

A Proposal for
A Regio- , Stereo- , and Enantioselective Synthesis of
Menthol

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Table of Contents

Introduction	page 4
Sources of commercial menthol	page 4
The four menthol stereoisomers	page 5
The two menthol enantiomers	page 5
An industrial synthesis of racemic and L-(–)-menthol	page 6
A highly selective new route to L-(–)-menthol	page 8
Vig's route to dipentene	page 9
Summary of the proposed route to L-(–)-menthol	page 10
Step 1 : the preparation of 1-chloro-3-butenone	page 11
Step 2 : the preparation of 3-keto-1-butenyl acetate	page 12
Step 3 : the Diels-Alder reaction	page 14
enantioselective catalysis	page 16
Step 4 : the Wittig reaction	page 18
Step 5 : hydroboration of the olefin bonds	page 19
stereochemically assisted hydroboration	page 21
protonolysis of the tertiary borane	page 21
References	page 22

Illustrations

The four menthol stereoisomers	page 5
The two menthol enantiomers	page 5
An industrial synthesis of menthol	page 7
Vig's synthesis route to dipentene	page 9
Summary of the proposed synthesis route to L-(–)-menthol	page 10
Acetylation of cyclohexene and acetylene	page 13
Diels-Alder reactions of anthracene with maleic acid and fumaric acid	page 15
Diels-Alder reactions of isoprene with acrolein , catalyzed and uncatalyzed	page 16
S-phenylalanine and R-phenylalanine	page 16
Diazaaluminolidine (enantioselective catalyst)	page 17
Brown and Pfaffenberger's hydroboration of R-(+)-limonene to D-(–)-carvomenthol	page 20
Pelter's hydroboration of R-(+)-limonene , followed by carbonylation	page 21

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Introduction

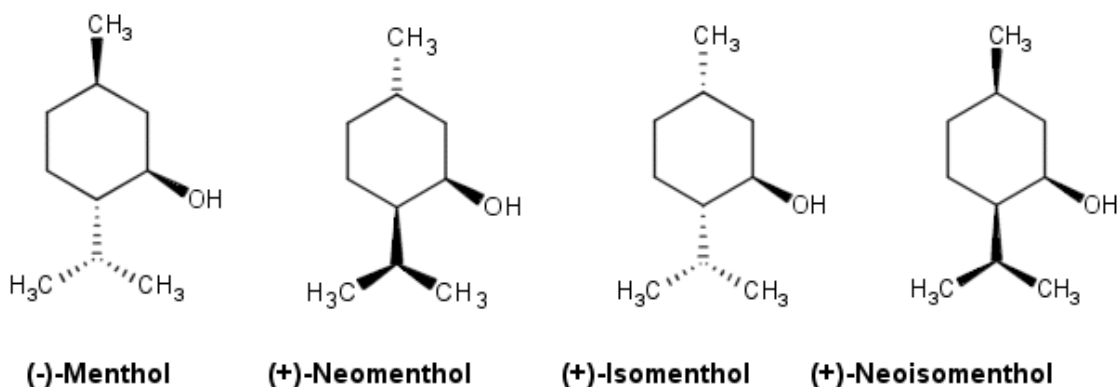
Menthol is a familiar flavoring and scenting agent in many commercial products such as chewing gum, toothpaste, skin care products, medicines, candies, and cigarettes. It holds a prominent position in the fragrances and flavoring chemical specialties market (ref. 1, page 22). Menthol is usually obtained from two different sources: the **natural product**, from mint (a very common plant, found in temperate and tropical regions); and the **industrial product**, which is manufactured from a variety of simpler bulk chemicals, including both petrochemicals and other feedstocks such as turpentine.

Certainly there is no need for another synthesis for producing additional commercial menthol. Yet, there is still an intellectual challenge, especially for “student organic chemists”, to study and devise a highly specific new route to menthol. Its molecule is deceptively simple in chemical composition: 2-isopropyl-5-methyl-cyclohexanol. It should be noted in this regard that the **natural product** has a well-defined stereochemistry, and consists of a single mirror image molecule [**enantiomer**], namely (1R,2S,5R)-(-)-menthol, which exhibits the familiar “cooling” menthol odor to the human nose. The “unnatural” (1S,2R,5S)-(+)- enantiomer apparently is less odiferous, or perhaps has a somewhat different smell than the natural product. The **racemic** mixture of industrial menthol, with 50% of each enantiomer, still has a pronounced “menthol smell” and is often suitable for many commercial applications.

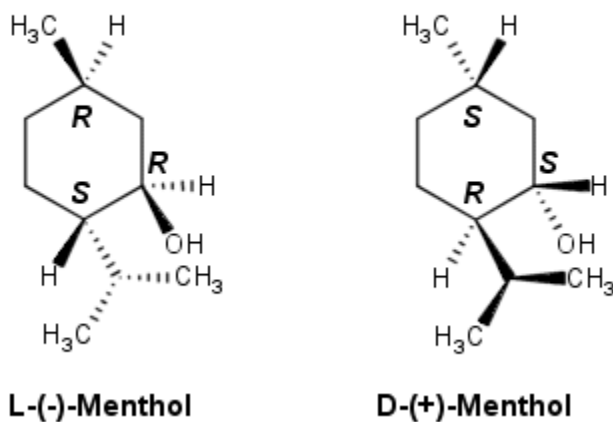
To make things even more interesting, there are four **stereoisomers** of 2-isopropyl-5-methyl-cyclohexanol: menthol itself, isomenthol, neomenthol, and neoisomenthol (the structural formulas for these molecules are shown on the next page). The natural product from the mint plant is the single, highly specific molecule: levo-(-)-menthol. This has the most pronounced menthol fragrance and flavoring properties, is the most in demand, and is the costliest. However, industrial chemical manufacturing processes invariably generate racemic mixtures of the four stereoisomers.

For example , hydrogenation of thymol (2-isopropyl-5-methyl-phenol) over a Raney cobalt catalyst provides a high yield of the racemic stereoisomers , most of which – about 85% – consists of **isomenthol** (ref. 2 , [page 23](#)) :

The Four Menthol Stereoisomers



The Two Menthol Enantiomers



For references pertaining to the stereochemical structures and to the absolute configurations of levo (L) and dextro(D) menthol , see in ref. 3 , [page 23](#) .

