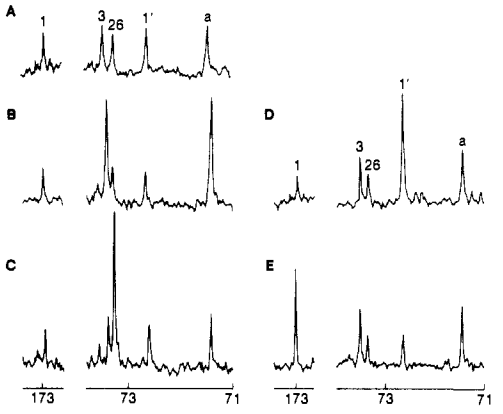


Figure 2. Portions of ^{1}H-decoupled 100.6-MHz ^{13}C NMR spectra of **1** in methanol-d_4 after incorporation of (A) no labeled precursor, (B) [1-^{13}C]acetate, (C) [2-^{13}C]acetate, (D) [3-^{13}C]octanoate, and (E) [1-^{13}C]octanoate. Peak a is due to C-5, C-7, C-9, or C-11; see ref 17.

display enhancements of specific resonances which are listed in Table I. As expected for polyketide biosynthesis,[7-9] carbon atoms derived from the carboxyl and methyl of acetate alternate around the lactone ring of **1**. Specific enrichment of C-15 by [1-^{13}C]-propionate indicates that positions 15, 16, and 29 originate from one propionate unit. However, there was no significant labeling of C-1, C-2, or the saturated side chain (C-1′ to C-6′) of fungichromin (**1**) in any of these three experiments (Figure 2A-C). Incorporation of sodium [1,2-$^{13}C_2$]acetate followed by detection of coupled resonances in **1** by double quantum coherence NMR spectroscopy (2D INADEQUATE)[9] demonstrated that the macrolide portion contains two groups of six intact acetate units connected in head to tail fashion (Figure 1). In the normal ^{13}C NMR spectrum of this sample the presence of small coupled satellites flanking the natural abundance C-6′ singlet showed that a low level of acetate incorporation does occur in the saturated side chain.[13]

To determine the origin of the eight-carbon fragment (C-1, C-2, and C-1′ to C-6′), sodium [1-^{13}C]octanoate and [3-^{13}C]octanoate[14] were fed[10] in separate experiments to *S. cellulosae*. The resulting fungichromin (**1**) samples exhibit large specific enhancements (Table I) at C-1 and C-1′, respectively (Figure 2D,E). Although [1-^{13}C]octanoate causes very slight labeling of positions derived directly from [1-^{13}C]acetate (25% enhancement), [3-^{13}C]octanoate gives no detectable enrichment at those sites. This suggests that a small amount of β-oxidation[15] of [1-^{13}C]octanoate to [1-^{13}C]-acetate and hexanoate occurs. In a separate experiment, no incorporation of [1-^{13}C]hexanoate[14] could be observed. Clearly octanoate is the preferred specific precursor for the eight-carbon unit that terminates the polyketide chain in fungichromin (**1**) (Figure 1). This contrasts the usual tendency of microorganisms to degrade longer chain fatty acids to acetate before incorporation.[8,16] Degradation of fats[15] present in the medium (e.g., Span 85)[12] probably accounts for octanoate formation under normal circumstances; this may explain the requirement for fats (especially oleic acid esters) to obtain good fungichromin (**1**) production.[12] Additional studies on details of the biosynthesis of polyene antibiotics are in progress.

Acknowledgment. We thank Dr. Ramesh C. Pandey (Xechem Inc.) for a generous gift of authentic fungichromin. We are grateful to Dr. Thomas T. Nakashima, Laird A. Trimble (University of Alberta), and Dr. Charles Rogers (Bruker Canada) for assistance in spectral acquisition. These studies were supported by the Natural Sciences and Engineering Research Council of Canada and by the Alberta Heritage Foundation for Medical Research.

Registry No. 1, 6834-98-6; $Me(CH_2)_6CO_2H$, 124-07-2.

