Effects of Olefin Substitution on the Ring-Closing Metathesis of Dienes

Thomas A. Kirkland and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, 91125

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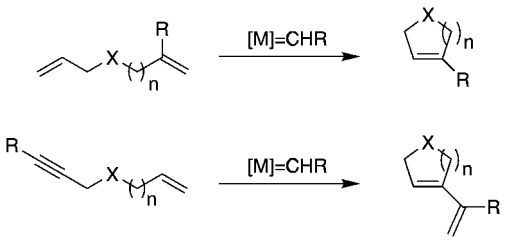
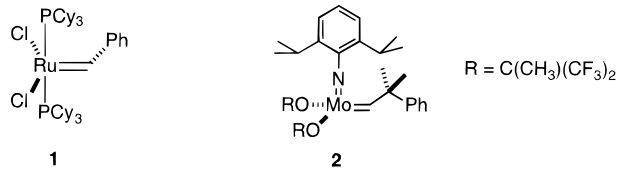
Ruthenium alkylidene **1** and molybdenum alkylidene **2** have been utilized in the ring-closing metathesis (RCM) of dienes containing *gem*-disubstituted olefins to yield tri- and tetrasubstituted cyclic olefins. Dienes with sterically demanding and/or electron-withdrawing substituents such as Ph, CO_2Me, and ^tBu were cyclized successfully with **2**, but did not cyclize with **1**. Tetrasubstituted cyclic olefins could be formed with **2**, but not using alkylidene **1**. Dienes with allylic functional groups yielded functionalized cyclic olefins when treated with **1**.

Introduction

Ring-closing metathesis (RCM) is a versatile technique for the formation of five- to seven-membered carbocycles and heterocycles.[1−5] In addition, several examples of macrocycle formation through RCM have been reported.[5−12] Ruthenium alkylidene **1**[13] and molybdenum alkylidene **2**[14] are two of the most commonly used initiators for RCM (Scheme 1), and reports of their use in organic synthesis have increased steadily.[8,15−19] However, relatively little effort has been directed toward converting substituted dienes to substituted cyclic olefins (Scheme 1).[1,2,7,8,17,20−24] Since many protocols exist for the elaboration of functionalized olefins, substituted cyclic olefins are attractive synthetic intermediates in organic synthesis.

Scheme 1. Catalytic RCM Yielding Substituted Cyclic Olefins





Several examples of the RCM of alkyl-substituted dienes with highly active group VI alkylidenes have been reported. Molybdenum alkylidene **2** has been used for the synthesis of a variety of methyl- and ethyl-substituted cyclic olefins through RCM.[1,2,7,8,17,20] Additionally, cyclic enol ethers have been synthesized from acyclic enol ethers using alkylidene **2**.[7,20,23] The high activity displayed by alkylidene **2** is accompanied by both a lack of tolerance for some common functional groups and the requirement that substrates and solvents be rigorously purified, dried, and degassed.[3] Ruthenium alkylidene **1** will perform RCM in the presence of most of the functional groups commonly used in organic synthesis and requires far less rigorous conditions than **2**.[3,5,13]

An alternative method for synthesizing functionalized cyclic olefins via olefin metathesis is through the RCM of acetylene containing substrates, which has been explored with several alkylidenes (Scheme 1).[21,22,24−26] However, formation of substituted cyclic olefins through metathesis of *substituted dienes* has not been reported for alkylidene **1** and has been confined to the few examples listed above with alkylidene **2**. In this report,

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(1) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−5427.
(2) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324−7325.
(3) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.
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(7) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123−126.
(8) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943.
(9) König, B.; Horn, C. *Synlett* **1996**, 1013−1014.
(10) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614.
(11) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorenson, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. *J. Am. Chem. Soc.* **1997**, *119*, 2733−2734.
(12) Nicolau, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem. Int. Eng. Ed.* **1996**, *35*, 2399−2401.
(13) Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.
(14) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.
(15) Martin, S. F.; Liao, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691−694.
(16) Borer, B. C.; Derrenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191−3194.
(17) Houri, A. F.; Xu, Z.; Cogan, D.; Hoyveda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944.
(18) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621−1624.
(19) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547−550.
(20) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127−130.
(21) Kim, S.-H.; Zuercher, W. J.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073−1081.
(22) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801−10802.
(23) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029−4031.
(24) Kinoshita, A.; Miwako, M. *Synlett.* **1994**, 1020−1022.
(25) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737−738.
(26) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356−8357.

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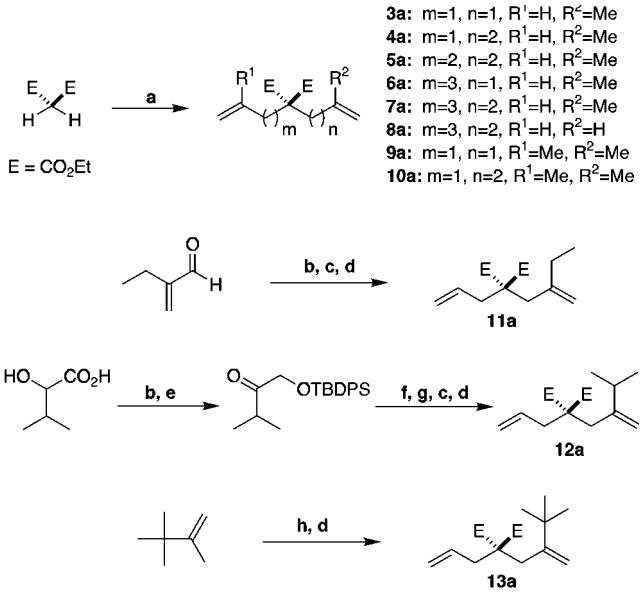
Scheme 2. Synthesis of Alkyl Substituted Dienes Derived from Diethyl Malonate[a]



[a] (a) $CH_2{=}CHR^{1,2}(CH_2)_{m,n}Br$, NaOEt, DMF, 33−72%; (b) $LiAlH_4$, Et_2O, 79%; (c) PPh_3, CBr_4, CH_2Cl_2, 65−90%; (d) $(EtO_2C)_2CHCH_2CH{=}CH_2$, NaOEt, DMF, 33−75%; (e) TBDPSiCl, NEt_3, CH_2Cl_2, then PCC, CH_2Cl_2, 83%; (f) Ph_3PCH_3Br, BuLi, THF, 93%; (g) TBAF, THF, 65%; (h) NBS, CCl_4, 66%.

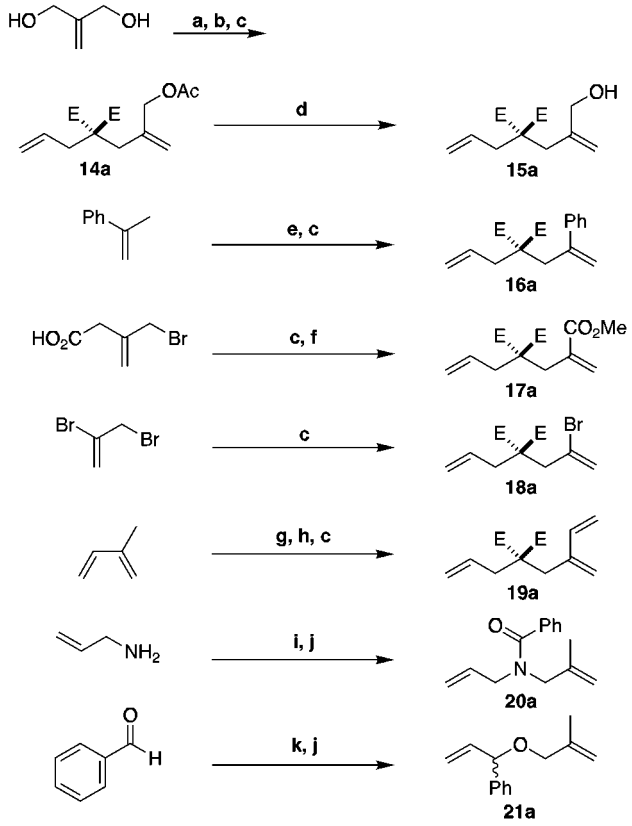
the synthesis of a variety of substituted dienes and their reactivities with these two common metathesis-active alkylidenes is presented. The substrates were chosen to test the limits of reactivity of both alkylidenes and to provide guidelines for their use in constructing complex synthetic targets.

Results and Discussion

Substrate Synthesis. Standard alkylation of diethyl malonate with alkyl halides was used to prepare the alkyl-substituted dienes **3a**−**10a** (Scheme 2).[27] Halides used in the syntheses of these dienes were either commercially available or obtained from the corresponding alcohol.[28] Reduction of ethyl acrolein, subsequent conversion of the alcohol to the bromide,[29,30] and coupling to diethyl allylmalonate (DAM) provided diene **11a**. Synthesis of 2-(bromomethyl)-3-methyl-1-butene[31] (Scheme 2) followed by coupling to DAM afforded diene **12a**. Allylic bromination of 2,2,3-trimethylbutene[32] followed by coupling to DAM yielded diene **13a**.

