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New and General Synthesis of Polycyclic γ-Lactones by Double Annulation

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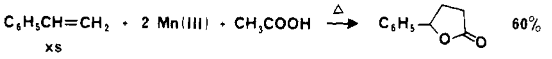
The polycyclic C_{15}[1] and C_{20}[2] polylactones obtained from the gingko tree are for their size among the most complex and structurally interesting of organic natural products. The realization of simple syntheses of the members of this "gingkolide" group, e.g., bilobalide (**1**), depends on the 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–γ-butyrolactone ring pair and allows elaboration of a preexisting cyclic network.

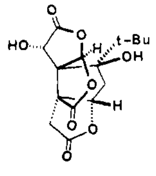
It has been known for some time that manganese (III) acetate in acetic acid at reflux converts a variety of olefins (generally used in excess) to γ-lactones as illustrated by the following example.[3,4]



The mechanism of this process has been viewed as (1) generation of $\cdot CH_2COOH$ (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 γ-lactone.[3] Manganese(III) acetate appears to be much more effective as a reagent than other metal oxidants (e.g., Pb(IV), Ce(IV), Co(III)).

Manganese(III) acetate is known to be structurally analogous to the trinuclear iron(III) and chromium(III) acetates and to possess the formula $Mn_3O(OAc)_7$.[5] The three Mn ions are at the vertices of a triangle having a shared 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 Mn.[5] α-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 $\cdot CH_2COO^-$. 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 $Mn_3O(OAc)_7$ (1 equiv) react even at 23 °C in acetic acid for ca. 10 min to afford in 50% isolated yield of the corresponding bicyclic α-cyano γ-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.

4-(2-Cyclohexenyl)-3-oxobutanoic acid (**2**)[8] was stirred with 1.3 equiv of $Mn_3O(OAc)_7$ in acetic acid at 23 °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 °C.[9] Methylation of **3** using 2.5 equiv of methyl iodide and 1.2 equiv of sodium hydride in THF at 0 °C for 1 h produced **4**, mp 77–78 °C, in 88% yield. The all-cis ring fused stereochemistry is strongly indicated for **3** and **4** by analogy with many previous instances of 5-membered radical ring closures.[10] No cyclization products stereoisomeric with **3** could be detected by thin-layer chromatography.



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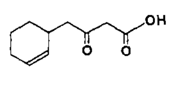

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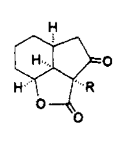
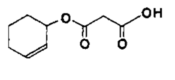


3, R = H
4, R = CH_3



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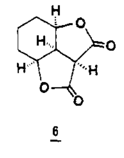

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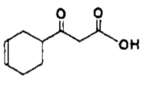

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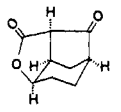

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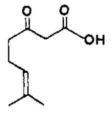

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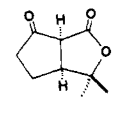

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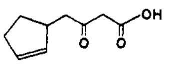

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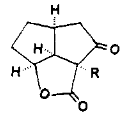
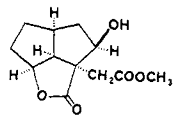


12, R = H
13, R = CH_2COOCH_3



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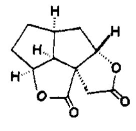

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The half malonate ester of 2-cyclohexen-1-ol (**5**)[11] upon treatment with 1.3 equiv of $Mn_3O(OAc)_7$ in acetic acid at 40 °C for 24 h gave the bis(γ-lactone) **6**, mp 155–156 °C, in 64% yield. In similar experiments keto acid **7** was transformed into the tricyclic bridged lactone **8**, mp 110–111 °C (23 °C for 24 h, 61% yield), and keto acid **9** was converted into **10**, mp 82–83 °C, (23 °C, 20 min, 80% yield).[12]

Carbolactonization of keto acid **11** (prepared by the method used for **2**) as described above (23 °C, 1 h, 52% yield) produced tricyclic lactone **12**, mp 72–73 °C, which was used as a model to demonstrate further transformations that would be required for the synthesis of bilobalide (**1**). Reaction of **12** with 1.5 equiv of sodium hydride and 2.5 equiv of methyl bromoacetate in THF at 0 °C for 20 min afforded keto ester **13** (oil), which upon treatment with aluminum amalgam in 20:1 THF–water (23 °C,

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[1] Nakanishi, K.; Habaguchi, K.; Nakadaira, Y.; Woods, M. C.; Maruyama, M.; Major, R. T.; Alauddin, M.; Patel, A. R.; Weinges, K.; Bähr, W. *J. Am. Chem. Soc.* **1971**, *93*, 3544.

[2] Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89.

[3] See: Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977 and previous papers of the series cited therein.

[4] The same type of reaction had also been reported as a minor pathway for the corresponding reaction of olefins with lead tetraacetate. See: Criegee, R. In "Oxidation in Organic Chemistry"; Part A, Wiberg, K., Ed., Academic Press: New York, 1965; Part A, p 277.

