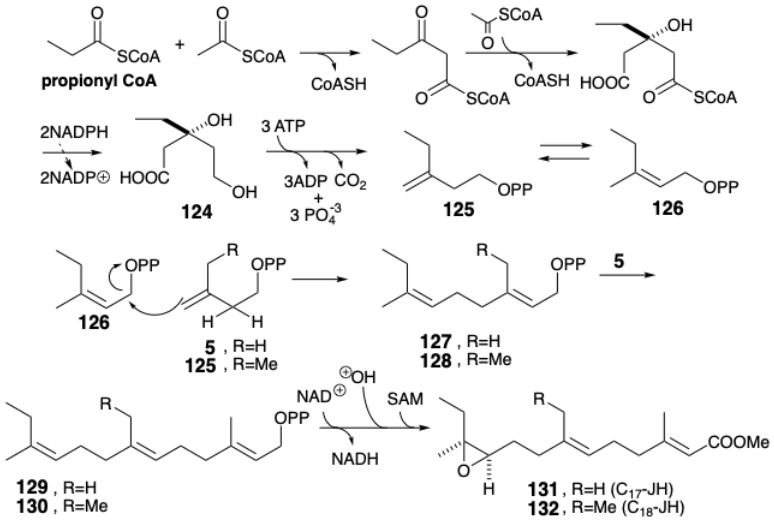
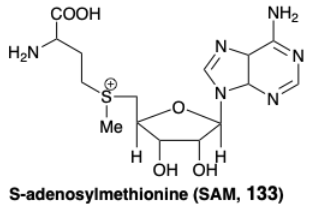
4.5: Homo and Bishomo Sesquiterpenes ii Cecropia Juvenile Hormones

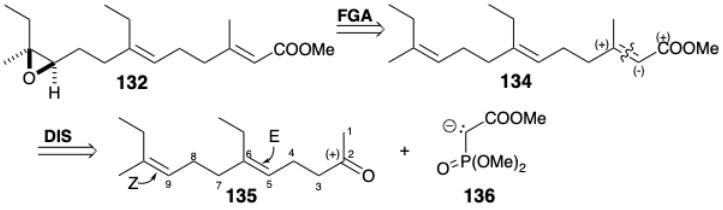
The Cecropia juvenile hormones are biogenetic close relatives of farnesol that contain one or two extra carbon atoms in their sesquiterpenoid carbon skeletons. These terpenoid homologues are referred to as homo and bishomo sesquiterpenes respectively. The extra carbon atoms arise through the incorporation of one or two molecules of propionate in place of acetate during a biosynthetic skeletal construction that is otherwise identical to that of farnesol. Thus, propionyl CoA condenses with two molecules of acetyl CoA to give homomevalonic acid (**124**) after reduction with NADPH. Conversion of **124** to **125** via decarboxylative elimination and isomerization to **126** is followed by addition of the allylic electrophile **126** to the terminal C=C bond in Δ^3-isopentenyl-PP (**5**) or to its six carbon homologue (**125**). The allylic electrophiles **127** or **128** then alkylate Δ^3-isopentenyl-pyrophosphate to deliver homo and bishomo farnesylpyrophosphates **129** or **130**, respectively. These are oxidized to the corresponding acids by hydride donation to NAD+. Enantio-selective epoxidation, and O-methylation of the carboxyl by methyl transfer from S-adenosyl-methionine (**SAM, 133**) gives optically active epoxyesters **131** and **132** which are known as C_{17} and C_{18} juvenile hormones respectively.

