T.R.
SAKARYA UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

PHOTOBROMINATION OF (+)-CAMPHENE AND EFFICIENT SYNTHESIS OF NOVEL CAMPHENE BASED COMPOUNDS THROUGH SUITABLE REACTIONS

Ph.D. THESIS

Md. Zahidul ISLAM

Chemistry Department

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The thesis work titled “PHOTOBROMINATION OF (+)-CAMPHENE AND EFFICIENT SYNTHESIS OF NOVEL CAMPHENE BASED COMPOUNDS THROUGH SUITABLE REACTIONS” prepared by Md. Zahidul ISLAM was accepted by the following jury on 30/10/2023 by unanimously/majority of votes as a Ph.D. THESIS in Sakarya University Graduate School of Natural and Applied Sciences, Chemistry department, Organic Chemistry program.

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Md. Zahidul ISLAM

Dedicated to my father Md. Shattar Mahmud, who awaited for my successful Ph.D. graduation but passed away during the time of my Ph.D. thesis….

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Md. Zahidul ISLAM

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ABBREVIATIONS

AIBN : Azo-bis-isobutyronitrile
$CDCl_3$: Deuterated chloroform
^{13}C NMR : Carbon-13 nuclear magnetic resonance
DBU : 1,8-diazabicyclo[5.4.0]undec-7-ene
DMSO : Dimethylsulfoxide
DMAP : 4-(Dimethylaminopyridine)
DMF : Dimethylformamide
DIPEA : *N*,*N*-Diisopropylethylamine
FTIR : Fourier transform infrared spectroscopy
GCMS : Gas chromatography mass spectrometry
^{1}H NMR : Proton nuclear magnetic resonance
HBr : Hydrogenbromide
Hz : Hertz
HOAc : Acetic acid
K.C.P : Kinetic controlled product
LCMS : Liquid chromatography mass spectrometry
MHz : Megahertz
mL : Milliliter
NMR : Nuclear magnetic resonance
PTLC : Preparative thin layer chromatography
ppm : Parts per million
rpm : Revolutions per minute
THF : Tetrahydrofuran
TEA : Triethylamine
***t*-BuOK** : Potassium *tert*-butoxide
TLC : Thin layer chromatography
T.C.P : Thermodaynamic controlled product
UV-vis : Ultraviolet-visible

SYMBOLS

c	: Concentration
l	: Length
m	: Multiplet
M	: Mass
q	: Quartet
s	: Singlet
t	: Time
T	: Temperature
W	: Watt
$[\alpha]^{T}_{\lambda}$	: Specific rotation
α	: Flip angle
β	: Beta
λ	: Wavelength
ρ	: Length of polarimeter cell
Φ	: Quantum yield

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PHOTOBROMINATION OF (+)-CAMPHENE AND EFFICIENT SYNTHESIS OF NOVEL CAMPHENE BASED COMPOUNDS THROUGH SUITABLE REACTIONS

SUMMARY

(1*S*,4*R*)-2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane (2) is an isomer of naturally occurring mono-terpene called camphene 1 which has high therapeutic and medicinal values as potential lipid lowering agent. It is a potential candidate for cardiovascular diseases as well as their derivatives showing significant bioactive properties like anti-viral, anti-tuberculosis, anti-oxidant, anti-bacterial and anti-fungal activities. The bicyclic skeleton of (+)-camphene (2) is used to form rearrangement products via bromination reactions which are toxic, though non-rearrangement derivatives of (+)-camphene 2 are biologically active.

In this thesis, the ring regulation tendency of bicyclic structure of (+)-camphene (2) was inhibited by suitable method, besides, high yield of non-rearrangement mono-brominated compounds were produced by the repair of bicyclic skeleton via repeated Wagner-Meerwein rearrangement and synthesized considerable amounts of non-rearrangement optically active chiral compounds from mono-brominated (+)-camphene 277. Additionally, rearrangement mono-brominated compound 279, di-brominated compound 276 and tri-brominated compounds 280-284 were synthesized from rearrangement compounds with different reaction conditions. In this study, the high temperature bromination of (+)-camphene (2) was carried out in presence of different light intensity and the mixture of non-rearrangement compounds 274 and 275 was obtained at 650 watt of light in presence of molecular bromine and CCl_4 as a solvent. Compounds 274 and 275 were completely transformed into rearrangement compound 276 via Wagner-Meerwein rearrangement in presence of SiO_2 in the purification process. Compound 276 was treated with *t*-BuOK in presence of THF at reflux temperature and mono-bromo bornene 279 was obtained which was treated with molecular bromine at low (0°C) and high (77°C) temperature and compounds 280 and 281-284 were synthesized respectively. Additionally, compound 279 was treated again with *t*-BuOK in presence of sodium metal and compound 286 was obtained.

Compound 276 was treated with aniline for the reconstruction of the structure of (+)-camphene (2) at reflux temperature and high yield (86%) mono-brominated compound 277 was synthesized with small amount (14%) of compound 278. Compound 277 was treated with molecular bromine at very low temperature (-15°C) and rearrangement compound 285 was obtained. Furthermore, Suzuki-Miyaura coupling reaction of compound (1*S*,4*R*,*E*)-3-(bromomethylene)-2,2-dimethylbicyclo-[2.2.1]heptane (277) was carried out with five different boronic acid compounds in presence of $[Pd(PPh_3)]_4$ and non-rearrangement compounds 288, 290, 292, 294 and 296 were synthesized. Nucleophilic substitution reaction of compound 277 was performed and non-rearrangement compounds 297 and 298 were synthesized in presence of $NaOCH_3$ and CuCN respectively. The structure of all synthesized compounds was determined by

the ^{1}H NMR, ^{13}C NMR, FTIR and a few of them were characterized also by ^{19}F NMR, COSY NMR, X Ray crystallography for addressing the exact structural skeleton. The polarimetry analysis of all the synthesized compounds was performed with polarimeter for their optical activity to distinguish the isomers. The coupling constant, shielding and de-shielding effects were discussed for addressing the connection of the substituent groups to the structural skeleton.

(+)-KAMFENİN FOTOBROMİNASYONU VE UYGUN REAKSİYONLAR YOLUYLA YENİ KAMFEN TEMELLİ BİLEŞİKLERİN ETKİLİ SENTEZİ

ÖZET

Terpenler, hayvanlarda, bitkilerde, bitki kısımlarında, deniz organizmalarında ve mantarlarda doğal olarak oluşan ikincil metabolitler olarak adlandırılan uçucu yağların ana bileşenleridir. Terpen bileşiklerinin her biri, yapılarında bu bileşiklere özgü ana yapı taşı olan $(C_5H_8)_n$ moleküler formülüne sahip bir izopren birimi [CH_2=C(CH_3)-CH=CH_2] bulundurur. Terpenoidler ve terpen bazlı kimyasal bileşikler uzun yıllardır ilaç keşfi için tanımlanmakta ve test edilmektedir. Oldukça gelecek vaad eden terapötik etkiler gösterdikleri ve yeni tıbbi bileşikler için geniş bir kaynak oluşturdukları düşünülmektedir. Geleneksel olarak uzun zincirli terpen ve terpenoid bileşikleri birçok rahatsızlık için tedavi edici olarak kullanılmıştır. Araştırmacılar terpenlerin ve ekstraktlarının antikanser, anti-tümör, anti-inflamatuar, anti-oksidan ve anti-viral aktiviteler gibi potansiyel tıbbi özellikler gösterdiğini bildirmiştir. Terpen bileşiklerinin kanser hücrelerine ve tümörlere karşı güçlü direnç oluşturabilen ve aynı zamanda bağışıklık sistemini baskılayan özellikte olduğu gösterilmiştir.

Monoterpenler, en fazla on karbon içerebilen iki izopren biriminden oluşur ve tüm monoterpenlerin her biri gül, narenciye ve üzüm gibi, kaynaklarına bağlı olarak farklı bir tada sahiptir. Birçok monoterpen bileşiği deniz kaynaklarından izole edilmiştir. Doğal izole edilmiş bileşikler olarak monoterpenler potansiyel bir tıbbi değere sahiptir.

(1*S*,4*R*)-2,2-Dimetil-3-metilbisiklo[2.2.1]heptan (2), potansiyel lipid düşürücü ajan olarak yüksek terapötik ve tıbbi değerlere sahip, doğada oluşan ve kamfen 1 adı verilen monoterpenin bir izomeridir. Bu nedenle kardiyovasküler hastalıklar ve bunların türevleri için anti-viral, anti-tüberküloz, anti-oksidan, anti-bakteriyel ve anti-fungal aktiviteler gibi önemli biyoaktif özellikleri olan potansiyel bir adaydır. (+)-Kamfen (2)'nin bisiklik iskeleti, toksik olan brominasyon reaksiyonları yoluyla yeniden düzenleme ürünleri oluşturmak için kullanılır, ancak (+)-kamfen (2)'nin yeniden düzenlenmeyen türevleri biyolojik olarak aktiftir.

2009 yılında yapılan bir araştırmada, pulmoner inflamasyonun kamfen tarafından önemli ölçüde korunduğu tespit edilmiştir. 2011'deki başka bir çalışmada, kamfenin trigliseritler ve kolesterol düşürücü ajan olarak potansiyel umut verici özellikler gösterdiği, kardiyovasküler temelli sağlık tedavisi üzerinde büyük olumlu etkisi olduğu sonucuna varılmıştır. 2012 yılında gerçekleştirilen bir çalışmada ise kamfenin anti-inflamatuar ve ağrı kesici özellikler göstermesi nedeniyle önemli bir tıbbi ajan olduğu ortaya çıkmıştır. Kenevir terpenlerinde tıbbi bir bileşen olarak bulunan kamfen cilt rahatsızlıklarının tedavisinde kullanılmasıyla da ayrı bir öneme sahiptir. Aynı şekilde (+)-kamfen (2), süperoksit ve hidroksil radikallerine karşı potansiyel radikal süpürücü aktiviteler gösterirken, *in vitro* TRAP, TAR ve TBARS analizlerinde daha güçlü özellikler gösterdiği bulunmuştur.

Bu çalışma kapsamında , (+)-kampenin (2) bisiklik yapısının halka düzenleme eğilimi uygun yöntemle engellenmiş, ayrıca tekrarlanan Wagner-Meerwein yeniden düzenlemesi yoluyla bisiklik iskeletin onarılmasıyla yüksek verimde yeniden düzenlenmemiş mono-bromlu bileşikler üretilmiş ve mono-bromlu (+)-kampen 277'den önemli miktarda yeniden düzenlenmemiş optikçe aktif kiral bileşikler sentezlenmiştir. Ayrıca, yeniden düzenleme bileşiklerinden farklı reaksiyon koşulları ile yeniden düzenleme mono-bromlu bileşik 279, di-bromlu bileşik 276 ve tri-bromlu bileşikler 280-284 sentezlenmiştir. Bu çalışmada, (1*S*,4*R*)-2,2-dimetil-3-metilenbisiklo-[2.2.1]heptan (2)'nin yüksek sıcaklıkta farklı ışık şiddetlerinde brominasyonu ve yeniden düzenlenmeyen bileşiklerin karışımı olan 274 ve 275'in brominasyonu, moleküler brom ile CCl_4 varlığında 650 watt ışıkta gerçekleştirilmiştir.

Bileşik 274 ve 275 silikajel kolon kromatografisi yardımıyla saflaştırma işleminde Wagner-Meerwein yeniden düzenlemesi yoluyla tamamen yeniden düzenleme bileşiği 276'ya dönüştürüldü. Bileşik 276 THF varlığında *t*-BuOK ile muamele edildi, mono-bromobornen 279 elde edilirken düşük (0°C) ve yüksek (77°C) sıcaklıkta moleküler brom ile muamele edildiğinde sırasıyla 280 ve 281-284 elde edildi. Bunlara ek olarak bileşik 279, *t*-BuOK ve sodyum metal parçaları ile muamele edildiğinde bileşik 286 elde edildi. Bileşik 276 refluks sıcaklığında (+)-kamfen (2) yapısının yeniden düzenlenmesi için anilin ile muamele edildi ve yüksek verimle (%86) mono-bromlu bileşik 277, az miktarda (%14) bileşik 278 elde edildi.

Bileşik 277 çok düşük sıcaklıkta (-15°C) moleküler brom ile etkileştirildiğinde yeniden düzenleme ürünü olan bileşik 285 elde edildi. Ayrıca, (1*S*,4*R*,*E*)-3-(bromometilen)-2,2-dimetilbisiklo-[2.2.1]heptan 277 bileşiğinin $[Pd(PPh_3)]_4$ varlığında beş farklı boronik asit ile Suzuki-Miyaura çapraz kenetleme reaksiyonu gerçekleştirildi ve yeniden düzenlenmeyen bileşikler 288, 290, 292, 294 ve 296 sentezlendi. Bileşik 277'nin sırasıyla $NaOCH_3$ ve CuCN varlığında nükleofilik yer değiştirme reaksiyonu gerçekleştirildi ve yeniden düzenlenmeyen bileşikler 297 ve 298 sentezlendi. Bu çalışma kapsamında yeniden düzenleme aşamasında komşu grupların rolü tartışıldı. Mono-, di-, tri-bromlu yeniden düzenleme ve yeniden düzenleme olmayan ürünlerin oluşum mekanizması ve ayrıca sübstitüent grubun iskelet yeniden düzenlemesindeki rolü tartışıldı. Sentezlenen tüm bileşiklerin yapıları, ^{1}H NMR, ^{13}C NMR, FTIR ile belirlendi ve bunlardan birkaçı, tam yapısal iskeleti tanımlamak amacıyla ^{19}F NMR, COSY NMR, X-Ray kristalografisi ile de karakterize edildi. Sentezlenen tüm bileşiklerin polarimetri analizi, optikçe aktif izomerleri ayırt etmek için polarimetre cihazı yardımıyla ile yapıldı. Sübstitüe gruplarının yapısal iskelete bağlanmasını ele almak için birleştirme sabiti, koruma ve korumayı kaldırma etkileri tartışılmıştır.

Bisiklik (+)-kamfenin brominasyon reaksiyonları sonucu Wagner-Meerwein yeniden düzenlemesi ile düzenleme ürünleri elde edildi ve bu ürünler klasik veya klasik olmayan karbokatyonlardan veya radikal oluşumundan türetilebilir. Bileşik 2'nin iskelet düzenlenmesi 650 watt ışık kullanılarak durduruldu ve radikalik brominasyon yoluyla yeniden düzenlenmeyen bileşikler 274 ve 275 elde edildi. Silikajel kolon kromatografisi ile saflaştırma sırasında ise klasik olmayan karbokatyon üzerinden norbornan yeniden düzenleme ürünü 276 elde edilirken piridin, anilin, DBU veya TEA varlığında monobromlu alkenler 277 ve 278 elde edildi.

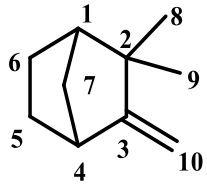
Bu tez temel olarak birçok tıbbi bileşik için başlangıç materyali olacak yüksek verimli mono-bromlu bileşiklerin sentezi için yeni bir tekniğin geliştirilmesine odaklanmıştır. Bu çalışmalar, yüksek verimli mono-bromlu bileşikler 276 ve 277'yi, (+)-kamfene (2)

benzeyen bisiklik yapının yeniden düzenlenmesi yoluyla yeni bir teknikle sentezledi. Yüksek verimli mono-bromlu bileşiklerin sentezlenmesi için yeni yöntemin geliştirilmesi, gelecek yıllar için kamfenin bazı analoglarının sentezine yeni boyutlar katarak katkı sağlayacaktır.

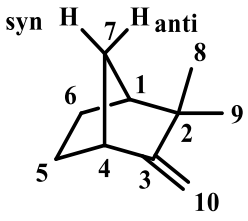
Başlangıç materyali 2 karaciğer ve kardiyovasküler hastalıklar için potansiyel lipid düşürücü maddelerden biridir. Ayrıca Piruvat kinazın bağlanma tarafı ile benzerlik gösteren 288, 290, 292, 294 ve 296 gibi bazı yeni kamfen bileşikleri ve bunların türevleri karaciğer kanseri için potansiyel ilaç olarak sentezlenmiştir. Önceki çalışmalarda organo-siyanür türevlerinin potansiyel antikanser ajanlar olduğu gözlenmiştir. (+)-Kamfenin ise lipit düşürücü bir ajan olduğu göz önünde bulundurularak gelecek araştırmalarda yan zincir ile siyanür grubunu bu doğal biyoaktif moleküle bağlayan potansiyel tıbbi değerler içerecek yeni türevlerin sentezi mümkün olabilecektir.

1. INTRODUCTION

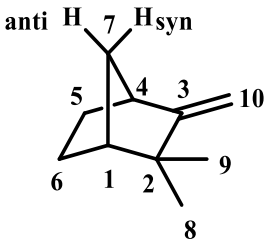
Camphene (2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane) 1 included in mono terpenes has two isomers, (1*S*,4*R*)-2,2-dimethyl-3-methylenebicyclo[2.2.1]-heptane (2) and (1*R*,4*S*)-2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane (3), both of which are commonly naturally occurring aromatic white plastic semi-solid substances with their own taste and fragrance. Basically, camphene and its isomer are constituent part of essential oils of natural plants and have a wide range of medicinal applications. Terpene occupies the camphene in their family which is the mixture of a number of molecular compounds, have their own properties, though mixture of terpenes and cannabinoids is more effective in the synergistic healing (Quintans-Júnior et al., 2013). Camphene is commonly used in cannabis based creams, salves and lotions. Its ability to potentially treat skin conditions such as eczema and psoriasis indicate that camphene could hold anti-fungal and antibacterial efficacy. Camphene is usually more prevalent in indica strains with medicinal potential well worth noting (Vallianou et al., 2011).



Camphene 1



(+)-camphene 2



(-)-camphene 3

Figure 1.1. Isomers of camphene

Pulmonary inflammation was being reduced by camphene considerably as well as it showed promising properties like triglycerides and cholesterol lowering agent, and thus has great positive impact on cardiovascular based health treatment. It was found that camphene is an important medicinal agent which is showing anti-inflammatory, antioxidant and pain relieving properties (Tiwari et al., 2009). The potential of camphene as a medicinal component in cannabis terpenes makes it suitable for treatment in skin diseases (Tiwari et al., 2009). Likewise, (+)-camphene (2) shows potential radical scavenging activities against superoxide and hydroxyl radicals, and also stronger properties *in vitro* TRAP, TAR and TBARS assays (Quintans-Júnior et al., 2013).

The increment of cholesterols, lipids and triglycerides in the intima of artery is responsible for coronary heart disease called dyslipidemia. Chios mastic gum's essential oils showed hypolipidemic properties due to the presence of camphene in the oil working as a key component for hypolipidemic action. An investigation carried out on hyperlipidemic rats showed the reduction of 54%, 54.5% and 34.5% of low density of lipoprotein (LDL), total cholesterol and triglycerides respectively after administration of 30 mg/gm of their body weight (Vallianou et al., 2011). In treatment of HepG2 cells with camphene, diminution of cholesterol content occurred to the same level like mevinolin which is called HMG-CoA reductase inhibitor (Vallianou et al., 2011). The hypotriglyceridemic and hypocholesterolemic effects of camphene are different and free from HMG-CoA reductase activity, indicating that camphene could be an effective alternative lipid lowering agent (Vallianou et al., 2011). Nimesulide is used as analgesic and anti-inflammatory drug but it has hepatotoxic effect, apart from camphene prevented the cellular damages and reduced hepatotoxicity when it was applied with the combination of geraniol with 1:1 (Singh et al., 2012). In 2020, it was observed that (-)-camphene based derivatives showed potential antibacterial activity against two gram positive critical pathogenic bacteria including S. aureus and Enterococcus spp (de Freitas et al., 2020). Recently, some Russian scientists discovered that camphene derivatives are more effective against some pathogenic viruses such as influenza, Ebola and Hantan with IC50 = 45.3 μM, IC50 = 18.3 μM and IC50 = 9.1 μM respectively (Sokolova et al., 2021). Terpenes are defined as a group of natural compounds and the promising source of bioactive molecules as some of them are using as effective anti-cancer drugs (González and Gómez., 2013). They

can be transformed into new derivatives via some synthesis technique as a part of novel drug discovery. Monoterpene can be transformed into monoterpnic ether and ester in presence of alcohols and carboxylic acids respectively via suitable acid-catalyzed chemical process. Camphene and its isomers are attractive targeted bioactive compounds for synthesizing novel compounds due to their structural skeleton which contain sp^2 hybridized carbon that facilitates their easy functionalization. Bicyclic skeleton of camphene undergoes rearrangement reaction via formation of classical or non-classical carbocations as reaction intermediates which can be progressed easily into isoborneol and borneol as well as their ether and ester derivatives (González and Gómez., 2013). These derivatives can play significant role for manufacturing cosmetic products such as soaps, perfumes, fragrances and pharmaceuticals. In addition, they can be used as key components in synthetic chemistry for synthesizing novel medicinal derivatives (González and Gómez., 2013).

Camphene is considered as an important starting material for the synthesis of camphor which adds a vital role in perfumery and pharmaceutical industries (Setzer and Setzer, 2008; Smith, 2014; Quot, 2015). Camphene is naturally occurring bioactive compound and it can also be synthesized via the isomerization techniques which are frequently using for the large scale production for industrial purposes (González and Gómez., 2013). Many cheap and durable catalysts are investigated for the production of camphene via isomerization. TiO_2 is chief among them and is denoted as a reliable acidic catalyst for the synthesis of camphene from pinene (González and Gómez., 2013).

Natural chiral compounds are very important in asymmetric synthesis chemistry as a starting material, as chiral auxiliaries, or preparing chiral reagents. For this reason, functionalization of these compounds is of interest for scientists. Halogenated compounds are key component for functionalization of organic compounds (Sahin et al., 2008). Bromination is significant thriving sound out for synthesizing of key compounds for many novel compounds (Ökten and Çakmak., 2015). The bromination of camphene started from the mid-nineteenth century and several groups studied about the bromination of camphene. All of them reported that bicyclic structure of camphene regulated for producing rearrangement compounds via bromination. Lastly, Barkhash re-investigated bromination of camphene and he reported the same about the formation of four rearrangement products from his reactions (Barkhash, 1984). There is no report

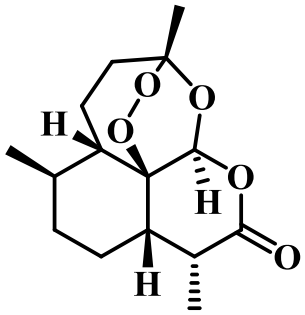
in the literature about formation of *non*-rearrangement products with spectral evidence because it gets challenging due to the Wagner-Meerwein rearrangement of the bicyclic structures. The ring regulation of the bicyclic skeleton of camphene is concerning issues for synthesizing novel non-rearrangement compounds in a large scale. So, a new strategy for the inhibition of the ring regulation of camphene as well as synthesizing high yield mono-brominated chiral compounds as a key component of many non-rearrangement camphene based derivatives will add a new dimension in the synthetic research field of camphene.

It is crucial to explore the new derivatives and analogues of (+)-camphene due to the biological activity of camphene and its derivatives. Many synthesis methods have been developed but photo induced reactions of (+)-camphene at high and moderate temperature were not reported. Synthesis of camphene derivatives could be done by several synthesis technique directly from camphene, besides, camphene formed rearrangement products under bromination reaction. This approach presents a significant limitation of the synthesis of (+)-camphene derivatives. In this research, firstly, alkene portion in the structure (+)-camphene was brominated by investigating suitable conditions for the effective bromination of (+)-camphene compounds for producing non-rearrangement di-bromo-(+)-camphene derivatives. Secondly, elimination reaction of di-bromo-camphene compounds was done for mono-bromo-camphene derivatives. Finally, the resulting mono-brominated (+)-camphene derivatives were subjected to electrophilic and nucleophilic substitution reactions in a suitable conditions for the synthesis of new (+)-camphene derivatives.

2. RESEARCH BACKGROUNDS

2.1. Terpene and Terpenoids

Terpenes are the main components of essential oils called secondary metabolites that occur naturally in animals, plants, plant parts, marine organisms and fungi. Each of the all terpene compounds contains an isoprene unit [CH_2=C(CH_3)-CH=CH_2] with the molecular formula $(C_5H_8)_n$, which is said to be the main building block of all terpene compounds. Mono-terpene compounds contain two isoprene units (n=2), sesquiterpenes contain three (n=3) units, diterpenes contain four (n=4) units, sesterpenes contain five (n=5) units, triterpenes contain six (n=6) units and tetraterpenes contain eight isoprene units (n=8).

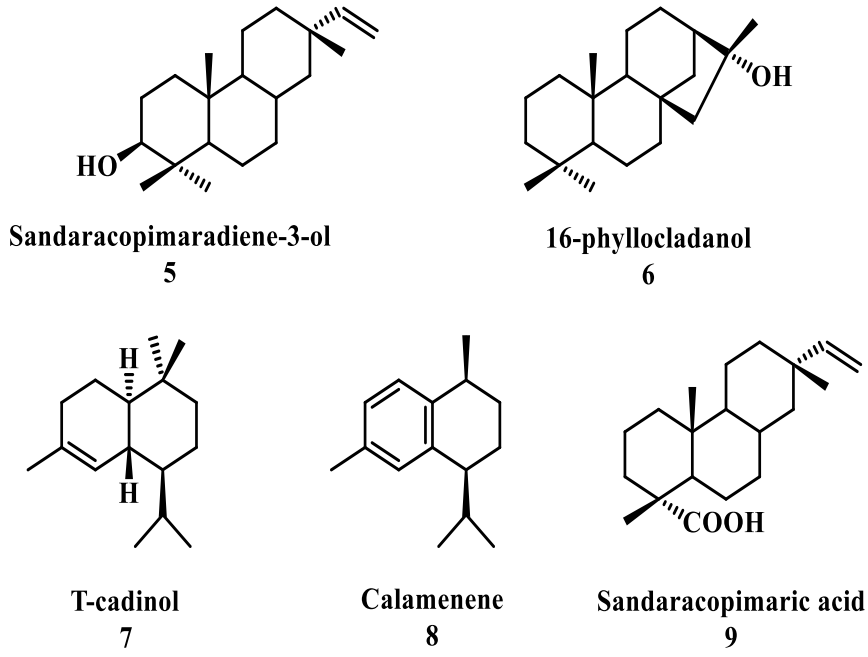


Artemisinin 4

Figure 2.1. Molecular structure of artemisinin

Terpenoids and terpene based chemical compounds have been identified and tested for drug discovery for many years. They have shown excellent therapeutic effects and are a vast source of new medicinal compounds. Traditionally, long-range terpene and terpenoid compounds have been used as good remedies for many kinds of ailments (González and Gómez., 2013). Artemisinin is a fifteen-carbon sesquiterpene compound that occurs naturally from the medicinal plant *Artemisia annua* (Figure 2.1). Professor Tu Yue discovered artemisinin and its derivatives as a potential antimalarial drug and was awarded the Nobel Prize for physiology and medicine in 2015 (González and Gómez., 2013). Recently, researchers have reported that terpenes and its extracts have shown potential medicinal properties such as anticancer, anti-tumor, anti-

inflammatory, anti-oxidant and anti-viral activities. Among them are certain compounds that can build strong resistance against cancer, tumors as well as act as immunosuppressants. T-cadinol and calamenene are sesquiterpenes, besides, sandaracopimaric acid, sandaracopimara-diene-beta-ol and 16-phyllocladanol are diterpenes. They are known to be effective against cancer, tumors and potential immunosuppressants (Figure 2.2) (González and Gómez., 2013).



Sandaracopimaradiene-3-ol **5**

16-phyllocladanol **6**

T-cadinol **7**

Calamenene **8**

Sandaracopimaric acid **9**

Figure 2.2. Bioactive sesqui- and di-terpenes

2.1.1. Nomenclature of the bicyclic mono-terpene compounds

Bicyclic monoterpenes contain a double bond in their structural skeleton. They are classified into major four categories depend on their structure such as 10, 11, 12 and 13 as well as their dimethyl derivatives 14-16. Systematic nomenclature of compounds can also be made by following general rules applied for their bicyclic structure (Figure 2.3).

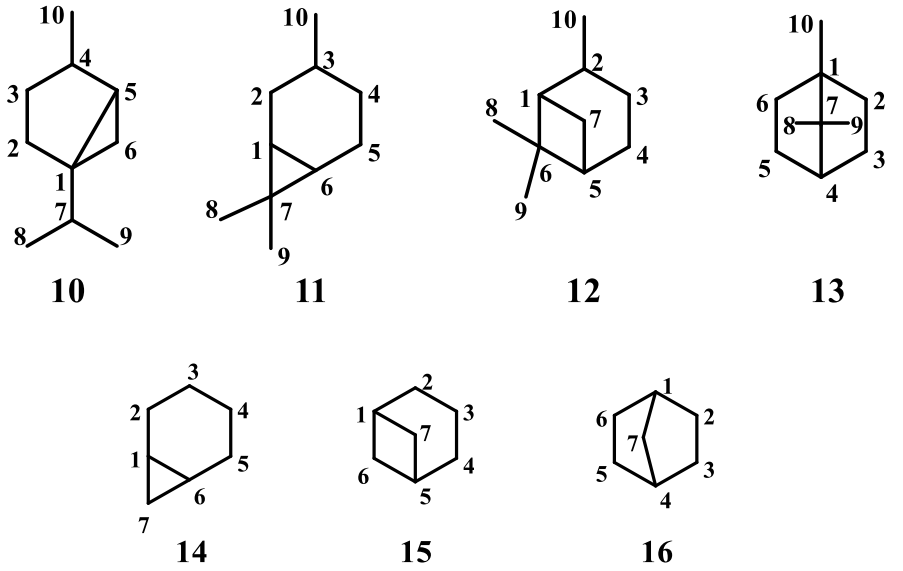


Figure 2.3. Systematic nomenclature of bicyclic monoterpenes

The double bond-containing pinane derivatives α- and β-pinenes (17 and 18) are well-known compounds, among them the mono-terpene containing camphene nuclei. camphene (2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane) 1, camphor (2-camphanone-2-bornanone-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptanone) 19, borneol (*endo*-2-camphanol, *endo*-2-bornanol, *endo*-1,7,7-trimethylbicyclo[2.2.1]-2-heptanol) 20 and its derivatives are important molecules with pinane structure (Figure 2.4).

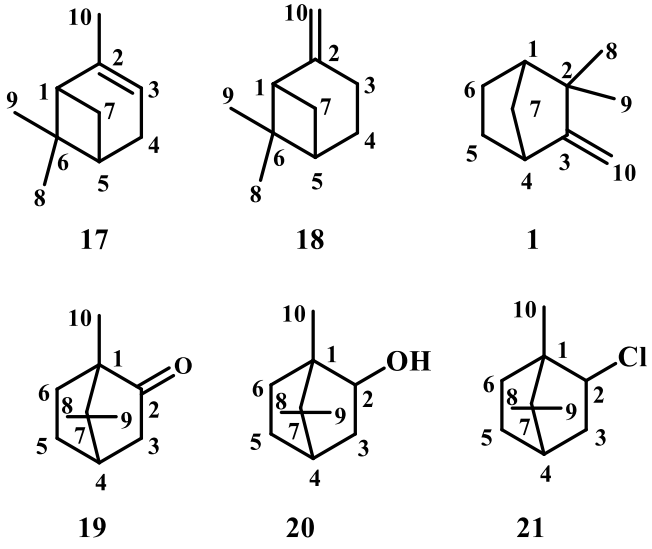
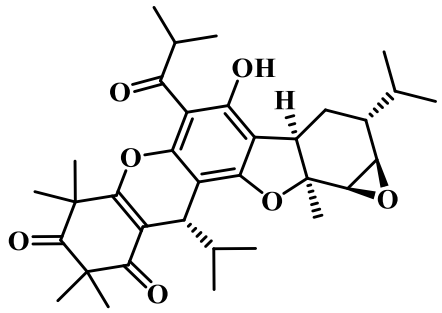


Figure 2.4. Bicyclic monoterpene derivatives with pinane structure

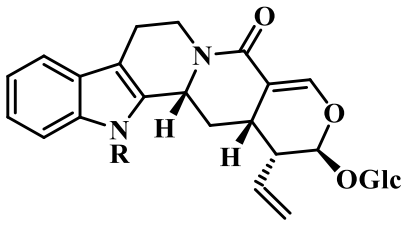
2.1.2. Source and biological importance of monoterpene compounds

Monoterpenes are composed of two isoprene units which may contain no more than ten carbons, each of all monoterpenes has a different flavor depending on their sources

such as rose, citrus and grape. Many monoterpene compounds are isolated from marine sources. As naturally isolated compounds, monoterpenes have a potential medicinal value. Vincosamide is a monoterpene isolated from the leaves of the Brazilian plant *Psychotrea liocarpa*, a potential anti-dengue medicinal compound (Costa et al., 2020). Additionally, monterpenes calistrilones, plaxinones A and B and melodinins Y1 show moderate anti-HSV-1 (Cao et al., 2018), moderate anti-carcinoma of the breast **(**Knotta et al., 2019), and promising anti-lung cancer activity respectively (Zhang et al., 2021).



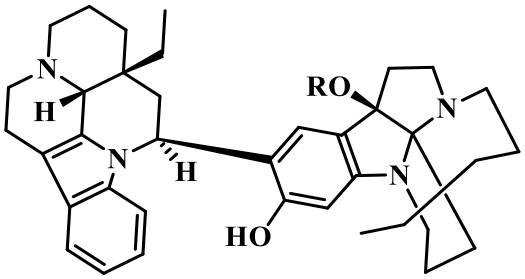
Callistrilone A 22



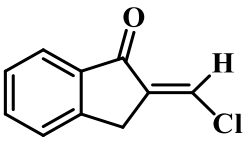
N-glucopyranosyl Vincosamide 23

Figure 2.5. Bioactive monoterpene based compounds

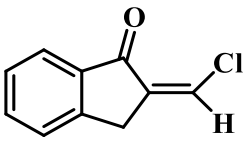
Monoterpenes are used as a starting material for the synthesis of many compounds. Scientists are increasingly interested in monoterpene based compounds because they have potential medicinal values. Many research articles have been published in journals on the chemical reactions of monoterpenes to produce flavor compounds (Swift, 2004). Monoterpenes can produce many aroma compounds through biotransformation processes (Bicas et al., 2009). Limonene is an inexpensive and naturally abundant monoterpene obtained from orange peel oil in over 90% of citrus by-products (Bauer et al., 2008). In recent studies on the degradation properties of limonene have focused on a variety of transformation products such as carvone, perillic compounds and carveol, which may be more useful in chemical synthesis, food ingredients, cosmetics and medicine. Recent research has also shown that *P. fluorescens* is capable of metabolizing limonene to alpha-terpineol at a concentration of about 11 gram per liter (Bicas et al., 2008). Besides this, perillic acid can be produced from limonene by *Pseudomonas putida* GSI up to 11 gram per liter, when the bacteria is cultured in unlimited percentages of limonene, glycerol and ammonia (Mars et al., 2021).



Melodinines Y_1 24



Plaxenone A 25



Plaxenone B 26

Figure 2.6. Monoterpene based compounds

Citronellol: Citronellol is a naturally occurring linear monoterpene in various citrus plants. The (+)-citronellol isomer is obtained from the essential oil of Rutaceae, while (-)-citronellol is obtained in minimal amounts from citronella and geranium oils. Citronellol is of increasing interest in the flavor and food industry, in addition, it is used as a flavoring agent in insect repellents, cosmetics and detergents. In 1915, Neuberg and Mayer produced (+)-citronellol from (+)-citronellal in the presence of yeast cells. Geraniol and nerol can be produced from citral and citronellol through a biotransformation process in the presence of the fungus *Botrytis cinerea*. This fungus imparts a sweet taste to wine by infecting ripe grapes (Demyttenaere, 2001).

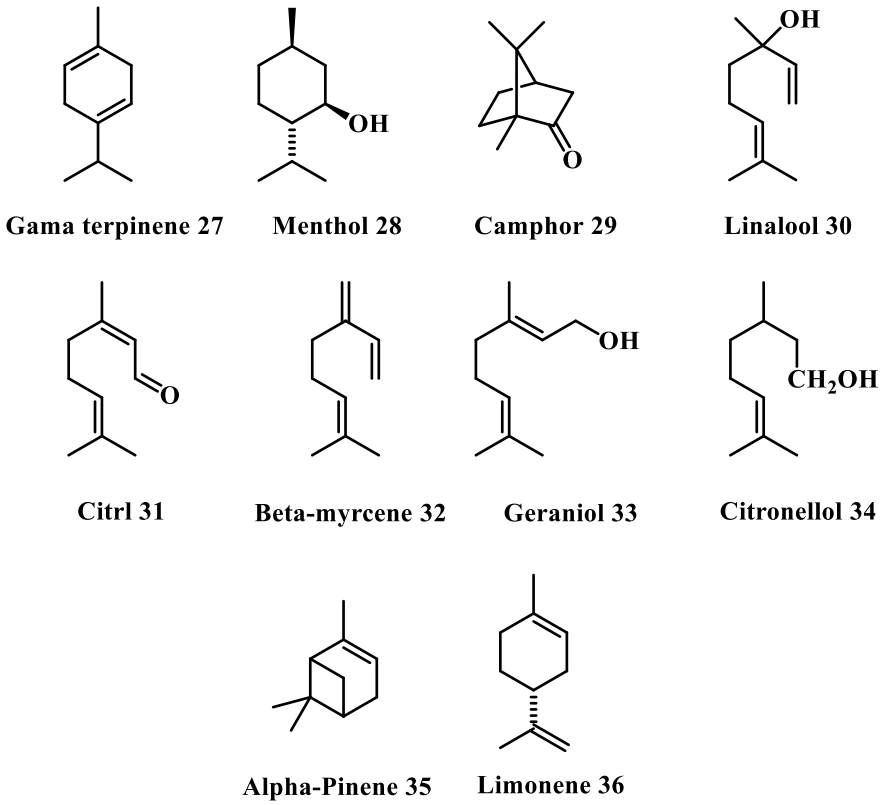


Figure 2.7. Naturally obtained monoterpene compounds

Pinenes: Pinenes are bicyclic monoterpenes found mainly in plants of the Pinaceae family. It is the main component of turpentine oil. A large amount of turpentine is obtained as a by-product from the paper and pulp industry and alpha-pinene is the main component of turpentine (Molina et al., 2014). Alpha-pinene is an important starting material for the industrial synthesis of many compounds. Verbenol is a flavoring agent often used in meat, ice cream, sugar cane, soft drinks and soups. In addition, verbenone has great value in the food industry as a flavoring agent such as menthol and camphor. It is the main component of the raspberry, spearmint and strawberry flavor complex. Verbenol can also be used as a precursor for the synthesis of taxol, which is used as a chemotherapeutic agent. These two products can be obtained from alpha-pinene by biotransformation process in the presence of yeast *Hormonenma* sp. (Van Dyk et al., 1998).

Linalool: Linalool is an important natural molecule with a floral odor and for this reason its two isomers (+) and (-)-linalool are often used in detergents, decorative cosmetics, shampoos, household cleaners, and soaps. These compounds have important therapeutic value because they are bioactive and curative for many diseases (Huo et al., 2013). This monoterpene is found in nature and in many plants that grow

in nature such as *Citrus bergamia*, *Melissa officinalis, Cananga dorata, Salvia sclerea, Citrus aurantium* and other natural resources (Cheng et al., 2012). Many compounds are obtained from these terpenes through biotransformation processes. Linalool is converted to 2,6-dimethyl-2,7-octadiene-1,6-diol in the presence of the fungus *Botrytis cinerea* in grape must. Apart from these, several compounds can be found such as 8-carboxylinalool, furanoid oxide of linalool, 8-hydroxylinalool, perillic acid, oleuropeic acid, 2-vinyl-2-methyl-tetrahydrofuran-5-one and alpha-terpineol via hydroxylation and oxidation process in presence of linalool and *Pseudomonas* (Demyttenaere and Willemen, 1998).

Geraniol: Geraniol is a type of terpene alcohol and an acyclic compound found in the essential oils of various natural plants such as citronella, rose, palma rosa and geranium. Geraniol has a rose-like odor and is used by biotransformation processes to produce a number of terpenes such as nerol, citronellol, hydroxygeraniol, cineol, linalool, 6-metheyl-5-hepten-2-one and alpha-terpineol (Katiki et al., 2011; Limberger et al., 2003). This monoterpene shows significant bactericidal and anti-cancer activity as it inhibits the growth of *Sulmonella* sp when it is used with other food microorganisms (Kobilinsky et al., 2007), also, it is used as an effective chemotherapeutic agent for renal-cancer suppression, tumor incidence and renal oxidative stress (Ahmad et al., 2011), as well as it reduces the maturation of prostate and hepato cancer cells (Kim et al., 2011; Polo et al., 2011).

Citral: Citral is usually an aldehyde mixture of the two isomers geranial (*E*) and neral (*Z*). This terpene is found in abundance in plant parts such as ginger, sweet basil and lemon grass (Iijima et al., 2006). In the food and perfume industries, citral is a valuable flavoring ingredient because it has a lemon-like aroma and is frequently used in food and cosmetic products (Iijima et al., 2006). Many studies in the past reported the biotransformation of citral into other compounds showing useful properties in the food and flavor industries. For example, thymol is a natural preservative used to prevent fungal growth in cheese products. Tavassoli and Esmaeili reported that thymol could be produced by the biotransformation of citral in the presence of *Penicillium digitatum* (Esmaeili and Tavassoli., 2010). Similarly, they produced citronellol from citral through a biotransformation process in the presence of *Saccharomyces cereyisiae* (Esmaeili et al., 2012) cells. Also, it was reported that *Pseudomonas* is an important biocatalyst for the production of geranic acid from citral (Hayashi et al., 1967).

Menthol: Menthol is a widely used monoterpene globally and applied in medicine, cosmetics, candy, toothpaste, chewing gum and cigarettes (Caputi et al., 2011). Menthol consists of three carbon atoms that are asymmetric and fully four pairs of optically active menthol isomers are found in nature but (-)-menthol is found in abundance in peppermint oil, others in lesser amounts. This compound has a minty odor and produces a cooling sensation when in contact with mucosal surfaces and skin, destined for the food, fragrance and cosmetic industries (Koroch et al., 2007). The oil isolated from the mentha plant is the best source of menthol and is usually found in the free form (Caputi and Aprea, 2011). It is not only important in industry but also has some medical applications. It is used as an analgesic and facilitates the penetration of other analgesic substances into the skin (Willis et al., 2011). Many bioactive compounds are obtained through the biotransformation of menthol (Esmaeili et al., 2009).

Beta-myrcenes: Beta-myrcenes is also an acyclic monoterpene like menthol and is naturally found in the essential oils of various plants. It is found mostly in *Artemisia scoparia* essential oil and also in hop, verbena, bay and lemongrass (Oliveira et al., 1997). This monoterpene is used in cosmetics, soaps, food flavoring and detergents, as well as being analgesic, tyrosinase inhibitor and anti-mutagenic (Santos and Sá-Correia, 2009**)**. Also, in the flavor industry, the biotransformation products of beta-myrcene are important due to their characteristic lilac-type aroma. Biotransformation products such as linalool, dihydrolinalool, *cis*-ocimene-8-oxo and *cis*-beta-dihydroterpineol are obtained from beta-myrcenes in presence of *Pseudomonas putida* and the main product depends mainly on the incubation time (Esmaeili, 2011). In addition, many biotransformation compounds are obtained from this monoterpene (Thompson, 2010).

Terpinenes: Terpinenes such as α-terpinene and *γ*-terpinene are generally monocyclic unlike menthol, which are used in the perfumery and pharmaceutical industries. They are potential antioxidants and can be found as a major component of tea tree essential oil, likewise, they are found in various natural sources as components of essential oils (Pyka and Bober, 2002). These monoterpenes are biologically active and show anti-fungal, anti-cancer, anti-bacterial, anti-inflammatory and acaricidal activity but require further research for use in pharmaceutical applications (Çetin et al., 2010). A study showed that the biotransformation of *α*-terpinene can produce two compounds namely

p-mentha-1,4-dien-9-ol and *p*-cymene-9-ol. Another *γ*-terpinene didn't undergo biotransformation due to its chemical instability because of the addition of oxygen atoms to non-activated carbons in the enzymatic process (Chizzola et al., 2004; Krings et al., 2005).

Many other monoterpenes occur in nature that also have great value, and are used as starting compounds in biosynthesis processes, but are less used and have faced limited investigation. For example, camphor, which is a bicyclic monoterpene ketone derived from naturally occurring plant material, shows potential biological activity and is also used in the perfumery and fragrance industry (Chizzola et al., 2004). Besides these, fenchone is a terpenic ketone obtained from thuja and fennel oils (Croteau et al., 1980) with camphor-like odor and has almost similar properties like camphor. Fenchone is used in the food and flavoring industries because of its biological activity and camphor-like odor (Zuzarte et al., 2011).

2.2. Classical Carbocations

Classical carbocations are such type of species which are stabilized by the relocation of either C-H σ electrons or lone pair of electrons or π electrons in conjugation to the positively charged carbon atom and form new π bond are known as classical carbocations (Figure 2.8).

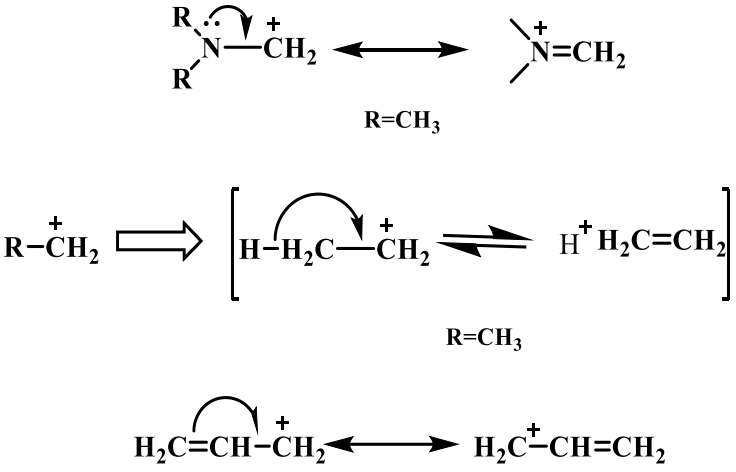


Figure 2.8. Lone pair, σ and π electrons participation in classical carbocation

2.3. Non-Classical Carbocations

In case of non-classical carbocation, the positive charge can not get conjugated with the π-bond unlike the classical carbocation, besides, the resonating configuration can

not be written in normal way. In few cases the resonance shape can be written by the participation of the neighboring groups, which results in the participation of bridged positive charge also called non-classical carbocation. In this type of carbocation, positive charge is delocalized either by C-H bond or σ electrons of C-C or by π electrons of C=C, which are not in allylic emplacement (Figure 2.9 and 2.10).

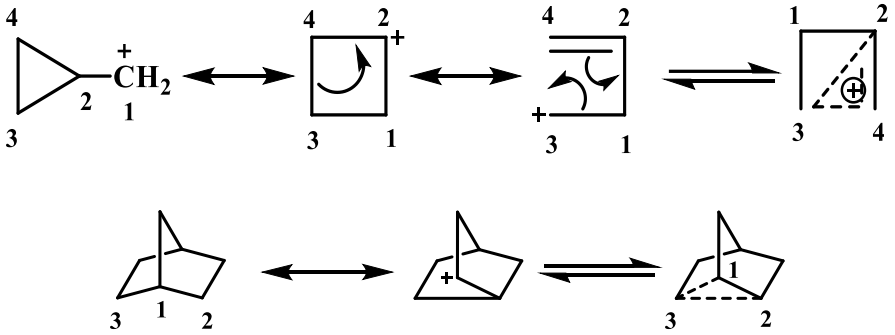


Figure 2.9. σ electrons participation in cyclic and bicyclic non-classical carbocation

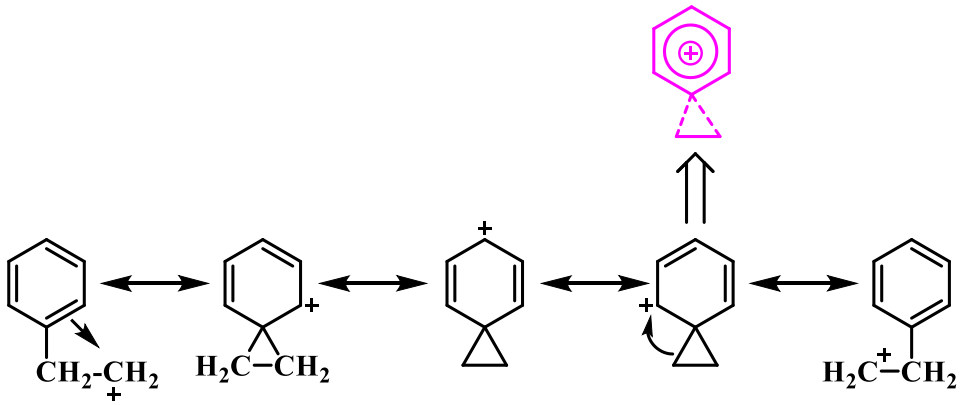


Figure 2.10. π electrons participation in bicyclic non-classical carbocation

2.4. Carbocation Rearrangement

A rearrangement reaction can be take place by the non-classical or classical carbocation or both of them. In a reaction, major and minor products can be produced by non-classical or classical carbocation (Figure 2.11).

