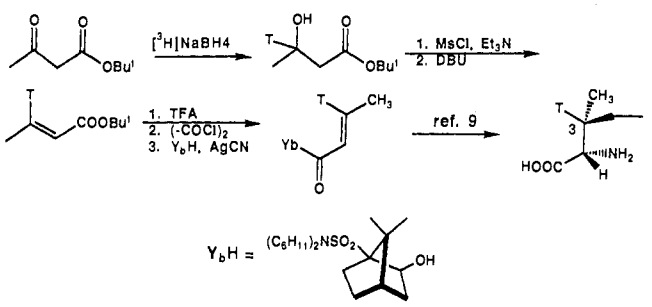
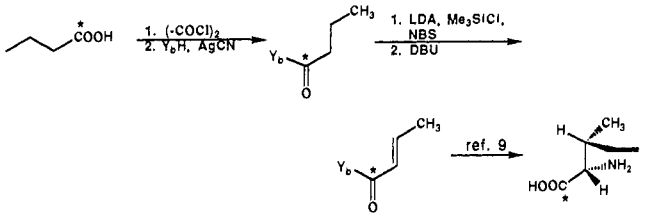
Table I. Incorporation of Labeled Precursors into Coronatine Methyl Ester

expt	precursor ($^3H/^{14}C$)	% enrichmnt or incorporatn	labeling pattern
1	(1-^{13}C)-L-isoleucine	9	C-1′
2	(1-^{13}C)-L-alloisoleucine	60	C-1′
3	(6-^{13}C)-DL-isoleucine + (6-^{13}C)-DL-alloisoleucine	31	C-6′
4	(6-^{13}C,6-$^{2}H_3$)-DL-isoleucine + (6-^{13}C,6-$^{2}H_3$)-DL-alloisoleucine	0.5	^{13}C and 2 D at C-6′
5	[1-^{14}C,3-^{3}H]-L-alloisoleucine (3.89)	1.8	$^3H/^{14}C$ = 3.67 (94% ^{3}H retention)

Scheme I



Scheme II



The loss of only one hydrogen atom from C-6 of L-alloisoleucine during coronamate formation rules out the intermediacy of species with a C-6 oxidation level higher than that of an alcohol. Putative intermediates with the appropriate oxidation level would therefore include 3-methylene-L-norvaline and 6-hydroxy-L-alloisoleucine. The possible intermediacy of the former amino acid was evaluated by means of a precursor incorporation experiment with [1-^{14}C,3-^{3}H]-L-alloisoleucine. [3-^{3}H]-L-Alloisoleucine was synthesized as shown in Scheme I, while [1-^{14}C]-L-alloisoleucine was prepared as outlined in Scheme II. Administration of a mixture of these two amino acids to *Ps. syringae* gave doubly labeled coronatine methyl ester, which was purified chromatographically and then reduced to the corresponding alcohol with lithium tri-*tert*-butoxyaluminum hydride. The alcohol was further chromatographed to remove any lingering radiochemical impurities. The results of this experiment (Table I, experiment 5) demonstrate that L-alloisoleucine is converted to coronamic acid without loss of the hydrogen atom present at C-3. 3-Methylene-L-norvaline is thereby ruled out as an intermediate. The potential intermediacy of the 6-hydroxy-L-alloisoleucine was examined by administration of a mixture of (1-^{13}C)-6-hydroxy-DL-isoleucine and (1-^{13}C)-6-hydroxy-DL-alloisoleucine to *Ps. syringae*.[10] No incorporation into coronatine methyl ester was observed.

