Macrocycle Formation by Catalytic Intramolecular Cyclopropanation. A New General Methodology for the Synthesis of Macrolides

Michael P. Doyle,*,†,§ Chad S. Peterson,† Marina N. Protopopova,† Alan B. Marnett,† Dann L. Parker, Jr.,† Doina G. Ene,† and Vincent Lynch*,‡

Contribution from the Department of Chemistry, Trinity University, San Antonio, Texas 78212, and the Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

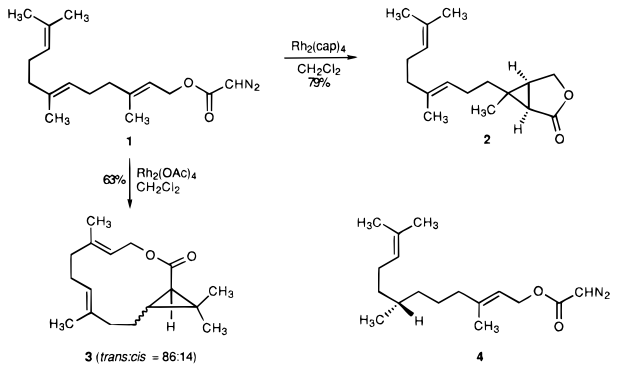
Received May 22, 1997[⊗]

Abstract: Catalytic intramolecular cyclopropanation by diazoacetates onto a remote carbon−carbon double bond resulting in the formation of 9- to 20-membered ring lactones is reported. When competition exists between proximal allylic and remote olefinic cyclopropanation, macrocyclization is favored by catalysts of increasing electrophilicity: $Rh_2(pfb)_4$ > $Rh_2(OAc)_4$, $Cu(MeCN)_4PF_6$ > $Rh(cap)_4$, and $Cu(acac)_2$. Terpene systems, *cis*-nerolidyl diazoacetate and related structures, malonic ester derivatives, and those with 1,2-benzenedimethanol, pentaerythritol, and *cis*-2-buten-1,4-diol linkers all undergo cyclopropanation onto the most remote carbon−carbon double bond in good yield. Generally, only one cyclopropane diastereoisomer is observed, but increasing ring size allows stereochemistries in macrocyclization reactions that resemble those of their intermolecular cyclopropanation counterparts. In one system (**25**) macrocyclic addition is accompanied by ylide formation/[2,3]-sigmatropic rearrangement resulting in the formation of a 10-membered ring lactone. Overall, few limits to macrocycle formation are evident, and the methodology appears to have general applicability.

The synthesis of macrocycles is rich in methodology and important for the construction of numerous biologically significant compounds.[1−4] Although macrocyclic systems can be generated by cleavage of internal bonds in polycyclic systems and by ring expansion,[5] the methods of choice involve entropically disfavored end-to-end cyclization of open, long-chain precursors, generally with the required use of high dilution techniques.[6] Rates for macrocyclization are intermediate between highly favored five- or six-membered ring formation and the intermolecular transformation, and a variety of ingenious processes have been devised to circumvent competition from intermolecular reactions in large ring syntheses.

A recent communication has suggested catalytic cyclopropanation to be a new methodology for the construction of macrocyclic lactones. Doyle, Poulter, and co-workers have reported that whereas *trans,trans*-farnesyl diazoacetate (**1**) underwent intramolecular cyclopropanation exclusively at the allylic double bond to form **2** with the use of dirhodium(II) carboxamidates, including dirhodium(II) caprolactamate [$Rh_2(cap)_4$] and those with chiral ligands, with the use of dirhodium(II) carboxylates addition took place solely at the terminal double bond to produce a 13-membered cyclopropane-fused lactone (Scheme 1).[7] High dilution was not required, and macrocycle **3** was formed in relatively high yield and with diastereoselectivity that was dependent on the catalyst ligands. With consideration that the internal double bond could be responsible, at least in part, for the macrocyclization, (−)-(7*R*)-6,7-dihydrofarnesyl diazoacetate (**4**) was treated with the same selection of catalysts only to find similar results: $Rh_2(cap)_4$ catalyzed intramolecular allylic cyclopropanation exclusively, whereas with $Rh_2(OAc)_4$ or dirhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$] macrolide formation was the major outcome. We now wish to report investigations with diverse sets of molecular frameworks possessing terminal alkene and diazoacetate units that demonstrate the broad applicability of this catalytic intramolecular cyclopropanation methodology for macrolide formation.

Scheme 1



Results

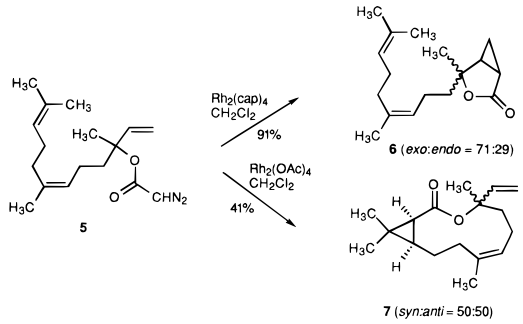
***cis*-Nerolidol and Related Systems.** We have previously reported that the diazoacetate formed from (+)-*cis*-nerolidol underwent allylic cyclopropanation in reactions catalyzed by $Rh_2(cap)_4$ but that $Rh_2(OAc)_4$ catalysis resulted in macrocyclization without significant competition from cyclopropanation of the allylic double bond (Scheme 2). Only the *cis*-fused cyclopropane stereoisomer of the 11-membered macrocycle **7**

† Department of Chemistry, Trinity University.
‡ Department of Chemistry and Biochemistry, The University of Texas at Austin.
§ Current address: Department of Chemistry, University of Arizona, Tucson, AZ 85721.
⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1997.

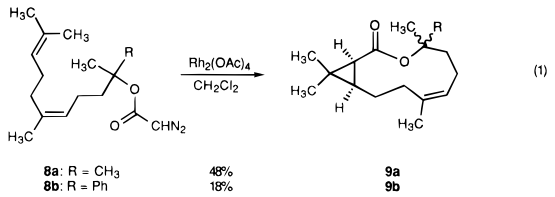
(1) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683−710.
(2) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624.
(3) Tius, M. A. *Chem. Rev.* **1988**, *88*, 719−732.
(4) Bradshaw, J. S.; Scott, P. E. *Tetrahedron* **1980**, *36*, 461−570.
(5) Stach, H.; Hesse, M. *Tetrahedron* **1988**, *44*, 1573−1590.
(6) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767−9822.
(7) Doyle, M. P.; Protopopova, M. N.; Poulter, C. D.; Rogers, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 7281−7282.

S0002-7863(97)01687-9 CCC: $14.00

Scheme 2



was produced, but diastereocontrol at the methyl/vinyl-substituted carbon was random (50:50). In addition, limited diastereocontrol, anticipated from prior studies,[8,9] was achieved in the formation of **6**. Structural modification of **5** resulting from Grignard addition to nerylacetone followed by diazoacetate formation gave **8a,b**, which also underwent macrocyclization in reactions catalyzed by $Rh_2(OAc)_4$ (eq 1). Once again, only the *cis*-fused cyclopropane isomers were formed and, although



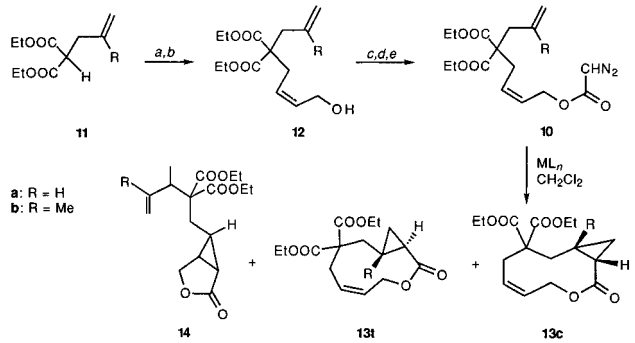
(1)

only a single isomer of **9a** could be produced, diastereoselectivity for **9b**, like that for **7**, was low (<60:40). With $Rh_2(pfb)_4$, a catalyst proven to be most suitable for macrocyclic aromatic cycloaddition,[10] complex product mixtures were observed in which **9** was a minor product. The *cis*-cyclopropane stereochemistry of **9** was evident from the coupling constant between cyclopropane hydrogens ($J = 9.2-9.4$ Hz).[11,12]

Malonic Ester Derivatives. The syntheses of **10a,b** provided the frame work for evaluation of competitive intramolecular cyclopropanation of allylic and remote double bonds. The preparation of **10a,b** was accomplished in high yield by sequential alkylation followed by diketene-derived diazoacetate formation (Scheme 3). Catalytic diazo decomposition of **10a,b** produced the 10-membered ring macrocycle **13** and γ-lactone **14** in high yields and with regioselectivities that were dependent on the catalyst and the substituent R (Table 1).

Use of $Rh_2(cap)_4$ with **10a** resulted in the allylic cyclopropanation product **14a** virtually exclusively, but with the methallyl derivative **10b** the macrocyclic product **13c** was the major product even in reactions catalyzed by $Rh_2(cap)_4$. The copper catalyst $Cu(MeCN)_4PF_6$ is similar to $Rh_2(OAc)_4$ in its reactivity and selectivity, but $Cu(acac)_2$ is comparable to $Rh_2(cap)_4$. Both *cis* and *trans*-macrolide cyclopropanes were formed from **10a** with $Rh_2(pfb)_4$, $Rh_2(OAc)_4$, and $Cu(MeCN)_4PF_6$, but only the cis isomer was produced from **10b**. The *cis/trans* ratio (**13ac/13at**) was relatively independent of the catalyst employed.

Scheme 3[a]



[a] (a) NaH/THF, then *cis*-TBDMSOCH$_2$CH=CHCH$_2$OMs; (b) Bu_4NF/THF; (c) diketene/Et_3N (catalyst)/THF; (d) $MeSO_2N_3/Et_3N$; (e) LiOH, THF/H_2O, 0 °C.

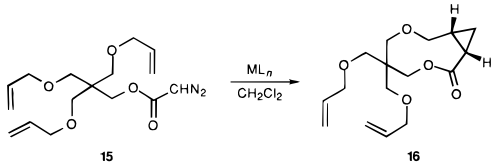
Table 1. Product Distributions from Diazo Decomposition of **10**[a]

substrates, R =	catalyst	isolated yield,[b]	relative yield,[c] % 13c	13t	14
H	$Rh_2(pfb)_4$	68	55	44	1
	$Rh_2(OAc)_4$	72	50	40	10
	$Rh_2(cap)_4$	82	1	*t*	99
	$CuPF_6$	66	60	35	5
	$Cu(acac)_2$	55			100
CH_3	$Rh_2(pfb)_4$	87	96		4
	$Rh_2(OAc)_4$	87	96		4
	$Rh_2(cap)_4$	53	62		38
	$CuPF_6$	89	93		7

[a] Reactions performed in refluxing CH_2Cl_2 using 1.0 mol % of catalyst. [b] Product yield after chromatography. [c] Determined by GC analysis.

Stereochemistry at the cyclopropane ring was elucidated from proton coupling constants ($J_{trans} = 9.0$ Hz, $J_{cis} = 13.5$ Hz).

Pentaerythritol as Linker. The diazoacetate of pentaerythritol triallyl ether (**15**) is constructed to undergo competitive ylide formation/[2,3]-sigmatropic rearrangement[13,14] and intramolecular cyclopropanation, but only intramolecular cyclopropanation resulting in the nine-membered ring lactone **16** having the *cis*-disubstituted cyclopropane geometry is observed (eq 2). Oxonium ylide generation would have required the



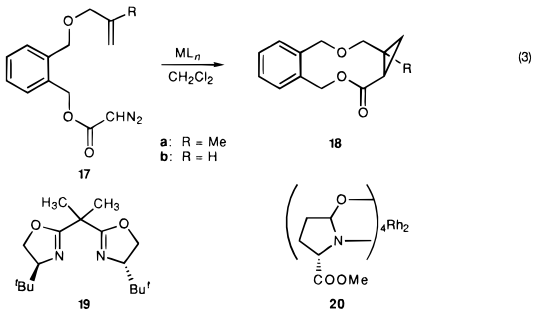
(2)

formation of a seven-membered ring which, although not previously reported for allyl ether derivatives,[13,14] has been achieved in O−H insertion reactions[15] and in sulfur ylide chemistry even for the formation of eight- and nine-membered rings.[16] However, the product expected from sigmatropic rearrangement was not observed, and, instead, cyclopropane-fused lactone **16** was formed in good yield by reaction with a spectrum of dirhodium(II) and copper catalysts: $Rh_2(pfb)_4$ (62%), $Rh_2(OAc)_4$ (71%), $Rh_2(cap)_4$ (33%), and $Cu(MeCN)_4PF_6$ (62%) with isolated yields of the purified product given in

(8) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493−4494.
(9) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021−11022.
(10) Doyle, M. P.; Protopopova, M. N.; Peterson, C. S.; Vitale, J. P.; McKervey, M. A.; Garcia, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 7865−7866.
(11) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometal.* **1984**, *3*, 44−52.
(12) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906−1912.
(13) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 2, Chapter 5.2.
(14) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263−309.
(15) Doyle, M. P.; Peterson, C. S.; Parker, D. L., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1334−1336.
(16) (a) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 4887−4906. (b) Kido, F.; Yamaji, K.; Sinha, S. C.; Abiko, T.; Kato, M. *Tetrahedron* **1995**, *51*, 7697−7714.

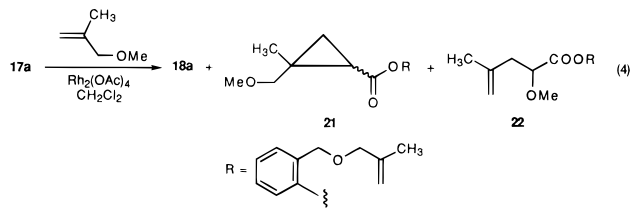
parentheses; $Cu(acac)_2$ did not cause cyclopropanation in refluxing CH_2Cl_2, but **16** was isolated in 42% yield following diazo decomposition of **15** using this catalyst in refluxing $ClCH_2$-CH_2Cl. With catalysts of decreasing reactivity toward remote double bonds, the amounts of carbene dimer and water insertion byproducts increase.

