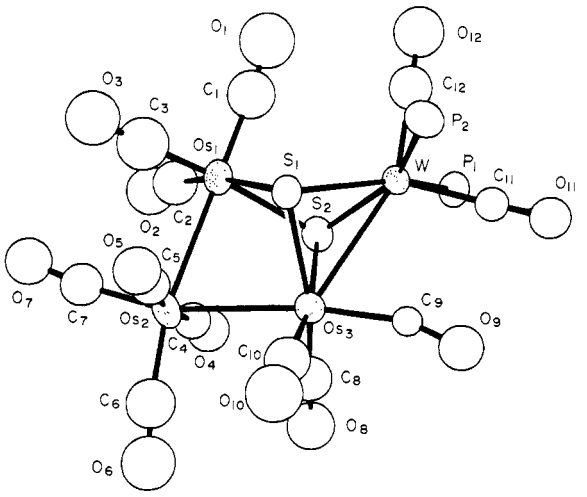

Figure 2. ORTEP diagram of $Os_3W(CO)_{12}(PMe_2Ph)_2(\mu_3\text{-}S)_2$ (III) showing 50% probability thermal ellipsoids.

terminal carbonyl ligands. The tungsten atom, in addition, contains one dimethylphenylphosphine ligand.

Compound II adds 1 mol of PMe_2Ph, 7 h/room temperature in CH_2Cl_2 solvent, to give 69% yield of $Os_3W(CO)_{12}(PMe_2Ph)_2(\mu_3\text{-}S)_2$ (III).[16] The molecular structure of III was determined by a single-crystal X-ray diffraction analysis, and an ORTEP drawing of its structure is shown in Figure 2.[9,17] The cluster is structurally similar to that of the compound $Os_4(CO)_{13}(\mu_3\text{-}S)_2$, which is formed by the addition of CO to I.[6] It consists of a planar cluster of four metal atoms containing three metal–metal bonds.[18] The two Os–Os bonds, Os(1)–Os(2) = 2.895 (1) Å and Os(2)–Os(3) = 2.887 (1) Å, are similar to those found in $Os_3(CO)_{12}$, 2.877 (3) Å.[12] The tungsten–osmium bond, W–Os(3) = 3.044 (1) Å, is similar to those found in II. Two triply bridging sulfido ligands bonded to the Os(1), Os(3), and W atoms are symmetrically disposed about the M_4 plane. Metal atom Os(1) contains three linear terminal carbonyl ligands and Os(2) contains four. Os(3) contains two linear carbonyl ligands and one semibridge (C(9)–O(9)) leading toward the tungsten atom. The tungsten atom contains two linear terminal carbonyl ligands and the two dimethylphenylphosphine ligands.

The formation of III from II has occurred apparently via phosphine addition to the tungsten atom, one of the "wing-tip" atoms of the cluster. This is accompanied by a CO ligand shift, a cleavage of the two elongated metal–metal bonds, and a shift of one of the sulfido ligands from one "hinge" metal atom to the other (e.g., from Os(2) to Os(3)).

The principal results gleaned from this study are (1) sulfido ligands by virtue of their ability to serve as bridging ligands can play an important role in the *synthesis* of new metal cluster compounds, especially mixed-metal clusters, (2) there may be a series of mixed-metal clusters analogous to I that exhibit the same unusual reactivity of I, and (3) mechanistically the point of ligand entry into II is a "wing-tip" metal atom and not the "hinge" atom which ultimate acquires one additional ligand. Whether or not this latter result is a feature of a greater affinity of the tungsten atom than an osmium atom for the phosphine ligand or due to the intrinsic reactivity of the cluster remains to be established. Studies focusing on the synthesis of mixed-metal analogues of I, the addition of other ligands to I and II, and the nature of ligand loss from III are currently in progress.

Acknowledgment. This research was supported by the National Science Foundation, Grant CHE-8019041. NMR studies were supported by Grant CHE-7916210 to the Northeast Regional NSF-NMR Facility from the National Science Foundation. We thank Engelhard Industries for a loan of osmium tetraoxide.

Supplementary Material Available: Tables of structure factor amplitudes, fractional atomic coordinates, bond distances, and bond angles are available for both structures (54 pages). Ordering information is given on any current masthead page.

(14) We have assumed that the sulfido ligands serve as four-electron donors. The structure of this cluster does, however, conform with the requirements of the polyhedral skeletal electron-pair theory, if the cluster is viewed as a *nido*-pentagonal bipyramid containing eight skeletal electron pairs.[15]

(15) Wade, K. In "Transition Metal Clusters"; Johnson, B. F. G., Ed.; Wiley: Chichester, England, 1980; Chapter 3, p 193.

