STUDIES ON NEW SYNTHETIC STRATEGIES FOR *O*- AND *S*-DERIVATIVES OF MONOTERPENES

Thesis submitted to

THE UNIVERSITY OF MYSORE

for the degree of

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

by

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DECLARATION

I hereby declare that the thesis entitled ***STUDIES ON NEW SYNTHETIC STRATEGIES FOR O- AND S-DERIVATIVES OF MONOTERPENES*** submitted to the **UNIVERSITY OF MYSORE** for the award of degree of **DOCTOR OF PHILOSOPHY IN CHEMISTRY** is the result of work carried out by me at laboratories of Plantation Products, Spices and Flavour Technology department under the guidance of **Dr. P. Srinivas**, Scientist, Central Food Technological Research Institute, Mysore - 570 013, India, during the period 1999-2003. I further declare that the results are not submitted for the award of any other degree or fellowship.

Mysore **(BETTADAIAH, B. K.)**

Date:

Dr. P. Srinivas
Scientist

CERTIFICATE

I hereby certify that the thesis entitled ***STUDIES ON NEW SYNTHETIC STRATEGIES FOR O- AND S-DERIVATIVES OF MONOTERPENES*** submitted by **Mr. B. K. Bettadaiah** for the degree of **DOCTOR OF PHILOSOPHY IN CHEMISTRY** to the **UNIVERSITY OF MYSORE** is the result of research work carried out by him at Plantation Products, Spices and Flavour Technology department of Central Food Technological Research Institute, Mysore-570013, India, under my guidance and supervision during the period 1999-2003.

Mysore **(P. SRINIVAS)**

Date:

DEDICATED TO

MY BELOVED PARENTS
AND BROTHERS

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Bettadaiah, B. K.

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SYNOPSIS

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Synopsis

The main objectives of the present investigation are development of new or improved, reagents and methods for the functionalization of monoterpenic hydrocarbons, investigation of reaction mechanisms, especially of stereo- and regio-selectivities, with an ultimate aim of developing efficient synthetic routes to aroma chemicals or their precursors. Based on this investigation, a thesis consisting of five chapters has been prepared. A summary of its contents is given below.

Chapter 1 Oxygenated Monoterpene and Their Sulfur Analogs: Introduction

A brief account of the natural occurrence of oxygenated and their sulfur analogs and their importance as aroma chemicals as well as synthetic approach to them are given, as an introduction to the present investigation. Functionalization of hydrocarbons is an important area in classical synthetic organic chemistry, and it continues to be a topic of active research even now. The present challenges are, the achievement of better regio- and stereoselectivities, clean reaction and facile workup of the product. In this context, there is growing interest in the use of electromagnetic radiation and ultrasound energy in chemical reactions. The potential of these techniques as synthetic tools is being vigorously explored by researchers world over.

Monoterpenes – acyclic, mono and bi-cyclic hydrocarbons - are abundantly available in nature as constituents of a host of essential oils e.g., (+)-limonene from citrus oils and α-pinene, β-pinene, and 3-carene from turpentine. The corresponding oxygenated derivatives - alcohols, carbonyl compounds, esters and ethers – and their sulfur analogs form a major and important group of aroma chemicals. These compounds- both natural and synthetic- find extensive applications in food flavor and perfumery formulations. They have been employed as chiral starting materials for multi step natural products synthesis. Therefore, conversion of terpenic hydrocarbons into their *O*- and *S*- derivatives is of economic importance.

Several methods exist for the conversion of monoterpene hydrocarbons to the corresponding oxygen and sulfur derivatives. These include metal salt-catalyzed direct oxidation, solvation, metallation, epoxidation, thiiration, cohalogenation, halogenation

and various transformation reactions of the halo- and epoxy- intermediates. Among these, halogenation, cohalogenation and epoxidation, being relatively inexpensive, are the preferred methods for the large scale production of the flavor chemicals.

Chapter 2: Preparation and Reactions of Monoterpene Bromohydrins and Epoxides

This chapter gives an account of preparation and synthetic reactions of bromohydrins and epoxides, especially of those derived from monoterpenic hydrocarbons. It has four sections. While Section 2.1 and 2.2 describes the reactions of bromohydrins, Section 2.3 deals with the reaction and preparation of terpene epoxides. The Section 2.4 details the preparation, isolation and purification of bromohydrins.

Section 2.1: Direct conversion of *tert-β* –bromo alcohols to ketones

The reaction of a selected group of monoterpenes and other olefins with *N*-bromosuccinimide in aqueous acetone yields the corresponding *β*-bromo alcohols in excellent yields (80-95 %) with *trans*-stereochemistry. Attempts at oxidation of *tert-β*-bromo alcohols with DMSO in the presence of a base to the corresponding carbonyl compounds results only in their cyclization to epoxides. In order to avoid this but at the same time for accepting the bromine group, ZnS is employed and the reaction conditions optimized. In this reaction, the expected *α*-hydroxy ketones (Kornblum oxidation products) are formed as only minor products (13-39 %), whereas the corresponding anhydro-ketones are the major ones (41-66 %). From a detailed study of the reaction, the following mechanism is proposed. The abstraction of proton on the carbon *β*- to the hydroxyl group is followed by an attack of the neighboring hydroxyl moiety on the sulfur of the dimethylsulfoxonium intermediate and its subsequent collapse to an enol, which tautomerizes to a saturated ketone.

Section 2.2: Allylic bromides from *tert-β*-bromo alcohols

In case of cohalogenated derivatives, the transformation of the halide functionality has been studied extensively whereas the reports on dehydration reactions are scanty. In this section, an efficient method for dehydration of *tert-β*-bromo alcohols to respective allyl bromides using catalytic amounts of anhydrous $BF_3.OEt_2$ reagent in benzene is delineated. However, in case of 2-bromo-1-hydroxy-*p*-

menth-8-ene, exclusive formation of 2-bromo-1,8-cineole, a cyclic ether, is observed. The present method affords a useful synthetic access to terpenic alcohols and thence to carbonyl compounds. It also provides an easy access to Hoffmann elimination product from styryl-*β*-bromo alcohols.

2.3: The reaction of terpene and aryl substituted epoxides with bromodimethylsulfonium bromide (BDMSB)

The efficacy and orientation of ring opening of tri-substituted epoxides using bromodimethylsulfonium bromide, prepared *in situ* from bromine and dimethyl sulfide, is reported here. The reaction with the selected monoterpene and related di- and trisubstituted epoxides is found to be regiospecific, with the epoxide opening at the tertiary or benzylic positions. With the terminal epoxides it yields the respective aldehydes. In case of styrene oxide, the corresponding bromo aldehyde is the major product.

Section 2.4: Preparation of Bromohydrins

The bromohydrins of monoterpenic hydrocarbons and few other alkyl and aryl substituted olefins are prepared by known procedures. They are prepared by reaction with one equivalent each of NBS and the olefin in aqueous acetone. The reactions are fast (0.5-3 h) and high yielding (80-95 %). The isolation and purification of these bromohydrins have been standardized to get the maximum yield and purity (> 97 %).

Chapter 3: Photochemical Studies on Epoxides and Bromohydrins

The bromohydrins and epoxides mentioned in section 2.3 and 2.4 are also explored for their cleavage in the presence of uv light. This chapter has two sections; section 3.1 describes the kinetic resolution of terpene epoxides under the light assisted methanolysis in presence of Lewis acids whereas section 3.2 gives an elementary account of photo-cleavage of aryl substituted bromohydrins to yield benzoic acid methyl esters.

Section 3.1: Photo-assisted kinetic resolution of monoterpene epoxides

Both *R*-(+)-limonene and *R*-(+)-carvomenthene, which have one chiral center, on epoxidation with peracetic acid yield 1:1 mixtures of two diastereomeric epoxides (*cis*- and *trans*-). Production of pure isomer by simple fractional distillation is not efficient and preparation by chemical means involves a number of steps. In hitherto

reported methods of kinetic resolution of limonene oxide, the strategy of selective reactivity of one of the diastereomer towards a specific reagent is exploited. In the present investigation the photo-assisted methanolysis has been explored to achieve this objective. When a mixture of *cis*- and *trans*-limonene oxide is irradiated (240-366 nm) in methanol in presence of Lewis acid catalyst, the *trans*- isomer remains unreacted whereas the *cis*-oxide is cleaved selectively to afford *trans*-1-methoxy-2-hydroxy-*p*-menth-8-ene. The photo-addition of methanol to carvomenthene 1,2-oxide is likewise found to be selective and affords the unreacted *trans*-oxide and *trans*-1-methoxy-2-hydroxy-*p*-menthane from *cis*-epoxide, which can be easily separated.

Section 3.2: Light-induced direct conversion of styrene bromohydrins to benzoic acid esters

While the photochemistry of epoxides has been studied in some detail, reports on the photochemical reactions of bromohydrins are scanty. Tandem radical cyclization as well as direct conversion of bromohydrins to ketones in PTS catalyzed photolysis in aprotic solvent has been reported earlier. As a model study, photoreaction of styrene bromohydrin in methanol in the presence of Lewis acid catalysts ($ZnCl_2$, $ZnBr_2$, ZnI_2, and $InCl_3$) was investigated. The reaction with $ZnBr_2$ in methanol affords methyl benzoate in over 85 % yield. A mechanism envisaged is as follows; predominant formation of methyl benzoate from styrene bromohydrin is apparently due to the formation of zinc bromide salt by reaction of $ZnBr_2$ with hydroxyl group of bromohydrin. Subsequent radical elimination of hydrogen bromide yields zinc enolate. This tautomerizable enolate transforms to a stable keto-form, acetophenonezinc bromide. The latter compound under photo-irradiation undergo Norrish type I cleavage at benzylic carbonyl carbon and subsequent addition of methanol yields the methyl benzoate. In case of Lewis acids like $ZnCl_2$ and ZnI_2, formation of methyl benzoate is minor but formation of 1,1-dimethoxy-2-phenyl-ethane and 1,2-dimethoxy-2-phenylethanol is major. This is possibly due to preferential formation of phenylacetaldehyde, a rearranged product, which undergoes acid catalyzed addition of methanol to give 1,1-dimethoxy-2-phenylethane. On the other hand the enolic-form of phenylacetaldehyde while transforming to keto-form abstracts methoxyl radical, and undergoes photoacetalization in methanol to give 1,2-dimethoxy-2-phenylethanol. The alkyl substituted bromo alcohols such as 1-bromo-3-phenyl-propan-2-ol and also

terpenic *tert-β*-bromo alcohols are non-reactive under this condition. Photolysis of 2′,4′-dimethylstyrene bromohydrin in the presence of $ZnBr_2$ in methanol yields methyl 2′,4′-dimethyl benzoate in 70 % yield. The reaction in ethanol is very slow and only traces of ethyl benzoate is observed and the same in isopropanol is non-reactive (>24 h irradiation). Direct formation of methyl esters from styrene bromohydrins in photo-assisted methanolysis is being reported for the first time.

Chapter 4: New D-glucal Derivatives of Terpene Alcohols: Synthesis of 2,3 Unsaturated Acetylglucopyranosides

In this chapter, a general preparative method for D-glucal derivatives of monoterpene alcohols using Ferrier rearrangement reaction is described. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-O-acetyl-D-glucal) is a versatile synthetic intermediate in the synthesis of 2-deoxyglycosides, which occur in nature as biologically important compounds. Reaction of D-glucal with alcohols in the presence of Lewis acids to afford 2,3-unsaturated-1-*O*-glucose derivatives *via* allylic rearrangement is referred to as Ferrier reaction. Monoterpene glycosides represent hydrophilic derivatives of free aroma or essential oil compounds. In order to synthesize the new glucal derivatives of some terpene alcohols by Ferrier reaction, 4-terpinenol is selected as model compound and different Lewis acids *viz*, $BF_3{\cdot}OEt_2$, BBr_3, $ZnCl_2$ and also PTS are tried in dichloromethane. $ZnCl_2$ is found to be the most efficient catalyst at ambient temperature yielding ~65 % D-glucal derivative. Reaction of tri-*O*-acetyl-D-glucal with other terpene alcohols affords glucosides in 60-74 % yields. The specific rotations of the products reveal that little racemization of the alcohols occur under the experimental conditions. Also, in case of benzylic alcohols the respective glucal derivatives are obtained in excellent yields (81-91 %).

Chapter 5: Preparation of Alkyl Thiocyanates and Thiols

In this chapter, preparation of *tert*-alkyl and aryl substituted thiocyanates which are precursors of tertiary thiols of important organoleptic properties is described. It has two parts; while part A deals with the preparation of tertiary halides and tertiary thio- and isothiocyanates by nucleophilic substitution of S_N1-active halides with zinc

and titanium thiocyanates under the influence of ultrasound, part B describes the reduction of thiocyanates to thiols using LAH reagent.

Part A: Ultrasound-assisted nucleophilic substitution of S_N1-active halides with zinc and titanium thiocyanate

With a view to developing an improved method of preparation of thiocyanates, which act as synthetic precursors for thiols (mercaptans) of aroma value, nucleophilic substitution of S_N1-active halides derived from monoterpene hydrocarbons with zinc thiocyanate under the influence of ultrasound has been undertaken. It is observed that not only thio- to isothiocyanate ratio improved (5-8:1) but also the reactions rates are faster (5-16 h). *α*-Terpinyl thiocyanate could be thus prepared in 64 % yield.

Nucleophilic substitution reaction of titanium thiocyanate prepared *in situ* from $TiCl_4$ and $Zn(SCN)_2$, with S_N1-active halides is studied under sonic conditions. The reaction rate is accelerated (1-10 h) and yields of substitution products are superior (65-85 %) with improvement in the overall ratio of thio- to isothiocyanates (3-9:1). The study demonstrates the efficacy of ultrasound in bringing about substitution at tertiary carbon atom.

Part B: Reduction of thiocyanates: preparation of thiols

Thiols (mercaptans) form a small but important group of flavoring compounds of several fruits and spices. For example, *p*-menth-1-ene-8-thiol is the flavor-impact constituent of grapefruit juice having a threshold value of $<10^{-4}$ ppb. The corresponding thiocyanate would serve as the stable precursor. The *tert*-alkyl substituted thiocyanates could be reduced with LAH in dry ether to afford the corresponding *tert*-thiols of important aroma value. The reactions are fast (< 12 h) and yields are excellent (>90 %).

(Dr. P. Srinivas) (Bettadaiah, B. K.)
Guide and Supervisor Research Fellow

List of Publications Based on the Thesis work

Papers

1 Direct Conversion of *tert-β*-Bromo Alcohols to Ketones with Zinc Sulfide and DMSO**,** Bettadaiah, B. K.**;** Gurudutt, K. N.; Srinivas, P**.** *J. Org. Chem*. **2003,** *68***,** 2460-62.

2 $ZnCl_2$ Catalyzed Ferrier Reaction; Synthesis of 2,3-unsaturateed 1-*O*-glucopyranosides of Allylic, Benzylic and Tertiary alcohols, Bettadaiah, B. K.; Srinivas, P. *Tetrahedron Lett*. **2003,** *44*, 7257-59.

3. Ultrasound-assisted nucleophilic substitution of tertiary alkyl halides with zinc and titanium thiocyanate, Bettadaiah, B. K.; Gurudutt, K. N.; Srinivas, P. *Synth. Commun*. **2003**, *33(13)*, 2393-99.

4 An expedient synthesis of allylic/secondary bromides from dehydration of *tert-β*-bromo alcohols, Bettadaiah, B. K.; Srinivas, P. *Synth. Commun*. **2003**, *33(20)*, 3615-20.

5 Regio-specific ring opening of terpene and aryl substituted epoxides with Br_2/DMS reagent Bettadaiah, B. K.; Srinivas, P. *Indian. J. Chem. Sec. B*, **2003 (**In print**)**

Patent

1 An improved process for the preparation of *tertiary* alkyl thiocyanates, stable intermediates for *tertiary* thiols, Bheemanakere Kempaiah Bettadaiah, Pullabhatla Srinivas & Kambadoor Nagarajarao Gurudutt, Indian Patent Application No. **Del/1074/00**.

Poster presentation in conference

1 Photolytic conversion of styrene bromohydrins to benzoic acid esters, Bettadaiah, B. K.; Gurudutt, K. N.; Srinivas, P. **5th International Food Convention, 2003,** Dec 5-8, Central Food Technological Research Institute, Mysore India.

Notes to the Experimental Section

The reagents and solvents used in the present investigation were purified and dried according to standard procedures.[1-4] Anhydrous sodium sulfate was activated by heating over naked flame for 3-4 h, cooled in desiccator over fused calcium chloride and stored in air-tight bottle. Anhydrous zinc chloride and zinc bromide were dried in a drying pistol at 137-142^{o}C (xylene vapors) under reduced pressure (1 Torr). Limonene used in the experiments was obtained by the fractionation of the cold-pressed orange feel oil (supplier: Nagpur Orange Growers Association, Nagpur, India). Rest of the terpenes and other fine chemicals used as substrates in this work were obtained from commercial sources and purified before use (purity checked by GLC and physical constants).

Melting points were determined in open capillaries and boiling points were determined by distillation under reduced pressure. They are uncorrected. Optical rotations (α) were recorded on Perkin-Elmer-243 digital polarimeter at 20^{o}C with sodium D-line (λ = 589 nm).

Thin layer chromatography (TLC) was performed using Silica gel, E-Merck India. TLC spots were visualized by exposure to iodine vapor and/or under uv-light 366 nm.

Gas liquid chromatography (GLC) analyses were carried out on Fisons-8000 gas chromatograph with HP-3380A integrator. The normal GC conditions were as follows: Carrier gas: nitrogen at the rate of 5 ml/min. Detector: Flame Ionization Detector (FID) using hydrogen at the rate of 20 ml/min and air 200 ml/min. Injection port and detection port temperatures were maintained in the ranges of 160-200^{o}C and 220-260^{o}C. The general program used for the analysis was 60^{o}C (2-6 min)/8^{o}C/220^{o}C (5-10 min). Columns used: 1) HP-1, 30 m x 0.53 mm x 0.88 μm. 2) HP-5, 30 m x 0.53 mm x 0.88 μm. 3) HP-101, 25 m x 0.32 mm x 0.3 μm. 4) HP-20M, 20 m x 0.32 mm x 0.3 μm. The percent composition of GC peaks was calculated on the Hewlett Packard 3380A integrator.

Gas chromatograph-mass spectrometer (GC-MS) analyses were carried out on Shimadzu-QP5000 instrument working on electron impact mode with energy of 70 eV.

Carrier gas: helium 1 ml/min, split ratio of 1:15, fused silica column SE-30 column, 30 m x 0.2 mm x 0.53 μm.

Infrared spectra were recorded on Perkin-Elmer FT-IR spectrophotometer with spectrum 2000 software. The absorption bands are expressed in cm^{-1}. The liquid samples were smeared as thin film on KBr prism and the solid samples were taken as pellets of 2-3 % substance in KBr. Proton magnetic resonance (PMR) spectra were recorded on Varian EM-390 NMR spectrometer in carbon tetrachloride containing 5 % tetramethysilane (TMS) as the internal standard. The chemical shift (δ) values are expressed in ppm with relation to TMS peak. The coupling constants (J) are expressed in Hertz (Hz). The peak descriptions are abbreviated as s for singlet, d for doublet, dd for doublet of doublet, m for multiplet, br for broad. For some of the newer derivatives of monoterpenes, the PMR and ^{13}C-NMR were recorded on Bruker AMX-400 NMR spectrometer in $CDCl_3$ solvent at Indian Institute of Science, Bangalore, India.

Generally, IUPAC nomenclature of organic compounds has been followed. However, in case of monoterpenes, the more familiar trivial names have been used alternatively. The abbreviations used for solvents are as those mentioned in reference number 1 & 4. Rest of the abbreviations and notations used are in accordance with IU system.

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ABBREVIATIONS

Nomenclature

b. p.	boiling point
Ac	acetyl
Et	ethyl
Hz	hertz
Me	methyl
m. p.	melting point
Ph	phenyl
Pr	propyl
R	alkyl/aryl

Reagents and Solvents

AIBN	α, α^1-azobisisobutyronitrile
AcOH	acetic acid
BDMSB	bromodimethylsulfonium bromide
$BF_3.OEt_2$	boron trifluoride etherate
DBPO	di-*tert*-butyl peroxyoxalate
DCC	d icyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
LAH	lithium aluminium hydride
MCPBA	*m*-chloroperbenzoic acid
MeOH	methanol
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
PhH	benzene
PTS/TsOH	*p*-toluene sulphonic acid/tosic acid
ppm	parts per million
Py	pyridine
SiO_2	silica
THF	tetrahydrofuran
TMS	tetramethysilane
uv	ultraviolet

CHAPTER – 1

OXYGENATED MONOTERPENES AND THEIR SULFUR ANALOGS: INTRODUCTION

1.1 Oxygenated Monoterpenes from Natural Sources

Monoterpenes, the major components of essential oils, belong to the group of isoprenoids containing ten carbon atoms. They are widely distributed in the plant kingdom and are, especially, present in spices and herbs, which are extensively used in cuisines and human healthcare products. As essential oils have a pleasant odor and taste when used in low concentration, they have been extracted since ancient times from many plants and plant parts for use as food additives, mainly for flavoring purposes.[1] Essential oils and their constituent monoterpenes, being lipophilic compounds, readily cross cell membranes and are, therefore, absorbed through skin[2] and lung.[3] There is, therefore, a long history of use of essential oils and monoterpenes for many medical applications in ointments, balms and bath additives for relief of headache and chest colds as well as muscle pain. It has been found that several herbs rich in essential oils and their monoterpene components affect the bone metabolism and inhibit the resorption *in vivo* and *in vitro*, an example being the report of pine oil preventing bone loss in an osteoporosis model.[4a] Also, essential oils which are rich in terpenic compounds have specific action against pests, fungi and some important plant pathogens and this has been recently reviewed.[4b] The use of natural substances such as essential oils which are safer to consumers as well as to environment, for the control of post-harvest preservation of crops, is assuming lot of importance.[5]

1.11 The Essential Oils

The most important natural source of oxygenated monoterpenes is the essential oils derived from spices, herbs, fruits and flowers; extractives and exudates (resins) and certain animal secretions (e. g. musk) are also important source of fragrance materials. Essential oils are volatile oils obtained from odoriferous plant parts, possessing the odor and other flavor properties of the source material. The volatile components of essential oils, generally referred to as aroma chemicals, are responsible for the characteristic flavor. Flavor can be defined[6] as an integrated response to a complex mixture of stimuli, primarily on the senses of smell and taste but also on those associated with sight (color and appearance), tactile sensations (texture and mouth feel) and pain (pungency). It is one of the critical attributes

that help animals (including human beings) to recognize the food, evaluate its edibility and stimulate secretions needed for its digestion. By virtue of their volatile nature, the aroma chemicals also play a significant role in the propagation of plants, e.g. flowers attract the pollinating agents with their attractive color and fragrance. These secondary metabolites produced by plants also play an important role in offering protection against predators like pests and microbes.

Aroma chemicals are biosynthesized during the normal metabolic process in plants; they are also generated during cooking or processing of foods. While the aroma of a food material is due to volatile chemicals, generally low-molecular weight organic compounds with osmophoric groups usually containing hetero atoms like oxygen, nitrogen and sulfur, other attributes like pungency or astringency are due to the nonvolatile components. The flavor of the material depends on the combined effect of these characteristics. However, the odor of the foodstuffs is the predominant contributor to their distinctive and diagnostic flavor profile. The study of the volatile components, therefore, assumes greater importance in flavor chemistry.

The aroma chemicals, both from natural and synthetic sources are extensively used in several food flavor formulations[7,8] and in fragrance compositions[9] for use in products like soaps, detergents, cosmetics, and toiletries. As the positive trend towards the discovery of new flavor and fragrance compounds and understanding of enantioselective perception of odorants[10] is growing day-by-day, this area is attracting interdisciplinary networking involving the fields of synthetic chemistry (asymmetric as well as classical), natural products chemistry, flavor chemistry and aromatherapy.

Composition of essential oils

Some of the common essential oils, which have been used for long time for several applications, are oil of cumin (*Oleum carvi*), oil of eucalyptus (*Oleum eucalypti*), oil of fennel (*Oleum foeniculi*), oil of juniper berries (*Oleum juniperi e baccis,* purum), pine oil (*Oleum pini sibiricum*), dwarfpine oil (*Oleum pini pumilionis*), oil of cardamom (*Elettaria cardamomum*), oil of rosemary (*Oleum rosmarini,* DAB), and sage oil (*Oleum salviae,* Dalmatian). The genus *Mentha of Lamiaceae* family consists of more than 25 species of

which species like *M. arvensis, M. piperita, M. spicata* and *M. pulegium* have essential oils consisting of monoterpenes like menthol, menthone, carvone and pulegone as major constituents. These oils are widely used by industries in food, pharmaceutical, flavor and fragrance formulations.[11] Among the several mint species, *Mentha arvensis*, or Japanese mint, is the preferred one and covers large cultivation areas in India. Owing to the diverse biological activity of their monoterpenoids, *Mentha* species have been extensively studied.[12]

The several chemical components present in essential oils may be broadly classified as follows:

1. Terpenic hydrocarbons
2. Oxygenated terpenoids
3. Straight chain aliphatic compounds
4. Benzenoid compounds and
5. Compounds containing heteroatom like nitrogen and sulphur.

Terpenic hydrocarbons are the major constituents of essential oils. These are simple C-10 compounds, which are made up of two isoprenoid units joined in head to tail fashion e.g. limonene (Scheme 1.1, **1**, 90-95 % in orange), α-pinene (**2**, 50 % in parsley seed), β-pinene (**3**), γ-terpinene (**4**), terpinolene (**5**), α-phellandrene (**6**), α-terpinene (**7**, 40 % in marjoram) and camphene (**8**). These hydrocarbons have little contribution to the total flavor value of the essential oil.

Oxygenated terpene compounds include a variety of alcohols, aldehydes, ethers, ketones and esters. They are the major contributors to the distinctive odor of the essential oils. Some of the important flavor-impact compounds of this class are shown in Scheme 1.1. They include linalool (**9**, coriander), carveol (**10**, spearmint), geraniol (**11,** rose), nerol (**12,** rose), citral (**13**, citrus), carvone (**14**, spearmint, caraway), piperitone (**15**, mint), pulegone (**16**, peppermint), α- and β-ionones (**17**, **18**, violet), and esters of α-terpineol such as α-terpinyl acetate (**19**, cardamom, bergamot), α-terpinyl formate (floral, citrus) and α-terpinyl propionate (floral, lavender) and carvyl acetate (**20**, spearmint).

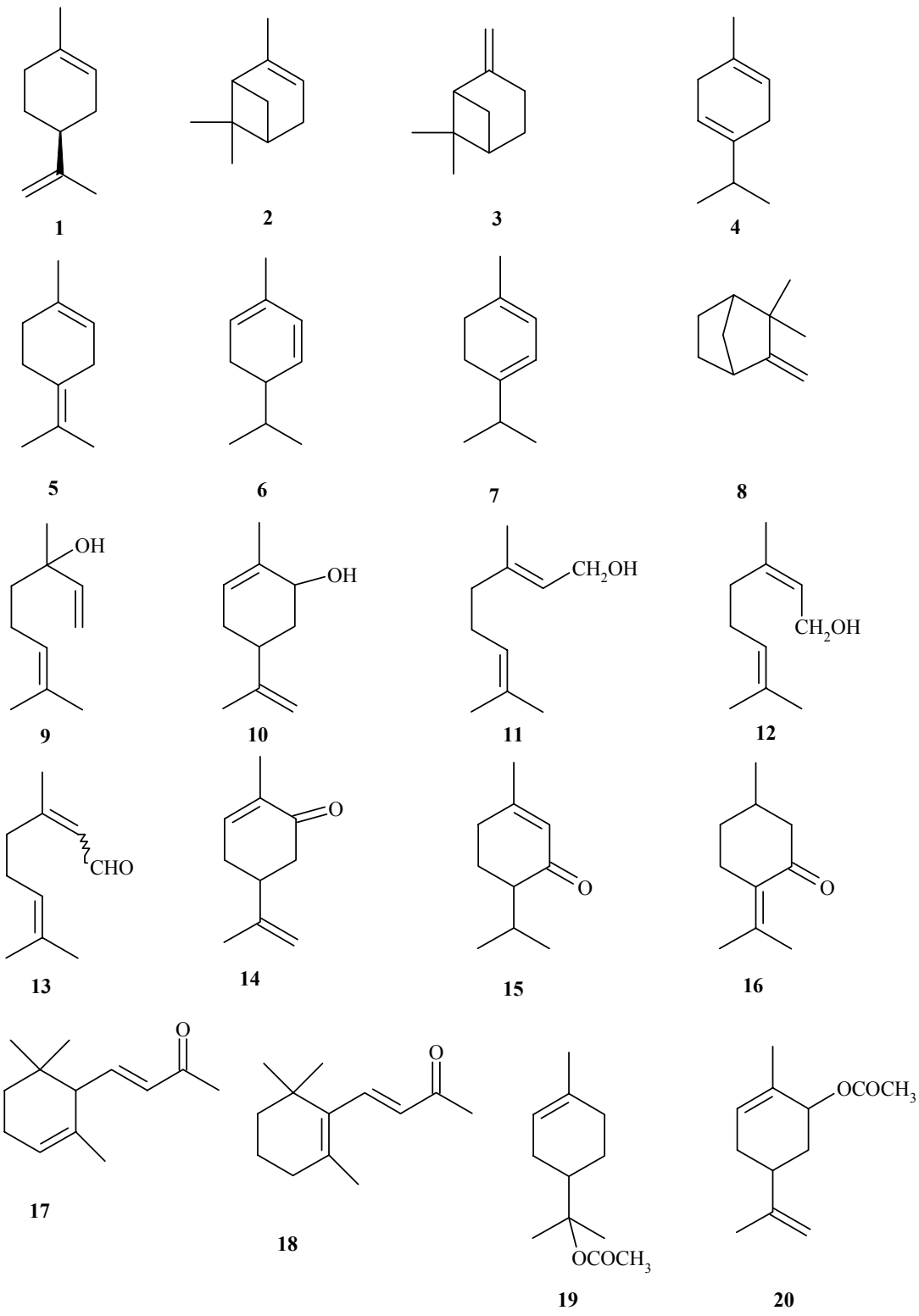
The constituents of essential oils of some fruits also contain certain aroma compounds, which are straight chain aliphatic compounds. These include alcohols, carbonyl compounds and esters, having one to twelve carbon atoms in the chain.

Certain benzenoid compounds present in the essential oils contribute towards the aroma. Examples of these are eugenol (Scheme 1.2, **21**) in clove, vanillin (**22**) in vanilla, heliotropin (**23**) in hops and anethole (**24**) in fennel.

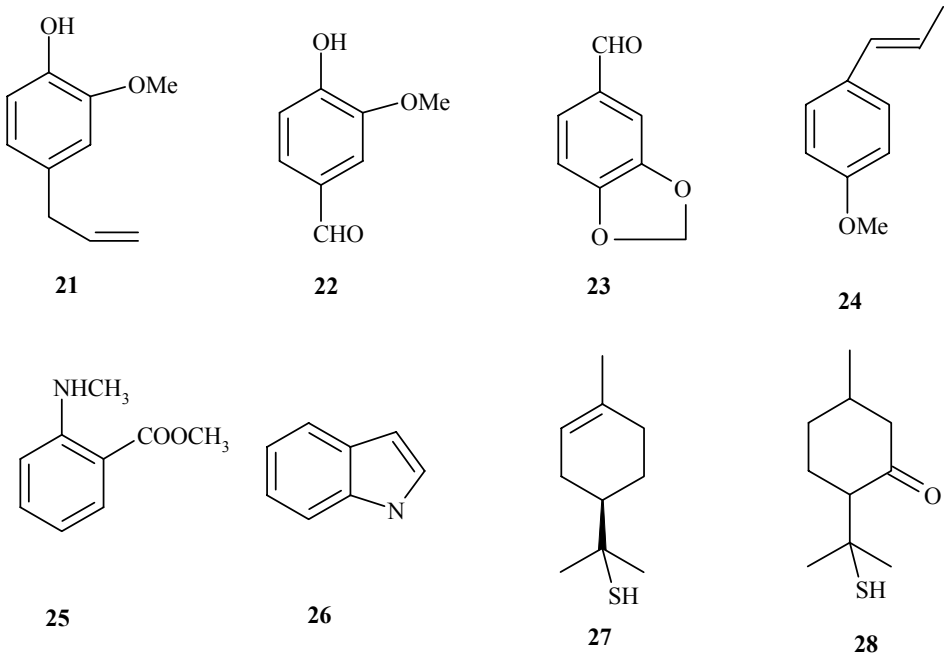
Nitrogen and sulfur containing aroma compounds are also found as constituents of essential oils. Nitrogen containing aroma compounds in essential oils include dimethyl anthranillate (**25**) from tangerine oils and indole (**26**) in jasmine. Sulfur containing compounds, mainly sulfides and disulfides, are present in minute amounts but have been shown to be important flavor components of allium species - onion, garlic, leek and chive. Examples of naturally occurring monoterpene thiols are (+)-4*R*-*p*-menth-1-en-8-thiol (**27**) in grapefruit and *p*-Menthan-3-one-8-thiol (**28**) in buchu leaf oil.

1.2 Sulfur Analogs of Oxygenated Monoterpenes

In nature a variety of organosulfur compounds are abundantly available. These are used in foods mainly because of their pungency or irritant properties and by their ability to prevent the spoilage of food and fermentation of fruit juices. Two such substances are allyl and benzyl isothiocyanates. Isothiocyanates are known to be present in trace amounts in plants of brassica family and those from the marine source form the largest group of naturally occurring isothiocyanates.[13] Glucosinolates and *β*-thioglucosulphonate oximes (Scheme 1.3) with side chain –R, are the biogenetic precursors for isothiocyanates. Hydrolysis of the glucosinolates is catalyzed by myrosinase, which is located separately in intact tissues, and it is released only when plants are crushed. The unstable aglycon so obtained forms predominantly an isothiocyanate by Lossen rearrangement. In this process, thiocyanates and nitriles may also be formed to a small extent. Thio- and isothiocyanates are present in many foods and vegetables and contribute to their odor and flavor (Table 1.1).[14a,b]

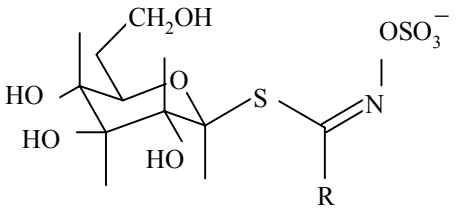

1
2
3
4
5
6
7
8
OH
9
OH
10
CH2OH
11
CH2OH
12
CHO
13
O
14
O
15
O
16
O
17
O
18
OCOCH3
19
OCOCH3
20

Scheme 1.1

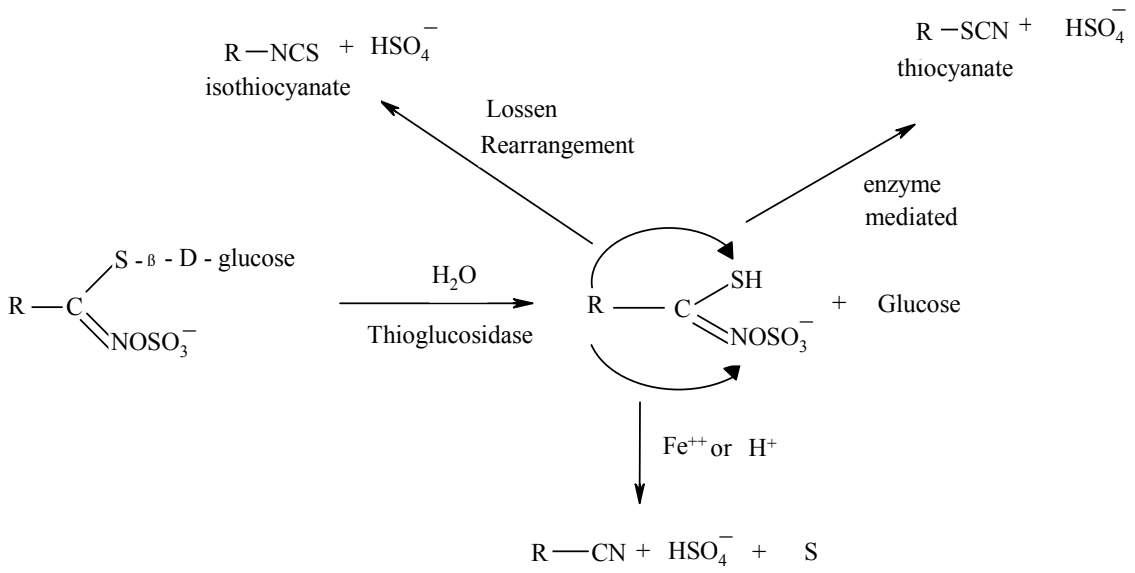


21 **22** **23** **24** **25** **26** **27** **28**

Scheme 1.2



Glucosinolate

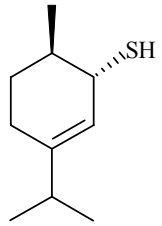


Scheme 1.3

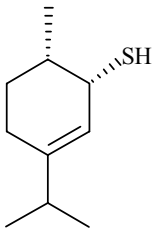
In organic chemistry, alkyl and phenyl isothiocyanates find extensive use in (1) the determination of primary structure of proteins, (2) labeling of proteins, (3) modification of enzymes, and (4) as metabolic inhibitors, Thio- and isothiocyanates are also useful intermediates in the synthesis of thiols and amines respectively. Terpene thiols have found numerous applications in foods, cosmetics, and toiletries.[15-17] α-Terpinyl thiol (*p*-menth-1-en-8-thiol) has been identified as the flavor impact constituent of grapefruit (*Citrus paradisii*). It is the most powerful aroma compound in nature having threshold value of $< 10^{-4}$ ppb in water. The presence of α-terpinyl thiol and a few other sulfurous odor compounds is essential for the full-bodied flavor of grapefruit juice. Many chemical methods have been introduced for the synthesis of this major flavor impact compound. The direct addition of the hydrogen sulfide to *d*-limonene takes place at very low temperature in presence of $AlCl_3$[18] or $RAlCl_2$[19,20] catalysts. Another method involves the reduction of limonene 8,9-episulfide with LAH. The episulfide, in turn, is prepared from the limonene-8,9-oxide and sodium thiocyanate[15] or thiourea.[21] Some of the important sulfur containing monoterpenoid derivatives natural and synthetic are depicted in Scheme 1.4.[22]

1.3 Chirality, Odor & Bioactivity of Aroma Compounds

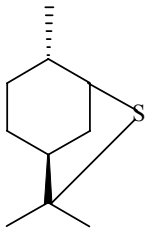
The chirality and bioactivity are closely interrelated and this subject matter has been recently reviewed.[10,23] This relationship is exemplified in more than 285 enantiomeric pairs where individual enantiomers exhibit either differing odors or odor thresholds. This aspect is quite pronounced in case of chiral monoterpenes. For example, (*4S*)-(+)-carvone (Scheme 1.5) has a distinct caraway odor as compared to (*4R*)-(-)-carvone, which has a sweet spearmint odor.[24] Similarly (-)-menthol has got sweet, fresh, minty and strong cooling effect as compared to (+)-menthol which has dusty, vegetable, less minty and little cooling effect. Also (*4R*)-(+)-limonene, which is available in orange, has got orange odor, where as the (*4S*)-(-)-limonene has got turpentine odor (Scheme 1.5).



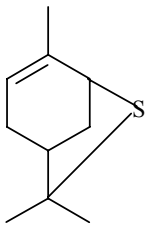
p-menth-3-en-*trans*-2-thiol



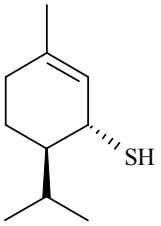
p-menth-3-en-*cis*-2-thiol



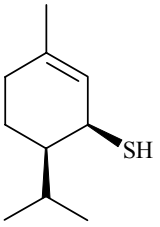
2,8-*epi*-thio-*trans*--*p*-menthane



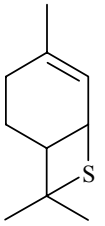
6,8-*epi*--*p*-menth-1-ene



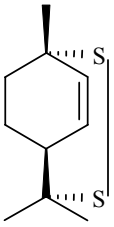
p-menth-1-en-*trans*-3-thiol



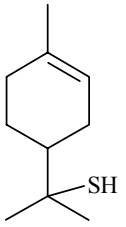
p-menth-1-en-*cis*-3-thiol



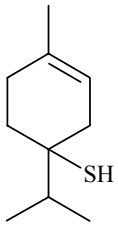
3,8-*epi*-thio-*p*-menth-1-ene



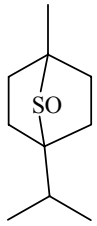
cis-1,4-*epi*-bithio-*p*-menth-2-ene



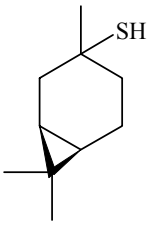
p-menth-1-en-8-thio



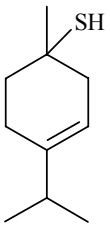
p-menth-1-en-4-thio



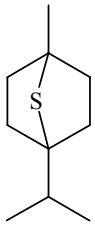
1,4-sulphinyl-*p*-menthane



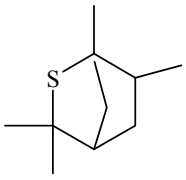
3,7,7-trimethyl[4.1.0]
heptan-3-thiol(*cis* + *trans*)



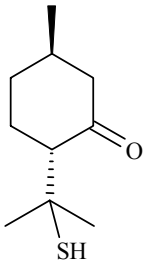
p-menth-3-en-1-thiol



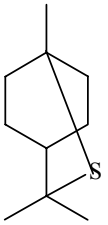
1,4-*epi*-thio-*p*-menthane



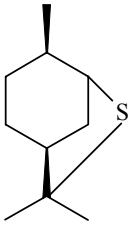
1,3,3,6-tetramethyl-2-thia-bicyclo
[2.2.1]heptane



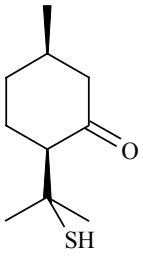
8-mercapto-trans-*p*-menth-3-one



1,8-*epi*-thio-*p*-menthnae



2,8-*epi*-thio-*cis*-p-menthane

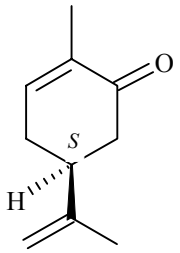


8-mercapto-*cis*-*p*-menth-3-one

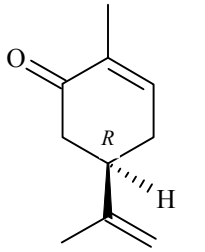
Scheme 1.4

Table 1.1: Thio- and Isothiocyanates occurring in foods.

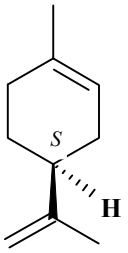
Compound	***Occurrence***
Thiocyanates	
Allyl thiocyanate	Horseradish, Onion
Isobutyl thiocyanate	Cocoa
Benzyl thiocyanate	Milk, Papaya
Methyl thiocyanate	Papaya
Isothiocyanates	
Methyl isothiocyanate	Cabbage
Allyl isothiocyanate	Cabbage, Black mustard, Cauliflower, Brussel sprouts
p- Hydroxybenzyl isothiocyanate	White mustard
Benzyl isothiocyanate	Papaya
But-3-enyl- isothiocyanate	Brown mustard



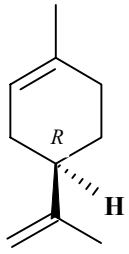
***4S*-(+)-carvone**
Caraway odour



***4R*-(-)-carvone**
Spearmint odour



***4S*-(-)-limonene**
Turpentine odour



***4R*-(+)-limonene**
Orange odour

Scheme 1.5

1.4 Synthetic Aroma Chemicals

Essential oils of aromatic plants, fruits and spices have long been natural sources for a variety of flavor chemicals. The quality and composition of essential oils are not always reproducible. Their cost and availability fluctuate and, even at best of the times, they are quite expensive. With the ever increasing requirement for the aroma chemicals, the supply for these from natural sources always falls short of demand. Hence, finding a subsidiary source becomes necessary. The obvious solution to this problem is through synthesis.

The complete duplication of essential oil is often difficult and also not so necessary as the main flavor of the essential oil, usually, is due to the presence of specific character-impact components. At the same time, majority of the components contribute little organoleptically and synthesis of all the components is often expensive. Hence, the important aroma chemicals are generally synthesized in pure form and are used either as such or in specific blends with other compounds to achieve the characteristic notes of the essential oil.

A number of aliphatic, aromatic and terpenic compounds are being produced synthetically. They are commonly used as flavors in foods like soft drinks, ice creams, candies and baked goods. Oxygenated monoterpenes constitute a major portion of these synthetic flavor chemicals. Monoterpenes are naturally occurring products widely used in flavor and fragrance industry, which is known to be essentially based on the chemistry of terpenes.[25-27] Terpenic aldehydes, alcohols and esters often show valuable organoleptic properties as well as biological activities. Extensive studies on oxyfunctionalization of some monoterpenes have been conducted by Gusevskaya and coworkers.[28-35] A selective $PdCl_2/CuCl_2$ catalyzed oxidations of limonene[28] and myrcene[35] with dioxygen, have been reported. An alternative $Pd(OAc)_2/LiNO_3$ catalytic system promotes a tandem coupling-oxidation of camphene with dioxygen.[32] $CoCl_2$ catalyzed oxidation of limonene, α-pinene and β-pinene with dioxygen in acetic acid and acetonitrile have been developed.[34,35]

In view of the abundant availability and relative inexpensiveness of the corresponding naturally occurring monoterpenic hydrocarbons, they have been considered as excellent starting materials for functionalization to oxygenated derivatives. Monoterpenes

are not only useful for perfumery and flavor industry but also their release into the atmosphere by green vegetation is of great relevance to the environment. These usually react with hydroxyl radicals, ozone and nitrates. With the ozone, ozonide formation and its subsequent decomposition afford carbonyl compounds. The terpene oxidation products are environmentally significant.[36]

Compounds to be added to food and beverages are subjected to strict regulations. Usually natural or nature-identical ones are preferred, because chiral natural flavorants occur in enantiomerically enriched form. Chemists have systematically investigated the absolute configuration of natural flavors, and tried to establish a correlation between cultivar and geographic origin, and the enantiomeric excess of a certain aroma.[37] Many reviews are there on enantioselective perception of chiral odorants[10] and exhaustive discussion on synthetic methods and the optimization of structure–odor relationships for the rational design of odorants.[38,39]

1.41 Availability of Hydrocarbons

1. Turpentine

Turpentine, obtained by distillation of the oleogum exudates of the pine trees or by steam distillation of the pine-stump chips, is rich in monoterpenic hydrocarbons. While the Indian turpentine is the richest source of (+)-3-carene, which forms about 55-60 % of the oil, the European and North American turpentine, is essentially a mixture of α- and β-pinenes. The most important flavor chemical obtainable from (+)-3-carene is (-)-menthol,[40] others being sylvestryl and terpinyl esters.[41] Some of the reactions of (+)-3-carene which yield important fragrance chemicals are depicted in Scheme 1.6.

2. Petrochemicals

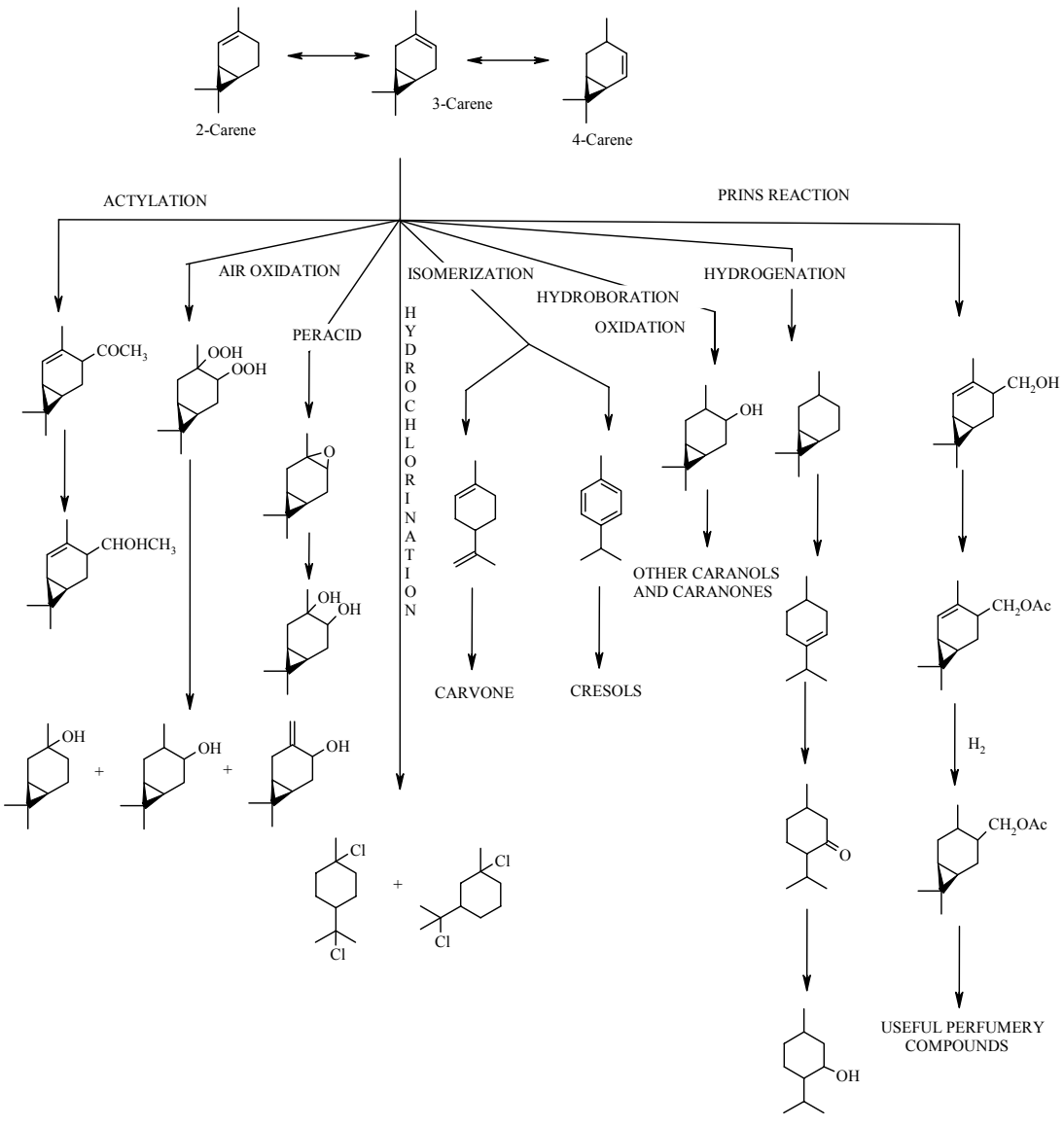
The petrochemical industry forms the chief source of hydrocarbons, important among them being ethylene, propylene, benzene and toluene. The first two are the raw materials for bulk production of acetone, acetic acid, ethanol and acetaldehyde. Isoprene (2-mehtyl-1,3-butadiene), obtainable by condensation of acetone and acetylene followed by partial hydrogenation and dehydration,[42] is another important hydrocarbon, extensively used

for manufacture of synthetic rubber. It is known that the terpenes are made up of isoprene units; dimerization of isoprene in a controlled manner (telomerization) has a number of applications. Important terpenes obtainable from teleomerization of isoprene are geranyl chloride,[43] geraniol, *α*-terpineol[44] and 8-chloro-*p*-menthene.[45]

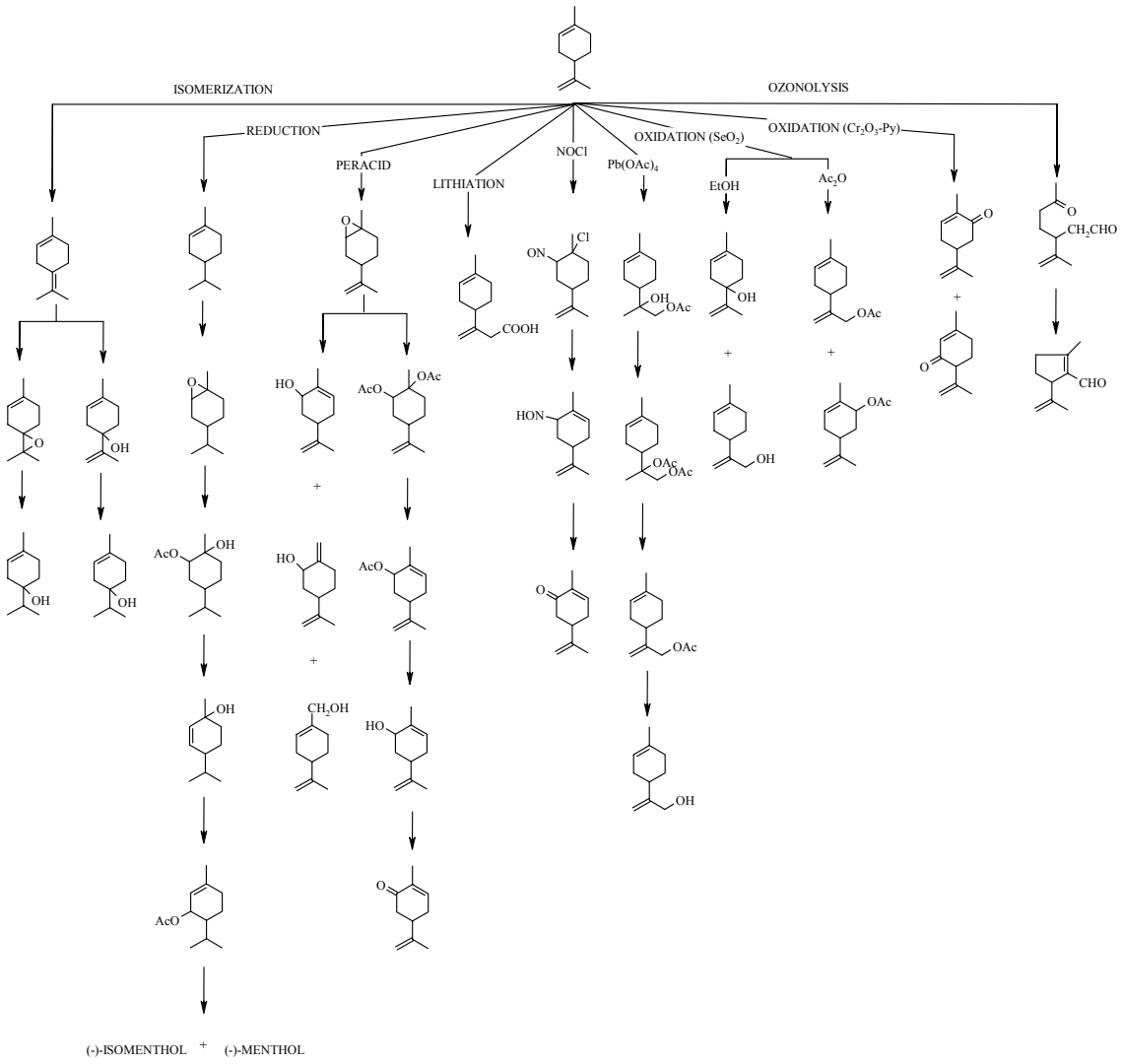
3. Citrus oils

Almost every part of the citrus fruit is useful and an integrated citrus industry yields several commercially important products. Essential oil, which is found in the peel and obtained by the method of expression or cold pressing, constitutes to about 1 % by weight of the fresh fruit. Citrus essential oils are characterized by their high content of monoterpene hydrocarbon, (+)-limonene.[46] The hydrocarbons are prone to undergo auto-oxidation and resinification, leading to the deterioration of the flavor of the essential oil. High proportion of these in the oil also renders the oils relatively insoluble in water-based foods such as soft drinks. For these reasons hydrocarbons are removed (partially or totally) from the essential oils, by distillation, solvent partition, chromatographic separation or hydrotropic extraction. This process is called deterpenation and the resultant oil is referred to as terpeneless or folded oil.

The terpenic hydrocarbons so removed are not well used, the suggested uses being are as thinners for paints, in manufacture of resins, in insect sprays, as *anti*-skimming agents in organic coatings, in waterless hand lotions and as industrial solvents.[47] (+)-Limonene, the main by-product of the citrus industry, has a chiral center and two double bonds of different reactivity which makes it an ideal starting material for the synthesis of perfumery and flavor chemicals based on *p*-menthane skeleton. Commercially it has been used for the synthesis of (-)-carvone by nitrosyl chloride method[48] and has been used as the starting material for the synthesis of important insect hormone, juvabione.[49] Several possible transformations of limonene have been reported (Scheme 1.7).[50]


2-Carene
3-Carene
4-Carene
ACTYLATION
PRINS REACTION
AIR OXIDATION
ISOMERIZATION
HYDROBORATION
OXIDATION
HYDROGENATION
PERACID
HYDROCHLORINATION
COCH3
CHOHCH3
OOH
OOH
O
OH
OH
OH
OH
OH
OH
CARVONE
CRESOLS
OTHER CARANOLS
AND CARANONES
CH2OH
CH2OAc
CH2OAc
H2
O
Cl
Cl
Cl
Cl
OH
USEFUL PERFUMERY
COMPOUNDS

Scheme 1.6



Scheme 1.7

1.42 Functionalization of Olefins *via* Halohydrins

α-Halogen substituted alcohols (1,2-*vicinal* halo alcohols) are generally referred to as halohydrins. Functionalization of olefins *via* halohydrin intermediates is an important method in synthetic organic chemistry. Bromohydrins are widely used as synthetic intermediates for the formation of regio-, stereo-, and chemoseletive carbon-heteroatom bond.[51] Electrophilic addition of halogens to alkenes yields a halonium ion intermediate, which in the presence of nucleophilic solvents like water, DMSO, DMF, carboxylic acids, and alcohols leads to the formation of halohydrins and their derivatives in very high *trans*-

stereoselective fashion. This process is known as cohalogenation.[52] This halofunctionalization of olefins is a widely applied procedure for the introduction of number of functional groups into the molecule such as thiocyanates,[53] sulfones,[54] selenocyanate,[55] perchlorates,[56] and nitrates.[57]

This reaction with cyclic olefins is largely *trans*-1,2-bifunctionalized and good yields are obtained with the fluorine,[58] chlorine,[59] bromine,[60] and iodine[61] containing nucleophiles (Scheme 1.8). This reaction has been limited from the formation of dihalogenation products; the selectivity depends on the nature of the nucleophile, concentration of the electrophile in the medium and the temperature of the reaction.

Of the cohalogenation reactions applied in the organic synthesis, bromohydrins are more extensively studied compared to the corresponding chloro- and iododerivatives. Bromohydrins easily undergo cyclization in good yield to afford the stereospecific epoxides. In case of decalin, epoxide formation was found to be *endo, via* bromohydrin route, while direct epoxidation with the *m*-chloroperbenzoic acid gives *exo*-epoxide.[62] A new indirect and stereospecific method of *cis*-1,2-dihydroxylation of olefins has been reported.[63] This involves esterification of bromohydrins with the enolizable acids (cyanoacetic, malonic) and its subsequent treatment with a base followed by acid hydrolysis. Similarly *cis*-dihydroxylation of olefins is achieved through acetoxy halogenation with wet acetic acid.[64] Bromohydrin mediated synthesis of alkyl substituted crown ethers[65] and corresponding thiocrown ethers are reported.[66] Base-promoted dehydrohalogenation of bromohydrins derived from both *cis*- and *trans*-stilbenes to produce enol ethers is reported.[67] Tin mediated generation of reactive radical intermediates is facile, and hence tandem cohalogenation-homolytic carbocyclization strategy is widely applied in organic synthesis.[68]

1.43 Monoterpenes as Substrates

Terpenic hydrocarbons containing double bonds are ideal for the functionalization *via* halohydrin intermediates for the synthesis of important oxygenated compounds. This method is applied to the synthesis of *trans*-epoxide of terpenes by base-catalyzed cyclization.[69] Similarly *cis*-3-carene-oxide has been obtained by base-catalyzed cyclization of the 3-carene bromohydrin.[70] *tert*-Methyl-*β*-bromo-alkylethers have also been synthesized

from monoterpenes by using NBS in methanol.[71] A crucial intermediate in the synthesis of *trans*-chrysanthemic acid has been prepared from the *cis*-carene-1,2-diol. This starting material is synthesized by sequential cohologenation and dehydrohalogenation and subsequent hydrolysis.[72] Some of these important reactions that involve the bromohydrin intermediates in monoterpene series are depicted in Scheme 1.9 (references in parenthesis).

1. 44 Functionalization of Olefins *via* Epoxides

Epoxides (oxirans) are very useful synthetic intermediates in organic chemistry. Oxirans are compounds with a three-membered ring composed of an oxygen atom and two sp^3-hybridized carbon atoms.[73] They are widely distributed in nature and are of industrial, mechanistic and biological interest. Preparation, properties, and applications of epoxides have been reviewed.[74] Epoxides generally undergo several reactions which are illustrated in Scheme 1.10.

