Palladium-Catalyzed Thiono–Thiolo Allylic Rearrangement of *O*-Allyl Phosphoro- and Phosphonothionates

Yoshinao Tamaru and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

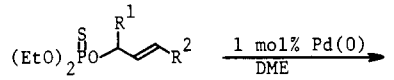
Yoshimi Yamada,* Kunio Mukai, and Hirosuke Yoshioka

Pesiticide Division, Institute for Biological Science, Sumitomo Chemical Co. Ltd., Takarazuka, Hyogo 665, Japan

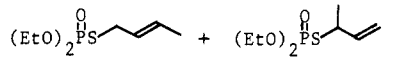
Received September 7, 1982

The thiono–thiolo allylic rearrangement of *O*-allyl phosphoro- and phosphonothionates is effected by catalysis with Pd(0). A wide variety of *O*-allyl thionates (17 kinds) are rearranged selectively to the thermodynamically more stable regio- and stereoisomers via a (π-allyl)palladium intermediate. Thermal rearrangement of α- and γ-methallyl diethyl phosphorothionates is reinvestigated in relation to the regioselectivity observed in the palladium(0) catalysis.

The rearrangement of organophosphorus thiono esters to thiolo esters (thiono–thiolo rearrangement) is known to be effected thermally as well as by the catalysis of alkyl halides,[1] Lewis acids,[2] and protic acids.[3] In addition to these, we have found that palladium(0) complex also catalyzes this rearrangement very efficiently.[4] Interestingly these procedures show a sharp contrast in their regioselectivity with respect to the migrating allylic moiety. Thermal rearrangement is reported to give the allylic inversion product[5] and protic acid catalyzed rearrangement the allylic retention product selectively,[3] while the palladium-catalyzed rearrangement was found to provide mainly the products in which the sulfur atom was bonded to the least substituted carbon atom, regardless of the substitution pattern of allylic groups (eq 1).



[R^1=H, R^2=Me or R^1=Me, R^2=H]



93% 2% (1)

Besides its characteristic regioselectivity, the palladium-catalyzed rearrangement gives high product yields with a wide variety of substituents both on the phosphorus atom and allylic moiety. In this paper we report details and studies of the mechanistic aspects of the palladium-catalyzed thiono–thiolo allylic rearrangement of *O*-allyl phsphoro- and phosphonothionates.

Results and Discussion

In order to test the generality of palladium catalysis for the thiono–thiolo allylic rearrangement, we investigated the reaction mainly with respect to (a) variations of substituents on the phosphorus atom and (b) the substitution pattern of allylic moiety. These results are summarized in Tables I and II, which indicate that the present procedure could be successfully applied to many types of substrates. Almost all reactions were examined in the presence of 1 mol % of $Pd(Ph_3P)_4$ in dimethoxyethane (DME) or bis(2-methoxyethyl) ether (diglyme) and attained completion at 80 °C within 10–25 min. The effect of solvent on the reaction was quite dramatic, with these ethereal solvents being the solvents of choice. In acetonitrile or xylene, reaction was very slow and in some cases gave only low conversion. A small amount of K_2CO_3 (1 mol %) was applied in order to maintain the reaction mixture as neutral or somewhat basic. In the absence of palladium(0), no rearrangement was observed under the conditions in entry 1 (Table I) or even after prolonged reaction times. It is reported that Pd(II), and not Pd(0), effectively catalyzes similar types of rearrangement (e.g., Cope rearrangement, 1,3-rearrangement of allylic acetates, S → N rearrangement of *S*-allyl thioimidates);[6] however, in the present reaction, the situation was quite the opposite, and Pd(0) was found to be an active species. Palladium(II) showed a catalytic activity for some limited cases but was not generally effective. Palladium(II) [as bis(acetonitrile)palladium chloride] catalyzed the rearrangement of diethyl allyl phosphorothionate to give results similar to those in entry 2 (Table I; 1 mol % of catalyst, at 80 °C for 20 min), but for the rearrangements of diethyl *trans*-crotyl phosphorothionate (1 mol % of catalyst, DME, 80 °C for 1 h; cf. entry 3, Table II) and *O-trans*-crotyl *O*-ethyl phenylphosphonothionate [**1**, Ph(EtO)P(=S)OCH_2CH=$CHCH_3$-*trans*; 1 mol % of catalyst, diglyme, 120 °C for 1 h], Pd(II) did not show any catalytic activity, just resulting in the recovery of the starting materials.[7]

Concerning the results in Table I, the following points deserve some comments. The first is the specific migration of allylic groups. No trace of alkyl migration product was observed even in the case of dimethyl allyl phosphorothionate (entry 1). This is quite interesting, taking into consideration that the methyl group shows an exceptionally high migratory ability.[2] The second is the small effect of substituents on phosphorus atom on the rate of migration. The third is an exceptionally low conversion observed in entry 6. The reaction proceeded with similar ease to other cases, but ceased essentially at 80% conversion, regardless of reaction temperatures and reaction times. This behavior might be explained by deactivation of the catalyst by some mercaptan-containing degradation products. The last point is a low isolated yield in entry 1, which is apparently