(16) Compound III is also a minor product in the reaction that yields compound II. Compound III was isolated by TLC on silica gel. IR ν(CO) (hexane) 2092 s, 2050 s, 2037 m, 2014 s, 2007 sh, 1982 m, 1978 m, 1970 m, 1942 m, 1912 w, 1895 w, 1837 s, 1833 sh. ^{1}H NMR ($CDCl_3$ at 28 °C) δ 7.41 m C_6H_5, 2.16 d CH_3, $^2J_{PH}$ = 9.2 Hz.

(17) For III: space group $P2_1/n$, No. 14, a = 19.917 (9) Å, b = 9.560 (3) Å, c = 21.392 (8) Å, β = 113.74 (3)°, V = 3728 (5) Å^3, Z = 4, ρ_{calcd} = 2.55 g/cm^3. The structure was solved by direct methods (MULTAN, 264 reflections, E_{min} = 1.78) and after correction for absorption was refined by the method of full-matrix least squares (3135 reflections, $F^2 \geq 3.0\sigma(F^2)$) to the final values of the residuals R = 0.046 and R_w = 0.051.

(18) Selected interatomic distances (Å) and angles (deg) for III: Os(1)–Os(2) = 2.895 (1), Os(2)–Os(3) = 2.887 (1), Os(3)–W = 3.044 (1), Os(1)–S(1) = 2.440 (4), Os(1)–S(2), = 2.482 (5), Os(3)–S(1) = 2.447 (4), Os(3)–S(2) = 2.461 (4), W–S(1) = 2.470 (4), W–S(2) = 2.497 (4), Os(1)–Os(2)–Os(3) = 70.90 (2), Os(2)–Os(3)–W = 123.20 (3).

Chemistry of the Dianions of 3-Heteroatom-Substituted Cyclopent-2-en-1-ones: An Expedient Route to *dl*-Coriolin

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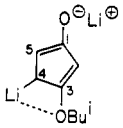
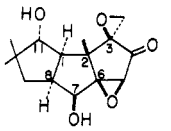
The 3-heteroatom-substituted cyclopent-2-en-1-ones smoothly generate dianions upon treatment with 2 equiv of a strong base, and the resulting dianions (e.g., **1**) undergo efficient dialkylations



1



2

at both C-4 and C-5.[1] The most synthetically attractive example of such a reaction is the one-step synthesis of the *cis*-4-alkoxybicyclo[3.3.0]oct-3-en-2-one system from reaction with 1,3-diiodopropane.[1] We have further explored this versatile reaction in conjunction with the synthesis of polycyclopentanoid natural products.[2] In this communication, we wish to delineate a highly expedient route to the antitumor agent coriolin (**2**).[3,4] The

(1) Koreeda, M.; Liang, Y.-P.; Akagi, H. *J. Chem. Soc., Chem. Commun.* **1979**, 449.

(2) For excellent reviews on the synthesis of polycyclopentanoids, see: (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (b) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. (c) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820.

(3) Isolation of coriolin: (a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (b) Takeuchi, T.; Iinuma, H.; Takahashi, S.; Umezawa, H. *Ibid.* **1971**, *24*, 631. Structure: (c) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. (d) Nakamura, H.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y. *J. Antibiot.* **1974**, *27*, 301.

(4) For previous syntheses of coriolin, see: (a) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097. Danishefsky, S.; Zamboni, R. *Tetrahedron Lett.* **1980**, *21*, 3439. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460. (b) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Antibiot.* **1980**, *33*, 100; *Tetrahedron* **1981**, *37*, 4365. (c) Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 3587. Iseki, K.; Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Tetrahedron* **1981**, *37*, 4411. (d) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. (e) Mehta, G.; Reddy, A. V.; Murthy, A. N.; Reddy, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 540. (f) Ito, T.; Tomiyoshi, N.; Nakamura, K.; Azuma, S.; Izawa, M.; Maruyama, F.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1982**, *23*, 1721. (g) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477.

