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THE SYNTHESIS OF POLYENE ISOPRENOIDS BY THE HORNER VARIANT OF THE WITTIG REACTION

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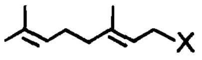
The celebrated Wittig reaction constitutes the most general and flexible approach towards the synthesis of all types of substituted olefins. Furthermore, by judicious choice of reaction conditions, the steric course of the olefination can be controlled to produce Z- or E-disubstituted alkenes $R^1CH{=}CHR^2$. Although conditions are known for the synthesis of polyenes from α-unsaturated aldehydes and α-unsaturated ylides whereby the Z- or E-geometry in these substrates is preserved, the olefinations themselves invariably produce mixtures of Z- and E-isomers about the newly introduced double bond;[1] laborious chromatography is then usually necessary to separate the stereoisomers. The related Wadsworth-Emmons reaction, using phosphonate anions, is more stereoselective leading to largely E-olefination, but the scope of this reaction is limited to those phosphonate anions containing additional stabilizing substituents (e.g. $-CO_2R$, $-CN$) attached to the carbanion centre.

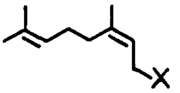
In recent years there has been a renaissance of interest in the potential for phosphine oxide anions (i.e. the Horner variant of the Wittig reaction) in the synthesis of isomeric alkenes. Available evidence suggests that this variant offers convenience and many advantages over the Wittig sequence for the controlled synthesis of isomeric 1,3-dienes, for example, from α-unsaturated phosphine oxide and aldehyde precursor molecules.[2] In connection with studies on the structure and synthesis of stereoisomeric polyene isoprenoids found in Nature, we have explored the utility of this reaction in the synthesis of polyisoprenoid trienes and higher polyenes.

The Z- and E-phosphine oxides (2a; m.p. 93-94°) and (1a; m.p. 113-114°)[3] were first prepared from the corresponding allylic chlorides, following reaction with lithium diphenylphosphide and oxidation of the resulting tertiary phosphines with hydrogen peroxide; they were clearly distinguished by their ^1H and ^{13}C n.m.r. data. Metallation of the individual phosphine oxides at -78°C using n-BuLi, followed by reaction with *Z*- or *E*-citral and warming to 25°, led (∿ 20%) to the corresponding isomeric trienes, showing complete preservation of the *Z*- or *E*-geometry in the starting materials, and with > 98% *E*-olefination. Thus, phosphine oxide (2*a*) and *Z*-citral led to (3) and phosphine oxide (2*a*) and *E*-citral, or phosphine oxide (1*a*) and *Z*-citral led to (4). These results are to be contrasted with those obtained with the corresponding *Z*- and *E*-phosphoranylides (*i.e.* from 2*b* and 1*b*) which give rise to the corresponding *Z*-olefination products (*Z*:*E* *ca* 1:1) concurrently.[1] The isolation of only *E*-olefination products in the Horner reactions was fortuitous, and due entirely to the much slower rates of β-elimination from the *erythro*-β-hydroxyphosphine oxide intermediates produced in the reactions. This feature was substantiated when the *threo* and *erythro* intermediates (*i.e.* 5) were separated from reactions quenched after short periods of time, and the individual intermediates treated in a separate step with NaH in DMF.[4] Thus the *threo*-intermediate from *E*-phosphine oxide (1*a*) and *E*-citral with NaH in DMF led to the all-*E*-triene (6) (70%) within 0.5 hr whereas the corresponding *erythro*-intermediate, under the same conditions and in the same period of time gave only a 15% yield of a mixture of *E*, *Z*, *E*-(7) and all-*E* trienes (85:15), the major product being the *E*-phosphine oxide (1*a*). The reversibility of the first stage in these reactions coupled with the slow rates of β-elimination from the intermediate β-hydroxyphosphine oxides go someway to explaining the low yields (∿ 20%) of trienes in the one-step reaction, and also the accumulation with time of the by-product (8)[5] produced from self-condensation of citral (upwards of 20%). Interestingly, a Horner condensation between the *E*-phosphine oxide (1*a*) and cyclohexanone led in one step to the *E*-diene (9) in 80% yield (cf. ref. 2*a*), and by contrast *E*-citral and ethyldiphenylphosphine oxide led only to a mixture of *erythro*- and *threo*-β-hydroxyphosphine oxide intermediates; in the latter, the corresponding dienes (10) were only obtained by decomposition in a separate step using NaH in DMF.