(1) Burn, A. J.; Cadogan, J. I. G. *J. Chem. Soc.* **1961**, 5532.
(2) Teichmann, H.; Hilgetag, G. *Angew. Chem.* **1967**, *79*, 1077.
(3) Stec, W. J.; Uznanski, B.; Michalski, J. *J. Org. Chem.* **1976**, *41*, 1291.
(4) Yamada, Y.; Mukai, K.; Yoshioka, H.; Tamaru, Y.; Yoshida, Z. *Tetrahedon Lett.* **1979**, 5015.
(5) Pudovik, A. N.; Aladzheva, I. M. *Zh. Obshch. Khim.* **1960**, *30*, 2617.
(6) (a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321. (b) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865. (c) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *J. Org. Chem.* **1980**, *45*, 5221. (d) Idem. *Tetrahedron Lett.* **1981**, *22*, 4245.
(7) In contrast to Pd(II), 1 mol % of Pd(0) catalyzed the rearrangement of 1 (at 80 °C, 1 h; see Experimental Section).

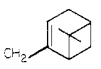
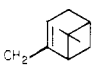
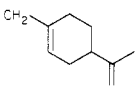
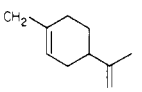
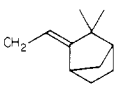
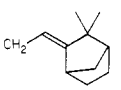
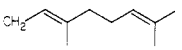
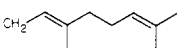
0022-3263/83/1948-1293$01.50/0

Table I. Palladium-Catalyzed Thiono-Thiolo Allylic Rearrangement of Phosphoro- and Phosphonothionates[a]

entry	starting material	time, min	conv, %	product (% isolated yield)[b]
1	$(MeO)_2P(=S)OCH_2CH=CH_2$	25	100	$(MeO)_2P(=O)SCH_2CH=CH_2$ (73)
2	$(EtO)_2P(=S)OCH_2CH=CH_2$	10	100	$(EtO)_2P(=O)SCH_2CH=CH_2$ (96)
3	$Ph(EtO)P(=S)OCH_2CH=CH_2$	20	100	$Ph(EtO)P(=O)SCH_2CH=CH_2$ (97)
4	$Ph(Et_2N)P(=S)OCH_2CH=CH_2$	20	99	$Ph(Et_2N)P(=O)SCH_2CH=CH_2$ (95)
5	$Ph(EtNH)P(=S)OCH_2CH=CH_2$	20	100	$Ph(EtNH)P(=O)SCH_2CH=CH_2$ (98)
6	$Ph(EtS)P(=S)OCH_2CH=CH_2$	10	80	$Ph(EtS)P(=O)SCH_2CH=CH_2$ (95)

[a] Phosphoro- or phosphonothionate (5.0 mmol) and K_2CO_3 (0.05 mmol) in anhydrous diglyme (6 mL) are heated at 70 °C (entry 1) or 80 °C (entries 2–6) in the presence of 1 mol % of tetrakis(triphenylphosphine)palladium under argon. [b] Yield based on the conversion.

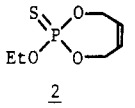
Table II. Palladium-Catalyzed Thiono-Thiolo Allylic Rearrangement of Diethyl Allyl Phosphorothionates[a]

entry	starting material, $(EtO)_2P(=S)OR$	catalyst, mol %	time, min	conv, %	product,[b] $(EtO)_2P(=O)SR'$ (% yield)
1	$CH_2CMe=CH_2$	1	20	99	$CH_2CMe=CH_2$ (93)
2	$CHMeCH=CH_2$	1	20	100	*trans*-$CH_2CH=CHMe$ [95] (93), $CHMeCH=CH_2$ [5] (2)
3	*trans*-$CH_2CH=CHMe$	1	20	100	*trans*-$CH_2CH=CHMe$ [94] (93), $CHMeCH=CH_2$ [6] (2)
4	*cis*-$CH_2CH=CHMe$	1	60	100	*trans*-$CH_2CH=CHMe$ [95] (94), $CHMeCH=CH_2$ [5] (3)
5	*trans*-$CH_2CH=CHPh$	1	20	100	*trans*-$CH_2CH=CHPh$ (92)
6	$CH_2CH=CMe_2$	1	20	100	$CH_2CH=CMe_2$ (67)[c]
7	$CH_2CH=CHCH=CHMe$	1	60	100	$CH_2CH=CHCH=CHMe$ (83)[c]
8		5	300	91	 (100)
9		5	300	95	 (83)
10		5	300	100	 (79)[c]
11		5	420	100	 (43)[c]

[a] Phosphorothionate (5.0 mmol) and K_2CO_3 (0.05 mmol) in anhydrous DME (6 mL, entries 1 and 4–11) or diglyme (6 mL, entries 2 and 3) are heated at 80 °C in the presence of $Pd(Ph_3P)_4$ under argon. [b] Values in brackets denote product distribution obtained by VPC. Values in parentheses denote isolated yields based on conversion. [b] Overall yield based on diethyl chlorothiophosphate.

attributed to mechanical losses due to volatility and solubility of product in the water layer during workup.

