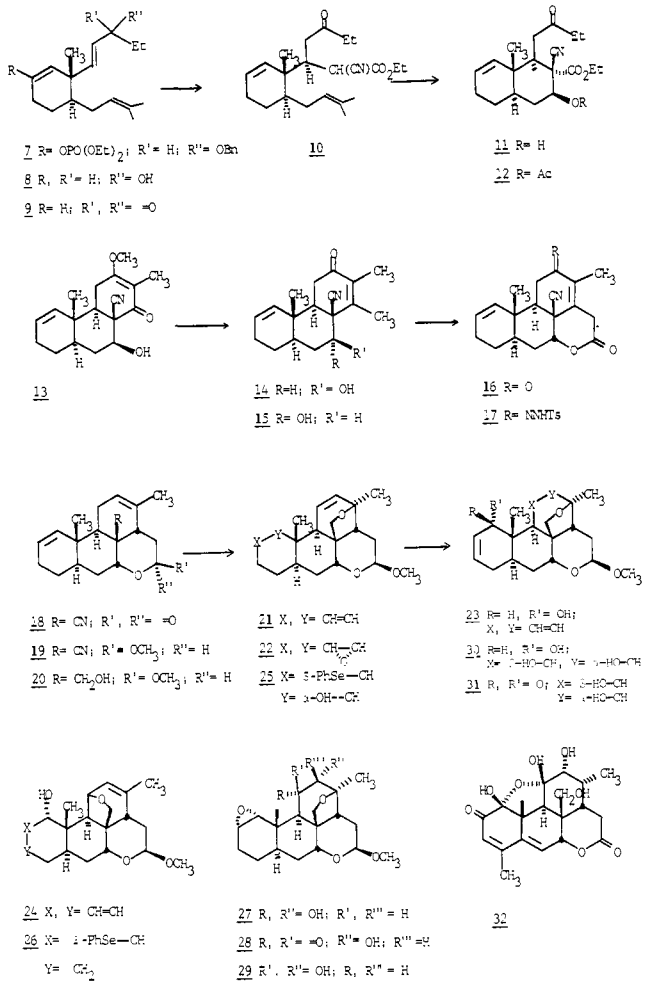
Scheme I



perature, 10 min) led to ketone **13** after enol etherification [$HC(OCH_3)_3$, *p*-TsOH, room temperature; 83% from **10**].

Methyllithium addition–hydrolysis converted **13** to **14**. This enone was epimerized upon Jones oxidation, DIBAL reduction, and MnO_2 reoxidation to furnish **15** (52% overall from **13**). Besides the establishment of the axial C9 configuration in both **14** and **15** from C9–C11 coupling constants, 300-MHz ^1H NMR spectroscopy also verified the C7 stereochemical assignments, since the axial C7 hydroxyl in **15** caused a 0.3 ppm downfield shift in its C9 hydrogen resonance (relative to **14**). Treatment of **15** with 1,1′-carbonyldiimidazole (THF, reflux) then with KH (12 equiv, room temperature) afforded tetracyclic lactone **16**, mp 242–244 °C, in over 90% yield.

Hydride reagents reduced the C12 ketone of **16** stereoselectively from the less hindered α-face. This preference was exploited to establish the correct configuration at C14 and complete the pentacyclic system. Thus, tosylhydrazone **17** underwent reductive rearrangement ($NaBH_3CN$–HOAc, 68 °C)[9] to a single diene **18** (55% from **16**). By stepwise DIBAL reductions, cyanolactone **18** furnished acetal **19** then alcohol **20**. Selenocyclization of **20** (PhSeCl, CH_2Cl_2, 3 h)[10] followed by oxidative elimination of PhSeOH furnished diene **21** in 62% yield. Long-range W coupling between the C12 and C14 hydrogens in **21** verified the diaxial fusion of ring D to the carbocyclic system.

Regio- and stereoselective monoepoxidation of **21** furnished **22**, which rearranged to allylic alcohol **23** with *n*-butyllithium or lithium diisopropylamide (LDA). Upon standing at room temperature or during prolonged exposure to silica gel, **23** isomerized completely to the pentacyclic structure **24**. While diene **21** showed no tendency to rearrange, hydroxy selenide **25** also isomerized quantitatively to C11-bridged **26**, thus implicating some anchimeric assistance by the C1 α-hydroxyl group. Such participation seems plausible in view of the recently reported quassinoid hemiketal karinolide **32**.[11] *With this serendipitous discovery, both structural classes of ring-C bridging ethers now become synthetically accessible.* Progress toward the synthesis of a fully functionalized C13-bridged quassinoid is documented below.

