Stereochemistry of Addition of Allylic Grignard Reagents to α,β-Ethylenic Ketones

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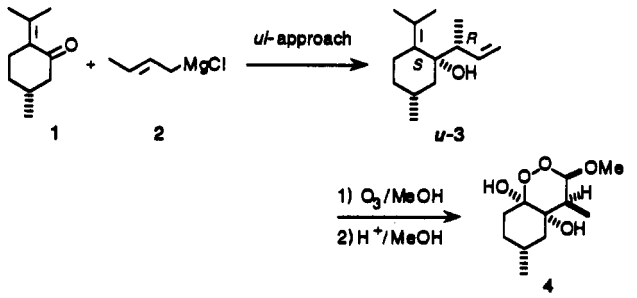
The stereochemistry of the addition of allylic Grignard reagents, (mainly crotylmagnesium chloride) to various conjugated enones has been investigated and a compact transition state is postulated. For *s-cis*-enones bearing no bulky substituents, a boat transition state, involving a *trans*-crotylmagnesium chloride, occurs leading to *erythro*-1,5-hexadien-3-ols as the major or only product.

Although the addition of Grignard reagents to carbonyl compounds is a major synthetic reaction and some efforts have been devoted to its mechanism, due to the variable nature of the species present in the solution, few positive results have been obtained.[1,2] Allylic Grignard reagents constitute a particular case because of their structure[3,4] and the possibility of addition without preliminary formation (Barbier reaction).[5] The reaction of allylic Grignard reagents with ketones to form carbon–carbon bonds has found wide application in organic synthesis.[6] The data can be accommodated by assuming that carbonyl compounds react with allylic Grignard reagents via a noncyclic, bimolecular mechanism (S_E2')(substitution anti).[7] Recently, we have discovered that unprecedented stereoselectivity is achieved in the addition of allylic Grignard reagents to (*R*)-pulegone (1).[8] The stereochemistry of the allylpulegol (3) (no other isomer detectable) resulting from the addition of crotylmagnesium chloride



(2) has been determined by ozonolysis in methanol solution and X-ray crystallographic measurements of the endoperoxide 4.[9] A "compact approach" stabilized by orbital interaction has been proposed as the mechanism.[8]

The stereochemical outcome of the addition of an allylic Grignard reagent to an unsaturated ketone can be divided into two areas: the facial selectivity at the electrophilic center and the facial selectivity at the nucleophilic center. Moreover, the geometry of the reagents adds a complication. We can expect that the stereochemistry of the addition should result both from the conformation of the enone and from that of the allylic Grignard reagent. A "compact approach" stabilized by orbital interaction should be sensitive to the presence of sterically bulky groups in the molecules. In the present paper, we report the results obtained from the reaction of the aliphatic acyclic enones **5**, aromatic enones **8**, aliphatic cyclic enones **11**, **13**, **15**, **19**, **20**, and **25** with crotylmagnesium chloride (**2**), 4-methyl-2-pentenylmagnesium chloride (**17**), 2-cyclopentenylmagnesium chloride (**23**), crotyltitanium ate complex **27** and crotylchromium complex **28**.

Results and Discussion

Addition of crotylmagnesium chloride on aliphatic acyclic enones **5** leads to 1,5-hexadien-3-ols **6** and **7**.

The relative configurations of the isomers[10] were assigned by comparison of their IR spectra using VPC/FT-IR. The **6** isomers possess a conformation stabilized by a hydrogen bond between the π-system of the vinyl group and the hydrogen atom of the hydroxy group.[11] Thus this isomer has the shorter retention time and in the vapor phase FT-IR spectrum, an absorption in the range 3602–3594 cm^{-1}. For **6a**, we have calculated the relative energies of the stable conformations by empirical molecular orbital energy calculations.[12] According to the AM1 method, the

(1) (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954. (b) For a compilation of reviews, see: March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 820–822.

(2) For a review on the mechanism of Grignard reagent formation, see: Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286.

(3) (a) Benkeser, R. A. *Synthesis* **1971**, 347. (b) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1. (c) Hill, E. A. *J. Organomet. Chem.* **1975**, *91*, 123.

(4) The thermochemical bond dissociation energy of the carbon–magnesium bond is higher in allylmagnesium bromide (69 kcal/mol) than in *n*-propylmagnesium bromide (50 kcal/mol), see: Holm, T. *J. Chem. Soc. Perkin Trans. 2*, **1981**, 464.

(5) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.

(6) (a) Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555. (b) Sjöholm, R. E. *Acta Chem. Scand.* **1990**, *44*, 82 and refs therein.

(7) (a) Felkin, H.; Gault, Y.; Roussi, G. *Tetrahedron* **1970**, *26*, 3761. (b) Cherest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1971**, 379. (c) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1971**, 383. (d) Wickham, G.; Young, D.; Kitching, W. *Organometallics* **1988**, *7*, 1187. For theoretical predictions on the stereochemistry of S_E2' reactions, see: (d) Anh, N. T. *J. Chem. Soc., Chem. Commun.* **1968**, 1089.

(8) El Idrissi, M.; Santelli, M. *J. Org. Chem.* **1988**, *53*, 1010.

(9) Pierrot, M.; El Idrissi, M.; Santelli, M. *Tetrahedron Lett.* **1989**, *30*, 461.

(10) For the tertiary alcohol, the prefixes syn and anti present an ambiguous character, so we describe the relative configuration *R*,R** as *l* (like) and *R*,S** as *u* (unlike), the relative topicity *re*,re** is termed *lk* (like), *re*,si**, *ul* (unlike). See: Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654. Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(11) (a) Sicher, J.; Cherest, M.; Gault, Y.; Felkin, H. *Collect. Czech. Chem. Commun.* **1963**, *28*, 72. (b) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309. (c) Tyblewski, M.; Bauder, A. *J. Mol. Struct.* **1983**, *102*, 267. (d) Cartaya-Marin, C. P.; Jackson, A. C.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 2443. (e) Bakke, J. M.; Chadwick, D. J. *Acta Chem. Scand., Ser. B.* **1988**, *B42*, 223. (d) Reference 6b. (e) Bacon, J. F.; Van der Maas, J. H. *Spectrochim. Acta, Part A* **1988**, *44A*, 1215.

(12) Calculations were performed with the GenMol program see: Cavelier-Frontin, F.; Pèpe, G.; Verducci, J.; Siri, D.; Jacquier, R. *J. Am. Chem. Soc.* **1992**, *114*, 8885; and AM1 program, see: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

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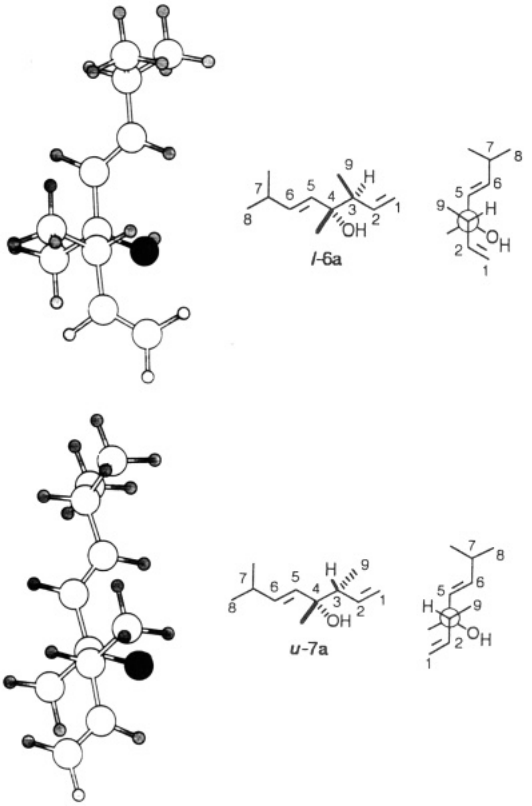
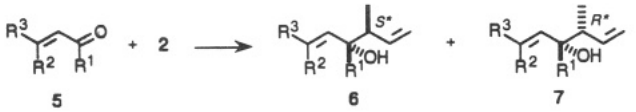


Figure 1.

Scheme I



5 **6** **7**

a: R^1 = Me; R^2 = H; R^3 = *i*-Pr; ***l*-6a** : ***u*-7a** = 60:40[a]

b: R^1 = Me; R^2 = H; R^3 = *t*-Bu; ***l*-6b** : ***u*-7b** = 60:40[a]

c: R^1 = *i*-Pr; R^2 = H; R^3 = Me; ***u*-6c** : ***l*-7c** = 85:15[a]

d: R^1 = *t*-Bu; R^2 = H; R^3 = Me; ***u*-6d** : ***l*-7d** = 85:15[a]

e: R^1 = *i*-Pr; R^2 = Me; R^3 = *i*-Pr; ***l*-6e** : ***u*-7e** = 90:10[a]

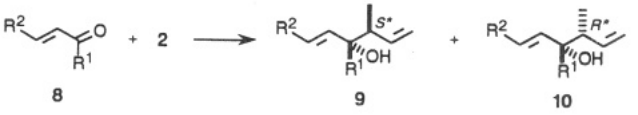
f: R^1 = *t*-Bu; R^2 = Me; R^3 = *t*-Bu; ***l*-6f** : ***u*-7f** = >97:3[a]