1,2-Benzenedimethanol as Linker. Recently reported results with diazoacetates derived from allyl-substituted 1,2-benzenedimethanol have shown that macrocyclization occurs in high yields in reactions (eq 3) catalyzed by $[Cu(MeCN)_4](PF_6)$/bis-oxazoline **19** and dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$ (**20**).[15] The extent of catalyst effectiveness for this transformation is evident in the broad spectrum of catalysts that produce **18** in high yield: $Rh_2(pfb)_4$,



72%; $Rh_2(OAc)_4$, 77%; $Rh_2(cap)_4$, 85%; $Cu(MeCN)_4PF_6$, 74%; and $Cu(acac)_2$, 86%. In contrast to reactions with **10**, which in cyclopropanation at the allylic position afforded an alternative pathway to macrocyclization for $Rh_2(cap)_4$ and $Cu(acac)_2$ catalysts (Table 1), all rhodium(II) and copper catalysts were effective for macrocyclization with **17**; product(s) from aromatic cycloaddition onto the 1,2-benzenedimethyl linker were not observed, nor were those from ylide formation. The allyl ether analog **17b** also underwent intramolecular cyclopropanation catalyzed by $Cu(MeCN)_4PF_6$, and macrocycle **18b** was isolated in 63% yield. The cis stereochemistry for **18b** was established from the coupling constants for cyclopropane ring hydrogens. The trans cyclopropane isomer of **18b** was not detected.

To ascertain the degree to which intramolecular cyclopropanation is favored over intermolecular cyclopropanation, competition reactions with methallyl methyl ether were performed. Methallyl methyl ether was selected, because it resembled the methallyl ether of **17a** most closely. Diazo compound **17a** was added to the reaction mixture containing methallyl methyl ether and $Rh_2(OAc)_4$ by controlled addition so that at any one time there was a large molar excess of external alkene, relative to internal alkene, present throughout the addition. In addition to intramolecular cyclopropanation product **18a**, both *E*- and *Z*-cyclopropane isomers from intermolecular cyclopropanation (**21**) and the product from intermolecular ylide formation/[2,3]-sigmatropic rearrangement (**22**) were formed (eq 4). Figure 1



reports relative yields of intramolecular (**18a**) and intermolecular (**21** + **22**) reaction products as a function of alkene concentration. Isolated yields were 85 ± 2%, and the ***E*-/*Z*-21** product ratio was 1.0:1.0. The extent of ylide formation varied slightly

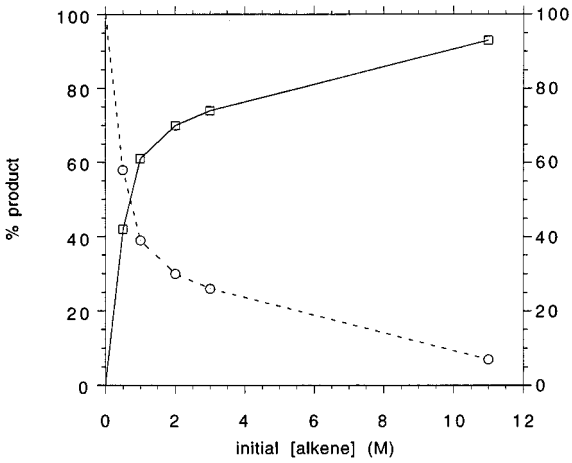
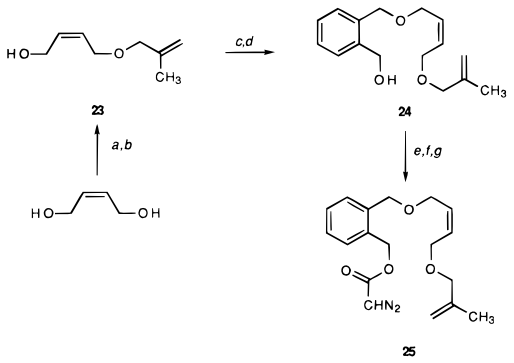


Figure 1. Relative yield of intramolecular (○) and intermolecular (□) reaction products from **17a** catalyzed by $Rh_2(OAc)_4$ as a function of alkene concentration.

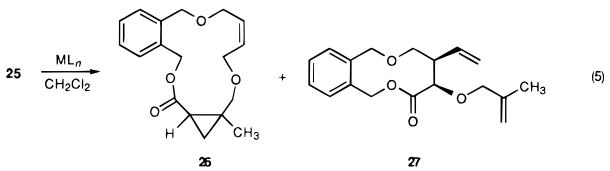
Scheme 4[a]



[a] (a) NaH; (b) $H_2C{=}C(Me)CH_2Br$; (c) MsCl, Et_3N, O °C; (d) 1,2-benzene−dimethanol, NaH/THF; (e) diketene, Et_3N/THF; (f) MsN_3, Et_3N/THF; (g) LiOH (4 equiv), H_2O/THF, 0 °C.

(21 → 29% relative yield of intermolecular reaction products) over the range of olefin concentrations employed.

Further extension of the distance between the carbene center and a site for intramolecular cyclization was achieved with the use of *cis*-2-buten-1,4-diyl as an extender onto 1,2-benzenedimethanol (Scheme 4). With this system potential competition exists not only between cyclopropanation, aromatic cycloaddition, and ylide formation/rearrangement but also in regioselectivity (1 → 10 versus 1 → 15 addition) and diastereoselectivity (*cis*- or *trans*-cyclopropane product). Catalytic diazo decomposition of **25** resulted in the formation of products (eq 5) from intramolecular cyclopropanation at the 15,16-double bond, solely

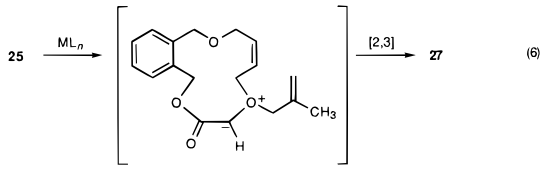


as the *Z*-cyclopropane stereoisomer (**26**), and from ylide formation/[2,3]-sigmatropic rearrangement (**27**). The product from intramolecular cyclopropanation at the 10,11-double bond was not observed, nor were there products from intramolecular aromatic cycloaddition. The influence of catalyst on selectivity is seen in the results presented in Table 2. The production of **27**, which arose from oxonium ylide formation with regioselective and stereoselective [2,3]-sigmatropic rearrangement (eq 6) into the *cis*-2-buten-1,4-diyl linker rather than into the methallyl ether, became more than marginally competitive with

Table 2. Product Distributions from Diazo Decomposition of **25***a*

		relative yield,[c] %	
catalyst	isolated yield,[b] %	**26**	**27**
$Rh_2(pfb)_4$	68	53	47
$Rh_2(OAc)_4$	71	94	6
$Rh_2(cap)_4$	65	>99	<1
$CuPF_6$	70	84	16

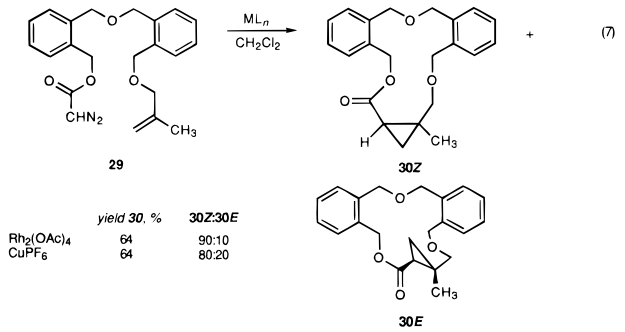
[a] Reactions performed in refluxing CH_2Cl_2 using 1.0 mol % of catalyst. [b] Product yield after chromatography. [c] Determined by GC analysis.



intramolecular cyclopropanation only with $Rh_2(pfb)_4$. Only the *cis*-isomer **27** was observed based on NOE experiments on the lactone formed by hydrogenolysis.

The structure of **26** was determined by X-ray diffraction analysis of a crystal grown from hexanes/ethyl acetate (Figure 2) which established the Z-geometry of substituents on the cyclopropane ring. In this structure the carbonyl oxygen is directed inward and syn to the cyclopropane ring. Oxygens are positioned so as to avoid dipolar repulsions.

Ylide formation does not occur in diazo decomposition of the benzene dimethanol analog **29** whose formation follows the sequence of steps outlined in Scheme 4. Instead, two products (**30*Z*** and **30*E***), diastereoisomers of each other, are formed by macrocyclic cyclopropanation (eq 7). Whereas only the *Z*-cyclopropane isomer **26** was formed from **25**, both *Z*- and *E*-cyclopropane isomers were formed from **29**, and the diastereoisomer ratio varied with the catalyst employed. Higher Z:E diastereomer ratios were obtained from $Rh_2(OAc)_4$ than from $Cu(MeCN)_4PF_6$ catalyzed reactions. Product yields are for pure **30Z** and pure **30E**, obtained following chromatography, and are not optimized.



	yield 30, %	**30*Z*:30*E***
$Rh_2(OAc)_4$	64	90:10
$CuPF_6$	64	80:20

Finally, in an effort to evaluate the potential of this methodology in the formation of macrocycles even larger than **26** and **30**, diazoacetate **32** was conveniently produced from the same alcohol (**28**) employed in the formation of **29** (Scheme 5). Diazoacetate **32** was formed in 39% overall yield from **28**. Treatment of **32** with $Cu(MeCN)_4PF_6$ formed products from intramolecular cyclopropanation (eq 8) of which only the *Z*- and *E*-cyclopropanes from addition to the remote carbon−carbon double bond (**33*Z*** and **33*E***) were identifiable (in a 2:1 molar ratio). Similar results were obtained using $Rh_2(OAc)_4$ but with higher product yields (59% vs 42% with $CuPF_6$) and a higher Z:E diastereomer ratio. In fact, the crude product from reactions catalyzed by $Rh_2(OAc)_4$ was >65% **33**.

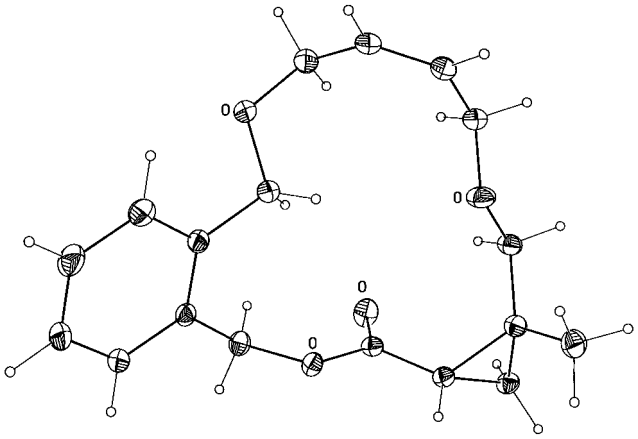
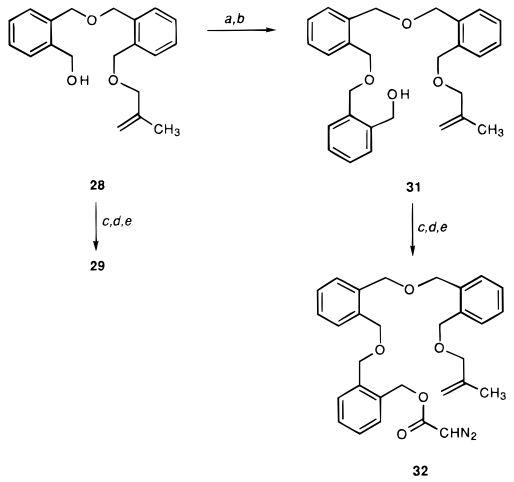
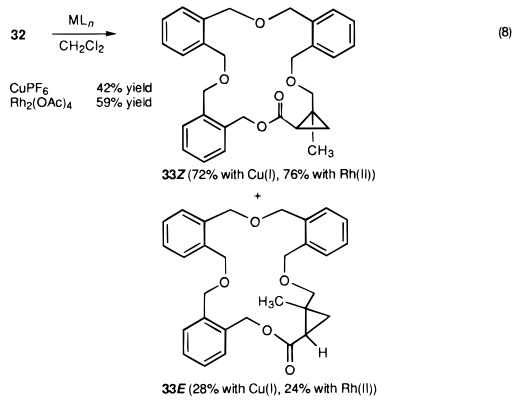


Figure 2. View of $C_{18}H_{22}O_4$ (**26**). Thermal elipsoids are scaled to the 30% probability level. Hydrogen atoms are drawn to an arbitrary scale.

Scheme 5*a*



[a] (a) MsCl, Et_3N, 0 °C; (b) 1,2-benzenedimethanol/NaH in THF; (c) diketene, Et_3N/THF; (d) MsN_3, Et_3N/THF; (e) LiOH, H_2O/THF, 0 °C.

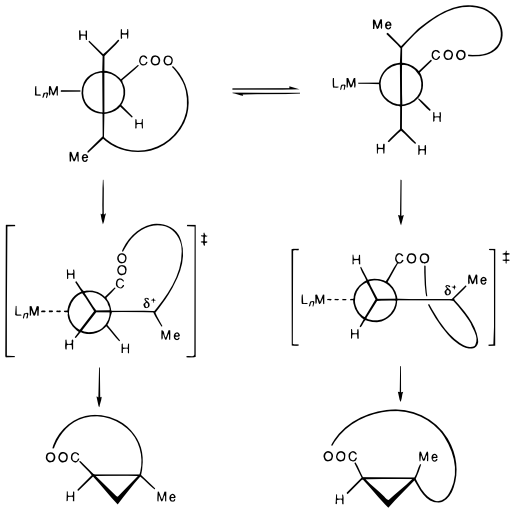


Discussion

As seen by the extent to which macrocylic cyclopropanation can be achieved, there appears to be a global advantage of this methodology for macrolide syntheses. The formation of rings containing nine to 20 atoms is reported, and, with few exceptions, product yields are generally greater than 50%. A *cis*-2-buten-1,4-diyl or 1,2-benzenedimethyl linker, which brings the remote reaction centers closer together, favors macrocyclization, but, as is the case with **1**, **4**, and **15**, this geometrical constraint is not a prerequisite.