An important characteristic of the palladium-catalyzed rearrangement is the good regio- and stereoselectivity, compared with thermal and protic acid catalyzed reactions (vide supra). Both *O*-*trans*-crotyl and *O*-α-methallyl thionates rearranged to provide the similar mixtures of products favoring *S*-*trans*-crotyl over *S*-α-methallyl thiolates in a ratio of 95:5 (eq 1, entries 2 and 3 in Table II). *O*-*cis*-Crotyl thionate also rearranged to give the same distribution of products (entry 4). In these reactions no *S*-*cis*-crotyl isomer was detectable. Similar, but higher regioselectivity was observed for γ-phenyl (entry 5, Table II), γ-propenyl (entry 7), andd γ,γ-dimethyl (entry 6) allylic groups, providing the S–C (primary) products exclusively. Entries 8–11 demonstrate the rearrangement of naturally occurring monoterpenoids, which also produce the S–C (primary) products exclusively. However, in these cases, 5 mol % of catalyst and prolonged reaction times were required for efficient conversion of the starting thionates. The yields recorded in entries 6, 10, and 11 are the overall yields based on diethyl chlorothiophosphate. These *O*-allyl thionates with two substituents at the γ-position are unstable and prone to rearrange to the corresponding thiolates upon silica gel (in low yield), and hence the crude thionates were directly subjected to rearrangement. This process, combined with an alkaline hydrolysis,[8] might provide a viable method to convert naturally occurring allylic alcohols to the corresponding thiols. The cyclic allylic thionate **2** did not undergo a rearrangement under usual conditions and was recovered unchanged (eq 2).



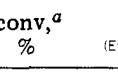
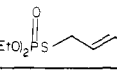
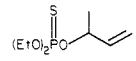
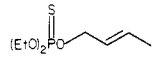
2

$$\xrightarrow[2\text{ h, DME}]{1\text{ mol\% } Pd(PPh_3)_4} \text{no reaction} \quad (2)$$

In order to clarify the differences in regioselectivity between thermal and Pd(0)-catalyzed rearrangements, we reinvestigated the thermal rearrangement of diethyl *trans*-crotyl and α-methallyl phosphorothionates. Reportedly, these isomers rearranged selectively to *S*-α-methallyl and *S*-*trans*-crotyl phosphorothiolates, respectively (in a neat state at 120–140 °C for 3–6 h),[5] suggesting a [3.3] sigmatropic rearrangement. However, Table III clearly indicates that the regioselectivity in these rearrangements largely depends on the reaction times and concentrations. The high regioselectivity in dilutions supports a sigmatropic process in these rearrangements. The significant reduction of regioselectivity for the rearrangement of *O*-*trans*-crotyl to *S*-α-methallyl in a neat state (or even in dilutions after prolonged reaction times) might be caused by multistep nucleophilic substitution of

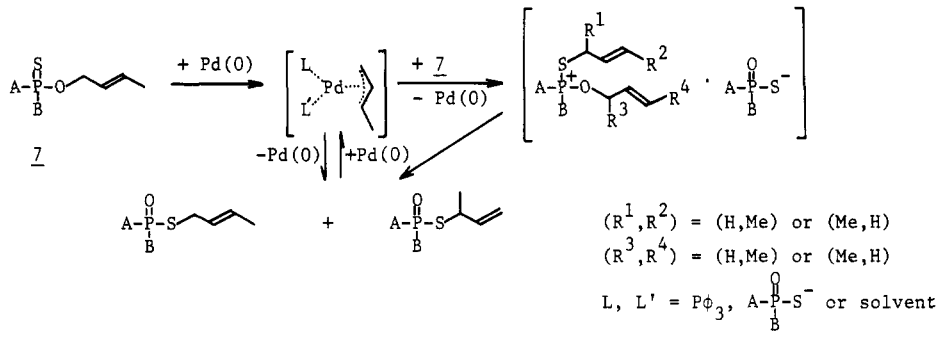
(8) Bruzik, K.; Stec, W. J. *J. Org. Chem.* **1979**, *44*, 4488.

