

Synthesis of the Racemic Dibutyroxynonane, a Sex Pheromone

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Abstract

The orange wheat blossom midge (*Sitodiplosis mosellana*) is a significant agricultural pest whose larvae feed on developing wheat grains, resulting in substantial losses in crop yield and quality. The sex pheromone of this species has been identified as (2*S*,7*S*)-dibutyroxynonane, and commercial monitoring traps containing a racemic mixture of this compound are widely used for population monitoring and pest management.

The aim of this study was to develop a synthetic route to racemic dibutyroxynonane using batch chemistry and to investigate the applicability of continuous-flow chemistry to selected stages of the synthesis. The batch synthesis involved silylation of 5-hexen-2-ol and 1,4-pentadien-3-ol using di-tert-butylsilyl bis(trifluoromethanesulfonate), followed by ring-closing metathesis, deprotection, alkene reduction, and esterification to afford the target molecule. Under continuous-flow conditions, two nucleophilic substitution steps involved in the silicon-tethering sequence were investigated: the reaction of di-tert-butylsilyl bis(trifluoromethanesulfonate) with 5-hexen-2-ol, and the subsequent reaction of di-tert-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate with 1,4-pentadien-3-ol. The first substitution was investigated under continuous-flow conditions across a range of flow rates and residence times, although quantitative comparison of reaction efficiency was limited by the use of crude products, while prolonged low-temperature operation caused freezing and reactor blockage. The second substitution was also investigated under continuous-flow conditions, with formation of the desired silicon-tethered product supported by ^1H and ^{13}C NMR spectroscopy.

Reaction progress and product formation were monitored and characterized by ^1H and ^{13}C NMR spectroscopy throughout the synthesis. The batch route successfully delivered the key cyclic intermediate by ring-closing metathesis in up to 70% calculated crude yield, followed by TBAF-mediated deprotection to give the dienediol in 63% isolated yield and hydrogenation to afford 56 mg of nonane-2,7-diol. Final esterification afforded racemic dibutyroxynonane, with its formation supported by both ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum showed characteristic signals for the butyrate α -methylene protons at δ 2.16–2.22 ppm and terminal methyl protons at δ 0.85–0.91 ppm, while the ^{13}C NMR spectrum showed the characteristic ester carbonyl resonances at δ 173.4 and 173.6 ppm, consistent with incorporation of the two butyrate ester groups.

Keywords: racemic dibutyroxynonane, silicon-tethering, ring-closing metathesis, continuous-flow chemistry, *Sitodiplosis mosellana*, sex pheromone

Abbreviations

OAc	Acetate
^{13}C -NMR	Carbon nuclear magnetic resonance
<i>ddt</i>	<i>Doublet of doublet of Triplet</i>
<i>d</i>	<i>Doublet</i>
DMAP	4-Dimethylaminopyridine
<i>dd</i>	<i>Doublet of doublet</i>
<i>ddd</i>	<i>Doublet of doublet of doublet</i>
<i>ddq</i>	<i>Doublet of doublet of quartet</i>
<i>dt</i>	<i>Doublet of triplet</i>
e.e.	Enantiomeric Excess
<i>et al.</i>	et alii- and others
EtOAc	Ethyl acetate
eq.	Equivalent
FR	Flow rate
g	Gram
°C	Degree Celsius
<i>h</i>	<i>Heptet</i>
h	Hour
^1H -NMR	Hydrogen nuclear magnetic resonance
IUPAC	International Union of Pure and Applied Chemistry
M_w	Molecular Weight
<i>m</i>	<i>Multiplet</i>

mL	Millilitre
mm	Millimeter
mmol	Millimoles
M	Molar, mol/dm ³
mol %	Mol percentage
Min.	Minute
MeOH	Methanol
Me	Methyl
NMR	Nuclear Magnetic Resonance
OWBM	Orange Wheat Blossom Midge
<i>p</i>	<i>Pentet</i>
<i>qd</i>	<i>Quartet of doublet</i>
RCM	Ring-Closing Metathesis
res.	Resistance
RT	Residence time
r.t.	Room Temperature
ROMP	Ring-Opening Metathesis Polymerization
<i>s</i>	<i>Singlet</i>
<i>t</i>	<i>Triplet</i>
TST	Temporary Silicon-Tethering
THF	Tetrahydrofuran
TBAF	Tetra-n-butylammonium fluoride
TLC	Thin-layer chromatography

<i>td</i>	<i>Triplet of Doublet</i>
<i>tdd</i>	<i>Triplet of doublet of doublet</i>
<i>tdq</i>	<i>Triplet of doublet of quartet</i>
<i>tp</i>	<i>Triplet of Pentet</i>

Chapter 1: Introduction

1.1 Orange Wheat Blossom Midge

The orange wheat blossom midge (OWBM), *Sitodiplosis mosellana*, is an important agricultural pest that affects wheat production across regions of Asia, Europe, and North America (Figure 1-1)¹. Larval feeding on developing wheat kernels can result in significant reductions in grain yield and quality, leading to economic losses in cereal agriculture.²



Figure 1-1 An adult *Sitodiplosis mosellana*.¹

1.1.1 Life Cycle of OWBM

As illustrated in Figure 1-2³, the life cycle of OWBM follows a seasonal pattern. During winter, the insect overwinters in the soil as dormant cocoons until environmental conditions become favourable. In spring, adult midges emerge during the wheat flowering stage. Following mating, female midges deposit eggs on developing wheat heads, where the hatched larvae feed on immature kernels.⁴ Larval feeding damages the grain, resulting in shrivelling, seed abortion, and reduced crop yield. Upon completion of larval development, the insects return to the soil to pupate and overwinter before the next emergence cycle.⁵

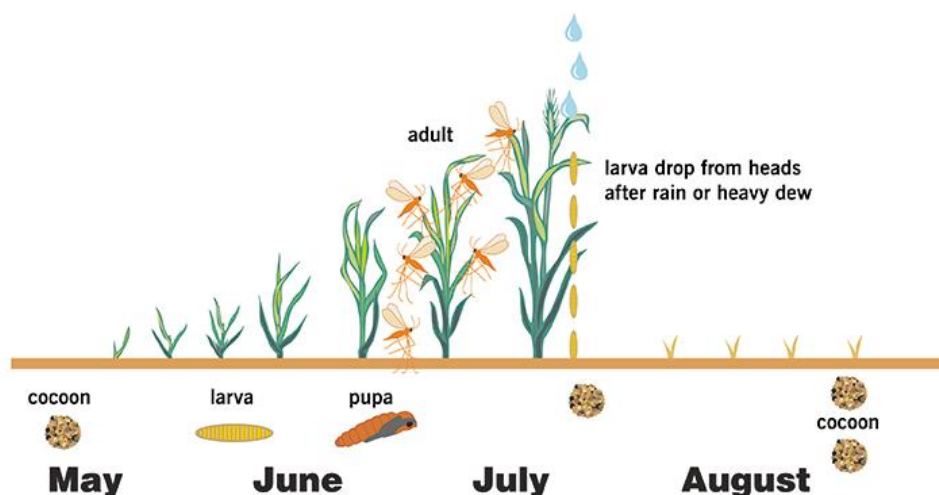


Figure 1-2 *Sitodiplosis mosellana*'s life cycle.³

1.1.2 Monitoring and Management Strategies

Various monitoring techniques are employed to manage *Sitodiplosis mosellana* populations effectively, including pheromone trapping, larval sampling from wheat heads, and soil sampling to assess overwintering larvae and cocoons.⁶ Among these approaches, pheromone-based monitoring has emerged as one of the most effective and environmentally sustainable strategies for pest management due to its high specificity and minimal environmental impact.⁷

Synthetic pheromones are widely employed in integrated pest management (IPM) systems, including mating disruption, mass trapping, attract-and-kill strategies, push-pull approaches, and population assessment. These methods reduce reliance on conventional insecticides while providing selective control of target pest species. In addition to agricultural applications, synthetic pheromones are also employed in quarantine and biosecurity programmes to detect and monitor invasive insect species near international ports and transportation centres.⁸

In the case of the orange wheat blossom midge, pheromone-based monitoring systems provide early detection of adult populations and assist in optimising the timing of pest-control measures. Consequently, pheromone technology represents an important component of sustainable wheat protection and integrated pest management strategies.⁹

As climate conditions and agricultural practices continue to evolve, ongoing research and adaptive management strategies remain essential for minimising the impact of OWBM and supporting sustainable wheat production.¹⁰

1.2 Pheromones

Pheromones are chemical signalling molecules released by organisms to elicit behavioural or physiological responses in members of the same species. These compounds play an important role in communication, particularly among insects, where they regulate

behaviours such as mating, aggregation, and alarm signalling.¹¹ Representative examples of pheromone structures are shown in Figure 1-3. Sex pheromones are especially important in reproductive communication and are widely utilised in integrated pest management strategies due to their high specificity and low environmental impact.¹²

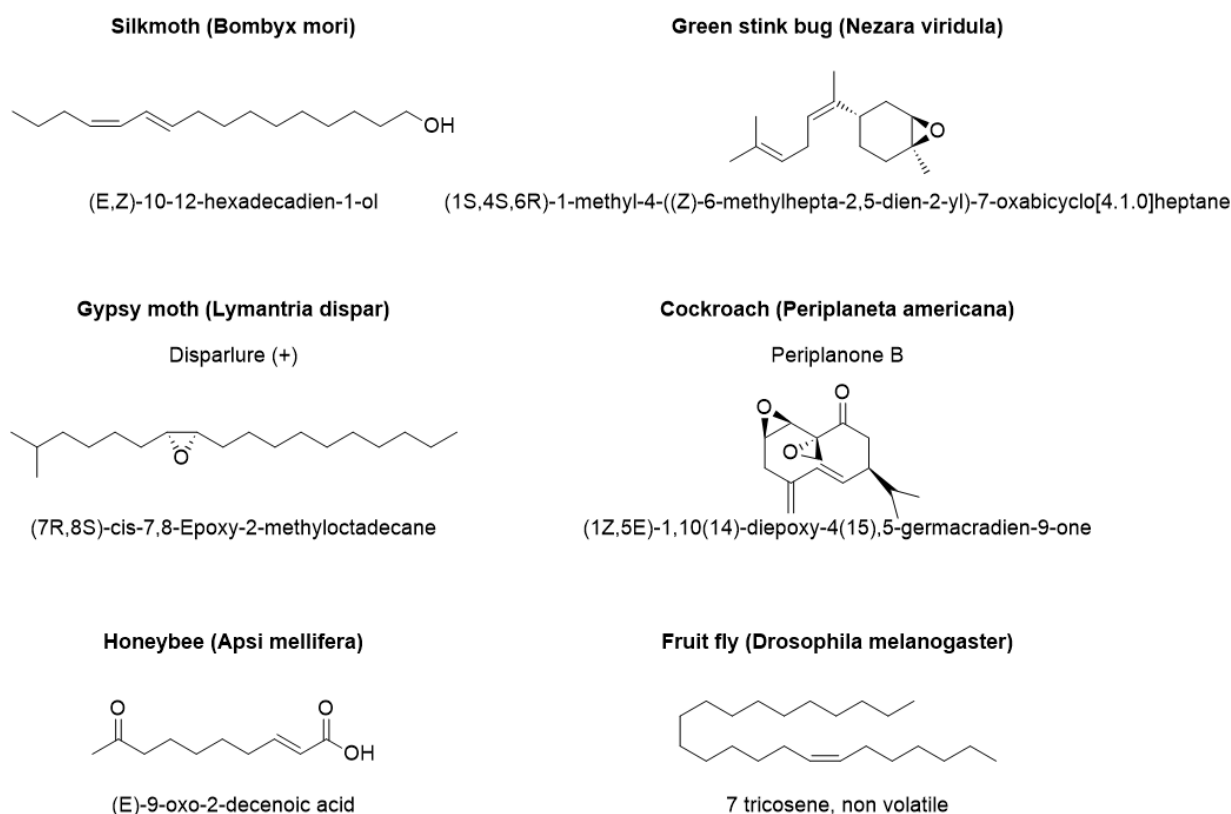


Figure 1-3 Chemical Structures of Some Pheromones.

1.3 History

The first pheromone to be identified was bombykol, a sex pheromone produced by female silk moths (*Bombyx mori*), which was isolated by Adolf Butenandt in 1959.¹³ This discovery established the foundation of pheromone research and significantly advanced the understanding of chemical communication in insects. Since then, numerous pheromones have been identified across a wide range of insect species, leading to important applications in integrated pest management and agricultural pest control.^{14,15}

1.4 Properties

Pheromones exhibit considerable structural diversity and may contain linear or cyclic hydrocarbon frameworks with a variety of functional groups, including alcohols, aldehydes, ketones, esters, carboxylic acids, epoxides, and unsaturated carbon-carbon bonds. Representative functional groups commonly found in insect pheromones are illustrated in Figure 1-4. Many insect pheromones are also derived from terpenes, a large class of naturally occurring compounds biosynthesized from isoprene (C₅H₈) units.

R-OH	R-CHO	R-COOR'	R-CH=CH-R'	(C ₅ H ₈) _n	$\left[\begin{array}{c} \text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2 \\ \text{Isoprene Unit} \end{array} \right]$
Alcohol	Aldehyde	Ester	Alkene	Terpene	

Figure 1-4 Representative functional groups commonly found in insect pheromones, including alcohol, aldehyde, ester, alkene, and terpene-derived motifs.

Terpene-based pheromones contribute to a wide range of biological functions, including mate attraction, aggregation, and alarm signaling. The structural diversity of pheromones is closely related to their highly specific biological activities and species-selective communication.^{16–18}

Their biological activity is often highly dependent on stereochemistry, as only specific stereoisomers or stereoisomeric mixtures may elicit the desired behavioural response.¹⁹ This stereochemical requirement arises because insect olfactory receptors are chiral and can distinguish between different stereoisomeric forms of the same molecule. Consequently, only the naturally occurring stereoisomer may bind effectively to the receptor and trigger the appropriate behavioural response, whereas incorrect stereoisomers may exhibit reduced activity, no activity, or even inhibit attraction. In the case of sex pheromones, precise stereochemical recognition is essential for successful mate location and species-specific communication. For the orange wheat blossom midge, the correct stereochemical composition of the pheromone is therefore important for achieving biological activity and effective monitoring of pest populations.²⁰

Due to the extremely small quantities in which natural pheromones are typically produced, chemical synthesis is often required to confirm their structure, determine absolute configuration, and evaluate biological activity under laboratory and field conditions.²⁰

1.5 Functions of Pheromones

Pheromones regulate a wide range of behavioural and physiological processes within a species and may function as releaser, primer, or signal pheromones. Releaser pheromones trigger immediate behavioural responses, whereas primer pheromones induce longer-term physiological changes. Among these, sex pheromones are particularly important in insect communication because they mediate mate attraction and reproductive behaviour. Owing to their high specificity and effectiveness at very low concentrations, sex pheromones have become valuable tools in integrated pest management (IPM), particularly for population monitoring and mating disruption.¹¹

1.6 Types of Pheromones

Pheromones may be classified according to the behavioural or physiological responses they elicit. Releaser pheromones trigger immediate behavioural responses, such as attraction, aggregation, or alarm reactions, whereas primer pheromones induce longer-term physiological or developmental changes. Signal pheromones convey information about an

individual, such as identity, social status, or reproductive condition. Among these classes, sex pheromones are particularly important in insect communication because they regulate mate attraction and reproductive behaviour and are widely utilized in integrated pest management (IPM) programmes for population monitoring, mating disruption, and mass trapping. Other pheromone types include aggregation, alarm, trail, territorial, and oviposition pheromones, which coordinate a variety of ecological and social behaviours within a species.^{21,22} **Type I pheromones** are typically straight-chain, unsaturated C₁₀–C₁₈ compounds containing terminal functional groups such as alcohols, aldehydes, or acetates. **Type II pheromones** are generally longer-chain C₁₇–C₂₅ polyunsaturated hydrocarbons and their corresponding epoxide derivatives. Type I and Type II pheromones differ primarily in their carbon-chain length, degree of unsaturation, and characteristic functional groups, as illustrated in Figure 1-5.

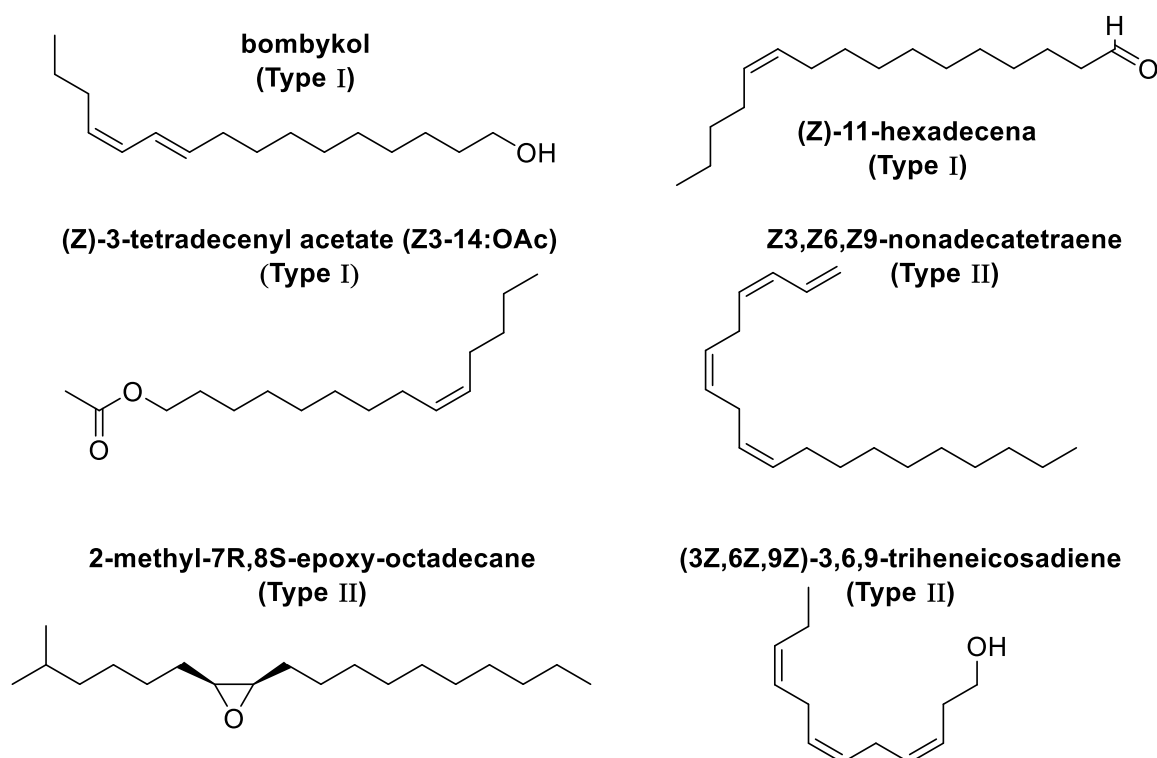


Figure 1-5 Type I and Type II Pheromones with Different Functional Groups.

1.7 Use of Pheromones in IPM

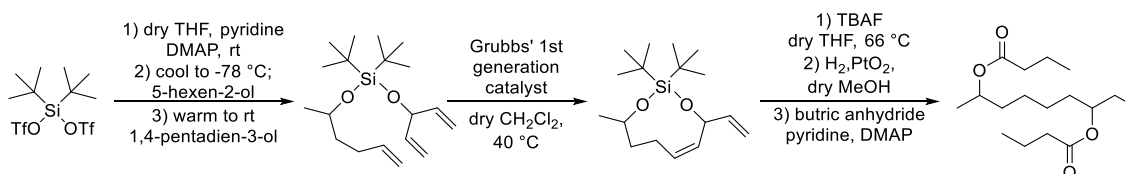
Synthetic pheromones are widely used in integrated pest management (IPM) strategies due to their high specificity, sensitivity, and low environmental impact. Applications include population monitoring, mating disruption, mass trapping, attract-and-kill systems, and push-pull approaches.²³⁻²⁴ These methods reduce reliance on conventional insecticides while improving the timing and selectivity of pest-control measures. In the case of the orange wheat blossom midge, pheromone-based monitoring systems are particularly important for detecting adult populations and supporting sustainable wheat protection strategies.

1.8 Racemic Dibutyroxynonane

The primary aim of this research was to develop an efficient synthetic route toward racemic dibutyroxynonane, the sex pheromone of the orange wheat blossom midge (*Sitodiplosis mosellana*), as illustrated in Scheme 1-1. This compound is an important semiochemical used in integrated pest management strategies for monitoring OWBM populations in wheat cultivation.

The study focused on the synthesis of the racemic target through temporary silicon-tethering and ring-closing metathesis methodologies, together with optimisation of reaction conditions to improve overall synthetic efficiency. In addition, the feasibility of adapting key transformations from conventional batch processing to continuous-flow chemistry was investigated.

Continuous-flow processing offered several potential advantages for the silicon-tethering reactions examined in this work, including improved temperature control, enhanced mixing efficiency, and safer handling of reactive intermediates. The integration of flow chemistry into the synthetic sequence therefore provided an opportunity to evaluate process efficiency and reaction control during pheromone synthesis.²⁵



Scheme 1-1 Synthesis of racemic dibutyroxynonane.

1.9 Batch Chemistry

Conventional batch chemistry was initially employed for the synthesis of racemic dibutyroxynonane due to its operational simplicity and suitability for preliminary reaction optimisation. In batch processing, reactants are combined within a single reaction vessel and undergo discrete reaction stages under controlled conditions.²⁶ Batch methods provide flexibility for adjusting reaction parameters such as temperature, reagent stoichiometry, solvent selection, and catalyst loading, making them particularly useful during early-stage synthetic development.²⁷ In the present work, batch chemistry was used to establish and optimise the silicon-tethering and ring-closing metathesis reactions prior to investigating continuous-flow processing.²⁸

1.10 Flow Chemistry

Continuous-flow chemistry has become an increasingly important methodology in synthetic organic chemistry due to its improved control over reaction conditions and enhanced process efficiency.²⁹ In continuous-flow systems, reactants are continuously passed through a reactor, allowing precise control of temperature, residence time, mixing, and reagent stoichiometry. Compared with conventional batch processing, flow chemistry can provide improved heat and mass transfer together with safer handling of reactive intermediates.³⁰ A general continuous-flow set-up is illustrated in Figure 1-6.

These advantages are particularly beneficial for low-temperature silicon-tethering reactions involving highly reactive silyl triflate intermediates. In the present work, continuous-flow processing was investigated as a potential alternative to batch chemistry for improving reaction control, reproducibility, and process efficiency during key synthetic transformations.^{31, 32}

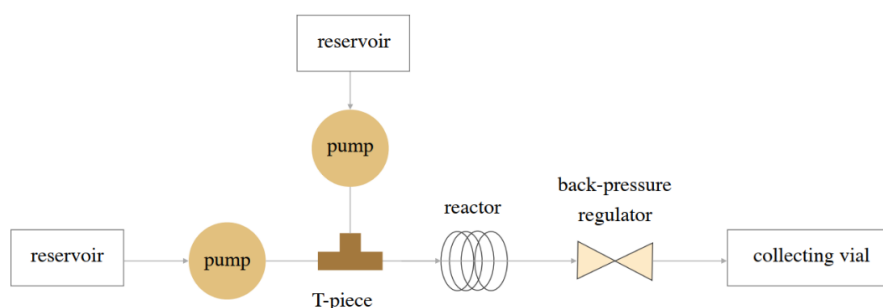


Figure 1-6 General Continuous-Flow Set-Up.

1.11 Comparison: Batch vs. Continuous-Flow Processing

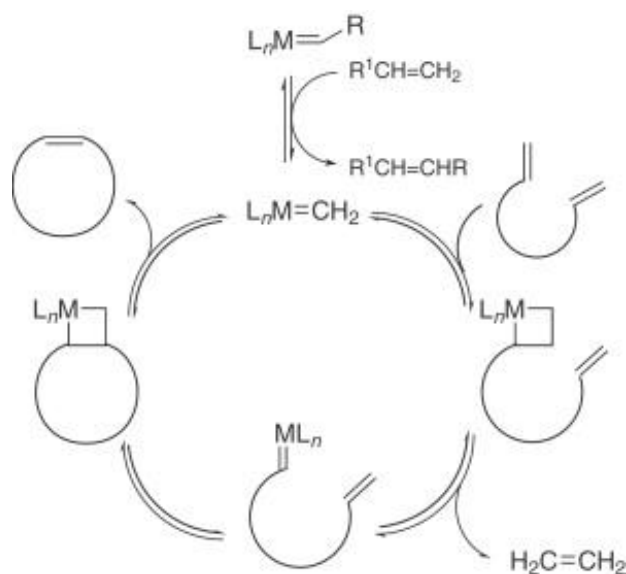
Continuous-flow chemistry differs from conventional batch processing primarily in reactor design and operational mode. In batch chemistry, reactants are combined within a single reaction vessel and processed in discrete stages, whereas continuous-flow systems continuously pass reactants through a reactor under controlled conditions.³³ A comparison between conventional batch processing and continuous-flow processing is presented in Table 1-1.³⁴

Table 1-1 Batch vs. Continuous-Flow Processing

Feature	Batch Processing	Continuous-Flow Processing
Material Flow	Discrete processing	Continuous processing
Flexibility	High; suitable for reaction optimisation	Lower; designed for consistent operation
Reaction Control	Easier manual adjustment	Precise automated control
Heat & Mass Transfer	Moderate efficiency	Enhanced efficiency
Safety	Larger reaction volumes	Reduced hazardous material accumulation
Scalability	Suitable for small-scale synthesis	Suitable for process scale-up
Reproducibility	Potential batch-to-batch variation	Improved consistency and reproducibility

1.12 Ring-Closing Metathesis

Ring-closing metathesis (RCM) is one of the most widely used methods for the synthesis of cyclic organic compounds and has become an important strategy for the construction of heterocyclic frameworks.³⁵ Grubbs extensively investigated the mechanism of olefin metathesis, establishing the catalytic cycle involving reversible [2+2] cycloaddition and metallacyclobutane intermediates, as illustrated in Scheme 1-2.³⁶



Scheme 1-2 Ring-Closing Metathesis.

