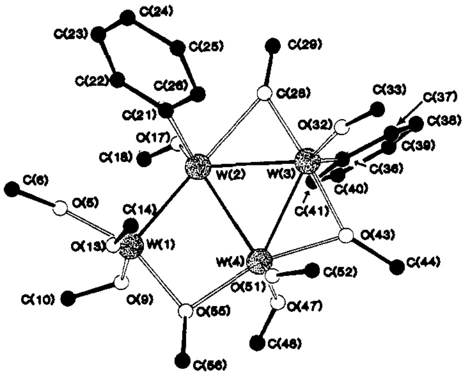
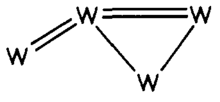


Figure 1. Ball-and-stick drawing of the central $W_4(p\text{-tolyl})_2(OC)_{10}$ core of the $W_4(p\text{-tolyl})_2(O\text{-}i\text{-}Pr)_{10}$ molecule. Pertinent bond distances (Å) and bond angles (deg), averaged where appropriate: W(1)–W(2) = 2.4780 (18); W(2)–W(3) = 2.5507 (17); W(3)–W(4) = 2.6088 (18); W(2)–W(4) = 2.7452 (17); W(1)–W(4) = 3.0105 (17); W–C(aryl) = 2.14 (5); W–O(terminal) = 1.90 (5); W–O(bridging) = 2.05 (5) except W(2)–O(28) = 2.265 (20) and W(3)–O(28) = 1.949 (20). W(1)–W(2)–W(4) = 70.18 (5); W(3)–W(2)–W(4) = 58.89 (5); W(2)–W(3)–W(4) = 64.28 (5); W(2)–W(4)–W(3) = 56.83 (5).

may describe the M–M bonding in terms of the valence bond description shown in A. This represents a grossly distorted rhombus of metal atoms.



A

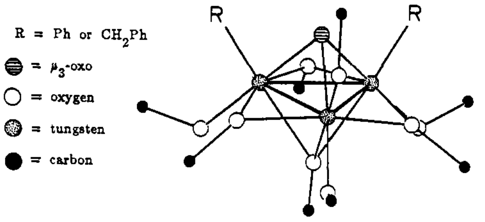
A similar strategy can be used to prepare trinuclear-alkyl and σ-bound-aryl tungsten clusters. The comproportionation reaction, eq 2, has been employed in the attempted syntheses of compounds

$$W_2R_2(O\text{-}i\text{-}Pr)_4(HNMe_2)_x{}^{10} + OW(O\text{-}i\text{-}Pr)_4 \rightarrow W_3O(R)_2(O\text{-}i\text{-}Pr)_8 + xHNMe_2 \quad (2)$$

$$\mathbf{2}\text{: } R = Ph, x = 1; R = CH_2Ph, x = 0$$

of formula $W_3O(R)_2(O\text{-}i\text{-}Pr)_8$ (**2**), but only when R = Ph or CH_2Ph has this proved successful. When R = $CH_2\text{-}t\text{-}Bu$ and CH_2SiMe_3 reactions proceed via a more complex pathway involving elimination of RH.

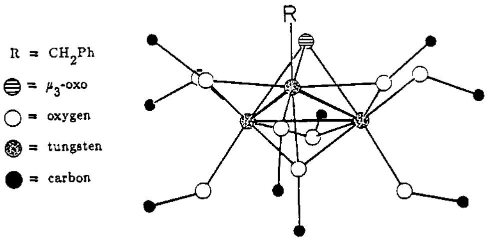
The ^1H and $^{13}C\{^1H\}$ NMR spectra of **2** are consistent with a static structure containing equivalent R groups and one molecular plane of symmetry as shown in B.



B

Structure B is related to that established for $M_3(\mu_3\text{-}O)(\mu_3\text{-}OR)(\mu\text{-}OR)_3(OR)_6$ compounds (M = Mo and W; R = *i*-Pr and $CH_2\text{-}t\text{-}Bu$)[11] where two terminal O-*i*-Pr ligands cis to the oxo capping ligand are substituted by R groups.

From reactions involving R = Ph, crystals of **2** have been isolated in ca. 30% yield and the proposed structure B has been confirmed by single-crystal X-ray crystallography.[8] For R = CH_2Ph, **2** is unstable and a further reaction occurs to give $W_3O(CH_2Ph)(O\text{-}i\text{-}Pr)_9$ (**3**) and other as yet uncharacterized tungsten-containing compounds. NMR data[6] for **3** reliably establish this compound as a six-electron W_3 cluster having the structure diagramatically depicted by C.



