extracted with 4 × 50 mL of hexane. The combined hexane portions were dried ($MgSO_4$), filtered, and concentrated in vacuo (1 mmHg) at 25 °C.

The oily residue was chromatographed on a 20-cm column of 230-400-mesh silica (Sigma) using hexane (or 2:1 hexane/CH_2Cl_2 for **11a**) as eluent. The diazirines eluted in the first fraction (light yellow). Diazirine **11e** was colorless; its elution was followed by TLC. Hexane was stripped from the eluted diazirines at 1 mmHg. The residues (except **11a**) were distilled, 40 °C/0.1 mmHg, on a Kugelrohr apparatus to afford 3-bromo-3-aryldiazirines **11**. Yields and spectral properties appear in Table I. All diazirines **11** gave appropriate ^1H NMR spectra, including aryl resonances and CH_3 signals [$\delta(CDCl_3)$ 3.70, **11a**; 2.33, **11b**].

3-Fluoro-3-aryldiazirines (12). These compounds were prepared by the reactions of bromodiazirines **11** with molten *n*-$Bu_4N^+F^-$ (see Results section and ref 9 and 13); a general procedure follows. Molten *n*-$Bu_4N^+F^-$ was prepared from 4 g of the trihydrate in a 25-mL round-bottom flask as described above. The fluoride melt was cooled to 25 °C, and ~1 g of a bromodiazirine (**11**) was added. The reaction mixture was stirred magnetically at 25 °C in the dark for 4 h. (Crystals of *n*-$Bu_4N^+Br^-$ were usually observed to form after ~10 min.) The reaction product was quenched with 20 mL of water and the resulting solution was extracted with 6 × 5 mL of pentane. The combined pentane extract was dried ($MgSO_4$), filtered, and concentrated (aspirator). The residue was distilled at 40 °C (1-20 mmHg) on a Kugelrohr apparatus to afford 3-fluoro-3-aryldiazirines **12**. Yields and spectral properties of these new diazirines appear in Table II. All compounds **12** gave appropriate ^1H NMR spectra including aryl resonances and CH_3 signals [$\delta(CDCl_3)$ 3.76, **12a**; 2.36, **12b**].

Tetrabutylammonium Azide (TBAAz). This salt was prepared by a modification of Brändström's procedure.[15] A solution of 13 g (0.2 mol) of sodium azide (Aldrich) in 30 mL of water was added to 26 g (0.1 mol) of *n*-$Bu_4N^+OH^-$ (40% in water, Aldrich). Then, 150 mL of CH_2Cl_2 was added, and the organic layer was removed via a separatory funnel. The aqueous phase was extracted with 3 × 50 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were dried ($MgSO_4$), filtered, and stripped at 25 °C to afford a white crystalline mass. This was dried at 40 °C/0.02 mmHg for 24 h, carefully ground in a mortar (drybox), and then dried for an additional 24 h. We thus obtained 25 g (0.092 mol, 92%) of TBAAz: mp 82-84 °C (unchanged after recrystallization from toluene) [lit.[15] mp 80 °C]. IR (Nujol mull) showed ν_{N_3} at 2000 cm^{-1} (very strong and broad).

Reactions of Diazirines 12 with TBAAz. A large test tube fitted with a side arm and stopcock was used as the reaction vessel. It was charged in a drybox with a magnetic stirring bar, 1.8 g (6.7 mmol) of TBAAz, and 2 mL of CH_3CN (distilled from P_2O_5). The tube was sealed with a rubber septum and immersed in a water bath thermostated at 25.5 ± 0.1 °C. Light was excluded. The side arm was connected through a $CaCl_2$ drying tube to a gas buret. The reaction solution was stirred magnetically and thermally equilibrated, and then 1.0 mmol of a selected bromodiazirine (**11**) in 0.5 mL of CH_3CN was injected through the septum. Nitrogen evolution was measured at 2-min (**11a**), 5-min (**11b,c**), or 10-min (**11d,e**) intervals until 85-90% of the theoretical volume was liberated. Rate constants were calculated from the volume/time data, as described above, and are collected in Tables III, IV, and V. In several experiments, diazirine **12b** was reacted with 3 mmol of TBAAz and 3 mmol of *n*-$Bu_4N^+X^-$; cf., Table V.

Products were isolated by evaporation of CH_3CN from the reaction mixture (aspirator). The residue was diluted with 7 mL of water and extracted with 7 × 2 mL of pentane. The combined pentane extracts were dried ($MgSO_4$) and analyzed by GC and TLC, demonstrating the presence of only the expected ArCN. The nitriles were isolated by removal of the pentane,[16] and their identities were confirmed by GC and IR comparisons with authentic samples.

Acknowledgments. We are grateful to the National Science Foundation for financial support. We thank Dr. Leon A. Perez for initial preparations of benzamidine salts (**10**). R.A.M. is grateful to the Weizmann Institute of Science for an Erna and Jacob Michael Visiting Professorship and for its hospitality during the composition of much of this manuscript. Generous grants of computer time by the Rutgers Center for Computer and Information Services and an equipment grant from the National Science Foundation (PCM-8306023) are also gratefully acknowledged.

Stereocontrolled Functionalization in the Cyclohexane Ring Using Organomolybdenum Chemistry

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Abstract: The reaction between (η^4-cyclohexadiene)$Mo(CO)_2Cp$ (**1**) or (η^4-5-methylcyclohexadiene)$Mo(CO)_2Cp$ (**3**) cations and a range of stable enolate nucleophiles has been studied and was found to occur with high regio- and stereoselectivity to give (π-allyl)$Mo(CO)_2Cp$ complexes. The C-C bond formation between **1** and unsymmetrical enolates was diastereoselective: reaction with methyl 1-oxo-2-sodiocyclopentanecarboxylate gave a single diastereomer, the relative stereochemistry of which was determined by X-ray methods. Decomplexation of the product (π-allyl)$Mo(CO)_2Cp$ complexes was accomplished by treatment with iodine. Complexes containing a pendant carboxylic acid produced lactones with high regio- and stereocontrol, while complexes lacking a nucleophilic group gave substituted iodocyclohexenes which could be further manipulated. The value of this method for stereocontrol is illustrated by the preparation of an acyclic fragment having relative stereochemistry corresponding to the C(4), C(5), and C(6) centers in the macrolide antibiotics tylosin and magnamycin B.

By a process of nucleophile addition/reactivation/second nucleophile addition, olefin-transition-metal complexes offer a rich variety of opportunities for the control of relative stereochemistry during carbon-carbon bond formation. The wide range of complexes available with various metals and counterligands allows the use of cyclic unsaturated organic ligands with almost any number from 2 to 7 carbon atoms bonded to the metal, thereby leading to complementary modes of stereocontrol for different metals in a particular ring size.[2] As an illustrative example, we can consider the six-membered carbon ring. Reactive cyclohexadienyl complexes of iron are well-known[3] and can be used to promote stereocontrol at vicinal positions,[4] shown schematically

(1) (a) Case Western Reserve University. (b) Cornell University.

(2) For a comprehensive account of the various types of cyclic polyolefin complexes available, see: Deganello, G. "Transition Metal Complexes of Cyclic Polyolefins"; Academic Press: London, 1979.

(3) Reviews: Peason, A. J. *Acc. Chem. Res.* **1980**, *13*, 463. Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds. "Comprehensive Organometallic Chemistry"; Pergamon Press: New York, 1982; Chapter 58. *Transition Met. Chem.* **1981**, *6*, 67.

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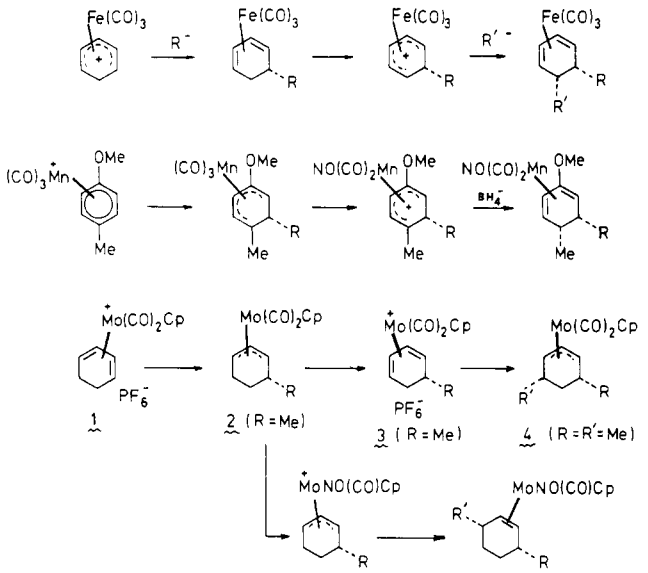


Figure 1. Double nucleophile additions to six-membered rings using iron, manganese, and molybdenum complexes.

in Figure 1. Manganese forms cationic arene complexes which give neutral dienyl systems on reaction with nucleophiles. These are activated by CO/NO^+ ligand exchange, and the resultant dienyl complexes undergo nucleophile addition, though the scope of this reaction has not been studied.[5] Cationic diene complexes of molybdenum are reactive toward a range of nucleophiles to give π-allyl complexes (Figure 1). Reaction of the derived substituted diene complexes with nucleophiles can lead to disubstituted π-allyl complexes, stereospecifically, and similar reaction of the activated π-allyl complexes may lead to disubstituted η^2-alkene complexes.[6] The former reaction gives 1,3-stereocontrol, while the latter corresponds to 1,4-stereocontrol, though this has not been rigorously studied.

This paper is concerned with the use of (cyclohexadiene)Mo$(CO)_2$Cp complexes in the stereocontrolled preparation of cyclohexene derivatives bearing two or more substituents[7] and using the following sequence: diene complex → π-allyl complex → diene complex → π-allyl complex. In the first instance this presents itself as a very useful means of introducing two functionalized substituents onto the six-membered ring. However, a problem arises in the manipulation of the final product π-allyl molybdenum complex, since this obviously cannot be decomplexed without some alteration of the π-allyl group. Such a problem is not encountered with, e.g., (diene)Fe$(CO)_3$ complexes, the products of nucleophile addition to (dienyl)Fe$(CO)_3$ cations, since removal of the metal leads to a stable entity.[8]

Partial solution to the problem of decomplexation of π-allyl molybdenum complexes has been presented by Faller et al.,[6] who converted the neutral compounds to cationic (allyl)Mo(CO)(NO)Cp derivatives and subjected these to reduction to give a η^2-alkene complex which could be converted to uncomplexed alkene by simple oxidation. These authors also showed that the sequence of reactions **1** → **2** → **3** → **4** could be carried out (see Figure 1). While methylation of the diene complex **3** occurs with excellent regio- and stereocontrol to give **4**, the yield of this particular conversion is rather low (27%). Reduction of the

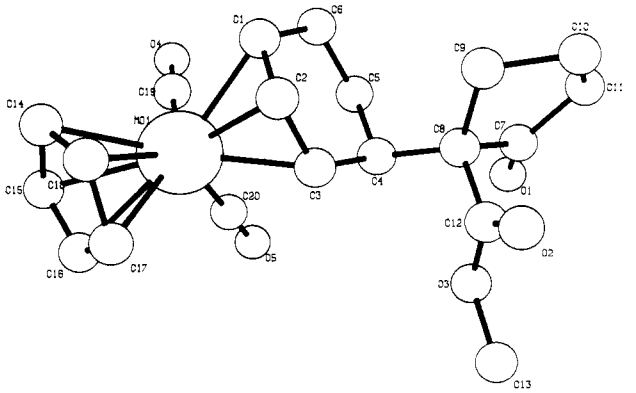
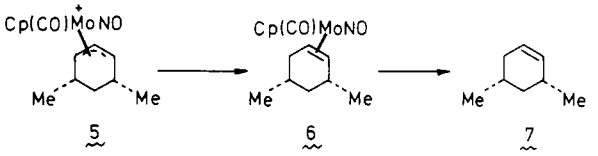


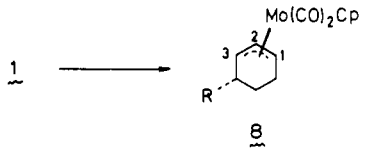
Figure 2. X-ray structure of complex **8e**.

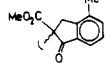
symmetrical complex **5** with sodium cyanoborodeuteride is nonstereospecific,[6] giving olefin complex **6** which is converted to the cyclohexene **7** on treatment with oxygen. It is unlikely that such reaction would lead to a single cyclohexene derivative in cases where two different substituents are present, and it is unlikely that the ligand exchange could be effected in the presence of sensitive functional groups. Inspired by Faller's results, we set out to find a better, mild procedure for decomplexation of the π-allyl molybdenum complexes and to seek areas of potential application to organic synthesis.