Ruthenium-based Grubbs catalysts are widely employed in RCM reactions due to their high functional-group tolerance, operational stability, and compatibility with a broad range of substrates. The development of second-generation Grubbs catalysts significantly expanded the scope of metathesis reactions and enabled the efficient formation of more sterically hindered alkenes.³⁵

The synthesis of nine-membered heterocyclic systems through RCM remains challenging due to unfavourable entropic and enthalpic factors associated with medium-sized ring formation. Flexible acyclic precursors possess multiple conformations, only a limited number of which position the alkene termini appropriately for productive cyclisation. In addition, medium-sized rings often experience torsional strain and transannular interactions that reduce cyclisation efficiency.³⁷

These factors may favour competing pathways such as ring-opening metathesis or oligomerisation reactions, reducing yield and selectivity. Consequently, optimisation of catalyst systems and reaction conditions is often required to achieve efficient cyclisation during medium-sized ring synthesis.³⁸

1.13 Catalyst

Catalysts play a central role in olefin metathesis reactions by lowering the activation energy required for carbon–carbon bond reorganisation while remaining regenerated during the catalytic cycle³⁹. In ring-closing metathesis, ruthenium-based Grubbs catalysts are particularly important due to their high functional-group tolerance, operational stability, and compatibility with a wide range of substrates.⁴⁰ These catalysts operate through reversible formation of metallacyclobutane intermediates, enabling efficient alkene exchange and cyclisation reactions.⁴¹ The development of second-generation Grubbs catalysts containing N-heterocyclic carbene (NHC) ligands significantly improved catalyst stability and reactivity, expanding the applicability of ring-closing metathesis in complex organic synthesis.

1.13.1 Industrial Importance of Catalysis

Catalysis plays a central role in modern synthetic organic chemistry and is particularly important in olefin metathesis reactions. Ruthenium-based catalysts have become widely used due to their high functional-group tolerance, operational stability, and compatibility with diverse reaction conditions.⁴² In ring-closing metathesis, efficient catalyst performance is essential for promoting selective cyclization while minimizing competing pathways such as oligomerisation and ring-opening reactions. The development of Grubbs catalysts significantly expanded the applicability of metathesis chemistry in the synthesis of complex cyclic organic molecules.

1.13.2 Grubbs Catalysts and Their Role in Olefin Metathesis

Ruthenium-based Grubbs catalysts are among the most widely used catalysts for olefin metathesis reactions due to their high functional-group tolerance, operational stability, and compatibility with a broad range of substrates and solvents.⁴³ In contrast to many other late transition metal carbene complexes, ruthenium systems exhibit efficient metathesis activity while maintaining relatively high tolerance toward air and moisture, making them particularly useful in synthetic organic chemistry.

Grubbs catalysts operate through reversible formation of metallacyclobutane intermediates, enabling redistribution of carbon–carbon double bonds during olefin metathesis reactions. The development of second-generation Grubbs catalysts significantly expanded the scope of ring-closing metathesis by improving catalyst stability and reactivity toward sterically hindered substrates. These improvements were largely attributed to the incorporation of N-heterocyclic carbene (NHC) ligands, which form stronger Ru–C bonds and enhance catalyst performance.⁴⁴

In the present work, Grubbs catalysts were employed for intramolecular ring-closing metathesis of silicon-tethered intermediates during the synthesis of racemic dibutyroxynonane.

1.13.2.1 Grubbs Catalyst Type I

The development of ruthenium-based olefin metathesis catalysts represented a major advancement in organometallic chemistry. In the 1960s, it was discovered that ruthenium trichloride (RuCl_3) could catalyse olefin metathesis reactions, leading to the development of homogeneous ruthenium catalyst systems for industrial applications.⁴⁵ Although these early catalysts exhibited significant metathesis activity, their molecular structures were not well defined, limiting mechanistic understanding and catalyst optimisation.

A major breakthrough occurred with the development of well-defined ruthenium alkylidene catalysts in Grubbs' laboratory at Caltech. The earliest catalyst systems, such as compound A illustrated in Figure 1-7, displayed limited activity and primarily promoted polymerisation of highly strained cycloolefins, including norbornene and bicyclo[3.2.0]hept-6-ene. Subsequent studies demonstrated that catalyst activity was strongly influenced by ligand electronics and steric effects. In contrast to molybdenum-based systems developed by Schrock, where electron-withdrawing ligands improve activity, ruthenium(II) complexes require strongly electron-donating ligands to achieve efficient metathesis activity.⁴⁶

This understanding led to the development of catalyst systems containing tricyclohexylphosphine (PCy_3) ligands, such as compound B shown in Figure 1-7, which exhibited significantly improved catalytic performance. Ligand steric effects were also found to play an important role in catalyst efficiency. While tricyclohexylphosphine and triisopropylphosphine produced highly active catalysts, excessively bulky phosphines such as tri-*tert*-butylphosphine reduced activity because of steric crowding around the ruthenium centre. These studies highlighted the importance of both electronic and steric tuning in the optimisation of ruthenium-based metathesis catalysts.

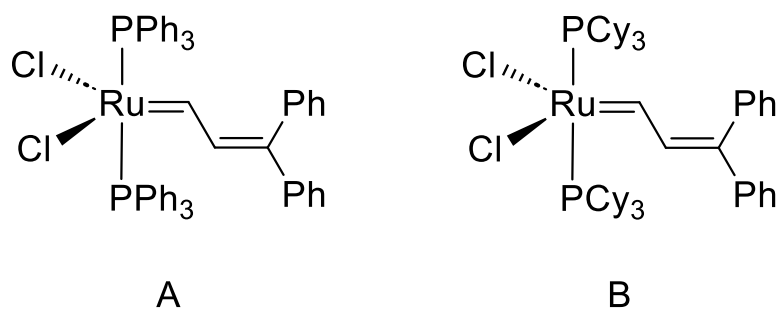


Figure 1-7 First well-defined olefin metathesis catalyst.

The first well-characterised Grubbs catalyst, shown in Figure 1-8, was reported in 1992 through the reaction of $\text{RuCl}_2(\text{PPh}_3)_4$ with diphenylcyclopropene, providing a stable and structurally defined ruthenium alkylidene complex for olefin metathesis reactions.⁴⁶ This catalyst established the foundation for subsequent developments in ruthenium-based metathesis chemistry.

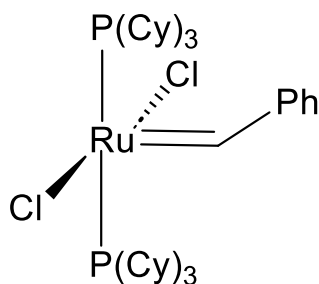
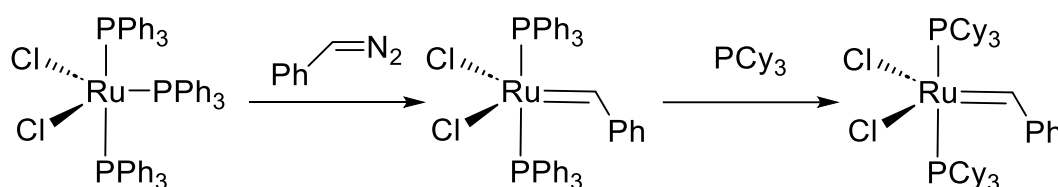


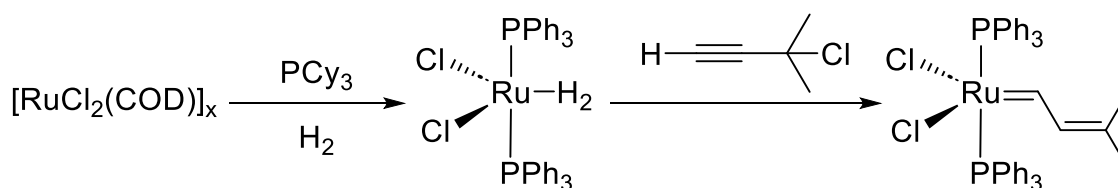
Figure 1-8 First-generation Grubbs catalyst.

Further studies identified the $L_2X_2Ru=CHR$ framework as an effective structural motif for metathesis initiators, leading to the development of scalable synthetic routes for ruthenium alkylidene complexes. One widely adopted synthetic route employed phenyldiazomethane as a carbene transfer reagent to introduce a benzylidene ligand onto $RuCl_2(PPh_3)_3$, followed by phosphine exchange with tricyclohexylphosphine (PCy_3).⁴⁷ The synthesis of the first-generation Grubbs catalyst is illustrated in Scheme 1-3. This process generated $RuCl_2(=CHPh)(PCy_3)_2$ as a stable purple microcrystalline solid with high catalytic activity and broad functional-group tolerance.



Scheme 1-3 Synthesis of Grubbs First-Generation Catalyst.

An alternative synthetic route utilised rearrangement of propargyl halides as vinylcarbene precursors in a one-pot process, as shown in Scheme 1-4. In this method, introduction of the PCy_3 ligand during the initial step eliminated the need for phosphine exchange and reduced intermediate isolation procedures. Although the resulting dimethylvinylalkylidene catalyst displayed slightly lower activity than the benzylidene-based Grubbs catalyst, its lower cost and scalability made it attractive for industrial applications, particularly ring-opening metathesis polymerisation (ROMP).⁴⁷

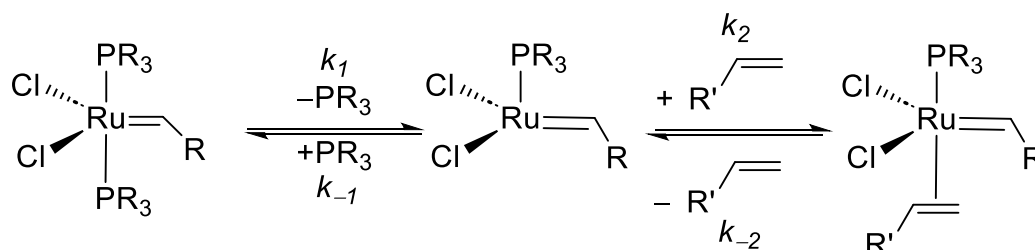


Scheme 1-4 Synthesis of Ruthenium Alkylidene Complex.

1.13.2.2 Grubbs Catalyst Type II

The second-generation Grubbs catalyst was developed to fulfil the same fundamental role as the first-generation catalyst while providing significantly enhanced catalytic activity and improved operational stability.⁴⁸ One of its major advantages is its increased tolerance toward air and moisture, which facilitates handling under laboratory conditions and broadens its practical applications in synthetic organic chemistry.

Detailed mechanistic investigations of first-generation ruthenium catalysts demonstrated that diphosphine complexes generate a highly reactive monophosphine intermediate during the catalytic cycle, formally described as a 14-electron species. As illustrated in Scheme 1-5, catalytic activity is governed by the relative rates of phosphine dissociation (k_1), phosphine reassociation (k_{-1}), and olefin coordination (k_2). Productive metathesis requires efficient formation of the coordinatively unsaturated intermediate together with preferential olefin binding over phosphine reassociation.⁴⁹ Consequently, high catalytic activity is achieved when phosphine dissociation occurs readily and when the resulting intermediate reacts preferentially with olefinic substrates rather than free phosphine.



Scheme 1-5 Proposed Mechanistic Pathway for the Activation of Ruthenium Alkylidene.

These mechanistic studies provided the basis for the development of mixed-ligand ruthenium complexes in which one phosphine ligand was replaced by an N-heterocyclic carbene (NHC) ligand. Prior to the formal introduction of the second-generation Grubbs catalyst, several closely related NHC-containing ruthenium catalysts were independently reported. In March 1999, Nolan⁵⁰ and Grubbs⁵¹ disclosed catalysts containing unsaturated NHC ligands based on 1,3-bis(2,4,6-trimethylphenyl)imidazole. Shortly afterwards, Fürstner reported a similar NHC-containing catalyst system. In August 1999, Grubbs introduced the second-generation Grubbs catalyst incorporating a saturated NHC ligand derived from 1,3-bis(2,4,6-trimethylphenyl)dihydroimidazole, as shown in Figure 1-9.⁵²

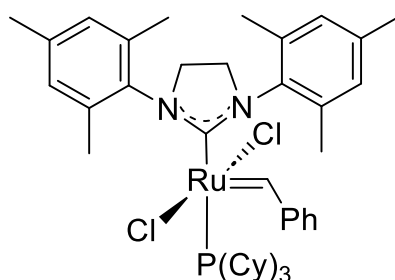


Figure 1-9 Second-generation Grubbs catalyst.

The defining structural feature of second-generation Grubbs catalysts is the replacement of one phosphine ligand with an NHC ligand. This modification significantly enhances catalyst stability, reactivity toward sterically hindered substrates, and functional-group tolerance while enabling efficient metathesis reactions at lower catalyst loadings.⁵³ NHC ligands act as substantially stronger σ -donors than phosphines, generating Ru–NHC bonds that are considerably stronger than Ru–PR₃ interactions. Although substitution of PCy₃ with an NHC decreases the phosphine dissociation rate, it dramatically increases olefin selectivity and favours productive substrate coordination over phosphine reassociation. Consequently, mixed NHC/phosphine ruthenium complexes exhibit substantially higher catalytic activity than either bis(phosphine) or bis(NHC) systems.⁵⁴

Further structural studies demonstrated that NHC ligands containing mesityl substituents on nitrogen are particularly important for catalyst stability because the ortho-methyl substituents restrict rotational flexibility and help stabilise the ruthenium centre. Typical metathesis initiators therefore adopt distorted square-pyramidal geometries with the alkylidene ligand occupying the apical position. In contrast, ruthenium carbene complexes containing strong π -acceptor ligands such as carbon monoxide adopt trigonal-bipyramidal geometries and display little or no metathesis activity.⁵⁵

The introduction of NHC ligands into ruthenium metathesis catalysts represented a major advancement in olefin metathesis chemistry and significantly expanded the scope of ring-closing metathesis reactions. These catalysts enabled more efficient synthesis of sterically demanding and structurally complex cyclic molecules while maintaining excellent functional-group tolerance and operational stability.⁵⁶ In the present work, second-generation Grubbs catalysts were employed for ring-closing metathesis of silicon-tethered intermediates during the synthesis of racemic dibutyrononane.

1.13.2.3 Hoveyda–Grubbs catalysts

The Hoveyda–Grubbs catalysts represent an important development in ruthenium-based olefin metathesis catalysts through incorporation of a chelating ortho-isopropoxybenzylidene ligand in place of a phosphine ligand.⁵⁷ The ortho-isopropoxy substituent, commonly referred to as the Hoveyda chelate, is directly attached to the benzylidene aromatic ring and provides enhanced catalyst stability compared with non-chelating Grubbs catalysts.

The first-generation Hoveyda–Grubbs catalyst was introduced in 1999 by Amir H. Hoveyda and co-workers.⁵⁸ This catalyst exhibited improved robustness due to chelation of the oxygen donor atom to the ruthenium centre, eliminating the need for a dissociating phosphine ligand. Shortly afterwards, second-generation Hoveyda–Grubbs catalysts were independently developed by Hoveyda⁵⁹ and Siegfried Blechert⁶⁰ through incorporation of an N-heterocyclic carbene (NHC) ligand while retaining the chelating ortho-isopropoxybenzylidene framework. The structures of the first- and second-generation Hoveyda–Grubbs catalysts are illustrated in Figure 1-10.

Although Hoveyda–Grubbs catalysts are generally more expensive and often initiate more slowly than conventional Grubbs catalysts, their enhanced thermal stability and resistance toward air and moisture make them particularly valuable for demanding metathesis transformations. The development of ruthenium complexes containing monodentate and chelating ligands with O, N, P, or Cl donor atoms further expanded the scope of olefin metathesis catalysts. In particular, styrenyl ether complex A shown in Figure 1-10 and its non-phosphine analogue complex B exhibit exceptional stability under atmospheric conditions and can be purified and recycled using standard chromatographic methods without specialised precautions.⁵³

Chelation of the ether oxygen significantly influences catalyst initiation and propagation kinetics. Compared with the first-generation Grubbs catalyst shown previously in Figure 1-8. In contrast, complex A in Figure 1-10 initiates approximately thirty times more slowly but propagates nearly four times faster once activated. In contrast, complex B in Figure 1-10, a highly air-stable green ruthenium complex, exhibits rapid initiation together with excellent efficiency in cross-metathesis reactions involving electron-deficient olefins. In

many cases, this catalyst displays superior reactivity and selectivity relative to phosphine-containing second-generation Grubbs catalysts.

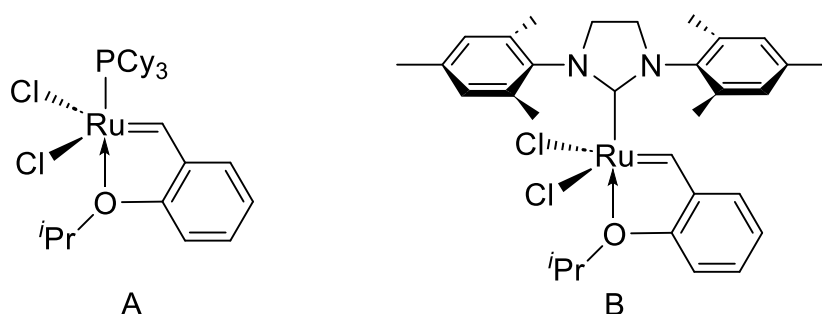
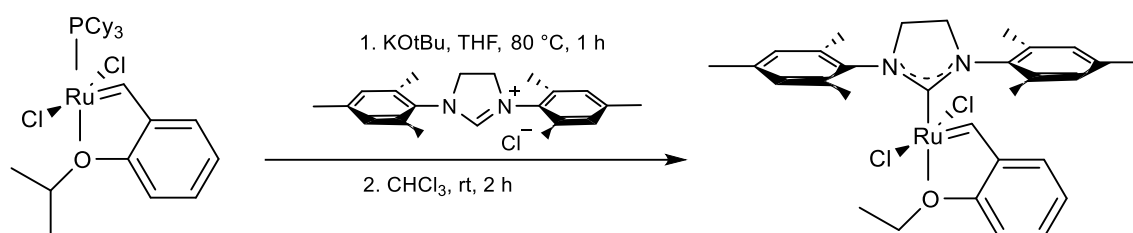


Figure 1-10 First- and Second-Generation Hoveyda–Grubbs Catalysts.

The initiation rates of Hoveyda–Grubbs catalysts can be modulated through steric and electronic modification of the chelating ligand, an approach further developed in Zhan-type catalyst systems.^{61,62}

Synthetic routes to Hoveyda–Grubbs catalysts generally involve introduction of the ortho-isopropoxybenzylidene ligand together with phosphine abstraction using copper(I) chloride⁵⁹ and subsequent incorporation of an NHC⁶⁰ ligand to generate second-generation complexes. The synthesis of second-generation Hoveyda–Grubbs catalysts is illustrated in Scheme 1-6.



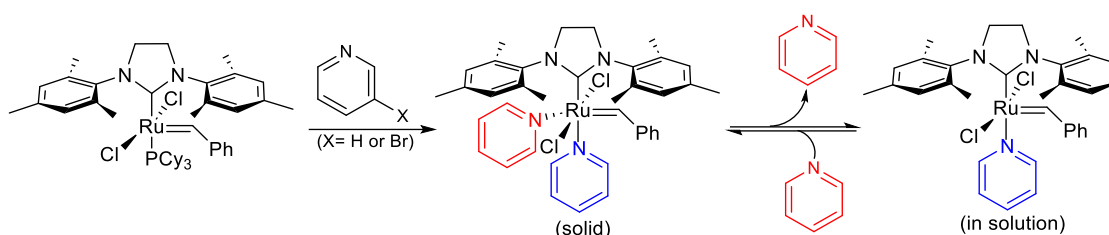
Scheme 1-6 Second-generation Hoveyda–Grubbs catalysts Synthesis.

Further development of ruthenium metathesis catalysts led to the introduction of water-soluble Grubbs catalysts by Grubbs and Hong in 2006.⁶³ Modification of the imidazolidine ligand with polyethylene glycol (PEG) chains enabled ring-closing metathesis reactions to be performed in aqueous media, particularly for substrates containing ammonium salt functionalities. This development significantly expanded the applicability of metathesis chemistry to environmentally compatible and biomolecule-related transformations.

Overall, Hoveyda–Grubbs catalysts have had a major impact on olefin metathesis chemistry by improving catalyst stability, substrate compatibility, and reaction efficiency.⁶⁴ Their enhanced robustness and functional-group tolerance have enabled increasingly challenging metathesis transformations in synthetic organic chemistry, polymer chemistry, and related fields. In the present work, ruthenium-based metathesis catalysts played a central role in ring-closing metathesis of silicon-tethered intermediates during the synthesis of racemic dibutyrononane.

1.13.2.4 Grubbs Catalyst Type III

The reactivity of Grubbs catalysts can be further enhanced through replacement of phosphine ligands with more labile pyridine-based ligands. In particular, incorporation of 3-bromopyridine produces a dramatic increase in catalyst initiation rate, exceeding that of analogous phosphine-containing systems by more than six orders of magnitude.⁶⁵ Both pyridine and 3-bromopyridine ligands have been employed in catalyst design, although 3-bromopyridine exhibits significantly greater lability and therefore facilitates more rapid catalyst activation. These catalysts are typically isolated as bis-pyridine complexes; however, upon dissolution one pyridine ligand readily dissociates, generating the highly reactive ruthenium species responsible for catalytic activity.⁶⁶ The structure of a representative third-generation Grubbs catalyst is shown in Scheme 1-7.



Scheme 1-7 Third-generation Grubbs catalyst.

The exceptionally rapid initiation rates of these catalysts have made them particularly valuable in ring-opening metathesis polymerisation (ROMP), where efficient initiation is essential for achieving controlled polymer growth.⁶⁷ Because of their superior initiation behaviour, these catalysts are commonly referred to as third-generation Grubbs catalysts. Their high initiation-to-propagation rate ratio is especially advantageous in living polymerisation processes, enabling the synthesis of polymers with narrow molecular-weight distributions and low polydispersity indices.

Beyond ROMP, third-generation Grubbs catalysts have broadened the scope of olefin metathesis by providing greater control over polymer architecture, including the preparation of block copolymers, star-shaped polymers, and other well-defined macromolecular structures. Their rapid initiation characteristics have also attracted interest for industrial applications where reaction efficiency and productivity are important considerations. Furthermore, ongoing catalyst development continues to focus on improving stability, recyclability, and functional-group tolerance, thereby expanding the applicability of ruthenium-based metathesis catalysts to increasingly diverse synthetic transformations.⁶⁸

1.14 Silicon-tethering

Silicon-tethering is a valuable synthetic strategy that converts intermolecular reactions into intramolecular processes through the temporary covalent linkage of reacting partners. By holding the reactive groups in close spatial proximity, the tether increases their effective molarity without changing their actual concentration in solution. This preorganisation restricts their relative separation and conformational freedom, thereby increasing the

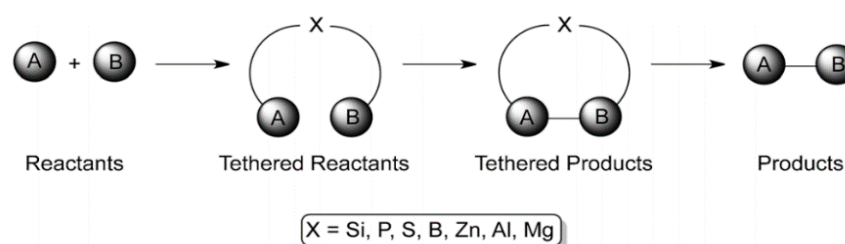
probability of productive intramolecular reaction over competing intermolecular pathways. Consequently, silicon-tethering can improve regio- and stereoselectivity, reduce competing side reactions, and facilitate transformations such as ring-closing metathesis.⁶⁹

The application of silicon tethers in organic synthesis was independently explored by Nishiyama⁷⁰ and Stork⁷¹ during the mid-1980s in studies involving free-radical additions. These investigations demonstrated the advantages of temporary tethering strategies and highlighted the benefits of intramolecular reaction pathways over intermolecular alternatives. Since then, silicon-tethering methodologies have become increasingly important in synthetic organic chemistry.

