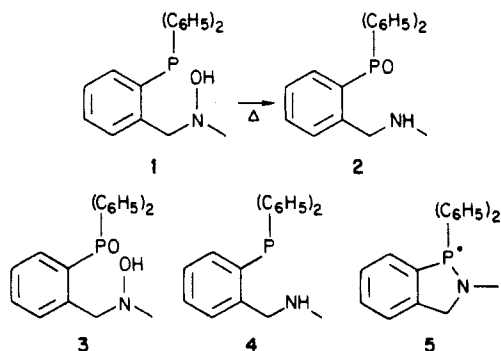


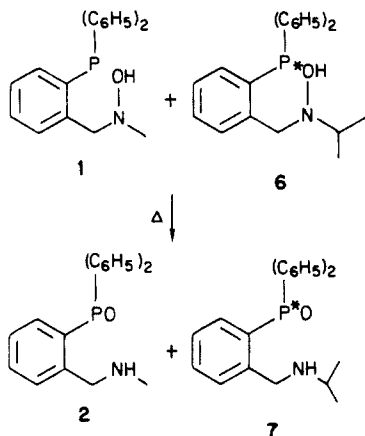
wish to report the use of this approach to evaluate the geometry of a formal displacement at oxygen.

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.<sup>5</sup> The disappearance of **1** and the appearance of **2** are kinetically first order in **1** with a rate constant of  $k = 5.0 (\pm 0.6) \times 10^{-2} \text{ min}^{-1}$  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**.<sup>6</sup> Independently prepared **3** and **4** provide **2** at a rate



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.

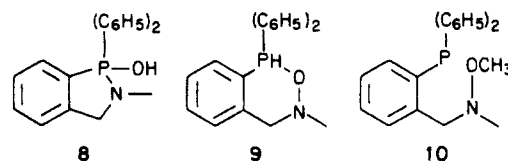
A free radical chain reaction with an adventitious initiator and reaction via **5** could be kinetically first order.<sup>7</sup> To test this possibility, which would involve intermolecular transfer of oxygen, a double-labeling experiment was carried out. A 49:51 ratio of unlabeled **1** and **6** bearing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



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**<sup>8</sup> or addition of

oxygen and hydrogen to phosphorus to give **9**.<sup>9,10</sup> The latter is favored because **10** is inert upon heating in toluene at 100 °C even in the presence of acetic acid.



The present work shows that the mechanistic analogy of backside displacement for nucleophilic substitution at carbon cannot be extended to displacement by phosphines 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.

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

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Received February 28, 1986

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

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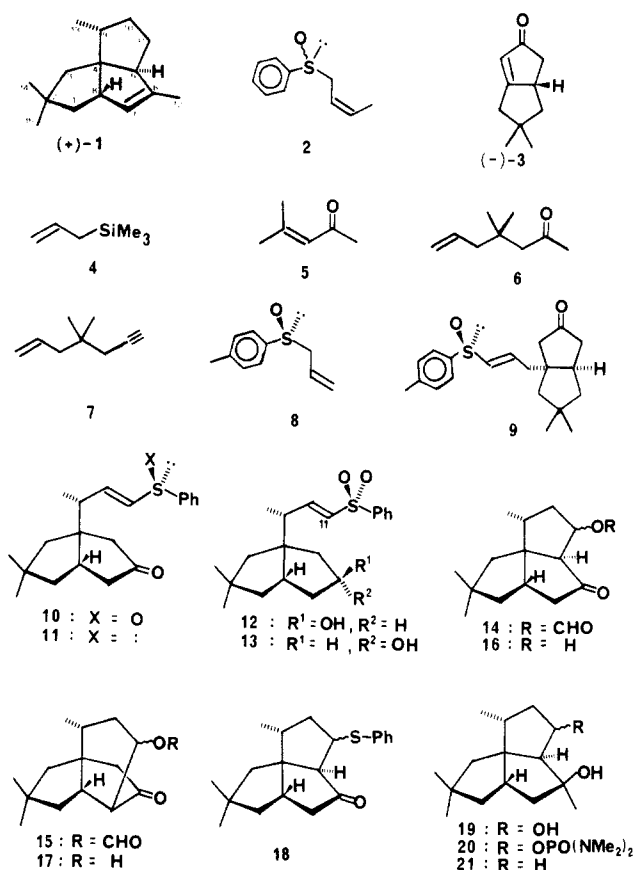
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of the *S. griseochromogenes* organism which also produced pentalenolactones and pentalenic acid. The antibiotic properties of pentalenolactone<sup>4,5</sup> (an agent which is active against Gram-positive/negative bacteria and fungi and which inhibits the enzyme glyceraldehyde-3-phosphate dehydrogenase) and the antitumor activity of deoxypentalenylglucuron<sup>6</sup> have prompted widespread synthetic efforts.<sup>7</sup> Although the total synthesis of (±)-pentalenene [(±)-1] has been reported,<sup>7a</sup> the absolute configuration of (+)-1 remained unknown.<sup>2</sup> We report here an efficient asymmetric total synthesis of (+)-1, starting with racemic *cis*-crotyl phenyl sulfoxide (2) and (–)-(*S*)-7,7-dimethylbicyclo[3.3.0]octen-3-one [(–)-3], and establish its absolute configuration.

