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BISMUTH-MEDIATED ORGANOMETALLIC REACTIONS IN AQUEOUS MEDIA

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Master of Science

by

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Abstract

Recently, organometallic reactions in aqueous media have received considerable attention in organic synthesis because of environmental and economical concerns and synthetic efficiency. In this connection, the synthetic utility of environmentally benign non-toxic bismuth metal for aqueous organometallic reactions is investigated. Bismuth metal activated by ammonium hydrogen fluoride can efficiently reduce a wide variety of α-halocarbonyl compounds in aqueous media to provide the corresponding dehalogenated reduction products in excellent yields. Zinc fluoride is also found to be effective in activating bismuth to mediate the crossed aldol type reactions of diverse α-bromocarbonyl compounds with aldehydes in aqueous media to afford the corresponding β-hydroxycarbonyl compounds in moderate to high yields. The scope of bismuth-mediated aqueous organometallic reactions is successfully extended to the Reformatsky type reactions. The factors that affect the reactivity of these reactions are examined and plausible reaction mechanisms are proposed.

Résumé

Récemment, les réactions organométalliques en milieu aqueux utilisées en synthèse organique ont fait l'objet de beaucoup d'intérêt, du fait de leur impact sur l'environnement, de leur coût, ainsi que de leur efficacité. Parmi ces réactions, nous avons envisagé l'utilisation du bismuth métallique, métal non toxique pour l'environnement. En effet, le bismuth métallique, une fois activé par le fluorure d'ammonium, permet de réduire une grande variété de composés α-halogénés en milieu aqueux en leurs dérivés non halogénés avec d'excellents rendements. Le bismuth métallique, activé cette fois par le fluorure de zinc a aussi permis de synthétiser des dérivés β-hydroxycarbonylés, par des réactions d'aldolisation ou apparentés entre des composés α-bromocarbonylés et divers aldehydes. Les rendements varient entre moyen et très bons. L'utilisation du bismuth en milieu aqueux a été étendue avec succès à des réactions de type Reformastsky. Les facteurs qui affectent la réactivité de ces réactions sont étudiés, et des mécanismes plausibles sont proposés.

List of Abbreviations

br	broad
CI	chemical ionization
δ	chemical shift
d	doublet
eq.	equivalent
FAB	fast atom bombardment
J	coupling constant
mp	melting point
MS	mass spectroscopy
HRMS	high resolution mass spectroscopy
hr	hour
Hz	herz
IR	infrared spectroscopy
m	multiplet
ppm	parts per million
q	quartet
quint	quintet
r. t.	room temperature
s	singlet
sept	septet
SET	single electron transfer
t	triplet

Chapter 1.

Introduction

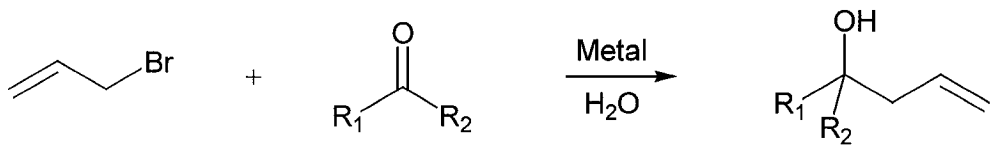
1.1. Organometallic Reactions in Aqueous Media

Organometallic chemistry bridges both organic and inorganic chemistry by considering compounds containing direct metal-carbon bonds. Since the discovery of the formation of alkylzinc compounds by Frankland in 1849,[1] organometallic chemistry has grown rapidly and become one of the most important parts in organic chemistry. In general, organometallic reactions can be carried out more efficiently under milder reaction conditions with a wider array of substances than other alternative methods due to the high reactivity of active metals. However, most of organometallic compounds should be prepared and treated under strictly anhydrous conditions because of their sensitivity to moisture.

Recently, organometallic reactions in aqueous media have attracted considerable interest in organic synthesis. Such reactions in aqueous media may offer several significant advantages over conventional organometallic reactions in anhydrous organic solvents. There are possible environmental and economical benefits and the practical convenience of not having to use inflammable anhydrous organic solvents and a troublesome inert atmosphere. The tedious task of protection-deprotection processes for certain functional groups, such as reactive hydroxy or acidic functional groups, often encountered in organic synthesis may be avoided, which contributes to the overall synthetic efficiency. Water-soluble compounds, such as carbohydrates, can be reacted directly without the need of derivatization. In addition, the regioselectivity and

stereoselectivity of organometallic reactions may alter due to the change from organic solvents to aqueous media, which offers new opportunities in organic synthesis.[2]

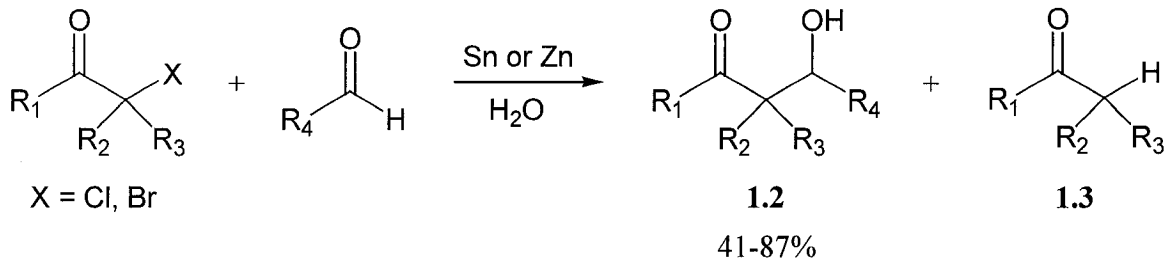
Among the wide variety of organic reactions, the development of organometallic reactions for carbon-carbon bond formation in aqueous media is one of the most intriguing challenges in organic synthesis. In particular, the metal-mediated Barbier type allylation reactions of carbonyl compounds in aqueous media have been extensively studied during the past two decades. Various metals, such as Zn,[3] Sn,[4] In,[5] Mn,[6] Sb,[7] Bi,[8] Pb,[9] and Mg,[10] have been reported to be effective in mediating the coupling between allyl halides and carbonyl compounds in aqueous media to give the corresponding homoallylic alcohols **1.1** (Scheme 1.1).



1.1

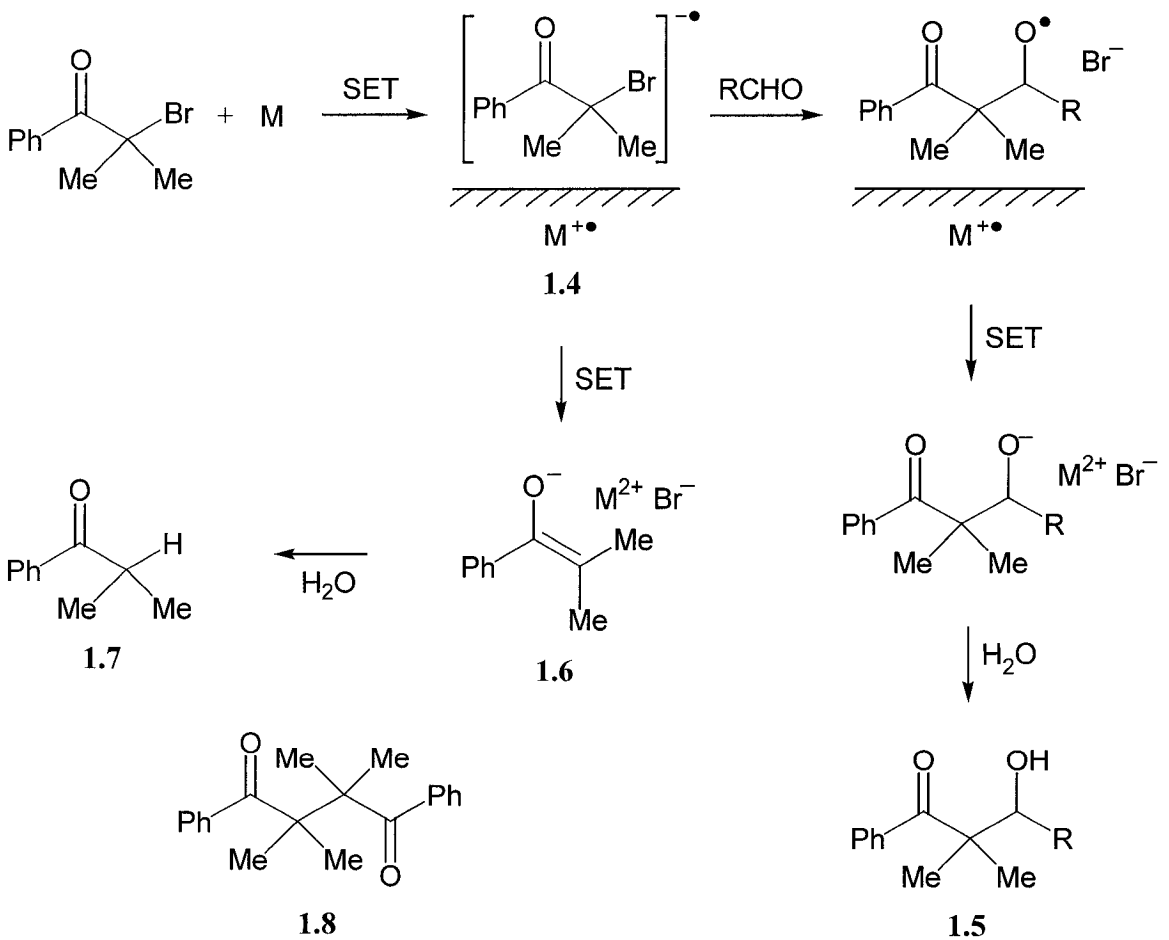
Scheme 1.1

The scope of organometallic reactions in aqueous media was successfully expanded to the crossed aldol type reaction, which is one of the most powerful tools for the formation of carbon-carbon bonds affording synthetically useful β-hydroxycarbonyl compounds. In 1990, Chan *et al.* reported that metallic zinc or tin could mediate the crossed aldol type reactions of α-halocarbonyl compounds with aldehydes in aqueous media to provide the corresponding crossed aldol products **1.2** in moderate to high yields together with the reduction products **1.3** as major side products (Scheme 1.2).[11]



Scheme 1.2

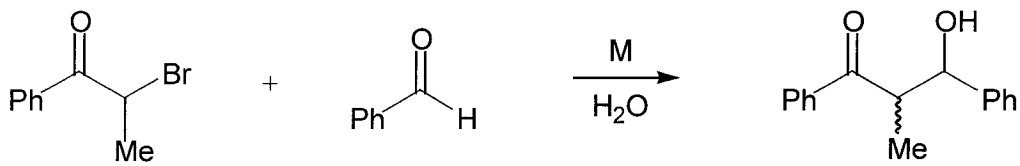
Based on their experimental observations, it was suggested that the aqueous crossed aldol type reaction proceeded by way of a single electron transfer (SET) on the metal surface involving the formation of a radical anionic intermediate **1.4** as outlined in Scheme 1.3.



Scheme 1.3

The proposed reaction mechanism shows that the reduction product **1.7** is more likely to be formed from a metal enolate intermediate **1.6**, which is a pathway apparently different from that giving the crossed aldol product **1.5**. In support of this mechanism, they obtained the compound **1.8** as a minor side product, which is presumably derived from the coupling of the radical intermediates.

A study on the crossed aldol type reaction mediated by indium in aqueous media was also reported by Chan's group.[12] The crossed aldol type reaction of α-bromopropiophenone **1.9** with benzaldehyde carried out with indium instead of zinc or tin in water resulted in a slight improvement in yield but a dramatic increase in diastereoselectivity (Scheme 1.4).



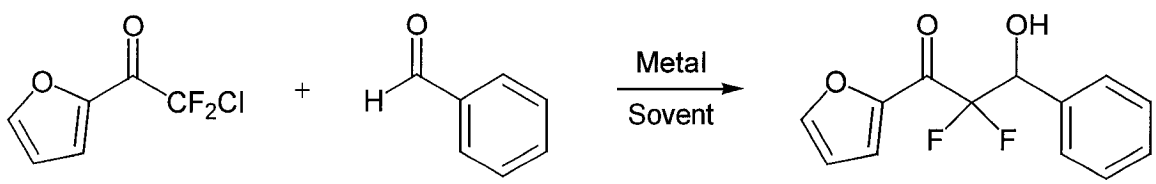
1.9 **1.10**

Method	Yield of **1.10** (%)	**1.10** (*erythro* : *threo*)
Zn, r. t.	82	2.5 : 1
Sn, 80 °C	67	1 : 1.1
In, r. t.	85	12 : 1

Scheme 1.4

Very recently, Chung *et al.* reported the synthetic utility of the indium-mediated crossed aldol type reaction in aqueous media for the introduction of a difluoromethylene functionality.[13] The crossed aldol type reaction of 2-chloro-2,2-difluoro-1-furan-2-yl ethanone **1.11** with benzaldehyde was examined using different metals under diverse

reaction conditions (Scheme 1.5). The crossed aldol type reaction mediated by indium in a mixture of H_2O and THF (4 : 1) at room temperature was found to be the method of choice. The generality of this procedure was illustrated by the reactions of the compound **1.11** with various aldehydes to afford the corresponding α,α-difluoro-β-hydroxyketones in moderate to good yields (42-80%). Moreover, the effect of solvent system on the reaction was systematically investigated in their study.

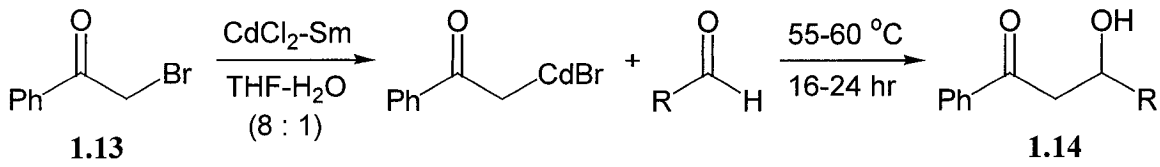


1.11 **1.12**

Metal	Solvet	Tempterature	Yield of **1.12** (%)
Zn (Cu)	DMF	Ultrasound	0
Zn (Cu)	DMF	70 °C	68
Zn / CuCl	Ether-THF (4 : 1)	Reflux	75
In	H_2O-THF (4 : 1)	r. t.	80

Scheme 1.5

Recently, Xu *et al.* discovered that the active metallic cadmium produced from cadmium chloride in the presence of samarium could mediate the crossed aldol type reactions of α-bromoacetophenone **1.13** with aromatic and aliphatic aldehydes in aqueous media under a nitrogen atmosphere to provide the corresponding β-hydroxyketones **1.14** in good yields (Scheme 1.6).[14]



1.13 **1.14**

55-75%

Scheme 1.6

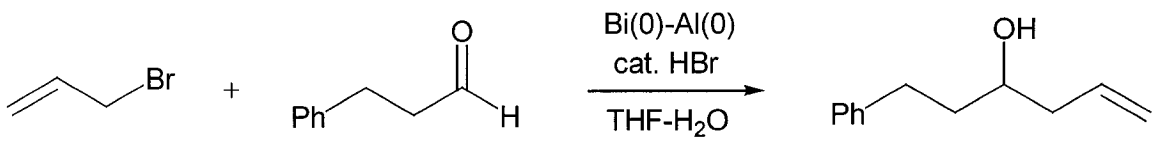
1.2. Bismuth-Mediated Organometallic Reactions in Aqueous Media

Bismuth belongs to the group 15 of the periodic table. Despite being in the same group, the properties of the elements vary to a considerable degree as the group descends. Thus, whereas nitrogen and phosphorus are typical non-metals, arsenic and antimony are usually classified as metalloids or semi-metals. Bismuth is clearly more metallic and has many properties associated with its metallic behavior.[15] Bismuth, the 83rd member of the periodic table, has an electron configuration of $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$ which results in the common oxidation states of +3 (III) and +5 (V). The stable form of bismuth is crystalline and has a grey metallic luster. Although bismuth is comparatively soft, it is brittle. Bismuth is as rare as silver, mercury and platinum, but it is not so expensive because large amounts are recovered as a by-product from the refining process of copper, lead, tin, zinc and silver ores.[16] In contrast to arsenic and antimony, bismuth has proven to be benign in its effects on humans. Compounds, such as bismuth subsalicylate, have been used for many years as a palliative for upset stomachs and intestinal distress as well as for outlining the alimentary tract during X-ray examination.[17]

Bismuth was already known in the Middle Ages and identified as a specific element in the middle of the eighteenth century. However, the usefulness and the promising potential of this element as a reagent in organic synthesis have been little

recognized until the last decade. Various applications of bismuth compounds for organic transformations have been recently investigated.[18] This section will provide a literature survey of the bismuth-mediated organometallic reactions, especially those carried out in aqueous media.

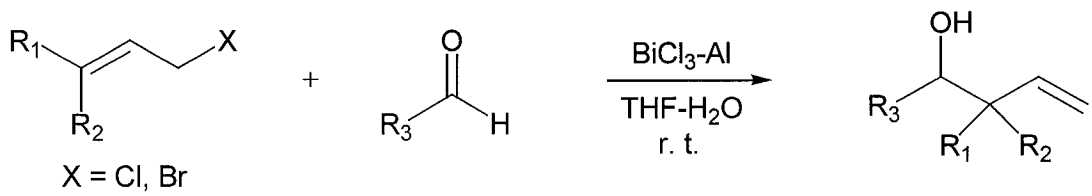
In 1990, Wada *et al.* first reported that metallic bismuth could promote the Barbier type allylation reactions of aldehydes in aqueous media using metallic aluminum and hydrobromic acid as activators.[19] The reaction of allyl bromide and 3-phenylpropionaldehyde **1.15** in a THF-H_2O mixture at room temperature utilizing Bi(0) and Al(0) in the presence of a catalytic amount of hydrobromic acid was carried out smoothly to give the corresponding homoallylic alcohol in high yield (Scheme 1.7).



1.15 90%

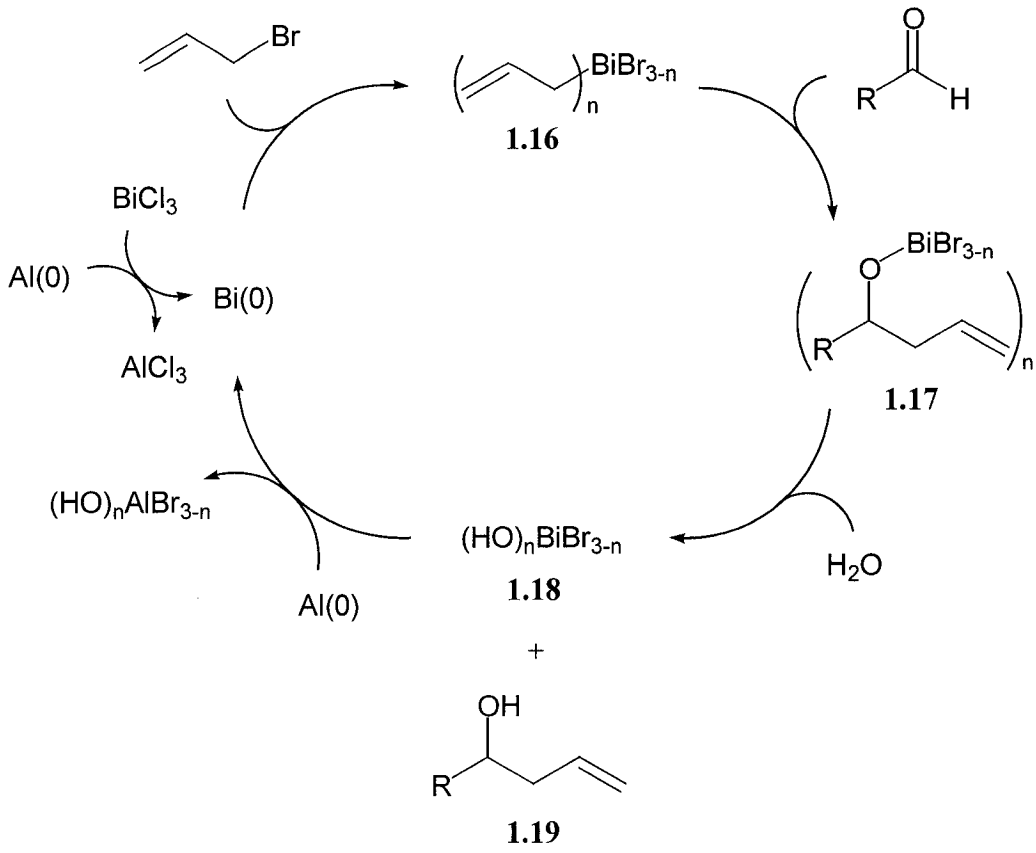
Scheme 1.7

Later, they also reported that the aqueous Barbier type allylation reactions of aldehydes with allyl halides could proceed by a bimetallic system of bismuth(III) chloride ($BiCl_3$) and metallic aluminum in a mixture of THF and H_2O at room temperature (Scheme 1.8). It was found that the use of $BiCl_3$ was essential to effect this reaction.



Scheme 1.8

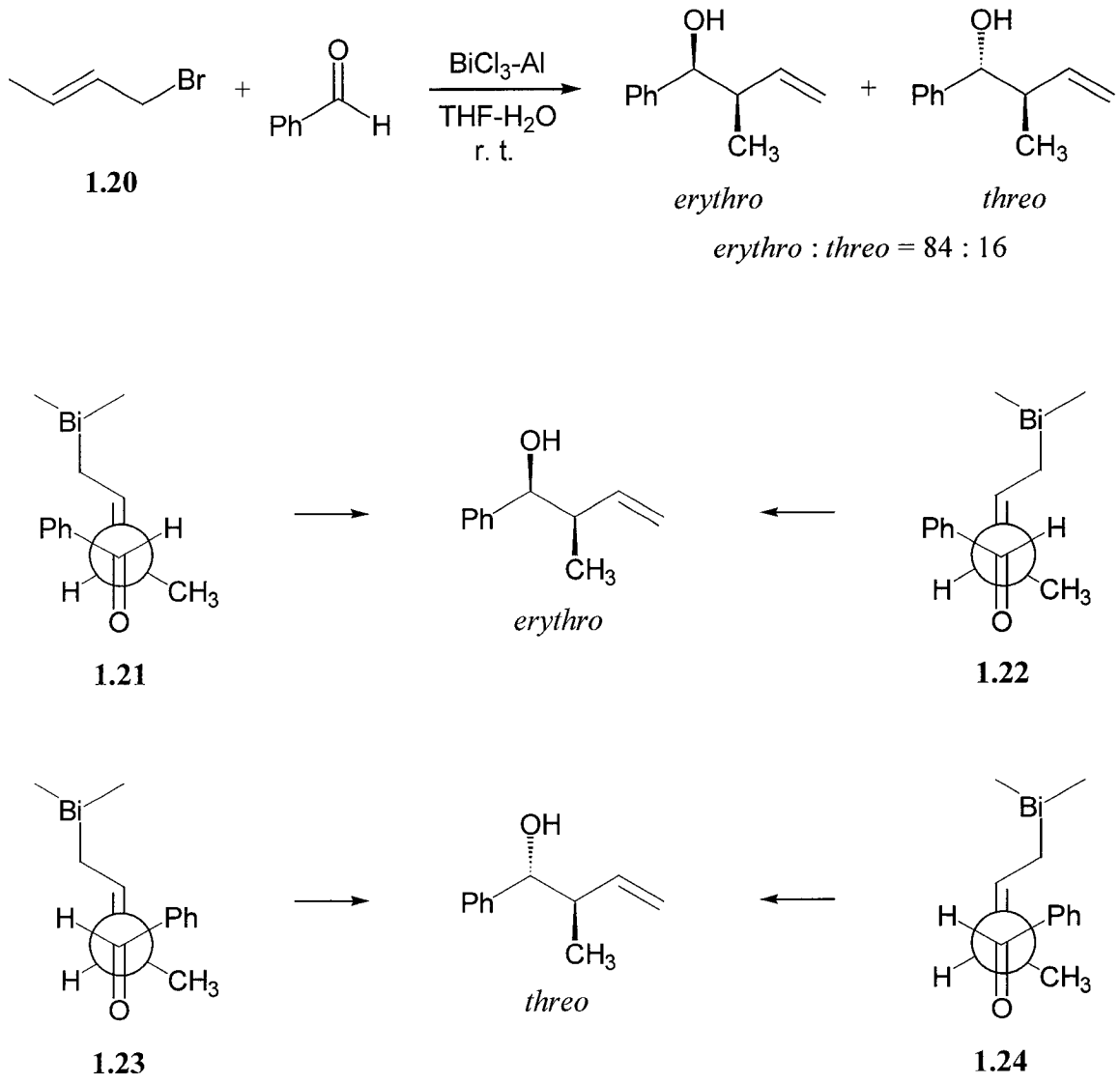
Although the details for the intermediate species of this reaction are not yet known, a catalytic cycle can be presumed in which an allylbismuth reagent **1.16** is formed through the oxidative addition of an allyl halide to Bi(0) generated *in situ* by the reduction of $BiCl_3$ with Al(0). Hydrolysis of **1.17** with water yields a homoallylic alcohol **1.19** and a bismuth(III) compound **1.18**, which is reduced by Al(0) regenerating the Bi(0) catalyst (Scheme 1.9).



Scheme 1.9

In the reaction of crotyl bromide **1.20** with benzaldehyde, predominant *erythro* diastereoselectivity was observed although crotyl bromide was a mixture of *cis* and *trans* isomers (30 : 70) (Scheme 1.10). In order to account for this stereochemical result, an acyclic transition state[20] was proposed for the present reaction system instead of a

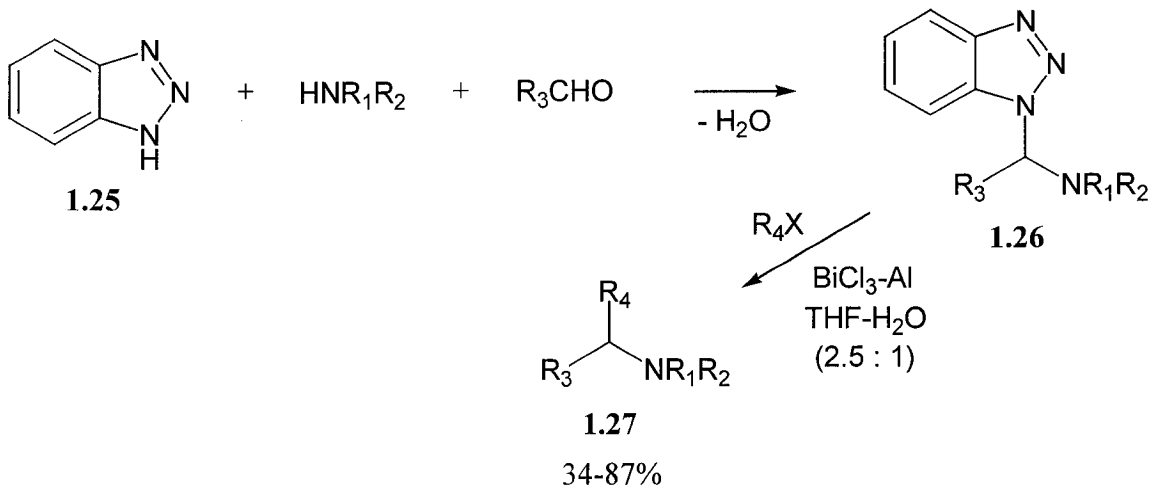
conventional cyclic mechanism.[21] Among several possible transition state geometries, two conformations (**1.21** and **1.22**) leading to the *erythro* isomer must be favored for steric reasons in comparison with those (**1.23** and **1.24**) leading to the *threo* isomer.



