# An Efficient Synthesis of Geminal-Dialkyl Dienes for Olefin Metathesis Polymerization

**William J. Wolf**[†],

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

**Jiaming Li**[†],

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

**Simon C. Jones**,

Electrochemical Technologies Group, Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California 91109, United States

**Brian M. Stoltz**,

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States

**Robert H. Grubbs**[*]

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

## Abstract

A robust synthesis of *gem*-dialkyl acyclic diene monomers has been developed. This route is scalable, flexible, and biorenewable, allowing for the production of a wide range of diene monomers of different lengths and different *gem*-dialkyl substitution starting from unsaturated esters derived from seed oils. The metathesis polymerization of these monomers and the hydrogenation of the resulting polyolefins leads to telechelic *gem*-dialkyl polyethylenes, which can be used as elastomers in the synthesis of polyurethanes and other block polymers.

## Graphical Abstract

[*]**Corresponding Author: Robert H. Grubbs**–The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States; rhg@caltech.edu.
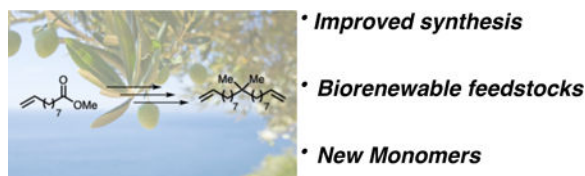[†]These authors contributed equally.

- *Improved synthesis*
- *Biorenewable feedstocks*
- *New Monomers*

## INTRODUCTION

Poly(isobutylene) (PIB, Scheme 1, equation 1) is a homopolymer of isobutylene that has a number of unique properties, among them being low permeability, excellent chemical compatibility and oxidative stability. PIB is particularly useful as a component of elastomeric polyurethanes as these properties provide superior performance over other polyester and polyether based materials. Poly(ethylene)-*co*-isobutylene (PEIB, Scheme 1, equation 2) is a copolymer of ethylene and isobutylene that has shown promise as an alternative to PIB, especially as telechelic PEIB. The *gem*-dimethyl quaternary substitutions along the polymer backbone act as defects to interfere with the crystallization of the polymer, and so amorphous materials with low glass transition temperatures can be produced that are especially attractive for use in thermoplastic polyurethanes.

PEIB and its analogues have been difficult to produce due to the different reactivities of ethylene and isobutylene. Nevertheless, there are numerous examples of its synthesis using metallocene catalysts, [1] Lewis acid catalysts, [2] and olefin metathesis catalysts. Ring opening metathesis polymerization (ROMP) is well-suited for the production of these types of polymers, and it has been used by the Grubbs (Scheme 2A),[3] Buchmeiser (Scheme 2B),[4] and Hillmyer groups (Scheme 2C) [5] to access PEIB and its related derivatives.

Linear polyolefins with precisely spaced *gem*-dimethyl groups, analogous to PEIB, have been synthesized using Acyclic Diene Metathesis (ADMET) polymerization, as first reported by Schwendeman and Wagener (Scheme 2D).[6, 7] They showed that a higher frequency of *gem*-dimethyl groups in the polymer backbone leads to amorphous polymers.[6] These "liquid rubbers" were incorporated into telechelic diols using Ru catalysis. Telechelic PEIB has also been synthesized using ring-opening metathesis polymerization (ROMP) from (*Z*)-5,5-dimethylcyclooct-1-ene (**5**)[5] and *cis*-1,4-diacetoxy-2-butene to afford polyolefins of different molecular weights (Scheme 2C). Hydrogenation of these polymers afforded the telechelic PEIB, which has been used in PEIB-polyurethane (PU) thermoplastic elastomers that perform exceptionally well for biomedical applications.[8] Due to the amorphous PEIB component, the oxidative, hydrolytic, thermal stability, and barrier properties of these copolymers are much improved compared to conventional PUs containing polyesters and polyethers as soft segments.[9]

The synthesis of any polymer is predicated on the synthetic accessibility of the constituent monomers, which may be challenging to produce. For *gem*-dialkyl containing monomers, several different routes have previously been developed. Hillmyer and co-workers synthesized (*Z*)-5,5-dimethylcyclooct-1-ene (**5**) in five steps.[5] Starting from inexpensive 1,5-cyclooctadiene (1,5-COD), the *tert*-butyl ester **1** was prepared through a Pd-catalyzed alkoxycarbonylation. Methylation with LDA and iodomethane gave α-methyl *tert*-butyl ester

**2**. Then **2** was reduced to the primary alcohol **3** by LiAlH$_4$, and the alcohol was converted to a tosylate derivative that was reduced by LiAlH$_4$, producing the monomer **5** in 40% overall yield (Scheme 3).