Functionalized dienes **14a**−**21a** were prepared in a similar manner to the alkyl-substituted dienes (Scheme 3). Bromination of 2-(acetoxymethyl)-3-propen-1-ol followed by coupling to DAM gave diene **14a**, and subsequent deprotection afforded diene **15a**. Diene **16a** was prepared by allylic bromination of α-methylstyrene[33] followed by coupling to DAM. Reaction of 2-(bromomethyl)acrylic acid with DAM followed by esterification afforded diene **17a**. The coupling of 2,3-dibromopropene to DAM yielded diene **18a**. Electrocyclic addition of isoprene to SO_2, bromination of the resultant cyclic sulfone, and thermally induced elimination of SO_2 gave 2-(bromomethyl)-1,3-butadiene,[34−36] which was reacted with DAM to yield **19a**. Amide **20a** and ether **21a** were synthesized through standard alkylation reactions.

Scheme 3. Synthesis of Functionalized RCM Substrates[a]

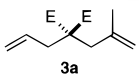
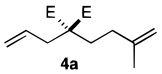
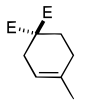
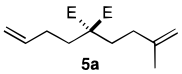
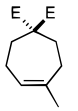
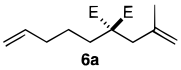
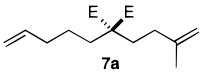
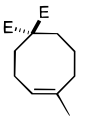
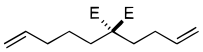
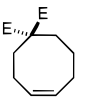
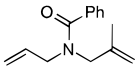
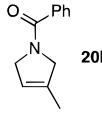
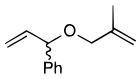
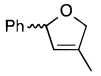


[a] (a) Ac_2O (1 equiv), NEt_3, CH_2Cl_2, 48%; (b) PPh_3, CBr_4, CH_2Cl_2, 75%; (c) $(EtO_2C)_2CHCH_2CH{=}CH_2$, NaOEt, DMF, 54−96%; (d) Na, EtOH, 57%; (e) NBS, CCl_4, 27%; (f) CH_3I, K_2CO_3, acetone, 55%; (g) SO_2, benzoquinone, CH_3OH, 47%; (h) NBS, $CHCl_3$, then 160 °C, neat, 62%; (i) PhCOCl, NEt_3, CH_2Cl_2, 64%; (j) $CH_2{=}C(CH_3)CH_2Cl$, NaH, DMF, 38−78%; (k) $CH_2{=}CHMgBr$, THF, 56%.

RCM of Methyl-Substituted Dienes. Initially, it was necessary to determine if ruthenium alkylidene **1** was active for the RCM of dienes containing a *gem*-disubstituted olefin. When diene **3a** (0.01 M, CH_2Cl_2)[37,38] was exposed to 5 mol % of **1** for 24 h, cyclopentene **3b**

(27) Doran, W. J.; Shonle, H. A. *J. Am. Chem. Soc.* **1937**, *59*, 1625−1626.
(28) Bhanot, O. S.; Dutta, P. C. *J. Chem. Soc. (C)* **1968**, 2583−2588.
(29) Borg, R. M.; Heuckeroth, R. O.; Lan, A. J. Y.; Quillen, S. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109*, 2728−2737.
(30) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084−7085.
(31) Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. (C)* **1971**, 1968−1974.
(32) White, W. N.; Norcross, B. E. *J. Am. Chem. Soc.* **1961**, *83*, 3265−3269.
(33) Reed, S. F. *J. Org. Chem.* **1965**, *30*, 3258.
(34) Frank, R. L.; Seven, R. P. *Org. Synth.* **1955**, *Collect. Vol. 3*, 499−500.
(35) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281−3289.
(36) Krug, R. C.; Yen, T. F. *J. Org. Chem.* **1956**, *21*, 1082−1084.
(37) CH_2Cl_2 was chosen as the optimal solvent for reactions with **1** based on slightly lower yields obtained in other solvents employed (C_6H_6, $CHCl_3$). C_6H_6 was used as the solvent for reactions with **2** based on previous work done in this laboratory.[1,2]
(38) All RCM reactions using alkylidene **1** were performed at room temperature. Comparison of the conversion obtained at a variety of temperatures for substrate **3a** showed that while RCM was faster at elevated temperatures, the accelerated decomposition of the ruthenium methylidene led to a decrease in overall conversion to ring-closed product under the conditions used. In some other studies with alkylidene **1** involving different conditions, increased temperature has resulted in higher overall conversions, notably at higher substrate concentrations.[21,40] With alkylidene **2**, elevated temperatures resulted in the increased conversion of **10a** to **10b**, and 65 °C was eventually chosen as the optimal temperature for all RCM reactions with **2**.

Table 1. Results of the RCM of Methyl Substituted Dienes

Entry	Substrate	Product	Yield With **1**	Yield With **2**
1	 **3a**	 **3b**	93%	(100%)[1]
2	 **4a**	 **4b**	97%	(100%)
3	 **5a**	 **5b**	96%	(100%)
4	 **6a**	 **6b**	(25%)	96%
5	 **7a**	 **7b**	No RCM product[2]	No RCM product[2]
6	 **8a**	 **8b**	No RCM product[2]	No RCM product[2]
7	 **20a**	 **20b**	97%	(100%)
8	 **21a**	 **21b**	98%	(100%)

[1] Numbers in parentheses represent the conversion to product as measured by ^{1}H NMR. [2] In these cases, only starting material and a product which was assigned as an acyclic dimer based on ^{1}H NMR and TLC were observed.

was obtained in 93% isolated yield with no side products detected (Table 1, entry 1). A relatively low concentration of substituted diene is required for optimized yields when RCM is performed with alkylidene **1**. Upon addition of **1** to a 0.1 M solution of **3a**, significant formation of another species is observed. This species is postulated to be the dimer formed through acyclic diene metathesis of the monosubstituted olefins of two molecules of **3a**.[39] Several examples of dimerization have been seen in other RCM applications of **1**.[10,40] However, no dimerization could be detected upon analysis of all of the reactions using **1** at a substrate concentration of 0.01 M. Therefore, the conditions reported above were used as the standard conditions for RCM with **1** for all of the reactions reported.

Exposure of **3a** (0.1 M, C_6D_6)[37,38] to the molybdenum alkylidene **2** (5 mol %) also showed high reactivity in converting this substrate to **3b**. Upon examining the reactions of trisubstituted dienes with alkylidene **2** at this concentration, no dimer formation was detected. In addition, RCM of some substituted dienes which are unreactive with **1** can be carried out in good synthetic yield with alkylidene **2**.

The difference in reactivity between **1** and **2** can be understood through an examination of the kinetics of formation of trisubstituted cyclic olefins through RCM (Figure 1). From this analysis, it can be seen that the catalyst dependent term for productive RCM vs dimer formation is k_{more}/k_{less}. Because this ratio is much smaller for the more selective ruthenium alkylidene ($k_{less} >> k_{more}$ for **1**), dimer formation is frequently competitive with RCM. Since the rate of dimer formation is dependent upon the concentration of substrate but the rate of RCM is independent of substrate concentration, performing RCM reactions under dilute conditions can reduce the rate of dimerization to the point where it is not observed. Because the molybdenum alkylidene **2** is much less selective than **1**, the intramolecular reaction occurs much faster than any intermolecular reaction under the range of concentrations examined in this study.

In order to explain the increased conversion observed when the concentration of substrate is increased in molybdenum-mediated cyclizations, another kinetic term involving the methylidene[41] must be considered. Due to the limited stability of the molybdenum methylidene,[14] the decomposition of the catalytic species is competitive with the rate of RCM. Because the rate of RCM increases with the concentration of substrate, the increased yield results from higher turnover of substrate before catalyst decomposition. This problem is significantly reduced in the case of the ruthenium methylidene, which is much more stable in solution and can even be isolated as a solid which is stable indefinitely at room temperature.[13] However, in cases where reaction with the more substituted olefin is extremely slow for the ruthenium alkylidene, the rate of catalyst decomposition exceeds the rate of RCM and little or no conversion to product is observed. In these cases decreasing the substrate concentration and increasing catalyst loading can significantly increase the conversion of substrate to product for the reasons outlined above.

Under the standard conditions discussed previously, alkylidenes **1** and **2** converted diene **4a** to the substituted cyclohexene **4b** in good yield (Table 1, entries 2−4). Formation of the seven-membered cyclic **5b** with alkylidene **1** required extended reaction times (4 days) to achieve a 96% yield. However, formation of the structural isomer **6b** was less favorable, with only 25% conversion to **6b** observed after 5 days. Quantitative conversion of both **5a** and **6a** to the respective cycloheptenes is seen with alkylidene **2**.