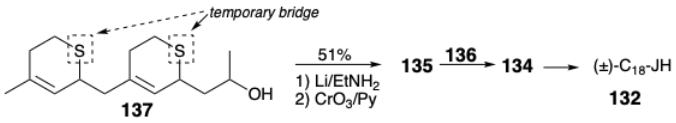




Stereocontrolled Generation of Trisubstituted Alkenes

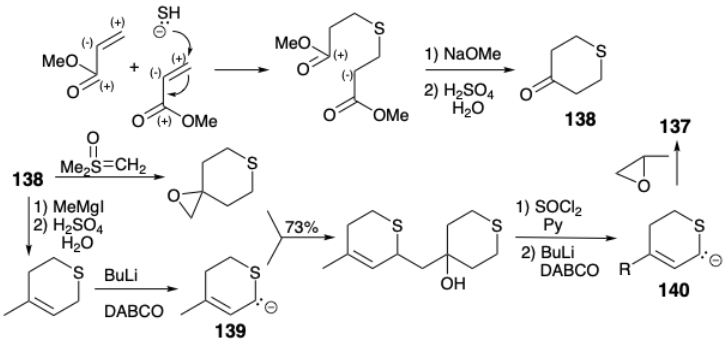
The primary synthetic challenge presented by the Cecropia juvenile hormones is stereocontrol during the construction of trisubstituted C=C double bonds. Temporary rings may be effectively utilized to control alkene geometry. A variety of different applications of this tactic have been employed to achieve stereocontrolled syntheses of juvenile hormones. These syntheses generally involve stereocontrolled construction of methyl bishomo farnesoate (**134**), that is converted into C_{18}-JH (**132**) by regioselective epoxidation as in the biosynthesis of **132**. Polar analysis of **134** suggests a synthesis from the phosphono ester-stabilized carbanion **136** and dienone **135**.



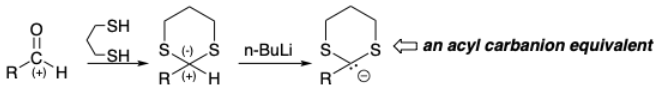


A Temporary Bridge Strategy

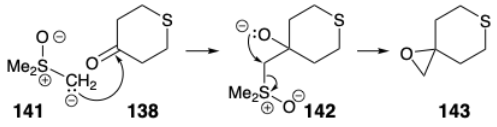
One tactic for stereocontrolled synthesis of **135** employs temporary thioether bridges in **137** to enforce the 5-E and 9-Z configurations.8 The sulfur bridges are reductively cleaved after the carbon skeleton of **135** is complete. Both of dihydrothiapyran fragments in **137** were derived from a common intermediate, tetrahydro-1,4-thiapyrone (**138**). Sulfur serves a dual strategic role in this scheme. Besides enforcing the required configuration at the carbon-carbon p-bonds (stereocontrol), sulfur stabilizes a neighboring nucleophilic center (reactivity control) in the carbanions **139** and **140**. The mercapto and sulfide functional groups readily provide activation for either nucleophilic or electrophilic reactivity. They are *biphilic* functional groups, and, as previously encountered for the biphilic nitrile functional group (see pages 19 and 31), they can be used to produce polar reactivity inversion. We encountered this phenomenon previously in the conversion of an electrophilic carbonyl into a nucleophilic dithiane carbanion, an acyl carbanion equivalent.



In the present synthesis of JH, the electrophilic β-carbon of methyl acrylate is transformed by the thioether functional group into a nucleophilic center in **139** and **140**.

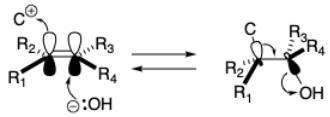


Another instance of biphilic activation by sulfur is found in the reaction of the electrophilic carbonyl carbon of **138** with dimethyloxosulfonium methylide (**141**), a *sulfur stabilized nucleophile*, to produce epoxide **143**. Sulfur then provides *electrophilic* activation at the same carbon by serving as a nucleofuge in the intermediate betaine **142**.



