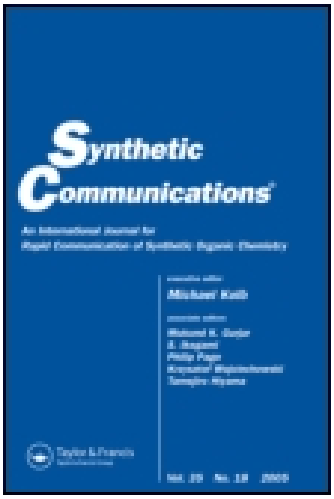

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SYNTHESIS OF A NEW C-15 PHOSPHORUS YLIDE USED FOR THE PREPARATION OF SOME β-END-GROUP RETINOID DERIVATIVES

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A synthesis of a new C-15 phosphorus ylide from a C-14 enaminone is reported. This reagent, which undergoes selective 1,2- or 1,4-additions with saturated and unsaturated aldehydes, may find some synthetic use for the preparation of β-end-group retinoid derivatives.

Keywords: Enaminones; phosphorus ylide; retinoids

Phosphorus ylides react with aldehydes or ketones to give alkenes, wherein *Z* olefins predominate in aliphatic systems and *E* olefins predominate in conjugated systems[1–3] (Scheme 1).

This reaction, discovered by Wittig, was used in the BASF processes for vitamin A, β-carotene, and other carotenoid productions.[4–6] (Scheme 2 illustrates the last steps of vitamin A synthesis.)

We have recently published some research in the retinoid field, using a new enaminone **1**, derived from β-ionone.[7] This compound could be obtained directly, in nearly quantitative yield (Scheme 3), by condensation with *N,N*-dimethyl formamide dimethylacetal (DMF-DMA).

Benary's synthesis[8] (reaction of organometallic derivatives on enaminoketones) yielded β-substituted α,β-unsaturated ketones (Scheme 4). These enaminoketones were further named enaminones by Greenhill.[9]

Enaminones have been used previously for the synthesis of natural products[10] and heterocyclic derivatives.[11]

Reaction of the Wittig reagent, methylene triphenylphosphorane (generated in situ by reaction of *t*BuOK on methyl triphenylphosphonium chloride or bromide) with **1** led to a new C-15 phosphorus ylide **2**, which, taking into consideration of its complex ^{1}H NMR spectrum, could be represented by several mesomeric forms (Scheme 5). This ylide could be stored for several months at −20 °C, which makes it an interesting intermediate in the retinoid field.

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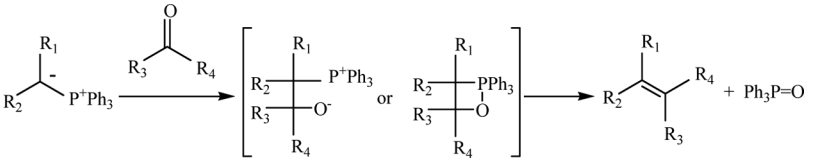
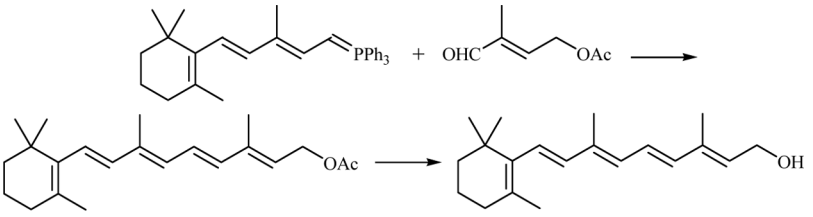
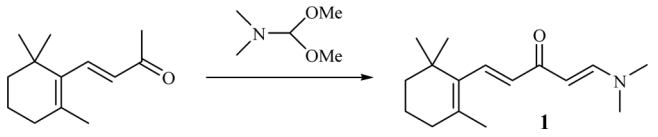


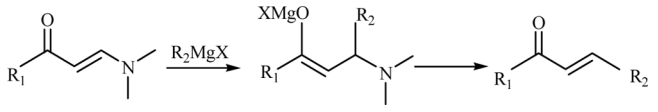
Scheme 1. Usual Wittig reaction.



Scheme 2. Last steps of BASF synthesis of vitamin A.

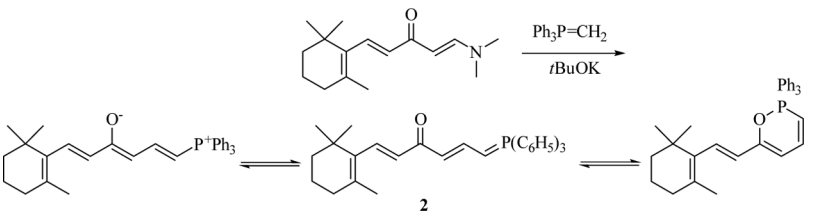


Scheme 3. β-Ionone, DMF-DMA (1.5 eq), Dean–Stark, 80 °C, 6 h, and reflux, 12 h.