Scheme 1.10

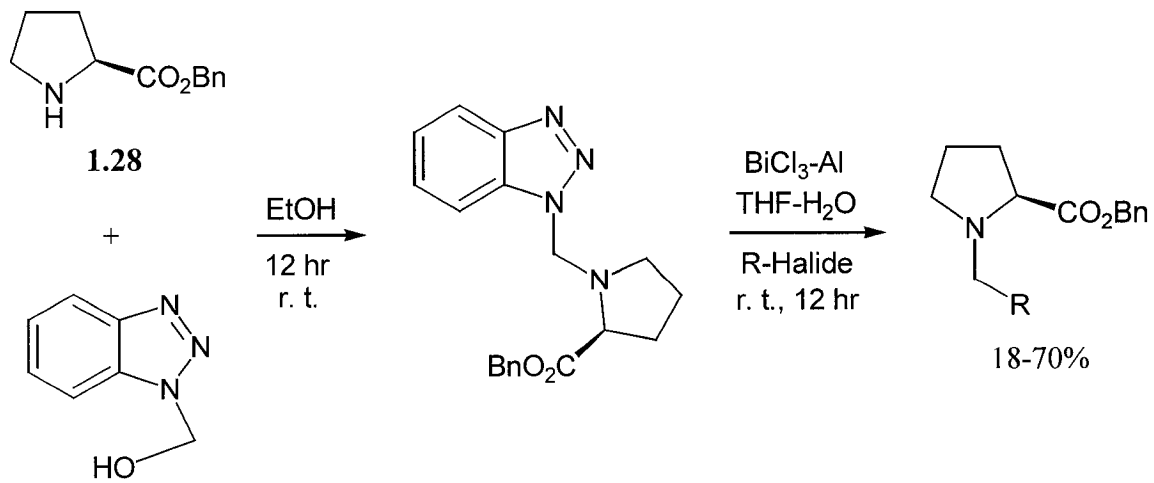
The synthetic usefulness of the $BiCl_3$-Al system in the *N*-alkylation of amines using benzotriazole as a synthetic auxiliary was reported by Katritzky *et al.* (Scheme 1.11).[22] Initially, an amine undergoes a Mannich condensation with benzotriazole **1.25**

and an aldehyde producing an *N*-(aminoalkyl)benzotriazole **1.26**, which is then alkylated by $BiCl_3$ in the presence of Al in a THF-H_2O mixture at room temperature providing an *N*-alkylated amine **1.27** on elimination of benzotriazole.

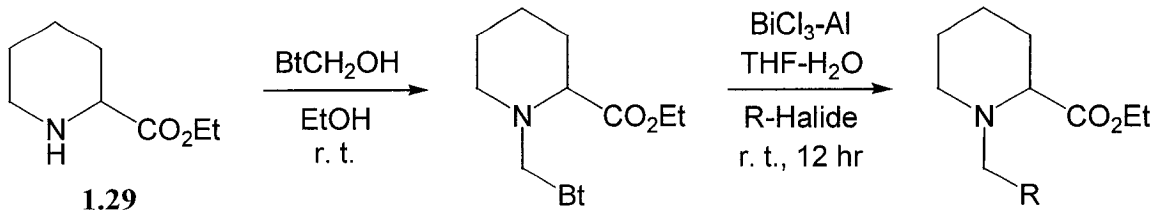


Scheme 1.11

This methodology was successfully extended to include the *N*-derivatization of the protected optically pure α-amino acid, *L*-proline benzyl ester **1.28**, (Scheme 1.12) and the racemic pipecolinic acid ethyl ester **1.29** (Scheme 1.13).[23]



Scheme 1.12

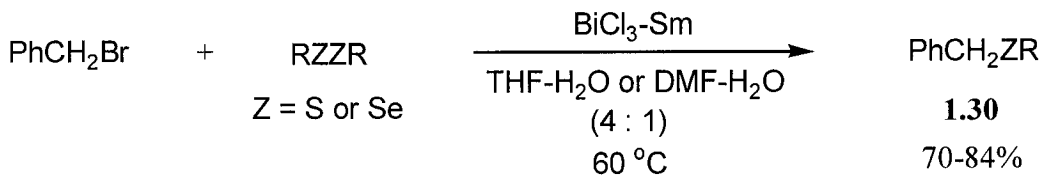


1.29

33-55%

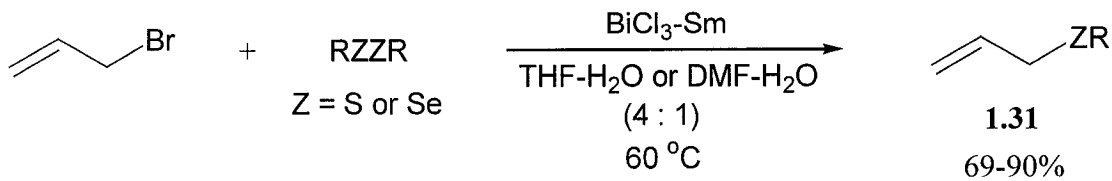
Scheme 1.13

Recently, Zhang *et al.* have explored the potential applications of $BiCl_3$-Sm system in organic synthesis. In 1998, they reported a novel method for the synthesis of benzyl sulfides and benzyl selenides **1.30** in good yields mediated by $BiCl_3$ in combination with Sm in aqueous media (Scheme 1.14).[24]



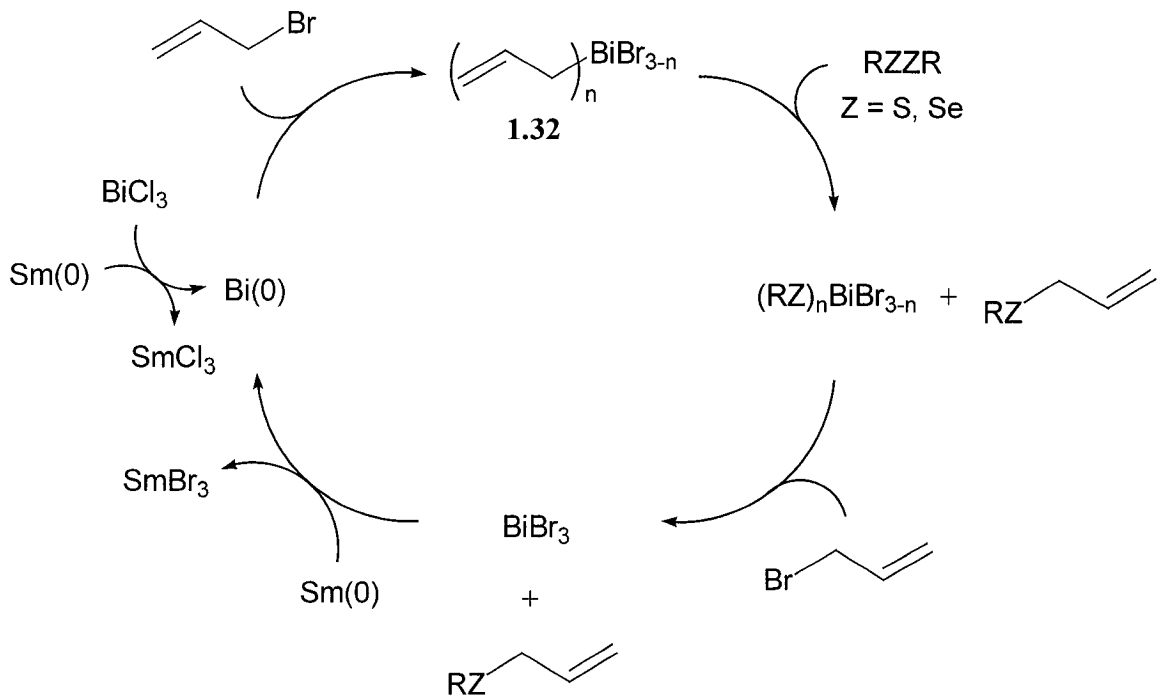
Scheme 1.14

Later, they also found that the $BiCl_3$-Sm system could mediate the reactions of allyl bromide with disulfides and diselenides in THF-H_2O or DMF-H_2O under a nitrogen atmosphere to afford the corresponding allyl sulfides and allyl selenides **1.31** in reasonably high yields (Scheme 1.15).[25]



Scheme 1.15

Although the reaction mechanism for the $BiCl_3$-Sm system-mediated cleavage of S–S and Se–Se bonds is not clear, a catalytic cycle can be presumed in which an allylbismuth reagent **1.32** is formed as shown in Scheme 1.16.

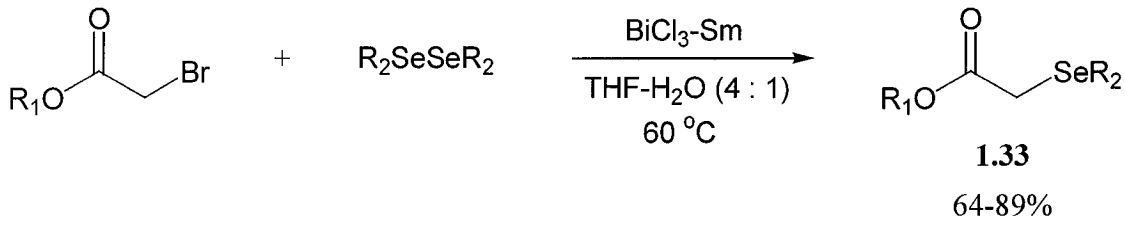


Scheme 1.16

From a synthetic point of view, the present methodology offers a number of advantages over other alternative synthetic methods which involve the cleavage of S–S bond in disulfides and Se–Se bond in diselenides. Major limitations, such as the necessity to synthesize the organometallic complex, the loss of the half unit of disulfides and diselenides, the use of strong base catalyst, and the need for anhydrous organic solvents, can be overcome with the $BiCl_3$-Sm system.

The further investigation of the $BiCl_3$-Sm system led to the successful synthesis of α-selenoesters **1.33** (Scheme 1.17) and β-aminoesters **1.34** (Scheme 1.18) in moderate to

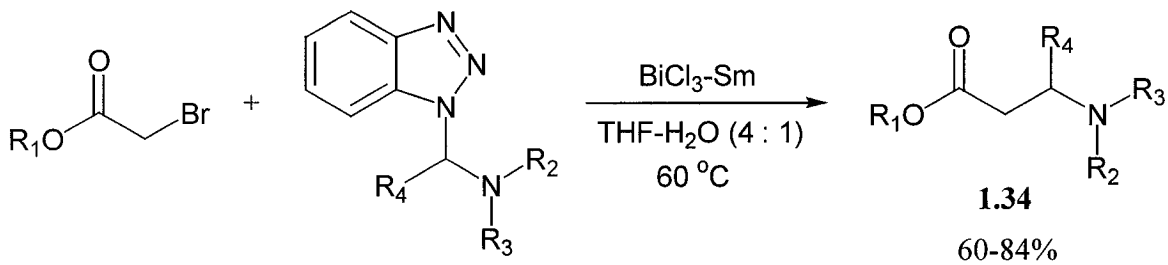
high yields in aqueous media.[26]



1.33

64-89%

Scheme 1.17

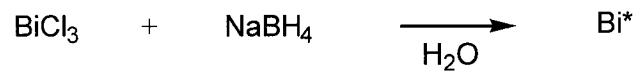


1.34

60-84%

Scheme 1.18

In 1996, Ren *et al.* reported that the active bismuth metal (Bi*), which was prepared by the combination of $BiCl_3$ and $NaBH_4$ in water, could efficiently mediate the Barbier type allylation reactions of various aldehydes in aqueous media at room temperature to give the corresponding homoallylic alcohols in excellent yields with high chemoselectivity (Scheme 1.19).[27]

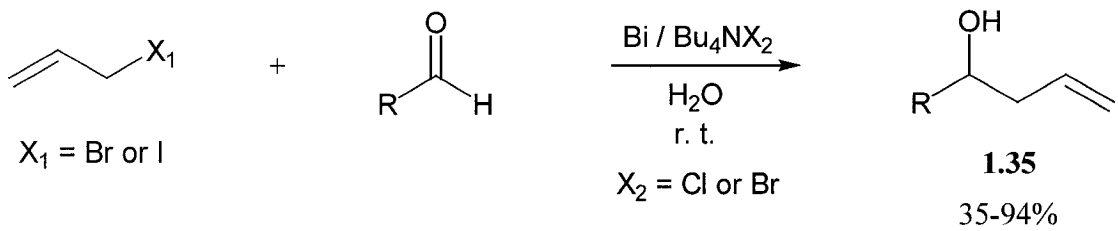


75-96%

Scheme 1.19

Their experimental results suggest that the reaction mechanism involves the formation of an allylbismuth reagent through the oxidative addition of an allyl bromide to the active bismuth generated *in situ* from the combination of $BiCl_3$ and $NaBH_4$ and an acyclic transition state rather than a conventional cyclic mechanism as shown by Wada *et al.* Furthermore, based on their observations of solvent effect on the reaction, it is believed that the function of water in the reaction is to accelerate the formation of the allylbismuth reagent and to make the aldehyde more vulnerable to the attack by the allylbismuth reagent in acidic media.

Recently, Chan and Isaac found that bismuth could mediate the coupling of allyl halides with aldehydes in the presence of tetrabutylammonium halide in aqueous media at room temperature to provide the corresponding homoallylic alcohols **1.35** in moderate to high yields (Scheme 1.20).[28] Bismuth showed remarkable chemoselectivity in comparison to other metals used for this coupling reaction.



Scheme 1.20

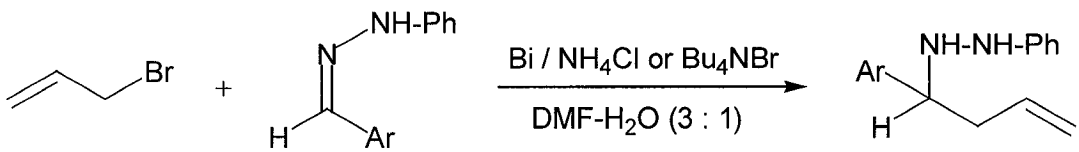
More recently, the first example of using bismuth for the allylation of aldonitrones and hydrazones in aqueous media was reported by Laskar *et al.*[29] The reactions of allyl bromide with diverse aldonitrones **1.36** mediated by bismuth in the presence of NH_4Cl or Bu_4NBr in a mixture of DMF and H_2O at room temperature afforded the corresponding homoallylic hydoxylamines **1.37** in good yields (Scheme 1.21).

1.36 **1.37**

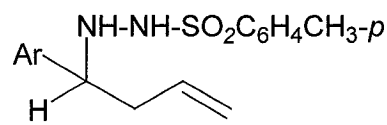
65-75%

Scheme 1.21

Similarly, the allylbismuth reagents generated *in situ* by the combination of allyl bromide, bismuth, and NH_4Cl or Bu_4NBr underwent the addition to the carbon-nitrogen double bonds of aryl and tosyl hydrazones **1.38** under the same reaction conditions to provide the corresponding homoallylic hydrazides **1.39** and **1.40** in 60-65% yields (Scheme 1.22).



1.38 **1.39**



1.40

Scheme 1.22

The bismuth-mediated allylation of aldonitrones and hydrazones in aqueous media proceeded smoothly without the formation of any undesirable side products, such as *N*-allylated products, homoallylic alcohols (allylation products of hydrolyzed imines),[30] 1,2-diamines (coupling products of imines),[31] or reduction products. In addition, when the same experiments were performed under microwave irradiation at 2450 MHz frequency,

not only the rate of the reactions (from 6-12 hours to 4-5 minutes) but also the yields of the products were significantly improved (80-95%). Although the detailed mechanism of this reaction is not clear, it is likely that NH_4Cl or Bu_4NBr affects the generation of an active allylbismuth reagent.

1.3. Research Proposal

Since the breakthrough of water as an alternative reaction medium in organic chemistry in the 1980's, metal-mediated organometallic reactions in aqueous media have been extensively explored. However, the type of aqueous organometallic reactions seems to have been somewhat limited. Most metallic elements have been used for synthetic purposes with diverse utility and selectivity. Among various heavy metals, such as indium, tin, antimony, and lead, bismuth is relatively cheap and non-toxic but comparatively little studied. Therefore, it is of our great interest to investigate the synthetic potential of bismuth metal as a reagent for organic synthesis in aqueous media. In the following chapters, we will describe our efforts to develop novel bismuth-mediated organometallic reactions in aqueous media and understand the mechanisms of the reactions.

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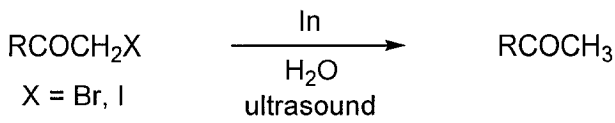
Chapter 2.

Bismuth-Mediated Reductive Dehalogenation of α-Halocarbonyl Compounds in Aqueous Media

2.1. Introduction

The reductive dehalogenation of α-halocarbonyl compounds without affecting the carbonyl group has received considerable attention in organic chemistry. A number of reagents have been developed for this selective reduction including (1) reducing agents, such as zinc in acetic acid,[1] sodium dithionate,[2] organotin hydrides,[3] borohydride,[4] and low-valent transition metal salts (e.g. titanium(III),[5] vanadium(II),[6] and chromium(II)[7]); (2) strong nucleophiles that may act as reducing agents, such as iodide ions,[8] phosphines,[9] iodophosphines,[10] iodotrimethylsilane,[11] thiols,[12] selenols,[13] tellurolates,[14] and amines[15]; (3) stoichiometric amounts of zero-valent transition metal carbonyls of iron,[16] cobalt,[17] and molybdenum[18]; (4) heterogeneous hydrogenation catalysts involving transition metal surfaces[19]; and (5) composite reducing systems of tin or silicon hydrides with transition metal catalysts, such as palladium[20] and molybdenum.[21] The choice of a reducing agent usually depends on what other functional groups are present. Typically, these methods have to be carried out in organic solvents as reaction media.

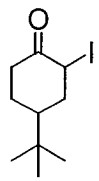
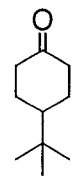
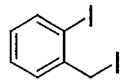
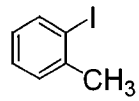
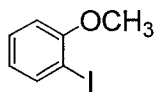
Recently, Ranu *et al.* reported an efficient and general methodology for the chemoselective reduction of α-halocarbonyl compounds in aqueous media.[22] They discovered that indium metal could reduce α-halocarbonyl compounds to the corresponding dehalogenated carbonyl compounds in water under sonication (Scheme 2.1).



Scheme 2.1

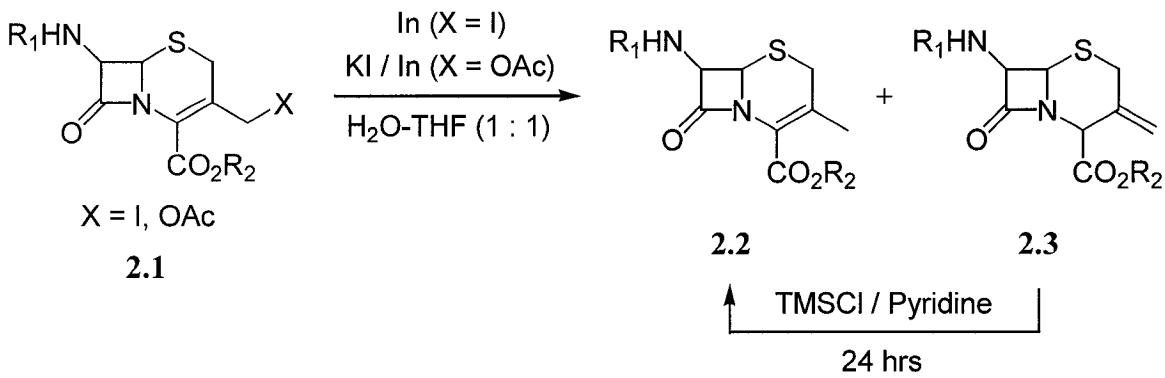
A wide range of structurally different α-bromo and α-iodoketones and esters was found to undergo the reductive dehalogenation by this procedure to provide the corresponding reduction products in excellent yields (Table 2.1). Although alkyl and aryl iodides (entries 8 and 9) remained inert under these conditions, the chemoselective reduction of benzyl iodides (entries 6 and 7) proceeded smoothly.

Table 2.1. Selected examples for reduction of α-halocarbonyl compounds and benzyl halides mediated by indium metal in aqueous media

Entry	Substrate	Time (hr)	Product	Yield (%)[a]
1	$PhCOCH_2Br$	8	$PhCOCH_3$	86
2	$PhCOCH_2I$	3	$PhCOCH_3$	90
3		2.5		89
4	$BrCH_2CO_2CH_2CH_3$	6.5	$CH_3CO_2CH_2CH_3$	78
5	$ICH(CO_2Et)_2$	6	$CH_2(CO_2Et)_2$	75
6	$PhCH_2I$	5	$PhCH_3$	85
7		11		85
8	$CH_3(CH_2)_{13}CH_2I$	19	No Reaction	
9		24	No Reaction	

[a] Isolated yield.

More recently, a useful employment of indium metal for the reductive dehalogenation reaction in aqueous media was reported by Chae *et al.*[23] They demonstrated a new and convenient synthesis of 7-amino-3-desacetoxycephem derivatives by the reduction of 3-iodomethylcephems with indium in aqueous media (Scheme 2.2).



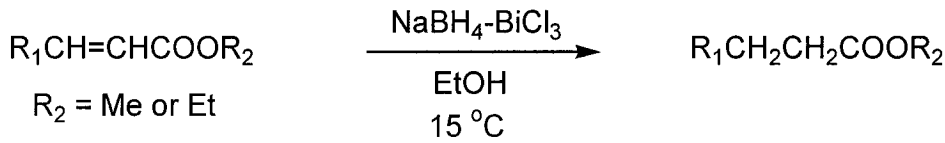
Scheme 2.2

Treatment of 3-iodomethylcephems **2.1** (X = I) with indium powder in a mixture of H_2O and THF (1 : 1) at room temperature gave a 1 : 1.2 mixture of **2.2** and **2.3** in 60-74% yields. With 3-acetoxymethylcephems **2.1** (X = OAc), the compounds were reacted with potassium iodide and then dehalogenated with indium *in situ* in the same solvent system at 40-60 °C to produce a mixture of **2.2** and **2.3** in 71-79% yields. The subsequent reaction of the crude product mixture with trimethylsilyl chloride in the presence of pyridine afforded the compound **2.2** as a sole product.

One very important aspect of these reduction systems involving indium metal is the use of water as a reaction medium, which has attracted considerable interest in recent years in the context of green chemistry.

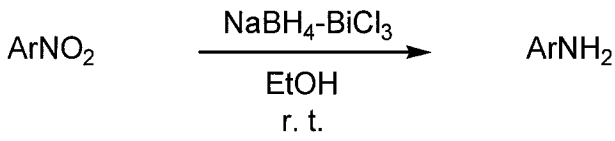
2.2. Bismuth as a Reducing Agent

In 1995, Ren *et al.* reported the selective reduction of carbon-carbon double bonds in α,β-unsaturated esters by sodium borohydride in combination with bismuth chloride (Scheme 2.3).[24] It was found that α,β-unsaturated esters, in which the double bond was either non-conjugated or conjugated with an aromatic ring, could be converted to the corresponding saturated esters in moderate to high yields with this $NaBH_4$-$BiCl_3$ system in 95% ethanol at 15 °C.



Scheme 2.3

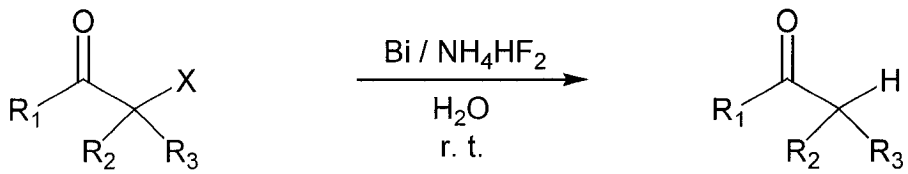
Shortly after this discovery, they also found the $NaBH_4$-$BiCl_3$ system to be very effective for the reduction of nitroarenes to primary amines (Scheme 2.4).[25] Various nitroarenes with either an electron-donating or an electron-withdrawing group could be reduced in ethanol at room temperature to the corresponding primary amines in reasonably good yields.



Scheme 2.4

During a preliminary investigation on the crossed aldol type reactions of α-halocarbonyl compounds with aldehydes mediated by bismuth metal in the presence of

ammonium hydrogen fluoride as a promoter in aqueous media, we observed a competing reductive dehalogenation process. This prompted us to initiate a systematic investigation into the reduction of α-halocarbonyl compounds by bismuth metal with ammonium hydrogen fluoride in aqueous media (Scheme 2.5). The results are summarized in Table 2.2.



Scheme 2.5

As can be seen in Table 2.2, bismuth metal activated by ammonium hydrogen fluoride could effectively reduce various α-halocarbonyl compounds in aqueous media at room temperature to provide the corresponding dehalogenated reduction products in fairly high yields. The reduction of chloro compound (entry 3) was found to be much slower in comparison with that of bromo compounds. It is important to note that this reduction system is highly chemoselective. Usually, the nitro group is very sensitive to the reduction by metals. However, under these reduction conditions, *p*-nitroacetophenone could be obtained successfully without reducing the nitro group (entry 11). Furthermore, in the case of 2,4'-dibromoacetophenone, the bromo group on the aromatic ring also remained unaffected (entry 12). These results indicate that the present reaction conditions for the reduction of α-halocarbonyl compounds to dehalogenated carbonyl compounds are compatible with the nitro groups and the halo groups (haloaryl) as well as the carbonyl groups (ketone, acid, and ester).

