PALLADIUM-CATALYZED STEREO-SELECTIVE 1,2-ADDITION REACTIONS OF γ,δ-EPOXY-α,β-UNSATURATED ESTERS WITH ORGANOBORONES

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ABSTRACT

PALLADIUM-CATALYZED STEREO-SELEVCTIVE 1,2-ADDITION REACTIONS OF γ,δ-EPOXY-α,β-UNSATURATED ESTERS WITH ORGANOBORONES

Transition metal-catalyzed S_N2-type addition reactions of allylic compounds having good leaving groups is a valuable reaction procedure in organic chemistry. Vinyl epoxides, as a derivative of allylic compounds, are suitable reagents for substitution reactions with their high reactivity due to the presence of an epoxide ring tensions and a conjugated C-C double bond attached to this ring. The occurrence of a substitution reaction of such reagents over the allylic position allows synthesis of homoallylated alcohols, one of the key building blocks in the synthesis of natural compounds. Organoborans are stable against moisture and air and environmentally friendly compounds and are thought by us to be suitable nucleophiles in these reactions.

Within the context of this research, Pd-catalyzed stereo-selective S_N2-addition type arylation reactions of γ,δ-epoxy-α,β-unsaturated esters with organoborons were investigated. The reaction mechanism proceeds through formation of π-allylpalladium complex with the help of Pd-$AsPh_3$ combination. The method has enabled to formation of γ-Aryl-δ-hydroxy-α,β-unsaturated esters with high regio- and stereo- selectivity.

ÖZET

γ,δ -EPOKSİ- α,β -DOYMAMIŞ ESTERLERİN ORGANOBORLAR İLE PALADYUM KATALİZLİ STEREO SEÇİMLİ 1,2-KATILMA TEPKİMELERİ

Kolay bir terkeden gruba sahip allilik bileşiklerin geçiş metal katalizli, S_N2-sübstitüsyon tepkimeleri organik kimyada önemli bir reaksiyon çeşididir. Allilik bileşiklerin bir türevi olan vinil epoksitler, epoksit halka gerginliği ve bu halkaya bağlı konjuge C-C çift bağı bulunmasından dolayı sahip oldukları yüksek reaktivite ile sübstitüsyon reaksiyonları için elverişli reaktiflerdir. Bu tür reaktiflerin allilik pozisyonu üzerinden bir sübstitüsyon tepkimesi gerçekleşmesi doğal bileşiklerin sentezinde önemli yapı taşlarından biri olan homoallilik alkollerin sentezine olanak sağlar Organoborlar da nem ve havaya karşı kararlı ve çevre dostu bileşikler olup bu reaksiyonlarda elverişli nükleofiller olabileceği tarafımızdan düşünülmüştür.

Bu çalışma kapsamında, γ,δ-epoksi-α,β-doymamış esterlerin organoborlar ile paladyum katalizli stereo seçimli S_N2-katilma tepkimeleri araştırılmıştır. Reaksiyon mekanizması Pd-$AsPh_3$ kombinasyonunun yardımı ile π-allilpalladyum kompleksinin oluşumu üzerinden ilerlemektedir. Yöntem, γ-aril-δ-hidroksi-α,β-doymamış ester yapılarının yüksek regio- ve stereo seçimlilikte sentezlenmesine olanak sağlamıştır.

TABLE OF CONTENTS

LIST OF FIGURES

Figure **Page**

LIST OF TABLES

Table **Page**

ABBREVIATIONS

Ac	Acetate
Ar	Aryl
aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bu	*n*-Butyl
t-Bu	*tert*-Butyl
^{t}BuOMe	*tert*-Butyl Methtlether
Cy	Cyclohexane
DBA	Dibenzylideneacetone
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMM	Dimethoxymethane
DMSO	Dimethyl sulfoxide
DPEPhos	Bis-[2-(diphenylphosphino)phenyl]ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppm	Bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dr.	Diastereomeric ratio
Et	Ethyl
Etc.	and other things

eq.	Equivalent
Et_2O	Diethyl ether
FTIR	Fourier-transform infrared spectroscopy
h	hour
m	Meta
IPA	Isopropyl alcohol
m-CPBA	meta-chloroperoxybenzoic acid
M	Molar
Me	Methyl
mg	Miligram
min.	Minute
mL	Mililiter
mmol	Milimoles
MS	Mass spectrometry
N.D.	Not determined
NMR	Nuclear Magnetic Resonance
o	Ortho
p	Para
Ph	Phenyl
PhBneop	Phenylboronic acid neopentylglycol ester
Pr	Propyl
RT	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

CHAPTER 1

INTRODUCTION

Transition metal-catalyzed reactions of allylic compounds, which are substituted with various leaving groups have enabled significant methods for substitution reactions in organic synthesis. The reaction of the allylic compounds generally proceeds through S_N2'-manner substitution. In the present study, however the reactions favored S_N2-pathway.

On the other hand, nucleophilic substitution reactions of vinyl oxiranes enable the formation of biologically active natural products and the other synthetically valuable products. The two important characteristics of vinyl epoxide compounds are ring strain on the epoxide ring and C-C double bond that is conjugated to epoxide ring. Due to these characteristics of vinyl epoxides, three different regio-isomerizms are possible, as shown in Figure 1.1. The reactions usually resulted in S_N2'-addition product to yield biologically active allylic alcohols (2) which are widely used as intermediaries in organic synthesis.(Bandini 2011, Lu and Ma 2008).

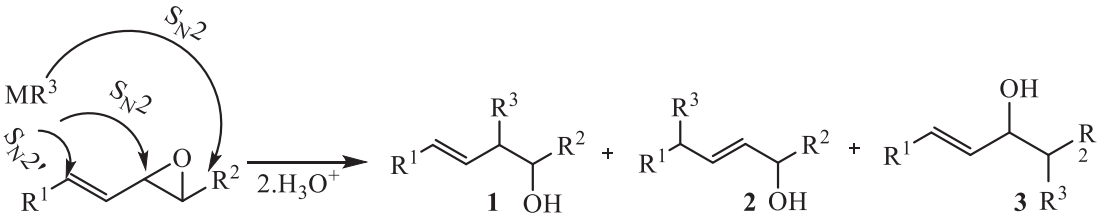


Figure 1.1. Possible products of reactions of vinyl epoxides with organometallics.

In S_N2-type reactions, generally Grignard reagents, organolithium, and organozinc compounds are preferred as nucleophiles. However, use of these hard nucleophiles generally meets with restrictions due to their air and moisture sensitivities. The use of organoborons as a nucleophilic source, which are air and moisture stable reagnets have enabled smooth reaction conditions.

There are only a few reports about S_N2-substitution processes of epoxides with organometallics in the literature. This study presented that Pd-catalyzed arylation reactions of vinyl epoxides in the form of γ,δ-epoxy-α,β-ester with organoborons. The reactions resulted in the formation of homoallylic alcohols (γ-Aryl-δ-hydroxy-α,β-unsaturated ester types) via S_N2-substitution.

CHAPTER 2

LITERATURE WORKS

2.1. Palladium-Catalyzed Reactions of Allylic Compounds

Palladium-catalyzed reactions of allylic compounds, substituted with various leaving groups such as esters, alcohols, and halides etc., proceed through the formation of π-allylpalladium intermediate and offer significant methods in organic synthesis. In 1965, for the first time, Tsiju *et al.* reported the Pd(0)-catalyzed formation of π-allylpalladium intermediate and explained the electrophilic feature of these complexes and the main catalytic reaction pathways, as shown in Figure 2.1 (Tsuji, *et al.* 2004).

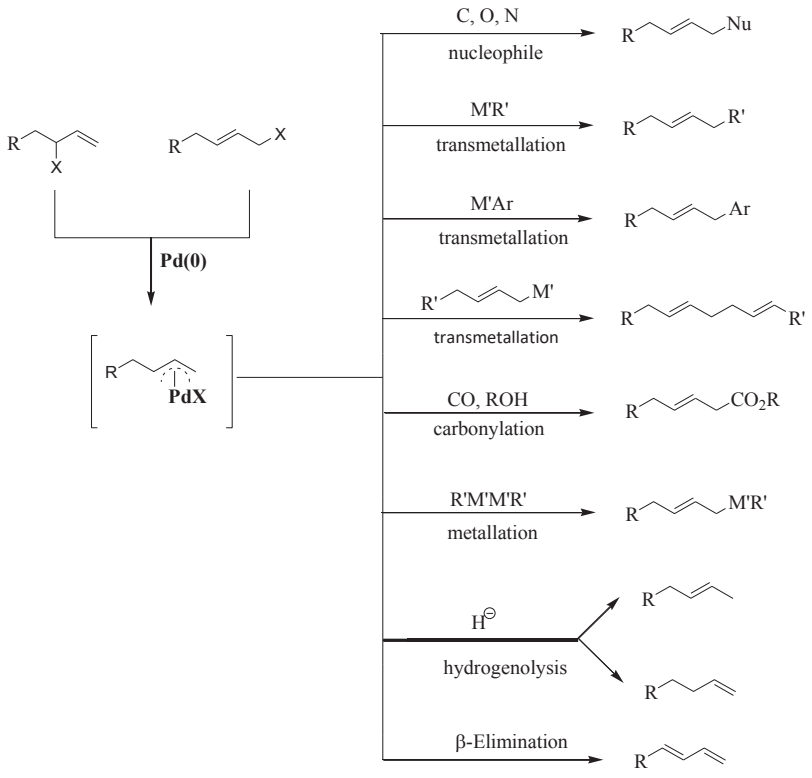


Figure 2.1. Pd-catalyzed reactions of allylic compounds.

2.1.1 Palladium-Catalyzed Reactions of Allylic Esters

Allylic acetates are less reactive than other allylic ester derivatives. Reactions of allylic acetates generally take place in the presence of a base, such as triethylamine or sodium acetate. However, Giambastiani and Poli showed that the reaction of β-keto esters with allylic acetates gave the desired allylated products under neutral conditions. This report proved that the reaction of allylic acetates can even be carried out under neutral conditions (Figure 2.2) (Giambastiani and Poli 1998).

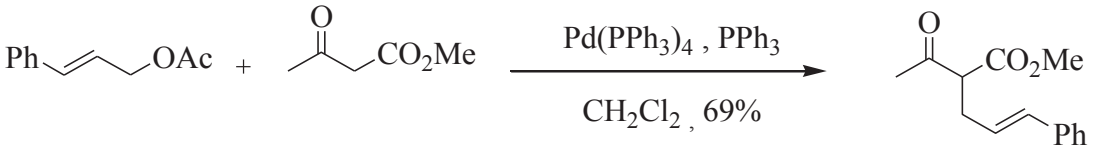
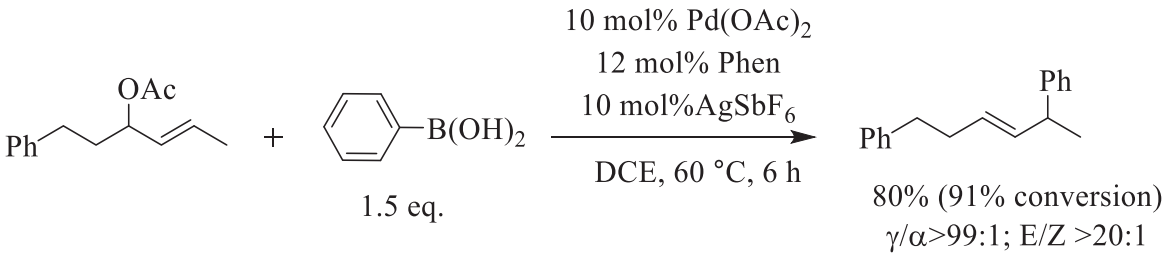


Figure 2.2. Pd-catalyzed reaction of allylic acetates in the absence of a base.

In 2010, Ohmiya *et al*. reported the arylation reaction of allylic acetates with arylboronic acids under Pd-catalyst. The developed methodology gave the desired allylic arylated products with good yields and selectivities (Figure 2.3) (Ohmiya, *et al.* 2010).



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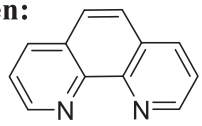


1,10-phenanthroline

Figure 2.3. Arylation of allylic acetates with arylboronic acid under Pd-catalyst.

Allylic carbonates are more reactive then the corresponding acetate derivatives. Unlike acetates, generally, the reaction of allylic carbonates is carried out in the absence of a base.

In 1988, Masuyama *et al*. reported the reaction between allylic carbonates and aryl-aldehydes under $PdCl_2(PhCN)_2$-$SnCl_2$ catalytic system. The reaction of 1-methylallyl carbonate with benzaldehyde under the specified reaction conditions, gave the corresponding homoallylic alcohol with good yield (95%). The regioselectivity of the process was also good but the diastereoselectivity was moderate (syn : anti / 31:69), as shown in Figure 2.4 (Masuyama, *et al.* 1988).

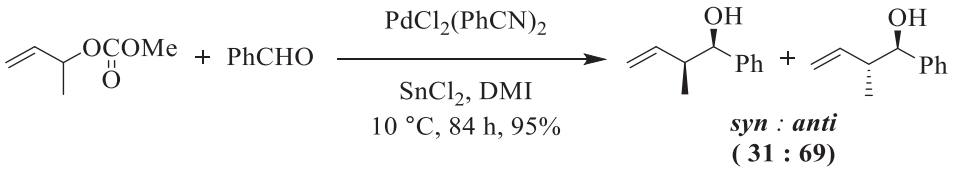


Figure 2.4. γ-selective allylation of allyl carbonate with benzaldehyde with $PdCl_2(PhCN)_2$-SnCl2 catalytic system.

Allylic carbonates are also suitable precursors in Pd-catalyzed carbonylation reactions. For example (Figure 2.5), the reaction of allylic carbonates with carbon monoxide under Pd-catalyst and in the presence of a phosphine ligand at 50 °C, resulted in the formation of β,γ-unsaturated esters through the decarboxylation-carbonylation process. The reaction proceeded through the formation of a key π-allylpalladium intermediate, which was initiated with the oxidative addition of Pd(0) to the C-O bond of the allylic carbonate. Final β,γ-unsaturated ester product was formed after reductive elimination with the regeneration of the active Pd(0)-catalyst (Figure 2.6) (Tsuji, *et al.* 1984).

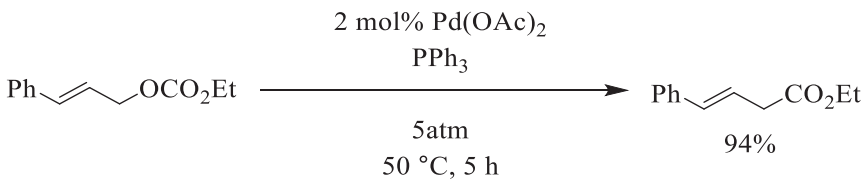


Figure 2.5. The Pd-catalyzed decarboxylation-carbonylation reaction of allylic carbonates.

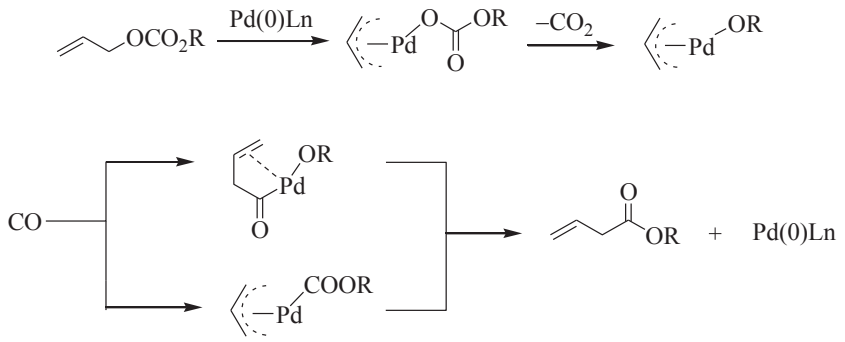


Figure 2.6. A plausible reaction mechanism of the alkoxycarbonylation of allylic carbonates.

2.1.2 Palladium-Catalyzed Reactions of Allylic Alcohols

Although allylic alcohols are the least reactive species in Pd-catalyzed coupling and substitution reactions, in 1991, Jeffery showed that the Pd-catalyzed reaction of allylic alcohols with aromatic halides gave an opportunity to the formation of β-substituted aromatic carbonyl compounds or arylated allylic alcohols depending on the two different catalytic system. As shown in Figure 2.7, by using of catalytic system (I) the target β-substituted aromatic carbonyl compounds were formed via usual Heck-type coupling reaction. Highly selective construction of arylated allylic alcohols were achieved if the catalytic system (II) would preferred (Jeffery 1991).

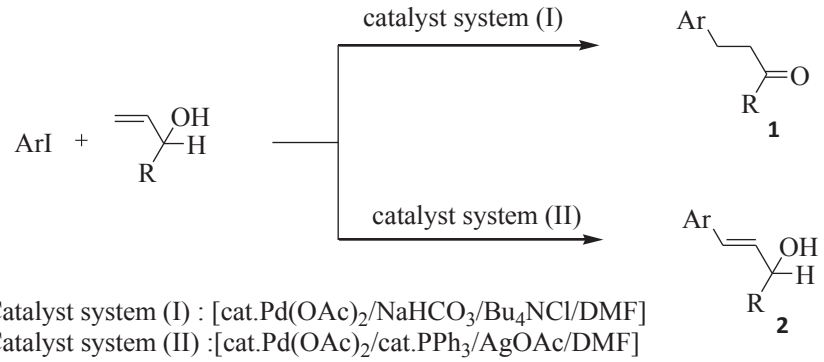


Figure 2.7. Pd-catalyzed arylation of allylic alcohols with aromatic halides.

(cont.on next page)

Ar	R	Catalytic System	T (°C)	Time	Yield (%)
p-$CH_3OC(O)C_6H_4$	Me	I	30-55	16 h	90
p-$CH_3OC(O)C_6H_4$	Me	II	70-75	24 h	90

Figure 2.7 (cont.)

Furthermore, Kimura *et al.* showed that the Pd(0)-catalyzed nucleophilic allylation reaction of allylic alcohols with aldehydes. As shown in Figure 2.8, the reaction of cinnamyl alcohol with benzaldehyde yielded the homoallylic alcohol with moderate yield. The desired product was formed through the nucleophilic allylboron intermediate, which was formed as a result of transmetallation of π-allylpalladium(II) complex with Et_3B and followed by Pd(0)-catalyzed coupling of this intermediate with the aldehyde (Kimura *et al.* 2000).

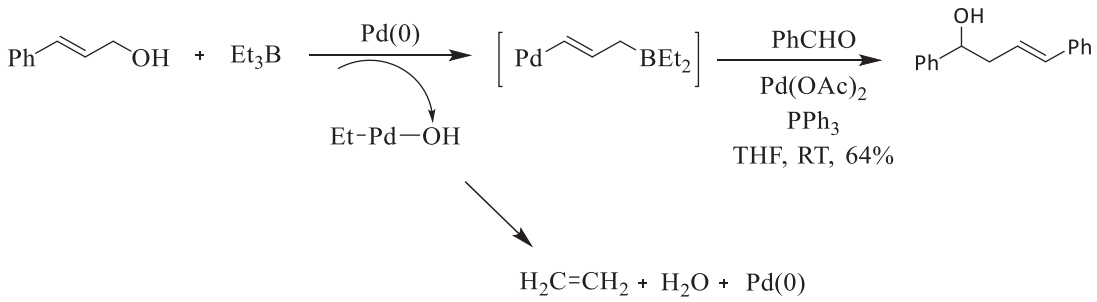
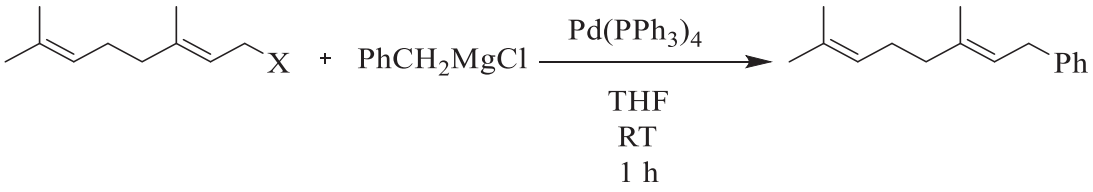


Figure 2.8. Pd-catalyzed allylation of benzaldehyde with allyl alcohol

2.1.3 Palladium-Catalyzed Reactions of Allylic Halides

As allylic carbonates, acetates and alcohols, allylic halides are also proper reagents in Pd-catalyzed nucleophilic substitution reactions. Pd-catalyzed α-alkylation of geranyl halides (-Br, -Cl) with benzylic Grignard reagents resulted in the formation of all trans polyenehomobenzene with high yields and regioselectivities as shown in Figure 2.9 (Rosales, *et al.* 2002).

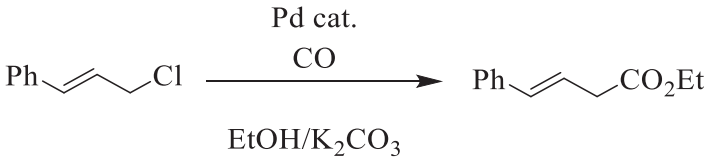


X: –Cl,–Br

X	Yield (%)
-Cl	82
-Br	94

Figure 2.9. Pd-catalyzed alkylation of allylic halides with benzylic Grignard reagents.

In 1995, Kiji *et al.* reported the Pd-catalyzed alkoxycarbonylation reaction of allylic chlorides with alcohols under atmospheric pressure of carbon monoxide, which afforded β,γ-unsaturated esters in high yields. Although harsh reaction conditions were needed, such as high CO pressure and temperature, the reaction tolerates different Pd-catalyst precursors as shown in figure 2.10 (Kiji, *et al.* 1996).



Catalyst	atm	T (°C)	Time	Yield (%)
$Pd(OAc)_2$	1	20	50 min	94
$Na_2[PdCl_4]$	50	50	180 min	95
$[PdCl_2(PPh_3)_2]$	50	50	60 min	94

Figure 2.10. Pd-catalyzed alkoxycarbonylation of allylic halides

2.1.4. Palladium-Catalyzed Reactions of Allylic Oxiranes

Pd-catalyzed nucleophilic substitution reaction of alkenyl oxiranes may afford either S_N2- or S_N2'-addition products. The reaction mainly gives S_N2-addition products under usual reaction conditions due to electronic effect and the interaction of the epoxide oxygen and Pd-metal center (Figure 2.11) (Tsuji, *et al* 1984, Trost and Molander 1981).

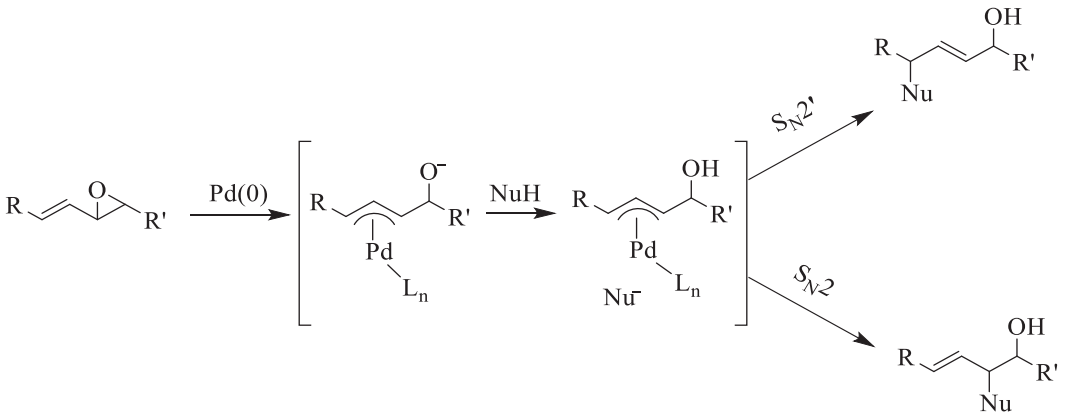
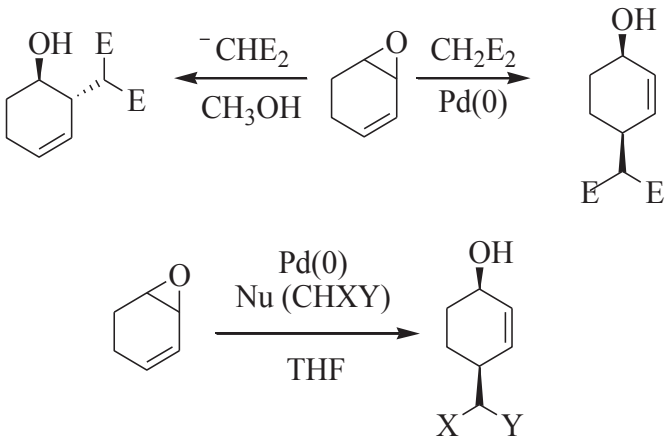


Figure 2.11. Pd-catalyzed nucleophilic substitution reaction of allylic oxiranes

In 1981, Trost *et* al. showed that the Pd(0)-catalyzed reaction of 1,3-cyclohexadien monoepoxide with acetoacetate gave the corresponding allylated 1,4-addition product with high yield.(Trost and Molander 1981) The observed regio- and stereoselectivity of the reaction is depend on the both nucleophile and the presence of Pd-catalyst. In the presence of Pd-catalyst, as we discussed in Figure 1.11, the first step is the attack of Pd(0) to the allylic oxirane resulted in the formation of π-allylpalladium intermediate with inversion of configuration (*anti*-attack). Subsequent reaction of this intermediate with nucleophiles occurs in different stereochemistry depending on the nature of the nucleophiles. The soft-stabilized nucleophiles, such as active methylene compounds (*e.g.,* acetoacetate), attack to the π-allylpalladium intermediate from the backside of the Pd-atom and afforded the *syn*-product. When the reaction was conducted in basic conditions and in the absence of Pd(0)-catalyst, the reaction cleanly give the S_N2-addition product in anti-mode as expected from the ordinary S_N2'-type reactions. Also, substituents on the nucleophile (-X, -Y) affected the yield of the reaction (Figure 2.12). (Trost and Molander 1981).



Nu	Yield (%)
X = Y = CO_2Me	74
X = CO_2Me, Y = CO_2Ph	61
X = Y = CO_2Ph	85

Figure 2.12. Pd-catalyzed nucleophilic substitution reaction of allylic oxirane

In 1982, for the first time, Miyaura *et al.* reported the Suzuki-Miyaura cross coupling reaction of vinyl oxiranes with 1-alkenylborons under Pd-catalyst, as shown in Figure 2.13. The reaction gave the corresponding coupling products with high yields but low in regioselectivities (Miyaura *et al.* 1982).

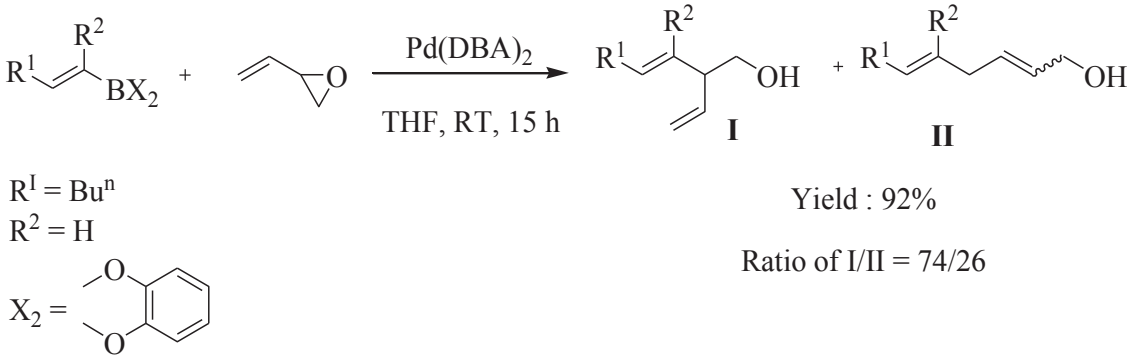
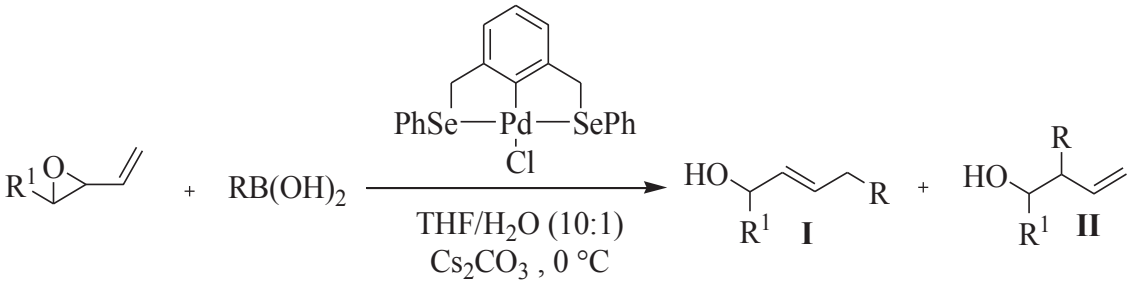


Figure 2.13. Pd-catalyzed cross-coupling reactions of vinyl oxiranes.

Szabo *et al*. reported the Pd-Pincer catalyzed allylic alkenylation and arylation reaction of vinyl epoxides with organoboronic acids. They applied the Suzuki-Miyaura

coupling reaction conditions, using base and water as additives, and after tuning the reaction parameters the process cleanly afforded the allyl alcohols in high regio- and diastereoselectivities (Figure 2.14) (Kjellgren *et al.* 2005).



R^1	R	Time	I/II	Yield (%)
H	Ph	16	11/1	94
Ph		3	>20/1	95

Figure 2.14. Pd-Pincer catalyzed Suzuki-Miyaura coupling reactions of vinyl oxiranes.

In addition to this, Szabo group also applied their methodology to the cyclic epoxide containing an endocyclic double bond and obtained the desired arylated product with high diastereoselectivity, but unfortunately low regioselectivity was observed (Figure 2.15) (Kjellgren *et al.* 2005).

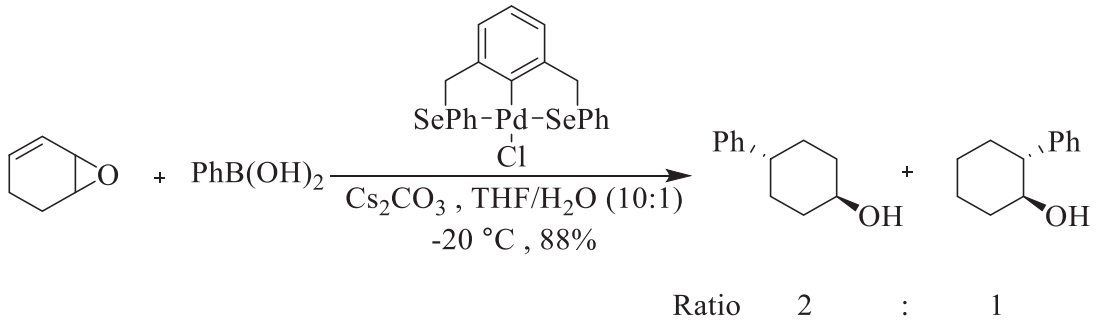


Figure 2.15. Pd-Pincer catalyzed reaction of 1,3-cyclohexadien monoepoxide with phenylboronic acid.

Hirai *et al.* reported the Pd(0)-catalyzed epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with organoboronic acids. The reaction proceeded with double inversion of the configuration and the desired condensation product was obtained with regio- and stereoselectively as shown in Figure 2.16 (Hirai *et al.* 2003).

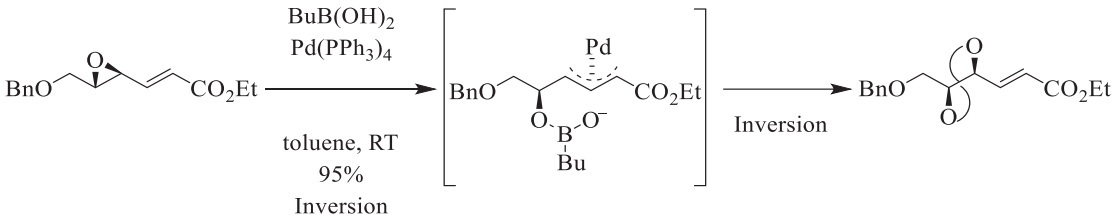


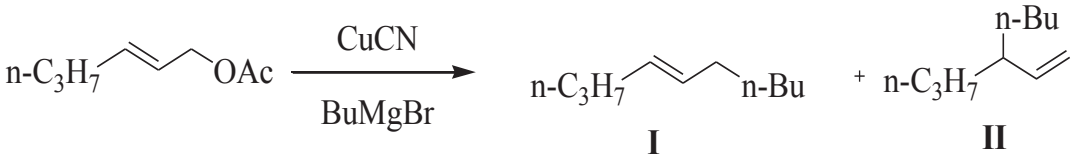
Figure 2.16. Pd-catalyzed stereospesific epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with alkylboronic acid.

2.2. Metal-Catalyzed Reactions of Allylic Compounds

In the literature, apart from Palladium-catalyst, there are also several examples related with transition metal-catalyzed (Cu, Rh, Ir, Fe, Ni, Li) transformations of allylic compounds such as allylic acetates, carbonates, phosphates, alcohols, halides, oxiranes with different nucleophile source such as Grignard reagents, organozinc compounds, organoboron reagents.

2.2.1 Metal-Catalyzed Reactions of Allylic Esters (acetate, carbonate, phosphate)

In 1990, Backvall *et al*. reported the Cu(I)-catalyzed reaction of allylic acetates with Grignard reagents. The developed methodology enables to control the regioselectivity of the reaction depending on the solvent, addition time of Grignard reagent and the temperature. After tuning the reaction parameters properly, the method allowed the formation of α- or γ-substituted products selectively (Figure 2.17) (Baeckvall, *et al.* 1990).



Solvent	Addition time of *n*-BuMgBr	T (°C)	Yield (%) I/II
THF	25min	0	99/1
THF	3h	0	99/1
Et_2O	2min	-78	38/62
Et_2O	1,5h	0	3/97
Et_2O	3,5h	0	0/100

Figure 2.17. CuCN catalyzed reactions of allylic acetates.

In 2003, Hayashi group reported the Rh(I)-chiral phosphino-oxazoline catalyzed asymmetric allylic alkylation of allylic acetates with dimethyl malonate in the presence of a base. The developed method allowed the formation of the desired alkylated products with high enantioselectivities (Figure 2.18) (Hayashi *et al.* 2003).

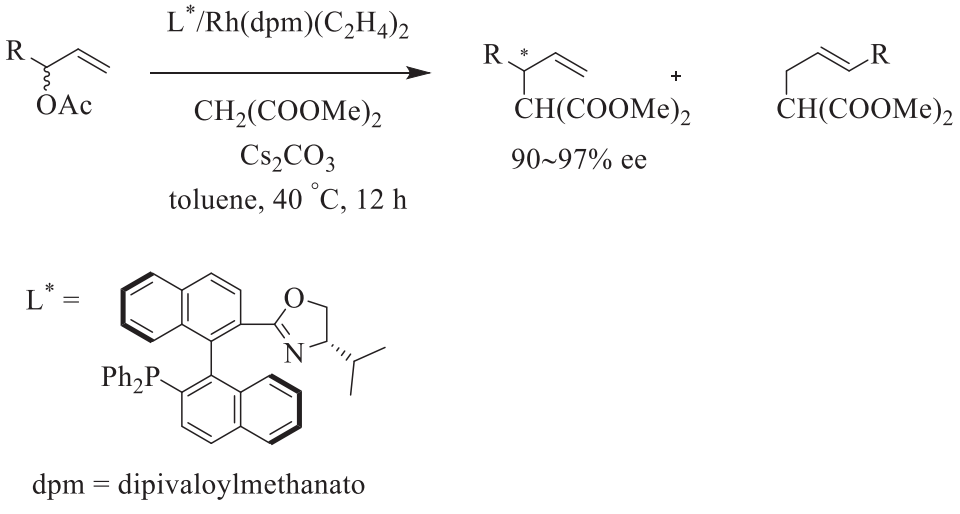


Figure 2.18. Rh-catalyzed asymmetric allylic alkylation of allylic acetates with dimethyl malonate in the presence of a base

(cont. on next page)

R	Yield (%)	I/II	ee (%)
Ph	94	98/2	97
p-Me-C_6H_4	97	88/12	94
p-CF_3-C_6H_4	97	99/1	97
p-Cl-C_6H_4	93	97/3	95
1-napthyl	94	60/40	95

Figure 2.18 (cont.)

The research group of Evans showed for the first time that Rh-catalyzed asymmetric allylic alkylation reaction of enantiomerically enriched allylic carbonates with sodium salt of acetoacetate. The reactions were resulted in the formation of the desired alkylated product with almost complete transfer of chirality (Evans and Nelson 1998).

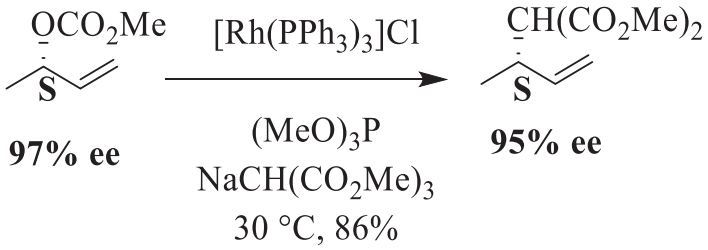
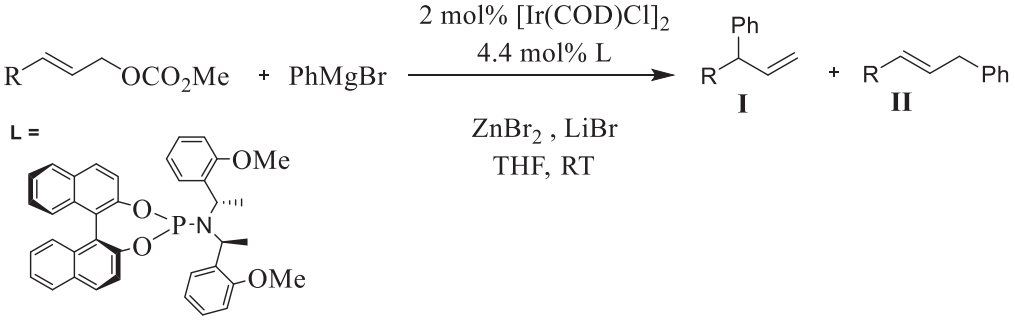


Figure 2.19. Rh-catalyzed asymmetric alkylation of allylic carbonates with sodium salt of acetoacetate.

In 2009, Polet *et al*. reported the Ir-catalyzed arylation of allylic carbonates with Grignard reagents in the presence of $ZnBr_2$, LiBr, and the chiral ligand. Several substituted group were also tested. Although the method yielded the substitution products with high enantioselectivities, the regioselectivities of the process were very low, as shown in Figure 2.20 (Polet, *et al.* 2009).



R	I/II	Yield (%)	ee (%)
p-MeO-C_6H_4	36/67	78	91
p-F-C_6H_4	50/50	83	93
p-Cl-C_6H_4	55/45	83	>99
p-CF_3-C_6H_4	56/44	98	97
2-furyl	73/27	100	79
2-napthyl	53/47	93	92

Figure 2.20. Ir-catalyzed arylation of allylic carbonates.

Transition-metal catalyzed substitution reaction of allylic phosphates with Grignard reagents was published by Yanagisawa *et al*. in 1994. When the reaction was performed with Ni- and Fe-catalyst, the reaction proceeded through the S_N2-pathway. But instead of Ni or Fe, when the reaction was conducted with catalytic amount of CuCN.2LiCl salt, the reaction favored S_N2'-pathway (Figure 2.21). The methodology allows us for the synthesis of whether S_N2 or S_N2' product depending of the metal chosen as the catalyst (Yanagisawa, *et al.* 1994).

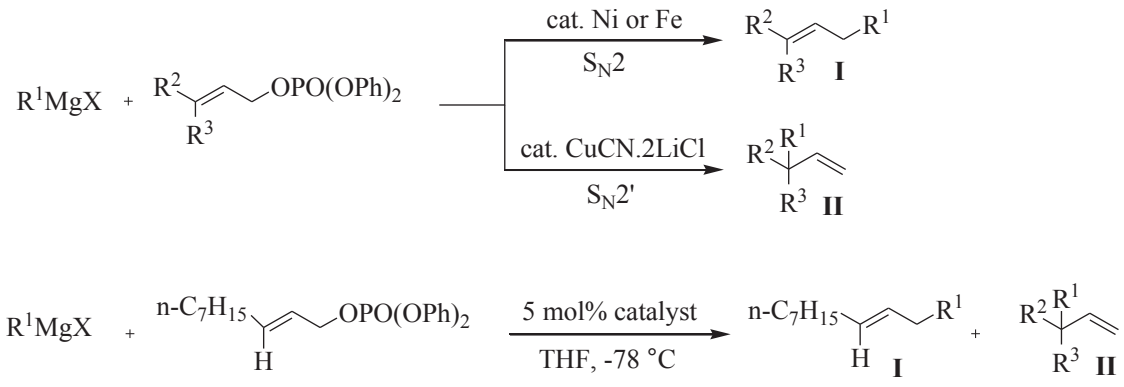


Figure 2.21. Transition-metal catalyzed substitution reaction of allylic phosphates with Grignard reagents.

(cont. on next page)

R^1	Catalyst	Yield (%)	I/II
BuMgCl	$Ni(acac)_2$	73	>99/1
BuMgCl	$Fe(acac)_3$	94	99/1
BuMgCl	CuCN.2LİCl	98	1/99
MeMgI	$Ni(acac)_2$	26	94/6
MeMgI	$Fe(acac)_3$	87	97/3
MeMgI	CuCN.2LiCl	87	2/98

Figure 2.21 (cont.)

In 2007, Kacprzynski, *et al*. reported the asymmetric arylation reaction of silly substituted allylic phosphates with diaryl zinc reagents and in the presence of a chiral N-heterocyclic carbene (NHC) ligand, resulted in S_N2'-selective arylation with high yield and enantioselectivity, as shown in Figure 2.22 (Kacprzynski, *et al*. 2007).

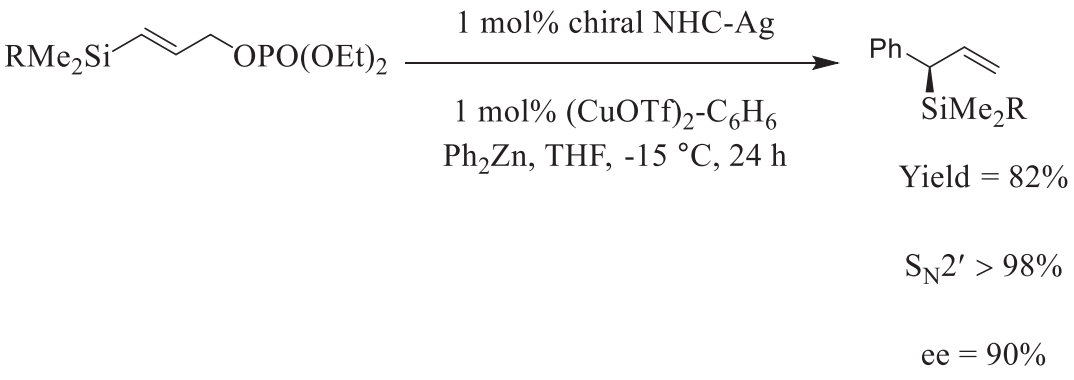


Figure 2.22. Enantioselective allylic arylation of allylic phosphates with Cu/NHC.

In 2014, Takeda *et al*. achieved to generate quaternary carbon stereocenters from the reaction of γ,γ-substituted allylic phosphates with aryl boronates by using Cu/NHC catalytic system. The methodology was highly regio- and enantioselective and gave the desired arylated products with high yields (Figure 2.23) (Takeda, *et al.* 2014).

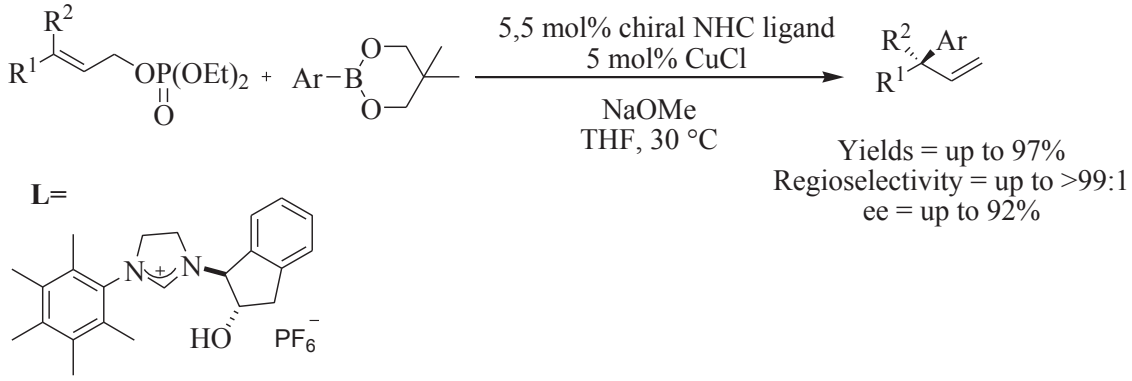


Figure 2.23. Cu/NHC-catalyzed asymmetric arylation reaction of allylic phosphates with aryl boronates.

2.2.2 Metal-Catalyzed Reactions of Allylic Halides

In 1990, Backvall *et al.* developed a method for the regioselective (S_N2'-selective) alkylation of allyl chlorides with Grignard reagents under Cu-catalyst. On contrary to the general trend, under their developed conditions, allyl chlorides are more reactive than allyl acetates and the reaction yielded the γ-substitution product in *anti*-mode, as shown in Figure 2.24 (Baeckvall, *et al.* 1990).

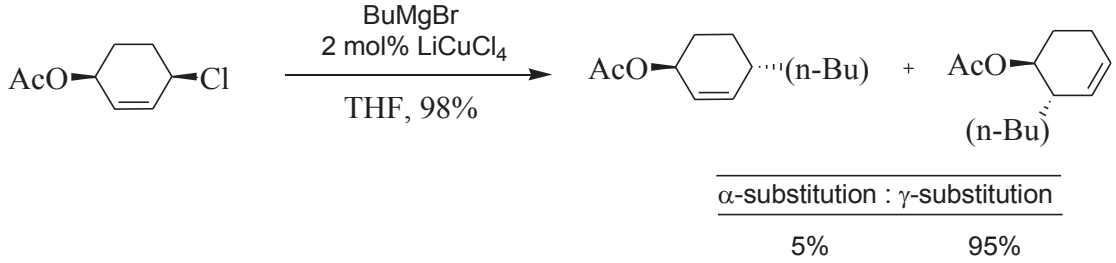
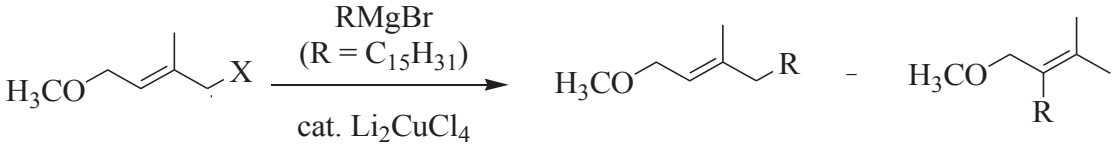


Figure 2.24. Cu-catalyzed substitution reactions of allylic chlorides.

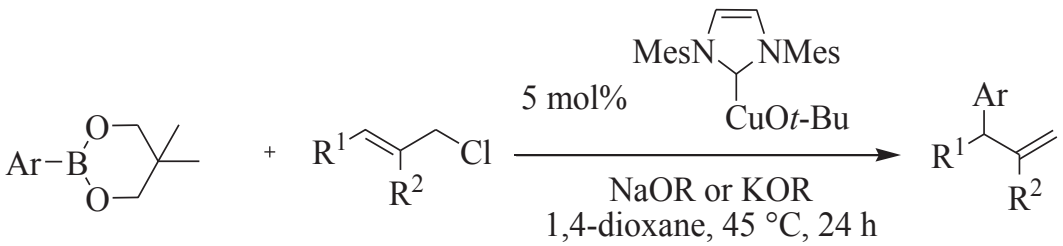
They also showed that the leaving groups on the allylic terminus exhibited different reactivity, concordantly the regioselectivity of the process was affected dramatically from this variation (-OAc, -Cl or -Br) and the process gave the alkylated products either α- or γ-substitution pattern (Figure 2.25).



X	α- (%)	γ- (%)
-OAc	97.5	2.5
-Cl	55	45
-Br	9	91

Figure 2.25. Cu-catalyzed substitution reaction of allylic compounds substituted with different leaving groups.

The Cu/NHC-catalyzed reaction of allylic chlorides with aryl boronates was shown by Whittaker group. The reaction proceeded through the S_N2'-pathway. The developed conditions tolerate a wide variety of allyl chlorides and gave the substitution products with high yields and selectivities, as shown in Figure 2.26 (Whittaker, *et al.* 2010).



Ar	Catalyst (%)	Base	S_N2/S_N2'	Yield (%)
p-MePh	10	KO*t*-Bu	42/1	92
p-MePh	5	KO*t*-Bu	48/1	98
p-(CHO)Ph	5	KO*t*-Bu	18/1	91
p-(CHO)Ph	5	NaO*t*-Bu	20/1	95

Figure 2.26. Cu/NHC-catalyzed arylation of allyl chlorides with aryl boronates.

2.2.3 Metal-Catalyzed Reactions of Allylic Oxiranes

In 2007, Millet and Alexakis showed a convenient method for the synthesis of enantio-enriched allylic alcohols by using Cu-catalyst and chiral ferrocenyl type ligand. The reaction of 1,3-cyclohexadien monoepoxide with Grignard reagents and in the presence of CuBr and chiral ferrocenyl diphenylphosphine ligand gave the substitution products with excellent regio- and enantioselectivities (Figure 2.27) (Millet and Alexakis 2007).