Table III. Thermal Rearrangement of Diethyl α- and γ-Methallyl Phosphorothionates

entry	starting thionate	solvent	temp, °C	time, h	conv,[a] %	product distribution,[b] %	
							
1	 I	none[c]	130	3	100	97.1	2.9
2	I	diglyme[d]	140	0.3	100	99.5	0.5
3	 II	none[c]	130	3	100	31.8	68.2
4	II	diglyme[d]	140	0.5	89	8.5	91.5
5	II	diglyme[d]	140	1	97	21.1	78.9
6	II	diglyme[e]	140	0.5	64	4.1	95.9
7	II	diglyme[e]	140	3	99[f]	18.6	81.4
8	II	diglyme[e]	140	10	100[g]	41.9	58.1

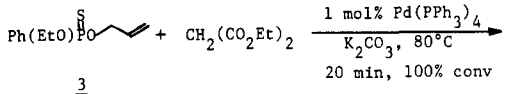
[a] Conversion, based on VPC area intensities. [b] Calculated from the area intensities on VPC. [c] Neat α- or γ-methallyl phosphorothionate was heated in a sealed tube under nitrogen. [d] α- or γ-methallyl phosphorothionate (0.83 M in diglyme) was heated under argon. [e] α- or γ-methallyl phosphorothionate (0.05 M in diglyme) was heated under argon. [f] A mixture of products was isolated in 84% yield. [g] A mixture of products was isolated in 75% yield.

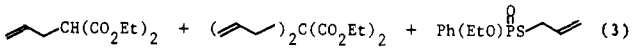
Scheme I

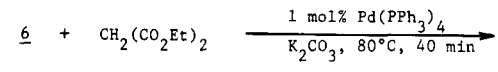


an allylic moiety, initiated by an S_N2 reaction of *trans*-crotyl diethyl phosphorothionate with *S*-α-methallyl diethyl phosphorothiolate. The selective thermal rearrangement of cinnamyl dimethylphosphinothionate to the corresponding *S*-cinnamyl ester, reported by Stec et al.,[3] might be rationalized in a similar fashion, because the *S*-CH(Ph)CH=CH_2 group is expected to be much more susceptible to such an S_N2-type substitution than the *S*-α-methallyl group.

The characteristic regio- and stereoselectivity presented in Table II might be rationalized by invoking a (π-allyl)-palladium complex as an intermediate, and this is supported by the reaction of allyl ethyl phenylphosphonothionate (**3**) with diethyl malonate (eq 3).[9] In the presence







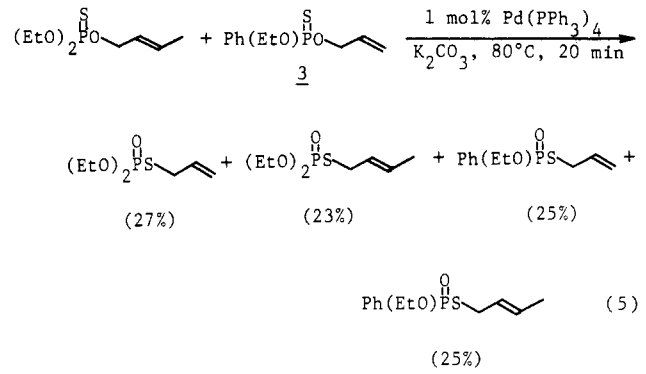
of 1.1 equiv of diethyl malonate, **3** was converted to give allylmalonate **4**, diallylmalonate **5**, and thiolate **6**. Under similar conditions, in the absence of Pd(0), no reaction proceeded. Interestingly, **6** was found to react further with diethyl malonate to give **4** and **5**, indicating that Pd(0) adds oxidatively to the C–S bond of **6** to also form a (π-allyl)-palladium intermediate. The noticeably high regioselectivity (Table II) might be rationalized as a result of the thermodynamic control through this reversibility (Scheme I).[10] Furthermore, the intermolecular character of the reaction was demonstrated by the complete crossover in the following experiment (eq 5): an equimolar mixture of diethyl crotyl phosphorothionate and **3** was rearranged under the usual conditions to provide a mixture of possibly four kinds of thiolates in an almost statistical ratio. This result requires the exchange of thiophosphate counterion in (π-allyl)palladium complex and/or the nucleophilic attack of phosphorothionate on a (π-allyl)palladium complex, as shown in Scheme I.

Experimental Section

Unless otherwise indicated, short-path (bulb-to-bulb) distillations were carried out in a Kugelrohr apparatus. Microanalyses

(9) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (b) For the palladium catalyzed C–O bond cleavage of allyl phosphates, see: Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S.-I. *Tetrahedron Lett.*, in press.

(10) Dimethyl α- and γ-methallylmalonates (in a ratio of 45:55) were obtained by the palladium(0)-catalyzed reaction of α- or γ-methallyl acetate and dimethyl malonate in the presence of K_2CO_3: Tamaru, Y.; Yamada, Y.; Yoshida, Z., unpublished data. See also: Tamura, R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 3727.



(5)

were performed by the Microanalysis Center of Kyoto University. Analyses agreed with calculated values within ±0.3% unless otherwise noted. Infrared spectra were measured with a Hitachi Model EPI-G3 grating spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were determined either at 60 MHz on a JEOL JNM-PMX 60 instrument or at 100 MHz on a Varian HA-100 instrument with tetramethylsilane as an internal standard. Mass spectra were measured either on a Hitachi Model RMU 6C instrument or on a JEOL D-300 instruments (high-resolution mass spectrophotometer).

