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Reactions of Molecules with Two Equivalent Functional Groups. 5. Anomalous Reactivity of 1,10-Cyclooctadecanedione. Crystal and Molecular Structures of *cis,cis*-1,10-Diphenyl-1,10-cyclooctadiene and the Stereoisomers of 1,10-Diphenyl-1,10-cyclooctadecanediol[1]

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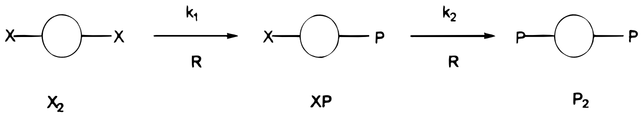
The reaction of the title diketone (**3**) with phenyl Grignard produces (with rate constant k_1) the conjugate base **(6-M)** of 10-hydroxy-10-phenylcyclooctadecanone (**6**), which is subsequently converted (with rate constant k_2) to the conjugate base of the title diol, as a mixture of the *cis* (**7**, 55%) and *trans* (**8**, 45%) isomers. The ratio k_2/k_1, 2.2 ± 0.4, indicates that the carbonyl group in **6-M** is 4.4 times as reactive as each carbonyl in **3**. Competition experiments further demonstrate that the relative rates (per carbonyl) for addition of phenylmagnesium bromide to **3**, 10-methylenecyclooctadecanone **(11)**, and cyclopentadecanone **(12)** are 1.0:0.60:1.92. Possible reasons for this order of reactivity are discussed. Diols **7** and **8** undergo facile double dehydration to form the title diene **13**, which is predicted by molecular mechanics calculations to be the most stable of the four possible symmetrical diene isomers. The structures of **7**, **8**, and **13** were secured by single-crystal X-ray studies.

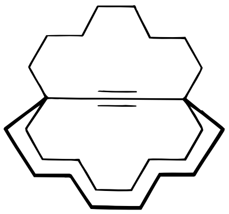
In 1980 we described a mathematical model[2a] for testing the degree of independent reactivity of two separate but equivalent functional groups in the same bifunctional molecule $\mathbf{X_2}$. The sequence below depicts the reaction of $\mathbf{X_2}$ with reagent **R** which converts functional group X to derivative functionality P. The reaction occurs in two discrete steps, first producing "monoadduct" **XP** which is subsequently converted to "diadduct" $\mathbf{P_2}$. If the functional groups (X and X or P and X) act *independently*, and the reactions are irreversible, the ratio of rate constants k_2/k_1 ($\equiv\kappa$) should equal 0.50.[2a]



In the past we reported detailed kinetic studies which test this "independent functional groups" (IFG) model. For example, while the hydroxyl groups of para and meta bis(hydroxymethyl)benzene **(1)** underwent acetylation independently ($\kappa = 0.55$ and 0.52, respectively), the ortho isomer deviated from IFG behavior to a modest extent ($\kappa = 0.61$).[2b] Interestingly, acetylation of the much more flexible 1,6-hexanediol conformed closely to IFG behavior ($\kappa = 0.48$).[3] By contrast, nucleophilic substitution reactions of a homologous series of α,ω-dibromoalkanes exhibited increasing deviation from IFG behavior as the alkane chain length decreased from five carbons ($\kappa = 0.61$) to four ($\kappa = 0.77$) to three ($\kappa = 1.15$).[2c] These effects can be even more pronounced in heterogeneous reactions. In the oxidation of the isomers of **1** with solid γ-MnO$_2$, the κ values ranged from 0.08 and 0.12 for the ortho and meta isomers ($k_1 \gg k_2$) to 1.5 for the para isomer.[1]

Clearly, κ values substantially less than 0.5 indicate the ability of a given reaction to produce useful amounts of monoadduct. But even more importantly, the actual k_1 and k_2 values, when compared to rate constants of appropriate monofunctional model compounds, also provide quantitative measures of the interactions between the functional groups.

During separate studies directed toward the synthesis of novel tricyclic alkyne **2**,[4a] it was observed that attempts to add nucleophiles to just one of the carbonyl groups of 1,10-cyclooctadecanedione (**3**) gave predominately the diadduct (and unreacted **3**),even when the mole ratio of reagent to **3** was less than 1:1.[4b,c] For example, attempts to prepare the mono ethylene ketal of **3** led instead to the diketal and unreacted **3**.[4a,b] Similarly, reaction with 1 equiv of typical Wittig reagents (*vide infra*) gave predominantly the dialkene, minor amounts of ketoalkene, and unreacted **3**.[4a,b] Most important *vis á vis* the synthesis of **2**, addition of a limiting amount of lithium (or dilithium) acetylide to **3** gave diadduct **5** (and unre-



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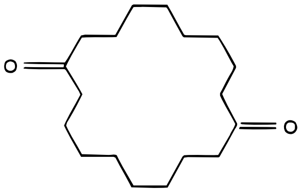

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[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1996.

(1) For paper 4 in the series, see: Constantinides, I.; Macomber, R. S. *J. Org. Chem.* **1992**, *57*, 6063.

(2) (a) Macomber, R. S.; Bopp, T. T. *Synth. Commun.* **1980**, *10*, 767. (b) Constantinides, I.; Lourdes-Guerra, M.; Macomber, R. S. *J. Phys. Org. Chem.* **1990**, *3*, 789. (c) Constantinides, I.; Macomber, R. S. *J. Phys. Org. Chem.* **1992**, *5*, 327.

(3) Constantinides, I. Ph.D. Dissertation, University of Cincinnati, 1992.

(4) (a) Macomber, R. S.; Hemling, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 343. (b) Hemling, T. C. Ph.D. Dissertation, University of Cincinnati, 1985. (c) Kersman, D. A.; Hemling, T. C.; Ho, D. M.; Macomber, R. S. *J. Chem. Res., Synop.* **1989**, 270; *J. Chem. Res., Miniprint* **1989**, 2001.

