hexene, 7642-09-3; bicyclo[2.2.1]hept-2-ene, 498-66-8; bicyclo-[2.2.1]hepta-2,5-diene, 121-46-0; 1,4-cyclohexadiene, 628-41-1; *trans*-2-butene, 624-64-6; (*R*)-2-butanol, 14898-79-4; 1,5-cyclo-octadiene, 111-78-4; (*R*)-*exo*-norbornyl alcohol, 61277-93-8; (1*R*,2*S*)-(+)-*exo*-5-norbornen-2-ol, 71030-15-4; (*R*)-2-butylboronic acid, 92116-84-2.

Supplementary Material Available: ^{11}B NMR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **5c-e** (9 pages). Ordering information is given on any current masthead page.

Preparation, Reactions, and Stereochemistry of 4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Oxide and Derivatives

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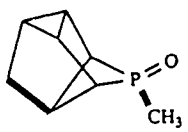
Received July 23, 1991

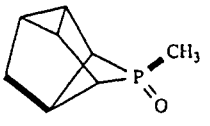
The cis isomer **1b** of the title compound was observed for the first time. It was prepared as a mixture with the previously reported trans isomer **1a**. Reduction of the latter under sterically controlled conditions enabled selective formation of either the cis or trans tetracyclic phosphine **7**. Although oxidation of the phosphine gave none of the expected phosphine oxide, stereoselective reactions with sulfur or selenium gave the cis and trans sulfides and selenides. Likewise, each phosphine isomer was transformed into several phosphonium salts by quaternization with methyl bromide, benzyl bromide, and *p*-nitro- and *p*-fluorobenzyl bromide. Stereochemical assignments for **1a** and **1b** were based on NMR lanthanide shift experiments. Corresponding assignments for the phosphines, sulfides, selenides, and phosphonium salts were based on both ^{1}H and ^{13}C NMR spectral data and the expected outcome of the reaction by literature precedent. For **1a**, **1b** and a series of derivatives, the ^{31}P-^{13}C coupling constants were found to be much larger than those observed in less rigid heterocyclic systems. They were consistent with previously reported Karplus relationships, provided a multiple-coupling path correction was made and coupling through nonbonded interactions was considered. Differences in the P-C coupling constants between the cis and trans isomers are also discussed. The $^{2}J_{PC}$ coupling constants were dependent upon the geometry about phosphorus in the phosphines and in the oxides. Several reactions of the title compound and the salt derivatives are described. These include reaction of the dimethyl salt **13** with methyllithium to give norbornylene and trimethylphosphine as well as a ring-opened product **22**. With the exception of the *p*-nitrobenzylphosphonium salt **12** which exhibited exocyclic P-C cleavage on treatment with aqueous NaOH, all of the salts led to ring opening. Treatment of both **1a** and salt **13** with aqueous sodium deuteroxide gave ring opening with selective deuterium incorporation at the syn-C-7 position.

Introduction

Four-membered phosphorus-containing rings, or phosphetanes, have received extensive study during the last two decades and have proven to be a class of compounds rich in unusual chemical reactivity, stereochemistry, and physical properties.[1] Earlier reports[2] on the synthesis of 4-methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-oxide[3] (**1**) were of special interest to us,[4] because oxide **1** possesses a conformationally rigid four-membered phosphorus heterocycle. The fixed and symmetrical geometry of the



1a (trans)



1b (cis)

tetracyclic skeleton provides a useful model to test the generality of stereospecific ^{31}P-^{13}C coupling constants which we[5] and others[6-8] previously observed. In the original reports[2] only one isomeric oxide with unspecified geometry was isolated. We anticipated from work with monocyclic phosphetanes[1a] that alteration of the reaction workup would provide both isomers, **1a** and **1b**, whose cis vs trans configuration[9] about phosphorus could be estab-

† This paper is dedicated in memory of John M. Cowles, deceased Jan 12, 1990.

(1) (a) Cremer, S. E.; Weitl, F. L.; Farr, F. A.; Kremer, P. W.; Gray, G. A.; Hwang, H.-O. *J. Org. Chem.* **1973**, *38*, 3199 and references cited therein. (b) See appropriate chapters in: *Specialist Periodical Reports, Organophosphorus Chemistry*; Trippett, S., Ed.; The Chemical Society: London, 1970-1988; Vol. 1-20. (c) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; Wiley-Interscience: New York, 1981; Chapter 4 and references cited therein.

(2) (a) Green, M. *Proc. Chem. Soc.* **1963**, 177. (b) Green, M. *J. Chem. Soc.* **1965**, 541.

(3) The nomenclature of this molecule has varied from 2-methyl-2-phosphatetracyclo[3.2.1.0^{3,6}.0^{4,7}]octane 2-oxide[2b] to 8-methyl-8-phosphatetracyclo[2.2.1.1^{2,6}.0^{3,5}]octane 8-oxide in: *Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony and Bismuth*, 2nd ed.; Mann, F. G., Ed.; Wiley-Interscience: New York, 1970; pp 154-156. The preferred systematic name used in this manuscript was supplied by Dr. Kurt Loenig, Nomenclature Director, Chemical Abstracts.

(4) A preliminary account of this work has appeared (Cremer, S. E.; Farr, F. R.; Kremer, P. W.; Hwang, H.-O.; Gray, G. A.; Newton, M. G. *J. Chem. Soc., Chem. Commun.* **1975**, 374) and was presented: Cowles, J. M.; Farr, F. R.; Kremer, P. W.; Hwang, H.-O.; Cremer, S. E. *Abstracts of Papers*, 20th Great Lakes Regional Meeting, Milwaukee, WI; American Chemical Society: Washington, DC, June 2-4, 1986; Abstract 286.

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(6) (a) Wetzel, R. B.; Kenyon, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 9230. (b) Wetzel, R. B.; Kenyon, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 5189.

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(8) (a) Quin, L. D.; Gallagher, M. J.; Cunkle, G. T.; Chesnut, D. B. *J. Am. Chem. Soc.* **1980**, *102*, 3136. (b) Quin, L. D. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: New York, 1987; Chapter 8 and referencs cited therein.

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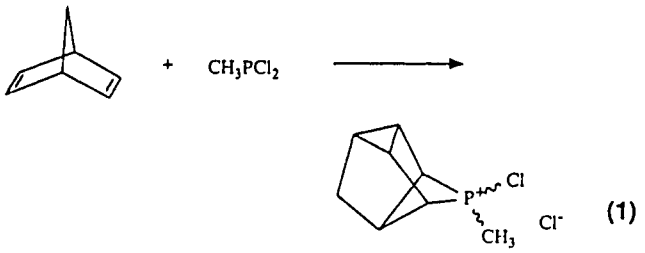
lished by ^1H or ^{13}C NMR spectroscopy. Additional objectives of this study included extended NMR studies, the stereoselective preparation and characterization of derivatives of the parent oxide, and investigation of the reaction behavior of these systems with protic and aprotic nucleophilic reagents.

Results and Discussion

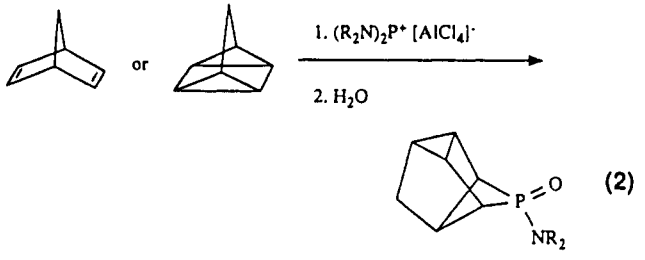
Synthesis and Stereochemistry (Scheme I). The parent tetracyclic phosphetanium chloride **2** was most conveniently prepared in 60–70% yield by treating an excess of norbornadiene with dichloromethylphosphine at 65–80 °C for 1 week (eq 1). Contrary to the earlier reports,[2] the reaction at room temperature was comparatively slow, affording only 21% of the desired product after 11 days. A dissertation[10] described the preparation of **1** in 47% overall yield from dibromomethylphosphine and norbornadiene at room temperature for several days, followed by aqueous hydrolysis. Our attempts to vary the phosphorus substituent were unsuccessful; treatment of the diene with phosphorus tribromide, dichlorophenylphosphine, or *tert*-butyldichlorophosphine gave no tetracyclic adduct.[11] Employment of dibromophenylphosphine at room temperature followed by aqueous workup gave *trans*-4-phenyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-oxide (**3**) in low yield, but efforts to reproduce the preparation were peculiarly unsuccessful.



(1)

2

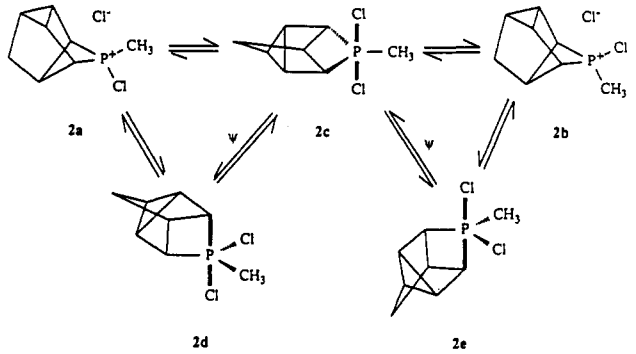
Recently, Baxter and Weissman have entered the tetracyclic system by homo-1,4-cycloaddition of phosphenium ions to either norbornadiene or quadricyclane (eq 2).[12] The number of tetracyclic derivatives is greatly expanded by this new methodology.

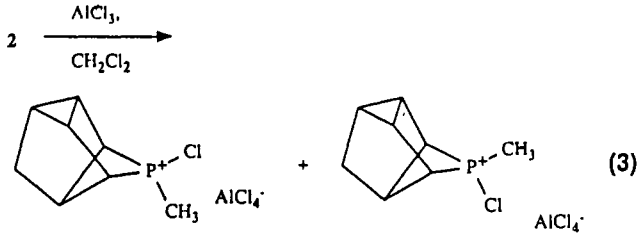


(2)

Similar to 1-chloro-1,2,2,3,4,4-hexamethylphosphetanium chloride (**4**)[1a] and 1-chloro-1,2,5-trimethyl-3-phospholenium chloride (**5**),[13] **2** consisted of isomers **2a** and **2b** in equilibrium at room temperature. At −20 °C, the interconversion was sufficiently slow to observe the separate isomers by ^1H NMR spectroscopy. The addition of anhydrous aluminum chloride to **2** trapped the chloride counterion as the tetrachloraluminate anion and permitted NMR observation of the individual isomers **6a** and **6b** at room temperature (eq 3). Isomer enrichment of **6a** or **6b** was accomplished by fractional recrystallization.

Scheme I





(3)

6a **6b**

Isomer equilibration of **2a** and **2b** can occur via pseudorotation through a series of pentacoordinate phosphorus intermediates in which the ring bonds span apical–equatorial positions of a trigonal bipyramid, **2d** and **2e** (Scheme I). Alternatively, the ring can span two equatorial positions in a "distorted" trigonal bipyramidal configuration, **2c**, which has lost its original stereochemical integrity.[13] Apical departure of either chloride from **2c** would provide a pathway for isomer interconversion between **2a** and **2b**. Several reports suggest that the four-membered ring can indeed subtend a diequatorial position.[14] In those cases, however, apicophilic fluoro or alkoxy groups were present to stabilize the phosphorane. Addition of water to a solution of **2a** and **2b** in dichloromethane or inverse addition of **2a** and **2b** to a large excess of water gave the previously reported isomer **1a**. The key to the synthesis of the other isomer involved slow addition of the mixture of **6a** and **6b** to ice–water. As anticipated,[1a] 2:1, 4:1, and 2:3 mixtures of **1a** and **1b** were formed starting from 2:1, 5:2, and 1:6 mixtures, respectively, of salts **6a** and **6b**. If salts **6a** and **6b** reacted with water at the same rate, we would expect the ratio of **1a**:**1b** to more closely parallel the ratio of **6a**:**6b**. However, contact of salts **6a** and **6b** with any water would result in chloride ion formation, which could promote **6a** and **6b** isomerization. Subsequent reaction of the salts would show a dominance of the oxide, in this case **1a**, derived from the salt that reacted fastest.[1a] The elusive

(9) The cis and trans nomenclature in this work refers to the relationship between the P–Me bond and C-6 to C-7 bonds in the tetracyclic system. In the earlier report[4] **1a** was termed the exo isomer and **1b** the endo isomer.

(10) Barash, L. Ph.D. Thesis, Rutgers University, Jan 1972.