Over the past several decades, silyl tethers have been widely employed in a variety of transformations because they can be introduced efficiently and removed selectively under mild conditions following completion of the desired reaction.⁷² Their ability to promote controlled intramolecular reactions has made them particularly valuable for the synthesis of structurally complex molecules.

In addition to their application in radical chemistry, silicon tethers have been used extensively in olefin metathesis reactions involving allylic and homoallylic alcohol derivatives.⁷³ By linking two alkene-containing fragments through a temporary silicon bridge, the tether promotes productive cyclization and facilitates ring-closing metathesis reactions that may otherwise be difficult to achieve under intermolecular conditions. This strategy is particularly useful for the synthesis of medium-sized ring systems, where conformational and entropic factors can reduce cyclization efficiency.

In the present work, silicon-tethering was employed to connect allylic alcohol intermediates prior to ring-closing metathesis, thereby enabling efficient intramolecular cyclization during the synthesis of racemic dibutyroxynonane. The general concept of silicon-tether-assisted cyclization is illustrated in Scheme 1-8.



Scheme 1-8 Application of temporary tethers in organic synthesis.

1.14.1 Symmetrical Silaketals

Symmetrical silaketals represent one of the most widely employed classes of temporary silicon tethers in organic synthesis. They are typically prepared through the reaction of hydroxyl-containing substrates with tethering reagents bearing a reactive dichlorosilane functionality, resulting in efficient formation of silicon-bridged intermediates.⁶⁹ The structures of commonly used silicon-based tethering reagents are illustrated in Figure 1-11.

The formation of symmetrical silaketals constitutes the initial stage of temporary silicon-tethering (TST) methodology. Silicon is particularly well suited for this purpose because of its tetravalent nature and its ability to form stable yet selectively cleavable Si–O bonds. Consequently, the silylating reagents employed in TST generally contain two leaving groups together with two identical alkyl or aryl substituents attached to the silicon center, as shown in Figure 1-11. This structural arrangement enables controlled tether formation while maintaining predictable reactivity throughout subsequent synthetic transformations.

The use of symmetrical silaketals provides several advantages in synthetic chemistry. By temporarily linking two reacting partners through a silicon bridge, intermolecular reactions can be converted into intramolecular processes, thereby increasing effective molarity and improving reaction selectivity. Following completion of the desired transformation, the silicon tether can be removed under relatively mild conditions, regenerating the corresponding hydroxyl functionalities. The ease of installation and cleavage, combined with the stability of the intermediate silaketals, has made symmetrical silicon tethers valuable tools in a wide range of catalytic and stereoselective transformations.⁶⁹

In metathesis chemistry, silicon-tethering strategies have proven particularly useful for promoting efficient cyclization reactions by preorganising alkene-containing substrates into favourable conformations. This principle forms the basis of the silicon-tethering approach employed in the present work for the synthesis of racemic dibutyroxynonane.

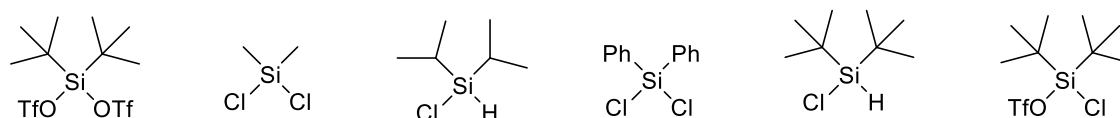


Figure 1-11 Silicon-based Starting Materials Used for Temporary Silicon-Tethering.

1.14.2 Unsymmetrical Silaketals

The synthesis of unsymmetrical bis(alkoxy)silanes is generally more challenging than that of symmetrical silaketals because of the competing formation of symmetrical by-products.⁷⁴ The most widely employed strategy involves a stepwise silylation sequence in which the first alcohol is reacted with an excess of dialkyldichlorosilane under dilute conditions to minimise formation of symmetrical products. The resulting monochlorosilane intermediate is then isolated, and a second alcohol is subsequently introduced to generate the desired unsymmetrical silaketal.⁷⁴ This approach remains the most practical and commonly used method for the preparation of unsymmetrical silicon tethers.

Despite its effectiveness, stepwise silylation presents several limitations. Excess dialkyldichlorosilane must be removed carefully under reduced pressure to avoid undesired side reactions, and the preparation of higher-molecular-weight bis(alkoxy)silanes can become impractical when high-boiling dichlorosilanes are employed.⁷⁵ Nevertheless, the stepwise approach offers excellent control over tether formation and minimises the formation of symmetrical by-products through careful stoichiometric control. Typically, the first alcohol is monosilylated in the presence of a base such as triethylamine or

imidazole, followed by reaction with the second alcohol under modified conditions to complete tether formation.

To overcome the limitations associated with conventional stepwise silylation, a variety of alternative synthetic methodologies have been developed. These include the use of disubstituted alkene intermediates, incorporation of spiroketal-containing natural-product frameworks, synthesis of annonaceous acetogenin derivatives, long-range asymmetric induction strategies, and relay ring-closing metathesis approaches.^{76,77} These developments have expanded the versatility of silicon-tethering methodology and enabled the synthesis of increasingly complex molecular architectures.

Alternative routes to unsymmetrical silicon tethers include dehydrogenative coupling reactions, in which silanols react with hydrosilanes under catalytic conditions to generate unsymmetrical silyl ethers with hydrogen gas as the sole by-product. This strategy offers a highly atom-economical and environmentally attractive route to silicon-tether formation while providing excellent control over product selectivity. Similarly, dealkynative coupling methodologies utilise alkynylsilanes in the presence of catalysts such as potassium bis(trimethylsilyl)amide (KHMDs), generating acetylene as the only by-product and allowing efficient synthesis of unsymmetrical silicon-containing products under mild reaction conditions.

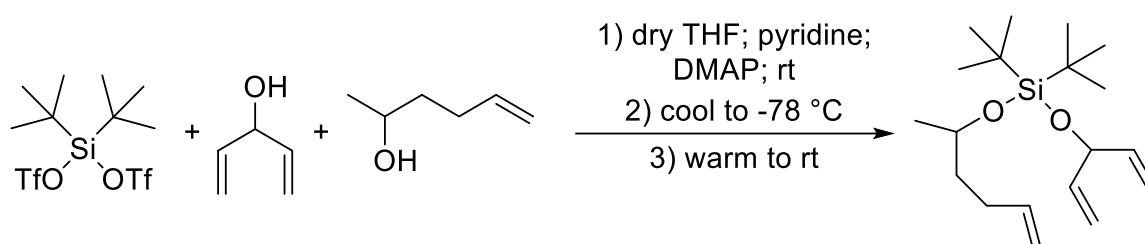
In situations where stereochemical control at silicon is required, organocatalytic asymmetric methodologies provide an additional level of sophistication. These approaches often involve desymmetrisation of symmetrical bis(methallyl)silanes using chiral catalysts such as imidodiphosphorimidate (IDPi) systems.⁷⁸ Such methods enable the preparation of enantiomerically enriched unsymmetrical silicon tethers and have become increasingly important for applications in stereoselective synthesis.

1.14.3 Unsymmetrical Silaketal of di-tert-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane

The practical application of temporary silicon-tethering in the present study is illustrated by the synthesis of the unsymmetrical silaketal di-tert-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane, shown in Scheme 1-9. This intermediate was prepared through sequential nucleophilic substitution of di-tert-butylsilyl bis(trifluoromethanesulfonate) with two different allylic alcohols, namely 5-hexen-2-ol and 1,4-pentadien-3-ol. The stepwise tethering strategy enabled selective formation of the desired unsymmetrical silicon-linked intermediate while avoiding formation of competing symmetrical silaketals.

As illustrated in Scheme 1-9, attachment of both alcohol fragments to the silicon centre generated a temporary tether that brought the terminal alkene functionalities into close spatial proximity. This preorganisation reduced the entropic penalty associated with cyclisation and provided favourable conformational control for the subsequent ring-closing metathesis (RCM) reaction. The resulting unsymmetrical silaketal therefore served as a key intermediate in the synthetic sequence, facilitating efficient intramolecular cyclisation of the tethered diene precursor.

Following ring closure, the silicon tether could be selectively removed using tetra-n-butylammonium fluoride (TBAF), regenerating the corresponding diol for subsequent hydrogenation and esterification steps in route to racemic dibutyroxynonane. The successful use of this unsymmetrical silicon-tethering strategy demonstrates the utility of temporary silicon tethers for promoting medium-ring formation, where conventional intermolecular approaches often suffer from reduced efficiency because of conformational and entropic limitations.



Scheme 1-9 Synthesis of unsymmetrical silaketal of di-tert-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane.

1.15 Research Aims and Objectives

The primary aim of this project is to develop an efficient synthetic route towards racemic dibutyroxynonane, the sex pheromone of the orange wheat blossom midge (*Sitodiplosis mosellana*), using temporary silicon-tethering and ring-closing metathesis as key synthetic strategies. The specific objectives of this work are:

1. To establish a reproducible batch synthesis of racemic dibutyroxynonane through alcohol formation, sequential silicon-tethering, ring-closing metathesis, deprotection, hydrogenation, and esterification.
2. To investigate the formation of an unsymmetrical silicon-tethered intermediate from 5-hexen-2-ol and 1,4-pentadien-3-ol and evaluate its suitability as a precursor for ring-closing metathesis.
3. To optimise key batch transformations, particularly the silicon-tethering and ring-closing metathesis steps, by examining reaction conditions that influence reaction efficiency and product formation.
4. To investigate the transfer of the two nucleophilic substitution steps involved in silicon-tether formation from batch to continuous-flow processing.
5. To evaluate the effects of flow parameters, particularly temperature, flow rate and residence time, on these nucleophilic substitution reactions and assess the feasibility of continuous-flow processing for these transformations.
6. To characterise the intermediates and final product using ^1H and ^{13}C NMR spectroscopy and thereby assess the progress of the synthetic sequence.

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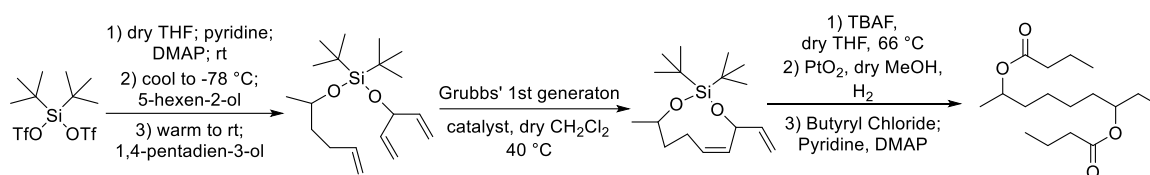
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Chapter 2: Synthesis of Racemic-Dibutyroxynonane via Batch Processing

The synthesis of racemic dibutyroxynonane was initially investigated using conventional batch processing. The synthetic strategy employed temporary silicon tethering followed by ring-closing metathesis to construct the required carbon framework, with subsequent deprotection, hydrogenation, and esterification providing the target compound. The overall synthetic route investigated in this chapter is outlined in Scheme 2-1.

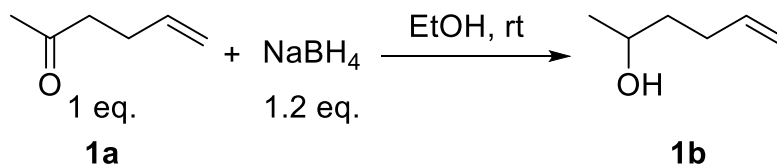


Scheme 2-1 Synthesis of racemic dibutyroxynonane.

Unless otherwise stated, intermediates were used in crude form in subsequent synthetic steps. Consequently, isolated yields were not determined for all intermediates, and reaction performance was primarily assessed by TLC and NMR analysis.

2.1 Synthesis of 5-hexen-2-ol

Reduction of 5-hexen-2-one using sodium borohydride in ethanol afforded 5-hexen-2-ol in reproducible isolated yields of 64–70% over the range of reaction scales investigated (Table 2-1). The synthetic transformation is shown in Scheme 2-2. Reaction completion was initially assessed by TLC analysis, which showed disappearance of the starting material and the presence of a product spot (**R_f** = **0.40**, ethyl acetate/petroleum ether, 1:4).



Scheme 2-2 Synthesis 5-hexen-2-ol.

Formation of 5-hexen-2-ol was further supported by NMR spectroscopy (Appendices iii and iv). In the ¹³C NMR spectrum, disappearance of the ketone carbonyl resonance at **δ 208.1 ppm** and appearance of the hydroxyl-bearing carbon resonance at **δ 67.7 ppm** provided clear evidence for reduction of 5-hexen-2-one to the corresponding secondary alcohol. The product was obtained in sufficient purity for use in subsequent transformations without further purification.

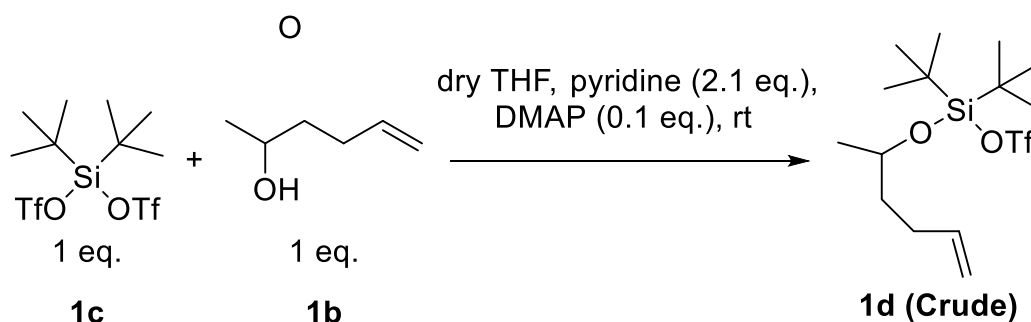
The reduction gave comparable isolated yields across the investigated reaction scales, with yields of 64%, 70%, and 64% obtained on small-, intermediate-, and larger-scale reactions, respectively (Table 2-1). The similar yields indicate that the NaBH₄/EtOH reduction was reproducible over the investigated scale range. The slightly lower isolated yield obtained on the largest scale may reflect differences in work-up and product handling rather than a significant change in reaction performance.

Table 2-1 Effect of reaction scale on the synthesis of 5-hexen-2-ol.

Entry	Reaction scale (mmol)	Yield (%)
1	5	64
2	10	70
3	200	64

2.2 Silylation of 5-hexen-2-ol with Di-*tert*-butylsilyl Bis(trifluoromethanesulfonate)

The first silicon-tethering step involved nucleophilic substitution of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**) with 5-hexen-2-ol (**1b**) to form the monosilylated intermediate (**1d**), as shown in Scheme 2-3. The reaction was performed under anhydrous conditions at low temperature in the presence of pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP). Following addition of the alcohol, the reaction mixture was allowed to warm gradually to room temperature.



Scheme 2-3 Nucleophilic substitution of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**) with 5-hexen-2-ol (**1b**) to form the monosilylated intermediate (**1d**).

Reaction progress was assessed by TLC after 5 h. The starting alcohol (**1b**) had an **R_f** value of **0.53** (ethyl acetate/petroleum ether, 3:7), whereas analysis of the reaction mixture showed disappearance of this spot and appearance of a new, less polar spot at **R_f ≈ 0.93–0.95** under the same conditions. This change was consistent with conversion of the starting alcohol to the monosilylated intermediate.

Formation of **1d** was further supported by NMR analysis of the crude reaction mixture. The ^1H NMR spectrum showed an oxygenated methine resonance at δ 3.70–3.66 ppm and a singlet corresponding to the two *tert*-butyl groups at δ 0.97 ppm (18H). The corresponding oxygenated carbon resonance was observed at δ 67.7 ppm in the ^{13}C NMR spectrum. Together with the TLC results, these spectroscopic features supported formation of the monosilylated intermediate **1d**.

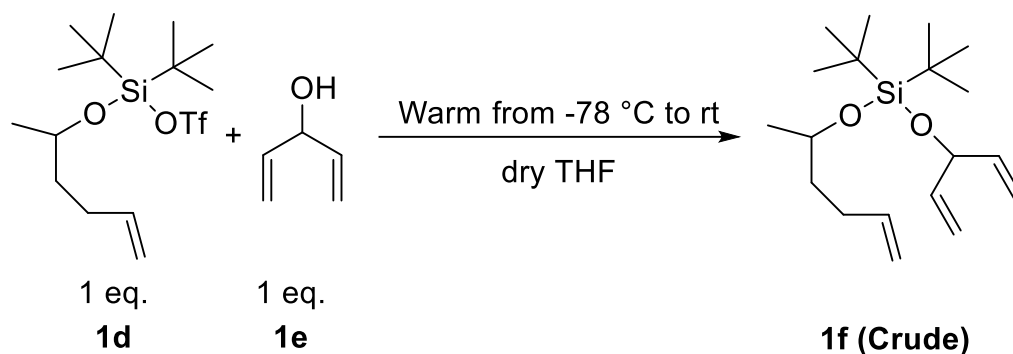
The crude intermediate was used directly in the subsequent silicon-tethering reaction without isolation or further purification. Consequently, an isolated yield was not determined for this step. The reaction was investigated using different reagent proportions and reaction scales, as summarised in Table 2-2. In particular, the amount of 5-hexen-2-ol relative to **1c** was varied at the smaller scale, while a larger-scale experiment was also examined. Since **1d** was not isolated, these experiments were assessed primarily by TLC and NMR analysis rather than by comparison of isolated yields.

Table 2-2 Reaction scales and relative amount of 5-hexen-2-ol investigated in the formation of monosilylated intermediate **1d**.

Entry	Scale of 1c (mmol)	1b (equiv.)	Outcome
1	2	1.0	Crude intermediate carried forward
2	2	0.75	Crude intermediate carried forward
3	4	1.0	Crude intermediate carried forward

2.3 Unsymmetrical Silicon tethering of Di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate with 1,4-pentadien-3-ol

Following formation of the monosilylated intermediate **1d**, the second silicon-tethering reaction was carried out with 1,4-pentadien-3-ol (**1e**) to form the unsymmetrical bis-silyl ether **1f**, as shown in Scheme 2-4. The approach was informed by the findings of Hooper et al.⁷⁹ The crude intermediate **1d** obtained from the preceding reaction was used directly without isolation or purification.



Scheme 2-4 Nucleophilic substitution of di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate (**1d**) with 1,4-pentadien-3-ol (**1e**) to form the unsymmetrical bis-silyl ether **1f**.

Formation of **1f** was assessed by NMR spectroscopy of the crude reaction mixture. In the ^1H NMR spectrum, the hydroxyl proton signal of 1,4-pentadien-3-ol (**1e**), observed at δ 2.81 ppm, was absent following the reaction. In addition, two closely spaced *tert*-butyl singlets were observed at δ 0.95 and 0.96 ppm. The presence of two distinct *tert*-butyl environments is consistent with formation of the unsymmetrical silicon-tethered product. Together, these spectroscopic changes supported formation of the desired bis-silyl ether **1f**.

The product was obtained and carried forward as a crude material without isolation of analytically pure **1f**. Consequently, an isolated yield was not determined, and the recorded crude product masses were not used to assess reaction efficiency or conversion. The reaction was nevertheless investigated at different scales, as summarised in Table 2-3. The crude product obtained from each experiment was subsequently used in the ring-closing metathesis step.

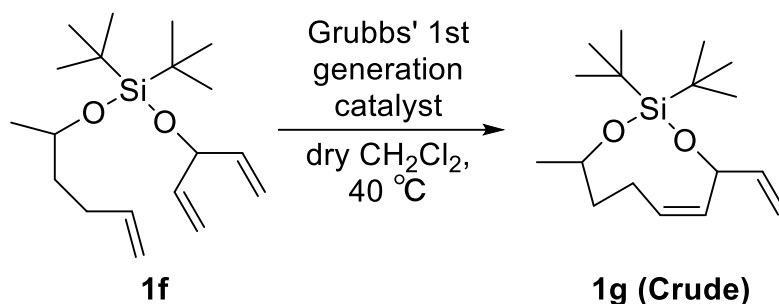
Table 2-3 Reaction scales investigated for the formation of the unsymmetrical bis-silyl ether **1f**.

Entry	Reaction scale of 1e (mmol)	Crude material recovered (g)*
1	2	1.174
2	2.5	1.75
3	4	2.92

* Crude masses are reported only as material recovery and should not be interpreted as isolated yields.

2.4 Ring-Closing Metathesis (RCM) Utilizing Grubbs' Catalyst

Ring-closing metathesis (RCM) of the unsymmetrical silicon-tethered precursor **1f** was investigated using Grubbs' catalyst to form the cyclic intermediate **1g**, as shown in Scheme 2-5. The reaction was conducted under anhydrous conditions in dichloromethane, and the effects of reaction scale and catalyst loading on the calculated crude yield were examined (Table 2-4).



Scheme 2-5 Ring-closing metathesis of **1f** to form (Z)-2,2-di-*tert*-butyl-4-ethenyl-9-methyl-1,3-dioxo-2-silacyclonon-5-ene (**1g**).

The material obtained following the RCM reaction and passage through neutral alumina using 1% MeOH in CH₂Cl₂ (1:99, v/v) remained crude. Consequently, the values reported in Table 2-4 represent **crude yields** rather than isolated yields of analytically pure **1g**. These values should therefore be interpreted with caution, as the mass of the recovered material may include residual impurities and does not necessarily represent the amount of pure RCM product present.

The calculated crude yields ranged from 20 to 70% under the conditions investigated (Table 2-4). Entries 1 and 2 were performed using the same amount of precursor **1f** and the same catalyst loading but gave calculated crude yields of 20 and 50%, respectively. Since the recorded reaction conditions were identical, the difference cannot be attributed to a deliberate change in the reaction parameters. Furthermore, because reaction conversion and product purity were not independently quantified, it is not possible to determine whether this difference resulted from variation in reaction conversion, recovery of material during work-up, differences in the composition of the crude products, or a combination of these factors.

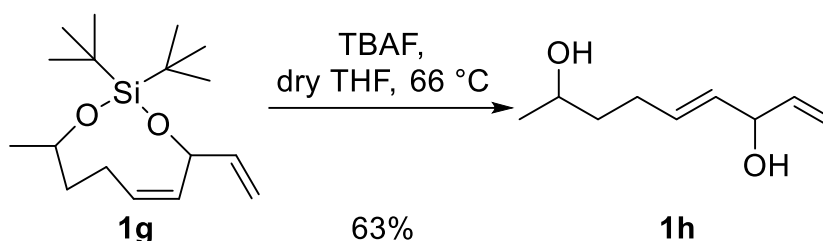
Entry 3 was performed on a smaller scale and with a lower catalyst loading and gave the highest calculated crude yield of 70%. However, both reaction scale and catalyst loading were changed simultaneously, and the purity of the recovered material was not independently established. Therefore, the higher crude yield cannot be attributed specifically to either reduced reaction scale or reduced catalyst loading. Further controlled experiments, together with quantitative analysis of reaction conversion and product purity, would be required to determine the influence of these variables on the RCM reaction.

Table 2-4 Effect of reaction scale and catalyst loading on the ring-closing metathesis of **1f**.

Entry	Amount of 1f (mg)	Grubbs' catalyst (mol%)	Calculated crude yield of 1g (%)
1	300	5	20
2	300	5	50
3	150	2.5	70

2.5 Deprotection of Silyl Ether Using Tetra-*n*-butylammonium fluoride (TBAF)

Cleavage of the silicon tether in the cyclic intermediate **1g** was carried out using tetra-*n*-butylammonium fluoride (TBAF) to afford the corresponding acyclic diol **1h**, as shown in Scheme 2-6. Following purification, **1h** was obtained in 63% isolated yield.



Scheme 2-6 TBAF-mediated cleavage of the silicon tether in **1g** to afford nona-5,8-diene-2,7-diol (**1h**).

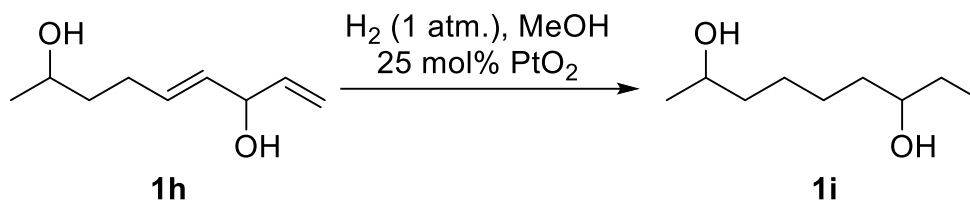
Formation of the deprotected diol **1h** was supported by TLC and NMR analysis. TLC showed a product spot at $R_f = 0.77$ using diethyl ether as the eluent, consistent with formation of a new product following cleavage of the silicon tether.

