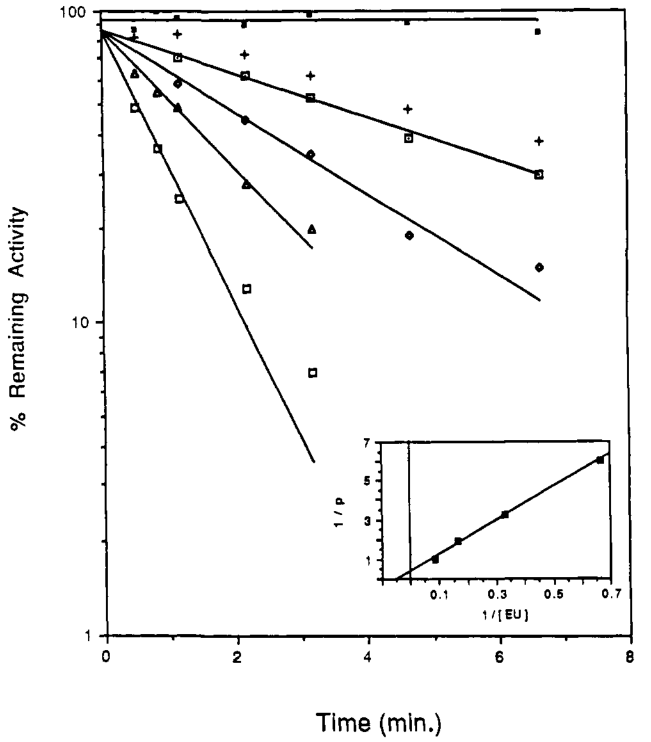

Figure 1. Time-dependent inactivation of thymine 7-hydroxylase by **4** at the following concentrations: 12 μM (□), 6 μM (△), 3 μM (◇), 1.5 μM (▣), 0 μM (■), 12 μM without αKG (+). A double reciprocal plot of rate constant vs concentration (inset) yields a straight line (correlation coefficient = 0.999), from which $K_i = 22 \pm 7$ μM and $t_{1/2} = 16 \pm 5$ s can be derived. Note that slow inactivation occurs in the absence of αKG and is presently under investigation.

was dependent on the presence of O_2 and α-ketoglutarate; furthermore, high concentrations of thymine provided complete protection (data not shown). To determine if the inactivation resulted from covalent modification of the protein, enzyme was incubated with ^3H-labeled **4** for 5 min and then passed through a Sephadex G-25 column. The amount of label bound to protein was determined by scintillation counting. Assuming a M_r of 42 kD and 90% homogeneous protein, a stoichiometry of 1 equiv of inhibitor/equiv of enzyme is observed. The labeled protein sample was diluted 10-fold into 1% SDS in 0.1% aqueous trifluoroacetic acid (pH 2.4) and dialyzed for 24 h. Ninety percent of the label remained in the dialysis bag, indicating covalent modification of the protein. These results demonstrate that 5-ethynyluracil possesses all of the criteria required of a potent mechanism-based inhibitor of thymine 7-hydroxylase. Studies are presently underway to investigate the detailed mechanism of this inactivation as well as the normal catalytic mechanism of α-ketoglutarate dioxygenases in general.

Acknowledgment. We thank John S. Wishnok for obtaining the GC-MS data and Don Bergstrom for his generous gift of 5-(2-hydroxyethyl)uracil. The mass spectrometer was purchased with DHHS Shared Instrument Grant No. 1-S10-RR01901. L.T. was supported by an NIH predoctoral training grant to the University of Wisconsin—Madison. This research is supported by GM 29595 from the National Institutes of Health.

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(10) Inactivation reactions were carried out in 410 μL containing 40 mM HEPES (pH 7.5), 0.54 mM α-ketoglutarate, 12 μM $FeSO_4$, 2.4 mM ascorbate, 22 μg (0.006 units) thymine 7-hydroxylase, 1 mg mL^{-1} BSA, 2% glycerol, 0.2% DMSO, and variable amounts of 5-ethynyluracil (0–12 μM). At various times, a 10-μL aliquot was diluted into a standard assay mixture (200 μL) containing 1 mg/mL BSA, [2-^{14}C]thymine (1100 cpm/nmol), 40 mM HEPES (pH 7.5), 0.54 mM α-ketoglutarate, 12 μM $FeSO_4$, and 2.4 mM ascorbate. After 5 min, the assays were quenched with 40 μL of 10% perchloric acid; chloroform (50 μL) was added, the samples were neutralized with 10 μL 6 N KOH in 1 M Tris, and the products were analyzed by HPLC.