[5] Hessel, L. W.; Romers, C. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 545. For preparation of manganese(III) acetate, see: Lux, H. In "Handbook of Preparative Inorganic Chemistry"; Brauer, G., Ed.; Academic Press: New York, 1965; p 1470.

[6] See: Baikie, A. R. E.; Hursthouse, M. B.; New, D. B.; Thornton, P. *Chem. Commun.* **1978**, 62.

[7] Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

[8] Prepared by alkylation of the dilithio derivative of methyl acetoacetate (2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF): Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082) with 3-bromocyclohexene (0 °C, 10 min, 88% yield) followed by saponification of the resulting keto methyl ester (1:1 1 M aqueous lithium hydroxide–dimethoxyethane, 23 °C, 24 h, 81% yield).

[9] Satisfactory infrared, ^1H NMR, and mass spectral data were obtained for each reaction product.

[10] See, for example: Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821 and references cited therein.

[11] Prepared in 72% yield from the corresponding acetate by sequential treatment with 1.1 equiv of LDA in THF at −78 °C and excess CO_2 at −78 °C for 30 min.

[12] The keto acids **7** and **9** were prepared from the corresponding methyl ketones by lithiation (LDA, −78 °C) and carbonation.

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20 min) gave a single hydroxy ester **14**, mp 78–79 °C (65% from **12**). Conversion of **14** to the tetracyclic dilactone **15** was accomplished by the sequence (1) mesylation (1.5 equiv of triethylamine, 3 equiv of mesyl chloride at −20 °C in CH_2Cl_2 for 30 min, yield 94%) and (2) methyl ester hydrolysis (0.1 N lithium hydroxide in THF–water at 23 °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 α-deprotonation may be rate limiting in these cases. If this is indeed so, it must also be true that the reactive intermediate in the C–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 $Mn_3O(OCOCH_3)_7$.

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; $Mn_3O(OAc)_7$, 63338-46-5; $CH_3C(O)CH_2C(O)OMe$, 105-45-3; $BrCH_2C(O)OMe$, 96-32-2; 3-bromocyclohexene, 1521-51-3.

Supplementary Material Available: Spectral data for compounds **3**, **4**, **6**, **8**, **10**, and **12–15** (1 page). Ordering information is given on any current masthead page.

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[13] This research was assisted financially by a grant from the National Science Foundation.

$(i\text{-PrO})_3Mo{\equiv}Mo(CH_2Ph)_2(O\text{-}i\text{-}Pr)(PMe_3)$: 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 $(M{\equiv}M)^{6+}$ Center

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Of all the compounds containing multiple bonds between metal atoms,[1] the d^3–d^3 dimers of molybdenum and tungsten show the most varied and fascinating coordination chemistry. There are compounds with M–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 d^3–d^3 dimers. However, compounds with bridging atoms are known as in $W_2Cl_6(py)_4$[4] and the salts containing $M_2X_9^{3-}$ ions (X = Cl, Br)[5] which adopt structures based on edge- and face-shared octahedra, respectively. Within the former group of compounds of formula $X_nM{\equiv}MX_n$ or $X_nY_mM{\equiv}MX_nY_m$, where X and Y = 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 $Mo_2(NMe_2)_6$, $Mo_2(O\text{-}i\text{-}Pr)_6(py)_2$, $W_2Me_2(O_2CNEt_2)_4$, and $W_2(O_2CNMe_2)_6$ 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 by the pair-wise insertion of CO_2 into OR[6] and NMe_2[7] ligands and the cooperative binding of Lewis bases to $M_2(OR)_6$ compounds:[8] $M_2(OR)_6 + 2L \rightarrow M_2(OR)_6L_2$. 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.

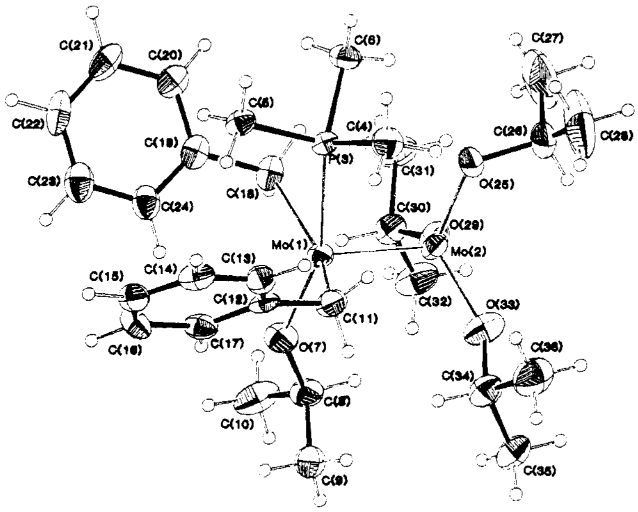

Figure 1. ORTEP view of the $(i\text{-PrO})_3Mo{\equiv}Mo(CH_2Ph)_2(O\text{-}i\text{-}Pr)(PMe_3)$ molecule. Some pertinent bond distances (Å) and angles (°) (averaged where appropriate): Mo–Mo = 2.235 (1) Mo–C = 2.22 (1), Mo(1)–O(7) = 1.920 (4), Mo(2)–O = 1.89 (2), Mo–P = 2.581 (2); Mo–Mo–C = 101.3 (6), Mo(2)–Mo(1)–O(7) = 106.5 (1), Mo–Mo–P = 94.65 (4), Mo(1)–Mo(2)–O = 107.2 (20), Mo–C–C = 114.4 (11).