1, 2: Homolytic ring cleavage (thermal and photochemical)

3: Electrophilic attack on the ring oxygen,

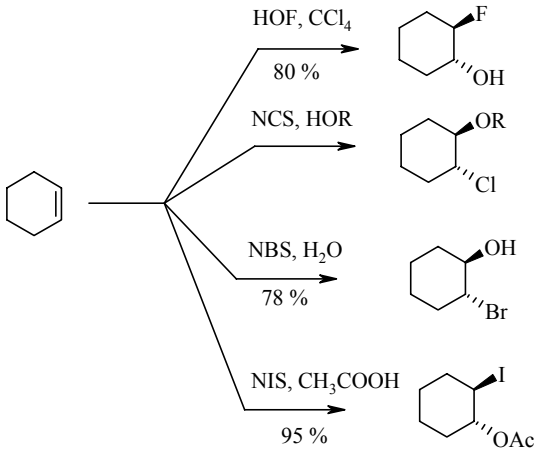
4: Nucleophilic attack on ring carbon

5: Nucleophilic attack on ring proton (proton abstraction),

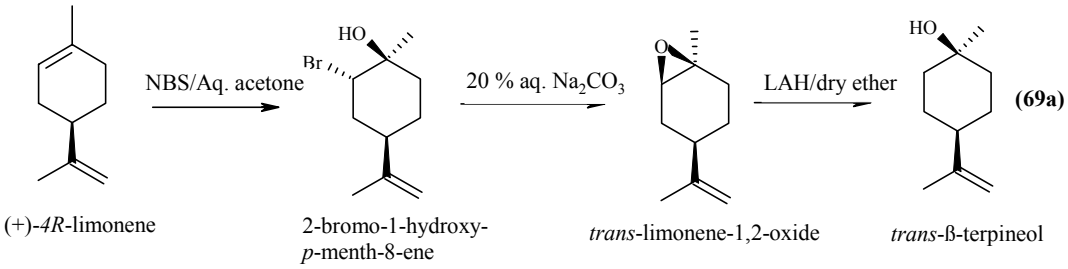
6: Reaction with electrons and surface reaction,

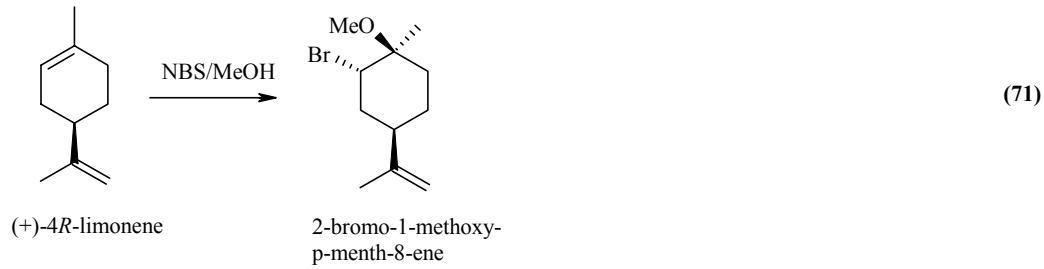
7: Cycloaddition and

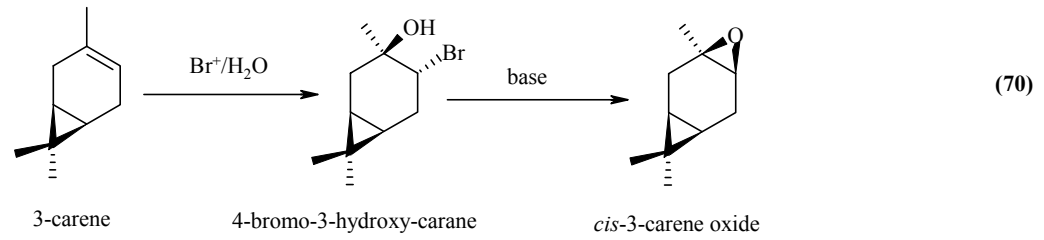
8: Reactions of substituents.

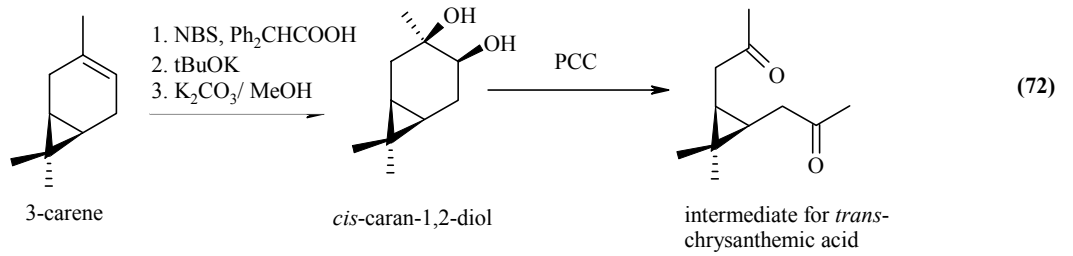


Scheme 1.8

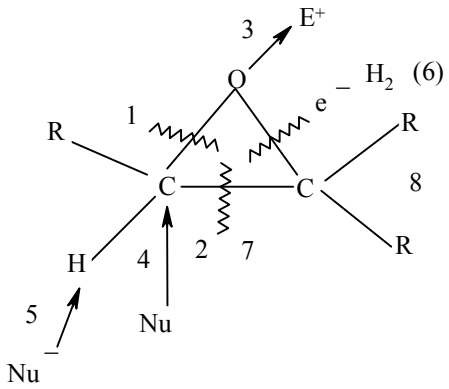








Scheme 1.9



Scheme 1.10

The most important method of oxiran syntheses is by addition of an oxygen atom to a carbon-carbon double bond. The ease of preparation of these and facile ring opening have made them important intermediates in organic chemistry for the past several decades. In the present decade, emphasis has been given on the development of milder conditions, which are enantio-, diastereo-, regio-, and chemoselective.[75]

Alkenes undergo easy epoxidation with organic peroxy acids and also with inorganic peroxides in presence of metal catalysts (Scheme 1.11). The stereochemistry of olefin is retained in the epoxide. It involves nucleophilic attack on the *O-O* bond by the Л–electrons of the olefin. The epoxidation rate increases with electron donating groups in the olefin and electron withdrawing groups on the peroxy acid. In the case of polyunsaturated systems the stereochemistry can be easily predicted. The more substituted double bond is more reactive. For example in case of limonene the tri- substituted *endo*-cyclic double bond gets epoxidized in preference to the disubstituted *exo*-cyclic double bond. In case of olefins having one or two chiral centers, the diastereomeric ratio of epoxides is determined by the ease of facial approach of the reagent. Thus, chiral limonene affords two diastereomeric *cis*- and *trans*-epoxides in ~1:1 ratio. The epoxidation of olefins are extensively carried out with *m*-chloroperbenzoic acid. In case of acid sensitive epoxides usually pH of the medium is controlled by buffer action with $NaHCO_3$, Na_2CO_3, Na_2HPO_4, or KF[76] The other commonly used peroxy acids[77]includes peracetic acid (40 % commercially available, prepared from the H_2O_2 > 95 % with acetic acid catalyzed by conc. H_2SO_4), basic H_2O_2, trifluoroacetic acid, 4-nitroperbenzoic acid, 3,5-dinitroperbenzoic acid, magnesium monoperphthalate and dialkyl dioxiran.[78]

1.45 Monoterpene Epoxides

The epoxidation and subsequent reactions for the preparation of variety of useful compounds from monoterpene series is widely employed. Epoxides can be transformed into alcohols, esters and carbonyl compounds by a variety of reactions such as reduction, solvolytic ring opening and acid/base catalyzed rearrangements.[77] Epoxides may be reduced by catalytic hydrogenation, or by an electron transfer process either electrochemically or by alkali metals in liquid ammonia, ether and THF.[78] *trans*-Limonene oxide yields by reduction

with lithium in ethylamine, *trans*-*β*-terpineol while *cis*-limonene oxide yields not only *cis*-*β*-terpineol but also neodihydrocarveol and isodihydrocarveol.[79] LAH reduction of 1:1 mixture of *cis*- and *trans*-limonene-1,2-oxide yields a mixture of *β*-terpineols and neodihydrocarveol with the *trans*-isomer reacting faster than *cis*-isomer.[80] Terpinolene oxide, being a tetrasubstituted spiroepoxide, is relatively resistant towards both catalytic hydrogenation and LAH reduction. Two strategies have been developed for the reduction this oxide; one involves the use of metallic sodium in ether[81] and the other is use of LAH-$AlCl_3$,[82] both of which afford 4-terpinenol as the major product. Epoxides are capable of undergoing rearrangements, the main products produced being carbonyl compounds and *α,β*-unsaturated alcohols. This can be brought by acid, alkali, thermal, photochemical and other catalysts like Al_2O_3, SiO_2, MgO, TiO_2, and ZnO. Limonene-1,2-oxide with basic alumina yields *cis*-*p*-menth-1(7),8-diene, *cis*- and *trans*-carveols and perillyl alcohol.[83] *α*-Pinene oxide on similar treatment yields *cis*- and *trans*-pinocamphones and campholenic aldehyde.[84] The same oxide in the presence of $BF_3{\cdot}OEt_2$[85] and $ZnBr_2$[86] gives campholenic aldehyde. In Wharton reaction (keto-epoxides heating with hydrazine) *cis*- and *trans*-piperitone oxide gives *cis*- and *trans*-*p*-menth-2-ene-1-ols respectively.[87] The representative examples of reactions of the terpene epoxides are depicted in Scheme 1.12 and 1.13 (references in parenthesis).

1.46 Functionalization of Olefins *via* Alkyl Halides

Alkyl halides are very common intermediates in the syntheses of many natural and organometallic products.[88,89] They are generally synthesized by the addition of hydrogen halides (HF, HCl, HBr, and HI) to alkenes. This reaction has been well studied from both mechanistic and synthetic viewpoints.[90] It is one of the earliest methods employed for the synthesis of alkyl halides. In general the ease of addition of H-X to simple alkenes follows the relative acidity, HI > HBr > HCl and the addition follows Morkovnikov rule. Since these reactions involve strong acids, rearrangements are common.

The addition of HCl to alkenes is easy and there are numerous examples of the direct addition of HCl to alkenes.[91] Dry HCl gas is passed through alkenes either neat or in inert solvent such as pentane, dichloromethane or ether. This process is facile in cases of formation of tertiary and/or benzylic chlorides[92] and yields are generally high (Scheme

1.14).[93] Addition of HCl to alkenes bearing electron-withdrawing groups provides a useful approach to the functionalized organic halides.

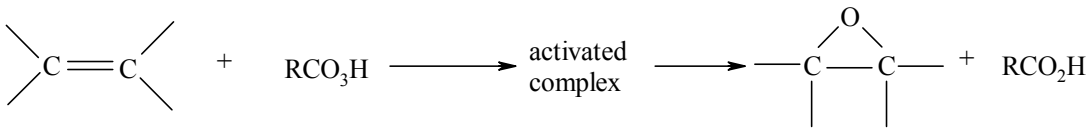
The electrophilic addition of HBr to alkenes has been extensively studied.[91] Competing *anti*-Markovnikov products are predominant in presence of light and organic peroxides.[94] HBr addition is exothermic and more rapid than HCl addition. This is usually carried out neat or in inert solvents or in water/acetic acid. Less reactive alkenes react with HBr in presence of Lewis acid catalysts. The alkyl halides- primary, secondary, and tertiary- undergo various reactions like solvolysis, rearrangement, nucleophilic substitution, and organometallic coupling reactions.[95]

1.47 Monoterpene Halides

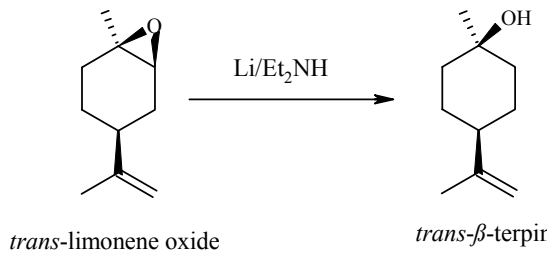
Alkyl halides are very useful intermediates in terpene synthesis. Monoterpenic hydrocarbons undergo easy addition of hydrogen halides to give, in good yield, the corresponding alkyl halides. Isoprene, the fundamental terpenic unit, is monohydrochlorinated in the presence of cuprous chloride to yield 1-chloro-3-methyl-2-butene.[96] This is the key step in the conversion of isoprene into aroma chemicals like linalool, geraniol, nerol, citral and ionones.[97] Citronellene is obtained by the selective hydrogenation of myrcene[98] or pyrolysis of pinane,[99a,b] which in turn is obtained by hydrogenation of α- and β-pinenes.[100] Citronellene on reaction with anhydrous hydrogen chloride at 20-25^{o}C yields 2-chloro-2,6-dimethyl-7-octene[101] from which a wide range of aroma chemicals are prepared (Scheme 1.15).

Halogen derivatives of α- and β-pinenes and (+)-3-carene, are intermediates in the preparation of some important flavor chemicals. Hydrochlorination of α-pinene gives unstable hydrochloride which rearranges to bornyl chloride. Hydrodehalogenation of this halide gives camphene,[102] an important intermediate in the synthesis of camphor (Scheme 1.16). Hydrochlorination of (+)-3-carene below -10^{o}C, affords (+)-limonene dihydrochloride and (+)-sylvestrene dihydrochloride,[103] which on base induced hydrolysis yield α-terpineol and sylvesterpineol (Scheme 1.17).[104] Terpinolene with bromine yields a dibromide which on further treatment with HBr gives tribromide. This on reaction with zinc in acetic acid results in the formation γ-terpinyl acetate (Scheme 1.17).[105] A review on the synthesis of

aroma chemicals from alkyl halide intermediates that have tertiary, allylic and benzylic chlorides/bromides is available.[106] A group of oxygenated and sulfur aroma chemicals synthesized *via* alkyl and aryl halides are alcohols, esters, ethers, thioethers and thiolesters and they have been obtained by substitution of alkyl and aryl halides with S_N1-active halides in the form of zinc salts.

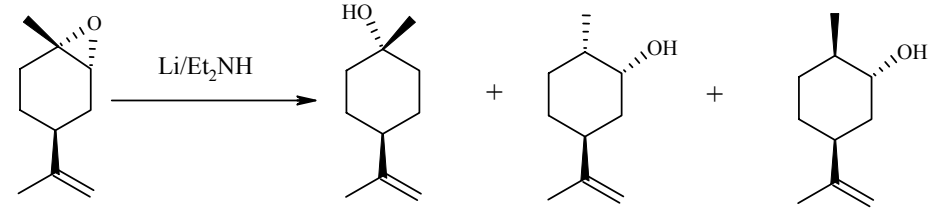


Scheme 1.11



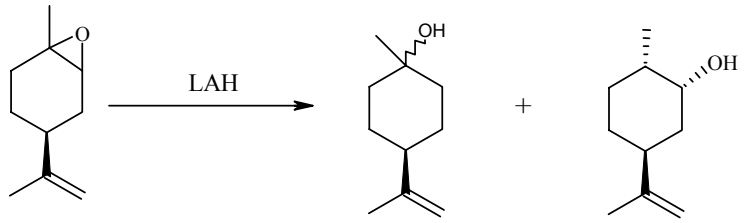
trans-limonene oxide — *trans*-ß-terpineol

(79)



cis-limonene oxide — *cis*-ß-terpineol — neodihydrocarveol — isodihydrocarveol

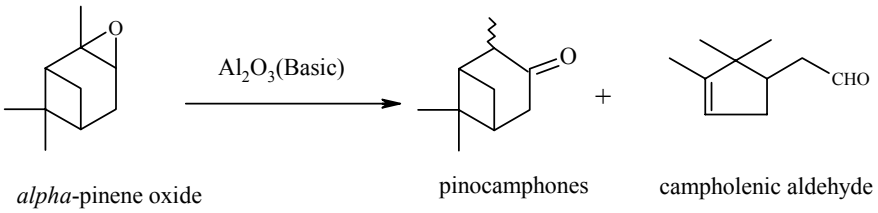
(79)



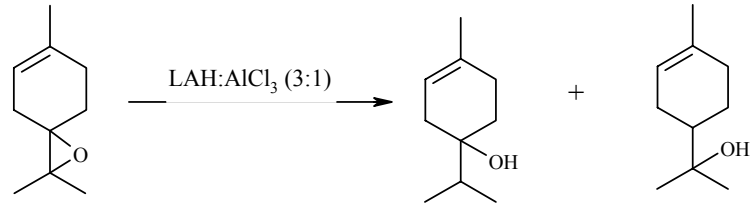
1:1 cis-and *trans*-limonene oxide — *cis-and trans-ß-terpineols* — *neodihydrocarveol*

(80)

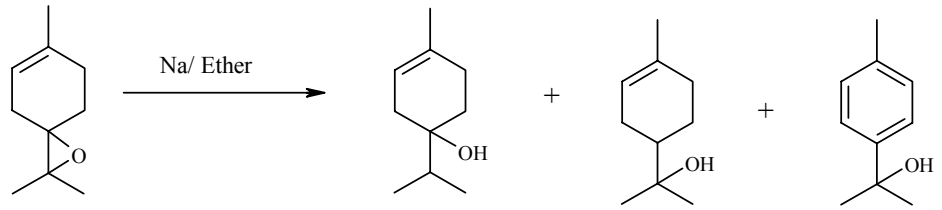
Scheme 1.12



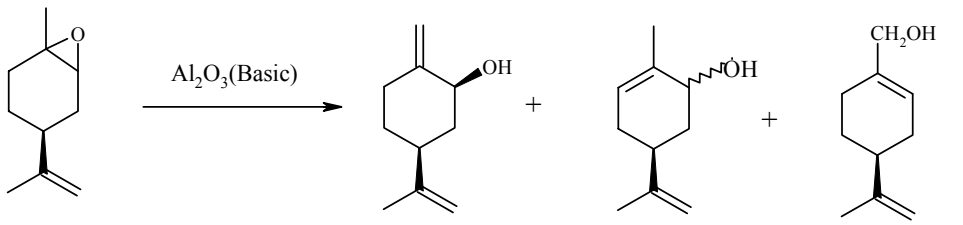
alpha-pinene oxide — pinocamphones — campholenic aldehyde **(84)**



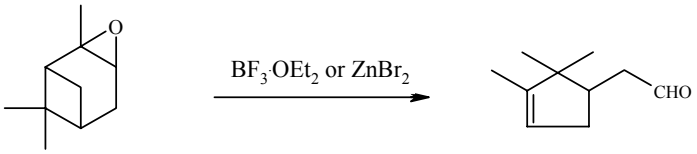
terpinolene oxide — 4-terpinenol — *alpha*-terpineol **(81)**



terpinolene oxide — 4-terpinenol — *alpha*-terpineol — 8-*p*-cymenol **(82)**

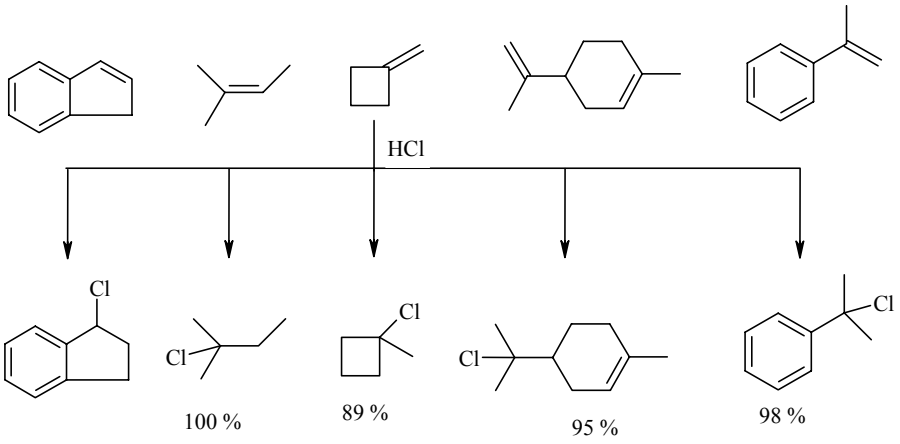


limonene oxide-1,2-oxide — *cis*-p-menth-1(7),8-diene-2-ol — *cis*- and *trans*-carveols — perillyl alcohol **(83)**

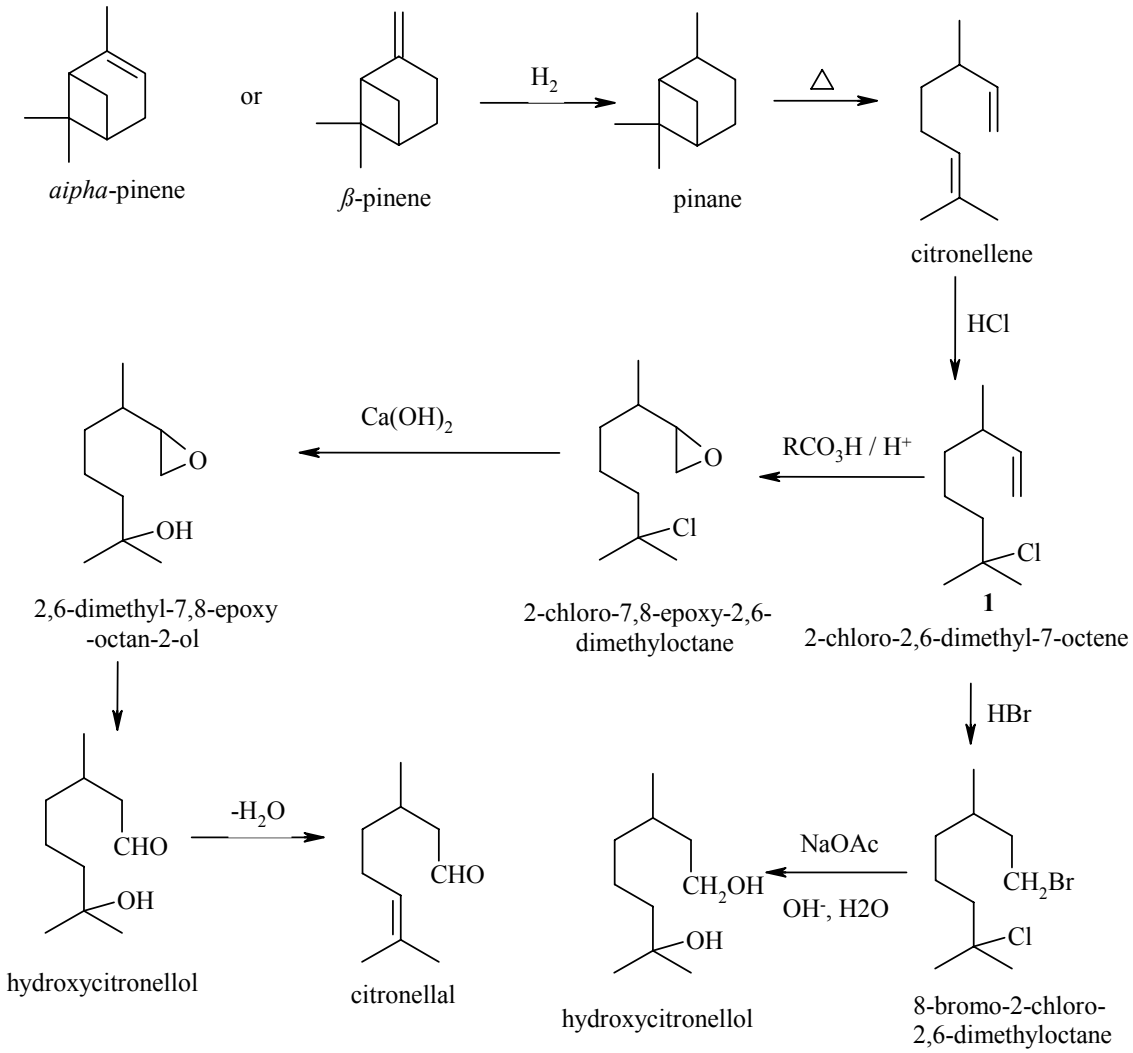


alpha-pinene oxide — campholenic aldehyde **(85, 86)**

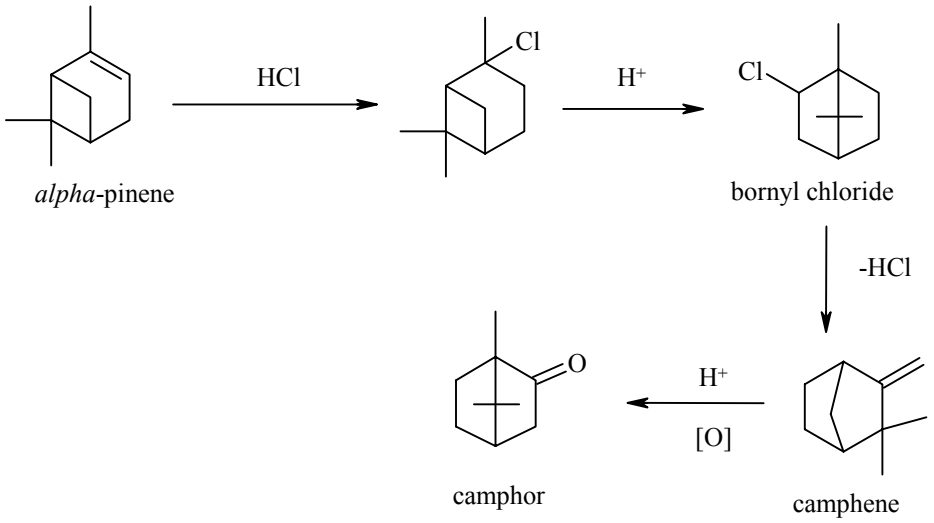
Scheme 1.13



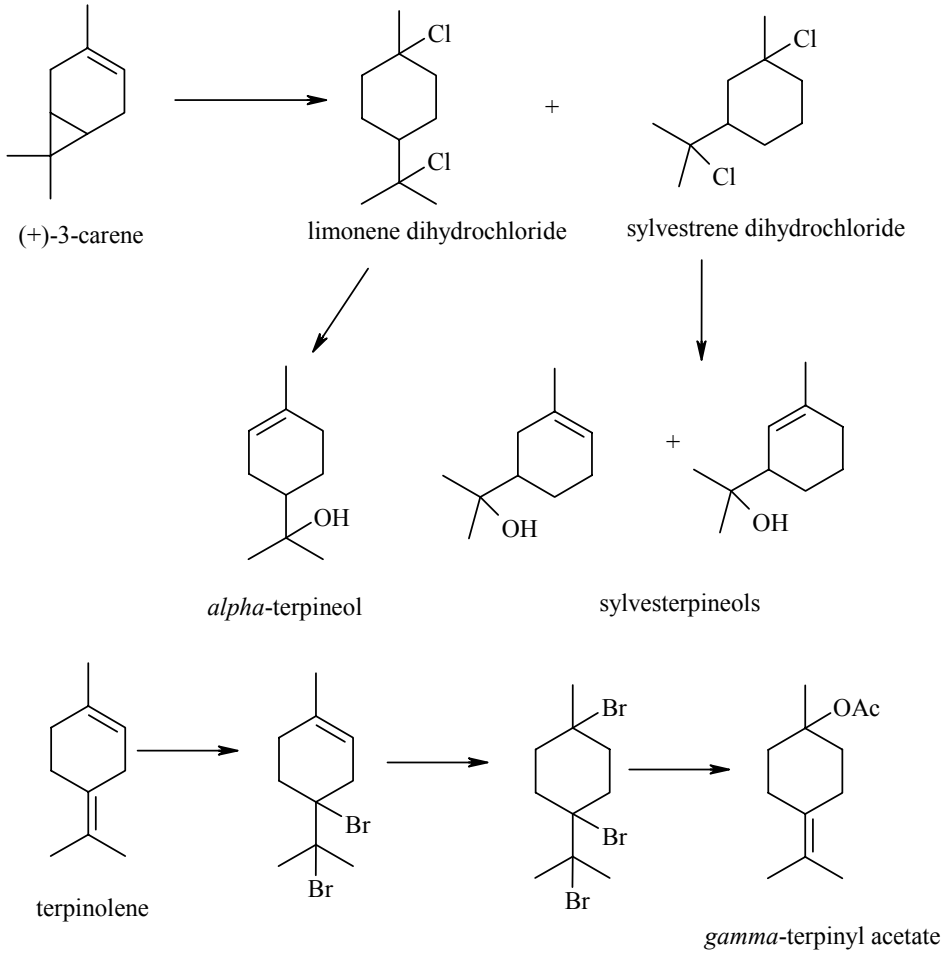
Scheme 1.14



Scheme 1.15



Scheme 1.16



Scheme 1.17

1.5 Present Investigation: Scope and Objectives

From the foregoing discussion, it is obvious that the terpenic hydrocarbons are abundantly available in nature and the corresponding oxygenated derivatives like alcohols, esters, carbonyls, ethers and sulfur derivatives like thiols, thiocyanates, thioethers and thiolesters are important flavor chemicals. The synthesis of newer oxygenated and thio-derivatives of monoterpenes is apparently an important field of synthetic organic chemistry. The strategy for obtaining relatively expensive oxygenated and thio- derivatives from the inexpensive hydrocarbons, *via* reactive intermediates like epoxides, alkyl halides and to a lesser extent from halohydrins, is well employed in the synthesis of several aroma chemicals. However, preparation of the oxygenated and thio- derivatives of monoterpenes still has a vast scope in terms development of mild, easy, chemo-, regio-and stereoselective synthetic methodologies. Although bromohydrin intermediates of monoterpenes have been known for quite some time, their application with special reference to the preparation of oxygenated derivatives needs to be further explored.

In the present investigation, special emphasis has been given to developing newer strategies for the oxygenated, thio- and new glucoside derivatives of monoterpenes. The main objectives of the study were development of new, improved reagents, and methods for the functionalization of hydrocarbons, investigation of reaction mechanisms, especially of stereo- and regioselectivities, with an ultimate aim of developing efficient synthetic routes to aroma chemicals and their intermediates.

Among the intermediates, bromohydrins, epoxides and alkyl halides of monoterpenes and also few other alkyl and aryl intermediates have been prepared. Techniques like ultrasound and photo-irradiation have been applied successfully. The present study is also directed towards development of viable synthetic methods using inexpensive methods and simple reagents, with optimization of the conditions to obtain the desired product in high yield and purity. Newer glucoside derivatives of monoterpenes have been prepared.

The present work is described in five chapters. A brief account of the natural occurrence of oxygenated and their sulfur analogs, and their importance as aroma chemicals

and synthetic approach to them are given in chapter 1. In chapter 2 (Sections 2.1 to 2.4) preparation and reaction of monoterpene bromohydrins and epoxides have been described. Chapter 3 (Section 3.1 and Section 3.2) deals with the photochemical reactions of epoxides and bromohydrins. Preparation of new D-glucal derivatives of S_N1-active alcohols, *via* Ferrier rearrangement reaction, is described in chapter 4. Results of nucleophilic substitution of *tert*-halides with zinc and titanium thiocyanate under the influence of ultrasound are discussed in chapter 5, part A. part B describes the reduction of terpene thiocyanates to thiols using LAH reagent in dry ether. The summary of this thesis is given in the end.

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CHAPTER 2

PREPARATION AND REACTIONS OF MONOTERPENE BROMOHYDRINS AND EPOXIDES

Section 2.1: Direct Conversion of *tert*-*β*-Bromo Alcohols to Ketones

Section 2.2: Allylic Bromides from *tert*-*β*-Bromo Alcohols

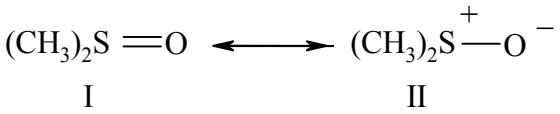
Section 2.3: The Reaction of Terpene and Aryl Substituted Epoxides with Bromodimethylsulfonium Bromide

Section 2.4: Preparation of Bromohydrins

Section 2.1: Direct Conversion of *tert*-*β*-Bromo Alcohols to Ketones

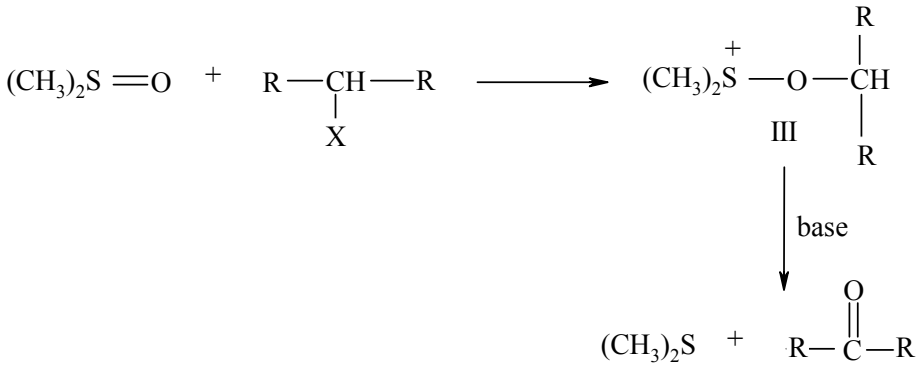
I. Oxidation Reactions of DMSO

DMSO was first prepared in 1866 by Saizew.[1] It was used as a mere solvent until Kornblum *et al*.[2] reported its oxidizing ability and used it as a reagent. The easy experimental procedure, uncomplicated work-up and high yield of the product have rendered DMSO a very useful reagent.[3] The sulfur oxygen bond in DMSO is semi-polar in nature, and it can be represented by the following resonance structures (Scheme 2.1.1).



Scheme 2.1.1

The resonance structure II owes its existence to the ability of the 3d orbital of sulfur to accommodate an additional electron pair. It can act like a nucleophile; its basicity is slightly greater than water and nucleophilicity has been estimated to exceed that of ethanol toward alkyl sulfonate ester. The oxidizing ability of DMSO arises from the nucleophilic attack of the oxygen coordinated to the sulfur atom to form a dimethylalkoxysulfonium salt (Scheme 2.1.2, III). Subsequent breakdown of this intermediate, in the presence of a base, yields oxidized product and DMS (DMS).



Scheme 2.1.2

1. Oxidations of alcohols

Alcohols can be oxidized to aldehyde or ketone with dicyclohexyl carbodiimide (DCC) in DMSO in presence of a proton source like phosphoric acid or pyridinium trifluoroacetate (Pfitzer-Moffatt technique).[4] Application of this oxidation technique to carbohydrates results in the oxidation of most free hydroxyl groups to the corresponding carbonyl compounds.[5] Primary and secondary alcohols can also be oxidized to respective carbonyl compounds with DMSO activated by organic acid anhydrides.[6] Alcohols when converted to corresponding chloroformates act as activator for DMSO and they get oxidized to carbonyl compounds when treated with bases. This reaction passes through an intermediate dimethylalkoxysulfonium salt, which collapses in the presence of base to give carbon dioxide and carbonyl compound.[7] Oxidation of alcohols using activated DMSO has been reviewed.[8] The electrophilic reagents that activate DMSO include trifluoroacetic anhydride, thionyl chloride, oxalyl chloride, *t*-butyl hypochlorite, chlorine, acetic anhydride, acetyl, benzoyl, methanesulfonyl and toluenesulfonyl chlorides, carbonchloridates, sulfur trioxide/pyridine, DCC, P_2O_5, polyphosphoric acid, bromine, and ethoxyacetylene.

2. Oxidation of halides and tosylates (Kornblum oxidation)

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized using DMSO to aldehydes easily and in good yields.[2,9,10] In this reaction, formation of a dimethylalkoxysulfonium salt is followed by prior nucleophilic displacement of halide by oxygen of DMSO. Usually this reaction takes place in the presence of bases such as sodium bicarbonate to scavenge the hydrogen halide formed during the reaction. The reaction proceeds by a S_N2 displacement by the oxygen atom of the DMSO, followed by proton loss and 3,2-sigmatropic rearrangement of the resulting sulfur ylid. It works best with activated halides such as benzyl halides[9b], α-haloesters (Br, Cl, I) or acids,[11] phenacyl halides,[2] primary sulfonates[9a] and primary iodides.[12] This method proves to be an alternative to selenium dioxide oxidation for the synthesis of 1,2-diketone system. Apart from some significant applications for the preparative procedures for carbonyl compounds, Kornblum oxidation has got some limitations. Secondary halides undergo competing elimination reactions under these conditions.[9a] Primary alkyl iodides need to be derivatized to respective

tosylates for the oxidation to proceed.[9b] Johnson and Pelter, however, showed primary iodides can be oxidized without converting them to tosylates.[12] Addition of a silver salt ($AgBF_4$)[13,14] to DMSO solution is found to be effective in increasing the reactivity of halides. Kornblum showed that the oxidation of unactivated chlorides, bromides and iodides could be increased by increasing the nucleofugacity with conversion to tosylate with silver tosylate followed by reaction in DMSO (Scheme 2.1.3).[9b] However, this method fails in case of neopentyl halides. Triethyl amine has been used as a base after the formation of dimethylsulfoxoniun salt. Silver perchlorate is claimed to be superior to silver nitrate.[15] The method is not successful with unactivated chlorides and bromides and for the substrates where solvolysis is possible.

II. Oxidations of Halides by other Reagents

1. Krohnke oxidation

An important method of oxidation of activated halides is the three-step Krohnke oxidation.[16] It involves: i) Quaternization of the halide with pyridine, ii) deprotonation in presence of base and reaction of the resulting pyridinium ylid with *N,N*-dimethyl-4-nitrosoaniline, and iii) acid hydrolysis of the nitrone to the carbonyl compound (Scheme 2.1.4). This reaction gives good yield of products with secondary halides but is unsuitable for the oxidation of unactivated halides. Reaction is limited to substrates, which are stable to alkoxide bases and aqueous acids. This is an excellent method for the preparation of heterocyclic aldehydes.[17] Krohnke oxidation gives good yield of oxidation products where methods like Sommelet and Hass-Bender reactions fail to give the oxidation products.[18]

2. The Hass-Bender reaction

The replacement of halide ion by the oxygen of nitronate ion followed by the loss of oxime leading to the formation of carbonyl compounds is referred as Hass-Bender reaction (Scheme 2.1.5).[19] The method has been applied to the synthesis of a number of aldehydes from respective primary allylic and benzylic halides.[20] There are no reports of oxidation of secondary halides to ketones by this method.

3. Oxidation with N-oxides

a) With pyridinium oxide and derivatives

Oxidation of alkyl halides with pyridine or derivatives like picoline oxide is a popular and general method, applicable even to unactivated substrates. This reaction can be performed in two ways. Pyridinium salt obtained from pyridinium oxide and halide is isolated and then treated with base. In another method, the substrate is heated with the *N*-oxide in the presence of base such as sodium hydrogen carbonate (Scheme 2.1.6).[21] This method is excellent for the preparation of 1,2-dicarbonyl compounds from α–bromo esters or acids in the presence of silver nitrate.[22] Mukiyama *et al.* have reported that 4-dimethylaminopyridine *N*-oxide in the presence or absence of DBU is an efficient agent for oxidation of alkyl halides.[23] This method can be applied to primary or secondary alkyl halides, or α–bromoesters. This reaction also passes through initial formation of salt and subsequent de-protonation using base to yield carbonyl compound. 1,8-Diazabicyclo-[5.4.0]undec-7-ene is shown to be most suited for the deprotonation step. Primary bromides, chlorides and secondary bromides work well with this procedure. A bi-functional approach towards the mild oxidation of organic halides using 2-dimethylamino-*N,N*-dimethylaniline *N*-oxide is reported.[24] Primary benzylic, phenacyl and primary allylic bromides work well with this procedure. However benzyl chloride and unactivated bromides do not react with this reagent even under reflux conditions.

b) Amine oxides

Amine oxides can be used instead of pyridine oxides for the oxidation of activated and unactivated bromides and iodides (Scheme 2.1.7).[25]

4. With metal nitrites and nitrates

a) Silver nitrate

Nitrate esters derived from α–bromo ketones and esters can be easily obtained from respective halides with silver nitrate; these esters decompose smoothly in the presence of a base in DMSO to yield carbonyl compounds.[26] This is a very useful procedure for the synthesis of 1,2-dicarbonyl compounds. However, this method gives variable results for benzylic halides.

b) Mercury nitrate

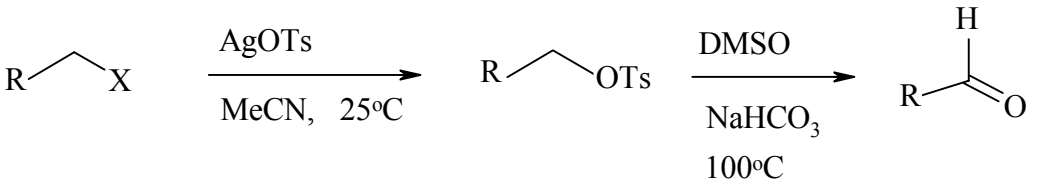
The use of mercury nitrate solves the problem associated with the preparation of benzylic nitrates from respective halides. This method affords high yields of nitrate esters for a wide variety of benzylic substrates.[27] However; the method suffers in the hydrolysis step, where benzyl alcohol will be the product instead of benzaldehyde, if substrates contain alkoxy groups at 2 or 4 positions.

c) Sodium nitrite

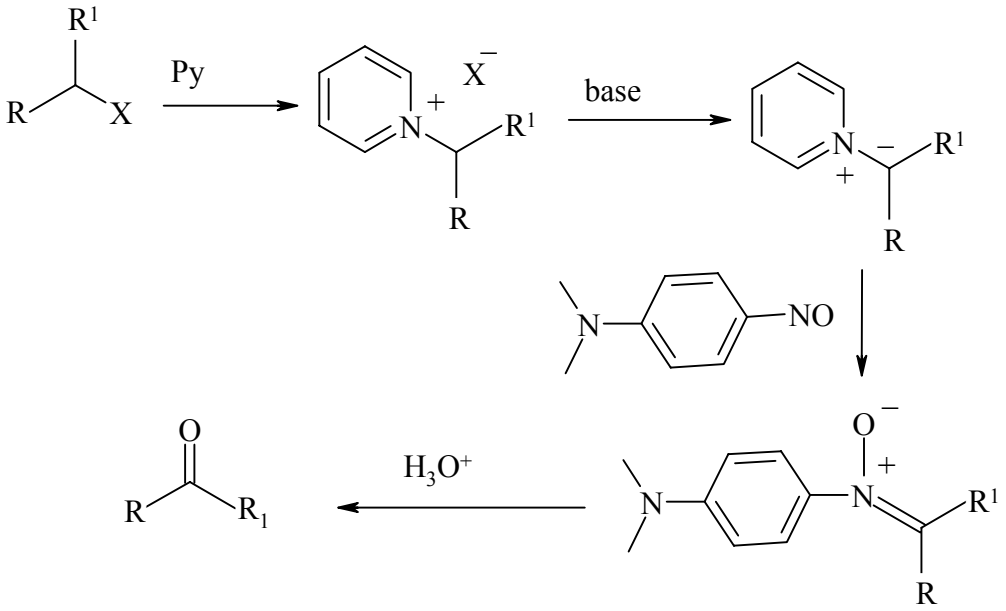
Sodium nitrite in DMSO has been used in a very mild, non-hydrolytic method for the oxidation of activated and unactivated bromides.[28] This method offers successful oxidation of secondary unactivated bromides which are prone to competitive elimination reactions. Among metal nitrates promoted oxidations, copper (II) nitrate affords good yield in benzylic systems.[29]

5. Miscellaneous methods

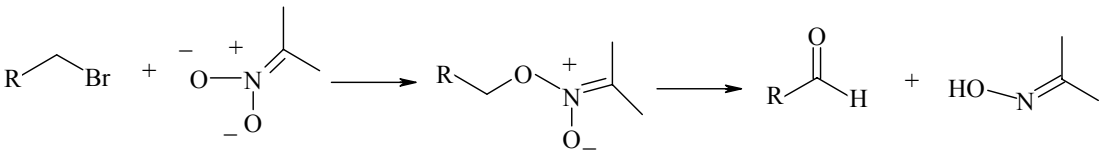
Pummerer rearrangement of pyrazinyl sulfoxide with trifluoroacetic anhydride and subsequent base treatment yields aldehyde. This method is applied to both activated and unactivated bromides.[30] Chlorination of sulfides, prepared from alkyl halide and NaSPh with *N*-chlorosuccinimide (NCS) in CCl_4 and subsequent decomposition of intermediate yields aldehyde.[31] *N*-phenyltriflamide replaces the halide ion of both activated and un-activated halides under mild conditions. Upon treatment with base it loses triflinate to give anil, which is then hydrolyzed in acid to the aldehyde (Scheme 2.1.8).[32]



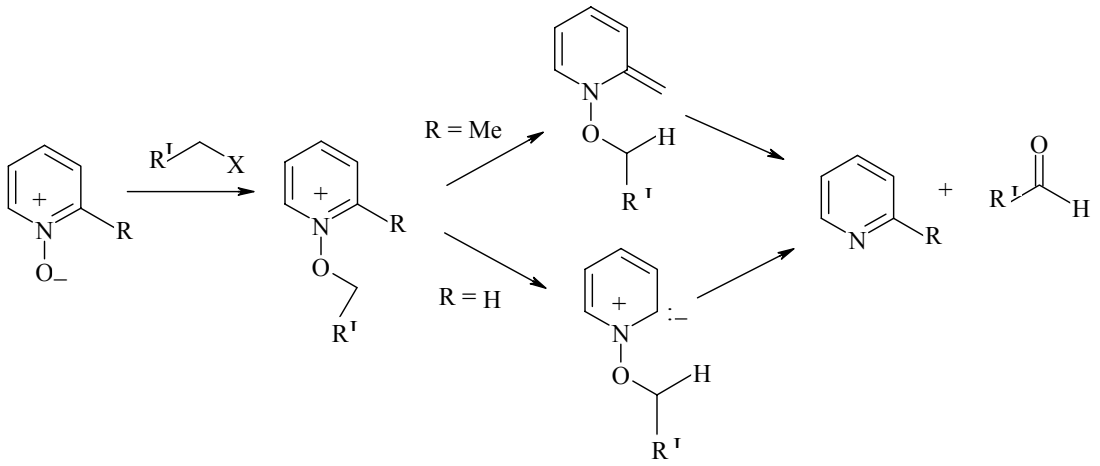
Scheme 2.1.3



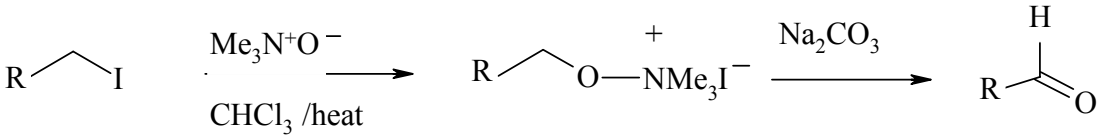
Scheme 2.1.4



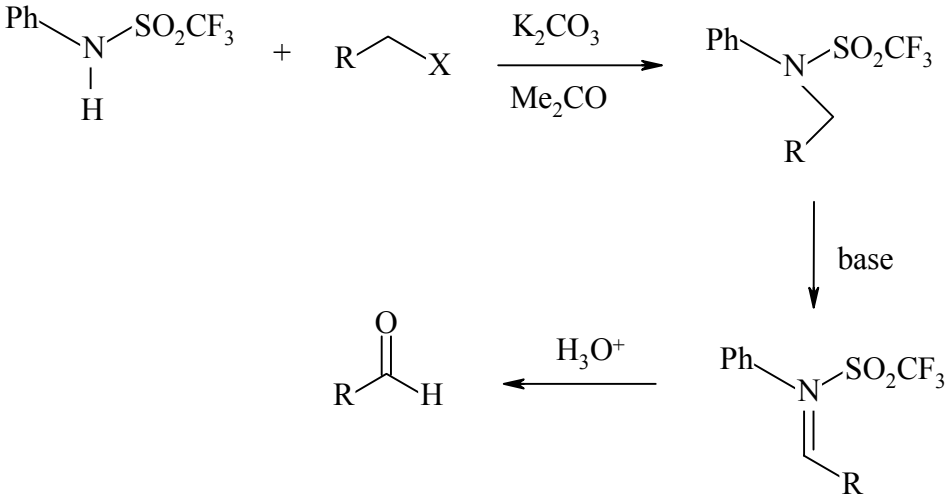
Scheme 2.1.5



Scheme 2.1.6



Scheme 2.1.7



Scheme 2.1.8

III. Direct Oxidation of Bromohydrins (*β*-Bromo Alcohols)

Elements of I B & II B groups are good halogen acceptors, and among them, zinc being moderately electropositive, has the property of polarizing the C-X bond without actually leading to the formation of a carbocation[34]. The zinc salts can, thus, be expected to increase the nucleofugacity of halides, besides acting as HX scavengers. In the oxidation of *α*- and *β*-phenyl substituted alkyl bromides, it has been found that benzyl and 1-phenylethyl bromides are oxidized to benzaldehyde and acetophenone respectively by DMSO in the presence of zinc salts with moderate to high yield.[35] Among the zinc salts, $ZnCO_3$ and ZnS, the latter has been found to be more efficient. Their specific role in activating the halides is established from the study. Kornblum oxidation, in its original method, is not applicable for wide range of substrates. It needs to be modified in terms of omission of base, especially for the substrates which are unstable in basic media, reduction in reaction temperature and activation of substrates by special reagents. Oxidation reactions, which run under mild reaction conditions, neutral reagent system and simultaneous activation of unactivated halides, will have a wider scope of application in organic chemistry. The reaction of bromohydrins with di-*tert*-butyl peroxyoxalate (DBPO) involves free-radical elimination of the hydrogen bromide to afford a ketone and is generally applicable to *sec*-*β*-bromo alcohols.[36] Similarly photo-assisted conversion of bromohydrins to ketones has been reported.[37] In both these instances, *tert*-*β*-bromo alcohols are unreactive due to lack of proton on the carbon adjacent to the bromo group for elimination of hydrogen bromide and the formation of enol. The reactions of bromohydrins wherein the direct oxidation of the bromo group is attempted are not found in literature. Thus, in the present work, a number of such *tert*-*β*-bromo alcohols derived easily from monoterpenes were prepared and their reactions with DMSO investigated.

Present work

Keeping in view the earlier studies of the reaction of activated bromides with DMSO, the reaction of bromohydrins, which are unactivated bromides, was investigated. A detailed study on the reaction of terpenic bromohydrins with DMSO as a new method of oxidation and conversion of halide group for the preparation of carbonyl compounds was initiated. In the present study, efficacy of various zinc salts for the activation of bromide was explored as zinc has been shown to have a special affinity towards halides. Activation of halides for DMSO oxidation by zinc salts has not been reported earlier. Among zinc salts, the effectiveness of ZnS, $ZnCO_3$, and ZnO in DMSO was studied.

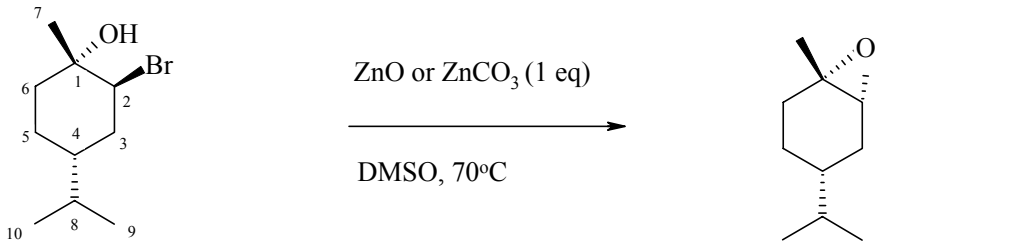
In the first instance, the reaction of 2-bromo-1-hydroxy-*p*-menthane (Table 2.1.2, **2**) with various zinc salts in DMSO was undertaken. When the reaction was performed with equivalent quantity of ZnS in DMSO, the reaction did not occur even for several days (seven) at room temperature. At higher temperature (50^oC), it was found to lead to the formation of two major products. The reaction, however, was slow and some portion of the substrate (20 %) remained unreacted even after several hours. The reaction temperature of 70^oC was found to be optimum when the substrate was completely consumed in shorter reaction time. The products were isolated by column chromatography on SiO_2 using hexane-EtOAc mixtures.

The product (Table 2.1.2, **2a**) that eluted first from the column clearly showed a sharp absorption band at 1712 cm^{-1} in the IR region indicating the presence of a carbonyl group. The PMR spectrum of the product showed the signal at 1.2 ppm as doublet and it integrated to three protons. The methyl signal which in the substrate **2** appeared as a singlet was absent and the signal now appeared as a doublet indicating the presence of hydrogen on C-1 carbon instead of the hydroxyl group. Also in the PMR spectrum of the product it was observed that the signal at 4.13 ppm (br), for the proton attached to the carbon atom containing bromine in the substrate, was absent. This indicated the formation of carbonyl at C-2 position. The mass spectrum of the **2a** showed M^+ of 154, along with other characteristic fragments of *p*-menthane skeleton (m/z = 139, 125, 111, 97, 83, 69, 55, 41). From the elemental analysis molecular formula for the compound was calculated as

$C_{10}H_{18}O$. Hence the product could be identified as a ketone, *p*-menthan-2-one (**2a**). Further, the specific rotation value found for this compound $[\alpha]_D^{20} = -4^o$, was in agreement with the reported value for pure *trans*-carvomenthone[39] ($[\alpha]_D^{20} = -6^o$).

The second product obtained from the column (**2b**) showed the characteristic IR absorption peaks for hydroxyl as well as carbonyl group at 3448 and 1710 cm^{-1} respectively. The absence of proton at C-2 position was indicated by the absence of broad peak in the PMR spectrum at 4.13 ppm. Also the methyl group on C-1 was found to be singlet as in **2** indicating the presence of parent hydroxyl at this position. From the mass spectral data, the molecular ion peak was found at 170. The characteristic mass fragments of *p*-menthane skeleton were seen in the mass spectrum. From the elemental analysis report the molecular formula of the compound was deduced as $C_{10}H_{18}O_2$. From these data, the structure of compound was elucidated as 1-hydroxy-*p*-methan-2-one (**2b**).

Formation of the saturated ketone **2a** from the oxidation of 2-bromo-1-hydroxy-*p*-menthane was a new observation, hitherto unreported. In order to understand the mechanism of this reaction, it was studied under different conditions. The results and discussion pertaining to these reactions are as follows. This reaction was carried out at higher temperatures of 100°C, 120°C and 140°C. In all these cases, the reaction rate increased considerably but formation of number of side products was observed. In another variation, the oxidation of bromohydrins with zinc oxide in DMSO was studied. Reaction of **2** **w**ith an equivalent quantity of ZnO in DMSO was studied at 70°C wherein the formation of a single major product was observed. A close look at the PMR spectrum of the product showed the presence of a doublet at 2.96 ppm (J = 5.3 Hz), which is characteristic of proton attached to the epoxide ring.[38] The GC-MS (M^+= 154) spectrum was in close agreement with that of standard *trans*-carvomenthene oxide. The product could, thus, be identified as *trans*-carvomenthene-1,2-oxide, a compound often formed readily by base catalyzed ring closure of a bromohydrin. This reaction when carried out at different temperatures (50°C, 100°C, and 120°C) afforded the same product. This result confirmed the basic nature of the zinc oxide and its ability towards the ring closure of vicinal *trans*-bromo alcohols (Scheme 2.1.9).



trans-2-bromo-1-hydroxy-*p*-menthane

trans-Carvomenthene-1,2-oxide

Scheme 2.1.9

The oxidation reaction of 2-bromo-1-hydroxy-*p*-menthane was also studied with one equivalent zinc carbonate in DMSO at 70°C. Here again formation of *trans*-carvomenthene oxide was observed as the major product as in case of ZnO mediated reaction. Similar result was observed in the reaction employing zinc dust which occurred even at room temperature (15 h). The results of the various experiments are summarized in Table 2.1.1.

The results of the above reactions revealed that the use of zinc and its salts for the activation of inactive bromide towards oxidation by DMSO resulted in the formation of epoxides from vicinal bromohydrins. However, in reactions where zinc sulfide was used formation of two different products, one normal oxidation product and the other a product apparently formed by internal rearrangement, was observed. In this reaction, it was observed that ZnS not only assisted the activation of halide towards oxidation but also played a decisive role in the DMSO oxidation of the bromohydrins. Hence, this new reagent system was further studied in detail to explore the scope of the reaction and the efficacy of the reagent.

In the reaction of bromocyclohexane (Scheme 2.1.10, equation 1), a secondary halide, with equivalent quantity of ZnS in DMSO, the reaction was very slow under normal conditions. Only when the reaction was carried out at high temperature (100°C) for a long time (48 h) it afforded cyclohexanone, the Kornblum oxidation product and also in only a moderate yield (30 %). This demonstrated that direct oxidation of a secondary bromide to carbonyl moiety was more difficult compared to secondary bromide containing α-hydroxyl group.

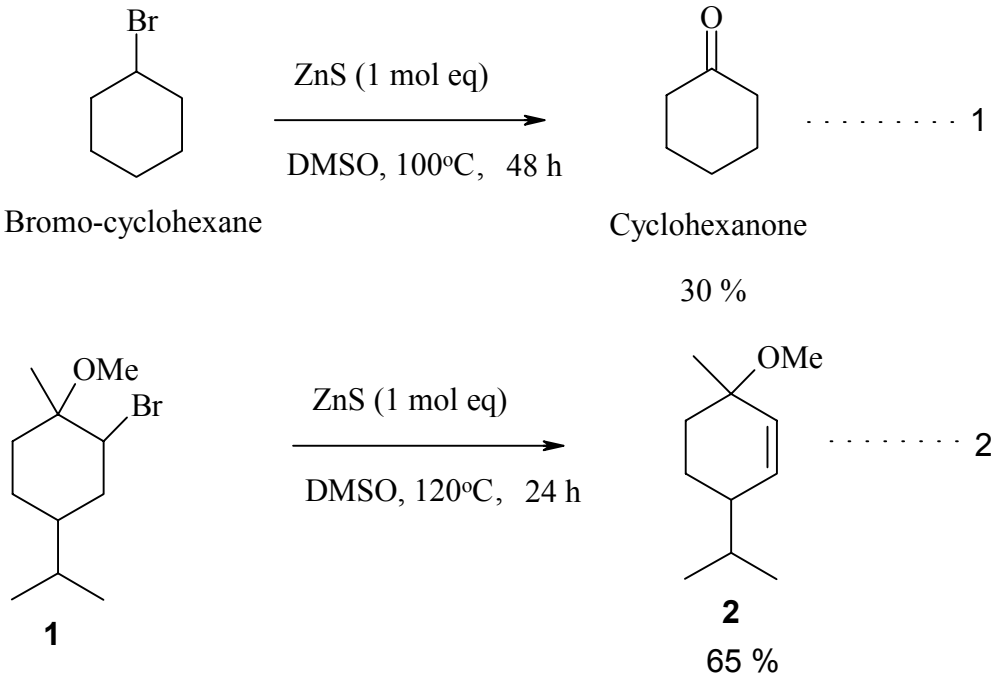
Table 2.1.1: Results of reaction of 2-bromo-1-hydroxy-*p*-menthane with ZnS, ZnO, $ZnCO_3$, and Zn dust in DMSO at 70°C

Reagent	ZnS	ZnO	$ZnCO_3$	Zn dust
Quantity (g, 10 mmol)	0.97	0.81	1.26	0.64
Substrate quantity (g, 10 mmol)	2.35	2.35	2.35	2.35
Time (h)	5	2	4	1
Product(s) Yield (%)	A = 66 B = 13	C = 65 ---	C = 70 ---	C = 75 ---

A= Carvomenthone: B = 1-hydroxy-*p*-menth-2-one: C = *trans*-Carvomenthene oxide

In the reaction of the 2-bromo-1-methoxy-*p*-menthane (Scheme 2.1.10, equation 2, **1)** with DMSO in the presence of zinc sulfide, the substrate remained unreacted even on prolonged stirring (50 h) at 70°C. When the temperature was raised to 120°C and stirred for 24 h, the reaction afforded a product (65 %), which could be identified as 1-methoxy-*p*-menth-2-ene (**2**). This product showed characteristic methoxy protons at 3.33 ppm as a singlet in its PMR spectrum. Also presence of two separate peaks at 4.63 ppm (s, 1H) and 4.76 ppm (m, 1H) indicated the presence of an olefenic bond between 2,3-position. In the mass spectrum molecular ion peak appeared at 168 along with the characteristic *p*-menthane skeleton fragments (m/z = 139, 125, 111, 97, 83, 69, 55, 41). This product, apparently, resulted from dehydrohalogenation of 2-bromo-1-methoxy-*p*-menthane.

These results clearly indicated that the *β*-hydroxyl group in the bromohydrin had the neighboring group effect and hence, affected the rate of reaction, suggesting the involvement of the hydroxyl moiety in the oxidation of the halide on the adjacent carbon.



Scheme 2.1.10

Next the scope of the reaction of ZnS in DMSO was investigated with various *tert-β*-bromo alcohols. In case of 2-bromo-1-methylcyclohexanol (Table 2.1.2, **1**), the reaction was complete in 6 h and afforded the 2-hydroxy-2-methyl-cyclohexanone, a normal Kornblum oxidation product and 2-methylcyclohexanone a rearranged ketone in 39 % and 41 % respectively (**1b** & **1a**). The product 2-methylcyclohexanone **1a** was identified based on the physical and spectral data by comparison with the authentic sample. IR spectrum of the second product had bands at 1705 (sharp) and 3398 cm^{-1} (broad) corresponding to carbonyl and hydroxyl groups respectively. In the PMR mass spectrum of the product, absence of peak at 4.30 ppm as double doublet for the proton at C-2 position in **1** indicated formation of the carbonyl group at this position. The mass spectrum showed the molecular ion peak at 128. From the elemental analysis report the molecular formula was determined as $C_7H_{12}O_2$. Thus, **1b** was identified as 2-hydroxy-2-methylcyclohexanone.

In case of reaction of 2-bromo-1-hydroxy-*p*-menth-8-ene (Table 2.1.2, **3**) with ZnS and DMSO, the reaction was complete in 10 h and afforded two major products in 60 % and 22 % yield (**3a** & **3b**). Both the products were characterized by their IR, PMR, mass spectral and elemental analysis data (table 2.1.3). IR spectrum of **3a** had a band at 1715 cm^{-1} (sharp)

indicating the presence of a carbonyl group in the compound. In its PMR spectrum, the presence of a doublet at 1.36 ppm indicated the presence of one methyl at C-1 and the presence of a proton on this carbon. The singlet at 1.83 ppm for 3 protons indicated a methyl at C-8, which is attached to an olefenic bond. In both the products presence of double bond at the C-8 of the substrate was intact as evident by the presence of PMR peak at 4.89 ppm for the two olefenic protons. In the mass spectrum of the product **3a,** the molecular ion appeared at 152 along with other characteristic *p*-menthane skeleton fragments (137, 109, 95, 67, 55, 41). Further, the elemental analysis report indicated the C to H ratio 1:1.6. Hence, molecular formula of the product was deduced as $C_{10}H_{16}O$. From all the spectral evidence, the structure of the compound was identified as *p*-menth-8-ene-2-one. IR data of the second product indicated the presence of both hydroxyl and carbonyl as it had sharp absorption at 1725 and broad absorption at 3450 cm^{-1} respectively. In its PMR spectrum, the C-1 methyl was a singlet and appeared at 1.40 ppm indicating the presence of hydroxyl on this carbon. The mass spectrum of the compound indicated the molecular weight to be 168. From the elemental report the molecular formula was calculated as $C_{10}H_{16}O_2$. From all the spectral data, this compound could be identified as 1-hydroxy-*p*-menth-8-ene-2-one. Synthesis of dihydrocarvone (**3a**) from limonene *via* bromohydrin intermediate by the present method affords an alternative route to **3a**, whose preparation otherwise selective reduction of *α,β*-double bond of carvone with a special reagent.