Solvents. 1,2-Dimethoxyethane (DME) and bis(2-methoxyethyl) ether (diglyme) were dried over CaH_2, distilled, and kept under an argon atmosphere.

***O*-Allyl Phosphoro- and Phosphonothionates.** Starting thionates were prepared according to standard methods.[11] Allyl dimethyl phosphorothionate (entry 1, Table I), allyl diethyl phosphorothionate (entry 2, Table I), β-methallyl diethyl phosphorothionate (entry 1, Table II), α-methallyl diethyl phosphorothionate (entry 2, Table II), *trans*-crotyl diethyl phosphorothionate (entry 3, Table II), *cis*-crotyl diethyl phosphorothionate (entry 4, Table II), *trans*-cinnamyl diethyl phosphorothionate (entry 5, Table II), 3-methyl-2-buten-1-yl diethyl phosphorothionate (entry 6, Table II), *trans,trans*-hexa-2,4-dien-1-yl diethyl phosphorothionate (entry 7, Table II), (−)-myrtenyl diethyl phosphorothionate (entry 8, Table II), *l*-perillyl diethyl phosphorothionate (entry 9, Table II), *dl*-patchenyl diethyl phosphorothionate (entry 10, Table II), and geranyl diethyl phosphorothionate (entry 11, Table II) were prepared by the reaction of diethyl chlorothiophosphate and the corresponding allylic alcohol in THF with sodium hydride as a base. Allyl ethyl phenylphosphonothionate (entry 3, Table I), *O*-allyl *N,N*-diethylphenylphosphonothioamidate (entry 4, Table I), *O*-allyl *N*-ethylphenylphosphonothioamidate (entry 5, Table I), and *O*-allyl *S*-ethyl phenylphosphonodithionate (entry 6, Table I) were prepared by the stepwise reaction of phenylphosphonothioic dichloride with allyl alcohol [Et_3N, 4-methyl-2-pentanone (MIBK)] and then with ethyl alcohol (NaH, THF), diethylamine (aqueous NaOH, benzene), ethylamine (aqueous NaOH, benzene), or ethanethiol (aqueous NaOH, benzene). *cis*-Crotyl alcohol was prepared by the partial hydrogenation of 2-butyn-1-ol (5% Pd/C, $BaSO_4$, *s*-colidine, MeOH).[12] *trans,trans*-2,4-Hexadien-1-ol was obtained by the reduction of ethyl sorbate ($LiAlH_4$, ether).

General Procedure (Tables I and II). Reactions were performed uniformly as follows. Into an argon-purged mixture of tetrakis(triphenylphosphine)palladium (0.05 or 0.25 mmol) and potassium carbonate (0.05 mmol) was added a solution of allylic thionate (5 mmol) in 6 mL of solvent. This solution was stirred and heated at the temperatures indicated in Tables I and II. The reaction was monitored by VPC at an appropriate time. After the reaction was completed or essentially ceased, the mixture was poured into water and extracted twice with ether. The combined ether extracts were washed with saturated NaCl and dried over magnesium sulfate. Evaporation of the solvents and subsequent purification by column chromatography on silica gel gave the spectroscopically pure product(s) in the yield(s) indicated in the tables.

(11) Sasse, K. "Methoden der Organischen Chemie (Houben-Weyl)"; Georg Thieme Verlag: Stuttgart, 1964; Band 11/2, p 550.
(12) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

Similarly *O-trans*-crotyl *O*-ethyl phenylphosphonothionate (1) was rearranged by the calalysis of 1 mol % of tetrakis(triphenylphosphine)palladium to provide *S-trans*-crotyl *O*-ethyl phenylphosphonothiolate and *S*-α-methallyl *O*-ethyl phenylphosphonothiolate (diastereoisomeric mixture) in isolated yields of 91% and 3%, respectively (in diglyme at 80 °C for 1 h).

The spectral and analytical data of new compounds are summarized at the end of this section.

Palladium-Catalyzed Rearrangement of Diethyl *trans*-Crotyl Phosphorothionate in the Presence of Allyl Ethyl Phenylphosphonothionate (A Crossover Experiment, Eq 5). Into an argon-purged mixture of tetrakis(triphenylphosphine)-palladium (23.1 mg, 0.02 mmol) and potassium carbonate 2.8 mg (0.02 mmol) was added a solution of diethyl crotyl phosphorothionate (224 mg, 1 mmol) and allyl ethyl phenylphosphonothionate (242 mg, 1 mmol) in 2.4 mL of diglyme. This mixture was stirred and heated at 80 °C for 20 min, and the mixture was analyzed by VPC. Small amount of α-methallyl phosphoro- and phosphonothiolates were neglected for simplicity. The corrected ratio of four main products was determined to be 26.6:23.4:24.6:25.4.

