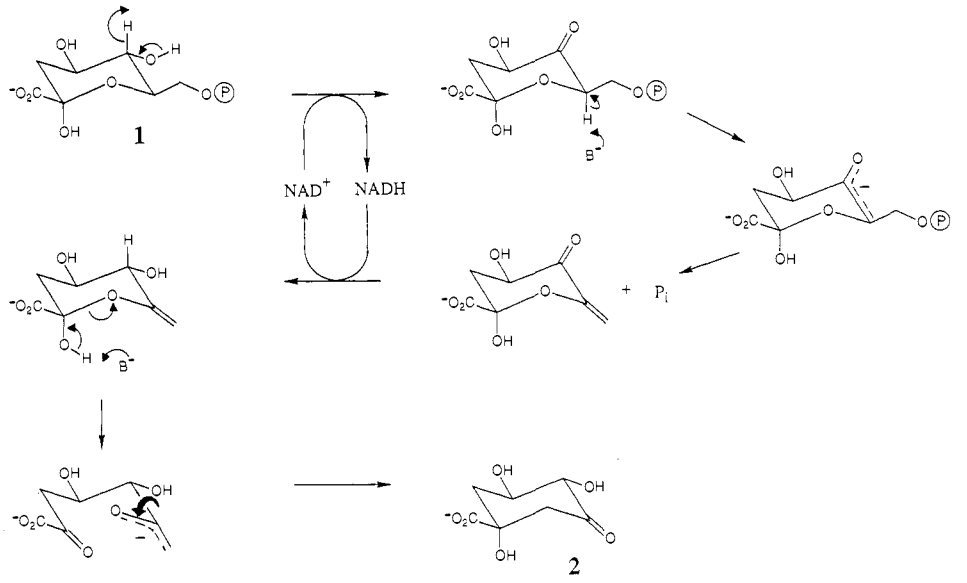
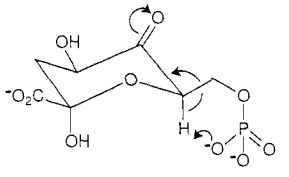
Scheme I. Suggested Mechanistic Pathway for Dehydroquinate Synthase



All these results are simply accommodated by postulating that the base responsible for removal of the proton at C-6 is a peripheral oxygen of the phosphate group of the substrate DAHP itself (or, for **3** and **6**, of the analogous phosphonate group). This suggestion (i) requires the enzyme to bind a conformer of DAHP that is mimicked by **6**, accounting for the relatively tight binding of this analogue; (ii) explains the fact that the analogue **4** does not undergo exchange even though it is tightly bound; and (iii) explains why the *E*-vinyl homophosphonate **5** is poorly bound and does not suffer either oxidation or exchange.

This proposal has several attractive features. First, the enzyme exploits one of the strongest bases available at physiological pH: the dianionic phosphate ester group. Second, the enzyme avoids the steric problem associated with deprotonating a tertiary center where the proton is 1,3 diaxial to a hydroxyl group (at C-2). Third, the difficulty of bringing an enzymic base close to the charged phosphate side chain is side-stepped. Finally, the act of substrate deprotonation produces a better leaving group for the (presumably subsequent) departure of P_i. Several of these features have gratifying precedent, for example in the facile intramolecularly-catalyzed elimination of P_i from 3-hydroxypropionaldehyde phosphate.[14]

The present proposal, coupled with the recent suggestion of Bartlett and his group[5] that the pyranose ring opening and the aldol reaction (the last two steps of Scheme I) may occur off the enzyme, helps to explain how a relatively small monomeric protein can catalyze such a complicated molecular transformation. Oxidation of DAHP (bound as in **7**) at C-5 results in the facile



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elimination of P_i to give the ene-one, reduction of which provides the enol pyranose that is then lost from the enzyme and rearranges rapidly and stereospecifically to DHQ. Although the evidence presented herein is only suggestive, the possibility that the phosphate group of DAHP promotes the β-elimination of P_i both accommodates all that we know about the mechanism of this unusual enzyme and reduces the number of required catalytic groups to what might reasonably exist at the active site of the enzyme. What appeared at first sight to be an impressively complex mechanism may, in fact, be ingeniously simple.