As an alternative to ROMP, acyclic diene metathesis (ADMET) polymerization has also been used to prepare *gem*-dimethyl containing polymers. To prepare the monomer for ADMET polymerization, the Wagener group developed a synthetic route to diene monomers with different numbers of methylene units between the *gem*-dimethyl branch point and the terminal alkenes.[6] Propionic acid was treated with LDA and alkylated by the addition of two equivalents of an alkenyl bromide to form the carboxylic acid intermediate (**7a-c**). Reduction of the carboxylic acid with LiAlH$_4$ generates the primary alcohol (**8a-c**), which was deoxygenated through tosylation and reduction with LiAlH$_4$ to give the requisite symmetrical *gem*-dimethyl substituted diene monomers possessing 3, 6, and 9 methylene "spacer" units (**10a-c**, Scheme 4).

We have developed a new synthetic route to *gem*-dialkyl diene monomers for ADMET polymerization using the Claisen condensation of an unsaturated ester as the key step. This approach offers several benefits in terms of cost, safety, and scalability as well as synthetic flexibility. In particular, the unsaturated ester can be sourced from seed oils enabling a biorenewable route to these polymers. Telechelic polymers were prepared using Ru-catalyzed olefin metathesis, and they exhibited the desired thermal properties (low glass transition temperature).

## DEVELOPMENT OF SYNTHETIC ROUTES TO *GEM*-DIALKYL DIENES

In Hillmyer's synthesis of *gem*-dimethyl cyclooctene monomers, the major disadvantage is the use of LiAlH$_4$ for reductive deoxygenation to furnish the all-carbon structure. Our initial proposal was to directly oxidize 1,5-COD to the ketone **11** using modified Wacker oxidation conditions with hydrogen peroxide as oxidant. *Gem*-dimethylation of ketones using TiMe$_2$Cl$_2$ was reported by Reetz and co-workers in 1980,[10] and has been applied in the syntheses of a variety of *gem*-dimethyl containing molecules.[11] However, when the ketone **11** was subjected to TiMe$_2$Cl$_2$, a complex mixture of products was formed; the desired product **5** was never observed. We reasoned that a fast transannular reaction was plausible, preventing the formation of **5** (Scheme 5).

After several attempts to convert the ketone **11** using various approaches, we found that α-methylation with 2.5 equivalents KO*t*-Bu and 5 equivalents iodomethane gave the α,α-*gem*-dimethyl ketone **12** as the major product (dimethyl product **12**:monomethyl product **13** > 50:1), which was used as a precursor to the *gem*-dimethyl cyclooctene monomer upon deoxygenation. Ketone **12** was first reduced to the secondary alcohol **14** by Red-Al, then the alcohol was converted to xanthate **15**. Treatment of the crude xanthate **15** to radical deoxygenation conditions developed by Wood and co-workers[12] finally provided the (*Z*)-4,4-dimethylcyclooct-1-ene (**16**, Scheme 6). However, this route still requires 5 steps to synthesize the *gem*-dimethyl cyclooctene monomer from 1,5-COD, and potential scale up of the sequence could be a challenge.

In light of these synthetic difficulties, we decided to focus on the preparation of linear diene monomers instead of cyclooctene-based monomers. We were initially drawn to the Claisen condensation as a key step. The Claisen condensation reaction has been an important synthetic reaction for more than 100 years.[13] The β-ketoester intermediate from the Claisen condensation can be transformed into a symmetric linear ketone by hydrolysis and decarboxylation, and so the use of unsaturated esters provides linear dienes containing a ketone for further synthetic manipulations. Watson and Wagener used this transformation to synthesize diene monomers *en route* to ethylene/CO copolymers.[14] These long chain ketones provided a convenient starting point for our synthesis. Importantly, established ethenolysis chemistry can provide methyl 9-decenoate (**17**) from methyl oleate from seed oils,[15] providing an opportunity for a biorenewable synthesis of the ketone **18**, which can be used to synthesize the subsequent *gem*-dimethyl containing diene monomers such as **21** (Scheme 7). Other seed oils may provide the appropriate ketones, allowing for synthetic flexibility in preparing dienes in this manner.