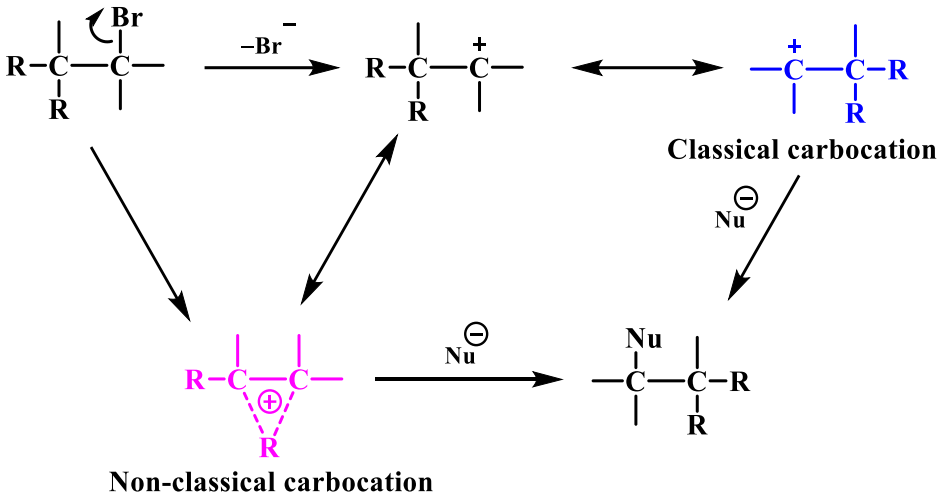


Figure 2.11. Formation of classical and non-classical carbocation in a reaction

Reaction intermediate can be rearranged in two process such as Wagner-Meerwein rearrangement and Pinacolone rearrangement. Generally, carbocation rearrangement occurs more rapidly than carbanion and redical involving rearrangement.

2.4.1. Wagner-Meerwein rearrangement

Wagner-Meerwein rearrangement is a process that can be interpreted as a reflection of the 1,2-rearrangement reaction of carbocation. In this process, alkyl or aryl and hydrogen atoms can be transferred to the adjacent carbons as well as those located within a particular compound. This process was first described by a German-born Russian scientist and the rearrangement process is named after him, the Wagner-Meerwein rearrangement. This rearrangement was first observed in a bicyclic terpene and it was visualized that nor-borneol was fully rearranged to camphene in presence of acid catalyst (Figure 2.12). It is a simple process and often observed in organic reactions and this phenomenon can occur at as low as -120°C.

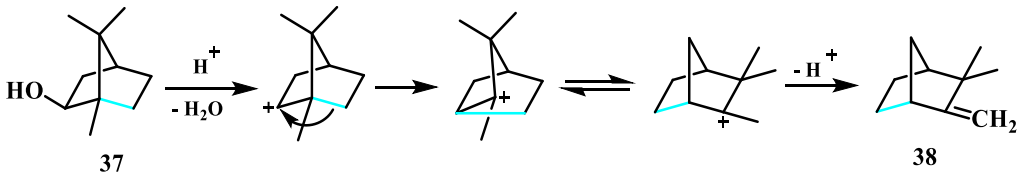


Figure 2.12. Wagner-Meerwein rearrangement in the bicyclic norborneol

Ionic addition reactions in bicyclic monoterpenes occur as a result of the Wagner-Meerwein rearrangement. It has been reported that isobornyl chloride (40) is formed as a result of the addition of hydrogen chloride to camphene (39), while bornyl chloride

(43) is formed in α, β-pinene (41 and 42) (Smith, 1999; Fieser, 1963). The mechanism shown in Figure 2.14 has been proposed for these products.

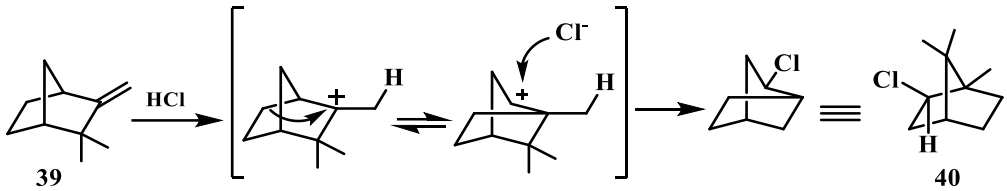


Figure 2.13. Wagner-Meerwein rearrangement in presence of HCl

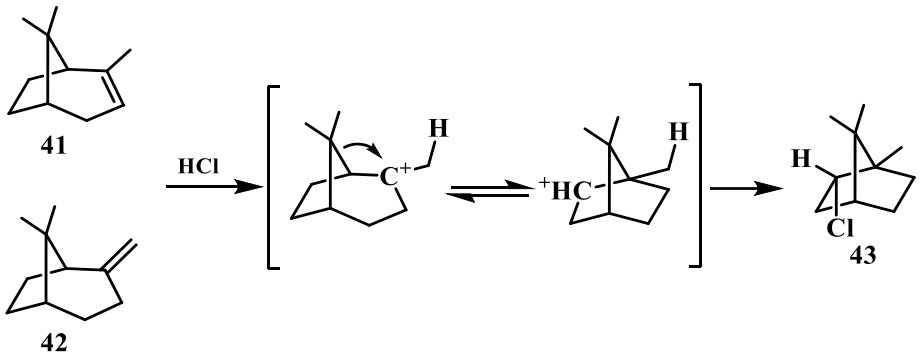


Figure 2.14. Wagner-Meerwein rearrangement of α and β-pinene (41 and 42)

In a chemical reaction, this process is observed more in the reaction at low temperatures and the intensity of this rearrangement decreases with the increment of reaction temperature (Zubkov, 2011).

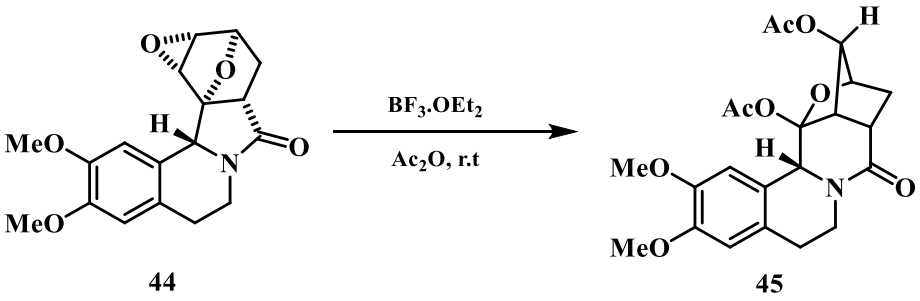


Figure 2.15. Wagner-Meerwein rearrangement of diepoxide

Recently, Zubkov (2011) investigated the cleavage of the oxirane ring of diepoxide in various conditions but the best result was obtained by using acetic anhydride as a reaction medium and boron trifluoride diethyl etherate as an electrophilic catalyst at room temperature (Zubkov, 2011). In this condition, the reaction proceed smoothly and obtained the Wagner-Meerwein rearrangement products 4,6-epoxy-cyclo-pental-pyridines were obtained (Figure 2.15 and 2.16). The mechanism of the reaction is mentioned in Figure 2.16. It's vital to use acetic anhydride to get high yield rearranged

product. The solvent neutralized the carbocation during the last stage of rearrangement, and even inhibited the formation of others side products. On the other hand, the use of acetic acid produced the mixture of different products.

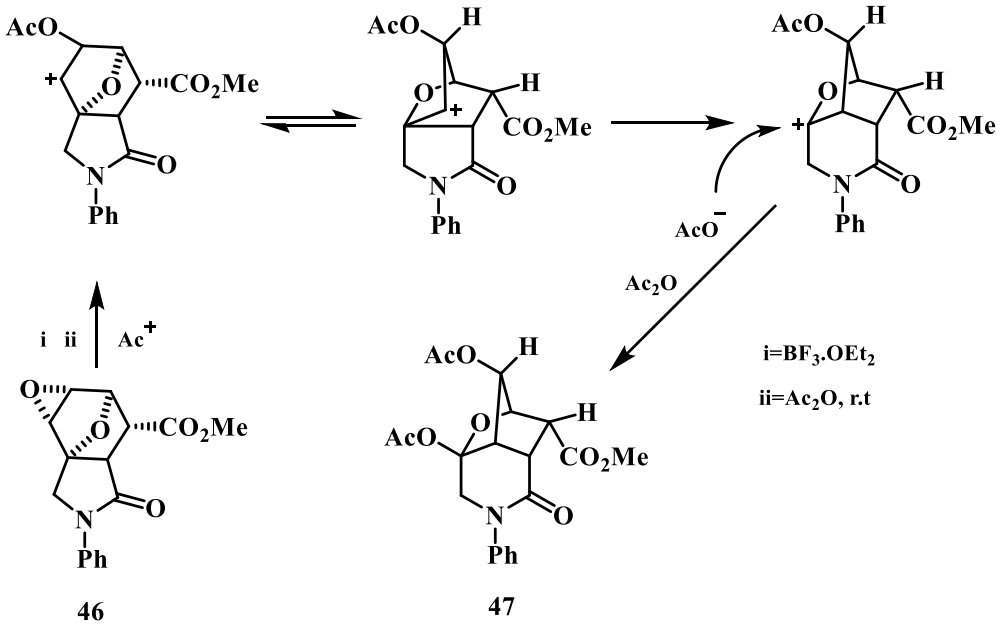


Figure 2.16. Wagner-Meerwein rearrangement (type 1) of oxirane ring of diepoxide (46)

Although, diepoxide can possess two alternative sigma bonds, both are able to perform the rearrangement (Figure 2.16 and 2.17), but just one of them participated in the reaction like the mechanism showed in Figure 2.16. Now, the selectivity can be explained, why the reaction didn't proceed like in the mechanism of Figure 2.17 in sense of higher strength of the sigma bond in six carbon cycle carbocation ring in Figure 2.17. In case of Figure 2.16, the carbocation formed with five carbon involved cyclic ring. Moreover, the Wagner-Meerwein rearrangement proceeds regio- and stereo specifically in all cases of a chemical reaction for producing rearrangement products.

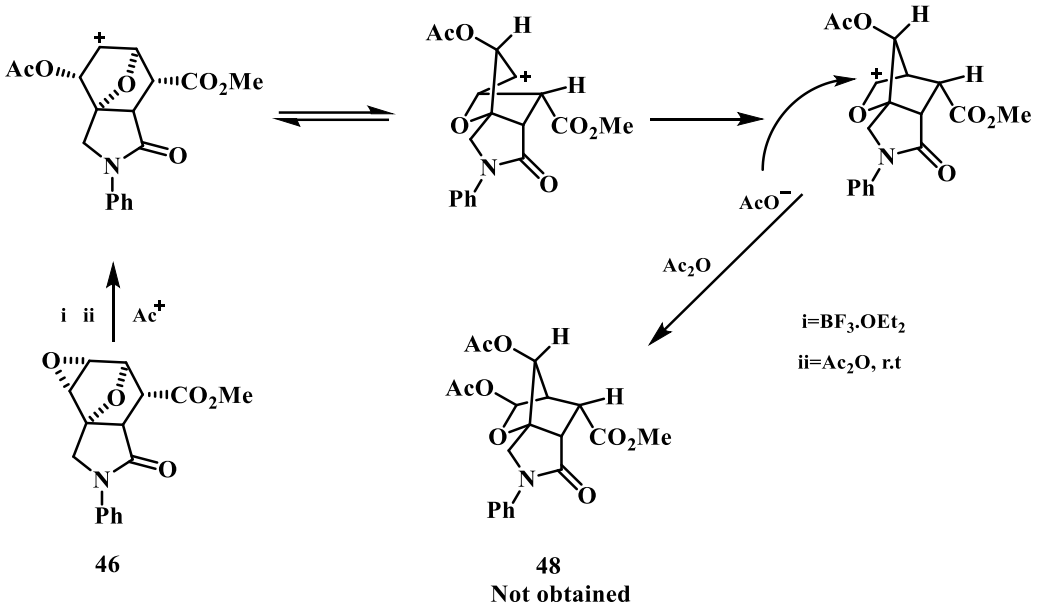


Figure 2.17. Wagner-Meerwein rearrangement (type 2) of oxirane ring of diepoxide (46)

In the case of carbocyclic rings, the Wagner-Meerwein rearrangement can be defined as an intramolecular reaction.

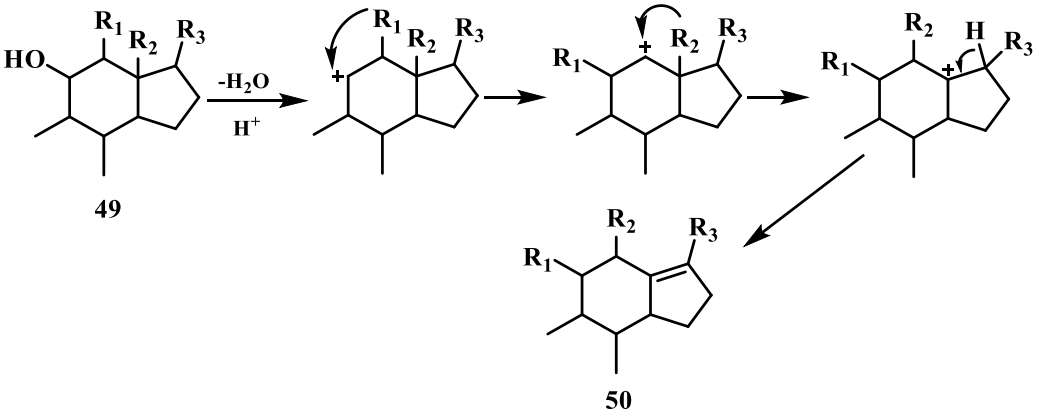


Figure 2.18. Wagner-Meerwein rearrangement of compound 49

Migrating substituents are transferred to the face end of the structure where at least one hydrogen atom is found as shown in Figure 2.18. Hence, the migrating group crosses three carbon orbitals and is neutralized by the hydrogen atom attached to the migrating carbon. In this case, the transition states up to the final stage of the transitional carbocation correspond to a cyclic array and each state contains two electrons from the transition group (Paul de Mayo, 1964).

The Wagner-Meerwein rearrangement also covers another type of process in which the transferring substituents split to form new bonds but the configuration of the molecule remains unchanged as shown in Figure 2.19. In this process, various new bonds can be formed by moving substituents to appropriate positions in a molecule (Paul de Mayo, 1964).

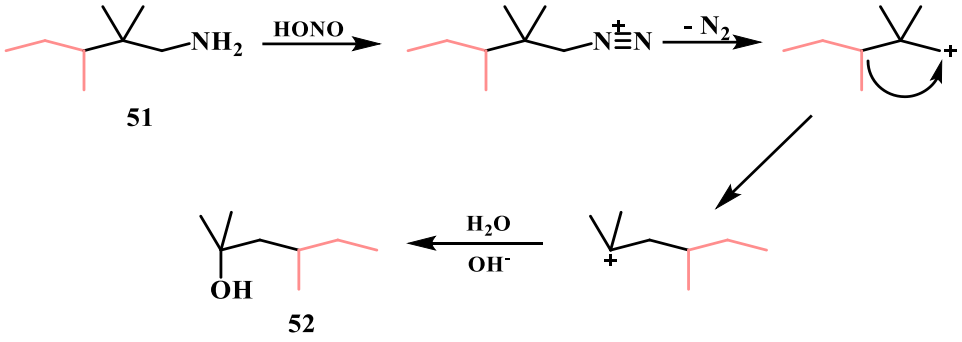


Figure 2.19. Wagner-Meerwein rearrangement of compound 51

2.4.2. Synthesis via Wagner-Meerwein rearrangement

Camphor can be produced by a multi-step synthesis process where camphene (1) is treated with anhydrous acetic acid to form isobornyl acetate (53), followed by saponification of isobornyl acetate in the presence of KOH to form isoborneol (54), in addition, camphor (55) is synthesized by oxidation of isoborneol in the presence of chromic acid. A maximum yield of 16% of camphor was obtained in this process, although yields of isobornyl acetate and isoborneol were 82% and 65%, respectively (Setzer and Setzer, 2008; Smith, 2014; Quot, 2015).

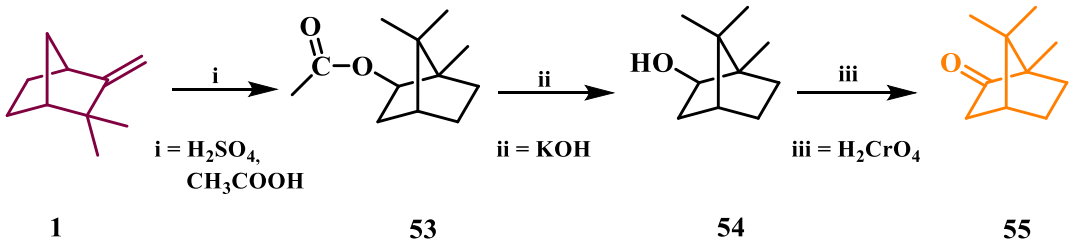


Figure 2.20. Synthesis of camphor (55)

Camphene undergoes carbocation rearrangement in the presence of acetic acid and the final product is obtained as Wagner-Meerwein rearrangement product by the process shown in Figure 2.21.

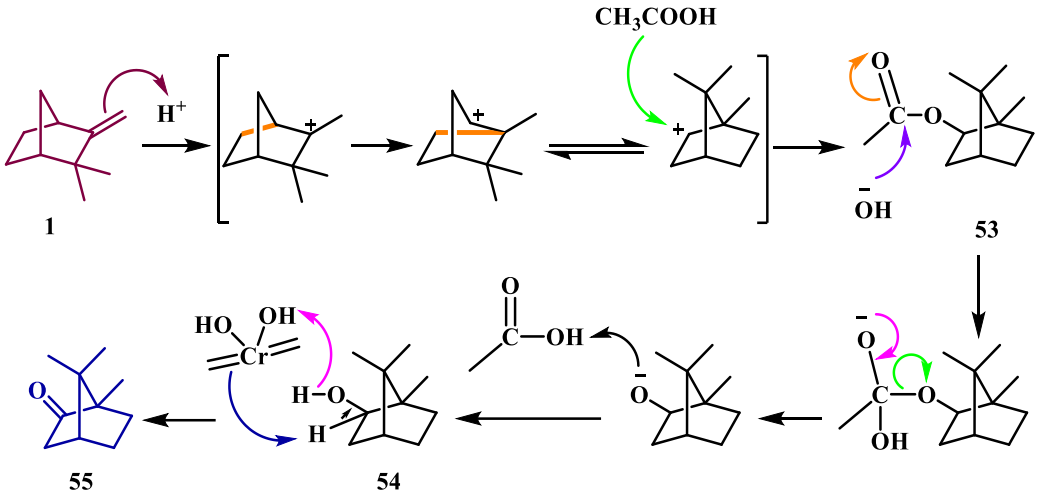


Figure 2.21. Mechanism for the synthesis of camphor (55)

The presence of heteroatoms in the cyclic rings facilitates the direct formation of carbocations which are produced by treatment of bicyclic oxo-acetates with Tf_2O in the presence of organic bases or $TiCl_4$. In this process, carbocations are formed at heteroatoms containing carbon atoms, and the final product is obtained by Wagner-Meerwein rearrangement. In this method, amines and tertiary alcohols are easily obtained but alcohol or amines analogues are difficult to obtain in other methods. The bicyclic acetamide (57) was obtained as a rearrangement product via the Wagner-Meerwein rearrangement from oxoacetate (56) as shown in Figure 2.22 (Ductor, 2005).

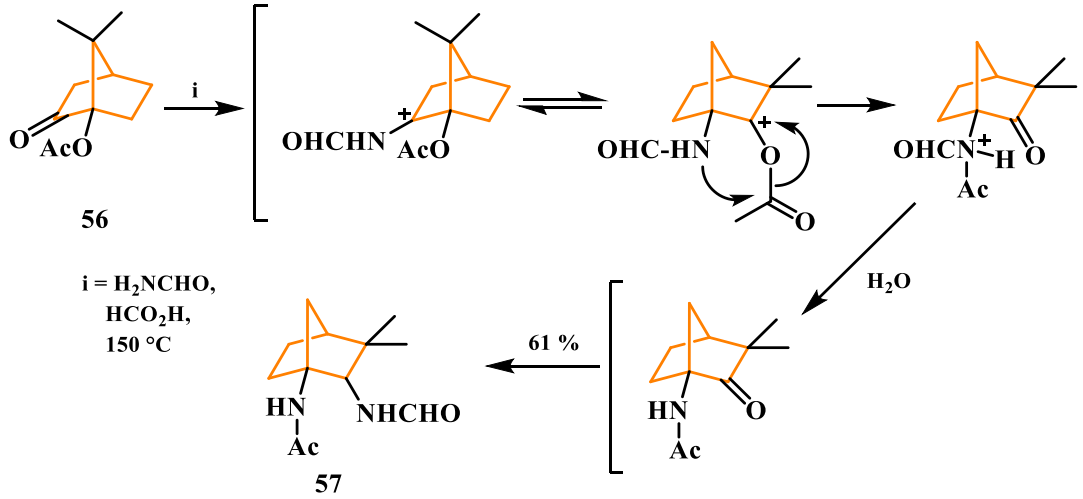


Figure 2.22. Synthesis of bicyclic acetamide (57)

Ducrot 2005, also investigated the synthesis of pivalamine and observed the Wagner-Meerwein rearrangement of fenchone derivatives in the presence of alcohol and hydrochloric acid (10 M).

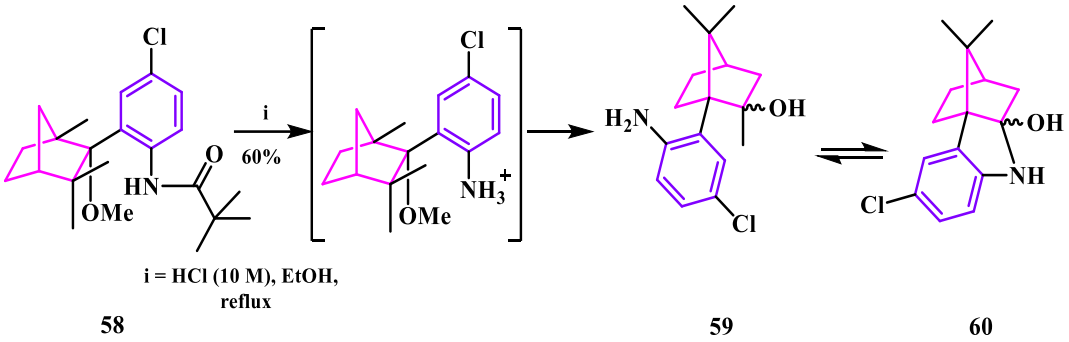


Figure 2.23. Synthesis of Pivalamine (60)

He noted that the oxygen atom dominates the reaction pathway in the presence of water or alcohol to form carbocation and inhibit deprotonation. However, the treatment of fenchone with ethanolic hydrochloride solution was investigated, the carbocation can be intermolecularly or intramolecularly trapped by nitrogen atoms or water molecules, respectively. In this process, chemical equilibrium was observed after one day in acidic condition and thermodynamically controlled product was pyrrolidine (60) but amino alcohol (59) was produced as kinetically controlled product as shown in Figure. 2.23. Ritter reactions for the synthesis of *N*-alkyl amines are remarkably rich in terms, the process uses strong protic acids to form low energy isomeric carbenium ions that follow the Wagner-Meerwein rearrangement for high energy reaction products.

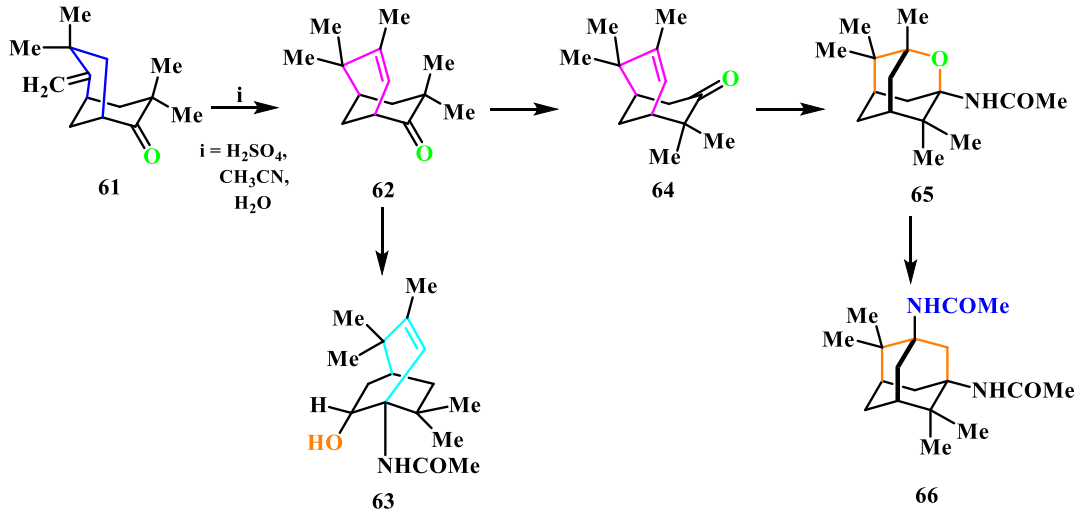


Figure 2.24. Synthesis of *N*-alkyl-amine via Ritter reaction

Kinetic and thermodynamic controlled products (K.C.P and T.C.P) are produced in this process based on the reaction conditions. K.C.P is available in very mild conditions but different techniques are involved for the synthesis of T.C.P. In this process, experimental methods and synthetic design lead to Ritter processes and skeletal rearrangements, respectively. However, treatment of bicyclic nonan-2-one under Ritter conditions produces the five products shown in Figure 2.24. A multiple response parameter was applied to search for optimal conditions of the reaction and the following response was described as a best typical example of a Ritter response. In this reaction, strong H_2SO_4, CH_3CN and water are used as Ritter reagents, both isomeric and rearrangement products are obtained as well as *N*-alkyl amines as shown in Figure 2.24 (Knochel and Molander, 2014).

In the scope of Ritter reaction, the treatment of compound 61 with dilute sulphuric acid and methyl cyanide produced two isomeric products 62 and 64 via Wagner-Meerwein rearrangement. The carbocation was formed at alkene connected carbon in compound 61 and it is neutralized by the one of two methyl groups connected to the neighboring carbon in the same compound and formed two isomers 62 and 64. Furthemore, isomeric products undergo skeletal rearrangement again due to presence of heteroatom oxygen in their skeleton and produced compounds 63 and 65. Surprisingly, one isomer produced alcoholic acetamide (63) and another isomer produced monoacetamide (65) which introverted to diacetamide (66). It was investigated that Wagner-Meerwein rearrangement also depend on the molecular structure of the compounds though most of the bicyclic compounds are used to perform Wagner-Meerwein rearrangement at low temperature but this phenomenon can be different for linear or aromatic cyclic compounds. In short, Wagner-Meerwein rearrangement depended on the reaction conditions, hetero-atom and structure of the organic compounds.

2.5. Synthesis of Camphene Based Derivatives

2.5.1. Bromination of camphene

Radical and electrophilic bromine addition reactions are significant enrichment terms for chemical processes, especially for the synthesis of complex molecules with multiple sites forming carbon-heteroatom bonds that are being used on a large scale as active pharmaceutical ingredients as well as industrial applications. It is usually carried out under radical or ionic conditions depending on the various reagents used in the

reaction. Bromination reactions under ionic conditions cause skeletal rearrangements in the bicyclic system as it passes through carbocation intermediates. Ionic addition of bromine atom to bicyclic monoterpenes results in Wagner-Meerwein rearrangement based on classical or non-classical carbocations. Intramolecular delocalization with σ-electrons instead of π-electrons can result in non-classical carbocations being distributed to different carbons in an organic compound. However, in the radical state, the tendency of radical intermediates to be deregulated makes it possible to obtain the desired brominated product.

Addition of bromine to unsaturated bicyclic system (C=C) is a formally complex one in organic chemistry, however, the reaction is controlled by several factors such as steric effects, temperature, nature of solvent, torsional effects, formation of intermediate classical and non-classical ions, bonds in π and σ electron participation in transition states (De la Mare, 2013; Barkhash, 1984). Generally, halogenation of alkenes is stereoselective and involves the formation of three-membered reaction intermediates to form trans-1,2-dibromides (Slebocka Tilk, 1985). Conversely, the addition of bromine to an unsaturated cyclic system is a more complex reaction than that of other organic compounds, especially in the skeletal rearrangement of bicyclic compounds (Barkhash, 1984; Daştan et al.,1994). In early development of the bromination of unsaturated olefinic cyclic systems, it was shown that temperature plays a key role in the formation of rearrangement and non-rearrangement products (Daştan et al., 1994).

The bromination reaction of campane (1) dates back to the late 19th century but the first serious study was done by Titova and co-workers (1995) and they proposed that low temperature bromination of non-conjugated bicyclic compounds produces the four products as shown in Figure 2.25. They found higher amounts of rearrangement products included 67 and 69 with lower amounts of non-rearrangement products 68a,b but didn’t provide any spectral reports.

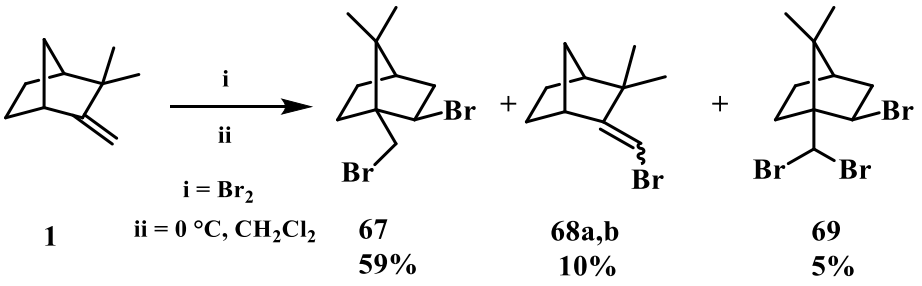


Figure 2.25. Bromination of the camphene

In this study, it was reported that the formation of products walked through non-classical carbocation and they proposed rearrangement product can be formed according to the following mechanism (Titova et al., 1995) (Figure. 2.26).

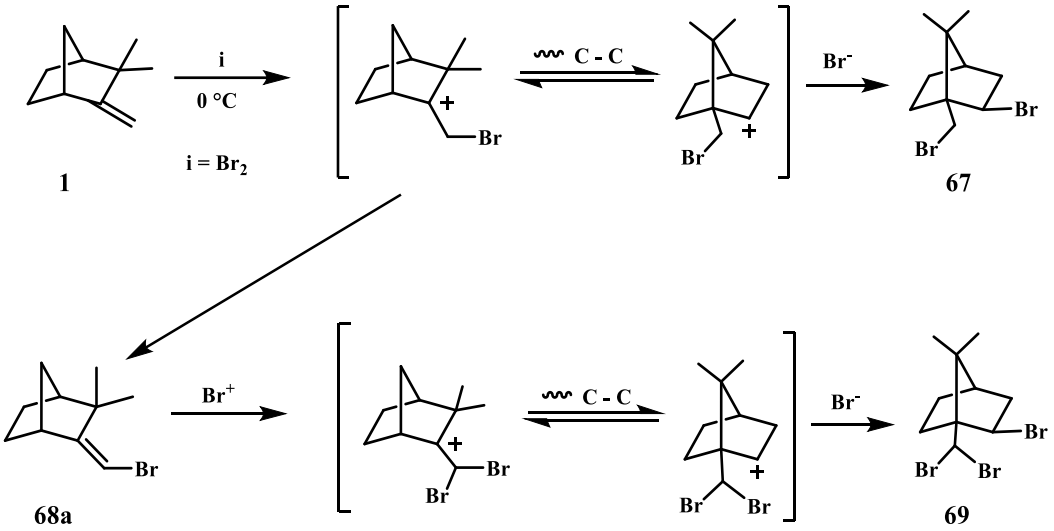


Figure 2.26. Mechanism of the bromination of camphene at low temperature

In 1949, Robert and Trumbull reported that the (+)-camphene (2) nucleus didn't undergo the Wagner-Meerwein regulation in the presence of NBS but formed radical products as shown in Figure 2.27. They obtained bromocamphene (68a,b) but had no spectroscopic evidence of their results (Robert and Trumbull, 1949).

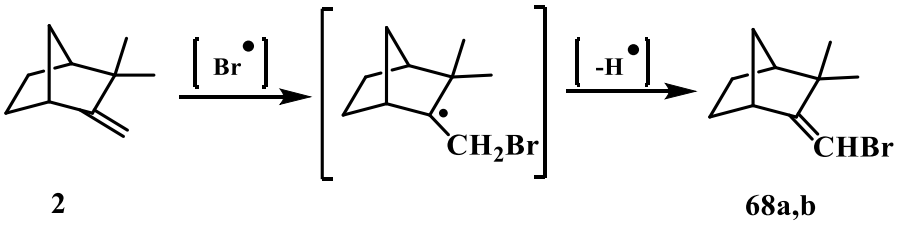


Figure 2.27. Radical bromination of (+)-camphene (2)

Paukstelis and Macharia 1970, obtained 10-camphor (71) compound as a result of Wagner-Meerwein rearrangement of 1-hydroxy camphene (70) under electrophilic conditions (Figure 2.28).

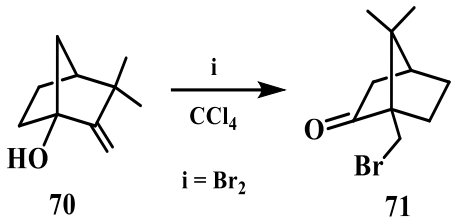


Figure 2.28. Bromination of 1-hydroxy camphene under electrophilic condition

2.5.2. Chlorination of camphene

Chlorination of camphene was first performed in 1953 and the actual mechanism was established by computational studies in 1999 (Figure 2.29). Chlorination of camphene in the presence of HCl was expected to yield compound 72 but unless it produced compound 76 by the mechanism shown in Figure 2.29. (Smith, 1999).

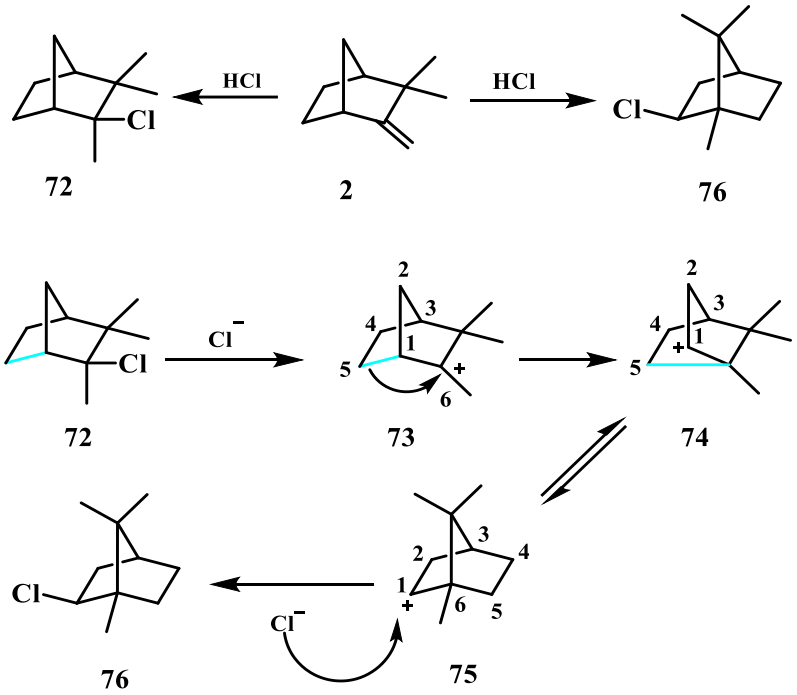


Figure 2.29. Formation mechanism of compounds 76

They proposed that when camphene hydrochloride was formed and some HCl was also present in the freshly prepared hydrochloride solution. The chlorine atom from the structural skeleton of compound 72 is dissociated over time and formed carbocation 73 and one of the neighboring bonds is shifted to the carbon number 6 of compound

73 (Figure 2.29) and stabilized the carbocation. The plus charge was transferred to carbon number 1 of 74 which is similar to the carbocation 75 and in this case, HCl attacked the plus charge and they got the iso-bornyl chloride product 76.

Moreover, the carbocation rearrangement explanation disagrees with this mechanism and suggests that it has lost the value of the explanation because the tertiary carbocation is more stable than the secondary and primary carbocation, therefore, the carbocation survives with strong stability and can't be transferred to the lower stability. Furthermore, they proposed that carbocation 73 forms non-classical carbocations such as 74a (Figure 2.30) and chloride ions attack non-classical carbocations and they obtained the desired product 76. They proposed that 74a is a reaction intermediate and 74 is the transition state. According to the energy diagram, they proposed that camphane hydrochloride 72 was in the lowest energy level, besides, intermediate 74a was relatively in higher energy level than 72, and transition state 74 was in the highest energy level from 72 and 74a (Figure. 2.31). They also noted that the non-classical carbocation is intermediates but chemical reaction intermediates are species that should have lower energy than the transition state but generally the intermediate species 74a has higher stability than 74. They proposed that the transition state 74 was at a higher energy level. This phenomenon proves that the reaction cannot proceed in this particular way.

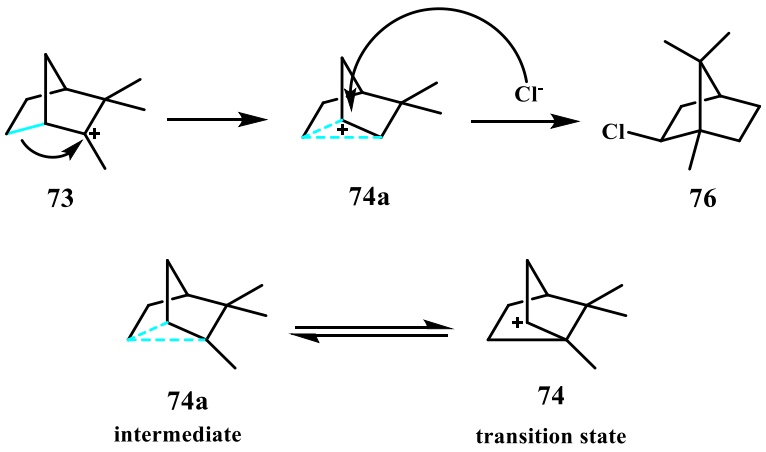


Figure 2.30. Formation of compound 76 via Wagner-Meerwein rearrangement

In addition, the attack of chloride ion on the specific carbocation of 74 is not favorable because the reaction always produces 76 in which Cl^- is attached at the equatorial position rather than the exial position as in 77 (Figure 2.31), so, this was one of the reasons why product 76 achieved at the highest regioselectivity (Smith, 1999).

However, all the contradictions were resolved again by computational studies in 1999 and it was observed that the reaction went through a cyclic transition state, but what actually happened was that they found that the reaction was second order in the presence of camphene hydrochloride and HCl (Smith, 1999).

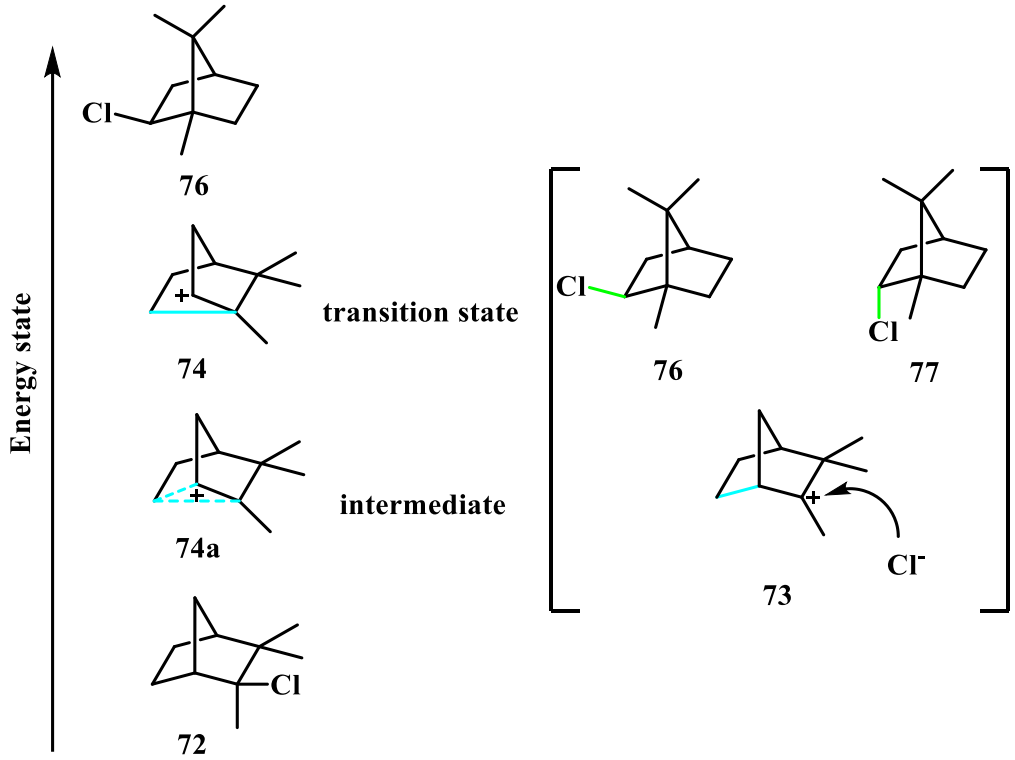


Figure 2.31. Energy diagram for the chlorination of camphene

In the previous reaction, carbocation 73 was formed and was not second order or even first order as in the S_N1 reaction (Figure 2.30). Furthermore, they considered that different issues were present with these reaction pathways and found that the reaction, when performed at low temperatures, produced very small amounts of camphene hydrochloride 72 and most of them were converted to rearrangement products 76. Based on this phenomenone, they proposed that the formation of carbocations can't be involved in the reaction and introduced an authentic mechanism which is shown in Figure 2.32. Hence, the reaction is second order because hydrochloride acid is involved in the reaction at the same time. It can be assumed that the transition state (79) is at the highest energy level regardless of the final product in which Cl is attached to the axial position, since it has come from the phase simultaneously.

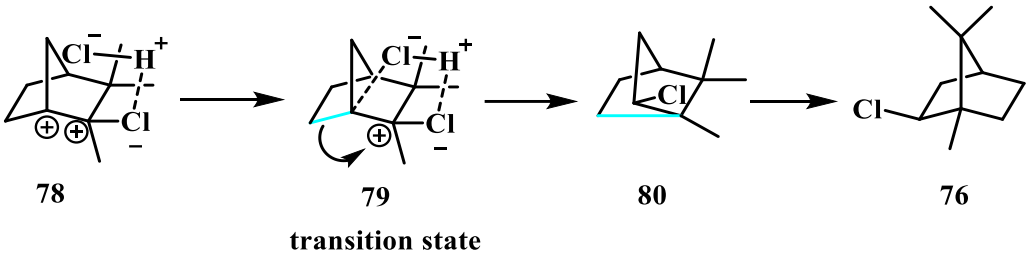


Figure 2.32. Formation mechanism of rearrangement compound 76

In other words, in the kinetically controlled product 72, the chlorine atom and methyl group are oriented with the eclipse conformation but the thermodynamically controlled product 76 is sterically freer due to two hydrogen instead of two methyl groups (Figure 2.33). For this reason K.C.P. can be rearranged to the thermodynamically controlled product. Similarly, thermodynamically controlled product 81 can be produced by the similar type of mechanism is shown in Figure 2.33 (Smith, 1999).

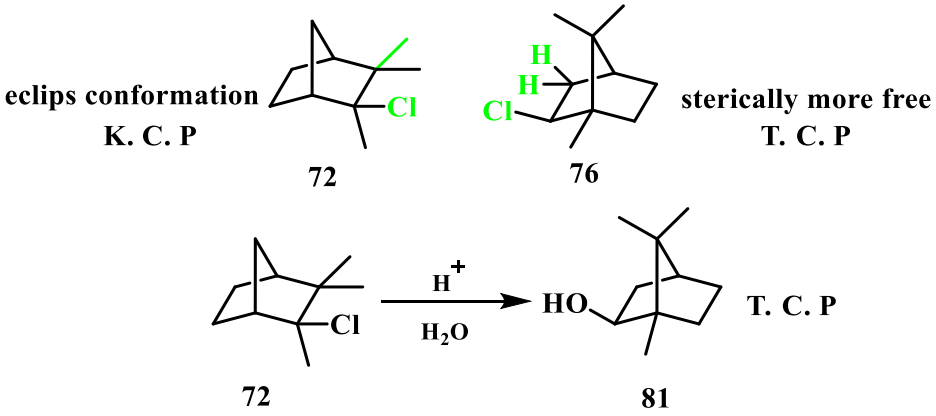


Figure 2.33. Conformation assessment of chlorinated bicyclic compounds

It was observed that kinetically control product is produced at higher temperature and thermodynamically control products are produced at lower temperature. The kinetically control products can be transformed into thermodynamically control products at lower temperature in which they rearranged themselves to the stable molecular structure.

2.5.3. (-)-Camphene based thiosemicarbazones

Souza and co-workers (2019), synthesized a wide number of (-)-camphene based derivatives. In the reaction pathway, first, they produced thiosemicarbazide (83) as an initial reaction materials via the reaction of thiocyanic acid with (-)-camphene followed by the reaction of hydrazine with isocyanoterpene (82) (Figure 2.34).

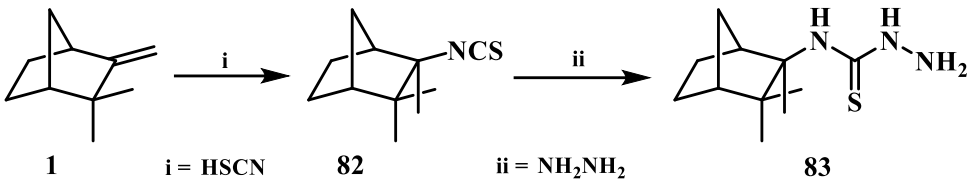


Figure 2.34. Synthesis of thiosemicarbazide (83)

Furthermore, (-)-camphene thiosemicarbazones (85-98) were produced by the condensation reaction of thiosemicarbazide with benzaldehyde derivatives in presence of dilute sulphuric acid and silicon dioxide (Figure 2.35).

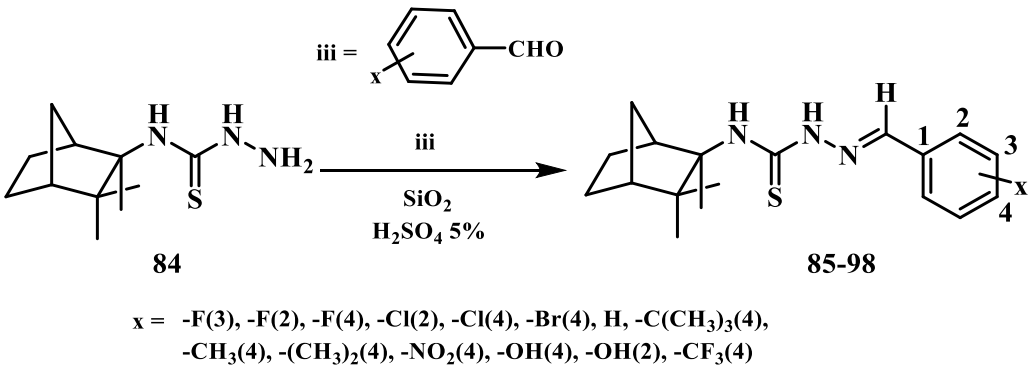


Figure 2.35. Synthesis of thiosemicarbazones (85-98)

Additionally, (-)-camphene thio-semicarbazone 99 was produced via the reaction with heterocyclic aldehyde in presence of dilute sulphuric acid and silicon dioxide (Figure 2.36).

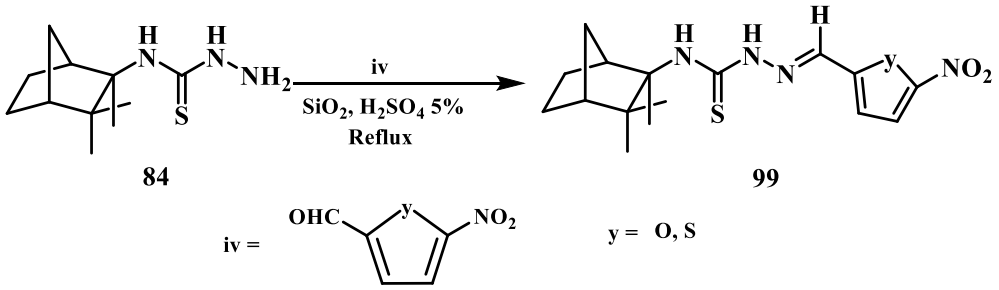


Figure 2.36. Synthesis of compound 99

Beside, isatin (-)-camphene based thiocarbazone 100 was synthesized by the condensation method in presence of thoisemicarbazide, isatin in ethanol and 5% sulfuric acid as acid catalyst as shown in Figure 2.37. They also reported that compound 100 was obtained in high yield with high purity up to 99% after recrystallization.

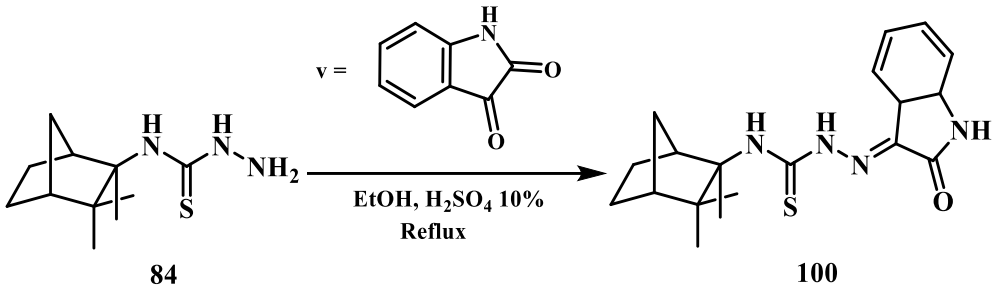


Figure 2.37. Synthesis of compound 100

2.5.4. Synthesis of (±)-camphene based heterocyclic derivatives

Sokolova and co-workers (2021) also synthesized (+)-camphene based heterocyclic derivatives in two steps (Figure 2.38). At the initial step, alkylation of (+)-camphene was carried out with 3-bromo-propan-1-ol and 2-bromo-ethanol in presence of catalyst clay K-10 formed 101a,b via Wagner-Meerwein rearrangement. Alkylation of (+)-camphene with alcohol produced the racemic mixture of the rearrangement products 101a,b. Furthermore, a series of reactions were progressed with different types of N containing heterocyclic compounds such as azepane, morpholine, piperidine, pyrrolidine, 1-methyl piperazine, 4-methyl piperidine, 1-benzyl piperazine and compounds 102-108a,b were produced in presence of potassium carbonate and methyl cyanide.