Further evidence for deprotection was obtained from the ^1H NMR spectrum. Alkene resonances were observed at δ 5.86, 5.51–5.40 and 5.13 ppm, while oxygenated methine resonances were observed at δ 4.92 and 3.75 ppm. The ^{13}C NMR spectrum showed alkene carbon resonances at δ 139.7, 132.6, 131.3 and 114.9 ppm and two oxygenated carbon resonances at δ 68.4 and 66.3 ppm. The presence of two oxygenated carbon environments is consistent with formation of the acyclic diol following cleavage of the silicon tether.

Changes were also observed in the aliphatic region relative to the cyclic precursor **1g**, including a methylene resonance at δ 1.47 ppm. Taken together, the TLC and NMR data supported successful cleavage of the silicon tether and formation of the deprotected diol **1h**.

2.6 Hydrogenation of Nona-5,8-diene-2,7-diol (**1h**) to Nonane-2,7-diol (**1i**)

Hydrogenation of nona-5,8-diene-2,7-diol (**1h**) was carried out using platinum(IV) oxide (PtO_2) as the catalyst under a hydrogen atmosphere to afford the fully saturated diol **1i**, as shown in Scheme 2-7.



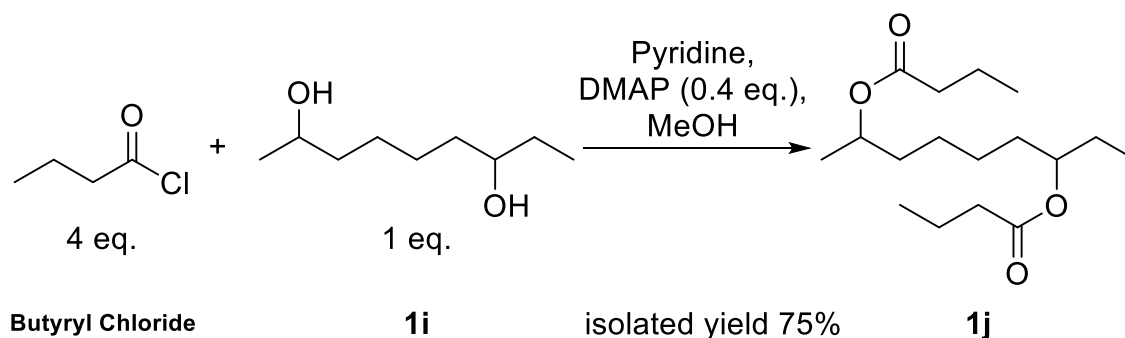
Scheme 2-7 Hydrogenation of nona-5,8-diene-2,7-diol (**1h**) to afford nonane-2,7-diol (**1i**).

Formation of **1i** was supported by NMR analysis. In the ^1H NMR spectrum, the vinylic resonances of the diene precursor **1h**, previously observed at δ 5.86, 5.51–5.40 and 5.13 ppm, were no longer present following hydrogenation. The product spectrum instead contained signals characteristic of the saturated carbon framework, including a terminal methyl triplet at δ 0.87 ppm ($J = 7.5$ Hz, 3H) and a methyl doublet at δ 1.13 ppm ($J = 6.8$ Hz, 3H).

Further evidence for hydrogenation was obtained from the ^{13}C NMR spectrum. The alkene carbon resonances of **1h**, previously observed at δ 139.7, 132.6, 131.3 and 114.9 ppm, were absent from the product spectrum. The remaining resonances were observed in the oxygenated and saturated aliphatic carbon regions, consistent with formation of nonane-2,7-diol (**1i**). Together, the disappearance of the alkene resonances from both the ^1H and ^{13}C NMR spectra supported hydrogenation of the carbon–carbon double bonds and formation of the saturated diol **1i**.

2.7 Acylation of Nonane-2,7-diol (**1i**) to Racemic Dibutyroxynonane (**1j**)

The final step of the synthetic sequence involved acylation of nonane-2,7-diol (**1i**) with butyryl chloride to afford racemic dibutyroxynonane (**1j**), as shown in Scheme 2-8. The reaction was carried out in the presence of pyridine and DMAP, and following purification, **1j** was obtained in 75% isolated yield.



Scheme 2-8 Acylation of nonane-2,7-diol (**1i**) with butyryl chloride to afford racemic dibutyroxynonane (**1j**).

Formation of **1j** was supported by TLC and NMR analysis. TLC showed a product spot at **R_f = 0.31** using ethyl acetate/petroleum ether (1:9, v/v) as the eluent, consistent with formation of a new product following acylation.

Further evidence for ester formation was obtained from the ¹H NMR spectrum. The oxygen-bearing methine protons were observed at **δ 4.82 and 4.74 ppm**, shifted downfield relative to the corresponding alcohol-bearing environments of precursor **1i**, consistent with conversion of the hydroxyl groups to butyrate esters. Resonances attributable to the incorporated butyrate groups were also observed, including the methylene protons adjacent to the ester carbonyl groups at **δ 2.22–2.16 ppm (4H)**, the β-methylene resonances at **δ 1.63–1.54 ppm**, and terminal methyl resonances at **δ 0.91–0.85 ppm**.

The ¹³C NMR spectrum provided additional evidence for acylation through the appearance of two ester carbonyl resonances at **δ 173.6 and 173.4 ppm**. Resonances attributable to the butyrate chains were also observed at **δ 36.6, 35.9, 18.6 and 13.7 ppm**. The appearance of the ester carbonyl resonances and butyrate-chain signals, together with the changes observed in the ¹H NMR spectrum and TLC analysis, supported formation of racemic dibutyroxynonane (**1j**).

2.8 Process Optimisation and Future Work

The batch studies described in this chapter identified several opportunities for further optimisation of the synthetic route to racemic dibutyroxynonane. Future work should focus on improving reaction conversion, product recovery and purity, reproducibility, and scalability, while reducing reaction times where possible. In addition, selected transformations could be evaluated under continuous-flow conditions to determine whether improved control of reaction parameters provides advantages over the corresponding batch processes.

The sequential silicon-tethering reactions represent an important area for further investigation. In particular, the reaction of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) with 5-hexen-2-ol could be systematically optimised by varying reaction temperature, reagent stoichiometry, concentration, addition rate, and reaction time. Adaptation of this transformation to continuous-flow processing could provide improved control over mixing, temperature, and residence time and may improve reproducibility and facilitate scale-up. The potential advantages of flow processing should, however, be established through direct comparison with the corresponding batch reaction.

Further optimisation of the ring-closing metathesis step is also required. The batch experiments gave variable crude yields under nominally identical conditions, while the highest calculated crude yield was obtained when both reaction scale and catalyst loading were reduced. Since these variables were not investigated independently and the recovered material was not obtained in analytically pure form, their individual effects on reaction performance could not be established. Future studies should therefore independently investigate catalyst identity and loading, substrate concentration, reaction temperature, reaction time, and solvent. Quantitative assessment of conversion and product purity would also be required to distinguish changes in reaction performance from differences in material recovery or crude-product composition. Following optimisation in batch, implementation

of the RCM reaction under continuous-flow conditions could be investigated to determine whether improved control of reaction parameters enhances reproducibility or process efficiency.⁸⁰

The TBAF-mediated removal of the silicon tether afforded dienediol **1h** in 63% isolated yield but required overnight reflux followed by chromatographic purification. Future work should therefore focus on reducing reaction time and improving product recovery and purity by systematically investigating the effects of TBAF equivalents, temperature, reaction time, and solvent. Alternative desilylation conditions could also be evaluated where appropriate, with their effectiveness and compatibility with the substrate assessed experimentally.⁸¹

For the hydrogenation of dienediol **1h** to nonane-2,7-diol **1i**, future work should focus on reproducible and complete reduction of both carbon–carbon double bonds while minimising substrate degradation and improving the purity and recovery of **1i**. Catalyst identity and loading, hydrogen pressure, solvent, temperature, and reaction time could be systematically investigated. The principal chemoselectivity requirement in this transformation is reduction of the C=C bonds while retaining the two alcohol functionalities and avoiding undesired side reactions.⁸²

Finally, optimisation of the acylation of nonane-2,7-diol **1i** should focus on achieving complete conversion of both hydroxyl groups to the corresponding butyrate esters while improving isolated yield and product purity. Variables including the equivalents of acylating reagent, reaction time, temperature, catalyst loading, and purification conditions could be systematically investigated. Alternative acylation methods could also be explored where appropriate. If biocatalytic esterification is investigated in future work, the intended chemo-, regio-, or stereoselectivity should be clearly defined and experimentally evaluated rather than described using the general term “selectivity.”⁸³

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Chapter 3: Towards the Synthesis of Racemic-Dibutyroxynonane by Flow Chemistry

3.1 Flow Set-up and Reaction Parameters

Following the development of the batch synthetic route described in Chapter 2, this chapter investigates the application of continuous-flow processing to selected steps in the synthesis of racemic dibutyroxynonane. In particular, the two sequential nucleophilic substitution reactions involved in formation of the unsymmetrical silicon-tethered intermediate were investigated under flow conditions. The effects of key processing parameters, including temperature, flow rate, and residence time, were examined, together with practical challenges associated with transferring the low-temperature batch reactions to a continuous-flow system. The results obtained under flow conditions were subsequently compared with the corresponding batch procedures to evaluate the feasibility and limitations of this approach.

3.1.1 Two-step Flow Set-up

Figure 3-1 illustrates the two-stage continuous-flow system used for sequential reagent addition. In the first stage, two reagent streams were introduced using syringe pumps and combined through a T-piece mixer before entering **Reactor A**, which could be maintained at low temperature using a cooling bath. The effluent from **Reactor A** was then directed to a second mixing point, where an additional reagent stream was introduced using a third syringe pump. The combined stream subsequently entered **Reactor B** for the second reaction stage.

The two reactors were connected in series, with reagent delivery controlled by the syringe pumps. The system therefore allowed temperature, flow rate, and residence time to be varied during investigation of the sequential transformations. Following passage through the reactors, the reaction mixture could be collected for subsequent work-up and analysis.

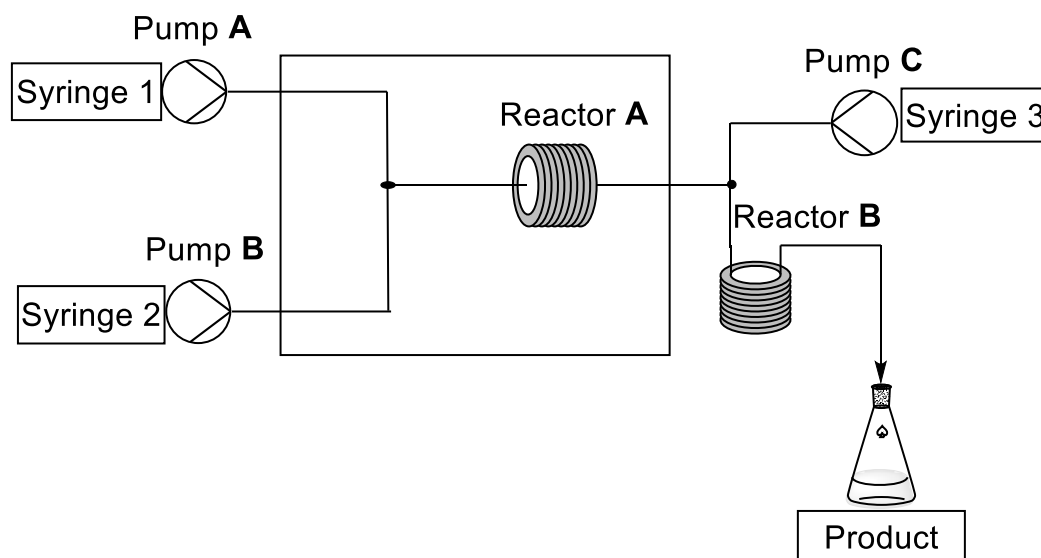


Figure 3-1 Two-Step Flow Set-up.

3.1.2 One-step Flow Set-up

The one-step flow apparatus used in this study is illustrated in Figure 3-2. The system consisted of two syringes, labelled Syringe 1 and Syringe 2, mounted on syringe pumps (Pump A and Pump B), respectively. Each syringe contained a separate reagent solution that was delivered at a controlled flow rate into a T-piece mixer, where the two streams were combined before entering Reactor A. The reactor provided a defined internal volume in which the reaction proceeded under controlled temperature and flow conditions. This arrangement allowed reaction parameters including flow rate, residence time, temperature, and concentration to be varied during the investigation. Following reaction, the outflow from Reactor A was collected for subsequent work-up and analysis.

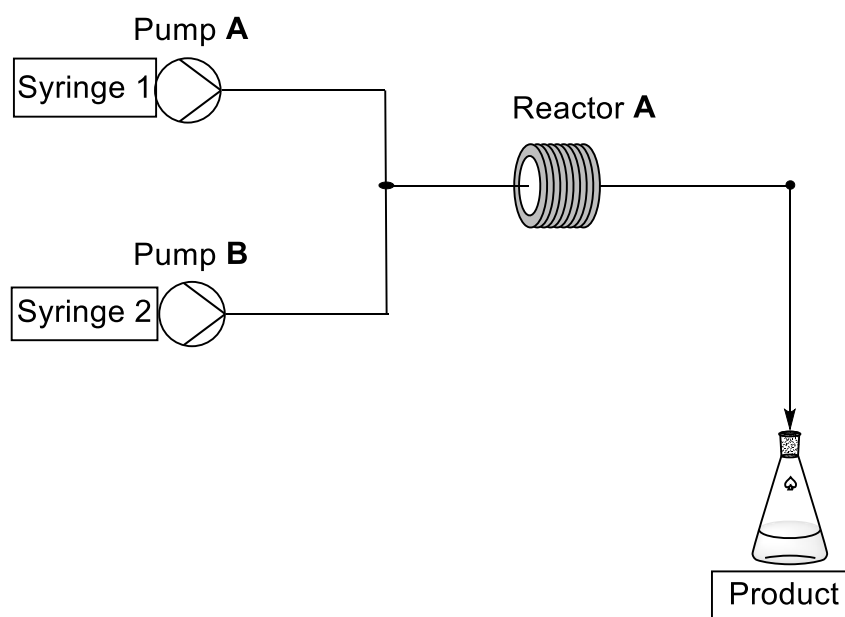


Figure 3-2 One-Step Flow Set-up.

3.1.3 Flow Reaction Parameters

Equation 3-1 defines molarity as the ratio of the amount of substance to the volume of solution, where C_M represents molar concentration in moles per liter ($\text{mol}\cdot\text{L}^{-1}$), n the number of moles of solute, and V is the volume of the solution in liters. This parameter is fundamental in flow chemistry because it determines the concentration of reagents entering the reactor, directly influencing reaction kinetics, stoichiometry, and overall efficiency.

$$C_M \left(\frac{\text{mol}}{\text{L}} \right) = \frac{n}{V}$$

Equation 3-1 Molarity.

Equation 3-2 calculates residence time, which is the duration the reaction mixture remains inside the reactor, where t_{res} is measured in minutes or seconds, V_{reactor} is the internal volume of the reactor (typically in milliliters or liters), and ϑ_{total} is the combined volumetric flow rate of all reagent streams ($\text{mL}\cdot\text{min}^{-1}$). Residence time is a critical parameter for controlling conversion and selectivity in continuous-flow systems, as it dictates how long reactants interact under defined conditions.

$$t_{\text{res.}}(\text{min}) = \frac{V(\text{mL})}{\vartheta \left(\frac{\text{mL}}{\text{min}} \right)}$$

Equation 3-2 Residence Time.

Equation 3-3 describes the molar flow rate, which indicates the quantity of substance delivered per unit time, where $\dot{n}$ is the molar flow rate in $\text{mol}\cdot\text{min}^{-1}$, C_M is the molar concentration ($\text{mol}\cdot\text{L}^{-1}$), and ϑ is the volumetric flow rate ($\text{L}\cdot\text{min}^{-1}$). This calculation is essential for scaling reactions and maintaining precise stoichiometric ratios in flow chemistry, ensuring that each reagent is introduced at the correct rate to achieve optimal reaction performance.

$$\dot{n} = C\vartheta$$

Equation 3-3 Molar Flow Rate.

3.2 Transitioning from Batch to Continuous Flow Processing

The transition from conventional batch processing to a continuous-flow system was a key aspect of this phase of the research. Continuous-flow processing can offer improved control over reaction conditions, particularly temperature, mixing, flow rate, and residence time, and may provide advantages in terms of reproducibility, heat and mass transfer, scalability, and automation. These potential advantages provided the basis for investigating whether selected steps of the batch synthesis described in Chapter 2 could be transferred to a continuous-flow system.

To investigate this transition, key reaction parameters including concentration, residence time, reactor volume, temperature, and flow rate were considered. Concentration and flow rate determine reagent delivery and stoichiometry, while reactor volume and total flow rate determine the residence time available for reaction. These parameters were therefore varied where appropriate to evaluate the behaviour of the reactions under continuous-flow conditions.⁸⁴

Finally, flow rate was controlled to regulate the speed at which reagents entered and exited the reactor, directly influencing residence time and reaction kinetics. These parameters were varied to investigate the behaviour of the reactions under continuous-flow conditions and to assess the practical effects of flow rate, residence time, and temperature on the operation of the system.

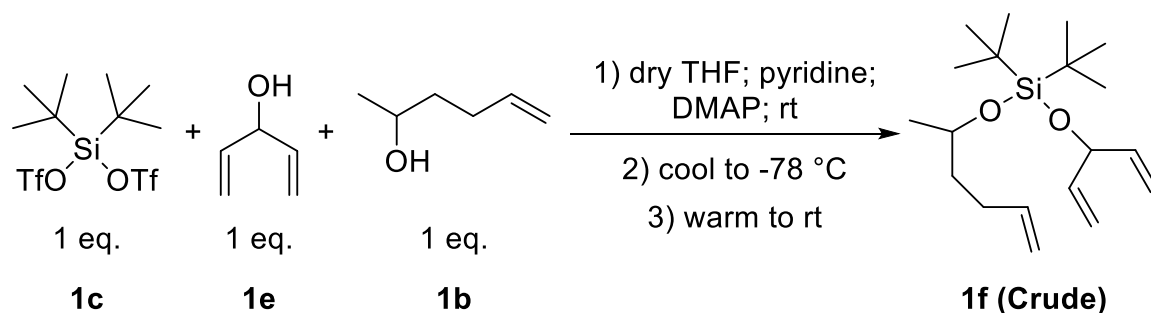
3.3 Initial Two Steps in the Flow-Based Synthesis of Racemic Dibutyroxynonane

This section investigates the application of flow chemistry to the unsymmetrical silicon-tethering sequence used in the synthesis of racemic dibutyroxynonane. The two sequential nucleophilic substitution steps were examined under continuous-flow conditions and compared qualitatively with the corresponding batch reactions.

3.3.1 Unsymmetrical Silicon-tethering of Di-*t*-Butylsilyl

Bis(Trifluoromethanesulfonate) with Two Alcohols in a Flow Reactor

This step aimed to achieve the sequential nucleophilic substitution of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**) with 5-hexen-2-ol (**1b**) and 1,4-pentadien-3-ol (**1e**) under continuous-flow conditions, as illustrated in Scheme 3-1. The experimental set-up was designed to provide controlled reagent addition and reaction conditions during the two sequential substitution reactions. Formation of the unsymmetrical silicon-tethered product **1f** had previously been supported in the corresponding batch reaction by the spectroscopic evidence described in Section 2.3, providing a basis for comparison with the material obtained under flow conditions.



Scheme 3-1 Unsymmetrical silicon tethering of **1c** with 5-hexen-2-ol (**1b**) and 1,4-pentadien-3-ol (**1e**) under continuous-flow conditions.

3.3.1.1 Flow Setup

The two-stage flow system used for the sequential silicon-tethering reaction is shown in Figure 3-3. Three reagent streams were delivered using separate syringe pumps and combined sequentially through T-piece mixers. The first two streams entered Reactor A, while the third reagent stream was introduced before Reactor B to carry out the second substitution step. This configuration allowed the two sequential reactions to be investigated within a continuous-flow system. Detailed reagent quantities, solution preparation, and experimental procedures are provided in Chapter 4.

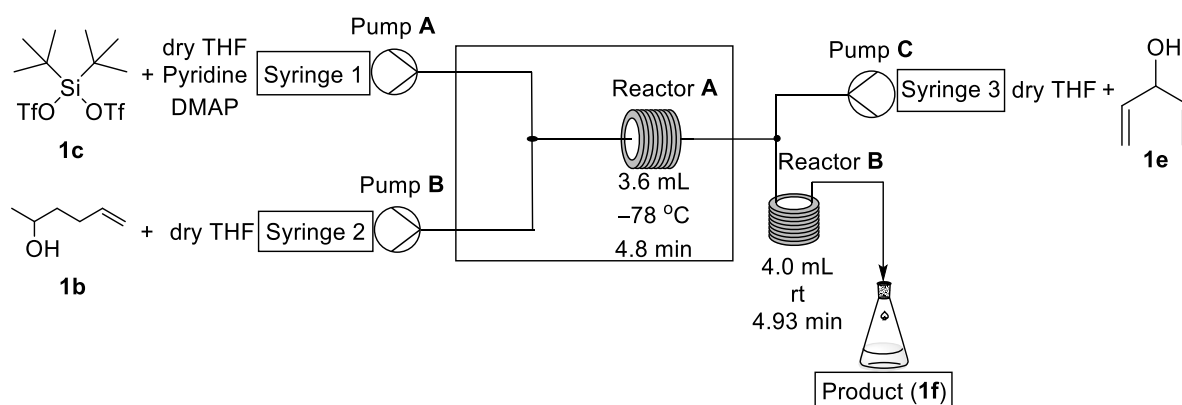


Figure 3-3 Flow Set-up for the Silicon-Tethering Reaction.

3.3.1.2 Reaction Parameters and Flow Conditions

The sequential silicon-tethering reaction was investigated using a two-stage continuous-flow system. Reactor A was operated at $-78\text{ }^{\circ}\text{C}$ with reagent streams at molar concentrations of 0.2 M and 0.4 M (Equation 3-1), delivered at flow rates of 0.50 and 0.25 mL min^{-1} , respectively. The combined volumetric flow rate was therefore 0.75 mL min^{-1} , which, together with the 3.6 mL internal volume of Reactor A, gave a calculated residence time of approximately 4.8 min (Equation 3-2). The resulting stream was subsequently combined with the third reagent solution before entering Reactor B. Detailed reagent quantities, solution preparation, flow conditions, and experimental procedures are provided in Chapter 4.

Analysis of the crude reaction mixture by ^1H NMR spectroscopy provided evidence for the formation of the unsymmetrical silicon-tethered product **1f** under flow conditions. The hydroxyl proton resonance of 1,4-pentadien-3-ol (**1e**), observed at δ 2.81 ppm, was absent from the crude product spectrum, consistent with consumption of the alcohol during formation of the second Si–O bond. In addition, two closely spaced *tert*-butyl singlets were observed at δ 0.95 and 0.96 ppm (9H each), consistent with chemically non-equivalent *tert*-butyl environments in the unsymmetrical product. The spectrum also contained alkene resonances at δ 5.83–5.67, 5.16, 5.00, and 4.93–4.78 ppm, together with an oxygenated proton resonance at approximately δ 4.08 ppm. These diagnostic features were consistent with those observed for **1f** prepared by the corresponding batch reaction described in

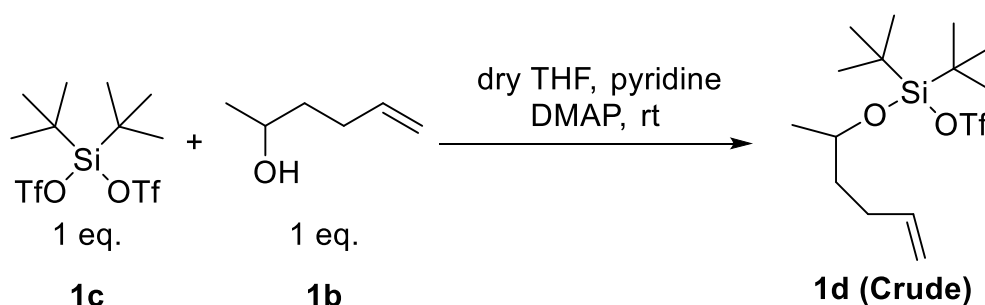
Section 2.3, supporting formation of the desired unsymmetrical silicon-tethered product under flow conditions.

3.3.1.3 Experimental Challenges and Observations

Despite the well-structured flow conditions, the reaction did not proceed as expected due to significant freezing of the reaction mixture within the reactor maintained at $-78\text{ }^{\circ}\text{C}$. The freezing of the reaction stream resulted in partial blockage of the reactor tubing, causing Pumps **A** and **B** to shut down intermittently at approximately one-minute intervals and preventing continuous delivery of the reagent solutions. As a consequence, the intended reagent flow could not be maintained throughout the experiment. Furthermore, no reaction mixture emerged from the reactor outlet until Pump **C** was activated, indicating that the blockage had disrupted the planned sequence of nucleophilic substitution and adversely affected the overall performance of the continuous-flow process.