Remote cyclopropanation is a function of the catalyst employed. With dirhodium(II) compounds, macrocyclization

Scheme 6



is favored by ligands that increase the electrophilic character of the dirhodium(II) core: $Rh_2(pfb)_4$ > $Rh_2(OAc)_4$ > $Rh_2(cap)_4$.[17,18] With copper catalysts the same is true so that $Cu(MeCN)_4PF_6$ can be said to resemble $Rh_2(OAc)_4$, and $Cu(acac)_2$ provides results that are comparable to those obtained with $Rh_2(cap)_4$. For systems in which alternative path ways for the intermediate metal carbenes are not favorable (e.g., **15**, **17**, **29**, and **32**), all catalysts form product(s) from cyclopropanation at the remote double bond. In early investigations of intramolecular cyclopropanation,[19] the absence of reports of macrocyclization can be understood in terms of the catalyst that was employed—those like $CuSO_4$ or Cu powder whose reactivity/selectivity resembles that of $Rh_2(cap)_4$.

Alkene reactivity plays a significant role in determining the competitiveness of a reacting system for remote versus proximal allylic cyclopropanation, and no where is this more evident than in catalytic reactions of **10**. Methallyl is more reactive than allyl because of the stabilization provided by substituent groups in the transition state for electrophilic cyclopropanation. As a result, proximal intramolecular allylic cyclopropanation is disfavored relative to addition to the remote methallyl group, so that with $Rh_2(cap)_4$ and $Cu(acac)_2$ only γ-lactone formation occurs with **10a**, but the γ-lactone is the minor product from reactions with **10b**. However, as seen in reactions of the pentaerythrityl diazoacetate **15**, addition to an unactivated allylic double bond that is remote from the carbene center can be favorable even with the least reactive catalytic systems.

Macrocyclization is consistent with the formation of an intermediate π-complex between the carbon−carbon double bond and the carbene carbon (Scheme 6), which is an explanation initially advanced to explain stereoselectivity in intermolecular reactions[20] and substantiated by others.[21,22] Rotation of the alkene on the carbene center to maximize charge development at the more substituted carbon of the carbon−carbon double bond in the transition state provides the orientation conducive to cyclopropane formation. Proximal allylic double bonds are sterically inhibited from π-complex formation with the net effect that macrocyclization is favored over γ-lactone production for those catalytic systems in which highly electrophilic metal carbene formation can be achieved. In this respect, π-complex formation effectively lowers the activation energy for cyclopropanation and allows macrocyclization to compete effectively with proximal allylic cyclopropanation, which is favored entropically.

The competitive experiment whose results are presented in Figure 1 suggests the extent to which entropic effects are important for macrocyclization. Even at its lowest concentration, the external alkene is present initially in >100-fold greater amount than the remote double bond of **17a**. This signifies that entropic effects, even from remote sites, are principal determinates of reaction selectivity and, taken together with the high yields achieved in the formation of the 20-membered ring **33**, suggests the enormous potential of this methodology.

Experimental Section

General Methods. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were obtained as solutions in $CDCl_3$, unless indicated otherwise, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal Me_4Si (TMS). Infrared spectra were recorded as a thin film on sodium chloride plates or as KBr pellets, and absorptions are reported in wave numbers (cm^{-1}). Mass spectra were obtained using electron ionization at 70 eV on a quadrupole instrument. Elemental analyses were performed at Texas Analytical Laboratories, Inc. Diketene was distilled under reduced pressure prior to use. Methanesulfonyl azide was prepared from methanesulfonyl chloride and sodium azide[23] and was used without distillation. Rhodium(II) acetate was obtained commercially and recrystallized prior to use.[24] The preparation of $Rh_2(pfb)_4$,[25] $Rh_2(cap)_4$,[17a] and $Cu(MeCN)_4PF_6$[26] have been previously reported. Dichloromethane was distilled from CaH_2 prior to use. Tetrahydrofuran was distilled from sodium and benzophenone. Pentaerythritol triallyl ether (commercial, 70% purity) was purified by column chromatography on silica gel (6:1 hexanes:EtOAc) prior to use.

***cis*-3,7,11-Trimethyl-1,6,10-undecatrien-3-yl diazoacetate (5)** was prepared from nerolidol, glyoxylic acid chloride *p*-toluenesulfonylhydrazone, and triethylamine according to the procedure of Corey and Myers[27] and isolated in 69% yield after column chromatography on silica (20:1 hexanes:ethyl acetate): ^{1}H NMR (C_6D_6, 300 MHz) δ 5.91 (dd, J = 17.5, 11.0 Hz, 1 H), 5.30−5.18 (m, 1 H), 5.15 (d, J = 7.0 Hz, 1 H), 5.07 (dd, J = 17.5, 1.0 Hz, 1 H), 4.97 (dd, J = 11.0, 1.0 Hz, 1 H), 3.97 (s, 1 H), 2.17−1.94 (m, 7 H), 1.83−1.71 (m, 1 H), 1.68 (s, 3 H), 1.67 (s, 3 H), 1.56 (s, 3 H), 1.51 (s, 3 H); ^{13}C NMR (C_6D_6, 75 MHz) δ (C=O not detected), 142.2, 135.5, 131.4, 125.1, 124.8, 113.2, 83.7, 46.0, 40.4, 32.2, 27.0, 25.9, 24.3, 23.6, 22.6, 17.7; IR (film) 2112 (C=N_2), 1700 (C=O), 1651 (C=C) cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.03; N, 9.64. Found: C, 70.34; H, 9.08; N, 9.61.

(1α,5α)-4-Methyl-4-(4,8-dimethyl-*cis*-3,7-nonadien-1-yl)-3-oxabicyclo[3.1.0]hexan-2-one (6). To a refluxing solution of anhydrous CH_2Cl_2 (10 mL) containing 6.1 mg (92 μmol) of $Rh_2(cap)_4$ was added via syringe pump over 8 h a 10 mL CH_2Cl_2 solution of **5** (0.280 g of 95% pure **5**, 0.92 mmol). After addition was complete, the reaction mixture was filtered through a 3-cm plug of silica to separate the catalyst, and this plug was washed three times with 5-mL portions of CH_2Cl_2. After evaporation of the solvent, GC and NMR analyses showed the presence of only two products, ***exo*-6** and ***endo*-6** in a ratio of 71:29. Chromatographic purification of the reaction mixture on silica (10:1 hexanes:ethyl acetate) afforded 75 mg of ***exo*-6**, 34 mg of ***endo*-**

(17) (a) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958−964. (b) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906−1912.

(18) Padwa, A.; Austin, A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797.

(19) Burke, S. D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361−475.

(20) (a) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometal.* **1984**, *3*, 53−61. (b) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348−356.

(21) Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057−5060.

(22) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *46*, 7341−7358.

(23) Boyer, J. H.; Mack, G. H.; Goebel, W.; Morgan, L. R. *J. Org. Chem.* **1959**, *24*, 1051−1053.

(24) Rampel, G. A.; Legzdins, P.; Smith, H.; Wilkinson, G. *Inorg. Synth.* **1972**, *13*, 90−91.

(25) Doyle, M. P.; Shanklin, M. S. *Organometal.* **1994**, *13*, 1081−1088.

(26) G. J. Kubas *Inorg. Synth* **1979**, *19*, 90−92.

(27) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3359−3362.

6, and 110 mg of the mixture of isomers for a combined isolated yield of 90%. ***Exo*-6**: ^{1}H NMR (C_6D_6, 300 MHz) δ 5.24−5.17 (m, 1 H), 5.06 (t, J = 7.0 Hz, 1 H), 2.18−2.00 (m, 6 H), 1.68 (d, J = 1.3 Hz, 3 H), 1.67 (s, 3 H), 1.61−1.38 (m, 3 H), 1.58 (s, 3 H), 1.17 (ddd, J = 7.7, 5.7, 4.5 Hz, 1 H), 0.96 (s, 3 H), 0.37 (ddd, J = 7.6, 4.7, 4.2 Hz, 1 H), 0.27 (ddd, J = 8.8, 7.6, 4.9 Hz, 1 H); NOESY experiment showed interaction between CH_3 (0.96 ppm) and anti-H (0.37 ppm) of cyclopropane; correlations also made by COSY, APT, and HETCOR for structural identification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.15−5.05 (m, 2 H), 2.22−2.00 (m, 8 H), 1.76 (dd, J = 9.6, 3.2 Hz, 1 H), 1.74 (dd, J = 9.6, 3.9 Hz, 1 H), 1.69 (s, 3 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.35 (s, 3 H), 1.12 (ddd, J = 8.8, 7.6, 5.1 Hz, 1 H), 0.94 (ddd, J = 5.1, 4.6, 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 136.1, 131.7, 124.1, 123.8, 84.6, 42.4, 31.8, 26.4, 26.2, 25.7, 23.3, 22.6, 21.6, 19.3, 17.6, 10.5; IR (film) 1770 (C═O), 1670 (C═C) cm^{-1}; mass spectrum, *m/z* (relative abundance) 262 (M, 4), 219 (10), 206 (12), 147 (20), 136 (33), 135 (21), 123 (21), 122 (40), 121 (44), 119 (20), 111 (99), 107 (70), 105 (25), 93 (97), 81 (99), 69 (100), 68 (60), 67 (71), 55 (81). ***Endo*-6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.15−5.05 (m, 2 H), 2.16−1.97 (m, 8 H), 1.79−1.51 (m, 2 H), 1.69 (s, 3 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.47 (s, 3 H), 1.12 (ddd, J = 8.8, 7.6, 5.1 Hz, 1 H), 0.96 (ddd, J = 5.1, 4.8, 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 136.1, 131.7, 124.1, 123.9, 84.9, 42.4, 37.7, 31.9, 26.8, 26.5, 26.3, 25.7, 23.3, 22.8, 18.8, 10.7; mass spectrum, *m/z* (relative abundance) 262 (M, 2), 219 (7), 206 (3), 147 (13), 136 (19), 135 (12), 123 (16), 122 (29), 121 (25), 119 (13), 111 (73), 107 (45), 105 (17), 93 (59), 81 (94), 69 (100), 68 (46), 67 (42), 55 (48). Anal (exo/endo mixture). Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.76; H, 10.05.

(1α,11α)-4,8,12,12-Tetramethyl-4-vinyl-3-oxabicyclo[9.1.0]dodeca-7-en-2-one (7). To a solution of anhydrous CH_2Cl_2 (10 mL) at room temperature containing 4.3 mg (97 μmol) of $Rh_2(OAc)_4$ was added via syringe pump over 7 h a 10 mL CH_2Cl_2 solution of **7** (0.280 g, 0.97 mmol). After addition was complete, the reaction mixture was filtered through a 3-cm plug of silica to separate the catalyst, and this plug was washed three times with 5-mL portions of CH_2Cl_2. After evaporation of the solvent, GC and NMR analyses showed the presence of two major products whose crude yield was 41%, subsequently identified as two diastereoisomers (50:50 distribution of ***exo*-7** and ***endo*-7**). Other products identified in the crude mixture were **6** (9.5%) and the product from water insertion into the carbene generated from **5** (<15%). Chromatographic purification of the reaction mixture on silica (50:1 → 30:1 hexanes:ethyl acetate) afforded 50 mg of pure **7** (21% yield). ^{1}H NMR (C_6D_6, 300 MHz) of 50:50 *exo:endo*-**7**: δ 6.26 (dd, J = 11.0, 17.6 Hz, 0.5 H), 5.78 (dd, J = 11.0, 17.4 Hz, 0.5 H), 5.26 (dd, J = 17.4, 1.4 Hz, 0.5 H), 5.22−5.14 (m, 1 H), 5.03 (d, J = 17.6 Hz, 0.5 H), 4.98 (dd, J = 11.0, 0.5 Hz, 0.5 H), 4.92 (dd, J = 11.0, 0.8 Hz, 0.5 H), 2.46−2.10 (m, 4 H), 1.93−1.70 (m, 4 H), 1.67 (s, 3 H), 1.52 (s, 1.5 H), 1.44 (d, J = 9.3 Hz, 0.5 H), 1.42 (d, J = 9.3 Hz, 0.5 H), 1.35 (s, 1.5 H), 1.35 (s, 1.5 H), 1.32 (s, 1.5 H), 0.89−0.81 (m, 1.0 H), 0.83 (s, 1.5 H), 0.82 (s, 1.5 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 170.7, (144.0, 143.0), (135.8, 135.6), 125.1, (112.4, 112.3), (82.5, 82.3), (36.1, 35.9), (35.3, 35.2), (31.0, 30.0), (29.04, 29.00), 26.3, (25.1, 24.9), (24.3, 24.1), (23.4, 23.3), 22.1, (21.7, 21.5), 15.1. COSY, HETCOR, APT correlations were made for structure identification; the cis geometry for the cyclopropane was assigned from the coupling constants (J = 9.3 Hz) for doublet absorptions centered at δ 1.44 and 1.42 which were correlated (COSY) with absorptions at δ 0.89−0.83. Mass spectrum, *m/z* (relative abundance): first GC eluent, 262 (M, 2), 152 (22), 151 (19), 135 (12), 121 (18), 107 (24), 95 (30), 93 (43), 83 (26), 82 (45), 81 (36), 79 (29), 68 (77), 67 (100), 55 (40), 53 (35); second eluent, 262 (M, 2), 152 (20), 151 (17), 135 (12), 121 (18), 107 (25), 95 (30), 93 (47), 83 (23), 82 (47), 81 (35), 79 (31), 68 (75), 67 (100), 55 (42), 53 (35). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.80; H, 10.02.