Differences in the rates of formation of isomeric cycloheptenes have been reported elsewhere,[42,43] although the reason for this drop in reactivity is unclear. In the case of substrates derived from malonic acid, the *gem*-diesters on the backbone of the substrate favor cyclization due to a Thorpe−Ingold effect.[44,45] Thus, the higher reactivity of **5a** may be due to the *gem*-diesters biasing the substrate to adopt a conformation which is favorable for cyclization. This bias may be less in the asymmetrical substrate **6a**. Another possible explanation is that the esters in **6a**, being closer to the disubstituted olefin,

(39) Tentative assignment of the species which did not correspond to the desired product in the reaction mixture as dimeric was done through ^{1}H NMR.

(40) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640.

(41) The methylidene ($L_nM{=}CH_2$) is the active catalytic species in RCM of dienes which contain only mono- and *gem*-disubstituted olefins. It is formed through reaction of the starting alkylidene with one molecule of substrate. After this, the methylidene is the propagating species for the remainder of the catalytic cycles.

(42) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309−2322.

(43) Rutjes, F. P. J. T.; Shoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677−680.

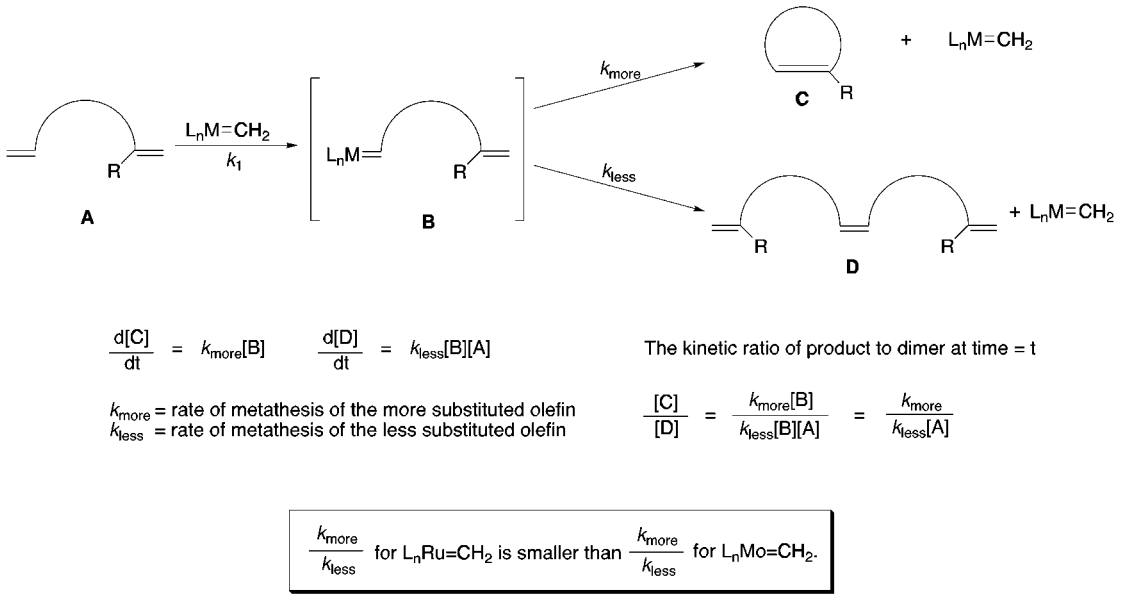
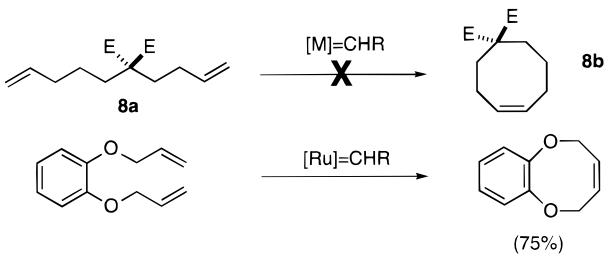


Figure 1. The kinetics of ring-closing versus dimerization for monosubstituted dienes.

hinder the tethered alkylidene as it approaches the disubstituted olefin to form the cyclic product. The higher conversion observed with alkylidene **2** is believed to be due to the higher reactivity of this alkylidene, which overrides the factors inhibiting alkylidene **1** discussed above.

Exposure of the diene **7a** to alkylidene **1** or **2** under standard conditions yielded only dimeric products (Table 1, entry 5). In order to determine if the methyl group substituent on **7a** had prevented productive RCM from occurring, the analogous diene **8a** without olefinic substituents was synthesized (Table 1, entry 6). Again, only dimeric products were observed upon exposure to both alkylidenes. This result is in good agreement with previous work from these laboratories,[46] showing that formation of eight-membered cyclics through RCM only occurs in systems where the dienes are conformationally predisposed for ring formation as in the catechol derivative shown below. Unconstrained systems failed to yield eight-membered cyclics through RCM in almost all cases, and it has been demonstrated for several other cyclizations that formation of eight-membered rings is less favorable than formation of five-, six-, or seven-membered rings.[47] Clearly, the diester moiety does not provide enough conformational bias to favor RCM in the cases of **7a** and **8a**.



In order to demonstrate that this methodology is general to a variety of substituted dienes, amide **20a** and ether **21a** were examined (Table 1, entries 7 and 8). Alkylidene **1** cyclized amide **20a** and ether **21a** to the corresponding heterocycles **20b** and **21b** in 97% and 98% yield, respectively. In accordance with previous reports from this laboratory,[1,2] it was found that the molybdenum alkylidene **2** also converted **20a** and **21a** quantitatively to the expected cyclic products.

Table 2. Results of the RCM of Several Functionalized Dienes

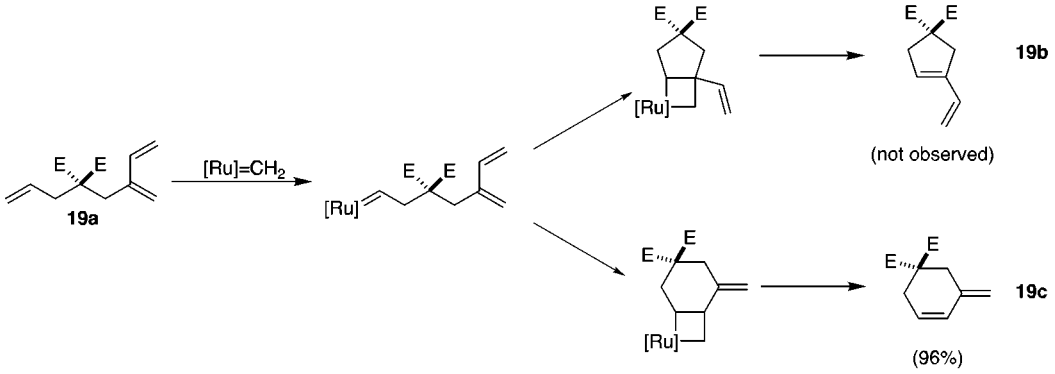
Entry	Substrate		Product		Yield With **1**	Yield With **2**
1	R = Et	(**11a**)	R = Et	(**11b**)	93%	(100%)[1]
2	R = ^{i}Pr	(**12a**)	R = ^{i}Pr	(**12b**)	98%	(100%)
3	R = ^{t}Bu	(**13a**)	R = ^{t}Bu	(**13b**)	NR	96%
4	R = Ph	(**16a**)	R = Ph	(**16a**)	(25%)	97%
5	R = CO_2Me	(**17a**)	R = CO_2Me	(**17b**)	(5%)	89%
6	R = Br	(**18a**)	R = Br	(**18b**)	NR	NR
7	R = CH_2OH	(**15a**)	R = CH_2OH	(**15b**)	98%	decomp
8	R = CH_2OAc	(**14a**)	R = CH_2OAc	(**14b**)	97%	(100%)

[1] Numbers in parentheses represent the conversion to product as measured by ^{1}H NMR.

Effect of Olefin Substitution. Once it had been established that formation of substituted cyclics with **1** was feasible, attention was turned toward the olefinic substituent (Table 2, entries 1−3). The steric bulk tolerated by each alkylidene was examined through the use of dienes **11a**, **12a**, and **13a**. The cyclization of ethyl-substituted diene **11a** with **1** proceeded in 93% yield over 24 h. Reaction of isopropyl-substituted diene **12a** with **1** required 48 h for 98% yield of **12b** to be achieved, presumably due to the presence of additional steric bulk on the olefin. Alkylidene **1** showed no reaction with *tert*-butyl-substituted diene **13a** over 5 days, demonstrating that further increasing the steric bulk on the olefin inhibits RCM with **1**. Due to the more active nature of

(44) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978−10980.
(45) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232, and references contained therein.
(46) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.
(47) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

Scheme 4. Possible Products Resulting from the RCM of 19a



alkylidene **2**, it was presumed that **2** would be more active toward the RCM of more hindered dienes such as **12a** and **13a**. In fact, **2** converts all three of these alkyl-substituted dienes into the corresponding cyclopentenes in high yield over 24 h.

