

Table I. ^1H and ^{13}C NMR Data for Varacin (1) and 2

C	varacin (1) ^a		2 ^b		LR ^1H to ^{13}C corr
	^{13}C ^c	^1H ^d	^{13}C ^c	^1H ^d	
1	135.94		130.03		
2	141.89		138.21		
3	151.14		150.40		
4	156.54		154.40		
5	117.03	7.07 (s, 1 H)	115.54	7.48 (s, 1 H)	H ₃ , H ₁ , H ₄ (wk)
6	140.13		137.26		
7	35.10	3.15 (m, 2 H)	29.70	3.57 (m, 2 H)	H ₅ , H ₆
8	41.66	3.25 (m, 2 H)	67.07	3.86 (m, 2 H)	
9	62.15	3.80 (s, 3 H)	60.14	3.78 (s, 3 H)	H ₃
10	56.88	3.94 (s, 3 H)	56.88	3.92 (s, 3 H)	H ₄
C ₁ SMe			20.79	2.36 (s, 3 H)	H ₁
C ₂ SMe			19.47	2.47 (s, 3 H)	H ₂
NMe			53.50	3.51 (s, 6 H)	H ₈

^aRecorded in CDCl_3 . ^bRecorded in acetone- d_6 . ^cRecorded at 100 MHz. ^dRecorded at 400 MHz.

A MeOH extract of *L. vareau* obtained by soaking 55.7 g of homogenized, freeze-dried tissue was subjected to a solvent partition scheme giving 360 mg of CHCl_3 -soluble material. Silica gel flash chromatography using a stepwise solvent gradient (CHCl_3 to MeOH) followed by reverse-phase HPLC (Rainin Dynamax C18, $\text{CH}_3\text{CN}/0.1\%$ aqueous TFA, 45:55) gave varacin (1)⁸ as a light brown glass (40 mg, 0.07% yield).

A molecular formula of $\text{C}_{10}\text{H}_{13}\text{NO}_2\text{S}_5$ was suggested by the FAB mass spectrum of the *N*-trifluoroacetate (*N*-TFA) derivative, which displayed a prominent ion at m/z 435 (HREIMS 434.9378, Δ 0.5 mmu, calculated for $\text{C}_{12}\text{H}_{12}\text{NO}_3\text{S}_5\text{F}_3$). The ^{13}C NMR spectrum (Table I) showed 10 signals including six aromatic carbons, two arylmethoxy carbons, and two methylene carbons. The ^1H NMR spectrum (Table I) contained strongly coupled methylene signals centered at δ 3.15 and 3.25 for the methylenes of a phenethylamine side chain and a singlet at δ 7.07 for a lone proton of a pentasubstituted benzene. Difference NOE experiments indicated that the lone aromatic proton exhibited dipolar coupling to the methylene protons H₇ and Me₁₀, and the two O-methyls showed cross relaxation, consistent with structure 1. To confirm these assignments, varacin was reduced with tritert-butoxyaluminum hydride in THF at room temperature, followed by a MeI quench to give derivative 2.⁹ Mass spectroscopy established a formula of $\text{C}_{12}\text{H}_{23}\text{NO}_2\text{S}_2$, indicating loss of three sulfur atoms and addition of four methyl groups. A dimethylamine terminus on the side chain was confirmed by a 25.41 ppm downfield shift of C₈ in the ^{13}C NMR spectrum, together with the observation of an intense m/z = 58 ion in the EIMS corresponding to $[(\text{CH}_3)_2\text{NCH}_2]^+$. The ^1H NMR spectrum also contained singlets at δ 2.36 and 2.47 for a pair of aryl SCH₃ groups.¹⁰ A long-range HETCOR experiment (J = 8 Hz, Table

I) allowed assignment of the four XCH₃ groups to their respective aromatic carbons by three-bond correlations from each methyl group to a single quaternary carbon. Additionally, aromatic proton H₅ exhibited three-bond coupling to C₁ and C₃, while methylene protons H₇ correlated to C₅ and C₆. Furthermore, irradiation of H₇ in a selective INAPT experiment resulted in signal enhancement for C₁, C₅, and C₆. These data combined with difference NOE results that indicated cross relaxation of H₅ to a single methyl group, Me₁₀, are fully consistent with structure 2 for the reduction product.