(*Z*)-2,6,10-Trimethyl-5,9-undecadien-2-yl diazoacetate (8a) was prepared from (*Z*)-2,6,10-trimethyl-5,9-undecadien-2-ol (obtained from nerylacetone and methylmagnesium bromide, 87% yield), glyoxylic acid chloride *p*-toluenesulfonylhydrazone, and triethylamine according to the procedure of Corey and Meyers[27] and isolated in 55% yield after column chromatography on silica (10:1 hexanes:ethyl acetate): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.10−5.06 (m, 2 H), 4.58 (br s, 1 H), 2.07−1.96 (m, 6 H), 1.78−1.71 (m, 2 H), 1.66 (br s, 6 H), 1.59 (s, 3 H), 1.45 (s, 6 H); ^{1}H NMR (C_6D_6, 300 MHz) δ 5.36−5.25 (m, 1 H), 5.32 (dt, J = 7.1, 1.2 Hz, 1 H), 3.95 (s, 1 H), 2.18−2.04 (m, 6 H), 1.80−1.74 (m, 2 H), 1.70 (d, J = 1.3 Hz, 3 H), 1.68 (s, 3 H), 1.57 (s, 3 H), 1.39 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (C═O not detected), 135.5, 131.6, 124.6, 124.3, 83.4, 46.6, 41.5, 31.9, 26.6, 26.2, 25.7, 23.4, 22.4, 17.6; IR (film) 2106 (C═N_2), 1693 (C═O) cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.95; H, 9.44; N, 10.12.

***cis*-4,4,8,12,12-Pentamethyl-3-oxabicyclo[9.1.0]dodec-7-en-2-one (9a).** To a solution of anhydrous dichloromethane (6 mL) containing 3.2 mg (7.2 mmol) of $Rh_2(OAc)_4$ at room temperature was added a 10 mL solution of **8a** (0.180 g, 0.647 mmol) in CH_2Cl_2 via syringe pump over 4 h. After addition was complete, the reaction mixture was filtered through a short plug of silica to remove the catalyst, and this plug was rinsed with 15 mL of CH_2Cl_2. After evaporation of the solvent, GC and NMR analyses showed the presence of one major product. Purification by radial chromatography on silica (20:1 hexanes:ethyl acetate) afforded 78 mg of the title compound (0.311 mmol, 48% yield) as a colorless oil: ^{1}H NMR (C_6D_6, 300 MHz) δ 5.19 (dd, J = 9.7, 6.2 Hz, 1 H), 2.43−2.28 (m, 2 H), 2.10−2.00 (m, 1 H), 1.92−1.60 (m, 3 H), 1.68 (s, 3 H), 1.58−1.35 (m, 2 H), 1.41 (d, J = 9.2 Hz, 1 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 0.84 (dt, J = 9.2, 2.4 Hz, 1 H), 0.84 (s, 3 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 171.2, 135.6, 125.3, 81.2, 37.4, 35.1, 31.0, 30.3, 29.1, 27.8, 27.0, 24.3, 23.3, 22.2, 15.1. A COSY experiment shows correlation between absorptions at δ 1.41 and 0.84, and the coupling constant (J = 9.2 Hz) signifies the cis geometry. Mass spectrum, *m/z* (relative abundance) 251 (0.4, M + 1), 250 (2.3, M), 195 (5), 181 (5), 152 (34), 123 (21), 109 (34), 107 (25), 95 (37), 93 (26), 82 (82), 81 (78), 79 (28), 69 (36), 68 (86), 67 (100), 55 (32). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.65; H, 10.41.

(*Z*)-6,10-Dimethyl-2-phenyl-5,9-undecadien-2-yl diazoacetate (8b) was prepared from (*Z*)-6,10-dimethyl-2-phenyl-5,9-undecadien-2-ol (obtained from nerylacetone and phenylmagnesium bromide, 95% yield) according to the procedure of Corey and Meyers[27] and isolated in 33% yield after column chromatography on silica (30:1 hexanes:ethyl acetate): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.17 (m, 5 H), 5.05−5.00 (m, 2 H), 4.71 (br s, 1 H), 2.05−1.82 (m, 8 H), 1.87 (s, 3 H), 1.65 (s, 3 H), 1.62 (s, 3 H), 1.56 (s, 3 H); ^{1}NMR (C_6D_6, 300 MHz) δ 7.27−7.01 (m, 5 H), 5.16 (t, J = 5.5 Hz, 1 H), 5.09 (t, J = 5.4 Hz, 1 H), 4.01 (br s, 1 H), 2.20−1.93 (m, 8 H), 1.83 (s, 3 H), 1.66 (s, 3 H), 1.65 (s, 3 H), 1.53 (s, 3 H); ^{13}C NMR (C_6D_6, 300 MHz) δ (C═O not detected), 145.4, 135.6, 131.4, 128.4, 127.1, 125.0, 124.9, 124.8, 84.9, 46.2, 43.1, 32.1, 27.0, 25.9, 25.7, 23.5, 22.8, 17.7; IR (film) 2108 (C═N_2), 1699 (C═O) cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.92; H, 8.34; N, 8.20.

***cis*-4,8,12,12-Tetramethyl-4-phenyl-3-oxabicyclo[9.1.0]dodec-7-en-2-one (9b).** To a solution of anhydrous dichloromethane (5 mL) containing 3.0 mg (6.8 mmol) of $Rh_2(OAc)_4$ at room temperature was added a 10 mL solution of **8b** (0.209 g, 0.615 mmol) in CH_2Cl_2 via syringe pump over 4 h. After addition was complete, the reaction mixture was filtered through a short plug of silica, and the plug was rinsed with 15 mL of CH_2Cl_2. After evaporation of the solvent, GC and NMR analyses showed the presence of four major products of which **9b** was dominant (45%). Carbene dimer formation was minimal, and aromatic cycloaddition did not occur. Purification by radial chromatography on silica (30:1 hexanes:ethyl acetate) afforded 35 mg of a nearly equimolar mixture of the two diastereoisomers of the title compound (0.111 mmol, 18% yield) as a colorless oil: ^{1}H NMR (C_6D_6, 300 MHz) δ 7.45−7.00 (m, 5 H), 5.24 (dd, J = 11.6, 5.2 Hz, 0.4 H), 5.16 (dd, J = 9.7, 5.6 Hz, 0.6 H), 2.70−1.76 (m, 8 H), 1.75 (s, 1.8 H), 1.68 (s, 1.2 H), 1.65 (s, 1.8 H), 1.56 (d, J = 9.2 Hz, 0.4 H), 1.53 (d, J = 9.4 Hz, 0.6 H), 1.45 (s, 3 H), 1.21 (s, 1.2 H), 0.93−0.85 (m, 1 H), 0.87 (s, 1.8 H), 0.80 (s, 1.2 H); ^{13}C NMR (C_6D_6, 75 MHz, δ (171.6, 171.0), (148.1, 147.4), (136.8, 135.9), 128.7, (127.8, 127.7), (126.1, 125.6), (126.0, 125.9), (85.3, 83.6), (37.6, 36.7), (36.5, 35.6), 32.0, 31.9), (31.1, 30.7), (30.4, 30.0), (30.0, 29.9), (25.1, 24.9), (24.5, 24.4), 23.45, 22.51, (16.2, 15.9). The coupling constants for the hydrogens at C1 (9.2 and 9.4 Hz for absorptions at δ 1.56 and 1.53, respectively) are consistent with a *cis*-cyclopropane geometry for both diastereoisomers. Mass spectrum, *m/e* (relative abundance): first GC eluent,

313 (6, M + 1), 312 (24, M), 297 (7), 194 (14), 161 (23), 152 (39), 151 (28), 143 (95), 131 (21), 119 (30), 118 (100), 117 (69), 105 (65), 91 (62), 82 (78), 79 (38), 77 (46); second eluent, 313 (2, M + 1), 312 (8, M), 297 (13), 194 (10), 161 (9), 143 (37), 131 (56), 119 (20), 118 (100), 117 (38), 105 (59), 91 (46), 82 (22), 79 (25), 77 (32).

5,5-Bis(carboethoxy)-*cis*-2,7-octadien-1-ol (12a). Diethyl allylmalonate (9.95 g, 50.2 mmol), dissolved in 20 mL of anhydrous THF, was added via syringe to a stirred suspension of NaH (2.21 g, 55.2 mmol) in 150 mL of THF at 0 °C. Stirring was continued for an additional 30 min, at which time the mesylate of 4-(*tert*-butyldimethylsiloxy)-*cis*-2-buten-1-ol, dissolved in 20 mL of THF, was added. The solution was allowed to come to room temperature overnight, water was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 50 mL). The organic layer was washed with brine (40 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield the crude product, which was dissolved in 50 mL of THF and treated with 70 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF. After stirring for 12 h, water was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 40 mL). The organic layer was washed with brine (30 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude alcohol. Purification by column chromatography (7:1 hexanes:ethyl acetate) yielded 11.8 g (92% yield) of product as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78−5.60 (comp, 2 H), 5.44−5.37 (m, 1 H), 5.15−5.10 (comp, 2 H), 4.25−4.13 (comp, 6 H), 2.67−2.20 (comp, 4 H), 1.25 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 132.3, 132.1, 125.3, 119.1, 61.3, 58.1, 57.2, 37.0, 30.2, 13.9; IR (neat) 3440, 1745, 1648 cm^{-1}; mass spectrum, *m/z* (relative abundance) 196 (2), 183 (16), 179 (18), 165 (12), 151 (18), 137 (44), 125 (15), 108 (100), 91 (22), 79 (40), 67 (19). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.07; H, 8.23.

5,5-Bis(carboethoxy)-*cis*-2,7-octadien-1-yl Diazoacetate (10a). Prepared by the one-pot modification of the three-step procedure of Doyle[28] using 9.00 g (33.5 mmol) of 5,5-bis(carboethoxy)-*cis*-2,7-octadien-1-ol. The alcohol was dissolved in 100 mL of THF and treated sequentially with diketene (4.23 g, 50.3 mmol) and a catalytic amount of triethylamine at 0 °C for 12 h, methanesulfonyl azide (4.27 g, 35.2 mmol), triethylamine (4.07 g, 40.3 mmol) for 12 h, and then lithium hydroxide (3.22 g, 134 mmol) in 100 mL of water at 0 °C for 4 h. After the cleavage was complete (monitored by ^{1}H NMR analysis), 100 mL of ether was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). The organic layer was washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure and purification by column chromatography (5:1 hexanes:ethyl acetate) yielded 7.60 g (67% yield) of the title compound as an intensely yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70−5.59 (comp, 2 H), 5.56−5.49 (m, 1 H), 5.14−5.09 (comp, 2 H), 4.75 (bs, 1 H), 4.70 (dt, J = 7.1, 0.8 Hz, 2 H), 4.25−4.15 (comp, 4 H), 2.69 (dt, J = 7.5, 0.8 Hz, 2 H), 2.64 (dt, J = 7.5, 1.2 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 166.4, 132.0, 128.0, 127.0, 119.1, 76.6, 61.2, 60.3, 56.9, 45.9, 36.8, 13.9; IR (neat) 2110, 1731, 1643. Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.62; H, 6.48; N, 8.28.

General Procedure for Diazo Decomposition of 10a. The procedure for diazo decomposition with $Rh_2(OAc)_4$ is representative. Diazoacetate **10a** (170 mg, 500 μmol) was dissolved in 5 mL of freshly distilled CH_2Cl_2 and added via syringe pump over 5 h to a solution of $Rh_2(OAc)_4$ (2.2 mg, 1.0 mol %) in 5 mL of refluxing CH_2Cl_2. After the addition was complete, the solution was passed through a plug of silica gel to remove the catalyst. The solvent was removed under reduced pressure, and the crude reaction mixture was purified by column chromatography (3:1 hexanes:ethyl acetate) to yield 58 mg (37% yield) of **13ac**, 45 mg (29% yield) of **13at**, and 10 mg (6% yield) of the γ-lactone **14a**, all as colorless oils.

8,8-Bis(carboethoxy)-3-oxa-*cis*-bicyclo[8.1.0]undec-*cis*-5-en-2-one (13ac): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.57 (dddd, J = 12.0, 5.2, 2.0, 1.9 Hz, 1 H), 4.99 (ddddd, J = 12.4, 12.0, 4.6, 2.9, 0.9 Hz, 1 H), 4.9 (ddd, J = 15.1, 5.2, 0.9 Hz, 1 H), 4.62 (dddd, J = 15.1, 3.1, 2.9, 2.0 Hz, 1 H), 4.30−4.13 (comp, 4 H), 3.28 (dd, J = 14.4, 13.5 Hz, 1 H), 2.61 (dddd, J = 14.4, 4.6, 3.1, 1.9 Hz, 1 H), 2.53 (dt, J = 15.2, 1.7 Hz, 1 H), 1.96 (ddd, J = 13.5, 7.8, 5.8 Hz, 1 H), 1.44 (dd, J = 15.2, 11.4 Hz, 1 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 1 H), 1.01 (ddd, J = 6.4, 5.8, 4.6 Hz, 1 H), 0.92 (ddd, J = 8.6, 7.8, 4.6 Hz, 1 H), 0.91−0.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 171.4, 171.1, 170.4, 128.4, 125.7, 62.7, 61.4, 61.3, 58.7, 31.0, 29.1, 20.2, 16.3, 14.1, 8.4; IR (neat) 1755 (C═O), 1654 (C═C) cm^{-1}; mass spectrum, *m/z* (relative abundance) 199 (3), 195 (25), 191 (16), 173 (17), 166 (22), 163 (12), 145 (18), 140 (12), 138 (35), 127 (15), 117 (27), 107 (21), 91 (38), 81 (54), 79 (42), 55 (100). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.78; H, 7.13.