(11) Hwang, H.-O. Masters Thesis, Marquette University, Aug 1973.

(12) Weissman, S. A.; Baxter, S. G. *Tetrahedron Lett.* **1987**, *28*, 603.

(13) Quin, L. D.; Barket, T. P. *J. Am. Chem. Soc.* **1970**, *92*, 4303.

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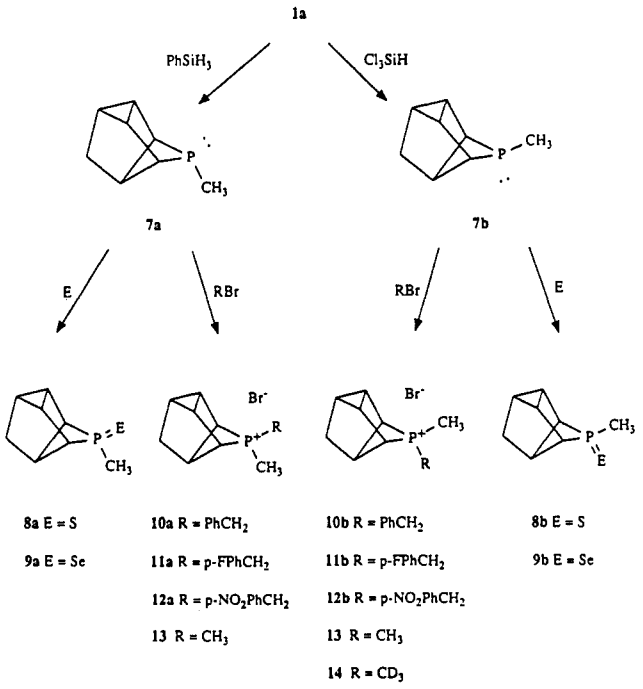
Scheme II



minor isomer **1b** was separated from **1a** by fractional recrystallization. When **1b** was exposed to the atmosphere, the crystals rapidly hydrated. Examination of the hydrated crystals by NMR spectroscopy showed substantial conversion to oxide **1a**. Trace amounts of water were presumably responsible for the isomeric crossover from oxide **1b** to the thermodynamically more stable oxide **1a**. Surprisingly, no epimerization of **1b** was observed in either aqueous 1,4-dioxane containing NaOH or dichloromethane–HCl after 1 year. The facile exchange of ^{18}O in **1a** in acidic aqueous dioxane, reported by Samuels and Silver,[15] suggested that an isomerization pathway from **1b** to **1a** existed. A sealed ampule of the minor oxide **1b** was also found to isomerize to **1a** in the apparent absence of atmospheric moisture. Solid-state isomer crossover was reported by Quin et al.[16] for 1-phenyl-2,5-dimethyl-3-phospholene oxide.

A dilute solution of oxide **1a** (0.06 M) in benzene was reduced with predominant overall inversion to the phosphine **7b** with trichlorosilane (Scheme II). Similar results were observed by others[17] for the reduction of **1a** with trichlorosilane. The reduction of phosphine oxides with trichlorosilane usually proceeds with overall retention of configuration about phosphorus.[18] Trace amounts of HCl in the reaction mixture were surmized[4] to cause the inversion, since inversion of other phosphines with HCl was previously observed.[19] However, evidence[17,20] indicates that chlorosilane derivatives can be responsible for phosphine isomerization. Reduction of more concentrated solutions of oxide resulted in formation of a white, polymeric powder and little phosphine. The phosphine **7b** partially polymerized upon distillation and was best kept in a cold, dilute benzene solution. Attempts to confirm the stereochemistry of reduction failed because hydrogen peroxide or *tert*-butyl hydroperoxide oxidation of **7b**, precedented to proceed with retention of configuration,[21] gave neither **1a** nor **1b**. However, treatment of the phosphine **7b** with elemental sulfur in benzene solution[22] did yield sulfide **8b**. The stereochemical assignments were made from ^1H and ^{13}C NMR spectral studies.

A dilute solution of oxide **1a** (0.14 M) in benzene was reduced with phenylsilane via a retention pathway[23] (Scheme II). Addition of elemental sulfur gave **8a**. Reduction of oxide **1a** with triethylamine and trichlorosilane,[24] followed by treatment with elemental sulfur, also gave sulfide **8a**. The reduction of oxide **1a** with 2:1 pyridine–trichlorosilane in benzene was reported[17] to give a 67:33 ratio of phosphines **7b**:**7a**.

Quaternization of phosphine **7a** with benzyl bromide, *p*-nitrobenzyl bromide, *p*-fluorobenzyl bromide, and methyl bromide resulted in the formation of salts **10a**, **11a**, and **12a**, respectively (Scheme II). Similar treatment of phosphine **7b** with benzyl bromide, *p*-fluorobenzyl bromide, *p*-nitrobenzyl bromide, methyl bromide, and methyl-d_3 bromide resulted in the formation of salts **10b**, **11b**, **12b**, **13**, and **14**, respectively (Scheme II).

Isomerization of salts **10a** with **10b** and **12a** with **12b** occurred in the presence of catalytic amounts of pyridine. The benzyl salts attained a final 55:45 ratio of **10b**:**10a**, and the *p*-nitrobenzyl salts resulted in a 60:40 mixture of **12b**:**12a** after 2 weeks at room temperature. Isomerization under these conditions is unusual, as several monocyclic phosphetanium salts showed no such behavior.[25] Adventitious water in the reaction mixture could react with pyridine to form trace amounts of hydroxide ion which could also cause isomerization. When the salt **12b** was treated with pyridine containing 0.2 equiv of H_2O, isomerization also occurred. An alternative explanation involves reversible coordination of pyridine to the phosphonium salt to form a phosphorane intermediate. The phosphorane intermediate could undergo rapid ligand reorganization (pseudorotation) with scrambling of stereochemistry prior to ejection of pyridine. Efforts to observe a species containing pyridine coordinated to phosphorus were unsuccessful. Although phosphoranes containing coordinated amines are unusual, their existence was implicated in several studies.[26]

The benzyl salts **10a** and **10b** also isomerized with 0.2 equiv of NaOH in both D_2O and a two-phase $CDCl_3/H_2O$ solvent mixture. The salts all reached an approximate 1:1 ratio after 1 day in D_2O. The rate of isomerization of the salts was much slower in the two-phase $CDCl_3$–H_2O system. Isomerization preceded any noticeable decomposition

(15) Samuel, D.; Silver, B. L. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic: London, 1965; p 179.
(16) Quin, L. D.; Stocks, R. C. *Phosphorus Sulfur Relat. Elem.* **1977**, *3*, 151.
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(21) Horner, L. *Pure Appl. Chem.* **1964**, *9*, 225.
(22) The addition of elemental sulfur to a phosphine was shown to proceed with retention of configuration about phosphorus: Horner, L.; Winkler, H. *Tetrahedron Lett.* **1964**, 175.
(23) Marsi, K. L. *J. Am. Chem. Soc.* **1969**, *91*, 4724.
(24) Cremer, S. E.; Chorvat, R. J. *J. Org. Chem.* **1967**, *32*, 4066.
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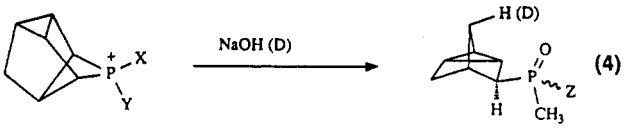
(26) (a) Yamazaki, N.; Niwano, M.; Kawabata, J.; Higashi, F. *Tetrahedron* **1975**, *31*, 665. (b) Milbrath, D. S.; Verkade, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 6607. (c) Clardy, J. C.; Milbrath, D. S.; Springer, J. P.; Verkade, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 623. (d) Carpenter, L. E.; de Ruiter, B.; van Aken, D.; Buck, H. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1986**, *108*, 4918. (e) Mueller, E.; Burgi, H.-B. *Helv. Chem. Acta* **1987**, *70*, 1063. (f) Lensink, C.; Xi, S.-K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478. (g) Laramay, M. A. H.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421.

to phosphine oxides in both solvent systems. Monocyclic benzylphosphetanium salts isomerized under similar conditions.[27]

When the benzylphosphonium salt **10b** was stirred with aqueous sodium hydroxide, the only phosphorus-containing product observed was the tricyclic oxide **15** (eq 4).



10b X = CH_3; Y = CH_2Ph; counter ion Br^-

13 X = Y = CH_3; counter ion Br^-

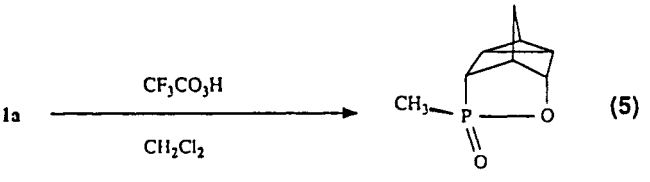
1a X = O^-; Y = CH_3

15 Z = CH_2Ph

17 Z = CH_3

18 Z = OH

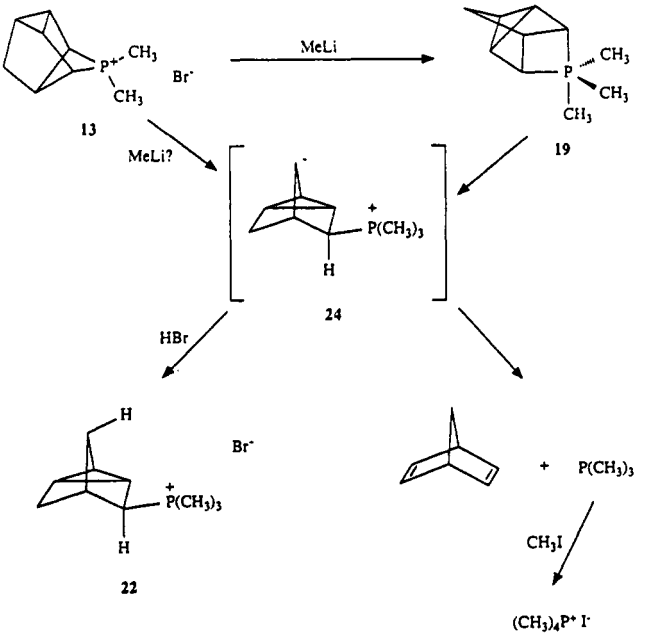
This result is in contrast to previous work on monocyclic benzylphosphetanium salts which showed exclusive benzyl departure without ring opening upon reaction with hydroxide solutions.[28] However, treatment of the *p*-nitrobenzyl salt **12b** with aqueous sodium hydroxide did not appear to cleave the ring; instead, both oxides **1a** and **1b** were formed in a 65:35 ratio, along with *p*-nitrotoluene and bis(4,4'-dinitrodibenzyl).[29] A ^{31}P NMR spectrum (in $CDCl_3$) of the CH_2Cl_2 extract of the product mixture was taken. In addition to signals for the oxides **1a** and **1b**, six signals between 43 and 46 ppm, representing about 20 mol % of the total phosphorus-containing product, were observed. The identification of these additional products was not pursued. The enhanced leaving-group ability of the *p*-nitrobenzyl moiety tipped the energy balance in favor of substitution over the previously predominant ring-cleavage pathway. The reactivity of the strained four-membered phosphorus-containing ring in the tetracyclic system was previously demonstrated by Quin and coworkers[30] by the insertion of oxygen into the carbon–phosphorus bond in oxide **1a** with trifluoroperoxyacetic acid to give the tetracyclic oxaphospha derivative **16** (eq 5).



16

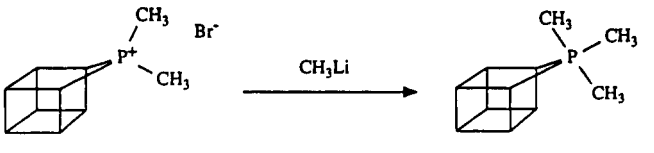
Because methyl is a poorer leaving group than benzyl, the dimethyl salt **13** gave only ring-opened product, tricyclic phosphine oxide **17**, upon treatment with aqueous base (eq 4). Treatment of salt **13** with deuteroxide in D_2O resulted in no deuterium incorporation at the P–Me sites in the product oxide **17**. Ring opening is apparently very rapid because deuterium exchange at the P–Me sites in the monocyclic phosphetane system is fast.[31] However,

Scheme III



the reaction did result in selective incorporation of one deuterium at the syn-C-7 position of the tricyclic skeleton, as shown by integration of proton NMR signals. In the ^1H NMR spectrum the nondeuterated ring-opened oxides showed a broad doublet at δ 1.87 (J = 11 Hz, 1 H) for the syn-C-7 proton which is deshielded due to the close proximity of the phosphoryl group.[32] This coupling constant is consistent with geminal J_{HCH} couplings in nortricyclene derivatives.[33] The signal at δ 1.87 disappeared after deuterium incorporation. Also, the ^{13}C NMR spectrum showed a triplet for C-7 at δ 30.45 after deuterium incorporation. The ^1H NMR assignments of the protons at C-7 in **17** were confirmed by a lanthanide shift study.[34,35] The treatment of **13** with D_2O/NaOD was also monitored by ^{31}P NMR spectroscopy; only one product signal appeared. Likewise, treatment of oxide **1a** with 2 N NaOH afforded the tricyclic phosphinic acid **18** after acidification (eq 4). Treatment of oxide **1a** with deuteroxide also resulted in the incorporation of deuterium at the syn-C-7 position in acid **18**.

