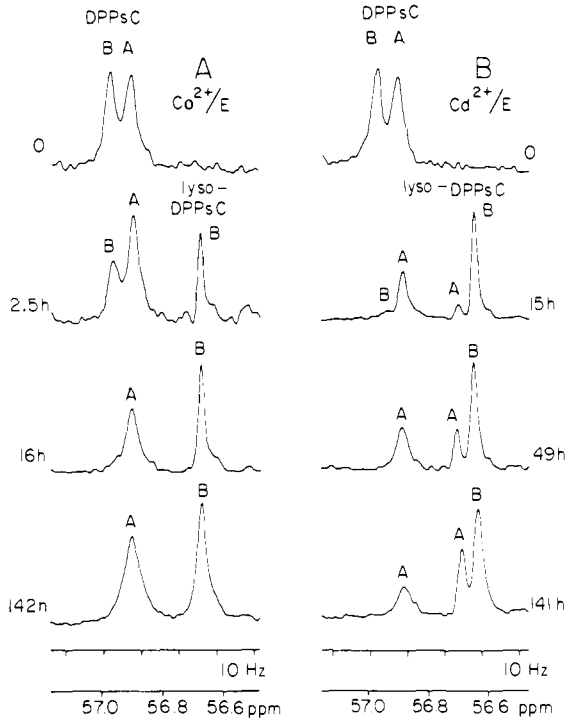

Figure 3. Hydrolysis of DPPsC(A + B) by bee venom phospholipase A_2 followed by ^{31}P NMR (81.0 MHz). Sample conditions: 20 μmol of DPPsC(A + B) in 2 mL of buffer containing 50 mM MOPS·Na, pH 7.2; 0.25 mM EDTA, 35% D_2O, 5% Triton X-100, and (A) 2.5 mM puratronic grade $Ca(NO_3)_2$ and 3.8 μg of enzyme, (B) 2.5 mM puratronic grade $Cd(NO_3)_2$ and 350 μg of enzyme. NMR parameters are same as in Figure 1 except for the number of scans. The probe temperature was set at 37 °C and samples were incubated at 37 °C. A small Gaussian multiplication (LB = −1, GB = 0.05) was applied (which did not effect relative intensities greatly) to resolve overlapped peaks.

enzyme, the phospholipases A_2 from *Naja naja* venom (Sigma, 200–600 units/mg) and from porcine pancreas (Sigma, 600 units/mg) also specifically hydrolyze the isomer B of DPPsC. Figure 2 shows the plot of initial velocity vs. substrate concentrations for DPPC, DPPsC(A), and DPPsC(B) in the reaction of bee venom phospholipase A_2 by use of the spectrophotometric assay of Kupferberg et al.[19] The results indicate that the reaction rates of DPPsC isomers are considerably slower (<10%) than that of DPPC, which is consistent with the properties of the sulfur analogues of adenine nucleotides.[12] In addition, the DPPsC isomers show "sigmoidal" curves which may support either a cooperative interaction between protomers[17] or the presence of an allosteric site and a catalytic site, if the effect of substrate concentration in mixed micelles (DPPsC/triton X-100 as described in the legend of Figure 2) is the same as that in normal homogeneous catalysis.

The observed stereospecificity of phospholipase A_2 in the experiments described above suggests that the phosphate group is involved in binding, most likely with Ca^{2+}. To further support this, we have investigated the metal-ion dependence in stereospecificity. Figure 3 shows ^{31}P NMR spectra of the reaction mixture at different time intervals for the hydrolysis of DPPsC(A + B) at a saturating concentration (10 mM) catalyzed by the bee venom phospholipase A_2 in the presence of Ca^{2+} (Figure 3A) and Cd^{2+} (Figure 3B).[22] In Figure 3A, approximately 50% of DPPsC(B) was hydrolyzed at 2.5 h, but no hydrolysis of DPPsC(A) can be detected up to 142 h. In Figure 3B (in which 92 times as much enzyme was used since Cd^{2+} substitution caused a substantial decrease in enzyme activity) an additional peak (0.057 ppm downfield from the isomer B of lyso-DPPsC) apeared even before DPPsC(B) is completely hydrolyzed (at 15 h). After 49 h it was quite obvious that this new peak was from the hydrolysis of DPPsC(A). On the basis of the work of Jaffe and Cohn,[23] the decreased stereospecificity of phospholipase A_2 toward isomer B in the presence of Cd^{2+} is a positive evidence for a direct coordination between the divalent metal ion and the phosphate group.

