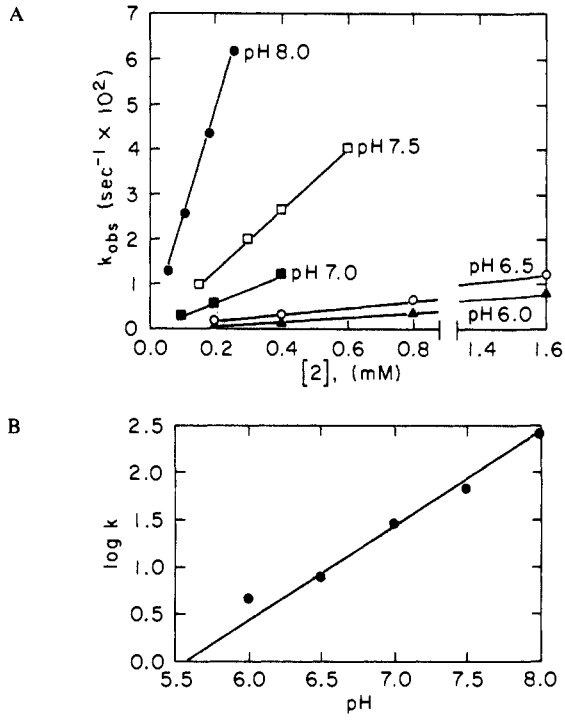

Figure 1. Reduction of ferricytochrome *c* with **2**. (A) Plot of pseudo-first-order rate constant (k_{obsd}) for the reduction of horse heart ferricytochrome *c* (Sigma, Type III, 8 μM at pH 6.0, 6.5, 7.5; 2 μM at pH 7.0, 8.0) by **2** vs [**2**] at 23 °C. Reactions were 0.10 mM in diethylenetriaminepentaacetic acid, buffered (ionic strength 0.05) with 2-*N*-morpholinoethanesulfonic acid (pH 6.0 and 6.5) or *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (pH 7.0, 7.5, and 8.0), monitored at 550 nm for up to 2 half-lives. Rate constants were calculated from plots of ln ($A_\infty - A_t$) vs time; A_∞ was obtained by reduction with $Na_2S_2O_4$. (B) Plot of log second-order rate constant for reduction of ferricytochrome *c* by **2** vs pH. Data taken from (A). Indicated line is best line of slope 1 through the data points.

required of an antioxidant in the repair/destruction of free radicals. A preliminary survey indicated that **2** reacts at least one order of magnitude more rapidly than glutathione with several one-electron acceptors, including Fremy's salt,[15] Banfield's radical,[16] galvinoxyl radical,[17] and horse heart ferricytochrome *c*. The latter system was investigated in some detail.

The pseudo-first-order reaction of ferricytochrome *c* with excess **2** was studied as a function of pH and [**2**]. Unlike glutathione, whose reactivity with ferricytochrome *c* is negligible,[18] **2** reacts with ferricytochrome *c* at an appreciable rate. **2** reacts in a process that is first order in each of the two starting materials (Figure 1A). The second-order rate constant is strongly pH dependent in the range 6 to 8, a range in which the reduction potential of the cytochrome is known to be invariant;[19] a plot of the log of the second-order rate constant vs pH (Figure 1B) is linear with a slope of 1. Gel filtration afforded a 95% yield of the disulfide of **2**, identified and quantified by UV.

The simplest interpretation of the data in Figure 1 is that in the concentration range studied the mercaptoimidazole **2** reduces ferricytochrome *c* by outer-sphere single-electron transfer. The linearity of log *k* vs pH from pH 6 to 8 further indicates that the predominant reduction initiating species is the thiolate anion **2** (Im-S^-), not the zwitterion **2** (ImH^+-S^-).[20,21] If all reduced cytochrome *c* is attributed to this pathway, a rate constant of 4×10^4 M^{-1} s^{-1} can be estimated for the reaction of **2** (Im-S^-) with ferrocytochrome *c*.[22] We speculate that the superiority of **2** (relative to glutathione) as a one-electron donor has its origin in the thermodynamic advantage of forming an aromatic rather than aliphatic thiyl radical.[23]

In summary, the thiol groups of **2** and glutathione are chemically distinct. The mercaptoimidazole in solution at physiological pH is both more nucleophilic and more reactive as a one-electron donor, the latter despite the fact that the oxidation of 2 mole of thiol to one of disulfide is less favorable for ovothiol by 4 kcal.[2a] While generic differences between aliphatic and aromatic thiols account in part for these differences, the unusual pK_a's of the thiol and imidazole functions are also important in fine tuning the chemical reactivity of the mercaptoimidazoles. The antioxidant activities of ovothiol and glutathione will likely be significantly different from one another; the ovothiols warrant further investigation as biological antioxidants.

