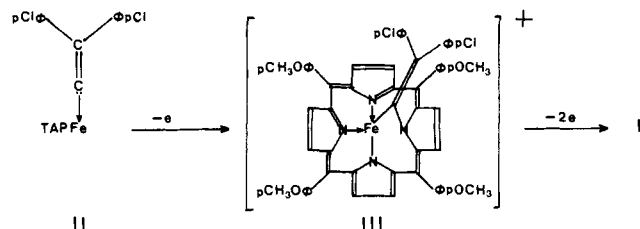


low-temperature spin-decoupling study performed to identify sets of coupled protons. Models indicate that the anisyl substituents at C10 and C20 (related by reflection in the σ plane) should be deshielded by the *p*-chlorophenyls. Interaction with the bridging group should also restrict rotation and resolve the *o*- and *m*-anisyl protons into nonequivalent sets above and below the porphyrin plane. Spin saturation transfer between protons of the two most deshielded anisyl quartets demonstrates rotational interchange of the protons which are above- and below-plane sets. Rotation is still hindered at ambient temperature (coalescence into a single quartet through rapid rotation on an NMR time scale is not observed from -70 to 25 °C). Hence, these quartets have been assigned to the C10 and C20 anisyls.

The C5 and C15 anisyl substituents are indistinguishable at 250 MHz, resulting in the two remaining anisyl quartets representing the ortho and meta protons on opposite faces of the porphyrin plane. Less hindered rotation than for the C10 and C20 anisyls would be expected and is evident in the NMR spectrum at 25 °C which indicates relatively rapid rotation on the NMR time scale (broadened resonances at δ 7.1 and 8.0 suggest a coalescence temperature slightly above 25 °C). The σ plane and the bridging vinylidene are confirmed by ^{13}C NMR, which shows three sp^3 carbon resonances for the anisyl methoxy groups (62.89 MHz, CD_2Cl_2 : δ 56.08, 56.13, and 56.25 are the only ^{13}C resonances with shifts <113 ppm) and two resonances (62.89 MHz, CDCl_3 : δ 160.7, 129.7) for the vinylidene carbons.

We propose the following scheme for the formation of I:



Preliminary optical and ESR spectra of III are consistent with the proposed structure.¹³ An analogous reaction of (carboethoxy)carbene and cobalt(II) octaethylporphyrin has been reported^{25,26} to occur through an intermediate similar to the proposed intermediate III in which the carbene has inserted into a cobalt-pyrrole bond. Compound III, unlike the cobalt complex, cannot disproportionate to the cis-bridged porphyrin by a redox pathway but requires an additional two-electron oxidation; so stability of III in the absence of excess oxidant is expected.

The proposed reaction scheme is without precedent in porphyratoiron chemistry; however, a compound obtained by reversible one-electron oxidation¹² of the [2,2-bis(*p*-chlorophenyl)-vinylidene]carbene complex of tetraphenylporphyratoiron is more likely to have structure III than the suggested iron(IV) ylide. A footnote in ref 12 reports that further irreversible oxidation yields an unidentified compound, having an optical spectrum identical with the tetraphenylporphyrin analogue of I. Reference 12 is entirely consistent with our proposed reaction scheme.

P-450-carbene complexes are strongly implicated in both oxidative and reductive metabolism of compounds known to inactivate P-450. A mechanism such as the proposed scheme may be operative in the inactivation of the enzyme. An intermediate similar to III could explain the observation⁸ that P-450 substrates with terminal unsaturation are the only efficient suicide inactivators which produce iron-free N-alkylated porphyrin derivatives.

Acknowledgment. This work was supported by PHS Grant 1R01-CA 28622-01 and American Cancer Society Institutional Grant 1N 15U. We are grateful to Professor M. Brookhart for helpful discussions.