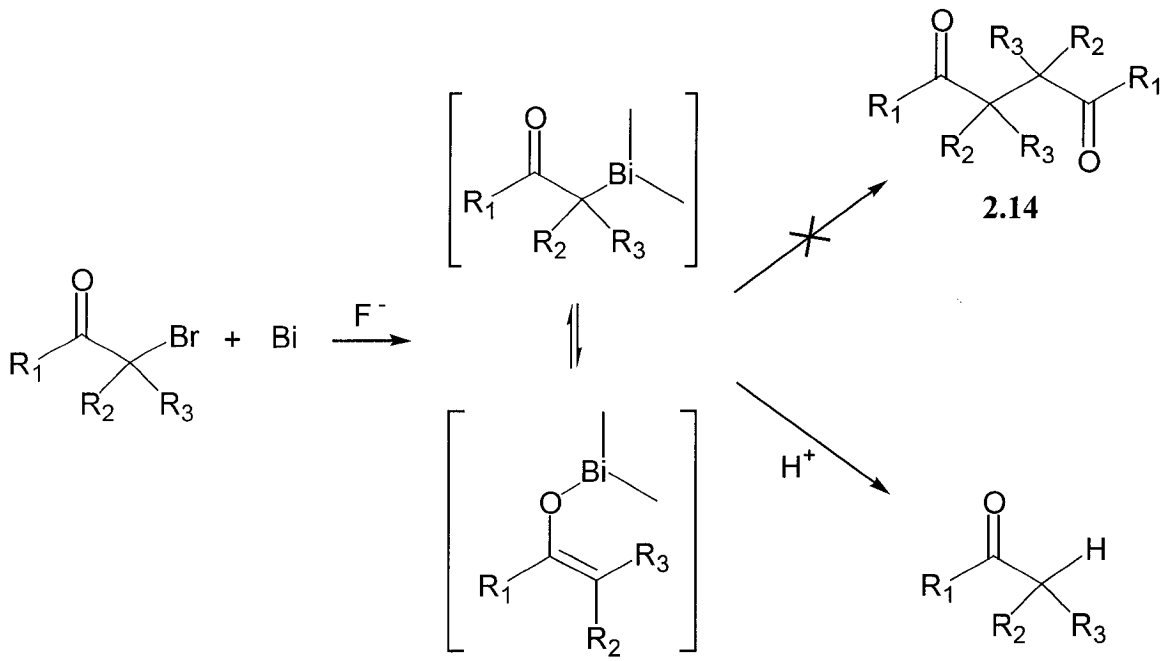
Table 2.2. Reduction of α-halocarbonyl compounds mediated by bismuth metal in the presence of NH_4HF_2 in aqueous media

Entry	*a*-Halocarbonyl compound	Time (hr)	Product		Isolated yield (%)
1	$MeCOCHMeBr$	2	$MeCOCH_2Me$	**2.4**	100[a]
2	$EtCOCH_2Br$	5	$EtCOCH_3$		100[a]
3	$MeCOCH_2Cl$	14 days	$MeCOCH_3$		63[a]
4	$PhCOCH_2Br$	2	$PhCOCH_3$	**2.5**	88
5	$PhCOCHMeBr$	4	$PhCOCH_2Me$	**2.6**	92
6	$PhCOCMe_2Br$	5	$PhCOCHMe_2$	**2.7**	95
7	$HO_2CCHMeBr$	24	HO_2CCH_2Me	**2.8**	100[a]
8	$HO_2CCHPhBr$	1	HO_2CCH_2Ph	**2.9**	65
9	HO_2CCOCH_2Br	4	HO_2CCOCH_3		100[a]
10	MeO_2CCH_2Br	16	MeO_2CCH_3	**2.10**	100[a]
11	*p*-$NO_2PhCOCH_2Br$	3	*p*-$NO_2PhCOCH_3$	**2.11**	94
12	*p*-$BrPhCOCH_2Br$	20	*p*-$BrPhCOCH_3$	**2.12**	92

[a] Determined by ^1H NMR. The product could not be isolated due to its low boiling point.

Metal-mediated reactions in aqueous media may proceed by different mechanisms depending on the metal used. In many cases, it is considered that metal-mediated aqueous reactions go through a single electron transfer (SET) process on the metal surface generating a radical anion intermediate.[26] The precise mechanism for the bismuth-mediated reductive dehalogenation of α-halocarbonyl compounds cannot be discussed in full detail at this point (further discussion in Chapter 4). However, the fact that the radical self-coupling product **2.14** was not observed as a side product under these reaction conditions suggests that the reduction did not undergo the SET process. It is more likely that the reduction by bismuth metal in the presence of ammonium hydrogen

fluoride in aqueous media proceeds through the formation of a bismuth enolate intermediate **2.13** as illustrated in Scheme 2.6.



Scheme 2.6

2.3. Conclusion

The bismuth-mediated reductive dehalogenation of α-halocarbonyl compounds in aqueous media was investigated. Bismuth metal activated by ammonium hydrogen fluoride was found to reduce various α-halocarbonyl compounds efficiently under the mild conditions to afford the corresponding dehalogenated reduction products in excellent yields. The results showed that the reduction was highly chemoselective and suggested that the reduction products were presumably formed from the bismuth enolate intermediate.

2.4. Experimental

General Information:

Chemicals were purchased from Aldrich or Alfa Aesar Chemical Company. Thin layer chromatography was performed on plastic plates precoated with silica gel (60 F_{254}), which were developed using a mixture of hexane and ethyl acetate as an eluent. Analytes were visualized by UV light or by dipping the plate into a developing agent (a solution of ammonium molybdate and ceric sulfate in dilute sulfuric acid) and heating with a heat gun. Column chromatography was performed on 230-400 mesh silica gel.

Melting points were determined using a Gallenkamp apparatus and were uncorrected. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury 300 or 400 MHz spectrometer or a Varian Unity 500 MHz spectrometer at ambient temperature. Chemical shifts (δ) were reported in parts per million (ppm) and referenced to $CDCl_3$ at δ 7.25 ppm for ^{1}H and δ 77.00 ppm for ^{13}C. The multiplicity of each signal was indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet) and m (multiplet). Coupling constants (*J*) were reported in Hertz (Hz).

General Procedure for Bismuth-Mediated Reductive Dehalogenation:

To a mixture of an α-halocarbonyl compound (1 mmol), bismuth powder (1.5 mmol), and NH_4HF_2 (1.5 mmol) was added distilled water (1 ml). The reaction mixture was vigorously stirred at room temperature until the reaction was completed (1-24 hrs). Additional distilled water (10 ml) was added in the reaction mixture, and the product was extracted with diethyl ether (3 × 30 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the evaporation of solvent under reduced pressure,

the crude product was purified by flash column chromatography on silica gel using 2% ethyl acetate in hexane as an eluent to give the corresponding pure reduction product.

2-Butanone (2.4): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.36, 36.93, 29.57, 7.95.

Acetophenone (2.5): colorless liquid; IR (neat): 1684 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.55-7.51 (m, 1H), 7.44-7.40 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.77, 136.77, 132.86, 128.31, 128.04, 26.62.

Propiophenone (2.6): colorless liquid; IR (neat): 1687 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.53-7.48 (m, 1H), 7.43-7.39 (m, 2H), 2.97 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.34, 136.55, 132.59, 128.26, 127.67, 31.72, 8.23.

Isobutyrophenone (2.7): colorless liquid; IR (neat): 1684 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.91 (m, 2H), 7.52-7.48 (m, 1H), 7.44-7.39 (m, 2H), 3.53 (sept, J = 6.7 Hz, 1H), 1.21 (d, J = 1.2 Hz, 3H), 1.19 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.98, 135.84, 132.51, 128.32, 128.01, 35.25, 19.13.

Propionic acid (2.8): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (q, J = 7.4 Hz, 2H), 1.17 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.43, 27.30, 8.99.

Phenylacetic acid (2.9): white solid; mp 76-77 °C; IR (neat): 1700 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.41 (br s, 1H), 7.45-7.29 (m, 5H), 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.10, 133.01, 129.18, 128.44, 127.15, 41.10.

Methyl acetate (2.10): ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.37, 51.68, 20.85.

***p*-Nitroacetophenone (2.11):** pale yellow solid; mp 77-79 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28-8.25 (m, 2H), 8.10-8.06 (m, 2H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.00, 150.03, 141.10, 129.10, 123.64, 27.04.

***p*-Bromoacetophenone (2.12):** white solid; mp 50-52 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.55-7.52 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.57, 135.45, 131.57, 129.56, 128.00, 26.55.

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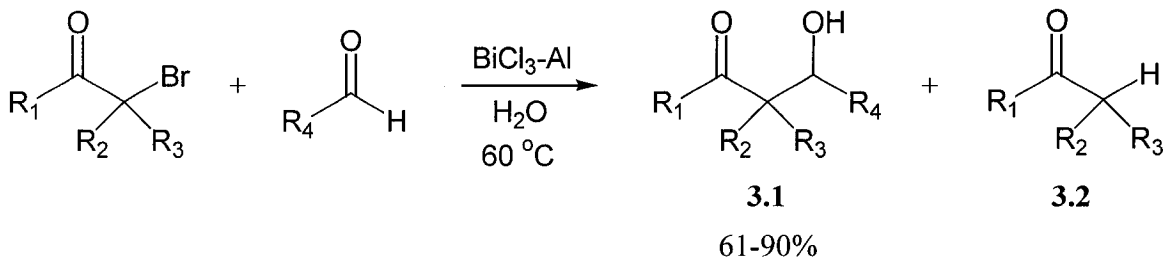
Chapter 3.

Bismuth-Mediated Crossed Aldol Type Reactions in Aqueous Media

3.1. Introduction

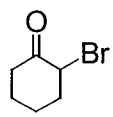
The aldol reaction has played an important role in organic synthesis for the formation of carbon-carbon bonds providing synthetically useful β-hydroxycarbonyl compounds. However, under the classical aldol reaction conditions involving basic media, side products, such as dimers, polymers, self-condensation products, and α,β-unsaturated carbonyl compounds, are invariably formed as well. The formation of these side products is often attributed to the fact that the aldol reaction is an equilibrium process.[1] In order to circumvent this problem, the useful modifications of the classical aldol reaction, particularly using Lewis acid promoted reactions of enol silyl or tin ethers with carbonyl compounds, have been developed.[2] In general, these methods employ organic solvents as reaction media.

In 1997, Shen *et al.* reported the first example of using bismuth to mediate the crossed aldol type reactions in aqueous media.[3] In the presence of bismuth(III) chloride and metallic aluminum, α-bromocarbonyl compounds were found to react with various aldehydes in water under a nitrogen atmosphere at 60 °C to afford the corresponding β-hydroxycarbonyl compounds **3.1** in good yields together with the dehalogenated products **3.2** (Scheme 3.1).



Scheme 3.1

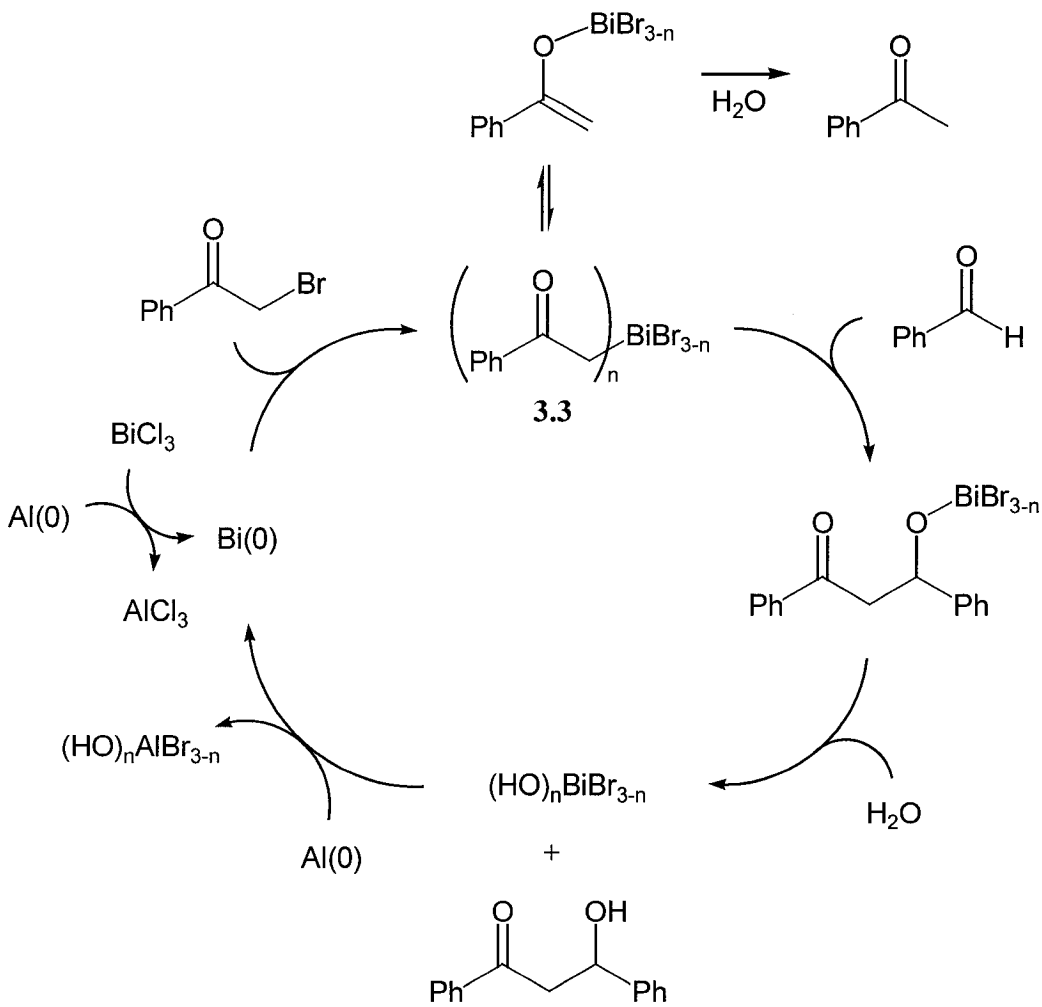
Table 3.1. Selected examples for $BiCl_3$-Al mediated crossed aldol type reactions of α-bromoketones with aldehydes in aqueous media[a]

Entry	*a*-Bromoketone	Aldehyde	Temp.(°C) / Time (hr)	Yield (%) (*erythro* : *threo*)	Reduction product (%)
1	$PhCOCH_2Br$	PhCHO	60 / 4	82	28
2	$PhCOCH_2Br$	PhCHO	60 / 48	80[b]	25
3	$PhCOCH_2Br$	*p*-ClPhCHO	60 / 4	86	25
4	$PhCOCH_2Br$	*p*-ClPhCHO	85 / 4	41	63
5	$PhCOCH_2Br$	*p*-MeOPhCHO	70 / 4	61	46
6	$PhCOCH_2Br$	*n*-$C_8H_{17}CHO$	60 / 4	81	31
7	*p*-$BrPhCOCH_2Br$	PhCHO	60 / 4	83	25
8		PhCHO	60 / 4	80 (84 : 16)	32

[a] Molar ratio *a*-bromoketone : aldedyde : $BiCl_3$: Al = 1.2 : 1 : 1 : 2. [b] $BiCl_3$: Al = 0.1 : 0.2.

As shown in Table 3.1, the aldol addition reactions proceeded well with both aromatic and aliphatic aldehydes. Raising the reaction temperature resulted in a dramatic increase in the yield of the reduction product (entry 4). It was found that only a catalytic amount of $BiCl_3$ was needed to effect the reaction (entry 2). A catalytic cycle could be presumed in which an organobismuth reagent **3.3** was formed through the oxidative

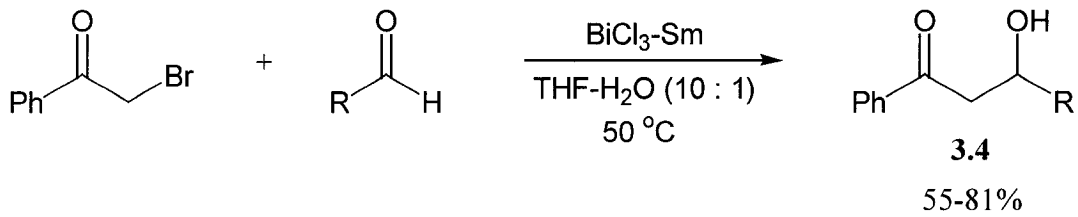
addition of α-bromoacetophenone to Bi(0) generated *in situ* by the reduction of $BiCl_3$ with Al(0) (Scheme 3.2). Moreover, predominant *erythro* aldol products were obtained under these reaction conditions (entry 8). Based on these experimental observations, it was proposed that the reaction involved an acyclic transition state[4] rather than a conventional cyclic one[5] or a single electron transfer (SET) mechanism.[6]



Scheme 3.2

Very recently, Zhang *et al.* demonstrated that a bimetallic system of bismuth(III) chloride and samarium could mediate the crossed aldol type reactions of α-

bromoacetophenone with a variety of aldehydes in a mixture of THF and H_2O at 50 °C to give the corresponding β-hydroxyketones **3.4** in moderate to good yields (Scheme 3.3).[7] The reaction appeared to be chemoselective in that the desired aldol addition product could not be obtained when a ketone, acetophenone, was used to react with α-bromoacetophenone under these reaction conditions.



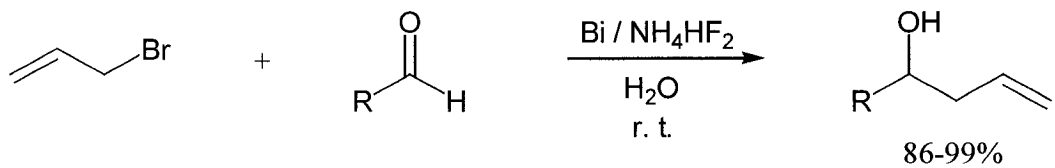
3.4

55-81%

Scheme 3.3

3.2. Preliminary Study with Ammonium Hydrogen Fluoride as a Promoter

The previous reports from our research group have shown that fluoride salts are quite effective in activating metals, such as aluminum[8] and antimony,[9] to mediate organometallic reactions in aqueous media. More recently, we found that ammonium hydrogen fluoride (NH_4HF_2) could efficiently activate commercially available bismuth metal to mediate the Barbier type allylation reactions of various aldehydes in aqueous media at room temperature to provide the corresponding homoallylic alcohols in excellent yields (Scheme 3.4).

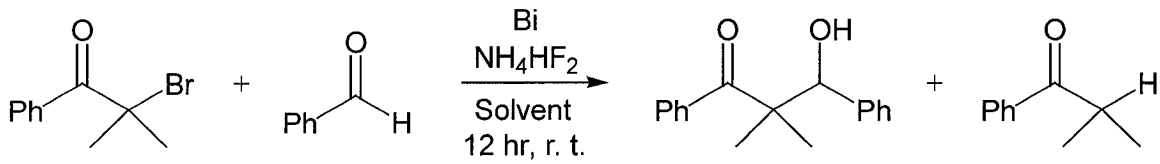


86-99%

Scheme 3.4

This new discovery is especially valuable in terms of green chemistry since environmentally benign non-toxic bismuth as well as water is used under the mild reaction conditions. Our interests in both extending the scope of aqueous organometallic reactions and applying bismuth to organic synthesis have led us to investigate the bismuth-mediated crossed aldol type reactions in aqueous media.

The initial study of the bismuth-mediated aqueous crossed aldol type reaction was performed with 2-bromoisobutyrophenone **3.5** and benzaldehyde in the presence of NH_4HF_2 at room temperature (Scheme 3.5). The results are summarized in Table 3.2.



3.5 **3.6** **3.7**

Scheme 3.5

Table 3.2. Bismuth-mediated crossed aldol type reaction of 2-bromoisobutyrophenone with benzaldehyde in the presence of NH_4HF_2 in aqueous media[a]

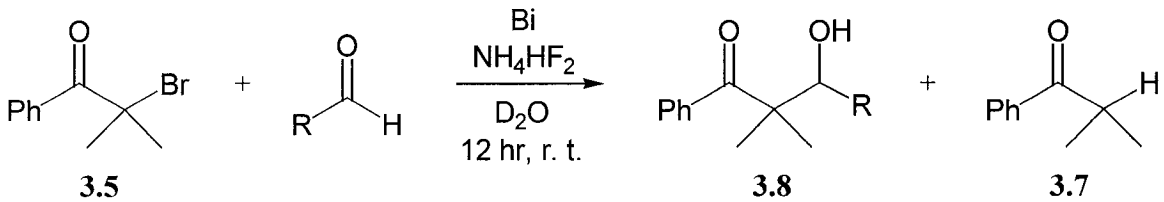
Entry	Solvent (ml)	Yield (%) of **3.6**[b]	Yield (%) of **3.7**[b]
1	H_2O (5)	37	63
2	H_2O (1)	56	44
3	D_2O (5)	76	24
4	D_2O (1)	82	18

[a] Ratio **3.5** : benzaldehyde : Bi : NH_4HF_2 = 1 : 1.1 : 1.5 : 1.5 mmol. [b] Determined by ^1H NMR of the crude product.

When water was used as the reaction medium, the reduction of the compound **3.5**

became a serious side reaction substantially lowering the yield of the aldol product **3.6** (entries 1 and 2). In an effort to minimize the reduction product **3.7**, the reaction was carried out in deuterium oxide instead of water. As expected, a significant increase in the yield of the aldol adduct was observed due to the kinetic isotope effect in the protonation step (entries 3 and 4). In addition, by reducing the amount of the solvent, the yield of the aldol addition product could be further improved (entries 2 and 4).

Employing D_2O as the solvent, the bismuth-mediated crossed aldol type reactions of the compound **3.5** with a representative selection of substituted benzaldehydes were examined in the presence of NH_4HF_2 at room temperature (Scheme 3.6, Table 3.3).



Scheme 3.6

Table 3.3. Electronic effect of substituents on the bismuth-mediated crossed aldol type reaction in the presence of NH_4HF_2 in D_2O[a]

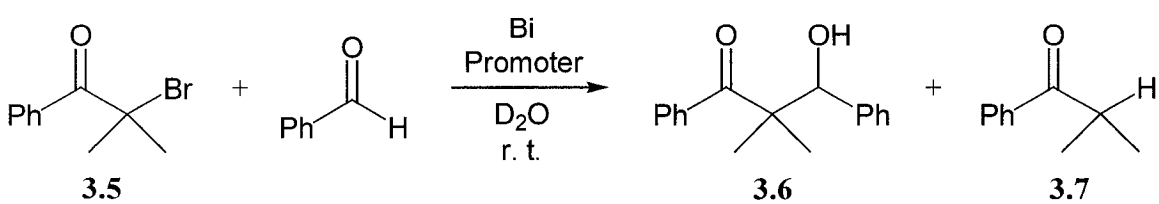
Entry	R	Yield (%) of **3.8**[b]		Yield (%) of **3.7**[b]
1	Ph	82 (78[c])	**3.8a**	18
2	*p*-CH_3Ph	72 (53[c])	**3.8b**	28
3	*p*-CH_3OPh	61		39
4	*p*-CNPh	77 (86[c])	**3.8c**	10

[a] Ratio **3.5** : aldehyde : Bi : NH_4HF_2 = 1 : 1.1 : 1.5 : 1.5 mmol and 1 ml of D_2O.
[b] Determined by ^1H NMR of the crude product. [c] Isolated yield based on reacted **3.5**.

The results, as summarized in Table 3.3, illustrated that an electron-donating group on the aromatic ring, such as the methyl or methoxy group, led to the lower yield of the aldol addition product **3.8** due to the diminished electrophilicity of the aldehyde (entries 2 and 3). In contrast, the higher yield of the aldol addition product was obtained with benzaldehyde bearing an electron-withdrawing group, which enhanced the electrophilicity of the aldehyde (entry 4).

3.3. Optimization of Bismuth-Mediated Aqueous Crossed Aldol Type Reaction

In the previous section, the use of ammonium hydrogen fluoride was found to be essential since neither the crossed aldol type reaction nor the reduction proceeded with bismuth alone. In general, mechanically atomized metals are less reactive than metals chemically prepared by the reduction of metal salts with alkali metals or other reducing agents.[10] The low reactivity of the bismuth metal powder may result from the insufficient removal of metal oxide layers from the metal surface and the low surface area of the metal particles. Thus, it is obvious that the activation of bismuth metal is needed for the reaction to proceed. In an attempt to search for the most effective promoter for bismuth, a wide range of fluoride salts was screened using the reaction of the compound **3.5** with benzaldehyde as a model reaction (Scheme 3.7), and the results are shown in Table 3.4.



3.5 **3.6** **3.7**

Scheme 3.7

Table 3.4. Screening of promoters for the bismuth-mediated crossed aldol type reaction of 2-bromoisobutyrophenone with benzaldehyde in aqueous media[a]

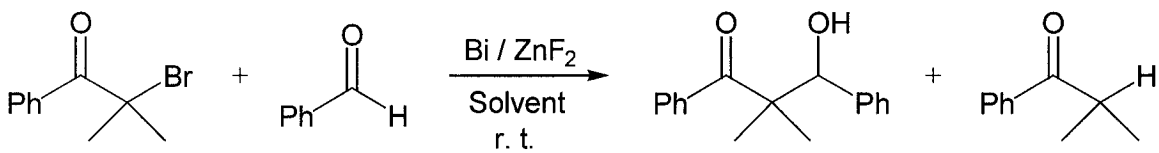
Entry	Promoter	Time (hr)	Unreacted **3.5** (%)[b]	Yield (%) of **3.6**[b]	Yield (%) of **3.7**[b]
1	KF	24	100	0	0
2	CaF_2	24	100	0	0
3	AlF_3	24	100	0	0
4	NH_4F	24	40	53	7
5	NH_4HF_2	12	0	82 (78[c])	18
6	Bu_4NF	24	100	0	0
7	TiF_4	18	0	75	25
8	VF_4	16	0	50	50
9	CrF_3	18	0	75	25
10	MnF_2	24	99	trace	trace
11	FeF_2	24	84	15	trace
12	CoF_2	24	89	10	trace
13	NiF_2	24	87	12	trace
14	CuF_2	12	0	58	42
15	ZnF_2	12	0	95 (90[c])	5
16	$ZnCl_2$	24	100	0	0

[a] Ratio **3.5** : benzaldehyde : Bi : promoter = 1 : 1.1 : 1.5 : 1.5 mmol and 1 ml of D_2O.
[b] Determined by ^1H NMR of the crude product. [c] Isolated yield.

As can be seen from Table 3.4, the main group metal fluorides, KF, CaF_2, and AlF_3, could not activate bismuth to mediate the reaction in D_2O (entries 1-3). Most of the

transition metal fluorides tested were found to be inefficient in activating bismuth leading to the unsatisfactory yields of the aldol product (entries 7-14). However, the reactions with TiF_4, VF_4, CrF_3, and CuF_2,[8] which are not commonly used reagents in organic synthesis, afforded the corresponding aldol adducts in moderate yields. Surprisingly, in the case of zinc fluoride, the aldol addition product was obtained exclusively along with a minimal amount of the reduction product (entry 15). On the other hand, in the presence of zinc chloride, the reaction did not occur indicating that fluoride anions seemed to have a special activating effect on bismuth in aqueous media (entry 16).

