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Reactions of Substituted (2-Butene-1,4-diyl)magnesium Complexes with Carboxylic Esters and Lactones: Formation of a Versatile Intermediate Capable of Generating Substituted Cyclopentenols, Fused-Ring Cyclopentenols, or β,γ-Unsaturated Ketones

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Abstract: Reaction of the magnesium complexes of substituted 1,3-dienes with either carboxylic esters or lactones at low temperature (−78 to −10 °C) generates the magnesium salt of a cyclopropanol (**4**). This intermediate can either be trapped as an acetate of the cyclopropanol (**9**) or it can be heated to yield substituted cyclopentenols. Moreover, when this intermediate is protonated, it undergoes an intramolecular rearrangement to yield β,γ-unsaturated ketones. Accordingly, this protocol allows the generation of a wide range of complex molecules from a single intermediate in high isolated yields.

Introduction

In this paper, we describe a general approach for the synthesis of cyclopentenols, β,γ-unsaturated ketones, and cyclopropanols from 1,3-conjugated dienes. The Diels−Alder reaction is widely recognized as one of the most powerful methods for the construction of six-membered rings. The analogous process for conversion of conjugated dienes to five-membered rings is also of great interest in synthetic organic chemistry. The most important approach for the construction of five-membered carbocycles via cyclopropane precursors is the vinylcyclopropane−cyclopentene rearrangement.[1] A traditional method utilized to accomplish this transformation involves carbene addition to a diene, followed by thermal rearrangement of the resulting vinylcyclopropane.[2] The usefulness of this approach is severely limited, owing to the high temperatures (250−600 °C) required for the thermolysis of the vinylcyclopropane intermediate. To obviate this problem, Danheiser and associates have developed an efficient method for the synthesis of cyclopentene derivatives from conjugated dienes via alkoxy- or carbanion-accelerated vinylcyclopropane rearrangement at ambient temperature.[3] Corey and Myers reported a novel nonthermal version of the vinylcyclopropane−cyclopentene rearrangement as a key step in the synthesis of (±)-antheridium using diethylaluminum chloride at 0 °C to effect the transformation.[4]

The high propensity of β,γ-unsaturated ketones toward prototropic rearrangement producing conjugated α,β-unsaturated ketones, complicates the synthesis of this class of molecules. Many methods to effect the construction of β,γ-unsaturated ketones are available to the synthetic organic chemist, but many of these approaches afford isomeric mixtures of α,β- and β,γ-unsaturated ketones.[5] The use of transition metals such as rhodium and nickel has been reported, but these methods suffer

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(2) For a review, see: Goldschmidt, Z.; Crammer, B. *Chem Soc. Rev.* **1988**, *17*, 229−267.

(3) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579−4581 and references cited therein.

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from poor regioselectivity.[6] Recently, Brown reported the high-yield formation of β,γ-unsaturated ketones via allylation of (Z)-1-halo-1-alkenyl-1,3,2-dioxaborolane.[7]

One of the recent significant accomplishments in organomagnesium chemistry is the development of a nontraditional approach to halide-free organomagnesium reagents based on the direct metalation of conjugated dienes with activated magnesium.[8] These substituted (2-butene-1,4-diyl)magnesium complexes contain two formal magnesium−carbon bonds and can function as bis-nucleophiles.[9] This chemistry has been extended to exocyclic conjugated dienes utilizing highly reactive magnesium,[10] providing a facile route to spirocarbocycles.[11] We recently reported a straightforward method of synthesizing fused carbocyclic enols by reaction of 1,2-bis(methylene)cycloalkane−magnesium reagents with carboxylic esters.[12] We now wish to report expanded details of this chemistry, including other dienes such as 2,3-dimethyl-1,3-butadiene and unsymmetric dienes, including isoprene, 2-methyl-3-phenyl-1,3-butadiene, and myrcene. Furthermore, the incorporation of a lactone as the electrophile has been accomplished, affording a substituted cyclopentenol containing both a primary and a tertiary hydroxyl group within the same molecule. Upon low-temperature hydrolysis of this intermediate, a β,γ-unsaturated ketone containing a terminal hydroxyl is afforded. It is significant that the same intermediate leading to substituted cyclopentenol molecules can also afford β,γ-unsaturated ketones by simple protonation followed by warming to room temperature. Mechanistic considerations will also be discussed.

Results and Discussion

Preparation of 1,3-Diene−Magnesium Reagents. In the preparation of 1,3-diene−magnesium complexes, Rieke magnesium has been shown to be superior to that of ordinary magnesium in that the latter requires forcing conditions which lead to the dimerization, trimerization, and oligomerization of the 1,3-dienes. Prior to the advent of Rieke magnesium, the development of this class of organomagnesium reagents, especially the more difficult to form diene−magnesium complexes such as (2,3-dimethyl-2-butene-1,4-diyl)magnesium as well as all unsymmetrically substituted 1,3-dienes, was severely restricted. The problems associated with ordinary magnesium are avoided owing to the high reactivity of Rieke magnesium, which allows formation of the magnesium−diene complex under extremely mild conditions.

Highly reactive magnesium was prepared by the Rieke method[13] of metal activation. This method involves the reduction of anhydrous magnesium chloride with 2 equiv of lithium and a catalytic amount of naphthalene (electron carrier). The resulting finely divided black powder was treated with the appropriate diene at room temperature. The diene−magnesium complexes reported here are soluble in THF and formed in between 4 and 8 h, depending on which diene was incorporated.

Reactions of 1,2-Bis(methylene)cycloalkane−Magnesium with Carboxylic Esters. While the magnesium complexes of 1,3-dienes appear to be bis-Grignard reagents, their reaction with various electrophiles demonstrates that they are powerful nucleophiles and exhibit a range of reactions not observed by ordinary Grignard reagents. Yet another curious feature of these reagents is that they react with 100% regioselectivity in the 2-position with soft carbon electrophiles. These electrophiles include imines, alkyl halides, epoxides, ketones, aldehydes, and, as we report here, esters and lactones. In contrast, they react with 100% regioselectivity in the 1-position with harder electrophiles such as silicon, tin, or boron halides.

Initial studies found that treatment of the magnesium complex of 1,2-bis(methylene)cyclohexane[14] with ethyl acetate at low temperature (−78 to −10 °C) and quenching the reaction at −10 °C resulted in the formation of (2-methyl-1-cyclohexenyl)-propan-2-one. Conversely, warming the mixture to reflux followed by workup afforded a fused-ring cyclopentenol in excellent yield. Moreover, addition of acetyl chloride to the solution at −20 °C generated the acetate of a cyclopropanol. Subsequent detailed studies clearly supported the generation of a common intermediate, which, depending on workup, would lead to three separate manifolds of products.

A detailed suggested mechanism for these observations is presented in Scheme 1. The initial attack of **2** on the ester is assumed to occur at the 2-positon of the diene−magnesium complex. This is partially supported by the observed trapped cyclopropanol (**9**).[15] Accordingly, addition of **2** to the ester carbonyl group followed by elimination of ethoxide anion would yield **3**. Intramolecular addition of the primary Grignard to the ketone carbonyl would generate **4**. Intermediate **4** underwent ring expansion upon reflux and, after protonation, afforded 2,3,4,5,6,7-hexahydro-2-methyl-1*H*-inden-2-ol (**6**) in 91% isolated yield (Table 1, entry 1). The overall process from 1,2-bis(methylene)cycloalkanes to the corresponding fused carbocyclic enols represents a formal [4 + 1] annulation which offers one-pot access to polyhydroindene, polyhydropentalene, and polyhydroazulene bicyclic systems.[16]

Alternatively, protonation of **4** at −10 °C, followed by warming the reaction mixture to room temperature, yielded the corresponding spiro enol **7**, which rearranged *in situ* to the more thermodynamically stable β,γ-unsaturated ketone **8** in 72% isolated yield (Table 2, entry 1). The rearrangement of **7** to **8** occurs at or below ambient temperature, with the driving force

(5) (a) Snider, B. B.; Jackson, A. C. *J. Org. Chem.* **1982**, *47*, 5393−5395. (b) Shono, T.; Nishiguchi, I.; Sasaki, M.; Ikeda, H.; Kurita, M. *J. Org. Chem.* **1983**, *48*, 2503−2505. (c) Sevrin, M.; Krief, A. *Tetrahedron Lett.* **1978**, 187−190.

(6) (a) Jun, C. H. *J. Organomet. Chem.* **1990**, *390*, 361−370. (b) Onaka, M.; Goto, T.; Mukaiyama, T. *Chem. Lett.* **1979**, 1483−1486.

(7) Brown, H. C.; Soundararajan, R. *Tetrahedron Lett.* **1994**, *35*, 6963−6966.