Scheme 4. Benary's synthesis of β-substituted α,β-unsaturated ketones.

The condensation of **2** with saturated aliphatic aldehydes, such as acetaldehyde, propionaldehyde, or butyraldehyde, led to alkenes **3**–**5**, and their formation could be explained by the mechanism show in Scheme 6.



Scheme 5. Methylenetriphenylphosphonium bromide (2 eq.) and tBuOK (2 eq.), ether, reflux, 30 min, then enaminone **1**, ether, reflux, 45 min.

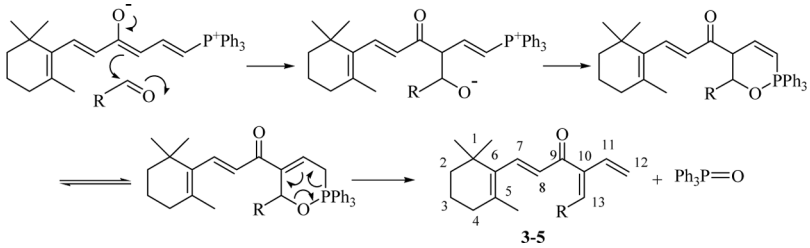
A single isomer was obtained for compounds **3** to **5** (double bond $C_{10}=C_{13}$) that suggested the mechanism reported in Scheme 6.

It was previously shown that ketones (in particular cases) reacted with phosphorus ylides, according to a Michael reaction,[12] and this nonclassical Wittig reaction has been previously reported by Corey et al.[13] (Scheme 7).

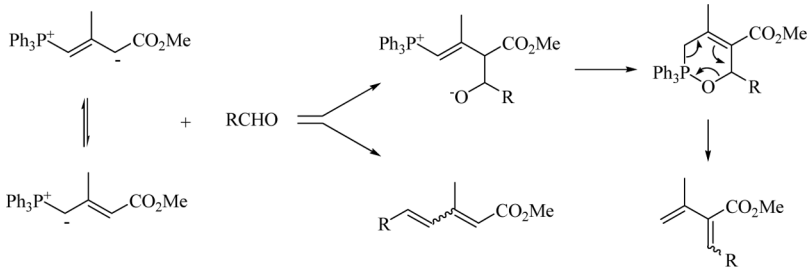
Surprisingly, the condensation with α,β-unsaturated aldehydes, such as acrolein, 2-butenal, and 2-methylacrolein, led to cyclohexadiene derivatives **6**–**8**.

This formation could be explained by the mechanism pathway described in Scheme 8.

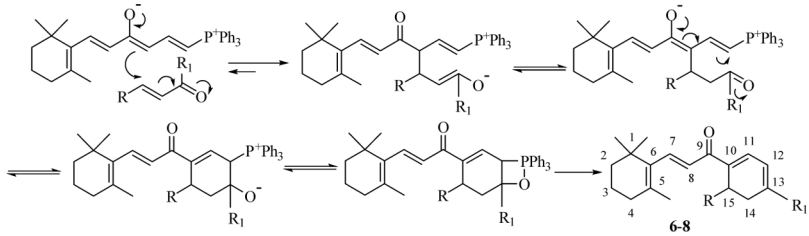
When the β-carbon of conjugated aldehyde was dialkyl-substituted, such as 3-methyl-2-butenal, citral, or was inaccessible, such as benzaldehyde, the reaction proceeded according to the first way (Scheme 6, products **3**–**5**) and led to **9**–**11**



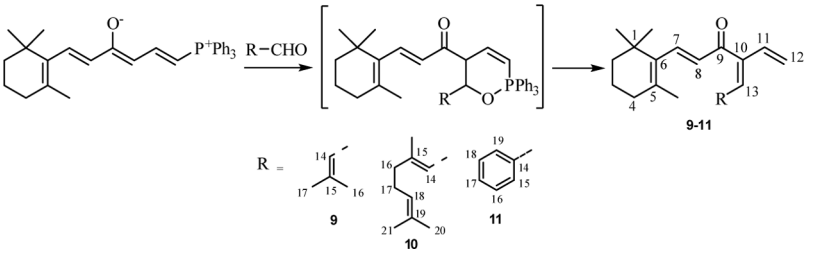
Scheme 6. (**3**) R=Me; (**4**) R=Et; (**5**) R=Pr. Ylure **2**, aldehyde (4 eq. for volatile or 2 eq. for others), ether, reflux, 1 h.