[a] product ratios

6a isomer is favored by ca. 1.17 kcal/mol (final heat of formation, **6a**: −33.96 kcal/mol, **7a**: −35.13 kcal/mol). The results are shown in Figure 1. The calculated dihedral angle 2-3-4-5 for the totally relaxed conformations of **6a** and **7a** are 166° and 175°, respectively, and for the dihedral angle 1-2-3-9, 127° and 104°, respectively.[13] These results confirm that for alcohols **6a**–**7a**, the isomer **6a** is most likely to possess an OH···π hydrogen bond. The lowering of the OH stretching frequencies has been widely used as an infallible sign of the formation of a hydrogen bond.[11b] A study by vapor phase FT-IR spectroscopy indicated **6a**, 3630 (60%), 3598 (40%) cm^{-1}, ($\Delta\nu$ = 32 cm^{-1}); **7a**, 3636 (100%) cm^{-1}. As expected, IR absorption at 3594 cm^{-1} is weak in the case of the alcohol **u-3** whose structure was unambiguously established previously.[9]

The known relative insensitivity of allylic Grignard reagents toward steric crowding is clearly confirmed by our results, thus even with the more hindered ketones **5e** or **5f**, 1,2-addition occurs in excellent yield (85–90% with an excess of **2**). Although the addition of allylmagnesium halides to hindered ketones is a reversible process,[14] only the kinetic alcohol products with a terminal monosubstituted double bond were formed. The diastereoselectivity increases with the size of the substituents on the ketone and for **5f**, alcohol **6f** is obtained with excellent selectivity (more than 97%).[15]

Scheme II



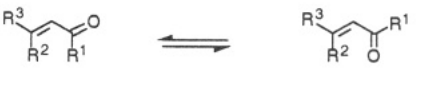
8 **9** **10**

a: R^1 = Me; R^2 = Ph; ***l*-9a** : ***u*-10a** = 54 : 46

b: R^1 = Ph; R^2 = Me; ***u*-9b** : ***l*-10b** = 52 : 48

c: R^1 = Ph; R^2 = Ph; ***l*-9c** : ***u*-10c** = 50 : 50

Open chain enones can exist in two conformations, s-cis and s-trans. The conformational behavior of these compounds is sensitive to the substitution pattern at the double bond. The geometry of the most stable conformation is determined mainly by the repulsive interaction between R^1 and R^2.[16a] For hindered ketones, calculations show that the potential surface in the vicinity of the energy minimum is very shallow and hence that large oscillations about the minimum are to be expected.[16b] It is well recognized that β-methyl substitution cis to the carbonyl results in the predominance of the s-cis form, while α-methyl substitution shifts the equilibrium toward the s-trans form.[16c] For ketones **5** bearing a (*Z*)-β-substituent (R^2) and with a hindered α'-substituent (R^1), the s-cis or twisted s-cis conformation can be expected to predominate.[17]



The proportion of the major diastereoisomer **6** increases with the importance of the s-cis conformation of the enones **5**.[18]

In marked contrast to the aliphatic compounds, addition to aryl-substituted enones occurs without any selectivity at all (Scheme II). For such aryl enones, the occurrence of a single-electron transfer process has been invoked

(13) Pons, J. M.; Rajzmann, M.; Santelli, M., to be published.

(14) (a) Benkeser, R. A.; Broxterman, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 5162. (b) Benkeser, R. A.; Siklosi, M. P. *J. Org. Chem.* **1976**, *41*, 3212. (c) Holm, T. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 985. (d) Barbot, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1977**, 113. (e) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134.

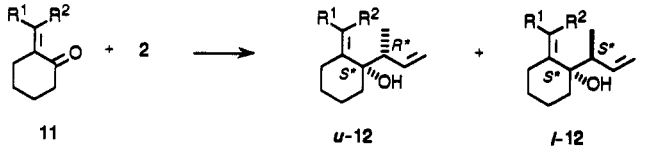
(15) The diastereoselectivity observed in the addition of crotylmagnesium bromide to unsymmetrical ketones is quite low, except with *t*-Bu ketones, see ref 6b.

(16) (a) Faulk, D. D.; Fry, A. *J. Org. Chem.* **1970**, *35*, 364. (b) Liljefors, T.; Allinger, N. L. *J. Am. Chem. Soc.* **1976**, *98*, 2745. (c) Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.

(17) A surprisingly low internal rotation barrier has been found for 2,2,5-trimethyl-4-isopropylhex-4-en-3-one, see: Nuss, J. M.; Bark, S. J.; Borchardt, D. B.; Morton, T. H. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1435.

(18) The problem of the relationship between conformational equilibrium and the distribution of the products, known as the "Curtin–Hammett principle" is far from a solution. In the cases studied, the conformational barrier for the equilibrium s-cis to s-trans of the hindered ketones and the activation barrier for the addition reaction are expected to be of the same magnitude (intermediate case). Consequently, we can assume that the product ratio is related to the conformational equilibrium, see: (a) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw Hill: New York, 1962; p 237. (b) Zefirov, N. *Tetrahedron* **1977**, *33*, 2719. (c) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

Scheme III

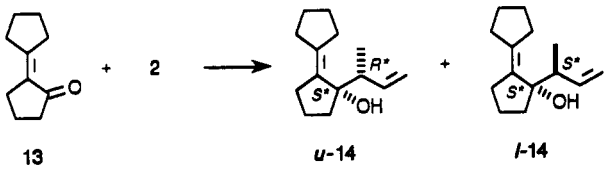


11 *u*-12 *l*-12

a: R^1 = Me; R^2 = Me; *u*-**12a** : *l*-**12a** = 100 : 0
b: R^1 = *i*-Pr; R^2 = Me; *u*-**12b** : *l*-**12b** = 100 : 0
c: R^1 = Me; R^2 = *i*-Pr; *u*-**12c** : *l*-**12c** = 100 : 0
d: R^1 = *i*-Pr; R^2 = H; *u*-**12d** : *l*-**12d** = 85 : 15

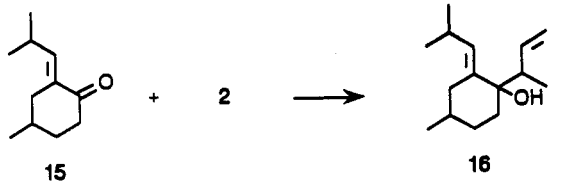
previously,[19] and it is well established that poor diastereoselectivity is observed when a carbon–carbon bond is formed by radical–radical combination.[20]

The same *u*-configuration of the product observed with (*R*)-pulegone occurs with alkylidenecyclohexanones. For ketones **11a**, **11b**, or **11c** with a tetrasubstituted double bond, only one alcohol ***u*-12** is observed in each case. But, the diastereoselectivity decreases when the double bond is only trisubstituted, **11d**. In the same way, good selectivity is observed in the addition of crotylmagnesium chloride to cyclopentylidenecyclopentanone **13** (***u*-14**/***l*-14** = 88:12).



13 *u*-14 *l*-14

Addition of crotylmagnesium chloride to the ketone **15** leads to the sesquiterpene type alcohol **16**. Unfortunately and in contrast to the results above, this addition occurs with quite low diastereoselectivity, and in inseparable mixture of the four possible diastereoisomers (50:24:14:12) is obtained.

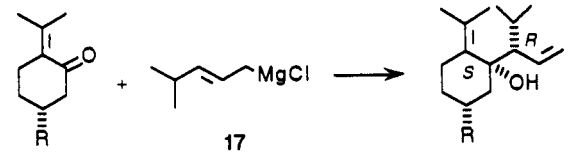


15 16

Because the selectivity of the addition to acyclic enones is dependent on the substitution pattern of the double bond of the enone, the importance of the substitution of the allylic Grignard reagent was also investigated. Addition of 4-methyl-2-pentenylmagnesium chloride **17** to ketone **11a** and (*R*)-pulegone (**1**) leads to the alcohols **18** as major products with the same *u*-configuration as in **3**.

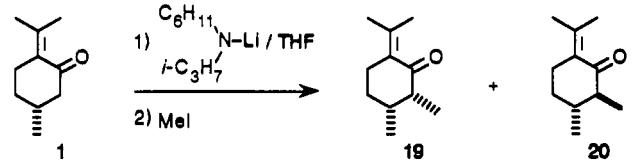
With the aim of increasing the size of the α'-substituent of pulegone, monomethylation was effected[21] (dialkylation occurs to give only the α,α'-product). Two methylpulegones **19** and **20** were obtained (15:85). The stereochemistry at C-6 was revealed by the H(6)–H(5) coupling constant in the ^{1}H NMR spectrum. The major isomer **20** exhibits a coupling constant (H(6) δ 1.92, dq, J = 10.0, 6.7 Hz) consistent with a trans arrangement of the methyl groups. On the other hand, minor isomer **19** displays a lower-field signal and a smaller coupling constant (H(6) δ 2.47, qd, J = 6.9, 4.9 Hz) in agreement with a cis configuration.