Osmylation of alkene **22** furnished *cis*-diol **27** (62%), which was further oxidized selectively to hydroxy ketone **28** by using pyridinium dichromate.[12] In keeping with the model study published by Fuchs,[13] **28** could be reduced by using Bu_4NBH_4 (4 equiv, EtOAc, room temperature, 7 h) to afford crystalline trans-diaxial diol **29** exclusively (40% from **27**). Epoxide **29** was smoothly isomerized (PhSeNa, H_2O_2) to **30**. Selective oxidation of the allylic hydroxyl produced enone **31**, a potentially bioactive quassinoid whose pharmacological properties are presently under investigation.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for generous financial assistance. Support of the Cornell Nuclear Magnetic Resonance Facility by the National Science Foundation (CHE 7904825; PCM 8018643) is gratefully acknowledged.

Registry No. **7**, 89827-65-6; **8**, 89827-66-7; (±)-**9**, 89827-67-8; **10**, 89827-68-9; (±)-**11**, 89827-69-0; (±)-**13**, 89827-70-3; (±)-**14**, 89827-71-4; (±)-**15**, 89827-72-5; (±)-**16**, 89827-73-6; (±)-**17**, 89848-04-4; (±)-**18**, 89827-74-7; (±)-**20**, 89827-75-8; (±)-**21**, 89827-76-9; (±)-**22**, 89827-77-0; (±)-**23**, 89827-79-2; (±)-**24**, 89848-05-5; (±)-**25**, 89827-78-1; (±)-**26**, 89848-06-6; (±)-**27**, 89827-82-7; (±)-**28**, 89827-83-8; (±)-**29**, 89827-84-9; (±)-**30**, 89827-80-5; (±)-**31**, 89827-81-6; ethyl cyanoacetate, 105-56-6.

Supplementary Material Available: Physical properties, NMR (^1H and ^{13}C), and IR data of all new compounds described (7 pages). Ordering information is given on any current masthead page.

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(10) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784.

(11) Polonsky, J.; Gallas, J.; Varenne, J.; Prange, T.; Pascard, C.; Jacquemin, H.; Moretti, C. *Tetrahedron Lett.* **1982**, *23*, 869.

(12) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(13) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216.

(*E*)-β-(Fluoromethylene)-*m*-tyrosine: A Substrate for Aromatic L-Amino Acid Decarboxylase Liberating an Enzyme-Activated Irreversible Inhibitor of Monoamine Oxidase

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The concept of enzyme-activated irreversible inhibition has proven to be extremely fruitful for the design of highly specific inhibitors of selected target enzymes.[1] For the therapeutic application of enzyme inhibitors, however, it is often desirable to achieve site specificity in addition to target enzyme specificity. An example where such dual specificity would be advantageous is the inhibition of monoamine oxidase[2] (MAO; EC 1.4.3.4). Although inhibitors of MAO[3] are effective antidepressants,[2a] their

(1) Seiler, N.; Jung, M. J.; Koch-Weser, J. "Enzyme-Activated Irreversible Inhibitors"; Elsevier/North-Holland Biomedical Press: Amsterdam, 1978.

(2) (a) Gilman, A. G.; Goodman, L. S.; Gilman, A. "The Pharmacological Basis of Therapeutics", 6th ed.; Macmillan: New York, 6th Edition, 1980; pp 427–430. (b) Folks, D. G. *J. Clin. Psychopharmacol.* **1983**, *3*, 249–252.

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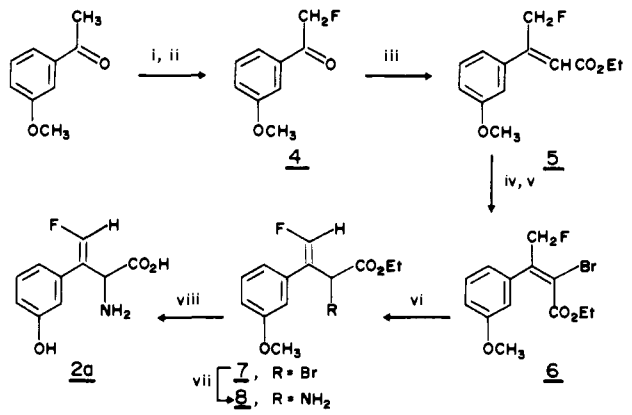
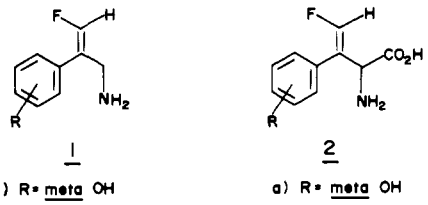
Scheme I[a]



