nitrogen. The reaction mixtures were titrated with 0.100 N HCl to a phenolphthalein end point. Near the end point, the DBE flask requires vigorous shaking (~10 s) between each drop in order to decolorize the DBE layer without overshooting the end point. The DBE layer should be decolorized with ~0.1 mL of 0.100 N HCl beyond the amount required to decolorize the water layer. The end point should be checked by back-titration with 0.100 N NaOH until the technique has been mastered. The DBE titration measures the residual base, and the difference between the $H_2O$ and DBE titrations give the active butyllithium. About 2.5 M solutions were usually used in order to minimize the amount of hexane added but still allow accurate measurement. Aliquots were measured to the nearest 0.01 mL with gas-tight syringes (Hamilton) fitted with Chaney adapters when several reaction mixtures were set up simultaneously.

When butyllithium standardized in this way was used to initiate anionic polymerizations, molecular weights within 3% of the theoretical weights were obtained.[40]

### Typical Experimental Procedures

**0.3 M Reactions.** To 1.10 mmol of Cu(I) salt in a septum-sealed 10-mL recovery flask also containing a magnetic stir bar was added 50 μL of nonane (weighed to the nearest 0.1 mg). The flask was cooled to 0 °C, and 2.2 mL of dry THF was added. The contents were stirred magnetically to dissolve the nonane and suspend the Cu(I) salt, and then the flask was cooled to −50 °C in a 2-propanol bath, the temperature of which was controlled by the occasional addition of powdered dry ice. A 0.85-mL aliquot of 2.60 M (0.12 M residual base) butyllithium (2.21 mmol) was added, and the reaction mixture was stirred for 15 min at −50 °C before being cooled to −78 °C (dry ice/2-propanol slurry). A 0.3-mL sample (10% of the total volume) was withdrawn with a cooled syringe and injected into a septum-sealed vial containing 1 mL of nitrogen-purged 3 M aqueous ammonium chloride solution. This "prequench" was used to measure the amount of octane formed during the preparation of the cuprate. After 10 min at −78 °C, 210 mg (1.00 mmol) of iodocyclohexane and 50 μL of dodecane (weighed to the nearest 0.1 mg) dissolved in 0.5 mL of THF at 0 °C were added. The reaction mixtures prepared this way were quenched after times ranging from 1 s to 3 h by adding 2 mL of nitrogen-purged 3 M ammonium chloride solution or $D_2O$ (99.8% *d*, Aldrich). The quenched reaction mixtures were allowed to warm to room temperature, and 3 mL of ether was added. The organic phase was withdrawn with a disposable pipet and dried over anhydrous sodium sulfate. The products were analyzed by GLC calibrated with the dodecane internal standard.

**0.18 M Reactions.** These were carried out in the same manner as the 0.3 M reactions, but with 2.20 mmol of Cu(I) salt suspended in ~9 mL of dry THF in a 25-mL recovery flask, to which was added 4.40 mmol of BuLi (in ~2 mL of hexane) to form the cuprate in 11.0 mL of solution. Often, not all of the CuCN dissolved at −50 °C; these mixtures were stirred at 0 °C for 1-5 min, until they were homogeneous. A 1.0-mL prequench was removed at −78 °C with a cooled syringe. Unless otherwise noted, 1 equiv of substrate was added in 1.00 mL of THF cooled to 0 °C. Samples (1.0 mL) were withdrawn after various times at various temperatures with B-D disposable syringes cooled with dry ice. For the reaction mixtures that were quenched after short times, the procedure was carried out on half the above scale and the entire reaction mixture was quenched with 3 M ammonium chloride solution or $D_2O$. With $^1/_2$ in. × $^5/_8$ in. stir bars (Bel-Art No. F37110), it was possible to stir six flasks simultaneously with a Corning PC351 stirrer. PVC foam ice buckets (SGA No. P-1047-5) cut down to a depth of 6 cm were used for the cooling bath. Generally, two such sets of six reaction mixtures were run simultaneously, although on occasion three sets were run together.

(40) Bates, F. Unpublished results.

**Acknowledgment.** S.H.B. thanks H. Taube, M. Newcomb, J. San Filippo, E. Ashby, and D. Peters for helpful discussions.

# Annulation via Alkylation–Alder Ene Cyclizations. Pd-Catalyzed Cycloisomerization of 1,6-Enynes

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**Abstract:** A Pd(0)-catalyzed alkylation of an allyl substrate with a nucleophile containing a double or triple bond to permit subsequent thermal Alder ene reactions constitutes a novel annulation protocol. In the case of a triple bond, a Pd(2+) complex catalyzes an equivalent of an Alder ene reaction. This new cyclization is probed in terms of the effect of substitution on the olefin, the acetylene, and the tether connecting the two. The reaction produces both 1,4-dienes (Alder ene-type products) and 1,3-dienes. Mechanisms to account for the diversity of products are presented. The Pd(2+)-catalyzed reaction shows an ability to interact with remote nonreactive parts of substrates to affect conformation and thereby selectivity. Several advantages accrue to the Pd(2+)-catalyzed reaction. First, the reaction normally proceeds at temperatures between 25 and 65 °C instead of the >250 °C (in static systems) to >500 °C (in flow systems) for the thermal reaction. Second, reactions that fail thermally succeed via the metal-catalyzed process. Third, complementary regioselectivity may be observed. Fourth, the ligating properties of the metal catalyst offer opportunities for exercising control not possible in a simple thermal process. A novel cyclopentannulation of allyl alcohols and related derivatives evolves in which Pd(0) catalyzes formation of the first bond and a simple electronic switch to Pd(2+) catalyzes formation of the second bond.

Carbametalations of carbonyl groups, i.e., the additions of main-group organometallics to the carbon–oxygen π bond, represent a major classical synthetic reaction. Carbametalations of less polarized π systems, especially olefins and acetylenes, have only relatively recently come to be recognized as a general reaction type with certain types of metals, in particular those having accessible d-orbitals. Two such reactions have achieved synthetic importance. Carbacupration of acetylenes rapidly became a major synthetic entry to olefins of defined geometry.[1] The Heck arylation and vinylation involves the relatively rare carbametalation (i.e., carbapalladation) of an unactivated olefin.[2] The feasibility of such processes greatly expands the possibility of using olefins and acetylenes as versatile functional groups for C–C bond formation.[3]

* Address correspondence to this author at Stanford University.

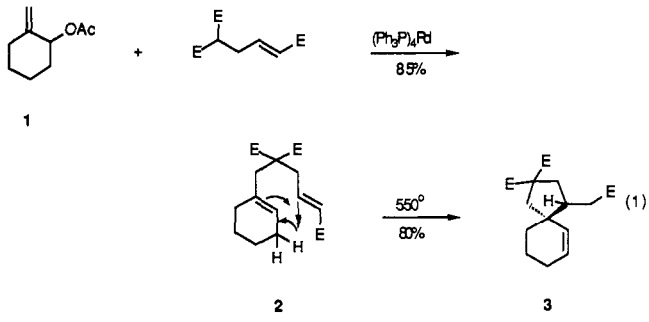
(1) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
(2) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146; *Org. React.* **1982**, *27*, 345.

0002-7863/91/1513-636$02.50/0 

In considering the existing reactions that effect allylations of olefins and acetylenes, the Alder ene reaction appears to have much greater potential than currently realized.[4] Being a condensation in which the product is a direct sum of the reactants, it maximizes chemical efficiency. Performed intramolecularly, cyclization becomes an isomerization. The harshness of the thermal reaction appears to limit its applicability. The development of a Lewis acid catalyzed[4c] version begins to address this issue but intrinsically suffers limitations. For example, the enophile must possess a Lewis basic site as is present in $\alpha,\beta$-unsaturated carbonyl compounds. The requirement for relatively strong Lewis acids is incompatible with many substrates of interest. The potential for higher chemoselectivity of transition-metal catalysts makes them attractive alternatives. In this paper, we report a palladium-catalyzed cyclization of 1,6-enynes to methylenecyclopentanes, which formally corresponds to an Alder ene product. In an ancillary study, we developed an annulation based upon allylic alkylation–Alder ene cyclization.[5]

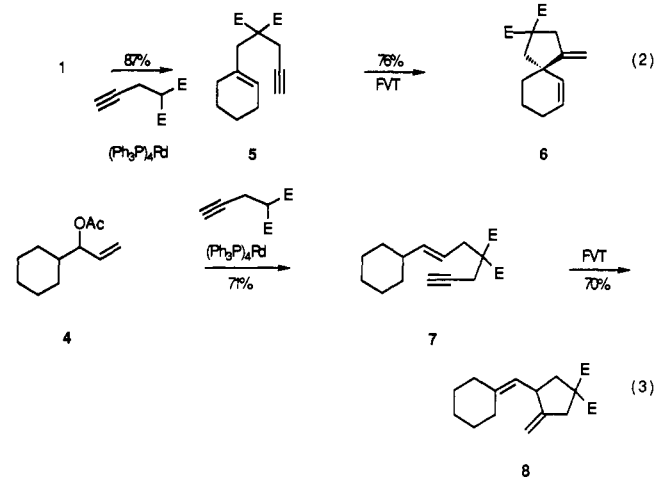
### Annulation via Sequential Alkylation–Alder Ene Cyclization

In the course of our studies of regiocontrolled allylic alkylation,[6,7] we envisaged an annulation sequence involving allylic alkylation followed by an intramolecular ene reaction according to eq 1.

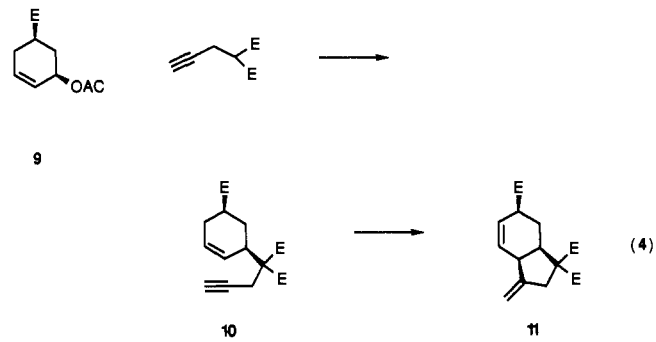



Indeed, alkylation proceeded chemo- and regioselectively to form **2**. As expected, high temperatures were required to effect the Alder ene reaction. Whereas thermolysis in mesitylene up to 220 °C led to either no reaction or decomposition, flash vacuum thermolysis (FVT) produced the cyclic compound as a single diastereomer in good yield, even though 550 °C was required. On the basis of the mechanism of the Alder ene reaction and precedent,[4,8] the stereochemistry depicted in **3** is assigned.