The findings just described limit the number of mechanisms that can be envisioned for the conversion of L-alloisoleucine to coronamic acid. At the present time it is tempting to conclude that the mechanism may represent a diversion of an enzymatic hydroxylation reaction into an oxidative cyclization. Such processes have recently been uncovered in the biosynthesis of clavaminic acid,[11] isopenicillin N,[12] and deacetoxycephalosporin C.[12] The mechanism of coronamic acid biosynthesis may also be related to the sulfur insertion reactions involved in biotin and lipoic acid biosynthesis.[13]

Acknowledgment. We thank the National Institutes of Health (GM 26569) and The Robert A. Welch Foundation (C-729) for financial support and Dr. Alan M. Kook for the ^{1}H, ^{2}H decoupling experiment.

Registry No. 1, 62251-96-1; **3**, 63393-56-6; **5**, 1509-34-8.

(10) The synthesis of these compounds will be described elsewhere.

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Intramolecular Enyne Metathesis Reaction. Route to Bridged Bicycles with Bridgehead Olefins

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Ever since the discovery of the remarkable olefin metathesis, this fundamentally new process has generated great excitement as to its applicability to other unsaturated substrates and its mechanism.[1] While it has been extended to alkynes,[2] to our knowledge, no examples of a crossed metathesis involving an olefin with an acetylene have been recorded. Further, while early mechanistic speculation centered on the possible involvement of four-membered carbocyclic rings, such interpretations were not supported by subsequent studies.[1] We report the development of a catalyst that converts a mechanistic curiosity into a preparatively useful crossed enyne metathesis that likely proceeds via a four-membered carbocyclic intermediate.[3] This new method provides a very simple route to bridged bicycles possessing bridgehead olefins, interesting molecular structures that also may be useful building blocks for the synthesis of natural products (cf. taxanes,[4] shikodomedin,[5] etc.).

The reaction of enyne **1a** with a catalyst derived from 2,3,4,5-tetrakis(methoxycarbonyl)palladacyclopentadiene (TCPC, **4**, R = CH_3) gave a 2.8:1 ratio of the cyclorearrangement product **2a** to the "Alder ene type" product **3a** in 68% yield (eq 1).[3,6]

(1) For general references on metathesis, see: (a) Dragutan, V.; Balaban, H. T.; Dimonie, M. *Olefin Metathesis and Ring-opening Polymerization of Cyclo-Olefins*; Wiley: New York, 1985. (b) Ivin, K. J. *Olefin Metathesis*; Academic Press: London, 1983. (c) Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley: New York, 1988; Chapter 7.

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(6) Reinvestigation of this reaction revealed the presence of the Alder ene type product **3** in addition to the cyclorearrangement product **2a**.