Proton-decoupled ^{31}P NMR (81.0 MHz) of an aqueous dispersion of DPPsC(A + B) at 45 °C shows a line shape characteristic of lipid bilayers, with a chemical shift anisotropy $\Delta\sigma$ = 32 ppm (compared to 47 ppm for DPPC under the same condition). ^{14}N NMR (21.7 MHz) of the same sample shows two quadrupolar splittings, $\Delta\nu_Q$ = 7.43 and 7.60 KHz, possibly due to the two diastereomers[24] (compared to 10.26 KHz for DPPC). When such NMR techniques (and ^2H NMR for ^2H-labeled DPPsC) and other physical methods are applied to study the interaction of *separate isomers* of DPPsC with other membrane components, valuable information concerning the biological role of the phosphate head group in membrane functions should be generated.

Registry No. 1, isomer 1, 82482-77-7; **1**, isomer 2, 82482-78-8; **2**, isomer 1, 82482-79-9; **2**, isomer 2, 82482-80-2.

(22) Although phospholipase A_2 is highly specific to Ca^{2+}, we have been able to remove Ca^{2+} by extensive dialysis against MOPS buffer (which resulted in complete deactivation) and reactivate the enzyme with Ca^{2+} or Cd^{2+}. The Cd^{2+} enzyme is only 1/120 as active as the Ca^{2+} enzyme based on the spectrophotometric assay (ref 19) at 1 mM DPPC. In Figure 3, the enzyme used was first dialyzed to remove Ca^{2+} and then added to the two reaction mixtures containing Ca^{2+} and Cd^{2+}. The activity of the enzyme (in units) was always assayed at 1 mM DPPC by the procedure of Figure 2.

(23) Jaffe, E. K.; Cohn, M. *J. Biol. Chem.* **1979**, *254*, 10839.

(24) An alternative but less likely interpretation is that there are two doublets with $\Delta\nu_Q$ = 7.52 KHz but separated by 85 Hz (3.9 ppm). The reduced $\Delta\nu_Q$ in DPPsC (relative to DPPC) suggests that the motion of the choline side chain is less ordered in DPPsC.

Dibenzyltetrakis(dimethylamido)dimolybdenum and -ditungsten (M≡M) Compounds and Their Reactions with Carbon Dioxide and 1,3-Diaryltriazenes. A Radical Difference

M. J. Chetcuti, M. H. Chisholm,* K. Folting, J. C. Huffman, and J. Janos

Department of Chemistry and Molecular Structure Center Indiana University, Bloomington, Indiana 47405

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Both molybdenum and tungsten have a rich dinuclear chemistry that in many ways, but by no means all ways, is very similar.[1] The search and ultimate discovery of a successful route to a tungsten $M_2(O_2CR)_4$ ($M\overset{4}{-}M$) compound is an interesting story[2] and reveals what is now generally accepted: the $(W\overset{4}{-}W)^{4+}$ unit is notably more reactive toward oxidative-addition reactions than the $(Mo\overset{4}{-}Mo)^{4+}$ unit. McCarley's[3] spectacular success in preparing pure $MoW(O_2C\text{-}t\text{-}Bu)_4$ ($M\overset{4}{-}M$) used this principle. We report here an intriguing difference between reactions involving $(M\equiv M)^{6+}$ units (M = Mo and W)[4] that reveals the comple-

(1) Cotton, F. A.; Walton, R. A. In "Multiple Bonds between Metal Atoms"; Wiley: New York, 1982.

(2) Sattelberger, A. P.; McLaughlin, K. W.; Huffman, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 2880 and references therein.

(3) From the reaction among $Mo(CO)_6$, $W(CO)_6$, and *t*-BuCOOH, mixtures of $Mo_2(O_2C\text{-}t\text{-}Bu)_4$ and $MoW(O_2C\text{-}t\text{-}Bu)_4$ were obtained. Addition of I_2 to a benzene solution of a mixture of these Mo_2- and MoW-containing compounds selectively precipitated the heterobimetallic single-electron oxidation product $MoW(O_2C\text{-}t\text{-}Bu)_4I$, and a crystal structure analysis of the acetonitrile adduct revealed axial coordination of I^- to W and MeCN to Mo. The compound has a bond order of 3.5, and reduction, using powdered zinc in acetonitrile at 25 °C, yielded the heterobimetallic quadruply bonded compound $MoW(O_2C\text{-}t\text{-}Bu)_4$. Katovic, V.; Templeton, J. L.; Hoxmeier, R. J.; McCarley, R. E. *J. Am. Chem. Soc.* **1975**, *97*, 5300.