Acknowledgment. This work was supported by the National Institutes of Health and Merck Sharpe & Dohme. We are grateful to Dr. Gary Glick for helpful discussions.

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Symmetric Addition of SO_2 to Linear Bi- and Trinuclear Gold(I) Compounds. Partial Oxidation To Form $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2(SO_2)_2$ and $Au_2Pt(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4(SO_2)_2$

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A gold-gold bond forms when $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2$ (Au···Au = 2.977 (1) Å) is oxidized to $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2XY$ (XY = Cl_2, CH_3Br, CF_3CH_2I, $(NO_2)_2$, etc.) (Au-Au = 2.55-2.7 Å).[1,2] Metal-metal bond formation may occur during the initial step of the oxidative addition[3] or subsequent to metal-ligand bond formation. To further explore possible metal-metal bond formation related to this initial step, we have crystallized and structurally studied the adduct of SO_2 with $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2$. SO_2 coordinates axially as a Lewis acid by removing electron

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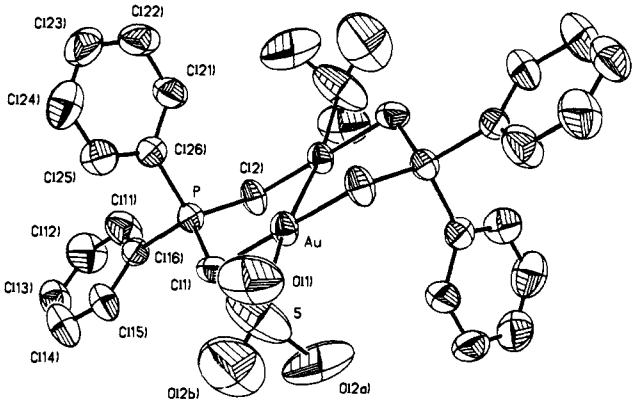

Figure 1. Structure of **1** with 50% thermal ellipsoids. Oxygen atom O(2) is disordered between two positions. Au–Au = 2.838 (1), Au–S = 2.581 (5), S–O(1) = 1.401 (15), S–O(2a) = 1.468 (25), S–O(2b) = 1.221 (35), Au–C(1) = 2.083 (11), Au–C(2) = 2.084 (10) Å; Au–S–O(1) = 104.8 (6), Au–S–O(2a) = 104.2 (11), Au–S–O(2b) = 112.5 (16), O(1)–S–O(2a) = 114.6 (12), O(1)–S–O(2b) = 134.7 (19), O(2a)–S–O(2b) = 80.6 (23), S–Au–C(1) = 88.2 (3), S–Au–C(2a) = 90.5 (3), S–Au–Au(a) = 171.0 (2)°.

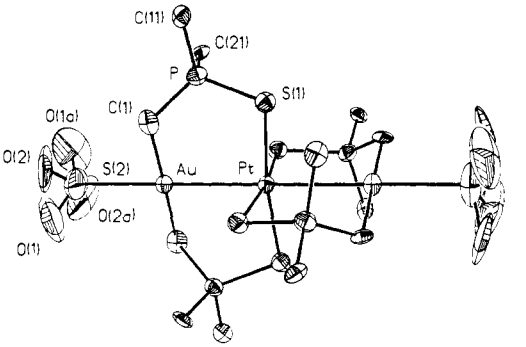

Figure 2. Structure of **2** with 50% thermal ellipsoids. Only ipso carbons of the phenyl rings are shown. The SO_2 is disordered between O(1)–S(2)–O(2a) and O(1a)–S(2)–O(2). Au, S(2), and Pt lie on an S_4 axis. Au–Pt = 2.868 (1), Au–S(2) = 2.567 (6), S(2)–O(1) = 1.250 (35), S(2)–O(2) = 1.474 (31), Au–C(1) = 2.088 (13), Pt–S(1) = 2.360 (3) Å; Au–S(2)–O(1) = 109.6 (14), Au–S(2)–O(2) = 103.3 (11), O(1)–S(2)–O(2) = 68.4 (30), O(1)–S(2)–O(2a) = 102.3 (30), S(2)–Au–C(1) = 89.5 (3), Au–Pt–S(1) = 94.8 (1)°.

density from the binuclear compound without completely oxidizing it. The adduct therefore resembles the structure presumably formed during electrophilic attack (or electron loss) at a gold(I) center. A partial Au–Au bond forms in this adduct as deduced from the reduced (0.14 Å) Au–Au distance.