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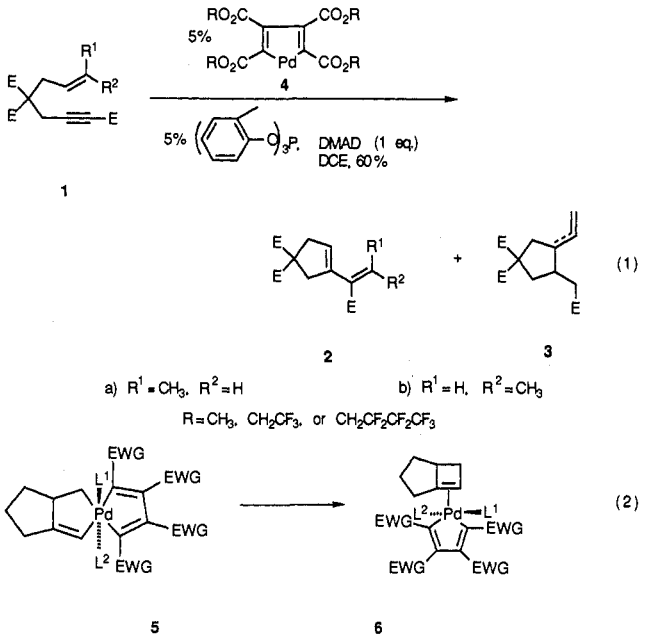
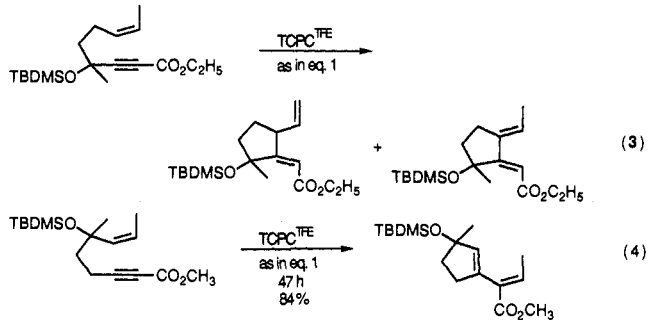
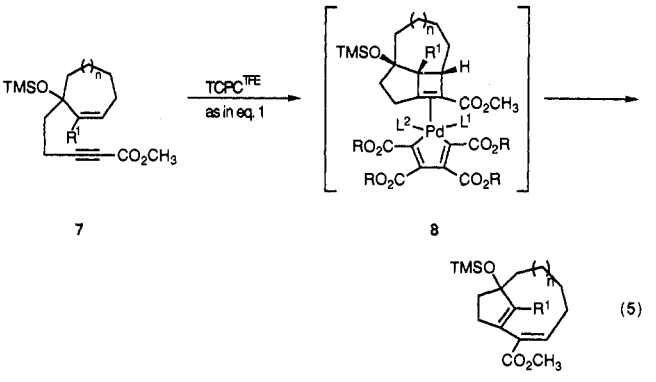
Envisioning the requirement for a transformation of a metallaspirocycle **5** to a very strained complexed cyclobutene **6** (eq 2), we felt that increasing the electronegativity of the electron-withdrawing groups (EWG) would promote this reductive elimination. We therefore prepared the trifluoroethyl (**4**, R = CH_2CF_3, TCPC^{TFE}) and heptafluorobutyl (**4**, R = $CH_2CF_2CF_2CF_3$, TCPC^{HFB}) ester analogues,[7,8] which proved to be considerably more soluble than TCPC. A dramatic improvement in both yield and ratio of **2a** to **3a** occurred with both catalysts: 80% of 6.8:1 and 91% of 15.6:1 with TCPC^{TFE} and TCPC^{HFB}, respectively.[9] A kinetic advantage with the new complexes was clearly noted with enyne **1b**, which reacted only to the extent of 50% with TCPC after 4.5 days to a mixture of **2a**, **2b**, and **3**, whereas TCPC^{HFB} gave complete conversion in 84% yield to a 3.4:1 ratio of **2b** and **3b** in 4 days. Terminal substitution on both the olefin and the acetylene (particularly an electron-withdrawing group on the acetylene) promotes the metathesis. Whereas geminal substitution at the propargylic position disfavors metathesis (eq 3), geminal substitution at the allylic position strongly promotes metathesis (eq 4).



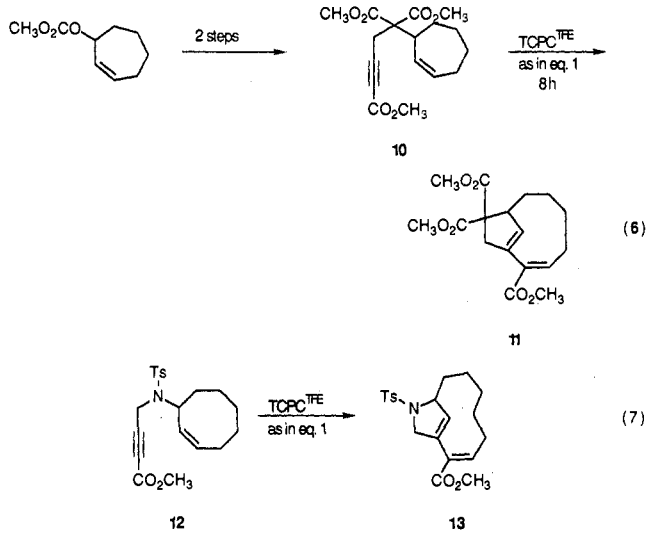


With a view toward natural products like the taxanes and shikodomedin and related antitumor compounds, we examined the feasibility of generating bridged bicycles possessing bridgehead olefins according to eq 5. Such an extension introduces another level of strain by bridging of the already strained cyclobutene unit with a chain of limited length to the five-membered ring as in **8**.