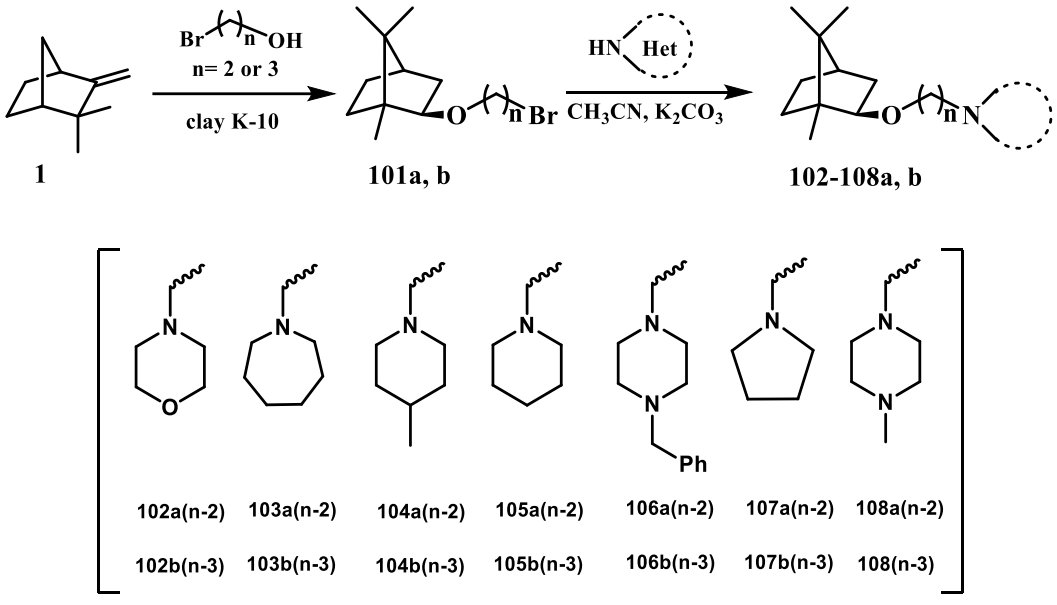


Figure 2.38. Synthesis of camphene based heterocyclic derivatives

2.6. Hydroamination of Terpene

Alkene hydroamination is an important reaction strategy for terpene processing for the functionalization of many terpenoids. In this chemical process, the amine-induced reactant attacks the unsaturated carbon of the primary reactant and forms the amine products (Figure 2.39).

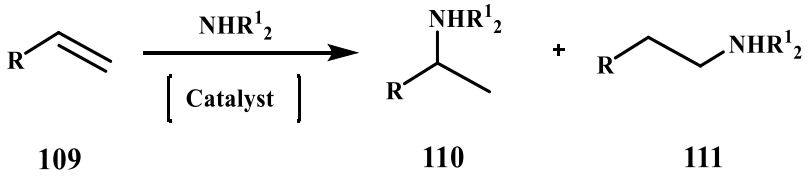


Figure 2.39. Hydroamination of alkene 109

This reaction is particularly well known for processing monoterpenes. Industrially, this reaction has great impact and several important chemical products are produced by hydroamination of monoterpenes. Myrcene is an acyclic monoterpene, its hydroamination products play an important role in the formation of many terpene based compounds such as myrcenol, (-)-menthol, nerol, hydroxycitronellol, (+)-citronellal, linalool, (+)-citronellol, geraniol (Behr and Johnen, 2009) (Figure 2.40 and 2.41).

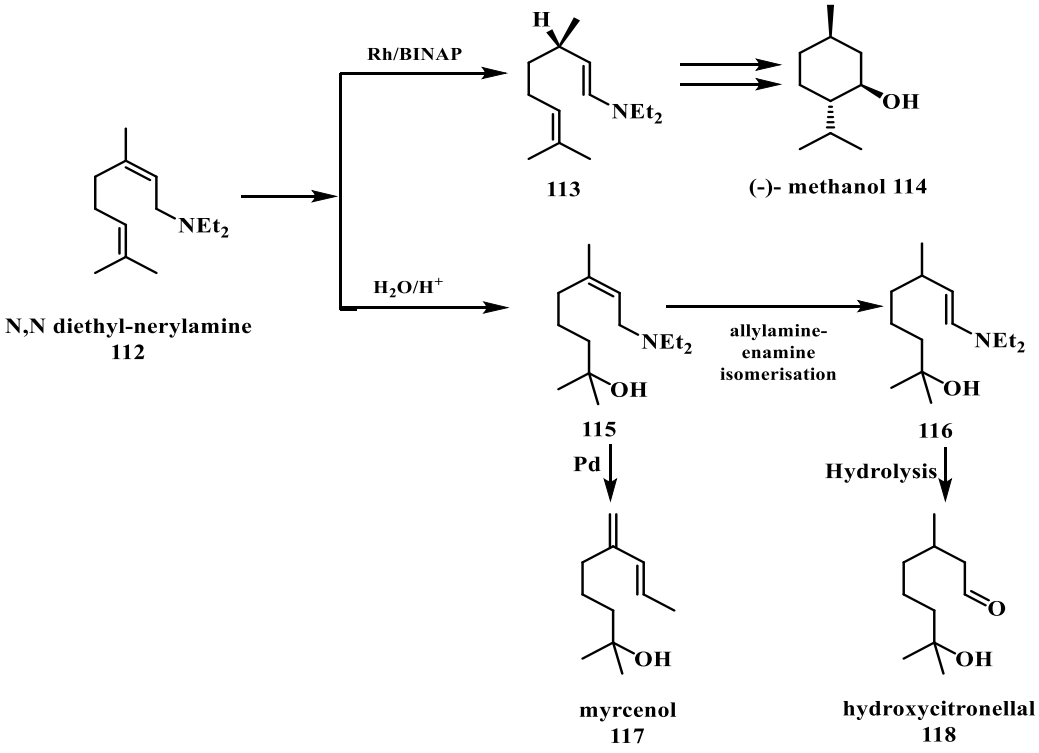


Figure 2.40. Synthesis of monoterpene based compounds

Hydroamination is a type of reaction whereby monoterpenes undergo nucleophilic addition of amine substrates to their structure. In this reaction, the amine substrate attacks the 1 and 2 positions of the olefinic monoterpene molecule containing the carbon-carbon double bond (Figure 2.41). In the context of hydroamination of myrcene containing 1,3-dienes, addition of amine substrate occurs at positions 1 and 4 of the molecule (Figure 2.42). The most commonly used catalysts for hydroamination reactions are transition metals or alkali metals with chiral carbon ligands. Generally, morpholine and diethylamine are used in metal catalyst induced hydroamination reactions. Fujita and co-workers (1974), proposed the hydroamination of myrcene, carrying out the reaction at room temperature with diethylamine in the presence of 16.7 mol% naphthalene and 33.3 mol% sodium. They continued the reaction for one hour and found that 80% of the geranylamine and 53% of the amine were produced in the chemical reaction. They used magnesium, chalk and sodium at much lower concentrations of 1.7 mol% as active catalysts. The reaction was carried out with various dialkylamines at 50 °C for four hours and it was found that the amine yield was up to 83 percent during this time.

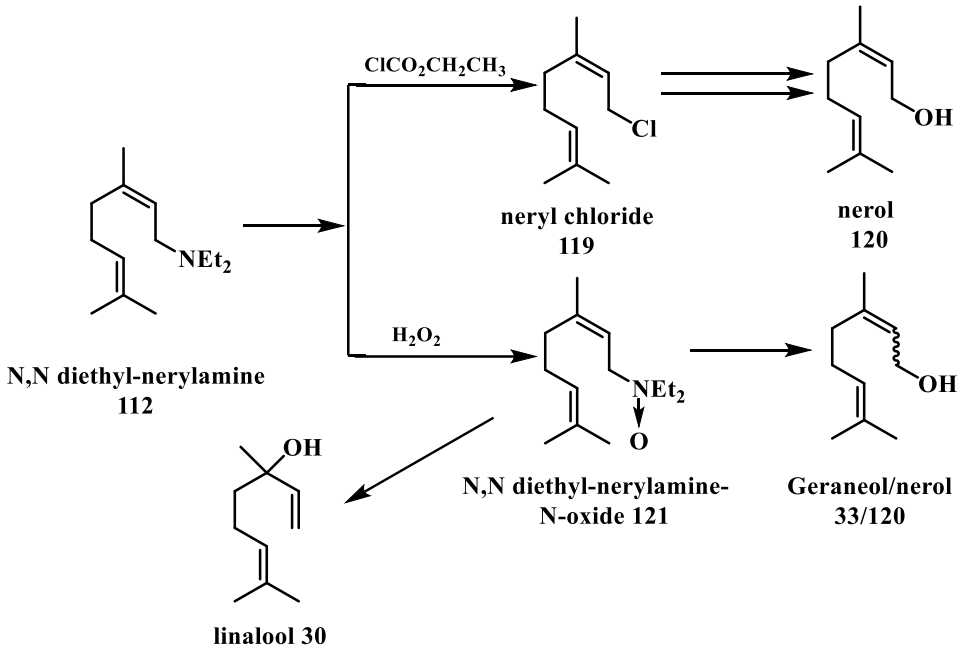


Figure 2.41. Synthesis of alcohol derivatives of monoterpene

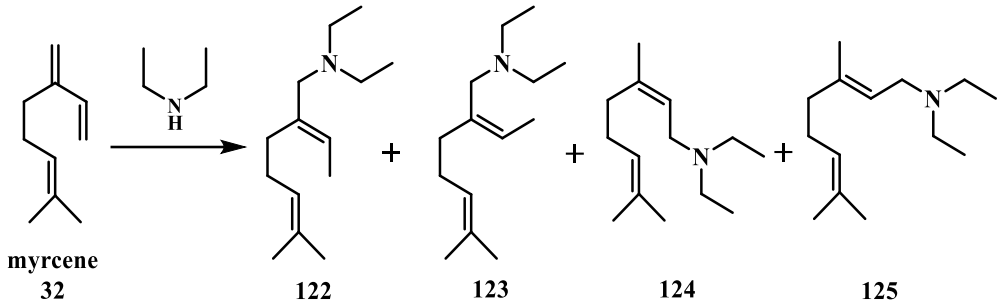


Figure 2.42. Hydroamination reaction of myrcene in presence of diethylamine

Finally, they concluded that lithium instead of sodium could play an important role in the hydroamination reaction as a catalyst. In the case of hydroamination reactions, many studies have used lithium from butyl lithium and many research papers have been published on it. It is conclusively proved that lithium metal plays an active role as like sodium metal in the hydroamination reaction (Figure 2.43). Diethylamine is a model substrate for the hydroamination reaction, although morpholine and piperidine tested as well as transition metal catalysts have been found to be more active than alkali metal catalysts. (-)-Menthol is a compound which is one of the most widely used chemicals in modern times and often used in the flavoring and pharmaceutical industries due to its anesthetic and cooling properties.

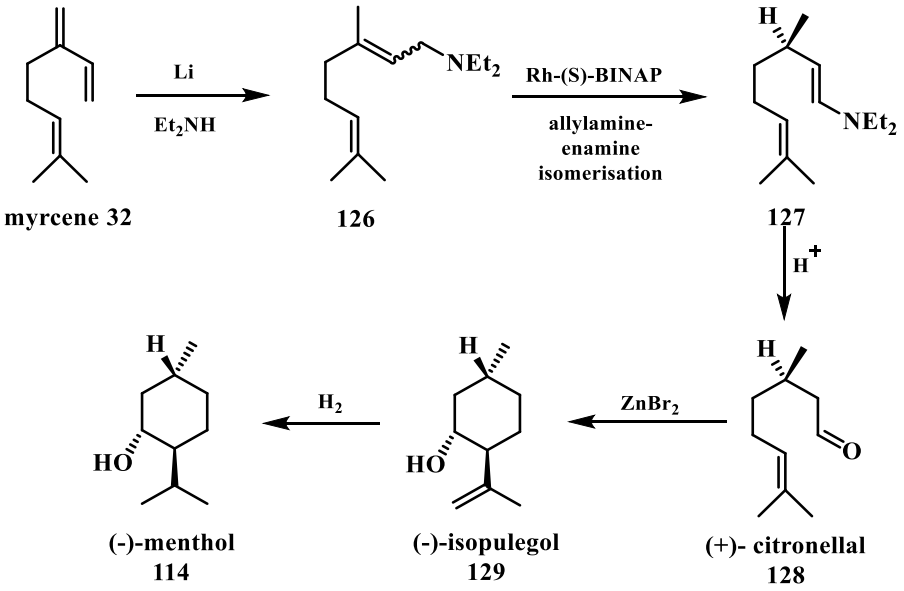


Figure 2.43. Hydroamination of myrcene

2.7. Hydroamination of Alpha-pinene and Citronellyl-acetate

First, the hydroamination of alpha-pinene in the presence of silver catalyst was described by Behr and Wintzer (2014). They observed that the hydroamination of

alpha-pinene with 4-toluene-sulfon-amide ($TsNH_2$) differs from other amination processes. Hydroamination occurred in the absence of solvent and rearrangement product *N*-tosyl-isobornylamine was obtained by hydroamination of the carbon-carbon double bond in alpha-pinene (Figure 2.44). They used alkyne and amine ratio as 4:1 and obtained 98% yield in 14 hour reaction at 85 °C in presence of 5 mole percent silver triflate (AgOTf), also, they obtained 66% yield using 1 mole percent of triflic acid (HOTf) under the same reaction conditions. It was investigated that the yield of the hydroamination reaction depended on the amine substrate and the silver catalyst was better than the gold catalyst. Additionally, upon hydroamination of citronellyl acetate in the presence of $TsNH_2$ and AgOTf, the internal carbon-carbon double bond participated in the reaction and produced the terminal amine product surprisingly (Figure 2.44).

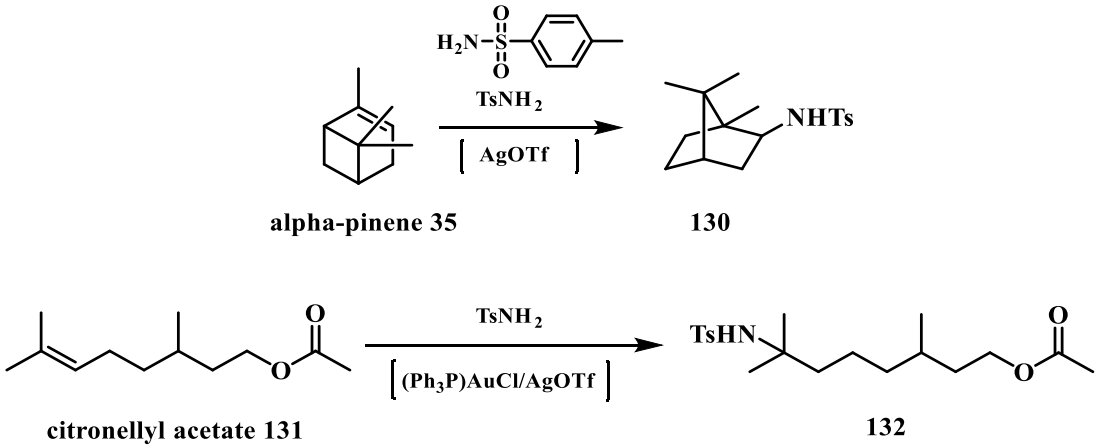


Figure 2.44. Catalytic hydroamination of citronellyl acetate and alpha-pinene

2.8. Hydroaminomethylation of Monoterpene

Hydroaminomethylation reaction of terpenoide is one kind of tandem reaction in which carbonylation occurs via hydroformylation, condensation and hydrogenation process. Generally, carbonmonoxide and hydrogen gas are used for the hydroformylation, besides, amine and hydrogen undergo condensation and hydrogenation process respectively. Many research papers have been published on hydroaminomethylation process via using different types of catalyst and substates. In terms of hydroaminomethylation, Reppe used CO, ammonia and amines (secondary and primary) for the hydroformylation, condensation and hydrogenation respectively in presence of $Fe(OH)_5$ as a catalyst in case of hydroaminomethylation (HAM) of ethylene. In the same time, Larson used cobalt and copper catalysts with

carbonmonoxide, hydrogen and amine for HAM. Furthermore, the optimization of HAM reaction was well described in a patent and finally in 1993 primary amine derivative was synthesized by HAM reaction (Behr and Wintzer, 2014). Knifton and co-workers (1993), synthesized primary amine from 1-hexene in presence of 28% ammonia and $Co_2(CO)_8$ as catalyst for HAM reaction at high temperature 200°C and high pressure 200 bar (Knifton and Lin, 1993).

However, HAM reaction of some monoterpene such as limonene (Knifton and Lin, 1993), beta-pinene and camphene were investigated (Behr and Wintzer, 2014). Hydroaminomethylated derivatives of limonene were synthesized in presence of $[Rh(cod)Cl]_2$ catalyst, diethylamine and morpholine and got 81% and 93% of yields at 120°C and 80°C respectively with 80 bar pressure of gas (Figure 2.45). Additionally, the HAM reaction of limonene was proceeded via two steps including hydroformylation and hydrogenation (Behr and Wintzer, 2014).

The hydroaminomethylation of some monoterpene i.e. limonene, camphene and beta-pinene as shown in Figure 2.45 and Figure 2.46 respectively in one step in presence of new catalyst composed of a precursor $[Rd(cod)(\mu\text{-}OMe)]_2$ and a ligand triphenyl phosphine (Melo et al., 2012). They performed the HAM reaction with 1 equivalent (10 mmol) of amine substrate using three different amine such as morpholine, *n*-butylamine and di-*n*-butylamine in presence of different concentration of catalyst at 100°C and 60 bar of $CO:H_2$ (1:1) gas into the 20 ml toluene for optimizing the reaction condition to find out the high yield of amine products.

In the HAM reaction of limonene, a combination of 2.5 ratios of the catalytic ligand and 2.5 ratios of morpholine and di-*n*-butylamine respectively produced the best yields of amine products with 88 and 81 percent under the same reaction conditions. In the case of the *n*-butyl amine substrate, hydrogenation did not occur in the presence of the catalytic ligand triphenylphosphine but in the absence of the ligand, 75% yield of the amine product was obtained (Figure 2.45).

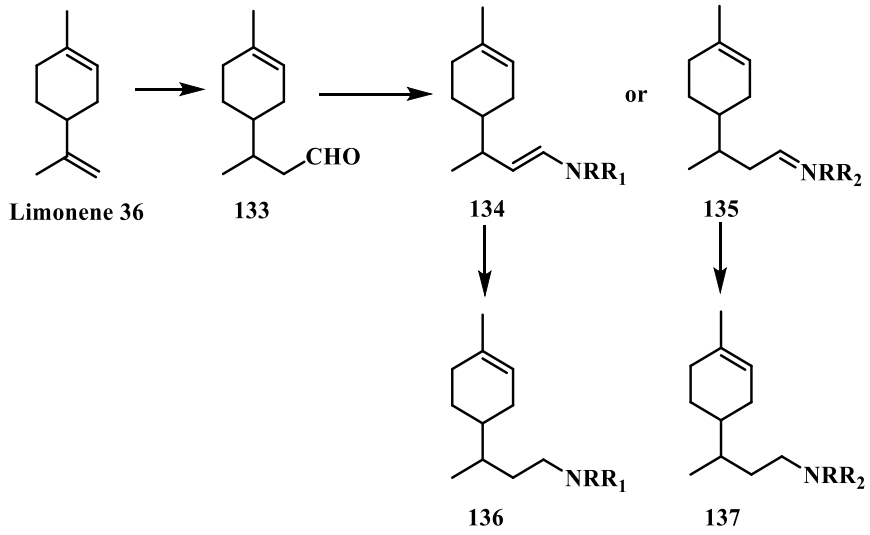


Figure 2.45. Hydroaminomethylation of limonene

In the case of the HAM reaction of camphene, almost identical results were obtained as for limonene, as the highest amine product yield was 87% from morpholine and 83% for the substrate di-*n*-butylamine in the presence of the same 2.5 ratio of triphenyl phosphine and $[Rh(cod)Cl]_2$. Similarly, 94% of the amine product was obtained from the substrate *n*-butyl amine in the presence of the catalytic precursor (Figure 2.46).

In terms of hydroaminomethylation of β-pinene (Figure 2.46), side reactions in the presence of di-*n*-butyl amine substrate with a TPP/Rh ratio of 2.5 yielded 29% α-pinene. Furthermore, the ligand and precursor ratio was increased up to 20 and the isomerization of α-pinene was significantly reduced to 3%.

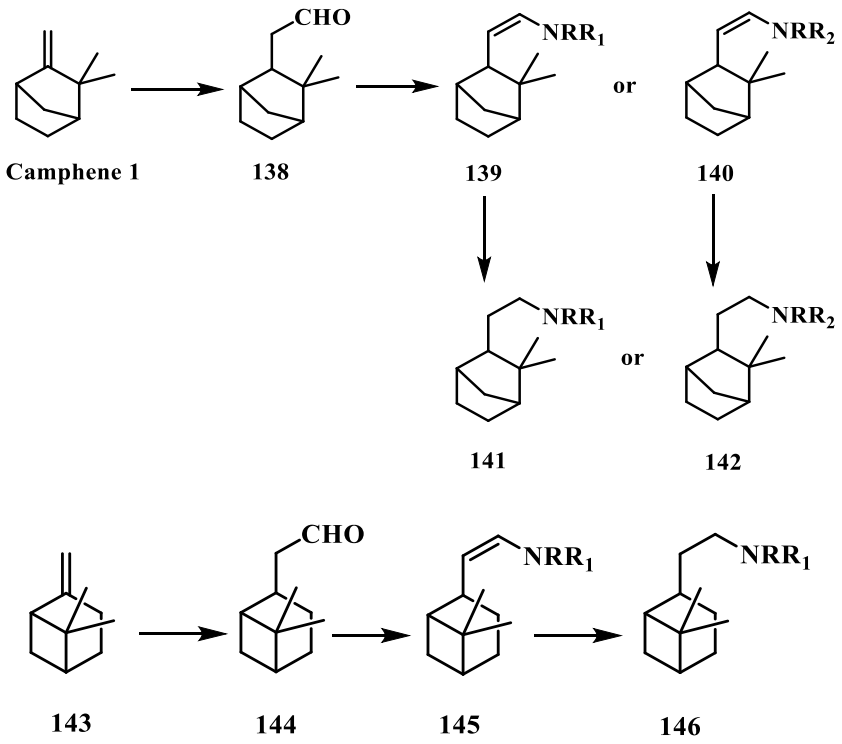


Figure 2.46. Hydroaminomethylation of camphene (1) and β-pinene (143)

2.9. Electrophilic Addition of Alkene

Scientists have discovered many novel organic compounds through the electrophilic addition reaction over the years, which have been playing an effective role in the development of new compounds. The addition of bromine to olefinic compounds by electrophilic process is considered as a very common reaction in organic chemistry. As a result of many years of research, it has been demonstrated that when the bromination reaction is carried out with a carbon-carbon double bond, an intermediate called bromonium ion is formed which invariably produces the racemic *trans* products. The formation of bromonium ion as an intermediate during the electrophilic bromination reaction of alkene was first realized by Roberts and Kimball in 1937. They were unable to conclusively prove the origin of the bromonium ion because the reaction was carried out very quickly. Subsequently, since the reaction takes place in the presence of bromine ions, many studies have been conducted to prove the presence of bromonium ions in the reaction. Later, Weinberg observed the presence of tri-bromide bromonium ion in the laboratory via reacting molecular bromine with adamantylidenedamantane in the presence of carbon tetrachloride, which was obtained as a yellow substance and finally it was proved by Slebocka-Tilk, 1985, via the

experimental evidence of X-Ray structure (Figure 2.47), (Weinberg and Slebocka-Tilk, 1985).

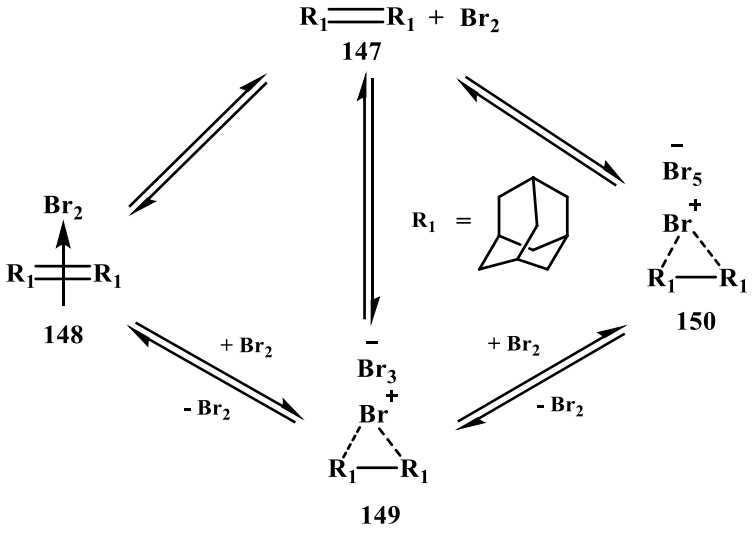


Figure 2.47. Electrophilic addition via formation of bromonium ions

Adamantylidenedamantane (R_1) is very stable compound and its molecular weight is high. The back side nucleophilic attack is difficult, consequencely, *trans* di-bromide didn't obtain because of the steric hindrance. When the salt of bromonium ion dissolved in organic solvent like 1,2-dichloroethane, it dissociated the bromine and formed charge transfer complex 148, tribromide bromonium ion 149 and pentabromide bromonium ion 150 as shown in Figure 2.47. However, the stereo selectivity can be described by bromonium ion in terms of electrophilic addition of bromine to alkene. The mechanism is proceeded by the formation of the complex, then, bromonium ion is formed and end with the formation of product via nucleophilic attack like Figure 2.48. Cyclic bromonium ion is more stable than acyclic carbocation and a mild energy (104.5 kJ/mol) is required for the conversion of cyclic carbocation to acyclic carbocation. Generally, bromination of alkene produces non-classical carbocation which forms 3 center-transition state.

In addition to this, bromination reactions can be produced *cis* and *trans* products simultaneously if there is a free rotation between carbon-carbon single bonds of the reactants. Previously, two possible mechanism drawn out for the bromination reaction of alkene, addressed that when one equivalent molecular bromine participated in the reaction formed cyclic bromonium ion but tri-bromide bromonium ion was produced in presence of two equivalent of molecular bromine as shown in Figure 2.48.

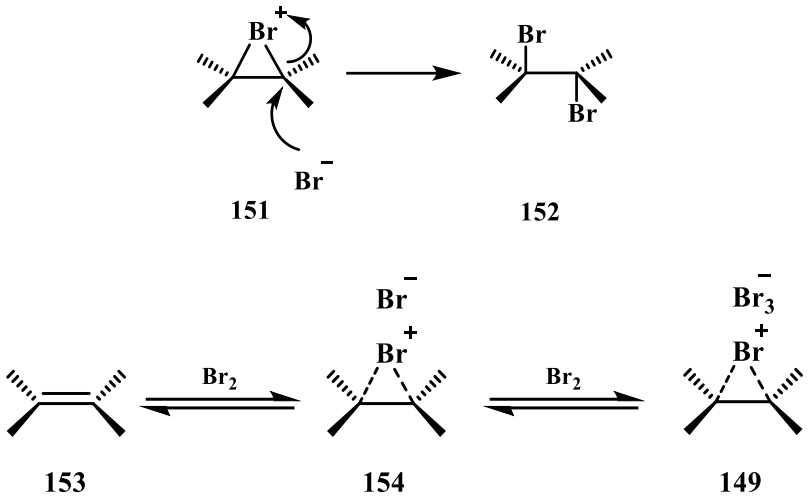


Figure 2.48. Formation of bromonium ions

Bromination reaction of alkene with molecular bromine produce 1,2-dibromides called vicinal dibromide. In this reaction, carbon-carbon π bond breaks forms two new C-Br bonds. Simply, anti-addition of bromine occur in this reaction, means bromine atoms are connected to the opposite side of the carbon-carbon double bond. The most common solvent CCl_4 is used for this reaction as it has no effect on reaction, more briefly if H_2O is used in this reaction it would form bromohydrin.

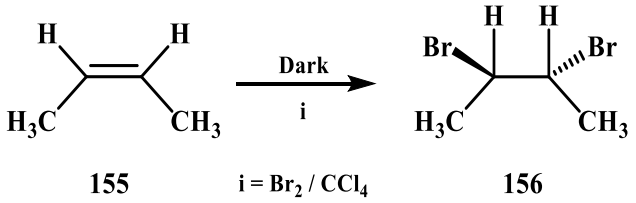


Figure 2.49. Bromination reaction of alkene in absence of light

The reaction products of the bromination of alkene can be different based on the initial reactant components. In case of the bromination reaction of compounds 157, 160 and 163, enantiomers are produced in presence of molecular bromine and carbon tetrachloride, besides, compounds 166 and 169 are produced as diastereomers in the same reaction conditions as shown in Figure 2.50 and 2.51.

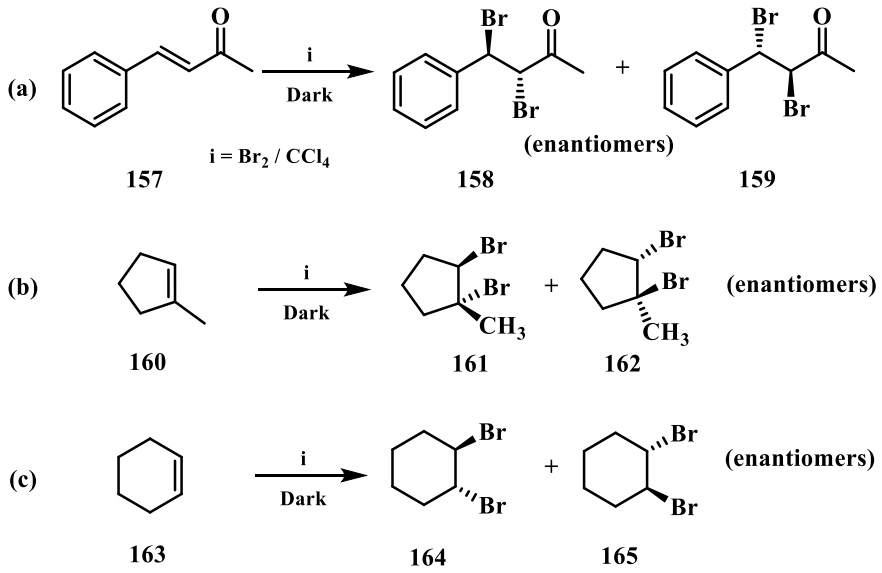


Figure 2.50. Bromination of compounds 157, 160 and 163

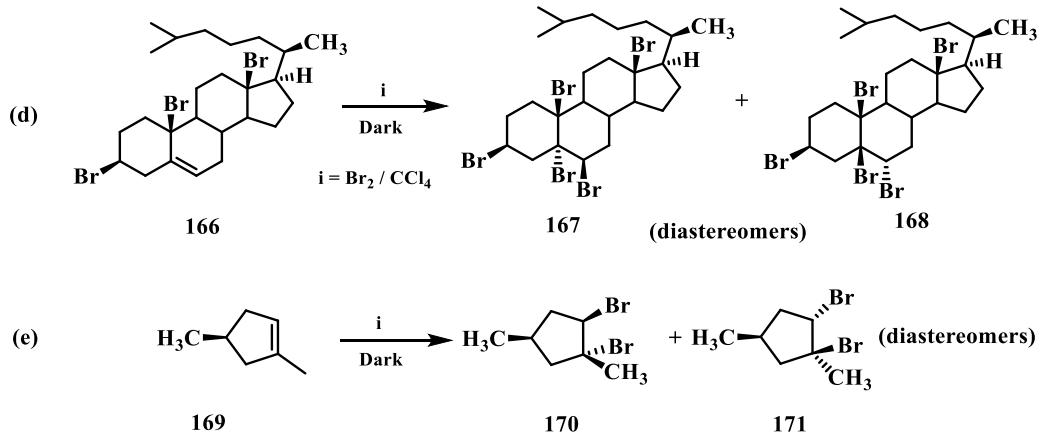


Figure 2.51. Bromination of compounds 166 and 169

2.10. Low Temperature Bromination Reactions of Unsaturated Bicyclic Compounds

Electrophilic addition of bromine to acyclic unsaturated system is an easy reaction but bromine addition to a bicyclic skeleton is slightly difficult. Generally, bicyclic compounds often habituated to produce rearrangement products in bromination reaction through Wagner-Meerwein rearrangement and products may be obtained from either classical carbocation or non-classical carbocation. In acyclic system, open ion pair is stabilized by the electron donating neighboring groups and configuration of the compound was remained unchange. In cyclic system, the carbocation is formed by elimination of leaving groups and they can't be rotate freely and produce only anti-products. The brominated products of the bicyclic system whether they are

rearrangement or arrangement mainly depend on the reaction conditions such as choice of solvent, temperature, pressure and reaction time. It was studied that, bromination of benzonorbornadiene with molecular bromine in presence of chloroform at low temperature produced only rearrangement product as shown in Figure 2.52. In this case, the rearrangement product was obtained from the non-classical carbocation 173 which was formed as reaction intermediate 174 is shown in Figure 2.52 (Wittig and Knauss, 1958; Cristol and Nachtigall, 1967; Wilt, 1967).

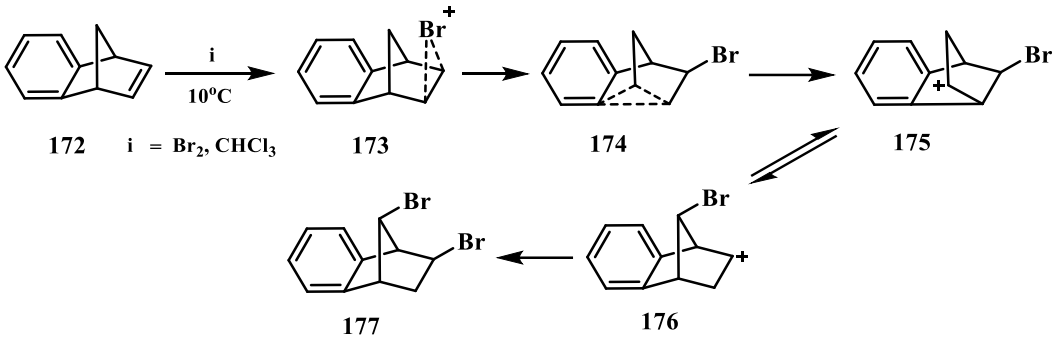


Figure 2.52. Bromination of compound 172 at low temperature

2.11. Radical Bromination

Radical atom is such kind of species which are formed by the homolysis or homolytic fission in which neutral intramolecular bond breaks and each fragments occupies one electron from their original bond. During the homolysis, neutral molecules even involved with many electrons form two free radicals and two electron of a bond equally distributed themselves and introduced two new radical species as shown in Figure 2.53.

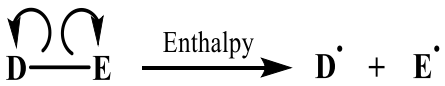


Figure 2.53. Homolysis process

It takes a certain amount of strength to break any bond and the amount of force that will break the bond depends on the bond stability. Similarly, breaking any bond and turning it into a radical species requires involvement of energy such as light, temperature and pressure. To give an example, the oxygen-oxygen bond of peroxide is relatively weak, so little energy is required to break it. On the other hand, the carbon-carbon bond is stronger than the oxygen-oxygen bond, so a little higher temperature is required to convert this bond into a radical species. Any bond can be broken to form a

radical species by heat, usually above at 200°C. Also, pressure plays an important role in generating radicals, for example, applying more pressure causes electrons to occupy an independent orbital, which is very useful for generating radical species.

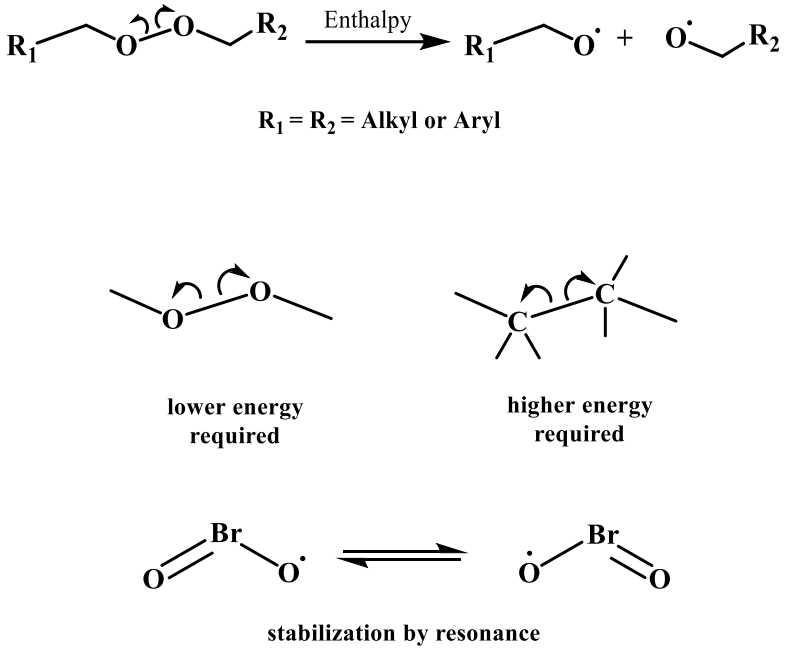


Figure 2.54. Formation of radical species

Nevertheless, the amount of energy required to break a bond to form a radical species depends on how much energy a compound can absorb. If a compound has a very high temperature absorption capability, a very small amount of energy is required to break the bond and turn it into a radical. There are also other important factors that play an important role in the generation of radical species such as orbital hybridization, electronegativity, polarizability, resonance and hyperconjugation.

In terms of electronegativity, molecules with higher electron density require more energy to convert a compound into a radical species. In the polarization case, if an atom has more electron density, it can easily stabilize the radical. In the case of orbital hybridization, it can be seen that hybridizations with more S character make radicals a little harder, while hybridizations with less S character require very little energy to convert molecule to radical species. Radical species which have the ability to delocalize electrons can easily stabilize radical simply by donating the negative charge from the resonance. Radical species can also be stabilized by hyperconjugation. It is generally found that compounds with more substituted carbons are more stable, requiring less energy to break the bond that stabilizes the radical. Radical reactions

generally occur in four forms: abstraction of an atom (f), reduction of an electron via breaking of a bond (g), fragmentation via bond cleavage (h) and addition via bond cleavage (i).

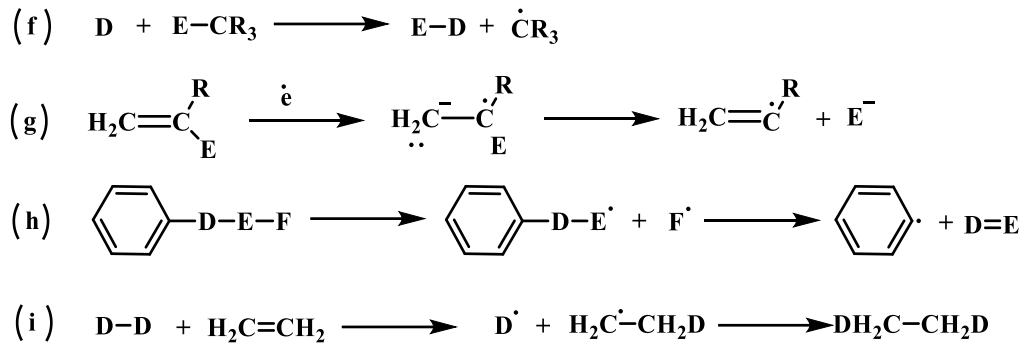


Figure 2.55. General mechanism for a radical reaction

The most satisfactory of the radical reactions with the huge applications is the radical bromination of the carbon-carbon double bond. This reaction is similar to the normal electrophilic bromine addition in which bromination occurs readily and the reaction proceed to completion, as well as producing *cis* and *trans* products as shown in the Figure 2.56.

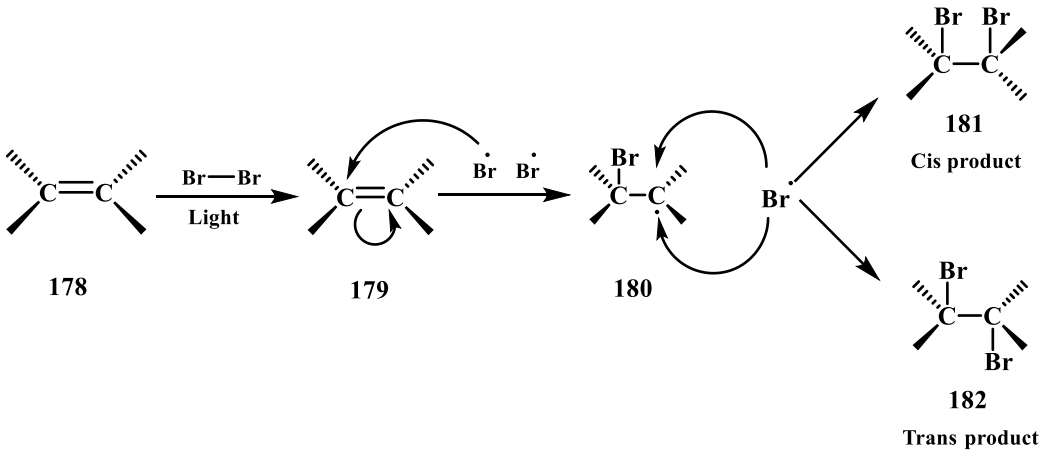


Figure 2.56. Radical bromination of alkene

2.12. High Temperature Bromination of Bicyclic System

Bromination of the bicyclic system is also influenced by the reaction conditions especially for the reaction temperature. In case of bicyclic system, bromination products can be different with the variation of reaction temperature and reaction medium. Bromination at low temperature produces only rearrangement products which are formed by the Wagner-Meerwein rearrangement and most of the

rearrangement products are obtained by the formation of non-classical carbocation as reaction intermediate. In contrast, high temperature bromination of the bicyclic systems produces non rearrangement products but in some cases rearrangement products can also be found in lower amount at high temperature.

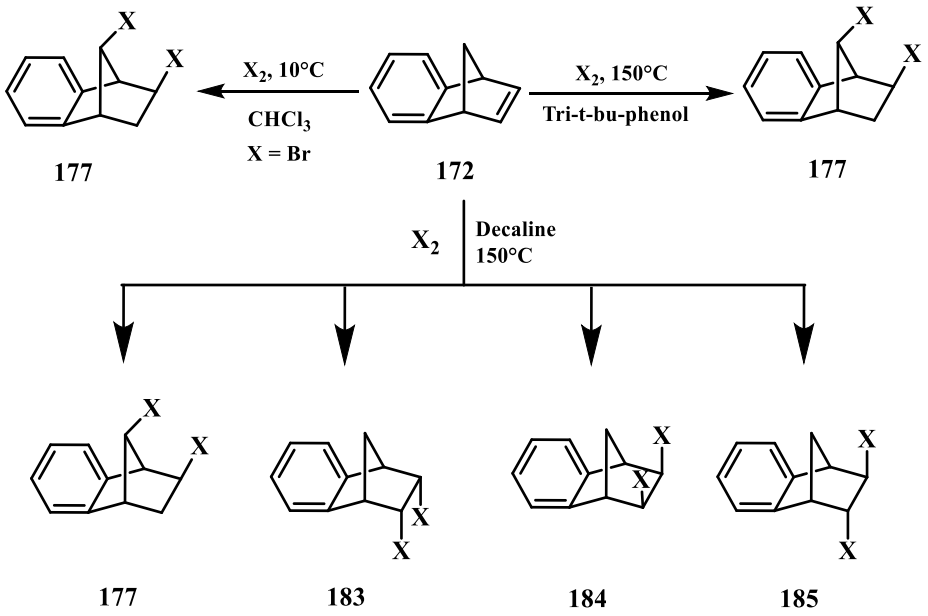


Figure 2.57. Bromination of compound 172 at different conditions

Bromination of benzonorbornadiene (172) was performed at 150°C in presence of dekalin, it was observed that in total four products (177, 183-185) were produced, among them 98% was arrangement products and only 2% was rearrangement product 177 as shown in Figure 2.57. In another investigation, high temperature bromination of dibromohomobenzonorbornadienes (186 or 187) formed only non-rearrangement products (188-191) as shown in Figure 2.58. (Daştan et al., 1994)

Surprisingly, it was observed that bicyclic compound 192 can also produce rearrangement products (194, 195 and 196) in higher proportion through Wagner-Meerwein rearrangement even at high temperature (Daştan et al. 1994) is shown in Figure 2.59. Moreover, bicyclic brominated products mainly depend on reaction intermediate whether they are rearrangement or non-rearrangement. So, bromination products of the bicyclic system not only depend on reaction temperature but also many factors such as pressure in the reactor, type of solvents, reaction time, type of reactant materials, proportion of reactants are used in a reaction and others.

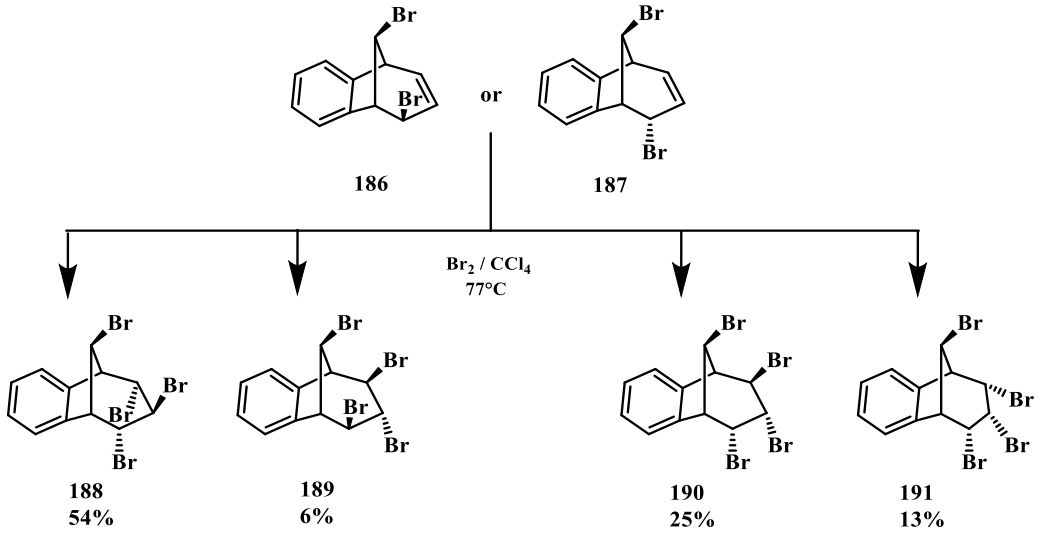


Figure 2.58. Bromination of compounds 186 or 187 at boiling temperature

However, bicyclic compounds are used to produce rearrangement product via formation of non-classical carbocation as reaction intermediate and arrangement products are produced by the formation of radical ion as intermediate of a bromination reaction of bicyclic compounds.

In terms of the mechanism analysis of the high temperature bromination of benzonorbornadiene at 150°C in presence of decaline (Figure 2.60), non-rearrangement compounds 183-185 were produced by the radical mechanism, beside, compounds 194-196 were obtained from the non-classical carbocations which were formed as reaction intermediate in the reaction pathway like the low temperature bromination mechanism which showed in previous section. Hence, electrophilic and radical addition reaction occur simultaneously shown in Figure 2.59.

The isomer 183 of the *endo* type was first observed in the reaction (Figure 2.57). It is generally observed that lower temperature bromination reactions produce reaction products via bromonium ions, but the appearance of isomer 183 in this reaction cannot be explained by bromonium ions. It was approved that *cis*-adduct could be obtained directly from the *syn*-collapse or *anti*-type collapse of the ions due to the rotation of the carbon-carbon bonds, but the compound was found to be too strong for the carbon-carbon bond and it wasn't possible to make them. It was assumed that the reaction may undergo a radical excursion in the reaction to the product 183.

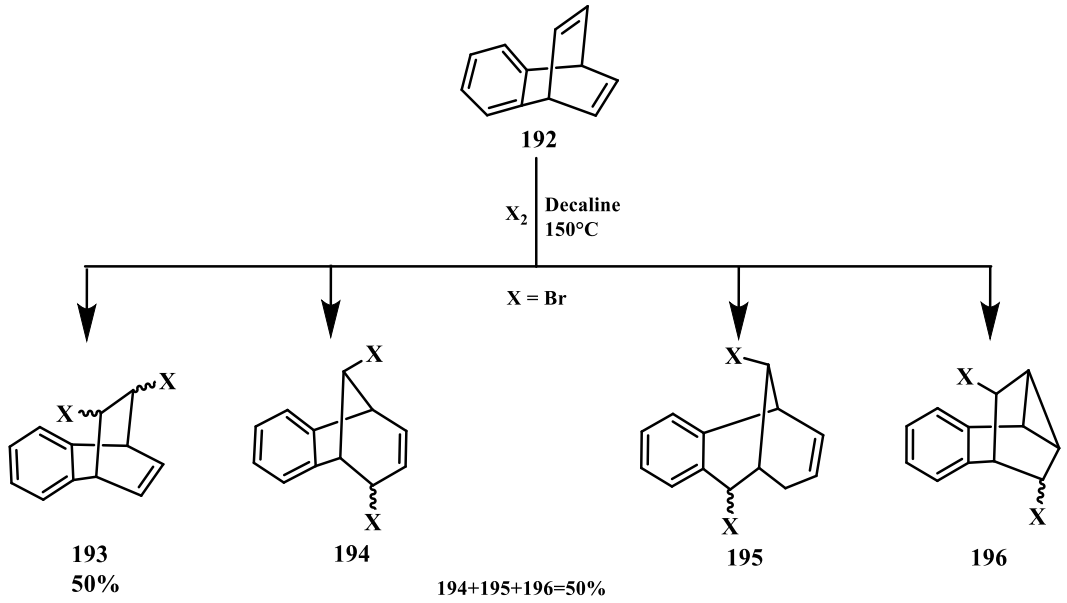


Figure 2.59. Bromination of compound 192 at high temperature

The same reaction was carried out again in the presence of an *anti*-radical reagent to prove that product 183 was produced by a radical mechanism. It was found that this type of isomer 183 was not formed, only the rearrangement product was formed, and that it was due to the formation of bromonium ions or non-classical carbocations in the reaction pathway.