Therefore, zinc fluoride was chosen as the promoter for bismuth metal, and several different solvents were screened using the model reaction at room temperature (Scheme 3.8). The results are summarized in Table 3.5. It is interesting to note that the nature of the solvent controlled the formation of aldol addition products. Hardly any desired product was observed when ethanol or THF was employed as the solvent (entries 4 and 6). In a mixture of water and THF (1 : 1), the reduction product was formed to a significant extent as well (entry 5). As the results in Table 3.5 show, aqueous media, water or deuterium oxide, were proven to be the most suitable solvents for this bismuth-mediated crossed aldol type reaction (entries 2 and 3).



3.5 **3.6** **3.7**

Scheme 3.8

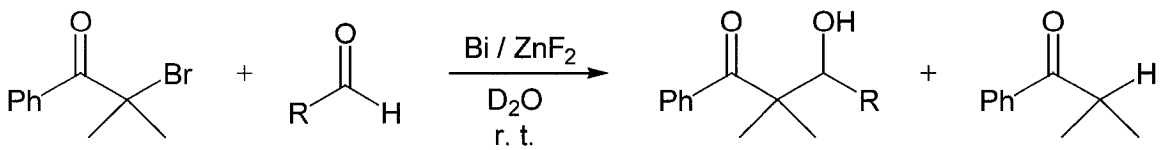
Table 3.5. Screening of solvents for the bismuth-mediated crossed aldol type reaction of 2-bromoisobutyrophenone with benzaldehyde in the presence of ZnF_2[a]

Entry	Solvent	Time (hr)	Unreacted **3.5** (%)[b]	Yield (%) of **3.6**[b]	Yield (%) of **3.7**[b]
1	Neat	24	78	21	trace
2	H_2O	12	0	85 (81[c])	15
3	D_2O	12	0	95 (90[c])	5
4	EtOH	24	100	0	0
5	H_2O-THF (1:1)	24	0	77	23
6	THF	24	100	0	0

[a] Ratio **3.5** : benzaldehyde : Bi : ZnF_2 = 1 : 1.1 : 1.2 : 1.2 mmol and 1 ml of solvent.
[b] Determined by ^1H NMR of the crude product. [c] Isolated yield.

3.4. Application of Bismuth-Mediated Aqueous Crossed Aldol Type Reaction

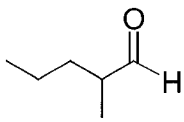
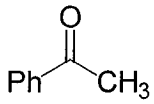
With a set of optimized reaction conditions, the bismuth-mediated aqueous crossed aldol type reactions of 2-bromoisobutyrophenone **3.5** with a variety of aldehydes were surveyed (Scheme 3.9), and the results are presented in Table 3.6. In general, both aromatic and aliphatic aldehydes reacted smoothly with the compound **3.5** to provide the corresponding aldol products in moderate to high yields (entries 1-7).



3.5 **3.9** **3.7**

Scheme 3.9

Table 3.6. Bismuth-mediated crossed aldol type reactions of 2-bromoisobutyrophenone with various aldehydes in the presence of ZnF_2 in aqueous media[a]

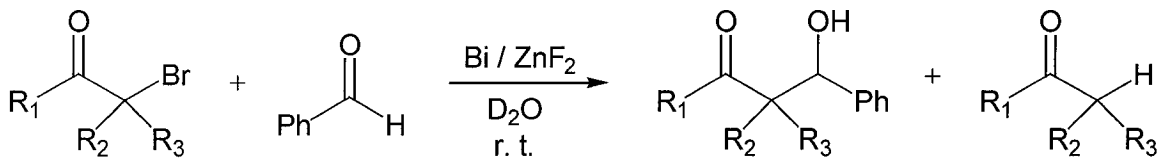
Entry	R	Time (hr)	Unreacted **3.5** (%)[b]	Yield (%) of **3.9**[b]		Yield (%) of **3.7**[b]
1	Ph	12	0	95 (90[c])		5
2	*p*-CH_3Ph	24	10	80 (66[c])		10
3	*p*-CH_3OPh	24	98	trace		trace
4	*p*-ClPh	16	26	69 (91[c])	**3.9a**	5
5	*p*-CNPh	16	19	80 (98[c])		trace
6	*n*-C_5H_{11}	12	0	53 (35[c])	**3.9b**	47
7	$Ph(CH_2)_2$	12	20	67 (56[c])	**3.9c**	13
8		12	7	0		93
9		20	10	0		90

[a] Ratio **3.5** : aldehyde : Bi : ZnF_2 = 1 : 1.1 : 1.2 : 1.2 mmol and 1 ml of D_2O.
[b] Determined by ^1H NMR of the crude product. [c] Isolated yield based on reacted **3.5**.

The aldol addition reactions of aromatic aldehydes with either an electron-donating or an electron-withdrawing group showed the same trend as was previously observed with NH_4HF_2. However, in the present case, the substituent on the aromatic ring appeared to have a much greater electronic effect on the reaction (entries 2-5). Moderate yields were obtained with linear aliphatic aldehydes due to the competing reduction of the compound **3.5** (entries 6 and 7). In the case of branched aliphatic aldehydes, the aldol addition reaction could not proceed probably because of steric hindrance, and only the reduction

product **3.7** was obtained as the major product (entry 8). The attempted aldol addition reactions with ketones were also unsuccessful under these conditions giving the reduction products exclusively (entry 9).

In order to explore the generality of this methodology, the bismuth-mediated aqueous crossed aldol type reactions of various α-bromocarbonyl compounds with benzaldehyde were carried out under the similar reaction conditions (Scheme 3.10). The results are summarized in Table 3.7.

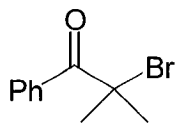
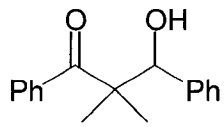
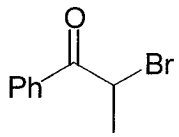
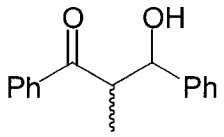
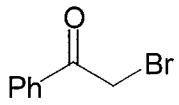
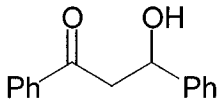
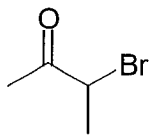
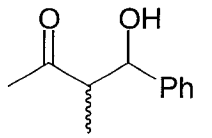
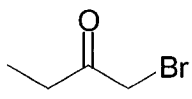
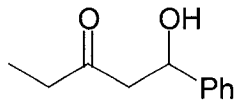
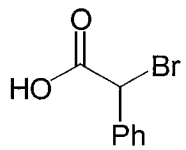
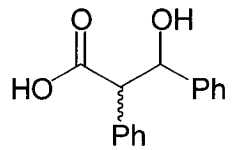
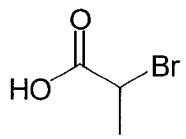
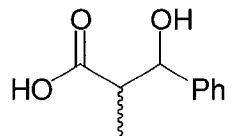


3.10 **3.11** **3.12**

Scheme 3.10

As shown in Table 3.7, aromatic α-bromoketones generally reacted better to provide the corresponding β-hydroxyketones in higher yields (entries 1-3) in comparison with aliphatic α-bromoketones (entries 4 and 5). The reactions of α-bromocarboxylic acids with benzaldehyde resulted in the formation of the corresponding reduction products as the major product (entries 6 and 7). It should be noted that in the case of monomethyl substituted α-bromoketones, *syn* diastereoselectivity of varying degrees was observed (entries 2, 4 and 6). At this stage, the exact mechanism for the bismuth-mediated aqueous crossed aldol type reaction is still unclear. However, these results strongly suggest that the generation of a more stable bismuth enolate intermediate can lead to a higher yield of the corresponding aldol addition product.

Table 3.7. Bismuth-mediated crossed aldol type reactions of α-bromocarbonyl compounds with benzaldehyde in the presence of ZnF_2 in aqueous media

Entry	**3.10**	Isolated yield (%) of **3.11** (*syn* : *anti*)[f]		% Yield of **3.12**[f]
1				90[a] 5
2			**3.11a**	98[a] (55 : 45) trace
3			**3.11b**	55[b] 43
4			**3.11c**	50[c] (73 : 27) 43
5				12[c] 88
6				22[d,f] (64 : 36) 78
7				0[e,f] 100

[a] Ratio **3.10** : aldehyde : Bi : ZnF_2 = 1 : 1.1 : 1.2 : 1.2 mmol / 12 hrs.

[b] Ratio **3.10** : aldehyde : Bi : ZnF_2 = 1 : 2 : 2 : 2 mmol / 40 hrs.

[c] Ratio **3.10** : aldehyde : Bi : ZnF_2 = 1 : 2 : 3 : 2 mmol / 40 hrs.

[d] Ratio **3.10** : aldehyde : Bi : ZnF_2 = 1 : 1.1 : 1.5 : 1.5 mmol / 6 hrs.

[e] Ratio **3.10** : aldehyde : Bi : ZnF_2 = 1 : 1.1 : 2 : 2 mmol / 24 hrs.

[f] Determined by ^1H NMR of the crude product.

3.5. Conclusion

The bismuth-mediated aqueous crossed aldol type reaction was investigated. The preliminary study showed that bismuth activated by ammonium hydrogen fluoride could mediate the aldol addition reaction of 2-bromoisobutyrophenone with benzaldehyde in aqueous media. After screening an array of fluoride salts, zinc fluoride was found to be the promoter of choice for the activation of bismuth metal in aqueous media. The generality of this bismuth-mediated aqueous crossed aldol type reaction was demonstrated with the formation of diverse β-hydroxycarbonyl compounds in moderate to high yields.

3.6. Experimental

General Information:

Chemicals were purchased from Aldrich or Alfa Aesar Chemical Company. All the aldehydes were purified by distillation or column chromatography prior to use. Thin layer chromatography was performed on plastic plates precoated with silica gel (60 F_{254}), which were developed using a mixture of hexane and ethyl acetate as an eluent. Analytes were visualized by UV light or by dipping the plate into a developing agent (a solution of ammonium molybdate and ceric sulfate in dilute sulfuric acid) and heating with a heat gun. Column chromatography was performed on 230-400 mesh silica gel.

Melting points were determined using a Gallenkamp apparatus and were uncorrected. Infrared spectra were recorded on an Avatar 360 FT-IR spectrometer and reported in cm^{-1}. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian

Mercury 300 or 400 MHz spectrometer or a Varian Unity 500 MHz spectrometer at ambient temperature. Chemical shifts (δ) were reported in parts per million (ppm) and referenced to $CDCl_3$ at δ 7.25 ppm for ^1H and δ 77.00 ppm for ^{13}C. The multiplicity of each signal was indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet) and m (multiplet). Coupling constants (*J*) were reported in Hertz (Hz). Mass spectra were recorded on a Kratos MS25RFA mass spectrometer by Dr. N. Saade at the department of McGill University or on a HP 5980A mass spectrometer by Dr. O. Mamer at the Biomedical Mass Spectrometry Unit of McGill University.

General Procedure for Bismuth-Mediated Aqueous Crossed Aldol Type Reaction:

To a mixture of 2-bromoisobutyrophenone (1 mmol), an aldehyde (1.1 mmol), bismuth powder (1.2 mmol), and ZnF_2 (1.2 mmol) was added D_2O (1 ml). The reaction mixture was vigorously stirred at room temperature for the indicated time in Table 3.6 (12-24 hrs). Additional distilled water (10 ml) was added in the reaction mixture, and the product was extracted with diethyl ether (3 × 30 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the evaporation of solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel using 5% ethyl acetate in hexane as an eluent to give the corresponding pure aldol addition product.

3-Hydroxy-2,2-dimethyl-1,3-diphenyl-1-propanone (3.8a): white solid; mp 105-107 °C; IR ($CHCl_3$): 3475 (O—H), 1672 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58-7.54 (m, 2H), 7.48-7.25 (m, 8H), 5.15 (d, *J* = 3.5 Hz, 1H), 2.92 (d, *J* = 4.0 Hz, 1H), 1.27

(s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.59, 140.04, 139.51, 130.37, 127.86, 127.81, 127.64, 127.58, 126.98, 78.82, 52.52, 24.34, 19.70.

3-Hydroxy-2,2-dimethyl-3-(4-methylphenyl)-1-phenyl-1-propanone (3.8b): white solid; mp 83.5-85.0 °C; IR ($CHCl_3$): 3490 (O—H), 1673 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.55 (m, 2H), 7.47-7.42 (m, 1H), 7.40-7.36 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.10 (s, 1H), 2.94 (br s, 1H), 2.36 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.62, 139.59, 137.19, 137.06, 130.30, 128.30, 127.83, 127.68, 126.98, 78.67, 52.54, 24.34, 21.21, 19.62.

3-(4-Cyanophenyl)-3-hydroxy-2,2-dimethyl-1-phenyl-1-propanone (3.8c): colorless oil; IR ($CHCl_3$): 3477 (O—H), 2229 (C≡N), 1673 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.49 (m, 4H), 7.43-7.31 (m, 5H), 5.13 (d, J = 3.3 Hz, 1H), 3.72 (d, J = 3.8 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.73, 145.52, 138.80, 131.30, 130.75, 128.54, 127.95, 127.03, 118.58, 111.18, 77.93, 52.38, 24.03, 19.63; MS (CI, NH_3): *m/z* 280 ($M + H^+$, 5), 148 (51), 130 (48), 105 (100), 77 (13); HRMS (FAB): calcd for $C_{18}H_{17}NO_2 + H^+$ 280.1337, found 280.1338.

3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethyl-1-phenyl-1-propanone (3.9a): white solid; mp 57-59 °C; IR ($CHCl_3$): 3475 (O—H), 1673 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.44-7.39 (m, 1H), 7.36-7.32 (m, 2H), 7.26-7.19 (m, 4H), 5.04 (s, 1H), 3.61 (br s, 1H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

211.25, 139.17, 138.53, 133.15, 130.46, 129.07, 127.83, 127.65, 126.96, 77.95, 52.36, 24.10, 19.53.

3-Hydroxy-2,2-dimethyl-1-phenyl-1-octanone (3.9b): colorless oil; IR ($CHCl_3$): 3489 (O—H), 1671 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.44-7.40 (m, 1H), 7.37-7.33 (m, 2H), 3.85 (dd, J = 10.0, 2.1 Hz, 1H), 2.69 (br s, 1H), 1.61-1.14 (m, 14H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.75, 139.01, 130.52, 127.80, 127.19, 76.96, 52.11, 31.75, 31.59, 26.48, 22.89, 22.64, 21.20, 14.09; MS (FAB): *m/z* 249 ($M + H^+$, 15), 231 (7), 149 (27), 131 (30), 105 (100), 77 (16); HRMS (FAB): calcd for $C_{16}H_{24}O_2 + H^+$ 249.1855, found 249.1855.

3-Hydroxy-2,2-dimethyl-1,5-diphenyl-1-pentanone (3.9c): colorless oil; IR ($CHCl_3$): 3489 (O—H), 1669 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63-7.60 (m, 2H), 7.48-7.44 (m, 1H), 7.41-7.36 (m, 2H), 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 3.91 (dd, J = 10.4, 2.4 Hz, 1H), 3.02-2.95 (m, 1H), 2.77 (br d, J = 5.7 Hz, 1H), 2.71-2.63 (m, 1H), 1.85-1.71 (m, 2H), 1.34 (d, J = 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.72, 141.86, 138.73, 130.80, 128.32, 128.22, 127.95, 127.32, 125.68, 76.57, 51.93, 33.57, 33.06, 23.18, 21.24.

3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (3.11a): *syn* isomer: white solid; mp 71-73 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96-7.92 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.23 (m, 7H), 5.25 (d, J = 2.6 Hz, 1H), 3.71 (qd, J = 7.3, 3.2 Hz, 1H), 3.69 (br s, 1H), 1.21 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.53, 141.63, 135.46, 133.47,

128.67, 128.36, 128.13, 127.19, 125.91, 73.03, 47.03, 11.24; *anti* isomer: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-7.95 (m, 2H), 7.59-7.53 (m, 1H), 7.49-7.25 (m, 7H), 4.99 (d, J = 8.1 Hz, 1H), 3.84 (quint, J = 7.3 Hz, 1H), 3.09 (br s, 1H), 1.07 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.63, 142.00, 136.54, 133.15, 128.50, 128.30, 127.77, 126.58, 76.68, 47.96, 15.76.

3-Hydroxy-1,3-diphenyl-1-propanone (3.11b): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97-7.93 (m, 2H), 7.61-7.55 (m, 1H), 7.48-7.27 (m, 7H), 5.35 (dd, J = 7.7, 4.4 Hz, 1H), 3.73 (br s, 1H), 3.39-3.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.74, 142.77, 136.29, 133.41, 128.46, 128.33, 127.95, 127.43, 125.56, 69.86, 47.34.

3-Hydroxy-1,2-dimethyl-3-phenyl-1-propanone (3.11c): *syn* isomer: colorless oil; IR ($CHCl_3$): 3443 (O—H), 1703 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 5.05 (d, J = 4.1 Hz, 1H), 3.25 (br s, 1H), 2.82 (qd, J = 7.1, 4.1 Hz, 1H), 2.11 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.20, 141.54, 128.04, 127.14, 125.69, 72.96, 53.20, 29.43, 10.29; *anti* isomer: colorless oil; IR ($CHCl_3$): 3431 (O—H), 1705 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 4.72 (d, J = 8.8 Hz, 1H), 3.02 (br s, 1H), 2.92 (quint, J = 7.2 Hz, 1H), 2.22 (s, 3H), 0.92 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.19, 141.67, 128.32, 127.83, 126.46, 76.44, 53.66, 30.12, 14.21.

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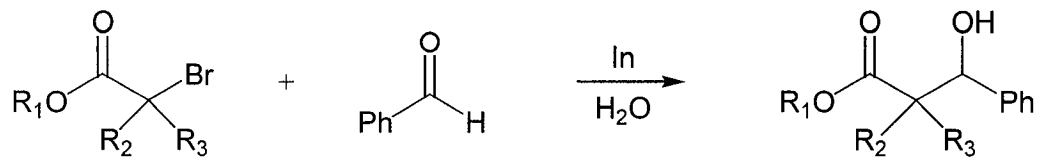
Chapter 4.

Bismuth-Mediated Reformatsky Type Reactions in Aqueous Media

4.1. Introduction

Since the first discovery by Reformatsky in 1887, the Reformatsky reaction, which employs an α-haloester, a carbonyl compound, and zinc metal to produce a β-hydroxyalkanoate, has become one of the most useful synthetic methods for the formation of carbon-carbon bonds along with the aldol addition reaction.[1] However, the yield and the stereoselectivity of the Reformatsky reaction have remained at a lower lever than those of the aldol reaction. In addition, the reaction usually has to be carried out at a high temperature, which causes concurrent undesirable side reactions such as reduction. A great deal of efforts have been made to overcome these problems, and considerable progress has been attained by continuously increasing the reactivity of zinc by the application of various other metals or metal salts.[2] All of these reactions are performed in organic solvents.

In 1993, the indium-mediated aqueous Reformatsky type reactions were successfully achieved by Chan *et al.*[3] It was found that indium could mediate the reactions of α-bromoesters and acids **4.1** with aromatic aldehydes in aqueous media to afford the corresponding β-hydroxyesters **4.2** in moderate yields (Scheme 4.1). On the other hand, aliphatic aldehydes were recovered unchanged, and the reduced esters and acids were obtained as the major products under the identical reaction conditions.

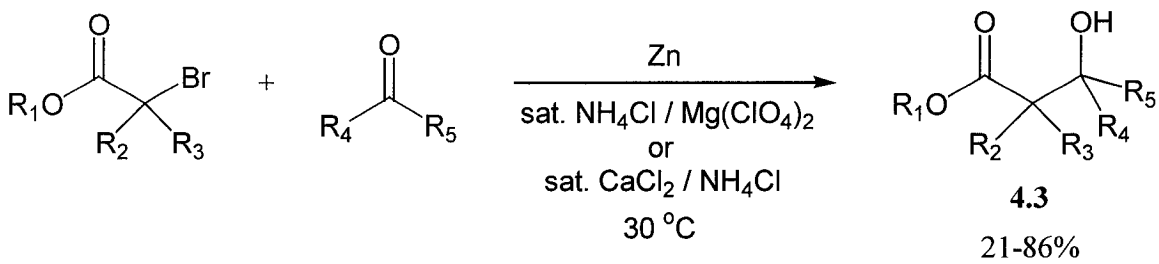


4.1 **4.2**

5-52%

Scheme 4.1

More recently, Bieber *et al.* reported that the Reformatsky reactions of α-bromoesters with a wide variety of carbonyl compounds in the presence of zinc could be carried out in concentrated aqueous salt solutions (saturated ammonium chloride/magnesium perchlorate or saturated calcium chloride/ammonium chloride) without any cosolvent at 30 °C to provide the corresponding Reformatsky adducts **4.3** in moderate to good yields (Scheme 4.2).[4]

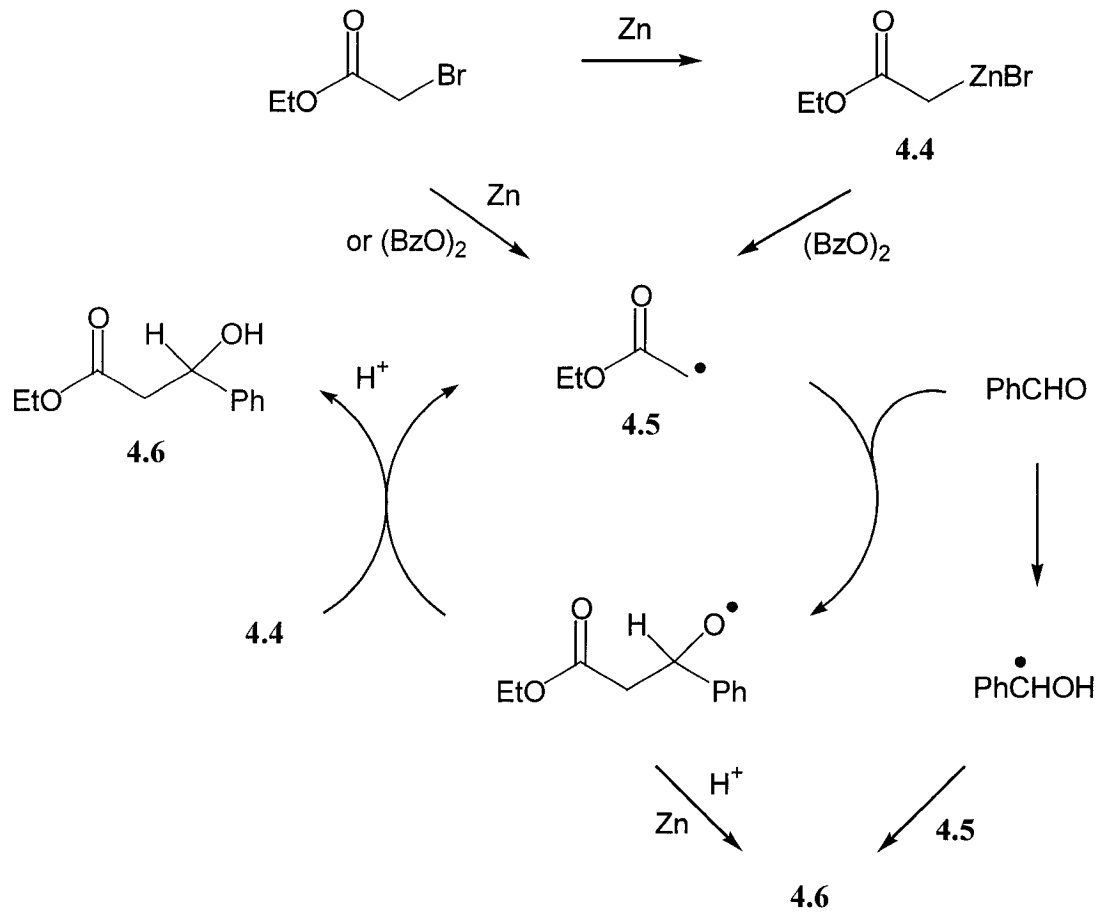


4.3

21-86%

Scheme 4.2

Furthermore, it was observed that the yield could be greatly improved by the addition of a catalytic amount of benzoyl peroxide or peracids. From these findings, a radical chain mechanism, initiated by electron abstraction from the organometallic Reformatsky reagent **4.4**, was proposed (Scheme 4.3). Two alternative non-chain pathways involving radicals directly produced on the metal surface were also suggested, especially in the case of secondary and tertiary halides.



Scheme 4.3

4.2. Hydrophobic Effect in Organic Reactions

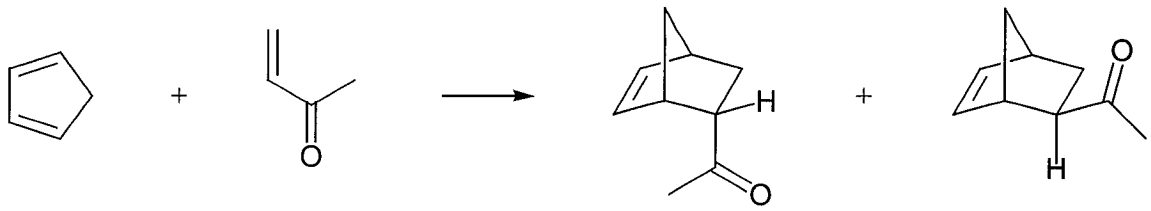
The hydrophobic effect[5] is the tendency of nonpolar substances to aggregate in aqueous solutions in order to minimize the interfacial area between the nonpolar species and water. This hydrophobic interaction is due not to the mutual attraction of the nonpolar molecules but to the high cohesive energy density of water, which causes the polar water molecules surrounding the nonpolar compounds to associate with each other. Hydrophobic aggregation can be driven by either entropy or enthalpy. An improved

enthalpy of solvation of a substrate can come at the expense of solvent restriction and entropy loss.[6]

The hydrophobic effect plays a crucial role in biological systems. It is a principal force determining the tertiary structures of proteins and nucleic acids, the binding of substrates to enzymes, and the binding of antigens to antibodies. It also causes the self-assembly of amphiphiles in micelles or membranes. Apart from its importance in biological processes, the hydrophobic effect is critical for various solution phenomena, such as surfactant aggregation, mineral flotation, coagulation, and detergency.[6,7]

In 1980, Breslow *et al.* reported intriguing solvent effects of water on common Diels-Alder reactions.[8] They observed remarkable rate acceleration and a striking increase in stereoselectivity by using water as a solvent for the Diels-Alder reaction of cyclopentadiene with butenone (Scheme 4.4). These special effects operating in water were attributed not to simple solvent polarity or hydrogen-bonding ability but to the hydrophobic packing of the diene with the dienophile in the transition state. It was further supported by the finding that the reaction was also catalyzed in the presence of appropriate cyclodextrin via close association of the reactants in the hydrophobic cyclodextrin cavity.