The sequence proves to be general. Thus, alkylation of dimethyl propargylmalonate with allyl acetates **1** or **4** under our typical conditions[9] produces the alkylation products **5** and **7**. FVT generates the carbocycles **6** and **8** in good yields.




Extension of the sequence to the formation of a fused-ring system led to employment of the allyl acetate **9**.[9] In effecting the Pd(0)-catalyzed alkylation of **9** with dimethyl propargylmalonate for an overnight reaction time, we observed the direct formation of the desired annulation product **11**, albeit in only 35% yield.




Since the Alder ene reaction normally required temperatures in excess of 200 °C in solution or 500 °C in a flow system, its proceeding at 65 °C seemed peculiar. Furthermore, alkylation under more carefully controlled conditions led only to the simple alkylation product **10** with no cyclization, even after prolonged reaction times. Surprisingly, thermolysis up to 650 °C led only to the recovery of enyne and in excess of 675 °C to decomposition. No thermal process effects the Alder ene reaction! Reasoning that the presence of adventitious amounts of oxygen might have produced Pd(2+) led us to investigate the effect of palladium acetate on the reaction. Indeed, even at room temperature, enyne was consumed with production of the methylenecyclopentane **11**. Interestingly, this one-pot annulation involves palladium in both C–C bond forming steps—Pd(0) to form the first and, after throwing an electronic switch, Pd(2+) to form the second. The dramatic effect of Pd(2+) in achieving a cyclization that failed thermally at any temperature attests to the usefulness of this metal-catalyzed reaction.

### Pd(2+)-Catalyzed Cycloisomerization of Enynes

A detailed study of the cyclization of enyne **10** with various palladium species revealed that the fastest reaction occurred with palladium acetate but its high reactivity did cause product degradation. Thus, the yield of **11** decreased from 60% at room temperature to 50% at the reflux temperature of THF. Phosphine ligands slowed the reaction such that elevated temperatures (>60 °C) were required but minimized product decomposition. Using 5 mol % of bis(triphenylphosphine)palladium acetate (**12**) in warm THF improved the yield to 70%. Switching to less polar benzene further enhanced the yield to 85%. On the other hand, bis(benzonitrile)palladium chloride effected cyclization only to the extent of 16%.

Using Pd(0) alkylation, we prepared enynes **13** and **14** from the corresponding acetates in 85% and 55% yields, respectively.

(3) For related reactions of general synthetic promise, see: Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. Dotz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587.

(4) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 557. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (c) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (d) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. (e) For a recent study, see: Mikami, K.; Takahashi, K.; Nakai, T. *Synlett* **1989**, *45*; *Chem. Lett.* **1987**, 2347.

(5) For preliminary studies of portions of this work, see: Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887. Trost, B. M.; Jebaratnam, D. J. *Tetrahedron Lett.* **1987**, *28*, 1611.

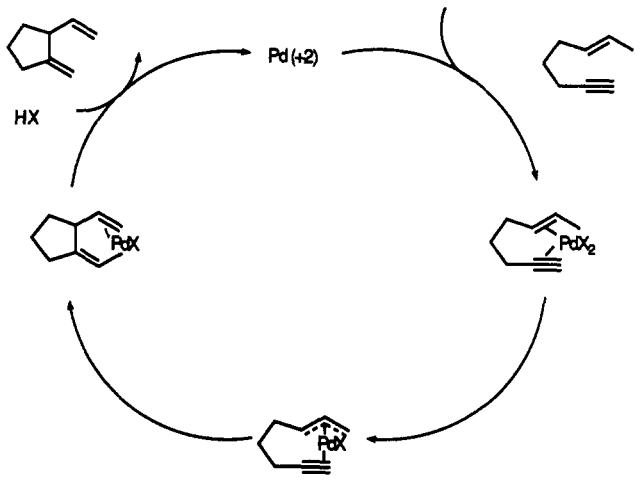
(6) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. Trost, B. M. *Fundam. Res. Homogeneous Catal.* **1984**, *4*, 117. Trost, B. M. *J. Organomet. Chem.* **1986**, *300*, 263.

(7) For some recent references, see: Trost, B. M.; Merlic, C. A. *J. Org. Chem.* **1990**, *55*, 1127. Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176. Trost, B. M.; Lautens, M. *Tetrahedron* **1987**, *43*, 4817. Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469. Trost, B. M.; Vercauteren, J. *Tetrahedron Lett.* **1985**, *26*, 131. Trost, B. M.; Lautens, M.; Hung, M.-H.; Carmichael, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 1641. Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837. Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757.

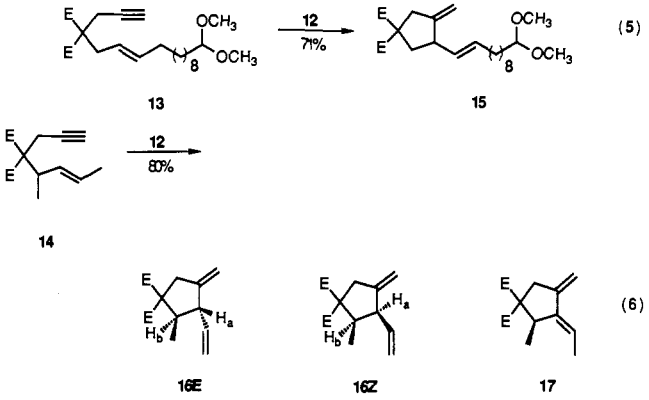
(8) Oppolzer, W.; Mahalanabis, K. K.; Battig, K. *Helv. Chim. Acta* **1977**, *60*, 2388.

(9) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

**Scheme I.** $\pi$-Allyl Pathway

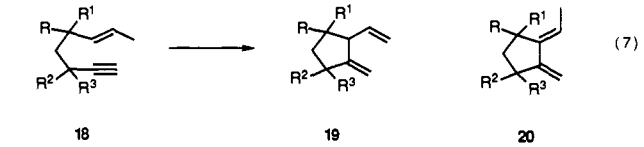



Cyclization of enyne **13** under our standard conditions (5 mol % **12**, PhH, reflux) gave the expected product **15** with the olefin geometry being pure *E*. Cyclization of enyne **14** gave the expected products **16*E*** and **16*Z*** but also an olefin-isomerized product **17** (4.5:1.5:1.0). The vicinal coupling constant $J_{ab}$ for **16*E*** of 6 Hz

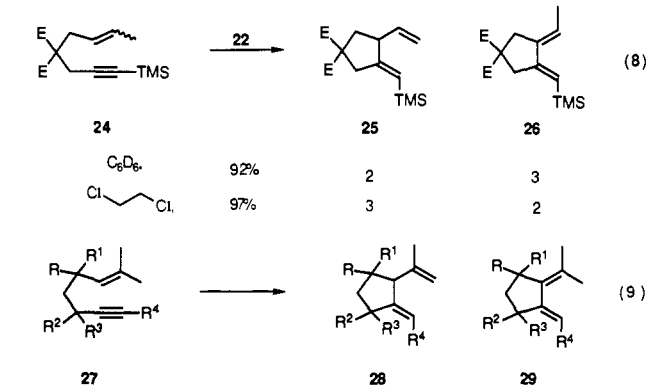



agrees with the coupling assigned for the *E* isomer in an analogous system where the *Z* isomer showed this coupling to be 4.5 Hz (vide infra). The diastereoselectivity (3:1) observed in this metal-catalyzed reaction significantly exceeds that found in thermal cyclization (1.8:1.0). The minor product, the conjugated diene **17**, did not arise by isomerization of the 1,4-dienes **16*E*** or **16*Z***. As will become apparent, varying amounts of such conjugated dienes arise depending upon substrate and ligand.

We systematically explored the effect of (1) olefin, (2) acetylene, and (3) tether substitution on the course of this reaction. In all cases where the olefin bears a terminal methyl group, substantial amounts of the conjugated 1,3-dienes were formed (eqs 7–11). Several trends are noted. The simpler the substitution pattern, the higher the proportion of 1,3-diene (cf eqs 7 and 8 vs eqs 9–11) formed.



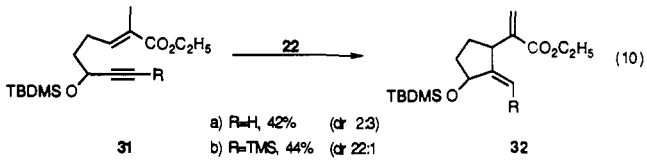

| | R | R¹ | R² | R³ | cat. | yield (%) | ratio (dr) 19 | 20 |
|---|---|---|---|---|---|---|---|---|
| a | PMBO | H | H | H | **21** | 42 | 1 (1:7.5) | 8 |
| | | | | | **22** | 33 | 4.5 (8:1) | 1 |
| | | | | | $Pd(OAc)_2$ | 17 | 12 (>99:1) | 1 |
| b | H | H | H | PMBO | **12** | 41 | 1 (3.5:1) | 1 |
| | | | | | **22** | 33 | 2 (1:1) | 1 |
| | | | | | $Pd(OAc)_2$ + TNP | 52 | 1 (2:1) | 2 |
| c | $CH_3$ | TBDMSO | H | H | **12** | 54 | 1 (2:1) | 1 |
| | | | | | **21** | 64 | 2 (1:2) | 5 |
| | | | | | $Pd(OAc)_2$ | 15 | only (2:1) | |
| d | H | H | $CH_3$ | TBDMSO | **12** | 80 | 3 (2:1) | 7 |
| | | | | | **21** | 86 | 1 (3.5:1) | 10 |
| | | | | | $Pd(OAc)_2$ | 87 | 2 (10:7) | 7 |

