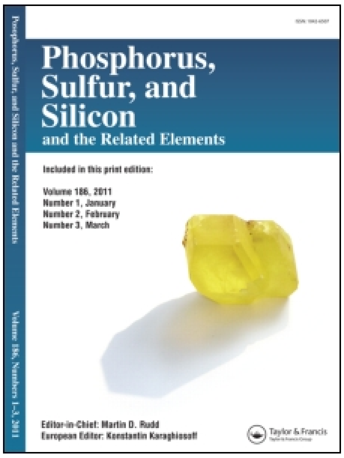

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STUDIES ON THE WITTIG REACTION (VIII).† STEREOSELECTIVITY OF DIPHENYL ALLYLIC PHOSPHONIUM YLIDS IN WITTIG REACTION

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Ylids generated from diphenyl allylic phosphonium salts reacted with aliphatic aldehydes containing a terminal oxygen functionized group in the absence of lithium salt to give E,E-conjugated dienes. The stereoselectivity depends mainly on the base used, the allylic part of phosphonium salts also shows some effect on stereochemistry. Eight conjugated dienic insect sex pheromones and related analogues with different E-selectivities were obtained.

INTRODUCTION

It is known to every organic chemist that in no field have stereoselective Wittig reaction achieved importance as rapidly as in the area of natural product synthesis.[1] But unfortunately, it is of limited use to the creation of E-double bond for the synthesis of some aliphatic insect sex pheromones. The reason is that most insect sex pheromones are aliphatic alcohols, aldehydes and acetates consisting 10- to 18-membered straight carbon chains with mono- and di-double bonds and the position of electronwithdrawing groups i.e. —OH, —CHO, —OAC, are far away from the double bonds which may be formed via Wittig reaction. Moreover, the stereochemistry of Wittig reaction which has mostly been concerned with triphenyl phosphonium ylids stated that the stereoselectivity of semistable ylids is frequently poor with comparable yields of both Z and E olefin, thus it is of little stereoselective synthetic utility.

However, as we have reported previously,[2] a simple change in phosphorous substituents from $Ph_3P{=}CHR$ to $Ph_2P(R'CH_2){=}CHR$ (R'=alkenyl or H, R=Alkenyl) greatly increased the proportion of E-olefin formed from semistable ylids and aliphatic aldehydes. Stimulated by this interesting results, we tried to find out a new route to the synthesis of E,E-dienic insect pheromones. We noticed that the E-selectivity depends mainly on the base used and allylic groups of phosphonium salts also play some role.

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RESULTS AND DISCUSSION

The key reaction is the Wittig olefination of diphenyl allylic phosphonium salts and ω-oxygen functionized aliphatic aldehydes.

$$\mathrm{Ph_2\overset{+}{P}(CH_3)CH_2CH{=}CHRI^- + OHC(CH_2)_{n-1}Y \rightarrow}$$
$$\mathrm{RCH{=}CHCH{=}CH(CH_2)_{n-1}Y + Ph_2P(CH_3){=}0} \quad (1)$$

$\mathrm{R = Me, Et, Bu}$
$n = 5, 6, 8, 9, 10$
$\mathrm{Y = OTHP, OAC}$

Diphenyl allylic phosphonium salts were prepared from allylic halides which were obtained by an improved Knoevenagel Doebner condensation[3] followed by esterification, reduction and bromination. After the treatment with lithium diphenylphosphide, we got phosphonium salt with E-isomer almost exclusively.

$$\mathrm{CH_2(COOH)_2 \xrightarrow{a} RCH{=}CHCOOH \xrightarrow{b} RCH{=}CHCOOMe}$$
$$\mathrm{\xrightarrow{c} RCH{=}CHCH_2OH \xrightarrow{d} RCH{=}CHCH_2Br \xrightarrow{e} Ph_2\overset{+}{P}(CH_3)CH_2CH{=}CHRI^-} \quad (2)$$

$\mathrm{a = RCHO(R = Et, Bu)}$; $\mathrm{b = MeOH, H}$; $\mathrm{c = AlCl_3, LiAlH_4}$;
$\mathrm{d = PBr_3, C_5H_5N}$: $\mathrm{e = Ph_2PCl, Li, CH_3I}$

Oxygen functionized aldehydes were derived from corresponding diols. It may be obtained either by the reaction of diols and acetic acid in suitable solvent or by treating with dihydropyran in acidic medium and followed by oxidation.

$$\begin{tikzcd}
& \mathrm{HO(CH_2)_nOAC} \arrow[r] & \mathrm{OHC(CH_2)_{n-1}OAC} \\
\mathrm{HO(CH_2)_nOH} \arrow[ur, "f"] \arrow[dr, "g"'] & & \\
& \mathrm{HO(CH_2)_nOTHP} \arrow[r, "h"] & \mathrm{OHC(CH_2)_{n-1}OTHP}
\end{tikzcd} \quad (3)$$

$f = \mathrm{HOAc}$; $g = $ dihydropyran; $h = \mathrm{PCC}$

Experimental results were listed in Table I.