Results and Discussion

(a) Reactions of Complexes 1 and 3 with Stabilized Enolate Nucleophiles. In order to try and produce results of potential use in organic synthesis we investigated methods for the stereospecific introduction of functionalized substituents, using stable enolate nucleophiles such as those derived from malonic esters, etc. Reaction of complex **1** with dimethyl sodiomalonate gave a single product in 85% yield, readily assigned the structure **8a** by comparison of its ^1H NMR spectrum with reported spectra[6] of other (π-allyl)Mo$(CO)_2$Cp complexes and with our own spectra for complexes **1** and **3**. Similarly, reaction of **1** with dimethyl methylmalonate anion gave a single product **8b**, again in high yield. Treatment of **1** with enolates of unsymmetrical esters led to some interesting results. Thus, **1** was found to alkylate the anion from methyl phenylsulfonylacetate to give a high yield of an 8:1 mixture of diastereomers **8c**. So far we have been unable to assign relative stereochemistry at the two centers of asymmetry, due to the fact that epimerization at the acidic side chain methine occurs to give an equimolar mixture of the diastereoisomers on attempted chromatographic separation. Similarly, reaction of **1** with methyl sodioacetoacetate gave a 2:1 mixture of diastereoisomers **8d** which



(a) R = $CH(CO_2Me)_2$
(b) R = $CMe(CO_2Me)_2$
(c) R = $CH(SO_2Ph)CO_2Me$
(d) R = $CH(COMe)CO_2Me$
(e) R = $C(CO_2Me)COCH_2CH_2CH_2$
(f) R = 
(g) R = p-C_6H_4OMe
(h) R = $CH(CO_2Me)CO_2H$
(i) R = $CMe(CO_2Me)CO_2H$
(j) R = CH_2CO_2Me
(k) R = CH_2CO_2H

(4) Pearson, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 488. Pearson, A. J.; Chandler, M. *Tetrahedron Lett.* **1980**, *21*, 3937. Pearson, A. J.; Chandler, M. *J. Chem. Soc., Perkin Trans 1* **1982**, 2641. Pearson, A. J.; Ong, C. W. *J. Org. Chem.* **1982**, *47*, 3780.

(5) Chung, Y. K.; Choi, H. S.; Sweigart, D. A. *J. Am. Chem. Soc.* **1982**, *104*, 4245.

(6) Faller, J. W.; Murray, H. H.; White, D. L.; Chao, K. H. *Organometallics* **1983**, *2*, 400.

(7) Preliminary communications on this work: Pearson, A. J.; Khan, Md. N. I. *J. Am. Chem. Soc.* **1984**, *106*, 1872. Pearson, A. J.; Khan, Md. N. I. *Tetrahedron Lett.* **1984**, *25*, 3507.

(8) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1974**, 336.

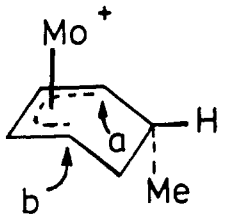
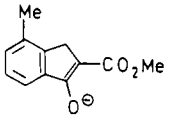


Figure 3. Nucleophile addition to complex **3** depicting sterically disfavored trajectory (a) and favored trajectory (b). (CO and Cp ligands are omitted for clarity.)

were readily equilibrated to give the equimolar mixture. In order to test this diastereoselectivity further we examined the reaction between complex **1** and a keto ester enolate which would not give epimerisable products. Accordingly, **1** was treated with the sodium salt of methyl 2-cyclopentanonecarboxylate, to give the complex **8e** which was obtained as a *single diastereoisomer*, as indicated by high-field proton- and carbon-13 NMR spectra of the *crude* reaction product. The purified crystalline material was subjected to X-ray analysis to reveal the structure and relative stereochemistry shown in Figure 2. (Details of analysis are given in the Experimental Section.) This also confirms that addition of stable enolate nucleophiles does indeed occur trans to the metal moiety. It also affirms that the η^3-cyclohexenyl ligand adopts a chair-like conformation with the relatively large keto ester substituent axial. This is useful in confirming the assignment of coupling constants made by Faller et al.[6] and in making assignments for the series of compounds presented here. Particularly noteworthy are the patterns observed for endo-5-H and exo-5-H in which the coupling constants reflect the dihedral angles expected from the chair-like conformation, as discussed previously.[6] (Exo refers to substituents on the side of the ring opposite to the $Mo(CO)_2Cp$, while endo substituents are on the same side as the metal; while not entirely satisfactory, this does conform to currently accepted practice for a range of metal–olefin complexes.) The indanone keto ester enolate **9** reacted with complex **1** with poorer diastereoselectivity to give ca. a 1.5:1 mixture of diastereomers **8f**. So far we have no explanation for the stereoselectivity shown during these reactions. The origins may be steric or electronic, and we must await results of nucleophile addition to a wider range of complexes before meaningful interpretation can be made.



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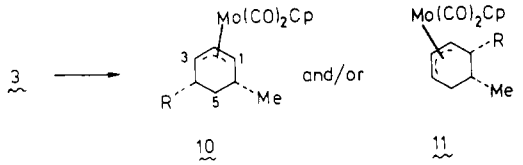
Turning our attention to the methyl-substituted diene complex **3**, we can see that nucleophile addition to this molecule can in principle occur at either diene terminus to give products of type **10** or **11**. The position α to the substituted carbon atom is



3 → **10** and/or **11**

(a) R = $CH(CO_2Me)_2$ (d) R = $CH(CO_2Me)CO_2H$

(b) R = $CH(SO_2Ph)CO_2Me$ (e) R = CH_2CO_2Me

(c) R = $\overline{C(CO_2Me)COCH_2CH_2CH_2}$ (f) R = CH_2CO_2H

sterically encumbered, since the methyl group is pseudoaxial, as shown in Figure 3. (The shape of the diene ligand in these complexes generally resembles a boat cyclohexene as depicted.[9])

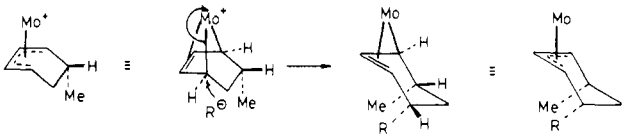


Figure 4. Pseudo-S_N2 representation for nucleophile addition to (cyclohexadiene)$Mo(CO)_2Cp$ cations. (CO and Cp ligands are omitted for clarity.)

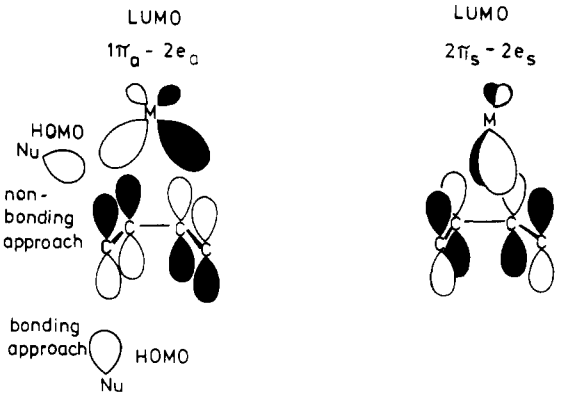


Figure 5. Possible orbital combinations giving LUMO of (diene)$Mo(CO)_2Cp$ complexes. Interaction with nucleophile HOMO is depicted for probable lower energy LUMO combination.

Although the exact mode of nucleophilic attack on these systems is not known, a useful working model pictures the nucleophile approaching the carbon–metal bond along the bond vector and trans to the metal.[10] This is effectively the same as a S_N2 displacement, occurring with pseudoinversion at the reaction center, as depicted in Figure 4. A frontier orbital interaction between nucleophile highest occupied MOs and electrophile lowest unoccupied MOs has been presented to account for the stereochemistry of nucleophile attack on η^2-alkene metal complexes,[10a] again analogous to S_N2 reactions.[11] Similar HOMO/LUMO interactions are proposed for reactions of (dienyl)$Fe(CO)_3$ complexes with nucleophiles,[10b] but the exact nature of the LUMO of (diene)$Mo(CO)_2Cp$ complexes is not known. By comparison with calculations on uncharged (diene)$Fe(CO)_3$ systems,[12] we might expect a LUMO which is an antibonding combination of either diene $1\pi_a$ or $2\pi_s$ orbitals with metal $2e_a$ or $2e_s$ orbitals, respectively, as shown in Figure 5. HOMO/LUMO interaction at a terminal carbon atom would be favored trans to the metal (Figure 5), giving the stereospecific bond formation described in the introduction.

On this basis, we favor the view that stereoelectronic, rather than simple steric, effects control the stereochemistry of nucleophilic attack on these complexes. This being the case, we would expect to observe nucleophilic attack on complex **3** favored at C-1 and *always* trans to the metal, as already reported for its reaction with methylmagnesium bromide.[6]

Reaction of **3** with dimethyl sodiomalonate at room temperature afforded the expected product **10a** contaminated with a minor amount (<10%) of a second product, assumed to be **11a**, which was detected in the 200-MHz ^1H NMR spectrum of the crude product (singlet for Cp ligand at δ 5.297, compared to **10a** at δ

(9) For X-ray structure determinations of related (cyclohexadiene)$Fe(CO)_2L$ complexes, see: Ireland, R. E.; Brown, G. G., Jr.; Stanford, R. H., Jr.; McKenzie, T. C. *J. Org. Chem.* **1974**, *39*, 51. Pearson, A. J.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 395. Pearson, A. J.; Raithby, P. R. *J. Chem. Soc., Dalton Trans.* **1981**, 884.

(10) (a) Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308. (b) Eisenstein, O.; Butler, W. M.; Pearson, A. J. *Organometallics* **1984**, *3*, 1150. (c) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *J. Chem. Soc., Chem. Commun.* **1984**, 345.

(11) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: Chichester, 1976; p 74.

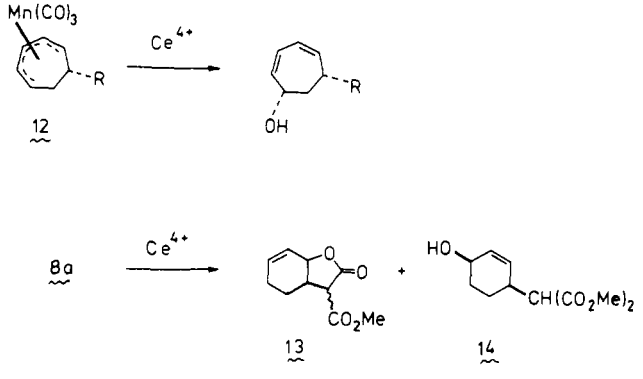
(12) Mingos, D. M. P. "Comprehensive Organometallic Chemistry"; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 3, p 62.

5.287; doublet for malonate methine at δ 3.39 compared to **10a** at δ 3.49). The NMR data for the major compound was fully consistent with structure **10a**, by comparison with Faller's data for the symmetric molecule **4**. The multiplet observed for endo-5-H (dt, J = 14.9, 7.1 Hz) and exo-H (dt, J = 14.9, 2.63 Hz) is particularly diagnostic for this structure (and stereochemistry). Improvement was obtained by conducting this reaction at −78 °C, when compound **10a** accounted for >95% of the product mixture.

Treatment of **3** with methyl phenylsulfonylsodioacetate at −78 °C afforded **10b** as an approximately 2.5:1 mixture of diastereoisomers, apparently free from regioisomeric impurities (see later). Similarly, reaction with the sodium enolate of methyl 2-cyclopentanonecarboxylate afforded **10c** as a 2:1 mixture of diastereoisomers. No attempt was made to separate these compounds and determine the relative stereochemistry. It is noteworthy that the diastereoselectivity during these reactions is lower for the methyl-substituted complex **3** than for **1**, presumably due to the steric influence of the pseudoaxial methyl substituent.

Reaction of these complexes with Grignard reagents[6] also provides a means of introducing functionalized substituents. Since we wished to examine general decomplexation of (π-allyl)Mo(CO)$_2$Cp complexes, **1** was allowed to react with *p*-methoxyphenylmagnesium bromide, to give the aryl-substituted π-allyl complex **8g** in 95% yield after purification.

