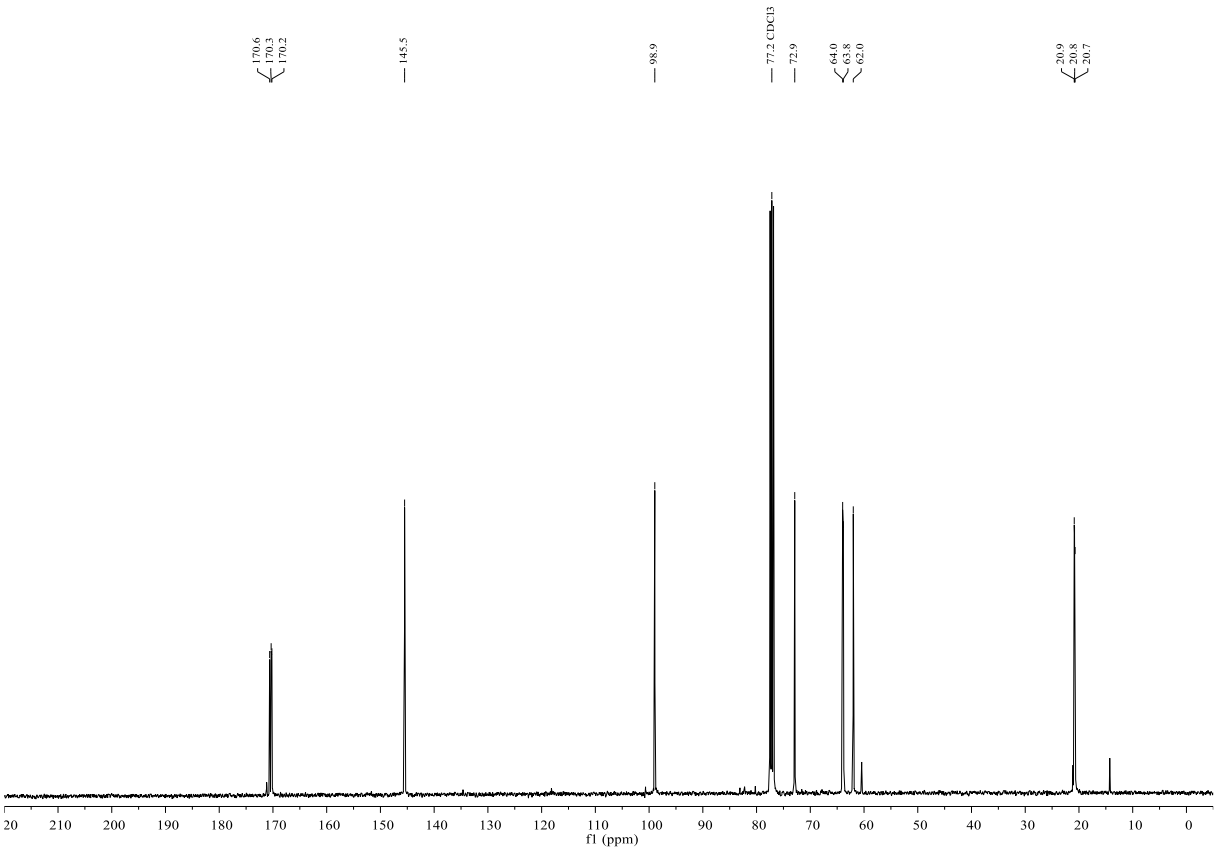

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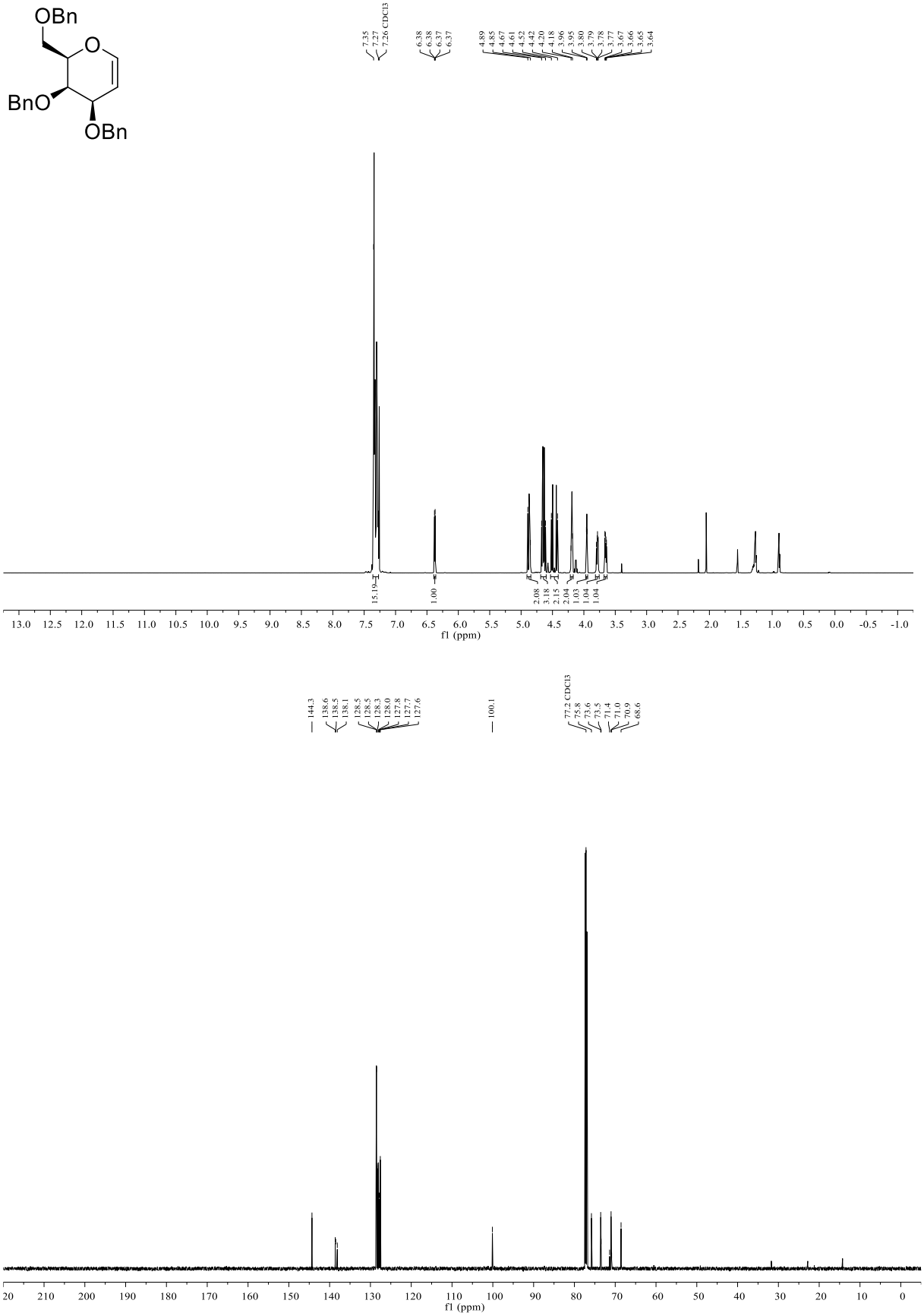

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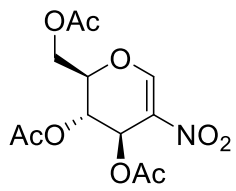

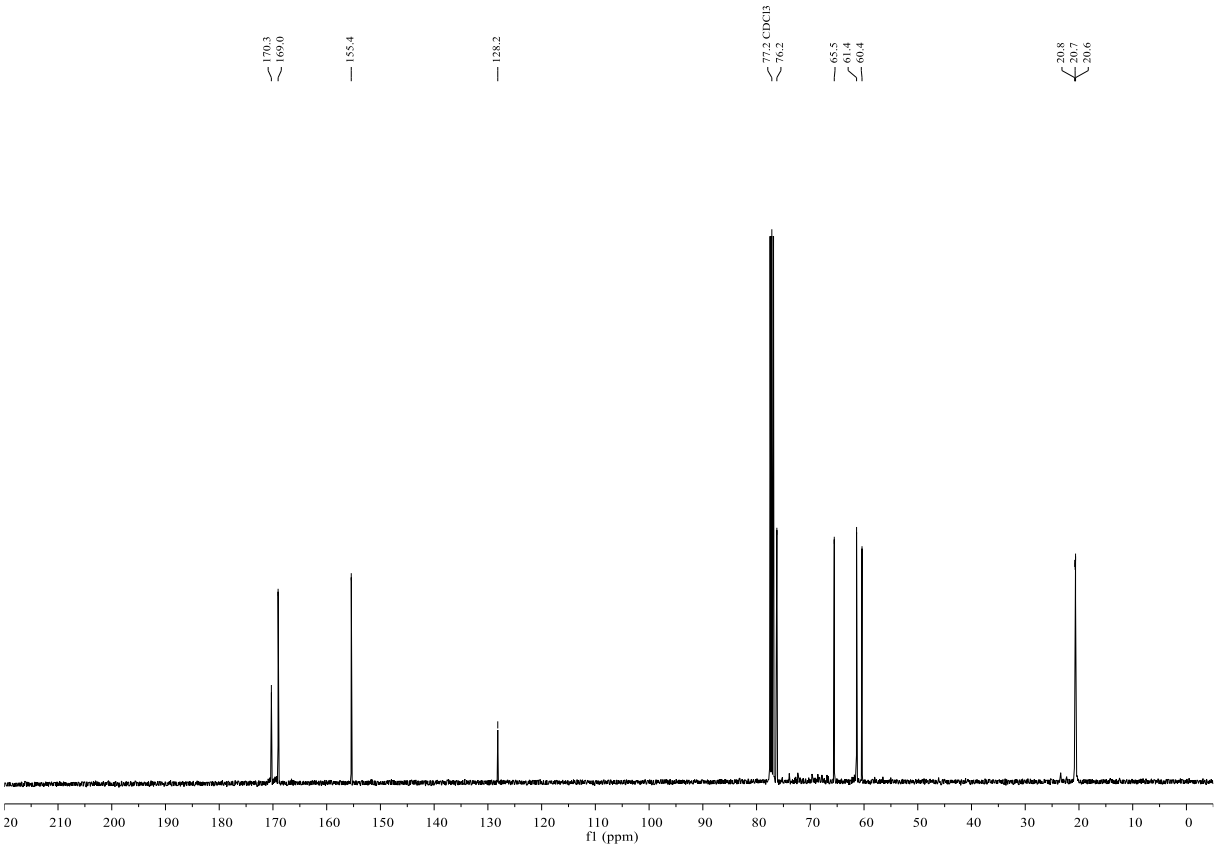

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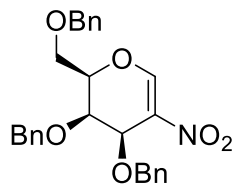

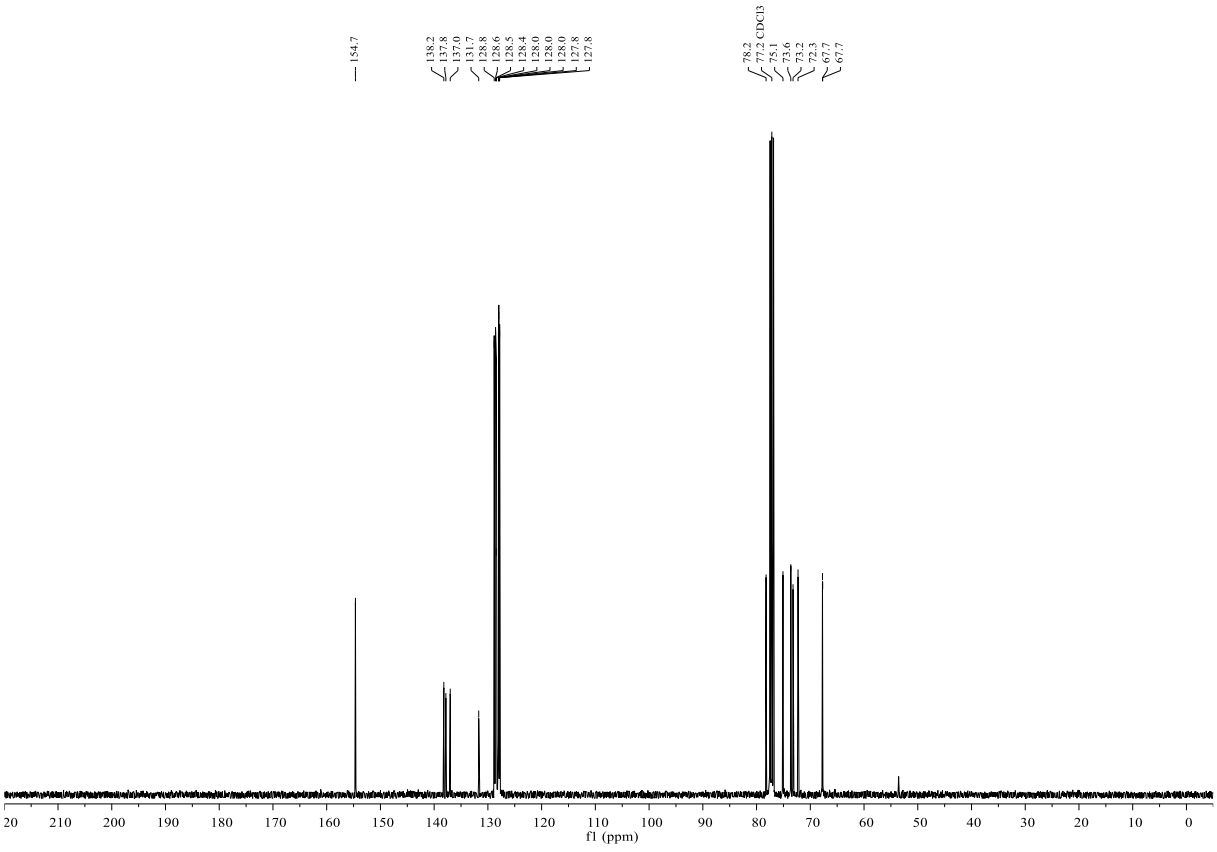

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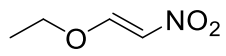

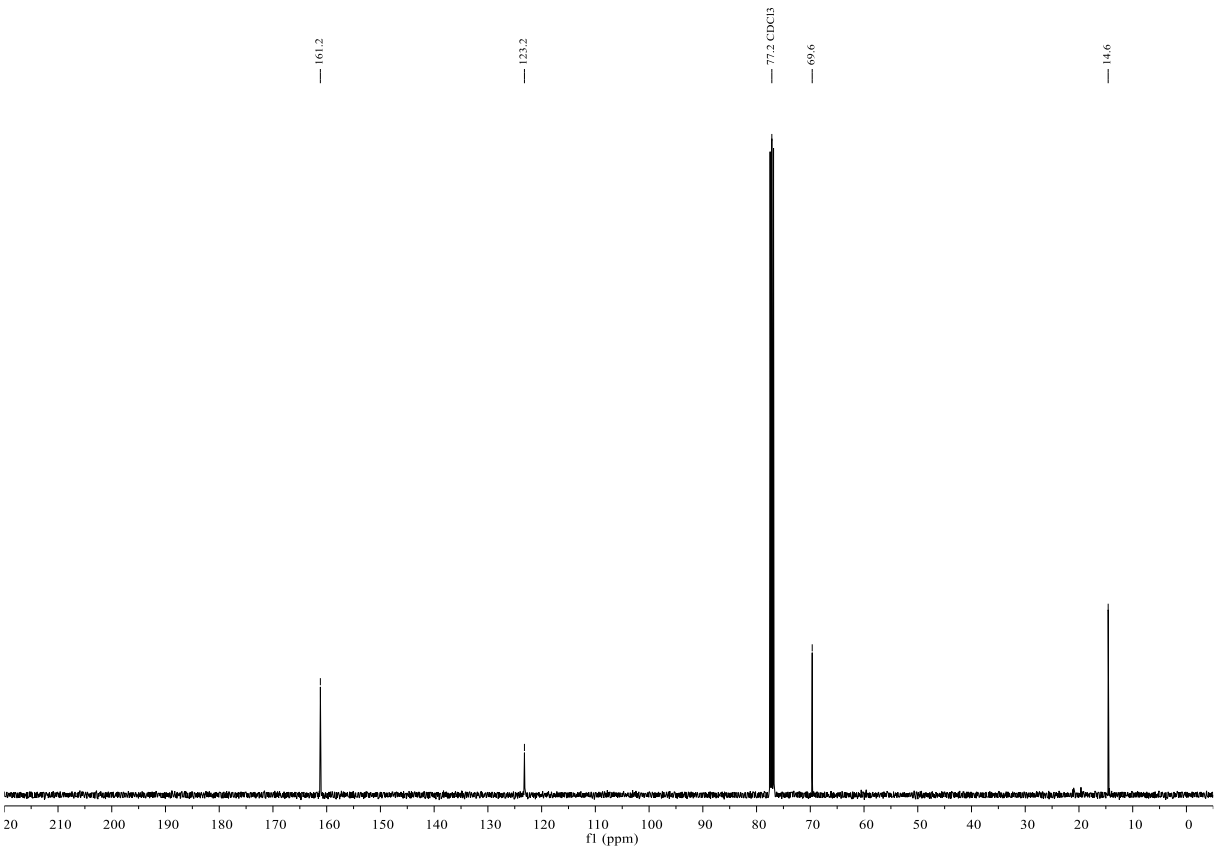

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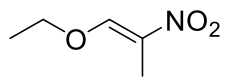

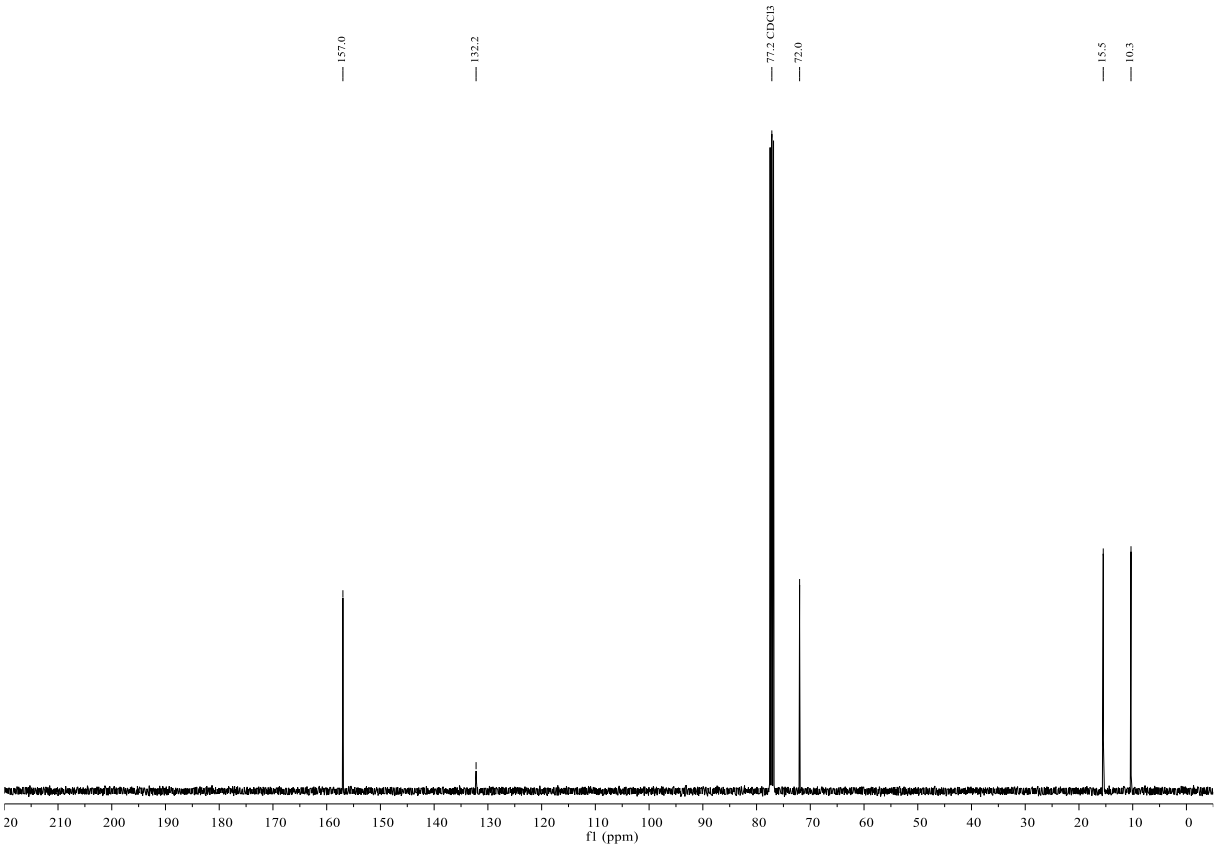

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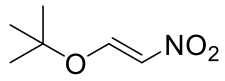

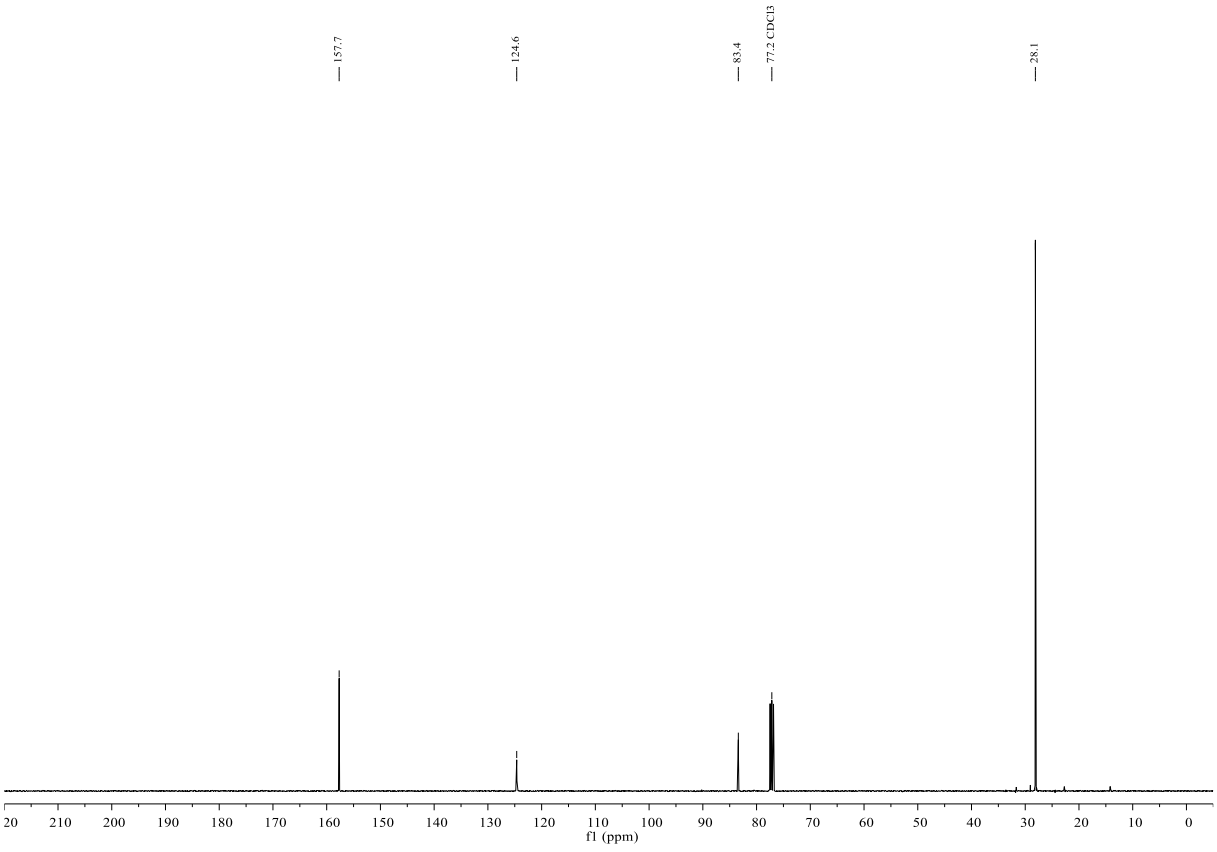

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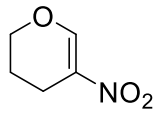
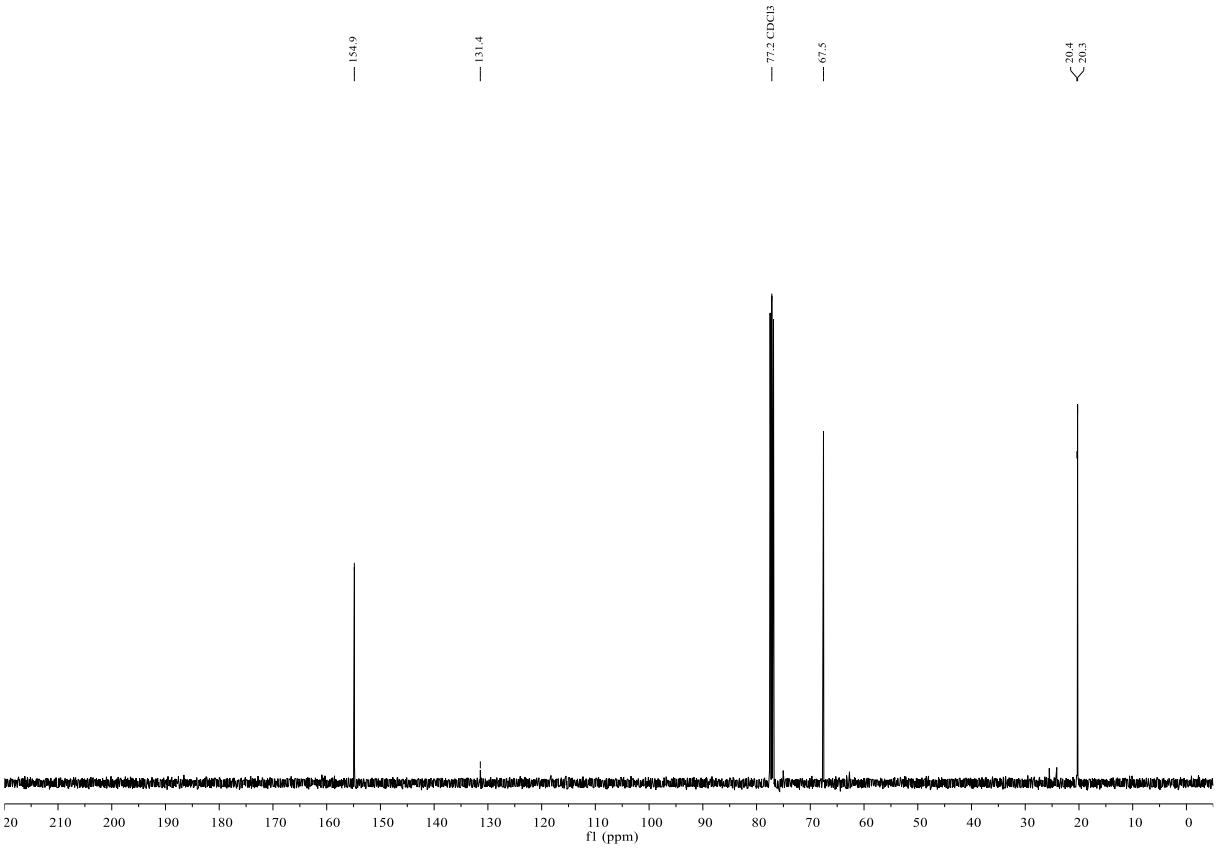
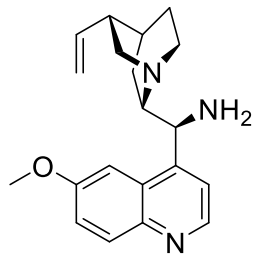
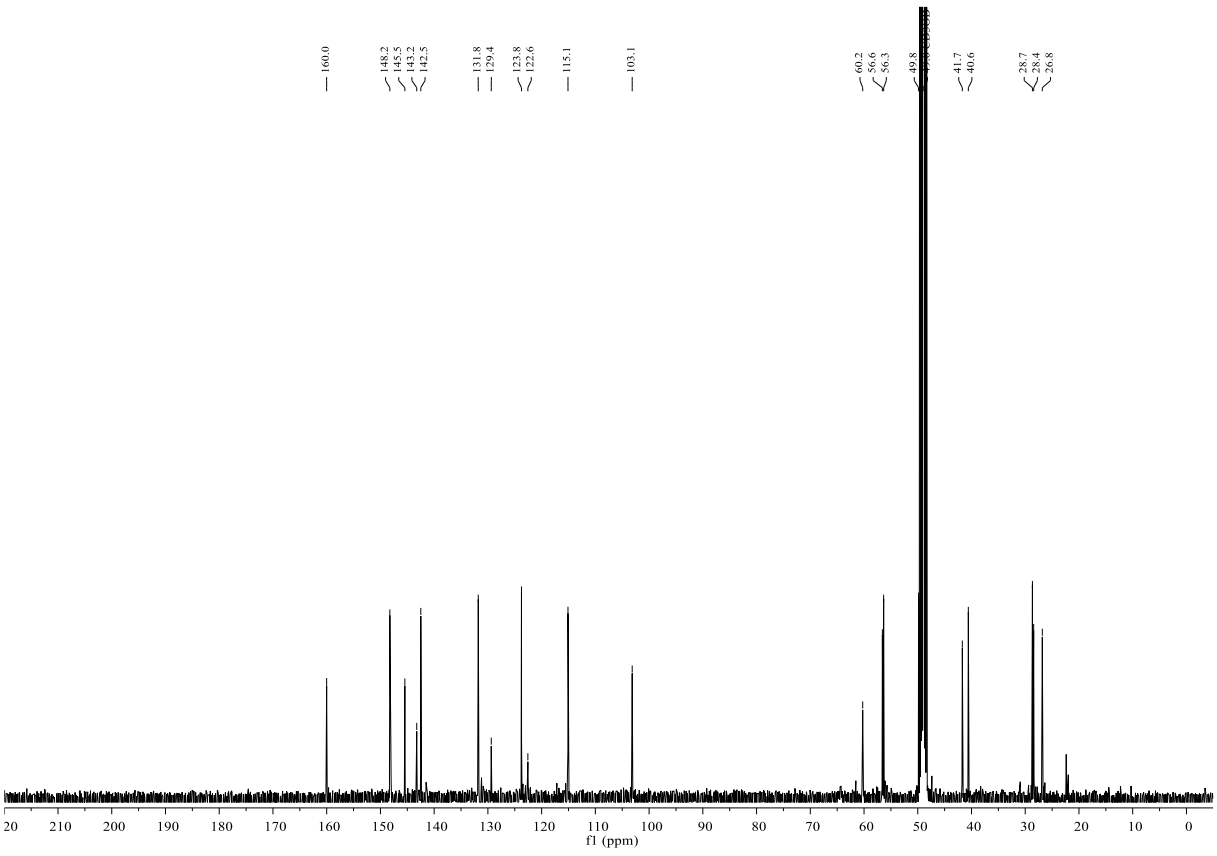


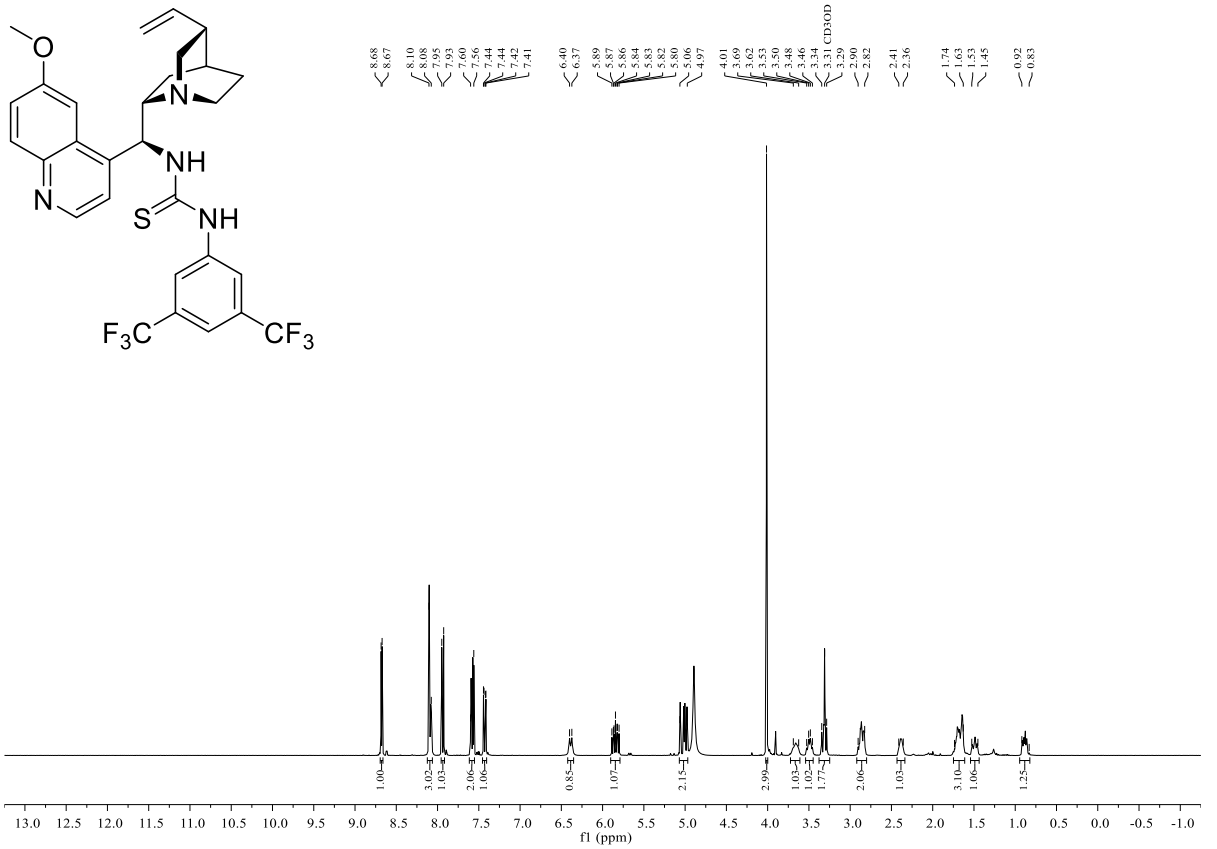


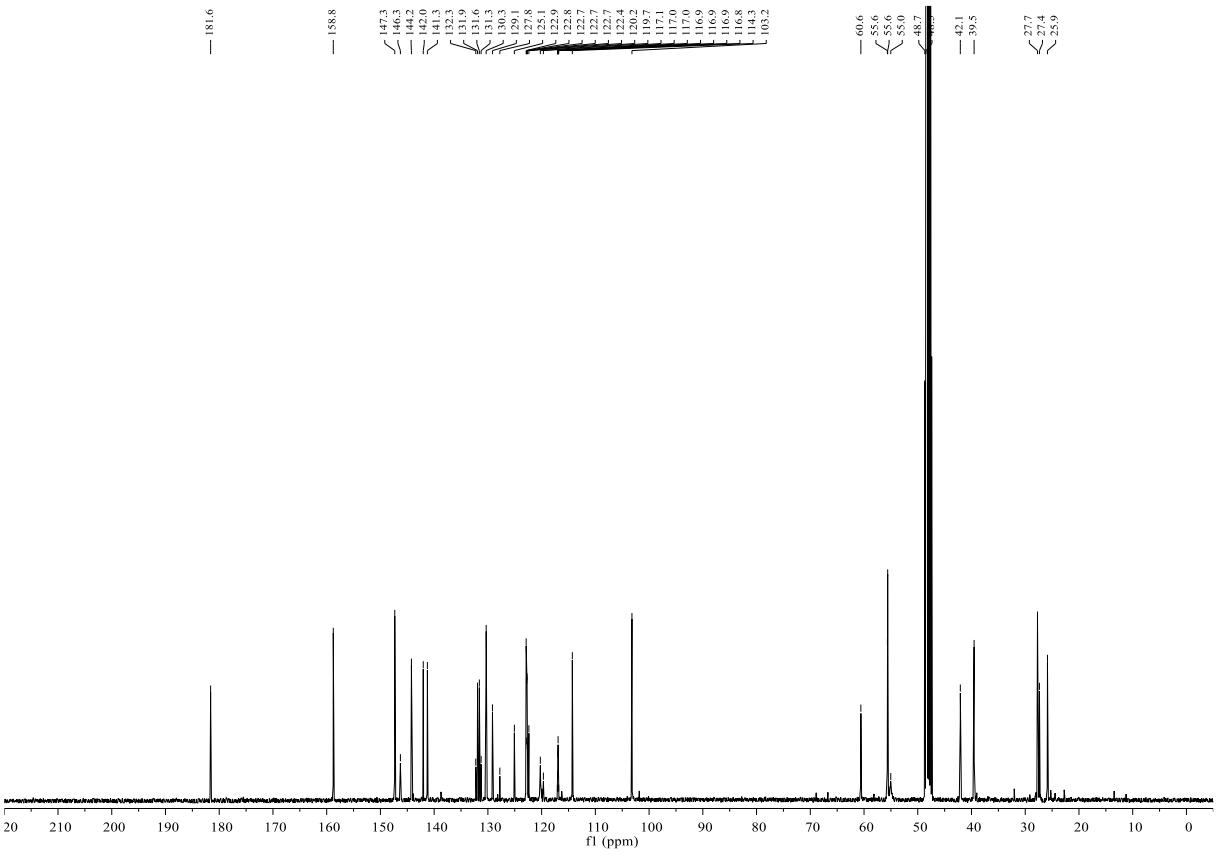
9-amino(9-deoxy)epiquinine





9-amino(9-deoxy)epiquinine Thiourea





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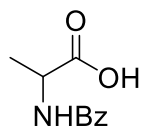

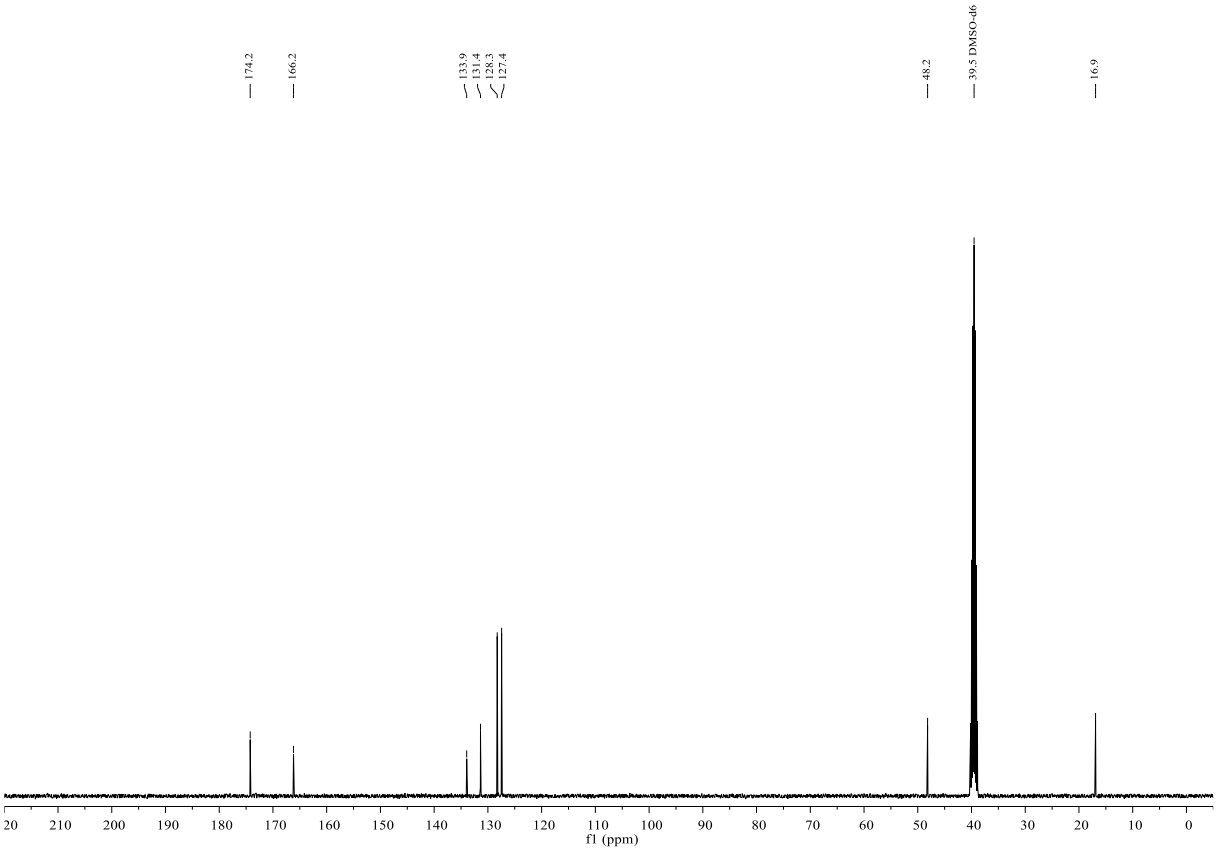

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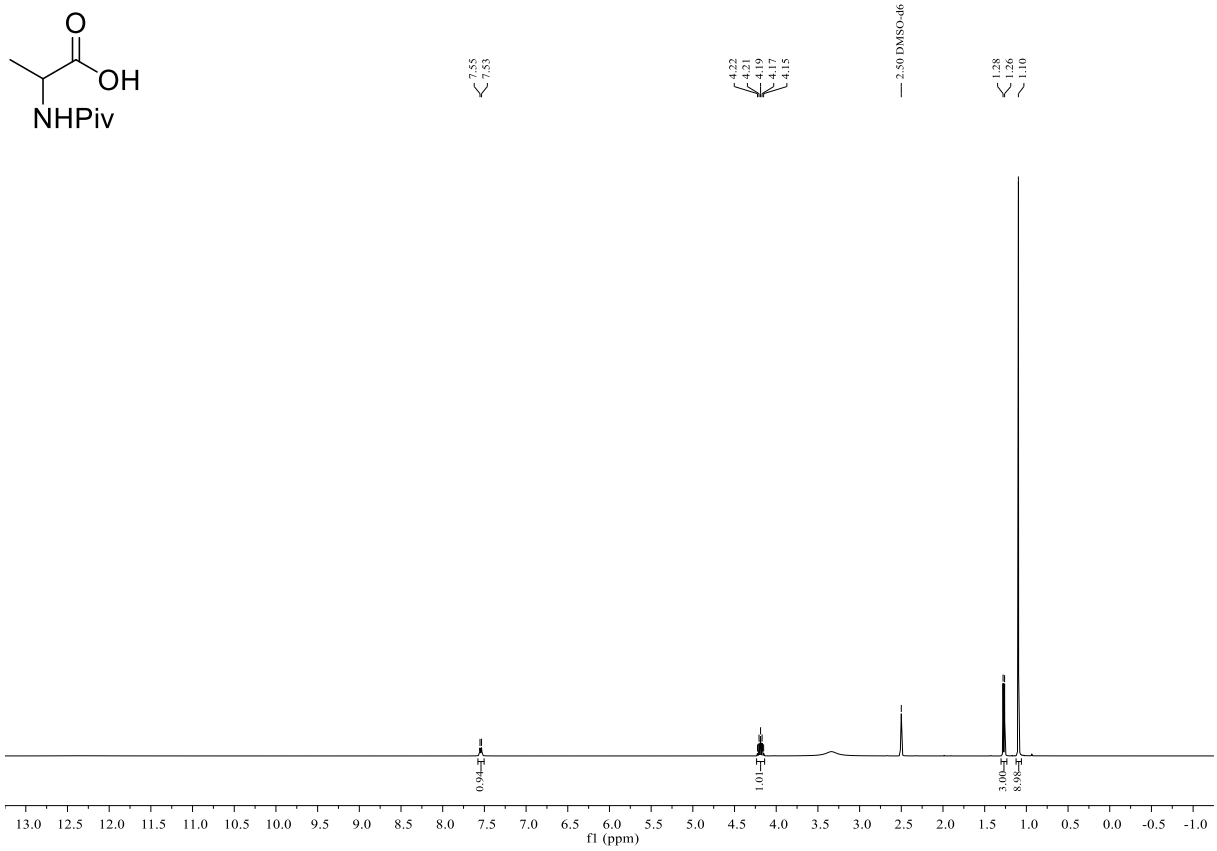

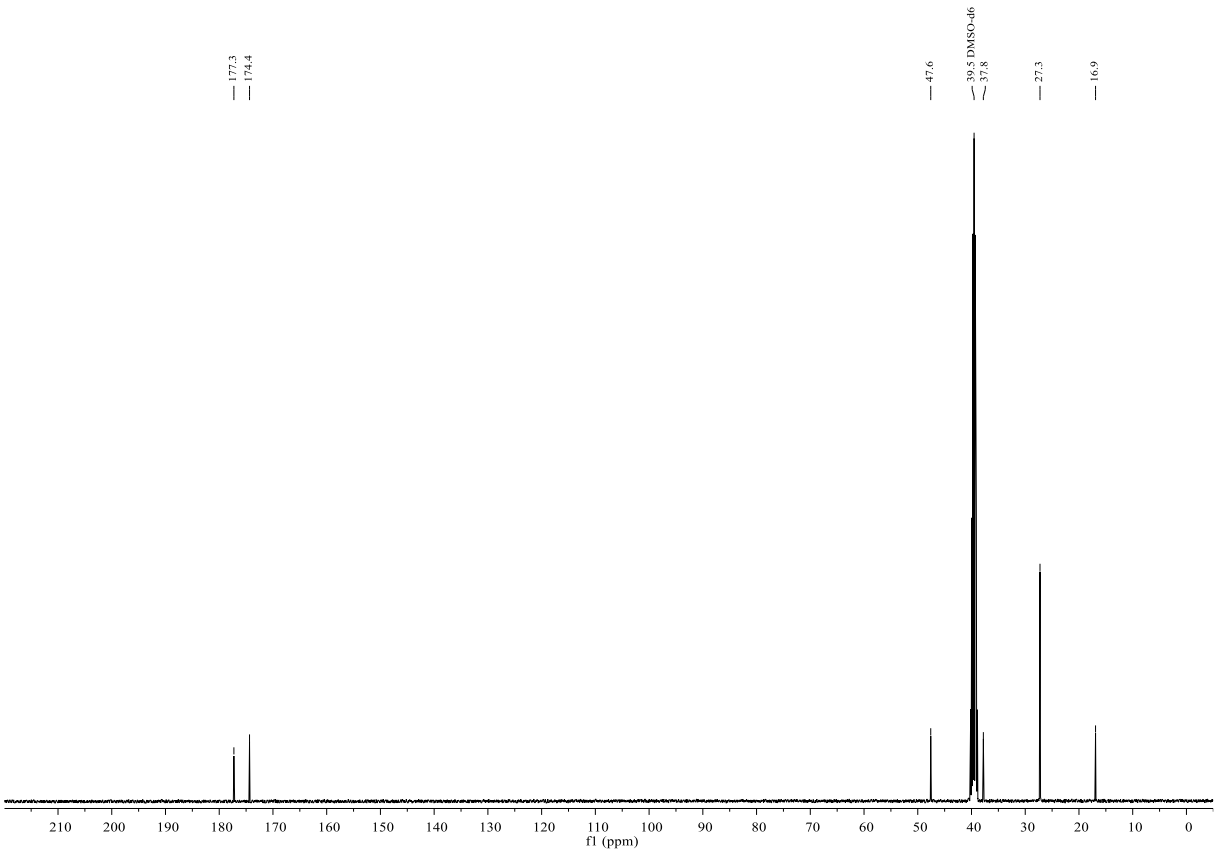

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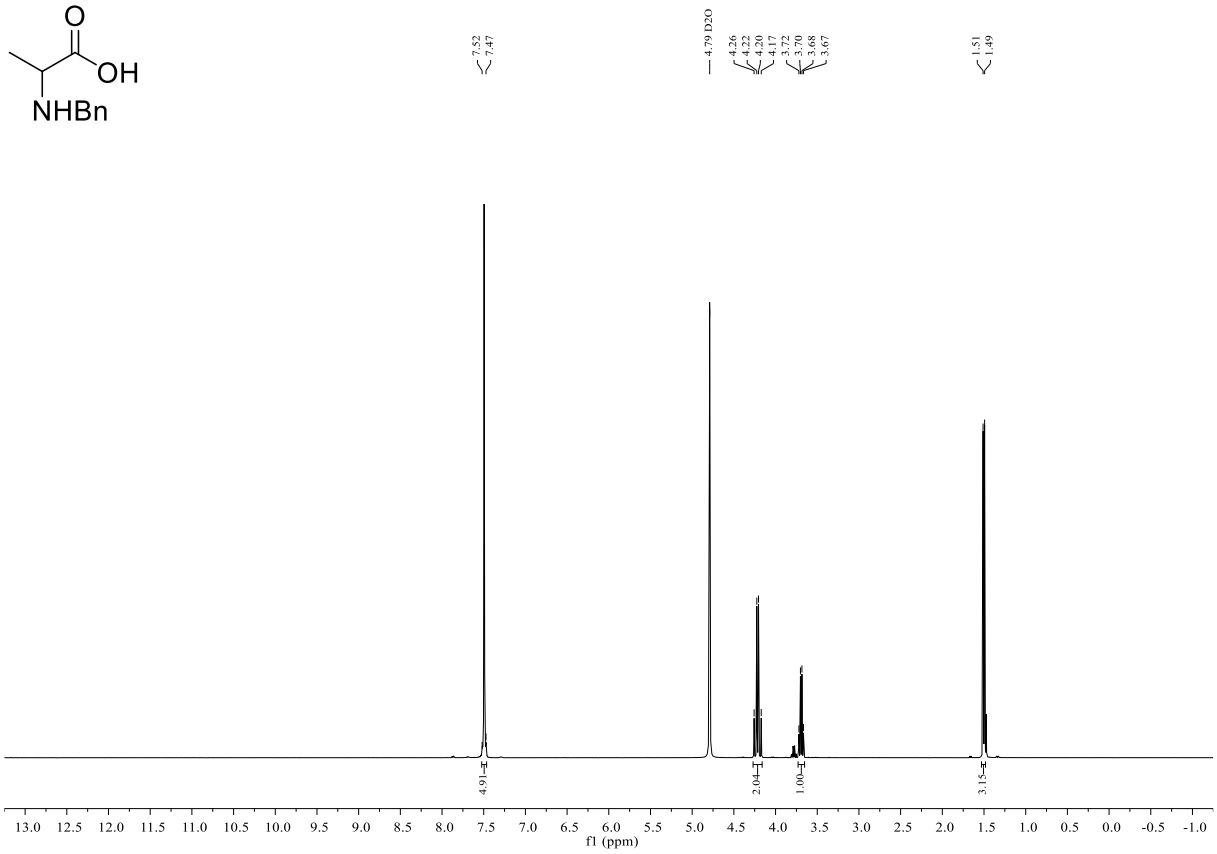

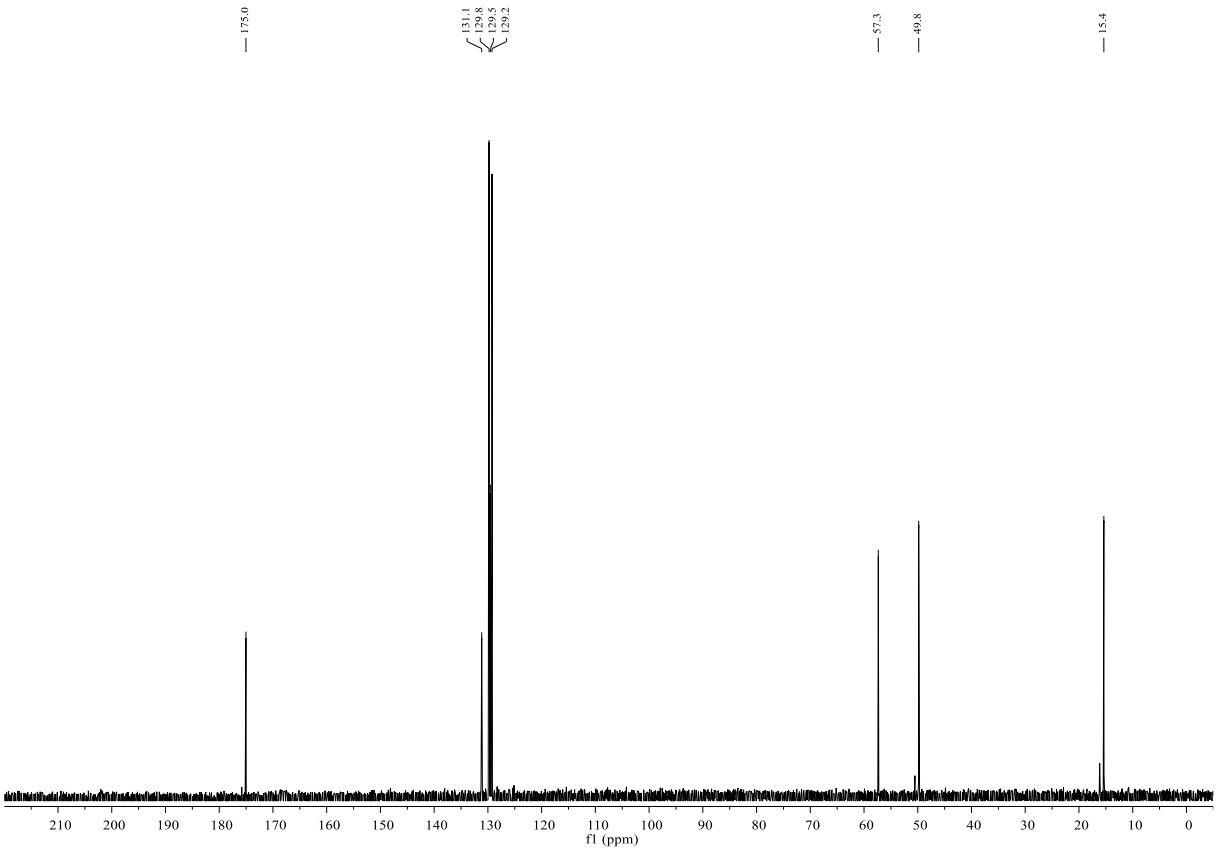

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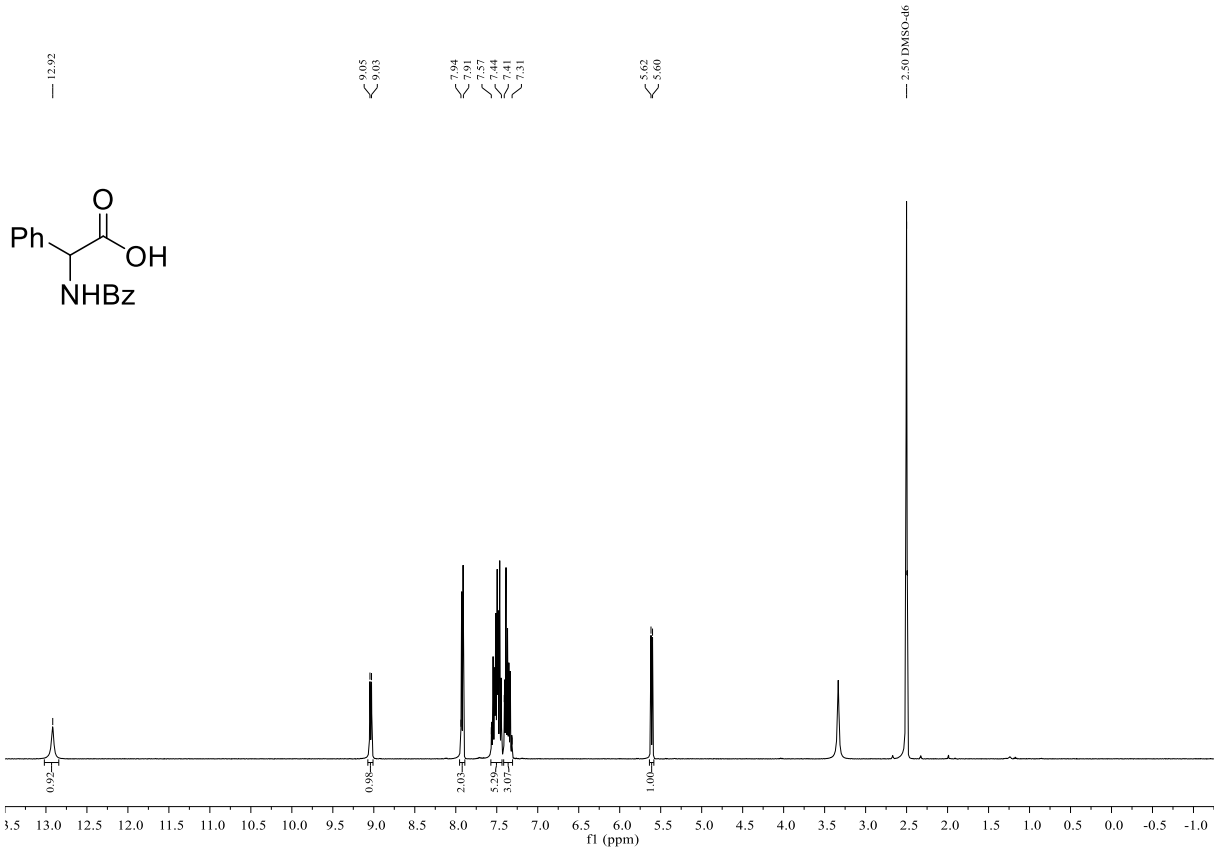