Additional evidence for a pentathiepin ring fused to a substituted benzene system was provided by tandem mass spectral studies performed in the negative-ion FAB mode on the *N*-TFA derivative of varacin. Selection of the $[\text{M} - \text{H}]^-$ ion at 434 generated a daughter spectrum with ions at m/z 370 and 338 for loss of S₂ and S₃, respectively, from the molecular ion. Benzopentathiepins with ortho substituents have been reported to equilibrate with their corresponding trithiole in protic solvents,¹⁰ which presents the possibility that varacin is a mixture of S₃ and S₅ compounds; however, the tandem mass spectral studies seem to argue against this. Therefore varacin must have structure 1.

Although ascidians have been the source of a large number of modified amino acid derived metabolites¹¹ and marine algae have yielded simple cyclic polysulfides,¹² this is the first report of a naturally occurring polysulfide modified amino acid. It is also the first report of a naturally occurring benzopentathiepin. Varacin bears an obvious structural and biosynthetic relationship to dopamine; thus it is perhaps not surprising that it exhibits potent biological activity.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of varacin in CD_3OD , ^1H NMR spectrum of 2 in acetone- d_6 , and daughter ion spectrum of the molecular ion of varacin *N*-trifluoroacetate in the negative FAB mode (4 pages). Ordering information is given on any current masthead page.

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(8) 1: IR (film) ν 3354, 3282, 2923, 2851, 1574, 1460, 1410, 1241, 1062 cm^{-1} ; UV (MeOH) λ_{max} 214, 244 nm; EIMS of *N*-TFA derivative m/z (relative intensity) 435 (M^+ , 25), 403 ($\text{M}^+ - \text{S}$, 5), 371 ($\text{M}^+ - \text{S}_2$, 100), 339 ($\text{M}^+ - \text{S}_3$), 245 (80). The TFA amide derivative of 1 was obtained by heating a dichloromethane solution of 1 and an excess of trifluoroacetic anhydride for 5 min at 150 °C in a sealed Pyrex tube. The excess TFA was removed under a stream of nitrogen and the sample used for mass spectral studies without further purification.

(9) 2: IR (film) ν 3420, 2921, 2851, 1684, 1463, 1418, 1202, 1071 cm^{-1} ; GC EIMS m/z (rel int) 300 ($\text{M}^+ - 1$, 0.5), 299 (2), 254 (16), 242 (10), 58 (100); CIMS (NH_3) m/z (rel int) 302 ($\text{M}^+ + 1$, 24), 257 (16), 243 (100); HRCIMS (NH_3) calcd for $\text{C}_{14}\text{H}_{24}\text{NO}_2\text{S}_2$, 302.1248, found 302.1247.

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Isolation of a New Series of Seven-Coordinate Hydride Compounds of Tantalum(V) and Their Involvement in the Catalytic Hydrogenation of Arene Rings

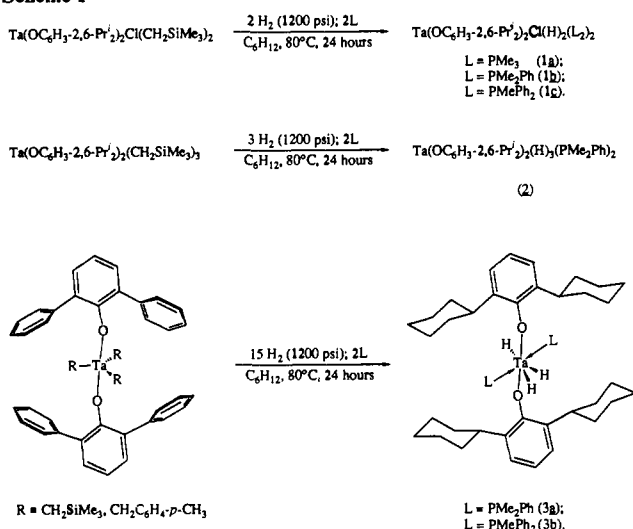
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There is currently intense research interest into the synthesis, structure, bonding, and reactivity of transition-metal hydride compounds.¹⁻⁴ A significant amount of this interest has been stimulated by the recognition that nonclassical structures may exist for di- or polyhydride compounds.⁵⁻⁷ We wish to report here the isolation of a new series of seven-coordinate hydride compounds of tantalum that contain aryloxy ligation. Besides possessing interesting structure and spectroscopic characteristics, these