(10) Week-old cultures of *Streptomyces cellulosae* ATCC 12625 grown on Bacto yeast/malt extract agar were used to inoculate 100 mL of sterile liquid media (per liter: 5.0 g of bactopeptone; 2.5 g of yeast extract; 4 g of NaCl; 10 g of glucose; 10 mL of Span 85;[12] $NaHCO_3$ to adjust pH to 7.0). After a 48-h incubation at 26 °C in the dark on a rotary shaker (165 rpm), 2 mL of the resulting suspension was transferred to each of 10 500-mL flasks containing the same medium (100 mL/flask). These were incubated (same conditions) for 7-8 days. Labeled precursors (≥98% isotopic purity) (6-8 mg/flask/day, except for acetates: 10-20 mg/flask/day) were added in H_2O after 3, 4, 5, and 6 days growth. The mycelium and filtrate were extracted separately (2:1 hexane/benzene, then hot ethyl acetate). The combined ethyl acetate extracts were concentrated in vacuo and chromatographed on Sephadex LH-60 in methanol. Chromatography of the polyene antibiotic fractions on a Merck Lobar RP-8 column (65:35 methanol/water) gave 10-30 mg of pure fungichromin (**1**).

(11) The ^{1}H and ^{13}C NMR spectra were assigned by using a variety of techniques; these include homonuclear decoupling, COSY, spin echo, and heteronuclear shift correlation on unlabeled fungichromin (**1**) as well as INADEQUATE on **1** enriched by [1,2-$^{13}C_2$]acetate. The full details will be reported later. For reviews of modern methods of NMR assignment, see: (a) Benn, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350-380. (b) Shoolery, J. N. *J. Nat. Prod.* **1984**, *47*, 226-259.

(12) McCarthy, F. J.; Fisher, W. P.; Charney, J.; Tytell, A. A. *Antibiot. Annu.* **1955**, 719-723.

(13) Increased sensitivity of detection of labeling by observation of coupled satellites is well precedented: (a) Leete, E. *J. Nat. Prod.* **1982**, *45*, 197-205. (b) Hedges, S. H.; Herbert, R. B.; Wormald, P. C. *J. Chem. Soc., Chem. Commun.* **1983**, 145-147.

(14) The [1-^{13}C]octanoic acid (99% ^{13}C) and [1-^{13}C]hexanoic acid (98% ^{13}C) were purchased from Cambridge Isotope Laboratories, Woburn, MA. To prepare [3-^{13}C]octanoate, the [1-^{13}C]hexanoic acid was transformed to [1-^{13}C]hexyl tosylate by reduction (diborane, THF, 25 °C, 48 h) and esterification (*p*-toluenesulfonyl chloride, pyridine-CH_2Cl_2, 25 °C, 48 h). This product was condensed with diethyl sodiomalonate (1 equiv, DMF, 70 °C, 16 h) and then hydrolyzed (NaOH, dioxane-H_2O, 25 °C, 16 h; then HCl, dioxane-H_2O, 80 °C, 16 h) to afford [3-^{13}C]octanoic acid (47% overall yield). This was converted to its sodium salt with NaOH. All compounds gave satisfactory spectra and analyses.

(15) Kindl, H. In *Fatty Acid Metabolism and Its Regulation*; Numa, S., Ed.; Elsevier: Amsterdam, 1984; pp 181-204 and references therein.

(16) Vederas, J. C.; Graf, W.; David, L.; Tamm, Ch. *Helv. Chim. Acta* **1975**, *58*, 1886-1898.

(17) Definitive assignment of these carbon resonances has not yet been completed.

Geometry of Formal Nucleophilic Substitution at First-Row Heteroatoms: The Transfer of Oxygen from Nitrogen to Phosphorus

Peter Beak* and DeKai Loo

Department of Chemistry, University of Illinois Urbana, Illinois 61801

Received January 16, 1986

The geometry of reaction at nonstereogenic atoms can, in principle, be determined by studies of systems in which the atom of interest and its reaction partners are joined by a small number of intervening atoms. When the ring required to bring the reactants together is geometrically well-defined, limits are placed on the bond angles allowed for intramolecular reaction, particularly for endocyclic displacements. If the bond angle required for reaction cannot be met in a cyclic mode, the process is expected to be intermolecular. Although the same product may result from intra- and intermolecular pathways, experimental distinction can be made and limits assigned to the reaction trajectory. The general approach has been used to investigate displacement at carbon,[1] to define the possibilities for facile ring formation,[2] to investigate radical substitution at sulfur,[3] and to provide a mechanistic distinction for a formal displacement at anionic nitrogen.[4] We now

(1) Tenud, L.; Farooq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059.