***S*-Allyl *N,N*-diethylphenylphosphonothioloamidate (entry 4, Table I):** bp 170 °C (1 mmHg); IR (neat) 1635, 1200, 930 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.06 (6 H, t, J = 7.0 Hz), 3.06 (4 H, dq, J = 12.0, 7.0 Hz), 3.34 (2 H, dd, J = 11.0, 7.0 Hz), 4.76–6.10 (3 H, m), 7.26–8.02 (5 H, m); mass spectrum m/e (relative intensity) 269 (M^+, 10), 197 (47), 196 (100). Anal. Calcd for $C_{13}H_{20}NOPS$: C, 57.97; H, 7.48; P, 11.50. Found: C, 57.91; H, 7.19; P, 11.42.

***S*-Allyl *N*-ethylphenylphosphonothioloamidate (entry 5, Table I):** bp 205 °C (0.5 mmHg); IR (neat) 1620, 1185, 1100 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.14 (3 H, t, J = 7.0 Hz), 2.63–3.50 (2 H, m), 3.26 (2 H, dd, J = 12, 6.8 Hz), 4.62–6.09 (4 H, m), 7.25–8.05 (5 H, m); mass spectrum, m/e (relative intensity) 241 (M, 12), 184 (18), 168 (100), 140 (29). Anal. Calcd for $C_{11}H_{16}NOPS$: C, 54.76; H, 6.68; P, 12.84. Found: C, 54.48; H, 6.87; P, 12.81.

***S*-Allyl *S*-ethyl phenylphosphonodithiolate (entry 6, Table I):** bp 180 °C (2 mmHg); IR (neat) 1635, 1200, 1105 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.35 (3 H, t, J = 7.3 Hz), 2.85 (2 H, dq, J = 7.0, 7.0 Hz), 3.50 (2 H, dd, J = 12.0, 7.0 Hz), 4.88–6.20 (3 H, m), 7.33–8.13 (5 H, m); mass spectrum, m/e (relative intensity) 258 (M, 16), 197 (37), 157 (100), 102 (79). Anal. Calcd for $C_{11}H_{15}OPS_2$: C, 51.14; H, 5.85; P, 11.99. Found: C, 51.42; H, 5.83; P, 11.72.

***S*-β-Methallyl diethyl phosphorothiolate (entry 1, Table II):** bp 140 °C (5 mmHg); IR (neat) 1650, 1255, 1020, 970 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.33 (6 H, t, J = 7.0 Hz), 1.83 (3 H, s), 3.37 (2, H, d, J = 14 Hz), 4.03 (4 H, dq, J = 9.0 Hz, 7.0 Hz), 4.78 (1 H, br s), 4.93 (1 H, br s); mass spectrum, m/e (relative intensity) 224 (M, 100), 191 (86), 153 (63), 135 (64), 86 (87); calcd for $C_8H_{17}O_3PS$ m/e 224.0635, found m/e 224.0617.

***S*-Cinnamyl diethyl phosphorothiolate (entry 5, Table II):** bp 200 °C (0.3 mmHg); IR (neat) 1255, 1015, 965, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (6 H, t, J = 7.2 Hz), 3.64 (2 H, dd, J = 15, 6.6 Hz), 4.15 (4 H, dq, J = 9.0, 7.0 Hz), 5.92–6.82 (2 H, m), 7.28 (5 H, br s); mass spectrum, m/e (relative intensity) 286 (M, 17), 149 (5), 117 (100), 115 (27); calcd for $C_{13}H_{19}O_3PS$ m/e 286.0788, found m/e 286.0774.

***S-trans,trans*-2,4-Hexadien-1-yl diethyl phosphorothiolate (entry 7, Table II):** bp 150 °C (0.2 mmHg); IR (neat) 1655, 1255, 1015, 970, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (6 H, t, J = 7.0 Hz), 1.78 (3 H, d, J = 6.0 Hz), 3.56 (2 H, dd, J = 15, 7.2 Hz), 4.22 (4 H, dq, J = 8.6, 7.0 Hz), 5.21–6.75 (4 H, m); mass spectrum, m/e (relative intensity) 250 (M, 24), 113 (26), 81 (100), 80 (92), 79 (51); calcd for $C_{10}H_{19}O_3PS$ m/e 250.0792, found m/e 250.0782.

***S*-(−)-Myrtenyl diethyl phosphorothiolate (entry 8, Table II):** bp 170 °C (0.2 mmHg); IR (neat) 1640, 1255, 1015, 970, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, s), 1.32 (3 H, s), 1.38 (6 H, t, J = 7.2 Hz), 1.69–2.67 (6 H, m), 3.49 (2 H, d, J = 11.2 Hz), 4.17 (4 H, dq, J = 9.0, 7.2 Hz), 5.59 (1 H, br); mass spectrum, m/e (relative intensity) 304 (M, 0.5), 171 (53), 134 (100), 119 (73). Anal. Calcd for $C_{14}H_{25}O_3PS$: C, 55.24; H, 8.28; P, 10.18. Found: C, 55.51; H, 8.58; P, 9.95.