For **2**, both hydrolysis and acetylation were needed to get the final product, pheromone. For **1** and **7**, only hydrolysis was needed. Data of ^{1}HNMR of related compounds were shown in Table IV. Table II and III summarized some data which have been reported before.[4,5]

Examining these data, we may conclude that in Wittig reaction, diphenyl allylic ylids are much more stereoselective than that of corresponding triphenyl ones. The E/Z ratio either in Table II or in Table III range from 1.5:1 ~ 1:1, but E/Z ratio in Table I are much larger with very few exceptions. Secondly, in contrast to triphenyl allylic ylids, stereoselectivity of diphenyl allylic ylids is affected remarkably by the absence or presence of lithium salt. For instance, E-selectivity of **7** and **8** are rather poor due to the base, butyl lithium. Thirdly, the smaller the allylic group is, the better E-selectivity it will be. As we have seen, the tendency of increasing E/Z ratio from butyl to methyl is quite clear.

TABLE I

E/Z ratios of dienes in reaction (1)

No.	R	Y	*n*	Reaction condition	Yield%	E:Z	Name of insect
1	Me	CH_2OTHP	6	*t*-BuOK, −18°C	76	98:2	Laspeyresia pomonella
2	Me	CH_2OTHP	8	*t*-BuOK, −18°C	75	90:10	Amorbia cuneana
3	Me	CH_2OAC	7	*t*-BuOK, −18°C	80	84:16	Coptoterme formosanus†
4	Et	CH_2OAC	8	*t*-BuOK, −18°C	79	86:14	Spodoptera litura†
5	Et	CH_2OAC	7	*t*-BuOK, −5°C	80	78.2:21.8	Epiphyas postvittana
6	Bu	CH_2OAC	8	*t*-BuOK, −18°C	75	78.6:21.4	Endromis versicolora†
7	Et	CH_2OTHP	4	BuLi, −15°C	61	70:30	Phthorimaea operculella†
8	Bu	CH_2OAC	7	BuLi, −19°C	68	58.7:41.3	Silk worm†

Notes: E/Z ratios were obtained by GC analysis (HP 5880-A, 50 m, SE-54) and checked by ^{13}CNMR.

† Analogue.

TABLE II

Z/E ratios of dienes in the reaction of

$$Ph_3\overset{+}{P}CH_2CH{=}CHEtBr^- + OHC(CH_2)_8OAC \rightarrow EtCH{=}CHCH{=}CH(CH_2)_8OAC + Ph_3PO$$

Reaction conditions	Z:E
t-BuOK/C_6H_6	40:60
glyme/*n*-BuLi	50:50
$NaCH_2SOMe$/DMSO	60:40

TABLE III

E/Z ratios of dienes in the reaction of

$$Ph_3\overset{+}{P}CH_2CH{=}CHMeBr^- + OHC(CH_2)_7OTHP \rightarrow MeCH{=}CHCH{=}CH(CH_2)_7OTHP + Ph_3PO$$

Reaction conditions	E:Z
$NaNH_2/NH_3$(liq.)	54:28
n-BuLi/Et_2O	50:30
t-BuOK/DMF	41:40
Schlosser-metallation	44:36

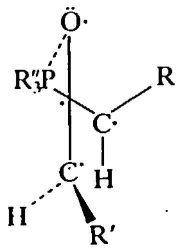
The reason for the different selectivities may be understood by taking a closer look at the mechanism of the Wittig reaction. However, there is at present no concensus regarding the detail mechanism of this reaction. It can only be recognized under certain condition for specific ylids and carbonyl compounds. For Wittig reactions occurring under salt free conditions, a couple of different mechanisms have been proposed.[6–10] In spite of the arguments of these interpretations, the existence of oxaphosphetane is generally accepted.

TABLE IV

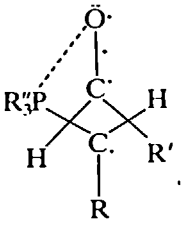
^{1}HNMR of dienes in reaction (1)