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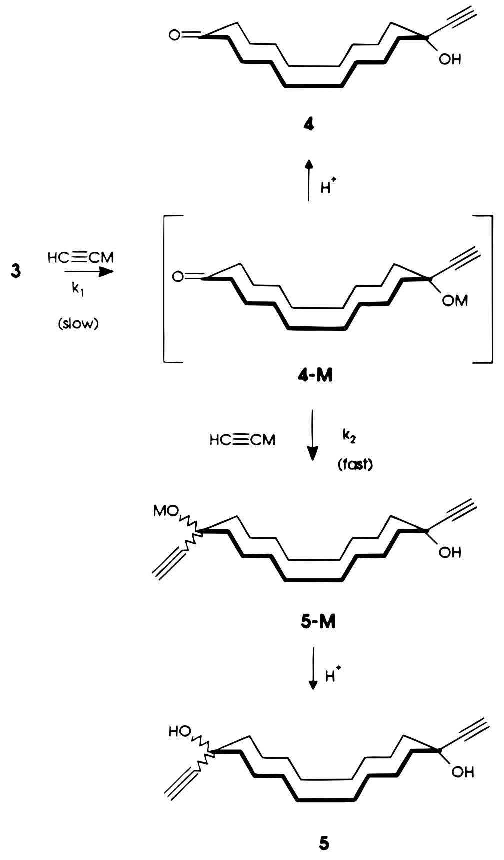
Scheme 1



acted **3**); no monoadduct **4** could be detected by NMR (Scheme 1).[4b,c] These observations suggested that in the reactions of **3** the ratio k_2/k_1 must be significantly greater than 0.5, either because monoadduct formation (k_1) is retarded or diadduct formation (k_2) is accelerated, relative to the reactivity of "normal" ketones.

Interestingly, diol **5** could be crystallized, and the crystalline material was demonstrated by an X-ray study to possess the *trans* configurations.[4c] Because no other signals were seen in the ^{1}H and ^{13}C NMR spectra of chromatographically homogeneous crude **5**, it was presumed that this *trans* isomer was the predominant or perhaps exclusive product. We have now secured evidence (see Experimental Section) for the formation of a minor amount of *cis*-**5**.

Because neither **4** (if formed) nor the isomers of **5** could be readily quantitated by any of the common analytical techniques, we have undertaken a detailed study of the reaction between **3** and phenyl Grignard. It was anticipated that the four potential components of this reaction mixture (**3**, **6**, **7**, and **8**, Scheme 2) could be readily separated by HPLC with UV detection, leading to a determination of κ and, thereby, an assessment of the nature of transannular interactions between the functional groups in **3** and its derivatives. The results of this study are described below.

Results and Discussion

In order to quantify the amounts of **3**, **6**, **7**, and **8** by UV it was first necessary to determine the chromatographic retention characteristics and relative UV response factors (ϵ ratios) for **6**−**8** vs **3**. Diketone **3** was prepared by published procedures.[5] Interestingly, highly purified **3** exhibits two well-defined maxima in its UV spectrum: 286 (ϵ 45) and 208 nm (ϵ 33). The former band can be assigned to the n → π^* transition of the carbonyl group. The latter band, however, may be evidence for a weak transannular electronic interaction between the carbonyls.

Reaction of **3** with 1 molar equiv of phenyl Grignard provided a product mixture from which pure diols **7** and **8** could be isolated by fractional crystallization. The structures of **7** and **8** were determined by single-crystal X-ray analysis (Figures 1 and 2) to be the *cis* and *trans* diols, respectively. [Interestingly, both **7** and **8** crystallize with four independent molecules (each with a slightly different conformation) per unit cell.] Monoadduct **6** could be isolated in small amounts by HPLC.

The rate of reaction between a Grignard reagent and a ketone to give the metal alkoxide is quite fast even at very low temperature, making the direct measurement of rate constant using classical techniques (mixing the reactants and analyzing the mixture as a function of time) very difficult. However, for the consecutive-competitive reactions in Scheme 2 a different approach can be adopted to find κ. Specifically, the ratio of rate constants $\kappa = (k_2 + k_2')/k_1$ can be readily obtained from experiments where the Grignard reagent is added in measured incremental portions to a solution of diketone **3** with known initial concentration. A small hydrolyzed aliquot of the reaction mixture is analyzed after each addition, giving the experimentally observed concentrations of **3**, **6**, **7**, and **8** as functions of the amount of reagent consumed. Two independent methods are then used to calculate the best fit value of κ. In the first method, the entire concentration data set is compared to values calculated by an "incremental" kinetics simulation program,[6] where κ is varied to give the best least-squares fit between observed and calculated concentrations of the reaction mixture components. Alternatively, the value of κ can be determined iteratively for each aliquot using an equation derived form the appropriate integrated rate equations[2b,7] (see Experimental Section). Both methods give comparable values of κ.

Table 1 summarizes the results of three reactions where phenyl Grignard was added incrementally to a solution of **3**. The value of κ for each run was determined by the former method. The average value of κ for the three runs is 2.2 ± 0.4; i.e., the second addition is more than twice as fast as the first, indicating that the reactivity of the carbonyl group in **6-M** is 4.4 times that of either carbonyl in **3**. The detailed concentration data for run 1 are shown in Table 2, along with the aliquot-by-aliquot κ values generated by the second method. The average κ value by the latter method, 2.7 ± 1.3, agrees with the former value, though there is greater experimental uncertainty, owing to the lower precision in the measurement of the small amount of **3** remaining late in the reaction. There is a modest 55/45 preference for formation of the *cis* diol **7** over the *trans* isomer **8**, indicating that $k_2/k_2' = 1.22$. Figure 3 illustrates the agreement between the observed concentrations and