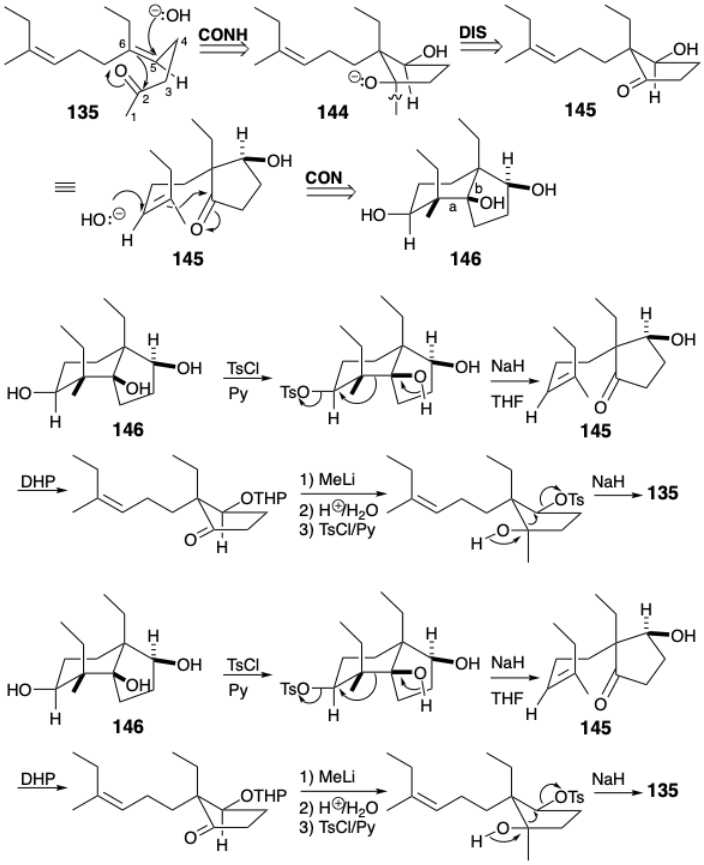
SEC in Fragmentations

Another stereocontrolled synthesis of **135** exploits reversible stereospecific, anti-periplanar addition to a carbon-carbon π-bond to transpose the stereochemical relationships in monocyclic and bicyclic intermediates into those of acyclic products.[9] The anti-periplanar arrangement allows continuous overlap during a concerted fragmentation. Thus, the E configuration of the 5,6-π-bond in **135** is preserved in latent form in the cyclic intermediate **144** by a dislocation involving anti-periplanar addition of a carbon electrophile and hydroxyl nucleophile to **1 3 5** . A new electrophilic carbonyl carbon is generated by the dislocation **144** fi

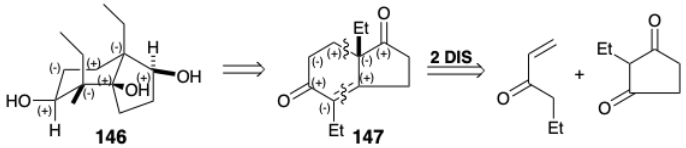


145. The Z configuration of the C=C bond in **145** is preserved in latent form by a dislocation involving antiperiplanar addition of a carbon electrophile and hydroxyl nucleophile to the C=C bond in **145**. Thus, all of the stereochemical information in the acyclic intermediate **135** is contained in latent form in the bicyclic precursor **146**. Control of alkene geometry in an acyclic carbon skeleton is thereby transposed to control of relative stereochemistry in a multicyclic carbon network. Since the conformations of multicyclic carbon networks are more rigid than acyclic ones, the influences of steric and neighboring group effects are more easily predicted and usually more pronounced.

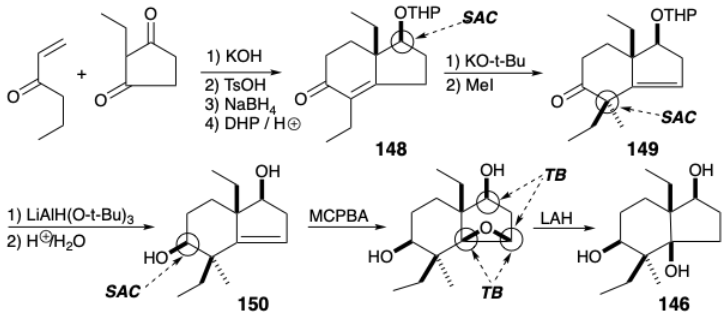
Fragmentation of bonds a and b in **146** was promoted by converting hydroxyl into toluenesulfonate leaving groups. The triol **146** was readily selectively monotosylated at the least sterically congested secondary hydroxyl. Fragmentation of the resulting b-tosyloxy 3° alcohol delivering the Z-alkene **145** proceeded stereospecifically upon treatment with NaH. Addition of MeLi to the tetrahydropyranyl derivative of **145** occurred stereoselectively (57%). After deprotection and selective tosylation of the secondary hydroxyl in the resulting diol, fragmentation of an intermediate β-tosyloxy 3° alcohol occurred smoothly to afford **135** stereospecifically (80%).