There are several reports of the direct transformation of ketones to the *gem*-dimethyl moiety. Unfortunately, $TiCl_2Me_2$,[16] $AlMe_3$,[17] and $AlMe_3$ in the presence of $Me_3SiOTf$[18] were all unsuccessful for the direct transformation of **18** to the desired monomer **21**. Instead, either olefin polymerization by $TiCl_2Me_2$ or the addition of a methyl nucleophile to the ketone by $AlMe_3$ was observed. The two methyl groups were installed sequentially: the first by a Grignard addition to **18**, and the second by the conversion of the corresponding tertiary alkyl halide with a nucleophilic alkylating reagent (Scheme 8). Precedent for the use of both alkyl zinc[10] and alkyl aluminum[19] nucleophiles to accomplish this transformation prompted us to explore these options. The addition of methylmagnesiumbromide to **18** proceeded in high yield and the resulting tertiary alcohol (**19**) was easily transformed into the tertiary chloride **20** using $SOCl_2$. Substitution of **20** using $AlMe_3$ completed the sequence. The transformation of tertiary alcohol **19** to **21** can be achieved in a single pot procedure.[20] $Me_2Zn$ was also a viable nucleophile, but $AlMe_3$ gave higher yields and is more economical. Importantly, no trisubstituted olefin resulting from elimination of **20** was observed. After workup, **21** was isolated by passing a hexanes solution through a silica plug and removing of the solvent *in vacuo*. The overall yield starting from methyl oleate was 74%, and the route was robust on multigram scale (up to 15 g of **21** isolated from a single synthesis).

Following this success, several other linear diene monomers were prepared from ketones of varying lengths. Ethyl pent-4-enoate (**22**) was easily converted to nona-1,8-dien-5-one (**23**)[21] and the subsequent 9-carbon *gem*-dimethyl monomer **24**. Alkylation of acetone dimethylhydrazone **25** with 5-bromo-1-pentene provided the medium length ketone **26** in good yield (Scheme 9), which was readily transformed into the 13-carbon monomer **27** in 58% yield over three steps. Longer linear diene monomers were also synthesized from long chain unsaturated esters. Ethyl 10-undecenoate **28**, a precursor to Nylon-11,[22] was readily transformed into the ketone **29**, which was used to make the 21-carbon monomer **30** (Scheme 9). The Claisen condensation of the methyl ester **17** consistently gave the highest yields using NaH as the base in toluene, while the condensation of the ethyl ester **28** was achieved using NaOEt as the base under dynamic vacuum to remove EtOH. NaOMe was not a viable base for the Claisen condensation of **17**. The ethyl ester **22** was too volatile for any

conditions requiring vacuum, but the use of NaH in toluene proved to be a reliable and high yielding transformation.

The *gem*-dialkyl groups can be easily varied by using different Grignard and alkylzinc or alkylaluminum reagents to provide both homo- and heterodialkyl substitution, as demonstrated by the preparation of **32**, **33**, **34**, and **35** (Scheme 10). This route tolerates both terminal and internal olefins with no detectable olefin isomerization, as demonstrated by the synthesis of **36** from **31**. The shortest monomer **24** was purified by distillation, while the other monomers were purified using a short silica plug and eluting with hexanes.

The ADMET polymerization[23] of **21**, **24**, **27**, and **30** using the 2nd generation Ru olefin metathesis catalyst (**G2**) produced the desired polyolefins with targeted molecular weights of 2000 g/mol. The polymerization of **24** was complicated by the formation of both polyolefin **poly-24** and the 7-membered cyclic olefin **37** (Scheme 11). ADMET polymerization is well-known to produce cyclic oligomers[24] as the reaction proceeds, but the *gem*-dimethyl substitution of **24** results in a pronounced Thorpe-Ingold effect[25] that favors cyclization. The cyclic olefin **37** also possesses low ring-strain, and did not fully incorporate into the growing polymer chain; prolonged reaction times (up to 5 days) did not result in full consumption of **37** (equilibrium ratios of ~3:1 **poly-24**:**37** were observed, in both the ADMET polymerization of **24** and **36**). However, once the desired molecular weight is achieved, **37** can easily be removed *in vacuo* and recycled in a subsequent ring-opening polymerization. The ROMP of **37** afforded the same distribution of **poly-24** and **37** as was achieved in the ADMET of **24**.