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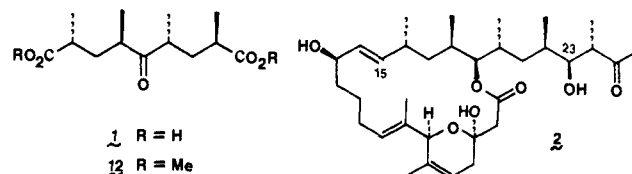
Symmetry in Synthesis. Preparation and Methylation of Spiro Dilactones

Thomas R. Hoye,* David R. Peck,¹ and Peter K. Trumper

Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455

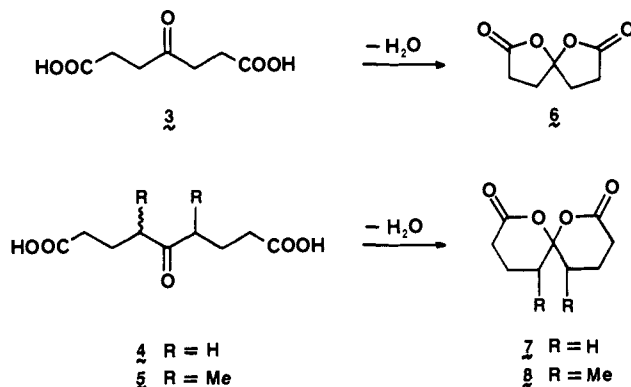
Received June 1, 1981

Increase in molecular complexity by simultaneous reaction at two or more symmetrically and, therefore, functionally equivalent sites is a potentially powerful and relatively unexplored synthetic concept. We describe here an efficient, highly stereoselective scheme for the construction of a single diastereomer of the keto diacid **1**, a molecule whose every other carbon atom is chiral, which utilizes this notion in a sequential fashion. The structural similarity between **1** and the C₁₅-C₂₃ fragment of the aglycon (**2**)² of the



venturicidinmacrolide antibiotics catalyzed this investigation. The chemistry of spiro dilactones plays an important role in this study.

Keto diacids **3**³ and **4**⁴ were prepared by known procedures. The dimethyl keto diacids **5** were synthesized as a nearly 1:1 mixture of meso and *d,l* isomers by twofold Michael reaction⁵ of the pyrrolidine enamine of 3-pentanone with 3 equiv of methyl acrylate followed by acidic hydrolysis of the enamine [77% yield of keto diesters,^{6a} bp 142 – 144 °C (1.25 torr)] and saponification (95% of mixture, mp of *d,l*-**5**^{6a,7} 86 – 89 °C). Dehydration of **3** by dissolution in neat acetyl chloride at room temperature was accompanied by vigorous gas evolution and provided the known,⁸ racemic spiro[4.4]dibutyrolactone (**6**). Similar treatment of **4**



gave the spiro[5.5]divalero lactone **7** (66%, mp 143 – 144 °C)^{6a} as the major of several products.⁹ Brief exposure of the $\sim 1:1$

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(3) (a) Micheel, F.; Flitsch, W. *Chem. Ber.* **1955**, *88*, 509. (b) Rajagopalan, S.; Raman, P. V. A. *Org. Synth. Collect. Vol. III* **1953**, 425.

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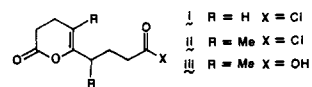
(5) Stock, G.; Brizzolara, A.; Landesman, H.; Szmuszko, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(6) This compound was fully characterized spectroscopically. The molecular composition was confirmed by (a) elemental analysis or (b) high-resolution mass spectrometry. Yields refer to isolated and purified material.

(7) Pure *d,l*-**5** was obtained by fractional crystallization of a diastereomeric mixture of **5** and correlated with the keto diacid arising from hydrolysis of **8a**.

(8) Volhard, J. *Liebigs Ann. Chem.* **1889**, 253, 206.

(9) Included among these undesired products was the enol lactone acid chloride i.



mixture of diastereomers **5** to AcCl gave two of the three possible diastereomeric γ,γ' -dimethyl dilactones (**8**) in very low yield but equal portion.¹⁰ From ¹H and ¹³C NMR analysis the less polar ($R_f = 0.27$, 1:1 hexanes-EtOAc) of these isomers possessed C_2 symmetry and the more polar ($R_f = 0.19$) did not. The former presumably was derived from *d,l*-**5** and the latter, which must have the relative stereochemistry shown in **8b** (mp 80–83 °C),^{6b} from *meso*-**5**. A more efficient preparation of **8** involved acid-catalyzed, azeotropic removal of water with benzene in which case a single, crystalline (mp 107–110 °C) dilactone, identical with the symmetric isomer described above, was isolated in ~50% yield after sublimation.^{6a,11} We assumed that this thermodynamically preferred isomer would adopt a conformation in which each noncarbonyl oxygen would occupy, for anomeric-like reasons,¹² a pseudoaxial orientation and that the γ - and γ' -methyl groups would each orient themselves equatorially to the flattened chair conformation of the valerolactone ring to which they were attached (see **8a–c**).^{13,14} Thus, structure **8a** in preference to **8c** was tentatively assigned to the readily accessible¹¹ γ,γ' -dimethyl dilactone.