In continuation of study of oxidation of *tert*-*β*-bromo alcohols with ZnS in DMSO, the next terpene bromohydrin taken was 4-bromo-3,7,7-trimethyl-bicylo[4.1.0]heptan-3-ol (Δ^3-carene bromohydrin) (Table 2.1.2, **4**). Here the reaction was comparatively slower (30 h). The relative slow reaction rate could be due to the steric crowding in the substrate for approach of the reagent as well as DMSO. The reaction afforded two major products as seen in earlier substrates in 50 % (**4a**) and 31 % yield (**4b**) respectively.

The IR spectrum of the first product **4a** showed the presence of carbonyl absorption at 1711 cm^{-1}. The mass spectral data indicated the molecular weight of the product as 152. In its PMR spectrum, the presence of singlet at 0.93 ppm for six protons indicated the unaffected cyclopropyl ring system, and doublet at 1.03 ppm for three protons indicated the

presence of a proton at C-3. Further, the elemental data indicated the ratio of C to H to be 1:1.57. The molecular formula of the compound was deduced as $C_{10}H_{16}O$. The structure of the product **4a** could, thus, be identified as bicyclo[4.1.0]heptan-4,7,7-trimethyl-3-one (4-carone). The other product had the following spectral characteristics. It showed IR absorption for both carbonyl and hydroxyl groups (1710 and 3451 cm^{-1}). The mass spectrum indicated the molecular weight as 168. In its PMR spectrum, presence of singlet for six protons at 0.93 indicated the unaffected cyclopropyl ring system, and presence of singlet at 1.36 ppm for three protons indicated the presence of hydroxyl at C-3 carbon. From the elemental data the molecular formula of the compound was determined as $C_{10}H_{16}O_2$. The structure of the product **4b** could, thus, be confirmed as bicyclo[4.1.0]heptan-4,7,7-trimethyl-4-hydroxy-3-one (3-hydroxy-4-carone). This method affords a facile access to 4-carone (**4a**) from Δ^3-carene in 50 % yield *via* the bromohydrin intermediate.

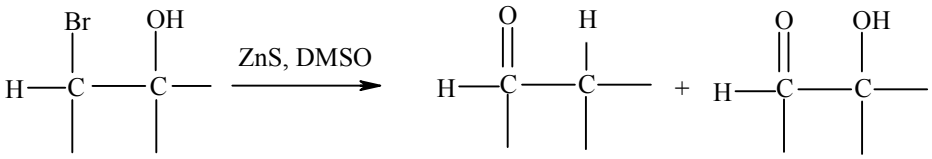
The reaction of 2-bromo-1,8-dihydroxy-*p*-menthane (Table 2.1.2, **5**) with ZnS in DMSO was complete in 10 h and afforded only one isolable product (**5a)** in 62 % yield. IR spectrum of the product showed absorption peak for carbonyl 1702 (sharp) and hydroxyl 3449 (broad) cm^{-1}. The mass spectrum of the product indicated the molecular weight as 170. Also, in the PMR spectrum presence of doublet at 1.20 ppm for methyl protons indicated the presence of a proton on C-1 and also absence of hydroxyl at this position. The presence of singlet at 1.03 ppm for six protons indicated the tertiary nature of the C-8 carbon. The presence of hydroxyl at this position was clearly observed from the signal at 3.03 ppm. From elemental analysis report molecular formula of the compound was deduced as $C_{10}H_{18}O_2$. From all the spectral data, the product **5a** was identified as 8-hydroxy-*p*-menth-2-one. The participation of the hydroxyl group of isopropenyl side chain in the reaction was negligible, apparently due to its distant location from bromine compared to neighboring α-hydroxyl group.

In yet another example, the reaction of 2-bromo-1-hydroxy-*p*-menth-3-one (Table 2.1.2, **6**) with ZnS and DMSO was undertaken. This reaction afforded two major products (50 % and 15 %). The first compound showed presence of strong absorption band in IR absorption at 1711 cm^{-1} indicating the presence of carbonyl moiety. The presence of doublet

at 0.96 ppm and 1.46 ppm for six and three protons respectively indicated the presence of two methyl groups and one methyl group on C-8 and C-1 respectively. From the mass spectral data, the molecular weight of the compound was found to be 168. From elemental analysis report C to H ratio was calculated as 1:1.57 and the molecular formula of the compound was deduced as $C_{10}H_{16}O_2$. From all the spectral evidence, the structure of the product **6a** was identified as *p*-menthan-2,3-dione. The next compound (**6b**) isolated showed the IR bands for both carbonyl and hydroxyl moieties (1709 and 3437 cm^{-1}). The mass spectrum indicated the molecular weight of the product as 184. In its PMR spectrum doublet appeared for six protons at 0.96 ppm indicating the presence of a proton on C-8 carbon atom. The other methyl appeared as singlet at 1.50 ppm indicating the presence of hydroxyl group at C-1 position. This hydroxyl appeared distinctly at 3.01 ppm. From elemental analysis report the molecular formula of the compound was deduced as $C_{10}H_{16}O_3$. From all the spectral evidence, the compound was identified as 1-hydroxy-*p*-menth-2,3-dione. The spectral data of all the products are presented in Table 2.1.3.

Hence, the oxidation of secondary bromides in presence of ZnS in DMSO has followed an unusual path especially when there is a hydroxyl group α to it. The role of neighboring hydroxyl group in determining the course of the reaction was interesting and the mechanism for this reaction needed to be understood. A plausible mechanism is presented in Scheme 2.1.12. The nucleophilic attack of DMSO on the carbon atom attached to bromide and concomitant abstraction of the latter by zinc sulfide apparently led to a dimethylsulfoxonium intermediate. One of the methyl protons in the latter was, apparently, abstracted by $Zn(Br)S^-$ species to afford the ylid and ZnBrSH. Subsequent loss of DMS afforded a hydroxy ketone, the Kornblum oxidation product (path a). Alternatively, the intermediate could undergo rearrangement (path b), wherein the hydroxyl group on α-carbon atom migrated to sulfur with the formation of a double bond between the carbon atoms involved. Subsequent breakdown of the rearranged intermediate afforded besides DMSO, an enol that readily tautomerized to a saturated ketone. Path b was preferred because of the participation of the neighboring hydroxyl group in the reaction, as substantiated by experiments in case of cyclohexyl bromide and methyl ether of carvomenthene bromohydrin.

Table 2.1.2: Reaction of Bromohydrins with Zinc Sulfide and DMSO at 70°C



1-6 **1a-6a** **1b-6b**

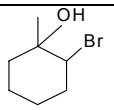
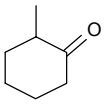
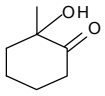
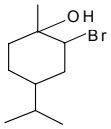
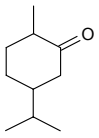
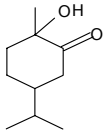
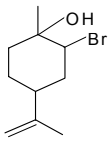
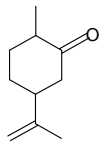
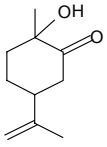
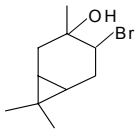
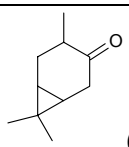
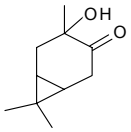
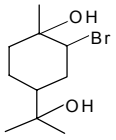
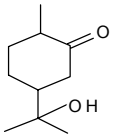
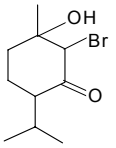
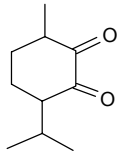
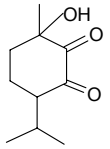
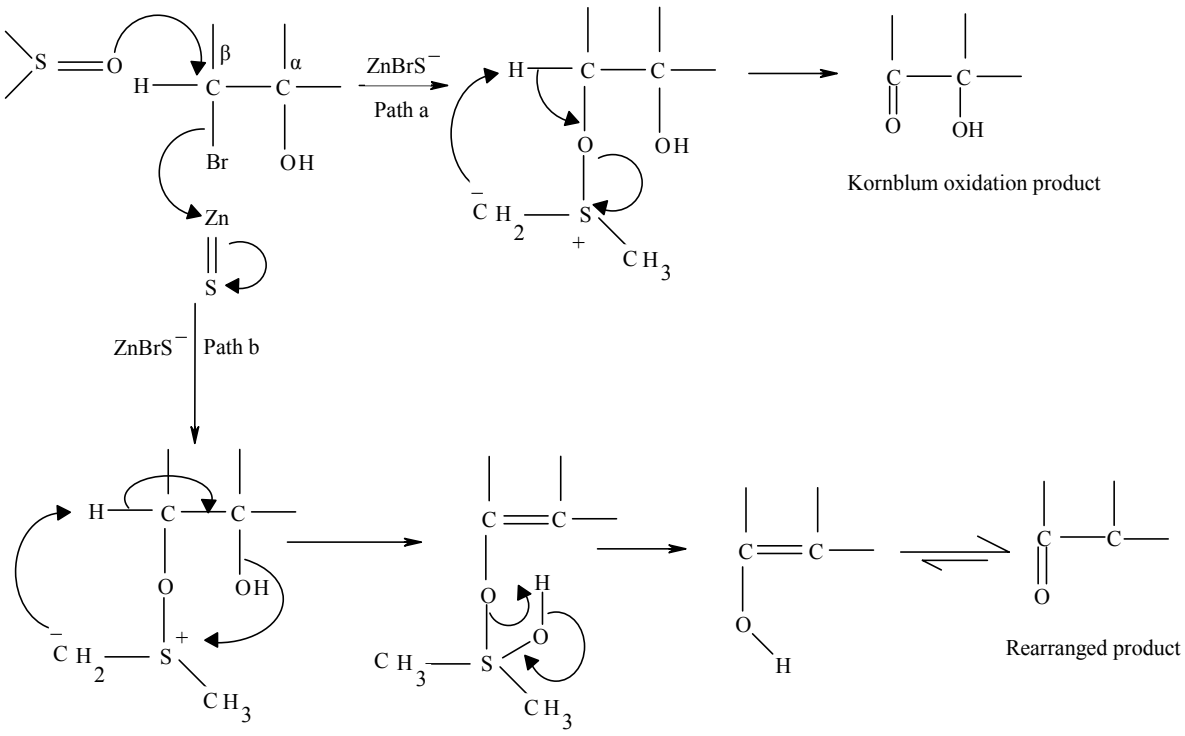
Entry No.	Bromohydrin	Reaction time (h)	Product **a** (% Yield)	Product **b** (% Yield)
1		6	 (41)	 (39)
2		5	 (66)	 (13)
3		10	 (60)	 (22)
4		30	 (50)	 (31)
5		10	 (62)	———
6		12	 (50)	 (15)

Table 2.1.3: PMR, IR and mass spectral data of products

Product	^{1}H NMR δ ppm (J=Hz)	IR γ cm^{-1}	MS (m/z)
1a	1.13(d, 3H, J = 6 Hz), 1.56-2.06(m, 6H), 2.20-2.36(m, 3H)	2935, 1712(s)	112(18), 97(4), 84(12), 68(95), 55(65), 41(100)
1b	1.43(s, 3H), 1.53-2.66(m, 8H), 3.16(s, 1H)	3398(br), 2935, 1705(s)	128(2), 113(5), 112(25), 97(60), 84(35), 79(40), 68(40), 55(50), 41(100)
2a	0.86(d, 6H, J = 6 Hz), 1.20(d, 3H, J = 6 Hz), 1.23-2.16(m, 6H), 2.20-2.46(m, 3H)	2872, 1712	154(12), 139(2), 125(5), 111(60), 97(15), 83(12), 69(18), 55(100), 41(55)
2b	0.86(d, 6H, J = 6 Hz), 1.36(s, 3H), 1.39-2.50(m, 8H), 3.26(s, 1H)	3448(br), 2960, 1710	170(2), 154(10), 152(2), 139(5), 126(4), 111(10), 97(15), 82(50), 69(60), 55(60), 43(100)
3a	1.36(d, 1H, J = 6 Hz), 1.83(s, 3H), 1.90-2.86(m, 8H), 4.89 (s, 2H)	2972, 1715	152(9), 137(6), 109(15), 95(52), 67(100), 55(35), 41(80)
3b	1.40(s, 1H), 1.83(s, 3H), 1.90-2.83(m, 7H), 3.20(s, 1H), 4.89(s, 2H)	3450(br), 2975, 1725	168(2), 152(3), 140(4), 125(18), 111(7), 97(9), 82(30), 71(90), 67(55), 55(35), 43(100)
4a	0.93(s, 6H), 1.03(d, 3H, J = 3 Hz), 1.13-1.20(m, 4H), 2.13-2.50(m, 3H)	3004, 1711(s)	152(15), 137(9), 109(24), 82(32), 81(75), 67(100), 41(90)
4b	0.93(s, 6H), 1.36(s, 3H), 1.16-1.23(m, 4H), 2.16-2.20(m, 2H), 2.50(s, 1H)	3451(br), 2950, 1710(s)	168(2), 150(4), 135(18), 119(75), 107(20), 91(90), 79(50), 55(70), 43(100)
5a	1.03(s, 6H), 1.20(d, 3H, J = 4.5 Hz), 1.26-2.26(m, 8H), 3.03(s, 1H)	3449(br), 2972, 1702(s)	170(2), 155(3), 152(3), 137(3), 112(52), 97(50), 84(22), 70(40), 59(100), 43(80)
6a	0.96(d, 6H, J = 4.5 Hz), 1.46(d, J = 4.5 Hz, 3H), 1.56-2.56(m, 7H)	2962(s), 1711(s)	168(2), 153(3), 139(15), 125(15), 111(7), 97(23), 83(12), 69(90), 55(80), 41(100)
6b	0.96(d, 6H, J = 4.5 Hz), 1.50(s, 3H), 1.50-2.67(m, 6H), 3.01(s, 1H)	3437(br), 2961, 1709(s)	184(2), 168(8), 150(8), 126(54), 108(30), 91(15), 69(40), 55(50), 41(100)

Thus, in the present investigation, a new reagent system of ZnS in DMSO for the direct oxidation of bromohydrins to ketones was developed. This reagent has got special application to monoterpene series especially in the synthesis of carbonyl compounds, which are important flavour constituents of essential oils. This method affords functionalization of monoterpene hydrocarbons at a selected position. As these monoterpene hydrocarbons possess double bonds and many allylic positions as well as reactive groups, direct oxidation usually results in the formation of mixture of products. The selectivity in the formation of bromohydrins can be controlled as these reactions are dependent on the stoichiometric quantity of the reagent NBS and temperature conditions. In case of limonene, a compound containing two double bonds, formation of bromohydrin can be controlled by the addition of one equivalent NBS at 0^{o}C affording 2-bromo-1-hydroxy-*p*-menth-8-ene in near quantitative yield (Table 2.1.2, **3**). The same reaction when carried out at higher temperatures, however, yields a complex mixture of products. In the present study, the selective introduction of carbonyl group at C-2 position (Product **3a**) was achieved *via* bromohydrin intermediate. The usual oxidation of halides with DMSO involves the use of a base for the removal of HBr (Kornblum oxidation). In the reaction now developed, ZnS was used for the dual role of removal of hydrogen bromide and activation of the bromide. Many direct oxidation reactions described in the introduction part of this chapter fail to give oxidation product for unactivated chlorides and deactivated bromides. But in the present method unactivated secondary bromides are oxidized by activation with the ZnS. Also, the neighboring hydroxyl group involvement with the dialkoxysulfonium intermediate was found to play an important role in the oxidation process. Zinc sulfide being, inexpensive, can be used in place of base especially for those substrates which are labile under basic conditions in DMSO oxidations. The α-hydroxy ketones, obtained as side products in these reactions, are easily separable form the ketones and they can also be dehydrated to the corresponding α,β-unsaturated ketones. This reaction can be conveniently carried out on large scale and hence, industrially viable.


ZnBrS⁻
Path a
Kornblum oxidation product
ZnBrS⁻
Path b
Rearranged product

Scheme 2.1.12

Experimental

1. Drying of reagents

Commercially procured DMSO was dried as per the standard procedure.[40] DMSO (1 l) was taken in 2 l round-bottomed flask along with calcium hydride (50 g) and set for fractional distillation under reduced pressure. The first fraction (50 ml) was discarded and the fraction, which distilled at 75-76^{o}C at 12 Torr was collected and stored over type 4A molecular sieves.

ZnS, ZnO, and $ZnCO_3$ were dried using a drying pistol at 110^{o}C and under reduced pressure (0.1 Torr) for 4 h. These anhydrous reagents were stored in a desiccator over P_2O_5 (12 h).

2. Reaction of 2-bromo-1-methylcyclohexanol with ZnS in DMSO

2-Bromo-1-methylcyclohexanol (1.93g, 10 mmol) was taken in dry DMSO (15 ml) in a two-necked round-bottomed flask. Dry zinc sulfide (0.97 g, 10 mmol) was added to it and mixture was set for stirring under nitrogen atmosphere. The temperature was slowly raised to 70^{o}C and maintained until completion of reaction. The progress of the reaction was monitored for the disappearance of substrate on GC. At the end of the reaction (6 h), the reaction mixture was cooled to room temperature and 150 ml of water was added to it and the contents transferred to a 500 ml separatory funnel. The product was extracted into CH_2Cl_2 (20 ml x 3). The combined organic layer was washed with water (50 ml x 2) and dried over anhydrous Na_2SO_4. Distillation of the solvent afforded a crude product which was chromatographed over silica gel (100-200 mesh, 16 g) using 1 % EtOAc in hexane. The column fractions, which had similar retention time on GC, were combined, concentrated and distilled.

Compound 1: 2-Methylcyclohexanone:

Yield: 41 %, 0.46 g, b. p.162-163^{o}C [Lit[40]160-164^{o}C].

IR (cm^{-1}) γ = 2935, 1712(s).

PMR: δ = 1.13(d, 3H, J = 6 Hz), 1.56-2.06(m, 6H), 2.20-2.36(m, 3H).

MS (*m/z*): 112(18), 97(4), 84(12), 68(95), 55(65), 41(100).

Elemental data: calculated for $C_7H_{12}O$, C = 74.95 and H = 10.78; found: C = 74.84 and H = 10.63.

Compound 2: 2-hydroxy-2-Methylcyclohexanone:

Yield: 39 %, 0.50 g, b. p.152-154^oC.

PMR: δ = 1.43(s, 3H), 1.53-2.66(m, 8H), 3.16(s, 1H).

IR (cm^{-1}) γ = 3398(br), 2935, 1705(s).

MS (*m/z*): 128(2), 113(5), 112(25), 97(60), 84(35), 79(40), 68(40), 55(50), 41(100).

Elemental data: calculated for $C_7H_{12}O_2$, C = 65.60 and H = 9.44; found: C = 65.78 and H = 9.31.

3. Reaction of 2-bromo-1-hydroxy-*p*-menthane

2-Bromo-1-hydroxy-*p*-menthane (2.35 g, 10 mmol) was taken with 15 ml of dry DMSO in a two-necked 100 ml round-bottomed flask. Dry zinc sulfide (0.97 g, 10 mmol) was added to it and mixture was set for stirring under nitrogen atmosphere. The temperature was slowly raised to 70^oC and maintained until completion of the reaction. The progress of the reaction was monitored for the disappearance of substrate on GC. At the end of the reaction (6 h), reaction mixture was cooled to room temperature and 150 ml of water was added to it and the contents transferred to a 500 ml separatory funnel. The product was extracted into CH_2Cl_2 (20 ml x 3). The combined organic layers were washed with water (50 ml x 2) and dried over anhydrous Na_2SO_4. Distillation of the solvent afforded a crude product which was chromatographed over silica gel (100-200 mesh, 16 g) using 1 % EtOAc in hexane. The column fractions, which had similar retention time on GC, were combined, concentrated and distilled under reduced pressure.

Compound 1: p-Menth-2-one (trans-carvomenthone)

Yield: 66 %, 1.01 g, b. p. 73-75^oC /1.5 Torr, [Lit[39] 218-219^oC/705 mm] $[\alpha]_D^{20} = -4^o$ (c = 1, $CHCl_3$).

PMR: δ =0.86(d, 6H, J = 6 Hz), 1.20(d, 3H, J = 6 Hz), 1.23-2.16(m, 6H), 2.20-2.46(m, 3H).

IR (cm^{-1}) γ = 2872, 1712.

MS (*m/z*): 154(12), 139(2), 125(5), 111(60), 97(15), 83(12), 69(18), 55(100), 41(55).

Elemental data: calculated for $C_{10}H_{18}O$, C = 77.87 and H = 11.76; found: C = 77.80 and H = 11.50.

Compound 2: 1-Hydroxy-p-menth-2-one

Yield: 13 %, 0.22 g, b. p. 74-75°C/8 Torr, $[\alpha]_D^{20}$ = -25° (*c* = 2, $CHCl_3$).

PMR: δ =0.86(d, 6H, *J* = 6 Hz), 1.36(s, 3H), 1.39-2.50(m, 8H), 3.26(s, 1H).

IR (cm^{-1}) γ = 3448(br), 2960, 1710(s).

MS (*m/z*): 170(2), 154(10), 152(2), 139(5), 126(4), 111(10), 97(15), 82(50), 69(60), 55(60), 43(100).

Elemental data: calculated for $C_{10}H_{18}O_2$, C = 70.55 and H = 10.66; found: C = 70.40 and H = 10.52.

4. Reaction of 2-bromo-1-hydroxy-*p*-menth-8-ene

2-Bromo-1-hydroxy-*p*-menth-8-ene (2.33 g, 10 mmol) was taken with 15 ml of dry DMSO in a two-necked 100 ml round-bottomed flask. Dry zinc sulfide (0.97 g, 10 mmol) was added to it and mixture was set for stirring under nitrogen atmosphere. The temperature was slowly raised to 70°C and maintained until completion of the reaction. The progress of the reaction was monitored for the disappearance of substrate on GC. At the end of the reaction (10 h), reaction mixture was cooled to room temperature and 150 ml of water was added to it and the contents transferred to a 500 ml separatory funnel. The product was extracted into CH_2Cl_2 (20 ml x 3). The combined organic layers were washed with water (50 ml x 2) and dried over anhydrous Na_2SO_4. Distillation of the solvent afforded a crude product which was chromatographed over silica gel (100-200 mesh, 20 g) using 1 % EtOAc in hexane. The column fractions, which had similar retention time on GC, were combined, concentrated and distilled under reduced pressure.

Compound 1: 8-p-menthen-2-one

Yield: 60 %, 0.91 g, b. p. 85-87°C/3 Torr, [Lit[41] 220°C/750 Torr], $[\alpha]_D^{20}$ = -18° (*c* = 2, $CHCl_3$).

PMR: δ = 1.36(d, 3H, *J* = 6 Hz), 1.83(s, 3H), 1.90-2.86(m, 8H), 4.89 (s, 2H).

IR (cm^{-1}) γ = 2972, 1715.

MS (*m/z*): 152(9), 137(6), 109(15), 95(52), 67(100), 55(35), 41(80).

Elemental data: calculated for $C_{10}H_{16}O$, C = 78.90 and H = 10.59; found: C = 79.02 and H = 10.62.

Compound 2: 1-Hydroxy-p-menth-8-ene-2-one

Yield: 22 %, 0.37 g, b. p. 71-72°C/8 Torr, $[\alpha]_D^{20}$ = +55.3° (*c* = 1.5, $CHCl_3$).

PMR: δ = 1.40(s, 3H), 1.83(s, 3H), 1.90-2.83(m, 7H), 3.20(s, 1H), 4.89(s, 2H).

IR (cm^{-1}) γ = 3450(br), 2975, 1725.

MS (*m/z*): 168(2), 152(3), 140(4), 125(18), 111(7), 97(9), 82(30), 71(90), 67(55), 55(35), 43(100).

Elemental data: calculated for $C_{10}H_{16}O_2$ C = 71.39 and H = 9.59 Found: C = 71.20 and H = 9.39.

5. Reaction of 4-bromo-3,7,7-trimethyl-bicylo[4.1.0]heptan-3-ol (Δ^3-Carene bromohydrin)

4-Bromo-3,7,7-trimethyl-bicylo[4.1.0]heptan-3-ol (2.33 g, 10 mmol) was taken with 15 ml of dry DMSO in a two-necked 100 ml round-bottomed flask. Dry zinc sulfide (0.97 g, 10 mmol) was added to it and mixture was set for stirring under nitrogen atmosphere. The temperature was slowly raised to 70°C and maintained until completion of the reaction. The progress of the reaction was monitored for the disappearance of substrate on GC. At the end of the reaction (30 h), reaction mixture was cooled to room temperature and 150 ml of water was added to it and the contents transferred to a 500 ml separatory funnel. The product was extracted into CH_2Cl_2 (20 ml x 3). The combined organic layers were washed with water (50 ml x 2) and dried over anhydrous Na_2SO_4. Distillation of the solvent afforded a crude product which was chromatographed over silica gel (100-200 mesh, 20 g) using 1 % EtOAc in hexane. The column fractions, which had similar retention time on GC, were combined, concentrated and distilled under reduced pressure.

Compound 1: Bicyclo[4.1.0]heptan-4,7,7-trimethyl-3-one (4-Carone)

Yield: 50 %, 0.76 g, b. p. 76-77°C/2 Torr, [Lit[42] 48°C /0.5 Torr], $[\alpha]_D^{20}$ = -140° (*c* = 2, $CHCl_3$).

PMR: δ = 0.93(s, 6H), 1.03(d, 3H, *J* = 3 Hz), 1.13-1.20(m, 4H), 2.13-2.50(m, 3H).

IR (cm^{-1}) γ = 3004, 1711(s).

MS (*m/z*): 152(15), 137(9), 109(24), 82(32), 81(75), 67(100), 41(90).

Elemental data: calculated for $C_{10}H_{16}O$, C = 78.90 and H = 10.59; found: C = 78.78 and H = 10.34.

Compound 2: Bicyclo[4.1.0]heptan-4,7,7-trimethyl-4-hydroxy-3-one

Yield: 31 %, 0.52 g, b. p. 124-126^{o}C, $[\alpha]_D^{20}$ = -5^{o} (*c* = 2, $CHCl_3$).

PMR: δ = 0.93(s, 6H), 1.36(s, 3H), 1.16-1.23(m, 4H), 2.16-2.20(m, 2H), 2.50(s, 1H).

IR (cm^{-1}) γ = 3451(br), 2950, 1710(s).

MS (*m/z*): 168(2), 150(4), 135(18), 119(75), 107(20), 91(90), 79(50), 55(70), 43(100).

Elemental data calculated for $C_{10}H_{16}O_2$ C = 71.39 and H = 9.59; found: C = 71.20 and H = 9.40.

6. Reaction of 2-bromo-1,8-dihydroxy-*p*-menthane

2-Bromo-1,8-dihydroxy-*p*-menthane (2.51 g, 10 mmol) was taken with 15 ml of dry DMSO in a two-necked 100 ml round-bottomed flask. Dry zinc sulfide (0.97 g, 10 mmol) was added to it and mixture was set for stirring under nitrogen atmosphere. The temperature was slowly raised to 70^{o}C and maintained until completion of the reaction. The progress of the reaction was monitored for the disappearance of substrate on GC. At the end of the reaction (10 h), reaction mixture was cooled to room temperature and 150 ml of water was added to it and the contents transferred to a 500 ml separatory funnel. The product was extracted into CH_2Cl_2 (20 ml x 3). The combined organic layers were washed with water (50 ml x 2) and dried over anhydrous Na_2SO_4. Distillation of the solvent afforded a crude product which was chromatographed over silica gel (100-200 mesh, 25 g) using 1 % EtOAc in hexane. The column fractions, which showed peaks of same retention time on GC, were combined, concentrated and distilled.

8-Hydroxy-p-menth-2-one:

Yield: 62 %, 1.05 g, b. p. 160-162^{o}C, $[\alpha]_D^{20}$ = +82^{o} (*c* = 0.5, $CHCl_3$).

PMR: δ = 1.03(s, 6H), 1.20(d, 3H, *J* = 4.5 Hz), 1.26-2.26(m, 8H), 3.03(s, 1H).

IR (cm^{-1}) γ = 3449(br), 2972, 1702(s).

MS (*m/z*): 170(2), 155(3), 152(3), 137(3), 112(52), 97(50), 84(22), 70(40), 59(100), 43(80).

Elemental data: calculated for $C_{10}H_{18}O_2$, C = 70.55 and H = 10.66; found: C = 70.02 and H = 10.16.

7. Reaction of 2-bromo-1-hydroxy-*p*-menth-3-one

2-Bromo-1-hydroxy-*p*-menth-3-one (2.33 g, 10 mmol) was taken with 15 ml of dry DMSO in a two-necked 100 ml round-bottomed flask. Dry zinc sulfide (0.97 g, 10 mmol) was added to it and mixture was set for stirring under nitrogen atmosphere. The temperature was slowly raised to 70^{o}C and maintained until completion of the reaction. The progress of the reaction was monitored for the disappearance of substrate on GC. At the end of the reaction (12 h), reaction mixture was cooled to room temperature and 150 ml of water was added to it and the contents transferred to a 500 ml separatory funnel. The product was extracted into CH_2Cl_2 (20 ml x 3). The combined organic layers were washed with water (50 ml x 2) and dried over anhydrous Na_2SO_4. Distillation of the solvent afforded a crude product which was chromatographed over silica gel (100-200 mesh, 25 g) using 1 % EtOAc in hexane. The column fractions, which showed peak of same retention time on GC, were combined, concentrated and distilled under reduced pressure.

Compound 1: p-Menth-2,3-di-one

Yield: 50 %, 0.84 g, b. p. 79-80^{o}C/1Torr, $[\alpha]_D^{20}$ = +10.4^{o} (*c* = 2.3, $CHCl_3$),

PMR: δ = 0.96(d, 6H, *J* = 4.5 Hz), 1.46(d, *J* = 4.5 Hz, 3H), 1.56-2.56(m, 7H).

IR (cm^{-1}) γ = 2962(s), 1711(s).

MS (*m/z*): 168(2), 153(3), 139(15), 125(15), 111(7), 97(23), 83(12), 69(90), 55(80), 41(100).

Elemental data: calculated for $C_{10}H_{16}O_2$, C = 71.39 and H = 9.59; found: C = 71.53 and H = 9.03.

Compound 2: 1-Hydroxy- p-menth-2,3-di-one

Yield: 15 %, 0.27 g, b. p. 71-72^{o}C/8 Torr, $[\alpha]_D^{20}$ = -25^{o} (*c* = 2, $CHCl_3$).

PMR: δ = 0.96(d, 6H, *J* = 4.5 Hz), 1.50(s, 3H), 1.50-2.67(m, 6H), 3.01(s, 1H).

IR (cm^{-1}) γ = 3437(br), 2961, 1709(s).

MS (*m/z*): 184(2), 168(8), 150(8), 126(54), 108(30), 91(15), 69(40), 55(50), 41(100).

Elemental data: calculated for $C_{10}H_{16}O_3$, C = 65.19 and H = 8.75; found: C = 65.71 and H = 8.90.

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Section 2.2: Allylic Bromides from *tert*-*β*-Bromo Alcohols

Organic bromides are generally reactive and form an important and large group of synthetic intermediates. They can serve as starting materials for many oxygen, thio- and amino derivatives and condensation reactions in organic chemistry. Brominated derivatives are especially useful as precursors for organometallic compounds.[1] They can undergo variety of classical and radical reactions leading to the formation of cyclic as well as stereospecific compounds. Bromine attached to carbon is less stable than C-Cl and C-F bonds but more reactive than corresponding chlorine analogues. Hence C-Br bond cleavage occurs under milder conditions at faster reaction rates. Among reactive bromides, allylic bromides are prominent as they can form resonance-stabilized system by delocalization of π-electrons. Substituted allylic anions are most important in allylic type rearrangement especially with metals like lithium, magnesium, palladium, chromium, tellurium, cobalt, aluminum, and zinc; therefore, halogen-substituted species have special significance in synthetic organic chemistry.[2]

Reactions of allylic halides is one of the viable methods by which new *C*-*C* bonds as well as C-heteroatom bonds can be constructed.[3] A large number of palladium catalyzed allylic activation processes are adopted in organic synthesis.[4] Nucleophilic substitution of allylic substrate catalyzed by copper are also important in the synthesis of several allylic compounds.[5] Indium mediated allylic coupling reactions have gained importance recently as these reactions can be conveniently carried out even under moist conditions. Indium mediated monoallylation of carbonyl compounds with allylic chlorides and bisallylation of 2-pyridyl carboxylates with allylic halides in aqueous conditions are carried out.[6] Allylation of *α*-keto esters with allyl halides in presence of indium has also been carried out effectively.[7] In aqueous conditions indium mediated allylation of acyl cyanides produces *β,γ*-unsaturated ketones in moderate to good yield under mild and neutral conditions.[8] Allylation of 1,2-dicarbonyl compounds with indium and allylic bromides in the presence of tetrabutylammonium iodide or ammonium chloride affords mono- and/or diallylated products.[9] Metal zinc promotes allylic activation of allylic halides and this strategy has been conveniently employed in a number of reactions. A selective keto allylation of *β*-keto and *γ*-

esters with allyl, crotyl, and cinnamyl halides in zinc mediated aqueous ammonium chloride in THF affords completely selective keto allylated *β*- and *γ*-hydroxy esters.[10] Allylation of acid chlorides in the presence of zinc affords *β*,*γ*-unsaturated ketones.[11] Zinc mediated aqueous Barbier-Grignard reaction of cyclic allylic bromides with various aromatic aldehydes and ketones affords good yield of homoallylic alcohols with good diastereoselectivity. Non-aromatic aldehydes and ketones give only poor yields of homoallylic alcohols.[12] Allyl zinc intermediate generated *in situ* with allyl chloride on reaction with acid chlorides in the presence of catalytic amount of chlorotrimethylsilane affords gem bis-allylated products.[13]

Reactions of allylic compounds are of particular interest for chemists from both practical and theoretical point of view. The double bond in allylic system undergoes replacement readily. Compounds with allylic moiety are widely distributed in many natural products such as alkaloids, steroids and terpenes. Allylic substitution is common among terpenes and is widely used in the synthesis of essential oils, vitamin A and analogous unsaturated compounds.[14]

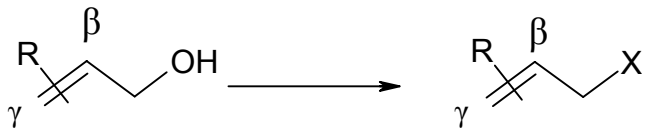
Reaction of allyl metal reagents with carbonyl compounds offers a complementary approach to aldol reaction for acyclic stereo-control. Hence, these allyl metallic reagents are called 'aldol equivalents'.[15] Allylic and benzylic halides dimerize (homo-coupling) in the presence of number of metals like Co,[16] Ni,[17] Te,[18] Ti.[19] Allylic halides may be coupled in the presence of $Ni(CO)_4$, an approach which is very attractive for the synthesis of terpenes by sequential addition of isoprene units. But this gives very low yield due to competitive homocoupling.[20] Allyl metallic reagents are of particular interest as they can under go metallo-ene reactions.[21]

Allylic halides can be directly synthesized by the reaction of an olefin with *N*-haloimides in non-protic solvents. These reactions are often problematic due to formation of mixtures of products like dibromo and vinylic compounds along with allyl halides.[22] In the literature NBS is the reagent of choice for allylic and benzylic bromination. The chemistry and uses of NBS in organic chemistry has been reviewed.[23] Allylic halides have been synthesized by a number of methods, which are described briefly in the following section.

1. Allylic Bromination of Alkenes with NBS

In Wohl-Ziegler reaction, alkenes are selectively brominated at the carbon α to the double bond with NBS to give bromo alkene. The rate of reaction proceeds in the order of secondary > primary > tertiary. As a free radical intermediate is involved in this reaction, a mixture of allylic bromides is to be expected as the reaction product, besides small quantities of dibromo compound and adduct with NBS itself. The other major disadvantage of this reaction is the formation of new double bond by dehydrobromination, especially when there is a formation of extended conjugation of double bonds resulting in aromatization. The light-induced bromination of simple olefins has been found to give allylic bromide and to cause geometric isomerization of the double bonds in the parent allkene.[24] The reaction of NBS with di- and poly-olefins leads to abnormal products by allylic rearrangement. Thus, 1,5-hexadiene gives 1-bromohexa-2,5-diene along with some 3-bromo isomer.[25] Hence, at the outset although NBS looks a general reagent for allylic bromination, due to its drawbacks synthetic chemists do look for an alternative approach to synthesize allylic bromides.

2. Formation of Allylic Halides from Alcohols



Scheme 2.2.1

The substitution of hydroxyl group in the allylic systems, by the halogen atom is an important reaction for the preparation of allylic halides (Scheme 2.2.1). A review on the nucleophilic and organometallic displacement reactions of allylic compounds in terms of stereo- and regiochemistry has been reported.[26] In order to develop a suitable synthetic procedure it must have the following features. a) The reaction must be regiospecific, leading exclusively to either α-substituted or γ-substituted compound in a predictable manner, b) stereochemistry of the double bond must be preserved, c) high optical yields should be obtained when C-α is chiral and d) the conditions of the reaction work-up and isolation must be mild enough without competition from side reaction like allylic rearrangement, solvolysis

or elimination. However, presently there are no general methods satisfying all the above conditions. The use of $SOCl_2$ gives exclusively rearranged product from both α- and γ-methyl allyl alcohols. The method is not satisfactory for tertiary allylic alcohols, which are known to give mixtures of regioisomers.[27] Phosphorus halides work quite well with primary allylic alcohols to give clean products under varying sets of conditions.[28] Meyers and Collington[29] have developed a useful and selective reaction from allylic alcohols involving *in situ* formation of the methane sulfonate and subsequent displacement by chloride anion. The combination NCS or NBS with DMS produces a salt, which is a regio- and stereospecific reagent for the conversion of allylic alcohols to halides.[30] In yet another development, the use of halogen sources like CCl_4,[31] CBr_4,[32] hexachloroacetone[33] along with triphenylphosphine has been applied as halogenating agent for various allylic systems.

3. Other Methods:[14]

a) Additions to conjugated systems

Allylic halides are formed when hydrogen halides are added to conjugated dienes under variety of experimental conditions. Mixtures of allylic halides are obtained as both addition and isomerization of allylic halides results under experimental conditions (Scheme 2.2.2, equation A).

b) Dehydrohalogenation of dihalides

Treatment of 1,2- and 1,3-dihalides with alkali or quinoline yields mixture of dehydrohalogenated products, which contain allylic halides (Scheme 2.2.2, equation B).

c) Dehydration of α–halo alcohols

Dehydration of α–halo alcohols with P_2O_5 or thionyl chloride often results in formation of allylic halides (Scheme 2.2.2, equation C).[34]

4. Dehydration of Alcohols

$BF_3.OEt_2$ is a well known reagent and being a Lewis acid it is useful in many organic reactions. Organocopper reagents with BF_3 form complex, which add on to unsaturated ketones and esters in regio-, stereo- and chemoselective manner.[35] $BF_3.OEt_2$ has been used for dehydration of hexacarbonyldicobalt protected tertiary propargylic alcohols to

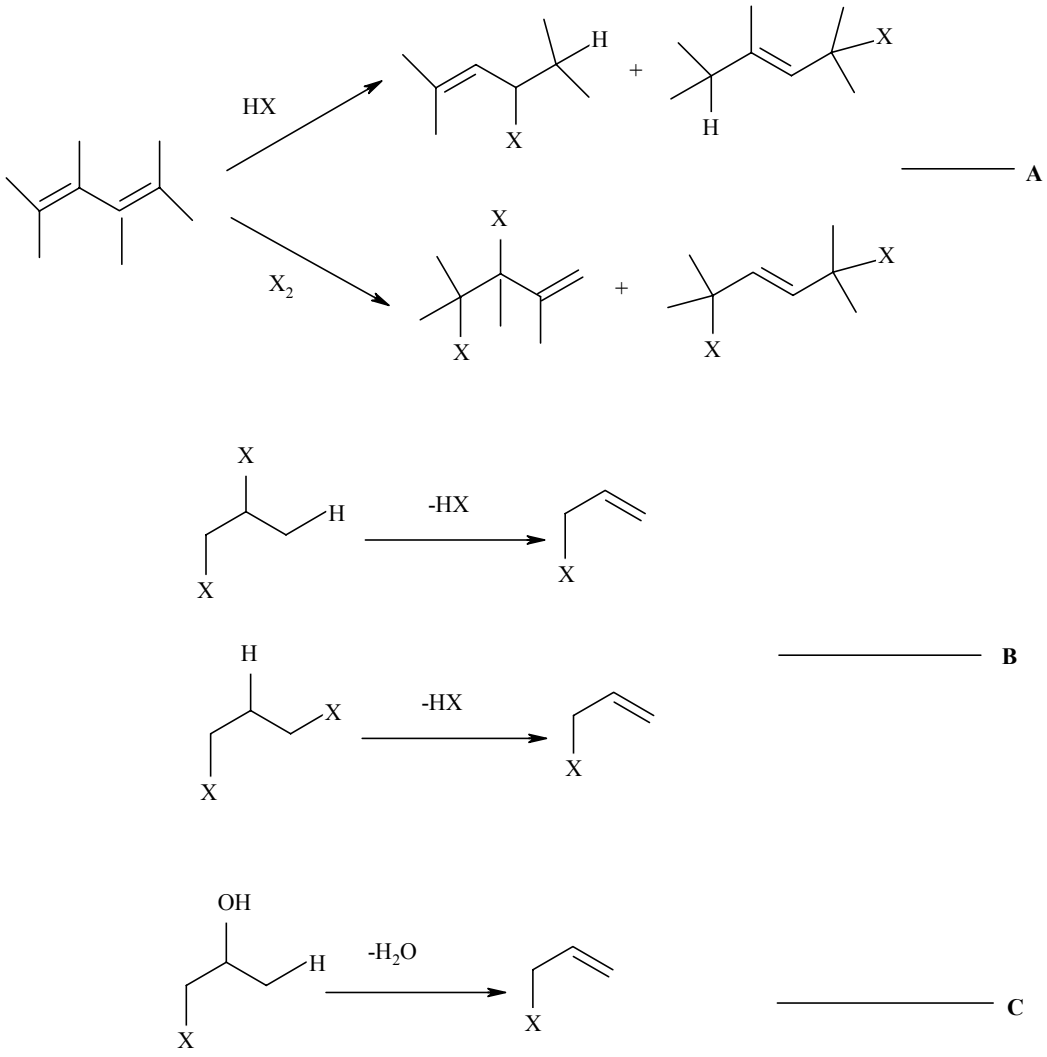
yield enynes. The stereochemistry of product formation has been compared with other dehydrating agents like trifluoroacetic acid and P_2O_5. A similar type of dehydration with trifluoroacetic acid under mild conditions (25^oC, 24 h) has been reported.[36] The dehydration of alcohols leading to formation of olefins has been carried out by number of catalysts. Strong acids like H_2SO_4, H_3PO_4 are found to be effective for dehydration; but in many cases formation of rearranged products occurs and ethers are obtained as side products. Vapor phase reaction over alumina is an excellent method wherein side reactions are greatly reduced. The conversion of alcohols to esters followed by pyrolysis of these is also a useful method where in side reactions are controlled. The ease of dehydration increases with α-branching and tertiary alcohols are dehydrated easily even with traces of acid catalysts. The other common dehydrating agents that are extensively applied are: P_2O_5, I_2, $ZnCl_2$, DMSO, $KHSO_4$, KOH, anhydrous $CuSO_4$, and phthalic anhydride.[37]

Tertiary alcohols are dehydrated regioselectively under mild conditions (25^oC, 2 h) using $BF_3.OEt_2$ in CH2Cl2 to yield thermodynamically more stable alkenes. It is observed that the more substituted alkenes are formed in good yield compared to dehydration reactions with $SOCl_2/Et_3N$ and TsOH/PhH.[38] Another efficient reagent, triphenylbismuth dibromide-iodine is used for efficient dehydration of tertiary alcohols.[39] Montmorillonite-K 10 in dioxane also catalyzes the dehydration of tertiary alcohols to olefins.[40]

5. Dehydration of Bromohydrins

The difficulties associated with synthesis of allylic bromides by conventional methods, especially where there is a possibility of getting mixture of products (polyenes especially monoterpenes), do warrant development of alternative indirect methods. In allylic bromination of di- and polyenes with NBS always results in the formation of mixture of products as they contain many allylic positions. The distribution of product ratio is dependent on the reaction conditions and structure of olefin. In the present study, preparation of substituted allylic/secondary bromides of terpene hydrocarbons and aromatic compounds from bromo alcohols was studied. The latter are conveniently prepared from olefins with NBS in nucleophilic solvents like water, DMSO and aqueous dioxane. Stereospecific *trans*-cohalogenated product could thus be obtained.[41] These and similar

halohydrins can serve as useful intermediates for synthesis of a number of useful organic compounds. Preparation of bromohydrin from NBS with diene like limonene is high yielding and regioselective depending on the reaction conditions.[42] In this bromohydrin hydroxyl and bromide are *trans* to each other, either stereospecific alcohol or stereo-specific bromide can be obtained depending on the selection of either dehalogenation or dehydration reactions. As a number of dehydration catalysts are available, one can achieve the dehydration of bromohydrins to get stereospecific allylic bromides. Thus, bromo alcohols of several olefins were prepared by using NBS and aqueous acetone (Chapter 2, Section 2.4). Dehydration of these bromohydrins was studied in detail by using different acid catalysts.



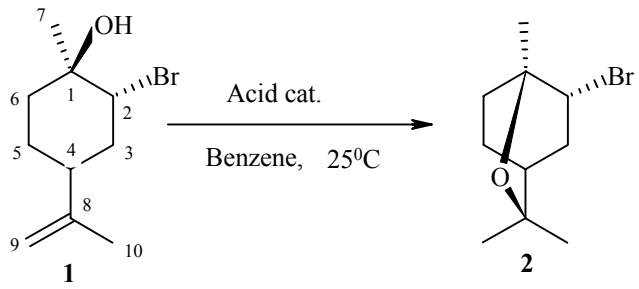
Scheme 2.2.2

Present Work

The dehydration of *tert*-*β*-bromo alcohols using catalytic quantity of $BF_3.OEt_2$ in refluxing benzene was studied in detail. In the first instance, dehydration of 2-bromo-1-hydroxy-*p*-menth-8-ene (Scheme 2.2.3, **1**) with catalytic quantity $BF_3.OEt_2$ in refluxing benzene was investigated. Formation of a cyclic ether, 2-bromo-1,8-cineol (**2**) was observed. This apparently is formed by internal cyclic addition of hydroxyl group to the olefenic bond of **1** (position between C-8 and C-9). This new compound in monoterpene series was characterized based on spectral data (Table 2.2.3, **2e**). This product showed the characteristic M^+ and $[M+2]^+$ peaks (1:1 ratio of 232 and 234) in its mass spectrum, which indicated the presence of a bromine atom. The other characteristic skeletal fragments 153(55), 135(10), 109(20), 95(45), 82(25), 71(60), 55(40), 43(100), 41(95) of *p*-menthane moiety were also observed. In PMR spectrum of the compound presence of a broad singlet peak integrating to single proton at 3.86 ppm corresponding to the proton attached to carbon containing bromine atom was seen. Presence of singlet at 1.44 ppm for three protons indicated that this methyl is connected to carbon containing oxygen atom. Also olefenic protons of the substrate **1** at 4.76 ppm were absent in the product. From ^{13}C-NMR, the number of carbon atoms was found to be ten. The presence of 56.8 and 55.9 peaks indicated the two carbon atoms attached to oxygen atom. Also the presence 53.1 peak indicated that carbon containing halogen atom. From the elemental analysis report, the molecular formula was calculated as $C_{10}H_{17}BrO$. Formation of this compound has prompted the study of this reaction in detail as **2** may be useful as a precursor for several terpene derivatives, like naturally occurring acetoxy-1,8-cineoles.[43] Thus, this reaction was studied in presence of various acid catalysts and the results are summarized in Table 2.2.1.

Reaction of limonene bromohydrin with reagents like $ZnCl_2$, $ZnBr_2$, PTS, H^+-resin and natural clay also resulted in the formation of 2-bromo-1,8-cineol. Lewis acids like $BF_3.Et_2O$ and $ZnBr_2$ promoted the reaction in catalytic quantity (10 mol %, 25^{o}C) and afforded the product in excellent yield (>90 %). The reaction in the presence of PTS and cation exchange resin was rapid compared to others (7 h and 2 h), but the yield was relatively less due formation of intractable side products in these cases. In the presence of

natural clay in equivalent quantity at room temperature, substrate was unreactive even after two days of stirring at ambient temperature. The reaction had to be carried out under reflux conditions and here formation of unidentified side products was also observed with resultant reduction in the yield of the product **2**.



1 **2**

Acid cat. = $BF_3.Et_2O$, $ZnBr_2$, PTS, Clay and H^+-resin

Scheme -2.2.3

Table 2.2.1: Result of reactions of 2-bromo-1-hydroxy-*p*-menth-8-ene (limonene bromohydrin) with various acid catalysts in dry benzene.

Catalyst	Time (h)	Temperature (^oC)	Yield (%)
$BF_3.Et_2O$	23	25	90
$ZnBr_2$	20	25	91
PTS	07	25	84
H^+-resin	02	25	85
Natural clay	02	70	72

In continuation of the study of dehydration of *tert-β*-bromo alcohols, 2-bromo-1-methylcyclohexanol (Table 2.2.2, **1a**) was chosen as a substrate. This in presence of presence of catalytic quantity of $BF_3.Et_2O$ in dry benzene afforded regioselectively the product **2a** in 60 % yield. This product was characterized by mass, PMR and ^{13}C-NMR spectral data (Table 2.2.3, **2a**). In its mass spectrum the presence of M^+ and $[M+2]^+$ peaks in

1:1 ratio (174 and 176) indicated the presence of a bromine atom. The PMR spectrum of the compound indicated the presence of olefenic bond (5.55 ppm, broad singlet integrated to one proton). Also, the proton attached to carbon containing bromine appeared at 4.63 ppm, which was 0.33 ppm downfield from that in the bromohydrin **1a**. ^{13}C-NMR indicated the presence of seven carbon atoms in the molecule including two olefenic carbons at 134.3 and 127.1 ppm. Also the carbon attached to bromine appeared at 54.7 ppm. From the elemental analysis the molecular formula was calculated as $C_7H_{11}Br$. From the spectral information the structure of the compound was established as 6-bromo-1-methylcyclohexene.

In the *p*-menthane series, the dehydration of 2-bromo-1-hydroxy-*p*-menthane (Table 2.2.2, **1b**) with $BF_3.Et_2O$ was undertaken. Here again catalytic quantity of the reagent was found to efficiently convert the bromohydrin into allylic bromide. The reaction was complete in 2 h to give the **2b** in 75 % yield. The product was characterized by its mass, PMR and 13C-NMR data (Table 2.2.3, **2b**). Mass spectral analysis indicated the presence of a bromine atom as M^+ and $[M+2]^+$ peaks appeared in 1:1 ratio at 216 and 218 respectively. In the PMR spectrum a broad singlet for proton attached to carbon containing bromine atom appeared at 4.60 ppm and one for the olefenic proton at 5.53 ppm. The methyl group attached to C-1 of **1b** appeared at 1.80 ppm but the methyl in **2b** now appeared at 1.26 ppm. The ^{13}C-NMR indicated ten carbon atoms in the molecule. Two of them appeared in the olefenic region (134.1 and 127.3 ppm) and one at 55.8 ppm corresponding to the carbon attached to a bromine atom. From the elemental analysis data, the molecular formula was deduced as $C_{10}H_{17}Br$. From all the spectral information the compound was identified as 6-bromo-*p*-menth-1-ene.

In the aromatic series, 1-bromo-2-phenylpropan-2-ol (Table 2.2.2, **1c**) was selected for study of the dehydration reaction with $BF_3.Et_2O$. In this case, reaction was complete in 2 h and afforded product (**2c)** in 82 % yield. The minor product obtained was identified as 1-bromo-2-phenyl-prop-1-ene, a trisubstituted olefin (vinylic bromide, 15 %). The less substituted Hoffmann elimination product, *i.e.* 1,1-disubstituted olefin **2c** was the major product instead of the more thermodynamically stable tri-substituted olefin. Formation of 1,1-disubstituted product can be attributed to the steric hindrance of the methyl as well as

bulky bromine atom for the approach by the Lewis acid. Hence, one of the methyl protons was lost during the reaction. The product **2c** was identified on the basis of spectral data (Table 2.2.3, **2c**). The mass spectral analysis showed the presence of prominent M^+ and $[M+2]^+$ peaks at 196 and 198 indicating the presence of a bromine atom. In the PMR spectrum of the compound, a singlet at 4.41 ppm integrating to two protons confirmed protons attached to the carbon attached to the olefenic carbon and bromine atom. Two separate singlets appeared at 5.51 and 5.58 each integrating to the single proton indicated that these are olefenic. The ^{13}C-NMR spectra indicated presence of nine carbon atoms, of which eight were in the sp^2 region. The other carbon, which was connected to the bromine and olefenic carbon appeared at 54.2 ppm. Further confirmation of the structure of the compound was obtained from the elemental analysis data, which indicated molecular formula to be C_9H_9Br. The structure of the compound could be established as 3-bromo-2-phenyl-prop-1-ene.

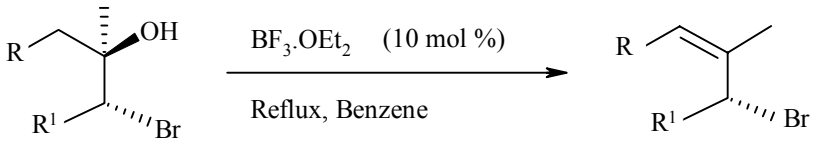
Reaction of $BF_3.Et_2O$ with another monoterpene bromohydrin, 2-bromo-1-hydroxy-*p*-menth-3-one (Table 2.2.2, **1d**) in dry benzene was complete in 1.5 h. In this case, yield of allylic bromide (45 %, **2d**) was less due to possibility of formation of many side products as the substrate was prone to aromatization very easily under acidic conditions. Hence, the yield of actual allylic bromide was found to be less compared to other cases. The product was identified based on the spectral data (Table 2.2.3, **2d**). The mass spectrum contained molecular ion peak and $[M+2]^+$ peaks in 1:1 ratio (230 and 232). The IR spectrum indicated the presence of sharp absorption band at 1712 cm^{-1} for carbonyl group. In its PMR spectrum the proton attached to carbon containing bromine atom appeared at 4.96 ppm, which was 0.13 ppm downfield from that in the parent bromohydrin **1d**. The ^{13}C-NMR showed the presence of ten carbons, of which three were in the sp^2 region. The carbonyl carbon appeared at 152.8 ppm. Further confirmation of the structure of the product was obtained from the elemental analysis report, which indicated the molecular formula as $C_{10}H_{15}BrO$. From the spectral evidence, the compound was identified as 6-bromo-*p*-menth-1-en-5-one.

Next 2-bromo-1,8-dihydroxy-*p*-menthane (Table 2.2.2, **1f**) was taken as a substrate for reaction with $BF_3.Et_2O$. Here the reaction was complete in 2 h. The spectral data (Table

2.2.3, **2f**) of the product obtained in this case was found to be same as that of the product **2e** (Scheme 2.2.1). Hence this product was also identified as 2-bromo-1,8-cineol (Table 2.2.2, **2f**). The yield of the product, 2-bromo 1,8-cineole was moderate (50 %). As this substrate contained many functional groups the possibility of dehydration, hydrodehalogenation does arise under acidic conditions leading to the formation of aromatized products.

Thus, a useful synthetic methodology for the preparation of allylic bromides *via* bromohydrin route by dehydration with a catalytic quantity of $BF_3.Et_2O$ in dry benzene was developed. These reactions take place rapidly and can be conveniently carried out on large scale to afford corresponding allylic bromides. This method also affords the less substituted Hoffman elimination products in good yield in case of benzylic *tert-β*-bromo alcohols. The method adopted here to get the reactive halides from the corresponding olefins through bromohydrin intermediates provides a new synthetic methodology useful for the preparation of oxygenated terpene derivatives, which are important flavor constituents of several essential oils.

Table 2.2.2: Reaction of *tert*-*β*-bromo alcohols with $BF_3.OEt_2$ in benzene at 70°C



1a-1f **2a-2d**

R = Alkyl or aryl, R^1 = Alkyl 45-75 %

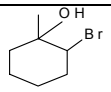
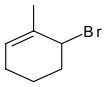
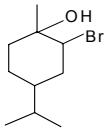
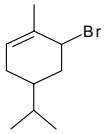
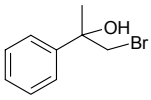
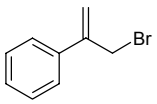
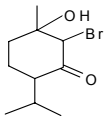
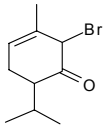
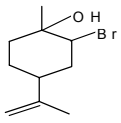
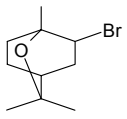
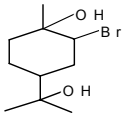
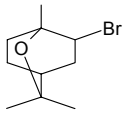
Entry No.	*β*-Bromo alcohol **1**	Product **2**	Yield (%)	Reaction Time (h)
a			60	1
b			75	2
c			82	2
d			45	1.5
e			90	1
f			50	2

Table 2.2.3: PMR, ^{13}C-NMR and mass spectral data of allylic/secondary bromides

Allylic/ secondary bromides	PMR δ ($CDCl_3$, TMS)	^{13}C-NMR	Mass (*m/z*) (relative intensities)
2a	1.79(s, 3H), 1.33-1.65 and 1.94-2.23(m, 6H), 4.63(s, 1H), 5.55(br, 1H)	134.3, 127.1, 54.7, 33.1, 25.2, 22, 17.4	176(2.5), 174(2.5), 161(2), 159(0.5), 149(0.5), 147(1.5), 135(2), 133(0.5), 121(3), 119(3), 96(10), 95(100), 79(45), 77 (35), 67(80), 55(50), 41(45)
2b	0.86(d, 6H, *J* = 3Hz), 1.80(s, 3H), 1.13-1.56 and 1.86-2.26(m, 6H), 4.60(s, 1H), 5.53(br, 1H)	134.1, 127.3, 55.8, 36.5, 34.4, 31.7, 29, 21.4, 19.7, 19.4	218(2), 216(2), 203(0.5), 201(0.5), 175(1), 173(1), 138(6), 137(48), 95(48), 93 (30), 81(100), 79(33), 67(33), 41(50)
2c	4.41(s, 2H), 5.58(s, 1H), 5.51(s, 1H), 7.36-7.42(m, 3H), 7.52-7.54(m, 2H)	144.4, 128.5, 128.3, 127.8, 127.6,126.2, 126, 117.2, 54.2	198(22), 196(22), 117(100), 115(75), 103 (8), 102(6), 91(30), 77(10), 58(35), 51(22), 39(18)
2d	1.28(d, J = 6.9 Hz, 6H), 2.17(s, 1H), 2.29(s, 3H), 1.86-2.05(m, 2H), 3.18-3.27(m 1H), 4.93(br, 1H), 5.26(s, 1H)	152.8, 126.2, 121.5, 52.7, 33.2, 26.8, 22.7, 22.4, 20.8, 20.6	232(0.5), 230(0.5), 217(0.5), 215(0.5), 204(1), 202(1), 190(6), 188(6), 152(3), 151(12), 135(9), 121(1), 109(12), 107(3), 82(100), 69(6), 54(15), 41(28)
2e	0.92(s, 3H), 0.94(s, 3H), 1.44(s, 3H), 1.53-1.57(m, 1H), 1.62-1.67(m, 2H), 1.72-1.75(m, 1H), 1.99-2.02(m, 1H), 2.3-2.35(m,1H), 2.51-2.57(m,1H), 3.86(br, 1H)	55.9, 56.8, 53.1, 22.8, 22, 21.7, 21.3, 21, 20.4, 19.8	234(3), 232(3), 219(2), 217(2), 191(20), 189(24), 153(55), 135(10), 109(20), 95(45), 82(25), 71(60), 55(40), 43(100), 41(95)
2f	0.92(s, 3H), 0.94(s, 3H), 1.44(s, 3H), 1.53-1.57(m, 1H), 1.62-1.67(m, 2H), 1.72-1.75(m, 1H), 1.99-2.02(m, 1H), 2.3-2.35(m,1H), 2.51-2.57(m,1H), 3.86(br, 1H)	55.9, 56.8, 53.1, 22.8, 22, 21.7, 21.3, 21, 20.4, 19.8	234(3), 232(3), 219(2), 217(2), 191(20), 189(24), 153(55), 135(10), 109(20), 95(45), 82(25), 71(60), 55(40), 43(100), 41(95)

Experimental

The reagent $BF_3.Et_2O$ was purchased from Aldrich Chemical Company, USA and it was distilled under reduced pressure (b. p. 51-53^oC/40 Torr) before use. Benzene was dried by the standard method.

1. Reaction of 2-bromo-1-hydroxy-*p*-menth-8-ene with $BF_3.Et_2O$

2-Bromo-1-hydroxy-*p*-menth-8-ene (1.15 g, 5 mmol) was taken in a 100 ml two-necked, round-bottomed flask and 20 ml of dry benzene was added. $BF_3.Et_2O$ (70 mg, 10 mol %) was then added under nitrogen atmosphere slowly and the mixture stirred under reflux. The progress of the reaction was monitored for the disappearance of the bromohydrin on GC. After completion of the reaction (1 h), the contents were allowed to cool to r. t. after which saturated Na_2HCO_3 solution (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 ml x 2). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent the crude product was chromatographed over SiO_2 using 2 % EtOAc in hexane. The product obtained from column was further purified by distillation under reduced pressure.

Yield: 90 % (purity 98 %), b. p. 78-80^oC/0.7 Torr, $[\alpha]_D^{20} = +8.6^o$(*c* = 3, $CHCl_3$).