(8) For a review, see: Dzhemilev, U. M.; Ibragimov, A. G.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, *406*, 1−47. For typical examples, see: (a) Ramsden, H. E. U.S. patent 3,388,179, 1968; *Chem. Abstr.* **1968**, *69*, 67563d. (b) Fujita, K.; Ohnuma, Y.; Yasuda, H.; Tani, H. *J. Organomet. Chem.* **1976**, *113*, 201−213. (c) Yang, M.; Yamamoto, K.; Otake, N.; Ando, M.; Takase, K. *Tetrahedron Lett.* **1970**, 3843−3846. (d) Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N.; Mashima. K.; Yasuda, H.; Nakamura, A. *Chem. Lett.* **1982**, 1277−1280. (e) Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1976**, *98*, 7420−7421.

(9) (a) Sell, M. S.; Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1993**, *34*, 6007−6010. (b) Sell, M. S.; Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1993**, *34*, 6011−6012. (c) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1989**, *54*, 3247−3252. (d) Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109−3118. (e) Herberich, G. E.; Boveleth, W.; Hessner, B.; Hostalek, M.; Koeffer, D. P. J.; Ohst, H.; Soehnen, D. *Chem. Ber.* **1986**, *119*, 420−433. (f) Richter, W. J. *Chem. Ber.* **1983**, *116*, 3293−3300. (g) Richter, W. J. *J. Organomet. Chem.* **1985**, *289*, 45−49. (h) Sell, M. S.; Klein, W. R.; Rieke, R. D. *J. Org. Chem.* **1995**, *60*, 1077−1080.

(10) (a) Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. *High Energy Processes in Organometallic Chemistry*; Suslick, K. S., Ed; ACS Symposium Series 333; American Chemical Society: Washington, DC, 1987; pp 223−245. (b) Rieke, R. D. *Science* **1989**, *246*, 1260−1264.

(11) Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 5269−5272.

(12) Xiong, H.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 4415−4417.

(13) Rieke, R. D. *CRC Crit. Rev. Surf. Chem.* **1991**, *1*, 131−166 and references cited therein.

(14) Preparation of 1,2-bis(methylene)cyclohexane: Arenz, T.; Vostell, M.; Frauenrath, H. *Synlett* **1991**, 23−24.

(15) Attack at the 1-position cannot be ruled out on the basis of our evidence. However, substantial support for the initial attack being at the 2-position comes from earlier work which clearly demonstrated that all carbon electrophiles initially add in the 2-position. Significantly, ketones and aldehydes were found to add in the 2-position.

Scheme 1

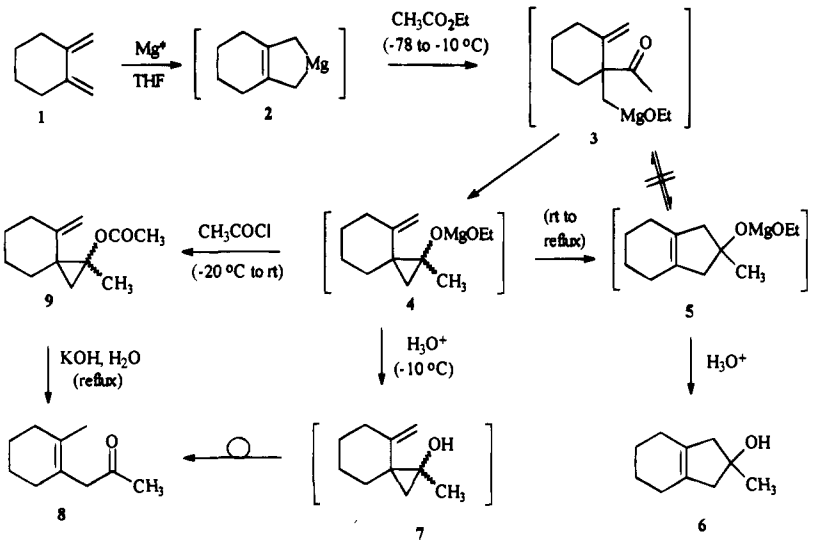
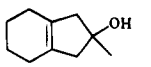
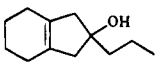
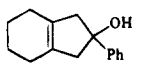
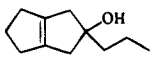
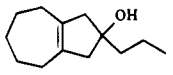
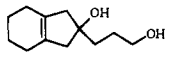
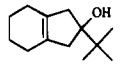
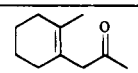
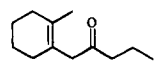
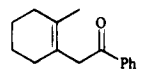
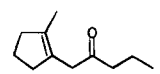
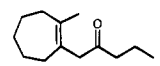
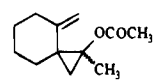
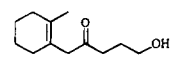


Table 1. High-Temperature Reactions of Cyclic Diene–Magnesium Reagents with Carboxylic Esters or a Lactone. Formation of Fused-Ring Cyclopentenols

Entry	Diene[a]	Ester		Product[b]	% Yield[c]
1	A	CH_3CO_2Et	6		91
2	A	n-$PrCO_2Et$	14		96
3	A	$PhCO_2Et$	10		55
4	B	n-$PrCO_2Et$	11		59
5	C	n-$PrCO_2Et$	12		74
6	A		13		76
7	A	t-$BuCO_2Et$	50		83[d]

[a] Dienes utilized: **A**, 1,2-bis(methylene)cyclohexane; **B**, 1,2-bis(methylene)cyclopentane; C, 1,2-bis(methylene)cycloheptane. [b] All products have been fully characterized by ^1H NMR, ^{13}C NMR, FTIR, or mass spectra or elemental analysis. [c] Fused bicyclic product was obtained at reflux (isolated yield). [d] Product formed after quenching at −20 °C with no refluxing.

Table 2. Low-Temperature Reactions of Cyclic Diene–Magnesium Reagents with Carboxylic Esters or a Lactone. Formation of β,γ-Unsaturated Ketones

Entry	Diene[a]	Ester		Product[b]	% Yield[c]
1	A	CH_3CO_2Et	8		72
2	A	n-$PrCO_2Et$	19		81
3	A	$PhCO_2Et$	15		62
4	B	n-$PrCO_2Et$	16		76
5	C	n-$PrCO_2Et$	17		84
6	A	CH_3CO_2Et	9		75[d]
7	A		18		67

[a] Dienes utilized: **A**, 1,2-bis(methylene)cyclohexane; **B**, 1,2-bis(methylene)cyclopentane; **C**, 1,2-bis(methylene)cycloheptane. [b] All products have been fully characterized by ^1H NMR, ^{13}C NMR, FTIR, or mass spectra or elemental analysis. [c] Quenching the reaction at −10 °C gave the β,γ-unsaturated ketone (isolated yield). [d] The mixture was stirred at −78 °C for 30 min after addition of ethyl acetate to the magnesium–diene complex and then gradually warmed to −10 °C. Addition of acetyl chloride at −20 °C afforded 8 (cis/trans = 90:10).

of the reaction presumably being relief of ring strain by the cyclopropane ring opening and the formation of the carbonyl group. It is significant to note that none of the conjugated ketone product was formed. Addition of acetyl chloride to **4** at −20 °C and subsequent workup afforded 1-methyl-4-methylenespiro[2.5]oct-1-yl acetate (**9**) (Table 2, entry 6) as a mixture of two stereoisomers (cis/trans = 90:10), thus establishing the identity of the initial adduct. Significantly, basic hydrolysis of **9** also gave the enone **8**, providing additional support that the β,γ-unsaturated ketone **8** was formed via a bond reorganization of the intermediary spiro enol **7**. It is paramount that the reaction temperature is kept at or below −10 °C to obtain the enone product. However, the formation of the cyclopentenol was not completed until refluxing temperature was achieved.