8,8-Bis(carboethoxy)-3-oxa-*trans*-bicyclo[8.1.0]undec-*cis*-5-en-2-one (13at): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (dddd, J = 11.0, 10.2, 4.2, 1.3 Hz, 1 H), 5.57 (dd, J = 11.0, 11.0, 5.5 Hz, 1 H), 5.20 (dd, J = 12.9, 11.0 Hz, 1 H), 4.46 (dd, J = 12.9, 4.2 Hz, 1 H), 4.35−4.11 (comp, 4 H), 2.95 (d, J = 14.8 Hz, 1 H), 2.90−2.82 (m, 2 H), 1.67 (ddd, J = 9.0, 7.5, 4.7 Hz, 1 H), 1.56 (ddd, J = 9.0, 4.9, 4.7 Hz, 1 H), 1.50−1.41 (m, 1 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 0.81 (dd, J = 14.8, 10.7 Hz, 1 H), 0.61 (ddd, J = 7.5, 5.8, 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 171.6, 169.5, 129.9, 125.8, 62.4, 61.7, 61.3, 56.5, 40.9, 30.8, 21.7, 19.1, 13.9, 13.8, 11.7; IR (neat) 1755 (C═O), 1662 (C═C) cm^{-1}; mass spectrum, *m/e* (relative abundance) 199 (2), 195 (2), 191 (20), 173 (40), 166 (13), 163 (15), 145 (21), 140 (19), 138 (13), 127 (28), 117 (30), 107 (27), 91 (54), 81 (52), 79 (61), 55 (100). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.78; H, 7.20.

***syn*-6-[1,1-Bis(carboethoxy)-3-buten-1-yl]-3-oxabicyclo[3.1.0]hexan-2-one (14a):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.65 (dddd, J = 16.8, 10.2, 7.4, 7.2 Hz, 1 H), 5.13 (ddd, J = 16.8, 3.3, 1.4 Hz, 1 H), 5.12 (ddd, J = 10.2, 2.9, 1.0 Hz, 1 H), 4.39 (dd, J = 10.1, 5.3 Hz, 1 H), 4.28−4.12 (comp, 5 H), 2.76 (dddd, J = 14.4, 7.4, 1.2, 1.0 Hz, 1 H), 2.71 (dddd, J = 14.4, 7.2, 1.3, 1.2 Hz, 1 H), 2.24 (dddd, J = 6.2, 6.0, 5.3, 1.0 Hz, 1 H), 2.18 (ddd, J = 8.9, 6.2, 1.2 Hz, 1 H), 2.01 (dd, J = 14.8, 6.1 Hz, 1 H), 1.89 (dd, J = 14.8, 7.0 Hz, 1 H), 1.50 (dddd, J = 7.0, 6.2, 6.1, 6.0 Hz, 1 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 170.6 (2), 131.9, 119.5, 65.7, 61.5$_3$, 61.4$_6$, 56.9, 37.9, 26.4, 22.8, 22.4, 17.6, 13.9$_8$, 13.9$_2$; IR (neat) 1755 (C═O), 1644 (C═C cm^{-1}; mass spectrum, *m/z* (relative abundance) 199 (51), 191 (34), 179 (37), 163 (20), 152 (79), 144 (31), 133 (40), 123 (67), 108 (48), 85 (81), 79 (100). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.82; H, 7.09.

5,5-Bis(carboethoxy)-7-methyl-*cis*-2,7-octadien-1-ol (12b). Diethyl (2-methyl-2-propen-1-yl)malonate (**11b**) was prepared from NaH (0.76 g, 19 mmol) in 120 mL of freshly distilled THF to which was added a 10-mL THF solution of diethyl malonate (3.07 g, 19.2 mmol) and, after 30 min at room temperature, a 10-mL THF solution of 3-bromo-2-methylpropene (2.71 g, 20.2 mmol) dropwise over 10 min. After the solution was stirred, for 24 h diethyl ether (250 mL) was added, and the resulting solution was washed with 190 mL of water. The aqueous phase was washed with ether (100 mL) and then with ethyl acetate (100 mL). The combined organic solution was washed with brine (150 mL) and then dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure yielded a 4.5:1 mixture of mono- to dialkylated malonate. Purification by chromatography on silica gel (5:1 hexanes:EtOAc) furnished 2.90 g (70% yield) of diethyl (2-methyl-2-propen-1-yl)malonate (**11b**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.79−4.78 (m, 1 H), 4.73−4.72 (m, 1 H), 4.19 (q, J = 7.1 Hz, 4 H), 3.58 (t, J = 7.8 Hz, 1 H), 2.62 (d, J = 7.8 Hz, 2 H), 1.75 (t, J = 0.9 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 6 H).

To a gray suspension of NaH (0.55 g, 14 mmol) stirred at 0 °C in 120 mL of freshly distilled THF was added a 10-mL solution of diethyl (2-methyl-2-propen-1-yl)malonate (2.80 g, 13.1 mmol). The reaction mixture was stirred at 0 °C for 15 min, then warmed to room temperature for 15 min, and cooled once again to 0 °C, at which time a 10-mL solution of 4-(*tert*-butyldimethylsilyloxy)-*cis*-2-buten-1-yl methanesulfonate (3.43 g, 13.7 mmol) was added dropwise over 10 min. The resulting mixture was warmed to room temperature, and stirring was continued for an additional 24 h. Diethyl ether (150 mL) was added, and the mixture was washed with water (120 mL). The organic phase was then washed with brine (150 mL) and dried over

(28) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763−5775.

anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield 4.64 g of the TBDMS derivative of **12b** (90%) as a slightly yellow oil. After dissolving in 125 mL of THF at 0 °C, 18 mL of a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF (18 mmol, 1.5 equiv) was added with stirring over 5 min. The resulting orange solution was warmed to room temperature, and stirring was continued for 25 h. Purification by chromatography on silica gel (10:1 → 0:1 hexanes:EtOAc) afforded 2.03 g (61% yield) of **12b** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77−5.70 (m, 1 H), 5.49−5.42 (m, 1 H), 4.88−4.87 (m, 1 H), 4.76−4.75 (m, 1 H), 4.18 (q, J = 7.1 Hz, 4 H), 4.15 (d, J = 6.5 Hz, 2 H), 2.72 (d, J = 0.7 Hz, 2 H), 2.69 (dt, J = 7.6, 0.9 Hz, 2 H), 1.67 (dd, J = 1.4, 0.8 Hz, 2 H), 1.57 (s, 1 H), 1.26 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 140.5, 132.0, 126.0, 115.6, 61.4, 58.3, 56.9, 40.5, 30.4, 23.1, 13.9; IR (film) 3446, 1739, 1720, 1645 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.17; H, 8.42.

5,5-Bis(carboethoxy)-7-methyl-*cis*-2,7-octadien-1-yl Diazoacetate (10b). To alcohol **12b** (1.60 g, 5.79 mmol) in 20 mL of THF at 0 °C was added freshly distilled diketene (0.723 g, 8.60 mmol) and triethylamine (6.8 mmol) followed by methanesulfonyl azide (0.726 g, 5.99 mmol). The resulting orange solution was warmed to room temperature, and stirring was continued for 37 h. The reaction mixture was then cooled with an ice bath, and $LiOH{\cdot}H_2O$ (0.546, 22.8 mmol) was added. The resulting brown solution was stirred for 2.5 h, then poured into ether (70 mL) and washed with water (30 mL). The aqueous phase was washed with ether (2 × 20 mL) and then with EtOAc (2 × 20 mL). The combined organic solution was washed with brine (30 mL) and then dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the resulting orange oil was chromatographically purified on silica gel (hexanes:EtOAc 10:1 → 2:1) to yield 1.16 g (57% yield from **12b**) of a light yellow oil identified as **10b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66−5.58 (m, 1 H), 5.56−5.48 (, 1 H), 4.86−4.85 (m, 1 H), 4.72−4.71 (m, 1 H), 4.68 (br s, 1 H), 4.67 (dd, J = 6.7, 1.2 Hz, 2 H), 4.15 (q, J = 7.1 Hz, 4 H), 2.71−2.69 (comp, 2 H), 2.69 (d, J = 0.6 Hz, 2 H), 1.64 (dd, J= 1.4, 0.8 Hz, 2 H), 1.23 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 140.4, 128.4, 126.9, 115.8, 61.4, 60.6, 56.6, 46.1, 40.2, 30.3, 23.1, 14.0; IR (film) 2112 (C═N_2), 1733 (C═O), 1645 (C═C) cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.87; N, 7.95. Found: C, 57.83; H, 6.78; N, 8.01.

Diazo decomposition of 10b followed the same procedure previously described for **10a** using 1.0 mol % of catalyst. Evaporation of the solvent left a viscous oil that was subjected to GC analysis. Chromatographic purification on silica gel (10:1 → 2:1 hexanes:EtOAc) provided a clear colorless oil.

8,8-Bis(carboethoxy)-10-methyl-3-oxa-*cis*-bicyclo[8.1.0]undec-*cis*-5-en-2-one (13bc): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.52 (dddd, J = 12.0, 5.0, 2.7, 1.8 Hz, 1 H), 4.94 (ddddd, J = 12.8, 12.0, 4.6, 2.7, 1.1 Hz, 1 H), 4.80 (ddd, J = 15.1, 5.0, 1.1 Hz, 1 H), 4.60 (dq, J = 15.1, 2.7 Hz, 1 H), 4.28−4.04 (comp, 4 H), 3.10 (dd, J = 14.5, 12.8 Hz, 1 H), 2.78 (dddd, J = 14.5, 4.6, 2.7, 1.8 Hz, 1 H), 2.56 (dd, J = 15.6, 1.1 Hz, 1 H), 1.72 (dd, J = 7.5, 6.0 Hz, 1 H), 1.66 (d, J = 15.6 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.08 (dd, J = 6.0, 5.0 Hz, 1 H), 1.00 (s, 3 H), 0.67 (dd, J = 7.5, 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4, 170.9, 170.3, 127.6, 125.6, 62.7, 61.4, 61.3, 57.7, 34.5, 30.0, 28.6, 23.5, 23.1, 19.6, 14.0, 13.8; IR ($CDCl_3$) 1731, 1601 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.78; H, 7.37.

***syn*-6-[1,1-Bis(carboethoxy)-3-methyl-3-buten-1-yl]-3-oxabicyclo-[3.1.0]hexan-2-one (14b):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.88 (quin, J = 1.6 Hz, 1 H), 4.76−4.74 (m, 1 H), 4.38 (dd, J = 10.0, 5.2 Hz, 1 H), 4.31−4.08 (comp, 5 H), 2.83 (d, J = 15.2 Hz, 1 H), 2.78 (d, J = 15.2 Hz, 1 H), 2.26−2.13 (comp, 2 H), 2.01 (dd, J = 14.9, 6.3 Hz, 1 H), 1.92 (dd, J = 14.9, 6.6 Hz, 1 H), 1.67 (br s, 3 H), 1.59−1.48 (m, 1 H), 1.28 (t, J = 6.9 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 171.2, 171.1, 140.2, 115.9, 65.7, 61.7, 61.5, 56.3, 41.3, 26.4, 23.1, 22.8, 22.4, 17.7, 13.9$_4$, 13.8$_7$; IR ($CDCl_3$) 1765, 1725 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.80; H, 7.43.

***O,O,O*-Triallylpentaerythrityl Diazoacetate (15).** To pentaerythritol triallyl ether (5.86 g, 22.9 mmol) and triethylamine (0.5 mL, 4 mmol) in 50 mL of HPLC-grade THF cooled at 0 °C was added via syringe freshly distilled diketene (4.62 g, 55 mmol) over 5 min. The resulting light orange-brown solution was stirred for 1 h at 0 °C and then warmed to room temperature. After 18 h triethylamine (5.57 g, 55 mmol) and methanesulfonyl azide (6.679 g, 55.2 mmol) were added via syringe, and the solution was stirred for 18 h at room temperature. The diazoacetoacetate was isolated, after adding 25 mL of water, by extraction with ether (3 × 50 mL). The organic phase was washed with water (3 × 50 mL) and brine (3 × 50 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the crude dark orange diazoacetoacetate was generally used without further purification in the subsequent acetyl cleavage step. Purification by column chromatography over silica gel (4:1 hexanes: EtOAc) afforded the diazoacetoacetate as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) 5.95−5.78 (comp, 3 H), 5.25 (dq, J = 17.2, 2.2 Hz, 3 H), 5.20−5.12 (comp, 3 H), 4.26 (s, 2 H), 3.98−3.92 (comp, 6 H), 3.44 (s, 6 H), 2.47 (s, 3 H).

Acetyl cleavage of the diazoacetoacetate was performed in THF (8 mL) to which was added $LiOH{\cdot}H_2O$ (6.71 g, 159 mmol) in 10 mL of water. The dark brown solution was stirred at room temperature for 15 min and then extracted with ether (3 × 25 mL). The organic phase was washed with water (3 × 25 mL) and brine (3 × 25 mL) and then dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure 5.96 g of crude diazoacetate was obtained. Purification by column chromatography on silica gel (2:1 hexanes:ethyl acetate) afforded the title compound as a yellow liquid (5.44 g, 16.8 mmol, 73% yield from the alcohol): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86 (ddt, J = 17.2, 10.4, 5.4 Hz, 3 H), 5.25 (dq, J = 17.2, 1.6 Hz, 3 H), 5.15 (dddd, J = 10.4, 1.6, 1.6, 1.3 Hz, 1 H), 4.72 (s, 1 H), 4.26 (s, 2 H), 3.94 (ddd, J = 5.3, 1.6, 1.3 Hz, 6 H), 3.43 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3 (s), 134.8 (d), 116.3 (t), 72.2 (t), 68.8 (t), 64.2 (t), 44.5 (d), 33.2 (s); IR ($CHCl_3$) 2114 (C═N_2), 1693 (C═O), 1647 (C═C) cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.18; H, 7.41; N, 8.57.

