

compound **4**, which had a shorter retention time when passed through an HPLC silica gel column, was designated the *R,R* isomer.¹² The resolved amide **4** was subjected to acid hydrolysis and then hydride reduction, giving (*R*)-(methylenecyclopropyl)-methanol **6** in 63% yield.¹³ The stereochemical assignment of this sample was further confirmed by ¹H NMR analysis of its Mosher ester, whose methoxyl signal showed a greater lanthanide-induced shift than that of the *S* isomer derived from **5**.¹⁴ Chain elongation converting **6** to **8** via the cyanide intermediate **7** was accomplished in four steps, with an overall yield of 52%.¹⁵ Condensation of **8** with isobutyl chloroformate followed by coupling to coenzyme A in aqueous THF solution (pH 8–8.5)^{5,16} afforded the desired (*S*)-MCPA-CoA (**9**).¹⁷ The corresponding *R* epimer was synthesized from compound **5** by an identical sequence. The crude MCPA-CoA was chromatographed on an HPLC Partisil-C₁₈ column and eluted with 30% methanol in 50 mM potassium phosphate buffer, pH 5.3.¹⁸ Fractions containing MCPA-CoA gave a negative result to the nitroprusside test¹⁹ and had an *A*₂₂₃/*A*₂₅₆ ratio of 0.45–0.5. After removal of methanol in vacuo, the pooled fractions were desalted by reversed-phase chromatography (eluting with water and then methanol)¹⁸ and then lyophilized.

The effect of the MCPA-CoA isomers on the catalytic activity of GAD was analyzed by the method of successive titration used by Wenz et al.^{4a,20} As shown in Figure 1, a plot of the residual activity observed under aerobic conditions versus total equivalents of MCPA-CoA added gave a partition ratio of 4.4 and 5.0 for (*R*)- and (*S*)-MCPA-CoA, respectively. These results unequivocally demonstrated that both stereoisomers of MCPA-CoA are competent inhibitors. Since the racemic mixture gave a partition ratio of 4.4 under identical conditions,²¹ the aforementioned results clearly indicated that the inactivation of GAD by either epimer of MCPA-CoA follows the same course. Namely, the inactivation is nonstereospecific. Such a lack of stereospecificity of bond rupture at C₈ of MCPA-CoA in the enzyme active site strongly suggests that the ring-opening step leading to inactivation is likely a spontaneous event, induced by an α -cyclopropyl radical. Since the rearrangement of α -cyclopropyl radicals to ring-opened alkyl radicals is extremely rapid, the ring cleavage may bypass the chiral discrimination normally imposed by the enzyme.²² Thus, the

mechanistic insights deduced from this study support our early notion that GAD is capable of mediating one-electron oxidation–reduction.

Note Added in Proof. Similar results were reported in a recent publication by Baldwin et al.²³

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Asymmetric Tandem Claisen–Ene Strategy for Steroid Total Synthesis: An Efficient Access to (+)-9(11)-Dehydroestrone Methyl Ether

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The concept of the “tandem reaction sequence”¹ has currently stimulated interest as an efficient strategy for the stereocontrolled synthesis of complex molecules. Steroids have played vital roles as synthetic targets in the development of new strategies because their well-defined structures provide an opportunity to test new methods and explore their stereochemistry.^{2,3} Herein we report a conceptually new, efficient strategy for the asymmetric total synthesis of (+)-9(11)-dehydroestrone methyl ether (**1**), a key intermediate for estrogens.^{2,4} The key transformation is the asymmetric Claisen–ene sequence (I $\rightarrow$ II $\rightarrow$ III), which proceeds in tandem^{1,5} and in a highly stereocontrolled fashion (Scheme I).

Our total synthesis starts with the preparation of the requisite *S*-Z allylic alcohol **2** from (*R*)-glyceraldehyde acetonide **3**. Thus, the Wittig olefination⁷ of methyl ketone **6** derived from **3** was carried out in THF at –78 °C using [5-(trimethylsilyl)-4-pentynyl]phosphonium salt and butyllithium to afford, after desilylation (*n*-Bu₄NF), (*Z*)-enyne **7** exclusively⁹ (Chart I). Methoxy-

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(12) Chromatographed on a preparative silica gel column (Spherisorb 5 μ , 10 mm $\times$ 25 cm) eluting with 10% 2-propanol/CH₂Cl₂ at a flow rate of 4 mL/min, amide **4** and **5** gave a retention time of 4.5 and 5.1 min, respectively. The enantiomeric purity of the resolved **4** and **5** was determined to be greater than 99% based on the integration of the eluted peaks.

(13) This chemically synthesized racemic mixture could also be resolved at the alcohol stage (**6** and its *S* epimer) by the conversion of the alcohols to the corresponding Mosher esters followed by an HPLC separation of the diastereomeric esters with a DAICEL Chiralcel OJ column (10% 2-propanol/hexane). Attempts to resolve the racemic alcohols (**6** and its *S* epimer) by a double resolution sequence based on the lipase-catalyzed esterification and hydrolysis (Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250. Dreckhammer, D. G.; Barbas, C. F.; Nozaki, K.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 1607) were futile.