Partial metal–metal bond formation upon oxidation is observed in extended linear chains such as tetracyanoplatinates.[4] The linear trinuclear compound $Au_2^{I}Pt^{II}(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4$ (Au···Pt = 3.034 (1) Å) is known to undergo axial oxidative addition. Two gold–platinum bonds form when this compound is oxidized[5] to $Au_2^{II}Pt^{II}(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4X_2$ (X = Cl, Br, or I) (Au–Au = 2.67–2.69 Å). The adduct of SO_2 with $Au_2^{I}Pt^{II}(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4$ shows formation of partial Au–Pt bonds. These are the first crystallographically characterized multinuclear compounds with axial coordination of SO_2. Bridging SO_2 has been observed previously in binuclear complexes.[6]

Bubbling SO_2 through CH_2Cl_2 solutions of $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2$ and $Au_2Pt(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4$ gave $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2(SO_2)_2$, **1**, and $Au_2Pt(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4(SO_2)_2$, **2**, respectively.[6] Crystals of these compounds lose SO_2 over several hours.

The structures[8] of **1** and **2** are shown in Figures 1 and 2. Compound **1** has an inversion center, and **2** is centered on a position with the disorder giving a crystallographic S_4 symmetry to the molecule. The Au–Au distance in **1** (2.838 (1) Å) and the Au–Pt distance in **2** (2.868 (1) Å) are less than in the Au(I) starting materials (2.977 (1) and 3.034 (1) Å, respectively[1,5]) and greater than in the corresponding Au(II) compounds.[1,5] The SO_2 moieties are disordered; electron density contour maps show three distinct peaks for the oxygen atoms in **1** and four distinct peaks in **2**. The SO_2 occupies two sites equally. In **1** these sites are O(1)–S–O(2a) and O(1)–S–O(2b). In **2** these sites are O(1)–S(2)–O(2a) and O(1a)–S(2)–O(2). The librationally corrected[9] sulfur–oxygen distances in **1** are 1.436, 1.482, and 1.222 Å for O(1), O(2a), and O(2b), respectively; in **2** they are 1.313 and 1.545 Å for O(1) and O(2). The S–O distance is chemically too short in S–O(2b) of **1** and S(2)–O(2) of **2**; in gaseous SO_2 it is 1.43 Å, which indicates that the disorder models are imperfect. The other S–O distances are slightly longer than in free SO_2 as expected when the π^* orbital is partially populated. Clearly, however, the geometry about the sulfur atom is pyramidal rather than planar, as shown by the Au–S–O and O–S–O angles.

Coordinated SO_2 resembles the NO^+ ligand. Its geometry is planar when bonded as a Lewis base (MNO is linear) to electron-poor transition metals and pyramidal (MNO is bent) when bonded as a Lewis acid to electron-rich metals.[6] SO_2 is pyramidal in **1** and **2**, showing that the metal is donating electrons into the SO_2 π^* LUMO. The gold orbitals in the binuclear compound mix, forming filled σ and σ^* orbitals.[1] The Au–Au distance shortens in **1** because electron density has been removed from the σ^* orbital by the two SO_2 units. A similar description of the bonding accounts for the shortened Au–Pt distance in **2**.

Metal–metal separations decrease as electron density is removed from the axial orbitals of these d^{10}–d^{10} and d^{10}–d^8–d^{10} compounds. In the compounds of this study adducts are bonded to two of the metal atoms, whereas during oxidative addition a substrate presumably attacks only one metal center at a time. Usón et al.[10] have added $(Et_2O)Au^{III}(C_6F_5)_3$ to just one metal center of $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2$, giving $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2Au(C_6F_5)_3$.[10] Attachment of the Au^{III} to the Au^{I} caused the Au^{I}–Au^{I} separation to decrease to 2.769 (1) Å. This supports our conclusion that partial metal–metal bond formation occurs during the initial step of the oxidative addition to these polynuclear compounds, a step in which electron density is shifted nucleophilically from the metal system to the substrate.

Acknowledgment. We acknowledge the support of the Welch Foundation, the National Science Foundation (Grant CHE 8708625), and the Texas A&M Available University Fund.