After examining the steric bulk tolerated by these alkylidenes, several substituents which affect the electronic nature of the olefin were examined. Previous reports from this laboratory had shown that enol ethers did not undergo RCM when exposed to **1**.[23] For this reason we turned our attention away from electron-donating substituents and toward electron-withdrawing substituents (Table 2, entries 4 and 5). When the phenyl-substituted **16a** was subjected to RCM conditions with **1**, only 25% conversion to cyclized product was observed. In the case of the more electron-deficient diene **17a**, 5% conversion was observed. The failure of **16a** and **17a** to yield the desired product in higher yield when exposed to alkylidene **1** is postulated to be a combination of the steric effect of the substituent and the electron-withdrawing effects of the phenyl and methyl ester groups. Alkylidene **1** is capable of cyclizing substrates which contain substituents of approximately equal steric demand to these substituents such as the isopropyl group in diene **12a**. Examples have been reported of α,β-unsaturated carbonyl- and phenyl-substituted acetylenes[21] and dienes[3,19,43] reacting with alkylidene **1** to form cyclic products. However, when both the steric bulk and electron-withdrawing character are combined in the same diene substituent, the rate of RCM with alkylidene **1** becomes so slow that catalyst decomposition is competitive with RCM and high yields are not obtained.

In contrast to **1**, alkylidene **2** was reported to convert dienes containing an enol ether to cyclic enol ethers in high yield.[23] Treatment of substrates **16a** and **17a** with alkylidene **2** afforded the expected cyclopentenes in good yield as well (Table 2, entries 4 and 5). The higher reactivity exhibited by **2** toward olefins containing both electron-withdrawing and electron-donating substituents as compared to **1** underscores its generally higher activity toward *gem*-disubstituted olefins.

Next, vinyl halide containing dienes were examined. Exposure of **18a** to either alkylidene **1** or **2** afforded no cyclic product (Table 2, entry 6). In all cases, only **18a** and alkylidene decomposition products were detected upon examination of the reaction mixtures. The explanation for this lack of reactivity with alkylidene **1** is presumed to be the same as for dienes **16a** and **17a**. Acetylenic halides have been shown to react with alkylidene **1** through halide exchange, but will not undergo RCM.[21] It has also been shown that other vinyl halides do not react productively with alkylidene **1**.[48] The explanation for the failure of alkylidene **2** to react with **18a** has not been determined.

Due to the failure of alkylidene **1** to effectively cyclize dienes containing substituents in conjugation with an olefin, functional groups which do not electronically deactivate the substrate but could be used to efficiently derivatize the cyclic olefin after RCM were investigated. Allylic alcohol **15a** was the target molecule for this approach. Because the alcohol should have only an inductive effect on the olefin, it was hoped that the diene would not be deactivated for RCM with **1**. The reactivity of **1** toward **15a** was therefore presumed to be similar to its reactivity toward the ethyl substituted diene **11a**. In fact, both the alcohol **15a** and the acetate **14a** react with **1** to yield the expected cyclopentenes in excellent yields (Table 2, entries 7 and 8). As expected, molybdenum alkylidene **2** decomposes in the presence of the primary alcohol present in **15a** to give no ring-closed product, although it does convert protected diene **14a** to the cyclized product.

Due to the fact that three olefins are present in substrate **19a**, reaction of **19a** with either alkylidene **1** or **2** could yield either cyclopentene **19b** or cyclohexene **19c** (Scheme 4). On the basis of the kinetic scheme described previously (Figure 1), it was predicted that alkylidene **1** would preferentially react with the two less substituted olefins on **19a** to give **19c**. This prediction proved correct, and **19c** is formed in 96% yield upon treatment of **19a** with **1**.[49,50] Due to the lower selectivity of molybdenum alkylidene **2** for monosubstituted olefins, it was believed that a mixture of **19b** and **19c** might be formed. However, reaction of **19a** with **2** also showed quantitative conversion to cyclohexene **19c** with none of the cyclopentene **19b** detected. This result suggests that while **2** is not as selective for less substituted olefins than **1**, it will still preferentially react with the less substituted olefin when two olefins with different substitution are present.[51] This formation of *exo*-methylene ring systems such as **19c** represents a complementary diene system

(48) Kim, S-H., Unpublished results.

(49) The product of the metathesis of **19a** was determined not to be **19b** through comparison to the spectral data of **19b** as reported.[50]

(50) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050.

(51) Although the mechanism presented explains the formation of **19c** (Scheme 4), there are two other obvious means by which **19c** could be formed from **19a**. If the alkylidene initiates at the conjugated terminal olefin, the only possible RCM product is **19c**. Additionally, it is possible that cyclopentene **19b** is formed initially and undergoes subsequent reaction to produce the thermodynamically more stable cyclohexene **19c**. However, in NMR experiments formation of **19b** is not observed.

Scheme 5. Reaction of the Ruthenium Methylidene with Substituted Alkene and Alkyne Substrates

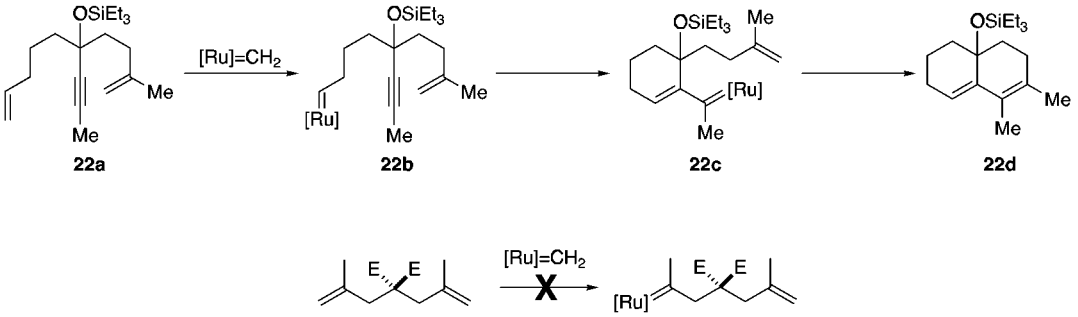
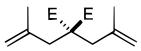
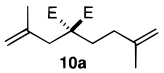
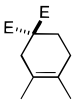


Table 3. RCM of Dienes To Form Tetrasubstituted Cyclics

Entry	Substrate	Product	Yield With **1**	Yield With **2**
1	 **9a**	 **9b**	NR	93%
2	 **10a**	 **10b**	NR	61%

to the vinyl systems afforded through enyne metathesis (Scheme 1).

Synthesis of Tetrasubstituted Olefins. Having demonstrated the formation of a variety of trisubstituted cyclic olefins, formation of tetrasubstituted cyclic olefins through the RCM of dienes **9a** and **10a** was investigated. Formation of cyclopentenes with tetrasubstituted olefins analogous to **9b** with molybdenum alkylidene **2** has been reported.[1,4] Indeed, when **9a** was exposed to **2** under standard RCM conditions, **9b** was obtained in 93% yield (Table 3). Formation of the cyclohexene **10b** using alkylidene **2** proceeded in 61% yield.

Exposure of **9a** or **10a** to alkylidene **1** afforded no cyclic product under standard RCM conditions. Even when the concentration of substrate was increased 10-fold neither ring-closed product nor dimerization were observed. However, previous studies in this laboratory have shown that tetrasubstituted cyclic olefins can be generated through reaction of **1** with acetylene containing substrates.[21] The key difference between these two systems lies in the initial reaction of alkylidene with the substrate. In acetylene-containing substrates such as **22a**, the monosubstituted olefin is the site of initiation (Scheme 5). Once the alkylidene has initiated to yield intermediate **22b**, the intramolecular reaction is favored to form intermediate **22c**. The new alkylidene present in **22c** performs another intramolecular reaction with the disubstituted olefin at the end of the tether to form the fused bicyclic compound **22d** containing a tetrasubstituted olefin. As discussed earlier, an intramolecular reaction is also observed in the formation of trisubstituted dienes through metathesis of *gem*-disubstituted olefins, although only at high dilution. Initiation occurs through the less substituted olefin and the new alkylidene undergoes the intramolecular reaction providing the desired product. When no monosubstituted olefin is present on the RCM substrate, however, reaction with **1** is not observed. In fact, the isolation of disubstituted alkylidenes of ruthenium which are metathesis active has not been reported. The low reactivity of **1** with *gem*-disubstituted olefins intermolecularly indicates that formation of tetrasubstituted cyclic olefins through dienes such as **9a** is not feasible using alkylidene **1**.