No.	Compounds	^{1}HNMR, $CDCl_3$
1	$CH_3(CH=CH)_2(CH_2)_9OH$	1.33 (m, 10H, $(CH_2)_5$), 1.55 (s, 1H, OH), 1.74 (d, 3H, CH_3), 2.05 (m, 2H, $=CCH_2$), 3.62 (t, 2H, CH_2O), 5.6 $\sim$ 6.4 (m, 4H, $(CH=CH)_2$)
2	$CH_3(CH=CH)_2(CH_2)_9OAC$	1.1 $\sim$ 1.68 (m, 14H, $(CH_2)_7$), 1.75 (d, 3H, $CH_3C=C$, 2.05 (s, 3H, $CH_3C=O$), 2.15 (m, 2H, $CH_2C=C$), 4.08 (t, 2H, CH_2O), 5.4 (6.3 (m, 4H, $(CH=CH)_2$)
3	$CH_3(CH=CH)_2(CH_2)_8OAC$	1.1 $\sim$ 1.65 (m, 12H, $(CH_2)_6$), 1.75 (d, 3H, $CH_3C=C$), 2.05 (s, 3H, $CH_3C=O$), 2.15 (m, 2H, $CH_2CH=CH$), 4.1 (t, 2H, CH_2O), 5.4 $\sim$ 6.3 (m, 4H, $(CH=CH)_2$
4	$C_2H_5(CH=CH)_2(CH_2)_9OAC$	0.9 $\sim$ 1.7 (m, 17H, $(CH_2)_7$, CH_3), 1.95 (s, 3H, $CH_3C=O$), 2.1 (m, 4H, $CH_2(C=C)CH_2$) 4.0 (*t*, 2H, CH_2O), 5.2 6.2 (m, 4H, $(CH=CH)_2$)
5	$C_2H_5(CH=CH)_2(CH_2)_8OAC$	0.9 $\sim$ 1.7 (m, 15H, $(CH_2)_6$, CH_3), 2.1 2.5 (m, 4H, $CH_2(C=C)_2CH_2$, 1.95 (s, 3H, $CH_3C=O$), 4.0 (*t*, 2H, CH_2O), 5.2 $\sim$ 6.2 (m, 4H, $(CH=CH)_2$)
6	$C_4H_9(CH=CH)_2(CH_2)_9OAC$	0.85 $\sim$ 1.7 (m, 21H, $(CH_2)_7$, C_3H_7), 2.0 (s, 3H, $CH_2C=O$), 2.1 (m, 4H, $CH_2(CH=CH)_2$ CH_2, 4.1 (*t*, 2H, CH_2O), 5.2 $\sim$ 6.4 (m, 4H, $(CH=CH)_2$)
7	$C_2H_5(CH=CH)_2(CH_2)_8OH$	0.9 $\sim$ Z1.7 '(M, 9H, $(CH_2)_3$, CH_3), 2.0 $\sim$ 2.3 (m, 4H, $CH_2(C=C)_2CH_2$), 2.7 (s, 1H, OH)
8	$C_4H_9(CH=CH)_2(CH_2)_8OAC$	0.85 $\sim$ 1.7 (m, 19H, $(CH_2)_6$, C_3H_7), 2.0 (s, 3H, $CH_3C=O$), 2.1 (m, 4H, CH_2 $(CH=CH)_2$) 4.1 (*t*, 2H, CH_2O), 5.2 $\sim$ 6.4 (m, 4H, $(CH=CH)_2$)

What we are now interested in is the spin paired diradical mechanism[10,11] which is consistent with most experimental data, including the data we present here, and theoretical treatment.[12,13] It stated that under salt free condition, a spin paired diradical formation preceeds oxaphosphetane formation.



1.



2.

The crisscrossed approach[7] of an aldehyde to an ylide gives two spin paired diradicals 1 and 2, of which 1 is the predominant initial unstable intermediate. If R is a simple alkyl group, the bond reorganization and ring closure would be favoured to the cis-oxaphosphetane. If R is an alkenyl group, as in the case we described, a well stabilized allylic radicaloid center would be long enough to permit rotation about either or both P—C or O—C bonds during bond reorganization and ring closure, therefore a thermodynamically stable oxaphosphetane resulted predominately. Compared with corresponding triphenyl phosphonium ylides, the smaller steric hindrance and also its electrondonating property of the methyl group (i.e. one of the phosphorus ligands in diphenyl phosphonium ylids) would benefit the stabilization and cycloaddition. The bulkier butyl group appeared in allylic part seems to be an unfavorable factor to the formation of a trans oxaphosphetane. Nevertheless, more experimental observations are needed to support this new mechanism.

From the practical point of view, there is no general method for the synthesis of E,E-dienic insect pheromones. Type of E,Z-; Z,E- and Z,Z- were described in Alexakis's report,[14] but E,E-type was not presented. Thus, this route may be served as a general methodology for this purpose.

EXPERIMENTAL

^{1}HNMR and ^{13}CNMR were recorded on a Varian XL-200MHz spectrometer. IR were measured as liquid film using Perkin-Elmer-983 spectrometer. All solvents and materials were reagent grade and were purified as required.