Scheme I



molecules are also active for the homogeneous hydrogenation of arene rings.⁸⁻¹¹

The mixed alkyl, aryloxide compounds Ta(OC₆H₃Pr'₂-2,6)₂Cl(CH₂SiMe₃)₂ and Ta(OC₆H₃Pr'₂-2,6)₂(CH₂SiMe₃)₃ (OC₆H₃Pr'₂-2,6 = 2,6-diisopropylphenoxide) prove to be useful substrates for the synthesis of tantalum-hydride derivatives. In the presence of phosphine ligands, cyclohexane solutions of these alkyl compounds undergo hydrogenolysis (80 °C, 1200 psi of H₂) to produce the seven-coordinate di- and trihydride compounds (1a-c and 2) as shown (Scheme I). When either of the 2,6-diphenylphenoxide substrates Ta(OC₆H₃Ph₂-2,6)₂(CH₂C₆H₄-4Me)₃ or Ta(OC₆H₃Ph₂-2,6)₂(CH₂SiMe₃)₃ is used the trihydride compounds obtained, Ta(OC₆H₃cy₂-2,6)₂(H)₃(L)₂ (L = PMe₂Ph

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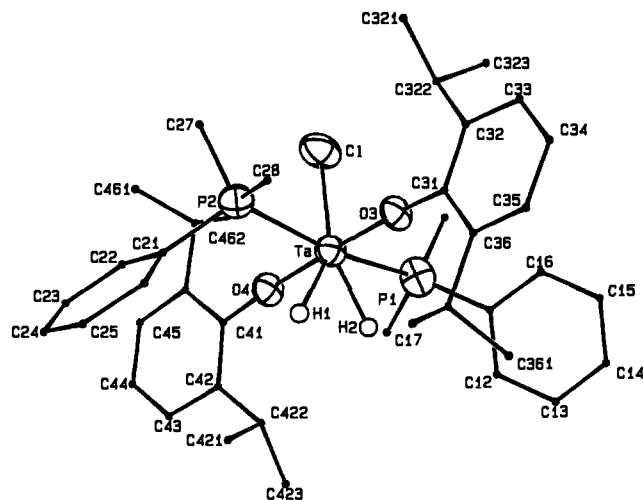


Figure 1. ORTEP view of **1b** emphasizing the central coordination sphere. Selected bond distances (Å) and angles (deg): Ta-O(3), 1.899 (5); Ta-O(4), 1.900 (5); Ta-P(1), 2.616 (3); Ta-P(2), 2.617 (3); Ta-Cl, 2.532 (2); Ta-H(1), 1.90 (9); Ta-H(2), 1.76 (7); O(3)-Ta-O(4), 178.6 (2); P(1)-Ta-P(2), 168.86 (8); P(1)-Ta-O(3), 90.1 (2); P(2)-Ta-O(4), 90.9 (2); Cl-Ta-P(1), 84.03 (9); Cl-Ta-O(4), 90.2 (2); H(1)-Ta-H(2), 61 (3); H(1)-Ta-Cl, 152 (3); Ta-O(3)-C(31), 174.2 (5); Ta-O(4)-C(41), 171.4 (5).

(3a), PMePh₂ (3b)), contain 2,6-dicyclohexylphenoxide ligands formed by a stoichiometric hydrogenation of the substituent arene rings of the aryloxide ligands (Scheme I).¹² All of these new colorless or pale-yellow hydride compounds are obtained in high yield and can be readily recrystallized from hydrocarbon solvents.¹³ The dihydride and trihydride compounds **1b** and **3a** were subjected to single-crystal X-ray diffraction analysis, and in both cases the hydride ligands were located and refined.¹³ It can be seen (Figures 1 and 2) that both structures are best described as pentagonal bipyramidal with trans-axial aryloxide groups. In dihydride **1b** the two hydride groups are mutually cis and each one is also cis to a PMe₂Ph ligand. In **3a**, the new 2,6-dicyclohexylphenoxide ligands are clearly evident (Figure 2). Furthermore, the trihydride and dihydride compounds are closely related with the third hydride in **3a** occupying a similar position to the chloride group in **1b**.