[a] (i) Br_2, $CHCl_3$, 0 °C, 3 h, 88% yield; (ii) KHF_2, triethylene glycol, 100 °C, 3 h, 54% yield; (iii) triethyl phosphonoacetate, NaH, toluene, <15 °C, 30 min, 80% yield; (iv) Br_2, CCl_4, −5 °C, 3 h; (v) piperidine, ether, 5 °C, 2½ h; (vi) (a) LDA, −78 °C, 30 min; (b) H^+, −78 to 0 °C; (vii) (a) NH_3, Me_2SO, room temperature, 2½ h; (b) HCl, 20% overall yield from 5; (viii) (a) aqueous HBr, reflux, 4 h; (b) propylene oxide, CH_3OH, room temperature, 3 h, 86% yield.

use has been limited by adverse side effects,[2b] some of which could be expected to be greatly reduced if enzyme inhibition could be restricted to aminergic neurons and, particularly, to those located in the brain.[4a,b] We recently reported[5] that ring-substituted (*E*)-2-phenyl-3-fluoroallylamine derivatives (**1**) are potent enzyme-activated irreversible inhibitors of MAO. As the structures of **1** are closely related to phenethylamines, we envisaged the possibility of generating **1** from the corresponding α-amino acids **2** through the action of aromatic L-amino acid decarboxylase (AADC; EC 4.1.1.28), an enzyme predominantly located in monoamine nerves.



The success of this approach depends on the ability of **2** to serve as a substrate[6] for AADC and of the corresponding allylamine **1** to inhibit MAO. With these considerations in mind and since *m*-tyrosine is a good substrate for mammalian AADC,[7] we have prepared (*E*)-β-(fluoromethylene)-*m*-tyrosine (**2a**) and the allylamine **1a**. The synthesis of **1a**[8] (HCl mp 142–143 °C) from (*m*-methoxyphenyl)acetic acid followed the published procedure.[5,9] (*E*)-β-(Fluoromethylene)-*m*-tyrosine (**2a**) was prepared according to Scheme I. **5**[8] was obtained as a mixture of isomers (*Z*/*E* = 8/1; bp 112–116 °C/0.25 mm) from α-fluoro-3-methoxyacetophenone[8] (**4**; mp 53–54 °C). Bromination of **5** followed by dehydrobromination and deconjugation gave essentially the *E* bromide **7**,[8] which was converted to the amine **8**[8,11] (HCl, mp 141–142 °C) using ammonia in dimethyl sulfoxide.[10] Deprotection yielded **2**[8] as a colorless powder (mp 214–215 °C).

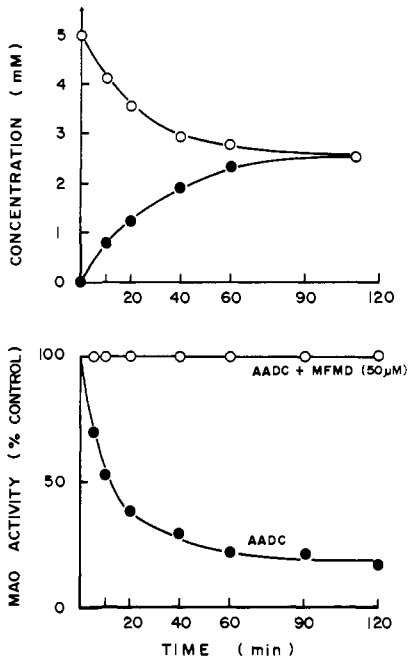


Figure 1. **2a** (5 mM) was incubated at 37 °C with AADC (25 μL; specific activity with L-Dopa as substrate was 5148 (nmole/min)/mL) in phosphate buffer (0.1 M, pH 7.2; 4 mL) containing pyridoxal phosphate (4 mM) and mercaptoethanol (7.9 mM) in the presence or absence of (DL)-α-(monofluoromethyl)dopa (MFMD, 50 μM). At various intervals, aliquots (20 μL) were treated with 0.05 M $HClO_4$ (980 μL) and assayed for **1a** (●) and **2a** (○) by HPLC[13] (upper part of figure). Different aliquots (20 μL) were diluted with phosphate buffer (0.1 M, pH 7.2; 5 mL) containing MFMD (50 μM), then a portion (25 μL) of this solution was added to phosphate buffer (2 mL) containing [^{14}C]-tyramine (1 μCi), MFMD (50 μM), and rat brain mitochondrial preparation (1 mL) and assayed for MAO activity[15] (lower part of Figure).