Since the functionality in **146** was introduced by polar reactions, it is a foregone conclusion that the functional groups are connected by consonant circuits. Polar analysis of **146** shows that all circuits in the cyclohexane ring are consonant. This allows disconnection of bonds to the ring fusion *common atoms*. However, activation of nucleophilic reactivity vicinal to the secondary hydroxyls requires conjugation that is only afforded by carbonyl groups as in **147**. Polar disconnection of **147** then suggests propyl vinyl ketone and 2-ethylcyclopentan-1,3-dione as starting materials.

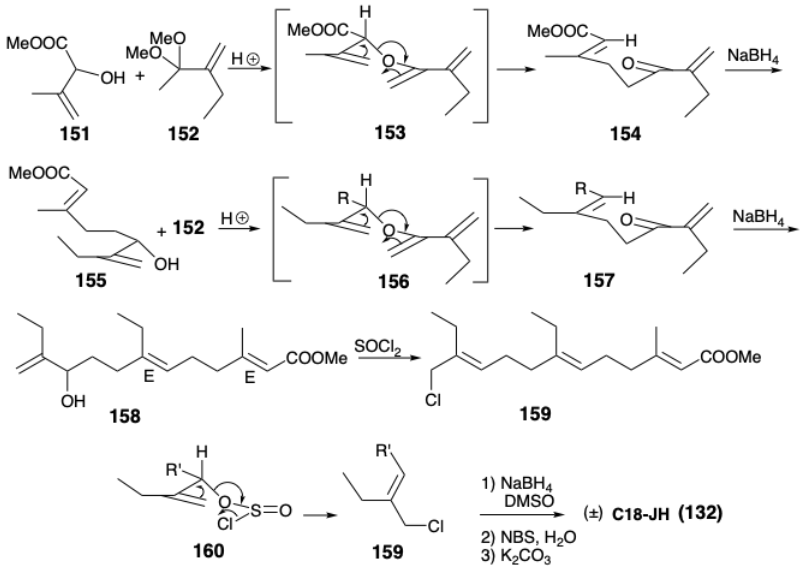


A synthesis of **146** based on the strategy outlined above began with Robinson annelation of 2-ethylcyclopentane-1,3-dione with propyl vinyl ketone. Steric approach controlled hydride delivery to the resulting dione provided **148** after protection of the hydroxyl. Steric approach control also resulted in stereoselective methylation from the less sterically congested α-face of the enolate from **148**. Similarly, hydride delivery to the less sterically congested face of **1 4 9** gave **1 5 0** stereoselectively. The stereochemistry of the final hydroxyl group required for the triol **146** was dictated by the effect of the neighboring hydroxyl in **150** on the epoxidation of this alkene. The hydroxyl group hydrogen bonds with MCPBA thereby enforcing oxygen delivery *cis* to the neighboring hydroxyl as for **250** in section 3.6.