The dimethyl salt **13** was treated with methyllithium in an attempt to synthesize the pentaalkylphosphorane **19** (Scheme III). Turnbloom and Katz[36] isolated pentaalkylphosphorane **21** in another strained multicyclic system by treatment of the corresponding dimethylhomocubylphosphonium salt **20** with methyllithium (eq 6). Because



20 **21**

(27) Cremer, S. E.; Chorvat, R. J.; Trivedi, B. C. *Chem. Commun.* **1969**, 769.

(28) Cremer, S. E.; Trivedi, B. C.; Weitl, F. L. *J. Org. Chem.* **1971**, *36*, 3226.

(29) (a) The formation of bis(4,4'-dinitrodibenzyl) from the anion of 4-nitrotoluene in basic solutions has been investigated. For example, see: Buncel, E.; Menon, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 3499. (b) An 85:15 mixture of **12a** to **12b** was hydrolyzed under similar conditions and gave an 84:16 mixture of oxides **1a**:**1b**. Correcting for the amount of **1a** and **1b** produced from the hydrolysis of **12b** in the mixture results in the formation of an 87:13 mixture of oxides **1a**:**1b** produced from the aqueous hydrolysis of **12a** alone. Because the final ratio of oxides from hydrolysis of **12a** is different from hydrolysis of **12b**, hydrolysis is competitive with isomerization under these reaction conditions.

(30) Quin, L. D.; Kisalus, J. C.; Mesch, K. A. *J. Org. Chem.* **1983**, *48*, 4466.

(31) Cremer, S. E.; Chang, C. H. *Chem. Commun.* **1969**, 1456.

(32) Reference 1c, Chapter 7 and references cited therein.

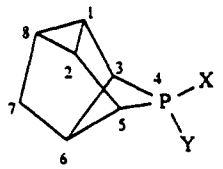
(33) See for example: Chizhov, A. O.; Zefirov, N. S.; Zyk, N. V.; Morrill, T. C. *J. Org. Chem.* **1987**, *52*, 5647.

(34) A lanthanide shift study was similarly used to aid in the determination of the position of deuterium in a deuterated nortricyclyl alcohol: Morrill, T. C.; Greenwald, B. E. *J. Org. Chem.* **1973**, *38*, 616.

(35) (a) Reference 1c, Chapter 7 and references cited therein. (b) Mazur-Ul-Haque; Cremer, S. E. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1000.

(36) Turnbloom, E. W.; Katz, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 4292.

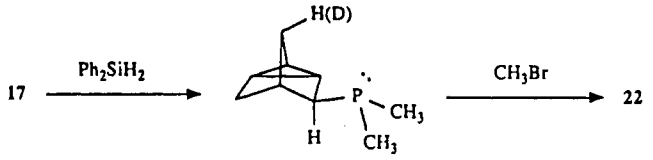
Table I. ^{13}C NMR Chemical Shifts of Tetracyclic Derivatives[a]



compd	X	Y	C-1(2)	C-3(5)	C-6	C-7	C-8	C-X	C-Y
1a	O	CH_3	13.85	48.08	31.03	31.76	24.11		11.73
1b	CH_3	O	10.36	45.60	39.49	33.48	17.82	13.45	
3	O	Ph	14.33	48.67	31.65	32.16	25.15		
6a[b]	Cl	CH_3	16.48	52.27	38.40	35.43	28.78		14.50
6b[b]	CH_3	Cl	12.56	50.04	42.83	32.41	26.10	16.23	
7a[c]		CH_3	17.90	40.52	47.36	36.01	25.51		8.54
7b[c]	CH_3		21.34	40.47	40.17	34.64	34.32	9.63	
8a	S	CH_3	16.05	49.37	37.11	34.36	26.52		17.62
8b	CH_3	S	14.79	49.47	41.32	33.73	24.81	19.30	
9a	Se	CH_3	16.91	47.87	39.11	35.80	26.72		18.70
9b	CH_3	Se	15.92	48.86	41.88	33.52	27.03	20.35	
10a	$PhCH_2$	CH_3	15.63	44.12	40.42	33.64	27.75	31.02	5.46
10b	CH_3	$PhCH_2$	15.17	43.30	40.62	34.14	26.76	7.87	30.01
11a	*p*-$FPhCH_2$	CH_3	15.62	45.03	40.35	33.63	27.74	30.81	5.96
11b	CH_3	*p*-$FPhCH_2$	15.18	43.95	40.58	34.10	26.68	8.25	29.44
12a	*p*-NO_2PhCH_2	CH_3	15.92	45.45	41.03	33.41	28.22	31.48	6.46
12b	CH_3	*p*-NO_2PhCH_2	15.23	44.21	40.85	34.26	26.89	8.45	30.11
13	CH_3	CH_3	15.02	44.04	40.65	33.99	27.27	10.24	8.45
14	CH_3	CD_3	14.93	43.82	40.52	33.88	27.19	10.13	*d*

[a] Chemical shifts (in $CDCl_3$ unless otherwise noted) in ppm from TMS–^{13}C (internal 1–5%) accurate to ±0.2 ppm. [b] Tetrachloroaluminate salt. [c] In C_6D_6, 1% TMS. [d] Not observed.

the reaction of a phosphonium salt with lithium bases usually results in ylide formation, formation of the phosphorane was exceptional and was presumably due to relief of ring strain on formation of a pentacoordinated phosphorane.[37] In the tetracyclic system no pentaalkylphosphorane was isolated; its intermediacy was implied by a transient peak at −101 ppm (^{31}P NMR; toluene-d_8 at −80 °C) and the products formed (Scheme III). Decomposition of the intermediate to norbornadiene and trimethylphosphine (trapped with methyl iodide to give tetramethylphosphonium iodide) is merely the reverse of the addition of dichloromethylphosphine to the diene. That such retro-cycloaddition reactions can occur is well-known.[17,36,38] The major product was the tricyclic trimethylphosphonium salt **22**. Salt **22** was prepared independently by reduction of tricyclic oxide **17** with diphenylsilane to the tricyclic phosphine **23**, followed by quaternization with CH_3Br (eq 7). The tricyclic salt **22** was hydrolyzed using solid NaOH and regenerated the oxide **17** in 73% yield.



(7)

Nucleophilic attack on salt **13** forms the phosphorane **19** which subsequently undergoes ring opening to the zwitterionic intermediate **24** (Scheme III). Concerted ring opening of **13** by nucleophilic attack through an S_N2-type process to give **24** seems less likely. Stepwise or concerted rearrangement of **24** could then result in norbornadiene and trimethylphosphine. Variable-temperature ^{31}P NMR studies are currently in progress to determine complete mechanistic details of the reaction.

The rates of hydrolysis of cyclic phosphonium salts are dependent on ring size and increase from larger to smaller rings.[28] Relief of ring strain in the pentacoordinate intermediate has been proposed as one of several factors responsible for the dramatic rate enhancement.[37] Among phosphetane derivatives, the tetracyclic system is the most puckered with a dihedral angle (defined by planes C-3, P-4, C-5 and C-3, C-6, C-5) of 46.6°.[39] The flap-angle found in other phosphetane systems ranged from 4.6 to 41°.[40] In addition, the internal C–P–C angle of 74.8° in the tetracyclic system[39] is significantly more acute than the 76.9–85.9° range found in phosphetane systems.[40] With this in mind, a rate study of the hydrolysis of the dimethyl salt **13** was undertaken. Using the kinetic procedure of Aksnes and Bergesen,[41] the average third-order rate constant at 0 °C was found to be 2.75 × 10^4 L^2/m^2-s.[42] This

(37) (a) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. (b) Muetterties, E. L.; Mahler, W.; Schmutzler, R. *Inorg. Chem.* **1963**, *2*, 613.
(38) (a) Chang, L. L.; Denney, D. Z.; Denney, D. B.; Hsu, Y. F. *Phosphorus* **1974**, *4*, 265. (b) Scott, G.; Hammond, P. J.; Hall, C. D.; Bramblett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1977**, 882. (c) Hammond, P. J.; Lloyd, J. R.; Hall, C. D. *Phosphorus Sulfur Relat. Elem.* **1981**, *10*, 47. (d) Quin, L. D.; Caster, K. C. *Tetrahedron Lett.* **1983**, *24*, 5831.
(39) Mazur-Ul-Haque; Rashid, M.; Cremer, S. E. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1115.
(40) (a) Swank, D. D.; Caughlan, C. N. *Chem. Commun.* **1968**, 1051. (b) Moret, C.; Trefonas, L. M. *J. Am. Chem. Soc.* **1969**, *91*, 2255. (c) Mazur-Ul-Haque *J. Chem. Soc. B* **1970**, 934, 938. (d) Mazur-Ul-Haque *J. Chem. Soc. B* **1971**, 117. (e) Fitzgerald, A.; Campbell, J. A.; Smith, G. D.; Caughlan, C. N. *J. Org. Chem.* **1978**, *43*, 3513. (f) Mazur-Ul-Haque *Acta Crystallogr., Sect. B: Struct. Sci.* **1979**, *B35*, 2601. (g) Mazur-Ul-Haque; Horne, W.; Cremer, S. E.; Kremer, P. W.; Kafarski, P. K. *J. Chem. Soc., Perkin Trans 2* **1981**, 1138. (h) Mazur-Ul-Haque; Horne, W. *Acta Crystallogr., Sect. B: Struct. Sci.* **1982**, *B32*, 2944. (i) Campbell, J. A.; Caughlan, C. N.; Fitzgerald, A.; Campana, C.; Cremer, S. E. *Acta Crystallogr., Sect. C: Struct. Commun.* **1984**, *C40*, 1918. (j) Mazur-Ul-Haque; Ahmed, J.; Horne, W. *Acta Crystallogr., Sect. C: Struct. Commun.* **1985**, *C41*, 975. (k) Campbell, J. A.; Larsen, R.; Campana, C.; Cremer, S. E. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987**, *C43*, 340. (l) Mazur-Ul-Haque; Horne, W.; Cremer, S. E.; Kremer, P. W.; Kafarski, P. K. *J. Cryst. Spectrosc. Res.* **1989**, *19*, 267. (m) Bennett, D. W.; Grubisha, D. S.; Cremer, S. E.; Peterson, A. C. *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 83.
(41) Aksnes, G.; Bergesen, K. *Acta Chem. Scand.* **1965**, *19*, 931.