The stereochemical relationship of the γ - and γ' -methyl groups in **8a** (or **8c**) was proper for a synthesis of the target keto diacid **1**. What remained was the stereocontrolled introduction of two additional methyl units α to each lactone carbonyl. Attempted formation and alkylation of the bis-enolate anion of the base-sensitive⁸ dibutylolactone **6** (2.2 equiv of LDA, THF, -70 °C, 1 h; 3 equiv of MeI, THF, with or without HMPA, -70 °C to room temperature) resulted in complete destruction of the dilactone functionality. Analogous treatment of the divalerylolactone **7** provided a ~2:1 mixture of two, readily separable, diastereomeric, crystalline α,α' -dimethyl dilactones. One isomer had C_2 symmetry; later comparison with **11a** (vide infra) suggested it to be **9a** (~25%, mp 87–89 °C)^{6a} rather than **9c**. The second isomer lacked symmetry; it is, necessarily, **9b** (~17%, mp 87–88 °C).^{6a} In addition, minor amounts of monomethyl dilactones **10a** (~2%, mp 132–136 °C)^{6b} and **10b** (~2%, mp 79–81 °C)^{6b} were isolated from one alkylation experiment. The ratios of **9a** to **9b** and **10a** to **10b** may reflect an initial competitive axial vs. equatorial methylation of the dianion of **7**. If so, this would suggest that conformational rigidity alone (i.e., in the absence of additional substituents) in the spiro[5.5]dilactone bis-enolate anion is insufficient to impart high stereoselectivity in the alkylation reaction.

In contrast and to our delight, bis-methylation of the γ,γ' -dimethyldivalerylolactone of C_2 symmetry, presumed to be **8a**, provided one major $\alpha,\alpha',\gamma,\gamma'$ -tetramethyldivalerylolactone which also possessed a C_2 axis (58%, mp 114–115 °C).^{6a,b,15} This material was therefore either **11a** or **11c**. ¹H NMR analysis suggested¹⁶ the former structure, but in order to verify many of

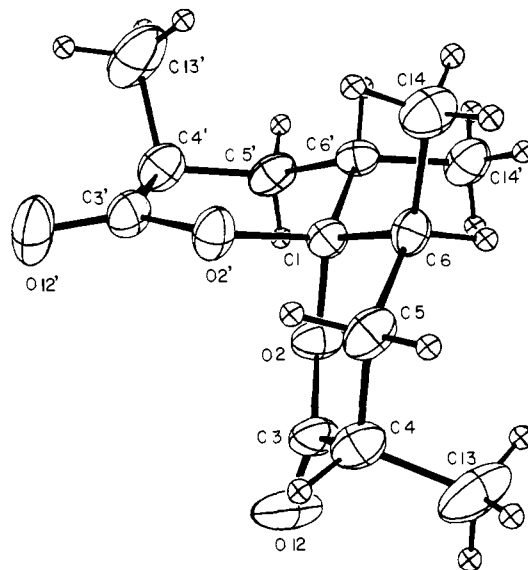


Figure 1. ORTEP drawing of **11a** from the perspective of **8–11**.

the assumptions involved in the structure assignments in all of the compounds **8–11**, a single-crystal X-ray diffraction analysis was performed.¹⁷ The result is indicated by the ORTEP drawing