Additional evidence was found in the effects of two special additives, salting-out and salting-in agents.[9] Salting-out agents, such as lithium chloride, increase the hydrophobic effect decreasing the water solubility of hydrocarbons by stabilizing the water structure. On the contrary, salting-in agents, such as guanidinium chloride, decrease the hydrophobic effect increasing the water solubility of hydrocarbons by breaking up the ordered water structure.



endo *exo*

Kinetics

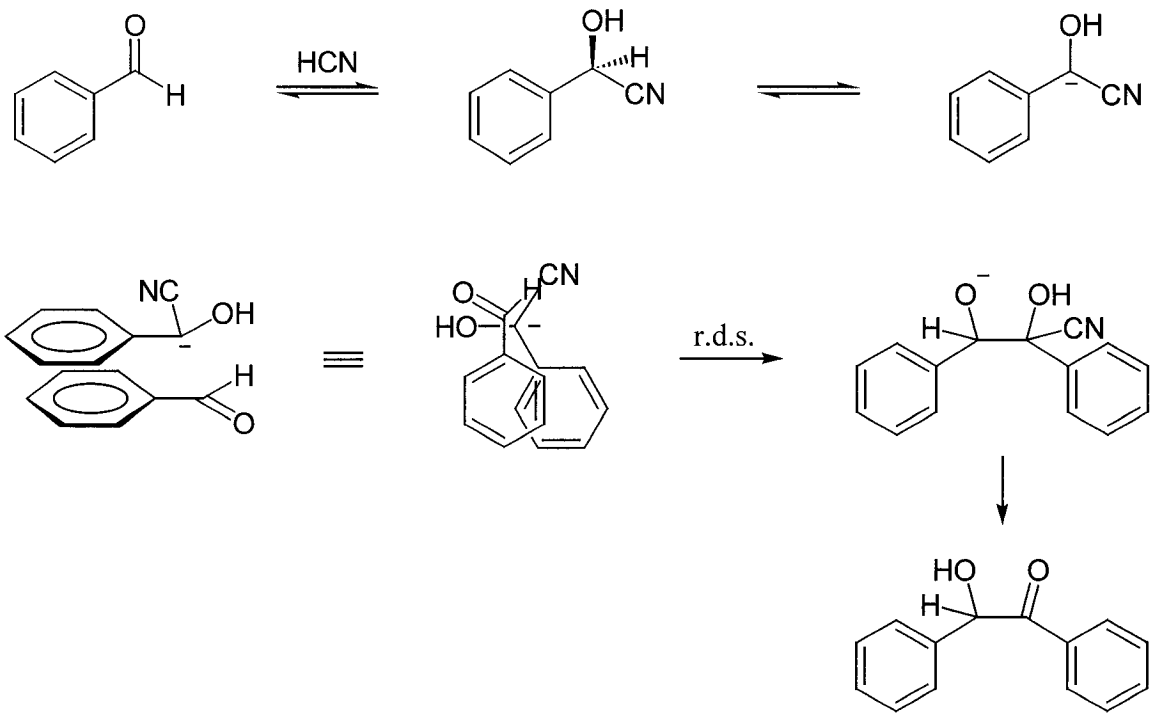
Solvent	Additives	$K_2 \times 10^5$ ($M^{-1}S^{-1}$)
Isooctane		5.94 ± 0.3
Methanol		75.5
H_2O		4400 ± 70
H_2O	β-cyclodextrin (10 mM)	10900
H_2O	α-cyclodextrin (10 mM)	2610
H_2O	LiCl (4.86 M)	10800
H_2O	$C(NH_2)_3Cl$ (4.86 M)	4300

Selectivity

Solvent	Additives	*Endo*/*exo* ratio
Cyclopentadiene		3.85
Ethanol		8.5
H_2O		25 ± 0.5
H_2O	LiCl (4.86 M)	28 ± 0.4
H_2O	$C(NH_2)_3Cl$ (4.86 M)	22 ± 0.8

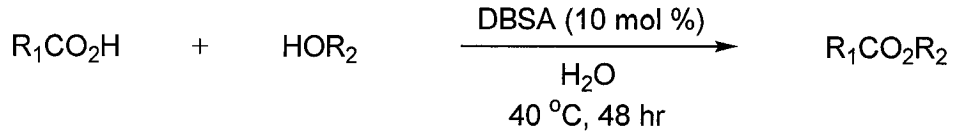
Scheme 4.4

In addition to Diels-Alder reactions, Breslow's group established that the hydrophobic effect was also involved in the cyanide-catalyzed aqueous benzoin condensation.[10] The correlation between the salt effects and the observed rate effects strongly suggested the hydrophobic stacking of the aromatic rings in the transition state so as to diminish the hydrocarbon surface exposed to water (Scheme 4.5).



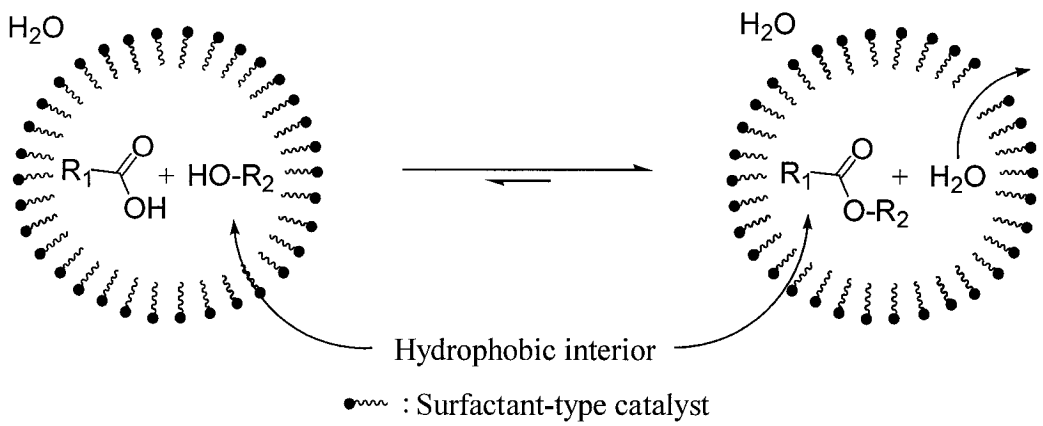
Scheme 4.5

Very recently, the direct formation of esters from carboxylic acids and alcohols in water was realized by Kobayashi *et al.* using a surfactant-type Brønsted acid catalyst.[11] They showed that the esterification of lipophilic carboxylic acids could efficiently proceed in the presence of 10 mol % *p*-dodecylbenzenesulfonic acid (DBSA) in water at 40 °C to give the corresponding esters in high yields (Scheme 4.6). Furthermore, selective esterification based on the difference in the hydrophobicity of substrates was observed as well. The catalyst and the substrates in the present system assemble together through hydrophobic interactions to form devices for dehydration reactions, in which the catalyst enhances the reaction rate, and the hydrophobic interior of emulsion droplets facilitates the exclusion of water molecules generated as the reaction proceeds (Scheme 4.7). Dehydration in water is really unusual and surprising since in general, hydrolysis takes place in water.



R_1	R_2	Yield (%)
$CH_3(CH_2)_{10}$	$(CH_2)_3Ph$	89
$CH_3(CH_2)_{10}$	$(CH_2)_{11}CH_3$	97
$Ph(CH_2)_4$	$(CH_2)_{13}CH_3$	97
c-Hex	$(CH_2)_{13}CH_3$	95

Scheme 4.6

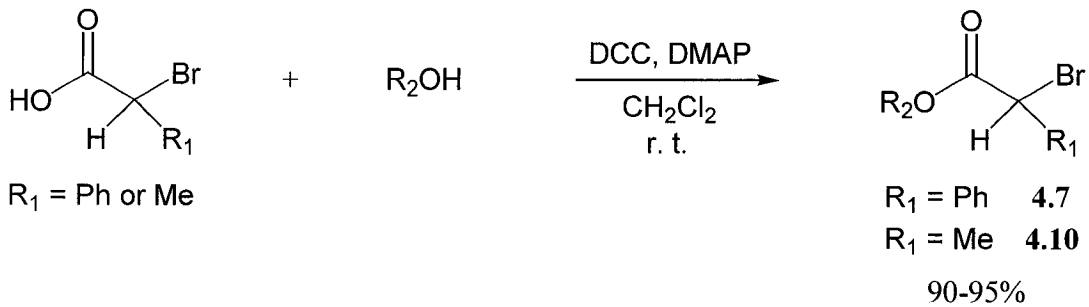


Scheme 4.7

4.3. Study of Hydrophobic Effect in Bismuth-Mediated Aqueous Reformatsky Type Reaction

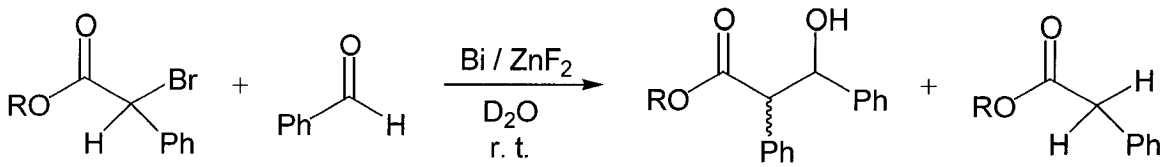
The success in utilizing bismuth metal for the aqueous crossed aldol type reactions as demonstrated in the previous chapter encouraged us to investigate the bismuth-mediated Reformatsky type reactions in aqueous media. However, the preliminary trials

with the two simple α-bromocarboxylic acids led to the unsatisfactory results affording the corresponding reduced acids as the major product (Table 4.1, entry 1 and Table 4.2, entry 1). Since the hydrophobic effect has been used successfully in improving organic reactions in aqueous media, a systematic study of hydrophobic effect in the bismuth-mediate aqueous Reformatsky type reaction was undertaken. Two series of α-bromoesters were synthesized by the esterification reactions of those two α-bromocarboxylic acids with several alcohols using a procedure reported in the literature[12] with a minor modification. In the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP), α-bromophenylacetic acid and α-bromopropionic acid could be completely converted to the corresponding α-bromoesters with alkyl groups of varying length in high yields at room temperature under essentially neutral reaction conditions (Scheme 4.8). With all of the α-bromoesters prepared, the effect of alkyl groups on the bismuth-mediated aqueous Reformatsky type reaction was explored.



Scheme 4.8

The first attempted bismuth-mediated Reformatsky type reactions were carried out with a series of α-bromophenylesters **4.7** and benzaldehyde in the presence of zinc fluoride in aqueous media at room temperature (Scheme 4.9). The results are summarized in Table 4.1.



4.7 **4.8** **4.9**

Scheme 4.9

Table 4.1. Effect of alkyl groups on the bismuth-mediated Reformatsky type reaction in the presence of ZnF_2 in aqueous media[a]

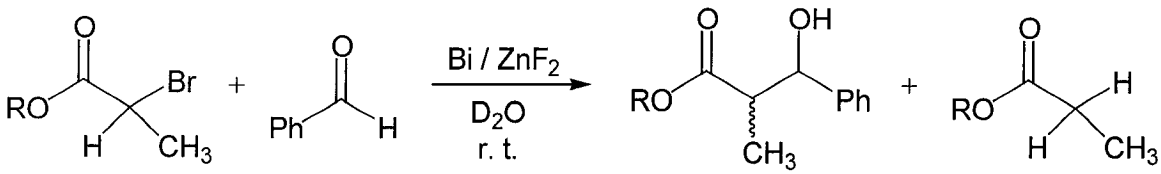
Entry	R		Time (hr)	% Yield of **4.8** (*syn* : *anti*)[b]	% Yield of **4.9**[b]	**4.8** : **4.9**[b]
1	H		6	22 (64 : 36)	78	1 : 3.5
2	C_2H_5		12	37 (67 : 33)	63	1 : 1.7
3	C_4H_9		12	61 (67 : 33)	39	1.6 : 1
4	C_6H_{13}	**4.7a**	12	66 (67 : 33)	34	1.9 : 1
5	C_8H_{17}	**4.7b**	12	66 (67 : 33)	34	1.9 : 1

[a] Ratio **4.7** : benzaldehyde : Bi : ZnF_2 = 1 : 1.1 : 1.5 : 1.5 mmol and 1 ml of D_2O.
[b] Determined by ^1H NMR of the crude product.

The Reformatsky reaction of ethyl α-bromophenylacetate with benzaldehyde provided the corresponding β-hydroxyester only in 37% yield with a *sin* : *anti* ratio of 2 : 1, and the reduced ester was formed as the major product (entry 2). However, gratifyingly, when hexyl α-bromophenylacetate was employed to react with benzaldehyde, the yield of the corresponding Reformatsky adduct could be moderately increased without any significant change in diastereoselectivity (entry 4). No further improvement either in the yield of the desired addition product or in the diastereoselectivity of the reaction was observed in the Reformatsky reactions of α-bromo

esters with longer alkyl groups (entry 5).

The next series of bismuth-mediated aqueous Reformatsky type reactions was studied with α-bromopropanoate esters **4.10** and benzaldehyde using small excess amounts of bismuth metal and zinc fluoride (Scheme 4.10). The results are summarized in Table 4.2.



4.10 **4.11** **4.12**

Scheme 4.10

Table 4.2. Effect of alkyl groups on the bismuth-mediated Reformatsky type reaction in the presence of ZnF_2 in aqueous media[a]

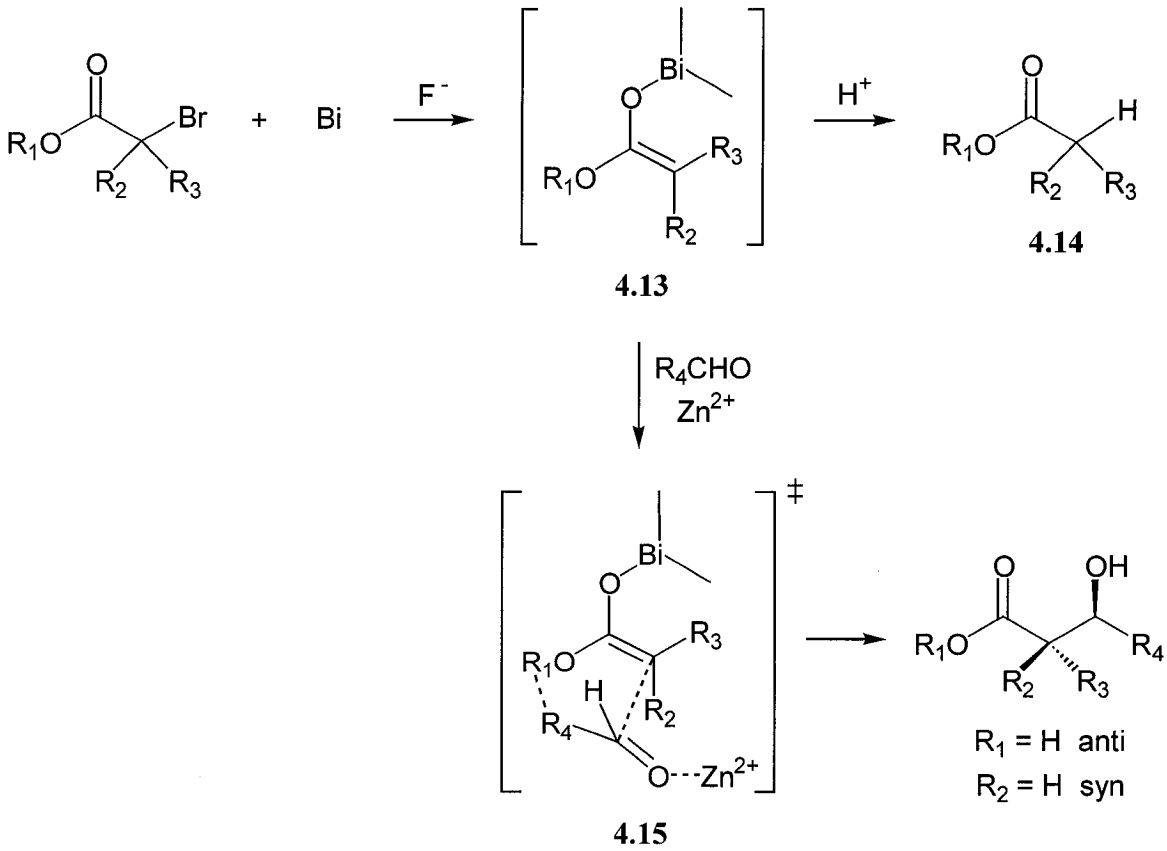
Entry	R	Time (hr)	% Yield of **4.11** (*syn* : *anti*)[b]	% Yield of **4.12**[b]	**4.11** : **4.12**[b]
1	H	24	0	100	
2	C_2H_5	36	31 (66 : 34)	69	1 : 2.2
3	C_4H_9	48	54 (65 : 35)	46	1.2 : 1
4	C_6H_{13}	48	38 (62 : 38)	29	1.3 : 1
5	C_8H_{17}	48	31 (61 : 39)	23	1.3 : 1

[a] Ratio **4.10** : benzaldehyde : Bi : ZnF_2 = 1 : 1.1 : 2 : 2 mmol and 1 ml of D_2O.
[b] Determined by ^1H NMR of the crude product.

As shown in Table 4.2, the Reformatsky reactions were found to be considerably slower in comparison with the previous case, and consequently, much longer reaction times were required in order to complete the reactions (entries 2 and 3). Nevertheless, the

same trends were observed as before. It is apparent that the higher yield of the corresponding Reformatsky adduct **4.11** could be obtained by increasing the length of the alkyl group on the α-bromoester. All of the Reformatsky reactions in the present case proceeded with nearly constant diastereoselectivity favoring the *syn* isomer.

A detailed analysis of the reaction mechanism offers a basis for understanding the relationship between the enolate geometry and the stereochemistry of the product. No attempt has been made to determine the enolate geometry and the oxidation state of the bismuth species in the present reactions. However, based on the above observations together with the results obtained in the previous chapter, a plausible mechanism for these bismuth-mediated organometallic reactions can be proposed as presented in Scheme 4.11.



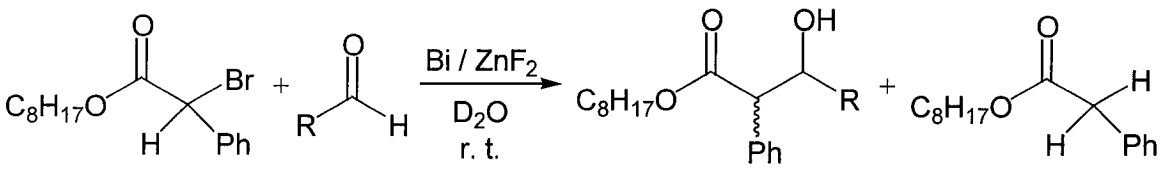
Scheme 4.11

Upon the activation of bismuth metal by the fluoride anion, a bismuth enolate intermediate **4.13** is formed, which is subjected to the competition between the reduction and the crossed aldol reaction or the Reformatsky reaction. The subsequent protonation of the bismuth enolate intermediate affords the reduction product **4.14**. A preference for *syn* diastereoselectivity in crossed aldol reactions and Reformatsky reactions can be explained in terms of an acyclic extended *antiperiplanar* transition state[13] **4.15** rather than a six-membered cyclic transition state[14] with a chairlike conformation in which the metal cation is coordinated to both the enolate oxygen and the carbonyl oxygen. The open chain transition state is characterized by variable, though often high *syn* diastereoselectivity, which is practically independent of starting enolate geometry.[15] The aldehyde is activated by virtue of the increased electrophilicity of the carbonyl functional group upon coordination to the Lewis acidic zinc cation. Moreover, as demonstrated above, there is the hydrophobic interaction between the alkyl group R_1 of the bismuth enolate and the alkyl group R_4 of the aldehyde, which is quite commonly observed in the reactions carried out in aqueous media.

4.4. Application of Bismuth-Mediated Aqueous Reformatsky Type Reaction

The generality of the bismuth-mediated aqueous Reformatsky type reactions of octyl α-bromophenylacetate **4.16** was surveyed with a representative array of aldehydes under the standard conditions (Scheme 4.12). The results are summarized in Table 4.3. Both aromatic and aliphatic aldehydes reacted smoothly with the compound **4.16** to give the corresponding Reformatsky adducts in moderate yields (entries 1-4). In the case of

substituted aromatic aldehydes, the electron-donating group resulted in the lower yield of the desired adduct, whereas the electron-withdrawing group led to the slightly higher yield (entries 2 and 3). Once again, the diastereoselectivity of the present Reformatsky reactions was found to be uniform in favor of the *syn* isomer.



4.16 **4.17** **4.18**

Scheme 4.12

Table 4.3. Bismuth-mediated Reformatsky type reactions of octyl α-bromophenylacetate with various aldehydes in the presence of ZnF_2 in aqueous media[a]

Entry	R	Time (hr)	% Yield of **4.17**[b]		*syn* : *anti*[b]	% Yield of **4.18**[b]
1	Ph	6	65 (37[c])	**4.17a**	67 : 33	35
2	*p*-CH_3OPh	10	49 (18[c])	**4.17b**	67 : 33	51
3	*p*-CNPh	12	60 (38[c])	**4.17c**	67 : 33	31
4	*n*-C_5H_{11}	3	22[c]	**4.17d**	-[d]	-[d]

[a] Ratio **4.16** : benzaldehyde : Bi : ZnF_2 = 1 : 1.1 : 1.5 : 1.5 mmol and 1 ml of D_2O.
[b] Determined by ^1H NMR of the crude product. [c] Isolated yield based on reacted **4.16**.
[d] Unable to determine by ^1H NMR due to the overlap of peaks.

4.5. Conclusion

In our effort to extend the scope of the bismuth-mediated organometallic reactions in aqueous media, the Reformatsky type reactions were investigated with two series of α-bromoesters, which were prepared by the esterification reactions of α-bromocarboxylic acids with several alcohols. It was found that the yield of the Reformatsky adduct could be improved to a certain extent by increasing the length of the alkyl group on α-bromoester due to the enhanced hydrophobic effect in aqueous media. The observed stereochemical outcomes of the bismuth-mediated aqueous crossed aldol reactions and Reformatsky reactions could be accounted for by an acyclic extended *antiperiplanar* transition state. The generality of this methodology was illustrated with the formation of various octyl β-hydroxyesters in moderate yields.

4.6. Experimental

General Information:

See Experimental Section in Chapter 3.

General Procedure for the Preparation of Esters:

To a stirred solution of a carboxylic acid (10 mmol) and an alcohol (11 mmol) in dry dichloromethane (50 ml) was added *N*,*N*-dicyclohexylcarbodiimide (11 mmol) and 4-(dimethylamino)pyridine (1 mmol) under nitrogen at 0 °C, and the reaction mixture was stirred at room temperature for 3 hrs. The white precipitate (*N*,*N*-dicyclohexylurea) was filtered, and the filtrate was washed with distilled water (3 × 50 ml), 5% acetic acid

solution (3 × 50 ml) and again with distilled water (3 × 50 ml). The organic layer was dried over anhydrous $MgSO_4$ and filtered. After the evaporation of solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel using 1% ethyl acetate in hexane as an eluent to give the corresponding pure ester.

General Procedure for Bismuth-Mediated Aqueous Reformatsky Reaction:

To a mixture of an α-bromoester (1 mmol), an aldehyde (1.1 mmol), bismuth powder (1.5 mmol), and ZnF_2 (1.5 mmol) was added D_2O (1 ml). The reaction mixture was vigorously stirred at room temperature for the indicated time in Table 4.3 (3-12 hrs). Additional distilled water (10 ml) was added in the reaction mixture, and the product was extracted with diethyl ether (3 × 30 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the evaporation of solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel using 2% ethyl acetate in hexane as an eluent to give the corresponding pure Reformatsky adduct.

Hexyl α-bromophenylacetate (4.7a): colorless liquid; IR (neat): 1747 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56-7.53 (m, 2H), 7.38-7.31 (m, 3H), 5.35 (s, 1H), 4.22-4.13 (m, 2H), 1.65 (quint, J = 6.6 Hz, 2H), 1.36-1.23 (m, 6H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.05, 135.68, 129.03, 128.58, 128.45, 66.55, 46.97, 31.33, 28.35, 25.40, 22.55, 14.06; MS (FAB): *m/z* 299 ($M + H^+$, 9), 171 (36), 135 (78), 118 (20), 107 (32), 91 (80), 77 (47), 55 (100); HRMS (FAB): calcd for $C_{14}H_{19}O_2Br + H^+$ 299.0647, found 299.0647.

Octyl α-bromophenylacetate (4.7b): colorless liquid; IR (neat): 1748 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H), 7.38-7.31 (m, 3H), 5.35 (s, 1H), 4.22-4.13 (m, 2H), 1.65 (quint, J = 6.8 Hz, 2H), 1.33-1.26 (m, 10H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.06, 135.70, 129.04, 128.59, 128.47, 66.57, 46.97, 31.78, 29.18, 29.13, 28.40, 25.75, 22.71, 14.21; MS (FAB): *m/z* 327 ($M + H^+$, 3), 169 (19), 136 (21), 118 (21), 91 (58), 77 (23), 57 (100); HRMS (FAB): calcd for $C_{16}H_{23}O_2Br + H^+$ 327.0958, found 327.0960.

Octyl 3-hydroxy-2,3-diphenylpropanoate (4.17a): *syn* isomer: white solid; mp 58-60 °C; IR ($CHCl_3$): 3504 (O−H), 1731 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43-7.25 (m, 10H), 5.25 (d, J = 8.2 Hz, 1H), 3.98-3.84 (m, 2H), 3.89 (d, J = 8.2 Hz, 1H), 2.82 (br s, 1H), 1.61-1.04 (m, 12H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.91, 140.78, 134.88, 128.83, 128.25, 127.91, 127.67, 127.53, 126.50, 75.06, 64.83, 59.81, 31.69, 29.06, 29.01, 28.26, 25.57, 22.62, 14.12; *anti* isomer: colorless oil; IR ($CHCl_3$): 3484 (O−H), 1731 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.06 (m, 10H), 5.17 (d, J = 9.1 Hz, 1H), 4.18-4.07 (m, 2H), 3.87 (d, J = 9.1 Hz, 1H), 3.25 (br s, 1H), 1.61-1.55 (m, 2H), 1.31-1.22 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.31, 140.60, 135.18, 128.36, 128.25, 127.90, 127.58, 127.29, 126.45, 76.49, 65.36, 59.92, 31.80, 29.20, 29.17, 28.51, 25.78, 22.73, 14.23; MS (FAB, NaCl): *m/z* 377 ($M + Na^+$, 9), 337 (13), 219 (28), 181 (31), 136 (23), 107 (39), 91 (44), 57 (100); HRMS (FAB): calcd for $C_{23}H_{30}O_3 + Na^+$ 377.2091, found 377.2093.