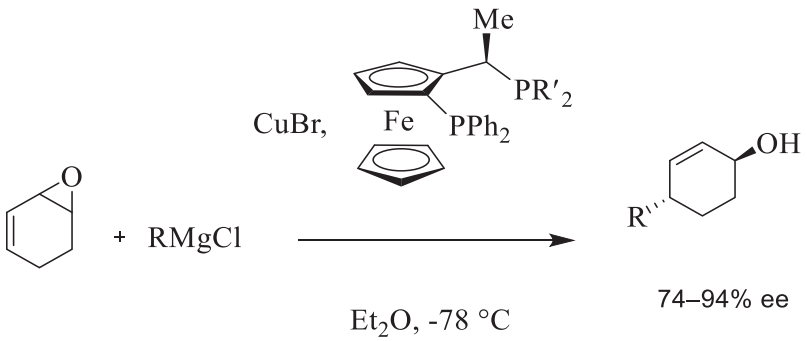


Figure 2.27. Cu-catalyzed reaction of 1,3-cyclohexadien monoepoxide with Grignard reagents.

In 2010, Hata, *et al*. reported the Fe-catalyzed transformation of γ,δ-epoxy-α,β-unsaturated esters and amides with aryl or alkyl Grignard reagents. According to the methodology, δ-hydroxy-γ-alkyl or aryl-α,β-unsaturated esters and amides were obtained as single isomers with the inversion of the configuration. The products were obtained in moderate yields but good regio- and stereoselectivities (Figure 2.28) (Hata, *et al.* 2010).

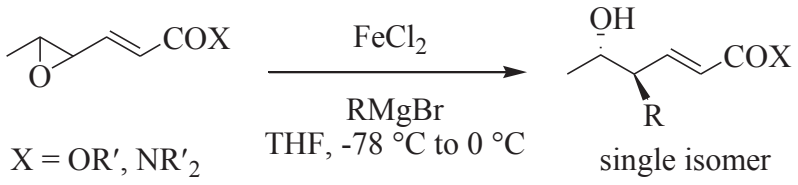


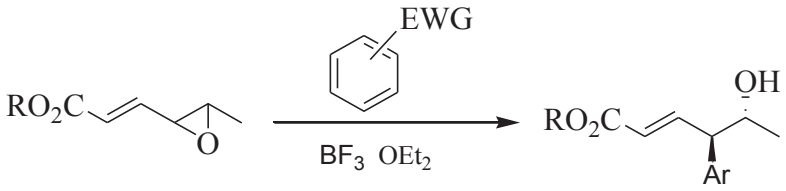
Figure 2.28. Fe-catalyzed arylation and alkylation reaction of γ,δ-epoxy-α,β-unsaturated esters and amides with Grignard reagents.

(cont. on next page)

X	R	Yield (%)
OEt	Ph	60
	o-$MeOC_6H_4$	57
	Me	81
NEt_2	Me	89
	Et	49

Figure 2.28 (cont.)

Also, δ-hydroxy-γ-aryl-α,β-unsaturated esters could be obtained from the reaction of γ,δ-epoxy-α,β-unsaturated esters with Lewis acid-catalyzed Friedel-Craft reaction. The process proceeded with S_N2-addition manner and it should be noted that the arylating reagents must be substituted with electron withdrawing groups (Figure 2.29) (Ono, *et al*. 2005, Fujii, *et al.* 2009).



Ar	R	Yield (%)
p-MeOPh	Me	72
o-MeO-5-MePh	Me	80
3,4-$(MeO)_2$Ph	Me	92

Figure 2.29. Lewis acid-catalyzed Friedel-Craft reaction of allylic oxiranes.

Cu-catalyzed borylation of allylic oxiranes allows the formation of biologically active S_N2'-addition products with high diastereoselectivities either *anti*- or *syn*-mode, (Figure 2.30) (Tortosa, 2011).

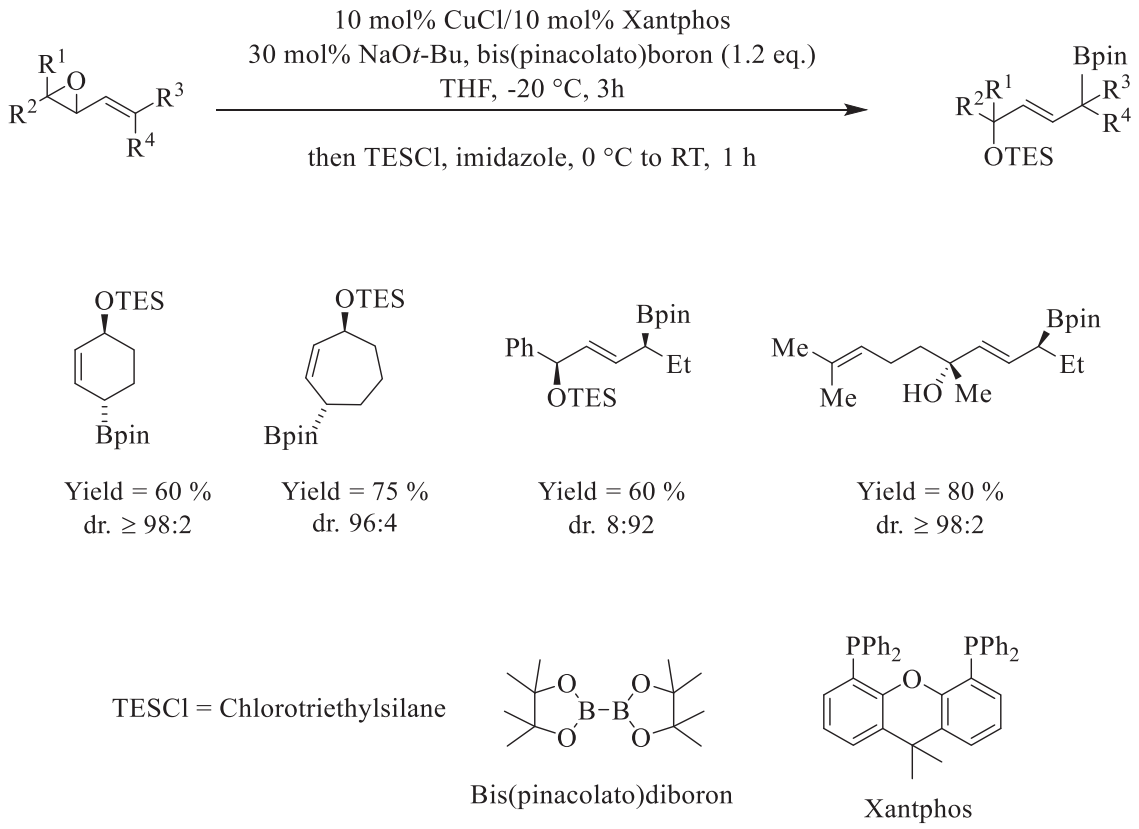


Figure 2.30. Generation of S_N2'-substitution products from Cu-catalyzed reaction of allylic oxiranes with bis(pinacolato)diboron.

In 2009, Crotti *et al*. described the Ni-catalyzed regio- and diastereoselective borylative ring-opening reaction of allylic oxiranes. The desired final oxidation product was obtained after the selective borylation of allylic oxiranes and followed by the reaction of this intermediate with aldehyde (Figure 2.31) (Crotti, *et al.* 2009).

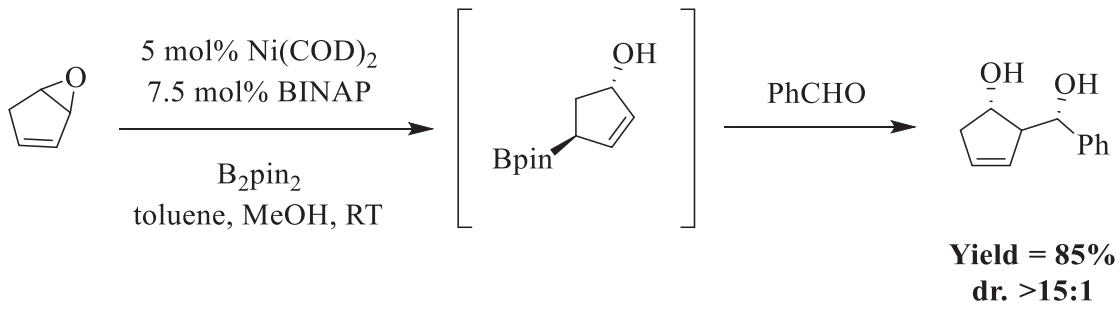


Figure 2.31. Ni-catalyzed borylative ring opening and oxidation reaction of allylic oxiranes.

CHAPTER 3

EXPERIMENTAL

3.1. General Procedures for Drying the Solvents

Et_2O, DME, and 1,4-dioxane solvents were distilled from benzophenone-ketyl under nitrogen gase prior to use. Distilled 1,4-dioxane solvent was stored over 4Å molecular sieves in the dark. THF solvent were purified by a solvent purification system or distilled from benzophenone-ketyl under nitrogen gase prior to use. THF and Et_2O were used freshly. DMF was purified by a solvent purification system (MBRAUN SPS-800). DCM and Methanol were dried using molecular sieve 3Å under nitrogen atmosphere. DMSO was distilled over calcium hydride (5 w/v) under reduced pressure (12 mm Hg) and stored over molecular sieve 4Å. Methyl tert-butyl ether solvent was distilled from $CaSO_4$ under nitrogen gase prior to use. Toluene was dried using molecular sieve 3Å under nitrogen atmosphere, stored 24 h before use.

3.2.Synthesis of Vinyl Oxiranes

The syntheses of all compounds were performed under nitrogen gas and all reactions were monitored by TLC (Thin-layer chromatography) analysis. The column chromatography purification of the synthesized vinyl oxirane compounds was applied on silica gel material (60-200 mesh) treated by triethylamine (NEt_3) before use. NEt_3 was added to silica gel and stirred for 20 minutes. Purification of all other compounds were performed on untreated silica gel (60-200 mesh).

FTIR spectra were taken on ATR.

Air sensitive rialkylphosphine ligands were used after conversion to $[R_3PH]BF_4$ form (Netherton, 2002). $Pd_2(DBA)_3CHCl_3$ complex was synthesized at our laboratory (Ukai, 1974).

3.2.1. Synthesis of ethyl E-3-(3-propyloxiran-2-yl)acrylate (1a)

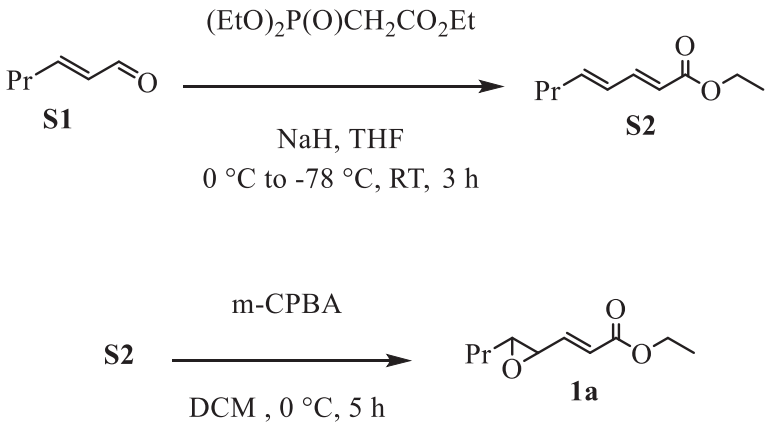


Figure 3.1. Synthesis of ethyl E-3-(3-propyloxiran-2-yl)acrylate.

Triethyl phosphonoacetate (1.5 eq., 75 mmol, 14.9 mL) was added dropwise to the suspension of NaH (60% dispersion in mineral oil, 1.7 eq., 85 mmol, 3.26 mg) in 125 mL dry THF at 0 °C, and the mixture was stirred for 1 h at room temperature. Then, the reaction mixture was cooled to -78 °C and commercially available trans-2-hexen-2-1-al **(S1)** (50 mmol, 5.8 mL) was added dropwise to reaction mixture and stirred for 2 h at room temperature. Completion of the reaction was monitored with thin-layer chromatography (TLC). The reaction was quenched cautiously with saturated $NH_4Cl_{(aq)}$ and the aqueous phase extracted with diethyl ether (Et_2O). Then the organic layer was washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to provide Ethyl (2E,4E)-octa-2,4-dienoate (**S2)** (Hexane, light yellow oil, yield: 5.9 g, 70.3%) (Urabe, *et al.* 1997).

To a solution of Ethyl (2E,4E)-octa-2,4-dienoate (**S2)** (10 mmol, 1.68 g)) in DCM (30 mL) was added meta-chloroperoxybenzoic acid (*m*-CPBA) (2.63 eq., 26.3 mmol, 5.9 g) at 0 °C and stirred for 5 h at the same temperature. Completion of the reaction was monitored with TLC. The reaction was quenched with saturated $NaHCO_{3(aq)}$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to provide the vinyl epoxide **1a** (Hexane/EtOAc, 100:1-50:1, colorless oil, yield: 1.23 g, 68%) (Kuş, *et al.* 2015).

3.2.2. Synthesis of Ethyl E-3-(3-methyloxiran-2-yl)acrylate (1b)

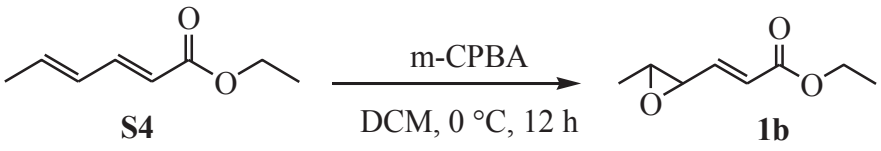


Figure 3.2. Synthesis of Ethyl E-3-(3-methyloxiran-2-yl)acrylate.

To a solution of commercially available Ethyl Sorbate **(S4)** (5 mmol, 0.73 mL) in DCM (12 mL) was added *m*-CPBA (1.4eq, 7mmol, 1.57 g) at 0 °C and stirred for 12 h at the same temperature. The reaction was quenched with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to provide the vinyl epoxide **1b** (Hexane/EtOAc, 100:1, light yellow oil, yield: 541 mg, 69%) (Kuş, *et al.* 2015).

3.2.3. Synthesis of Ethyl E-3-(3-phenyloxiran-2-yl)acrylate (1c)

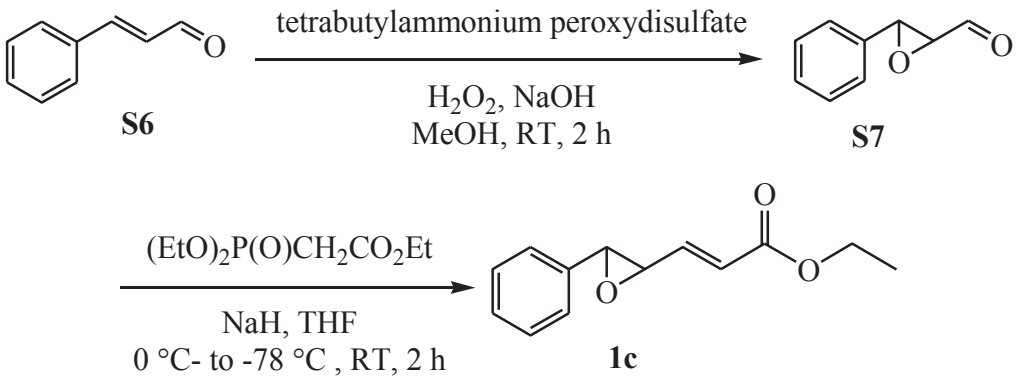


Figure 3.3. Synthesis of Ethyl E-3-(3-phenyloxiran-2-yl)acrylate.

Tetrabutylammonium hydrogensulfate (64.0 mmol, 21.2 g) and potassium persulfate (32.0 mmol, 8.70 g) were dissolved in distilled water (140 mL) and the reaction mixture was stirred for 30 min at RT. The solution was extracted with DCM, and the

combined organic layers were washed with distilled water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the tetrabutylammonium peroxydisulfate salt as a white solid and the compound was used directly without further purification.

To a solution of commercially available trans-cinnamaldehyde **(S6)** (5 mmol, 0.58 mL) in MeOH (20 mL) were added tetrabutylammonium peroxydisulfate (5 mmol, 3.34 g), H_2O_2 (30% in H_2O, 5 mmol, 0.5 mL), and NaOH (5 mmol, 200 mg) at RT and stirred for 2 h at the same temperature. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to provide the 3-phenyloxirane-2-carbaldehyde **(S7)** (Hexane/EtOAc, 15:1, yellow oil, yield: 538 mg, 73%) (Yang *et al.* 2007).

Triethyl phosphonoacetate (1.5mmol, 0.297 mL) was added dropwise to the solution of NaH (60% dispersion in mineral oil, 1.7 mmol, 65.5 mg) in dry THF (12 mL) at 0 °C, and the mixture stirred 1h at RT. Then, the reaction mixture was cooled to -78 °C and the aldehyde **S7** (1 mmol, 148 mg) was added dropwise to the reaction mixture and stirred for 1h at RT. The reaction was quenched cautiously with saturated $NH_4Cl_{(aq)}$ and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to afford the vinyl epoxide **1c** (Hexane/EtOAc, 100:1, light yellow oil, yield: 131 mg, 60%) (Urabe, *et al.* 1997).

3.2.4. Synthesis of Ethyl E3-(3-((benzyloxy)methyl)oxiran-2-yl)acrylate (1d)

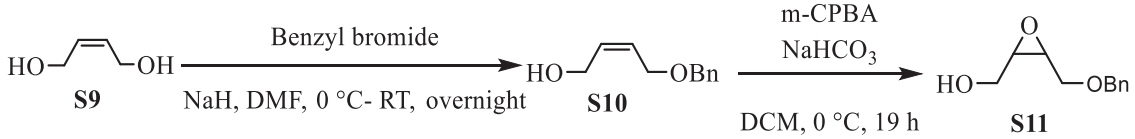


Figure 3.4. Synthesis of Ethyl E-3-(3-((benzyloxy)methyl)oxiran-2-yl)acrylate.

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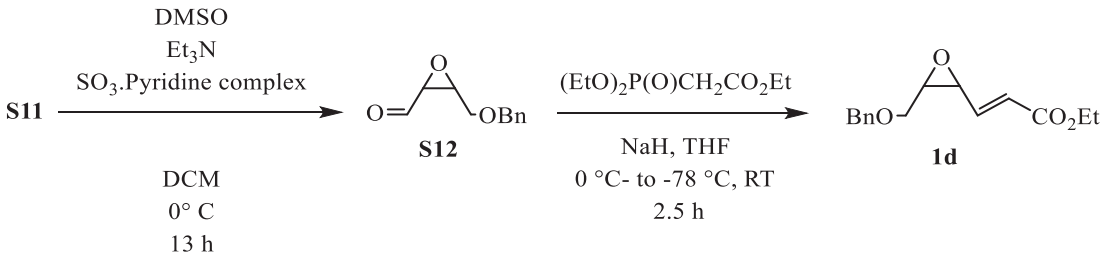


Figure 3.4 (cont.)

To a suspension of NaH (60% dispersion in mineral oil, 766.7 mg, 20 mmol) in dry DMF (15 ml) was added commercially available (Z)-but-2- ene-1 ,4-diol **(S9)** (1.64 mL, 20 mmol) in DMF (7.5 mL) at 0 °C. Then, benzyl bromide (2.97 mL, 25 mmol) was added in DMF (7.5 mL) at the same temperature and the reaction mixture was stirred overnight at RT. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to afford (Z)-4-(benzyloxy)but-2-en-1-ol **(S10)** (Hexane/EtOAc, 20:1, light yellow oil, yield: 3.39 g, 95%) (Schomaker, *et al.* 2004).

To a solution of **S10** (7 mmol) in DCM (50 mL) was added *m*-CPBA (1.3 eq., 9.1 mmol, 2.04 g) and $NaHCO_3$ (2.4 eq., 16.8 mmol, 1.4 g) at 0 °C and stirred for 19 h at the same temperature. The reaction was quenched with saturated $NaHCO_{3(aq)}$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to afford the (3-((benzyloxy)methyl)oxiran-2-yl)methanol **S11** (Hexane/EtOAc, 7:1, light yellow solid, yield: 760 mg, 85%).(Kuş, *et al.* 2015).

To a solution of epoxy alcohol **S11** (3.91 mmol) in dry DCM (10 mL) was added dry DMSO (5.6eq, 21.9 mmol, 1.55 mL) and Et_3N (5.3eq, 20.7 mmol, 2.89 mL). To this solution SO_3.Pyridine complex was added portionwise at 0 °C and stirred for 13h at the same temperature. The reaction was quenched with distilled water, extracted with Et_2O. The organic layer was washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the 3-((benzyloxy)methyl)oxirane-2-carbaldehyde **(S12)** which was used directly in the next step. It was noticed that, 30.5% of the epoxy aldehyde was in the water layer. Then the water layer was also extracted with EtOAc to recover **S12** effectively (Chen, *et al.* 2014).

Triethyl phosphonoacetate (1.5 eq., 7.29 mmol, 1.45 mL) was added dropwise to a solution of NaH (60% dispersion in mineral oil, 1.7 eq., 8.26 mmol, 330 mg) in dry THF (85 mL) at 0 °C, and the mixture was stirred for 1h at RT. Then, the reaction mixture was cooled to -78 °C and the crude aldehyde **S12** (4.86 mmol, 933 mg) in THF (15 mL) was added and stirred for additional 1 h at RT. The reaction was quenched cautiously with saturated $NH_4Cl_{(aq)}$ solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to afford the vinyl epoxide **1d** (Hexane/EtOAc 10:1, yellow oil, combined yield: 682 mg, 60%) (Urabe, *et al.* 1997).

3.2.5. Synthesis of Ethyl (E)-3-(3-cyclohexyloxiran-2-yl)acrylate (1e)

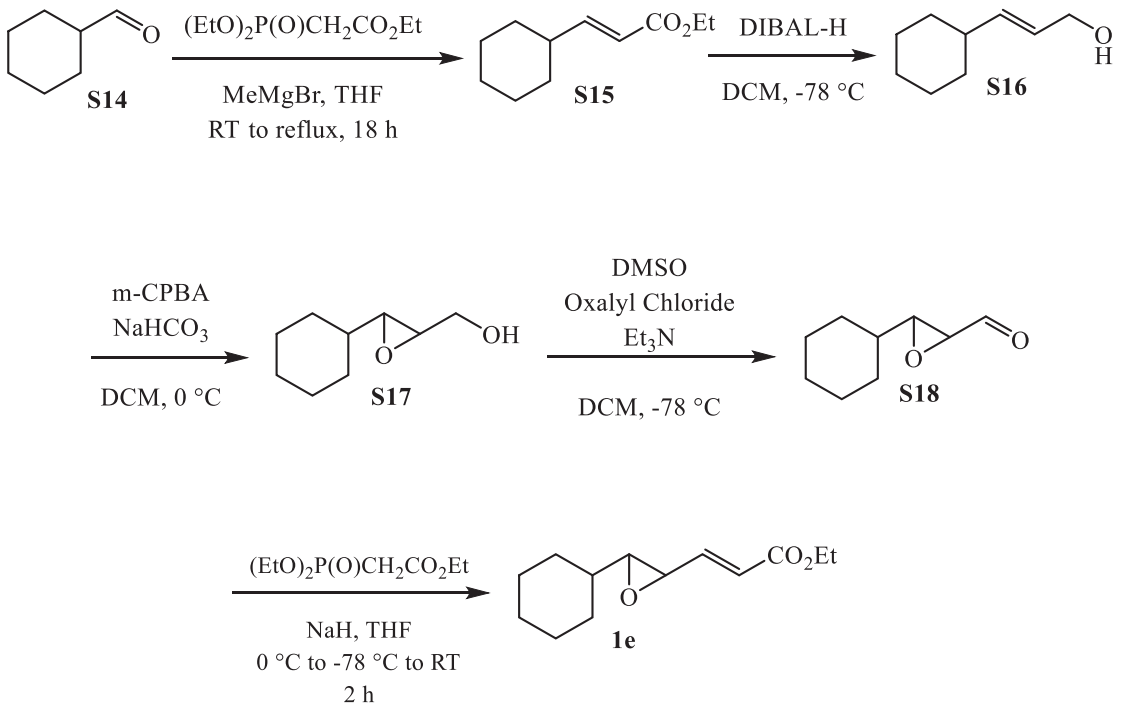


Figure 3.5. Synthesis of Ethyl (E)-3-(3-cyclohexyloxiran-2-yl)acrylate.

To a solution of triethyl phosphonoacetate (0.9 eq., 22.5 mmol, 4.95 mL) in dry THF (200 mL) was added MeMgBr (3.0 M in Et_2O, 0.9 eq., 22.5 mmol, 8.99 mL) solution dropwise and stirred for 15 min at RT. To this solution, commercially available cyclohexanecarbaldehyde **(S14)** (25 mmol, 3.04 mL) in THF (100 mL) was added

dropwise and the mixture was heated at reflux for 18 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to afford the ethyl (E)-3-cyclohexylacrylate **S15** (Hexane/EtOAc 15:1, colorless oil, yield: 3.65 g, 80%) (Claridge, *et al.* 2008).

To a stirred solution of **S15** in DCM (100 mL) at -78 °C, DIBAL (1 M in DCM, 3eq, 70 mL) solution was added drop by drop and stirred for 1h at -78 °C. A saturated aqueous solution of sodium potassium tartrate tetrahydrate (200mL) was added to the reaction mixture and stirred for 3 h at RT and the aqueous solution was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to provide the (E)-3-cyclohexylprop-2-en-1-ol **(S16)** (Hexane/EtOAc, 16:1, colorless oil, yield: 2.39 g, 85%) (Pippel, *et al.* 2001).

To a solution of **S16** (17 mmol) in DCM (130 mL) was added *m*-CPBA (1.3 eq., 22.1 mmol, 4.95 g) and $NaHCO_3$ (2.4 eq., 40.8 mmol, 3.4 g) at 0 °C and stirred for 2.5 h at the same temperature. The reaction was quenched with saturated $NaHCO_{3(aq)}$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to afford the (3-cyclohexyloxiran-2-yl)methanol **(S17)** (Hexane/EtOAc, 7:1, light yellow oil, yield: 1.6 g, 60%) (Kuş, *et al.* 2015).

To a stirred solution of DMSO (3 eq., 27 mmol, 1.9 mL) in dry DCM (20 mL) added to oxalyl chloride (1.5 eq., 13.5 mmol, 1.15 mL) at -78 °C and stirred for 20 min. Then the epoxy alcohol **S17** (9 mmol, 1.4 g) in DCM (7.5 mL) was added to the reaction mixture, stirred for 105 min. and Et_3N (4eq., 36 mmol, 5 mL) was added to reaction mixture. The mixture was allowed to attain RT and stirred for additional 30 min. The reaction was quenched with distilled water and extracted with Et_2O. The organic layer was washed with distilled water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the 3-cyclohexyloxirane-2-carbaldehyde **(S18)** which was used directly in the next step (Lindström and Somfai 1998).

The HWE reaction of **S18** (9 mmol, 1.38 g) and isolation of the product (E)-ethyl 3-(3-cyclohexyloxiran-2-yl)acrylate (**1e)** was performed as specified for **1d.** (Hexane only, yellow oil, combined yield: 832 mg, 60%) (Urabe, *et al.* 1997).

3.2.6. Synthesis of tert-butyl (E)-3-(3-methyloxiran-2-yl)acrylate (1f)

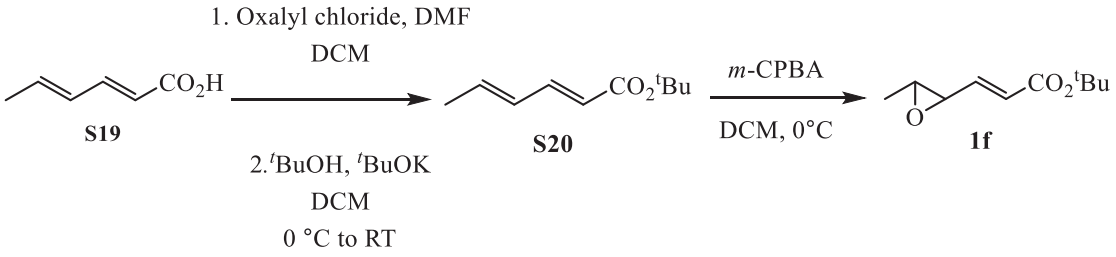


Figure 3.6. Synthesis of tert-butyl (E)-3-(3-methyloxiran-2-yl)acrylate (1f)

To a stirred solution of sorbic acid (10 mmol, 1.12 g) in DCM (20 mL) was added dimethylfoormamide (DMF) (10%) at 0 °C. To the mixture was added dropwise oxalyl chloride (3 eq, 30 mmol, 2.6 mL) at 0 °C and stirred for 30 minutes at the same temperature. After that the mixture was allowed to attain room temperature and the mixture stirred for additional 2 h. The reaction completion was monitored by thin-layer chromatography (TLC). The solution of sorbic chloride was directly used in the next reaction.

To a solution of potassium tert-butoxide ($KOBu^t$) (25 mmol, 2.8 g) and tert-butyl alcohol (^{t}BuOH) (25 mmol, 2.4 mL) in DCM (30 mL) at 0 °C was added dropwise above solution (sorbic chloride) and stirred for 3 days. The reaction completion was monitored by TLC. The reaction mixture was quenched with saturated aqueous sodium bicarbonate ($NaHCO_3$) and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered to afford the tert-butyl (2E,4E)-hexa-2,4-dienoate **(S20)**. (Hexane/EtOAc 100:1-50:1, light yellow oil, 1.25 g, 74%) (Oe, *et al.* 2014).

To a solution of **S20** (2.6 mmol, 450 mg) in DCM (130 mL) was added *m*-CPBA (1.3 eq., 3.38 mmol, 757 mg) at 0 °C and stirred for 2 days at the same temperature. The reaction was quenched with saturated $NaHCO_{3(aq)}$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on Et_3N treated silica gel to afford the tert-butyl (E)-3-(3-methyloxiran-2-yl)acrylate (**1f)** (Hexane/EtOAc, 50:1, colorless oil, yield: 325 mg, 68%) (Kuş, *et al.* 2015).

3.3. Characterization of Vinyl Oxirans

The synthesized reactants were analyzed by GC-MS and the NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm downfield from Me_4Si.

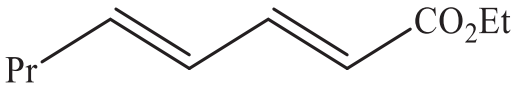


Figure 3.7. (2E,4E)-ethyl octa-2,4-dienoate **S2**.

S2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 1H), 6.20 – 6.05 (m, 2H), 5.77 (dd, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.13 (dd, *J* = 13.6, 7.1 Hz, 2H), 1.49 – 1.38 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.29, 145.06, 144.45, 128.46, 119.14, 60.13, 34.98, 21.91, 14.29, 13.63.

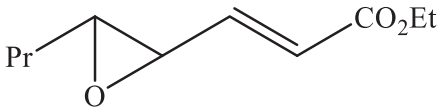


Figure 3.8. Ethyl (E)-3-(3-propyloxiran-2-yl)acrylate **1a**

1a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, J = 15.7, 7.2 Hz, 1H), 6.11 (dd, J = 15.7, 0.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 1H), 3.20 (ddd, J = 7.1, 2.0, 0.5 Hz, 1H), 2.91 – 2.85 (m, 1H), 1.62 – 1.54 (m, 1H), 1.52 – 1.43 (m, 1H), 1.28 (t, J = 7.1 Hz, 2H), 0.96 (t, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.68, 144.81, 123.52, 61.27 , 60.56 , 56.29, 33.87 , 19.13 , 14.19 , 13.84 . MS (EI, *m/z*): 139(45), 112(72), 101(63), 73(111), 55(129).

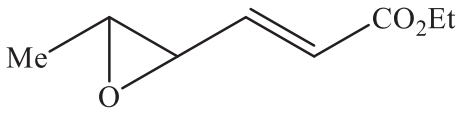


Figure 3.9. Ethyl (E)-3-(3-methyloxiran-2-yl)acrylate **1b**.

1b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.11 (dd, *J* = 15.7, 0.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.16 (dd, *J* = 7.2, 2.0 Hz, 1H), 2.96 (qd, *J* = 5.2, 2.0 Hz, 1H), 1.37 (d, *J* = 5.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.65, 144.60 , 123.67 , 60.56 , 57.37 , 57.21 , 17.51 , 14.19 . MS (EI, *m/z*): 112(44), 73(83), 55(101).

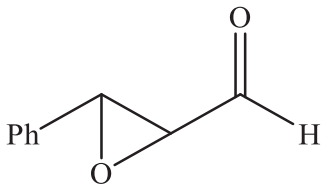


Figure 3.10. 3-phenyloxirane-2-carbaldehyde **S7**.

S7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 6.0 Hz, 1H), 7.39 – 7.35 (m, 3H), 7.31 – 7.27 (m, 2H), 4.17 (d, *J* = 1.8 Hz, 1H), 3.45 (dd, *J* = 6.1, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.83, 134.14, 129.19, 128.79, 125.69, 62.92, 56.61.

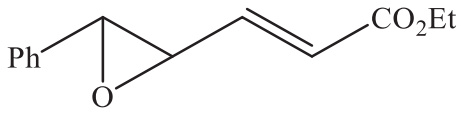


Figure 3.11. Ethyl (E)-3-(3-phenyloxiran-2-yl)acrylate **1c**.

1c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.81 (dd, *J* = 15.7, 6.9 Hz, 1H), 6.19 (dd, *J* = 15.7, 0.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 1.8 Hz, 1H), 3.47 (dd, *J* = 6.9, 1.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.59, 143.52, 136.03, 128.62, 125.48, 124.07, 61.02, 60.68, 60.58, 14.20.

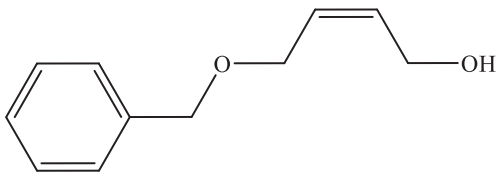


Figure 3.12. (Z)-4-(benzyloxy)but-2-en-1-ol **S10**.

S10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 5.79 (dtd, *J* = 16.8, 11.0, 6.2 Hz, 2H), 4.53 (s, 2H), 4.13 (dd, *J* = 28.6, 5.5 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.85, 132.39, 128.45, 128.20, 127.85, 127.79, 72.48, 65.65, 58.69.

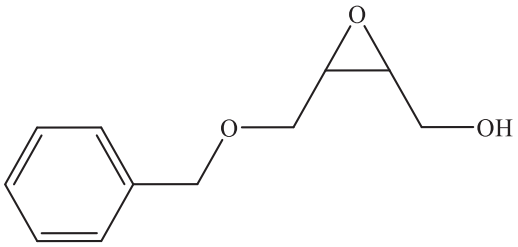


Figure 3.13. (3-((benzyloxy)methyl)oxiran-2-yl)methanol **S11**.

S11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 4.58 (dd, *J* = 34.4, 11.8 Hz, 2H), 3.77 – 3.70 (m, 2H), 3.65 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.30 (ddd, *J* = 6.0, 5.0, 4.5 Hz, 1H), 3.23 (ddd, *J* = 6.0, 5.2, 4.4 Hz, 1H), 3.12 (dd, *J* = 14.6, 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.33, 129.73, 128.54, 128.01, 127.87, 127.84, 73.50, 68.07, 60.75.

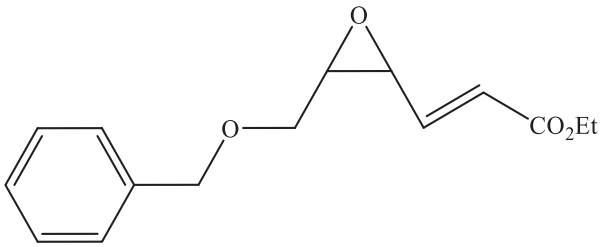


Figure 3.14. ethyl (E)-3-(3-((benzyloxy)methyl)oxiran-2-yl)acrylate **1d**.

1d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 6.76 (dd, *J* = 15.7, 6.6 Hz, 1H), 6.14 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 2H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.67 – 3.55 (m, 3H), 3.45 (dt, *J* = 6.0, 4.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.34 , 140.90 , 137.54 ,128,88 , 128.47, 127.84 ,125.69 , 73.37 , 67.42 , 60.70 , 57.55 , 54.27, 14.20.

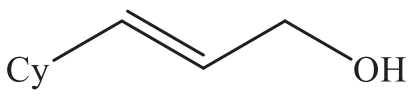


Figure 3.15. (E)-3-cyclohexylprop-2-en-1-ol **S16**.

S16: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 – 5.53 (m, 2H), 4.08 (d, *J* = 3.8 Hz, 2H), 2.00 – 1.90 (m, 1H), 1.75 – 1.68 (m, 4H), 1.67 – 1.61 (m, 1H), 1.44 (br s, 1H), 1.29 – 1.02 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.17, 126.27, 63.98, 40.27, 32.74, 29.54, 26.05.

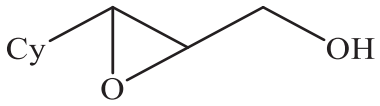


Figure 3.16. (3-cyclohexyloxiran-2-yl)methanol **S17**.

S17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (dd, *J* = 12.5, 2.6 Hz, 1H), 3.59 (dd, *J* = 12.5, 4.5 Hz, 1H), 3.43 (d, *J* = 6.4 Hz, 1H), 2.99 – 2.95 (m, 1H), 2.75 (dd, *J* = 6.8, 2.4 Hz, 1H), 1.92 (br s, 1H), 1.88 – 1.81 (m, 1H), 1.78 – 1.62 (m, 5H), 1.29 – 1.17 (m, 4H), 1.11 (ddd, *J* = 14.5, 6.8, 2.9 Hz, 2H).

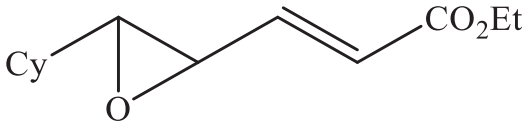


Figure 3.17. Ethyl (E)-3-(3-cyclohexyloxiran-2-yl)acrylate **1e**.

1e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.04 (dd, *J* = 15.7, 0.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.20 (ddd, *J* = 7.1, 2.1, 0.7 Hz, 1H), 2.63 (dd, *J* = 6.8, 2.1 Hz, 1H), 1.82 – 1.57 (m, 6H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.17 – 1.00 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.74, 145.06, 123.29, 65.69, 60.54, 55.13, 40.02, 29.49, 28.80, 26.15, 25.56, 25.43, 14.19.

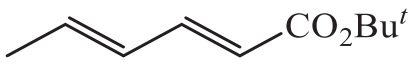


Figure 3.18. tert-butyl (2E,4E)-hexa-2,4-dienoate **S20**.

S20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 15.1, 10.1 Hz, 1H), 6.20 – 6.01 (m, 2H), 5.69 (d, *J* = 15.4 Hz, 1H), 1.83 (d, *J* = 5.7 Hz, 3H), 1.48 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.68, 143.85, 138.41, 129.76, 120.94, 80.00, 28.16, 18.57.

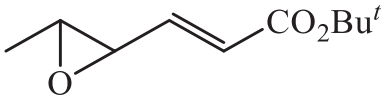


Figure 3.19. tert-butyl (E)-3-(3-methyloxiran-2-yl)acrylate **1f**.

1f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 15.7, 7.2 Hz, 1H), 6.03 (dd, *J* = 15.7, 0.7 Hz, 1H), 3.14 (dd, *J* = 7.2, 1.8 Hz, 1H), 2.95 (qd, *J* = 5.2, 2.0 Hz, 1H), 1.46 (s, 8H), 1.36 (d, *J* = 5.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.91, 143.34, 125.61, 80.68, 57.28, 57.21, 28.04, 17.47.

3.4. Synthesis of Organoborons

3.4.2. Synthesis of Sodium Tetrakis(4-methylphenyl)borate (2b)

$NaBF_4$ was purified in kugelrohr for 16 h at 70 °C before use.3.4.2. Synthesis of Sodium Tetrakis(4-methylphenyl)borate (**2b**).

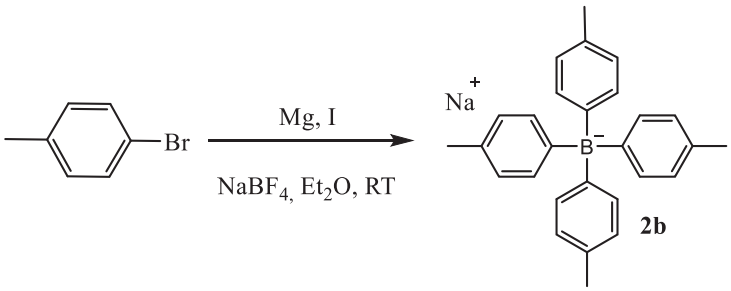


Figure 3.20. Synthesis of Sodium Tetrakis(4-methylphenyl)borate.

Mg turnings (3.24 g, 133 mmol) and 100 mL dry Et_2O were added successively to two-necked flask which was dried in oven and cooled under Nitrogen gas before use. A crystal of iodine was added to this suspension. The mixture was stirred until the color of iodine disappeared. A solution of 4-bromotoluene (13.6 mL, 111 mmol) in Et_2O (100 mL) was added to the reaction mixture dropwise over 2h and the reaction mixture was stirred over 2h until Mg consumed. After Mg was consumed, $NaBF_4$ was added to reaction mixture and stirred for 3days at RT. The reaction was quenched with the

$Na_2CO_{3(aq)}$ (10% in distilled water, 500 mL) solution and stirred over 1h, filtered by filtration apparatus, extracted with Et_2O, dried over $MgSO_4$, filtered again, and concentrated under reduced pressure. The solid residue was washed with $CHCl_3$/Hexane (5:1) and dried under high vacuum overnight. (Yield: 40%) (Shintani, *et al.* 2009).

3.4.3. Synthesis of Sodium Tetrakis(3-methoxyphenyl)borate (2c)

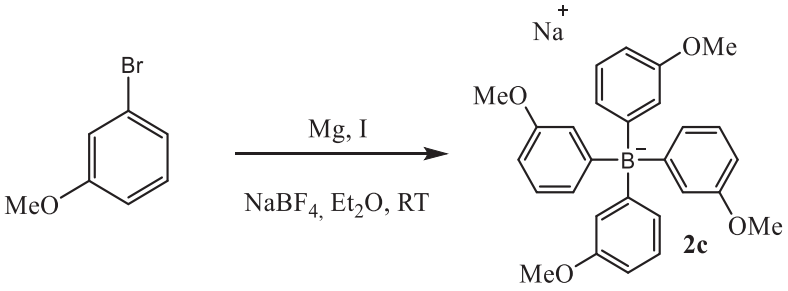


Figure 3.21. Synthesis of Sodium Tetrakis(3-methoxyphenyl)borate.

Synthesis of the organoboron **2c** from 3-bromoanisole and purification of the product were performed as specified for **2b** (Yield 40%).

3.4.4.Synthesis of sodium tetrakis(4-(trifluoromethyl)phenyl)borate (2d)

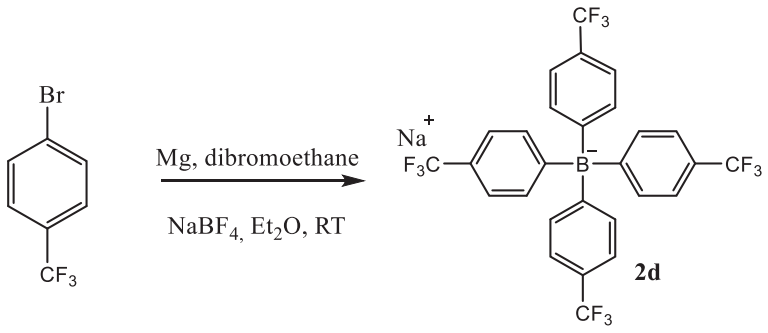


Figure 3.22. Synthesis of sodium tetrakis(4-(trifluoromethyl)phenyl)borate

Mg turnings (30 mmol, 720 mg) and 45 mL dry Et_2O were added successively to three-necked flask which was dried in oven and cooled under Nitrogen gas before use. $NaBF_4$ (7.5 mmol, 825 mg) was added to suspension. A solution of *p*-bromobenzotrifluoride (30 mmol, 4.2 mL) in Et_2O (15 mL) was added to the dropping funnel and 3 mL of it and dibromoethane (1-2 mL) added to reaction mixture rapidly. When the reaction start, rest of the *p*-bromobenzotrifluoride solution was added the reaction mixture dropwise over 2h. The mixture was allowed to attain RT and stirred for additional 30 min. 100 mL of crushted ice was added to reaction mixture and dilute sodium hydroxide solution was added to make the mixture alkaline. The solution was added to seperating funnel and ether layer was seperated. Aqueous layer was saturated with NaCl and extracted with diethyl ether (50x3). 100 mL of water was added to it and the mixture was concentrated. The residue was dissolved in H_2O:MeOH (1:1, 80 ml) and filtered from celite and concentrated under reduce pressure for 3days to attain the sodium tetrakis(4-(trifluoromethyl)phenyl)borate (**2d)** (Yield: 15%) (Vandkberg, *et al* 1969).

3.5. Characterizatıon of Organoborons

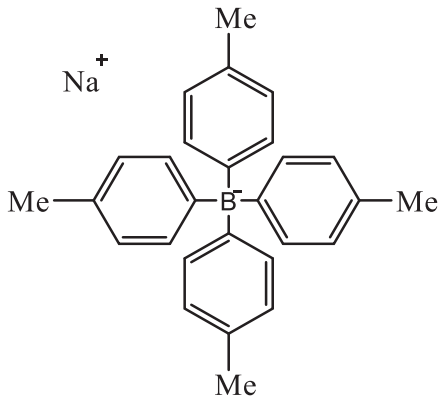


Figure 3.22. Sodium Tetrakis(4-methylphenyl)borate

2b: ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (ddd, J = 7.8, 5.2, 2.6 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 2.20 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 135.83, 129.60, 125.67, 19.85. ^{11}B NMR (128 MHz, CD_3OD) δ -7.32.

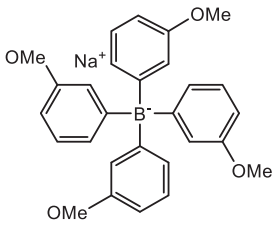


Figure 3.23. Tetrakis(3-methoxyphenyl)borate

2c: ^{1}H NMR (400 MHz, CD_3OD) δ 6.96 – 6.89 (m, 1H), 6.45 – 6.41 (m, 1H), 4.87 (s, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 129.22, 125.52, 121.05, 107.11. ^{11}B NMR (128 MHz, CD_3OD) δ -6.52.

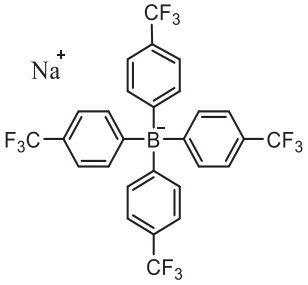


Figure 3.24. sodium tetrakis(4-(trifluoromethyl)phenyl)borate

2d: ^{1}H NMR (400 MHz, DMSO) δ 7.33 (s, 16H). ^{13}C NMR (100 MHz, DMSO) δ 167.2 (q, J = 51 Hz), 135.7, 125.8 (q, J = 270 Hz), 122.9. ^{19}F (326.27 MHz, DMSO) δ -60.1. ^{11}B (128.31 MHz, DMSO) δ -6.5.

3.6. Synthesis of Enantio-pure γ,δ-epoxy-α,β-Unsaturated Ester

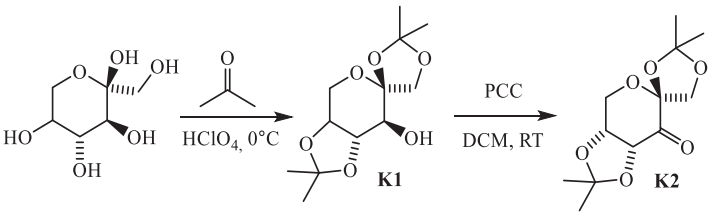


Figure 3.25. Synthesis of Shi Ketone.

To the acetone-containing flask was added D- fructose (204.7 mmol, 36.84 g) and dimethoxypropane (120 mmol, 14.8 mL) respectively under Nitrogen gase. The mixture was cooled to 0 ºC and Perchloric acid (70%, 8.6 mL) was added dropwise to the solution. After the mixture was stirred for 6 h, pH adjusted to approximately 7-8 with the addition of concentrated ammonium hydroxide solution, stirred at the same pH for 10 min, and concentrated. The crude solid was crystallized from hexane/DCM (4/1) to afford **K1**. (Yield: 21 g, 51%).

The alcohol obtained in the previous step (**K1)** was dissolved in dry DCM (100 mL) under Nitrogen gase. Powdered 3 Å molecular sieves (activated under vacuum at 300 ºC for 24 h before use) added to solution at RT and PCC (54 mmol, 11.64 g) was added dropwise and stirred for 3 h. After the reaction was complited, the mixture was filtered from Celite, concentrated, and purified with solid column chromatography. (Hexane:Ether 8:1-3:1, yield: 4.5 g, 88%). The ketone (**K2)** was recrystallized from hexane-DCM (Shi, *et al* 1997).

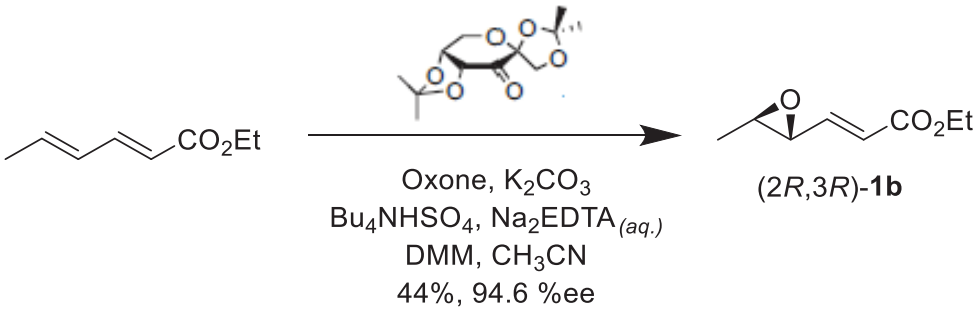


Figure 3.26. Enantio-pure Synthesis of Alkenyl Oxirane **1b** with Shi method.