	γ				α				C_2 sym
	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	
8a	H	Me	Me	H	H	H	H	H	yes
8b	Me	H	Me	H	H	H	H	H	no
8c	Me	H	H	Me	H	H	H	H	yes
9a	H	H	H	H	H	Me	Me	H	yes
9b	H	H	H	H	Me	H	Me	H	no
9c	H	H	H	H	Me	H	H	Me	yes
10a	H	H	H	H	Me	H	H	H	no
10b	H	H	H	H	H	Me	H	H	no
11a	H	Me	Me	H	H	Me	Me	H	yes
11b	H	Me	Me	H	Me	H	Me	H	no
11c	H	Me	Me	H	Me	H	H	Me	yes
11d	H	Me	Me	H	H	Me	H	H	no
11e	H	Me	Me	H	Me	Me	Me	H	no
11f	H	Me	Me	H	Me	Me	Me	Me	yes

in Figure 1 and confirms the structure of **11a**. The similarity of our initial assumptions about the configuration and conformation of **8–11** and those actually found in **11a**, even though in the

(10) Treatment of **5** with neat oxalyl chloride gave no detectable amount of **8** but produced enol lactone acid chloride ii in good yield.

(11) Unconverted keto acids **5** and undesired enol lactone acid iii (mp 75–77 °C),^{6a} a product which accumulates at higher conversion of **5**, could be readily removed in a bicarbonate extract which, when acidified after several hours at room temperature, returned crystalline **5** (~1:1 mixture). This efficient recycle means a >90% effective yield of one isomer of **8** can be routinely realized.

(12) (a) Evans, D. A.; Sacks, C. E.; Whitney, R. A.; Mandel, N. G. *Tetrahedron Lett.* **1978**, 727. (b) Cresp, T. M.; Probert, C. L.; Sondheimer, F. *Ibid.* **1978**, 3955.

(13) For a similar analysis (and experimental verification) of the dimethyl spiro ketals analogous to **8**, see: Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauv , T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

(14) Although analysis of molecular models suggests that a true chair-chair conformation might have a severe dipole-dipole repulsion (estimated to be several kcal/mol destabilizing by assuming point dipole-point dipole interaction), this effect is greatly ameliorated in the flattened half-chair arrangement which maximizes ester resonance energy (dipole-dipole repulsion diminishes as r^{-3}). See: Philip, T.; Cook, R. L.; Malloy, T. B.; Allinger, N. L.; Chang, S.; Yuh, Y. *J. Am. Chem. Soc.* **1981**, *103*, 2151 for studies of the conformations of the parent δ -valerylolactone.

(15) In addition, a minor amount of α,γ,γ' -trimethylated material, assigned **11d** (mp 99–100 °C),^{6a} from monomethylation is frequently observed. On one occasion CH₃I was added at -70 °C only 15 min after exposure of **8a** to LDA. Traces of $\alpha,\alpha,\alpha',\gamma,\gamma'$ -penta- and $\alpha,\alpha,\alpha',\alpha',\gamma,\gamma'$ -hexamethylated dilactones **11e** and **11f** were isolated. Bis-enolate formation apparently was not yet complete and polyalkylation ensued.

(16) (a) Three guiding principles used throughout much of the structural assignment work for **8–11** were that (i) in the ¹H NMR spectra the γ -methyl group doublets were broader (~1/2 the height), were further upfield ($\delta \sim 1.0$ – 1.1), and had smaller coupling constants ($J = 5$ – 6 Hz) than their α counterparts ($\delta \sim 1.2$ – 1.3 , $J = 7$ Hz); (ii) the axial α -methyl groups were found at slightly higher field than the corresponding equatorial methyl doublets^{16b} whereas the equatorial α -H of a methyl-bearing methine carbon gave rise to a characteristic downfield ($\delta \sim 2.8$) six-line multiplet at 80 MHz; (iii) more highly methylated isomers eluted faster than less and axial α -methylated isomers eluted faster than equatorial on silica gel HPLC and MPLC. (b) Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthuis, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, 4029. Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1978**, *43*, 378.