Supplementary Material Available: End view of **2** showing labeling of phenyl rings and tables of crystal data, atomic coor-

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(7) Synthesis of **1**: In a typical reaction SO_2 was bubbled for about 2 min through 15 mg of $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2$ in 1.5 mL of CH_2Cl_2. The resulting red solution was filtered, layered with heptane, and stored at −5 °C for 2 days. Green/red dichroic crystals of $[Au(\mu\text{-}(CH_2)_2PPh_2)]_2(SO_2)_2$ were obtained. Synthesis of **2**: This was prepared similarly. Diffusion of Et_2O saturated with SO_2 into a red (λ_{max} 490 nm) CH_2Cl_2 solution of $Au_2Pt(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4(SO_2)_2$ gave red/green dichroic octahedral crystals of $Au_2Pt(\mu\text{-}C,S\text{-}CH_2PPh_2S)_4(SO_2)_2\cdot 4CH_2Cl_2$. (Red plates were obtained from pentane diffusion into the solution.)

(8) Crystal data were collected on a Nicolet R3m/E diffractometer and refined using the SHELXTL crystallographic package. All non-hydrogen atoms were refined anisotropically. Hydrogen positions were calculated assuming C–H distances of 0.96 Å. Crystallographic data: **1**; sealed in epoxy, $T = 25$ °C, monoclinic, space group $C2/c$, $a = 13.708$ (5) Å, $b = 12.639$ (4) Å, $c = 17.385$ (3) Å, $\beta = 103.28$ (2)°, $V = 2931$ (1) Å^3, $Z = 4$, $R = 0.0438$, $R_w = 0.0474$ on 181 variables for 1974 reflections with $F^2 > 3\sigma(F^2)$. **2**; $T = -60$ °C, tetragonal, space group $I4_1/a$ (no. 88) with $a = b = 21.500$ (8) Å, $c = 14.758$ (5) Å, $V = 6821$ (3) Å^3, $Z = 4$, $R = 0.0350$, $R_w = 0.0305$ on 193 variables for 1249 reflections with $F^2 > 3\sigma(F^2)$.

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dinates, thermal parameters, and bond angles and lengths for **1** and **2** (8 pages); tables of calculated and observed structure factors (29 pages). Ordering information is given on any current masthead page.

Total Synthesis of Ptaquilosin: The Aglycon of Ptaquiloside, a Potent Bracken Carcinogen

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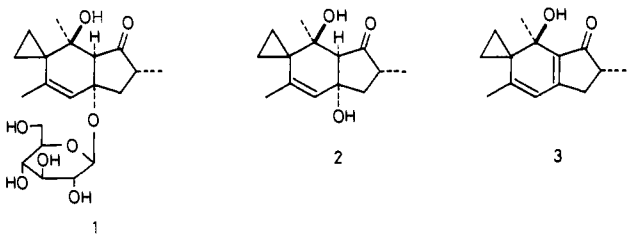
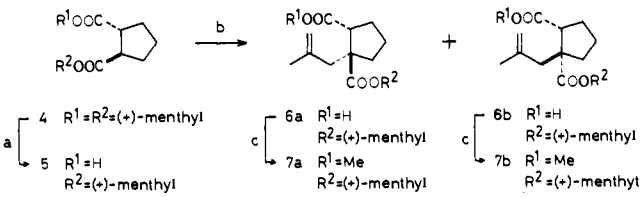
Since the carcinogenicity of bracken fern (*Pteridium aquilinum*) was discovered in 1960,[1] isolation of the carcinogen(s) has been a long-standing problem. We isolated a new type of carcinogen ptaquiloside (**1**) from bracken in 1983, determined the novel structure,[2] and proved its potent carcinogenicity.[3] Both ptaquiloside (**1**) and its aglycon ptaquilosin (**2**) are converted under weakly basic or neutral conditions into dienone **3**,[2a,d] which is the active form of **1** and causes base-specific cleavage of DNA.[4] The first total synthesis of optically active ptaquilosin (**20**), the enantiomer of natural **2** is described herein.