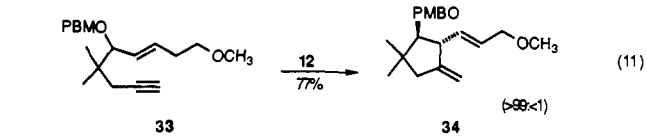






| | R | R¹ | R² | R³ | R⁴ | cat. | yield (%) | ratio (dr) 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|
| a | TBDMSO | H | H | H | H | **21** | 10 | 3.4 (1:1) | 1 |
| | | | | | | **22** | 14 | only (>99:<1) | |
| | | | | | | $Pd(OAc)_2$ | 14 | only (>99:<1) | |
| b | TBDMSO | $CH_3$ | H | H | H | **21** | 67 | only (2.3:1) | |
| | | | | | | **22** | 50 | only (2:1) | |
| | | | | | | $Pd(OAc)_2$ | 42 | only (3:1) | |
| c | H | H | PMBO | H | H | **12** | 19 | 6 (1:2) | 1 |
| | | | | | | **22** | 40 | 3.5 (1.2:1) | 1 |
| | | | | | | **23** | 47 | 4 (1:1) | 1 |
| d | H | H | TBDMSO | $CH_3$ | H | **12** | 44 | 3.5 (4:1) | 1 |
| | | | | | | **22** | 52 | 2 (3:1) | 1 |
| | | | | | | **23** | 43 | 5 (1:2) | 1 |
| e | H | H | HO | $CH_3$ | H | **12** | 18 | 12 (4:1) | 1 |
| | | | | | | **30** | 49 | 10 (4:1) | 1 |
| f | H | H | PMBO | H | $CO_2CH_3$ | **22** | 77 | 1.3 (>99:<1) | 1 |
| | | | | | | **23** | 49 | 1 (>99:<1) | 1 |




Ligands also have an effect on the 1,3- vs 1,4-diene ratio. In addition to catalyst **12**, we have examined complexes between palladium acetate and tri-*o*-tolylphosphine (**21**), *N*,*N*-bis(benzylidene)ethlenediamine (BBEDA, **22**), and triphenylarsine (**23**). The absence of any ligands favored the 1,4-diene product (eq 7, **18a,c**). The bulkier tri-*o*-tolylphosphine ligand favors formation of the 1,3-diene, whereas triphenylarsine (eq 9, **27c,d**) and BBEDA (eq 7, **18a,b**; eq 9, **27c,d**) enhance 1,4-diene formation.

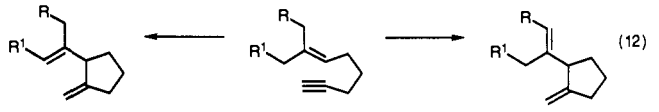
The nature of an oxygen substituent can play a role. Whereas the silyl ether **27d** gave a 3.5:1 ratio of 1,4- to 1,3-diene, the corresponding alcohol **27e** saw this ratio improve to 12:1. The yield of this cyclization improved upon using the complex of palladium acetate and 4-ethyl-2,6,7-trioxa-1-phosphabicyclo-[2.2.2]octane (**30**) formed in situ with no deterioration in this ratio.

The diastereoselectivity varied with substitution pattern. Whereas substrates bearing terminal acetylenes gave low to moderate diastereoselectivity, excellent diastereoselectivity was observed in all cases using a disubstituted acetylene (eqs 9f and 10b). Since a vinylsilane can be easily converted to the parent olefin, the silyl group serves as a diastereochemical control element. As shown in eq 10, a nonstereocontrolled reaction becomes highly stereocontrolled simply by incorporating the silicon substituent. Introducing the *gem*-dimethyl substituents as in **33** also imparts high diastereoselectivity (eq 11). In the terminal acetylene examples, a substituent at the allylic position provides good 1,2-diastereoselectivity but a substituent at the propargylic position does not provide good 1,3-diastereoselectivity. In **19a**, the stereochemistry of the major adduct is assigned as *E* based upon the comparison of the observed vicinal coupling constants of 6.5 and 4.5 Hz for the major and minor isomers, with the values of 7.1 and 5.6 Hz, respectively, calculated with molecular mechanics. Such an assignment agrees with the observation that the sterically bulkier substrate **27a** gives even higher vicinal diastereoselectivity.

By analogy, we assign the *E* stereochemistry to cyclized product **34**.

### Control of Regioselectivity by Remote Binding

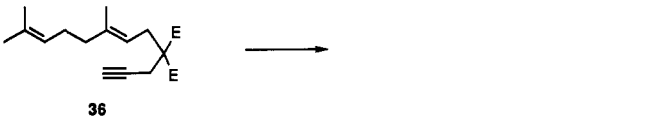
With a substrate containing a trisubstituted olefin like **35**, two possible 1,4-diene (ene-type) products can result (eq 12). We



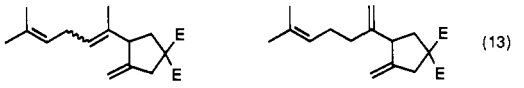
(12)

**35**

chose to explore this question in terms of the geranylmalonate **36**, which was readily available by Pd(0)-catalyzed alkylation of geranyl acetate (75%). To learn the intrinsic regiochemical bias



**36**



(13)

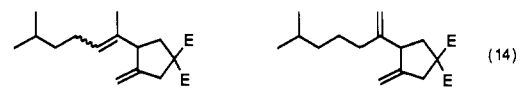
**37** **38**

| | | ratio (dr) | |
|---|---|---|---|
| cat. | yield (%) | **37** | **38** |
| FVT (625 °C) | 83 | only (1.2:1) | |
| $Pd(OAc)_2$ | 80 | 1 (>99:<1) | 16 |
| **12** | 73 | 1 (>99:<1) | 2.9 |
| **21** | nd | 1 (>99:<1) | 2.4 |

of this substrate in an Alder ene reaction, we examined the FVT that produced exclusively the diene **37**. From ene reactions of related examples, it appears that such regioselectivity is dependent upon this enophile, which suggests the selectivity derives from conformational factors.[10]

In contradistinction to the thermolysis of enyne **36**, palladium acetate catalyzed reaction produces the complementary 1,4-diene **38**. On the other hand, the phosphine-ligated catalyst **12** produced a nearly statistical distribution. In order to assess the role, if any, of the 10,11 double bond, we examined the related substrate lacking this unsaturation (**39**), which also was prepared by Pd-(0)-catalyzed alkylation of (*E*)-3,7-dimethyl-2-octenyl acetate (75% yield). The thermolysis of enyne **39** produced only 1,4-diene **40** in identical fashion to enyne **36**. However, the palladium acetate catalyzed reaction produced a 1.5:1 ratio of 1,4-diene, favoring the complementary isomer **41**. Addition of phosphine ligands did not appreciably alter the result.

**39**



(14)

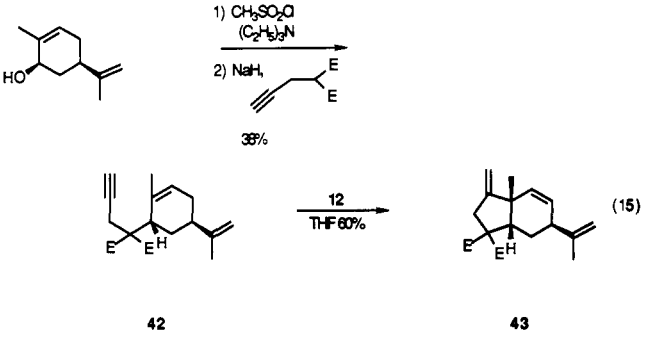
**40** **41**

| | | ratio (dr) | |
|---|---|---|---|
| cat. | yield (%) | **40** | **41** |
| FVT (575 °C) | 80 | only (1.2:1) | |
| $Pd(OAc)_2$ | 70 | 1.0 (1.5:1) | 1.5 |
| **12** | 70 | 1.0 (2:1) | 2.7 |
| **21** | 70 | 1.0 (4:1) | 1.4 |

The sharp contrast in behavior between enynes **36** and **39** clearly indicates that the remote double bond plays a significant role in the palladium-catalyzed cyclization of enyne **36**. The ratio of geometrical isomers of **37** also indicates a role for this double bond since **37** is produced as a single geometrical isomer in all the palladium reactions but in a nearly equal mixture in the thermolysis—a selectivity not exhibited by enyne **39**.

### Stereocontrolled Annulation

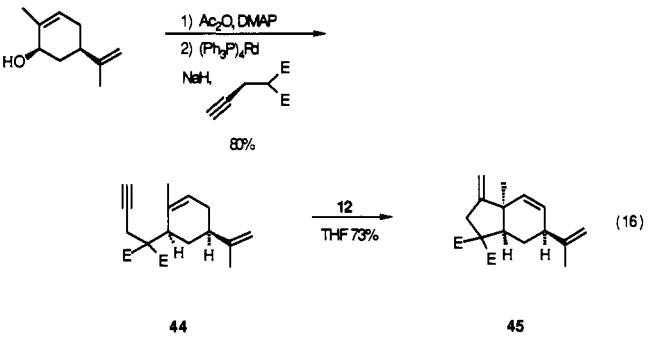
To illustrate the utility of this sequence, stereocomplementary annulation sequences were developed from a single diastereomeric alcohol. A classic displacement reaction with *cis*-carveol gave the inverted stereoisomeric product **42** (eq 15). Palladium-catalyzed



(15)

**42** **43**

cycloisomerization produces the annulated product wherein the five-membered ring is trans with respect to the isopropenyl group. On the other hand, Pd(0)-catalyzed alkylation gave the alkylated product with retention of configuration **44** (eq 16). Cyclo-



(16)

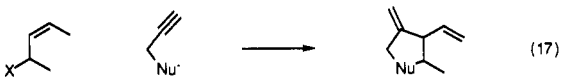
**44** **45**

isomerization creates the annulated product with the five-membered ring cis to the isopropenyl substituent. The overall result is an unusual annulation of allyl alcohols in which the stereochemistry is defined by the stereochemistry of the initial alkylation.