PMR: δ = 0.92(s, 3H), 0.94(s, 3H), 1.44(s, 3H), 1.53-1.57(m, 1H), 1.62-1.67(m, 2H), 1.72-1.75(m, 1H), 1.99-2.02(m, 1H), 2.3-2.35(m, 1H), 2.51-2.57(m, 1H), 3.86(br, 1H).

^{13}C-NMR: δ = 56.8, 55.9, 53.1, 22.8, 22, 21.7, 21.3, 21, 20.4, 19.8.

MS (*m/z*): 234(3), 232(3), 219(2), 217(2), 191(20), 189(24), 153(55), 135(10), 109(20), 95(45), 82(25), 71(60), 55(40), 43(100), 41(95).

Elemental data: calculated for $C_{10}H_{17}BrO$, C = 51.52 and H = 7.35; found 51.79 and 7.35.

2. Reaction of 2-bromo-1-methyl-cyclohexanol with $BF_3.Et_2O$

2-Bromo-1-methyl-cyclohexanol (0.96 g, 5 mmol) was taken in a 100 ml two-necked, round-bottomed flask along with 20 ml of dry benzene. $BF_3.Et_2O$ (70 mg, 10 mol %) was added slowly under nitrogen atmosphere and stirred under reflux. After completion of the reaction (1 h), the contents were allowed to cool to r. t. and saturated Na_2HCO_3 solution (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 ml x 2). The combined organic layer was washed with brine and

dried over Na_2SO_4. After removal of solvent, the crude product was chromatographed over SiO_2 using 2 % EtOAc in hexane. The product obtained from column was further purified by distillation under reduced pressure.

Yield: 60 % (purity 96 %), b. p. 62-64^oC/4.5 Torr, $[\alpha]_D^{20} = +1.5^o$ (c = 2, $CHCl_3$).

PMR: δ = 1.79(s, 3H), 1.33-1.65 and 1.94-2.23(m, 6H), 4.63(s, 1H), 5.55(br, 1H)

^{13}C NMR: δ = 134.3, 127.1, 54.7, 33.1, 25.2, 22, 17.4.

MS (*m/z*): 176(2.5), 174(2.5), 161(2), 159(0.5), 149(0.5), 147(1.5), 135(2), 133(0.5), 121(3), 119(3), 96(10), 95(100), 79(45), 77 (35), 67(80), 55(50), 41(45).

Elemental data: calculated for $C_7H_{11}Br$, C = 48.02 and H = 6.33; found C = 48.31 and H = 5.77.

3. Reaction of 2-bromo-1-hydroxy-*p*-menthane with $BF_3.Et_2O$

2-Bromo-1-hydroxy-*p*-menthane (1.15 g, 5 mmol) was taken in a 100 ml two-necked, round-bottomed flask along with 20 ml of dry benzene. $BF_3.Et_2O$ (70 mg, 10 mol %) was added slowly under nitrogen atmosphere and the reaction carried out under reflux. After completion of the reaction (2 h), the contents were allowed to cool to r. t. and saturated Na_2HCO_3 solution (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 ml x 2). The combined organic layer washed with brine and dried over Na_2SO_4. After removal of solvent the crude product was chromatographed over SiO_2 using 2 % EtOAc in hexane. The product obtained from column was further purified by distillation under reduced pressure.

Yield: 75 % (purity 95 %), b. p. 78-80^oC/1.5 Torr, $[\alpha]_D^{20} = +16^o$ (c = 2, $CHCl_3$).

PMR: δ = 0.86(d, 6H, J = 3Hz), 1.80(s, 3H), 1.13-1.56 and 1.86-2.26(m, 6H), 4.60(s, 1H), 5.53(br, 1H).

^{13}C-NMR: δ = 134.1, 127.3, 55.8, 36.5, 34.4, 31.7, 29, 21.4, 19.7, 19.4.

MS (*m/z*): 218(2), 216(2), 203(0.5), 201(0.5), 175(1), 173(1), 138(6), 137(48), 95(48), 93 (30), 81(100), 79(33), 67(33), 41(50).

Elemental data: calculated for $C_{10}H_{17}Br$, C = 55.60 and H = 7.89, found C = 55.61 and H = 7.20.

4. Reaction of 1-bromo-2-phenylpropan-2-ol with $BF_3.Et_2O$

1-Bromo-2-phenyl-propan-2-ol (1.07 g, 5 mmol) was taken in a 100 ml two-necked, round-bottomed flask along with 20 ml of dry benzene. $BF_3.Et_2O$ (70 mg, 10 mol

%) was added slowly under nitrogen atmosphere and the reaction carried out under reflux. After completion of the reaction (2 h) the contents were allowed to cool to r. t. and saturated Na_2HCO_3 solution (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH2Cl2 (10 ml x 2). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent, the crude product was chromatographed over SiO_2 using 2 % EtOAc in hexane. The product obtained from column was further purified by distillation under reduced pressure.

Yield: 82 % (purity 98 %), b. p. 80-82^oC/1.5 Torr.

PMR: δ = 4.41(s, 2H), 5.58(s, 1H), 5.51(s, 1H), 7.36-7.42(m, 3H), 7.52-7.54(m, 2H).

^{13}C-NMR: δ = 144.4, 128.5, 128.3, 127.8, 127.6, 126.2, 126, 117.2, 54.2.

MS (*m/z*): 198(22), 196(22), 117(100), 115(75), 103 (8), 102(6), 91(30), 77(10), 58(35), 51(22), 39(18).

Elemental data: calculated for C_9H_9Br, C = 54.85 and H = 4.60; found C = 54.85 and H = 4.62.

5. Reaction of 2-bromo-1-hydroxy-p-menth-3-one with $BF_3.Et_2O$

2-Bromo-1-hydroxy-*p*-menth-3-one (1.25 g, 5 mmol) was taken in a 100 ml two-necked, round-bottomed flask along with 20 ml of dry benzene. $BF_3.Et_2O$ (70 mg, 10 mol %) was added slowly under nitrogen atmosphere and contents were refluxed. After completion of the reaction (1.5 h), the reaction mixture was cooled and saturated Na_2HCO_3 solution (50 ml). The organic layer was separated and the aqueous layer was extracted with CH2Cl2 (10 ml x 2). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent, the crude product was chromatographed over SiO_2 gel using 2 % EtOAc in hexane. The product obtained from column was further purified by distillation under reduced pressure. The physical and spectral data of the product are given below.

Yield: 45 % (purity 94 %), b. p. 96-98^oC/1.5 Torr.

PMR: δ = 1.28(d, J = 6.9 Hz, 6H), 2.17(s, 1H), 2.29(s, 3H), 1.86-2.05(m, 2H), 3.18-3.27(m 1H), 4.93(br, 1H), 5.26(s, 1H).

^{13}C-NMR: δ = 152.8, 126.2, 121.5, 52.7, 33.2, 26.8, 22.7, 22.4, 20.8, 20.6.

IR (γ, cm^{-1}) = 2862, 1712.

MS (*m/z*): 232(0.5), 230(0.5), 217(0.5), 215(0.5), 204(1), 202(1), 190(6), 188(6), 152(3), 151(12), 135(9), 121(1), 109(12), 107(3), 82(100), 69(6), 54(15), 41(28).

Elemental data: calculated for $C_{10}H_{15}BrO$, C = 51.96 and H = 6.54; found C = 51.86 and H = 6.63.

6. Reaction of 2-bromo-1,8-dihyoxy-*p*-menthane with $BF_3.Et_2O$

2-Bromo-1,8-dihyoxy-*p*-menthane (1.25 g, 5 mmol) was taken in a 100 ml two-necked, round-bottomed flask along with 20 ml of dry benzene. $BF_3.Et_2O$ (70 mg, 10 mol %) was added slowly under nitrogen atmosphere and contents were refluxed until the completion of the reaction (2 h). After the addition of saturated $NaHCO_3$ solution (50 ml), the organic layer was separated and the aqueous layer was extracted with CH2Cl2 (10 ml x 2). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent the crude product was flash chromatographed in short column over SiO_2 using 2 % EtOAc in hexane. The product obtained from column was further purified by distillation under reduced pressure.

Yield: 50 % (purity 97 %), b. p. 78-80^oC/0.7 Torr, $[\alpha]_D^{20} = +8.6^o$ (*c* = 3, $CHCl_3$).

PMR: δ = 0.92(s, 3H), 0.94(s, 3H), 1.44(s, 3H), 1.53-1.57(m, 1H), 1.62-1.67(m, 2H), 1.72-1.75(m, 1H), 1.99-2.02(m, 1H), 2.3-2.35(m, 1H), 2.51-2.57(m, 1H), 3.86(br, 1H).

^{13}C-NMR: δ = 55.9, 56.8, 53.1, 22.8, 22, 21.7, 21.3, 21, 20.4, 19.8.

MS (*m/z*): 234(3), 232(3), 219(2), 217(2), 191(20), 189(24), 153(55), 135(10), 109(20), 95(45), 82(25), 71(60), 55(40), 43(100), 41(95).

Elemental data: calculated for $C_{10}H_{17}BrO$, C = 51.52 and H = 7.35; found C = 51.61 and H = 7.38.

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Section 2.3: The Reaction of Terpene and Aryl Substituted Epoxides with Bromodimethylsulfonium bromide

Bromodimethylsulfonium bromide (BDMSB) generated *in situ* from bromine and DMS reacts with aromatic and epoxy substrates to afford electrophilic substitution of bromine and bromo ketones respectively in good yields. The advantages of this reagent are, i) it is easy to prepare and ii) the reactions are generally rapid and uncomplicated. In reactions of oxirans with BDMSB that have been studied, only disubstituted epoxides which possessed no additional functionality in their structure are investigated. In case of arenes, mainly bromination is reported but its application towards the reactions at side chains has not been fully explored. Specifically, epoxides that are present in side chain of the aromatic compounds have not been studied. In the reaction products of BDMSB with disubstituted epoxides, the regio-specificity of the reagent is not clear because products from opening *via* either side would lead to bromo ketones of similar structure. The mechanism of the reaction involves attack of the lone pair of electrons on the epoxide oxygen on electrophilic sulfur followed by opening of the ring by halogen and subsequent breakdown of the intermediate in the presence of a base leading to the formation of halo ketones. The addition of a base is necessary to abstract proton from the carbon, which is bonded to sulfur through the oxygen. In case of tri-substituted epoxides only one carbon has such a structural feature. The tertiary carbon does not have any proton and must be attacked by the free bromide to open epoxide selectively at this position to give the *tert*-*β*-keto bromides. Above all, this type of reaction leads to tertiary bromides, which can be dehydrobrominated easily to get *α,β*-unsaturated ketones.

The Nature and Reactions of Sulfonium Salts

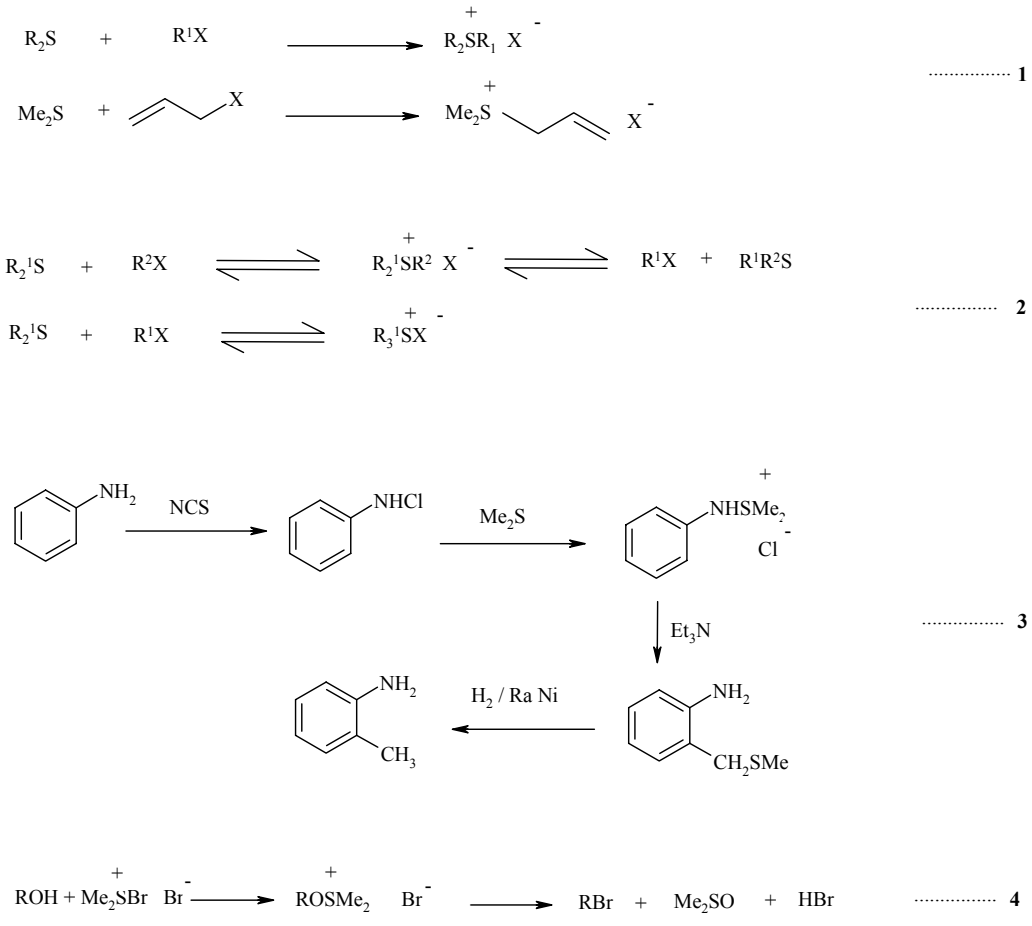
The structure, chemistry, reactions, and synthesis of positive sulfur atom containing compounds like sulfonium salts (sulfur attached to three carbon atoms), sulfur ylids (sulfur connected to carbanion), sulfinium compounds (sulfur attached to a nitrogen), and sulfilimines (sulfur attached to nitrogen bearing negative charge) have been well studied and documented in literature.[1] These sulfonium salts have been extensively used in organic

synthesis. These can be represented as R_3S^+ similar to hydronium ion (OH_3^+). In this type of species, sulfur is trivalent and bears a positive charge. Of the five valence shell electrons, three are bonded and the lone pair electron is on positive sulfur. Sulfonium salts can be easily synthesized from dialkyl sulfides and primary alkyl halides at ambient temperature. Alkyl iodides are most reactive and ease of reaction follows the order allyl > benzyl > halocarbonyl halides (Scheme 2.3.1, equation 1). Secondary and tertiary alkyl halides are generally unreactive towards dialkyl sulfides. An activation group in secondary halide and presence of silver tetraflouroborate are required for the product formation. Alkylation of sulfides is a reversible reaction, the sulfonium ion generated can be dealkylated by the halide ion and it can lead to series of reactions depicted in Scheme 2.3.1 equation 2.

DMS has been used extensively for the preparation of many reactive sulfonium salts. These can be easily prepared, because DMS has no branching at the carbon, which facilitates the formation of sulfonium salts. For instance, DMS with *N*-halosuccinimides gives labile halosulfonium salt, which easily oxidizes secondary alcohol to ketone in presence of a base like triethyl amine.[2] Similarly DMS reacts with chlorine to give a charge-transfer complex, chlorodimethylsulfonium chloride and with bromine to give bromodimethylsulfonium bromide; also aminosulfonium salts are formed from amines with *N*-chlorosuccinimide (NCS). Aniline when treated with NCS gives a complex, which reacts with DMS to give anilinedimethylsulfonium chloride. In the presence of a base like triethyl amine, the complex breaks down into *o*-aminobenzyl methyl ether. Raney nickel hydrogenation yields *o*-toludine (Scheme 2.3.1, equation 3).[3] Alcohols are directly converted into alkyl bromides by bromodimethylsulfonium bromide reagent (Scheme 2.3.1, equation 4).[4]

BDMSB is a very useful synthetic reagent because of the ease of its preparation and the wide variety of transformations it facilitates. It can be prepared *in situ* from DMS and elemental bromine.[5] It can also prepared from dimethyl sulfoxide by treatment with aqueous hydrobromic acid,[6] or by treatment of dimethyl sulfoxide with trimethylsilyl bromide.[7] It has been successfully applied for the oxidative coupling of thiols to disulfides.[8] It adds on to the olefenic bond to produce sulfonium bromides.[5b] BDMSB generated *in situ* from HBr and

DMSO, oxidatively converts acetophenones to glyoxal hydrates.[9] Activated benzenoid compounds like phenols and anilines with BDMSB, produce *p*-halogenated compounds in good yield regioselectively.[10] More recently, a systematic study on halogenation of activated arenes with BDMSB (unactivated arenes do not react) using different solvents and experimental procedures demonstrates that BDMSB is a very efficient brominating agent compared to others like bromine in carbon tetrachloride or bromine in acetic acid.[11] BDMSB efficiently cleaves the disubstituted epoxides and enamines to give α-bromoketones.[12] We were interested in the study of the reaction of BDMSB with the trisubstituted epoxides derived from monoterpenes and aryl hydrocarbons. The investigation was undertaken with a view to obtaining α-bromo ketones which could readily afford the corresponding α,β-unsaturated ketones.



Scheme 2.3.1

Present Work

The reagent BDMSB was prepared *in situ* from DMS and elemental bromine in CH2Cl2 (Scheme 2.3.2) as per the reported procedure.[12] First, its reaction was studied with the *p*-menthane-1,2-oxide (Scheme 2.3.2, **1**), a trisubstituted epoxide. Addition of base to cleave the intermediate was found necessary, after completion of the reaction, which was found to a give a mixture of products. This was probably due to high reactivity of the reagent under the experimental conditions. Of the reaction products, it was observed that one major product was obtained in about 45 % yield. It was obtained in about 94 % purity by chromatographic isolation and distillation under reduced pressure. It was characterized by the spectral data (Table 2.3.1, **1**). The compound gave a sharp absorption peak at 1714 cm^{-1} indicating the presence of a carbonyl group. Further characterization of the product by mass spectral analysis revealed the presence of a bromine as indicated by the presence characteristic M^+ and $[M+2]^+$ peaks in 1:1 ratio (232 and 234). Mass fragmentation pattern of the molecule indicated the *p*-menthane skeleton was unaffected (139, 125, 111, 97, 83, 69, 55, 43). The proton NMR spectra of the product showed the absence of epoxide ring proton at 2.96 ppm. The methyl protons at C-1 position now appeared at 1.70 ppm as against the appearance of same in the parent epoxide at 1.30 ppm, which was 0.4 ppm downfield. From these spectral data the product was identified as 1-bromo-*p*-menth-2-one (Scheme 2.3.2, **2**). Hence the product of reaction of BDMSB with trisubstituted epoxide was a bromo ketone that had bromine on the tertiary carbon. This study revealed that the epoxide ring cleaves at the tertiary position leading to the formation of *tert*-*β*-keto bromides. A study of this reaction with other terpene and aryl substituted epoxides was undertaken.

Next substrate chosen for the reaction with BDMSB was 4-hydroxy-*p*-menthane-1,2-oxide (Scheme 2.3.3, **1**). The epoxide **1** was prepared from its bromohydrin **3** by base induced cylization in aqueous ethanol (Scheme 2.3.3, equation B). The preparation of bromohydrin is described in chapter 2, section 2.4. The epoxide, obtained in excellent yield by this route, has been characterized by its IR, PMR and mass spectral data. The reaction of epoxide with BDMSB was complete in 12 h at 0^oC and afforded a product, 1-bromo-4-hydroxy-*p*-menth-2-one (**2**), which was isolated by column chromatography in 60 % yield.

This product was characterized by the spectral data (Table 2.3.1, **2**).The carbonyl functionality was identified by the presence of sharp IR absorption band at 1715 cm^{-1}. Also the hydroxyl absorption band at 3450 cm^{-1} indicated its interference with the reagent under experimental conditions was negligible. The mass spectra of the compound showed the characteristic M^+ and $[M+2]^+$ peaks in 1:1 ratio (248 and 250). Further mass fragments are characteristic of *p*-menthane skeleton (135, 127, 111, 97, 93, 81, 55, 43). Absence of epoxide ring proton in PMR at 2.66 ppm in the product indicated the possible formation of carbonyl group at this position. The C-1 methyl protons in the product now appeared at 1.70 ppm as against the same at 1.30 ppm in the epoxide **1**. This confirms the attack of the bromine atom at this position, and hence the product was identified as 1-bromo-4-hydroxy-*p*-menth-2-one. As expected, the oxide ring cleaved at the tertiary carbon to give *tert*-*β*-keto bromide.

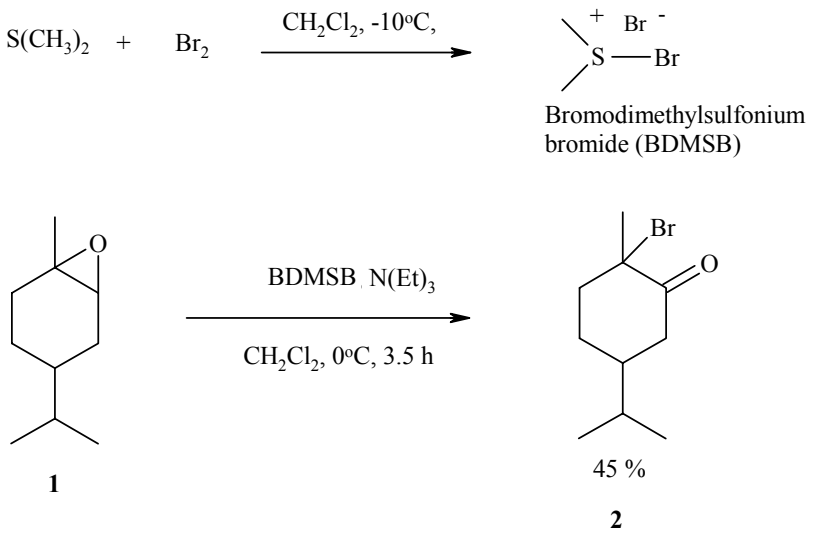
In continuation of reaction of BDMSB with the terpene epoxides, next a tricyclic trisubstituted epoxide was selected for the study. The reaction of 3-carene oxide (Scheme 2.3.4, **1**) with BDMSB was undertaken. The reaction proceeded smoothly at 0^oC and was complete in 8 h. This afforded a product (60 %), which after isolation by column chromatography was characterized based on spectral data (Table 2.3.1, **3**). The presence of the IR absorption band as sharp at 1715 cm^{-1} indicated the carbonyl group in the molecule. The mass spectral data showed the presence of M^+ and $[M+2]^+$ peaks in 1:1 ratio (230 and 232). One of the methyl group appeared as a singlet at 1.70 ppm in PMR spectra. This indicated the attachment of the methyl to a carbon containing bromine atom. The other two methyls appeared distinctly at 0.76 and 1.06 ppm were for the methyls of the cyclopropyl group showing that the strained cyclopropane ring in the substrate was unaffected under the reaction conditions. Thus, the product was identified as 4-bromo-4,7,7-trimethyl-bicyclo[4.1.0]heptan-3-one (Scheme 2.3.4, **2**).

Next the aryl substituted epoxides *viz*. styrene oxide and *α*-methylstyrene oxide were taken up for the study. When the reaction of styrene oxide (Scheme 2.3.5, **1**) with the BDMSB was carried out, the product was obtained in 71 % yield after 3 h. After isolation by silica column chromatography, it was identified as 2-bromo-2-phenylethanal based on the

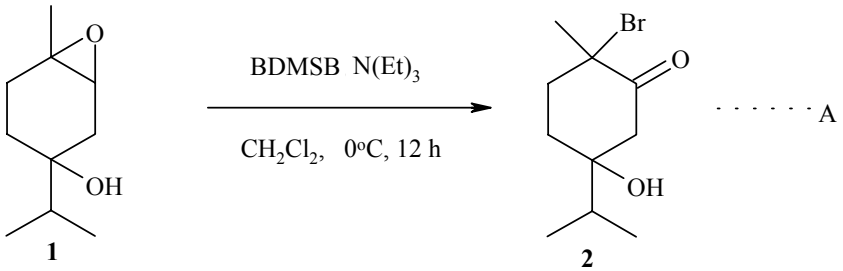
spectral data (Table 2.3.1, **4**). The presence of carbonyl was observed as it gave sharp IR absorption band at 1727 cm^{-1}. Its PMR spectra showed a peak at 9.66 ppm, for a single proton, which is characteristic of the aldehydic proton. In the mass spectrum of the compound presence of M^+ and $[M+2]^+$ peaks in ~1:1 ratio (198 and 200), indicated the presence of a bromine atom. At 3.76 ppm, a singlet for a single proton appeared, which was identified as the proton attached to carbon containing bromine atom. Its formation is rationalized in Scheme 2.3.5. Hence the reaction of BDMSB with aryl substituted epoxides affords aldehyde as the main product. The reagent showed regiospecificity in terms of attack on the epoxy carbon atom. Formation of epoxide-dialkylsulfonium bromide intermediate from styrene oxide and dialkylsulfonium and subsequent breaking down of the intermediate by base leads the formation of a regio-specific product with the epoxide ring opening at the benzylic position.

The next benzylic substituted epoxide chosen for the study was 2-methyl-2-phenyloxiran (Scheme 2.3.5, **3**). This epoxide was in turn, prepared from its bromohydrin using 10 % K_2CO_3 in aqueous ethanol in 86 % yield (Equation C) and characterized by its PMR and mass spectral data. The reaction of BDMSB with this substrate was also rapid and was complete in three hours. The isolation of the product by silica column chromatography afforded a product (70 %), which had the following spectral characteristics (Table 2.3.1, **5**). The presence of carbonyl group was indicated by the sharp absorption of the IR radiation at 1725 cm^{-1}. The PMR spectrum of the product showed the presence of a singlet at 9.66 ppm indicating the aldehydic group in the molecule. Apart from the aromatic protons, which integrated to five protons at 7.33-7.60 ppm, a singlet integrating for three protons at 2.13 ppm for a methyl group was seen in the PMR spectrum. The mass spectrum of the compound showed the presence of bromine atom as indicated by the presence of M^+ and $[M+2]^+$ peaks in ~1:1 ratio at *m/z* = 212, 214. Also, other characteristic benzylic fragments were observed (77, 63, 55). From the above spectral data, product of the reaction was identified as 2-bromo-2-phenylpropanal (Scheme 2.3.5, **4**). Here, regiospecific opening of the epoxide ring at the benzylic and tertiary carbon-oxygen bond took place to give a *tert-β*-keto bromide.

The present study revealed that the BDMSB could be used to cleave the tertiary and benzylic carbon-oxygen bond of an epoxide ring regiospecifically. In case of aryl disubstituted epoxide, like styrene oxide the bromine regiospecifically enters at the benzylic positions. Benzylic trisubstituted epoxides, cleave preferentially at the benzylic position to yield the respective bromoaldehydes. Thus, the utility of the BDMSB reagent for regiospecific cleavage of terpene and aryl substituted epoxides was demonstrated. The bromo ketone intermediates obtained from these reactions can be further converted to *α,β*-unsaturated ketones by dehydrohalogenation reactions. These products could, thus, serve as useful intermediates for the preparation oxygenated terpenes, which are important aroma chemicals.

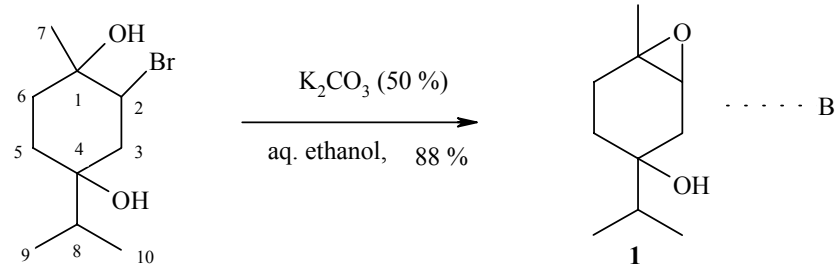


Scheme 2.3.2



1 4-hydroxy-*p*-menthane -1,2-oxide

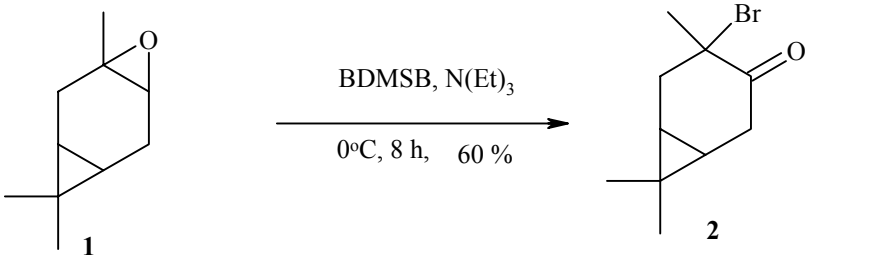
2 60 %



3 2-bromo-1,4-dihydroxy-*p*-menthane

1 4-hydroxy-*p*-menthane -1,2-oxide

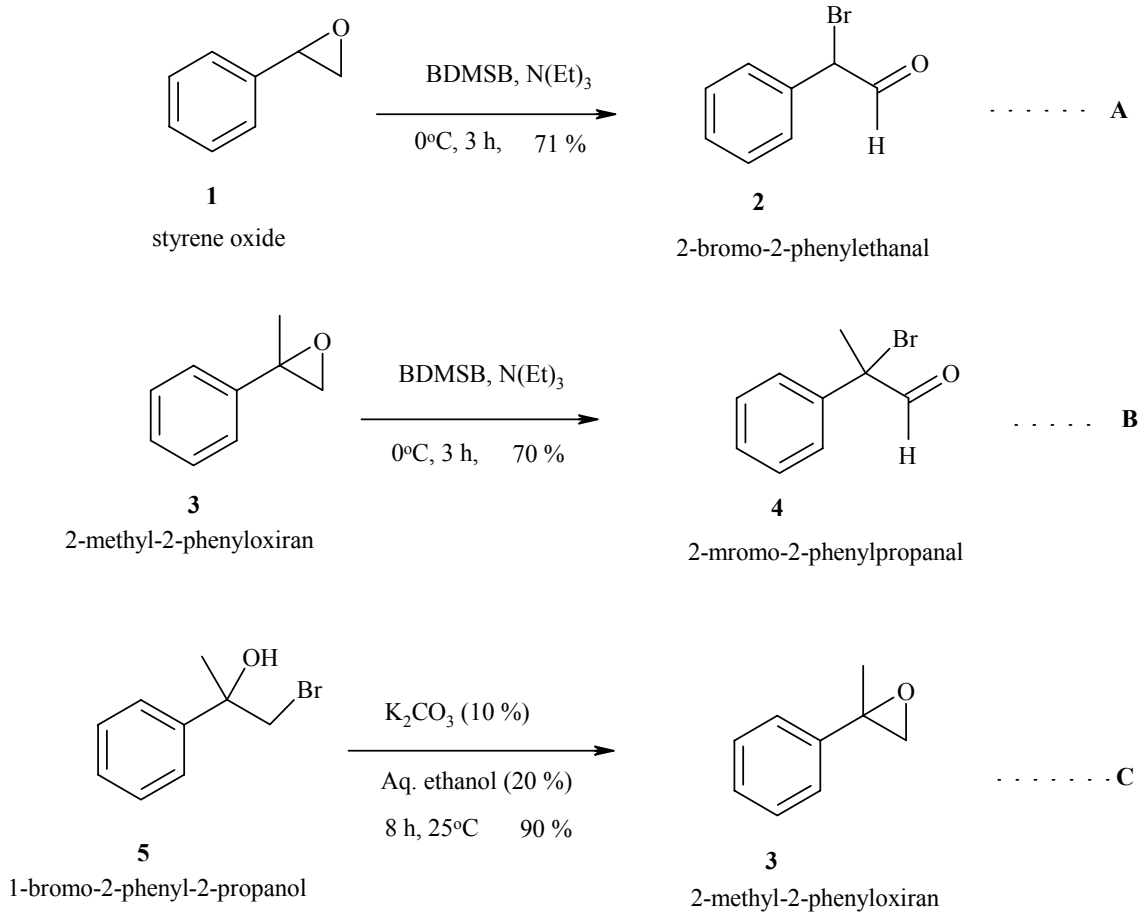
Scheme 2.3.3



1 3-carene oxide

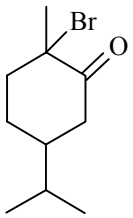
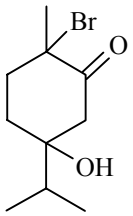
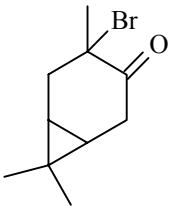
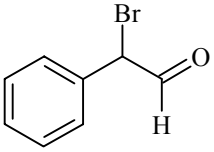
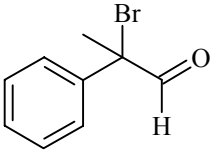
2 4-bromo-4,7,7-trimethyl -bicyclo[4.1.0]heptan-3-one

Scheme 2.3.4


O
BDMSB, N(Et)3
0oC, 3 h, 71 %
Br
O
H
A
1
styrene oxide
2
2-bromo-2-phenylethanal
O
BDMSB, N(Et)3
0oC, 3 h, 70 %
Br
O
H
B
3
2-methyl-2-phenyloxiran
4
2-mromo-2-phenylpropanal
OH
Br
K2CO3 (10 %)
Aq. ethanol (20 %)
8 h, 25oC 90 %
O
C
5
1-bromo-2-phenyl-2-propanol
3
2-methyl-2-phenyloxiran

Scheme 2.3.5

Table 2.3.1: Spectral data of α-bromocarbonyls

Entry No.	α-Bromocarbonyls	PMR	Mass (m/z)	IR (γ) cm^{-1}
1		0.86(d, J = 6 Hz, 6H), 1.70(s, 3H), 1.30-1.66 & 1.80-2.90(m, 8H)	234(10), 232(8), 191(35), 189(40), 152(4), 125(15), 111(10), 109(70), 83(12), 81(75), 69(70), 55(85), 43(60), 41(100)	2864, 1715
2		0.90(d, J = 6 Hz), 1.70(s, 3H), 1.33-1.66 & 1.80-3.06(m, 8H)	250(1), 248(1), 221(3), 219(3), 153(4), 135(5), 127(100), 111(3), 97(20), 93(15), 81(30), 55(20), 43(80)	3450, 2864, 1715
3		0.40-0.50(m, 2H), 0.76(s, 3H), 1.06(s, 3H), 1.70(s, 3H), 1.26-1.60 & 1.80-2.40(m, 4H)	232(4), 230(2), 189(4), 187 (4), 152(10), 135(40), 119(10), 109(20), 93(40), 81(20), 67(30), 55 (30), 43(100), 41 (60)	2864, 1715
4		3.76(s, 1H), 7.30-7.60(m, 5H), 9.63(s, 1H)	200(4), 198(2), 171(25), 169(30), 119(50), 91(60), 80(10), 65(20), 44(100)	2864, 1727
5		2.13(s, 3H), 7.33-7.60(m, 5H), 9.66(s, 1H)	214(2), 212(3), 185(40), 183(35), 132(100), 105(80), 104(80), 103(75), 77(80), 63(15), 51(60)	2864, 1725

Experimental

DMS was purchased from Merck USA (purity 99 %, GC). Bromine was procured from E-Merck, India. CH_2Cl_2 was dried initially over fused $CaCl_2$ and then distilled from calcium hydride. The fraction distilling at 40-41^oC was collected and stored over molecular sieves (3A) in amber colored bottle.

1. Preparation of *p*-menthane-1,2-oxide (carvomenthene oxide)

p-Menth-1-ene (0.5 mol, 69 g) was taken in a 500 ml flask, 200 ml CH_2Cl_2 was added and the mixture cooled to 0^oC. Peracetic acid (90 gm, 38 %) saturated with sodium acetate was added slowly under stirring at 0^oC. The progress of the reaction was monitored for the disappearance of the olefin by GC. After completion of reaction (4 h), the mixture was poured into water (200 ml) and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (25 ml x 2) and the combined organic layer was washed with water followed by brine. The product was dried over anhydrous Na_2SO_4 and distilled to afford crude *p*-menthane-1,2-oxide. This was further purified by distillation under reduced pressure.

Yield: 77 g, 91 % (purity 98 %,) b. p.51-52^oC/2.0Torr, $[\alpha]^D_{20}$ = +49.84^o(neat).

PMR: 0.82(d, *J* = 6.8, 6H), 1.0-1.15(m, 2H), 1.30(s, 3H), 1.48-1.65(m, 4H) 1.90-2.0(m, 2H), 2.98(br, 1H).

MS (m/z): 154(2), 139(10), 125(8), 111(30), 97(10), 83(15), 69(45), 55(50), 43(100).

2. Reaction of *p*-menthane-1,2-oxide with BDMSB

Bromine (1.6 g, 10 mmol) was taken in CH_2Cl_2 (15 ml), cooled to 0–10^oC and a solution of DMS (0.93 g, 15 mmol) in CH_2Cl_2 (10 ml) was added gradually without allowing the temperature to rise. The complex BDMSB so obtained was orange yellowish in color. After 10 minutes stirring, a solution of epoxide (1.54 g, 10 mmol) in 10 ml CH2Cl2 was added slowly maintaining the temperature at –10 to 0^oC and the progress of the reaction was monitored by GC. At the end of the reaction (3.5 h), a solution of dry NEt_3 (1.01 g, 10 mmol) in CH_2Cl_2 (5 ml) was added and stirred for 10 min. The product after aqueous work up (50 ml) was dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude

product, which was chromatographed over silica using 5 % EtOAc in hexane to afford pure compound which was distilled under reduced pressure.

Yield: 1.04 g, 45 %, b. p. 86-87^{o}C/1.6 Torr.

IR (γ cm^{-1}) = 2864, 1715.

PMR: δ = 0.86(d, J = 6 Hz, 6H), 1.70(s, 3H), 1.30-1.66 & 1.80-2.90(m, 8H).

MS (*m/z*): 234(10), 232(8), 191(35), 189(40), 152(4), 125(15), 111(10), 109(70), 83(12), 81(75), 69(70), 55(85), 43(60), 41(100).

3. Preparation of 4-hydroxy-*p*-menth-1,2-oxide from 1-bromo-2,4-dihydroxy-*p*-menthane

1-Bromo-2,4-dihydroxy-*p*-menthane (5.02 g, 20 mmol) was taken in a flask with 30 ml of 20 % aqueous EtOH. Potassium carbonate (1.4 g, 10 mmol) was added and the mixture was stirred. The progress of the reaction was monitored for the disappearance of substrate by GC. After completion of the reaction (3 h), alcohol was distilled under vacuum followed by aqueous work up and extraction with CH_2Cl_2 (25 ml x 3) to afford the crude product. It was further purified by distillation under reduced pressure.

Yield: 3.0 g, 88 %, (purity 96 %) b. p. 82-84/1 Torr.

IR (γ cm^{-1}) = 3458, 2864.

PMR: δ = 0.86(d, J = 6 Hz, 6H), 1.30(s, 3H), 1.33-1.66 & 1.80-2.90(m, 8H), 2.66(s, 1H).

MS (*m/z*): 170(4), 152(5), 137(10), 119(8), 109(24), 93(20), 79(22), 67(60), 43(100).

4. Reaction of 4-hydroxy-*p*-menth-1,2-oxide with BDMSB

Bromine (1.6 g, 10 mmol) was taken in CH_2Cl_2 (15 ml), cooled to 0 –10^{o}C. A solution of DMS (0.93 g, 15 mmol) in CH2Cl2 (10 ml) was added gradually without allowing the temperature to rise. The complex BDMSB so obtained was orange yellowish in color. After 10 minutes of stirring, a solution of epoxide (1.70 g, 10 mmol) in 10 ml CH2Cl2 was added slowly maintaining the temperature at –10 to 0^{o}C and the progress of the reaction was monitored by GC. At the end of the reaction (12 h), a solution of dry NEt_3 (1.01 g, 10 mmol) in CH_2Cl_2 (5 ml) was added and stirred for 10 min. The product after aqueous work up (50 ml) was dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude

product, which was chromatographed over silica using 5 % EtOAc in hexane to afford one pure compound which was distilled under reduced pressure.

Yield: 1.50 g, 60 %, b. p. 86-88/1 Torr.

IR (γ cm^{-1}) = 3450, 2864, 1715.

PMR: δ = 0.90(d, J = 6 Hz), 1.70(s, 3H), 1.33-1.66 & 1.80-3.06(m, 8H).

MS (*m/z*): 250(1), 248(1), 221(3), 219(3), 153(4), 135(5), 127(100), 111(3), 97(20), 93(15), 81(30), 55(20), 43(80).

5. Preparation of 3-carene oxide from Δ^3-carene

Δ^3-Carene (0.5 mol, 68 g) was taken in CH_2Cl_2 (200 ml) and cooled to 0^oC. Peracetic acid (90 gm, 38 %) saturated with NaOAc was added slowly to it and the mixture stirred at 0^oC. The progress of the reaction was monitored for the disappearance of substrate by GC. After completion of reaction (1 h), the product was taken in water (200 ml) and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (25 ml x 2) and the combined organic layer was washed with the water followed by brine. It was dried over Na_2SO_4 and the solvent was distilled to afford crude 3-carene oxide. Its distillation under reduced pressure afforded pure 3-carene oxide.

Yield: 60.8 g, 80 % (purity 97 %) b. p. 76-78^oC/6 Torr.

PMR: δ =0.40-0.50(m, 2H), 0.76(s, 3H), 1.06(s, 3H), 1.20(s, 3H), 1.43-2.33(m, 4H), 2.63(s, 1H).

MS (*m/z*): 152(4), 138(2), 137(10), 119(22), 109(25), 91(15), 81(18), 67(55), 43(100).

6. Reaction of 3-carene epoxide with BDMSB

Bromine (1.6 g, 10 mmol) was taken in CH_2Cl_2 (15 ml), cooled to -10^oC and a solution of DMS (0.93 g, 15 mmol) in CH_2Cl_2 (10 ml) was added gradually without allowing the temperature to rise. The complex BDMS so obtained was orange yellowish in color. After 10 minutes of stirring, a solution of epoxide (1.52 g, 10 mmol) in 10 ml CH2Cl2 was added slowly maintaining the temperature at –10 to 0^oC and the progress of the reaction was monitored by GC. At the end of the reaction (8 h), a solution of dry NEt_3 (1.01 g, 10 mmol) in CH_2Cl_2 (5 ml) was added and stirred for 10 min. The product after aqueous work up (50 ml) was dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed over silica using 5 % EtOAc in hexane. From the

column one product was isolated which was distillation under reduced pressure to afford a pure compound.

Yield: 1.40 g, 60 %, b. p. 98-100^{o}C/2 Torr.

IR (γ cm^{-1}) = 2864, 1715.

PMR: δ = 0.40-0.50(m, 2H), 0.76(s, 3H), 1.06(s, 3H), 1.70(s, 3H), 1.26-1.60 & 1.80-2.40(m, 4H).

MS (*m/z*): 232(4), 230(2), 189(4), 187 (4), 152(10), 135(40), 119(10), 109(20), 93(40), 81(20), 67(30), 55 (30), 43(100), 41 (60).

7. Reaction of styrene oxide with BDMSB

Bromine (1.6 g, 10 mmol) was taken in CH_2Cl_2 (15 ml), cooled to 0 –10^{o}C and a solution of DMS (0.93 g, 15 mmol) in CH_2Cl_2 (10 ml) was added gradually without allowing the temperature to rise. The complex BDMS so obtained was orange yellowish in color. After 10 minutes of stirring, a solution of epoxide (1.20 g, 10 mmol) in 10 ml CH_2Cl_2 was added slowly maintaining the temperature at –10 to 0^{o}C and the progress of the reaction was monitored by GC. At the end of the reaction (3 h), a solution of dry NEt_3 (1.01 g, 10 mmol) in CH_2Cl_2 (5 ml) was added and stirred for 10 min. The product after aqueous work up (50 ml) was dried over anhydrous Na_2SO_4. Removal of solvent afforded the crude product, which was chromatographed over silica using 5 % EtOAc in hexane. From the column one major product was isolated and it was distilled under reduced pressure to afford a pure compound.

Yield: 1.41 g, 71 %, b. p. 75-77^{o}C/1.5 Torr.

IR (γ cm^{-1}) = 2864, 1727.

PMR: δ = 3.76(s, 1H), 7.30-7.60(m, 5H), 9.63(s, 1H).

MS (*m/z*): 200(3), 198(2), 171(25), 169(30), 119(50), 91(60), 80(10), 65(20), 44(100).

8. Preparation of 2-methyl-2-phenyl-oxiran from 2-bromo-2-phenyl-propan-1-ol

2-Bromo-2-phenyl-propan-1-ol (4.30 g, 20 mmol) was taken in a flask in a 30 ml of 20 % aqueous ethanol. Potassium carbonate (1.4 g, 10 mmol) was added and the reaction mixture was stirred. The progress of the reaction was monitored for the disappearance of bromohydrin by GC. After completion of the reaction (8 h), alcohol was removed under

vacuum followed by aqueous work up and extraction with CH_2Cl_2 (25 ml x 3) which afforded a crude product. It was further purified by distillation under reduced pressure.

Yield: 2.43 g, 90 %, b. p. 68-70^oC/4 Torr.

PMR: δ = 1.66(s, 3H), 2.60(d, J = 6 Hz, 1H), 2.83(d, J = 6 Hz, 1H), 7.30-7.63(m, 5H).

MS (*m/z*): 134(10), 133(15), 115(2), 105(100), 91(8), 77(20), 63(6), 51(20).

9. Reaction of 2-methyl-2-phenyloxiran with BDMS

Bromine (1.6 g, 10 mmol) was taken in CH_2Cl_2 (15 ml), cooled to 0 –10^oC and a solution of DMS (0.93 g, 15 mmol) in CH_2Cl_2 (10 ml) was added gradually without allowing the temperature to rise. The complex BDMSB so obtained was orange yellowish in color. After 10 minutes of stirring, a solution of epoxide (1.35 g, 10 mmol) in 10 ml CH_2Cl_2 was added slowly maintaining the temperature at –10 to 0^oC and the progress of the reaction was monitored by GC. At the end of the reaction (3 h), a solution of dry NEt_3 (1.01 g, 10 mmol) in CH_2Cl_2 (5 ml) was added and stirred for 10 min. The product after aqueous work up (50 ml) was dried over anhydrous Na_2SO_4. Removal of solvent afforded the crude product, which was chromatographed over silica using 5 % EtOAc in hexane. From the column one pure major product was isolated and it was distilled under reduced pressure to afford pure compound.

Yield: 1.49 g, 70 %, b. p. 83-84^oC/1.6 Torr.

IR (γ cm^{-1}) = 2864, 1725.

PMR: δ = 2.13(s, 3H), 7.33-7.60(m, 5H), 9.66(s, 1H).

MS (*m/z*): 214(2), 212(3), 185(40), 183(35), 132(100), 105(80), 104(80), 103(75), 77(80), 63(15), 51(60).

10. Preparation and estimation of peracetic acid:

a) Concentration of hydrogen peroxide

Commercial H_2O_2 (1000 ml, 30 %) was taken in a 2 l round-bottomed socket joint flask equipped with inner T-joint, which carries an air leak and a bent to condenser. A water condenser was connected to the flask for distillation under reduced pressure. The vacuum was set at 30 mm Hg and water (695 ml) was distilled at a constant rate by maintaining the water bath at 50^oC. The residual concentrated H_2O_2 (305 ml) was estimated iodometrically.

Estimation of hydrogen peroxide:[13]

Reagents required: KI solution, 10 % v/v
H_2SO_4 2N solution
$Na_2S_2O_3$ solution0.1 N
Ammonium molybdate 3 % solution

Diluted hydrogen peroxide (25 ml, 1 ml concentrated ~ 95 % H_2O_2 in 100 ml H_2O), was transferred into a conical flask. H_2SO_4 (100 ml, 2N solution) and KI (10 ml, 10 %) were added followed by addition of 3 drops of ammonium molybdate. The liberated iodine was titrated with standard sodium thiosulfate solution.

1 ml of 1N $Na_2S_2O_3$ = 0.01701 g H_2O_2

The concentration of H_2O_2 was found to be 98 %.

b) Preparation of peracetic acid:[13]

Glacial acetic acid (400 ml) was taken in 2 l conical flask, concentrated H_2SO_4 (4 m) was added and the flask was cooled to about 15^oC. Concentrated H_2O_2 (280 ml, 98 %) was cautiously added over a period of 30 minutes keeping the temperature at 15-20^oC with occasional shaking. The mixture was allowed to equilibrate overnight at ambient temperature before the estimation of the peracetic acid content.

Estimation of peracetic acid:[14]

Reagents required: ***KI solution, 15 % v/v***
Acetic acid 0.1 N solution
$Na_2S_2O_3$ solution0.1 N
And Ammonium molybdate 3 % solution

Acetic acid (10 ml, 0.1 N) solution was taken in a 500 ml conical flask; a thermometer was inserted to it and cooled the flask to 5^oC. An accurately weighed 1.0 g of sample to be analyzed was added to it. Potassium iodide solution (10 ml, 15 %) was transferred to the flask at the same moment stopwatch was also started. The liberated iodine was titrated against standard sodium thiosulfate solution using starch indicator. Titration continued till the disappearance of blue color at least for 2 minutes.

Burette reading (X_1) and stopwatch reading (t_1) were recorded when the blue color next returned. Titration was continued as before for further 3 or 4 minutes and second titre

value (X_2) and corresponding time (t_2) were recorded. About three drops of molybdate was added and titrated till the end point (X_t) persists for one minute.

X_o at zero time t_o was calculated according to

$$X_o = X_1 - t_1 (X_2 - X_1) / t_2 - t_1$$

$$\text{Peracid content} = X_o \, N \, E / 10W$$

N = Normality of $Na_2S_2O_3$
W = Weight of the sample
E = Equivalent weight of peracid.

The strength of peracetic acid was estimated to be ~ 40 %.

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Section 2.4: Preparation of Bromohydrins

Generally halohydrins are synthesized from olefins by reaction with positive halogen compounds like *N*-haloamide,[1] N-haloimide,[2] chlorourea,[3] and chloramines T.[4] Earlier these have been synthesized by direct addition of halogen and water to olefins.[5] As interest towards the production of regio- and stereospecific functionalization of olefins has grown, the use of DMSO[6] and aqueous acetone[7] as solvents for cohalogenation came to fore. Apart from the aqueous mediated reactions, the development of other methods, where the use of participating agents like hydrogen peroxide,[8] alcohols[9] and carboxylic acid derivatives[10] gained much importance, as the resultant derivatives were highly useful to the synthetic chemists. However, the use of H_2O_2 did not emerge as a general method for cohalogenation reaction because of the formation of mixtures of dihalogenated compounds. The use of carboxylic acid derivatives in the cohalogenation has been applied to the extensive synthesis of *cis*-1,2-diols.

Bromohydrins have also been synthesized by a number of reactions that involve the cleavage of epoxides. Majority of them involve application of some metal and inorganic salts. The use of metal halides for regio- and chemoselective synthesis of halohydrins by cleavage of oxirans has been reviewed.[11] The generation of hypohalous acids *in situ* from H_5IO_6 and $NaBrO_3$ in the presence of $NaHSO_3$ for the cleavage of epoxides is described.[12] The use of combination of both metal salts and ammonium halides have been reported for the synthesis of β-halohydrins from 1,2-epoxides.[13] Metal halide complex of Ti(IV) chloride-lithium halides,[14] dilithium tetrabromonickelate (Li_2NiBr_4)[15] and lithium halides[16] in the presence of an acid are also important in terms of regioselective conversion of epoxides to halohydrins. Few other reported methods in recent literature are summarized below.

Optically active halohydrins are produced by a tandem enzyme reaction.[17] Lithium halides supported on silica gel are used to transform epoxides to halohydrins under solvent free conditions.[18] Regio-selective conversion of epoxides to halohydrins with molecular halogens catalyzed by metaloporphyrins,[19] crown ethers,[20] phenyl-2-(2-pyridyl)imidazolidine[21] and phenylhydrazine[22] are reported. Cohalogenation of limonene,

carvomenthene and related unsaturated monoterpenic alcohols using copper acetate in aqueous dioxane has been carried out to prepare some stereospecific monoterpene derivatives.[23] As a mild source of hydrogen bromide for chemoselective ring opening of epoxides with triphenylphosphonium bromide has been also developed.[24] Two efficient borane derivatives, namely, dibromoborane-dimethylsulfide and monobromoborane-dimethylsulfide have been developed as superior reagents for conversion of epoxides to bromohydrins.[25] A biomimetic regioselective cleavage of epoxides to halohydrins in the presence of *β*-cyclodextrin has been reported.[26] A high stereo- and regio- control is achieved for the synthesis of unsaturated bromohydrins from unsaturated epoxides with triphenylphosphine and bromine or with tetrabromomethane.[27] 2-Bromo-1-hydroxy-*p*-menthane (carvomenthene bromohydrin) was first synthesized for the production of high *trans*/*cis* ratio of epoxide by Leffingwell *et al*.[28] In the following section, the synthesis of the bromohydrins derived from monoterpenes and other monocyclic olefins are described with main emphasis on the standardization of the procedure and optimization of reaction conditions to get the pure products in near quantitative yields.

Present Work

In the first instance, the bromohydrin of (+)-(*4R*)-limonene (Table 2.4.1, **1a**) was prepared.[7b] Limonene was treated at 0-5°C with equivalent quantity of NBS in aqueous acetone (15 %). The product obtained after usual workup was subjected to silica column chromatography. During this isolation, it was observed that the compound developed a dark color on the gel in the column. Also, generation of heat was seen during the isolation process. To avoid decomposition moderately active silica gel was employed for the isolation process, which afforded excellent yield of product. The product was further purified by distillation under reduced pressure. The physical and spectral data of the pure compound were in close agreement with the reported data (Table 2.4.2, **2a**).[7b]

p-Menth-1-ene (Table 2.4.1, **1b**) was prepared by catalytic hydrogenation of (*R*)-(+)-limonene in ethanol in presence of Raney nickel catalyst as described by Jackman *et al*.[29] The reaction was monitored for the disappearance of isopropenyl double bond, which appeared at 4.76 ppm in PMR spectrum. Fractional distillation of the product under reduced pressure afforded pure (*R*)-(+) *p*-menth-1-ene (>99 % purity by GC). The bromohydrin of *p*-menth-1-ene was prepared by its reaction with equivalent quantity of NBS in aqueous acetone (15 %) at 0-5°C. The product isolated by the column chromatography was distilled to afford a pure compound which was characterized by its spectral data (Table 2.4.2, **2b**). The IR spectrum of the compound showed a broad absorption at 3419 cm^{-1} indicating the presence of hydroxyl group. The mass spectrum of the compound gave M^+ and $[M+2]^+$ peaks at 234 and 236 in 1:1 ratio indicating the presence of a bromine atom. The olefenic bond appearing at 5.26 ppm in PMR spectrum of the olefin was absent indicating the addition of the hypobromous acid at this double bond. At 4.13 ppm, a broad singlet appeared for single proton which corresponded to a proton attached to carbon containing bromine atom. The C-1 methyl appeared at 1.26 ppm indicating the presence of hydroxyl group at this carbon. Based on the spectral data the product was identified as *trans*-2-bromo-1-hydroxy-*p*-menthane (Table 2.4.1, **2b**).

For the synthesis of 2-bromo-1-methylcyclohexanol (Table 2.4.1, **2c**) 1-methylcyclohexene (**1c**) was initially prepared from cyclohexanone by Grignard

reaction. Methylmagnesium iodide, prepared *in situ* by reaction of freshly activated magnesium turnings and methyl iodide in dry ether, on reaction with cyclohexanone afforded 1-methylcyclohexanol. The identity of 1-methylcyclohexanol was confirmed by IR (3317 cm^{-1}) and PMR spectrum which showed multiplet at 1.26-2.20 (10H) for alkyl protons, apart from the C-1 methyl at 1.06 ppm, which indicated the presence of hydroxyl at C-1. In the next step of the reaction 1-methylcyclohexanol was dehydrated by reaction with orthophosphoric acid (85 %) followed by distillation to afford 1-methylcyclohexene (**1c**). Its PMR showed a peak which integrated to single proton in the olefenic region at 5.33 ppm. The other alkyl protons appeared at 1.20-2.20 (m, 8H) and C-1 methyl at 1.56 ppm. The bromohydrin of 1-methylcyclohexene was prepared by its reaction with NBS in aqueous acetone. The product after completion of the reaction was isolated by usual workup and followed by silica column chromatography and distillation. It had the following spectral characteristics (Table 2.4.2, **2c**). The IR absorption at 3418 cm^{-1} as a broad band indicated the presence of hydroxyl group. In its PMR spectrum presence of methyl group at 1.33 ppm indicated the presence of hydroxyl at C-1 carbon. The mass spectrum of the compound showed the M^+ and $[M+2]^+$ ions at 192 and 194, indicating the presence of a bromine atom. Appearance of double doublet for one proton at 4.30 ppm (J = 3 Hz) indicated that it was attached to the carbon containing bromine atom. From the above analytical data the product was identified as *trans*-2-bromo-1-methylcyclohexanol.

4-Bromo-3,7,7-trimethyl-bicyclo[4.1.0]heptan-3-ol (*trans*-4-Bromo-caran-3-ol, Table 2.4.1, **2d**) was prepared by the reaction of Δ^3carene (**1d**) with NBS in aqueous acetone. On completion of reaction (GC), usual workup followed by silica chromatographic purification afforded the product as a low melting solid. During the isolation, it was found that the product was prone to ready decomposition compared to other bromohydrins. Hence isolation was completed in a short SiO_2 column followed by recrystalization of the compound in 1:1 mixture of ether and petroleum ether (40-60^oC). The compound had melting point which was in close agreement with the reported value (found 49-51^oC-decomposition, Lit[33] 50-52^oC-decomposition). The other spectral data (Table 2.4.2, **2d**) and specific rotation value were in close agreement with the reported values.

2-Bromo-1-hydroxy-*p*-menth-3-one (Table 2.4.1, **2e**) was prepared similarly by reaction of piperitone (**1e**) with NBS in aqueous acetone. Usual workup followed by silica gel column chromatography afforded white crystalline solid. Here again it was observed that the product was labile and prone to decomposition. This product was further purified by crystallization in 1:1 mixture of ether and petroleum ether (40-60^{o}C). It had the following spectral characteristics (Table 2.4.2, **2e**). The broad and sharp IR absorptions at 3425 and 1719 cm^{-1} respectively indicated the presence of both hydroxyl and carbonyls. Mass spectrum showed M^{+} and $[M+2]^{+}$ at 248 and 250 indicating the presence of a bromine and also provided the molecular weight of the compound. Presence of singlet at 4.83 ppm in its PMR spectrum indicated the proton attached to carbon containing bromine atom. From the above spectral evidence, this product was identified as *trans*-2-bromo-1-hydroxy-*p*-menth-3-one.

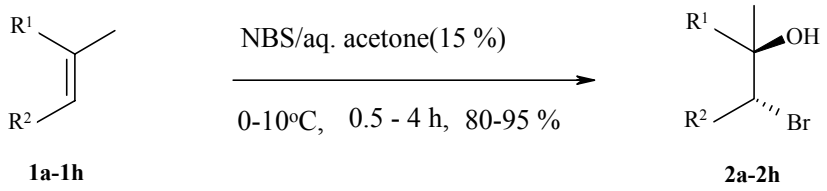
2-Bromo-1,8-dihydroxy-*p*-menthane (Table 2.4.1, **2f**) was prepared by reaction of the *p*-menth-1-en-8-ol (*α*-Terpineol, **1f**) with NBS in aqueous acetone. *α*-Terpineol was obtained from *α*-terpinyl chloride by its reaction with ZnO in aqueous acetone.[30] Usual workup followed by silica column chromatography and recrystalization from mixture of 1:1 ether and petroleum ether (40-60^{o}C) afforded the product, which was characterized by the following spectral data (Table 2.4.2, **2f**). IR broad absorption at 3458 cm^{-1} and C-1 methyl at 1.13 ppm on PMR indicated the tertiary nature of this carbon atom. Singlet at 0.90 ppm for six protons indicated the hydroxyl at the C-8 has not been affected. Mass spectrum indicated the M^{+} and $[M+2]^{+}$ are in 1:1 ratio at 250 and 252 confirmed the presence of bromine atom and molecular weight of the product. A broad singlet at 4.06 ppm indicated the presence single proton attached to carbon containing bromine atom. The product could thus be identified as *trans*-2-bromo-1,8-dihydroxy-*p*-menthane.

2-Bromo-1-phenylethanol and 1-bromo-2-phenyl-propan-2-ol (Table 2.4.1, **2g** & **2h**) were prepared in similar manner starting from styrene and *α*-methylstyrene (**1g** & **1h**) and the products were characterized based on their spectral data (Table 2.4.2, **2g** & **2h**). Spectral data of product **2g** is in close agreement with the reported data.[34] Product **2h** showed broad IR absorption at 3451 cm^{-1} indicating the presence of hydroxyl group. In its PMR spectrum

presence of singlet at 1.70 ppm for three protons indicating the methyl group attached to carbon containing the hydroxyl group. The presence of hydroxyl was further confirmed by the peak at 3.0 ppm for single proton. Also, the presence of peak at 3.70 ppm for two protons confirmed that these are attached to carbon containing bromine atom. The aromatic protons integrating for five protons appeared at 7.36-7.63 ppm. The mass spectrum of the product showed M^+ and $[M+2]^+$ peaks in 1:1 ratio at 214 and 216 indicating the presence of a bromine atom and also contained the characteristic benzylic fragments (105, 91, 77, 65, 43). From the spectral evidence, the product **2h** was identified as 1-bromo-2-phenyl-propan-2-ol. Similarly 2′,4′-dimethyl styrene bromohydrin was prepared by reaction of 2′,4′-dimethylstyrene with NBS in aqueous acetone. It was recrystallized from a 1:1 mixture of ether: petroleum ether (40-60^{o}C). It was characterized based on the IR, PMR, and mass spectral data.

Thus, the bromohydrins prepared in the present work were obtained in excellent yields from the respective olefins wherein the reaction conditions were optimized and better isolation and procedures adopted. The products are characterized by their IR, PMR, and mass spectral data. These bromohydrins were utilized for the synthetic work described in Chapter 2 (Sections 2.1 and 2.2) and Chapter 3 (Section 3.2).

