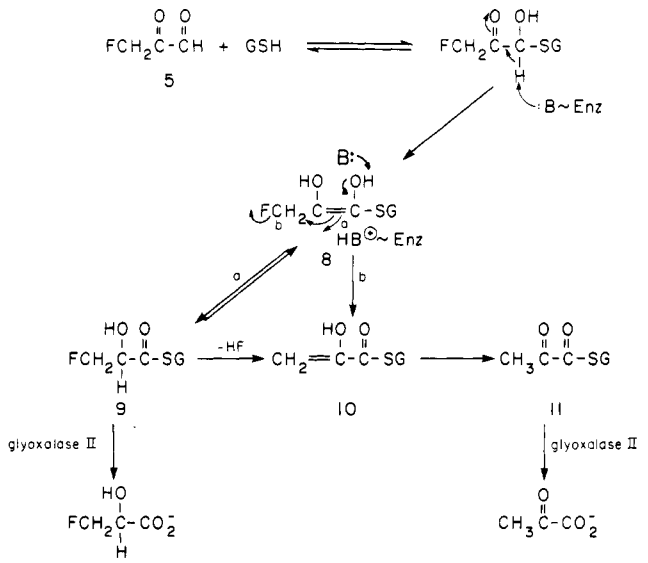
Scheme III



elimination is subtracted from the kinetics of total release in the absence of glyoxalase II, the remaining fluoride elimination is sigmoidal, implicating its dependence upon the accumulation of thioester.[12]

The identity of fluoride-containing products was established by ^{19}F NMR spectroscopy (Figure 2). The glyoxalase I only reaction gave a sharp singlet for fluoride ion as expected. The glyoxalase I and II reaction afforded, in addition to the fluoride ion singlet, a proton-coupled sextet ($J_{2H,F}$ = 47, $J_{H,F}$ = 30 Hz) identical with authentic fluorolactate. This product eluted with fluorolactate from a Dowex 1 (formate; 0 → 6 M formic acid) column, and enzymatic and ORD analysis[13] suggested that it was predominantly (at least) the D isomer.

The unique glyoxalase I catalyzed partitioning of **5** is most simply explained by a partitioning of the enediol intermediate **8** between protonation to yield *S*-fluorolactoylglutathione (**9**) (path a) and elimination to form initially the enol (**10**) of *S*-pyruvylglutathione (**11**) (path b), which could tautomerize to **11** (Scheme III). Hydrolysis of the thioesters by glyoxalase II would yield pyruvate and fluorolactate which is inert to further elimination. In the absence of glyoxalase II the initially formed *S*-fluorolactoylglutathione (**9**) is susceptible to enzyme-catalyzed elimination due to backreaction as well as to chemical β elimination of fluoride. Quantitation of pyruvate formed by NADH and L-lactate dehydrogenase (L-lactate: NAD oxidoreductase EC 1.1.1.27) has verified that it is essentially identical with the amount of fluoride released under both enzyme reaction conditions. No inactivation of the yeast glyoxalase I was observed after as many as 2000 substrate turnovers.[14]

This is to our knowledge the first example of product partitioning of a fluorinated substrate.[15] Moreover, it provides strong support for the enediol intermediate since the elimination of fluoride is best accounted for by carbanionic character at C-2.[16]

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM-26985) for support of this research. We thank Dr. Ian Armitage for use of the Bruker CXP 200 NMR spectrometer which is supported by the National Science Foundation (PCM 77-18941). Discussions with Professors JoAnne Stubbe, Christopher Walsh, and David Vander Jagt were especially helpful. J.W.K. thanks the Bristol-Myers Co. for a special grant.

(11) Interestingly, our recent results demonstrate that this partition ratio is species dependent. The enzyme from rat erythocyte gives a ratio of 0.08, while the ratio for the mouse liver enzyme is 0.26.

(12) This point is also established by addition of glyoxalase II at any time during the glyoxalase-I-only elimination. This results in the immediate cessation of any further fluoride release.

(13) Craig, J. C.; Dummel, R. J.; Kun, E.; Roy, S. K. *Biochemistry* **1965**, *4*, 2547.