Scheme 7.



Scheme 8. (**6**) $R_1=R_2=H$; (**7**) $R_1=H$, $R_2=Me$; (**8**) $R_1=Me$, $R_2=H$.



Scheme 9.

(Scheme 9). This fact could strength the idea that the two suggested mechanisms could be concurrent.

In conclusion, this new phosphorane, which possesses good reactivity, was easily obtained in two steps from β-ionone. New ethylenic or cyclohexadienic retinoids could be easily synthesized using this useful synthon.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recordeded at 100 MHz on a Bruker Avance DPX-400 instrument with $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) at room temperature (23 °C). Infrared (IR) spectra (KBr) were run on a Bruker IF 55 spectrometer and absorbances are reported in centimeters^{-1}.

Compound 2: A mixture of 14.2 g (40 mmol) of methylenetriphenylphosphonium bromide in 50 mL of dry ether and 4.5 g (40 mmol) of tBuOK was refluxed for 30 min, and 4.95 g (20 mmol) of enaminone **1** in 30 mL of ether was added. The reflux was prolonged for 45 min. The crude mixture was cooled, and the KBr was filtered off. The ether was removed under reduced pressure, and the phosphorus ylide **2** was washed with ethyl acetate, filtered off quickly, and stored at −25 °C (7.60 g, 81%). ^{1}H and ^{13}C NMR spectra showed complex data, because of the presence of mesomeric forms.

General Procedure for Synthesis of Compounds 3 to 11

Ylure **2** (500 mg, 1.05 mmol) in 15 mL of ether was added to 4 eq. of aldehyde for volatile aldehydes (i.e., those with 4 carbons or less) or 2 eq. for the others. After 1 h at reflux, the solvent and residual volatile aldehydes were removed under reduced pressure, and the crude products were purified by chromatography (SiO_2, CH_2Cl_2); yellow to orange oils.

Selected Data

Compound 3. R=Me, reaction with acetaldehyde, yield 40%. IR (film): $\nu_{C=O}$: 1655. ^{1}H NMR: 1.10 (sl, 6H, 1a-CH_3, 1b-CH_3); 1.50 (m, 2H, 2-CH_2); 1.60 (m, 2H,

3-CH_2); 1.80 (s, 3H, 5a-CH_3); 1.90 (d, 3H, $J = 7.2$, 14-CH_3); 2.09 (m, 2H, 4-CH_2); 5.42 (m, 2H, 12-CH_2); 6.33 (m, 1H, 13-CH); 6.35 (q, 1H, $J = 7.2$, 11-CH); 6.50 (d, 1H, $J = 16.0$, 8-CH); 6.65 (dd, 1H, $J = 11.5$, $J = 17.7$, 11-CH); 7.40, (d, 1H, $J = 16.0$, 7-CH). ^{13}C NMR: Cq: 34.0 (1); 136.0; 136.4; 140.9; 194.1 (CO). CH: 128.6; 129.4; 134.1; 143.9. CH_2: 18.8; 33.5; 39.7; 119.1. CH_3: 14.1; 21.6; 28.65 (1a, 1b). Anal. calc. for $C_{17}H_{24}O$: C, 83.55; H, 9.90; O, 6.55. Found: C, 83.32; H, 9.99; O, 6.69.

Compound 4. R=Et, reaction with propionaldehyde, 85%. IR (film): $\nu_{C=O}$ 1660. ^{1}H NMR: 1.08 (s, 6H, 1a-CH_3, 1b-CH_3); 1.10 (t, 3H, $J = 7.5$, 15-CH_3); 1.49 (m, 2H, 2-CH_2); 1.63 (m, 2H, 3-CH_2); 1.80 (s, 3H, 5a-CH_3); 2.09 (m, 2H; 4-CH_2); 2.35 (m, 2H, 14-CH_2); 5.40 (m, 2H, 12-CH_2); 6.20 (t, 1H, $J = 8.0$, 13-CH); 6.40 (d, 1H; $J = 15.3$, 8-CH); 6.60 (dd; 1H, $J = 11.2$, $J = 17.7$, 11-CH); 7.40 (d, 1H; $J = 15.3$, 7-CH). ^{13}C NMR: Cq: 34.1 (1); 136.2; 136.4; 139.3; 194.6 (CO). CH: 129.0; 129.7; 140.9; 144.2. CH_2: 18.8; 21.6; 33.6; 39.7; 119.1. CH_3: 13.7; 21.7; 28.65; 28.6 (1a, 1b). Anal. calc. for $C_{18}H_{26}O$: C, 83.67; H, 10.14; O, 6.19. Found: C, 83.51; H, 10.23; O, 6.26.