Conclusions

We have demonstrated the formation of trisubstituted and tetrasubstituted olefins via ring-closing metathesis of *gem*-disubstituted olefins. This is a general reaction for the formation of five-, six-, and seven-membered carbocycles and heterocycles. The reactivities of all substrates examined supports the general observation that five-membered ring formation is the most kinetically favorable and eight-membered ring formation is the least favorable regardless of the alkylidene used. Ruthenium alkylidene **1** will cyclize dienes with olefinic substituents as sterically demanding as isopropyl in good yield, but will not cyclize a *tert*-butyl-substituted diene. In addition, dienes containing an electron-withdrawing olefinic substituent do not undergo RCM when exposed to **1**. The more active and less selective molybdenum alkylidene **2** does catalyze the RCM of many of the substrates for which **1** was not active. Both alkylidenes **1** and **2** are shown to efficiently convert trienes such as **19a** to the *exo*-methylenecyclohexene **19c**. Tetrasubstituted cyclic olefins can be synthesized from bis-*gem*-disubstituted dienes using the more active alkylidene **2**, but **1** is unreactive toward that class of dienes. However, alkylidene **1** does perform RCM in excellent yield to form a carbocycle containing an allylic alcohol.

The differing reactivities of alkylidenes **1** and **2** suggest that both have a role in the synthesis of complex molecules through RCM. The more active molybdenum alkylidene **2** is required for the RCM of highly substituted dienes. However, RCM using **2** frequently requires a substantial number of substrate protection and deprotection steps which are not required when **1** is used. Another advantage of ruthenium alkylidene **1** is that rigorous purification, drying, and degassing of substrates is not required for RCM. Therefore, total syntheses of many densely functionalized targets may be more simply and efficiently carried out using **1**.

Experimental Section

General. NMR spectra were recorded on either a General Electric QE-300 (300.1 MHz for ^{1}H; 75.49 MHz for ^{13}C) or a Jeol GX-400 (399.65 MHz ^{1}H; 100 MHz ^{13}C) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane with reference to internal solvent. In cases where more than one rotamer is observed, both rotamers are reported. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000 FT-IR. High-resolution mass spectra were provided by either the Chemistry and Biology Mass Spectrometry Facility (Caltech) or the Southern California Mass Spectrometry Facility (University of California,

Riverside). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[52] Alkylidenes **1** and **2** were prepared according to published procedures.[13,14]

4,4-Dicarbethoxy-2-methyl-1,6-heptadiene (3a). To a suspension of sodium ethoxide (5.09 g, 74.9 mmol) in DMF (100 mL) was added diethyl allylmalonate (10.0 g, 49.9 mmol). After 15 min, methallyl chloride was added (4.52 g, 49.9 mmol). After stirring for 24 h at room temperature, the reaction was quenched with water (100 mL) and extracted with Et_2O (4 × 50 mL). Purification of the resultant orange oil on silica gel (10% EtOAc in hexanes) yielded **3a** (8.26 g, 65%) as a clear, colorless oil, as first reported by Doran:[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79−5.68 (m, 1H), 5.05−4.96 (m, 2H), 4.80 (s, 1H), 4.77 (s, 1H), 3.95−3.92 (m, 4H), 2.85−2.80 (m, 4H), 1.59 (s, 3H), 0.93 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 141.1, 133.4, 118.8, 115.9, 61.1, 57.2, 40.6, 37.4, 23.3, 14.0; IR (neat, cm^{-1}) 3079, 2982, 1731, 1644, 1446, 1367; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1507, found 254.1518.

4,4-Dicarbethoxy-1-methylcyclopentene (3b). To a solution of catalyst **1** (16 mg, 0.02 mmol) in dry, degassed methylene chloride (40 mL) was added diene **3a** (102 mg, 0.4 mmol). After stirring at room temperature for 24 h the reaction was concentrated and purified on silica gel (5% EtOAc in hexanes) to yield the product **3b** (83 mg, 91%) as a clear, colorless oil. The spectral data are in good agreement with that first reported by Schweizer.[53]

5,5-Dicarbethoxy-2-methyl-1,7-octadiene (4a). The diester **4a** was prepared in a manner similar to **3a** using 1-bromo-3-methyl-3-butene.[28] Compound **4a** was isolated as a clear, colorless oil (50%) in good agreement with the spectral data reported by Sato.[54]

4,4-Dicarbethoxy-1-methylcyclohexene (4b). Cyclohexene **4b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **3b**. The spectral data are in good agreement with those first reported by Schweizer.[53]

5,5-Dicarbethoxy-2-methyl-1,8-nonadiene (5a). The diester **5a** was prepared in a manner similar to that of **3a** using 1-bromo-3-methyl-3-butene and 1,1-dicarbethoxy-4-pentene. 1,1-Dicarbethoxy-4-pentene was also synthesized in a manner similar to that of **3a** using diethyl malonate and 1-bromo-3-butene. Compound **5a** was isolated as a clear, colorless oil (50%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77−5.66 (m, 1H), 5.05−4.89 (m, 2H), 4.80 (s, 1H), 4.74 (s, 1H), 3.95 (q, J = 7.7 Hz, 4H), 2.32−2.20 (m, 4H), 2.13−2.04 (m, 4H), 1.60 (s, 3H), 0.92 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 145.0, 137.9, 115.1, 110.7, 60.9, 57.4, 32.7, 32.2, 31.4, 28.9, 22.4, 14.0; IR (neat, cm^{-1}) 3077, 2797, 2939, 1732, 1643, 1454, 1367; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1900, found 283.1909.

5,5-Dicarbethoxy-1-methylcycloheptene (5b). To a solution of catalyst **1** (16 mg, 0.02 mmol) in dry, degassed methylene chloride (40 mL) was added diene **5a** (113 mg, 0.4 mmol). After stirring at room temperature for 4 days the reaction was concentrated and purified on silica gel (5% EtOAc in hexanes) to yield the product **5b** (98 mg, 96%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40 (s, 1H), 4.15 (q, J = 7.1 Hz, 4H), 2.19−2.12 (m, 8H), 1.65 (s, 3H), 1.22 (t, J = 7.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 138.9, 124.9, 61.3, 58.3, 32.2, 31.1, 29.7, 25.9, 25.9, 23.8, 14.2; IR (neat, cm^{-1}) 2966, 2853, 1732, 1447, 1367, 1292, 1180, 1035; HRMS calcd for $C_{14}H_{23}O_4$ (MH^+) 255.1588, found 255.1596.

5,5-Dicarbethoxy-2-methyl-1,9-decadiene (7a). The diester **7a** was synthesized in a manner similar to that of **3a** using 1,1-dicarbethoxy-4-pentene, which was prepared from diethyl malonate and 1-bromo-4-pentene. Compound **7a** was isolated as a clear, colorless oil (33%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78−5.69 (m, 1H), 5.01−4.90 (m, 2H), 4.67−4.66 (m, 2H), 4.14 (q, J = 7.1 Hz, 4H), 2.06−1.95 (m, 4H), 1.89−1.83 (m, 4H), 1.68 (s, 3H), 1.23−1.18 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 145.0, 138.2, 115.1, 110.3, 61.2, 57.3, 33.9, 31.7, 31.5, 30.6, 23.6, 23.2, 14.2; IR (neat, cm^{-1}) 3078, 2980, 2938, 1731, 1643, 1447, 1380, 1255, 1181, 1030; HRMS calcd for $C_{17}H_{29}O_4$ (MH^+) 297.2054, found 297.2066.

5,5-Dicarbethoxy-1,9-decadiene (8a). The diester **8a** was synthesized in a manner similar to that of **3a** using 1,1-dicarbethoxy-4-pentene and 1-bromo-4-pentene. **8a** was isolated as a clear, colorless oil (44%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76−5.65 (m, 1H), 4.99−4.87 (m, 4H), 4.11 (q, J = 7.2 Hz, 4H), 2.03−1.80 (m, 8H), 1.25−1.15 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 138.1, 137.7, 115.05, 114.98, 61.1, 57.2, 33.8, 31.7, 31.5, 28.4, 23.3, 14.1; IR (neat, cm^{-1}) 3079, 2980, 2874, 1732, 1642, 1447, 1368, 1260, 1032, 913; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1914, found 283.1909.