(14) Enzyme inactivation could conceivably have occurred via Michael addition of an active site nucleophile to the enol **10** prior to tautomerization to **11**:

$$H_2C{=}C(OH)C(=O)SG \xrightarrow{\text{Enz Nuc:}} CH_3C(=O)C(=O)SG + \text{Enz-Nuc-}CH_2C(H)(OH)C(=O)SG$$

Since **10** is at once an enol and an α,β-unsaturated thioester, this possibility is intriguing. That no inactivation is observed suggests that either **10** is not sufficiently activated for Michael addition or that no active site base is available. We are currently attempting to trap **10** in solution via nucleophilic attack. Kuo et al. (Kuo, D. J.; O'Connell, E. L.; Rose, I. A. *J. Am. Chem. Soc.* **1979**, *101*, 5025) have demonstrated that the enol of pyruvate has a $t_{1/2}$ for tautomerization of 30 s at pH 7.0. This supports the idea that **10** might be sufficiently long lived for Michael addition to occur.

(15) A large number of fluorinated substrate analogues have been designed for pyridoxal-dependent enzymes where the rate-determining step is usually Schiff's base hydrolysis. It is not surpising, therefore, that total fluoride elimination is observed. In contrast, the reaction of β-fluoroalanine with D-amino acid oxidase which presumably involves an α carbanionic intermediate resulted in the exclusive formation of fluoropyruvate (i.e., no elimination): Dang, T.-Y.; Cheung, Y.-F.; Walsh, C. *Biochem. Biophys. Res. Commun.* **1976**, *72*, 960. Clearly, fluoromethylglyoxal constitutes a unique intermediary case.

(16) Preliminary studies indicate that chloro- and bromomethylglyoxal give exclusively elimination (i.e., pyruvate formation). This is consistent with their superior leaving group abilities (1:0.02:0.001 Br–Cl–F): Kosower, E. M. In "Physical Organic Chemistry"; Wiley: New York, 1968; p 81. An argument can be made for the possibility of a hydride transfer mechanism to afford **9** directly followed by a "fortuitous" enzyme-catalyzed elimination of fluoride. In this case, the partitioning observed could be due to competition of elimination with product release from the enzyme. Indeed, this sequence of events could also be used to explain the low amounts of solvent incorporation observed previously[1a] or the observations in this paper. Using substrate deuterated at C-1, we have recently observed an increase in the partitioning reaction (from 0.32 to 0.41). This effect is explainable by a selective primary isotope effect on the formation of **9** relative to fluoride elimination resulting in an overall increase in fluoride release. A hydride transfer, base-catalyzed elmination mechanism would have yielded a decrease in fluoride partitioning. Details of these findings will be published elsewhere.

Dicoordinated 2*H*-Phospholes as Transient Intermediates in the Reactions of Tervalent Phospholes at High Temperature. One-Step Synthesis of 1-Phosphanorbornadienes and Phosphorins from Phospholes

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We have recently shown that conveniently substituted λ^3 phospholes reacted easily with maleic anhydride and *N*-phenylmaleimide to give the expected [4 + 2] Diels–Alder cycloadduct.[1] The discovery that λ^3 phospholes could be rather reactive dienes prompted us to investigate their reactions with other dienophiles. Among acetylenic dienophiles, only the highly electrophilic dimethyl acetylenedicarboxylate has been reacted with phospholes previously.[2] The reactions were rather complicated but always started by an electrophilic attack on the phosphorus lone pair. We thus decided to investigate the reactions of the less electrophilic tolane with 1-phenyl-3,4-dimethylphosphole (**1**) and 1,2,5-triphenylphosphole (**2**).

At 170 °C, **1** reacted with tolane to give quite unexpectedly 3,4-dimethyl-2,5,6-triphenyl-1-phosphanorbornadiene (**3**) in quantitative yield.[3] The structure of **3** was unambiguously es-

(1) Mathey, F.; Mercier, F. *Tetrahedron Lett.* **1981**, *22*, 319.

(2) Hughes, A. N.; Uaboonkul, S. *Tetrahedron* **1968**, *24*, 3437. Waite, N. E.; Tebby, J. C. *J. Chem. Soc. C* **1970**, 386. Holah, D. G.; Hughes, A. N.; Kleemola, D.; *J. Heterocycl. Chem.* **1978**, *15*, 1319.