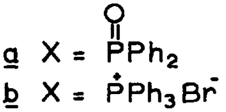
In related investigations, the isomeric phosphine oxides (1*a*) and (2*a*) were used in reactions with the C_5-aldehyde (11)[6] to give the *Z*-2, *E*-4, *E*-6 and *Z*-2, *E*-4, *Z*-6-triene acids (12) and (13) respectively. The yields in these reactions were low (∿ 10%), but once again > 98% *E*-olefination was observed (by ^{13}C and ^{1}H n.m.r.); the corresponding Wittig reactions with (11) lead to upwards of 40% *Z*-olefination, but overall yields are higher (∿ 75%).[7] By contrast, the reaction between (2*a*) (4 mole equiv.) and all-*E*-2,7-dimethylocta-2,4, 6-trien-1,8-dial led to the C_{30}-heptaene (15), λ_{max} 422, 398, 377, 360 (inf.) nm, δ 24.2 (C-5-Me), 32.8 (C-4) p.p.m, in one step, and in 87% yield. Use of 2 mole equivalents of (2*a*) permitted the separation of the intermediate



(1)

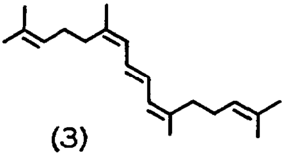


(2)



a X = $\overset{O}{\overset{\|}{P}}Ph_2$

b X = $\overset{+}{P}Ph_3Br^-$



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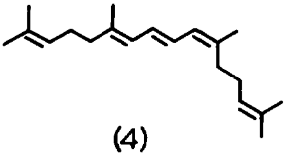

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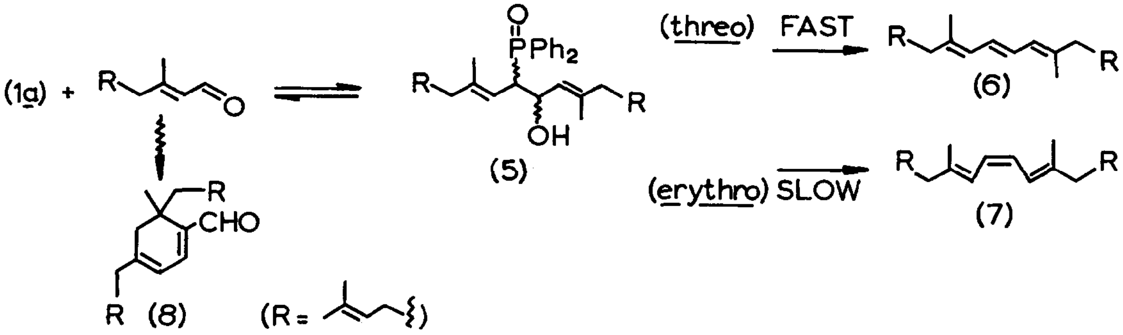

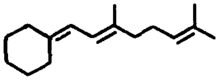

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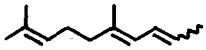

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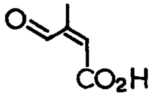
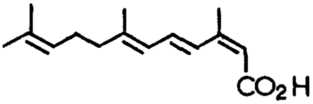


(11)



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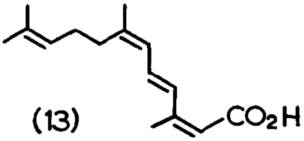
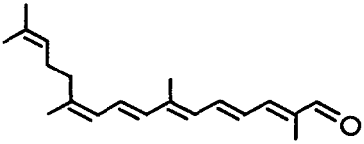


(13)



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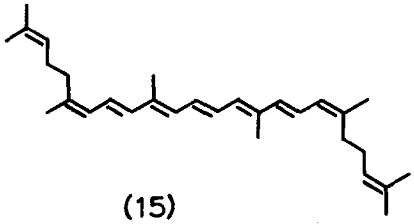

(15)

C_{20}-aldehyde (14), λ_{max} 406, 384, 367, 352 (inf), δ 24.3 (C-5-Me), 32.9 (C-4) p.p.m, and this, in a second condensation with (2a) gave (15); although these olefinations proceeded with complete E-stereoselectivity, the condensation between (14) and (2a) was accompanied by stereomutation about the double bond in (2a) (upwards of 20%). It is interesting that the C_{40}-prenylogue of (15) (i.e. 9, 10, 9', 10'-di-Z-ζ-carotene) has recently been found along with other poly-Z-carotenoids in tangerine tomatoes.[8]

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