Octyl 3-hydroxy-3-(4-methoxyphenyl)-2-phenylpropanoate (4.17b): colorless oil; IR ($CHCl_3$): 3498 (O−H), 1731 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *syn* isomer: δ 7.41-6.68 (m, 9H), 5.21 (d, J = 8.2 Hz, 1H), 3.97-3.84 (m, 2H), 3.86 (d, J = 8.2 Hz, 1H), 3.79 (s, 3H), 2.56 (br s, 1H), 1.44-1.37 (m, 2H), 1.32-1.05 (m, 10H), 0.90 (t, J = 7.3 Hz, 3H); *anti* isomer: δ 7.41-6.68 (m, 9H), 5.12 (d, J = 9.5 Hz, 1H), 4.17-4.08 (m, 2H), 3.85 (d, J = 10.4 Hz, 1H), 3.72 (s, 3H), 3.23 (br s, 1H), 1.61-1.55 (m, 2H), 1.32-1.05 (m, 10H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *syn* isomer: δ 171.97, 159.00, 135.03, 132.91, 128.86, 128.41, 127.80, 127.66, 113.41, 74.84, 64.91, 59.97, 55.14, 31.78, 29.13, 29.12, 28.36, 25.67, 22.69, 14.19; *anti* isomer: δ 173.30, 158.68, 135.26, 132.78, 128.34, 128.18, 127.59, 127.16, 113.23, 75.97, 65.25, 59.97, 55.08, 31.76, 29.16, 29.13, 28.48, 25.75, 22.69, 14.19; MS (FAB, NaCl): *m/z* 407 ($M + Na^+$, 6), 367 (21), 248 (12), 137 (66), 121 (19), 91 (34), 77 (42), 57 (100); HRMS (FAB): calcd for $C_{24}H_{32}O_4$ + Na^+ 407.2198, found 407.2198.

Octyl 3-(4-cyanophenyl)-3-hydroxy-2-phenylpropanoate (4.17c): white solid; mp 81-83 °C; IR ($CHCl_3$): 3483 (O−H), 2229 (C≡N), 1728 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *syn* isomer: δ 7.56-7.00 (m, 9H), 5.35 (dd, J = 6.5, 1.3 Hz, 1H), 4.03-3.94 (m, 2H), 3.79 (d, J = 6.5 Hz, 1H), 3.11 (d, J = 2.2 Hz, 1H), 1.45 (quint, J = 6.5 Hz, 2H), 1.30-1.08 (m, 10H), 0.88 (t, J = 7.4 Hz, 3H); *anti* isomer: δ 7.56-7.00 (m, 9H), 5.20 (dd, J = 9.2, 3.9 Hz, 1H), 4.18-4.07 (m, 2H), 3.76 (d, J = 9.6 Hz, 1H), 3.53 (d, J = 3.9 Hz, 1H), 1.58-1.53 (m, 2H), 1.30-1.08 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *syn* isomer: δ 172.07, 146.00, 133.59, 131.66, 128.89, 128.33, 127.82, 127.19, 118.47, 111.25, 73.95, 65.26, 58.97, 31.67, 29.06, 28.99, 28.25, 25.57, 22.60, 14.13; *anti*

isomer: δ 172.75, 145.97, 134.30, 131.46, 128.42, 128.16, 127.61, 127.10, 118.44, 111.08, 75.56, 65.46, 59.80, 31.67, 29.06, 29.02, 28.35, 25.63, 22.60, 14.13; MS (FAB): *m/z* 380 ($M + H^+$, 62), 248 (18), 206 (68), 192 (41), 154 (98), 136 (100), 77 (66); HRMS (FAB): calcd for $C_{24}H_{29}NO_3 + H^+$ 380.2225, found 380.2226.

Octyl 3-hydroxy-2-phenyloctanoate (4.17d): *syn* isomer: colorless oil; IR ($CHCl_3$): 3530 (O—H), 1731 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.21-4.16 (m, 1H), 4.12-4.02 (m, 2H), 3.57 (d, J = 6.3 Hz, 1H), 2.42 (br s, 1H), 1.59-1.23 (m, 20H), 0.89 (t, J = 6.7 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.11, 135.07, 129.03, 128.44, 127.53, 72.19, 65.07, 57.41, 34.50, 31.81, 29.22, 29.18, 28.51, 25.84, 25.50, 22.73, 22.71, 14.22, 14.17; *anti* isomer: colorless oil; IR ($CHCl_3$): 3492 (O—H), 1720 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H), 4.17-4.02 (m, 3H), 3.56 (d, J = 8.9 Hz, 1H), 2.82 (br s, 1H), 1.59-1.44 (m, 4H), 1.31-1.14 (m, 16H), 0.87 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.60, 136.23, 128.59, 128.20, 127.39, 73.24, 65.15, 58.63, 33.94, 31.81, 31.70, 29.22, 29.17, 28.53, 25.79, 25.17, 22.74, 22.68, 14.24, 14.15; MS (CI, NH_3): *m/z* 349 ($M + H^+$, 62), 331 (51), 249 (48), 219 (16), 173 (13), 136 (43), 118 (100), 91 (94); HRMS (FAB): calcd for $C_{22}H_{36}O_3 + H^+$ 349.2742, found 349.2743.

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Conclusion

In pursuit of environmentally benign and synthetically efficient methodologies for organic synthesis, the organometallic reactions mediated by non-toxic bismuth metal in aqueous media were investigated. Bismuth activated by ammonium hydrogen fluoride was found to reduce a wide variety of α-halocarbonyl compounds in aqueous media to afford the corresponding dehalogenated reduction products in excellent yields. Zinc fluoride was also effective as a promoter for the activation of bismuth in aqueous media. As a result, diverse β-hydroxycarbonyl compounds were obtained in moderate to high yields from the crossed aldol type reactions of α-bromocarbonyl compounds with aldehydes in aqueous media. In addition, the scope of bismuth-mediated aqueous organometallic reactions was successfully extended to the Reformatsky type reactions. However, there still remains a challenge to perform these aqueous organometallic reactions in a highly stereoselective manner. Although the reaction mechanism proposed in Chapter 4 gives a reasonable explanation for the results obtained, further work focusing on structural effects and attempts to identify possible intermediates will be necessary to fully understand the nature of the bismuth-mediated aqueous organometallic reactions in the future. Nevertheless, bismuth shows interesting potential for organic synthesis and opens up new possibilities in organic chemistry

Appendix

NMR and Mass Spectral Data for Newly Synthesized Compounds

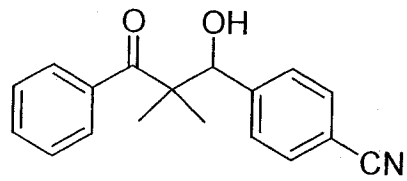
5-125-product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 20.0 C / 293.1 K

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 2.000 sec
Width 4189.4 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 32768
Total time 0 min



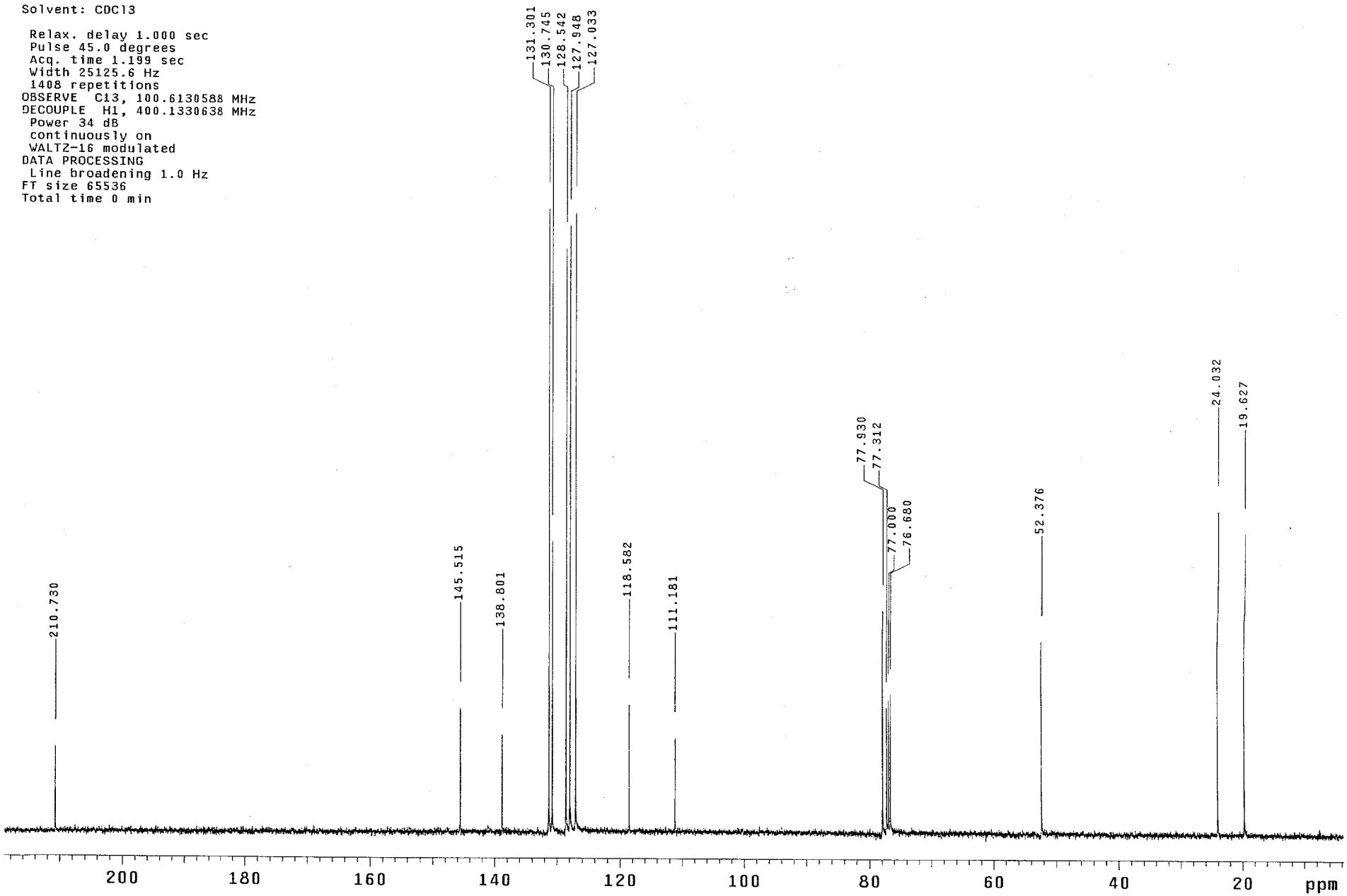
3.8c

5-128 product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
1408 repetitions
OBSERVE C13, 100.6130588 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 0 min



Elemental Composition Date : 21-AUG-2002

Heteroatom Max: 20 Ion: Both Even and Odd
Limits:

				-0.5	0	0	0	0
280.133650	38.5			20.0	200	400	2	5

Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O
280.133650	-36.3	-129.5	280.097368	11.5	17	14	1	3
	-33.6	-119.9	280.100048	16.0	20	12	2	
	-27.7	-99.0	280.105922	7.0	13	16	2	5
	-23.7	-84.6	280.109945	11.0	18	16		3
	-21.0	-75.1	280.112625	15.5	21	14	1	
	-15.2	-54.1	280.118498	6.5	14	18	1	5
	-12.5	-44.5	280.121178	11.0	17	16	2	2
	-8.4	-30.2	280.125201	15.0	22	16		
	-2.6	-9.2	280.131074	6.0	15	20		5
	0.1	0.4	280.133754	10.5	18	18	1	2
	8.7	30.9	280.142307	6.0	14	20	2	4
	12.7	45.3	280.146330	10.0	19	20		2
	21.2	75.8	280.154883	5.5	15	22	1	4
	23.9	85.4	280.157563	10.0	18	20	2	1
	33.8	120.7	280.167460	5.0	16	24		4
	36.5	130.3	280.170140	9.5	19	22	1	1

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Montreal, Quebec, Canada. H3A 1A3

HARDWARE PEAK MATCH ZAB 2F HS Date 21 Aug 02

NAME Lee SAMPLE 5-128

FORMULA $C_{18}H_{17}NO_2 + H^+$

MASS 280 ELECTRON IMPACT: _____eV _____μA

CHEM. ION. GAS: NH_3___ *i*-BUT___ CH_4___ ____ x 10^{-5} TORR

RESOLUTION 12,000 SOURCE RT PROBE FAB

MASS REF: PFK___ GLYCEROL ✓ OTHER_____

REFERENCE ION: $C_9H_{25}O_4$ = 277.14986

PEAK MATCH RATIO: 1.010766

SAMPLE EXACT MASS: 280.13365

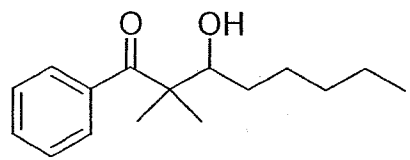
___ERROR IN YOUR MW CALC. ___SEE OVER ⇒

5-129-product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 1.998 sec
Width 3765.1 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



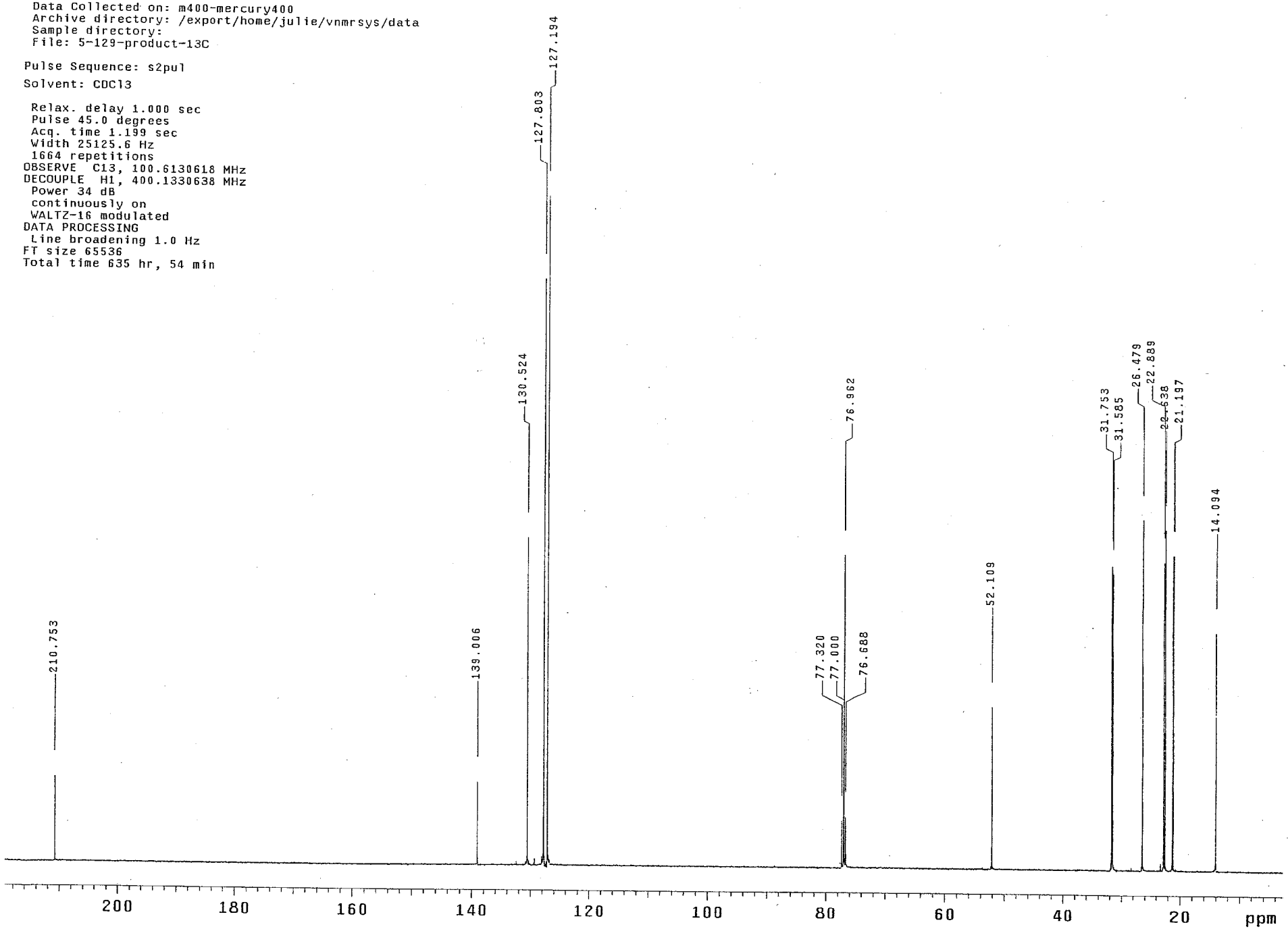
3.9b

5-129-product-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: 5-129-product-13C

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
1664 repetitions
OBSERVE C13, 100.6130618 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 635 hr, 54 min



Elemental Composition Date : 21-AUG-2002

Heteroatom Max: 20 Ion: Both Even and Odd
Limits:

				-0.5	0	0	0	0
249.185510	38.5			20.0	200	400	2	5

Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O
249.185510	-36.4	-146.2	249.149070	5.5	15	21		3
	-33.8	-135.5	249.151750	10.0	18	19	1	
	-27.9	-111.9	249.157623	1.0	11	23	1	5
	-25.2	-101.2	249.160303	5.5	14	21	2	2
	-21.2	-85.0	249.164326	9.5	19	21		
	-15.3	-61.4	249.170199	0.5	12	25		5
	-12.6	-50.7	249.172879	5.0	15	23	1	2
	-4.1	-16.4	249.181433	0.5	11	25	2	4
	-0.1	-0.2	249.185455	4.5	16	25		2
	8.5	34.1	249.194009	0.0	12	27	1	4
	11.2	44.9	249.196689	4.5	15	25	2	1
	21.1	84.6	249.206585	-0.5	13	29		4
	23.8	95.3	249.209265	4.0	16	27	1	1
	32.3	129.7	249.217818	-0.5	12	29	2	3
	36.3	145.8	249.221841	3.5	17	29		1

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1130 Pine Ave West (514) 398-3661
Montreal, Quebec, Canada. H3A 1A3

HARDWARE PEAK MATCH ZAB 2F HS Date 21 Aug 2002

NAME Lee SAMPLE 5-129

FORMULA $C_{16}H_{24}O_2 + H^+$

MASS 249 ELECTRON IMPACT: _____eV _____μA

CHEM. ION. GAS: NH_3 ___ *i*-BUT ___ CH_4 ___ ____ x 10^{-5} TORR

RESOLUTION 12,000 SOURCE RT · PROBE FAB

MASS REF: PFK ___ GLYCEROL ✓ OTHER _____

REFERENCE ION: $C_9H_{25}O_9$ = 277.14986

PEAK MATCH RATIO: 1.112223

SAMPLE EXACT MASS: 249.18551

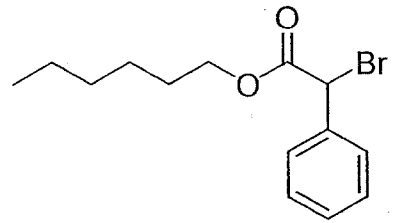
___ERROR IN YOUR MW CALC. ___SEE OVER ⇒

SM-CHPhBrCOOHe

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 2.000 sec
Width 3870.0 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.7a

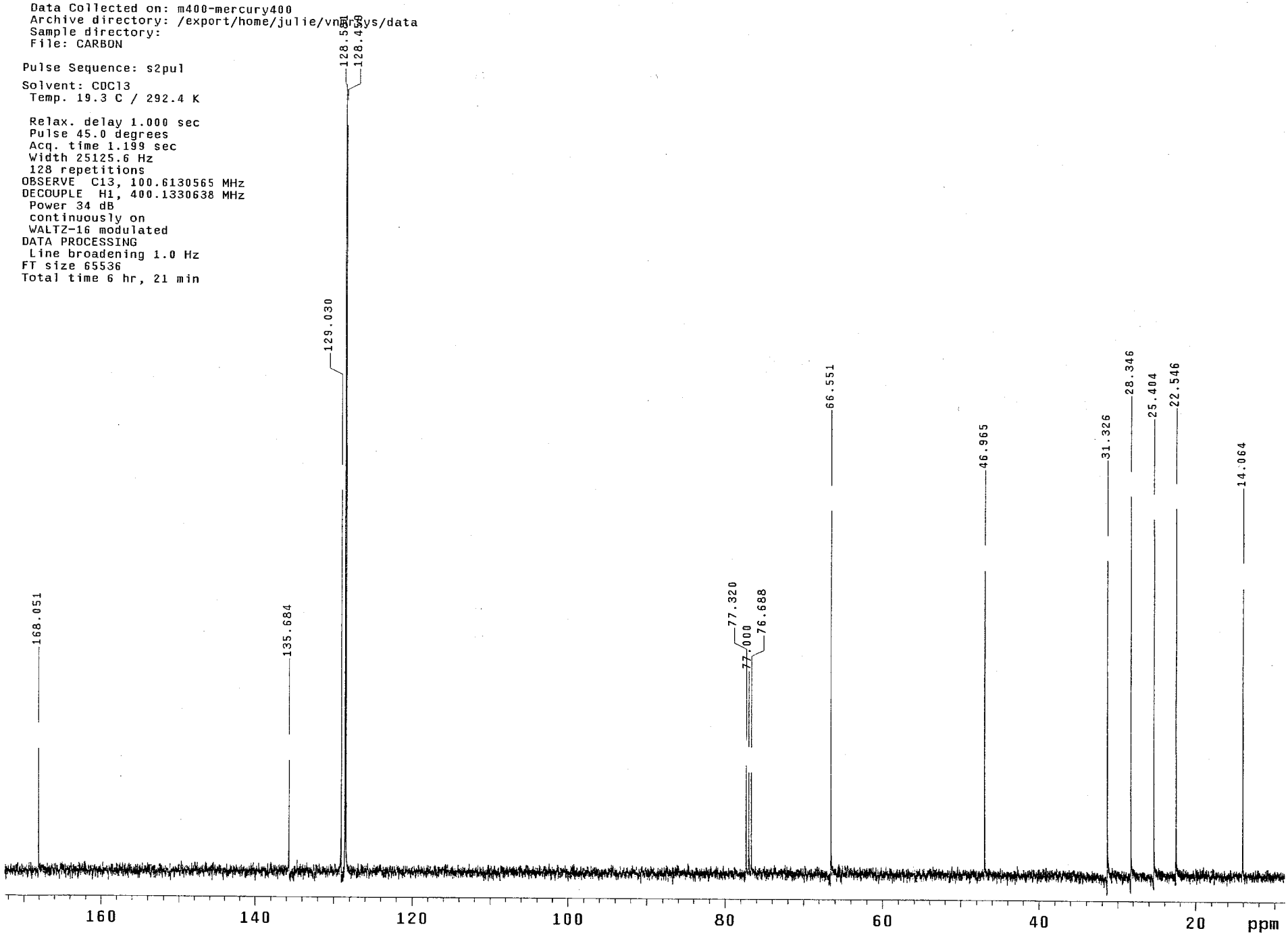
SM-CHPhBrCOOHe-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 19.3 C / 292.4 K

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
128 repetitions
OBSERVE C13, 100.6130565 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 6 hr, 21 min



Elemental Composition Date : 21-AUG-2002

Heteroatom Max: 20 Ion: Both Even and Odd
Limits:

				-0.5	0	0	0	0	0
299.064650	38.5			20.0	200	400	2	5	1

Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O	Br
299.064650	-36.4	-121.6	299.028281	5.5	13	16		3	1
	-33.7	-112.6	299.030961	10.0	16	14	1		1
	-30.2	-101.0	299.034434	16.5	19	7		4	
	-27.8	-93.0	299.036834	1.0	9	18	1	5	1
	-25.1	-84.0	299.039514	5.5	12	16	2	2	1
	-21.1	-70.6	299.043537	9.5	17	16			1
	-19.0	-63.5	299.045667	16.5	18	7	2	3	
	-15.2	-51.0	299.049410	0.5	10	20		5	1
	-12.6	-42.0	299.052090	5.0	13	18	1	2	1
	-6.4	-21.4	299.058243	16.0	19	9	1	3	
	-4.0	-13.4	299.060643	0.5	9	20	2	4	1
	0.0	0.1	299.064666	4.5	14	20		2	1
	2.1	7.2	299.066797	11.5	15	11	2	5	
	6.2	20.6	299.070819	15.5	20	11		3	
	8.6	28.7	299.073220	0.0	10	22	1	4	1
	8.8	29.6	299.073499	20.0	23	9	1		
	11.2	37.6	299.075900	4.5	13	20	2	1	1
	14.7	49.2	299.079373	11.0	16	13	1	5	
	17.4	58.2	299.082053	15.5	19	11	2	2	
	21.1	70.7	299.085796	-0.5	11	24		4	1
	21.4	71.6	299.086075	19.5	24	11			
	23.8	79.7	299.088476	4.0	14	22	1	1	1
	27.3	91.3	299.091949	10.5	17	15		5	
	30.0	100.2	299.094629	15.0	20	13	1	2	
	32.4	108.3	299.097029	-0.5	10	24	2	3	1
	36.4	121.7	299.101052	3.5	15	24		1	1

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Montreal, Quebec, Canada. H3A 1A3

HARDWARE PEAK MATCH ZAB 2F HS Date 21 Aug 2002

NAME Lee SAMPLE 20 5M

FORMULA $C_{14}H_{19}O_2Br + H^+$

MASS 299 ELECTRON IMPACT: _____eV _____μA

CHEM. ION. GAS: NH_3__ *i*-BUT__ CH_4__ ____ x 10^{-5} TORR

RESOLUTION 12.000 SOURCE_____ · PROBE_____ ·

MASS REF: PFK__ GLYCEROL ✓ OTHER_____

REFERENCE ION: $C_9H_{25}O_9$ = 277.14986

PEAK MATCH RATIO: 1.079072

SAMPLE EXACT MASS: 299.06465

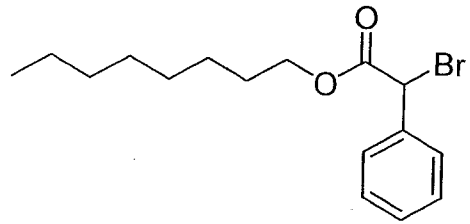
___ERROR IN YOUR MW CALC. ___SEE OVER ⇒

21-SM

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 2.001 sec
Width 3709.2 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.7b