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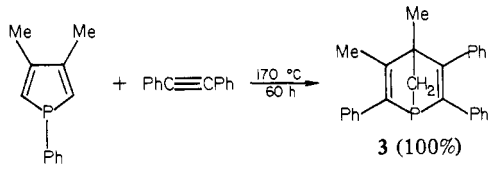
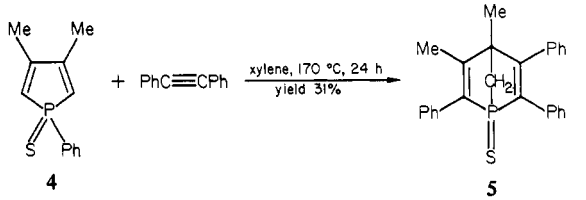
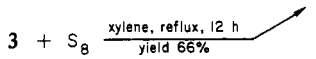


1 3 (100%)

tablished by X-ray crystal structure analysis. Although the discovery of 1-phosphanorbornadienes was interesting in itself, we were mainly interested in the possible mechanism for the formation of **3**. In order to check whether or not the reaction started by an electrophilic attack of tolane on the phosphorus lone pair, we reacted tolane with the *P*-sulfide of **1**. We obtained



4 5



mainly **5**[4] which was also prepared directly from **3** (the lone pair of **3** appears to have a low reactivity). Since an electrophilic attack at phosphorus must be discarded, we postulated a 1,5 migration of the phenyl group leading to **6** by analogy with a work of Barton on 1-silylsiloles.[5a] Then, transient 2-*H*-phosphole **6** was supposed to react as a diene with tolane to give **3**.[5b] Three facts strongly support this hypothesis.

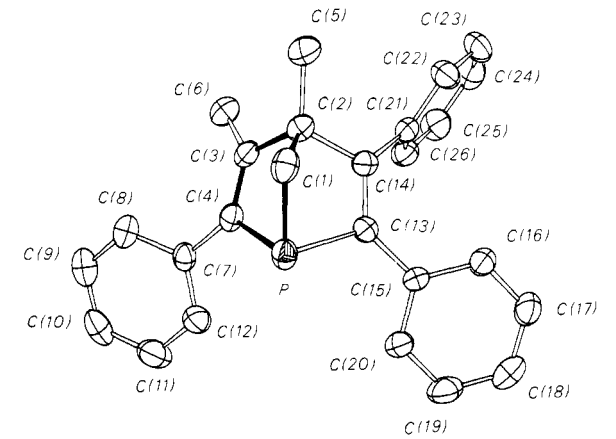
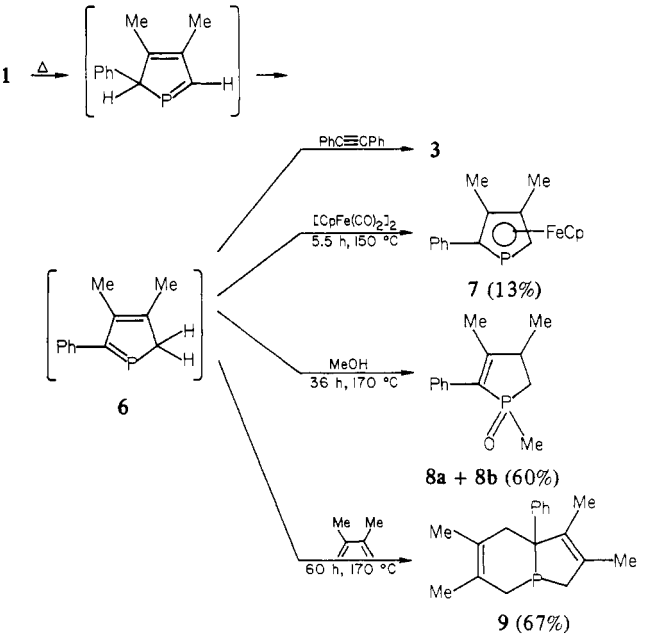


Figure 1. Structure of 1-phosphanorbornadiene **3** showing the 50% probability ellipsoids. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) are P–C(1), 1.835 (4); P–C(4), 1.869 (4); P–C(13), 1.869 (3); C(1)–C(2), 1.540 (5); C(2)–C(3), 1.544 (5); C(3)–C(4), 1.327 (5); C(13)–C(14), 1.341 (5); C(2)–C(14), 1.553 (1). Mean C–C (phenyl groups) = 1.378 (2) Å. Selected bond angles C(4)–P–C(13), 96.1 (2); C(1)–P–C(4), 85.5 (2); P–C(1)–C(2), 97.6 (2)°.