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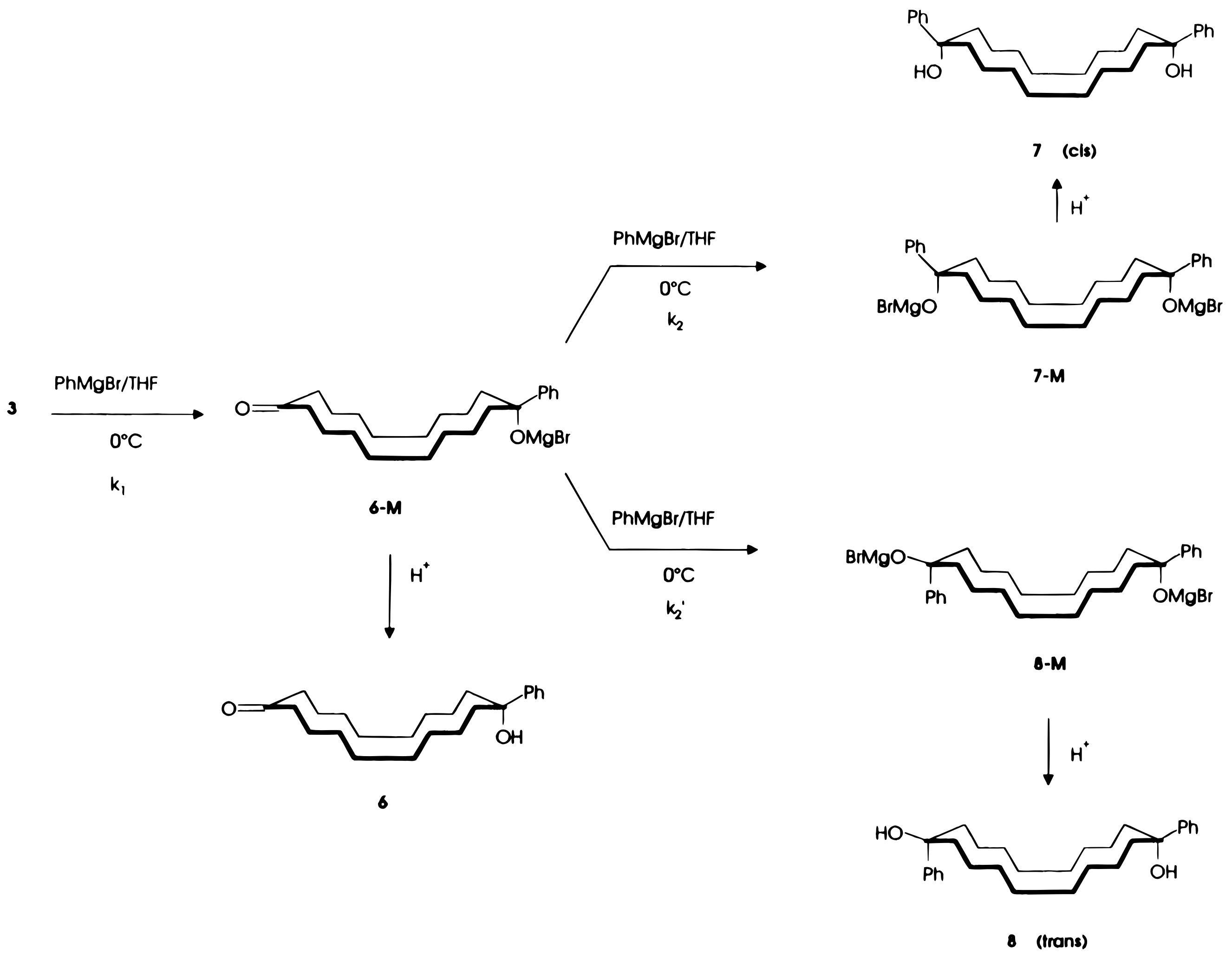
[5] (a) Blomquist, A. T.; Prager, J.; Wolensky, J. *J. Am. Chem. Soc.* **1955**, *77*, 1804. (b) Ruzicka, L.; Stall, M.; Huyser, H. W.; Bookenoogen, H. A. *Helv. Chim. Acta* **1930**, *13*, 1152.

[6] Macomber, R. S.; Constantinides, I. *J. Chem. Educ.* **1991**, *68*, 985.

[7] (a) Wideqvist, S. *Acta Chem. Scand.* **1962**, *16*, 1119. (b) Wideqvist, S. *Arkiv Kemi* **1955**, *8*, 545. (c) McMillan, W. G. *J. Am. Chem. Soc.* **1957**, *79*, 4838.

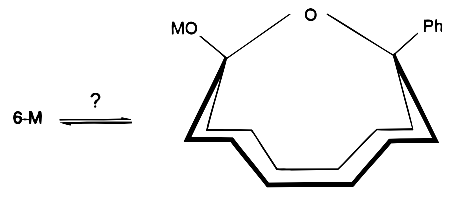
Scheme 2



those calculated from the best fit value of κ (2.36) for run number 1, Table 1.

It is clear from the observed κ value for **3** of 2.2 that either (a) the rate constant (k_1) for addition of phenyl Grignard to a carbonyl group of **3** is slower than expected (b) the rate constant (k_2) for addition to the carbonyl of **6-M** is accelerated, or (c) some combination of both effects is occurring.

It would be straightforward to account for **6-M** having *reduced* reactivity toward carbonyl additions by invoking, for example, formation of "ketal" **9** to protect the remaining carbonyl. But for **6-M** to be *more* reactive than **3**, the



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alkoxide functionality in **6-M** would somehow have to activate the second addition.[8] Moreover, the fact that a variety of nucleophiles[4b,c] give qualitatively the same result as phenyl Grignard indicates that the increase in κ is not due to some unique property of the PhMgBr reagent.[8]

It is informative to consider certain other anomalous physical properties of **3** in addition to its weak UV band at 208 mm (*vide supra*). The molecule crystallizes in a C_{2h} conformation with the two carbonyl dipoles trans, and zero net dipole moment.[9] Essentially the same conformation was found by Allinger using MM2 calculations[9] to be the lowest energy one accessible to "free" **3**. Surprisingly, in solution **3** exhibits a dipole moment of 2.78 D, compared to 2.47 D for cyclooctadecanone itself.[9] This suggests that *in solution* **3** adopts a set of easily accessible conformations where the carbonyl dipoles do not cancel one another. It can be estimated from a simple trigonometric calculation that the observed dipole moment is consistent with a time-averaged angle between coplanar carbonyls of 111°. This factor may also be associated with the 208 nm UV band.

One interpretation of the above facts is that in solution **3** spends a substantial fraction of its time in folded

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[8] One reviewer has suggested that the preferential formation of diadduct is a result of the Grignard reagent being dimeric under these conditions. Such a possibility has been demonstrated by concentration-dependence studies in the lithiation of 3,3′-dibromostilbene (Beak, P.; Liu, C. *Tetrahedron* **1994**, *50*, 5999). We feel this is unlikely for two reasons. First, the same preference is observed in a variety of different types of reactions, most of which involve reagents that are undeniably monomeric. Moreover, during our experiments the Grignard is diluted to <0.01 M during addition, well below the concentrations where dimers are believed to form: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; p 183ff.

[9] Allinger, N. L.; Gorden, B. J.; Newton, M. G.; Norskov-Lauritsen, L.; Profeta, S. *Tetrahedron* **1982**, *38*, 2905.