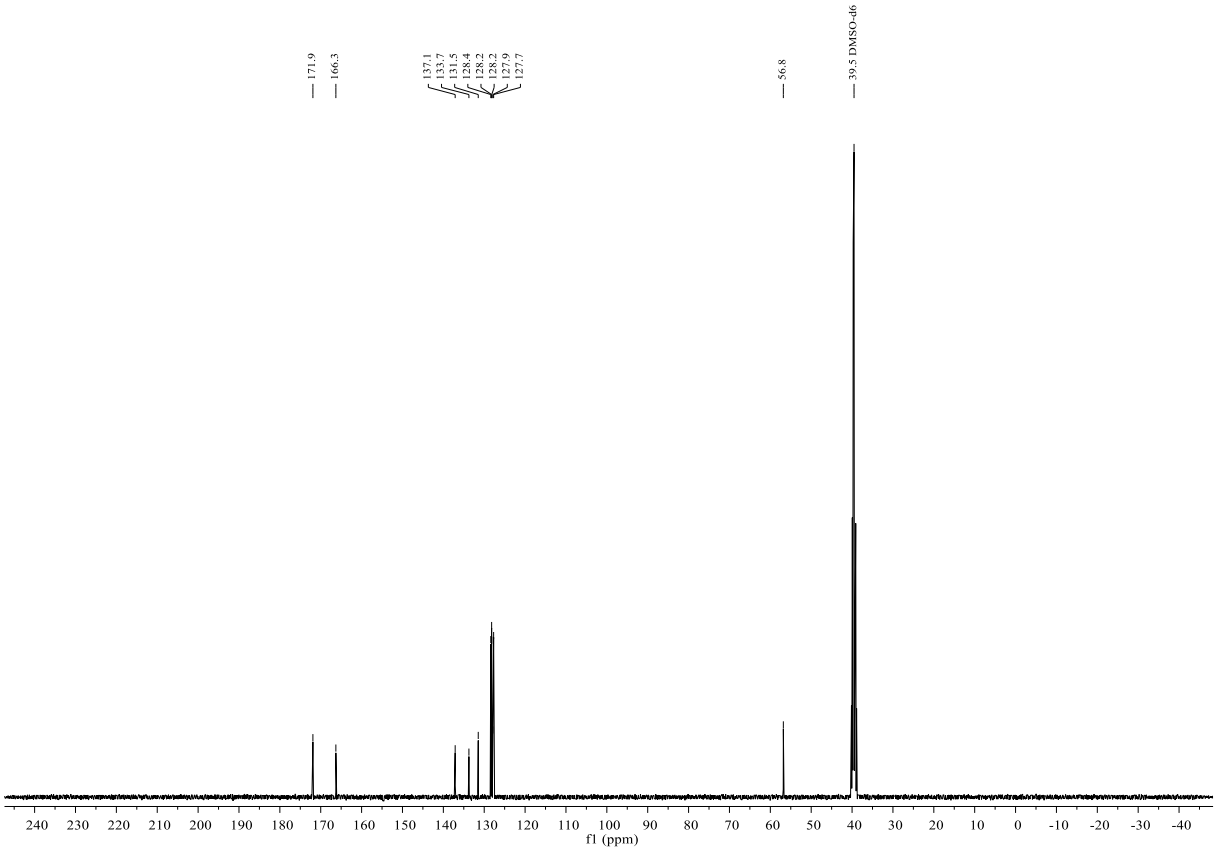

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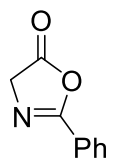

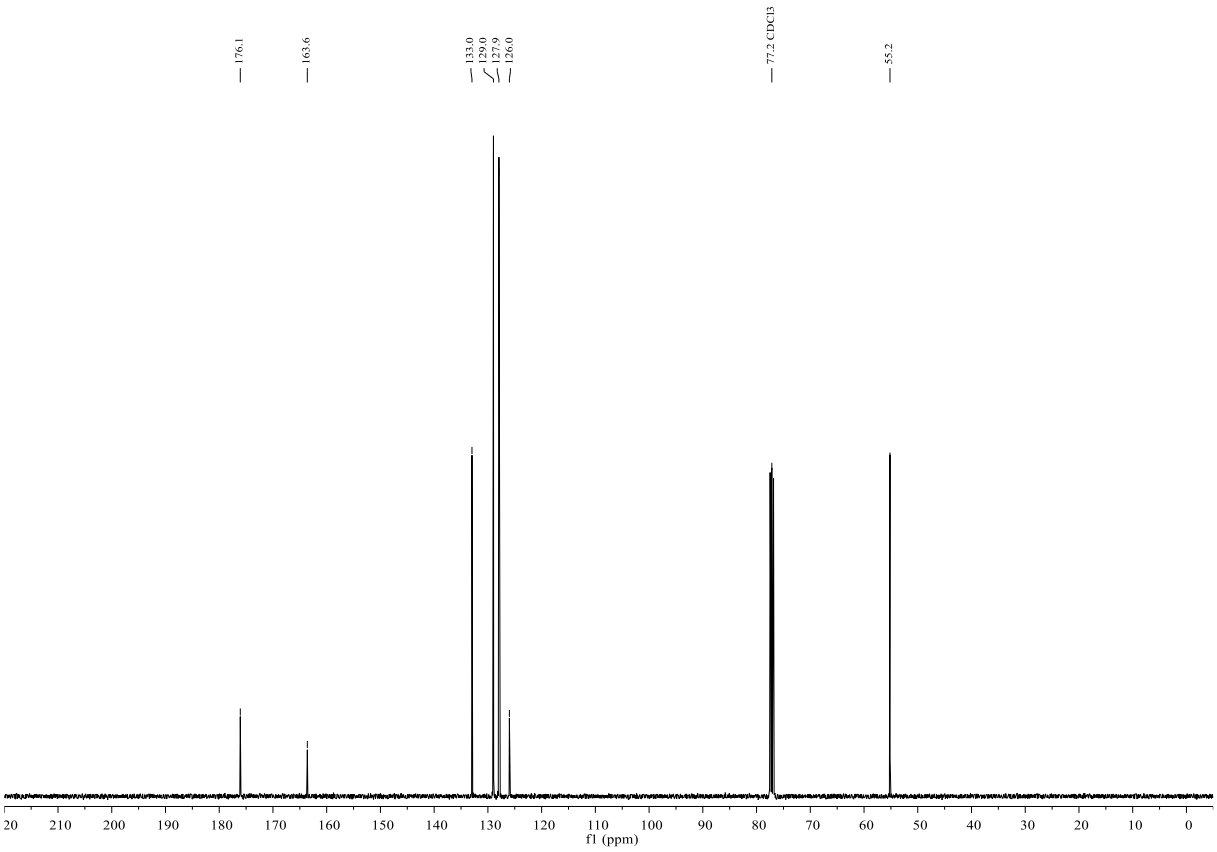

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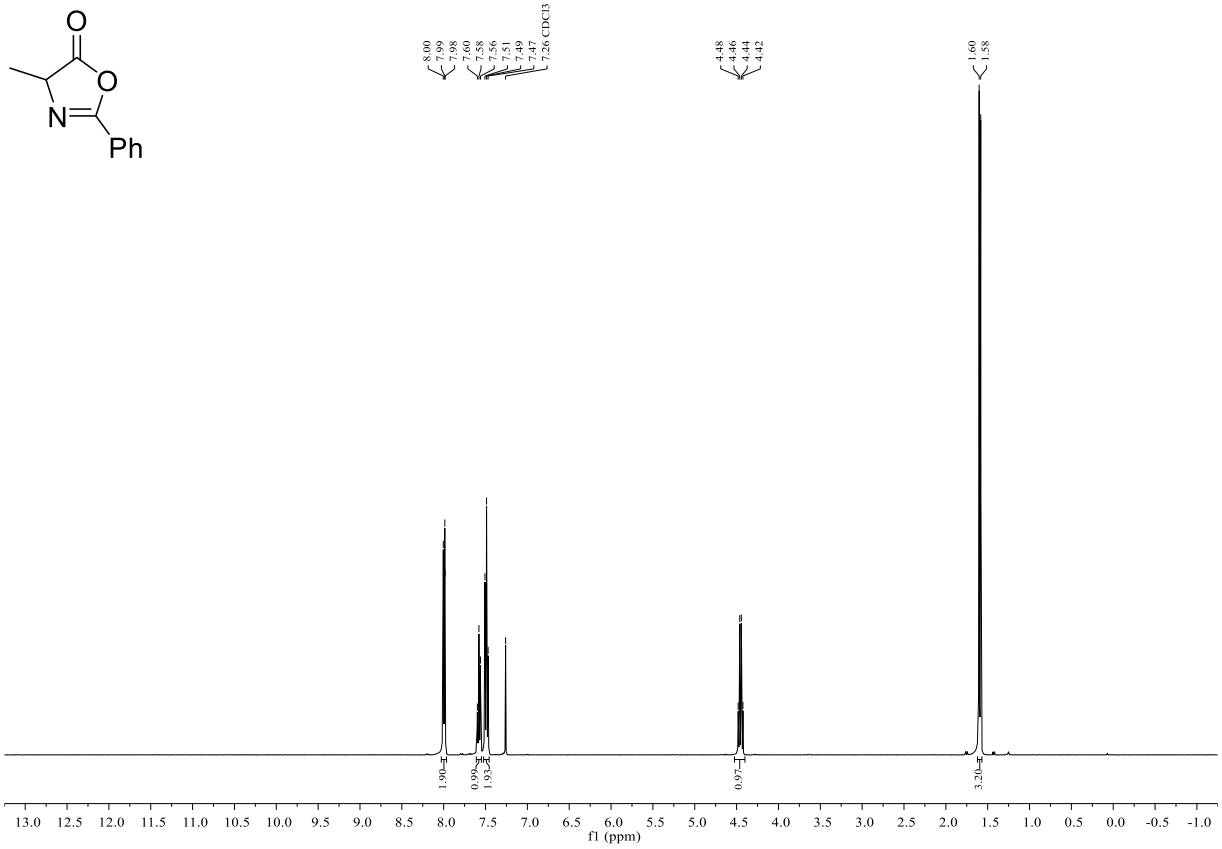

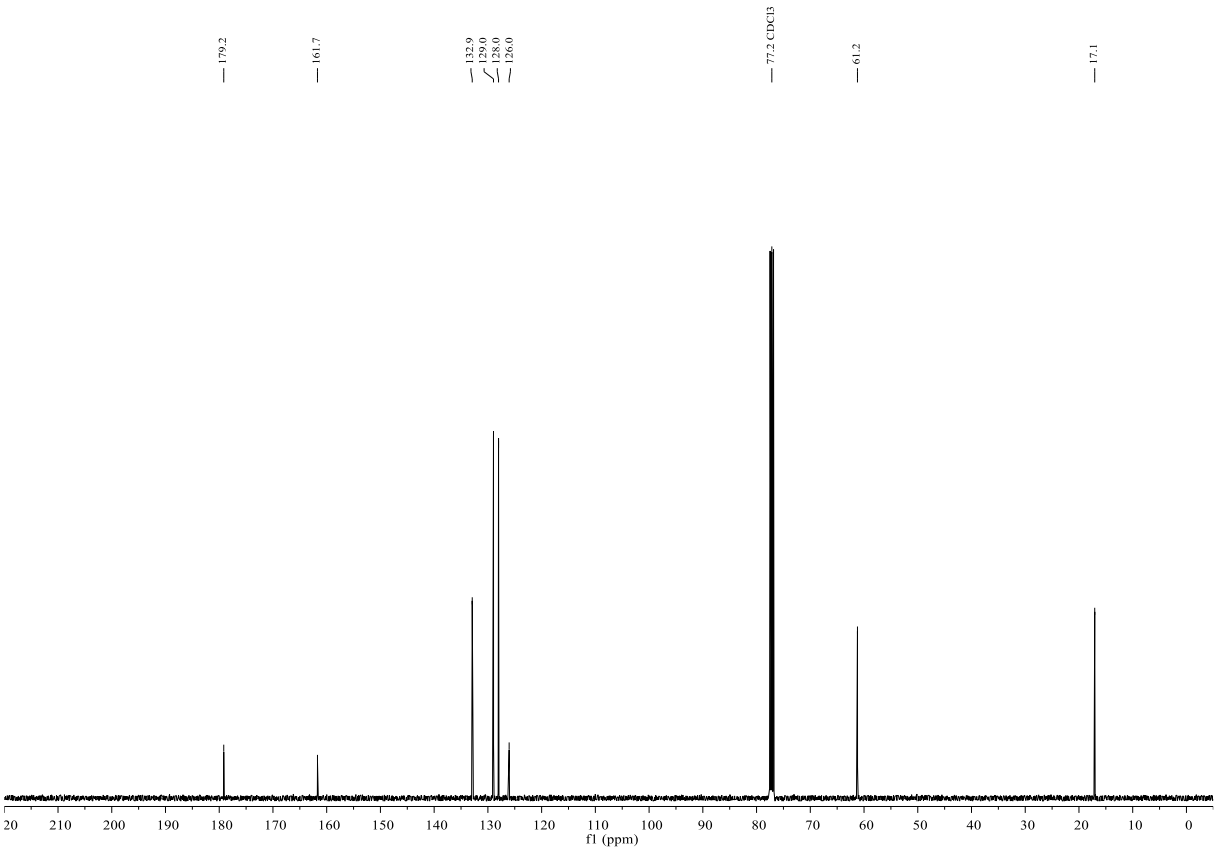

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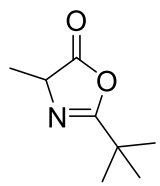

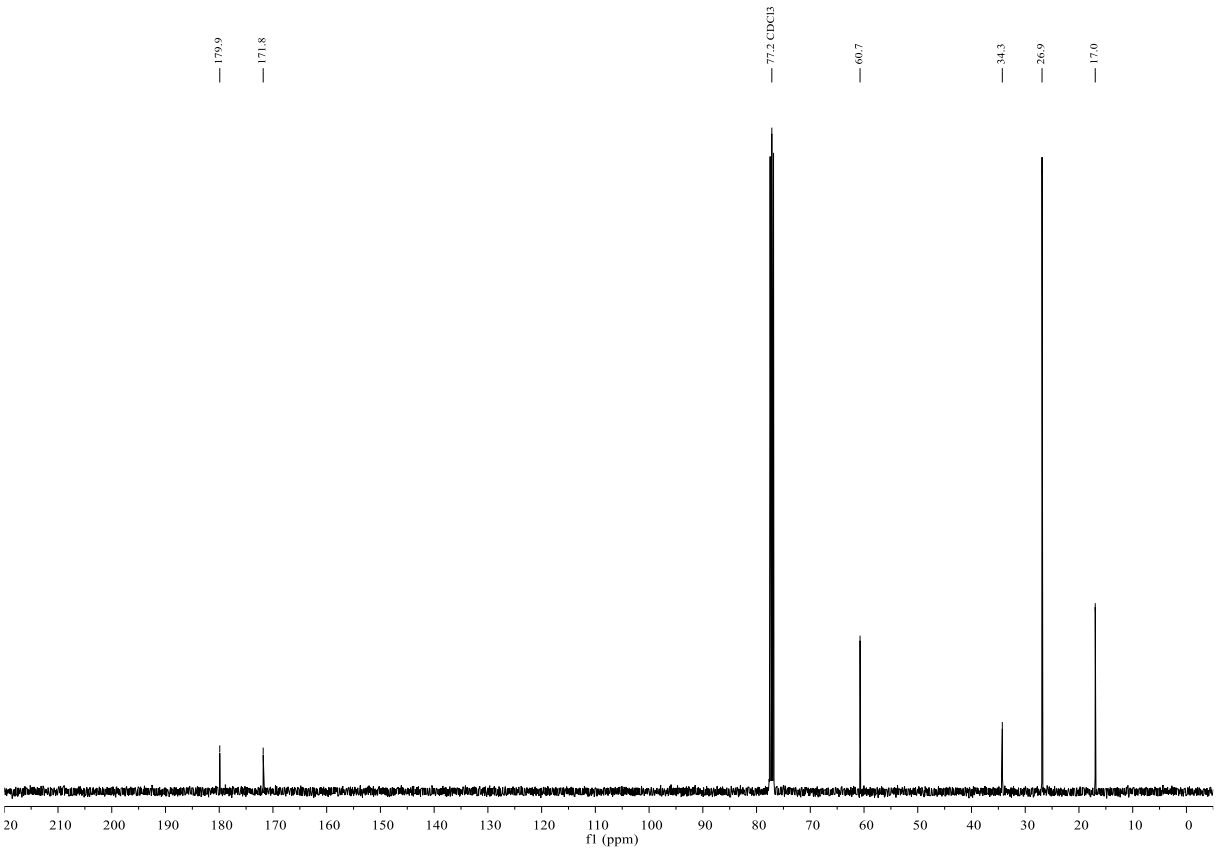

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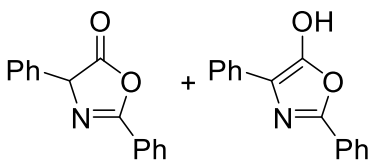

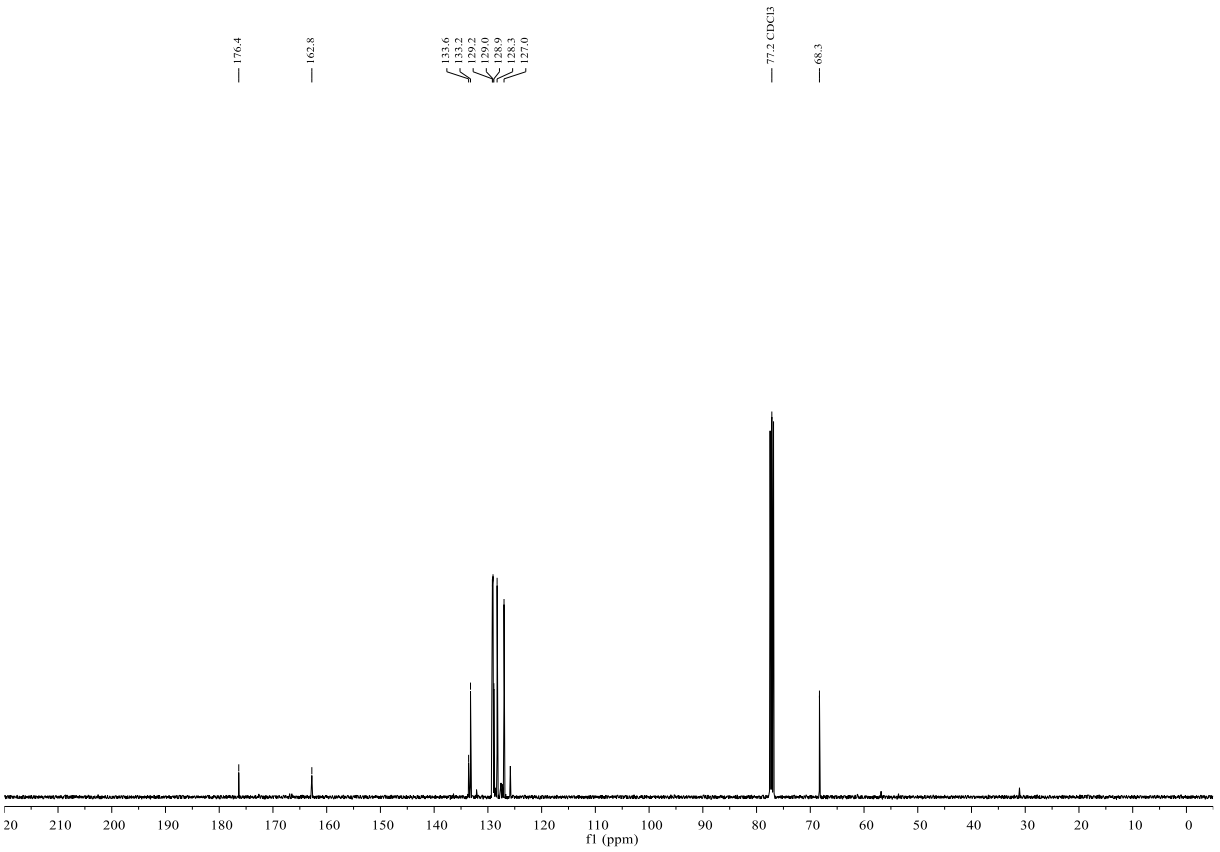

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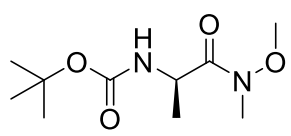
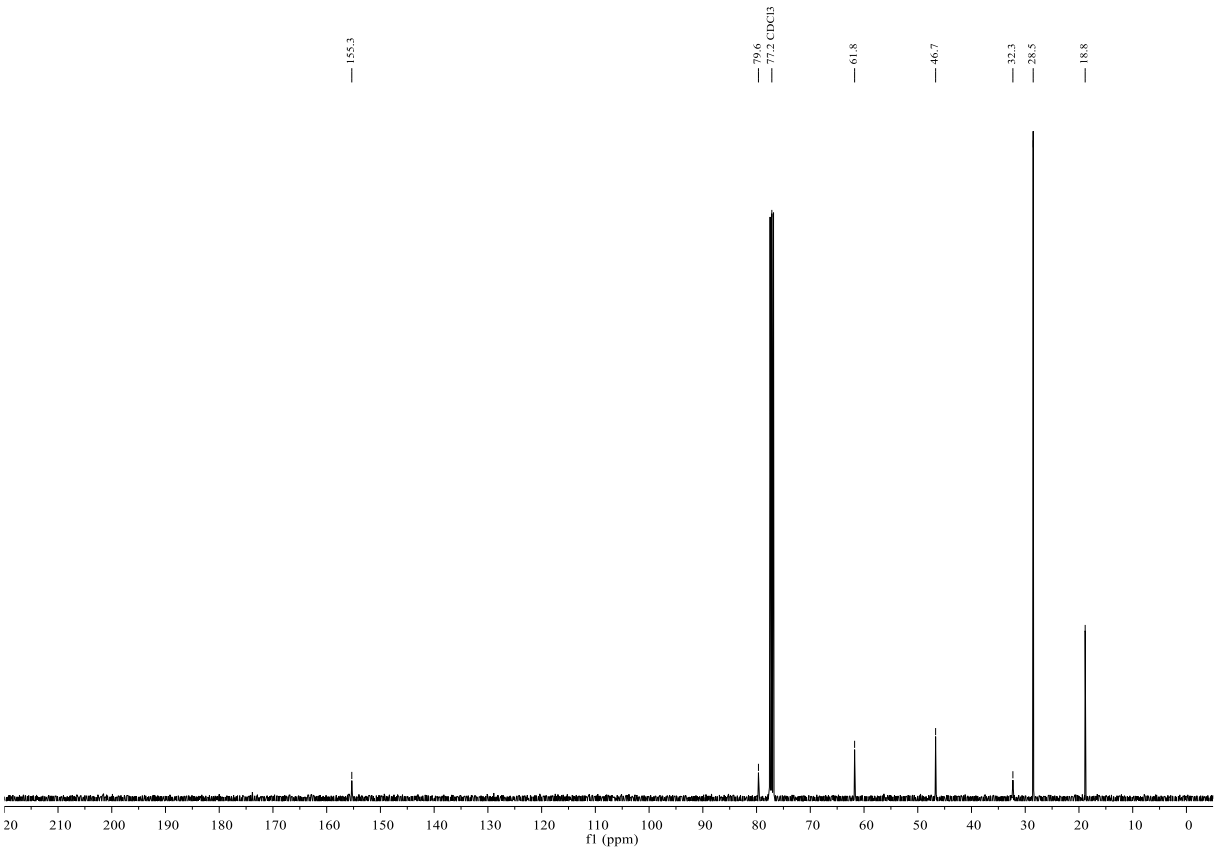
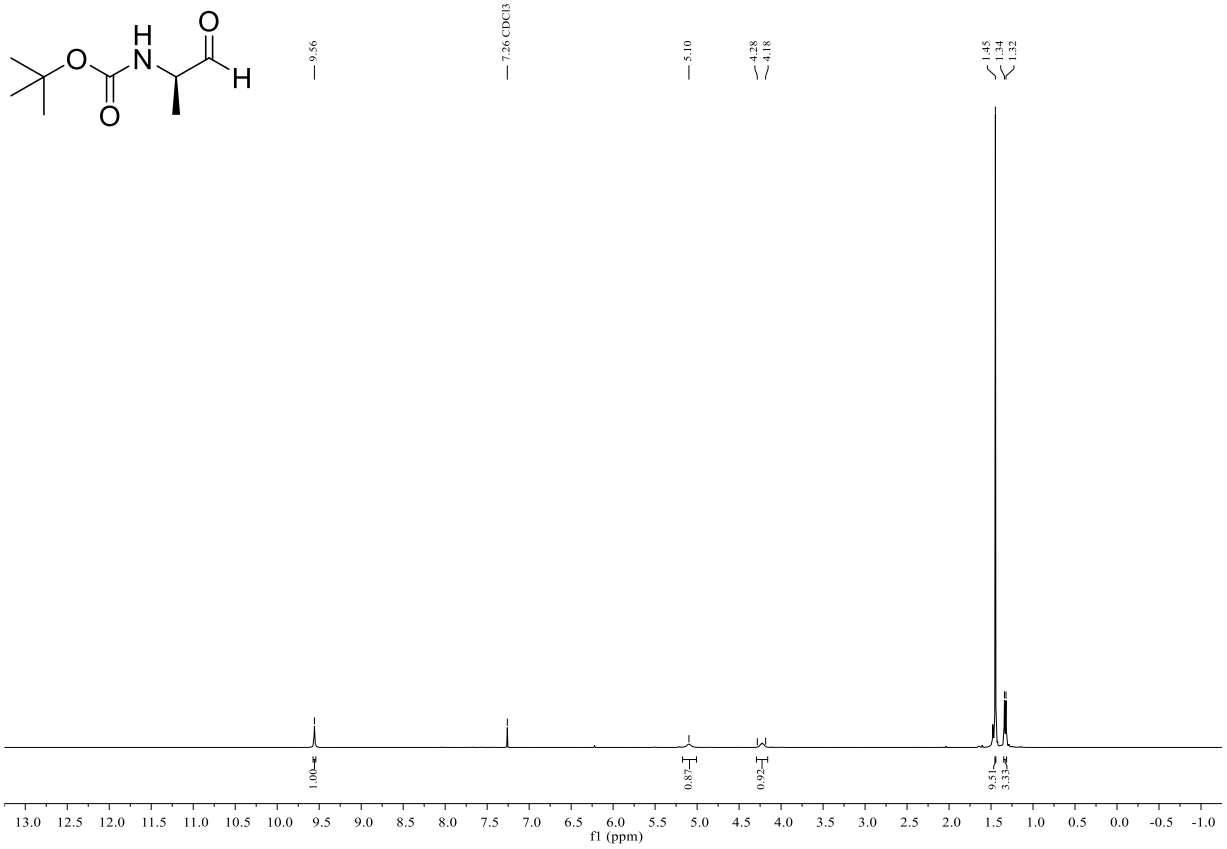
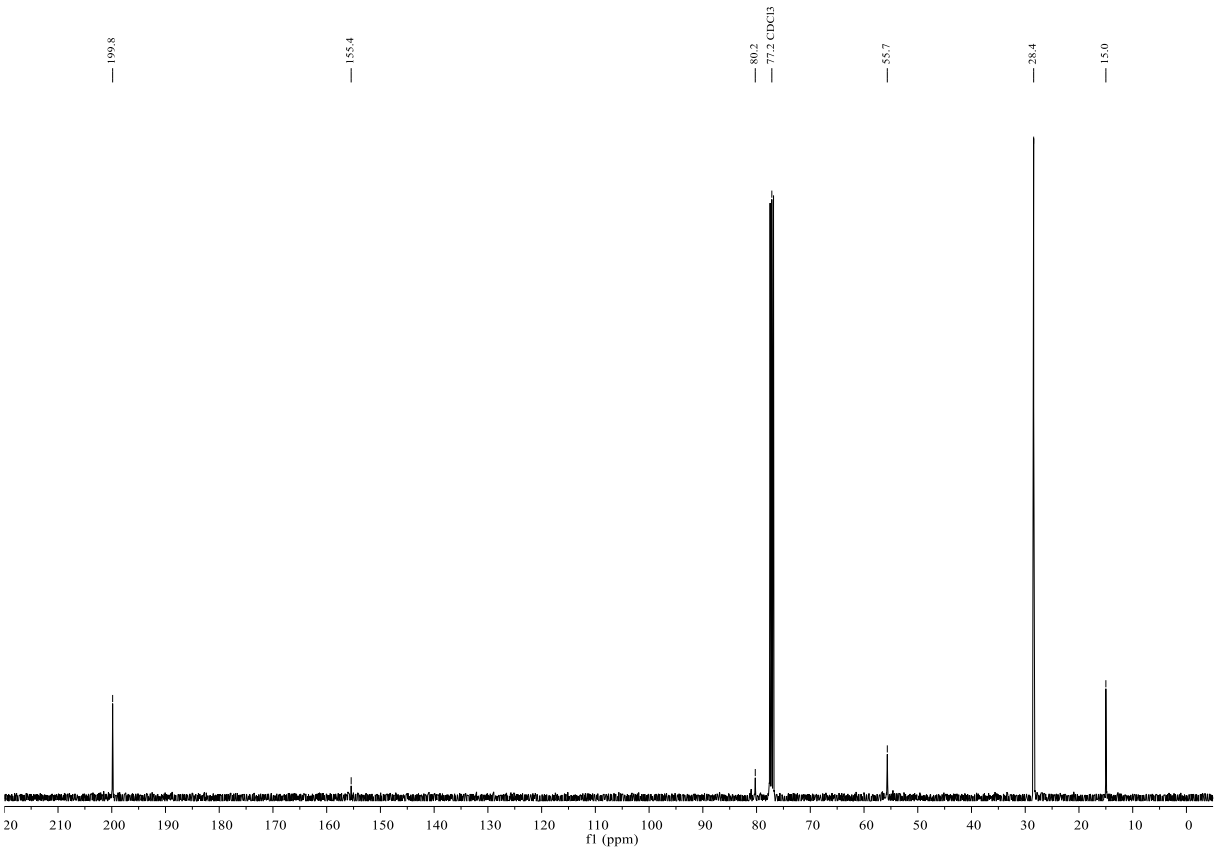


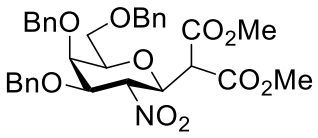


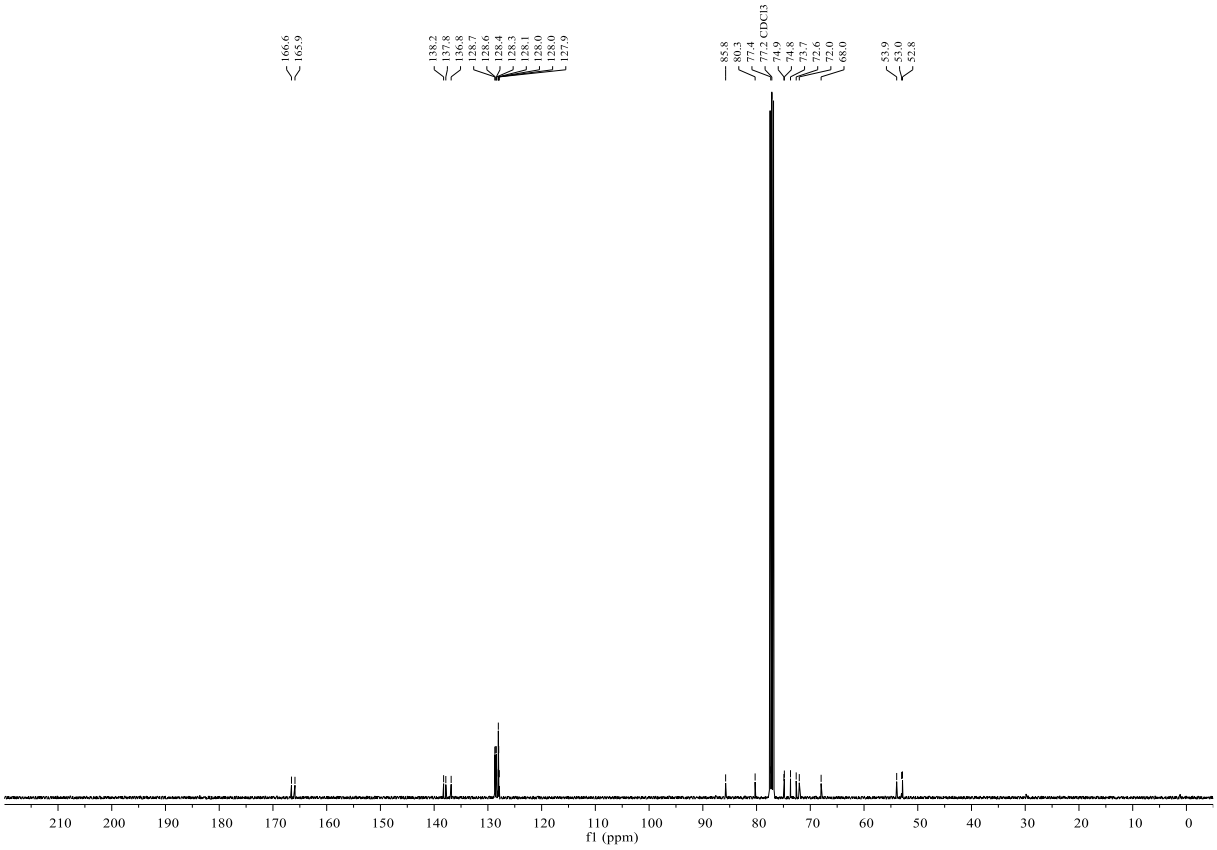
tert-Butyl (*S*)-(1-oxopropan-2-yl)carbamate





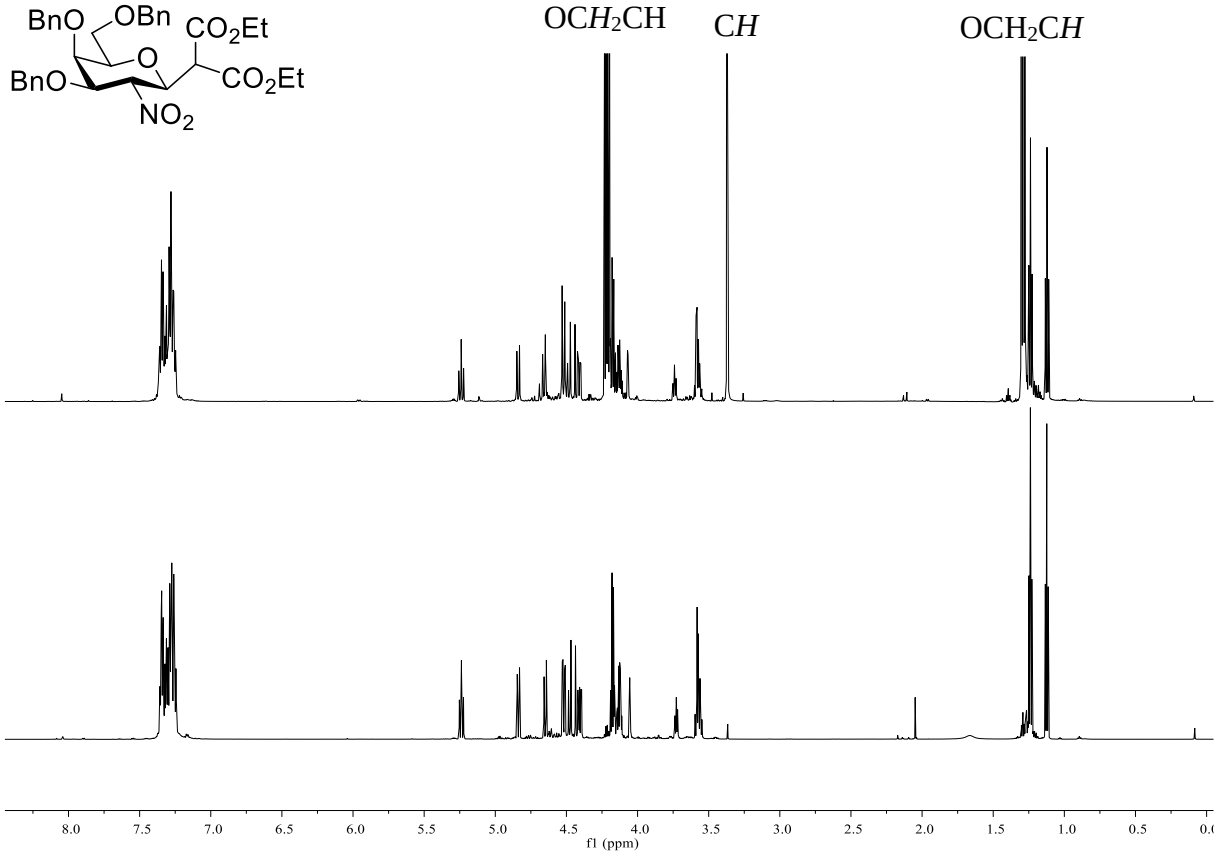
Dimethyl-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-*β*-D-galactopyranosyl)-malonate

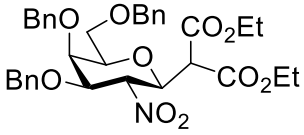




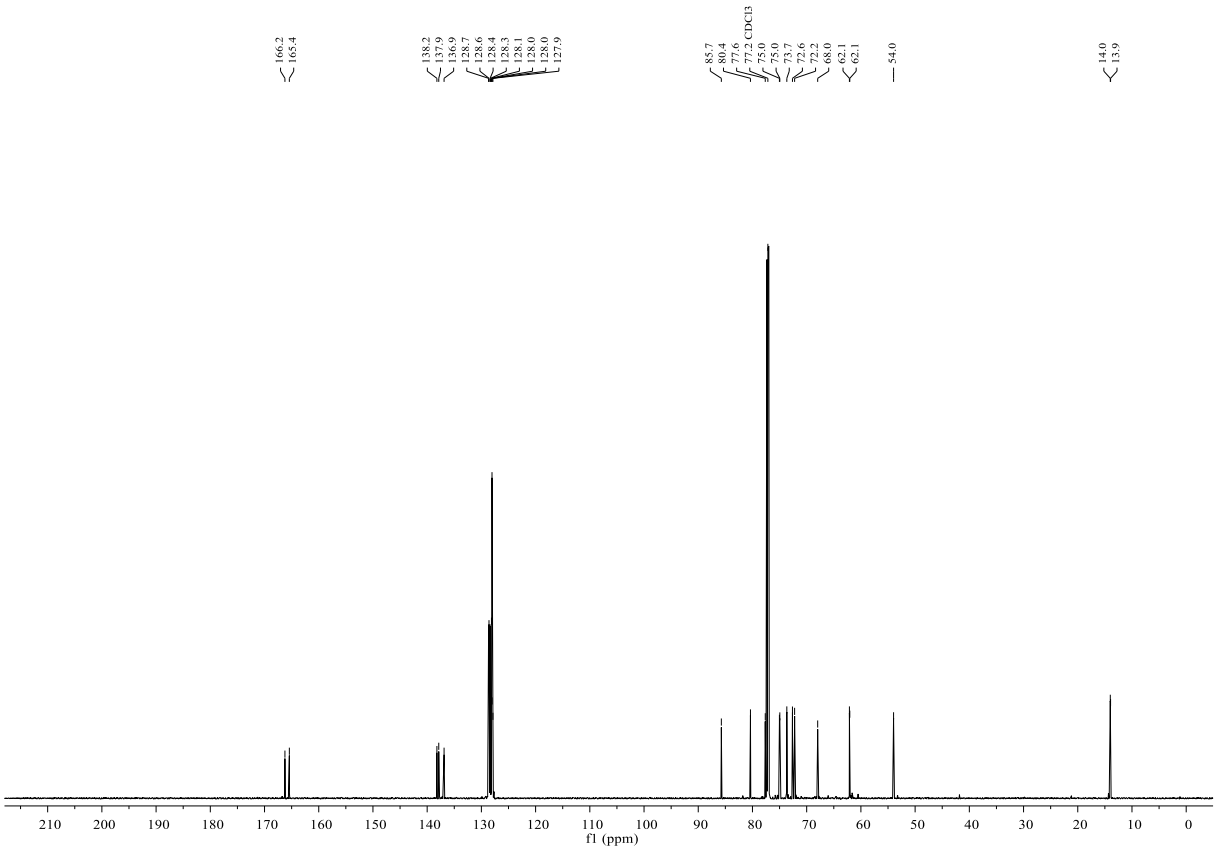
Diethyl-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-*β*-D-galactopyranosyl)-malonate

A comparison of the spectra of the reaction mixture after workup (top) to the spectra of the purified product (bottom) shows the exclusive formation of the desired product. The nitrogalactal is consumed quantitatively, and no side products are apparent. This indicates the quantitative formation of only the desired product. Therefore, the problem concerning the isolation of the product is most likely rooted in the purification process i.e., column chromatography. It could be observed that with certain (rather unipolar) eluent mixtures, a strong tailing of the carbohydrates occurred on the column. With an increase in polarity of the eluent, the separation efficiency declined rapidly, but the tailing still occurred. Signals corresponding to the malonate-starting material are assigned.



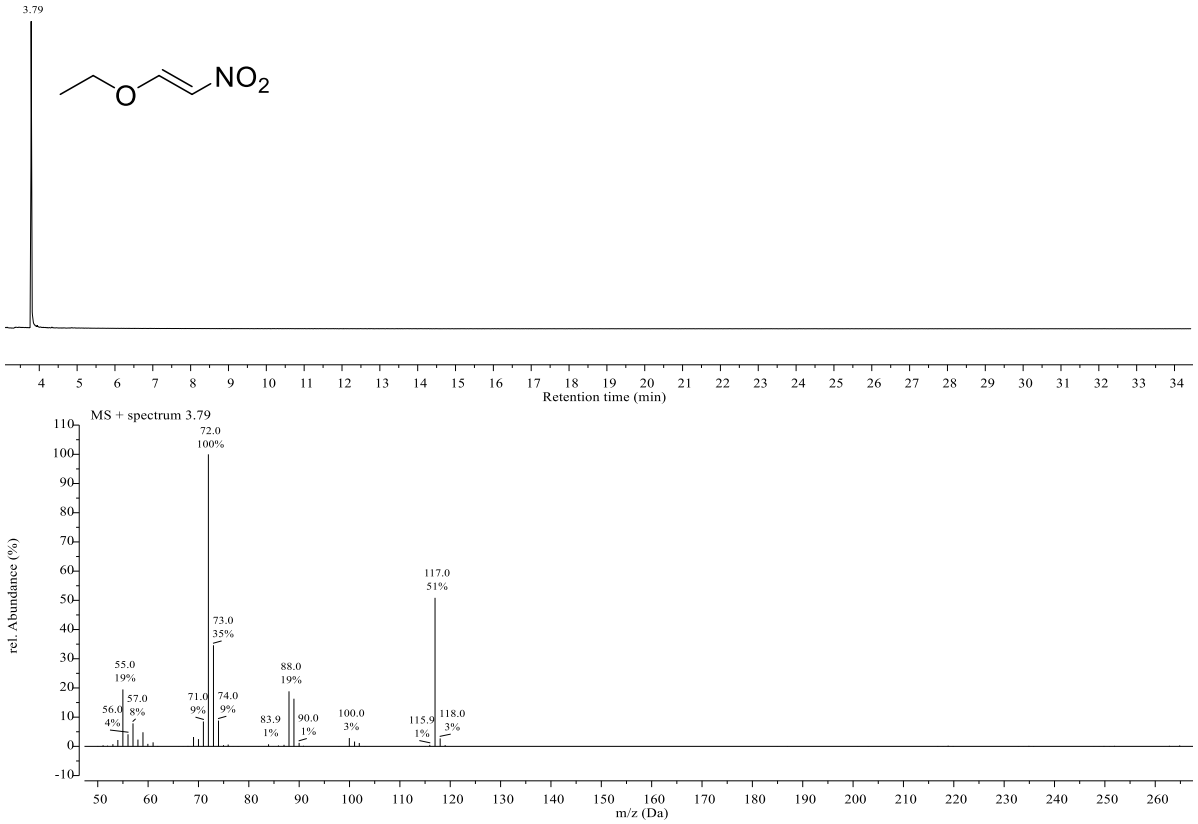

BnO
OBn
CO2Et
O
BnO
CO2Et
NO2

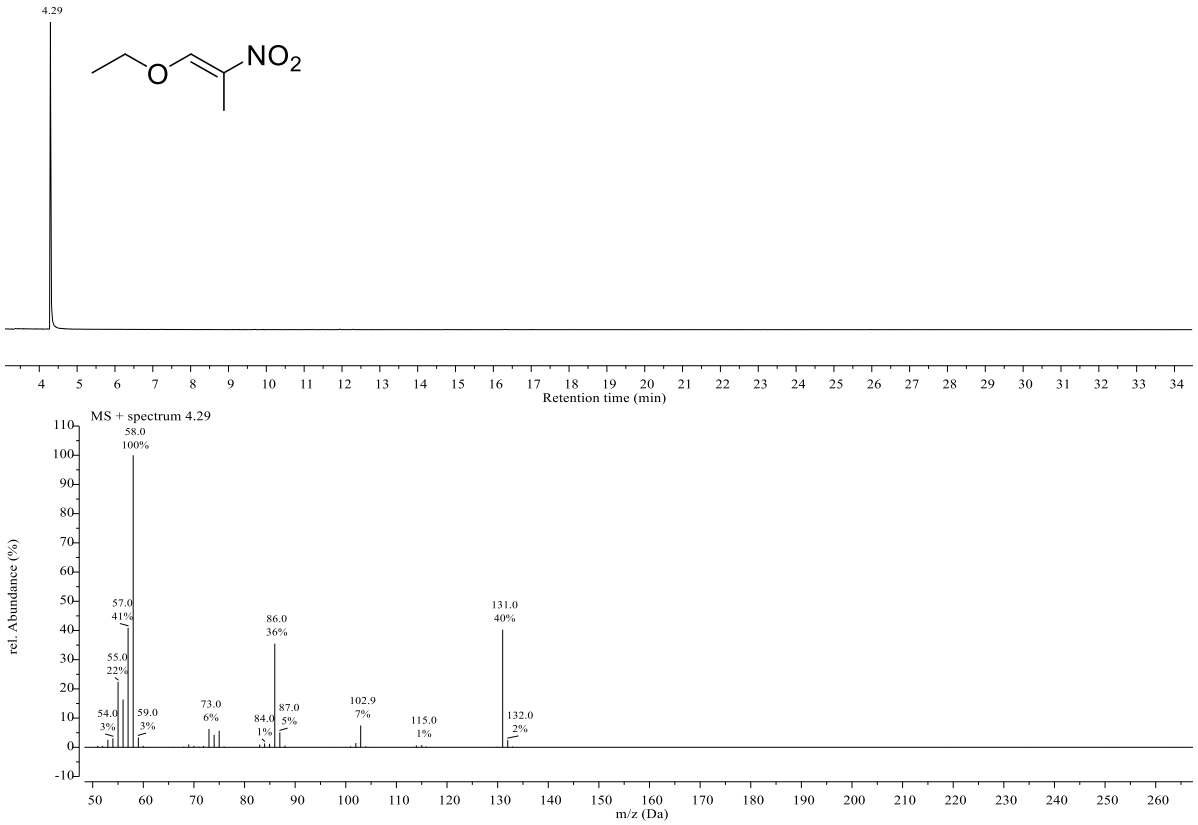
7.36
7.26 CDCl3
7.24
5.25
5.24
5.22
4.85
4.83
4.66
4.64
4.53
4.52
4.51
4.51
4.49
4.48
4.47
4.44
4.42
4.41
4.41
4.40
4.39
4.19
4.11
4.06
4.05
4.05
4.05
3.74
3.72
3.60
3.55
1.25
1.24
1.23
1.13
1.12
1.11
18.91
1.00
1.04
1.11
2.24
1.17
1.10
1.12
5.52
1.00
1.03
3.13
3.26
2.95
f1 (ppm)

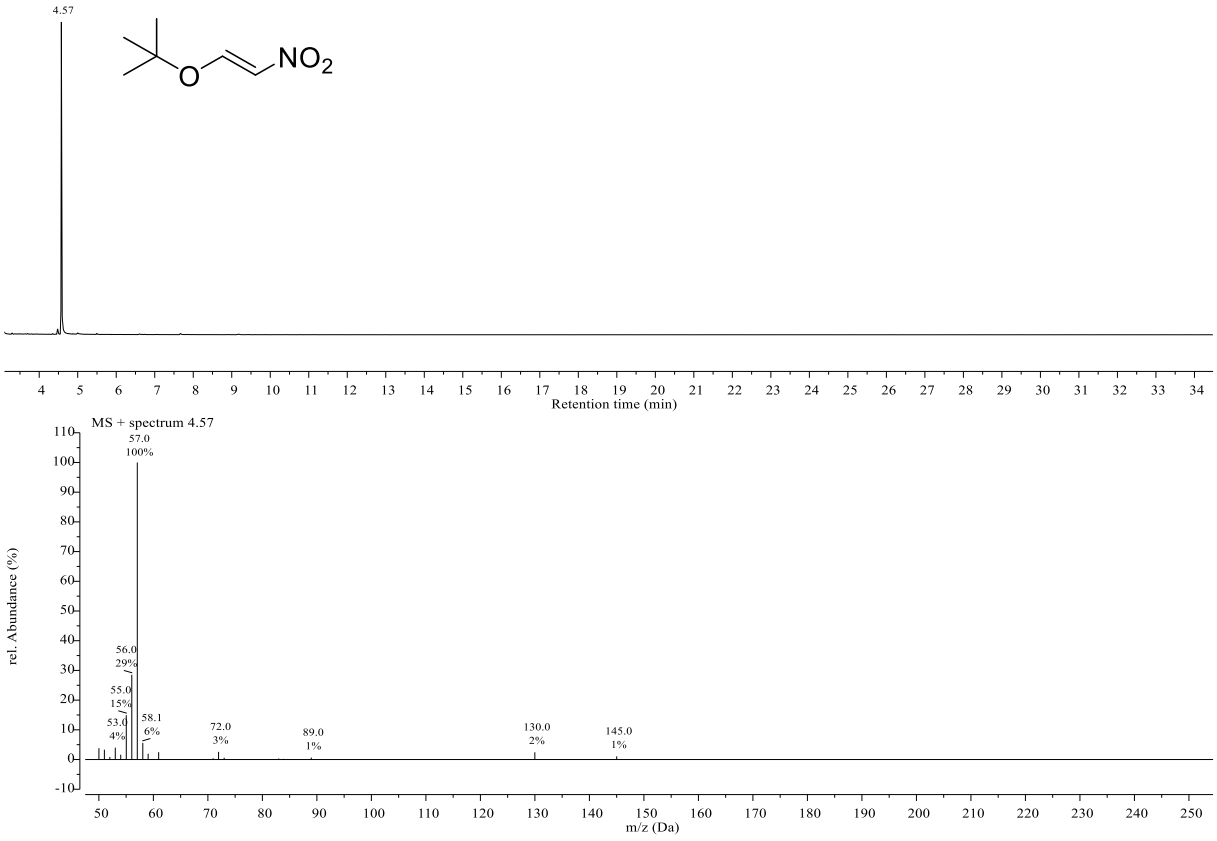

166.2
165.4
138.2
137.9
136.9
128.7
128.6
128.4
128.3
128.1
128.0
128.0
127.9
85.7
80.4
77.6
77.2 CDCl3
75.0
75.0
73.7
72.6
72.2
68.0
62.1
62.1
54.0
14.0
13.9
f1 (ppm)