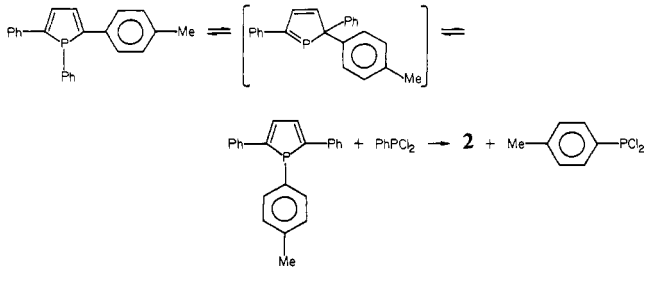
(A) The reaction of **1** with $[CpFe(CO)_2]_2$ at 150 °C produces 2-phenyl-3,4-dimethylphosphaferrocene (**7**) among other products.[6] The formation of **7** by radical arylation of 3,4-dimethylphosphaferrocene as initially proposed is not very likely since ferrocene cannot be arylated in this way.[7] On the contrary, an isomerization of **1** into **6** before reaction with $[CpFe(CO)_2]_2$ offers a perfectly logical explanation.

(B) Methylenephosphines are known to add methanol to give methyl phosphinites.[8] We thus reacted **1** with methanol at 170 °C. At this temperature the expected 1-methoxy-3-phospholene undergoes an Arbuzov rearrangement and a double-bond migration to give the 1-methyl-2-phospholene oxide (**8**) as a roughly 50:50 mixture of two diastereoisomers.[9]

(3) The reaction is performed in a sealed glass tube under argon; ratio tolane:**1** = 1.3; **3** is purified by chromatography on silica gel (hexane–C_6H_6 = 80:20). mp 131 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H, Me), 2.0 (s, 3 H, Me), 2.0 (*A*BX, 1 H, $^2J_{A-B} \sim 10$ Hz, $^2J_{A-P}$ 9.8 Hz, CH_AP), 2.12 (A*B*X, 1 H, $^2J_{B-P}$ = 10.4 Hz, CH_B–P), 7.20 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.8 (s, Me), 21.0 (s, Me), 65.1 (pseudo s, CH_2), 72.4 (d, $^2J_{C-P}$ = 5.9 Hz, Me*C*), 126.3–161.4 (sp^2 carbons). The high deshielding of the CH_2 bridge is characteristic of the norbornadiene skeleton. See: Lippmaa, E.; Pehk, T.; Paasivirta, J.; Belikova, N.; Platé, A. *Org. Magn. Reson.* **1970**, *2*, 581. ^{31}P NMR (H_3PO_4, $CDCl_3$, δ+ for downfield shifts) δ −8.4; quaternary salt with MeI δ +38.7; mass spectrum, (70 eV, 120 °C), *m/e* 366 (M, 90%); 188 (M − C_2Ph_2, 100%).

(4) When synthesized from **4**, **5** is purified by chromatography on silica gel with toluene. mp 170 °C (toluene/hexane). ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H, Me), 2.03 (d, 3 H, $^4J_{H-P}$ = 2.7 Hz, Me), 2.72 (m, 2 H, CH_2), 6.97–7.13 (m, 15 H, Ph); ^{31}P NMR δ +50.2 ($CDCl_3$); mass spectrum (70 eV, 200 °C), *m/e* 398 (M, 37%), 220 (M − C_2Ph_2, 100%).