4,4-Dicarbethoxy-2,6-dimethyl-1,6-heptadiene (9a). The diester **9a** was synthesized in a manner similar to that of **3a** using diethyl methallylmalonate. Compound **9a** was isolated as a clear, colorless oil (72%) as first reported by Doran:[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.88−4.85 (m, 4H), 3.95 (q, J = 7.1 Hz, 4H), 3.01 (s, 4H), 1.68 (s, 6H), 0.91 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 141.6, 115.3, 61.1, 57.1, 41.0, 23.7, 13.9; IR (neat, cm^{-1}) 3078, 2981, 2937, 1732, 1446, 1367; HRMS calcd for $C_{15}H_{25}O_4$ (MH^+) 269.1755, found 269.1753.

4,4-Dicarbethoxy-1,2-dimethylcyclopentene (9b). A solution of **9a** (107 mg, 0.4 mmol) in dry, degassed benzene (4 mL) was added to alkylidene **2** (12.0 mg, 0.02 mmol) and heated to 65 °C. After stirring for 24 h the reaction was concentrated and purified on silica gel (10% EtOAc in hexanes) to yield **9b** as a clear, colorless oil (89 mg, 93%):[55] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (q, J = 7.0 Hz, 4H), 2.90 (s, 4H), 1.57 (s, 6H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 128.2, 61.6, 57.2, 45.9, 14.2, 13.5; IR (neat, cm^{-1}) 3468, 2981, 2859, 1732, 1446, 1366, 1253, 1076, 1020; HRMS calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362, found 240.1362.

4,4-Dicarbethoxy-2,7-dimethyl-1,7-octadiene (10a). The diester **10a** was synthesized in a manner similar to that of **3a** using diethyl methallylmalonate and 1-bromo-3-methyl-3-butene. Compound **10a** was isolated as a clear, colorless oil (65%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (s, 1H), 4.68 (s, 1H), 4.62 (s, 2H), 4.17−4.10 (m, 4H), 2.66 (s, 2H), 1.99-1.93 (m, 2H), 1.84−1.79 (m, 2H), 1.65 (s, 3H), 1.59 (s, 3H), 1.19 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 144.9, 140.6, 115.6, 110.3, 61.2, 56.6, 40.0, 32.2, 30.4, 23.1, 22.5, 14.1; IR (neat, cm^{-1}) 3077, 2981, 2940, 1732, 1650, 1448, 1368, 1259, 1093, 1031; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1915, found 283.1909.

4,4-Dicarbethoxy-1,2-dimethylcyclohexene (10b). Cyclohexene **10b** was obtained as a clear colorless oil (61%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (q, J = 7.1 Hz, 4H), 2.43 (s, 2H), 2.11−2.07 (m, 2H), 1.99−1.97 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 124.7, 123.0, 61.3, 54.0, 36.6, 28.8, 28.2, 19.2, 18.9, 14.3; IR (neat, cm^{-1}) 2982, 2913, 1732, 1446, 1367, 1297, 1177, 1090, 1031; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1513, found 254.1518.

4,4-Dicarbethoxy-2-ethyl-1,6-heptadiene (11a). The diester **11a** was synthesized in a manner similar to that of **3a** using 2-(bromomethyl)-1-butene.[30] Compound **11a** was isolated as a clear, colorless oil (50%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65−5.53 (m, 1H), 5.02−4.97 (m, 2H), 4.80 (s, 1H), 4.70 (s, 1H), 4.14−4.03 (m, 4H), 2.62 (s, 2H), 2.57 (d, J = 7.4 Hz, 2H), 1.84 (q, J = 7.4 Hz, 2H), 1.16 (t, J = 7.1 Hz, 6H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 146.1, 132.8, 118.9, 113.1, 61.2, 57.1, 38.3, 36.8, 29.3, 14.1, 12.4; IR (neat, cm^{-1}) 3080, 2982, 2879, 1732, 1642, 1446, 1368, 1288, 1096, 1042; HRMS calcd for $C_{15}H_{25}O_4$ (MH^+) 269.1751, found 269.1753.

4,4-Dicarbethoxy-1-ethylcyclopentene (11b). Cyclopentene **11b** was obtained as a clear, colorless oil (93%) under

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conditions analogous to the reaction producing **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.18−5.16 (m, 1H), 4.15 (q, J = 7.1 Hz, 4H), 2.95 (s, 2H), 2.89 (s, 2H), 2.06−1.99 (m, 2H), 1.23 (t, J = 7.1 Hz, 6H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 143.7, 119.2, 61.6, 59.2, 43.2, 40.7, 23.8, 14.2, 12.2; IR (neat, cm^{-1}) 3057, 2969, 2878, 1732, 1464, 1367, 1252, 1183, 1097, 1015; HRMS calcd for $C_{13}H_{20}O_4$ (M^+) 240.1353, found 240.1362.

4,4-Dicarbethoxy-2-phenyl-1,6-heptadiene (16a). The diester **16a** was synthesized in a manner similar to that of **3a** using α-(bromomethyl)styrene.[33] Compound **16a** was isolated as a clear, colorless oil (74%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.23 (m, 5H), 5.67−5.55 (m, 1H), 5.26 (s, 1H), 5.16 (s, 1H), 5.08−5.02 (m, 2H), 3.96−3.75 (m, 4H), 3.16 (s, 2H), 2.58 (d, J = 7.3 Hz, 2H), 1.13 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 144.6, 141.7, 132.6, 128.0, 127.5, 127.0, 119.2, 118.7, 61.1, 57.2, 37.2, 36.1, 14.0; IR (neat, cm^{-1}) 3082, 2983, 1732, 1642, 1627, 1601, 1575, 1446, 1368, 1287, 1047; HRMS calcd for $C_{19}H_{25}O_4$ (MH^+) 317.1743, found 317.1753.

4,4-Dicarbethoxy-1-phenylcyclopentene (16b). Cyclopentene **16b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.25 (m, 5H), 6.03 (t, J = 2.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 4H), 3.44−3.42 (m, 2H), 3.24−3.22 (m, 2H), 1.28 (t, J = 7.1 Hz, 6H); ^{13}C NMR (C_6D_6, 75 MHz) δ 172.2, 140.2, 136.1, 129.0, 128.0, 126.4, 123.0, 61.9, 59.6, 42.0, 41.9, 14.4; IR (neat, cm^{-1}) 3058, 2982, 2867, 1732, 1600, 1576, 1447, 1367, 1258, 1183, 1073, 1017; HRMS calcd for $C_{17}H_{21}O_4$ (MH^+) 289.1431, found 289.1440.

2-Carbomethoxy-4,4-dicarbethoxy-1,6-heptadiene (17a). To a suspension of K_2CO_3 (1.09 g, 7.91 mmol) in acetone (50 mL) was added 4,4-dicarbethoxy-1,6-heptadiene 2-carboxylic acid (1.50 g, 5.28 mmol) and CH_3I (9.9 mL, 158.3 mmol). After stirring for 24 h at room temperature, the reaction was quenched with $NaHCO_3$ (saturated aqueous, 75 mL) and extracted with Et_2O (4 × 60 mL). After concentration, the yellow oil obtained was purified with silica gel (20% EtOAc in hexanes). 4,4-Dicarbethoxy-1,6-heptadiene 2-carboxylic acid was prepared in a manner similar to that of **3a** using 2-(bromomethyl)acrylic acid. Compound **17a** was obtained as a pale yellow, colorless oil (1.02 g, 65%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.17 (s, 1H), 5.67−5.56 (m, 2H), 5.02−4.97 (m, 2H), 4.11−4.01 (m, 4H), 3.62 (s, 3H), 2.87 (s, 2H), 2.49 (d, J = 7.3 Hz, 2H), 1.15 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 167.3, 135.9, 132.5, 129.3, 119.2, 61.3, 57.5, 51.8, 37.1, 33.6, 14.0; IR (neat, cm^{-1}) 3080, 2983, 2908, 1732, 1632, 1445, 1368, 1155, 1053, 1008; HRMS calcd for $C_{15}H_{23}O_6$ (MH^+) 299.1482, found 299.1495.

1-Carbomethoxy-4,4-dicarbethoxycyclopentene (17b). Cyclopentene **18b** was obtained as a clear, colorless oil (89%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.56 (s, 1H), 4.14 (q, J = 7.1 Hz, 4H), 3.67 (s, 3H), 3.20−3.19 (m, 2H), 3.13−3.12 (m, 2H), 1.20 (t, J = 7.1 Hz, 6Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 164.5, 139.9, 133.5, 61.9, 58.7, 51.7, 41.1, 39.5, 14.1; IR (neat, cm^{-1}) 2984, 1732, 1644, 1436, 1367, 1246, 1184, 1069, 1015; HRMS calcd for $C_{13}H_{19}O_6$ (MH^+) 271.1180, found 271.1182.