(b) Manipulation of (π-Allyl)Mo(CO)$_2$Cp Complexes. Since the π-allyl ligand does not translate directly into a stable organic compound on demetallation, this process must be accompanied by introduction of new functionality. A similar problem allays the manipulation of neutral (dienyl)Mn(CO)$_3$ complexes, such as **12**, which are obtained from nucleophile addition to (triene)Mn(CO)$_3$ cations. We recently found[13] that (dienyl)Mn(CO)$_3$ complexes undergo smooth decomplexation accompanied by stereospecific introduction of the OH group on treatment with ceric ammonium nitrate in buffered wet acetone. Treatment of the diester complex **8a** with this oxidizing system gave two products, identified as the γ-lactone **13** (36% isolated yield) and a hydroxy diester tentatively assigned the structure **14** (24%). This does illustrate the possibility for direct decomplexation, but sine the regiocontrol during attachment of the oxygen substituent is poor, we did not further investigate the procedure. Instead, we focussed our attention on a possible analogy between neutral π-allyl–metal complexes and uncomplexed alkenes.



There are a number of instances in the literature where treatment of olefin metal complexes with electrophiles, usually proton, results in attachment of electrophile to the metal.[14] We envisaged that such a process might be used to activate the (π-allyl)Mo(CO)$_2$Cp complex, and in this respect we can make a direct comparison with uncomplexed alkenes. Treatment of alkenes with electrophiles in the presence of a suitable nucleophilic

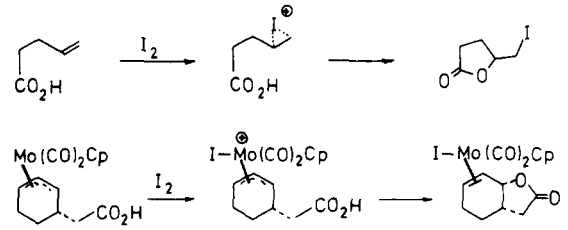
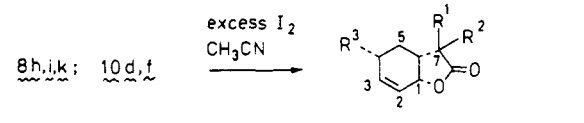


Figure 6. Comparison between iodolactonization of alkenoic acids and possible reaction between (π-allyl)Mo(CO)$_2$Cp complexes and iodine.

moiety leads to a reaction in which electrophile and nucleophile become attached to vicinal carbon atoms. We recall the familiar iodolactonization of alkenoic acids, exemplified in Figure 6.

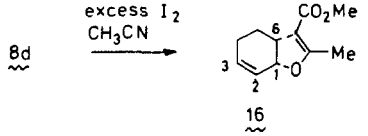
The following question now arises: can we perform similar electrophile/nucleophile addition to the π-allyl molybdenum complex? A suitable test reaction would be the iodolactonization depicted in Figure 6.

Accordingly, the ester-substituted π-allyl complexes obtained above were converted to carboxylic acid derivatives, as follows. Diesters **8a**, **8b**, and **10a** were hydrolyzed to give the half esters **8h**, **8i**, and **10d**, respectively. Complexes **8h** and **10b** were obtained as 2:1 and equimolar mixtures of diastereoisomers, respectively, while **8i** was isolated as a single isomer, possibly indicating the importance of steric factors during the reaction. The phenylsulfonylacetates **8c** and **10b** were desulfonylated to the single monoesters **8j** and **10e** (confirming the high regioselectivity during formation of **10b**), which were hydrolyzed to monoacids **8k** and **10f** in good overall yield. The acid complexes were each treated with iodine in acetonitrile solution, and the reaction was monitored by infrared spectroscopy. A gradual disappearance of the Mo(CO)$_2$Cp carbonyl bands at ca. 1950 and 1860 cm^{-1} and the CO$_2$H carbonyl absorption at ca. 1730 cm^{-1} was accompanied by the appearance of first two new bands at 2082 and 2050 cm^{-1} and then γ-lactone absorption at ca. 1790 cm^{-1} in each case. By using this technique to follow the progress of the reaction, it was found that 3.5–4 equiv of iodine were necessary for complete conversion in 30 min at room temperature. The appearance of absorptions at 2082 and 2050 cm^{-1} during this reaction is consistent with the intermediacy of a cationic (π-allyl)Mo(CO)$_2$ICp complex, as shown in Figure 6. Presumably, cyclization of this compound gives the (η^2-alkene)Mo(CO)$_2$ICp intermediate which is very easily oxidized by the iodine present to give the demetallated γ-lactones **15**, which were isolated by normal extractive workup in 90–95%



(a) R^1 = H; R^2 = CO_2Me; R^3 = H
(b) R^2 = Me; R^2 = CO_2Me; R^3 = H
(c) R^1 = R^2 = R^3 = H
(d) R^1 = H; R^2 = CO_2Me; R^3 = Me
(e) R^1 = R^2 = H; R^3 = Me

yield after chromatographic purification. Similarly, the keto ester complex **8d** was converted to the tetrahydrobenzofuran derivative **16** (85% yield) on treatment with excess iodine, the reaction



proceeding in an analogous fashion via internal nucleophile attack by the enol form of the keto ester. The products of these reactions were readily assigned the structures shown on the basis of IR and NMR spectroscopy, with double resonance experiments, details

(13) Pearson, A. J.; Richards, I. C.; Bruhn, P. *Tetrahedron Lett.* **1984**, 387. Pearson, A. J.; Richards, I. C.; Bruhn, P. *Isr. J. Chem.* **1984**, *24*, 93.
(14) Young, D. A. T.; Holmes, J. R.; Kaesz, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 6968. Greaves, E. O.; Knox, G. R.; Pauson, P. L.; Toma, S.; Sim, G. A.; Woodhouse, D. I. *J. Chem. Soc., Chem. Commun.* **1974**, 257. Birch, A. J.; Raverty, W. R.; Hsu, S.-Y.; Pearson, A. J. *J. Organomet. Chem.* **1984**, *260*, C59.

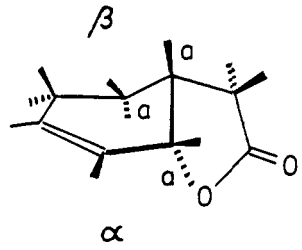
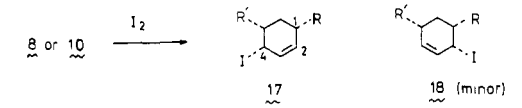


Figure 7. Conformation of lactones **15** from ^1H NMR spectral data. Axial substituents are marked (a).

of which are given in the Experimental Section.

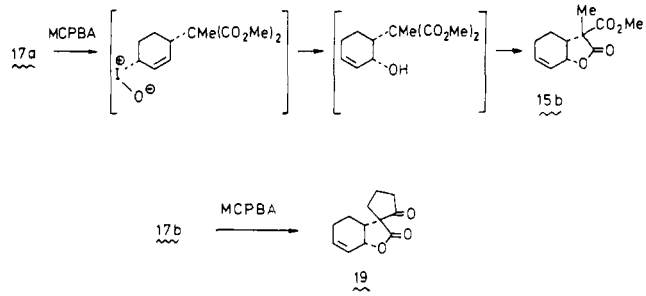
From the analysis of NMR spectral data for these lactones, it is apparent that they all adopt the conformation shown in Figure 7, in which the lactone oxygen (C-1 substituent, numbering is arbitrary) is quasiaxial and the lactone methylene is quasiequatorial on the cyclohexene pseudochair. This is reflected in the coupling constants obtained from double-resonance experiments and given in the Experimental Section. As an example, lactone **15e** shows 5β-H as a doublet of triplets with J_{gem} = 13 Hz and $J_{5\beta,6} = J_{4,5\beta}$ = 4.5 Hz, the latter two being the expected value for axial/equatorial proton couplings, while 5α-H is obtained as a quartet with coincident J_{gem}, $J_{5\alpha,6}$ (axial–axial), and $J_{4,5\alpha}$ (axial–axial) coupling constants (13 Hz). The other lactones displayed similar patterns.

The success of these cyclofunctionalization/demetallation reactions prompted us to examine the reaction of (π-allyl)Mo(CO)$_2$Cp complexes with iodine in the absence of appended nucleophiles. Accordingly, complexes **8b**, **8e**, **8g**, and **10a** were treated directly with an excess of iodine in acetonitrile, followed by the usual extractive workup to afford substituted iodocyclohexenes. Complex **8b** gave iodide **17a** together with a minor amount (<10%) of the isomeric iodide (**18a**). Complex **8e** gave a single iodide **17b**, **8g** gave **17c**, and complex **10a** gave a mixture of **17d** and **18d** (4:1 mixture by NMR spectroscopy). Confir-

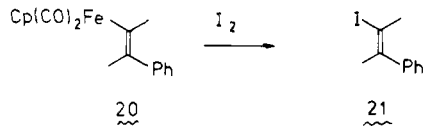


(a) R = CMe(CO$_2$Me)$_2$, R' = H
(b) R = C(CO$_2$Me)COCH$_2$CH$_2$CH$_2$, R' = H
(c) R = p-C$_6$H$_4$OMe, R' = H
(d) R = CH(CO$_2$Me)$_2$, R' = Me

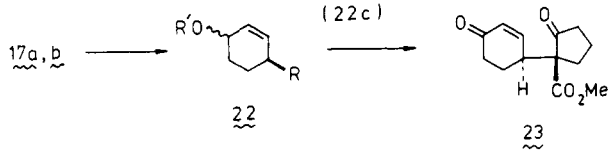
mation of the structures of these iodides was obtained from a study of their further reactions. Thus, careful treatment of **17a** with (*m*-chloroperoxy)benzoic[17] acid resulted in the formation of a γ-lactone identical with that obtained by iodolactonization of half-acid complex **8i** and assigned the structure **15b**. Similar treatment of allylic iodide **17b** gave the γ-lactone **19**. It has been



reported previously[15] that treatment of allylic iodides with (*m*-chloroperoxy)benzoic acid gives allylic alcohols via rearrangement of an intermediate iodoso derivative, as indicated. This is similar to the [2,3] sigmatropic rearrangement of allylic selenoxides[16] and sulfoxides[17] and is expected to occur with retention of configuration. The formation of γ-lactones **15b** and **19** is strongly indicative that the stereochemistry of the iodides is that shown in structure **17**. A plausible mechanism for their formation is given in Figure 8, involving addition of iodide to the intermediate cationic (π-allyl)Mo(CO)$_2$ICp complex, trans to the metal, followed by oxidative demetallation. This contrasts with the reaction of, e.g., vinyl–Fp derivatives such as **20** with iodine, which gives the vinyl iodide **21**, presumably via oxidative addition of iodine followed by a reductive elimination of the vinyl iodide, therefore occurring with retention of stereochemistry.[18]



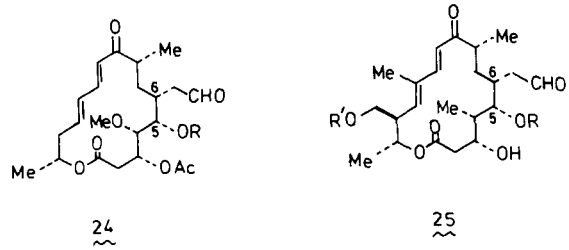
Further transformations of the allylic iodides were also possible. Treatment of **17b** with silver acetate gave the allylic acetate **22a**, obtained as a mixture of stereoisomers (due to the part S_N1 nature of the reaction). Deacetylation of **22a** gave the mixture of alcohols **22b** which was readily oxidized to the single cyclohexenone **23**. The sequence of reactions from cyclohexene via 3-bromocyclohexene through diene molybdenum complexes **1** and **3** to enones of type **23** represents a potentially valuable stereocontrolled route to these compounds.



(a) R = CMe(CO$_2$Me)$_2$, R' = Ac
(b) R = C(CO$_2$Me)COCH$_2$CH$_2$CH$_2$, R' = Ac
(c) R = C(CO$_2$Me)COCH$_2$CH$_2$CH$_2$, R' = H

Conclusions

Double nucleophile additions to (cyclohexadiene)Mo(CO)$_2$Cp cations, coupled with iodine-promoted demetallation of π-allyl complexes, lead to a variety of stereospecifically substituted cyclohexene derivatives. The potential importance of this as emerging methodology for organic synthesis is clearly illustrated by the stereochemical relationship between the lactone **15e** and the C(5), C(6), and C(8) centers of magnamycin B (**23**) and tylosin (**24**),[19] both important 16-membered macrolide antibiotics.



Indeed, ring cleavage of **15e** at the double bond translates it to

(15) Yamamoto, S.; Itani, H.; Tsuji, T.; Nagata, W. *J. Am. Chem. Soc.* **1983**, *105*, 2908.
(16) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154; **1973**, *95*, 2697. Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570.
(17) Carruthers, W. "Some Modern Methods of Organic Synthesis", 2nd ed.; Cambridge University Press: New York, 1978; pp 103–106.
(18) Reger, D. L.; McElligott, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 5923.
(19) For recent synthetic approaches to these macrolides, see the following references. Tylosin: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027, 2030. Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523. Grieco, P. A.; Inanaga, J.; Lin, N.-H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781. Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577. Magnamycin B.; Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837.