C

Further studies are in progress.[12]

Supplementary Material Available: Fractional coordinates, anisotropic thermal parameters, and complete listings of bond distances and angles for $W_3O(Ph)_2(O\text{-}i\text{-}Pr)_8$ and $W_4(p\text{-tolyl})_2(O\text{-}i\text{-}Pr)_{10}$ (10 pages). Ordering information is given on any current masthead page.

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(10) Chisholm, M. H.; Eichhorn, B. W.; Folting, K.; Huffman, J. C.; Tatz, R. J. *Organometallics* **1986**, *5*, 1599.

(11) Chisholm, M. H.; Folting, K.; Huffman, J. C.; Kirkpatrick, C. C. *Inorg. Chem.* **1984**, *23*, 1021. Chisholm, M. H.; Folting, K.; Huffman, J. C.; Kober, E. M. *Inorg. Chem.* **1985**, *24*, 241.

(12) We thank the Department of Energy, Office of Basic Science, Chemistry Division, and the Wrubel Computing Center for support. B.W.E. is the 1986/1987 Indiana University SOHIO fellow.

Total Synthesis of (±)-Grosshemin

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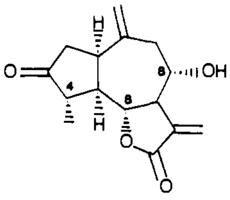
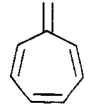
Received January 26, 1987

The guaianolide family is one of the largest and most widely distributed groups of naturally occuring sesquiterpene lactones.[1] Until recently no member of this intriguing class of natural products had succumbed to total synthesis and to date only three groups have reported syntheses in this area.[2] This surprising paucity of activity is in dramatic contrast to the host of synthetic successes that have been forthcoming in the closely related pseudoguaianolide field.[3] We wish to report the first total synthesis of (±)-grosshemin (**1**) starting from the readily available seven-membered ring species tropone (**2**).



1



2

The strategy used in this synthesis focuses on assembling, early in the scheme, a functionalized hydroazulene intermediate which has the A-ring substitution pattern intact in its final form. This approach differs significantly from previous efforts in this area which generally have postponed manipulation of the A ring until the end of the synthesis.[2a,4] The γ-butyrolactone unit would then

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(1) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.

(2) (a) Rigby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217. (b) Devreese, A. A.; Demuynck, M.; DeClercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3049. (c) Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 7498.

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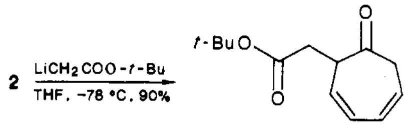
(4) For an alternative route into the C_8 oxygenated guaianolide system, see: Rigby, J. H.; Wilson, J. Z. *J. Org. Chem.* **1987**, *52*, 34.

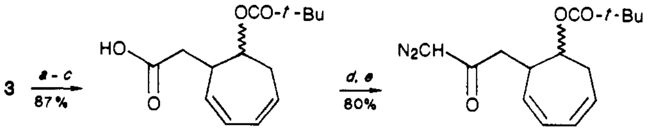
0002-7863/87/1509-3147$01.50/0

be elaborated by opening of an appropriately substituted oxirane with dilithioacetate.

The hydroazulene assembly sequence commenced with the 1,8-addition of *t*-butyl lithioacetate to tropone to provide keto ester **3** in 90% yield.[5] Next, a series of routine manipulations were performed on dihydrotropone **3** to ensure the regiochemical integrity of the diene system. This sequence provided the corresponding acid **4**[6] in 87% yield from **3**. Finally, diene acid **4** was converted into diazo ketone **5** by consecutive treatment with oxalyl chloride and diazomethane. The key cyclopropylketone **6**[6] was obtained in 75% yield when diazo ketone **5** was refluxed in cyclohexane in the presence of Cu/$CuSO_4$.[7] To simplify subsequent steps, the major C_{10} epimer was isolated at this stage and used in the diastereomerically pure form for the remaining operations. Cyclopropyl ketone **6** offered a number of interesting opportunities for introduction of the requisite α-oriented oxygen substituent at either C_6 or C_8 in the hydroazulene species. A Lewis acid mediated homoconjugate addition of an appropriate nucleophile appeared as a plausible solution to this problem.[8] Treatment of **6** with a large excess of Ac_2O and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 to −40 °C resulted in a *single* acetoxyhydroazulene which was assigned structure **7**.[6,9] This fascinating process, if general, could have applications to a wide variety of synthetic problems.