### Discussion

The palladium-catalyzed cyclization of 1,6-enynes provides a mild chemoselective approach to functionalized five-membered rings. Compared to thermal Alder ene reactions, it has several advantages. Typical temperatures range from ambient to 65 °C, in contrast to the >250 °C necessary for a static thermolysis and >500 °C for a flow system. Thus, some reactions that fail thermally now succeed.

In cases where both a thermal and metal-catalyzed reaction succeeds, they may complement each other. The enyne cyclization of eq 13 illustrates this point. The ability to use Pd(0) and Pd(2+) to catalyze sequential formation of each of two carbon–carbon bonds from an allyl acetate permits a facile one-pot annulation protocol of the type illustrated in eq 17 in which the regio- and



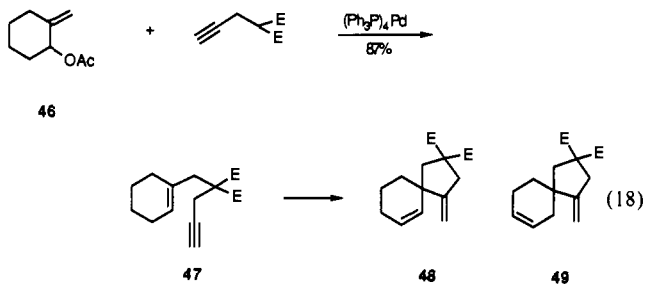
(17)

stereochemistry is dictated by the initial Pd(0) alkylation. To establish this point experimentally, the annulation of eq 4 was performed in a one-pot operation in 68% yield. This annulation extends to allyl systems bearing other leaving groups that can be either directly displaced (such as halide or sulfinate esters) or substituted with metal assistance (including but not limited to

(10) For no selectivity, see: Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023. For high selectivity, see: Cookson, R. C.; Duff, E.; Rigby, R. D. G. Unpublished work quoted in ref 4b.

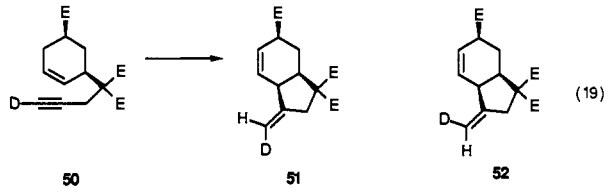
carboxylate,[7] carbonate,[11] phosphate,[12] alcohol,[13] ether,[14] epoxide,[15] nitro,[16] and sulfone[17]).

In one case, the palladium-catalyzed reaction led to some olefin isomerization. Spirocycle annulation using allyl acetate **46** gave both the expected cyclized product **48** as well as the olefin isomerization product **49** by use of 5 mol % of **12** in benzene at 66 °C (**48**:**49** = 3:1). Switching to acetonitrile as solvent decreased



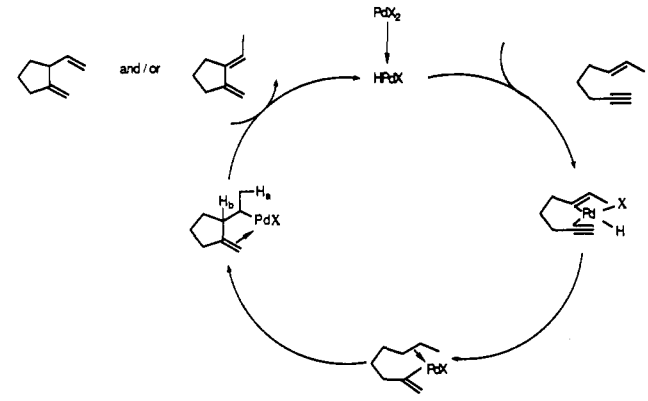

this ratio to 1.4:1.0. Use of 1,4-bis(diphenylphosphino)butane (dppb) improved this ratio to 5.7:1.0 (75% yield), whereas use of 1,2-bis(diphenylphosphino)ethane (dppe) completely inhibited reaction. In this case, the thermolysis at 575 °C proceeds with better regioselectivity since it produces only **48** in 76%. It is curious that, of the two olefins present in **48**, the endocyclic olefin is more labile to isomerization.

In order to provide some understanding of the above results as well as probe the mechanism of the reaction, we examined the fate of the monodeuterated substrate **50** (eq 19) containing >95%

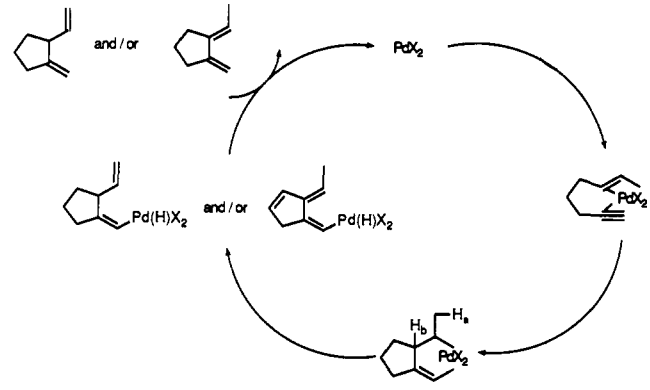



$d_1$ as determined by NMR spectroscopy. Performing the reaction with **12** as the catalyst in benzene-$d_6$ and following it by NMR spectroscopy revealed that the signal intensity for the vinyl protons of cyclohexene to the exocyclic olefin remained constant at 2:1, indicating no loss of deuterium. Also, the starting enyne **50** shows no loss of deuterium during the course of the reaction. On the other hand, the stereochemical integrity of the exocyclic olefin deteriorated from 4.5:1 for **51**–**52** after 30 min to 2.9:1 after 60 min and 1.9:1 after 90 min. The $^2$H NMR spectrum of this final product showed two signals at $\delta$ 5.11 (major) and 4.91 (minor) in this same ratio. Thus, isomer **51** represents the kinetic product that is equilibrated under the conditions of the reaction. No migration of either double bond is detectable. Since we subsequently established that H–D exchange of the acetylenic hydrogen

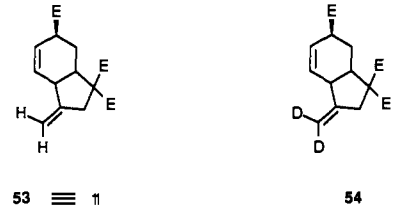
**Scheme II.** Hydridopalladation Pathway




**Scheme III.** Palladacyclopentene Pathway




is possible,[18] the appearance of signals for both syn and anti deuterium may arise by the presence of the disproportionation products **53** and **54**. The fact that the starting material showed




no evidence for proton incorporation and the terminal methylene group remained $^1$H over the course of the entire reaction suggests the unlikelihood of any scrambling. Spectroscopy also showed no evidence for the presence of appreciable amounts of either **53** or **54**.

Extrapolating the ratio of **51** to **52** to time zero indicates a high selectivity for forming a single isomer **51**. The scrambling appears to be a side reaction unrelated to the cyclization pathway.

Three mechanisms appear most reasonable, as outlined in Schemes I–III. The known ability to form $\pi$-allyl complexes from olefins and Pd(2+)[19] and the addition of such units to unsaturation[20] support the $\pi$-allyl pathway. Such a pathway has several deficiencies. It fails to satisfactorily account for the total lack of reactivity of 1,6-dienes since an acetylene should not be required for either step. More importantly, it fails to account for the competitive formation of 1,3-dienes—a process that can become the exclusive pathway depending upon the substitution of the substrate.[5] Furthermore, the ability to effect cyclization of

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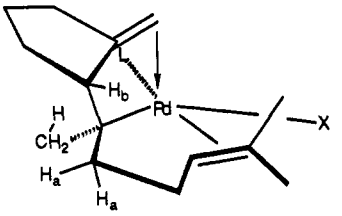
(20) For intramolecular examples, see: Trost, B. M.; Luengo, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8239. Negishi, E.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 291. Oppolzer, W.; Swenson, R. E.; Pachinger, W. *Helv. Chim. Acta* **1989**, *72*, 14 and earlier references in that series.

substrates to 1,3-dienes that lack allylic hydrogens also detracts from the attractiveness of Scheme I.[5] It is possible that 1,4- and 1,3-diene products form by two totally different pathways. However, since it is not necessary to invoke totally separate parallel pathways (see Schemes II and III), requring such a complication should not be invoked unless necessary.

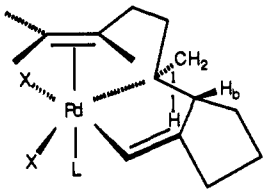
The well-documented ability of palladium–hydrogen and palladium–carbon bonds to add across sites of unsaturation provides support for Scheme II.[2,21] Support for Scheme III derives from the documented formation of metallacyclopentadienes from two acetylenes[22,23] and metallacyclopentanes from an olefin and acetylene.[24,25]

Schemes II and III account for most of the available facts. The initiation of cyclization in both by reactions at the acetylene accounts for the requirement of such a functional group in the substrate. Both accommodate competitive formation of both 1,4- and 1,3-dienes arising by palladium insertion into either C–$H_a$ or C–$H_b$, respectively. The general preferential formation of the 1,4-diene involves preferential insertion into C–$H_a$. The requirement of a dihedral angle between C–Pd and the β-C–H to be as close to 0° as possible accounts for this observation since C–$H_b$ is nearly orthogonal to the C–Pd bond in Scheme III and >90° in Scheme II in the critical intermediates. In fact, the internal coordination depicted in Scheme II must be broken for formation of the conjugated 1,3-dienes. The requirement for bidentate coordination of the enyne accounts for shutting down the catalytic cycle by the addition of dppe but not with dppb. Schemes II and III permit monodentate coordination of a ligand since pentacoordinate Pd(2+) forms easily and rapidly.[26] The inability to expel one of the phosphine ligands of dppe from Pd in contrast to the greater dissociability of a phosphine of dppb accounts for this observation.

Both Schemes II and III nicely explain the regioselectivity observed with the geranyl substrate of eq 13. The cyclic structures **55** and **56** arise by complexation of the remote double bond.