Reactions of (2,3-Dimethyl-2-butene-1,4-diyl)magnesium with Lactones. As shown in Scheme 2, treatment of Rieke magnesium with 2,3-dimethyl-1,3-butadiene at room tempera-

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Scheme 2

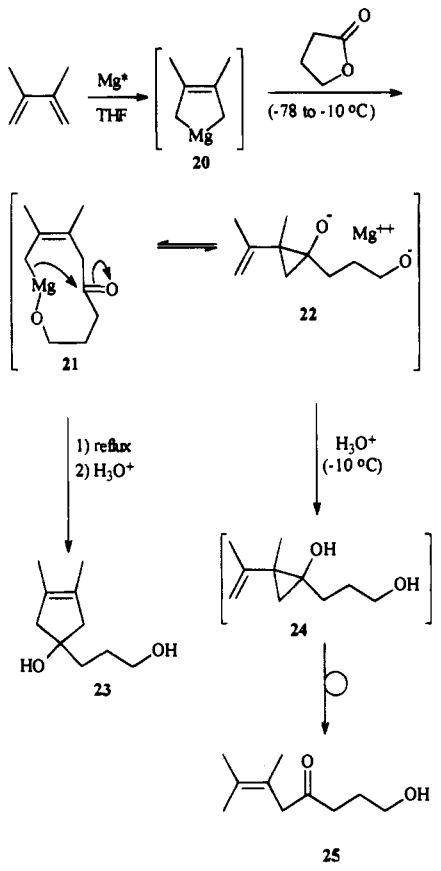
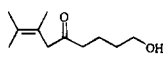
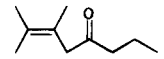
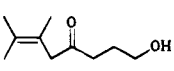
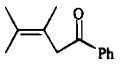


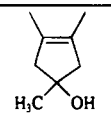
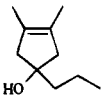
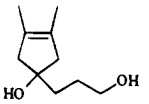
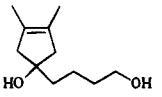
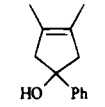
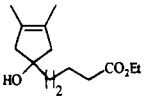
Table 3. Low-Temperature Reactions of Acyclic Diene–Magnesium Reagents with Carboxylic Esters or a Lactones. Formation of β,γ-Unsaturated Ketones

Entry	Diene[a]	Ester		Product[b]	% Yield[c]
1	D		30		62
2	D	n-PrCO$_2$Et	31		66
3	D		25		66
4	D	PhCO$_2$Et	32		55

[a] Dienes utilized: **D**, 2,3-dimethyl-1,3-butadiene. [b] All products have been fully characterized by ^{1}H NMR, ^{13}C NMR, FTIR, or mass spectra or elemental analysis. [c] Quenching the reaction at −10 °C gave the β,γ-unsaturated ketone (isolated yield).

ture afforded the (2,3-dimethyl-2-butene-1,4-diyl)magnesium complex **20**. Magnesium–diene complex **20** was subsequently treated with γ-butyrolactone at low temperature (−78 to −10 °C), affording the cyclopropane intermediate **22**, (**22** may be in equilibrium with **21**), which was transformed into two different products depending upon workup. Intermediate **22** was refluxed, followed by acidic hydrolysis at 0 °C, affording 3,4-dimethyl-1-(3-hydroxypropanol)-3-cyclopentenol (**23**) in 73% isolated yield (Table 4, entry 3) containing both a tertiary and a primary hydroxyl moiety. Alternatively, when intermediate **22** was protonated at −10 °C, followed by warming to room temperature, the corresponding diol (**24**) was presumably afforded, which underwent rearrangement to form 1-hydroxy-6,7-dimethyl-6-octen-4-one (**25**) in 66% yield (Table 3, entry 3), which contains a primary alcohol.

Table 4. High-Temperature Reactions of Acyclic Diene–Magnesium Reagents with Carboxylic Esters or Lactones. Formation of Cyclopentenols

Entry	Diene[a]	Ester		Product[b]	% Yield[c]
1	D	CH$_3$CO$_2$Et	26		81
2	D	n-PrCO$_2$Et	27		65
3	D		23		73
4	D		28		54
5	D	PhCO$_2$Et	29		89
6	D	EtO$_2$C(CH$_2$)$_4$CO$_2$Et	33		36

[a] Dienes utilized: **D**, 2,3-dimethyl-1,3-butadiene. [b] All products have been fully characterized by ^{1}H NMR, ^{13}C NMR, FTIR, or mass spectra or elemental analysis. [c] Cyclopentenol product was obtained at reflux (isolated yield).

Several mechanisms may be postulated for the vinylcyclopropanol–cyclopentenol rearrangement (**22** to **23**, Scheme 2): (a) initial heterolytic cleavage of the cyclopropane ring to a ketone (**21**) followed by intramolecular Grignard addition to the ketone, yielding the cyclopentenol (**23**) as shown in Scheme 2; (b) homolytic cyclopropane cleavage to a stabilized diradical intermediate, followed by internal coupling; (c) a concerted [1,3] sigmatropic rearrangement.[17]

Table 1 contains some representative results for the reactions of cyclic diene–magnesium complexes with carboxylic esters at low temperature followed by refluxing conditions, affording fused-ring products in good to excellent isolated yields. When the diene–magnesium complex of 1,2-bis(methylene)cyclohexane was treated with γ-butyrolactone at −78 °C followed by reflux, 2,3,4,5,6,7-hexahydro-2-(3-hydroxypropyl)-1*H*-inden-2-ol resulted in 76% isolated yield (Table 1, entry 6). This molecule is interesting because it contains both primary and tertiary hydroxyl groups which have been introduced in one synthetic step. Also, Table 1, entry 7, shows the formation of 2,3,4,5,6,7-hexahydro-2-*tert*-butyl-1*H*-inden-2-ol in 83% isolated yield, which resulted by reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with ethyl trimethylacetate at −78 °C and quenched at −20 °C with no refluxing. The initially formed cyclopropanol may have been destabilized by the steric hinderance of the *tert*-butyl group, forming the Grignard ketone analogous to intermediate **21** (shown in Scheme 2), affording the cyclopentenol product. As a result, use of a hindered ester produces only the cyclopentenol product without refluxing.

Similarly, Table 2 shows representative molecules which were prepared by quenching the reaction at −10 °C with subsequent

(17) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340–1341.

warming to room temperature, affording the β,γ-unsaturated ketone products in good yields. It should be noted that the synthesis of β,γ-unsaturated ketones is quite difficult because of their high propensity toward prototropic rearrangement to conjugated isomeric α,β-unsaturated ketones.[18] When the diene−magnesium complex of 1,2-bis(methylene)cyclohexane was treated with γ-butyrolactone at −78 °C followed by protonation at −10 °C with subsequent warming to room temperature, the β,γ-unsaturated ketone containing a primary hydroxyl group was afforded in good isolated yield (Table 2, entry 7). Using this methodology, the formation of β,γ-unsaturated ketones has been realized. Importantly, the method outlined in Scheme 1 has also been applied to the magnesium complexes of 1,2-bis(methylene)cyclopentane (Table 1, entry 4; and Table 2, entry 4) and 1,2-bis(methylene)cycloheptane (Table 1, entry 5; and Table 2, entry 5), making this a very general approach for accessing substituted ring cyclopentenols or β,γ-unsaturated ketones by simply controlling the reaction temperature and workup conditions.

Reactions of (2,3-Dimethyl-2-butene-1,4-diyl)magnesium with Carboxylic Esters or Lactones. Significantly, this chemistry is equally applicable to the magnesium complexes of acyclic dienes, such as 2,3-dimethyl-1,3-butadiene. Table 3, entries 2 and 4, shows the low-temperature products from treatment of the 2,3-dimethyl-1,3-butadiene−magnesium reagent with carboxylic esters, affording β,γ-unsaturated ketones. When (2,3-dimethyl-2-butene-1,4-diyl)magnesium complexes were treated with lactones (Table 3, entries 1 and 3) and protonated at low temperature, β,γ-unsaturated ketones containing a terminal hydroxyl group were isolated. Similarly, Table 4, entries 1, 2, 5, and 6, depicts the high-temperature products formed by treatment of the diene−magnesium complex with carboxylic esters, affording cyclopentenols in good yields. Also, when the diene−magnesium complex derived from 2,3-dimethyl-1,3-butadiene was reacted with lactones at low temperature followed by reflux, the cyclopentene molecules containing both primary and tertiary hydroxyl groups were isolated in fair to good yields (Table 4, entries 3 and 4). It is interesting that, when diethyl adipate was added to the (2,3-dimethyl-2-butene-1,4-diyl)magnesium complex at low temperature followed by reflux, the cyclopentenol containing a terminal ester group was afforded (Table 4, entry 6).

Reactions of Unsymmetric 1,3-Diene−Magnesium Reagents with Carboxylic Esters. It was observed that the overall process of the [4 + 1] annulation generates only one isomeric cyclopentene ring regardless of the symmetry of the starting diene. Accordingly, the application of this annulation approach to unsymmetrical 1,3-diene−magnesium complexes affords an efficient method for the preparation of substituted 3-cyclopentenols.

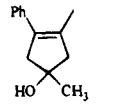
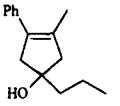
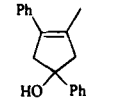
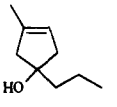
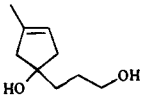
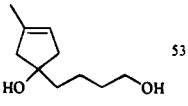
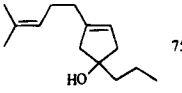
The magnesium−diene complexes of unsymmetric, acyclic dienes were also found to react with the carboxylic esters in analogous fashion, as did the symmetric diene−magnesium complexes, affording unsymmetrically substituted cyclopentenols in good isolated yield. Reactions of the magnesium complexes of 2-methyl-3-phenyl-1,3-butadiene, isoprene, and myrcene, followed by the addition of a carboxylic ester and subsequent reflux, afforded the cyclopentenols shown in Table 5.

