## New and General Synthesis of Polycyclic $\gamma$-Lactones by Double Annulation

E. J. Corey* and Myung-chol Kang

Department of Chemistry, Harvard University<br>Cambridge, Massachusetts 02138

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The polycyclic $\mathrm{C}_{15}{ }^{1}$ and $\mathrm{C}_{20}{ }^{2}$ polylactones obtained from the gingko tree are for their size among the most complex and structurally interesting of organic natural products. The realization of simple syntheses of the members of this "gingkolide" group, e.g., bilobalide (1), depends on the availability of methods for the concurrent generation of more than one cyclic subunit. We describe herein the development of a new synthetic method which seems ideally suited to this and related problems. The reaction forms in one step a cis-fused cyclopentanone- $\gamma$-butyrolactone ring pair and allows elaboration of a preexisting cyclic network.

It has been known for some time that manganese (III) acetate in acetic acid at reflux converts a variety of olefins (generally used in excess) to $\gamma$-lactones as illustrated by the following example. ${ }^{3,4}$


The mechanism of this process has been viewed as (1) generation of $\cdot \mathrm{CH}_{2} \mathrm{COOH}$ (or equivalent) and addition to the olefin and (2) oxidation of the resulting carbon radical to a carbocation by electron transfer to Mn (III) and electrophilic attack on carboxylate oxygen to form the $\gamma$-lactone. ${ }^{3}$ Manganese(III) acetate appears to be much more effective as a reagent than other metal oxidants (e.g., $\mathrm{Pb}(\mathrm{IV}), \mathrm{Ce}(\mathrm{IV}), \mathrm{Co}(\mathrm{III})$ ).

Manganese(III) acetate is known to be structurally analogous to the trinuclear iron(III) and chromium(III) acetates and to possess the formula $\mathrm{Mn}_{3} \mathrm{O}(\mathrm{OAc})_{7}{ }^{5}$ The three Mn ions are at the vertices of a triangle having a shared $\mathrm{O}^{2-}$ ligand at the center, and each pair of Mn ions is bridged by two acetate ions with the final acetate ligand being attached equatorially to a single $\mathrm{Mn}^{5}$ $\alpha$-Deprotonation of a bridging acetate in this trinuclear complex, which should be facilitated both by the electron deficiency of Mn (III) ions and the stability of the resulting (electron delocalized) complex, ${ }^{6}$ would provide an equivalent of the reactive intermediate $\cdot \mathrm{CH}_{2} \mathrm{COO}^{-}$. This idea suggests that ligands such as cyanoacetate or acetoacetate should undergo the olefin carbolactonization reaction much more readily than acetate, an expectation which is in accord with previous results ${ }^{3}$ and with our initial observation that cyanoacetic acid ( 3 equiv), cyclohexene ( 1 equiv), and $\mathrm{Mn}_{3} \mathrm{O}(\mathrm{OAc})_{7}$ (1 equiv) react even at $23^{\circ} \mathrm{C}$ in acetic acid for ca. 10 min to afford in $50 \%$ isolated yield of the corresponding bicyclic $\alpha$-cyano $\gamma$-lactone. Finally, it was conjectured that the intramolecular version of this carbolactonization should be at least as efficient, especially for the formation of two 5 -membered rings. ${ }^{7}$ The results that follow verify this hypothesis.

[^0]4-(2-Cyclohexenyl)-3-oxobutanoic acid (2) ${ }^{8}$ was stirred with 1.3 equiv of $\mathrm{Mn}_{3} \mathrm{O}(\mathrm{OAc})_{7}$ in acetic acid at $23^{\circ} \mathrm{C}$ for 20 min to give after removal of solvent in vacuo, extraction of product into 1:1 ether-chloroform and chromatography on Florisil (ethyl acetate-hexane for elution) $63 \%$ of the keto lactone 3, mp 82-84 ${ }^{\circ} \mathrm{C}$. ${ }^{9}$ Methylation of $\mathbf{3}$ using 2.5 equiv of methyl iodide and 1.2 equiv of sodium hydride in THF at $0^{\circ} \mathrm{C}$ for 1 h produced 4, mp $77-78^{\circ} \mathrm{C}$, in $88 \%$ yield. The all-cis ring fused stereochemistry is strongly indicated for $\mathbf{3}$ and 4 by analogy with many previous instances of 5 -membered radical ring closures. ${ }^{10}$ No cyclization products stereoisomeric with $\mathbf{3}$ could be detected by thin-layer chromatography.