The longer diene monomers (**21**, **27** and **30**) did not suffer from the competing ring-closing metathesis and readily polymerized using **G2** under static vacuum. We used the "polymerization/depolymerization" method developed by Wagener[7] to produce the target telechelic diols. The chain transfer agent (CTA) **38**[26] was added to the polyolefin mixture after sufficient reaction time to cleave the longer polyolefins and install the protected telechelic endgroups. Hydrogenation of the unsaturated polymers was accomplished using Pd/C under $H_2$ and the resulting telechelic PEIB derivatives were isolated in high yield after filtration and concentration *in vacuo* (Scheme 12).

Differential scanning calorimetry (DSC) was used to determine the effects of substitution and molecular weight on the thermal behavior for the series of polymers (see DSC traces in SI). The measured $T_g$ values (Table 1) were in agreement with those for the PEIB analogues prepared by both Wagener[6,7] and Hillmyer[5], and a higher density of substitution (e.g. **poly-24b**) resulted in amorphous materials without melting points. Polymers derived from the longer monomers **21** and **30** displayed broad, multimodal melting points indicating the semicrystalline nature of the longer saturated segments of the polymer, as described by Wagener.[7]

## CONCLUSION

We have described a new synthetic route to *gem*-dialkyl diene monomers for ADMET polymerization. This route enables the use of unsaturated fatty acid esters from seed oils as a

raw material source and offers several benefits in terms of cost, scalability, yield, and synthetic flexibility. Several different diene monomers have been prepared and polymerized using Ru-catalyzed ADMET polymerization to access short ($M_n$ ~2–7 kDa) amorphous telechelic polymers. These telechelic polymers are desirable as the soft segment of polyurethane elastomers for biomedical applications, and this work demonstrates a cost-effective and convenient route for their preparation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEGDEMENTS

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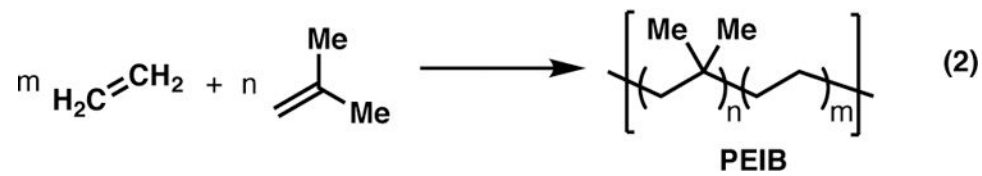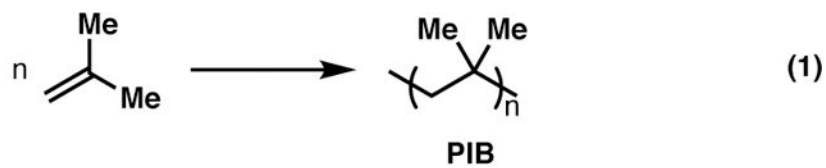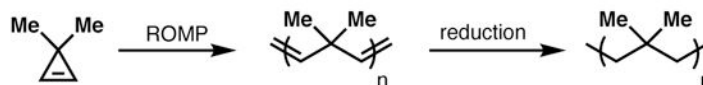
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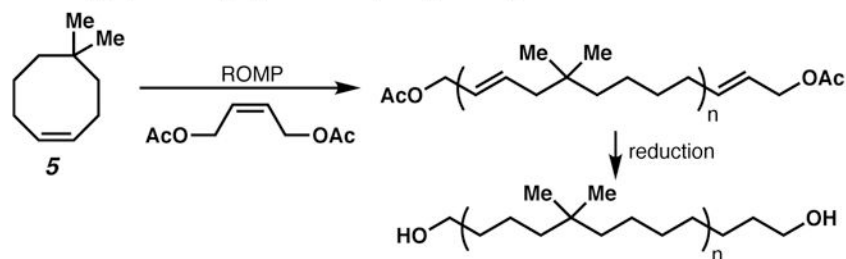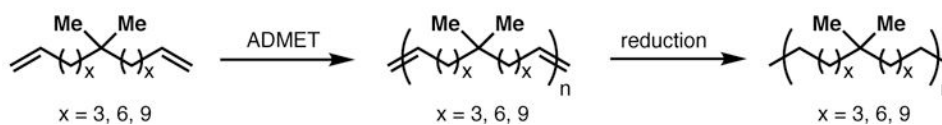Poly(isobutylene) and Poly(ethylene)-co-isobutylene
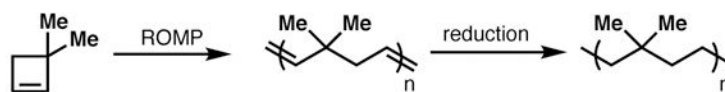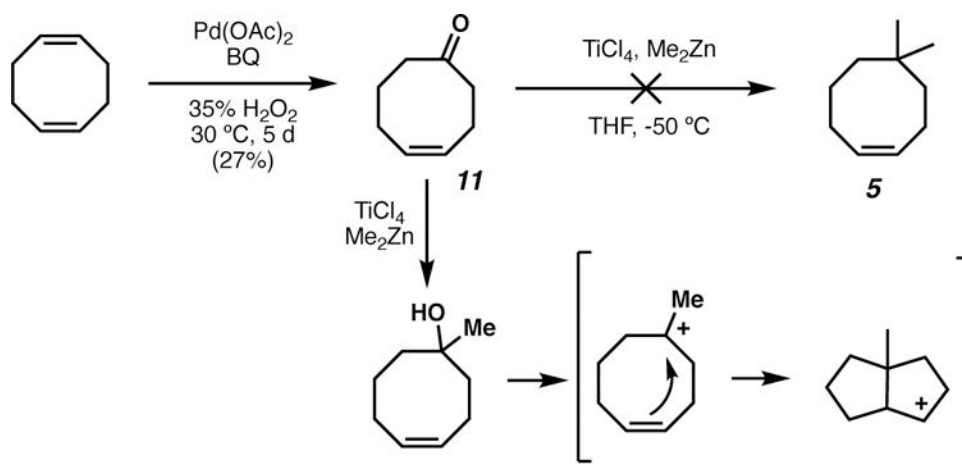