We have found that reactions of the magnesium complex of 2-methyl-3-phenyl-1,3-butadiene with carboxylic esters resulted in the generation of substituted 3-cyclopentenols in good isolated yields (Table 5, entries 1−3). Also, reaction of (2-methyl-2-butene-1,4-diyl)magnesium with an ester (Table 5, entry 4) or lactones (Table 5, entries 5−6) resulted in good isolated yields of the substituted 3-cyclopentenols. Finally, reaction of the magnesium complex derived from myrcene with ethyl butyrate afforded 3-(4-methylpent-3-enyl)-1-*n*-propyl-3-cyclopentenol (Table 5, entry 7) in 75% isolated yield.

Scheme 3 represents the proposed pathways for the reaction of (2-methyl-2-butene-1,4-diyl)magnesium with ethyl butyrate. Since the original diene is unsymmetrically substituted, the intermediates derived from treatment of **47** with ethyl butyrate at low temperature are believed to be a mixture of two

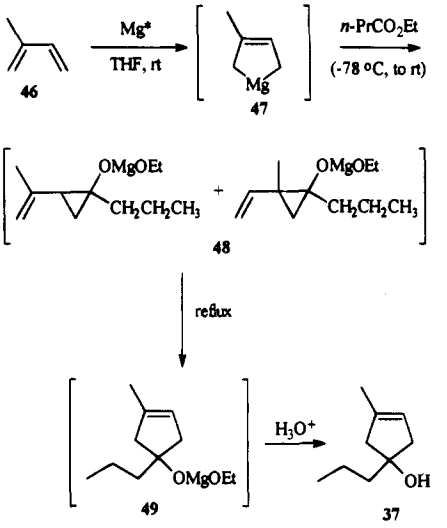
(18) Noyce, D. S.; Evett, M. *J. Org. Chem.* **1972**, *37*, 394−396.

Table 5. High-Temperature Reactions of Unsymmetric, Acyclic Diene−Magnesium Reagents with Carboxylic Esters or Lactones. Formation of Cyclopentenols

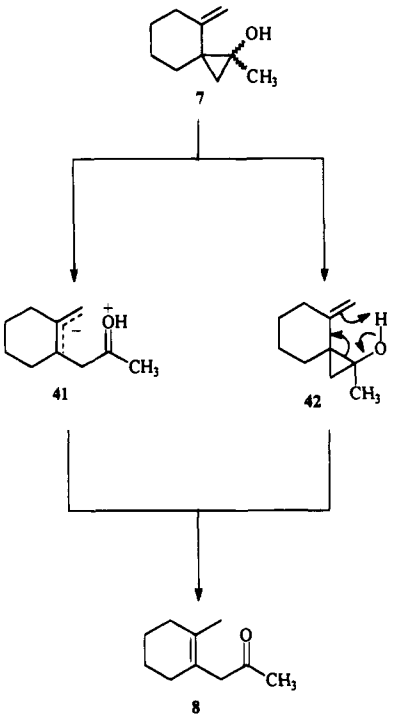
Entry	Diene	Ester[a]		Product[b]	% Yield[c]
1	**E**	CH_3CO_2Et	**34**		68
2	**E**	*n*-$PrCO_2Et$	**35**		70
3	**E**	$PhCO_2Et$	**36**		53
4	**F**	*n*-$PrCO_2Et$	**37**		66
5	**F**		**38**		72
6	**F**		**39**		53
7	**G**	*n*-$PrCO_2Et$	**40**		75

[a] Dienes utilized: **E**, 2-methyl-1,3-phenyl-1,3-butadiene; **F**, isoprene; **G**, myrcene. [b] All products have been fully characterized by ^1H NMR, ^{13}C NMR, FTIR, or mass spectra or elemental analysis. [c] Cyclopentenol product was obtained at reflux (isolated yield).

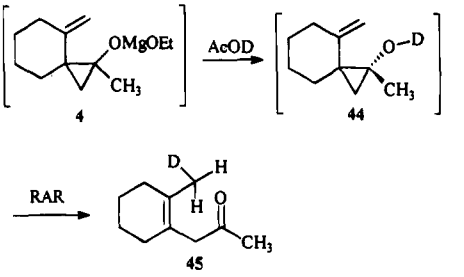
Scheme 3



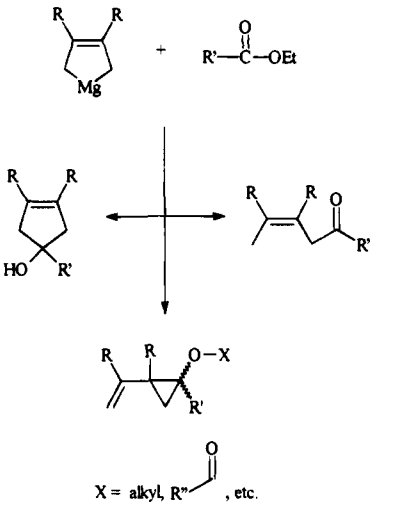
Scheme 4



Scheme 5



Scheme 6



regioisomers (**48**). Upon warming to reflux followed by hydrolysis, 3-methyl-1-*n*-propyl-3-cyclopentenol (**37**) was afforded in 66% isolated yield (Table 5, entry 4). The trapping of the intermediates (**48**) proved to be very difficult, since it seemed that the ring expansion from **48** to **49** began to take place before the initial reaction from **47** to **48** was completed. As a result, trapping the intermediates **48** was not realized.

The method delineated in Scheme 3 for the preparation of substituted 3-cyclopentenols worked well for both aliphatic (Table 5, entries 1−2, 4, and 7) and aromatic carboxylic esters (Table 5, entry 3) and lactones (Table 5, entries 5 and 6).

Unfortunately, attempts to form β,γ-unsaturated ketones by low-temperature reaction of unsymmetric diene−magnesium complexes with carboxylic esters and lactones were fruitless. This is probably due to the fact that the initial attack by the unsymmetrical diene−magnesium complexes was not totally regioselective. It is important to note that the ring enlargement from **4** to **5** in Scheme 1 (and **22** to **23** in Scheme 2) represents a rearrangement of the magnesium salt of a 2-vinylcyclopropanol to a cyclopentenol, which has been observed for lithium salts of 2-vinylcyclopropanol systems.[19]

On the other hand, the rearrangement of **7** to **8** in Scheme 1 (and **24** to **25** in Scheme 2) is formally a 2-vinylcyclopropanol ring opening with a proton transfer. To our knowledge, this is the first report of such a rearrangement, although the facile thermal ring expansion from vinylcyclopropanol into cyclobutanone derivatives has been well documented.[20]

At least two mechanistic pathways may be postulated for the 2-vinylcyclopropanol rearrangment and are shown in Scheme 4: (a) heterolytic cleavage of the cyclopropane ring (**7**) to a protonated ketone (**41**), followed by a proton transfer; (b) a concerted six-membered cyclic transition state (**42**). The latter mechanism can be formally regarded as an intramolecular retro−ene process.[21]

As shown in Scheme 5, when intermediate **4** was deuterated using acetic acid-*d*, greater than 95% deuterium was incorporated into the methyl group, suggesting that the O−D is syn to the vinyl group as shown in intermediate **44,** leading to (2-(methyl-*d*)-1-cyclohexenyl)propan-2-one (**45**) in 73% yield via presumably an intramolecular, concerted six-membered transition state. This is supported by the fact that the rearrangement occurs between −20 °C and ambient temperature. Also, when the cyclopropanol intermediate was trapped with acetyl chloride, the resulting cyclopropane ring was found to be a mixture of cis/trans = 90:10, thus providing further support for a six-membered transition state and not an intermolecular proton transfer process.

Summary

The reaction of 1,3-diene−magnesium complexes with esters and lactones provides a convenient approach to three general classes of molecules: cyclopropanols, cyclopentenols, and β,γ-unsaturated ketones. The reaction is quite general, and the isolated yields are generally excellent. It is also possible to use 1,2-bis(methylene)cycloalkanes as the starting diene, which allows the construction of a number of bicyclic structures. Reaction of the diene−magnesium complexes with lactones results in a number of highly useful molecules in which R′ (see Scheme 6) has a terminal hydroxyl group. Use of a diester as an electrophile results in a terminal carboxylic ester group on R′.

The reactions leading to β,γ-unsaturated ketones were found to be completely regioselective since no double-bond scrambling to the conjugated α,β-unsaturated ketones was observed. This

(19) (a) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340−1341. (b) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443−2446.