Synthesis and Characterization of a Novel Bimetallic μ-Malonyl Complex. The First X-ray Crystal Structure of Alkali Metal Chelation by a Neutral Malonyl Compound

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Carbon-bound malonyl (β-oxoacyl) transition-metal complexes ($MCOCH_2COR$), in contrast to simple metal acyls ($MCOCH_3$), are remarkably elusive compounds.[1] The properties and reactivity of this ligand class are expected to vary considerably from those of typical metal acyls due to the increased acidity of the α-hydrogens, the increased lability of the carbon–carbon bonds, and the potential of the malonyl oxygens to chelate to an additional metal. We recently developed a synthetic route into bimetallic μ-malonyl complexes, which are stabilized by chelation of a malonyl oxygen to one of the transition metals. Thus reaction of $(\eta^5\text{-}C_5Me_5)Re(NO)(PPh_3)(COCH_2Li)$, **1**,[2] and $Re(CO)_5(OSO_2CF_3)$, **2**, led to isolation of $(\eta^5\text{-}C_5Me_5)Re(NO)(PPh_3)(\mu\text{-}COCH_2CO)_4Re(CO)_4$, **3**, in 71% yield.[3] We wish to report here the synthesis and characterization of a novel μ-malonyl complex, $(\eta^5\text{-}C_5Me_5)Re(NO)(PPh_3)(\mu\text{-}COCH_2CO)Re(CO)_4(PMe_3)\cdot Li^+\text{-}OSO_2CF_3^-$, **4**, in which the neutral 1,3-dicarbonyl bridge serves as a bidentate chelate to an alkali metal cation. The X-ray crystallographic characterization of **4** represents the first solid-state structure of an alkali metal ion chelated by both carbonyl oxygens of a neutral malonyl compound.

When the reaction of rhenaenolate **1** and triflate **2** is followed by low-temperature $^{31}P\{^1H\}$ NMR spectroscopy, evidence is obtained for clean, quantitative formation of an intermediate species which, upon warming to 23 °C, undergoes conversion to **3**. Addition of excess PMe_3 to solutions of the intermediate at −78 °C generates the lithium-chelated complex $(\eta^5\text{-}C_5Me_5)Re(NO)(PPh_3)(COCH_2CO)Re(CO)_4(PMe_3)\cdot Li^+OSO_2CF_3^-$, **4**, in 45% isolated yield. The malonyl ligand in **4** exhibits an extremely large ^1H NMR chemical shift difference ($CDCl_3$) for the diastereotopic methylene hydrogens [δ 1.48 (d, J = 14.6 Hz, 1 H), 5.18 (d, J = 14.7 Hz, 1 H)]. In the ^1H NMR spectrum of the isotopically enriched complex $(\eta^5\text{-}C_5Me_5)Re(NO)(PPh_3)(^{13}COCH_2CO)Re(CO)_4(PMe_3)\cdot Li^+OSO_2CF_3^-$, **4-^{13}CO**, the methylene resonance at δ 1.48 is observed as a doublet of doublets ($^2J_{HH}$ = 14.5 Hz, $^2J_{CH}$ = 5.5 Hz), whereas the 5.18 resonance remains a doublet ($^2J_{HH}$ = 14.7 Hz). For comparison we prepared the corresponding ^{13}C-enriched complex $(\eta^5\text{-}C_5Me_5)Re(NO)(PPh_3)(^{13}COCH_2CO)Re(CO)_4$, **3-^{13}CO**, which exhibits resonances in the ^1H NMR spectrum ($CDCl_3$) at δ 3.10 ($^2J_{HH}$ = 20.6 Hz, $^2J_{CH}$ = 1.6 Hz) and 2.49 (dd, $^2J_{CH}$ = 2.5 Hz). In the solid-state structure of **3**, the malonyl ligand is incorporated into a nearly planar five-membered ring. We believe that the differential $^2J_{CH}$ coupling and the large chemical shift difference in the ^1H NMR

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(1) Blake, D. M.; Vinson, A.; Rye, R. *J. Organomet. Chem.* **1981**, *214*, 257. Chaudhari, F. M.; Knox, G. R.; Pauson, P. L. *J. Chem. Soc. C* **1967**, 2255. Davies, S. G.; Watts, O.; Aktogu, N.; Felkin, H. *J. Organomet. Chem.* **1983**, *243*, C51. Aktogu, N.; Felkin, H.; Baird, G. J.; Davies, S. G.; Watts, O. *J. Organomet. Chem.* **1984**, *262*, 49. Bodnar, T. W.; Crawford, E. J.; Cutler, A. R. *Organometallics* **1986**, *5*, 947. Forschner, T. C.; Cutler, A. R. *Organometallics* **1985**, *4*, 1247. Schulze, W.; Hartl, H.; Seppelt, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 185.