When TCPC^{TFE} is used, the seven-membered (**7**, n = 1, R′ = H, 72 h), eight-membered (7, n = 2, R′ = H, 20 h) and twelve-membered (**7**, n = 6, R′ = H, 26 h) rings react smoothly to give the bridged bicycles in 53%, 86%, and 73% yields, respectively. The facility of the reaction appears to correlate with the strain anticipated in the proposed cyclobutene intermediate **8**. Thus, subjecting enyne **7** (n = 0) to the same conditions produces the normal ene-type products rather than resulting in reductive elimination to **8** (n = 0). Reaction of the methyl-substituted substrate **7** (n = 2, R′ = CH_3, 25 h), which probes steric hindrance, proceeds with equal facility to the desmethyl analogue with production of a 77% yield of **9** (n = 2, R′ = CH_3) under identical conditions.

The effect of the nature of the tether was also examined. The presence of the malonate unit in **10**, readily available via palladium-catalyzed allylic alkylation, enhanced the reactivity toward metathesis as evidenced by shorter reaction times and a higher yield of the metathesis product **11** (eq 6, 76%) compared to **7** (R′ = H, n = 1). Incorporation of a nitrogen in the tether as in **12** provides the azabicyclic product **13** in 58% yield (eq 7).



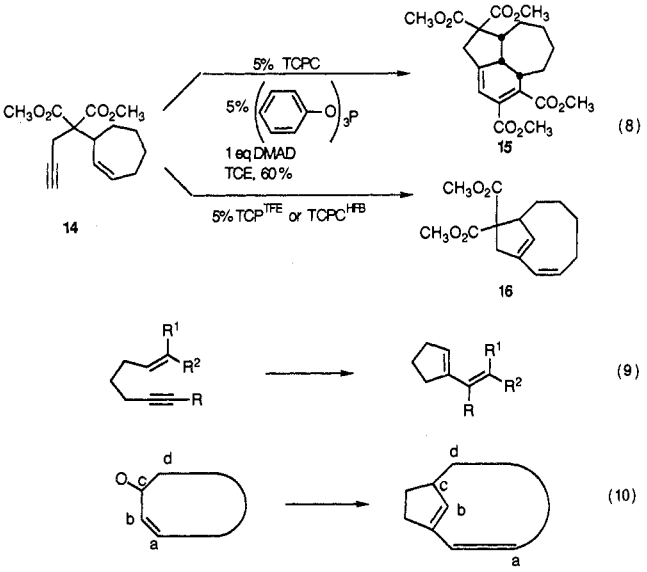
These new catalysts promote the metathesis reaction to a sufficient degree that some substrates even lacking the acetylene substituent can now lead to preparatively useful yields of the metathesis product. For example, the enyne **14** provides only the [2 + 2 + 2] cycloaddition product **15** in 60% yield with TCPC as the catalyst. On the other hand, the same reaction but with TCPC^{TFE} or preferably TCPC^{HFB} as the catalyst now produces the metathesis product **16** in 57% yield along with a 31% yield of the [2 + 2 + 2] product **15** (eq 8).

The enyne metathesis is a very useful strategy for construction of rings accompanied by skeletal rearrangement as summarized in eqs 9 and 10. Clearly, the advent of these new catalysts has

(7) Analogous to the method for TCPC, see: Mosely, K.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1974**, 169.