It can be easily stated that cyclic carbocations can produce rearrangement products through the Wagner-Meerwein rearrangement. In the reaction, it was observed that they produced rearrangement products only in the presence of anti-radical agents, but not radical products. It can therefore be easily taken as evidence that products are produced via radical mechanisms at high temperature in cyclic systems.

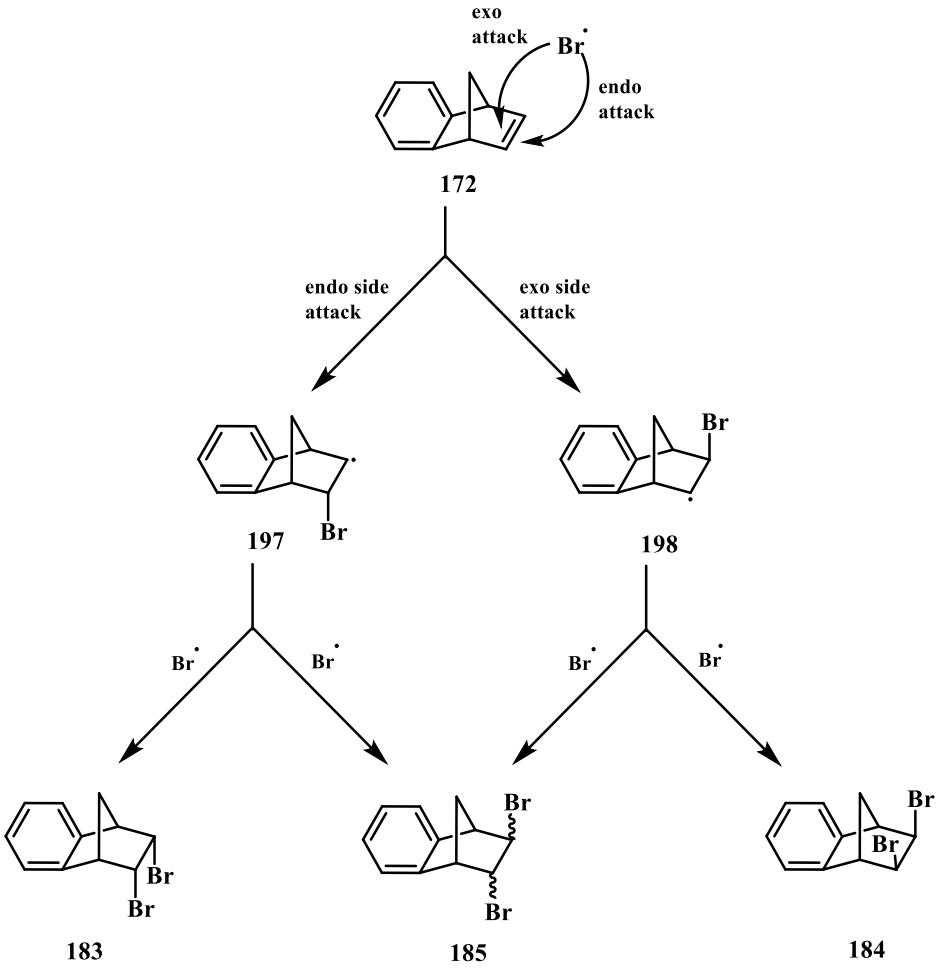


Figure 2.60. Radical mechanism in the bicyclic system

In other words, cationic species can be transformed into non-classical carbocations, thus they are capable of producing rearrangement products. Radical atoms, on the other hand, never undergo transformation, so, they always produce non-rearrangement products (Figure 2.61).

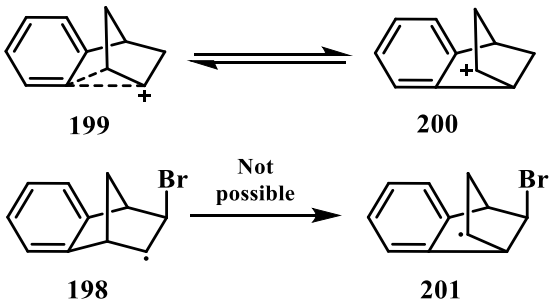


Figure 2.61. Reaction intermediate at low and high temperature

2.13. Steric Factors of the Bromination with Bicyclic System

Heteroatoms that are attached to the cyclic system can affect the bromination products, so steric factors have a great influence on the bromination products. It was hypothesized that the bromination products are either non-rearrangement or rearrangement when the reaction is carried out at high temperatures. In some cases, both rearrangement and arrangement products are obtained even at high temperature. On the other hand, most of the rearrangement products are produced by low temperature bromination with a very trace 1 or 2 percent non-rearrangement product.

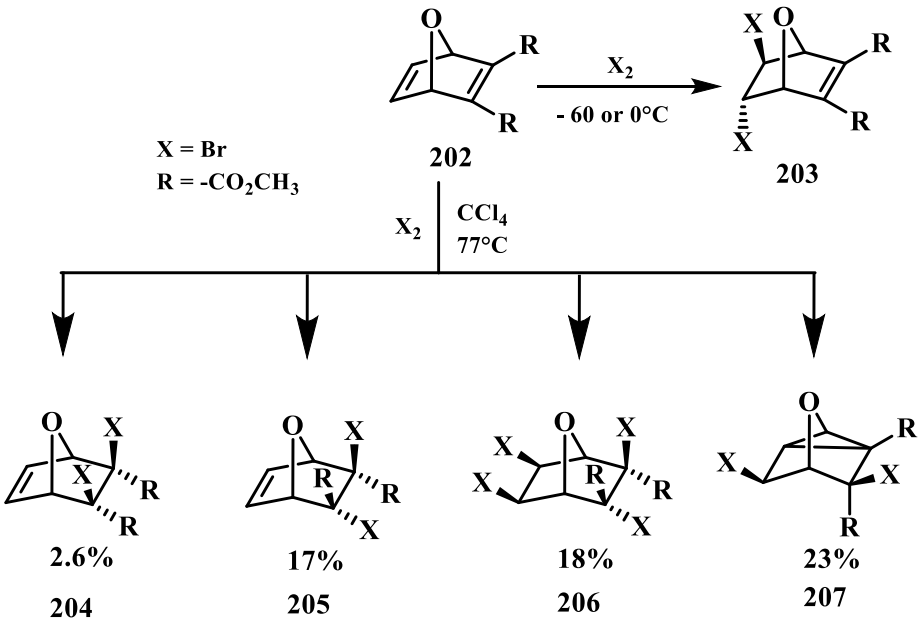


Figure 2.62. Hetaroatom effects on the bicyclic systems

However, compound 202 produced only non-rearrangement product 203 in low temperature bromination reaction but at higher temperature, compound 202 produced three non-rearrangement products 204-206 and rearrangement product 207 in 23%. (Figure 2.62)

In another investigation, it was found that compound 208 produced only non-rearrangement products 209 and 210 at high temperature but produced rearrangement products 211 and 212 in low temperature bromination reaction (Figure 2.63).

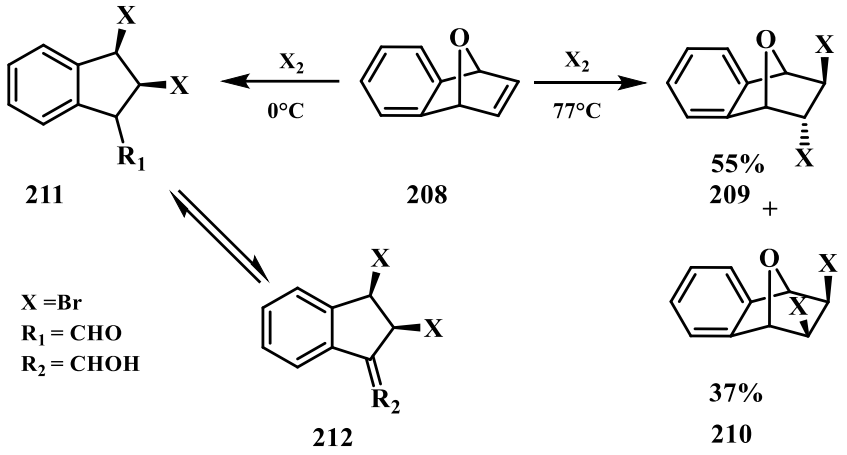


Figure 2.63. Effect of oxygen atom on bicyclic system

The introduction of bridging nitrogen atom instead of oxygen atom in compound 213 showed different results in high temperature bromination (Figure 2.64).

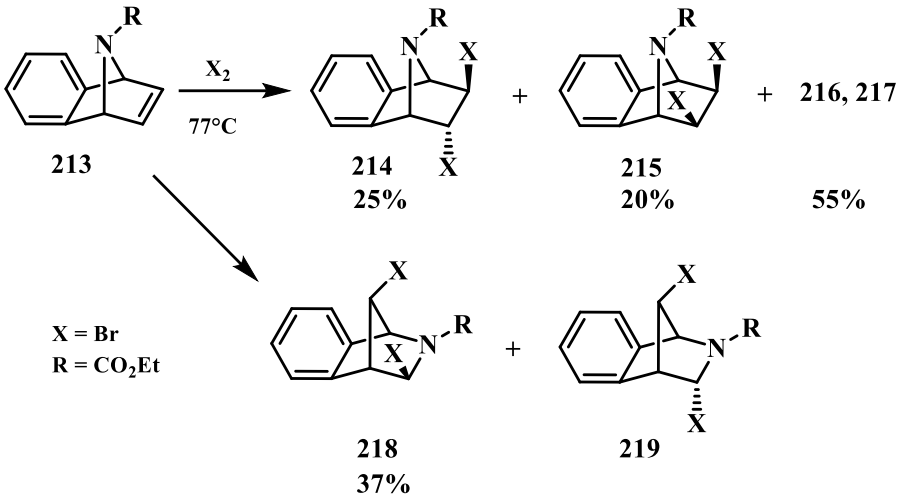


Figure 2.64. Effect of nitrogen atom on the bicyclic system.

Thus, both non-rearrangement products 214, 215 and rearrangement products 218, 219 are obtained from bridged nitrogen atom introduced compound 213 (Figure 2.64) whereas oxygen atom introduced compound 208 produces only non-rearrangement products (Figure 2.63). So, a comprehensive investigation of heteroatom effects on bicyclic brominated products concluded that brominated bicyclic compounds are most capable of inhibiting the Wagner-Meerwein rearrangement and form non-rearrangement products at high temperature via radical processes. In other words, benzobarrelene and benzonorbonadiene produced non-rearrangement products with small amount of rearrangement products at high temperature (Daştan et al., 1994) but their sister products 2,3,5-bromobenzobarrelene 220 and 2-benzonorbonadien 221

produced high yields of non-rearrangement products at higher temperatures, even, compound 220 produces non-rearrangement products at lower temperature (Altundaş et al., 2002; Balcı et al., 1992).

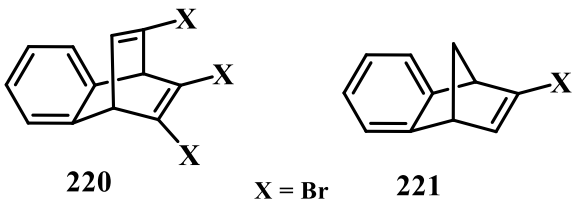


Figure 2.65. Sister compounds of benzobarrelene and benzonorbornadiene

2.14. Elimination Reactions in Bicyclic System

Elimination reactions in E2 mechanism observed as a rare previously in case of the leaving groups at bridgehead carbon because of the absence of *trans* geometry between the bridged leaving group and any beta hydrogen of other six carbon of the bicyclic structure. In addition to this, bicyclic skeleton hinder the bridgehead carbon to be planner, besides, carbocation formation at the bridgehead carbon produces more strain in the structure and makes the structure more unstable, resulting the bridgehead carbon can't occupy the double bond. However, elimination reaction in the bicyclic system can occur in E1 and E2 mechanism except that the formation of double bond between bridged carbon and the leaving groups connected with the bridged carbon can't be eliminated by the elimination reaction. Nevertheless, bulky base plays a suitable role for the elimination of leaving groups and forms carbon-carbon double bond in any of E1 or E2 mechanism as shown in Figure 2.66.

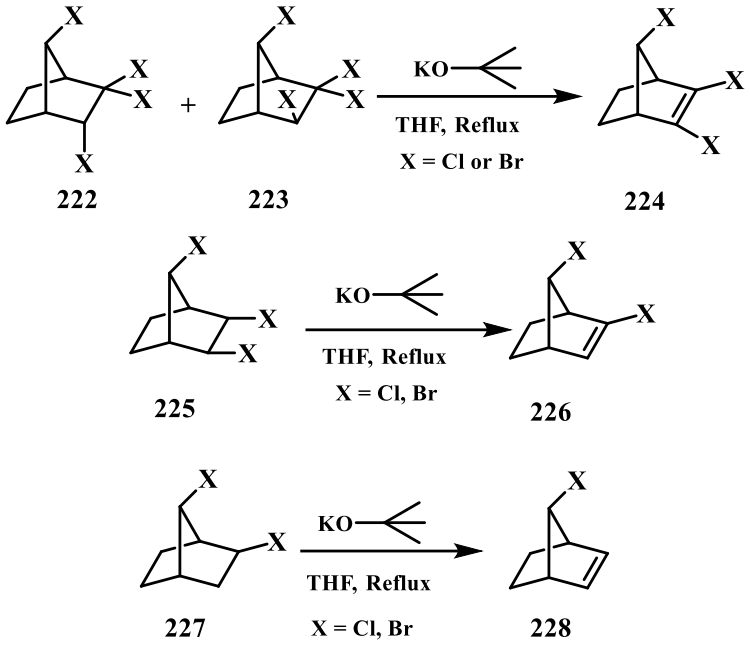


Figure 2.66. Elimination reactions of the bicyclic compounds

2.15. Suzuki Coupling Reaction

Suzuki coupling is a game changing reaction in organic chemistry for the formation of C-C linkage, which was discovered in 1979 by a Japanese Scientist called Akira Suzuki who got the noble prize in 2010 for the invention of carbon-carbon coupling reaction. Suzuki reaction is basically the Pd catalyzed reaction of organoboron compounds with organic halide in presence of a suitable base, hence, palladium is at zero oxidation state and attached with ligands**.**

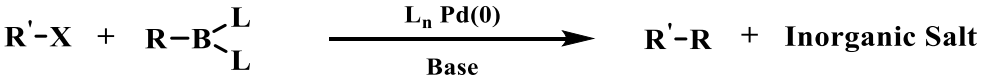


Figure 2.67. Suzuki coupling reaction

Suzuki coupling reaction is superior than modern C-C bond formation reaction due to some issues involved with them. In modern coupling reaction, Grignard and Gilman reagents are used which are more reactive, lower chemo selective and higher water sensitive, therefore, green chemistry synthesis is difficult with this reaction. Alternatively, Suzuki coupling reaction doesn't undergo these kind of difficulties. Coupling reactions involving aryl or vinyl halides and compounds such as boronic acids, boronic esters or borates in the presence of a base and palladium catalyst are known as Suzuki-Miyaura coupling reactions. Low toxicity, stability and easy

preparation of boronic acid compounds enable the widespread and effective use of Suzuki-Miyaura coupling reactions.

The first example of the Suzuki coupling is the reaction in which bi-aryls are synthesized by Akira Suzuki, 1980. These reactions are one of the methods used for the formation of bi-aryl bonds. Suzuki et al. (1980) synthesized stereoselectively arylated (*E*)-alkenes 231 as a result of the reaction of 1-alkenylboranes 229 and aryl halides 230 in the presence of palladium catalyst (Miyaura et al., 1980) (Figure 2.68).

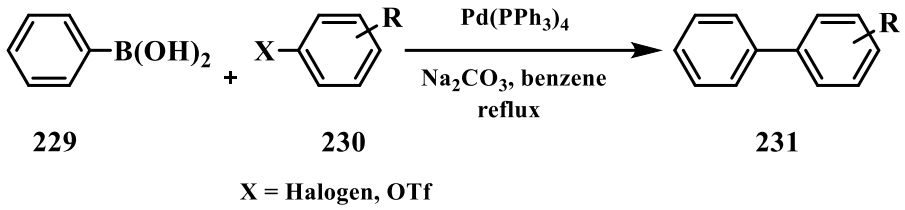


Figure 2.68. Synthesis of compound 231 via Suzuki coupling reaction

In recent scientific developments, the field of application of this method has expanded to a great extent. The term "Suzuki Coupling" also includes alkyl, alkenyl, aryl, allyl and alkynyl groups. The "Suzuki Coupling" method also has some advantages over other coupling reactions. The Suzuki reactions taking place in mild conditions, initial organoboron compounds are generally easier to form and it has applicability to various functional groups (Miyaura et al., 1981). Another important advantage is that the "Suzuki Coupling" reactions occur with high efficiency with sterically hindered aromatic rings and this way provides the synthesis of different compounds (Suzuki, 1999; 2002).

Boronic acid derivatives are the most widely used compounds because they are commercially available, stable in air and can withstand moisture, in addition, they are more environment friendly than other organometallic species. Also, it is important that the boronic acid-derived products are non-toxic and the reaction can be performed in various types of solvents, including water and alcohol, which facilitates the synthesis of compounds with many functional groups. In addition, base addition is required to activate boron derivatives (Özdemir et al., 2005).

Aryl boronic acids are the most commonly used nucleophilic groups in Suzuki reactions. Aryl boronic acids and aryl iodides, bromides and activated aryl chlorides showed high activity in Suzuki reactions with many Pd-NHC complexes (Dastagir et al., 2006). Aryl chlorides are attractive in industrial cross-coupling reactions due to

their low price and easy availability. However, aryl chlorides are known to be less reactive than aryl bromides and iodides (Bedford et al., 2002). Suzuki-Miyaura cross-coupling reactions involving aryl iodide and aryl bromide substituted with electron withdrawing groups occur even at room temperature with any palladium salt or complex such as palladium acetate (Zim et al., 2000). The general mechanism of Suzuki cross-coupling reactions consists of four main steps (Figure 2.69). These are the oxidative addition, metathesis, transmetalation and reductive elimination steps, respectively. In the oxidative addition step, Pd(0) species are oxidized with organic halides to form Pd(II) (step A). This oxidation is also the rate determining step of the reaction. Alkyl halides with β-hydrogen are very useful in the oxidative addition step because the oxidant addition step is the slowest step and σ-organopaladium(II) compounds compete with β-hydride elimination. In step B, the anion bound to the palladium is replaced by the anion of the base added to the medium (metathesis). In the C step, transmetallation takes place between Pd(II) and the alkylborate complex and organo-paladium compound is obtained. Finally, in the D step (reductive elimination), Pd(0) is obtained again by the reductive separation of the C-C σ bond and the chelating product is formed by reductive elimination (Mora et al., 2008).

In Suzuki cross-coupling reactions (Heck, Suzuki, etc.), proton dissociation does not occur unless base is used. The Suzuki-Miyaura coupling reaction occurs in basic medium via transmetalation and this process doesn't occur under normal conditions. The characterization of boron chemistry differs from that of other organometallic reagents. The base commonly used in the Suzuki-Miyaura cross-coupling reaction is Na_2CO_3 but this base is generally not effective for sterically hindered substrates. For example, $Ba(OH)_2$ or K_3PO_4 are used to obtain cross-linking products in good yields. Other bases used in Suzuki-Miyaura cross-coupling reaction are Cs_2CO_3, K_2CO_3, KOMe, TiOH, NaOH, KOH and NaOAc. In addition, using as much water as organic solvent in the Suzuki cross-coupling reaction increases the solubility of the base (Chen et al., 2007; Patil et al., 2009).

Suzuki cross-coupling reactions play an important role in the synthesis of natural, pharmaceutical and organic photo-electronic materials. Many commercial products, including pharmaceutical ingredients and optical materials contain aromatic C-C and C-N bonds, and the Suzuki cross-coupling reaction is therefore very important for synthesizing new compounds.

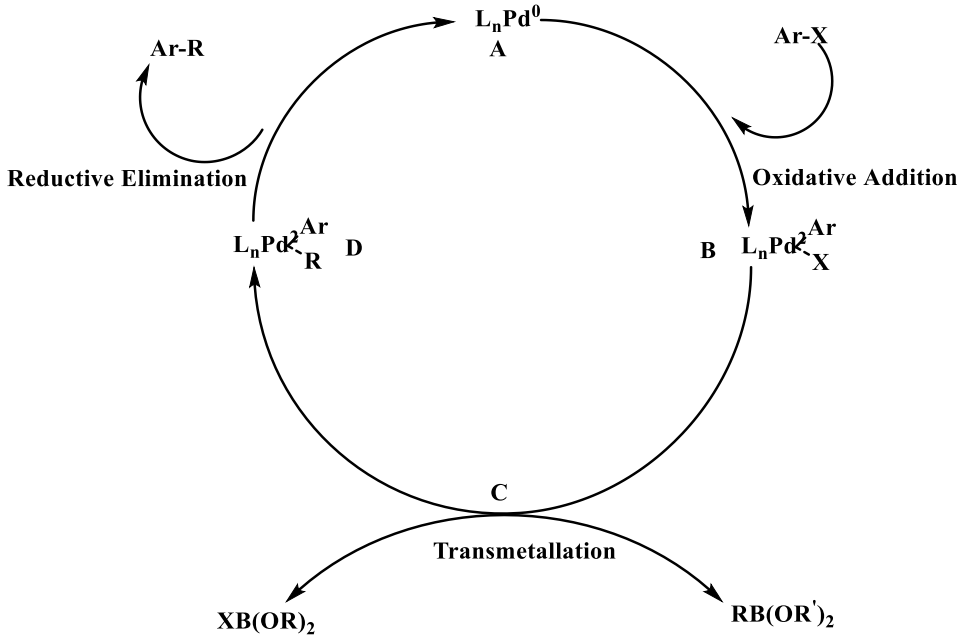


Figure 2.69. Mechanism of Suzuki coupling reaction

Halogenated compounds can be converted to new derivatives by many methods, especially displacement and transition metal-catalyzed reactions. Therefore, the synthesis of brominated derivatives of organic compounds is of great importance because organobromine compounds provide unique key and intermediate compound properties (Ekiz et al., 2016). Aryl boronic acids and organobromine compounds react under platinum or palladium catalyzed basic reaction conditions in the scope of Suzuki-Miyaura cross-coupling reaction and new organic compounds are synthesized in high yields as single products (Hayashi et al., 2011). Such coupling reactions are still up to date.

2.16. Nucleophilic Substitution Reaction at an Allylic Carbon

Nucleophilic substitution reactions mainly occur rapidly in case of allylic substrate. Double bond in β-position of a compound mostly prefer the S_N1 reaction and the rate of the reaction is increased when reactants contain the double bond in β-position, because, cations can be stabilized by the resonance. Generally, connection of any substituents at 1 and 3 position in allylic substrate occurred instantly and in a high rate through S_N1 reaction because there is a great facilities for the stabilization of carbocation by hyper conjugation or resonance. Likewise, S_N2 rates for benzylic and allylic systems can also be increased by the resonance in transition state.

In allylic rearrangement, allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained, one is non-rearrangement and another is rearrangement.

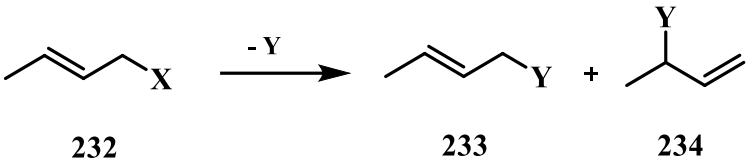


Figure 2.70. Nucleophilic substitution reaction at allylic position

Allylic type carbocation is a resonance hybrid and produced two product because C1 and C3 contain partial positive charges and both are connected with Y. The rearrangement of symmetrical allylic carbocation is indiscernible, as in case of R=H, unless isotropic labeling is used. IUPAC designation is ($1/D_n + 3/A_n$).

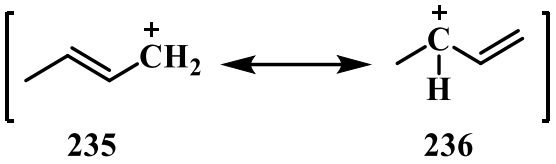


Figure 2.71. Allylic type carbocations

The above mechanism is known for S_N1 reaction, the nucleophiles attack to the 1 and 3 positions and the double bond is migrated by the elimination of leaving group (Figure 2.71). Nucleophilic substitution reactions can also be take place by S_N2 mechanism at an allylic position, in this case, nucleophile only attack the number 3 or γ-position of the allylic carbon rather than the α-carbon. This is called $1/3/A_nD_n$ in terms of IUPAC designation.

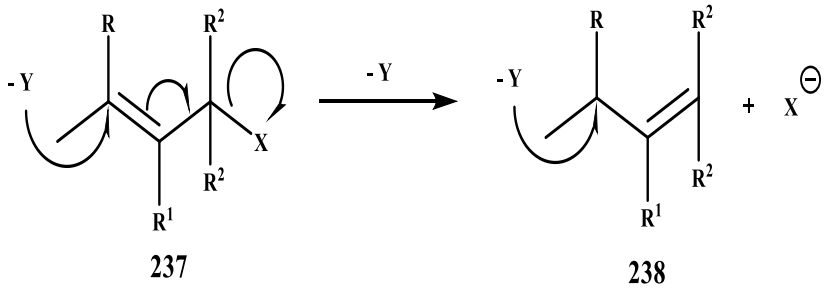


Figure 2.72. Mechanism for the nucleophilic substitution reaction at allylic position

2.17. Nucleophilic Substitution Reaction at a Vinylic Carbon

Nucleophilic substitution reaction is comparatively difficult at sp^2 hybridized carbon than allylic carbon because sp^2 hybridized carbon is more electronegative than sp^3 hybridized carbon and thus there is a strong bond between two carbons and bond breaking needs high energy due to strong attraction of electrons to the bond. According to the acidity concept, sp-H bond is higher acidic than sp^2-H which is more acidic than sp^3-H bond. Additionally, the bond length of a compound decreases with increasing s character. The bond length of allylic C-Cl bond is 1.78 A°, whereas it is 1.73 A° for vinyllic or aryllic C-Cl bond. In sp-H bond, there is a great hole on electrons in sp carbon that's why it's retain the electron easily by the elimination of H. In case of nucleophilic substitution reactions this situations are completely altered because the leaving groups take the lone pair of electrons with them. In sp^3-H or allylic bond is less stronger than sp^2-H or vinylic bond, consequencely, sp^3-H bond can be deprotonated more easily than sp^2-H bond.

S_N1 reactions at vinylic position are difficult and can be progressed in certain cases by elimination-addition or addition-elimination mechanism.

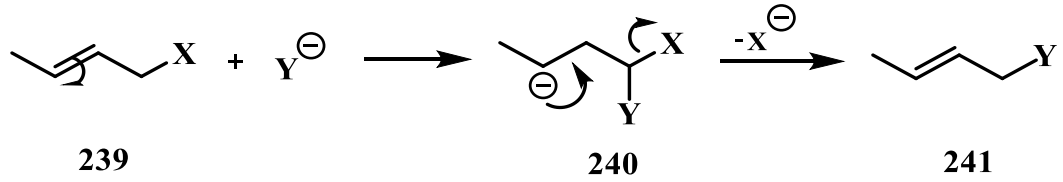


Figure 2.73. Nucleophilic substitution reaction at vinylic position

In terms of the nucleophilic substitution reactions of vinylic substrate, the carbon atom occupies the negative charge in the reaction intermediate. Carbon is less electronegative than nitrogen, oxygen and florine. The rate of nucleophilic reaction depends on the electronegativity of the leaving groups. The rate of reaction increases with the increase of the electronegativity of the leaving groups. Halogen group elements such as F, Cl, Br and I are leaving groups but the rate of the reaction is higher in case of F than Cl which is called the element effect. The content of C-F bond in any substrate facilitates the carbon to be more positive and hence more susceptible to nucleophilic attack because F is elevated electrons withdrawing groups. It is clearly illustrated that C-halogen bonds do not break in the *R* and *S*, where F is the poorest leaving group in both S_N2 and S_N1 reactions.

2.18. Phase Transfer Catalysis

In nucleophilic substitution reactions, the substrates are usually insoluble in polar solvent like water or others and the nucleophile is an anion which is insoluble in organic solvents and substrate but soluble in water, so it's a concerning issues in case of nucleophilic substitution reactions. In this case it can be understood that, the reaction does not reflect as expected due to the different concentrations of the reactants in the same solvent phase. This problem can be solved by two methods, one among of them is the use of a convenient solvent that can solubilize both the nucleophile and the substrate. Another one is the use of a convenient catalyst through which the nucleophile can be transferred to the organic phase. Catalysts that can be used for phase transfer are divided into two categories. One can include phosphonium salts and quaternary ammonia and the other may contain crown ethers and other kryptands.

To give an example, heating with aqueous sodium cyanide in only 1-chloro-octane, cyano octane is not found quantitatively as expected. It has been found that the addition of a very small amount of quaternary ammonium salt produces the product correctly. One of the reasons for this phenomenon is that the reaction doesn't occur without a catalyst and the cyanide ions cannot cross the inter phase of the two solvent but in a very least amounts. The main reason is that the potential energy required to dissolve sodium ions in water which is not present in the organic phase. Cyanide ions are unable to move from one phase to another due to its electrical neutrality without sodium ions. In other words, phosphonium ions and quaternary ammonia (R_4P^+ and QR_4N^+) are very sparingly soluble in water, but they dissolve well in organic solvents. To solve this problem, if a very small amount of any salt is added, it is possible to establish the expected three equilibrium (Figure 2.74).

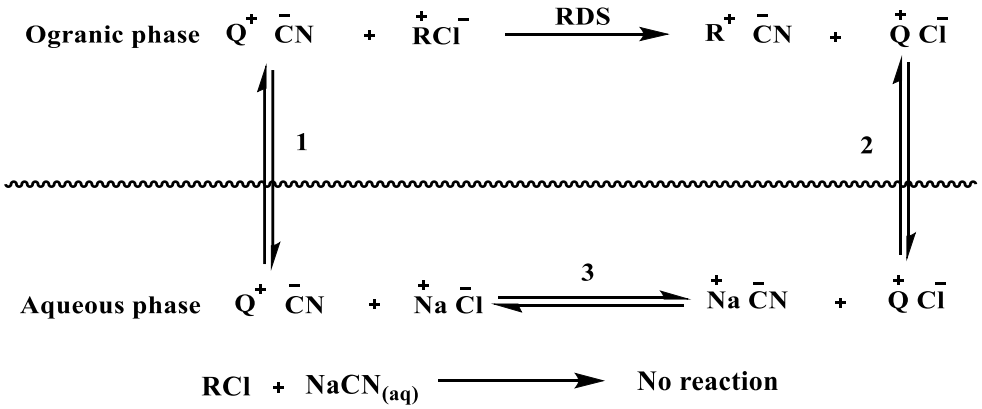


Figure 2.74. Phase transfer mechanism

Sodium ion dissolves in water, so it cannot go to organic phase, also, cyanide ions cannot go to other phase i.e. organic phase, without sodium ions. On the other hand, R_4P^+ and R_4N^+ are sparely soluble in water but they prefer organic solvent. Firstly, the Q^+ leads CN^- from the aqueous phase to the organic page (Equation 1), within the organic page, the Q^+ CN^- react with R^+ Cl^- to form R^+ CN^- and Q^+ Cl^-. Secondly, Q^+ Cl^- moves from the organic page to aqueous phase (Equation 2), and finally, Q^+ Cl^- is converted to Q^+ CN^- by ion exchange (Equation 3), thus, all cycles of the reaction are successfully completed.

Nucleophilic substitution reactions usually produce comparatively small proportion of reaction products than other reactions, so, the reaction products can be increased proportionally by adopting certain techniques. One of these techniques is the application of ultrasound to the reaction mixture. In this technique, a maximum of 20 KHz sound waves are introduced into the reaction mixture and it has been observed that application of sound waves causes bubble formation in the reaction. These bubbles create extremely powerful shock waves that increase the temperature and pressure in the reaction chamber, thereby increasing the magnitude of the reaction as well as the reaction products. In this process, a metal is used as a catalyst or reactant which is introduced into the liquid phase so that the molecules in the liquid phase can come into close contact with metal atoms. Ultrasound is then applied to inhibit side reactions and increase the yield of the main reactions.

2.19. Synthesis by Nucleophilic Substitution Reactions

Aryl halides, especially bromides and iodides, can be used in the synthesis of many new derivatives by replacing nucleophiles under simple conditions. Aryl halides are less reactive towards nucleophilic reagents such as CN^-, NH_3, OR^-, OH^-. Although, these reagents play an important role in the chemistry of aliphatic halides, the same efficiency is not available for nucleophilic aromatic substitution (Bunnett and Zahler, 1951). If an electron withdrawing group such as NO_2 is attached, the reactivity of aryl halides, especially at the ortho or para position, is greatly enhanced. However, long reaction times and effective conditions are required to achieve the desired efficiency under conventional heating.

In the preparation of nitrile derivatives, aryl halides are the starting compounds. Aryl halides can be converted to nitriles by a process known as the Rosenmund-von Braun

reaction. This reaction was carried out by heating CuCN and aryl halides in heterocyclic basic solvents such as quinoline and pyridine at 100-200°C. However, it has been reported that the best yields are obtained in polar aprotic solvents such as DMF and DMSO (Newman and Boden, 1961; Friedman and Shechter, 1961; Bacon and Hill, 1964). Anionic CuCN complexes have been reported to inhibit CuCN from nitriding vinyl halides and aryl halides despite their high solubility in DMF (House and Fisher, 1969). To solve this situation, Friedman and Schechter prepared an aqueous solution of ferric chloride and applied it to the extraction stage and the resulting complexes dissociated (Friedman and Schechter, 1961). Much research has been done to obtain alkyl or aryl ethers. In fact, Bacon and Rennison reported the production of alkyl aryl ethers in high yields (80-100%) between primary alcohol, alkoxides and aryl halides at 100-120 °C under copper iodide catalysis (Bacon and Rennison, 1969). In this type of reaction, the optimum ratio of aryl halide:alkoxide:CuI was determined to be 1:3:0.5 (Lindley, 1984). Again, one of the best aspects of such reactions is that in a single reaction step, all bromine atoms in the framework can be replaced by alkoxides such as methoxides. As it is known, the methoxide group enriches the aromatic structure to which it is attached with electrons and makes it a donor.

The researchers divided the reactions of aryl halides and alkoxides of the type C_6H_5-nXnHal (Hal = I, Br; X = OCH_3) in the presence of CuI into three categories. The first division increases the number of methoxy groups. In the absence of ortho substituents, the ether is formed in high yield. In the second, dehalogenation occurs by reducing the aryl halide to attach a methoxy group at the ortho position. In the last category, reduction occurs by dehalogenation, when the methoxy group is attached to the ortho position of the aryl halide (Lindley, 1984).

Methoxy and cyano naphthalene derivatives were synthesized by nucleophilic substitution reaction from aryl bromide such as 1,3-dibromonaphthalene (242) which was converted to dimethoxy derivative with 85% yield by nucleophilic substitution under CuI catalysis for 12 hours. The same reaction was repeated for 5 hours and 1,3-dimethoxynaphthalene (243) was isolated in 48%, 1-bromo-3-methoxynaphthalene (245) in 32%, 3-bromo-1-methoxynaphthalene (246) in 4% yield. The same group was converted to dicyano (244) derivative with 1,3-DBN 72% conversion at boiling temperature (150°C) in DMF (Figure 2.75), (Demirtaş et al., 2002).

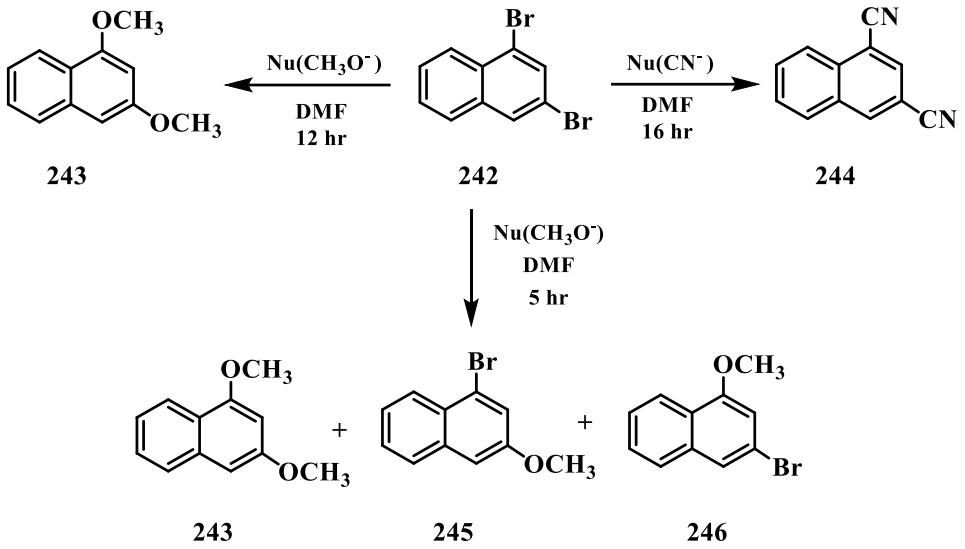


Figure 2.75. Nucleophilic substitution reaction of compound 242

Besides, electrophilic substitution reactions of aryl halides proceed via metal-halogen exchange. To achieve metal halogen exchange, *n*-BuLi, *tert*-BuLi, Bu_3MgLi and Grignard reagents are used. Gilman in 1939, made some observations for the lithium-halogen exchange reaction. They noted that aryl fluorides are not exchangeable and the rate of halogen exchange is I > Br > Cl (Gilman et al., 1939). Like lithium-hydrogen exchange, lithium-halogen exchange reactions are useful in industrially important areas of aromatic and heteroaromatic chemistry.

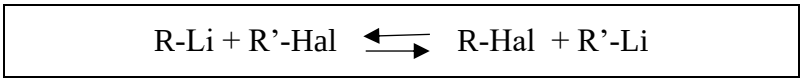


Figure 2.76. Lithium-halogen exchange reactions

Lithium-halogen exchange reactions can accompany alkylation because butyl bromide or iodide is always formed as a by-product. However, these reactions are carried out at low temperature to avoid unwanted side effects and for high reaction percentage. In fact, many reactions are performed at -90°C (Schlosser, 1994). After this reaction, it interacts with a suitable electrophile and substitutions occurs (Ekiz et al., 2016).

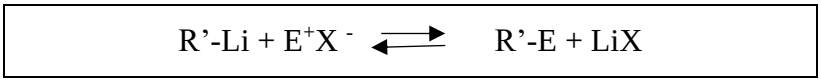
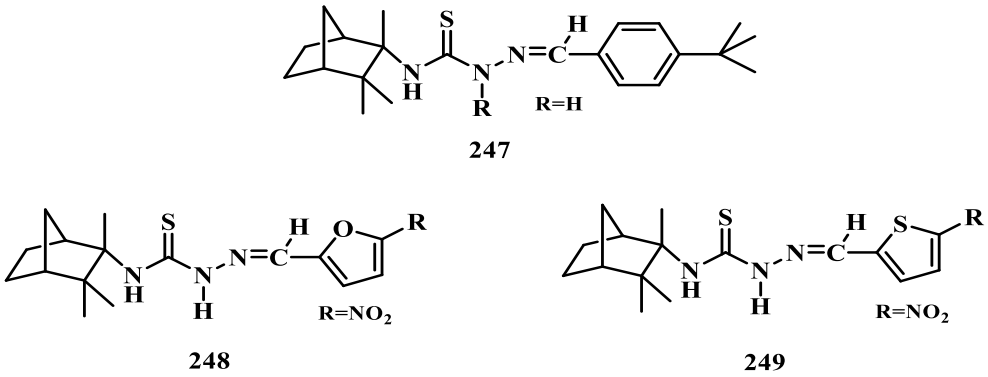


Figure 2.77. Electrophilic reaction in presence of lithium

2.20. Importance of Camphene Based Compounds

Camphene based derivatives as anti-tuberculosis agents: According to the World Health Organization (WHO), Tuberculosis (TB) causes serious illness and one of the

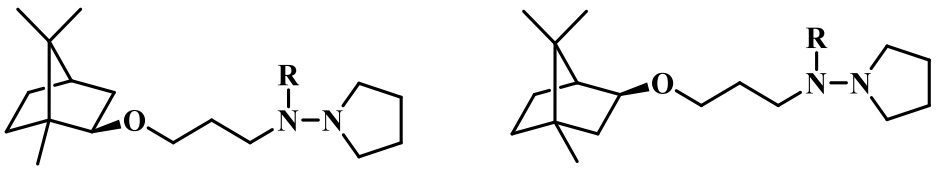
best from 10 pathogenic, which was responsible for height date in 2015 all over the world. Thiosemicarbazones (TSM) are biologically active compounds and effective against virus (Cases et al., 2000), tumor (Dos Santos et al., 2016), bacteria (Domagk et al., 1946) and so on. In 2019, some Brazilian scientists synthesized (-)-camphene based derivatives (247-249) with the combination TSM which showed potential anti-tuberculosis activity (Souza et al., 2019).



247 248 249

Figure 2.78. Anti-tuberculosis agents

Camphene based derivatives as anti-viral agents: Virus infection is a serious threat for human being and economy of any countries when it spread quickly and creates pandemic. Currently, worlds are facing the scourge of COVID-19 due to the SARS-CoV-2 virus. So, anti-viral drug development is urgent need for protecting the mankind. Recently in one investigation, camphene based compounds (250 and 251) containing pyrolidine cycle in their skeletal showed anti-viral activities against Ebola, Hantaan and Influenza Virus (Sokolova et al., 2021). These compounds were synthesized by the two step process, firstly, alkalization of camphene was carried out with 3-bromo-propan-1-ol and secondly, mono-brominated camphene was interacted with nitrogen containing heterocyclic compounds (Sokolova et al., 2021).



250 251

Figure 2.79. Antiviral camphene based compounds

Antibacterial camphene based compounds: Camphene based compounds also effective against pathogenic bacteria which are responsible for different types of health difficulties. Compounds 252 and 253 are promising antibacterial agent against two

gram positive pathogens *Enterococcus spp.* and *Staphylococcus aureus* with MIC 1.9 to 31.2 μg/mL, indicated that this two camphene based derivatives can be potential candidate for drug discovery (de Freitas et al., 2020).

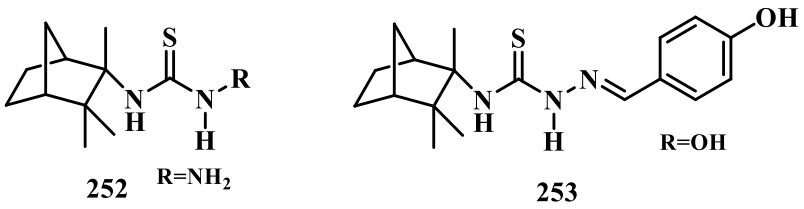


Figure 2.80. Antibacterial camphene based compounds

Antifungal camphene based derivative: Thiosemicarbazide (TSC) is a potential bioactive compounds and shows antifungal activities with minimum inhibition concentration (MIC) 548 μmolL^{-1} against *T. mentagrophytes*. Besides, camphene based compound (254) incorporated synthetically with thiosemicarbazide showed higher antifungal activities than TSC against *T. mentagrophytes* with MIC values 55 μmolL^{-1}. This camphene derivative is bioactive and can be used as a antifungal agent which efficiency much more higher than limonene (MIC-735), camphene (MIC- 735 plus), *N*-(4)-2,2-dimethyl-3-methyl-norbornane-thiosemicarbazide (MIC-548) and another TSC derivatives (Yamaguchi et al., 2009).

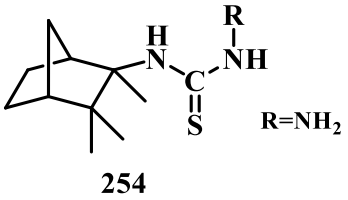


Figure 2.81. Antifungal camphene based compounds

Camphene based derivatives as antioxidant agents: Camphene based compounds are potential anti-oxidant agent as showed considerable radical scavenging activities. The anti-oxidant properties of some camphene based compounds with thiosemicarbazones were tested by peroxyl and DPPH radical scavenging methods. All tested six compounds showed potential antiradical activities in both DPPH and peroxyl methods (Figure 2.82). Compound 254 showed best radical scavenging activity with lowest EC_{50} = 0.208 μmole DPPH and height rate constant K_b (4218 M^{-1} S^{-1}) which is much higher than Trolox. In addition to this, compound 256 also showed lowest EC_{50} = 1.27 μmole in peroxyl anti-radical method (Yang et al., 2020)

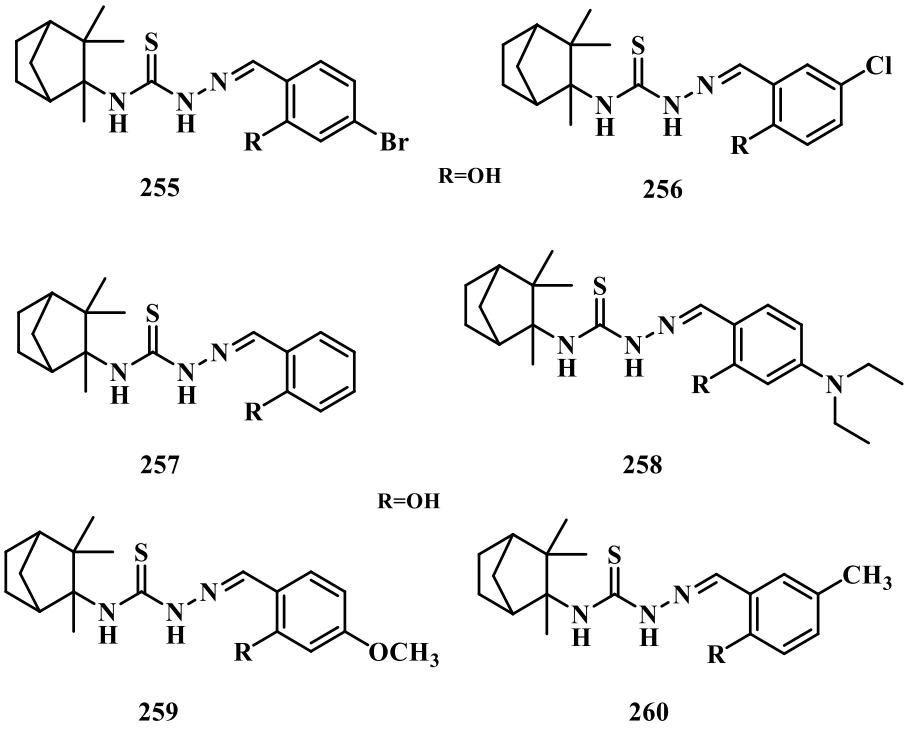


Figure 2.82. Antioxidant camphene based compounds

2.21. Importance of Brominated Derivatives

First, bromine was produced by the oxidation of bromide in presence of chlorine over an absorption and purification process. Nowadays, plenty of brominated derivatives are producing due to their growing interest in many areas.

Bromine compounds as pesticides: Brominated derivative EDB (1,2-dibromoethane) was used first time for controlling the pest of stored grains, furthermore, it was tested many years in soil for controlling the related pest. It was observed that, EDB was working well for soil pest control. Production cost of EDB is cheap and production procedure is also easy, so, this product was widely used for a long for controlling the pest of the land and facilitates farmers to get good quality crops. After that, another bromine compound called methyl bromide is used as most well-known soil pest controlling product.

Disinfectants: Halogens are soluble in aqueous medium and they are used in a broad ranges as biocide in both element and compound forms. Bromine and some of its derivatives are able to inhibit microbial growth and widely using as disinfectants. Dissolved form of halogens such as bromine, chlorine and iodine are active biocides using as disinfectants. Bromine and chlorine biocides have been using for many

applications. Bromine was being used as disinfectants in the nine-tenth century, but had very little application. Although, chlorine heads is the most important water disinfectant especially for swimming pools and drinking water, currently, the using rate of bromine disinfectant is increasing day by day. Recently, organic bromine compound was chlorinated and formed 1-bromo-3-chloro-5,5-dimethyl hydantoin which was called as Halobrom. The disinfecting property of chlorine introduced bromine derivative is stronger than only brominated derivative and showed more potential disinfecting properties.

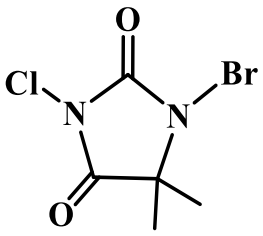


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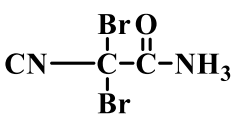
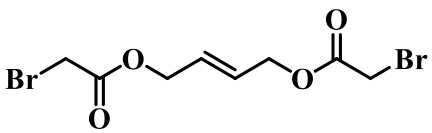
Figure 2.83. Molecular structure of halobrom

Generally, halobrom is water soluble solid substances and supplied as tablet for slow releasing. It is more popular and effective disinfectant for water treatment in swimming pools. Halobrom is also used in closed-circuit cooling system especially for industrial purposes. The bromine and chlorine are key components in this compound, when added to the water, chemical reaction occur, forms hypochlorous acid, hypobromous acid as well as $ClO^-_{(aq)}$ and $BrO^-_{(aq)}$ ions. Hypobromous acid (HBA) is more effective than hypochlorous acid (HCA) as it decomposes only at high pH. HBA generates $Br^-_{(aq)}$ ion during disinfection process. The $Br^-_{(aq)}$ ions instantly forms HOBr which is potential disinfecting agent. In the reaction, bromine is recycled frequently to active form and introduced more potential disinfecting properties of the compound (Cincinelli et al., 2012). There are many complex formed of disinfectants are available but they are not use in a large scale, as for example, biobrom and BBAB.