To a mixture of DMM (50 mL) and acetonitrile (25 mL) was added $Na_2B_4O_7$ (borax) containing Na_2EDTA (50 mL, 4x10-4 M) and ethyl sorbate (5 mmol, 700 mg, 0.74 mL). The mixture was cooled to 0 oC then tetrabutylammonium hydrogensulfat (150 mg) and Shi-ketone **(K2)** (2.5 mmol, 630 mg) was added respectively to the mixture. After the mixture was stirred for 5 min., Oxone (5.6 mmol, 3.45 g) in 30 mL Na_2EDTA (4x10-4 M) and potassium carbonate (25 mmol, 3.45 g) in 30 mL ultra pure-water was added over 4.5 h simultaneously with the help of peristaltic syringe pump. When the addition was complete, 50 mL Et_2O was added to mixture and extraxted with water. The combined organic layer was washed with brine, dried over Na_2SO_4(k), and concentrated. The crude mixture was prufied from 1% NEt_3-containig silica gel column. (Hexane:DCM

100:2-100:8, 1% NEt_3-containing, yield 44%) The enantiomeric purity was established to be 94.6 % ee by HPLC analysis. [(2R,3R)-**1b**: t_R¼7.599 min, λ: 210 nm; Chiralcel ®OD-3 Hexane:IPA (98:2), 1.0 ml/min]. (Uchida et al. 2006).

3.7. Characterization of Shi-ketone

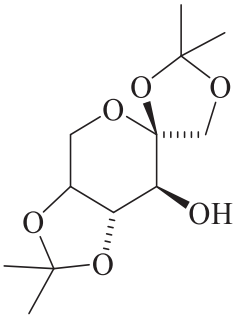


Figure 3.27. (4S,7'S,7a'S)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolane-4,6'-[1,3]dioxolo[4,5-c]pyran]-7'-ol

K1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (ddd, *J* = 5.7, 2.7, 0.9 Hz, 1H), 4.19 (d, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 6.8, 5.7 Hz, 1H), 4.12 (dd, *J* = 13.2, 2.7 Hz, 1H), 4.01 (dd, *J* = 13.2, 0.9 Hz, 1H), 3.98 (d, *J* = 9.0 Hz, 1H), 3.67 (dd, *J* = 8.1, 6.8 Hz, 1H), 1.99 (d, *J* = 8.1 Hz, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.0, 109.6, 104.7, 77.48, 73.53, 73.52, 70.60, 60.96, 28.13, 26.62, 26.46, 26.14.

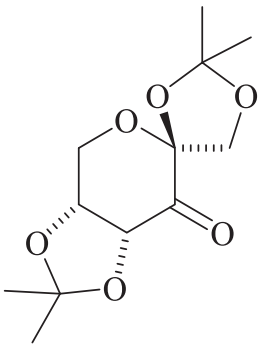


Figure 3.28. (3a'R,4S,7a'R)-2,2,2',2'-tetramethyldihydrospiro[[1,3]dioxolane-4,6'-[1,3]dioxolo[4,5-c]pyran]-7'(4'H)-one

K2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, *J* = 5.7 Hz, 1H), 4.61 (d, *J* = 9.5 Hz, 1H), 4.55 (ddd, *J* = 5.7, 2.2, 1.0 Hz, 1H), 4.39 (dd, *J* = 13.4, 2.2 Hz, 1H), 4.12 (d, *J* = 13.4 Hz, 1H), 4.00 (d, *J* = 9.5 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 114.0, 110.8, 104.3, 78.11, 76.07, 70.20, 60.28, 27.33, 26.70, 26.24, 26.20. $[\alpha]^{25}_{D}$ -125° (c 1.0, $CHCl_3$).

3.8. General Method for Palladium-Catalyzed Reactions of Vinyl Oxiranes

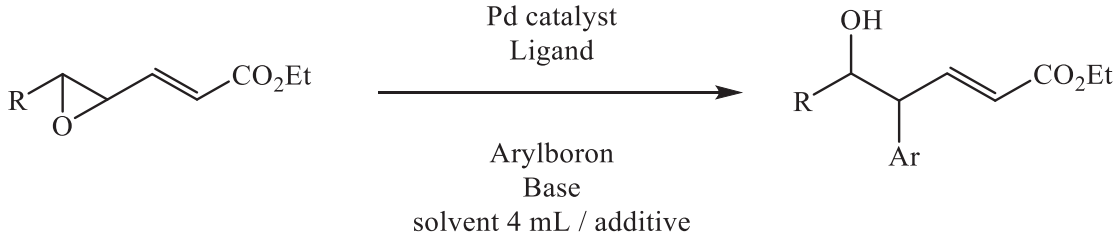


Figure 3.29. General Method for Palladium-Catalyzed Reactions of Vinyl Oxiranes

The reactions were carried out in 2-necked Schlenk attached to a condenser or closed Schlenk system. The Pd-catalyst, ligand and dry solvent (half of the volume required for reaction) were added to Schlenk (dried in oven and cooled under Ar gas). The mixture was stirred for 5 min. at RT. Then, organoboron, solution of the epoxide compound in dry solvent (a quarter of the volume required for the reaction), additive, and base (in other quarter volume of the dry solvent) were added respectively to the reaction mixture and it was stirred in a preheated oil bath. The reaction process was monitored with TLC. When the reaction was judged to be complete the reaction mixture was filtered from a short silica gel column (height: 10 cm and width: 2 cm), washed with Et_2O and concentrated under reduced pressure. The crude product was analyzed by ^{1}H NMR using benzaldehyde as the internal standard. Then, the residue was purified using silica gel on column chromatography to afford the target product homoallylic alcohol as a colorless oil. When the reaction was performed in sealed Schlenk, the completion of the reaction was judged from color change of the mixture from light yellow to black.

3.9. Characterization of Homoallylic Alcohols

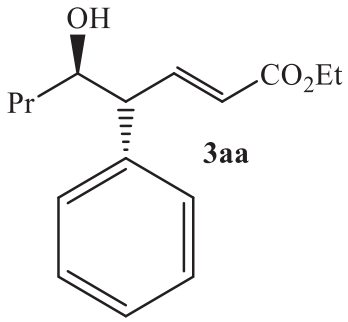


Figure 3.30. Ethyl (E)-5-hydroxy-4-phenyloct-2-enoate

3aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 1H), 7.28 – 7.18 (m, 2H), 5.89 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 1H), 3.90 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.42 (dd, *J* = 8.8, 6.8 Hz, 1H), 1.78 (s, 1H), 1.53 – 1.45 (m, 1H), 1.38 – 1.31 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 2H), 0.86 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.30, 147.87, 140.11, 128.87, 128.21, 127.09 123.59, 74.07, 60.40, 55.39, 36.94, 18.85, 14.24, 13.88. MS (EI, *m/z*): 190(72), 162(100), 144(118), 91(117), 55(207), 45(217) FTIR (νmax/cm^{-1}): 3420, 2959, 2924, 1715 (C=O), 1649, 1601, 1453, 1369, 1260, 1171, 1091, 1028, 982, 849, 799, 699, 553.

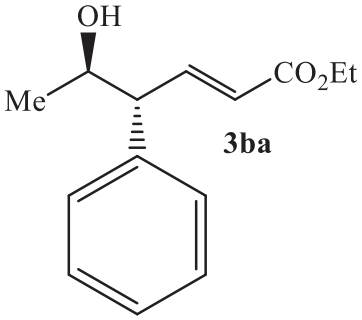


Figure 3.31. Ethyl (E)-5-hydroxy-4-phenylhex-2-enoate

3ba: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 1H), 5.91 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 4.14 – 4.05 (m, 1H), 3.38 – 3.31 (m, 1H), 1.80 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 1H), 1.11 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.29, 147.91, 139.87, 128.89, 128.18, 127.20, 123.70, 70.50, 60.44, 56.98, 21.28, 14.24. MS (EI, *m/z*): 217(17), 190(44), 162(72), 144(90), 115(119), 91(143), 51(183), 45(189). FTIR

(νmax/cm^{-1}): 3425, 2976, 2927, 1714 (C=O), 1699, 1650, 1601, 1493, 1453, 1391, 1369, 1315, 1261, 1240, 1173, 1095, 1031, 982, 933, 862, 802, 759, 700, 537.

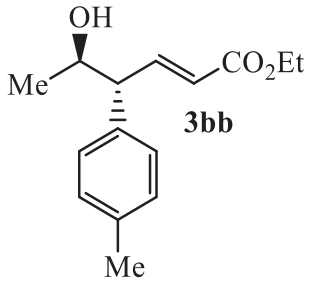


Figure 3.32. Ethyl-(E)-5-hydroxy-4-(p-tolyl)hex-2-enoate

3bb: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.7, 8.9 Hz, 1H), 7.16 – 7.06 (m, 4H), 5.90 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.07 (dt, *J* = 12.9, 6.4 Hz, 1H), 3.32 (t, *J* = 8.1 Hz, 1H), 2.32 (s, 3H), 1.84 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 4H), 1.10 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.33, 148.19, 136.83, 129.55, 128.03, 123.46, 70.50 60.38, 56.59 21.24, 21.01, 14.23. MS (EI, *m/z*): 204(44), 175(73), 158(90), 131(117), 115(133), 91(157), 77(171), 44(204). FTIR (νmax/cm^{-1}): 3224, 2978, 2928, 1898, 1715 (C=O), 1649, 1513, 1447, 1369, 1315, 1238, 1167, 1131, 1039, 982, 930, 878, 812, 779, 723, 599, 547.

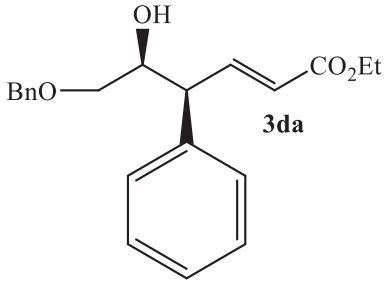
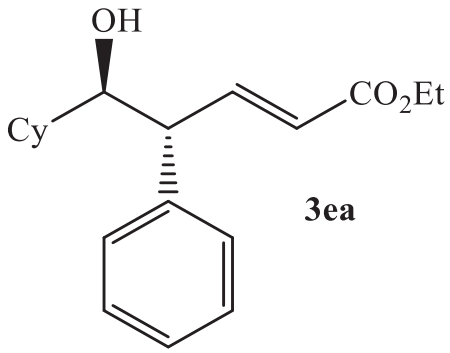


Figure 3.33. (E)-ethyl 6-(benzyloxy)-5-hydroxy-4-phenylhex-2-enoate

3da: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 10H), 7.12 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.87 (dd, *J* = 15.6, 1.1 Hz, 1H), 4.54 (q, *J* = 11.8 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 3H), 3.65 (t, *J* = 8.2 Hz, 1H), 3.57 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.51 – 3.41 (m, 1H), 1.63 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.30, 147.32, 138.58, 137.68, 128.86, 128.66, 128.47, 127.86, 127.83, 127.37, 122.91, 73.50, 72.41, 72.00, 60.42, 51.84, 30.31, 14.24. FTIR (νmax/cm^{-1}): 3447, 3062, 3029,

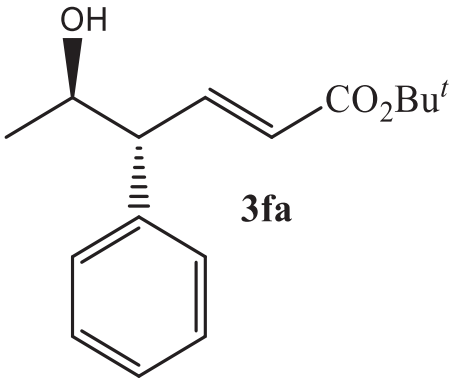
2956, 2923, 2853, 1954, 1881, 1808, 1715(C=O), 1650, 1602, 1542, 1495, 1454, 1367, 1314, 1268, 1238, 1168, 1120, 1095, 1028, 983, 909, 895, 845, 814, 736. HRMS (ESI) : $C_{21}H_{25}O_4$ $(MH)^+$, 341,1747 (calculated); 341,1751 (found).



3ea

Figure 3.34. (E)-ethyl 5-cyclohexyl-5-hydroxy-4-phenylpent-2-enoate

3ea: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.14 (m, 6H), 5.88 (d, *J* = 15.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.74 – 3.51 (m, 2H), 1.88 – 1.54 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.02 (m, 5H).^{13}C NMR (100 MHz, $CDCl_3$) δ 166.34, 148.14, 140.55, 128.87, 128.13, 127.00, 123.45, 60.35, 51.68, 39.90, 29.96, 26.71, 26.32, 26.15, 25.81, 14.23. FTIR (νmax/cm^{-1}): 3458, 3085, 3061, 3028, 2980, 2926, 2853, 2669, 2249, 1946, 1880, 1715(C=O), 1649, 1600, 1583, 1494, 1450, 1392, 1369, 1314, 1266, 1238, 1166, 1115, 1095, 1068, 1040, 982, 943, 910, 892, 867, 842, 807, 764, 735, 701.



3fa

Figure 3.35. tert-butyl (E)-5-hydroxy-4-phenylhex-2-enoate.

3fa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 7H), 5.85 (dd, *J* = 15.6, 1.0 Hz, 1H), 4.08 (dq, *J* = 12.5, 6.2 Hz, 1H), 3.32 (t, *J* = 8.1 Hz, 1H), 1.83 (s, 1H), 1.46 (s, 9H), 1.10 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.62, 146.66, 140.06,

128.85, 128.19, 127.12, 125.43, 80.48, 70.47, 56.99, 28.10, 21.19. FTIR (νmax/cm^{-1}): 3430, 3084, 3062, 3029, 2981, 2979, 2871, 2248, 1951, 1709(C=O), 1650, 1601, 1584, 1493, 1477, 1454, 1392, 1368, 1318, 1249, 1152, 1132, 1084, 1056, 1032, 981, 934, 911, 882, 850, 811, 757, 735, 701.

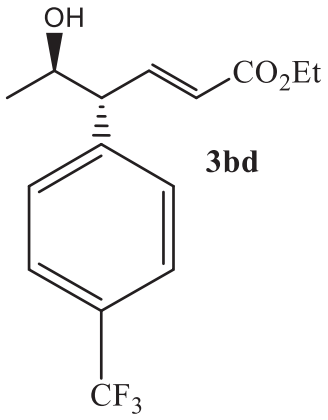


Figure 3.36. ethyl (E)-5-hydroxy-4-(4-(trifluoromethyl)phenyl)hex-2-enoate.

3bd: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.24 (ddd, *J* = 10.5, 7.4, 1.8 Hz, 1H), 5.90 (d, *J* = 15.0 Hz, 1H), 4.19 (q, *J* = 8 Hz, 2H), 4.15 – 4.09 (m, 1H), 3.43 (t, *J* = 7.8 Hz, 1H), 1.28 (t, *J* = 8 Hz, 3H), 1.13 (dd, *J* = 6.2, 1.7 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 146.8, 144.2, 129.7 (q, *J* = 32.6 Hz), 128.8, 125.9 (q, *J* = 4Hz), 124.6, 124.18 (q, *J*= 271 Hz), 70.4, 60.7, 56.7, 21.7, 14.4. FTIR (νmax/cm^{-1}): 3452, 2987, 2929, 2870, 2249, 1716 (C=O), 1653, 1619, 1457, 1420, 1393, 1371, 1327, 1271, 1243, 1167, 1130, 1069, 1040, 1018, 984, 910, 837, 768, 736.

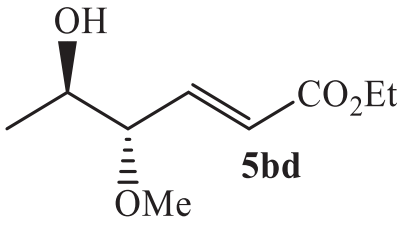


Figure 3.37. ethyl (E)-5-hydroxy-4-methoxyhex-2-enoate.

5bd: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 15.8, 7.1 Hz, 1H), 6.06 (d, *J* = 15.8 Hz, 1H), 4.22 (dd, *J* = 14.5, 7.7 Hz, 2H), 3.67 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.48 (dd, *J* = 15.1, 8.1 Hz, 2H), 3.35 (s, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 1H).

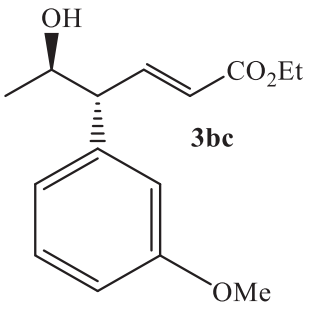


Figure 3.38. ethyl (E)-5-hydroxy-4-(3-methoxyphenyl)hex-2-enoate

3bc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 6.81 – 6.73 (m,2H), 6.75 – 6.72 (m, 1H), 5.90 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.08 (dq, *J* = 12.5, 6.2 Hz, 1H), 3.79 (s, 3H), 3.31 (t, *J* = 7.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 160.0, 147.9, 141.6, 130.0, 123.81 120.6, 114.4, 112.3, 70.6, 60.6, 57.1, 55.3, 21.4, 14.4. FTIR (νmax/cm^{-1}): 3439, 3052, 2978, 2983, 2904, 2887, 2872, 2249, 1925, 1712 (C=O), 1649, 1600, 1584, 1487, 1465, 1453, 1437, 1392, 1369, 1264, 1238, 1177, 1152, 1130, 1096, 1042, 983, 943, 910, 876, 864, 779, 735, 700.

3.10. Characterization of Enantio-pure Product

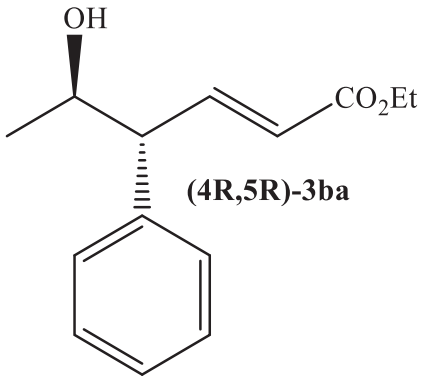


Figure 3.39. ethyl (4R,5R,E)-5-hydroxy-4-phenylhex-2-enoate

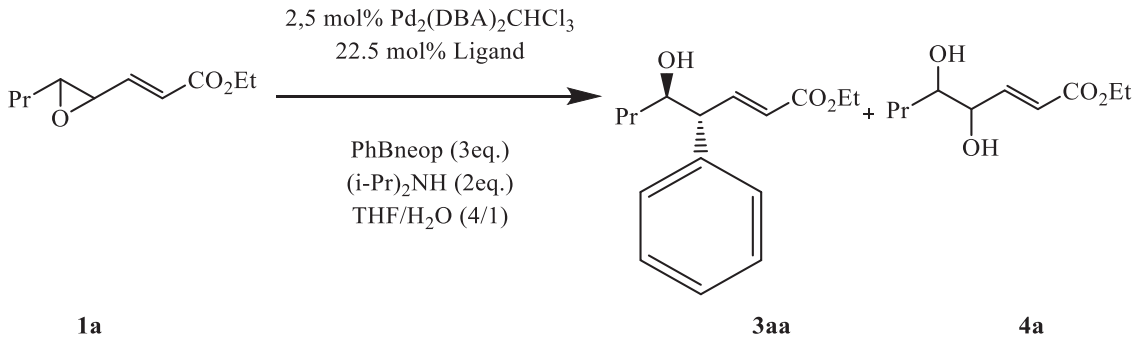
[(4R,5R)-3ba: The enantiomeric purity was established to be 90% ee by HPLC analysis [(4R,5R)-3bb: t_R¼14.5 min (Yield: 89%), Chiralcel ®OD-3 λ: 220 nm, Hexane:IPA (98:2), 1.0 ml/min].

CHAPTER 4

RESULT AND DISCUSSION

In this study, Pd-catalyzed arylation reaction of γ,δ-epoxy-α,β-unsaturated esters were performed first time. The reaction conditions were optimized using γ,δ-epoxy-α,β-unsaturated ester **1a** with arylborons to afford homoallylic alcohols (γ-Aryl-δ-hydroxy-α,β-unsaturated ester type). We initiated our first experiment using 2.5 mol% $Pd_2(DBA)_3CHCl_3$, 22.5 mol% $AsPh_3$ as the ligand, 3eq. PhBneop as the aryl source, and 2eq. $(i\text{-}Pr)_2NH$ as the base in dry THF/water (4/1) mixture at RT. However, the homoallyl alcohol (**3a)** was obtained only in 54% yield along with other intricate (Table 4.1, entry 1). We proved that in the absence of ligand, the starting vinyl epoxide **1a** was unreactive and hence, no conversion was observed (Table 4.1,entry 2). The use of Xphos and DPEPhos ligands reduced the formation of homoallyl alcohol further (Table 4.1, entries 3 and 4). Unexpectedly, the reaction resulted in the formation of 1,2-diol product (**4a)** with the use of some of the ligands (Table 4.1, entries 5-11). The optimization studies showed that some of the ligands gave no conversion and target product homoallyl alcohol could not be determined (Table 4.1, entries 12-16).

Table 4.1 Effect of Ligands on the Pd-catalyzed Reactions of Vinyl Epoxide ethyl (E)-3-(3-propyloxiran-2-yl)acrylate (**1a)** with Arylborons.



1a **3aa** **4a**

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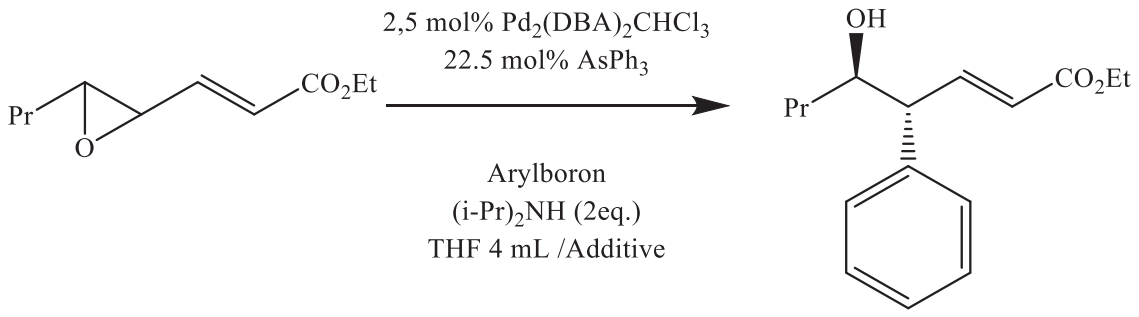
Table 4.1 (cont.)

Entry	Ligand	T (°C)	Time	3aa/4a	Yield (%)[a]
1	$AsPh_3$	RT	48 h	100:0	54
2	-	RT	48 h	-	-
3	Xphos	RT	O.N.	100:0	30
4	DPEPhos	RT	O.N.	100:0	36 (32)[b]
5	Tris *p*-(4-OMePh) Phosphine	RT	3 min	0:100	40 (38)[b]
6	dppb	RT	O.N.	0:100	43
7	dppe	RT	O.N.	0:100	77 (69)[b]
8	PPh_3	RT	45 min	0:100	34
9	Xantphos	RT	15 min	0:100	54
10	dppf	RT	O.N.	59:41	78
11	Tris *p*-(4-CF_3Ph) Phosphine	RT	O.N.	29:71	45
12	Tris *p*-(2-furyl) Phosphine	RT	O.N.	-	complex mixture
13	HP(c-Hex)$_3BF_4$	50	1 h	-	complex mixture
14	$SbPh_3$	50	5h	-	complex mixture
15	2,2'-bipyridyl	50	3h	-	-
16	1,3-dimesitylimidazolium chloride	50	3h	-	complex mixture

[a] Determined by ^{1}HNMR using benzaldehyde as internal standard. [b]Isolated yield.

Having determined that $AsPh_3$ would be a suitable ligand as compared to the other phosphine ligands, which were tested in optimization studies. The effect of other parameters, such as reaction temperature, additive, and organoboron derivatives as aryl source was also investigated (Table 4.2). The use of less amount of PhBneop in the presence of 1 mL of H_2O as an additive, at RT, decreased the formation of desired homoallyl alcohol product (**3aa**) (Table 4.2, entries 1 and 2). In the absence of arylboron or water, the desired product could not be determined (Table 4.2, entries 3and 4). When the amount of water was reduced by half, the yield was increased somewhat, but no noticeable improvement was gained by the application of a higher temperature (50 °C) (entry 6). The replacement of H_2O with MeOH had no effect on the reaction fate (Table 4.2, entries 7 and 8). Lower yields were obtained with the use of $PhB(OH)_2$ or $NaBPh_4$ as organoboron reagents (Table 4.2, entries 9 and 10). Nevertheless, interestingly $NaBPh_4$ afforded better at 50 °C as compared to the other organoboron ester (Table 4.2, entry 11). Interestingly again MeOH was more competent additive than water. (Table 4.2, entries 10-14). Changing the palladium compound from $Pd_2(DBA)_3CHCl_3$ to $Pd(OAc)_2$ and increasing the reaction temperature and increasing the reaction temperature to 70°C even further improved the reaction yield (Table 4.3, entry 15). The use of higher alcohols as additives completely deactivated the catalyst activity (Table 4.2, entries 16 and 17). Apparently $KPhBF_3$ would not be the good choice of organoboron for the method at all (Table 4.2, entry 18).

Table 4.2. Effect of Arylboron Derivative, Additive, and The Reaction Temperature on the Pd-catalyzed Reactions of Vinyl Epoxide **1a**.



1a **3aa**

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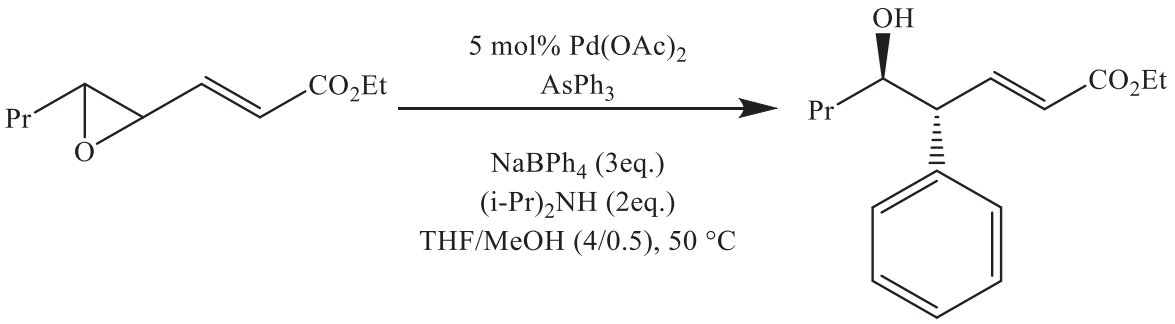
Table 4.2 (cont.)

Entry	Arylboron (eq.)	Additive (mL)	T (°C)	Time (h)	Yield (%)[a]
1	PhBneop (1.1)	H_2O (1)	RT	48	33
2	PhBneop (1.5)	H_2O (1)	RT	48	43
3	PhBneop (3)	-	RT	48	complex mixture
4	-	H_2O (1)	RT	48	complex mixture
5	PhBneop (3)	H_2O (0.5)	RT	48	55
6	PhBneop (3)	H_2O (0.5)	50	O.N.	55
7	PhBneop (3)	MeOH (1)	50	2.5	53
8	PhBneop (3)	MeOH (0.5)	50	3	55
9	$PhB(OH)_2$ [c](3)	H_2O (1)	RT	O.N.	41
10	$NaBPh_4$ (3)	H_2O (1)	RT	O.N.	30
11	$NaBPh_4$ (3)	H_2O (0.5)	50	5	65
12	$NaBPh_4$ (3)	MeOH (0.25)	50	3.5	60
13	$NaBPh_4$ (3)	MeOH (0.5)	RT	48	62
14	$NaBPh_4$ (3)	MeOH (0.5)	50	3.5	76
15	$NaBPh_4$ (3)	MeOH (0.5)	70[e]	1	82[b]
16	$NaBPh_4$ (3)	EtOH (0.5)	50	72	complex mixture
17	$NaBPh_4$ (3)	i-PrOH (0.5)	50	72	complex mixture
18	$KPhBF_3$ (3)	MeOH (0.5)	50	1	38

[a] Determined by ^{1}HNMR using benzaldehyde as internal standard. [b]5 mol % $Pd(OAc)_2$ was used as the catalyst, [c]The catalyst was used 5 mol %. [e]The reaction was performed in closed Schlenk system.

We also investigated the $AsPh_3$/Pd ratio on the reaction efficacy; it seems that the molar ration 4:1 would be the optimal for the method (Table 4.3, entries 1-3).

Table 4.3. Effect of Ligand Amount on Pd-catalyzed Reactions of Vinyl Epoxide (1a) with Arylborons.



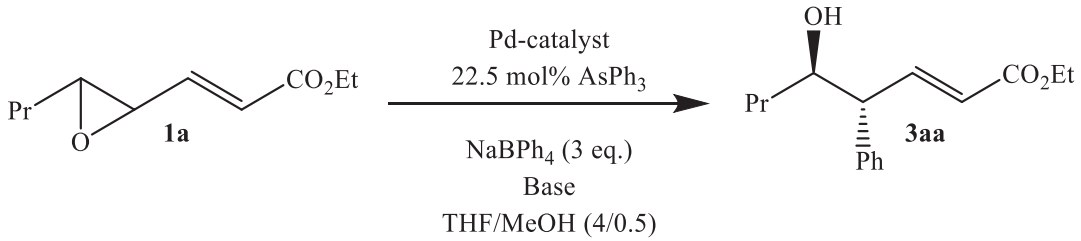
1a **3aa**

Entry	As/Pd	Time (h)	Yield (%)[a]
1	3	3.5	64
2	4	4	78
3	5	2.5	62

[a] Determined by ^{1}HNMR using benzaldehyde as internal standard.

In the next stage, the optimization studies were continued to determine the effect of type and amount of base additive. It seems the use of 2 equivalents of $(i\text{-}Pr)_2NH$ is sufficient (Table 4.4, entries 1-6) when using $Pd_2(DBA)_3CHCl_3$ (2.5). In the absence of base, the formation of the target product was observed to decrease significantly (Table 4.4., entry 7). In addition to this, when the reaction was started without catalyst, no conversion was observed (Table 4.4., entry 8). In the presence of $Pd(OAc)_2$, a number of inorganic and organic bases were surveyed. Either lower yields or no desired product formation could be obtained with the presence of other bases that used in this study. (Table 4.4., entries 9-16). $Pd(PPh_3)_2Cl_2$ showed no catalytic activity (Table 4.4., entry 17).

Table 4.4. Effects of Base on the Pd-catalyzed Reactions of Vinyl Epoxide **1a**.



Entry	Base (eq.)	Catalyst (mol%)	T (°C)	Time	Yield (%)[a]
1	$(i\text{-}Pr)_2NH$ (1)	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	3.5 h	72
2	$(i\text{-}Pr)_2NH$ (1.5)	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	3.5 h	75
3	$(i\text{-}Pr)_2NH$ (2)	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	3.5 h	76
4	$(i\text{-}Pr)_2NH$ (2)	$Pd(OAc)_2$ (5)	70[c]	1 h	82
5	$(i\text{-}Pr)_2NH$ (2.5)	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	3.5 h	60
6	$(i\text{-}Pr)_2NH$ (4)	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	3.5 h	58
7	-	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	48 h	48
8	$(i\text{-}Pr)_2NH$ (2)	-	RT	48 h	no conversion[b]
9	Cs_2CO_3 (2)	$Pd(OAc)_2$ (5)	70[c]	40 min.	13
10	Et_3N (2)	$Pd(OAc)_2$ (5)	70[c]	30 min.	55
11	NaOAc (2)	$Pd(OAc)_2$ (5)	70[c]	37 min.	65
12	AgOTf (2)	$Pd_2(DBA)_3CHCl_3$ (2.5)	50	3.5 h	66
13	Na_2HPO_4 (2)	$Pd(OAc)_2$ (5)	70[c]	35 min.	71
14	DBU (2)	$Pd(OAc)_2$ (5)	70[c]	2 h	complex mixture

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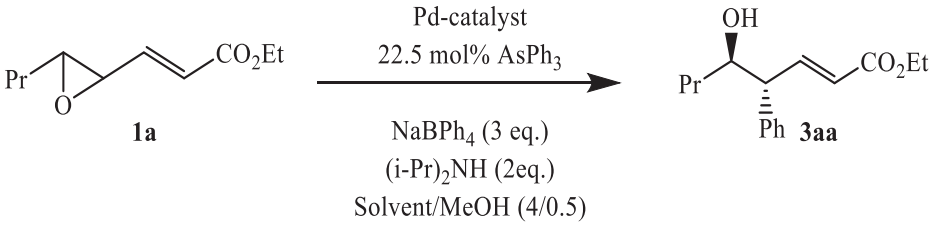
Table 4.4 (cont.)

15	LiOH (2)	$Pd(OAc)_2$ (5)	70 [c]	15 min.	complex mixture
16	CsF[b] (1.75)	$Pd(OAc)_2$ (5)	70 [c]	4 min.	complex mixture
17	$(i\text{-}Pr)_2NH$ (2)	$Pd(PPh_3)_2Cl_2$	70 [c]	1 h	complex mixture

[a]Determined by ^{1}H-NMR using benzaldehyde as the internal standard. [b]PhBneop was used as arylboron derivative. Additive was H_2O (1 mL). [c]The reaction was performed in closed Schlenk system.

We also surveyed catalyst, solvent, and temperature effects over the method. When the reaction was conducted in the presence of 2.5 mol% $Pd_2(DBA)_3CHCl_3$ at 50 °C, THF appears to be a better solvent than DME, tert-BuOMe, DMF, and toluene solvents (Table 4.5, entries 1-5). In the presence $Pd(OAc)_2$ 1,4-dioxane can substitute THF and the highest yield could be obtained with this solvent when the reaction temperature was elevated to 110 ℃ (Table 4.5, entries 6-10).

Table 4.5. Effect of Catalyst, Solvent, and Reaction Temperature on the Pd-catalyzed Reactions of Vinyl Oxirane **1a**.



Entry	Catalyst (mol%)	Solvent	T (°C)	Time	Yield (%)[a]
1	$Pd_2(DBA)_3CHCl_3$ (2.5)	THF	50	3.5 h	76
2	$Pd_2(DBA)_3CHCl_3$ (2.5)	DME	50	O.N.	58
3	$Pd_2(DBA)_3CHCl_3$ (2.5)	^{t}BuOMe	50	O.N.	38
4	$Pd_2(DBA)_3CHCl_3$ (2.5)	DMF	50	O.N.	complex mixture

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Table 4.5 (cont.)

5	$Pd_2(DBA)_3CHCl_3$ (2.5)	Toluene	50	O.N.	complex mixture
6	$Pd(OAc)_2$ (5)	THF	50	4 h	78
7	$Pd(OAc)_2$ (5)	THF	70	1 h	82
8	$Pd(OAc)_2$ (5)	1,4-dioxane	70	40 min.	85
9	$Pd(OAc)_2$ (5)	1,4-dioxane	100	5 min.	82
10	$Pd(OAc)_2$ (5)	1,4-dioxane	110	2 min.	90 (87)[b]
11	$Pd(OAc)_2$ (5)	1,4-dioxane	110	5 min.	55[c]

[a]Determined by ^{1}H-NMR using benzaldehyde as the internal standard. [b]Isolated yield. [c]PhBneop was used as aryl source.

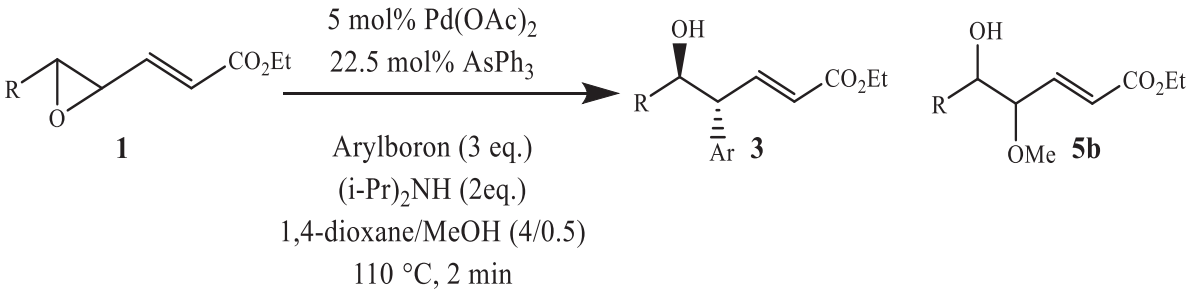
After the optimal conditions were determined, After the optimum conditions were determined, the applicability of the method to the various ester group alkenyl oxiranes (**1**) and $NaBAr_4$ derivatives (**2**) was investigated. As is the case with the substrate **1a**, the reaction of epoxide **1b** having a methyl group at the oxirane terminus with $NaBPh_4$ (**2a**) also afforded the homoallyl alcohol product **3ba** with a high yield. (Table 4.5, entries 1 and 2). Compared to literature, this product shows anti-form. According to this diastereomeric structure, it was clear that the substitution reactions proceed by inversion of configuration. Reaction of *p*-methyl substituted $NaB(p\text{-}CH_3C_6H_4)_4$ (**2b**) with alkenyl oxirane **1b** gave the homoallylic **3bb** product with 79% yield. (Table 4.5, entry 3). The method apparently is not suitable for the substrate having a phenyl group at the oxirane terminus (Table 4.5 entry 4).

CH_2OPh group substituted alkenyl oxirane (**1d**), which have Z-configuration gave the homoallyl product **3da** with low yield (Table 4.5, entry 5). With this reagent, it will be investigated whether the decrease in reaction efficiency is caused by the oxygen group or the difference in the configuration of the epoxy ring. Cy group substituted aklenyl oxirane **1e** gave the product **3ea** with average yield (Table 4.5, entry 6). This result shows that the method is affected by the steric dimension of the R group.

When the ester group contained a volatile t-butyl group (**1f**), the method could be successfully applied and thus yielded a phenylated homoallylic product (**3fa**) with high yield (Table 4.5, entry 7).

Reaction of *m*-methoxy substituted NaB(*m*-$OCH_3C_6H_4)_4$ (**2c**) with alkenyl oxirane **1b** gave the homoallylic **3bc** product with 81% yiled (Table 4.5, entry 8). However, with electron-poor aryl group substituted NaB(4-$CF_3C_6H_4)_4$ **2d** the desired homoallyl product **3bd** was obtained with 57% yield and beside this the methoxylated homoallyl product **5b** was also formed with 26% yield. (Table 4.5, entry 9).

Table 4.6. Effects of Substituted Groups on The Formation of Target Products Homoallyl Alcohols.



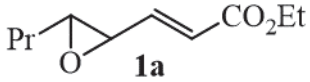
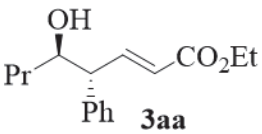
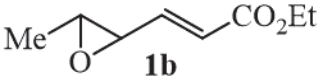
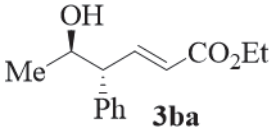
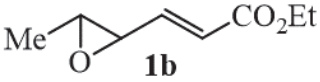
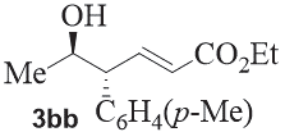
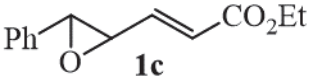
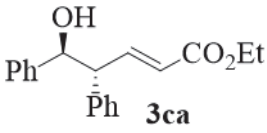
Entry	Reactant	$NaBAr_4$	Product	Yield (%)[a]
1	 **1a**	2a	 **3aa**	90(87)[b]
2	 **1b**	2a	 **3ba**	90[b]
3	 **1b**	2b	 **3bb** C_6H_4(*p*-Me)	79[b]
4	 **1c**	2a	 **3ca**	N.D.

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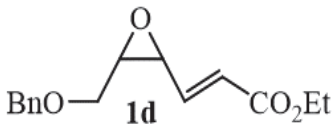
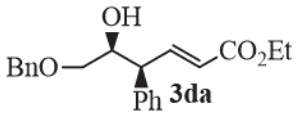
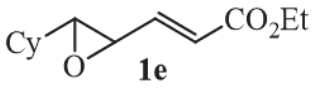
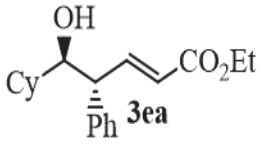
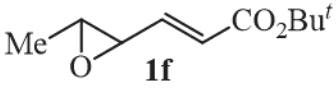
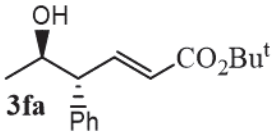
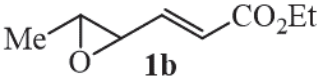
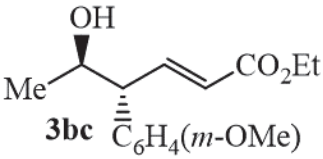
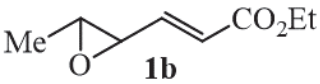
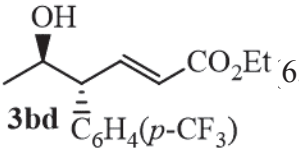
Table 4.6 (cont.)

5		2a		43[b]
6		2a		68(67)[b]
7		2a		82[b]
8		2c		;(81)[b]
9		2d		65)57[b]

[a]Determined by [1]HNMR using benzaldehyde as an internal standard. [b]Isolated yield

4.1. Chirality Transfer

Enantio-enriched alkenyl oxirane **1b** was synthesized according to Shi-method (94,6% ee). In the optimized reaction condition, the reaction of **1b** with $NaBPh_4$ gave the corresponding homoallylic alcohol product **3ba** with high yield and almost complete chirality transfer (90.1% ee). This proved that the method appropriate for the synthesis of enantio-pure homoallyl alcohols. (Yield: 89%).

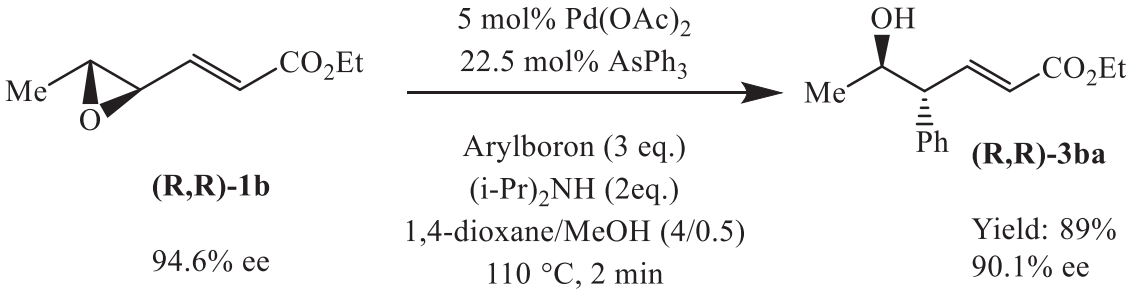


Figure 4.1. Chirality Transfer

4.2 Reaction Mechanism

A plausible reaction mechanism is proposed. The reaction starts with the opening of the oxirane ring by approaching the palladium from the *anti*-position to the structure (**1**). It is generally known that palladium participates to allylic compounds from the *anti*-position. The resulting π-allylpalladium intermediate (**I**) undergoes transmetallation (**II**) in the next step, and eventually with the reductive elimination the desired homoallylic alcohol product (**3**) is formed in S_N2-manner.

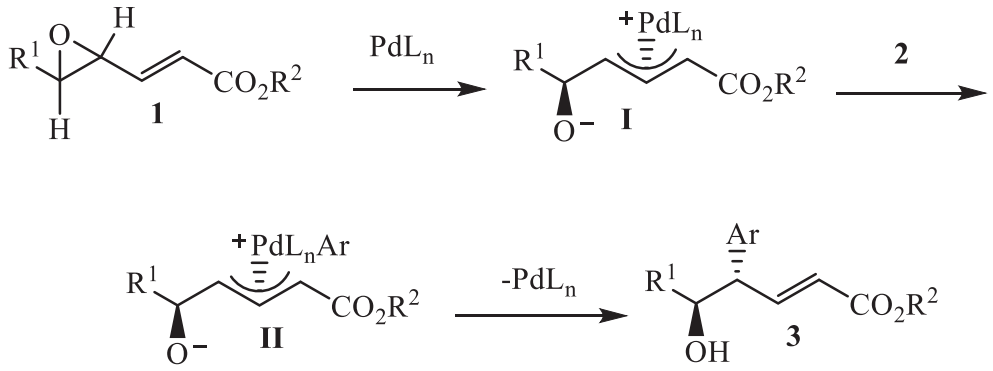


Figure 4.2. A Plausible Reaction Mechanisim.

CHAPTER 5

CONCLUSION

In this study, we developed a novel method for the synthesize of γ-Aryl-δ-hydroxy-α,β-unsaturated esters with high regio- and stereo- selectivities in S_N2-addition manner. In the optimization studies, a number of factor were investigated such as palladium compounds, organoboron derivatives, ligand, solvent, base, and temperature. It was proved that the most suitable aryl source is $NaBAr_4$ compounds are among the tested organoborons, $Pd(OAc)_2$ as palladium compound, $AsPh_3$ as ligand, $(i\text{-}Pr)_2NH$ as base, 1,4-dioxane/MeOH mixture, and the most appropriate reaction temperature is 110 °C. At this temperature, to preserve the volatile base and methanol in the liquid phase the closed Schlenk system must be required. The use of phosphine ligands generally caused to nucleophilic substitution of the allylic position with structures such as water and methanol. γ-Aryl-δ-hydroxy-α,β-unsaturated ester derivatives (**3**) were afforded with high regio- and stereoselectivities.

The reactions mainly gave the desired product in *anti*-mode. A reaction with an enantio-pure alkenyl oxirane (**1b**) enabled to formation of desired enantio-pure product [(4R,5R)]-(**3bb**).

There are only a few reactions in the literature which were achieved in S_N2-addition pathway. This work has enabled to synthesize of biologically active homoallyl alcohols from γ,δ-epoxy-α,β-unsaturated esters with organoborons in the presence of Pd-catalysts and $AsPh_3$ ligand via the formation of π-allylpalladium complex.