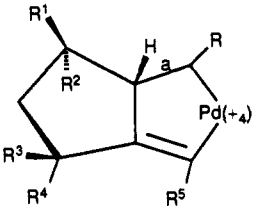

**55**




**56**

Assuming that hydrogen migration is initiated by β-hydrogen insertion, the dihedral angle between the C–Pd bond and the β-C–H bond wants to be as close to 0° as possible. By virtue of the ring structures, the methylene hydrogens ($H_a$) are constrained to have a dihedral angle of >90° and therefore geometrically are inaccessible for such an insertion. Similarly, the allylic hydrogen $H_b$ is not situated favorably for insertion by the palladium as pointed out earlier. Thus, the hydrogens of the methyl group constitute the geometrically most favorably disposed, which accounts for the high selectivity observed for palladium acetate. Two observations confirm the critical role of binding of the remote double bond. First, the substrate lacking this functional group gives nearly a statistical distribution of the two possible 1,4-diene products. Second, addition of a ligand that can effectively compete with the olefin, such as a phosphine, also moves the product distribution toward a statistical mixture. Thus, we have an excellent illustration of how simple transition-metal catalysts may exercise enzyme-like control of an organic compound. As in an enzymatic reaction, the palladium recognizes more than the reacting centers. By binding to the remote double bond, palladium changes the conformation of the tether and thereby the selectivity.

The diastereoselectivity is also accommodated within the context of either Scheme II or III. Considering the palladacyclopentene intermediate of Scheme III, the preference for the trans vicinal diastereoselectivity is obvious as revealed in **57**. The palladacyclopentene bond "a" and C–$R^2$ are nearly eclipsed, which destabilizes the transition state leading to the cis product, thereby favoring trans. The factors favoring the high 1,3-diastereoselectivity are more subtle. The model reveals that a substantial $A_{1,3}$ strain exists between $R^4$ and $R^5$. Thus, when $R^5$ is H, the minimization of this strain leads to low selectivity, but when $R^5$ is larger than H, a strong preference for the trans isomer should exist. Thus, the $R^5$ substituent serves as a stereochemical relay group. The fact that $R^5$ = TMS gave very high selectivity allows formation of products in which the silicon is ultimately replaced by hydrogen with high diastereoselectivity as well. Unfortunately, we have not yet been able to establish independently that the 1,3-stereochemistry is trans. At present, such an assignment derives only from consideration of the above model. A parallel




**57**

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set of arguments lead to the same predictions if we invoke Scheme II.

Ligand effects on these reactions appear largely to attenuate the reactivity of palladium acetate. Rates appear fastest with use of the salt alone, but yields frequently suffer. Ligands slow the reaction (a room-temperature reaction may require 60 °C in the presence of a ligand) but improve yields substantially. The beneficial effect of BBEDA on yields may also derive from its greater amelioratiing effect on palladium acetate because of its stronger donor properties. However, the fact that substrates involving disubstituted acetylenes react very slowly, if at all, with phosphine ligands but proceed nicely with BBEDA suggests a more substantive role for this ligand. Nitrogen ligands are known to stabilize Pd(4+).[27-29] Thus, it would be reasonable to suggest that BBEDA promotes the pathway of Scheme III in which such an unusual oxidation state of palladium is involved.

Mechanistically, we cannot distinguish between the pathways of Schemes II and III. It is possible that both may be operative depending upon the substrate and the ligands. Nevertheless, synthetically, this metal-catalyzed cyclization of 1,6-enynes to 1-methylene-2-vinylcyclopentanes provides an excellent complement to the thermal Alder ene chemistry. Most importantly, the ligating properties of the metal offer opportunities to control selectivity not possible in the thermal process. We have demonstrated this ability with respect to regio- and diastereoselectivity. Further efforts will focus on asymmetric induction by the use of chiral ligands.

## Experimental Section

**General Techniques.** Reactions were generally run under a positive pressure of dry nitrogen. Anhydrous solvents or reaction mixtures were transferred by oven-dried syringe or cannula. Solvents and reagents were generally distilled before use: acetonitrile, dichloromethane, dichloroethane, diisopropylamine, and dimethylformamide from calcium hydride; benzene, dioxane, ether, tetrahydrofuran (THF), and toluene from sodium benzophenone ketyl; and pyridine and triethylamine from potassium hydroxide. Flash chromatography following the method of Still employed E. Merck silica gel (Kieselgel 60, 200–400 mesh). Analytical thin-layer chromatography was performed with 0.2-mm coated commercial silica gel plates (E. Merck, DC-Plaskitkfolien, Kieselgel 60 $F_{254}$). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are also uncorrected. Several reactions were performed in an NMR tube in benzene-$d_6$ and ratios of products determined before and after chromatography.

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Bruker WP-200, Bruker WP-270, Bruker AM-500, Varian Gemini 300, Varian XL-400, or Nicolet 300 instrument. Chemical shifts are reported in $\delta$, downfield from tetramethylsilane. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; b, broad. Coupling constants are reported in hertz. Carbon-13 nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Joel FX-60 (15-MHz), Joel FX-200 (50.1-MHz), Bruker AM-500 (125-MHz), or Varian Gemini 300 (75-MHz) instrument and are reported in $\delta$ relative to the center line of a triplet at 77.00 ppm for deuteriochloroform.

Infrared (IR) spectra were recorded in 0.1-mm path length sodium chloride cavity cells on a Beckman Acculab 7, Perkin-Elmer 1420, or Mattson Polaris. Mass spectra (MS) were recorded on an AE1-MS902, Kratos MS25, or Kratos MS80 spectrometer at an ionizing current of 98 mA and an ionizing voltage of 70 eV, unless otherwise noted, and are reported as $m/e$ (relative intensity). Microanalyses were performed by Spang Microanalytical Laboratories.

**Preparation of Methyl 5,5-Bis(methoxycarbonyl)-6-(1-cyclohexenyl)-2(*E*)-hexenoate (2).** After a mixture of 264 mg (1.15 mmol) of methyl 5,5-bis(methoxycarbonyl)-2(*E*)-pentenoate[30] and 0.238 mL (1.15 mmol) of BSA in THF was heated at reflux for 1 h, 8 mg (3 mol %) of triphenylphosphine, 154 mg (1.0 mmol) of 2-acetoxymethylenecyclohexane (**1**), and 35 mg (3 mol %) of tetrakis(triphenylphosphine)-palladium were added, and the resultant solution was heated at reflux for 16 h. Evaporation of solvent in vacuo followed by flash chromatography (4:1 hexane–ether) yielded 271 mg (85%) of the titled compound. IR (neat): 1740, 1651, 1449 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.76 (1 H, dt, $J$ = 15, 7 Hz), 5.79 (1 H, dt, $J$ = 15, 1.5 Hz), 5.42 (1 H, bs), 3.69 (9 H, s), 2.72 (1 H, dt, $J$ = 7.0, 1.5 Hz), 2.59 (2 H, s), 1.92 (2 H, bs), 1.75 (2 H, bs), 1.48 (4 H, m). Molecular weight (MW) for $C_{17}H_{24}O_6$: calcd 324.1573, found 324.1566.

**Preparation of 2,2-Bis(methoxycarbonyl)-4-[(methoxycarbonyl)-methyl]spiro[4.5]dec-6-ene (3).** The neat diene **2** (40 mg, 0.17 mmol) was distilled (180 °C (0.1 mm)) into a horizontally mounted nonpacked quartz tube that was heated in an oven at 550 °C in a 0.1-mm vacuum and the product collected in a dry ice trap. Flash chromatography (3:1 hexane–ether) gave 32 mg (80%) of the titled compound. IR (neat): 1740 cm$^{-1}$. $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 5.68 (1 H, dt, $J$ = 10.0, 3.5 Hz), 5.49 (1 H, d, $J$ = 6.4 Hz), 3.70 (3 H, s), 3.62 (3 H, s), 2.58 (1 H, m), 2.33 (2 H, d, $J$ = 6.4 Hz), 2.40–2.05 (4 H, m), 1.94 (2 H, bs), 1.70–1.40 (4 H, m). MW for $C_{17}H_{24}O_6$: calcd 324.1573, found 324.1565.

**Preparation of Methyl 2-(1′-Cyclohexenylmethyl)-2-(methoxycarbonyl)-4-pentynoate (5).** BSA (0.020 mL, 0.10 mmol), allylic acetate **4**[31] (83 mg, 0.5 mmol), triphenylphosphine (7 mg, 5 mol %), and 0.75 mL of a THF solution of tetrakis(triphenylphosphine)palladium (30 mg, 5 mol %) were added to a solution of sodium dimethyl propargylmalonate prepared from 170 mg (1.0 mmol) of dimethyl propargylmalonate and 36 mg (60% dispersion, 0.9 mmol) of sodium hydride in 0.75 mL of THF. After 3-h heating at reflux, 3 mL of hexane was added and the mixture directly flash chromatographed (6:1 hexane–ether) to give 120 mg (85%) of the titled product. IR ($CDCl_3$): 3304, 2120, 1731, 1650, 1435 cm$^{-1}$. $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 5.57 (1 H, s), 3.74 (6 H, s), 2.80 (2 H, d, $J$ = 2.5 Hz), 2.77 (2 H, bs), 2.05 (1 H, m), 2.00 (2 H, bs), 1.79 (2 H, bs), 1.55 (4 H, bs). Anal. Calcd for $C_{14}H_{20}O_4$: C, 68.16: H, 7.63. Found: C, 68.02; H, 7.45.

**Preparation of 3,3-Bis(methoxycarbonyl)-1-methylenespiro[4.5]dec-6-ene (6).** As above, FVT of 25 mg (0.09 mmol) of enyne **5** gave 19 mg (76%) of the titled compound after purification by flash chromatography (2:1 hexane–ether). IR ($CDCl_3$): 1730, 1652, 1434 cm$^{-1}$. $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 5.72 (1 H, dt, $J$ = 9.8, 3.6 Hz), 5.30 (1 H, dt, $J$ = 9.8, 2.0 Hz), 4.90 (1 H, s), 4.72 (1 H, s), 3.73 (3 H, s), 3.68 (3 H, s), 3.21 (1 H, dt, $J$ = 14 Hz), 2.90 (1 H, dt, $J$ = 16.4, 1.0 Hz), 2.40 (1 H, d, $J$ = 14 Hz), 2.32 (1 H, d, $J$ = 14 Hz), 1.95 (2 H, m), 1.50 (4 H, m). MW for $C_{15}H_{20}O_4$: calcd 264.1362, found 264.1360.