(17) (a) The crystal is orthorhombic, $a = 10.539$ (4), $b = 10.613$ (5), $c = 11.523$ (4) Å, with space group $Ab\bar{a}2$. There are four molecules of C₁₃H₂₀O₄, $M_r = 240.30$, per unit cell; $d(\text{calcd}) = 1.238$ g cm⁻³. A total of 536 reflections with $\theta < 26^\circ$ were measured of which the 402 with $I > 2\sigma(I)$ were used in the calculations.^{14b} Mo K α radiation ($\lambda = 0.7107$ Å) was used. The hydrogen atoms are included at their idealized positions. Refinement converged at a conventional R factor of 0.047. (b) Calculations were carried out on PDP 8A and 11/34 computers by using the Enraf-Nonius CAD 4-SDP programs. This crystallographic package is described by: Frenze, B. A. in "Computing in Crystallography"; Schenck, H., Olthof-Hazekamp, R., van Koningsveld, H., Bassie, G. S., Eds; Delft University Press: Delft, Holland, 1978; pp 64–71. Also in: "CAD 4 and SDP Users Manual"; Enraf-Nonius: Delft, Holland, 1978.

crystalline state, was, nonetheless, satisfying. In addition to **11a** small quantities of two other tetramethyl dilactones, **11b** (mp 115–116 °C)^{6b} and **11c** (mp 124–129 °C),^{6b} are observed in the bis-methylation reaction. The isomer ratio as well as reaction rate is temperature dependent—**11a**:**11b**:**11c**, temperature (time to achieve >90% bis-methylation): 58:10:1, -40 °C (4 h); 73:10:1, -78 °C (16 h); 9:1:trace, ~-110 °C (90 h).

The acid stability of **8a** and **11a** is exemplified by their inertness to AcOH–H₂O–THF (1:1:15) at room temperature. Use of trifluoroacetic acid in lieu of AcOH resulted in a smooth opening to racemic keto diacids *d,l*-**5** and **1** [99% (>95% pure), mp 125–126 °C]^{6a,18} without epimerization. Diazomethane converted **1** to **12**.^{6a,18} Exploitation of the structural relationship between **1** and the venturicin aglycon (**2**) via this stereoselective, five-step, premeditated synthesis of **1** is under way.

Acknowledgment. This work was supported with funds provided by the National Institutes of Health (CA 24056). We thank Professor L. Pignolet and M. McGuigan for their assistance in the X-ray study. National Science Foundation Grant CHE 77-28505 aided in the purchase of the Enraf–Nonius diffractometer.

Supplementary Material Available: Lists of final atomic positional parameters, atomic thermal parameters, and bond distances and angles (12 pages). Ordering information is given on any current masthead page.

(18) No evidence for pseudoester formation was observed in CH₂N₂ mediated conversions of **1** → **12** or **4** and **5** to their dimethyl esters.

Synthesis and Characterization of a Cyclic Bimetallic Complex of the Trisulfide Ion

C. Mark Bolinger, Thomas B. Rauchfuss,* and Scott R. Wilson

School of Chemical Sciences
University of Illinois
Urbana, Illinois 61801

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We wish to report the synthesis and characterization of a new inorganic ring system and the first example of a metal complex of the S₃ moiety. These results bear on the rapidly expanding field of the coordination chemistry of sulfur rich metal complexes, previous studies having identified examples of S₂,¹ S₄,² and S₅^{2–4} fragments functioning as ligands. Such compounds are of potential relevance to sulfur transfer catalysis by metal ions in biology^{4,5} and industry.^{6,7}

Treatment of (η⁵-C₅H₅)₂TiS₅⁸ (**1**) with PPh₃ (2 equiv) in refluxing dichloromethane resulted in a rapid color change from red to black. Extraction of the resultant microcrystalline precipitate with dichloromethane gave an intensely blue solution which afforded black crystals from toluene (38% yield). Analytical and

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Table I. Important Metrical Parameters for (CH₃C₅H₄)₄Ti₂S₆

Bond Distances (Å)			
Ti(1)–S(1)	2.416 (1)	S(2)–S(3)	2.054 (1)
Ti(1)–S(4)	2.434 (1)	Ti(1)–CpA	2.067 (4)
S(1)–S(2)	2.058 (1)	Ti(1)–CpB	2.059 (4)
Bond Angles (Deg)			
S(1)–Ti(1)–S(4)	96.08 (3)	S(5)–S(4)–Ti(1)	113.97 (4)
S(2)–S(1)–Ti(1)	116.93 (5)	CpA–Ti(1)–CpB	132.6 (2)
S(3)–S(2)–S(1)	109.07 (6)		
Dihedral Angles (Deg)			
Ti(1)–S(1)–S(2)–S(3)	62.7	S(1)–Ti(1)–S(4)–S(5)	59.1
Ti(1)–S(4)–S(5)–S(6)	66.6	S(2)–S(1)–Ti(1)–S(4)	68.6