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(22) We recognize that this need not be correct. If, for example, steps 2 and 3, below, are fast relative to 1 under these conditions, the observed rate of consumption of ferricytochrome *c* would be twice the rate of step 1.

$$RS^- + \text{cyt } c_{(ox)} \rightarrow RS^\bullet + \text{cyt } c_{(red)} \quad (1)$$

$$RS^\bullet + RS^- \rightarrow RSSR^{\bullet-} \quad (2)$$

$$RSSR^{\bullet-} + \text{cyt } c_{(ox)} \rightarrow RSSR + \text{cyt } c_{(red)} \quad (3)$$

(23) The best currently available estimate of the thermochemical superiority of benzenethiolate over methanethiolate anion in aqueous solution as a one-electron donor is 6 ± 3 kcal/mol, based upon the known solution-phase acidities and gas-phase S-H bond dissociation energies of the corresponding thiols.[24] This estimate does not account for any differences in solvation energy of the thiols and thiyl radicals, a difference that has been previously suggested to be small.[25]
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A Versatile Route to Diastereomeric Tungstenocene Complexes Containing Chiral Metal Centers[1]

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The availability of two adjacent coordination sites in bent tungstenocene complexes has resulted in the observation in this system of examples of many of the fundamental reactions of organometallic chemistry,[4] and mechanistic studies of these reactions would be facilitated by access to derivatives in which differentially substituted cyclopentadienyl ligands resulted in a prochiral or chiral metal center;[5] "the most valuable single type

(1) Dedicated to Professor E. J. Corey on the occasion of his 60th birthday, with gratitude for his continuing inspiration, stimulation, and scientific leadership.
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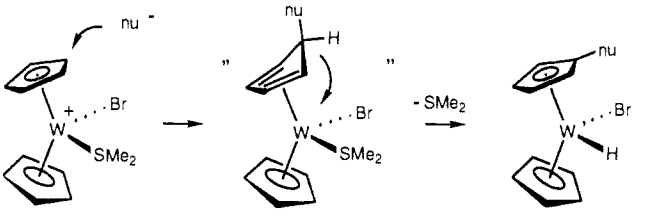
Table I. Differentially Substituted Tungstenocene Complexes Prepared by Addition of Anionic Nucleophiles to $[W(\eta\text{-}C_5H_5)_2(SMe_2)Br]PF_6$ (**1**)

nucleophilic addend	solvent	product isolated	yield, %
$KOCMe_3$	THF	$[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4OCMe_3)HBr]$ (**2**)	66
$NaS(i\text{-}Pr)$	toluene/THF (3:1)	$[W(\eta\text{-}C_5H_5)\{\eta\text{-}C_5H_4S(i\text{-}Pr)\}HBr]$ (**3**)	90
$LiPPh_2$	toluene	$[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4PPh_2)HBr]$ (**4**)	79
NaOMe	THF or MeOH	none	
$i\text{-}PrMgBr$	THF	$[W(\eta\text{-}C_5H_5)\{\eta\text{-}C_5H_4(i\text{-}Pr)\}Br_2]$ (**5**)	29
PhMgBr	THF	$[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4Ph)Br_2]$ (**6**)	27
Me_3CMgBr	THF or toluene	none	
Me_3CLi	THF	none	
$NaBD_4$	THF	$[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4D)HBr]$ (**7**)	80
$KOCH(i\text{-}Pr)Ph$	toluene	$[W(\eta\text{-}C_5H_5)\{\eta\text{-}C_5H_4OCH(i\text{-}Pr)Ph\}HBr]$ (**8**)	70

of information to have in characterizing the mechanism of a reaction that makes or breaks bonds at a tetrahedral carbon atom is the stereochemistry of the transformation at that carbon",[6] and stereochemical changes at the metal center are equally informative in the case of reactions in which metal–carbon bonds are made or broken.[7] We now wish to report a simple and versatile route to differentially substituted tungstenocene complexes $[W(\eta\text{-}C_5H_4R)(\eta\text{-}C_5H_5)XY]$, an example of the separation of the diastereomers formed when a chiral substituent is used, and the application of NMR to the identification of the diastereomers.

Differentially substituted tungstenocene complexes can be prepared by addition of anionic nucleophiles to $[W(\eta\text{-}C_5H_5)_2(SMe_2)Br]PF_6$[8] (**1**) as shown in eq 1. In contrast with displacement of the SMe_2 from **1** by PMe_2Ph and Br^-,[8b] bulky heteroanionic nucleophiles, including alkoxides, phosphides, and sulfides, attack a cyclopentadienyl ring with eventual displacement of SMe_2 by a ring hydride to give racemic complexes $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4X)HBr]$ (Table I).