Incubation of an MAO preparation[5] from rat brain for varying time periods with different concentrations of **1a** resulted in a time-dependent and irreversible loss of enzyme activity, which followed pseudo-first-order kinetics for more than two half-lives. When the remaining MAO activity was measured with either serotonin (a preferred type A substrate) or phenethylamine (type B), a several-fold preference for inactivation of the A form was observed ($t_{1/2}$ = 3 min at 5 × 10^{-8} M, type A, and $t_{1/2}$ = 7.5 min at 7.5 × 10^{-7} M, type B).

Upon incubation with partially purified hog kidney AADC,[12] racemic **2a** was smoothly consumed to give the amine **1a** (Figure 1). The formation of **1a** and the disappearance of **2a** was conveniently monitored by HPLC.[13] The reaction stopped when 50% of **2a** had been decarboxylated, which is consistent with the stereochemical selectivity of AADC. If the incubation was run in

(3) MAO exists in two forms, designated MAO A and MAO B, which differ in their substrate specificity, their sensitivity to inhibitors, and their cellular localization. For a review, see: Tipton, K. F.; Houslay, M. D.; Mantle, T. J. *Ciba Found. Symp.* **1976**, *39*, 5–31.

(4) (a) Murphy, D. L.; Cohen, R. M.; Siever, L. J.; Roy, B.; Karoum, F.; Wyatt, R. J.; Garrick, N. A.; Linnoila, M. *Mod. Probl. Pharmacopsychiatry* **1983**, *19*, 287–303. (b) Youdim, M. B. H.; Finberg, J. P. M. *Ibid.* **1983**, *19*, 63–74.

(5) Bey, P.; Fozard, J.; Lacoste, J. M.; McDonald, I. A.; Zreika, M.; Palfreyman, M. G. *J. Med. Chem.* **1984**, *27*, 9–10.

(6) From the outset we were aware, based on the mechanism of action of AADC, that **2a** could be a potential enzyme-activated inhibitor of AADC. See, for example, ref 10.

(7) (a) Lancaster, G. A.; Sourkes, T. L. *Can. J. Biochem.* **1972**, *50*, 791–797. (b) Boulton, A. A.; Juorio, A. V. *Experentia* **1983**, *39*, 130–134.

(8) All new compounds were fully characterized by NMR and elemental analysis.

(9) The removal of the methoxyl group from (*E*)-1-fluoro-2-(3-methoxyphenyl)-3-phthalimidopropene was achieved with 3.3 equiv of BBr_3 in CH_2Cl_2 at −75 to 20 °C.

(10) Chari, R. V. J.; Wemple, J. *Tetrahedron Lett.* **1979**, 111–114.

(11) The *E* stereochemistry was established by X-ray structural analysis kindly undertaken by Professor R. Weiss at the Laboratoire de Cristallochimie, Institut Le Bel, Université Louis Pasteur, Strasbourg, France.

(12) We thank Dr. M. Jung for providing the AADC, which was purified according to the procedure of: Ribereau-Gayon, G.; Danzin, C.; Palfreyman, M. G.; Aubry, M.; Wagner, J.; Metcalf, B. W.; Jung, M. J. *Biochem. Pharmacol.* **1979**, *28*, 1331–1335.

(13) HPLC analysis: μBondapack C_{18} column (30 cm × 3.9 mm); 10-μm particle size; UV detection (254 or 280 nm); linear gradient elution (0.1 M, NaH_2PO_4/CH_3CN, from ratio 94/6 (v/v; pH 2.50) to 74/26 (v/v; pH 3.05) over 30 min); octanesulfonic acid (8 mM) as the ion-pairing agent in the eluant, flow rate, 1.5 mL/min; 40 °C. Retention times were 7.5 and 19.0 min for **2a** and **1a**, respectively. The identity of **1a** was confirmed by GC/MS (*O*,*N*-trifluoroacetate).

the presence of (DL)-α-(monofluoromethyl)dopa (50 μM), a potent enzyme-activated irreversible inhibitor of AADC,[14] formation of **1a** from **2a** was completely blocked. In addition, incubation of an MAO preparation with aliquots from the solution containing AADC and **2a** resulted in an inhibition of MAO activity that increased with the amount of conversion of **2a** into **1a**. No MAO inhibition occurred when AADC was omitted from the incubation medium nor when both AADC and (DL)-α-(monofluoromethyl)dopa were added together, indicating that **2a** is not an inhibitor of MAO per se but must be decarboxylated to **1a** before inhibition takes place. A comparison of the V_{max} values for **2a** and L-Dopa, a natural substrate of AADC, showed that the rate of decarboxylation of **2a** by AADC was approximately 65% of that of L-Dopa.