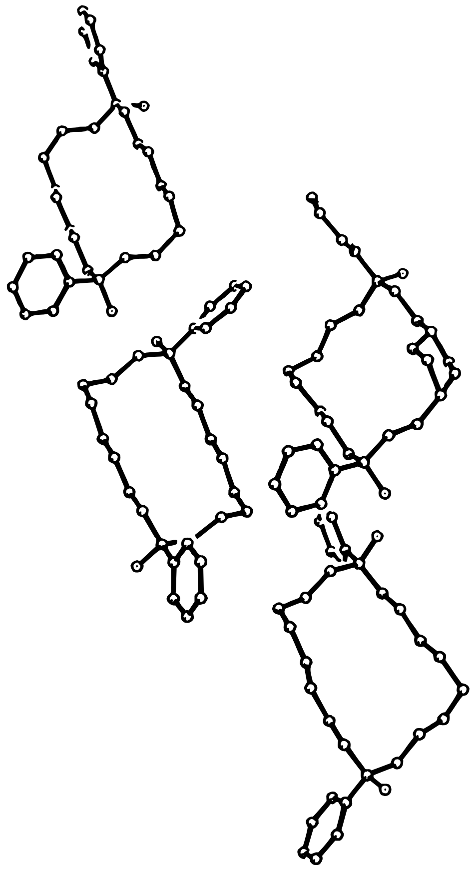
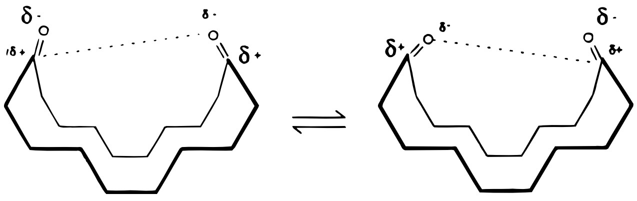


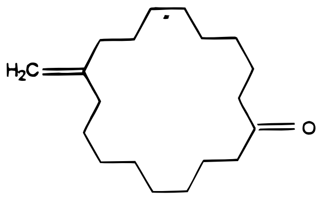
Figure 1. PLUTO structural diagram from X-ray analysis of **7** (cis isomer). There are four independent molecules per unit cell.

conformations such as **10**, where two of the four carbonyl faces are blocked from nucleophilic attack. But once attack does take place, the resulting **6-M** adopts a different conformation so that subsequent nucleophilic attack occurs at a faster than normal rate.



10 **11**

The folded conformation of **3** could be attributed either to a dipole–dipole interaction between the carbonyls (as in **10**) or simply to a conformational consequence of the two sp^2-hybridized carbons in an 18-membered ring. In order to differentiate between these factors, as well as establish the relative reactivity of **3** *vs* a “normal” ketone,



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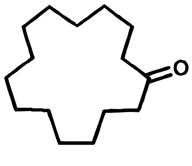

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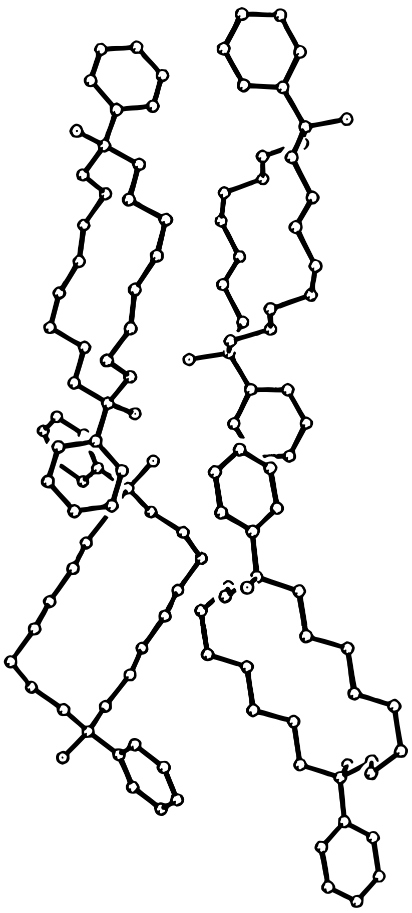

Figure 2. PLUTO structural diagram from X-ray analysis of **8** (trans isomer). There are four independent molecules per unit cell.

Table 1. Kinetic Data for the Reaction of 3 with PhMgBr^a in THF at 0 °C

run	[**3**]$_0$, M	κ^b	deviation^c
1	0.0204	2.36	0.0031
2	0.0254	2.57	0.0040
3	0.0209	1.73	0.0015
	average	2.2 ± 0.4^d	

[a] A 1.0 M solution of PhMgBr in THF was used. [b] $\kappa = (k_2 + k_2')/k_1$, calculated with the method described in ref 6. [c] Square root of sum of squared deviations of experimental concentrations from theoretically calculated[6] concentrations. [d] ± standard deviation.

Table 2. Complete Concentration Data for Run 1 of Table 1

PhMgBr consumed, equiv	[**3**], mM	[**6**], mM	[**7**], mM	[**8**], mM	[**7**]/[**8**]	$\kappa^{a,b}$
0.0	20.4	0.0	0.0	0.0		
0.16	17.9	2.0	0.2	0.2	50/50	4.3
0.74	11.0	3.6	3.3	2.5	57/43	3.3
0.94	9.1	3.6	4.1	3.6	53/47	3.0
1.42	4.1	3.7	6.9	5.7	55/45	1.8
1.67	1.6	3.7	8.0	7.1	53/47	1.1
		averages^c			54 ± 3/46 ± 3	2.7 ± 1.3

[a] From the equation[7c]

$$\frac{1}{\kappa-1}\left[1-\left(\frac{[\mathbf{3}]}{[\mathbf{3}]_0}\right)^{\kappa-1}\right]-\frac{[\mathbf{6}]}{[\mathbf{3}]}=0$$

[b] The incremental model[6] gave $\kappa = 2.36$. [c] ± standard deviation.

diketone **3** has been allowed to compete (in separate experiments) with 10-methylenecyclooctadecanone (**11**)[4a,b] and cyclopentadecanone (**12**) for a limiting amount of