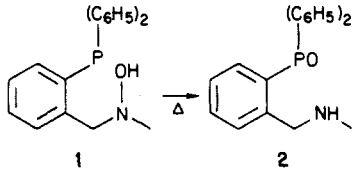
(2) Baldwin, J. E.; Lusch, M. J. *Tetrahedron*, **1982**, *19*, 2939 and references cited therein.

(3) Kampmeier, J. A. *ACS Symp. Ser.* **1978**, *No. 69*. **Note Added in Proof**: This approach has also been used to investigate nucleophilic substitution at sulfur(IV and VI). Andersen, K. K.; Malver, O., *J. Org. Chem.* **1983**, *48*, 4803.

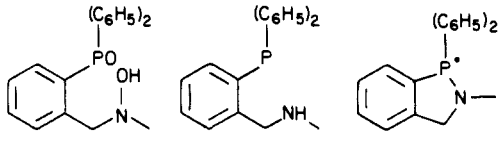
0002-7863/86/1508-3834$01.50/0

wish to report the use of this approach to a evaluate the geometry of a formal displacement at oxygen.

The conversion of **1** to **2**, in which an oxygen is transferred from nitrogen to phosphorus, proceeds in toluene at 100 °C in 1 h in 95% yield.[5] The disappearance of **1** and the appearance of **2** are kinetically first order in **1** with a rate constant of $k = 5.0\ (\pm 0.6) \times 10^{-2}\ min^{-1}$ over a 5-fold concentration range. If the reaction proceeded by an S_N2 pathway, with phosphorus acting as a nucleophile and a geometrical requirement of a bond angle of 180° between the entering and leaving groups in the transition state, the reaction would be expected to be second order and to involve **3** and **4**.[6] Independently prepared **3** and **4** provide **2** at a rate



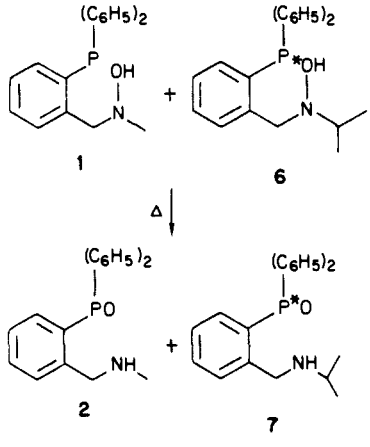
1 **2**



3 **4** **5**

that is much slower than the rate of formation of **2** from **1**. Accordingly this formal nucleophilic substitution at oxygen does not proceed by a classic S_N2 process.

A free radical chain reaction with an adventitous initiator and reaction via **5** could be kinetically first order.[7] To test this possibility, which would involve intermolecular transfer of oxygen, a double-labeling experiment was carried out. A 49:51 ratio of unlabeled **1** and **6** bearing 44% (±4) ^{18}O gives **2** which is unlabeled and **7** which has 42% (±4) ^{18}O. The rate of reaction of **6** is within

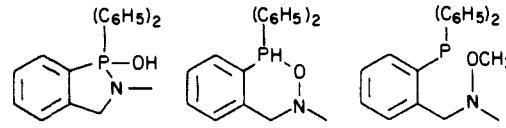


1 **6**

2 **7**

25% that of **1** in this mixture. By the labeling criterion, the oxygen transfer from nitrogen to phosphorus is intramolecular and the radical chain reaction is not operative.

Mechanisms for oxygen transfer which meet the bond angle requirement for the intramolecular transfer are biphilic addition between the nitrogen and oxygen to provide **8**[8] or addition of oxygen and hydrogen to phosphorus to give **9**.[9,10] The latter is favored because **10** is inert upon heating in toluene at 100 °C even in the presence of acetic acid.



8 **9** **10**

The present work shows that the mechanistic analogy of backside displacement for nucleophilic substitution at carbon cannot be extended to displacement by phosphenes at oxygen. The present evidence suggests that, in fact, this formal displacement by phosphorus on oxygen is initiated by addition of oxygen and hydrogen to the phosphorus. Further tests using this general approach to provide previously unavailable information about the reaction geometry at nonstereogenic atoms are under way.

Acknowledgment. We are grateful to Dr. W. G. Bentrude, Dr. S. G. Mills, and D. R. Chrisope for discussions and to the National Institute of Health and National Science Foundation for support.

(4) Beak, P.; Basha, A.; Kokko, B. *J. Am. Chem. Soc.* **1984**, *106*, 1511.