Thus , a synthesis route to the specific L-(-)-menthol molecule turns out

to be more challenging than originally anticipated ! That is the objective of this brief report : to propose a multi-stage synthesis of L-(-)-menthol , identical to the natural product from mint . The proposed synthesis will be **regioselective** : that is , the hydroxyl , isopropyl , and methyl groups will be located at the correct positions on the cyclohexane ring ; it will be **stereoselective** , in that those three substituents will have the correct relative configurations to each other ; and I'll suggest a possible method for inducing at least some optical activity in the product , although enantioselective organic synthesis is still more of an art than a science at this stage . I hope – with my fingers crossed when I say this – that the proposed route to menthol will be partly **enantioselective** (for the desired levo enantiomer) as well .

An industrial synthesis of racemic and L-(-)-menthol

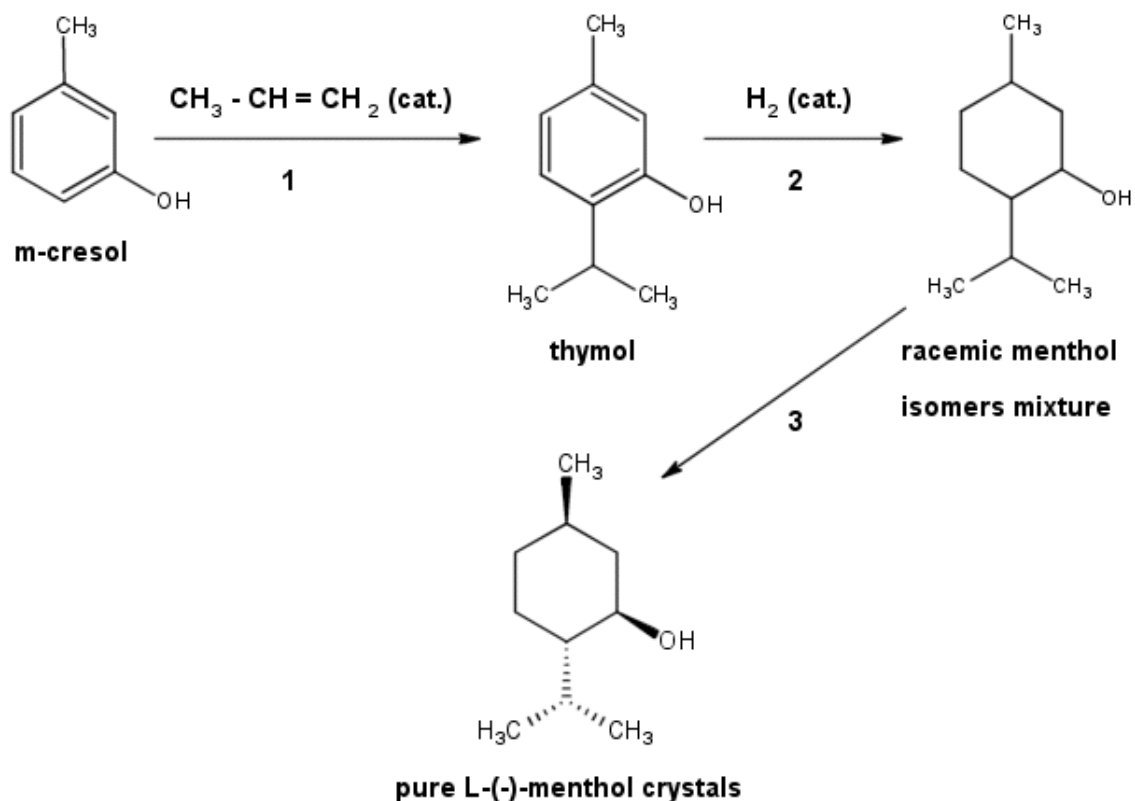
Before embarking on a discussion of the proposed new route , I thought it might be interesting to briefly mention an industrial process in which the menthol racemates , and L-(-)-menthol itself , are produced on a relatively large scale . The following synthesis route is described in an article in Chemical Engineering magazine (ref. 4 , [page 23](#)) .

First , the feedstock , meta-cresol [3-methyl-phenol] – a bulk industrial organic chemical – is alkylated ortho to the hydroxyl to produce **thymol** [2-isopropyl-5-methyl-phenol] . An unspecified alkylating agent is used , with the reaction carried out over a “heterogeneous catalyst” . Propylene gas has been condensed with m-cresol in the presence of hydrofluoric acid as the Friedel-Crafts catalyst to produce a monoalkylated product melting at 43 °C (ref. 5 , [page 23](#) ; pure thymol melts at 51 °C) .

In the second step , thymol is hydrogenated , again under unspecified conditions . As mentioned earlier , thymol has been hydrogenated to the corresponding cyclohexanol with Raney cobalt catalyst , although the main isomer (about 85%) seems to be isomenthol (ref. 2 , [page 23](#)) .

The key step in this industrial menthol synthesis is undoubtedly the third

one , in which the mixture of menthol racemates and related stereoisomers is catalytically “cracked” , or rearranged , into predominately the two menthol racemates ; again , the nature of the catalyst wasn’t disclosed : a closely-guarded “trade secret” , I suppose :



The racemic menthol , produced in about 50% yield after the rearrangement reaction , is separated from the unwanted stereoisomers (which are recycled to the rearranger) by fractional distillation . Industrial-scale “spinning band” distillation columns are now widely used in the production of very pure fine organic chemicals ; they are especially valuable in the fractionation of high-boiling oils under vacuum or inert atmospheres .

The Chemical Engineering article is somewhat vague about how the menthol racemates are separated into the two separate enantiomers , although it does mention that they are converted into “esters” , and that it is the esters that are

resolved , with subsequent saponification into the levo [retained] and dextro [recycled back to the catalytic rearranger] enantiomers . The process technology is proprietary , of course , but it reminds me of an organic experiment in which the enantiomers of 2-octanol are resolved by conversion into the “half-phthalate ester” , followed by salt formation with the optically-active alkaloid **brucine** (ref. 6 , page 24) . The brucine salts can then be fractionally precipitated from solution , followed by alkaline treatment to release the half-phthalate ester , then saponify it to the 2-octanol enantiomer .