1


5

$\underline{2}$


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$3, \mathrm{R}=\mathrm{H}$
$4, \mathrm{R}=\mathrm{CH}_{3}$


7




10


14


11


15
13. $\mathrm{R}=\mathrm{CH}_{2} \mathrm{COOCH}_{3}$

The half malonate ester of 2-cyclohexen-1-ol (5) ${ }^{11}$ upon treatment with 1.3 equiv of $\mathrm{Mn}_{3} \mathrm{O}(\mathrm{OAc})_{7}$ in acetic acid at $40^{\circ} \mathrm{C}$ for 24 h gave the bis( $\gamma$-lactone) $6, \mathrm{mp} 155-156^{\circ} \mathrm{C}$, in $64 \%$ yield. In similar experiments keto acid 7 was transformed into the tricyclic bridged lactone 8, mp $110-111^{\circ} \mathrm{C}\left(23^{\circ} \mathrm{C}\right.$ for $24 \mathrm{~h}, 61 \%$ yield), and keto acid 9 was converted into $10, \mathrm{mp} 82-83^{\circ} \mathrm{C}$, ( 23 ${ }^{\circ} \mathrm{C}, 20 \mathrm{~min}, 80 \%$ yield) ${ }^{12}$
Carbolactonization of keto acid 11 (prepared by the method used for 2 ) as described above ( $23^{\circ} \mathrm{C}, 1 \mathrm{~h}, 52 \%$ yield) produced tricyclic lactone $12, \mathrm{mp} 72-73^{\circ} \mathrm{C}$, which was used as a model to demonstrate further transformations that would be required for the synthesis of bilobalide (1). Reaction of $\mathbf{1 2}$ with 1.5 equiv of sodium hydride and 2.5 equiv of methyl bromoacetate in THF at $0^{\circ} \mathrm{C}$ for 20 min afforded keto ester 13 (oil), which upon treatment with aluminum amalgam in 20:1 THF-water $\left(23^{\circ} \mathrm{C}\right.$,

[^1]$20 \mathrm{~min})$ gave a single hydroxy ester $14, \mathrm{mp} 78-79^{\circ} \mathrm{C}(65 \%$ from 12). Conversion of $\mathbf{1 4}$ to the tetracyclic dilactone 15 was accomplished by the sequence (1) mesylation ( 1.5 equiv of triethylamine, 3 equiv of mesyl chloride at $-20^{\circ} \mathrm{C}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ for 30 min , yield $94 \%$ ) and (2) methyl ester hydrolysis ( 0.1 N lithium hydroxide in THF-water at $23^{\circ} \mathrm{C}$ for 2 h ) and acidification ( $84 \%$ yield). The short and simple synthesis of 15 illustrates the synthetic potential of the methodology described herein.

The widely different rates of the carbolactonization reaction with keto acids $2,7,9$, and 11 would seem to indicate that cyclization rather than $\alpha$-deprotonation may be rate limiting in these cases. If this is indeed so, it must also be true that the reactive intermediate in the $\mathrm{C}-\mathrm{C}$ bond-forming step of the carbolactonization is not a conventional free radical but a Mn -stabilized "radicaloid" species, perhaps that derived by deprotonation of a bridged acetate in $\mathrm{Mn}_{3} \mathrm{O}\left(\mathrm{OCOCH}_{3}\right)_{7}$.