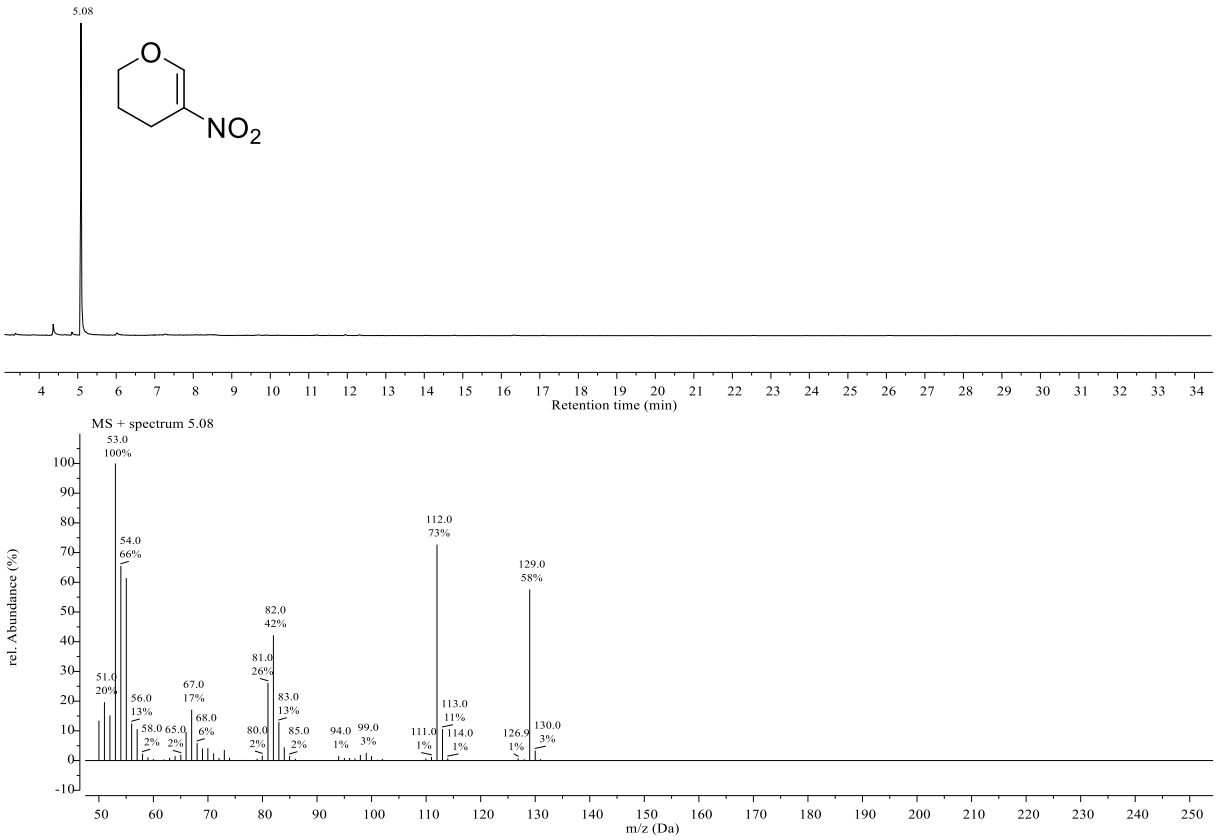
8.1 – GC-MS Chromatograms and Spectra

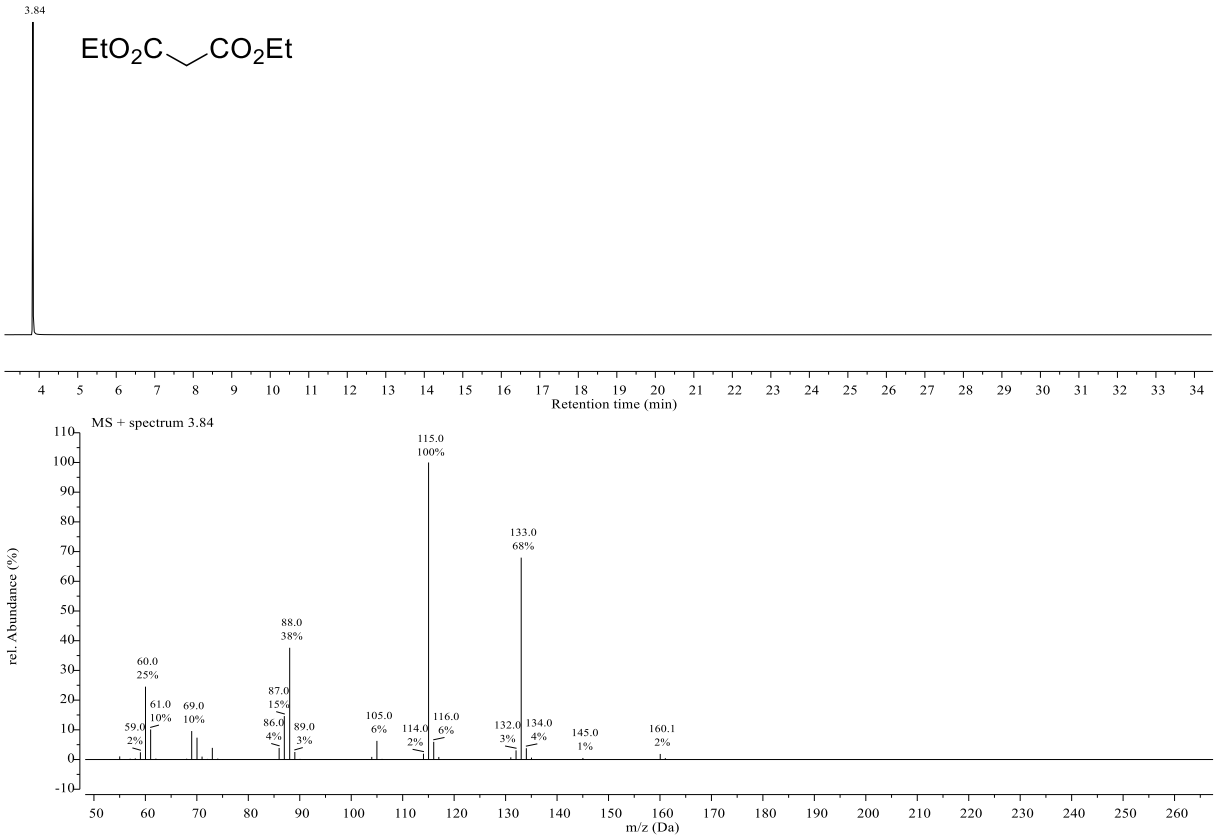
Standards

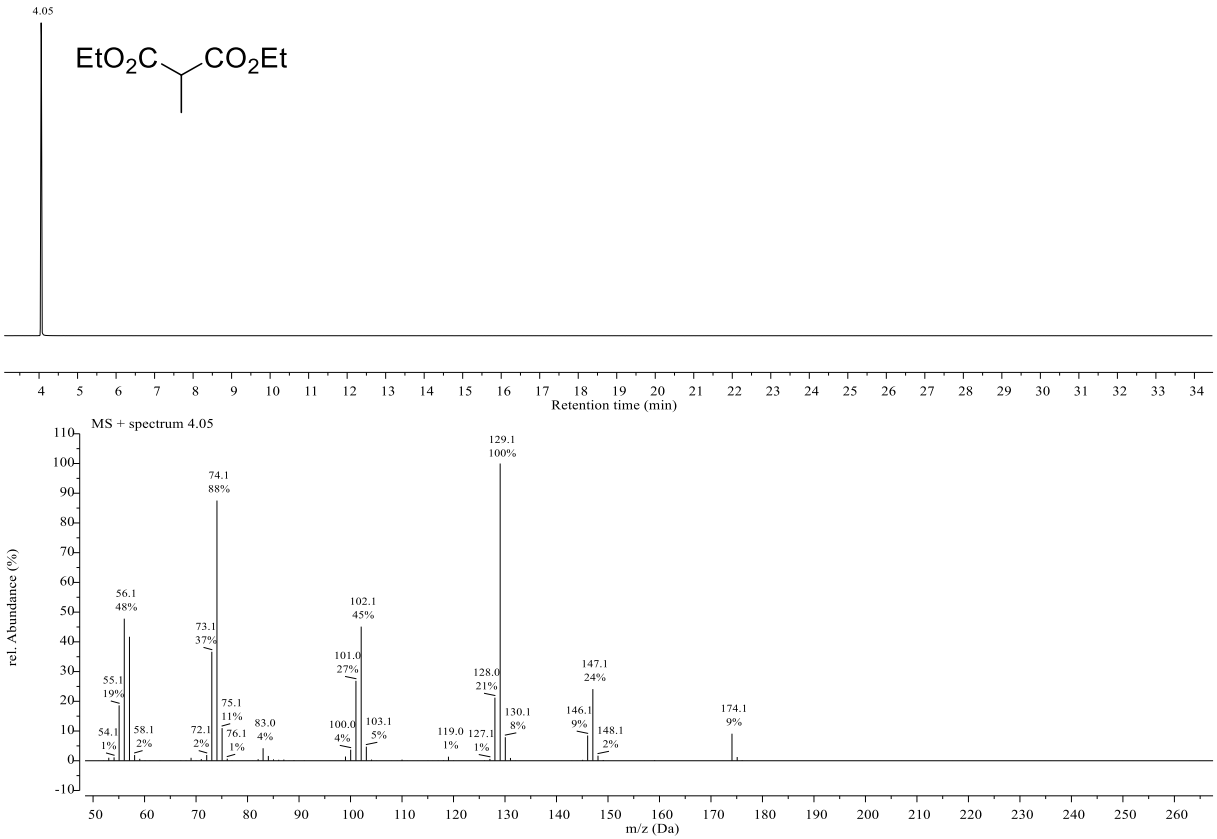


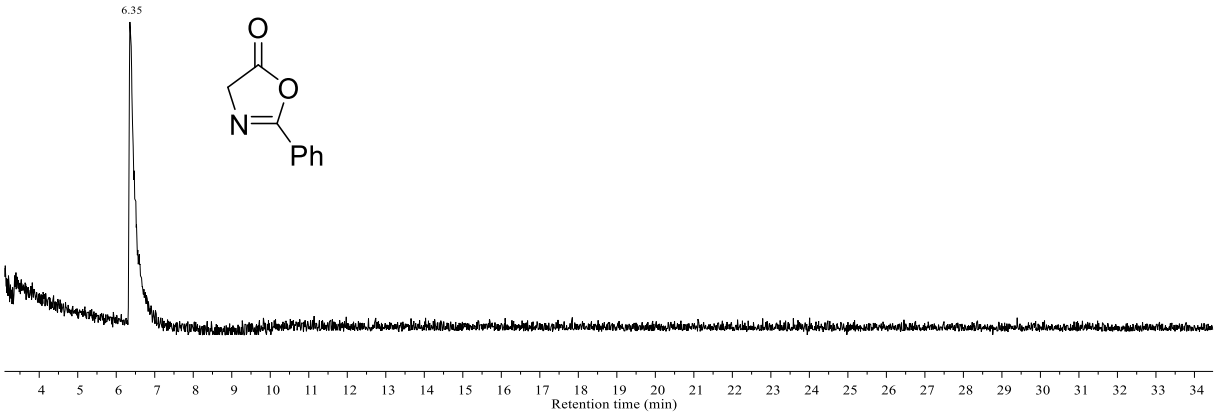


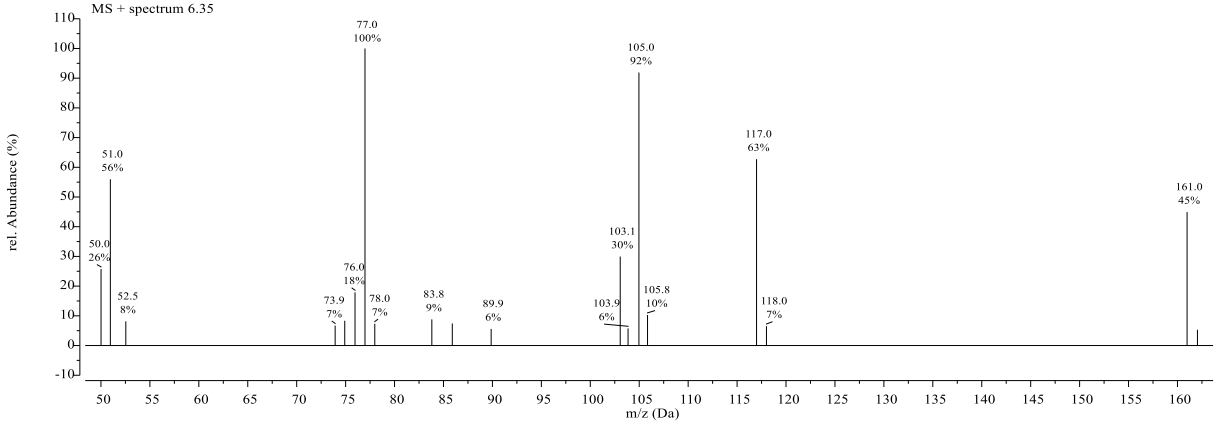

4.57
NO2
O
Retention time (min)
MS + spectrum 4.57
57.0
100%
56.0
29%
55.0
15%
53.0
4%
58.1
6%
72.0
3%
89.0
1%
130.0
2%
145.0
1%
rel. Abundance (%)
m/z (Da)

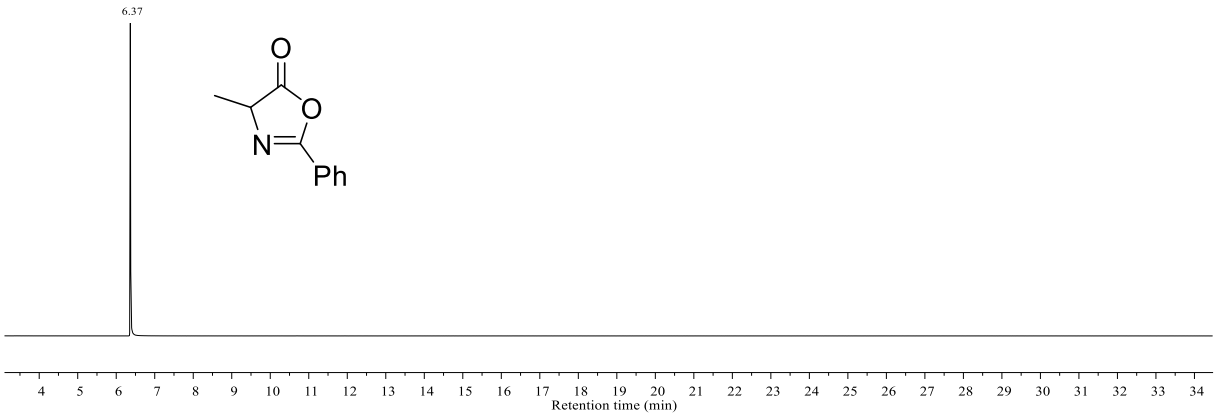

5.08
O
NO2
Retention time (min)
MS + spectrum 5.08
53.0
100%
54.0
66%
112.0
73%
129.0
58%
82.0
42%
81.0
26%
51.0
20%
67.0
17%
56.0
13%
83.0
13%
113.0
11%
58.0
2%
65.0
2%
68.0
6%
80.0
2%
85.0
2%
94.0
1%
99.0
3%
111.0
1%
114.0
1%
126.9
1%
130.0
3%
rel. Abundance (%)
m/z (Da)

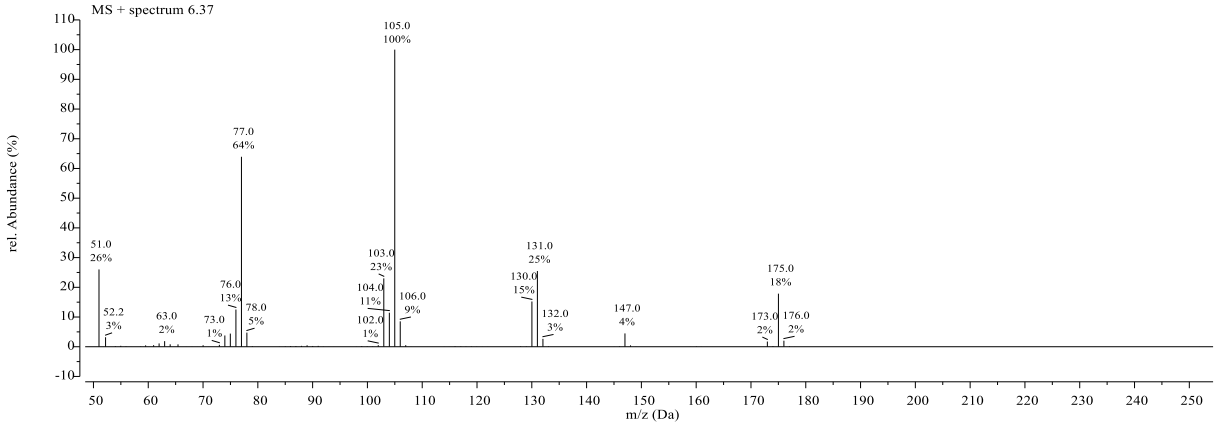

3.84
EtO2C CO2Et
Retention time (min)
MS + spectrum 3.84
rel. Abundance (%)
m/z (Da)
115.0 100%
133.0 68%
88.0 38%
60.0 25%
61.0 10%
69.0 10%
87.0 15%
59.0 2%
86.0 4%
89.0 3%
105.0 6%
114.0 2%
116.0 6%
132.0 3%
134.0 4%
145.0 1%
160.1 2%

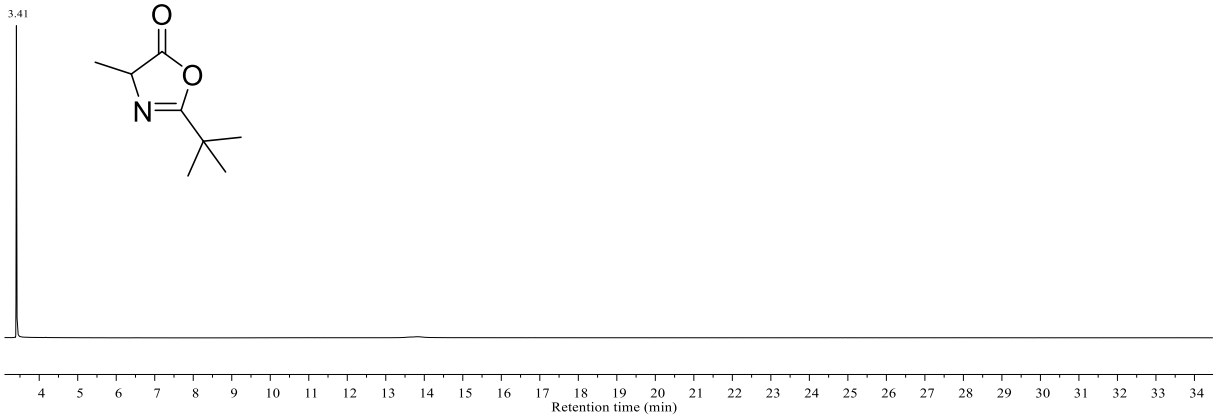

4.05
EtO2C CO2Et
Retention time (min)
MS + spectrum 4.05
rel. Abundance (%)
m/z (Da)
129.1 100%
74.1 88%
56.1 48%
102.1 45%
73.1 37%
101.0 27%
55.1 19%
128.0 21%
147.1 24%
75.1 11%
146.1 9%
174.1 9%
130.1 8%
54.1 1%
58.1 2%
72.1 2%
76.1 1%
83.0 4%
100.0 4%
103.1 5%
119.0 1%
127.1 1%
148.1 2%

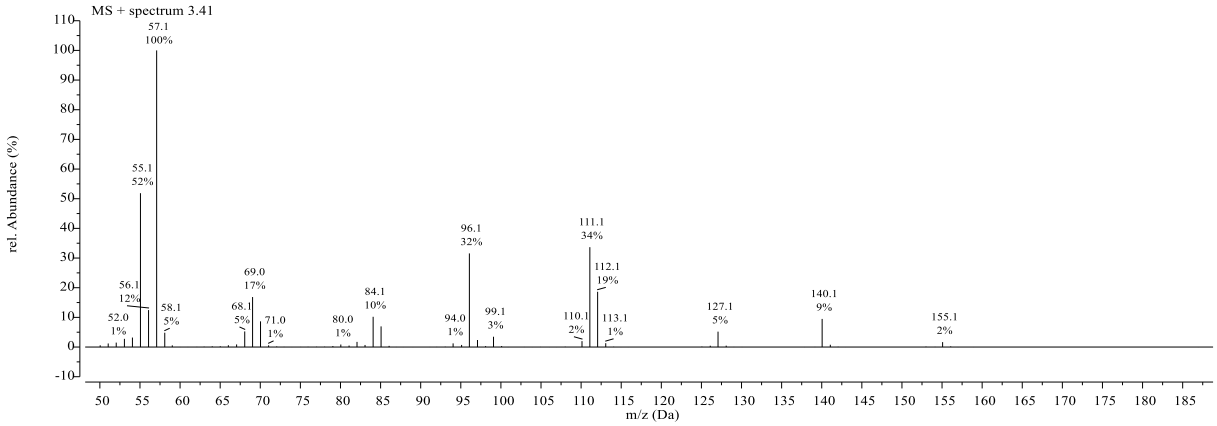

6.35
O
O
N
Ph
Retention time (min)

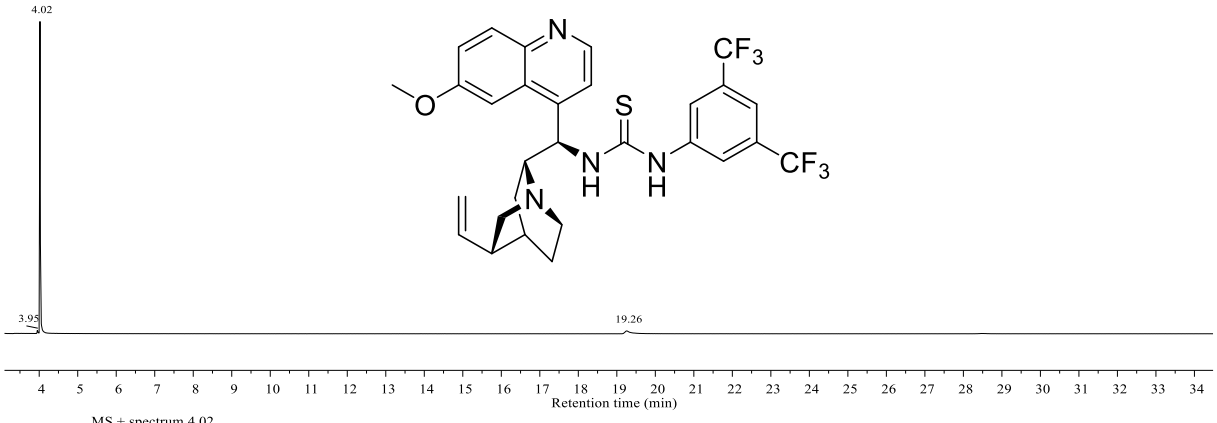

MS + spectrum 6.35
rel. Abundance (%)
77.0
100%
105.0
92%
117.0
63%
161.0
45%
51.0
56%
103.1
30%
50.0
26%
76.0
18%
105.8
10%
78.0
7%
83.8
9%
89.9
6%
103.9
6%
118.0
7%
52.5
8%
73.9
7%
m/z (Da)

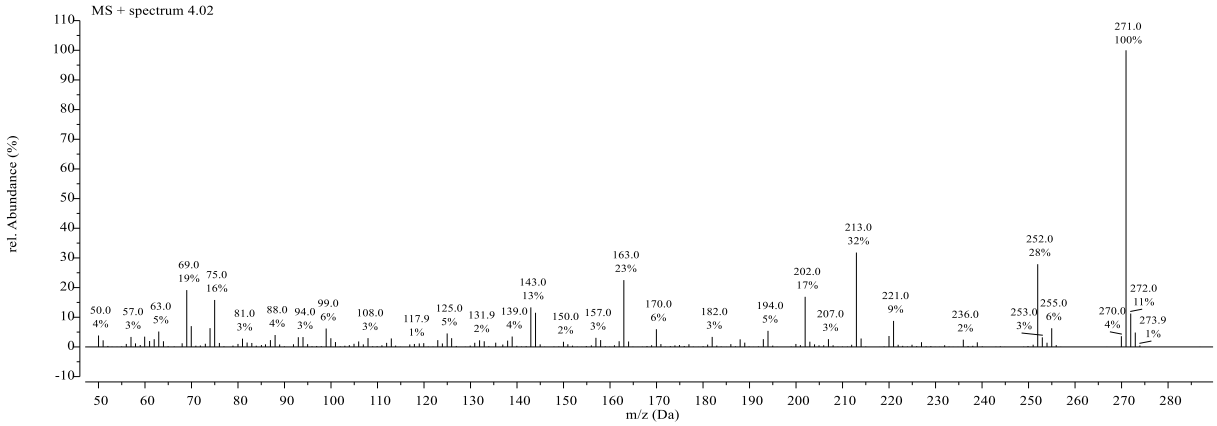

6.37
O
O
N
Ph
Retention time (min)


MS + spectrum 6.37
rel. Abundance (%)
105.0
100%
77.0
64%
51.0
26%
103.0
23%
131.0
25%
175.0
18%
76.0
13%
104.0
11%
130.0
15%
106.0
9%
78.0
5%
132.0
3%
147.0
4%
52.2
3%
63.0
2%
73.0
1%
102.0
1%
173.0
2%
176.0
2%
m/z (Da)

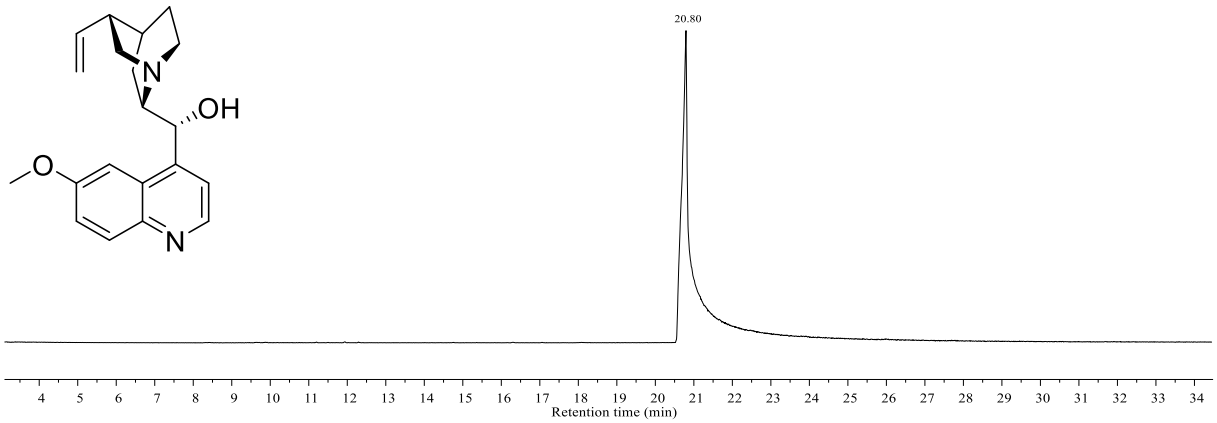


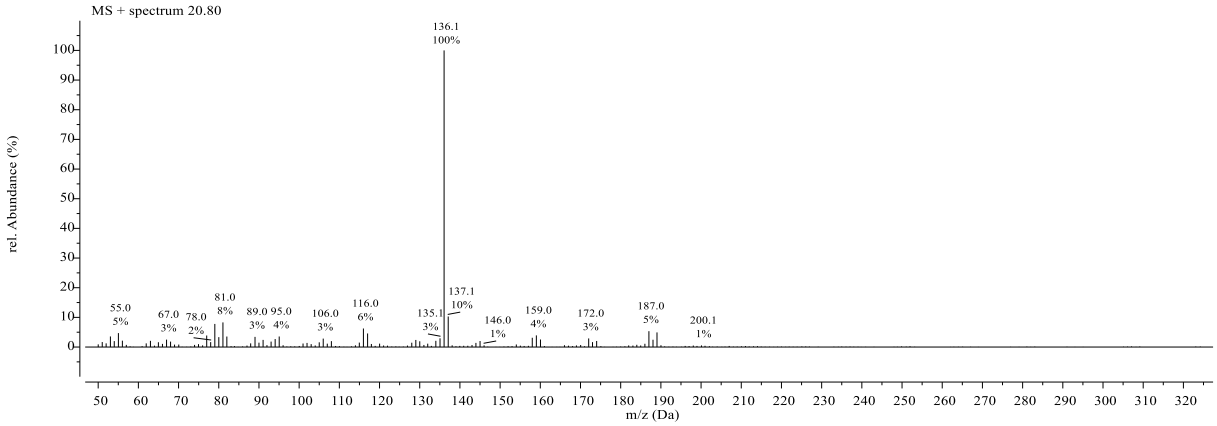


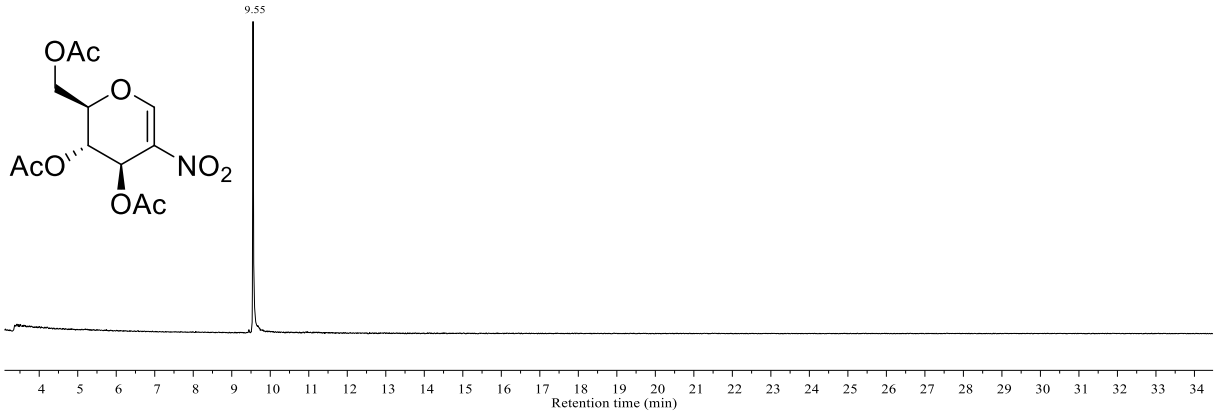


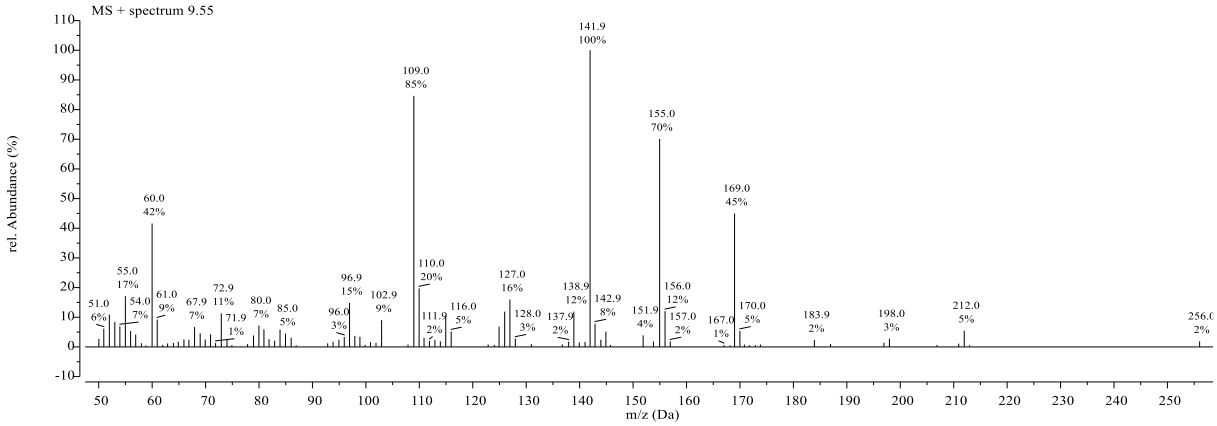


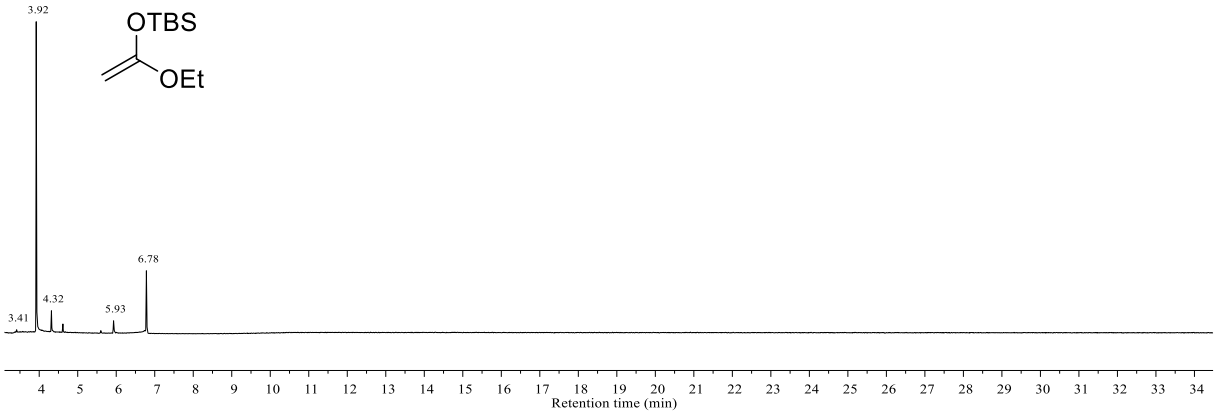
It should be noted that the catalyst shown above decomposes upon injection onto the GC-MS, and the species detected at t_R = 4.02 min. is 3,5-Bis-(trifluoromethyl)-phenylisothiocyanate.

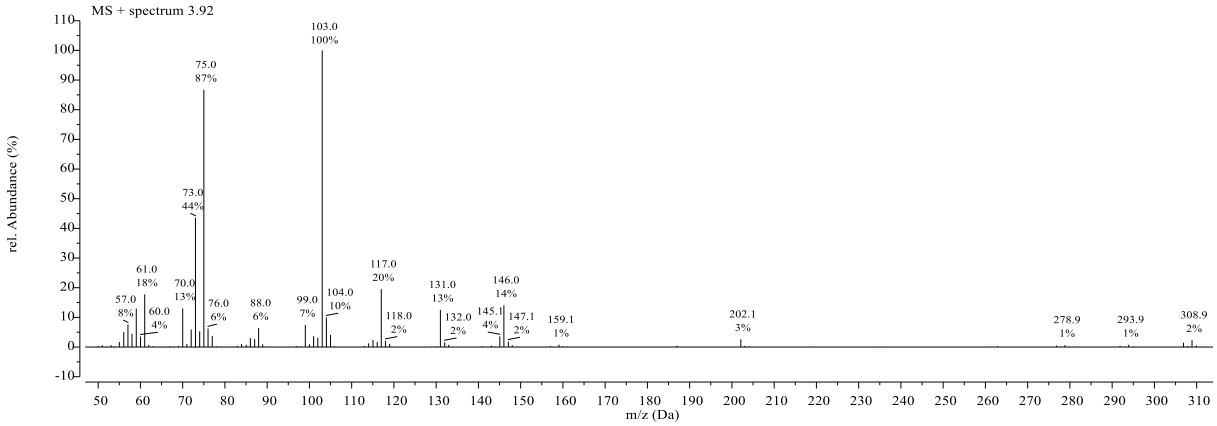

N
OH
O
N
20.80
Retention time (min)

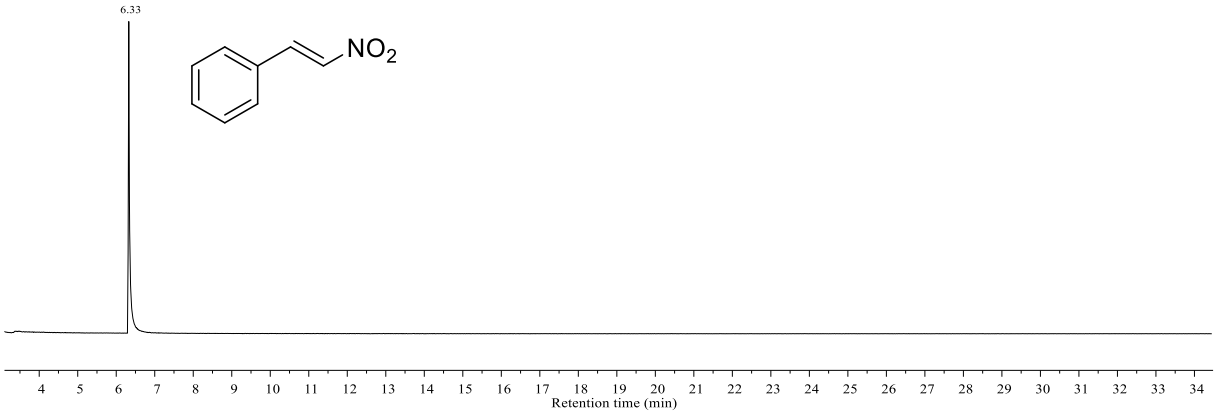

MS + spectrum 20.80
rel. Abundance (%)
136.1
100%
137.1
10%
55.0
5%
67.0
3%
78.0
2%
81.0
8%
89.0
3%
95.0
4%
106.0
3%
116.0
6%
135.1
3%
146.0
1%
159.0
4%
172.0
3%
187.0
5%
200.1
1%
m/z (Da)

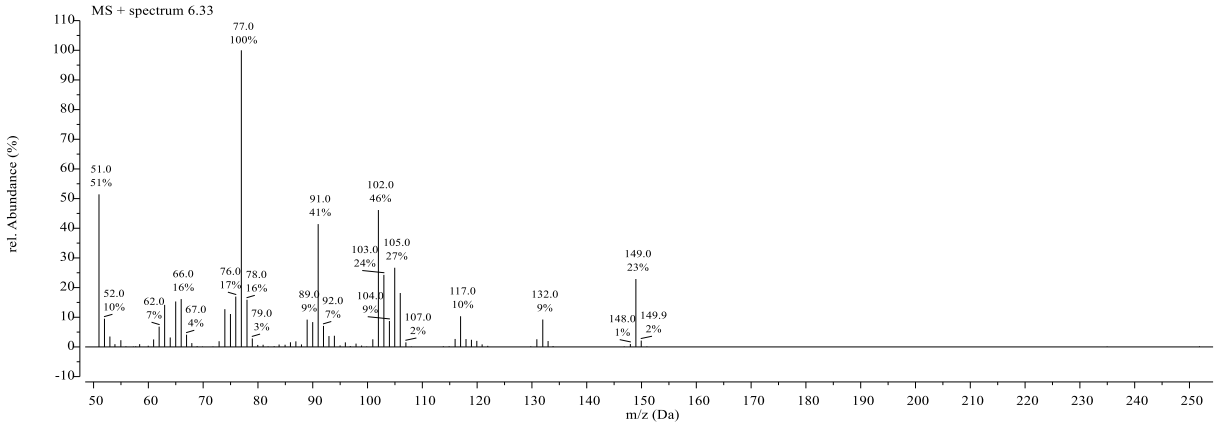

OAc
O
AcO
NO2
OAc
9.55
Retention time (min)


MS + spectrum 9.55
rel. Abundance (%)
141.9
100%
109.0
85%
155.0
70%
169.0
45%
60.0
42%
110.0
20%
127.0
16%
156.0
12%
55.0
17%
61.0
9%
72.9
11%
96.9
15%
102.9
9%
138.9
12%
142.9
8%
51.0
6%
54.0
7%
67.9
7%
71.9
1%
80.0
7%
85.0
5%
96.0
3%
111.9
2%
116.0
5%
128.0
3%
137.9
2%
151.9
4%
157.0
2%
167.0
1%
170.0
5%
183.9
2%
198.0
3%
212.0
5%
256.0
2%
m/z (Da)


3.92
OTBS
OEt
3.41
4.32
5.93
6.78
Retention time (min)

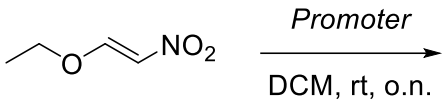

MS + spectrum 3.92
rel. Abundance (%)
m/z (Da)
103.0 100%
75.0 87%
73.0 44%
61.0 18%
70.0 13%
57.0 8%
60.0 4%
76.0 6%
88.0 6%
99.0 7%
104.0 10%
117.0 20%
118.0 2%
131.0 13%
132.0 2%
145.1 4%
146.0 14%
147.1 2%
159.1 1%
202.1 3%
278.9 1%
293.9 1%
308.9 2%


6.33
NO2
Retention time (min)


MS + spectrum 6.33
rel. Abundance (%)
m/z (Da)
77.0 100%
51.0 51%
91.0 41%
102.0 46%
103.0 24%
105.0 27%
52.0 10%
62.0 7%
66.0 16%
67.0 4%
76.0 17%
78.0 16%
79.0 3%
89.0 9%
92.0 7%
104.0 9%
107.0 2%
117.0 10%
132.0 9%
148.0 1%
149.0 23%
149.9 2%

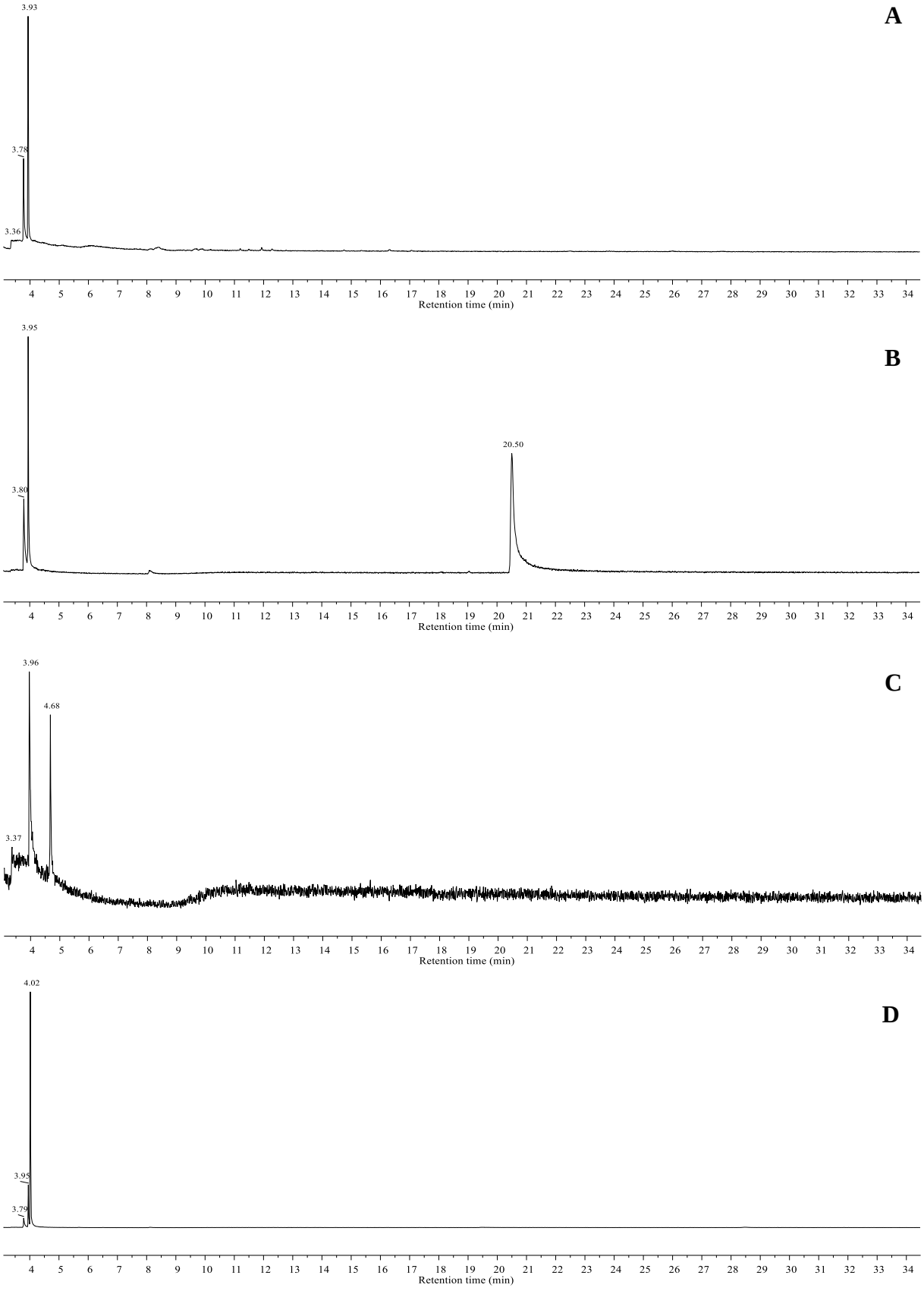
Additions to (1*E*)-1-Ethoxy-2-nitroethene

Blind Reactions

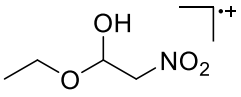


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

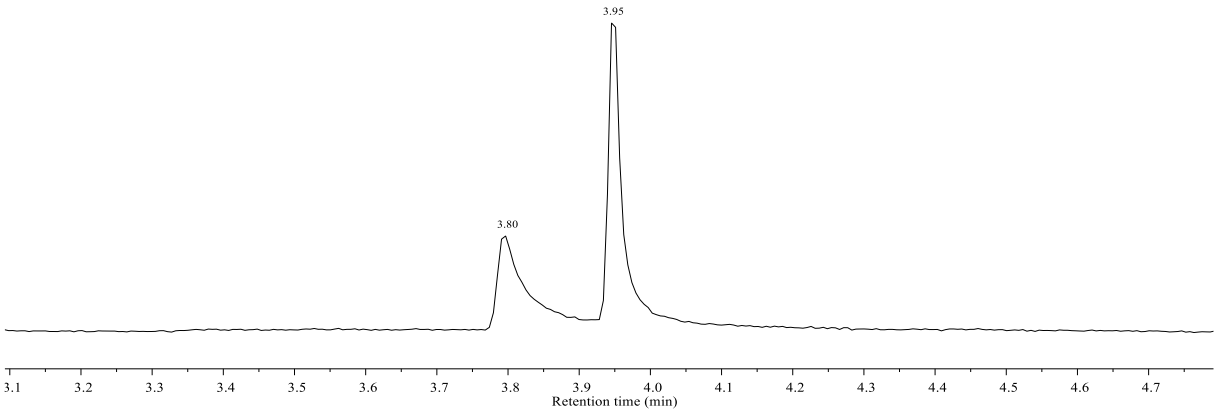
Entry	Compound	Retention time / min
1	Vinyl ether	3.79
2	Quinine	20.50
3	**130**	4.02
4	^{t}BuOH-adduct	4.68
5	Water adduct	3.95

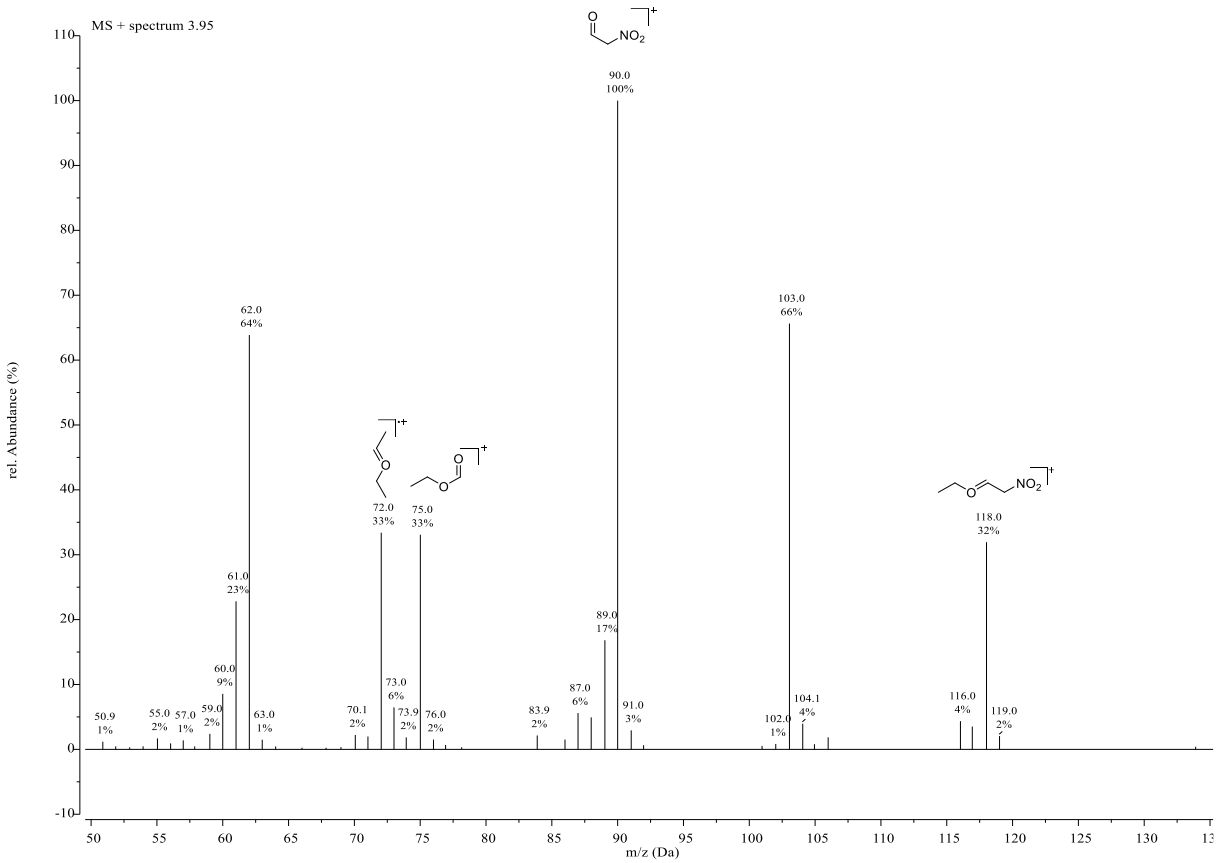

A
3.93
3.78
3.36
B
3.95
20.50
3.80
C
3.96
4.68
3.37
D
4.02
3.95
3.79
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **B**

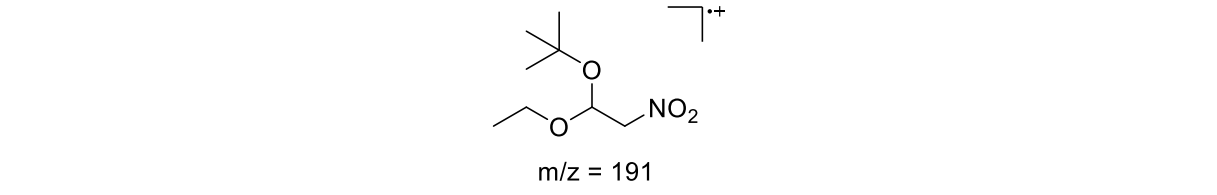


m/z = 135

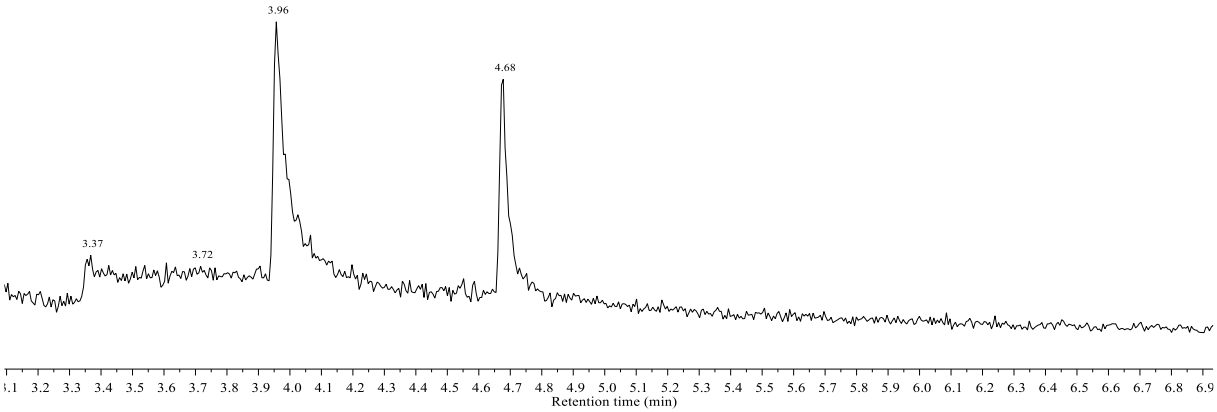


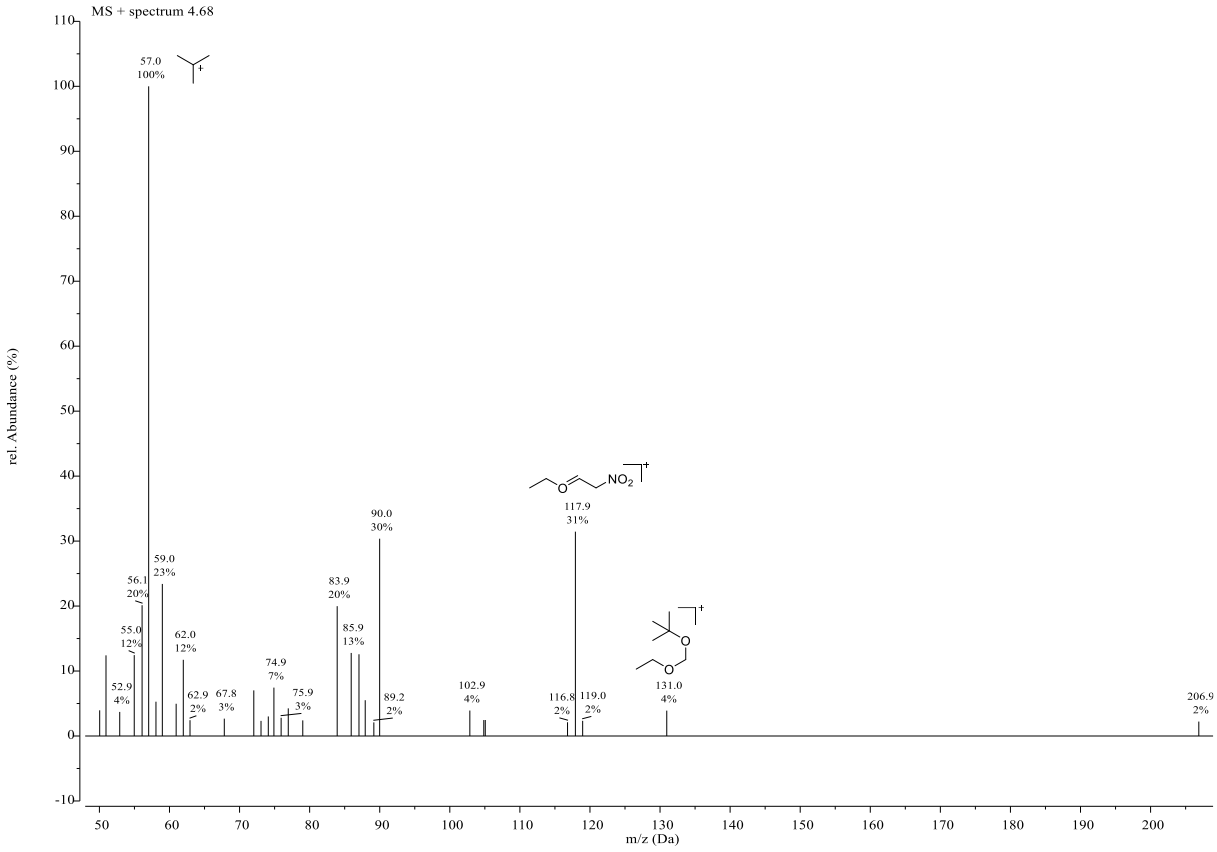


Chromatogram **C**

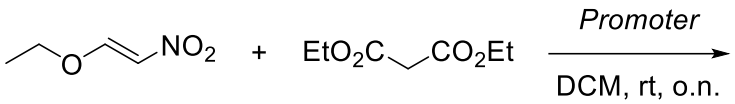


m/z = 191



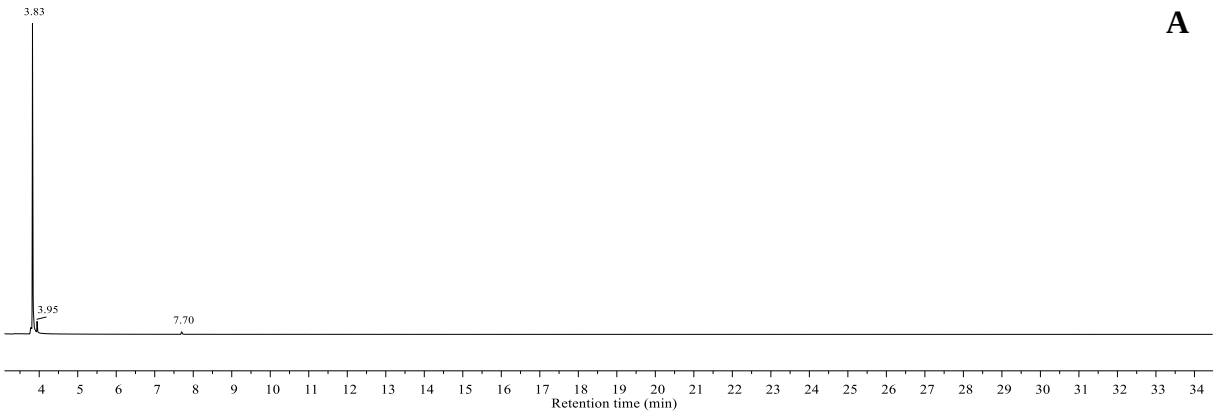


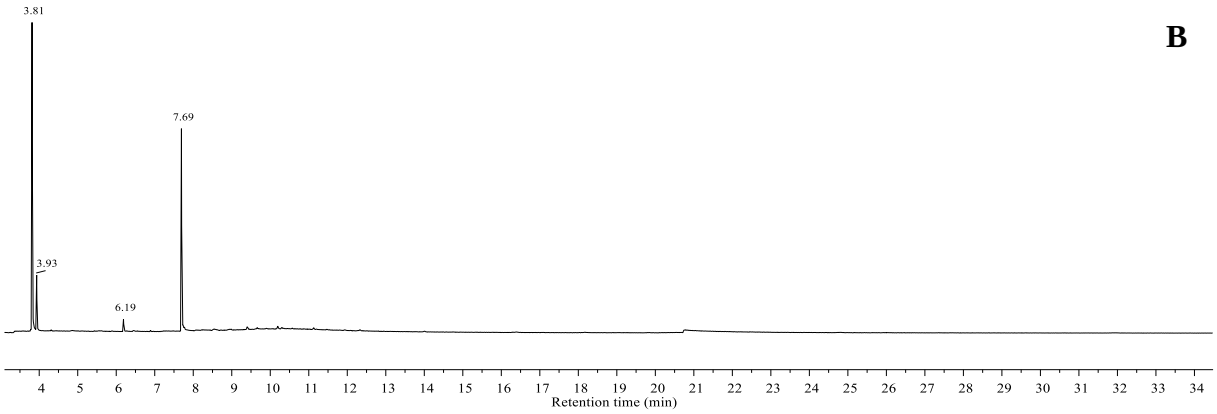
Addition of Diethyl Malonate

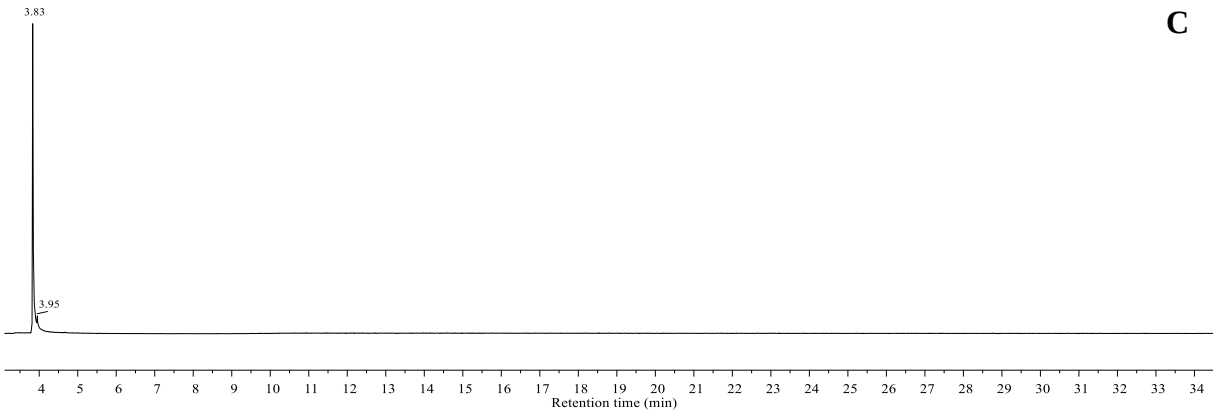


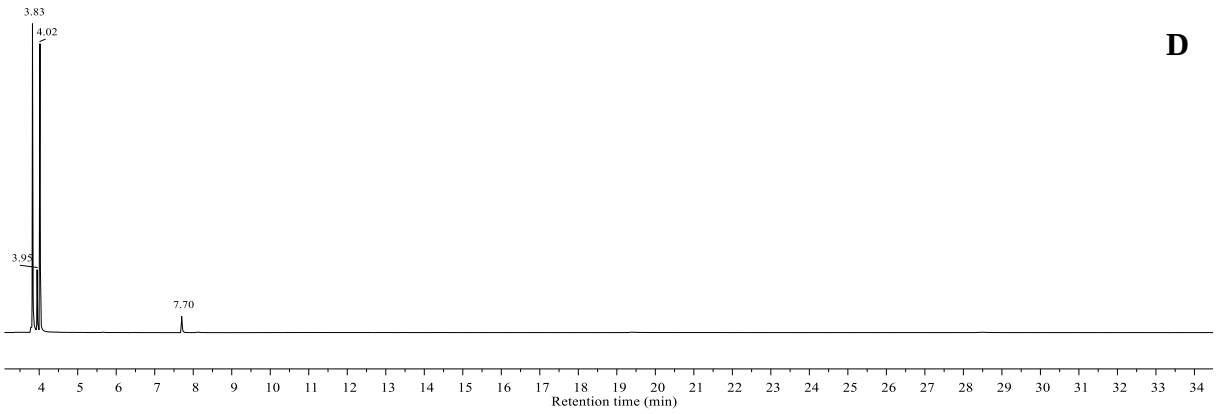
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	3.79
2	Quinine	20.50
3	**130**	4.02
4	Diethyl Malonate	3.84
5	Water Adduct	3.95
6	Product	7.70