3.3.2 Silylation of 5-Hexen-2-ol with Di-*t*-Butylsilyl Bis(Trifluoromethanesulfonate) in a Flow System

This section focuses on optimizing the silylation reaction of 5-hexen-2-ol (**1b**) with di-*t*-butylsilyl bis(trifluoromethanesulfonate) (**1c**) under continuous flow conditions. Unlike the previous experiment, which involved multiple alcohols, this study specifically investigated the impact of reaction parameters, flow rates, and residence times on a single alcohol substitution process, as depicted in Scheme 3-2. Formation of the corresponding monosilylated intermediate **1d** had previously been supported by TLC and NMR analysis of the batch reaction described in Section 2.2, providing a basis for comparison with the material obtained under flow conditions.



Scheme 3-2 Silylation of 5-hexen-2-ol (**1b**) with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**) under continuous-flow conditions.

3.3.2.1 Flow Reactor Setup

The flow reactor setup used for the silylation of 5-hexen-2-ol with di-*t*-butylsilyl bis(trifluoromethanesulfonate) is illustrated in Figure 3-4. Two reagent streams were delivered to the reactor through separate syringe pumps under anhydrous conditions. One stream contained di-*t*-butylsilyl bis(trifluoromethanesulfonate) together with the required base and catalyst, while the second stream contained 5-hexen-2-ol. The reagent streams were combined within the flow reactor under controlled conditions to investigate the

feasibility of the silylation reaction in a continuous-flow system. This configuration enabled precise control of reagent delivery, mixing efficiency, and residence time, allowing the performance of the reaction to be evaluated under reproducible flow conditions. Detailed experimental procedures and reagent quantities are provided in Chapter 4.

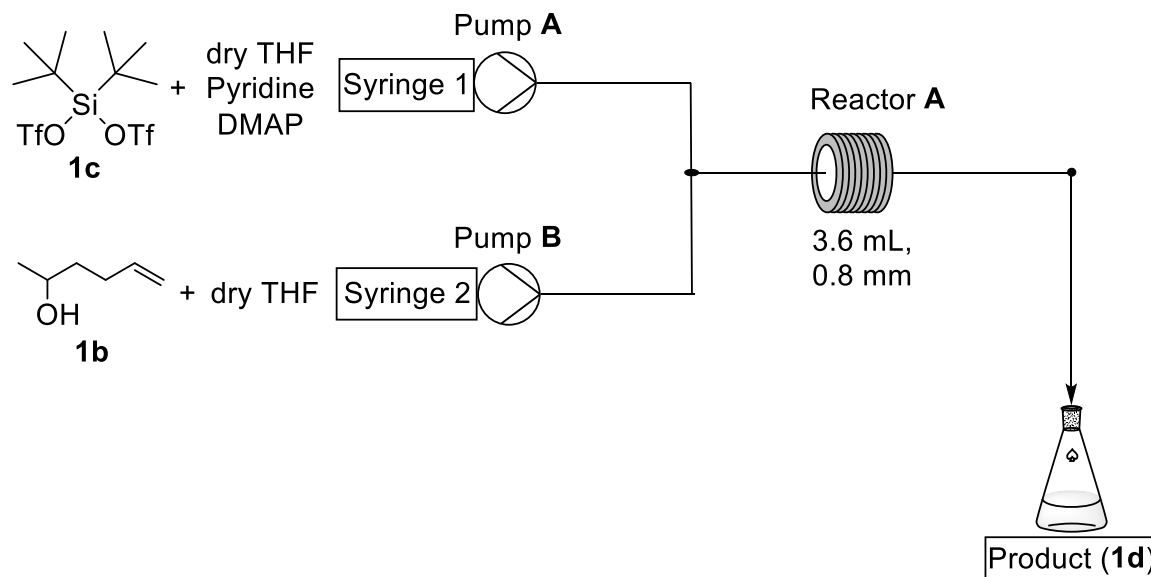


Figure 3-4 Flow Set-up of Silylation of 5-Hexen-2-ol.

3.3.2.2 Reaction Parameters and Optimization

and reaction temperature. The reagent concentrations were maintained at 0.2 M and 0.4 M for Syringes 1 and 2, respectively, while the flow rates were varied between experiments. Reagent delivery time refers to the time required to deliver the selected volume of each syringe solution at the stated flow rate, whereas residence time represents the calculated time spent by the combined reagent stream within the 3.6 mL flow reactor. These parameters were distinguished to allow the effects of reagent delivery, residence time, and temperature on the operation of the continuous-flow reaction to be evaluated.

Table 3-1 summarizes the continuous-flow experiments conducted for the nucleophilic substitution of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) with 5-hexen-2-ol. As the products were carried forward in crude form, the recorded masses are presented only as an indication of material recovery and should not be considered a direct measure of reaction efficiency or used for quantitative comparison between experiments. The study examined the influence of several operating parameters, including molar concentration (C_M ; Equation 3-1), reagent delivery time, molar flow rate ($\dot{n}$; Equation 3-3), volumetric flow rate (ϑ), reactor residence time ($t_{res.}$; Equation 3-2) and reaction temperature. The reagent concentrations were maintained at 0.2 M and 0.4 M for Syringes 1 and 2, respectively,

while the flow rates were varied between experiments. Reagent delivery time refers to the time required to deliver the selected volume of each syringe solution at the stated flow rate, whereas residence time represents the calculated time spent by the combined reagent stream within the 3.6 mL flow reactor. These parameters were distinguished to allow the effects of reagent delivery, residence time, and temperature on the operation of the continuous-flow reaction to be evaluated.

Table 3-1 Nucleophilic Substitution of di-*t*-butylsilyl bis(trifluoromethanesulfonate) with 5-hexen-2-ol under continuous-flow conditions.

Entry	C _M (M)		Reagent delivery time*, t _{delivery} (min)		ṅ (mmol min ⁻¹)		θ (mL min ⁻¹)		T _{res.} (min)	T (°C)	Crude product (g)
	S ₁ *	S ₂ *	S ₁	S ₂	S ₁	S ₂	S ₁	S ₂			
1	0.2	0.4	20	20	0.10	0.10	0.5	0.25	4.80	0	0.772
2	0.2	0.4	83.33	83.33	0.024	0.024	0.12	0.06	20.00	0	Frozen at the reactor
3	0.2	0.4	83.33	83.33	0.024	0.024	0.12	0.06	20.00	rt	0.251
4	0.2	0.4	125	125	0.008	0.008	0.04	0.02	60.00	rt	0.178
5	0.2	0.4	250	250	0.004	0.004	0.02	0.01	120.00	rt	0.182
6	0.2	0.4	625	625	0.0016	0.0016	0.008	0.004	300.00	rt	0.219

* S₁ = Syringe 1; S₂ = Syringe 2.

* Reagent delivery time refers to the time required to deliver the selected syringe solution volume at the stated flow rate and should not be confused with residence time in the flow reactor. Residence time (t_{res.}) was calculated from the 3.6 mL reactor volume and the combined volumetric flow rate of S₁ and S₂ according to Equation 3-2.

3.3.2.3 Flow Conditions and Product Analysis

The continuous-flow silylation experiments were conducted using a flow reactor with an internal volume of 3.6 mL. The concentrations of the solutions delivered from Syringes 1 and 2 were maintained at 0.2 M and 0.4 M, respectively, while the flow rates and reaction temperature were varied as summarised in Table 3-1. The corresponding molar flow rates were calculated according to Equation 3-3, and the residence time of the combined reagent stream within the reactor was calculated from the reactor volume and total volumetric flow rate according to Equation 3-2. Detailed reagent quantities, solution preparation, flow conditions, and experimental procedures are provided in Chapter 4.

The first experiment (Entry 1) was conducted at 0 °C using flow rates of 0.50 and 0.25 mL min⁻¹ for Syringes 1 and 2, respectively, corresponding to a calculated reactor residence time of 4.80 min. Reducing the flow rates to 0.12 and 0.06 mL min⁻¹ increased the calculated residence time to 20.00 min (Entry 2); however, freezing occurred within the reactor at 0 °C. The same flow conditions were therefore investigated at room temperature in Entry 3. Further reductions in the flow rates at room temperature increased the calculated

reactor residence times to 60, 120, and 300 min for Entries 4–6, respectively. Although the reagent concentrations remained unchanged throughout these experiments, the total volumes of reagent solutions delivered in Entries 4–6 were approximately half of those used in the initial low-temperature experiments.

Formation of the monosilylated intermediate **1d**, di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate, was assessed by comparison with the analytical characteristics established for **1d** in the corresponding batch reaction described in Section 2.2. In the batch study, formation of **1d** was supported by disappearance of the starting 5-hexen-2-ol (**1b**) spot at $R_f = 0.53$ and appearance of a less polar product spot at $R_f \approx 0.93$ (EtOAc/petroleum ether, 3:7), together with characteristic NMR resonances including the *tert*-butyl signal at δ 0.97 ppm (18H) and the oxygenated methine resonance at δ 3.70–3.66 ppm. These established analytical characteristics were used as the reference for assessing formation of **1d** during the continuous-flow experiments. As the material was carried forward in crude form and separate complete spectroscopic datasets were not obtained for each individual flow experiment, the flow results were interpreted qualitatively rather than used for quantitative assessment of conversion or product purity.

3.3.2.4 Experimental Challenges and Observations

Several experimental challenges were encountered during the continuous-flow silylation experiments, particularly in relation to temperature control and flow stability.

A significant challenge was observed during the experiments conducted at 0 °C (Entries 1 and 2). Entry 1 was performed using flow rates of 0.50 and 0.25 mL min⁻¹ for Syringes 1 and 2, respectively, corresponding to a calculated reactor residence time of 4.80 min, and 0.772 g of crude material was recovered. When the flow rates were reduced to 0.12 and 0.06 mL min⁻¹ in Entry 2, the calculated reactor residence time increased to 20.00 min. Under these conditions, freezing occurred within the reactor, resulting in blockage of the reactor channel and disruption of reagent flow. Consequently, normal collection of the reaction mixture was not possible.

Conducting the reaction at room temperature prevented the freezing observed in Entry 2. Entry 3 was performed using the same flow rates as Entry 2, corresponding to a calculated reactor residence time of 20.00 min, and afforded 0.251 g of crude material. Further reductions in flow rate increased the calculated residence times to 60, 120, and 300 min for Entries 4–6, respectively, with corresponding recovered crude masses of 0.178, 0.182, and 0.219 g. However, the total reagent volumes used in Entries 4–6 were approximately half of those used in the earlier experiments. Consequently, the recovered crude masses cannot be directly compared between all entries as a measure of reaction efficiency or conversion.

Overall, these experiments demonstrated that the low-temperature flow conditions were associated with an operational limitation at the lower flow rates, as illustrated by freezing and reactor blockage in Entry 2. Operation at room temperature avoided this problem and allowed the reaction mixture to pass through the reactor over the range of flow rates investigated. However, because the products were carried forward in crude form, the reagent volumes differed between some experiments, and conversion and product purity were not independently quantified, the effect of increasing residence time on reaction performance cannot be determined conclusively from the recovered masses alone. Further

experiments under directly comparable conditions, together with quantitative analysis of conversion and product purity, would be required to establish the influence of residence time and temperature on the continuous-flow silylation.

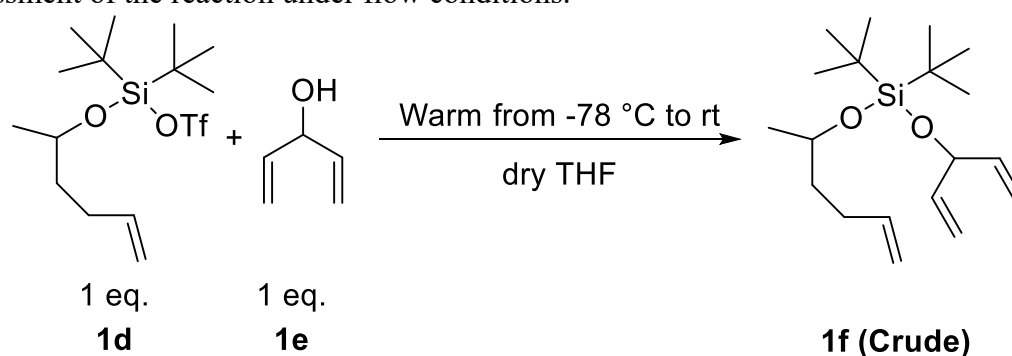
3.3.3 Silicon Tethering of Di-*tert*-butyl(hex-5-en-2-yloxy)silyl

Trifluoromethanesulfonate (**1d**) with 1,4-Pentadien-3-ol (**1e**)

The second silicon-tethering step involved nucleophilic substitution of di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate (**1d**) with 1,4-pentadien-3-ol (**1e**) to form the unsymmetrical bis-silyl ether **1f**, as shown in

Scheme 3-3 and

Figure 3-5. Formation of **1f** had previously been supported in the corresponding batch reaction by the spectroscopic evidence described in Section 2.3, providing a basis for assessment of the reaction under flow conditions.



Scheme 3-3 Silicon tethering of **1d** with 1,4-pentadien-3-ol (**1e**) to form **1f**.

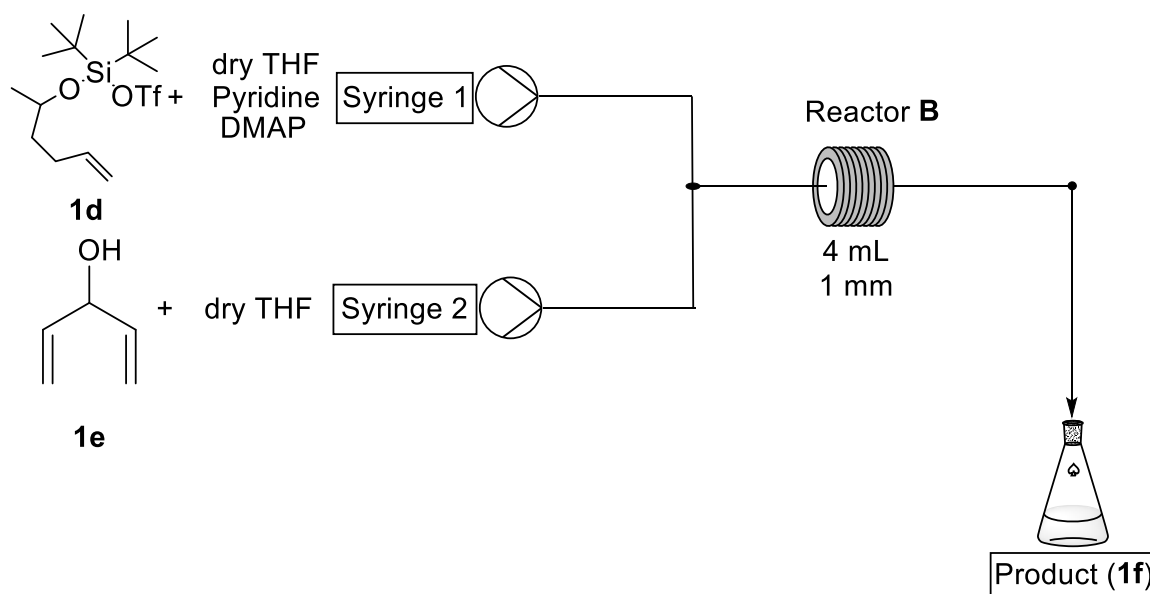


Figure 3-5 Flow set-up for the silicon-tethering reaction of **1d** with 1,4-pentadien-3-ol (**1e**).

3.3.3.1 Reaction Set-up and Conditions

The subsequent continuous-flow experiment investigated the reaction of the crude monosilylated intermediate **1d**, obtained from Entry 3 of the preceding flow experiment, with 1,4-pentadien-3-ol (**1e**) at room temperature. The crude **1d** was used without further purification. The two reagent streams were delivered separately and combined within the continuous-flow system. For the solution of **1e**, a concentration (C_M) of 0.4 M was employed (Equation 3-1) at a volumetric flow rate (Q) of 0.025 mL min⁻¹, corresponding to a molar flow rate ($\dot{n}$) of 0.010 mmol min⁻¹ (Equation 3-3). The reagent solution was delivered over 200 min. Detailed reagent quantities, solution preparation, reactor residence time, and experimental procedures are provided in Chapter 4.

Formation of the unsymmetrical silicon-tethered product **1f** had previously been supported in the corresponding batch synthesis by the spectroscopic evidence described in Section 2.3. The analytical characteristics of the crude material obtained from the flow experiment were consistent with those previously observed for **1f**, supporting formation of the unsymmetrical silicon-tethered product under the flow conditions investigated.

3.3.3.2 Evaluation of the Continuous-Flow Approach

The second silicon-tethering reaction was investigated under continuous-flow conditions at room temperature using crude **1d** obtained from Entry 3 of the preceding flow experiment and 1,4-pentadien-3-ol (**1e**). The solution of **1e** was delivered over a period of 200 min; this value represents the reagent delivery time rather than the residence time within the flow reactor. Following the reaction, crude material was recovered. Detailed reagent quantities, solution preparation, flow conditions, work-up, and experimental procedures are provided in Chapter 4.

Formation of the unsymmetrical silicon-tethered product **1f** was assessed by comparison with the analytical characteristics established for **1f** in the corresponding batch synthesis described in Section 2.3. The characteristics of the crude material obtained from the flow experiment were consistent with those previously observed for **1f**, supporting formation of the desired unsymmetrical silicon-tethered intermediate under the flow conditions investigated. However, because the product was obtained and carried forward in crude form and conversion and purity were not independently quantified, the recovered mass should not be interpreted as an isolated yield or as a quantitative measure of reaction efficiency.

The investigation demonstrated that the two sequential nucleophilic substitution steps involved in silicon tethering could be examined using continuous-flow processing, although practical limitations were encountered during transfer of the low-temperature batch conditions to the flow system. In particular, operation at low temperature resulted in freezing and reactor blockage at reduced flow rates, whereas conducting the reaction at room temperature avoided this operational problem. These observations demonstrate the importance of considering temperature and flow rate when adapting the silicon-tethering reactions to continuous processing.

Only the nucleophilic substitution steps of the synthetic sequence were investigated under continuous-flow conditions in this study. Consequently, direct comparison of the complete batch and flow synthetic routes was not possible. Furthermore, because the flow products were carried forward as crude materials and quantitative conversion and purity data were not obtained for each experiment, the relative efficiency of the batch and flow processes cannot be established from the present results alone.

Future work should therefore focus on improving the operational stability of the low-temperature flow process and establishing reaction performance using quantitative analytical methods. Temperature, flow rate, reactor residence time, reagent concentration, and solvent composition could be investigated systematically while maintaining the remaining variables constant. Alternative reactor configurations and more precise temperature-control systems could also be evaluated to reduce the risk of freezing and blockage. Incorporation of suitable in-line analytical techniques could additionally allow reaction conversion and product formation to be monitored during continuous operation. These studies would provide a more reliable basis for determining whether continuous-flow processing offers advantages over the corresponding batch reactions and for assessing the feasibility of extending flow processing to subsequent steps of the synthetic sequence.⁸⁵⁻⁸⁷

3.4 Comparison of Batch and Flow Chemistry Methodologies

The batch synthesis described in Chapter 2 and the continuous-flow experiments investigated in this chapter demonstrated different practical characteristics for the silicon-tethering reactions. Under batch conditions, the sequential nucleophilic substitution reactions were performed using established low-temperature procedures, and formation of the corresponding silicon-tethered intermediates **1d** and **1f** was supported by TLC and NMR analysis. In the continuous-flow experiments, the same transformations were investigated by varying parameters including temperature, flow rate, reagent delivery time, and reactor residence time.

Transfer of the low-temperature conditions to the continuous-flow system presented an important operational challenge. At reduced flow rates, freezing of the reaction mixture resulted in reactor blockage and disruption of reagent delivery. Conducting the experiments at room temperature avoided the freezing observed under the low-temperature conditions and allowed continuous operation over the range of flow rates investigated. However, because the flow-derived products were carried forward in crude form and conversion and product purity were not independently quantified for each experiment, it is not possible to conclude from the present data that the room-temperature flow conditions provided greater reaction efficiency or product yield than the corresponding batch procedures.

The present study therefore demonstrates the feasibility of investigating the two sequential silicon-tethering steps using continuous-flow processing while also identifying temperature control and reactor blockage as important practical limitations. A quantitative comparison of the batch and flow methodologies would require experiments performed under directly comparable conditions together with measurements of conversion, isolated yield, product purity, and process reproducibility.

Only the two nucleophilic substitution steps were investigated under continuous-flow conditions in this study, and the remaining transformations in the synthesis were performed using batch processing. Future work could investigate the extension of continuous-flow processing to subsequent steps, including ring-closing metathesis, silicon-tether deprotection, hydrogenation, and acylation. Such studies, together with systematic optimisation and quantitative analytical evaluation, would be required to determine whether a more extensively continuous process offers practical advantages over the batch route.

3.5 Conclusions and Outlook

This chapter investigated the feasibility of applying continuous-flow processing to selected steps in the synthesis of racemic dibutyroxynonane, the racemic counterpart of the sex pheromone associated with the orange wheat blossom midge (OWBM). The complete synthetic sequence was established using batch processing, whereas the flow investigation focused on the two sequential nucleophilic substitution reactions involved in formation of the silicon-tethered intermediates **1d** and **1f**.

The batch route provided a practical basis for evaluating the corresponding transformations under flow conditions. Racemic 5-hexen-2-ol (**1b**) was prepared from 5-hexen-2-one (**1a**) and subsequently employed in the silicon-tethering sequence described in Chapter 2. Formation of the monosilylated intermediate **1d** and the unsymmetrical bis-silyl ether **1f** was supported by TLC and NMR analysis in the batch studies, and these analytical characteristics provided a reference for assessment of the corresponding flow experiments.

The continuous-flow experiments demonstrated that the silicon-tethering reactions could be investigated using a flow system, but also identified important practical limitations. In particular, transfer of the low-temperature conditions to the flow reactor resulted in freezing and reactor blockage at reduced flow rates, disrupting continuous reagent delivery. Operation at room temperature avoided the freezing observed under the low-temperature conditions and allowed the reaction mixtures to pass through the reactor over the range of flow rates investigated. However, because the products obtained from the flow experiments were carried forward in crude form and conversion and product purity were not independently quantified for each experiment, the relative reaction efficiency of the different flow conditions could not be established quantitatively.

The results therefore provide an initial assessment of the feasibility and limitations of transferring the silicon-tethering reactions from batch to continuous-flow processing rather than demonstrating an optimised continuous process. A rigorous comparison of the two methodologies would require experiments under directly comparable conditions together with quantitative determination of conversion, isolated yield, product purity, and process reproducibility.

Future work should focus initially on improving the operational reliability of the silicon-tethering reactions under flow conditions. Parameters including temperature, volumetric flow rate, reactor residence time, reagent concentration, solvent composition, and reactor configuration could be investigated systematically while controlling the remaining

variables. Improved temperature-control systems and alternative reactor configurations could also be evaluated to minimise freezing and blockage during low-temperature operation. Quantitative analytical methods would be required to determine how these changes affect conversion and product formation.

Further development could investigate whether subsequent transformations in the synthetic sequence, including ring-closing metathesis, silicon-tether deprotection, hydrogenation, and acylation, are suitable for continuous-flow processing. Integration of appropriate in-line analytical techniques, such as NMR, FTIR, or UV–Vis spectroscopy, could also be explored to monitor reaction progress and provide quantitative information during process development.⁸⁸ Such studies would allow the practical advantages and limitations of batch and continuous-flow processing to be evaluated on the basis of directly comparable experimental data.

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Chapter 4: Experimental

4.1 Spectroscopic Analysis and General Experimental Information

Reaction progress and product formation were monitored using thin-layer chromatography (TLC) and nuclear magnetic resonance (NMR) spectroscopy, as appropriate. Products and intermediates were characterised primarily by ^1H and ^{13}C NMR spectroscopy, with the spectroscopic data used to support structural assignments and assess product formation. Unless otherwise stated, the experimental procedures, reaction conditions, quantities of reagents, and analytical data for the compounds prepared in this study are provided in the following sections.

NMR spectra were recorded using Bruker Fourier 300 MHz, Bruker DPX 400 MHz, and Bruker DPX 500 MHz spectrometers. ^1H and ^{13}C NMR spectroscopy were used as the principal methods for structural characterisation of the synthesised intermediates and final products.

4.2 Materials and Reagents

All reagents, solvents, and starting materials used throughout this research were obtained from commercial suppliers, primarily Sigma-Aldrich, and were used as received unless otherwise stated. Anhydrous solvents and moisture-sensitive reagents were handled under an inert atmosphere when required.

4.3 Synthesis of racemic-dibutyroxynonane via batch Processing

The synthesis of racemic dibutyroxynonane was investigated through a multistep synthetic sequence involving alcohol formation, silicon tethering, ring-closing metathesis, deprotection, hydrogenation, and acylation. The detailed experimental procedures, including reagent quantities, reaction conditions, work-up, purification, and characterisation data, are provided in the following sections.