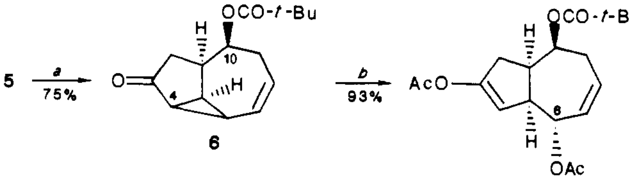


3



4 **5**

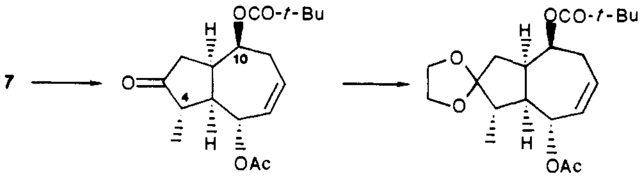
[a]$NaBH_4$, MeOH. [b]*t*-BuOCCl, Et_3N, DMAP. [c]TFA, room temperature. [d]$(COCl)_2$ collidine, DMF, 0 °C. [e]CH_2N_2, Et_2O, 0 °C.



6 **7**

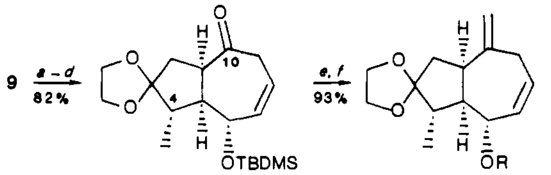
[a]Cu/$CuSO_4$, C_6H_{12}. [b]Ac_2O, BF_3Et_2O, −78 to −40 °C.

Of critical importance to the grosshemin problem was the regiospecific formation of a single enol acetate which provided a potential pathway for appending the methyl group at C_4 via the corresponding enolate anion.[10] This operation was predicated on selective nucleophilic cleavage of the vinyl acetoxy group in the presence of an alkyl-substituted acetate. Exposure of diacetate **7** to 2 equiv of methyllithium in DME at −50 °C followed by addition of excess methyl iodide in HMPA at the same temperature gave ketone **8**[6] in 61% yield as a single isomer. The methyl group stereochemistry was assigned on the basis of least hindered approach of the alkylating agent. The C_3 ketone was then protected as the dioxolane **9** in 92% yield by using Noyori's mild procedure.[11]



8 **9**

With ketal **9** available in reasonably large quantities, the introduction of the exocyclic methylene carbon at C_{10} became the next objective in the synthesis. A series of four routine manipulations converted **9** into enone **10**[6] in 82% overall yield. The resulting β,γ-unsaturated enone was quite sensitive and a mild, nonenolizing method for methylenation was indicated. Lombardo's modification of technology originated by Oshima[12] (Zn/CH_2Br_2/$TiCl_4$) proved to be excellent and provided diene **11** in 95% yield. Fluoride ion promoted desilylation gave the key diene-alcohol **12**[6] (mp: 88–9 °C) in 98% yield. Directed epoxidation[13] of the allylic alcohol proceeded uneventfully to give *syn*-epoxy alcohol **13**[6] (mp 120–121 °C) in 86% yield.



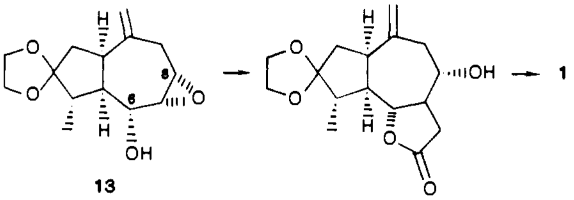
10

11, R = TBDMS
12, R = H

[a]K_2CO_3/MeOH. [b]TBDMSCl, imidazole. [c]$LiAlH_4$/Et_2O. [d]$(COCl)_2$/Me_2SO/Et_3N. [e]Zn/CH_2Br_2/$TiCl_4$. [f]Bu_4NF/THF.

The final operation in the synthesis necessitated a regioselective opening of this epoxide with dilithioacetate to give the butyrolactone. Pertinent to the successful outcome of this endeavor was an earlier observation by Danishefsky and co-workers that syn-epoxy alcohols generally experience preferential attack by acetic acid dianion at the carbon adjacent to the alcohol substituent.[14]

In the event, a single hydroxy lactone **14**[6] (mp 143–146 °C) was isolated in 76% yield when compound **13** was treated with 30 equiv of dilithioacetate in DME at 60 °C. Routine introduction of the methylene group onto the lactone was achieved by using technology employing Eschenmoser's salt as the source of the new carbon,[15] and hydrolysis of the ketal group gave (±)-grosshemin (**1**) in 71% yield. The synthetic material prepared by this efficient route was shown to be identical with an authentic sample of natural grosshemin by comparison of the ^1H NMR, ^{13}C NMR, IR, and TLC data.