The ¹H NMR spectra of these seven-coordinate hydride compounds are highly informative.¹³⁻¹⁴ In most cases nonequivalent Pr' (1 and 2) or cyclohexyl (3) groups are seen due to restricted rotation about the Ta-O-Ar bonds. Furthermore, the Ta-H groups are found to resonate at low field, typically in the +12- to +18-ppm region.¹⁴ For the dihydride compounds **1a-c** the resonance for the two chemically equivalent hydride ligands appears as a complex multiplet. Analysis and simulation of the multiplet as an AA'XX' system yields all four coupling constants, including the ¹H-¹H coupling constant of 7 Hz.^{6,7} This value

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(13) Details of microanalytical data for all compounds and X-ray data for **1b** and **3a** can be found in the supplementary material.

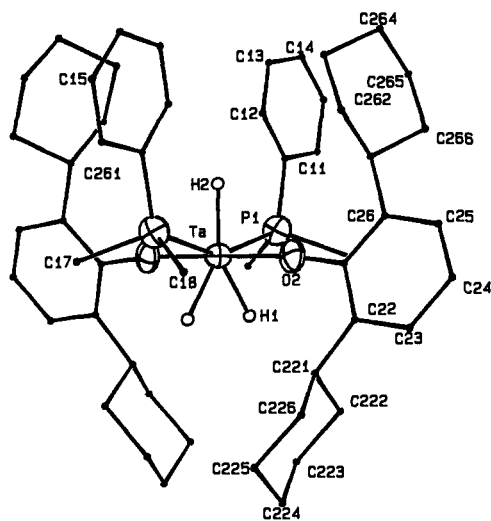


Figure 2. ORTEP view of **3a** emphasizing the central coordination sphere. Selected bond distances (Å) and angles (deg): Ta-O(2), 1.901 (6); Ta-P(1), 2.615 (3); Ta-H(1), 1.77 (9); Ta-H(2), 1.6 (2); O(2)-Ta-O(2), 179.2 (5); P(1)-Ta-P(1), 155.0 (1); P(1)-Ta-O(2), 89.0 (2), 91.2 (2); H(1)-Ta-H(1), 75 (5); H(1)-Ta-H(2), 143 (3); Ta-O(2)-C(21), 172.1 (8).

combined with the structural and infrared data unequivocally rule out the presence of an η^2 -H₂ group in **1**.⁵⁻⁷ The ¹H NMR spectra of the trihydride compounds (**2** and **3**) clearly resolve different multiplets in the ratio of 2:1 for the chemically nonequivalent hydride groups.¹⁴ Although the unique hydride appears as a triplet of triplets, the remaining two hydrides are a complex pattern. The NMR spectroscopic data for all of the compounds show that exchange of the two chemically equivalent, *cis* hydride ligands is slow on the NMR time scale.^{15,16}

Solutions of the trihydride compound (**3a**) in cyclohexane will carry out the catalytic hydrogenation of naphthalene to tetralin. Preliminary studies of this reactivity show a lack of pressure dependence above 300 psi of H₂, while at lower pressures the conversion rate decreases.¹⁷ Furthermore the reaction is inhibited by addition of an extra equivalent of PMe₂Ph to the reaction mixture. Further mechanistic studies of this and of other reactivity of these new hydride compounds are underway.

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Supplementary Material Available: Microanalytical and full spectroscopic data for the new compounds, full details of the crystallographic studies, and tables of fractional coordinates, anisotropic thermal parameters, and full bond distances and angles (41 pages); tables of observed and calculated structure factors for **1b** and **3b** (26 pages). Order information is given on any current masthead page.

(14) Selected ¹H NMR data (200 MHz; C₆D₆): (**1a**) δ 15.89 (m, 2 H, Ta-H); ²J(P-H) = 65.8 Hz, ²J(P'-H) = 7.0 Hz, ²J(H-H) = -7.4 Hz, ²J(P-P) = 163.6 Hz. (**1b**) δ 16.55 (m, 2 H, Ta-H); ²J(P-H) = 64.4 Hz, ²J(P'-H) = 7.2 Hz, ²J(H-H) = -7.9 Hz, ²J(P-P) = 159.0 Hz. (**1c**) δ 17.77 (m, 2 H, Ta-H); ²J(P-H) = 65.0 Hz, ²J(P'-H) = 7.0 Hz, ²J(H-H) = -6.2 Hz, ²J(P-P) = 156.7 Hz. (**2**) δ 13.54 (m, 2 H); δ 12.80 (tt, 1 H), ²J(P-H) = 36.4 Hz, ²J(H-H) = 5.5 Hz. (**3a**) δ 13.60 (m, 2 H, Ta-H), δ 12.98 (tt, 1 H, Ta-H); ²J(P-H) = 34.0 Hz, ²J(H-H) = 5.6 Hz. (**3b**) δ 13.52 (m, 2 H, Ta-H), δ 13.34 (m, 1 H, Ta-H).