(1)

In a typical reaction, addition of 75 mL of precooled THF (−78 °C) to a mixture of **1** (1.0 g, 1.7 mmol) and $K[OC(CH_3)_3]$ (0.28 g, 2.5 mmol) yielded a lavender slurry which became an intense red brown solution when warmed to room temperature (4 h). Solvent was removed under vacuum, and the solids were triturated with warm toluene (75 mL). The filtered red brown solution was concentrated, and $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4OCMe_3)HBr]$ (**2**, 0.51 g, 1.1 mol = 66%) was isolated as red brown crystals by slow crystallization at low temperature. Similar procedures with $Na[SCHMe_2]$ and $Li[PPh_2]$ led to good yields of $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4SCHMe_2)HBr]$ (**3**) and $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4PPh_2)HBr]$ (**4**), while the less sterically demanding NaOMe gave a complex mixture of unidentified products.

Reactions of carbon nucleophiles such as Grignards and alkyllithiums (Table I) are more complex than those of heteroatomic anions. PhMgBr and *i*-PrMgBr initially formed the expected hydrobromides $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4R)HBr]$ (^1H NMR), but these partially converted to dibromides during isolation, and the reported yields are for the formation of $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4C_6H_5)Br_2]$ (**5**) and $[W(\eta\text{-}C_5H_5)\{\eta\text{-}C_5H_4CH(CH_3)_2\}Br_2]$ (**6**) after addition of $CHBr_3$. The best yields with carbon nucleophiles are modest, and in some cases, such as *t*-BuMgBr, *t*-BuLi, and Me_3SiCH_2MgBr, complex mixtures are formed with negligible amounts of differentially substituted products.

Nucleophilic attack on the $(\eta\text{-}C_5H_5)$ ring of a tungstenocene complex is rare but not unprecedented. Low yields of a differentially substituted product were obtained from C_6F_5Li and $[W(\eta\text{-}C_5H_5)_2Cl_2]$,[9] and $[W\{\eta\text{-}C_5H_4Si(SiMe_3)_3\}_2H_2]$ has been prepared from $[W(\eta\text{-}C_5H_5)_2Cl_2]$ and $[LiSi(SiMe_3)_3]$.[10] Norton has also reported that $Na[D_2Al(OCH_2CH_2OCH_3)_2]$ reduction of $[W(\eta\text{-}C_5H_5)_2(OCOPh)CH_3]$ gives $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4D)(CH_3)H]$,[4n] and we have similarly observed that BD_4^- reduction of **1** gives $[W(\eta\text{-}C_5H_5)(\eta\text{-}C_5H_4D)HBr]$ (**7**) (Table I).

The versatility of eq 1 potentially permits the formation of differentially substituted tungstenocene complexes with a range of chiral substituents which would render complexes diastereomeric and permit their separation, and we have observed that the reaction of **1** with the bulky chiral alkoxide K[(R,S)-OCH(*i*-Pr)Ph] gives $[W(\eta\text{-}C_5H_5)\{(R,S)\eta\text{-}C_5H_4OCH(i\text{-}Pr)Ph\}WHBr]$ (**8a,b**) in good yields as an approximately equal mixture of two diastereomeric pairs of enantiomers.[11] The diastereomers are readily distinguished by ^1H NMR—most resonances are distinct, and the ABCD patterns of the substituted rings differ by up to 0.5 δ.[12]

The OCH(*i*-Pr)Ph substituent was intended to have a marked interaction with the chiral metal, and it did prove possible to separate **8a** and **8b**. In typical procedures microcrystalline **8a,b** (0.10 g) was triturated with warm acetone (20 mL) to give a red brown solution over approximately 0.01 g of undissolved solid shown to be **8b** (>95%, ^1H NMR).[13] Pure **8a** was isolated by

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(12) Brunner has noted that organometallic diastereomers with aryl groups at a chiral center generally show large differences in the chemical shifts of their resonances.[7b]

(13) The enrichment reflects more rapid dissolution of **8a**—the difference in thermodynamic solubilities is not as great.

chromatography of **8a,b** (0.085 g)[14] through a grade III alumina column with toluene eluant. The front of the red brown band typically contains >98% **8a** (ca. 0.005 g), and further crops can be obtained by recycling material. The separation of **8a** and **8b** suggests that related diastereomers may also be separable in this system and that detailed stereochemical studies will be feasible for many of the important reactions known to occur in tungstenocene complexes.[4]

Diastereomers and enantiomers of pseudotetrahedral bent metallocene complexes have been prepared previously by the Dijon group[15] and have been used to probe the mechanisms of insertion of SO_2 into Ti–C bonds[16] and of σ-ligand exchange[17] in titanocene complexes. Their approach, however (sequential addition of unsubstituted and substituted cyclopentadienides to transition-metal halides), is limited in terms of the accessible functionalities and the halides which are suitable substrates. We have not, for example, been able to prepare chiral tungstenocene derivatives in this way.[18] Nucleophilic addition to **1** represents a fundamentally new approach to the preparation of complexes with functionalized cyclopentadienyl ligands, and similar methods may be applicable in other systems.