(2) Heah, P. C.; Patton, A. T.; Gladysz, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 1185.

(3) O'Connor, J. M.; Uhrhammer, R.; Rheingold, A. L. *Organometallics* **1987**, *6*, 1987. O'Connor, J. M.; Uhrhammer, R. *J. Am. Chem. Soc.* **1988**, *110*, 4448. O'Connor, J. M.; Uhrhammer, R.; Rheingold, A. L. *Organometallics* **1988**, *7*, 2422.

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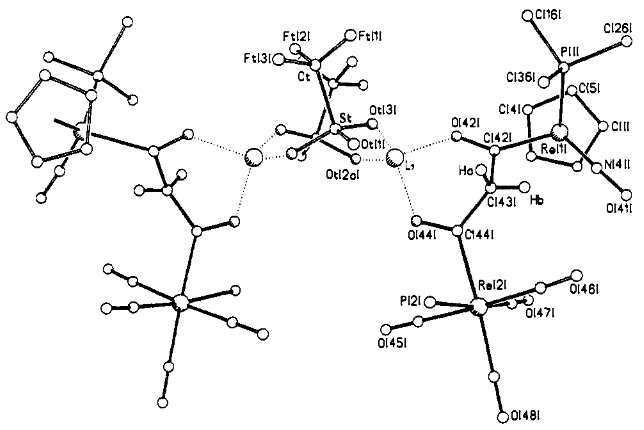
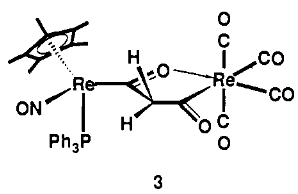


Figure 1. Molecular structure of **4** showing orientation of $CF_3SO_3^-$ and Li^+ ions in relation to the dirhenium backbone. Bond distances (Å) and angles (deg) are as follows: Re(1)–C(42) 2.069 (9), Re(2)–P(2) 2.453 (5), Re(2)–C(44) 2.194 (11), C(42)–C(43) 1.563 (16), C(43)–C(44) 1.516 (16), C(42)–O(42) 1.228 (12), C(44)–O(44) 1.254 (13), C(43)–H(a) 0.935 (98), C(43)–H(b) 0.939 (148); C(42)–C(43)–C(44) 116.5 (9), Re(1)–C(42)–C(43) 120.5 (7), Re(2)–C(44)–C(43) 123.6 (7), Re(1)–C(42)–O(42) 124.9 (8), Re(2)–C(44)–O(44) 119.9 (8), C(43)–C(42)–O(42) 114.6 (8), C(43)–C(44)–O(44) 116.4 (9), C(42)–Re(1)–P(1) 86.6 (3), C(44)–Re(2)–P(2) 84.3 (3)° Li–O(42) 1.940, Li–O(44) 1.908, Li–Ot(3) 1.922, Li–Ot(2a) 1.902 Å; the average O–Li–O angle is 109.1.

Chart I



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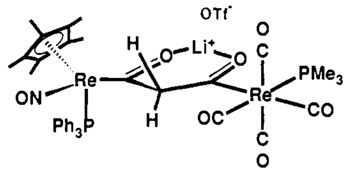

4

spectrum of **4** are indicative of a favored nonplanar conformational preference in the malonyl ligand. Application of differential $^2J_{CH}$ coupling to malonyl or acyl ligand conformation awaits detailed spectroscopic and structural studies on a series of complexes related to **3** and **4**.