(20) (a) Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375−2376. (b) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556−6558. (c) Ollivier, J.; Salaun, J. *Tetrahedron Lett.* **1984**, *25*, 1269−1272. (d) Trost, B. M.; Mao, M. K. *J. Am. Chem. Soc.* **1983**, *105*, 6753−6755.

(21) (a) Alder, K.; Brachel, H. *Liebigs Ann. Chem.* **1962**, *651*, 141. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (c) Keung, E. C.; Alper, H. *J. Chem. Educ.* **1972**, *49*, 97.

property provides a new entry to the regioselective synthesis of β,γ-unsaturated ketones from 1,3-dienes.[22]

In conclusion, it has been demonstrated that fused bicyclic systems containing a substituted five-membered ring and substituted 3-cyclopentenols containing both primary and tertiary hydroxyl groups can be conveniently prepared by the reactions of cyclic, acyclic, and unsymmetric dienes with carboxylic esters or lactones mediated by highly reactive magnesium. The reaction proceeds via a magnesium salt intermediate containing a cyclopropane ring. Quenching the intermediate at low temperature (−10 °C) followed by warming to room temperature creates a novel pathway to the regioselective synthesis of β,γ-unsaturated ketones.

Experimental Section

General Methods. NMR spectra were obtained from a Nicolet NT-360, Varian VXR-200, G. E. Omega-500, or G. E. Omega-300 spectrophotometer. All NMR samples were dissolved in $CDCl_3$. ^1H NMR spectral chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. ^{13}C NMR chemical shifts (δ) were reported in reference to the 77.00 ppm peak for $CDCl_3$. Infrared spectra were recorded on an Analect RFX-65 FTIR spectrophotometer. Mass spectra were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska—Lincoln. Elemental analyses were performed by Desert Analytics (Tucson, AZ).

All manipulations were carried out under an atmosphere of argon on a dual manifold vacuum/argon system. The Linde prepurified-grade argon was further purified by passage over a BASF R3-11 catalyst column at 150 °C, a phosphorus pentoxide column, and a column of granular potassium hydroxide. Lithium, naphthalene, and $MgCl_2$ were weighed out and charged into reaction flasks under argon in a Vacuum Atmospheres Co. drybox. Tetrahydrofuran was distilled immediately before use from a Na/K alloy under an atmosphere of argon.

Gas chromatographic analyses were done on a Hewlett-Packard 5890A chromatograph using stainless steel columns (12 ft × $^1/_8$ in.) packed with GP 10% SP 2100 on 100/120 Supelcoport. Analytical thin-layer chromatography was performed using Merck 5735 indicating plates precoated with silica gel 60 F_{254} (layer thickness 0.2 mm). The product spots were visualized with either iodine or a solution of vanillin. Preparative thin-layer chromatographic separations were obtained using Analtech silical gel GF (layer thickness 2 mm) preparative plates. Liquid chromatographic purifications were performed by flash column chromatography, using glass columns packed with Merck silica gel 60 (230−400 mesh). Low-temperature conditions were obtained by utilizing dry ice/acetone baths.

Preparation of Highly Reactive Magnesium (Mg*). Highly reactive magnesium was prepared by the reduction of anhydrous magnesium chloride with lithium using naphthalene as the electron carrier. In a typical preparation, lithium (9.68 mmol), naphthalene (1.48 mmol), anhydrous magnesium chloride (4.71 mmol) were *vigorously* stirred in freshly distilled THF (15 mL) for 3.5 h at room temperature. After the addition of 10 mL of THF, the newly formed magnesium slurry (black powder) was allowed to settle for 2 h, and the supernatant was drawn off via cannula, leaving 4 mL of solvent covering the Mg*. Freshly distilled THF was added (10 mL), followed by the appropriate 1,3-diene. 1.5 mL quantity of freshly distilled 2,3-dimethyl-1,3-butadiene (excess) was added to the magnesium. All other dienes were added in a Mg*/diene = 1.5−1.8:1. (Note: The number of millimoles of Mg* cited in this paper refers to the theoretical amount possible, based on the original amount of anhydrous magnesium chloride.) All dienes except 2,3-dimethyl-1,3-butadiene (8 h) formed their respective magnesium complexes within 4 h.

(22) (a) Kachinsky, J. L. C.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 1393−1401. (b) Marceau, P.; Gautreau, L.; Beguin, F.; Guillaumet, G. *J. Organomet. Chem.* **1991**, *403*, 21−27. (c) Hoffmann, H. M. R.; Tsushima, T. *J. Am. Chem. Soc.* **1977**, *99*, 6008−6011. (d) Masson, S.; Saquet, M.; Thuillier, A. *Tetrahedron* **1977**, *33*, 2949−2954. (e) Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 649−652. (f) Calas, R.; Dunogues, J.; Pillot, J. P.; Biran, C.; Pisciotti, F.; Arreguy, B. *J. Organomet. Chem.* **1975**, *85*, 149−158.

Typical Preparation of Fused Ring: 2,3,4,5,6,7-Hexahydro-2-methyl-1*H*-inden-2-ol (6). 1,2-Bis(methylene)cyclohexane (3.11 mmol) was added via a disposable syringe to the highly reactive magnesium (4.7 mmol) in 14 mL of THF. After the mixture was stirred at room temperature for 4 h, THF (10 mL) was added, and the reaction mixture was allowed to stand until the solution became transparent (*ca.* 2 h). The yellowish-gold THF solution of the complex was then separated from the excess magnesium by cannulating the solution into a new flask topped with a reflux condenser under argon. The solution was cooled to −78 °C, and ethyl acetate (0.2851 g, 3.24 mmol) was added via a disposable syringe. After being stirred at −78 °C for 30 min, the mixture was gradually warmed to room temperature, at which time an oil bath was used to heat the reaction mixture to reflux. Refluxing was continued for 1 h (oil bath temperature: 85 °C). The reaction mixture was allowed to cool, and an aqueous solution of 3 M HCl (10 mL) was added at 0 °C. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (1 × 20 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvents and flash chromatography afforded 2,3,4,5,6,7-hexahydro-2-methyl-1*H*-inden-2-ol in 91% isolated yield. ^1H NMR δ 2.40 (d, J = 16.0 Hz, 2H), 2.31 (d, J = 16.0 Hz, 2H), 2.01 (s, 1H), 2.00−1.85 (m, 4H), 1.67−1.57 (m, 4H), 1.40 (s, 3H); ^{13}C NMR δ 132.3, 77.8, 52.2, 28.6, 25.6, 22.9; IR (neat) 3349 (br), 2962, 2925, 2854, 2832, 1438, 1369, 1301, 1282, 1236, 1147, 1112, 1051, 941, 906 cm^{-1}; EIMS *m/z* (relative intensity) 152 ($M^{\bullet+}$, 29), 137 (5), 134 (4), 109 (100), 94 (42), 67 (52); HRMS calcd for $C_{10}H_{16}O$ 152.1201, found 152.1203.

2,3,4,5,6,7-Hexahydro-2-*n*-propyl-1*H*-inden-2-ol (14): 96% yield; ^1H NMR δ 2.43 (d, J = 15.9 Hz, 2H), 2.22 (d, J = 15.9 Hz, 2H), 2.02−1.83 (m, 4H), 1.73 (s, 1H), 1.68−1.55 (m, 6H), 1.47−1.36 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 132.1, 80.3, 50.7, 43.9, 25.6, 22.9, 17.8, 14.6; IR (neat) 3365 (br), 2954, 2927, 2871, 2854, 2830, 1455, 1438, 1376, 1355, 1297, 1282, 1263, 1249, 1205, 1145, 1116, 1066, 1024, 998, 914, 862 cm^{-1}; EIMS *m/z* (relative intensity) 180 ($M^{\bullet+}$, 8), 162 (2), 137 (9), 133 (5), 119 (5), 109 (42), 91 (16), 79 (12), 71 (100); HRMS calcd for $C_{12}H_{20}O$ 180.1514, found 180.1512.

2,3,4,5,6,7-Hexahydro-2-phenyl-1*H*-inden-2-ol (10): 55% yield; ^1H NMR δ 7.53−7.46 (m, 2H), 7.36−7.29 (m, 2H), 7.25−7.19 (m, 1H), 2.88 (d, J = 16.0 Hz, 2H), 2.59 (d, J = 16.0 Hz, 2H), 2.19 (s, 1H), 2.10−1.90 (m, 4H), 1.75−1.60 (m, 4H); ^{13}C NMR δ 147.8, 132.0, 128.0, 126.5, 124.7, 81.1, 53.9, 25.5, 22.9; IR (neat) 3382 (br), 3085, 3060, 3025, 2927, 2854, 2832, 1600, 1494, 1446, 1282, 1027, 786, 759, 700 cm^{-1}; EIMS *m/z* (relative intensity) 214 ($M^{\bullet+}$, 8), 196 (2), 105 (100), 94 (5), 77 (17); HRMS calcd for $C_{15}H_{18}O$ 214.1357, found 214.1353.