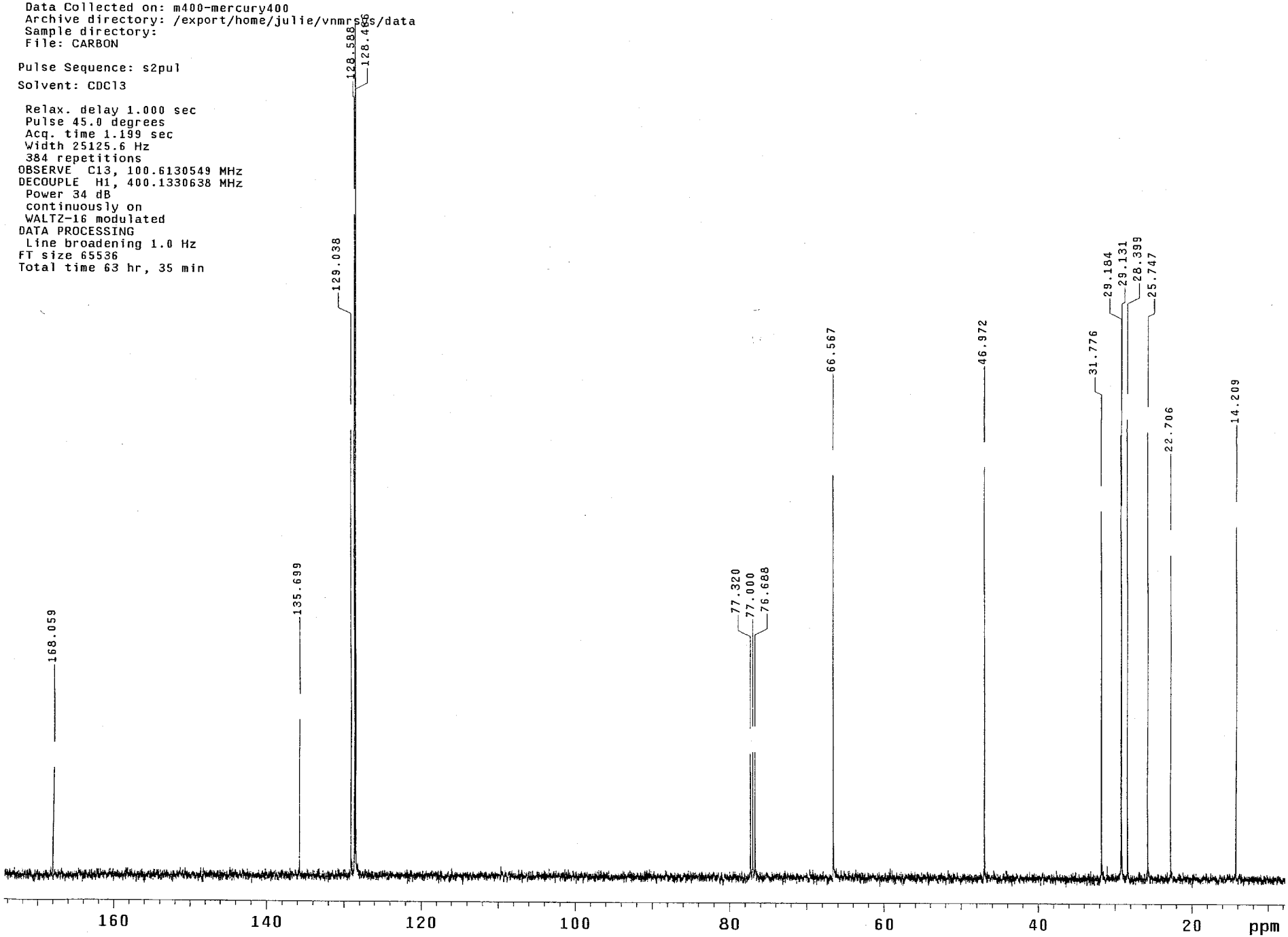
SM-CHPhBrCOOOc-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
384 repetitions
OBSERVE C13, 100.6130549 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 63 hr, 35 min



Elemental Composition Date : 21-AUG-2002

Heteroatom Max: 20 Ion: Both Even and Odd
Limits:

				-0.5	0	0	0	0	0
327.095820	38.5			20.0	200	400	2	5	1
Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O	Br
327.095820	-36.2	-110.8	327.059581	5.5	15	20		3	1
	-33.6	-102.6	327.062261	10.0	18	18	1		1
	-30.1	-92.0	327.065734	16.5	21	11		4	
	-27.7	-84.6	327.068134	1.0	11	22	1	5	1
	-25.0	-76.4	327.070814	5.5	14	20	2	2	1
	-21.0	-64.1	327.074837	9.5	19	20			1
	-18.9	-57.6	327.076967	16.5	20	11	2	3	
	-15.1	-46.2	327.080710	0.5	12	24		5	1
	-12.4	-38.0	327.083390	5.0	15	22	1	2	1
	-6.3	-19.2	327.089543	16.0	21	13	1	3	
	-3.9	-11.9	327.091944	0.5	11	24	2	4	1
	0.1	0.4	327.095966	4.5	16	24		2	1
	2.3	7.0	327.098097	11.5	17	15	2	5	
	6.3	19.3	327.102120	15.5	22	15		3	
	8.7	26.6	327.104520	0.0	12	26	1	4	1
	9.0	27.5	327.104800	20.0	25	13	1		
	11.4	34.8	327.107200	4.5	15	24	2	1	1
	14.9	45.4	327.110673	11.0	18	17	1	5	
	17.5	53.6	327.113353	15.5	21	15	2	2	
	21.3	65.0	327.117096	-0.5	13	28		4	1
	21.6	65.9	327.117376	19.5	26	15			
	24.0	73.2	327.119776	4.0	16	26	1	1	1
	27.4	83.9	327.123249	10.5	19	19		5	
	30.1	92.0	327.125929	15.0	22	17	1	2	
	32.5	99.4	327.128329	-0.5	12	28	2	3	1
	36.5	111.7	327.132352	3.5	17	28		1	1

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HARDWARE PEAK MATCH ZAB 2F HS Date 21 Aug 2002

NAME Lee SAMPLE 215M

FORMULA $C_{16}H_{23}O_2Br + H^+$

MASS 327 ELECTRON IMPACT: _____ eV _____ μA

CHEM. ION. GAS: NH_3 ___ *i*-BUT ___ CH_4 ___ ____ x 10^{-5} TORR

RESOLUTION 12,000 SOURCE RT · PROBE FAB+

MASS REF: PFK ___ GLYCEROL ✓ OTHER + KCl

REFERENCE ION: $C_9H_{24}O_9K$ = 315.10574

PEAK MATCH RATIO: 1.038051

SAMPLE EXACT MASS: 327.09582

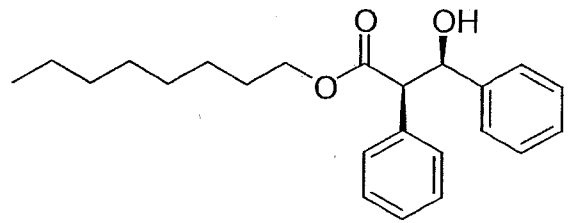
___ERROR IN YOUR MW CALC. ___SEE OVER ⇒

21-syn-product

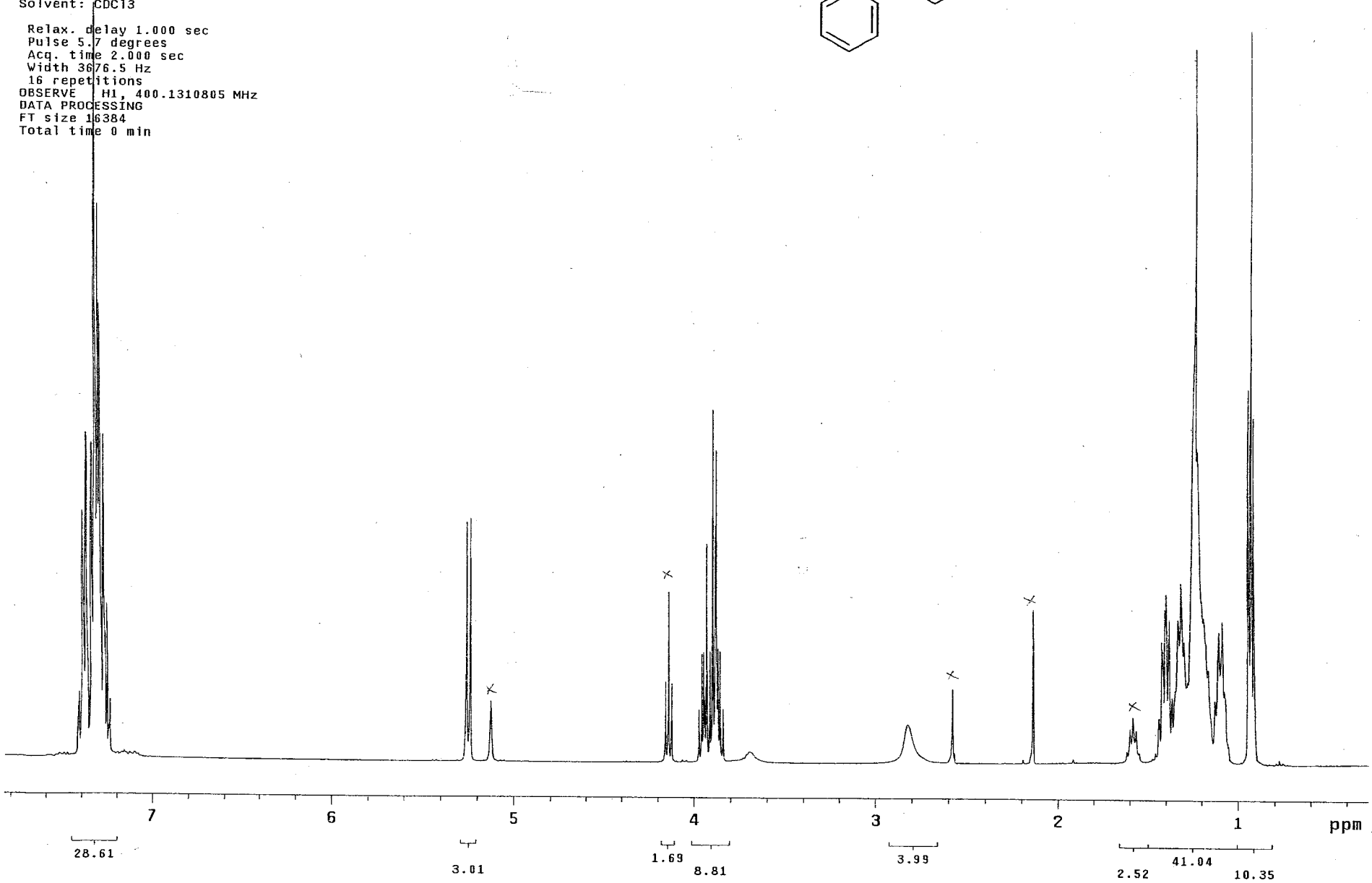
Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 5.7 degrees
Acq. time 2.000 sec
Width 3676.5 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.17a



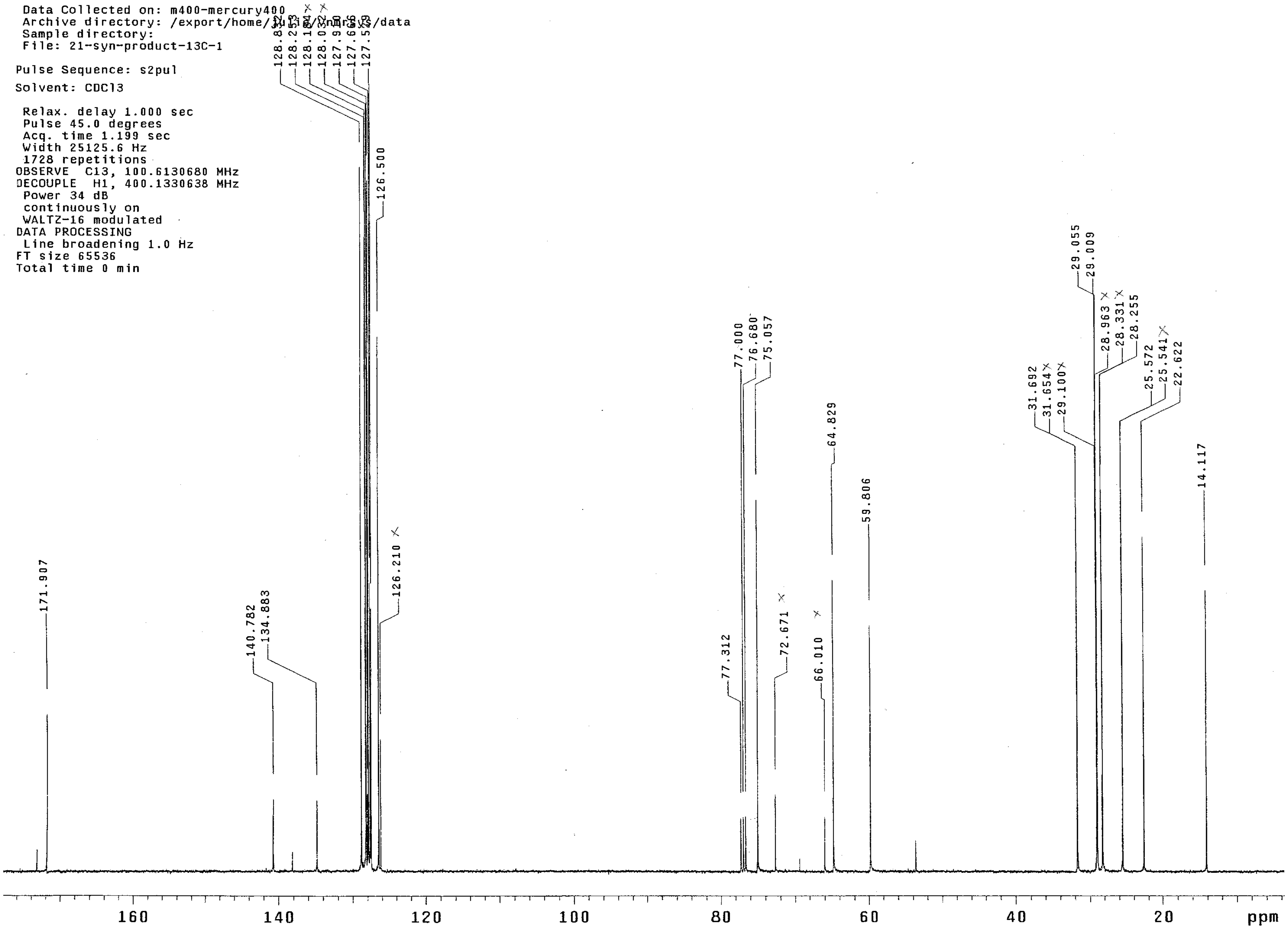
21-syn-product-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/
Sample directory:
File: 21-syn-product-13C-1

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
1728 repetitions
OBSERVE C13, 100.6130680 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 0 min

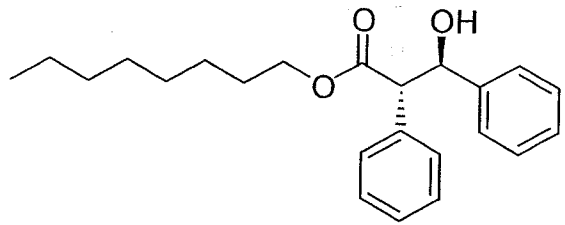


21-anti-product

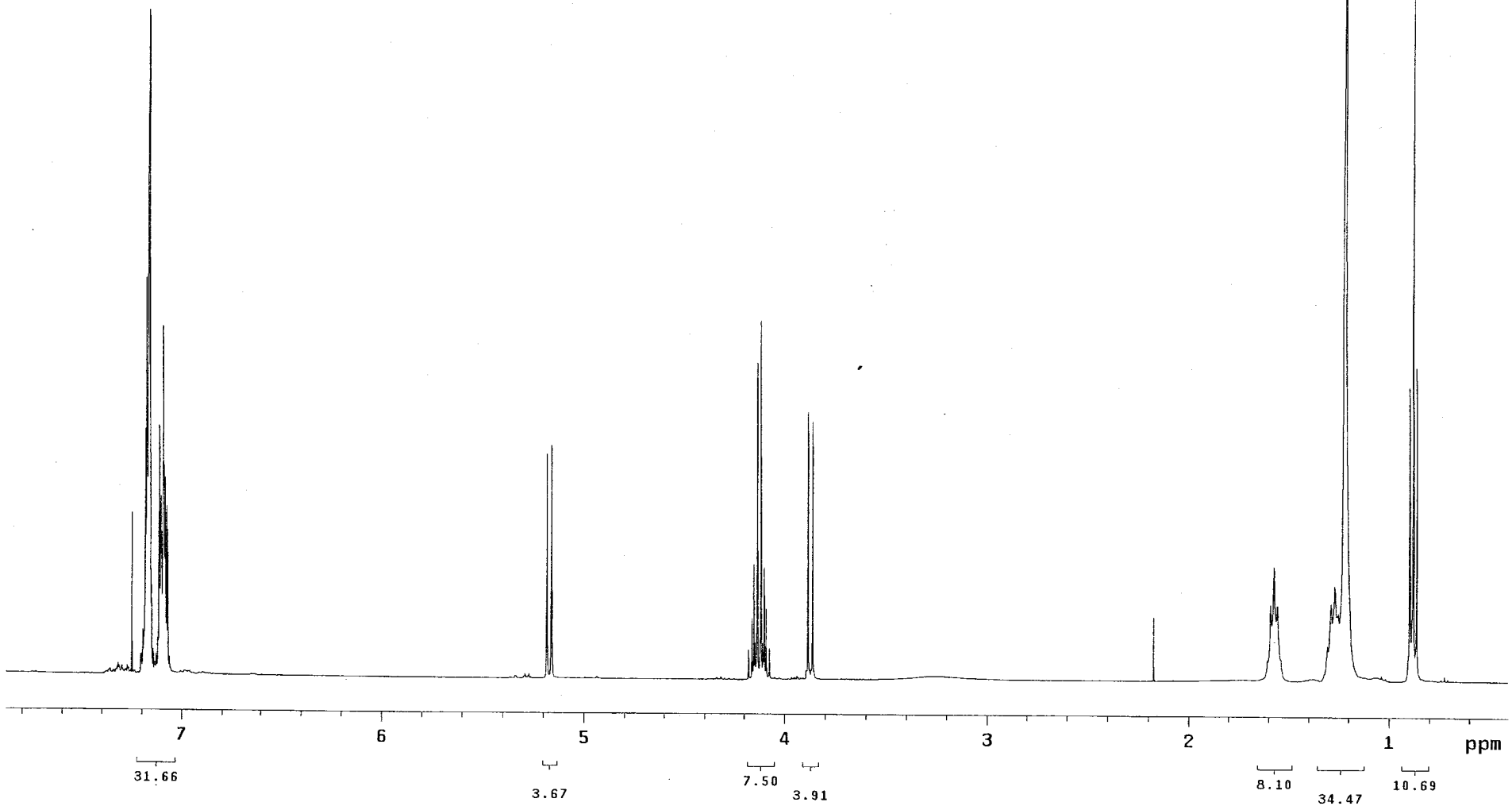
Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 22.8 degrees
Acq. time 1.997 sec
Width 3387.5 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.17a

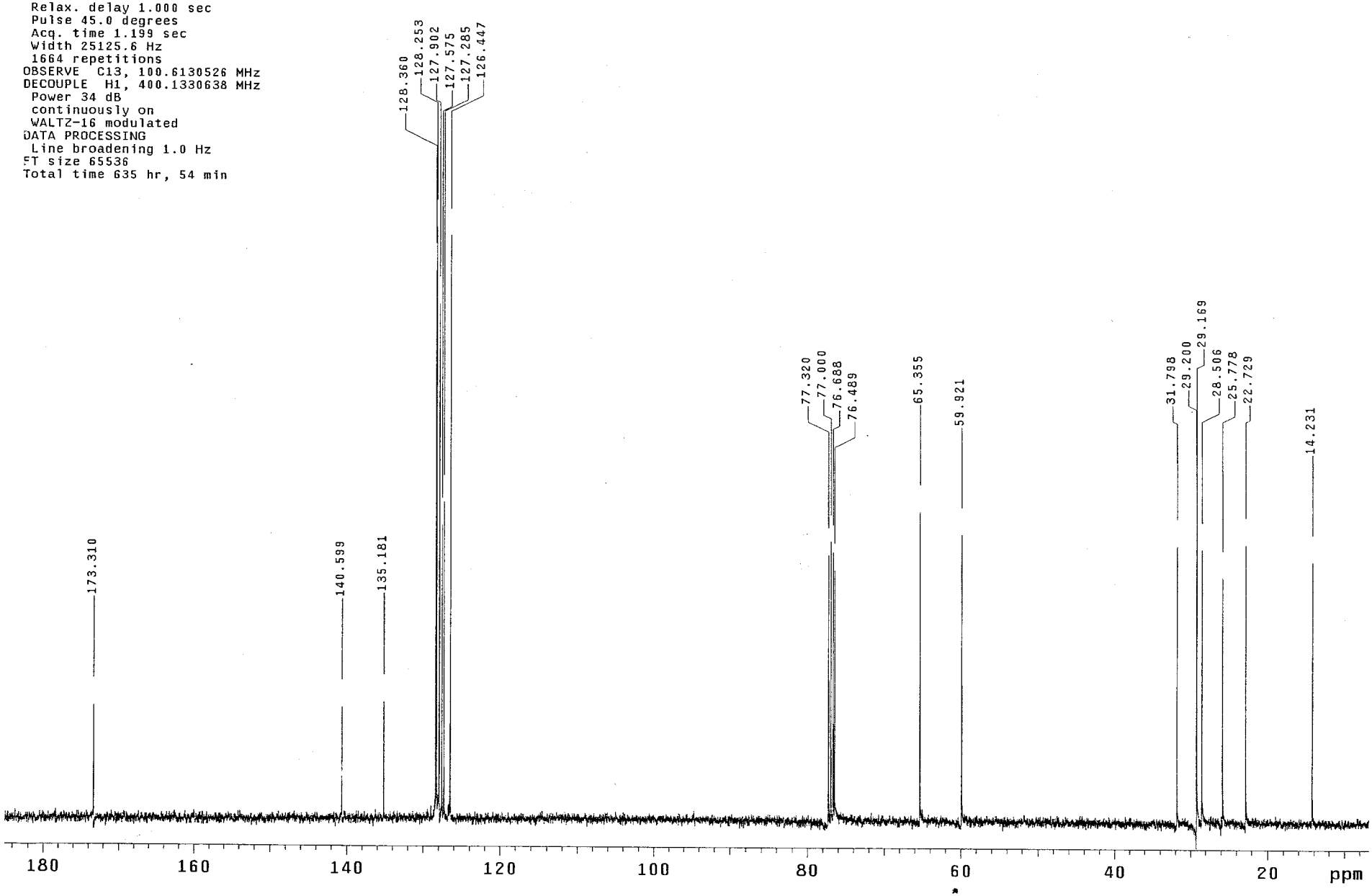


21-anti-product-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
1664 repetitions
OBSERVE C13, 100.6130526 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 635 hr, 54 min



Elemental Composition Date : 21-AUG-2002

Heteroatom Max: 20 Ion: Both Even and Odd
Limits:

				-0.5	0	0	0	0	0
377.209140	26.8			20.0	200	400	2	5	1
Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O	Na
377.209140	-25.0	-66.3	377.184113	9.5	21	26	2	3	1
	-22.6	-60.0	377.186518	12.5	23	25	2	3	
	-21.0	-55.7	377.188135	13.5	26	26		1	1
	-18.6	-49.3	377.190541	16.5	28	25		1	
	-12.5	-33.0	377.196689	9.0	22	28	1	3	1
	-10.0	-26.6	377.199094	12.0	24	27	1	3	
	-9.8	-25.9	377.199369	13.5	25	26	2		1
	-7.4	-19.5	377.201774	16.5	27	25	2		
	-3.9	-10.3	377.205242	4.5	18	30	2	5	1
	-1.5	-4.0	377.207647	7.5	20	29	2	5	
	0.1	0.3	377.209265	8.5	23	30		3	1
	2.5	6.7	377.211670	11.5	25	29		3	
	2.8	7.4	377.211945	13.0	26	28	1		1
	5.2	13.8	377.214350	16.0	28	27	1		
	8.7	23.0	377.217818	4.0	19	32	1	5	1
	11.1	29.4	377.220223	7.0	21	31	1	5	
	11.4	30.1	377.220498	8.5	22	30	2	2	1
	13.8	36.5	377.222903	11.5	24	29	2	2	
	15.4	40.8	377.224521	12.5	27	30			1
	17.8	47.2	377.226926	15.5	29	29			
	21.3	56.3	377.230394	3.5	20	34		5	1
	23.7	62.7	377.232800	6.5	22	33		5	
	23.9	63.5	377.233074	8.0	23	32	1	2	1
	26.3	69.8	377.235480	11.0	25	31	1	2	

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HARDWARE PEAK MATCH ZAB 2F HS Date 21 Aug 2002

NAME Lee SAMPLE 21-2-ANTI

FORMULA $C_{23}H_{30}O_3 + Na^+$

MASS 377 ELECTRON IMPACT: _____ eV _____ μA

CHEM. ION. GAS: NH_3 ___ *i*-BUT ___ CH_4 ___ _____ x 10^{-5} TORR

RESOLUTION 12,000 SOURCE RT · PROBE FAB

MASS REF: PFK ___ GLYCEROL ✓ OTHER _____

REFERENCE ION: $C_{12}H_{33}O_{12}$ = 369.19720

PEAK MATCH RATIO: 1.021701

SAMPLE EXACT MASS: 377.20914

___ERROR IN YOUR MW CALC. ___SEE OVER ⇒

1

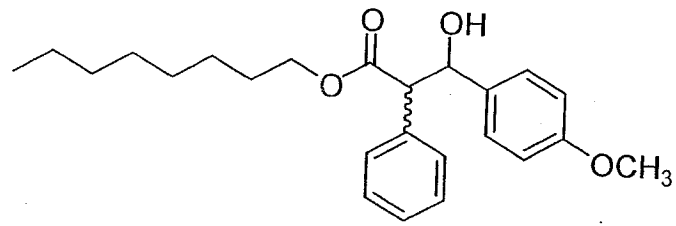
21-3-product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: 21-3-product

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 1.999 sec
Width 3720.2 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.17b