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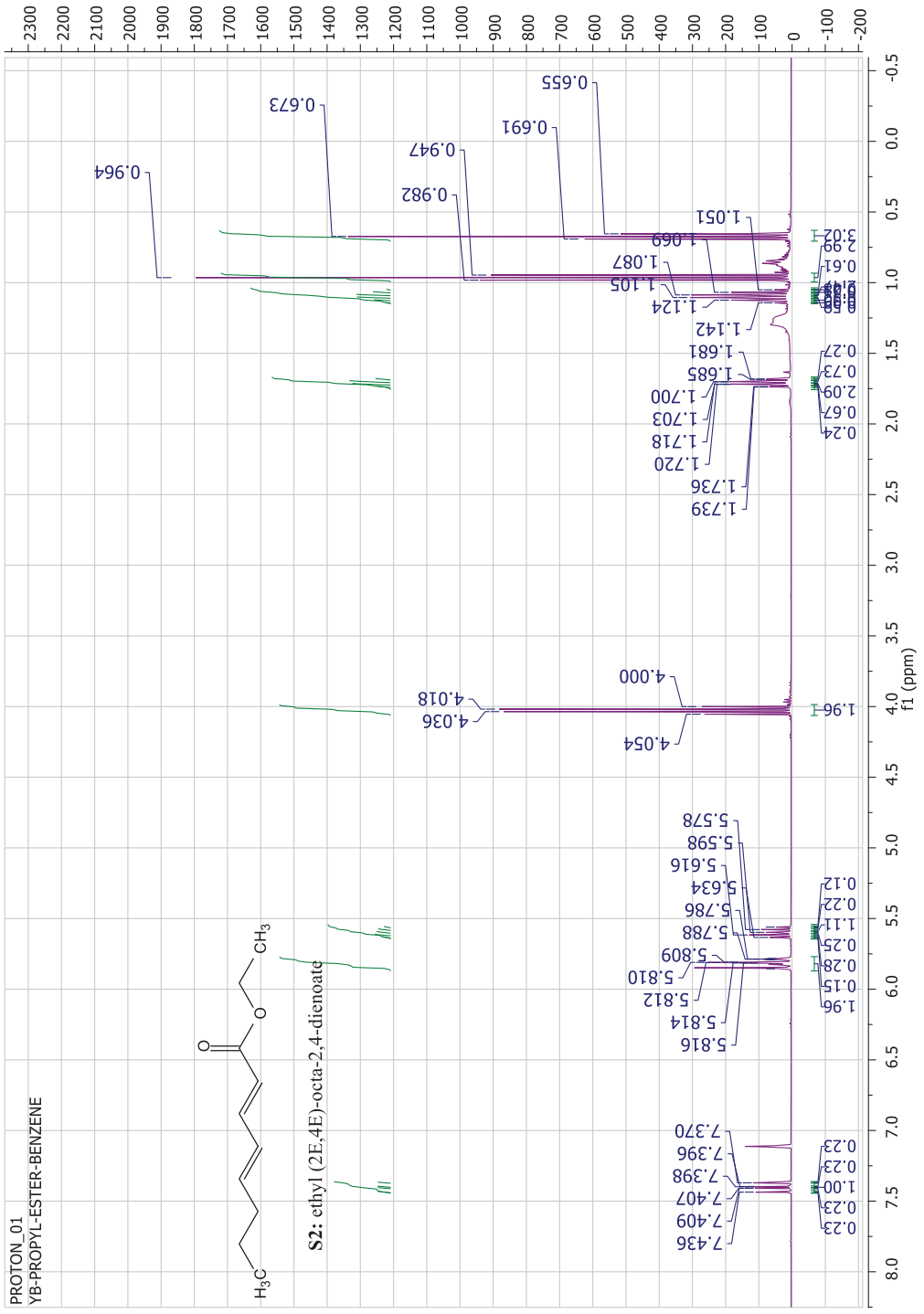
APPENDIX A

^{1}H NMR AND ^{13}C NMR SPECTRUMS OF REACTANTS AND ^{1}H NMR, ^{13}C NMR AND ^{11}B NMR OF ORGANOBORONS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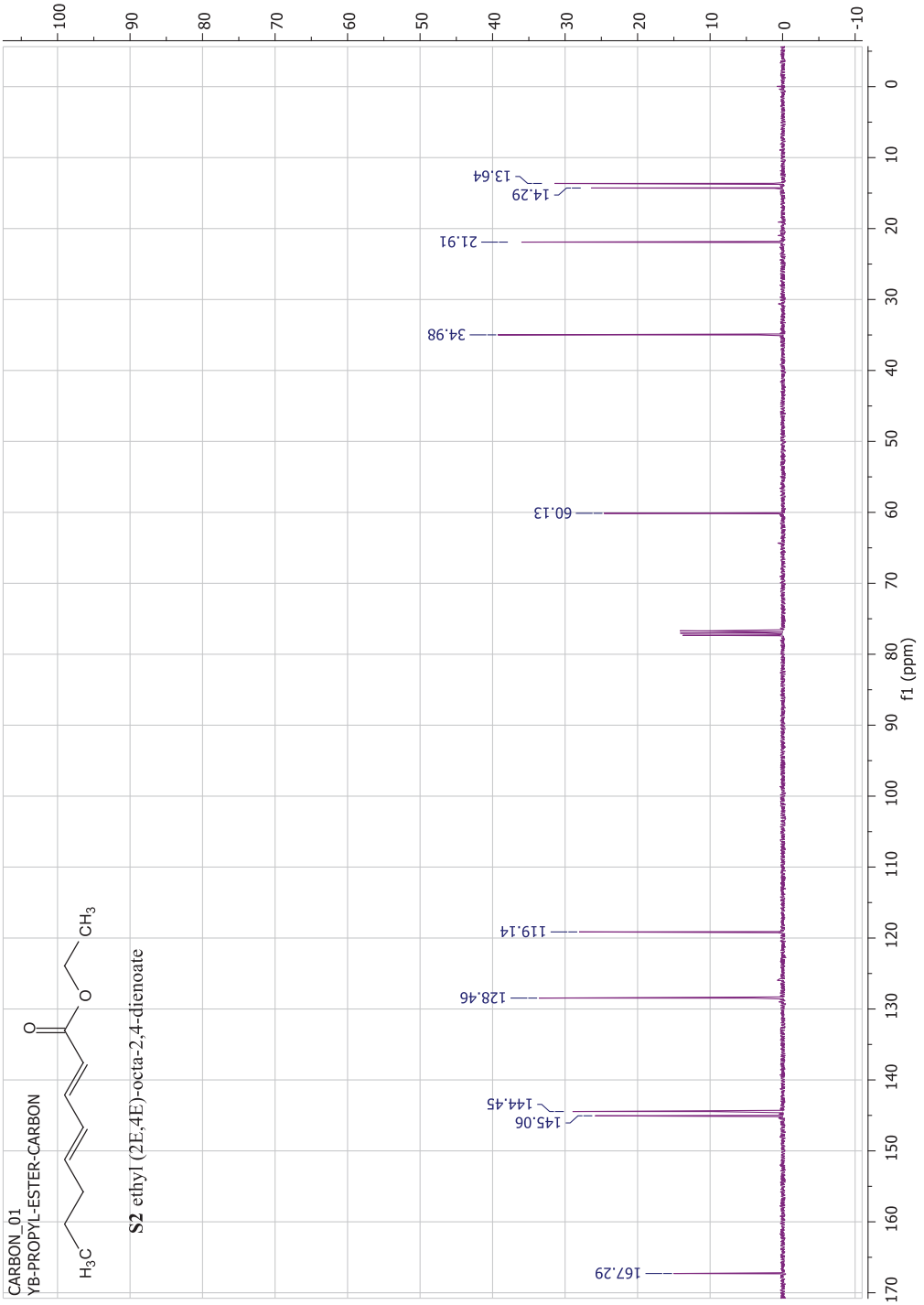
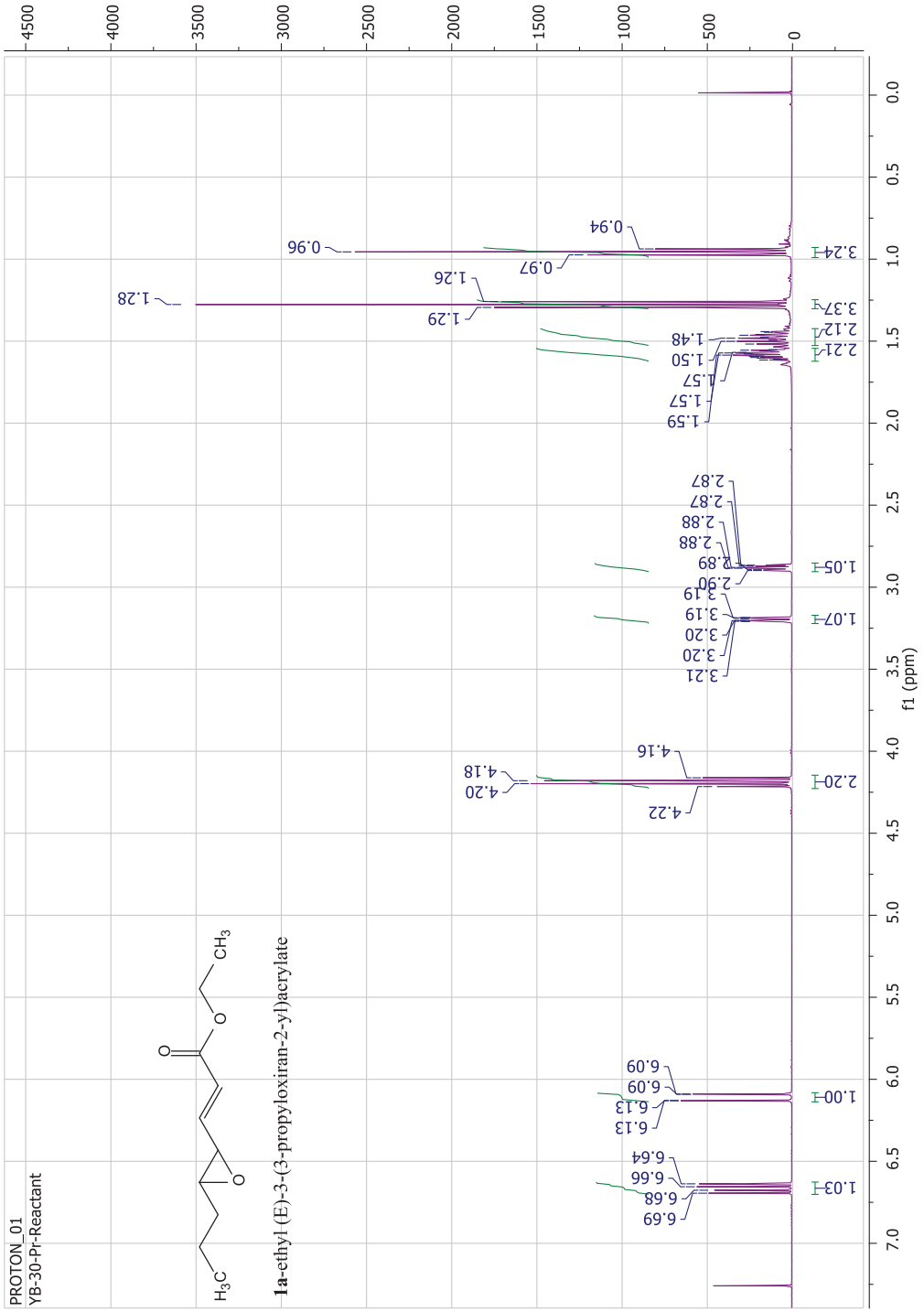
YB-PROPYL-ESTER-BENZENE
S2: ethyl (2E,4E)-octa-2,4-dienoate
f1 (ppm)


CARBON_01
YB-PROPYL-ESTER-CARBON
O
O
CH3
H3C
S2 ethyl (2E,4E)-octa-2,4-dienoate
167.29
145.06
144.45
128.46
119.14
60.13
34.98
21.91
14.29
13.64
f1 (ppm)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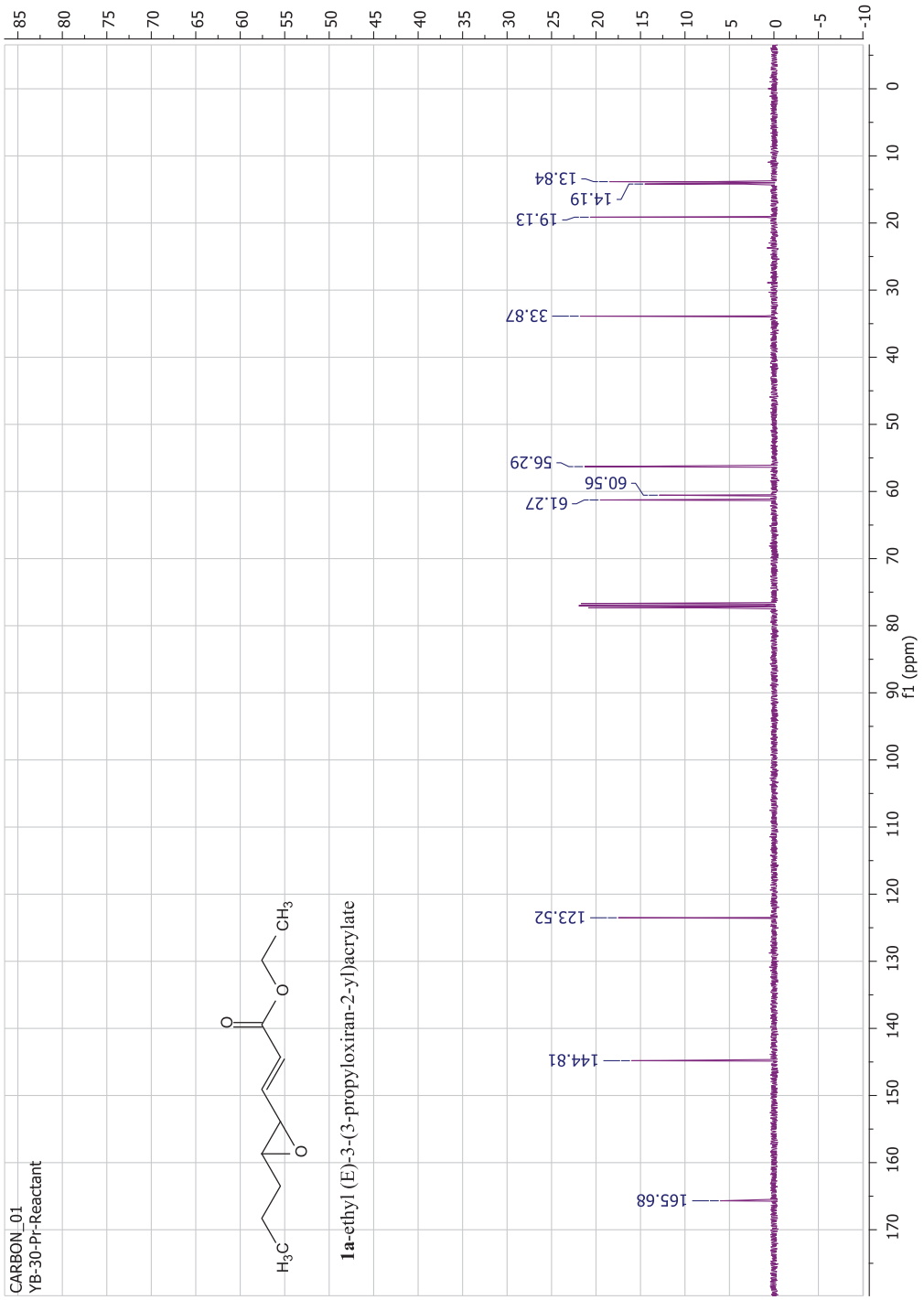
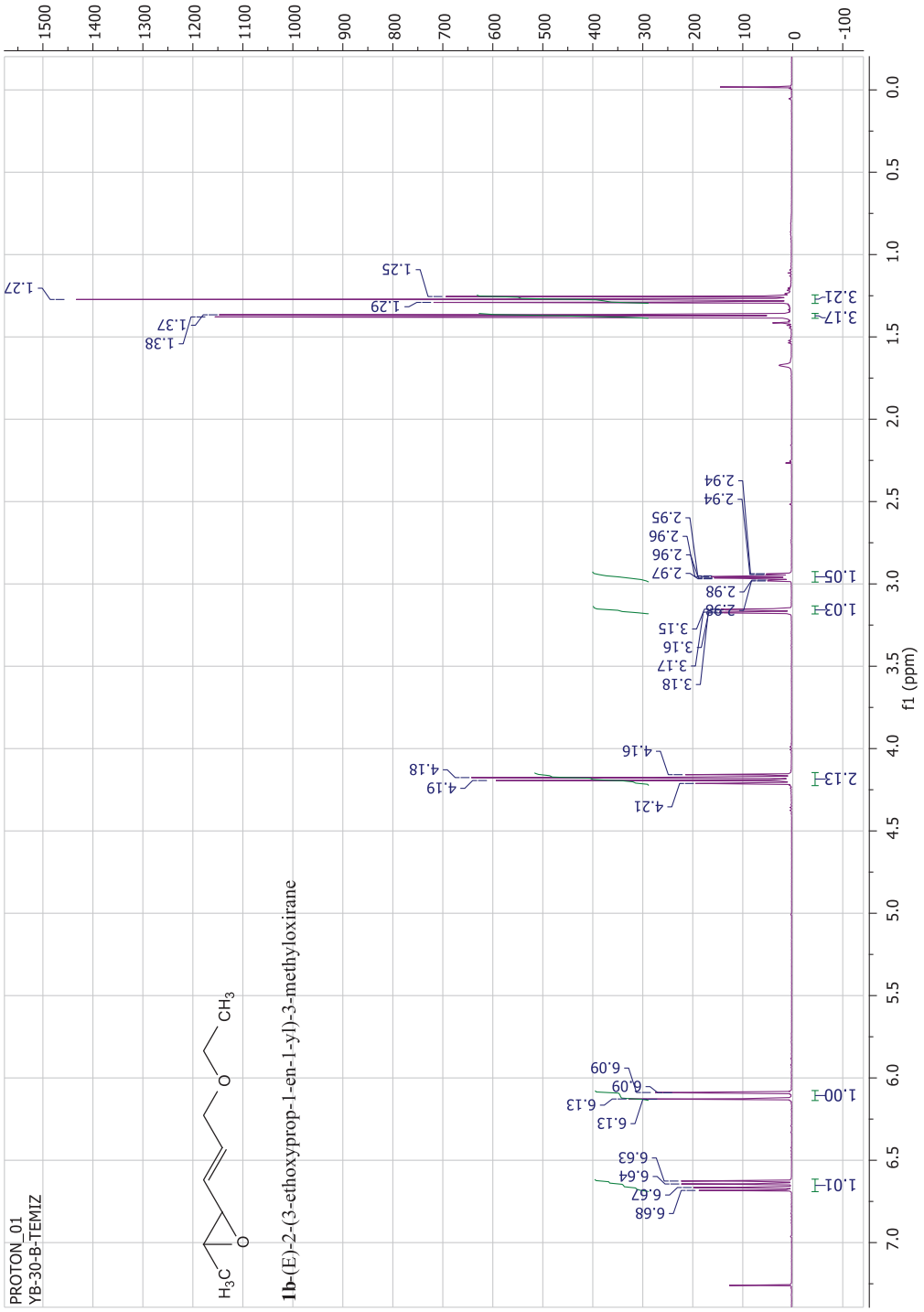
YB-30-Pr-Reactant
1a-ethyl (E)-3-(3-propyloxiran-2-yl)acrylate
f1 (ppm)


CARBON_01
YB-30-Pr-Reactant
1a-ethyl (E)-3-(3-propyloxiran-2-yl)acrylate
H3C
CH3
O
O
O
165.68
144.81
123.52
61.27
60.56
56.29
33.87
19.13
14.19
13.84
f1 (ppm)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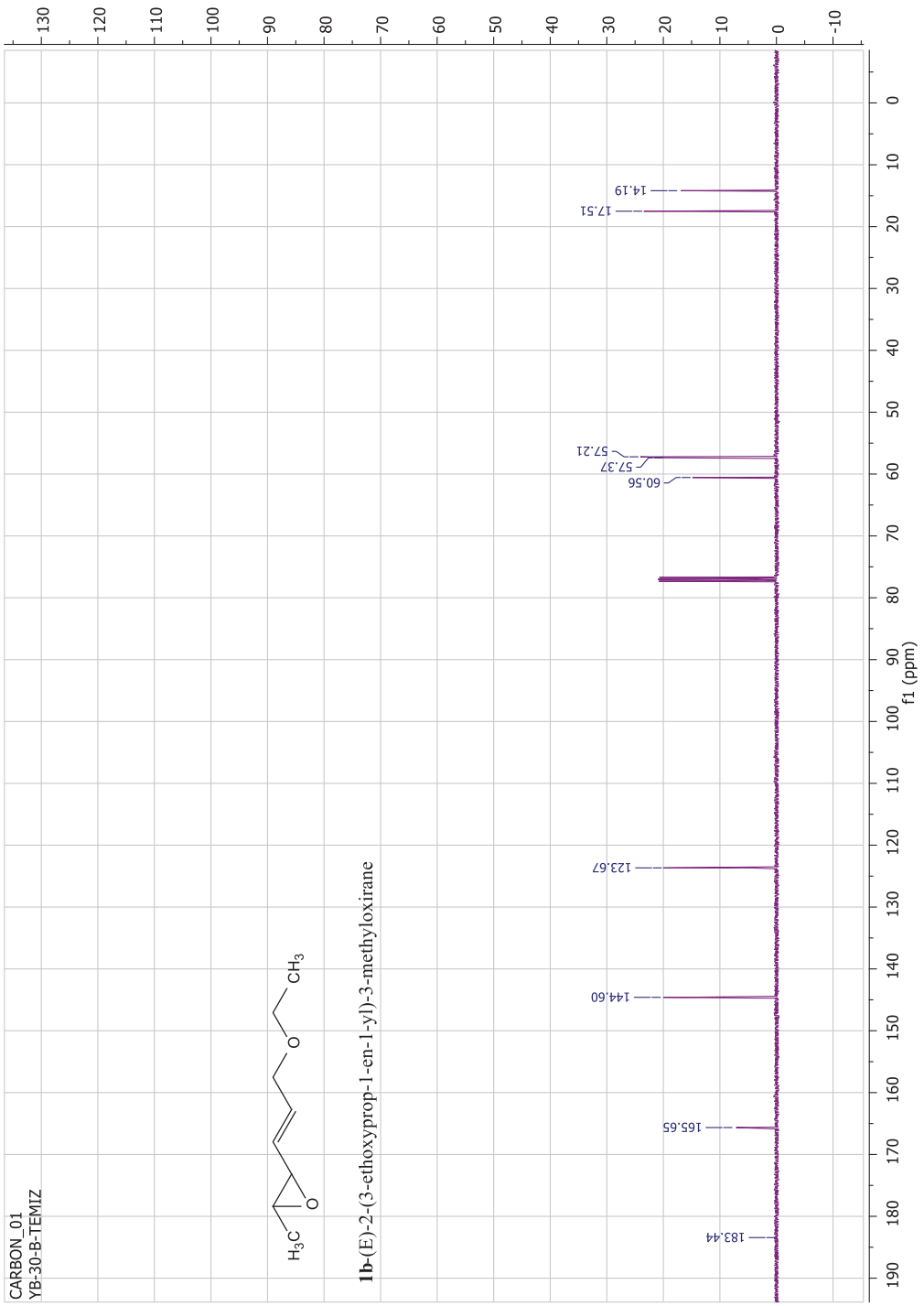
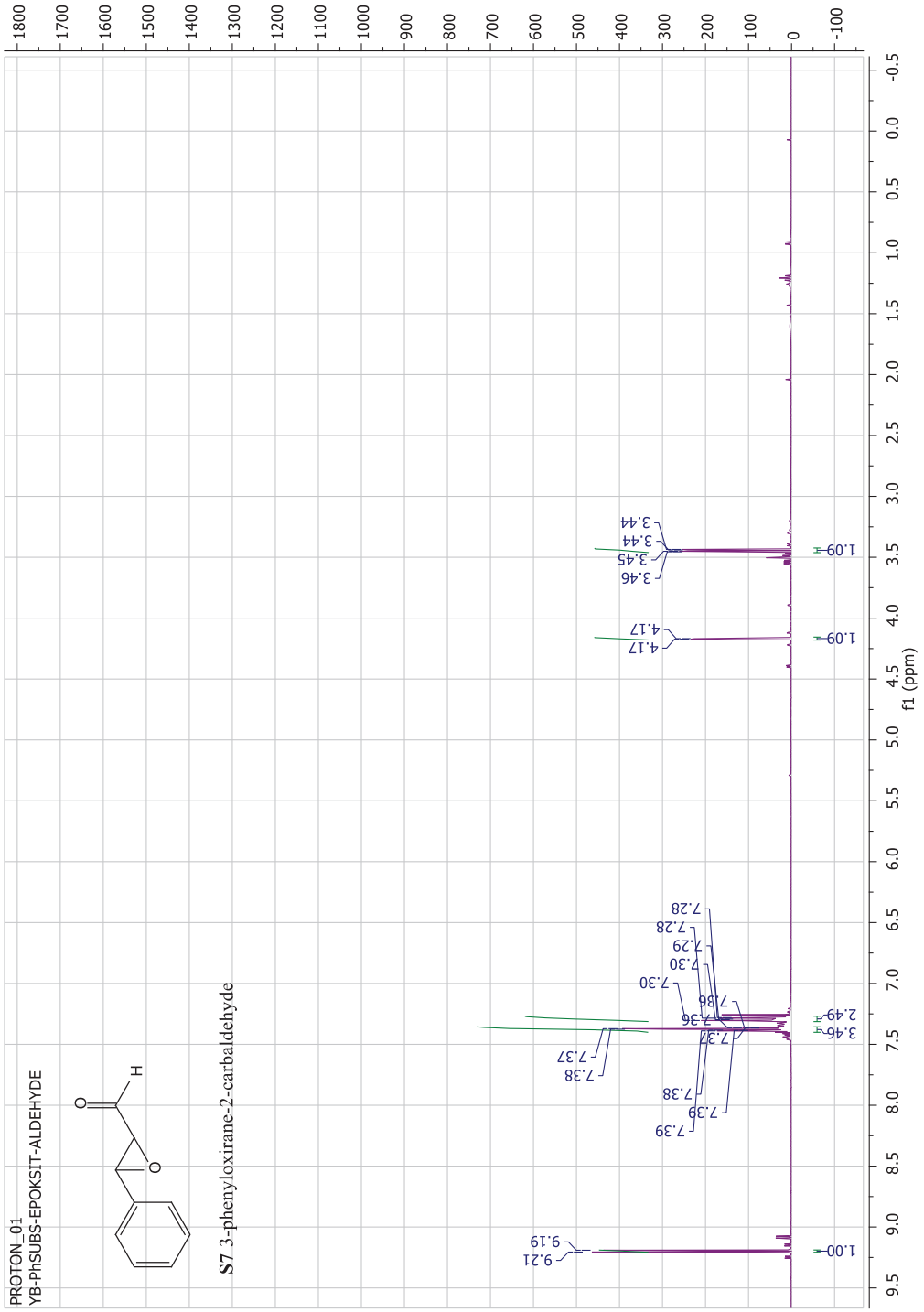
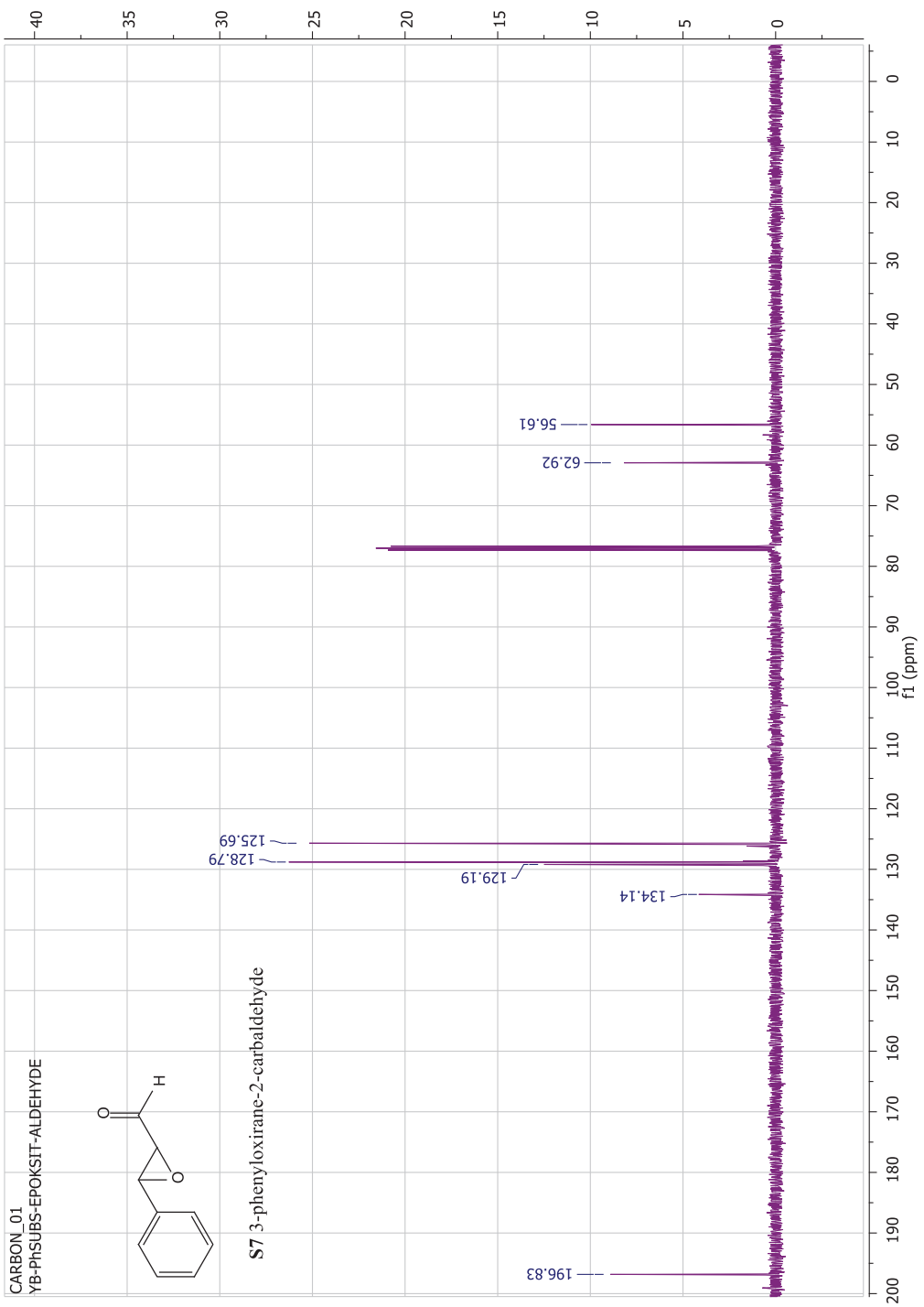
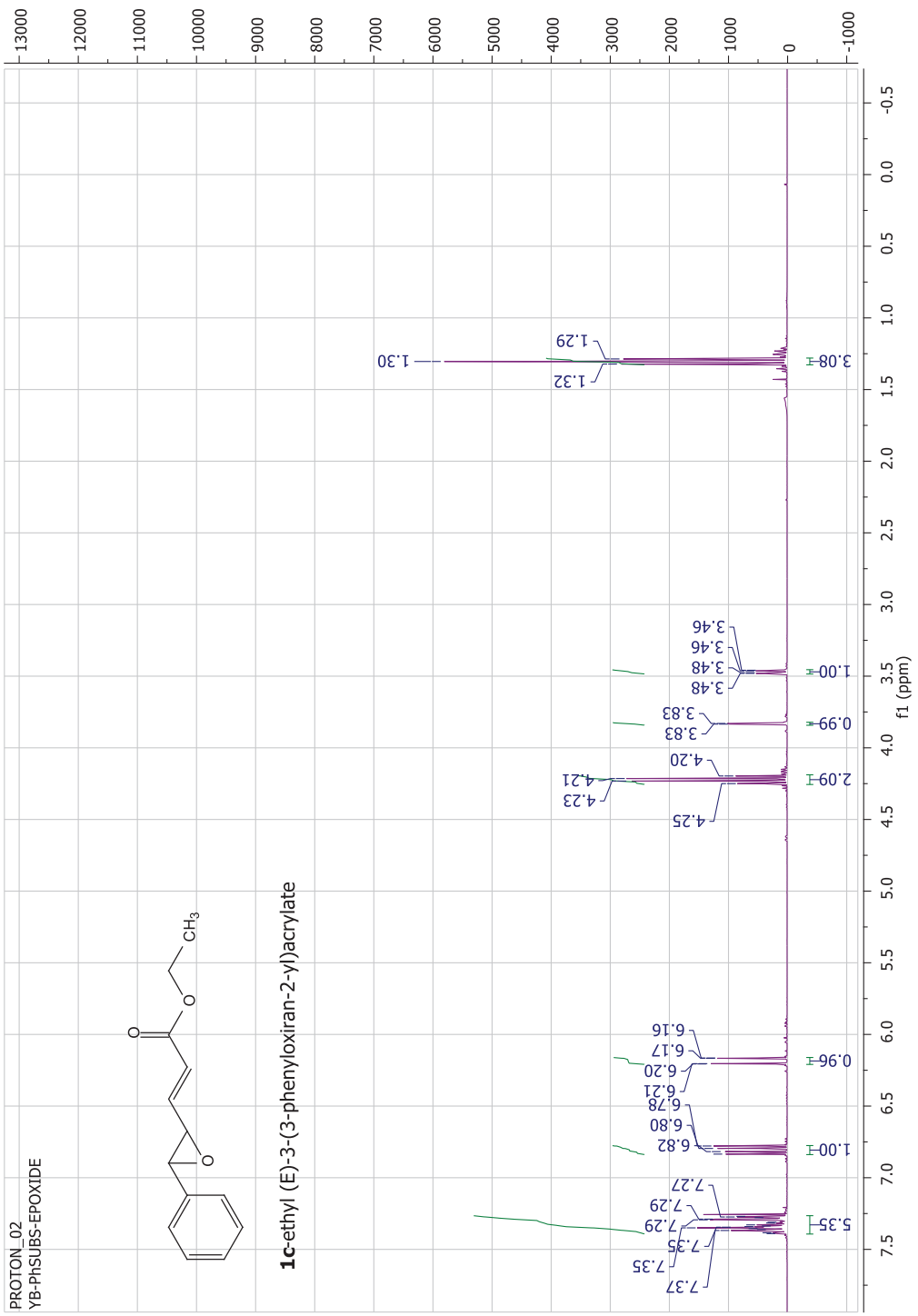
YB-30-B-TEMIZ
1b-(E)-2-(3-ethoxyprop-1-en-1-yl)-3-methyloxirane
f1 (ppm)

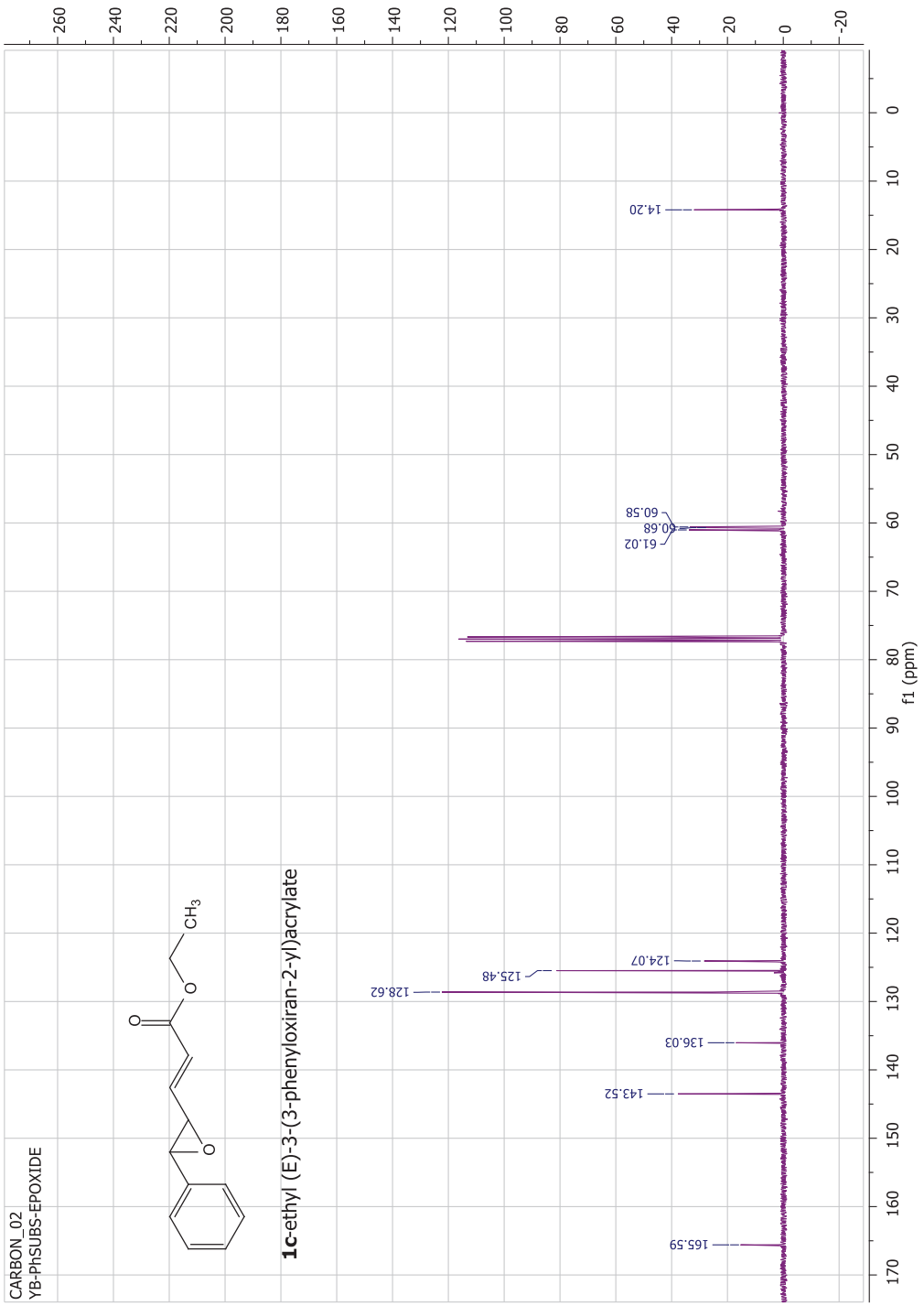

CARBON_01
YB-30-B-TEMIZ
1b-(E)-2-(3-ethoxyprop-1-en-1-yl)-3-methyloxirane
f1 (ppm)
183.44
165.65
144.60
123.67
60.56
57.37
57.21
17.51
14.19

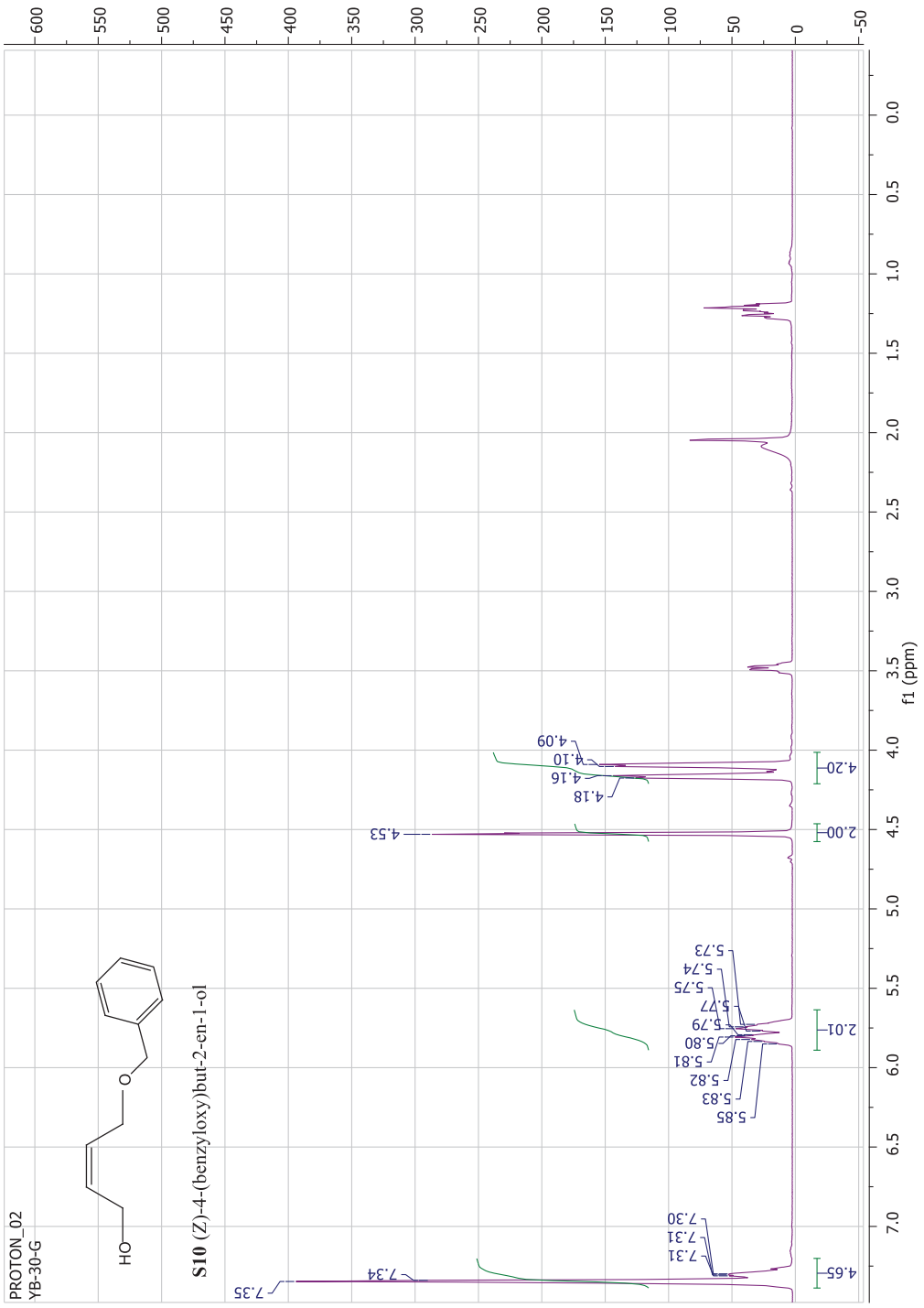


S7 3-phenyloxirane-2-carbaldehyde


CARBON_01
YB-PhSUBS-EPOKSIT-ALDEHYDE
S7 3-phenyloxirane-2-carbaldehyde
196.83
134.14
129.19
128.79
125.69
62.92
56.61
f1 (ppm)


PROTON_02
YB-PhSUBS-EPOXIDE
1c-ethyl (E)-3-(3-phenyloxiran-2-yl)acrylate
CH3
O
O
O
f1 (ppm)
7.37
7.35
7.35
7.29
7.27
6.82
6.80
6.78
6.21
6.20
6.17
6.16
4.25
4.23
4.21
4.20
3.83
3.83
3.48
3.48
3.46
3.46
1.32
1.30
1.29
5.35
1.00
0.96
1.00
2.09
0.99
1.00
3.08


CARBON_02
YB-PhSUBS-EPOXIDE
1c-ethyl (E)-3-(3-phenyloxiran-2-yl)acrylate
CH3
O
O
O
14.20
60.58
60.68
61.02
124.07
125.48
128.62
136.03
143.52
165.59
f1 (ppm)


PROTON_02
YB-30-G
HO
O
S10 (Z)-4-(benzyloxy)but-2-en-1-ol
7.35
7.34
7.31
7.31
7.30
5.85
5.83
5.82
5.81
5.80
5.79
5.77
5.75
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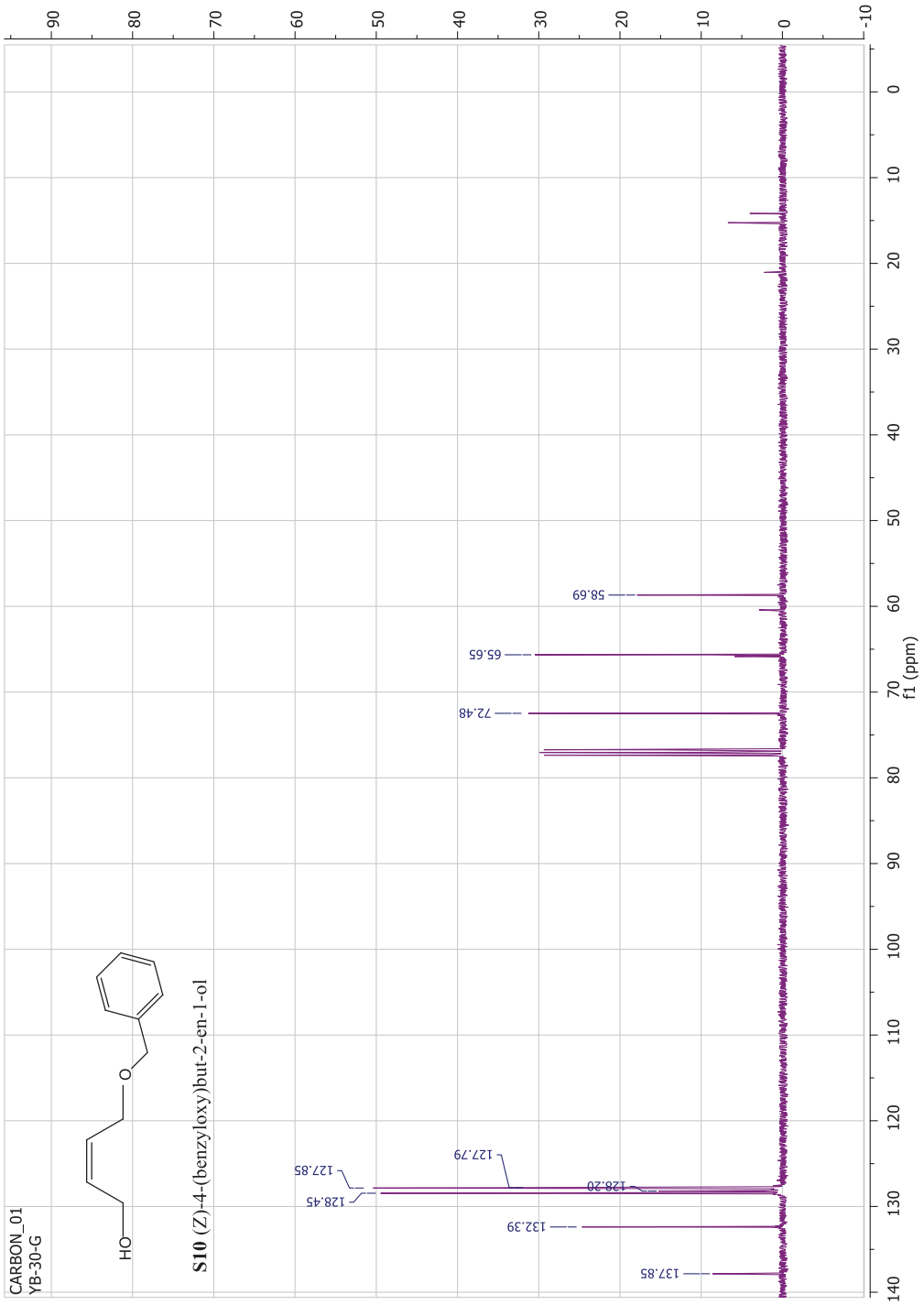
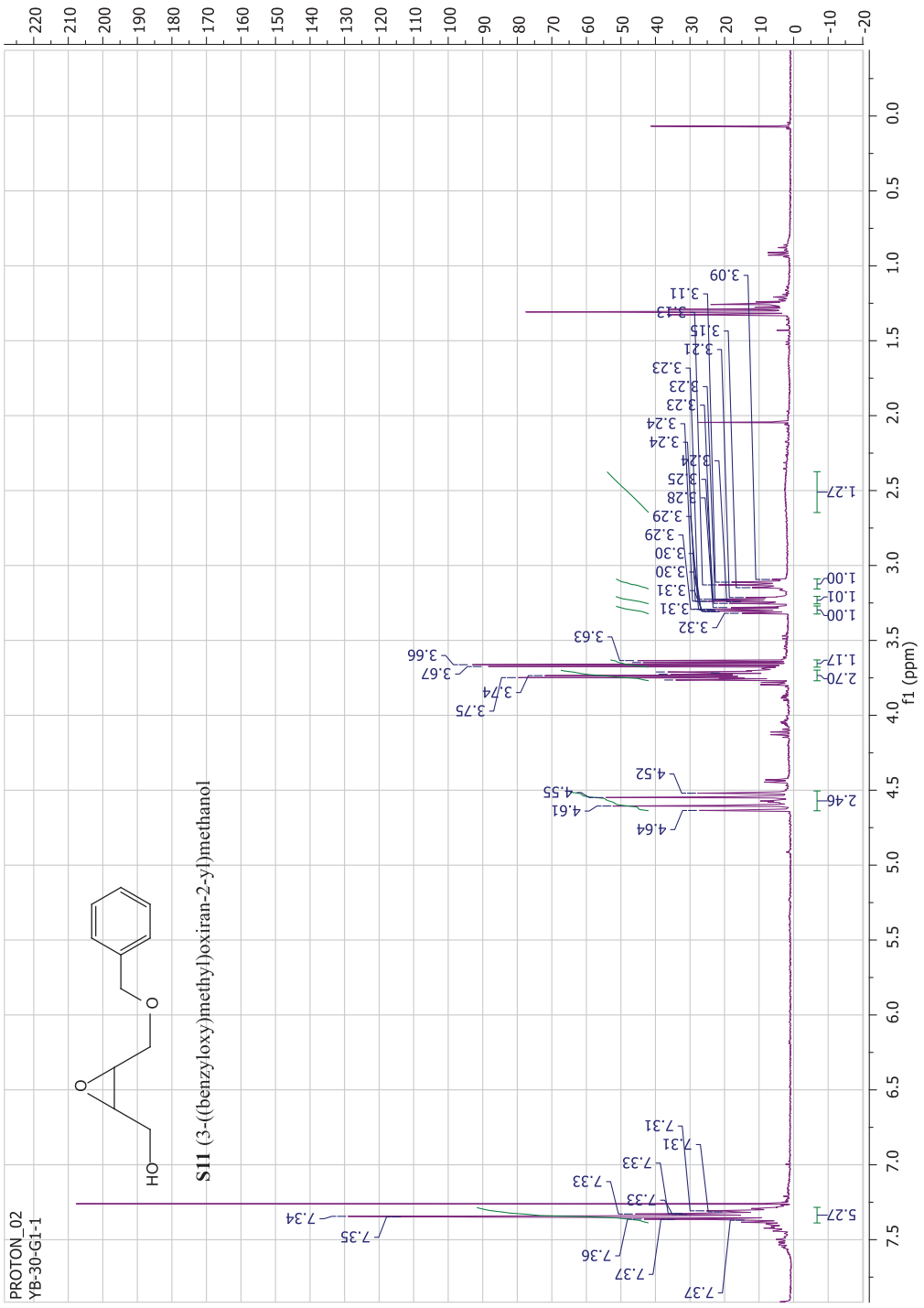
4.65
2.01
2.00
4.20
f1 (ppm)


CARBON_01
YB-30-G
HO
O
S10 (Z)-4-(benzyloxy)but-2-en-1-ol
137.85
132.39
128.20
127.79
128.45
127.85
72.48
65.65
58.69
f1 (ppm)