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(17) A typical experiment utilized 0.10 mmol of (OAr)₂Ta(H)₃(PMe₂Ph)₂ (**3a**) and 2.0 mmol of naphthalene in 3.0 mL of cyclohexane and was run unstirred in a Parr series 4561 minireactor. After 24 h at 90 °C/1200 psi of H₂, analysis of the reaction mixture by ¹H NMR spectroscopy showed 61% conversion to tetralin with <95% of the original trihydride compound still present.

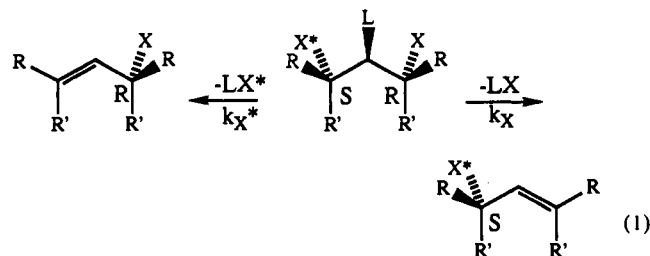
General Method for Determining Kinetic Isotope Effects That Utilizes Isotopically Engendered Chirality

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Kinetic isotope effects (KIE) are particularly useful in deducing transition-state characteristics in a variety of chemical transformations. Such measurements have typically involved inter- and intramolecular competitive rate studies of isotopically labeled substrates or mass spectral analysis of reaction products to determine the isotope distribution. We now introduce a method based on the relative rates of the formation of "nominal enantiomers" from a single chiral precursor that contains two isotopes of the same element. The method can be applied to reactions in which a molecule with a plane of symmetry gives, under normal conditions, a racemic mixture. If the plane of symmetry is removed by stereospecific isotopic substitution, then the ratio of an enantiomer to its isotopically labeled optical antipode in the product arises directly from the kinetic isotope effect. In any system the rates of reaction of enantiotopic atoms (X) are identical. However, this degeneracy of rates can be removed by an isotopic substitution (X*), and preferential reaction involving X or X* will, in principle, lead to an excess of one stereoisomer. The measurement of the optical purity of the starting material and the product can then be used to determine the ratio of rate constants k_X/k_{X^*} (eq 1). Strictly speaking, the reaction does not produce two enantiomers. Although the primary chiral units will be of opposite absolute configuration, one of the stereoisomers will be isotopically labeled. The chirality at C₃, as a result of isotopic substitution (X*), should have a negligible effect upon the optical rotation of the final product.



To formulate an equation in which the k_H/k_D is determined from optical purity, the definition of enantiomeric excess (ee) can be used to derive an expression for the KIE utilizing initial (ee_i) and final (ee_f) optical purities.

$$ee = \frac{\text{atoms of } R - \text{atoms of } S}{\text{atoms of } R + \text{atoms of } S} = \frac{k_H - k_D}{k_H + k_D} \text{ and } \frac{k_H}{k_D} = \frac{ee_i - ee_f}{ee_i + ee_f} = \frac{([\alpha]^{25}_i - [\alpha]^{25}_f)}{([\alpha]^{25}_i + [\alpha]^{25}_f)}$$

The validity of this method has been demonstrated by applying it to the enantiomeric selectivity in the formation of the chiral alkene (*E*)-cyclooctene (**1**). The highly strained (*E*)-cyclooctene (**1**) is formed by a suprafacial (*syn*) mode of elimination from **2** (eq 2) irrespective of the base-solvent system employed.^{1a,b,c} With strong bases such as RLi,^{1b} CH₃SOCH₂-Na⁺ in DMSO,^{1e} or KNH₂,^{1a} the elimination proceeds through an α,β (ylide) mechanism while an E2 pathway has been established for the

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