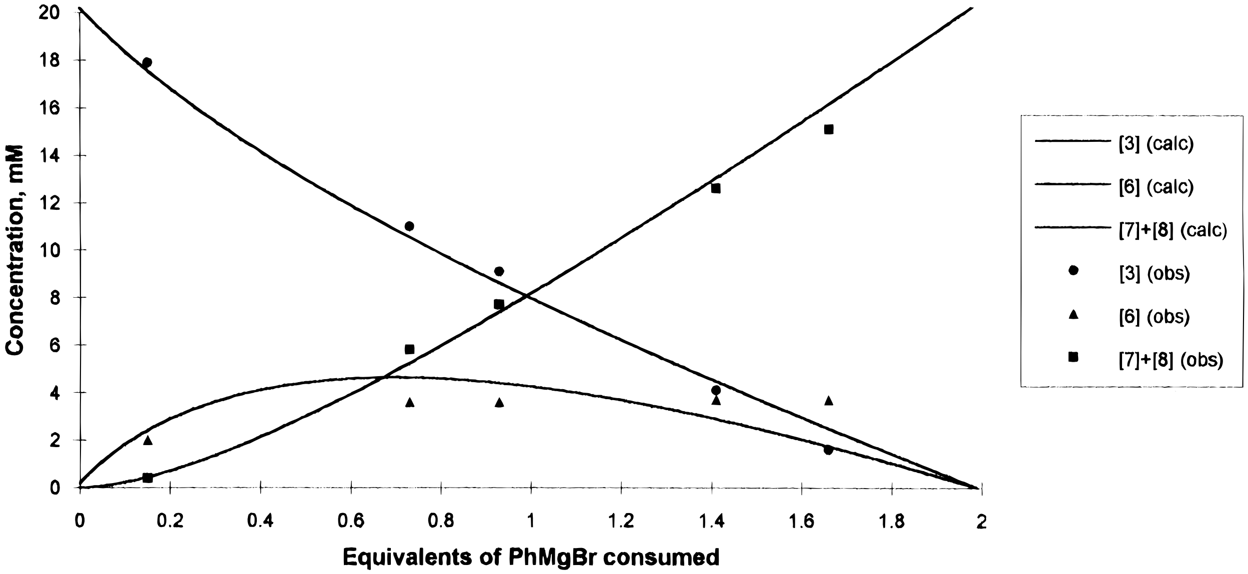

Figure 3. Plot of observed concentrations of **3**, **6**, and **7** + **8** (symbols) and calculated concentrations (lines, using $\kappa = 2.36$) vs molar equivalents of PhMgBr consumed.

phenyl Grignard. If the reagent were to react preferentially (per carbonyl) with **11** and **12**, the lower reactivity of **3** must be due to reasons other than the sp^2-hybridization of two ring carbons. On the other hand, comparable reactivity (per C═O) of **3** with **11** or **12** would be evidence that there is no significant carbonyl dipole interaction in **3**.

When **3** and enone **11** were allowed to compete for a limiting amount of phenyl Grignard, the rate constant ratio $k(\mathbf{11})/k_1(\mathbf{3})$ was 0.30, indicating that enone **11** is only 60% as reactive as **3** on a per carbonyl basis. Interestingly, a UV spectrum of **11** exhibits a maximum at 225 nm (ϵ 121) with a shoulder of 278 nm (ϵ 53.4). It is tempting to attribute the former band to a weak transannular interaction between the C═O and C═C bonds, as has been seen in some related compounds.[10]

In a similar competition experiment between **3** and ketone **12** the ratio **[3]/[12]** decreased only 5% through 68% consumption of total carbonyls. Computer simulation[6] of the competitive consumption of PhMgBr by **3**, **6-M**, and **12** indicated that the rate constant ratio $k(\mathbf{12})/k_1(\mathbf{3})$ is 0.96. Thus, on a *per carbonyl* basis, **3** is only half as reactive as **12**.

Thus, the relative *per carbonyl* reactivity of the four compounds of interest are **11**, 0.60; **3**, 1.0; **12**, 1.9; and **6-M**, 4.4. Assuming the reactivity of monoketone **12** can be taken as "normal", it is clear that the anomalous behavior of **3** must be attributed to a combination of a nearly 50% retardation of the first addition and a >100% enhancement of the rate of the second addition. Furthermore, whatever factors cause the retardation of the first addition to **3** apparently causes an even larger (70%) retardation in the addition to **11**.

A C═O group bent at an angle to the mean ring plane presents a more accessible exo face, and a less accessible endo face. Ketone **12** and monoadduct **6-M** thus both appear to have only one accessible face in their respective most stable conformation. Diketone **3**, whether cis or trans, has two exo and two endo faces. Interestingly, enone **11**, with the most "open" C═O angle, appears to present two reasonably accessible faces. Clearly, intuitive estimates of steric accessibility do not seem to correlate with the observed patterns of reactivity.

In an attempt to identify factors that might be responsible for the rate retardations and enhancements, we have carried out molecular mechanics calculations on the four carbonyl substrates.[11] In addition to the expected conformation of **3** with the carbonyls *trans* (18.5 kcal/mol), we also located a minimum at 17.4 kcal/mol with essentially C_s symmetry that has the carbonyls *cis*. Similarly, in monoadduct **6-M** there are two minima. The more stable (19.1 kcal/mol) has the C—O and C═O bonds *cis* (and the oxygens 5.3 Å apart), while the *trans* conformation has an energy of 22.5 kcal/mol. The lowest energy conformation of **11** also has the $H_2C{=}C$ bond *cis* to the C═O bond.

The first generalization that can be made is that all four structures yield minimum energy conformations with the C═O bond(s) more or less perpendicular to the mean plane of the ring. The O═C- - -C angles (where the latter C represents the ring carbon most nearly opposite the carbonyl carbon) were found to be **11**, 132°; *trans*-**3**, 116.6°/103.0°; cis-**3**, 92.3°/92.1; **12**, 98.2°; *cis*-**6-M**, 57.6°, where the larger the angle the more the C═O bond is flattened toward the outside of the ring (Figure 4). On the basis of a comparison of the angle trends with the relative rates, it seems that the more the carbonyl is bent back toward the center of the ring, the faster it reacts.

During the isolation of diols **7** and **8** it was observed that when the HCl used for workup was not efficiently neutralized, recrystallization of the crude 55/45 mixture of **7** and **8** resulted in deposition of a new crystalline solid with molecular formula $C_{30}H_{40}$ (i.e., double dehydration of **7** and **8**). Spectroscopic analysts suggested a highly symmetrical diene structure. The material was ultimately identified by X-ray diffraction (Figure 5) as *cis,cis*-