(5) (a) Barton, T. J.; Wulff, W. D.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 2733. (b) That the phenyl group of **1** migrates in the absence of tolane was demonstrated by thermolysis experiments with **1** alone. A mixture of products containing the 2-phenyl-3,4-dimethylphospholyl moiety was obtained. These experiments will be described in due course. As noted by one of the referees, the postulated mechanism requires that the phenyl groups of **2** scramble around 200 °C. An unexplained observation by Cadogan (Cadogan, J. I. G.; Scott, R. J.; Gee, R. D.; Gosney, I. *J. Chem. Soc., Perkin Trans. I* **1974**, 1694) shows that this is indeed the case. When reacting 1-phenyl-4-*p*-tolylbuta-1,3-diene and phenyldichlorophosphine at 215 °C, besides the expected 1,2-diphenyl-5-*p*-tolylphosphole, a notable amount of **2** was produced. We propose the following explanation:



Similar results were obtained when reacting 1,4-di-*p*-tolylbutadiene with phenyldichlorophosphine. Cadogan suggested a Lewis acid induced demethylation of the tolyl groups, but this explanation is not valid since the reaction of *p*-tolyldichlorophosphine with 1,4-di-*p*-tolylbutadiene produces only 1,2,5-tritolylphosphole.

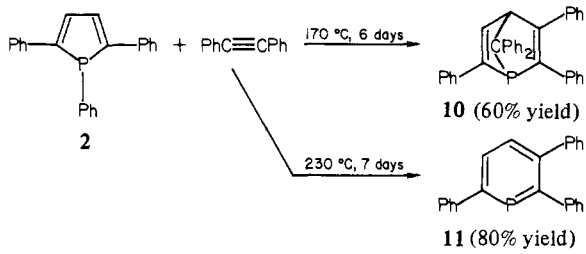
(6) Mathey, F. *J. Organomet. Chem.* **1977**, *139*, 77.

(7) Beckwith, A. L. J.; Leydon, R. J. *Aust. J. Chem.* **1966**, *19*, 1853 and references cited.

(8) Klebach, Th. C.; Lourens, R.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1978**, *100*, 4886.

(C) Methylenephosphines are known to give [2 + 4] Diels–Alder cycloadducts with conjugated dienes.[10] We thus reacted **1** with 2,3-dimethyl-1,3-butadiene at 170 °C. We obtained the expected adduct **9** together with a minor byproduct which was not fully characterized.[11]

Then we wanted to check if the formation of **6** by thermolysis of **1** was a general phenomenon. Indeed 2,5 disubstitution could prevent the 1,5 migration of the 1-phenyl substituent. We thus reacted **2** with tolane. In fact we noted that the reaction was more sluggish and gave a lower yield but, nevertheless, produced the expected 1-phosphanorbornadiene **10**.[12]



10 (60% yield)

11 (80% yield)

In the mass spectrum of **10** we noted strong peaks corresponding to the loss of the CPh_2 bridge. We thus suspected that the thermolysis of **10** could produce the phosphorin **11**. Indeed when **2** was reacted with tolane at 230 °C, 2,3,6-triphenylphosphorin[13] was directly obtained in high yield. The diphenylcarbene was mainly recovered as diphenylmethane[14] which is known to be one of the main products resulting from the evolution of this carbene at high temperature.[15] This very simple one-step synthesis of phosphorins from phospholes offers numerous possibilities and supplements nicely the earlier procedures.[16] Since the structure of **3** was a key point of our demonstration, we decided to perform a full X-ray crystal structure analysis of this product. Suitable single crystals of **3** were selected from the recrystallization vessel. They belong to the monoclinic system, space group $P2_1/n$ (C_{2h}^5) with a = 10.588 (1), b = 10.694 (1), c = 17.676 (2) Å; β = 92.83 (2)°; V = 1999 Å^3; z = 4; ρ_{calcd} = 1.218 g/cm^{-3}; F_{000} = 776 e.

Diffraction data were collected in the $\theta/2\theta$ scan mode by using a CAD4 Enraf–Nonius automatic diffractometer and Ni-filtered Cu Kα radiation. The structure was solved by direct methods[17] using the Enraf–Nonius SDP/V17[18] package on a PDP11/60 computer. Full matrix refinement using 1770 reflections having $I > 3\sigma(I)$ converged to conventional agreement factors R_1 and R_2 of 0.048 and 0.066. Hydrogen atoms were introduced by their computed coordinates but not refined.