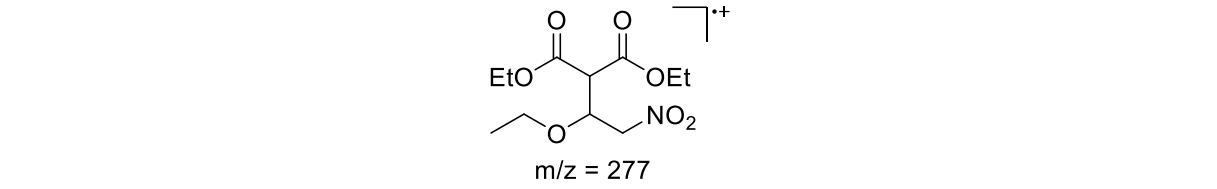

A
3.83
3.95
7.70
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

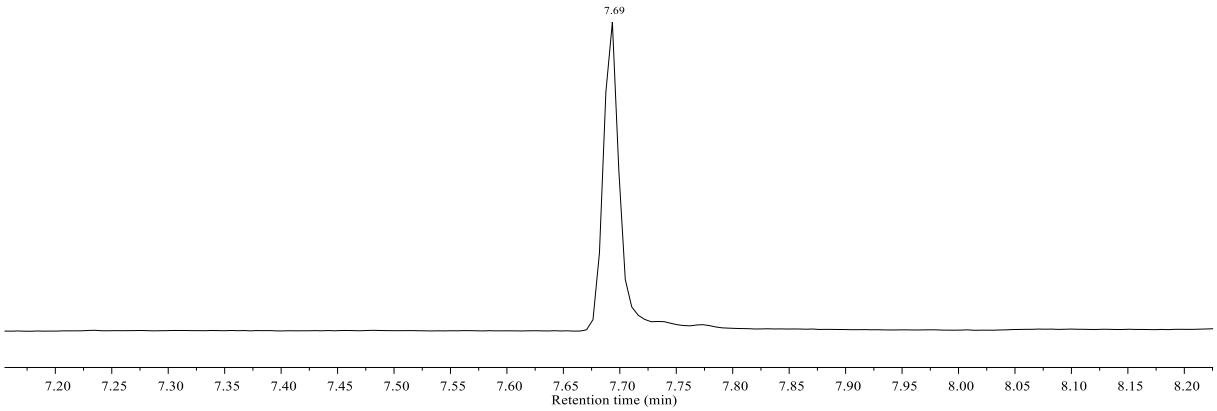

B
3.81
7.69
3.93
6.19
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

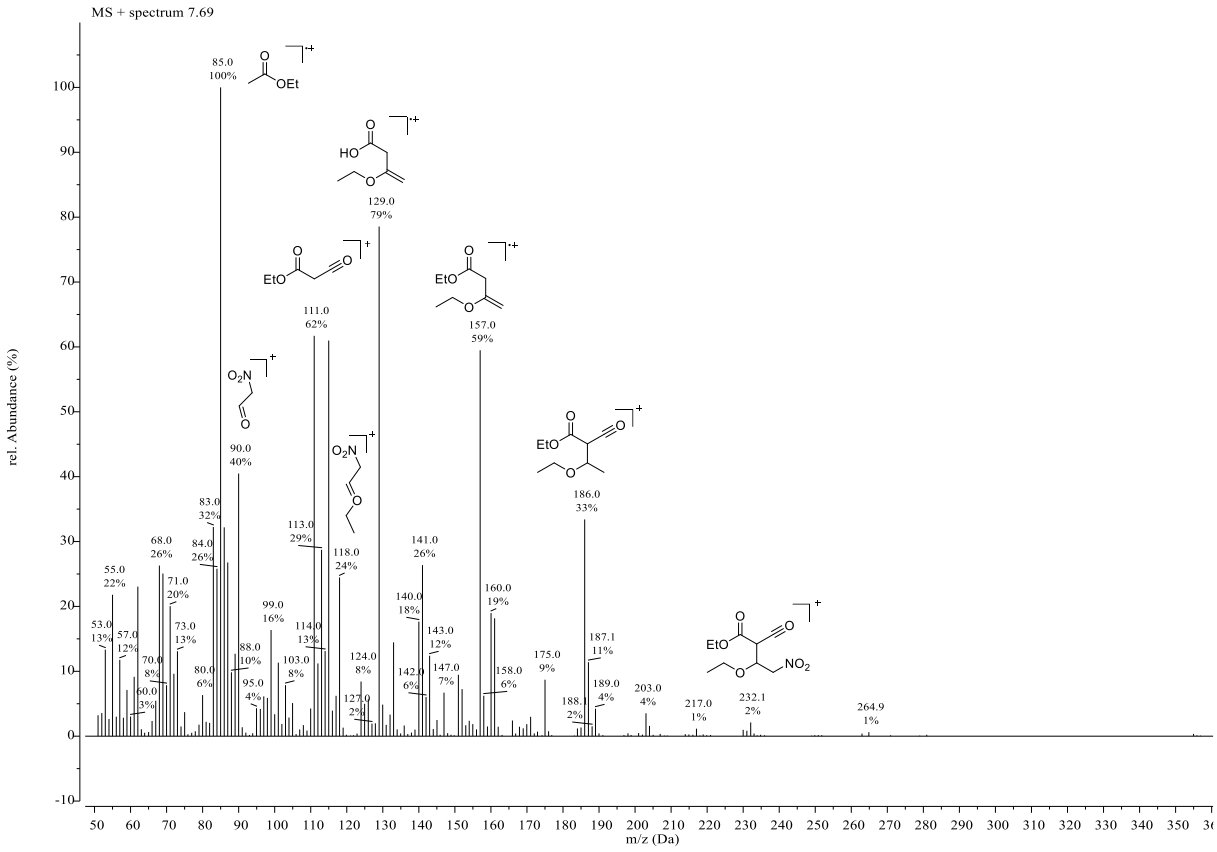

C
3.83
3.95
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


D
3.83
4.02
3.95
7.70
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

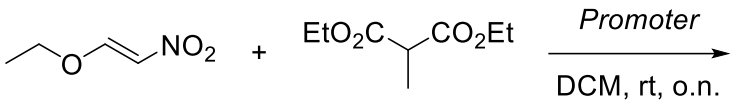
Chromatogram **B**





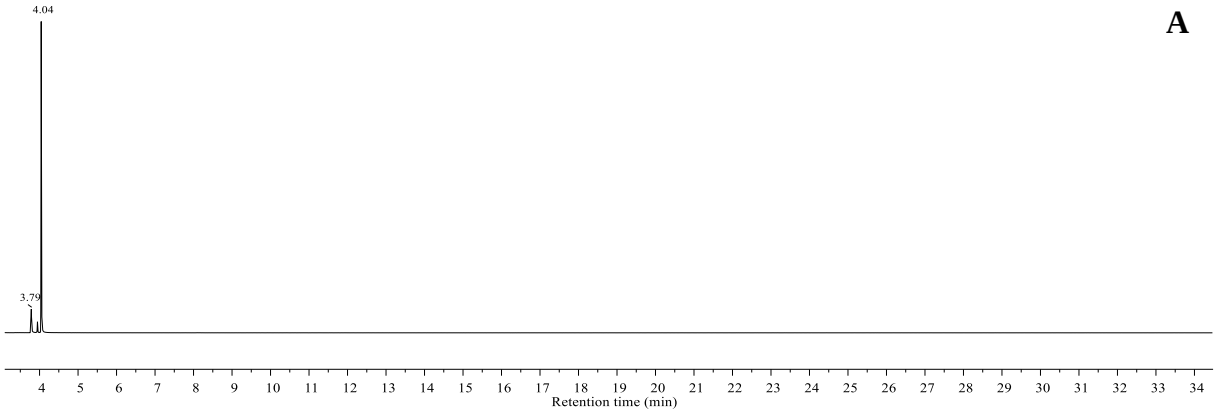


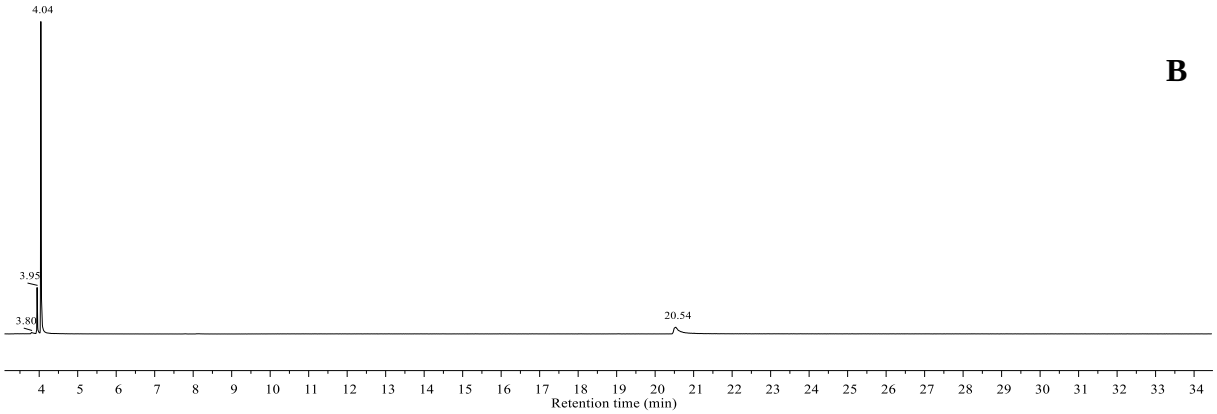
Addition of Diethyl Methylmalonate

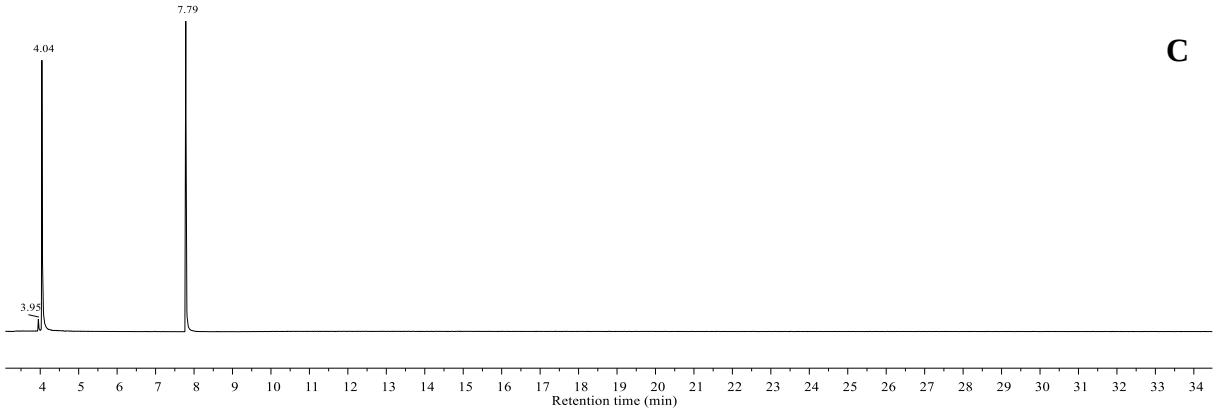


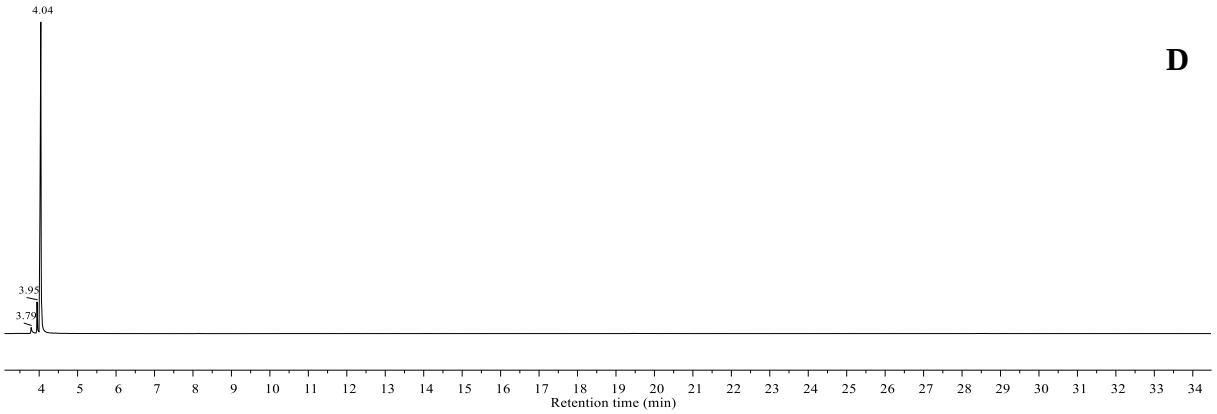
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	3.79
2	Quinine	20.50
3	**130**	4.02
4	Diethyl Methylmalonate	4.05
6	Water Adduct	3.95
7	Product	7.79

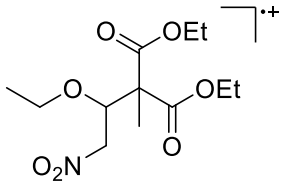

A
4.04
3.79
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


B
4.04
3.95
3.80
20.54
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

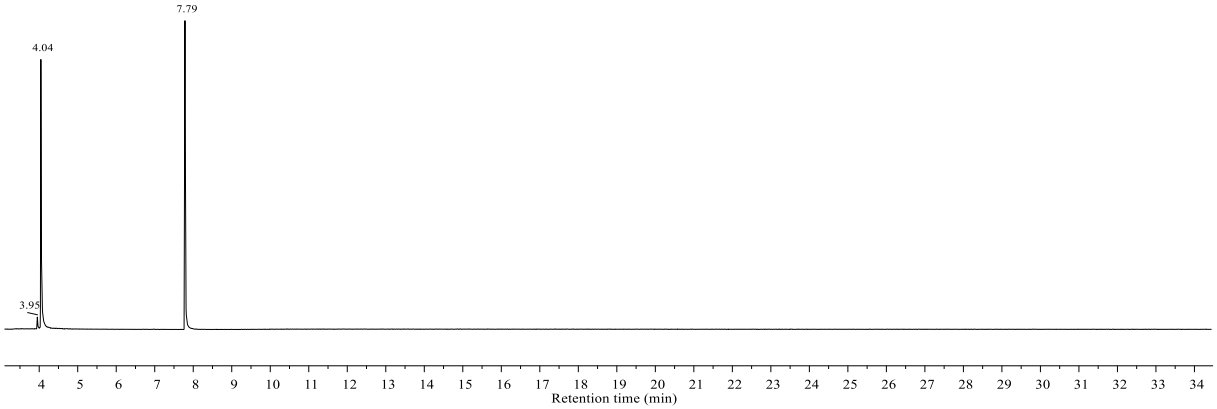

C
7.79
4.04
3.95
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

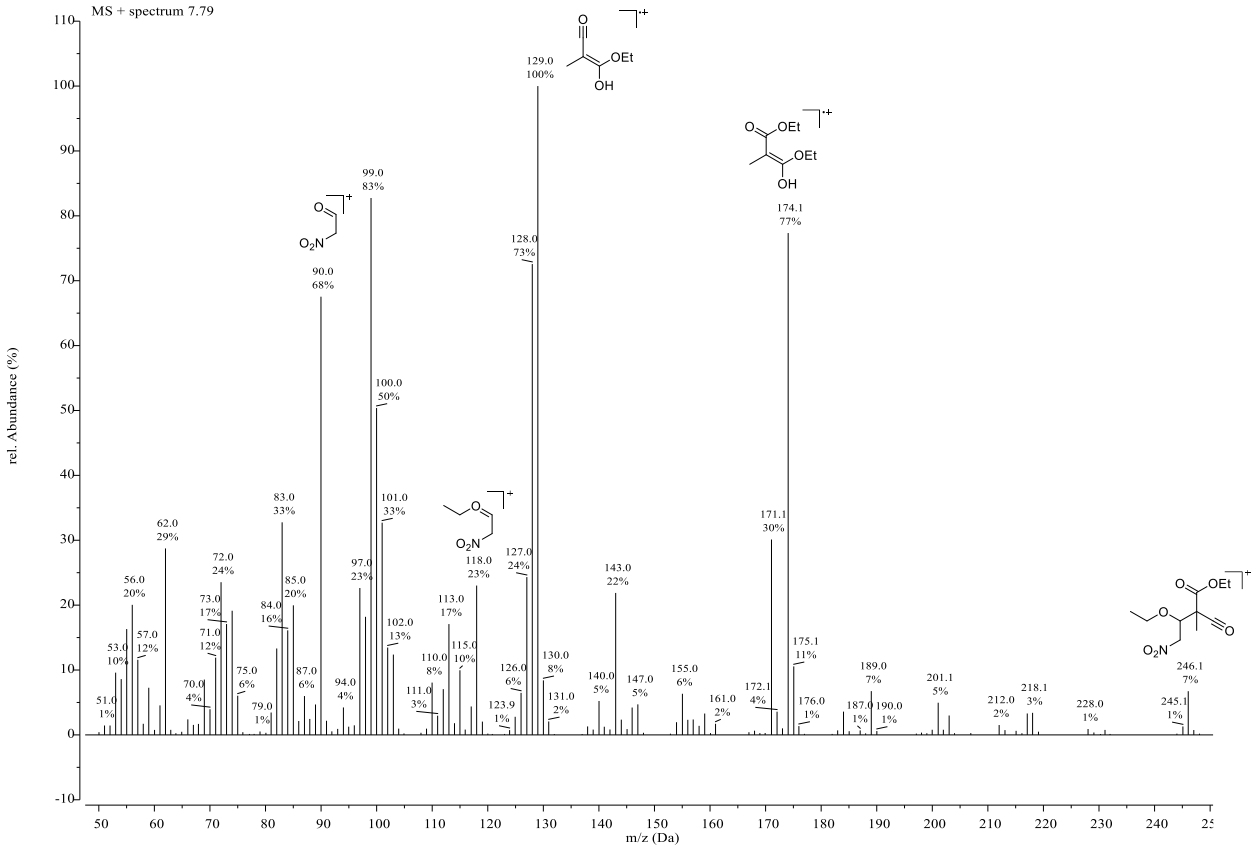

D
4.04
3.95
3.79
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatgram **C**

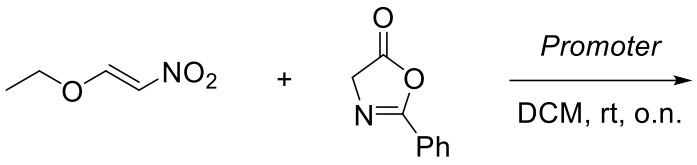


m/z = 291



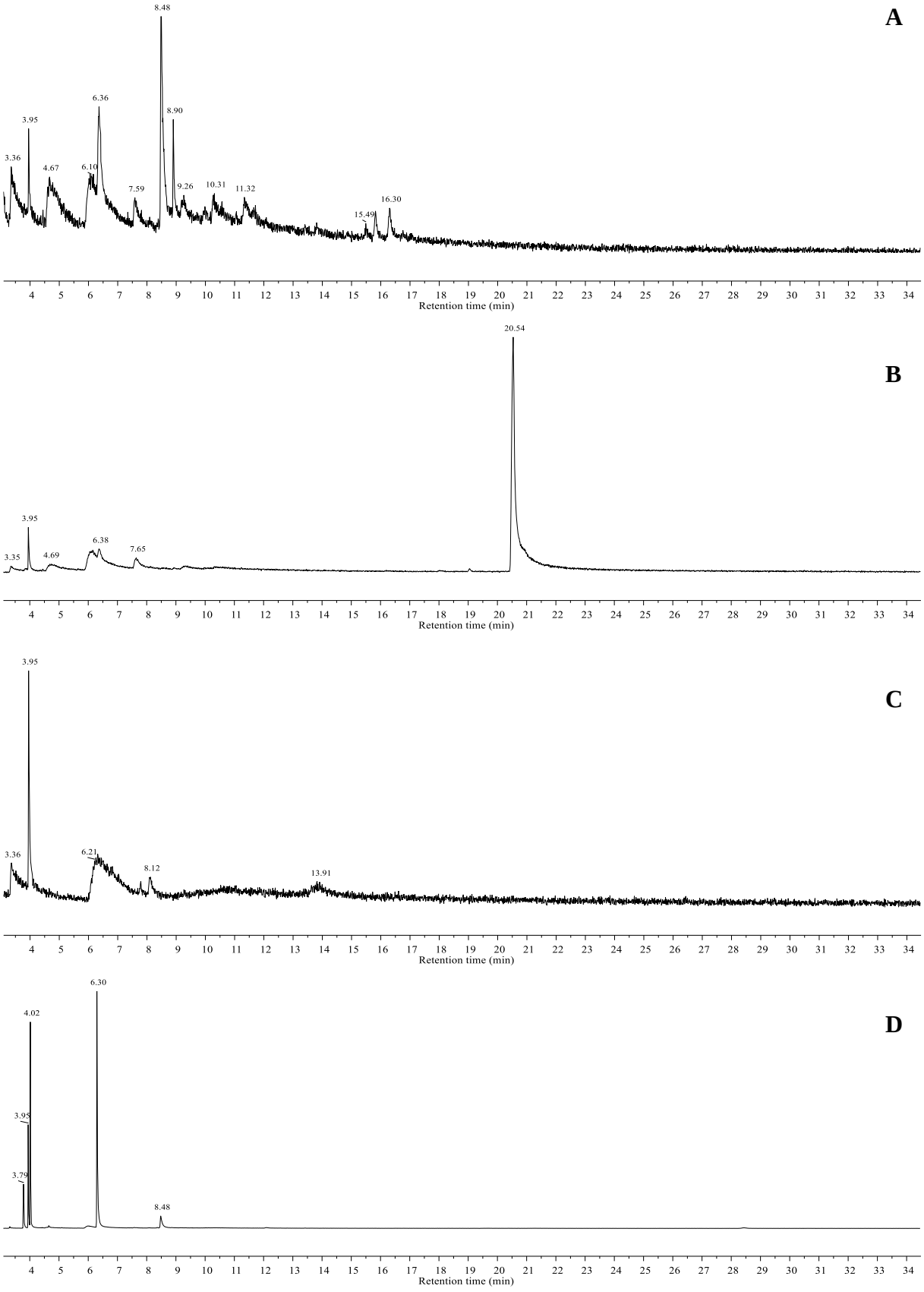


Addition of 2-Phenyl-5(4*H*)-oxazolone

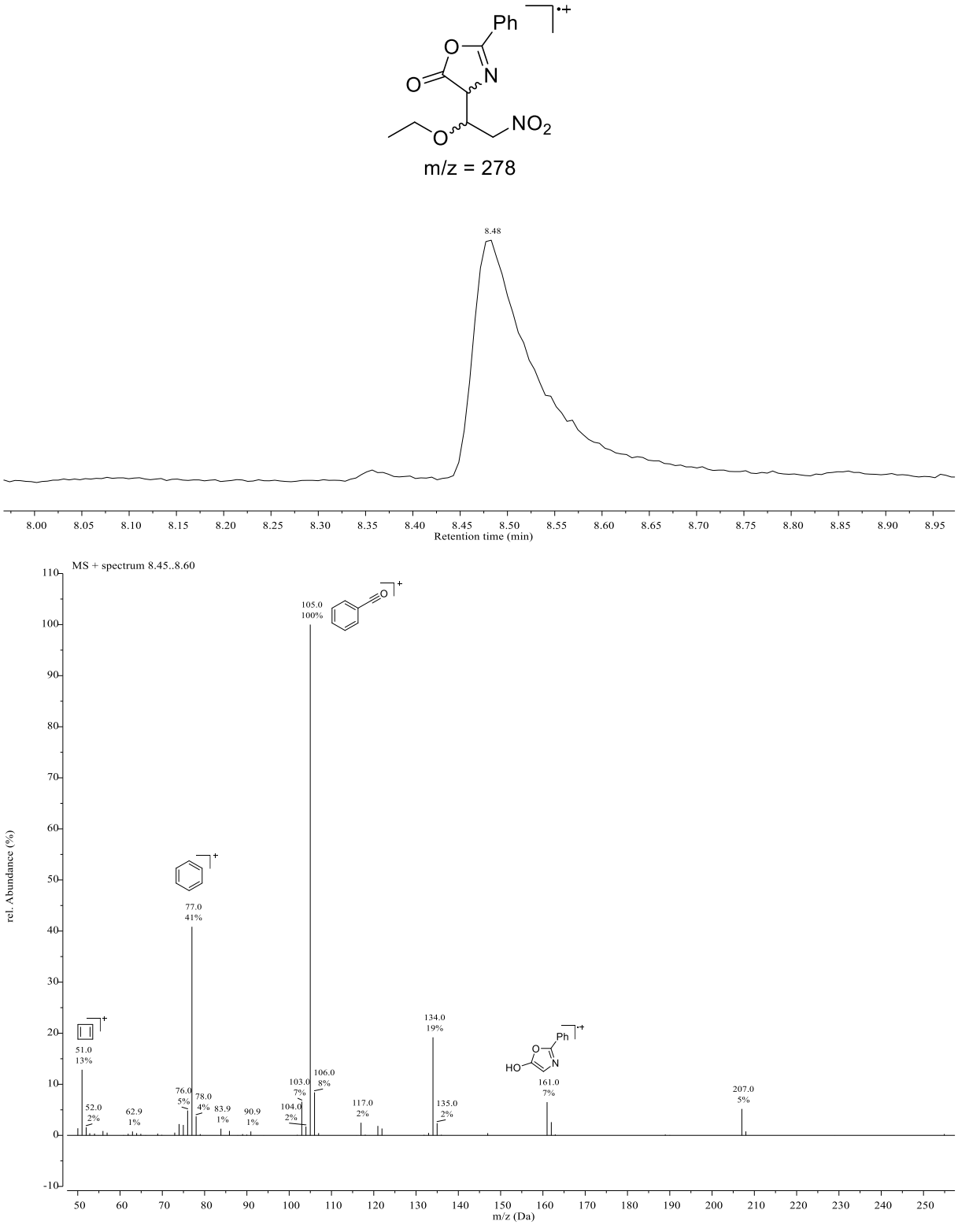


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	3.79
2	Quinine	20.50
3	**130**	4.02
4	Azlactone	6.35
5	Water Adduct	3.95
6	Product	8.48

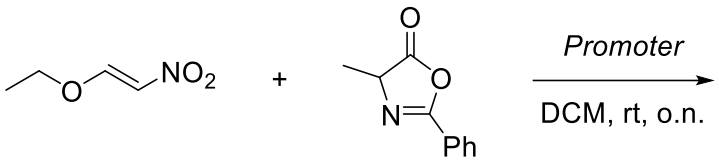

A
8.48
6.36
3.95
8.90
3.36
4.67
6.10
7.59
9.26
10.31
11.32
15.49
16.30
Retention time (min)
B
20.54
3.95
6.38
3.35
4.69
7.65
Retention time (min)
C
3.95
3.36
6.21
8.12
13.91
Retention time (min)
D
6.30
4.02
3.95
3.79
8.48
Retention time (min)

Chromatogram **D**



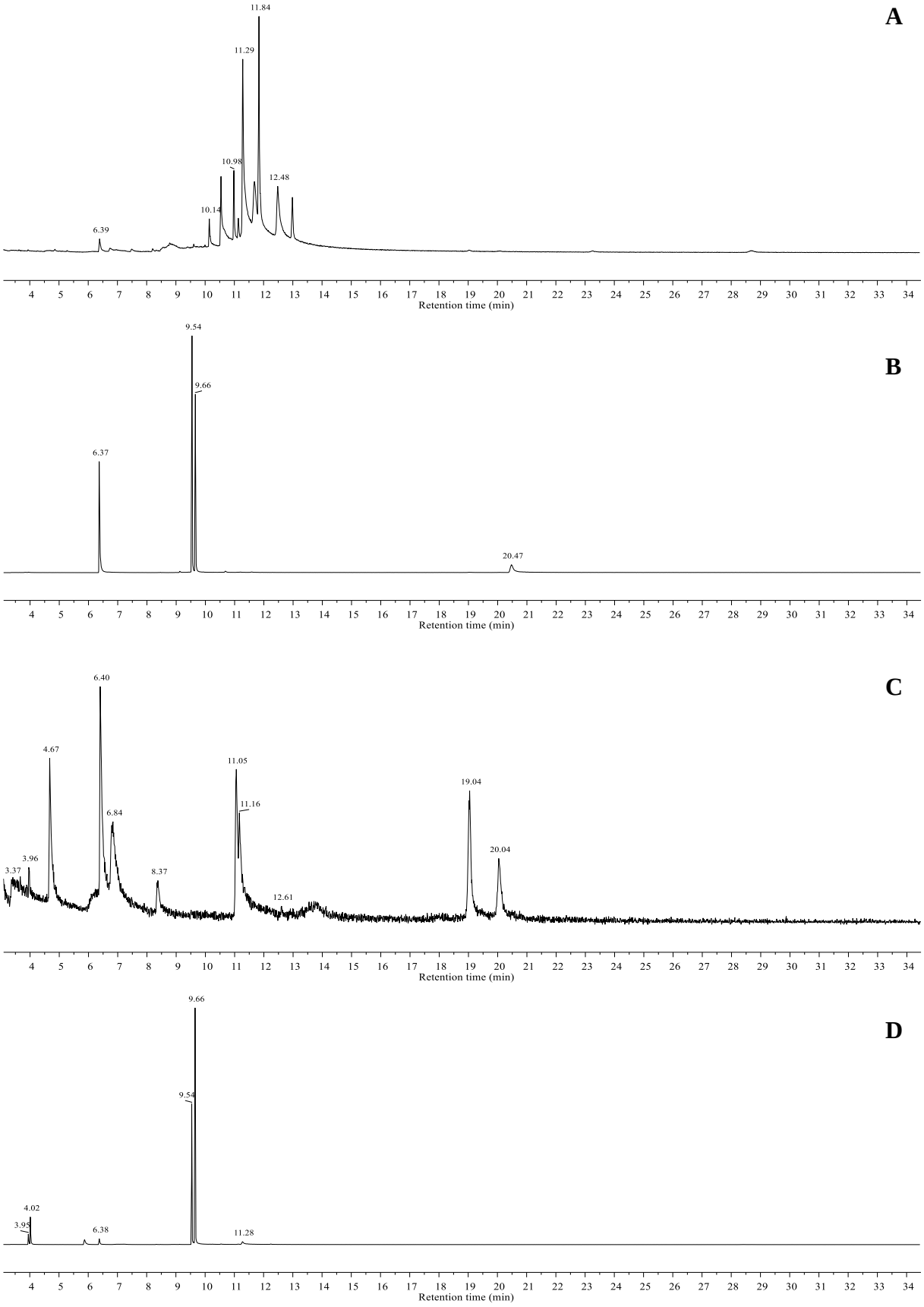
Due to a lack of sufficient fragments, the presence of the desired compound was also confirmed via HRMS (ESI) of the crude reaction mixture after an acidic workup with 1 N HCl.

Addition of 2-Phenyl-4-methyl-5(4*H*)-oxazolone

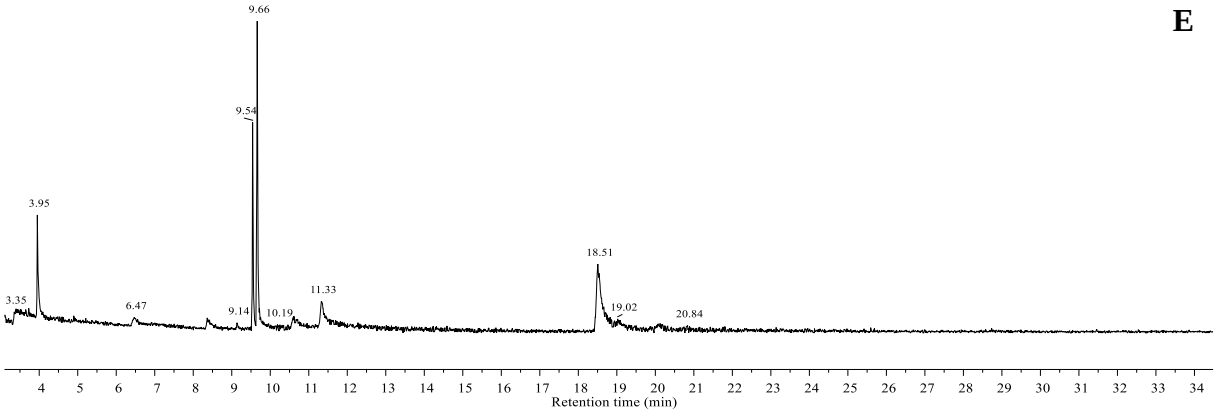


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**
5	$(DHQ)_2PHAL$	1.2	**E**
6	LiHMDS	3.5	**F**

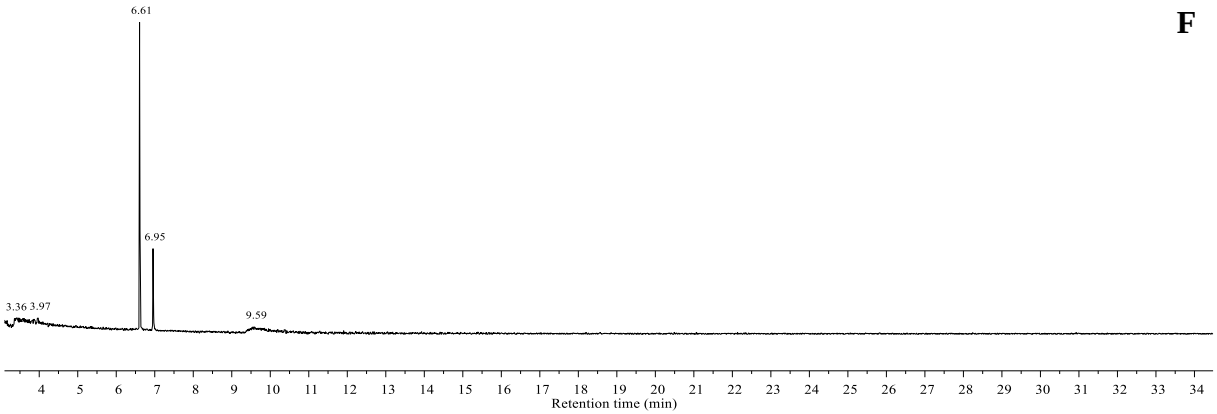
Entry	Compound	Retention time / min
1	Vinyl ether	3.79
2	Quinine	20.50
3	**130**	4.02
4	Azlactone	6.37
5	Water Adduct	3.95
6	Product	9.54 & 9.66
7	Azlactone Dimer	19.04 & 20.04


A
11.84
11.29
10.98
12.48
10.14
6.39
B
9.54
9.66
6.37
20.47
C
6.40
4.67
11.05
19.04
11.16
6.84
3.96
3.37
8.37
20.04
12.61
D
9.66
9.54
4.02
3.95
6.38
11.28
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

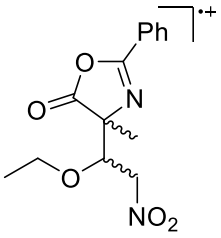
E


9.66
9.54
3.95
18.51
11.33
3.35
6.47
9.14
10.19
19.02
20.84
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

F


6.61
6.95
3.36 3.97
9.59
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **B**



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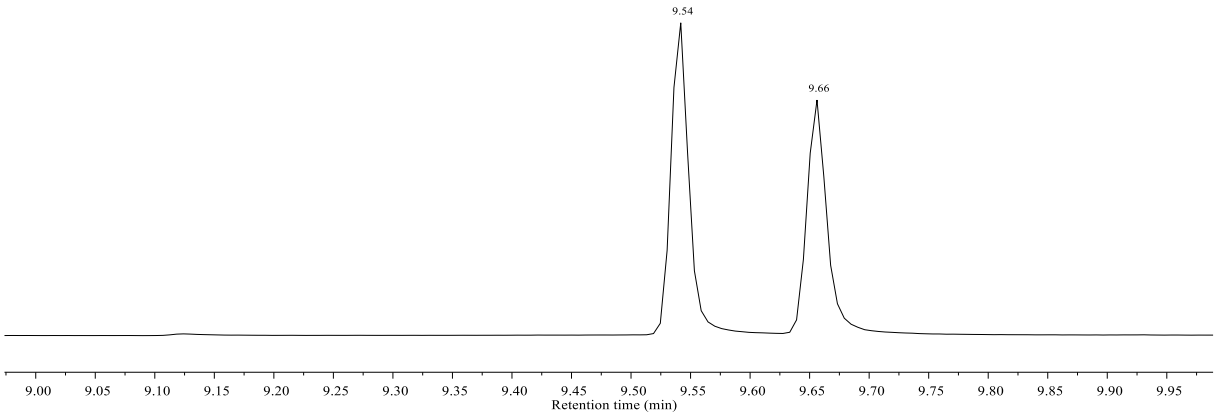
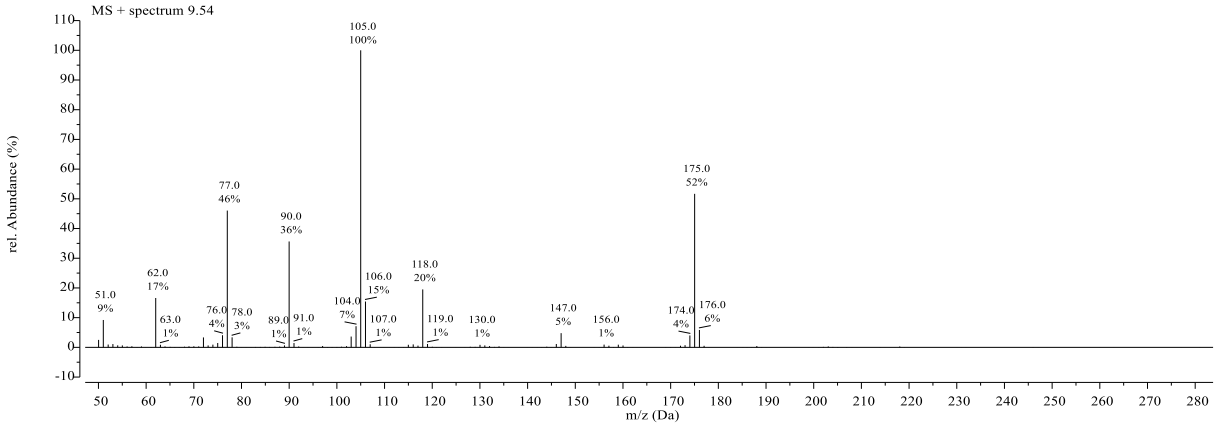
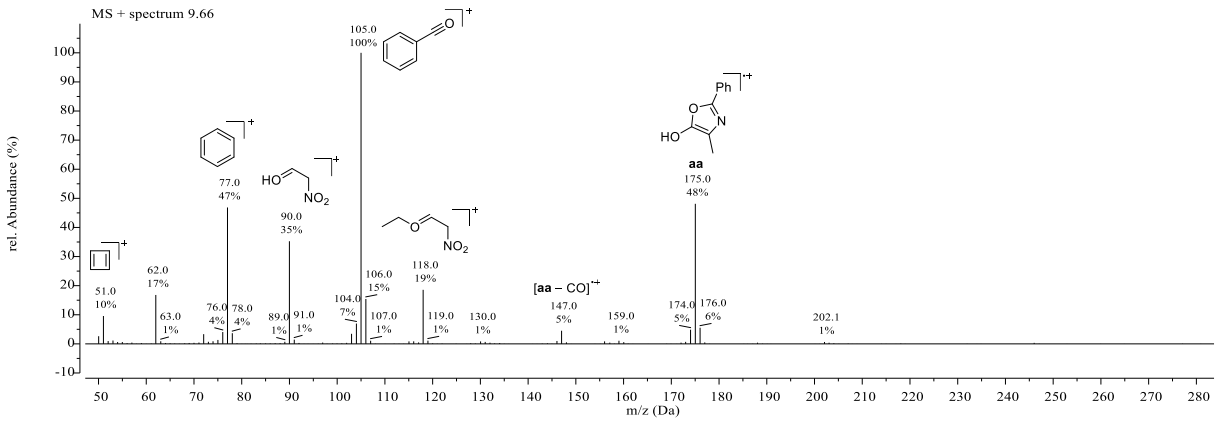
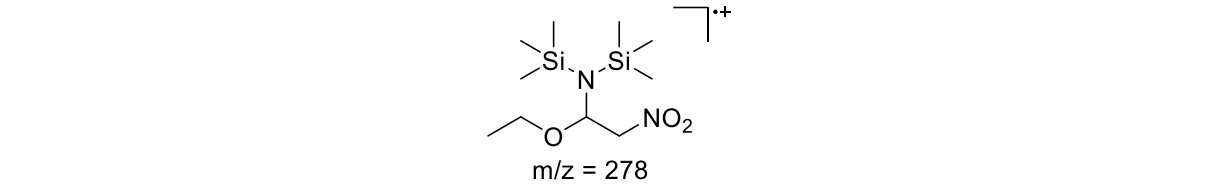


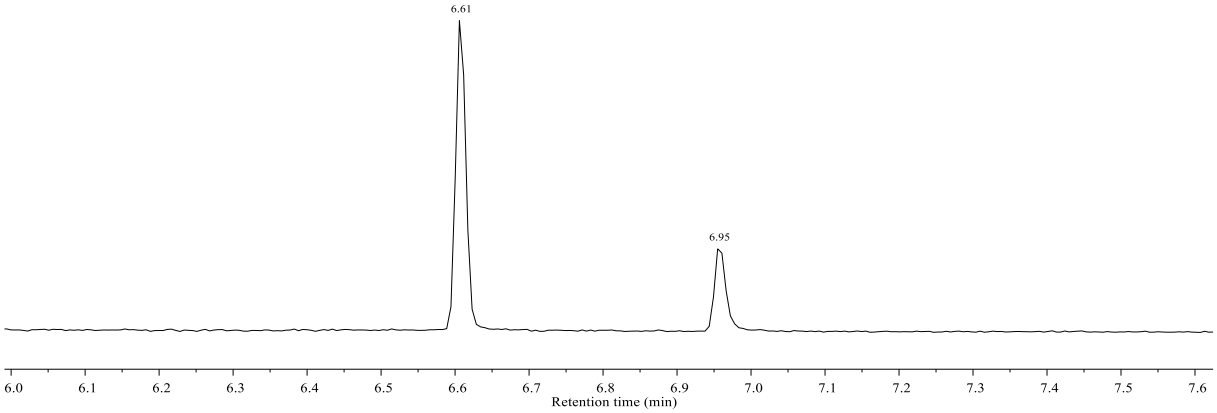


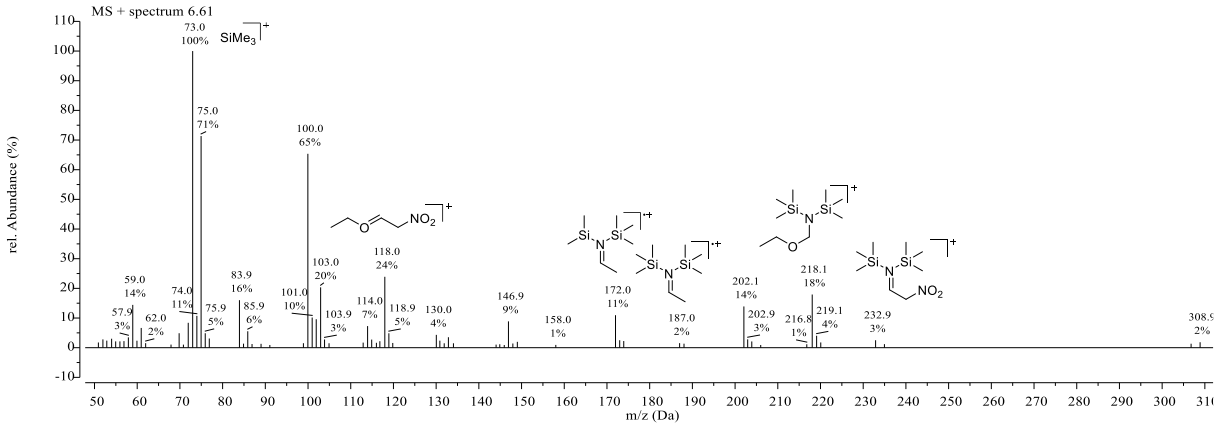


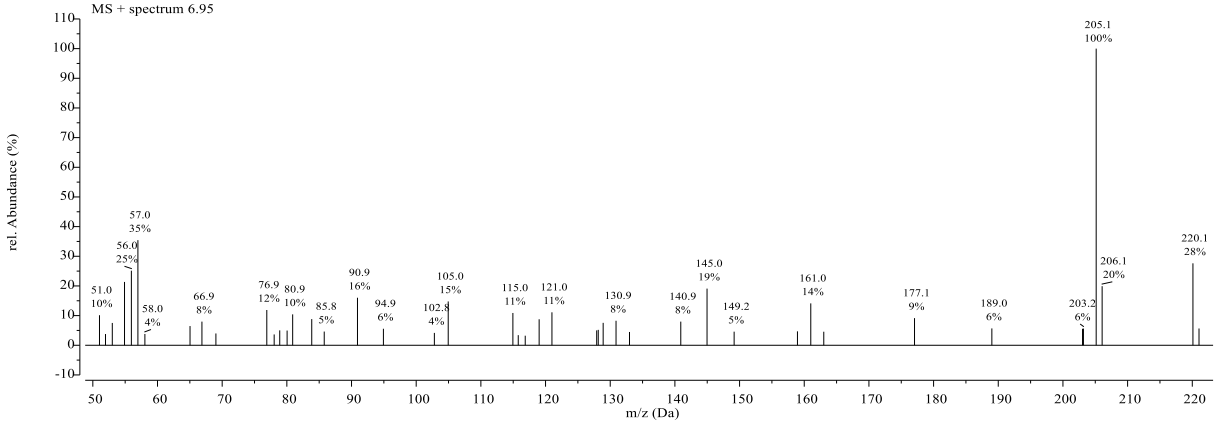
In Addition to fragmentation analysis, HRMS measurements were carried out to confirm the presence of the desired product in the reaction mixture.