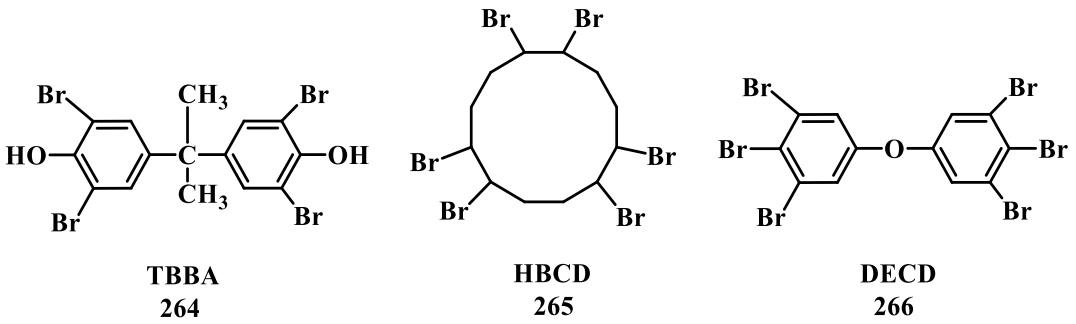
Biobrom
262



BBAB
263

Figure 2.84. Disinfecting agents

Flame retardants: Brominated derivatives such as TBBA, HBCD and DECD are most common and well known flame retardants. Magnesium hydroxide is sometimes incorporated with flame retardants for increasing the efficiency of flame retardants as it reduces the smoke development during firing.



TBBA
264

HBCD
265

DECD
266

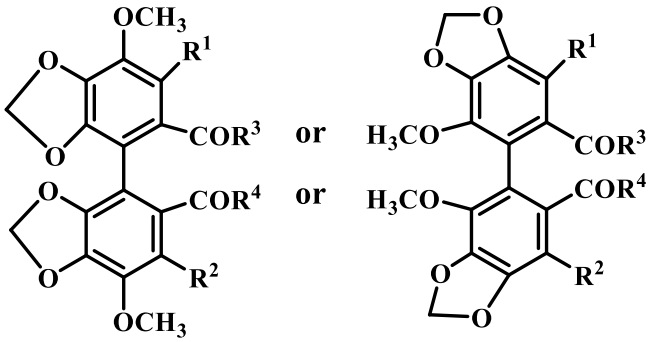
Figure 2.85. Flame retardant agents

Brominated derivatives are more effective flame retardants than chlorinated derivatives since bromines and its radicals are heavier than chlorines and its radicals respectively. Brominated derivatives are more capable to absorb combustion energy than chlorinated derivatives due to their higher molar mass comparatively. Though, chlorine is less expensive than bromine, brominated derivatives are more preferable because small amount of brominated compounds is sufficient enough to achieve the flame retardant property as like the high amount of chlorinated compounds (Alaee et al., 2003).

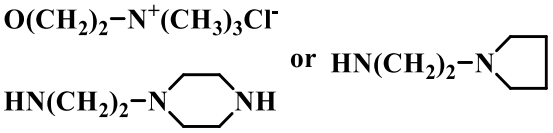
Textile Industry: Brominated compounds are important for textile industry, for example, sodium bromate is frequently used for the treatment of wool as bleaching agent. In addition to this, it is also used for fading jeans facilitates some dyes to make insoluble in water by the oxidation process at the end of the treatment (Kesner, 1999).

Food Industry: Brominated compounds (potassium bromate) are used as preservatives and anti-oxidants in beer and bleaching of baking flour in food industry. It forms S-S linkages between proteins which produces traps for getting gasses from the rising of droug and prevent them from escaping (Ahmad et al., 2012). Besides, brominated derivatives are effective against HIV-1 infection. It was observed that 3-bromo-4,4-dimethoxy-5,6-bimethylenedioxy-2,2-dimethoxy-carbonyl biphenyl and 3,3'-dibromo-4,4'-dimethoxy-5,6,5'6'-bimethylenedioxy-2,2'-dimethoxy-carbonylbiphenyl are immune boosters and form antibodies gp-41 and gp-120 for HIV-1 (Kesner, 1999). Skeletal structure of invented immune booster brominated compounds are given in

Figure 2.86, wherein R is hydrogen or bromine, with the provision that at least one of R is bromine.



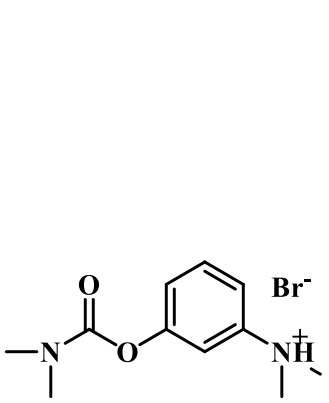
267



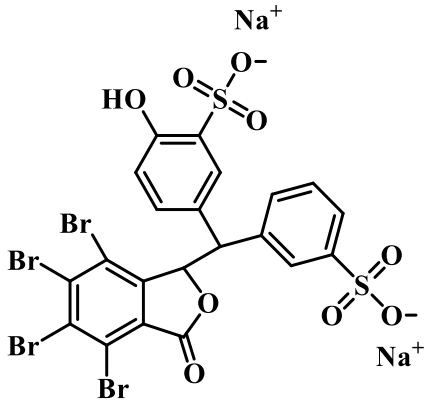
268

Figure 2.86. Molecular structure of immune booster agent

Pharmaceutical applications of brominated compounds: Brominated compounds are biologically active potential medicinal components and bromine atom in the molecule is responsible for its medicinal properties. Neostigmine bromide 269, which is a salt of neostigmine, is a drug that inhibits cholinesterase enzyme. Cholinesterase inhibitors are effective against muscle relaxants such as tubocurarine and gallamine (Petcher et al., 1971). Bromosulfophthalein 270 is a bromine containing compound which is used as an indicator of live of any animal (Figure 2.87).



Neostigmine bromide
269

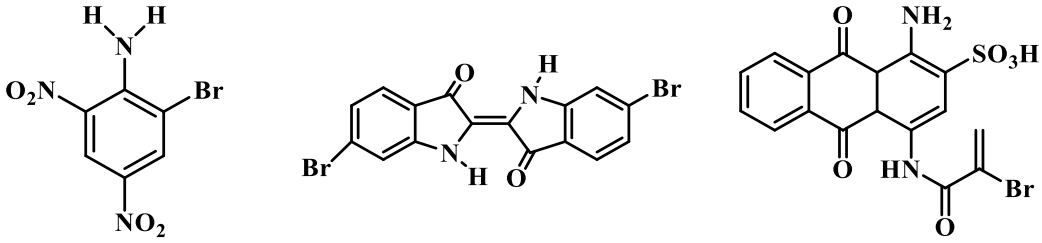


Bromosulfophthalein
270

Figure 2.87. Molecular structure of enzyme inhibitors

Organic synthesis: Synthetic brominated compounds are key materials for synthesis of many new derivatives, as for example, it is difficult for the connecting of boronic acid to the camphene but when camphene is brominated (Titova et al., 1995), then it's possible to synthesis new compounds through electrophilic and nucleophilic substitution reactions. Reactive efficiency of halogen with alkene and saturated hydrocarbon is quite different. Fluorine is at the top of halogen group in periodic table, resulted more reactive with organic compounds and sometimes responsible for rapid explosive reaction. Iodine is less reactive with organic compounds and it forms unstable compounds, so, it is not preferable for organic reaction. Chlorine is more reactive than bromine but brominated compounds are more active than chlorinated compounds that's why brominated derivatives are widely used as initial reactant products for the synthesis of new organic compounds.

Paint Industry (α-bromoacrylamide reactive dyes): Brominated compounds aren't found more from natural sources. Most of the brominated derivatives are synthesized products. The purple molecule of dibromide occurs in the sea mollusk, which has been used in the paint industry since the time of the Phoenicians and Romans. In the paint industry, brominated derivatives are used as color compounds or as intermediate. 2-Bromo-4,6-dinitroaniline 271 is an important chemical for the production of azo dyes, beside, α-bromoacrylamide 273 reactive dyes are used for dyeing wool (Zhang et al., 2015).



2-bromo-4,6-dinitro aniline
271

natural color compound
272

Bromoacrylamide dye
273

Figure 2.88. Brominated color dyes

3. MATERIAL AND METHODS

The studies carried out within the scope of the thesis project at Organic Chemistry Research Laboratory-1, Faculty of Science, Sakarya University, Turkey.

3.1. Materials

3.1.1. Reagents

(+)-Camphene (Aldrich), molecular bromine (Merck), potassium *tert*-butoxide (Aldrich), pyridine, aniline, phenyl boronic acid (Aldrich), ethylphenyl boronic acid (Aldrich), 4-methoxyphenyl boronic acid (Aldrich), thiomethylphenyl boronic acid (Aldrich), 4-trifluoromethoxyphenyl boronic acid (Aldrich), copper iodide (Merck), sodium metal (Merck), potassium metal (Merck), copper cyanide (Aldrich), ferric chloride (Aldrich), potassium carbonate (Merck), palladium catalyst (Aldrich), NaOH (Merck), all these reagents are commercially available.

3.1.2. Solvent and driers

Dichloromethane, chloroform, hexane, carbontetrachloride, ethylacetate, benzene, toluene, diethylether, dimethylformamide, methanol, tetrahydrofuran, dimethylsulfoxide, sodium sulfate (anhydrous), calcium oxide were used after purification according to the literature procedure (Read, 1997). $CDCl_3$ was used for ^{1}H NMR and ^{13}C NMR analysis which was obtained as pure from Merck.

Tetrahydrofuran: THF (Merck, 99%) (250 mL) might be contained impurities like water and peroxide that's why it was treated with NaOH (5 g) overnight to remove most of the water. After filtering, a small amount of benzophenone (2 g) as an indicator with a small piece of potassium or sodium metals (5 g) were added and boiled under reflux until a blue color appeared, indicated that no water remained. It was distilled in nitrogen atmosphere and stored on molecular sieve (4 A°) at (66°C).

Methanol: Methanol (100 mL) (Merck 99.5%) was boiled over calcium oxide (15 g) at reflux temperature for 2-3 h and transferred to a tapped balloon containing molecular sieves under a nitrogen atmosphere.

Dimethylformamide: DMF (250 mL) was distilled over molecular sieves (30 g) under nitrogen atmosphere in presence of sodium sulfate (Na_2SO_4) and calcium chloride ($CaCl_2$) are used as drier (150°C).

Toluene: Toluene (Merck, 99%) was shaken twice (100 mL/1 L) with H_2SO_4, then washed once with water and 5% $NaHCO_3$. It was again washed with water and dried over $CaSO_4$ and purified by fractional distillation at 110.6°C.

Molecular Sieve: Commercially purchased in Merck quality.

Sodium sulphate: Technical grade of Na_2SO_4 was used for drying process. It was dried overnight in an oven at 80°C.

Column fillers: Classical column chromatography was used mostly in separation and purification processes. Mark branded silica gel 60-230 mesh was used as filler and silica gel 60 (0.063-0.200 mm) was used for the separation of isomers. In column chromatography, hexane-dichloromethane, hexane-ethylacetate, hexane-chloroform and chloroform-methanol mixtures were used as mobile phases.

3.1.3. Instruments

Table 3.1. Instruments used under the scope of the thesis

Instruments Used	Source	Brand Name
Rotary evaporator	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Heidolph Laborota 4003-Degital
N_2 gas supplier	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Unspecified
Heating mantle	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Unspecified
Magnetic stirrer with hot plate	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Heidolp-MR Hei-Standard
Precision balance	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Precisa
Cooling water circulation device	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Senur 24 L
Immersion cooler (-90°C)	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Julabo FT902

Table 3.1.(Continued) Instruments used under the scope of the thesis

Oven	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Thermo, Heraeus
Immersion cooler (-40°C)	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Thermo EK45
Thermostat	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Kerman
Laboratory fume hood	Organic Chemistry Lab-1 Dept. of Chemistry, SAU, Turkey	Unspecified
^{1}H NMR (300 MHz)	Dept. of Chemistry, SAU, Turkey	Varian Infinity Plus 300 MHz
^{13}C NMR (300 MHz)	Dept. of Chemistry, SAU, Turkey	Varian Infinity Plus 75 MHz
FTIR	Dept. of Chemistry, SAU, Turkey	1. PerkinElmer 2. Shimadzu Prestige-21 (200 VCE)
Melting point apparatus	Dept. of Chemistry, SAU, Turkey	MPM-H1
Polarimeter	Dept. of Chemistry, SAU, Turkey	WZZ-2S Digital Polarimeter SenLab

3.2. Methods

3.2.1. Purification process

Column chromatography, thin layer chromatography and crystallization techniques are applied for the separation and purification of the obtained crude products.

3.2.2. Column chromatography

Synthesized compounds were separated from reaction product mixtures and purified by Silica gel column chromatographic technique. Silica gel 60 (0.063-0.200 mm, 70-230 mesh ASTM, Merck) was used as stationary phase and hexane, dichloromethane, chloroform and ethylacetate were used as mobile phase. The glass column (long or short) was filled with a certain amount of silica gel slurred with hexane depending on the amount of material had to be separated. In terms of the separation process, the crude products were loaded into the column drop by drop in a concentrated manner. The polarity of the moving phase was adjusted according to the polarity of the compounds in the mixture loaded in the column. The separation process starts with hexane, which is a nonpolar solvent. Then, the extraction process is continued with solvents whose polarity was adjusted and fractions were collected. The substances in

the collected fractions were examined by thin layer chromatography and similar eluents were combined and the solvent was removed with a rotary evaporator.

3.2.3. Crystallization

Crystallization is an important technique for the separation of pure synthesized compounds. At the end of the reaction, the isolated products were dissolved in a solvent mixture of dichloromethane/hexane or chloroform/hexane or any other suitable solvent combination and the mixture was concentrated by application of heat and kept at room temperature to cool and carefully observed at the intervals of one hour or a whole day. When crystallization begins, it is kept in the refrigerator. After crystallization is completed, the crystal is separated and left to recrystallize. Finally, the separated crystals were dried with a rotary evaporator.

3.2.4. Bromination reaction at high temperature

A bromine solution was prepared with the required amount of molecular bromine in CCl_4 in a pressure-balanced dropping funnel and added drop wise to the reaction solution at the boiling temperature of CCl_4 and the reaction was carried out under a laboratory fume hood. Excess bromine and solvent were removed by rotary evaporation, next, the reaction products were passed through column silica gel to remove unwanted substances and finally purified by column chromatographic technique.

Figure 3.1. Bromination reactors

3.2.5. Bromination reaction at low temperature

Bromination at low temperature (0 to -40°C) is mainly carried out by a special process consisting of an immersion cooler, ice-water bath, ice-salt bath or acetone-liquid nitrogen mixture. Generally, this reaction is called ionic bromination, it requires suitable polar solvents like chloroform, methylene chloride, ethyl acetate, etc. This reaction is investigated by TLC to determine the reaction time. When TLC indicates that products are formed then the reaction is terminated, furthermore, purification of the synthesized compounds is followed.

3.2.6. Suzuki coupling reaction

In the Suzuki coupling reaction, toluene, ethanol or methanol and water are added to two necked balon in the ratio of 2, 2 and 1 respectively, then the required amount of halogenated compound and base (K_2CO_3) solution are also added to the solvent mixture in the reaction flask under nitrogen atmosphere. Further, the reaction solution is heated at reflux temperature under nitrogen gas. The reaction is stopped after 20 to 24 hours and the required amount of water is added to the cooled solution of the reaction products and the organic phase is extracted with a suitable solvent and dried over Na_2SO_4. Finally, the reaction products are separated and purified by chromatographic techniques using appropriate mobile phases.

4. EXPERIMENTS

4.1. Bromination of (+)-Camphene at High Temperature

0.5 g (3.7 mmole, 1 eq) of (+)-camphene (2) was dissolved in 15 mL of CCl_4 in the photobromination reactor's chamber and the (+)-camphene (2) solution was heated with magnetic stirring with 650 W light. While the (+)-camphene (2) solution was refluxed, 0.64 g (4.1 mmole, 1.1 eq.) of molecular bromine was dissolved in another 15 mL of CCl_4 and taken up in a pressure balanced dropping funnel and slowly dropped into the reaction solution over 15 min. The reaction was terminated as soon as the bromine solution was exhausted. The reaction solution was continuously stirred with a magnetic stirrer from the beginning to the end of the reaction until it reached at room temperature. Furthermore, the solvent was evaporated using a rotary evaporator and ^{1}H and ^{13}C NMR spectra of the crude product showed that the awaited non-rearrangement dibrominated products were produced (Figure 4.1). Dark orange mixture (1.02 g) of *endo* and *exo* dibrominated products 274 and 275 were obtained respectively in 95% yield.

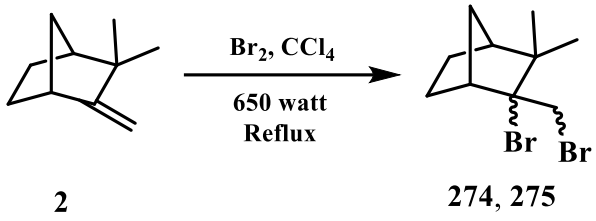


Figure 4.1. High temperature bromination of (+)-camphene (2)

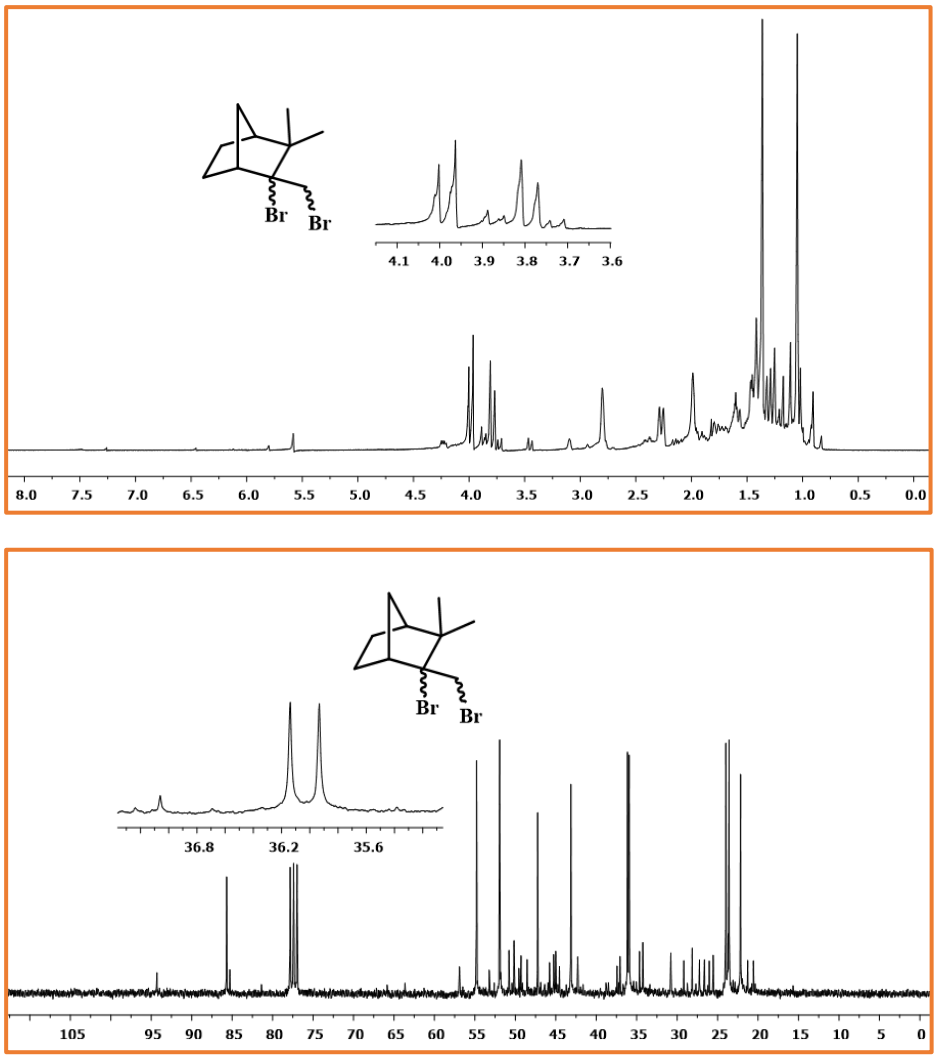


Figure 4.2. ^{1}H NMR and ^{13}C NMR of 274 and 275

4.2. Rearrangement of Dibrominated (+)-Camphene (274 and 275) to Bromobornane (276)

High temperature brominated product mixture of 274 and 275 was subjected to purification via silica gel column chromatographic technique and only bromobornane 276 was obtained as colorless crystal of 0.99 g in 98%.

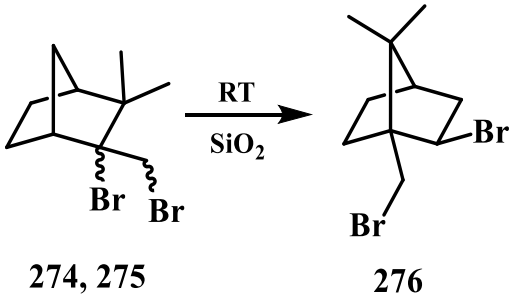


Figure 4.3. Transformation of dibromocamphene to dibromobornane

4.2.1. Synthesis of 2-bromo-1-bromomethyl-7,7-dimethylbicyclo[2.2.1]heptane (276)

Colourless crystal (0.99 g, 98%), melting point 74-76°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.25 ($J_{3,5exo}$ = 8.6 Hz, $J_{2,3exo}$ = 4.7 Hz, 1H, H_3), 3.80–3.68 (d, one proton of CH_2, J_{CH2} = 9.9 Hz, 1H, H_{CH2Br}), 3.47 (d, one proton of CH_2, J_{CH2} = 9.9 Hz, 1H, H_{CH2Br}), 2.42 (t, $J_{3,4}$ = $J_{4,5ex}$= 4.4 Hz, 1H, H_4), 2.15 (d, J = 8.6 Hz, 1H, H_2), 2.01–1.87 (m, 2H, H_{6ex} and H_{6en}), 1.84–1.71 (m, 2H, H_{6ex} and H_{6en}), 1.54 (m, 2H, H_{6ex} and H_{6en}), 1.18 (s, 3H, CH_3), 0.92 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 56.9, 53.0, 49.6, 48.3, 42.3, 37.3, 34.4, 26.4, 21.1, 20.5.

FTIR (cm^{-1}) ν = 2967 (-CH), 1421 (CH of CH_2), 1227 (CH of CH_3), 646 (Br).

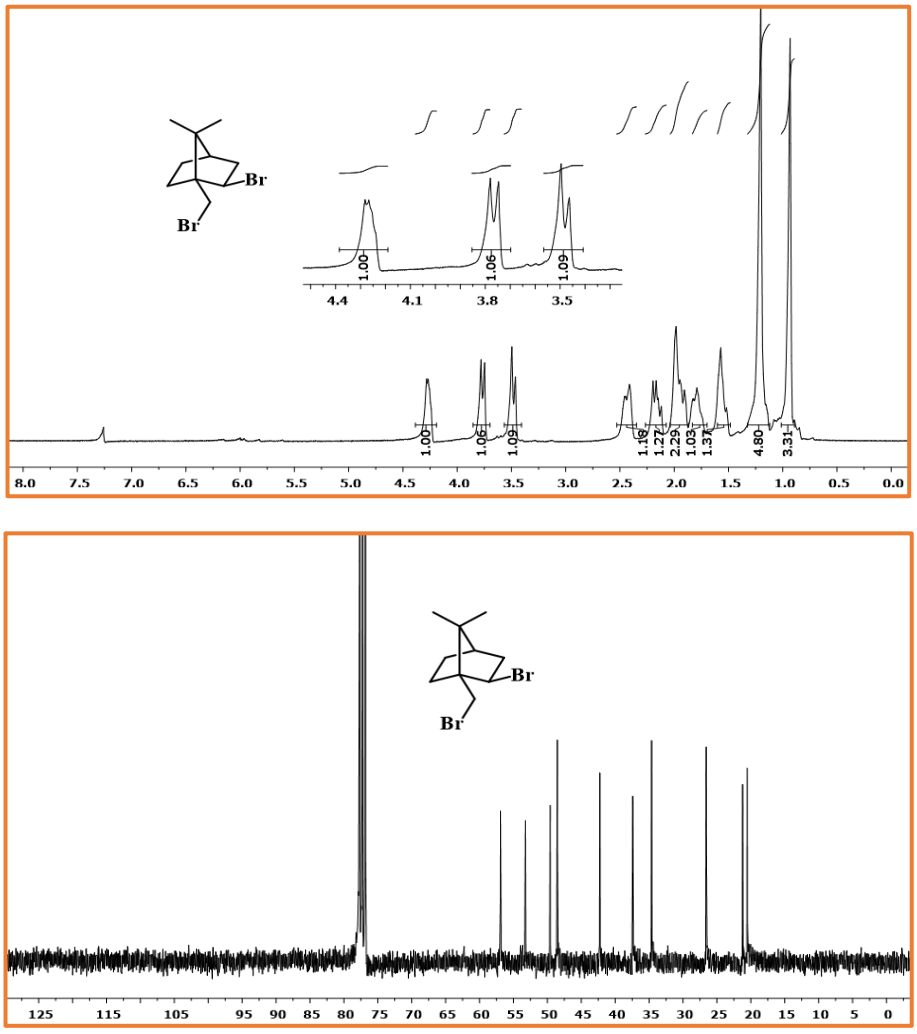


Figure 4.4. ^{1}H NMR and ^{13}C NMR of compound 276

4.3. Elimination Reaction of Bromobornane in Presence of Pyridine

Treatment of compound 276 (2 g, 6.8 mmole) with excess pyridine (20 mL) at reflux temperature for 2 h achieved 86% and 14% yields of *E* isomer 277 (major) and *Z* isomer 278 (minor), respectively as shown in Figure 4.5 and both of them are colorless liquids. The eluted products were separated and purified by column chromatography.

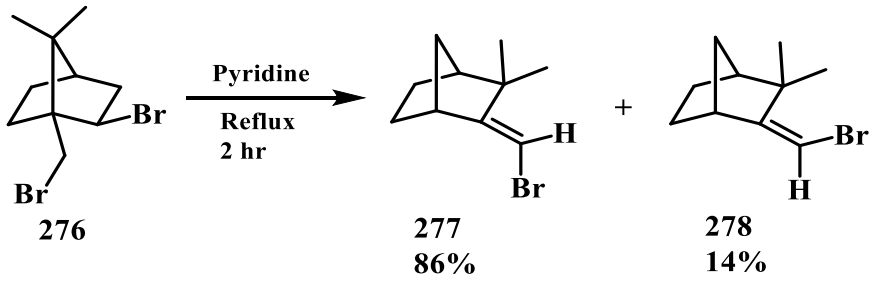


Figure 4.5. Reconstruction of bromobornane 276 to bromocamphene 277 and 278

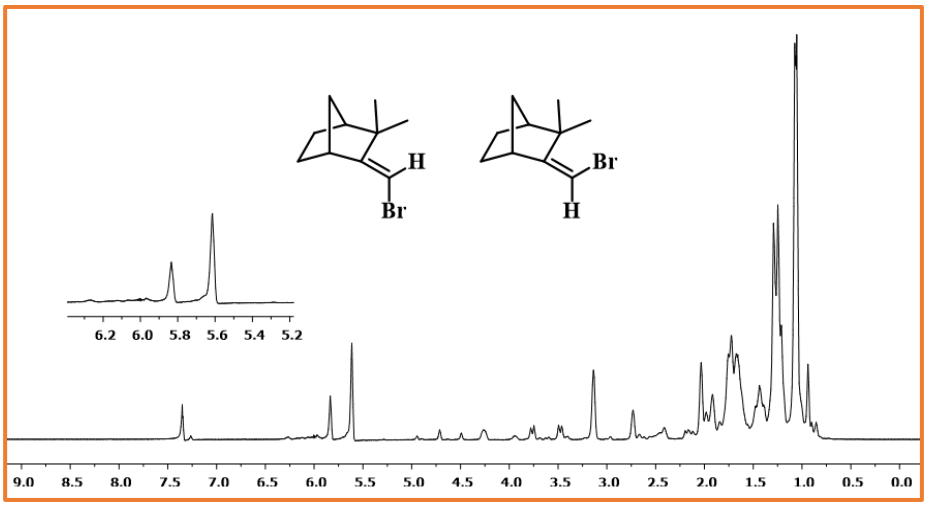


Figure 4.6. ^{1}H NMR of the racemic mıxture of compound 277 and 278

4.3.1. Synthesis of *E*-3-bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane (277)

Colourless viscous liquide (0.76 g, 36%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 5.63 (s, 1H), 3.13 (dqd, $J_{1,6exo}$ = 4.3, $J_{1,7syn}$ = 2.8, $J_{1,7anti}$ = 1.8 Hz, 1H), 2.09-2.01 (d, $J_{4,5exo}$ = 3.7 Hz, 1H), 1.92-1.79 (m, 2H), 1.59 (s, 1H), 1.57-1.51 (m, 1H), 1.51-1.37 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 161.0, 94.0, 49.3, 45.3, 44.4, 37.2, 29.5, 27.5, 26.0, 23.7.

FTIR (cm^{-1}) ν = 2916 (-CH), 1730 (C=C), 1471 (CH of CH_2), 1390 (CH of CH_3), 718 (Br).

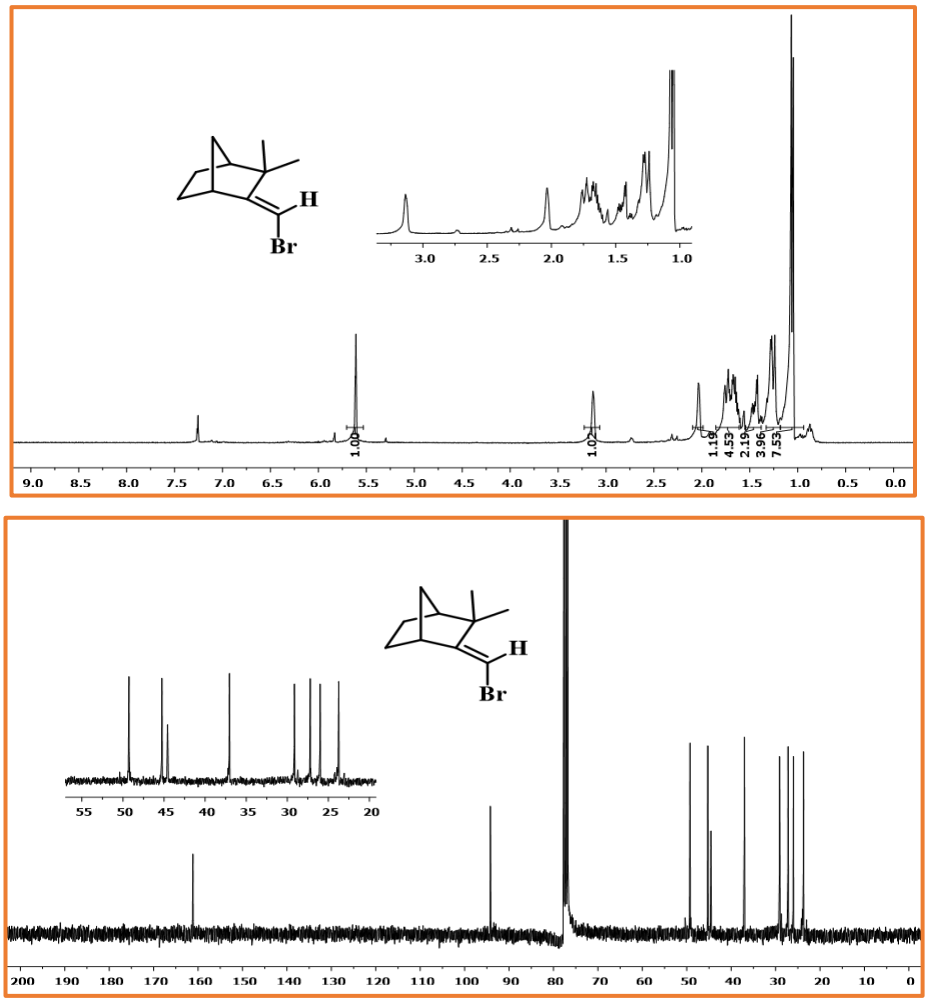


Figure 4.7. ^{1}H NMR and ^{13}C NMR of compound 277

4.3.2. Synthesis of *Z*-3-bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane (278)

Colourless viscous liquide (0.12 g, 6%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 5.83 (s, 1H), 2.73 (dqd, $J_{1,6exo}$ = 4.3, $J_{1,7syn}$ = 2.8, $J_{1,7anti}$ = 1.8 Hz, 1H), 1.92 (d, $J_{4,5exo}$ = 3.7 Hz, 1H), 1.84-1.69 (m, 2H), 1.47-1.42 (m, 1H), 1.42-1.29 (m, 1H), 1.29-1.22 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 158.8, 94.1, 50.7, 49.2, 45.4, 36.0, 29.2, 27.5, 25.8, 24.1, 23.5.

FTIR (cm^{-1}) ν = 2916 (-CH), 1730 (C=C), 1471 (CH of CH_2), 1390 (CH of CH_3), 718 (Br).

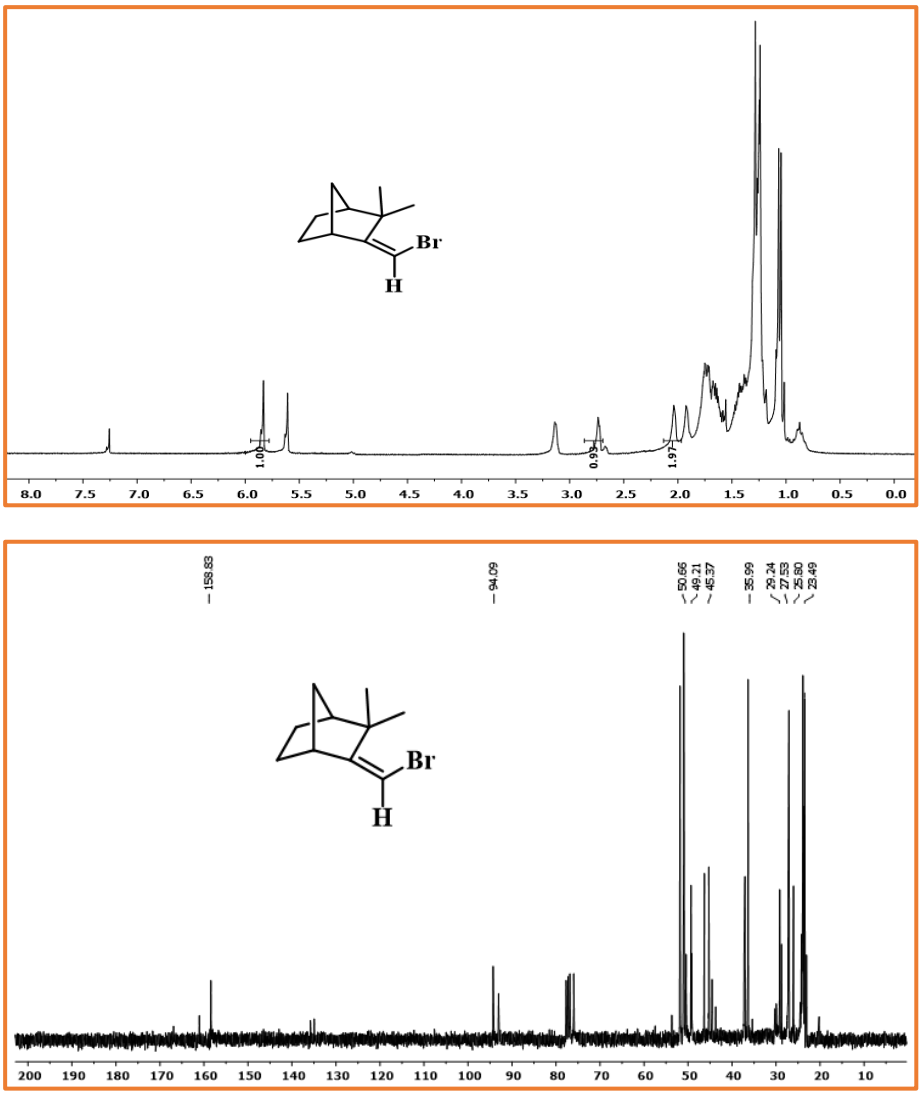


Figure 4.8. ^{1}H NMR and ^{13}C NMR of compound 278

4.4. Elimination Reaction of Norbornane (276) in Presence of Potassium *tert*-butoxide

0.5 g (3.6 mmole, 1 eq.) of dibromobornane (276) was dissolved in freshly prepared THF (15 mL) in a reaction flask and 2.05 g (18.3 mmol, 5 eq) of potassium *tert*-butoxide was added dropwise to the hot solution of dibromobornane (276) which was heated at reflux temperature by an electric heater. The reaction solution was continuously stirred with a magnetic stirrer from the beginning to the end of the reaction until it reached at room temperature. Further, the reaction solution was washed with distilled water (3x50 mL) and extracted with chloroform (3x50 mL). The solvent was evaporated by rotary evaporator and ^{1}H NMR spectra of the crude product was taken with a 300 MHz NMR instrument. It was observed that the expected colourless

crystals of monobromobornene (279) were formed in 83% and purified with hexane and dichloromethane (95:5) by column chromatographic technique.

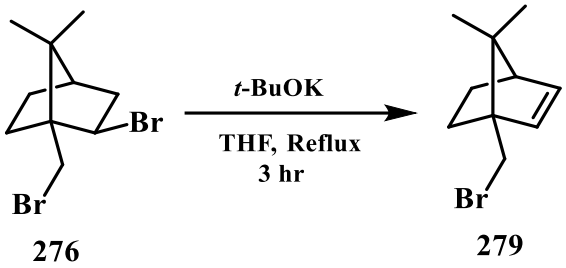


Figure 4.9. Elimination reaction of 276 in presence of potassium *tert*-butoxide

4.4.1. Synthesis of 1-bromomethyl-7,7-dimethylbicyclo[2.2.1]hept-2-ene (279)

Colourless liquide (0.52 g, 26%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 6.09-5.89 (m, 2H, $1H_2$, $1H_3$), 3.61 (d, one proton of CH_2, J_{CH2} = 9.9 Hz, 1H, H_{CH2Br}), 3.50-3.39 (d, one proton of CH_2, J_{CH2} = 9.9 Hz, 1H, H_{CH2Br}), 2.41 (t, $J_{3,4}$ = $J_{4,5exo}$ = 4.4 Hz, 1H, H_4), 1.87 (ddd, $J_{5,3exo}$ = 15.5, $J_{5,4exo}$ = 8.0, $J_{5,4}$ = 3.7 Hz, 1H), 1.71 (ddd, $J_{5,3exo}$ = 15.5, $J_{5,4exo}$ = 8.0, $J_{5,4}$ = 3.7 Hz, 1H), 1.35-1.23 (m, 1H), 1.03 (tdd, $J_{6,2exo}$ = 11.7, $J_{6,2exo}$ = 8.1, $J_{6,2endo}$ = 5.2 Hz, 1H), 0.91-0.87 (s, 3H, CH_3), 0.84-0.75 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 136.0, 135.0, 57.8, 57.3, 53.7, 35.2, 30.2, 24.5, 20.2, 19.9.

FTIR (cm^{-1}) v = 2954 (-CH), 1714 (C=C), 1458 (CH of CH_2), 1368 (CH of CH_3), 715 (Br).

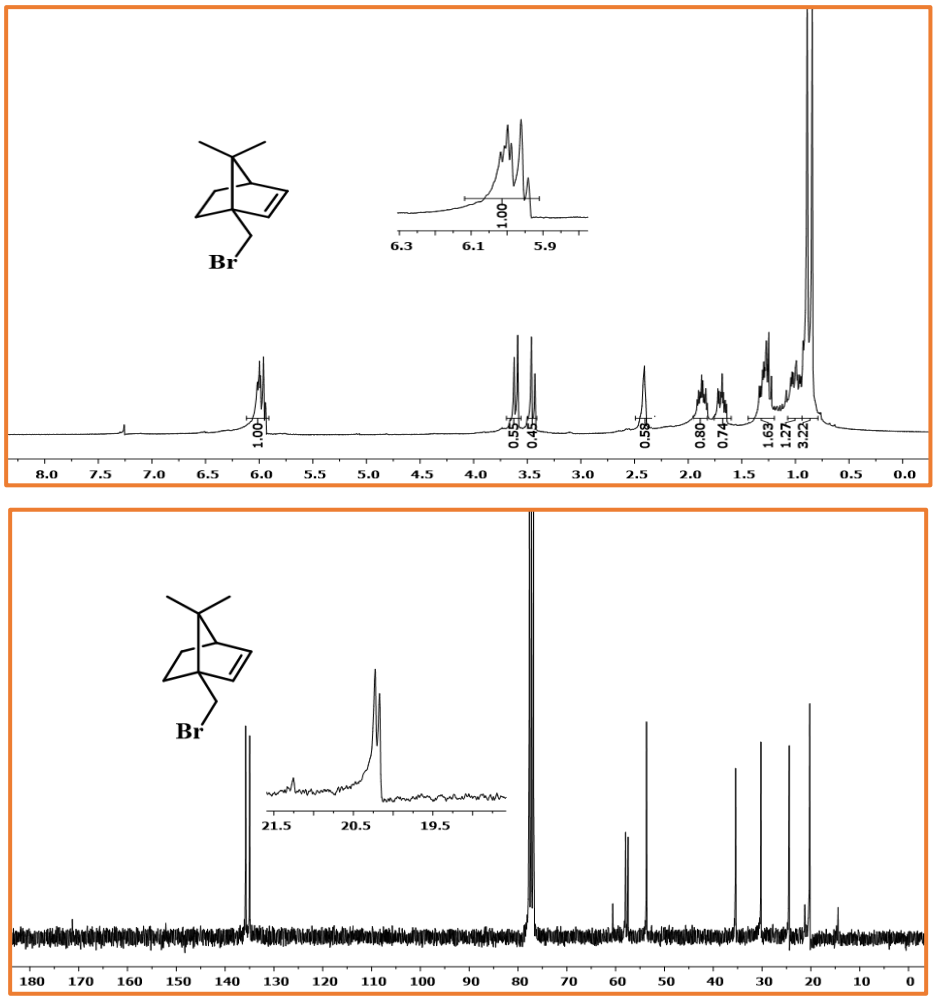


Figure 4.10. ^{1}H NMR and ^{13}C NMR of compound 279

4.5. Bromination of Norbornene 279

4.5.1. Bromination of norbornene 279 at low temperature

1-(Bromomethyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene (279) (0.15 g 0.7 mmole, 1 eq.) was dissolved in dichloromethane (10 mL) in a double neck reaction flask (100 mL) wrapped with aluminium foil. Bromine (0.12 g, 0.7 mmole, 1 eq.) solution dissolved in dichloromethane (10 mL) was added drop wise with the help of a dropping funnel at 0°C within 5 minutes. Solvent and excess bromine were removed under reduced vacuum at room temperature. In the ^{1}H NMR spectrum of the crude product, it was determined that the starting material was completely consumed. The crude product was purified by column chromatography (hexane) and 3,7-dibromo-1-(bromomethyl)-2,2-dimethylbicyclo[2.2.1]heptane (280) was isolated as colourless crystal in 97% yield.

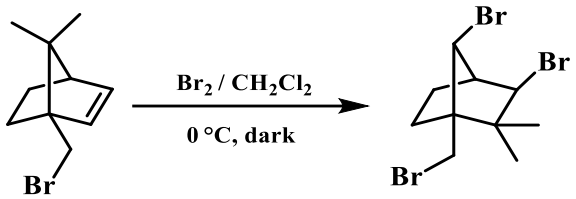


Figure 4.11. Low temperature bromination of compound 279

4.5.2. Synthesis of (1*R*,3*R*,4*R*,7*S*)-3,7-dibromo-1-(bromomethyl)-2,2-dimethyl-bicyclo[2.2.1]heptane (280)

Colourless crystal (0.99 g, 98%), melting point 75-77°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.07 (s, 2H), 3.72 (d, A part of AB system, J_{CH2} = 10.7 Hz, 1H, H_{CH2Br}), 3.51 (d, B part of AB system, J_{CH2} = 10.7 Hz, 1H, H_{CH2Br}), 2.75 (d, J = 5.2 Hz, 1H), 1.91-1.73 (m, 3H), 1.54 (s, 3H, CH_3), 1.45 (m, 1H), 1.18 (s, 3H, CH_3),

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 67.3, 57.8, 54.8, 51.0, 46.5, 34.4, 28.9, 28.1, 27.9, 26.7.

FTIR (cm^{-1}) v = 2966 (-CH), 1461 (CH of CH_2), 1302 (CH of CH_3), 768 (Br).

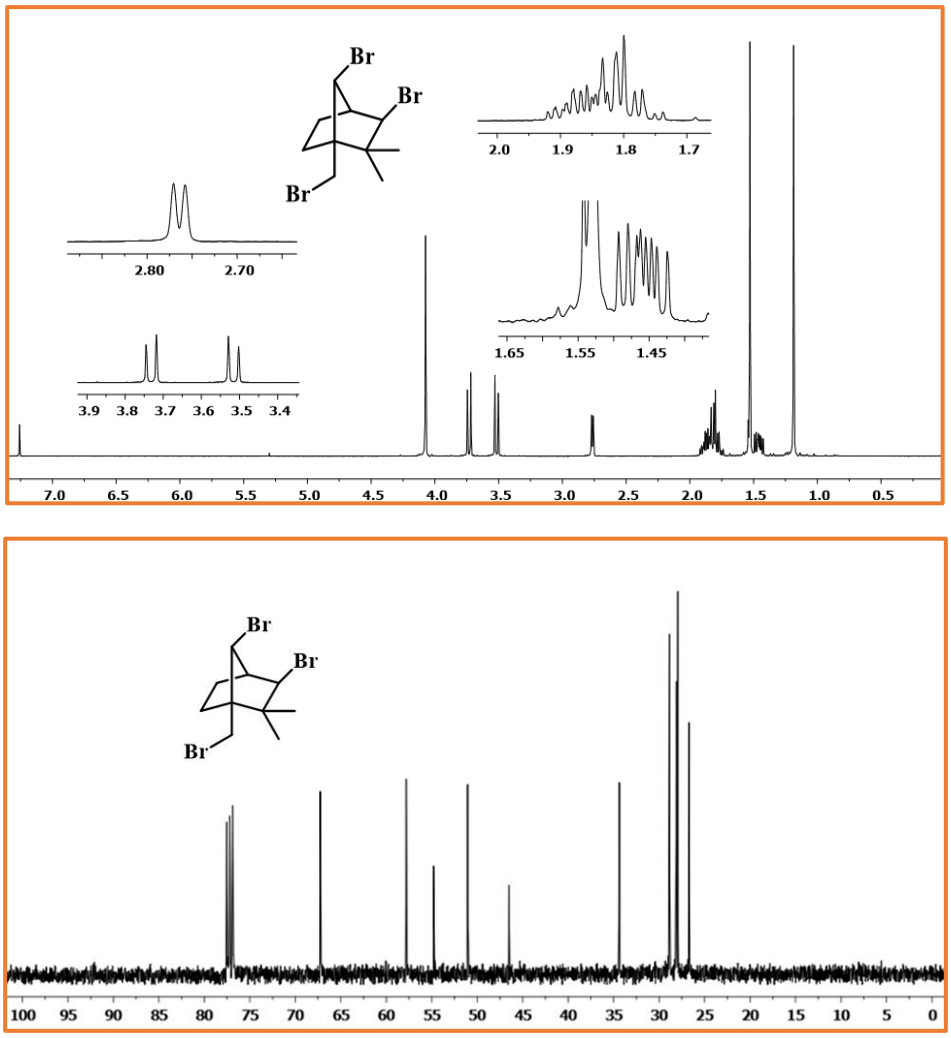


Figure 4.12. ^{1}H NMR and ^{13}C NMR of compound 280

4.5.3. Bromination of norbornene 279 at high temperature

1-(Bromomethyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene (279) (0.53 g, 2.5 mmole, 1 eq.) was dissolved in CCl_4 (25 mL) in the photobromination chamber . The reaction was initiated with 250 watt of light placed in the innermost part of the photobromination system. While the reaction was continuing, molecular bromine (0.45 g, 2.8 mmole, 1.1 eq.) dissolved in CCl_4 (25 mL) was added drop wise to the reaction mixture with the aid of a dropping funnel. Bromine was added for 3.5 hours under effective mixing, effective cooling and effective condensation. The reaction was terminated as soon as the bromine addition was completed. The reaction solution was cooled to room temperature. Solvent and excess bromine were removed under reduced vacuum. It was observed that more than one product was formed in the ^{1}H NMR spectrum of the crude product. The products were purified by column chromatography (hexane:dichloromethane; 9:1). Very low amounts of monobrominated isomers (277a,

b) were observed among the products. Since more than one product was detected in successive fractions, purification processes were carried out several times by column chromatography (Figure 4.13).

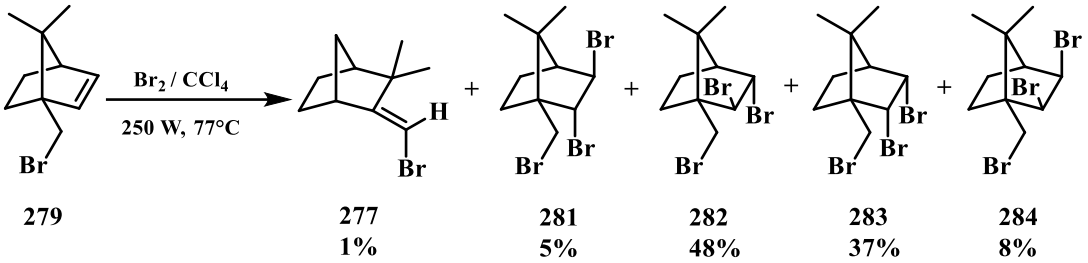


Figure 4.13. High temperature bromination of compound 279

4.5.4. Synthesis of 2,3-dibromo-1-bromomethyl-7,7-dimethylbicyclo[2.2.1]heptane (281)

Colourless crystal (0.02 g, 5%), melting point 73-75°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.98 (dd, A part of AB, $J_{2,3}$ = 9.9 Hz, $J_{2,6ex}$ = 2.8 Hz, 1H, H_2), 4.86 (ddd, B part of AB, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 4.0 Hz, 1H, H_3), 3.48 (d, A part of AB, J_{CH2} = 11.4 Hz, 1H, H_{CH2Br}), 3.42 (d, B part of AB, J_{CH2} = 11.4 Hz, 1H, H_{CH2Br}), 2.08-1.94 (m, 2H), 1.72 (m, 1H), 1.61-1.53 (m, 2H), 1.18 (s, 6H, 2xCH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 60.1, 55.4, 54.1, 53.5, 48.1, 32.6, 29.1, 22.5, 22.2, 20.6.