1,2,3,4,5,6-Hexahydro-2-*n*-propyl-2-pentalenol (11): 59% yield; ^1H NMR δ 2.36 (d, J = 15.2 Hz, 2H), 2.25−2.12 (m, 8H), 1.84 (s, 1H), 1.68−1.62 (m, 2H), 1.48−1.37 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 142.8, 87.6, 44.8, 44.4, 29.6, 27.3, 17.7, 14.6; IR (neat) 3367 (br), 2954, 2929, 2871, 2844, 1465, 1455, 1378, 1251, 1186, 977, 786, 765 cm^{-1}; EIMS *m/z* (relative intensity) 166 ($M^{\bullet+}$, 13), 148 (4), 123 (9), 119 (11), 105 (5), 95 (42), 71 (100); HRMS calcd for $C_{11}H_{18}O$ 166.1357, found 166.1354.

1,2,3,4,5,6,7,8-Octahydro-2-*n*-propyl-2-azulenol (12): 74% yield; ^1H NMR δ 2.54 (d, J = 15.3 Hz, 2H), 2.28 (d, J = 15.3 Hz, 2H), 2.17−1.98 (m, 4H), 1.70 (s, 1H), 1.70−1.50 (m, 8H), 1.46−1.35 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 134.9, 80.0, 53.8, 43.6, 30.5, 30.2, 27.6, 17.8, 14.6; IR (neat) 3365 (br), 2954, 2917, 2871, 2848, 2830, 1465, 1446, 1376, 1290, 1251, 1201, 1118, 995 cm^{-1}; EIMS *m/z* (relative intensity) 194 ($M^{\bullet+}$, 15), 176 (3), 151 (12), 123 (32), 108 (22), 91 (15), 81 (51), 71 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1671, found 194.1673.

2,3,4,5,6,7-Hexahydro-2-(3-hydroxypropyl)-1*H*-inden-2-ol (13): 76% yield; ^1H NMR δ 3.68 (t, J = 5.7 Hz, 2H), 2.49−2.47 (m, 3H), 2.43−2.42 (m, 1H), 2.29 (s, 1H), 2.24 (s, 1H), 1.94−1.92 (m, 4H), 1.78−1.70 (m, 4H), 1.64−1.60 (m, 4H). ^{13}C NMR δ 132.1, 80.1, 63.2, 50.8, 38.4, 28.1, 25.6, 22.9; IR (neat) 3282 (br), 3221 (br), 2924, 2856, 2833, 1439, 1311, 1284, 1236, 1140, 1055, 955, 910, 756 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1463.

2,3,4,5,6,7-Hexahydro-2-*tert*-butyl-1*H*-inden-2-ol (50): 83% yield; product formed without reflux; ^1H NMR δ 2.66 (d, J = 15.5 Hz, 2H), 2.03 (d, J = 16.4 Hz, 2H), 1.94−1.92 (m, 4H), 1.70 (s, 1H), 1.63−

1.61 (m, 4H), 0.94 (s, 9H); ^{13}C NMR δ 131.9, 85.2, 46.6, 36.4, 25.6, 25.5, 22.8; IR (neat) 3475 (br), 2910, 2871, 2856, 2834, 1477, 1467, 1438, 1392, 1365, 1282, 1199, 1188, 997, 902, 854, 815 cm^{-1}; HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1671.

Typical Preparation of β,γ-Unsaturated Ketone: (2-Methyl-1-cyclohexenyl)propan-2-one (8). Freshly prepared **2** (3.11 mmol based on 1,2-bis(methylene)cyclohexane) in 15 mL of THF was cooled to −78 °C, and ethyl acetate (3.19 mmol) was added. The mixture was stirred at −78 °C for 30 min and then gradually warmed to −10 °C over 2 h. Stirring was continued at −10 °C for 1 h. An aqueous solution of HCl (3 M, 10 mL) was added at −10 °C. After being warmed to room temperature, the reaction mixture was extracted with diethyl ether (3 × 20 mL), then washed with water (1 × 20 mL), and then dried over anhydrous $MgSO_4$. Removal of solvents and flash chromatography afforded (2-methyl-1-cyclohexenyl)propan-2-one in 72% isolated yield: ^{1}H NMR δ 3.08 (s, 2H), 2.11 (s, 3H), 2.03−1.90 (m, 4H), 1.64 (s, 3H), 1.62−1.57 (m, 4H); ^{13}C NMR δ 207.8, 130.6, 123.7, 49.0, 31.8, 30.5, 28.9, 23.2, 23.0, 19.5; IR (neat) 2925, 2888, 2857, 2830, 1712, 1448, 1436, 1378, 1353, 1245, 1211, 1159, 1141 cm^{-1}; EIMS *m/z* (relative intensity) 152 ($M^{\bullet+}$, 25), 109 (100), 94 (37), 81 (23), 67 (73); HRMS calcd for $C_{10}H_{16}O$ 152.1201, found 152.1195.

1-(2-Methyl-1-cyclohexenyl)-2-pentanone (19): 81% yield; ^{1}H NMR δ 3.07 (s, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.02−1.88 (m, 4H), 1.63 (s, 3H), 1.63−1.55 (m, 6H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 209.7, 130.3, 123.7, 48.3, 43.5, 31.8, 30.5, 23.2, 23.1, 19.6, 17.2, 13.7; IR (neat) 2960, 2927, 2871, 2857, 2829, 1710, 1448, 1409, 1376, 1355, 1137, 1122, 1033 cm^{-1}; EIMS *m/z* (relative intensity) 180 ($M^{\bullet+}$, 10), 109 (52), 94 (12), 81 (11), 71 (100); HRMS calcd for $C_{12}H_{20}O$ 180.1514, found 180.1511.

1-Methyl-2-((phenylcarbonyl)methyl)-1-cyclohexene (15): 62% yield; ^{1}H NMR δ 8.01−7.94 (m, 2H), 7.58−7.52 (m, 1H), 7.50−7.42 (m, 2H), 3.69 (s, 2H), 2.05−1.90 (m, 4H), 1.65 (s, 3H), 1.62−1.56 (m, 4H); ^{13}C NMR δ 198.7, 137.3, 132.8, 130.1, 128.5, 128.1, 123.9, 43.6, 31.9, 30.4, 23.2, 23.1, 19.6; IR (neat) 3085, 3062, 3025, 2927, 2886, 2857, 2830, 1689, 1596, 1579, 1448, 1328, 1280, 1207, 989, 752, 690 cm^{-1}; EIMS *m/z* (relative intensity) 214 ($M^{\bullet+}$, 7), 105 (100), 94 (4), 77 (19); HRMS calcd for $C_{15}H_{18}O$ 214.1357, found 214.1349.

1-(2-Methyl-1-cyclopentenyl)-2-pentanone (16): 76% yield; ^{1}H NMR δ 3.11 (s, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.40−2.25 (m, 4H), 1.79 (m, 2H), 1.67 (s, 3H), 1.58 (m, 2H), 0.90 (s, 3H); ^{13}C NMR δ 209.2, 135.6, 128.1, 43.8, 43.5, 38.3, 36.5, 21.6, 17.2, 14.0, 13.7; IR (neat) 2960, 2929, 2873, 2840, 1714, 1455, 1409, 1378, 1361, 1297, 1162, 1122, 1029 cm^{-1}, EIMS *m/z* (relative intensity) 166 ($M^{\bullet+}$, 12), 123 (2), 95 (47), 71 (100); HRMS calcd for $C_{11}H_{18}O$ 166.1357, found 166.1359.

1-(2-Methyl-1-cycloheptenyl)-2-pentanone (17): 84% yield; ^{1}H NMR δ 3.12 (s, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.20−2.10 (m, 4H), 1.73 (s, 3H), 1.75−1.67 (m, 2H), 1.58 (m, 2H), 1.49−1.38 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 209.9, 136.7, 129.4, 50.1, 43.6, 35.8, 34.3, 32.3, 26.3, 25.9, 21.7, 17.2, 13.7; IR (neat) 2960, 2921, 2848, 1710, 1454, 1409, 1376, 1361, 1145, 1122, 1046 cm^{-1}; EIMS *m/z* (relative intensity) 194 ($M^{\bullet+}$, 15), 151 (4), 123 (32), 108 (17), 95 (7), 81 (68), 71 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1671, found 194.1674.