Chromatogram **F**

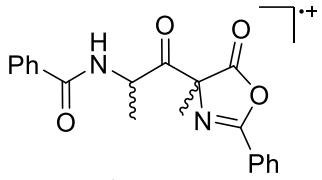




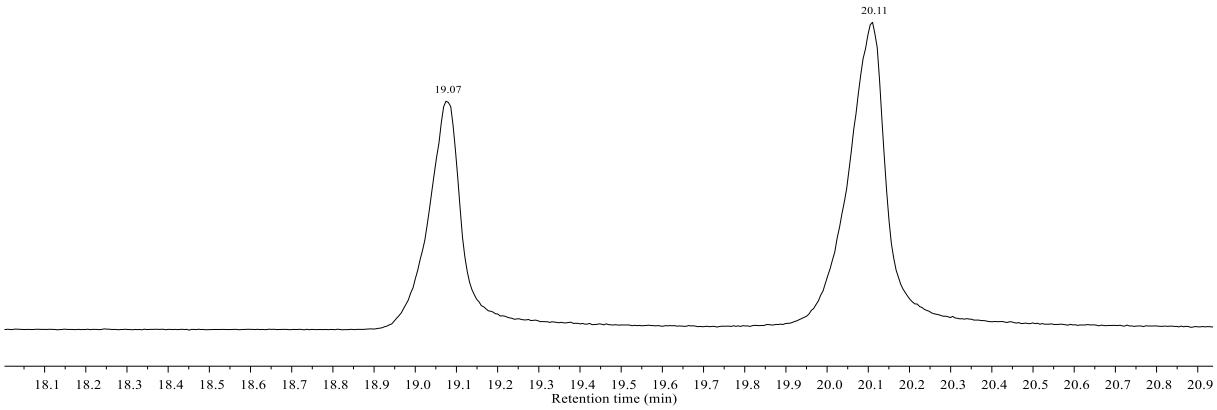


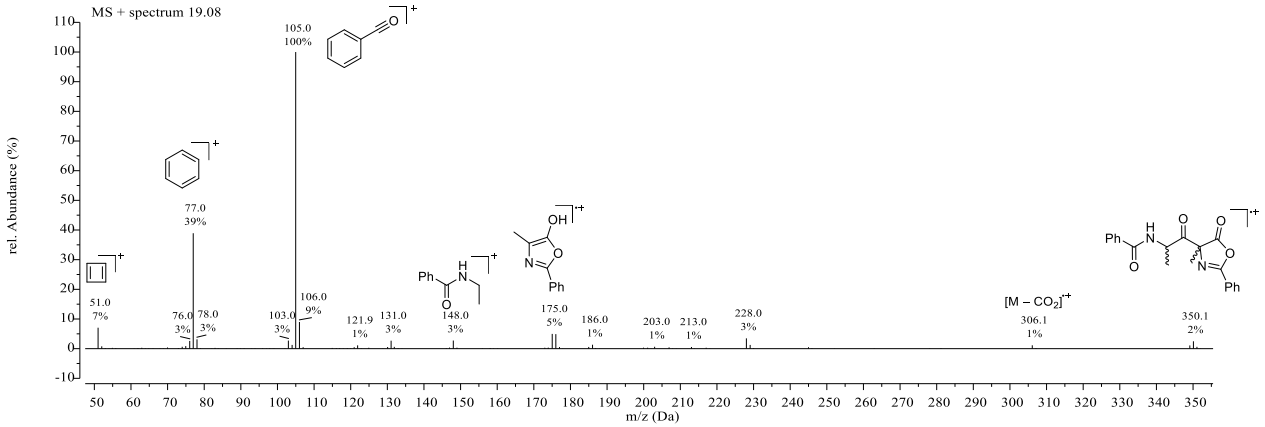


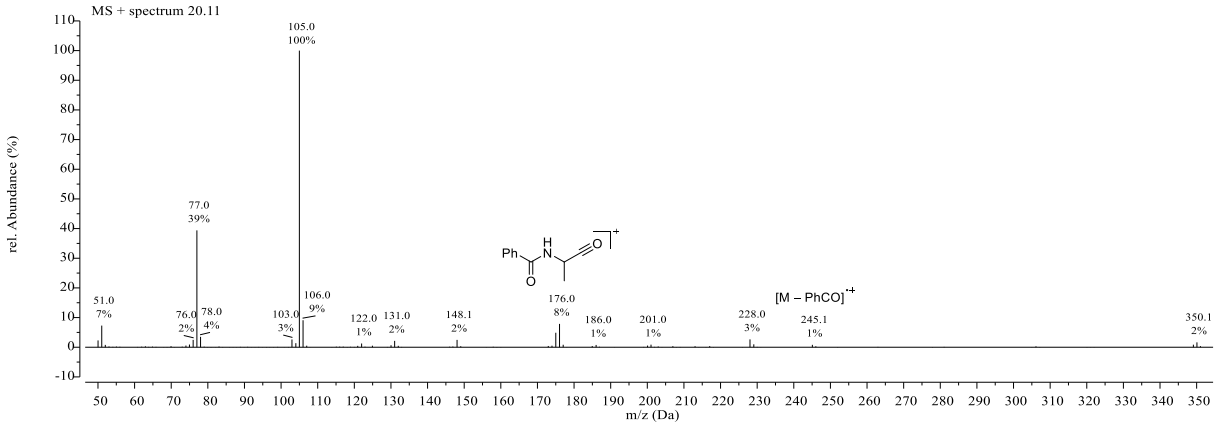
Self-acylation product of 2-Phenyl-4-methyl-5(4*H*)-oxazolone



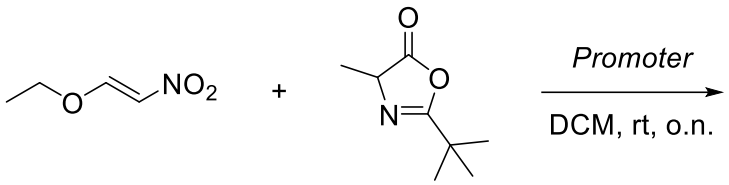
m/z = 350





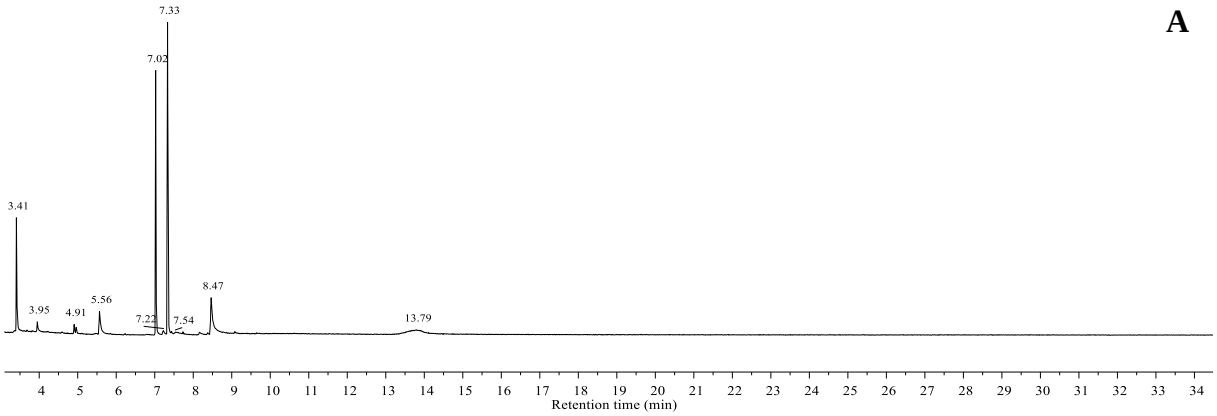


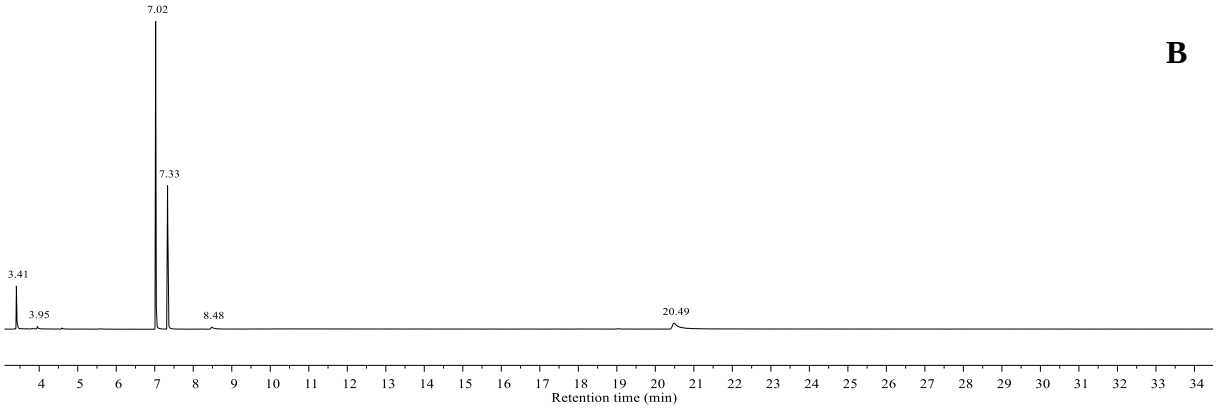
Addition of 2-*tert*-Butyl-4-methyl-5(4*H*)-oxazolone

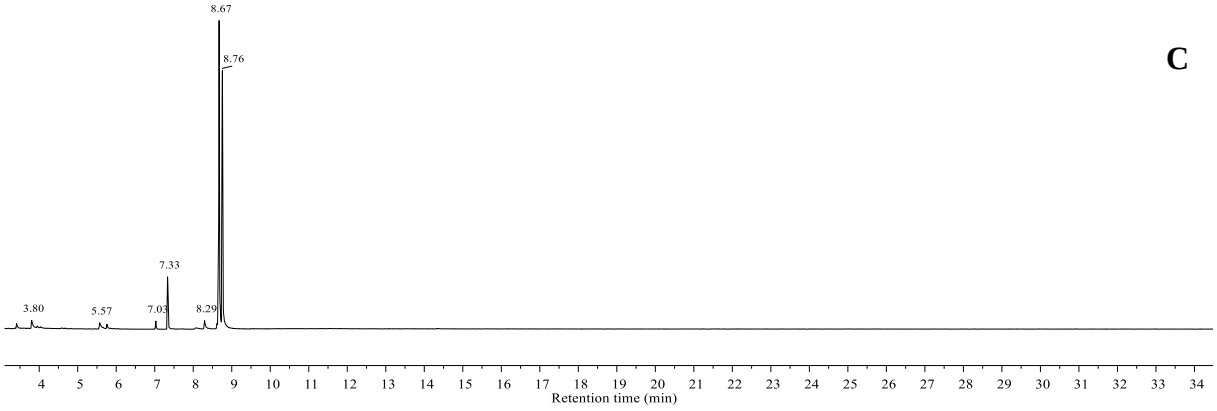


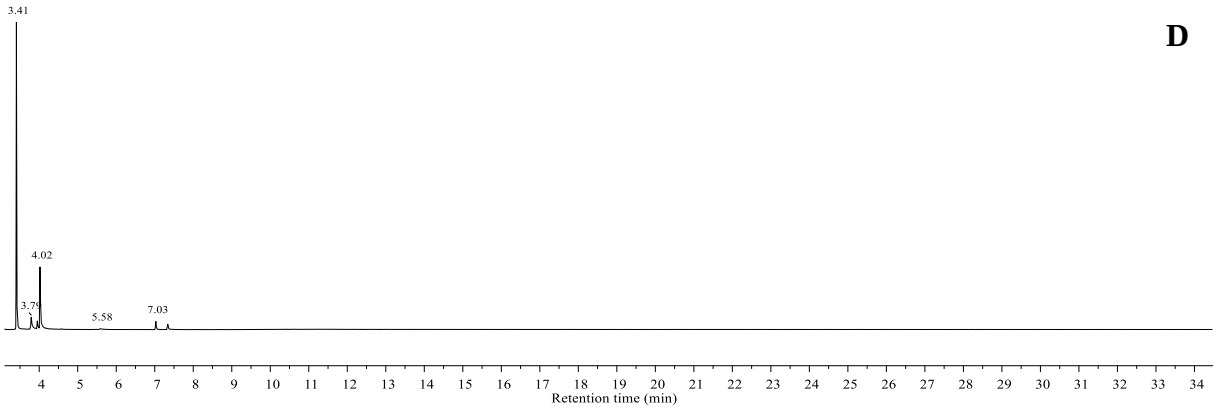
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	3.79
2	Quinine	20.50
3	**130**	4.02
4	Azlactone	3.41
5	Water Adduct	3.95
6	Product	7.02 & 7.33
7	Azlactone Dimer	8.67 & 8.76

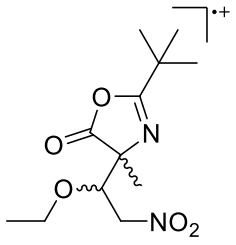

A
7.33
7.02
3.41
3.95
4.91
5.56
7.22
7.54
8.47
13.79
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


B
7.02
7.33
3.41
3.95
8.48
20.49
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


C
8.67
8.76
7.33
3.80
5.57
7.03
8.29
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


D
3.41
4.02
3.79
5.58
7.03
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **B**



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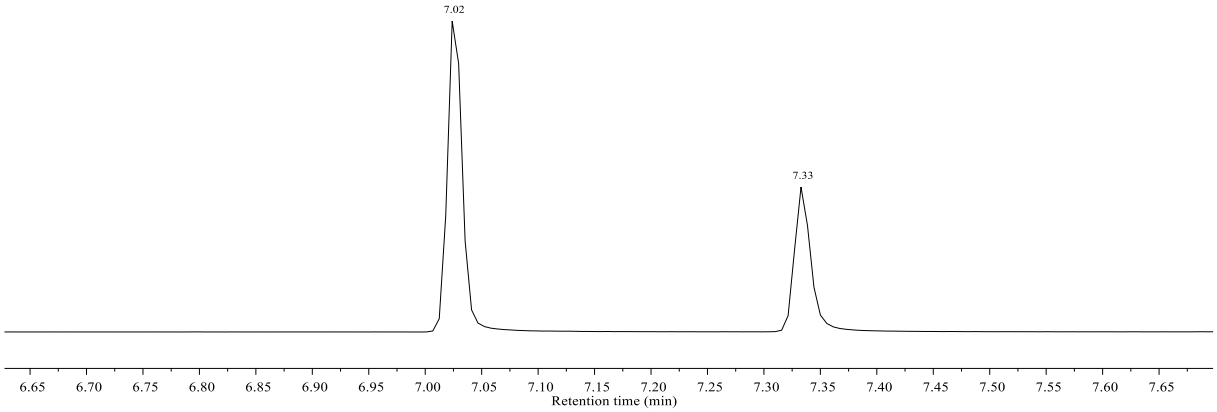
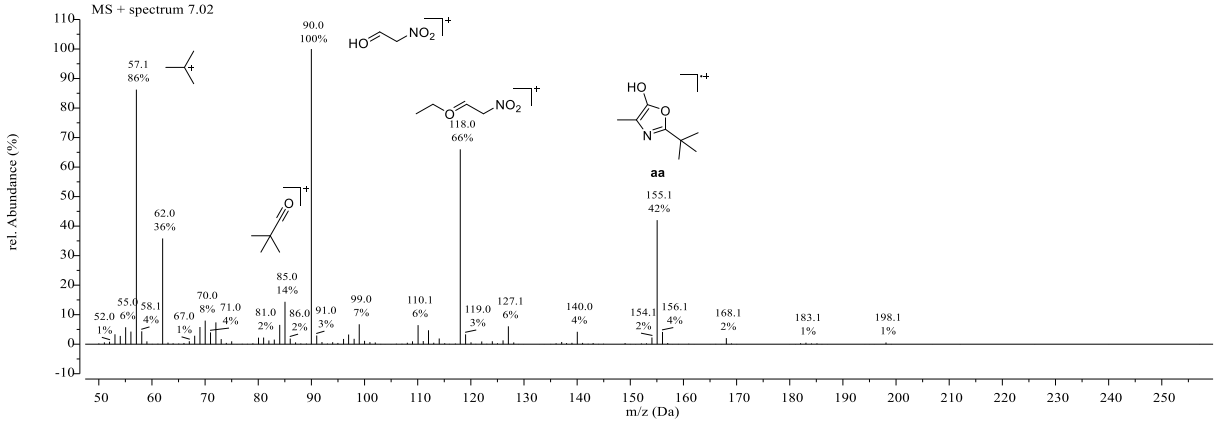
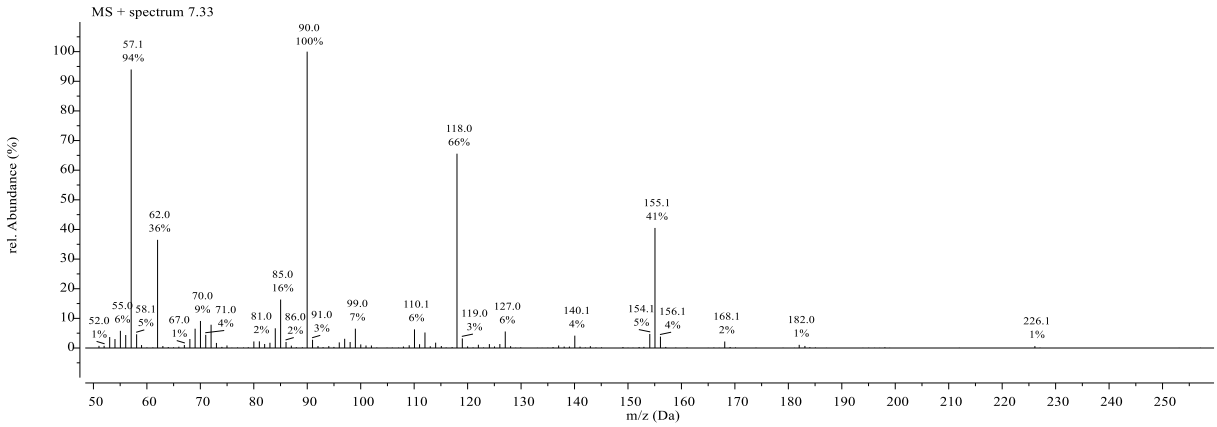
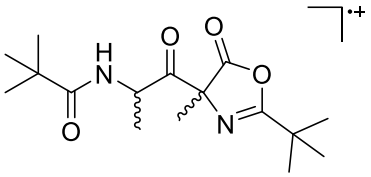


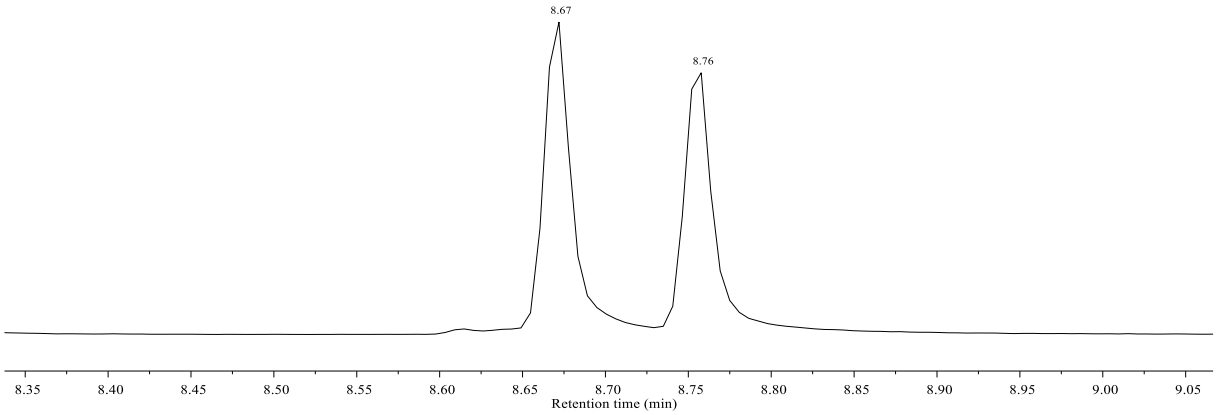


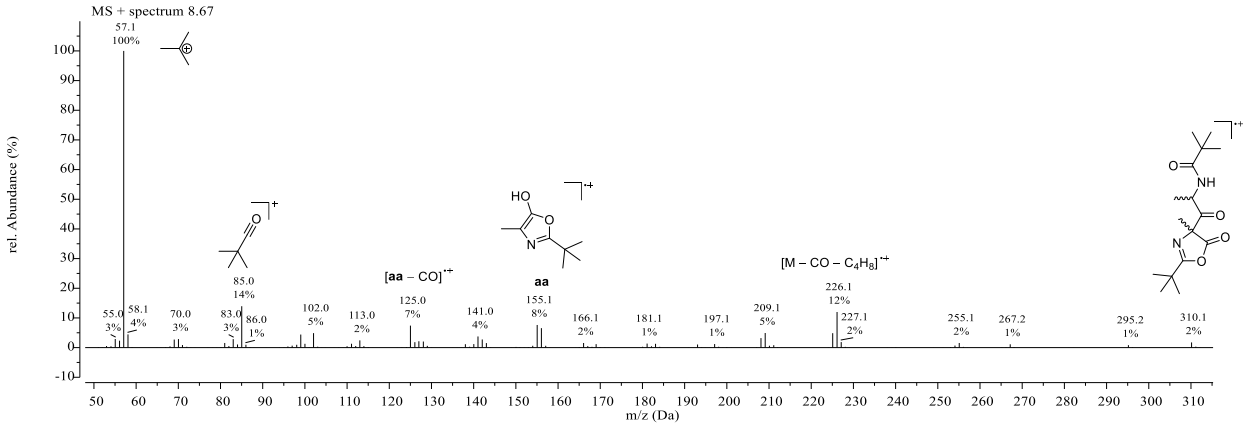


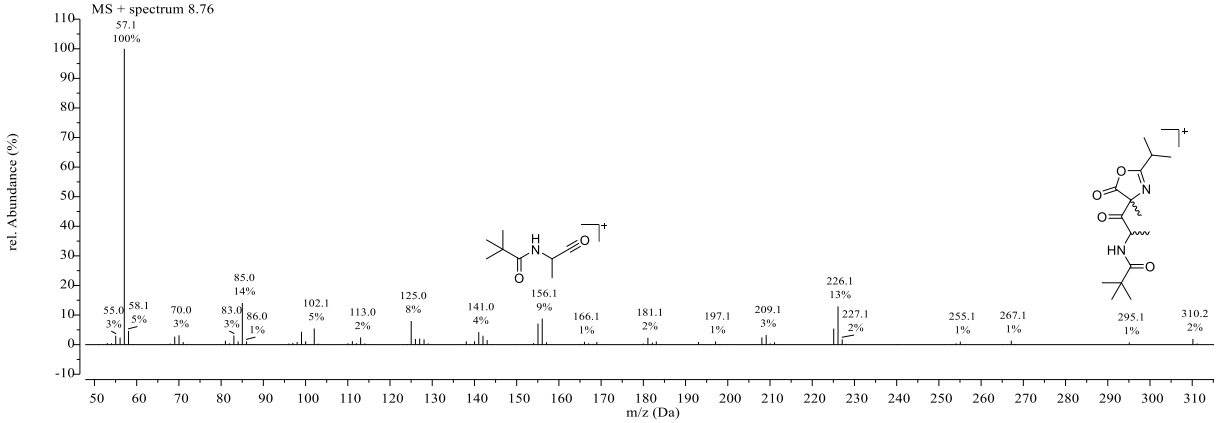
Chromatogram **C**



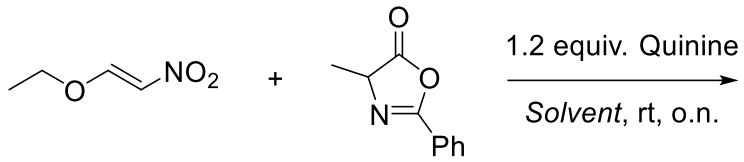
m/z = 310



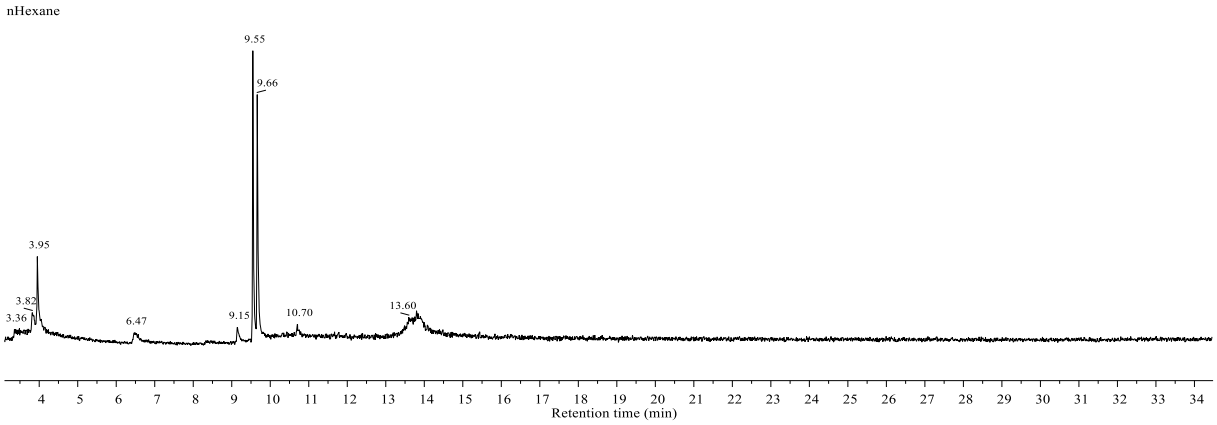


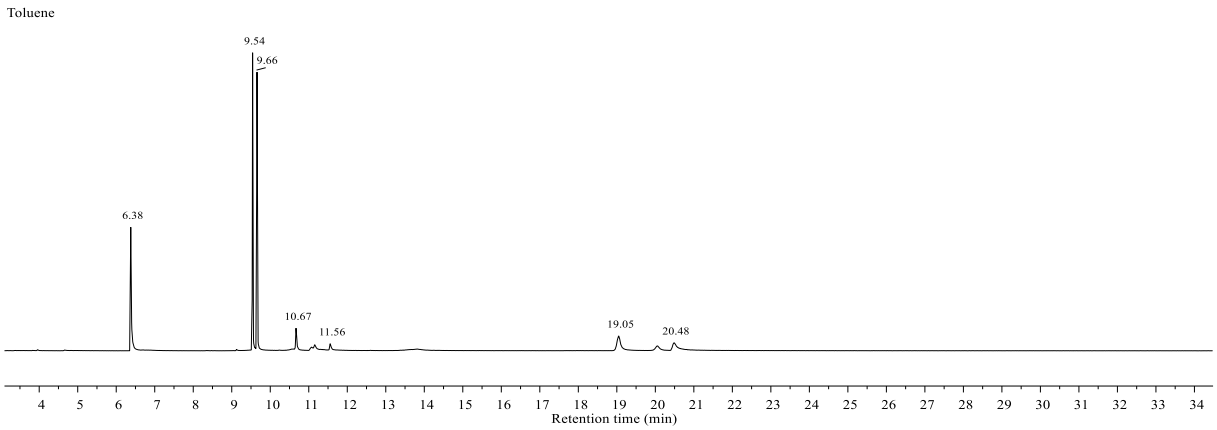


Solvent effect evaluation

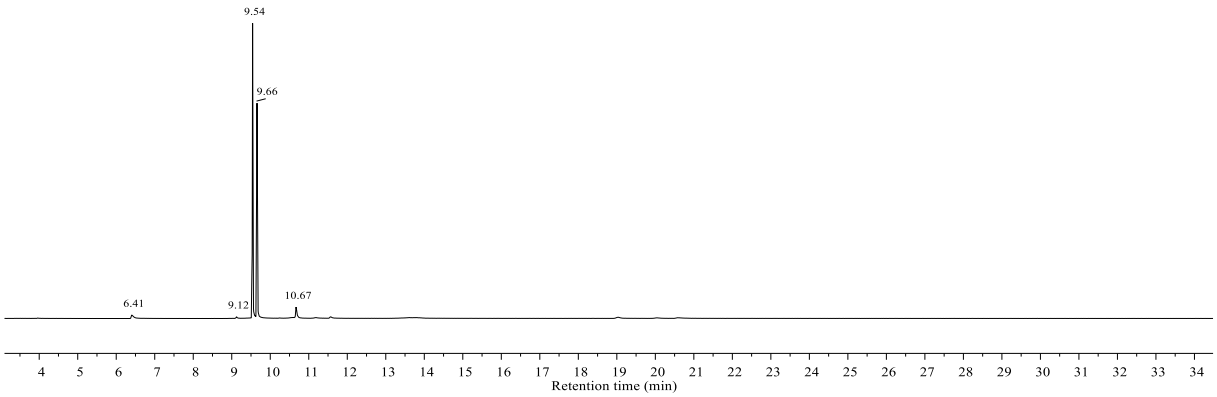


Entry	Compound	Retention time / min
1	Vinyl ether	3.80
2	Quinine	20.50
4	Azlactone	6.37
5	Product	9.55 & 9.66
6	Water Adduct	3.95
7	Azlactone dimer	19.04 & 20.04

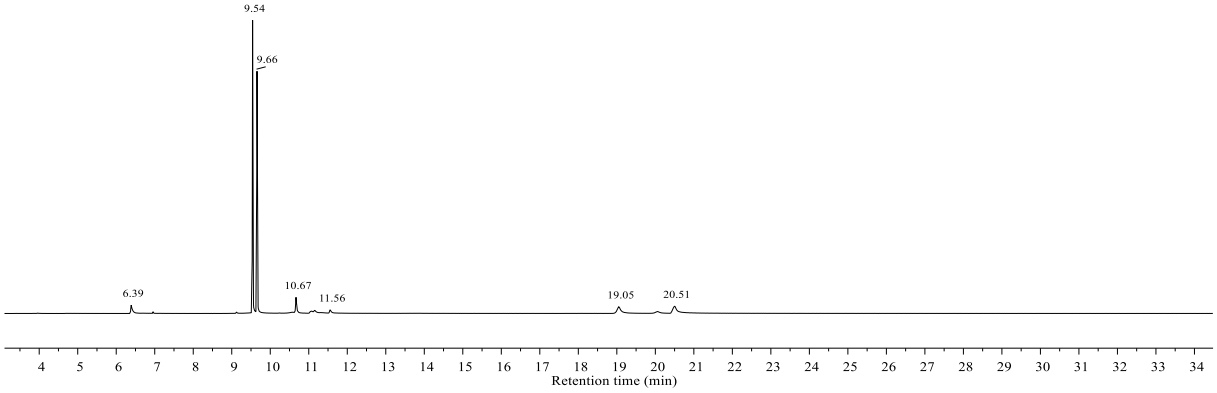




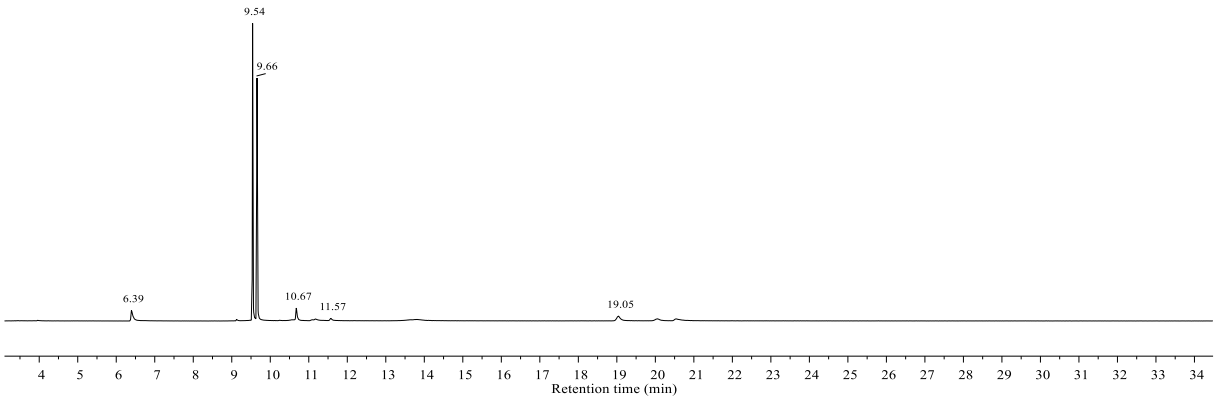
Diethyl Ether



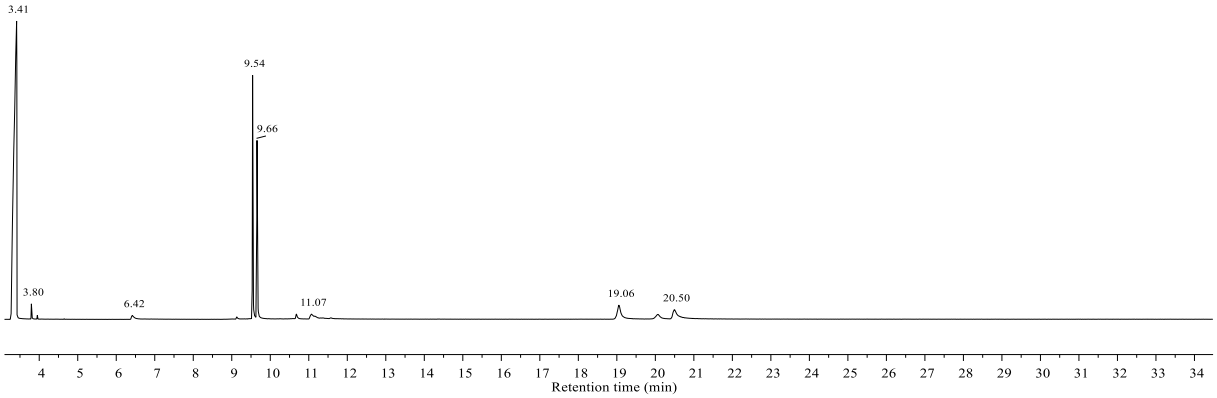
THF



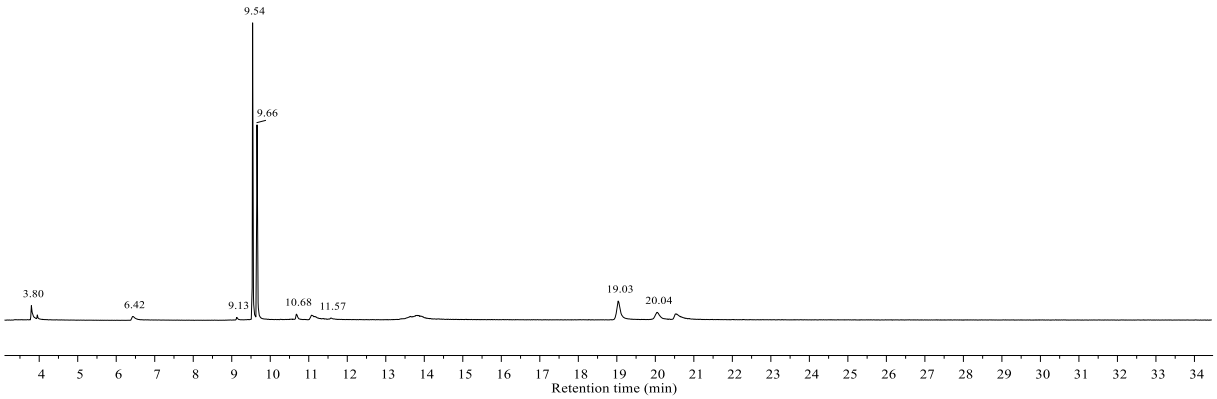
Dimethoxyethane



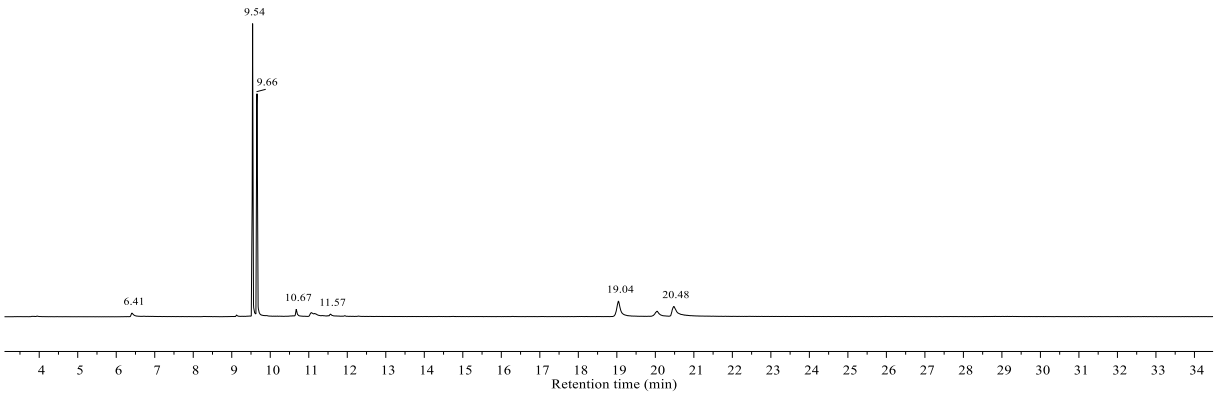
Propylene Carbonate



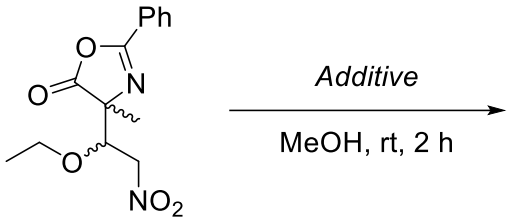
Acetonitrile



Ethyl Acetate

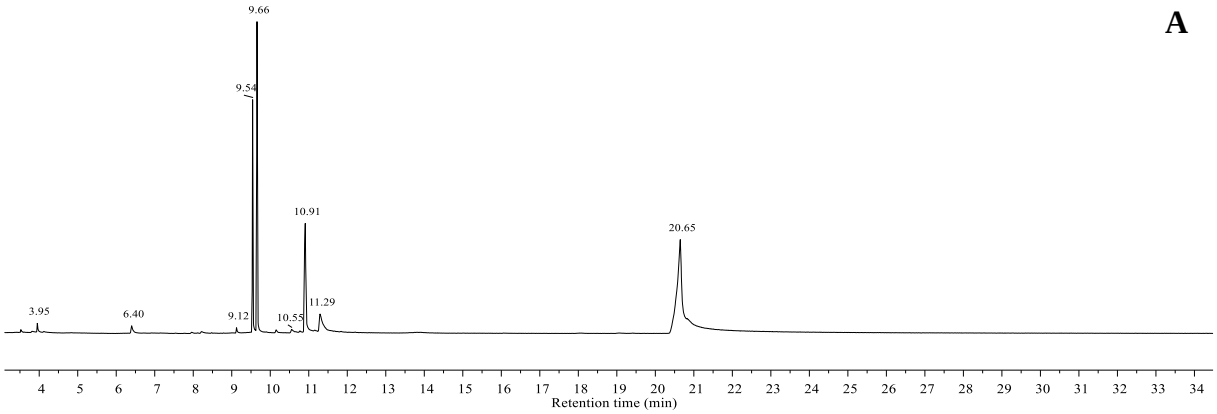


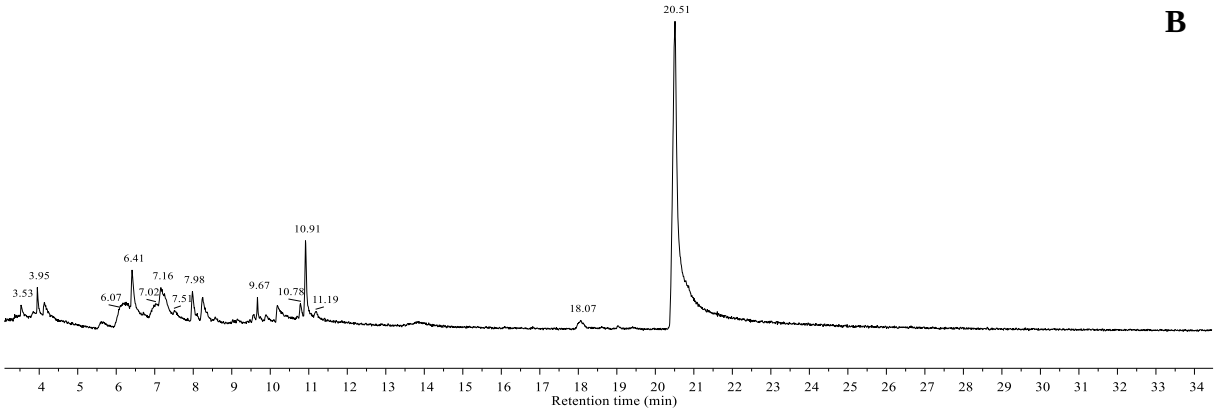
Esterification/Functionalization Attempts

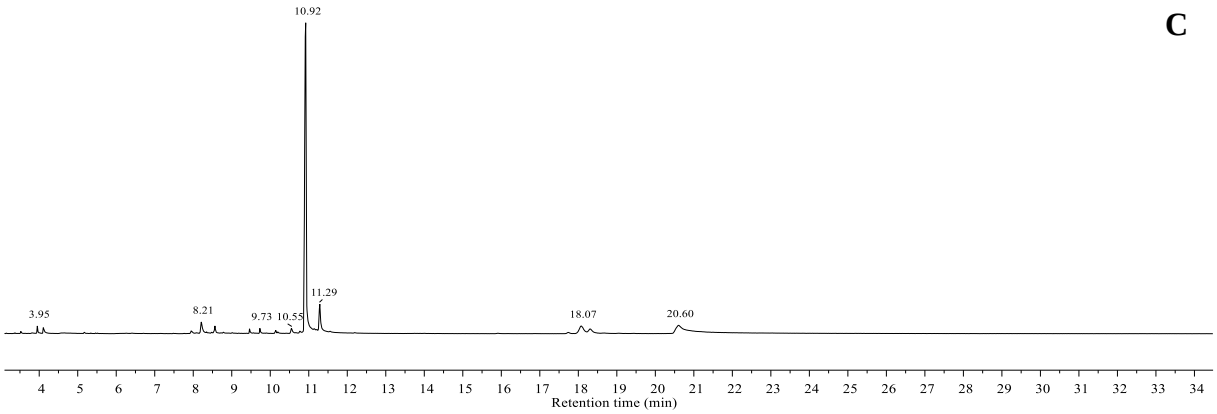


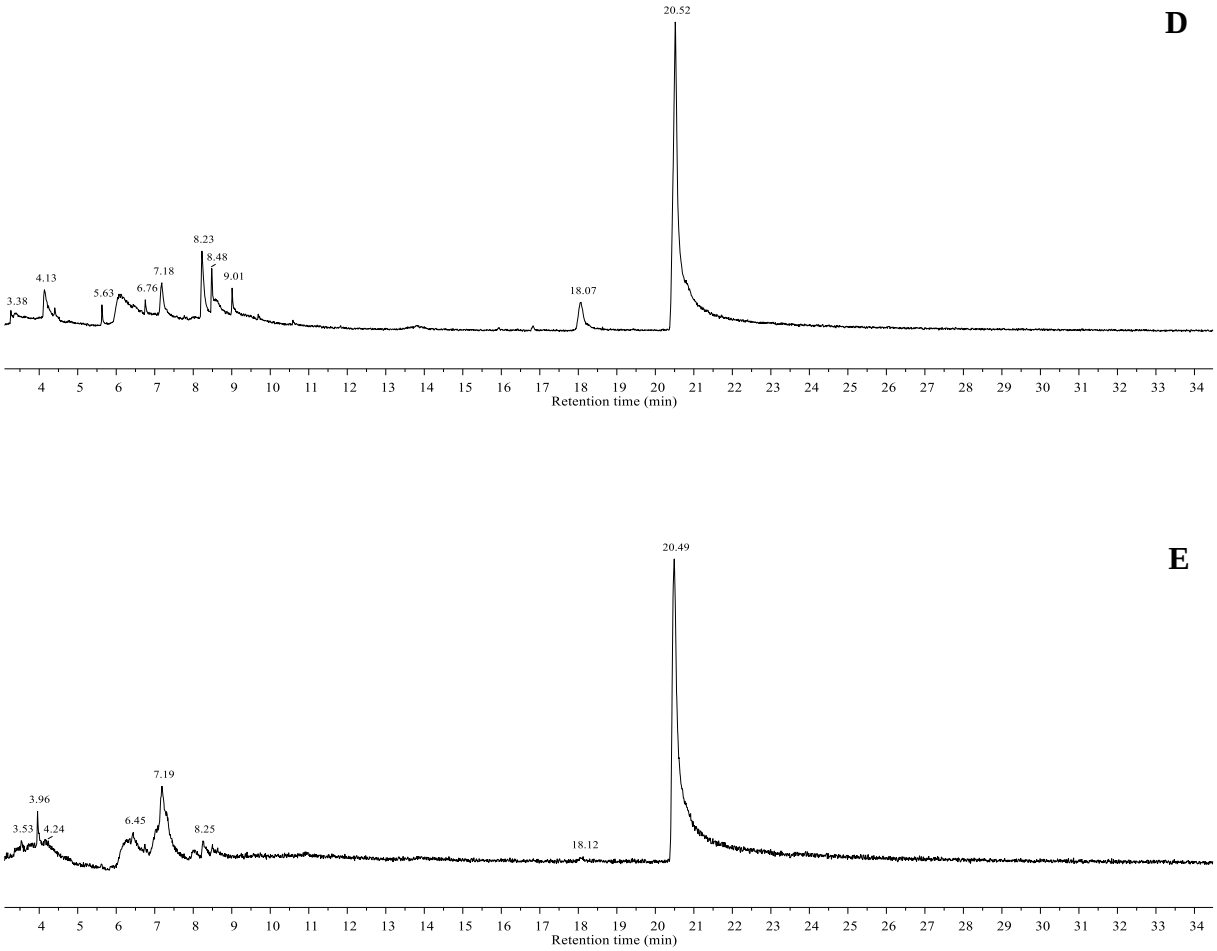
Entry	Additive	Chromatogram
1	–	**A**
2	$LiClO_4$	**B**
3	TMSCl	**C**
4	NaOMe	**D**
5	$NaBH_4$	**E**

Entry	Compound	Retention time / min
1	Educts	6.54 & 9.66
2	Quinine	20.50
3	Azlactone	6.37
4	**223**	3.80


A
9.66
9.54
10.91
20.65
3.95
6.40
9.12
10.55
11.29
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


B
20.51
10.91
6.41
3.95
3.53
7.16
7.98
6.07
7.02
7.51
9.67
10.78
11.19
18.07
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

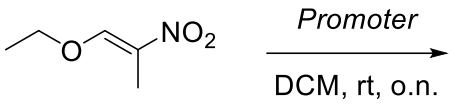

C
10.92
11.29
3.95
8.21
9.73
10.55
18.07
20.60
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)



Various attempts have been made to identify, isolate, and characterize the species formed during the esterification/functionalization attempts. All the attempts undertaken were futile.

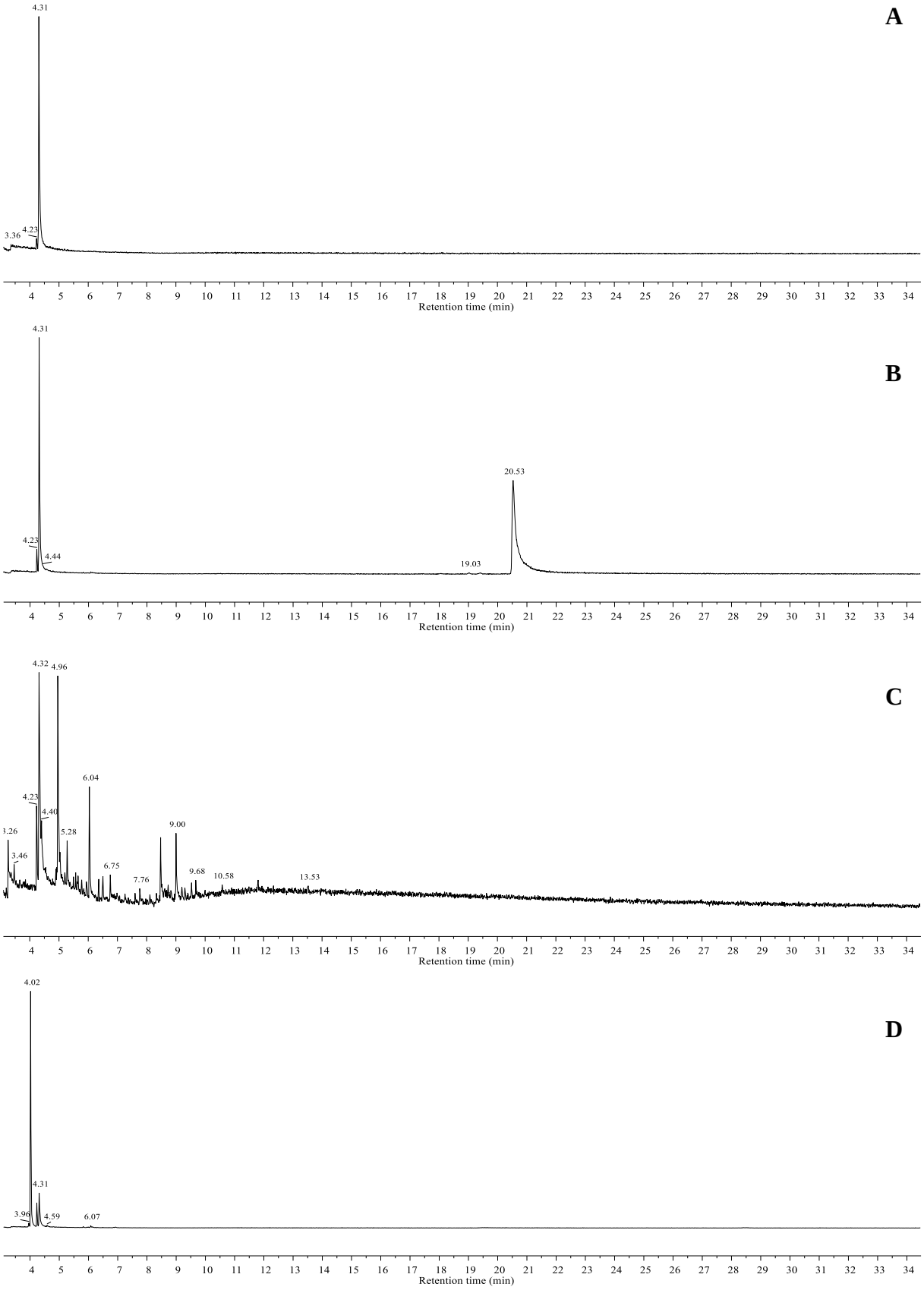
Additions to (1E)-1-Ethoxy-2-nitropropane

Blind Reactions

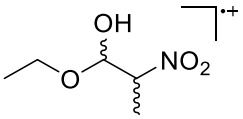


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	4.31
2	Quinine	20.50
3	**130**	4.02
5	Water Adduct	4.23


A
4.31
3.36
4.23
B
4.31
20.53
4.23
4.44
19.03
C
4.32
4.96
6.04
4.23
4.40
5.28
9.00
3.26
3.46
6.75
7.76
9.68
10.58
13.53
D
4.02
4.31
3.96
4.59
6.07
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **B**



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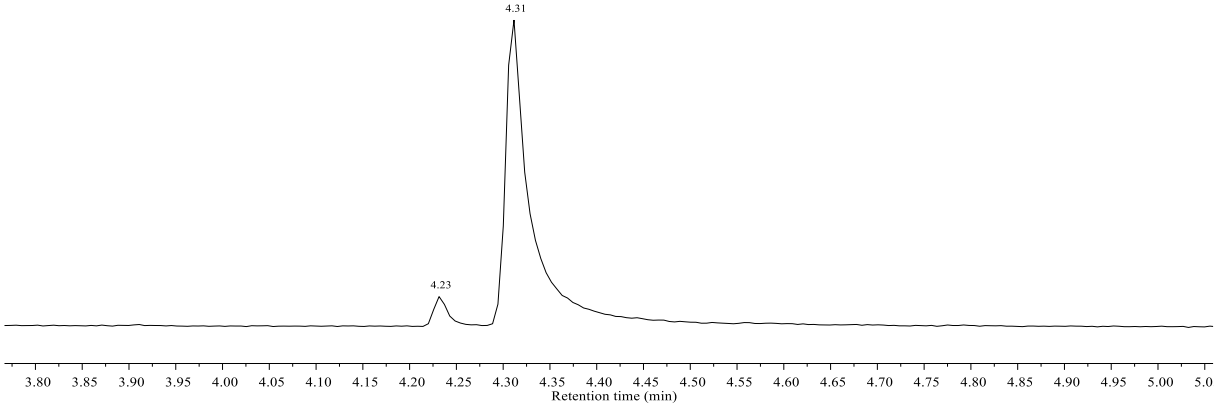
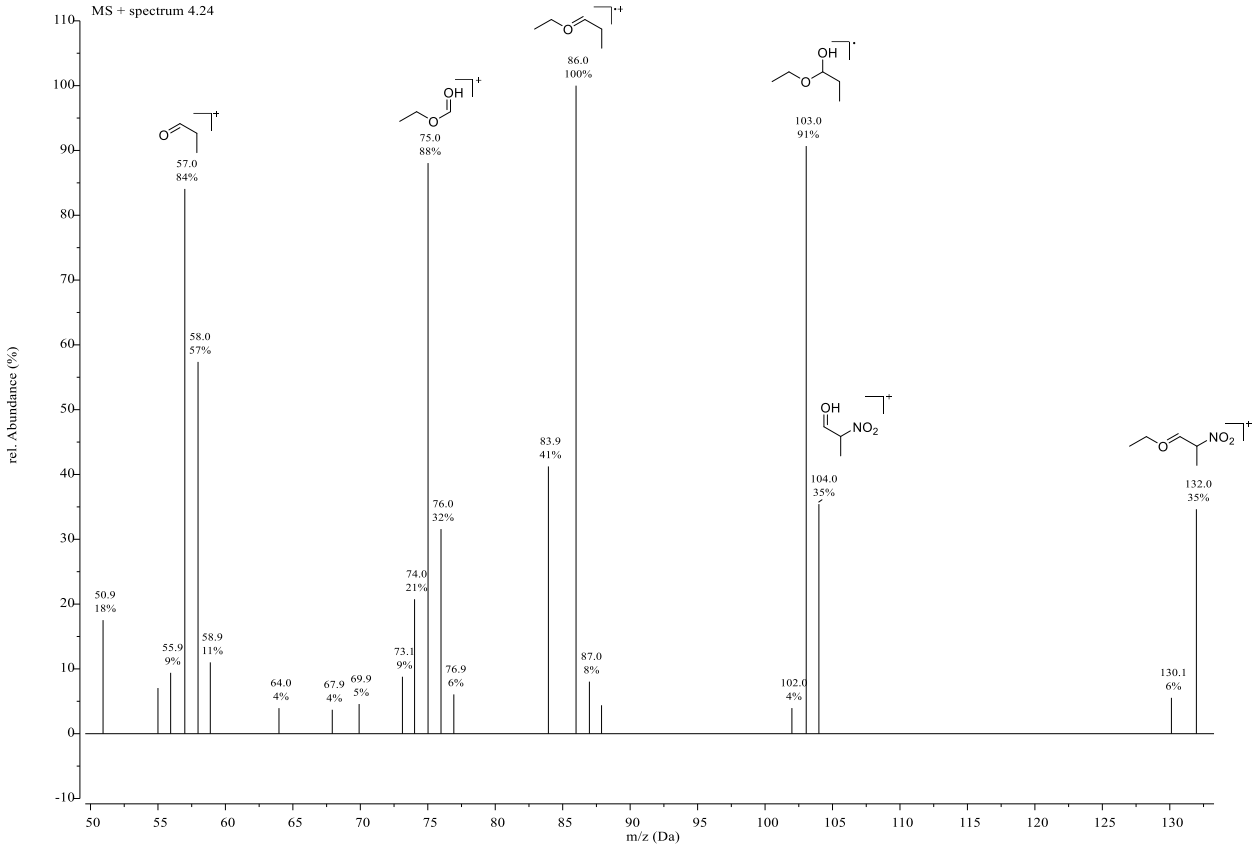
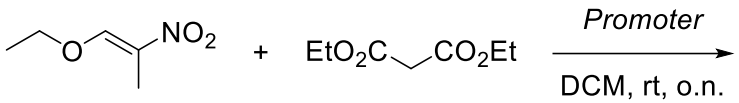