2-(Acetoxymethyl)-4,4-dicarbethoxy-1,6-heptadiene (14a). To a solution of 2-methylene-1,3-propanediol (5.0 g, 56.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Ac_2O (5.8 g, 56.7 mmol) and NEt_3 (8.6 g, 85.1 mmol). This solution was allowed to warm to rt for 5 h and then quenched with water (75 mL) and washed with $NaHCO_3$ (saturated aqueous, 75 mL). Upon concentration of the organic portion, a pale yellow oil was isolated and the crude acetate was used without further purification. To a solution of this 2-(acetoxymethyl)-3-propen-1-ol (3.6 g, 27.5 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added PPh_3 (10.8 g, 41.3 mmol) and CBr_4 (13.7 g, 41.3 mmol). After stirring for 40 min the solvent was removed and the red viscous oil was eluted through a plug of silica gel with Et_2O. Concentration of the resulting solution gave a clear, colorless oil, and this crude bromide was used without further purification. The triester **14a** was synthesized in a manner similar to that of **3a** using this 1-bromo-2-(acetoxymethyl)-2-propene. Compound **14a** was isolated as a clear, colorless oil (28%, 3 steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56−5.46 (m, 1H), 5.04−4.86 (m, 4H), 4.27 (s, 2H), 4.07−3.96 (m, 4H), 2.57 (s, 2H), 2.51 (d, J = 7.3 Hz, 2H), 1.92 (s, 3H), 1.09 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.1, 138.9, 132.2, 119.1, 117.2, 66.6, 61.2, 56.9, 37.0, 35.4, 20.7, 13.9; IR (neat, cm^{-1}) 3082, 2984, 2908, 1732, 1644, 1446, 1368, 1226, 1031, 922; HRMS calcd for $C_{16}H_{25}O_6$ (MH^+) 313.1641, found 313.1651.

1-(Acetoxymethyl)-4,4-dicarbethoxycyclopentene (14b). Cyclopentene **14b** was obtained as a clear, colorless oil (98%) under conditions analogous to the reaction producing **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.51 (br s, 1H), 4.54 (s, 2H), 4.14 (q, J = 7.1 Hz, 4H), 2.98 (s, 2H), 2.95 (s, 2H), 2.02 (s, 3H), 1.20 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 170.8, 136.3, 125.6, 62.3, 61.7, 59.1, 40.9, 40.5, 20.9, 14.1; IR (neat, cm^{-1}) 2984, 2909, 1732, 1446, 1367, 1242, 1097, 1022, 972; HRMS calcd for $C_{14}H_{20}O_6$ (M^+) 284.1260, found 284.1260.

4,4-Dicarbethoxy-2-(hydroxymethyl)-1,6-heptadiene (15a). Lump Na (100 mg, 4.34 mmol) was added to anhydrous ethanol (50 mL). After the metal was no longer visible, **14a** (1.24 g, 3.95 mmol) was added to the solution. After stirring for approximately 30 min at room temperature, no starting material spot was observed by TLC (33% EtOAc in hexanes, anisaldehyde). The reaction was quenched with NH_4Cl (saturated aqueous, 30 mL) and extracted with EtOAc (5 × 30 mL). After purification on silica gel (33% EtOAc in hexanes) **15a** was obtained as a clear, colorless oil (57%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65−5.56 (m, 1H), 5.09−5.01 (m, 3H), 4.84 (s, 1H), 4.14−4.06 (m, 4H), 3.90 (s, 2H), 2.73 (s, 1H), 2.63−2.59 (m, 4H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 144.3, 132.3, 119.4, 114.7, 65.6, 61.5, 57.5, 38.0, 35.8, 14.1; IR (neat, cm^{-1}) 3544, 3080, 2983, 2937, 1738, 1644, 1446, 1418, 1368, 1046, 918; HRMS calcd for $C_{14}H_{22}O_5$ (M^+) 270.1469, found 270.1467.

4,4-Dicarbethoxy-1-(hydroxymethyl)cyclopentene (15b). Cyclopentene **15b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.45−5.43 (m, 1H), 4.18−4.09 (m, 6H), 2.98−2.95 (m, 4H), 2.46 (br s, 1H), 1.20 (t, J = 7.1 Hz, 6H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 141.6, 122.2, 61.7, 61.3, 59.2, 40.7, 40.5, 14.1; IR (neat, cm^{-1}) 3462, 2982, 2871, 1732, 1446, 1392, 1368, 1257, 1184, 1072, 1017; HRMS calcd for $C_{12}H_{18}O_5$ (M^+) 242.1148, found 242.1154.

4,4-Dicarbethoxy-2-isopropyl-1,6-heptadiene (12a). The diester **12a** was synthesized in a manner similar to that of **3a** using 2-(bromomethyl)-3-methyl-1-butene.[31] Compound **12a** was obtained as a clear, colorless oil (33%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69−5.58 (m, 1H), 5.08−5.01 (m, 2H), 4.86 (s, 1H), 4.70 (s, 1H), 4.18−4.08 (m, 4H), 2.69−2.62 (m, 4H), 2.03−1.98 (m, 1H), 1.21 (t, J = 7.1 Hz, 6H), 0.97 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 151.1, 133.0, 119.0, 111.0, 61.4, 57.5, 37.3, 37.3, 37.0, 33.8, 22.1, 14.2; IR (neat, cm^{-1}) 3082, 2964, 2874, 1732, 1641, 1443, 1366, 1288, 1209, 1050; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1912, found 283.1909.

4,4-Dicarbethoxy-1-isopropylcyclopentene (12b). To a solution of catalyst **1** (16 mg, 0.02 mmol) in dry, degassed methylene chloride (40 mL) was added diene **12a** (113 mg, 0.4 mmol). After stirring at room temperature for 2 days the reaction was concentrated and purified on silica gel (5% EtOAc in hexanes) to yield the product **12b** (100 mg, 98%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.16−5.14 (m, 1H), 4.20−4.12 (m, 4H), 2.94 (s, 2H), 2.92 (s, 2H), 2.30−2.24 (m, 1H), 1.21 (t, J = 8.6 Hz, 6H), 1.00 (d, J = 8.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 148.2, 118.2, 61.5, 59.3, 41.3, 40.4, 29.6, 21.3, 14.2; IR (neat, cm^{-1}) 3062, 2963, 1732, 1466, 1447, 1367, 1248, 1182, 1097, 1074; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1519, found 254.1518.

4,4-Dicarbethoxy-2-*tert*-butyl-1,6-heptadiene (13a). The diester **13a** was synthesized in a manner similar to that of **3a** using 2-(bromomethyl)-3,3-dimethyl-1-butene.[32] Compound **13a** was obtained as a clear, colorless oil (75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70−5.61 (m, 1H), 5.09−5.03 (m, 2H), 4.92 (s, 1H), 4.62 (s, 1H), 4.17 (q, J = 7.2 Hz, 4H), 2.80 (d, J = 7.5 Hz, 2H), 2.72 (s, 2H), 1.23 (t, J = 7.1 Hz, 6H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 152.2, 132.9, 118.9, 107.0, 61.4, 56.7, 36.8, 36.7, 32.8, 29.4, 14.2; IR (neat, cm^{-1})

3080, 2970, 2873, 1732, 1639, 1466, 1445, 1365, 1298, 1220, 918; HRMS calcd for $C_{17}H_{29}O_4$ (MH^+) 297.2058, found 297.2066.

4,4-Dicarbethoxy-1-*tert*-butylcyclopentene (13b). Cyclopentene **13b** was obtained as a clear, colorless oil (96%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (br s, 1H), 4.16 (q, J = 7.0 Hz, 4H), 2.92 (s, 4H), 1.21 (t, J = 7.0 Hz, 6H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 151.0, 117.5, 61.4, 59.6, 40.2, 39.8, 32.7, 28.9, 14.1; IR (neat, cm^{-1}) 2964, 2870, 1732, 1464, 1392, 1365, 1249, 1185, 1062; HRMS calcd for $C_{15}H_{25}O_4$ (MH^+) 269.1747, found 269.1753.

5,5-Dicarbethoxy-3-methylene-1,7-octadiene (19a). The diester **19a** was synthesized in a manner similar to that of **3a** using 2-(bromomethyl)-1,3-butadiene.[34−36] Compound **19a** was isolated as a clear, colorless oil (54%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25−6.16 (m, 1H), 5.64−5.55 (m, 1H), 5.20−5.10 (m, 2H), 5.03−4.91 (m, 3H), 4.11−3.98 (m, 4H), 2.76 (s, 2H), 2.57 (d, J = 7.2 Hz, 2H), 1.15 (t, J = 6.9 Hz, 6H); ^{13}C NMR (C_6D_6, 75 MHz) δ 170.7, 142.1, 139.5, 133.5, 118.91, 118.89, 113.8, 61.1, 57.6, 37.3, 34.0, 14.0; IR (neat, cm^{-1}) 3085, 2982, 1732, 1641, 1595, 1446, 1367, 1296, 1207, 907; HRMS calcd for $C_{15}H_{23}O_4$ (MH^+) 267.1607, found 267.1596.