Compound 5. R=C_3H_7, reaction with butyraldehyde, 70%. IR (film): $\nu_{C=O}$ 1660. ^{1}H NMR: 0.91 (t, $J = 7.4$, 16-CH_3); 1.08 (s, 6H, 1a-CH_3, 1b-CH_3); 1.34 (m, 2H, 15-CH_2); 1.50 (m, 2H, 2-CH_2); 1.64 (m, 2H, 3-CH_2); 1.79 (s, 3H, 5-CH_3); 2.08 (m, 2H, 4-CH_2); 2.32 (q, 2H, $J = 7.4$, 14-CH_2); 5.39 (dd, 2H, $J = 16.0$, $J = 11.3$, 12-CH_2); 6.20 (t, 1H, $J = 7.4$, 13-CH); 6.43 (d, 1H, $J = 16.0$, 8-CH); 6.61 (dd, 1H, $J = 16.0$, $J = 11.3$, 11-CH); 7.37 (d, 1H, $J = 16.0$, 7-CH). ^{13}C NMR: Cq: 33.8 (1); 134.6; 136.5; 137.0; 194.5 (CO). CH: 129.1; 127.7; 138.7; 144.0. CH_2: 18.8; 21.7; 31.3; 33.6; 39.7; 119.1. CH_3: 13.9; 22.3; 28.7 (1a, 1b). Anal. calc. for $C_{19}H_{28}O$: C, 83.77; H, 10.36; O, 5.87. Found: C, 83.55; H, 10.44; O, 6.01.

Compound 6. Reaction with acrolein, 85%. IR (film) $\nu_{C=O}$ 1646. ^{1}H NMR: 1.08 (s, 6H, 1a-CH_3, 1b-CH_3); 1.50 (m, 2H, 2-CH_2); 1.63 (m, 2H, 3-CH_2); 1.80 (s, 3H, 5a-CH_3); 2.08 (m, 2H, 4-CH_2); 2.30 (m, 2H, 14-CH_2); 2.53 (m, 1H, $J = 10$, 15-CH_2); 6.10 (m, 1H, 13-CH); 6.25 (m, 1H, 12-CH); 6.70 (d, 1H, $J = 15.7$, 8-CH); 6.90 (d, 1H, $J = 5.2$, 11-CH); 7.38 (d, 1H, $J = 15.7$, 7-CH). ^{13}C NMR: Cq: 33.8 (1); 134.6; 136.5; 137.0; 189.9 (CO). CH: 124.0; 125.0; 132.5; 134.6; 141.8. CH_2: 18.7; 20.0; 22.7; 33.8; 39.5. CH_3: 21.6; 28.6 (1a, 1b). Anal. calc. for $C_{18}H_{24}O$: C, 84.32; H, 9.44; O, 6.24. Found: C, 84.03; H, 9.60; O, 6.37.

Compound 7. Reaction with 3-methyl-acrolein, 80%. IR (film) $\nu_{C=O}$ 1647. ^{1}H NMR: 0.98 (d, 3H, $J = 7.1$, 15-CH_3); 1.07 (s, 6H, 1a-CH_3, 1b-CH_3); 1.47 (m, 2H, 2-CH_2); 1.61 (m, 2H, 3-CH_2); 1.79 (s, 3H, 5a-CH_3); 2.06 (m, 2H, 4-CH_2); 2.76 (m, 2H, 14-CH_2); 3.02 (m, 1H, 15-CH); 6.10 (m 1H, 12-CH); 6.73 (d, 1H, $J = 15.75$, 8-CH); 6.88 (m, 1H, 11-CH); 7.38 (d, 1H, $J = 15.75$, 7-CH). ^{13}C NMR: Cq: 33.9 (1); 134.7; 165.5; 137.1; 189.8 (CO). CH: 34.0; 123.2; 125.2; 131.5; 132.8. CH_2: 18.9; 30.8; 33.4; 39.7. CH_3: 19.0; 21.6; 28.6 (1a, 1b). Anal. calc. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.26; H, 9.89; O, 5.85.