Racemic enone 3 was easily prepared in a three-stage reaction sequence: (i) 1,4-addition reaction of allyltrimethylsilane (4) with mesityl oxide (5)–TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub><sup>8</sup> to provide 4,4-dimethyl-6-hepten-2-one (6) (87% yield); (ii) formation of the enol phosphate of ketone 6 by treatment with LDA–CPO(OEt)<sub>2</sub>–THF, followed by in situ dehydroposphonation with 2 equiv of LDA<sup>9</sup> to provide 4,4-dimethyl-6-hepten-1-yne (7) (61% yield); and (iii) intramolecular cyclization of α,σ-enyne 7 with 1 equiv of CO<sub>2</sub>(CO)<sub>8</sub> in heptane (6 mL/g) and CO atmosphere in a sealed tube at 120 °C for 3 days (58% yield).<sup>10</sup> Kinetically selective resolution of 3 was effected by treating (*S*)-allyl *p*-tolyl sulfoxide (8)<sup>1</sup> with 1 equiv of LDA in THF at –78 °C for 1 h, adding 2 equiv of racemic 3 in THF at –78 °C, and maintaining the mixture for 30 min; adduct 9 (80% yield) and (–)-(*S*)-3 [45% yield; [α]<sub>D</sub><sup>25</sup> = –141° (*c* 0.14, CHCl<sub>3</sub>)] were obtained.<sup>11</sup> Addition of the sulfinylallyl anion, derived from the reaction of 2 equiv of racemic *cis*-crotyl phenyl sulfoxide (2)<sup>12</sup> with 2 equiv of LDA in THF at –78 °C, to 1 equiv of (–)-(*S*)-3 in THF at –78 °C and maintaining the mixture for 45 min afforded 91% yield of sulfoxide 10<sup>13</sup> (82% optionally pure). Its optical purity was determined by <sup>1</sup>H NMR spectra of the Mosher derivatives<sup>14</sup> of alcohols 12 and 13, these alcohols being obtained from 10 by reduction with NaBH<sub>4</sub>–MeOH at –20 °C for 20 min followed by oxidation with *m*-chloroperbenzoic acid–CH<sub>2</sub>Cl<sub>2</sub> at 0 °C (95% overall yield; 12:13 = 73:27) and separation by low-pressure liquid chromatography.

The difficulty of hydrolyzing vinyl sulfides possessing an α-CH to the corresponding aldehydes with HgCl<sub>2</sub> or under strongly acidic conditions has been reported.<sup>15</sup> We found that vinyl sulfide 11,