5,5-Di(2-propen-1-oxymethyl)-3,7-dioxabicyclo[9.1.0]decan-2-one (16). To a refluxing solution of anhydrous CH_2Cl_2 (5.0 mL) containing catalyst (10 μmol, 1.0 mol %) was added diazoacetate **15** (324 mg, 1.00 mmol) in 10 mL of CH_2Cl_2 at 1.0 mL/h. After addition was complete, the reaction solution was refluxed for an additional hour, then cooled to room temperature and filtered through a short plug of silica gel to remove the catalyst. After removal of the solvent under reduced pressure, the residue was analyzed directly by GC and ^{1}H NMR methods. Product isolation of the colorless liquid was achieved by column chromatography on silica gel (4:1 hexanes:EtOAc): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (ddt, J = 17.4, 10.5, 5.4 Hz, 1 H), 5.86 (ddt, J = 17.3, 10.4, 5.5 Hz, 1 H), 5.28−5.21 (comp, 2 H), 5.17−5.13 (comp, 2 H), 4.68 (d, J = 11.4 Hz, 1 H), 4.27 (d, J = 11.4 Hz, 1 H), 4.23 (dd, J = 11.7, 5.1 Hz, 1 H), 3.97 (dt, J = 5.5, 1.3 Hz, 2 H), 3.92 (dt, J = 5.5, 1.3 Hz, 2 H), 3.74 (d, J = 11.3 Hz, 1 H), 3.46 (d, J = 9.4 Hz, 1 H), 3.41 (d, J = 9.4 Hz, 1 H), 3.34 (d, J = 9.3 Hz, 1 H), 3.30 (d, J = 9.3 Hz, 1 H), 3.27 (dd, J = 11.7, 7.9 Hz, 1 H), 1.84 (ddd, J = 13.6, 7.9, 5.8 Hz, 1 H), 1.58−1.48 (m, 1 H), 1.34 (q, J = 5.8 Hz, 1 H), 1.06 (dt, J = 5.0, 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4 (s), 134.8 (d), 134.6 (d), 116.5 (t), 116.3 (t), 76.3 (t), 73.6 (t), 72.2 (t), 70.7 (t), 70.0 (t), 69.8 (t), 66.1 (t), 44.5 (s), 19.9 (d), 19.2 (d), 12.2 (t); IR ($CHCl_3$) 1723 (C═O), 1647 (C═C) cm^{-1}; mass spectrum, *m/z* (relative abundance) 199 (1), 197 (4), 157 (7), 139 (22), 127 (22), 99 (100), 97 (20), 83 (27), 82 (24), 81 (51), 71 (35), 55 (77). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.61; H, 8.20.

1,2-Benzenedimethanol. To a stirring solution of phthalide (25.0 g, 186 mmol) in 350 mL of THF at 0 °C was added 225 mL of a 1.0 M solution of LAH in THF. This solution was allowed to warm to room temperature overnight, and the reaction was quenched by the sequential addition of 6.5 mL of water, 6.5 mL of 15% aqueous NaOH, and 19.5 mL of water. The solid was removed by filtration and washed with 300 mL of ethyl acetate. The solution was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield 23.9 g (93% yield) of 1,2-benzenedimethanol as a pale yellow crystalline solid, mp 63−64 °C (lit mp[29] 63−65 °C).

2-(2-Methyl-2-propen-1-yloxymethyl)benzyl Alcohol. Sodium hydride (2.67 g, 66.7 mmol, 60% dispersion in oil) was washed with

(29) Adkins, H.; Wojcik, B.; Covert, L. W. *J. Am. Chem. Soc*. **1933**, *55*, 1669.

hexanes and suspended in 250 mL of THF, and the suspension was cooled to 0 °C. To this vigorously stirred suspension was added 1,2-benzenedimethanol (21.5 g, 155 mmol) dissolved in 100 mL of THF. After addition was complete, stirring was continued for an additional 15 min, whereupon methallyl bromide (6.00 g, 44.4 mmol) dissolved in 10 mL of THF was added in one portion via syringe. The solution was allowed to warm to room temperature overnight, and the reaction was quenched by addition of 80 mL of 10% aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Filtration, solvent removal, and purification via column chromatography (2:1 hexanes:ethyl acetate) yielded 8.28 g (97% yield) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.29 (comp, 4H), 4.99 (d, J = 1.0 Hz, 1H), 4.94 (d, J = 1.6 Hz, 1H), 4.70 (s, 2H), 4.59 (s, 2H), 3.96 (s, 2H), 2.98 (bs, 1H), 1.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 141.5, 137.0, 130.9, 129.8, 128.9, 114.0, 75.3, 71.9, 64.6, 20.6; IR ($CHCl_3$) 3450, 3109, 2882, 1658, 1484, 1082, 916 cm^{-1}; mass spectrum, *m/z* (relative abundance) 193 (M, 2), 174 (8), 163 (11), 135 (9), 119 (100), 104 (53), 91 (99), 77 (51), 65 (18), 55 (14). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.46. The column was then flushed with 750 mL of 100% ethyl acetate to yield 14.43 g (94% recovery) of pure 1,2-benzenedimethanol.

2-(2-Propen-1-yloxymethyl)benzyl Alcohol. Sodium hydride (2.48 g, 62.0 mmol, 60% dispersion in oil) was treated with 1,2-benzenedimethanol (20.0 g, 144 mmol) as in the previous procedure, and the resulting anion was alkylated with allyl bromide (5.00 g, 41.3 mmol). Workup and purification via column chromatography (2:1 hexanes: ethyl acetate) yielded 7.01 g (95% yield) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.29 (comp, 4H), 5.96 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.31 (ddd, J = 17.2, 2.7, 1.5 Hz, 1H), 5.24 (ddd, J = 10.4, 2.7, 1.3 Hz, 1H), 4.67 (s, 2 H), 4.63 (s, 2H), 4.08 (dt, J = 5.8, 1.4 Hz, 2H), 2.58 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 135.7, 133.9, 129.8, 129.4, 128.7, 127.8, 117.8, 71.1, 71.0, 63.4; IR ($CHCl_3$) 3458, 3082, 2864, 1746, 1466, 1422, 1072, 1012, 959 cm^{-1}; mass spectrum, *m/z* (relative abundance) 160 (10), 120 (100), 91 (84), 77 (62), 65 (65). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.04; H, 7.68. The column was then flushed with 750 mL of 100% ethyl acetate to yield 13.29 g (93% recovery) of pure 1,2-benzenedimethanol.

2-(2-Methyl-2-propen-1-yloxymethyl)benzyl diazoacetate (17a) was prepared by a one-pot modification of the procedure of Doyle[28] in which 2-(2-methyl-2-propen-1-yloxymethyl)benzyl alcohol (4.57 g, 23.7 mmol), dissolved in 100 mL of THF, was treated with triethylamine (240 mg) and diketene (2.48 g, 29.5 mmol) at 0 °C. The solution was allowed to come to room temperature overnight, at which point ^{1}H NMR analysis of the crude reaction mixture indicated complete conversion of the starting alcohol to the desired acetoacetate. The solution was cooled to 0 °C, triethylamine (2.88 g, 28.4 mmol) and methanesulfonyl azide (3.15 g, 26.1 mmol) were added sequentially, the solution was allowed to warm to room temperature, and stirring was continued until ^{1}H NMR analysis indicated that the diazo transfer reaction was complete. The solution was again cooled to 0 °C, and LiOH (2.28 g, 94.8 mmol), dissolved in 100 mL of water, was added. The temperature of the solution was maintained at 0 °C until ^{1}H NMR analysis revealed the cleavage to be complete, at which time 100 mL of ether was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). The organic layer was washed with brine (1 × 50 mL) and dried over $MgSO_4$. Removal of solvent under reduced pressure and purification by column chromatography (6:1 hexanes:ethyl acetate) yielded 3.89 g (63% yield) of pure product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.30 (m, 4H), 5.31 (s, 2H), 4.99 (s, 1H), 4.92 (s, 2H), 4.78 (s, 1H), 3.94 (s, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 141.9, 136.7, 134.2, 129.2, 129.0, 128.4, 128.0, 112.4, 74.4, 69.5, 46.3, 19.5; IR (neat), 2121 (C═N_2), 1702 (C═O) cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.50; H, 6.23; N, 10.63.

2-(2-Propen-1-yloxymethyl)benzyl diazoacetate (**17b**) was prepared by the one-pot procedure described above and purified by column chromatography (6:1 hexanes:ethyl acetate) to yield 2.23 g (65% yield) of pure product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.26 (comp, 4H), 5.95 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.32 (ddd, J = 17.2, 3.0, 1.6 Hz, 1H), 5.31 (s, 2H), 5.23 (ddd, J = 10.4, 3.0, 1.0 Hz, 1H), 4.79 (bs, 1H), 4.59 (s, 2H), 4.02 (dt, J = 5.6, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 136.4, 134.1, 129.1, 128.9, 127.9, 117.1, 69.6, 63.8, 46.1; IR (neat), 2104 (C═N_2), 1693 (C═O) cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found; C, 63.47; H, 5.71; N, 11.34.

General Procedure for Formation of Macrocyclic Lactones from 17. In a typical experiment, 1.00 mmol of diazoacetate was dissolved in 10 mL of freshly distilled CH_2C1_2 and added via syringe pump over 10 h to 3.7 mg (1.0 mol %) of $Cu(MeCN)_4PF_6$ in 10 mL of refluxing CH_2Cl_2. Upon completion of addition, the solution was passed through a short plug of silica gel to remove the catalyst. The plug was washed with 100 mL of CH_2Cl_2, the solvent was removed, and the crude reaction mixture was purified by flash chromatography in the solvent system indicated.

5,6-Benzo-3,8-dioxa-10-methyl-*cis*-bicyclo[8.1.0]undecan-2-one (18a): 6:1 hexanes:ethyl acetate; 74% yield with $Cu(MeCN)_4PF_6$; mp 69.0−69.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.28 (comp, 4H), 5.36 (d, J = 12.1 Hz, 1H), 5.8 (d, J = 12.1 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.28 (d, J = 11.7 Hz, 1H), 3.74 (d, J = 10.6 Hz, 1H), 3.28 (d, J = 10.6 Hz, ^{1}H), 1.61 (dd, J = 7.9, 5.8 Hz, 1H), 1.35 (dd, J = 5.4 Hz, 1H), 1.25 (s, 3H), 0.88 (dd, J = 8.1, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 136.8, 135.8, 131.1, 130.7, 128.8, 128.4, 73.2, 72.2, 66.3, 27.6, 27.5, 23.8, 20.5; IR ($CHCl_3$): 2969, 2882, 1719, 1283, 1117 cm^{-1}; mass spectrum, *m/z* (relative abundance) 232 (M^+, 3), 175 (8), 162 (11), 145 (13), 120 (63), 104 (100), 91 (52), 55 (94). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.26; H, 6.90. The cyclopropane moiety was determined to have the cis-configuration due to the observation of an NOE interaction between the proton adjacent to the carbonyl group and the methyl group.

5,6-Benzo-3,8-dioxa-*cis*-bicyclo[8.1.0]undecanan-2-one (18b): 6:1 hexanes:ethyl acetate; 63% yield with $CuPF_6$; mp 64−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (comp, 4H), 5.30 (d, J = 12.1 Hz, 1H), 5.18 (d, J = 12.1 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.26 (d, J = 11.6 Hz, 1H), 4.06 (dd, J = 10.7, 6.0 Hz, 1H), 3.14 (dd, J = 10.7, 9.2 Hz, 1H), 1.85 (ddd, J = 9.1, 7.9, 5.8 Hz, 1H), 1.72−1.62 (m, 1H), 1.28 (ddd, J = 6.1, 5.8, 4.9 Hz, 1H), 1.10 (ddd, J = 8.1, 7.9, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 136.9, 135.8, 131.1, 129.0, 128.5, 72.7, 68.8, 66.5, 20.7, 19.9, 13.4; IR ($CHCl_3$) 2882, 1728, 1291, 1108 cm^{-1}; mass spectrum, *m/z* (relative abundance) 218 (M^+, 4), 145 (12), 129 (28), 120 (100), 99 (43), 91 (39), 78 (15), 65 (11), 55 (17). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.48; H, 6.43.

Intra- versus Intermolecular Cyclopropenation of 17a. Diazoacetate **17a** (130 mg, 0.500 mmol) was dissolved in 5 mL of freshly distilled CH_2Cl_2 and added via syringe pump at 1.0 mL/h to a solution of $Rh_2(OAc)_4$ (2.2 mg, 1.0 mol %) and variable amounts of methyl methallyl ether in 5 mL of refluxing CH_2Cl_2. After the addition was complete, the reaction solution was passed through a short plug of silica to remove the catalyst. The reaction mixture was directly analyzed by GC and, following evaporation of the solvent and excess ether, by ^{1}H NMR. Chromatographic separation of the products on silica (5:1 hexanes:ethyl acetate) provided intermolecular cyclopropanation products **21** and ylide rearrangement product **22** in 83% isolated yield from the reaction performed in methylmethallyl ether as the solvent.

2-(2-Methyl-2-propen-1-yloxymethyl)benzyl 2-Methyl-2-methoxy methylcyclopropanecarboxylate (21). Colorless oil; identified from the mixture of ***E*** and ***Z*** isomers; **21*E*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.25 (comp, 4 H), 5.25 (d, J = 12.8 Hz, 1 H), 5.19 (d, J = 12.8 Hz, 1 H), 5.02−4.99 (m, 1 H), 4.94−4.91 (m, 1 H), 4.57 (s, 2 H), 3.94 (s, 2 H), 3.33 (s, 3 H), 3.24 (d, J = 9.9 Hz, 1 H), 3.19 (d, J = 9.9 Hz, 1 H), 1.77 (d, J = 0.9 Hz, 3 H), 1.72 (dd, J = 8.2, 5.6 Hz, 1 H), 1.25 (s, 3 H), 1.12 (dd, J = 5.6, 4.6 Hz, 1 H), 1.01 (dd, J = 8.2, 4.6 Hz, 1 H); **21*Z***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.24 (comp, 4 H), 5.25 (d, J = 12.8 Hz, 1 H), 5.20 (d, J = 12.8 Hz, 1 H), 4.81−4.79 (m, 1 H), 4.75−4.73 (m, 1 H), 4.58 (s, 2 H), 3.94 (s, 2 H), 3.53 (d, J = 10.1 Hz, 1 H), 3.42 (d, J = 10.1 Hz, 1 H), 3.22 (s, 3 H), 1.77 (s, 3 H), 1.64 (dd, J = 7.9, 5.5 Hz, 1 H), 1.23 (s, 3 H), 1.22 (dd, J = 5.5, 4.5 Hz, 1 H), 0.91 (dd, J = 7.9, 4.5 Hz, 1 H). ***trans*-3-(2-Methyl-2-propen-1-oxy)-4-vinyl-8,9-benzo-1,6-dioxocyclodecan-2-one (22):** colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52−7.21 (comp, 4 H), 5.86 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.37 (s, 2 H), 5.20 (ddd, J = 17.2, 1.6, 1.0

Hz, 1 H), 5.16 (ddd, J = 10.4, 1.6, 0.6 Hz, 1 H), 4.96−4.95 (m, 1 H), 4.88−4.87 (m, 1 H), 4.67 (d, J = 9.8 Hz, 1 H), 4.48 (d, J = 9.8 Hz, 1 H), 4.21 (d, J = 12.4 Hz, 1 H), 3.95 (d, J = 3.5 Hz, 1 H), 3.84 (d, J = 12.4 Hz, 1 H), 3.84 (t, J = 10.3 Hz, 1 H), 3.51 (dd, J = 10.3, 3.5 Hz, 1 H), 3.20−3.13 (m, 1 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 141.6, 136.1, 134.9, 134.8, 131.6, 128.6, 128.1, 127.9, 117.7, 112.9, 77.8, 74.9, 72.2, 68.8, 66.8, 46.8, 19.6. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.81; H, 8.18.