Table II. ^{13}C–^{31}P Coupling Constants of Tetracyclic Derivatives[a]

compd	X	Y	C-1(2)	C-3(5)	C-6	C-7	C-8	C-X	C-Y
1a	O	CH_3	2.9	63.2	7.1	28.0	29.6		50.6
1b	CH_3	O	11.4	63.7	20.1	22.4	34.6	46.4	
3	O	Ph	3.6	65.0	6.9	30.7	29.4		
6a[b]	Cl	CH_3	5.0	47.9	5.2	32.8	38.0		24.4
6b[b]	CH_3	Cl	15.6	50.2	18.8	26.9	42.9	21.5	
7a[c]		CH_3	25.9	0.0	1.9	5.1	19.9		34.0
7b[c]	CH_3		7.9	6.1	14.7	14.7	2.5	36.6	
8a	S	CH_3	6.5	52.5	8.6	23.3	32.3		37.5
8b	CH_3	S	7.6	52.1	13.5	23.3	31.0	33.8	
9a	Se	CH_3	8.2	47.3	9.5	21.4	33.3		29.9
9b	CH_3	Se	5.8	47.0	11.3	23.5	29.3	25.6	
10a	$PhCH_2$	CH_3	6.4	52.3	12.4	22.9	31.0	27.4	37.2
10b	CH_3	$PhCH_2$	5.0	52.8	14.2	23.8	31.2	35.5	29.6
11a	p-$FPhCH_2$	CH_3	5.9	52.7	12.7	22.5	29.8	29.3	38.6
11b	CH_3	p-$FPhCH_2$	5.4	52.2	14.2	22.9	30.8	35.6	30.8
12a	p-NO_2PhCH_2	CH_3	6.1	52.2	13.4	23.5	30.5	26.6	37.2
12b	CH_3	p-NO_2PhCH_2	5.5	52.8	14.0	22.9	31.4	35.4	30.5
13	CH_3	CH_3	6.3	56.2	13.6	23.4	31.1	36.7	38.7
14	CH_3	CD_3	6.2	56.3	13.8	23.4	31.1	36.5	d

[a] Spectra taken in $CDCl_3$ unless otherwise noted; coupling constants in Hz. [b] Tetrachloroaluminate salt. [c] In C_6D_6. [d] Not observed.

rate is 10^2 times faster than the fastest rate observed for exocyclic benzyl cleavage in a monocyclic phosphetanium salt.[28]

Spectral Data. Due to the symmetry of the tetracyclic structure, the ^{13}C NMR signals for each carbon were readily assigned for the P(IV) derivatives (Tables I and II). The peak height of carbons 1(2) and 3(5) were twice that of the other carbons. The directly bonded carbons 3(5) were furthest downfield due to the deshielding effect of P(IV). In addition, the $^1J_{PC}$ for carbons 3(5) were much larger than the P–C couplings of the other signals. By contrast, the signals for carbons 1(2) were upfield (δ 10.4–16.9) and were consistent with monosubstituted cyclopropyl carbons.[43] Carbon 7 was differentiated by the number of attached protons; the off-resonance ^{13}C NMR spectrum showed a triplet. Carbons 6 and 8 were assigned by noting that C-6 was found downfield of cyclopropyl carbon 8. The benzyl carbon in the benzyl salts was identified by selective proton irradiation of the sharp doublet at approximately δ 4 (J = 14–15 Hz). The P–Me carbons exhibited a quartet in the ^{13}C NMR off-resonance spectra. The P–Me carbons in the dimethyl salt **13** were assigned by comparison to the trideuterated analogue **14**. The ^{13}C NMR spectra of **13** and **14** are almost identical except for the signal at δ 8.45 in the spectrum of **14** which was reduced in intensity and split into a multiplet. All the carbon assignments were further reinforced by the expected correlation of $^1J_{CH}$ in **1a** with the bond angle (hybridization) at each carbon (supplementary material). The largest $^1J_{CH}$ was observed for the cyclopropyl carbons, whereas the methylene and methyl carbons had the smallest one-bond C–H couplings.[44]

Isomer assignments for **6** were made by assuming that the signals for the trans salt **6a** corresponded to the trans oxide **1a** with respect to ^{13}C NMR chemical shifts and ^{31}P–^{13}C coupling constants. Internal consistency between oxides and salts was maintained by this assignment.

To confirm our preliminary isomer assignments, a lanthanide shift ($Eu(fod)_3$) study of oxides **1a** and **1b** by both ^1H and ^{13}C NMR spectroscopy was undertaken. Although the original ^1H NMR spectra were complex, proton assignments were made from area integration of the lanthanide shifted spectra and extrapolated back to the original proton spectrum.[45] Only the protons at P–Me for both isomers and at carbon 6 for **1b** were easily assigned in the original proton spectra. The phosphoryl bond in **1b** exerts a significant anisotropic deshielding effect on the neighboring proton at carbon 6 in **1b**.[4,32] Prentice-Hall Framework Molecular Models of **1a** and **1b** revealed that the distances between different atomic sites and the P=O varied significantly. Because the protons or carbons closest to the complexed oxygen usually give the largest lanthanide-induced shift values,[35] a very large shift was found for carbon 6 and its attached proton in oxide **1b**. A less dramatic shift was found for carbon 6 and its allied proton in oxide **1a**. Conversely, larger shifts at carbons 1(2) and the associated protons were observed in **1a** relative to **1b**. The slopes calculated for each proton and carbon confirmed our original assignments (supplementary material).

Because neat samples of both tetracyclic phosphines **7a** and **7b** were found to undergo rapid decomposition, the NMR experiments were conducted on the phosphines prepared in situ. The isomerically pure phosphines prepared in this way gave peaks which did not overlap with those of the reducing reagents. Phosphine **7b** was stable for at least 2 weeks as a dilute solution in benzene. However, phosphine **7a** often isomerized to phosphine **7b** within 12 h at ambient temperatures. The ^1H and ^{13}C NMR chemical shift assignments for phosphines **7a** and **7b** (Tables I and II) were made from the combined results of the following high-field (300-MHz) NMR experiments: ^1H NMR spectrum (clearly integrative), ^{13}C–^1H correlation (HETCOR),[46] attached proton test (APT),[47] and ^{13}C NMR (^1H coupled) spectrum.

Most of the P–C coupling constants in the tetracyclic oxides **1a** and **1b** were larger than analogous couplings in the corresponding 1,2,2,3,4,4-hexamethylphosphetane oxides **25a** and **25b**.[48] In **25a** and **25b** conformational mobility with concurrent averaging of P–C coupling exists. Because the tetracyclic skeleton is rigid, no conformational averaging of P–C couplings can occur, and the observed P–C coupling constants can be larger. It was suggested that the large couplings between bridgehead atoms in the

(42) A third-order rate constant of $(1.3 \pm 0.4) \times 10^4$ L^2 mol^{-2} s^{-1} was obtained by D. W. Allen of Sheffield Polytechnic using a conductimetric method, private communication.

(43) For example, see: Lippma, E.; Pehk, T.; Paasivirta, J. *Org. Magn. Reson.* **1973**, *5*, 277.

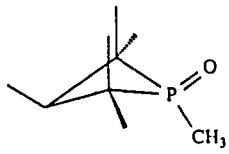
(44) For example, see: Stothers, J. B. *Carbon-13 Spectroscopy*; Academic Press: New York, 1972; Chapter 10.

(45) A HETCOR experiment[46] of oxide **1a** confirmed the ^1H NMR assignments.

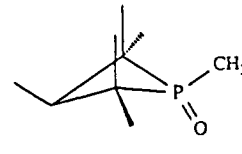
(46) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.

(47) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.

(48) Gray, G. A.; Cremer, S. E. *J. Org. Chem.* **1972**, *37*, 3458, 3470.

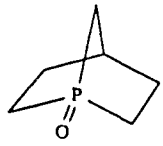


25a

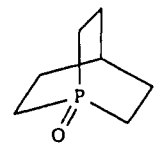


25b

rigid phosphine oxides **26** and **27** were due to multiple



26



27

coupling pathways and that an additive process was involved.[6] We have evidence suggesting that the additivity of multiple coupling pathways is mainly responsible for the large $^{31}P-^{13}C$ coupling constants observed in the tetracyclic system. Previously, workers have noted a definite relationship between the magnitude of three-bond $^{31}P-^{13}C$ coupling and the torsional angles relating these atoms.[8] Using the Karplus-type curve established by Quin and co-workers[8a] from data for several exocyclic dimethylalkylphosphine oxides, the predicted $^3J_{PC}$ for carbon 7 in oxide **1b** (11.8 Hz at ϕ = 142.2°)[49] was much lower than the observed value of 22.4 Hz. However, if the additivity of the two equivalent coupling pathways is considered, 23.6 Hz is predicted. Because the structures of the tetracyclic derivatives differ significantly from the structures used to generate the Karplus relationships, the calculated values represent estimates.[50] If the additivity of multiple coupling pathways were the only contribution to the P–C couplings, then the couplings should be identical for oxides **1a** and **1b**. However, the observed $^{31}P-^{13}C$ coupling constant at carbon 7 in **1a** was larger than **1b** by 5.6 Hz. In fact, most of the $^{31}P-^{13}C$ coupling constants are significantly different between cis and trans isomers. This difference converges along the series: oxides, sulfides, selenides. The constraints imposed by the tetracyclic skeleton preclude any major structural changes between isomers. The similarity of the coupling constants between cis and trans isomers of the tetracyclic salts provides further evidence against major structural distortions. Differences in hybridization are also not evident because the $^1J_{PC}$ couplings to carbons 3(5) are nearly the same between isomers. It is known that one-bond couplings in P(IV) species are dominated by s-orbital electron densities and are reflective of hybridization.[51] However, because the endocyclic $^1J_{PC}$ couplings also contain contributions from $^3J_{PC}$ couplings, the similarity in the isomers may be fortuitous. Nonbonded interactions from the rear orbital lobe of the phosphorus–chalcogen bond to the rear orbital lobes on the coupled carbon provide an additional coupling pathway. The same type of argument was applied to explain the magnitudes of coupling between bridgehead atoms and bridgehead substituents in rigid [*n.n.n*] bicyclic systems.[52] The convergence of the $^{31}P-^{13}C$ coupling differences along the oxide to selenide series may be due to a decrease in the magnitude of the pπ–dπ backbonding in the phosphorus–chalcogen bond[53] which apparently decreases the nonbonding interaction. This result further suggests a dependence of $^2J_{PC}$ with the torsional angle defined by the phosphorus–chalcogen bond and the coupled carbon. Similar angular dependence of $^2J_{PX}$ (X = H, F) with P=O was reported.[50,54]

Consideration of both additivity of multiple coupling pathways and coupling through nonbonded interactions successfully explains the magnitudes of the P–C coupling constants in both the P(III) and the P(IV) derivatives, except for carbon 8 which is 2–4 times the predicted value. This apparent discrepancy is likely due to the cyclopropyl ring within the coupling pathway.[55]

The ^{13}C NMR chemical shifts and P–C coupling constants of the P(IV) derivatives in the tricyclic series (**15**, **17**, **18**, and **22**) were assigned by the usual methods (Table III). Methylene carbons 5 and 7 were readily identified by an APT experiment.[47] Assignment of carbon 7 was confirmed by deuterium labeling. Cyclopropyl carbons 1, 2, and 6 were found upfield and were assigned with the aid of a 2D-INADEQUATE experiment[56] of oxide **17**. The ^{13}C NMR shifts for the phosphine **23** were assigned by comparison to the chemical shifts and $^{31}P-^{13}C$ coupling constants for the corresponding carbons in both *exo*- and *endo*-dimethyl-2-norbornylphosphines.[8a] The cyclopropyl carbons were tentatively assigned by comparison to the P–C couplings for the analogous carbons in the P(IV) tricyclic derivatives. Carbons 5 and 7 were again assigned with the aid of an APT experiment[47] and deuteration at carbon 7. Carbon 3 was distinguished by its low-field absorption. Opening the four-membered ring in the tetracyclic system made the magnitude of $^{31}P-^{13}C$ coupling constants in the resultant tricyclic derivatives unexceptional. The $^3J_{PC}$ coupling constants of the tricyclic derivatives correlated well with known Karplus-type relationships.[8a,57]

Table IV contains ^{31}P NMR shifts which illustrate the correlation of phosphorus functionality and cis–trans stereochemistry along a well-defined series of compounds. The ^{31}P NMR shifts for the phosphines **7a** and **7b** (+47.5 and +39.7, respectively) are in agreement with previously reported values.[17] The signal for the *trans*-phosphine **7a** was downfield from the *cis*-phosphine **7b**. This trend for phosphetanes was noted before.[58] The ^{31}P NMR shift differences between isomeric bridging phosphines was discussed by Quin et al. in detail.[17]

The ^{31}P shift differences between isomers of the oxides, sulfides, and selenides converge along the series with the trans isomers upfield of the cis isomers for each isomer pair. The degree of pπ–dπ backbonding in the phosphorus–chalcogen bond decreases along the same series.[53] Therefore, the shifts for rigid phosphine oxides are the most sensitive to perturbations in the degree of pπ–dπ backbonding. The γ-type interaction[50,59] between the C-6

(49) The torsional angles for the tetracyclic derivatives were determined from the fractional coordinates of the X-ray crystal structure of salt **12b** using a computer program developed by D. W. Bennett of the University of Wisconsin—Milwaukee.

(50) Gorenstein, D. G. *Prog. Nucl. Magn. Reson. Spectrosc.* **1983**, *16*, 1 and references cited therein.

(51) Reference 8b, Chapter 6 and references cited therein.