FTIR (cm^{-1}) v = 2919 (-CH), 1461 (CH of CH_2), 1174 (CH of CH_3), 721 (Br).

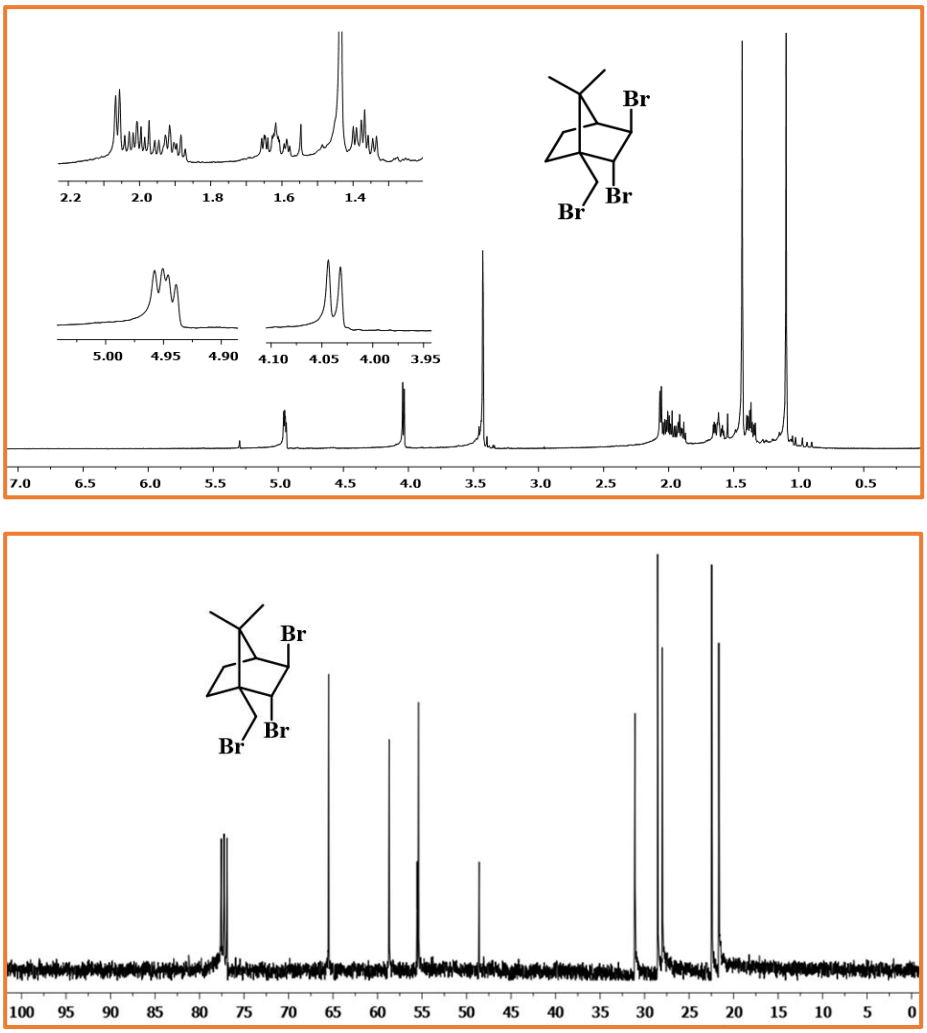


Figure 4.14. ^{1}H NMR and ^{13}C NMR of compound 281

4.5.5. Synthesis of 2,3-dibromo-1-(bromomethyl)-7,7-dimethylbicyclo[2.2.1] heptane (282)

White crystal (0.17 g, 48%), melting point 73-75°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.83 (dt, $J_{2,3} = J_{3,4} = 4.5$ Hz, $J_{3,5ex} = 2.2$ Hz, 1H, H_3), 4.15 (d, $J_{2,3} = 4.5$ Hz, 1H, H_2), 3.63 (d, A part of AB, $J_{CH2} = 10.1$ Hz, 1H, H_{CH2Br}), 3.45 (d, B part of AB, $J_{CH2} = 10.1$ Hz, 1H, H_{CH2Br}), 2.16 (t, $J_{3,4} = J_{4,5ex} = 4.5$ Hz, 1H, H_4), 2.08-1.96 (m, 2H, H_{6ex} and H_{6en}), 1.82 (m, 1H, H_{5ex}), 1.68 (m, 1H, H_{5en}), 1.24 (s, 3H, CH_3), 1.03 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 64.3, 61.2, 55.5, 54.3, 49.9, 35.7, 34.9, 22.2, 21.8, 20.2.

FTIR (cm^{-1}) v = 2916 (-CH), 1461 (CH of CH_2), 1180 (CH of CH_3), 740 (Br).

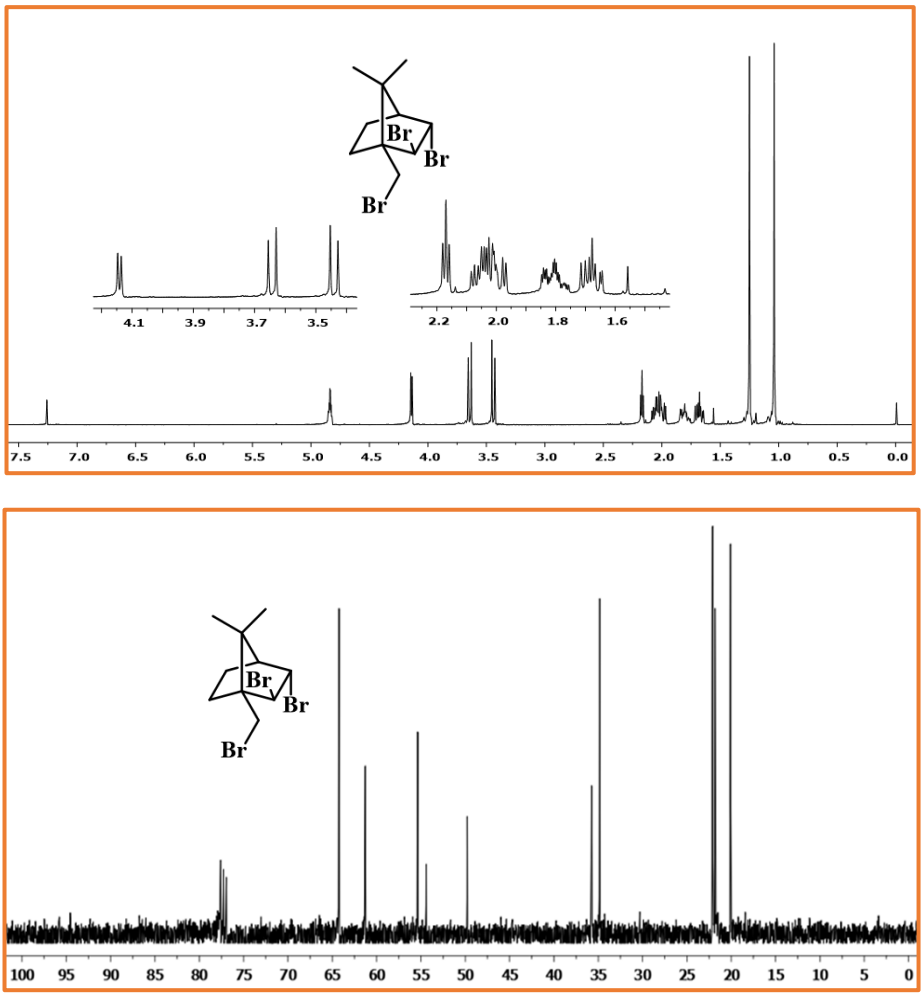


Figure 4.15. ^{1}H NMR and ^{13}C NMR of compound 282

4.5.6. Synthesis of 2,3-dibromo-1-bromomethyl-7,7-dimethylbicyclo[2.2.1] heptane (283)

White crystal (0.22 g, 37%), melting point 73-75°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.94 (dd, $J_{2,3}$ = 4.7 Hz, $J_{2,6ex}$ = 2.8 Hz, 1H, H_2), 4.03 (d, $J_{2,3}$ = 4.7 Hz, 1H, H_3), 3.42 (d, A part of AB, J_{CH2} = 11.5 Hz, 1H, H_{CH2Br}), 3.43 (d, B part of AB, J_{CH2} = 11.5 Hz, 1H, H_{CH2Br}), 2.05 (d, $J_{4,5ex}$ = 4.5 Hz, 1H, H_4), 2.03 (m, 1H, H_{6en}), 1.92 (m, 1H, H_{5ex}), 1.89 (m, 1H, H_{6ex}), 1.43 (s, 3H, CH_3), 1.38 (m, 1H, H_{5en}), 1.11 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 65.4, 58.8, 55.5, 55.3, 48.7, 31.2, 28.4, 28.0, 22.4, 21.6.

FTIR (cm^{-1}) v = 2919 (-CH), 1458 (CH of CH_2), 1374 (CH of CH_3), 740 (Br).

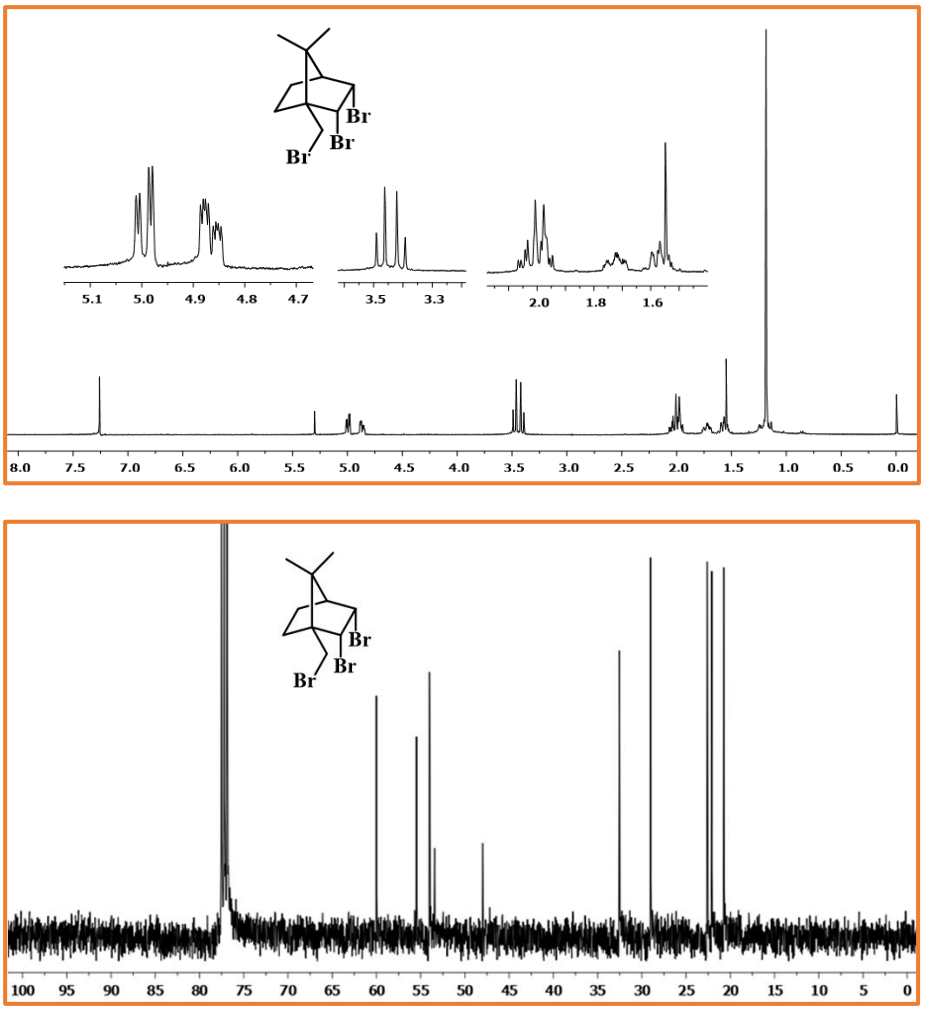


Figure 4.16. ^{1}H NMR and ^{13}C NMR of compound 283

4.5.7. Synthesis of 2,3-dibromo-1-(bromomethyl)-7,7-dimethylbicyclo[2.2.1] heptane (284)

White crystal (0.08 g, 8%), melting point 73-75°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.51 (d, A part of AB, $J_{2,3}$ = 8.1 Hz, 1H, H_2), 4.37 (d, B part of AB, $J_{2,3}$ = 8.1 Hz, 1H, H_3), 3.77 (d, A part of AB, J_{CH2} = 10.0 Hz, 1H, H_{CH2Br}), 3.51 (d, B part of AB, J_{CH2} = 10.0 Hz, 1H, H_{CH2Br}), 2.39 (d, $J_{4,5ex}$ = 4.2 Hz, 1H, H_4), 1.96-1.90 (m, 2H, CH_2), 1.61 (m, 1H, CH_2), 1.43 (s, 3H, CH_3), 1.28 (m, 1H, CH_2), 0.92 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 60.8, 57.2, 55.2, 54.5, 50.2, 37.3, 34.1, 27.4, 22.2, 21.7.

FTIR (cm^{-1}) ν = 2922 (-CH), 1458 (CH of CH_2), 1374 (CH of CH_3), 671 (Br).

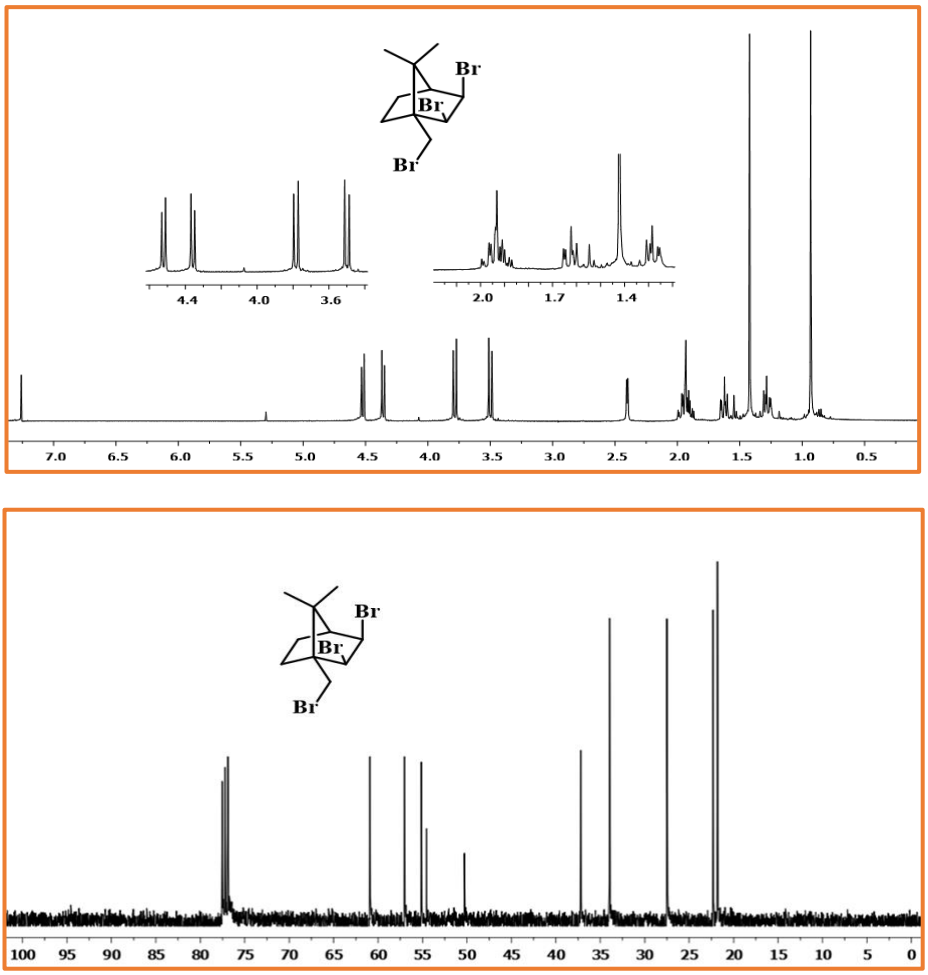


Figure 4.17. ^{1}H NMR and ^{13}C NMR of compound 284

4.6. Bromination of (+)-Monobromocamphene (277) at Low Temperature

Mono-brominated (+)-camphene compound (277) (1.5 g, 7 mmole, 1 eq.) was dissolved in dichloromethane (20 mL) in a double neck reaction flask (100 mL) and placed in acetone which temperature was lowered to -15°C by the inner cooler system. Molecular bromine (1.23 g, 7.7 mmole, 1.1 eq.) dissolved in dichloromethane (20 mL) was added drop wise to the reaction flask with the help of a dropping funnel at -15°C within 5 minutes and small amount of SiO_2 was also added to the reaction mixture. Solvent and excess bromine were removed under reduced vacuum at room temperature. In the ^{1}H NMR spectrum of the crude product, it was determined that the starting material was completely consumed. The crude product was purified by column chromatography (hexane) and single compound (285) (2.15 g) was isolated as yellowish viscous liquid in 81% yield.

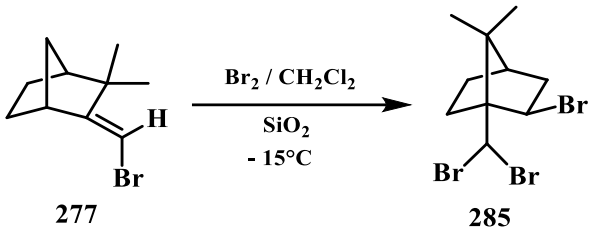


Figure 4.18. Bromination of compound 277 at low temperature

4.6.1. Synthesis of compound (1*R*,2*R*,4*R*)-2-bromo-1-(dibromomethyl)-7,7-dimethylbicyclo[2.2.1]heptane (285)

Yellowish viscous liquide (2.15 g, 81%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 6.18 (s, 1H), 4.31 (dd, *J* = 8.6, 4.9 Hz, 1H), 2.60-2.35 (m, 2H), 2.25 - 2.09 (m, 2H), 2.05-1.79 (d, 1H), 1.59 (ddd, *J* = 26.6, 12.1, 4.2 Hz, 2H), 1.28 (s, 3H), 1.17 (s, 3H).

^{13}C NMR ($CDCl_3$,75 MHz, ppm) δ_C 59.7, 57.9, 51.0, 50.6, 41.5, 31.2, 30.5, 26.3, 25.1, 20.3.

FTIR (cm^{-1}) *v* = 2954 (-CH), 1458 (CH of CH_2), 1374 (CH of CH_3), 705 (Br).

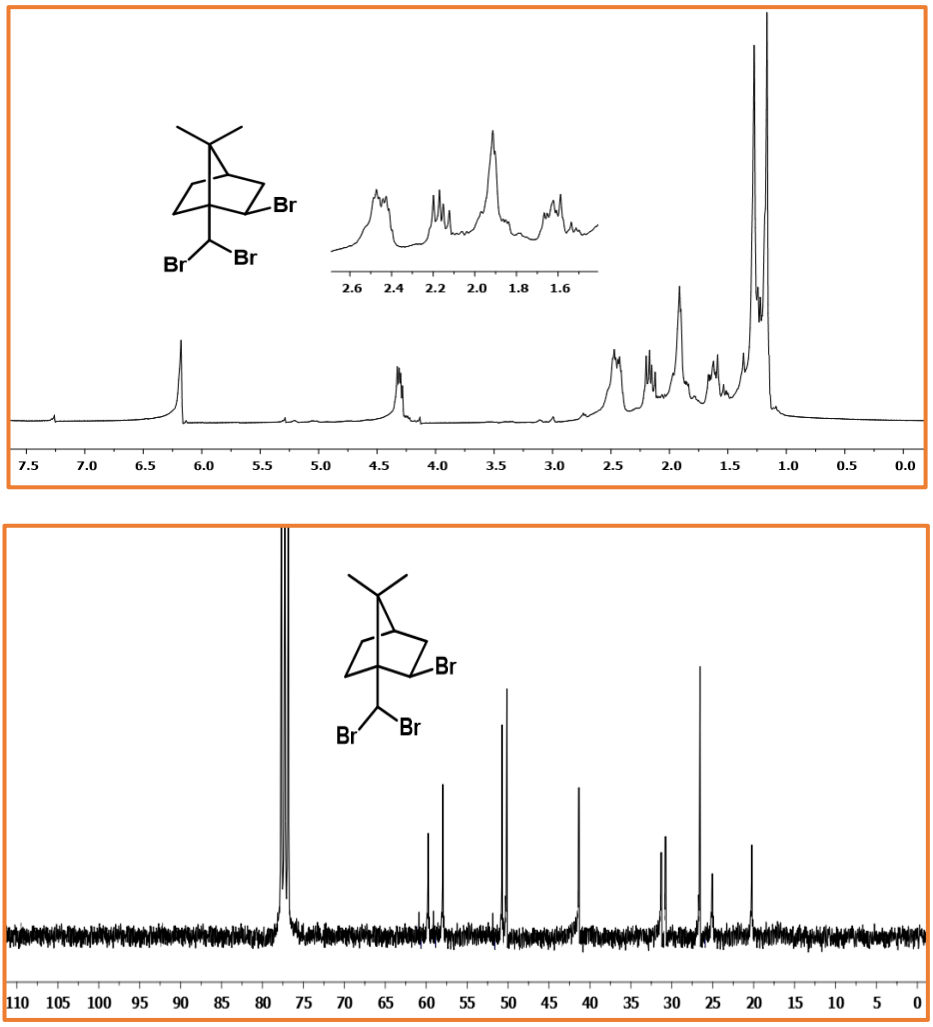
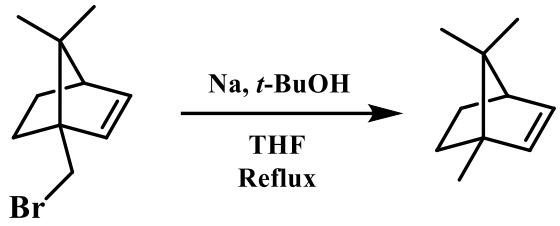


Figure 4.19. ^{1}H NMR and ^{13}C NMR of compound 285

4.6.2. Elimination reaction of compound 279

Compound 279 (1 g, 4.7 mmole, 1 eq.) was dissolved in freshly dried THF (20 mL) in a two-necked reaction flask and 4.5 mL (3.5 g, 47 mmole, 10 eq.) of *tert*-butanol was added to the solution. Furthermore, sodium metal (1.1 g, 47 mmole, 10 eq.) was dissolved in THF (20 mL) and added to the reaction mixture which was heated at 120°C for 16 hour with reflux and cooled at room temperature. A small amount of dried methanol (15 mL) was added to the cooled solution of reaction products for neutralizing unreacted sodium remained in the solution. After, the reaction solution was washed with distilled water (3x50 mL) and extracted with diethyl ether (3x50 mL). The solvent was evaporated by rotary evaporation and ^{1}H NMR spectra of the crude product was taken with a 300 MHz NMR instrument. It was observed that the awaited product 286 was formed in 52.4%.



279 286

Figure 4.20. Elimination reaction of compound 279

4.6.3. Synthesis of (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (286)

Colourless viscous liquide (0.32g, 52.4%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 5.90 (dd, *J* = 5.6, 3.0 Hz, 1H), 5.65 (d, *J* = 5.8 Hz, 1H), 2.27 (s, 1H), 1.91-1.71 (m, 2H), 1.59-1.48 (m, 1H), 1.26 (ddd, *J* = 18.2, 8.5, 4.1 Hz, 1H), 1.03 (s, 3H), 0.99-0.87 (m, 2H), 0.77 (s, 3H), 0.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 139.3, 134.1, 56.5, 52.9, 52.3, 31.7, 24.4, 19.7, 19.5, 13.5.

FTIR (cm^{-1}) *v* = 2926 (-CH), 1711 (C=C), 1458 (CH of CH_2), 1377 (CH of CH_3).

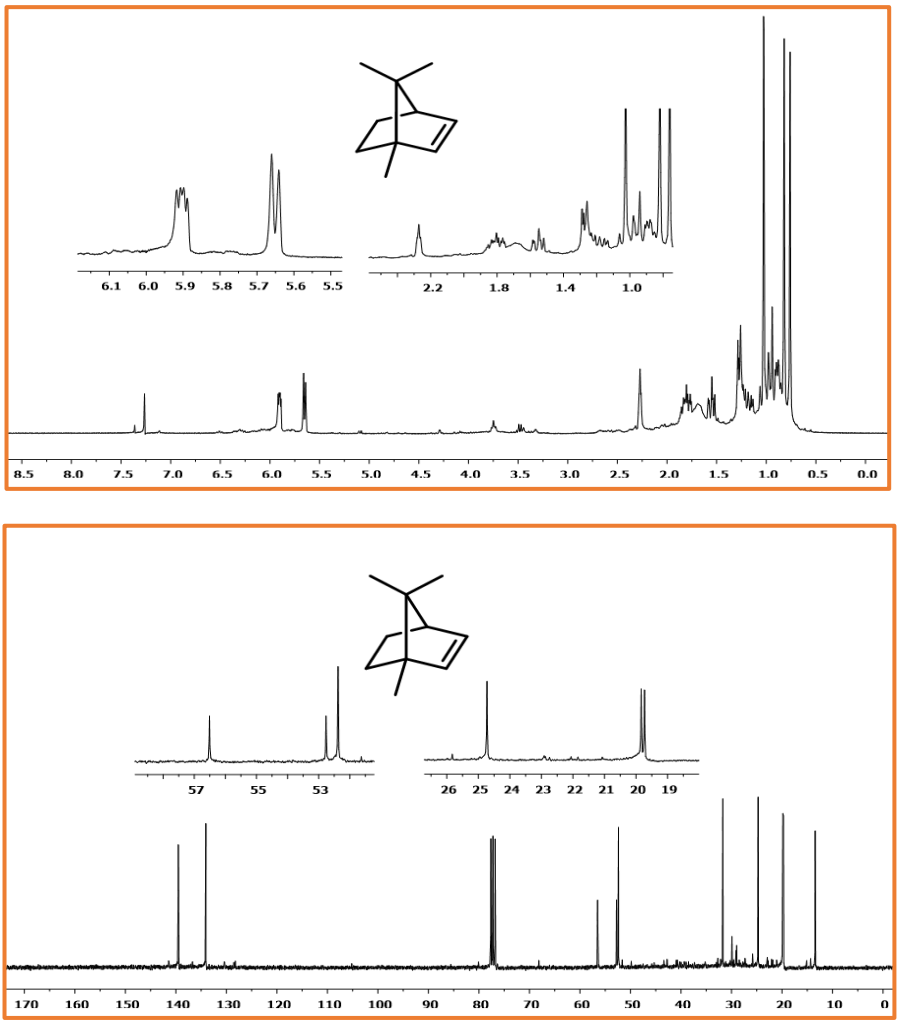


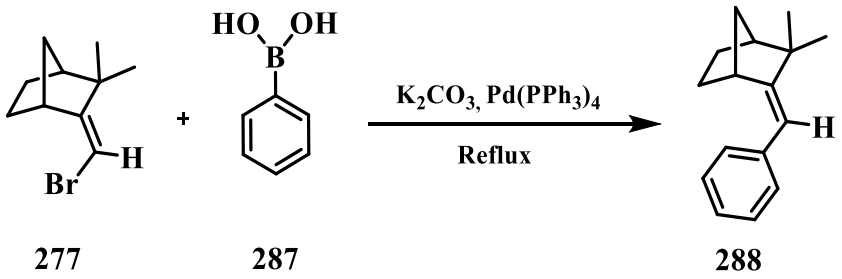
Figure 4.21. ^{1}H NMR and ^{13}C NMR of compound 286

4.7. Suzuki Coupling Reaction of Monobrominated (+)-Camphene (277)

Corresponding boronic acid (2 eq.), toluene (30 mL), and monobromo-(+)-camphene 277 (1 eq.) were added to a two-necked reaction flask (100 mL) at room temperature under a nitrogen atmosphere. A catalytic amount of $[Pd(PPh_3)_4]$ (0.3 eq.) and K_2CO_3 solution (3 eq.) dissolved in ethanol (30 mL) were added to the reaction flask. The reaction mixture was refluxed under nitrogen gas for 24 h. After, the reaction solution was cooled, water (100 mL) was added and extracted with chloroform (3x50 mL). The organic phase was dried over Na_2SO_4. After removing the organic solvent under reduced vacuum, it was purified by column chromatography (SiO_2, 90 g, 50 cm length, 4 cm diameter column) with dichloromethane/petroleum ether (2:1) solvent system as mobile phase. Coupling products 288, 290, 292, 294 and 296 were obtained from monobromocamphene (277).

4.7.1. Synthesis of 3-((*E*)-benzylidene)-2,2-dimethylbicyclo[2.2.1]heptane (288)

Compound 288 was synthesized by the use of monobromocamphene (277) (1 g, 4.7 mmole, 1 eq.) and phenylboronic acid (1.13 g, 9.4 mmole, 2 eq.) through the general synthesis method of Suzuki-Miyaura coupling reaction.



277 287 288

Figure 4.22. Synthesis of compound 288

Brown viscous liquide (0.59 g, 60%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 7.40-7.25 (m, 5H), 6.07 (s, 1H), 3.31 (d, *J* = 3.8 Hz, 1H), 1.97 (d, *J* = 3.9 Hz, 1H), 1.99-1.80 (t, *J* = 11.3 Hz, 1H), 1.79-1.66 (m, 2H), 1.65-1.60 (m, 1H), 1.58-1.42 (m, 1H), 1.37-1.24 (m, 1H), 1.24 (s, 3H), 1.10 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 159.4, 139.5, 128.5, 128.2, 126.0, 116.4, 47.4, 43.6, 42.5, 38.1, 29.5, 28.1, 26.6, 23.7.

FTIR (cm^{-1}) *v* = 2954 (-CH), 1658 (C=C), 1446 (CH of CH_2), 1368 (CH of CH_3).

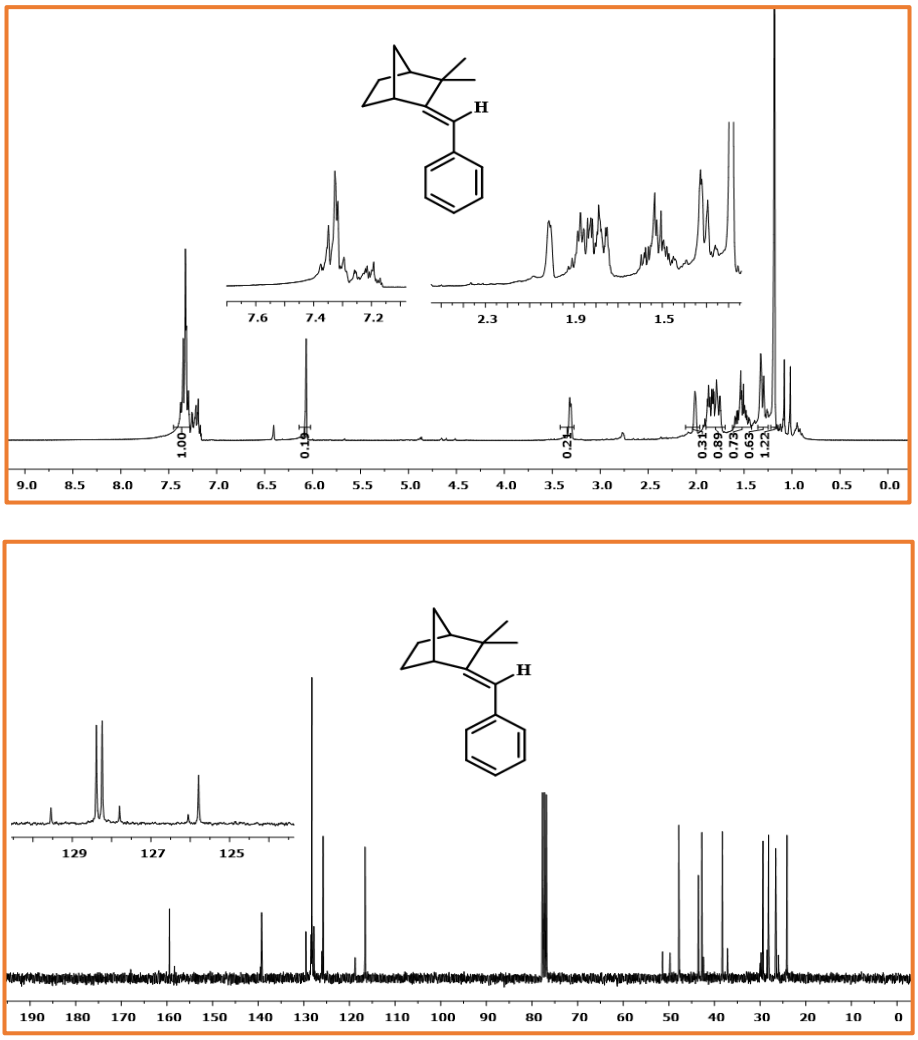


Figure 4.23. ^{1}H NMR and ^{13}C NMR of compound 288

4.7.2. Synthesis of 3-((*E*)-4-ethylbenzylidene)-2,2-dimethylbicyclo[2.2.1]heptane (290)

Compound 290 was synthesized by the use of mono-bromocamphene (277) (0.5 g, 2.3 mmole, 1 eq.) and 4-ethylphenylboronic acid (0.65 g, 4.6 mmole, 2 eq.) (289) through the general method of Suzuki-Miyaura coupling reaction.

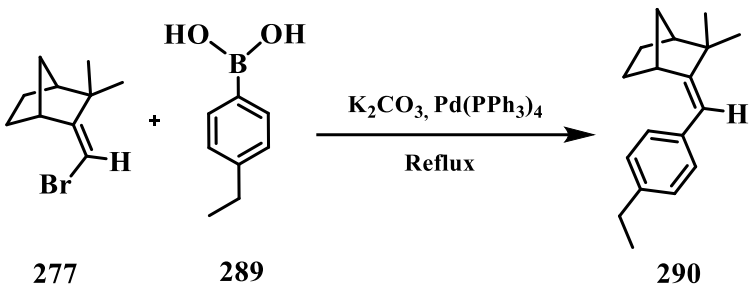


Figure 4.24. Synthesis of compound 290

Brown viscous liquide (0.41 g, 74%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 7.32-7.15 (m, 4H), 6.02 (s, 1H), 3.30 (d, *J* = 4.6 Hz, 1H), 2.66 (dd, *J* = 15.0, 7.5 Hz, 2H), 1.99 (d, *J* = 1.7 Hz, 1H), 1.92-1.81 (m, 2H), 1.81-1.51 (m, 2H), 1.40-1.30 (m, 2H), 1.30-1.23 (m, 3H), 1.15 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 158.6, 142.0, 136.7, 128.6, 127.8, 116.4, 47.8, 43.7, 42.9, 38.3, 29.4, 28.9, 28.1, 26.3, 24.0, 15.9.

FTIR (cm^{-1}) *v* = 2963 (-CH), 1661 (C=C), 1461 (CH of CH_2), 1380 (CH of CH_3).

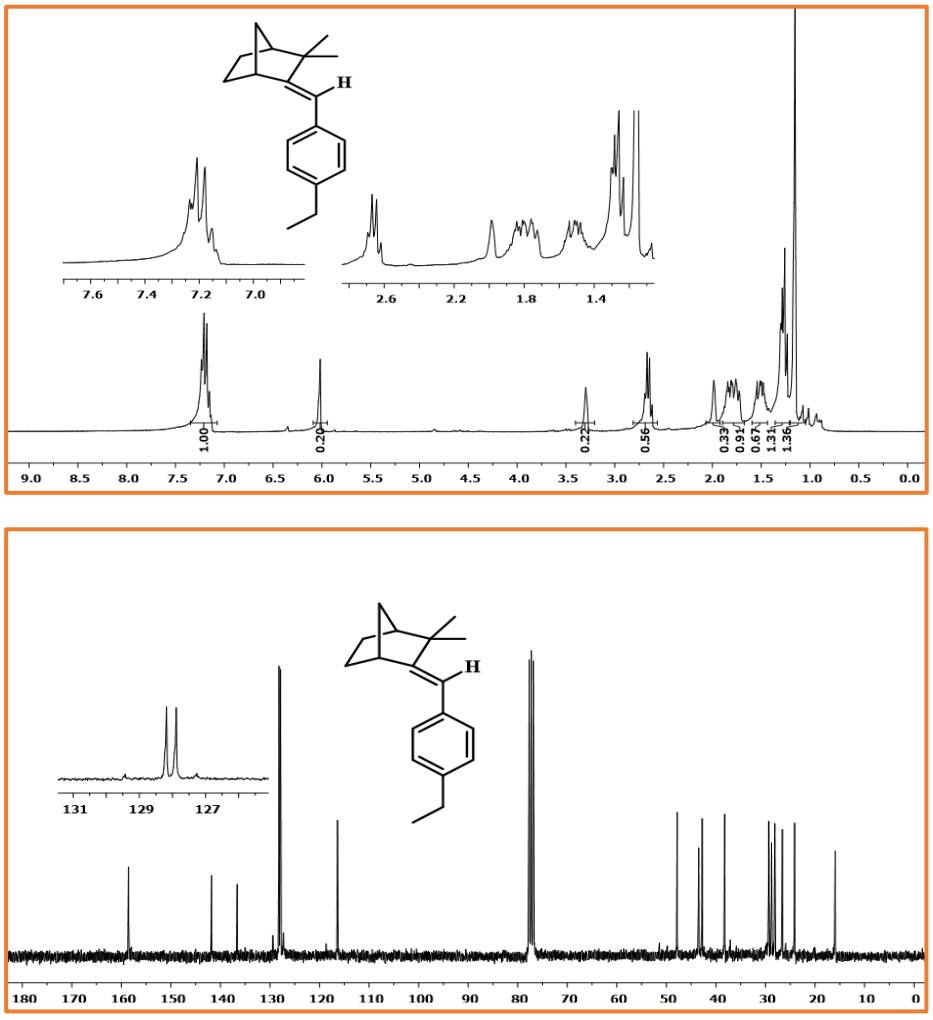


Figure 4.25. ^{1}H NMR and ^{13}C NMR of compound 290

4.7.3. Synthesis of 3-((*E*)-4-methoxybenzylidene)-2,2-dimethylbicyclo[2.2.1] heptane (292)

Compound 292 was synthesized by the use of monobromocamphene (277) (0.5 g, 2.3 mmole, 1 eq.) and 4-methoxyphenylboronic acid (291**)** (0.71 g, 4.6 mmole, 2 eq.) followed by the general method of Suzuki-Miyaura coupling reaction.

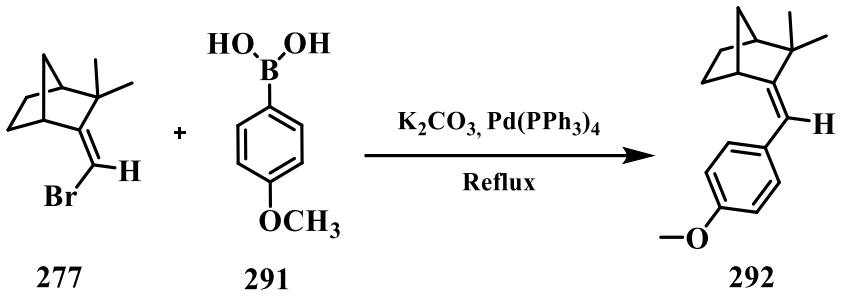


Figure 4.26. Synthesis of compound 292

Colourless crystal (0.41 g, 73%), melting point 73-75°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 7.27 (d, *J* = 7,5 Hz, 2H), 6.92 (d, *J* = 7,5 Hz, 2H), 5.97 (s, 1H), 3.82 (s, 3H), 3.24 (d, *J* = 3.3, 1H), 1.97 (d, *J* = 3.3 Hz, 1H), 1.88-1.65 (m, 2H), 1.57 (d, *J* = 5.8 Hz, 1H), 1.45 (ddt, *J* = 17.2, 13.9, 7.4 Hz, 1H), 1.23 (d, *J* = 11.4 Hz, 2H), 1.12 (s, 3H), 1.11 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 158.0, 157.4, 132.0, 129.3, 115.6, 113.7, 55.4, 47.5, 43.4, 42.3, 38.2, 29.5, 27.9, 26.7, 24.0.

FTIR (cm^{-1}) *v* = 2947 (-CH), 1608 (C=C), 1454 (CH of CH_2), 1239 (CH of CH_3), 1177 (C-O-C).

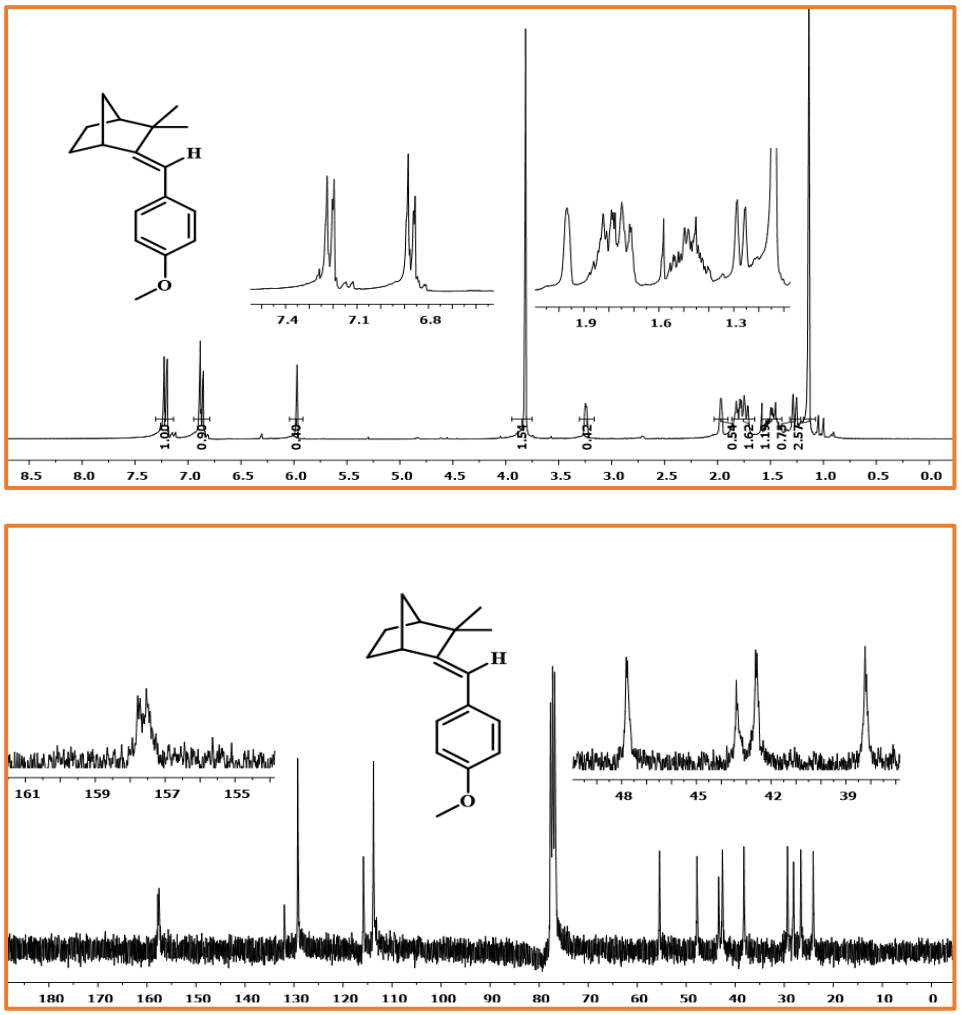


Figure 4.27. ^{1}H NMR and ^{13}C NMR of compound 292

4.7.4. Synthesis of 4-(*E*)-3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)-methyl)-phenyl)-(methyl)-sulfane (294)

Compound 294 was synthesized by the use of monobromocamphene (277) (0.5 g, 2.3 mmole, 1 eq.) and 4-thiomethylphenylboronic acid (293) (0.78 g, 4.6 mmole, 2 eq.) followed by the general method of Suzuki-Miyaura coupling reaction.

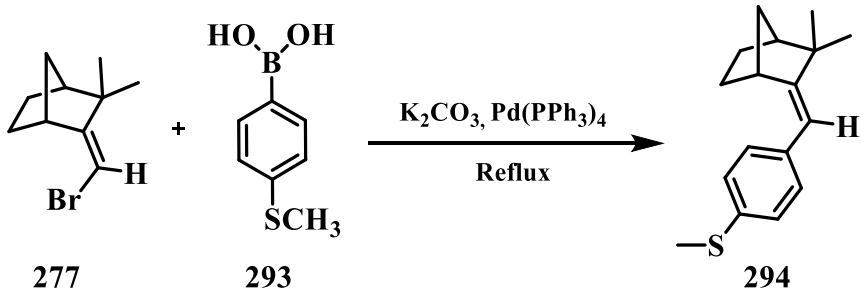


Figure 4.28. Synthesis of compound 294

Colourless crystal (0.29 g, 48%), melting point 68-70°C.

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 7.31-7.27 (m, 2H), 7.24-7.20 (d, *J* = 2.8 Hz, 2H), 6.0 (s, 1H), 3.26 (d, *J* = 4.6 Hz, 1H), 2.51 (s, 3H), 1.99 (s, 1H), 1.91-1.67 (m, 2H), 1.63 (s, 1H), 1.59-1.40 (m, 1H), 1.31 (dd, *J* = 10.8, 9.4 Hz, 2H), 1.12 (s, 3H), 1.11 (s, 3H),

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 159.2, 136.2, 134.9, 128.5, 126.7, 115.9, 47.4, 43.2, 42.4, 38.0, 29.0, 28.0, 26.1, 23.5, 16.0.

FTIR (cm^{-1}) *v* = 2938 (-CH), 1655 (C=C), 1489 (CH of CH_2), 1352 (CH of CH_3).

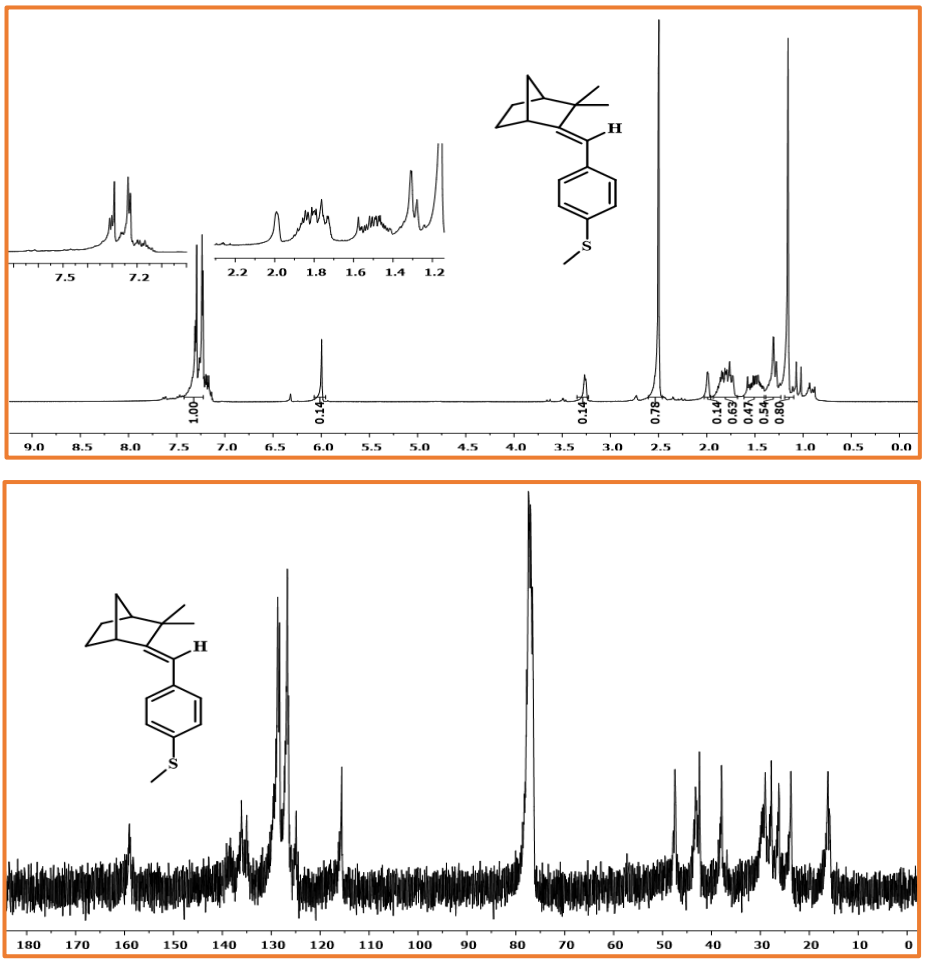
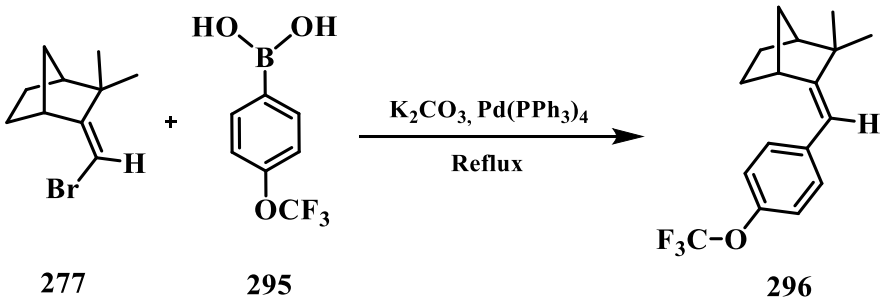


Figure 4.29. ^{1}H NMR and ^{13}C NMR of compound 294

4.7.5. Synthesis of 2,2-dimethyl-3-((*E*)-4-(trifluoromethoxy)benzylidene) bicyclo [2.2.1]heptane (296)

Compound 296 was synthesized by the use of monobromocamphene (277) (0.5 g, 2.3 mmole, 1 eq.) and 4-trifluoromethoxyphenylboronic acid (295) (0.96 g, 4.6 mmole, 2 eq.) followed by the general method of Suzuki-Miyaura coupling reaction.