Scheme IV



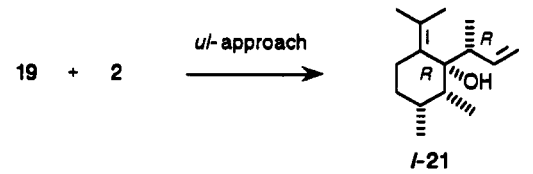
R = H, : **11a**
R = Me, : **1**

R = H, : *u*-**18a**
R = Me, : *u*-**18b**



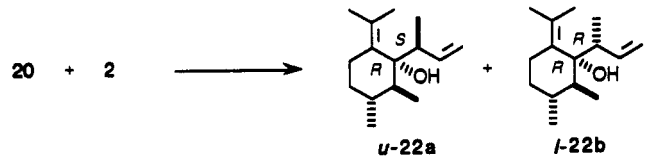
1 **19** **20**

Addition of crotylmagnesium chloride to **19** affords a single pulegol derivative **20** with *l*-configuration. In



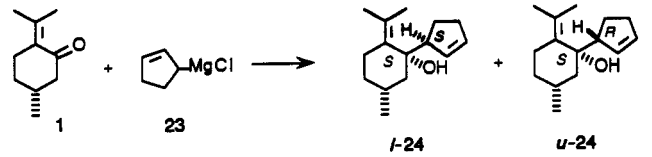
l-**21**

contrast, addition to the ketone **20** leads to two alcohols ***u*-22a** (*l*-approach) and ***l*-22b** (*ul*-approach) (respectively 1:1.5) (configurational assignments must be considered tentative). Hence, the presence of the *trans*-methyl group results in reduced stereoselectivity.



u-**22a** *l*-**22b**

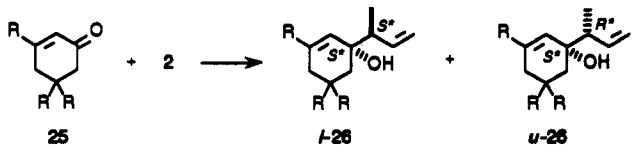
Open chain allylic Grignard reagents exist as equilibrium mixtures of *Z*- and *E*-isomers and either conformation can be present at the transition state.[22] To assess the significance of the conformation of the allylic Grignard reagent, we studied the addition of 2-cyclopentenylmagnesium chloride **23** with pulegone (**1**).[23] The diastereoselectivity of the reaction is very poor. Hence, the configuration of the allylic Grignard reagent strongly affects the selectivity (***l*-24**/***u*-24** = 56:44).[24]



1 23 *l*-24 *u*-24

(19) (a) Blomberg, C.; Salinger, R. M.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2385. (b) Lopp, I. G.; Buhler, J. D.; Ashby, E. C. *J. Am. Chem. Soc.* **1975**, *97*, 4966. (c) Ashby, E. C.; Buhler, J. D.; Lopp, I. G.; Wiesemann, T. L.; Bowers, Jr. J. S.; Laemmle, J. T. *J. Am. Chem. Soc.* **1976**, *98*, 6561. (d) Matsuyama, T.; Yamataka, H.; Hanafusa, T. *Chem. Lett.* **1988**, 1367.
(20) Bartlett, P. D.; McBride, J. M. *Pure Appl. Chem.* **1967**, *15*, 89.
(21) Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, 965.
(22) Hutchison, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. *J. Am. Chem. Soc.* **1973**, *95*, 7075.
(23) Branner-Jorgensen, S.; Berg, A. *Acta Chem. Scand.* **1966**, *20*, 2192.
(24) Decreasing selectivity has been observed with **21** versus **2** during the addition to nitroalkanes, see: Bartoli, G.; Marcantoni, E.; Petrini, M. *J. Chem. Soc., Chem. Commun.* **1991**, 793.

Scheme V

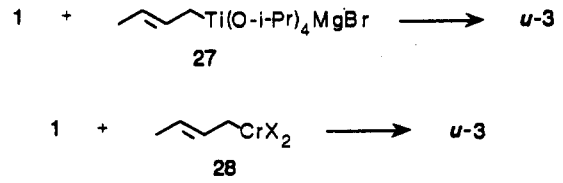


25 **l-26** **u-26**

a: R = H; *l*-**26a** : *u*-**26a** = 60 : 40
b: R = Me; *l*-**26b** : *u*-**26b** = 57 : 43

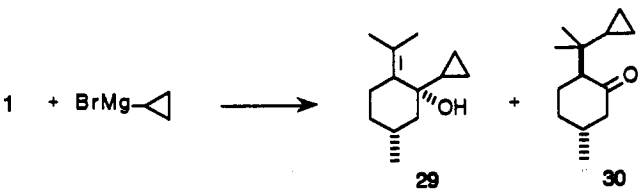
Taken together, our results seem to indicate that the observed diastereoselectivity is related to the conformation of the enones. This hypothesis was confirmed by the results of the addition of crotylmagnesium chloride to 2-cyclohexenone **25a** and isophorone **25b**. In each case, a mixture of alcohols *l*-**26** (major isomer) and *u*-**26** (minor isomer) was obtained (configurational assignments must be considered tentative).

To test the selectivity of different crotyl–metal derivatives, we have added crotyltitanium ate complex[25] **27** and crotylchromium(II) complex[26] **28** to (*R*)-pulegone. In each case, we have determined that the alcohol *u*-**3** is the sole addition product.[27]



27 **28**

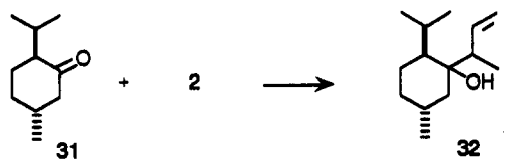
Finally, it is interesting to compare the selectivity of crotylmagnesium chloride with that of cyclopropylmagnesium bromide,[28] a saturated Grignard reagent with a similar geometry. Here we observed not only axial 1,2-addition leading to alcohol **29** (48% yield), but we also



29 **30**

isolated ketone **30** (24% yield) resulting from 1,4-addition.

To test the specific role of the exocyclic carbon–carbon double bond, we studied the addition of crotylmagnesium chloride to (−)-*trans*-menthone (**31**). Two diastereoisomers of structure **32** were obtained in a ratio of 4:1.



31 **32**

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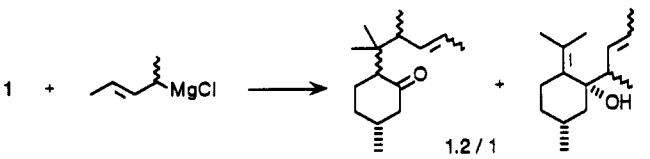
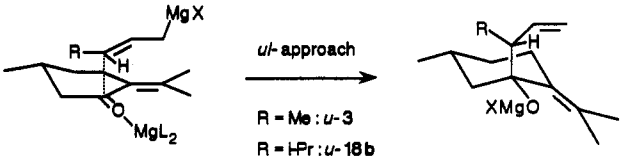
The stereochemical results provide considerable information about the course of the addition of allylic Grignard reagents to α,β-unsaturated ketones. First, in relation to the addition to (*R*)-pulegone (**1**) and analogous ketones, several results are of interest: addition of open chain allylic Grignard reagents occurs with very high selectivity with formation of the kinetic-controlled alcohols resulting from axial addition (*si* face) which corresponds to the least-motion path.[29] As previously reported,[8] one striking exception was the addition of 3-penten-2-ylmagnesium chloride which shows neither regioselectivity nor stereoselectivity. The presence of a methyl group adjacent to



1.2 / 1

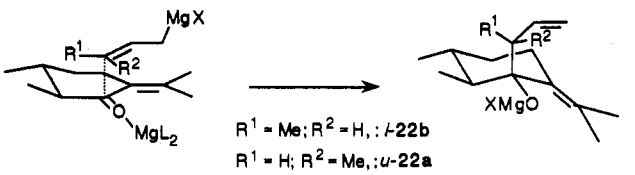
the magnesium results in a major modification of the transition state and the reaction products. In contrast to pulegone, *s-trans*-enones like the cyclohexenones **25** afford mixtures of alcohols **26**.

The stereo- and regioselectivity data can be nicely accommodated by assuming an open transition state with respect to the Grignard reagent and a boat-like conformation of the two reactants with respect to each other corresponding to a compact approach. The addition of allylmagnesium halides to pulegone represents the model reaction because this ketone has a rigid and planar conformation.[30] The observation that the approach is solely *ul* demands that, for a boat-like transition state, the addition takes place with the trans form of the allylic Grignard reagent.



ul-approach
R = Me : *u*-**3**
R = *i*-Pr : *u*-**18b**

As the steric bulk of the substituent at the α′-position of the ketone increases (as in methylpulegone **20**), the diastereoselectivity decreases because the crotylmagnesium halide will react both in the cis and the trans form. The unfavorable 1,2 eclipsing interaction resulting from the presence of an equatorial α′-methyl and R^1 (= methyl) becomes similar in magnitude to the 1,2 eclipsing inter-



R^1 = Me; R^2 = H, : *l*-**22b**
R^1 = H; R^2 = Me, : *u*-**22a**

action between the large bulky oxygen–magnesium complex[31] and R^2 (= methyl).

The postulate of a chair-like conformation for the transition state would require the reverse configuration for the allylic Grignard reagent: the formation of *u*-**3** would

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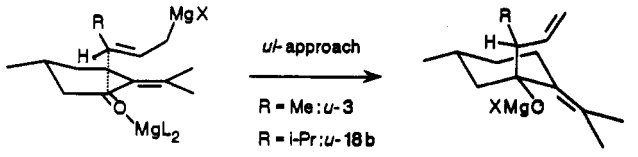
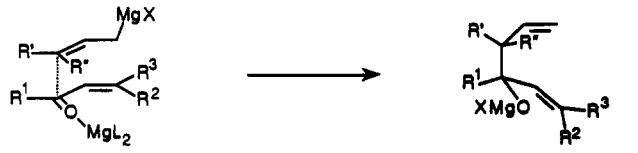
result from the addition of the cis form of the allylmagnesium chloride. The very poor diastereoselectivity observed in the addition of 2-cyclopentenylmagnesium chloride, a cis-allylic Grignard reagent, argues against this proposal. In our previous paper,[8] when considering the hypothesis of a chair-like conformation, the requirement for the allylic Grignard reagent to react in the cis configuration was not clear, particularly for the formation of *u*-18.