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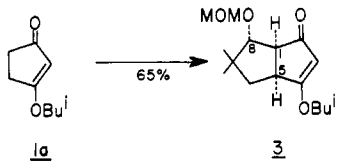
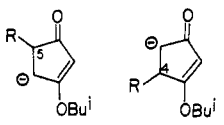
Scheme I



1a 3

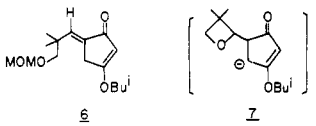
synthesis exploits the one-step construction of the bicyclo[3.3.0]octenone system (Scheme I) which should generally be applicable to the synthesis of a large number of polycyclopentanoid natural products possessing the structural unit **17** or its equivalent.

The dianion **1**,[5] generated from 3-isobutoxycyclopent-2-en-1-one (**1a**) with 2.5 equiv of lithium diisopropylamide (LDA) in THF at −78 °C for 2 h, was treated with excess 3-iodo-2,2-dimethylpropanal (2.5 equiv)[6] at −78 °C for 48 h, which was followed by addition of methoxymethyl (MOM) chloride. This one-pot procedure gave rise to the hydroxy-protected product **3** in 65% overall yield. The regio- and stereochemistry indicated in **3** rests upon proton NMR data obtained at 360 MHz; particularly, the coupling constants ($^3J_{1,8}$ = 6.0, $^3J_{1,5}$ = 7.6, and $^4J_{3,5}$ = 0.5 Hz) are indicative of the assigned structure **3**.[4] This remarkable



4 5

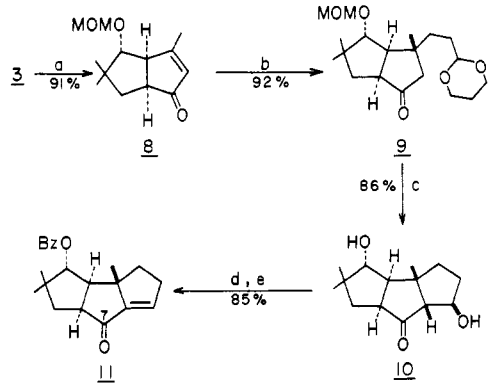
reaction, involving nucleophilic attack on two neopentyl carbons, evidently proceeds through the initial stereoselective addition at C-5 of the dianion **1** to the aldehyde carbon,[7] followed by intramolecular ring closure. The observed regioselectivity appears to be general for this system[1] and may be explained in terms of the relative stability of the initial monocarbanion adduct at C-5 (**4**) over the one at C-4 (**5**). Thus, the carbanion in **4** has extended resonance stabilization with the enone moiety, whereas the carbanion in **5** is in cross-conjugation with the enone. As it is known, the first equivalent of LDA deprotonates from C-5;[8] as far as we are aware, this is the first example among various dianions where the kinetically more acidic site (C-5) is selectively alkylated.[9] Furthermore, the reaction was found to be highly temperature dependent. Thus, when the reaction medium was warmed above −40 °C, the rearranged product **6** was isolated in 72% yield



6 7

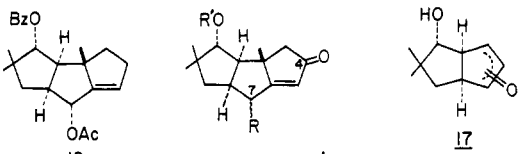
together with a trace amount of the bicyclic product **3**. The dienone **6** presumably arose via the oxetane **7**.[10]

Scheme II[a]



[a] Conditions: (a) MeLi (5 equiv)/ether, −78 °C; warm to 0 °C; 3 h at 0 °C; acidic workup with 0.1 N HCl, room temperature, 5 min. (b) (2-(1,3-Dioxan-2-yl)ethyl)magnesium bromide (20 equiv)/THF, −78 °C; add 0.25 equiv of CuBr·Me_2S in THF/Me_2S (10/1); −78 °C, 1 h; add **8**; −78 °C, 2 h; −40 °C, 30 min; 0 °C, 5 min; workup at 0 °C with NH_4Cl. (c) **9** (700 mg) in 25% aqueous HCl (0.5 mL) and THF (50 mL), room temperature, 10 h; standard workup. (d) BzCl (10 mol equiv), pyridine/CH_2Cl_2 (1/40), room temperatue, 24 h. (e) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (2 equiv), THF, room temperature, 12 h, standard workup.