**Preparation of 1-Cyclohexyl-4,4-bis(methoxycarbonyl)-1(*E*)-hepten-6-yne (7).** Following the method for the preparation of **5**, reaction of 150 mg (0.82 mmol) of allyl acetate **4**, 7 mg (3 mol %) of triphenylphosphine, and 30 mg (3 mol %) of tetrakis(triphenylphosphine)palladium with the nucleophile prepared from 204 mg (1.2 mmol) of dimethyl propargylmalonate and 46 mg (60% dispersion, 1.15 mmol) of sodium hydride in a total of 1.0 mL of THF at reflux for 8 h gave 170 mg (71%) of the product, which slowly crystallized (mp 36–7 °C) after flash chromatography (10:1 hexane–ether). IR ($CDCl_3$): 3305, 2140, 1738, 1452 cm$^{-1}$. $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 5.45 (1 H, dd, $J$ = 15, 6.8 Hz), 5.11 (1 H, dt, $J$ = 15, 7.4 Hz), 3.69 (6 H, s), 2.72 (2 H, d, $J$ = 2.7 Hz), 2.65 (2 H, d, $J$ = 7.5 Hz), 1.95 (1 H, t, $J$ = 1.7 Hz), 1.85 (1 H, m), 1.60 (4 H, m), 1.20–0.90 (6 H, m). MW for $C_{17}H_{24}O_4$: calcd 292.1675, found 292.1677.

**Preparation of [[4,4-Bis(methoxycarbonyl)-1-methylene-2-cyclopentyl]methylidene]cyclohexane (8).** FVT as above of 30 mg (0.10 mmol) of enyne **7** gave 21 mg (70%) of the titled product after purification by flash chromatography (10:1 hxane–ether). IR ($CDCl_3$): 1734, 1445 cm$^{-1}$. $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 4.89 (1 H, s), 4.85 (1 H, s), 4.75 (1 H, s), 3. 74 (3 H, s), 3.69 (3 H, s), 3.38 (1 H, m), 3.00 (2 H, AB, $J$ = 16.8 Hz), 2.52 (1 H, dd, $J$ = 13.5, 6.7 Hz), 2.10 (4 H, m), 1.86 (1 H, t, $J$ = 13.5 Hz), 1.50 (6 H, m). MW for $C_{17}H_{24}O_4$: calcd 292.1675, found 292.1664.

**Preparation of Methyl 2-[*cis*-5-(Methoxycarbonyl)-2-cyclohexenyl]-2-(methoxycarbonyl)-4-pentynoate (10).** Following the method for the preparation of **5**, reaction of 95 mg (0.49 mmol) of allyl acetate **9**,[9] 7 mg (3.3 mol %) of triphenylphosphine, and 19 mg (3.3 mol %) of the Pd(0)

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(30) Prempree, P.; Radviroongit, S.; Thebtaronth, Y. *J. Org. Chem.* **1983**, *48*, 3553.

(31) Lautens, M. Ph.D. Thesis, University of Wisconsin, 1985.

catalyst with the nucleophile derived from 170 mg (1.0 mmol) of dimethyl propargylmalonate and 39 mg (60% dispersion, 0.98 mmol) of sodium hydride in 1.0 mL of THF at reflux gave 120 mg (79%) after purification by flash chromatography (4:1 hexane–ether). IR ($CDCl_3$): 3302, 2120, 1731, 1720, 1650 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 5.78 (2 H, s), 3.78 (3 H, s), 3.72 (3 H, s), 3.69 (3 H, s), 3.25 (1 H, m), 2.90 (1 H, dd, $J$ = 17.3, 2.4 Hz), 2.82 (1 H, dd, $J$ = 17.3, 2.4 Hz), 2.73 (1 H, m), 2.40–2.10 (3, H, m), 2.09 (1 H, t, $J$ = 2.4 Hz), 1.50 (1 H, q, $J$ = 12.6 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 175.3, 169.7, 169.4, 127.2, 126.8, 78.8, 71.5, 59.9, 52.3, 52.1, 51.5, 39.7, 38.9, 27.5, 26.6, 22.4. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.20; H, 6.65.

**Preparation *cis*,*cis*-4,7,7-Tricarbomethoxy-9-methylenebicyclo-[4.3.0]non-2-ene (11).** A solution of 30 mg (0.097 mmol) of enyne **10** and 3.7 mg (5 mol %) of **12** in 1 mL of benzene-$d_6$ was heated at 66 °C for 3 h. Direct flash chromatography (3:1 hexane–ether) gave 26 mg (85%) of the titled compound. IR ($CDCl_3$): 1730, 1652 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 5.97 (1 H, d, $J$ = 10.1 Hz), 5.86 (1 H, d, $J$ = 10.1 Hz), 5.01 (1 H, d, $J$ = 1.2 Hz), 4.87 (1 H, d, $J$ = 1.2 Hz), 3.79 (3 H, s), 3.75 (3 H, s), 3.70 (3 H, s), 3.35 (1 H, dd, $J$ = 17.5, 5.4 Hz), 3.28 (1 H, m), 3.15 (1 H, m), 2.95 (1 H, m), 2.89 (1 H, d, $J$ = 17.5 Hz), 1.72 (1 H, m), 1.68 (1 H, dt, $J$ = 12.5, 3.9 Hz), 1.36 (1 H, d, $J$ = 12 Hz), 1.28 (1 H, d, $J$ = 12.2 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 173.8, 171.8, 169.6, 149.5, 128.2, 124.1, 108.2, 62.2, 52.6, 52.5, 51.8, 42.7, 42.3, 41.6, 37.6, 24.4. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.30; H, 6.58.

**Preparation of 4,4-Bis(methoxycarbonyl)-1-methylene-2-(11′,11′-dimethoxyundec-1′(*E*)-en-1′-yl)cyclopentane (15).** A solution of 14 mg (0.03 mmol) of enyne **13**, 0.6 mg (5 mol %) of triphenylphosphine, and 1.3 mg (5 mol %) of **12** in 0.5 mL of benzene-$d_6$ was heated at 62 °C for 1.5 h. Direct flash chromatography (5:2 hexane–ether) gave 10 mg (71%) of the titled compound. IR ($CDCl_3$): 1731, 1650 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 5.45 (1 H, dt, $J$ = 15.6, 6.6 Hz), 5.20 (1 H, dd, $J$ = 15.2, 7.9 Hz), 5.34 (1 H, t, $J$ = 6.5 Hz), 3.72 (3 H, s), 3.30 (6 H, s), 3.10–2.90 (3 H, m), 2.52 (1 H, m), 2.00 (2 H, m), 1.58 (2 H, m), 1.28 (14 H, bs). Anal. Calcd for $C_{23}H_{38}O_6$: C, 67.22; H, 9.33. Found: C, 66.92; H, 9.36.

**Preparation of 3-(*tert*-Butyldimethylsiloxy)-3-methyl-1-ethylidene-2-methylenecyclopentane (20d).** A solution of 34.9 mg (0.14 mmol) of **18d** and 5.8 mg (5 mol %) of **21** in 0.5 mL of benzene-$d_6$ was heated at 60 °C for 1 h. Direct flash chromatography gave 30 mg (86%) of a mixture of **20d** and **19d** that was >10:1. IR (neat): 3065, 3005, 1465, 1455 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 5.98–5.86 (1 H, m), 5.17 (1 H, s), 4.88 (1 H, s), 2.48–2.10 (2 H, m), 1.89–1.58 (2 H, m), 1.67 (3 H, d, $J$ = 7.1 Hz), 1.29 (3 H, s), 0.83 (9 H, s), 0.03 (3 H, s), 0.01 (3 H, s). MW for $C_{15}H_{28}OSi$: calcd 252.1910, found 252.1897.

**Preparation of 3-(*tert*-Butyldimethylsiloxy)-2-isopropenyl-3-methyl-1-methylenecyclopentane (28b).** A solution of 21.9 mg (0.0823 mmol) of enyne **27b** and 3.43 mg (5 mol %) of **21** in 0.5 mL of benzene-$d_6$ at 60 °C for 50 min gave after direct flash chromatography (pentane) 14.6 mg (67%) of a 2.3:1 diastereomeric ratio of the title compound. IR (neat): 1655, 1635 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): (major) $\delta$ 4.91 (2 H, bs), 4.72 (2 H, bs), 2.77 (1 H, bs), 2.66–2.27 (2 H, m), 1.75 (3 H, s), 1.92–1.50 (2 H, m), 1.32 (3 H, s), 0.82 (9 H, s). 0.08 (3 H, s), 0.04 (3 H, s); (minor) $\delta$ 4.97 (1 H, bs), 4.88 (1 H, bs), 4.79 (1 H, bs), 4.75 (1 H, s), 3.06 (1 H, s), 2.48–2.32 (2 H, m), 1.71 (3 H, s), 1.85–1.61 (2 H, m), 1.13 (3 H, s), 0.83 (9 H, s), 0.06 (6 H, s). MW for $C_{16}H_{30}OSi$: calcd 266.2067, found 266.2061. Anal. Calcd for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 71.92; H, 11.39.

**Preparation of 2-Hydroxyl-2-methyl-5-isopropenyl-1-methylenecyclopentane (28e).** A solution of 1.14 g (7.50 mmol) of enyne **27e** in 20 mL of chloroform was added to a premixed solution of 84 mg (5 mol %) of palladium acetate and 122 mg (10 mol %) of 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane in 40 mL of chloroform. After 1 h at 60 °C, direct flash chromatography (pentane to 1:5 ether–pentane) gave 560 mg (49%) of the titled compound.