The similarity of the results obtained using crotyltitanium ate complex **27** and the crotylchromium(II) complex **28**, i.e. formation of only alcohol *u*-**3**, as with the allylic Grignard, lends support to the argument in favor of the addition of the trans form of the organometallic, for the crotyltitanium ate complex **27** has previously been argued to have the thermodynamically more favorable (*E*)-configuration.[27]

For the open chain enones **5**, only the results obtained from the enones with a high internal rotation barrier can be considered. The same transition state model as the pulegone with a boat-like conformation is operational. When the size of R^1 is greater than that of the oxygen–



magnesium complex, addition will occur with the cis form of the crotylmagnesium halide (R′ = H, R″ = Me). This is shown most dramatically for **5f**, where a complete reversal of the relative topicity is observed (*ul*-approach) and only the *l*-configuration alcohol **6f** is obtained.[32]

Conclusion

The addition of crotyl-Grignard compounds to saturated aldehydes or ketones gives rise to low diastereoselectivity and the reactions are thus of little preparative interest.[6] We attribute this low selectivity to the fact that the double bond of the allylic Grignard is not held in a single configuration. For a number of α,β-ethylenic ketones of definite geometry, we have observed very high diastereoselectivity. The results are in accord with a preferred trans configuration of the crotylmagnesium chloride which is changed into a cis one for addition to α'-hindered ketones. The high stereoselectivity of the process, the availability of the reagents, and the synthetic potential of the homoallylic alcohols which are formed are of major interest.

Experimental Section

General. All reactions were run under argon in oven-dried glassware. TLC was performed on silica gel 60 F_{254}. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 400 and 200 MHz, and 100 and 50 MHz, respectively. Carbon–proton couplings were determined by DEPT sequence experiments.[33] The coupling constants for alcohols **21** and **22** were determined on 1D-COSY spectra with semiselective excitation[34] using shaped pulses generated by the selective excitation unit[35] on a 400-MHz spectrometer. Diastereoselectivity was determined by GC or ^1H NMR analyses prior to any purification. Concentration in molarity is given for CCl_4 solutions of compounds for IR analysis.

Materials. Commercially available unsaturated ketones were distilled before use. Crotyl chloride was purchased from Fluka AG and distilled before use. (+)-Pulegone was obtained by distillation of *Mentha pulegenium* oil. Ketones **5b–d** were prepared according to Danishefsky's procedure.[36] Ketones **5e**[37] and **5f**[38] were prepared as described in the literature. (***E***) and (***Z***)**-2-(3-Methyl-2-butenylidene)cyclohexanone (11b and 11c)** were obtained by addition of 1-[(trimethylsilyl)oxy]cyclohexene on 3-methyl-2-butanone according to the Mukaiyama method[39] (50% yield): to a stirred solution of $TiCl_4$ (22 mL, 0.2 mol) and anhydrous CH_2Cl_2 (200 mL) cooled at −40 °C was added 3-methyl-2-butanone (17.5 g, 0.2 mol) in CH_2Cl_2 (50 mL) and then dropwise 1-[(trimethylsilyl)oxy]cyclohexene (17.1 g, 0.1 mol) in CH_2Cl_2 (50 mL). The stirring was maintained overnight and the reaction mixture was allowed to warm to room temperature. The solution was then poured onto ice, extracted with CH_2Cl_2, washed with 5% solution of K_2CO_3 and then with brine. The organic layer were dried ($MgSO_4$). The ketol obtained placed in a Dean–Stark apparatus was refluxed in CCl_4 with catalytic amount of *p*-TsOH. When the dehydration was completed, the solution was filtered on $HKCO_3$. After usual workup, the crude product was distilled. The fraction 78 °C (1 mmHg) (50% yield) was chromatographed on silica gel (ether–pentane 5:95). **11b,c**: IR (film) 1715, 1130, 1070 cm^{-1}; MS, *m*/*z* 166 (45), 151 (100), 137 (23), 123 (30), 109 (14), 95 (36); HRMS calcd for $C_{11}H_{18}O$ 166.1357, found 166.1354. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.31; H, 10.94. **11c** (first eluted): ^1H NMR δ 3.27 (1, sept, J = 6.8 Hz), 1.63 (3, s), 1.00 (3, d, J = 6.8 Hz), 0.975 (3, d, J = 6.8 Hz); ^{13}C NMR δ 205.5 (s), 148.7 (s), 132.5 (s), 43.4 (t), 30.95 (d), 30.5 (t), 25.3 (t), 25.0 (t), 20.95 (q)(2C), 12.9 (q). **11b**: ^1H NMR δ 2.85 (1, sept, J = 6.8 Hz), 1.79 (3, d, J = 1.2 Hz), 0.99 (6, d, J = 6.8 Hz); ^{13}C NMR δ 206.1 (s), 148.5 (s), 132.0 (s), 43.0 (t), 30.16 (d), 29.2 (t), 25.2 (t), 25.0 (t), 20.13 (q)(2C), 14.5 (q).

(*E*)-2-(2-Methylpropylidene)cyclohexanone (11d) and (*E*)-2-(2-methylpropylidene)-4-methylcyclohexanone (15) were prepared by addition of isobutyraldehyde to a solution of cyclohexanone or 4-methylcyclohexanone, respectively, in ethanol containing potassium hydroxide. **15**: bp 70–71 (1 mm); IR 1715 cm^{-1}; ^1H NMR δ 6.4 (1, d, J = 10 Hz), 1.06 (3, d, J = 6.1 Hz), 1.02 (3, d, J = 6.5 Hz), 0.997 (3, d, J = 6.6 Hz); ^{13}C NMR δ 201.1 (s), 145.7 (d), 133.4 (s), 39.0 (t), 35.0 (t), 31.3 (t), 29.9 (d), 26.8 (q), 22.1 (d), 21.7 (q), 21.6 (q); MS, *m*/*z* 166 (51), 151 (7), 124 (72), 123 (17), 109 (100), 107 (22); HRMS calcd for $C_{11}H_{18}O$ 166.1357, found 166.1362. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.27; H, 10.87.

(5*R*,6*R*)- and (5*R*,6*S*)-2-(1-methylethylidene)-5,6-dimethylcyclohexanone (19 and 20) were obtained by methylation of pulegone.[21] To *N*-cyclohexylisopropylamine (0.22 mol, 31 g) in

(32) The fact that alcohol **6f** has a different stereochemical designation (*l*-) and results from the *ul*-approach as the alcohol **3** is due to the quirks of the priority rule. Thus when R^1 is a methyl or a methylene group, R^1 has a *lower* priority than the double bond, but when R^1 is *tert*-butyl, R^1 has the *higher* priority of the two (see *J. Org. Chem.* **1970**, *35*, 2849). Hence two compounds of *opposite* inherent diastereoisomerism are given the *same* designator.

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(36) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1978**, *43*, 4604.
(37) Schulz, G.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 251.
(38) (a) Pirkle, W. H.; Hoover, D. J. *J. Org. Chem.* **1980**, *45*, 3407. (b) Miller, M. J.; Lyttle, M. H.; Streitwieser, A., Jr. *J. Org. Chem.* **1981**, *46*, 1977.
(39) Mukaiyama, T.; Ishihara, H.; Inomata, K. *Chem. Lett.* **1975**, 527.

anhydrous THF (100 mL) cooled at −40 °C was added 1.5 M BuLi in hexane (0.2 mol, 133 mL) and stirred for 1 h. Pulegone (0.19 mol, 28.8 g) in 20 mL of anhydrous THF was added dropwise. After 2 h, an excess of methyl iodide (0.6 mol, 85 g) was added. After 0.5 h of stirring, the solution was warmed to 0 °C and stirred for 0.5 h. After usual workup, the crude product was distilled. The fraction 62–64 °C (0.7 mmHg) (72% yield) was flash chromatographed on silica gel (ether–pentane 5:95 to 10:90) to afford **19** (15%) and **20** (85%). **19**: IR 1685 cm^{-1}; ^1H NMR δ 2.47 (1, qd, J = 6.9, 4.9 Hz), 1.81 (3, br, s), 1.69 (3, s), 0.93 (3, d, J = 6.9 Hz), 0.82 (3, d, J = 7.0 Hz). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.69; H, 10.86. **20**: IR 1685 cm^{-1}; ^1H NMR δ 2.62 (1, dt, J = 15.0, 4.3 Hz), 1.92 (1, dq, J = 10.0, 6.7 Hz), 1.81 (3 br, s), 1.68 (3, s), 1.03 (3, d, J = 6.7 Hz), 0.97 (3, d, J = 6.5 Hz); ^{13}C NMR δ 206.6 (s), 138.2 (s), 132.2 (s), 52.4 (d), 38.1 (d), 32.3 (t), 28.3 (t), 22.0 (q), 21.0 (q), 20.3 (q), 13.1 (q); MS, m/z 166 (65), 137 (27), 123 (69), 95 (100); HRMS calcd for $C_{11}H_{18}O$ 166.1357, found 166.1346. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.50; H, 10.95.

Representative Procedure for the Addition of Crotyl Chloride to Ketones in the Presence of Magnesium. In a dry, two-necked flask equipped with a magnetic stirrer, a reflux condenser, and a dropping funnel, magnesium (0.18 g-atom, 4.4 g, 3 equiv) was covered by anhydrous ether (40 mL). The reaction was started by the addition of one crystal of iodine and 0.5 mL of 1,2-dibromoethane. Upon cessation of gas evolution, the reaction flask was cooled with ice, and a solution of crotyl chloride (120 mmol, 10.9 g, 2 equiv) and unsaturated ketone (60 mmol, 1 equiv) in 250 mL of anhydrous ether was added over 3 h. The reaction mixture was stirred in an ice bath for 12 h. The reaction mixture was poured onto ice–NH_4Cl. Excess magnesium was filtered with glass wool and washed with ether. The aqueous layer was extracted with ether (3 × 100 mL), the combined organic layers were washed to neutrality and dried ($MgSO_4$). Concentration in vacuo gave the crude product that was subjected to flash chromatography on silica gel (Merck silica gel 60, 230–400 mesh ASTM), eluting with a gradient of pentane–ether containing triethylamine (1%).