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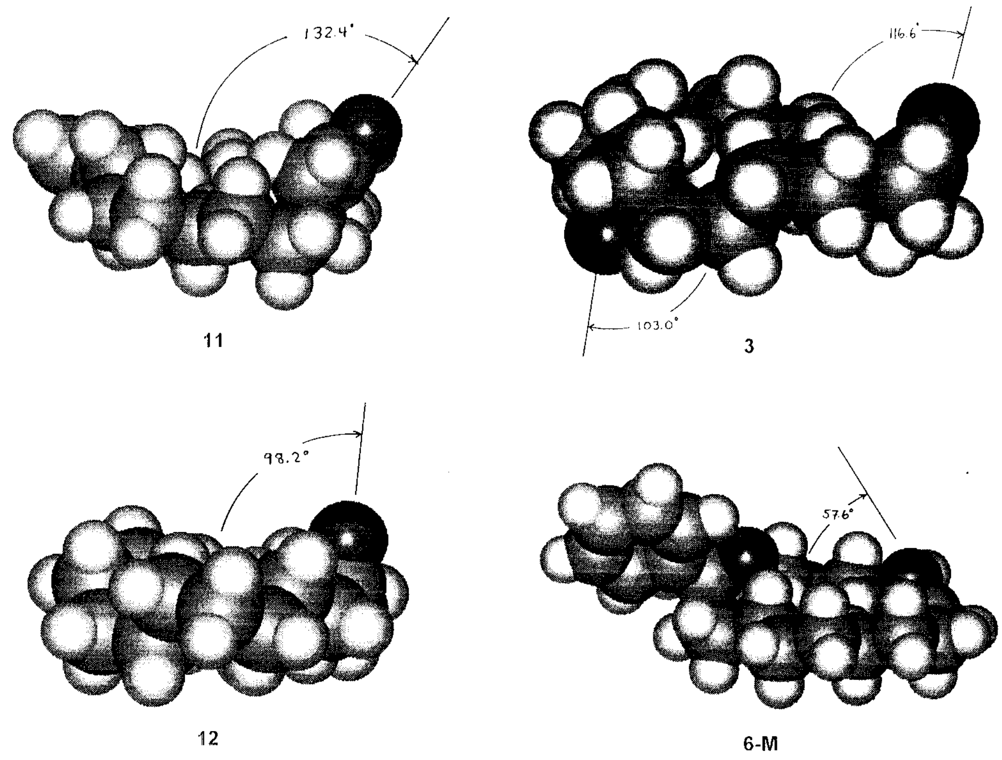
[10] A similar pair of bands is exhibited by 3-methylenecyclobutanone. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; John Wiley & Sons: New York, 1991; p 304.

[11] Molecular mechanics calculations were performed with the MM+ force fields of *Hyper-Chem* (Release 3 for Windows), AUTODESK (1992).



11 3 12 6-M

Figure 4. Space-filling models of the most stable conformations of **11**, *trans*-**3**, **12**, and *cis*-**6-M**.

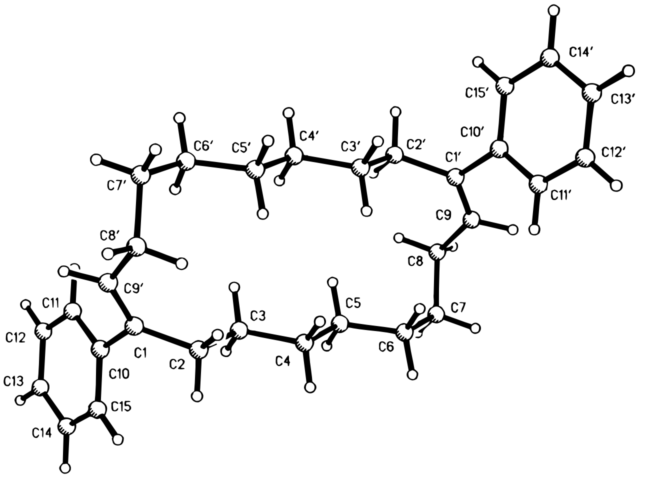
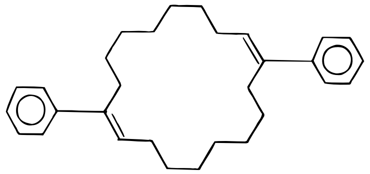


Figure 5. PLUTO structural diagram from X-ray analysis of **13**.

1,10-diphenyl-1,10-cyclooctadecadiene (**13**). Analysis of



13

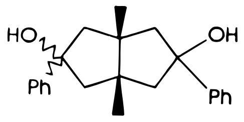
the mother liquor by ^{1}H NMR revealed that **13** was formed almost exclusively (~90%), accompanied by two other minor diene isomers; no **7** or **8** remained. When **13** was heated (50 °C) for several days with excess trifluoroacetic acid, equilibration of these diene isomers was observed, with **13** still constituting 70% of the equilibrium mixture. Thus, **13** is both the kinetically and thermodynamically preferred product.

Table 3. Molecular Mechanics Calculations on the Four Symmetrical Isomers of 1,10-Diphenylcyclooctadecadiene (13)[11]

isomer	rel energy, kcal/mol
trans,*trans*-1,10-diphenyl-1,9-cyclooctadecadiene	34.86
cis,*cis*-1,10-diphenyl-1,9-cyclooctadecadiene	29.26
trans,*trans*-1,10-diphenyl-1,10-cyclooctadecadiene	39.15
cis,*cis*-1,10-diphenyl-1,10-cyclooctadecadiene (**13**)	23.56

In an attempt to explain the regio- and stereoselective formation of **13** by acid-catalyzed dehydration of **7** and **8**, molecular mechanics calculations[11] were also performed for the four possible isomeric 1,10-diphenylcyclooctadienes that possess the C_s or C_2 symmetry observed in the NMR spectra of **13**. From the results of these calculations (Table 3), **13** is predicted to be the thermodynamically favored product. This correlation adds confidence that the results of calculations on **3**, **6-M**, **11**, and **12** (*vida supra*) are similarly reliable. The fact that **13** constitutes 90% of the initially formed diene mixture, and only 70% at equilibrium, suggests that there is a kinetic as well as thermodynamic preference for its formation.

The regiospecificity noted for the dehydration of **7** and **8** is more pronounced than that observed for dehydration of the isomers of 3,7-diphenylbicyclo[3,3,0]octane-3,7-diol (**14**) and related compounds,[12] where transannular com-



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munication between the functional groups is less likely owing to the rigidity of the molecule. It is interesting to note that nucleophilic attack by phenyl organometallic reagents on the precursor bicyclo[3.3.0]octadienones is modestly stereoselective, with the nucleophile preferring to approach from the less sterically hindered "exo" face.[12] Such factors are not present in **3**.

Experimental Section

General. The following instruments were used: Rigaku AFC5R four-circle diffractometer and a Siemens R_{3m}/v diffractometer (X-ray crystal structures); Bruker AC 250 (^{1}H and ^{13}C NMR, using $CDCl_3$/TMS); Hewlett-Packard Model 5995 (GC/MS); Perkin-Elmer 1600 FT-IR (IR); Spectra-Physics SP 8800 HPLC with Spectra 100 variable wavelength UV detector and Hewlett-Packard 3394 integrator (HPLC). The HPLC analyses were performed with a 235 × 4.70 (i.d.) mm Whatman P/5 ODS 3 reversed-phase column.