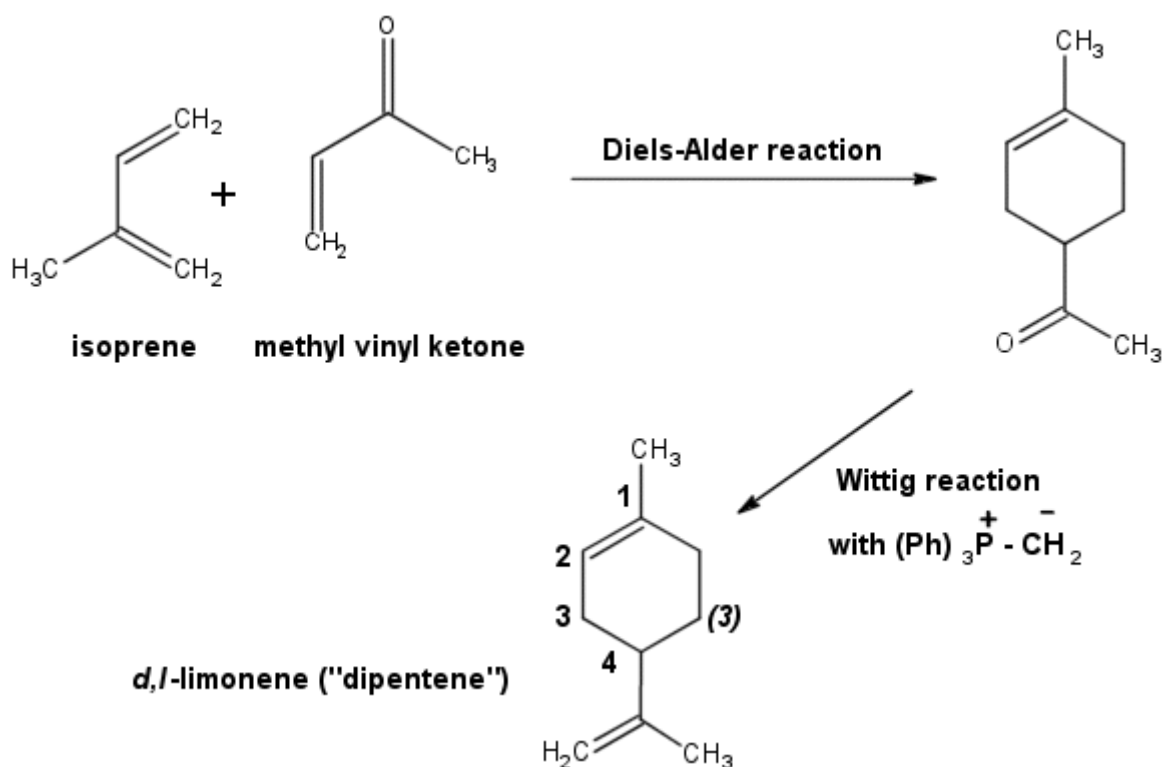
The two products from this synthesis route are racemic menthol , which is satisfactory for many applications , and the costlier L-(–)-menthol , which is still preferred by some customers . As you can see , this industrial route is quite straightforward , if somewhat brutal , organic chemistry ; or perhaps I should say , “unsophisticated” . Nevertheless , despite its inelegance , it succeeds admirably in producing a high yield and moderate tonnage of very pure , pharmaceutical grade racemic menthol and levo enantiomer .

Given the success of this and other industrial production processes for the production of menthol from petrochemicals and turpentine , why should we bother any more with devising a new method for synthesizing it in an elaborate laboratory route ? My objective in offering the proposed route to menthol discussed below is more “academic” than industrial in nature . It is really intended for **students** of organic chemistry , to examine , discuss, and possibly even to attempt as a research project (at least , for the more advanced undergraduates) . The chemistry and the molecules involved are fairly simple and readily understood , and I think readers will find the route both educational and mentally stimulating . And that’s what the study of chemistry should be , don’t you think ?

A highly selective new route to L-(–)-menthol

The proposed route is based on the synthesis of racemic limonene

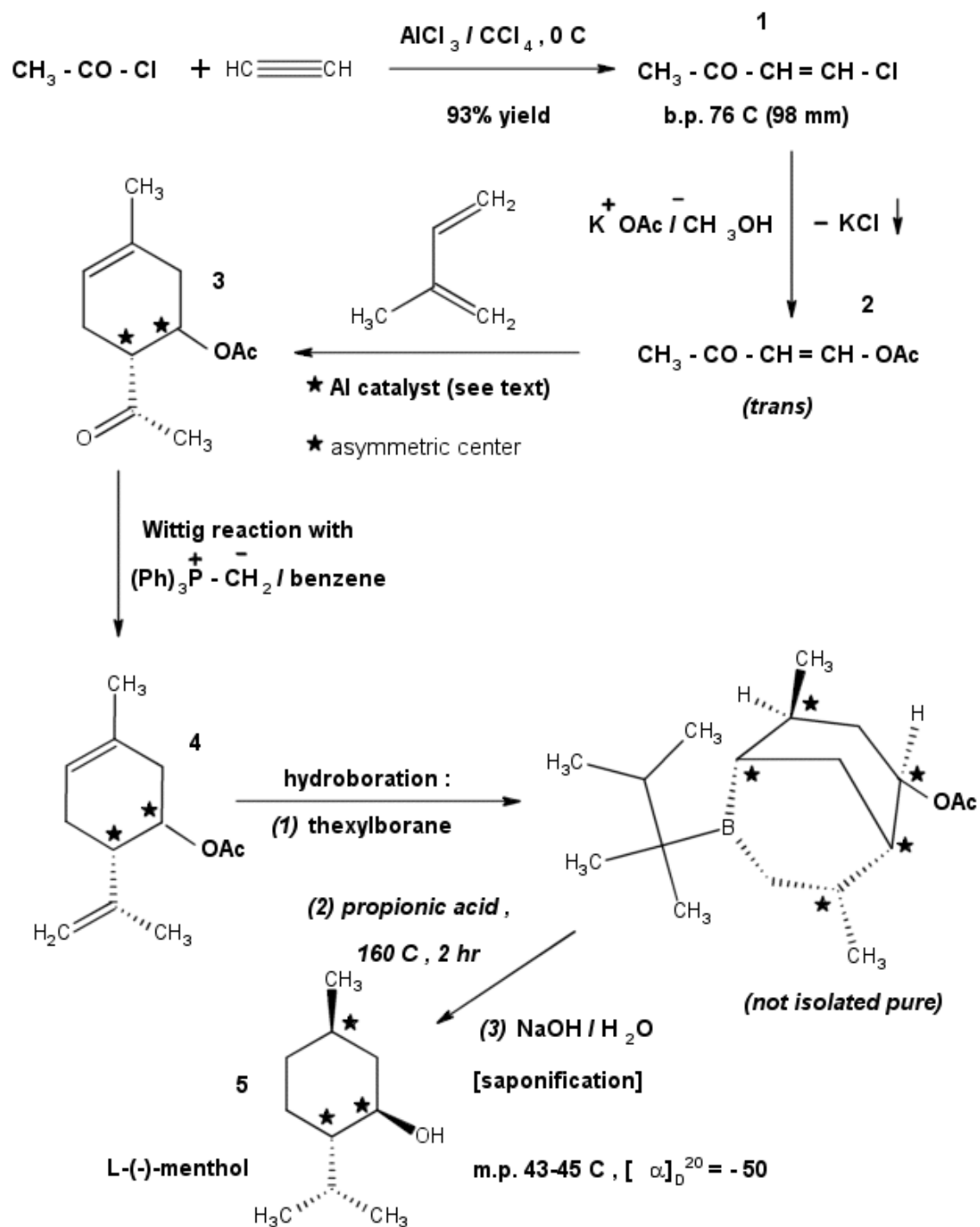
(“dipentene”), published by Vig and coworkers (ref. 7 , [page 24](#)) :