Cuprate addition to the enone **8**, followed by acid-catalyzed deacetalization/cyclization, gave the tricyclic cyclopentanoid system **10** (Scheme II). Unfortunately, under a variety of hydride reduction conditions, the required 7β-hydroxy derivative could not be generated stereoselectively from **11**.[11] Therefore, we developed the following route to the key synthetic intermediate **15**, which has been employed in previous coriolin syntheses,[4c,f,g]



12 13 R = α-OAc; R' = Bz
14 R = H; R' = Bz
15 R = H; R' = H
16 R = α-OH; R' = H
17

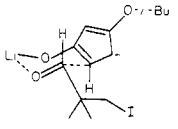
by its conversion into the Danishefsky intermediate **16**[4a] in three steps. Thus, reduction of **11** ($NaBH_4/CeCl_3$/MeOH, 0 °C, 10 min),[12] followed by acetylation with Ac_2O/pyridine/CH_2Cl_2, cleanly afforded the 7α-acetate **12** (95%), which was then subjected to Salmond oxidation[13] [81%; CrO_3–3,5-dimethylpyrazole complex (20 equiv), −20 °C, 7 h]. The 7α-acetoxyl in the resulting enone **13** was removed with Zn/AcOH, reflux, 2 h, to the enone **14**, which was further treated with 1 N LiOH/THF (1/10) (50 °C, 16 h) to afford **15** in 76% overall yield from **13**. The hydroxy enone **15**, synthesized in 20.5% overall yield in 11 steps from the readily available **1a**, gave satisfactory spectroscopic data, which are identical with those of the authentic **15**.[4f]

In summary, the versatile dianion strategy described herein, illustrated by the synthesis of a key coriolin precursor, should provide an expedient route to many polycyclopentanoid natural products possessing the partial structure **17** or its chemical equivalent.

(5) The structure **1** depicted for the dianion is based on its exclusive protonation and alkylations at C-4 and C-5 and should be regarded tentative at this point. Currently, efforts are under way in these laboratories to verify the structure of the dianion by NMR.

(6) Bp_{22} 79–80 °C. Prepared from 3-(*p*-tosyloxy)-2,2-dimethylpropanal (NaI/acetone, reflux, 12 h; 60%). The tosylate in turn was made starting from isobutyraldehyde following the literature procedure: Nerdel, F.; Frank, D.; Lengert, H.-J.; Weyerstahl, P. *Chem. Ber.* **1968**, *101*, 1850.

(7) The stereoselectivity of the C-8 hydroxyl may be envisioned as a result of the chair-like transition state shown below where the bulky *gem*-dimethyl adopts the equatorial orientation.



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(9) Review: Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509.

(10) Analysis of the crude products before MOMCl treatment revealed that under the reaction conditions most of the oxetane ring has opened up.

(11) This rather unexpected result may be ascribable to the steric hindrance exerted by the **11** benzoate. The acetate of **11** (obtained similarly from **10** in 86% overall yield), upon reduction with diisobutylaluminum hydride (1.5 equiv) in toluene at −78 °C for 1 h, gave rise, after acetylation, to a 1:1 epimeric diacetate mixture at C-7. The benzoate **11** afforded, under the identical conditions, the 7α-acetate **12** (92%).

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Acknowledgment. We thank Professor T. Matsumoto for the IR and ^1H NMR spectra of the hydroxy enone **15**. We are indebted to the National Science Foundation for its contribution to the purchase of a Bruker 360-MHz NMR spectrometer.

Supplementary Material Available: Physical properties, NMR (^1H and ^{13}C) and IR data, and analyses of all new compounds described (5 pages). Ordering information is given on any current masthead page.

A Method of Assigning Functionally Relevant Amino Acid Residue Resonances in Paramagnetic Hemoproteins Using Proton NOE Measurements

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Solution ^1H NMR spectroscopy has contributed significantly to our understanding of structure–function relationships in hemoproteins.[1-3] A major emphasis in this research area has been placed on paramagnetic forms because of the improved spectral resolution for the hyperfine-shifted resonances in the heme cavity.[4,5] The interpretation of spectral parameters, however, depends critically on unambiguous assignment of relevant resonances.[6] For b-type hemoproteins (Mb, Hb) the assignment of heme (A in Figure 1) resonances has been largely accomplished on the basis of systematic deuteration studies.[6-8] Such methods are not applicable to amino acid residues in the heme pocket, and consequently resonance of few of the functionally relevant residues have been assigned. Two such unassigned residues are the distal His E7 and FG5 (Ile-99 in Mb, Val-98 in Hb). The former sterically interacts with the ligand binding site,[9-12] while the latter has been implicated in the intrasubunit interaction in Hb.[13] While nuclear Overhauser effect, NOE, measurements provide one of the most powerful tools for assignments in diamagnetic proteins,[14-16] such applications to paramagnetic proteins have been rare,[17-20] probably because it is considered likely that paramagnetic leakage will render NOEs too small to observe. Another important reason for such assignments is that the observed dipolar shifts, together with the protein structure as determined from both X-ray crystallography and the NOE's themselves, will yield the elusive magnetic coordinate system for the magnetic anisotropic heme iron.[1,21]