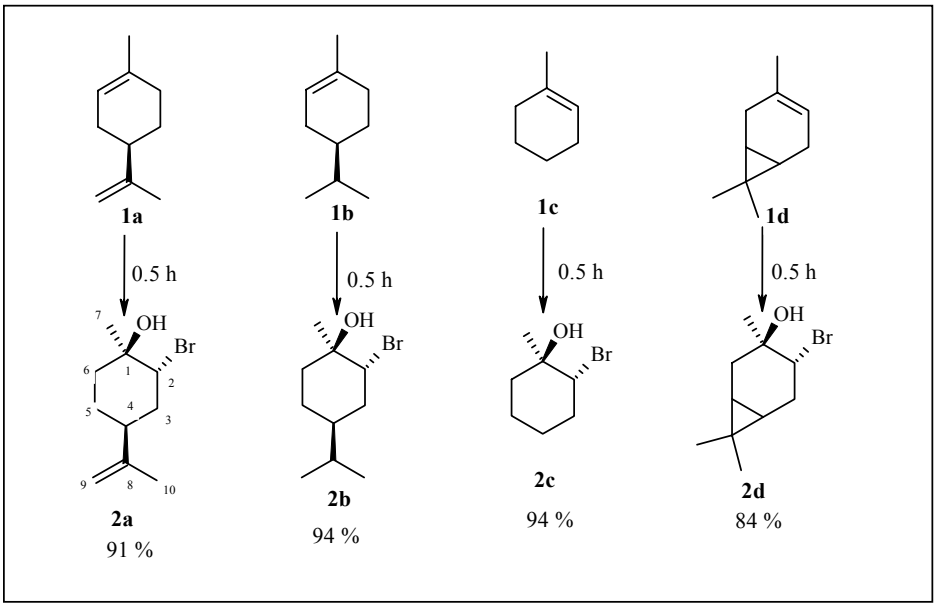
Table 2.4.1: Reaction of olefins with NBS in 15 % aqueous acetone at 0-10°C



1a-1h **2a-2h**

R^1 = H or part of cycloalkyl or aryl

R^2 = part of cycloalkyl or alkyl



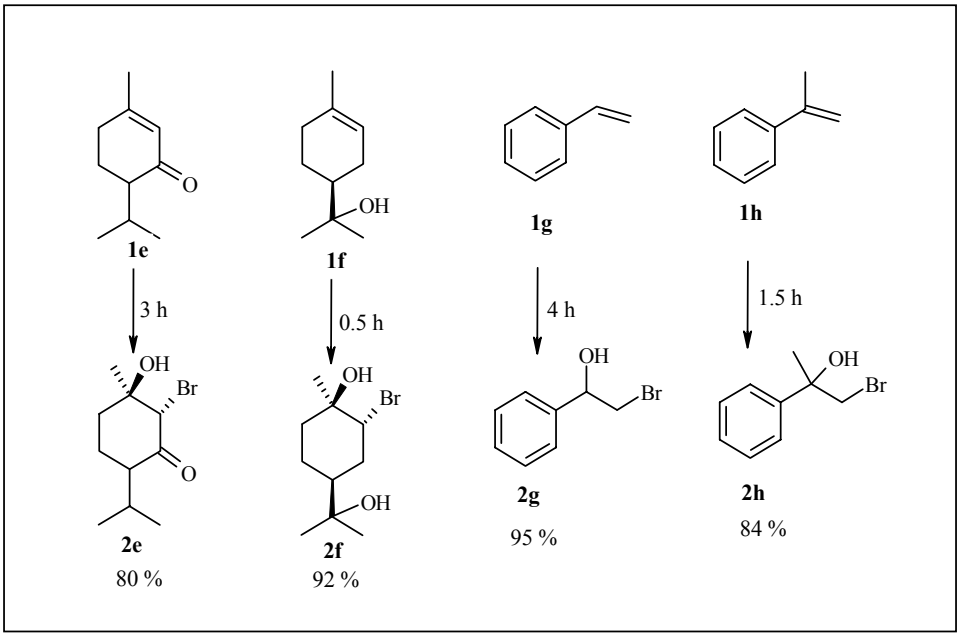


Table 2.4.2: PMR, mass and IR data of bromohydrins

Bromo-hydrin	PMR δ ($CDCl_3$, TMS)	Mass (m/z)	IR (γ cm^{-1})
2a	1.16(s, 3H), 1.46-1.66 and 1.83-2.43(m, 8H), 1.76(s, 3H), 4.16(br, 1H), 4.80(s, 2H)	234(0.2), 232(0.2), 216(1), 214(1), 152(8), 135(16), 93 (27), 91(20), 67(43), 43(100)	3428(br), 3082, 2938
2b	0.80(d, *J* = 3 Hz, 6 H), 1.26(s, 3H), 1.50-1.80(m, 6H), 1.96-2.13(m, 3H), 4.13(br, 1H)	236(0.5), 234(0.5), 221(1), 219(1), 203(1), 201(1), 176(43), 174(20), 155(4), 138(14), 121(4), 95(6), 71(100), 67(30), 55(20), 43(70)	3419(br), 2957, 2873
2c	1.33(s, 3H), 1.53-2.50(m, 8H), 2.93(s, 1H), 4.30(dd, *J* = 3 Hz, 1H)	194(1), 192(1), 179(2), 177(2), 161(1), 151(2), 149(3), 113(15), 97(4), 95(22), 81(2), 71(65), 58(18), 43(100)	3418(br), 2939, 2864,
2d	0.60-0.70(m, 2H), 0.89 and 0.99 (s, 6H), 1.16(s, 3H), 1.90-2.23(m, 4H), 2.30(s, 1H), 3.80(t, 1H, *J* = 9 Hz)	234(0.5), 232(0.5), 219(1), 217(1), 192(1), 174(1), 153(3), 151(1), 138(5), 135(15), 119(4), 109(5), 93(20), 71(15), 67(20), 55(10), 43(100)	3446(br), 2938, 2867
2e	1.09(d, 6 H, *J* = 4.5 Hz,), 1.20(s, 3H), 2.10-2.50(m. 6H) 2.70(s, 1H), 4.83(s, 1H)	250(0.5), 248(0.5), 235(2), 233(2), 217(2), 215(2), 204(2), 190(4), 188(3), 169(10), 160(3), 152(2), 109(28), 87(70), 69(75), 55(50), 43(100)	3425(br), 2965, 2873, 1719
2f	0.90(s, 6H), 1.13(s, 3H), 1.30-2.0(m, 7H), 2.96(s, 1H), 3.63(s, 1H), 4.06(br, 1H	252 (0.5), 250(0.5), 234(1), 232(1), 219(3), 217(3), 176(2), 174(2), 153 (3), 138(5), 111(5), 108(10), 95(70), 71(40), 59(90), 43(100)	3458(br), 2940, 2867
2g	2.64(d, J = 3 Hz, 1H), 3.58(d, J = 3 Hz, 2H), 4.93(m, 1H), 7.36-7.63(m, 5H)	202(6), 200(6), 184(2), 182(2), 120(5), 107(100), 91(10), 80(5), 79(50), 51(10)	3450, 2968, 2865
2h	1.70(s, 3H), 3.0(s, 1H), 3.70(s, 2H), 7.36-7.63(m, 5H)	216(1), 214(1), 199(1.5), 201(1.5), 121(55), 105(10), 91(10), 77(15), 65(8), 43(100)	3451(br), 3060, 1679

Experimental

1. Purification of NBS

NBS (E-Merck India) was purified by crystallization before use in the reaction. NBS (200 g) was suspended in distilled water (2 l) and heated to boiling, when a clear brown colored solution was obtained it was allowed to cool to room temperature. The colorless crystalline solid was then filtered using suction and washed with hot water (100 ml x 2). This product was then dried in a desiccator over anhydrous P_2O_5 for 12 h. White crystalline NBS (150 g, 75 % yield, m. p. 171^oC, decomp. Lit[31] 173^oC, decomposition) so obtained was used in the preparation of bromohydrins.

2. Fractionation of limonene

R-(+)-Limonene was isolated from orange peel oil; Source - Nagpur Orange Growers Association (NOGA). It was chromatographed over silica gel to remove the oxygenated terpenes. The hydrocarbon portion was then fractionated under reduced pressure to afford (+)-limonene (b. p. 55^oC/1 Torr, $[\alpha]_D^{20} = +126^o$, >98 %).

3. Reaction of *R*-(+)-limonene with NBS in aqueous acetone

R-(+)-Limonene (50 mmol, 6.80 g) in 60 ml of aqueous acetone (15 %) was taken in 250 ml round-bottomed flask and it was cooled to 0^oC. NBS (50 mmol, 8.95 g) was slowly added over 10 min. The temperature of flask was allowed to rise to 10^oC and stirring was continued. The reaction was monitored for the disappearance of limonene on TLC (hexane) and GC. At the end of the reaction (0.5 h), acetone was removed by flash evaporation. To the residue, water (200 ml) was added and the contents transferred to a separatory funnel. The product was extracted into CH_2Cl_2 (25 ml x 3) and the combined organic layer was passed through a bed of anhydrous Na_2SO_4. Solvent was evaporated to afford a crude product (11.5 g), which was then chromatographed over SiO_2 using 2 % EtOAc in hexane. Pure limonene bromohydrin thus obtained, was further purified by distillation under reduced pressure.

Yield: 10.60 g, 91 % (purity 98 %, GC), b. p. 88^oC/ 0.4 Torr, Lit[7b] 95^oC/1 Torr, $[\alpha]_D^{20} = +59^o$ (neat).

IR (γ cm^{-1}) = 3428(br), 3082, 2938.

PMR: δ = 1.16(s, 3H), 1.46-1.66 and 1.83-2.43(m, 8H), 1.76(s, 3H), 4.16(br, 1H), 4.80(s, 2H).

MS (*m/z*): 234(0.2), 232(0.2), 216(1), 214(1), 152(8), 135(16), 93 (27), 91(20), 67(43), 43(100).

4. Hydrogenation of *R*-(+)-limonene to *R*-(+)-*p*-menth-1-ene

Limonene (50 g) was taken in a hydrogenation flask with 200 ml of ethanol. Raney nickel (5.0 g) was added and the flask was pressurized to 2 atm in a hydrogenator and the contents were shaken with periodic replenishment of hydrogen as it was consumed. The reaction was monitored by NMR for the disappearance of the peak at 4.76 δ in the spectrum. After complete hydrogenation (4 h) of the double bond, the contents were filtered and washed with ethanol (50 ml) and transferred to a separatory funnel. The upper layer which contained essentially *R*-(+)-*p*-menth-1-ene (49 g) was separated, dried over anhydrous Na_2SO_4 and distilled under reduced pressure.

Yield: 96 % (purity >99 %) b. p.50-51^oC/2 Torr, $[\alpha]_D^{20}$ = +101.5^o(neat), Lit^{29} +96^o.

PMR: δ = 0.80(d, J = 3 Hz, 6H), 1.16(s, 3H), 1.46-1.66 and 1.83-2.13(m, 8H), 5.26(br, 1H).

5. Reaction of *R*-(+)-*p*-menth-1-ene with NBS in aqueous acetone

A solution of *R*-(+)-*p*-menth-1-ene (6.90 g, 50 mmol) in 60 ml of 15 % aqueous acetone was taken in a round-bottomed flask and cooled to 0^oC. NBS (8.95 g, 50 mmol) was added to it gradually over 10 min. The progress of the reaction was monitored by GC for the disappearance of the olefin. After completion of the reaction (0.5 h), acetone was flash evaporated and to the residue, water (200 ml) was added. The product was extracted into CH_2Cl_2 (25 ml x 3), combined organic layer washed and dried over anhydrous Na_2SO_4 and solvent evaporated. The crude product, thus obtained, was chromatographed over SiO_2. The fraction obtained with 2 % EtOAc in hexane (11.2 g) was further purified by distillation under reduced pressure.

Yield: 10.95 g, 94 %, b. p. 92-94 /0.8 Torr, $[\alpha]_D^{20}$ = +62^o (neat).

IR (γ cm^{-1}) = 3419(br), 2957, 2873.

PMR: δ = 0.80(d, *J* = 3 Hz, 6 H), 1.26(s, 3H), 1.50-1.80(m, 6H), 1.96-2.13(m, 3H), 4.13(br, 1H).

MS (*m/z*): 236(0.5), 234(0.5), 221(1), 219(1), 203(1), 201(1), 176(43), 174(20), 155(4), 138(14), 121(4), 95(6), 71(100), 67(30), 55(20), 43(70).

6. Preparation of 1-methylcyclohexanol from cyclohexanone by Grignard reaction

Magnesium turnings (2.75 g, 0.11 mol) were taken in dry ether (5 ml) in A 250 ml three-necked round-bottomed flask and a crystal of iodine was added. Reaction started immediately and violet color disappeared and the solution turned cloudy. Dry ether (50 ml) was added followed by slow addition of a solution of methyl iodide (14.2 g, 0.1 mol) in ether (50 ml). When all the magnesium was consumed, a solution of cyclohexanone (9.8 g, 0.1 mol) in ether (25 ml) was added gradually keeping the temperature below 15^{o}C. As the reaction mass solidified, the temperature was slowly raised to 25^{o}C and the resultant solution was stirred for 1 h. The worked up aliquot of the reaction mixture showed the completion of the reaction by GC. Reaction mixture was worked by adding 5 % HCl (50 ml) and the separation of the organic. Aqueous layer was further extracted with ether (15 ml x 2) and the combined organic layer was washed free of acid and was dried over anhydrous Na_2SO_4. Distillation of the product afforded the 1-methylcyclohexanol (10 g, 88 %).

Yield: 10 g, 88 %.

IR (γ cm^{-1}) = 3317(br), 2873.

PMR: δ = 1.06(s, 3H), 1.26-2.20(m, 10H), 2.43(s, 1H).

7. Dehydration of 1-methylcyclohexanol to 1-methylcyclohexene

1-Methylcyclohexanol (10 g) was taken along with 1 g of H_3PO_4 (85 %) in a 50 ml round-bottomed flask. The contents were refluxed for the 0.5 h. Downward distillation of the product afforded a fraction distilling in the range of 106-109^{o}C. The fraction was redistilled to get pure 1-methylcyclohexene (6 g, b. p. 106-108^{o}C), Lit[32] 108-110^{o}C.

8. Reaction of 1-methylcyclohexene with NBS

1-Methylcyclohexene (4.80 g, 50 mmol) was taken in 250 ml round-bottomed flask along with 60 ml of 15 % aqueous acetone and cooled to 0^{o}C. NBS (8.95 g, 50 mmol) was added slowly to it over 10 min. Progress of the reaction was monitored by GC. After completion of the reaction (0.5 h), acetone was removed by flash evaporation and water (200 ml) was added to the residue followed by extraction of the product into CH_2Cl_2 (25 ml

x 3). It was dried over anhydrous Na_2SO_4. Flash evaporation of solvent afforded crude product (10 g). This was purified by column chromatography over SiO_2 using 2 % EtOAc in hexane. The compound was further purified by distillation under reduced pressure (9.07 g).

Yield: 9.07 g, 94%, b. p. 58-60°C/0.6 Torr, $[\alpha]_D^{20} = +6^o$ (*c*=2, $CHCl_3$).

IR (γ cm^{-1}) = 3418(br), 2939, 2864.

PMR: δ = 1.33(s, 3H), 1.53-2.50(m, 8H), 2.93(s, 1H), 4.30(dd, *J* = 3 Hz, 1H).

MS (*m/z*): 194(1), 192(1), 179(2), 177(2), 161(1), 151(2), 149(3), 113(15), 97(4), 95(22), 81(2), 71(65), 58(18), 43(100).

9. Fractionation of Δ^3-carene

Δ^3-Carene obtained from pine oil was fractionated using Vigruex column to get a pure compound. The fraction that boiled at constant boiling range of 68-70°C/9 Torr was cut and separated. The physical and spectral data of this compound were in good agreement with reported values. b. p. 68-70°C/9 Torr, lit[35] 170°C, $[\alpha]_D^{20} = +11.7^o$ (neat).

10. Reaction of Δ^3-carene with NBS

Δ^3-Carene (6.80 g, 50 mmol) was taken with 60 ml of 15 % aqueous acetone in a 250 ml flask. It was cooled to 0°C and NBS (8.95 g, 50 mmol) was added slowly over 10 min. Progress of the reaction was monitored by GC and after completion of the reaction (0.5 h), acetone was removed by flash evaporation. The residue was taken in water (200 ml) and extracted with CH_2Cl_2 (25 ml x 3) and the combined organic layer dried over Na_2SO_4. Evaporation of the solvent afforded a crude product (10.50 g), which was chromatographed over SiO_2 to give a white crystalline solid. This product was further purified by recrystalization from a 1:1 mixture of ether and petroleum ether (40-60°C).

Yield: 9.78 g, 84 %, m. p. 49-51°C (decomp), $[\alpha]_D^{20} = -55^o$ (*c* = 2, $CHCl_3$), Lit[33] m. p. 50-52°C, $[\alpha]_D^{20} = -55^o$ (*c*=2, CCl_4).

IR (γ cm^{-1}) = 3446(br), 2938, 2867.

PMR: δ = 0.60-0.70(m, 2H), 0.89 and 0.99 (s, 6H), 1.16(s, 3H), 1.90-2.23(m, 4H), 2.30(s, 1H), 3.80(t, 1H, *J* = 9 Hz).

MS (*m/z*): 234(0.5), 232(0.5), 219(1), 217(1), 192(1), 174(1), 153(3), 151(1), 138(5), 135(15), 119(4), 109(5), 93(20), 71(15), 67(20), 55(10), 43(100).

11. Reaction of piperitone with NBS

(+)-Piperitone (7.65 g, 50 mmol) was taken with 60 ml of 15 % aqueous acetone in a 250 ml flask. It was cooled to 0^{o}C and NBS (8.95 g, 50 mmol) was added slowly over 10 min. Progress of the reaction was monitored by GC. The temperature was raised to 25^{o}C and the mixture stirred until the completion of the reaction (3 h). Acetone was removed by flash evaporation. The residue was taken in 200 ml of water and extracted with CH_2Cl_2 (25 ml x 3) and the combined organic layer was dried over Na_2SO_4. Evaporation of the solvent afforded a crude product (10.40 g), which was chromatographed over SiO_2 to give a white crystalline solid. This product was further purified by recrystalization from a 1:1 mixture of ether and petroleum ether (40-60^{o}C).

Yield: 9.96 g, 80 %, m. p. 92-94^{o}C, $[\alpha]_D^{20}$ = + 15.15^{o} (*c*=2, $CHCl_3$).

IR (γ cm^{-1}) = 3425(br), 2965, 2873, 1719.

PMR: δ = 1.09(d, 6 H, *J* = 4.5 Hz,), 1.20(s, 3H), 2.10-2.50(m. 6H) 2.70(s, 1H), 4.83(s, 1H).

MS (*m/z*): 250(0.5), 248(0.5), 235(2), 233(2), 217(2), 215(2), 204(2), 190(4), 188(3), 169(10), 160(3), 152(2), 109(28), 87(70), 69(75), 55(50), 43(100).

12. Reaction of *α*-terpineol with NBS

α-Terpineol (7.70 g, 50 mmol) was taken in 250 ml round-bottomed flask with 60 ml of 15 % aqueous acetone and cooled to 0^{o}C. NBS (8.95 g, 50 mmol) was added slowly to it over 10 minutes. Progress of the reaction was monitored by GC. After completion of the reaction (0.5 h), acetone was removed by flash evaporation and water (200 ml) was added to the residue followed by extraction of the product into CH_2Cl_2 (25 ml x 3). It was dried over anhydrous Na_2SO_4. Flash evaporation of solvent afforded crude product (12 g)). Evaporation of solvent afforded a crude product (12 g), which was chromatographed over SiO_2. The resultant white crystalline solid was further purified by recrystallization from a 1:1 mixture of ether and petroleum ether (40-60^{o}C).

Yield: 11.56 g, 92 % m. p. 111-113^{o}C, $[\alpha]_D^{20}$ = -57^{o} (*c*=2, $CHCl_3$).

IR (γ cm^{-1}) = 3458(br), 2940, 2867.

PMR δ = 0.90(s, 6H), 1.13(s, 3H), 1.30-2.0(m, 7H), 2.96(s, 1H), 3.63(s, 1H), 4.06(br, 1H).

MS (*m/z*): 252 (0.5), 250(0.5), 234(1), 232(1), 219(3), 217(3), 176(2), 174(2), 153 (3), 138(5), 111(5), 108(10), 95(70), 71(40), 59(90), 43(100).

13. Reaction of styrene with NBS

Styrene (5.20 g, 50 mmol) was taken in a 250 ml round-bottomed flask along with 60 ml of 15 % aqueous acetone and cooled to 0^{o}C. NBS (8.95 g, 50 mmol) was added slowly to it over 10 minutes. Progress of the reaction was monitored by GC. The temperature was raised to 25^{o}C and stirred till the completion of the reaction (4 h). After completion of the reaction acetone was removed by flash evaporation and water 200 ml was added to the residue followed by extraction of the product into CH_2Cl_2 (25 ml x 3) and drying over anhydrous Na_2SO_4. Flash evaporation of the solvent afforded a crude product (10.5 g). This was purified by column chromatography over SiO_2 using 2 % EtOAc in hexane followed by distillation under reduced pressure.

Yield: 9.97 g, 95 %, b. p. 106-107^{o}C/1.7 Torr, $[\alpha]_D^{20}$ = -29^{o} (*c*=2, $CHCl_3$), Lit[34] $[\alpha]_D^{20}$ = -29 ^{o} (*c*=2, $CHCl_3$).

IR (γ cm^{-1}) = 3395, 2968, 2865.

PMR: δ = 2.64(d, *J* = 3 Hz, 1H), 3.58(d, *J* = 3 Hz, 2H), 4.93(m, 1H), 7.36-7.63(m, 5H).

MS (*m/z*): 202(6), 200(6), 184(2), 182(2), 120(5), 107(100), 91(10), 80(5), 79(50), 51(10).

14. Reaction of α-methylstyrene with NBS

α-Methylstyrene (5.9 g, 50 mmol) was taken in a 250 ml round-bottomed flask along with 60 ml of 15 % aqueous acetone and cooled to 0^{o}C. NBS (8.95 g, 50 mmol) was added slowly to it over 10 minutes. Progress of the reaction was monitored by GC. After completion of the reaction (1.5 h), acetone was removed by flash evaporation and water (200 ml) was added to the residue followed by extraction of the product into CH_2Cl_2 (25 ml x 3 and drying over anhydrous Na_2SO_4. Flash evaporation of solvent afforded crude product (9.5 g). This was purified by column chromatography over SiO_2 using 2 % EtOAc in hexane followed by distillation under reduced pressure.

Yield: 9.02 g, 85 %, b. p. 88-90^{o}C/1 Torr.

IR (γ cm^{-1}) = 3451(br), 3060, 1679.

PMR: δ = 1.70(s, 3H), 3.0(s, 1H), 3.70(s, 2H), 7.36-7.63(m, 5H).

MS (*m/z*): 216(1), 214(1), 199(1.5), 201(1.5), 121(55), 105(10), 91(10), 77(15), 65(8), 43(100).

15. Reaction of 2′,4′-dimethylstyrene with NBS

2′,4′-Dimethylstyrene (6.60 g, 50 mmol) was taken in a 250 ml round-bottomed flask along with 60 ml of 15 % aqueous acetone and cooled to 0^{o}C. NBS (8.95 g, 50 mmol) was added slowly to it over 10 minutes. Progress of the reaction was monitored by GC. After completion of the reaction (1 h), acetone was removed by flash evaporation and water (200 ml) was added to the residue followed by extraction of the product into CH_2Cl_2 (25 ml x 3) and drying over anhydrous Na_2SO_4. Flash evaporation of solvent afforded crude product. This was purified by column chromatography over SiO_2 using 2 % EtOAc in hexane followed by recrystalization from 1:1 mixture of ether and petroleum ether.

Yield: 10.0 g, 87 %, m. p. 43-44^{o}C.

IR (γ cm^{-1}) = 3455(br), 3068, 1659.

PMR: δ = 2.33 (s, 6H), 2.66(br, 1H), 3.56(d, J = 3 Hz, 2H), 4.95(m, 1H), 7.33-7.53(m, 3H).

MS (*m/z*): 230(4), 228(4), 149(4), 147 (4), 135(100), 119(10), 107(30), 91(25), 77(15), 65(8), 51(7).

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CHAPTER – 3

PHOTOCHEMICAL STUDIES ON EPOXIDES AND BROMOHYDRINS

Section 3.1: Photo-assisted Kinetic Resolution of Monoterpene Epoxides

Section 3.2: Light-induced Direct Conversion of Styrene Bromohydrins to Benzoic Acid Esters

Section 3.1: Photo-Assisted Kinetic Resolution of Monoterpene Epoxides

Monocyclic Monoterpene Epoxides: Synthesis, Reactions and Kinetic Resolution

Monoterpenes are widely distributed in nature and as constituents of essential oils of higher plants in particular. Epoxy-terpenes often serve as starting materials for the synthesis of the fragrances, flavors, herbicides, fungicides and biologically active and therapeutically useful substances[1] and enantiopure epoxy-terpenes are valuable building blocks in the synthesis of natural products.[2] Cyclohexyl-based chiral auxiliaries have been shown to be highly effective at affording high diastereofacial selectivity in various reduction and *C*-*C* bond forming reactions.[3] Enantiomerically pure epoxides are synthetically useful for the construction of many chiral products.[2a,4] Limonene-1,2-oxide, which occur naturally in the essential oils of *Cymbopogon densiflorus* is a typical representative of monocyclic cyclohexene epoxides.[5] The present discussion is confined to commercially important limonene-1,2-oxide and its congener carvomenthene-1,2-oxide.

Synthesis

(+)-(*4R*)-Limonene 1,2-oxide can be synthesized commercially from the abundantly available natural (+)-(*4R)*-limonene by epoxidation with a peracid like *m*-chloroperbezoic acid (97 %).[6] Also, epoxidation can be effected with hydrogen peroxide-phosphorus-tungsten phase transfer system.[7] Usually, epoxidation of enantiomerically pure limonene results in the formation 1:1 mixture of *cis* and *trans*-limonene oxide. The diastereomeric *cis*- and *trans*- mixture of limonene oxide is not easily separable.[8]

The carvomenthene oxide, a congener of the limonene oxide, can be easily prepared from limonene,[9] by its partial hydrogenation followed by the usual epoxidation with a peracid. This product is also a mixture of diastereomeric *cis*- and *trans*-oxide in ~1:1 ratio. It has also been synthesized from limonene bromohydrin[10] as well as from the hydrogenation of the limonene oxide using Raney nickel catalyst.[11]

Reactions

The inherent stereochemistry associated with limonene and carvomenthene 1,2-oxides renders them very useful chiral synthons. Leffingwell's work on acid and base catalyzed reactions of these epoxides[5,12a] has helped in the confirmation of their

configuration. Studies on the reactions of epoxides derived cyclohexene and its derivatives with a number of nucleophilic and electrophilic reagents have shown that they proceed in accordance with the Fürst-Plattner rule.[12b] According to this rule the 4-alkyl substituents determine the conformation in which the *cis*- and *trans*-1,4-substituted cyclohexene-1,2-epoxides react with acidic reagents. Extensive work on the production of diols and related derivatives of epoxides for their structural confirmation is reported. Singaram *et al*.[13] have reported the preparation of *β*-amino alcohols from isomeric limonene epoxides. Here, only *trans*-oxide reacts with amine, offering the kinetic resolution of the *cis*-oxide. These amino alcohols are evaluated as effective catalysts for the enantioselective addition of dialkylzinc to benzaldehyde. Cyclohexyl-based chiral auxiliaries have been synthesized conveniently from limonene oxide.[2a]

Kinetic Resolution

Limonene and carvomenthene oxides are inexpensive chiral building blocks for the synthesis of natural products. Commercially made epoxides are usually a ~1:1 mixture of *cis*- and *trans*-diastereomers. The *cis*- and *trans*- refer to the stereoorientation of the alkyl substituents in the 1 and 4 position of *p*-menthane skeleton. The *cis*- and *trans*- oxides of limonene and carvomenthene are shown in the Scheme 3.1. The separation of these by simple fractional distillation is not efficient and preparation of pure isomers by chemical means involves a number of steps.[5] On the other hand, kinetic resolution process wherein one of the isomers is used up in a reaction, leaving behind the other unreacted obtained in good yield is often employed. In literature, a number of reports are available which make use of difference in the reactivity of either of these isomers towards different reagents. Enzymatic kinetic resolution of the mixtures of *cis*- and *trans*-(+)-limonene-1,2 oxide and (-)-carveol has been reported.[14a] Recently a review on the dynamic kinetic resolution has been reported.[14b]

Hydrolytic kinetic resolution (HKR) is easy and inexpensive. It involves only water as the reagent and low loading of recyclable catalyst provides a useful tool for the resolution of terminal epoxides. The catalysts employed usually are ‘salen’ complexes of transition metals like cobalt and chromium, which promote highly enatioselective reactions of

nucleophiles with diastereomeric epoxides.[15,16] In the application of this method to monocyclic terpene epoxides containing C-4 substituents, even racemic chromium salen complex has been found to effect kinetic resolution.[17] Diastereoselective ring opening of limonene oxide with water by the molybdenum camphor complex offers kinetic separation of the *trans*-isomer along with the *trans*-diaxial diol from the *cis*-isomer.[18] In another report, mercury (II) ion mediated addition of water to diastereomeric (*4S*)-limonene oxide offers separation of *trans*-oxide, while *cis*-oxide complexes preferentially with the metal ions and opens up easily in the presence of water; subsequent demetalation affords the diol.[19]

Photochemistry of Epoxides

Photolysis of ethers and epoxides in vapor phase uv radiation < 200 nm [20] and in solution with uv radiation > 200 nm[21] have been reported. Irradiation of epoxides with uv radiation of 253 nm leads to the carbon-oxygen bond cleavage. In case of unsymmetrical epoxides, carbon-oxygen bond cleaves in either way to yield the products from both the intermediates. Thus, a mixture of alcohols, ketones, and dimerized products are expected from these intermediates. Also irradiation of cyclic ethers in the presence of ketone sensitizers like acetone and bezophenone and the subsequent alcohol radical addition leads to the formation of carbinols.[22] In case of epoxides having the α-carbonyl group the photolysis is fast, because of the energy transfer through the carbonyl group assisting the ring opening of epoxide to yield unsaturated hydroxy ketone and saturated diketone. The product diketone is obtained by the result of the free radical rearrangement *via* the alkyl shift. The migration of alkyl is observed but not of the phenyl group.[23] Free radical reactions of epoxides involve four different types of chain initiation steps which are depicted in Scheme 3.2. Once these intermediates are formed, they can undergo a variety of reactions to yield various products.

Cleavage of Epoxides: Stereo- and Regioselectivity

Epoxides undergo variety of reactions, which lead to formation of various stereo- and regioselective products.[24] Mineral acids catalyze the cleavage of epoxides, mainly leading to the *trans*- product and also some rearrangement products due to carbocation intermediate. Organic acids add on to epoxides leading to *trans*-1,2-hydroxy acylates.[25] The

use of an alkali salt of the acid as catalyst enhances the reaction rate twenty fold. Epoxides also open up in the presence of bases, under forced conditions, leading to the formation of allylic alcohol and a carbonyl product as primary products.[25] Isomerization of epoxides to allylic alcohols is usually carried out in the presence of strong non-nucleophilic bases like lithium dialkyl amides.[26] Thermal reactions of epoxides generally afford allylic alcohols and carbonyl compounds, besides other rearrangement products.[27]

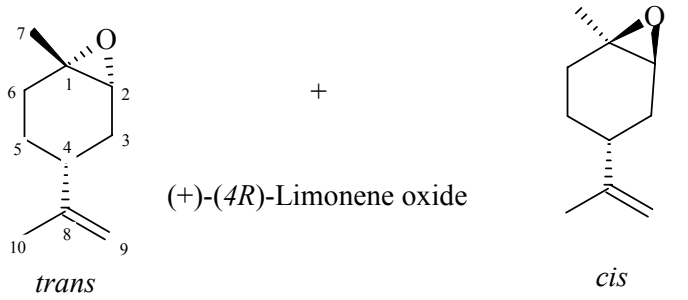
In recent times, extensive work on the search for relatively mild and neutral catalysts for the opening of epoxides particularly with hetero-atomic nucleophiles such as alcohols, thiols, and amines has been carried out, with special emphasis on chemo-, regio-, and stereoselectivities. Among the promoters that have been developed, neutral alumina,[28a] organotin phosphate condensate,[28b,c] and Nafion–H[28d] appear to be versatile. But they are not being used widely as they require large amount of promoters to attain high yield. DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) and CAN (ceric ammonium nitrate) catalyzed ring opening of epoxides with various alcohols, thiols, and acetic acid is reported.[29] A π-acid, one electron acceptor like tetracyanoethylene (TCNE) and π-acid having captodative olefin structure, *viz* dicyanoketene dimethyl acetal, have been developed as mild chemoselective and stereospecific catalysts for alcoholysis of epoxides.[30] In the presence of these catalysts and various alcohols, a trisubstituted epoxide opens up regioselectively to give a secondary alcoholic tertiary ether as the prime product. This result is similar to the acid-catalyzed opening of epoxides.

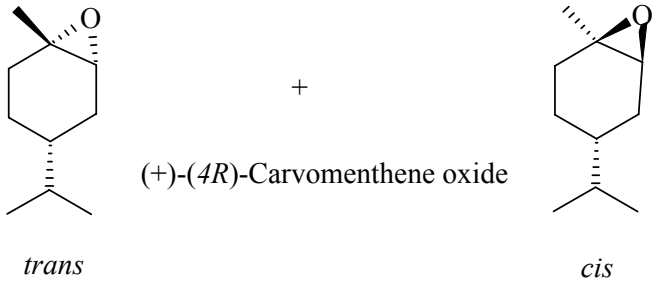
Alcoholysis of epoxides to give *β*-alkoxy alcohols in regio- and stereoselective manner is a useful synthetic methodology as these intermediates can be easily oxidized to *α*-alkoxy ketones or to *α*-alkoxy acids. Metal salts promote the alcoholysis of aliphatic and aromatic epoxides in stereo- and regioselective manner to give *β*-alkoxy alcohols as the prime products.[31] While magnesium perchlorate promotes the reaction most efficiently, $LiClO_4$, $NaClO_4$, $CaCl_2$ and $Zn(OSO_2CF3)_2$ can also be used to give high yield of products under mild conditions. Ytterbium triflate is an efficient, reusable catalyst for the alcoholysis of epoxides with various alcohols (1^o, 2^o, 3^o, C_1-C_4, cyclohexyl, allyl, and propargylic) to give regio- and stereo-selective *β*-alkoxy alcohols.[32]

Photochemical approach to the epoxide ring opening is another attractive strategy for the alcoholysis of the epoxides.[23] Compared to the acid and base-catalyzed ring opening of epoxides, photochemical method appears to be advantageous since these are run under comparatively neutral conditions and the products are highly regiospecific. In recent studies, it has been postulated that the endocyclic epoxides are solvated in the presence of methanol and ethanol due to intrinsic acidity of these alcohols as well as acidity developed during irradiation.[33] This could, in fact, arise not by photolysis, but by thermal process. However, the photochemical alcoholysis of epoxides in the presence of the isopropanol leads to formation of photoreduction along with the solvolysis products.[34a] These competing photoreduction and photosolvolysis reactions are influenced by the nature of the epoxides.[34b] Generally, the unsubstituted epoxides preferentially undergo photoreduction while those bearing substituents follow photosolvolysis. A high regio-selective reduction of epoxides by photochemical electron transfer with the triethylamine and $NaBH_4$ leads to formation of lesser substituted corresponding alcohol (*anti*-Morkovnokov product) in quantitative yield.[35] The photochemical ionic addition of alcohols to epoxides has been claimed advantageous as compared to acid catalysis brought about by air oxidation of the solvent.[36] Metal ion catalyzed ionic photo-addition of methanol to 1-methyl-1,2-epoxyethylcinnamate has been found to be stereo-differentiating.[37] While the *Z*-isomer reacts with EDTA purified methanol in the dark in presence of the $FeCl_3$, the *E*-isomer is inert, but when irradiated in the presence of the $FeCl_3$ it yields 10 % of the methanolysis product. On the other hand, both the *E*-and *Z*-isomers of the epoxide undergo alcoholysis when irradiated in the presence of the Fe_2O_3. This is contrary to the claims,[33] that the methanolysis of epoxide occurs even in dark, and in the absence of catalyst. Thus, metal ion Fe(III) complexes are shown to undergo charge transfer to Fe(II) ion under irradiation process and give radical-cation of the epoxide, to which methanol adds subsequently.

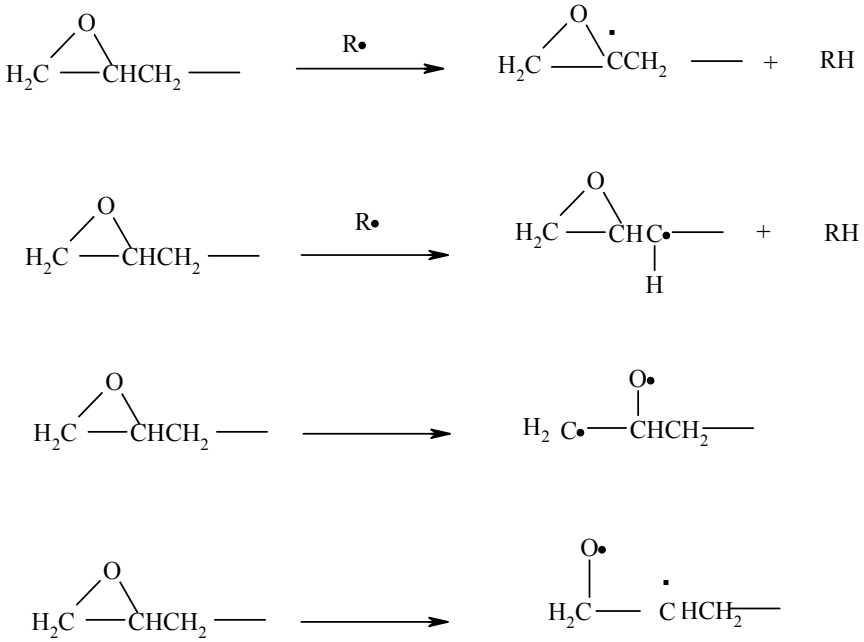
It is obvious that there is scope for the development of kinetic resolution of epoxides of terpene origin. This is very much useful in case of limonene and carvomenthene oxides as they are important chiral building blocks. The methods reported hitherto for such separations, employ expensive catalysts or high temperatures or both. In order to develop a

mild and efficient method of resolution, a detailed study was undertaken on the light-induced alcoholysis of epoxides of limonene and carvomenthene in the presence of Lewis acid catalysts.





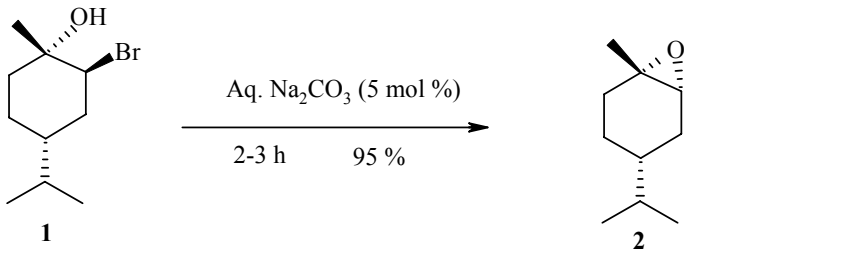
Scheme 3.1



Scheme 3.2

Present Work

Initially an exploratory study was carried out using carvomenthene oxide, which was prepared from limonene by partial reduction followed by peracetic acid treatment. The GC profile of the carvomenthene oxide showed two closely spaced peaks in about 1:1 ratio (Figure 3.1). The mass spectrum showed molecular weight of 154 for both peaks. The PMR spectrum of this compound had a doublet at 2.96 ppm and a singlet at 3.0 ppm and they integrated to one proton. The relative area of integration of these peaks was about 1:1. From this observation it was concluded that they are isomeric mixtures and are assigned as *cis*- and *trans*-carvomenthene oxide. The *cis*- and *trans*- refer to the orientation of alkyl substituents at 1 and 4 positions of cyclohexane ring. As endocyclic double bond of carvomenthene is epoxidized at both faces at nearly equal rate, it resulted in the formation of two diastereomeric epoxides. It is known that these are not easily separable by the simple fractional distillation,[12] the exact retention time on GC of individual oxides was determined by comparison with a standard sample of the *trans*-epoxide, which was prepared by the bromohydrin route (Scheme 3.3). It is similar to the preparation of *trans*-limonene oxide by the same route.[38] The 2-bromo-1-hydroxy-*p*-menthane (preparation is described in chapter 2, section 4.1) was treated with aqueous sodium carbonate and the product obtained was purified by SiO_2 column chromatography. The pure product when injected on GC showed single peak of >98 % purity and its retention time was similar to the one of the peak of the carvomenthene oxide GC profile. The *trans*-nature of the epoxide was further confirmed by the PMR spectrum and mass spectral analysis. PMR spectrum had singlet at 2.96 ppm and other characteristic *p*-menthane skeleton protons. Its GC profile is shown in Figure 3.2.



1 **2**

trans-(+)-(4R)-Carvomenthene oxide

Scheme 3.3

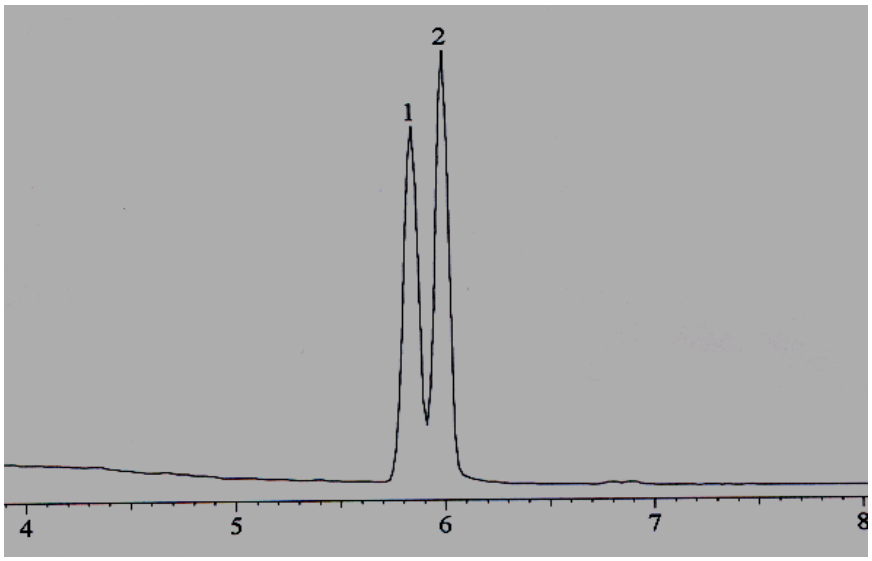


Figure 3.1: GC profile of diastereomeric mixture of *cis*- and *trans*-carvomenthene oxide (45:55)

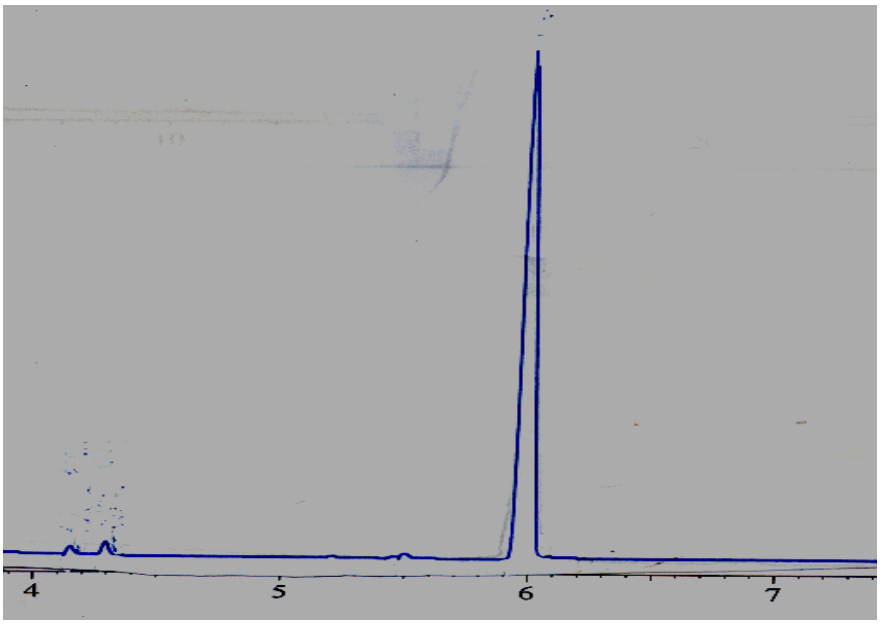


Figure 3.2: GC profile of *trans*-carvomenthene oxide (purity > 98 %)

The photochemical addition of methanol to limonene under photochemical condition is found to be highly regiospecific as methoxy radical add on to limonene and gives products which have tertiary methoxyl group and diastereoselectivity at this position can be controlled by experimental parameters such as use of co-solvents, temperature and with

different sensitizers.[39] In the present study the carvomenthene oxide was taken as a substrate and methanol as solvent. This mixture was irradiated with the uv light at 240-366 nm. It was found that, the reaction initially did not occur; even on prolonged irradiation (> 24 h), very little conversion was observed. As the presence of a metal oxide such as iron oxide is found to facilitate the addition of methanol to epoxides,[37] use of Lewis acid in the reaction was envisaged.

Accordingly the photoreaction of carvomenthene oxide was now conducted in methanol in the presence of 5 mol % $ZnCl_2$. Interestingly, only one product was observed and nearly an equal amount of unreacted oxide was seen in the GC profile of the product. After 8 h of irradiation when all the *cis*-oxide consumed, the product after aqueous workup was subjected to fractional distillation under reduced pressure. The fraction which distilled at 58-60^{o}C/2.5 Torr was collected and it was identified as *trans*-carvomenthene oxide, based on a comparison with the retention time of an authentic sample. The other fraction which distilled at 96-98^{o}C/2 Torr was identified as (*1S, 2S, 4R*)-*trans*-1-methoxy-2-hydroxy-*p*-menthane. The presence of two singlets at 3.17 and 3.63 ppm for three and one proton respectively indicated methoxy and hydroxyl groups in the product. These groups were assigned as being *trans*- to each other. This conclusion was arrived based on the fact that the effective diaxial ring opening of the *cis*-oxide. In both nucleophilic and acidic attack on the carvomenthene and limonene-1,2-oxides, the Furst-Plattner rule of diaxial opening predicts the predominant product.[12] According to this rule the 4-alkyl substituents determine the conformation in which the *cis*- and *trans*-1,4-substituted cyclohexene-1,2-epoxides react with acidic reagents. It is usually *via* a normal 'diaxial' opening and the normal diequatorial opening is not observed in case of *cis*-oxides and 'effective diequatorial' opening observed for the *trans*-epoxides.

In order to check the reactivity of pure *trans*-carvomenthene oxide (prepared *via* bromohydrin route), the reactions of the pure isomer in methanol under irradiation conditions in the presence of various Lewis acid catalysts were carried out. The reaction did not occur even after irradiating for 24 h except in case of $InCl_3$, which too progressed at a very slow rate. The reaction was studied at different levels of Lewis acid catalysts (5, 10 and

20 mol %) and observed their effect was negligible. Thus, this result indicated the difference in the reactivity of two diastereomeric cylohexyl based epoxides towards the addition of methanol under photochemical conditions. This observation, *viz*. the complete reaction of *cis*-oxide while leaving behind the *trans*-oxide unreacted, prompted further exploration of the method for kinetic resolution of the epoxides.

The reaction of carvomenthene epoxide in methanol in the presence of 5 mol % $ZnCl_2$ under reflux condition showed that the reaction was much faster (< 1 h); besides the *cis*-oxide, the *trans*-oxide was also consumed in the reaction as shown by the lower recovery of the *trans*-oxide. Apparently, the reactions at higher temperatures exhibited lesser selectivity. On the other hand, the same reaction at ambient temperature was found to be very slow and after four days stirring only partial amount of *cis*-oxide converted to ring opened *trans*-diaxial product. The *trans*-oxide was completely inert and as a result the final product had the mixture of three componenets *viz*. *cis*- and *trans*-carvomenthene oxides and (*1S, 2S, 4R*)-*trans*-1-methoxy-2-hydroxy-*p*-menthane.

For the standardization of methodology, the reaction of carvomenthene oxide was studied with different Lewis acid catalysts at 5 mol % level. When the *cis*-oxide was completely consumed, the irradiation was stopped and the reaction mixture worked up to yield the *trans*-oxide and the ring opened product in pure state. It must be mentioned that, the side products accounted for 3-5 %, but they could not be separated as pure compounds. The results of various experiments of carvomenthene oxide using different Lewis acid under three conditions are presented in Table 3.1.

Methanolysis of carvomenthene oxide, when carried out at room temperature (condition A) was incomplete. Though selectivity was observed, reaction was found to be very slow and only *cis*-oxide reacted partly after four days of stirring. In case of $InCl_3$ reaction was complete in 20 h and selectivity was also observed. The reactions carried out under uv irradiation (240-366 nm, condition B), at ambient temperature the reactions were complete in a shorter period (5-8 h). Also, a good measure of selectivity was observed and *cis*-oxide reacted preferentially to give *trans*-1-methoxy-2-hydroxy-*p*-menthane and the unreacted *trans*-oxide could be obtained in good optical purity (> 98 %) and in excellent

yield (49-54 %). Methanolysis under reflux condition (condition C), was faster (1-1.5 h) but the selectivity was poor. Simultaneous reactions of both the diastereomers with slight difference in the reaction resulted in isomeric ring-opened products.

Table 3.1: Reaction of carvomenthene oxide with methanol in presence of 5 mol % Lewis acid catalysts

Lewis acid		Time (h)	% *trans*-Carvomenthene-oxide [d]	% *cis*-Carvomenthene-oxide [d]	% *trans*-1-Methoxy-2-hydroxy-*p*-menthane [d]
$InCl_3$	A	20	45	0	48
	B	5	49	0	47
	C	1.5	30	0	43
$ZnCl_2$	A	96	54	25	15
	B	8	52	0	44
	C	1	45	9	35
$ZnBr_2$	A	96	50	23	25
	B	5	54	0	45
	C	1	45	13	40
ZnI_2	A	96	53	34	10
	B	24	52	38	8
	C	1	41	0	36

A: Stirring (25^{o}C), B: Light (240-366 nm) at 25^{o}C, C: Reflux, d: Yield determined by GC

Thus, under the standardized conditions of photo-irradiation of carvomenthene oxide in methanol in presence of 5 mol % Lewis acid catalyst, it could be established that, the kinetic resolution is possible. Under the same standardized conditions, the next substrate chosen for the study was limonene-1,2-oxide. Commercial (+)-limonene-1,2-oxide is a mixture of *cis*- and *trans*-isomers in the ratio of 1:1.3. These diastereomeric oxides resolved well on GC. The GC profile of diastereomeric limonene-1,2-oxde is shown in Figure 3.3.

On irradiation in the presence of 5 mol % $ZnCl_2$, methanol added preferentially to *cis*-limonene oxide leaving behind the *trans*-oxide unreacted. After aqueous workup, the

product was subjected to fractional distillation under reduced pressure. The fraction which distilled at 57-59^{o}C/2.5Torr was identified as trans-limonene-1,2-oxide based on the following spectral data. In the PMR spectrum, presence of proton attached to epoxide appeared at 2.98 ppm as doublet (5.3 Hz). The molecular weight by mass spectrum was 152 and characteristic *p*-menthane skeleton fragments appeared {137(3), 119(4), 108(20), 94(35), 79(30), 67(70), 43(100)}. Its identity was further confirmed by comparison of retention time of authentic sample of *trans*-oxide prepared *via* bromohydrin route (Figure 3.4). The fraction which distilled at 100-102^{o}C/2.5 Torr was identified as (*1S, 2S, 4R)-trans* 1-methoxy-2- hydroxy-*p*-menth-8-ene based on spectral data. Its PMR spectrum clearly showed the presence of methoxy group at 3.19 ppm and hydroxyl at 3.60 ppm. The presence of isopropenyl double bond was indicated by a broad peak at 4.66 ppm. From the mass spectral data molecular weight of the product was found to be 184. The 1,2-*trans*- nature was concluded similar to the conclusion in case of carvomenthene oxide ring opened product. Under a set of optimized reaction condition of 5 mol % of Lewis acid and in methanol, the study was further conducted and results are summarized in Table 3.2.

Table 3.2: Reaction of (+)-limonene-1,2-oxide with methanol in presence of 5 mol % Lewis acid catalysts

Lewis acid		Time (h)	% *trans*-Limonene-Oxide [d]	% *cis*-Limonene-Oxide [d]	% *trans*-1-Methoxy-2-hydroxy-*p*-menth-8-ene [d]
$InCl_3$	A	12	54	0	41
	B	3	48	0	41
	C	0.5	35	0	40
$ZnCl_2$	A	96	56	25	16
	B	20	55	0	40
	C	2	41	0	35
$ZnBr_2$	A	96	55	20	22
	B	10	52	0	42
	C	1	40	0	36
ZnI_2	A	96	55	20	23
	B	24	55	42	02
	C	1	52	0	27

A: Stirring (25^{o}C), B: Light (240-366 nm) at 25^{o}C, C: Reflux, d: Yield determined by GC

The influence of the Lewis acid on the course of the reaction and the product composition could be discerned from the above study. In case of $ZnBr_2$ the reaction was found to be faster compared to $ZnCl_2$, but prolonged irradiation caused *trans*-oxide to react albeit at a slower rate. In both these cases, the reaction at room temperatures was very slow and only about 20 % of *cis*-oxide converted to product after five days. Reaction of the limonene-1,2-oxide with methanol using these catalysts under reflux condition was non-selective, as both the isomers were consumed in short duration. Hence, photo-addition of methanol to diastereomeric carvomenthene and limonene 1,2-oxide provided optimum condition, wherein the isolation of pure *trans*-oxide was possible.

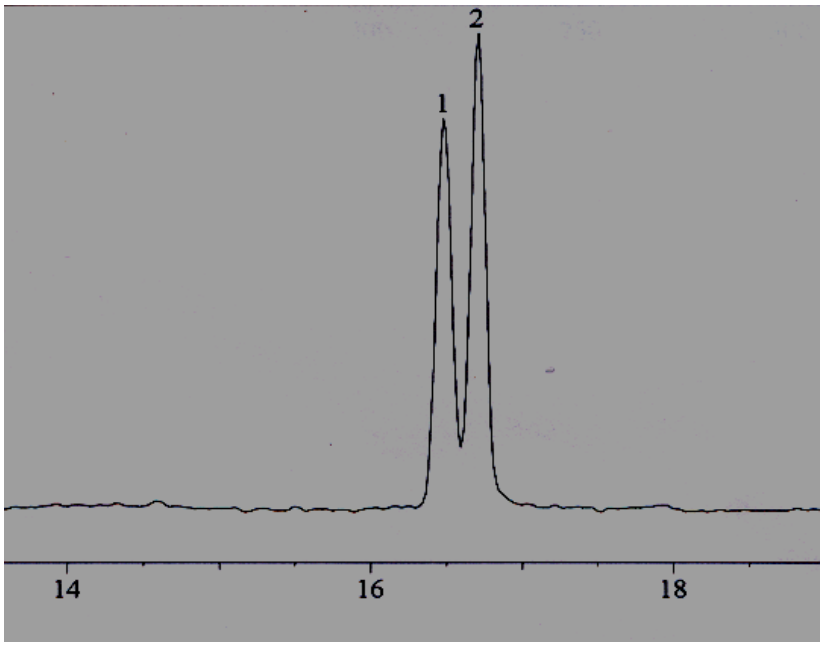


Figure 3.3: GC profile of diastereomeric mixture of *cis*- and *trans*-limonene oxide (44:56)

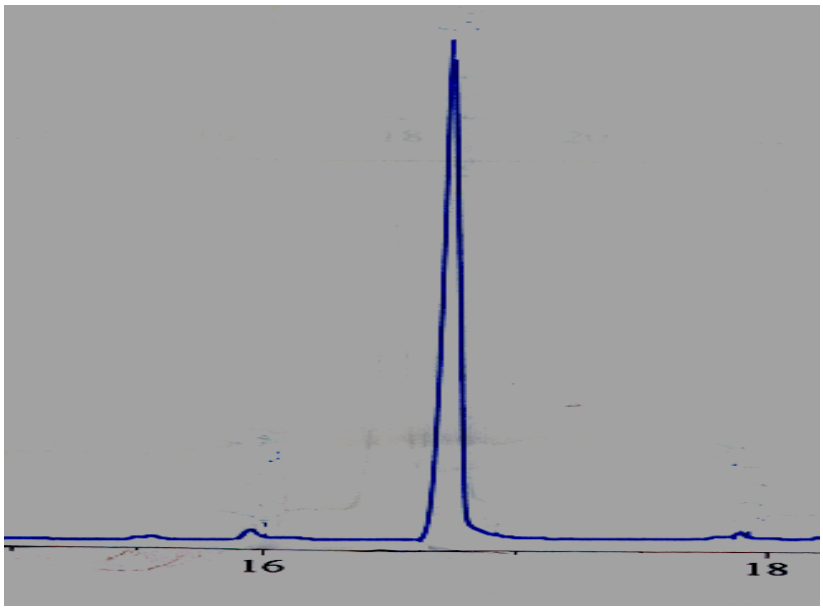


Figure 3.4: GC profile of trans-limonene oxide (purity >98 %)

In the case ZnI_2-catalyzed photo-addition of methanol, this method failed because of the non-availability of the Lewis acid. This might be due to its decomposition in presence of light. While irradiating it was observed that the solution turned to light yellow, indicating

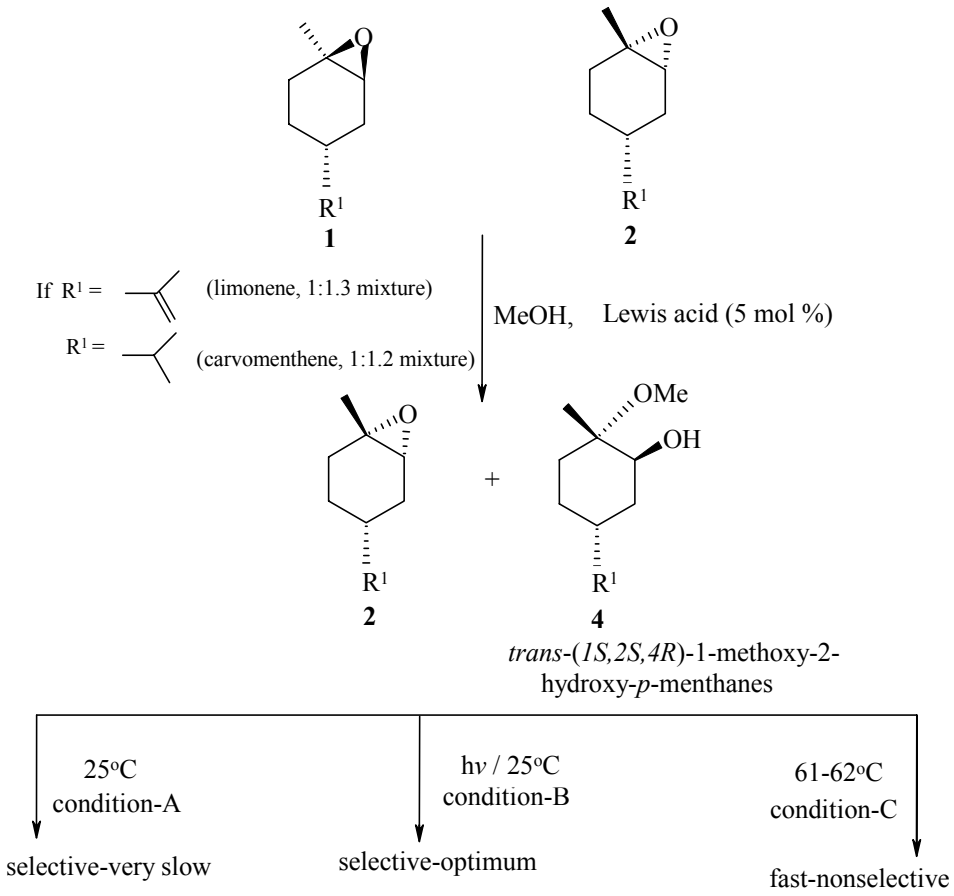
the release of iodine. So, the presence of Lewis acid intact was necessary for the opening of the epoxide ring.

In case of $InCl_3$ reactions, which were run under light and reflux, the results were similar to those with $ZnCl_2$ and $ZnBr_2$ except that their rates were faster. The reaction, at room temperature, was selective and went to completion in 12 h whereas, the one under reflux condition was too fast (0.5 h) and non-selective. Thus, the action of $InCl_3$ on the addition of methanol is more pronounced than of $ZnCl_2$ and $ZnBr_2$ as these are selective in case of only photo-addition while the former is selective in both photo-addition and room temperature reactions. The schematic representation of methanolysis reaction of diastereomeric (+)-limonene-1,2-oxide and (+)-carvomenthene oxide is depicted in Scheme 3.4.