***S*-*l*-Perillyl diethyl phosphorothiolate (entry 9, Table II):** bp 170 °C (0.15 mmHg); IR (neat) 1645, 1260, 1020, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (6 H, t, J = 7.0 Hz), 1.75 (3 H, br s), 1.85–2.41 (7 H, br), 3.46 (2 H, d, J = 13.6 Hz), 4.17 (4 H, dq, J = 8.8, 7.2 Hz), 4.75 (2 H, br s), 5.79 (1 H, br s); mass spectrum, m/e (relative

intensity) 304 (M, 1), 171 (100), 143 (47), 134 (100), 119 (63). Anal. Calcd for $C_{14}H_{25}O_3PS$: C, 55.24; H, 8.28; P, 10.18. Found: C, 55.17; H, 8.41; P, 10.30.

***S-dl*-Patchenyl diethyl phosphorothiolate (entry 10, Table II)**: bp 175 °C (0.3 mmHg); IR (neat) 1670, 1255, 1015, 970, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (6 H, br s), 1.37 (6 H, t, J = 7.2 Hz), 1.07–2.01 (7 H, m), 3.03 (1 H, br), 3.53 (2 H, dd, J = 12.4, 8.0 Hz), 4.19 (4 H, dq, J = 8.6, 7.2 Hz), 5.11 (1 H, t, J = 8.0 Hz); mass spectrum, m/e (relative intensity) 318 (M, 12), 149 (100), 107 (31), 93 (67). Anal. Calcd for $C_{15}H_{27}O_3PS$: C, 56.58; H, 8.55; P, 9.73. Found: C, 56.76; H, 8.66; P, 9.46.

***S*-Geranyl diethyl phosphorothiolate (entry 11, Table II)**: bp 170 °C (0.3 mmHg); IR (neat) 1655, 1255, 1020, 970, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (6 H, t, J = 7.2 Hz), 1.63 (3 H, s), 1.71 (6 H, br s), 1.97–2.24 (4 H, m), 3.52 (2 H, dd, J = 13, 8.0 Hz), 4.21 (4 H, dq, J = 8.5, 7.2 Hz), 4.73–5.60 (2 H, br m); mass spectrum, m/e (relative intensity) 306 (M, <0.01), 237 (7), 171 (93), 170 (54), 136 (68), 93 (100), 80 (70). Anal. Calcd for $C_{14}H_{27}O_3PS$: C, 54.88; H, 8.88; P, 10.11. Found: C, 54.60; H, 8.93; P, 10.25.

***S-trans*-Crotyl ethyl phenylphosphonothiolate (eq 7 and footnote 7)**: bp 175 °C (2 mmHg); IR (neat) 1650, 1230, 1025, 950, 690 cm^{-1}; ^1H NMR (CCl_4) δ 1.36 (3 H, t, J = 7.2 Hz), 1.54 (3 H, d, J = 6.6 Hz), 3.31 (2 H, dd, J = 13, 6.2 Hz), 4.12 (2 H, dq, J = 9.0, 7.2 Hz), 5.18–5.72 (2 H, m), 7.24–8.00 (5 H, m); mass spectrum, m/e (relative intensity) 256 (M, 34), 202 (60), 142 (47), 141 (100). Anal. Calcd for $C_{12}H_{17}O_2PS$: C, 56.24; H, 6.69; P, 12.08. Found: C, 56.03; H, 6.77; P, 11.93.