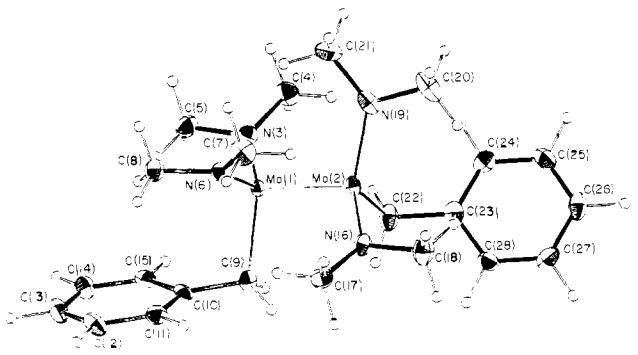

Figure 1. ORTEP view of the *gauche*-1,2-$Mo_2(benzyl)_2(NMe_2)_4$ molecule. Some pertinent bond distances (Å) and bond angles (deg) (averaged where appropriate) are Mo–Mo = 2.200 (1), Mo–N = 1.950 (5), Mo–C = 2.19 (1), Mo–Mo–N = 104 (1), and Mo–Mo–C = 100.0 (4). The Mo to ortho-carbon distances are essentially all the same at 3.7 Å.

mentary fact: reductive elimination occurs for molybdenum, $(M{\equiv}M)^{6+} \rightarrow (M\overset{4}{-}M)^{4+}$, but not for tungsten under comparable conditions.

As part of a continuing study of the properties and reactions of 1,2-$M_2R_2(NMe_2)_4$ (M≡M) compounds,[5] we have prepared 1,2-$M_2(benzyl)_2(NMe_2)_4$ compounds (M = Mo, W) from reactions involving 1,2-$M_2Cl_2(NMe_2)_4$ compounds[6] and benzyllithium or -Grignard reagents.[7] The new benzyl compounds are diamagnetic, air-sensitive, hydrocarbon-soluble, yellow-orange crystalline solids. A gauche $Mo_2(CH_2Ph)_2(NMe_2)_4$ molecule has been structurally characterized,[8] and a view of the molecule is shown in Figure 1. The benzyl ligands are σ bonded and as a result of forming a Mo≡Mo bond, three Mo–L σ bonds, and two Me_2N to Mo π bonds, each metal atom attains a 16 valence shell of electrons. The benzyl compounds are thus directly analogous to 1,2-$M_2R_2(NMe_2)_4$ compounds recently reported[5] for M = Mo and W and R = Me, Et, *n*- and *i*-Pr, and *n*-, *sec*-, and *t*-Bu, and in solution they exist in both anti and gauche rotamers.

The molybdenum and tungsten compounds differ in their reactions[9] with CO_2 and 1,3-diaryltriazenes as shown in reactions 1–4.

$$Mo_2(CH_2Ph)_2(NMe_2)_4 + CO_2 \text{ (excess)} \rightarrow Mo_2(O_2CNMe_2)_4 + PhCH_2CH_2Ph \quad (1)$$

$$Mo_2(CH_2Ph)_2(NMe_2)_4 + PhNNNHPh \text{ (excess)} \rightarrow Mo_2(PhN_3Ph)_4 + PhCH_2CH_2Ph + 4HNMe_2 \quad (2)$$

$$W_2(CH_2Ph)_2(NMe_2)_4 + CO_2 \text{ (excess)} \rightarrow W_2(CH_2Ph)_2(O_2CNMe_2)_4 \quad (3)$$

$$W_2(CH_2Ph)_2(NMe_2)_4 + PhNNNHPh \text{ (excess)} \rightarrow W_2(CH_2Ph)_2(NMe_2)_2(PhN_3Ph)_2 + 2HNMe_2 \quad (4)$$