The structure (Figure 1)[19] consists of discrete molecules only linked by van der Waals contacts and hydrogen bonds. Selected geometric details are given in the caption of Figure 1.

The most interesting observation is related to the strain around phosphorus. This strain appears to be higher in **3** than in 1-phosphanorbornanes[20] as monitored by the mean CPC angle values (89° in **3** vs. 96.2° in 1-phosphanorbornane 1-oxide[20]). This explains the loss of the CPh_2 bridge of **10** upon heating.

The broad new chemistry of 2*H*-phospholes will be described in due course.

Supplementary Material Available: Table I gives the atomic coordinates and β_{ij} for all nonhydrogen atoms and Table II lists the observed and calculated structure factors times 10 for all observed reflections (9 pages). Ordering information is given on any current masthead page.

(9) Phospholene oxide (**8**) is purified by chromatography on silica gel (AcOEt–MeOH = 90:10) and kugelrohr distillation (bp ca. 170 °C (0.1 torr)]. ^{1}H NMR ($CDCl_3$) δ 1.25 (d, $^3J_{H-H}$ = 7.1 Hz, *Me*CH), 1.34 (d, $^3J_{H-H}$ = 6.8 Hz, *Me*CH), 1.49 (d, $^2J_{H-P}$ = 12.9 Hz, MeP), 1.53 (d, $^2J_{H-P}$ = 12.7 Hz, MeP), 1.86 (d, $^4J_{H-P}$ = 2.4 Hz, MeC=), 1.87 (d, $^4J_{H-P}$ = 2.4 Hz, MeC=), 7.34–7.39 (m, Ph); ^{31}P NMR ($CDCl_3$) δ +58.2, +59.7; IR (Nujol) $\nu_{C=C}$ 1620 cm^{-1}; $\nu_{P=O}$ 1150 and 1190 cm^{-1}; mass spectrum (70 eV, 90 °C), *m/e* 220 (M, 100%).

(10) The reaction of methylenephosphines with conjugated dienes has been described in a preliminary communication: Klebach, Th. C.; Lourens, R.; Wisse, J.; Bickelhaupt, F. International Conference on Phosphorus Chemistry, Halle, Sept 1979 (ICPC 79). Conjugated dienes also cycloadd onto the P=C bond of 1,2,3-diazaphospholes: Carrié, R., personal communication. Arbuzov, B. A.; Dianova, E. N., ICPC 79.

(11) Chromatography on silica gel (hexane–toluene = 80:20) affords first the incompletely characterized minor byproduct (^{31}P NMR –9.37 δ), which seems to be an isomer of **9** according to its mass spectrum, and then **9** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.34 (m, 3 H, Me), 1.70 (m, 3 H, Me), 1.75 (pseudo s, 6 H, Me), 1.99–2.56 (complex m, 6 H, CH_2), 7.21 (narrow m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 12.0 (s, Me), 17.2 (s, Me), 20.4 (s, Me), 21.5 (s, Me), 31.0 (d, J_{C-P} = 20.5 Hz, CH_2), 36.2 (d, J_{C-P} = 14.6 Hz, CH_2), 37.9 (s, CH_2), 62.3 (d, $^1J_{C-P}$ = 12.7 Hz, PhCP), 125–148.7 (sp^2 carbons); ^{31}P NMR ($CDCl_3$) δ –5.60, mass spectrum (70 eV, 100 °C) *m/e* 270 (M, 73%), 188 (M – C_6H_{10}, 100%).

(12) The reaction is performed with a great excess of tolane: molar ratio **2**:tolane = 1:2.8. Compound **10** is purified by chromatography on silica gel (hexane–toluene = 80:20). Yellow crystals; mp 148 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 5.26 (A*M*X, 1 H, $^3J_{AM}$ = 3.9 Hz, $^3J_{M-P}$ = 3.05 Hz, saturated proton), 6.9–7.55 (m, 25 H, Ph), 7.65 (*A*MX, 1 H, $^3J_{A-P}$ = 6.60 Hz, ethylenic proton); ^{31}P NMR ($CDCl_3$) δ + 19.9; ^{13}C NMR ($CDCl_3$) δ 70.6 (d, $^2J_{C-P}$ = 4.9 Hz, saturated CH); 88.6 (pseudo s, $^1J_{C-P} \sim 0$ Hz, CPh_2), 125.6–157.7 (sp^2 carbons); mass spectrum (70 eV, 140 °C) *m/e* 490 (M, 100%), 166 (CPh_2, 22%), 165 (48%).