obtained from the reduction of sulfoxide 10 with Zn–AcOH at room temperature for 24 h (95% yield), underwent hydrolysis followed by rapid intramolecular cyclization with the ε enol moiety when treated with 88% HCO<sub>2</sub>H–CF<sub>3</sub>CO<sub>2</sub>H (70–0.1 mL/g) at 60 °C for 24 h to give 60% of formate 14, 8% of isomer 15,<sup>16</sup> 4% of alcohol 16, 2% of isomeric alcohol 17, 15% of sulfide 18, and benzenethiol. Formate 14 was transformed into alcohol 16 by treatment with 1 equiv of K<sub>2</sub>CO<sub>3</sub>–MeOH at room temperature for 15 min (100% yield); addition of 4 equiv of MeMgBr to 16 in ether (40 mL/g) at 0 °C provided 70% yield of 19 (30% recovery of alcohol 16). Finally, (+)-pentalenene [(+)-1]<sup>17</sup> was obtained by the sequence (i) phosphorylation of 19 with 1.2 equiv of *N,N,N',N'*-tetramethyldiamidophosphorochloridate–3 equiv of Et<sub>3</sub>N–2 equiv 4-(dimethylamino)pyridine in toluene (5 mL/g) at 60 °C for 10 h (96% yield of 20), (ii) deoxyphosphorylation<sup>18</sup> of 20 with 10 equiv of lithium–4 equiv *t*-BuOH in EtNH<sub>2</sub>–THF at 0 °C for 30 min (97% yield of 21), and (iii) dehydration of 21 with 0.5 equiv of BF<sub>3</sub>–ether in CH<sub>2</sub>Cl<sub>2</sub> (100 mL/g) at room temperature for 45 min [99% yield of (+)-1]. The spectral properties (IR, <sup>1</sup>H and <sup>13</sup>C NMR, and mass) of (+)-1 were identical with those of authentic material.<sup>19</sup> Sulfide 18 was also transformed into alcohol 21 by the sequence (i) desulfurization with Raney nickel (W-2)–EtOH and (ii) addition of 2 equiv of MeMgBr–ether (82% overall yield).

In summary, the utility of the asymmetric induction reaction of chiral sulfinylallyl anions and enones has thus been extended to another skeletal class. The method leading to the total synthesis

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(11) The absolute configuration of 3 is assigned as *S* configuration according to our previous study.<sup>18</sup> The relative stereochemistry at C-8, C-4, and sulfur of the 1,4-adduct of the carbanion derived from *p*-tolyl allyl sulfoxide with 2-((*tert*-butyldimethylsilyloxy)methyl)-7,7-dimethylbicyclo[3.3.0]-2-octen-3-one has been proven by X-ray diffraction. This work will be published elsewhere.

(12) Sulfoxide 2 was prepared from sodium benzenethiolate and *cis*-1-chloro-2-butene followed by oxidation with MCPBA in CH<sub>2</sub>Cl<sub>2</sub>.

(13) All enantiomers are being depicted with absolute stereochemistry as indicated. All new compounds displayed satisfactory <sup>1</sup>H NMR (400 MHz), <sup>13</sup>C NMR (100 MHz), UV, IR, and low-resolution mass spectra (both EI and CI) and satisfactory elemental analysis or high-resolution MS.

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of (+)-pentalenene [(+)-1] is stereocontrolled, short, and effective and should be applicable to the constructions of isocomene,<sup>20</sup> silphenene,<sup>21</sup> senoxydene,<sup>22</sup> pentalenic acid, and pentalenolactone. The hydrolytic ring closure reaction of vinyl sulfide and ketones seems to be general and should prove to be a valuable new reaction tool in other syntheses. Utilization with more highly oxidized members of the sesquiterpene is being explored.

**Acknowledgment.** We thank the NSF and Kansas State University for a grant for the purchase of the Bruker WM-400 NMR spectrometer. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE-8419265) for generous financial support. We are indebted to Professor Haruo Seto for providing the spectral data and Gurudas Sinai-Zingde and Ibraheem Badejo for technical assistance.

**Supplementary Material Available:** <sup>1</sup>H and <sup>13</sup>C NMR spectra for compound 1-3, 10, 11, and 14-21 (21 pages). Ordering information is given on any current masthead page.

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## Hydrogen-Deuterium Exchange during Propylene Epoxidation by Cytochrome P-450