***cis*-4-(2-Methyl-2-propen-1-yloxy)-2-buten-1-ol (23).** Sodium hydride (887 mg, 22.2 mmol, 60% dispersion in oil) was treated with *cis*-2-buten-1,4-diol (5.22 g, 59.2 mmol) according to the procedure for preparation of 2-(2-methyl-2-propen-1-yloxymethyl)benzyl alcohol, and the resulting anion was alkylated with methallyl bromide (2.00 g, 14.8 mmol) to yield, after workup and purification via column chromatography (2:1 hexanes:ethyl acetate), 2.06 g (98% yield) of the title compound as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83−5.73 (comp, 2H), 4.97 (bs, 1H), 4.91 (bs, 1H), 4.20 (d, J = 6.6 Hz, 2H), 4.03 (d, J = 6.1 Hz, 2H), 3.90 (s, 2H), 2.00 (s, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 131.7, 127.3, 112.0, 73.7, 64.8, 57.8, 18.8; IR (neat) 3388, 2921, 2853, 1647, 1239, 1086, 1035 cm^{-1}; mass spectrum, *m/z* (relative abundance) 142 (M, 8), 124 (63), 95 (55), 55 (75). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.61; H, 9.87.

2-[*cis*-4-(2-Methyl-2-propen-1-yloxy)-2-buten-1-yloxymethyl]benzyl Alcohol (24). *cis*-4-(2-Methyl-2-propen-1-yloxy)-2-buten-1-ol (2.06 g, 14.5 mmol) was dissolved in 50 mL of freshly distilled CH_2Cl_2, triethylamine (1.69 g, 16.7 mmol) was added, and the solution was cooled to 0 °C. Methanesulfonyl chloride (1.74 g, 15.2 mmol) was added via syringe and the solution was stirred at 0 °C for 1 h. The solution was diluted with 50 mL of CH_2Cl_2, water was added, and the layers were separated. The organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed to yield 2.94 g (92% yield) of product that was taken on without further purification.

To a suspension of NaH (775 mg, 19.3 mmol, 60% dispersion in oil) at 0 °C in 125 mL of THF was added 6.23 g (45.1 mmol) of 1,2-benzenedimethanol dissolved in 40 mL of THF. The above mesylate (2.84 g, 12.9 mmol) of the methallyl ether of 2-buten-1,4-diol was dissolved in 20 mL of THF and added in one portion via syringe. The solution was allowed to come to room temperature overnight, water was added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine (2 × 40 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to yield a pale yellow oil. Column chromatography (3:2 hexanes:ethyl acetate) yielded 2.94 g (87% yield) of pure product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.29 (comp, 4H), 5.80−5.74 (comp, 2 H), 4.95 (bs, 1 H), 4.90 (bs, 1 H), 4.67 (s, 2 H), 4.62 (s, 2 H), 4.15 (d, J = 5.0 Hz, 2 H), 4.00 (d, J = 5.0 Hz, 2H), 3.99 (s, 2H), 2.68 (bs, 1H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 140.4, 135.7, 130.2, 129.9, 129.5, 128.8, 128.4, 127.8, 112.4, 74.2, 71.1, 65.8, 65.4, 63.5, 19.5; IR (neat) 3440, 3083, 3032, 2930, 2857, 1650, and 1623 cm^{-1}; mass spectrum, *m/e* (relative abundance) 172 (6), 135 (10), 121 (82), 104 (24), 91 (100), 77 (64), 69 (23), 55 (81). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.16; H, 8.37. Washing of the column with 100% ethyl acetate allowed recovery of 4.36 g (98%) of excess 1,2-benzenedimethanol.

2-[*cis*-4-(2-Methyl-2-propen-1-yloxy)-2-buten-1-yloxymethyl]benzyl diazoacetate (25) was prepared by the one-pot procedure described for **10a** and purified by column chromatography (7:1 hexanes:ethyl acetate) to yield 2.68 g (62%) of pure product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 4H), 5.78−5.71 (m, 2H), 5.30 (s, 2H), 4.95 (bs, 1H), 4.89 (bs, 1H), 4.79 (bs, 1H), 4.57 (s, 2H), 4.11 (d, J = 3.7 Hz, 2H), 4.01 (d, J = 3.9 Hz, 2H), 3.87 (s, 2H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 141.9, 136.3, 134.2, 129.6, 129.2, 129.0, 128.9, 128.3, 128.0, 112.1, 112.0, 74.0, 69.8, 65.9, 65.3, 63.8, 46.1, 19.3; IR ($CHCl_3$) 2121 (C═N_2), 1693 (C═O) cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.26; H, 6.71; N, 8.41.

Diazo Decomposition of 25. To a solution of $Cu(MeCN)_4PF_6$ (3.7 mg, 1.0 mol %) in 10 mL of refluxing CH_2Cl_2 was added diazoacetate **25** (330 mg, 1.00 mmol) in 10 mL of anhydrous CH_2Cl_2 at a rate of 2.0 mL/h using a syringe pump. After addition was complete, the reaction mixture was passed through a plug of silica gel to remove the catalyst. The resulting solution was purified by flash chromatography on silica (8.1 hexanes:ethyl acetate) to yield 176 mg (58% yield) of **26** and 34 mg (12% yield) of **27**. For reactions involving dirhodium(II) catalysts the same procedure was employed except that addition of **25** occurred at a rate of 1.0 mL/h.

(*Z*)-5,6-Benzo-3,8,13-trioxa-15-methylbicyclo[13.1.0]-*cis*-hexadec-10-en-2-one (26): white solid, mp 96−97 °C; ^{1}H NMR (300 $CDCl_3$) δ 7.45 (d, J = 7.3 Hz, 1H), 7.39−7.28 (comp, 3H), 5.92−5.78 (comp, 2H), 5.64 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.24 (dd, J = 11.9, 7.8 Hz, 1H), 4.16 (dd, J = 11.9, 7.8 Hz, 1H), 4.05 (dd, J = 11.6, 7.0 Hz, 1H), 3.87 (dd, J = 11.6, 6.2 Hz, 1H), 3.66 (d, J = 10.2 Hz, 1H), 3.53 (dd, J = 10.2 Hz, 1H), 1.62 (dd, J = 7.6, 5.7 Hz, 1H), 1.21 (dd, J = 5.7, 4.7 Hz, 1H), 1.22 (s, 3H), 0.89 (dd, J = 7.6, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 139.2, 134.5, 132.1, 132.0, 130.3, 130.2, 129.6, 128.9, 73.0, 69.7, 66.8, 66.4, 66.1, 28.2, 26.8, 23.5, 20.1; IR ($CHCl_3$): 2873, 1728, 1466, 1414, 1169, 1090 cm^{-1}; mass spectrum, *m/z* (relative abundance) 302 (M^+, 1), 233 (13), 215 (18), 183 (8), 175 (9), 169 (3), 162 (5), 143 (7), 129 (10), 121 (39), 113 (100), 104 (70) 91 (48), 78 (20), 55 (59). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.38; H, 7.36.

***cis*-3-(2-Methyl-2-propen-1-oxy)-4-vinyl-8,9-benzo-1,6-dioxocyclodecan-2-one (27):** colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52−7.21 (comp, 4 H), 5.86 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.37 (s, 2 H), 5.20 (ddd, J = 17.2, 1.6, 1.0 Hz, 1 H), 5.16 (ddd, J = 10.4, 1.6, 0.6 Hz, 1 H), 4.96−4.95 (m, 1 H), 4.88−4.87 (m, 1 H), 4.67 (d, J = 9.8 Hz, 1 H), 4.48 (d, J = 9.8 Hz, 1 H), 4.21 (d, J = 12.4 Hz, 1 H), 3.95 (d, J = 3.5 Hz, 1 H), 3.84 (d, J = 12.4 Hz, 1 H), 3.84 (t, J = 10.3 Hz, 1 H), 3.51 (dd, J = 10.3, 3.5 Hz, 1 H), 3.20−3.13 (m, 1 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 141.6, 136.1, 134.9, 134.8, 131.6, 128.6, 128.1, 127.9, 117.7, 112.9, 77.8, 74.9, 72.2, 68.8, 66.8, 46.8, 19.6. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.48; H, 7.27. The cis geometry of **27** was established by NOE experiments on the lactone formed by hydrogenolysis, which conveniently removed the 1,2-benzenedimethyl linker.

X-ray Structure of 26.. Crystals grew as colorless prisms from hexanes:ethyl acetate. The data crystal was cut from a larger crystal and had approximate dimensions: 0.38 × 0.50 × 0.50 mm. Colorless crystals of **26** ($C_{18}H_{22}O_4$) were monoclinic, space group $C2/c$, with a = 28.055(2), b = 11.712(1), c = 9.883(1)Å, b = 98.425(5)°, V = 3211.3(3) Å ^{3}, Z = 8, ρcalc = 1.25 g/cm^{-3}. Data were collected out to 2θ = 60° by the ω-scan technique on a Siemens P4 diffractometer at −95 °C using graphite monochromatized Mo Kα radiation (λ = 0.71073Å). The 9983 reflections were measured of which 4690 reflections were unique [$R_{int}(F^2)$ = 0.022]. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-hydrogen atoms. The hydrogen atom positions were observed in a ΔF map and refined with isotropic displacement parameters. The final $R_w(F^2)$ = 0.109 with a goodness of fit = 1.022 for refining 288 parameters. The conventional $R(F)$ = 0.0430 for 3495 reflections with $F_o > 4(s(F_o))$. Data reduction, decay correction, structure solution, and refinement were done using the SHELXTL/PC softwarepackage.[30] Tables of positional and thermal parameters, bond lengths, and angles and torsion angles and figures are located in the Supporting Information.

Preparation of Alcohol 28. To a continuously stirred solution of NaH (0.71 g, 30 mmol, 60% dispersion in oil) in 150 mL of anhydrous THF was added 1,2-benzenedimethanol (9.60 g, 69.5 mmol) in 50 mL of THF. After cooling to 0 °C, 3-bromo-2-methylpropene (2.68 g, 19.9 mmol) was added by pipette, and the resulting solution was allowed to warm to room temperature while stirring for 3 days. Water (50 mL) was added, and the solution was extracted three times with 20-mL portions of ethyl acetate. The combined extract was washed with 40 mL of brine and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the product mixture was refrigerated overnight whereupon excess 1,2-benzenedimethanol crystallized and was filtered (5.75 g, 41.6 mmol, 84% recovery). The residual oil (3.67

(30) Sheldrick, G. M. SHELXTL/PC (Version 5.03); Siemens Analytical X-ray Instruments, Inc.: Madison, WI, U.S.A., 1994.

g, 19.1 mmol, 96% yield) was identified as 2-(2-methyl-2-propen-1-yloxymethyl)benzyl alcohol. This alcohol was dissolved in 60 mL of anhydrous CH_2Cl_2 to which was added, after cooling to 0 °C, triethylamine (2.89 g, 28.5 mmol) followed by methanesulfonyl chloride (2.30 g, 20.1 mmol). Stirring was continued at 0 °C for an additional 45 min, whereupon water (20 mL) was added and the organic layer was separated. The organic layer was washed with H_2O (30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 5.02 g of mesylate ester (18.6 mmol, 97% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47−7.35 (comp, 4 H), 5.39 (s, 2H), 5.00−4.98 (m, 1 H), 4.95−4.93 (m, 1 H), 4.59, 3.95 (s, 2 H), 2.92 (s, H), 1.77 (s, 3 H).

To sodium hydride (0.66 g, 28 mmol, 60% dispersion in oil) suspended in 65 mL of anhydrous THF at 0 °C was added 1,2-benzenedimethanol (8.94 g, 64.7 mmol) slowly but continuously. After stirring at room temperature for 15 min the previously prepared mesylate ester (5.02 g, 18.6 mmol) was added neat, and the resultant mixture was stirred for 20 h. Water (40 mL) was added, and the solution was extracted with two 30-mL portions of ethyl acetate. The combined organic extract was washed with brine (30 mL) and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to afford 4.33 g of colorless **28** (13.9 mmol, 79% yield) following crystallization of unreacted 1,2-benzenedimethanol (5.91 g, 42.8 mmol, 91% recovery). Spectral data were consistent with assigned structure **28**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.27 (comp, 12 H), 4.99−4.97 (m, 1 H), 4.92−4.90 (m, 1 H), 4.68 (s, 2 H), 4.67 (s, 2 H), 4.66 (s, 2 H), 4.53 (s, 2 H), 3.89 (quin, J = 0.5 Hz,), 2.95 (s, 1 H), 1.75 (dt, J = 0.5, 0.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.1, 136.6, 135.9, 135.7, 130.1, 129.6, 129.0, 128.9, 128.8, 128.0, 127.9$_4$, 127.9$_2$, 113.1, 112.4, 74.2, 71.3, 69.8, 69.6, 63.7, 19.6; IR (film) 3462, 3075, 2870, 1070, 1008, 777, 759, 752 cm^{-1}; mass spectrum, *m/z* (relative abundance) 222 (14), 174 (22), 145 (12), 131 (15), 121 (32), 120 (21), 119 (80), 118 (25), 105 (39), 104 (83), 93 (49), 91 (100), 77 (47), 55 (21). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.93; H, 7.68.