The Diels-Alder reaction is very important with respect to our menthol synthesis , because it will produce a cyclohexane ring with **regioselective control** of the substituents , and possibly **stereoselective control** of them as well , although not in this particular case of dipentene . In Vig’s product , the methyl and isopropenyl groups were located in the 1,4 positions of the ring , as in menthol . Of course , we will need additional functionality in our precursor **dienophile** (replacing methyl vinyl ketone) , so as to install an oxygen function – it will be an acetate ester group – on carbon 3/(3) , which will then become carbon 1 by priority .

The menthol synthesis will also require a highly selective sort of hydrogenation of the two olefin bonds . This might be accomplished by a **hydroboration** technique , which can be quite stereospecific in nature .

The overall route is summarized in the following scheme :



Step 1 : the preparation of 1-chloro-3-butenone

The dienophile we require , replacing Vig's methyl vinyl ketone , will be similar to it but with the addition of an oxygen function at C1 , which will become C1 in the cyclohexane ring formed in the Diels-Alder reaction . If the oxygen function is supplied by a simple group like acetate , the target dienophile molecule will then be $\text{CH}_3\text{-CO-CH=CH-OAc}$, 1-acetoxy-3-butenone (or 3-keto-1-butenyl acetate) .

As it turns out , the intermediate chloro compound is well known , with at least two preparations described for it (ref. 8 , [page 24](#)) . I hesitate to recommend the synthesis of 1-chloro-3-butenone to novice or otherwise inexperienced organic chemists . It is **an extremely unpleasant , potentially hazardous material** ! Price and Pappalardo , writing in 1950 , reported ,

“Methyl β -chlorovinyl ketone must be handled with great care . It is intensely lachrymatory and caused severe blistering of the skin . It decomposes within a day or so at room temperature but solidifies at about 5 °C and is much more stable in solid form” .
(ref. 8 , [page 24](#) , p. 2613) .

The damn stuff sounds to me like mustard gas ! [bis(2-chloroethyl)sulfide , the infamous chemical warfare agent deployed all too frequently during World War I] . Such vesicant chemicals , like mustard gas , can also be genetically damaging , exhibiting carcinogenic , mutagenic , and teratogenic properties . Clearly , excellent laboratory technique will be required here !

In a later (1964) paper , Benson and Pohland described the facile preparation of quaternary ammonium salts from the reaction of the chlorovinyl ketones with trimethylamine in toluene solution :

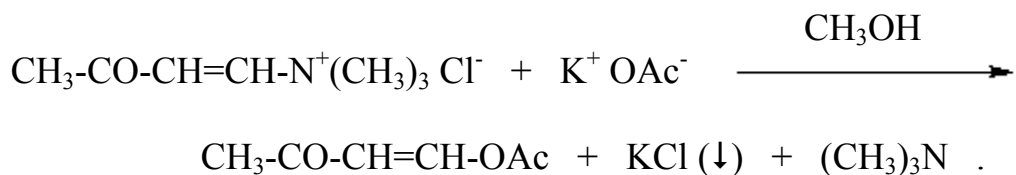
“When the β -chlorovinyl ketones were treated with trimethylamine in toluene , an immediate , exothermic reaction followed in all cases giving a nearly quantitative yield of the quaternary salt . These salts were white , water-soluble solids the solids appeared to decompose

before the melting point was reached . On standing , unless carefully purified , they slowly turned light brown “ .
(ref. 8 , [page 24](#) , p. 387) .

To minimize handling of the vile chloroketone , the reaction mixture from Friedel-Crafts acylation of acetylene gas with acetyl chloride could be extracted directly with toluene , dried , and treated with a slight excess of anhydrous trimethylamine in dry toluene to precipitate the insoluble quaternary ammonium salt . **Also , when cleaning up the glassware after the preparation , rinse it with a dilute (1% or so) solution of aqueous ammonia or ammonium bicarbonate to neutralize the highly reactive chloroketone .**

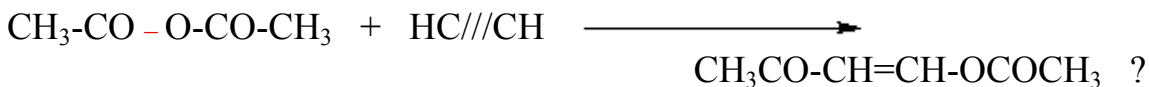
Step 2 : the preparation of 3-keto-1-butenyl acetate

It should be possible to displace the trimethylammonium group from C1 ; substituents there are remarkably labile , because of the electron-withdrawing and resonance stabilizing properties of the β -keto group . At this point the acetate would be introduced to C1 by the nucleophilic displacement of the quaternary ammonium group :

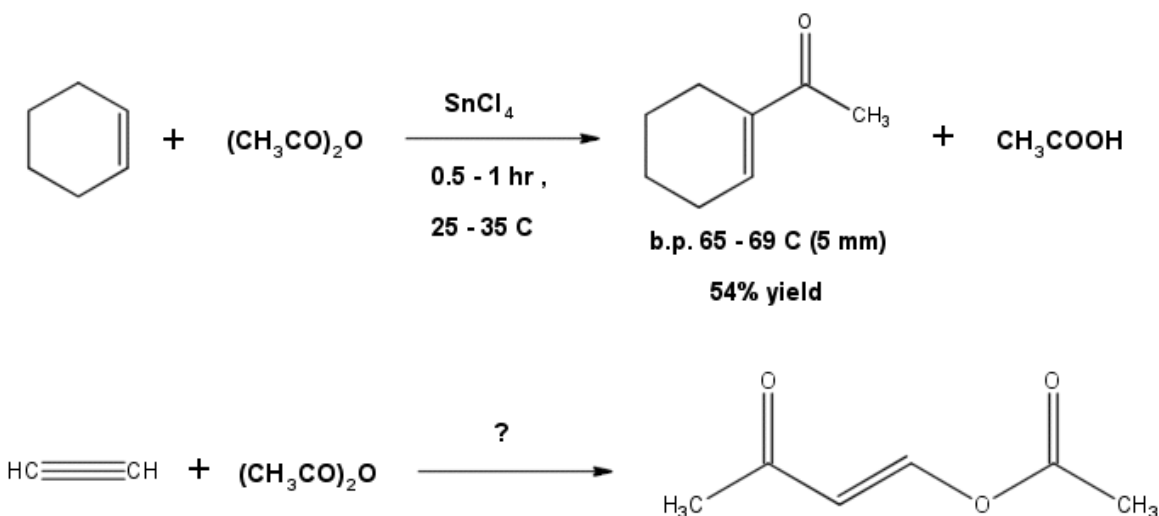


Granted , acetate is a feeble nucleophile at best , but precipitation of the insoluble potassium chloride by-product from the methanol solution , in which the reagent potassium acetate is quite soluble (242 g/L , ambient) , should help to force the displacement to completion .