**Scheme 2.**
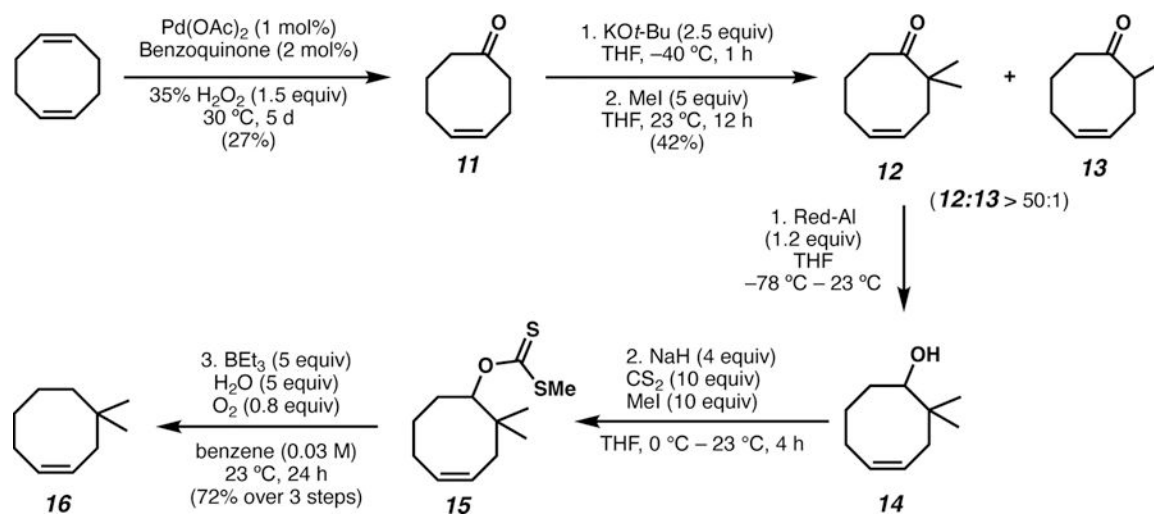PEIB Synthesis by Olefin Metathesis Polymerization
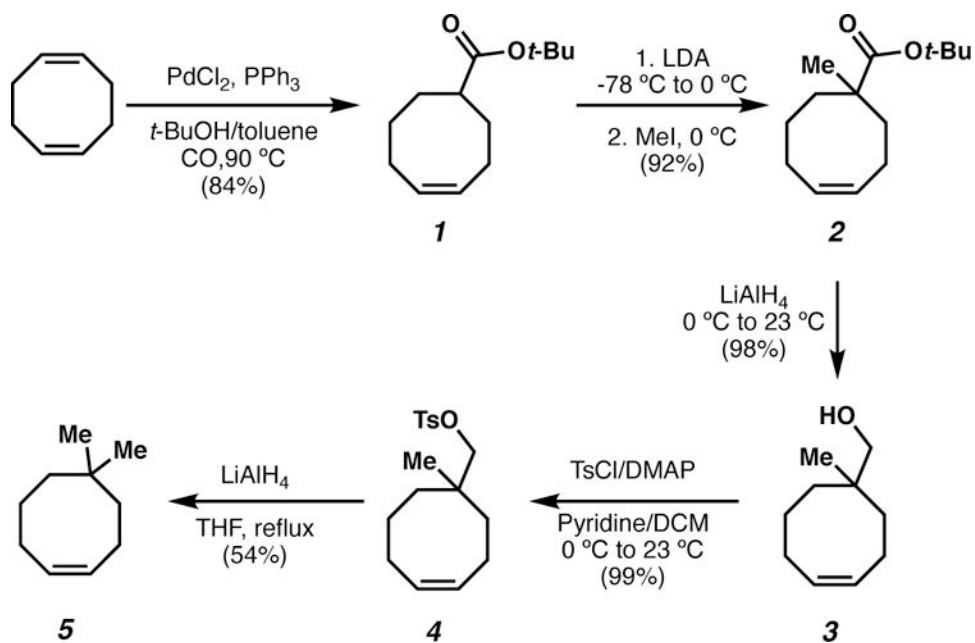
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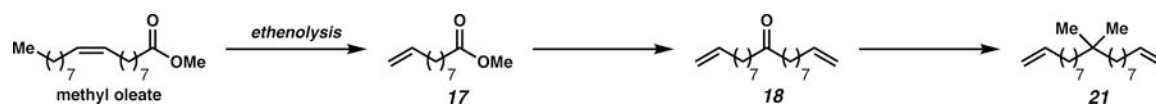Synthesis of 5,5-gem-dimethyl Cyclooctene by Hillmyer
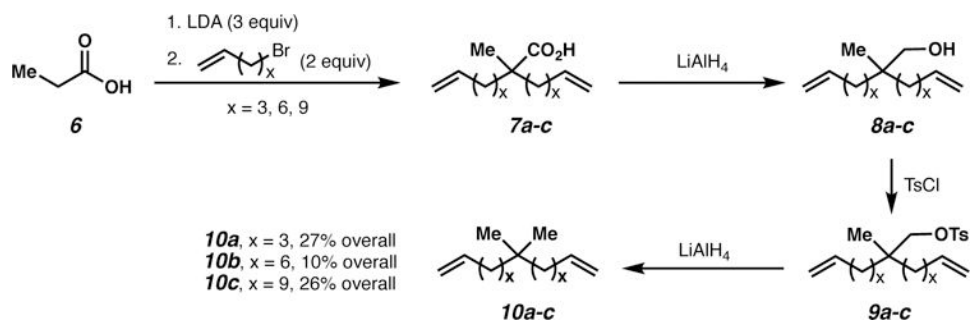
**Scheme 4.**
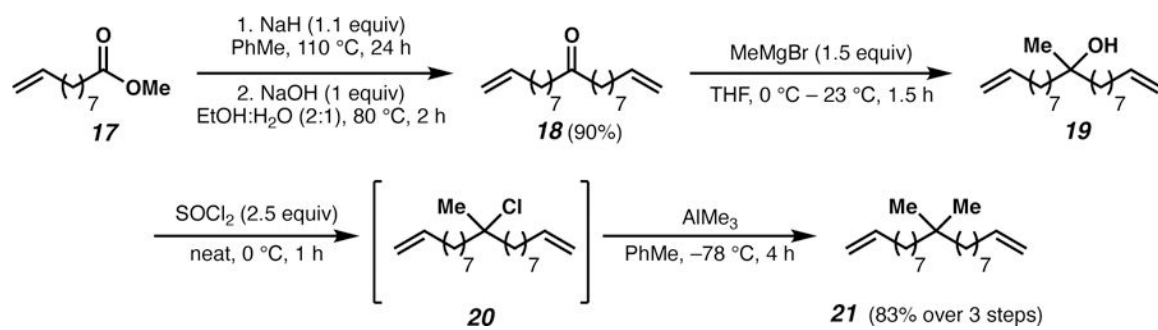Synthesis of Gem-dimethyl Diene Monomer by Wagener