**Major Diastereomer.** IR ($CDCl_3$): 3615, 1650 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.23 (1 H, d, $J$ = 2.8 Hz), 4.88 (1 H, d, $J$ = 2.8 Hz), 4.83 (2 H, s), 3.21 (1 H, m), 1.92–1.76 (3 H, m), 1.67 (3 H, s), 1.66–1.58 (1 H, m), 1.43 (3 H, s), 1.32 (1 H, bs). $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 159.8, 146.6, 112.5, 106.9, 78.0, 52.2, 40.2, 27.4, 26.7, 17.8.

**Minor Diastereomer.** IR ($CDCl_3$): 3610, 1650 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.25 (1 H, d, $J$ = 2.7 Hz), 4.89 (1 H, d, $J$ = 2.7 Hz), 4.80 (2 H, d, $J$ = 1.2 Hz), 3.37 (1 H, m), 1.97–1.83 (2 H, m), 1.79–1.72 (1 H, m), 1.63 (3 H, s), 1.57 (1 H, s), 1.58–1.49 (1 H, m), 1.36 (3 H, s). $^{13}C$ NMR ($CDCl_3$, 75.7 MHz): $\delta$ 160.0, 146.6, 112.2, 107.3, 78.8, 51.2, 40.7, 27.4, (2 C) 18.3. MS $m/e$ (mol %): 152 (42), 137 (100), 119, (24), 109 (19), 93 (12), 91 (16).

**Preparation of 1-(*tert*-Butyldimethylsiloxy)-3-(1-carbethoxyvinyl)-2-(*Z*)-(trimethylsilyl)-1-methylenecyclopentane (32b).** A solution of 35.8 mg (0.094 mmol) of enyne **31b**, 4.3 mg (20 mol) of palladium acetate, and 4.5 mg (20 mol %) of BBEDA in 0.5 mL of chloroform-$d_1$ at 60 °C for 118 h (repeated twice) gave, after evaporation and flash chromatography (1:24 ether–hexane), 4.1 mg (11%) of starting material and 11.7 mg (44% based upon recovered starting material) of **32b**. IR (neat): 1715, 1630 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 6.21 (1 H, d, $J$ = 1.8 Hz), 5.79 (1 H, dd, $J$ = 1.7, 1.2 Hz), 5.42 (1 H, s), 4.59 (1 H, s), 4.28–4.16 (2 H, m), 3.56 (1 H, t, $J$ = 7.5 Hz), 2.2–2.0 (1 H, m), 1.87–1.75 (1 H, m), 1.7–1.5 (1 H, m), 1.31 (3 H, t, $J$ = 7.1 Hz), 1.36–1.23 (1 H, m), 0.86 (9 H, s), 0.12 (9 H, s), 0.12 (3 H, s), 0.09 (3 H, s). MW for $C_{20}H_{38}O_3Si_2$: calcd 382.2359, found 382.2350.

**Preparation of 4,4-Dimethyl-3-[(*p*-methoxybenzyl)oxy]-2-(3′-methoxy-1(*E*)-propen-1′-yl)-1-methylenecyclopentane (34).** A solution of 155 mg (0.491 mmol) of enyne **33** and 18.4 mg (0.025 mmol) of catalyst **12** in 5 mL of benzene at 60 °C for 30 min gave, after direct flash chromatography (1:19 ether–hexane increasing to 1:9), 120 mg (77%) of the titled compound. IR (neat): 1650, 1608, 1580, 1505 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.22 (2 H, d, $J$ = 8.7 Hz), 6.84 (2 H, d, $J$ = 8.7 Hz), 5.66 (1 H, dt, $J$ = 15.3, 5.9 Hz), 5.57 (1 H, dd, $J$ = 15.3, 8.5 Hz), 4.88 (1 H, bs), 4.77 (1 H, bs), 4.59 (1 H, d, $J$ = 11.5 Hz), 4.49 (1 H, d $J$ = 11.5 Hz), 3.91 (2 H, td, $J$ = 6.0, 1.0 Hz), 3.78 (3 H, s), 3.32 (1 H, s), 3.30 (1 H, d, $J$ = 8.5 Hz), 3.14 (1 H, tq, $J$ = 8.5, 2.5 Hz), 2.22 (1 H, dt, $J$ = 16.3, 1.7 Hz), 2.12 (1 H, dq, $J$ = 16.3, 2.5 Hz), 1.03 (3 H, s), 0.96 (3 H, s). MW for $C_{20}H_{28}O_3$: calcd 316.2038, found 316.2026. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.82; H, 8.91.

**Preparation of Methyl 5,9-Dimethyl-2-(methoxycarbonyl)-2-(propyn-3′-yl)deca-4(*E*),8-dienoate (36).** Geranyl acetate (196 mg, 1.0 mmol), triphenylphosphine (7 mg, 2.5 mol %), and a solution of tetrakis(triphenylphosphine)palladium (30 mg, 2.5 mol%) in 1 mL of THF were added sequentially to a mixture of 204 mg (1.2 mmol) of dimethyl propargylmalonate and 46 mg (60 °C dispersion, 1.15 mmol) of sodium hydride washed free of mineral oil in 1 mL of THF. After the solution was refluxed for 16 h, flash chromatography (20:1 hexane–ether) gave 157 mg (51% based on recovered starting material) of the titled compound and 34 mg (17%) of recovered starting material. IR ($CDCl_3$): 3307, 2110, 1735, 1670 $cm^{-1}$. $^1H$ NMR (200 MHz, $C_6D_6$): $\delta$ 5.12 (2 H, bt, $J$ = 7 Hz) 3.35 (6 H, s), 3.25 (2 H, d, $J$ = 7.5 Hz), 3.03 (2 H, d, $J$ = 1.5 Hz), 2.04 (4 H, m), 1.73 (1 H, t, $J$ = 1.5 Hz), 1.70 (3 H, s), 1.61 (3 H, s), 1.52 (3 H, s). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.56; H, 8.52.

**Preparation of 4,4-Bis(methoxycarbonyl)-2-(6′-methylhepta-2′,5′-dien-2′-yl)-1-methylenecyclopentane (37).** FVT of 23 mg (0.075 mmol) of enyne **36** at 625 °C (0.05 mmHg) gave, after flash chromatography (5:1 hexane–ether) of the eluate, 19 mg (83%) of the titled compound for which VPC analysis (SE-30 on Chromosorb W, 8 ft × $^1/_8$ in) showed two peaks in a ratio of 1:1.16 for the two geometrical isomers. IR ($CDCl_3$): 1730, 1655 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 5.29 (1 H, m), 5.10 (1 H, m), 4.97 (0.55 H, m), 4.93 (0.45 H, m), 4.75 (0.55 H, m), 4.71 (0.45 H, m), 3.74 (2.35 H, s), 3.72 (3.30 H, s) 3.71 (1.35 H, s), 3.20–3.00 (2 H, m), 2.90 (1 H, m), 2.70 (2 H, m), 2.46 (1 H, m), 2.12 (1 H, m), 1.70 (3 H, s), 1.65 (1.65 H, s), 1.64 (1.35 H, s), 1.58 (1.65 H, s), 1.52 (1.35 H, s). MW for $C_{18}H_{26}O_4$: calcd 306.1832, found 306.1830.

**Preparation of 4,4-Bis(methoxycarbonyl)-2-(6′-methylhepta-1′,5′-dien-2′-yl)-1-methylenecyclopentane (38).** A solution of 15 mg (0.049 mmol) of enyne **36** and 0.6 mg (5 mol%) of palladium acetate in 0.45 mL of benzene-$d_6$ heated at 66 °C for 1.5 h gave, after flash chromatography (5:1 hexane–ether), 12 mg (80%) of the titled compound. IR ($CDCl_3$): 1731, 1650 $cm^{-1}$. $^1H$ NMR (270 MHz, $C_6D_6$): $\delta$ 5.18 (1 H, bt, $J$ = 6.4 Hz), 5.00 (1 H, s), 4.95 (1 H, s), 4.91 (2 H, s), 3.50 (1 H, m), 3.31 (3 H, s), 3.28 (3 H, s), 3.50–2.70 (3 H, m), 2.35 (1 H, t, $J$ = 9.5 Hz), 2.18 (2 H, m), 2.05 (2 H, m), 1.65 (3 H, s), 1.54 (3 H, s). $^{13}C$ NMR (50.1 MHz, $CDCl_3$): 167.9, 149.7, 148.9, 131.7, 124.1, 111.5, 108.2, 58.7, 52.7, 50.8, 41.0, 39.3, 32.4, 26.7, 25.6, 17.7. MW for $C_{18}H_{26}O_4$: calcd 306.1832, found 306.1838.

**Preparation of Methyl 5,9-Dimethyl-2-(methoxycarbonyl)-2-propyn-3-yl-4(*E*)-decenoate (39).** As for the preparation of **36**, 148 mg (0.75 mmol) of 1-acetoxy-3,7-dimethyloct-2(*E*)-ene,[32] 10 mg (5 mol %) of triphenylphosphine, 40 mg (5 mol %) of tetrakis(triphenylphosphine)-palladium, 165 mg (0.97 mmol) of dimethyl propargylmalonate, and 38 mg (60% dispersion, 0.95 mmol) of sodium hydride in a total of 2 mL of THF at reflux for 20 h gave 131 mg (50%, 75% based upon recovered starting material) of the titled compound and 40 mg (27%) of recovered starting material. IR ($CDCl_3$): 3307, 2115, 1740, 1670 $cm^{-1}$. $^1H$ NMR

(32) Prepared by standard acetylization of the corresponding alcohol. The latter was previously prepared as an *E*,*Z* mixture: Khan, N.; Loeber, D. E.; Toube, T. P.; Weedon, C. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1475. The geometrically pure *E* isomer was synthesized by adaptation of the method of Weiler. See: Sum, F. W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.

(270 MHz, $CDCl_3$) δ 4.88 (1 H, t, J = 6.5 Hz), 3.70 (6 H, s), 2.78 (4 H, m), 1.95 (3 H, m), 1.61 (3 H, s), 1.50 (1 H, m), 1.33 (2 H, m), 1.10 (2 H, m), 0.84 (6 H, d, J = 7.5 Hz). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.85; H, 9.22.