I was wondering : would it be possible to add acetic anhydride **directly** , in a one-pot reaction , to acetylene :



Acetic anhydride actually does acetylate olefins, but the product – generally in a fair yield – is the α,β -unsaturated ketone; for example:



(Royals and Hendry, ref. 9, [page 24](#)).

Presumably the β -acetoxy ketone is an intermediate in the addition of acetic anhydride across the olefinic bond, but it is unstable in the reaction conditions and expels acetic acid to produce the final stable product, the enone. If our target molecule, 3-keto-1-butenyl acetate, is sufficiently stable in the reaction environment, it should be possible to isolate and purify it. However, if this enol acetate behaves as other β -acetoxy ketones do, then the final product could be 3-buten-2-one, CH3-CO-C=CH2, b.p. 85 °C. By the same token, it would be impossible to prepare 3-keto-1-butenyl acetate by **any** method, since it would quickly decompose to butynone. Chemical intuition suggests that it should be reasonably stable. After all, 1-chloro-3-butenone is stable enough to be prepared at ambient temperature, and the acetate-olefin O-C bond is probably **less** labile than the corresponding Cl-C bond in 1-chloro-3-butenone.

Elimination of the β -acetoxy group may be caused by the Friedel-Crafts catalyst, which is generally an electrophilic metal halide; anhydrous aluminum chloride is probably the most popular Friedel-Crafts catalyst.

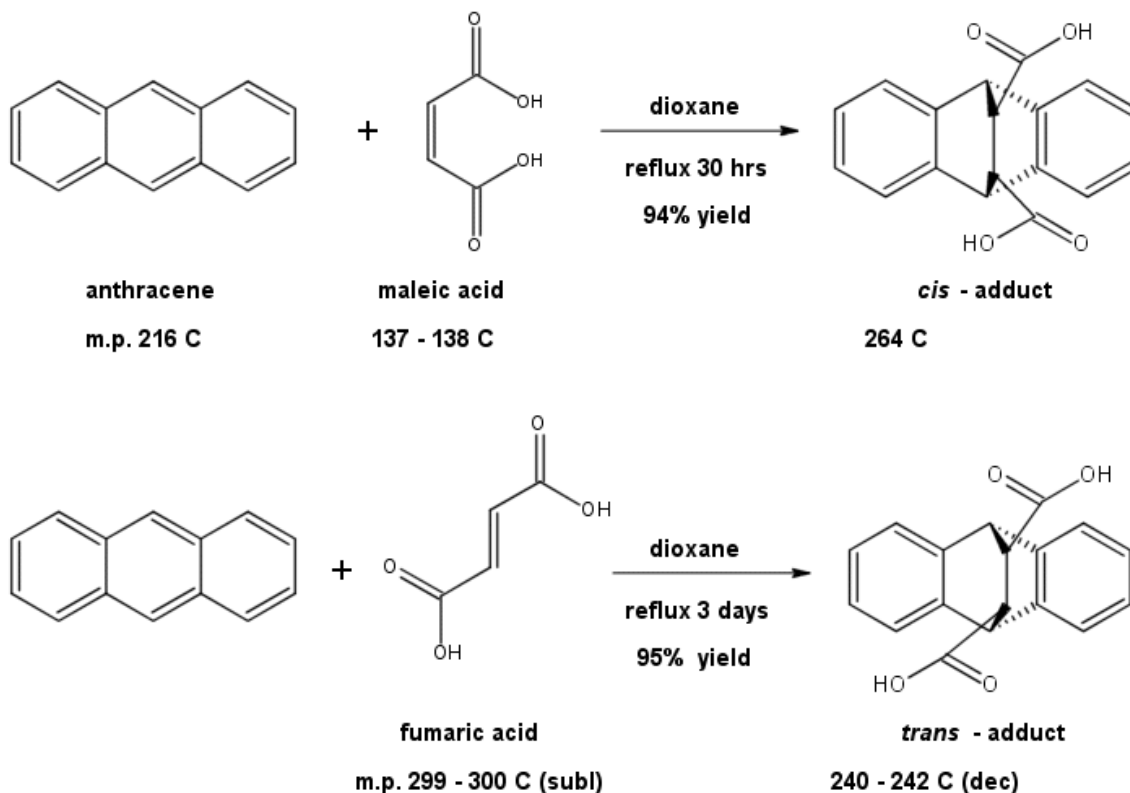
The metal-halide bond in these compounds is usually very labile, and they are well known to be susceptible to hydrolysis, which diminishes their catalytic capability. That is, the metal-oxygen bond is far stronger than the metal-halide bond. It could be that the metal atom in the Friedel-Crafts catalyst is strongly bonding to the acetate oxygen (linking to the olefin carbon atom), then “ripping it off” the hydrocarbon substrate. This suggests that a less aggressive catalyst should be tried for the acetic anhydride addition. Tin tetrachloride, used in the example above with cyclohexene, would be less electrophilic than AlCl_3 and more weakly bonding to acetate than it, and so would be a good candidate catalyst to look at first. Addition of acetic anhydride to acetylene to produce 3-keto-1-butenyl acetate directly in a one-pot reaction would be an interesting project.

Step 3 : the Diels-Alder reaction

This is probably the key step in the synthesis scheme. The Diels-Alder reaction is known to be highly **stereoselective**, and it can be quite regioselective too, as we will see. The 3-keto-1-butenyl acetate will have the trans (or “E”) configuration across the olefin bond, as shown in the sketch on the middle of [page 13](#). Benson and Pohland (ref. 8, [page 24](#)) stated that their quaternary salt products had such a geometry; they say so in the title of their paper. This trans configuration should be retained after displacement of the trimethylammonium substituent by the acetate anion.