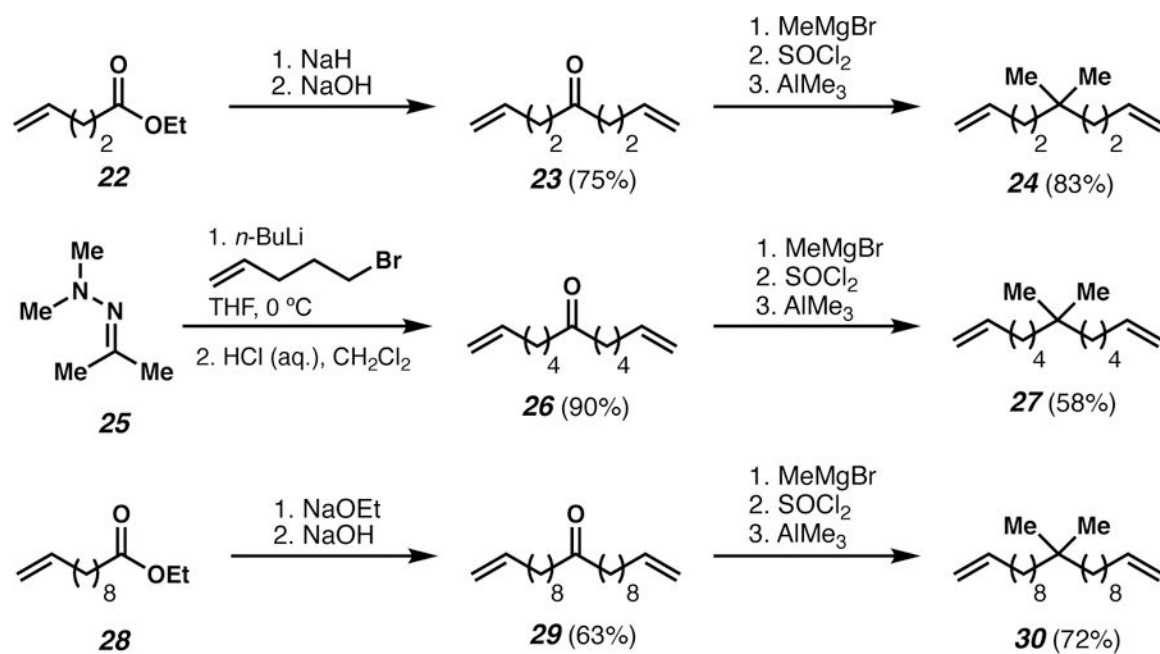**Scheme 5.**
Gem-dimethylation of Ketone **11**.