1-Methyl-4-methylenespiro[2.5]oct-1-yl acetate (9): 75% isolated yield from **2** and ethyl acetate followed by acetyl chloride (cis/trans = 90:10); pure isomeric form was not obtained **9**: ^{13}C NMR cis-isomer δ 171.0, 148.0, 107.5, 63.0, 35.5, 33.9, 33.1, 27.9, 25.4, 22.0, 21.2, 17.4; ^{13}C NMR trans-isomer δ 170.9, 149.1, 107.6, 63.7, 35.8, 33.5, 32.6, 28.0, 25.5, 22.2, 21.4, 17.0; IR (neat) 3079, 2987, 2933, 2856, 1749, 1652, 1444, 1367, 1247, 1213, 1170, 1159, 1095, 1020, 892 cm^{-1}; EIMS *m/z* (relative intensity) 194 ($M^{\bullet+}$, 0.33), 151 (30), 134 (34), 109 (100), 93 (60), 67 (37); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1313.

1-(2-Methyl-1-cyclohexenyl)-2-pentanon-5-ol (18): 67% yield; ^{1}H NMR δ 3.64 (t, *J* = 5.9 Hz, 2H), 3.11 (s, 2H), 2.56 (t, *J* = 6.9 Hz, 2H), 1.99−1.92 (m, 5H), 1.82 (t, *J* = 6.2 Hz, 2H), 1.63 (s, 3H), 1.60−1.57 (m, 4H); ^{13}C NMR δ 210.2, 130.5, 123.5, 62.0, 48.2, 38.3, 31.7, 30.4, 26.4, 23.1, 22.9, 19.4; IR (neat) 3417 (br), 2923, 2829, 1706, 1674, 1313, 1240, 1097, 1057 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1461.

1-Hydroxy-7,8-dimethyl-7-nonen-5-one (30): 62% yield; the same procedure as described for the synthesis of **7** was followed; ^{1}H NMR δ 3.62 (t, *J* = 6.4 Hz, 2H), 3.14 (s, 2H), 2.45 (t, *J* = 6.9 Hz, 2H), 1.80 (s, 1H), 1.71 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.66−1.52 (m, 4H); ^{13}C NMR δ 209.9, 128.6, 121.2, 62.2, 49.1, 41.2, 32.1, 20.8, 20.6, 19.6, 19.2; IR (neat) 3425 (br), 2925, 2868, 1710, 1670 cm^{-1}; Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.63; H, 10.93.

6,7-Dimethyl-6-octen-4-one (31): 66% yield; ^{1}H NMR δ 3.13 (s, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.71 (s, 3H), 1.68−1.66 (m, 6H), 1.59 (q, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 209.6, 128.3, 121.3, 49.1, 43.6, 20.7, 20.5, 19.2, 17.2, 13.7; IR (neat) 2964, 2933, 2875, 1716, 1456, 1375 cm^{-1}; HRMS calcd for $C_{10}H_{18}O$ 154.1357, found 154.1355.

1-Hydroxy-6,7-dimethyl-6-octen-4-one (25): 66% yield; ^{1}H NMR δ 3.63 (t, *J* = 6.2 Hz, 2H), 3.17 (s, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.11 (s, 1H), 1.83−1.78 (m, 2H), 1.71 (s, 3H), 1.68 (s, 6H); ^{13}C NMR δ 210.3, 128.6, 121.1, 62.1, 49.1, 38.4, 26.5, 20.8, 20.7, 20.5; IR (neat) 3444 (br), 2960, 2945, 2873, 1776, 1711, 1614 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1308.

3,4-Dimethyl-1-phenyl-3-penten-1-one (32): 55% yield; ^{1}H NMR δ 7.99−7.96 (m, 2H), 7.56−7.44 (m, 3H), 3.75 (s, 2H), 1.75 (s, 3H), 1.70 (s, 6H); ^{13}C NMR δ 198.8, 137.3, 132.8, 129.5, 128.5, 128.1, 121.4, 44.5, 20.8, 20.6, 19.2; IR (neat) 2952, 2910, 2857, 1683, 1597, 1579, 1448, 752, 690 cm^{-1}; HRMS calcd for $C_{13}H_{16}O$ 188.1202, found 188.1197.

1,3,4-Trimethyl-3-cyclopentenol (26): 81% yield; the same procedure as described for the synthesis of **5** was followed; ^{1}H NMR δ 2.48 (d, *J* = 16.0 Hz, 2H), 2.37 (d, *J* = 16.0 Hz, 2H), 1.67 (s, 1H), 1.61 (s, 6H), 1.38 (s, 3H); ^{13}C NMR δ 129.0, 77.4, 54.1, 28.3, 13.7; IR (neat) 3348 (br), 2954, 2904, 2852, 2831, 1441, 1371, 1301, 1219, 1122, 1093, 933 cm^{-1}; Anal. Calcd for $C_8H_{14}O$: C, 76.13; H, 11.19. Found: C, 75.94; H, 10.98.

3,4-Dimethyl-1-*n*-propyl-3-cyclopentenol (27): 65% yield; ^{1}H NMR δ 2.49 (d, *J* = 16.0 Hz, 2H), 2.27 (d, *J* = 16.0 Hz, 2H), 1.62 (s, 6H), 1.60−1.56 (m, 2H), 1.44−1.37 (m, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 128.7, 79.5, 52.5, 43.7, 17.8, 14.6, 13.7; IR (neat) 3371 (br), 2960, 2929, 2871, 1712, 1466, 1456, 1422, 1379 cm^{-1}; HRMS calcd for $C_{10}H_{18}O$ 154.1357, found 154.1353.

3,4-Dimethyl-1-(3-hydroxypropyl)-3-cyclopentenol (23): 73% yield; ^{1}H NMR δ 3.65 (t, *J* = 5.5 Hz, 2H), 3.18 (s, 2H), 2.49 (d, *J* = 16.0 Hz, 2H), 2.32 (d, *J* = 16.0 Hz, 2H), 1.72−1.67 (m, 4H), 1.61 (s, 6H); ^{13}C NMR δ 128.6, 79.1, 63.0, 52.5, 38.4, 27.9, 13.7; IR (neat) 3330 (br), 2902, 2854, 1442, 1381, 1315, 1242, 1221, 1057 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1306. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.83; H, 10.75.

3,4-Dimethyl-1-(4-hydroxybutyl)-3-cyclopentenol (28): 54% yield; ^{1}H NMR δ 3.67 (t, *J* = 6.2 Hz, 2H), 2.50 (d, *J* = 16.0 Hz, 2H), 2.28 (d, *J* = 16.0 Hz, 2H), 1.88 (s, 2H), 1.70−1.63 (m, 4H), 1.62 (s, 6H), 1.58−1.55 (m, 2H); ^{13}C NMR δ 128.7, 79.5, 62.7, 52.5, 40.8, 33.0, 20.8, 13.7; IR (neat) 3354 (br), 2925, 2870, 1714, 1442, 1378, 1236, 1072 cm^{-1}; HRMS calcd for $C_{11}H_{20}O_2$ 184.1464, found 184.1458.

3,4-Dimethyl-1-phenyl-3-cyclopentenol (29): 89% yield; ^{1}H NMR δ 7.49−7.22 (m, 5H), 2.95 (d, *J* = 16.0 Hz, 2H), 2.64 (d, *J* = 16.0 Hz, 2H), 2.13 (s, 1H), 1.69 (s, 6H); ^{13}C NMR δ 128.7, 128.1, 126.6, 124.8, 80.5, 55.5, 29.4, 13.7; IR (neat) 3405 (br), 3027, 2964, 2927, 2871, 1681, 1600, 1495, 1448, 760, 700 cm^{-1}; HRMS calcd for $C_{13}H_{16}O$ 188.1202, found 188.1197.

3,4-Dimethyl-1-(4-(ethoxycarbonyl)butyl)-3-cyclopentenol (33): 36% yield; ^{1}H NMR δ 4.16 (q, 2H), 2.48 (d, *J* = 16.0 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.27 (d, *J* = 16.0 Hz, 2H), 1.80 (s, 1H), 1.71−1.61 (m, 9H), 1.48−1.37 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 173.7, 128.7, 79.2, 60.1, 52.5, 40.9, 34.3, 25.4, 24.1, 14.2, 13.7; IR (neat) 3446 (br), 2856, 2921, 2869, 1738, 1463, 1446, 1377, 1182 cm^{-1}; HRMS calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1724. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.95; H, 10.07. Found: C, 69.92; H, 9.76.