The tungsten compounds $W_2(CH_2Ph)_2(O_2CNMe_2)_4$ and $W_2(CH_2Ph)_2(NMe_2)_2(PhN_3Ph)_2$ are spectroscopically analogous to compounds that have been characterized by single-crystal X-ray studies: $W_2Me_2(O_2CNMe_2)_4$ (M≡M)[10] and $Mo_2Me_2(NMe_2)_2(PhN_3Ph)_2$ (M≡M).[11] There can be little, if any, doubt that the $(W{\equiv}W)^{6+}$ unit is retained in the benzyl derivatives formed in reactions 3 and 4. The existence of the $(Mo\overset{4}{-}Mo)^{4+}$ unit in the compounds $Mo_2(O_2CNMe_2)_4$ and $Mo_2(ArN_3Ar)_4$ is similarly certain and has been established by single-crystal X-ray studies for Ar = phenyl[12] and *p*-tolyl.[13]

The transformation of the $(M{\equiv}M)^{6+}$ unit to $(M\overset{4}{-}M)^{4+}$, which occurs for molybdenum but not for tungsten, has a parallel in the reactions of 1,2-$M_2R_2(NMe_2)_4$ compounds with each of CO_2 and 1,3-diaryltriazenes, where R = Et, Pr, and Bu[13,14] (see eq 5).

$$Mo_2R_2(NMe_2)_4 + CO_2 \text{ (excess)} \rightarrow Mo_2(O_2CNMe_2)_4 + \text{alkene} + \text{alkane} \quad (5)$$

In reaction 5, alkyl group disproportionation is intramolecular and involves the transference of a β hydrogen of one alkyl ligand to the α carbon of the other: $M_2(CH_2CD_3)_2 \rightarrow M_2 + CH_2{=}CD_2 + CH_2DCD_3$. When R = CH_3 and CH_2SiMe_3, no reductive elimination occurs and $Mo_2R_2(O_2CNMe_2)_4$ compounds are obtained.[13]

A number of observations suggest that the formation of dibenzyl in eq 1 occurs by a radical pathway: (1) Reactions involving 1:1 mixtures of $Mo_2(CH_2Ph)_2(NMe_2)_4$ and $Mo_2(CH_2\text{-}p\text{-tolyl})_2(NMe_2)_4$ with CO_2 in hexane or benzene give a statistical mixture of coupled products, $PhCH_2CH_2Ph$, $PhCH_2CH_2$-*p*-tolyl, and *p*-tolyl-CH_2CH_2-*p*-tolyl, which were characterized by GC,[15] GC–MS, and high-field ^1H NMR spectroscopy. (2) In addition to dibenzyl, some toluene (or xylene) was always formed, and when reaction 1 was carried out in the presence of 1,4-cyclohexadiene, toluene (or xylene) was produced with concomitant suppression of dibenzyl (or *p*-tolyl-CH_2CH_2-*p*-tolyl). (3) Attempts to trap benzyl radicals during the course of eq 1 using nitrosodurene as a radical trap were thwarted by the fact that, in hexane, nitrosodurene and $Mo_2(CH_2Ph)_2(NMe_2)_4$ react, yielding the characteristic ESR signal of the trapped benzyl radical and as yet uncharacterized molybdenum-containing products.[16]

If one accepts the above as evidence for a radical elimination pathway, then tungsten by favoring the higher oxidation state should be less willing (than molybdenum) to undergo metal–carbon (alkyl) bond homolysis, which would result in an oxidation state change from 3 to 2.[17] Analogous reasoning has been used in cobalt–carbon chemistry, where it has been shown that ligand basicity affects D_{Co-R}. The more basic the ligand, the larger the value of D_{Co-R} which is attributed to the stabilizing effect on the higher oxidation state, Co(III) relative to Co(II), the latter being formed upon homolysis of the Co–alkyl bond.[18] In view of the similar values obtained[19] for D_{Co-R} in organocobalt Schiff base compounds [py(saloph)CoR], where py = pyridine and saloph = *N*,*N*′-bis(salicylidene)-*o*-phenylenediamine and R = alkyl (*n*- and *i*-Pr) and benzyl, it is possible and even quite probable that a radical mechanism could be involved in eq 5. Alkyl group disproportionation could occur by β-hydrogen abstraction within