In an effort to clarify the question of malonyl ligand conformation, the unusual spectroscopic data, and the mode of lithium cation interaction with the transition metal ligands, an X-ray diffraction study was performed on **4**.[4] Figure 1 shows the orientation of the $CF_3SO_3^-$ and Li^+ ions in relation to the dirhenium backbone of the molecule. The arrangement of oxygen atoms around the Li^+ ion is tetrahedral, with two oxygen atoms provided by the malonyl ligand, and two triflate ions each providing one oxygen atom. The Li–O(42)–C(42)–C(43)–C(44) and O(44) atoms form a six-membered ring which exists in a boat conformation with H_a axial and H_b equatorial. The Li–O(42) and Li–O(44) distances are 1.940 and 1.908 Å, respectively. These distances indicate a significant lithium–oxygen interaction, similar to that observed in the solid-state structure of 2,4-pentandionatolithium (Li–O distances: 1.941 and 1.923 Å).[5] Two oxygen atoms of each $CF_3SO_3^-$ ion bridge two lithium atoms with Ot(3)–Li and Ot(2a)–Li distances of 1.922 and 1.902 Å, respectively. Octahedral coordination exists at both rhenium atoms with only small deviations (angles range from 84.3 to 95.2° and from 173.8 to 176.8°). The ON–Re(1)–C(42)–O(42) torsion angle (θ) is 178.5°, which places O(42) anti to the NO ligand. The Re(1)–C(42) distance of 2.069 Å is significantly shorter than the 2.194 (11) Å Re(2)–C(44) distance, indicative of a greater degree of carbene character in the former bond. The bridging methylene hydrogens, H_a and H_b, were located on a difference map and refined. H_a is at a 2.88 Å nonbonded distance from both C(35) and C(36) of a phenyl ring on phosphorus and is 2.78 Å from the centroid of that phenyl ring. This nonbonded interaction between H_a and the phenyl rings is consistent with the unusual upfield shift (δ 1.48) of one methylene hydrogen in the ^1H NMR solution spectrum of **4**.[6] Studies are currently underway to determine the influence of metal ion chelation on the conformation, stability, and reactivity of **4** and related acyl compounds.

Acknowledgment. Partial support from the National Science Foundation (CHE-8721344) is gratefully acknowledged.

Supplementary Material Available: Tables of fractional coordinates, bond distances, bond angles, hydrogen atom coordinates, and thermal parameters and spectral (^1H NMR, $^{13}C\{^1H\}$, ^{13}C NMR, and IR) and analytical (elemental analysis) data for **4** and **4**-^{13}CO (6 pages); table of observed and calculated structure factors (28 pages). Ordering information is given on any current masthead page.

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[4] X-ray data for **4**, $[C_{38}H_{41}NO_7P_2Re_2Li]^+[CF_3SO_3]^-$: monoclinic, $C2/c$, $a = 18.269$ (3) Å, $b = 22.622$ (3) Å, $c = 22.903$ (4) Å, $\beta = 100.01$ (1)°, $V = 9322$ (3) $Å^3$, $Z = 8$, $\mu = 56.6\ cm^{-1}$, $D_{calc} = 1.73\ g\ cm^{-3}$, $T = 296$ K, Nicolet R3m/μ diffractometer with graphite monochromator and Mo Kα radiation ($\lambda = 0.71073$ Å). Two octants of data were collected (7436 reflections) of which 7043 were independent ($R_{int} = 2.44\%$) and 4697 were observed with $F_o \geq 5\alpha$. Solution by Patterson map located the Re atoms, blocked-cascade refinement, non-hydrogen atoms anisotropic, phenyl rings constrained to rigid hexagons, hydrogen atoms isotropic (fixed and idealized positions) except for the bridging methylene hydrogen atoms of the malonyl ligand which were located on a difference map and refined: $R_F = 4.53\%$, $R_{wF} = 4.92\%$, data/parameter = 9.3, GOF = 1.027, highest peak = 3.27 $e^-\ Å^{-3}$ (1.00 Å from Re(2)).

[5] Haigh, C. W.; Mallion, R. B. *Org. Magn. Reson.* **1972**, *4*, 203.

[6] Schröder, F. A.; Weber, H. P. *Acta Crystallogr.* **1975**, *B31*, 1745. Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, *26*, 764 and references therein.

A Concise Asymmetric Synthesis of the Seco Acid of Erythronolide B

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The erythromycins B (**1**) and A (**2**), which are broad spectrum anti-infectives originally isolated from *Streptomyces erythraeus*, are perhaps the best known members of the family of macrolide antibiotics.[2,3] These substances, which possess a molecular architecture richly endowed with stereochemical and functional complexities, have served admirably as a forum for the invention and development of new methods for asymmetric synthesis. Consequent to these efforts, a number of elegant achievements, including the total syntheses of the aglycons of **1** and **2** as well as of **2** itself, have already been recorded.[4] Despite these notable

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[1] Recipient of a PHS Postdoctoral Fellowship (HL07571), 1987–1989.

[2] McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* (*Washington, D.C.*) **1952**, *2*, 281.

[3] *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.

0002-7863/89/1511-7634$01.50/0