PROTON_02
YB-30-G1-1
S11 (3-((benzyloxy)methyl)oxiran-2-yl)methanol
HO
O
O
f1 (ppm)
7.37
7.36
7.35
7.34
7.33
7.33
7.33
7.31
7.31
4.64
4.61
4.55
4.52
3.75
3.74
3.67
3.66
3.63
3.32
3.31
3.31
3.30
3.30
3.29
3.29
3.28
3.25
3.24
3.24
3.24
3.23
3.23
3.23
3.21
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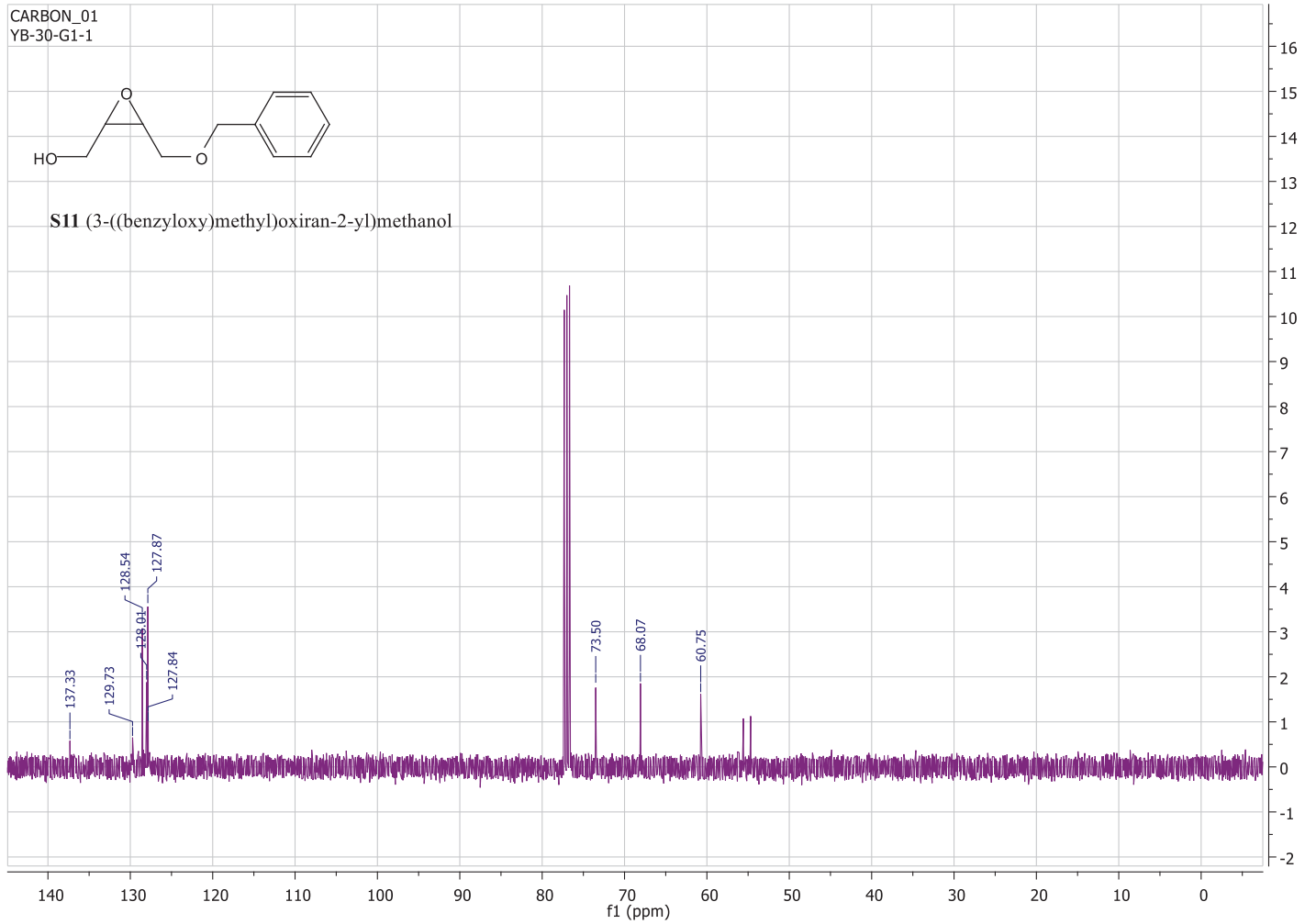
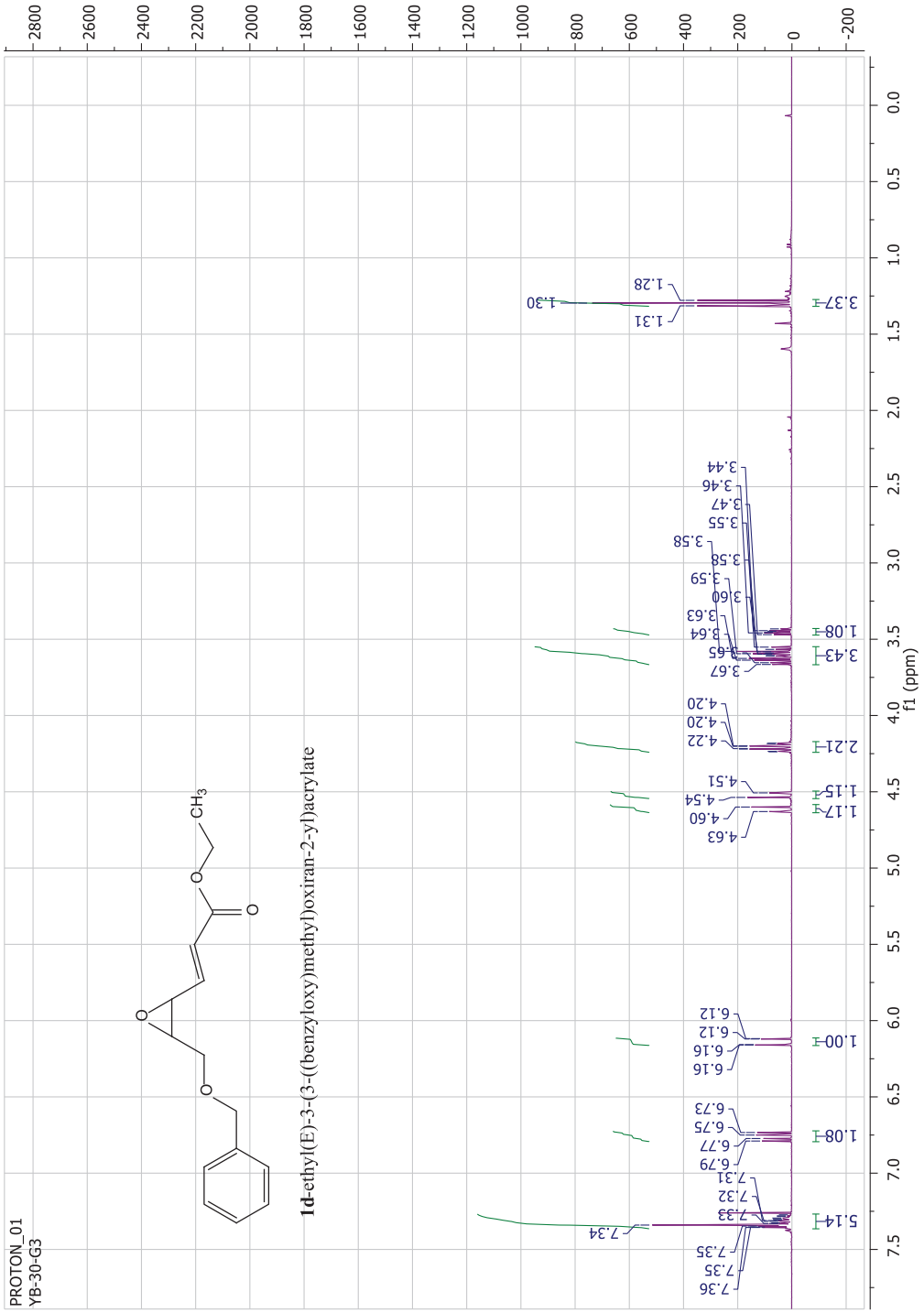
1.27
1.00
1.01
1.00
2.70
1.17


CARBON_01
YB-30-G1-1
HO
O
O
S11 (3-((benzyloxy)methyl)oxiran-2-yl)methanol
137.33
129.73
128.54
128.01
127.87
127.84
73.50
68.07
60.75
f1 (ppm)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YB-30-G3
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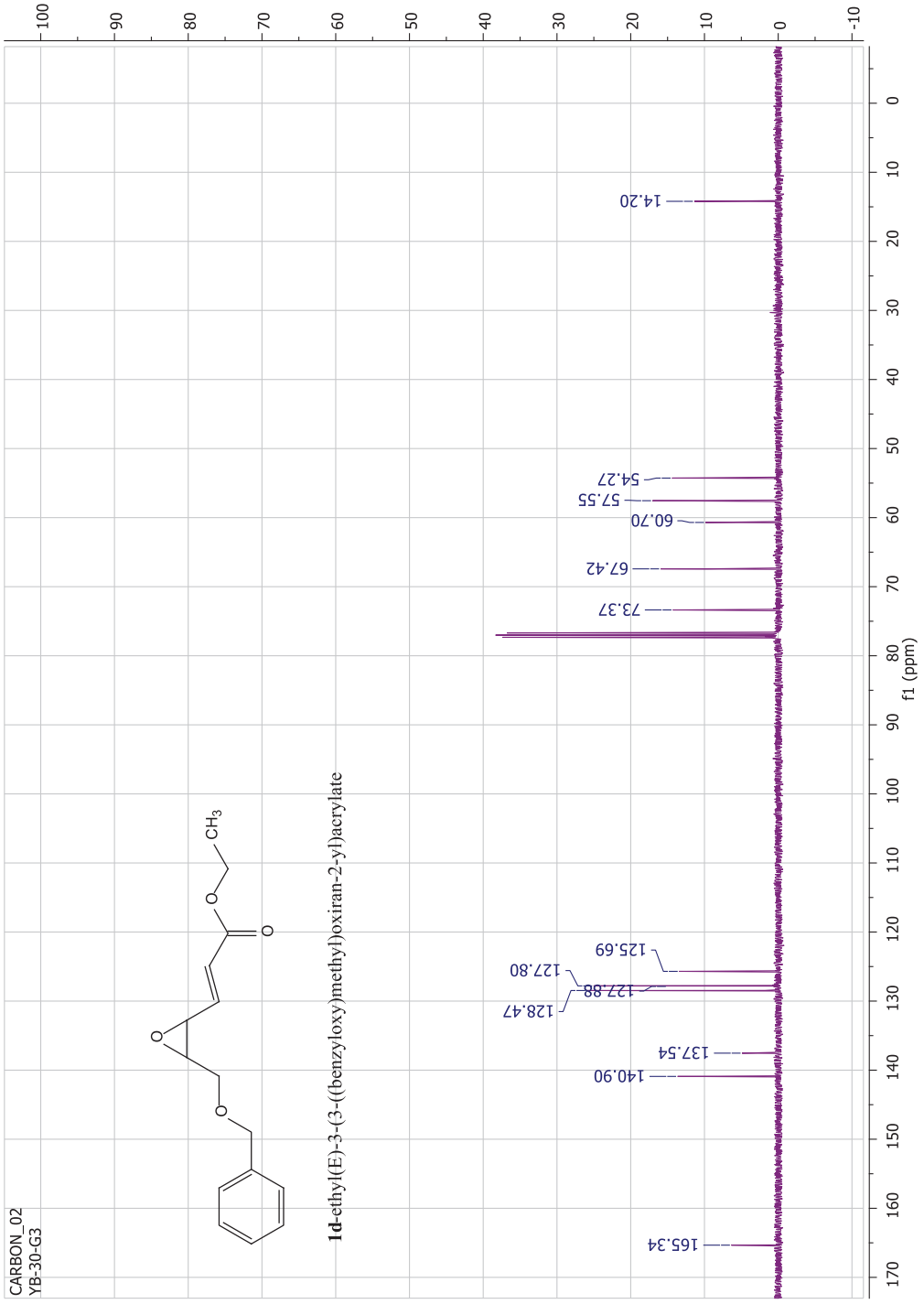
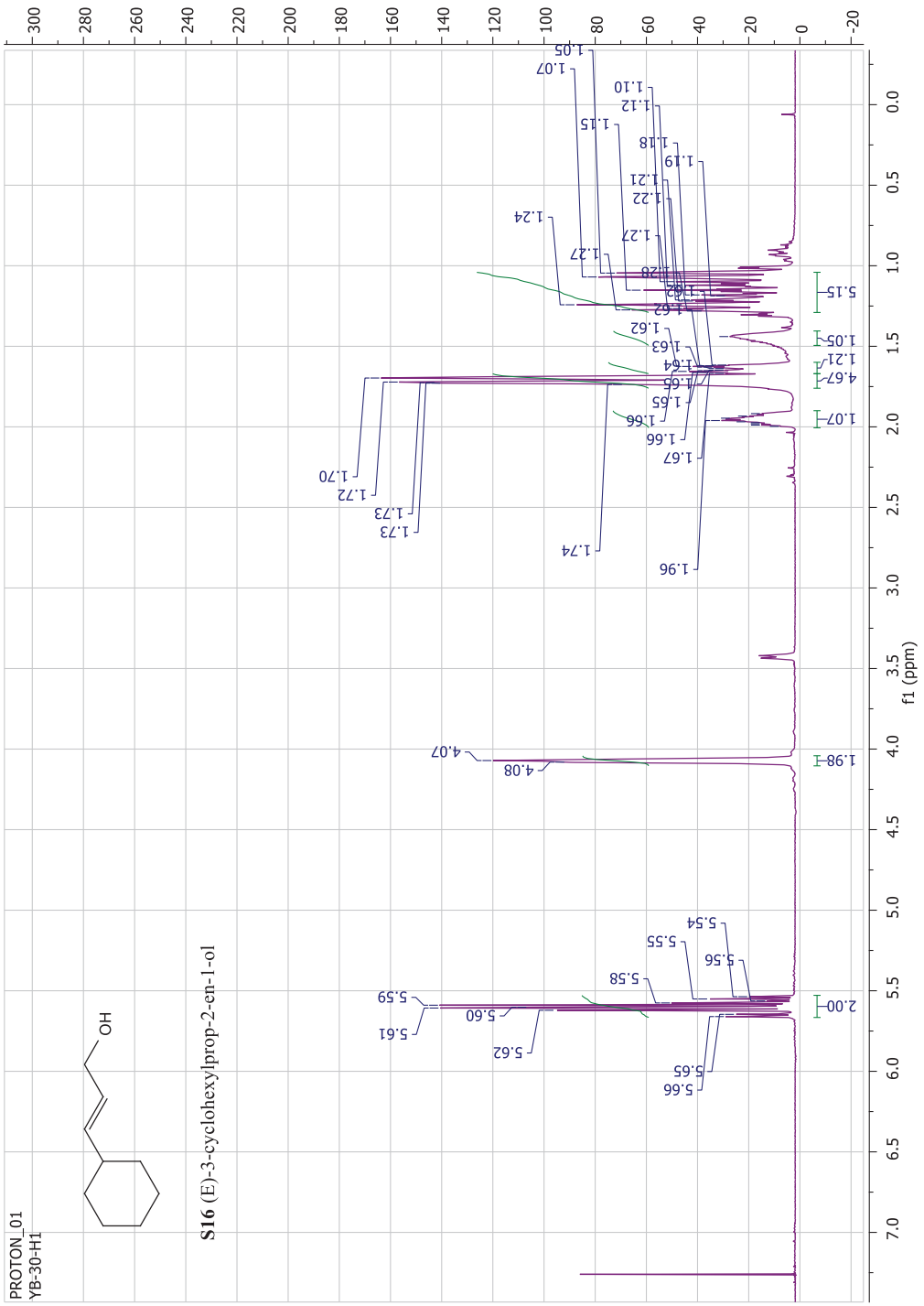
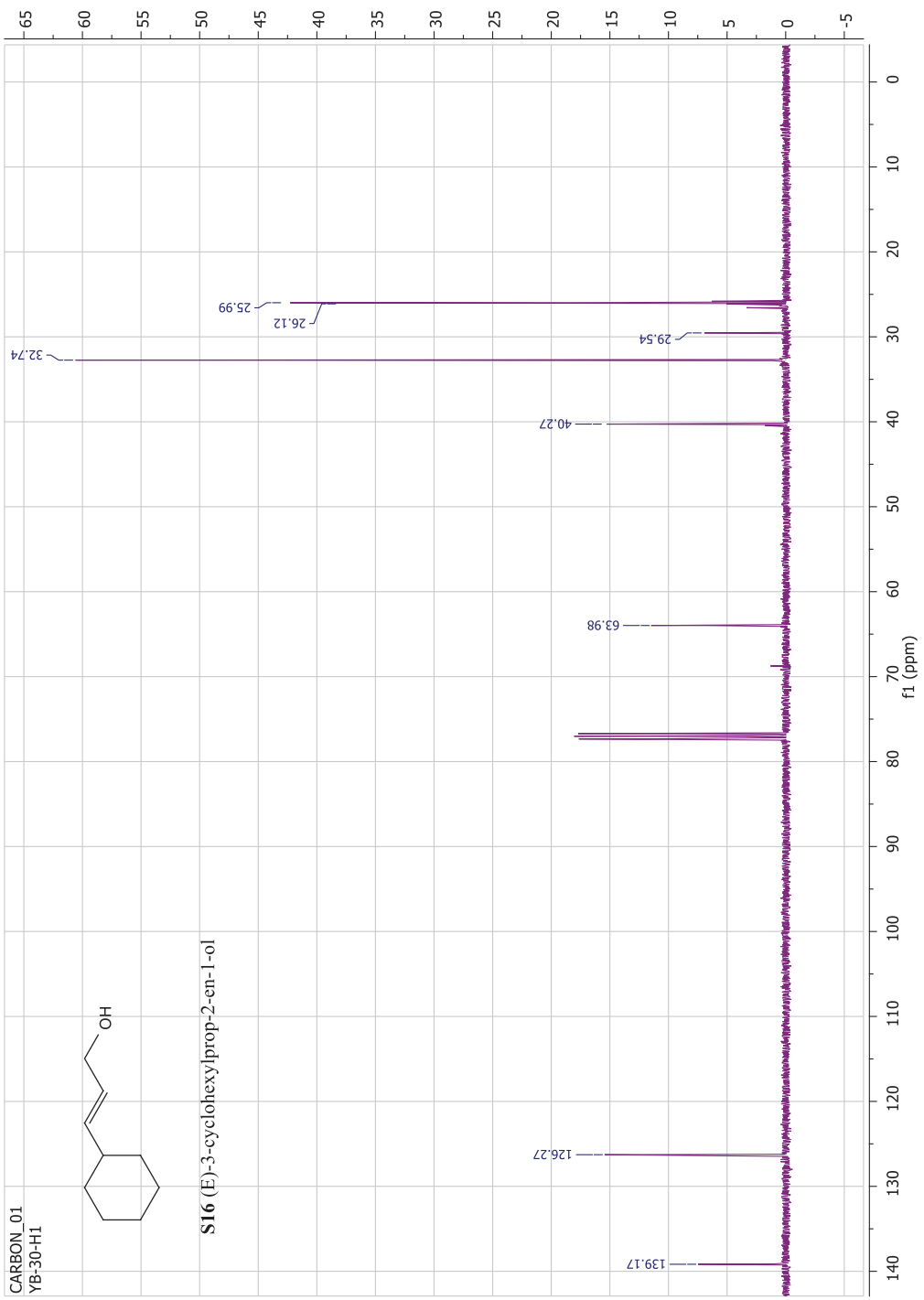
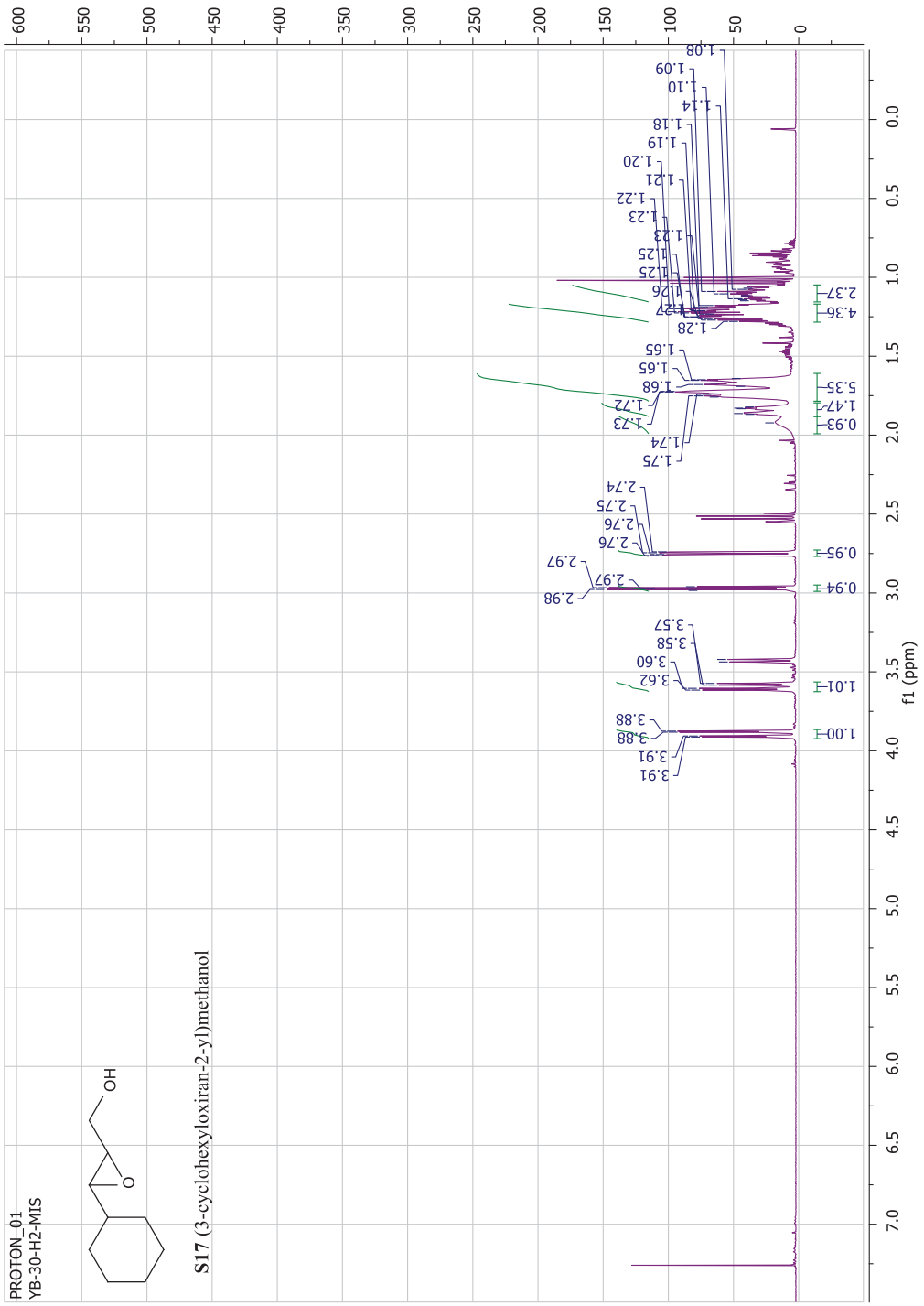
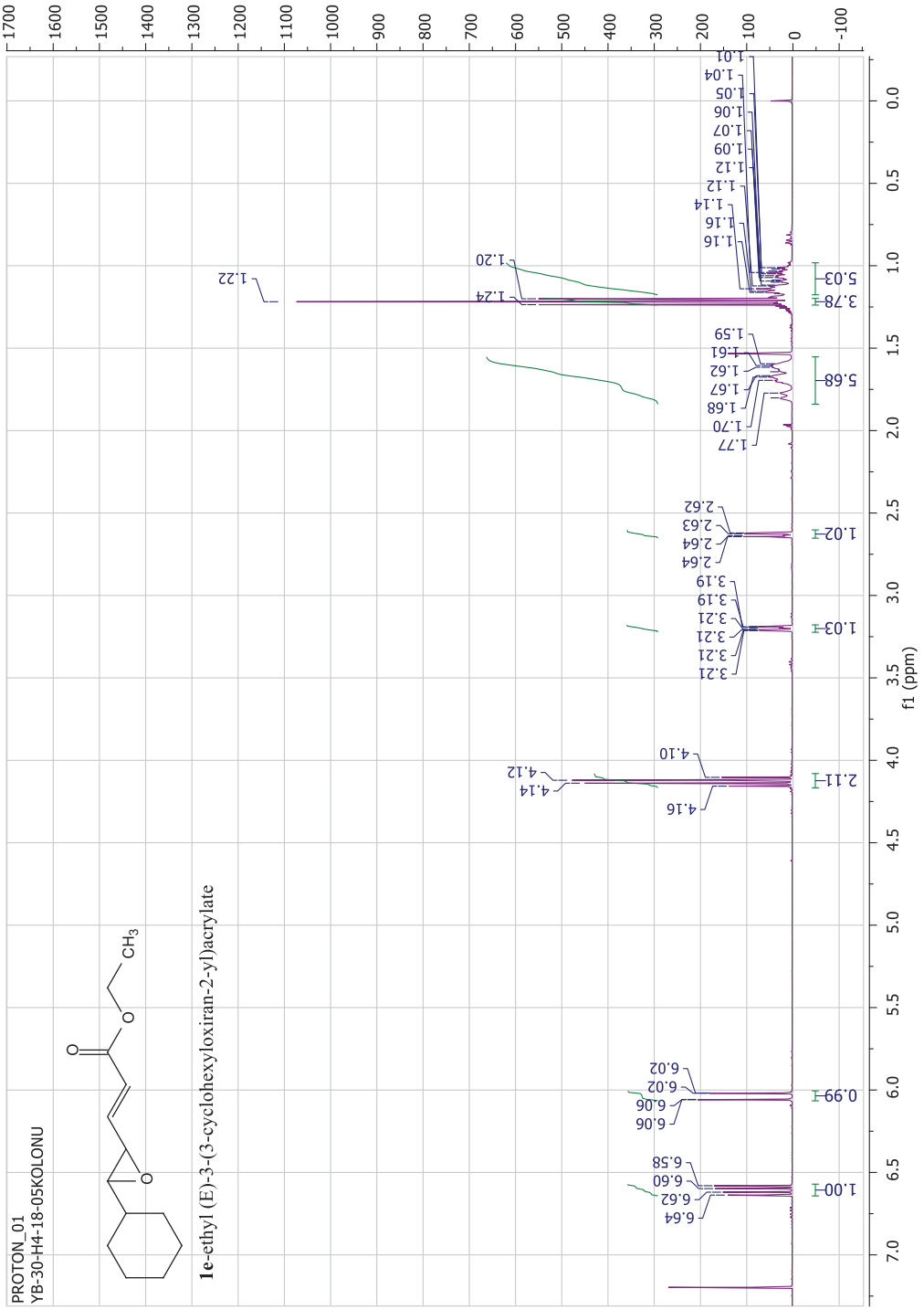
f1 (ppm)

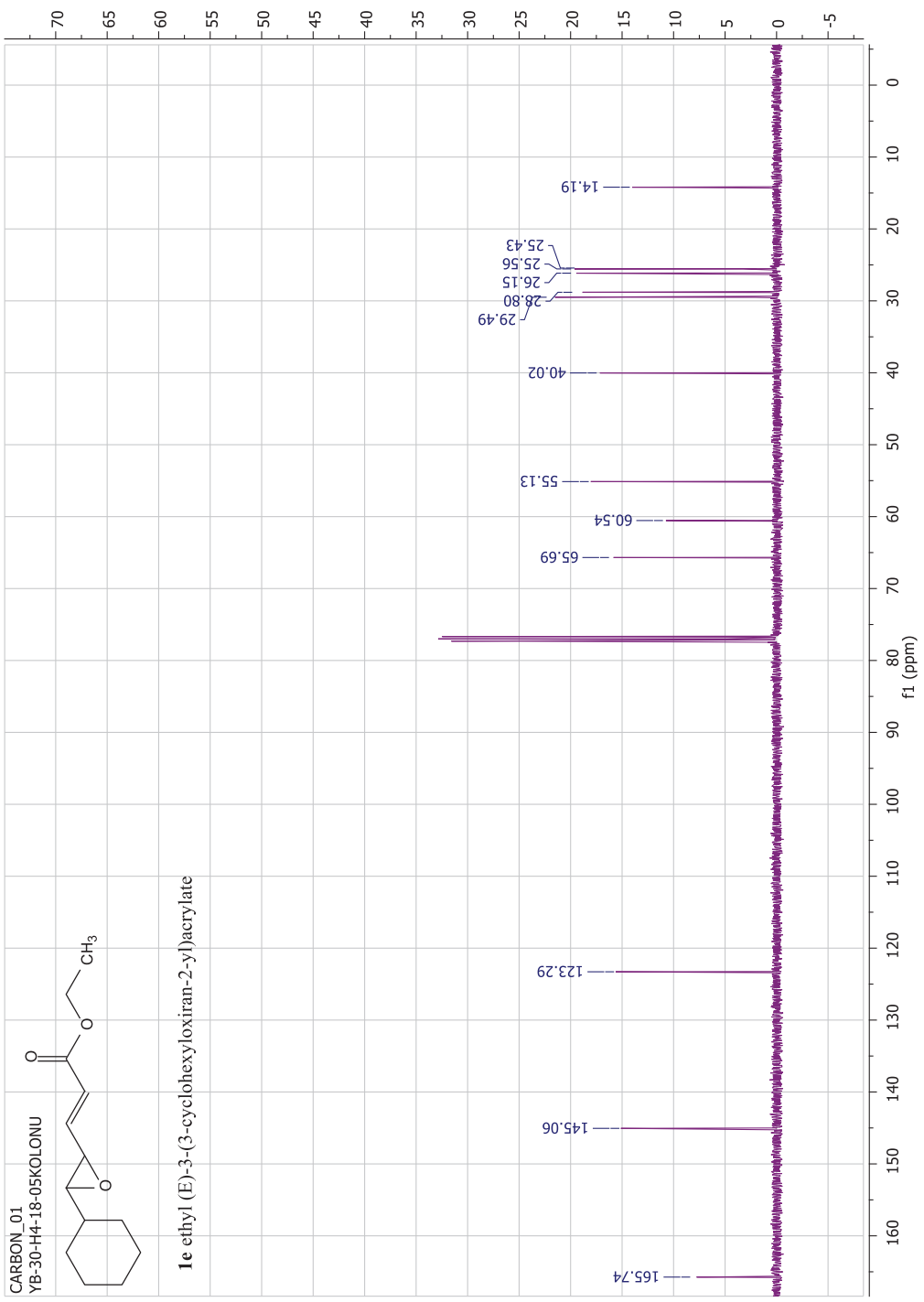

CARBON_02
YB-30-G3
1d-ethyl(E)-3-(3-((benzyloxy)methyl)oxiran-2-yl)acrylate
CH3
O
O
O
O
O
14.20
54.27
57.55
60.70
67.42
73.37
125.69
127.80
127.88
128.47
137.54
140.90
165.34
f1 (ppm)

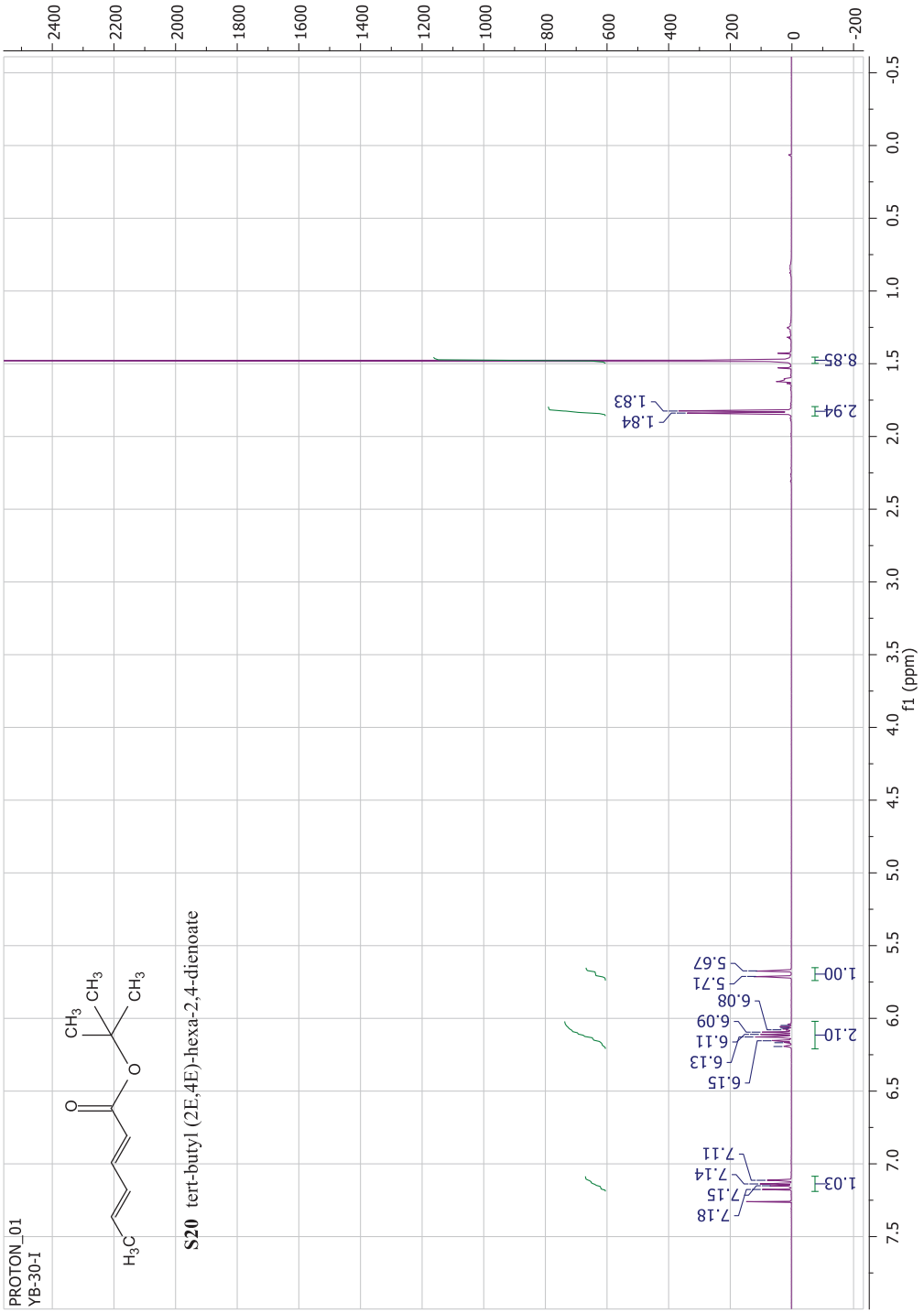

PROTON_01
YB-30-H1
OH
S16 (E)-3-cyclohexylprop-2-en-1-ol
f1 (ppm)

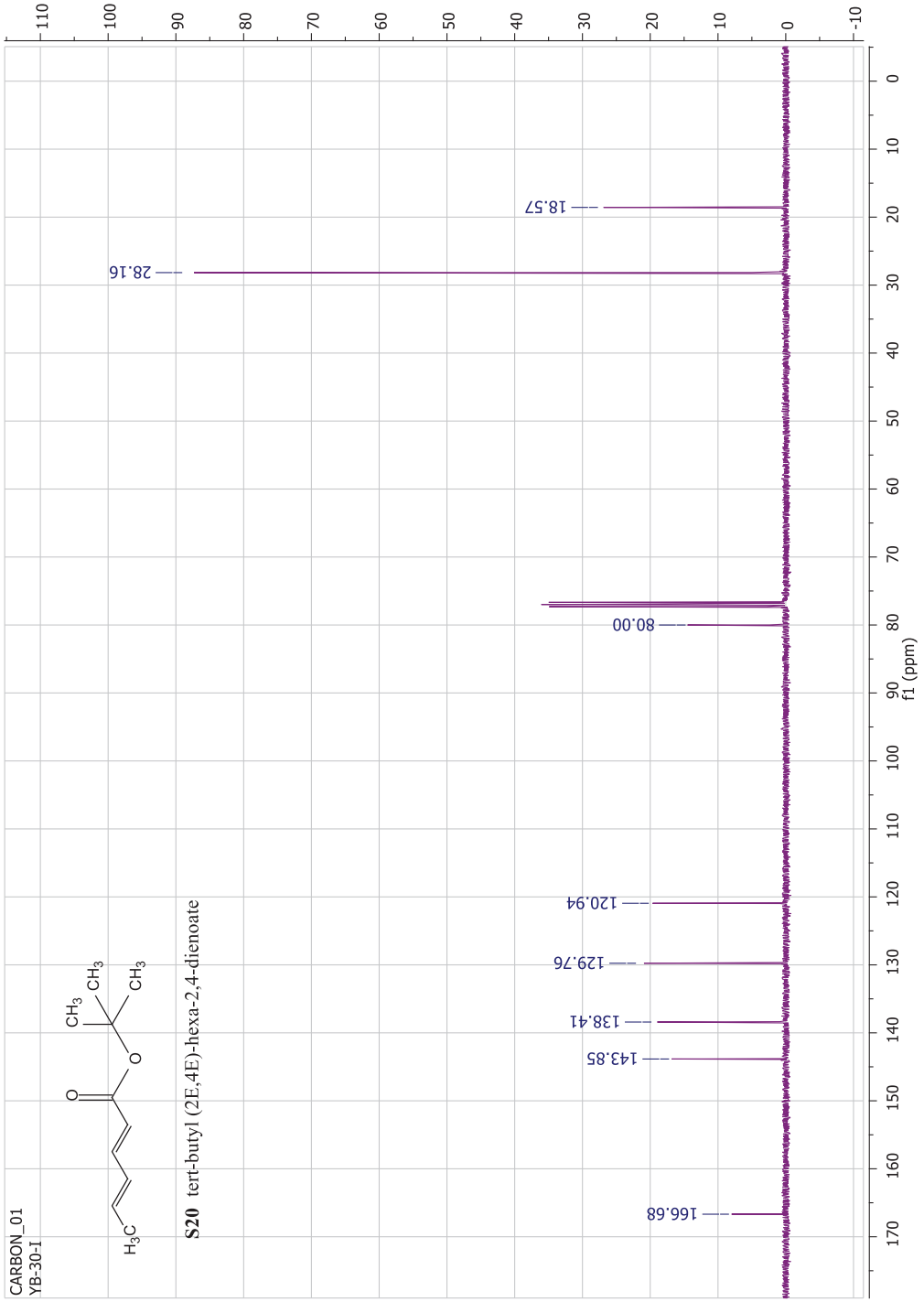

CARBON_01
YB-30-H1
OH
S16 (E)-3-cyclohexylprop-2-en-1-ol
139.17
126.27
63.98
40.27
32.74
29.54
26.12
25.99
f1 (ppm)

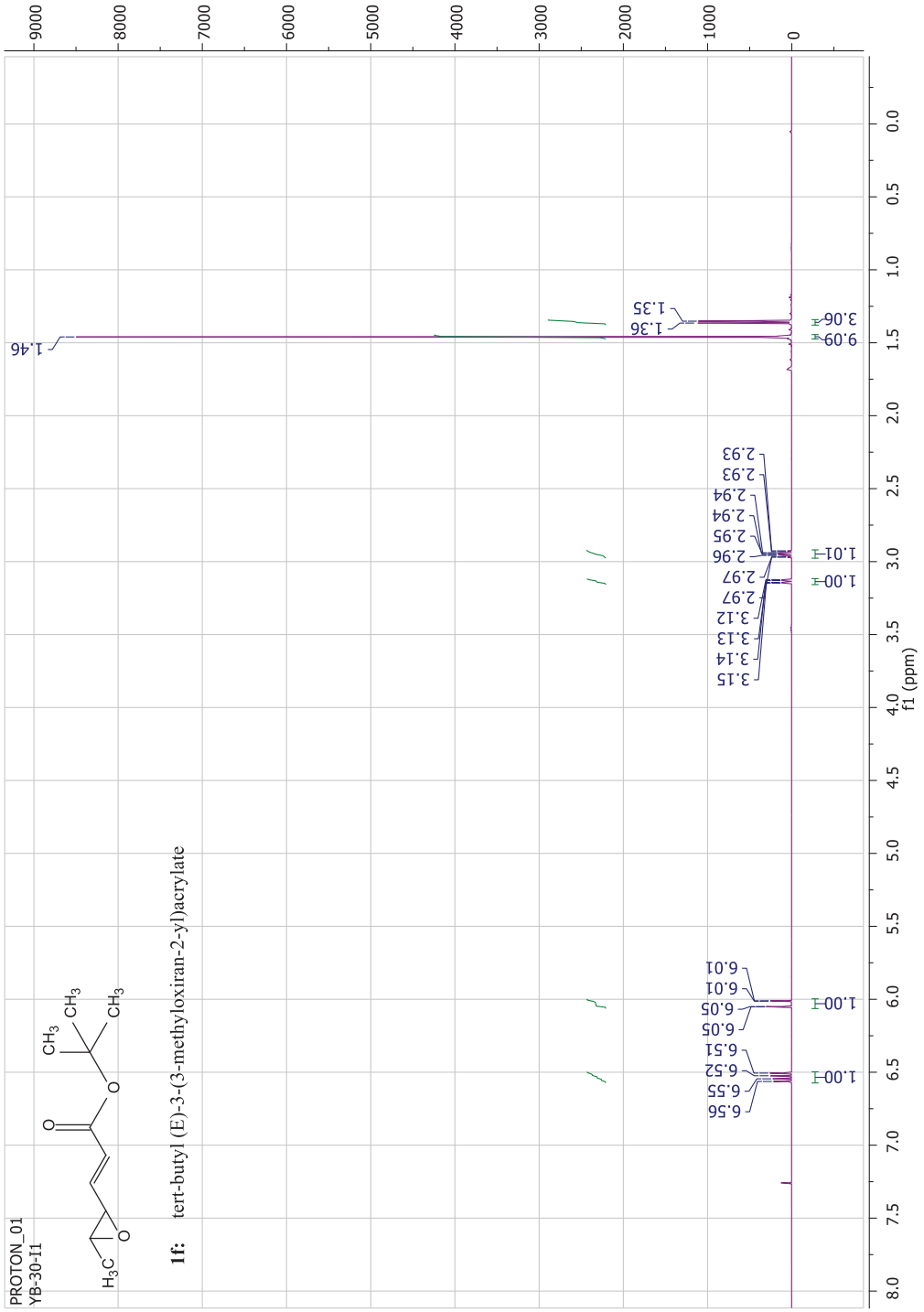

PROTON_01
YB-30-H2-MIS
OH
O
S17 (3-cyclohexyloxiran-2-yl)methanol
f1 (ppm)

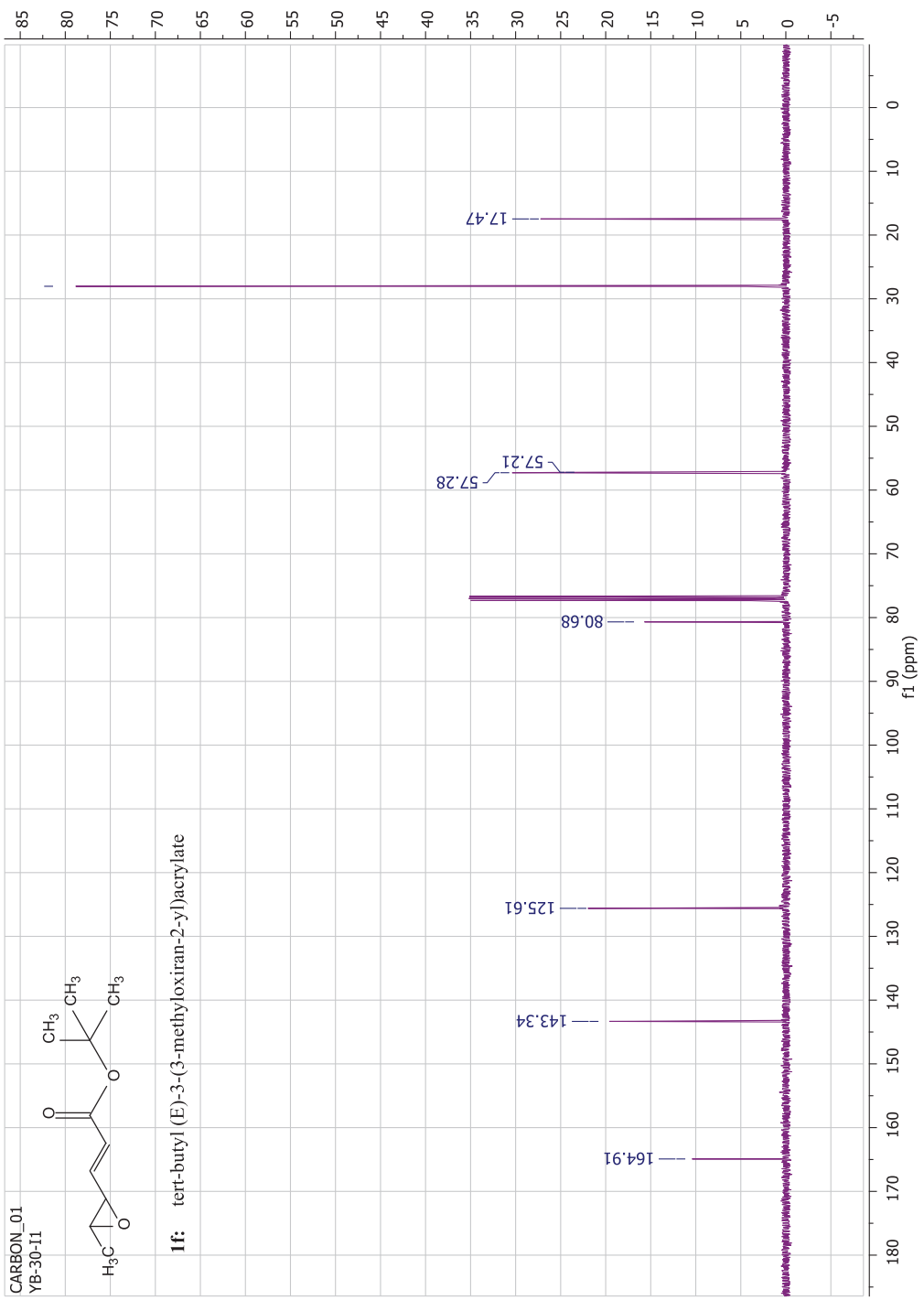

PROTON_01
YB-30-H4-18-05KOLONU
1e-ethyl (E)-3-(3-cyclohexyloxiran-2-yl)acrylate
f1 (ppm)

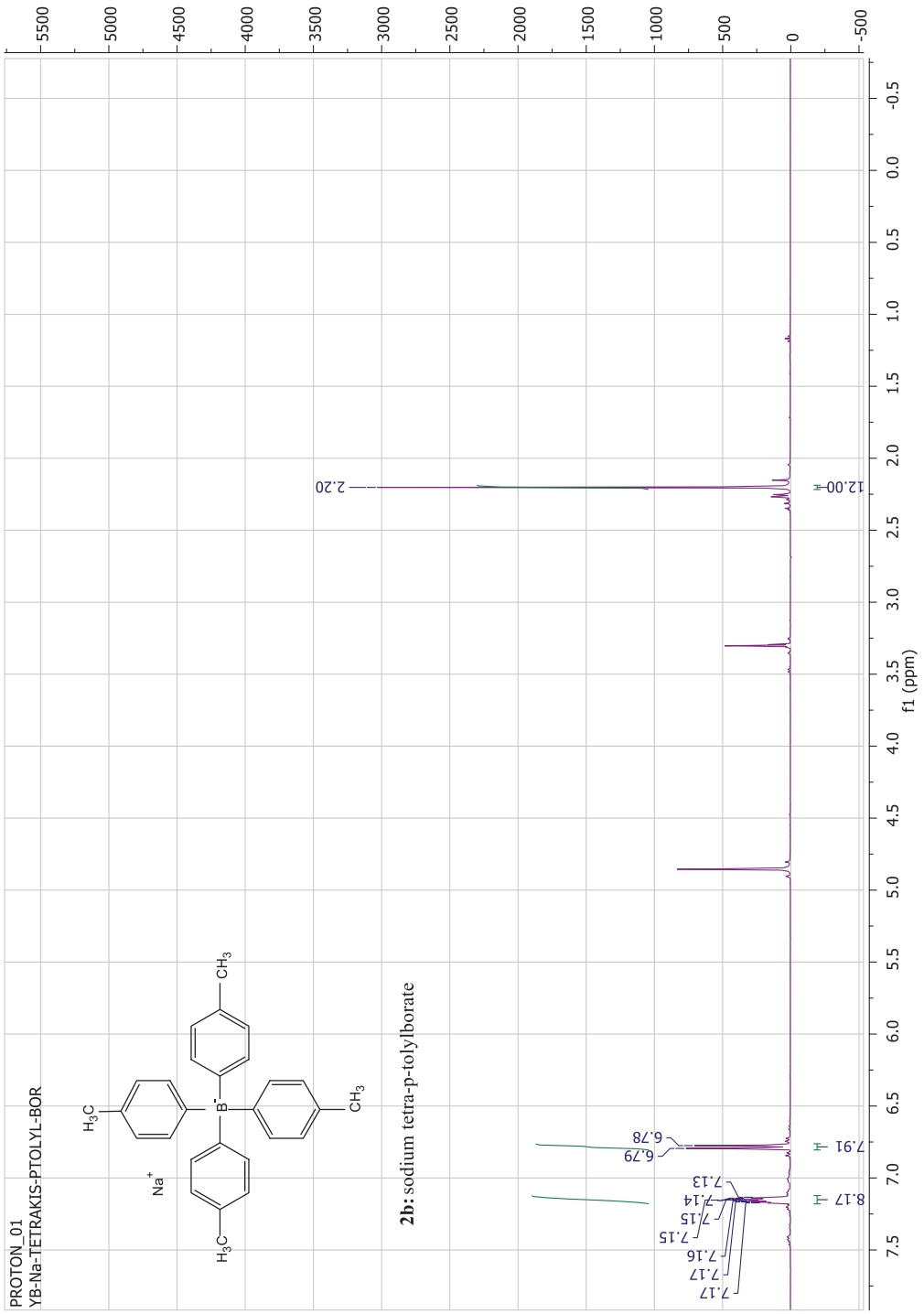

CARBON_01
YB-30-H4-18-05KOLONU
1e ethyl (E)-3-(3-cyclohexyloxiran-2-yl)acrylate
O
O
O
CH3
165.74
145.06
123.29
65.69
60.54
55.13
40.02
29.49
28.80
26.15
25.56
25.43
14.19
f1 (ppm)