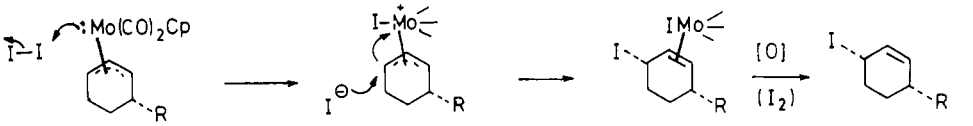
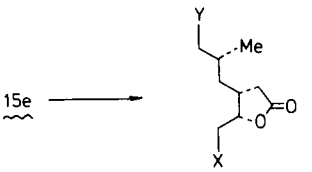


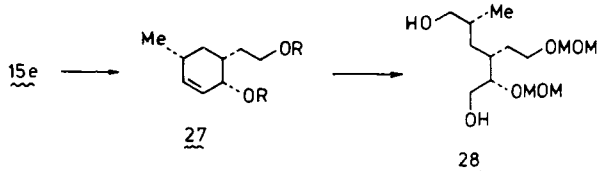
Figure 8. Reaction of (π-allyl)Mo(CO)$_2$Cp complex with iodine in the absence of internal nucleophile. (CO and Cp ligands are omitted for clarity.)

the stereodefined acyclic fragment **25**, a potential building block for such macrolides. While direct ozonolysis of **15e** gave dialdehyde **26** (X = Y = =O), this was found to be a capricious and low-yielding reaction. A much cleaner sequence was therefore



26

developed. Thus, the lactone **15e** was reduced to diol **27a** which was fully protected as the methoxymethyl ether **27b**. Ozonolysis of this compound was more reliable, giving the acyclic fragment **28** after reductive ($NaBH_4$) workup. This establishes that the diene–molybdenum system may be used as a template for constructing stereodefined acyclic molecules.

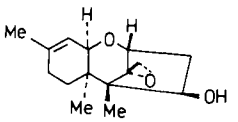


27 **28**

(a) R = H

(b) R = CH_2OMe

The somewhat fortuitous diastereoselective formation of complex **8e** and its conversion to enone **22** is also of potential significance, since these intermediates have relative stereochemistry corresponding to two centers in the much-publicized trichothecenes,[20] exemplified by trichodermol (**29**). Thus, it would be important to establish routes for the preparation of (1,4-dialkyl-substituted cyclohexadiene)Mo(CO)$_2$Cp complexes and to determine whether these show similar diastereoselectivity during reaction with nucleophiles.



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Experimental Section

Infrared spectra were recorded in carbon tetrachloride solution, unless otherwise stated, on a Perkin-Elmer 1420, and NMR spectra for solutions in deuteriochloroform were obtained with a Varian XL-200 instrument. Mass spectra were kindly provided by Professor H. Andrist, Cleveland State University, or by Dr. Robert P. Lattimer and Dr. Bill Kroenke of the B. F. Goodrich Co., Brecksville, OH. For molybdenum complexes the molecular ions corresponding to isotopes Mo-92, -94, -95, -96, -97, and -98 are quoted. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Solvents were freshly distilled under nitrogen as follows: tetrahydrofuran (THF) from sodium benzophenone; diethyl ether from lithium aluminum hydride; dichloromethane and acetonitrile from calcium hydride. All reactions were conducted under an atmosphere of dry nitrogen. Complexes **1** and **3** were prepared according to the method of Faller et al.[6] Combustion analyses were carried out by Galbraith Laboratories, Knoxville, TN. Compounds which were not submitted for analysis were ascertained to be at least 95% pure by TLC, 200-MHz ^{1}H NMR, and field desorption mass spectrometry.

CpMo(CO)$_2$[η^3-C$_6$H$_8$-4-CH(CO$_2$Me)$_2$] (8a). A solution of NaCH(CO$_2$Me)$_2$ in THF was prepared in the usual way by addition of dimethyl malonate (0.065 g, 0.49 mmol) in THF (5 mL) to a stirred suspension of sodium hydride (0.45 mmol, from 0.022 g of NaH 50% suspension in mineral oil, washed with dry THF in situ) in THF (1 mL). The reaction flask was opened briefly, with backflushing of nitrogen, and the diene complex **1** (0.20 g, 0.45 mmol) was added in one portion. The reaction could be monitored by dissolution of the THF-insoluble complex (**1**) (ca. 15 min), after which the mixture was poured into water (50 mL) and extracted with ether (2 × 25 mL). The combined ether extracts were washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated in vacuo to yield the crude product, purified by column chromatography (silica gel/dichloromethane) to give **8a** as a yellow solid (0.16 g, 85%). An analytical sample was obtained by recrystallization from a chloroform/ether/pentane mixture: mp 132 °C; IR ν_{max} 1940, 1860, 1750, and 1735 cm^{-1}; ^{1}H NMR δ 5.29 (5 H, s, Cp), 4.18 (1 H, t, J = 7.2 Hz, 2-H), 3.78 (3 H, s), 3.69 (3 H, s), 3.5 and 3.7 (1 H, m, each, 1-H and 3-H), 3.36 (1 H, d, J = 10.14 Hz, malonate CH, 2.5 (1 H, m, endo-4-H), 1.91 (1 H, td, J_{gem} = $J_{5\text{-endo}}$ = 15, $J_{5\text{-exo}}$ = 5.2 Hz, endo-6-H), 1.5 (1 H, br d, J_{gem} = 15 Hz, exo-6-H), 0.8 (1 H, dd, J = 15, 5.7 Hz, endo-5-H), 0.61 (1 H, m, exo-5-H); *m/e* (%) 430 (2.6), 429 (0.8), 428 (1.4), 427 (3.4), 426 (1.7 [M], 402 (1.8), 401 (0.9), 400 (0.9), 399 (0.8), 398 (0.4), 396 (1.0) [M − CO], 374 (12.6), 373 (5.0), 372 (25.3), 371 (15.8), 370 (18.7), 369 (14.3), 368 (11.8), 367 (1.3), 366 (10.8) [M − 2CO]. M$^+$ calcd for ^{98}Mo: C$_{18}$H$_{20}$O$_6$Mo, 430.0309. Found: 430.0913. Anal. Calcd for C$_{18}$H$_{20}$O$_6$Mo: C, 50.71; H, 4.69. Found: C, 50.74; H, 4.68.

Cp(CO)$_2$Mo[η^3-C$_6$H$_8$-4-CMe(CO$_2$Me)$_2$] (8b). Treatment of the diene complex **1** (0.050 g, 0.11 mmol) with NaCMe(CO$_2$Me)$_2$ (1.0 equiv) in THF (5 mL) at room temperature, followed by extractive workup and chromatography, as above, afforded complex **8b** as a yellow crystalline solid: mp 108 °C; IR ν_{max} 1940, 1860, and 1735 cm^{-1}; ^{1}H NMR δ 5.26 (5 H, s), 4.3 (1 H, t, J = 7.2 Hz, 2-H), 3.70 (3 H, s), 3.71 and 3.43 (1 H, m, each, 1-H and 3-H), 3.65 (3 H, s), 2.72 (1 H, m, endo-4-H), 1.92 (1 H, m, endo-6-H), 1.60 (1 H, m, exo-6-H), 0.81 (1 H, m, endo-5-H), 0.61 (1 H, m, exo-5-H). Anal. Found: C, 51.53; H, 4.97. C$_{19}$H$_{22}$O$_6$Mo requires C, 51.59; H, 5.01.

Cp(CO)$_2$Mo[η^3-C$_6$H$_8$-4-CH(SO$_2$Ph)CO$_2$Me] (8c). A solution of NaCH(SO$_2$Ph)CO$_2$Me in THF (10 mL) was prepared from methyl phenylsulfonylacetate (0.11 g, 0.5 mmol) and sodium hydride as above, and the complex **1** (0.20 g, 0.45 mmol) was added at room temperature. After the mixture was stirred for 30 min the reaction was worked up as above and the product was extracted in the usual manner. ^{1}H NMR spectroscopy on the crude product indicated an ca. 8:1 mixture of diasteromers. Purification by preparative TLC afforded an equimolar mixture of diastereomers **8c** as a yellow foam (0.20 g, 90%): IR ν_{max} 1940, 1860, 1740, 1450, 1330, and 1145 cm^{-1}; ^{1}H NMR δ 7.85 and 7.51 (5 H, m, Ar H), 5.28 (5 H, s, Cp, minor isomer), 5.23 (5 H, s, Cp, major isomer), 4.20 (1 H, t, J = 6.76 Hz, 2-H, minor isomer), 4.09 (1 H, t, J = 6.76 Hz, 2-H, major isomer), 4.07 (1 H, d, J = 9.11 Hz, C*H*(SO$_2$Ph)CO$_2$Me, minor), 3.95 (1 H, d, J = 9.11 Hz, major), 3.7 and 3.22 (1 H, m, each, 1-H and 3-H), 3.60 (3 H, s, CO$_2$Me, major), 3.41 (3 H, s, CO$_2$Me, minor), 2.66 (1 H, m, 4-H, minor), 2.48 (1 H, m, 4-H, major), 1.86 (1 H, m, endo-6-H), 1.56 (1 H, m, exo-6-H), 0.63 (1 H, m, endo-5-H), 0.56 (1 H, m, exo-5-H). Anal. Found: C, 51.89; H, 4.51. C$_{22}$H$_{22}$O$_6$SMo requires C, 51.77; H, 4.34.

Cp(CO)$_2$Mo[η^3-C$_6$H$_8$-4-CH(COMe)CO$_2$Me] (8d). Reaction of complex **1** (0.20 g, 0.45 mmol) with NaCH(COMe)CO$_2$Me (0.45 mmol), prepared as above from methyl acetoacetate and sodium hydride, in THF (5 mL), at room temperature for 15 min, followed by the usual workup, afforded complex **8d** as a 2:1 mixture of diastereomers. Purification by preparative TLC (silica gel, EtOAc/hexane) gave an equimolar mixture of isomers as a yellow crystalline solid: mp 136 °C (0.15 g, 80%); IR ν_{max} 1940, 1860, 1740, 1710 cm^{-1}; ^{1}H NMR, major isomer, δ 5.29 (5 H, s), 4.16 (1 H, t, J = 7 Hz, 2-H), 3.77 (3 H, s), 3.72 (1 H, m, obscured, 1-H or 3-H) 3.44 (1 H, d, J = 10 Hz, acetoacetate C*H*), 3.5 (1 H, obscured, 1-H or 3-H), 2.57 (1 H, m, endo-6-H), 2.16 (3 H, s, COCH$_3$), 1.87 (1 H, m, 4-H), 1.55 (1 H, br d, J = 15 Hz, exo-6-H), 0.6 (2 H, m, 5-H$_2$); ^{1}H NMR, Minor isomer δ 5.28 (5 H, s), 4.14 (1 H, t, J = 7 Hz),

(20) Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. Bamburg, J. R.; Strong, F. M. "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. 7, pp 207–292. Doyle, T. W.; Bradner, W. T. "Anticancer Agents Based on Natural Product Models"; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; pp 43–72.

3.67 (3 H, s), 3.47 (1 H, d, J = 10 Hz), 3.32 (1 H, br d, J = 7 Hz), 2.30 (3 H, s), remaining peaks overlap with signals for the major isomer, thereby preventing rigorous assignment of multiplicities; m/e (%) 414 (17), 413 (4), 412 (17), 411 (18), 410 (8), 408 (5) [M], 358 (18) 357 (8), 356 (30), 355 (21), 354 (21), 353 (6), 352 (13), 350 (9) [M − 2CO]. Anal. Calcd for $C_{18}H_{20}O_5Mo$: C, 52.69; H, 4.87. Found: C, 52.48; H, 4.98%.