277 295 296

Figure 4.30. Synthesis of compound 296

Colorless viscous liquide (0.23 g, 33%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 7.33-7.19 (m, 2H), 7.16 (t, *J* = 1.1 Hz, 2H), 5.99 (s, 1H), 3.22 (s, 1H), 1.95 (d, *J* = 18.4 Hz, 1H), 1.91-1.66 (m, 2H), 1.65-1.60 (s, 1H), 1.60-1.37 (m, 1H), 1.34-1.23 (m, 2H), 1.32 (s, 3H), 1.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 160.8, 147.2, 138.0, 129.2, 121.3, 115.2, 48.1, 43.7, 42.7, 38.5, 29.2, 28.0, 26.7, 24.3.

^{19}F NMR ($CDCl_3$, 282 MHz, ppm) δ_F -62.1.

FTIR (cm^{-1}) *v* = 2960 (-CH), 1658 (C=C), 1502 (CH of CH_2), 1258 (CH of CH_3), 1155 (C-O-C), 873 (F).

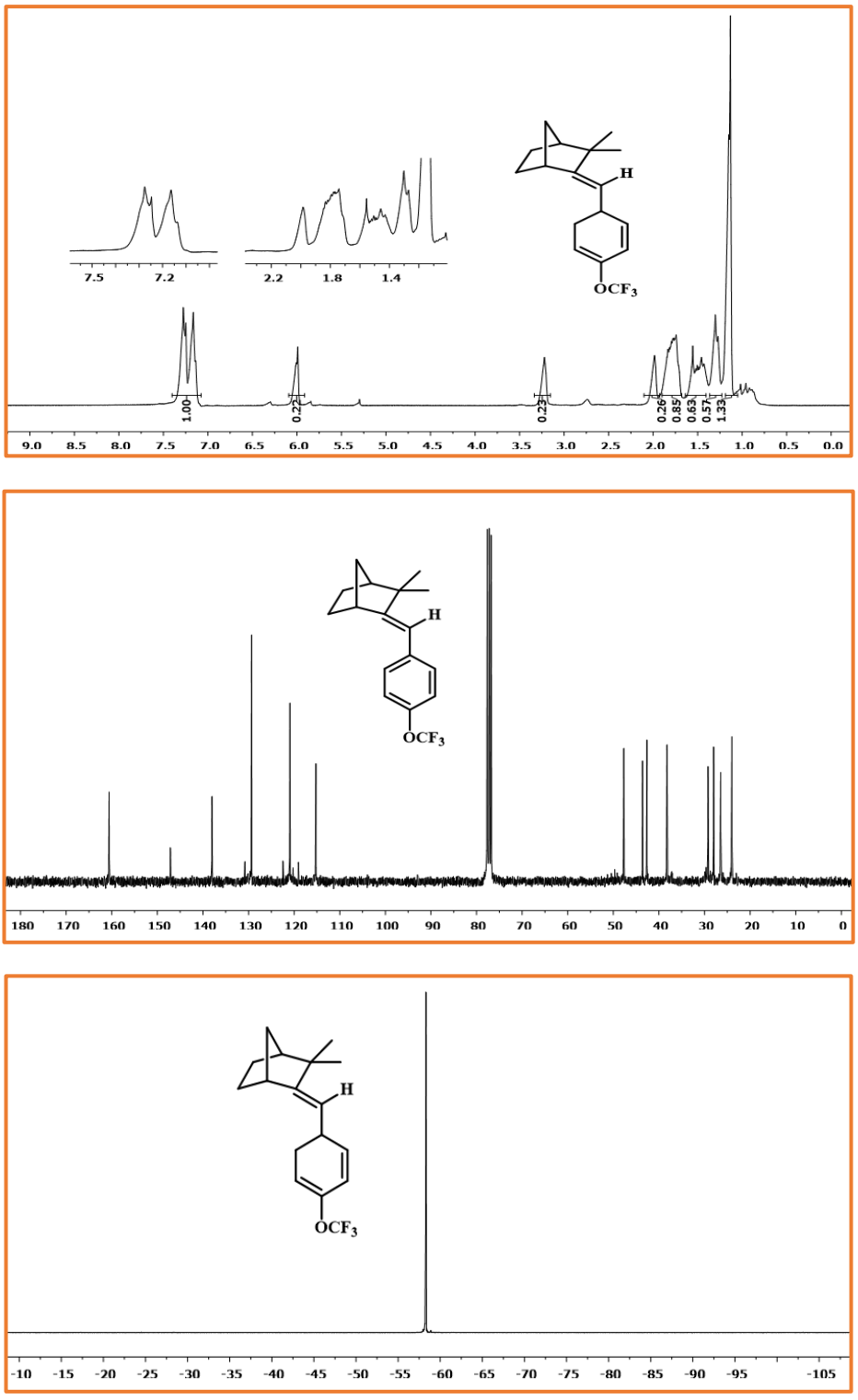
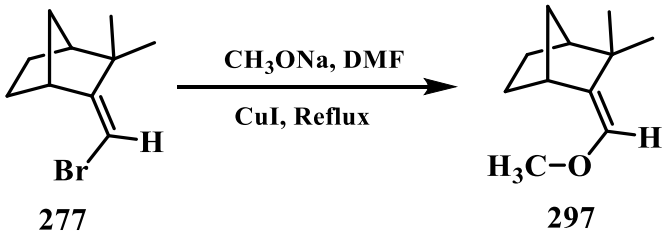


Figure 4.31. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR of compound 296

4.8. Nucleophilic Substitution Reactions of Compound 277

4.8.1. Synthesis of *E*-3-(methoxymethylene)-2,2-dimethylbicyclo[2.2.1]heptane (297)

Sodium methoxide was prepared by adding dry methanol (15 mL) and finely sliced sodium (0.5 g, 23 mmole, 10 eq.) to a three-necked reaction flask (100 mL) under nitrogen atmosphere. Freshly distilled DMF (10 mL) and Cul (0.22 g, 1.15 mmole, 0.5 eq.) were then added to the reaction flask. To this mixture, monobromocamphene (277) (0.5 g, 2.3 mmole, 1 eq.) dissolved in freshly distilled DMF (20 mL) was added drop wise via dropping funnel. The reaction mixture was refluxed under nitrogen atmosphere at 150°C for 24 hours. After, the reaction mixture was cooled, water (50 mL) was added and extracted with chloroform (3x50 mL). The organic phase was washed with brine (2x25 mL) and dried over Na_2SO_4. Then, the organic solvent was removed under reduced vacuum, it was purified by column chromatography in a hexane/chloroform (9:1) solvent system (SiO_2, 80 g, 40 cm length, 4 cm diameter column).



277 297

Figure 4.32. Synthesis of compound 297

Yellow viscous liquide (0.21 g, 54%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 5.59 (s, 1H), 3.52 (s, 3H), 3.04 (d, J = 4.1 Hz, 1H), 1.90-1.77 (s, 1H), 1.76-1.52 (m, 2H), 1.47-1.31 (m, 2H), 1.27-1.08 (m, 2H), 1.03 (s, 3H), 1.02 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 137.1, 134.4, 59.6, 48.6, 40.2, 39.7, 37.6, 30.4, 28.5, 26.8, 23.9.

FTIR (cm^{-1}) ν = 2916 (-CH), 1730 (C=C), 1461 (CH of CH_2), 1377 (CH of CH_3), 1177 (C-O-C).

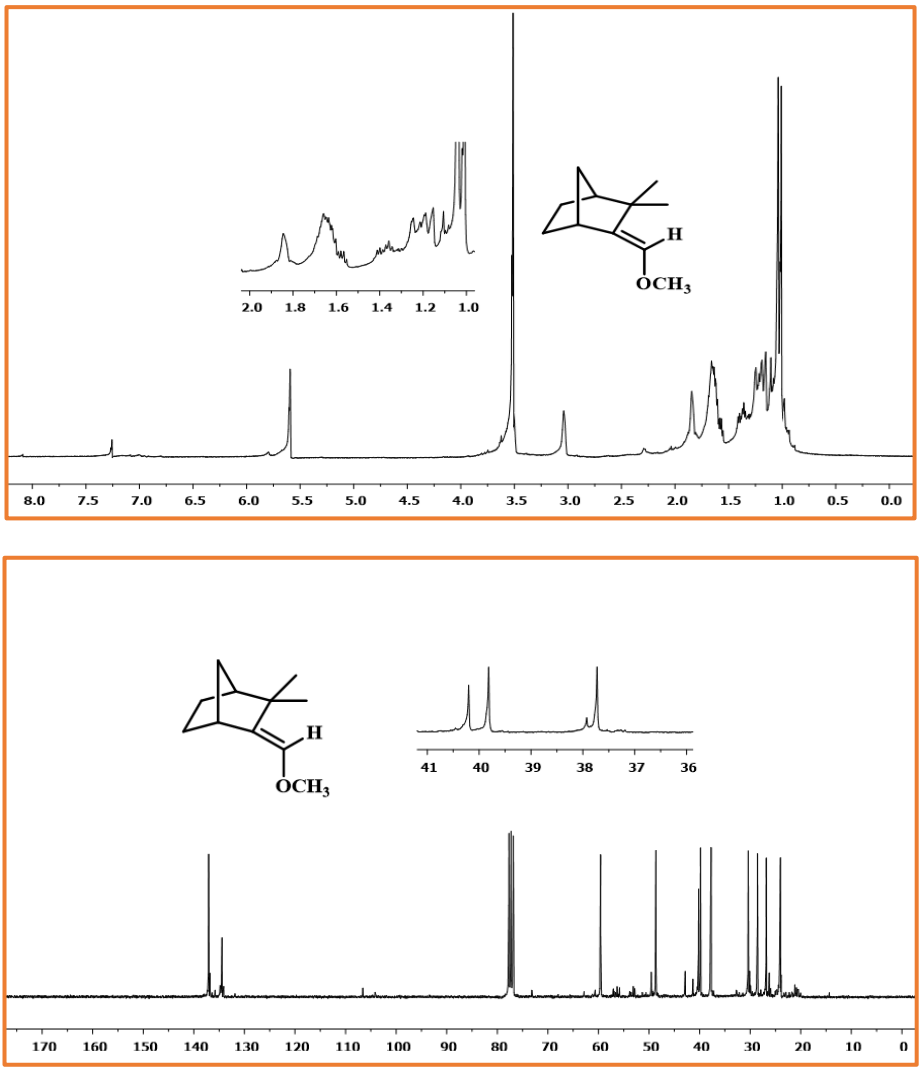


Figure 4.33. ^{1}H NMR and ^{13}C NMR of compound 297

4.8.2. Synthesis of *E*-2-(3,3-dimethylbicyclo[2.2.1]heptane-2-ylidene)acetonitrile (298)

The solution of monobromocamphene (277**)** (0.5 g, 2.3 mmole 1 eq.) in freshly distilled DMF (30 mL) and CuCN (0.83 g, 9.2 mmole, 4 eq.) was poured into a three-necked reaction flask (100 mL). The reaction mixture was refluxed at 150°C under nitrogen atmosphere. The reaction was followed by thin layer chromatography and at the end of the 8 hour, it was determined that there was no starting material left, and the reaction was terminated. The reaction mixture was brought to room temperature. A mixture of $FeCl_3$ (5 g), concentrated HCl (1 mL), and water (14 mL) were added to the reaction mixture. The resulting mixture was stirred at 70°C for 30 minutes, allowing the complex to break down. The reaction mixture was extracted with toluene (4x40 mL). The organic phases were combined and washed with dilute HCl (1:1, 25 mL), water and 10% NaOH solution, dried over Na_2SO_4, and the organic solvent was

removed under reduced vacuum. The crude product obtained was purified by column chromatography in a hexane/chloroform (9:1) solvent system (SiO_2, 80 g, 40 cm long, 4 cm diameter column).

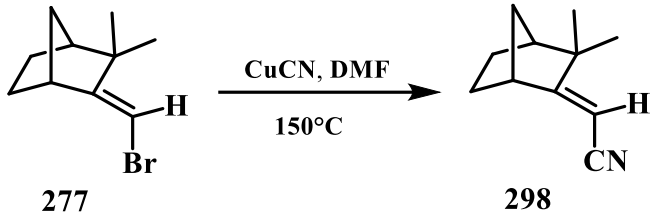


Figure 4.34. Synthesis of compound 298

Colourless viscous liquide (0.31 g, 83%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.85 (s, 1H), 3.26 (d, *J* = 4.1 Hz, 1H), 2.01 (s, 1H), 1.90-1.72 (m, 2H), 1.64 (d, *J* = 4.0 Hz, 1H), 1.48-1.44 (m, 1H), 1.38-1.32 (m, 2H), 1.08 (s, 3H), 1.07 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 185.3, 117.8, 85.8, 47.9, 46.4, 44.1, 37.4, 28.4, 27.9, 25.5, 23.1.

FTIR (cm^{-1}) *v* = 2963 (-CH), 2217 (-CN), 1645 (C=C), 1454 (CH of CH_2), 1364 (CH of CH_3).

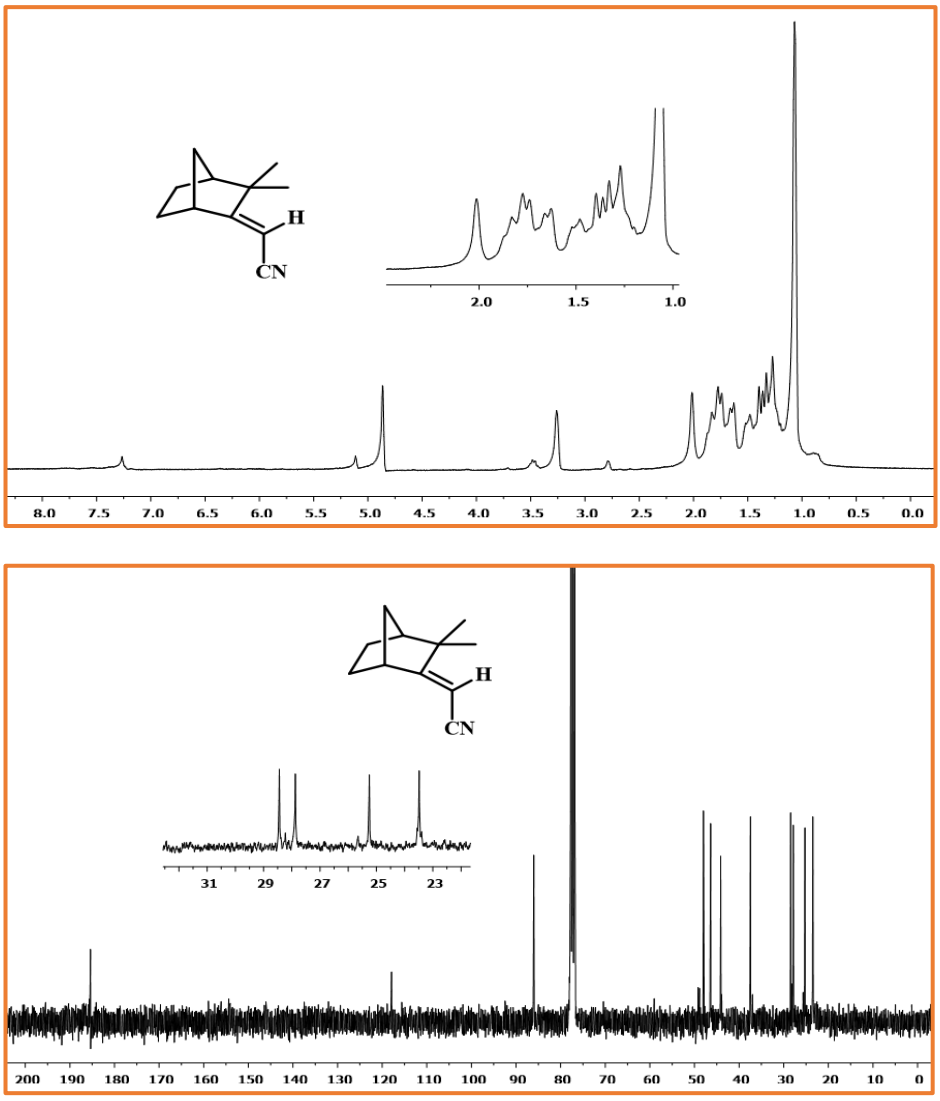


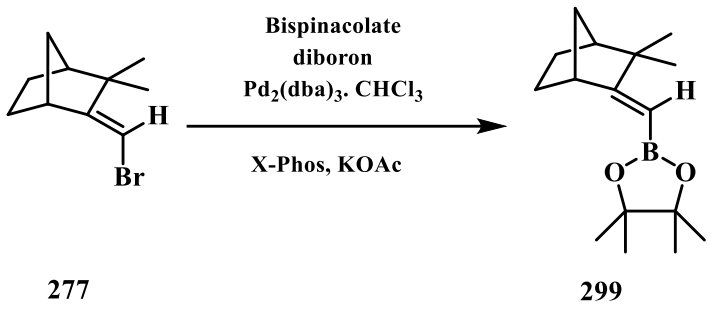
Figure 4.35. ^{1}H NMR and ^{13}C NMR of compound 298

4.8. Reaction of Monobromo Camphene (277) with Organoboron and *n*-BuLi

4.8.1. Synthesis of 2-((*E*)-((1*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]heptane-2-ylidene)-methyl) - 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (299)

0.3 g (1.4 mmole) monobromocamphene (277) was dissolved in dioxane (30 mL) and taken in a two neck reaction flask and 1.06 g (4.2 mmole) bispinacolate diboron, 0.014 g (0.014 mmole) $Pd_2(dba)_3.CHCl_3$, 0.026 g (0.056 mmole), potassium acetate 0.41 g (4.2 mmole) were adeed to the reaction flask and heated at reflux temperature for 24 h. After the reaction solution was cooled, water (50 mL) was added and extracted with chloroform (3x40 mL). The organic phase was dried over Na_2SO_4. After removing the organic solvent under reduced vacuum, it was purified by column chromatography (SiO_2, 90 g, 50 cm length, 4 cm diameter column) with dichloromethane/petroleum

ether (1:20) solvent system as a mobile phase and compound 299 was obtained as colourless viscous liquide.



277 299

Figure 4.36. Synthesis of compound 299

Colourless viscous liquide (0.24 g, 66%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.87 (s, 1H), 3.45-3.30 (d, *J* = 4.1 Hz, 1H), 2.27 (s, 1H), 2.02 (d, *J* = 5.8 Hz, 1H), 1.86 (s, 1H), 1.72-1.48 (m, 2H), 1.49-1.36 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H),

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C 156.6, 102.3, 83.7, 83.1, 82.6, 47.5, 46.0, 44.1, 37.7, 30.0, 29.2, 26.0, 25.5, 25.2, 24.7, 23.8.

FTIR (cm^{-1}) *v* = 2915 (-CH), 1735 (C=C), 1463 (CH of CH_2), 1372 (CH of CH_3).

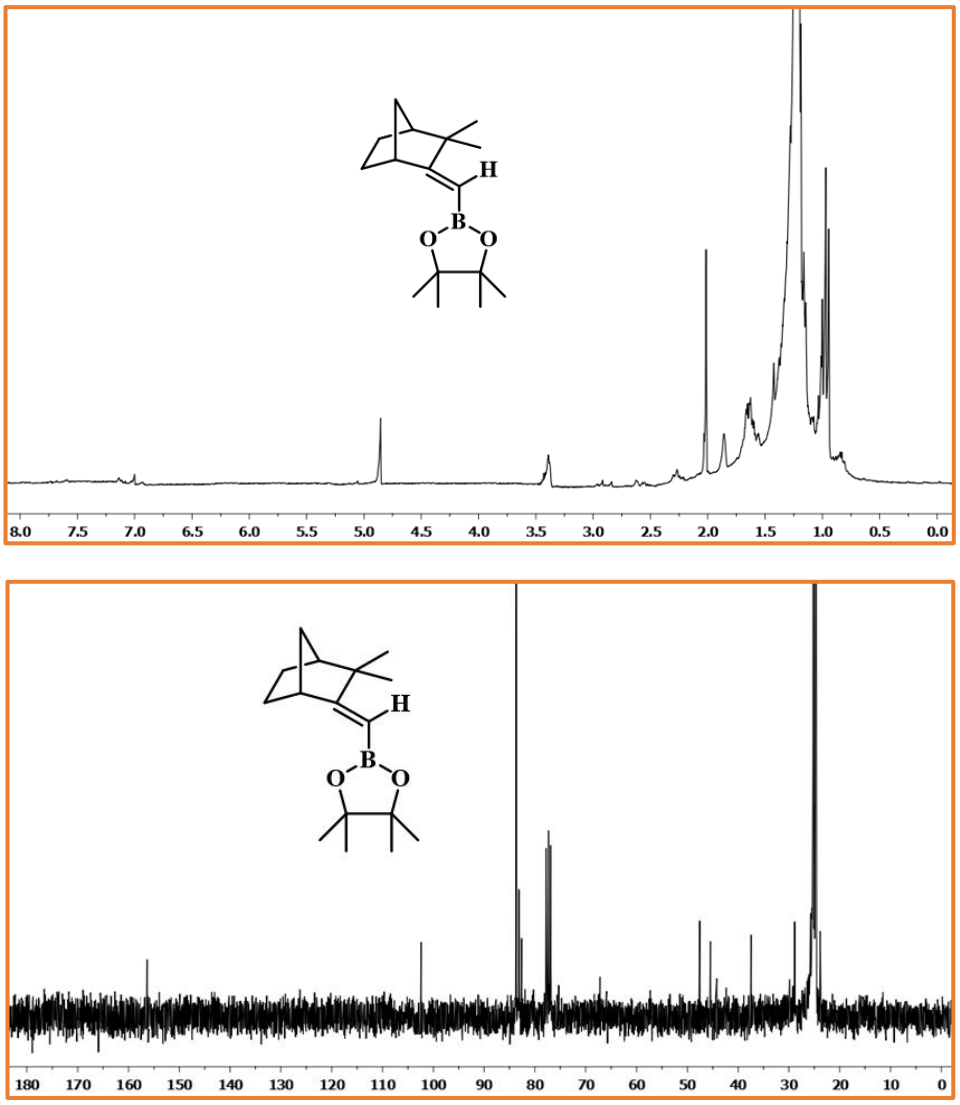
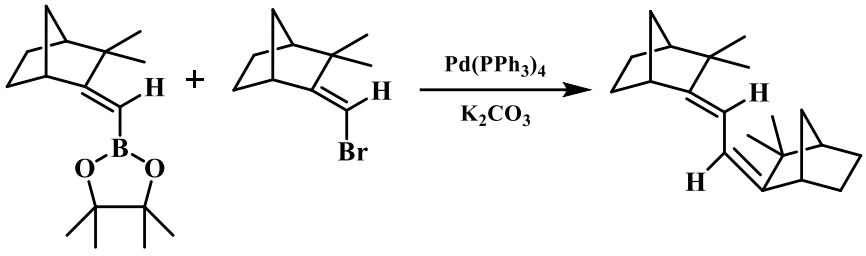


Figure 4.37. ^{1}H NMR and ^{13}C NMR of compound 299

4.8.2. Synthesis of (1*E*,2*Z*)-1-((1*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)-2-((1*S*,4*R*)-3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)ethane (300)

0.30 g (1.1 mmole) Bpin-camphene (299) was dissolved in 30 mL of toluene and taken in a two neck reaction flask and 0.47 g (3.3 mmole) K_2CO_3 dissolved in 10 ml water, 0.1 g (0.09 mmole) $Pd(PPh_3)_3$ dissolved in 14 mL ethanol, 0.37 g (1.7 mmole) monobromocamphene (277) were adeed to the reaction flask and heated at reflux temperature for 24 h. After, the reaction solution was cooled, water (100 mL) was added and extracted with chloroform (3x50 mL). The organic phase were dried over Na_2SO_4. The organic solvent was removed under reduced vacuum and proton NMR spectra showed that compound 300 was formed but in the purification steps this compound degrated completely and pure compound wasn't obtained.



299 277 300

Figure 4.38. Synthesis of compound 300

Colourless viscous liquide (0.19 g, 53% yield of the crude product).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 5.72 (d, *J* = 5.3 Hz, 1H), 5.61 (s, 1H), 3.16-3.07 (m, 2H), 2.30 (dd, *J* = 15.1, 12.2 Hz, 2H), 2.08-1.98 (m, 4H), 1.90 (s, 4H), 1.81-1.57 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H), , 1.23 (s, 3H), 1.21 (s, 3H).

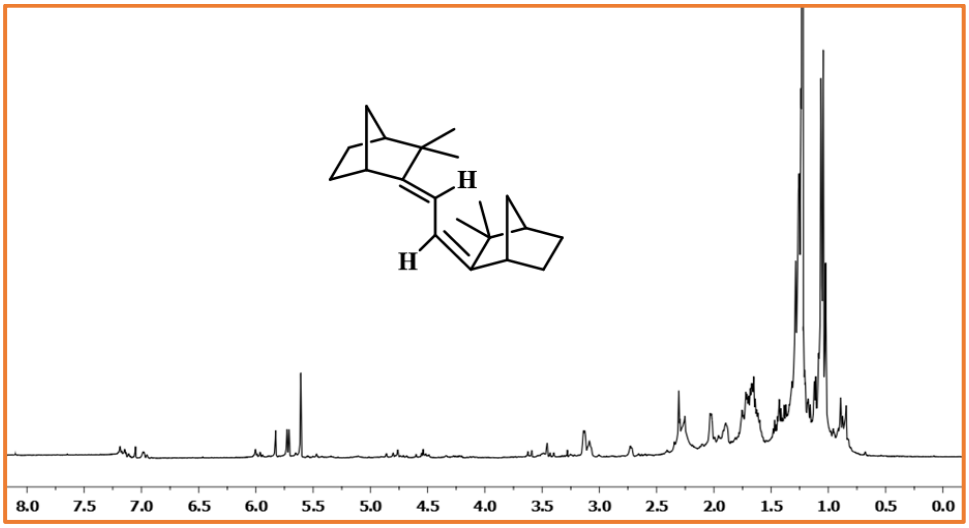


Figure 4.39. ^{1}H NMR of compound 300

4.8.3. Synthesis of ((*E*)-((1*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)-methyl)-(methyl)-sulfane (301)

Compound **277** (0.50 g, 0.7 mmole, 1 eq.) in freshly dried THF (dried over Na and benzophenone) (20 mL) was taken in a three-necked flask under nitrogen atmosphere and the reaction flask was cooled to -78°C with a dry ice acetone mixture, then *n*-butyl-lithium (2.5 M hexane solution) (2.1 mL, 5.10 mmole, 2.2 eq.) was added to the cooled and magnetically stirred reaction mixture via syringe over 10 min. The reaction mixture turned into brownish-red within a few minutes which was magnetically stirred at -78°C for 2 h. After this time, $S_2(CH_3)_2$ (0.4 mL, 4.6 mmole, 2 eq.) was added via syringe and the reaction mixture was magnetically stirred at the same temperature for

3 h. Water was added to the reaction mixture (10 mL) and extracted with diethyl ether (3x30 mL). The combined organic phases were washed with saturated brine, dried over Na_2SO_4, and the solvent was removed by rotary evaporator. It was observed that the compound 301 degraded during the purification with SiO_2 and completely pure compound could not found.

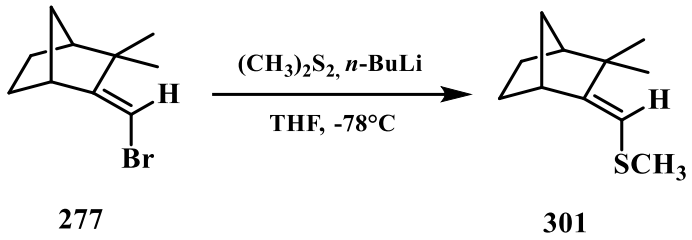


Figure 4.40. Synthesis of compound 301

Yellow liquide (0.66 g, 78% yield of the crude product).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 5.41 (s, 1H), 2.80 (d, *J* = 21.3 Hz, 1H), 2.05 (d, *J* = 7.6 Hz, 1H), 1.93 (dt, *J* = 14.2, 10.9 Hz, 2H), 1.92-1.85 (s, 1H), 1.84-1.74 (m, 1H), 1.61 (m, 2H), 1.13 (s, 6H), 0.90 (s, 3H).

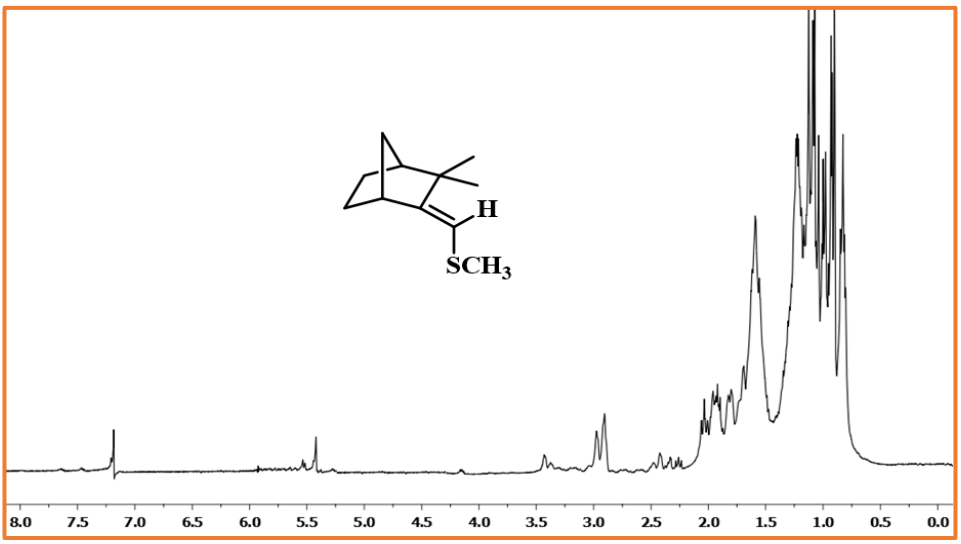
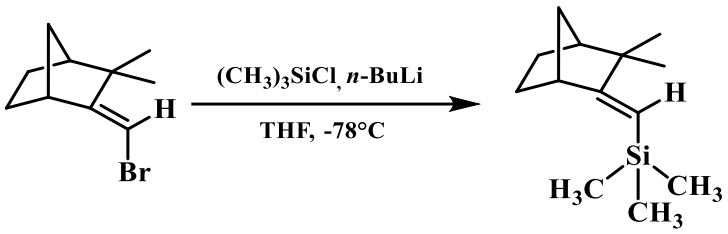


Figure 4.41. ^{1}H NMR of compound 301

4.8.4. Synthesis of ((*E*)-((1*R*,4*S*)-3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)-methyl)-trimethylsilane (302)

Compound 277 (0.4 g, 1.86 mmole, 1 eq.) was dissolved with 30 mL of freshly distilled THF (distilled over Na) in a three-necked reactin flask under nitrogen atmosphere, and the reaction flask was cooled to -78°C with a cryostat device. The solution of *n*-BuLi (in 2.5 M hexane solution) (1.9 mL; 4.7 mmole, 2.5 eq.) was added via syringe over 2

minutes to the cooled and magnetically stirred reaction mixture. The colour of the solution turned brown-red with the addition of *n*-BuLi. The reaction mixture was magnetically stirred at -78°C for 2 hours. After, $(CH_3)_3SiCl$ (0.7 mL, 5.8 mmole, 3 eq.) was added by syringe and the reaction mixture was magnetically stirred for 2 hours. Water was added (10 mL) to the reaction mixture and extracted (4x40 mL) with diethylether. The combined organic phases were washed with water, dried over Na_2SO_4 and the solvent was removed in vacuum. The ^1H NMR spectra of crude extract showed that compound 302 was formed but it was degraded during the purification process with SiO_2.



277 302

Figure 4.42. Synthesis of compound 302

Yellowish liquide (0.4 g, 81% yield of crude product).

^1H NMR ($CDCl_3$, 300 MHz, ppm) δ_H 4.90 (s, 1H), 2.80 (d, J = 21.3 Hz, 1H), 2.05 (d, J = 7.6 Hz, 1H), 1.93 (m, 1H), 1.92-1.85 (m, 1H), 1.61 (m, 2H), 1.13 (m, 2H), 0.90 (s, 6H), 0.06 (s, 9H).

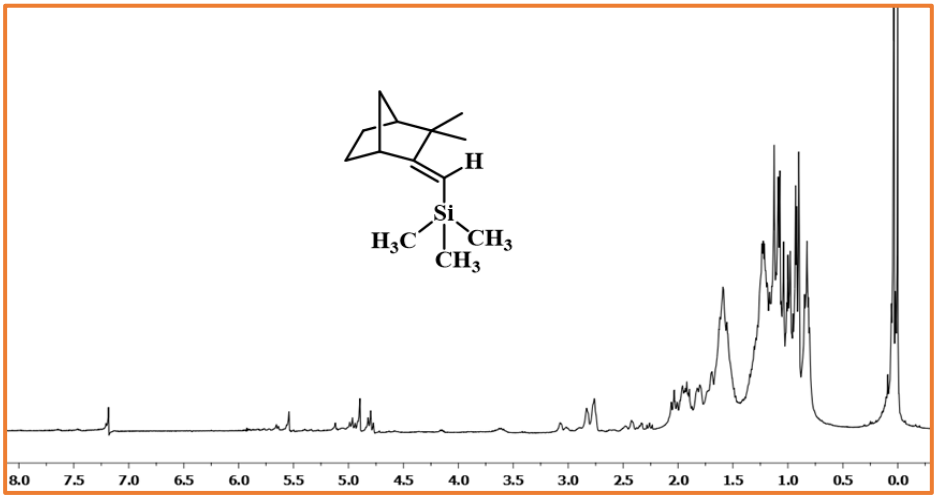


Figure 4.43. ^1H NMR of compound 302

4.9. Polarimetry Analysis

The synthesized compounds were dissolved in dichloromethane and 3 mL (3 mg/mL) of solution was taken in the polarimeter cell and plane polarized was created via passing ordinary light through a polarizing devise and rotation of the planed polarized light of all the compounds were noted and specific rotation were calculated by the following equation number 1 and showed in Table 4.1

$$[\alpha]^{T}_{\lambda} = (\alpha / c.\ \rho).100 \quad \text{..... (1)}$$

$[\alpha]^{T}_{\lambda}$ = Specific rotation

T = Temperature

λ = Wavelength of polarimeter light

α = Obtained flip angle

C = Concentration (1 g/100 mL) [Concentration = 1 = 1000 mg/mL or 30 mg/mL]

ρ = Length of the polarimeter cell (dm)

Table 4.1. Specific rotation of the synthesized compounds

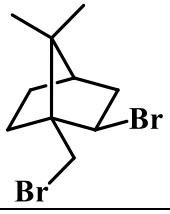
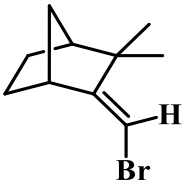
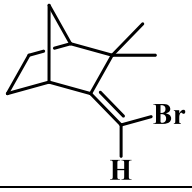
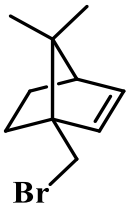
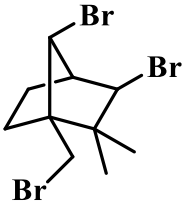
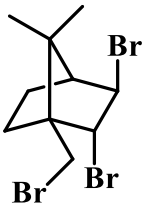
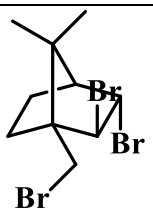
Com. no.	Compound structures	Obtained flip angle (α)	Concentration (C) 10 mg/mL (1) 5 mg/mL (0.5)	Length of the polarimeter cell (3.5 mL) (ρ)	Temperature (25 °C) and wavelength. (T and λ)	$[\alpha]_{\lambda}^{t}$
276		(-) 0.07	30 mg/3 mL	0.5 dm	589 nm	(-)14
277		(+) 0.08	30 mg/3 mL	0.5 dm	589 nm	(+)16
278		(+) 0.02	30 mg/3 mL	0.5 dm	589 nm	(+)4
279		(+**)** 0.07	30 mg/3 mL	0.5 dm	589 nm	(+)14
280		(-) 0.02	30 mg/3 mL	0.5 dm	589 nm	(-)4
281		(-) 0.02	30 mg/3 mL	0.5 dm	589 nm	(-)4
282		(+) 0.01	30 mg/3 mL	0.5 dm	589 nm	(+)2

Table 4.1. (Continued) Specific rotation of the synthesized compounds

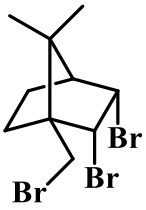
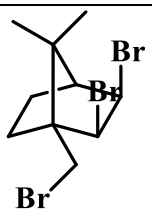
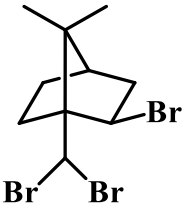
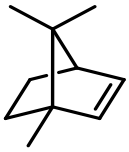
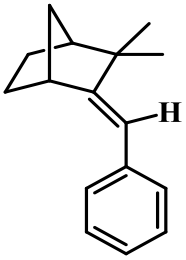
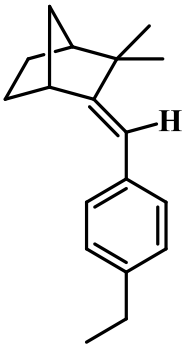
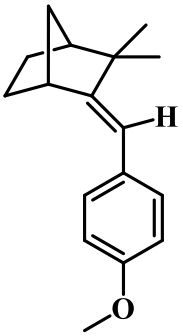
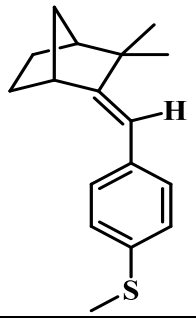
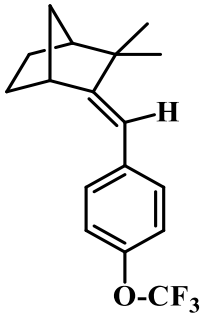
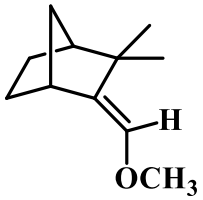
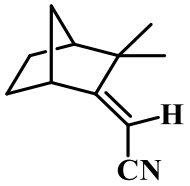
283		(+) 0.01	30 mg/3 mL	0.5 dm	589 nm	(+)2
284		(-) 0.03	30 mg/3 mL	0.5 dm	589 nm	(-)6
285		(-) 0.02	30 mg/3 mL	0.5 dm	589 nm	(-)4
286		(+) 0.07	30 mg/3 mL	0.5 dm	589 nm	(+)14
288		(+) 0.25	30 mg/3 mL	0.5 dm	589 nm	(+)50
290		(+) 0.24	30 mg/3 mL	0.5 dm	589 nm	(+)48
292		(+) 0.04	30 mg/3 mL	0.5 dm	589 nm	(+) 8

Table 4.1. (Continued) Specific rotation of the synthesized compounds

294		(+) 0.15	30 mg/3 mL	0.5 dm	589 nm	(+)30
296		(+) 0.18	30 mg/3 mL	0.5 dm	589 nm	(+)36
297		(+) 0.03	30 mg/3 mL	0.5 dm	589 nm	(+)6
298		(+) 0.10	30 mg/3 mL	0.5 dm	589 nm	(+)20

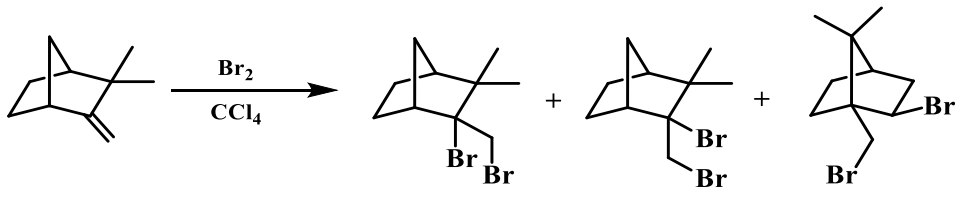
5. RESULT AND DISCUSSIONS

Bicyclic compounds are often used to produce rearrangement products in halogenation reactions via Wagner-Meerwein rearrangement (Tutar et al., 1996) and products can be derived from classical or non-classical carbocations. In this study, the skeletal rearrangement of compound 2 was inhibited by using 650 W of light and obtained non-rearrangement compounds 274 and 275 by radical bromination. Although, they produced the norbornane rearrangement product 276 through non-classical carbocation formation during purification with silica but this research enabled to repair the structure by the elimination of one bromine atom from the norbornane skeleton in the presence of pyridine or aniline or DBU or TEA and obtained the monobrominated alkenes 277 and 278.

5.1. Mechanism

5.1.1. Photobromination of (+)-camphene 2

The bromination of (+)-camphene 2 was carried out at 77°C and 250 W of light in presence of CCl_4. On the basis of the ^1H NMR spectral analysis, it was observed that reaction mixture composed of three products 274-276, two non-rearrangement di-brominated compounds 274 and 275 with one unexpected rearrangement dibrominated compound 276 (Figure 5.1).



2		274	275	276
	0°C	-	-	99%
	77°C, 250 W	20%	10%	70%
	77°C, 650 W	80%	20%	-
	77°C, 900 W	80%	20%	-

Figure 5.1. Bromination reactions of compound 2 at moderate and high temperature

Bromination of (+)-camphene (2) was irradiated at 250 W and targeted two non-rearrangement brominated products (274 and 275) were obtained but rearrangement product (276) also produced in higher yield with 70%. To avoid the rearrangement, the reaction was carried out in the interior light photobromination system developed by our group, cooled from its lower part and through the reflux system (Figure 3.1). Then, a new reactor was designed with the lighted-up and reflux system of the photobromination (Figure 3.1). In this system, temperature and intensity of light can be controlled to avoid the skeletal rearrangement of the bicyclic compounds during bromination process. In the new reactor, the reaction was carried out in different conditions and attempted at 100 W, 150 W, 200 W, 300 W, 400 W and then 500-1000 W, but the rearrangement product was observed in this reaction below 650 W of light and non-rearrangement products were obtained at above 650 W of light. When the intensity of the light was increased to 650 W, it was accomplished to stop the ring reagulation of bicyclic system and the reaction furnished the expected isomeric two non-rearrangement products 274 and 275 as a mixture in yields of 80% and 20%, respectively (Figure 4.1). Moreover, when the light intensity was increased to 900 W, non-rearrangement products 274 and 275 were obtained as a mixture in unchanged yields of 80% and 20%, respectively.

In terms of mechanism analysis, it was observed that the rearrangement product 276 can be produced due to the intermediate non classical carbocation IV followed by Wagner-Meerwein rearrangement in presence of comparatively lower intensity of light below 650 W (Figure 5.2).

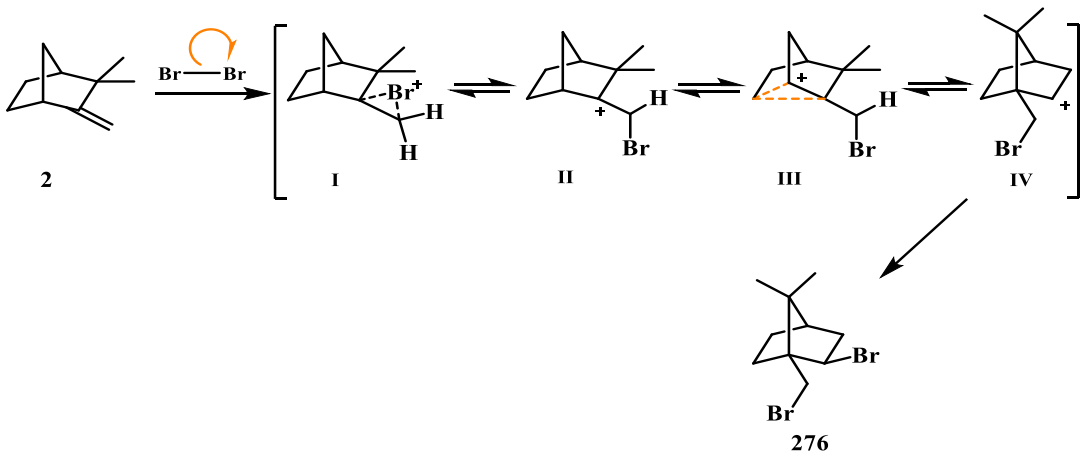


Figure 5.2. Mechanism for the formation of dibromide compound (276) at ionic condition

On the other hand, at 77°C and 650 W of light or above, radical intermediate V led to the formation of non-rearrangement products 274 and 275 (Figure 5.3). In case of the bromination of bicyclic (+)-camphene (2) at 650 W, the high intensity of light plays an important role in the synthesis of expected high yield non-rearrangement *endo*-product 274 with 80% and *exo*- product 275 with 20%. The light intensity raised at 650 W inhibited the formation of non-classical carbocation III, instead led to form radical intermediate V (Figure 5.3), which was facilitated to the expected non-rearrangement products 274 and 275.

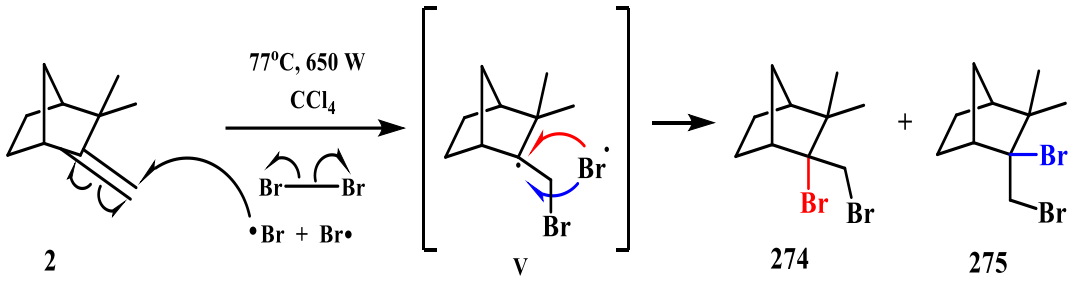


Figure 5.3. Mechanism for the formation of dibromide compounds at radical condition

5.1.2. Rearrangement of dibrominated camphene to dibromobornane (276)

At high temperature bromination, (+)-camphene (2) formed *endo* and *exo* di-brominated products (274 and 275) in presence of CCl_4 and 650 W of light in radical mechanism but they transformed into a single rearrangement product 276 within 2 to 3 hours at room temperature in presence of CH_2Cl_2 via the Wagner-Meerwein rearrangement. Additionally, the same result was obtained during the separation and purification process with silica gel column chromatographic technique (Figure 5.4).

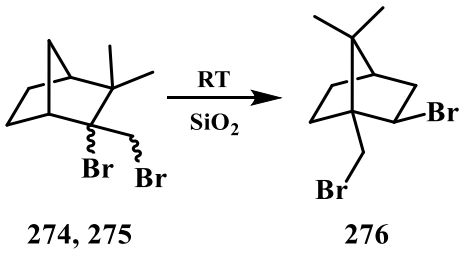


Figure 5.4. Formation of dibromobornane (276)

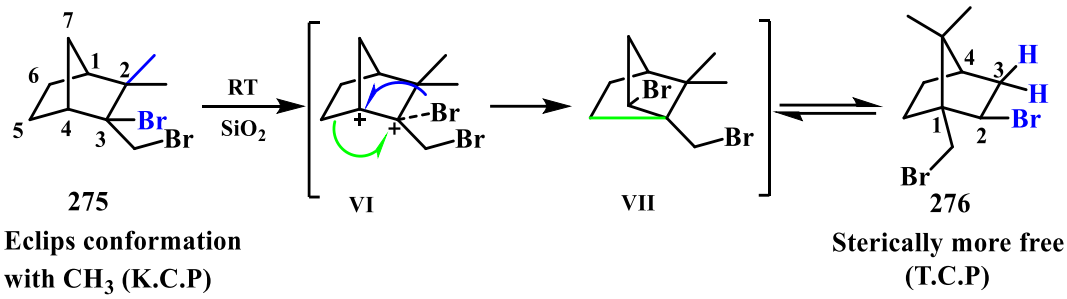


Figure 5.5. Mechanism for the formation of dibromobornane (276)

In terms of mechanism analysis (Figure 5.5), bromine was loosely connected with carbon number 3 of compound 275, because tertiary carbocation is more stable than secondary or primary and one methyl group at carbon number 2 of compound 275 and loosely attached bromine atom of carbon number 3 are in eclipse conformation. Besides, compound 276 is sterically freer than compound 275 because bromine atom binds with carbon number 2 is in eclipse conformation with hydrogen of carbon number 3 of compound 276. Kinetic controlled products 274 and 275 were formed at high temperature which were followed Wagner-Meerwein rearrangement in the solvent and produced thermodynamic controlled product 276 at room temperature.

5.1.3. Formation of monobrominated alkenes (277 and 278)

Monobrominated alkenes 277 and 278 were produced by elimination reactions from the mixtures of dibrominated alkanes (274 and 275) in the presence of the bulky base potassium *tert*-butoxide, but a related problem was the formation of products 279 with compounds 277 and 278 simultaneously (Figure 5.6). The monobrominated compound 279 was mainly derived from the dibrominated bornane 276 which was produced by the Wagner-Meerwein rearrangement during the preparation of the reaction. This phenomenone was associated with a decrease in the yield of monobrominated compounds 277 and 278, and needed for the separation of the unexpected rearrangement product 279. Compounds 274 and 275 are either partially or completely converted to dibrominated bornane 276 under any conditions due to their stability and this phenomenone was most concerning issues for further synthesis.