The extension of this methodology and its application to the synthesis of gingkolides will be described in subsequent papers. ${ }^{13}$

Registry No. 2, 91492-04-5; 2 methyl ester, 91492-15-8; 3, 91492-05-6; 4, 91492-06-7; 5, 2138-99-0; 6, 91492-07-8; 7, 91492-08-9; 8, 91492-09-0; 9, $65180-53-2 ; 10,91492-10-3 ; 11,5650-68-0 ; 12,91492-11-4 ; 13$, 91492-12-5; 14, 91492-13-6; 14 mesylate, 91492-16-9; 15, 91492-14-7; $\mathrm{Mn}_{3} \mathrm{O}(\mathrm{OAc})_{7}, \quad 63338-46-5 ; \quad \mathrm{CH}_{3} \mathrm{C}(\mathrm{O}) \mathrm{CH}_{2} \mathrm{C}(\mathrm{O}) \mathrm{OMe}, \quad 105-45-3$; $\mathrm{BrCH}_{2} \mathrm{C}(\mathrm{O}) \mathrm{OMe}$, 96-32-2; 3-bromocyclohexene, 1521-51-3.

Supplementary Material Available: Spectral data for compounds $\mathbf{3}, 4,6,8,10$, and $\mathbf{1 2 - 1 5}$ (1 page). Ordering information is given on any current masthead page.

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## ( $i-\mathrm{PrO})_{3} \mathbf{M o} \equiv \mathbf{M o}\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathbf{O}-i-\mathrm{Pr})\left(\mathrm{PMe}_{3}\right):$ The First Example of a Compound Containing a Triple Bond Uniting Three- and Four-Coordinate Molybdenum Atoms and the Observation of Phosphine-Promoted, Reversible Benzyl-Alkoxy Migrations at the (MM) ${ }^{6+}$ Center

Malcolm H. Chisholm,* John C. Huffman, and Robert J. Tatz

## Department of Chemistry and Molecular Structure Center Indiana University, Bloomington, Indiana 47405 <br> Received May 23, 1984

Of all the compounds containing multiple bonds between metal atoms, ${ }^{1}$ the $\mathrm{d}^{3-} \mathrm{d}^{3}$ dimers of molybdenum and tungsten show the most varied and fascinating coordination chemistry. There are compounds with $\mathrm{M}-\mathrm{M}$ triple bonds of configuration $\sigma^{2} \pi^{4}$ in which the metal atoms are each coordinated to three, four, five, and even six ligand atoms. ${ }^{2,3}$ Though ligand atoms may span the two metal atoms, there are no bridging atoms in this group of $\mathrm{d}^{3}-\mathrm{d}^{3}$ dimers. However, compounds with bridging atoms are known as in $\mathrm{W}_{2} \mathrm{Cl}_{6}(\mathrm{py})_{4}{ }^{4}$ and the salts containing $\mathrm{M}_{2} \mathrm{X}_{9}{ }^{3-}$ ions ( $\mathrm{X}=\mathrm{Cl}, \mathrm{Br}$ ) ${ }^{5}$ which adopt structures based on edge- and face-shared octahedra, respectively. Within the former group of compounds of formula $\mathrm{X}_{n} \mathrm{M} \equiv \mathrm{MX}_{n}$ or $\mathrm{X}_{n} \mathrm{Y}_{m} \mathrm{M} \equiv \mathrm{MX}_{n} \mathrm{Y}_{m}$, where X and $\mathrm{Y}=\mathrm{a}$ ligand atom and $n$ or $(n+m)=3 \rightarrow 6$, there has been no example of a compound where the coordination number at each metal atom has been different, e.g., in $\mathrm{Mo}_{2}\left(\mathrm{NMe}_{2}\right)_{6}, \mathrm{Mo}_{2}(\mathrm{O}-i-\mathrm{Pr})_{6}(\mathrm{py})_{2}$, $\mathrm{W}_{2} \mathrm{Me}_{2}\left(\mathrm{O}_{2} \mathrm{CNEt}_{2}\right)_{4}$, and $\mathrm{W}_{2}\left(\mathrm{O}_{2} \mathrm{CNMe}_{2}\right)_{6} n$ or $(n+m)=3,4$, 5 , and 6 , respectively. The apparent desire of the metal atoms to maintain this equality in coordination number is exemplified