$Cp(CO)_2Mo[\eta^3$-C_6H_8-4-$\overline{C(CO_2Me)COCH_2CH_2CH_2}]$ (8e). The sodium enolate of methyl 2-oxycyclopentanecarboxylate was prepared in THF (10 mL) as above from the keto ester (0.07 g, 0.50 mmol) and treated with complex **1** (0.20 g, 0.45 mmol) at room temperature (30 min). Workup as above gave the keto ester complex **8e** as a yellow crystalline solid, mp 173 °C (0.17 g, 85%), which showed a single isomer in the ^1H and ^{13}C NMR spectra of crude material (200 and 50 MHz, respectively). An analytical sample was obtained by preparative TLC (silica gel, 60:40, hexane/EtOAc). IR ν_{max} 1940, 1860, 1750 and 1720 cm^{-1}; ^1H NMR δ 5.29 (5 H, s, Cp), 4.26 (1 H, t, J = 7.13 Hz, 2-H), 3.75 (3 H, s, CO_2Me), 3.52 (1 H, br d, J = 7.13 Hz, 3-H), 3.15 (1 H, br d, 7.13 Hz, 1-H), 2.73 (1 H, m, 4-H), 2.31, 2.17, 2.04 (2 H, m, each, methylenes), 1.93 (1 H, m, endo-6-H), 1.68 (1 H, m, exo-6-H), 0.63 (2 H, m, 5-H_2); ^{13}C NMR, run to 180 ppm, δ 175.97, 97.42 (Cp), 73.09, 63.84, 60.01, 58.00, 57.61, 44.23, 42.11, 35.72, 25.79, 24.78, 24.67; m/e (%) 440 (28), 439 (11), 438 (19), 437 (19), 436 (8), 434 (12) [M], 412 (13), 411 (6), 410 (9), 409 (6), 408 (3), 406 (7) [M − CO], 384 (74), 383 (39), 382 (100), 381 (66), 380 (93), 378 (81), 377 (30) [M − 2CO]. Anal. Calcd for $C_{20}H_{22}O_5Mo$: C, 54.92; H, 5.26. Found: C, 54.92; H, 5.15.

$Cp(CO)_2Mo[\eta^3$-C_6H_8-4-{2-(2-(methoxycarbonyl)-4-methyl-1-indanone)}] (8f). Treatment of complex **1** (0.050 g, 0.11 mmol) with the sodium enolate of methyl 4-methylindanone-2-carboxylate, followed by aqueous workup, ether extraction, and preparative TLC as above gave **8f** as a mixture of diastereomers (ca. 1.5:1) as a yellow foam: IR ν_{max} 1940, 1860, and 1735 cm^{-1}; ^1H NMR, major isomer, δ 7.6–7.2 (3 H, m, Ar H), 5.23 (5 H, s, Cp), 4.15 (1 H, t, J = 7 Hz, 2-H), 3.67 (3 H, s, CO_2Me), 3.7 (1 H, obscured by CO_2Me from minor isomer), and 3.3 (1 H, d, J = 7 Hz, 1- and 3-H), 3.15 (2 H, ABq, benzylic CH_2), 2.45 (3 H, s, Me), 2.0–1.5 (2 H, m), 0.9–0.5 (2 H, m); ^1H NMR, minor isomer, δ 7.6.7.2 (3 H, m, Ar H), 5.31 (5 H, s, Cp), 4.39 (1 H, t, J = 7 Hz, 2-H), 3.75 (3 H, s, CO_2Me), 2.42 (3 H, s, Me), other peaks obscured by the major isomer; MS (FD), m/z (%) 502 (100), 501 (35), 500 (70), 499 (60), 498 (10), 496 (21).

$Cp(CO)_2Mo[\eta^3$-C_6H_8-4-(4-C_6H_4OMe)] (8g). A solution of 4-methoxyphenylmagnesium bromide was prepared in THF from p-bromoanisole and magnesium in the usual way and standardized by titration. To a stirred suspension of complex **1** (0.3 g, 0.78 mmol) in THF (10 mL) at 0 °C was added the Grignard reagent (0.83 mmol) via syringe. After the mixture was stirred for 30 min the reaction was worked up in the usual way to afford complex **8g** which was purified by preparative TLC (silica gel, EtOAc/hexane). Traces of 4,4′-dimethoxybiphenyl present (≤5%) could not be removed chromatographically (yield: 0.26 g, 95%). IR ν_{max} 1940 and 1860 cm^{-1}; ^1H NMR δ 7.33 (2 H, d, J = 6.72 Hz, Ar H), 6.86 (2 H, dd, J = 6.72, 2.0 Hz, Ar H), 5.3 (5 H, s), 4.44 (1 H, t, J = 7.13 Hz, 2-H), 3.83 (1 H, obscured, 1- or 3-H), 3.81 (3 H, s), 3.74 (1 H, br d, J = 7.13 Hz, 1- or 3-H), 3.02 (1 H, m, 4-H), 2.09 (1 H, m, endo-6-H), 1.67 (1 H, m, exo-6-H), 1.25 (1 H, m, endo-5-H), 0.83 (1 H, m, exo-5-H). Anal. Found: C, 59.37; H, 4.87. $C_{20}H_{20}O_3Mo$ requires C, 59.32; H, 4.97.

$Cp(CO)_2Mo[\eta^3$-C_6H_8-4-$CH(CO_2Me)CO_2H]$ (8h). The diester complex **8a** (0.50 g, 1.17 mmol) was dissolved in 1:1 methanol/THF (10 mL) and stirred while a solution of potassium hydroxide (0.13 g) in water (0.5 mL) was added. Stirring was continued for 10 h, the progress of the reaction being monitored by TLC. The reaction mixture was poured on to dilute HCl/ice and the product was extracted with ether (3 × 25 mL). The combined extracts were washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated to give the half-acid **8h** as a yellow foam (0.47 g, 98%). IR ν_{max} 1945, 2862, and 1745 (br) cm^{-1}; ^1H NMR δ 9.0 (1 H, br s, CO_2H), 5.34 (5 H, s), 4.24 (1 H, t, J = 6.7 Hz, 2-H), 3.81 (s, CO_2Me, major isomer), 3.72 (s, CO_2Me, minor isomer), 3.47 (2 H, overlapping d, J = 6.7 Hz, 1-H and 3-H), 3.43 (1 H, d, J = 9.89 Hz, malonate methine), 2.52 (1 H, m, 4-H), 1.64 (1 H, m, endo-6-H), 1.56 (1 H, m exo-6-H), 0.87 (1 H, m, endo-5-H), 0.55 (1 H, m, exo-5-H). Assignment of multiplicities was prevented by overlap of diastereomer peaks.

$Cp(CO)_2Mo[\eta^3$-$C_6H_8CMe(CO_2Me)CO_2H]$ (8i). Hydrolysis of diester complex **8b** (0.20 g), as for the preparation of **8h** above using a reaction time of 8 days, afforded the half-acid **8i** (70% yield). Only one diastereomer was found in the ^1H NMR spectrum. Several attempts to crystallize the compound failed. IR ν_{max} 1940, 1860, and 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6, 200 MHz), 13.86 (1 H, br s, CO_2H), 5.47 (5 H, s), 4.56 (1 H, t, J = 7.28 Hz, 2-H), 3.69 and 3.66 (1 H, t, each, J = 7.28 Hz, 1- and 3-H), 3.32 (3 H, s), 2.65 (1 H, m, 4-H), 1.89 (1 H, m, endo-6-H), 1.47 (1 H, m, obscured, exo-6-H), 1.41 (3 H, s, Me), 0.83 (1 H, m, endo-5-H), 0.39 (1 H, m, exo-5-H).

$Cp(CO)_2Mo(\eta^3$-C_6H_8-4-$CH_2CO_2Me)$ (8j). The phenylsulfonyl ester complex **8c** (0.60 g, 1.17 mmol) was stirred in dry MeOH (10 mL) and THF (2 mL) while Na_2HPO_4 (1.05 g, 7.3 mmol) was added. The mixture was stirred at room temperature for 15 min and cooled to 0 °C and 6% sodium–mercury amalgam (2.95 g) was added in small portions. The progress of the reaction was monitored by TLC (silica gel, 60:40 hexane/ethyl acetate). Aqueous workup and ether extraction followed by chromatographic purification (silica) gel, CH_2Cl_2) in the usual way afforded pure monoester complex **8j** as a yellow crystalline solid (0.37 g 85%): mp 106 °C; IR ν_{max} 1940, 1860, and 1750 cm^{-1}; ^1H NMR δ 5.28 (5 H, s, Cp), 4.15 (1 H, t, J = 7.14 Hz, 2-H), 3.71 (1 H, br d, obscured, 1- or 3-H), 3.66 (3 H, s, CO_2Me), 3.54 (1 H, br d, J = 7.17 Hz, 1- or 3-H), 2.44 (2 H, m, CH_2CO_2Me, diastereotopic), 2.28 (1 H, m, 4-H), 1.95 (1 H, m, endo-6-H), 1.54 (1 H, m, exo-6-H), 0.78 (1 H, dd, J = 13, 6.5 Hz, endo-5-H), 0.75 (1 H, m, exo-5-H). Anal. Found: C, 52.18; H, 4.88. $C_{16}H_{18}O_4Mo$ requires C, 51.90; H, 4.90.

$Cp(CO)_2Mo(\eta^3$-C_6H_8-4-$CH_2CO_2H)$ (8k). The monoester **8j** (0.26 g) was hydrolyzed in an analogous fashion to that described for **8a**, reaction time 8 h at room temperature, to afford the monoacid as a yellow crystalline solid (0.24 g, 97%): mp 173 °C; IR ν_{max} 3450, 1940, 1860, and 1735 cm^{-1}; ^1H NMR δ 5.30 (5 H, s), 4.17 (1 H, t, J = 7.1 Hz, 2-H), 3.73 (1 H, br, d, J = 7.1 Hz, 1- or 3-H), 3.50 (1 H, br d, J = 7.1 Hz, 1- or 3-H), 2.48 (2 H, m, CH_2CO_2H, diastereotopic), 2.31 (1 H, m), 1.97 (1 H, br td, J = ca. 14, 5 Hz, endo-6-H), 1.6 (1 H, br dm, J = 14 Hz, exo-6-H), 0.87 (1 H, br dd, J = 14, 6 Hz, endo-5-H), 0.60 (1 H, dt, J = 14, 6 Hz, exo-5-H). Anal. Found: C, 50.79; H, 4.56. $C_{15}H_{16}O_4Mo$ requires C, 50.57; H, 4.52.

$Cp(CO)_2Mo[\eta^3$-C_6H_7-4-$CH(CO_2Me)_2$-6-Me] (10a). Reaction of diene complex **3** (0.50 g, 1.09 mmol) with $NaCH(CO_2Me)_2$ in THF at −78 °C (30 min) in an identical manner to the preparation of complex **8a** afforded the diester **10a**: mp 163–164 °C (0.41 g, 95%); IR ν_{max} 1940, 1860, 1750, and 1730 cm^{-1}; ^1H NMR δ 5.28 (5 H, s), 4.17 (1 H, t, J = 7.05 Hz, 2-H), 3.78 (3 H, s), 3.75 (1 H, br d, J = 7.05 Hz), 3.69 (3 H, s), 3.62 (1 H, br d, J = 7.05 Hz), 3.48 (1 H, d, J = 11 Hz, malonate CH), 2.56 (1 H, m, 4-H), 1.89 (1 H, m, 6-H), 1.19 (3 H, d, J = 7.22 Hz, Me), 0.87 (1 H, dt, J = 14.84, 7.09 Hz, endo-5-H), 0.59 (1 H, dt, J = 14.84, 2.63 Hz, exo-5-H). Anal. Calcd for $C_{19}H_{22}O_6Me$: C, 51.59, H, 4.97. Found: C, 50.93; H, 5.04.

$Cp(CO)_2Mo[\eta^3$-C_6H_7-4-$CH(SO_2Ph)CO_2Me$-6-Me] (10b). Reaction of complex **3** (0.30 g, 0.65 mmol) with $NaCH(SO_2Ph)CO_2Me$ in THF at −78 °C for 30 min, otherwise as for the preparation of **8c**, afforded the complex **10a** as an ca. 8:1 mixture of diastereomers contaminated with a small amount of methyl phenylsulfonylacetate which could not be separated (0.33 g, 95%). This material could be used in the next step without further purification. IR ν_{max} 1940, 1860, 1740, 1450, 1330, and 1144 cm^{-1}; ^1H NMR, major isomer, δ 7.9, 7.6 (5 H, m, Ar H), 5.26 (5 H, s, Cp), 4.28 (1 H, d, J = 5.15 Hz, $CH(SO_2Ph)CO_2Me$), 4.16 (1 H, t, J = 7 Hz, 2-H), 3.76 (1 H, br d, J = 7 Hz, 1- or 3-H), 3.66 (3 H, s), 3.28 (1 H, d, J = 7 Hz, 1- or 3-H), 2.54 (1 H, br t, J = ca. 6 Hz, 4-H), 1.90 (1 H, m, 6-H), 1.62 (1 H, m, endo-5-H), 1.23 (3 H, d, J = 7.16 Hz, Me), 0.85 (1 H, m, exo-5-H); ^1H NMR, minor isomer, δ 5.34 (5 H, s, Cp), 4.16 (1 H, t, J = 7 Hz), 3.98 (1 H, d, J = 6 Hz, phenylsulfonylacetate CH), 3.71 (3 H, s), 2.66 (1 H, m, 4-H), 1.15 (3 H, d, J = 7.16 Hz, Me). Assignment of all protons in the minor isomer is prevented by overlap of peaks from the major component.