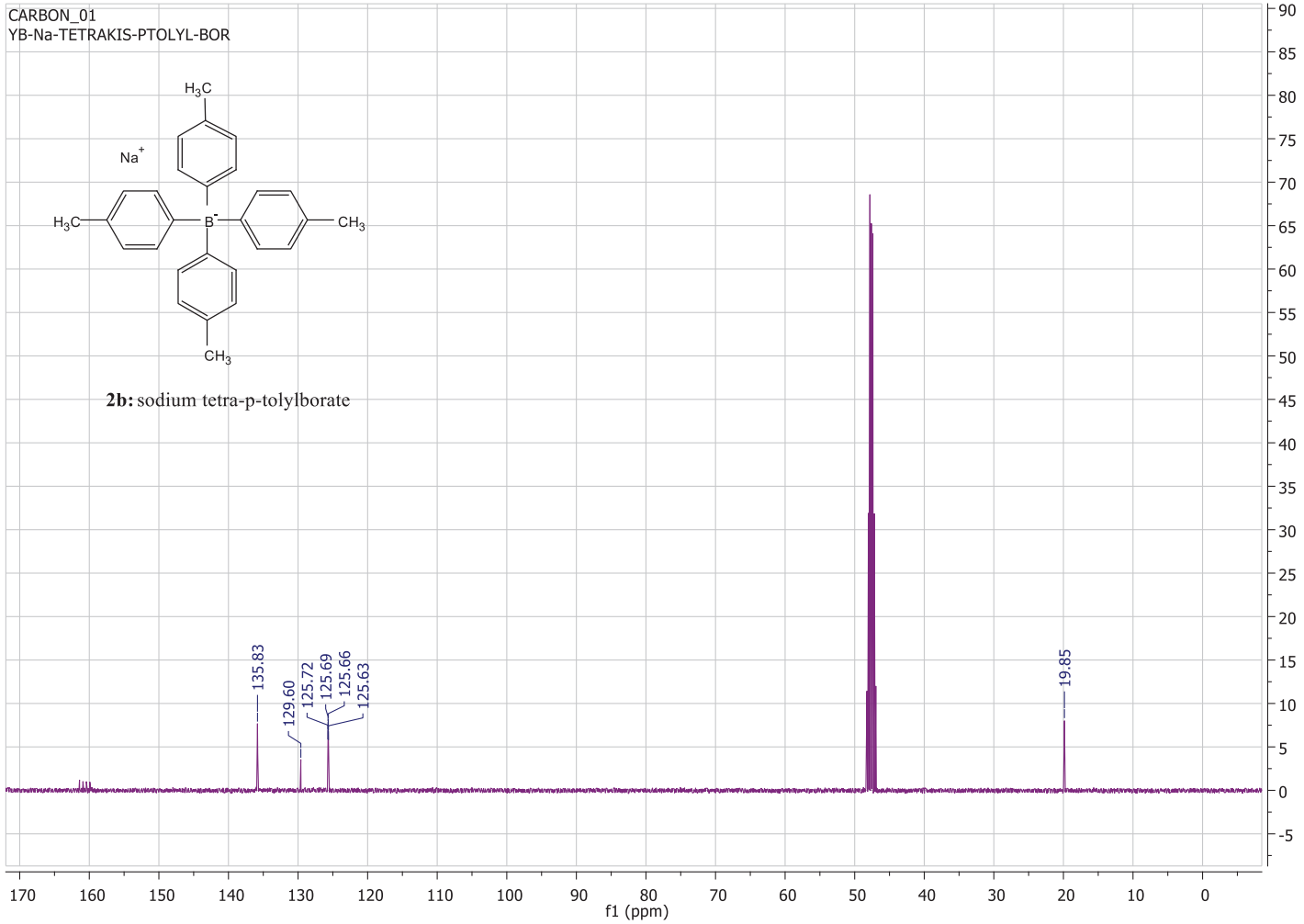

PROTON_01
YB-30-I
S20 tert-butyl (2E,4E)-hexa-2,4-dienoate
f1 (ppm)
8.85
2.94
1.03
1.00
2.10
1.84
1.83
7.18
7.15
7.14
7.11
6.15
6.13
6.11
6.09
6.08
5.71
5.67


CARBON_01
YB-30-I
S20 tert-butyl (2E,4E)-hexa-2,4-dienoate
CH3
CH3
CH3
O
O
H3C
166.68
143.85
138.41
129.76
120.94
80.00
28.16
18.57
f1 (ppm)


PROTON_01
YB-30-I1
1f: tert-butyl (E)-3-(3-methyloxiran-2-yl)acrylate
f1 (ppm)

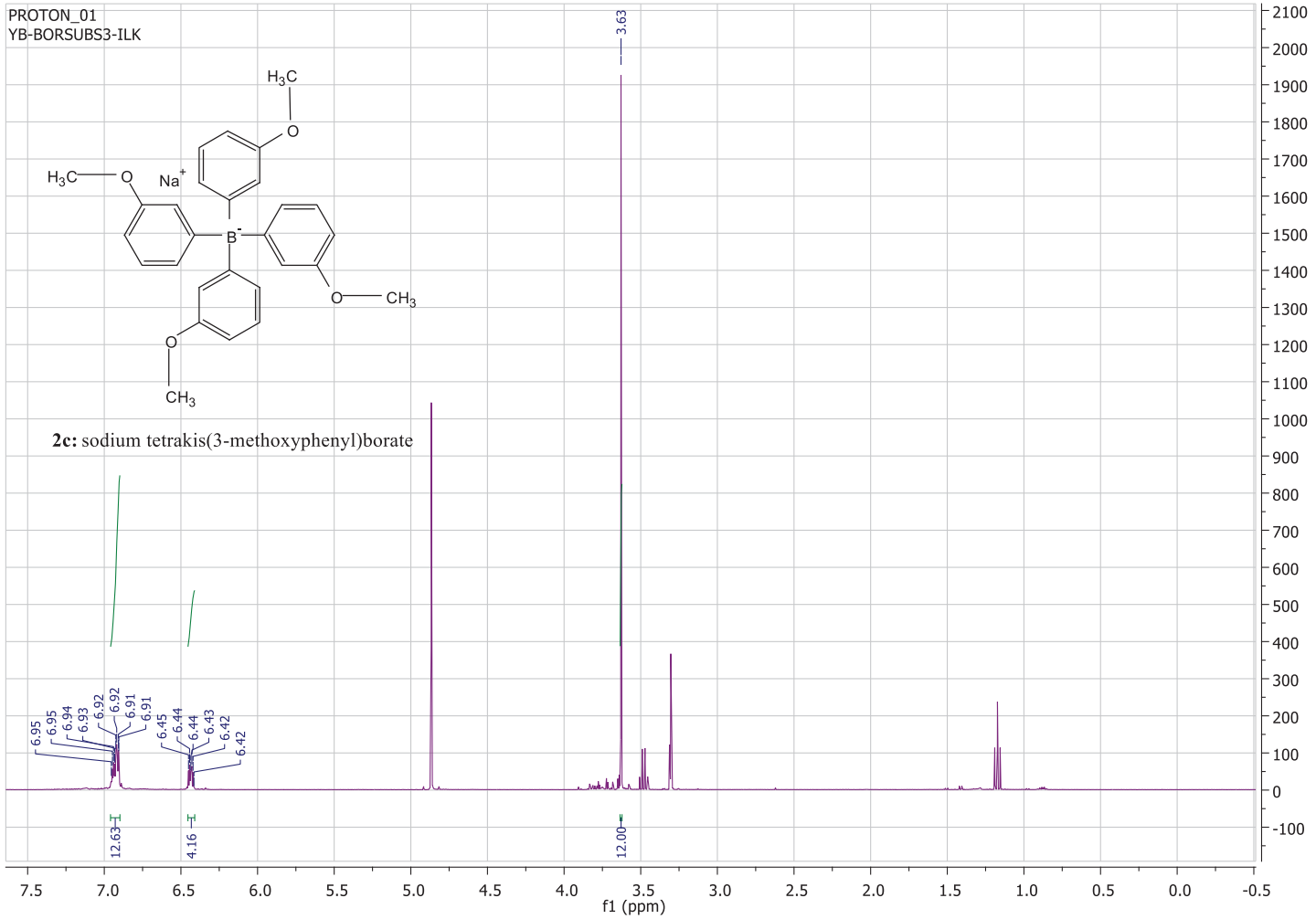

CARBON_01
YB-30-I1
1f: tert-butyl (E)-3-(3-methyloxiran-2-yl)acrylate
164.91
143.34
125.61
80.68
57.28
57.21
17.47
f1 (ppm)

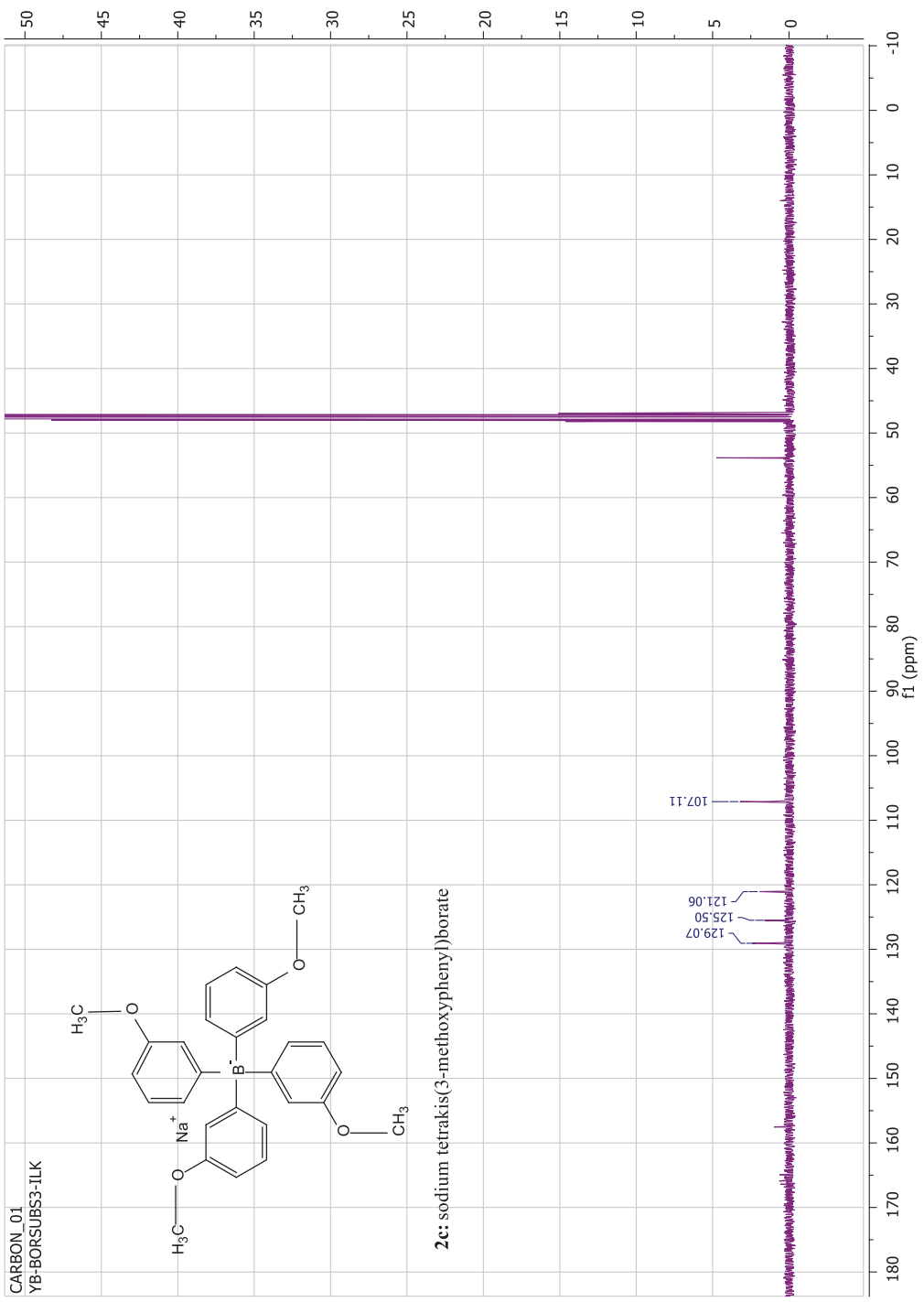

PROTON_01
YB-Na-TETRAKIS-PTOLYL-BOR
2b: sodium tetra-p-tolylborate
f1 (ppm)
2.20
12.00
7.91
8.17
6.79
6.78
7.13
7.14
7.15
7.15
7.16
7.17
7.17



2b: sodium tetra-p-tolylborate

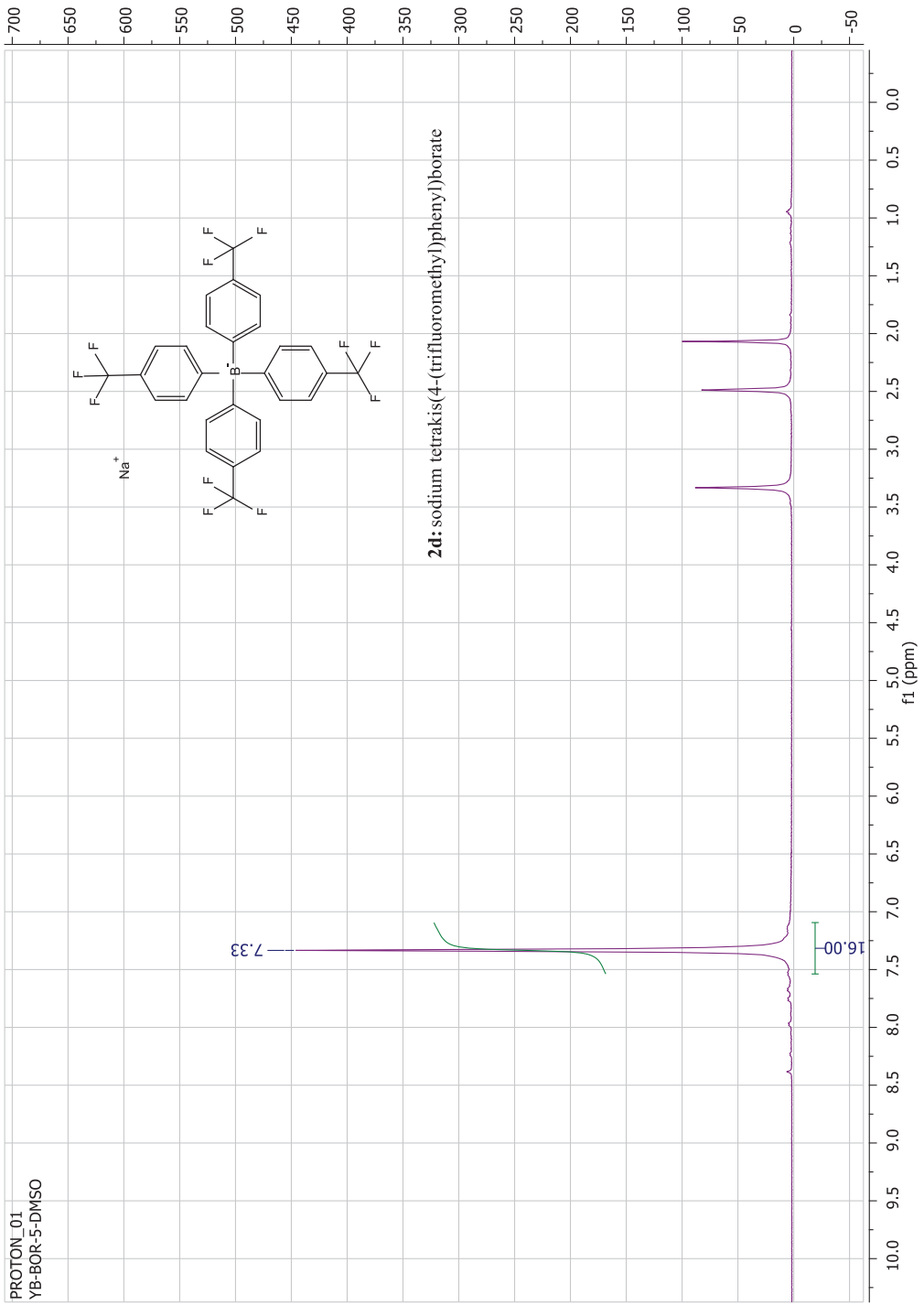

YB-NATETRAKIS-PTOLYLBOR-BOR
YB-NaTETRAKIS-PTOLLYBOR
-7.32
f1 (ppm)
2b sodium tetra-p-tolylborate

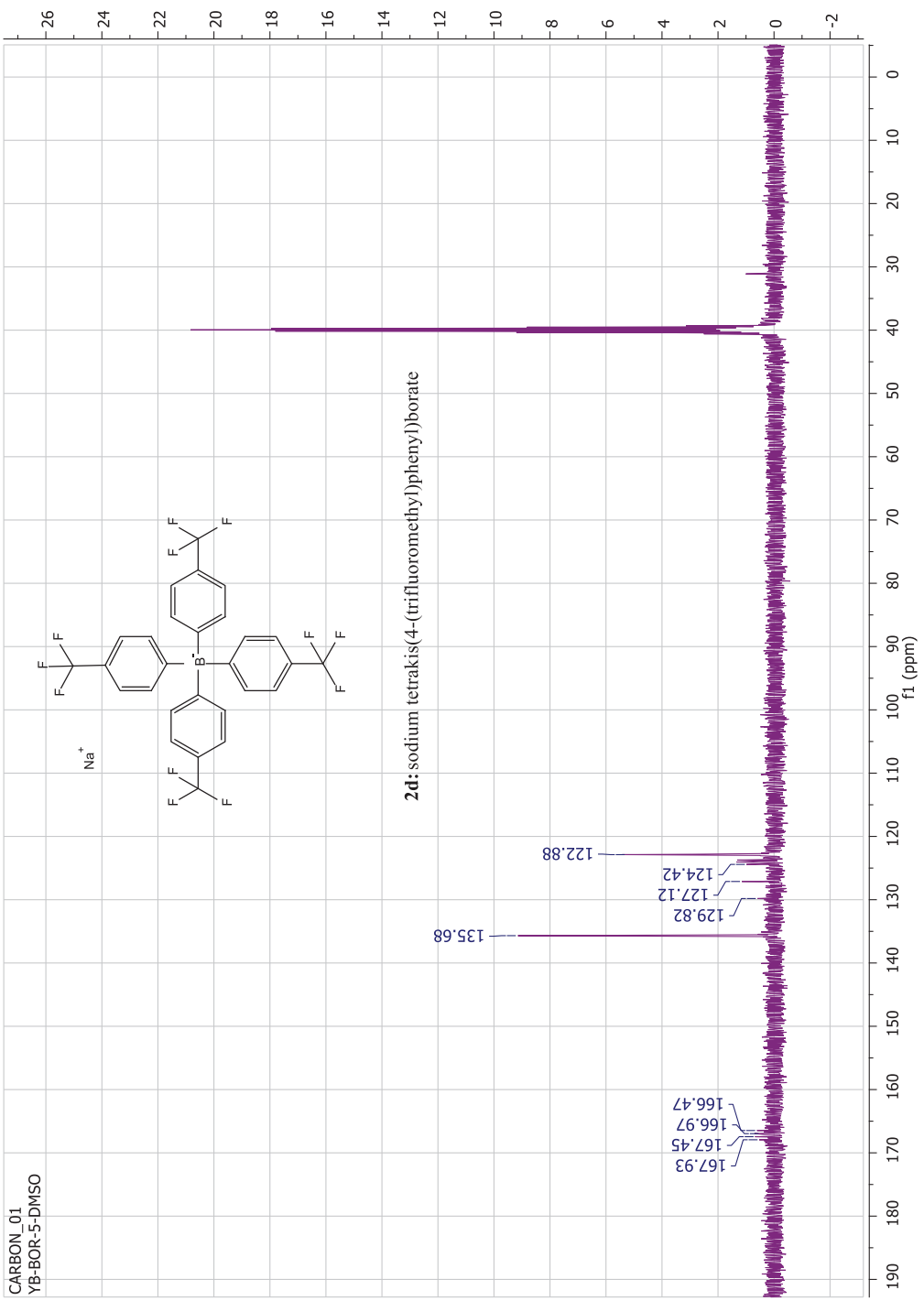

PROTON_01
YB-BORSUBS3-ILK
H3C
O
H3C
O
Na+
B-
O
CH3
O
CH3
2c: sodium tetrakis(3-methoxyphenyl)borate
3.63
6.95
6.95
6.94
6.93
6.92
6.92
6.91
6.91
6.45
6.44
6.44
6.43
6.42
6.42
12.63
4.16
12.00
f1 (ppm)

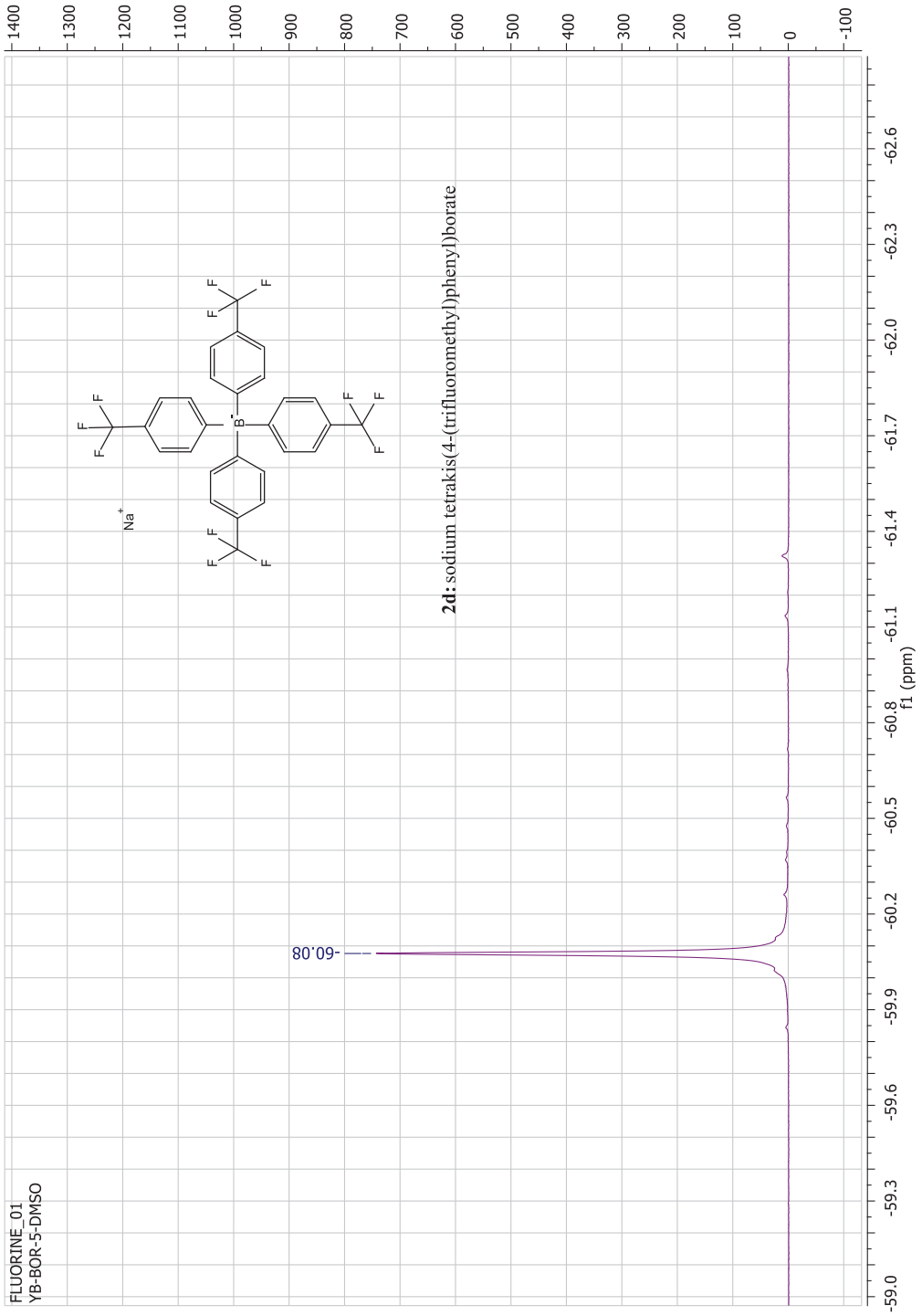


2c: sodium tetrakis(3-methoxyphenyl)borate


YB-BOR3-ILK-11B
YB-BOR3-ILK
-6.52
f1 (ppm)
2b sodium tetrakis(3-methoxyphenyl)borate


PROTON_01
YB-BOR-5-DMSO
7.33
16.00
f1 (ppm)
2d: sodium tetrakis(4-(trifluoromethyl)phenyl)borate

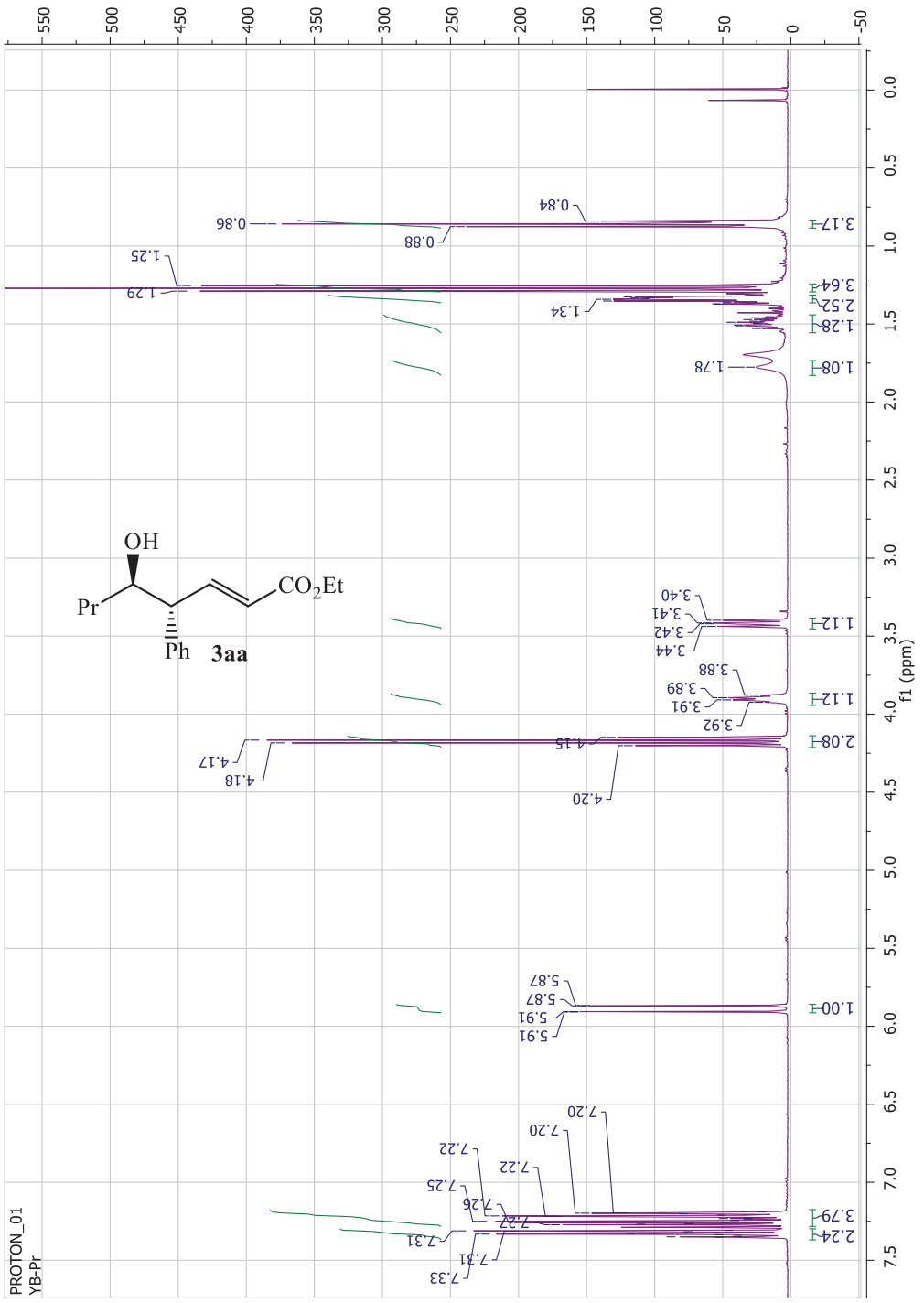

CARBON_01
YB-BOR-5-DMSO
2d: sodium tetrakis(4-(trifluoromethyl)phenyl)borate
Na+
B-
F
167.93
167.45
166.97
166.47
129.82
127.12
124.42
122.88
135.68
f1 (ppm)

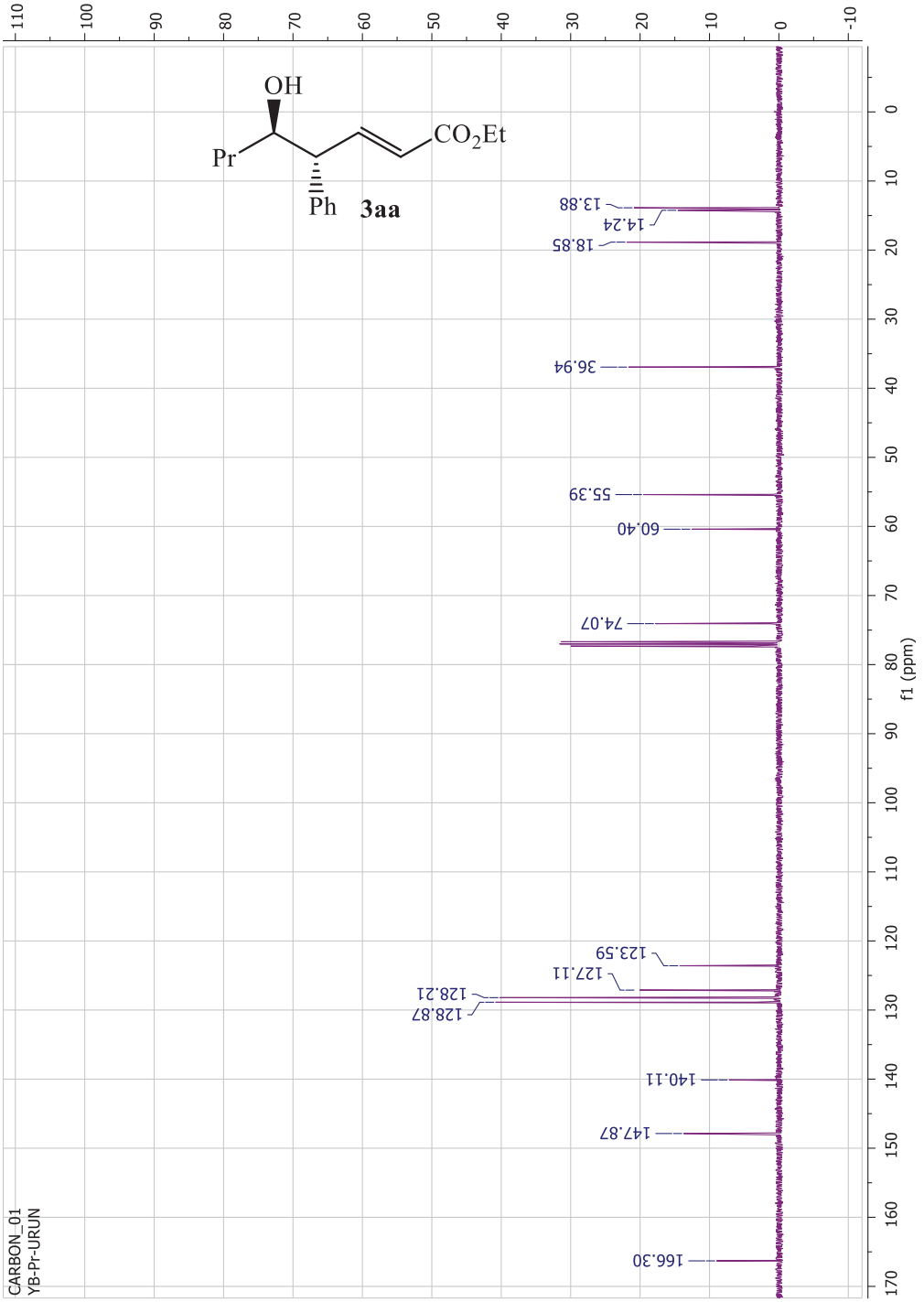

FLUORINE_01
YB-BOR-5-DMSO
-60.08
f1 (ppm)
2d: sodium tetrakis(4-(trifluoromethyl)phenyl)borate
Na+
B-

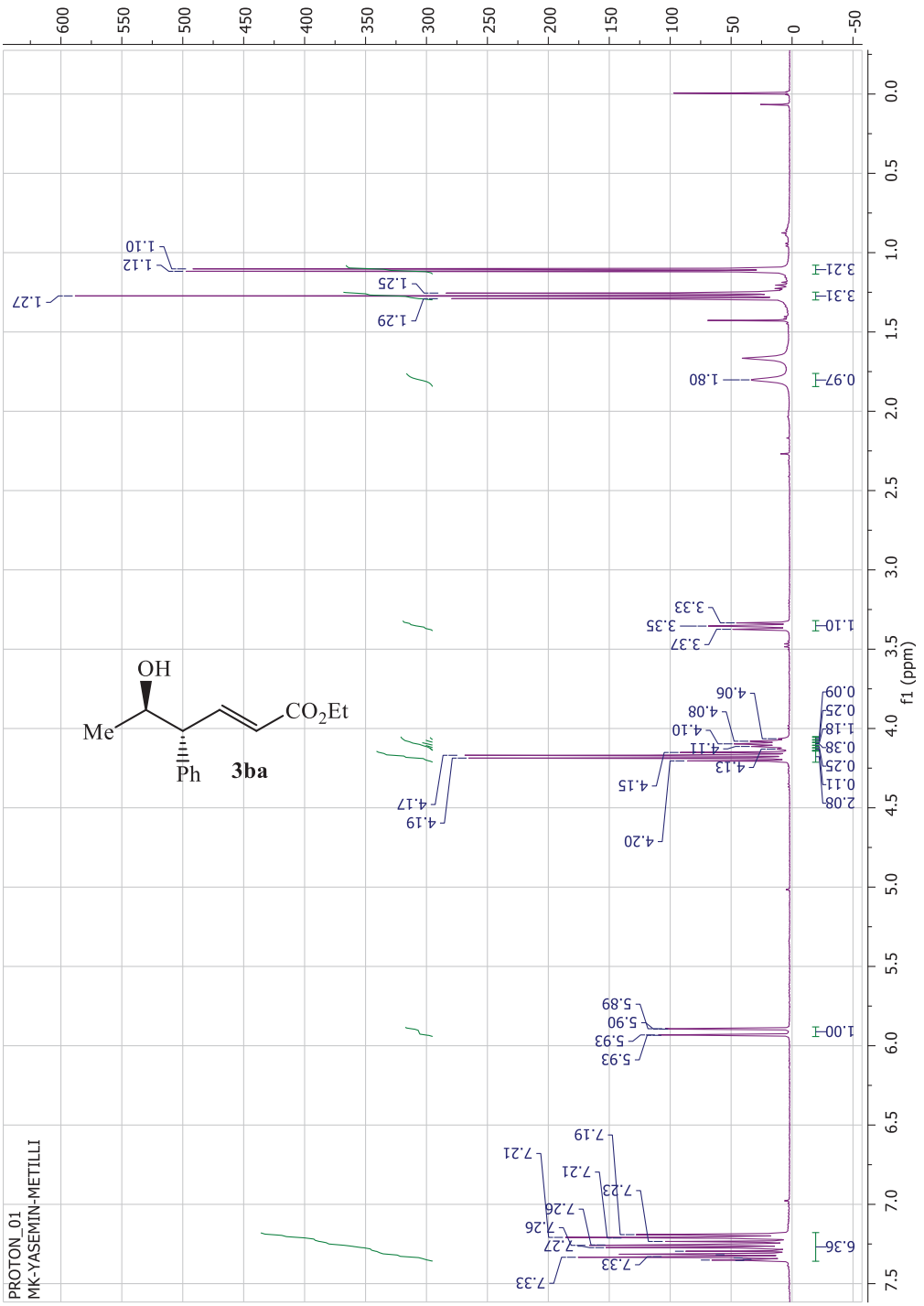
YB-BOR-5-DMSO
0.08 mg MeOH
-6.45
2d: sodium tetrakis(4-(trifluoromethyl)phenyl)borate
f1 (ppm)

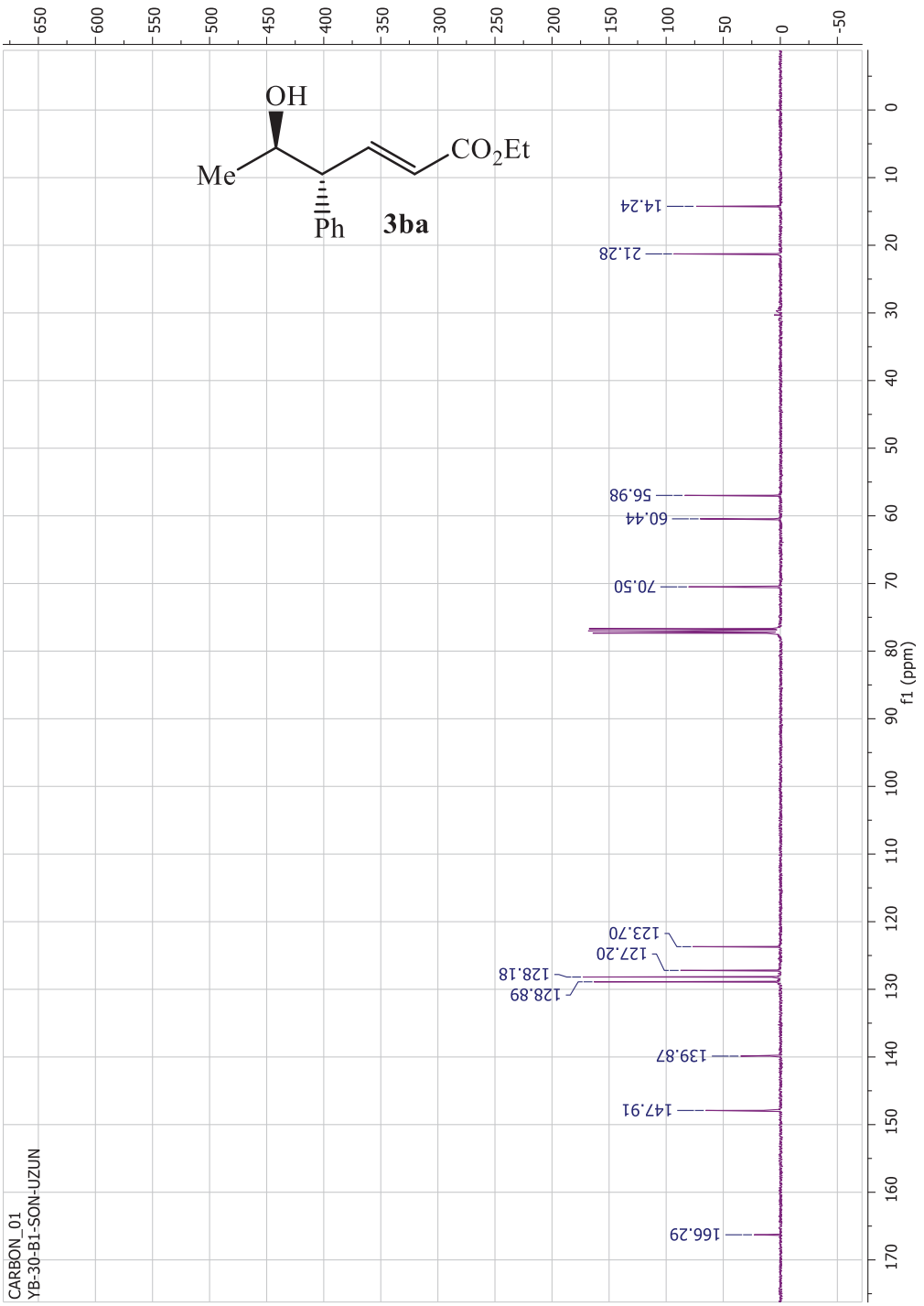
APPENDIX B

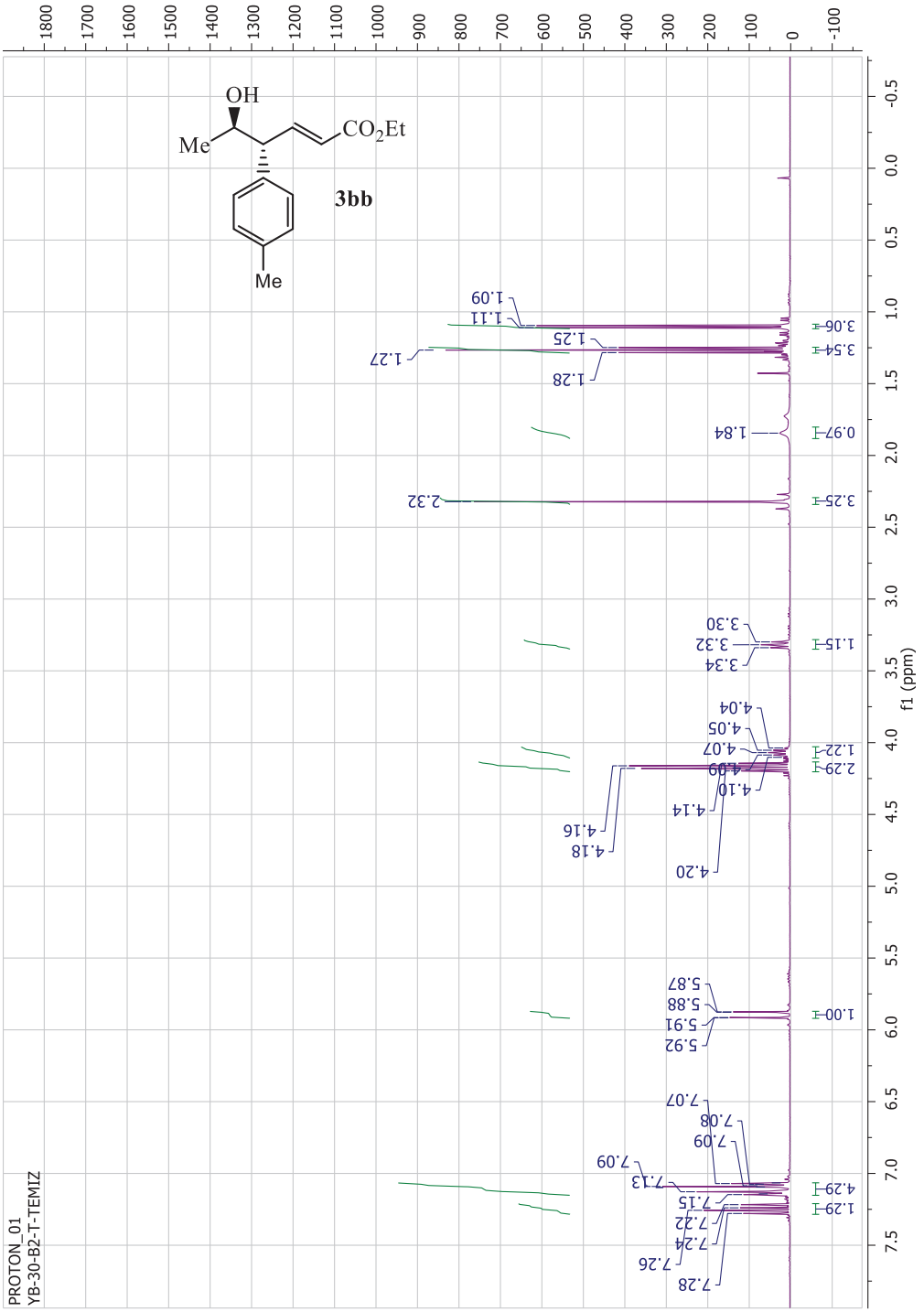
^{1}H NMR AND ^{13}C NMR SPECTRUMS OF PRODUCTS

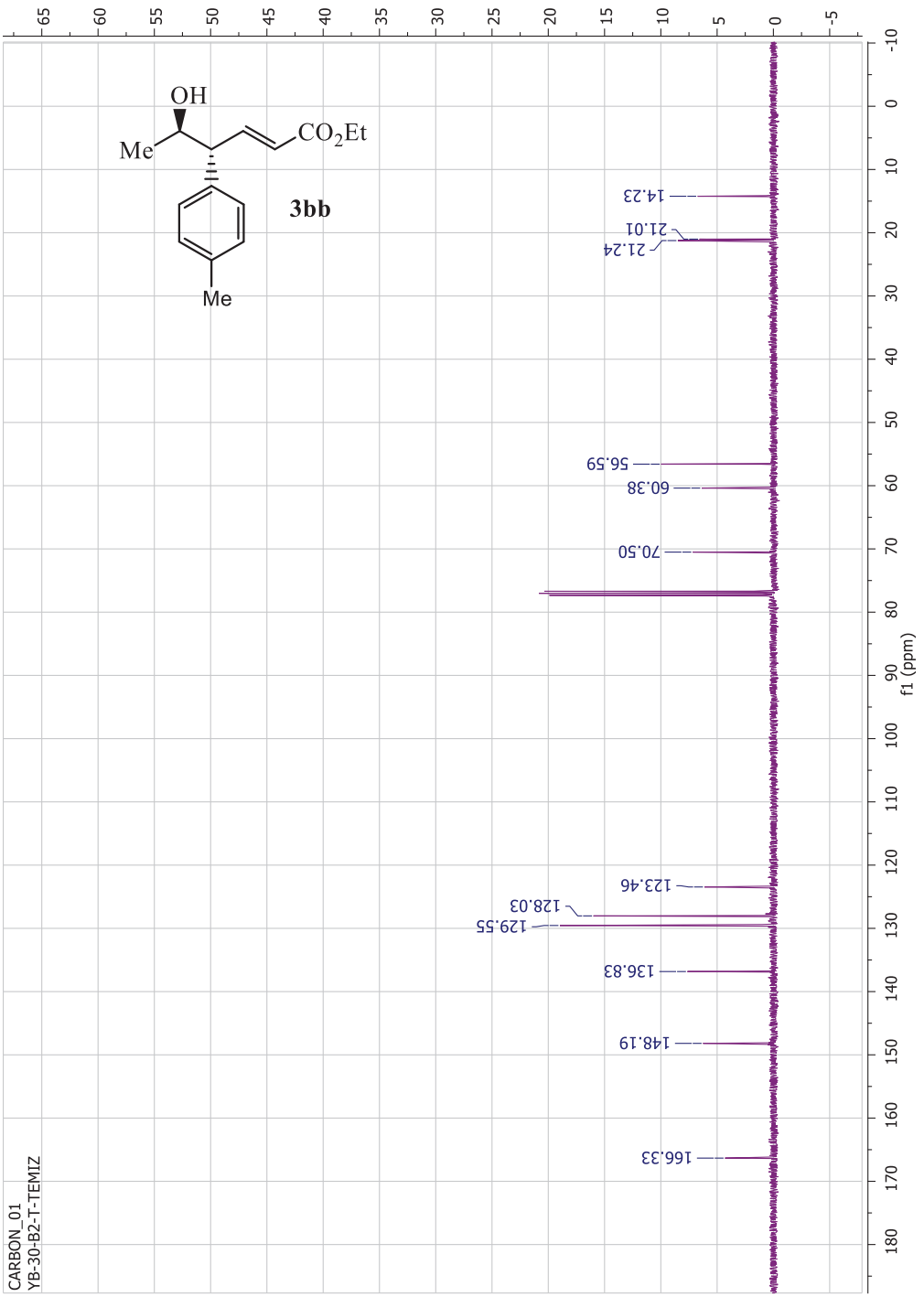

OH
Pr
CO2Et
Ph
3aa
PROTON_01
YB-Pr
f1 (ppm)

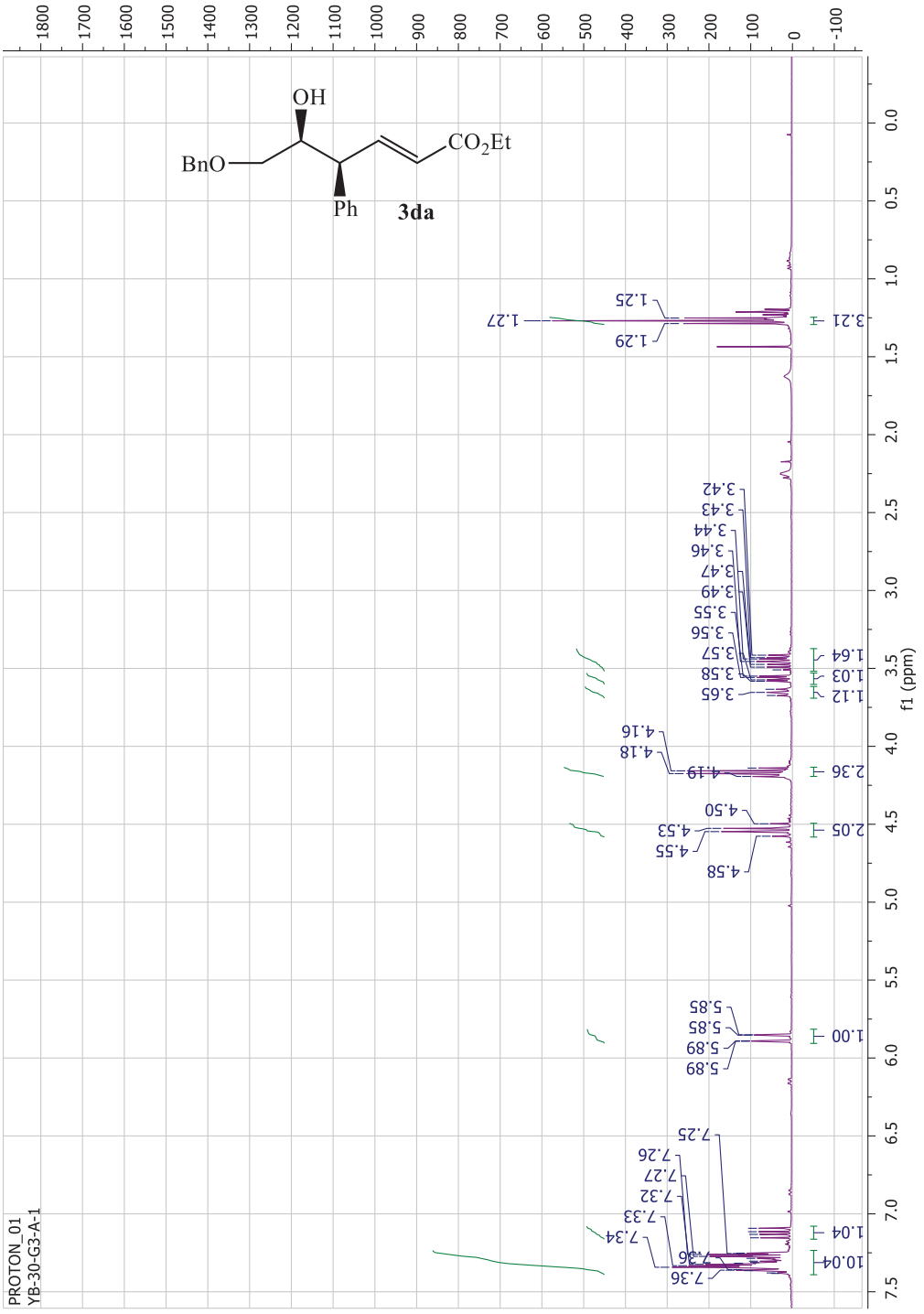

OH
Pr
Ph
CO2Et
3aa
13.88
14.24
18.85
36.94
55.39
60.40
74.07
123.59
127.11
128.21
128.87
140.11
147.87
166.30
CARBON_01
YB-Pr-URUN
f1 (ppm)