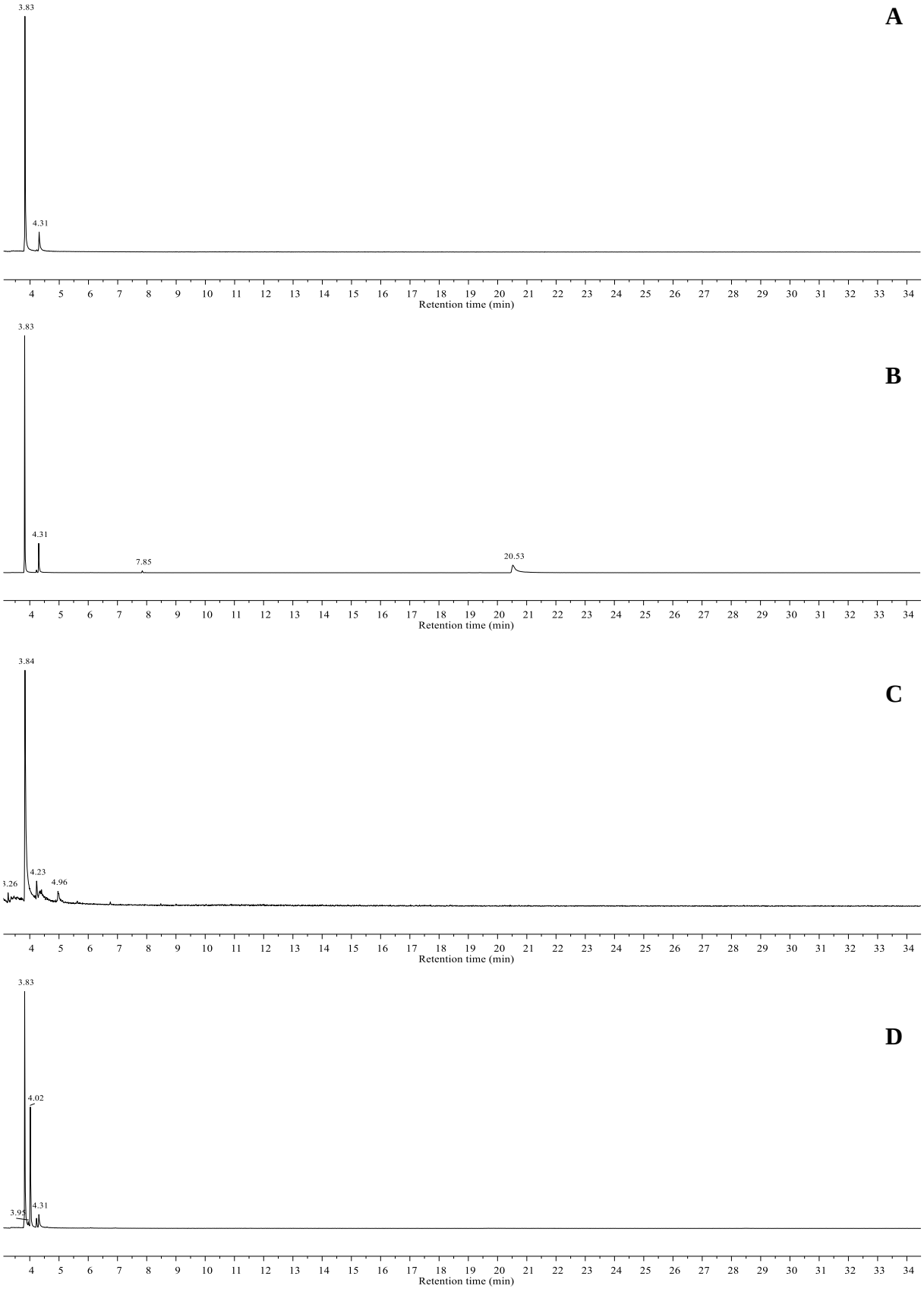


Addition of Diethyl Malonate

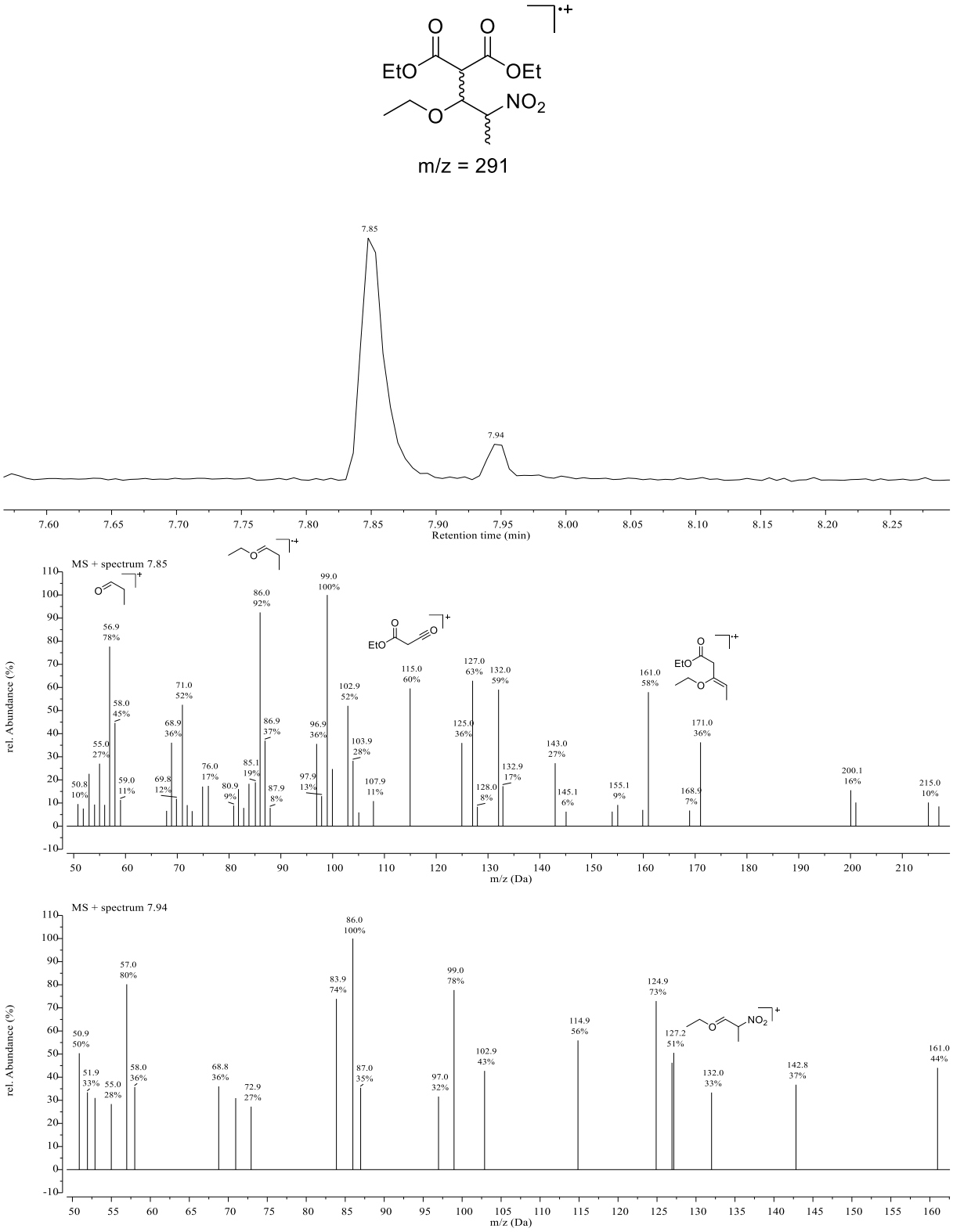


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

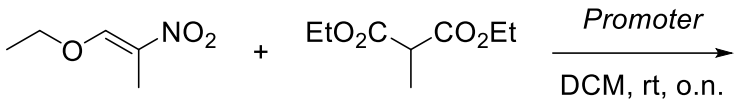
Entry	Compound	Retention time / min
1	Vinyl ether	4.31
2	Quinine	20.50
3	**130**	4.02
5	Water Adduct	4.23
6	Diethyl Malonate	3.83
7	Product	


A
3.83
4.31
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)
B
3.83
4.31
7.85
20.53
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)
C
3.84
3.26
4.23
4.96
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)
D
3.83
4.02
3.95
4.31
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **B**

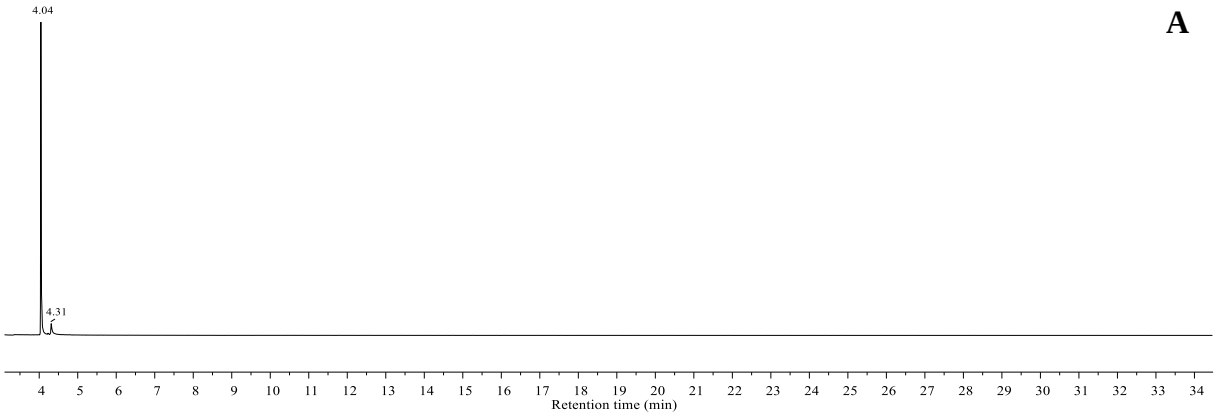


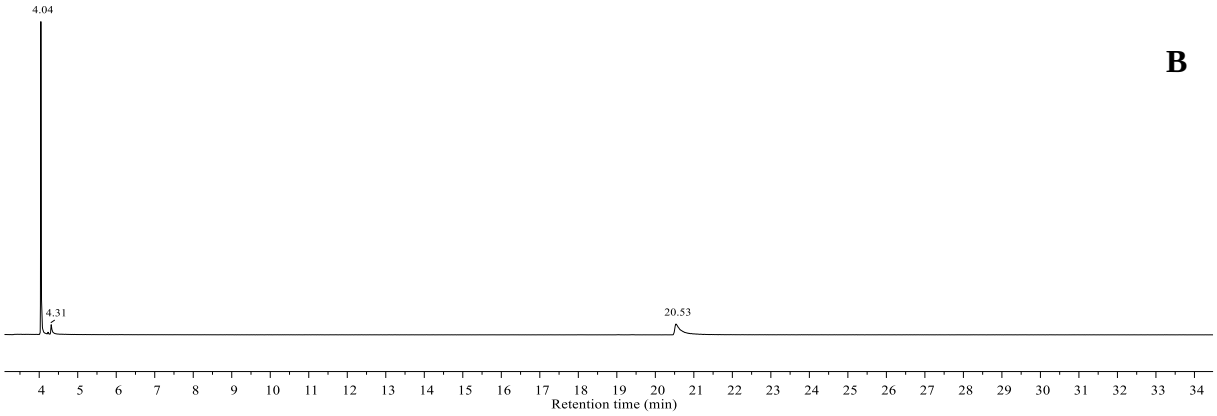
Addition of Diethyl Methylmalonate

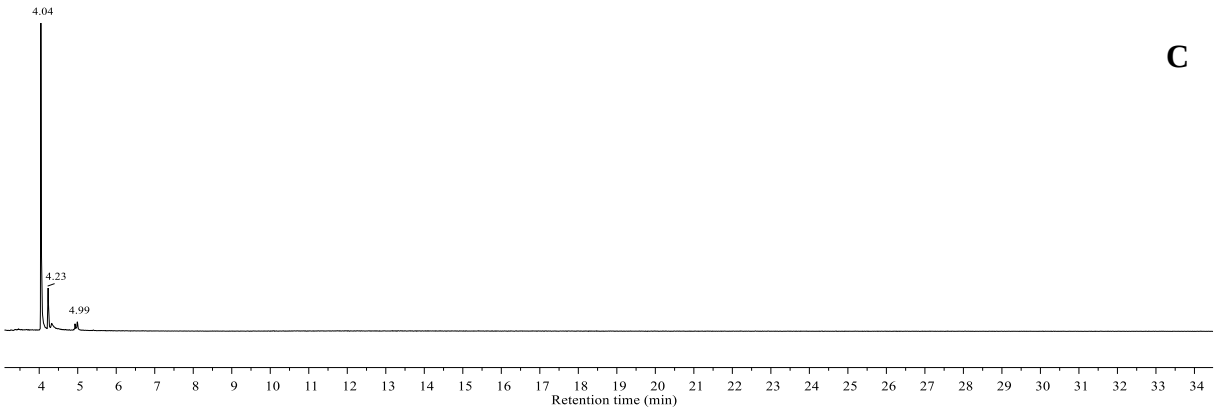


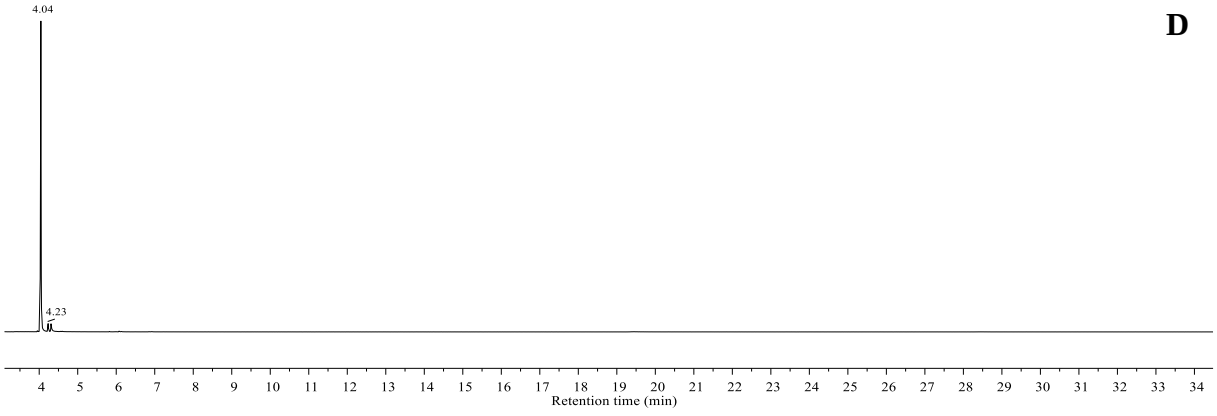
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	4.31
2	Quinine	20.50
3	**130**	4.02
5	Water Adduct	4.23
6	Diethyl Methylmalonate	4.04

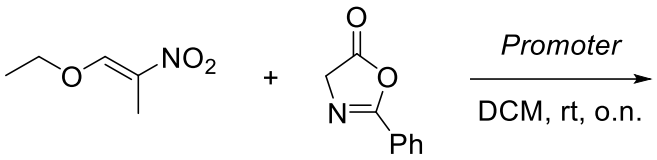

A
4.04
4.31
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


B
4.04
4.31
20.53
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


C
4.04
4.23
4.99
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

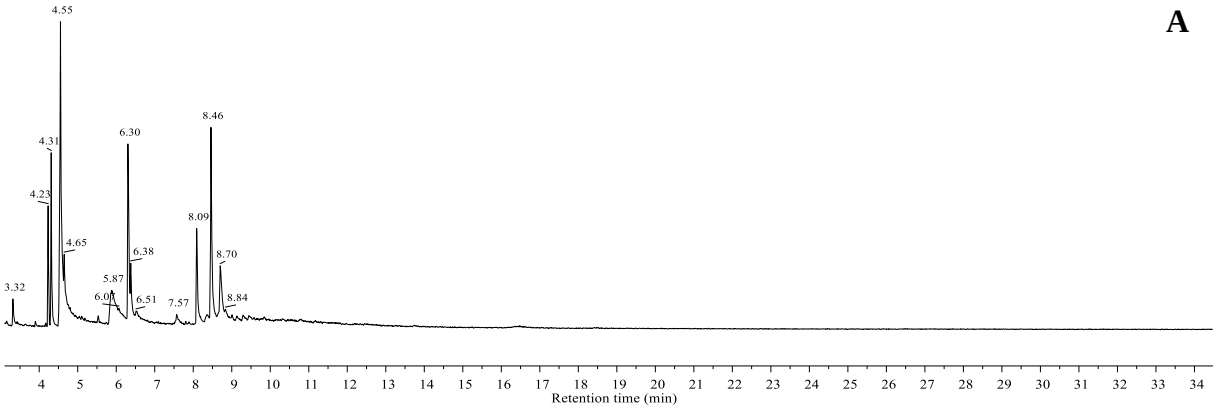

D
4.04
4.23
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

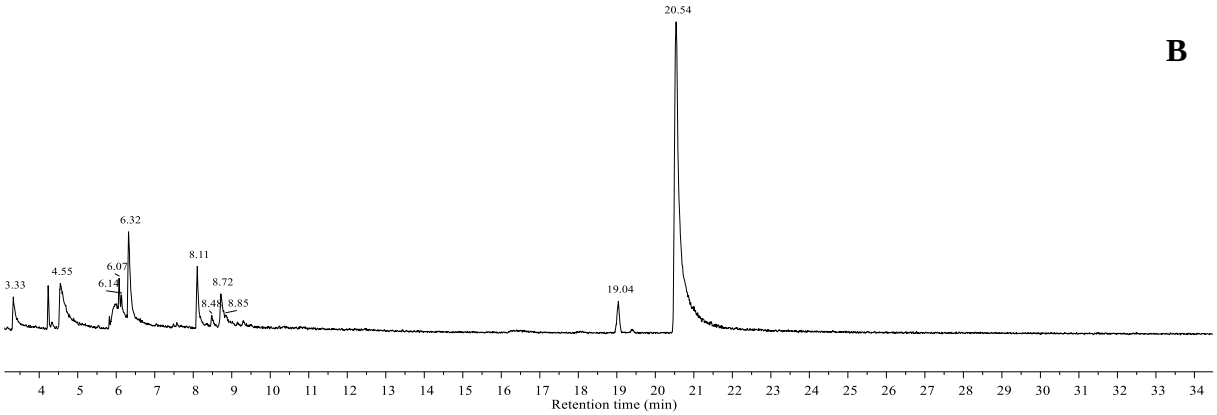
Addition of 2-Phenyl-5(4*H*)-oxazolone

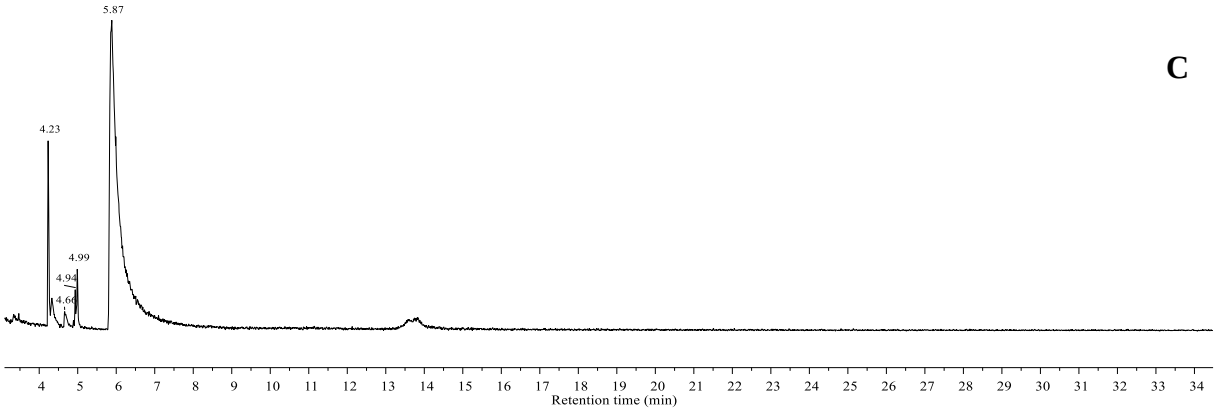


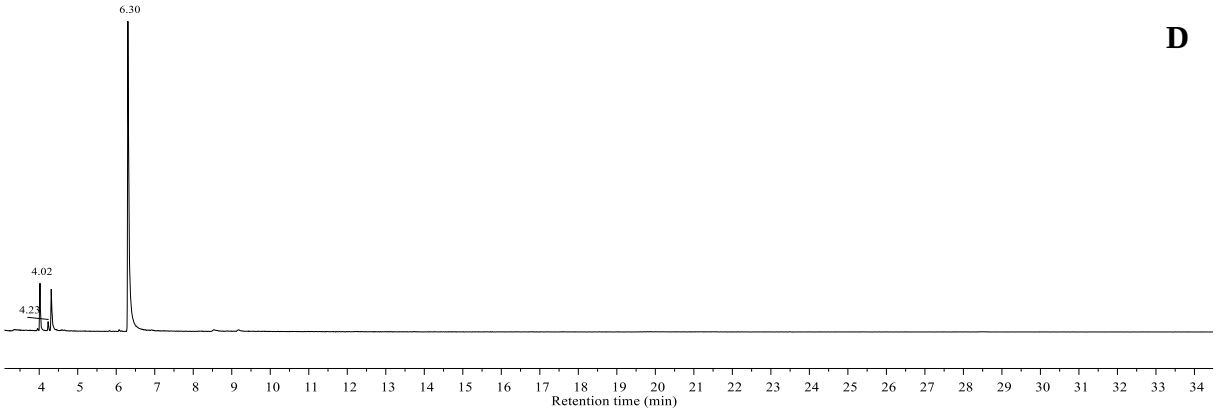
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	4.31
2	Quinine	20.50
3	**130**	4.02
5	Water Adduct	4.23
6	Azlactone	6.30

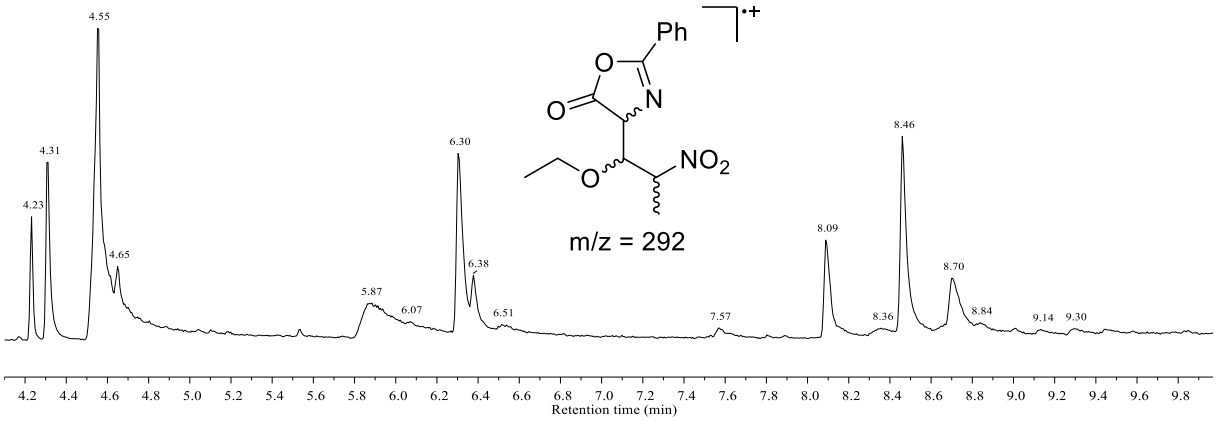

A
4.55
4.31
4.23
4.65
6.30
6.38
5.87
6.07
6.51
7.57
8.46
8.09
8.70
8.84
3.32
Retention time (min)

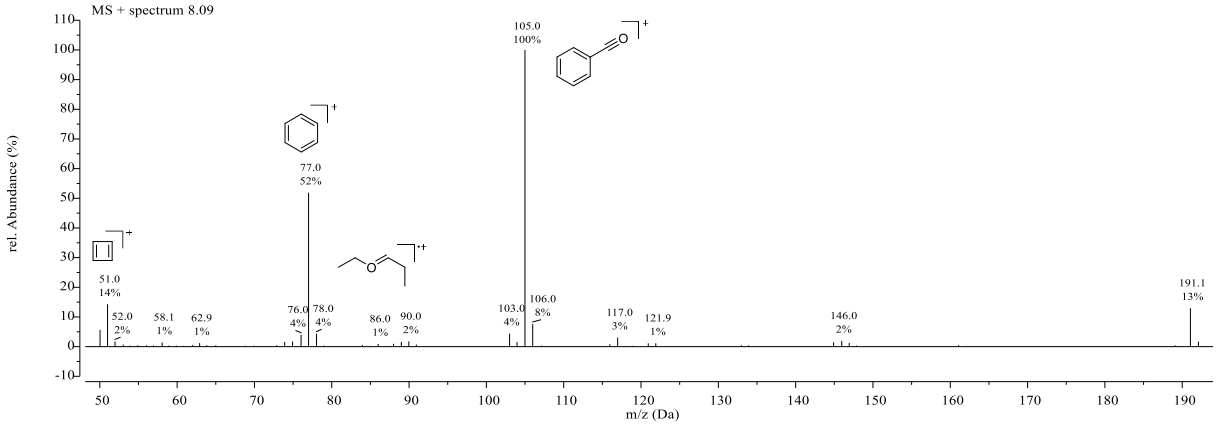

B
20.54
6.32
8.11
6.07
6.14
4.55
8.72
8.48
8.85
3.33
19.04
Retention time (min)

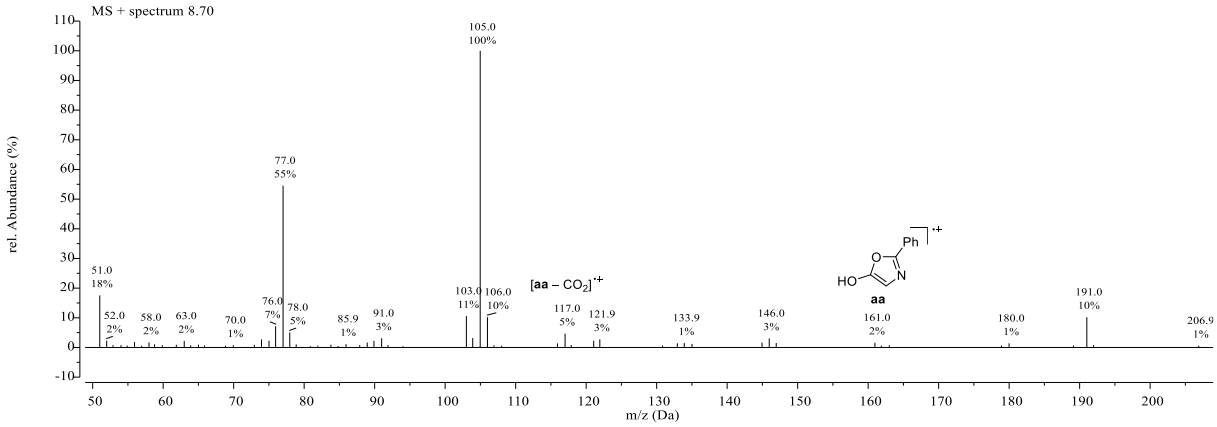

C
5.87
4.23
4.99
4.94
4.66
Retention time (min)

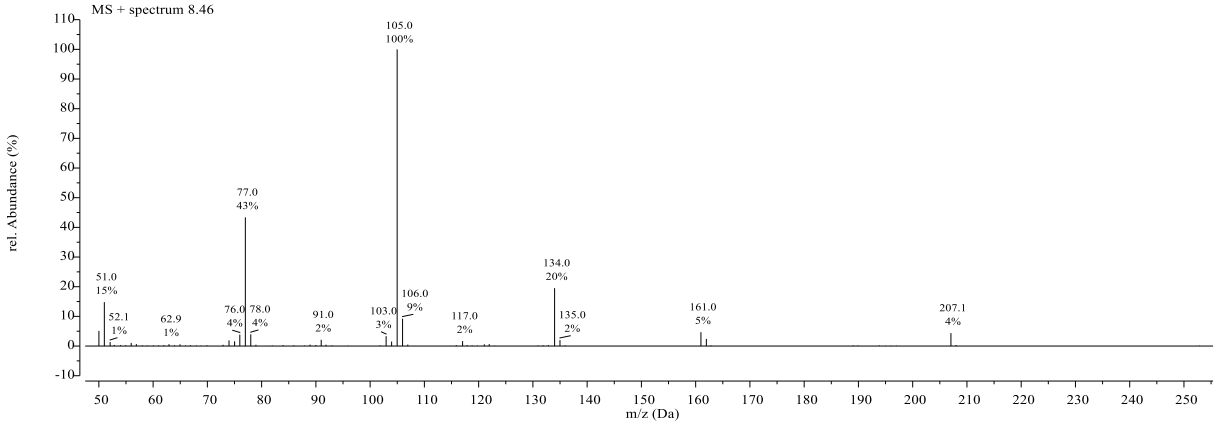

D
6.30
4.02
4.23
Retention time (min)

Chromatogram **A**

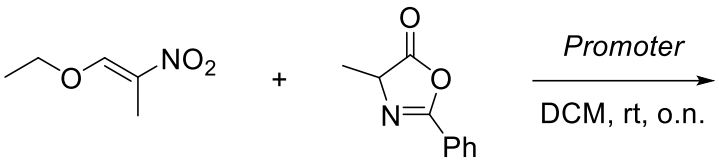






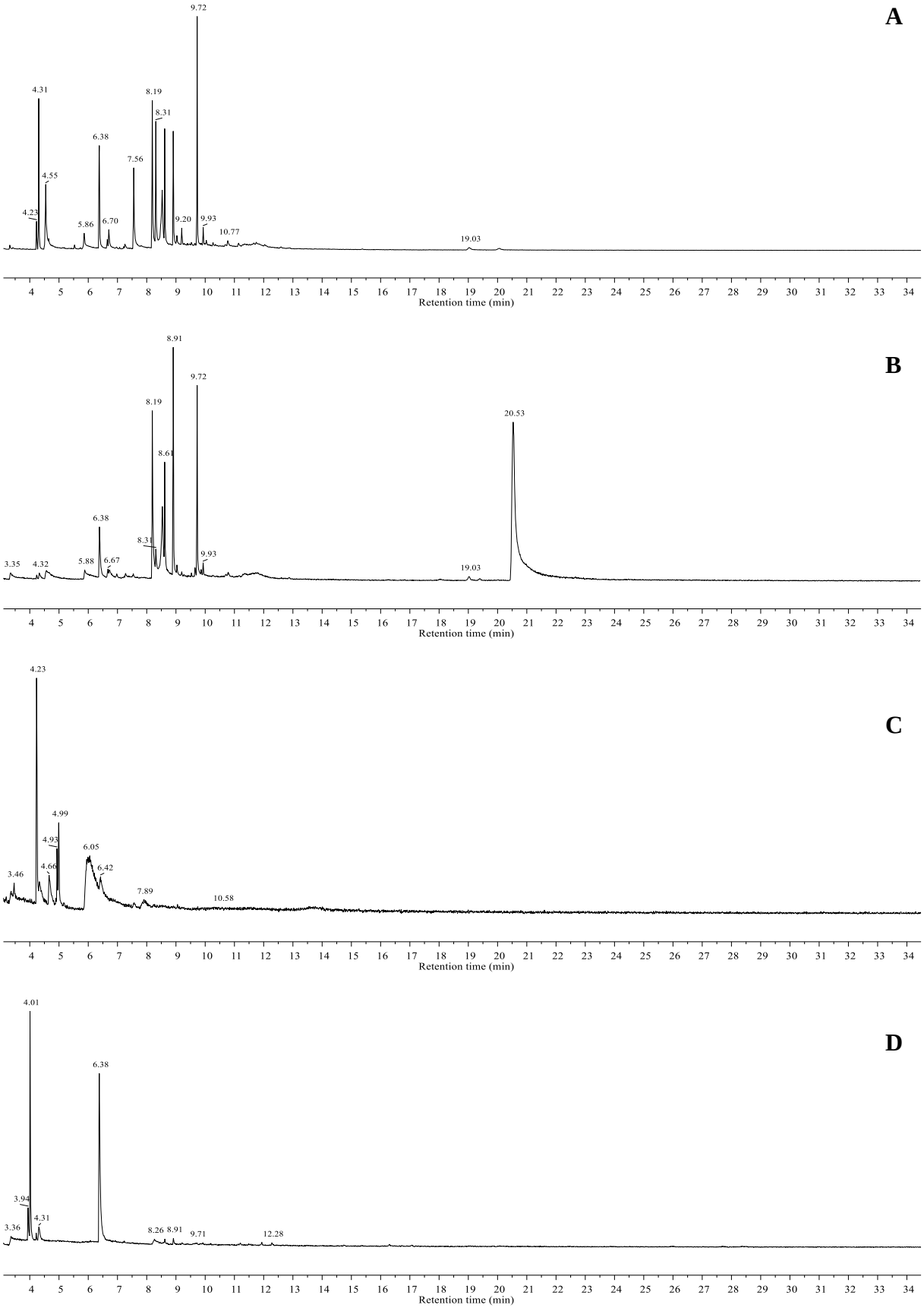


Addition of 2-Phenyl-4-methyl-5(4*H*)-oxazolone

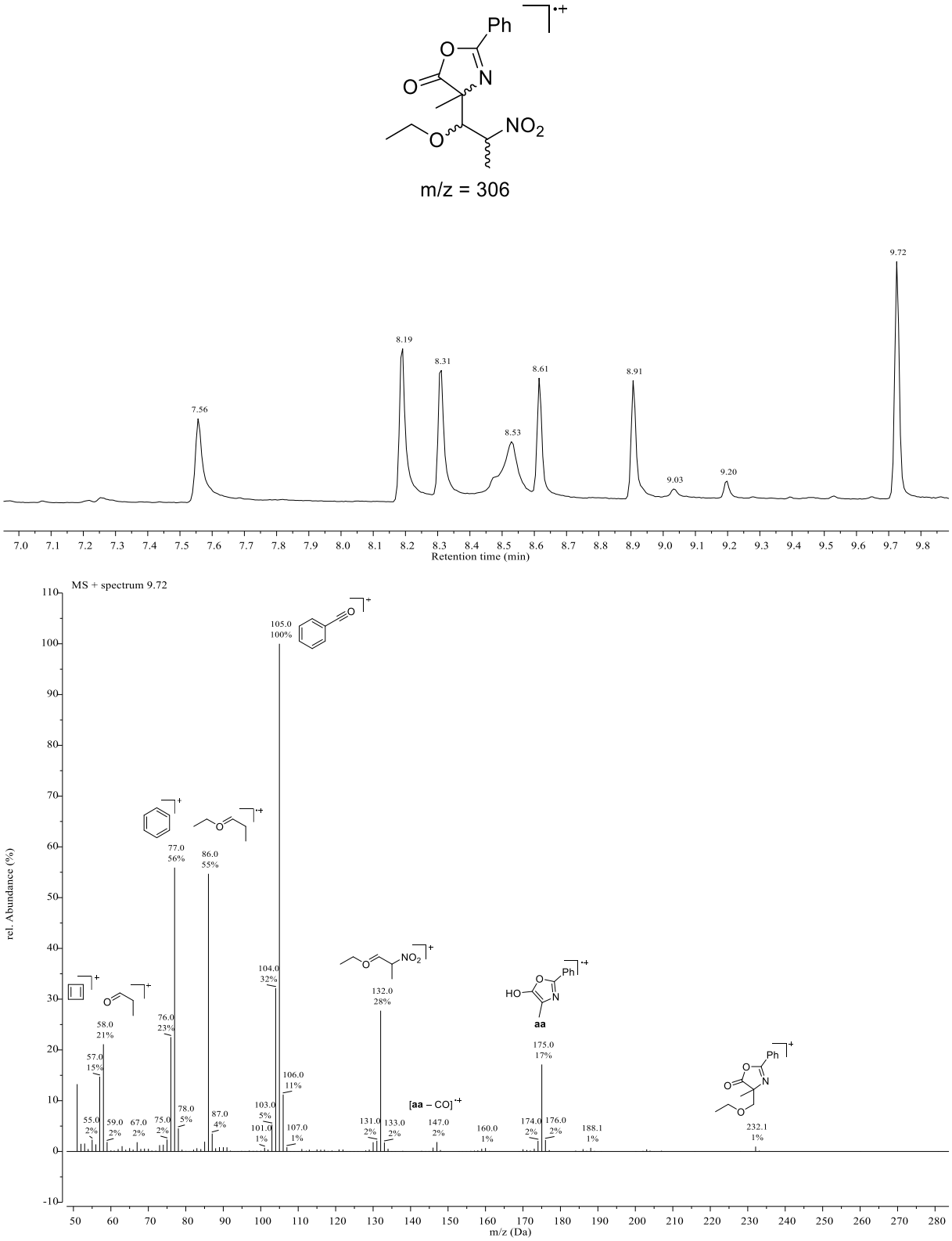


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

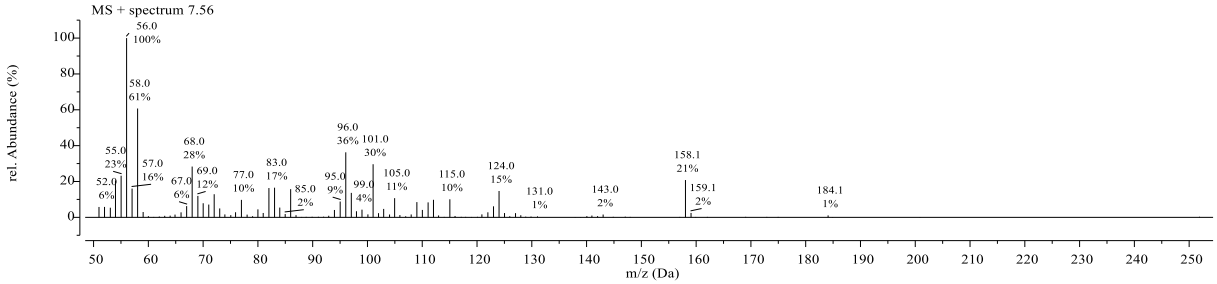
Entry	Compound	Retention time / min
1	Vinyl ether	4.31
2	Quinine	20.50
3	**130**	4.02
5	Water Adduct	4.23
6	Azlactone	6.38

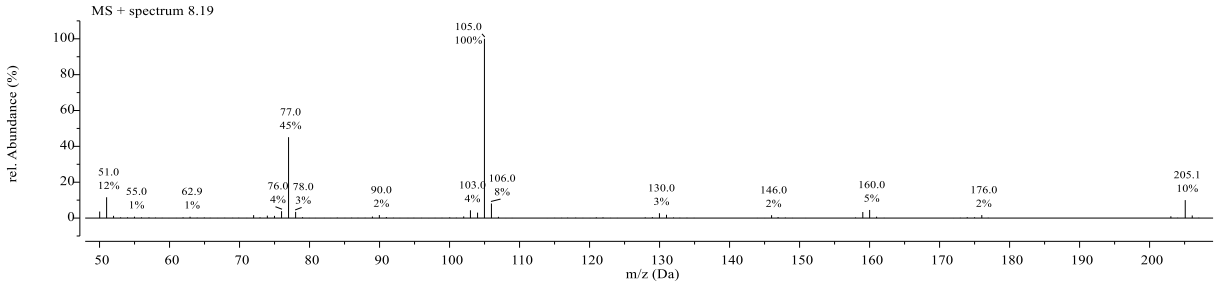

A
9.72
4.31
8.19
8.31
6.38
7.56
4.55
4.23
5.86
6.70
9.20
9.93
10.77
19.03
Retention time (min)
B
8.91
9.72
8.19
20.53
8.61
6.38
8.31
3.35
4.32
5.88
6.67
9.93
19.03
Retention time (min)
C
4.23
4.99
4.93
6.05
3.46
4.66
6.42
7.89
10.58
Retention time (min)
D
4.01
6.38
3.94
3.36
4.31
8.26
8.91
9.71
12.28
Retention time (min)

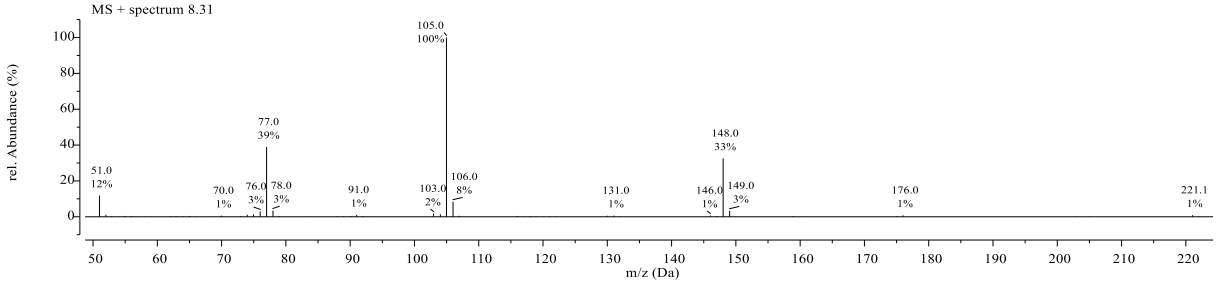
Chromatogram **A**

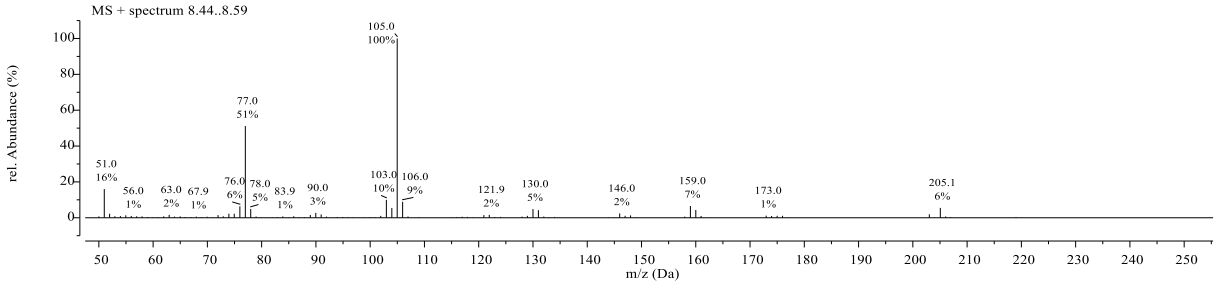


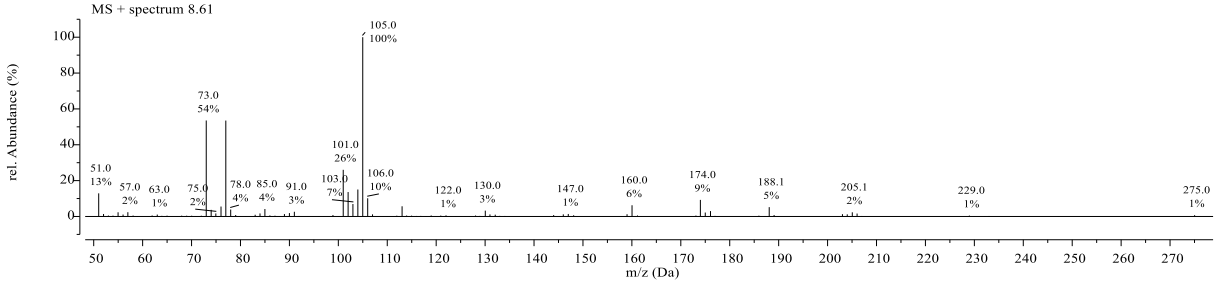
It should be noted that the other compounds detected also showed fragments corresponding to the azlactone, but no fragments of the corresponding ether could be detected. The Spectra are shown below.

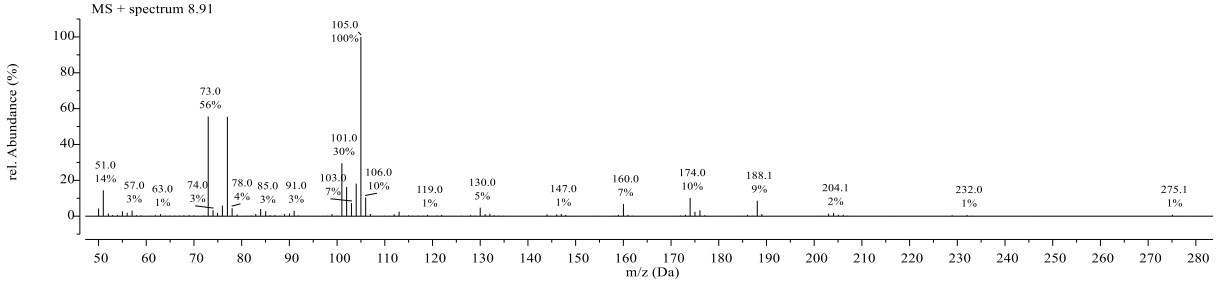

MS + spectrum 7.56
rel. Abundance (%)
m/z (Da)
56.0 100%
58.0 61%
55.0 23%
57.0 16%
68.0 28%
52.0 6%
67.0 6%
69.0 12%
77.0 10%
83.0 17%
85.0 2%
95.0 9%
96.0 36%
99.0 4%
101.0 30%
105.0 11%
115.0 10%
124.0 15%
131.0 1%
143.0 2%
158.1 21%
159.1 2%
184.1 1%


MS + spectrum 8.19
rel. Abundance (%)
m/z (Da)
105.0 100%
77.0 45%
51.0 12%
55.0 1%
62.9 1%
76.0 4%
78.0 3%
90.0 2%
103.0 4%
106.0 8%
130.0 3%
146.0 2%
160.0 5%
176.0 2%
205.1 10%


MS + spectrum 8.31
rel. Abundance (%)
m/z (Da)
105.0 100%
77.0 39%
148.0 33%
51.0 12%
70.0 1%
76.0 3%
78.0 3%
91.0 1%
103.0 2%
106.0 8%
131.0 1%
146.0 1%
149.0 3%
176.0 1%
221.1 1%

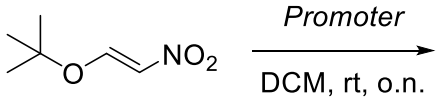

MS + spectrum 8.44..8.59
rel. Abundance (%)
m/z (Da)
105.0 100%
77.0 51%
51.0 16%
56.0 1%
63.0 2%
67.9 1%
76.0 6%
78.0 5%
83.9 1%
90.0 3%
103.0 10%
106.0 9%
121.9 2%
130.0 5%
146.0 2%
159.0 7%
173.0 1%
205.1 6%


MS + spectrum 8.61
rel. Abundance (%)
m/z (Da)
105.0 100%
73.0 54%
101.0 26%
51.0 13%
57.0 2%
63.0 1%
75.0 2%
78.0 4%
85.0 4%
91.0 3%
103.0 7%
106.0 10%
122.0 1%
130.0 3%
147.0 1%
160.0 6%
174.0 9%
188.1 5%
205.1 2%
229.0 1%
275.0 1%


MS + spectrum 8.91
rel. Abundance (%)
m/z (Da)
105.0 100%
73.0 56%
101.0 30%
51.0 14%
57.0 3%
63.0 1%
74.0 3%
78.0 4%
85.0 3%
91.0 3%
103.0 7%
106.0 10%
119.0 1%
130.0 5%
147.0 1%
160.0 7%
174.0 10%
188.1 9%
204.1 2%
232.0 1%
275.1 1%

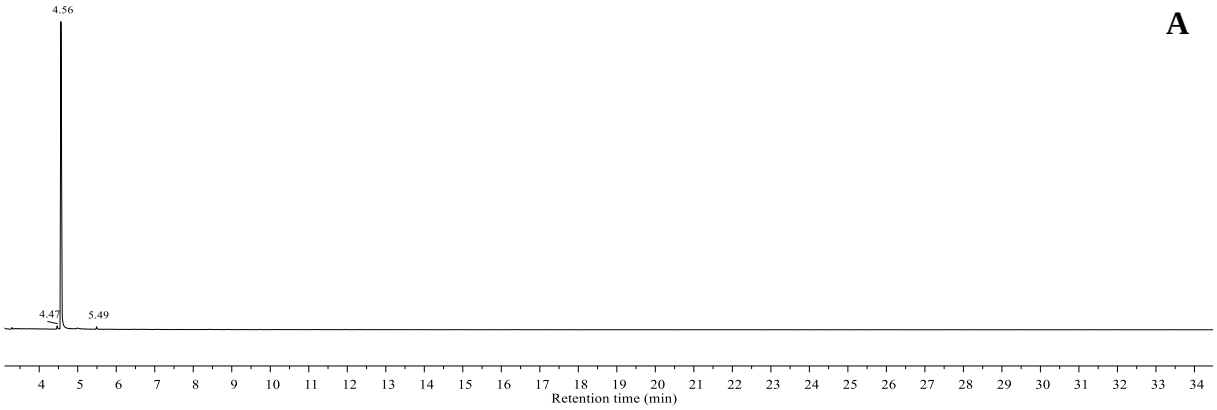
Additions to (1*E*)-1-*tert*-Butoxy-2-nitroethene

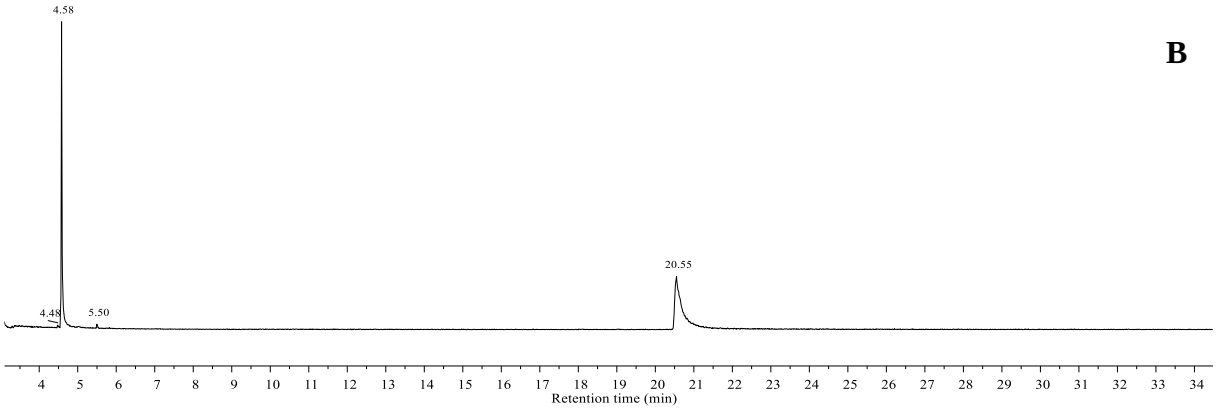
Blind Reactions

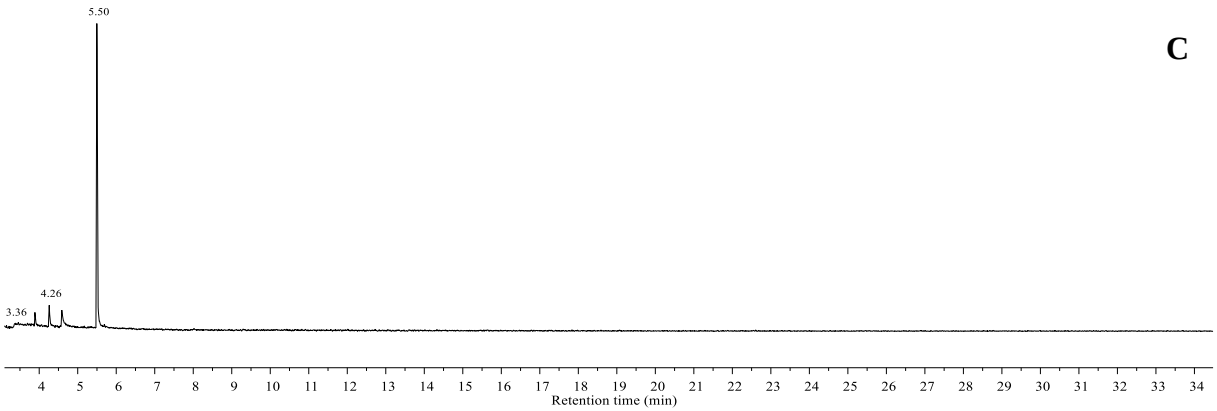


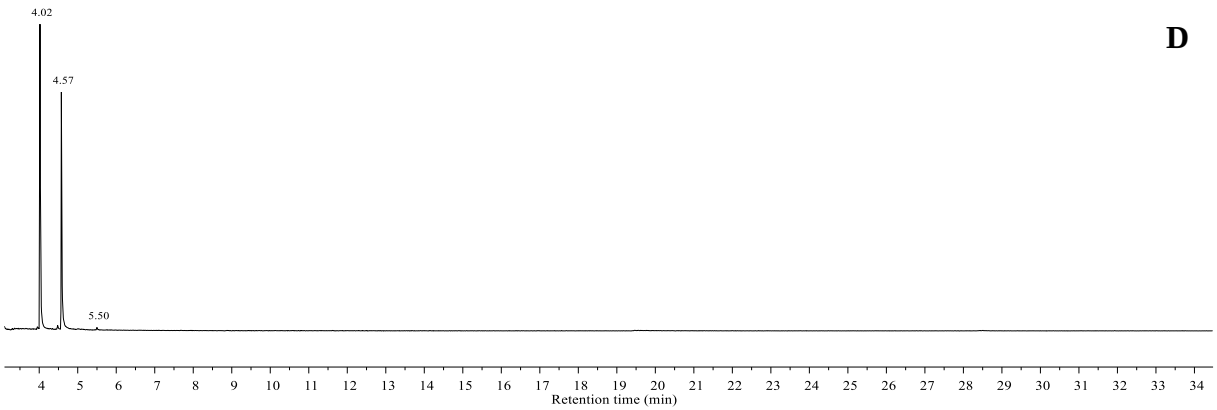
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	4.57
2	Quinine	20.55
3	**130**	4.02
5	Water Adduct	5.50

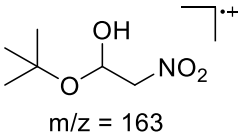

A
4.56
4.47
5.49
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


B
4.58
20.55
4.48
5.50
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

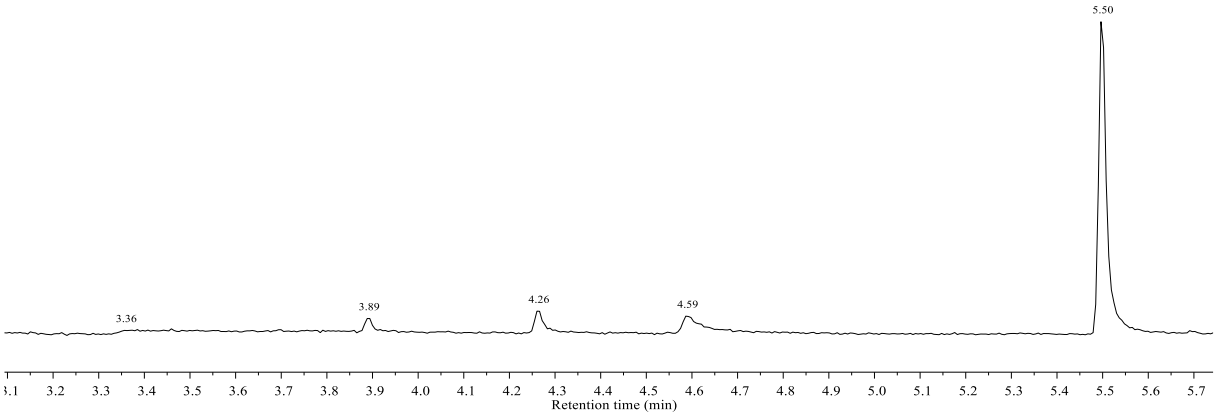

C
5.50
4.26
3.36
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

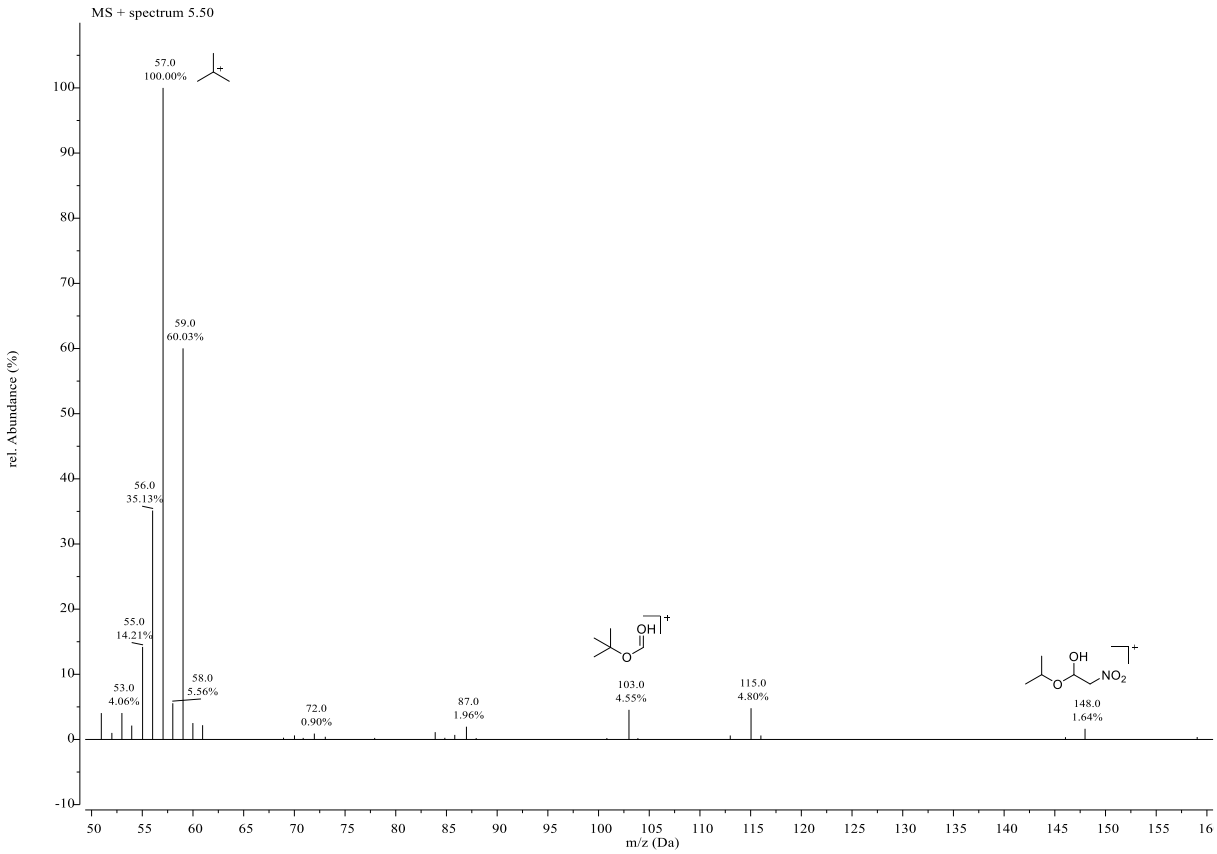

D
4.02
4.57
5.50
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **C**

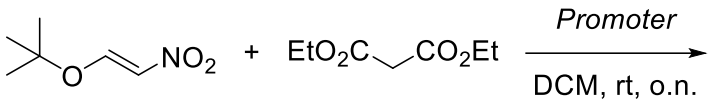


m/z = 163



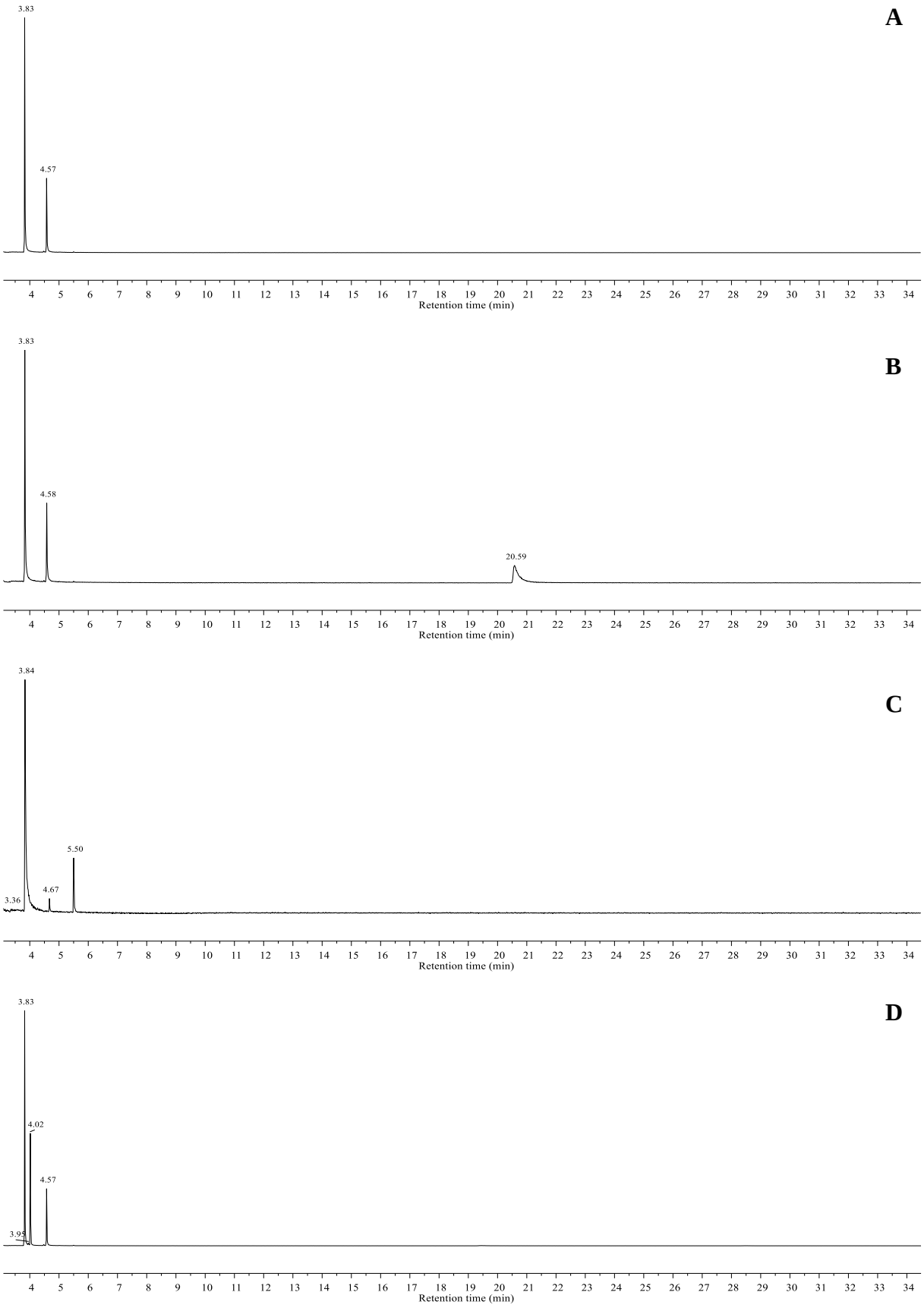


Addition of Diethyl Malonate

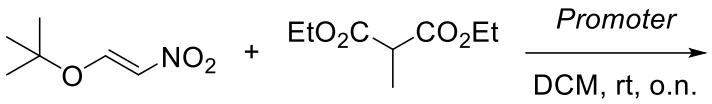


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	4.57
2	Quinine	20.55
3	**130**	4.02
5	Water Adduct	5.50
6	Diethyl Malonate	3.83