In conclusion, **2a** is the first example of an enzyme-activated irreversible inhibitor of MAO requiring activation by AADC.[16] This approach to enzyme inhibition, relying on a biosynthetic enzyme of a given metabolic pathway to generate in situ an enzyme-activated inhibitor of a catabolic enzyme in the same pathway, undoubtedly adds a new dimension of site selectivity to target enzyme specificity.[17]

Supplementary Material Available: X-ray experimental section and tables of positional and thermal parameters, temperature factors, and crystal structure data (10 pages). Ordering information is given on any current masthead page.

(14) (a) Jung, M. J.; Palfreyman, M. G.; Wagner, J.; Bey, P.; Ribereau-Gayon, G.; Zraika, M.; Koch-Weser, J. *Life Sci.* **1979**, *24*, 1037-1042. (b) Maycock, A. L.; Aster, S. D.; Patchett, A. A. *Biochemistry* **1980**, *19*, 709-718.
(15) Christmas, A. J.; Coulson, C. J.; Maxwell, D. R.; Riddel, D. *Br. J. Pharmacol.* **1972**, *45*, 490-503.
(16) In rats, **2a** (0.5 mg/kg given orally) inhibits brain MAO A and B by 63% and 34%, respectively. The amine **1a** at 0.25 mg/kg does not affect brain MAO activity.
(17) A similar dual enzyme-activated approach leading to site-selective inhibition of AADC has recently been reported by: Jung, M.; Hornsperger, J. M.; Gerhart, F.; Wagner, J. *Biochem. Pharmacol.* **1984**, *33*, 327-330.

Transformation of a Tungstenacyclobutadiene Complex into a Nonfluxional η^3-Cyclopropenyl Complex by Addition of a Donor Ligand. The X-ray Structure of $W(\eta^5\text{-}C_5H_5)[C_3(CMe_3)_2Me](PMe_3)Cl_2$

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We have reported recently that tungstenacyclobutadiene complexes are formed when internal acetylenes react with tungsten alkylidyne complexes. In trigonal-bipyramidal $W[C(CMe_3)C(Me)C(Me)]Cl_3$[1] (and two other trigonal-bipyramidal complexes[2]) the symmetric WC_3 ring is found in the equatorial plane. In $W(\eta^5\text{-}C_5H_5)[C(Ph)C(CMe_3)C(Ph)]Cl_2$,[3] however, the tungstenacyclobutadiene ring is bent and the bonds alternate (double–single–double–single) around the WC_3 ring. The bent WC_3 ring could be regarded as being halfway between a planar WC_3 ring and a WC_3 tetrahedron. Here we show that a molecule containing the WC_3 tetrahedron forms when trimethylphosphine is added to what is probably a bent WC_3 ring in a complex analogous to $W(\eta^5\text{-}C_5H_5)[C(Ph)C(CMe_3)C(Ph)]Cl_2$. This finding has important implications for the mechanism of acetylene metathesis and of forming cyclopentadienyl complexes from tungstenacyclobutadiene complexes and acetylenes,[1,3] and also raises some fundamental questions concerning the nature of MC_3R_3 complexes containing a tetrahedral MC_3 core.

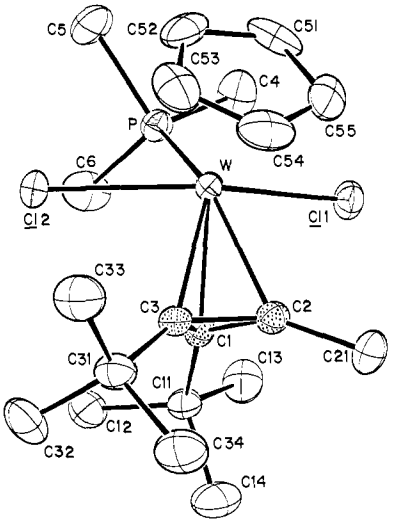

Figure 1. ORTEP II drawing of the structure of $W(\eta^5\text{-}C_5H_5)[C_3(CMe_3)Me](PMe_3)Cl_2$ (30% ellipsoids).