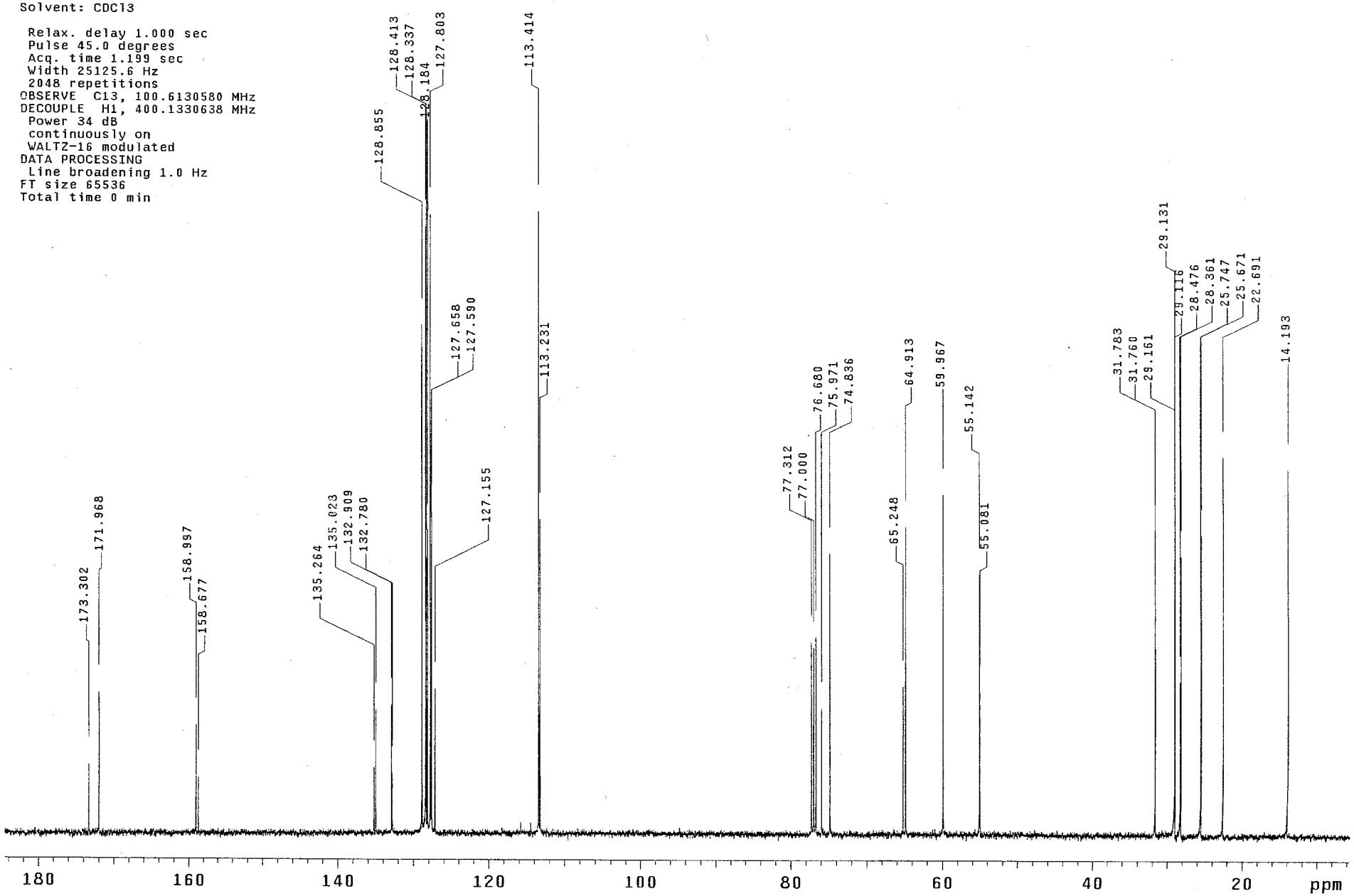
21-3-product-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
2048 repetitions
OBSERVE C13, 100.6130580 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 0 min



Elemental Composition Date : 5-SEP-2002

Heteroatom Max: 34 Ion: Both Even and Odd
Limits:

				-6.2	0	0	0	0
407.219840	18.8			24.8	200	400	8	1

Mass	mDa	PPM	Calc. Mass	DBE	C	H	O	Na
407.219840	-18.7	-46.0	407.201105	16.5	29	27	2	
	-15.3	-37.5	407.204573	4.5	20	32	7	1
	-12.9	-31.6	407.206979	7.5	22	31	7	
	0.0	0.0	407.219830	8.5	24	32	4	1
	2.4	5.9	407.222235	11.5	26	31	4	
	15.2	37.4	407.235086	12.5	28	32	1	1
	17.7	43.3	407.237491	15.5	30	31	1	

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HARDWARE PEAK MATCH ZAB 2F HS Date 5 Sept 2002

NAME Lee SAMPLE 21-3

FORMULA $C_{24}H_{32}O_4 + Na^+$

MASS 407 ELECTRON IMPACT: _____eV _____μA

CHEM. ION. GAS: NH_3___ *i*-BUT___ CH_4___ ____x 10^{-5} TORR

RESOLUTION 12,000 SOURCE RT · PROBE FAB

MASS REF: PFK___ GLYCEROL ✓ OTHER + NaCl

REFERENCE ION: $C_{12}H_{32}O_{12}Na$ = 391.19915

PEAK MATCH RATIO: 1.041006

SAMPLE EXACT MASS: 407.21984

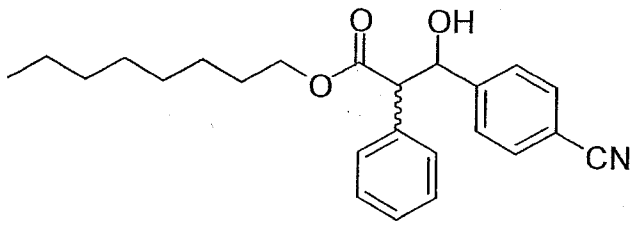
___ERROR IN YOUR MW CALC. ___SEE OVER →

21-4-product

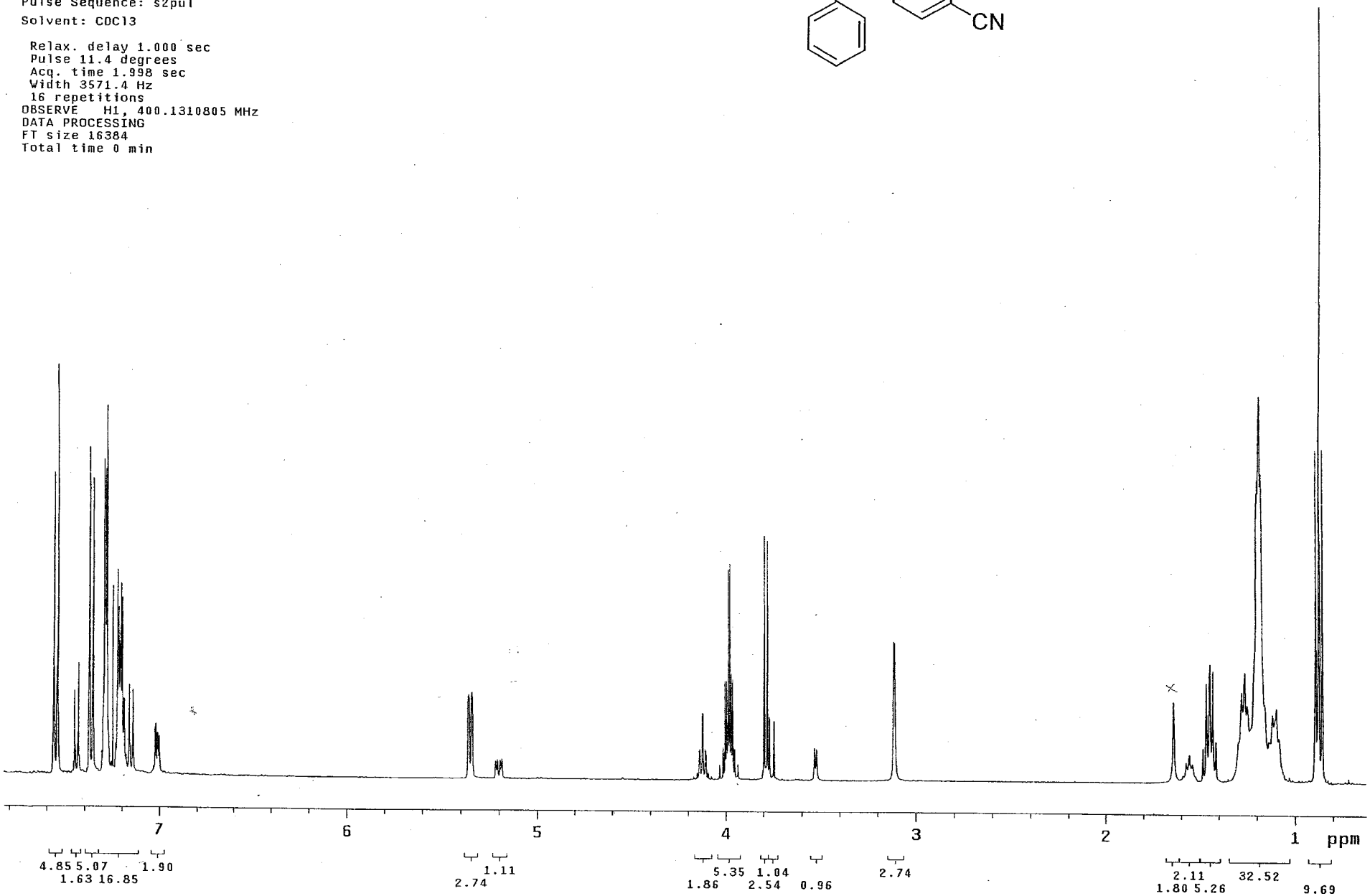
Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: 21-4-product-1

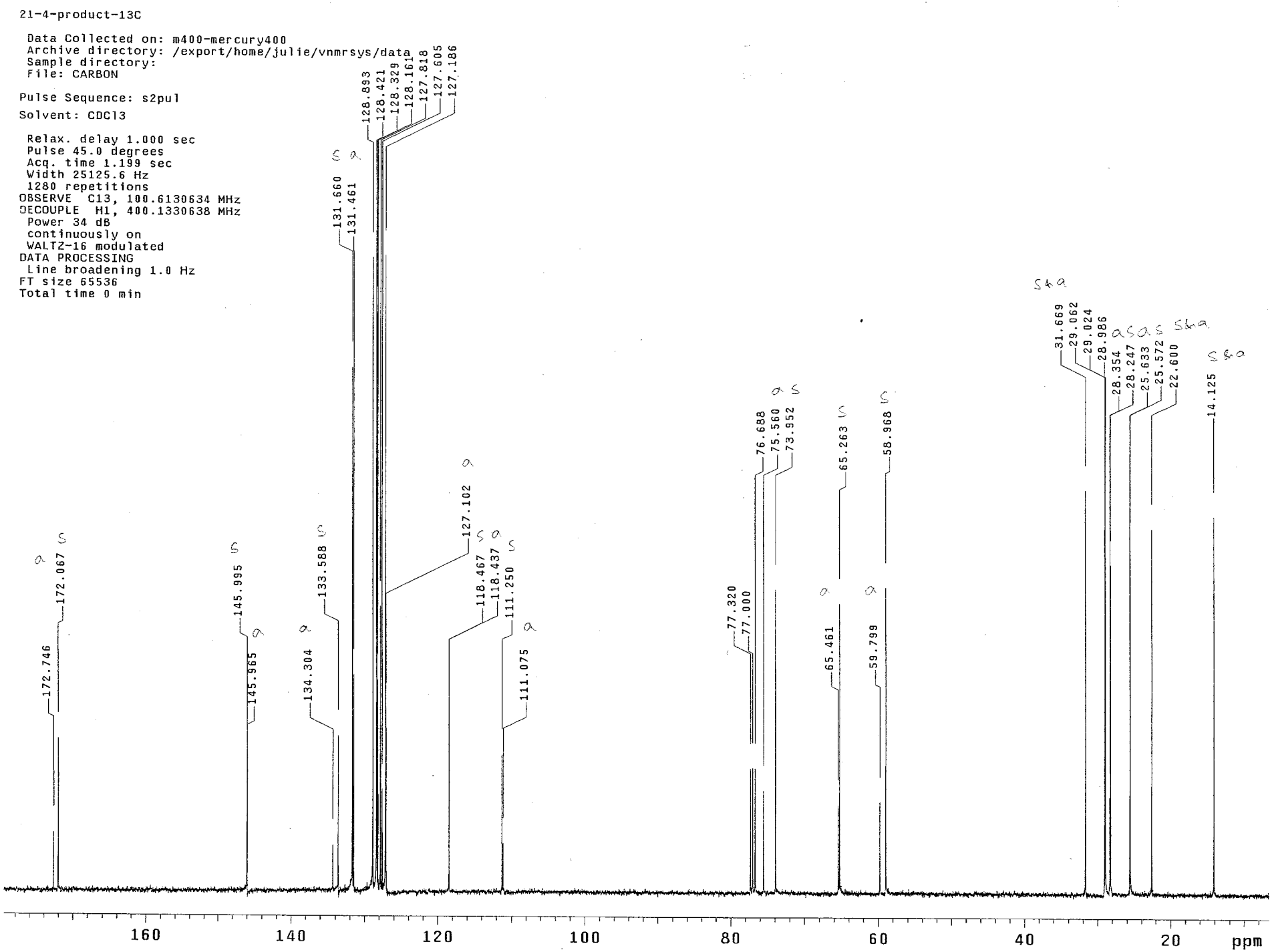
Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 1.998 sec
Width 3571.4 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.17c




21-4-product-13C
Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
1280 repetitions
OBSERVE C13, 100.6130634 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 0 min
172.746
172.067
145.995
145.965
134.304
133.588
131.660
131.461
128.893
128.421
128.329
128.161
127.818
127.605
127.186
127.102
118.467
118.437
111.250
111.075
77.320
77.000
76.688
75.560
73.952
65.461
65.263
59.799
58.968
31.669
29.062
29.024
28.986
28.354
28.247
25.633
25.572
22.600
14.125
160
140
120
100
80
60
40
20
ppm

Elemental Composition Date : 5-SEP-2002

Heteroatom Max: 34 Ion: Both Even and Odd
Limits:

				-6.2	0	0	0	0	0
380.222530	10.1			24.8	200	400	3	8	1

Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O	Na
380.222530	-9.9	-25.9	380.212673	15.5	26	26	3		
	-9.1	-23.9	380.213461	-1.0	14	33	2	8	1
	-8.5	-22.4	380.214016	15.0	28	28		1	
	-6.7	-17.5	380.215866	2.0	16	32	2	8	
	-6.4	-16.8	380.216141	3.5	17	31	3	5	1
	-5.0	-13.3	380.217484	3.0	19	33		6	1
	-4.0	-10.5	380.218546	6.5	19	30	3	5	
	-2.6	-6.9	380.219889	6.0	21	32		6	
	-2.4	-6.2	380.220164	7.5	22	31	1	3	1
	0.0	0.1	380.222569	10.5	24	30	1	3	
	0.3	0.8	380.222844	12.0	25	29	2		1
	2.7	7.2	380.225249	15.0	27	28	2		
	3.5	9.2	380.226037	-1.5	15	35	1	8	1
	5.9	15.6	380.228442	1.5	17	34	1	8	
	6.2	16.3	380.228717	3.0	18	33	2	5	1
	8.6	22.6	380.231122	6.0	20	32	2	5	
	8.9	23.3	380.231397	7.5	21	31	3	2	1

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HARDWARE PEAK MATCH ZAB 2F HS Date 5 Sept 2002

NAME Lee SAMPLE 21-4

FORMULA $C_{24}H_{29}NO_3 + H^+$

MASS 380 ELECTRON IMPACT: _____eV _____μA

CHEM. ION. GAS: NH_3___ *i*-BUT___ CH_4___ ____x 10^{-5} TORR

RESOLUTION 12.000 SOURCE RT PROBE FAB

MASS REF: PFK___ GLYCEROL ✓ OTHER_____

REFERENCE ION: $C_{12}H_{33}O_{12} = 369.19720$

PEAK MATCH RATIO: 1.029863

SAMPLE EXACT MASS: 380.22253

___ERROR IN YOUR MW CALC. ___SEE OVER →

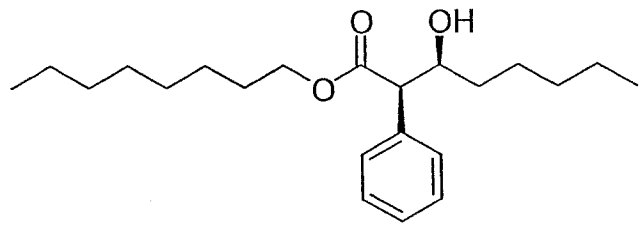
21-5-syn-product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 11.4 degrees
Acq. time 1.996 sec
Width 3440.0 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.17d

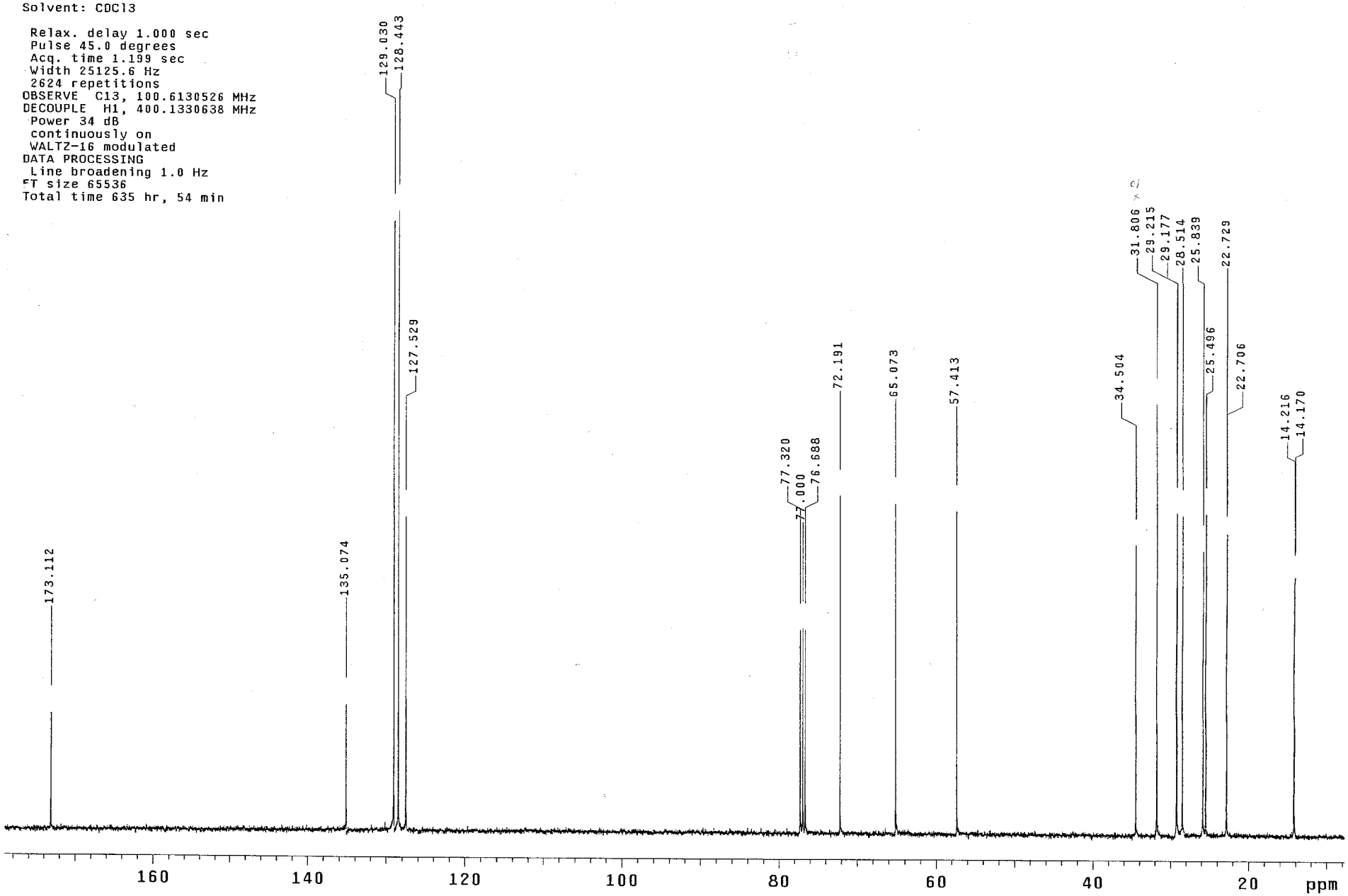
21-5-syn-product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
2624 repetitions
OBSERVE C13, 100.6130526 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 635 hr, 54 min

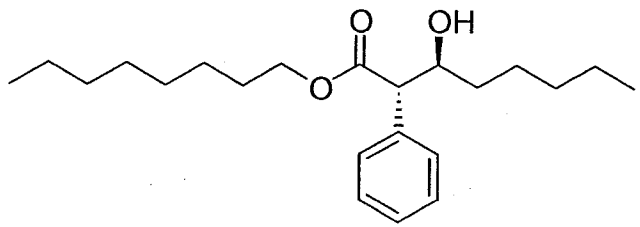


21-5-anti-product

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 34.2 degrees
Acq. time 1.998 sec
Width 4035.5 Hz
16 repetitions
OBSERVE H1, 400.1310805 MHz
DATA PROCESSING
FT size 16384
Total time 0 min



4.17d

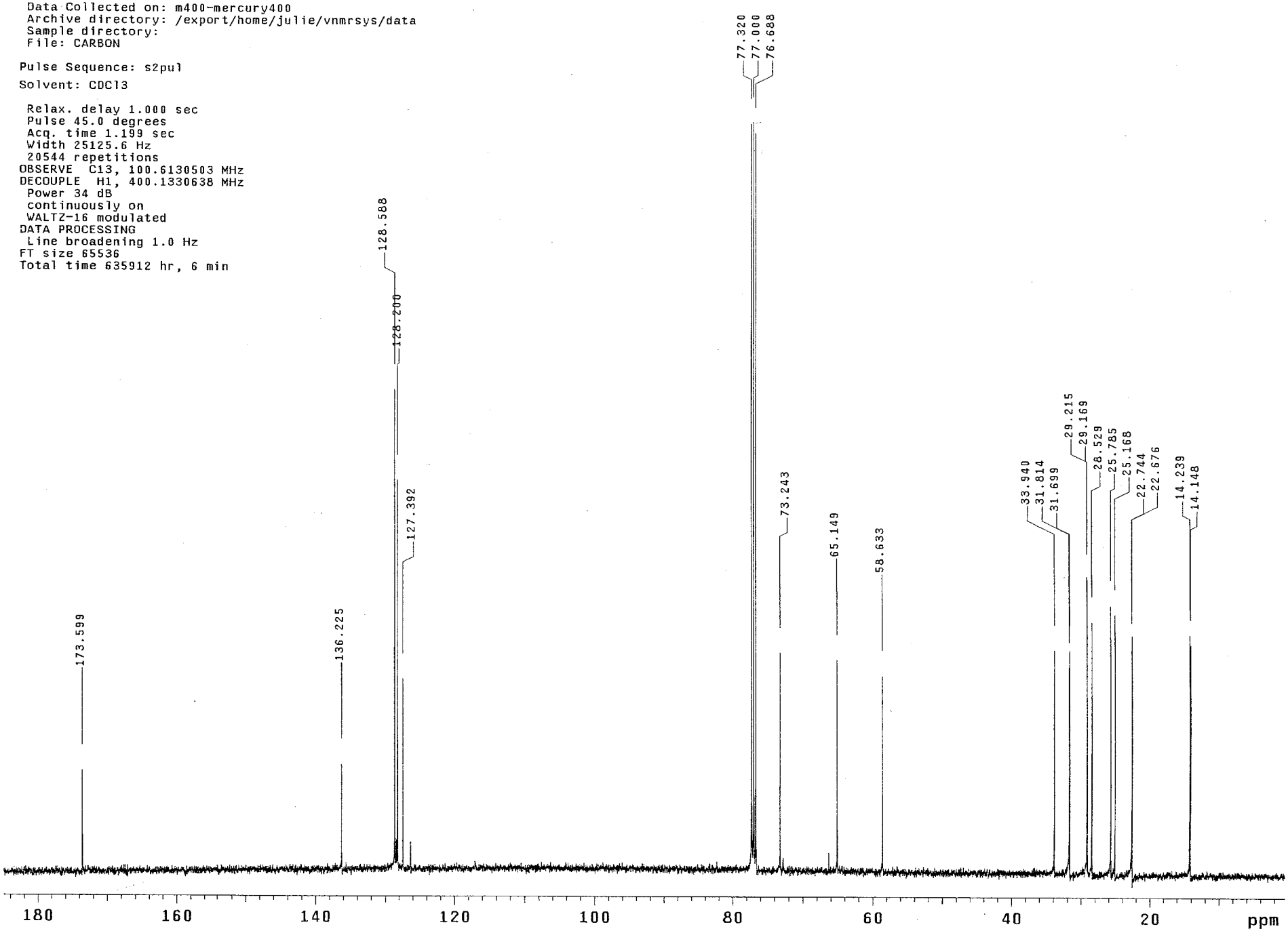
21-5-anti-product-13C

Data Collected on: m400-mercury400
Archive directory: /export/home/julie/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
20544 repetitions
OBSERVE C13, 100.6130503 MHz
DECOUPLE H1, 400.1330638 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 635912 hr, 6 min



Elemental Composition Date : 21-AUG-2002

Heteroatom Max: 20 Ion: Both Even and Odd
Limits:

				-0.5	0	0	0	0
349.274240	42.6			20.0	200	400	2	5

Mass	mDa	PPM	Calc. Mass	DBE	C	H	N	O
349.274240	-36.4	-104.1	349.237885	5.5	21	33		4
	-33.7	-96.4	349.240565	10.0	24	31	1	1
	-25.1	-71.9	349.249118	5.5	20	33	2	3
	-21.1	-60.4	349.253141	9.5	25	33		1
	-12.5	-35.9	349.261694	5.0	21	35	1	3
	-9.9	-28.2	349.264374	9.5	24	33	2	
	-4.0	-11.4	349.270248	0.5	17	37	2	5
	0.0	0.1	349.274270	4.5	22	37		3
	2.7	7.8	349.276950	9.0	25	35	1	
	8.6	24.6	349.282824	0.0	18	39	1	5
	11.3	32.2	349.285504	4.5	21	37	2	2
	15.3	43.8	349.289526	8.5	26	37		
	21.2	60.6	349.295400	-0.5	19	41		5
	23.8	68.3	349.298080	4.0	22	39	1	2
	32.4	92.7	349.306633	-0.5	18	41	2	4
	36.4	104.3	349.310656	3.5	23	41		2

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HARDWARE PEAK MATCH ZAB 2F HS Date 21 Aug 2002

NAME Lee SAMPLE 21-5-5YN

FORMULA $C_{22}H_{36}O_3 + H^+$

MASS 349 ELECTRON IMPACT: _____ eV _____ μA

CHEM. ION. GAS: NH_3 ___ *i*-BUT ___ CH_4 ___ ____ x 10^{-5} TORR

RESOLUTION 12.000 SOURCE RT PROBE FAB+

MASS REF: PFK ___ GLYCEROL ✓ OTHER _____

REFERENCE ION: $C_{12}H_{33}O_{12}$ = 369.19720

PEAK MATCH RATIO: 1.057041

SAMPLE EXACT MASS: 349.27424

___ERROR IN YOUR MW CALC. ___SEE OVER ⇒