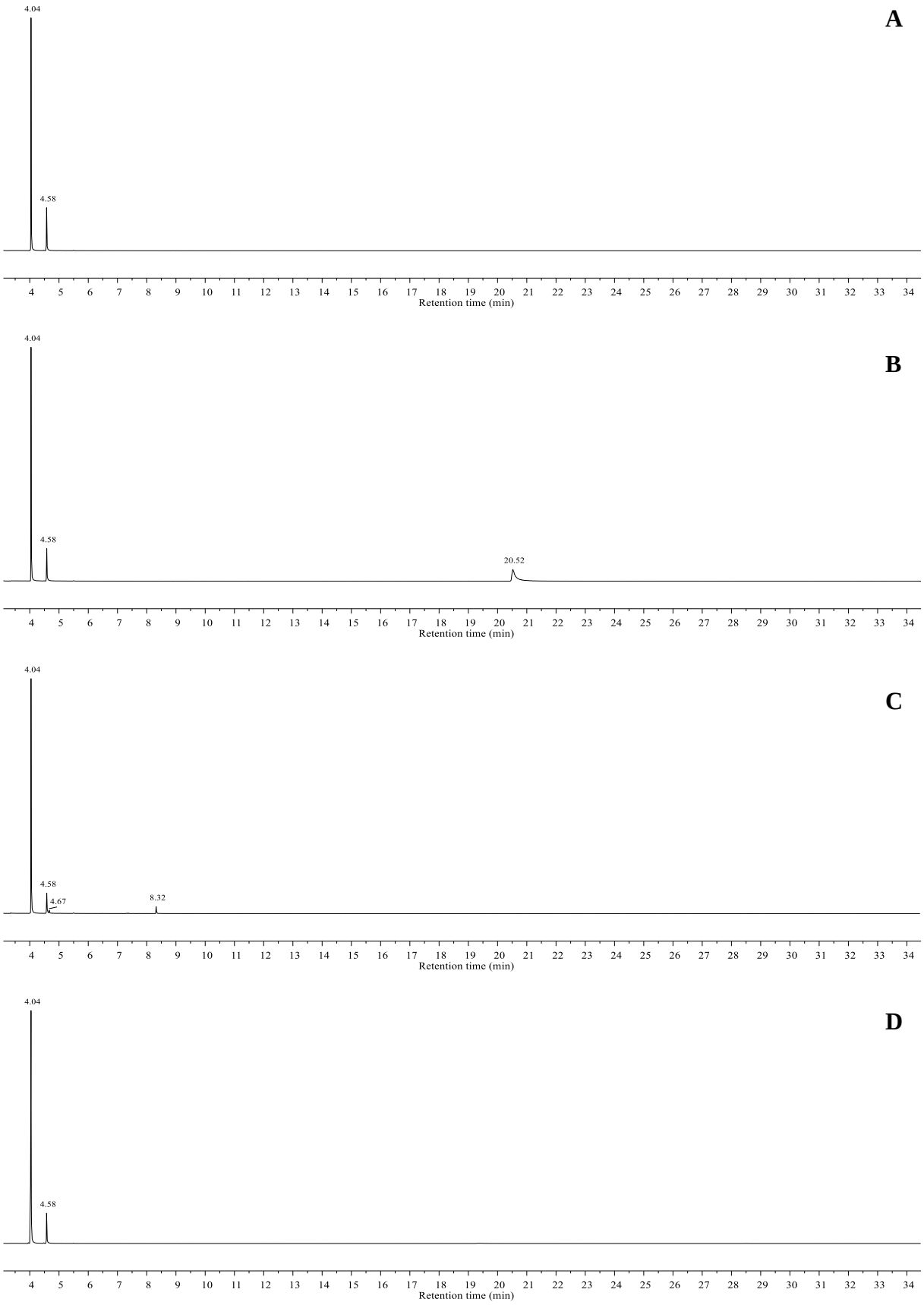

A
3.83
4.57
B
3.83
4.58
20.59
C
3.84
5.50
4.67
3.36
D
3.83
4.02
4.57
3.95
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Addition of Diethyl Methylmalonate

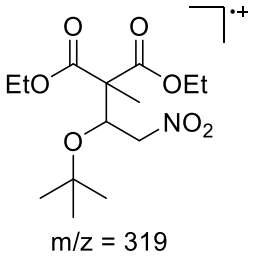


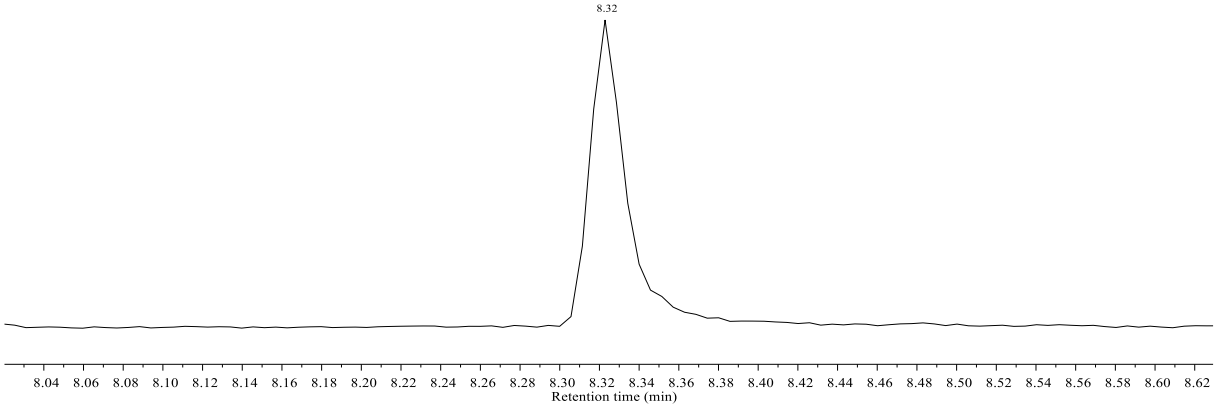
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

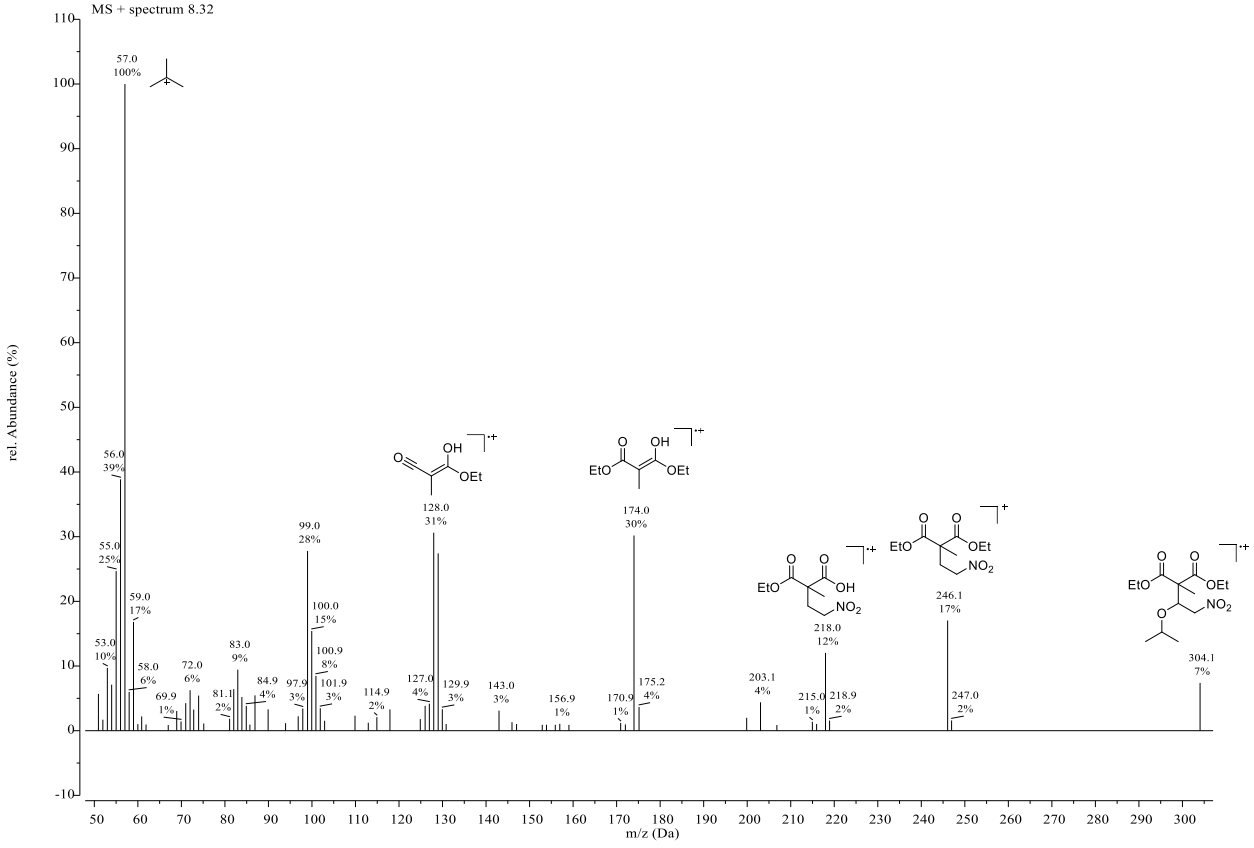
Entry	Compound	Retention time / min
1	Vinyl ether	4.57
2	Quinine	20.55
3	**130**	4.02
5	Water Adduct	5.50
6	Diethyl Methylmalonate	4.04
7	Product	8.32


A
4.04
4.58
B
4.04
4.58
20.52
C
4.04
4.58
4.67
8.32
D
4.04
4.58
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

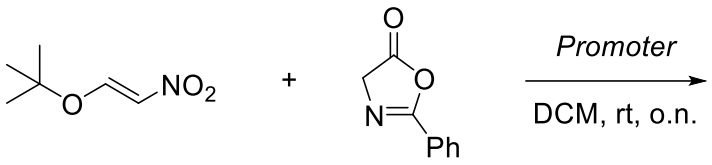
Chromatogram **C**





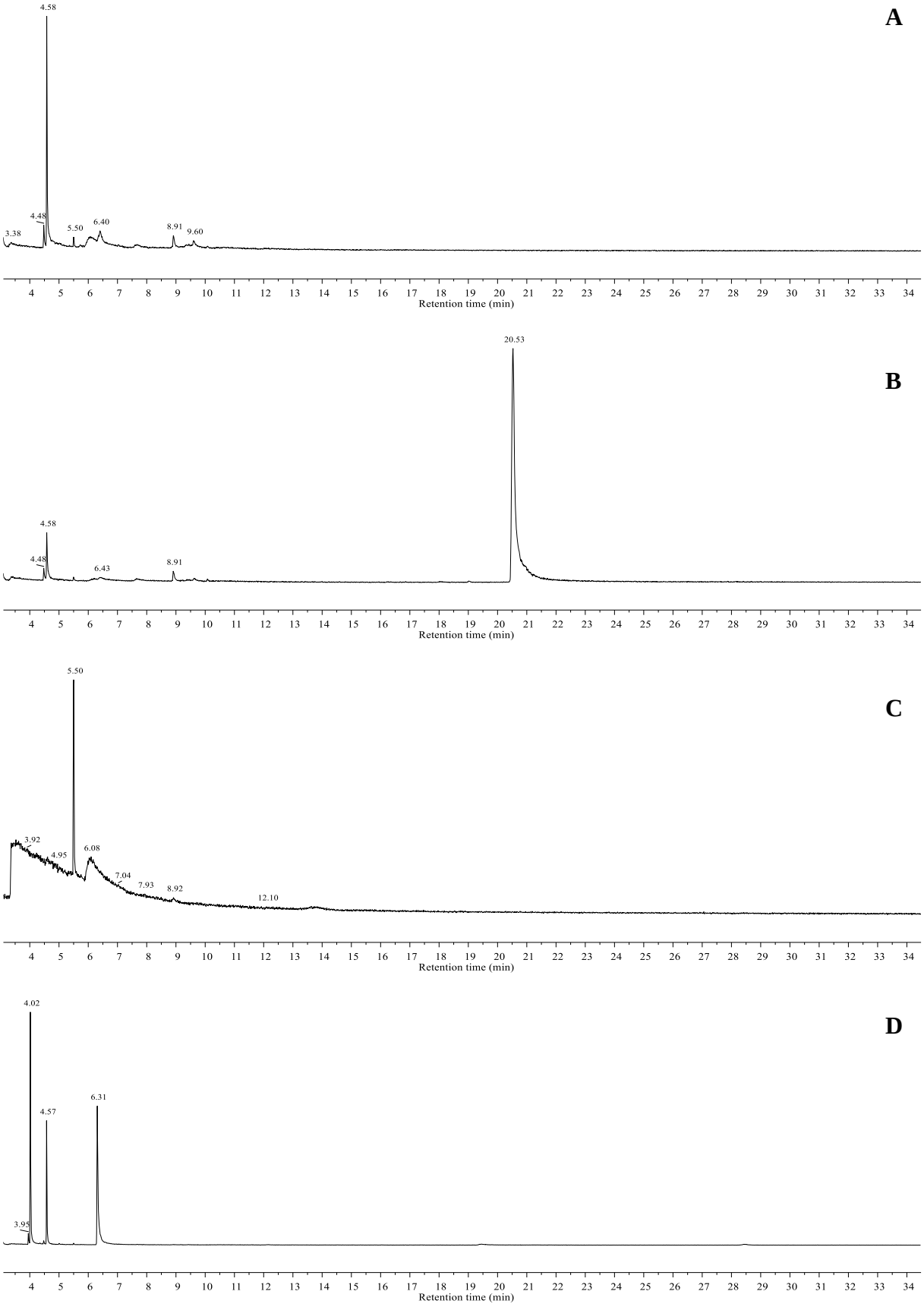


Addition of 2-Phenyl-5(4*H*)-oxazolone

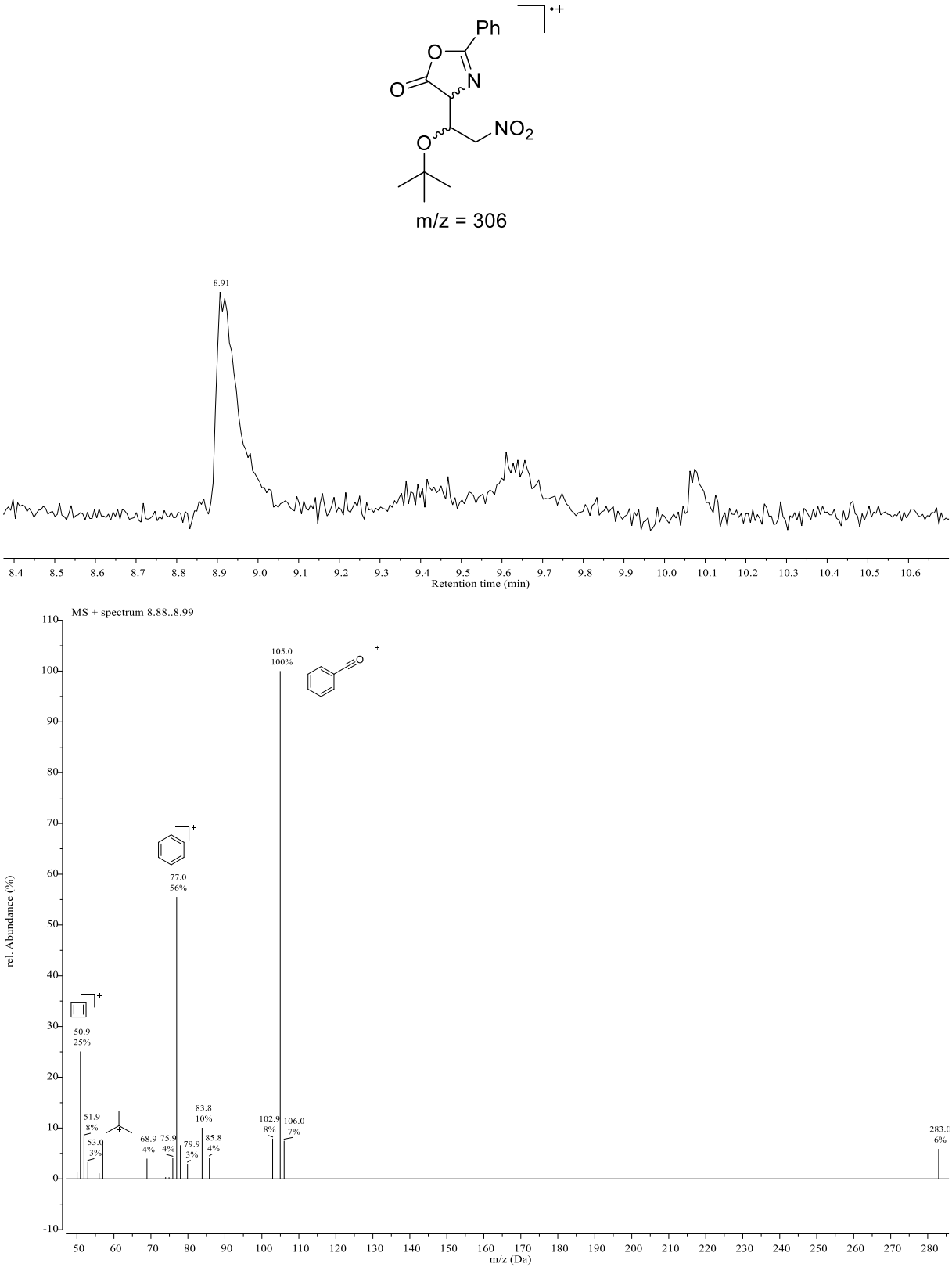


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	4.57
2	Quinine	20.55
3	**130**	4.02
5	Water Adduct	5.50
6	Azlactone	6.31
7	Product	8.32

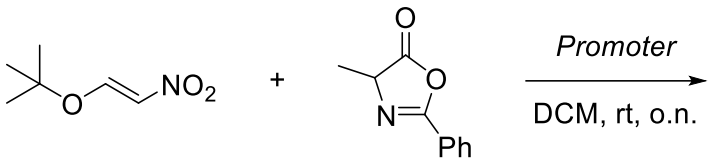

A
4.58
4.48
3.38
5.50
6.40
8.91
9.60
B
20.53
4.58
4.48
6.43
8.91
C
5.50
3.92
4.95
6.08
7.04
7.93
8.92
12.10
D
4.02
4.57
6.31
3.95
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **B**



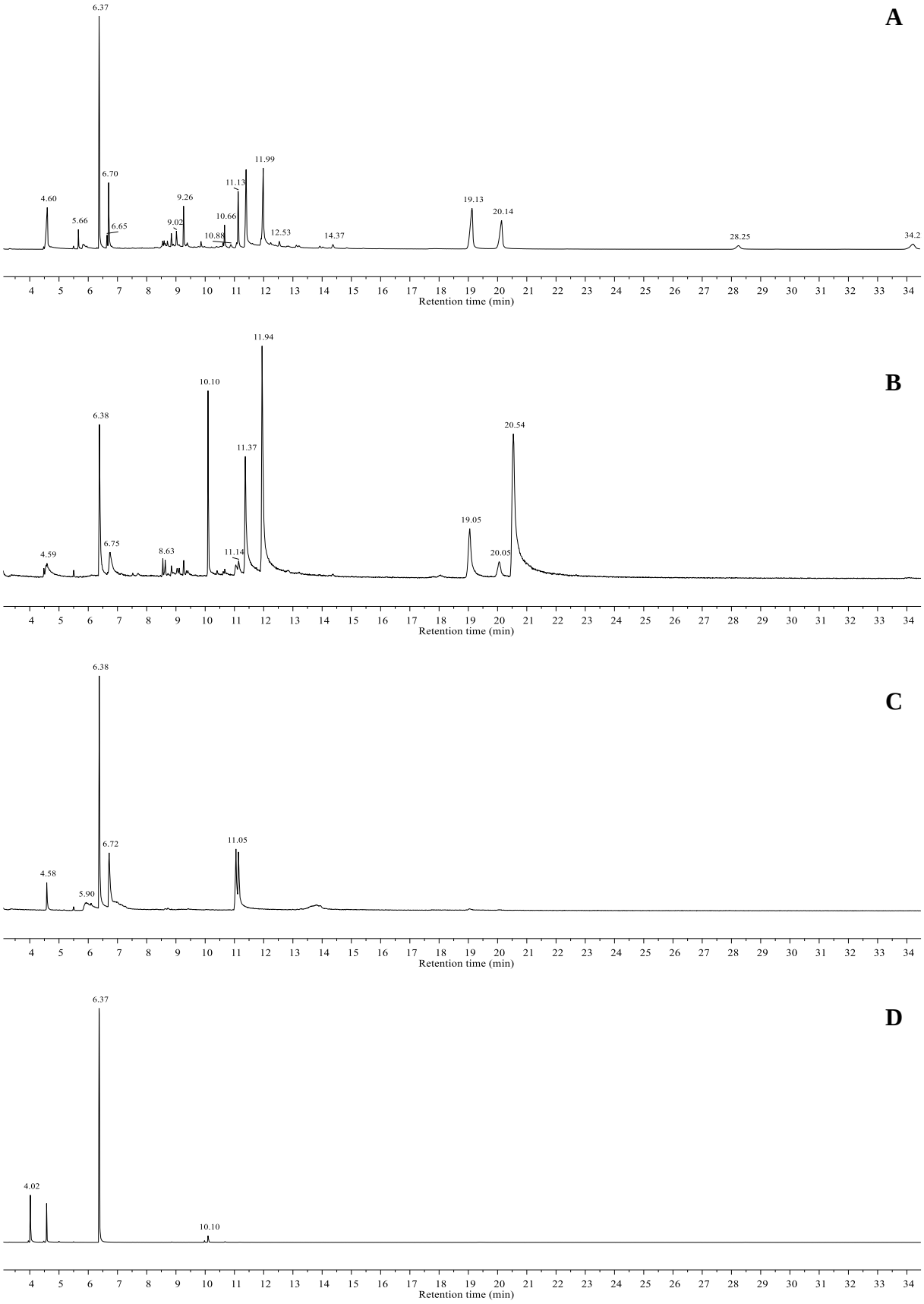
Due to a lack of fragments, ESI-MS of the reaction mixture was carried out to confirm the presence of the desired product.

Addition of 2-Phenyl-4-methyl-5(4*H*)-oxazolone

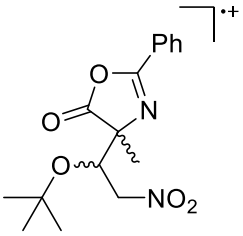


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

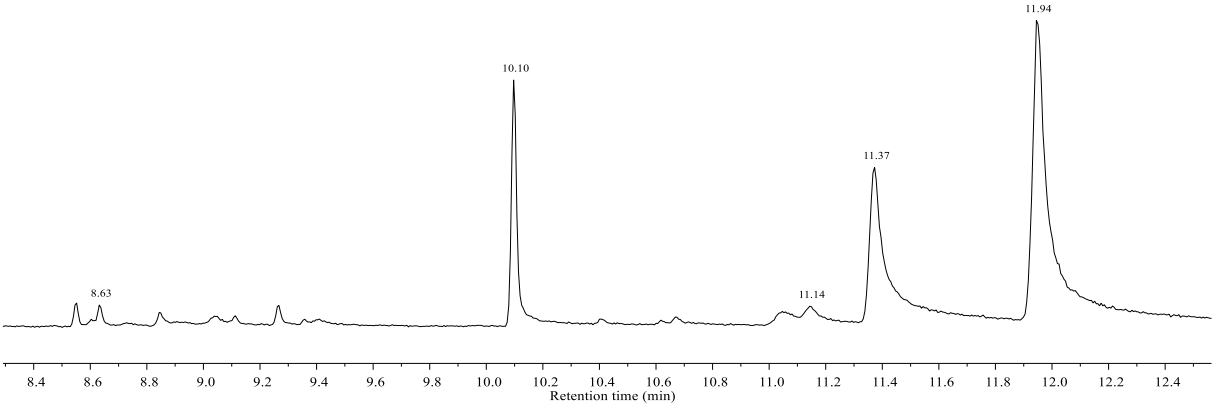
Entry	Compound	Retention time / min
1	Vinyl ether	4.57
2	Quinine	20.55
3	**130**	4.02
5	Water Adduct	5.50
6	Azlactone	6.37
7	Product	

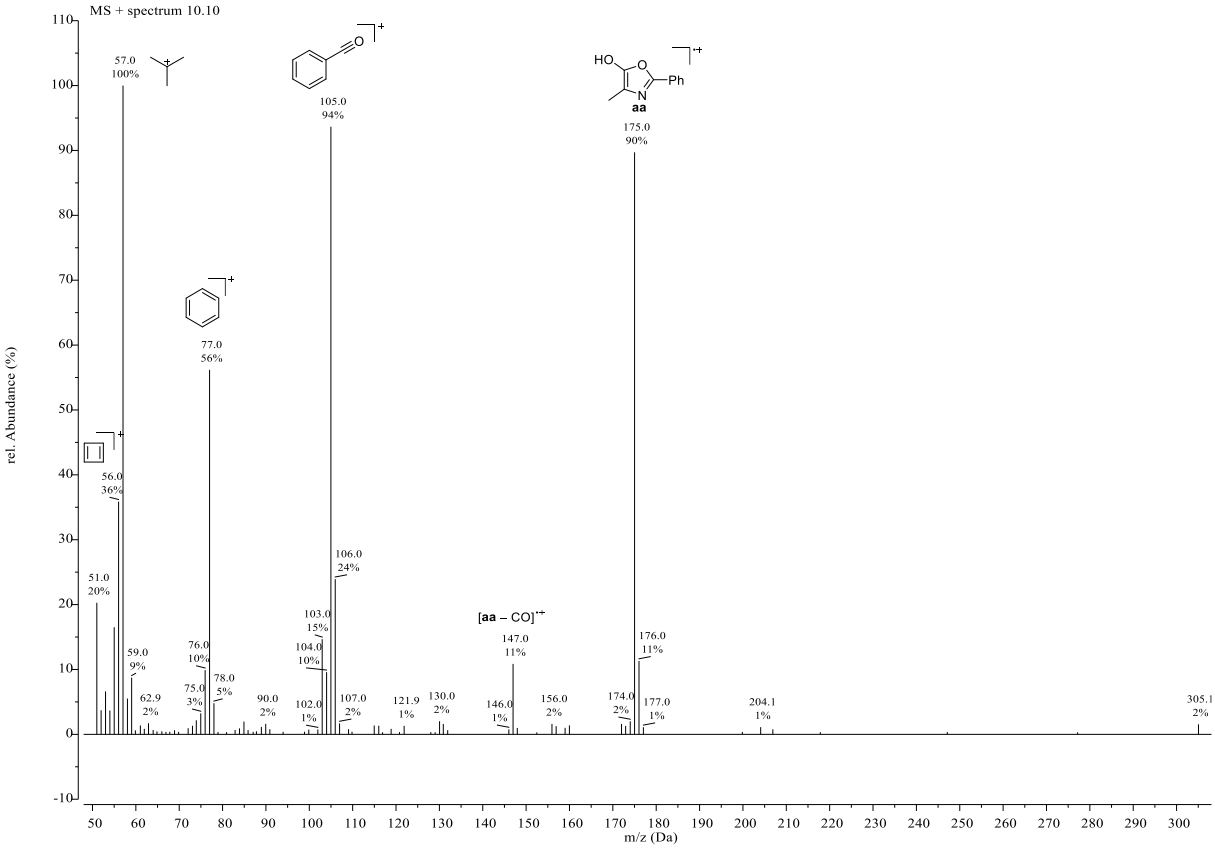

A
6.37
4.60
5.66
6.70
6.65
9.02
9.26
10.66
10.88
11.13
11.99
12.53
14.37
19.13
20.14
28.25
34.2
B
11.94
10.10
6.38
20.54
11.37
19.05
4.59
6.75
8.63
11.14
20.05
C
6.38
6.72
11.05
4.58
5.90
D
6.37
4.02
10.10
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

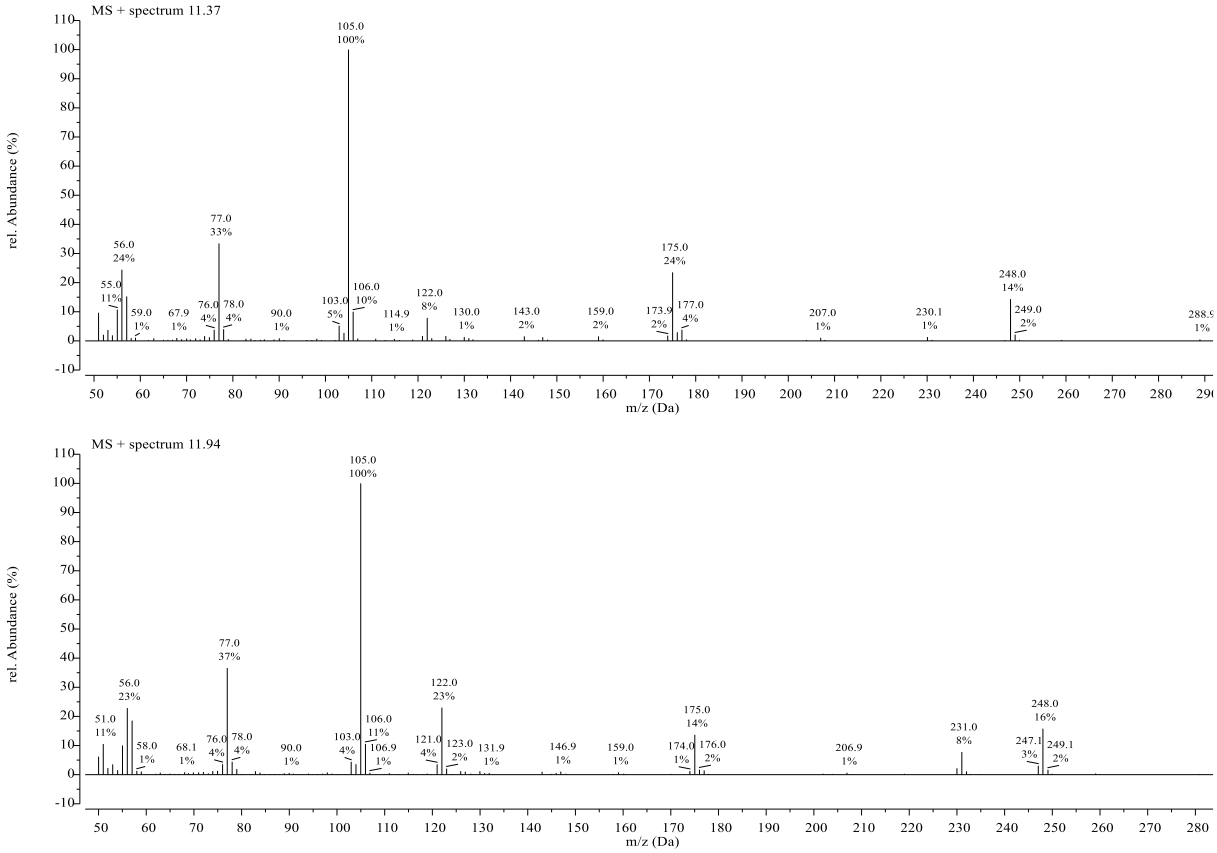
Chromatogram **B**



m/z = 320



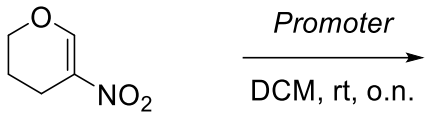




Considering, that the compound detected at t_R = 10.10 min. exhibits a dominant signal for a *tert*-butyl cation, it is reasonable to assume the signal belongs to the desired product. Although a similar signal for the corresponding diastereomer is missing, this can probably be attributed to the fact that a chiral base (quinine) was used in this reaction. The other signals at t_R = 11.37 min. and t_R = 11.94 min. exhibit a fragmentation pattern similar to each other, indicating they are diastereomers. Although they lack any fragments corresponding to the Vinyl ether (especially the *tert*-butyl cation signal), it is reasonable to assume that these signals correspond to a product formed in a follow-up reaction after the addition.

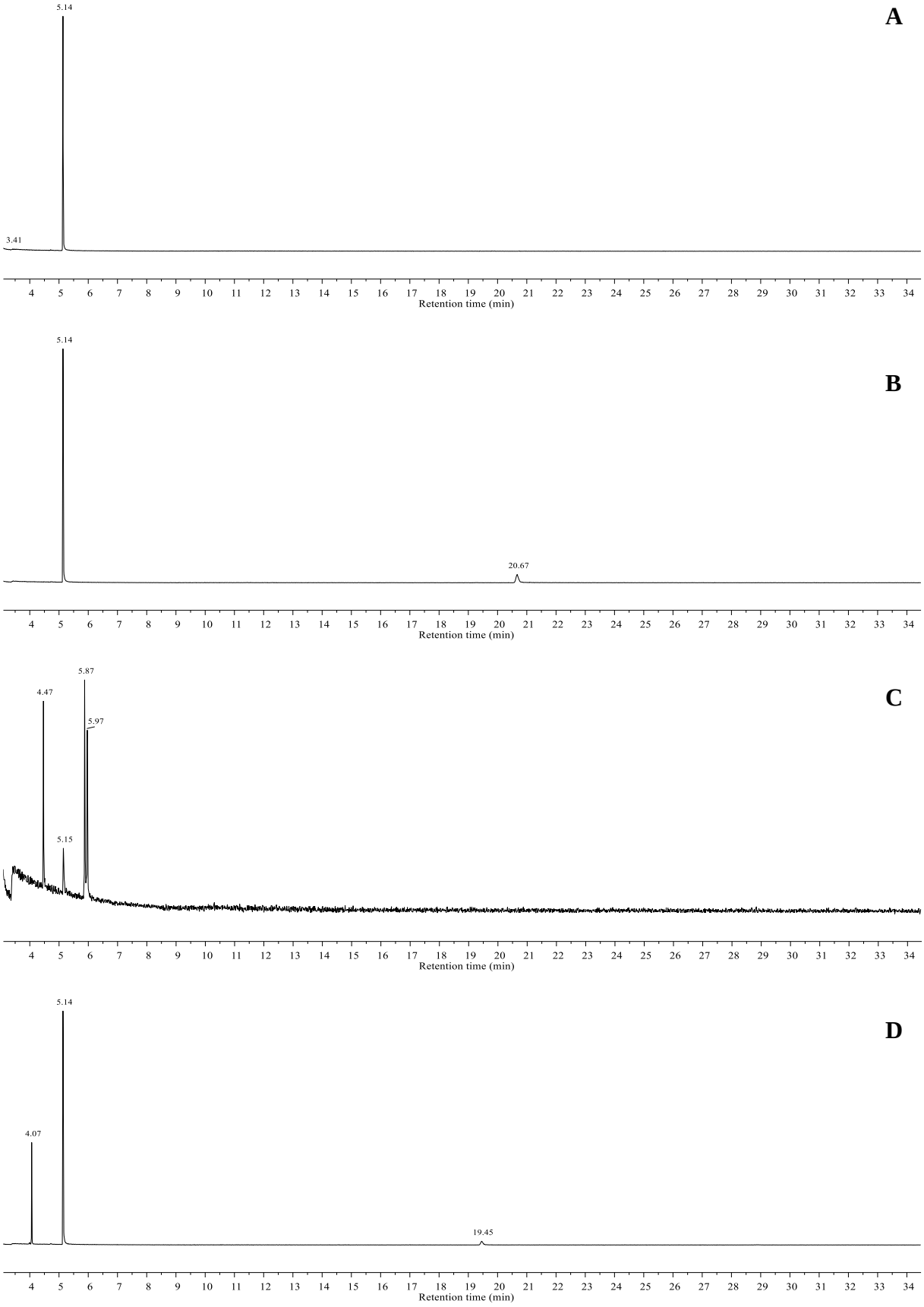
Additions to 3,4-Dihydro-5-nitro-2*H*-pyran

Blind Reactions

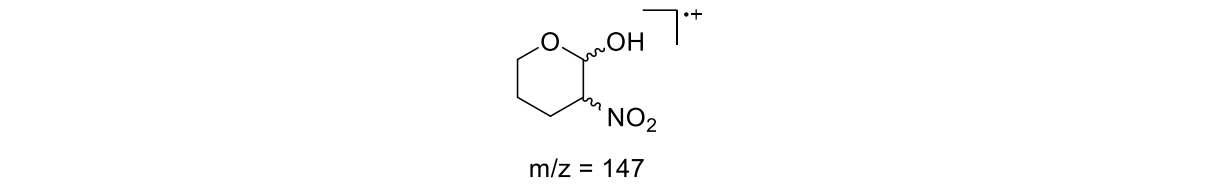


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

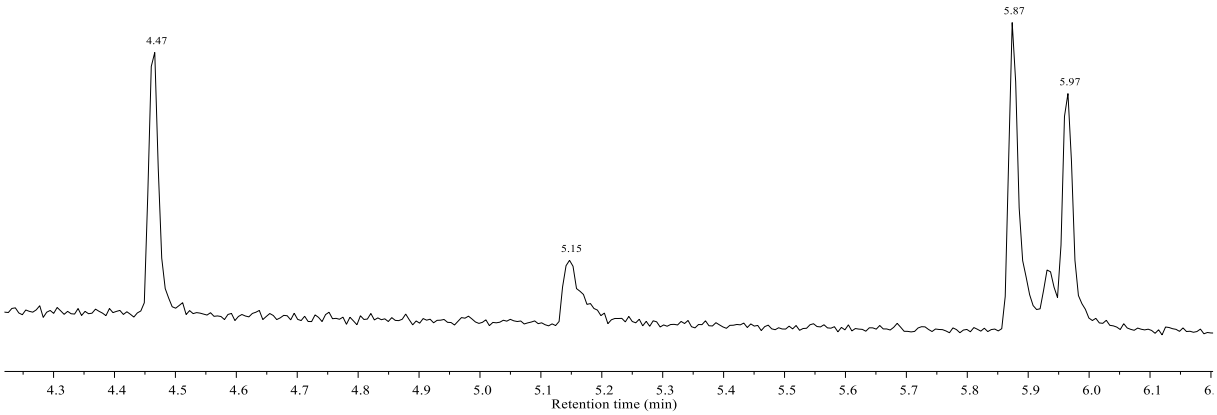
Entry	Compound	Retention time / min
1	**263**	5.14
2	Quinine	20.55
3	**130**	4.02
5	Water Adducts	5.87 & 5.97

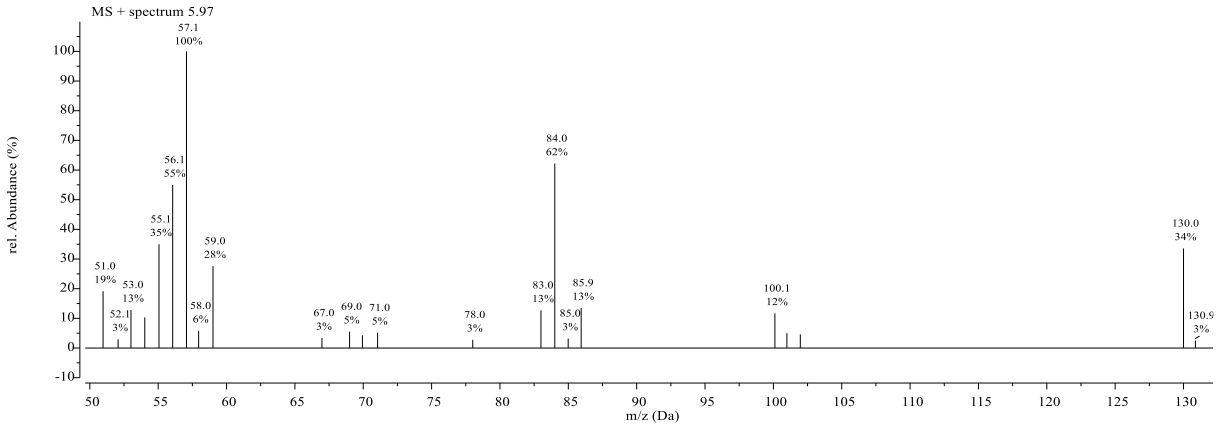

A
5.14
3.41
B
5.14
20.67
C
4.47
5.87
5.97
5.15
D
5.14
4.07
19.45
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

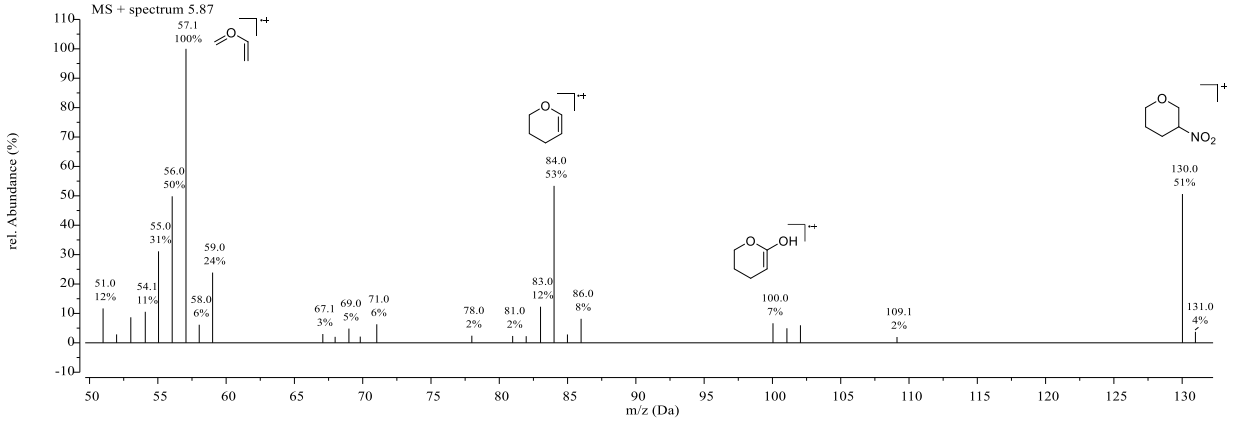
Chromatogram **C**



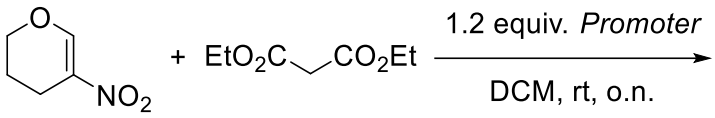
m/z = 147





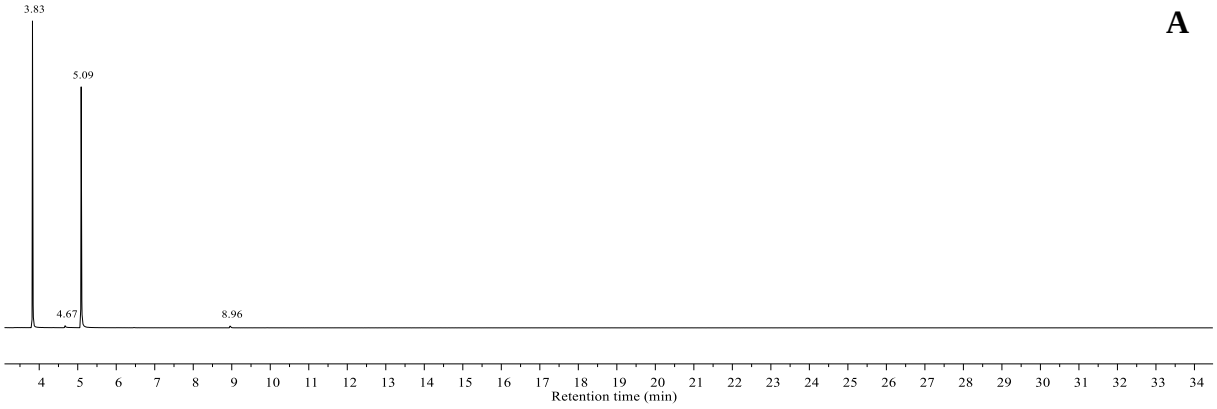


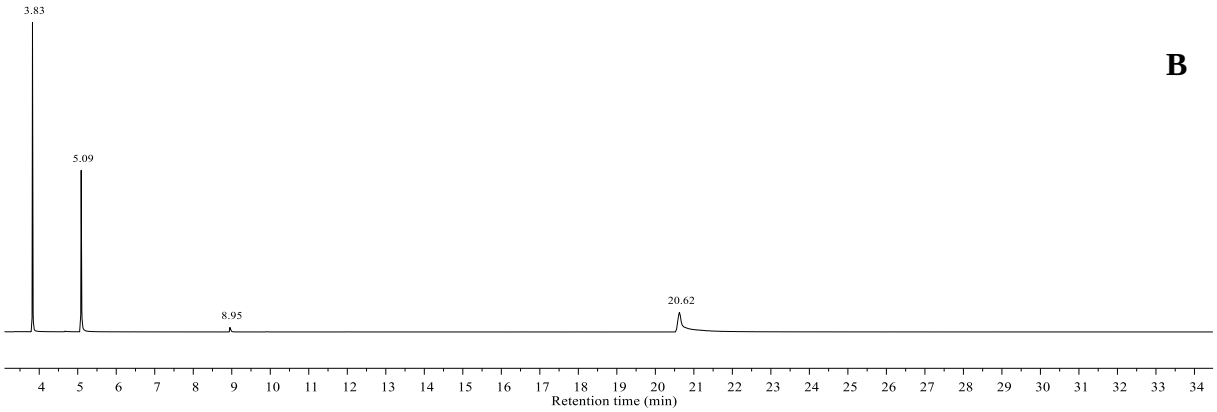
Addition of Diethyl Malonate

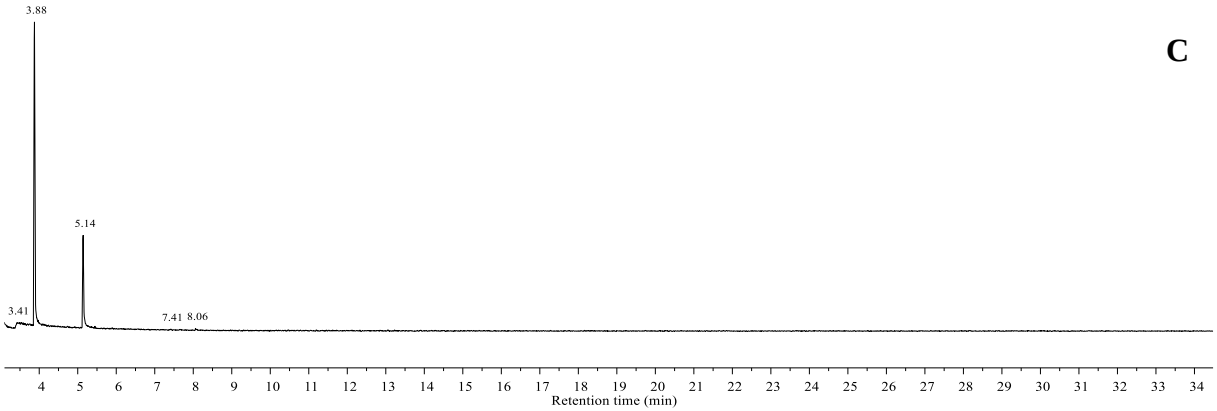


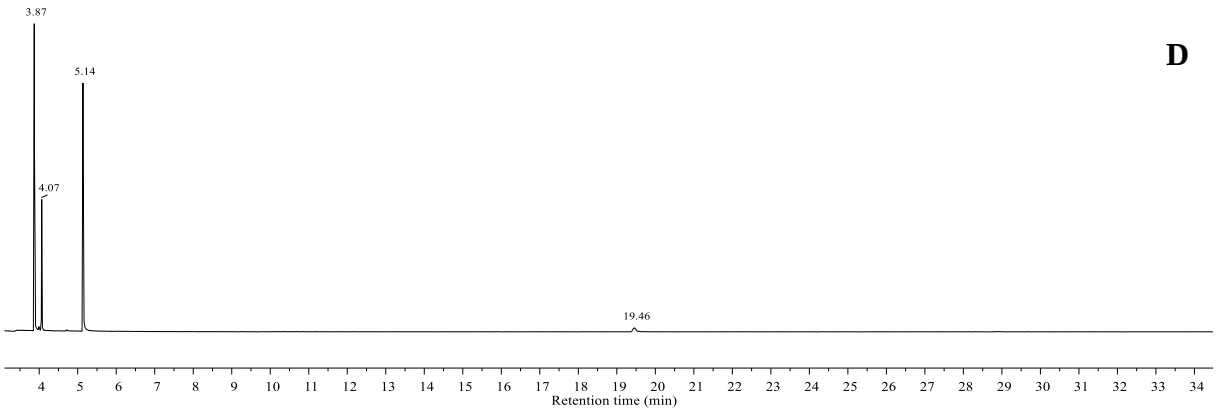
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	5.14
2	Quinine	20.55
3	**130**	4.02
5	Water Adducts	5.87 & 5.97
6	Diethyl Malonate	3.88