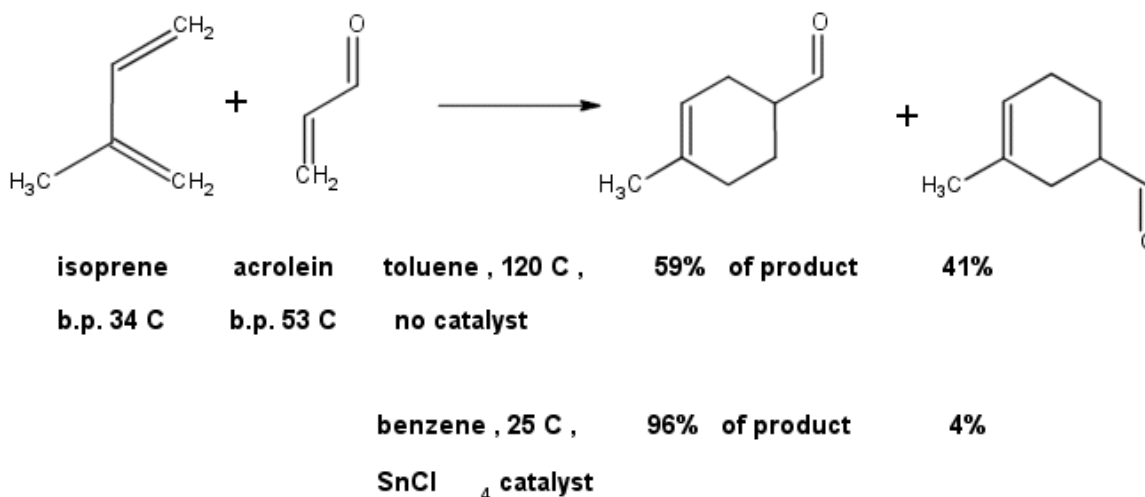
The trans geometry should also be retained after the enol acetate is combined with isoprene in the cyclization reaction. Of course, this trans configuration is found in the menthol stereoisomers (sketches, [page 5](#)). An example of stereochemical retention in the Diels-Alder reaction is the addition of maleic acid (cis, Z) and its stereoisomer, fumaric acid (trans, E) with anthracene, where the cis and trans geometry of the carboxylic acid groups, respectively, is retained in the products (sketch, top of the next page; ref. 10, [page 24](#)).

The Diels-Alder reaction can also be highly **regioselective** as well. Dienes substituted on C2 generally provide “para” products with monosubstituted olefins, while those substituted on C1 produce “ortho” cyclohexane

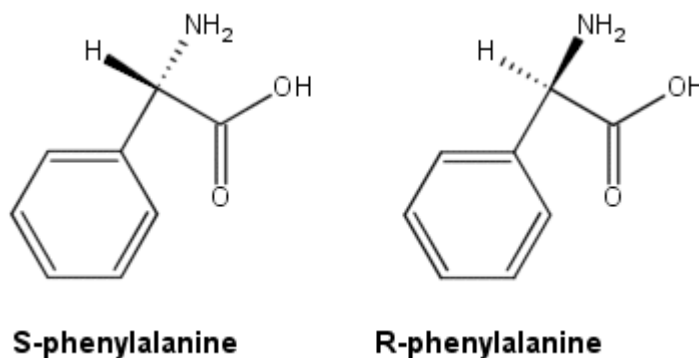


derivatives with $\text{CH}_2=\text{CH}-\text{X}$ dienophiles . Use of catalysts to speed up the reaction at ambient temperature can also dramatically influence the para-to-ortho ratio , as illustrated below (ref. 11 , [page 25](#) ; the sketch is at the top of the following page) .

Clearly , we will want to use some sort of catalyst in the proposed Diels-Alder reaction of 3-keto-1-butenyl acetate with isoprene . **First** , it will strongly favor the formation of the “para” isomer , which is what we want . **Second** , it will permit milder reaction conditions to be used ; it will speed up the reaction ; and it should result in a “cleaner” reaction with a purer product in a higher yield than without a catalyst . **Third** , if an enantiomeric catalyst is used , it might induce some enantioselectivity in the cyclization and in the product . Remember , we are aiming toward the synthesis of the L-(–)-menthol enantiomer , so we should be alert to any possibility of inducing enantioselection in one or other of the reaction steps in order to achieve this objective .



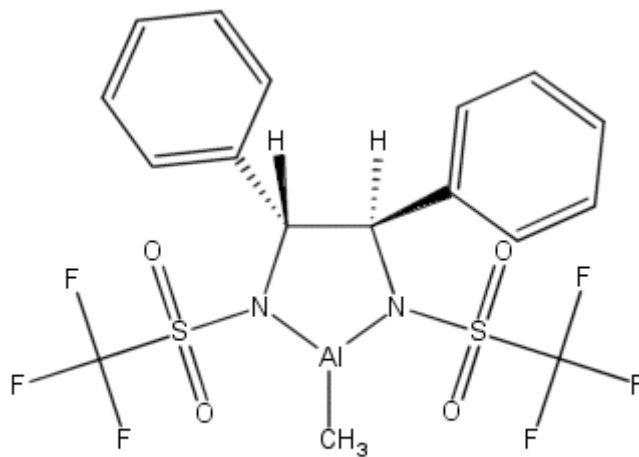
An interesting enantioselective catalyst has been used in the preparation of optically active polybenzofuran (ref. 12 , [page 25](#)) . The amino acid S-phenylalanine ,



was combined with anhydrous aluminum chloride in toluene at room temperature , to form an approximately 3:1 AlCl₃ : phenylalanine coordinate covalent complex as a clear , yellow-green solution . Although we would expect coordination of Al(III) to reduce its catalytic potency , this amino acid-based complex was successful in inducing the polymerization of benzofuran to its corresponding polymer at -75 °C . It is a simple and inexpensive catalyst to prepare , and does seem capable of both promoting the polymerization reaction – which likely has a free-radical mechanism – and of inducing enantioselection in the resulting product .

Aluminum chloride itself, and the Friedel-Crafts catalysts in general are known to accelerate many Diels-Alder reactions considerably (ref. 13, page 25). “Nafion H”, a fluorinated sulfonic acid polymer, will also catalyze the cyclization reaction (ref. 14, page 25), as will the Wurster Blue salt, tris(4-bromophenyl) aminium hexafluoroantimonate (ref. 15, page 25), which is a resonance-stabilized radical cation. Indeed, all of these Diels-Alder catalysts must function as electrophilic reagents, creating a cationic complex with the dienophile, making it more electrophilic toward the nucleophilic diene. Without such catalysts, the Diels-Alder reaction will succeed only when an electron-withdrawing group is attached to the olefin portion of the dienophile, in effect polarizing it and making it electrophilic to a certain extent.