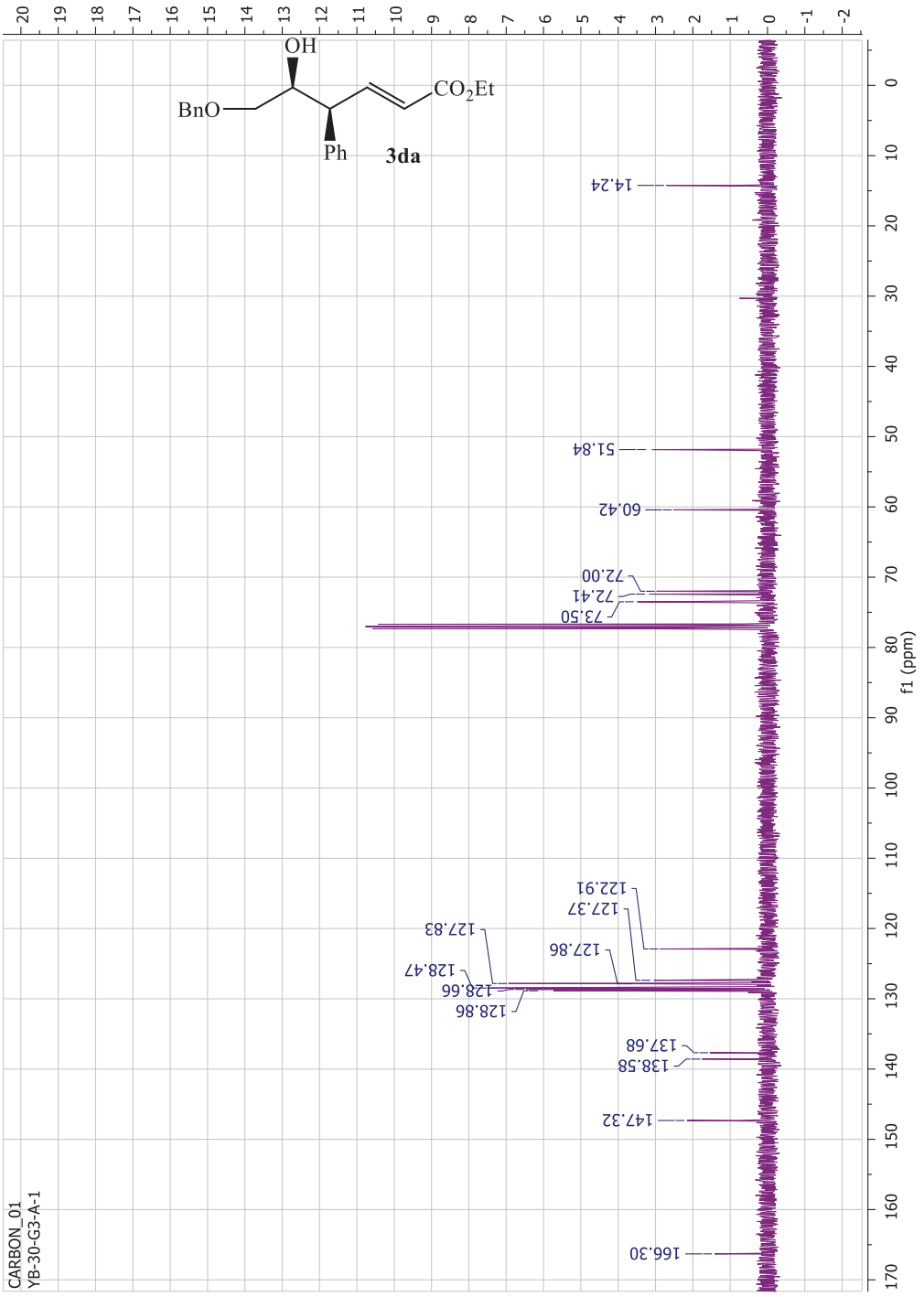

PROTON_01
MK-YASEMIN-METILLI
OH
Me
Ph
CO2Et
3ba
f1 (ppm)

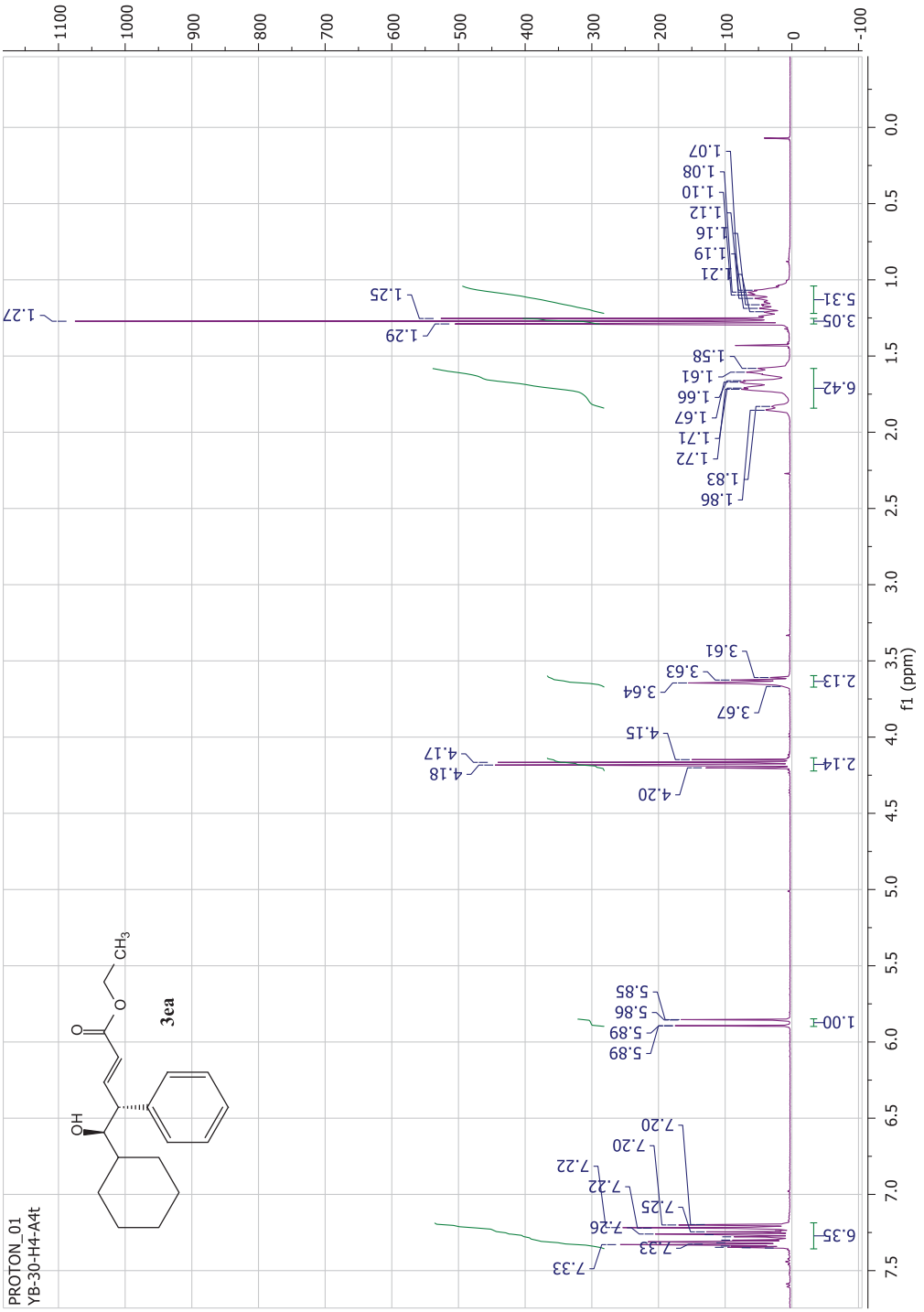

OH
Me
Ph
CO2Et
3ba
14.24
21.28
56.98
60.44
70.50
123.70
127.20
128.18
128.89
139.87
147.91
166.29
f1 (ppm)
CARBON_01
YB-30-B1-SON-UZUN

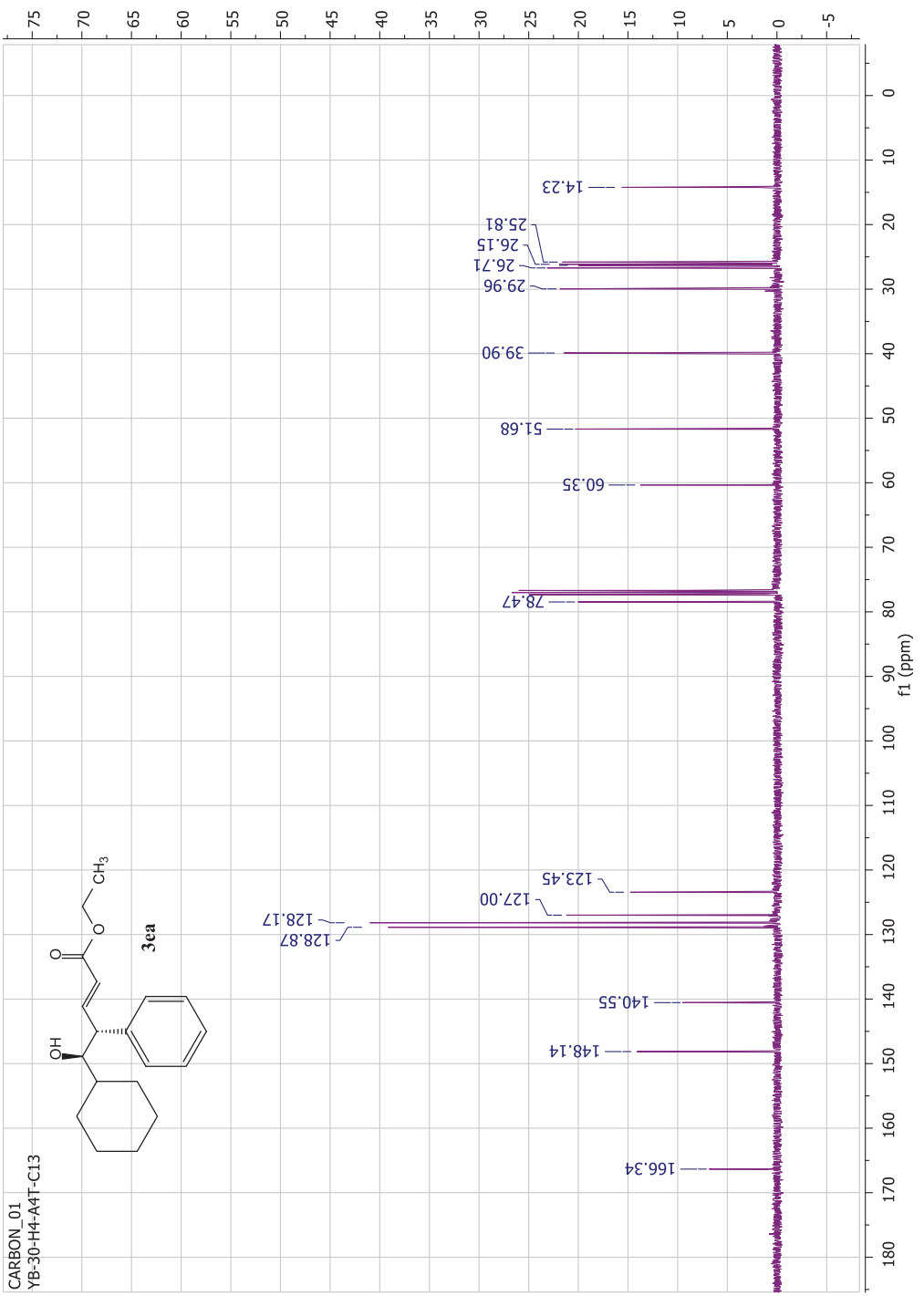

OH
Me
CO2Et
3bb
Me
PROTON_01
YB-30-B2-T-TEMIZ
f1 (ppm)

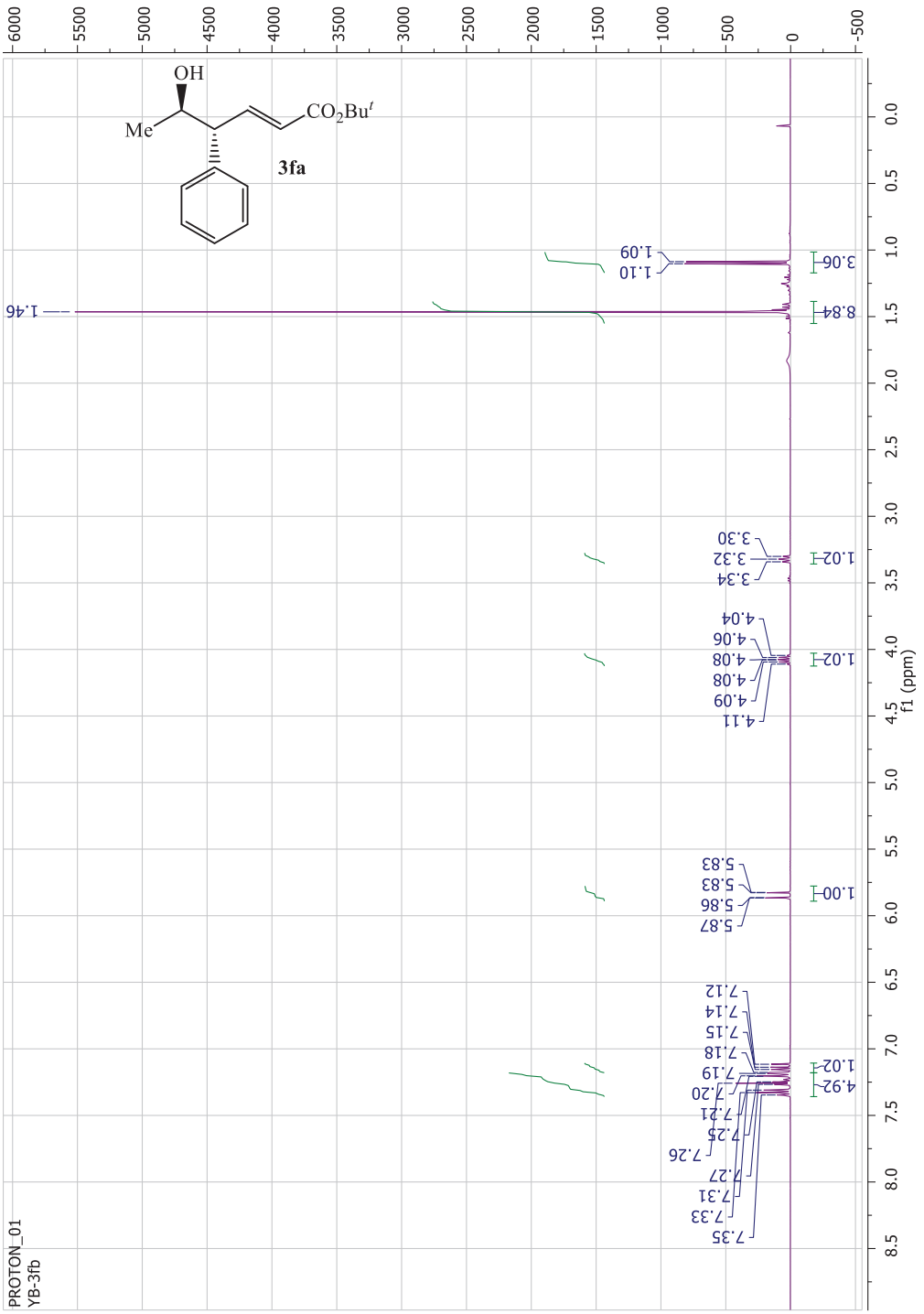

OH
Me
CO2Et
3bb
Me
14.23
21.01
21.24
56.59
60.38
70.50
123.46
128.03
129.55
136.83
148.19
166.33
CARBON_01
YB-30-B2-T-TEMIZ
f1 (ppm)

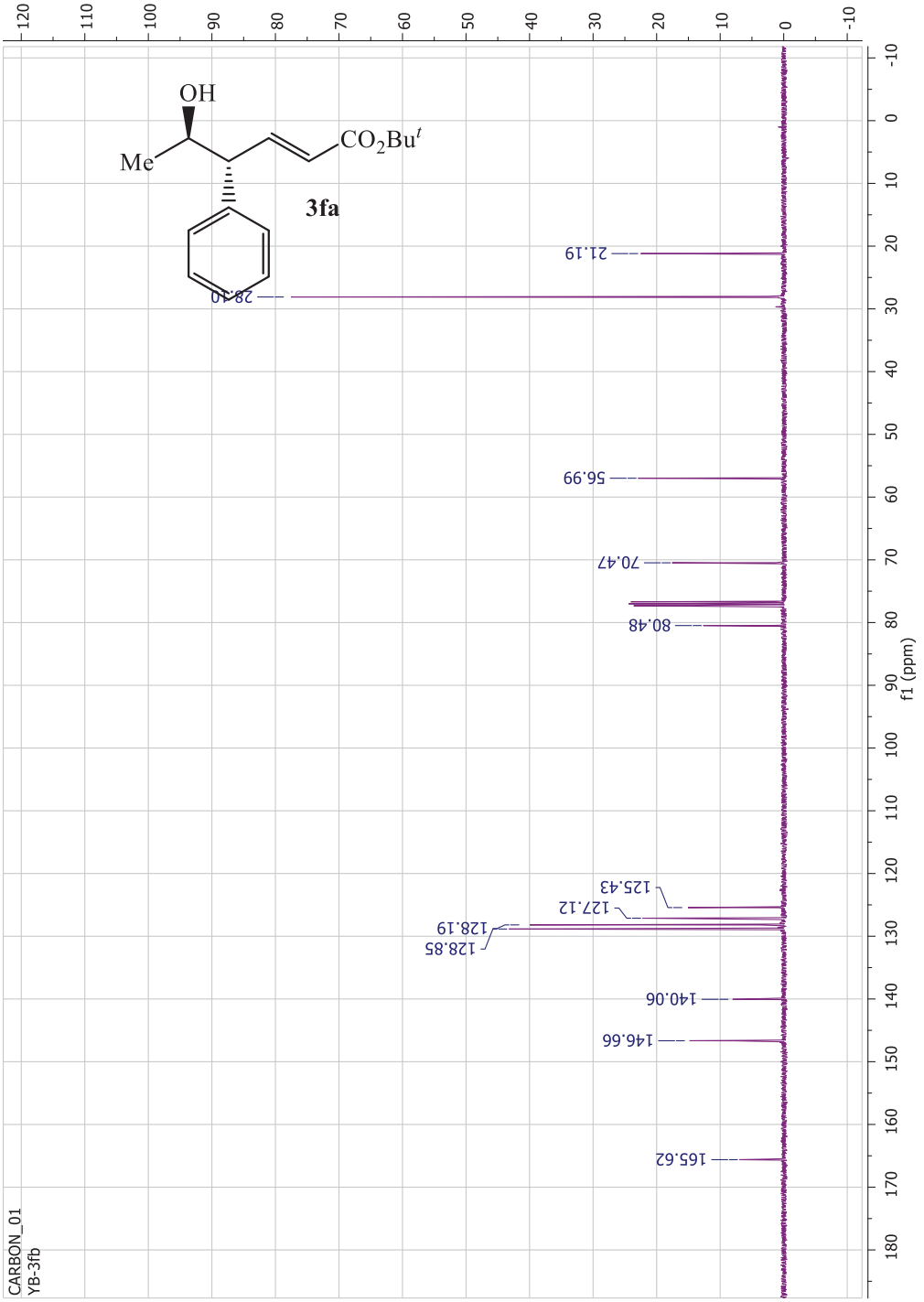

OH
BnO
CO2Et
Ph
3da
PROTON_01
YB-30-G3-A-1
f1 (ppm)

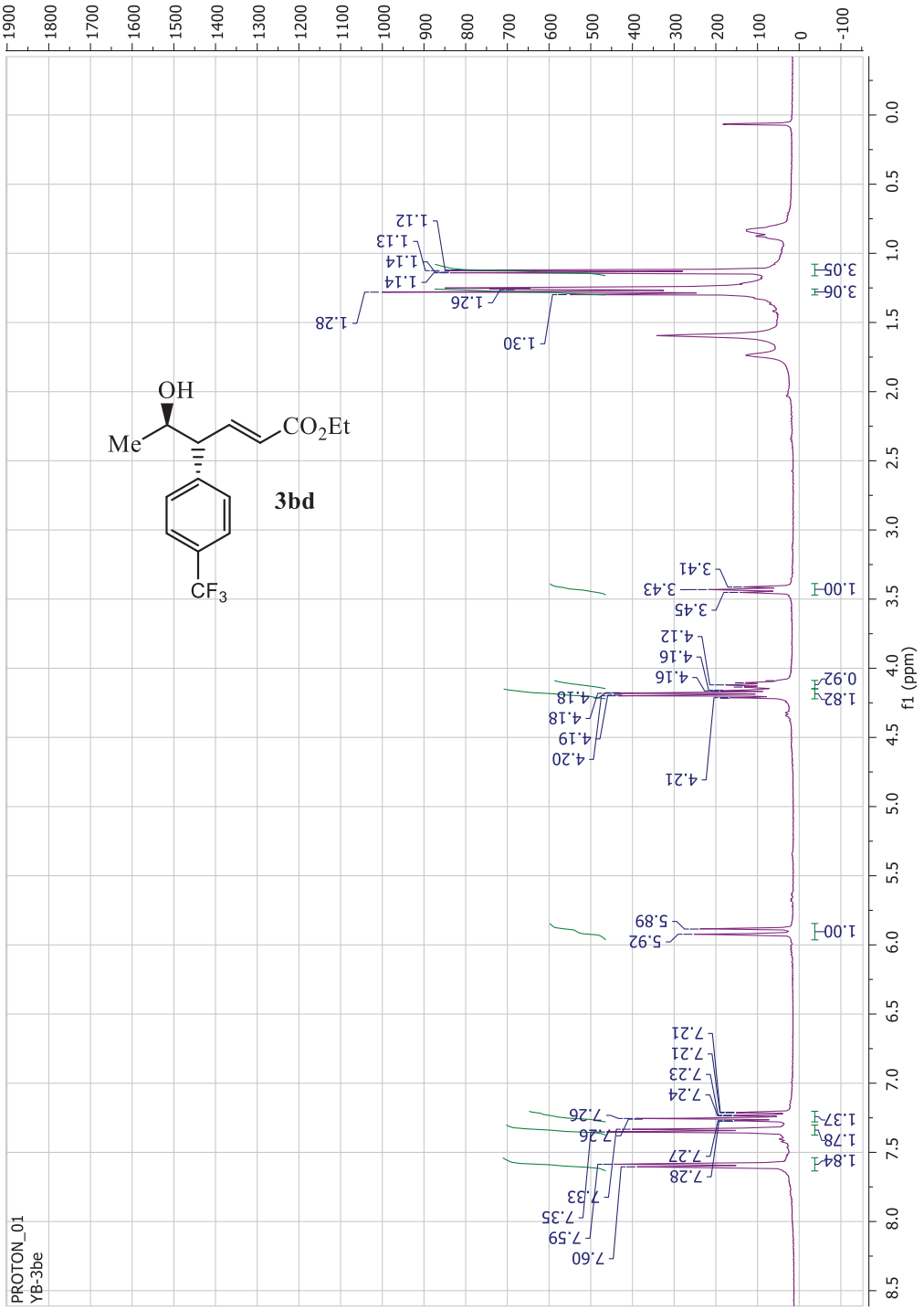

OH
BnO
CO2Et
Ph
3da
14.24
51.84
60.42
72.00
72.41
73.50
122.91
127.37
127.83
127.86
128.47
128.66
128.86
137.68
138.58
147.32
166.30
f1 (ppm)
CARBON_01
YB-30-G3-A-1

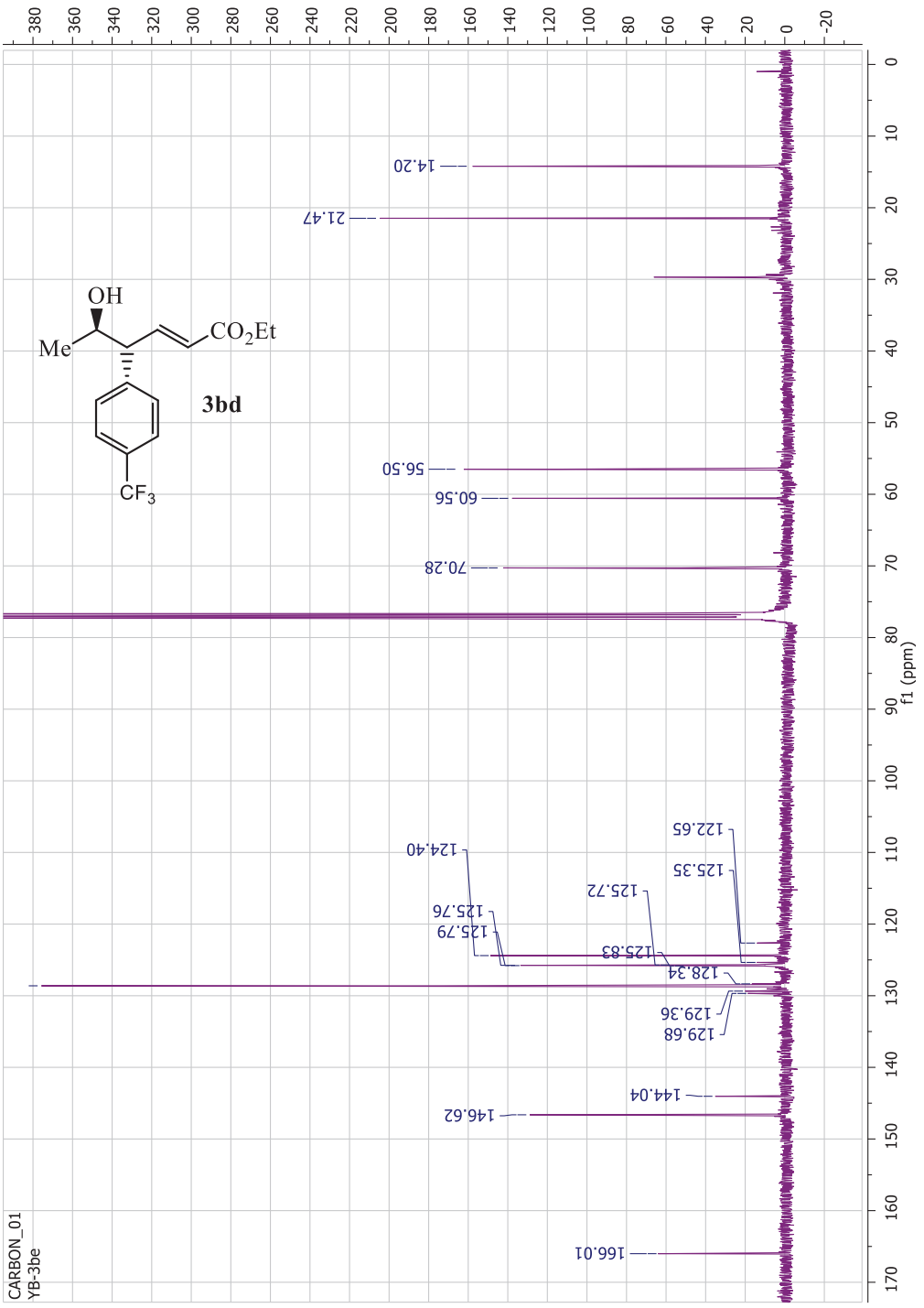

PROTON_01
YB-30-H4-A4t
3ea
OH
O
O
CH3
f1 (ppm)
1.27
1.29
1.25
1.86
1.83
1.72
1.71
1.67
1.66
1.61
1.58
1.21
1.19
1.16
1.12
1.10
1.08
1.07
4.20
4.18
4.17
4.15
3.67
3.64
3.63
3.61
5.89
5.89
5.86
5.85
7.33
7.26
7.25
7.22
7.22
7.20
7.20
6.35
2.14
2.13
1.00
6.42
3.05
5.31

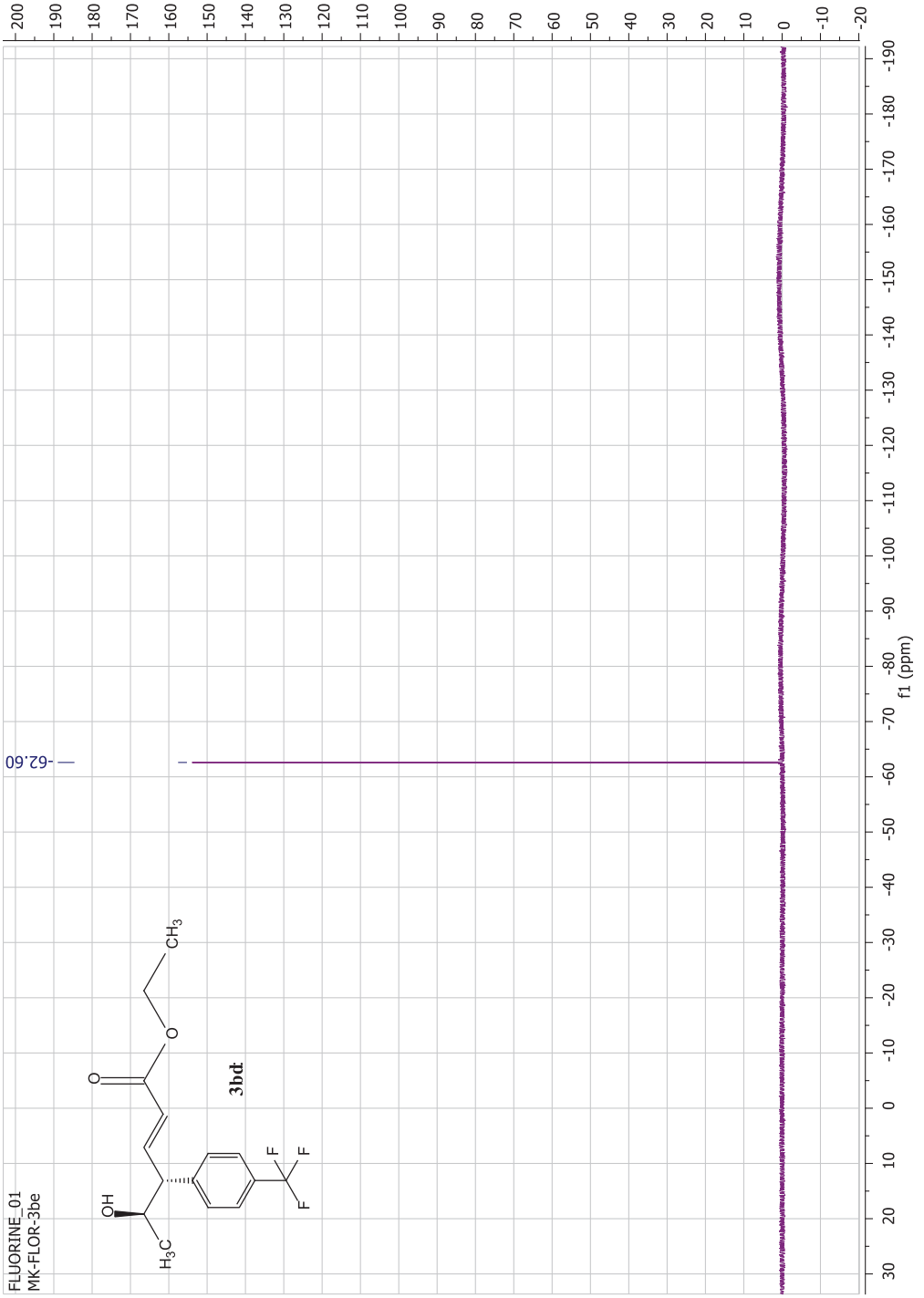

CARBON_01
YB-30-H4-A4T-C13
3ea
OH
O
O
CH3
166.34
148.14
140.55
128.87
128.17
127.00
123.45
78.47
60.35
51.68
39.90
29.96
26.71
26.15
25.81
14.23
f1 (ppm)

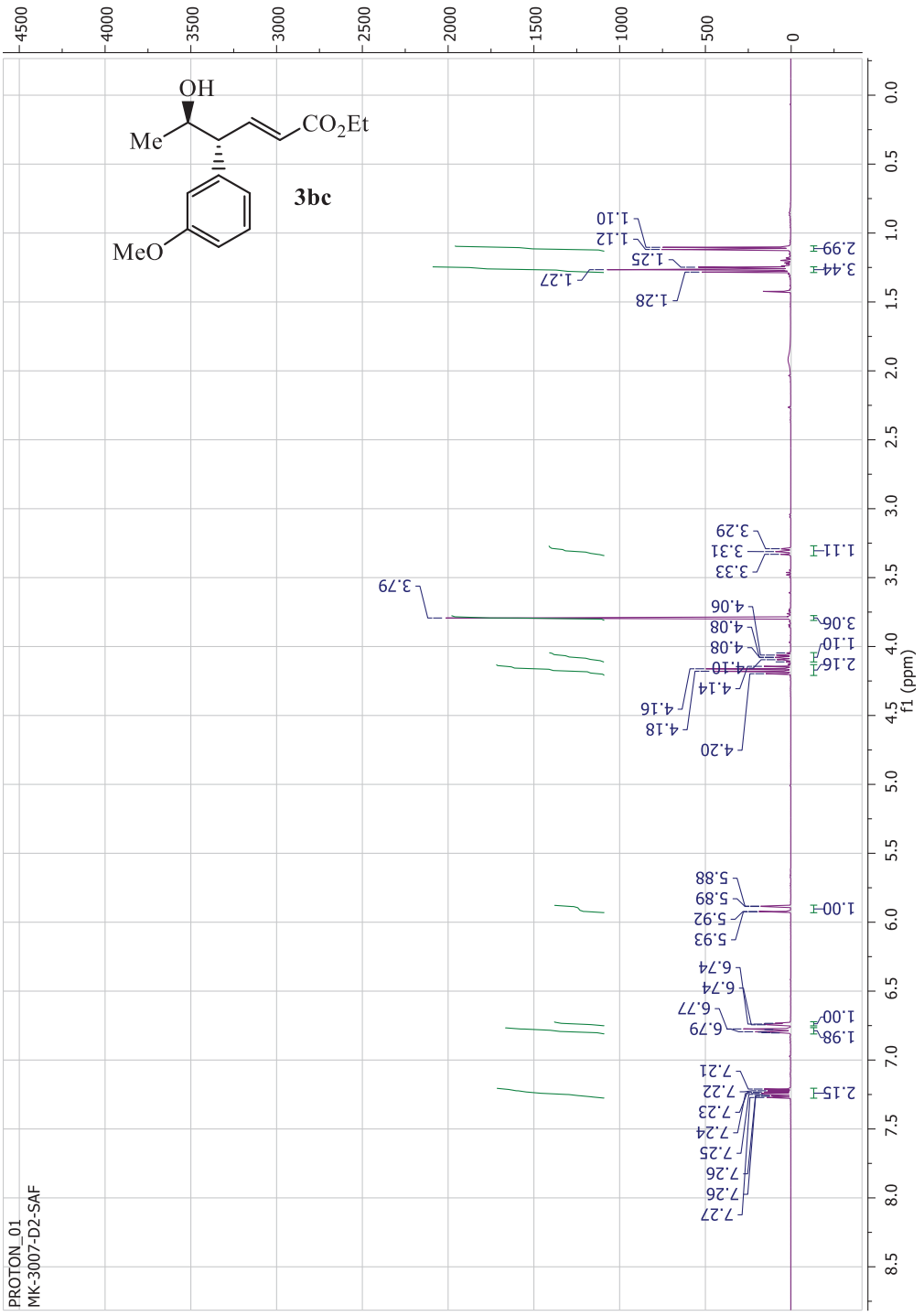

OH
Me
CO_2Bu^t
3fa
PROTON_01
YB-3fb
f1 (ppm)

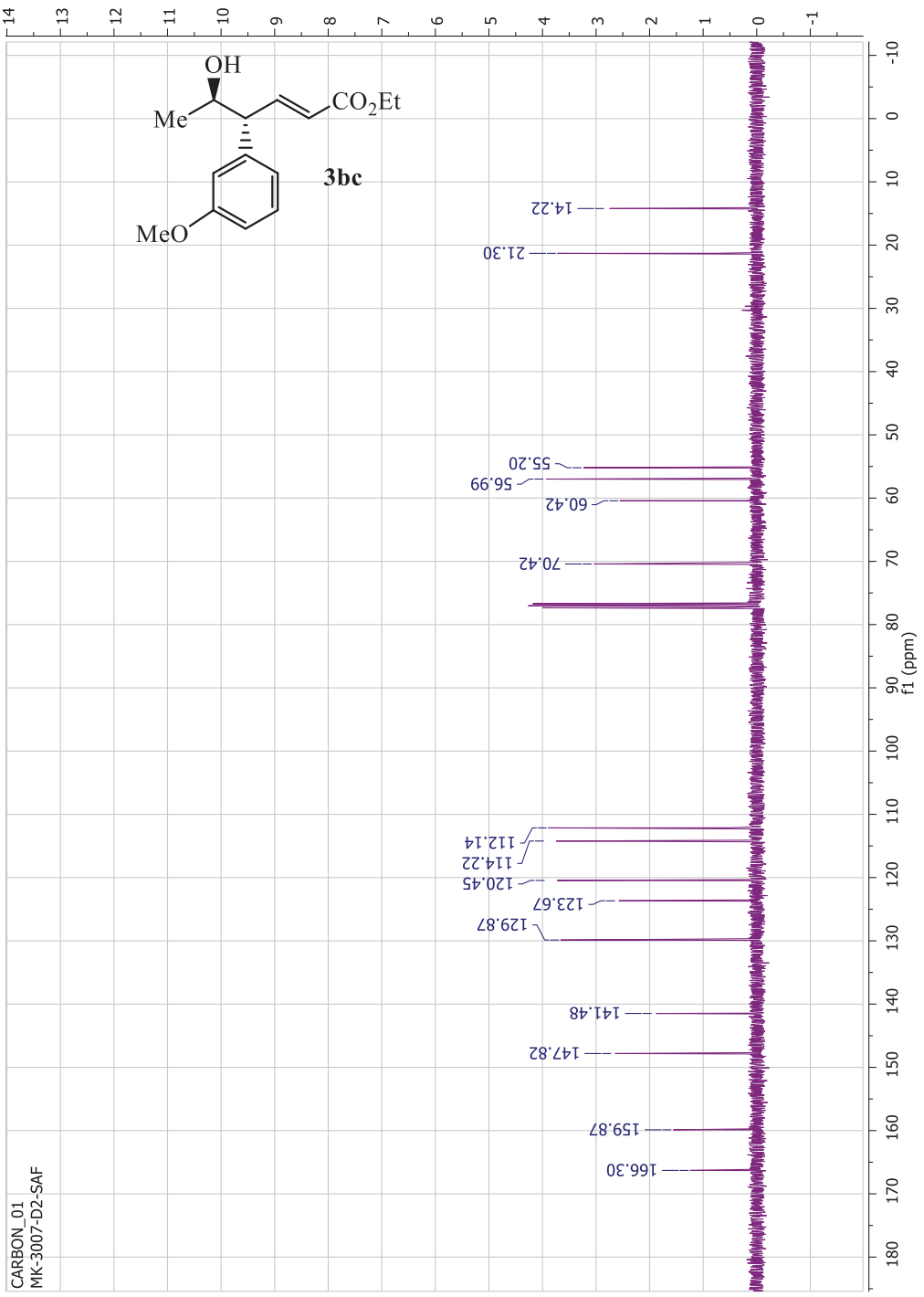

OH
Me
CO_2Bu^t
3fa
28.10
21.19
56.99
70.47
80.48
125.43
127.12
128.19
128.85
140.06
146.66
165.62
f1 (ppm)
CARBON_01
YB-3fb


OH
Me
CO2Et
CF3
3bd
PROTON_01
YB-3be
f1 (ppm)


OH
Me
CO2Et
CF3
3bd
14.20
21.47
56.50
60.56
70.28
122.65
124.40
125.35
125.72
125.76
125.79
125.83
128.34
129.36
129.68
144.04
146.62
166.01
CARBON_01
YB-3be
f1 (ppm)

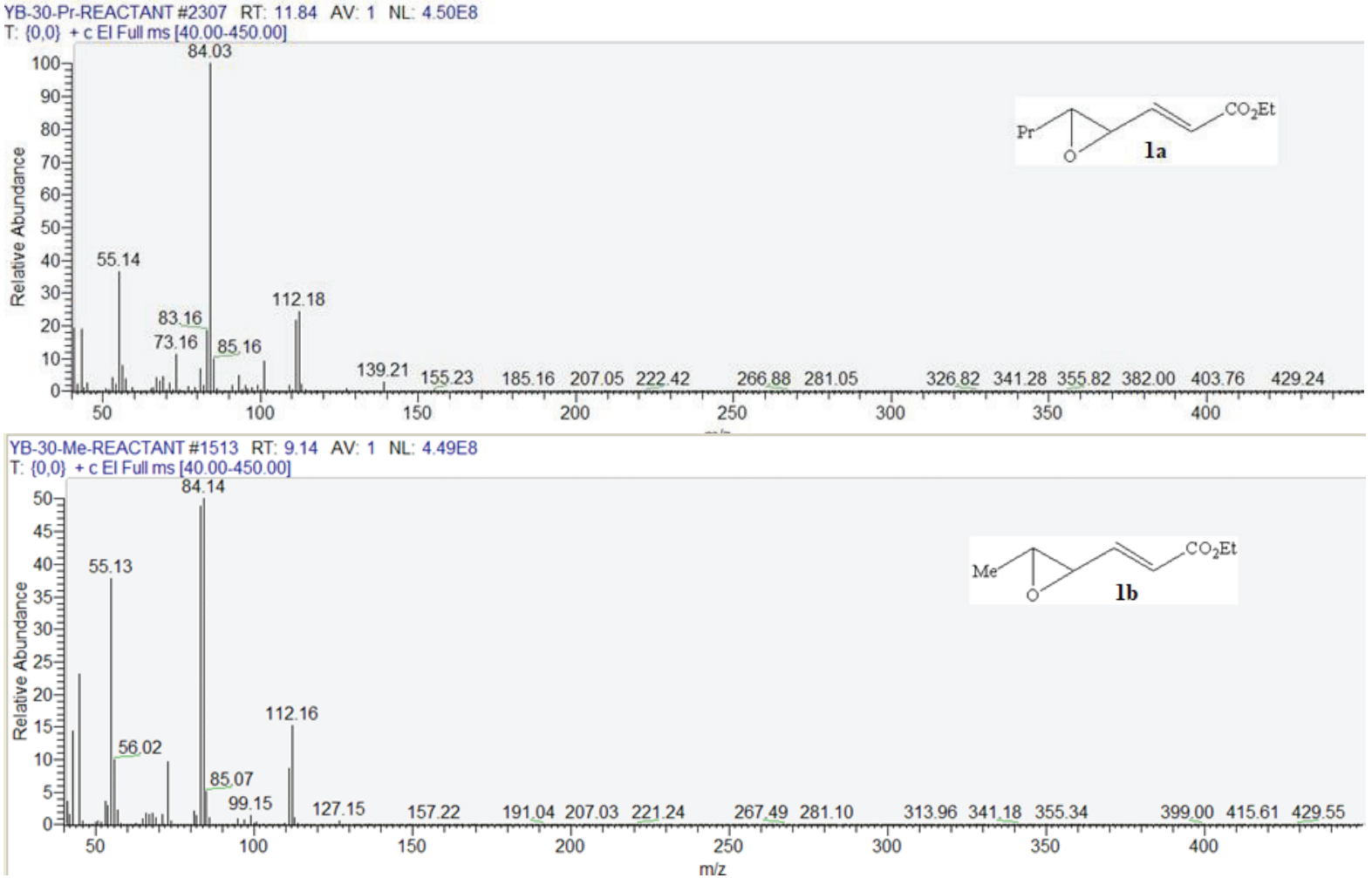

FLUORINE_01
MK-FLOR-3be
-62.60
3bd
f1 (ppm)


OH
Me
CO2Et
3bc
MeO
PROTON_01
MK-3007-D2-SAF
f1 (ppm)


OH
Me
CO2Et
3bc
MeO
14.22
21.30
55.20
56.99
60.42
70.42
112.14
114.22
120.45
123.67
129.87
141.48
147.82
159.87
166.30
CARBON_01
MK-3007-D2-SAF
f1 (ppm)

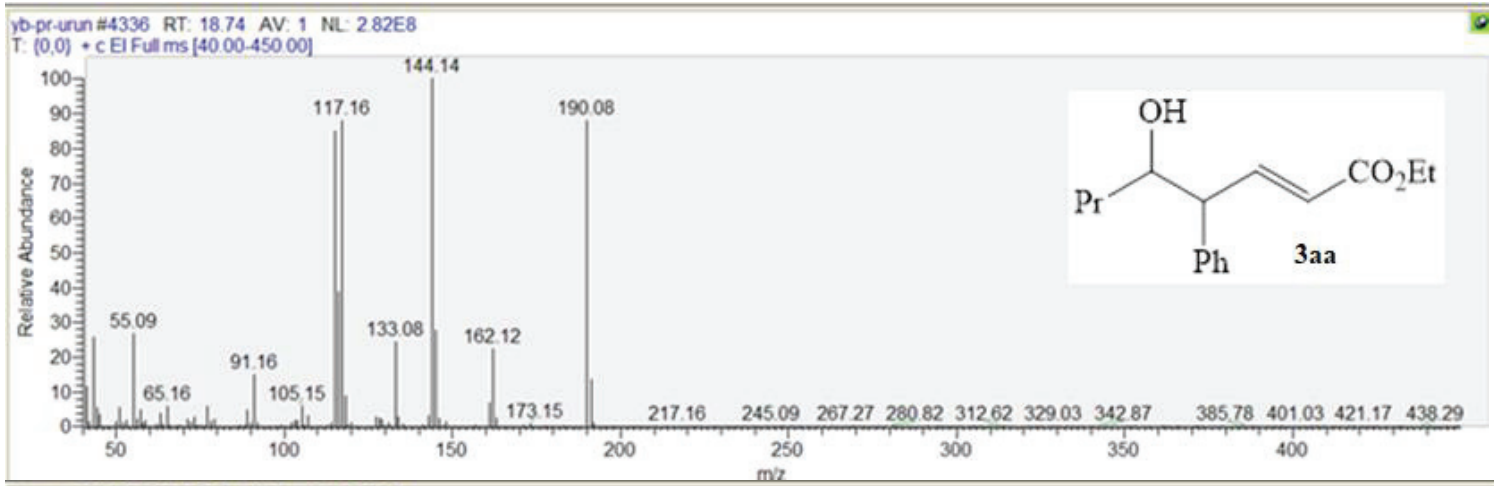
APPENDIX C

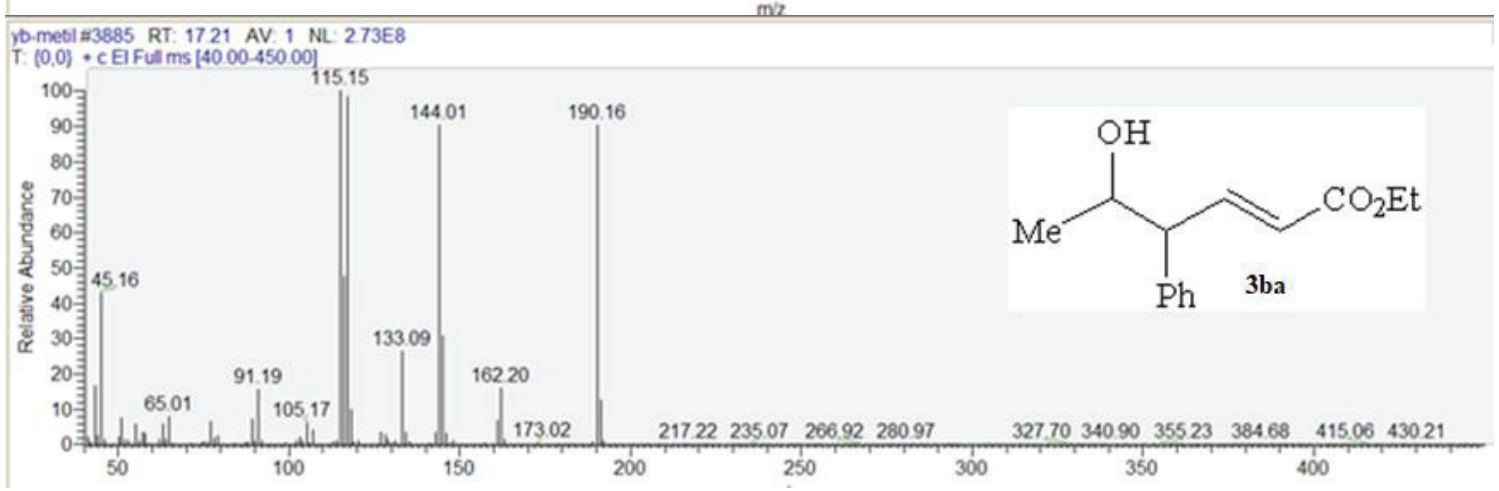
MASS SPECTRUMS OF VINYL OXIRANES

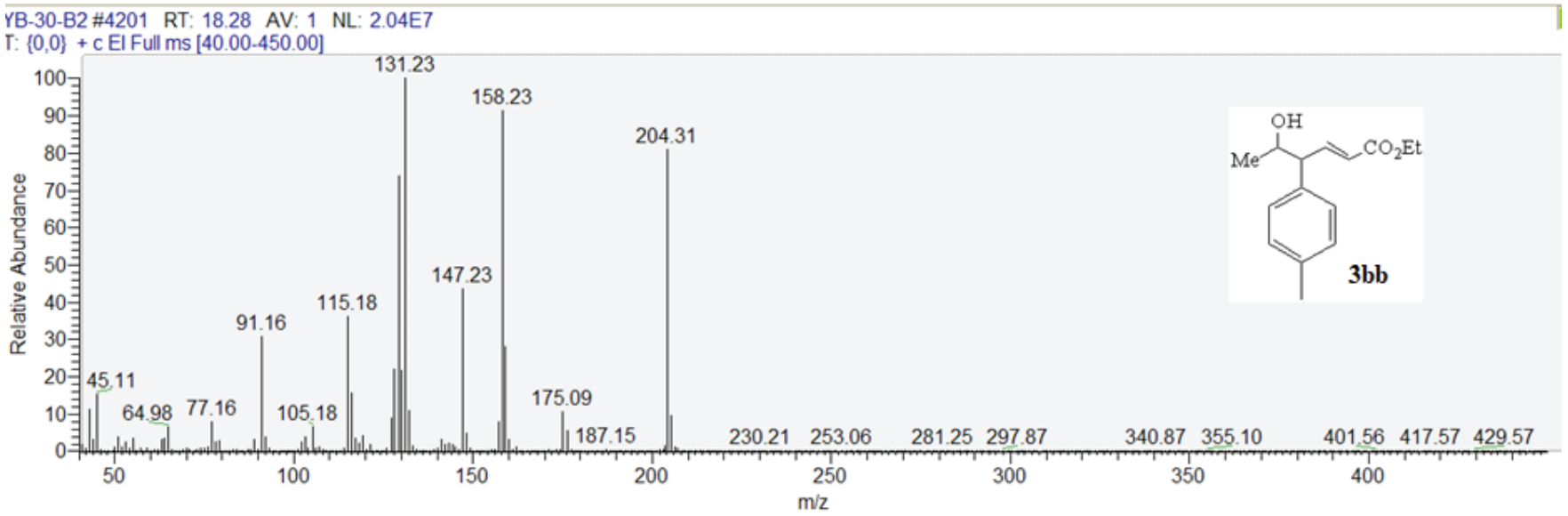

YB-30-Pr-REACTANT #2307 RT: 11.84 AV: 1 NL: 4.50E8
T: {0,0} + c EI Full ms [40.00-450.00]
Relative Abundance
84.03
55.14
83.16
73.16
85.16
112.18
139.21
155.23
185.16
207.05
222.42
266.88
281.05
326.82
341.28
355.82
382.00
403.76
429.24
Pr
CO2Et
1a
YB-30-Me-REACTANT #1513 RT: 9.14 AV: 1 NL: 4.49E8
T: {0,0} + c EI Full ms [40.00-450.00]
Relative Abundance
84.14
55.13
56.02
85.07
99.15
112.16
127.15
157.22
191.04
207.03
221.24
267.49
281.10
313.96
341.18
355.34
399.00
415.61
429.55
Me
CO2Et
1b
m/z