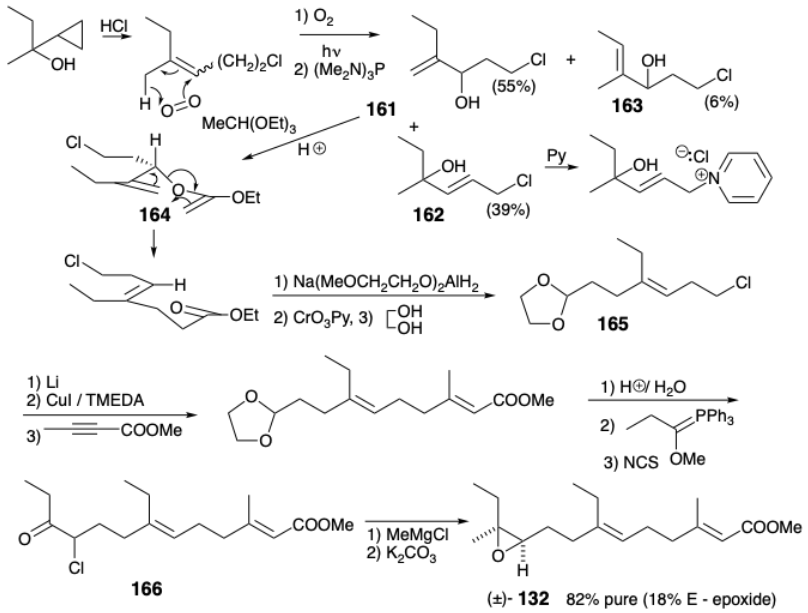


SEC Through Preferred Conformations

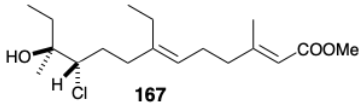
Conformational effects in cyclic *transition states* can also result in substantial, as well as predictable, stereoselectivity in the generation of acyclic alkenes. In another stereocontrolled synthesis of C_{18}-JH (**132**), Claisen rearrangement of the allyl vinyl ether **153** from transketalization of **152** with **151**, followed by elimination, generates the γ,δ-unsaturated ketone **154** stereoselectively.10 A chair transition state with an equatorial carbomethoxyl substituent is preferred for this [3.3] sigmatropic rearrangement. Borohydride reduction of **154** gives an allylic alcohol **155**, which was again homologated stereoselectively with **152** to give allylic alcohol **158** via **156** and **157**. A cyclic transition state is also the key to a stereocontrolled conversion of **158** to the allylically transposed chloride **159**. Thus, the chlorosulfite ester **160** of **158** gives **159** via S_Ni' rearrangement involving a chair conformation with the bulky substituent in an equatorial position.



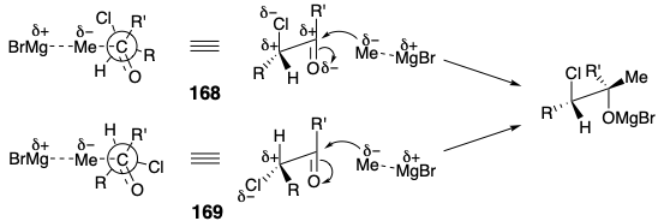
Another synthesis of C_{18}-JH (**132**) that exploits a Claisen rearrangement to generate the 6,7-trisubstituted double bond stereoselectively is outlined below.[11] An interesting step in this synthesis is the selective destruction of an undesired byproduct **162**. This allylic chloride is more reactive than the isomers **161** and **163** and, therefore, selectively forms a water soluble pyridinium salt. Claisen rearrangement occurs via a transition state conformation **164** with an equatorial chloroethyl group. The 2,3-double bond is generated stereoselectively by *cis*-1,4-addition of an organocuprate derived from **165** to methyl 2-butynoate.



In this synthesis, the epoxide is produced by base-induced cyclization of a chlorohydrin rather than epoxidation of an olefin. Stereoselective HO generation of the Z-epoxide is possible because the reaction of chloroketone **166** with methyl magnesium chloride leads predominately to one diastereomer, the *threo* chlorohydrin **167**.