13 **14**

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[5] It is imperative that this addition is performed at −78 °C. For other 1,8-additions to tropone, see ref 2a and references cited therein.

[6] This compound exhibited spectral (^1H NMR, ^{13}C NMR, IR, mass spectra) and analytical data consistent with the assigned structure.

[7] A simple hydroazulene has been prepared by an acid-promoted decomposition of a diazo ketone: Smith, A. B.; Dieter, R. K. *Tetrahedron* **1981**, *37*, 2407.

[8] (a) Demuth, M.; Rayhavan, P. R. *Helv. Chim. Acta* **1979**, *62*, 2338. (b) Dieter, R. K.; Pounds, S. *J. Org. Chem.* **1982**, *47*, 3174 and references cited therein.

[9] The location of the acetoxy group in the seven-membered ring was established by COSY experiments.

[10] (a) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341. (b) House, H. O.; Gall, M.; Olmstead, H. P. *Ibid.* **1971**, *36*, 2361.

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Acknowledgment. We thank the National Institutes of Health (GM-30771) for support of this research. We are also grateful to Dr. Matthew Suffness of the Natural Products Branch, Division of Cancer Treatment, NCI and Dr. M. Holob (Czechoslovak Academy of Science) for providing authentic samples of grosshemin.

Supplementary Material Available: IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and analytical data for **1**, **3–16**, and the hydrolysis product from **16** (5 pages). Ordering information is given on any current masthead page.

Structure of "Dioneheme". Total Synthesis of the Green Heme Prosthetic Group in Cytochrome *cd*$_1$ Dissimilatory Nitrite Reductase

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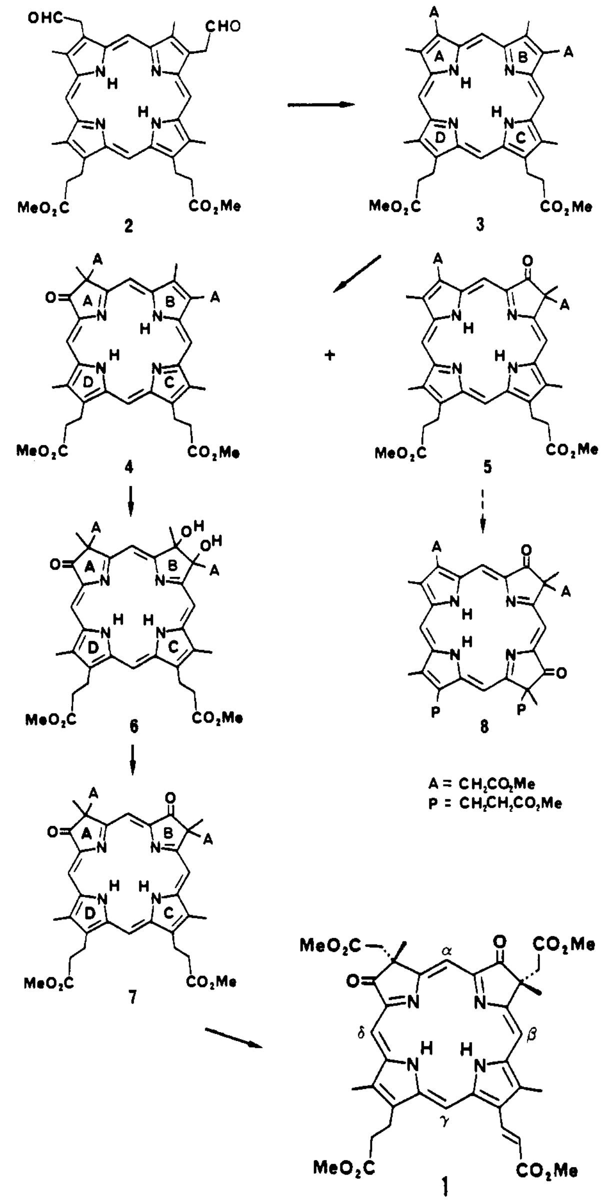
Bacterial denitrification which may have generated all of the nitrogen in the earth's atmosphere now maintains N_2 levels by continually reducing nitrates from soil and water.[1,2] A key redox enzyme occurring in many denitrifying bacteria is called cytochrome *cd*$_1$ which mediates the 4e reduction of nitrite to N_2O. In the absence of nitrite, this enzyme also functions as an oxidase reducing O_2 to H_2O.[3] A unique feature of this cytochrome is that it contains, in 1:1 ratio to the protein-linked heme *c*, a green, substrate-binding heme prosthetic group known as heme *d*$_1$.[4] Although the presence of this unusual heme has been demonstrated since 1961,[5] its chemical identity remained obscure. Timkovich and co-workers in 1984 presented detailed ^{1}H NMR, UV-vis, and mass spectra of the extracted and demetalated *d*$_1$ heme moiety.[6] They concluded that it has a chlorin core structure. We, however, proposed that a porphinedione (dioxoisobacteriochlorin) structure would fit the spectral data better and therefore *d*$_1$ is not a chlorin.[7] Strong support in favor of our unconventional structure (**1**) has been accumulating during the past year, drawing from various spectral correspondence between the natural pigment and synthetic analogues possessing the proposed dione nucleus.[8,9] While these spectral evidence have effectively argued that **1** must be correct, the ultimate proof of structure could only come from total synthesis or X-ray crystallography, as common in the natural products chemistry. We have now achieved this objective and report here the synthesis of the metal-free "dioneheme"[10] tetramethyl ester.