**Scheme 6.**
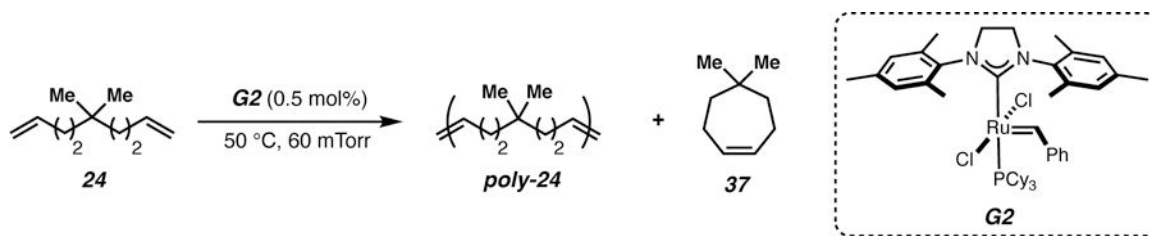Synthesis of Gem-dimethylcyclooctene Monomer **16**

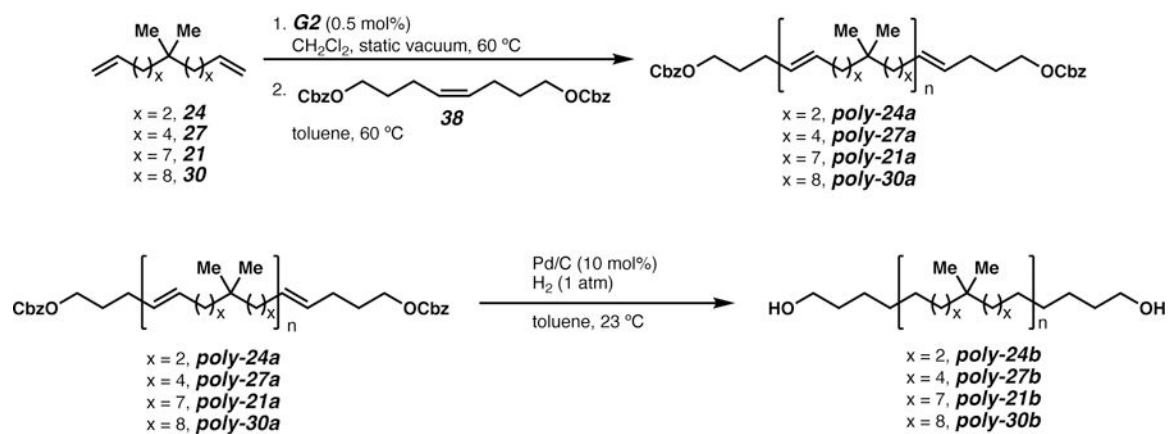**Scheme 7.**
Claisen Condensation Route

**Scheme 8.**
Synthesis of Gem-dimethyl Diene Monomer **21**

**Scheme 9.**
The Synthesis of Gem-dimethyl Diene Monomers with Different Lengths

**Scheme 10.**
Diene Monomers with Varied Alkyl Substitutients

**Scheme 11.**
ADMET Polymerization of Short Chain Monomer **24**

**Scheme 12.**
Synthesis of Gem-dimethyl Substituted Telechelic Polymers

**Table 1.**

Molecular Weight, Polydispersity, and Thermal Properties of Telechelic Polymers

| Polymer | $M_n{}^a$ | $PDI^b$ | $T_g$ | $T_m$ |
|---|---|---|---|---|
| **Poly-21b** | 4200 | 1.4 | No $T_g$ observed | $-50 - 8\ °C^c$ |
| **Poly-24b** | 2200 | 1.4 | $-60\ °C$ | $\_^d$ |
| **Poly-27b** | 2000 | 1.5 | $-60\ °C$ | $\_^d$ |
| **Poly-30b-1** | 3100 | 1.5 | $-50\ °C$ | $-24 - 0\ °C^c$ |
| **Poly-30b-2** | 6300 | 1.1 | $-60\ °C$ | $-14 - 10\ °C^c$ |
| **Poly-30b-3** | 17200 | 1.5 | $-26\ °C$ | $-12 - 50\ °C^c$ |
| **Poly-30b-4** | 28700 | 1.7 | $-30\ °C$ | $30\ °C$ |
| **Poly-32b** | 3200 | 1.1 | $-52\ °C$ | $\_^d$ |
| **Poly-34b** | 6800 | 1.4 | $-59\ °C$ | $-18\ °C^c$ |

[a] Determined by $^1$H NMR

[b] PDI = $M_w/M_n$ (determined by GPC)

[c] broad melting point

[d] no melting point observed