(52) Barfield, M.; Brown, S. E.; Canada, E. D., Jr.; Ledford, N. D.; Marshall, J. L.; Walter, S. R.; Yakala, E. *J. Am. Chem. Soc.* **1980**, *102*, 3355.

(53) (a) Postle, S. R. *Phosphorus Sulfur Relat. Elem.* **1977**, *3*, 269. (b) Albright, T. A.; Freeman, W. J.; Schweizer, E. E. *J. Org. Chem.* **1975**, *40*, 3437.

(54) Samitov, Y. Y. *J. Gen. Chem. USSR (Engl. Transl.)* **1982**, *52*, 1967; *Zh. Obshch. Khim.* **1982**, *52*, 2211.

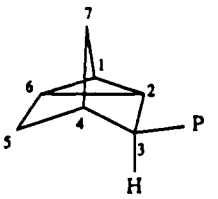
(55) Others have noted that $^{31}P-^{13}C$ coupling through cyclopropyl carbons did not agree with the Karplus relationships[8a] derived from pathways containing only sp^3-hybridized carbons: Buchanon, G. W.; Benezra, C. *Can. J. Chem.* **1976**, *54*, 231.

(56) Mareci, T. H.; Freeman, R. *J. Magn. Reson.* **1982**, *48*, 158.

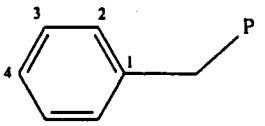
(57) The torsional angles for the tricyclic derivatives prepared for this study were estimated from torsional angles determined from the X-ray structure (see: Garratt, D. G.; Przybylska, M.; Cygler, M. *Can. J. Chem.* **1983**, *61*, 1176) of a 3,5-disubstituted nortricyclene.

(58) Cremer, S. E. *Chem. Commun.* **1970**, 616.

Table III. Chemical Shifts[a] (and $^{31}P-^{13}C$ Coupling Constants)[b] for Tricyclic Compounds



15, 17, 18, 22, 23



15

carbon	15 (diastereomers)[c]		17	18[d]	22	23[e]
1	10.84 (0.0)	10.84 (0.0)	10.58 (0.7)	10.99 (0.7)	11.15 (0.0)	11.01 (0.0)[f]
2	12.12 (0.0)	11.62 (0.0)	11.87 (0.0)	12.52 (0.0)	12.44 (0.0)	13.74 (8.6)[f]
3	44.43 (71.7)	44.23 (72.4)	46.26 (74.0)	46.63 (99.6)	40.08 (54.0)	50.60 (11.0)
4	32.24 (2.7)	32.06 (3.3)	31.88 (2.6)	32.49 (1.8)	32.98 (2.6)	33.26 (9.8)
5	35.70 (13.5)	35.70 (13.5)	35.79 (13.2)	36.12 (15.0)	35.87 (14.1)	35.56 (3.7)
6	11.66 (10.8)	11.56 (10.6)	11.56 (11.1)	11.82 (12.5)	12.26 (11.4)	12.06 (6.1)[f]
7	31.02 (0.0)	30.90 (0.0)	30.45 (0.0)	31.07 (0.0)	31.83 (0.0)	31.67 (12.2)
P-Me	14.11 (66.9)	13.68 (66.6)	16.73 (67.4)	16.13 (89.4)	9.69 (53.6)	14.52 (14.6)
			16.65 (67.4)			13.63 (14.7)

[a] Chemical Shifts (in $CDCl_3$) in ppm from TMS–^{13}C (internal 1–5%); accurate to ±0.02 ppm. [b] Coupling constants in Hz. [c] Benzyl carbons: $PhCH_2$, 39.10 (60.6), 38.87 (61.0); Ph-1, 132.71 (6.4), 132.71 (6.4); Ph-2, 129.54 (5.2), 129.54 (5.2); Ph-3, 128.68 (2.6), 128.68 (2.6); Ph-4, 126.72 (2.8), 126.72 (2.8). [d] In D_2O/NaOD in ppm from TSP. [e] In C_6D_6 in ppm from C_6D_6 (δ 128.50). [f] Tentative assignments; may be interchanged.

Table IV. ^{31}P NMR Chemical Shifts of Tetracyclic Derivatives[a]

compd	X	Y	chemical shift
1a	O	CH_3	55.9
1b	CH_3	O	76.7
3	O	Ph	48.3
6a[b]	Cl	CH_3	95.7
6b[b]	CH_3	Cl	86.6
7a[c]		CH_3	47.4[d]
7b[c]	CH_3		39.5[e]
8a	S	CH_3	74.7
8b	CH_3	S	83.6
9a	Se	CH_3	63.8
9b	CH_3	Se	67.9
10a	$PhCH_2$	CH_3	70.4
10b	CH_3	$PhCH_2$	73.4
11a	*p*-$FPhCH_2$	CH_3	70.1[f]
11b	CH_3	*p*-$FPhCH_2$	73.3[g]
12a	*p*-NO_2PhCH_2	CH_3	70.2
12b	CH_3	*p*-NO_2PhCH_2	73.2
13	CH_3	CH_3	69.2

[a] Chemical shifts (in $CDCl_3$ unless otherwise noted) in ppm from external 85% H_3PO_4. [b] Tetrachloroaluminate salt in CD_2Cl_2, 3:1 ratio of **6a** to **6b**. [c] In C_6D_6. [d] Lit.[17] 47.5. [e] Lit.[17] 39.7. [f] $^{31}P-^{19}F$ coupling constant is 6.1 Hz. [g] $^{31}P-^{19}F$ coupling constant is 6.1 Hz.

proton and the P–Me group in oxide **1a** leads to a ^{31}P NMR chemical shift for **1a** that is upfield of oxide **1b**. The ^{31}P NMR chemical shift for **1b** is further downfield than the typical range for phosphines oxides that contain only sp^3-hybridized carbon–carbon bonds.[50,60] The ^{31}P NMR chemical shift differences between the cis and trans isomers of the tetracyclic benzyl salts **10–12** were relatively small (3 ppm).

Experimental Section

Tetramethylsilane was used as an internal reference for ^1H and ^{13}C NMR spectra unless indicated otherwise. When D_2O was the solvent, $(CH_3)_3Si(CH_2)_3SO_3Na{\cdot}H_2O$ was the reference standard. ^{31}P NMR chemical shifts were recorded using external 85% H_3PO_4 as the reference with positive values denoting downfield shifts. All boiling and melting points are uncorrected. Reactions were conducted under a nitrogen atmosphere. Standard workup refers to drying extraction solvents over either $MgSO_4$ or Na_2SO_4 and evaporating in vacuo on a rotary evaporator at or below 40 °C. Manipulation of moisture sensitive intermediates was conducted in a glovebox.

4-Chloro-4-methyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]-octane Chloride (2). A 500-mL three-necked flask (equipped with a mechanical stirrer, reflux condenser, and nitrogen inlet) was changed with dichloromethylphosphine (88 g, 0.75 mol), freshly distilled bicyclo[2.2.1]hepta-2,5-diene (115 g, 1.25 mmol), 100 mL of cyclohexane, and 1 g of copper stearate. The reaction flask was covered with aluminum foil to exclude light. The mixture was stirred and heated at 65–80 °C for 1 week. A thick deposit of brown precipitate gradually formed. The precipitate was filtered in a glovebox and washed with dry ether to give 94.0 g (60%) of a light brown powder. The yield of crude product on several runs ranged from 60 to 70%. Use of an excess of diene or cyclohexane as a diluent facilitated stirring but did not decrease the yield. When the reaction of dichloromethylphosphine with the diene was run for 11 days at room temperature, only 21% of the desired adduct was obtained. The adduct was hygroscopic and was isolated using glovebox techniques. Purification was accomplished by dissolving in CH_2Cl_2–$CHCl_3$ at room temperature, followed by cooling to −78 °C to give a white solid: ^1H NMR (60 MHz, dilute in CD_2Cl_2) δ 3.55–3.35 (m, 2 H), 3.35–3.16 (m, 1 H), 3.04 (d, J_{PH} = 12.5 Hz, 3 H), 2.54–2.20 (m 1 H), 2.20–2.02 (m, 2 H), 1.98–1.77 (m, 2 H).

The ^1H NMR spectrum (60 MHz) of the chloride salt **2** showed a sharp doublet for the P–CH_3 signal in dilute CD_2Cl_2 solution. In concentrated solutions or in $CDCl_3$, the signal broadened considerably. At 0 °C in $CDCl_3$ the P–CH_3 doublet broadened, and at −20 °C an apparent triplet evolved (overlapping doublets). The spectrum reverted to its original form upon warming to ambient temperature. The P–Me doublets at −20 °C in $CDCl_3$ and at 25 °C in CD_2Cl_2 were reduced to singlets upon ^{31}P irradiation. The approximate ratio of isomers in a −20 °C $CDCl_3$ sample of **2**, by integration of the P–CH_3 peaks, was 3.2:1 (low field to high field). The proton-decoupled ^{13}C NMR spectrum (sealed NMR tube, 75 MHz, CD_2Cl_2) showed broad signals at ambient temperature. Upon cooling to −70 °C, the spectrum showed two components, which had chemical shifts and P–C coupling constants consistent with the tetrachloroaluminate salts **6a** and **6b**. The ^{31}P NMR spectra of salt **2** showed similar behavior: ^{31}P NMR (−76 °C, 121 MHz, CD_2Cl_2) δ 101.3 and 88.9 in 4:1 ratio.

(59) These interactions are well-known in ^{13}C NMR spectroscopy and are called enforced δ interactions in: Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: New York, 1987; Chapter 3.

(60) (a) Reference 1c, Chapter 5 and references cited therein. (b) Reference 8b, Chapter 1 and references cited therein.

***trans*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Oxide (1a).** The crude salt **2** was suspended in 200 mL of chloroform, cooled with an ice–water bath, and treated with 50 mL of water. Solid sodium bicarbonate was added until the aqueous layer was neutralized. The aqueous layer was extracted with three 200-mL portions of chloroform. Standard workup gave a white solid which was sublimed (110–120 °C, 0.05 mm) and recrystallized from benzene–cyclohexane to give a crystalline, hygroscopic solid in 70% yield, mp 156–157 °C (lit.[2] mp 157 °C): ^{1}H (300 MHz, $CDCl_3$) δ 2.59–2.45 (m, 2 H, H-3,5), 1.98–1.93 (m, 1 H, H-8), 1.88–1.83 (m, 1 H, H-6), 1.85–1.81 (m, 2 H, H-1,2), 1.74 (d, J_{PH} = 12.1 Hz, 3 H, P-Me), 1.57–1.53 (m, 2 H, H-7).

***trans*- and *cis*-4-Chloro-4-methyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane Tetrachloroaluminate (6a and 6b).** In a glovebox, a solution of phosphetanium chlorides **2a** and **2b** (44.2 g, 0.21 mol) in 300 mL of dry CH_2Cl_2 was cooled to 0 °C. Anhydrous $AlCl_3$ (28.2 g, 0.21 mol) was slowly added in several portions. A ^{1}H NMR spectrum of this solution (60 MHz, $CDCl_3$) showed two sharp doublets (P–CH_3) at δ 2.74 (J = 12 Hz) and δ 2.90 (J = 13 Hz) in an area ratio of 2:1, respectively. A CH_2Cl_2 solution of the tetrachloroaluminate salts **6a** and **6b** was filtered and the solvent removed in vacuo to give a semi-solid. The crude salt was dissolved in a minimum of dry acetonitrile and precipitated with anhydrous ether to give a white solid, **6a:6b** (1:6). Concentration of the mother liquor gave a syrup with an isomer ratio of approximately 5:2 (**6a:6b**).

Inverse H_2O Quench of the Tetrachloroaluminate Salts 6a and 6b; *cis*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]-octane 4-Oxide (1b). A solution of **6a:6b** (5:2, 4.4 g, 13 mmol) in 50 mL of anhydrous CH_2Cl_2 was slowly added to cold water (0–5 °C) over 1 h. The layers were separated, and the water was extracted twice with 50-mL portions of CH_2Cl_2. The water layer was cooled with an ice–water bath, slowly neutralized by addition of $NaHCO_3$, and extracted twice with 50-mL portions of CH_2Cl_2. Standard workup gave 1.6 g (81%) of a 4:1 mixture of oxides **1a:1b**. Enrichment of isomer **1b** in the mother liquor was achieved by repeated recrystallization from cyclohexane. The residue from the mother liquor was then sublimed (100 °C, (0.1 mm)), mp 71–74 °C (about 95% of isomer **1b**): ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.42–3.22 (m, 1 H), 2.45–2.38 (m, 2 H), 1.67 (d, J_{PH} = 12.5 Hz, 3 H), 2.10–1.60 (m, 3 H), 1.48–1.30 (m, 2 H). Similarly, 2:1 and 1:6 mixtures of **6a:6b** gave 2:1 and 2:3 mixtures of **1a:1b**, respectively. In another run the tetrachloroaluminate salts **6a** and **6b** (from 8 g of the chlorides in 100 mL CH_2Cl_2) were cooled and treated dropwise with 50 mL of water over 1 h. This workup procedure gave a 77% yield of oxide which was >90% of oxide **1a**.