When $Me_3CC{\equiv}CMe$ is added to an ether solution of purple $W(\eta^5\text{-}C_5H_5)(CCMe_3)Cl_2$, a green complex with the formula $W(\eta^5\text{-}C_5H_5)(CCMe_3)(Me_3CC{\equiv}CMe)Cl_2$ is formed.[4] This molecule appears to be a bent tungstenacyclobutadiene complex analogous to $W(\eta^5\text{-}C_5H_5)[C(Ph)C(CMe_3)C(Ph)]Cl_2$[3] on the basis of observing only one type of *tert*-butyl group by ^1H and ^{13}C NMR and a broad peak at ~202 ppm for the ring carbon atoms. We have proposed that such "bent" tungstenacycles are rearranging on the NMR time scale.[3] When PMe_3 is added to $W(\eta^5\text{-}C_5H_5)[C_2(CMe_3)_2CMe]Cl_2$ a red crystalline "monoadduct" is formed in which the two *tert*-butyl groups are inequivalent, and all three "ring" carbon atoms are inequivalent (88.59, 64.30, and 56.65 ppm) and coupled to phosphorus by 9.8, ~2, and ~0 Hz, respectively. Large red cubes grown slowly from pentane at ~−30 °C over a period of ~2 weeks were used for an X-ray study.[5]

The molecular geometry of the complex is illustrated in Figure 1. It is approximately a "four-legged piano stool" with the C_3 ring taking up the position trans to the PMe_3 ligand. The two tungsten–chloride distances (W–Cl(1) = 2.538 (2) and W–Cl(2) = 2.504 (2) Å) and the tungsten–phosphorus distance (W–P = 2.600 (2) Å) are normal. Individual W–C distances to the C_5 ring range from 2.334 (8) to 2.373 (9) Å, C–C distances within the C_5 ring range from 1.359 (12) to 1.408 (11) Å, and the W–C_5 ring centroid distance is 2.046 Å; all are unexceptional. The three carbon atoms of the C_3 ring are nearly equidistant from the metal [W–C(1) = 2.139 (5), W–C(2) = 2.150 (6), W–C(3) = 2.200 (6) Å]. Since the C(2)–C(3) bond roughly parallels the Cl-

(1) Pedersen, S. F.; Schrock, R. R.; Churchill, M. R.; Wasserman, H. J. *J. Am. Chem. Soc.* **1982**, *104*, 6808.
(2) The X-ray structures of $W(C_3Et_3)[O\text{-}2,6\text{-}C_6H_3(i\text{-}Pr)_2]_3$ and $W(C_3Et_3)[OCH(CF_3)_2]_3$ are similar to that of $W[C(CMe_3)C(Me)C(Me)]Cl_3$.[1] Full details in press.
(3) Churchill, M. R.; Ziller, J. W.; McCullough, L.; Pedersen, S. F.; Schrock, R. R. *Oganometallics* **1983**, *2*, 1046.
(4) Anal. Calcd for $WC_{17}H_{26}Cl_2$: C, 42.09; H, 5.40. Found: C, 41.75; H, 5.46.
(5) The complex crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ with a = 10.302 (3) Å, b = 15.314 (3) Å, c = 14.130 (2) Å, β = 98.036 (16)°, V = 2207.4 (8) Å^3, and D(calcd) = 1.69 g cm^{-3} for Z = 4 and M_r = 561.28. There is no crystallographic symmetry imposed upon the molecule. Diffraction data were collected on a Syntex $P2_1$ automated four-circle diffractometer via a coupled θ(crystal)–2θ(counter) scan technique[6] and were corrected for the effects of absorption (μ = 58.5 cm^{-1}). The structure was solved by a combination of Patterson, difference-Fourier, and least-squares refinement techniques; resulting discrepancy indices are R_F = 4.7% and R_{wF} = 3.4% for all 3913 unique data in the range 2θ = 4.5–50.0° (Mo Kα radiation) and R_F = 3.4% and R_{wF} = 3.2% for those 3290 data with $|F_o| > 3\sigma|F_o|$.
(6) Churchill, M. R.; Lashewycz, R. A.; Rotella, F. J. *Inorg. Chem.* **1977**, *16*, 265.

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