4.4 Continuous-Flow Silicon-Tethering Experiments

The application of continuous-flow processing to the two sequential silicon-tethering reactions was investigated using the flow systems described in Chapter 3. The experiments included the sequential reaction of di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**) with 5-hexen-2-ol (**1b**) and 1,4-pentadien-3-ol (**1e**), together with separate investigations of the first and second nucleophilic substitution steps. Detailed reagent preparation, flow conditions, and experimental observations are provided below.

4.4.1 Sequential Silicon Tethering of Di-*tert*-butylsilyl Bis(trifluoromethanesulfonate) with 5-Hexen-2-ol and 1,4-Pentadien-3-ol under Continuous-Flow Conditions

The reagent solutions were introduced into the flow system using separate syringe pumps. Syringe 1 contained di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**, 2.0 mmol, 0.65 mL), pyridine (4.2 mmol, 0.34 mL), and DMAP (0.2 mmol, 0.024 g) in dry THF (10 mL) under an argon atmosphere. Syringe 2 contained 5-hexen-2-ol (**1b**, 2.0 mmol, 0.24 mL) in dry THF (5 mL) under argon.

The solutions from Syringes 1 and 2 were delivered at flow rates of 0.50 and 0.25 mL min⁻¹, respectively, and combined through the first T-piece before entering Reactor A. Reactor A had an internal volume of 3.6 mL and was maintained at -78 °C using a dry ice–acetone bath. The combined volumetric flow rate was 0.75 mL min⁻¹, corresponding to a calculated residence time of approximately 4.8 min within Reactor A. The individual molar flow rates of the two reagent streams were each 0.10 mmol min⁻¹. Reagent delivery was continued for 20 min.

The effluent from Reactor A was subsequently directed to a second T-piece, where it was combined with a solution of 1,4-pentadien-3-ol (**1e**) delivered from Syringe 3. Syringe 3 contained 1,4-pentadien-3-ol (**1e**, 2.0 mmol) diluted with dry THF to a total solution volume of 1.0 mL, corresponding to a concentration of 2.0 M. This solution was delivered at a flow rate of 0.06 mL min⁻¹, corresponding to a molar flow rate of 0.12 mmol min⁻¹. The flow path between Syringe 3 and the second T-piece had an internal volume of 1.0 mL, corresponding to a transit time of approximately 16.7 min at this flow rate.

Following mixing at the second T-piece, the combined reagent stream entered Reactor B, which had an internal volume of 4.0 mL. The total volumetric flow rate entering Reactor B was 0.81 mL min⁻¹, corresponding to a calculated residence time of approximately 4.9 min.

During operation at -78 °C, freezing was observed within Reactor A, resulting in partial blockage of the reactor and intermittent disruption of reagent delivery from Pumps A and B. Consequently, the nominal flow conditions could not be maintained continuously throughout the experiment. The material collected from the reactor was therefore treated as crude product.

4.4.2 Silylation of 5-Hexen-2-ol with Di-*tert*-butylsilyl Bis(trifluoromethanesulfonate) under Continuous-Flow Conditions

The continuous-flow silylation experiments were performed using two syringe pumps connected through a T-piece mixer to a flow reactor with an internal volume of 3.6 mL. Reagent solutions were prepared under anhydrous conditions. Syringe 1 contained di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**, 2.0 mmol), pyridine (4.2 mmol), and DMAP (0.20 mmol) in dry THF, with the solution adjusted to a total volume of 10 mL. The concentration of **1c** in Syringe 1 was therefore 0.20 M. Syringe 2 contained 5-hexen-2-ol (**1b**, 2.0 mmol) in dry THF, with the solution adjusted to a total volume of 5 mL, corresponding to a concentration of 0.40 M. The same reagent quantities and solution

concentrations were used for Entries 1–6, while the flow rates and reaction temperature were varied as described below.

For Entry 1, the solutions from Syringes 1 and 2 were delivered at 0.50 and 0.25 mL min⁻¹, respectively, at 0 °C. The combined volumetric flow rate was 0.75 mL min⁻¹, corresponding to a calculated reactor residence time of 4.80 min. Reagent delivery was continued for 20 min, and 0.772 g of crude material was recovered.

For Entry 2, the flow rates were reduced to 0.12 and 0.06 mL min⁻¹ for Syringes 1 and 2, respectively, while the reactor was maintained at 0 °C. The combined volumetric flow rate was 0.18 mL min⁻¹, corresponding to a calculated reactor residence time of 20.00 min. Freezing occurred within the reactor under these conditions, resulting in reactor blockage and preventing normal collection of the reaction mixture.

Entry 3 was conducted using the same flow rates of 0.12 and 0.06 mL min⁻¹ at room temperature, corresponding to a calculated reactor residence time of 20.00 min. The reaction mixture was collected from the reactor outlet, and 0.251 g of crude material was recovered.

Entries 4–6 were conducted at room temperature using progressively lower flow rates. For Entry 4, Syringes 1 and 2 were delivered at 0.040 and 0.020 mL min⁻¹, respectively, corresponding to a calculated reactor residence time of 60.00 min, and 0.178 g of crude material was recovered. For Entry 5, flow rates of 0.020 and 0.010 mL min⁻¹ gave a calculated reactor residence time of 120.00 min, and 0.182 g of crude material was recovered. For Entry 6, flow rates of 0.008 and 0.004 mL min⁻¹ gave a calculated reactor residence time of 300.00 min, and 0.219 g of crude material was recovered.

The products obtained from these experiments were carried forward in crude form. Consequently, the recorded masses represent recovered crude material rather than isolated yields of purified **1d**.

4.4.3 Silicon Tethering of Crude **1d** with 1,4-Pentadien-3-ol under Continuous-Flow Conditions

The crude monosilylated intermediate **1d** obtained from Entry 3 of the preceding continuous-flow experiment (Section 4.4.2) was used directly in the second silicon-tethering reaction without isolation or further purification. Syringe 1 contained 12 mL of the crude solution containing **1d** obtained from the preceding flow experiment. Since **1d** was not isolated or purified before use, its exact amount and concentration in this solution were not determined. The crude solution was delivered at a volumetric flow rate of 0.060 mL min⁻¹. Delivery of the complete 12 mL solution therefore required 200 min.

Syringe 2 contained 1,4-pentadien-3-ol (**1e**, 2.0 mmol) in dry THF, with the solution adjusted to a total volume of 5.0 mL, corresponding to a concentration of 0.40 M. The solution was delivered at a volumetric flow rate of 0.025 mL min⁻¹, corresponding to a molar flow rate of 0.010 mmol min⁻¹. Delivery of the complete 5.0 mL solution also required 200 min.

The two reagent streams were delivered simultaneously and combined within the continuous-flow system at room temperature. The combined volumetric flow rate was $0.085 \text{ mL min}^{-1}$. With a reactor internal volume of 4.0 mL , this corresponded to a calculated reactor residence time of approximately 47.1 min . The 200 min period therefore represents the reagent delivery time for the two syringe solutions rather than the residence time within the reactor.

Following passage through the continuous-flow system, the reactor outflow was collected and passed through neutral alumina. The solvent was subsequently removed under reduced pressure to afford 0.0847 g of crude material. The recovered material was retained as crude product without further purification.

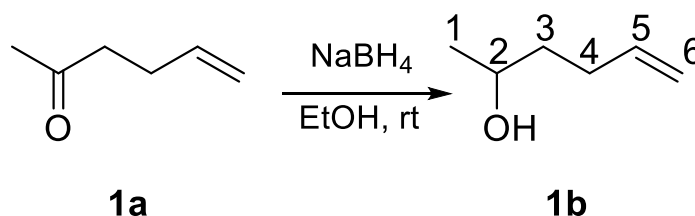
4.5 Synthesis and Characterisation of 5-Hexen-2-ol (**1b**)

The detailed experimental procedures and characterisation data for the compounds synthesised in this project are provided in the following sections.

4.5.1 5-hexen-2-ol (**1b**)

Synthesis of 5-Hexen-2-ol

The reduction of 5-hexen-2-one (**1a**) to 5-hexen-2-ol (**1b**) is illustrated in Scheme 4-1.



Scheme 4-1 Synthesis of 5-hexen-2-ol.

5-Hexen-2-one (**1a**) was dissolved in ethanol at room temperature, and sodium borohydride (1.2 equiv.) was added portionwise over 10 min with continuous stirring. The reaction mixture was stirred for 1 h at room temperature, and reaction completion was monitored by TLC using ethyl acetate/petroleum ether (1:4) as the eluent.

The reaction was investigated on three scales. On a 5 mmol scale, 5-hexen-2-one (**1a**, 5 mmol , 0.580 mL) was dissolved in ethanol (4 mL), and NaBH_4 (6 mmol , 0.238 g) was used, affording 5-hexen-2-ol (**1b**, 0.320 g , 64%). On a 10 mmol scale, 5-hexen-2-one (**1a**, 10 mmol , 1.159 mL) was dissolved in ethanol (10 mL), and NaBH_4 (12 mmol , 0.4539 g) was used, affording **1b** (0.703 g , 70%). On a 200 mmol scale, 5-hexen-2-one (**1a**, 200 mmol ,

23.17 mL) was dissolved in ethanol (160 mL), and NaBH₄ (240 mmol, 9.0792 g) was used, affording **1b** (12.86 g, 64%).

Following completion of the reaction, distilled water (4 mL) was added to the reaction mixture, followed by careful dropwise addition of 37% hydrochloric acid until approximately pH 7 was reached. The product was then subjected to three successive liquid–liquid separations. In each separation, distilled water (30 mL) and dichloromethane (40 mL) were used. The organic layers obtained from the three separations were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting 5-hexen-2-ol (**1b**) was obtained as a colourless product and was used in subsequent synthetic transformations without further purification.

¹H NMR Characterization

The formation of 5-hexen-2-ol (**1b**) was supported by ¹H NMR spectroscopy. The proton attached to the hydroxyl-bearing carbon, **CH(2)**, was observed at **δ 3.85–3.66 ppm**, while the hydroxyl proton was observed as a broad signal at **δ 4.14 ppm**. The methyl group **CH₃(1)**, coupled to **CH(2)**, appeared as a doublet at **δ 1.13 ppm** (*J* = 6.2 Hz, 3H).

The alkene functionality was retained, as indicated by the terminal vinylic proton signals at **δ 5.07–4.75 ppm** and the internal vinylic proton at **δ 5.77 ppm**. The remaining methylene resonances were observed in the expected regions and were consistent with the proposed structure.

¹H NMR (300 MHz, CDCl₃) δ 5.77 (*ddt*, *J* = 16.7, 10.2, 6.7 Hz, 1H), 5.07–4.75 (2H), 4.14 (s, 1H), 3.85–3.66 (*m*, 1H), 2.24–1.88 (*m*, 2H), 1.53–1.43 (*m*, 2H), 1.13 (*d*, *J* = 6.2 Hz, 3H) ppm.

¹³C NMR Characterization

The ¹³C NMR spectrum provided further evidence for the successful reduction of 5-hexen-2-one (**1a**) to 5-hexen-2-ol (**1b**). The ketone carbonyl resonance of the starting material at **δ 208.1 ppm** was absent from the product spectrum, while a resonance corresponding to the hydroxyl-bearing carbon appeared at **δ 67.7 ppm**. These changes are consistent with conversion of the ketone to the corresponding secondary alcohol.

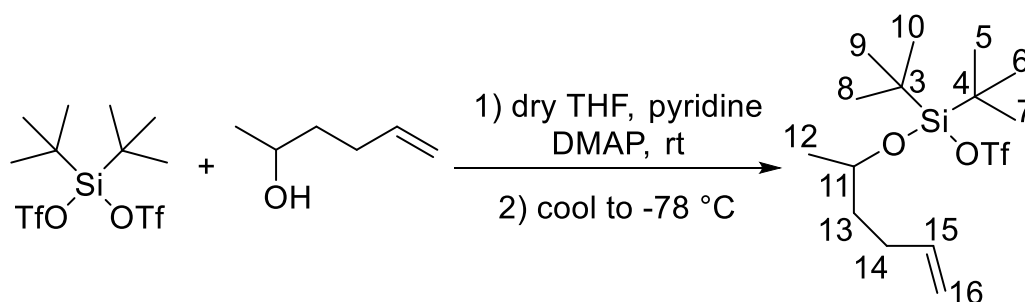
The alkene carbon resonances were observed at **δ 138.5** and **114.8 ppm**, while the remaining aliphatic carbon signals appeared at **δ 38.3, 30.2, and 23.5 ppm**, consistent with the proposed structure.

¹³C NMR (CDCl₃) δ 138.5, 114.8, 67.7, 38.3, 30.2, 23.5 ppm.

4.6 Racemic Dibutyroxynonane

4.6.1 Di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate

Di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate (**1d**) was prepared by reaction of 5-hexen-2-ol (**1b**) with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**), as shown in Scheme 4-2.



Scheme 4-2 Synthesis of di-*tert*-butyl(hex-5-en-2-yloxy)silyl trifluoromethanesulfonate (**1d**).

For the 2 mmol reaction using 0.75 equiv. of the alcohol, di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**, 2.0 mmol, 0.65 mL), pyridine (4.2 mmol, 0.34 mL), and DMAP (0.2 mmol, 0.0242 g) were dissolved in dry THF (10 mL) under an argon atmosphere. The reaction mixture was cooled to -78 °C using a dry ice–acetone bath. A solution of 5-hexen-2-ol (**1b**, 1.5 mmol, 0.18 mL) in dry THF (5 mL) was then added dropwise with continuous stirring. Following addition, the reaction mixture was allowed to warm gradually to room temperature over approximately 5 h.

For the corresponding 2 mmol reaction using 1.0 equiv. of the alcohol, **1c** (2.0 mmol, 0.65 mL), pyridine (4.2 mmol, 0.34 mL), and DMAP (0.2 mmol, 0.0242 g) were used, with 5-hexen-2-ol (**1b**, 2.0 mmol, 0.24 mL). The total volume of dry THF used for the sequential silicon-tethering procedure was 16 mL.

For the larger-scale reaction, **1c** (4.0 mmol, 1.30 mL), pyridine (8.4 mmol, 0.68 mL), and DMAP (0.4 mmol, 0.050 g) were employed, together with 5-hexen-2-ol (**1b**, 4.0 mmol, 0.48 mL). The total volume of dry THF used for the sequential silicon-tethering procedure was 32 mL.

Reaction progress was monitored by TLC after approximately 5 h. The starting 5-hexen-2-ol (**1b**) showed an *R_f* value of 0.53 (ethyl acetate/petroleum ether, 3:7), while the reaction mixture showed disappearance of the starting-material spot and appearance of a new spot at *R_f* ≈ 0.93–0.95 under the same conditions. The resulting monosilylated intermediate **1d** was not isolated or purified and was used directly in the subsequent silicon-tethering reaction. Consequently, an isolated yield was not determined for this step.

¹H NMR and ¹³C NMR Characterization

The crude material was analysed by ¹H and ¹³C NMR spectroscopy. The ¹H NMR spectrum showed retention of the alkene functionality, with the vinylic resonances observed at δ 5.77 and 5.07–4.75 ppm. The oxygenated methine resonance was observed at δ 3.70–3.66 ppm, and a singlet corresponding to the two *tert*-butyl groups of the silicon-containing intermediate was observed at δ 0.97 ppm (18H). The ¹³C NMR spectrum showed the oxygenated carbon at δ 67.7 ppm together with resonances consistent with the alkene and *tert*-butyl groups. These observations, together with the TLC analysis, supported formation of the monosilylated intermediate **1d**.

Additional signals at approximately δ 1.55 and 3.34 ppm in the ¹H NMR spectrum were attributed to residual THF in the crude material. Since **1d** was carried forward directly to the subsequent reaction without isolation or purification, complete removal of residual solvent was not pursued in order to minimise handling and potential material loss.

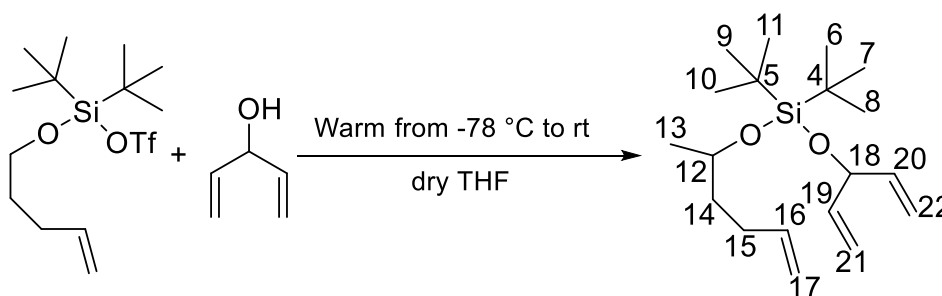
¹H NMR (500 MHz, CDCl₃) δ 5.77 (*ddt*, J = 6.7, 10.2, 17.4 Hz, 1H), 5.07–4.75 (2H), 3.70–3.66 (*m*, 1H), 2.24–1.88 (*m*, 2H), 1.53–1.43 (*m*, 2H), 1.13 (*d*, J = 6.2 Hz, 3H), 0.97 (*s*, 18H) ppm.

¹³C NMR (CDCl₃) δ 138.5, 114.7, 67.7, 38.2, 27.3, 23.4, 19.8 ppm.

4.6.2 Di-*tert*-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane (**1f**)

The formation of di-*tert*-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane (**1f**) through sequential silicon tethering is shown in

Scheme 4-3. The crude monosilylated intermediate **1d**, prepared as described in the preceding section, was used directly in the second silicon-tethering reaction without isolation or purification.



Scheme 4-3 Synthesis of di-*tert*-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane (**1f**).

For the 2 mmol sequential silicon-tethering experiment, di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (**1c**, 2.0 mmol, 0.65 mL), pyridine (4.2 mmol, 0.34 mL), and

DMAP (0.2 mmol, 0.0242 g) were dissolved in dry THF under an argon atmosphere. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ using a dry ice–acetone bath. A solution of 5-hexen-2-ol (**1b**) in dry THF (5 mL) was added dropwise with continuous stirring. Depending on the experiment, either 1.5 mmol (0.18 mL, 0.75 equiv.) or 2.0 mmol (0.24 mL, 1.0 equiv.) of **1b** was employed.

Following addition of **1b**, the reaction mixture was allowed to warm gradually from $-78\text{ }^{\circ}\text{C}$ to room temperature over approximately 5 h. The crude monosilylated intermediate **1d** formed during this stage was not isolated or purified. A solution of 1,4-pentadien-3-ol (**1e**, 2.0 mmol, 0.19 mL) in dry THF (1 mL) was then added dropwise to the reaction mixture with continuous stirring. The total volume of dry THF used throughout the sequential silicon-tethering procedure was 16 mL. The resulting reaction mixture was stirred overnight at room temperature.

For the larger-scale sequential reaction, **1c** (4.0 mmol, 1.30 mL), pyridine (8.4 mmol, 0.68 mL), DMAP (0.4 mmol, 0.050 g), 5-hexen-2-ol (**1b**, 4.0 mmol, 0.48 mL), and 1,4-pentadien-3-ol (**1e**, 4.0 mmol, 0.38 mL) were employed. The total volume of dry THF was increased proportionally to 32 mL. The same sequential addition procedure and temperature profile were employed.

An additional experiment was conducted using 1,4-pentadien-3-ol (**1e**, 2.5 mmol, 0.25 mL). The sequential tethering experiments employing 2.0, 2.5, and 4.0 mmol of **1e** afforded 1.174, 1.75, and 2.92 g of crude material, respectively. Since **1f** was not isolated or purified prior to weighing, these values represent crude product masses and were not used to calculate isolated yields.

Following completion of the second silicon-tethering reaction, the solvent was removed under reduced pressure. The crude material was filtered through a neutral alumina pad using 1% methanol in dichloromethane as the eluent. The solvent was subsequently removed under reduced pressure to afford crude **1f**, which was used directly in the subsequent ring-closing metathesis reaction without further purification.

^1H and ^{13}C NMR Characterization

Although **1f** was obtained and analysed in crude form, several diagnostic changes in the NMR spectra supported formation of the unsymmetrical silicon-tethered product. Most notably, the hydroxyl proton resonance of 1,4-pentadien-3-ol (**1e**), observed at $\delta\text{ }2.81\text{ ppm}$, was absent from the ^1H NMR spectrum of the crude product, consistent with conversion of the alcohol functionality during the second silicon-tethering reaction.

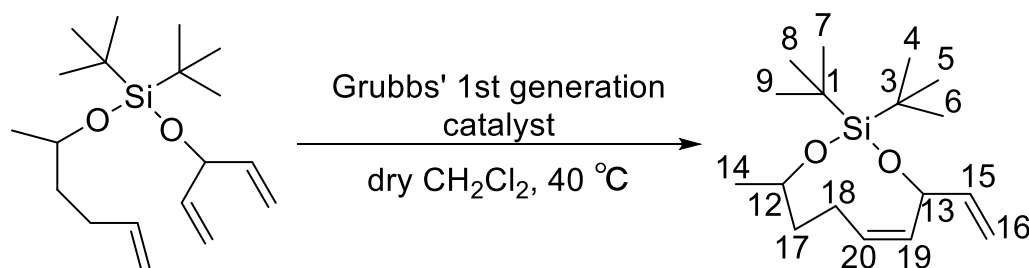
In addition, two separate *tert*-butyl singlets were observed at $\delta\text{ }0.95$ and 0.96 ppm , each integrating to 9H. The presence of two distinct *tert*-butyl resonances is consistent with the chemically non-equivalent environments generated upon formation of the unsymmetrical bis-silyl ether **1f**. The alkene resonances were retained in the product spectrum, consistent with preservation of the terminal alkene functionalities required for the subsequent ring-closing metathesis reaction.

^1H NMR (300 MHz, CDCl_3) δ 5.83–5.67 (*m*, 3H), 5.16 (*m*, 2H), 5.00 (*m*, 2H), 4.93–4.78 (*m*, 2H), 4.08 (*m*, 2H), 2.12–1.89 (*m*, 2H), 1.64–1.41 (*m*, 2H), 1.12 (*d*, $J = 6.8$ Hz, 3H), 0.96 (*s*, 9H), 0.95 (*s*, 9H) ppm.

^{13}C NMR (CDCl_3) δ 139.0, 114.3, 68.5, 38.9, 29.6, 27.6, 23.4, 20.5 ppm.

4.6.3 (*Z*)-2,2-Di-*tert*-butyl-4-ethenyl-9-methyl-1,3-dioxasilacyclonon-5-ene (**1g**)

The formation of (*Z*)-2,2-di-*tert*-butyl-4-ethenyl-9-methyl-1,3-dioxasilacyclonon-5-ene (**1g**) by ring-closing metathesis (RCM) of the unsymmetrical silicon-tethered precursor **1f** is illustrated in Scheme 4-4.



Scheme 4-4 Synthesis of (*Z*)-2,2-di-*tert*-butyl-4-ethenyl-9-methyl-1,3-dioxasilacyclonon-5-ene (**1g**) by ring-closing metathesis.

The crude silicon-tethered precursor **1f** was dissolved in anhydrous dichloromethane under an argon atmosphere. A separately prepared solution of Grubbs' catalyst in dry dichloromethane (10 mL) was transferred to the substrate solution by cannula under an inert atmosphere. The reaction apparatus and glassware were dried prior to use, and the reaction was maintained under argon.

The reaction mixture was heated at reflux for 1 h and subsequently allowed to cool to room temperature. The solvent was removed under reduced pressure. The resulting crude material was passed through a pad of neutral aluminium oxide (Al_2O_3 , chromatography grade), which had been pre-treated with distilled water for 1 h, using 1% MeOH in CH_2Cl_2 (MeOH/ CH_2Cl_2 , 1:99, v/v) as the eluent. This treatment was used to remove residual ruthenium catalyst and other strongly retained impurities; however, it did not provide complete purification of **1g**. The resulting material therefore remained crude and was characterised and used in the subsequent synthetic step without further purification.

Three RCM experiments were performed. In the first experiment, **1f** (300 mg) was treated with Grubbs' catalyst (5 mol%, 40 mg), affording 51 mg of crude **1g**. Under the same recorded substrate quantity and catalyst loading, a second experiment using **1f** (300 mg) and Grubbs' catalyst (5 mol%, 40 mg) afforded 137 mg of crude **1g**. In the third experiment, **1f** (150 mg) was treated with Grubbs' catalyst (2.5 mol%, 20 mg), affording 96 mg of crude **1g**.

Reaction progress and product formation were additionally assessed by TLC. Analysis using neutral alumina showed a product spot at **R_f = 0.50** using CH₂Cl₂/MeOH (49:1) as the eluent.

¹H NMR Characterization

Several diagnostic changes in the ¹H NMR spectrum supported formation of the cyclic RCM product **1g**. The oxygenated methine resonance shifted from **δ 4.16–3.98 ppm** in the acyclic precursor **1f** to **δ 4.82–4.79 ppm** following ring closure. Changes were also observed for neighbouring methylene resonances, including signals at **δ 1.87 and 2.71 ppm** in the cyclic product. These changes are consistent with the altered chemical environments generated upon cyclisation.