***trans*-4-Phenyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Oxide (3).** A mixture of distilled bicyclo[2.2.1]hepta-2,5-diene (27.6 g, 0.30 mol) and dibromophenylphosphine[61] (53.6 g, 0.20 mol) was allowed to stand for 2 weeks in a stoppered Erlenmeyer flask. The precipitate was filtered and washed with dry ether to give 16 g of impure solid. The product, in CH_2Cl_2, was cooled with an ice–water bath and treated with 100 mL of water which contained 30 g of $NaHCO_3$. The aqueous layer was extracted with 3 × 200 mL of $CHCl_3$. Standard workup gave a residue which was sublimed (100 °C (0.5 mm)) to give **3** (5.8 g, 13%), mp 130–141 °C. Repeated recrystallization from cyclohexane gave the analytical sample, mp 154–156 °C: ^{1}H NMR (300 MHz, C_6D_6) δ 7.75–7.64 (m, 2 H), 7.23–7.12 (m, 3 H), 2.35–2.27 (m, 2 H), 1.84–1.77 (m, 2 H), 1.61–1.54 (m, 1 H), 1.39–1.30 (m, 1 H), 1.14–1.06 (m, 2 H); IR (KBr) 1190 cm^{-1} (P=O). Anal. Calcd for $C_{13}H_{13}OP$: C, 72.14; H, 6.10; P, 14.37. Found: C, 72.09; H, 5.97; P, 14.13. Attempts to repeat this preparation under the conditions described, at elevated temperatures or with $AlCl_3$ or PBr_3 catalysis, were unsuccessful.

***cis*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane (7b).** A solution of the oxide **1a** (12.5 g, 82 mmol) in 1.2 L of anhydrous benzene was cooled to 10 °C. To this solution was added trichlorosilane (10.8 mL, 0.11 mol) in 125 mL of anhydrous benzene over 15 min. The reaction mixture was stirred at room temperature for 1–3 h, followed by heating at reflux temperature for 2 h. The solution was cooled to 5 °C, and 100 mL of 20% NaOH was added dropwise. The mixture was then stirred at room temperature until two clear layers were evident. The organic layer was washed with several portions of saturated NaCl. The yield, based on the overall yield on quaternization with alkyl bromide, ranged from 67–79% in five runs. Attempts to reduce higher concentrations of the oxide in benzene led to extensive formation of a white solid which was insoluble in both benzene and water.

In one run the phosphine was isolated by concentration of the benzene layer and distillation (bp 25 °C (1.0 mm)). This is not recommended since the phosphine polymerized when neat and persists for a longer period if diluted in benzene. A sample was prepared in an NMR tube by treating oxide **1a**, 0.3 M in C_6D_6, with 1 equiv of Cl_3SiH at room temperature. The phosphine prepared in this way was stable for 2 weeks at room temperature under nitrogen: ^{1}H NMR (300 MHz, C_6D_6) δ 2.15–2.08 (m, 1 H, H-6), 1.99–1.93 (m, 1 H, H-8), 1.95–1.85 (m, 2 H, H-3,5), 1.43–1.38 (m, 2 H, H-1,2), 1.27–1.23 (m, 2 H, H-7), 1.00 (d, J_{PH} = 4.0 Hz, 3 H, P-Me).

***cis*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Sulfide (8b).** The phosphine **7b** prepared from reduction of oxide **1a** (3.0 g, 20 mmol) with 1.3 equiv of Cl_3SiH was stirred with elemental sulfur (1.0 g, 31.8 mmol) in benzene at room temperature for 3 days. The excess sulfur was filtered, and the solvent evaporated to give a white solid which was recrystallized from cyclohexane and sublimed (80 °C (0.1 mm)) to give 2.55 g (75%), mp 111–113.5 °C: ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.54–3.24 (m, 1 H), 2.56–2.33 (m, 2 H), 2.20–1.92 (m, 1 H), 1.92 (d, J_{PH} = 12.5 Hz, 3 H), 1.72–1.51 (m, 4 H). Analyzed as a 1:1 mixture of isomers, see preparation of trans sulfide **8a**.

***cis*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Selenide (9b).** Using oxide **1a** (0.50 g, 3.3 mmol), the same procedure used to make sulfide **8b** was followed, except selenium metal (0.26 g, 3.3 mmol) was added to the phosphine. Evaporation left a crude yellow solid which was sublimed and then recrystallized from absolute ethanol, yielding white needles (0.45 g, 63%), mp 134–135 °C: ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.5–3.3 (m, 1 H), 2.7–2.4 (m, 2 H), 2.4–2.25 (m, 1 H), 2.12 (d, J_{PH} = 12.5 Hz, 3 H), 1.9–1.55 (m, 4 H). Anal. Calcd for $C_8H_{11}Se$: C, 44.26; H, 5.11. Found: C, 44.21: H, 5.01. The selenide turned pink on standing, but no change was observed in either ^{1}H, ^{13}C, or ^{31}P NMR spectra.

General Procedure: Quaternization of Phosphine 7b. The phosphonium salts **10b–12b** and **13** and **14** were prepared by treatment of the phosphine **7b** in benzene–ether with an excess of the required alkyl halide in a sealed flask under nitrogen for three days at room temperature. The isomer ratios were determined from the ^{1}H and ^{31}P NMR spectra.

***cis*-4-Benzyl-4-methyl-4-phosphoniateracyclo-[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (10b).** This salt, mp 163–164 °C, was prepared in 85% overall yield. In most runs a single isomeric product was formed. Occasionally, 5% or less of the trans isomer **10a** formed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.25 (m, 5 H), 4.75 (d, J_{PH} = 15.3 Hz, 2 H), 3.26–2.98 (m, 3 H), 2.27 (d, J_{PH} = 14.0 Hz, 3 H), 2.25 (m, 1 H, obscured), 2.1–1.9 (m, 2 H), 1.8–1.59 (m, 2 H). Analyzed as a 1:1 mixture of **10a:10b**. Anal. Calcd for $C_{15}H_{18}BrP$: C, 58.26; H, 5.87. Found: C, 58.14; H, 5.85. Bromine analysis conducted on a 73:27 mixture of **10b:10a**. Anal. Calcd: Br, 25.84. Found: Br, 25.86.

***cis*-4-(4′-Fluorobenzyl)-4-methyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (11b).** This salt was prepared in 42% yield to give a 90:10 mixture of isomers **11b:11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–6.90 (m, 4 H), 4.73 (d, J_{PH} = 15.3, 2 H), 3.05 (m, 3 H), 2.3 (m, 1 H, obscured), 2.22 (d, J_{PH} = 14.2 Hz, 3 H), 2.15–1.88 (m, 2 H), 1.80–1.55 (m, 2 H). The analytical sample of **11b**, mp 214–215 °C, was prepared by successive recrystallizations from CH_3CN–EtOAc. Anal. Calcd for $C_{15}H_{17}BrFP$: C, 55.07; H, 5.24. Found: C, 54.83; H, 5.13.

***cis*-4-Methyl-4-(4′-nitrobenzyl)-4-phosphoniatetracyclo-[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (12b).**[39] To the phosphine **7b** from the reduction of 12.5 g of oxide **1a** with trichlorosilane) was added 2 equiv of *p*-nitrobenzyl bromide in ether and the mixture stirred 3 days at room temperature under nitrogen. The precipitate was filtered and recrystallized from dry acetonitrile to give 17 g (71%) of salt, mp 213–215.5 °C. Repeated runs gave salt **12b** in 93–100% isomeric purity: ^{1}H NMR (60 MHz, CF_3COOH) δ 8.45–8.23 (m, 2 H), 7.83–7.60 (m, 2 H), 4.39 (d, J_{PH} = 14 Hz, 2 H), 3.48–3.32

(61) Quin, L. D.; Gratz, J. P.; Barket, T. P. *J. Org. Chem.* **1968**, *33*, 1034.

(m, 1 H), 3.19–2.98 (m, 2 H), 2.65–2.35 (m, 1 H), 2.10 (d, J_{PH} = 13.5 Hz, 3 H), 2.22–2.06 (m, 2 H), 2.00–1.87 (m, 2 H). Anal. Calcd for $C_{15}H_{17}O_2NBrP$: C, 50.86; H, 4.84; Br, 22.35. Found: C, 50.58; H, 5.02; Br, 22.49.

4,4-Dimethyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (13). This salt, mp 213–216 °C, was obtained in 75% overall yield. The analytical sample was prepared by recrystallization from CH_3CN–EtOAc: ^1H NMR (300 MHz, $CDCl_3$) δ 3.18–3.12 (m, 1 H), 3.08–3.02 (m, 2 H), 2.59 (d, J_{PH} = 14.3 Hz, 3 H), 2.36 (d, J_{PH} = 14.3 Hz, 3 H), 2.28–2.21 (m, 1 H), 2.04–1.97 (m, 2 H), 1.75–1.71 (m, 2 H). Anal. Calcd for $C_9H_{14}BrP$: C, 46.37; H, 6.06; P, 13.28; Br, 34.28. Found: C, 46.22; H, 6.07; P, 13.10; Br, 34.30. Treatment of the phosphine **7b** (from Cl_3SiH reduction) with CD_3Br gave salt **14** whose ^1H NMR spectrum ($CDCl_3$) was identical to the spectrum of salt **13** except for the absence of the lower field doublet at δ 2.59.

***trans*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane (7a).** To a solution of the oxide **1a** (1.35 g, 8.8 mmol) in 65 mL of dry benzene was added 1.3 equiv of phenylsilane. The reaction mixture was stirred at room temperature under nitrogen for 2–2.5 h. The yield, based on quaternization with alkyl bromide, ranged from 72 to 78%. Isolation of the phosphine was accompanied by extensive formation of polymer. Attempts to reduce higher concentrations of the oxide with phenylsilane resulted in formation of a white polymeric material, insoluble in benzene and water.

The sample for NMR spectral studies was prepared in situ by treating oxide **1a** (0.3 M in C_6D_6 in a centrifuge tube under nitrogen), cooled with an ice–water bath, with 1.1 equiv of triethylamine followed by 1.05 equiv of Cl_3SiH. The tube was shaken for 15 min to mix the components thoroughly and warmed to room temperature. The reaction mixture was centrifuged, and the supernatant was transferred into a NMR tube in the glovebox. The sample prepared in this way often isomerized to phosphine **7b** within 12 h at room temperature: ^1H NMR (300 MHz, C_6D_6) δ 3.21–3.17 (m, 1 H, H-6), 1.86–1.76 (m, 2 H, H-3,5), 1.72–1.66 (m, 2 H, H-1,2), 1.66–1.59 (m, 1 H, H-8), 1.33 (d, J_{PH} = 3.8 Hz, 3 H, P-Me), 1.26–1.20 (m, 2 H, H-7).

***trans*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Sulfide (8a).** To the oxide **1a** (0.50 g, 3.5 mmol) in 55 mL of dry benzene was added phenylsilane (0.6 mL, 4.8 mmol) and elemental sulfur (0.32 g, 10 mmol). The mixture was stirred for 2 days at room temperature. The excess sulfur was filtered and the solvent evaporated to afford a white solid which was recrystallized from cyclohexane to give 0.33 g (60%) of the sulfide **9a**, mp 134–135 °C: ^1H NMR (60 MHz, $CDCl_3$) δ 2.62–2.36 (m, 3 H), 2.10 (d, J_{PH} = 12.0 Hz, 3 H), 2.15–1.81 (m, 3 H), 1.71–1.51 (m, 2 H). A 1:1 mixture of isomers was submitted for elemental analysis. Anal. Calcd for $C_8H_{11}PS$: C, 56.45; H, 6.51. Found: C, 56.53; H, 6.30. Alternatively, the oxide **1a** (3.3 g, 21 mmol) was reduced and worked up using the procedure described for preparing sulfide **8b** except that triethylamine (5.5 g, 55 mmol) was added to the benzene prior to treatment with Cl_3SiH (3.7 g, 27 mmol). After recrystallization, 1.25 g (35%) of sulfide **8a** was obtained, mp 129–132 °C. The ^1H and ^{13}C NMR spectra were identical to those for the sulfide derived from phenylsilane reduction.