For the reaction of **3** with phenyl Grignard, the response factor for each alcohol product (P) relative to the starting diketone (S) was determined by HPLC analysis of standard solutions and application of the equation

$$\mathrm{RF_P} = \left(\frac{\text{moles of P}}{\text{moles of S}}\right)\left(\frac{\text{signal area of S}}{\text{signal area of P}}\right)$$

Standard solutions were prepared from pure materials or, in the case of **6**, a mixture with **3** quantitatively analyzed by integration of ^{13}C-NMR carbonyl signals ($\delta_{\mathbf{6}} = 212.22$ ppm, $\delta_{\mathbf{3}} = 211.93$ ppm). The response factors at 264 nm are given below: **6**, 0.192; **7**, 0.110; **8**, 0.115. Gradient elution with water/acetonitrile was used (45/55 for the first 2 min, then changing linearly to 35/65 over 60 min). The relative retention times were **3** < **6** < **8** < **7**.

For the competition reactions between **3** and **11** the following gradient elution was utilized:

time (min)	% CH_3OH	% H_2O
0	55	45
90	85	15
91	100	0

All solvent changes were linear from each time point given. The retention times were 32 min for **3** and 78 min for **11**.

For the competition reaction between **3** and **12**, the following gradient elution was utilized:

time (min)	% CH_3OH	% H_2O
0	54	46
60	60	40

Elution Times: **3**, 40 min; **12**, 70 min.

Materials. The Grignard reagent was prepared by published methods[13] and diluted with dry THF to give a concentration of 1.0 M. Bromobenzene used for the preparation of the phenyl Grignard was distilled prior to use. THF was freshly distilled over potassium. All glassware was oven-dried. Diketone **3** was prepared as previously described, except THF was used as solvent, rather than benzene.[5]

Kinetic Method. A 100 mL round bottomed flask containing 280 mg (1.00 mmol) of **3** in 50 mL of dry THF under nitrogen was inserted in an ice bath, and every 10–15 min a measured volume (0.2–0.5 mL) of 1.0 M PhMgBr in THF was added via syringe. Immediately before the addition of the following portion of the Grignard an aliquot (1 mL) of the reaction mixture was withdrawn, mixed with 1.0 mL of an aqueous solution of acetic acid (0.2 M) and a few drops of ethanol (if not homogeneous), and analyzed by HPLC. The concentrations of **3**, **6**, **7**, and **8** in each aliquot were determined from peak integrations (corrected for response factors) and the known initial concentration of **3**.

The ratio of rate constants $\kappa = (k_2 + k_2')/k_1$ for each aliquot (data point) was determined iteratively from the equation[2b,7]

$$\frac{1}{\kappa - 1}\left[1 - \left(\frac{[\mathbf{3}]}{[\mathbf{3}]_0}\right)^{\kappa-1}\right] - \frac{[\mathbf{6}]}{[\mathbf{3}]} = 0$$

The κ value for a given run was taken as the mean of point-by-point κ values. The κ value for the entire run was independently determined by varying κ to locate the best least-squares fit of the experimental concentrations of the entire run to the concentration predicted by an "incremental method" computer program.[6]

Isolation of 6, 7, and 8. A 100 mL round bottomed flask containing 280 mg (1.0 mmol) of **3** in 50 mL of dry THF under nitrogen gas was inserted in an ice bath, and 0.5 mL of a solution of PhMgBr (*ca.* 2.0 M) in THF was added at once via syringe. The reaction was left to warm to room temperature and stirred for 10 h. (HPLC analysis of a hydrolyzed aliquot, after response factors were determined, was found to have the following constitution: [**3**] = 6.0 mM, [**6**] = 3.2 mM, [**7**] = 5.9 mM, [**8**] = 4.9 mM.) The mixture was poured into 20 mL of 20% HCI. The organic layer was separated, and the aqueous layer was extracted twice with 30 mL of ether. The combined ether layers were washed with $NaHCO_3$ (1.0 M), water, and brine and dried over $MgSO_4$. Evaporation of the solvent left 300 mg of a pale yellow solid. Fractional crystallization with ethyl acetate/methanol (1/1 v/v) first deposited 60 mg of the less soluble trans isomer **8** (pure by HPLC); after concentration of the mother liquor a second crystallization afforded 30 mg of pure cis isomer **7**, both compounds occurring as colorless crystals. Analytical data for **8**: mp 169–171 °C; ^{1}H NMR δ 1.36 (m, 24 H), 1.60 (s, 2 H), 1.85 (m, 8 H) 7.2–7.6 (m, 10 H); ^{13}C NMR δ[14] 22.44, 27.13, 28.18, 39.66, 125.27, 126.61, 128.05, 147.75. Analytical data for **7**: mp 158–161 °C; the ^{1}H NMR spectrum of this material was virtually superimposable on that of **8**. Single crystals of both **7** and **8** were submitted for X-ray diffraction analysis to confirm their structure and determine their stereochemistry.[15] Diols **7** and **8** exhibited virtually identical mass spectra: no molecular ion was observed, only fragments resembling the mass spectrum of **13** (*vide infra*).

HPLC separation of the crude reaction mixture provided a small amount (ca. 1 mg) of **6**: ^{1}H NMR δ 1.1–1.4 (m, 20 H), 1.63 (m, 4 H), 1.81 (m, 4 H), 2.42 (m, 4 H), 7.1–7.4 (m, 5 H); ^{13}C (partial) δ 212.22; MS m/z 341 (M − OH), 340 (M − H_2O, base), 323, 322, 145, 144, 143, 142, 141, 131, 130, 129, 128, 119, 118, 117, 115, 105, 104, 91, 81, 77, 69, 67, 55, 43, 41.

Isolation of 13. When 71.5 mg (0.255 mmol) of **3** was treated with 2 mmol (excess) of PhMgBr, and the crude product was recrystallized with ethyl acetate/ethanol containing one drop of concd HCI, 68 mg (67%) of **13** precipitated as colorless

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[12] Quast, H.; Carlsen, J.; Herbert, T.; Janiak, R.; Roschert, H.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Liebigs Ann. Chem.* **1992**, 495.

[13] Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* (Vol. 1); John Wiley and Sons, Inc.: New York, 1967; pp 415–417.

[14] The signal for the OH-bearing carbons (*ca.* δ 65 ± 5) could not be located with confidence.