(1*S*,5*R*)-1-((1*R*)-1-Methyl-2-propen-1-yl)-2-(1-methylethylidene)-5-methylcyclohexanol (*u*-3). Addition of crotylmagnesium chloride to (*R*)-pulegone (11.5 g, 92%): IR (gas) 3638 (80%), 3594 (20%) cm^{-1}; ^{13}C NMR δ 140.2 (d), 133.2 (s), 125.1 (s) 115.5 (t), 79.6 (s), 50.0 (t), 42.6 (d), 35.4 (t), 29.6 (d), 28.6 (t), 23.7 (q), 22.4 (q), 22.1 (q), 14.3 (q), for other spectral data, see ref 8.

3,4,7-Trimethyl-1,5-octadien-4-ol (*l*-6a and *u*-7a). Addition of crotylmagnesium chloride to 5-methyl-3-hexen-2-one (**5a**) (9 g, 90%): IR (film) 3450, 3080, 1645, 1105, 980, 915 cm^{-1}; MS, m/z 168 (0.05), 150 (0.3), 125 (0.3), 113 (47), 97 (3), 95 (9), 71 (5), 67 (6), 55 (12), 43 (100); HRMS calcd for $C_{11}H_{18}$ ($M^+ - H_2O$) 150.1408, found 150.1413. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.26; H, 11.93. *l*-**6a** (60%): IR (gas) 3630 (60%), 3598 (40%) cm^{-1} ($\Delta\nu$ = 32 cm^{-1}); ^1H NMR δ 5.77 (1, ddd, J = 17.8, 9.7, 8.0 Hz), 5.55 (1, dd, J = 15.7, 6.5 Hz), 5.43 (1, d, J = 15.7 Hz), 5.09–5.02 (2, m), 2.27 (1, br octet, J = 6.7 Hz), 2.2 (1, m), 1.21 (3, s), 0.98 (3, d, J = 6.93), 0.97 (3, d, J = 6.75), 0.96 (3, d, J = 6.74); ^{13}C NMR δ 140.2 (d), 135.4 (d), 132.1 (d), 115.6 (t), 73.5 (s), 48.7 (d), 30.6 (d), 25.8 (q), 22.4 (q)(2C), 14.8 (q). *u*-**7a** (40%): IR (gas) 3636 cm^{-1}; ^1H NMR δ 5.70 (1, ddd, J = 18.1, 9.4, 8.7 Hz), 5.56 (1, dd, J = 15.7, 6.5 Hz), 5.43 (1, d J = 15.7 Hz), 5.09–5.02 (2, m), 2.27 (1, br octet, J = 6.7 Hz), 2.2 (1, m), 1.19 (3, s), 0.97 (3, d, J = 6.7 Hz), 0.96 (3, d, J = 6.7 Hz), 0.957 (3, d, J = 6.9 Hz); ^{13}C NMR δ 140.2 (d), 135.8 (d), 131.9 (d), 115.4 (t), 73.6 (s), 48.2 (d), 30.6 (d), 25.0 (q), 22.6 (q)(2C), 14.2 (q).

2,2,5,6-Tetramethyl-3,7-octadien-5-ol (*l*-6b and *u*-7b). Addition of crotylmagnesium chloride to 5,5-dimethyl-3-hexen-2-one (**5b**) (9.8 g, 90%): IR (film) 3550, 3080, 1640, 915 cm^{-1}; MS, m/z 127 (55), 111 (13), 109 (18), 85 (7), 83 (6), 71 (7), 67 (11), 43 (100); HRMS calcd for $C_8H_{15}O$ ($M^+ - C_4H_7$) 127.1123, found 127.1125. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.23; H, 12.19. *l*-**6b** (60%): IR (gas) 3633 (80%), 3600 (20%) cm^{-1} ($\Delta\nu$ = 33 cm^{-1}); ^1H NMR δ 5.8–5.63 (1, m), 5.58 (1, d, J = 16.0 Hz), 5.36 (1, d, J = 16.0 Hz), 5.06–5.0 (2, m), 2.17 (1, br quint, J = 7.3 Hz), 1.20 (3, s), 1.0 (3, d, J = 6.9 Hz), 0.97 (9, s); ^{13}C NMR δ 140.4 (d), 140.0 (d), 129.6 (d), 116.2 (t), 73.8 (s), 49.2 (d), 32.7 (s), 29.8 (q)(3C), 26.2 (q), 15.2 (q). *u*-**7b** (40%): IR (gas) 3640 cm^{-1}; ^1H NMR δ 5.8–5.63 (1, m), 5.58 (1, d, J = 16.0 Hz), 5.36 (1, d, J = 16.0 Hz), 5.06–5.0 (2, m), 2.21 (1, br quint, J = 7.1 Hz), 1.17 (3, s), 0.99 (3, d, J = 6.9 Hz), 0.974 (9, s); ^{13}C NMR δ 140.4 (d), 139.7 (d), 130.1 (d), 116.0 (t), 73.9 (s), 48.6 (d), 32.7 (s), 29.8 (q)(3C), 25.1 (q), 14.5 (q).

3-Methyl-4-(2-propyl)-1,5-heptadien-4-ol (*u*-6c and *l*-7c). Addition of crotylmagnesium chloride to 2-methyl-4-hexen-3-one (**5c**) (9.1 g, 90%): IR (film) 3550, 3080, 1640, 980, 915, 790 cm^{-1}; MS, m/z 125 (8), 113 (34), 95 (2), 71 (9), 69 (81), 55 (12), 43 (100); HRMS calcd for $C_8H_{13}O$ ($M^+ - C_3H_7$) 125.0966, found 125.0962. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.61; H, 12.01. *u*-**6c** (85%): IR (gas) 3639 (30%), 3598 (70%) cm^{-1} ($\Delta\nu$ = 41 cm^{-1}); ^1H NMR δ 5.72 (1, ddd, J = 17.9, 9.6, 9.1 Hz), 5.53 (1, dq, J = 15.5, 6.4 Hz), 5.33 (1, dq, J = 15.5, 1.6 Hz), 5.06–5.0 (1, m), 2.36 (1, q, J = 7.4 Hz), 1.78 (3, sept, J = 6.8 Hz), 1.70 (3, dd, J = 6.4, 1.6 Hz), 0.91 (3, d, J = 6.97), 0.84 (3, d, J = 6.72), 0.80 (3, d, J = 6.84); ^{13}C NMR δ 140.4 (d), 132.5 (d), 124.7 (d), 115.6 (t), 77.7 (s) 44.6 (d), 33.4 (d), 17.6 (q), 17.1 (q), 16.0 (q), 15.0 (q). *l*-**7c** (15%): IR (gas) 3642 cm^{-1}; ^1H NMR δ 5.75 (1, ddd J = 17.9, 9.9, 7.5 Hz), 5.53 (1, dq, J = 15.5, 6.4 Hz), 5.31 (1, dd, J = 15.5, 1.6 Hz), 5.06–5.0 (1, m), 2.47 (1, quint, J = 7.15 Hz), 1.81 (3, sept, J = 6.8 Hz), 1.69 (3, dm, J = 6.4 Hz), 0.935 (3, d, J = 6.81), 0.84–0.77 (3, m); ^{13}C NMR δ 140.4 (d), 133.2 (d), 124.4 (d), 115.0 (t), 77.75 (s), 43.3 (d), 33.2 (d), 17.3 (q), 17.1 (q), 16.1 (q), 13.1 (q).

3-Methyl-4-(2-methyl-2-propyl)-1,5-heptadien-4-ol (*u*-6d and *l*-7d). Addition of crotylmagnesium chloride to 2,2-dimethyl-4-hexen-3-one (**5d**) (9.9 g, 90%): IR (CCl_4) 3575, 3080, 1640, 915 cm^{-1}; MS, m/z 127 (17), 125 (13), 109 (3), 107 (2), 97 (4), 85 (9), 83 (11), 69 (77), 43 (100); HRMS calcd for $C_8H_{15}O$ ($M^+ - C_4H_7$) 127.1123, found 127.1125. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.86; H, 12.10. *u*-**6d** (85%): IR (gas) 3641 (20%), 3602 (80%) cm^{-1} ($\Delta\nu$ = 39 cm^{-1}); ^1H NMR δ 5.71 (1, ddd, J = 17.1, 10.1, 9.6 Hz), 5.60 (1, $^1/_2$ AB, J = 15.5 Hz), 5.55 (1, $^1/_2$ ABq, J = 15.5, 5.4 Hz), 5.04–4.88 (2, m), 2.49 (1, dq, J = 9.6, 7.0 Hz), 1.70 (3, d, J = 5.4 Hz), 1.01 (3, d, J = 7.0 Hz), 0.923 (9, s); ^{13}C NMR δ 142.4 (d), 132.4 (d), 124.0 (d), 114.9 (t), 78.4 (s), 45.4 (d), 38.3 (s), 26.6 (q)(3C), 18.2 (q), 17.6 (q). *l*-**7d** (15%): IR (gas) 3646 (44%), 3602 (56%) cm^{-1}; ^1H NMR (part) δ 0.96 (*t*-Bu, s); ^{13}C NMR δ 141.5 (d), 130.7 (d), 125.7 (d), 114.2 (t), 78.4 (s), 46.6 (d), 38.3 (s), 26.2 (q)(3C), 17.1 (q), 15.9 (q).