$Cp(CO)_2Mo[\eta^3$-C_6H_7-4-CH_2CO_2Me-6-Me] (10e). Desulfonylation of crude **10b** from the above reaction, using the method described for preparation of complex **8j**, afforded the monoester **10e**, free from contamination according to TLC and ^1H NMR (200 MHz), but which could not be crystallized (yield 0.44 g, from 0.86 g of **10b**; 70%). IR ν_{max} 1940, 1860, and 1740 cm^{-1}; ^1H NMR δ 5.28 (5 H, s, Cp), 4.15 (1 H, t, J = 7.08 Hz, 2-H), 3.70 (2 H, m, obscured, 1- and 3-H), 3.68 (3 H, s), 2.54 (2 H, d, J = 7.5 Hz, CH_2CO_2Me), 2.30 and 1.92 (1 H, m, each, 4- and 6-H), 1.21 (3 H, d, J = 7.32 Hz, Me), 0.84 (1 H, dt, J = 14.36, 7.16 Hz, endo-5-H), 0.64 (1 H, dt, J = 14.368 2 Hz, exo-5-H). Anal. Found: C, 53.46; H, 5.29. $C_{17}H_{20}O_4Mo$ requires C, 53.13; H, 5.24.

$Cp(CO)_2Mo(\eta^3$-C_6H_7-4-CH_2CO_2H-6-Me) (10f). Hydrolysis of the monoester **10e** (0.16 g, 0.42 mmol) as described previously for the preparation of acid **8k**, but using 8 equiv of KOH, afforded the acid **10f** (0.13 g, 85%), as a yellow crystalline solid: mp 174 °C; IR ν_{max} 3400 (br), 1940, 1860, and 1700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.2 (1 H, br, CO_2H), 5.44 (5 H, s), 4.36 (1 H, t, J = 7.14 Hz, 2-H), 3.69 (2 H, br d, J = 6.88 Hz, 1- and 3-H), 2.45–2.3 (2 H, m, CH_2CO_2H diastereotopic), 2.1 (1 H, m, 4-H), 1.79 (1 H, m, 6-H), 1.18 (3 H, d, J = 7.26 Hz, Me), 0.8–0.5 (2 H, m, 5-CH_2). The NMR spectrum in deuteriochloroform showed better resolution of the 5-methylene groups: δ 0.8 (1 H, dt, J = 14, 7 Hz), 0.65 (1 H, dt, J = 14, 2.5 Hz). Anal. Calcd for

$C_{17}H_{19}O_4Mo$: C, 51.90; H, 4.86. Found: C, 51.85; H, 4.90.

$Cp(CO)_2Mo(\eta^3$-C_6H_7-4-$\overline{C(CO_2Me)COCH_2CH_2CH_2}$-6-Me) (10c). This was prepared by treatment of complex **3** with the sodium enolate of methyl 2-oxocyclopentanecarboxylate, as described for the preparation of complex **8e**. **3** (0.3 g) gave **10c** (0.24 g, 80%) as a mixture of diastereomers (ca. 2:1) which would not crystallize: IR ν_{max} 1940, 1860, 1755, and 1735 cm^{-1}; ^1H NMR δ 5.27 and 5.21 (5 H, 2 × s, Cp), 4.40 (1 H, t, J = 6.65 Hz, 2-H), 3.77 (2 H, m, 1- and 3-H), 3.70 (3 H, s, CO_2Me, major isomer), 3.66 (3 H, s, CO_2Me, minor isomer), 2.49 (1 H, m, 4-H), 2.29 (1 H, m, 6-H), 2.06 (2 H, m), 1.91 (2 H, m), 1.73 (2 H, m), 1.09 (1 H, m, obscured, endo-5-H), 1.00 (3 H, d, J = 6.84 Hz, Me), 0.60 (1 H, m, exo-5-H). Multiplicities were not resolved due to diastereomeric mixture. MS (FD) m/z (%) 454 (100), 453 (25), 452 (60), 451 (55), 450 (13), 448 (23).

$Cp(CO)_2Mo(\eta^3$-C_6H_7-4-$CH(CO_2Me)CO_2H$-6-Me) (10d). Hydrolysis of diester complex **10a** with the procedure described for the preparation of **8h** (time, 24 h) afforded **10d** as an approximately equimolar mixture of diastereomers which could not be crystallized (0.30 g gave 0.26 g, 95% yield): IR ν_{max} 3400 (br), 1945, 1860, and 1730 (br) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.04 (1 H, br s, CO_2H), 5.45 (5 H, s, Cp), 4.42 and 4.40 (1 H, 2 × t, J = 7 Hz, 2-H, diastereomers), 3.85 and 3.52 ($^1/_2$ H, d, each, J = 7 Hz, 3-H diastereomers), 3.68 (1 H, d, J = 7 Hz, 1-H), 3.66 and 3.57 (3 H, 2 × s, CO_2Me, diastereomers), 3.34 (1 H, malonate methine), 2.26 (1 H, m, 4-H), 1.79 (1 H, m, 6-H), 1.13 (3 H, d, J = 7.17 Hz, Me), 0.69 (1 H, dt, J = 14.0, 6.78 Hz, endo-5-H), 0.42 (1 H, br d, J = 14.0 Hz, exo-5-H). Anal. Found: C, 49.95; H, 4.54. $C_{18}H_{20}O_6Mo$ requires C, 50.47; H, 4.70.

Decomplexation Experiments. Reaction of Complex 8a with Ceric Ammonium Nitrate. To a stirred solution of **8a** (0.25 g, 0.75 mmol) in reagent grade acetone (10 mL) was added sodium acetate (0.75 g, 9.14 mmol) followed by ceric ammonium nitrate which was added in small portions until no more evolution of carbon monoxide was detected and the mixture became pale yellow. The reaction mixture was poured into water and the product extracted with ether (3 × 20 mL). The combined ether extracts were washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. The products were separated by preparative TLC (silica gel, 40% EtOAc in hexane) to give the lactone **13a** (0.048 g), spectroscopically identical with **15a** (see later), and the hydroxy diester **14** (0.032 g): IR ν_{max} 3500, 1750, 1730, and 1620 cm^{-1}; ^1H NMR (60 MHz) δ 6.5–5.7 (2 H, m, vinyl), 5.4 (1 H, br m, C*H*OH), 3.70 (6 H, s, and 1 H obscured, 2 × CO_2Me and malonate methine), 3.0 (1 H, br m, allylic C*H*), 2.2–1.5 (4 H, m). This compound was not further characterized.

Iodolactonization Reactions. The procedure is described for the lactonization of complex **8h**, all others being essentially identical. The progress of each reaction was followed by infrared spectroscopy. To a stirred solution of monoacid **8h** (0.25 g, 0.59 mmol) in dry acetonitrile (8 ML) at room temperature was added iodine (0.30 g, 2.36 mmol). After 30 min the reaction was judged complete (IR), the mixture was poured into water, and the product was extracted with ether (3 × 10 mL). The combined extracts were washed with water, aqueous sodium thiosulfate solution, and water, dried ($MgSO_4$), and evaporated. The product was purified by preparative TLC (silica gel, 40% EtOAc in hexane) to afford ca. 95% single diastereomeric lactone **15a** as a colorless oil (0.090 g, 75%): IR ν_{max} 1790, 1745 cm^{-1}; ^1H NMR δ 6.08 (1 H, dt, J = 10, 5 Hz, 3-H), 5.82 (1 H, dm, J = 10 Hz, 2-H), 5.00 (1 H, m, 1-H), 3.82 (3 H, s, CO_2Me; small singlet at δ 3.80 indicates minor diastereomer), 3.38 (1 H, d, J = 6.6 Hz, 7-H), 3.01 (1 H, qd, $J_{1,6} = J_{5\alpha,6} = J_{6,7}$ = 6.6 Hz, $J_{5\beta,6}$ = 3.5 Hz, 6-H), 2.12 (2 H, m, 4-H_2), 1.83 (1 H, m, 5β-H), 1.65 (1 H, m, 5α-H). Decoupling experiments: irradiation at δ 1.83 caused collapse of δ 3.01 to q (J = 6.6 Hz); irradiation at δ 2.12 caused collapse of δ 6.08 to d (J = 10 Hz), collapse of 5.82 to dd (J = 10, 3.4 Hz), collapse of 5.0 to dd (J = 6.6, 3.4 Hz), sharpening of 3.01, collapse of 1.83 to dd (J = 13.8, 3.5 Hz), collapse of 1.65 to dd (J = 13.8, 6.6 Hz); irradiation at δ 5.82 caused collapse of 5.0 to br d (J = 6.6 Hz) and loss of 10 Hz coupling from δ 6.08; the coupling constants obtained from these experiments indicate α-stereochemistry of the 7-CO_2Me as shown in structure **15a**. HRMS, calcd for $C_{10}H_{12}O_4$: M = 196.0736. Found: M = 196.0646.

Lactonization of Monoacid Complex 8i. Treatment of **8i** (0.080 g, 0.18 mmol) with iodine as above afforded the lactone **15b** (0.030 g, 64%) as a colorless oil after purification by preparative TLC. IR ν_{max} 1780 and 1745 cm^{-1}; ^1H NMR δ 6.18 (1 H, dm, $J_{2,3}$ = 10 Hz, 3-H), 5.92 (1 H, dm, $J_{2,3}$ = 10 Hz, 2-H), 4.81 (1 H, m, 1-H), 3.76 (3 H, s), 2.68 (1 H, dt, J = 13.8, 3.8 Hz, 6-H), 2.16 (1 H, br dt, J = 17.3 Hz, 4α-H), 1.96 (1 H, tm, J_t = 17 Hz, 4β-H), 1.70 (1 H, dm, J_α = 13 Hz, 5β-H), 1.44 (3 H, s), 1.2 (1 H, tdd, J = 17, 13, 4.9 Hz, 5α-H). Anal. Found: C, 62.77; H, 6.53. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.71.

Lactonization of Complex 8k. Treatment of the acid **8k** (0.23 g, 0.65 mmol) with iodine (0.33 g, 2.62 mmol) as above afforded the lactone **15c** (0.080 g, 85%) as a colorless oil after purification by preparative TLC (silica gel, 40% EtOAc in hexane). IR ν_{max} 1780 cm^{-1}; ^1H NMR δ 6.12 (1 H, dt, J = 10, 4.5 Hz, 3-H), 5.86 (1 H, dm, J_α = 10 Hz, 2-H), 4.79 (1 H, br m, 1-H), 2.72 (1 H, dd, J = 16.6, 8.3 Hz, 7β-H), 2.57 (1 H, m, 6-H), 2.32 (1 H, dd, J = 16.6, 4.3 Hz, 7α-H), 2.09 (2 H, m, 6-H_2), 1.74 (1 H, dq, J_{gem} = 13, $J_{5,6} = J_{4\alpha,5\beta} = J_{4\beta,5\beta}$ = 4.3 Hz, 5β-H), 1.47 (1 H, m, J_{gem} = 13, $J_{5\alpha,6}$ = 8.3, others not determined, 5α-H); MS m/e (%) (chemical ionization) 139 (100, M + 1), 121 (3.8), 97 (2.1), 95 (3), 93 (7), 79 (6).

Lactonization of Half-Acid 10d. Treatment of the complex **10d** (0.390 g, 0.91 mmol) with iodine (0.50 g, 3.94 mmol), as described above, afforded the lactone **15d** (0.170 g, 90%) as a colorless oil after purification by preparative TLC (silica gel, 40% EtOAc in hexane). IR ν_{max} 1785, 1740 cm^{-1}; ^1H NMR δ 5.99 (1 H, d, J = 10.7 Hz, 3-H), 5.89 (1 H, dm, J_d = 10.7 Hz, 2-H), 4.98 (1 H, m, 1-H), 3.81 (3 H, s), 3.31 (1 H, s, 7-H), 2.81 (1 H, dt, $J_{5\alpha,6}$ = 13.7, $J_{1,6} = J_{5\beta,6}$ = 5.0 Hz, 6-H), 2.21 (1 H, m, 4-H), 1.81 (1 H, dt, J_{gem} = 12.7 Hz, $J_{5\beta,6} = J_{4,5\beta}$ = 5.0 Hz, 5β-H), 1.06 (3 H, d, Me), 1.04 (1 H, part obscured, ddd, J_{gem} = 12.7, $J_{5\alpha,6}$ = 13.7, $J_{4,5\alpha}$ = ca. 13 Hz, 5α-H). Decoupling experiments: irradiation of δ 1.05 causes collapse of δ 1.81 to t (J = 5 Hz), collapse of δ 2.21 to br s, collapse of δ 2.81 to t (J = 5.0 Hz); irradiation at δ 2.81 causes sharpening of δ 4.98, collapse of δ 1.04 to dd (J = 12.7, ca. 13 Hz (obscured by Me doublet), and partial collapse of δ 1.81; irradiation of δ 4.98 causes collapse of δ 2.8 to dd (J = 13.7, 5.0 Hz) and collapse of δ 5.89 to d (J = 10.7 Hz); irradiation of δ 5.89 causes collapse of δ 4.98 to d (J = 5 Hz), irradiation of δ 1.81 causes collapse of δ 2.81 to dd (J = 13.7, 5 Hz), partial collapse of δ 2.21, and collapse of δ 1.04 to dd (J = 13.7, ca. 13 Hz (part obscured)). MS m/e (%) (chemical ionization) 211 (4, M + 1), 165 (4), 151 (10), 147 (11), 120 (5), 119 (100), 93 (43).