[15] The authors have deposited atomic coordinates for the structures of **7**, **8**, and **13** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. Crystal data for **7**: $C_{30}H_{44}O_2$, $M = 436.7$, monoclinic space group $P2_1/n$, $a = 11.813(2)$ Å, $b = 47.652(7)$ Å, $c = 19.269(3)$ Å, $\beta = 93.53(1)°$, $Z = 16$, $U = 10{,}825(3)$ Å^3, $T = 21$ °C, $\rho_{\mathrm{calcd}} = 1.073$ g cm^{-3}, $\mu = 0.464$ mm^{-1}, Cu Kα radiation using a Rigaku AFC5R rotating anode diffractometer. Anisotropic refinement of the four crystallographic-independent molecules stands at $R_f = 7.64\%$, $R_{\mathrm{wf}} = 12.25\%$ for 5706 reflections (1172 variable parameters) with $F \geq 3\sigma(F)$. Large thermal motion is observed for the phenyl groups. Conformational disorder associated with carbons 4–6 of molecule C has been partially sorted out. Crystal data for **8**: $C_{30}H_{44}O_2$, $M = 436.7$, triclinic space group P-1, $a = 10.825(2)$ Å, $b = 11.238(2)$ Å, $c = 22.851(4)$ Å, $\alpha = 77.01(1)°$, $\beta = 85.28(2)°$, $\gamma = 86.65(2)°$, $Z = 4$, $U = 2697.1$ Å^3, $T = 20$ °C, $\rho_{\mathrm{calc}} = 1.075$ g cm^{-3}, $\mu = 0.061$ mm^{-1}, Mo Kα radiation using a Siemens R_{3m}/v diffractometer. Final $R_f = 8.95\%$, $R_{\mathrm{wf}} = 6.65\%$ for 5404 reflections 578 variable parameters) with $F \geq 3\sigma(F)$. Large thermal motion is observed for some of the phenyl groups; however, disorder could not be sorted out. Crystal data for **13**: $C_{30}H_{40}$, $M = 400.6$, orthorhombic space group $Pbca$, $a = 10.943(2)$ Å, $b = 7.531(2)$ Å, $c = 30.002(5)$ Å, $Z = 4$, $U = 2472.5$ Å^3, $T = 21$ °C, $\rho_{\mathrm{calc}} = 1.076$ g cm^{-3}, $\mu = 0.413$ mm^{-1}, Cu Kα radiation using a Rigaku AFC5R rotating anode diffractometer. Final $R_f = 4.76\%$, $R_{\mathrm{wf}} = 8.49\%$ for 1579 reflections (137 variable parameters) with $F \geq 4\sigma(F)$.

crystals, mp 133−135 °C: ^{1}H NMR δ 1.2−1.6 (m, 20 H), 2.19 (q,[16] 4 H), 2.52 (t, $J = 7$, 4 H), 5.63 (t, $J = 8$, 2 H), 7.2−7.4 (m, 8 H); ^{13}C NMR δ[17] 28.39, 28.64, 28.86, 29.15, 29.32, 29.58, 126.44, 128.14, 129.91, 140.12, 143.45. MS *m/z* 401, 400 (Mt), 143, 141, 131, 130, 129, 128, 118, 117, 116, 115, 105, 104, 103, 92, 91 (base), 79, 77, 67, 55, 41, 36; IR (CCl_4) 3084, 3062, 3022, 2926, 2854, 1597, 1493, 1461, 1446, 1260, 1075, 1031 cm^{-1}. The structure of **13** was confirmed by single-crystal X-ray analysis.[15]

Evidence for the Formation of *cis*-5. The mother liquor from $CHCl_3$ recrystallization of *trans*-**5** (mp 138−140 °C)[4c] was evaporated and the residue recrystallized twice from CCl_4. The resulting broad melting solid (mp 96−102 °C), which could not be further purified by recrystallization, exhibited a TLC R_f value (0.55) differentiable from the *trans*-**5** (0.64, neutral alumina, 1:1 ethyl acetate/ligroin, I_2 visualization) present as an inseparable minor (5−10%) impurity. However, the ^{13}C NMR spectrum of the broad melting impure *cis* isomer was superimposable on that of *trans*-**5**.

Synthesis of 11.[4a,b] To a suspension of 0.6169 g of Zn (9.43 mmol) and 0.0265 g (0.095 mmol) of $PbCl_2$ in 10 mL of dry THF was added 0.24 mL of CHI_3 (3.85 mmol). This suspension was placed under argon and in an ice bath, and 2.2 mL of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 was added.[18] After 15 min of stirring, 0.5679 g of **3** (2.03 mmol) in 4 mL of THF was added dropwise. After stirring at room temperature for 24 h, the mixture was filtered through Florisil (5 cm × 8 cm), and the filtrate was rotary evaporated. The product mixture was purified by column chromatography through 20 g of 230−400 mesh silica using ligroin to elute 1,10-dimethylenecyclooctadecane (0.1064 g, 19.1%), 1% EtOAc/ligroin to elute **11**, and 15% EtOAc/ligroin to elute **3**. Fractions containing **11** were combined and rotary evaporated to give 0.1524 g (0.548 mmol, 42.6%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.55 (s, 2H), 2.24 (t, $J = 6.9$, 4H), 1.46 (qnt, $J = 6.9$, 4H), 1.27 (qnt, $J = 6.9$, 4H), 1.13 (brs, 16H); UV λ 225 nm ($\epsilon_{\max} = 121.3$), shoulder at 278 nm ($\epsilon = 53.4$).

Grignard Competition Reaction between 3 and 11 (or 12). A solution of **3** (55.1 mg 0.197 mmol) and **11** (108.7 mg 0.391 mmol) in 4 mL of dry THF was placed in a 5 mL 2-neck flask equipped with a stirbar and a static Ar bubbler. A 0.10 mL aliquot was removed from the solution, and 1 drop of 0.1 M HCl was added. Small amounts of THF and/or ethanol were added to make the aliquot homogeneous. This initial aliquot was then analyzed by HPLC.

A 0.08 mL portion of a 1.0 M phenyl Grignard solution (equal to 10.2% of the total number of carbonyls in the reaction solution) was added. The solution was allowed to stir for 1 h at 0 °C; then another 0.10 mL aliquot was removed. The workup and analysis was as previously described. Additional measured portions of the Grignard reagent were added, and aliquots were analyzed, until either **3** or **11** was fully consumed (HPLC).

The integrated peak areas for each aliquot, together with the known initial ratio of **3** to **11**, were used to determine the ratios of **3** to **11** as a function of reagent added. Multiple analyses of each aliquot were performed until the ratios of **3** to **11** had a relative standard deviation of 10% or less.

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[16] A degenerate doublet of triplets with both *J* values equal.

[17] The signal at δ 29.15 is much more intense than those of the other five alkyl carbons, suggesting that it comprises two carbons. Also, we were not able to locate the vinyl CH carbon signal, expected in the region δ 115 ± 5.

[18] Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *27*, 2417.