¹H NMR (300 MHz, CDCl₃) δ 5.78 (*m*, 1H), 5.44 (*m*, 1H), 5.31–5.12 (*m*, 1H), 5.02 (*m*, 2H), 4.82–4.79 (*m*, 1H), 4.02–3.91 (*m*, 1H), 2.71 (*m*, 2H), 1.87 (*m*, 2H), 1.13 (*d*, *J* = 6.8 Hz, 3H), 0.97 (*s*, 9H), 0.96 (*s*, 9H) ppm.

¹³C NMR Characterization

The ¹³C NMR spectrum provided further evidence for structural changes associated with the RCM reaction. Comparison with the acyclic precursor **1f** showed changes in the alkene region consistent with consumption of the alkene functionalities involved in ring closure and formation of the internal alkene of the cyclic product. A resonance at **δ 114.1 ppm** remained in the product spectrum, consistent with retention of the terminal ethenyl substituent in **1g**, while resonances at **δ 140.4 and 139.0 ppm** were observed in the alkene region.

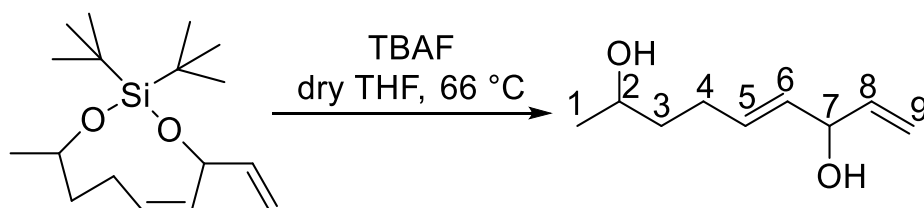
Changes were also observed in the oxygenated and aliphatic carbon environments following cyclisation. Taken together with the ¹H NMR and TLC data, these spectral changes supported formation of the cyclic RCM product **1g**.

¹³C NMR (CDCl₃) δ 140.4, 139.0, 114.1, 75.1, 68.5, 34.9, 27.4, 26.3, 23.4, 20.5 ppm.

The ¹H and ¹³C NMR spectra of **1g** are provided in Appendices and .⁹⁰

4.6.4 Nona-5,8-diene-2,7-diol (**1h**)

The TBAF-mediated cleavage of the silicon tether in **1g** to afford nona-5,8-diene-2,7-diol (**1h**) is illustrated in Scheme 4-5.



Scheme 4-5 TBAF-mediated cleavage of the silicon tether in **1g** to afford nona-5,8-diene-2,7-diol (**1h**).

Crude (*Z*)-2,2-di-*tert*-butyl-4-ethenyl-9-methyl-1,3-dioxo-2-silacyclonon-5-ene (**1g**, 220 mg) was dissolved in anhydrous THF (20 mL). Tetra-*n*-butylammonium fluoride (TBAF, 7.5 mmol, 7.5 mL) was added, and the resulting reaction mixture was heated at reflux overnight.

Following completion of the reaction, the reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the resulting crude material was purified by flash column chromatography using silica gel as the stationary phase and 100% diethyl ether as the eluent. The chromatography column had an internal diameter of approximately 2.5 cm and a silica gel bed height of approximately 15 cm. Nona-5,8-diene-2,7-diol (**1h**) was obtained as 73.2 mg of material, corresponding to an isolated yield of 63%.

¹H NMR Characterization

The ¹H NMR spectrum showed several changes consistent with cleavage of the silicon tether and formation of the acyclic diol **1h**. Alkene resonances were observed at δ 5.86, 5.51–5.40 and 5.13 ppm, while the two oxygenated methine environments were represented by resonances at δ 4.92 and 3.75 ppm. Changes were also observed in the aliphatic region relative to the cyclic precursor **1g**, including a methylene resonance at δ 1.50–1.45 ppm, consistent with the altered chemical environment following cleavage of the silicon tether.

A residual singlet at approximately δ 0.99 ppm, integrating to approximately 18H, was also observed and was attributed to a *tert*-butyl-containing silicon-derived impurity remaining after the deprotection and chromatographic purification. Related *tert*-butyl resonances had previously been observed at approximately δ 0.96 and 0.97 ppm in the silicon-containing precursor. The persistence of this signal indicated that chromatographic purification did not completely remove the silicon-derived impurity.

¹H NMR (500 MHz, CDCl₃) δ 5.86 (*ddd*, J = 17.2, 10.4, 5.7 Hz, 1H), 5.51–5.40 (*m*, 2H), 5.13 (*m*, 2H), 4.92 (*m*, 1H), 3.75 (*sext*, J = 6.4 Hz, 1H), 2.46–2.30 (*m*, 1H), 2.14–1.96 (*m*, 1H), 1.50–1.45 (*m*, 2H), 1.13 (*d*, J = 6.2 Hz, 3H) ppm.

¹³C NMR Characterization

The ¹³C NMR spectrum provided further evidence for cleavage of the silicon tether. Alkene carbon resonances were observed at δ 139.7, 132.6, 131.3 and 114.9 ppm, while the oxygenated carbon resonances at δ 68.4 and 66.3 ppm were consistent with the two alcohol-bearing carbon environments of the acyclic diol.

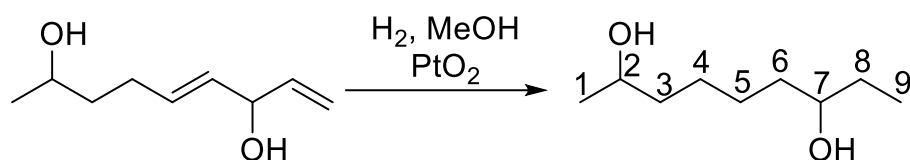
Importantly, the characteristic carbon resonances associated with the silicon-bound *tert*-butyl groups of precursor **1g** were absent from the product spectrum. The disappearance of these resonances, together with the changes observed in the ¹H NMR spectrum, supported cleavage of the silicon tether and formation of the acyclic diol **1h**.

¹³C NMR (CDCl₃) δ 139.7, 132.6, 131.3, 114.9, 68.4, 66.3, 38.1, 27.7, 23.7 ppm.

The ¹H and ¹³C NMR spectra of **1h** are provided in Appendices and v.⁹⁰

4.6.5 Nonane-2,7-diol (**1i**)

The hydrogenation of nona-5,8-diene-2,7-diol (**1h**) to nonane-2,7-diol (**1i**) is illustrated Scheme 4-6.



Scheme 4-6 Hydrogenation of nona-5,8-diene-2,7-diol (**1h**) to afford nonane-2,7-diol (**1i**).

Nona-5,8-diene-2,7-diol (**1h**, 73 mg) was dissolved in anhydrous methanol (8 mL) in a dry reaction vessel under an inert atmosphere. Platinum(IV) oxide (PtO₂, 57.5 mg, 25 mol%) was added, and the reaction vessel was placed under a hydrogen atmosphere (H₂, 1 atm) supplied using two hydrogen-filled balloons. The reaction mixture was stirred at room temperature for 40 min.

Following completion of the reaction, the mixture was filtered to remove the heterogeneous PtO₂ catalyst, and the filtrate was concentrated under reduced pressure to afford 56 mg of crude material containing nonane-2,7-diol (**1i**). The material was used in the subsequent synthetic transformation without further purification.

¹H NMR Characterization

Although **1i** was obtained in crude form and the ¹H NMR spectrum contained additional signals attributable to impurities, several diagnostic spectral changes supported hydrogenation of the carbon-carbon double bonds. Most notably, the vinylic resonances of precursor **1h**, previously observed at δ 5.86, 5.51–5.40 and 5.13 ppm, were absent from the product spectrum.

The product spectrum also contained a terminal methyl triplet at δ 0.87 ppm (J = 7.5 Hz, 3H) and a methyl doublet at δ 1.13 ppm (J = 6.8 Hz, 3H), consistent with formation of the saturated carbon framework. Taken together, the disappearance of the vinylic resonances and appearance of signals associated with the saturated product supported formation of nonane-2,7-diol (**1i**).

¹H NMR (500 MHz, CDCl₃) δ 3.73 (*m*, 1H), 3.42 (*s*, 1H), 2.40–2.31 (*m*, 1H), 2.20 (*s*, 1H), 1.62–1.16 (*m*, 10H), 1.13 (*d*, J = 6.8 Hz, 3H), 0.87 (*t*, J = 7.5 Hz, 3H) ppm.

¹³C NMR Characterization

The ^{13}C NMR spectrum provided further evidence for hydrogenation. The alkene carbon resonances of precursor **1h**, previously observed at δ 139.7, 132.6, 131.3 and 114.9 ppm, were absent from the product spectrum. Instead, the observed resonances were confined to the oxygenated and saturated aliphatic carbon regions.

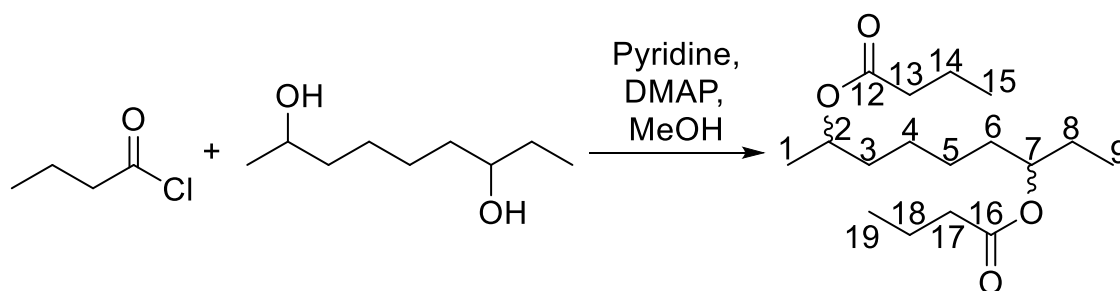
Oxygenated carbon resonances were observed at δ 73.30 and 68.15 ppm, while the remaining signals occurred in the saturated aliphatic region. The absence of resonances in the alkene region, together with the corresponding changes in the ^1H NMR spectrum, supported hydrogenation of both carbon–carbon double bonds and formation of the saturated diol **1i**.

^{13}C NMR (126 MHz, CDCl_3) δ 73.30, 68.15, 33.83, 30.16, 27.69, 23.83, 14.64 ppm.

The ^1H and ^{13}C NMR spectra of **1i** are provided in Appendices vi and vii.⁹⁰

4.6.6 Racemic Nonane-2,7-diyl Dibutyrate (**1j**)

The acylation of nonane-2,7-diol (**1i**) with butyryl chloride to afford racemic nonane-2,7-diyl dibutyrate (**1j**) is illustrated in Scheme 4-7.



Scheme 4-7 Synthesis of racemic nonane-2,7-diyl dibutyrate (**1j**) by acylation of nonane-2,7-diol (**1i**) with butyryl chloride.

Nonane-2,7-diol (**1i**, 56 mg, 0.35 mmol, 1.0 equiv.) was dissolved in anhydrous methanol (1.5 mL). Butyryl chloride (1.40 mmol, 0.147 mL, 4.0 equiv.) was added dropwise, followed by pyridine (1.5 mL) and DMAP (17.1 mg, 0.140 mmol, 0.4 equiv.). The reaction mixture was stirred at room temperature and monitored by TLC.

Following completion of the reaction, cold distilled water was added to quench the reaction mixture. The product was extracted with dichloromethane, and the organic phase was washed with aqueous sodium bicarbonate solution followed by brine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure.

The resulting crude material was purified by flash column chromatography to afford racemic nonane-2,7-diyl dibutyrate (**1j**) (78.7 mg, 75%). TLC analysis showed a product spot at R_f = 0.31 using ethyl acetate/petroleum ether (1:9, v/v) as the eluent. Although

chromatographic purification was performed, additional signals attributable to minor impurities remained in the NMR spectra.

¹H NMR Characterization

The ¹H NMR spectrum showed several diagnostic changes consistent with acylation of the two hydroxyl groups of **1i**. The oxygen-bearing methine protons were observed at **δ 4.82 and 4.74 ppm**, shifted downfield relative to the corresponding alcohol-bearing environments of precursor **1i**, consistent with conversion of the alcohol functionalities to ester groups.

Signals attributable to the incorporated butyrate groups were also observed. The methylene protons adjacent to the ester carbonyl groups appeared at **δ 2.22–2.16 ppm** (4H), while resonances associated with the butyrate β-methylene groups contributed to the region at **δ 1.63–1.54 ppm**. Terminal methyl resonances of the butyrate chains contributed to the signals observed in the **δ 0.91–0.85 ppm** region. The presence of these resonances, together with the downfield shifts of the oxygen-bearing methine protons, supported formation of the dibutyrate product **1j**.

¹H NMR (500 MHz, CDCl₃) δ 4.82 (*m*, 1H), 4.74 (*m*, 1H), 2.22–2.16 (*m*, 4H), 1.63–1.54 (*m*, 6H), 1.53–1.43 (*m*, 2H), 1.42–1.34 (*m*, 2H), 1.25–1.17 (*m*, 4H), 1.12 (*d*, *J* = 6.2 Hz, 3H), 0.91–0.85 (*m*, 9H), 0.80 (*t*, *J* = 7.4 Hz, 3H) ppm.

¹³C NMR Characterization

The ¹³C NMR spectrum provided further evidence for ester formation. Two ester carbonyl resonances were observed at **δ 173.6 and 173.4 ppm**, consistent with the two butyrate ester environments in **1j**. The oxygen-bearing carbon resonances were observed at **δ 75.1 and 70.6 ppm**.

Resonances attributable to the butyrate chains were also present, including signals at **δ 36.6 and 35.9 ppm** for carbons adjacent to the ester carbonyl groups, **δ 18.6 ppm** for the β-methylene carbons, and **δ 13.7 ppm** for the terminal methyl carbons. The appearance of the ester carbonyl and butyrate-chain resonances, together with the corresponding changes observed in the ¹H NMR spectrum, supported acylation of **1i** and formation of racemic nonane-2,7-diyl dibutyrate (**1j**).

¹³C NMR (CDCl₃) δ 173.6, 173.4, 75.1, 70.6, 36.6, 35.9, 29.7, 29.3, 27.0, 25.4, 25.2, 20.0, 18.6, 18.6, 13.7, 13.7, 9.6 ppm.

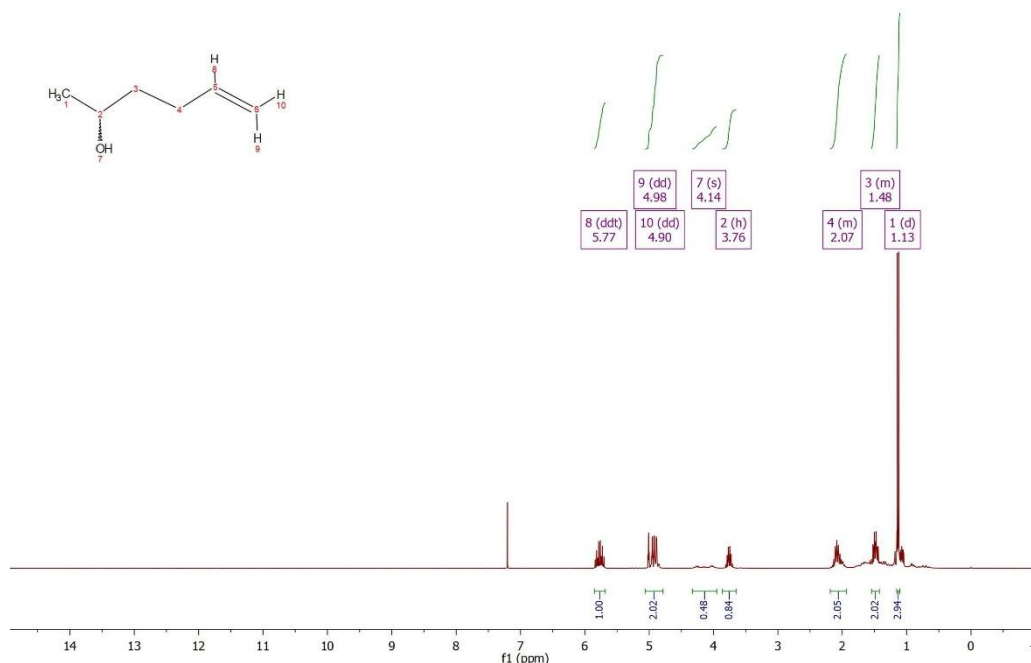
The ¹H and ¹³C NMR spectra of **1j** are provided in Appendices viii and ix.⁷⁹

References

89. A. Bhatia, S. Muthaiah. Synthesis of a Water-Soluble Ruthenium Complex and Its Catalytic Activity for Acceptorless Alcohol Dehydrogenation in Aqueous Medium. *Synlett* **2018**, 29 (12), 1644–1648.
90. Predicted NMR data calculated using Advanced Chemistry Development. Inc. (ACD/Labs) 2024.

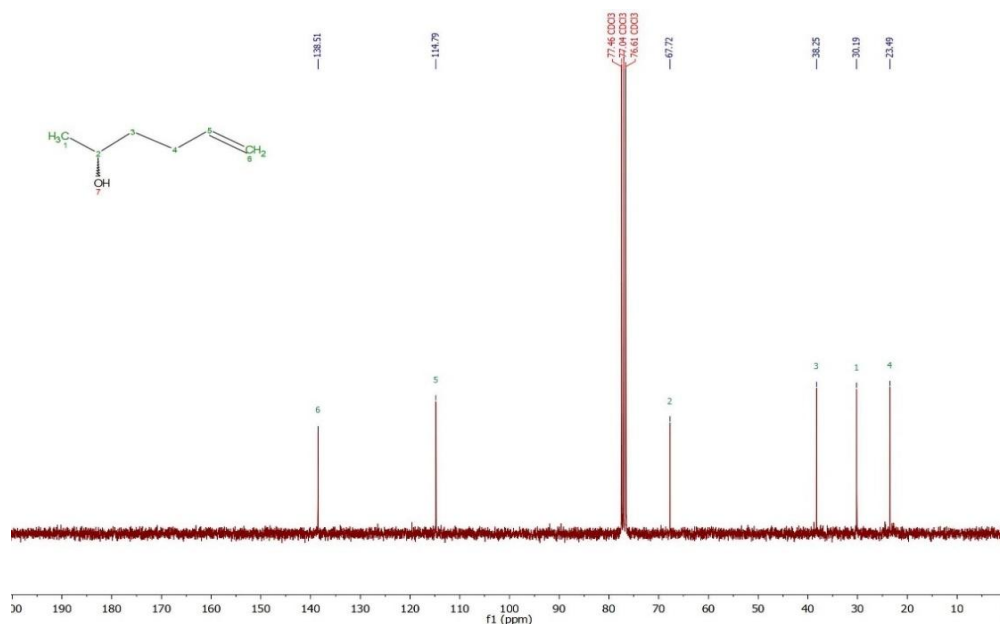
Appendix

i ^1H NMR of 5-hexen-2-ol



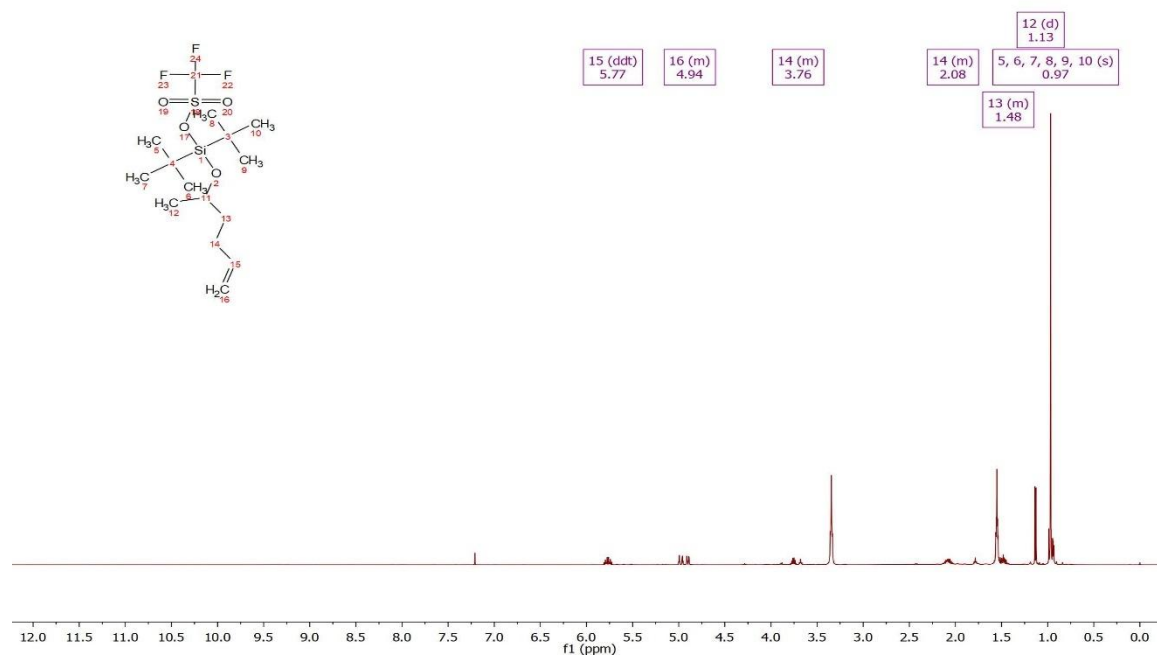
^1H NMR (300 MHz, Chloroform- d) δ = 5.77 (*ddt*, J = 16.7, 10.2, 6.7 Hz, 1H), 5.07 – 4.75 (*dd*, J = 1.2, 2.4 Hz, 1H and *dd*, J = 1.5, 1.8 Hz, 1H), 4.14 (*s*, 1H), 3.85 – 3.66 (*h*, J = 6.3 Hz, 1H), 2.24 – 1.88 (*m*, 2H), 1.53 – 1.43 (*m*, 2H), 1.13 (*d*, J = 6.2 Hz, 3H) ppm.

ii ^{13}C NMR of 5-hexen-2-ol



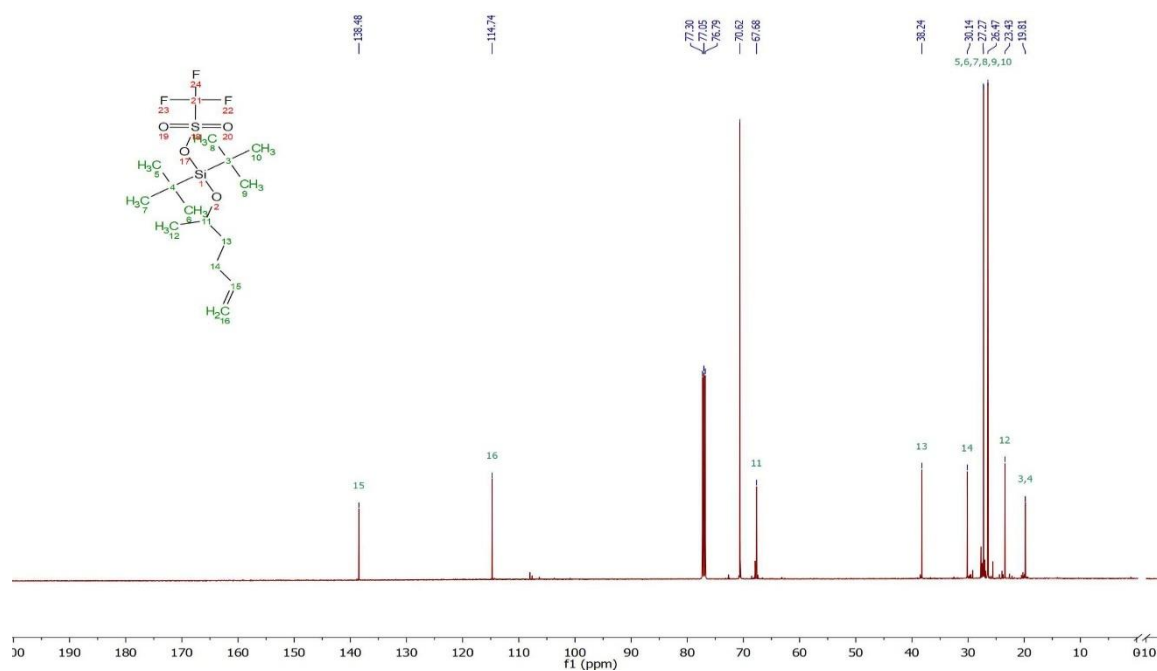
^{13}C NMR (Chloroform- d) δ = 138.5, 114.8, 67.7, 38.3, 30.2, 23.5 ppm.

iii ^1H NMR of 3-(hex-5-en-2-yloxy)-2,2,4,4-tetramethylpentan-3-yl trifluoromethanesulfonate.