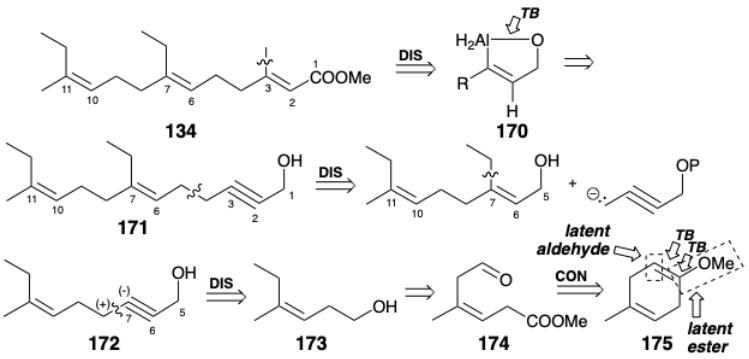


This stereoselectivity is not the consequence of a cyclic transition state. Rather, for acyclic ketones which contain polar α-substituents (e.g. halogens) that are unlikely to coordinate with metal atoms, a combination of torsional strain, steric interactions, and electrostatic interactions must be considered. Two models have been formulated to explain such stereoselectivity. One model presumes that the reactive conformation of such ketones is a structure (e.g., **168**) in which the carbonyl group and the polar α substituent are anti-periplanar to minimize dipole-dipole repulsion. Alternatively, the transition state may resemble **169** that allows maximum separation of the electronegative a substituent and the negatively charged nucleophilic reagent. Another example of such stereoelectronically controlled stereoselection is provided by the **48** + **49** → **53** conversion presented in Chapter 3 (section 3.3).

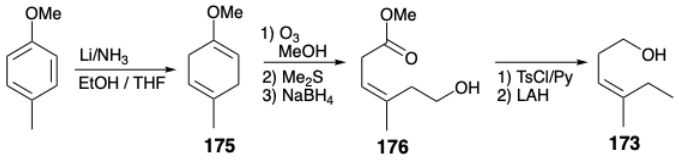


Other TB Strategies

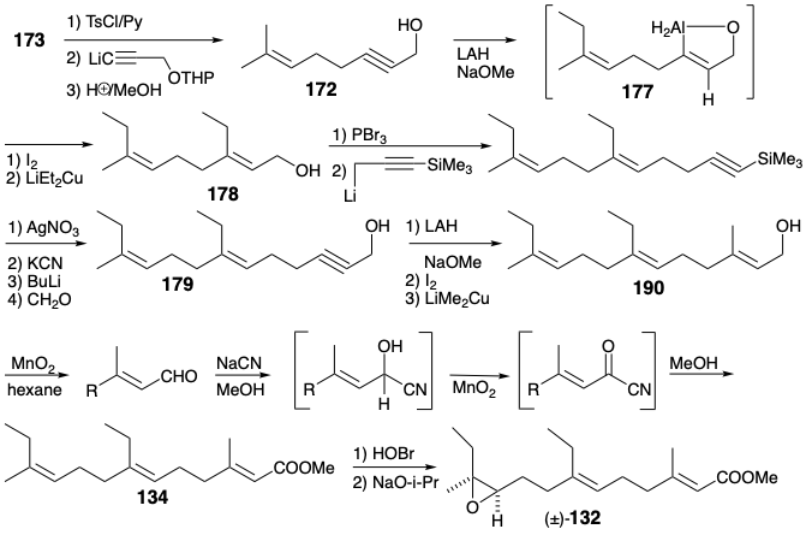
Two tactics for stereoselective construction of trisubstituted C=C bonds not encountered in the previous examples are exploited in a strategy for synthesis of C_{18}-JH that was devised by Corey.[12] The 2,3-E configuration in **134** can be assured by a temporary ring during pseudo-intramolecular hydroalumination of a propargyl alcohol **171** that produces an intermediate vinyl alane **170** which is subsequently alkylated. This tactic can also produce the 6,7-E configuration by a similar hydroalumination-alkylation sequence applied to **172**. The fact that a terminal alkyne is a latent carbanion suggests a polar dislocation of **172** to a propargyl alcohol-derived acetylide nucleophile and an electrophilic precursor **173**. The E configuration of **173** can be assured by a temporary bridge that is suggested by dislocation to a more highly functionalized precursor **174** with differentiated carbonyl groups. Thus, reductive coupling of these two carbonyl groups provides a bridged latent dicarbonyl precursor **175**.