(8) Bis(2,2,2-trifluoroethyl) acetylenedicarboxylate (4 equiv) was added to a suspension of tris(dibenzylideneacetone)dipalladium–chloroform (1 equiv) in acetone at room temperature. After 24 h, the resulting homogeneous orange solution was filtered and evaporated in vacuo to give an orange solid. Fractional crystallization from ether–hexane separated first the dibenzylideneacetone and subsequently TCPC^{TFC}, initially as an orange solid, which became purple in vacuo in 78% yield. TCPC^{HFB} was prepared in identical fashion.

(9) The minor product in these cases was the *Z* conjugated diene **3** in contrast to the deconjugated diene **3** being favored with TCPC.



opened a new type of reaction that has much synthetic potential and raises many intriguing mechanistic questions.

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Supplementary Material Available: Characterization data for **4** (R = CH_2CF_3), **4** (R = $CH_2CF_2CF_2CF_3$), **7** (n = 1, 2, 6, R′ = H), **7** (n = 2, R′ = CH_3), **9** (n = 1, 2, 6, R′ = H), **9** (n = 2, R′ = CH_3), and **10–16** (4 pages). Ordering information is given on any current masthead page.

Formation of a Crystalline Monolayer of Folded Molecules by Solution Self-Assembly of α,ω-Alkanedioic Acids on Silver

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The preparation of well-defined monolayers by solution self-assembly provides structures of great interest and utility for application to interface studies. Among the increasing number of applications that have been reported are fundamental wetting studies,[1] functionalized electrodes for electrochemical processes,[2-4]

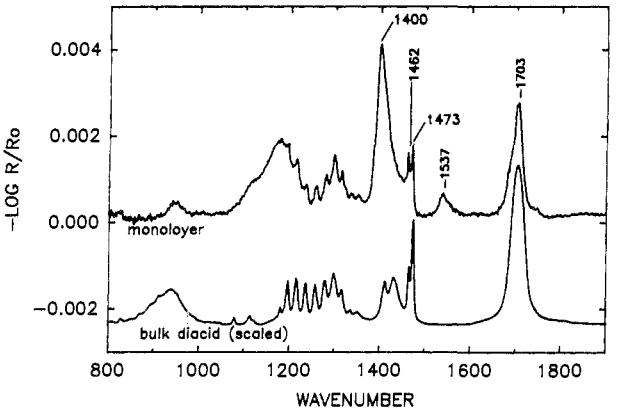

Figure 1. IR spectra of $HO_2C(CH_2)_{30}CO_2H$ after monolayer adsorption onto a Ag surface and after dispersion into a KBr pressed disk (the absorbance values have been scaled for presentation on the monolayer plot). The wavelength region from 800 to 1900 cm^{-1} is shown.

and templates for synthesis of organized structure multilayer films.[5,6] Most of the monolayer systems have involved alkylsiloxanes on silicon (oxide)[5,7] and gold,[3] divalent organosulfur compounds on gold,[1,2,8-11] and alkanoic acids on aluminum (oxide)[12] and silver (oxide).[13] In addition, some have displayed a marked flexibility in providing selected organic functionality at the ambient surface. This is particularly the case for the organosulfur/Au system.[14]

Generally, these assemblies consist of linear alkyl chains, usually highly conformationally ordered[3,8,11,13] and in some cases crystalline packed.[13,15] Since the *chains extend away from the substrate*, terminal functionality is provided. An alternative strategy for creating structured surfaces that has not yet been explored involves pinning both ends of each chain molecule to the substrate so that the chain must fold. The result is to provide *interior functionality* at the ambient interface. Such surfaces should be uniquely useful for the development of experimental model structures for biological systems as well as polymer surfaces which typically consist of chain folds.

We report here the first example of a crystalline-packed, self-assembled monolayer of a folded molecule in which *the interior of the molecule defines the ambient surface properties*. Specifically, we have observed that 1,32-dotriacontanedioic acid, $HO_2C(CH_2)_{30}CO_2H$,[16,17] adsorbed from dilute tetrahydrofuran

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