**Preparation of 4,4-Bis(Methoxycarbonyl)-2-(6'-methylhept-2'-en-2'-yl)-1-methylenecyclopentane (40).** FVT of 15 mg (0.049 mmol) of enyne **39** at 575 °C (0.01 mmHg) gave, after flash chromatography (15:1 hexane–ether), 12 mg (80%) of the titled compound for which VPC analysis indicated a 1.2:1 ratio of the two geometrical isomers. IR ($CDCl_3$): 1729, 1651 $cm^{-1}$. $^1H$ NMR (270 MHz, $C_6D_6$): δ 5.45 (0.5 H, t, J = 6 Hz), 5.37 (0.5 H, t, J = 7 Hz), 5.10 (0.5 H, s), 5.05 (0.5 H, s), 5.00 (0.5 H, s), 4.96 (0.5 H, s), 4.11 (0.5 H, t, J = 7 Hz), 3.58 (0.5 H, t, J = 7 Hz), 3.37 (1.5 H, s), 3.36 (1.5 H, s), 3.33 (1.5 H, s), 3.40–3.22 (2 H, m), 2.85 (1 H, m), 2.45 (0.5 H, t, J = 10 Hz), 2.41 (0.5 H, t, J = 13 Hz), 2.10 (2 H, m), 1.72 (1.5 H, s), 1.60 (1.5 H, s), 1.58 (1 H, m), 1.30 (2 H, m), 0.90 (3 H, d, J = 7 Hz), 0.89 (3 H, d, J = 7 Hz). MW for $C_{18}H_{28}O_4$: calcd 308.1988, found 308.1985.

**Pd(2+)-Catalyzed Cyclization of Enyne 39.** A solution of 10 mg (0.032 mmol) of enyne **39** and 1.2 mg (5 mol %) of catalyst **12** in 0.45 mL of benzene-$d_6$ heated at 66 °C for 1 h gave, after flash chromatography (20:1 hexane–ether), 7 mg (70%) of a 1:8.9:2.2 mixture of one geometrical isomer of **40**, **41**, and another geometrical isomer of **40**. IR ($CDCl_3$): 1728, 1655 $cm^{-1}$. $^1H$ NMR (270 MHz, $C_6D_6$): δ 5.10 (1 H, s), 5.05 (2 H, s), 4.98 (1 H, s), 3.58 (1 H, m), 3.50 (3 H, s), 3.45 (3 H, s), 3.40–3.20 (2 H, m), 2.90 (1 H, m), 2.46 (1 H, t, J = 10.5 Hz), 2.10 (2 H, m), 1.55–1.40 (3 H, m), 1.30–1.15 (2 H, m), 0.96 (6 H, d, J = 6 Hz). MW for $C_{18}H_{28}O_4$: calcd 308.1988, found 308.1979.

**Annulation of Carveol to Bicycle 43.** Sequential addition of 0.9 mL (6.5 mmol) of triethylamine and 274 mg (2.4 mmol) of methanesulfonyl chloride to a solution of 365 mg (2.40 mmol) of carveol in 3 mL of THF at −20 to 0 °C produced the corresponding mesylate. To this resultant solution were added a solution of 595 mg (3.50 mmol) of dimethyl propargylmalonate in 0.5 mL of THF and 3.5 mL (1 M in THF, 3.5 mmol) of lithium hexamethyldisilazide at 0 °C, and the resultant mixture was stirred for 1 h at room temperature. After addition of water, ether extraction, and drying ($MgSO_4$), flash chromatography (4:1 hexane–ether) gave 274 mg (38%) of enyne **42**. IR ($CDCl_3$): 3310, 1730, 1645 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ 5.42 (1 H, bs), 4.61 (2 H, m), 3.68 (3 H, s), 3.60 (3 H, s), 3.11 (1 H, bs), 2.78 (2 H, d, J = 2.5 Hz), 2.22–2.00 (2 H, m), 1.97 (1 H, t, J = 2.5 Hz), 1.80–1.65 (3 H, m), 1.62 (6 H, s). $^{13}C$ NMR (15 MHz, $CDCl_3$): δ 170.5, 170.3, 148.4, 133.0, 125.6, 108.8, 79.6, 71.0, 60.4, 52.4, 52.0, 41.1, 35.9, 30.4, 30.1, 24.7, 24.2, 20.6. MW for $C_{18}H_{24}O_4$: calcd 304.1675, found 304.1664.

A solution of 168 mg (0.552 mmol) of the above enyne and 21 mg (5 mol %) of catalyst **12** in 1 mL of benzene heated at 60 °C for 1 h gave, after flash chromatography (6:1 hexane–ether), 101 mg (60%) of bicycle **43**. IR ($CDCl_3$): 1740, 1725, 1655 1640 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ 5.52 (2 H, s), 4.84 (1 H, m), 4.76 (2 H, m), 4.63 (1 H, m), 3.68 (6 H, s), 3.25 (1 H, dt, J = 14.0, 2.2 Hz), 2.90 (1 H, dd, J = 8.3, 5.0 Hz), 2.80 (1 H, d, J = 14.0 Hz), 2.56 (1 H, bt, J = 5.0 Hz), 1.67 (3 H, bs), 1.65–1.35 (2 H, m), 1.10 (3 H, s). $^{13}C$ NMR (15 MHz, $CDCl_3$): δ 172.5, 170.5, 155.6, 146.8, 134.7, 127.2, 111.3, 105.6, 74.9, 61.6, 52.7, 52.3, 46.8, 45.9, 39.6, 28.1, 27.0, 21.3. MW for $C_{18}H_{24}O_4$: calcd 304.1675, found 304.1673.

**Annulation of Carveol to Bicycle 45.** A solution of 90 mg (0.463 mmol) of carveol acetate[33] (prepared in standard fashion from carveol,[34] acetic anhydride, and DMAP in methylene chloride), 23 mg (4.3 mol %) of tetrakis(triphenylphosphine)palladium, and 8 mg (6.5 mol %) of triphenylphosphine in 0.5 mL of THF was added to a solution of sodium dimethyl propargylmalonate at room temperature prepared by heating 120 mg (0.706 mmol) of the malonate and 15 mg (0.625 mmol) of sodium hydride in 1.5 mL of THF at 60 °C for 30 min. After the solution was heated at reflux for 1.5 days, evaporation in vacuo and flash chromatography (4:1 hexane–ether) gave 113 mg (80%) of enyne **44**. IR ($CDCl_3$): 3300, 2110, 1730, 1640 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ 5.58 (1 H, bs), 4.72 (2 H, bm), 4.68 (1 H, bs), 3.80 (3 H, s), 3.78 (3 H, s), 3.30 (1 H, bm), 3.00 (1 H, d, J = 3.0 Hz), 2.92 (1 H, dd, J = 15, 3 Hz), 2.76 (1 H, dd, J = 15, 3 Hz), 2.05 (1 H, t, J = 3 Hz), 2.00–1.75 (3 H, m), 1.71 (3 H, s), 1.65 (3 H, s), 1.35 (m, 1 H). $^{13}C$ NMR (15 MHz, $CDCl_3$): δ 170.4, 169.5, 148.9, 133.2, 126.8, 108.8, 80.1, 70.8, 60.6, 52.3 (2C), 44.7, 41.8, 31.2, 30.9, 24.2, 23.2, 20.7. MW for $C_{18}H_{24}O_4$: calcd 306.1675, found 306.1675.

A solution of 70 mg (0.23 mmol) of enyne **44** and 10 mg (5.7 mol %) of catalyst **12** in 0.5 mL of benzene heated at 60 °C for 1 h gave, after flash chromatography (2:1 hexane–ether), 51 mg (73%) of bicycle **45**. IR ($CDCl_3$): 1735, 1675, 1665 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ 5.63 (1 H, dd, J = 10.7, 2.9 Hz), 5.50 (1 H, d, J = 10.7 Hz), 4.85 (1 H, bs), 4.74 (1 H, t, J = 2.7 Hz), 4.68 (2 H, bs), 3.71 (3 H, s), 3.69 (3 H, s), 3.28 (1 H, dt, J = 18.3, 2.7 Hz), 3.02 (1 H, d, J = 18.3 Hz), 2.92 (1 H, dd, J = 14, 5 Hz), 2.70 (1 H, bd, J = 12.5 Hz) 1.60 (3 H, s), 1.35 (1 H, m), 1.15 (1 H, m), 1.04 (3 H, s). $^{13}C$ NMR (15 MHz, $CDCl_3$): δ 172.1, 169.9, 155.7, 148.2, 134.2, 128.3, 110.2, 106.0, 62.3, 52.9, 52.6, 49.9, 47.0, 43.1, 37.8, 30.5, 30.2, 20.2. MW for $C_{18}H_{24}O_4$: calcd 304.1675, found 304.1673.

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**Supplementary Material Available:** Experimental data for **13**, **14**, **16**, **18a–d**, **24**, **27a–f**, **31a,b**, **32a**, and **33** (14 pages). Ordering information is given on any current masthead page.

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# Nitrogen-15-Labeled Deoxynucleosides. 4. Synthesis of [1-$^{15}$N]- and [2-$^{15}$N]-Labeled 2'-Deoxyguanosines

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**Abstract:** The syntheses of [1-$^{15}$N]- and [2-$^{15}$N]-2'-deoxyguanosines are reported via transformation of 2'-deoxyadenosine. The $^{15}$N source for the [1-$^{15}$N] label is [6-$^{15}$N]-2'-deoxyadenosine, while for the [2-$^{15}$N] label it is [$^{15}$N]KCN. The synthetic route is particularly straightforward in that there are no protection and deprotection steps and only one chromatographic purification. Furthermore, it is directly applicable to preparation of the labeled ribonucleosides. These [1-$^{15}$N]- and [2-$^{15}$N]-labeled guanine nucleosides are now available by routes that give material in sufficient yields that they can be prepared for incorporation into nucleic acid fragments.

The potential utility of $^{15}$N-labeled oligonucleotides to probe uniquely nucleic acid structure, drug-binding, and nucleic acid–protein interactions[1-3] has led to considerable interest in the development of routes to the requisite $^{15}$N-labeled monomers. Our report of synthetic routes to [1-$^{15}$N]- and [6-$^{15}$N]-labeled deoxyadenosines[4] was quickly followed by an alternate route to the

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