Especially noteworthy is the synthetic role of the aldehyde carbonyl group in **174**. This functional group is exploited solely to facilitate stereocontrol.

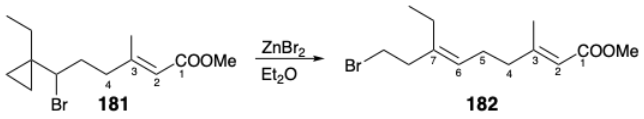


The substituents in the acyclic product **176**, from selective oxidative cleavage of **175**, are necessarily *cis* since only a *cis* double bond can be accommodated in a six membered ring. The *cis* relationship between the aluminum and hydroxymethyl substituent enforced in the intermediate **177** by a temporary bridge is preserved in the subsequent halogenolysis of the C-Al bond and alkylation of the resulting vinyl iodide delivering **178**. Both transformations occur with retention of configuration. A similar sequence delivers **180** stereoselectively from **179**. Conversion of the allylic alcohol **180** into key intermediate **134** requires oxidation followed by O-methylation.

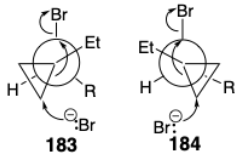


SEC Through Preferred Conformations

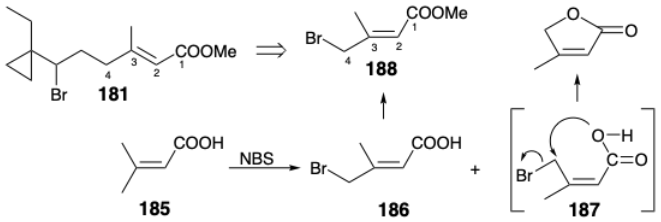
Highly stereoselective formation of trisubstituted alkenes can sometimes be achieved by processes not involving intermediates with temporary bridges or cyclic transition states. Thus, occasionally, a combination of conformational and stereoelectronic effects may produce high stereoselectivity in reactions of acyclic molecules. For example, the 6,7-C=C bond of JH can be generated stereoselectively during transformation of the cyclopropyl carbinyl bromide **181** into the homoallylic bromide **182**.[13]



Stereoselectivity arises from a stereoelectronic preference for an anti-periplanar arrangement of cleaving bonds that leads to generation of the new carbon-carbon double bond in a concerted stereocontrolled fashion. That is, a coplanar arrangement of the breaking C-C and C-Br bonds allows coupling of these bond cleavages with carbon-carbon double bond formation. Either transition state conformation **183** or **184** satisfies this requirement, but **183** is clearly preferred because the cyclopropyl group eclipses only hydrogen. Thus, a conformational bias, coupled with a stereoelectronic preference, favors a transition state **183**, that leads to E-olefin **182**.



The preparation of an early intermediate, **188**, for the C1 to C4 segment of **181** illustrates a useful tactic for the synthesis of pure stereoisomers: selective destruction of one of two isomeric products from a nonstereoselective reaction. Thus, N-bromosuccinimide brominates dimethyl acrylic acid (**185**) nonselectively to give a mixture of bromoacids **186** and **187**.



The undesired Z-isomer **187** undergoes spontaneous lactonization, leaving the desired E-isomer **186** as the only acidic organic product, that can be extracted into mild base and subsequently methylated to provide the intermediate **188** for the synthesis of JH. This is combined with a nucleophile derived from ketoester **190** that is available, in turn, from 1-acetyl-γ-buryrolactone **189**. Symmetry was exploited during completion of the JH carbon skeleton by alkylation of the enolate of 3,5-heptanedione with **182**. Chlorination of the product gave **191**. The extra propionyl group was cleaved in a retro Claisen reaction by $Ba(OH)_2$. The resulting chloroketone **166** reacted stereoselectively with MeMgCl to give **167** with less than 8% of the unwanted diastereomer (see section 4.6). Base-induced heterocyclization of the *threo* chlorohydrin **167** delivered racemic C_{18}-JH.[13]