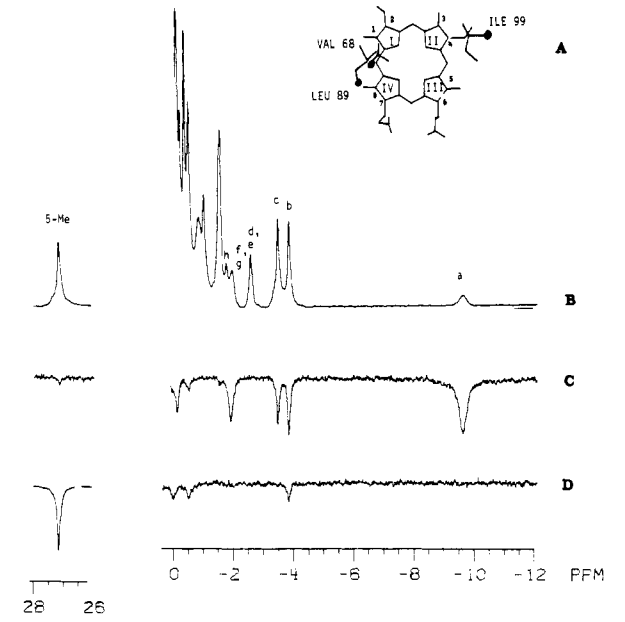

Figure 1. (A) The protohemin structure, with the non-hydrogen atoms of the Ile-99, Leu-89, and Val-68 amino acid side chains in sperm whale myoglobin. The dark circles are the α-carbon positions. Leu-86 and Ile-99 residues are on the proximal side of the heme, the Val-68 residue on the distal side. (B) The upfield and 5-methyl regions of the 360-MHz proton NMR spectrum of 3 mM sperm whale metcyanomyoglobin in D_2O, with 0.2 M NaCl, at 25 °C, pH 8.5 (uncorrected for isotope effect). All spectra shown were taken on a Nicolet 360-MHz spectrometer, using 8K data points over a ±10 000-Hz bandwidth, with delays between scans of 0.5 s. (C) NOE difference spectrum resulting from saturation of peak a, with sample as in B, spectrum intensity ×5 that of B. For a given difference spectrum, two spectra were obatined in an interleaved fashion: the first spectrum with the decoupler on the peak of interest, the second with the decoupler offset by 1500 Hz to provide a reference spectrum. (D) NOE difference spectrum resulting from saturation of the 5-methyl with sample as in B. Spectrum intensity of the region 28–26 ppm is ×1, the region 0 to −12 ppm is ×5.

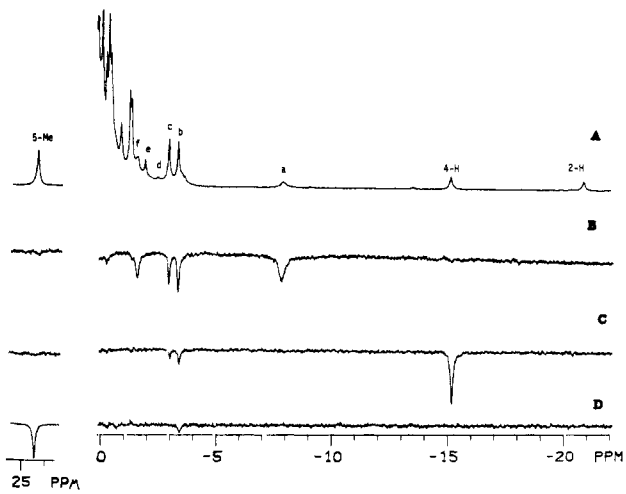

Figure 2. (A) Upfield of 5-methyl region of the 360-MHz spectrum of 3 mM sperm whale metcyanodeuteromyoglobin, 0.2 M NaCl, 25 °C, pH 8.5. (B) NOE difference spectrum resulting from saturation of peak a, spectrum intensity ×5. (C) NOE difference spectrum resulting from saturation of the heme 4-H resonance, spectrum intensity ×5. (D) NOE difference spectrum resulting from saturation of the 5-methyl resonance; spectrum intensity of the region 26–24 ppm ×1, for 0 to −12 ppm region, ×5.

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