(5) The reaction can be directly followed by ^1H NMR. The yield is based on that observation. The product was isolated in 75% yield from a reaction in refluxing dioxane. The reactants and products are fully characterized by analytical and spectral properties.

(6) Kirby, A. J.; Warren, S. G. *The Organic Chemistry of Phosphorus*; Elsevier: New York, 1967; pp 63-94. Smith, D. J. H. *Compr. Org. Chem.* **1979**, *2*. These authors provide a large number of examples of deoxygenations by phosphorus reagents and the reasonable rationale that many of these reactions are nucleophilic attacks on oxygen.

(7) Additions of alkoxy radicals to phosphines are well-established; Bentrude, W. G.; Moriyama, M.; Mueller, H. D.; Sopchik, A. E. *J. Am. Chem. Soc.* **1983**, *105*, 6053 and references cited therein. A recent attempt to observe a radical displacement on oxygen in a 5-exo-trig reaction showed this processes was not operative: Kraus, G. A.; Landgrebe, K. *Tetrahedron* **1985**, *19*, 4039.

(8) Reactions of peroxides with phosphines are formulated as biphilic insertions by phosphorus into the oxygen-oxygen bond to provide dialoxyphopholanes: Lloyd, J. R.; Lowther, N.; Hall, C. D. *J Chem. Soc., Perkin Trans. 2*, **1985**, 245. Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1981**, *46*, 4105. Baumstark, A. L.; McCloskey, C. J.; Williams, T. E.; Chrisope, D. R. *J. Org. Chem.* **1980**, *45*, 3593. Denney, D. B.; Denney, D. Z.; Hall, C. D.; Marsi, K. L. *J. Am. Chem. Soc.* **1972**, *94*, 245 and references cited therein. Retention at phosphorus is observed in such reactions: Wozniak, L.; Kowalski, J.; Chojnowski, J. *Tetrahedron Lett.* **1985**, 4965.

(9) Brazier, J. F.; Houalla, D.; Loenig, M.; Wolf, R. *Top. Phosphorus Chem.* **1976**, *8*, 99.

(10) Cadogan and Mackie (Cadogan, J. I. G.; Mackie, R. K. *Chem. Soc. Rev.* **1974**, *3*, 87) cite Emerson and Rees (Emerson, T. R.; Rees, C. W. *J. Chem. Soc.* **1964**, 2319) for a mechanism of deoxygenation of amine oxides which involves nucleophilic addition of oxygen to phosphorous.

Asymmetric Total Synthesis of (+)-Pentalenene via Chiral Sulfinylallyl Anions. Hydrolytic Ring Closure of Enol Thioether Ketones

Duy H. Hua

Department of Chemistry, Kansas State University
Manhattan, Kansas 66506

Received February 28, 1986

As part of our continued studies to apply asymmetric induction reactions involving chiral sulfinylallyl anions with enones,[1] the synthesis of the family of sesquiterpenes pentalenene,[2] pentalenic acid,[3] and pentalenolactone[4] was undertaken. (+)-Pentalenene (**1**) was isolated[2] from the less oxidized metabolites in the mycelia

(1) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. The diastereospecific addition reactions of carbanions derived from allylic sulfoxides and allylic phosphine oxides: (b) Binns, M. R.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1565. (c) Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1569. The 1,4-addition of carbanion of phenyl allyl sulfoxide and cyclopentenones: (d) Vasil'eva, L. L.; Mel'nikova, V. I.; Gainullina, E. T.; Pivnitskii, K. K. *J. Org. Chem. USSR* **1983**, *19*, 835. (e) Vasil'eva, L. L.; Mel'nikova, V. I.; Pivnitskii, K. K. *Zh. Org. Khim* **1984**, *20*, 690 and references cited therein.

(2) Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92.

(3) Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411.

(4) (a) Martin, G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1970**, 4901. (b) Duchamp, D. J.; Chidester, C. G. *Acta Crystallogr., Sect. B* **1972**, *B28*, 173. (c) Seto, H.; Sasaki, T.; Yonehara, H.; Uzawa, J. *Tetrahedron Lett.* **1978**, 923. (d) Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411. (e) Aizawa, S.; Akutsu, H.; Satomi, T.; Kawabata, S.; Sasaki, K. *J. Antibiot.* **1978**, *31*, 729. (f) Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973.

0002-7863/86/1508-3835$01.50/0