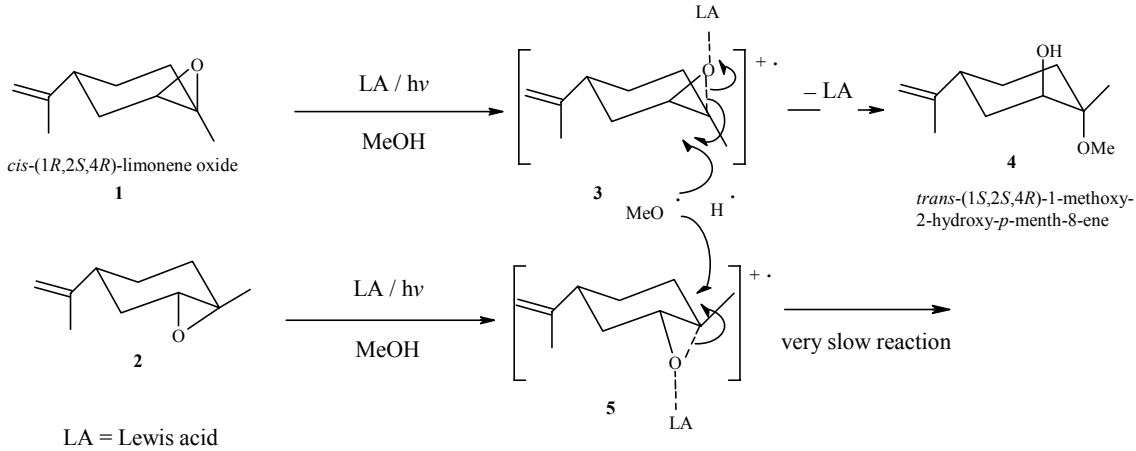
The mechanism of photo-assisted selective addition of methanol to the limonene and carvomenthene oxides under the influence of light in the presence of Lewis acid catalysts is explained in the Scheme 3.5. Here, *cis*- and *trans*-limonene oxides (**1** and **2**) are taken as representative cases. Initially photo-assisted cleavage of C_1 -O bond takes place, which was influenced by the presence of Lewis acid. In case of **1**, Lewis acid can easily makes association with the axially oriented epoxide oxygen to form radical cation **3**. In this case C-4 substituent oriented equatorially offers less hindrance for the approach of Lewis acid. Whereas this is difficult in case of **2**, because of the equatorial orientation of epoxide oxygen and also hindrance to the approach of Lewis acid due to the presence of C-4 substituted isopropenyl group. Formation of **4** from **3** is fast, as the methoxy and proton radicals generated in the presence of light quickly add to the intermediate **3** and simultaneously break the Lewis acid-oxygen association. Hence it is concluded that, the presence of C-4 substituent plays an important role in determining the difference in the reactivity of two diastereomeric epoxides for the association of Lewis acid and epoxide oxygen.

Thus, light induces the selectivity in respect of *cis*-oxide leaving behind the *trans*-oxide unreacted under mild conditions. The unreacted *trans*-oxide can be purified from the *trans*-diaxial product by distillation under reduced pressure. Since these have substantial difference in their boiling points, they could be separated without any difficulty. The *trans*-

oxide, thus obtained was pure (>98 %). The present strategy of kinetic resolution can be utilized as a simple and convenient method for the preparation of pure diastereomeric epoxides.



Scheme 3.4



Scheme 3.5

Experimental

The procedure for the synthesis of the carvomenthene oxide is described in the Chapter 2, Section 2.3. Limonene 1,2-oxide was purchased from Sigma-Aldrich Chemical Company, and it was distilled before use. Specially dried methanol was obtained from SD-Fine Chemicals. Zinc chloride was purchased from Nice Chemicals, India and zinc bromide was obtained Sigma-Aldrich chemical company and these were dried in a drying pistol at 110-120^{o}C under reduced pressure at 1 Torr. ZnI_2 was purchased from Fluka Chemical Company and $InCl_3$ was purchased from Sigma-Aldrich Chemical Company. A general experimental protocol for reactions of carvomenthene and limonene oxides in methanol in the presence of $ZnCl_2$ is described hereunder. Reactions of these oxides were carried out similarly in presence of other Lewis acids and the results are summarized in Table 3.1 & 3.2.

1. Reaction of *cis*- and *trans*-carvomenthene oxide with methanol in the presence of $ZnCl_2$

Condition A

In a flask carvomenthene oxide (1.54 g, 10 mmol) was taken in 15 ml dry methanol and dry $ZnCl_2$ (68 mg, 5 mol %) was added. The resultant solution was stirred under nitrogen atmosphere at room temperature. The progress of the reaction was monitored by GC programmed at 80^{o}-96^{o}C at the rate of 1^{o}C/min followed by 8^{o}C/min rise to 220^{o}C on a HP-5 column, 30 m x 0.53 mm i. d. x 0.88 μm film thickness. After 96 h composition of the reaction mixture as determined by GC was, unreacted *trans*-oxide (54 %), *cis*-oxide, (25 %) and *β*-methoxy alcohol (15 %).

Condition B

A solution of carvomenthene oxide (1.54 g, 10 mmol) in 250 ml of dry methanol was charged to a forced liquid circulating photo-reactor. Dry $ZnCl_2$ (68 mg, 5 mol %) was added to it. While circulating solution falls as a thin film, it was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. After complete consumption of the *cis*-oxide (8 h), solution was drained into a flask; methanol was evaporated, products were extracted into CH_2Cl_2 (15 ml x 2) by aqueous

workup. Removal of the solvent afforded the crude product, which was further purified by fractional distillation under reduced pressure.

Product 1

***trans-R*-(+)-Carvomenthene-1,2-oxide:**[40]

Yield: 52 %, b. p.58-60^{o}C/2.5 Torr, $[\alpha]^{D}_{20}$ = +52.52^{o}(neat).

PMR: ($CDCl_3$, *J* = Hz) δ = 0.82(d, *J* = 6.8, 6H), 1.0-1.15(m, 2H), 1.30(s, 3H), 1.48-1.65(m, 4H) 1.90-2.0(m, 2H), 2.96(d, J = 5.3 Hz, 1H).

MS (m/z): 154(2), 139(10), 125(8), 111(30), 97(10), 83(15), 69(45), 55(50), 43(100).

Product 2

***(1S, 2S, 4R)-trans*-1-Methoxy-2-hydroxy-*p*-menthane**

Yield: 44 %, b. p.96-98^{o}C/2 Torr, $[\alpha]^{D}_{20}$ = 38.21^{o}(neat).

PMR: ($CDCl_3$, *J* = Hz) δ = 0.86(dd, *J* = 6.7 and 5.0 Hz, 6H), 1.15(s, 3H), 1.18-1.72(m, 6H) 2.16(m, 2H), 3.17(s, 3H), 3.63(s, 1H).

MS (m/z): 186(3), 171(2), 154(3), 143(15), 125(7), 111(10), 97(4), 83(22), 71(50), 55(30), 43(100).

Condition C

In a flask carvomenthene oxide (1.54 g, 10 mmol) was taken in 15 ml dry methanol and dry $ZnCl_2$ (68 mg, 5 mol %) was added. This solution was stirred under reflux in nitrogen atmosphere. The progress of the reaction was monitored by GC. After 1 h reflux the resultant reaction mixture was checked by GC and its composition is presented below.

trans-*R*-(+)-Carvomenthene-1,2-oxide: 45 %.

cis-*R*-(+)-Carvomenthene-1,2-oxide (unreacted): 09 %.

(1*S*, 2*S*, 4*R*)-*trans*-1-Methoxy-2-hydroxy-*p*-menthane: 35 %.

2. Reaction of *cis*- and *trans*-limonene oxides with methanol in the presence of $ZnCl_2$

Condition A

In a flask limonene-1,2-oxide (1.52 g, 10 mmol) was taken in 15 ml dry methanol and dry $ZnCl_2$ (68 mg, 5 mol %) was added. The resultant solution was stirred under nitrogen atmosphere at room temperature. The progress of the reaction was monitored by

GC programmed at 80°-96°C at the rate of 1°C/min followed by 8°C/min rise to 220°C in a HP-5 column, 30 m x 0.53 mm i. d. x 0.88 μm film thickness. After 96 h, composition of the reaction mixture by GC contains unreacted *trans*-oxide (56 %), *cis*-oxide (25 %), *β*-methoxy alcohol (16%).

Condition B

A solution of limonene-1,2-oxide (1.52 g, 10 mmol) in 250 ml of dry methanol was charged to a forced liquid circulating photo-reactor. Dry $ZnCl_2$ (68 mg, 5 mol %) was added to it. While circulating solution falls as a thin film, it was exposed to uv light of wavelength in the range 240-366 nm. The progress of the reaction was monitored by GC by periodic injection of worked up reaction mixture. After complete consumption of the *cis*-oxide (20 h), solution was drained into a flask; methanol was evaporated, products were extracted into CH_2Cl_2 (15 ml x 2) by aqueous workup. Removal of the solvent afforded the crude product, which was purified by fractional distillation under reduced pressure. The following two products were obtained.

Product 1

***trans-R*-(+)-Limonene-1,2-oxide**:[31b]

b.p.57-59°C/2.5Torr, [Lit][40] 78.5-80.5°C/10 Torr, $[\alpha]^{D}_{20} = +76.66^{o}$(neat), [Lit] [40] +82°.

PMR ($CDCl_3$, *J* = Hz) *δ* = 1.31(s, 3H), 1.69(s, 3H), 1.40-1.50 and 1.70-2.30(m, 7H), 2.98(d, *J* = 5.2 Hz, 1H), 4.66(s, 2H).

MS (m/z): 152(2), 137(3), 119(4), 108(20), 94(35), 79(30), 67(70), 43(100).

Product 2

***(1S, 2S, 4R)-trans*-1-Methoxy-2-hydroxy-p-menthan-8(9)-ene**:

b. p. 100-102°C/2.5 Torr, $[\alpha]^{D}_{20} = +40.62^{o}$.

PMR: ($CDCl_3$) *δ* = 1.15(s, 3H), 1.69(s, 3H), 1.40-1.55 and 1.70-2.30(m, 7H), 3.19(s, 3H), 3.60(s, 1H), 4.66(s, 2H).

MS (m/z): 184(2), 169(5), 152(10), 139(2), 108(15), 85(100), 72(60), 55(50), 43(60).

Condition C

In a flask limonene-1,2-oxide (1.52 g, 10 mmol) was taken in 15 ml dry methanol and dry $ZnCl_2$ (68 mg, 5 mol %) was added. The resultant solution was stirred under reflux

in nitrogen atmosphere. The progress of the reaction was monitored by GC. After 2 h reflux, GC profile of the reaction mixture had the following composition of the products.

trans-*R*-(+)-Carvomenthene-1,2-oxide: 41 %.

cis-*R*-(+)-Carvomenthene-1,2-oxide (unreacted): 0 %.

(1*S*, 2*S*, 4*R*)-*trans*-1-Methoxy-2-hydroxy-*p*-menthane: 35 %.

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Section B: Light Induced Direct Conversion of Styrene Bromohydrins to Benzoic Acid Esters

1. Photochemistry of Styrenes and its Derivatives

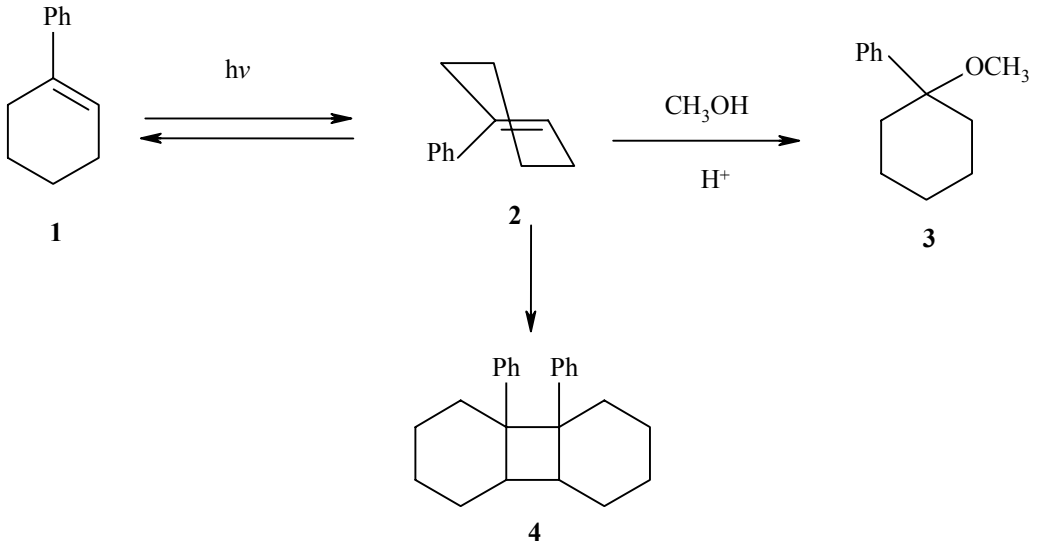
Styrenes

Photo-sensitized electron transfer reactions of styrenes have been well studied. Photoprotonation is common in solution mediated photoreactions of styrenes. 1-Phenylcyclohexene (Scheme 3.6, **1**), an aryl substituted cyclohexene, undergoes either direct or sensitized irradiation in methanol to afford methyl ether (**3**). This has been proved by the formation of *trans*-isomer (**2**) initially under photolytic condition, which subsequently gets protonated followed by the addition of methoxyl ion.[1a,b] The yield of ether (**3**) is greatly increased by the addition of a small amount of mineral acid. In the absence of mineral acid under direct irradiation, it results in the formation of mixture of dimers, the principal component of which is *cis-anti-cis* dimer (**4**). Also 1-phenylcyclohexene under both direct and sensitized conditions forms adduct with the acetic and propanoic acids.[2] In case of direct irradiation in neutral methanol or 2-propanol, formation of reduction and radical addition products have been observed.[1b] Several electron releasing substituted acyclic styryl systems on direct irradiation undergo Morkovnikov addition of alcohols. Styrenes undergo light induced electron transfer with both electron acceptors and donors.[3] In alcohol medium, the principal products are ethers.

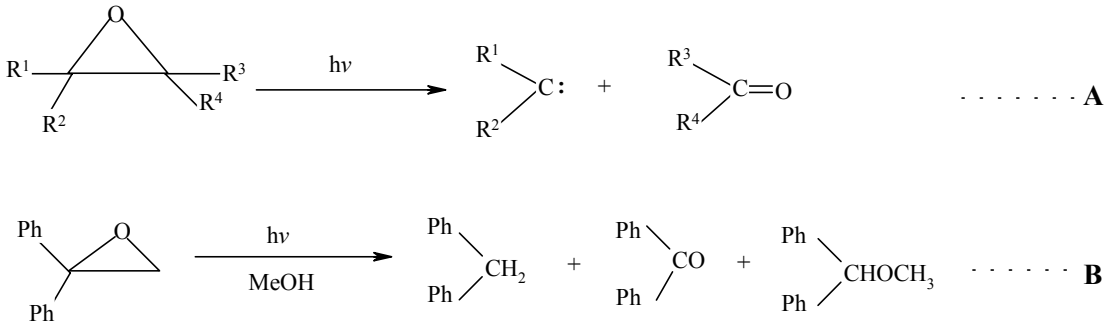
Styrene oxide

Photochemistry of several aryl oxiranes in solution has been studied by Griffin and coworkers.[4a,b] These reactions mainly give photo-fragmented products like arylcarbenes and carbonyl compounds (Scheme 3.7, equation A). Photosolvolysis of styrene oxide in alcohols is understood to be basically due to the acidity developed by the alcohols during the irradiation process.[5] The extensive study on the photosolvolysis of the styrene epoxides under neutral conditions in methanol, ethanol and isopropanol has been carried out by Sonawane *et al*.[6] The acidity developed during irradiation of styrene epoxides was neutralized by the addition of Na_2CO_3 and a plausible mechanism for the reaction is

proposed. Here, formation of photoproducts both from the scission of *C-O* and *C-C* bonds is observed (Equation B).



Scheme 3.6



Scheme 3.7

2. Bromo Alcohols

The radical reactions that involve scission of carbon-heteroatom bond in organic synthesis have been reviewed by Ramaiah[7a] and Curran *et al.*[7b] In these reactions, the halogen plays a critical role. In this class, the scission of *C-Br* bond, present next to *C-O* bond is most common among radical reactions.[7a] In these cases usually oxygen functionality is in the form of ethers or esters. The reaction with oxygen functionality in the form of hydroxyl group has not been fully explored except for a few reports on this subject. Radical

reaction of *trans*-bromo alcohols with trialkyl stannanes in the presence of AIBN to give 2-allyl substituted alcohols is reported.[8] Direct conversion of the alkyl and aryl substituted bromohydrins to ketones is reported in 1992 by Olivier Piva.[9] In his study, he has reported that the irradiation of the alkyl or aryl substituted vicinal *sec*-*β*-bromo alcohols in benzene or toluene in the presence of 0.5 equivalent PTS afforded the ketones in good yields. However *tert*-*β*-bromo alcohols are inert under these conditions. Iodohydrins give only traces of the expected ketones. The radical rearrangement reactions of several aryl-substituted *β*-bromo-oxyalkyls namely *β*-phosphonatooxyalkyl,[10] *β*-acyloxyalkyl,[11] allylhydroperoxy,[12] acyloxyalkylsilyl,[13] and *allyl*nitroxyl,[14] *β*-nitroxyalkyl and *β*-sulfonatoalkyl[15] generated by either heat or light with tributyltin hydride (TBTH) has been extensively studied. These reactions follow 1,2-migration of oxyalkyl group to give debrominated homo aryloxyalkyls. In another report on the free radical elimination of the hydrogen bromide from alkyl and aryl substituted vicinal bromo alcohols in the presence of a radical initiator like di-*tert*-butyl peroxyoxalate in cyclohexane or benzene, formation of the saturated ketones is observed.[16] This type of elimination is only facile with the sec-*β*-bromo alcohols and *tert*-*β*-bromo alcohols are non-reactive. This conversion occurs in solvents like cyclohexane and benzene but does not proceed in the presence of proton donor solvents like ethanol. Lodder and his co-workers[17] studied the photochemical behavior of the (*E*)-bromo styrene for the formation of vinyl cation and vinylic radicals. They observed photoproducts derived from both the intermediates.

While the photoprotonation is predominant in case of alkenes and aryl substituted alkenes in solution, the photolysis of epoxides in alcoholic solvents affords carbonyls and aryl carbenes. The radical substitution of halide functionality is also equally important. Photoreaction of aryl bromohydrins like styrene bromohydrin is usually carried out in the presence of the non-participating solvents. The course of the radical reaction generated by the styrene bromohydrin in the presence of participating solvents like alcohols has not been studied. In the present study styrene bromohydrin was chosen as the model substrate for a study of photo-induced transformation as a prelude to further studies on bromohydrins derived from monoterpenes.

Present Work

In the present investigation, photochemistry of styrene bromohydrin in a protic solvent medium like simple alcohols has been studied in detail. Initially a solution of styrene bromohydrin (Scheme 3.8, **1)** in methanol was irradiated with light of wavelength 240-366 nm in a falling film type photo-reactor. The reaction was monitored by GC, and the reaction mixture worked up when the substrate disappeared (9 h). GC Analysis of the product showed the presence of three compounds A, B and C in 6 %, 36 % and 40 % yield respectively. They were isolated in pure form by SiO_2 column chromatography using 2 % EtOAc in petroleum ether (60-80^oC) as eluant.

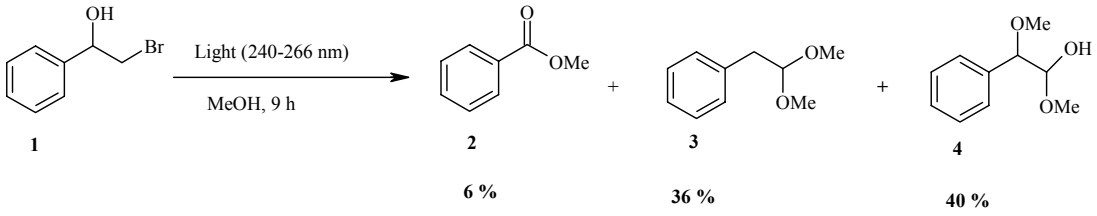
Compound A was identified as methyl benzoate in the following manner. It had sharp IR absorption band for the ester carbonyl at 1724 cm^{-1}. PMR spectrum showed, apart from five aromatic protons at 7.43-8.05 ppm (m), a singlet integrating to three protons at 3.96 ppm, for the methoxy group. Its mass spectrum had M^+ peak at *m/z* = 136 and fragments 105(100, M^+-OCH_3), 91(M^+-HCOO), 77($C_6H_5^+$). The ^{13}C-NMR spectrum indicated the presence of eight carbon atoms, of which seven were in the sp^2 region. Of these, one appeared at 167 ppm confirming the presence of carbonyl group. The saturated carbon appeared at 52.8 corresponding to the carbon attached to the oxygen atom. From the spectral data and comparison of boiling point and GC retention time of an authentic sample, the compound A was identified as methyl benzoate (**2**).

Compound B showed the following spectral characteristics. From the IR spectrum no functionality was detected except the C-H stretching absorption at 2831 cm^{-1}. In mass spectrum the highest mass peak at *m/z* = 165, was identified to be [M^+-1] peak. In the PMR spectrum the singlet for six protons at 3.34 ppm indicated presence of two methoxyl groups. Aromatic protons appeared as multiplet at 7.21-7.40 (5H) and one doublet for two protons and triplet for one proton appeared respectively at 2.91 and 4.54 ppm with coupling constant of *J* = 5.6 Hz, indicating A2X relation. From these data the structure of the compound B was concluded as 1,1-dimethoxy-2-phenylethane (**3**).

Compound C showed broad IR absorption band at 3460 cm^{-1} indicating the presence of hydroxyl group. Its mass spectrum showed highest mass as 181 and it was identified as

[M^+-1] peak. In its PMR spectrum the two singlets, each integrating to three protons at 3.24 and 3.44 ppm respectively, indicated the presence of two methoxyl groups. Two doublets (J = 6.3 Hz), each integrating to single proton were seen at 4.27 and 4.59 ppm (AB type). Aromatic protons appeared at 7.25-7.40 ppm (m, 5H). From these spectral data compound C was identified as 1,2-dimethoxy-2-phenylethanol (**4**).

The products **3** and **4** arose from regular photosolvolysis of the substrate under photo-irradiation conditions. Formation of methyl benzoate (**2**) as a minor product was, in fact, more interesting. Apparently, it must have arisen by the cleavage of benzylic *C-C* single bond, which is quite unusual in the presence of a more labile *C-Br* bond. This observation prompted a detailed investigation of the reaction.



Scheme 3.8

The reaction of styrene bromohydrin was carried out in methanol in presence of *p*-toluene sulfonic acid (PTS, 0.5 eq.) as the catalyst. Here, the reaction was very slow. The unreacted bromohydrin could be recovered to an extent of 90 % after irradiation for 24 h. Besides the aforesaid methanolysis products **2**, **3** and **4**, acetophenone and benzaldehyde were formed in < 2 % of the product. Here, methyl benzoate (2) was found only in trace amounts. This observation was at variance with the results of irradiation of the alkyl or aryl substituted vicinal *sec-β*-bromo alcohols in benzene or toluene in the presence of 0.5 equivalent PTS where aryl alkyl ketones are obtained as the major products in good yields (57-65 %).[9]

In another series of experiments, the photosolvolysis reaction of styrene bromohydrin was conducted in methanol in the presence of 0.5 equivalent of a Lewis acid.

Lewis acids, especially the zinc salts $ZnCl_2$, $ZnBr_2$ and ZnI_2, are known to have affinity to halide functionality and could play an important role in the reaction. In the presence of $ZnCl_2$, irradiation for 15 h afforded methyl benzoate in 19 % yield apart from the products **3** & **4** in 34 % & 32 % yield respectively. In the presence of $ZnBr_2$, the reaction was over after 8 h of irradiation and methyl benzoate was obtained as the major product (85 %); the product **3** formed as a minor product (13 %) whereas product **4** was not traceable. The reaction with ZnI_2 afforded two major products methyl benzoate (17 %) and product **3** **(**54 %) along with 12 % of unreacted substrate. In the presence of $InCl_3$ the reaction led to a complex mixture of products, among which only methyl benzoate (11 %) and the product **3** (17 %) could be identified.

Since the photoreactions of styrene bromohydrin with $ZnBr_2$ afforded methyl benzoate as a major product, the reaction was also tried in ethanol. The reaction was very slow and ethyl benzoate was formed in trace amount but with one equivalent of the $ZnBr_2$, the formation of 1,1-diethoxyphenylacetaldehyde (30 %) was observed after 24 h irradiation. With isopropyl alcohol, no product formation was observed even after 24 h irradiation.

When 2′,4′-dimethylstryrene bromohydrin, taken in methanol along with 0.5 equivalent $ZnBr_2$ was irradiated; the reaction proceeded at a fast rate and went to completion in 6 h. The major product obtained was methyl 2′,4′-dimethyl benzoate in 70 % yield. On the other hand, when the substrate was 1-bromo-3-phenyl-propane-2-ol, the reaction did not progress to any significant extent. Also, 2-bromo-1-hydroxy-*p*-menthane and 2-bromo-1-hydroxy-p-menth-8-ene derived respectively from carvomenthene and limonene were found to be non-reactive under these conditions. These results indicated that for the cleavage of *C-C* bond, phenyl activation was essential. In separate control experiments, the reaction of styrene bromohydrin with 0.5 equivalents of various Lewis acids ($ZnCl_2$, $ZnBr_2$, ZnI_2, and $InCl_3$) was carried out both at ambient temperature and under reflux. These reactions did not proceed even after 5 days of stirring at room temperature and 48 h in refluxing methanol. The results of photo-irradiation of styrene bromohydrin under different conditions are rationalized in Scheme 3.9.

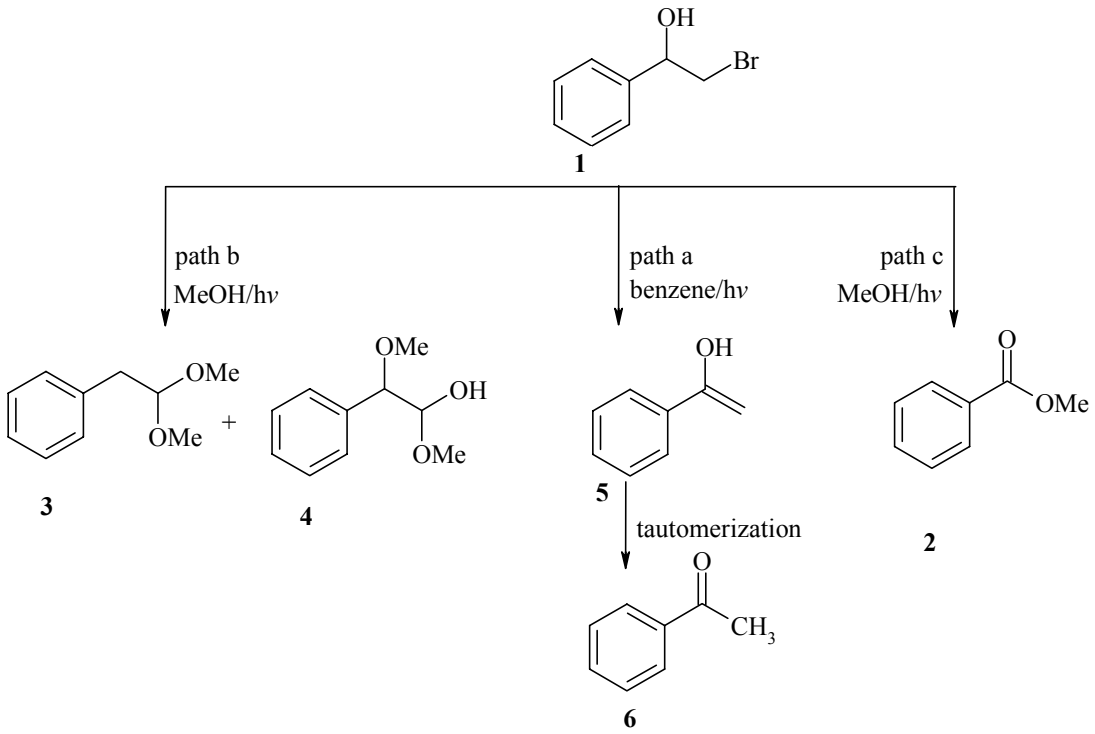
The reaction in nonprotic solvents like benzene or toluene and in the presence of PTS afforded acetophenone (**6**, path a). Initially elimination of hydrogen bromide from **1** occurs to afford an enol **5**, which tautomerizes to ketone **6**. The reaction in the presence of a zinc halide followed a different route, indicating that the later had a specific role. With zinc chloride or iodide, **3** and **4** were obtained as the major products, and methyl benzoate (**2**) as only a minor product.

The preponderant formation of methyl benzoate, in the above reaction in presence of zinc bromide was, in fact, the most interesting result. A mechanism envisaged for its formation is shown in Scheme 3.10. Initially, the substrate bromo alcohol reacts with the strong Lewis acid like $ZnBr_2$ to form a zinc salt of the bromo alcohol **2**. It easily eliminates a molecule of hydrogen bromide under photochemical conditions to afford the enolized zinc salt **3**. The latter gets converted into the more stable form; *i.e*. acetophenone zincbromide **4**. The existence of such a tautomeric form of the zincbromide salt in Reformatsky type reactions[18a-d] and zinc enolates[19] are known. The next step is the crucial photochemical scission of *C*-*C* bond (Norrish type I)[20] to yield phenylcarbonyl radical. Addition of methanol to it gives rise to methyl benzoate **2** and methylzincbromide salt as the side product. The presence of electron donating groups in the phenyl group apparently helped in the stabilization of phenyl carbonyl radical. Accordingly, the irradiation of 2′,4′-dimethylstyrene bromohydrin in methanol in presence of $ZnBr_2$ yielded the methyl-2′,4′-dimethylbenzoate in less than 6 h as compared to the formation of **2** in over 8h.

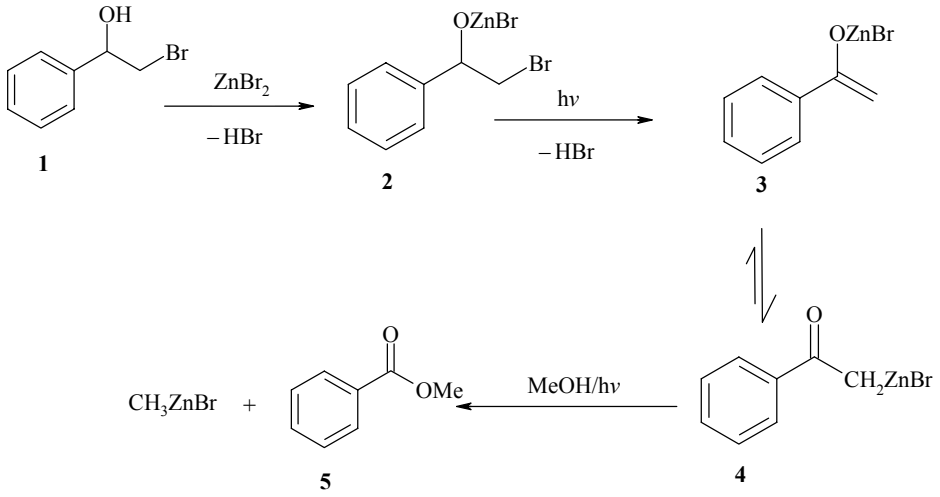
The possible formation of methylated products **3** & **4** in the presence of zinc chloride and zinc iodide (Scheme 3.9, path b) is explained in Scheme 3.11. Initially photochemical debromination takes place from **1** and gives unstable radical **2**. This radical loses proton and rearranges to give phenyl acetaldehyde **3** by migration of phenyl radical. Phenyl acetaldehyde was, indeed, observed as one of the products formed in the trace quantities (< 4 %) and identified by GC-MS analysis. Now this neutral molecule can undergo acid catalyzed addition of methanol to give an acetal, 1,1-dimethoxy-2-phenylethanal **5**. The photo-acetalization of α-aryloxy acetones in methanol, ethanol or benzyl alcohol is catalyzed by an acid in a low concentration.[21] In methanol acetalization is easy and gives good yield of

the product. On the other hand **3** can undergo enolization to give more stable 1-hydroxy styrene **4**. This is stable because it forms an extended conjugation with the phenyl group for the stabilization by delocalization of *Π*-electrons. Now this enol may either abstract proton to revert back to phenyl acetaldehyde or it can abstract methoxy radical to yield the 2-methoxy-2-phenyl-ethanal **6**. It further undergoes acid catalyzed addition of methanol to give an acetal, 1,2-dimethoxy-2-phenylethanol **7**.

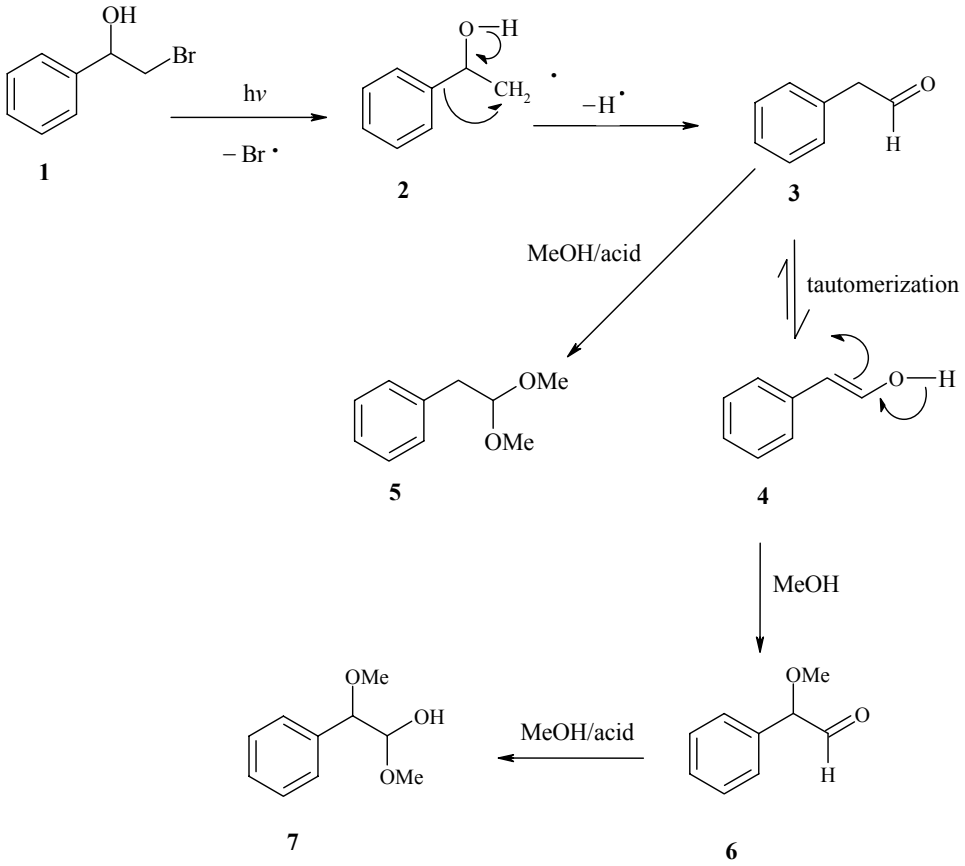
This investigation has shown that styrene and its alkyl substituted derivatives can be converted into methyl ester of benzoic acids *via* bromohydrin intermediates. The photochemical reactions, in the presence of zinc bromide in methanol easily convert the bromohydrins into methyl esters in near quantitative yield. It involves a novel and interesting C-C bond cleavage and the stability of the benzylic radical so generated appears to be the driving force.



Scheme 3.9



Scheme 3.10



Scheme 3.11

Experimental

1) Photoreaction of styrene bromohydrin in methanol

Styrene bromohydrin (1.0 g, 5 mmol) in 250 ml of methanol was loaded in to a photo-reactor. The circulating solution, falling as a thin film, was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. The progress of the reaction was monitored for the disappearance of the styrene bromohydrin by periodic injection of aliquot of the worked up sample by GC. After complete consumption of the substrate (9 h), the solution was drained off into a flask. Methanol was removed, the residue was dissolved in 50 ml of water and products were extracted into CH_2Cl_2 (25 ml x 3). The organic layer was dried over Na_2SO_4 and evaporation of the solvent afforded the crude product. The GC analysis of this crude product had two major compounds and one minor compound along with small components. It was chromatographed over silica gel (100-200 mesh) using 2 % EtOAc in petroleum ether (60-80^oC). Three major photoproducts were isolated by the column.

Product 1: Methyl benzoate

Yield: 06 %, b. p. 193-194^oC, [lit[21] 199.5^oC].

IR (γ = cm^{-1}): 1724 (s), 2952.

PMR: (400 MHz, $CDCl_3$, TMS internal standard) δ = 3.96(s, 3H), 7.43-7.55(m, 3H), 8.03-8.05(m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167, 133.7, 131, 130.4, 130, 129.8, 129.1, 52.8, M/S (*m/z*): 136(30), 105(100), 91(5), 77(90), 51(45).

Product 2: 1,1-Dimethoxy-2-phenylethane

Yield: 36 %.

IR (γ = cm^{-1}): 2831, 2931.

PMR: (400 MHz, $CDCl_3$, TMS internal standard) δ = 2.91(d, J = 5.6 Hz, 2H), 4.54(t, J = 5.6 Hz, 1H), 3.34(s, 6H), 7.21-7.40(m, 5H).

M/S (*m/z*): 165(1), 133(10), 119(5), 103(15), 91(80), 75(100), 65(20), 47(60).

Product 3: 1,2-Dimethoxy-2-phenylethanol

Yield: 40 %.

IR (γ = cm^{-1}): 3460(br), 2835, 2928.

PMR: (400 MHz, $CDCl_3$, TMS internal standard) δ = 3.24(s, 3H), 3.44(s, 3H), 4.27(d, J = 6.3 Hz, 1H), 4.59(d, J = 6.3 Hz, 1H), 7.25-7.33(m, 3H), 7.37-7.40(m, 2H).

M/S (*m/z*): 181(1), 166(2), 152(2), 151(10), 134(10), 119(15), 105(20), 91(50), 77(100), 65(10), 47(80).

2) Photoreaction of styrene bromohydrin with $ZnCl_2$ in methanol

Styrene bromohydrin (1.0 g, 5 mmol) and $ZnCl_2$ (0.34 g, 0.5 eq. 2.5 mmol) in 250 ml of methanol was loaded into a photo-reactor. The circulating solution falling as a thin film was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. The progress of the reaction was monitored by periodic injection of aliquot of the worked up sample by GC. After complete consumption of the substrate (15 h), the solution was drained off into a flask. Methanol was removed, the residue was dissolved in 50 ml of water and products were extracted into CH_2Cl_2 (25 ml x 3). The organic layer was dried over Na_2SO_4 and evaporation of the solvent afforded the crude product. Three major compounds were seen on GC and their composition is as follows.

Product 1: Methyl benzoate, 19 %.

Product 2: 1,1-Dimethoxy-2-phenylethane, 34 %.

Product 3: 1,2-Dimethoxy-2-phenylethanol, 32 %.

3) Photoreaction of Styrene bromohydrin with $ZnBr_2$ in methanol

Styrene bromohydrin (1.0 g, 5 mmol) and $ZnBr_2$ (0.56 g, 0.5 eq. 2.5 mmol) in 250 ml of methanol was loaded into a photo-reactor. The circulating solution falling as a thin film was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. The progress of the reaction was monitored by periodic injection of aliquot of the worked up sample by GC. After complete consumption of the substrate (8 h), the solution was drained off into a flask. Methanol was removed, the residue was dissolved in 50 ml of water and products were extracted into CH_2Cl_2 (25 ml x

3). The organic layer dried over Na_2SO_4 and evaporation of the solvent afforded the crude product. The GC chromatogram showed two major products and they were isolated by column chromatography over silica gel (100-200 mesh) using 2 % EtOAc in petroleum ether (60-80^oC) as eluant.

Product 1: Methyl benzoate, 85 %.

Product 2: 1,2-Dimethoxy-2-phenylethanol, 13 %.

4) Photoreaction of styrene bromohydrin with ZnI_2 in methanol

Styrene bromohydrin (1.0 g, 5 mmol) and ZnI_2 (0.80 g, 0.5 eq. 2.5 mmol) in 250 ml of methanol was loaded into a photo-reactor. The circulating solution falling as a thin film was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. The progress of the reaction was monitored by periodic injection of aliquot of the worked up sample by GC. Here while irradiating the solution turned to pinkish yellow colour. This was probably due to the decomposition of the salt under irradiation conditions. After 12 h exposure the contents were drained off and worked up as in earlier cases. The composition of product by GC is as follows.

Product 1: Methyl benzoate, 17 %.

Product 2: 1,2-Dimethoxy-2-phenylethanol, 54 %.

Un-reacted substrate: 12 %.

5) Photoreaction of styrene bromohydrin with $InCl_3$ in methanol

Styrene bromohydrin (1.0 g, 5 mmol) and $InCl_3$ (0.80 g, 0.5 eq. 2.5 mmol) in 250 ml of methanol was loaded into a photo-reactor. The circulating solution falling as a thin film was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. The progress of the reaction was monitored by periodic injection of aliquot of the worked up sample by GC. After 9 h irradiation, the product composition is as follows.

Product 1: Methyl benzoate, 11 %.

Product 2: 1,1-Dimethoxy-2-phenylethane, 17 %.

6) Photoreaction of 2′,4′-dimethylstyrene bromohydrin with $ZnBr_2$ in methanol

2′,4′-Dimethyl styrene bromohydrin (1.14 g, 5 mmol) and $ZnBr_2$ (0.56 g, 0.5 eq. 2.5 mmol) in 250 ml of methanol was loaded into a photo-reactor. The circulating solution falling as a thin film was exposed to uv light of wavelength in the range 240-366 nm generated from Normag, mercury high-pressure lamp TQ 150. The progress of the reaction was monitored by periodic injection of aliquot of the worked up sample by GC. After complete consumption of the substrate (6 h), the solution was drained off into a flask. Methanol was removed, the residue was dissolved in 50 ml of water and products were extracted into CH_2Cl_2 (25 ml x 3). The organic layer was dried over Na_2SO_4 and evaporation of the solvent afforded the crude product. The column chromatography isolation of the product over SiO_2 using 2 % EtOAc in hexane as eluant afforded one isolable pure compound.

Methyl-2′,4′-dimethyl benzoate:

Yield: 70 %.

IR (γ = cm^{-1}): 1722 (s), 2832, 2951.

PMR: (400 MHz, $CDCl_3$, TMS internal standard) δ = 2.36(s, 6H), 3.95(s, 3H), 7.43-7.55 and 8.03-8.05 (m, 3H).

M/S (m/z): 164(5), 163(30), 149(10), 133(40), 119(65), 103(15), 91(30), 75(100), 65(10), 47(90).

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CHAPTER – 4

NEW D-GLUCAL DERIVATIVES OF TERPENE ALCOHOLS; SYNTHESIS OF 2,3-UNSATURATED ACETYLGLUCOPYRANOSIDES

Introduction

Several important biologically active compounds have glycosyl functionality as their active center.[1] Chiral building blocks for bioactive natural products have been developed by glycosidation process.[2] In nature, synthesis of glycosides is a very common and important step leading to the production of a variety of compounds like oligosaccharides as such or glycoconjugates like those with lipids (glycolipids), proteins (glycoproteins), and other naturally occurring substances (glycosidically bound volatiles). The presence of compounds with complex carbohydrate structures as integral constituents of membranes and cell walls has created enormous interest and active research in this field.[3] Glycoconjugates are thought to be ideal carriers of biological information and specificity as well as multifarious functions are associated with the great structural diversity of oligosaccharide portion, which is inherent to the variability in glycoside bond formation. There are various chemical methods by which glycosides are synthesized. For a method to be of wide applicability, it must offer uniform steric activation of the anomeric center with the formation of a stable glycosyl donor having either α- or β-configuration. The next step should consist of a catalyzed, sterically uniform, irreversible glycosyl transfer to the acceptor, proceeding with either retention or inversion of configuration at the anomeric carbon in high chemical yield without affecting the other groups or bonds.

1. Glycosidically Bound Volatiles

The reports on the non-steam volatile components of the essential oils are limited compared to those on the volatile constituents of the essential oils. The volatile component of essential oils mainly contains the monoterpenoid hydrocarbons and their derivatives like alcohols, aldehydes, ketones and thiols. It is observed that increase in the essential oil content during the storage of peppermint,[4] which gives rise to suspicion that bound monoterpenes could be present from which the volatiles slowly emerge. In 1969, Francis *et al*. reported the occurrence of geranyl, neryl, and citronellyl-β-D-glucosides in rose petals.[5] There are also several reports of such compounds in the plant cells with aglycon part not only from the monoterpenes but also from various aliphatic alcohols. Stahl-Biskup *et al*.[3f,g]

report the structure, role and significance of the various glycosidically bound volatile derivatives. Of the various aglycons of these glycosides, monoterpenic alcohols are the major ones. The role of glycosides in essential oil plants as understood from the hypothesis of number of workers is that monoterpene glycosides represent hydrophilic derivatives of free aroma or essential oil compounds which serve as transport derivatives in the vegetable kingdom. However, there are number of contradictions to this hypothesis. The fact that the occurrence of glycosides in non-essential oil bearing plants is most interesting and Baerheim Svendsen put forward the phenomenon as 'Glycosidically bound volatile aliphatic and aromatic alcohols including terpenes seem to occur all over the vegetable kingdom'.[6]

2. Glycosidation Methods

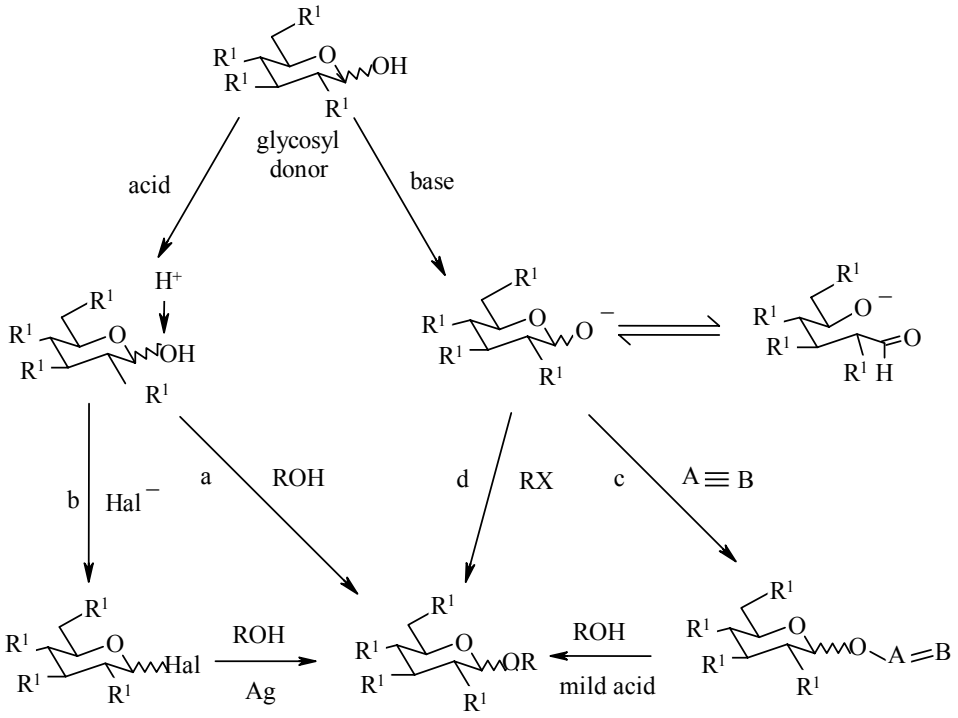
In majority of the synthetic strategies for glycosylation, anomeric activation in the glycoside moiety is largely employed. These can be mainly classified under the following groups. 1) Glycosyl halide, 2) thioglycoside, 3) 1-*O*-acyl sugar, 4) ortho-ester, 5) 1-*O* and *S*-carbonate, 6) trichloroacedimidate, 7) 4-pentenyl glycoside, 8) phosphate derivative, 9) 1-*O*-sulphonyl glycoside, 10) 1-*O*-silylated glycoside, 11) 1,2-anhydrosugar, 12) 1-hydroxyl sugar and 13) the glycal. Of these, general and important glycosidation methods are described here under the following heads (Scheme 4.1).[7]

1) The Fischer-Helferich method.
2) The Koenigs-Knorr method.
3) The trichloroacetimidate method.
4) The anomeric *O*-alkylation method.
5) The glycals.

2.1 The Fischer-Helferich Method

This is a classical method of *O*-glycosylation, which involves acid catalyzed reaction of hemiacetal and alcohols (Reaction a). This is a reversible reaction and therefore not applicable to compounds with more than one glycoside bond *i.e.* oligosaccharides and glycoconjugates. Also the diastereo control at the anomeric position depends on the thermodynamic stability of α- and β-anomers. This method is mainly applicable to the synthesis of simple glycosides required as starting materials in the oligosaccharide synthesis

and as chiral synthons.[8] In this method; the product control is difficult because of several acid catalyzed equilibration reactions with different kinetics.



a) Fischer-Helferich (acid activation); b) Koenigs-Knorr (Br, Cl, I) activation
c) trichloroacetimidate ($OC(NH)CCl_3$ activation; d)anomeric *O*-alkylation

Scheme 4.1

2.2 The Koenigs-Knorr Method and its Variants

This method involves activation of anomeric center of glycosyl donor so as to form sterically uniform donor (Reaction b), catalysis of the glycosyl transfer by simple means and maintaining irreversible reaction conditions. The activation of the glycosyl donor is achieved through the formation of glycosyl halides (chlorine or bromine). In the next step, glycosyl transfer is assisted by the presence of heavy metal salts (silver and mercury). The first step is carried out with typical halogenating agents, which lead mainly to the product with halogen atom at the axial position. The stability of the halogen activated anomeric center depends on the type of halogen and the nature of the protecting groups. The stability increases from bromides to chlorides and by substituting electron donating protective groups with electron withdrawing protective groups. Thus acetobromoglucose is stable at $0^{o}C$,

whereas benzyl-protected bromoglucose is thermally unstable even at – 78°C. Generally these reactions are catalyzed by mercury and silver salts. The general order of reactivity of these catalysts follows the order: $AgOTf/Ag_2CO_3$ > $AgClO_4/Ag_2CO_3$ > $Hg(CN)_2/HgBr_2$ > $Hg(CN)_2$.[3c] The solvents which favor the S_N2 reactions like dichloromethane, cyclohexane or petroleum ether are commonly employed. Due to the low thermal stability of glycosyl halides, reactions are preferably carried out at ambient temperatures. When all the groups are equatorial, the reactivity order follows 6-OH > 3-OH > 2-OH > 4-OH.[3c,d] Axial hydroxy groups are usually less reactive than the equatorial hydroxy groups.

2.3 The Trichloroacetimidate Method

Trichloroacetimidate-mediated glycosylation was first reported by Schmidt and his co-workers as an alternative useful method to the classical Koenigs-Knorr procedure and appears to be one of the most ideal glycosylation methods (Reaction c).[9a,b] It involves a high stereo-controlled activation of anomeric oxygen by base promoted anomerization of 1-OH or 1-O^-. Electron deficient nitriles such as trichloroacetonitrile (CCl_3CN) are known to undergo direct and reversible base-catalyzed addition to alcohols to give *O*-alkyl trichloroacetimidates. The anomerically substituted *α*- or *β*-imidates can be isolated in pure form and in high yield via kinetic and thermodynamic reactions with different bases. Both the anomers are stable and can be stored easily. The alcohol components for reaction as glycosyl acceptor generally require the presence of acid catalyst like $BF_3{\cdot}OEt_2$ at temperatures of – 40°C to ambient temperature in solvents like CH_2Cl_2 or CH_2Cl_2/hexane. The main features of the tricloroacetimidate glycosidations are a) it is catalyzed by Lewis acids under very mild conditions; b) the reaction is irreversible; c) other glycosidic bonds are not affected; d) affords high yields; and e) stereocontrol of the glycoside bond formation is good to excellent.

2.4 The Anomeric O-Alkylation Method

In the anomeric *O*-alkylation method, first the glycosyl donor is treated with the base and then with the excess of a simple alkylating agent to yield the *O*-alkylated derivative. The alkylating agents generally employed are methyl iodide or dimethyl sulfate. Schmidt and his co-workers initiated this methodology.[3a,10] This method has got limitation that, even when

all the hydroxyl groups protected the ring chain tautomerism between the anomeric forms and the open chain form (Reaction d) readily occurs offering three sites for the attack by alkylating agent. However, the success of the method depends on the stability of the deprotonated species, ring chain tautomeric equilibrium and its dynamics, and the relative reactivity of the three *O*-protonated species. The stereo-control over the product formation either *α*- or *β*- is unattainable by this method as the *O*-alkylation reactions are irreversible. The stereo-control could be influenced by intramolecular metal-ion complexation, by steric effects, and by taking the advantage of increased nucleophilicity of the equatorial anomeric oxide.[11] The method is effectively employed to get the *α*-glycosides of 3-deoxy-D-*manno*-2-octulosulonic acid.[12] Thus, it offers a simple procedure for glycosides and saccharide synthesis, giving generally high yields and distereoselectivities.

3. 2-Deoxyglycosides: Synthesis and Importance

The deoxy-sugars are formally derived from normal sugars by replacement of one or more hydroxyl group present in the normal sugars. 2-Deoxyglycosides are widely found in biologically important natural products, especially in antitumor antibiotics. Several types of *α*- and *β*-2-deoxyglycosides frequently appear in naturally occurring bioactive substances such as aureolic acid antibiotics, anthracycline antibiotics, cardiac glycosides, avermectins, erythromycins, and also in recently discovered enediyne antibiotics.[13] The efficient glycosidation for *β*-2-deoxyglycosides is difficult as lack of stereo-anchimeric assistance from the C-2 position and low stability of the glycosidic bond under acidic conditions due to lack of electron withdrawing C-2 substituents. Thiem and his co-workers have introduced the use of 2-bromo-2-deoxyglycosyl bromide which have the bromide as temporary participating group at the C-2 position for the *β*–selective glycosylation of complex aglycons.[14] Silver triflate promoted glycosidation of the 2-bromo-2-deoxyglycosyl bromide predominantly give the corresponding *β*–glycoside, subsequent debromination affords the desired 2-deoxy-*β*-glycosides by reductive debromination. Thiophenyl, selenophenyl, and N-formylamino groups are also employed as other temporary participating groups at the *C-2* position, which could be easily removed after glycoside formation. Nicolaou *et al*. have introduced 2-deoxy-2-phenylthioglycosyl fluoride that is prepared from the corresponding

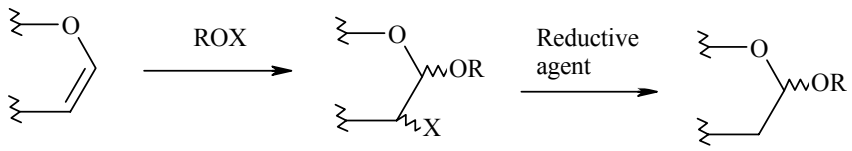
phenyl thioglycoside *via* 1,2-migration with (diethylamido)sulfur trifluoride (DAST), and its glycosylation using $SnCl_2$ gives both α- and β-glycosides, depending upon the solvent used in the reactions.[15] Treatment of glycals with PhSeCl and AgOAc affords 1,2-*trans*-acetoxy selenide, and its glycosylation with TMSOTf predominantly gives the β-glycoside.[16]

3.21 The Glycals

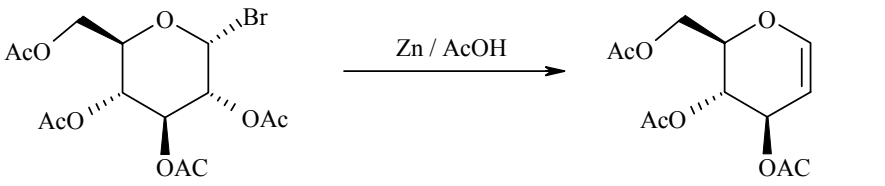
The 1,2-unsaturated derivatives of cyclic aldoses are known as 'glycals,' and this terminology is still used. Glycal is a very versatile synthetic intermediate especially in the synthesis of 2-deoxyglycosides (Scheme 4.2). The glycals having double bond between C-1 and C-2 are vinyl ethers and can take part in a variety of addition reactions and reduction of them easily gives the 2-deoxyglycosides. Both furanoid and pyranoid members are known and these can undergo rearrangement to give 2,3-unsaturated products. The simplest member of the family is 3,4,6-tri-*O*-acetyl-D-glucal.

3.22: 3,4,6-Tri-O-acetyl-D-glucal; Synthesis and Reactions

The first report of the synthesis of glucal was made by Emil Fisher in 1914. It described the preparation from α-D-glucopyranosyl bromide by reaction with zinc and acetic acid (Scheme 4.3).[17] Heating this glucal with hot water causes its dissolution by loss of one acetyl group by allylic substitution to give the 1-hydroxy, 2,3-unsaturated glucoside.[18] Lemiex and his co-workers investigated the synthesis of the 2-deoxyglycosides by the reaction of glucal with the simple alcohols in the presence of I_2, Ag salt, and base.[19] Subsequently a number of promoters like iodinium dicollidine perchlorate (IDCP),[20] NBS,[21] and NIS[22] have been introduced. Also, *O*-, *N*-linked unsaturated compounds, *p*-nitrophenol[23] and theophylline1[24] have been tried in the reaction.



Scheme 4.2



alpha-Acetobromo glucose

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

Scheme 4.3

a) Addition reactions[25]

Hydrogenation occurs smoothly, although hydrogenolysis of allylic ester group occasionally occurs as a competing process.[26] The polar addition to the double bond take place with high electro-specificity, the mesomeric influence of the ring oxygen atom ensures that the electrophile enters at position 2. Addition of water, alcohol and phenols require an acid catalyst and lead predominantly to 2-deoxy-aldoses, -aldosides, and –aldosyl esters. 2-Deoxy-pentoses, -hexoses and –disaccharides, have been prepared by this method. Since anomerization occurs in the presence of the acid, the method gives selectively the thermodynamically stable products (usually α-D).

Methoxymercuration of glycals and their acetates, brought about by treatment with mercuric acetate in methanol, gives methyl 2-deoxyglycosides having carbon-mercury bond at C-2. This reaction in the case of 3,4,6-tri-*O*-actyl-D-glucal and subsequent cleavage of the carbon-metal bond and deacetylation yields anomerically pure β-methyl-2-deoxyglycoside. Direct photolysis of these organomercurials also gives the corresponding 2-deoxyglycosides.[27] Direct halogenation of the 3,4,6-tri-*O*-actyl-D-glucal with bromine affords a mixture of 60 % *α-D-gluco* and 30 % *α-D-manno* products.[28] These on treatment with the methanol and silver carbonate yield 2-deoxy-β-D-*arabino*-hexopyranoside after reduction and deacetylation. Alternatively, 2-deoxy-α-D-*arabino*-hexopyranoside is obtained when halogenation and silver salt treatment is performed in alcoholic solutions. The dihalogenoadducts can be converted to 2-halogenoglycals by dehydrohalogenation reaction.[29] Hydrogen halides adds on the double bond of the glycal to yield 2-deoxyglycosyl halides, and this reaction is generally employed for the 2-

deoxyglycopyranoses, pyranosides, or pyranosyl purines or pyrimidines. Nitrosyl chloride adds on to 3,4,6-tri-*O*-actyl-D-glucal double bond to yield 2-deoxy-2-nitroso-α-D-glucopyranosyl chloride. This exists in dimeric form; further treatment with silver acetate followed by the reduction with copper-zinc acetic acid yields 2-amino-2-deoxy-D-glucosides.[30] Thiolacetic acid[31] and thiols[32] undergo photo-catalyzed addition to the double bond of tri-*O*-acetyl-D-glucal to afford epimeric mixture of 1,5-anhydro-2-thioalditols. Reaction of tri-*O*-acetyl-D-glucal with pseudo halogen like thiocyanogen in acetic acid is found to afford complex mixture of products and they have been isolated and characterized.[33]

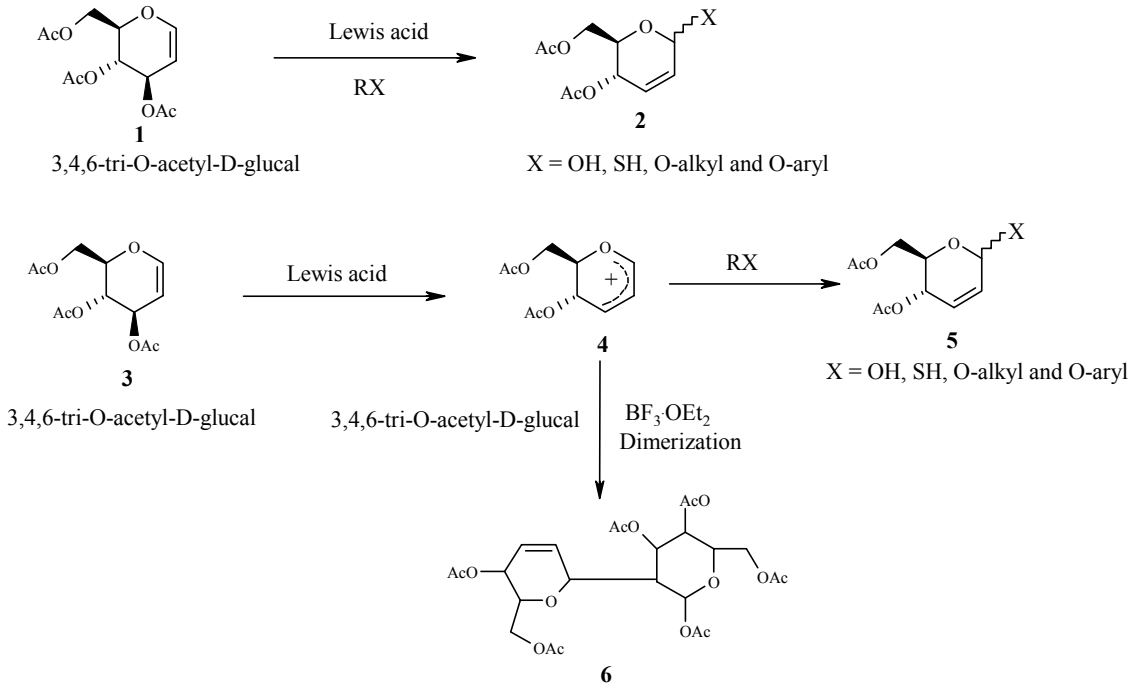
b) Allylic rearrangement of glycals: Ferrier Reaction[34a-e]

The Lewis acid catalyzed allylic rearrangement reaction of glycals is generally referred to as Ferrier rearrangement. This occurs with the substitution of nucleophile by allylic rearrangement and afford, 1-substituted-2,3-unsaturated glucoside derivative (Scheme 4.4). The mechanism of formation of **2** from **1** is thought to be anchimeric assistance of C-4 acetate for the migration of double bond from 1,2- to 2,3-position. The deacetylated carbocation (**4)** is now, at C-1 attacked by the nucleophile to give the substituted product (**5**). The reaction of tri-*O*-acetyl-D-glucal with water at 100^{o}C affords 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enose (*diacetyl pseudoglucal*) by nucleophilic displacement of the allylic acyloxy group and migration of double bond to the 2,3-position.[34d] High temperatures are required for the uncatalyzed reaction with alcohols, and mixture of anomers are produced. Boron trifluoride catalyzes this reaction of tri-*O*-acetyl-D-glucal with alcohols but causes the anomerization of the products. Higher concentration of the Lewis acid causes electrophilic addition of a presumed allylic oxonium ion (**4)** to the tri-O-acetyl-D-glucal to yield the dimeric product (**6**).[35a,b]

Since the last decade, there is considerable manifold interest in the synthesis of the various 2-deoxyglycosides. Of these, work on the allylic rearrangement of glycals by Lewis acid catalysts is most significant. There are various catalysts and a number of methodologies have been adopted for the synthesis of 2,3-unsaturated glycosides. A brief account of the role of various Lewis acid catalysts in promoting this reaction is as follows.