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Figure 1. ORTEP view of the $(i-\mathrm{PrO})_{3} \mathrm{Mo}=\mathrm{Mo}\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathrm{O}-i-\mathrm{Pr})\left(\mathrm{PMe}_{3}\right)$ molecule. Some pertinent bond distances $(\AA)$ and angles $\left(^{\circ}\right)$ (averaged where appropriate): $\mathrm{Mo}-\mathrm{Mo}=2.235$ (1) $\mathrm{Mo}-\mathrm{C}=2.22$ (1), $\mathrm{Mo}(1)-\mathrm{O}$ $(7)=1.920$ (4), $\mathrm{Mo}(2)-\mathrm{O}=1.89$ (2), $\mathrm{Mo}-\mathrm{P}=2.581$ (2); $\mathrm{Mo}-\mathrm{Mo}-\mathrm{C}$ $=101.3(6), \mathrm{Mo}(2)-\mathrm{Mo}(1)-\mathrm{O}(7)=106.5(1), \mathrm{Mo}-\mathrm{Mo}-\mathrm{P}=94.65$ (4), $\mathrm{Mo}(1)-\mathrm{Mo}(2)-\mathrm{O}=107.2$ (20), $\mathrm{Mo}-\mathrm{C}-\mathrm{C}=114.4$ (11).
by the pair-wise insertion of $\mathrm{CO}_{2}$ into $\mathrm{OR}^{6}$ and $\mathrm{NMe}_{2}{ }^{7}$ ligands and the cooperative binding of Lewis bases to $\mathrm{M}_{2}(\mathrm{OR})_{6}$ compounds: ${ }^{8} \quad \mathrm{M}_{2}(\mathrm{OR})_{6}+2 \mathrm{~L} \rightarrow \mathrm{M}_{2}(\mathrm{OR})_{6} \mathrm{~L}_{2}$. We report here the first example of a compound having a central $(M \equiv M)^{6+}$ unit in which the metal atoms have different coordination numbers, namely, 3 and 4.

Hexane solutions of $1,2-\mathrm{Mo}_{2}\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}\left(\mathrm{NMe}_{2}\right)_{4}{ }^{9}$ react with $i$ - PrOH (4 equiv) to yield $1,2-\mathrm{Mo}_{2}\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathrm{O}-i-\mathrm{Pr})_{4}{ }^{10}$ The ${ }^{1} \mathrm{H}$ NMR spectra ${ }^{11}$ confirm the 1,2-dibenzyl substitution pattern and are consistent with a rapidly interconverting (NMR time scale) mixture of anti and gauche rotamers, through the presence of only the anti rotamer cannot be excluded: the benzyl methylene protons appear as a singlet, and there is only one type of $\mathrm{O}-i-\mathrm{Pr}$ ligand which contains diastereotopic methyl groups.