Lactonization of Acid 10f. Treatment of the complex **10f** (0.13 g, 0.35 mmol) with iodine (0.18 g, 1.41 mmol), as above, gave the lactone **15e** (0.040 g, 70%) as a colorless oil after purification by preparative TLC. IR ν_{max} 1790 cm^{-1}; ^1H NMR δ 5.91 (2 H, m, vinyl H's), 4.70 (1 H, narrow m, 1-H), 2.84 (1 H, dd, J_{gem} = 17.3, $J_{6,7}$ = 8.5 Hz, 7β-H), 2.48 (1 H, m, neighboring resonances too close for satisfactory decoupling and analysis, 6-H), 2.26 (1 H, d, J_{gem} = 17.3 Hz, 7α-H), 2.16 (1 H, m, 4-H), 1.69 (1 H, dt, J_{gem} = 13 $J_{5\beta,6} = J_{4,5\beta}$ = 4.5 Hz, 5β-H), 1.04 (3 H, d, J = 7 Hz, Me), 1.01 (1 H , q obscured, $J_{gem} = J_{5\alpha,6} = J_{4,5\alpha}$ = 13 Hz, 5α-H). Decoupling experiments: irradiation at δ 5.91 causes collapse of δ 4.70 to dd (J = 5.5, 1.3 Hz) and partial collapse of δ 2.48; irradiation at δ 4.70 causes partial collapse of δ 2.48 and 5.91; irradiation at δ 2.48 causes collapse of δ 4.70 to br s, collapse of δ 1.69 to dd (J = 13, 4.5 Hz), and partial collapse of δ 1.01 (obscured by Me signal) irradiation of δ 1.69 causes partial collapse of δ 2.48 and collapse of δ 1.01 to t (J = 10 Hz); irradiation at δ 2.84 causes partial collapse of δ 2.48 and collapse of δ 2.26 to s; irradiation at δ 2.16 causes collapse of δ 1.69 to dd (J = 13, 4.5 Hz), collapse of δ 1.04 to s, and collapse of δ 1.01 to t (J = 13 Hz); irradiation at δ 1.04–1.01 causes partial collapse of δ 2.48, narrowing of δ 2.16, and collapse of δ 1.69 to t, J = 4.5 Hz. M/e(%) (Chemical Ionization) 153 (100, M + 1), 135 (5), 110 (11), 107 (8), 94 (7), 93 (82).

Cyclofunctionalization and Demetallation of Keto Ester 8d. The acetoacetate complex **8d** (0.100 g, 0.24 mmol) was treated with iodine (0.15 g) in acetonitrile (8 mL) as above to give the tetrahydrobenzofuran derivative **16** (0.040 g, 85%) obtained as a colorless oil from preparative TLC. IR ν_{max} 1700 and 1640 cm^{-1}; ^1H NMR δ 6.19 (1 H, m), 5.95 (1 H, m), 4.75 (1 H, dd, J = 8.5, 1.5 Hz, 1-H), 3.75 (3 H, s), 3.04 (1 H, m, 6-H), 2.22 (3 H, s, Me), 2.06 (1 H, m), 1.88 (1 H, m), 1.25 (2 H, m). MS (FD) m/e (%) 194 (100). No impurities were detected in the field desorption mass spectrum.

4-(4-Iodo-2-cyclohexenyl)anisole (17c) and Isomer 18c. Treatment of complex **8g** (0.12 g, 0.29 mmol) with iodine (0.11 g, 0.89 mmol) in dry acetonitrile (5 mL) as above gave a mixture of the iodides **17c** and **18c** (ca. 2:1) (0.060 g, 65%) as a pale yellow oil after purification by preparative TLC. NMR δ 7.16 (2 H, Ar H), 6.91 (2 H, Ar H), 6.17 (1 H, m, vinyl H), 5.71 (1 H, m, vinyl H), 5.20 (1 H, m, CHI of **17c**), 5.13 (m, CHI of **18c**), 3.83 (3 H, s), 3.79 (1 H, m, obscured, benzylic), 2.3–1.5 (4 H, m).

Dimethyl (4-Iodo-2-cyclohexenyl)methylmalonate (17a). Treatment of the diester derivative **8b** (0.100 g, 0.23 mmol) with iodine (0.12 g, 0.91 mmol) as above afforded the iodide **17a**, together with minor amounts of the isomer **18a** (ca. 10% by ^1H NMR), obtained as a pale yellow oil after preparative TLC (silica gel, 40% EtOAc in hexane) (0.064 g, 80%). IR ν_{max} 1745 cm^{-1}; ^1H NMR δ 6.02 (1 H, m, vinyl), 5.52 (1 H, br d, J = 9.9 Hz, vinyl), 5.05 (1 H, m, CHI), 3.76 (6 H, s, CO_2Me), 3.45 (1 H, m, 1-H), 2.3–1.5 (4 H, m), 1.41 (3 H, s, Me). The minor isomer showed peaks at δ 4.9 (CHI), 3.79 and 3.73 (CO_2Me), 1.33 (Me; m/e (%) (field desorption) 225 (100, M – 127). Molecular ion could not be obtained

with FD or electron impact MS. No impurity was detected in the FD mass spectrum.

Methyl 1-(4-Iodo-2-cyclohexenyl)-2-oxocyclopentanecarboxylate (17b). Treatment of the keto ester complex **8e** (0.100 g, 0.23 mmol) with iodine (0.090 g, 0.68 mmol) as above gave the iodide **17b** (0.070 g, 90%) as a pale yellow oil after preparative TLC (silica gel, 40% EtOAc in hexane). IR ν_{max} 1755, 1730 cm^{-1}; ^1H NMR, δ 6.04 (1 H, m, vinyl), 5.34 (1 H, br d, J = 9.8 Hz, vinyl), 5.05 (1 H, narrow m, CHI), 3.71 (3 H, s, CO_2Me), 3.58 (1 H, m, 1-H), 2.40 (4 H, br m), 2.11 (2 H, m), 1.87 (2 H, m), 1.65 (2 H, m); m/e (%) (field desorption) 221 (100, M − 127). Molecular ion could not be detected with electron impact MS. No impurity was observed in the FD mass spectrum.

Dimethyl (4-Iodo-5-methyl-2-cyclohexenyl)malonate (17d) and Dimethyl (2-Iodo-5-methyl-3-cyclohexenyl)malonate (18a). Treatment of complex **10a** (0.100 g, 0.22 mmol) with iodine (0.090 g, 0.65 mmol) as above afforded a 4:1 mixture of iodides **17d** and **18d** which were inseparable in TLC (0.070 g, 85%). IR ν_{max} 1755 and 1740 cm^{-1}; ^1H NMR of **17d**, δ 6.15 (1 H, dm, J_d = 9.6 Hz), 5.44 (1 H, d, J = 9.6 Hz), 4.92 (1 H, narrow m, CHI), 3.77 (3 H, s), 3.76 (3 H, s), 3.75 (1 H, d, obscured), 2.0–1.0 (4 H, m), 1.03 (3 H, d, J = 7 Hz). The minor iodide **18d** showed peaks at δ 6.0 (m), 5.5 (m), 5.2 (narrow m, CHI), 1.15 (d, J = 7 Hz, Me). The mixture obtained above contained ca. 10% of other impurities. Instability of the allylic iodide precluded rigorous purification.

Reaction of Iodide 17a with (*m*-Chloroperoxy)benzoic Acid. The iodide **17a** (0.030 g, 0.09 mmol) was added to a stirred mixture of (*m*-chloroperoxy)benzoic acid (MCPBA) (0.030 g, 0.18 mmol), sodium hydrogen carbonate (0.010 g, 0.14 mmol, 1.5 equiv), and ethyl acetate/water (2:1, 2 mL). After 60 min the mixture was poured into aqueous sodium hydrogen carbonate and stirred for 30 min. Ether extraction, followed by preparative TLC as above, afforded the lactone as a single diastereomer, spectroscopically identical with **15b** (0.020 g, 85%).

Reaction of Iodide 17b with (*m*-Chloroperoxy)benzoic Acid. The iodide **17b** (0.060, 0.19 mmol) was treated with MCPBA (0.060 g, 0.35 mmol) and $NaHCO_3$ (0.02 g, 0.28 mmol) as above, to afford the lactone **19** (0.030 g, 80%). A spectroscopically identical lactone was also prepared by hydrolysis of the keto ester **8e** as previous (14 days reaction time) followed by treatment of the derived keto with iodine. IR ν_{max} 1775 and 1745 cm^{-1}; ^1H NMR δ 6.17 (1 H, dd, J = 10, 8 Hz, vinyl), 5.94 (1 H, dt, J = 10, 3 Hz, vinyl), 5.18 (1 H, br t, J = 34 Hz, 1-H), 2.31 (4 H, m), 1.98 (4 H, m), 1.73 (1 H, m), 1.24 (2 H, m).

Methyl 1-(4-Acetoxy-2-cyclohexenyl)-2-oxocyclopentanecarboxylate (22a). The iodide **17b** (0.030 g, 0.08 mmol) was dissolved in acetic anhydride (1 mL) and added to a stirred mixture of silver acetate (0.030 g) in acetic anhydride (0.5 mL) and acetic acid (2 mL). The mixture was heated at 110 °C for 2 h, cooled, and poured into 10% aqueous $NaHCO_3$. Ether extraction (3 × 10 mL) followed by preparative TLC afforded the acetate **22a** (0.023 g, 96%) as a colorless oil. IR ν_{max} 1755, 1740, and 1730 cm^{-1}; ^1H NMR δ 5.7 (2 H, m, vinyl, major isomer, and one of vinyl, minor isomer), 5.45 (d, J = 10 Hz, vinyl H of minor isomer), 5.15 (br m, C*H*OAc of minor isomer), 5.10 (1 H, narrow m, C*H*OAc, major isomer, approximate ratio 3:1), 3.71 (3 H, s, CO_2Me, major isomer), 3.70 (s, CO_2Me, minor isomer), 3.1 (1 H, m, 1-H), 2.6–1.3 (10 H), 2.02 (3 H, s, OAc).

Methyl 1-(4-Hydroxy-2-cyclohexenyl)-2-oxocyclopentanecarboxylate (22b). The acetate **22a** (0.023 g) was stirred in methanol (1 mL) while a 20% aqueous solution of potassium hydroxide (0.2 mL) was added. The mixture was stirred for 5 h, after which time it was diluted with water (10 mL) and the product extracted with ether in the usual way to afford the crude alcohol **22b** (0.018 g, 95%) which was used in the next step without purification. IR ν_{max} 3650, 3400, 1750, 1725 cm^{-1}; ^1H NMR δ 5.6–6.0 (2 H, m, vinyl), 4.15 (1 H, m, C*H*OH), 3.68 (3 H, s, CO_2Me), 3.70 (1 H, m, obscured, 1-H), 2.5–1.3 (11 H).

Methyl 1-(4-Oxo-2-cyclohexenyl)-2-oxocyclopentanecarboxylate (23). The alcohol **22b** (0.050 g, 0.21 mmol) was stirred in dichloromethane (5 mL) containing chromium trioxide (0.12 g, 1.2 mmol) and pyridine (0.18 mL) at room temperature for 2 h. The reaction mixture was diluted with ether (20 mL) and filtered through Celite, and the solution was washed with dilute hydrochloric acid and water and dried ($MgSO_4$). Purification by preparative TLC (silica gel, 40% EtOAc in hexane) afforded the enone **23** (0.035 g, 70%). IR ν_{max} 1755, 1720, and 1690 cm^{-1}; ^1H NMR δ 6.88 (1 H, d, J = 11.5 Hz, 2-H), 6.04 (1 H, dd, J = 11.5, 2.4 Hz, 3-H), 3.75 (3 H, s, CO_2Me), 3.31 (1 H, br d, J = 10 Hz, 1-H), 2.5–1.5 (10 H, m); MS (chemical ionization m/e (%) 237 (11, M + 1), 177 (12), 143 (100), 142 (16), 123 (10). Anal. Found: C, 65.92; H, 6.75. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.82.