Hexane solutions of $1,2\text{-}Mo_2(CH_2Ph)_2(NMe_2)_4$[9] react with i-PrOH (4 equiv) to yield $1,2\text{-}Mo_2(CH_2Ph)_2(O\text{-}i\text{-}Pr)_4$.[10] The ^1H 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 O-i-Pr ligand which contains diastereotopic methyl groups.

Addition of PMe_3 (2 equiv) to a hexane solution of $1,2\text{-}Mo_2(CH_2Ph)_2(O\text{-}i\text{-}Pr)_4$ yields $(i\text{-PrO})_3Mo{\equiv}Mo(CH_2Ph)_2(O\text{-}i\text{-}Pr)(PMe_3)$ 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) Å, is comparable to those in $Mo_2(OCH_2\text{-}t\text{-}Bu)_6$[13] 2.222 (2) Å, and $Mo_2Me_2(O\text{-}t\text{-}Bu)_4(py)_2$[14] 2.256

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[1] Cotton, F. A.; Walton, R. A. In "Multiple Bonds Between Metal Atoms"; Wiley: New York, 1982.

[2] Chisholm, M. H.; Cotton, F. A. *Acc. Chem. Res.* **1978**, *11*, 356.

[3] Chisholm M. H. *Symp. Farad. Soc.* **1980**, *No. 14*, 194.

[4] Jackson, R. B.; Streib, W. E. *Inorg. Chem.* **1971**, *10*, 1760.

[5] See: Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry", 4th ed.; Wiley: New York, 1980; pp 864–866 and references cited therein.

[6] Chisholm, M. H.; Cotton, F. A.; Extine, M. W.; Kelly, R. L. *J. Am. Chem. Soc.* **1978**, *100*, 1727.

[7] Chisholm, M. H.; Cotton, F. A.; Extine, M. W.; Stults, B. R. *Inorg. Chem.* **1977**, *16*, 603.

[8] Chisholm, M. H. *Polyhedron* **1983**, *2*, 681.

[9] Chetcuti, M. J.; Chisholm, M. H.; Folting, K.; Haitko, D. A.; Huffman, J. C.; Janos, J. *J. Am. Chem. Soc.* **1983**, *105*, 1163.

[10] Dry and oxygen free solvents and atmospheres (N_2) were used throughout.

[11] ^1H NMR data obtained from toluene-d_8 at 360 MHz for $1,2\text{-}Mo_2(CH_2Ph)_2(O\text{-}i\text{-}Pr)_4$ (+20 °C): δ (CH_2Ph) 4.13 (s); (CH_2Ph) o 7.05 (d, J = 7.6 Hz), m 6.99 (dd, J = 7.6 Hz), p 6.79 (t, J = 7.6 Hz); (CHMe$_2$) 5.39 (sept, J = 5.8 Hz); (CHMe_2) 1.32 (d, J = 5.8 Hz), 1.26 (d, J = 5.8 Hz). $(i\text{-PrO})_3Mo{\equiv}Mo(CH_2Ph)_2(O\text{-}i\text{-}Pr)(PMe_3)$ (−20 °C): δ (CH_2Ph) 4.63 (2 H, dd, $^2J_{H\text{-}H'}$ = 11.8 Hz; $^3J_{H\text{-}P}$ = 15.5 Hz), 4.46 (2 H, dd, $^2J_{H'\text{-}H}$ = 11.8 Hz, $^3J_{H\text{-}P}$ = 11.8 Hz); (CH_2Ph) o 7.07 (4 H, d, J = 7.6 Hz), m 6.96 (4 H, d, J = 7.6 Hz), p 6.71 (2 H, d, J = 7.6 Hz); (OCHMe$_2$) 6.08 (1 H, sept, J = 5.8 Hz); (OCHMe_2) 1.83 (6 H, d, J = 5.8 Hz); (OCHMe_2)′ 4.68 (3 H, sept, J = 5.8 Hz); (OCHMe_2)′ 1.30 (18 H, d, J = 5.8 Hz).

[12] Crystal data at −159 °C: $a = 16.779$ (3) Å, $b = 10.104$ (1) Å, $c = 19.555$ (4) Å, $\beta = 90.59$ (1)°, $Z = 4$ and space group $P2_1/c$. Of the 4823 reflections collected using Mo Kα, $6° < 2\theta < 45°$, 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.

[13] Chisholm, M. H.; Cotton, F. A.; Murillo, C. A.; Reichert, W. W. *Inorg. Chem.* **1977**, *16*, 1801.

[14] Chisholm, M. H.; Huffman, J. C.; Tatz, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 2075.

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