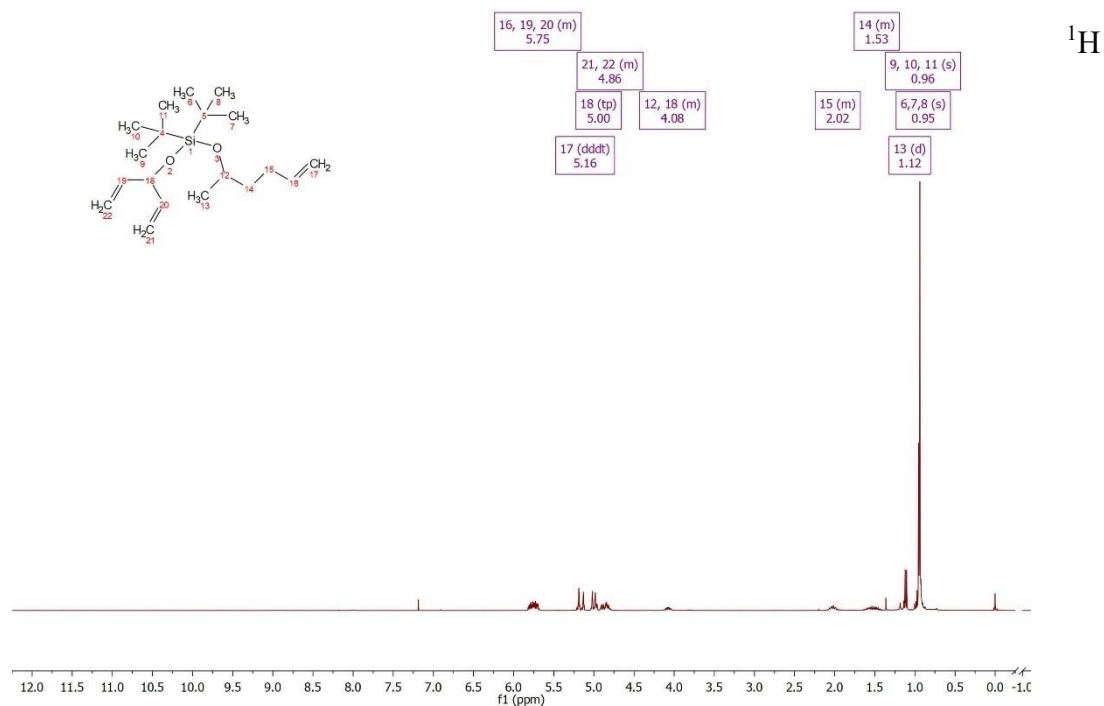
^1H NMR (500 MHz, Chloroform- d) δ = 5.77 (*ddt*, J = 16.7, 10.2, 6.7 Hz, 1H), 5.07 – 4.75 (*dd*, J = 1.2, 2.4 Hz, 1H and *dd*, J = 1.5, 1.8 Hz, 1H), 3.85 – 3.66 (*h*, J = 6.3 Hz, 1H), 2.24 – 1.88 (*m*, 2H), 1.53 – 1.43 (*m*, 2H), 1.13 (*d*, J = 6.2 Hz, 3H) ppm, 0.97 (*s*, 18H) ppm.

iv ^{13}C NMR of 3-(hex-5-en-2-yloxy)-2,2,4,4-tetramethylpentan-3-yl trifluoromethanesulfonate.



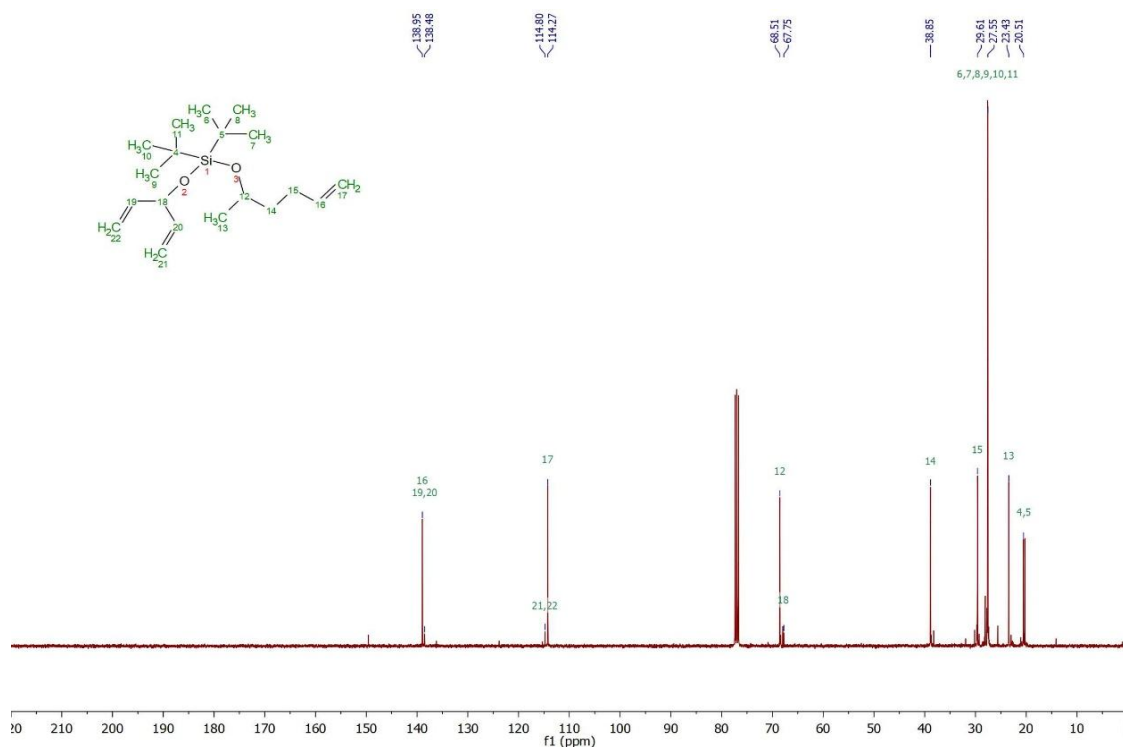
^{13}C NMR (Chloroform- d) δ = 138.5, 114.7, 67.7, 38.2, 27.3, 23.4, 19.8 ppm.

v ^1H NMR of di-*tert*-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane.



NMR (300 MHz, Chloroform- d) δ = 5.83 – 5.67 (*m*, 3H), 5.16 (*ddt*, J = 13.4, 8.4, 2.3, 1.1 Hz, 2H), 5.00 (*tp*, J = 6.1, 0.9 Hz, 1H), 4.93 – 4.78 (*m*, 4H), 4.08 (*h*, J = 6.9 Hz, 2H), 2.12 – 1.89 (*m*, 2H), 1.64 – 1.41 (*m*, 2H), 1.12 (*d*, J = 6.8 Hz, 3H), 0.96 (*s*, 9H), 0.95 (*s*, 9H) ppm.

vi ^{13}C NMR of di-*tert*-butyl(hex-5-en-2-yloxy)(penta-1,4-dien-3-yloxy)silane.

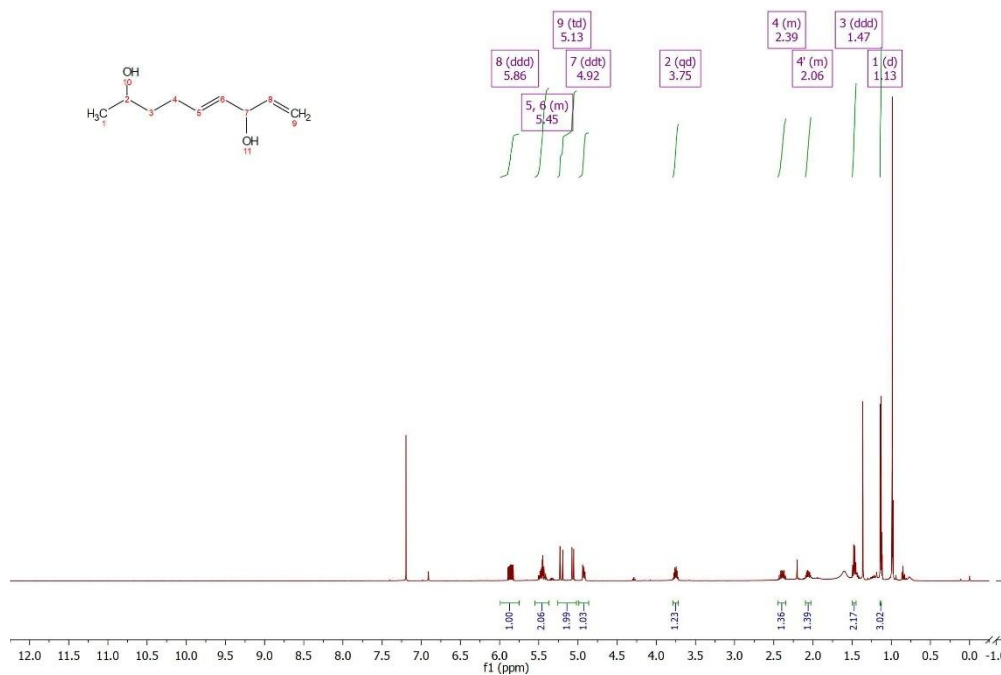


^{13}C NMR (Chloroform- d) δ = 139.0, 114.3, 68.5, 38.9, 29.6, 27.6, 23.4, 20.5 ppm.

^1H NMR (300 MHz, Chloroform- d) δ = 5.78 (*tdd*, J = 13.4, 6.2, 1.3 Hz, 1H), 5.44 (*ddd*, J = 10.8, 6.0, 1.1 Hz, 1H), 5.31 – 5.12 (*m*, 1H), 5.02 (*ddd*, J = 13.4, 2.2, 0.9 Hz, 2H), 4.82 (*ddd*, J = 7.1, 6.1, 0.9 Hz, 1H), 3.97 (*h*, J = 6.9 Hz, 1H), 2.71 (*tdd*, J = 7.0, 6.0, 1.7, 0.9 Hz, 2H), 1.87 (*dt*, J = 7.2, 1.7 Hz, 2H), 1.13 (*d*, J = 6.8 Hz, 3H), 0.97 (*s*, 9H), 0.96 (*s*, 9H) ppm.

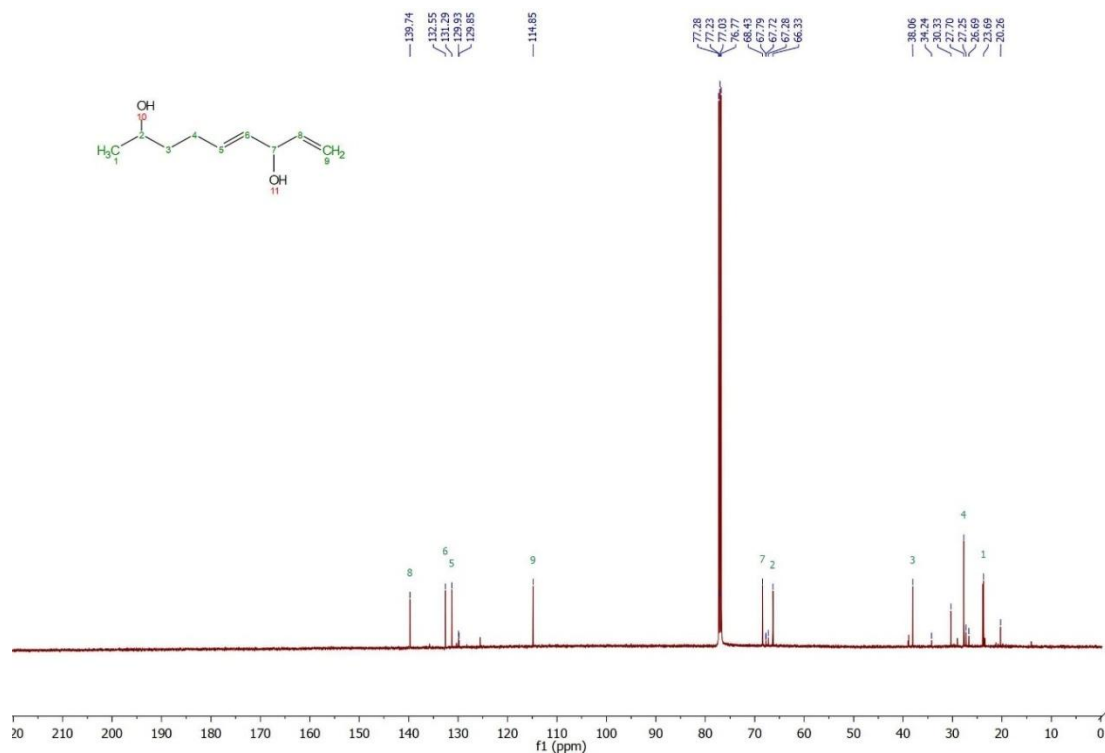
¹³C NMR (Chloroform-d) δ = 140.4, 139.0, 114.1, 75.1, 68.5, 34.9, 27.4, 26.3, 23.4, 20.5 ppm.

ix ^1H NMR of nona-5,8-diene-2,7-diol.



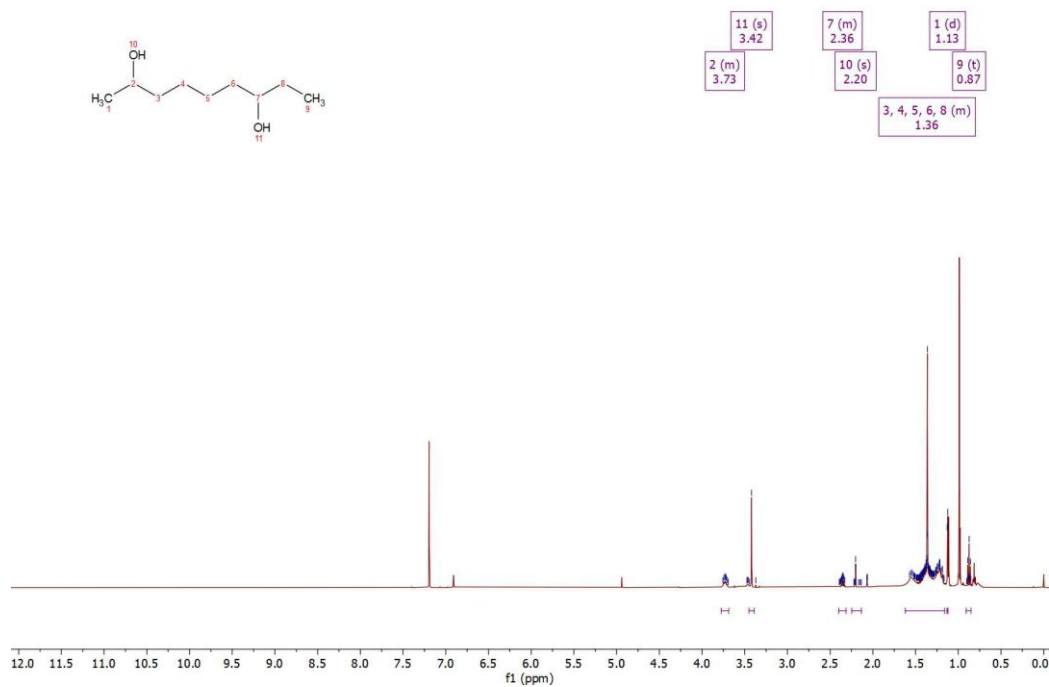
^1H NMR (500 MHz, Chloroform- d) δ = 5.86 (*ddd*, J = 17.2, 10.4, 5.7 Hz, 1H), 5.51 – 5.40 (*m*, 2H), 5.13 (*dt*, J = 10.4, 1.5 Hz, 2H), 4.92 (*ddt*, J = 7.1, 5.7, 1.3 Hz, 1H), 3.75 (*qd*, J = 6.9, 5.6 Hz, 1H), 2.46 – 2.30 (*m*, 1H), 2.14 – 1.96 (*m*, 1H), 1.47 (*dd*, J = 7.9, 2.4 Hz, 2H), 1.13 (*d*, J = 6.2 Hz, 3H) ppm.

v ^{13}C NMR of nona-5,8-diene-2,7-diol.



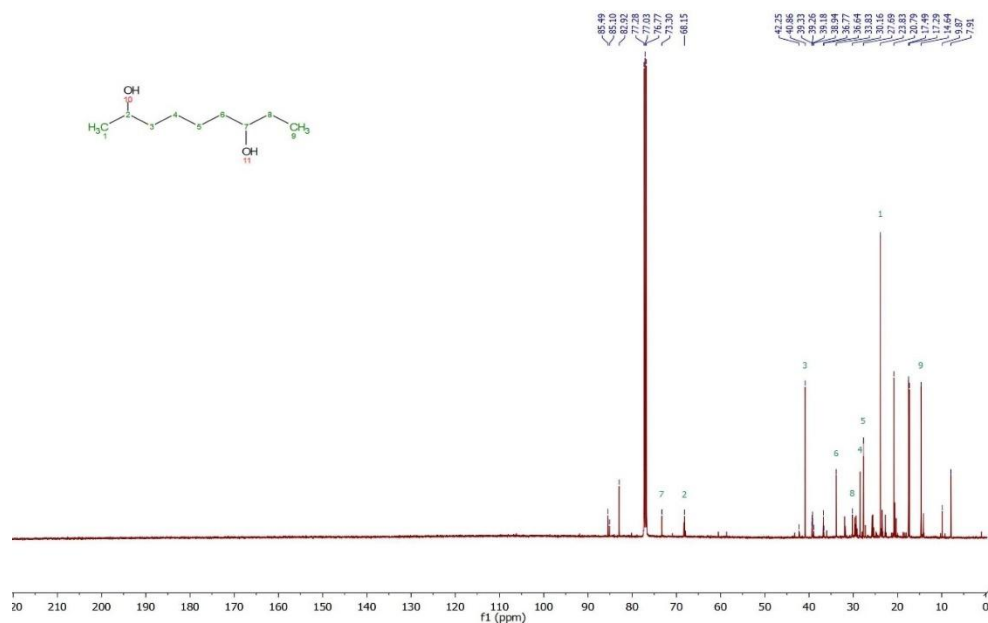
^{13}C NMR (Chloroform- d) δ 139.7, 132.6, 131.3, 114.9, 68.4, 66.3, 38.1, 27.7, 23.7 ppm.

vi ^1H NMR of nonane-2,7-diol.



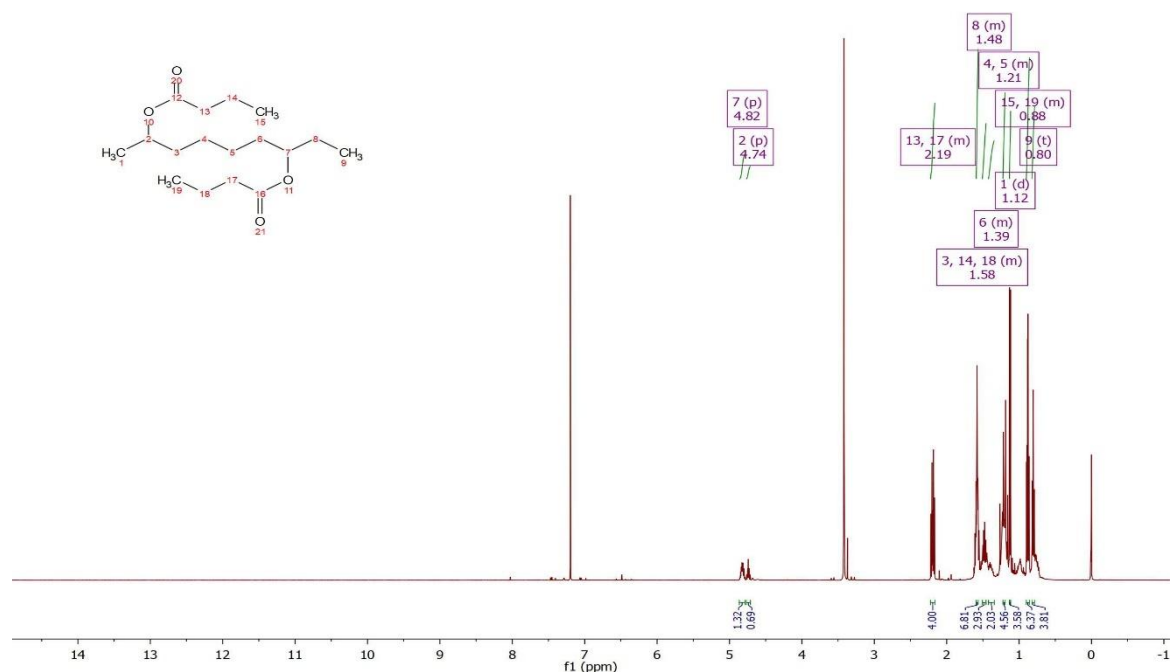
^1H NMR (500 MHz, Chloroform-*d*) δ 3.73 (*p*, $J = 6.2$ Hz, 1H), 2.40 – 2.31 (*m*, 1H), 2.20 (*d*, $J = 0.7$ Hz, 1H), 2.07 (*d*, $J = 8.1$ Hz, 1H), 1.62 – 1.16 (*m*, 10H), 1.13 (*d*, $J = 6.8$ Hz, 3H), 0.87 (*t*, $J = 7.5$ Hz, 3H) ppm.

vii ^{13}C NMR of nonane-2,7-diol.



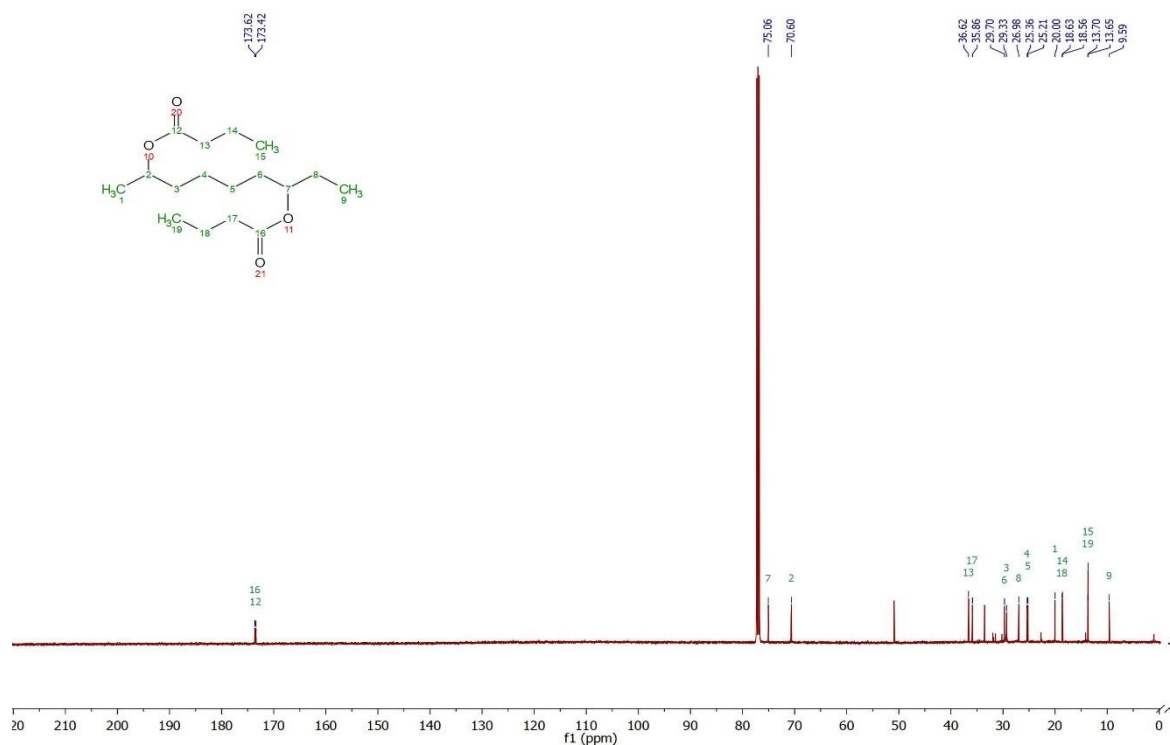
^{13}C NMR (126 MHz, Chloroform-*d*) δ 73.30, 68.15, 33.83, 30.16, 27.69, 23.83, 14.64 ppm.

viii ^1H NMR of nonane-2,7-diyl dibutyrate.



^1H NMR (500 MHz, Chloroform- d) δ 4.82 (*p*, $J = 7.1$ Hz, 1H), 4.74 (*p*, $J = 6.9$ Hz, 1H), 2.22 – 2.16 (*m*, 4H), 1.63 – 1.54 (*m*, 6H), 1.53 – 1.43 (*m*, 2H), 1.42 – 1.34 (*m*, 2H), 1.25 – 1.17 (*m*, 4H), 1.12 (*d*, $J = 6.2$ Hz, 3H), 0.91 – 0.85 (*m*, 9H), 0.80 (*t*, $J = 7.4$ Hz, 3H) ppm.

ix ^{13}C NMR of nonane-2,7-diyl dibutyrate.



^{13}C NMR (Chloroform- d) δ 173.6, 173.4, 75.1, 70.6, 36.6, 35.9, 29.7, 29.3, 27.0, 25.4, 25.2, 20.0, 18.6, 18.6, 13.7, 13.7, 9.6 ppm.