Registry No. **3**, 74070-90-9; **6**, 74070-96-5; $(MeO)_2P(=O)SCH_2CH=CH_2$, 66498-87-1; $(EtO)_2P(=O)SCH_2CH=CH_2$, 10428-96-3; $Ph(Et_2N)P(=O)SCH_2CH=CH_2$, 74070-97-6; $Ph(EtNH)P(=O)SCH_2CH=CH_2$, 74070-98-7; $Ph(EtS)P(=O)SCH_2CH=CH_2$, 74070-99-8; $(EtO)_2P(=O)SCH_2CMe=CH_2$, 85082-99-1; *trans*-$(EtO)_2P(=O)SCH_2CH=CHMe$, 85083-00-7; $(EtO)_2P(=O)SCHMeCH=CH_2$, 32811-23-7; *trans*-$(EtO)_2P(=O)SCH_2CH=CHPh$, 85083-01-8; $(EtO)_2P(=O)SCH_2CH=CMe_2$, 10006-38-9; $(EtO)_2P(=O)SCH_2CH=CHCH=CHMe$, 85083-02-9; $(MeO)_2P(=S)OCH_2CH=CH_2$, 65715-80-2; $(EtO)_2P(=S)OCH_2CH=CH_2$, 74070-89-6; $Ph(Et_2N)P(=S)OCH_2CH=CH_2$, 74070-91-0; $Ph(EtNH)P(=S)OCH_2CH=CH_2$, 74070-92-1; $Ph(EtS)P(=S)OCH_2CH=CH_2$, 74070-93-2; $(EtO)_2P(=S)OCH_2CMe=CH_2$, 85083-07-4; $(EtO)_2P(=S)OCHMeCH=CH_2$, 74070-94-3; *trans*-$(EtO)_2P(=S)OCH_2CH=CHMe$, 85083-08-5; *cis*-$(EtO)_2P(=S)OCH_2CH=CHMe$, 85083-09-6; *trans*-$(EtO)_2P(=S)OCH_2CH=CHPh$, 85083-10-9; $(EtO)_2P(=S)OCH_2CH=Me_2$, 85083-11-0; $(EtO)_2P(=S)OCH_2CH=CHCH=CHMe$, 85083-12-1; $Pd(Ph_3P)_4$, 14221-01-3; *S*-(−)-myrtenyl diethyl phosphorothiolate, 85083-03-0; *S*-*l*-perillyl diethyl phosphorothiolate, 85083-04-1; *S*-*dl*-patchenyl diethyl phosphorothiolate, 85083-05-2; *S*-geranyl diethyl phosphorothiolate, 85083-06-3; *S*-*trans*-crotyl ethyl phenylphosphonothiolate, 85115-22-6; *O*-(−)-myrtenyl diethyl phosphorothiolate, 85083-13-2; *O*-*l*-perillyl diethyl phosphorothiolate, 85082-98-0; *O*-*dl*-patchenyl diethyl phosphorothiolate, 85083-14-3; *O*-geranyl diethyl phosphorothiolate, 85083-15-4; diglyme, 111-96-6.

3,5-Disubstituted Isoxazoles as Synthons for (±)-Pyrenophorin and (±)-Vermiculine Synthesis

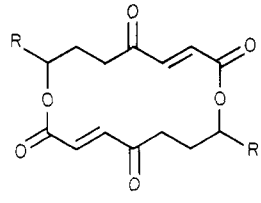
Pier Giovanni Baraldi,† Achille Barco,‡ Simonetta Benetti,‡ Fabio Moroder,† Gian Piero Pollini,*† and Daniele Simoni†

Istituto di Chimica Farmaceutica e Tossicologica and Istituto Chimico, Laboratorio di Chimica Organica, Università di Ferrara, Ferrara, Italy

Received August 3, 1982

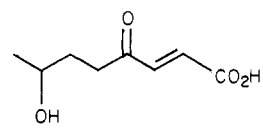
A new approach to suitably protected forms **21**, **29**, and **30** of the monomeric units **3** and **4**, which correspond to the dimeric macrolide antibiotics (±)-pyrenophorin (**1**) and (±)-vermiculine (**2**), involved ethyl 3-(3-butenyl)-5-isoxazolecarboxylate (**6**) as common starting material. The partial structure composed of an α,β-unsaturated acid with an oxygen function at the γ-position, featured in both the natural compounds, was efficiently created by reductive fission of the N–O bond of the isoxazole nucleus bearing a 5-carboxylate, which contains it in a latent form, followed by suitable operations. The terminal double bond of **6** allowed us to introduce the missing functions, namely, a hydroxyl group for **3** and a β-hydroxy ketone moiety for **4**. A Markovnikov hydration to give **8** and regiospecific cycloaddition of acetonitrile oxide followed by reductive opening of the formed isoxazoline **22** secured the appropriate functional groups for **3** and **4**, respectively.

A great deal of effort has been devoted toward the synthesis of pyrenophorin (**1**), a macrocyclic bis lactone

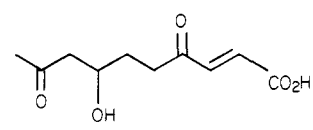


1, R = Me
2, R = CH_2COMe

antibiotic produced by the plant pathogenic fungus *Pyrenophora avenae*, and vermiculine (**2**), a structurally related antibiotic isolated from *Penicillum vermiculatum* Dangeard.[1] Both compounds are characterized by a 16-membered ring derived by head to tail lactonization of two identical C-8 and C-10 hydroxy acid subunits, **3** and **4**,



3



4

respectively. The preparation of these progenitors in a suitable protected form was the initial goal of most of the synthetic approaches to the targets **1** and **2**, which were

† Istituto di Chimica Farmaceutica e Tossicologica.
‡ Istituto Chimico.

(1) For a comprehensive review of previous synthetic studies, see: Mali, S. R.; Pohmakotr, M.; Weidmann, B.; Seebach, D. *Justus Liebigs Ann. Chem.* **1981**, 2272–2284.

0022-3263/83/1948-1297$01.50/0