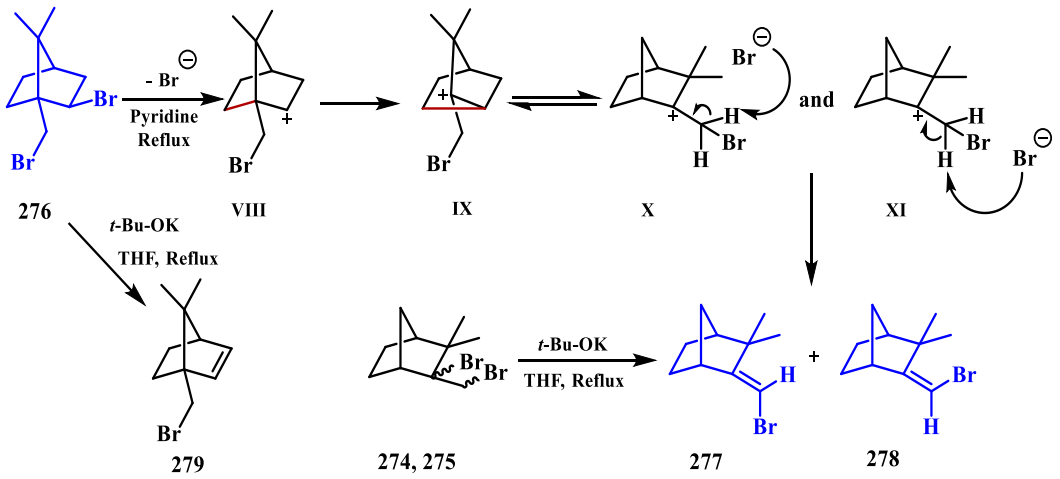


Figure 5.6. Mechanism for the formation of monobrominated alkene (277 and 278)

Rearrangement of compounds 274 and 275 with at room temperature and in the purification process disrupts the production of starting materials for further synthesis. However, after many experiments with different types of bases, a new strategy was addressed for producig the monobrominated alkenes 277 and 278 directly from the rearrangement product 276 in high yields in the presence of aniline or pyridine or DBU.

In terms of mechanism analysis, compound 276 was converted to secondary carbocation (VIII) through the dissociation of one bromine atom from their structural skeleton, and one bond was transferred to stabilize the secondary carbocation. Then, tertiary carbocation (IX) was formed in the presence of aniline or pyridine or DBU at reflux temperature. Furthermore, *syn* and *anti* HBr elimination of transition states (X) and (XI) produced *E* and *Z* monobromoalkenes 277 and 278 respectively. The elimination reaction proceeded stereo specifically and stereo selectively, demonstrating that the rearrangement product 276 undergoes a Wagner-Meerwein rearrangement and produces monobromoalkenes 277 and 278 (Figure 5.6). Apart from this, compound 276 did not undergo Wagner-Meerwein rearrangement in the presence of potassium *tert*-butoxide and followed the general mechanism of elimination reaction. Rearrangement product 276 produced compound 279 in the presence of the bulky base potassium *tert*-butoxide which was dissolved in THF and heated at reflux temperature.

5.1.4. Formation of tribrominated bornane (280) at low and high temperature

The bromination of compound 279 was carried out in two different conditions at 0°C in dark in CH_2Cl_2 and 77°C in light with CCl_4 as a solvent (Figure 5.7 and 5.8). At low temperature (0°C), it produced only rearrangement compound 280 due to the formation of non-classical carbocation XII (Figure 5.7), while six products were obtained at reflux temperature (77°C). Here, four tribrominated bornane 281-284 presumed to be formed by radicalic addition via XIV and XV respectively with very small amount (1%) of of non-rearrangement products 277 and 278 (Figure 5.8).

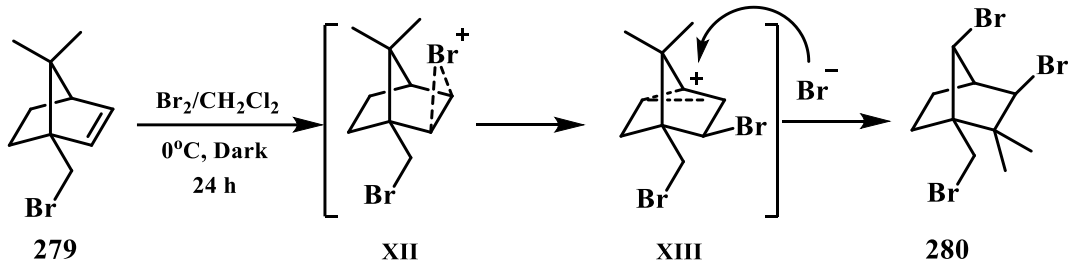


Figure 5.7. Mechanism for the formation of tribrominated bornane (280) in dark at 0°C

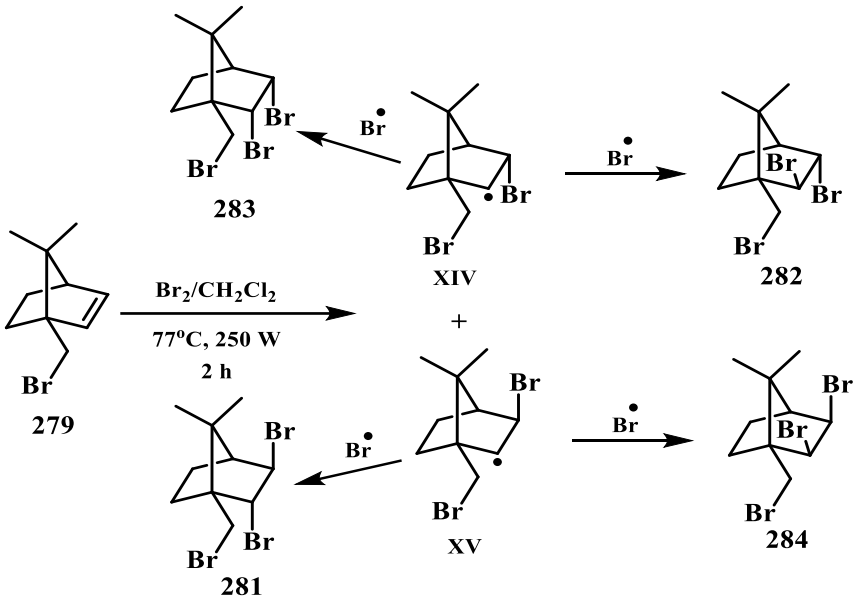


Figure 5.8. Mechanism for the formation of tribrominated bornane at reflux temperature

5.1.5. Bromination of compound 277 at low temperature

The bromination of compound 277 was carried out at -10°C in presence of molecular bromine and carbon tetrachloride. In terms of mechanism analysis, it was assumed that compound 285 was produced due to formation of nonclassical carbocation XVI shown

in Figure 5.9 and it was observed that molecular bromine directly took part in the reaction at -10°C and tri-brominated compound 285 was obtained.

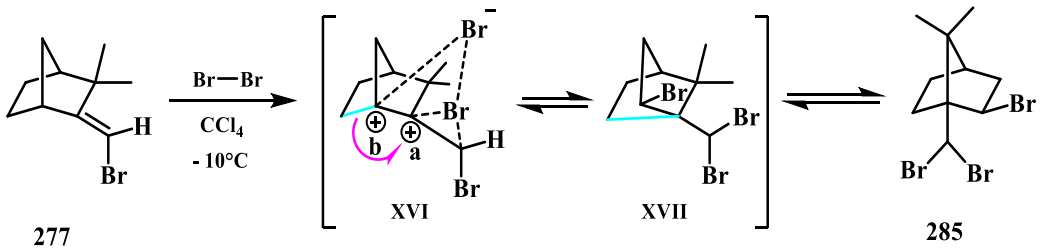


Figure 5.9. Formation mechanism of compound 285

5.1.6. Suzuki-Miyaura coupling reactions of monobromocamphene (277)

The attempted Suzuki-Miyaura cross-coupling of monobromocamphene 277 (1.0 eq.) with a mixture of unsubstituted phenyl and 4-substituted (4-ethyl-, 4-methoxy-, 4-thiomethyl-, and 4-trifluoromethoxy-) phenylboronic acids (2.0 eq.) and 2 M K_2CO_3 in ethanol in the presence of $Pd(PPh_3)_4$ afforded coupling products 288, 290, 292, 294 and 296 of monobromocamphene in a satisfactory yields (33-74%), (Table 5.1), (Rohand et al., 2006; Ökten, 2019; Yılmaz et al., 2023).

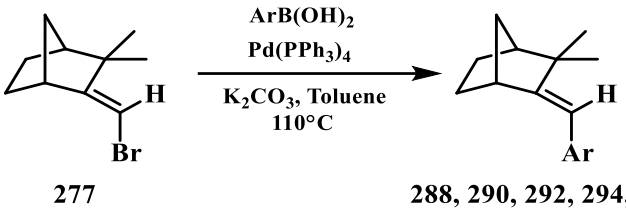
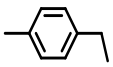
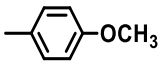
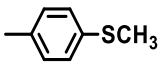
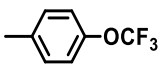


Figure 5.10. Suzuki coupling reaction of compound 277

Table 5.1. The yields of Suzuki-Miyaura coupling compounds

Product	Ar	Yield (%)
288		60
290		74
292		73
294		48
296		33

5.1.7. Synthesis of the methoxy (297) and cyano (298) derivatives of monobromocamphene (277)

Monobromocamphene (277) was treated with MeONa in the presence of CuI in boiling DMF for the synthesis of methoxy-camphene (297) according to reported procedure (Ökten et al., 2013; Ökten et al., 2015) (Figure 5.11). The crude product was applied to short column using SiO_2 with hexane/chloroform to isolate pure product. Methoxy camphene 297 was isolated as a pure compound in a yield of 54%. Finally, monobromocamphene 277 was treated with CuCN in boiling DMF. The nucleophilic substitutions of monobromocamphene 277 resulted in the formation of cyanocamphene 298 (Figure 5.11). The crude product was applied to short column using SiO_2 with hexane/chloroform to isolate pure product. Cyanocamphene 298 was isolated as a pure compound in a yield of 83%.

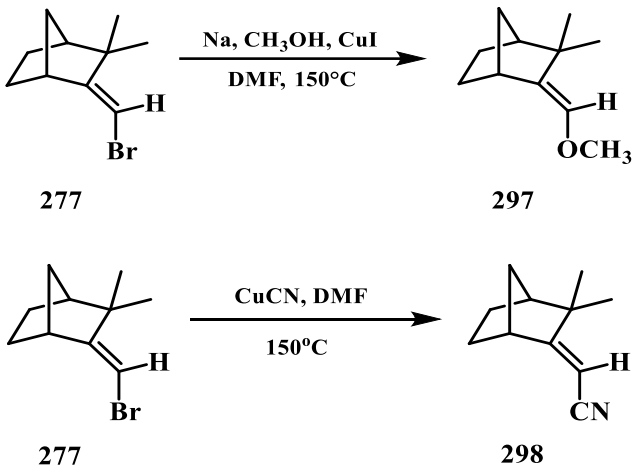


Figure 5.11. Nucleophilic substitution reaction of monobrominated camphene compound (277)

5.2. Structural Assignment of the Synthesized Compounds

The results of reported (Titova et al., 1995) and this study indicate that camphene and its isomers show different behaviour at various reaction conditions like other bicyclic compounds. The bromination of camphene (1) produced three rearrangement products with very small amount arrangement product at 0°C in CH_2Cl_2 but spectral prove of them was missing (Titova et al., 1995). This thesis displayed that the bromination of (+)-camphene (2) produced the rearrangement product 276 and non-rearrangement products 274 and 275 at 77°C under 250 W of light in presence of CCl_4. Moreover, This research accomplished to stop the skeletal rearrangement of (+)-camphene (2)

and only non-rearrangement products 274 and 275 were obtained from bromination of (+)-camphene (2) at 77°C under 650 W of light in presence of CCl_4.

In the bromination reaction of compound 2 under the condition of 77°C and 250 W of light, it was ascertained that the proportion of products due to non-classical carbocation III to products via radicals V is 7:3. In the case of high-intensity light (650 watt) photobromination, it was observed that the product formation ratio changed to 1:0 (radical products : non-classical carbocation products). These results approve that radical intermediates are more favourable than ionic intermediates at higher intensity of light.

5.2.1. Structural assignment of mono-brominated (+)-camphene based compounds

All isolated brominated (+)-camphene derivatives were characterized by ^{1}H and ^{13}C NMR spectral data and extended resonance analysis by comparing related spectral data from some published articles (Smith, 1985; Çakmak et al., 1990; Balci et al., 1992; Daştan et al., 1994; Tutar et al., 1996; Daştan et al., 1997; Daştan et al., 2005; Kazaz et al., 2005; Gültekin et al., 2008).

According to the Karplus rules in [2.2.1] heptane system (Tutar et al., 2002), the dihedral angle between bridge proton H-1 and H_{syn}-7 and H-1 to H_{anti}-7 are 90° and 40°, respectively, hence we obtained coupling constant (*J*) of bridge proton $H_{17syn\text{-}anti}$ is 1.8-2.8 Hz for compounds 277 and 278. In ^{1}H NMR spectral analysis, two protons attached to C-10 of (+)-camphene (2) give two singlets for each at δ_H 4.72 and 4.49 ppm (Figure 4.2). After base elimination to remove one bromine atom from compounds 274 and 275, H-10 was observed as a singlet at more downfield at δ_H 5.63 and 5.83 ppm for compounds 277 and 278, respectively. We also obtained multiplet for two alkene proton in the more downfield shift between δ_H 5.89-6.09 ppm, attached with carbon number 2 and 3 of the compound 279. In addition, downfield ^{13}C NMR chemical shift of alkene of compounds 277 and 278 at 158.0 and 161.1 ppm respectively and a long range coupling constant of J_{CH2} = 9.9 Hz at carbon ten of compound 279 indicate the successive formation of the monobrominated compounds 277, 278 and 279 (Figure 4.12). In case of dibrominated (+)-camphene based compounds, coupling constant $J_{2,3exo}$ = 4.7 Hz of compound 276 with high coupling constant values of J_{CH2} = 9.9 Hz for two hydrogen atoms at carbon ten supported the successive addition of two bromine atoms in their skeleton at carbon number 2 and 10.

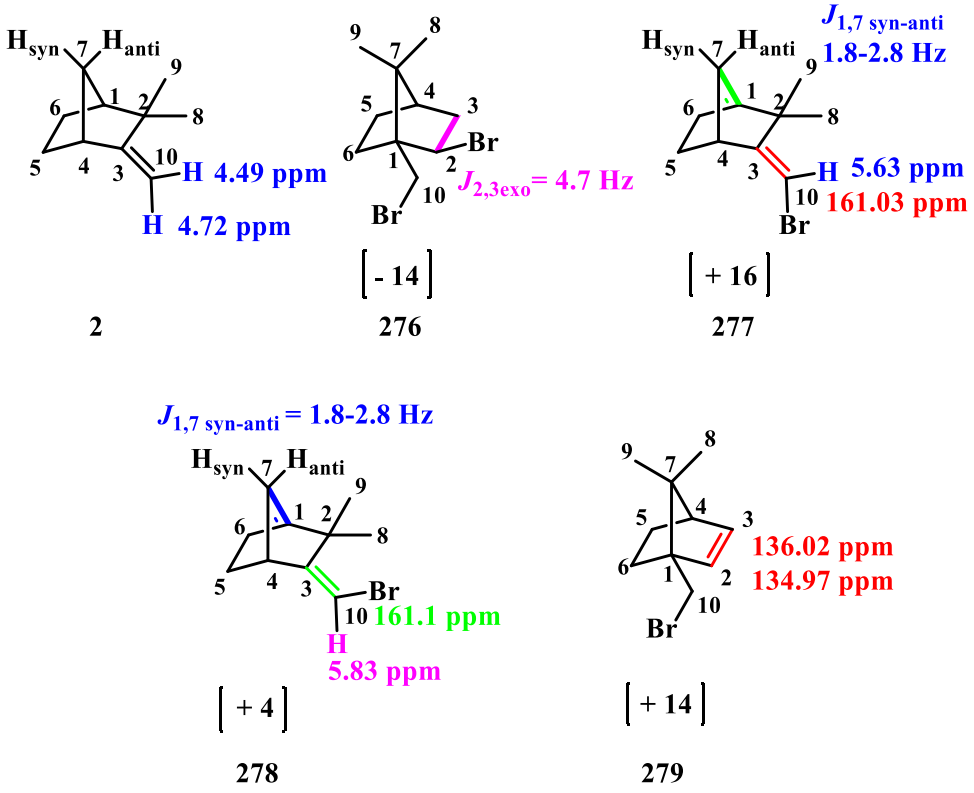


Figure 5.12. Structural assignment of monobrominated (+)-camphene based compounds

In case of polarimetry analysis, dibrominated compound 276 rotated the plane polarized light to the anti-clockwise in (-)14°, interestingly, after elimination of one bromine atom from compound 276, monobrominated compound 279 was obtained which rotated the plane polarized light to the clockwise direction in (+)14°, besides, monobrominated alkene 277 and 278 rotated the plane polarized light to the right side in (+)16° and (+)4° respectively.

5.2.2. Structural assignment of tri-brominated (+)-camphene based compounds

In addition to this, $J_{2,6exo}$ = 2.8, $J_{3,4exo}$ = 4 and $J_{3,4exo}$ = $J_{2,6exo}$ = 0 of compounds 281 and 282 respectively with high coupling constant of carbon number ten connected protons supported that, two *endo* orientated and two *exo* orientated bromine atoms are connected to the C-2 and C-3 in the structure of 281 and 282 respectively (Figure 5.13). It was very difficult to the determination of exact structure of the compound 280 by proton and carbon NMR spectral data, finally, the skeletal structure of 280 have been determined on the basis of X Ray analysis (Figure 5.14).

On the other hand, for the tribrominated (+)-camphene based derivatives, $J_{3,4exo}$ = $J_{2,6exo}$ = 0 of compounds 283 and 284, and downfield chemical shift of the related

proton at C-2 and C-3 positions and high range coupling constant of two protons at C-10 addressed to the *exo* and *endo* orientation of bromine atoms at position C-3 and C-2 respectively of compound 283, in contrast, *endo* and *exo* orientated bromine atoms are connected with C-3 and C-4 position respectively in compound 284 (Figure 5.13).

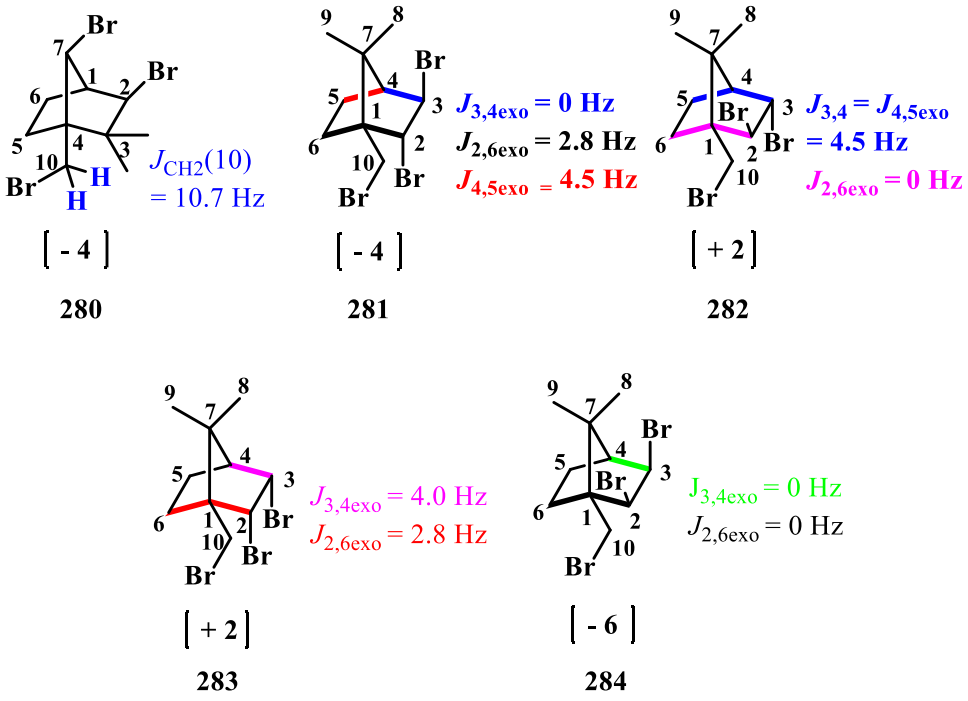


Figure 5.13. Structural assignment of tribrominated (+)-camphene based compounds

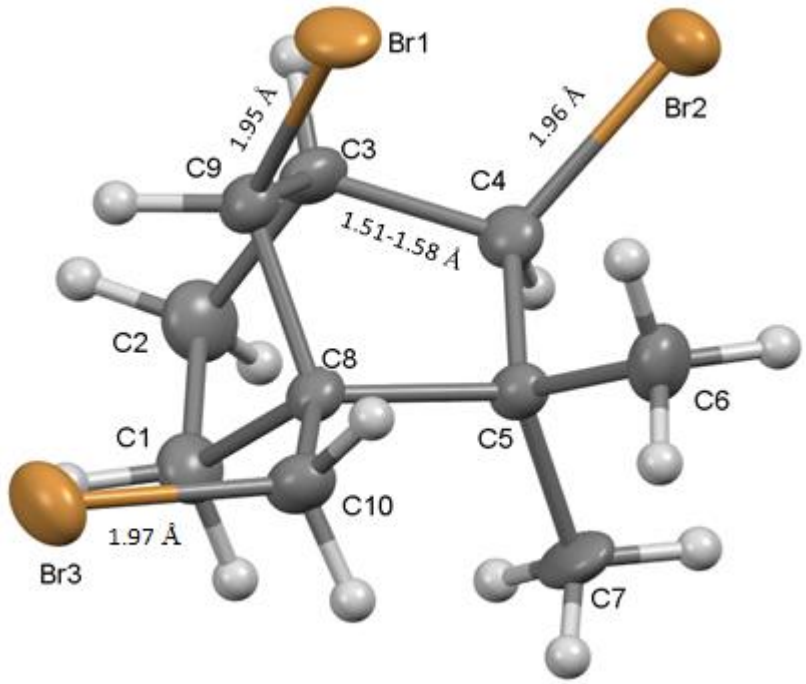
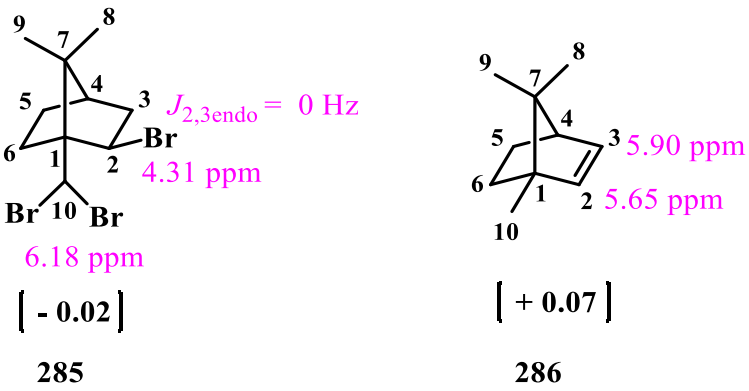


Figure 5.14. X Ray structure of compound 280 drawn at 0° angle

The polarimetry analysis of tribrominated compounds showed excellent result depending on the *exo* and *endo* orientation of bromine atoms to the skeletal structure of bicyclic compounds showed different result. Compound 281 rotated the plane polarized light to anti-clockwise direction in (-)-4°, whereas, it was clockwise direction (+)-2° for compound 282. Likewise, compound 283 rotated the polarized light to the clockwise direction in (+)-2° but the specific rotation was anti-clockwise in (-)-6° for the compound 284.



[- 0.02] **[+ 0.07]**

285 **286**

Figure 5.15. Structural assignment of tribrominated (+)-camphene based compounds

The downfield chemical shift at δ_H 4.31 ppm of the proton of the carbon number C-2 and $J_{2,3endo}$ = 0 Hz indicated the successive formation of compound 285, besides, two alkene protons showed downfield chemical shift at δ_H 5.65 ppm and δ_H 5.90 ppm at carbon number C-2 and C-3 are significant structural evidence of alkene for compound 286.

5.2.3. Structural assignment of boronic acids coupling compounds of (+)-camphene

The ^{1}H NMR spectrum of phenyl substituted (+)-camphene compound 288 is examined, the aromatic multiplet signal in the range of δ_H 7.25-7.40 ppm is the evidence for the existence of the phenyl group. The ^{13}C NMR of this compound 288 also supported the proposed structure, hence, four carbon signals in the aromatic region (two signals indicate two carbon) compared to the starting material 2. The ^{1}H NMR spectrum of the 4-ethylphenyl substituted (+)-camphene 290 compound was found to overlap with other aliphatic signals in the range of δ_H 1.30-1.23 ppm, unlike the ^{1}H NMR of the phenyl substituted (+)-camphene 288. Additionally, in ^{13}C NMR, four more carbon signals in the aromatic region (two signals indicate two carbon) and two more carbon signals in the aliphatic region are evidence that the 4-ethylphenyl group

is attached to the (+)-camphene compound 290. In the experiment with 4-methoxyphenylboronic acid, the 4-methoxyphenyl group was clamped to the (+)-camphene nucleus of 292. This is evidenced by the doublet (J = 7.5 Hz) signal at δ_H 7.27 and 6.92 ppm and the singlet methoxy signal at δ_H 3.82 ppm in the ^{1}H NMR spectrum. In addition, the carbon signal at δ_C 55.4 ppm in ^{13}C NMR indicates the presence of the methoxy group in the structure. Similarly, the structure characterization of 4-thiomethylphenyl (+)-camphene 294 was performed by ^{1}H NMR, and the thiomethyl signals resonated as singlet at δ_H 2.51 ppm. In the ^{13}C NMR spectrum, the carbon signal at 16.01 ppm belongs to the -SCH_3 carbon. The last of the studies with Suzuki coupling reactions was done with 4-trifluoro-methoxyphenyl-boronic acid. When the ^{13}C NMR spectrum of this compound 296 was examined, cleavages were observed in the carbon signals in the aromatic region with the effect of the fluorine atom in the -OCF_3 group. In addition, in the ^{19}F NMR spectrum, the fluorine atom resonated at -62.1 ppm (Figure 5.16).

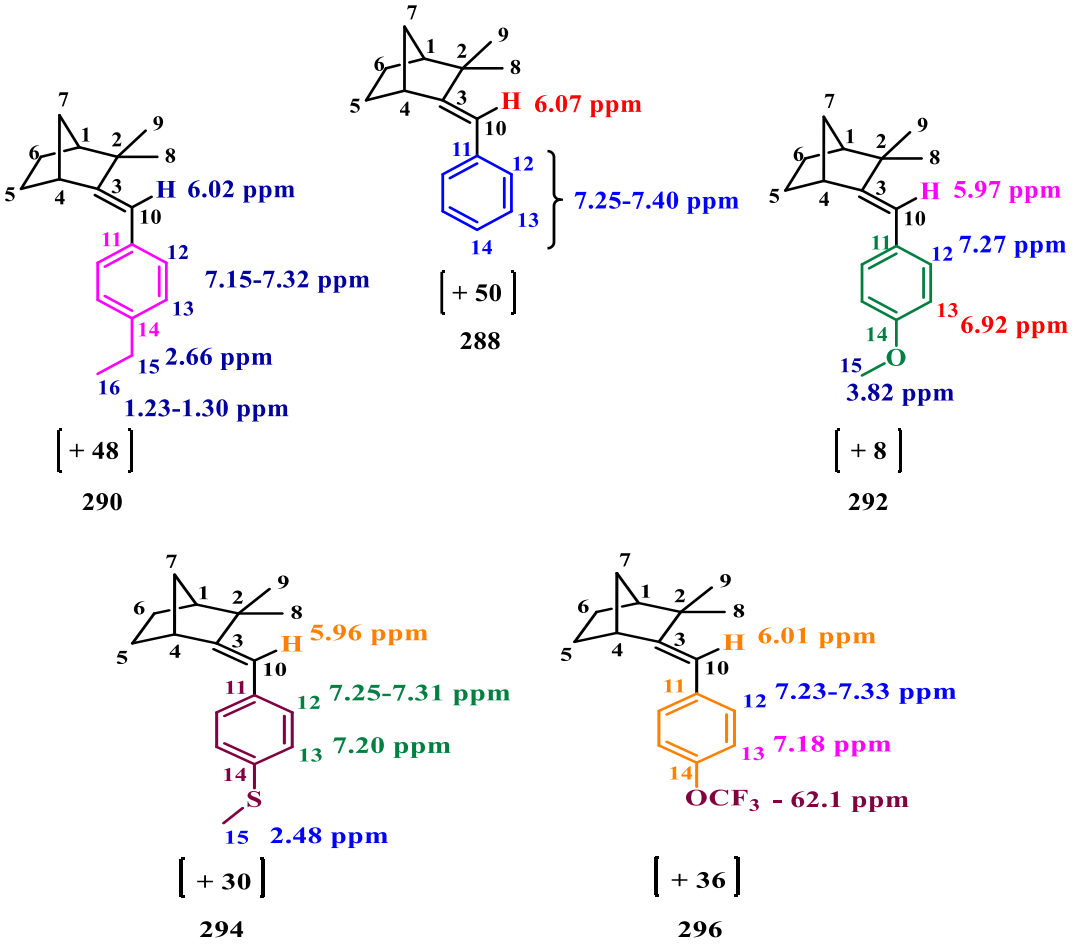


Figure 5.16. Structural assignment of boronic acids coupling compounds of (+)-camphene

All the coupling compounds 288, 290, 294 and 296 rotated the plane polarized light to the clockwise direction in different extend between (+)-30-50°, except compound 292 which rotated the polarized light in (+)-8° to the clockwise direction.

5.2.4. Structural assignment of methoxy (+)-camphene and cyano (+)-camphene compounds

This research obtained ^{1}H NMR spectrum of methoxy group at δ_H 3.52 ppm (singlet) for the methoxy substituted (+)-camphene compound 297. The methoxy signal shows that the targeted compound has been formed, additionally, the carbon signal at δ_C 59.6 ppm in ^{13}C NMR indicates the presence of the methoxy group in the structural skeleton of compound 297. Besides, the characteristic -CN carbon signal at δ_C 117.7 ppm in ^{13}C NMR of cyano-substituted (+)-camphene compound 298 indicate the presence of the nitrile group in the structure of 298, as well as it showed absorbtion stretching of –CN group at 2217 cm^{-1} in IR spectrum (Figure 5.17).

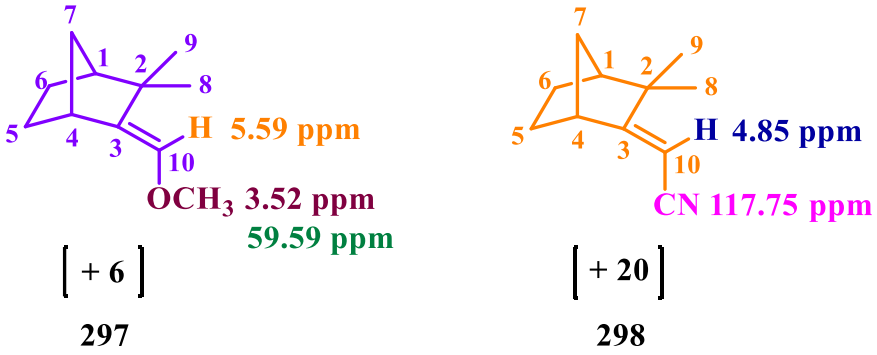


Figure 5.17. Structural assignment of methoxy (+)-camphene and cyano (+)-camphene compounds

Cyanide derivatives of (+)-camphene rotated the plane polarized light more in clockwise direction than the methoxy derivatives. The compound 298 rotated the polarized light to the clockwise direction in (+)-20°, whereas it was (+)-6° clockwise for compound 297.

In the scope of this thesis, five types (A-E) of structural diversity were obtained among all synthesized compounds. The chemical shifts of hydrogen atoms can be shifted to downfield regions due to the γ-gauche effect, while the chemical shifts of carbon atoms attached to these hydrogens might be shifted to upfield regions (Gheorghiu and Olteanu, 1987; Çakmak and Balcı, 1989; Menzek et al., 1995). The presence of single bromine atom in the A type of structure causes the γ-gauche effect of the compounds 276, 297 and 280-284 resulted the down field chemical shift as a duplet signal of every

H^y and H^z atom between 3.5 to 4.3 ppm. In case of B type structure of compounds 277, 278, 288, 290, 292, 294, 296, 297 and 298 the singlet signal of H^p atom is obtained in more downfield chemical shift between 4.8 to 6.2 ppm than A type compounds shown in (Figure 5.12-5.17). Compounds 277 and 278 of B type category are two isomers and the bromine attached carbon of them showed downfield chemical shift in between 158 to 162 ppm, while the hydrogen attached carbon of A type compounds showed more up field chemical shift in ^{13}C NMR (Figure 5.12 and 5.13).

Interaction constants (^3J) of hydrogens in cyclopropane rings are important for determining the structure of compounds such as two isomeric products, as $^3J_{cis}$ is higher than $^3J_{trans}$ (Menzek and Balcı, 1993; Menzek, 2000; Balcı, 2005). The higher and lower interaction constants (^3J) should be $^3J_{cis}$ and $^3J_{trans}$, respectively. The coupling constant (^3J) of hydrogen atom interaction of bridged proton was also investigated for the monobrominated compounds 277 and 278 of B category shown in Figure 5.13. The coupling constant ($^3J_{cis}$) of H^m and H^a *cis*-interaction was 2.8 Hz which is higher than the coupling constant ($^3J_{trans}$ = 1.8) of *trans*-interaction of H^m and H^b of B types compounds.

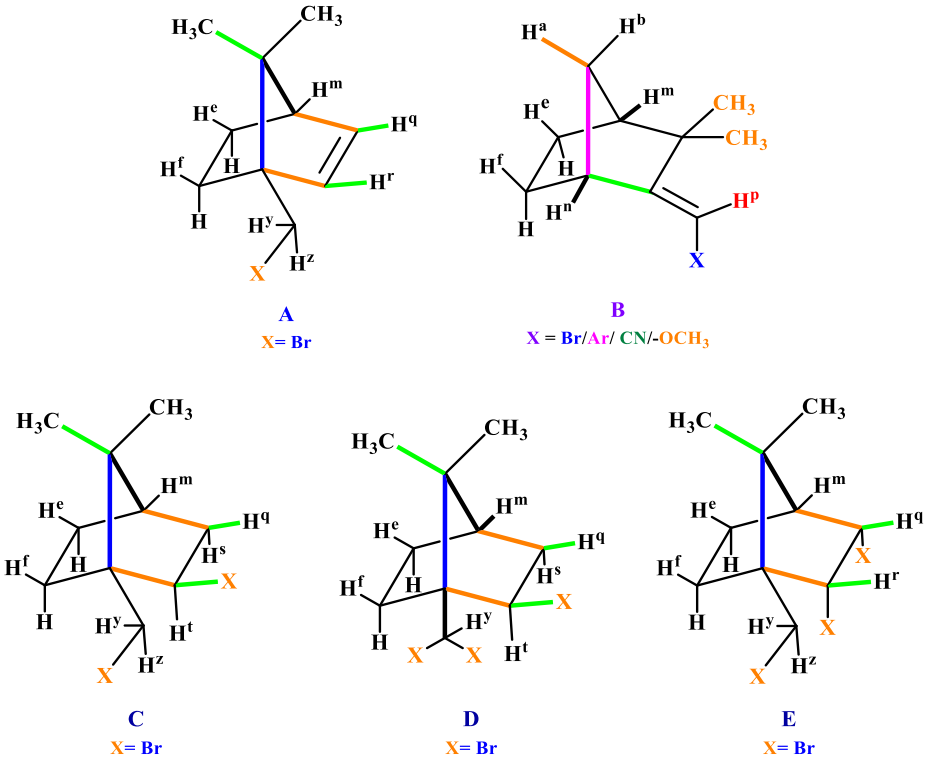


Figure 5.18. Structural skeleton of the bicyclic compounds

Apart from the bridged proton, the interaction of *exo-exo* and *endo-endo* protons of the C, D and E type compounds were also observed. In case of the connection of the bromine atom at *endo* position in the bicyclic structure, the relative *exo*-proton of the respective carbon interact with other *exo*-proton of the neighboring carbon. Likewise, *endo-endo* interaction between relative proton was also observed in terms of the connection of bromine atom in *exo* orientation. In another case, if two bromine atoms are connected with two different neighboring carbon atom in *endo* and *exo* orientation in the bicyclic ring, no proton interaction is obtained between them, rather than the proton of the neighboring carbon which can interact with other relative protons of the bicyclic ring as shown in Figure 5.12, and 5.13.

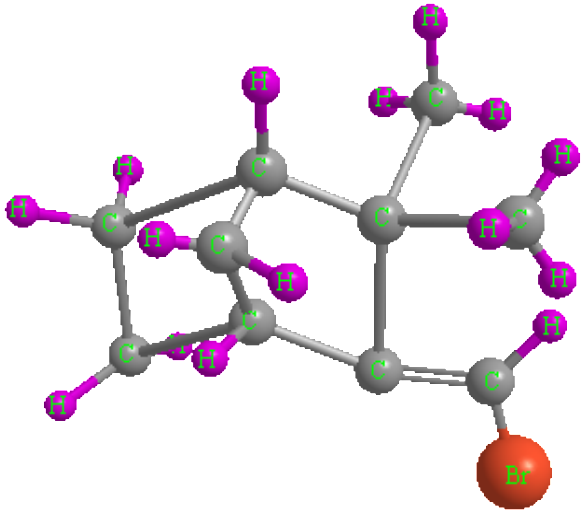


Figure 5.19. Structure of compound 277 drawn at 7° angle

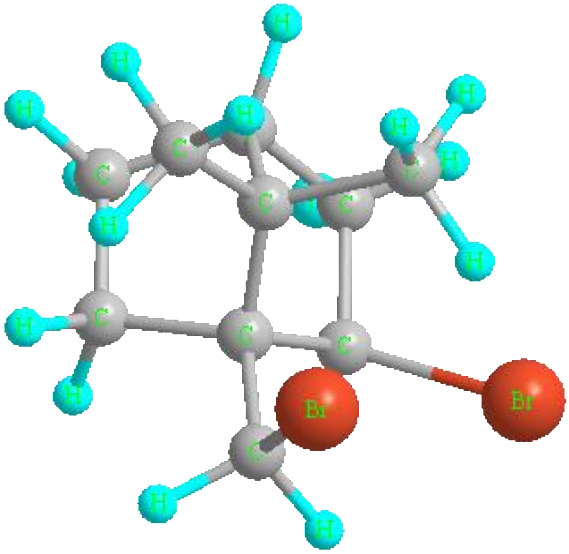


Figure 5.20. Structure of compound 276 drawn at 10° angle

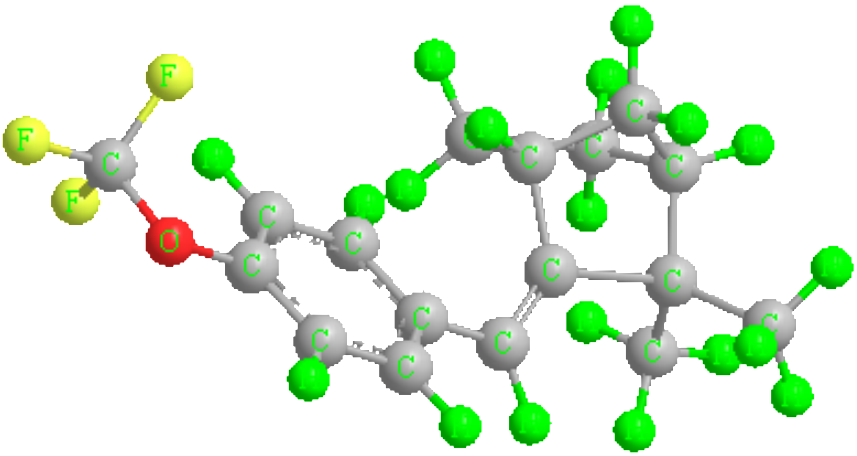


Figure 5.21. Structure of compound 296 drawn at 25° angle

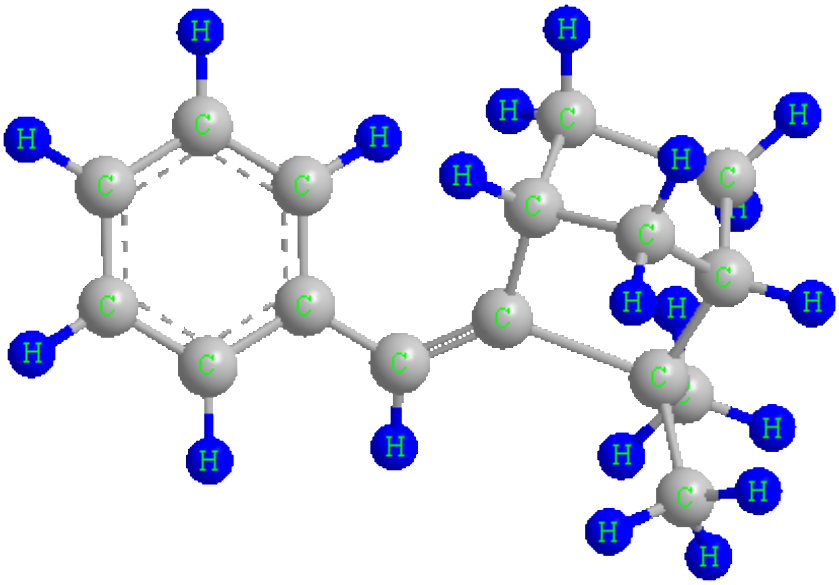


Figure 5.22. Structure of compound 288 drawn at 10° angle

The COSY spectrum of compounds 277 and 292 were taken for the more specification of the structure of initial and coupling products which cover the sturcture of the all synthesized bicyclic skeletons. In case of monobrominated alkene (277), it was observed that the proton (H-1) of carbon number C-1 is coupling with the bridzed syn-proton (H-7) of carbon number C-7. Additionally, H-4 is coupled with the proton (H-5) of carbon number C-5, besides, the coupling of H-5 and H-6 is also observed but there is no coupling of proton H-8, 9 and H-10 was observed in ^{1}H, 2D COSY NMR spectrum due to the absence of adjacent proton with them in the actual bicyclic skeleton of compound 277 (Figure 5.23).

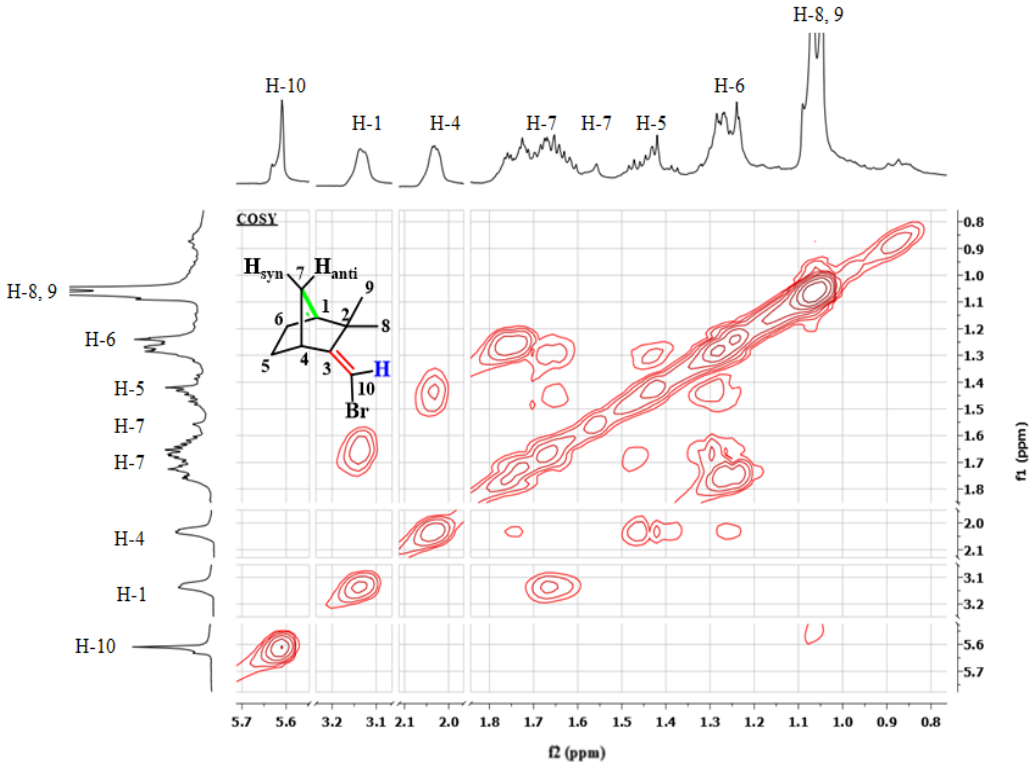


Figure 5.23. COSY NMR spectrum of compound 277

The assessment of 2D COSY NMR of the compound 292 showed the same corellated protons involved with the structure skeleton of initial reactant compound 277. In additon to this, the coupling of the corellated protons H-12 and H-13 is visualized in COSY NMR spectrum of compond 292, indicated that the succesive addition of benzene ring at carbon number C-10 of the structural skeleton of bicyclic system. Besides, there was no coupling obatined in case of the proton number H-10 and H-15 due to the absence of corellated adjacent protons with them (Figure 5.24).

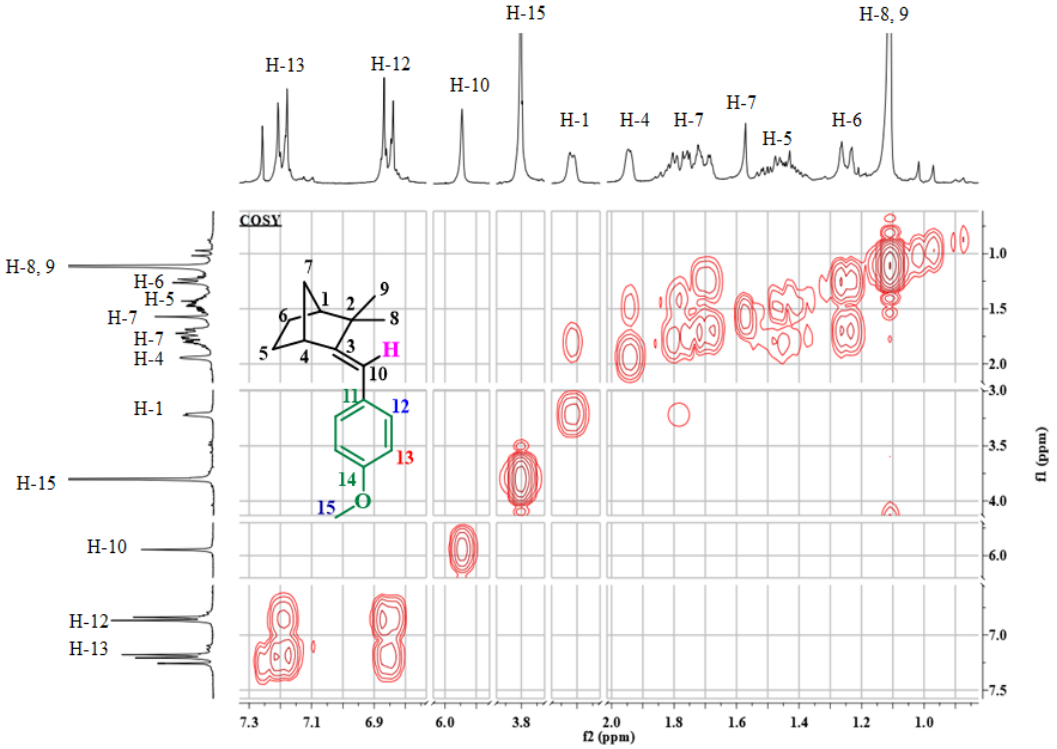


Figure 5.24. COSY NMR spectrum of compound 292

6. CONCLUSION

Many scientists from all over the world focused on the synthesis of non-rearrangement compounds from camphene and its isomers for many years. Ring regulation of the bicyclic skeletons was remained concerning for the synthesis of expected non-rearrangement chiral compounds which could be the mother component for the synthesis of many new medicinal compounds as camphene and its isomers have significant biological responses against many diseases.

This thesis mainly focused on the development of a new technique for the synthesis of high yield monobrominated compounds which would be starting materials for many medicinal compounds. These studies synthesized high yield of monobrominated compounds 276 and 277 in a novel technique involved with the re-construction of bicyclic structure resemble with the (+)-camphene (2). The invention of the new method for synthesizing high yield monobrominated compounds will add new dimension for the synthesis of camphene base analogus for future years.

Besides, this thesis included some novel (+)-camphene (2) based chiral compounds like 288, 290, 292, 294 and 296 which have the similarities with the binding side of the Pyruvate kinase, so, their derivatives would be possible drug for liver cancer, fatty liver and cardiovascular diseases because the starting material (2) was potential lipid lowering agents. In the previous research, it was observed that organocyanide derivatives are potential anticancer agents, when (+)-camphene is still lipid lowering agent and connecting the cyanide group as well as sides chain with this natural bioactive molecule may have contain potential medicinal values which need future research.

Additionally, this thesis also included mono-, di- and tri-brominated rearrangement compounds which were synthesized in this study may have medicinal properties, though the rearrangement compounds which are derived from camphene may have toxic effects due to their stable structural skeletons. Previous studies showed that many brominated derivatives were used for the treatment of different type of diseases, even effective against cancer and viruses. The brominated derivatives which were

synthesized in the scope of this thesis weren't investigated previously for biological activities. So, future research will be required to find out the possible medicinal agent from the (+)-camphene based derivatives which were synthesized under the scope of this thesis.

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OTHER PUBLICATIONS, PRESENTATIONS AND PATENTS:

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