Aluminum(III) has been incorporated into a coordinate covalent complex with another optically-active ligand, 1,2-diphenylethylene diamine, as the asymmetry-inducing reagent, “diazaaluminolidine” (p. 35 in ref. 11, page 25):



diazaaluminolidine

Several catalysts have been devised, including diazaaluminolidine above, that are remarkably effective in inducing asymmetry in organic reaction products. In several cases nearly quantitative “optical yields”, or **enantiomeric excesses**, were obtained in the syntheses. That is, the

product consisted almost entirely of one desired enantiomer, with little if any of the other enantiomer present. Unfortunately, there doesn't seem to be any established repertoire of asymmetric induction catalysts for various transformations of interest. The researcher is thus obliged to devise such catalysts on a case-by-case basis, as we must do in this Diels-Alder step.

Since two asymmetric centers are created in the cyclohexene product (page 10), it is probably a good idea, indeed essential, to "fix" the absolute configurations around those two carbons as soon as they are formed. The simple, inexpensive chiral catalyst $[(\text{AlCl}_3)_3 \text{ S-phenylalanine}]$, mentioned above, is a good place to start. If the wrong configurations are induced, the researcher could try using the same complex again, but substituting R-phenylalanine as the amino acid ligand. Both forms of phenylalanine are commercially available, eg. from the Aldrich Chemical Company. The S enantiomer is the "natural" one, widespread in Nature in proteins, while the R enantiomer is the rarer "unnatural" form, and is derived from the resolution of racemic phenylalanine from chemists' reaction flasks, rather than from Nature.

Pure enantiomeric forms of other amino acids, and of tartaric acid, are also commercially-available at moderate cost, and might form useful catalytic complexes with aluminum chloride and related Friedel-Crafts catalysts. An alkaloid such as quinine could be tried as a ligand; and the very common and cheap sugars glucose and sucrose (ordinary table sugar!) might form chiral catalytic complexes with aluminum chloride and other electrophilic metal halides. Keep in mind that the "exhausted" catalyst materials must be cleanly separated from the product at the end of the reaction.

Step 4 : the Wittig reaction

As in Vig's synthesis of dipentene (page 9), the acetyl group attached to the cyclohexene ring will be converted to the isopropylidene group by condensing it in the Wittig reaction with the phosphorus ylid, $\text{Ph}_3\text{P}^+-\text{CH}_2^-$. It was necessary to have the acetyl group in the dienophile in the Diels-Alder reaction: first, because obviously it is the logical precursor to the isopropylidene group, but then second, because as an electron-withdrawing

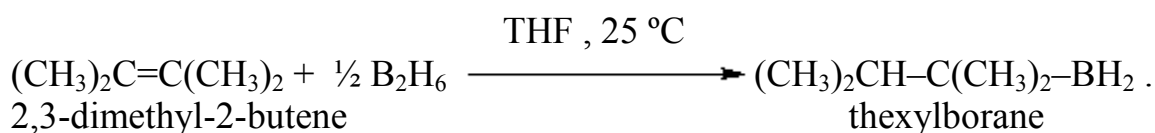
function it was capable of activating the olefin part of the 3-keto-1-butenyl acetate . That accomplished , it must now be converted into the desired isopropyl skeleton .

The Wittig reaction has been surveyed by Maercker and by House (ref. 16 , [page 25](#)) . The reader is referred to these reviews for useful information concerning actual experimental conditions and techniques , with many references provided to the original research literature .

Step 5 : hydroboration of the olefin bonds

This is the second-most important step of the overall proposed route to L-(–)-menthol ; I would rate the Diels-Alder cyclization as the critical step , as most of the molecule’s carbon skeleton is assembled in it . “Ordinary” catalytic hydrogenation of the olefin bonds in intermediate 4 ([page 10](#)) would be unsatisfactory , as no stereochemical control would be possible . We must search for , and find , a more subtle , sophisticated form of hydrogenation of those two olefin bonds , one which will permit full control of the stereochemistry of the hydrogenated product . Fortunately , the technique of hydroboration is seemingly custom-made for this application .

Hydroboration is a remarkably versatile , selective method of addition of various reagents , including hydrogen , to the olefin bond . Several hydroborating reagents are available , including the simplest of them , diborane (B₂H₆) itself . The hydroborating agent suggested in this present application is **thexylborane** , whose bulky alkyl group will increase the selectivity of the addition reaction to intermediate 4 :

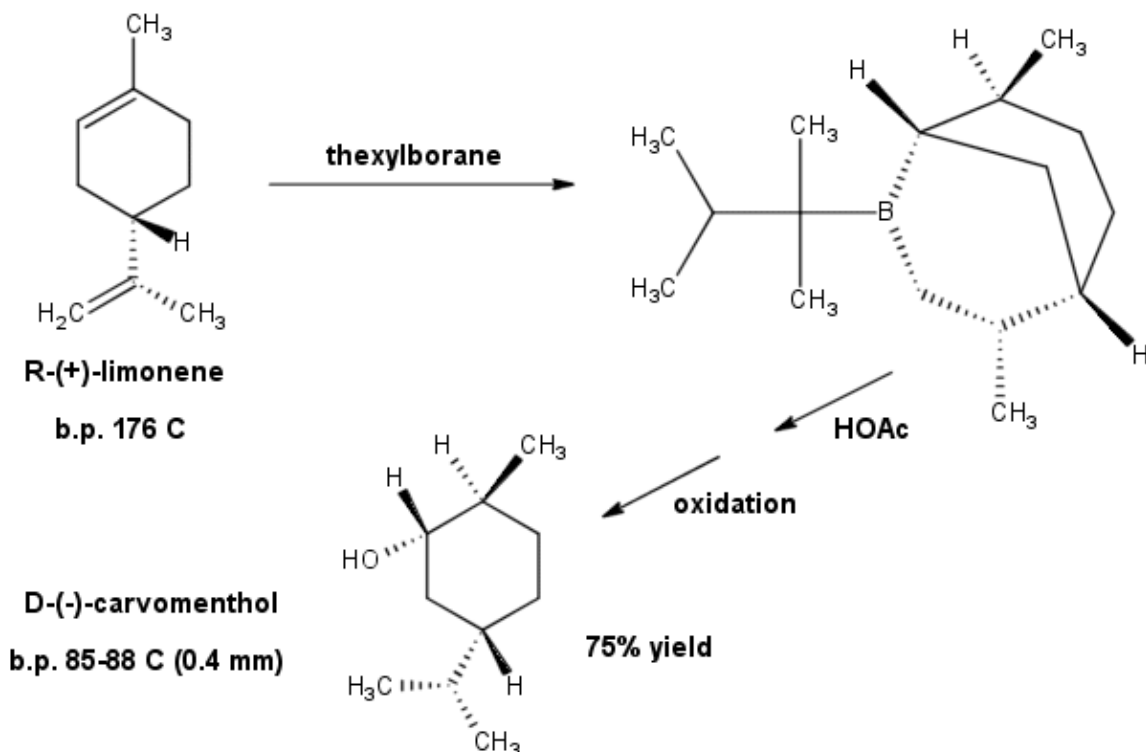


Diborane , and alkylborane derivatives like thexylborane , will add preferentially to olefins in the order , at the carbon atom “C” :