Compound 8. Reaction with 2-methyl-acrolein, 45%. IR (film) $\nu_{C=O}$ 1648. ^{1}H NMR: 1.0 (s, 6H, 1a-CH_3, 1b-CH_3); 1.0 (t, 3H, $J = 7.1$, 14-CH_3); 1.46 (m, 2H, 3-CH_2); 1.60 (m, 2H, 2-CH_2); 1.77 (s, 3H, 5a-CH_3); 2.04 (m, 2H, 4-CH_2); 2.20 and

2.68 (2 m, 2H, 14-CH_2); 2.47 (m, 1H, 15-CH); 5.44 (m, 1H, 12-CH); 6.69 (d, 1H, $J = 15.75$, 8-CH); 6.90 (m, 1H, 11-CH); 7.39 (d, 1H, $J = 15.75$, 7-CH). ^{13}C NMR: CO: 190.2. CH: 123.0; 125.4; 132.1; 141.1; 141.9. CH_2: 18.9; 28.7; 34.0; 39.6. CH_3: 18.9; 21.7; 28.7 (1a, 1b). Anal. calc. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.27; H, 9.90; O, 5.83.

Compound 9. Reaction with 3-methyl-2-butenal, 41%. IR (film) $\nu_{C=O}$ 1659. ^1H NMR: 1.10 (s, 6H, 1a-CH_3, 1b-CH_3); 1.50 (m, 2H, 2-CH_2); 1.64 (m, 2H; 3-CH_2); 1.72 (s, 3H, 5a-CH_3); 1.91 and 1.94 (2s, 6H, 15a-CH_3, 15b-CH_3); 2.09 (m, 2H, 4-CH_2); 5.46 (m, 2H, 12-CH_2); 6.39 (d, 1H, $J = 11.8$, 14-CH); 6.55 (d, 1H, $J = 15.75$, 8-CH); 6.76 (m, 1H, 11-CH); 7.39 (d, 1H, $J = 15.75$, 7-CH). ^{13}C NMR: CO: 193.4. CH: 121.0; 128.7; 130.1; 132.8; 143.0. CH_2: 18.8; 33.5; 39.7; 119.8. CH_3: 18.8; 21.7; 28.7 (1a, 1b). Anal. calc. for $C_{20}H_{28}O$: C, 84.45; H, 9.92; O, 5.62. Found: C, 84.39; H, 10.00; O, 5.61.

Compound 10. Reaction with citral, 50%. IR (film) $\nu_{C=O}$ 1659. ^1H NMR: 1.10 (s, 6H, 1a-CH_3, 1b-CH_3); 1.50 (m, 2H, 2-CH_2); 1.61 and 1.67 (6H, 19-CH_3); 1.63 (m, 2H, 3-CH_2); 1.65 (m, 2H; 17-CH_2); 1.67 (s, 3H, 5a-CH_3); 1.81 (s, 3H, 15a-CH_3); 2.09 (m, 2H, 4-CH_2); 2.20 (m, 2H, 16-CH_2); 5.10 (m, 1H, 18-CH); 5.47 (m, 2H, 12-CH_2); 6.38 (d, 1H, $J = 11.8$, 14-CH); 6.55 (d, 1H; $J = 15.8$, 8-CH); 6.73 (m, 1H, 11-CH); 7.10 (d, 1H, $J = 11.8$, 13-CH); 7.41 (d, 1H, $J = 15.8$, 7-CH). ^{13}C NMR: CO: 193.4. CH: 120.8; 123.4; 128.7; 130.2; 132.1; 132.9. CH_2: 18.9; 25.7; 33.6; 39.8; 40.8; 119.9. CH_3: 17.4; 17.7; 21.8; 25.0; 28.8 (1a, 1b). Anal. calc. for $C_{25}H_{36}O$: C, 85.17; H, 10.29; O, 4.54. Found: C, 85.01; H, 10.34; O, 4.65.

Compound 11. Reaction with benzaldehyde, 60%. IR (film) $\nu_{C=O}$ 1660. ^1H NMR: 1.11 (s, 6H, 1a-CH_3, 1b-CH_3); 1.51 (m, 2H, 2-CH_2); 1.64 (m, 2H, 3-CH_2); 1.82 (s, 3H, 5a-CH_3); 2.11 (m, 2H, 4-CH_2); 5.52 (m, 2H, 12-CH_2); 6.52 (d, 1H, $J = 16.1$, 8-CH); 6.76 (m, 1H, 11-CH); 7.04 (S, 1H, 13-CH); 7.35–7.45 (m, 5H, C_6H_5); 7.48 (d, 1H, $J = 16.1$, 7-CH). ^{13}C NMR: CO: 195.1. CH: 128.3; 128.6; 129.1; 129.9; 130.9; 144.7. CH_2: 18.8; 34.1; 39.8; 120.7. CH_3: 21.8; 29.6 (1a, 1b). Anal. calc. for $C_{22}H_{26}O$: C, 86.23; H, 8.55; O, 5.22. Found: C, 86.03; H, 8.85; O, 5.12.

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