Addition of $\mathrm{PMe}_{3}$ (2 equiv) to a hexane solution of $1,2-\mathrm{Mo}_{2}-$ $\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathrm{O}-i-\mathrm{Pr})_{4}$ yields $(i-\mathrm{PrO})_{3} \mathrm{Mo} \equiv \mathrm{Mo}\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathrm{O}-i-\mathrm{Pr})-$ ( $\mathrm{PMe}_{3}$ ) as red crystals upon cooling. The molecular structure, deduced from an X-ray study, ${ }^{12}$ is shown in Figure 1. The Mo-Mo distance, 2.235 (1) $\AA$, is comparable to those in $\mathrm{Mo}_{2}$ -$\left(\mathrm{OCH}_{2}-t-\mathrm{Bu}\right)_{6}{ }^{13} 2.222(2) \AA$, and $\mathrm{Mo}_{2} \mathrm{Me}_{2}(\mathrm{O}-t-\mathrm{Bu})_{4}(\mathrm{py})_{2}{ }^{14} 2.256$
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(11) 'H NMR data obtained from toluene- $d_{8}$ at 360 MHz for $1,2-\mathrm{Mo}_{2}-$ $\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathrm{O}-i-\mathrm{Pr})_{4}\left(+20^{\circ} \mathrm{C}\right): \delta\left(\mathrm{CH}_{2} \mathrm{Ph}\right) 4.13(\mathrm{~s}) ;\left(\mathrm{CH}_{2} \mathrm{Ph}\right) \circ 7.05(\mathrm{~d}, J=$ $7.6 \mathrm{~Hz}), m 6.99(\mathrm{dd}, J=7.6 \mathrm{~Hz}), p 6.79(\mathrm{t}, J=7.6 \mathrm{~Hz})$; $\left(\mathrm{CHMe}_{2}\right) 5.39$ (sept, $J=5.8 \mathrm{~Hz}) ;(\mathrm{CHMe}) 1.32(\mathrm{~d}, J=5.8 \mathrm{~Hz}), 1.26(\mathrm{~d}, J=5.8 \mathrm{~Hz})$. $(i$. $\mathrm{PrO})_{3} \mathrm{Mo} \equiv \mathrm{Mo}\left(\mathrm{CH}_{2} \mathrm{Ph}\right)_{2}(\mathrm{O}-i-\mathrm{Pr})\left(\mathrm{PMe}_{3}\right)\left(-20^{\circ} \mathrm{C}\right): \delta\left(\mathrm{CH}_{2} \mathrm{Ph}\right) 4.63(2 \mathrm{H}$, $\left.\mathrm{dd},{ }^{2} J_{\mathrm{H}-\mathrm{H}}=11.8 \mathrm{~Hz} ;{ }^{3} J_{\mathrm{H}-\mathrm{P}}=15.5 \mathrm{~Hz}\right), 4.46\left(2 \mathrm{H}, \mathrm{dd},{ }^{2} J_{\mathrm{H}-\mathrm{H}}=11.8 \mathrm{~Hz},{ }^{3} J_{\mathrm{H}-\mathrm{P}}\right.$ $=11.8 \mathrm{~Hz}) ;\left(\mathrm{CH}_{2} P h\right) o 7.07(4 \mathrm{H}, \mathrm{d}, J=7.6 \mathrm{~Hz}), m 6.96(4 \mathrm{H}, \mathrm{d}, J=7.6$ $\mathrm{Hz}), p 6.71(2 \mathrm{H}, \mathrm{d}, J=7.6 \mathrm{~Hz}) ;\left(\mathrm{OCH} \mathrm{Me}_{2}\right) 6.08(1 \mathrm{H}$, sept, $J=5.8 \mathrm{~Hz}) ;$ $\left.(\mathrm{OCHMe})^{2}\right) 1.83(6 \mathrm{H}, \mathrm{d}, J=5.8 \mathrm{~Hz}) ;(\mathrm{OCHMe})^{\prime} 4.68(3 \mathrm{H}$, sept, $J=5.8$ $\mathrm{Hz})$; $\left(\mathrm{OCH} M e_{2}\right)^{\prime} 1.30(18 \mathrm{H}, \mathrm{d}, J=5.8 \mathrm{~Hz})$.
(12) Crystal data at $-159^{\circ}{ }^{\circ} \mathrm{C}$ : $a=16.779$ (3) $\AA, b=10.104$ (1) $\AA, c=$ 19.555 (4) $\AA, \beta=90.59(1)^{\circ}, Z=4$ and space group $P 2_{1 / c}$. Of the 4823 reflections collected using Mo $\mathrm{K} \alpha, 6^{\circ}<2 \theta<45^{\circ}$, the 3665 having $F>3 \sigma(F)$ were used in the full-matrix least-squares refinement. All the H atoms were located and refined. Final residuals are $R(F)=0.037$ and $R_{w}(F)=0.041$. For general operating procedures and listings of programs employed at the IUMSC, see: Chisholm, M. H.; Folting, K.; Huffman, J. C.; Kirkpatrick, C. C., Inorg. Chem. 1984, 23, 1021.
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    (11) Prepared in $72 \%$ yield from the corresponding acetate by sequential treatment with 1.1 equiv of LDA in THF at $-78^{\circ} \mathrm{C}$ and excess $\mathrm{CO}_{2}$ at -78 ${ }^{\circ} \mathrm{C}$ for 30 min .
    (12) The keto acids 7 and 9 were prepared from the corresponding methyl ketones by lithiation (LDA, $-78^{\circ} \mathrm{C}$ ) and carbonation.

[^2]:    (13) This research was assisted financially by a grant from the National Science Foundation.

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