The efficacy of the $BF_3 \cdot OEt_2$ as a catalyst for the reaction of different glycals with various alcohols has been studied.[36] The reaction of 2,3-unsaturated glycosides (prepared *via* Ferrier rearrangement) with $BF_3 \cdot OEt_2$ promotes the *O*- to *C*-migration to yield the C-aryl substituted glycosides.[37] Trimethylsilyl triflate is used to catalyze this reaction for the production of *C*-glycosides; even *O*-glycosides can also be obtained from unsubstituted glycals at very low temperatures.[38] Alternatively DDQ is used to promote the reaction under neutral condition to catalyze displacement of allylic acyloxy group.[39] $SnCl_4$ has been used to effect the reaction both galactal and glucal with various alcohols in ethylene dichloride solvent and yields of the products are good.[40] The reaction of D-glucal with various alcohols in the presence of 0.1 equivalent $FeCl_3$ in CH_2Cl_2 and acetonitrile solvents is fast; in other solvents like toluene and ether it takes more than 12 h.[41] $Yb(OTf)_3$ is known to effect this reaction with various alcohols and thiols to afford the pseudoglycals with good α-anomeric selectivity.[42] Toshima *et al*.[43] have introduced Montmorillonite K-10 has been introduced as an environmental friendly catalyst. Here the efficacy of the reaction has been checked with several solid acids of which clay MK-10 and Nafion-H are best in CH_2Cl_2 at 25^oC and reaction completes in short duration with selective α-anomer. $Sc(OTf)_3$ has been used as a catalyst for Ferrier reaction to afford good yield of the substituted products with good anomeric selectivity.[44] Similarly $BiCl_3$,[45] and $InCl_3$[46] catalyze this reaction to yield respective glycosides with good anomeric selectivity.

From the foregoing discussion, it is evident that the synthesis of 2-deoxyglycoside derivatives by the Ferrier reaction is a well-studied reaction. This reaction has been successfully applied to various alcohols, which are achiral in nature. But few reports are there on the reaction with alcohols that are chiral. Since this reaction is catalyzed by Lewis acids, there is a possibility of side reactions due to interaction amongst the alcohols themselves. Monoterpene alcohols form a group of natural products which occur as pure enantiomers; many of them exist in plant tissues as glycosidically bound derivatives with common β-glycoside linkage. An attempt was made to synthesize D-glucal derivatives of some of these monoterpene alcohols.


AcO
AcO
OAc
O
1
3,4,6-tri-O-acetyl-D-glucal
Lewis acid
RX
AcO
AcO
O
X
2
X = OH, SH, O-alkyl and O-aryl
AcO
AcO
OAc
O
3
3,4,6-tri-O-acetyl-D-glucal
Lewis acid
AcO
AcO
O
+
4
3,4,6-tri-O-acetyl-D-glucal
RX
AcO
AcO
O
X
5
X = OH, SH, O-alkyl and O-aryl
BF3·OEt2
Dimerization
AcO
AcO
O
OAc
AcO
O
OAc
OAc
6

Scheme 4.4

Present Work

The scope of Ferrier reaction was studied with special reference to alcohols, which are allylic, benzylic, and trisubstituted and some of which are chiral as those derived from the monocyclic monoterpenes. Initially (+)-tepenin-4-ol (Table 4.1, **1g**), a tertiary alcohol, was taken as the model substrate and its reaction with tri-*O*-acetyl-D-glucal was studied. The tri-*O*-acetyl-D-glucal was prepared from glucose *via* acetobromo glucose and reduction of it with zinc in acetic acid as per the reported procedure.[47] The melting point and PMR spectral data were in good agreement with the authentic sample. When the reaction was conducted in dry benzene solvent and in the presence of PTS (10 mol %) as catalyst, at the room temperature over prolonged period only dehydration of the alcohol took place. The reaction in anhydrous CH_2Cl_2 medium also resulted in the formation of number of unidentified products. When the catalyst was changed to $BF_3.OEt_2$ a complex mixture of products was obtained and even glucal dimerization was observed, which is in concurrence with the earlier reports.[35a,b] The expected allylic substitution product could not be isolated in pure form. The use of BBr_3 as a Lewis acid catalyst was also not helpful as the reaction mixture became dark during the addition of the catalyst.

Earlier, in a study of solvolytic reactions of S_N1-active halides using zinc salts of nucleophiles, it has been reported that zinc halides formed do not affect the substituted products, because of the mild reaction conditions employed.[48] It is also known that Lewis acids catalyze the solvolytic reactions of tertiary alkyl halides.[49] Hence, the Ferrier reaction was investigated with zinc chloride as the catalyst.

When zinc chloride (10 mol %) was stirred with **1g** in CH_2Cl_2, at room temperature, the reaction progressed smoothly and went to completion in 10 h. The products isolated by workup were subjected to silica column chromatography. The hydrocarbons from the alcohol were in negligible amount whereas the glycoside was obtained in good yield. The latter product was characterized by PMR and ^{13}C-NMR and elemental analysis data (Table 4.2 & 4.3, **2g**). A sharp IR absorption band at 1746 cm^{-1} indicated the presence of acetyl carbonyl group in the product. The PMR spectrum of the compound showed two closely spaced singlets at 2.06 and 2.08 ppm, confirming the presence of two acetyl groups in the

molecule. A broad singlet which appeared at 5.16 ppm apart from an equal intensity peak at 5.06 ppm and their relative areas indicated the 1:1 anomeric ratio of the α- and β- forms. The olefenic protons which appeared at 5.75-5.89 ppm as multiplet indicated the unsaturation in the molecule. The aglycon part of the product was shown by the presence of characteristic protons from *p*-menthanyl skeleton and the presence of broad singlet for an olefenic proton at 5.26 ppm for the C-2 proton in the molecule. At 0.88 ppm, a doublet (J = 2.9 Hz) integrating to six protons appeared, corresponding to the two methyls on C-8 carbon, and the doublet due to one adjacent methine proton in the isopropyl group. Further confirmation was obtained by ^{13}C-NMR spectra of the compound. It indicated the presence of twenty carbon atoms. Of these two appeared at 170.1 and 170.7 ppm confirming the presence of two carbonyl carbons. A total of four sp^2 carbons were shown at 129.4, 127.4, 136.8, and 123.8 confirming two aglycon and two glycon olefenic carbons. Presence of peak at 93.7 corresponded to the anomeric carbon atom. Apart from these, four oxygen linked carbons appeared between 62.9 to 67.3 ppm corresponding to three from glycon part for C-4, C-5, C-6 and one from *p*-menthanyl C-4 carbon atom. The eleven carbons which appeared from 17.6 to 30.5 are of the alkyl carbons both from glycon and aglycon. From the elemental analysis the molecular formula was calculated as $C_{20}H_{30}O_6$. The specific rotation (+34.38^o) indicated little racemization of the aglycon part of the molecule. From the above spectral data the structure of the compound was identified as 4-(4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1-ene (Table 4.1, **2g**).

The Ferrier reaction of tri-*O*-acetyl-D-glucal with (+)-α-terpineol (Table 4.1, **1f**) another monoterpenic tertiary alcohol, was carried out in presence of $ZnCl_2$ catalyst (10 mol) in CH_2Cl_2 at room temperature. It was complete in a period of 12 h. Glycoside was obtained as the major product in good yield (60 %). The product after isolation by silica chromatography was characterized by PMR and ^{13}C-NMR and elemental analysis data (Table 4.2 & 4.3, **2f**). A sharp IR absorption band at 1744 cm^{-1} indicated the presence of –COMe group in the product. The PMR spectrum of the compound showed two closely spaced singlets at 2.05 and 2.07 ppm confirming the presence of two acetyl groups in the molecule. A broad singlet which appeared at 5.46 ppm apart from equal intensity peak at

5.33 ppm and their relative areas indicated 1:1 anomeric ratio of the α- and β- forms. The olefenic protons which appeared at 5.60-5.82 ppm as multiplet indicated the unsaturation in the molecule. At 1.27 ppm a singlet integrating to six protons appeared, corresponding to the two methyls of aglycon portion at the C-8 carbon atom, which was attached to glycon *via* C-O bond. The aglycon part of the product was evident from the presence of characteristic protons from *p*-menthane backbone and the presence of broad singlet for olefenic proton at 5.26 ppm corresponded to the C-2 proton in the molecule. Further confirmation was obtained by ^{13}C-NMR spectra of the compound. It indicated the presence of twenty carbon atoms. Of these two appeared at 171.1 and 170 ppm confirming the presence of two acetyl carbonyl carbons. A total of four sp^2 carbons were shown between 122.7 to 137.6.8 ppm confirming two aglycon and two glycon olefenic carbons. Presence of peak at 90.6 was due to the anomeric carbon atom. Apart from these, four oxygen linked carbons appeared between 64.8 to 74.5 ppm corresponding to three from glycon part for C-4, C-5, C-6 and one from *p*-menthanyl C-8 carbon atom. The eleven carbons which appeared from 20.7 to 39.9 are from the other alkyl carbons. From the elemental analysis the molecular formula was calculated as $C_{20}H_{30}O_6$. The specific rotation ($+32.9^o$) indicated little racemization of the aglycon part of the molecule. From the above spectral data the structure of the compound was identified as 8-(4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1-ene (Table 4.1, **2f**)

The next substrate tried was *tert*-amyl alcohol (Table 4.1, **1h**). This on reaction with tri-*O*-acetyl-D-glucal afforded product in 10 h. It was isolated by silica column chromatography using ethyl acetate: hexane mixture as eluant. This product was characterized by PMR and ^{13}C-NMR and elemental analysis data (Table 4.2 & 4.3, **2h**). A sharp IR absorption band at 1747 cm^{-1} indicated the presence of carbonyl group. The PMR spectrum showed two closely spaced singlets at 2.05 and 2.06 ppm, confirming the presence of two acetyl groups in the molecule. A broad singlet which appeared at 5.27 ppm apart from equal intensity peak at 5.12 ppm and their relative areas indicated 1:1 anomeric ratio of the α and β- forms. The olefenic protons which appeared at 5.70-5.83 ppm as multiplet indicated the unsaturation in the molecule. A triplet at 0.87 (J = 6.8 Hz) indicated the methyl

group in *tert*-amyl alcohol. Two closely spaced singlets at 1.21 and 1.22 each integrating to three protons indicated the methyls on the tertiary carbon in the aglycon portion. At 1.54 ppm a quartet integrating to two protons with J = 6.8 Hz indicated the methylene group attached to methyl in the aglycon. Further confirmation was obtained by ^{13}C-NMR spectra. It indicated the presence of fifteen carbon atoms. Of these, two appeared at 170.8.1 and 170.3 ppm confirming the presence of two acetyl carbonyl carbons. Two sp^2 carbons at 129.6 and 128.1 ppm corresponded to the two glycon olefenic carbons. Presence of a peak at 88.8 ppm confirmed the anomeric carbon atom. Apart from these, four oxygen linked carbons appeared between 63.3 to 72.8 ppm corresponded to three from glycon part for C-4, C-5, C-6 and one from *tert*-amyl carbon. The six carbons which appeared in between 8.4 to 34.2 are of the alkyl carbons both from glycon and aglycon. Also, from the elemental analysis the molecular formula could be calculated as $C_{15}H_{24}O_6$. The specific rotation ($+63.5^o$) of the product indicated it to be optically active. From the above spectral data, its structure was deduced as *tert*-amyl-4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranoside (Table 4.1, **2h**)

Next, the reaction was studied with enantiomerically pure monoterpene alcohols having allylic functionality. An easily available (-)-*cis*-6-hydroxy-*p*-menth-1,8-diene (carveol, Table 4.1, **1a**) was chosen as the substrate. The reaction of tri-*O*-acetyl-D-glucal with **1a** was carried out in CH_2Cl_2 in the presence of 10 mol % zinc chloride and the reaction was complete in 8 h. The product was isolated by silica column chromatography in good yield (70 %). It was characterized by PMR and ^{13}C-NMR and elemental analysis data (Table 4.2 & 4.3, **2a**). A sharp IR absorption band at 1735 cm^{-1} indicated the presence of carbonyl group in the product. The PMR spectrum of the compound showed two closely spaced singlets at 2.06 and 2.08 ppm, confirming the presence of two acetyls in the molecule. A broad singlet which appeared at 5.17 ppm apart from a peak at 5.08 ppm and their relative areas indicated 3:1 anomeric ratio of the *α* and *β*- forms. The olefenic protons which appeared at 5.86-5.90 ppm as multiplet indicated the unsaturation in the molecule. Presence of two peaks at 1.69 and 1.70 ppm each integrating to three protons indicated the two methyls of carveol at C-1 and C-8 positions. The presence of singlet at 4.72 ppm for two

protons and 5.28 (dd, J = 3.2 and 6 Hz) for one proton indicated the olefenic protons in the aglycon at C-9 and C-2 positions respectively. Further confirmation of the structure of the compound was obtained by ^{13}C-NMR spectra of the compound. It indicated the presence of twenty carbon atoms. Among these, two appeared at 170.9 and 170.3 ppm confirming the presence of two carbonyl carbons. A total of six sp^2 carbons were shown between 124.9-148.8 ppm confirming the presence of four aglycon and two glycon olefenic carbons. Presence of peak at 96.2 ppm confirmed the anomeric carbon atom. Apart from these, four oxygen linked carbons appeared between 63.4 to 79.7 ppm corresponding to three from glycon part for C-4, C-5, C-6 and one from *p*-menthanyl C-6 carbon atom. The seven carbons which appeared from 20.7 to 41 ppm are of the alkyl carbons both from glycon and aglycon. From the elemental analysis the molecular formula was calculated as $C_{20}H_{28}O_6$. The specific rotation (+55.5^o) of the product indicated that little racemization of the aglycon had occurred. From the above spectral data the structure of the compound was deduced as 6-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1,8-diene (Table 4.1, **2a**).

(-)-*cis*-6-Hydroxy-*p*-menth-1-ene (Table 4.1, **1b**) taken as the next substrate was prepared from the hydrogenation of *cis*-carveol in methanol using Raney nickel catalyst. After complete hydrogenation of isopropenyl double bond of the (-)-*cis*-carveol (monitored by the PMR for complete disappearance of 4.70 ppm peak), the product was distilled under reduced pressure. When the reaction of this substrate was conducted with tri-*O*-acetyl-D-glucal it was complete in 6 h and the product was isolated by silica column chromatography (80 %). The product was identified based on the following spectral data (Table 4.2 & 4.3, **2b**). A sharp IR absorption band at 1748 cm^{-1} indicated the presence of carbonyl group in the product. The PMR spectrum of the compound showed two closely spaced singlets at 2.04 and 2.06 ppm for the two acetyl groups in the molecule. A broad singlet which appeared at 5.10 ppm apart from the peak at 5.0 ppm and their relative integration ratio indicated 3.5:1 anomeric ratio of the *α* and *β*- forms. The olefenic protons which appeared at 5.86-5.90 ppm as multiplet indicated unsaturation in the molecule. Presence of a doublet (*J* = 2.5 Hz) at 0.81 ppm for six protons indicated the two methyls on C-8 in the aglycon. The

presence of double doublet (J = 3.2 and 6 Hz) at 5.29 ppm indicated the olefenic proton of aglycon at C-6 position. Further ^{13}C-NMR spectrum of the compound indicated the presence of twenty carbon atoms. Of these, two appeared at 170.8 and 170.2 ppm corresponding to two acetyl carbonyl carbons. A total of four sp^2 carbons appearing between 128-128.8 corresponded to two olefenic carbons from the glycon and two from the aglycon. Presence of peak at 96.2 ppm confirmed the anomeric carbon atom. Apart from these, four oxygen linked carbons appeared between 63.1 to 85.9 ppm corresponding to three from glycon part for C-4, C-5, C-6 and one from *p*-menthanyl C-6 carbon atoms. The nine carbons which appeared from 19.5 to 37.80 ppm are for the alkyl carbons both from glycon and aglycon. Further, the elemental analysis indicated the molecular formula of the product as $C_{20}H_{30}O_6$. The specific rotation (+66.53^o) of the product indicated that there was no racemization of the aglycon part. From the above spectral data, the structure of the compound was deduced as 6-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1-ene (Table 4.1, **2b**).

In the next example, 3-hydroxy-3-methyl-1-butene, an acyclic allylic alcohol (Table 4.1, **1c**) was taken for the reaction with tri-*O*-acetyl-D-glucal using in presence of $ZnCl_2$ catalyst. This reaction afforded 65 % isolated (silica column chromatography) product. The spectral properties of the product (Table 4.2, & 4.3, **2c**) are as follows. A sharp IR absorption band at 1747 cm^{-1} indicated the presence of carbonyl group in the product. The PMR spectrum of the compound showed two closely spaced singlets at 2.02 and 2.05 ppm for the two acetyl groups in the molecule. A broad singlet which appeared at 5.01 ppm apart from one at 4.99 ppm and their ratio indicated the 2:1 anomeric ratio of the *α* and *β*-isomers. The olefenic protons which appeared at 5.77-5.84 ppm as multiplet indicated the unsaturation in the molecule. Presence of double doublet (J = 1.3 and 9.6 Hz) at 5.26 ppm for one proton indicated the olefenic proton is split by the two ω-olefenic protons. These ω-olefenic protons appeared at 5.12 to 5.33 ppm as multiplet. Further, ^{13}C-NMR spectra of the compound indicated the presence of fifteen carbon atoms. Of these, two appeared at 170.7 and 170.2 ppm confirming the presence of two carbonyl carbons. A total of four sp^2 carbons appeared in between 128 to 128.8, corresponding to two olefenic carbons from glycon and

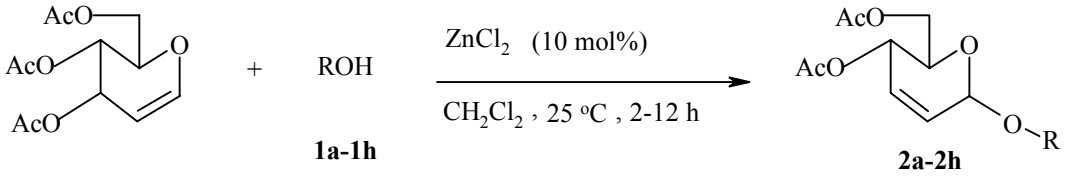
two in the aglycon. Presence of peak at 93.3 ppm confirmed the anomeric carbon atom. Apart from these, four oxygen linked carbons appeared between 63.1 to 66.9 ppm for three from glycon part for C-4, C-5, C-6 and one from aglycon carbon atom. The five carbons which appeared from 20.7 to 29.6 ppm are for the alkyl carbons both from glycon and aglycon. Further, the elemental analysis indicated the molecular formula to be $C_{15}H_{22}O_6$. The specific rotation ($+75^o$) of the product indicated that it was optically active. From the above spectral data the structure of the compound was deduced as 3-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-3-methyl-1-butene (Table 4.1, **2c**).

In order to extend the synthetic usefulness of the present method, Ferrier reaction was studied with benzyl alcohol (Table 4.1, **1d**). In this case, the reaction was found to be rapid (2 h) and gave an excellent yield (91 %) of the product. The reaction was fast apparently because, unlike in the tertiary substrate lesser steric hindrance was encountered by the glycon donor. The spectral data of the product (Table 4.2 & 3.3, **2d**) was in close agreement with the reported data.[50] The pure anomeric mixture was separated by column chromatography and ratio of *α*- and *β*-anomers was found to be 3:1 based on the integration of the anomeric protons at 5.31 ppm and 5.20 ppm in PMR spectrum. The product was found to be benzyl-4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosides (Table 4.1, **2d**).

The next substrate taken up for the study was 1-phenylethanol (Table 4.1, **1e**). It was obtained from the hydrogenation of the acetophenone in ethanol using Raney nickel catalyst. After completion of the reaction, product separated and distilled to get pure 1-phenylethanol. When reaction of this substrate was conducted with tri-*O*-acetyl-D-glucal in dichloromethane in the presence of $ZnCl_2$, it afforded the product, which was isolated by silica column chromatography in high yield (81 %). The spectral data of the product (Table 4.2 & 4.3, **2e**) are as follows. A sharp IR absorption band at 1745 cm^{-1} indicated the presence of carbonyl group in the product. The PMR spectrum of the compound showed two closely spaced singlets at 2.03 and 2.08 ppm for two acetyl groups in the molecule. A broad singlet which appeared at 5.27 ppm apart from the peak at 5.11 ppm corresponded to a 1.5:1 anomeric ratio of the *α* and *β*- forms. The olefenic protons which appeared at 5.86-5.89 ppm

as multiplet indicated the unsaturation in the molecule. Presence of doublet at 1.48 for three protons and a quartet at 3.99 ppm indicated the methine and methyl group attached to each other. Further ^{13}C-NMR spectra of the compound indicated the presence of eighteen carbon atoms. Of these, two appeared at 170.7 and 170.3 ppm confirming the presence of two carbonyl carbons. A total of eight sp^2 carbons appeared between 126 to 129.3 ppm corresponding to two from the glycon and six from the aglycon. Presence of a peak at 91.9 ppm confirmed the anomeric carbon.

Table 4.1: Reactions of 3,4,6-tri-*O*-acetyl-D-glucal with allylic, benzylic, and tertiary alcohols using $ZnCl_2$ as catalyst in dichloromethane at 25°C



R = Allylic, benzylic, tertiary

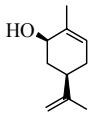
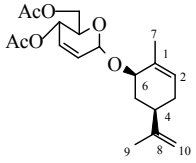
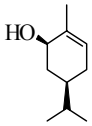
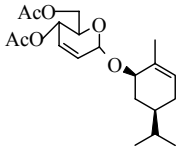
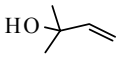
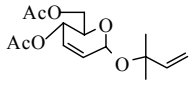
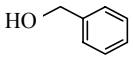
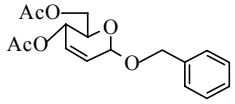
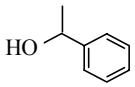
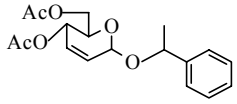
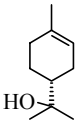
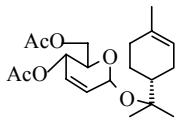
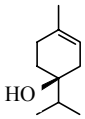
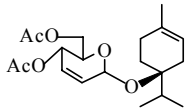
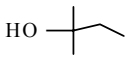
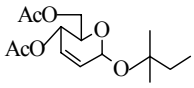
Entry	Substrate **1**	Product **2**	Reaction time (h)	Yield (%)	Anomeric Ratio α/β
a			8	70	3:1
b			6	80	3.5:1
c			6	65	2:1
d			2	91	3:1
e			6	81	1.5:1
f			12	60	1:1
g			10	65	1:1
h			12	74	1:1

Table 4.2: PMR and ^{13}C-NMR spectral data of products (Glycon followed by aglycon)

Product	^{1}H- NMR ($CDCl_3$, δ in ppm) (J in Hz)	^{13}C NMR ($CDCl_3$, proton decoupled)
2a	2.06(s, 3H), 2.08(s, 3H), 4.20-4.28(m, 4H), 5.17(s, 1H), 5.86-5.90(m, 2H) 1.19-1.24(m, 2H), 1.69(s, 3H), 1.70(s, 3H), 1.72-1.80(m, 3H), 4.72(s, 2H), 4.14(t, 1H, *J* = 6 Hz), 5.28(dd, 1H, *J* = 3.2 & 9.1 Hz)	170.9, 170.3, 128.8, 127.8, 96.2, 66.9, 65.5, 63.4, 20.9, 20.7 148.8, 128.3, 125.3, 124.9, 79.7, 41, 36, 35.2, 31, 30.9
2b	2.04(s, 3H), 2.06(s, 3H), 4.08-4.28(m, 4H), 5.10(s, 1H), 5.77-5.84(m, 2H) 0.81(d, 6H, *J* = 2.5 Hz), 1.0-1.65 and 1.70-1.90(m, 6H), 1.69(s, 3H), 3.08-3.16(m, 1H), 5.29(dd, 1H, *J* = 3.2 & 6 Hz)	170.8, 170.2, 128, 128.8, 96.2, 66.7, 65.3, 63.1, 20.9, 20.7, 128.6, 128.5, 85.9, 43.1 37.8, 32.7, 28.3, 19.8, 19.7, 19.4
2c	2.02(s, 3H), 2.05(s, 3H), 3.96-3.99(m, 1H), 4.15-4.26(m, 3H), 5.01(bs, 1H), 5.76-5.89(m, 2H) 1.65(s, 3H), 1.71(s, 3H), 5.26(dd, 1H, *J* = 1.3, 9.6 Hz), 5.12-5.33(m, 2H)	170.7, 170.2, 129.4, 128, 93.3, 65.4, 64.6, 63.1, 20.9, 20.7 129, 120.2, 66.9, 29.6, 28.2
2d	2.07(s, 3H), 2.09(s, 3H), 4.22-4.31(m, 1H), 4.60(d, 1H, *J* = 12 Hz), 4.79(d, 1H, *J* = 12 Hz), 5.13(s, 1H), 5.31-5.35(m, 1H) 4.13(s, 2H), 7.30-7.36(m, 5H)	170.7, 170.2, 129.3, 127.5, 93.6, 67.1, 65.4, 62.9, 20.9, 20.7 130.5, 128.5, 128, 126.9, 126, 70.3
2e	2.03(s, 3H), 2.08(s, 3H), 4.20-4.27(m, 2H), 4.78(dd, 1H, *J* = 4.2 & 8.2 Hz), 4.86-4.89(m, 1H), 5.27(bs, 1H), 5.86-5.89(m, 2H), 1.48(d, 3H, *J* = 4.1 Hz), 3.99 (q, 1H *J* = 4.1Hz), 7.30-7.36(m, 5H)	170.7, 170.3, 129, 127.8, 91.9, 67.4, 65.5, 63.2, 22.7, 21 129.3, 128.6, 128.3, 128.2, 126.4, 126, 75.1, 24.2
2f	2.05(s, 3H), 2.07(s, 3H), 3.92 (dd, 1H, *J* = 5.1& 9.9 Hz), 4.09-4.15(m, 2H), 4.23-4.30(m, 1H), 5.46(bs, 1H), 5.60-5.82(m, 2H) 1.16-1.20(m, 2H), 1.27(s, 6H), 1.35-1.57(m, 5H), 1.60(s, 3H), 5.26(bs, 1H)	171.1, 170, 137.6, 123.8, 90.6, 73.2, 71.2, 64.8, 21, 20.7 137.2, 122.7, 74.5, 39.9, 34, 28.5, 28, 27.6, 24.7, 23.9
2g	2.06(s, 3H), 2.08(s, 3H), 4.00-4.24(m, 3H), 4.33(dd, 1H, *J* = 5.5 & 12 Hz), 5.16(bs, 1H), 5.75-5.89(m, 2H) 0.88(d, 6H *J* = 2.9 Hz), 1.10-1.60 & 1.64-1.90(m, 7H), 1.63(s, 3H), 5.26(bs, 1H)	170.1, 170.7, 129.4, 127.4, 93.7, 67.1, 65.2, 62.9, 20.8, 20.7 136.8, 123.8, 67.3, 37.9, 30.5, 30.2, 29.5, 23.8, 20.6, 17.6
2h	2.05(s, 3H), 2.06(s, 3H), 4.12-4.29(m, 4H), 5.27(bs, 1H), 5.70-5.83(m, 2H) 0.87(t, 3H *J* = 6.8 Hz), 1.21(s, 3H), 1.22(s, 3H), 1.54(q, 2H *J* = 6.8 Hz),	170.8, 170.3, 129.6, 128.1, 88.8, 66.7, 65.4, 63.3, 21, 20. 72.8, 34.2, 26.2, 25.9, 8.4

Apart from these, four oxygen linked carbons appeared between 63.2 to 75.1 ppm for three from glycon part for C-4, C-5, C-6 and one from aglycon carbon atoms. The peak appearing at 75.1 ppm was identified for the carbon attached to both phenyl and oxygen of the glycon part. Further, the elemental analysis indicated the molecular formula of the compound to be $C_{18}H_{23}O_6$. From the above spectral data, the structure of the compound could be deduced as 1-phenethyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-eno-pyranoside (Table 4.1, 2e).

The anomeric ratios of the products were determined on the basis of the integration of α and β-forms by PMR spectra. In each unseparated mixture there was a weak signal for β–anomer at about 0.1 ppm up field from the α-anomer. The double doublet or broad singlet at 4.99-5.34 ppm for various alkyl pyranosides with coupling constant $J_{1,2}$ = 1.3-3.2 Hz and $J_{1,5}$ = 6-9.6 Hz are in close agreement with the literature values of various alkyl substituted unsaturated pyranosides.[34d]

This study, led to the successful synthesis of new glucal derivatives of allylic, benzylic and tert-alkyl alcohols by Ferrier reaction. The 2,3-unsaturated acetyl glucoside products of monoterpene alcohols are new derivatives. Also, the substrate chirality remained unaltered during glycosidation process. Thus, a new variant for Ferrier reaction of allylic, benzylic and tertiary alcohols was developed using the readily available, inexpensive zinc chloride as catalyst in CH_2Cl_2 solvent.

Table 4.3: Elemental analysis and specific rotation values of glycosides

Product	Anal. Calcd (Found)		Specific rotation
	C	H	$[\alpha]_D^{20}$ (c = 2, $CHCl_3$)
2a	65.89 (65.85)	7.74 (7.20)	+55.5
2b	65.53 (65.63)	8.25 (8.80)	+66.5
2c	60.39 (59.99)	7.43(7.59)	+75
2d	63.74 (63.05)	6.29 (6.15)	+28
2e	64.66 (64.38)	6.63(6.42)	+45
2f	65.55 (65.15)	8.25 (8.30)	+32.9
2g	65.55 (64.95)	8.25(8.47)	+34.4
2h	59.98 (59.75)	8.05 (7.75)	+63.5

Experimental

1. Preparation of 3,4,6-tri-*O*-acetyl-1,5-*anhydro*-2-deoxy-D-arabino-hex-1-enitol (3,4,6-tri-O-acetyl-D-glucal)[47]

In a three-necked 500 ml round-bottomed flask, dry acetic anhydride (200 ml) was taken and flask was cooled to 4°C. Perchloric acid (70 %, 1.2 ml) was added drop wise while stirring. The contents were allowed to attain room temperature, α-D-glucose (55 g, 0.3 mol) was added in portions with constant stirring while maintaining the temperature between 30-40°C. The flask was cooled to about 20°C and red phosphorus (15 g, 0.5 mol) was added in portions followed by drop-wise addition of bromine (90.5 g, 29 ml, 1.13 mol) keeping the temperature below 20°C. Water (18 ml) was added over half an hour (reaction highly exothermic) keeping the temperature below 20°C. Reaction mixture was allowed to stand at room temperature for 3 h, and then filtered and filter paper was washed with acetic acid. The filtrate containing α-acetobromoglucose was used in the next step of the reaction.

In a separate flask, 200 ml of glacial acetic acid and a solution of sodium acetate (200 g) in 290 ml of water were taken and cooled to –5 to 0°C. Cupric sulfate pentahydrate (7 g) and 110 g of zinc dust in 40 ml water were added to it. When the blue colour disappeared, α-acetobromoglucose (filtrate prepared as above) was added in portions over a period of 1 h. The contents were then stirred for 3 h at 0°C. The solids were filtered off using Buckner filter funnel and washed with 50 % acetic acid (50 ml) followed by 300 ml of cold water. The filtrate was transferred to a separatory funnel and extracted with $CHCl_3$ (5 x 100 ml). The organic layer washed with cold water followed by saturated $NaHCO_3$ solution, dried over calcium chloride and solvent evaporated at diminished pressure. To the crude product dry benzene (30 ml) was added and evaporated. To the resultant viscous mass 75 ml of dry ether was slowly added with warming and petroleum ether was added to the solution to opalescence. Tri-O-acetyl-D-glucal crystallized (41 g) was separated and to the mother liquor 20 ml of petroleum ether was added and second crop of the D-glucal (7 g) was isolated. The total product (48 g) was recrystallized from 1:1 mixture of light pet ether and ether to afford pure crystalline tri-O-acetyl-D-glucal (42 g, yield 50 %) m. p. 53-54°C.

2. Reaction of 3,4,6-tri-*O*-acetyl-D-glucal with 4-hydroxy-*p*-menth-1-ene (Terpinen-4-ol)

Terpenen-4-ol (0.77 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored for the complete consumption of the D-glucal, as well as the substrate by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (10 h) the product was added to water (25 ml), transferred to a separatory funnel and the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2) combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and pure glycoside was isolated.

4-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1-ene:

Yield: 1.19 g, 65 %, $[\alpha]_D^{20} = +34.4^o$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1746, 2965.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.06(s, 3H), 2.08(s, 3H), 4.00-4.24(m, 3H), 4.33(dd, 1H, *J* = 5.5 & 12 Hz), 5.16(bs, 1H), 5.75-5.89(m, 2H), Aglycon: 0.88(d, 6H *J* = 2.9 Hz), 1.10-1.60 & 1.64-1.90(m, 7H), 1.63(s, 3H), 5.26(bs, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.1, 170.7, 129.4, 127.4, 93.7, 67.1, 65.2, 62.9, 20.8, 20.7, Aglycon: 136.8, 123.8, 67.3, 37.9, 30.5, 30.2, 29.5, 23.8, 20.6, 17.6,

Elemental data: calculated for $C_{20}H_{30}O_6$, C = 65.55 & H = 8.25; found C = 64.95 & H = 8.47.

3. Reaction of 3,4,6-tri-*O*-acetyl-D-glucal with *p*-menth-1-ene-8-ol (*α*-Terpineol)

α-Terpineol (0.77 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed by anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (12 h), the mixture was added to water (25 ml), transferred to separatory a funnel when the organic layer separated. The aqueous layer was

extracted with the CH_2Cl_2 (15 ml x 2), combined organic layer washed with water, dried over Na_2SO_4 and solvent evaporated. The crude product (viscous oil) was column chromatographed on SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

8-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1-ene:

Yield: 1.10 g, 60 %, $[\alpha]_D^{20} = +32.9^o$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1744, 2937.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.05(s, 3H), 2.07(s, 3H), 3.92 (dd, 1H, *J* = 5.1& 9.9 Hz), 4.09-4.15(m, 2H), 4.23-4.30(m, 1H), 5.46(bs, 1H), 5.60-5.82(m, 2H).

Aglycon: 1.16-1.20(m, 2H), 1.27(s, 6H), 1.35-1.57(m, 5H), 1.60(s, 3H), 5.26(bs, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 171.1, 170, 137.6, 123.8, 90.6, 73.2, 71.2, 64.8, 21, 20.7.

Aglycon: 137.2, 122.7, 74.5, 39.9, 34, 28.5, 28, 27.6, 24.7, 23.9.

Elemental data: calculated for $C_{20}H_{30}O_6$, C = 65.55 & H = 8.25; found C = 65.15 & H = 8.30.

4. Reaction of 3,4,6-tri-*O*-acetyl-D-glucal with 2-methyl-butan-2-ol (*tert*-Amyl alcohol)

tert-Amyl alcohol (0.44 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (12 h), the mixture was added to water (25 ml), transferred to a separatory funnel when the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2), combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was column chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

tert-Amyl-4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranoside:

Yield: 1.12 g, 74 %, $[\alpha]_D^{20} = +63.5^o$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1747, 2974.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.05(s, 3H), 2.06(s, 3H), 4.12-4.29(m, 4H), 5.27(bs, 1H), 5.70-5.83(m, 2H).

Aglycon: 0.87(t, 3H *J* = 6.8 Hz), 1.21(s, 3H), 1.22(s, 3H), 1.54(q, 2H *J* = 6.8 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.8, 170.3, 129.6, 128.1, 88.8, 66.7, 65.4, 63.3, 21, 20.

Aglycon: 72.8, 34.2, 26.2, 25.9, 8.4.

Elemental data: calculated for $C_{15}H_{24}O_6$, C = 59.98 & H = 8.05; found C = 59.75 & H = 7.75.

5. Reaction of 3,4,6-tri-*O*-acetyl-D-glucal with 6-hydroxy-*p*-menth-1,8-diene (cis-Carveol)

cis-Carveol (0.76 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (8 h), the mixture was added to water (25 ml), transferred to a separatory funnel when the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2), combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was column chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

6-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1,8-diene

Yield: 1.27 g, 70 %, $[\alpha]_D^{20} = +55.5^o$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1735, 2967.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.06(s, 3H), 2.08(s, 3H), 4.20-4.28(m, 4H), 5.17(s, 1H), 5.86-5.90(m, 2H).

Aglycon: 1.19-1.24(m, 2H), 1.69(s, 3H), 1.70(s, 3H), 1.72-1.80(m, 3H), 4.72(s, 2H), 4.14(t, 1H, *J* = 6 Hz), 5.28(dd, 1H, *J* = 3.2 & 9.1 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.9, 170.3, 128.8, 127.8, 96.2, 66.9, 65.5, 63.4, 20.9, 20.7.

Aglycon: 148.8, 128.3, 125.3, 124.9, 79.7, 41, 36, 35.2, 31, 30.9.

Elemental data: calculated for $C_{20}H_{28}O_6$, C = 65.89 & H = 7.74; found C = 65.85 & H = 7.20.

6. Reaction of 3,4,6-tri-O-acetyl-D-glucal with 6-hydroxy-*p*-menth-1-ene

6-Hydroxy-*p*-menth-1-ene (0.77 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (6 h), the mixture was added to water (25 ml), transferred to a separatory funnel when the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2), combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was column chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

6-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-*p*-menth-1-ene:

Yield: 1.47 g, 80 %, $[\alpha]_D^{20} = +66.5^{O}$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1748, 2956.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.04(s, 3H), 2.06(s, 3H), 4.08-4.28(m, 4H), 5.10(s, 1H), 5.77-5.84(m, 2H).

Aglycon: 0.81(d, 6H, *J* = 2.5 Hz), 1.0-1.65 and 1.70-1.90(m, 6H), 1.69(s, 3H), 3.08-3.16(m, 1H), 5.29(dd, 1H, *J* = 3.2 & 6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.8, 170.2, 128, 128.8, 96.2, 66.7, 65.3, 63.1, 20.9, & 20.7.

Aglycon: 128.6, 128.5, 85.9, 43.1 37.8, 32.7, 28.3, 19.8, 19.7, 19.4.

Elemental data: calculated for $C_{20}H_{30}O_6$, C = 65.53 & H = 8.25; found C = 65.63 & H = 8.80.

7. Reaction of 3,4,6-tri-O-acetyl-D-glucal with 3-methyl-1-butene-3-ol

3-Methyl-1-butene-3-ol (0.43 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (6 h), the mixture was added to water (25 ml),

transferred to a separatory funnel when the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2), combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was column chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

3-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosyl)-3-methyl-1-butene:

Yield: 0.97 g, 65 %, $[\alpha]_D^{20} = +75^o$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1747, 2976.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.02(s, 3H), 2.05(s, 3H), 3.96-3.99(m, 1H), 4.15-4.26(m, 3H), 5.01(bs, 1H), 5.76-5.89(m, 2H).

Aglycon: 1.65(s, 3H), 1.71(s, 3H), 5.26(dd, 1H, *J* = 1.3, 9.6 Hz), 5.12-5.33(m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.7, 170.2, 129.4, 128, 93.3, 65.4, 64.6, 63.1, 20.9, 20.7.

Aglycon: 129, 120.2, 66.9, 29.6, 28.2.

Elemental data: calculated for $C_{15}H_{22}O_6$, C = 60.39 & H = 7.43; found C = 59.99 & H = 7.59.

8. Reaction of 3,4,6-tri-O-acetyl-D-glucal with 1-phenylethanol

1-Phenylethanol (0.61 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (6 h), the mixture was added to water (25 ml), transferred to a separatory funnel when the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2), combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was column chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

1-Phenethyl-4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranoside:

Yield: 1.42 g, 81 %, $[\alpha]_D$20 = +45o (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1745, 2965.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.03(s, 3H), 2.08(s, 3H), 4.20-4.27(m, 2H), 4.78(dd, 1H, *J* = 4.2 & 8.2 Hz), 4.86-4.89(m, 1H), 5.27(bs, 1H), 5.86-5.89(m, 2H).

Aglycon: 1.48(d, 3H, *J* = 4.1 Hz), 3.99 (q, 1H *J* = 4.1Hz), 7.30-7.36(m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.7, 170.3, 129, 127.8, 91.9, 67.4, 65.5, 63.2, 22.7, 21.

Aglycon: 129.3, 128.6, 128.3, 128.2, 126.4, 126, 75.1, 24.2.

Elemental data: calculated for $C_{18}H_{22}O_6$, C = 64.66 & H = 6.63; found C = 64.38 & H = 6.42.

9. Reaction of 3,4,6-tri-O-acetyl-D-glucal with benzyl alcohol

Benzyl alcohol (0.54 g, 5 mmol) dissolved in 10 ml anhydrous CH_2Cl_2, was taken in 50 ml round-bottomed flask. To this, was added D-glucal (1.36 g, 5 mmol) followed anhydrous $ZnCl_2$ (70 mg, 0.1 mmol, 10 mol %) and the mixture was stirred at room temperature. The progress of the reaction was monitored by t.l.c. using 15 % EtOAc in hexane. After completion of the reaction (2 h), the mixture was added to water (25 ml), transferred to a separatory funnel when the organic layer separated. The aqueous layer was extracted with the CH_2Cl_2 (15 ml x 2), combined organic layers washed with water, dried over Na_2SO_4 and solvent evaporated. The crude viscous product was column chromatographed over SiO_2 by elution with 10 % EtOAc in hexane and the glucoside was isolated in pure form.

Benzyl-4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranoside:[50]

Yield: 1.44 g, 91 %, $[\alpha]_D20 = +28^o$ (*c* = 2, $CHCl_3$).

IR (γ, cm^{-1}) = 1746, 2976.

PMR (400 MHz, $CDCl_3$, TMS internal standard) Glycon: 2.07(s, 3H), 2.09(s, 3H), 4.22-4.31(m, 1H), 4.60(d, 1H, *J* = 12 Hz), 4.79(d, 1H, *J* = 12 Hz), 5.13(s, 1H), 5.31-5.35(m, 1H).

Aglycon: 4.13(s, 2H), 7.30-7.36(m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$), Glycon: 170.7, 170.2, 129.3, 127.5, 93.6, 67.1, 65.4, 62.9, 20.9, 20.7.

Aglycon: 130.5, 128.5, 128, 126.9, 126, 70.3.

Elemental data: calculated for $C_{17}H_{20}O_6$, C = 63.74 & H = 6.29 found; C = 63.05 & H = 6.15.

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CHAPTER – 5

PREPARATION OF ALKYL THIOCYANATES AND THIOLS

Part A: **Ultrasound-Assisted Nucleophilic Substitution of S_N1-Active Halides with Zinc and Titanium Thiocyanate**

Part B: **Reduction of Thiocyanates; Preparation of Thiols**

Part A: Ultrasound-Assisted Nucleophilic Substitution of S_N1-Active Halides with Zinc and Titanium Thiocyanate

1. Zinc Salt-Assisted Substitution Reactions

The solvolysis reactions of *tert*-alkyl halides in the presence of equimolar quantities of zinc salt of the nucleophile to yield substitution products in high yields, is a discovery made in this laboratory.[1] Of IA and IB, IIA and IIB group metal acetates only copper, silver and zinc acetates afford good yields of the substitution products. Zinc acetate is superior to others especially in preparative methods.[2] The reactions are clean and isolation of the products is easy. The scope of the reaction is extended by the *in situ* generation of zinc salts in protic solvents and it has been successfully applied for the preparation of a series of monoterpenic alcohols, esters, and ethers.[3]

Following are the Salient features of the zinc salt-assisted substitution reactions: (1) Alkyl halides (tertiary, allylic, benzylic) undergo solvolysis affording predominantly the substitution products. (2) The reaction is applicable to water, low molecular weight primary alcohols and carboxylic acids. (3) Primary and secondary alkyl halides do not undergo substitution unless they are allylic or benzylic; the rate in these cases increases with the increasing in the substitution on the α-carbon atom. (4) No rearrangement product is formed in case of tertiary alkyl halides, but with allylic systems extensive isomerization is observed. (5) Bromides react at faster rate than the chlorides. (6) The reaction is not catalytic since molar equivalents of zinc salts are required for the completion of the reaction.

The scope of this reaction has been further extended under non-solvolytic conditions to the solid nucleophiles, viscous carboxylic acids and alcohols by carrying the reaction in solvents preferably those having low dielectric constant and high polarizability *viz*., CH_2Cl_2, benzene etc.[4] However, use of an organic base like pyridine in the reaction is mandatory to scavenge zinc chloride, which is formed during the reaction; otherwise it catalyzes the concomitant elimination and polymerization reactions. Similar to the solvolytic reaction, it is applicable to the tertiary, allylic, and benzylic systems. The preparative value of variant has been demonstrated by the preparation of several α-terpinyl, tert-butyl, and carvyl esters of the solid carboxylic acids.[5] The nucleophilic substitution reaction is subsequently extended

to the introduction of *S*- and *N*-nucleophiles, *viz*. mercaptides, thiocyanates, thiolacetates, isothiocyanates, and azides. Accordingly, thioethers (sulfides) have been prepared in excellent yields by reacting alkyl halides with zinc salt of the appropriate thiol in benzene-pyridine.[6] Interestingly, this applied not only to tertiary but also to the primary and to secondary alkyl halides, apparently owing to the superior nucleophilicity of the $^{-}$SR ion. Zinc azide, generated *in situ* from zinc chloride and sodium azide, is used for convenient synthesis of the azides from S_N1 active halides.[7] According to another report reduction of tertiary, allylic, benzylic alkyl halides has been carried out using zinc cyanoborohydride in anhydrous ether.[8]

2. Mechanism of Zinc Salt-Assisted Substitution Reactions

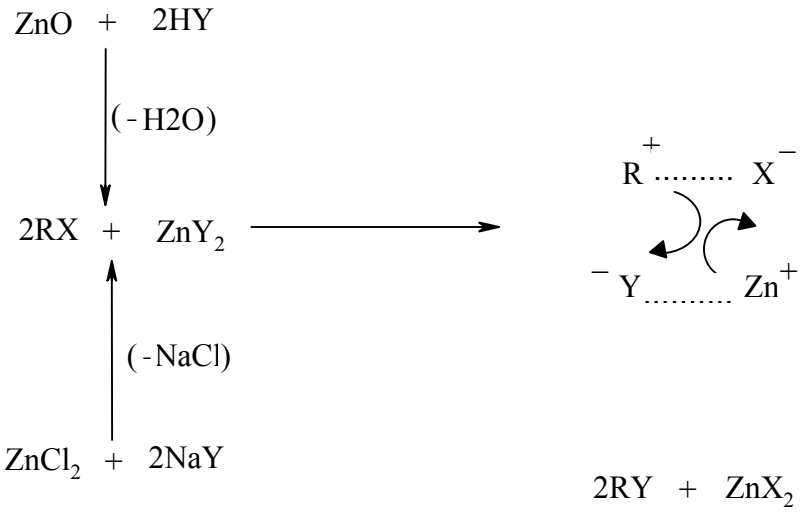
The aforesaid special features of the zinc salts displayed in the nucleophilic substitution reactions cannot be explained by either S_N1 or S_N2 mechanisms. Although the reaction is applicable to only S_N1 active substrates, the corresponding mechanism cannot explain certain special features observed. By S_N1 mechanism, one can expect the Wagner-Meerwein rearrangement products but these are not observed in the reaction. Back strain theory and pull-push mechanisms fail to explain these features. Since S_N1-active halides yield predominantly the substitution products, the reaction should proceed by initial ionization of the C-X bond. But the fact that no rearrangement is observed implied that the reaction proceeds through a tight ion-pair. For substitution to take place at the tertiary carbon, the incoming nucleophile needs to be close to the developing carbocation. To neutralize the charge, metal ion needs to be involved in the transition state. Hence, it is believed that the reaction of S_N1-active halides with zinc salts of nucleophiles proceed through an ion-quadruplet mechanism (Scheme 5.1).

Metal ions of high charge density and small size like alkali metal ions, being highly solvated, are not available for such ion-quadruplet formation and are thus ineffective in bringing about the substitution. Polar solvents and high temperatures could lead to dissociation of the ion-quadruplet, which may cause elimination.

Though a number of methods are available for direct introduction of thiocyanate group into an alkyl moiety, they are restricted either to primary or secondary alkyl halides.[9]

This is because of the isomerization of the initially formed thiocyanate under the influence of either heat or the reagent itself. Under normal experimental conditions, the thermodynamically more stable isothiocyanates are predominantly formed and it is difficult to introduce thiocyanate group at the tertiary carbon.

In case of zinc salt-assisted nucleophilic substitution reactions, it is established that the dissociation of halide from the alkyl group is almost concomitant with the dissociation of bond between zinc and the nucleophile. Hence, the formation of carbocation is suppressed due to formation of an ion quadruplet and thereby competitive elimination reaction is reduced considerably, leading to high yields of the substitution products.



RX (X = Cl, Br)	HY	RY
(R = Tertairy alkyl, Allylic or Benzylic	H_2O	Alcohols
	ROH	Ethers
	RCOOH	Esters
	RCOSH	Thioesters
	(M) (SCN)	Thiocyanates (Iso)
	(M) N_3	Azides

Scheme 5.1

3. Ultrasound in Organic Synthesis

3.1 Background

Sound wave frequency that lies in 20 to 10,000 kHz range is termed as 'ultrasound' in analogy to ultraviolet radiation. It has found manifold applications in the field of medical imaging, non-destructive testing of materials, underwater ranging, welding of thermoplastics, location of oil, mineral deposits, etc.[11]

Though the application of ultrasound in the chemical and biological field predates to 1940, but to the synthetic field it is more recent (1980). It is actually in the late 90s, its application in the area of synthetic organic chemistry has become most significant. The chemical effects of ultrasound do not arise from any direct input of sonic energy to species on molecular level. The wavelength associated with the sound energy lies in the range 7.5 to 0.015 cm, which is not enough to produce a chemical reaction. As the sound waves move through the liquid media, they generate a series of compressions and rarefactions. By this process, solvent molecules generate small and large bubbles. Large bubbles simply oscillate radially with the sound and are not responsible for chemical effects. This behavior is called 'stable cavitation'. The small bubbles re-dissolve as fast as they are formed. Their lifetime is a few acoustic seconds, during which they expand 2 to 3 times their initial size and these violently collapse there by producing enormous pressure and temperature. This process is termed 'transient cavitation' and chemical effects observed arise directly from this phenomenon. The simple laboratory sonochemical cleaning bath to conduct chemical reactions is shown in Figure 5.1.

3.11 Ultrasound in substitution reactions

One of the earliest examples refers to Finkelstein exchange by which ω-bromo fatty acid is transferred to I^{123}, the I-analog.[12] In a report on the solvolysis of *tert*-butyl chloride in water/ethanol mixture, Mason and co-workers surmise that the rate of reaction must be dependent on the degree of solvation in the transition state prior to ionization.[13] Aroyl nitriles are prepared from the corresponding chlorides by displacement with potassium cyanide.[14] For the synthesis of aryl nitriles by the substitution reaction, ultrasound is found to be essential.[15] *N*-Alkylation of pyrroles with alkyl halides such as methyl iodide, ethyl

bromide, and benzyl bromide is accelerated by ultrasound and good yield of the products result.[16] Wurtz-type coupling of alkyl and aryl halides[17] and *N*-alkylation of amines by alkyl halides are found to be accelerated by ultrasound.[18] The chemical and physical effects of ultrasound on the substitution reaction of alkyl halides with potassium thiocyanate and sodium benzoate has been reported by Xiaoyun *et al*.[19] Two phase sonochemical irradiation is the choice over the triphase system (phase transfer catalyst) for the synthesis of alkyl azides and α-azido ketones from alkyl halides and α-tosyloxyketones.[20] Preparation of *tert*-alkyl acetates from halides is very difficult due to complication of competitive elimination, the use of both a phase-transfer catalyst and ultrasound favors the displacement by $Zn(OAc)_2$.[21]

4. Preparation of *tert*-Thio-/Isothiocyanates

The reaction of S_N1-active halides with zinc thiocyanate prepared *in situ* leads to the formation of mixtures of thio- and isothiocyanates. Since the reaction is carried out under the influence of heat, the initially formed thiocyanates are to a considerable extent isomerized isothiocyanates which are thermodynamically more stable. Also, isomerization of the ambident nucleophile itself becomes more competitive under the reaction conditions. With idea that the application of milder reaction conditions could help in surmounting this problem and along with the observation that many zinc-mediated reactions are accelerated by ultrasonic irradiation,[10,11] the investigation of the reaction of *tert*-halides with the zinc thiocyanate and titanium thiocyanate, generated *in situ*, under the influence of ultrasound was undertaken.

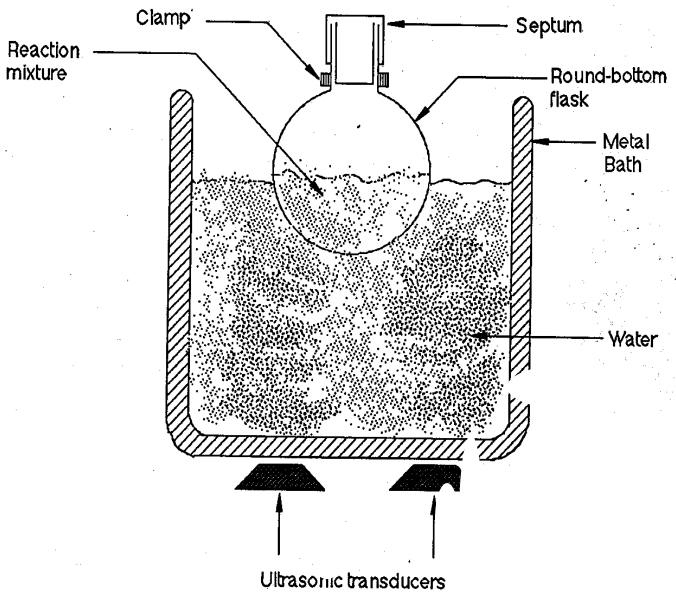

Clamp
Septum
Reaction mixture
Round-bottom flask
Metal Bath
Water
Ultrasonic transducers

Figure 5.1

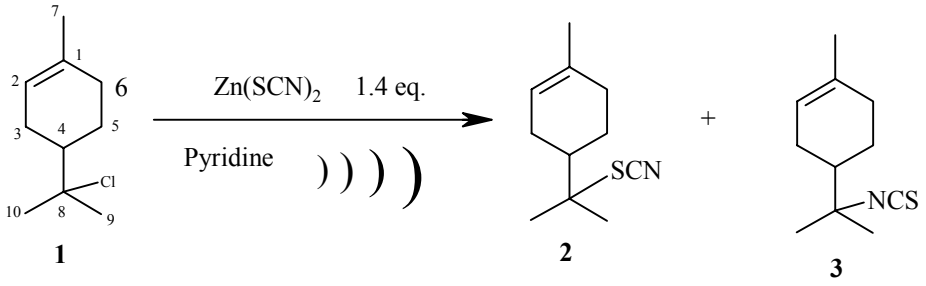
Present Work

α-Terpinyl chloride (Scheme 5.2, **1**), a tertiary halide, was chosen as a model substrate for the exploratory study of the reaction with zinc thiocyanate under the influence of ultrasound. The use of organic base like pyridine was mandatory to avoid formation of elimination products catalyzed by zinc chloride, generated *in situ*. Preparation of zinc thiocyanate from calcium thiocyanate and zinc sulfate in an aqueous media after removal of insoluble calcium sulfate is a subject matter of a patent.[22] Calcium thiocyanate, in turn, is prepared from ammonium thiocyanate and calcium hydroxide. In the present study it was prepared by reacting equimolar quantity of potassium thiocyanate with zinc chloride and procedure has been standardized.

The reaction of α- terpinyl chloride with zinc thiocyanate was carried out in a solvent of low dielectric constant and high polarizability like CH_2Cl_2. TLC analysis (hexane) of the products showed initially only one spot with R_f of 0.3 corresponding to the α-terpinyl thiocyanate appeared; but subsequently formation of a compound with higher R_f of 0.7 identified to be α-terpinyl isothiocyanate was also observed. Total yield of the substitution products, thio- and isothiocyanates, was found to be superior to that reported earlier[23] (there the reaction had been conducted in refluxing CH_2Cl_2). Also, the reaction time was less, showing that the substitution reaction was accelerated by the application of ultrasound. The products, after isolation in pure form by column chromatography, were identified as α-terpinyl thiocyanate and α-terpinyl isothiocyanate based on spectral data and also by a comparison of their physical and spectral data with those reported earlier.[23] The characteristic bands of SCN and NCS stretching of the thio- and isothiocyanates in the IR spectra appeared at 2140 cm^{-1} as a sharp peak and 2105-2060cm^{-1} as a broad signal respectively. In the mass spectra of the compounds, the intensity of the molecular ion peak for thiocyanate was found to be lesser compared to isothiocyanates (*m/z* of M^+ = 195(2) for thiocyanate and 195(22) for isothiocyanate). This feature was commonly observed with all the alkyl thio and isothiocyanates prepared now. Further confirmation of the structure of the molecule was obtained by the elemental analysis report (C: H: N: S = 5.62: 9.01: 0.52: 0.50). In this case the molecular formula could be deduced as $C_{11}H_{17}NS$. The selectivity of this

method was reflected by the superior yield of thiocyanate over isothiocyanate, where the corresponding ratio was 4:1 compared to 2.5:1 ratio achieved in earlier method.

Substitution of *α*-terpinyl chloride with zinc thiocyanate under the ultrasonic irradiation was then studied in different solvents. In $CHCl_3$, the reaction was found to be slower than in CH_2Cl_2 (16 h) and also the yield was lower (reduced to 60 % from 80 %). But increase in the ratio of thio- to isothiocyanate from 4:1 to 7:1 was observed. The reaction conducted in dry THF yielded only 35 % of substitution products with thio- to isothiocyanate ratio being 2.5:1. Here the reaction was found to be even slower (36 h). In benzene, reaction was found to be even slower (40 h) with a yield of 56 % and the ratio of thio- to isothiocyanate was 3:1. The results are summarized in the Table 5.1. Thus CH_2Cl_2 was found to be the solvent of choice. The method was successfully applied to the synthesis of tertiary alkyl thiocyanates in higher yields under milder reaction conditions by reaction of alkyl halides with zinc thiocyanate under ultrasonication in CH_2Cl_2.



Scheme 5.2

Table 5.1: Results of ultrasound-assisted nucleophilic substitution reaction of *α*–terpinyl chloride (8-chloro-*p*-menth-1-ene) with zinc thiocyanate in various solvents.

Solvent	Reaction time (h)	% Yield	% SCN	% NCS	SCN: NCS
Dichloromethane	16	80	64	16	4:1
Chloroform	32	60	52.5	7.5	7:1
Tetrahydrofuran	36	35	25	10	2.5:1
Benzene	40	56	42	14	3:1

The scope and limitation of this reaction was studied in detail with different substrates. A secondary alkyl halide like *trans*-carvyl chloride and benzylic substrate like benzyl chloride were found to be non-reactive even when the reactants were sonicated for 48 h. 1,1-Dimethylphenylcarbinyl chloride, which is a tertiary as well as benzylic halide, reacted at faster rate but afforded isomeric isothiocyanate as major product over the corresponding thiocyanate. The results are summarized in Table 5.2.

In a study of reaction of several *tert*-halides with zinc thiocyanate, 1-menthanyl chloride (Scheme 5.3, **2b**), took 37 h for completion, which was apparently due to the steric hindrance at the tertiary carbon atom. This reaction under ultrasonic conditions, however, was faster than the one carried out under classical conditions and also afforded higher yield of substitution products (52 %). The mixture was isolated by silica column chromatography; the first compound obtained identified was 1-menthene, a dehydrohalogenated product from the substrate. The next compound that eluted from the column was 1-menthanyl isothiocyanate (IR broad at 2088 cm^{-1}) followed by 1-menthanyl thiocyanate (IR sharp at 2149 cm^{-1}). The other characteristic PMR and mass spectral data (M^+ = 197 (2) and 197(1) for isothiocyanate and thiocyanate respectively) are comparable with that of authentic samples. The ratio of SCN: NCS was found to be 7:1. Elemental analysis data (C: H: N: S = 5.57: 9.97: 0.55: 0.50) indicated the molecular formula for the compound as $C_{11}H_{19}NS$.