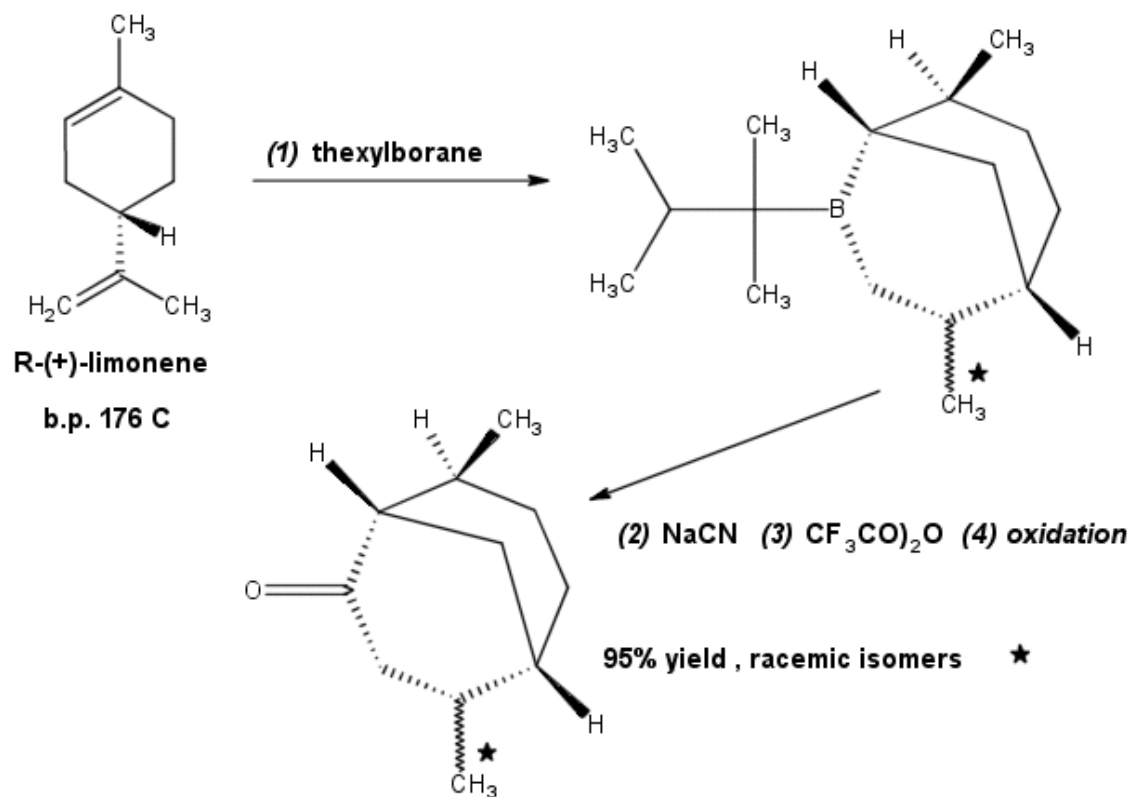
where X , Y , R₁ , and R₂ are various non-hydrogen substituents . The addition of the B–H reagent to the olefin also occurs with a **cis** geometry (ref. 17 , [page 26](#)) , which will be critical in the menthol stereochemistry .

These reaction characteristics of boranes are nicely illustrated in the following two additions of thexylborane to limonene . The first example :



(Brown and Pfaffenberger , ref. 18 , [page 26](#))

In the second example , the cycloborane intermediate was carbonylated to the corresponding dicyclic ketone by treatment with cyanide , trifluoroacetic anhydride , and an oxidizing agent (the sketch is on the next page) . These two examples are offered to illustrate the hydroborating technique suggested for our intermediate 5-acetylimonene ([page 10](#)) . The beauty of the technique is that the **first** step of the hydroboration , the addition of the thexylborane to the less-hindered isopropylidene function , will



(Pelter et al. , ref. 19 , [page 26](#)) .

stereochemically assist the **second** step , the addition of the remaining B–H proton to the ring olefin bond in its less-hindered position , and **on the same face of the molecule , its “underneath”** (as sketched) . And , since the B–H addition is cis , the limonene methyl group is pushed “upward” to the upper side of the molecule . It will thus have the correct stereochemistry relative to the “down” isopropyl group , as desired for the menthol molecule .

Protonolysis of alkylboranes to the corresponding hydrocarbons – in effect , “hydrogenating” them – requires surprisingly vigorous conditions . The standard technique consists of refluxing the alkylborane in diglyme [diethylene glycol dimethyl ether , b.p. 162 °C] , together with an excess of propionic acid (b.p. 141 °C) at 160 °C for 2 – 3 hours (ref. 20 , [page 26](#)) .

The final step of the proposed synthesis route to menthol would be the alkaline saponification of the acetate ester to the corresponding alcohol group, now at C1 in the cyclohexane ring. This might be achieved with a relatively dilute aqueous solution of sodium hydroxide, or methanolic NaOH. I included this saponification step with the hydroboration reactions to make a more compact sketch; however, it might be advisable in actual practice to extract, isolate, and purify the intermediate menthyl acetate. The experimentation could stop there, as the ester is well known, but it still might be fun to finish the synthesis at menthol, if for no other reason to inhale the sweet smell of success! I hasten to add that all the instrumental analyses, melting point, and polarimetry measurements should, of course, be carried out on the final product to ensure its correct identification as L-(–)-menthol.

In conclusion, the proposed synthesis route to menthol, based on Vig's earlier approach to dipentene, is fairly simple and straightforward, and has a good chance of success; at least, I think it "looks good on paper". The researcher can be, indeed often is, surprised and disappointed in actual laboratory practice, but this should be an incentive for the unleashing of creative energies to overcome experimental problems. One thing is certain: the devising of this synthesis route to L-(–)-menthol has been very educational and mentally stimulating for me, as I hope it has been for the reader to study and think about.

References

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