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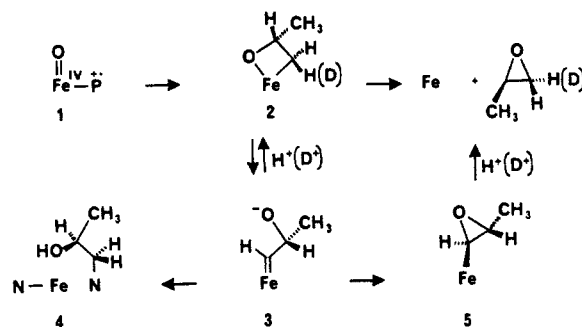
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The nature of the "active oxygen species" and the mechanism of the oxygen-transfer event in the catalytic cycle of cytochrome P-450<sup>1</sup> have been the subject of extensive investigation and speculation. A powerful approach to the study of such elusive intermediates has been the use of substrate molecules designed to reveal the chemistry of the ultimate oxidant. We have previously demonstrated that epimerization<sup>2</sup> and allylic rearrangement<sup>3</sup> occur during the aliphatic hydroxylation by cytochrome P-450. We report here that the epoxidation of *trans*-1-deuteriopropylene by a reconstituted cytochrome P-450 system proceeds with significant loss of the deuterium label. Further, the epoxidation of propylene by this enzymic system in D<sub>2</sub>O affords predominantly *trans*-1-deuteriopropylene oxide.

In a typical experiment cytochrome P-450<sub>LM2</sub> (5 nmol), cytochrome P-450 reductase (10 nmol), and dilauroyl-GCP (150-220 μL of a 1 mg/mL solution) were mixed and then diluted with 0.5 mL of phosphate buffer (pH 7.4) and 0.5 mL of water in a manner identical with that which we have previously described.<sup>3,4</sup> NADPH (250 μL of a 10 mg/mL solution) was added from a bent side neck and the mixture was cooled to 4 °C. After removal of air on a vacuum line, propylene (1.9-2.2 mmol) or *trans*-1-

Scheme I



deuteriopropylene (0.9-1.0 mmol, 70% d<sub>1</sub>) was admitted to the reaction vessel and the mixture was allowed to equilibrate for 15-30 min. After propylene was removed to 0.5 atm and replaced with oxygen, the mixture was allowed to stand at 4 °C overnight. After removal of oxygen from the frozen reaction mixture, volatile products were transferred to a cold trap. Unreacted propylene was removed from the reaction products by distillation, and propylene oxide was either condensed into a sample bulb or isolated from the product fraction by preparative gas chromatography on a 20% Carbowax column. The amount of propylene oxide was determined manometrically at this point. Simultaneous, quantitative analysis of propylene oxide, *trans*-1-deuteriopropylene oxide, *cis*-1-deuteriopropylene oxide, and unreacted propene was carried out by microwave spectroscopy as we have previously described.<sup>5</sup> Blank samples were determined before and after each run to assure that the vacuum line, gas chromatograph, and microwave cavity were free of contamination.

Typical data for a series of propylene oxidations presented as intensity ratios for five prominent microwave transitions are shown in Table I. Product yields and isotopomer distributions are presented in Table II. Remarkably, the epoxidation of *trans*-1-deuteriopropylene afforded 95% propylene-d<sub>0</sub> oxide. This apparent deuterium exchange was confirmed by the runs performed with unlabeled propylene in D<sub>2</sub>O which gave greater than 80% *trans*-1-deuteriopropylene oxide. Thus, the epoxidation of propylene with this reconstituted cytochrome P-450 system proceeded with a concomitant, stereospecific hydrogen/deuterium exchange from the aqueous milieu.

Electrophoretically homogeneous cytochrome P-450 alone catalyzed the epoxidation of propylene with iodosylbenzene to give an isotopomer ratio indistinguishable from that of the starting propylene. Further, the incubation of propylene oxide with the fully reconstituted P-450 system in D<sub>2</sub>O for 3 days caused no more than 10% exchange. The epoxidation of *trans*-1-deuteriopropylene with Fe(TPP)Cl or Mn(TPP)Cl and iodosylbenzene in wet methylene chloride gave products consistent with complete retention of configuration with the iron porphyrin and significant *trans*-*cis* rearrangement with the manganese porphyrin but with no H-D exchange. Similar results have been obtained for these synthetic porphyrin catalysts with other substrates.<sup>6</sup>

A number of mechanisms have been suggested for the substrate oxygenation catalyzed by cytochrome P-450.<sup>1</sup> No simple oxygen-transfer process would have predicted the stereospecific exchange of a carbon-bound hydrogen observed here, however. Two processes that do allow for the observed results are shown in Scheme I. We have described the preparation and characterization of an oxoiron(IV) porphyrin cation radical species (1) which is capable of epoxidizing olefins at low temperature.<sup>7</sup> Such a

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