2-Pentenic acid, **A.** To a mixture of pyridine (20.5 g, 0.26 mol) and malonic acid (20.8 g, 0.2 mol) was added propylaldehyde (15.08 g, 0.26 mol). After refluxing for 3 hrs., 50% H_2So_4 was added. The organic layer was separated and dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield 18.6 g (93%) of **A**. ^{1}HNMR ($CDCl_3$): 12.5 (s, 1H, COOH), 2.2 (m, 1H, =CHEt), 5.9 (d, 1H, =CH), 2.15 (m, 2H, CH_2), 1.1 (t, 3H, CH_3). ^{13}CNMR ($CDCl_3$): (12.2, 25.5 120.1, 153.7, 172.7). IR: 3400 2960 cm^{-1}, 1710 cm^{-1}, 1675 cm^{-1}, 985 cm^{-1}.

Methyl 2-pentenoate, **B.** A mixture of **A** (38 g, 0.38 mol), methanol (150 ml) and sulfuric acid (7 ml) was refluxed for 12 hrs. After removing partial methanol, the mixture was treated with sodium bicarbonate. **B** was obtained under reduced pressure. ^{1}HNMR: 0.85 (t, 3H, CH_3), 2.6 (m, 2H, CH_2), 3.5 (s, 3H, OCH_3), 5.6 (m, 1H, EtCH=), 6.3 (m, 1H, CH). ^{13}CNMR: (12.0, 25.0, 51.0, 120.1, 151.0, 167.2). IR: 2980, 1730, 1660, 1164, 985.

2-Pentenol, **C.** To a cooled suspension of $LiAlH_4$ (5.68 g, 0.15 mol) in ether, was added $AlCl_3$ (6.67 g, 0.5 mol) ether solution (200 ml) and stirred for 30 min. at room temperature. An ether solution of **B** (3.42 g, 0.03 mol) was gradually added and then stirred for 1 hr. After workup, the crude product was distilled under reduced pressure to give **C** 2.3 g (90%). ^{1}HNMR: 0.9 (t, 3H, CH_3), 1.9 (m, 2H, CH_2), 3.45 (s, 1H, OH), 3.95 (d, 2H, CH_2), 5.55 (m, 2H, CH=CH) ^{13}CNMR: (13.1, 25.0, 63.2, 128.2, 134.4). IR (cm^{-1}): 3300, 2850, 1665, 1020, 985.

2-Pentenyl bromide, **D.** A petroleum ether solution of PBr_3 (46 g, 0.17 mol) containing 2 drops of pyridine was added slowly to a solution of **C** (18.92 g, 0.22 mol) in an ice bath and stirred for 2 hrs. After treating with petroleum ether, $NaHCO_3$, saline and dried over anhydrous sodium sulfate, the crude product was distilled under diminished pressure to yield 17.7 g (70%) of **D**.

9-Hydroxyl nonanyl acetate, **E.** In a liquid–liquid extractor,[8] nonanediol (4g, 0.025 mol), water 360 ml, acetic acid 140 ml and a few drops of sulfuric acid were mixed in bottle A, in bottle B, 100 ml of both hexane and cyclohexane were added. Bottle B was heated to reflux for 36 hrs. The organic layer was dried over anhydrous sodium sulfate. After workup, the product **E** was isolated by column chromatography in yield of 90% (4.54 g). ^{1}HNMR: 1.2 ~ 1.8 (m, 14H, $(CH_2)_7$), 2.0 (s, 3H, CH_3), 2.3 (s, 1H, OH), 3.6 (t, 2H, CH_2O), 4.0 (t, 2H, CH_2OH).

9-Oxo-nonanyl acetate, **F.** A dichloromethane solution of **E** (8.6 g, 0.0426 mol) was added to a mixture of PCC (0.063 mol, 12.7 g), NaOAC (1.2 g, 0.014 mol) and dichloromethane in 30 min. Stirred for 2 hrs and then extracted with CH_2Cl_2. The organic layer was run through a silica gel column. After removing the solvent, product **F** was purified by chromatography in yield of 94% (8 g). ^{1}HNMR: 1.2 ~ 1.8 (m, 14H, $(CH_2)_7$), 2.0 (s, 3H, CH_3), 2.4 (m, 2H, $OCCH_2$), 4.0 (t, 2H, CH_2O), 9.78 (s, 1H, CHO).

10,12-Tetradecadien-1-yl acetate, **G**. A mixture of methyl butenyl-2 diphenyl phosphonium iodide[16] (12.6 g, 0.032 mol) and *t*-BuOK (90 ml THF solution, 0.03 mol) was stirred at −20°C for 2 hrs. **F** (4.48 g, 0.022 mol) was added gradually. The mixture was then poured into water and extracted with petroleum ether, ether and benzene sequently. After removing the solvent, **G** was purified by TLC (hexane/ether, 1:1) in yield of 75% (4.23 g). Related data see Table I and IV.

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