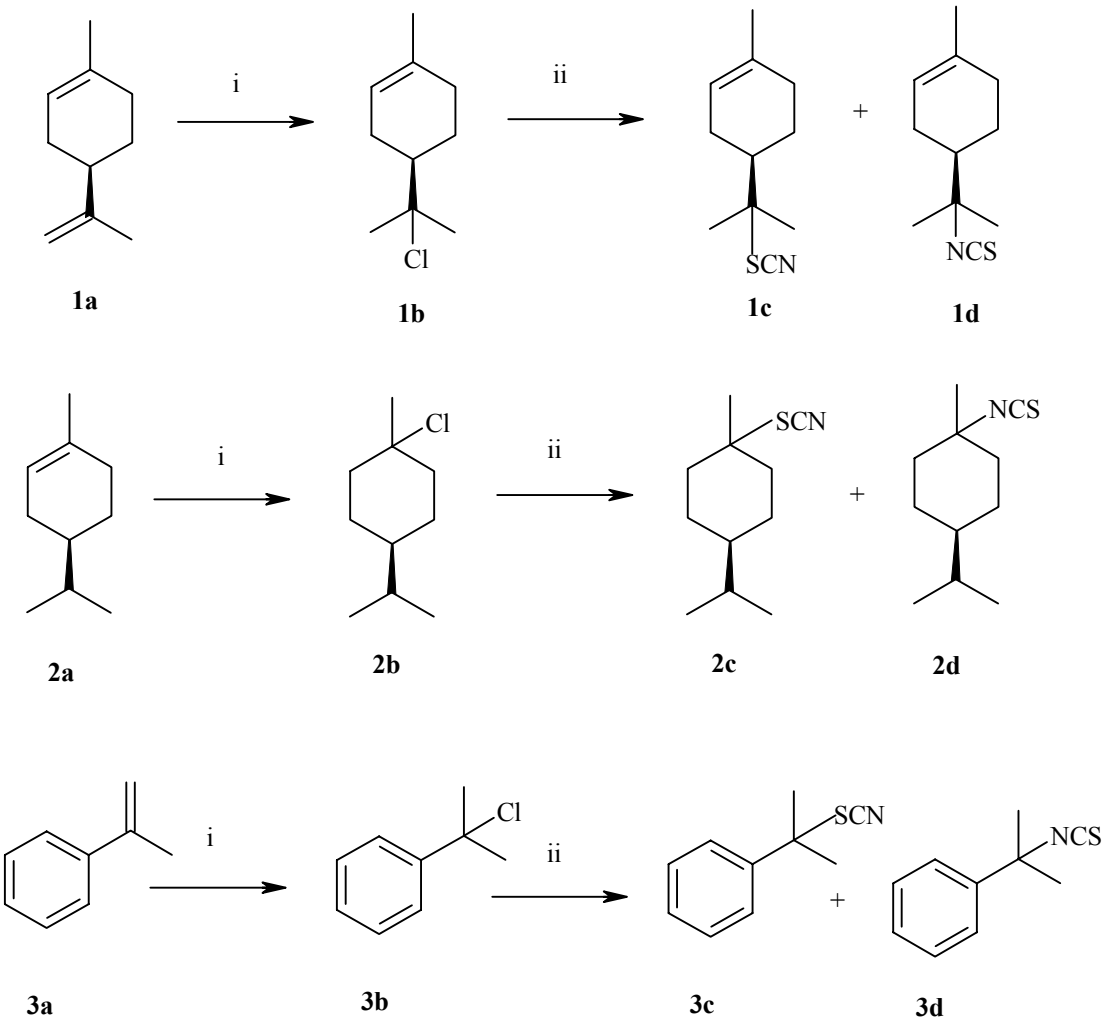
In case of *tert*-butyl chloride and *tert*-butyl bromide, acceleration of the reaction was observed with superior yields of the thiocyanate isomers under ultrasound conditions as compared to the reaction under classic conditions under reflux. The faster reaction time for bromides can be attributed to the higher reactivity of bromides compared to chlorides. In these two cases, two products isolated by silica column chromatography have been identified separately and found both had the similar physical and spectral characteristics as those reported for them in literature. Further they were characterized by the mass spectral (M^+ = 115(39) and 115(2) for isothiocyanate and thiocyanate respectively) and elemental analysis data (C: H: N: S = 4.37: 7.87: 1.01: 0.87). The molecular formula was deduced as C_5H_9NS.

Similarly, the reaction with *tert*-amyl chloride afforded superior yields of substitution products and also better selectivity as indicated by the thio- to isothiocyanate ratio of 7:1. In this case too, the two products isolated by silica column chromatography have been identified separately and found both had the similar physical and spectral characteristics as that of the *tert*-amyl isothiocyanate and *tert*-amyl thiocyanate. Further, their mass spectral (M^+ = 129(20) and 129(1) for isothiocyanate and thiocyanate respectively) and elemental analysis data (C: H: N: S = 4.63: 8.51: 0.77: 0.77) confirmed the molecular formula as $C_6H_{11}NS$.

In case of benzylic tertiary substrate like 1,1-dimethylphenylcarbinyl chloride, the (Scheme 5.3, **3b**) reaction was found to be very fast and gave overall substitution yield of 62 % in 3.5 h. Two products isolated by silica column chromatography have been identified separately and found both had physical and spectral characteristics similar as that for those reported for 1,1-dimethylphenylcarbinyl thio- and isothiocyanates. Further their identity was confirmed by the mass spectral (M^+ = 177(2) and 177(1) for isothiocyanate and thiocyanate respectively) and elemental analysis data (C: H: N: S = 5.62: 6.18: 0.55: 0.57). The molecular formula was deduced as $C_{10}H_{11}NS$. However, in this case formation of isothiocyanate was found to be more compared to thiocyanate (0.6:1). This difference can be explained by facile isomerization of initially formed thiocyanate especially at the benzylic tertiary position.

Table 5.2: Ultrasound-assisted nucleophilic substitution of alkyl halides with zinc thiocyanate-pyridine in CH_2Cl_2.

Substrate	Reaction time (h)	Yield (%)	SCN: NCS	SCN (% yield)
α–Terpinyl chloride	16	80	4:1	64
1-Menthanyl chloride	27	52	7:1	45
tert-Butyl chloride	12	55	8:1	50
tert-Butyl bromide	05	75	6:1	65
tert-Amyl chloride	08	86	7:1	76
1,1-Dimethylphenyl carbinyl chloride	3.5	62	0.6:1	24
Benzyl chloride	48	0	------	------
trans-Carvyl chloride	48	0	------	------



i: Dry HCl, 0°C, ii: $Zn(SCN)_2$ or $Ti(SCN)_4$, ultrasound

Scheme 5.3

Reaction of Tertiary Alkyl Halides with $Ti(SCN)_4$ in CH_2Cl_2-Pyridine under the Influence of Ultrasound

Reports on the synthesis and reaction of thiocyanate nucleophile in the form of titanium salt for *C-S* bond formation are scanty. Since, there is no general method available as such for the preparation of $Ti(SCN)_4$. Its preparation was now standardized and then it was employed for the *C-S* bond formation at the tertiary centre. The reaction of $TiCl_4$ with sodium or potassium thiocyanate in anhydrous CH_2Cl_2 analogous to the preparation of the

corresponding zinc thiocyanate, however, resulted in the darkening of the mixture and the resultant salt when employed in ultrasound assisted reaction with α–terpinyl chloride failed to yield the desired product even after 48 h. Alternatively, its preparation *in situ* from zinc thiocyanate and $TiCl_4$ was explored. On contacting catalytic quantity (10 mol %) of $TiCl_4$ with zinc thiocyanate in CH_2Cl_2, instantaneous formation of an orange yellow salt was seen. The salt, thus prepared, when employed in the reaction gave the substitution product in superior yield.

In the first instance, reaction of α–terpinyl chloride with $Ti(SCN)_4$ was conducted in CH_2Cl_2 under the influence of ultrasound. Interestingly, the reaction was further accelerated and found to afford higher yield of substitution products along with the increase in selectivity of thio- to isothiocyanates. In case of 1-menthanyl chloride, as the substrate was sterically crowded elimination reaction competed with the substitution. The results of substitution reaction of titanium thiocyanate with various other halides are given in Table 5.3. A comparison of results of ultrasound-assisted nucleophilic substitution of *tert*-halides with zinc and titanium thiocyanates are presented in Table 5.4

From the above results, it can be concluded that the application of titanium thiocyanate for the nucleophilic substitution at the tertiary centre has more pronounced effect than zinc thiocyanate. There were considerable acceleration of the reaction rate and improvement in the yields of the substitution products. Though the selectivity of thio- to isothiocyanate was little lesser in certain cases, the total yield of the thiocyanate was found to be greater than in zinc thiocyanate mediated reactions. Thus, the thiocyanate nucleophile can be introduced at the tertiary center by reaction with either zinc or titanium thiocyanate as a special application in the *C-S* hetero bond formation under sonic conditions. The present methodology can be adopted for the large-scale production of thiocyanates, since it requires the use of readily producible and inexpensive zinc and titanium thiocyanate salts. These reactions proceeds in a facile manner, the workup and product isolation are simple.

Table 5.3: Ultrasound-assisted nucleophilic substitution of tertiary alkyl halides with $Ti(SCN)_4$-pyridine in CH_2Cl_2.

Substrate	Reaction time (h)	Yield (%)	Quantity of substrate(g)	Quantity of product (g)	SCN: NCS	SCN (% yield)
α–Terpinyl chloride	6	83	5.17	4.84	4:1	66.4
1-Menthanyl chloride	10	65	5.23	3.83	3:1	48
tert-Butyl chloride	5	83	2.46	2.87	7:1	73
tert-Butyl bromide	1	63	4.11	2.19	6:1	54
tert-Amyl chloride	5	85	3.19	3.29	9:1	76.5

Table 5.4: Comparison of results of ultrasound-assisted nucleophilic substitution reactions of tertiary alkyl halides with zinc and titanium thiocyanates in CH_2Cl_2

Substrate	Reaction time (h)		Yield (%)		SCN: NCS		SCN (% yield)	
	A	B	A	B	A	B	A	B
α–Terpinyl chloride	16	6	80	83	4:1	4:1	64	66.4
1-Menthanyl chloride	27	10	52	65	7:1	3:1	45	48
tert-Butyl chloride	12	5	55	83	8:1	7:1	50	73
tert-Butyl bromide	5	1	75	63	6:1	6:1	65	54
tert-Amyl chloride	8	5	86	85	7:1	9:1	76	76.5

A = $Zn(SCN)_2$ mediated reaction; B = $Ti(SCN)_4$ mediated reaction

Experimental

1. Preparation of $Zn(SCN)_2$ (Salt A)

Zinc chloride (0.1 mol, 13.63 g) and potassium thiocyanate (0.1 mol, 19.44 g) were taken in dry benzene and refluxed for 8 h with azeotropic removal of traces of moisture. The solvent was first decanted. The salt was then dried first using a flash evaporator and then in a vacuum desiccator over P_2O_5 for 12 h. The resultant dry salt (Salt A, 33 gm) was used in experiments.

2. Preparation of $Ti(SCN)_4$ (Salt B)

Titanium tetrachloride (0.37 g, 2.1 mmol, 10 mol %) was added to zinc thiocyanate (Salt A, 6.8 g) in CH_2Cl_2. The mixture was sonicated for ten min. As soon as titanium tetrachloride was added to a solution containing zinc salt, color of the solution turned to orange yellow color. This titanium thiocyanate (Salt B) was used in reactions as such.

3. Reaction of *α*-terpinyl chloride with $Zn(SCN)_2$ in CH_2Cl_2: Preparation of *α*-terpinyl thio- and isothiocyanate.

Salt A (6.8 g), which contained 3.73 g (21 mmol) of $Zn(SCN)_2$ was taken in a 100 ml round-bottomed flask along with 40 ml of anhydrous CH_2Cl_2 and the flask was subjected to sonication as shown in Figure 5.1. The frequency range of ultrasonic bath used was in the range of 40-50 kHz and RF power of 80 watts. A solution of pyridine (2.37 g, 30 mmol) and α- terpinyl chloride (5.17 g, 30 mmol) in 10 ml of anhydrous dichloromethane was added and sonication continued till the completion of the reaction (16 h). Reaction was monitored for the disappearance of *α*-terpinyl chloride on both t.l.c. and GC. At the end of the reaction, the product was worked up by putting into 100 ml of 5 % HCl solution and the organic layer was separated. The organic layer was washed free of acid with water (50 ml X 2) and finally with brine (50 ml). It was then dried over anhydrous Na_2SO_4 and removal of solvent afforded a crude product (5.41 g). The products were isolated by column chromatography over silica gel (70 g) using hexane as eluant to afford *α*–terpinyl isothiocyanate. Subsequent elution with 2 % ethyl acetate gave pure α- terpinyl thiocyanate. The products thio- and isothiocyanates were further purified by distillation under reduced pressure.

α–Terpinyl isothiocyanate: 0.91 g, Yield 16 %, b. p. 96-97°C/1.5 Torr, [Lit[23] 96°C/1.5 Torr].

IR (γ cm^{-1}) = 2923, 2150(s) 2917, 2087.

PMR: δ = 1.43(3H, s) 1.46(3H, s) 1.70(3H, s) 1.73-2.03(7H, m, br) 5.46(1H, m, br).

MS (*m/z*): 195(22), 180(4), 162(2), 138(6), 1363(5), 121(60), 100(35), 93(100), 81(75), 67(60), 41(85).

Elemental Analysis: Found (Calculated).

C	H	N	S
67.51	9.01	7.30	16.04
(67.64)	(8.77)	(7.17)	(16.41)

α-Terpinyl thiocyanate: 3.74 g, Yield 64 %, b. p. 121-122°C/1 Torr, [Lit[23] 116°C/2 Torr].

IR (γ cm^{-1}) = 2923, 2150(s).

PMR: δ = 1.52(3H, s) 1.60(3H, s) 1.70(3H, s) 1.80-2.40(7H, m, br) 5.46(1H, m, br).

MS (*m/z*): 195(2), 180(2), 138(5), 136(35), 121(40), 107(20), 93(100), 68(75), 59(80). 41(42).

Elemental Analysis: Found (Calculated).

C	H	N	S
67.51	9.01	7.30	16.04
(67.64)	(8.77)	(7.17)	(16.41)

4. Reaction of *α*-terpinyl chloride with $Zn(SCN)_2$ in various organic solvents Preparation of *α*-terpinyl thio- and isothiocyanate.

Salt A (6.8 g), which contains 3.73 g (21 mmol) of $Zn(SCN)_2$ was taken in a 100 ml round-bottomed flask and in each separate experiment 40 ml of organic solvent like CH_2Cl_2, $CHCl_3$, THF, PhH was added and the flask was subjected to sonication as shown in Figure 5.1. The frequency range of ultrasonic bath used was in the range of 40-50 kHz and RF power of 80 watts. Then a solution of pyridine (2.37 g, 30 mmol) and *α*-terpinyl chloride (5.17 g, 30 mmol) in 10 ml of different organic solvents was added and sonicated as the time indicated in the Table 5.1.The reactions were monitored for the disappearance of *α*–terpinyl chloride by t.l.c. using hexane as solvent. After completion of reaction, aqueous workup of products and evaporation of solvent afforded crude product, which was subjected to column

chromatographic isolation over silica gel (70 g in each case) using hexane as eluant followed by 2 % EtOAc in hexane. The fractions having similar R_f's were combined and concentrated separately. These were further purified by distillation under reduced pressure. The yields of product, reaction time and ratio of thiocyanate to isothiocyanate are presented in Table 5.1.

5. Reaction of *α*-terpinyl chloride with $Ti(SCN)_4$ in CH_2Cl_2
Preparation of *α*-terpinyl thio- and isothiocyanate.

To the salt B generated *in situ* in 100 ml round-bottomed flask, a solution of *α*-terpinyl chloride (5.17 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in 10 ml of anhydrous CH_2Cl_2 was added. The contents were subjected to sonication at the frequency range of 40-50 kHz and RF power of 80 watts. The reaction was monitored for the disappearance of *α*-terpinyl chloride by TLC (hexane). After completion of reaction (6 h), it was poured into 5 % HCl (100 ml) and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (25 ml X 2) and combined with previous extract. Further washings of the organic layer with water (50 ml X 2) and concentration under vacuum afforded the crude product. It was isolated by column chromatography over silica gel (70 g) using hexane and 2 % EtOAc in hexane afforded *α*-terpinyl isothiocyanate and *α*-terpinyl thiocyanate. These were further purified by distillation under reduced pressure.

α–Terpinyl isothiocyanate: 0.95 gm, Yield 16 %.

α-terpinyl thiocyanate: 3.89 gm, Yield 66.4 %.

6. Reaction of 1-menthanyl chloride (1-chloro-*p*-menthane) with $Zn(SCN)_2$ in CH_2Cl_2: Preparation of 1-menthanyl thio- and isothiocyanate.

Salt A (6.8 g), which contains 3.73 g (21 mmol) of $Zn(SCN)_2$ was taken in a 100 ml round-bottomed flask along with 40 ml of anhydrous CH_2Cl_2. The flask was subjected to sonication in the frequency range of 40-50 kHz and RF power of 80 watts using ultrasonic bath. Then a solution of 1-menthanyl chloride (5.23 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in 10 ml anhydrous CH_2Cl_2 was added and sonicated as before. The reaction was monitored by GC for the disappearance of 1-menthanyl chloride by periodic injection of worked-up aliquot of sample. After completion of reaction (27 h), it was poured into 100 ml of 5 % HCl and organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (25

ml X 2) and combined organic layer was washed free of acid. Evaporation of the solvent afforded the crude product which was isolated over silica gel (70 g) chromatography using hexane as eluant followed by 2 % EtOAc in hexane. Fractions having similar retention time on GC were combined and evaporation of the solvent afforded two products. These were further purified by distillation under reduced pressure.

1-Menthanyl isothiocyanate: 0.40 g, Yield 6.7 %, b. p.117-119^{o}C /3.5 Torr [Lit[23] 117-119/3.5 Torr]

IR (γ cm^{-1}) = 2936, 2868, 2088(br).

PMR: δ = 0.93(6H, d) 1.43(3H, s) 1.03-1.40 & 1.50-2.13(10H, m).

MS (*m/z*): 197(2), 196(4), 164(4), 138(5), 139(15), 123(3), 97(15), 83(100), 69(50), 55(80), 41(60).

Elemental Analysis: Found (Calculated)

C	H	N	S
66.84	9.97	7.70	16.02
(66.95)	(9.70)	(7.09)	(16.24)

1-Menthanyl thiocyanate: 2.65 gm, Yield 45 %, b. p. 110-112^{o}C/1.5 Torr [Lit[23] 110^{o}C/3.5 Torr]

IR (γ cm^{-1}) = 2934, 2858, 2149(s).

PMR: δ = 0.93(6H, d) 1.56(3H, s) 1.00-1.50 & 1.60-2.10(10H, m).

MS (*m/z*): 197(1), 196(1), 164(1), 139(4), 138(18), 123(8), 96(10), 95 (100), 83(100), 68(45), 67(70), 55(40), 41(45).

Elemental Analysis: Found (Calculated)

C	H	N	S
66.84	9.97	7.70	16.02
(66.95)	(9.70)	(7.09)	(16.24)

7. Reaction of 1-menthanyl chloride (1-chloro-*p*-menthane) with $Ti(SCN)_4$ in CH_2Cl_2: Preparation of 1-menthanyl thio- and isothiocyanate.

To the salt B, prepared *in situ* in a 100 ml round-bottomed flask added a solution of 1-menthanyl chloride (5.23 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in 10 ml of anhydrous CH_2Cl_2 was added. The flask was subjected to sonication in the frequency range

of 40-50 kHz and RF power of 80 watts using ultrasonic bath. The reaction was monitored for the disappearance of 1-menthanyl chloride by GC. After completion of reaction (10 h), it was poured into 100 ml of 5 % HCl solution and organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (25 ml X 2) and combined with previous layer. It was washed free of acid with water (25 ml X 2), dried over anhydrous Na_2SO_4 and concentrated in a flash evaporator. The resultant crude product was isolated over silica gel (70 g) chromatography using hexane as eluant followed by 2 % Et_2OAc in hexane afforded two products.

1-Menthanyl isothiocyanate: 1.03 g, Yield 17.4 %.

1-Menthanyl thiocyanate: 2.80 g, Yield 47.3 %.

8. Reaction of *tert*-amyl chloride with $Zn(SCN)_2$ in CH_2Cl_2: Preparation of *tert*-amyl thio- and isothiocyanate.

Salt A (6.8 g), which contains 3.73 g (21 mmol) of $Zn(SCN)_2$ was taken in a 100 ml round-bottomed flask in 40 ml of anhydrous CH_2Cl_2. The flask was subjected to sonication in the frequency range of 40-50 kHz and RF power of 80 watts using ultrasonic bath. Then a solution of pyridine (2.37 g, 30 mmol) and *tert*-amyl chloride (3.19 g, 30 mmol) in 10 ml of dichloromethane was added and sonicated as before. The reaction was monitored for the disappearance of *tert*–amyl chloride by GC. After completion of reaction (8 h), the product was poured into 100 ml of 5 % HCl and organic layer separated. The aqueous layer was re-extracted with CH_2Cl_2 (25 ml X 2) and it was combined with previous layer. Organic layer washed free of acid with water and concentrated in flash evaporator. The crude product was chromatographed over silica gel (70 g) using hexane as eluant followed by 2 % EtOAc in hexane afforded *tert*-amyl isothiocyanate and *tert*-amyl thiocyanate. These were further purified by distillation under reduced pressure.

tert-Amyl isothiocyanate: 0.42 g, Yield 10 %, b. p. 76^{o}C/47 Torr, [Lit[25] 67-72^{o}C/23 Torr].

IR (γ cm^{-1}) = 2974, 2150(s).

PMR: δ = 1.06(3H, t) 1.46(6H, s) 1.70(2H, q).

MS (*m/z*): 129(20), 114(2), 100(22), 86(3), 71(40), 55(42), 43(100).

Elemental Analysis: Found (Calculated).

C	H	N	S
55.56	8.51	10.78	24.64
(55.77)	(8.57)	(10.83)	(24.81)

tert-Amyl thiocyanate: 2.94 g, Yield 76 %, b. p. 45-47^{o}C/15 Torr, [Lit^{25} 57-60^{o}C/10 Torr

IR (γ cm^{-1}) = 2967, 2075(br).

PMR: δ = 1.06(3H, t) 1.53(6H, s) 1.80(2H, q).

MS (*m/z*): 129(1), 100(4), 86(1), 71(25), 55(45), 43(100).

Elemental Analysis: Found (Calculated).

C	H	N	S
55.56	8.51	10.78	24.64
(55.77)	(8.57)	(10.83)	(24.81)

9. Reaction of *tert*-amyl chloride with Ti(SCN)$_4$ in CH_2Cl_2: Preparation of *tert*-amyl thio- and isothiocyanates.

To the salt B, a solution of *tert*-amyl chloride (3.19 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in 10 ml of anhydrous CH_2Cl_2 was added. The flask was subjected to sonication in the frequency range of 40-50 kHz and RF power of 80 watts using ultrasonic bath. The sonication was continued till the disappearance of *tert*-amyl chloride on GC. After completion of reaction (5 h), it was poured into 100 ml of 5 % HCl and organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (25 ml X 2) and it was combined with previous layer. Organic layer washed free of acid with water and concentrated in a flash evaporator. The crude product was chromatographed over silica gel (70 g) using hexane as eluant followed by 2 % EtOAc in hexane. Fractions having similar retention time were combined and concentrated separately followed by distillation under reduced pressure.

tert-Amyl isothiocyanates: 0.33 gm, Yield 8.5 %.

tert-Amyl thiocyanate: 2.96 gm, Yield 76.5 %.

10. Reaction of *tert*-butyl chloride with Zn(SCN)$_2$ in CH_2Cl_2: Preparation of *tert*-butyl thio- and isothiocyanate.

Salt A (6.8 g), which contains 3.73 g (21 mmol) of Zn(SCN)$_2$ was taken in a 100 ml round-bottomed flask in 40 ml of anhydrous CH_2Cl_2. The flask was subjected to

sonication in the frequency range of 40-50 kHz and RF power of 80 watts using ultrasonic bath. Then a solution of pyridine (2.37 g, 30 mmol) and *tert*-Butyl chloride (2.46 g, 30 mmol) in 10 ml of CH_2Cl_2 was added and sonicated as before. The reaction was monitored on ^1H NMR for the disappearance of methyl protons of *tert*-butyl chloride. After completion of reaction (12 h), it was poured into 100 ml of 5 % HCl solution and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (25 ml X 2) and it was combined with previous layer. This was washed free of acid with water and concentrated in a flash evaporator. The crude product was then chromatographed over silica gel (70 g) using hexane as eluant followed by 2 % EtOAc in hexane. Fractions having similar retention time on GC were combined and concentrated separately. These products were further purified by distillation under reduced pressure.

tert-Butyl isothiocyanate: 0.17 g, Yield 5 %, b. p.55^oC /35 Torr.

IR (γ cm^{-1}) = 2936, 2868, 2088(br).

PMR: δ = 1.60(9H, s).

MS (*m/z*): 115(30), 100(10), 84(4), 72(8), 57(60), 41(100).

Elemental Analysis: Found (Calculated).

C	H	N	S
52.45	7.81	12.29	26.98
(52.13)	(7.87)	(12.15)	(27.83)

tert-Butyl thiocyanate: 1.73 gm, Yield 50 %, b. p. 55^oC/35 Torr.

IR (γ cm^{-1}) = 2934, 2858, 2150(s).

PMR: δ = 1.45(9H, s).

MS (*m/z*): 115(2), 100(5), 84(1), 72(3), 57(85), 41(100).

Elemental Analysis: Found (Calculated).

C	H	N	S
52.45	7.81	12.29	26.98
(52.13)	(7.87)	(12.15)	(27.83)

11. Reaction of *tert*-butyl chloride with $Ti(SCN)_4$ in CH_2Cl_2: Preparation of *tert*-butyl thio- and isothiocyanate.

To the salt B, added a solution of *tert*-butyl chloride (2.46 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in 10 ml of anhydrous CH_2Cl_2. The flask was subjected to sonication in the frequency range of 40-50 kHz and RF power of 80 watts using an ultrasonic bath. The sonication process was continued till the disappearance of *tert*-butyl chloride on NMR. After completion of reaction (5 h), it was poured into 100 ml of 5 % HCl solution and organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (25 ml X 2) and it was combined with previous layer. Organic layer washed free of acid with water and concentrated in a flash evaporator. The crude product was then chromatographed over silica gel (70 g) using hexane as eluant followed by 2 % EtOAc in hexane. Fractions having similar retention time were combined and concentrated. These were further purified by distillation under reduced pressure.

t-Butyl isothiocyanate: 0.35 gm, Yield 10 %.

t-Butyl thiocyanate: 2.52 gm, Yield 73 %.

12. Reaction of *tert*-butyl bromide with $Zn(SCN)_2$ in CH_2Cl_2: Preparation of *tert*-butyl thio- and isothiocyanate.

Salt A (6.8 g), which contains 3.73 g (21 mmol) of $Zn(SCN)_2$ was taken in a 100 ml round-bottomed flask in 40 ml of CH_2Cl_2. The flask was subjected to sonication in the frequency range of 40-50 kHz and RF power of 80 watts using an ultrasonic bath. Then a solution of pyridine (2.37 g, 30 mmol) and *tert*-butyl bromide (4.11 g, 30 mmol) in 10 ml of dichloromethane was added and sonicated as before. The reaction was monitored on NMR for the disappearance of methyl protons of tertiary butyl bromide. After completion of reaction (5 h), it was poured into 100 ml of 5 % HCl solution and organic layer separated. The aqueous layer was re-extracted with CH_2Cl_2 (25 ml X 2) and it was combined with previous layer. This was washed free of acid with water and concentrated in a flash evaporator. The crude product was chromatographed over silica gel (70 g) using hexane as eluant followed by 2 % EtOAc in hexane. Fractions having similar retention time on GC were combined and concentrated and further purified by distillation under reduced pressure.

tert-Butyl isothiocyanate: 0.36 g, Yield 10 %, b. p. 55^{o}C /35 Torr.

tert-Butyl thiocyanate: 2.25 g, Yield 65 %, b. p. 55^{o}C/35 Torr.

13. Reaction of *tert*-butyl bromide with $Ti(SCN)_4$ in CH_2Cl_2: Preparation of *tert*-butyl thio- and isothiocyanate.

To the salt B, added a solution of *tert*-butyl bromide (4.11 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in 10 ml of anhydrous CH_2Cl_2. The flask was subjected to sonication in the frequency range of 40-50 kHz and RF power of 80 watts using ultrasonic bath. The sonication process was continued till the disappearance of *tert*-butyl bromide on NMR. After completion of reaction (1 h), it was poured into 100 ml of 5 % HCl solution and organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (25 ml X 2) and it was combined with previous layer. This was washed free of acid with water and concentrated in a flash evaporator. The crude product was then chromatographed over silica gel (70 g) using hexane as eluant followed by 2 % Et_2OAc in hexane. Fractions having similar retention time were combined and concentrated separately and further purified by distillation under reduced pressure.

tert-Butyl isothiocyanate: 0.32 g, Yield 9 %.

tert-Butyl thiocyanate: 1.87 g, Yield 54 %.

14. Reaction of 1,1-dimethylphenylcarbinyl chloride with $Zn(SCN)_2$ in CH_2Cl_2: Preparation of 1,1-dimethylphenylcarbinyl thio- and isothiocyanate.

Salt A (6.8 g), which contains 3.73 g (21 mmol) of $Zn(SCN)_2$ was taken in a 100 ml round-bottomed flask along with 40 ml of CH_2Cl_2 and flask is subjected to sonication. Then a solution of pyridine (2.37 g, 30 mmol) and 1,1-dimethylphenylcarbinyl chloride (4.27 g, 30 mmol) in 10 ml of CH_2Cl_2 were added and sonicated at 10-15^{o}C. After completion of reaction (3.5 h), usual workup followed by column chromatographic purification yielded 1,1-dimethylphenylcarbinyl thiocyanate and isothiocyanate.

1,1-Dimethylphenylcarbinyl isothiocyanate: 2.02 g, Yield 38 %, b.p.56-58^{o}C/1.5 Torr.

PMR: δ = 7.33-7.46(m, 5H), 1.56(s, 6H).

IR (γ, cm^{-1}) = 3024, 2982, 2071(br).

MS (*m/z*): 177(2), 162(5), 119(100), 103(40), 91(80), 77(40), 59(45), 51(30).

Elemental Analysis: Found (Calculated).

C	H	N	S
67.55	6.18	7.80	18.28
(67.76)	(6.25)	(7.90)	(18.09)

1,1-Dimethylphenylcarbinyl thiocyanate: 1.30 g, Yield 24 %, b.p.60-62^{o}C/1 Torr.

PMR: δ = 7.33-7.46(m, 5H), 1.66(s, 6H).

IR (γ, cm^{-1}) = 3024, 2977, 2078(s).

MS (*m/z*): 177(1), 162(3), 119(100), 103(25), 91(60), 77(30), 59(10), 51(15).

Elemental Analysis: Found (Calculated).

C	H	N	S
67.55	6.18	7.80	18.28
(67.76)	(6.25)	(7.90)	(18.09)

15. Preparation of tertiary halides

i) α-Terpinyl chloride

α-Terpinyl chloride was prepared by slow absorption of dry hydrogen chloride gas (36.5 g, 1 mol) through pre-cooled (0^{o}C) pure (+)- limonene (136 g, 1 mol) for 4 h. Hydrogen chloride gas was liberated by drop wise addition of conc. H_2SO_4 (300 ml) from pressure equalizing funnel to dry sodium chloride (500 gm) taken in a 2 L round-bottomed flask. The liberated gas was dried by bubbling through conc. H_2SO_4 and then passing through fused $CaCl_2$ before passing into limonene. After absorption of 36.5 g of hydrogen chloride, the flask was allowed to stand in an ice chest overnight. Then the product was washed with chilled water followed by 5 % $NaHCO_3$ solution to remove excess acid. The product was dried over fused $CaCl_2$ and fractionated using a Vigruex column under reduced pressure to yield pure α-terpinyl chloride (b. p. 63-65^{o}C / 1Torr, [Lit[2] 62-64^{o}C/1-2 Torr] 150 g, 87 %)

ii) 1-Menthanyl chloride (1-chloro-*p*-menthane)

(+)- Limonene (136 g) was taken in a 500 ml hydrogenation flask along with 6.0 g of Raney nickel (W-2) catalyst and set for hydrogenation at 1-2 atm pressure in a Par hydrogenator. Agitation was continued until the disappearance of double bond on PMR at

8(9) position of limonene. After completion of reaction (5 h) the product was filtered off and washed with ethanol (25 ml). The product, after removal of solvent was purified by distillation under reduced pressure (80^{o}C/10 mm, 130 g, 94 %). Dry HCl was passed through it for 4 h at 0^{o}C as in the case of limonene. The product was kept in a refrigerator over night and washed free of acid with water followed by 5 % $NaHCO_3$. The product was then purified by distillation under reduced pressure to yield 1-menthanyl chloride (1-chloro-*p*-menthane, b. p. 54-56^{o}C/1 Torr, 152 g, 87 %).

***iii) tert*-Amyl chloride**

A mixture of *tert*-amyl alcohol (26.4 g) and concentrated hydrochloric acid (75 ml) were shaken in a 250 ml separatory funnel for 10 min. The separated organic layer was washed free of acid with 5 % $NaHCO_3$ solution and dried over fused $CaCl_2$. The product was then distilled under reduced pressure to get pure *tert*-amyl chloride (b. p. 82-84^{o}C, [Lit[26] 83-85^{o}C], 23 g, 72 %).

***iv) tert*-Butyl chloride**

A mixture of *tert*-butyl alcohol (37 g) and conc. HCl (130 ml) were shaken in a 250 ml separatory funnel for 20 min. The separated organic layer was washed free of acid with 5 % $NaHCO_3$ solution and dried over fused $CaCl_2$. The product was then distilled to get pure *tert*-butyl chloride (b. p. 47-49^{o}C [Lit[26] 49-51^{o}C], 40 gm, 87 %).

***v) tert*-Butyl bromide**

A mixture of *tert*-butyl alcohol (25 g) and hydrobromic acid (35 g, 48 %) were shaken together in a 250 ml separatory funnel for 2 h. The separated organic layer was washed free of acid with 5 % $NaHCO_3$ solution and dried over fused $CaCl_2$. The product was then distilled to get pure *tert*-butyl bromide (72-73^{o}C, 25 gm, 54 %).

***vi)* 1,1-Dimethylphenyl carbinyl chloride**[27]

Dry HCl gas was bubbled through α-methylstyrene (59 g, 0.5 mol) at 10-15^{o}C. After absorption of ~0.5 mol (18 g) of HCl (4 h), it was kept overnight in a refrigerator. Excess of HCl was removed by stirring with dry K_2CO_3 and the product filtered at the pump. It was used as such in the reaction {distillation even under reduced pressure (1 Torr) caused excessive decomposition}.

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Part B: Reduction of Thiocyanates: Preparation of Thiols

Several biologically active thiols are known to occur in nature[1,2] and they undergo easy transformation under mild reaction conditions and at neutral pH. The best examples of biologically important thiols are cysteine and Co-enzyme A. Two new terpene thiols recently prepared from *cis*- and *trans*-1,2-epithio-*p*-menth-8-ene are of fragrance value.[3] Some of the alkyl thiols and their occurrence in food are presented in Table 5.5.[4]

Table 5.5: Volatile thiols and their occurrence in foods

Compounds	Occurrence in Foods
Methane thiol	Onion, garlic, coffee, beer, potato, beef
2-Furylmethane thiol	Coffee
1-methylthioethane thiol	Beef
p-Menth-1-en-8-thiol	Grapefruit
p-Manthan-8-thiol-3-one	Buchu leaf oil

Thiols (mercaptans) are usually prepared from alcohols, alkyl halides and alkenes.[5] The addition of H_2S to the alkenes or its reaction with alkyl halides and alcohols has a serious limitation of formation of the monosulfides as the side products and normally requires base catalysts, high temperature and pressure. In case of unsymmetrical olefins; Morkovnikov's adducts are obtained in presence of metal sulfides,[6] oxides,[7] and sulfur[8] whereas *anti*-Morkovnikov's adducts are formed by free-radical reaction.[9]

Primary and secondary alkyl thiols are prepared *via* intermediates like thiocyanate, thiourea and thioamide.[10] The preparation of intermediates itself involves several steps. *n*-Alkyl and benzylic halides are converted to thiols by α–trimethylsiloxy thiol.[11] Nucleophilic substitution of tertiary halides by metal hydrosulfides under non-solvolytic conditions is extremely difficult due to the elimination of HX leading to olefin. But when H_2S is bubbled through trityl chloride in the presence of Al_2O_3, the thiol is easily formed.[12]

Present Work

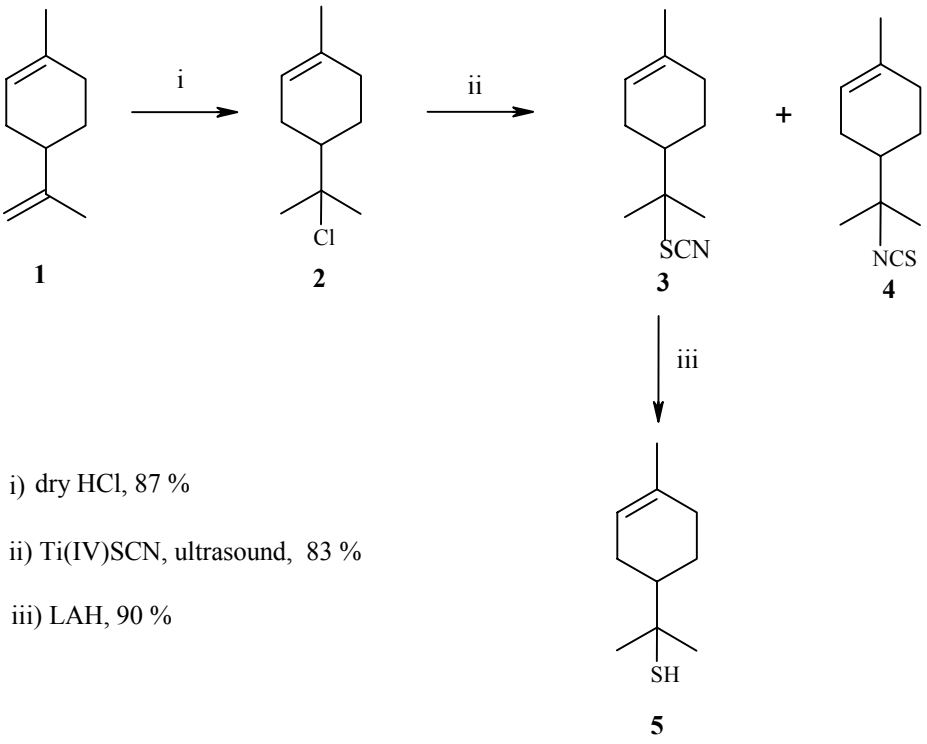
The difficulty associated with preparation of tertiary thiols by direct routes could be overcome by successful reduction of corresponding thiocyanates.[13] Thiocyanates are prepared in good yield by substitution of allylic, benzylic, and tertiary halides in the form of zinc or titanium thiocyanate. In the present investigation tertiary alkyl thiocyanates were obtained in yields superior to hitherto known procedures. Here the reduction of these thiocyanates in case of *α*-terpinyl and 1-menthanyl substrates was carried out. Corresponding thiols were obtained in excellent yield.

α-Terpinyl thiol

An improved synthesis of *α*-terpinyl thiol was envisaged from the (+)-limonene (Scheme 5.4, **1***) via* *α*-terpinyl chloride (**2**). *α*-Terpinyl thiocyanate (**3**) was prepared in good yield under the influence of ultrasound. Substitution with thiocyanate nucleophile in the form $Ti(SCN)_4$ salt under ultrasound afforded 83 % of substitution product. *α*-Terpinyl thiocyanate was obtained selectively in 66.4 % yield apart from isomeric isothiocyanate (**4**, 16.6 % yield). These isomers were separated by column chromatography and distilled to get pure compounds. Pure *α*-terpinyl thiocyanate (99 %, GC) was reduced with LAH to afford *p*-menth-1-en-8-thiol in near quantitative yield (**5**). The overall yield of thiol from the (+)-limonene was 52 %, which is superior to hitherto known procedures.

α-Terpinyl thiol was characterized by PMR and mass spectral data. In the PMR spectrum, the C-9 and C-10 methyl's appeared at 1.35 and 1.42 respectively. These are at the up field compared to their position in thiocyanate. The mass spectrum exhibited the characteristic M^+ at 170. The easy loss of a molecule of H_2S (mass unit 34) was detected by the presence of peak at *m/z* = 136. A peak at *m/z* 75 indicated the fragment $(CH_3)_2{}^+CSH$. Also, daughter ions at 121 and 93 were observed, which were characteristic of the *p*-menth-1-ene skeleton.

Thus, an improved preparation of *α*-terpinyl thiol from the stable terpinyl thiocyanate precursor provides an efficient synthetic method. This thiol is a highly labile aroma chemical as it can undergo internal cyclization easily under radical or protic conditions to form 1,8-epithio-*p*-menthane (Scheme 5.5, **1**) or 2,8-epithio-*p*- menthane (**2**).

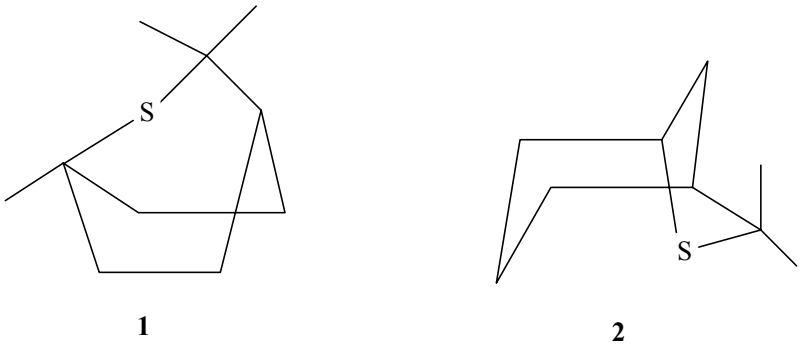


i) dry HCl, 87 %

ii) Ti(IV)SCN, ultrasound, 83 %

iii) LAH, 90 %

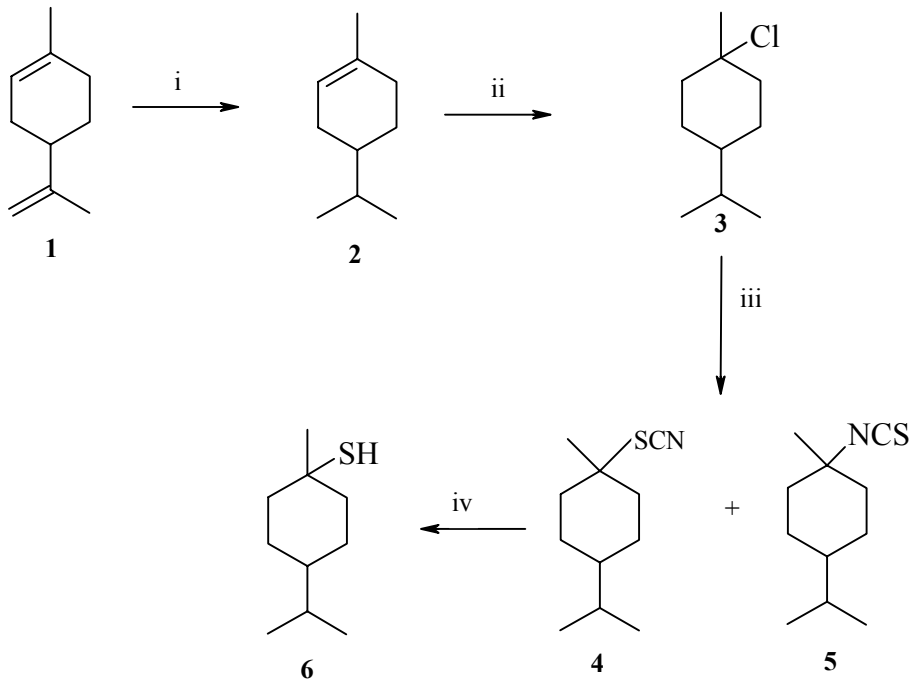
Scheme 5.4



Scheme 5.5

1-Menthanyl thiol

An improved synthesis of 1-menthanyl thiol (Scheme 5.6, **6**), was achieved by reduction of corresponding thiocyanate by reduction with LAH. As described earlier the synthesis of thiocyanate by substitution of 1-menthanyl chloride (**3**) by the thiocyanate nucleophile in the form of $Ti(SCN)_4$ under sonication afforded 1-menthanyl thiocyanate (**4,** 48 % yield) apart from the 1-menthanyl isothiocyanate (**5**, 17 % yield). After isolation and further purification by distillation under reduced pressure, it was taken for reduction. Reduction with LAH afforded nearly quantitative yield of the desired thiol. It was characterized by PMR and mass spectral analysis. The signal for C-7 methyl appeared at 1.33 as a singlet, which was 0.23 ppm lower than corresponding peak in thiocyanate. Mass spectra showed molecular ion peak at *m/z* 172, and peak for the loss of H_2S at *m/z* 138.



i) H_2, Raney Ni, 96 % ii) dry HCl, 87 %
iii) Ti(IV)SCN, ultrasound, 64 % iv) LAH, 92 %

Scheme 5.6

Experimental

Reduction of *α*–terpinyl thiocyanate with LAH

α-Terpinyl thiocyanate (1.95 g, 10 mmol) was taken with 25 ml dry ether in a flask. LAH (0.2 g) was added slowly to this and the reactants were stirred at room temperature. The progress of the reaction was monitored by TLC (2 % EtOAc in hexane). After completion of the reaction (4 h), the excess reagent was washed with slow addition of 5 % oxalic acid solution until effervescence ceased. The grey precipitate was filtered and washed twice with ether (25 ml) and the combined filtrate was washed with water (50 ml x 2). Organic layer was dried over Na_2SO_4 and evaporation of the solvent afforded *α*-terpene thiol. It was further purified by distillation under reduced pressure.

Yield: 1.53 g, 90 %, b. p. 68-69^oC/0.8 Torr, [Lit[14] 40^oC/0.1Torr]

PMR: 1.35(s, 3H), 1.42(s, 3H), 1.66(s, 3H), 1.80-2.20(m, 8H), 5.40(br, 1H)

MS (*m/z*): 170(3), 136(35), 121(40), 119(15), 107(15), 95(5), 93(100), 77(37), 75(10), 55(8), 41(29).

Reduction of 1-menthanyl thiocyanate with LAH

1-Menthanyl thiocyanate (1.97 g, 10 mmol) was taken with 25 ml dry ether in a flask. LAH (0.2 g) was added slowly to this and stirred the reactants at room temperature. The progress of the reaction was monitored by GC. After completion of the reaction (12 h), the excess reagent was washed with slow addition of 5 % oxalic acid till the effervescence ceased. The grey precipitate was filtered and washed twice with ether (25 ml) and combined filtrate was washed with water (50 ml x 2). Removal of solvent afforded crude 1-menthanyl thiol, which was further purified by distillation under reduced pressure.

Yield: 1.58 g, 92 %, b. p. 67^oC/1 Torr.

PMR: 0.86(d, J = 6 Hz, 6H), 1.33(s, 3H), 1.0-1.30 and 1.40-1.86(m, 11H).

MS (*m/z*): 172(10), 138(35), 123(15), 95(50), 83(100), 69(39), 55(29), 43(12).

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Summary

Chapter 1: Oxygenated Monoterpenes and their Sulfur Analogs: Introduction

Functionalization of hydrocarbons is an important area in classical synthetic organic chemistry, and it continues to be a topic of active research even now. The present challenges are, the achievement of better regio- and stereoselectivities, clean reaction and facile workup of the product. In this context, there is growing interest in the use of electromagnetic radiation and ultrasound energy in chemical reactions. The potential of these techniques as synthetic tools is being vigorously explored by researchers world over.

Monoterpenes – acyclic, mono- and bicyclic hydrocarbons - are abundantly available in nature as constituents of a host of essential oils e.g., (+)-limonene from citrus oils and *α*-pinene, *β*-pinene, and 3-carene from turpentine. The corresponding oxygenated derivatives - alcohols, carbonyl compounds, esters and ethers – and their sulfur analogs form a major and important group of aroma chemicals. These compounds- both natural and synthetic- find extensive applications in food flavor and perfumery formulations. Therefore, conversion of terpenic hydrocarbons into their *O*- and *S*-derivatives is of economic importance.

A brief account of the availability of various terpenic hydrocarbons in several essential oils is given. Preparation of useful synthetic intermediates *viz*. alkyl halides, epoxide and bromohydrins from these hydrocarbons and important methods known for their conversion to oxygenated flavor compounds and their sulfur analogs are described, by way introduction to the present work.

Chapter 2: Synthesis and Reactions of Monoterpene Bromohydrins and Epoxides

Section 2.1: Direct Conversion of tert-β –Bromo Alcohols to Ketones

NBS is known to effect the allylic bromination of olefins when reactions are carried out in the presence of a radical initiator and in a non-polar solvent like carbon tetrachloride. In the presence of nucleophilic solvents like water, DMSO and alcohols, it yields cohalogenated derivatives *via* the bromonium intermediate. The reaction of NBS with

selected group of monoterpenes and related olefins was studied in aqueous acetone. The yields of the bromohydrins obtained were excellent with the stereochemistry of *vicinal* 1,2-bromo alcohols being largely *trans*- *(*Section 2.4*)*. The DMSO oxidation of activated halides to the corresponding carbonyl compounds in the presence of the bases is termed as Kornblum oxidation. The presence of a base is necessary for this reaction to occur and also unactivated chlorides and bromides need prior conversion to more activated tosylates. In order to avoid the base in this reaction (bromohydrins undergo cyclization to epoxides) and to simultaneously activate the halide, use of ZnS was envisaged and reaction conditions optimized. While the expected hydroxy ketones were minor, saturated ketones were formed as major products. A detailed study on the scope and limitations of this reaction led to the understanding of the mechanism of this reaction. It involves the abstraction of proton on the carbon *β*- to the hydroxyl group followed by an attack of the neighboring hydroxyl moiety on the sulfur of the dimethylsulfoxonium intermediate and its subsequent collapse to an enol, which tautomerizes to a saturated ketone. The latter pathway is predominantly followed.

Thus, a general method of conversion of *tert*-*β*-bromo alcohols to saturated ketones by using ZnS and DMSO has been developed and successfully applied to the preparation of carbonyl compounds in monoterpene series. Also, a mechanism is proposed to explain the influence of neighboring hydroxyl group in the formation of ketones.

Section 2.2: Allylic Bromides *from tert*-*β*-Bromo Alcohols

Among the reactions of halohydrins, transformation of the halide functionality is dealt with more than that of the hydroxyl group. Importantly, reports on dehydration reactions of halohydrins are scanty. It was now shown that, they could be efficiently dehydrated to respective allyl bromides by reaction with catalytic amounts of $BF_3.OEt_2$ in dry benzene. It constituted an easy indirect route to the preparation of stereospecific allylic bromides. In case of 2-bromo-1-hydroxy-*p*-menth-8-ene, the reaction led to the formation of 2-bromo-1,8-cineole, a cyclic ether, by internal acid-catalyzed addition of hydroxyl group to the isopropenyl double bond. Dehydration of several other *tert*-*β*-bromo alcohols was affected smoothly by this method, showing its general utility to prepare the corresponding

allylic bromides, which could act as reactive intermediates for *O/S*-derivatives. It also allowed an easy access to Hoffmann elimination (less substituted alkenes) product in high yield in case of benzylic 1,2-bromo alcohols.

Section 2.3: The Reaction of Terpene and Aryl Substituted Epoxides with Bromodimethylsulfonium bromide

Bromodimethylsulfonium bromide (BDMSB) was prepared by reaction with bromine and dimethyl sulfide in anhydrous dichloromethane as described by known method. Its reaction with the disubstituted epoxides is known to yield the bromo ketones. In the present study, reaction of BDMSB with selected trisubstituted monoterpene and related epoxides was studied. The reaction was found to be regio-specific with the opening of oxiran ring at the tertiary and benzylic positions. With terminal epoxides, it yielded respective aldehydes. In case of styrene oxide, though a disubstituted epoxide, a high regioselectivity was observed in formation 1-bromo-1-phenylethanal as the major product. Thus, α-bromo ketones were prepared in good yield (45-70 %) from monoterpene epoxides.

Section 2.4: Preparation of Bromohydrins

Bromohydrins of terpenic hydrocarbons and few other cycloalkyl and aromatic olefins that were needed for the present work, were prepared by using NBS in aqueous acetone under standardized condition in excellent yield (80-95 %) and in high purity (>97 %). They were characterized systematically by their physico-chemical and spectroscopic properties.

Chapter 3: Photochemical Studies on Epoxides and Bromohydrins

Section 3.1: Photo-Assisted Kinetic Resolution of Monoterpene Epoxides

Limonene and carvomenthene 1,2-oxides were prepared from the respective hydrocarbons by treatment with 40 % peracetic acid prepared in the laboratory. These two hydrocarbons have one chiral carbon atom in their structure; their epoxidation with peracids always yields a mixture of two diastereomeric epoxides (*cis*- and *trans*-) in about equal proportion. Separation of these isomers in pure form by fractional distillation is not efficient and by chemical means involves a number of steps. In this study, photo-assisted

methanolysis of the epoxides was explored to achieve a kinetic resolution of the diastereoisomers. When a mixture of *cis*- and *trans*-limonene oxide was irradiated in the presence of Lewis acids ($ZnCl_2$, $ZnBr_2$, ZnI_2 and $InCl_3$) and light (240-366 nm) in methanol, the *trans*-oxide remain unreacted and the *cis*-oxide cleaved selectively to afford *trans*-(1*S,* 2*S,* 4*R*)-1-methoxy-2-hydroxy-*p*-menth-8-ene. The product after work up was subjected to distillation under reduced pressure. Since the two products had substantial difference in their boiling points, they could be fractionated easily. Pure *trans*-limonene oxide was obtained in 48-55 % yield.

Similarly, when reaction was carried out with about equal mixture of *cis*- and *trans*-carvomenthene oxide, the *trans*-oxide remain unreacted and *cis*-oxide afforded *trans*-(1*S,* 2*S,* 4*R*)-1-methoxy-2-hydroxy-*p*-menthane. They were separated by fractional distillation under reduced pressure. Pure unreacted *trans*-carvomenthene oxide was obtained in 49-54 % yield. Thus, a simple and efficient method of kinetic resolution of terpene oxides based on photo-assisted ring cleavage was developed.

Section 3.2: Light Induced Direct Conversion of Styrene Bromohydrins to Benzoic acid Esters

Photoreaction of bromohydrins in methanol was explored taking styrene bromohydrin as model substrate, in the presence of 5 mol % $ZnCl_2$, $ZnBr_2$, ZnI_2, and $InCl_3$. While reactions with other catalysts gave a mixture of products, the reaction with $ZnBr_2$ afforded methyl benzoate as the major product in over 85 % yield. When the reaction was carried out in an aprotic solvent like benzene and in the presence of PTS, acetophenone was the major product. A mechanism was envisaged for the predominant formation of methyl benzoate from styrene bromohydrin. It was apparently due to the formation of a complex salt by reaction of $ZnBr_2$ with hydroxyl group of bromohydrin. Subsequent radical elimination of hydrogen bromide yielded zinc enolate. The latter tautomerized to acetophenonezinc bromide, a stable keto-form. This on photo-irradiation underwent Norrish type I cleavage at benzylic carbonyl carbon and subsequent addition of methanol to benzoxyl radical yielded methyl benzoate. With $ZnCl_2$ and ZnI_2, formation of methyl benzoate was to a lesser extent but 1,1-dimethoxy-2-phenylethane and 1,2-dimethoxy-2-

phenylethanol were formed as major products. This was because of the preferential formation of phenyl acetaldehyde, a rearranged product, which underwent acid-catalyzed addition of methanol to give 1,1-dimethoxy-2-phenylethane. On the other hand the enolic-form of phenyl acetaldehyde while transforming to keto-form, abstracted methoxy radical, and to this intermediate methanol added under acid catalyzed conditions to give 1,2-dimethoxy-2-phenylethanol. While 2-alkyl substituted bromo alcohols such as 1-bromo-3-phenyl-propane-2-ol and also terpenic *tert-β*-bromo alcohols are non reactive under this reaction conditions, (2′,4′-dimethyl)-styrene bromohydrin (1-bromo-3-phenyl-propan-2-ol) in the presence of $ZnBr_2$ in methanol afforded methyl-(2′,4′-dimethyl) benzoate in 70 % yield. The reaction in ethanol was very slow and only trace of ethyl benzoate was observed and the same in isopropanol was non-reactive (>24 h irradiation). Thus, a direct formation of benzoic acid ester from styrene bromohydrin by photo-assisted methanolysis in the presence of $ZnBr_2$ *via* the zinc enolate intermediate is being reported for the first time.

Chapter 4: New D-glucal Derivatives of Terpene alcohols; Synthesis of 2,3-Unsaturated Acetylglucopyranosides

3,4,6-Triacetyl-D-glucal is a versatile synthetic intermediate in the synthesis of 2-deoxyglycosides, which are known to occur as biologically important natural products. Reaction of glucals with alcohols and mercaptans in the presence of Lewis acids affords 2,3-unsaturated-1-*O*- and *S*-derivatives *via* an allylic rearrangement is referred to as Ferrier reaction. For the synthesis of some D-glucal derivatives by Ferrier rearrangement reaction, some representative S_N1-active alcohols including monoterpene alcohols were selected. Initially, reaction of 4-terpinenol was studied with different Lewis acids, $BF_3{\cdot}OEt_2$, BBr_3, $ZnCl_2$ and also PTS in dichloromethane. Of these, $ZnCl_2$ was found to be the most efficient catalyst as the reaction afforded the 2,3-unsaturated acetylglucosides at ambient temperature in CH_2Cl_2 solvent. Reaction of glucal with other terpene alcohols afforded glucosides of 2,3-unsaturated-1-*O*-terpene alcohols (allyl and tertiary) in good yields (60-74 %). The specific rotations of the products revealed that little racemization of the alcohols occurred under the experimental conditions. This apparently was due to the formation of tight ion-pair of zinc

and alkoxyl groups. The efficacy of the reaction was also demonstrated with benzylic alcohols, wherein the respective glucoside derivatives were obtained in excellent yields (81-91 %). This constitutes a new variant of Ferrier reaction and the glucal derivatives of monoterpene alcohols thus prepared are new.

Chapter 5: Preparation of Alkyl Thiocyanates and Thiols

Part A: Ultrasound-Assisted Nucleophilic Substitution of S_N1-Active Halides with Zinc and Titanium Thiocyanate

A study of nucleophilic substitution of S_N1-active halides derived from monoterpene hydrocarbons with zinc thiocyanate under the influence of ultrasound was undertaken. These reactions in case of tertiary and benzylic halides proceeded smoothly and gave good yields of the substitution products. The thio-/isothiocyanate ratio improved (4-8:1) and the reactions rates were faster (5-16 h). Tertiary thiocyanates were obtained in superior yields as compared to those by hitherto known procedures. Thus *α*-terpinyl thiocyanate was obtained from the corresponding chloride in about 64 %. Preparation of zinc thiocyanate was by stirring potassium thiocyanate and zinc chloride together in benzene under reflux. Also, few other terpenic and *tert*-alkyl thiocyanates were prepared in good yield (45-76 %).

Nucleophilic substitution of S_N1-active of halides with titanium thiocyanate was explored for the first time. The reagent was prepared *in situ* from $TiCl_4$ and $Zn(SCN)_2$ and the reaction with S_N1-active halides was carried out under sonic conditions. It was found that not only the reactions were faster (1-10 h) but also the yields of substitution products were better (65-85 %) with improvement in the overall thio-/isothiocyanate ratio (3-9:1). Thus, the efficacy of ultrasound in bringing about substitution at tertiary carbon with thiocyanate (which is ambident in nature) selectivity was demonstrated.

Part B: Reduction of Thiocyanates; Preparation of Thiols

Thiols (mercaptans) form a small, but important group of flavoring compounds of several fruits and spices. Tertiary monoterpene thiols are found in nature as character-impact compounds in very low concentrations. A specific example is *p*-menth-1-ene-8-thiol, which is the flavor-impact constituent of grapefruit juice with a threshold value of $< 10^{-4}$ ppb. The

tert-alkyl thiocyanates prepared in the Part A were reduced with LAH in dry ether to afford the corresponding *tert*-thiols of important aroma value. The reaction was fast (< 12 h) and yields of thiols were excellent (>90 %). Incidentally, this constitutes an improved synthetic method for *p*-menth-1-ene-8-thiol. It was prepared in an overall yield of 51 % from (+)-limonene, the citrus terpene.

List of Publications Based on the Thesis work

Papers

1 Direct conversion of *tert*-*β*-bromo alcohols to ketones with ZnS and DMSO**,** Bettadaiah, B. K.**;** Gurudutt, K. N.; Srinivas, P**.** *J. Org. Chem*. **2003,** *68***,** 2460-62

2 $ZnCl_2$ catalyzed Ferrier reaction; Synthesis of 2,3-unsaturateed 1-*O*- glucopyranosides of allylic, benzylic and tertiary alcohols, Bettadaiah, B. K.; Srinivas, P. *Tetrahedron Lett*. **2003,** *44*, 7257-59.

3. Ultrasound-assisted nucleophilic substitution of tertiary alkyl halides with zinc and titanium thiocyanate, Bettadaiah, B. K.; Gurudutt, K. N.; Srinivas, P. *Synth. Commun*. **2003**, *33(13)*, 2393-99.

4 An expedient synthesis of allylic/secondary bromides from dehydration of *tert*-*β*-bromo alcohols, Bettadaiah, B. K.; Srinivas, P. *Synth. Commun*. **2003**, *33(20)*, 3615-20.

5 Regio-specific ring opening of terpene and aryl substituted epoxides with Br_2/DMS reagent Bettadaiah, B. K.; Srinivas, P. *Indian. J. Chem. Sec. B*, **2003 (**In print**)**

Patent

1 An improved process for the preparation of *tert*-alkyl thiocyanates, stable intermediates for *tert*-thiols, Bheemanakere Kempaiah Bettadaiah, Pullabhatla Srinivas & Kambadoor Nagarajarao Gurudutt, Indian Patent, Application No. **Del/1074/00**.

Poster Presentation in Conference

1. Photolytic conversion of styrene bromohydrins to benzoic acid esters, Bettadaiah, B. K.; Gurudutt, K. N.; Srinivas, P. **5th International Food Convention, 2003,** Dec 5-8, Central Food Technological Research Institute, Mysore India.