1 2 3

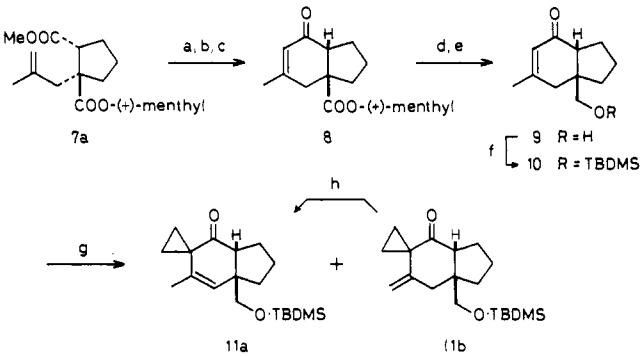
(+)-Dimenthyl (1*R*,2*R*)-cyclopentane-1,2-dicarboxylate (**4**) prepared according to the Yamamoto method[5] was partially hydrolyzed to give monomenthyl ester **5**.[6] The dianion generated from **5** (2.4 equiv of LDA, THF) reacted with methallyl chloride to afford a 4:1 mixture of diastereomeric esters, **6a** and **6b** (86%), which, after conversion into the corresponding methyl esters, was separated by chromatography on silica gel to give **7a** (77%) and **7b** (19%) (Scheme I). Contrary to the expectation the major diastereomer has the stereostructure **6a**.[7,8] The methyl ester group in **7a** was transformed via a two-step process into the acid chloride, which was subjected to cyclization with Lewis acid to give bicyclic enone **8** (81% from **7a**) (Scheme II). Conversion of **8** into enone **9** (81%) was accomplished by the following sequence: (1) reduction with $LiAlH_4$ and (2) oxidation with imidazolium dichromate.[9] A single recrystallization of this material (pentane/ether) provided pure **9**, mp 45-47 °C (>99% ee),[10] and subsequently silylation of **9** furnished enone **10** (quantitative). Spirocyclopropanation of **10** was effected by using 2-chloroethyldimethylsulfonium iodide[11] to form a separable 3:1 mixture of two ketones, **11a** (42%) and **11b** (15%), the latter **11b** being isomerized by acid catalysis[12] to the former **11a** (95%). Conversion of **11a** to conjugated ketone **12** (82%) was performed in two straightforward steps (Scheme III). Oxidation of the double bond conjugated with the keto group in **12** afforded epoxide **13**[13a] (88%), which on reduction (Ca, liquid NH_3/THF, -78 °C) provided β-hydroxy ketone **14** (91%). The reaction of the Grignard reagent (MeMgI) with **14** proceeded highly stereoselectively from the less hindered, convex face of the substrate and gave diol **15a**[13b] (89%),

Scheme I[a]



[a] (a) KOH, 30% H_2O_2, MeOH, 50 °C, 14 h; (b) LDA (2.4 equiv), THF, -25 °C, 1 h, then CH_2=C(Me)CH_2Cl (3.2 equiv), 23 °C, 16 h; (c) CH_2N_2, ether, 23 °C, 5 min.

Scheme II[a]



[a] (a) KOH, *i*-PrOH/H_2O (10:1), reflux, 6 h; (b) $(COCl)_2$, benzene, 23 °C, 3 h; (c) $SnCl_4$, CH_2Cl_2, -78 °C, 2 **h**; (d) $LiAlH_4$, THF, 23 °C, 50 min; (e) imidazolium dichromate, DMF, 23 °C, 1.5 h; (f) *t*-$BuMe_2SiCl$, imidazole, DMF, 23 °C, 45 min; (g) $ClCH_2CH_2SMe_2$·I, KI, *t*-BuOK, *t*-BuOH, 23 °C, 2 h; (h) *p*-TsOH, dioxane, reflux, 1 h.

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(6) All new compounds exhibited satisfactory spectral (IR, ^{1}H NMR, MS) and exact mass spectral data.

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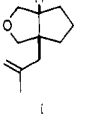
(8) Stereochemistry of **6a** and **6b** was determined as follows: **7b** could be converted into a tetrahydrofuran derivative i in two steps (1. $LiAlH_4$; 2. TsCl-pyr), whereas **7a** could not.



i

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(10) The enantiomeric purity of this compound was determined by analyzing the ^{1}H NMR spectrum of derived **10** in the presence of chiral shift reagent Eu(hfc)$_3$.

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(13) A small amount of the diastereomer was also obtained: (a) 7%; (b) 3%.

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