Scheme I



The pinacol–pinacolone-type rearrangement of *vic*-dihydroxychlorin is a proven method for introducing geminal alkyl as well as keto groups at the porphyrin periphery.[11,12] The knowledge of migratory aptitudes of different substituents associated with such rearrangement[13] also helped to formulate the synthetic plan. It was decided that double migration of the northern methyl groups in porphyrin **3** would lead to the target dione structure. Thus the dialdehyde **2**,[14] obtained by $Tl(NO_3)_3$/MeOH oxidation of protoporphyrin, was oxidized by Jones reagent to provide the starting porphyrin **3** in 92% yield. **3** was treated with osmium tetroxide in CH_2Cl_2/pyridine and quenched by H_2S after 24 h to obtain dihydroxylation occurring at all four pyrrole rings. The two northern diols (ring A and B, 20%) were separated from the southern diols (ring C and D, 35%) on silica gel and were subjected to the first rearrangement in 1:1 FSO_3H/H_2SO_4;[15] the resultant monoketones **4** and **5** were separated by chromatography. The

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[1] Payne, W. J. *Denitrification*; Wiley: New York, 1981.

[2] Delwiche, C. C. *Denitrification, Nitrification, and Atmospheric Nitrous Oxide*; Wiley: New York, 1981.

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[4] (a) Kuronen, T.; Ellfolk, N. *Biochim. Biophys. Acta* **1972**, *275*, 308. (b) Gudat, J. C.; Singh, J. S.; Wharton, D. C. *Biochim. Biophys. Acta* **1973**, *292*, 376.

[5] (a) Yamanaka, T.; Okunuki, K. *Biochim. Biophys. Acta* **1961**, *67*, 379. (b) Horio, T.; Higashi, T.; Yamanaka, T.; Matsubara, H.; Okunuki, K. *J. Biol. Chem.* **1961**, *236*, 944.

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[7] Chang, C. K. *J. Biol. Chem.* **1985**, *260*, 9520.

[8] Chang, C. K.; Wu, W. *J. Biol. Chem.* **1986**, *261*, 8593.

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[11] (a) Inhoffen, H. H.; Nolte, W. *Justus Liebigs Ann. Chem.* **1969**, *725*, 167. (b) Chang, C. K. *Biochemistry* **1980**, *19*, 1971. (c) Chang, C. K.; Wu, W. *J. Org. Chem.* **1986**, *51*, 2134.

[12] Chang, C. K.; Sotiriou, C.; Wu, W. *J. Chem. Soc., Chem. Commun.* **1986**, 1213.

[13] Chang, C. K.; Sotiriou, C. *J. Heterocycl. Chem.* **1985**, *22*, 1739.

[14] Kenner, G. W.; McCombie, S. W.; Smith, K. M. *Justus Liebigs Ann. Chem.* **1973**, 1329.

[15] The pinacolic rearrangements involving acetate substituents were plagued with poor yield and byproduct. In the first rearrangement, the conditions were optimized by using superacid FSO_3H/H_2SO_4/fuming H_2SO_4 (10:10:1) which gave about 55% of the monoketone **4** or **5**. If concentrated H_2SO_4 was used alone, yield was only 15% with the major product being the γ-lactone which resists rearrangement or hydrolysis. Using Nafion or Magic acid, only decomposition was observed. In the rearrangement of **6**, however, the presence of FSO_3H catalyzed the reduction of **6** to **4**.