APPENDIX D

MASS SPECTRUMS OF PRODUCTS

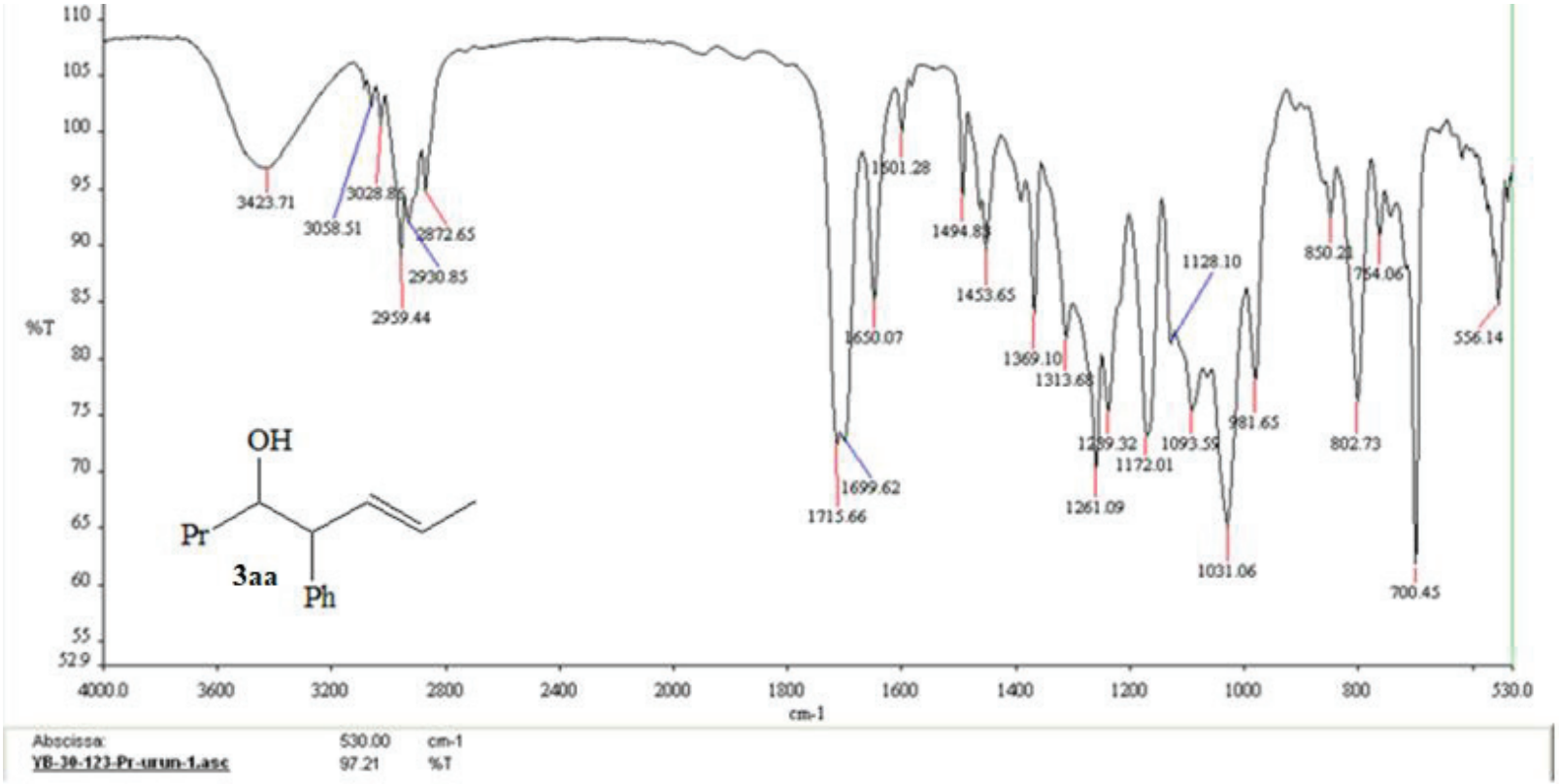

yb-pr-urun #4336 RT: 18.74 AV: 1 NL: 2.82E8
T: {0,0} + c EI Full ms [40.00-450.00]
Relative Abundance
m/z
144.14
117.16
190.08
55.09
133.08
162.12
91.16
65.16
105.15
173.15
217.16
245.09
267.27
280.82
312.62
329.03
342.87
385.78
401.03
421.17
438.29
OH
Pr
CO2Et
Ph
3aa

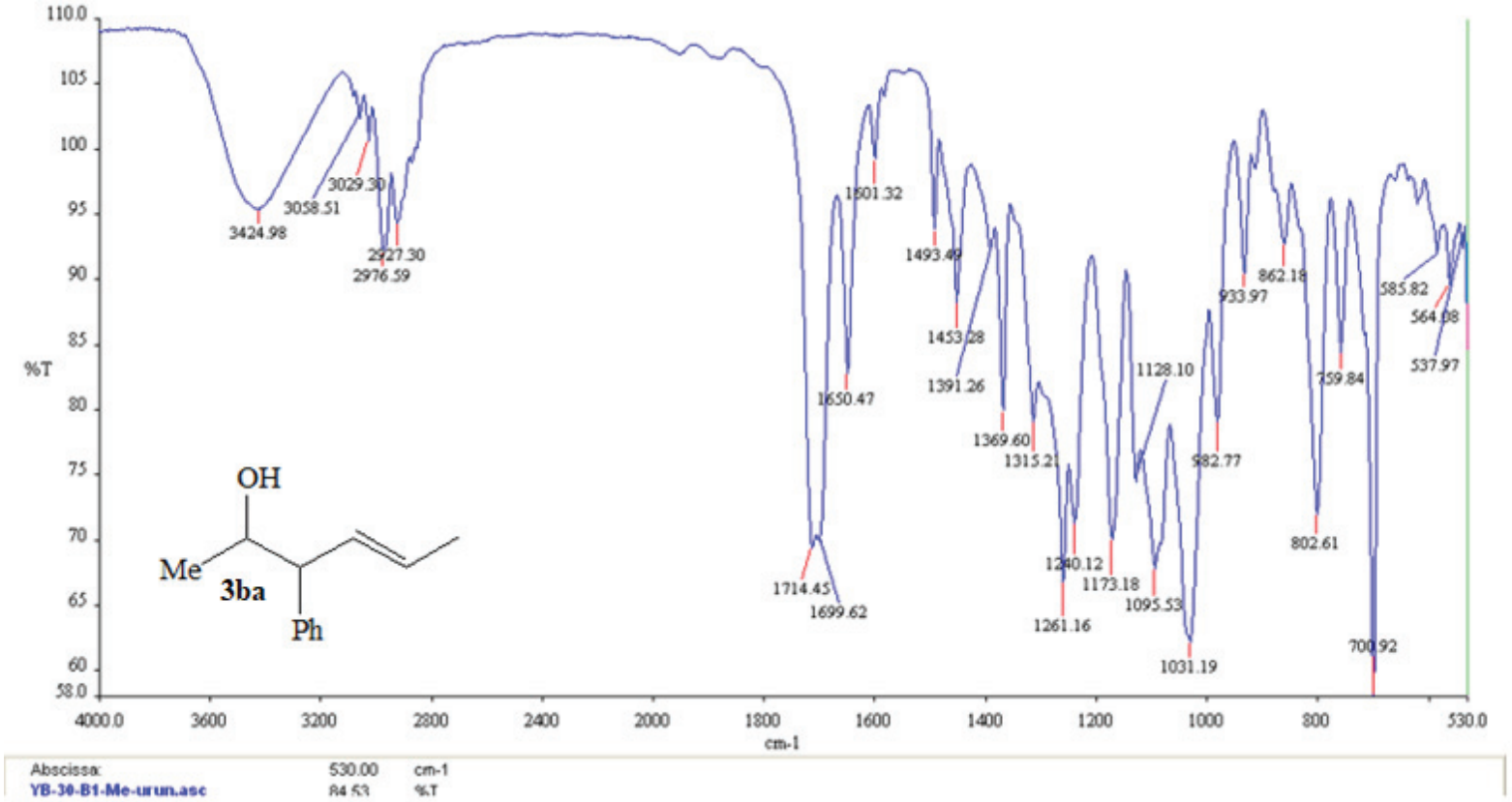

yb-metbl #3885 RT: 17.21 AV: 1 NL: 2.73E8
T: {0,0} + c EI Full ms [40.00-450.00]
Relative Abundance
115.15
144.01
190.16
45.16
133.09
91.19
162.20
65.01
105.17
173.02
217.22
235.07
266.92
280.97
327.70
340.90
355.23
384.68
415.06
430.21
OH
Me
CO2Et
Ph
3ba

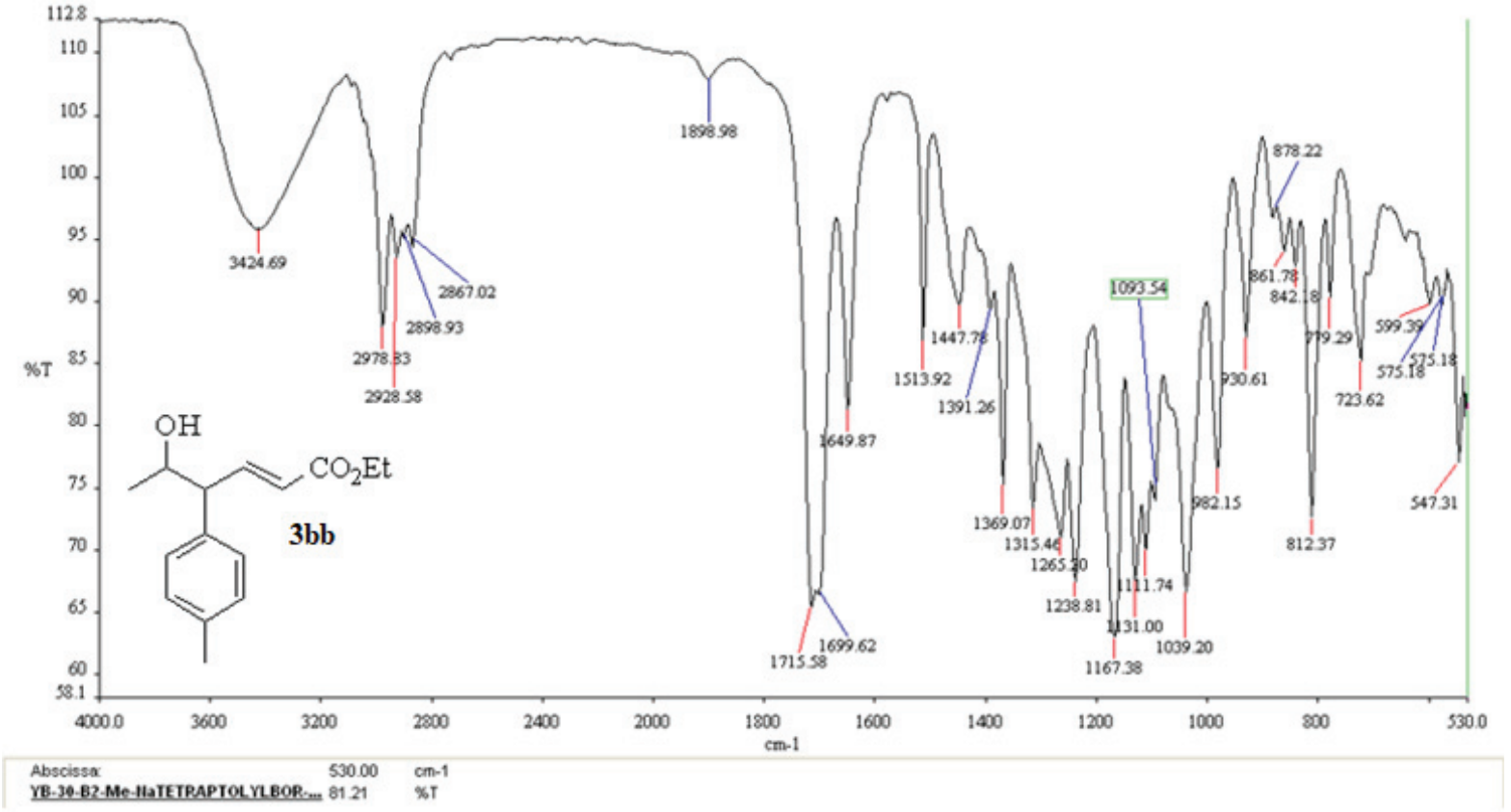

YB-30-B2 #4201 RT: 18.28 AV: 1 NL: 2.04E7
T: {0,0} + c EI Full ms [40.00-450.00]
Relative Abundance
m/z
131.23
158.23
204.31
147.23
115.18
91.16
45.11
64.98
77.16
105.18
175.09
187.15
230.21
253.06
281.25
297.87
340.87
355.10
401.56
417.57
429.57
OH
Me
CO2Et
3bb

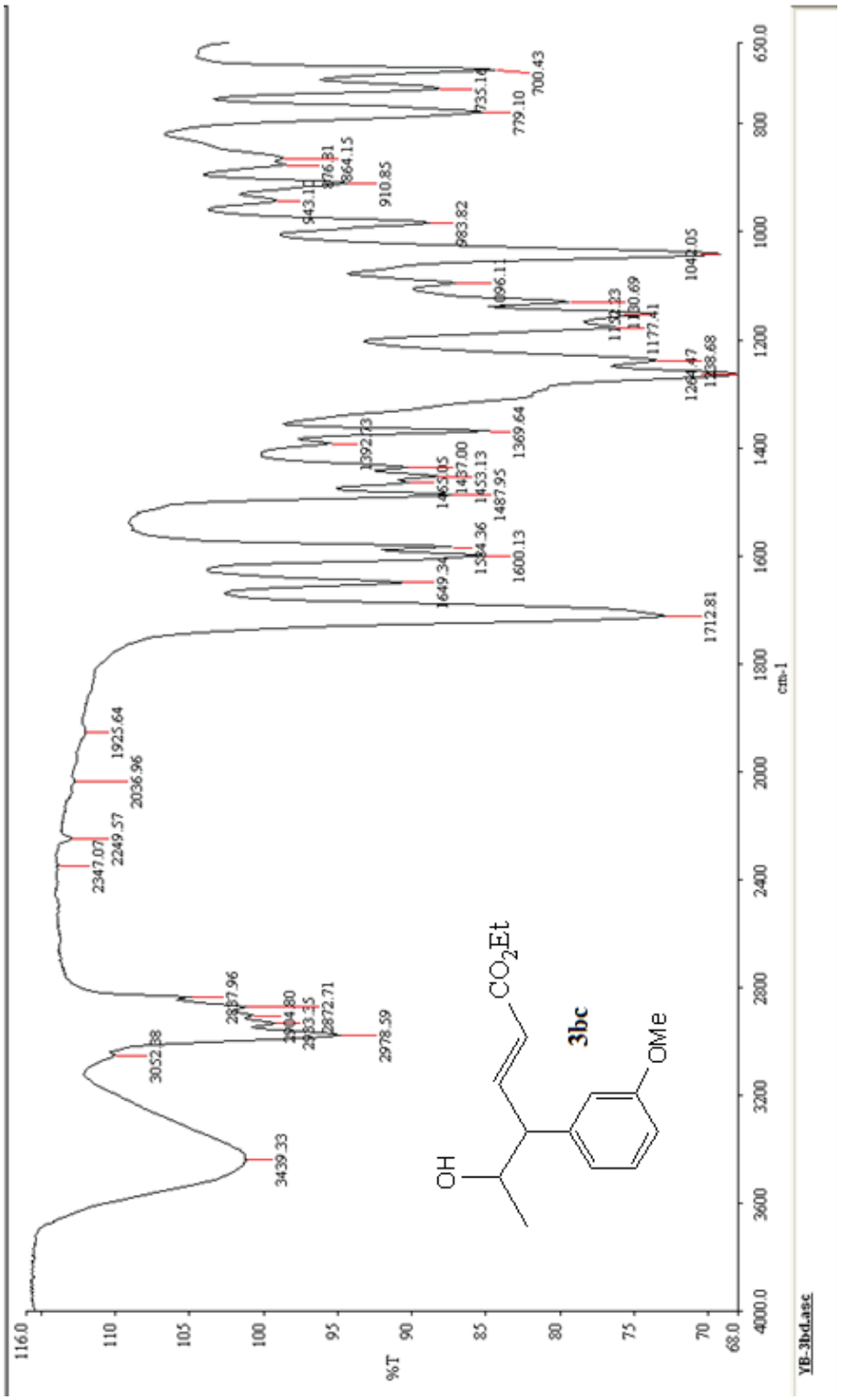
APPENDIX E

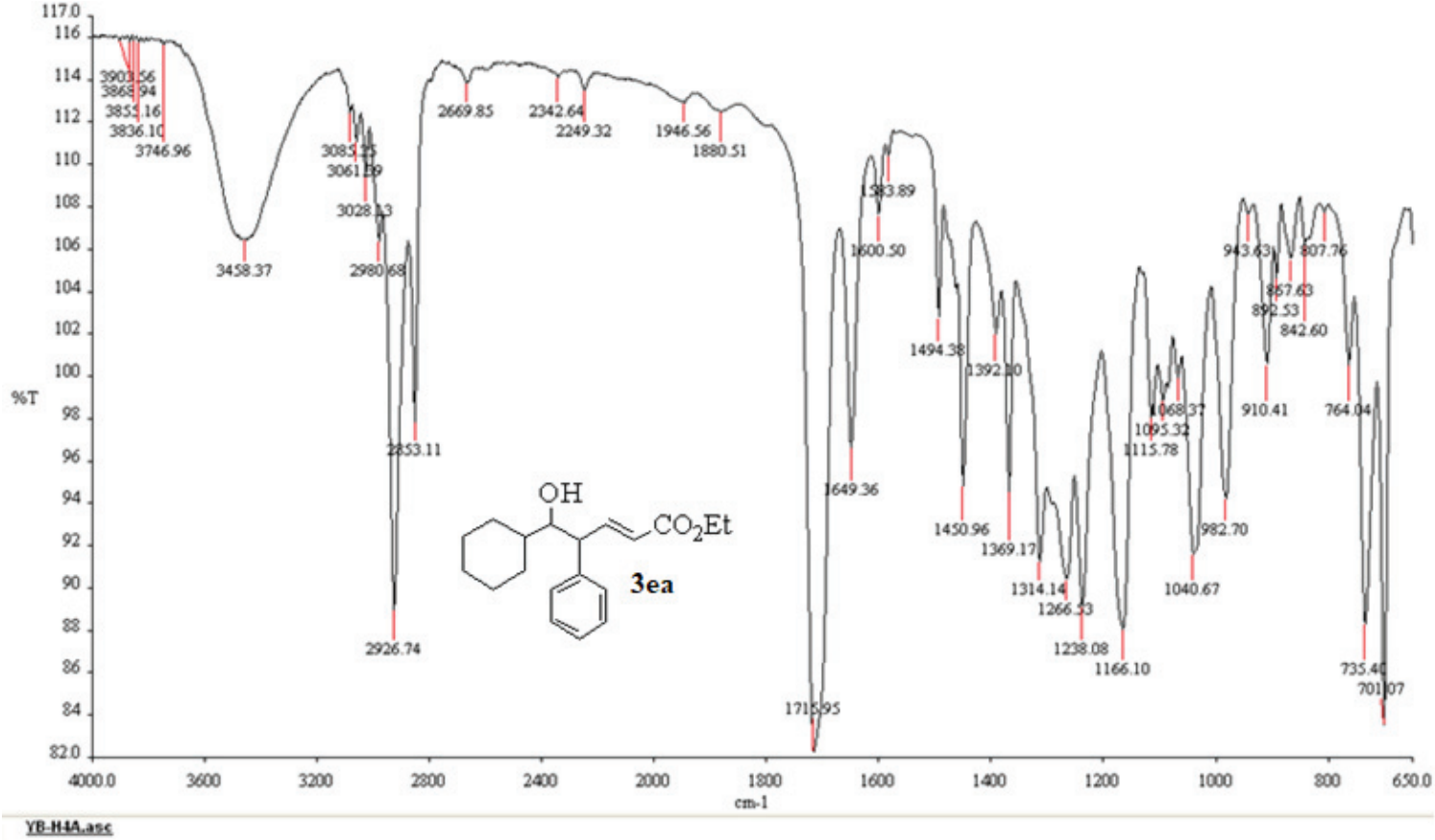
FTIR SPECTRUMS OF PRODUCTS

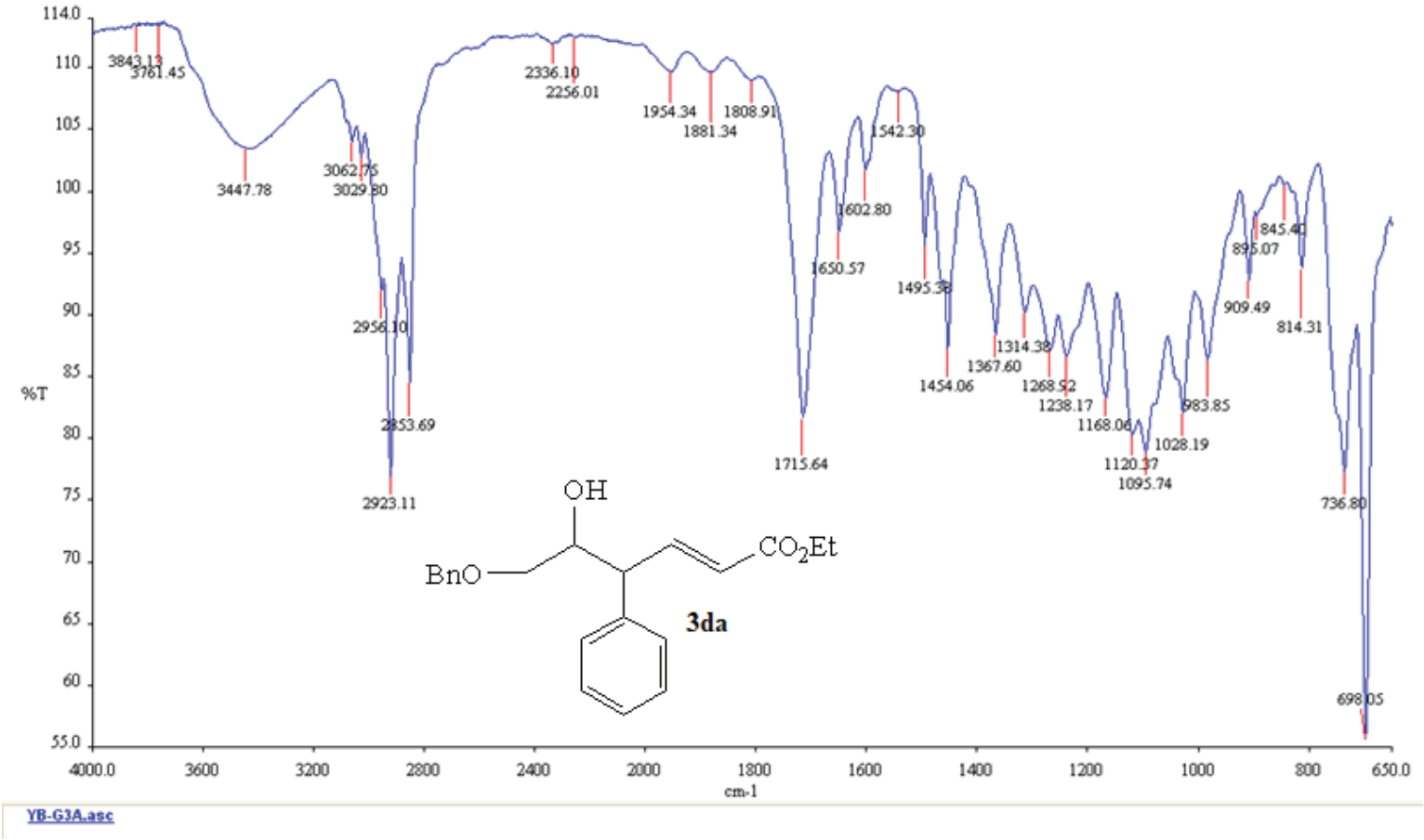

%T
cm-1
3423.71
3058.51
3028.86
2959.44
2930.85
2872.65
1715.66
1699.62
1650.07
1601.28
1494.83
1453.65
1369.10
1313.68
1261.09
1172.01
1128.10
1093.59
1031.06
981.65
850.23
802.73
754.06
700.45
556.14
OH
Pr
Ph
3aa
Abscissa: 530.00 cm-1
YB-30-123-Pr-urun-1.asc 97.21 %T

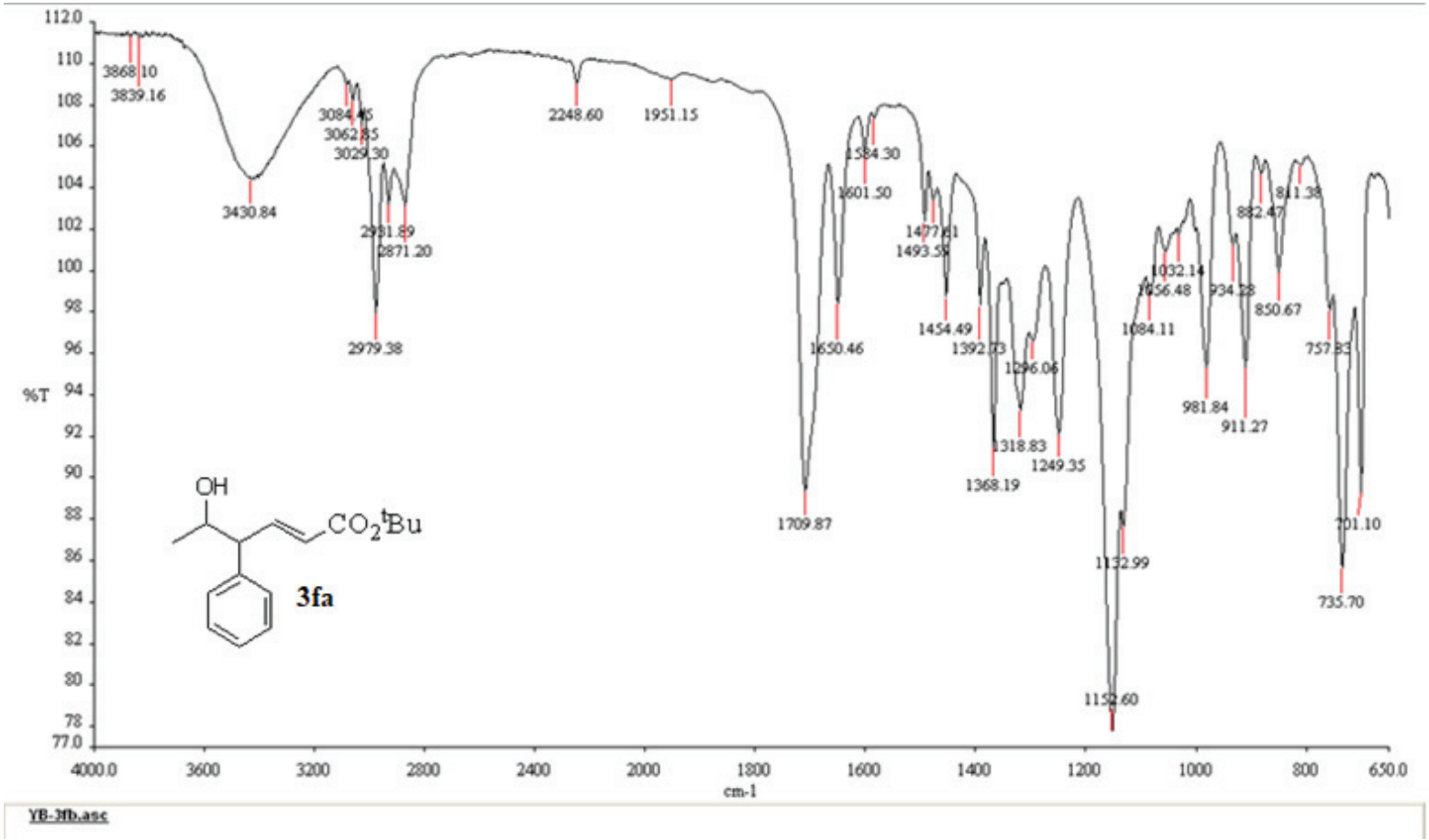

110.0
105
100
95
90
85
80
75
70
65
60
58.0
%T
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
530.0
cm-1
3424.98
3058.51
3029.30
2927.30
2976.59
1714.45
1699.62
1650.47
1601.32
1493.49
1453.28
1391.26
1369.60
1315.21
1261.16
1240.12
1173.18
1128.10
1095.53
1031.19
982.77
933.97
862.18
802.61
759.84
700.92
585.82
564.08
537.97
OH
Me
3ba
Ph
Abscissa:
530.00
cm-1
YB-30-B1-Me-urun.asc
%T

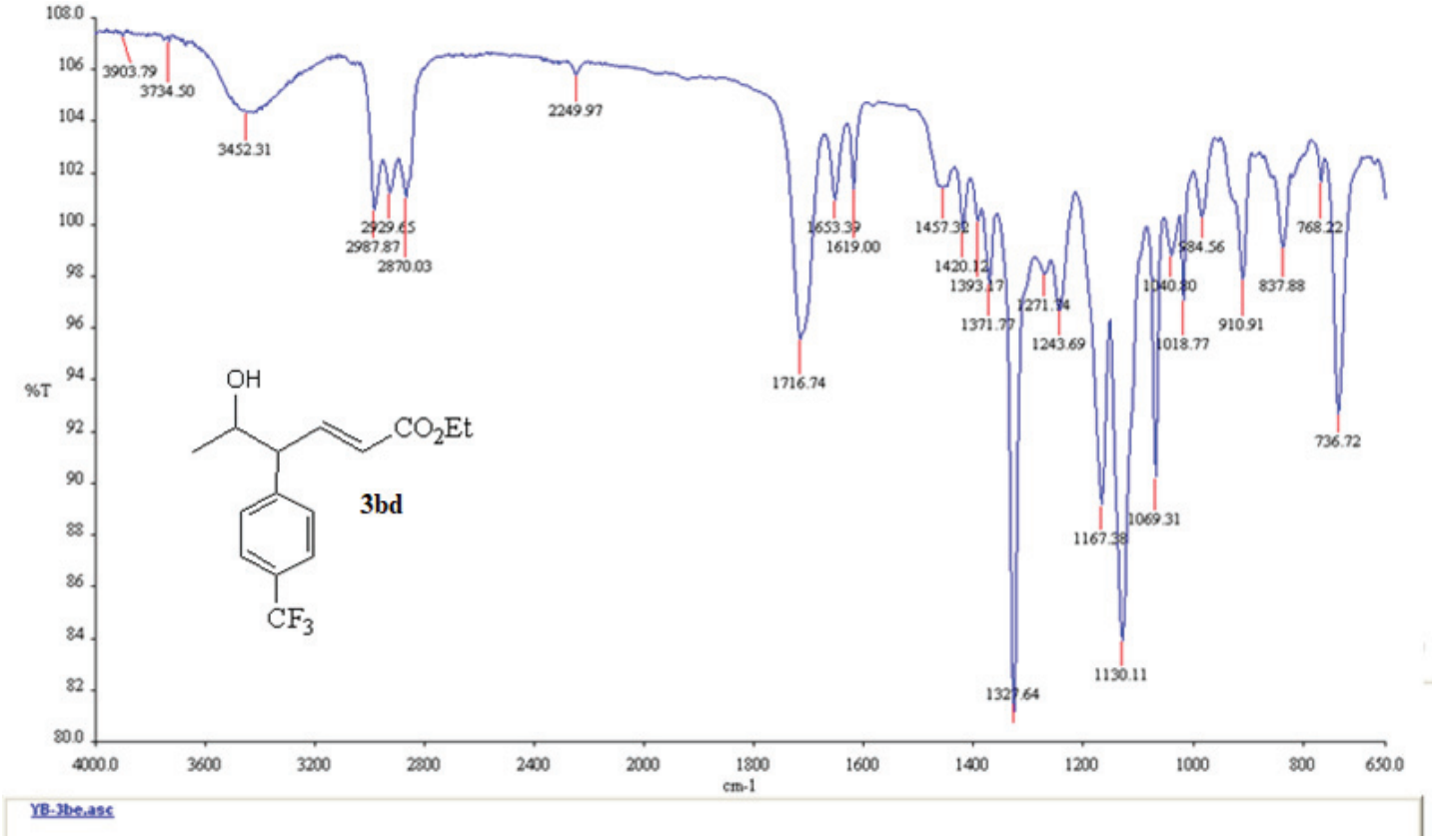

112.8
110
105
100
95
90
85
80
75
70
65
60
58.1
%T
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
530.0
cm-1
3424.69
2978.33
2928.58
2898.93
2867.02
1898.98
1715.58
1699.62
1649.87
1513.92
1447.78
1391.26
1369.07
1315.46
1265.20
1238.81
1167.38
1131.00
1111.74
1093.54
1039.20
982.15
930.61
878.22
861.78
842.18
812.37
779.29
723.62
599.39
575.18
547.31
OH
CO2Et
3bb
Abscissa: 530.00 cm-1
YB-30-B2-Me-NaTETRAPTOLYLBOR-... 81.21 %T


%T
cm-1
YB-3bd.asc
3439.33
3052.88
2978.59
2925.64
2036.96
2347.07
2249.57
1712.81
1649.34
1600.13
1584.36
1487.95
1453.13
1437.00
1369.64
1092.73
910.85
983.82
779.10
735.14
700.43
OH
CO2Et
OMe
3bc


%T
cm-1
3746.96
3458.37
2926.74
2853.11
2669.85
2342.64
2249.32
1946.56
1880.51
1715.95
1649.36
1600.50
1583.89
1494.38
1450.96
1392.20
1369.17
1314.14
1266.53
1238.08
1166.10
1115.78
1095.32
1068.37
1040.67
982.70
943.63
910.41
892.53
857.63
842.60
807.76
764.04
735.40
701.07
OH
CO2Et
3ea
YB-H4A.asc

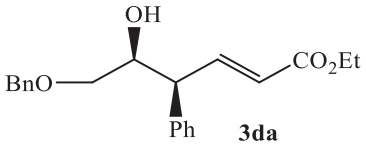

3843.13
3761.45
3447.78
3062.75
3029.80
2956.10
2923.11
2853.69
2336.10
2256.01
1954.34
1881.34
1808.91
1715.64
1650.57
1602.80
1542.30
1495.38
1454.06
1367.60
1314.38
1268.92
1238.17
1168.06
1120.37
1095.74
1028.19
983.85
909.49
895.07
845.40
814.31
736.80
698.05
%T
cm-1
OH
BnO
CO2Et
3da
YB-G3A.asc


3868.10
3839.16
3430.84
3084.45
3062.85
3029.30
2931.89
2871.20
2979.38
2248.60
1951.15
1709.87
1650.46
1584.30
1601.50
1477.61
1493.58
1454.49
1392.73
1368.19
1318.83
1296.06
1249.35
1152.60
1132.99
1084.11
1056.48
1032.14
981.84
934.28
911.27
882.47
850.67
841.38
757.83
735.70
701.10
%T
cm-1
OH
CO2tBu
3fa
YB-3fb.asc

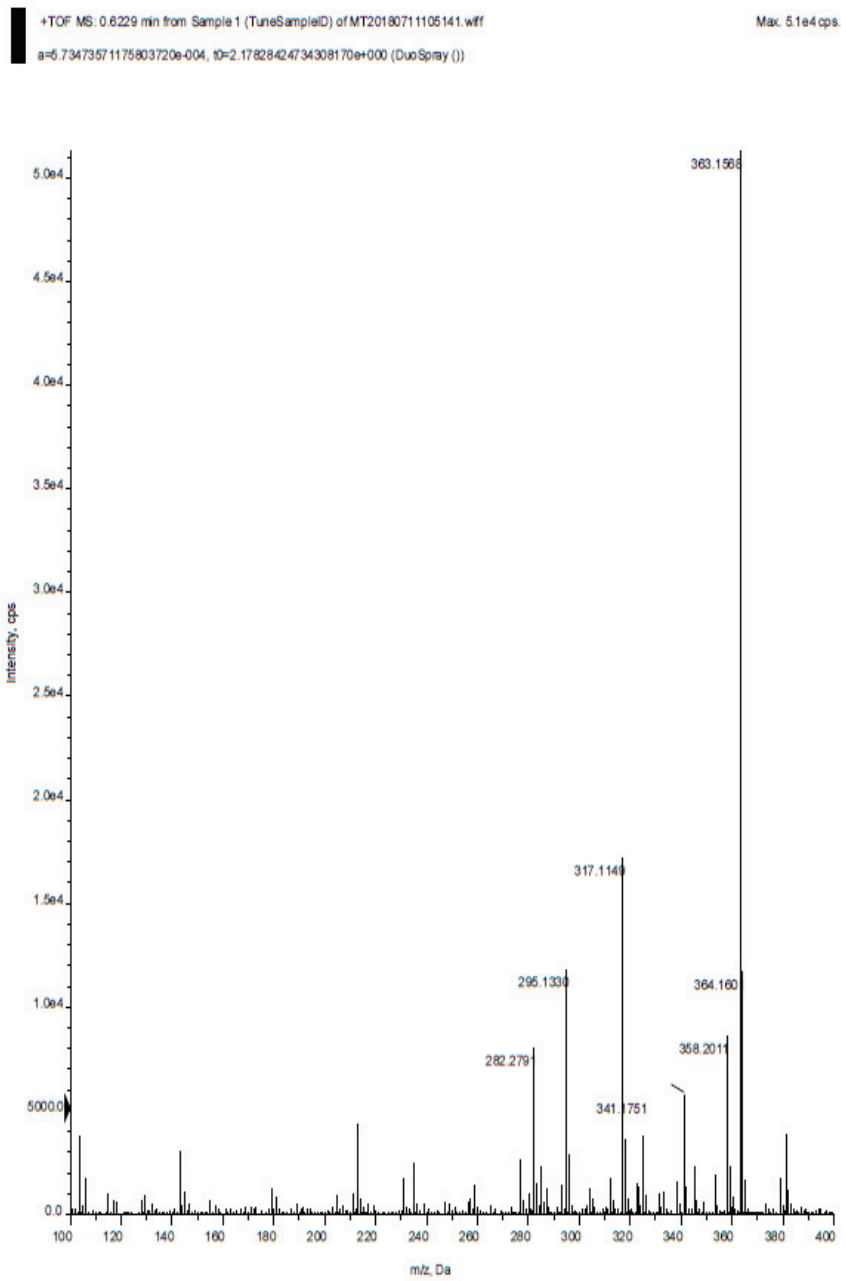

3903.79
3734.50
3452.31
2929.65
2987.87
2870.03
2249.97
1716.74
1653.39
1619.00
1457.32
1420.12
1393.17
1371.77
1327.64
1271.34
1243.69
1167.38
1130.11
1069.31
1040.80
1018.77
984.56
910.91
837.88
768.22
736.72
%T
cm-1
OH
CO2Et
CF3
3bd
YB-3be.asc

APPENDIX F

HRMS SPECTRUMS OF PRODUCT

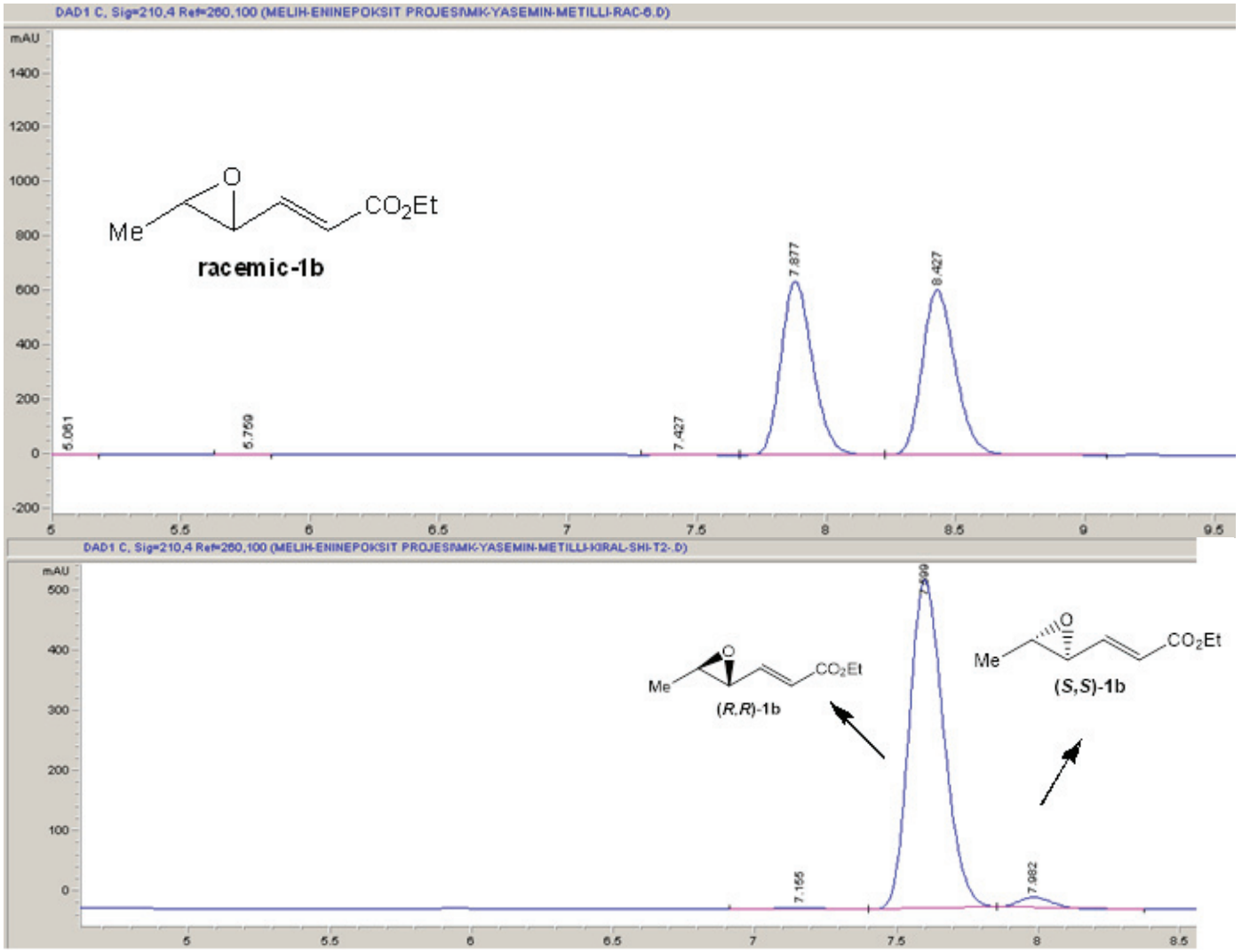

OH
BnO
CO2Et
Ph

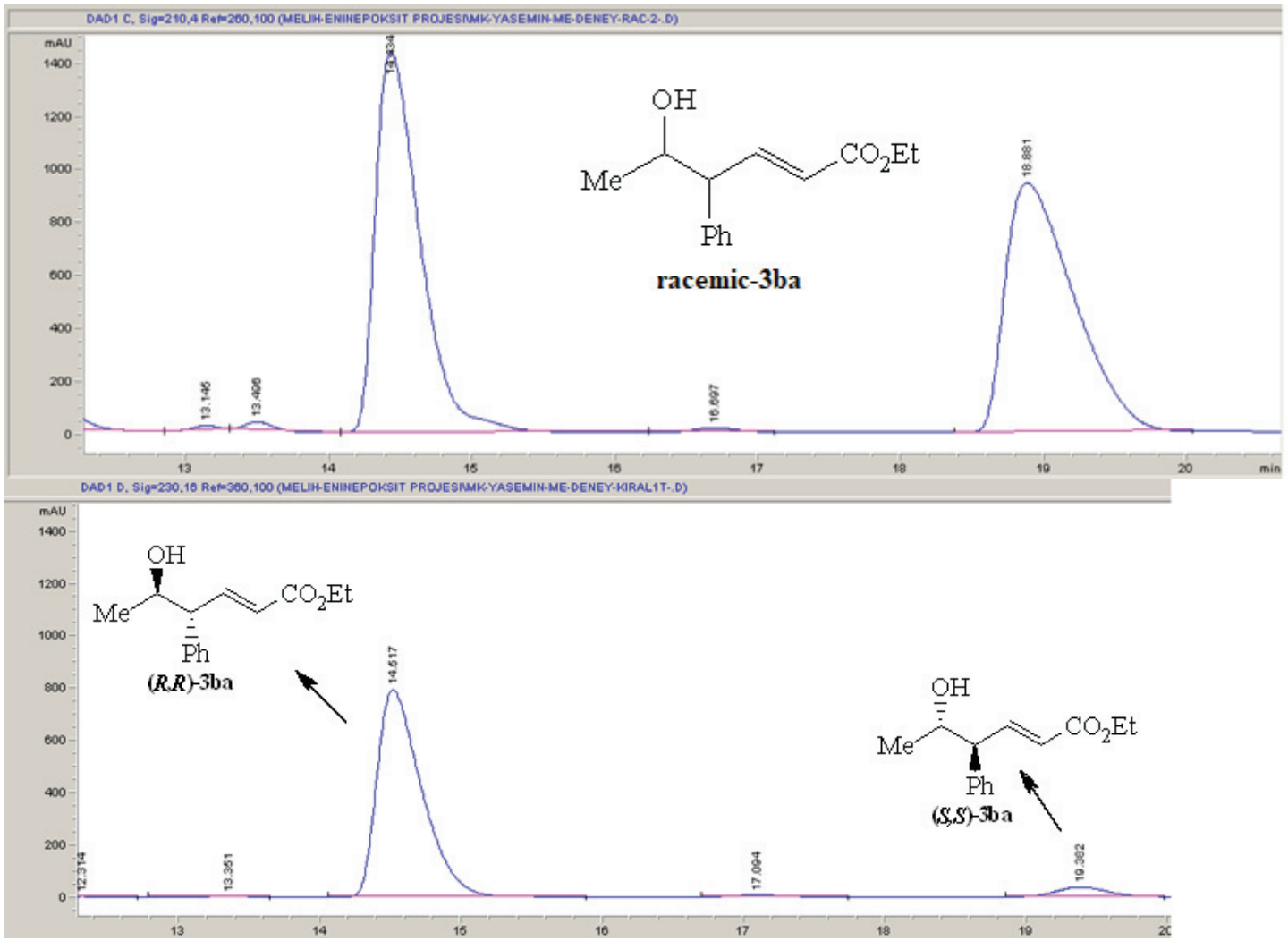
3da


+TOF MS: 0.6229 min from Sample 1 (TuneSampleID) of MT20180711105141.wiff
Max. 5.1e4 cps.
a=6.7347357117580372e-004, t0=2.1782842473430817e+000 (DuoSpray ())
Intensity, cps
m/z, Da
363.1566
317.1149
295.1330
364.160
358.2011
282.279
341.1751

APPENDIX G

HPLC CHROMOTOGRAMS


DAD1 C, Sig=210,4 Ref=260,100 (MELIH-ENINEPOKSIT PROJESI\MK-YASEMIN-METILLI-RAC-6.D)
mAU
racemic-1b
Me
CO2Et
6.061
6.759
7.427
7.877
8.427
DAD1 C, Sig=210,4 Ref=260,100 (MELIH-ENINEPOKSIT PROJESI\MK-YASEMIN-METILLI-KIRAL-SHI-T2-.D)
(R,R)-1b
(S,S)-1b
7.165
7.599
7.982


DAD1 C, Sig=210,4 Ref=260,100 (MELIH-ENINEPOKSIT PROJESI\MK-YASEMIN-ME-DENEY-RAC-2-.D)
mAU
13.145
13.406
13.434
16.697
18.881
racemic-3ba
DAD1 D, Sig=230,16 Ref=360,100 (MELIH-ENINEPOKSIT PROJESI\MK-YASEMIN-ME-DENEY-KIRAL1T-.D)
(R,R)-3ba
12.314
13.351
14.517
17.094
19.392
(S,S)-3ba
min