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(15) The optical rotations of compound **8** and the corresponding *R* epimer were +0.86 (CHCl₃, *c* 1.6) and –0.82 (CHCl₃, *c* 1.5), respectively.

(16) Belcher, M. *Methods Enzymol.* **1981**, *72*, 404.

(17) It should be noted that the configuration assignment at the chiral center was reversed when compound **6** was converted to **7/8/9** due to the change of the priority sequence of the substituents at the chiral center.

(18) Eberhard, A. *Chromatogram* **1987**, *8*, 10.

(19) Stadman, E. R. *Methods Enzymol.* **1957**, *3*, 931.

(20) The GAD used in this study was purified from pig kidney to homogeneity based on a procedure described by Thorpe (Thorpe, C. *Methods Enzymol.* **1981**, *71*, 366).

(21) The partition ratio of this inactivation found in our early study was slightly lower than the value reported here.⁵ Since the early racemic MCPA-CoA sample was only purified by conventional chromatography, it might still contain impurities that could inhibit GAD.

(22) It is worth noting that the inactivation caused by (*R*)-MCPA-CoA is faster than that observed for the *S* isomer. Such a rate distinction may arise from the rate difference of the α -proton abstraction step which is expected to be more sensitive to the steric environment around C₈ and the binding orientation of substrate in the enzyme active site.

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(8) The ketone **6** was prepared from **3** via the standard method [MeMgI; DMSO, (COCl)₂, Et₃N]; [α]_D²⁵ +74.1°; lit. [α]_D²⁰ +53.3°; Dumont, R. *Helv. Chim. Acta* **1983**, *66*, 814.

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Supplementary Material Available: Procedures for the preparation of **2**, the tandem Claisen–ene process, and the transformation of **5** to (+)-**1** (5 pages). Ordering information is given on any current masthead page.

Arsaoxanes as Reversible, Ligating Oxygen-Transfer Agents in the Synthesis of Neutral Metal–Oxo Clusters. The X-ray Structures of $\text{Cp}^*_2\text{W}_6\text{O}_{17}$ and $\text{Cp}^*_6\text{Mo}_8\text{O}_{16}$

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Methylarsaoxanes, $(\text{CH}_3\text{AsO})_n$, are heterocyclic oligomers of alternating methylarsenic groups and oxygen atoms where $n = 2$ –5.^{1,2} We form them by oxidation (under controlled conditions with dioxygen) of homocyclic pentamethylcyclopentarsine, $c\text{-(CH}_3\text{As)}_5$ (eq 1). We find that these heterocycles are reversible, ligating oxygen-transfer agents in their reactions with group 6 organometallic substrates. What distinguishes these systems from other oxygen-transfer agents reviewed by Holm³ is their ability to act simultaneously as controlled, reversible oxidants and to ligate in both reduced and oxidized forms using the same ligating atom. Throughout, As remains trivalent, retains its "soft" ligand properties, and ligates regioselectively.

We report the use of methylarsaoxanes as a new class of oxygen-transfer agent for the synthesis of novel, neutral, high-nuclearity M-oxo ($M = \text{Mo}, \text{W}$) clusters illustrated by $(\text{C}_5\text{Me}_5)_2\text{W}_6\text{O}_{17}$ (**1**) and $(\text{C}_5\text{Me}_5)_6\text{Mo}_8\text{O}_{16}$ (**2**) (Figures 1 and 2). There exists extensive knowledge about anionic oxomolybdate and oxotungstate clusters.⁴ Neutral organometallic analogues of these polymetalates have not previously been isolated, but would be of high interest as a means of studying their reactivity in organic media. **1** is the first example of a neutral, organically soluble organometallic tungstate and as such complements the work of Day and Klemperer⁵ in the chemistry of homonuclear and substituted heteronuclear polyoxoanions. **2** is the largest neutral organomolybdenum oxide characterized and the first example of an oxide containing two distinct molybdenum oxidation states.

Compounds **1** and **2** are formed as the major oxidation products from the sealed-tube reactions of the corresponding triply bonded pentamethylcyclopentadienyl metal carbonyl dimers $[\text{Cp}^*\text{M}(\text{CO})_2]_2$ ($M = \text{Mo}, \text{W}$)⁶ and either the cyclic polyarsine $c\text{-(AsCH}_3)_5$ containing 15–25% (NMR integration) of the arsaoxane or, additionally, in the case of **2**, with isolated crystalline $(\text{CH}_3\text{AsO})_4$.^{7,8} Other products accompanying the formation of