***trans*-4-Methyl-4-phosphatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane 4-Selenide (9a).** A slurry of oxide **1a** (2.0 g, 13 mmol) and phenylsilane (1.5 g, 14 mmol) in 50 mL of benzene was stirred for 1 h at room temperature. All solid material dissolved after 30 min. At this point selenium metal (1.1 g, 14 mmol) was added, and the mixture was stirred overnight. By morning, nearly all of the selenium had dissolved. The solution was filtered, the solvent was evaporated, and the crude white solid was recrystallized from ethanol. The crystals were then sublimed (90 °C, (0.025 mm)), affording 2.0 g (71%) of **9a**, mp 154–155 °C: ^1H NMR (60 MHz, $CDCl_3$) δ 2.7–2.55 (m, 2 H), 2.5–2.45 (m, 1 H), 2.3 (d, J_{PH} = 12.0 Hz, 3 H), 2.1–1.9 (m, 3 H), 1.7–1.55 (m, 2 H). Anal. Calcd for $C_8H_{11}PSe$: C, 44.26; H, 5.11. Found: C, 44.50; H, 5.23.

General Procedure: Quaternization of Phosphine 7a. The phosphonium salts **10a–12a** were made by treatment of phosphine **7a** (prepared by reduction of oxide **1a** with phenylsilane in benzene as described) with the requisite alkyl halide in a sealed flask under nitrogen for three days at room temperature. Isomer ratios were determined from the ^1H and ^{31}P NMR spectra.

***trans*-4-Benzyl-4-methyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (10a).** This salt (greater than 90% of one isomer) was prepared in 72% yield. The mixture was recrystallized from CH_3CN–EtOAc, mp 151–153 °C: ^1H NMR (60 MHz, $CDCl_3$) δ 7.54–7.21 (m, 5 H), 4.33 (d, J_{PH} = 14.2 Hz, 2 H), 3.25–3.0 (m, 2 H), 3.06–2.92 (m, 2 H), 2.36 (d, J_{PH} = 12.8 Hz, 3 H), 2.14 (m, 2 H), 1.87–1.62 (m, 2 H).

***trans*-4-(4′-Fluorobenzyl)-4-methyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (11a).** This salt (80% of one isomer on several runs) was prepared in 78% yield. The mixture was recrystallized from CH_3CN–EtOAc to give a white solid, mp 143–151 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 7.77–7.10 (m, 4 H), 4.34 (d, J_{PH} = 14.1 Hz, 2 H), 4.12–3.58 (m, 1 H), 3.20–2.78 (m, 2 H), 2.35 (d, J_{PH} = 13.3 Hz, 3 H), 2.3–1.7 (m, 2 H), 1.87–1.56 (m, 2 H), 1.68–1.12 (m, 1 H). A 1:1 mixture of **11a:11b** was submitted for elemental analysis. Anal. Calcd for $C_{15}H_{17}BrFP$: C, 55.07; H, 5.24. Found: C, 55.00; H, 5.15.

***trans*-4-(4′-Nitrobenzyl)-4-methyl-4-phosphoniatetracyclo[3.3.0.0^{2,8}.0^{3,6}]octane Bromide (12a).** This salt (80% of one isomer from several runs) was prepared in 75% yield. Recrystallization from ethanol–ether gave yellow crystals, mp 186–188 °C: ^1H NMR (60 MHz, CF_3COOH) δ 8.50–8.16 (m, 2 H), 7.77–7.43 (m, 2 H), 4.03 (d, J_{PH} = 15.1 Hz, 2 H), 3.41–3.13 (m, 1 H), 3.11–2.86 (m, 2 H), 2.75–2.38 (m, 1 H), 2.16 (d, J_{PH} = 13.5 Hz, 3 H), 2.33–1.98 (m, 2 H, obscured), 2.08–1.80 (m, 2 H). Anal. Calcd for $C_{15}H_{17}BrNO_2P$: C, 50.86; H, 4.84. Found: C, 50.68, H, 5.01.

General Procedure: Isomerization of Salts 10a, 10b, 12a, and 12b with Pyridine. A solution of salt **12b** (50 mg, 0.14 mmol) in 0.4 mL of $CDCl_3$ in a 5-mm NMR tube was treated with pyridine (distilled from KOH, 0.05 mL, 0.62 mmol) at room temperature. A ^1H NMR spectrum of the reaction mixture indicated a 3:2 mixture of **12b:12a** after 12 days at room temperature. Treatment an 85:15 mixture of salts **12a:12b** with pyridine under similar conditions also gave a 3:2 mixture of **12b:12a**. Similar treatment of salt **10b** (or a 85:15 mixture of **10a:10b**) with pyridine gave a 55:45 ratio of **10b:10a** after 12 days.

General Procedure: Isomerization of Salts 10a, 10b, 12a, and 12b with NaOH. A solution of benzyl salt **10b** (5 mg, 0.016 mmol) in 0.5 mL of $CDCl_3$ or D_2O in a 5-mm NMR tube was treated with one drop of 0.06 N NaOH (approximately 0.003 mmol) at room temperature. The reaction mixture was periodically monitored by ^1H and ^{31}P NMR spectroscopy. A 1:1 ratio of salts **10a:10b** was formed after 1 month in $CDCl_3$–H_2O and after 1 day in D_2O. An 85:15 ratio of **10a:10b** gave similar results. Treatment of **12a** or **12b** in $CDCl_3$ under identical conditions gave a 1:1 mixture of **12a:12b**.

Reaction of the Tetracyclic Oxide 1a with Base: Methyltricyclo[2.2.1.0^{2,6}]hept-3-ylphosphinic Acid (18). A solution of the oxide **1a** (1.54 g, 10 mmol) in 10 mL of 2 N NaOH was heated at reflux temperature for 48 h. The reaction mixture was cooled, made weakly acidic with dilute HCl and then extracted with three × 10 mL of $CHCl_3$. Standard workup gave 400 mg (23%) of crude, hygroscopic phosphinic acid **18** which solidified on standing. The solid **18** was triturated with cyclohexane and then sublimed, mp 70–74 °C: ^1H NMR (300 MHz, D_2O/NaOD) δ 2.20–2.15 (m, 1 H), 1.97 (br, d, 1 H), 1.70–1.67 (m, 1 H), 1.67–1.62 (br d, 1 H), 1.47–1.21 (m, 4 H), 1.35 (d, J_{PH} = 13.4 Hz, 3 H), 1.21–1.14 (br d, 1 H). On ^{31}P decoupling, the doublets at δ 1.67–1.62 and 1.35 became singlets: ^{31}P NMR (24 MHz, D_2O, NaOD) δ 51.5. Tetracyclic oxide **1a** heated at reflux in NaOD/D_2O gave phosphinic acid **18** whose ^1H NMR no longer had a peak at δ 1.97. Crude reaction rates were also followed using ^1H NMR spectroscopy. A solution of 100 mg of oxide **1a** was treated with 1 mL of 1 N NaOH; after 8 days at 25 °C the reaction was 50% complete. A similar run with 5 N NaOH at 35 °C was about 50% complete in 25 min and 90% complete in 75 min.

The hygroscopic phosphinic acid **18** was converted to a solid thiuronium salt for characterization. A suspension of the acid **18** (850 mg, 4.94 mmol) in 10 mL of water was neutralized with 1 N NaOH. To this solution, heated to 95 °C, was added a saturated ethanolic solution of *S*-(4-chlorobenzyl)thiuronium chloride (2.37 g, 10 mmol), and the mixture stirred for 10 min. A crystalline solid (1.50 g, 85%) was collected after 24 h. An analytical sample, mp 183–185 °C, was obtained by recrystallization from water: ^1H NMR (300 MHz, CD_3OD, δ 3.35) δ 7.49–7.39 (m, 4 H), 4.97 (br s, 4 H), 4.45 (s, 2 H), 2.16 (br s, 1 H), 1.97 (br

d, 1 H), 1.58 (br d, 1 H), 1.39–1.07 (m, 6 H), 1.23 (d, J_{PH} = 13.2 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD, δ 49.0) δ 171.41, 135.32, 134.52, 131.72, 130.15, one signal obscured by CD_3OD signal, 36.71 (J = 14.0 Hz), 35.41, 33.15 (J = 1.8 Hz), 31.38, 17.17 (J = 90.3 Hz), 13.15, 12.16 (J = 12.2 Hz), 11.44; ^{31}P NMR (121 MHz, CD_3OD) δ 42.3. Anal. Calcd for $C_{16}H_{22}ClN_2O_2PS$: C, 51.54; H, 5.95; N, 7.51. Found: C, 51.91; H, 6.12; N, 7.65.

Reaction of the Benzyl Salt 10b with Base: Benzylmethyltricyclo[2.2.1.0^{2,6}]hept-3-ylphosphine Oxide (15). A solution of the salt **10b** (0.93 g, 3 mmol) in 5 mL of water was stirred with 3 mL of 1 N NaOH for 1 h at room temperature. The solution was extracted with 3 × 20 mL $CHCl_3$. Standard workup gave 0.71 g (96%) of **15**, mp 118–127 °C. The analytical sample was prepared by recrystallization (benzene–cyclohexane) and sublimation to give a mixture of diastereomers, mp 124–129 °C: ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.4–7.3 (m, 5 H), 3.18 (broad unsymmetrical doublet, J_{PH} = 14 Hz, 2 H), 2.4–1.8 (m, 2 H), 1.7–1.0 (m overlapped with 2 doublets, J_{PH} = 12 Hz, 10 H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 44.6 and 44.0 in 1:1 ratio. Anal. Calcd for $C_{15}H_{19}OP$: C, 73.14; H, 7.79; Found: C, 72.88; H, 7.61.

GLPC Analysis of the Decomposition of 10b with Hydroxide. A solution of 3 g of salt **10b** in 3 mL of water was covered with 5 mL of 30–40 °C petroleum ether and then treated with 1 equiv of 1 N NaOH solution. Aliquots of the petroleum ether were sampled after 17 h by injection into a 13 ft × $^1/_4$ in. 20% DEGS on 80–100 mesh Chromosorb W column (100 °C, flow rate 80 cc He min^{-1}). A sample containing a weighed amount of toluene in petroleum ether (40 °C) was used as a standard and control. The retention time for toluene was 5.2 min. Less than 1% of the theoretical maximum (based on 100% benzyl cleavage) of toluene was detected.

Base Decomposition of the *p*-Nitrobenzylphosphonium Salt 12b. To the salt **12b** (3.52 g, 0.01 mol) in 10 mL of water, was added 10 mL of 1 N NaOH dropwise at 0 °C over 1 h. The pH was then adjusted to pH 7 with HCl and the mixture lyophilized to remove water. The residue was sublimed to give 1.4 g (91%) of a 65:35 mixture of **1a** to **1b**. In addition, *p*-nitrotoluene and bis(4,4′-dinitrodibenzyl) were isolated in about equal molar amounts. The byproducts were identified by mixture melting points; *p*-nitrotoluene (mp 50–51 °C) and bis(4,4′-dinitrodibenzyl) (mp 151–153 °C). Addition of the salt to base gave a 75:25 mixture of oxides **1a** to **1b**.

Reaction of the Dimethylphosphonium Salt 13 with Base: Dimethyltricyclo[2.2.1.0^{2,6}]hept-3-ylphosphine Oxide (17). A solution of 2.5 g of the salt **13** in 5 mL of water was stirred for 2 h with 5.3 mL of 2 N NaOH. The aqueous layer was extracted with 3 × 10 mL portions of $CHCl_3$. Standard workup gave **17** (1.60 g, 87%). The product was recrystallized from benzene–cyclohexane and sublimed (100 °C (0.1 mm)), mp 120–123 °C: ^{1}H NMR (300 MHz, $CDCl_3$; a HETCOR experiment[46] enabled the following signal identification) δ 2.29–2.23 (br s, 1 H, H-4), 1.87 (br d, J_{HH} = 11 Hz, 1 H, H-7 syn; signal disappears when **17** was generated by treatment of **13** with 0.07 N NaOD in D_2O), 1.56–1.52 (br s, 1 H, H-3), 1.43 (d, J_{PH} = 12.5 Hz, 3 H, P-Me), 1.42 (d, J_{PH} = 12.3 Hz, 3 H, P-Me), 1.38–1.28 (m, 1 H, not clearly observed, H-5), 1.38–1.17 (m, 2 H, not clearly observed, H-1, H-6), 1.33–1.24 (m, 1 H, not clearly observed, H-2), 1.30–1.20 (m, 1 H, not clearly observed, H-5), 1.18 (br d, J_{HH} = 11 Hz, 1 H, H-7 anti); ^{31}P NMR (24 MHz, $CDCl_3$) δ 42.6. Anal. Calcd for $C_9H_{15}OP$: C, 63.51; H, 8.88; P, 18.21. Found: C, 63.70; H, 8.66; P, 18.16.