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(5) Chisholm, M. H.; Haitko, D. A.; Folting, K.; Huffman, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 4046.
(6) Akiyama, M.; Chisholm, M. H.; Cotton, F. A.; Extine, M. W.; Murillo, C. A. *Inorg. Chem.* **1977**, *16*, 2407.
(7) All reactions were carried out by using dry and oxygen-free solvents and atmospheres. Satisfactory analytical data were obtained.
(8) Crystal data at −165 °C: a = 17.595 (7) Å, b = 16.038 (6) Å, c = 10.542 (4) Å, β = 122.11 (2)°, Z = 4, and d_{calcd} = 1.451 g cm^{-3} in the space group $P2_1/a$. Of the 5121 reflections collected, the 3916 having $F > 2.33\sigma(F)$ were used in the full-matrix refinement. Final residuals are R_F = 0.036 and R_{wF} = 0.037.
(9) Reactions were carried out in hexane or benzene at room temperature in a manner previously described in ref 13.
(10) Chisholm, M. H.; Cotton, F. A.; Extine, M. W.; Stults, B. R. *Inorg. Chem.* **1977**, *16*, 603.
(11) Chisholm, M. H.; Haitko, D. A.; Huffman, J. C. *Inorg. Chem.* **1981**, *20*, 2211.
(12) Cotton, F. A.; Rice, G. W.; Sekutowski, J. C. *Inorg. Chem.* **1979**, *18*, 1143.
(13) Chetcuti, M. J.; Chisholm, M. H.; Folting, K.; Haitko, D. A.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 2138.
(14) Chisholm, M. H.; Haitko, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 6784.
(15) We thank Dr. Kevin Gilbert for assistance in obtaining GC analytical data.
(16) We thank Dr. Willie Lau for assistance in obtaining ESR results.
(17) An alternate, but essentially similar argument can be made on the observed general trends for $\bar{D}$(M–L) in homoleptic transition-metal complexes. "In general the mean bond enthalpy, $\bar{D}$(M–L) decreases in the order of L = F > OR > Cl > NR_2 > CH_2R and the values increase monotonically from one transition series to another in the order M(3d) < M(4d) < M(5d).... The mean bond enthalpy D(M–CH_2R) increases with increasing atomic number in any one group whereas in the main-group (s, p-block) metals the mean bond enthalpy decreases in the same sense." Connor, J. A. *Top. Curr. Chem.* **1977**, *71*, 83–84.
(18) Ng, F. T. T.; Rempel, G. L.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 621.
(19) Tsou, T. T.; Loots, M.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 623.

the solvent cage of the geminate dimolybdenum-alkyl radical pair formed upon homolysis of one of the Mo-C (alkyl) bonds. Further studies aimed at extracting mechanistic information are planned.[20]

Supplementary Material Available: Fractional coordinates and isotropic thermal parameters (3 pages). Ordering information is given on any current masthead page.

(20) We thank the Office of Naval Research and the Petroleum Research Fund, administered by the American Chemical Society, for support.

Stereoselective Synthesis of the Chiral Sequence of Erythronolide A

Gilbert Stork,* Ian Paterson,† and Ferdinand K. C. Lee

Department of Chemistry, Columbia University
New York, New York 10027

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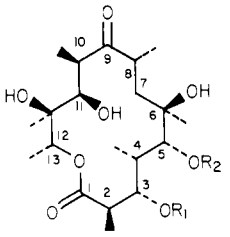
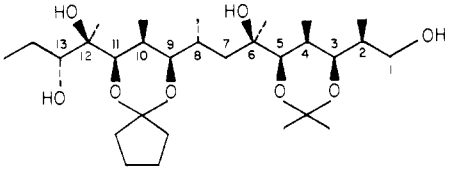
The sequence of ten chiral centers present in the aglycone derived from the well-known antibiotic erythromycin A (**1**)



1, R_1 = L-cladinose; R_2 = D-desosamine
2, $R_1 = R_2 = H$

presents a far from trivial synthetic challenge. The synthesis of the aglycone erythronolide A (**2**) has been achieved already by two Harvard groups,[1,2] one of which actually succeeded in putting together erythromycin A[2] itself.

We describe here a considerably simpler stereoselective synthesis of the protected polyol **3** in which all ten asymmetric centers of



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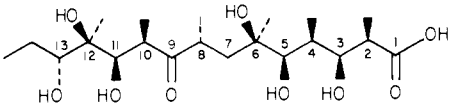
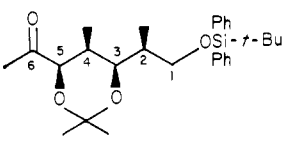


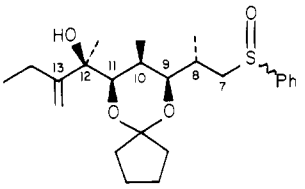
4

the seco acid **4** from erythronolide A are present in the correct absolute configuration.