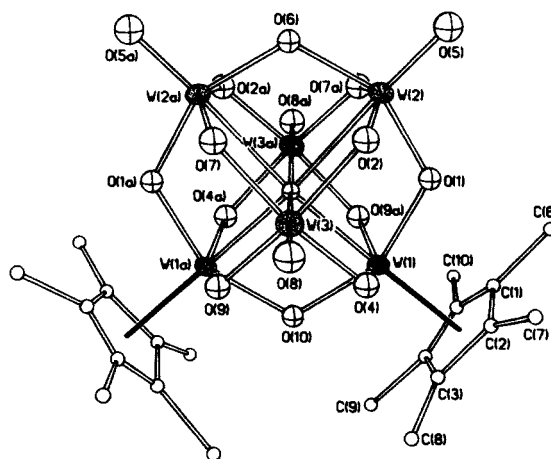


Figure 1. Molecular structure of $\text{Cp}^*_2\text{W}_6\text{O}_{17}$. The $\mu_6\text{-O}$ atom is O(3). Distances (Å): W(1)–C(1), 2.11 (4); W(1)–O(1), 1.941 (16); W(1)–O(4), 1.966 (16); W(1)–O(10), 1.928 (12); W(1)–O(9a), 1.921 (16); W(1)–O(3), 2.204 (13); W(2)–O(5), 1.692 (20); W(2)–O(1), 1.886 (16); W(2)–O(2), 1.930 (16); W(2)–O(6), 1.924 (11); W(2)–O(7a), 1.924 (17); W(2)–O(3), 2.502 (15); W(3)–O(8), 1.694 (17); W(3)–O(2), 1.939 (18); W(3)–O(4), 1.923 (18); W(3)–O(7), 1.937 (19); W(3)–O(9), 1.926 (18); W(3)–O(3), 2.355 (2).

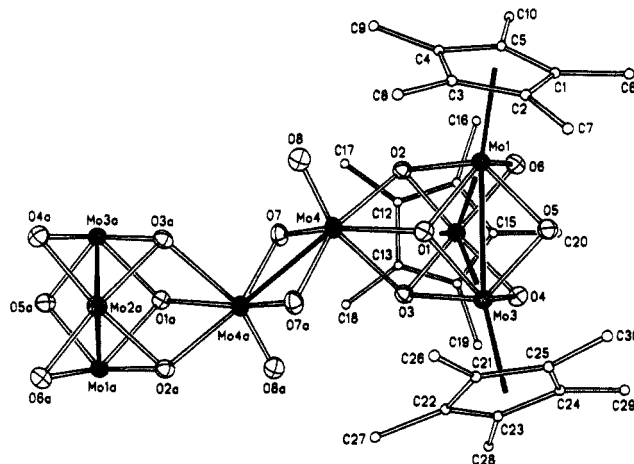
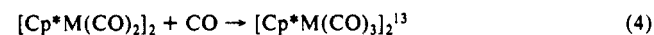
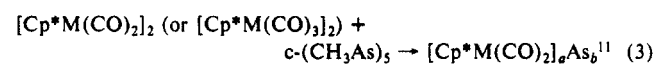
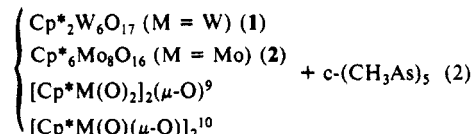
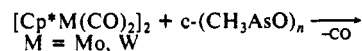
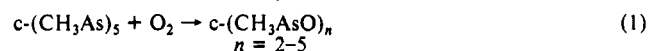


Figure 2. Molecular structure of $\text{Cp}^*_6\text{Mo}_8\text{O}_{16}$. Cp^* ligands are omitted from Mo(1a), Mo(2a), and Mo(3a) for clarity. Distances (Å): Mo(1)–Mo(2), 2.751 (1); Mo(1)–Mo(3), 2.748 (1); Mo(2)–Mo(3), 2.734 (1); Mo(1)–C(1), 2.046 (4); Mo(1)–O(1), 2.040 (2); Mo(1)–O(2), 2.035 (2); Mo(1)–O(5), 1.946 (2); Mo(1)–O(6), 1.958 (1); Mo(2)–C(1), 2.052 (2); Mo(2)–O(2), 2.027 (2); Mo(2)–O(3), 2.022 (2); Mo(2)–O(4), 1.940 (2); Mo(2)–O(6), 1.969 (3); Mo(3)–C(1), 2.055 (3); Mo(3)–O(1), 2.041 (2); Mo(3)–O(3), 2.021 (2); Mo(3)–O(4), 1.953 (1); Mo(3)–O(5), 1.957 (2); Mo(4)–Mo(4a), 2.572 (1); Mo(4)–O(1), 2.137 (2); Mo(4)–O(2), 2.150 (2); Mo(4)–O(3), 2.260 (2); Mo(4)–O(7), 1.949 (2); Mo(4)–O(7a), 1.943 (2); Mo(4)–O(8), 1.691 (3).

Scheme 1. Reaction Summary



1 and **2** include the oxo dimers, $\text{Mo}^{\text{VI}}\{[\text{Cp}^*\text{Mo}(\text{O})_2]_2(\mu\text{-O})\}^9$ and $\text{Mo}^{\text{V}}\text{cis-}[\text{Cp}^*\text{Mo}(\text{O})(\mu\text{-O})]_2^{10}$ (eq 2), the tetrahedrane-analogue

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