(3*S,4*S**)-3,6,7-Trimethyl-4-(2-propyl)-1,5-octadien-4-ol (*l*-6e).** Addition of crotylmagnesium chloride to 2,5,6-trimethyl-4-hepten-3-one (**5e**) (11.3 g, 90%): IR (gas) 3644 (20%), 3602 (80%) ($\Delta\nu$ = 42 cm^{-1}), 1640, 1381, 1002, 916 cm^{-1}; ^1H NMR δ 5.79 (1, ddd, J = 17.1, 10.4, 8.8 Hz), 5.09–5.01 (2, m), 4.93 (1, br s), 2.37 (1, dq, J = 8.8, 6.9 Hz), 2.20 (1, sept, J = 6.83 Hz), 1.78 (1, sept, J = 6.84 Hz), 1.78 (3, d, J = 1.2 Hz), 0.97 (6, d, J = 6.63 Hz), 0.96 (3, d, J = 6.9 Hz), 0.88 (3, d, J = 6.71 Hz), 0.85 (3, d, J = 6.86 Hz); ^{13}C NMR δ 143.7 (s), 140.8 (d), 123.0 (d), 115.7 (t), 80.1 (s), 46.2 (d), 39.1 (d), 35.6 (d), 21.8 (q)(2C), 17.5 (q), 16.4 (q), 15.2 (q), 14.5 (q); MS, m/z 167 (8), 155 (100), 137 (9), 111 (99), 95 (15), 83 (46), 71 (29), 55 (34), 43 (64); HRMS calcd for $C_{11}H_{19}O$ - ($M^+ - C_3H_7$) 167.1436, found 167.1436. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.96; H, 12.49.

(5*S,6*S**)-2,2,3,6-Tetramethyl-5-(2-methyl-2-propyl)-3,7-octadien-5-ol (*l*-6f).** Addition of crotylmagnesium chloride to 2,2,5,6,6-pentamethyl-4-hepten-3-one (**5f**) (12.1 g, 85%): IR (gas) 3640 (20%), 3597 (80%) ($\Delta\nu$ = 43 cm^{-1}), 3082, 1644, 1373, 1151, 1006, 916 cm^{-1}; ^1H NMR δ 5.82 (1, dt, J = 17.2, 9.8 Hz), 5.26 (1, d, J = 0.9 Hz), 5.08–4.97 (2, m), 2.49 (1, dq, J = 9.4, 6.8 Hz), 1.86 (3, d, J = 0.9 Hz), 1.06 (3, d, J = 6.8 Hz), 1.05 (9, s), 0.98 (9, s); ^{13}C NMR δ 143.9 (s), 142.8 (d), 121.8 (d), 115.0 (t), 81.1 (s), 47.3 (d), 40.2 (s), 37.7 (s), 29.5 (q)(3C), 26.8 (q)(3C), 18.4 (q), 13.3 (q); MS, m/z 183 (25), 181 (10), 165 (3), 126 (11), 125 (100), 123 (11), 109 (22), 57 (58); HRMS calcd for $C_{12}H_{23}O$ ($M^+ - C_4H_7$) 183.1749, found 183.1743. Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.79; H, 12.64.

(1*S)-1-((1*R**)-1-Methyl-2-propen-1-yl)-2-(1-methylethylidene)cyclohexanol (*u*-12a).** Addition of crotylmagnesium chloride to 2-(1-methylethylidene)-1-cyclohexanone (**11a**) (10.5 g, 90%): IR (film) 3550, 3080, 1640, 1155, 815 cm^{-1}; ^1H NMR δ 5.87 (1, ddd, J = 17.8, 9.5, 8.4 Hz), 5.07 (2, m), 2.67 (1, dq, J = 8.4, 7.15 Hz), 2.58 (1, m), 1.99 (3, s), 1.67 (3, s), 0.97 (3, d, J = 6.9 Hz); ^{13}C NMR δ 140.3 (d), 134.2 (s), 125.6 (s), 115.33 (t), 79.6 (s), 42.6 (d), 39.7 (t), 28.4 (t), 25.9 (t), 23.4 (q), 22.4 (q), 22.2 (t),

13.9 (q). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35 H, 11.41. Found: C, 80.55; H, 11.36.

(*E*)-(1*S)-1-((1*R**)-1-Methyl-1-propen-1-yl)-2-(3-methyl-2-butylidene)cyclohexanol (*u*-12b).** Addition of crotylmagnesium chloride to (*E*)-2-(3-methyl-2-butylidene)cyclohexanone (**11b**) (11.3 g, 85%): IR (CCl_4, 4×10^{-2}) 3626 (66%), 3575 (34%) cm^{-1}; IR (CCl_4) 3600, 3080, 1640, 1245, 1135, 1100, 1000, 960, 915 cm^{-1}; ^1H NMR δ 5.85 (1, ddd, J = 17.8, 9.7, 8.1 Hz), 5.1–5.03 (2, m), 2.93 (1, sept, J = 6.88 Hz), 2.78 (1, m), 1.88 (3, d, J = 1.6 Hz), 1.02–0.9 (9, m); ^{13}C NMR δ 140.3 (d), 134.8 (s), 133.8 (s), 115.3 (t), 79.6 (s), 42.9 (d), 39.1 (t), 31.3 (d), 27.1 (t), 26.1 (t), 21.6 (t), 20.76 (q)(2C), 13.8 (q), 13.4 (q); MS, m/z 222 (0.5), 204 (3), 189 (10), 175 (10), 167 (60), 161 (69), 133 (37), 119 (100); HRMS calcd for $C_{15}H_{26}O$ 222.1983, found 222.1966. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.30; H, 11.84.

(*Z*)-(1*S)-1-((1*R**)-1-Methyl-2-propen-1-yl)-2-(3-methyl-2-butylidene)cyclohexanol (*u*-12c).** Addition of crotylmagnesium chloride to (*Z*)-2-(3-methyl-2-butylidene)cyclohexanone (**11c**) (11.2 g, 85%): IR (CCl_4, 3.8×10^{-2}) 3624 (72%), 3572 (28%) cm^{-1}; IR (CCl_4) 3600, 3080, 1640, 1115, 1100, 1015, 970, 925 cm^{-1}; ^1H NMR δ 5.88 (1, ddd, J = 17.7, 9.8, 7.8 Hz), 5.1–5.03 (2, m), 3.93 (1, sept, J = 6.83 Hz), 2.74 (1, quint, J = 7.2 Hz), 1.56 (3, d, J = 0.65 Hz), 1.35–0.9 (9, m); ^{13}C NMR δ 140.4 (d), 135.7 (s), 134.0 (s), 115.2 (t), 79.6 (s), 43.2 (d), 38.7 (t), 29.3 (d), 27.9 (t), 25.0 (t), 21.7 (q), 21.1 (t), 20.5 (q), 13.9 (q), 13.8 (q). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.96; H, 11.75.

(*E*)-(1*S)-1-((1*R**)- and (*E*)-(1*S**)-1-((1*S**)-1-Methyl-2-propen-1-yl)-2-(2-methyl-1-propylidene)cyclohexanol (*u*-12d and *l*-12d).** Addition of crotylmagnesium chloride to (*E*)-2-(2-methylpropylidene)cyclohexanone (**11d**) (10.5 g, 84%); ***u*-12d**: IR (CCl_4, 2×10^{-2}) 3622 (62%), 3588 (38%) cm^{-1}; IR (film) 3500, 3085, 1640 cm^{-1}; ^1H NMR δ 5.89 (1, ddd, J = 16.4, 11.2, 8.6 Hz), 5.25 (1, dd, J = 9.0, 1.2 Hz), 5.09–4.94 (2, m), 2.59 (1, sept, J = 6.8 Hz), 2.55 (1, dd, J = 8.6, 6.5), 0.95 (3, d, J = 6.54 Hz), 0.92 (3, d, J = 6.65 Hz), 0.81 (3, d, J = 6.9 Hz); ^{13}C NMR δ 140.4 (d), 139.6 (s), 128.7 (d), 115.5 (t), 75.8 (s), 40.4 (d), 39.7 (t), 27.4 (t) 26.35 (d), 26.3 (t), 23.8 (q), 23.5 (q), 22.9 (t), 13.9 (q); MS, m/z 208 (0.4), 190 (1), 153 (100), 135 (15), 109 (15), 107 (17), 93 (33), 81 (23); HRMS calcd for $C_{14}H_{24}O$ 208.1827, found 208.1830. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.46; H, 11.64. ***l*-12d**: ca. 12%; ^1H NMR δ 5.76 (1, ddd, J = 17.3, 10.6, 6.6 Hz), 5.14 (1, d, J = 8.19, 1.2 Hz), 5.09–4.94 (2, m), 2.70 (1, sept, J = 6.8 Hz), 1.02 (3, d, J = 6.85), 0.89 (3, d, J = 6.93); ^{13}C NMR δ 140.4 (d), 139.7 (s), 128.3 (d), 114.6 (t), 75.4 (s), 39.0 (d), 37.6 (t), 26.3 (t), 26.38 (d), 26.3 (t), 23.7 (q), 23.5 (q), 22.9 (t), 12.0 (q).

(1*S)-1-((1*R**)-1-Methyl-2-propen-1-yl)-2-cyclopentylidenecyclopentanol (*u*-14).** Addition crotylmagnesium chloride to 2-cyclopentylidenecyclopentanone (**13**) (9.2 g, 75%): IR (CCl_4, 2×10^{-2}) 3628 (76%) 3574 (4%), 3500 (20%) cm^{-1}; IR (film) 3500, 3085, 1640 cm^{-1}; ^1H NMR δ 5.80 (1, ddd, J = 17.6, 9.8, 5.8 Hz), 4.99–4.88 (2, m), 2.80 (1, quint, J = 7.0 Hz), 2.40–2.10 (6, m), 2.05–1.60 (8, m), 1.03 (3, d, J = 7.0 Hz); ^{13}C NMR δ 140.4 (d), 136.6 (s), 136.5 (s), 113.7 (t), 83.4 (s), 43.2 (d), 36.6 (t), 32.9 (t), 32.8 (t), 29.7 (t), 27.3 (t), 25.3 (t), 21.9 (t), 13.0 (q); MS, m/z 188 (29), 173 (29), 159 (69), 151 (35), 145 (100), 131 (90), 117 (35), 91 (50); HRMS calcd for $C_{14}H_{20}$ ($M^+ - H_2O$) 188.1565, found 188.1569. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.78; H, 10.78.