Typical Preparation of Substituted 3-Cyclopentenol: 1,3-Dimethyl-4-phenyl-3−cyclopentenol (34). 2-Methyl-3-phenyl-1,3-butadiene (0.268 g, 1.86 mmol) was added via a disposable syringe to newly generated highly reactive magnesium (Mg*) (3.33 mmol) in 14 mL of THF. The reaction mixture was stirred for 4 h at room temperature. Note: isoprene− and myrcene−magnesium complexes were prepared in an analogous fashion. The resulting brownish orange THF solution of the magnesium complex of the diene was cannulated to another flask

after the mixture had settled for 3 **h**. The solution was cooled to −78 °C, and ethyl acetate (2.15 mmol) was added via a disposable syringe. After being stirred at −78 °C for 15 min, the mixture was gradually warmed to room temperature, at which time an oil bath was used to heat the reaction mixture to reflux. Refluxing was continued for 1 h (oil bath temperature: 85 °C). The reaction flask was allowed to cool, and an aqueous solution of 3 M HCl (10 mL) was added at 0 °C. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (1 × 20 mL) and dried over anhydrous $MgSO_4$. Removal of solvents followed by flash chromatography afforded 1,3-dimethyl-4-phenyl-3-cyclopentenol in 68% isolated yield: ^{1}H NMR δ 7.35−7.24 (m, 4H), 7.24−7.17 (m, 1H), 2.90 (dq, J = 16.0, 1.8 Hz, 1H), 2.80 (dq, J = 16.0, 1.6 Hz, 1H), 2.66 (dd, J = 17.0, 1.3 Hz, 1H), 2.59 (dd, J = 17.0, 1.1 Hz, 1H), 2.08 (s, 1H), 1.85 (s, 3H), 1.46 (s, 3H); ^{13}C NMR δ 137.8, 132.9, 132.8, 128.0, 127.6, 126.3, 76.9, 55.3, 52.7, 28.1, 15.5; IR (neat) 3359 (br), 3079, 3054, 3029, 2967, 2910, 2854, 2834, 1652, 1598, 1494, 1455, 1442, 1376, 1301, 1236, 1209, 1130, 1083, 939, 761, 698 cm^{-1}; EIMS *m/z* (relative intensity) 188 ($M^{\bullet+}$, 39), 173 (8), 155 (5), 145 (100), 129 (16), 117 (16), 103 (9), 91 (32), 77 (14); HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1199.

3-Methyl-4-phenyl-1-*n*-propyl-3-cyclopentenol (35): 70% yield; ^{1}H NMR δ 7.35−7.24 (m, 4H), 7.24−7.17 (m, 1H), 2.93 (dq, J = 16.1, 1.8 Hz, 1H), 2.70 (dq, J = 16.1, 1.6 Hz, 1H), 2.67 (dd, J = 17.2, 1.4 Hz, 1H), 2.50 (d, J = 17.2 Hz, 1H), 1.92 (s, 1H), 1.86 (s, 3H), 1.70−1.64 (m, 2H), 1.52−1.40 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 137.9, 132.7, 132.6, 128.0, 127.6, 126.3, 79.2, 53.8, 51.2, 43.6, 17.9, 15.5, 14.6; IR (neat) 3380 (br), 3077, 3052, 3019, 2956, 2927, 2910, 2869, 1652, 1598, 1494, 1455, 1442, 1394, 1378, 1253, 1205, 761, 698 cm^{-1}; EIMS *m/z* (relative intensity) 216 ($M^{\bullet+}$, 18), 173 (11), 145 (42), 129 (10), 115 (7), 103 (7), 91 (15), 71 (100); HRMS calcd for $C_{15}H_{20}O$ 216.1514, found 216.1516.

1,3-Diphenyl-4-methyl-3-cyclopentenol (36): 53% yield; ^{1}H NMR δ 7.55−7.51 (m, 2H), 7.37−7.30 (m, 6H), 7.27−7.18 (m, 2H), 3.40 (dq, J = 16.1, 1.8 Hz, 1H), 3.12 (dd, J = 17.2, 1.4 Hz, 1H), 3.05 (dd, J = 16.1, 1.3 Hz, 1H), 2.85 (dd, J = 17.2, 0.8 Hz, 1H), 2.28 (s, 1H), 1.92 (s, 3H); ^{13}C NMR δ 146.9, 137.5, 132.4, 132.3, 128.2, 128.1, 127.6, 126.8, 126.5, 124.9, 80.1, 56.4, 53.9, 15.4; IR (neat) 3382 (br), 3079, 3054, 3023, 2969, 2908, 2852, 1652, 1598, 1494, 1446, 1376, 1205, 1056, 759, 700 cm^{-1}; EIMS *m/z* (relative intensity) 250 ($M^{\bullet+}$, 15), 232 (3), 145 (9), 129 (4), 115 (4), 105 (100), 88 (10), 77 (16); HRMS calcd for $C_{18}H_{18}O$ and $C_{17}13CH_{18}O$ 250.1358 and 251.1391, found 250.1346 and 251.1390.

3-Methyl-1-*n*-propyl-3-cyclopentenol (37): 66% yield; ^{1}H NMR δ 5.26 (m, 1H), 2.44−2.19 (m, 4H), 1.80 (s, 1H), 1.72 (s, 3H), 1.64−1.58 (m, 2H), 1.48−1.35 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 138.2, 121.9, 82.0, 51.0, 47.3, 43.6, 17.8, 16.8, 14.6; IR (neat) 3402 (br), 2958, 2931, 2871, 1670, 1377, 1254 cm^{-1}; HRMS calcd for $C_9H_{16}O$ 140.1202, found 140.1196; Anal. Calcd for $C_9H_{16}O$: C, 77.08; H, 11.51. Found: C, 76.76; H, 11.79.

3-Methyl-1-3-(hydroxypropyl)-3-cyclopentenol (38): 72% yield; ^{1}H NMR δ 5.28 (m, 1H), 3.68 (t, J = 5.5 Hz, 2H), 2.61−2.56 (m, 2H), 2.52−2.24 (m, 4H), 1.79−1.66 (m, 9H); ^{13}C NMR δ 138.2, 121.9, 81.8, 63.1, 51.2, 47.4, 38.2, 28.0, 16.8; IR (neat) 3315 (br), 3039, 2904, 2871, 2852, 1649, 1444, 1377, 1059, 1018, 901 cm^{-1}; HRMS calcd for $C_9H_{16}O_2$ 156.1150, found 156.1148.

3-Methyl-1-(4-hydroxybutyl)-3-cyclopentenol (39): 53% yield; ^{1}H NMR δ 5.26 (m, 1H), 3.65 (t, J = 6.2 Hz, 2H), 2.70−2.26 (m, 4H), 1.83 (s, 1H), 1.74−1.69 (m, 3H), 1.66−1.50 (m, 5H); ^{13}C NMR δ 138.2, 121.9, 81.9, 62.4, 51.0, 47.2, 40.8, 32.9, 20.7, 16.8; IR (neat) 3373 (br), 3030, 2939, 2871, 1645, 1450, 1377, 1070, 1041, 937 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1300.

3-(4-Methylpent-3-enyl)-1-*n*-propyl-3-cyclopentenol (40): 75% yield; ^{1}H NMR δ 5.30 (m, 1H), 5.13−5.09 (m, 1H), 2.45−2.26 (m, 5H), 2.11−2.09 (m, 4H), 1.69−1.64 (m, 4H), 1.61−1.59 (m, 4H), 1.46−1.39 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 142.6, 131.5, 124.2, 121.0, 81.7, 49.4, 46.9, 43.5, 31.4, 26.2, 25.6, 17.9, 17.6, 14.6; IR (neat) 3386 (br), 3043, 2983, 2943, 2879, 2841, 2729, 1672, 1651, 1466, 1456,1379, 1254, 1205, 1109, 1009, 910, 893, 820 cm^{-1}; HRMS calcd for $C_{14}H_{24}O$ 208.1827, found 208.1822.

Preparation of β,γ-Unsaturated Ketone: (2-(methyl-*d*)-1-cyclohexenyl)propan-2-one (45): 73% yield. The same procedure as described for the synthesis of **8** was followed, except acetic acid-*d* was used as the hydrogen source (0.8 equiv relative to the diene), and greater than 95% deuterium was incorporated into the methyl group, as determined by ^{1}H NMR and HRMS. **45**: ^{1}H NMR δ 3.08 (s, 2H), 2.10 (s, 3H), 1.99−1.93 (m, 4H), 1.62 (s, 2H), 1.61−1.58 (m, 4H); ^{13}C NMR δ 207.6, 130.5, 123.7, 49.0, 31.8, 30.5, 28.8, 23.2, 23.0, 19.3; IR (neat) 2927, 2859, 2830, 1707, 1448, 1436, 1353, 1242, 1203, 1159, 1136 cm^{-1}; HRMS calcd for $C_{10}H_{15}DO$ 153.1201, found 153.1262.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **6, 8, 10−19, 23, 25−40,** and **50** (61 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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