The synthetic path we chose takes advantage of the fact that a cut of the molecule **3** and C_6 and C_7 as well as between carbons 12 and 13 produces two structurally and chirally identical fragments with the exception that C_2 and C_8 are antipodal. It is then possible to consider a construction in which chemically similar steps might be used to produce the two required fragments. These might also come from the same starting material. We now report the realization of this scheme in which the common chiral starting material for the two fragments **5** and **6** was chosen to be

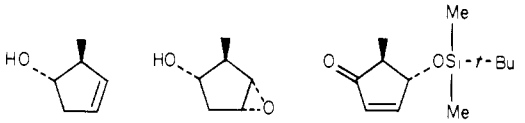


5



6

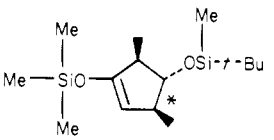
(1*S*,2*S*)-(+)-2-methyl-3-cyclopenten-1-ol (**7**), which is readily available from cyclopentadiene by the method of Partridge.[3] The cyclopentenol **7** was now transformed to the siloxycyclopentenone **9** by the sequence we had previously evolved[4] in connection with one of our prostaglandin syntheses.



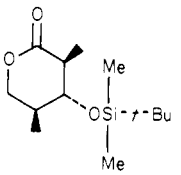
7 **8** **9**

Hydroxyl-directed epoxidation of **7** with $VO(acac)_2$ and *tert*-butyl hydroperoxide in benzene[5] gave a single[6] epoxide, **8**[7] (86%), which, upon Jones oxidation, (0 °C, 25 min), followed by kinetically controlled β elimination of the epoxide (triethylamine in methylene chloride, 0.5 h) and in situ silylation of the liberated hydroxyl group (*t*-$BuMe_2SiCl$, DMAP) gave the (-)-enone **9** (83% from **8**).[8] The bulky siloxy group was expected to[9] —and did—control the approach of lithiodimethylcuprate to enone **9**: addition (ether, -78 °C), followed by trapping of the resulting enolate (Me_3SiCl, Et_3N) gave the single enol ether **10** (88%, purified[10]) in which the chiral centers have been correctly introduced to become the centers at C_2, C_3, and C_4 of the "right-hand fragment" **5**.

Further elaboration of **10** now required controlled introduction



10



11

of the center at C_5, as well as the necessary minor structural

†SRC/NATO Postdoctoral Research Fellow 1979-1980. Present address: Department of Chemistry, University College, London.

(1) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.

(2) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K. Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan-Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Soc.* **1981**, *103*, 3210, 3213, 3215. For another, very imaginative, approach to erythronolide which derives chirality from carbohydrate precursors, see: Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843.

(3) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. The alcohol that was obtained in 50% yield via hydroboration of 5-methylcyclopentadiene with (-)-diisocampheylborane (from (+)-α-pinene and BH_3/THF) had $[\alpha]^{25}_D$ +170° (>95% ee).

(4) Stork, G.; Kowalski, C.; Garcia, G. *J. Am. Chem. Soc.* **1975**, *97*, 3258.

(5) Cf. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(6) All purifications were done by flash chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(7) The epoxide **8** (ether elution) had a boiling point of 32-35 °C (0.2 torr); R_f 0.55 (ether); $[\alpha]^{25}_D$ +45.6° (*c* 1.02, MeOH).

(8) Enone **9** (methylene chloride elution) $[\alpha]^{25}_D$ -58.2° (*c* .78, MeOH); MS found 226.139; IR 1720 cm^{-1}; NMR δ 5.90 (1 H d) 7.08 (1 H dd).

(9) This type of stereocontrol has been well established in related cyclopentenone intermediates in prostaglandin synthesis; cf.: Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

(10) Enol silyl ether **10** (CH_2Cl_2 elution): R_f 0.8 (CH_2Cl_2); $[\alpha]^{25}_D$ +10.6° (*c* 1.2, $CHCl_3$); MS found 314.2099.

0002-7863/82/1504-4686$01.25/0