(*E*)-1-(1-Methyl-2-propen-1-yl)-2-(2-methylpropylidene)-4-methylcyclohexanol (16). Addition of crotylmagnesium chloride to (*E*)-2-(2-methylpropylidene)-4-methylcyclohexanone (**15**) led to inseparable mixture of 4 diastereomers (4.2:2:1.2:1) (11.3 g, 85%): IR (film) 3500, 3085, 1640 cm^{-1}; ^1H NMR δ (major/second isomers) 6.0–5.62 (1, m), 5.28 (1, d, J = 9.0 Hz)/5.38 (1, J = 9.4 Hz), 5.18–4.85 (2, m), 2.58 (2, m), 1.08–0.8 (12, m); ^{13}C NMR δ (major/second isomers) 140.3/140.6 (d), 139.1 (s), 128.8/128.4 (d), 115.43/115.36 (t), 75.6/75.2 (s), 40.4/39.0 (d), 39.22/37.2 (t), 35.0/35.1 (t), 34.1 (d), 31.5/31.6 (t), 26.4 (q), 23.8 (q), 23.5 (q), 22.3 (q), 13.9/12.0 (q); MS, m/z 222 (0.2), 204 (3), 189 (6), 169 (7), 167 (100), 161 (17), 107 (18), 105 (23); HRMS calcd for $C_{15}H_{26}O$ 222.1983, found 222.1977. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.11; H, 11.83.

(1*S)-1-((3*R**)-4-Methyl-1-penten-3-yl)-2-(1-methylethylidene)cyclohexanol (*u*-18a).** Addition of 4-methyl-2-pentenylmagnesium chloride (**17**) to 2-(1-methylethylidene)cyclohexanone (**11a**) (10.0 g, 75%): IR (film) 3500, 3080, 1640, 915 cm^{-1}; ^1H NMR δ 5.81 (1, dt, J = 17.0, 10.0 Hz), 5.23–4.69 (2, m), 1.98 (3, s), 1.64 (3, s), 0.90 (3, d, J = 7.0 Hz), 0.82 (3, d, J = 7.0 Hz); ^{13}C NMR δ 135.4 (s), 135.1 (d), 124.8 (s), 117.7 (t), 81.3 (s), 53.2 (d), 42.0 (t), 29.0 (t) 27.2 (d), 26.7 (t), 24.0 (q), 23.6 (q), 23.0 (t), 22.3 (q), 19.0 (q); MS, m/z 222 (0.7), 139 (100), 137 (44), 124 (14), 109 (28); HRMS calcd for $C_{15}H_{26}O$ 222.1983, found 222.1977. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.73; H, 11.82.

(1*S*,5*R*)-1-((3*R*)-4-Methyl-1-penten-3-yl)-2-(1-methylethylidene)-5-methylcyclohexanol (*u*-18b). Addition of 4-methyl-2-pentenylmagnesium chloride (**17**) to (*R*)-pulegone (**1**) (10.6 g, 75%); IR (CCl_4, 1×10^{-2}): 3620 (78%), 3586 (22%) cm^{-1}; IR (film) 3500, 3080, 1640, 915 cm^{-1}; ^1H NMR δ 5.81 (1, dt, J = 17.0, 10.0 Hz), 5.23–4.69 (2, m), 1.98 (3, s), 1.64 (3, s), 0.87 (6, d, J = 7.0 Hz), 0.73 (3, d, J = 6.5 Hz); ^{13}C NMR δ 135.4 (d), 135.3 (s), 124.8 (s), 117.7 (t), 81.3 (s), 53.6 (d), 51.2 (t), 35.5 (t), 29.5 (d), 28.8 (t), 27.3 (d), 24.0 (q), 22.8 (q) 22.2 (q), 22.0 (q), 19.9 (q); MS, m/z 236 (1.2), 221 (0.6), 153 (100), 124 (39), 109 (54); HRMS calcd for $C_{16}H_{28}O$ 236.2140, found 236.2145. Anal. Calcd for $C_{16}H_{28}O$: C, 81.28; H, 11.95. Found: C, 81.39; H, 11.96.

(1*R*,5*R*,6*R*)-1-((1*R*)-1-Methyl-2-propen-1-yl)-2-(1-methylethylidene)-5,6-dimethylcyclohexanol (*l*-21). Addition of crotylmagnesium chloride to methylpulegone (**19**) (10.5 g, 80%); ***l*-21**: IR (gas) 3655 (62%), 3580 (38%), 3081, 2972, 2927, 2874, 1006, 914 cm^{-1}; IR (CCl_4, 1×10^{-2}) 3624 (58%), 3578 (42%) cm^{-1}; ^1H NMR δ 5.88 (1, ddd, J = 17.0, 10.7, 8.3 Hz), 5.1–4.95 (2, m), 2.93 (1, br quint, J = 7.3 Hz), 2.56 (1, ddd, J = 14.8, 4.7, 2.4 Hz), 1.98 (3, d, J = 1.77 Hz), 1.71 (1, qd, J = 6.8, 3.9 Hz), 1.69 (3, d, J = 1.0 Hz), 0.92 (3, d, J = 6.92 Hz), 0.80 (3, d, J = 6.78 Hz), 0.73 (3, d, J = 6.98 Hz); ^{13}C NMR δ 140.2 (d), 129.8 (s), 126.9, 115.6 (t), 83.4 (s), 44.3 (d), 42.1 (d), 31.1 (d), 28.7 (t), 28.2 (t), 24.0 (q), 22.2 (q), 19.7 (q), 14.1 (q), 7.1 (q). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.25; H, 11.74.

(1*R*,5*R*,6*S*)-1-((1*S*)- and (1*R*,5*R*,6*S*)-1-((1*R*)-1-Methyl-2-propen-1-yl)-2-(1-methylethylidene)-5,6-dimethylcyclohexanol (*u*-22a and *l*-22b). Addition of crotylmagnesium chloride to methylpulegone **20** (11.3 g, 85%). Two diastereomers were obtained after flash chromatography on silica gel (pentane–ether 1:99), order of elution ***u*-22a**, ***l*-22b** (respectively 1:1.5). ***u*-22a**: IR (gas) 3570 (70%), 3530 (30%), 3082, 1139, 1098, 1014, 911 cm^{-1}; IR (CCl_4, 1×10^{-2}) 3624 (40%), 3578 (60%) cm^{-1}; ^1H NMR δ 6.09 (1, ddd, J = 17.3, 10.2, 8.60 Hz), 5.05–4.90 (2, m), 2.77 (1, quint, J = 7.6 Hz), 1.99 (3, d, J = 1.4 Hz), 1.67 (3, d, J = 0.7 Hz), 0.95 (3, J = 7.1 Hz), 0.90 (3, d, J = 7.07 Hz), 0.85 (3, d, J = 6.2 Hz); ^{13}C NMR δ 143.1 (d), 135.7 (s), 123.1 (s), 113.7 (t), 82.1 (s), 53.5 (d), 42.1 (d), 36.04 (t), 35.97 (d), 28.7 (t), 23.9 (q), 22.2 (q), 20.8 (q), 17.2 (q), 14.7 (q); MS, m/z 222 (0.13), 167 (100), 123 (31), 109 (24), 107 (21); HRMS calcd for $C_{15}H_{26}O$ 222.1983, found 222.1977. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.88; H, 11.74. ***l*-22b**: IR (gas) 3600 (24%), 3507 (76%), 3082, 1127, 1006, 913 cm^{-1}; IR (CCl_4, 1×10^{-2}) 3626 (30%), 3570 (15%), 3508 (55%) cm^{-1}; ^1H NMR δ 5.92 (1, dt, J = 17.85, 9.0 Hz), 5.05–4.95 (2, m), 2.60 (1, quint, J = 7.4 Hz), 2.37 (q, ddd, J = 14.4, 7.1, 2.7 Hz), 1.94 (3, d, J = 1.6 Hz), 1.73 (1, dq, J = 9.2, 6.8), 1.67 (3, d, J = 1.14 Hz), 1.00 (3, d, J = 7.0 Hz), 0.89 (3, d, J = 6.80 Hz), 0.86 (3, d, J = 6.80 Hz); ^{13}C NMR δ 141.8 (d), 133.4 (s), 127.5 (s), 115.0 (t), 81.45 (s), 46.9 (d), 43.0 (d), 32.0 (d), 31.3 (t), 25.8 (t), 23.2 (q), 23.1 (q), 20.5 (q), 16.3 (q), 14.4 (q); MS, m/z 222 (0.26), 167 (100), 149 (12), 123 (27), 109 (17), 107 (18); HRMS calcd for $C_{15}H_{26}O$ 222.1983, found 222.1988. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.29; H, 11.80.