Preparation of diazoacetate 29 was accomplished by a modification of the three-step reaction described by Doyle[28] in which **28** (5.95 g, 19.1 mmol), dissolved in 65 mL of THF, was treated with triethylamine (0.50 g, 4.9 mmol) and, after cooling to 0 °C, diketene (2.25 g, 26.7 mmol) with continued stirring for 20 h, then triethylamine (2.13 g, 21.0 mmol), and methanesulfonyl azide (2.78 g, 23.0 mmol) for 20 h after which water (50 mL) was added, and the resulting mixture was extracted with five 40-mL portions of ethyl acetate. The combined extract was washed with brine (50 mL) and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Column chromatographic purification on silica gel (3:1 hexanes:EtOAc) provided the diazoacetoacetate (6.54 g, 15.4 mmol, 81% yield) as an orange oil. This purified diazoacetoacetate was dissolved in THF (50 mL) and cooled to 0 °C. A solution of LiOH (1.48 g, 61.7 mmol) in water (50 mL) was cooled to 0 °C and then added to the reaction solution. After the solution was stirred for 6 h, ethyl acetate (40 mL) was added, and the organic solution was washed twice with 30-mL portions of water and with brine (40 mL). After drying over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure. Column chromatographic purification on silica gel (3:1 hexanes:EtOAc) provided 3.89 g of a light yellow oil identified as **29** (10.2 mmol, 66% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.25 (comp, 8 H), 5.29 (s, 2 H), 4.99−4.97 (m, 1 H), 4.92−4.89 (m, 1 H), 4.75 (br s, 1 H), 4.65 (s, 2 H), 4.63 (s, 2 H), 4.54 (s, 2 H), 3.90 (br s, 2 H), 1.74 (br s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 142.0, 136.5, 136.1, 134.2, 129.2, 129.1, 128.6, 128.4, 128.0, 127.7, 127.7, 127.6, 112.4, 112.2, 74.1, 69.9, 69.8, 69.4, 63.8, 46.1, 19.4; IR (film) 2112 (C═N$_2$), 1695 (C═O), 1640 (C═C) cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_4N_2$: C, 69.43; H, 6.36, N, 7.36. Found: C, 69.45; H, 6.32; N, 7.40.

Diazo Decomposition of 29. To $Cu(MeCN)_4PF_6$ (3.7 mg, 1.0 mol %) dissolved in 5.0 mL of refluxing anhydrous CH_2Cl_2, contained in an oven-dried two-neck round bottom flask fitted with a condenser and septum, was added diazoacetate **27** (0.380 g, 1.00 mmol) in 5.0 mL of CH_2Cl_2 via syringe pump at a rate of 1.0 mL/h. The reaction solution was filtered through a plug of silica to remove the catalyst, and solvent was evaporated under reduced pressure to produce 320 mg of product (0.909 mmol, 91% yield) consisting of a mixture of **30*Z*** and **30*E***. These isomers were separated by column chromatography on silica gel (9:1 hexanes:ethyl acetate) to give 156 mg (0.443 mmol, 44% yield) of pure **30*Z*** and 69 mg (0.196 mmol, 20% yield) of pure **30*E***. In $Rh_2(OAc)_4$ catalyzed reactions, these same products were isolated in 57 and 7% yield, respectively. For **30*Z***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48−7.25 (comp, 8 H), 5.69 (d, J = 11.5 Hz, 1 H), 4.71 (d, J = 11.5 Hz, 1 H), 4.70 (d, J = 11.7 Hz, 1 H), 4.65 (d, J = 11.7 Hz, 1 H), 4.61 (d, J = 11.2 Hz, 1 H), 4.56 (d, J = 11.0 Hz, 1 H), 4.49 (d, J = 11.0 Hz, 1 H), 4.28 (d, J = 11.2 Hz, 1 H), 3.84 (d, J = 11.0 Hz, 1 H), 3.68 (d, J = 11.0 Hz, 1 H), 1.69 (dd, J = 7.7, 5.6 Hz, 1 H), 1.23 (s, 3 H), 1.19 (dd, J = 5.6, 4.6 Hz, 1 H), 0.89 (dd, J = 7.7, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 137.3, 136.7, 136.1, 134.3, 131.2, 130.4, 129.0, 128.9, 128.7, 128.3, 127.8, 127.7, 71.2, 70.9, 70.6, 69.2, 65.0, 26.9, 25.9, 22.2, 18.0; IR ($CDCl_3$) 1716 (C═O), 1173, 1078 cm^{-1}. For **30*E***: mp 110.5−112.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (dd, J = 7.6, 1.1 Hz, 1 H), 7.47 (dd, J = 6.0, 2.9 Hz, 1 H), 7.40−7.25 (comp, 6 H), 5.51 (d, J = 11.8 Hz, 1 H), 4.96 (d, J = 10.7 Hz, 1 H), 4.86 (d, J = 11.8 Hz, 1 H), 4.76 (d, J = 11.0 Hz, 1 H), 4.73 (d, J = 10.6 Hz, 1 H), 4.64 (d, J = 10.6 Hz, 1 H), 4.56 (d, J = 11.0 Hz, 1 H), 4.24 (d, J = 10.7 Hz, 1 H), 4.13 (d, J = 11.7 Hz, 1 H), 2.74 (d, J = 11.7Hz, 1 H), 1.84 (dd, J = 8.0, 5.7 Hz, 1 H), 1.22 (s, 3 H), 1.14 (dd, J = 5.7, 5.1 Hz, 1 H), 0.77 (dd, J = 8.0, 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 137.8, 136.5$_4$, 136.4$_9$, 133.6, 131.1, 131.0, 129.4$_4$, 129.4$_3$, 129.3, 128.1, 128.0$_8$, 128.0$_5$, 78.4, 71.1, 70.2, 69.2, 65.5, 27.3, 25.6, 15.6, 14.5; IR ($CDCl_3$) 1724, 1170, 1111 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_4$ (**30Z/E**): C, 74.98,; H, 6.86. Found: C, 74.91; H, 6.78.

Preparation of alcohol 31 followed the same procedure as that for the formation of **28**. Alcohol **28** (4.31 g, 13.8 mmol) dissolved in 75 mL of anhydrous CH_2Cl_2 was treated with Et_3N (2.09 g, 20.6 mmol) and then methanesulfonyl chloride (1.73 g, 15.1 mmol) to form the methanesulfonate in 94% yield. The ^{1}H NMR spectrum confirmed this product assignment with an absorption at δ 5.35. Treatment of this methanesulfonate ester with the sodium salt of 1,2-benzenedimethanol gave, after a reaction time of 5 h and workup, 4.65 g of the desired alcohol (10.8 mmol, 83% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.23 (comp, 12 H), 4.98−4.96 (m, 1 H), 4.90−4.88 (m, 1 H), 4.60 (s, 2 H), 4.58$_5$ (s, 4 H), 4.57$_6$ (s, 2 H), 4.56 (s, 2 H), 4.51 (s, 2 H), 3.87 (br s, 2 H), 3.02 (br s, 1 H), 1.72 (br s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.9, 140.2, 136.4, 136.3, 136.1, 135.7, 129.7, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 127.9$_4$, 127.8$_8$, 127.7, 127.6, 112.3, 112.2, 74.1, 71.0, 69.7$_3$, 69.6$_9$, 69.6$_6$, 69.3, 63.2, 19.4; IR (film) 3392, 3068, 3032, 2915, 2868, 1070, 1008 cm^{-1}. Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.61; H, 7.42.

Preparation of diazoacetate 32 was accomplished by the same procedure as that employed for the formation of **29**. Diketene condensation was performed with **29** (4.61 g, 10.7 mmol), diketene (1.26 g, 15.0 mmol), and Et_3N (0.5 g, 5 mmol), and stirring was continued for 22 h. Diazo transfer utilized Et_3N (1.19 g, 11.8 mmol) and MsN_3 (1.56 g, 12.8 mmol), and the reaction mixture was stirred for 23 h. Deacylation was performed using pyrrolidine (4.30 g, 55.4 mmol), and column chromatography using silica gel (3:1 hexanes:ethyl acetate) provided purification. Diazoacetate **32** (2.71 g, 5.41 mmol, 51% overall yield) was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.25 (comp, 12 H), 5.27 (s, 2 H), 4.98−4.96 (m, 1 H), 4.91−4.89 (m, 1 H), 4.73 (br s, 1 H), 4.62 (s, 2 H), 4.61$_4$ (s, 2 H), 4.60$_8$ (s, 2 H), 4.58 (s, 2 H), 4.53 (s, 2 H), 3.88 (quin, J = 0.5 Hz, 2 H), 1.73 (dt, J = 0.5, 1.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 136.4, 136.2$_2$, 136.1$_6$, 136.0$_8$, 134.1, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 127.9, 127.7, 127.6, 127.5, 112.1$_2$, 112.1$_0$, 74.1, 69.8$_3$, 69.8$_0$, 69.7$_0$, 69.6$_8$, 69.3, 63.8, 46.1, 19.4; IR (film) 2112 (C═N$_2$), 1695 (C═O), 1642 (C═C) cm^{-1}. Anal. Calcd for $C_{30}H_{32}O_5N_2$: C, 71.96; H, 6.44; N, 5.59. Found: C, 72.03; H, 6.40; N, 5.54.

Diazo Decomposition of 32. To $Rh_2(OAc)_4$ (1.1 mg, 2.5 mmol) dissolved in 2.5 mL of CH_2Cl_2 was added **32** (125 mg, 0.25 mmol) in 2.5 mL of CH_2Cl_2 via syringe pump according to the same procedure as that used for diazo decomposition of **29**. After the reaction was complete, the reaction solution was filtered through a short plug of silica gel, and the solvent was removed under reduced pressure to provide 80 mg of crude product consisting of a mixture of **33Z** and **33E**. This mixture was chromatographed on silica gel (10:1 hexanes:ethyl acetate) to provide 69.7 mg (0.15 mmol, 59% yield) of the purified

product; we were not able to separate the individual isomers, so products were analyzed from the two-component mixture. The $Cu(MeCN)_4PF_6$ catalyzed reaction of **32** was performed on a 1.00 mmol scale; crude product yield was 78%, and **33** was isolated after chromatography in 42% yield. For **33Z**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49−7.23 (comp, 12 H), 5.32 (d, J = 12.9 Hz, 1 H), 5.27 (d, J = 12.9 Hz, 1 H), 4.71 (d, J = 12.2 Hz, 1 H), 4.70 (s, 2H), 4.67 (d, J = 11.8 Hz, 1 H), 4.66 (d, J = 12.2 Hz, 1 H), 4.63 (s, 2 H), 4.63 (d, J = 11.2 Hz, 1 H), 4.59 (d, J = 11.2 Hz, 1 H), 4.59 (d, J = 11.2 Hz, 1 H), 4.38 (d, J = 11.8 Hz, 1 H); 3.66 (d, J = 10.0 Hz, 1 H), 3.59 (d, J = 10.0 Hz, 1 H), 1.68 (dd, J = 7.8, 5.6 Hz, 1 H), 1.24 (s, 3 H), 1.21 (dd, J = 5.6, 4.6 Hz, 1 H), 0.89 (dd, J = 7.8, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 136.7, 136.6, 136.3, 136.2, 136.1, 135.0, 129.5, 129.4, 129.2, 129.0_2, 129.0_1, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 72.1, 71.2, 71.1, 70.9, 70.3, 70.1, 63.7, 27.5, 25.4, 22.7, 19.7. For **33E**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50−7.25 (comp, 12 H), 5.22 (d, J = 12.0 Hz, 1 H), 5.18 (d, J = 12.0 Hz, 1 H), 4.77 (d, J = 12.0 Hz, 1 H), 4.76 (d, J = 11.7 Hz, 1 H), 4.68 (d, J = 12.0 Hz, 1 H), 4.67 (s, 2 H), 4.65 (d, J = 11.7 Hz, 1 H), 4.60 (d, J = 11.8 Hz, 1 H), 4.53 (d, J = 11.2 Hz, 1 H), 4.46 (d, J = 11.8 Hz, 1 H), 4.28 (d, J = 11.2 Hz, 1 H), 3.70 (d, J = 10.1 Hz, 1 H), 2.76 (d, J = 10.1 Hz, 1 H), 1.72 (dd, J = 8.2, 5.6 Hz, 1 H), 1.21 (s, 3 H), 1.06 (dd, J = 5.6, 4.6 Hz, 1 H), 0.84 (dd, J = 8.2, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 137.6, 137.3, 136.8, 136.4, 135.5, 134.0, 131.3, 130.5, 129.4, 129.2, 129.1, 129.0, 128.8, 128.4, 128.2, 128.0, 127.9, 127.4, 77.2, 76.6, 71.3, 71.2, 70.7, 70.1, 64.7, 29.7, 26.4, 25.1, 17.3. IR ($CDCl_3$) for **33Z** + **33E**: 3072, 3031, 2960, 2867, 1720, 1166, 1080 cm^{-1}. Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.25; H, 6.83. Found: C, 76.12; H, 6.74.

Acknowledgment. We are grateful to the Robert A. Welch Foundation and the National Science Foundation for their support of this research. We wish to thank Wietske Smid for preliminary work in the synthesis of selected macrocycle precursors. A Jean Dreyfus Boissevain Undergraduate Scholarship for Excellence in Chemistry from the Camille and Henry Dreyfus Foundation to A.B.M. is greatly appreciated.

Supporting Information Available: Tables of positional and thermal parameters, bond lengths, angles, and torsional angles and figures for the crystal structure of **26** (13 pages). See any current masthead page for ordering and Internet access instructions.

JA971687Z