Partial conversion (50%) of the salt to the oxide **17** in 0.07 N $NaOD/D_2O$ was also followed in the ^{1}H NMR. The P–CH_3 groups of the unreacted salt showed no apparent broadening, and the P–CH_3 groups of the oxide also appeared as a sharp doublet. Complete conversion with $NaOD/D_2O$ gave oxide with a sharp P–CH_3 doublet. ^{2}H NMR (46 MHz, broadband ^{1}H decoupled, $CHCl_3$ with 2% C_6D_6 (δ 7.25)) δ 1.78.

Kinetic Study of the Alkaline Hydrolysis of the Dimethylphosphonium Salt 13. The rate measurements were made using a Corning-12 pH meter with an expansion scale. The phosphonium salt **13** was weighed, dissolved in water, and equilibrated at 0 °C. A solution of 0.001 N KOH was prepared in distilled deionized water and equilibrated to 0 °C. A calomel combination electrode was first calibrated with standard buffers at pH = 4, 7, and 10 at 0 °C. The electrode was placed in an aliquot of base and allowed to stabilize to a constant value. One equivalent of equilibrated salt solution was then added to the base solution, and readings were taken through three half-lives. Because of the rapidity of the reaction, the first half-life was missed. Readings were taken every minute for 30 min on average. After 15 min the decomposition was 90% complete. A t_∞ was recorded after 24 h. The accuracy of the method was checked by running a blank using only base and distilled water; no variance in pH was observed after 1 h. The hydrolysis was assumed to be second order in $[OH^-]$. Using the formula[42] $k = 1/2t\,(1/C_0^2 - 1/C^2)$, where $C_0 = [OH^-]$ initially and $C = [OH^-]$ at time t, and assuming that the initial concentrations of salt and base were identical, the slope of a plot of t vs $^1/_2(1/C_0^2 - 1/C^2)$ gave $1/k$. Three runs at 0 °C were made and gave k values of 3.17 × 10^4 (L^2/m^2-s), 2.28 × 10^4 (L^2/m^2-s), and 2.80 × 10^4 (L^2/m^2-s).

Dimethyltricyclo[2.2.1.0^{2,6}]hept-3-ylphosphine (23). A mixture of the phosphine oxide **17** (1.0 g, 5.9 mmol) and diphenylsilane (1.1 mL, 6.0 mmol) was heated with the aid of an oil bath (oil bath temperature at 100–110 °C) for 2 h. The phosphine **23** was slowly distilled from the crude reaction mixture through a 4-cm Vigreaux at 0.1 mm (30 °C head temperature) to give 0.65 g (72%) of a clear, colorless liquid: ^{1}H NMR (300 MHz, C_6D_6; a HETCOR experiment[46] enabled the following signal identification) δ 2.06–1.99 (dm, J_{HH} = 10.0 Hz, 1 H), 1.78–1.74 (m, 1 H), 1.30–1.20 (m, 2 H), 1.19–1.13 (m, 1 H), 1.18–1.13 (m, 1 H), 1.12–1.07 (m, 1 H), 1.09–1.04 (m, 1 H), 0.98–0.92 (m, 1 H), 0.94 (d, J_{PH} = 3.0 Hz, 3 H), 0.85 (d, J_{PH} = 2.8 Hz, 3 H). ^{31}P NMR (24 MHz, C_6D_6) δ −54.9. The phosphine **23** rapidly oxidized when neat but was stable in solution. Reduction of the deuterated oxide by the same method produced the deuterated phosphine. The ^{1}H NMR spectrum of the deuterated phosphine was identical to the spectrum of the nondeuterated phosphine except for the lack of a resonance at δ 2.06–1.99. The ^{13}C NMR (75 MHz, C_6D_6) of the deuterated phosphine exhibited a six-line pattern at δ 31.7 (J_{PC} = 13.4 Hz, J_{CD} = 20.7 Hz).

Trimethyltricyclo[2.2.1.0^{2,6}]hept-3-ylphosphonium Bromide (22) by Reduction of Oxide 17. A mixture of the oxide **17** (1.70 g, 10 mmol) and diphenylsilane (1.84 g, 10 mmol) were combined and heated with the aid of an oil bath for 2 h (oil bath temperature at 100–110 °C). The solution was cooled to room temperature, diluted with 50 mL of dry ether, and treated with 3 mL of methyl bromide. The solid which precipitated was filtered after 2 days (2.06 g, 83%). Recrystallization from acetonitrile–ether gave **22**, mp 280–283 °C dec: ^{1}H NMR (60 MHz, D_2O) δ 2.60–2.18 (m, 2 H), 1.89 (d, J_{PH} = 14.0 Hz, 9 H), 1.67–1.33 (m, 7 H); ^{31}P NMR (24 MHz, $CDCl_3$) δ 26.9. Anal. Calcd for $C_{10}H_{18}BrP$: C, 48.22; H, 7.29; Br, 32.08. Found: C, 48.00; H, 7.11; Br, 32.20.

Reaction of Trimethyltricyclo[2.2.1.0^{2,6}]hept-3-ylphosphonium Bromide 22 with Base To Give Oxide 17. A mixture of the salt **22** (507 mg, 2 mmol) and NaOH powder (500 mg, 10 mmol) (prepared in glovebox) was stirred at 150 °C in a three-necked flask protected with a drying tube. White solid deposited in the upper part of the flask within 30 min. After 2 h the product was isolated and resublimed to give 242 mg (73%) of material which was identical (IR, mixture mp) to the oxide **17** from base decomposition of salt **13**.

Addition of Methyllithium to the Dimethylphosphonium Salt 13 To Give Tricyclic Salt 22. To a suspension of salt **13** (2.33 g, 1.0 mmol) in 250 mL of dry ether, methyllithium (1.1 M in ether, 10 mL, 11 mmol) was added at −67 °C. The reaction was allowed to warm to room temperature and stir overnight. The solution was cooled in an ice bath, and dry HBr gas was bubbled in until precipitation ceased. The precipitate was filtered (glovebox), treated with CH_2Cl_2, followed by H_2O, and then neutralized with $NaHCO_3$. The CH_2Cl_2 layer was treated with methyl iodide and gave 300 mg (13%) of $(CH_3)_4P^+I^-$, identical (^{1}H NMR and infrared spectra) to an authentic sample.

The water layer was evaporated under vacuum (using a dry ice–acetone trap) and the residue recrystallized from dry acetonitrile to give 1.30 g (57%) of salt **23** which was identical (mixture mp, NMR) to the sample prepared via reduction and quaternization of the oxide **17**.

In a separate run 2.33 g of the salt in ether was treated with methyllithium followed by an excess of methyl iodide as above. Aliquots of the solution were injected into a 13 ft × $^1/_4$ in. 20% SE-30 on Chromosorb W column (temperature 100 °C, flow rate

40 cc/min). Bicyclo[2.2.1]hepta-2,5-diene (retention time, 6.75 min) was collected (9.4% yield) and confirmed by comparison with an authentic sample (IR in CCl_4).

Acknowledgment. We are grateful to Mr. P. G. Elsey of the Ethyl Corporation for supplies of dichloromethylphosphine, to Susan Wehrli, formerly of the University of Wisconsin—Milwaukee, for obtaining ^{31}P NMR spectra, to D. W. Allen of Sheffield Polytechnic for kinetics, and to Prof. D. W. Bennett of the University of Wisconsin—Milwaukee for help in obtaining dihedral angles from X-ray crystal structures. S.E.C. wishes to acknowledge partial support for this research from the Marquette University Committee on Research, the Alfred P. Sloan Foundation for a Research Fellowship (1971–1975), and S. C. Johnson and Son, Inc. for a graduate student fellowship grant and research support. J.M.C. would also like to thank the Society of Sigma Xi for partial support of this project. The National Science Foundation is thanked for providing funding (CHE-89054650) to purchase the GE 300NB OMEGA spectrometer used in this study.

Supplementary Material Available: Aromatic and benzyl ^{13}C NMR chemical shifts and ^{13}C–^{31}P coupling constants of tetracyclic derivatives; ^{13}C–H coupling constants in oxide **1a**; lanthanide-induced ^{13}C and ^{1}H NMR chemical shift gradients of **1a** and **1b** (3 pages). Ordering information is given on any current masthead page.

Hyrtiosal, a New Sesterterpenoid with a Novel Carbon Skeleton from the Okinawan Marine Sponge *Hyrtios erectus*

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Received July 29, 1991 (Revised Manuscript Received October 16, 1991)

Hyrtiosal, a new sesterterpenoid possessing a novel rearranged tricarbocyclic skeleton, was isolated from the Okinawan marine sponge, *Hyrtios erectus* (Keller, 1891). This compound was shown to inhibit the proliferation of KB cells in vitro, and its structure was determined by chemical and spectral methods including two-dimensional ^{13}C–^{1}H long-range correlations. The relative stereochemistry was determined based on two-dimensional NOE correlations. A possible biosynthesis of hyrtiosal is briefly discussed.

Marine sponges are recognized as a rich source of structurally unique and biologically active terpenoids.[1,2] In the course of our investigation[3] on biologically active substances from Okinawan marine animals, we isolated a new sesterterpenoid, hyrtiosal (1), from the Okinawan sponge, *Hyrtios erectus* (Keller, 1891) (also called *Heteronema erecta*). The compound exhibited in vitro antiproliferative activity against KB cells with an IC_{50} of 3–10 μg/mL. From *H. erecta* which inhabits the Australian Great Barrier Reef, a scalarane type sesterterpenoid with a tetracarbocyclic skeleton, called heteronemin, was isolated by Kazlauskas et al.[4] Several scalarane type sesterterpenoids have also been isolated from Tongan *Hyrtios erecta* by Crews et al.[5] No scalarane type sesterterpenoid could be isolated from the present Okinawan sponge, but a new class of sesterterpenoid possessing a novel rearranged tricarbocyclic skeleton was obtained. Elucidation was made of the structure of hyrtiosal (1) on the basis of results from spectroscopic analysis and chemical reactions.

Wet specimens of *H. erectus*[6] (2.2 kg), obtained from the coral reef of Ishigaki Island (Okinawa, Japan), were extracted with methanol. The ethyl acetate soluble portion (3.7 g) of the methanol extract was chromatographed on a silica gel column. The fraction obtained by elution with hexane–ethyl acetate (1:1) was further purified by repeated silica gel column chromatography, followed by preparative TLC to give hyrtiosal (1) as colorless needles (21 mg, mp 119–121 °C).

The molecular formula $C_{25}H_{38}O_3$ of 1 was determined based on HRMS measurement. All 25 carbons were appeared in the ^{13}C NMR spectra measured in both $CDCl_3$ and C_6D_6 solutions, and DEPT indicated the presence of five methyls, seven methylenes, four sp^3 methines, three sp^2 methines, four sp^3 quaternary carbons, and two sp^2 quaternary carbons. Table I presents ^{13}C and ^{1}H NMR correlations found through examination of the two-dimensional ^{13}C–^{1}H COSY spectrum. IR, ^{1}H NMR ($CDCl_3$), and ^{13}C NMR ($CDCl_3$) spectra showed the presence of a formyl group (IR 1708 cm^{-1}, δ_H 9.45 (s), δ_C 205.7), secondary hydroxy group (IR 3547 cm^{-1}, δ_H 4.42 (dd, J = 6.0, 7.4 Hz), δ_C 64.2), and monosubstituted furan moiety (δ_H 6.37 (t, J = 1.1 Hz), 7.36 (s), 7.37 (br s), δ_C 109.5, 129.3, 139.8, 143.2). Partial structures of CH_2CH_2 (from C-1 to C-2), $CHCH_2CH_2$ (from C-5 to C-7), $CHCH_2$ (from C-9 to C-11) and $CHCH_2CHOH$ (from C-14 to C-16) were surmised based on analysis of ^{1}H coupling constants (Table I) and confirmed by two-dimensional ^{1}H–^{1}H COSY measurement.

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0022-3263/92/1957-0522$03.00/0