(1*S*,5*R*)-1-((1*S*)- and (1*S*,5*R*)-1-((1*R*)-2-cyclopentenyl)-2-(1-methylethylidene)-5-methylcyclohexanol (*l*-24 and *u*-24). Addition of 2-cyclopentenylmagnesium chloride (**23**) to (*R*)-pulegone (**1**). According to the general procedure described above, 3-chlorocyclopentene (12.3 g) (prepared from 1,3-cyclopentadiene)[23] and pulegone were added to magnesium. The crude product was purified by flash chromatography on silica gel, eluting with a gradient of pentane–ether. ***l*-24** (first eluted): 5.5 g, 42%; IR (gas) 3627 (28%), 3590 (72%) cm^{-1}; IR (CCl_4, 2.4×10^{-2}) 3620 (20%), 3578 (80%) cm^{-1}; IR (film) 3500, 3040, 990, 740 cm^{-1}; ^1H NMR δ 5.94 (1, m), 5.66 (1, dd, J = 5.73, 2.12 Hz), 3.30 (1, m), 2.01 (3, d, J = 1.2 Hz), 1.67 (3, s), 0.85 (3, d J = 6.0 Hz); ^{13}C NMR δ 135.0 (d), 132.9 (s), 129.4 (d), 124.0 (s), 79.3 (s), 51.3 (d), 50.0 (t), 35.6 (t), 32.3 (t), 30.1 (d), 28.6 (t), 24.1 (t), 23.6 (q), 22.2 (q),

22.1 (q); MS, *m/z* 202 (26), 187 (44), 173 (12), 159 (34), 153 (100), 145 (28), 131 (30), 120 (18), 105 (41), 93 (38); HRMS calcd for $C_{15}H_{22}$ ($M^+ - H_2O$) 202.1721, found 202.1711. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.63; H, 10.96. ***u*-24** (second eluted): 4.6 g, 35%; IR (gas) 3652 (30%), 3630 (30%), 3590 (40%) cm^{-1}; IR (CCl_4, 3×10^{-2}) 3626 (27%), 3580 (13%), 3495 (60%) cm^{-1}; IR (film) 3500, 3040, 1100, 735 cm^{-1}; ^1H NMR δ 5.75 (1, m), 5.45 (1, dd, J = 5.7, 2.2 Hz), 3.29 (1, m), 1.95 (3, s), 1.64 (3, s), 0.87 (3, d, J = 5.85 Hz); ^{13}C NMR δ 135.7 (s), 132.4 (d), 131.8 (d), 127.7 (s), 78.8 (s), 55.6 (d), 41.1 (t), 32.4 (t), 31.1 (t), 26.1 (t), 24.2 (t), 23.4 (d), 22.6 (q), 22.4 (q), 22.2 (q); MS, *m/z* 220 (1), 202 (35), 187 (57), 173 (14), 161 (17), 159 (39), 153 (74), 145 (47), 131 (35), 120 (23), 105 (46), 91 (53), 67 (100); HRMS calcd for $C_{15}H_{24}O$ 220.1870, found 220.1834. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.99.

1-(1-Methyl-2-propen-1-yl)-2-cyclohexenol (26a). Addition of crotylmagnesium chloride to 2-cyclohexenone (**25a**) (7.8 g, 85%) (inseparable mixture of isomers): IR (film) 3440, 3080, 3022, 1640, 922 cm^{-1}; ^1H NMR δ 6.0–5.7 (2, m), 5.6 (1, m), 5.05 (2, m), 2.54 (minor isom) (1, q, J = 7.0 Hz), 2.26 (major isom) (1, quint, J = 6.7 Hz), 1.04 (major isom) (1, d, J = 7.0 Hz), 1.00 (minor isom) (1, d, J = 7.0 Hz); ^{13}C NMR δ (major–minor isom) 140.0 (d), 131.2–130.1 (d), 131.5–130.6 (d), 114.9–115.6 (t), 77.1 (s), 47.2–48.0 (d), 32.1–31.8 (t), 25.0 (t), 18.4–18.2 (t), 13.3–14.5 (q); MS, *m/z* 134 (2), 119 (2), 105 (3), 98 (10), 97 (100); HRMS calcd for $C_{10}H_{14}$ ($M^+ - H_2O$) 134.1095, found 134.1096. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.77; H, 10.55.

1-(1-Methyl-2-propen-1-yl)-3,5,5-trimethyl-2-cyclohexenol (26b). Addition of crotylmagnesium chloride to isophorone (**25b**) (9.9 g, 85%) (inseparable mixture of isomers): IR (film) 3500, 3080, 1640, 910 cm^{-1}; ^1H NMR δ 6.23–5.5 (1, m), 5.30–4.8 (3, m), 1.66 (3, s), 1.36 (2, s), 0.99 (3, s), 0.93 (3, s), 0.9 (3, d, J = 5.3 Hz); ^{13}C NMR δ (major–minor isom) 140.1–140.3 (d), 136.5–136.2 (s), 124.5 (d), 115.3–116.0 (t), 72.9–72.7 (s), 48.7–49.7 (d), 44.3–44.5 (t), 44.0–44.3 (t), 32.2–32.3 (q), 29.7 (s), 26.9–26.8 (q), 24.0 (q), 13.4–14.05 (q); MS, *m/z* 194 (1), 176 (24), 161 (21), 105 (32), 91 (25), 55 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1678. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.44; H, 11.45.

Addition of (2-Butenyl)triisopropoxytitanium (27) to (*R*)-Pulegone (1). To a stirred solution of tetraisopropyl orthotitanate (0.05 mol, 14.2 g) in THF (120 mL) cooled at −78 °C, was added crotylmagnesium chloride previously prepared from 4.5 g of crotyl chloride (0.05 mol) and 3.6 g of magnesium (0.15 mol) in 100 mL of anhydrous THF. After 1 h of stirring, pulegone (0.05 mol, 7.5 g) in THF (20 mL) was added dropwise and the solution was stirred for 0.5 h and then slowly allowed to warm to 0 °C. After usual workup, the crude product was flash chromatographed eluting with a gradient of pentane–ether containing triethylamine (1%). Only pulegone 1 (15%) and alcohol ***u*-3** (85%) were obtained.

Addition of (2-Butenyl)chromium(II) (28) to (*R*)-Pulegone (1). To a stirred suspension of anhydrous chromium trichloride (13.5 mmol, 2.14 g) in THF (10 mL) cooled at 0 °C was added $LiAlH_4$ (6.75 mmol, 262 mg). After stirring 10 min at room temperature, pulegone (3.05 mmol, 0.463 g) and crotyl bromide (6.2 mmol, 0.91 g) in DMF (8 mL) were added dropwise for 20 min. Stirring for 3 h, followed by extraction with ether and workup with NH_4Cl–NaCl afforded the crude product (80%) which contained ***u*-3** and **1** (7:3).

Addition of Cyclopropylmagnesium Bromide to (*R*)-Pulegone. Cyclopropylmagnesium bromide was prepared at room temperature from Mg (3 g, 0.123 mol), bromocyclopropane (7.26 g, 60 mmol), and ether (120 mL). After refluxing for 1 h, the solution was cooled at −15 °C and a solution of (*R*)-pulegone (4.56 g, 30 mmol) in ether (170 mL) was added. After usual workup, a portion of the crude product was flash chromatographed eluting with a gradient of pentane–ether containing triethylamine (1%).

(2*S*,5*R*)-2-(1-Cyclopropyl-1-methylethyl)-5-methylcyclohexanone (30): first eluted (1.4 g, 24%); IR 1730 cm^{-1}; ^1H NMR δ 0.96 (3, d, J = 6.1 Hz), 0.81 (3, s), 0.75 (3, s), 0.22–0.12 (4, m); ^{13}C NMR δ 212.1 (s), 60.1 (d), 52.3 (t), 44.4 (s), 36.2 (d), 34.7 (t), 28.5 (t), 23.1 (q), 22.1 (q), 20.7 (q), 19.5 (d), 0.5 (t), −0.2 (t); MS, *m/z* 194 (4), 179 (100), 153 (47), 151 (22), 112 (46), 83 (54), 69 (35), 55 (74); HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1678. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.52; H, 11.38.

(1*S*,5*R*)-1-Cyclopropyl-2-(1-methylethylidene)-5-methylcyclohexanol (29): (2.8 g, 48%); IR 3490 cm^{-1}; ^1H NMR δ 1.95 (3, d, J = 1.7 Hz), 1.67 (3, s), 0.88 (3, d, J = 6.3 Hz), 0.53 (1, m), 0.42–0.31 (4, m); ^{13}C NMR δ 134.3 (s), 124.4 (s), 74.7 (s), 52.4 (t), 34.6 (t), 29.6 (d), 28.5 (t), 23.0 (q), 22.1 (q), 21.9 (q), 19.1 (d), 1.5 (t), 0.2 (t); MS, *m/z* 194 (2), 179 (7), 176 (45), 161 (63), 148 (51), 119 (60), 106 (70), 91 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1660. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.40; H, 11.41.

Addition of Crotylmagnesium Chloride to *trans*-Menthone (31). (2*S*,5*R*)(1-Methyl-2-propen-1-yl)-2-(1-methylethyl)-5-methylcyclohexanol (32): IR 3590, 3090, 1640, 1015 cm^{-1}; MS *m/z* 210 (0.4), 155 (65), 137 (40), 95 (51), 81 (100), 69 (53); HRMS calcd for $C_{14}H_{26}O$ 210.1983, found 210.1973. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.83; H, 12.48; major isomer: ^1H NMR δ 5.83 (1, dt, J = 18.0, 8.0 Hz), 5.23–4.83 (2, m), 2.57 (1, quint, J = 7.2 Hz), 0.9 (12, m); ^{13}C NMR δ 140.8 (d), 116.6 (t), 76.16 (s), 46.0 (d), 45.3 (d), 41.6 (t), 35.3 (t), 27.6 (d), 25.0 (d), 23.4 (q), 22.6 (q), 20.6 (t), 18.0 (q), 14.7 (q); minor isomer: ^{13}C NMR δ 140.4 (d), 115.2 (t) 76.63 (s), 46.8 (d), 44.9 (d), 40.7 (t), 35.0 (t), 27.9 (d), 24.6 (d), 23.2 (q), 22.6 (q), 20.7 (t), 18.1 (q), 14.0 (q).

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