5,5-Dicarbethoxy-3-methylenecycloxene (19c). Cyclohexene **19c** was obtained as a clear, colorless oil (96%) under conditions analogous to the reaction producing **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.11 (d, J = 9.8 Hz, 1H), 5.78−5.73 (m, 1H), 4.88 (br s, 2H), 4.19−4.08 (m, 4H), 2.82 (t, J = 1.5 Hz, 2H), 2.65−2.63 (m, 2H), 1.19 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 139.2, 129.0, 126.6, 113.6, 61.6, 54.0, 36.0, 31.1, 14.1; IR (neat, cm^{-1}) 3083, 2982, 1732, 1642, 1603, 1446, 1367, 1299, 1187, 1074, 1016; HRMS calcd for $C_{13}H_{18}O_4$ (M^+) 238.1206, found 238.1205.

***N*-Allyl-*N*-methallylbenzamide (20a).** To a solution of allyl amine (0.89 g, 15.5 mmol) in CH_2Cl_2 (50 mL) was added benzoyl chloride (2.2 g, 15.5 mmol). After 7 h, the reaction was quenched with water (30 mL) and washed with NH_4Cl (saturated aqueous, 30 mL). After concentration, a pale yellow oil was isolated and the crude amide was used without further purification. To a suspension of NaH (0.26 g, 10.9 mmol) in DMF (35 mL) was added this *N*-allylbenzamide (1.6 g, 9.9 mmol). After stirring for 15 min, methallyl chloride (0.98 mL, 9.9 mmol) was added. Once the reaction had stirred for 2 h, it was quenched with water (50 mL) and extracted with Et_2O (3 × 30 mL). After purification on silica gel (25% EtOAc in hexanes), **20a** was obtained as a clear, colorless oil (78%): ^{1}H NMR ($CDCl_3$, 300 MHz, rt, not coalesced) δ 7.33−7.23 (m, 5H), 5.84−5.76, 5.64−5.55 (2m, 1H), 5.13−5.00 (m, 2H), 4.86−4.75 (m, 2H), 4.04 (s, 2H), 3.70−3.64 (m, 2H), 1.68, 1.48 (2s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, rt, not coalesced) δ 171.6, 140.3, 140.0, 136.1, 132.9, 132.6, 129.3, 128.2, 126.3, 117.4, 112.1, 53.7, 50.2, 49.0, 46.8, 19.9; IR (neat, cm^{-1}) 3648, 3496, 3082, 2977, 2918, 1634, 1578, 1495, 1293, 1263, 1152, 923; HRMS calcd for $C_{14}H_{16}NO$ (M^+) 214.1230, found 214.1232.

***N*-Benzoyl-3-methyl-3-pyrroline (20b).** Pyrroline **20b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **12b**: ^{1}H NMR ($CDCl_3$, 300 MHz, rt, not coalesced) δ 7.46 (br s, 2H), 7.34 (br s, 3H), 5.45, 5.29 (2s, 1H), 4.36, 4.28 (2s, 2H), 4.10, 4.02 (2s, 2H), 1.76, 1.65 (2s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, rt, not coalesced) δ 169.8, 136.8, 135.6, 134.8, 129.9, 128.4, 126.9, 119.6, 119.0, 59.1, 56.5, 56.3, 53.8, 14.34, 14.26; IR (neat, cm^{-1}) 3545, 3062, 2914, 2858, 1674, 1634, 1576, 1418, 1334, 1226, 1149, 1025, 967; HRMS calcd for $C_{12}H_{13}NO$ (M^+) 187.0997, found 187.0997.

4,4-Dicarbethoxy-2-methyl-1,8-nonadiene (6a). The diester **6a** was synthesized in a manner similar to that of **3a** using 1,1-dicarbethoxy-5-pentene. Compound **6a** was isolated as a clear, colorless oil (68%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72−5.62 (m, 1H), 4.94−4.83 (m, 2H), 4.75 (s, 1H), 4.64 (s, 1H), 4.12−4.05 (m, 4H), 2.62 (s, 2H), 1.96 (q, J = 7.1 Hz, 2H), 1.83−1.77 (m, 2H), 1.56 (s, 3H), 1.26−1.14 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 140.7, 138.1, 115.4, 114.9, 61.1, 56.8, 40.1, 33.8, 31.6, 23.5, 23.2, 14.0; IR (neat, cm^{-1}) 3078, 2981, 2938, 1732, 1643, 1446, 1368, 1262, 1196, 1027; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1911, found 283.1909.

6,6-Dicarbethoxy-1-methylcycloheptene (6b). Cycloheptene **6b** was obtained as a clear, colorless oil (96%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (br s, 1H), 4.14 (q, J = 7.5 Hz, 4H), 2.61 (s, 2H), 2.18−2.14 (m, 2H), 2.04−2.00 (m, 2H), 1.72 (s, 3H), 1.61−1.58 (m, 2H), 1.21 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 135.2, 127.7, 61.2, 55.7, 37.6, 36.9, 28.0, 26.8, 22.9, 14.2; IR (neat, cm^{-1}) 2937, 2862, 1732, 1446, 1367, 1311, 1224, 1033, 857; HRMS calcd for $C_{14}H_{23}O_4$ (MH^+) 255.1601, found 255.1596.

2-Bromo-4,4-dicarbethoxy-1,6-heptadiene (18a). The diester **18a** was synthesized in a manner similar to that of **3a** using 2,3-dibromopropene. Compound **18a** was obtained as a clear, colorless oil (96%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.61−5.50 (m, 3H), 5.04−5.01 (m, 2H), 4.15−4.07 (m, 4H), 3.05 (s, 2H), 2.67 (d, J = 7.4 Hz, 2H), 1.17 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 132.1, 127.2, 122.0, 119.5, 61.5, 56.7, 42.8, 35.9, 14.0; IR (neat, cm^{-1}) 3081, 2983, 2938, 1732, 1641, 1626, 1445, 1367, 1287, 1218, 1149, 1041; HRMS calcd for $C_{13}H_{20}O_4Br$ (M^+) 319.0545, found 319.0545.

Methallyl 1-Phenylallyl Ether (21a). To a solution of benzaldehyde (1.6 g, 14.9 mmol) in THF (100 mL) at 0 °C was added vinylmagnesium bromide (1 M in THF, 15 mL). After 3 h, the reaction was quenched with water (100 mL) and extracted with Et_2O (3 × 75 mL). After concentration, a pale yellow oil was isolated and the crude alcohol was used without further purification. To a suspension of NaH (0.22 g, 9.10 mmol) in DMF (25 mL) was added this 1-phenyl-2-propen-1-ol (1.11 g, 8.27 mmol). After this mixture had stirred for 15 min, methallyl chloride (0.90 mL, 9.10 mmol) was added. After stirring for 2 h at room temperature, the reaction was quenched with water (25 mL) and extracted with Et_2O (3 × 30 mL). After purification on silica gel (25% toluene in hexanes), **21a** was obtained as a clear, colorless oil (21%, two steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.28 (m, 5H), 6.00−5.89 (m, 1H), 5.31−5.18 (m, 2H), 4.99 (s, 1H), 4.90 (s, 1H), 4.77 (d, J = 6.6Hz, 1H), 3.89 (s, 2H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4, 141.3, 139.1, 128.6, 127.7, 127.0, 116.2, 112.2, 81.9, 72.2, 19.8; IR (neat, cm^{-1}) 3078, 3030, 2977, 2918, 2856, 1657, 1452, 1092, 1070, 991, 925, 900, 701; HRMS calcd for $C_{13}H_{16}O$ (M^+) 188.1202, found 188.1201.

4-Methyl-2-phenyl-2,5-dihydrofuran (21b). Dihydrofuran **21b** was obtained as a clear, colorless oil (98%) under conditions analogous to the reaction producing **21b**:[56] ^{1}H NMR (C_6D_6, 300 MHz) δ 7.27−7.24 (m, 2H), 7.17−7.03 (m, 3H), 5.76−5.74 (m, 1H), 5.16−5.14 (m, 1H), 4.49−4.41 (m, 2H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8, 136.6, 128.6, 127.8, 126.5, 124.2, 88.6, 78.6, 12.4; IR (neat, cm^{-1}) 3064, 3030, 2837, 2630, 1668, 1491, 1453, 1258, 1061, 970, 760, 699; HRMS calcd for $C_{11}H_{11}O$ (M-H$^+$) 159.0806, found 159.0810.

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Supporting Information Available: ^{1}H NMR spectra of **5b**, **6a**,**b**, **11**−**21a**, **10**−**20b** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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