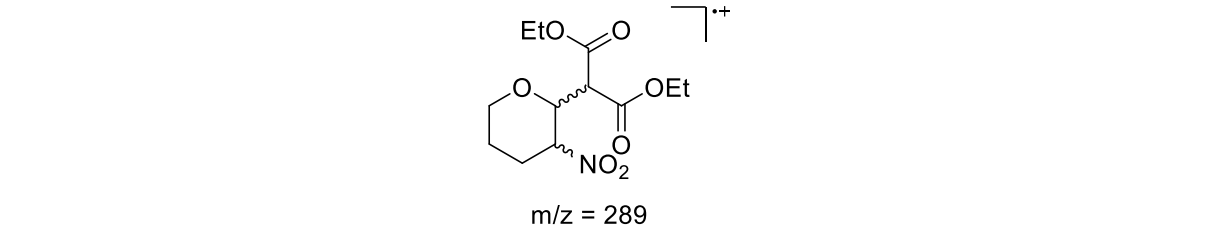

A
3.83
5.09
4.67
8.96
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

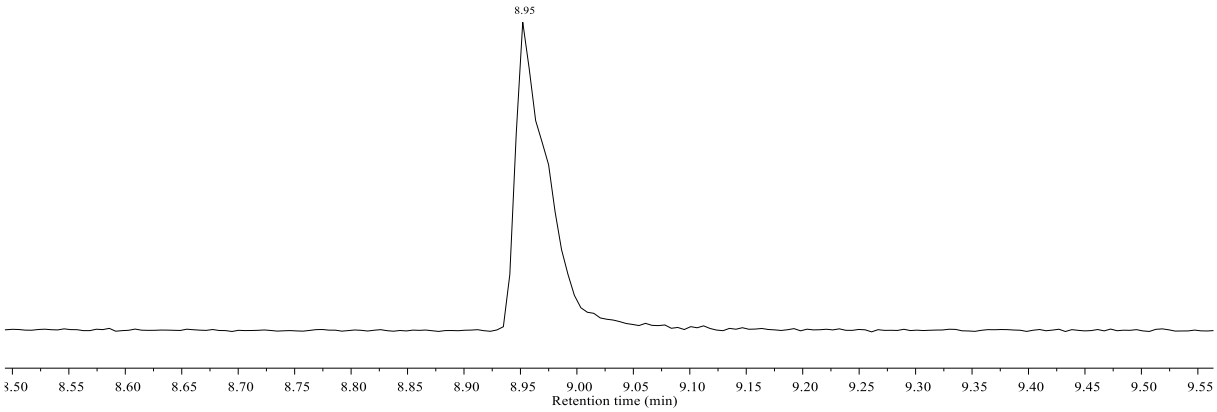

B
3.83
5.09
8.95
20.62
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

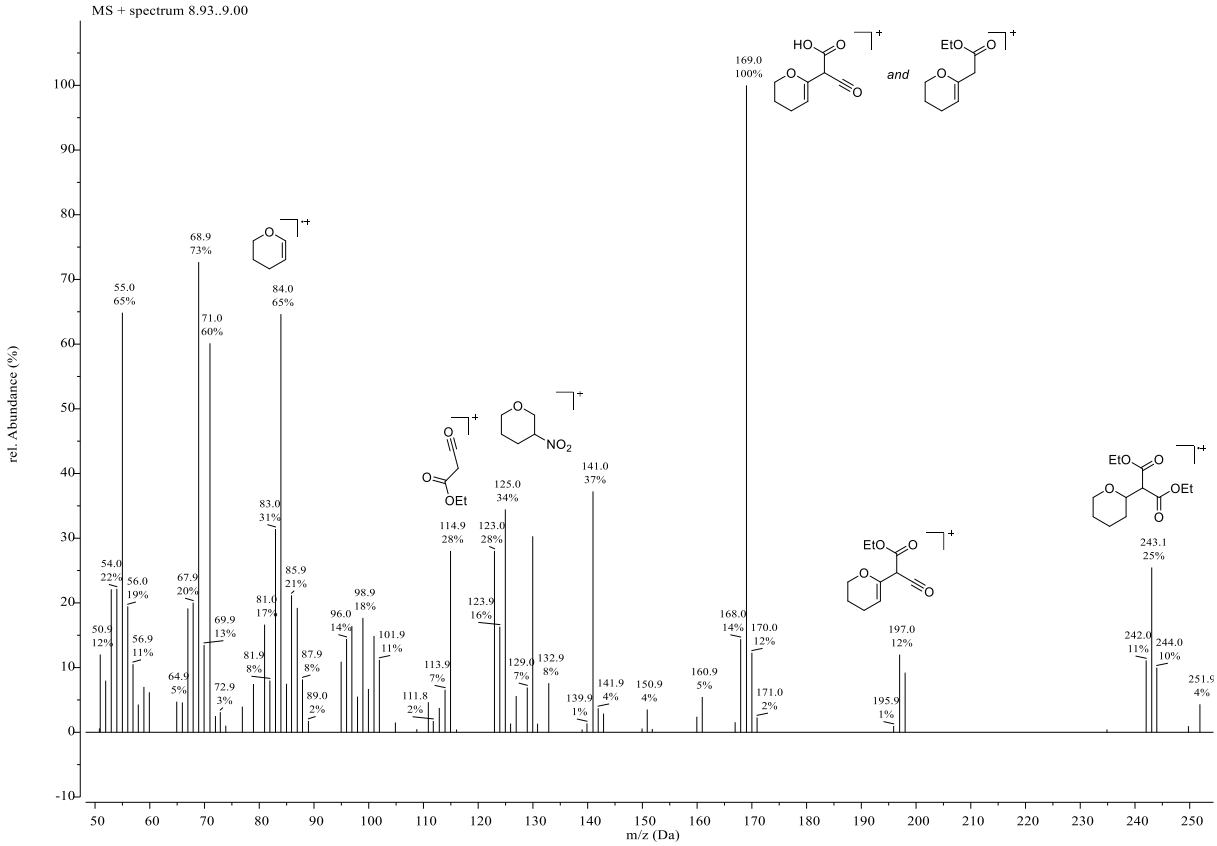

C
3.88
5.14
3.41
7.41
8.06
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)


D
3.87
5.14
4.07
19.46
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

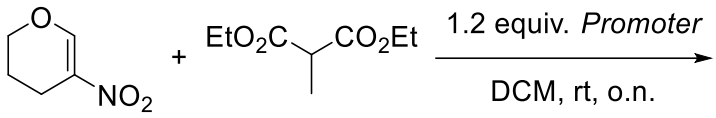
Chromatogram **B**





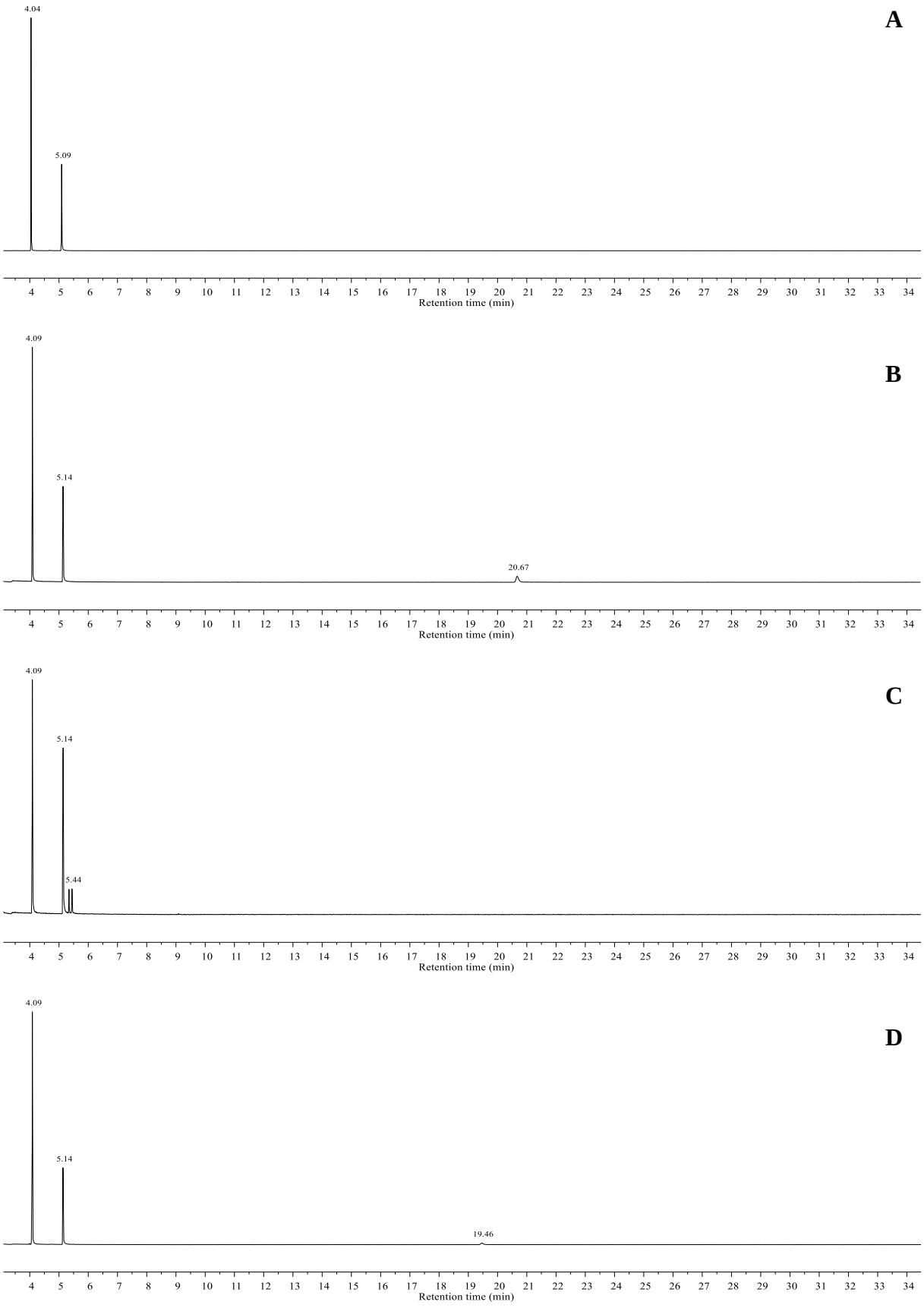


Addition of Diethyl Methylmalonate



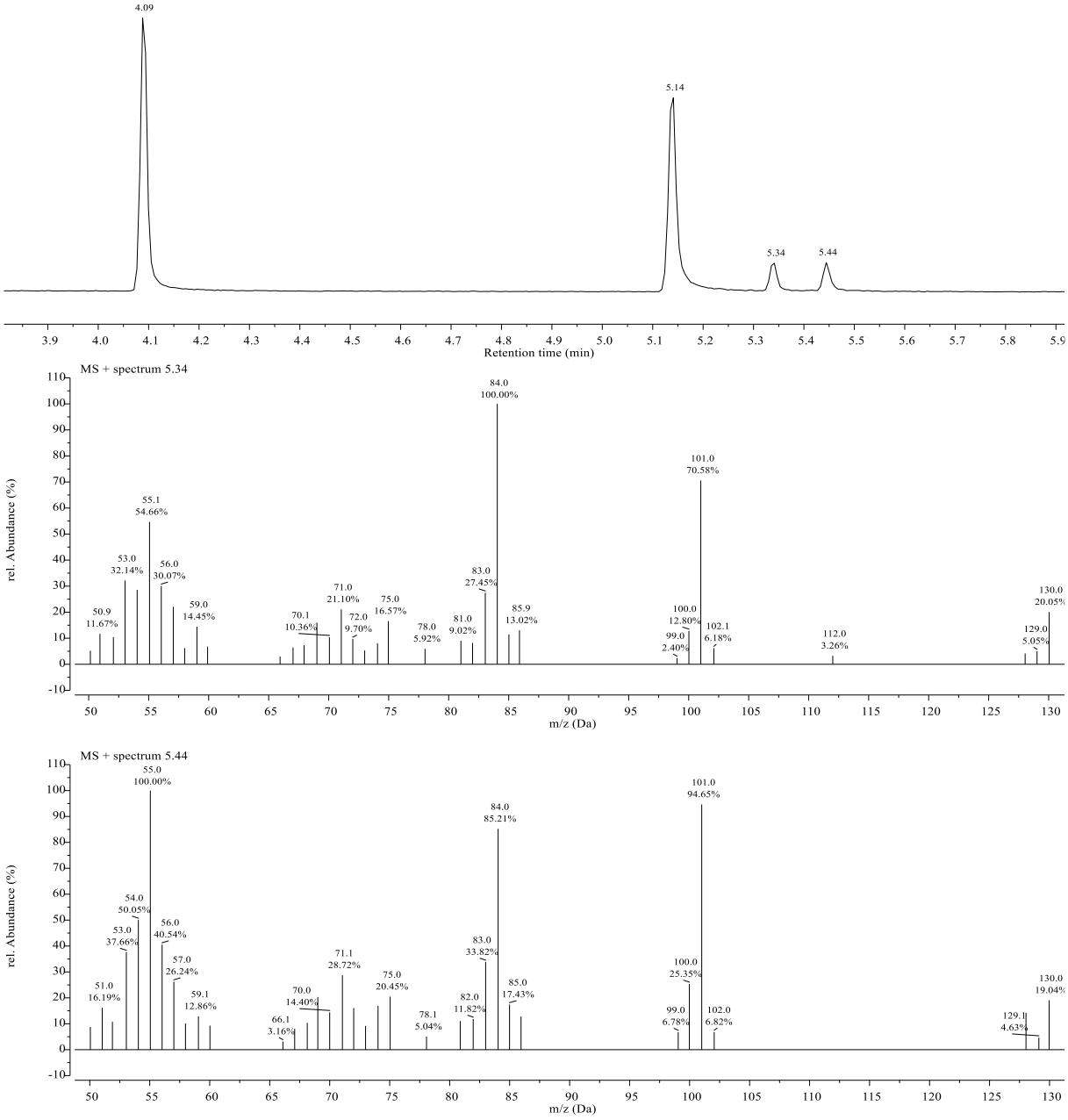
Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ether	5.14
2	Quinine	20.55
3	**130**	4.02
5	Water Adducts	5.87 & 5.97
6	Diethyl Methylmalonate	4.04

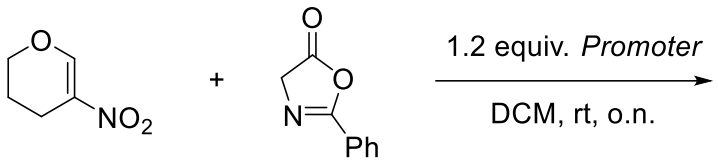

A
4.04
5.09
B
4.09
5.14
20.67
C
4.09
5.14
5.44
D
4.09
5.14
19.46
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

Chromatogram **C**

The fragmentations of the newly appeared signals are in good agreement with the ones found for the water addition product.

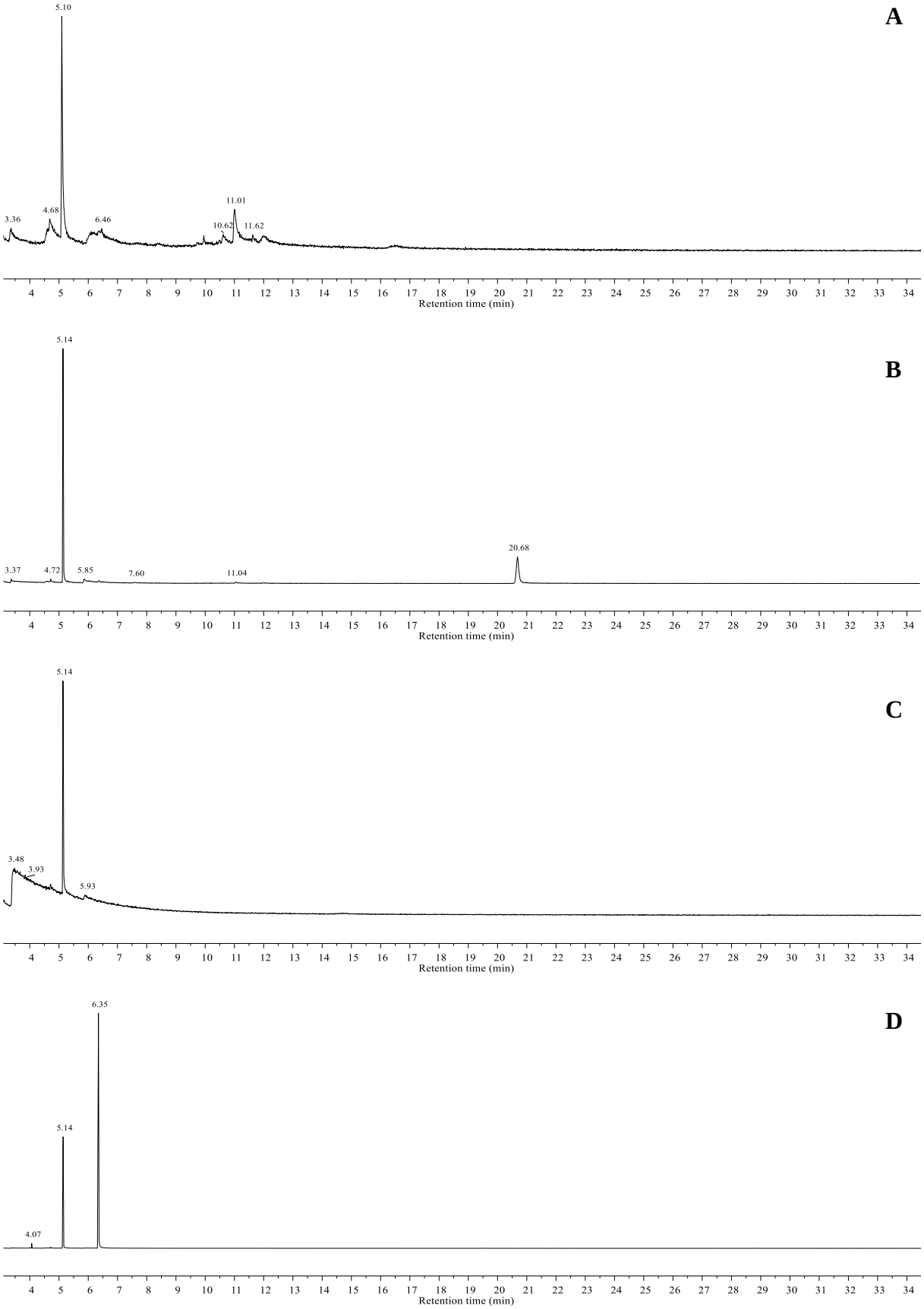


Addition of 2-Phenyl-5(4*H*)-oxazolone

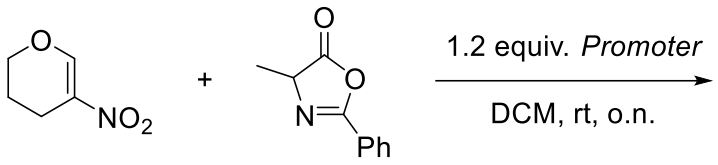


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	Vinyl ethers	5.14
2	Quinine	20.55
3	**130**	4.02
5	Water Adducts	5.87 & 5.97
6	Azlactone	6.37

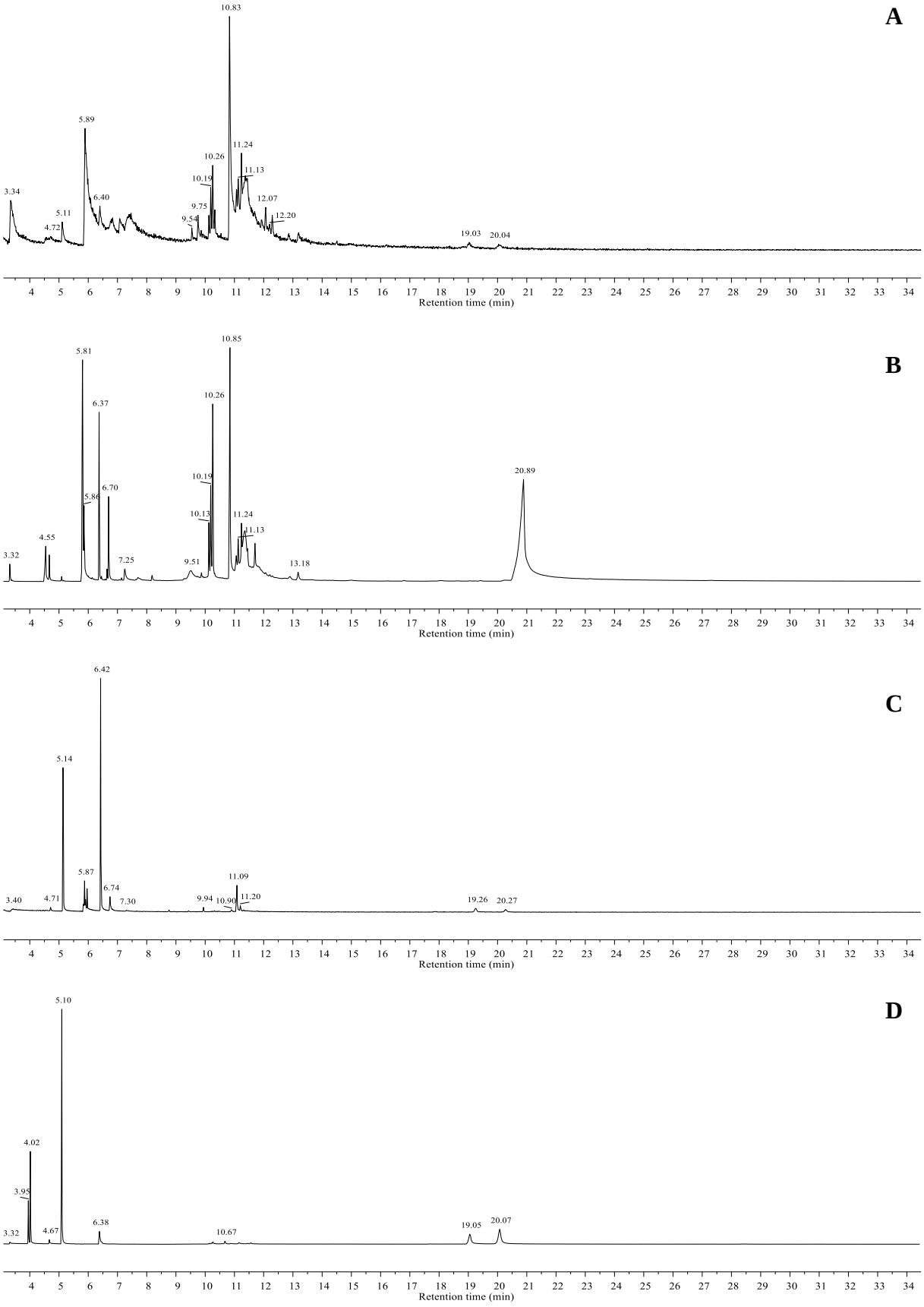

A
5.10
3.36
4.68
6.46
10.62
11.01
11.62
B
5.14
3.37
4.72
5.85
7.60
11.04
20.68
C
5.14
3.48
3.93
5.93
D
6.35
5.14
4.07
Retention time (min)

Addition of 2-Phenyl-4-methyl-5(4*H*)-oxazolone

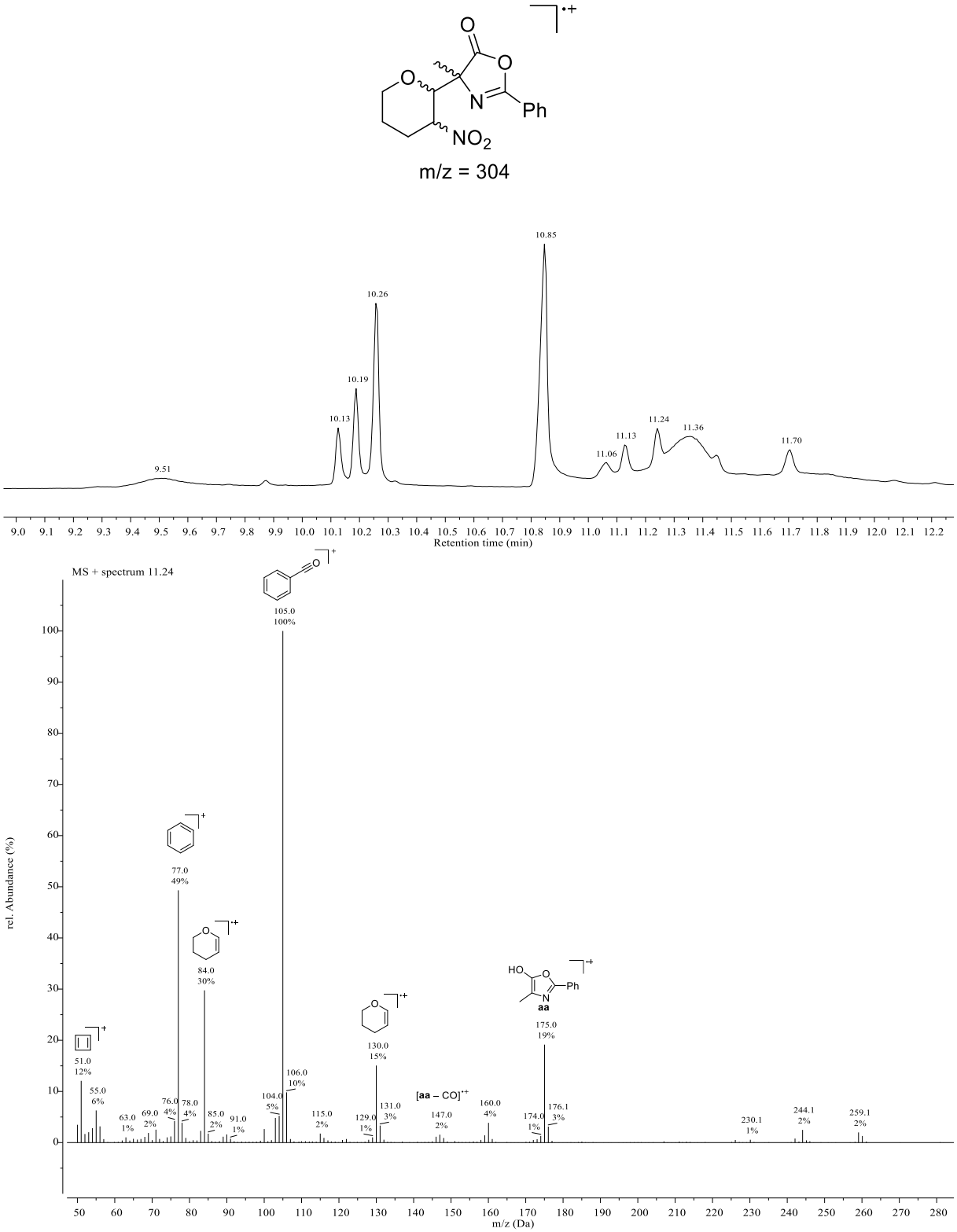


Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

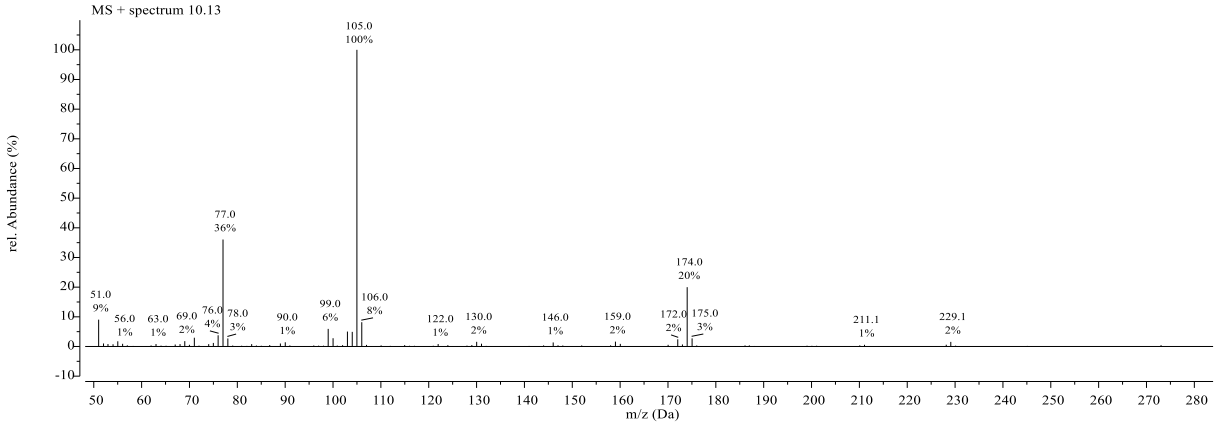
Entry	Compound	Retention time / min
1	Vinyl ethers	5.14
2	Quinine	20.55
3	**130**	4.02
5	Water Adduct	5.87 & 5.97
6	Azlactone	6.37

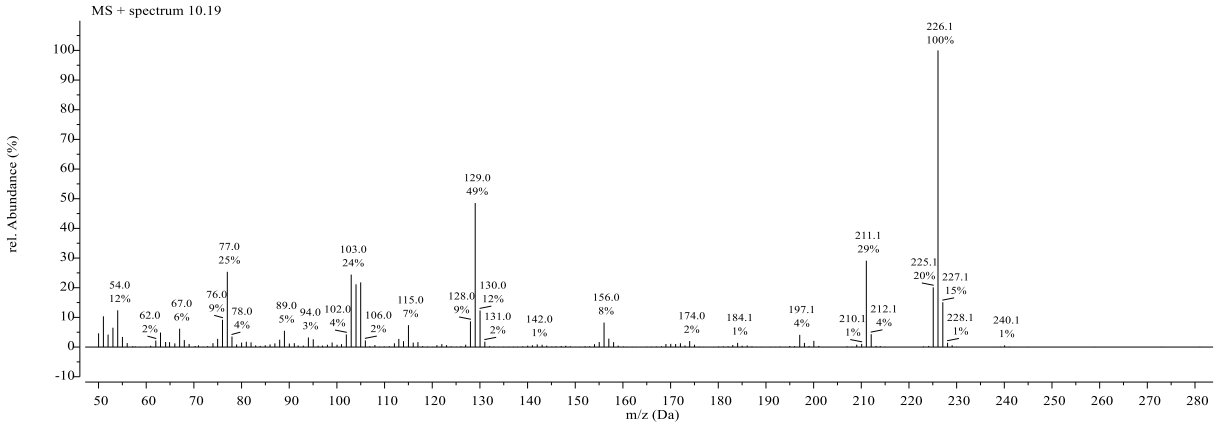

A
10.83
5.89
11.24
10.26
11.13
10.19
6.40
12.07
9.75
5.11
12.20
9.54
4.72
3.34
19.03
20.04
B
10.85
5.81
10.26
6.37
20.89
10.19
6.70
5.86
10.13
11.24
11.13
4.55
3.32
7.25
9.51
13.18
C
6.42
5.14
5.87
11.09
6.74
3.40
4.71
7.30
9.94
10.90
11.20
19.26
20.27
D
5.10
4.02
3.95
3.32
4.67
6.38
10.67
19.05
20.07
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

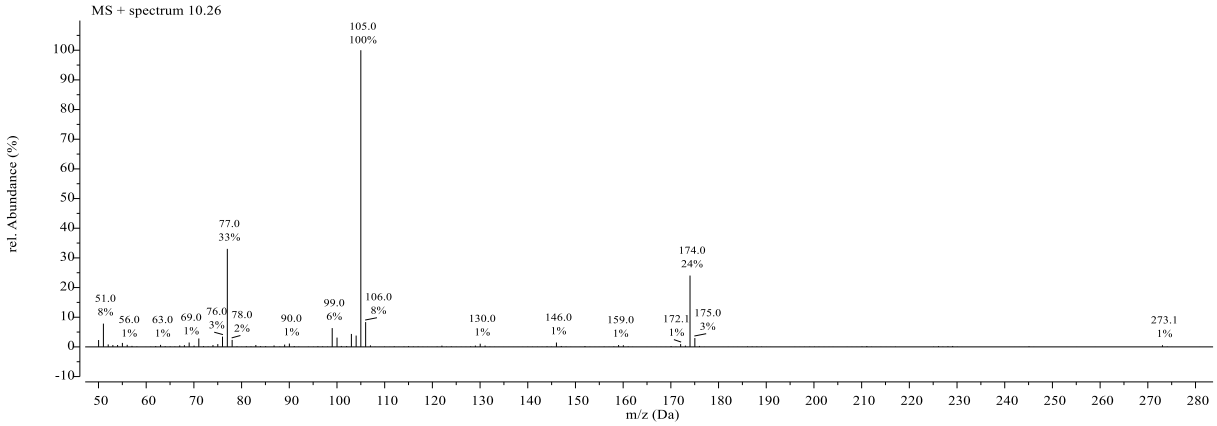
Chromatogram **B**

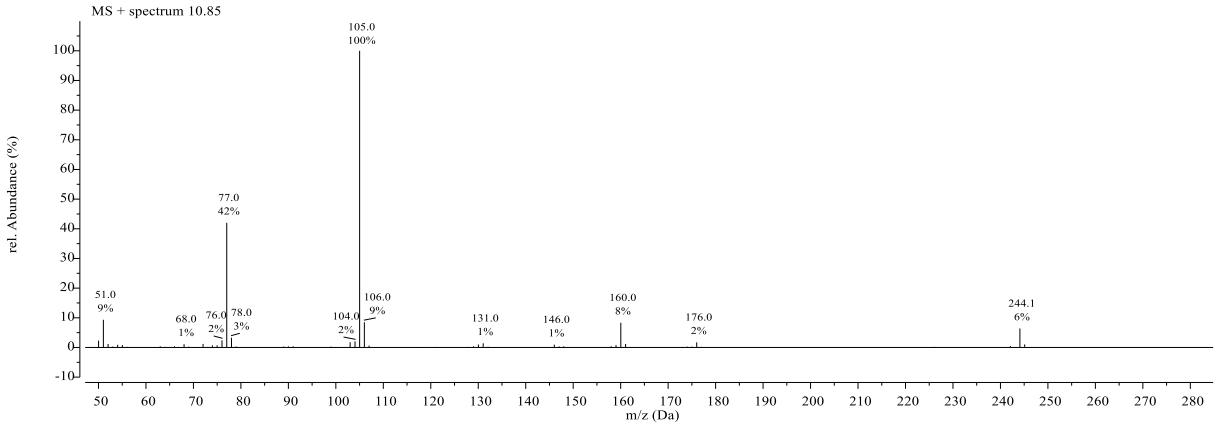


It should be noted that the other compounds detected also showed fragments corresponding to the azlactone, but no fragments of the corresponding ether could be detected. The Spectra are shown below.


MS + spectrum 10.13
rel. Abundance (%)
m/z (Da)
105.0 100%
77.0 36%
174.0 20%
51.0 9%
106.0 8%
99.0 6%
56.0 1%
63.0 1%
69.0 2%
76.0 4%
78.0 3%
90.0 1%
122.0 1%
130.0 2%
146.0 1%
159.0 2%
172.0 2%
175.0 3%
211.1 1%
229.1 2%

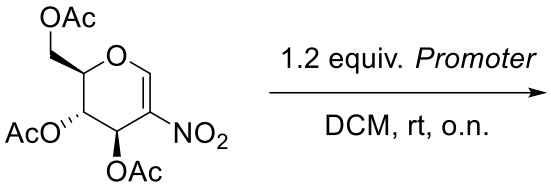

MS + spectrum 10.19
rel. Abundance (%)
m/z (Da)
226.1 100%
129.0 49%
211.1 29%
77.0 25%
103.0 24%
225.1 20%
227.1 15%
54.0 12%
130.0 12%
76.0 9%
128.0 9%
67.0 6%
78.0 4%
89.0 5%
94.0 3%
102.0 4%
106.0 2%
115.0 7%
131.0 2%
62.0 2%
142.0 1%
156.0 8%
174.0 2%
184.1 1%
197.1 4%
210.1 1%
212.1 4%
228.1 1%
240.1 1%


MS + spectrum 10.26
rel. Abundance (%)
m/z (Da)
105.0 100%
77.0 33%
174.0 24%
51.0 8%
106.0 8%
99.0 6%
56.0 1%
63.0 1%
69.0 1%
76.0 3%
78.0 2%
90.0 1%
130.0 1%
146.0 1%
159.0 1%
172.1 1%
175.0 3%
273.1 1%


MS + spectrum 10.85
rel. Abundance (%)
m/z (Da)
105.0 100%
77.0 42%
51.0 9%
106.0 9%
160.0 8%
244.1 6%
68.0 1%
76.0 2%
78.0 3%
104.0 2%
131.0 1%
146.0 1%
176.0 2%

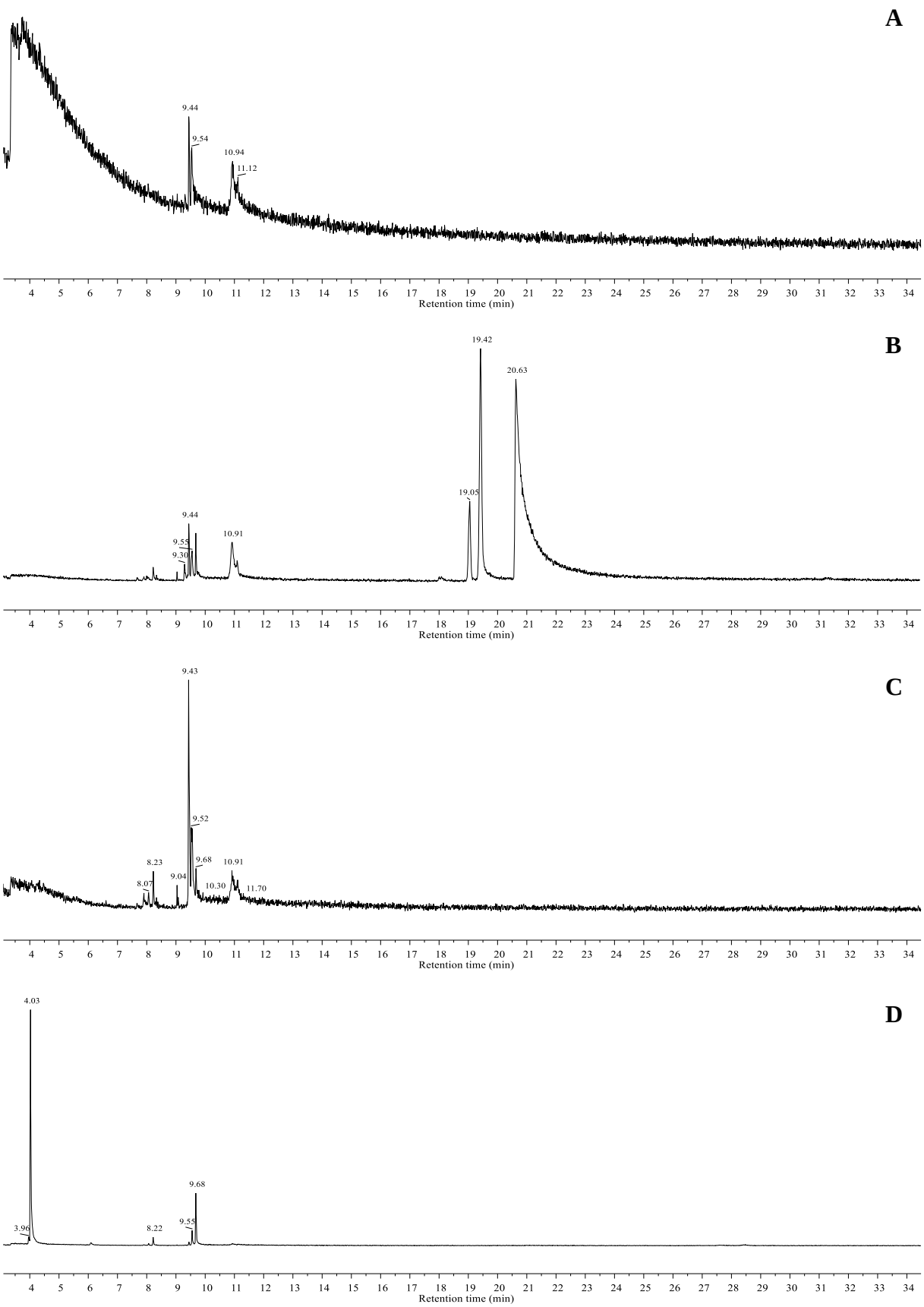
Addition to 2-Nitro-3,4,6-Tri-*O*-acetyl-D-glucal

Blind Reactions



Entry	Promoter	Equivalents	Chromatogram
1	Et_3N	1.2	**A**
2	Quinine	1.2	**B**
3	KO^tBu	1.2	**C**
4	**130**	0.2	**D**

Entry	Compound	Retention time / min
1	**44**	9.55
2	Quinine	20.55
3	**130**	4.02


A
9.44
9.54
10.94
11.12
B
19.42
20.63
19.05
9.44
9.55
9.30
10.91
C
9.43
9.52
8.23
9.68
10.91
8.07
9.04
10.30
11.70
D
4.03
9.68
3.96
8.22
9.55
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Retention time (min)

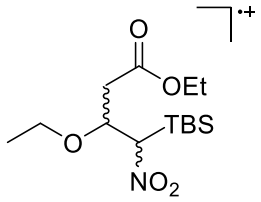
Reactions with Silyl Enol Ether

Entry	Nitro Vinyl Ether
1	**223**
2	**256**
3	**263**

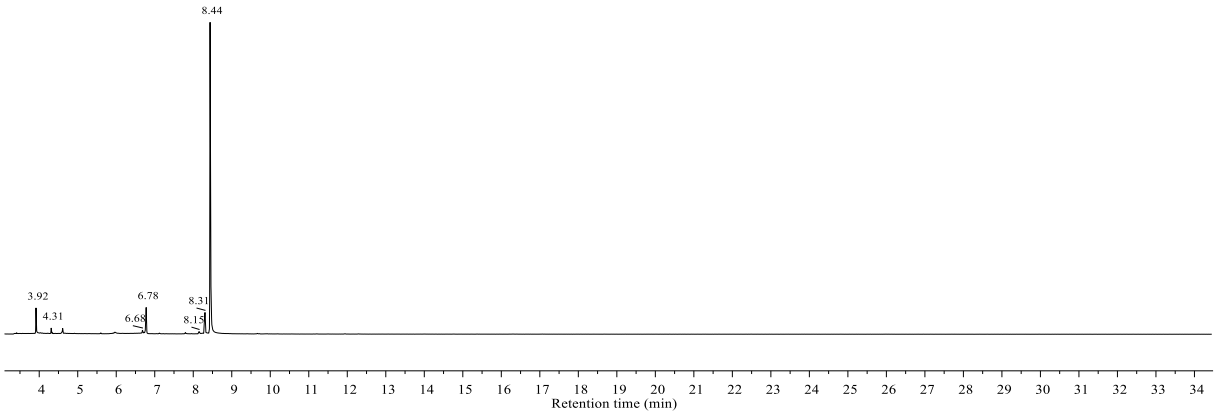
Entry	Compound	Retention time / min
1	Silyl Enol Ether	3.92, 4.32, 5.93, 6.78
2	**223**	3.79
3	**256**	4.57
4	**263**	5.08
5	*β*-Nitrostyrene	6.33

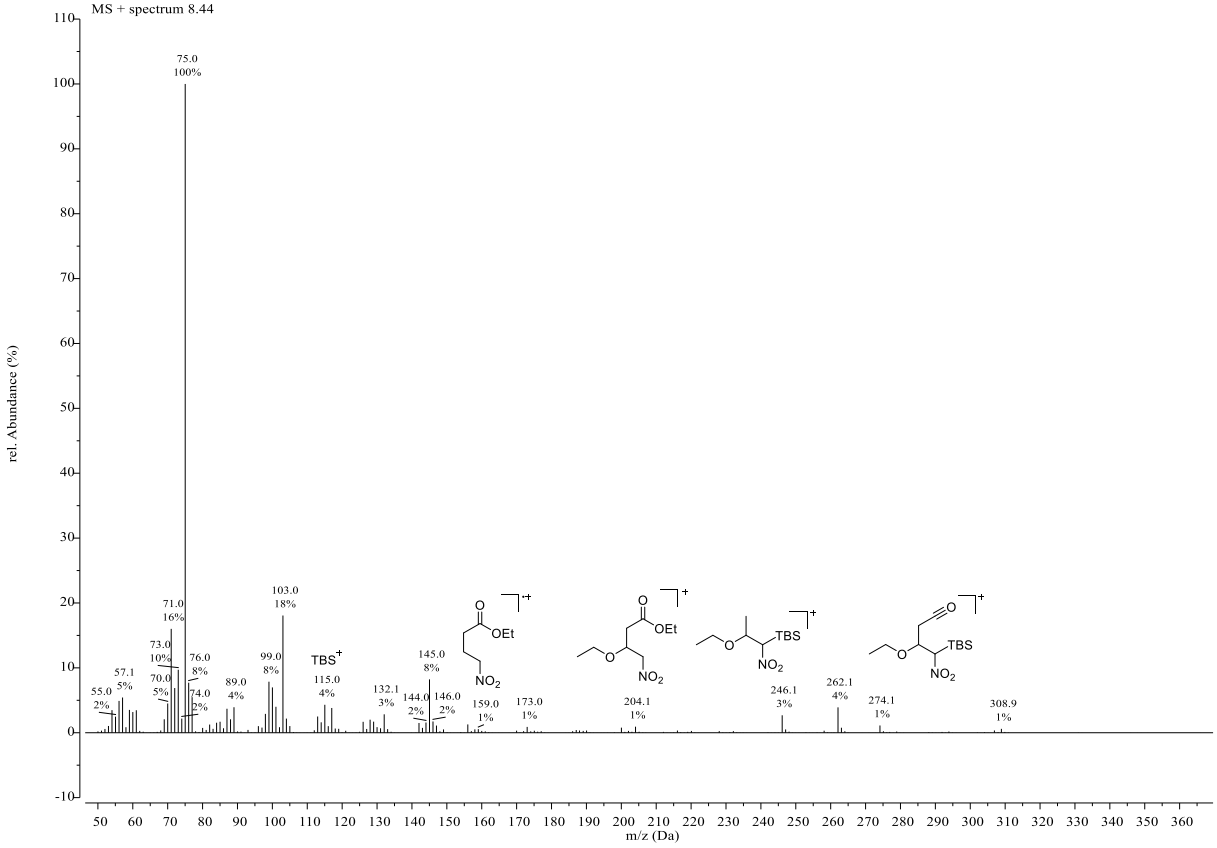
The presence of the desired products was established by ESI-MS, as masses corresponding to $[M + Na]^+$ and $[2M + Na]^+$ could be observed. The preliminary structural proposal is based on the observation of the $[M – TBS]^+$ fragment and the observation that the $[M + Na]^+$ signal was by far the most intense. Isolation of the product and assignment by NMR is still going on.

Addition to (1*E*)-1-Ethoxy-2-nitroethene

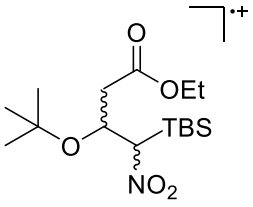


m/z = 319

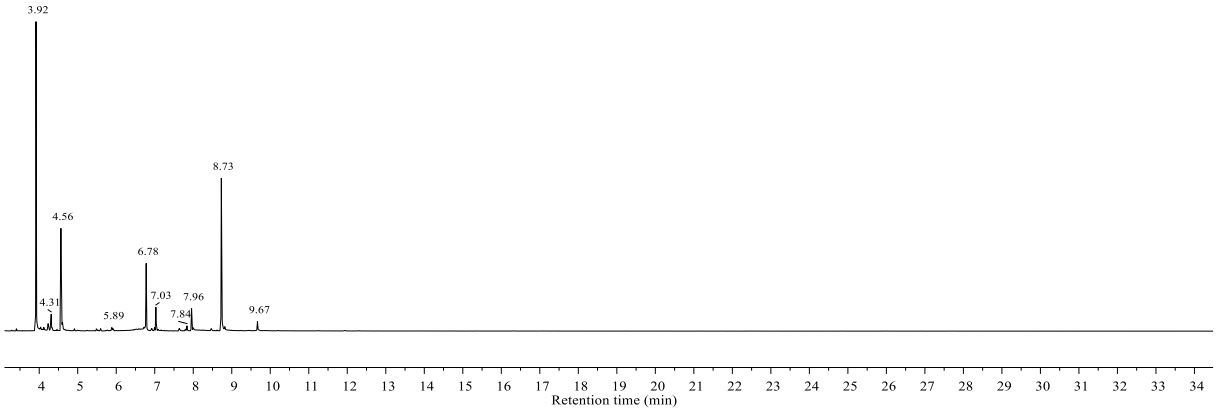


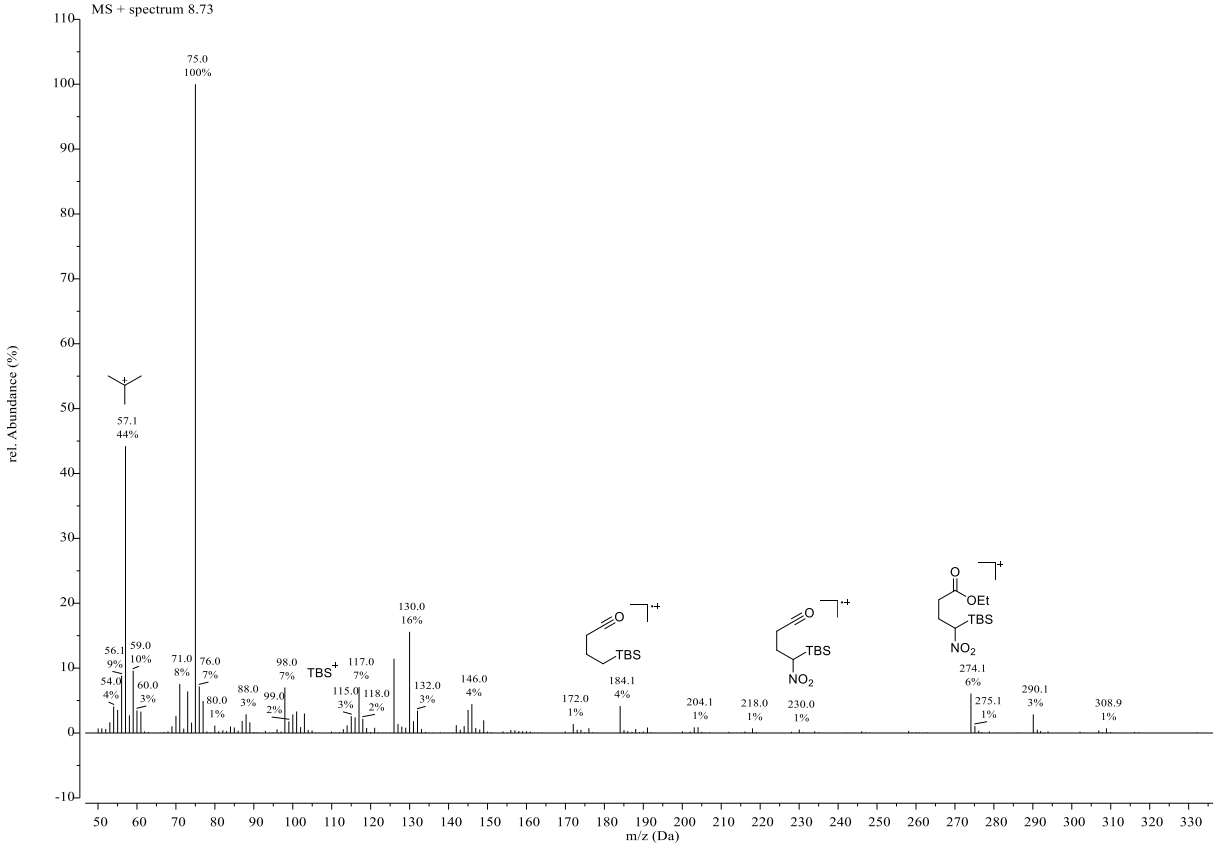


Addition to (1*E*)-1-*tert*-Butoxy-2-nitroethene

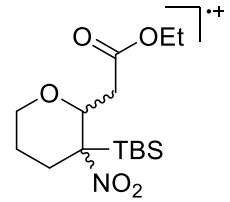


m/z = 347

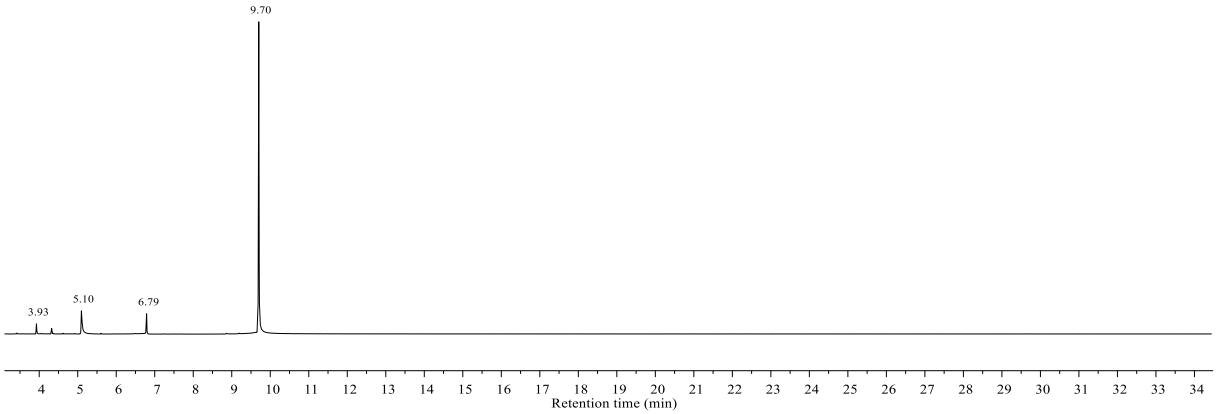


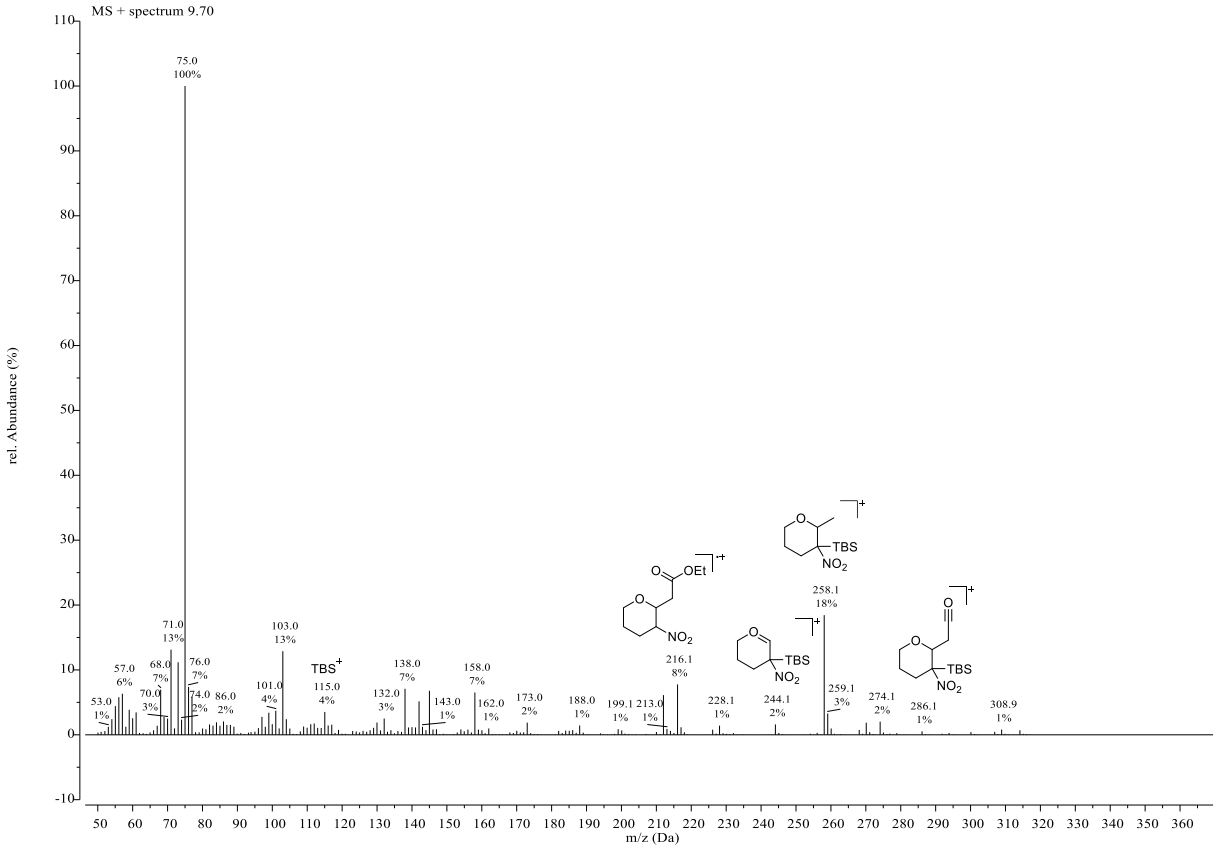


Addition to 3,4-Dihydro-5-nitro-2*H*-pyran

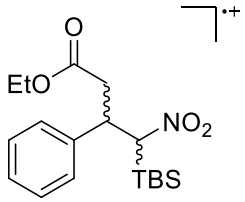


m/z = 331





Addition to β-Nitrostyrene



m/z = 351