Conversion of Lactone 15e to Acyclic Diol 28. To a stirred suspension of lithium aluminum hydride (4.1 mg, 0.11 mmol) in dry ether (1 mL) under N_2 at 0 °C was added a solution of lactone **15e** (11 mg, 0.072 mmol) in ether (0.5 mL). The mixture was allowed to warm to ambient temperature and stirred for a further 30 min (monitored by TLC), after which time water (2–3 drops) was added. The ether layer was decanted, and the residue was washed twice with ether. The combined organic phase was dried ($MgSO_4$) and evaporated to give the diol **27a** which was carried to the next stage without further purification. IR ($CHCl_3$) ν_{max} 3590, 3400; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.84 (1 H, m, vinyl), 5.72

Table II. Bond Distances (Å) for $Cp(CO)_2Mo[\eta^3\text{-}C_6H_8\text{-}4\text{-}C(CO_2Me)COCH_2CH_2CH_2]$[a]

C1–C2	1.432 (15)	C13–O3	1.458 (13)
C1–C6	1.522 (18)	C14–C15	1.494 (21)
C1–Mo	2.382 (12)	C12–O3	1.342 (14)
C2–C3	1.398 (15)	C12–O2	1.188 (16)
C2–Mo	2.205 (13)	C14–C18	1.486 (24)
C3–C4	1.540 (15)	C14–Mo	2.363 (14)
C3–Mo	2.370 (12)	C15–C16	1.368 (19)
C4–C5	1.561 (20)	C20–C20	1.963 (12)
C4–C8	1.530 (19)	C19–O4	1.212 (14)
C5–C6	1.505 (16)	C15–Mo	2.347 (16)
C7–C8	1.593 (17)	C16–C17	1.371 (23)
C7–O1	1.184 (16)	C16–Mo	2.373 (13)
C8–C9	1.555 (17)	C17–C18	1.413 (18)
C8–C12	1.540 (14)	C18–Mo	2.397 (13)
C9–C10	1.546 (22)	C19–Mo	1.885 (12)
C10–C11	1.525 (22)	C20–O5	1.138 (14)
C7–C11	1.512 (20)	C17–Mo	2.409 (16)

[a] The standard deviation of the least significant figure of each distance is given in parentheses.

Table III. Bond Angles (deg) for $Cp(CO)_2Mo[\eta^3\text{-}C_6H_8\text{-}4\text{-}C(CO_2Me)COCH_2CH_2CH_2]$[a]

C2–C1–C6	119.9 (11)	C1–Mo–C2	36.1 (4)
C2–C1–Mo	65.2 (6)	C1–Mo–C3	60.9 (4)
C6–C1–Mo	118.1 (9)	C1–Mo–C14	107.0 (5)
C1–C2–C3	116.7 (11)	C1–Mo–C15	140.2 (5)
C1–C2–Mo	78.7 (8)	C1–Mo–C16	157.9 (5)
C3–C2–Mo	78.8 (7)	C1–Mo–C17	127.4 (5)
C2–C3–C4	119.2 (8)	C1–Mo–C18	102.6 (5)
C2–C3–Mo	65.9 (7)	C1–Mo–C19	70.7 (5)
C3–C4–C5	111.7 (9)	C1–Mo–C20	109.4 (5)
C3–C4–C8	107.4 (9)	C2–Mo–C3	35.3 (4)
C5–C4–C8	114.6 (9)	C2–Mo–C14	110.3 (5)
C4–C5–C6	117.3 (10)	C2–Mo–C15	144.9 (5)
C1–C6–C5	113.7 (9)	C2–Mo–C16	130.0 (5)
C8–C7–C11	108.2 (11)	C2–Mo–C17	96.8 (5)
C8–C7–O1	124.2 (12)	C2–Mo–C18	85.6 (5)
C11–C7–O1	127.6 (12)	C2–Mo–C19	106.2 (5)
C4–C8–C7	110.9 (10)	C2–Mo–C20	108.9 (5)
C4–C8–C9	117.7 (9)	C3–Mo–C14	138.1 (5)
C4–C8–C12	110.7 (9)	C3–Mo–C15	152.4 (4)
C7–C8–C9	103.2 (9)	C3–Mo–C16	119.1 (4)
C7–C8–C12	104.4 (9)	C3–Mo–C17	94.8 (5)
C9–C8–C12	109.0 (10)	C3–Mo–C18	103.6 (5)
C8–C9–C10	104.3 (10)	C3–Mo–C19	114.5 (5)
C9–C10–C11	106.2 (13)	C3–Mo–C20	76.1 (5)
C7–C11–C10	106.6 (11)	C14–Mo–C15	37.0 (5)
C8–C12–O2	125.4 (11)	C14–Mo–C16	56.7 (4)
C8–C12–O3	111.4 (10)	C14–Mo–C17	59.1 (5)
O2–C12–O3	123.2 (9)	C14–Mo–C18	36.4 (6)
C15–C14–C18	105.5 (11)	C14–Mo–C19	95.2 (5)
C15–C14–Mo	70.9 (8)	C14–Mo–C20	139.9 (6)
C18–C14–Mo	73.1 (8)	C15–Mo–C16	33.7 (5)
C14–C15–C16	103.6 (13)	C15–Mo–C17	58.8 (5)
C14–C15–Mo	72.1 (9)	C15–Mo–C18	60.0 (6)
C16–C15–Mo	74.2 (9)	C15–Mo–C19	92.3 (5)
C15–C16–C17	116.9 (13)	C15–Mo–C20	103.0 (5)
C15–C16–Mo	72.1 (8)	C16–Mo–C17	33.3 (6)
C17–C16–Mo	74.8 (8)	C16–Mo–C18	44.3 (5)
C16–C17–C18	105.4 (13)	C16–Mo–C19	122.1 (6)
C16–C17–Mo	71.9 (8)	C16–Mo–C20	91.1 (5)
C18–C17–Mo	72.4 (7)	C17–Mo–C18	34.2 (4)
C14–C18–C17	108.5 (14)	C17–Mo–C19	150.6 (6)
C14–C18–Mo	70.6 (7)	C17–Mo–C20	108.1 (4)
C17–C18–Mo	73.4 (8)	C18–Mo–C19	128.8 (5)
C12–O3–C13	115.6 (9)	C18–Mo–C20	142.2 (4)
O4–C19–Mo	174.9 (11)	C19–Mo–C20	81.7 (5)
O5–C20–Mo	179.9 (12)		

[a] The standard deviation of the least significant figure of each angle is given in parentheses.

(1 H, d, J = 10 Hz, vinyl), 4.1 (1 H, m, br, allylic C*H*-O), 3.76 (2 H, td, J = 8, 4 Hz, CH_2OH), 2.3–1.5 (7 H, m), 1.17 (1 H, dd, J = 21, 9 Hz, one of ring CH_2), 1.00 (3 H, d, J = 7.1 Hz, Me).

The diol **27a** was protected as its bis(methoxymethyl) ether (**27b**) by the standard method as follows. To a solution of **27a** (10 mg, 0.064 mmol) in dry dichloromethane (1 mL) was added, via syringe, diisopropylethylamine (0.07 mL) and chloromethyl methyl ether (0.066 mL). The mixture was boiled under reflux for 5 h (monitored by TLC) and cooled to room temperature, and water (2 mL) was added. After the mixture was stirred for 5 min, the organic layer was separated and the aqueous layer was extracted with a further 5 mL of dichloromethane. The combined extracts were washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated to give **27b** (12.5 mg, 80%) which was judged sufficiently pure for the next step. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.90 (1 H, ddd, J = 10, 4.9, 2.3 Hz, vinyl), 5.73 (1 H, dt, J = 10, 1 Hz, vinyl), 4.76 and 4.63 (1 H each, ABq, J_{AB} = 6.9 Hz, allylic $-OCH_2O-$), 4.63 (2 H, s, primary $-OCH_2O-$), 3.86 (1 H, br t, J = 3.5 Hz, allylic CH–O), 3.63 (2 H, t, J = 6.3 Hz, CH_2O), 3.37 (3 H, s), 3.36 (3 H, s), 2.2–1.4 (5 H, m), 1.24 (1 H, dd, J = 21, 11 Hz, one of ring CH_2), 1.01 (3 H, d, J = 7 Hz, Me).

The crude protected diol **27b** (10.8 mg, 0.044 mmol) was dissolved in a 2:1 mixture of dichloromethane and methanol (3 mL) and cooled to −78 °C. Ozone–oxygen was bubbled through the solution for 2 min, and excess ozone was removed by bubbling argon through the mixture. Solvent was evaporated and replaced by methanol at 0 °C. Sodium borohydride (3.3 mg) was added, and the mixture was stirred and warmed to room temperature. After 30 min the mixture was taken up in ether (10 mL) and the solution washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated to yield the diol **28** which was purified by semipreparative HPLC (8.7 mg, 70%). IR ($CHCl_3$) ν_{max} 3580, 3400; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.76 and 4.70 (1 H each, ABq, J_{AB} = 8 Hz, secondary O–C*H*$_2$–OMe), 4.63 (2 H, s, primary, OC*H*$_2$OMe), 3.75–3.5 (6 H, 3 overlapping m, 3 × CH_2–O), 3.45 (3 H, s), 3.38 (3 H, s), 1.9–1.4 (8 H), 0.96 (3 H, d, J = 6.7 Hz, Me). Found: C, 55.60; H, 10.05. Calcd for $C_{13}H_{28}O_6$: C, 55.69; H, 10.07.

X-ray Structure Determination of Complex 8e. The complex was crystallized by addition of pentane to a solution of **8e** in chloroform–ether and setting aside at room temperature.

The crystals belong to the monoclinic space group $P2_1/c$ with a = 15.053 (5) Å, b = 8.327 (3) Å, c = 15.583 (3) Å, and β = 108.26 (2)°; molecular formula = $C_{20}H_{22}MoO_5$. All unique data with sing $\theta/\lambda \leq 0.54$ were collected and 1968 (79%) were judged observed ($|F_o| \geq 3\sigma(F_o)$).[1] Solution and refinement were routine, and the final discrepancy index is 0.070 for the 1968 observed reflections. All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were the following: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978. The structure is shown in Figure 2, numbering arbitrary. Bond distances are given in Table II and bond angles in Table III.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters (Table I) and torsion angles (Table IV) for **8e** (7 pages). Ordering information is given on any current masthead page.

Dynamic Transduction of Energy and Internal Equilibria in Enzymes: A Reexamination of Pyruvate Kinase†

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Abstract: The rate of interconversion of enzyme–substrate and enzyme–product complexes of pyruvate kinase was measured under equilibrium conditions using dynamic NMR methods. No evidence was found to support a significant contribution to the rate of catalysis by dynamic funneling of vibrational energy within the protein molecule. Furthermore, contrary to a previous report, the internal equilibrium constant between enzyme–substrate and enzyme–product complexes is different from unity. Serious reevaluation is necessary of the notion that enzymes in general match the free energies of bound intermediates.

An important goal of modern bioorganic chemistry is to understand how enzymes enormously enhance the rates of organic reactions.[1] In pursuit of this understanding, mechanisms for catalysis are often suggested that are not generally regarded as accessible to "normal" reactions in solution. Rather, these "special" mechanisms for enzymic catalysis are presumed to be uniquely accessible to macromolecules (i.e., enzymes). This paper concerns two suggested special mechanisms that have gained particular prominence recently.[2,3]

† Abbreviations: PK, pyruvate kinase; NMR, nuclear magnetic resonance spectroscopy; ATP, adenosine 5′-triphosphate; ADP, adenosine 5′-diphosphate; AMP, adenosine 5′-monophosphate; PEP, phosphoenolypyruvate; DTE, dynamic transduction of energy; EDTA, ethylenediaminetetraacetic acid; ES, enzyme–substrate complex; EP, enzyme–product complex.

(1) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw Hill: New York, 1969.

(2) (a) Welch, G. R.; Somogyi, B.; Damjanovich, S. *Prog. Biophys. Mol. Biol.* **1982**, *3*, 109–146. (b) Kell, D. B. *Trends Biochem. Sci.* **1982**, *7*, 1–2. (c) McCammon, J. A.; Wolynes, P. G.; Karplus, M. *Biochemistry* **1979**, *18*, 927–942. Karplus, M.; McCammon, J. A. *Annu. Rev. Biochem.* **1983**, *53*, 300.

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