Acknowledgment. We thank the National Science Foundation for financial support.

Supplementary Material Available: Spectroscopic and analytical data for compounds **2**, **3**, **4**, **5**, **6**, **7**, **8a**, and **8b** (all new complexes gave satisfactory analyses) (2 pages). Ordering information is given on any current masthead page.

(14) Chromatography was considerably simplified if the mixture was first enriched to ca. 2:1 **8a**:**8b** by selective crystallization of **8b** enriched solids from toluene at low temperature to leave an **8a** enriched supernatant.

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Macrolide Biosynthesis. 5. Intact Incorporation of a Chain-Elongation Intermediate into Nargenicin†

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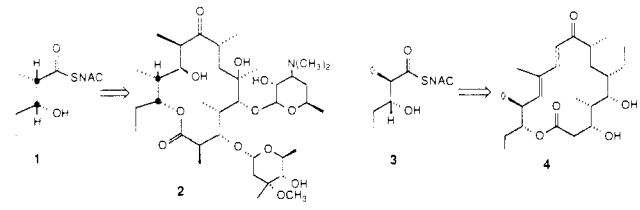
It is generally accepted that the formation of the polyketide carbon skeleton of macrolide antibiotics takes place by a mechanism analogous to the well-studied chain-elongation steps of fatty acid biosynthesis. Substantial indirect evidence, based on the origin of the carbon skeleton, oxygen atoms, and hydrogen atoms of macrolide and polyether antibiotics,[1] has led to the reasonable conclusion that the oxidation level and stereochemistry of the growing reduced polyketide chain are adjusted subsequent to each condensation step involving successive units of malonyl-, methylmalonyl-, and ethylmalonyl-CoA, as required. The absence of any detectable intermediates of the chain-elongation process even in mutants blocked in the biosynthesis of the parent polyketide chains[2] has been a significant impediment to further progress as has the lack of any viable cell-free preparations mediating the formation of any macrolide or polyether.

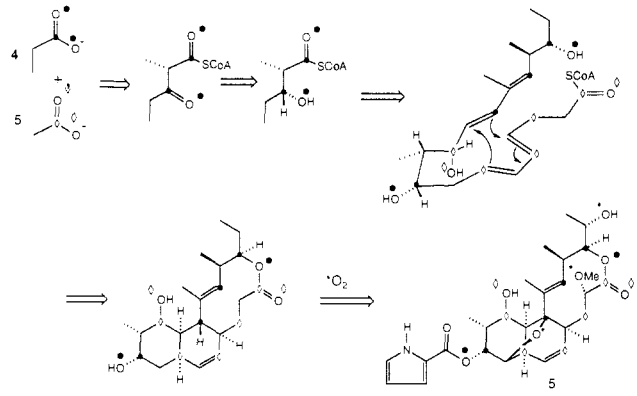
Recently, we reported the intact incorporation of an intermediate of polyketide chain elongation into the macrolide erythromycin.[3] Thus feeding of the *N*-acetylcysteamine (NAC) thioester of (2*S*,3*R*)-[2,3-$^{13}C_2$]-2-methyl-3-hydroxypentanoic acid (**1**) to cultures of *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*) gave erythromycin B (**2**) labeled at the expected positions C-12 and C-13, as determined by ^{13}C NMR analysis. Simultaneously, Hutchinson and his co-workers reported the analogous incorporation of the NAC thioester of (2*R*,3*R*)-2-methyl-3-hydroxypentanoate (**3**) into tylactone (**4**), the parent aglycone of the 16-membered ring macrolide tylosin.[4] Together, the results from the two laboratories have opened up the possibility of systematic analysis of macrolide and polyether chain-elongation by stepwise incorporation of successive polyketide intermediates.

In earlier work, we have established the origin of the carbon skeleton and oxygen atoms of nargenicin (**5**), a metabolite of *Nocardia argentinensis*,[5] by incorporation of a variety of [^{13}C]- and [$^{13}C^{18}O$]-labeled acetates and propionates as well as $^{18}O_2$ gas. These results, summarized in Scheme II, ruled out plausible epoxy-olefin cyclization schemes and suggested that the characteristic octalin ring system of nargenicin might be generated by an intramolecular Diels–Alder reaction of a reduced polyketide

Scheme I



Scheme II



† This paper is dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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