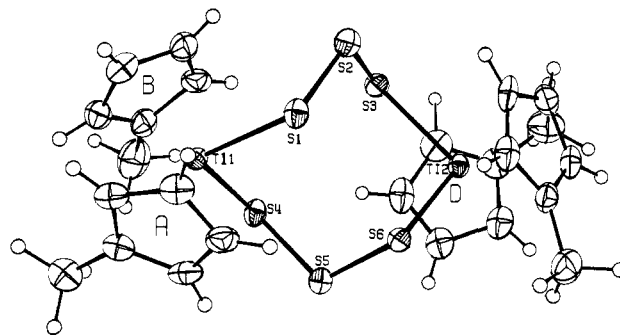


Figure 1. ORTEP plot of the (CH₃C₅H₄)₄Ti₂S₆ molecule with thermal ellipsoids drawn at the 50% probability level.

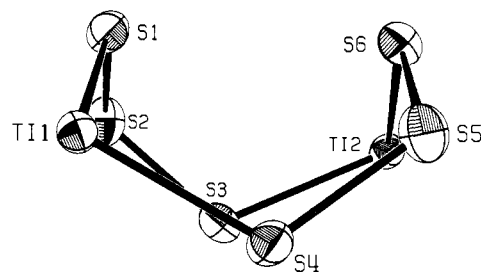


Figure 2. ORTEP plot of the Ti₂S₆ ring atoms of the (CH₃C₅H₄)₄Ti₂S₆ molecule.

¹H NMR data were consistent with a diamagnetic compound of the formula (η⁵-C₅H₅)₂Ti^{IV}S₃ which contained equivalent cyclopentadienyl rings.⁹ Field desorption mass spectrometry indicated that this new compound was a dimer, (C₅H₅)₄Ti₂S₆ (**2**), a result confirmed by an X-ray crystallographic analysis of the analogous [(η⁵-C₅H₄CH₃)₂TiS₃]₂.¹⁰

A 0.24 × 0.58 × 0.58 mm crystal obtained by slow diffusion of C₆H₁₄ into a CH₂Cl₂ solution of **2** at -20 °C was used for data collection. The space group and cell data are as follows: monoclinic, space group P2₁/c with a = 12.559 (2) Å, b = 15.054 (3) Å, c = 14.211 (2) Å, β = 99.24 (1)°, V = 2652.0 (7) Å³, d(calcd) = 1.514 g cm⁻³, d(found) = 1.49 g cm⁻³, and Z = 4. Three-dimensional diffraction data (a total of 6130 independent reflections having 2θ(Mo Kα) ≤ 55.0°) were collected on a Syntex P2₁ autodiffractometer, using graphite-monochromated Mo Kα radiation. The titanium atoms and four of the six sulfur atoms were located by direct methods.^{11,12} Subsequent difference Fourier maps revealed the positions of all remaining atoms. Least-squares refinement to convergence using anisotropic thermal parameters

(9) Anal. Calcd for C₁₀H₁₀S₃Ti: C, 43.79; H, 3.68; S, 35.07; Ti, 17.46. Found: C, 43.50; H, 3.71; S, 34.08; Ti, 17.17. ¹H NMR (CS₂, 220 MHz): at 15 °C, δ 6.03 (s, C₅H₅), at -50 °C, δ 6.01. Field desorption mass spectrum: m/e 548 (M⁺). IR (mineral oil mull): 1070, 1026, 1013, 818, 380, 275 cm⁻¹.

(10) [(CH₃C₅H₄)₂TiS₃]₂ is made in an analogous manner to that for the C₅H₅ analogue. This derivative is easily obtained as X-ray quality single crystals; however, due to its solubility characteristics it is more difficult to separate from the Ph₃PS than the C₅H₅ derivative.

(11) A full discussion of the X-ray analysis and refinement will be described in a full paper.

(12) Sheldrick, G. M. SHELX 76, University of Cambridge, England, 1976.