(13) Except for the temperature, the overall procedure is identical for the preparations of **10** and **11**. The phosphorin **11** is obtained as pale yellow crystals; mp 150 °C (hexane). ^{1}H NMR ($CDCl_3$) δ 7.61 (A*B*X, $^4J_{B-P}$ = 3.9 Hz, H_γ), 8.02 (*A*BX, $^3J_{A-P}$ = 5.5 Hz, $^3J_{A-B}$ = 8.66 Hz, H_β); ^{13}C NMR ($CDCl_3$) δ 169.7 (d, $^1J_{C-P}$ = 53.7 Hz, C_α), 170.4 (d, $^1J_{C-P}$ = 53.7 Hz, C_α); ^{31}P NMR ($CDCl_3$) δ +198; mass spectrum (70 eV, 150 °C), *m/e* 324 (M, 100%).

(14) Diphenylmethane was identified in the crude phosphorin by its ^{1}H and ^{13}C NMR spectra: ^{1}H NMR ($CDCl_3$) δ 3.94 (s, CH_2Ph_2); ^{13}C NMR ($CDCl_3$) δ 41.9 (s, CH_2Ph_2). See for comparison: Stibor, I.; Srogl, J.; Janda, M.; Salajka, Z.; Trška, P. *Collect. Czech. Chem. Commun.* **1977**, *42*, 987.

(15) Tomioka, H.; Griffin, G. W.; Nishiyama, K. *J. Am. Chem. Soc.* **1979**, *101*, 6009 and references cited herein.

(16) Märkl, G. *Phosphorus Sulfur* **1977**, *3*, 77. Ashe, A. J., III. *Acc. Chem. Res.* **1978**, *11*, 153. Mathey, F. *Tetrahedron Lett.* **1979**, *20*, 1753.

(17) Germain, G.; Main, P.; Woolfson, M. H. *Acta Crystallogr., Sect. B* **1970**, *26*, 274. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.

(18) Frenz, B. A. "The Enraf-Nonius CAD4-SDP. Computing in Crystallography"; Schenk, H., Olthof-Hazekamp, R., Van Koenigsveld, H., Bassi, G. C., Eds.; Delft University Press: Delft, Holland, 1978; p 64.

(19) Drawing performed by using program ORTEP II: Johnson, C. K. Report ORNL 3794, Oak Ridge, TN, 1965.

(20) Milbrath, D. S.; Verkade, J. G.; Kenyon, G. L.; Eargle, D. H., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 3167.

Synthesis of Thromboxane A_2 Analogues: DL-9,11:11,12-Dideoxa-9,11:11,12-diepithiothromboxane A_2

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Received April 23, 1981

The metabolic pathway of arachidonic acid involves the formation of cyclic endoperoxides which are rapidly converted into thromboxane A_2 (TXA_2), prostaglandin I_2(PGI_2), and other prostaglandins. TXA_2 is an unstable substance with potent thrombotic and vasoconstricting properties generated by platelets.[1] Samuelsson and his associates proposed formula A (Chart I) as a possible structure for TXA_2 on the basis of its origin and stable degradation products and deduced a physiological half-life ($t_{1/2}$ = 32 s in aqueous pH 7.4 solution at 37 °C).[2] TXA_2 with these biological activities has been identified in many tissues, including platelets, leucocytes, spleen, inflammatory glanuloma, brain, and kidney. It is of considerable pathophysiological interest in thrombotic diseases and anaphylatic reactions and plays a

(1) For review, see: Samuelsson, B.; Goldyne, M.; Granström, E.; Hamberg, M.; Hammarström, S.; Malmsten, C. *Annu. Rev. Biochem.* **1978**, *47*, 997.

(2) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994.

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