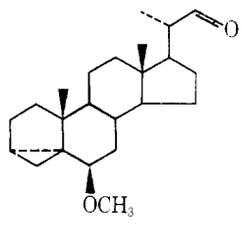
A Stereoselective Wittig Reagent and Its Application to the Synthesis of 25-Hydroxylated Vitamin D Metabolites

Summary: A method for the selective preparation of trans-homoallylic alcohols is described, and its mechanism discussed in terms of an internal Schlosser "trans-selective Wittig" reaction.

Sir: The Wittig reaction is one of the most important in synthetic organic chemistry.[1] We have made use of this condensation reaction in a number of syntheses of 25-hydroxycholesterol. For example, reaction of 3α,5α-cyclo-(20*S*)-formyl-6β-methoxypregnane (**1**) with dibromomethylenetriphenylphosphorane[2] or with dichloromethylenetris(dimethylamino)phosphorane[3] leads to the dihalovinyl compounds **2**.[4] The ylide **3** derived from isoprene condensed with the same aldehyde to give the diene **4**.[5,6] The compounds **2** and **4** were then converted to 25-hydroxycholesterol as described previously.[4,6]



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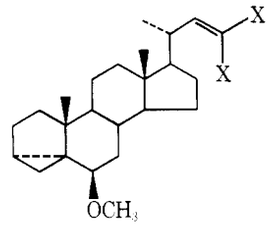

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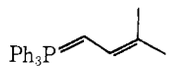

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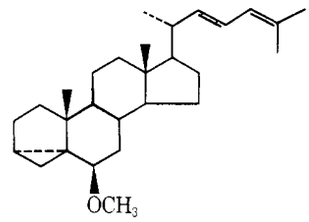

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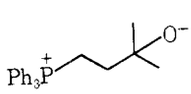
In this communication we wish to report a further preparation of 25-hydroxycholesterol through the agency of a novel stereoselective Wittig reagent.[7] Methylenetriphenylphosphorane, prepared in tetrahydrofuran from methyltriphenylphosphonium bromide and *n*-butyllithium, reacts with isobutylene oxide at 0 °C.[8] The product, which possesses either the betaine structure **5** or more likely the oxaphospholane structure **6**,[9] reacts with a further mole of *n*-butyllithium to yield the ylide **7**.[10]



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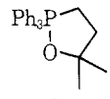

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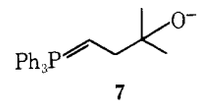

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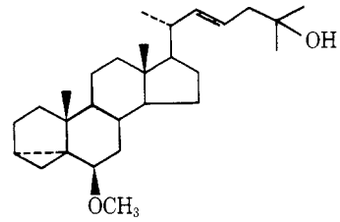
The aldehyde **1** reacts with this ylide to give the Δ^{22}-25-hydroxy product **8**. The manner in which the reaction is performed is important. In the first step of the preparation of the ylide **7** it is necessary to ensure that all of the methyltriphenylphosphonium bromide is converted to the methylene ylide, otherwise during the subsequent addition of *n*-butyllithium some of the methylene ylide will again be formed as a contaminant, giving rise to the methylene compound **9** as a by-product.

Similarly, if insufficient isobutylene oxide is added in the second step, the same methylene by-product will result. If too much isobutylene oxide is used and the excess is not removed, *n*-butyllithium will be consumed by the epoxide in the next stage. Finally, in the second addition of *n*-butyllithium an excess must be avoided lest the aldehyde **1** be consumed, giving rise to the alcohol **10**. In short, if the reaction is not conducted with due regard to the stoichiometry of the reagents, yields are adversely affected. In properly conducted reactions yields of isolated alcohol **8**[11] are in the range 75–86%.



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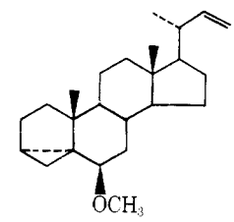

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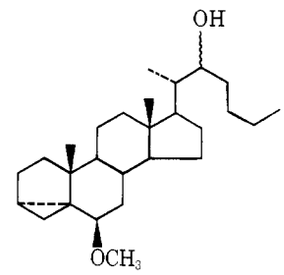

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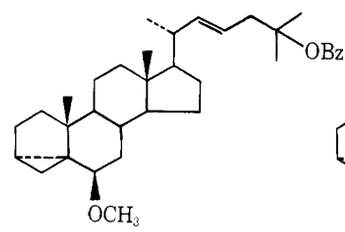
Two stereochemical considerations are germane to the reaction of the aldehyde **1** with the ylide **7**. The first is the retention of chirality at C-20; clearly any epimerization at this center would result in the lowering of yield of the desired product **8** having the correct natural 20*R* stereochemistry. Generally aldehydes are easily epimerized by base so at the outset of this work we were concerned about the presence of a fully developed alkoxide anion in the ylide **7**. Compounds **11**, **12**, and **13** were therefore independently prepared.[12]



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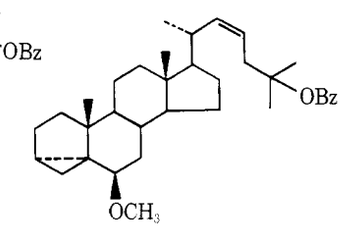

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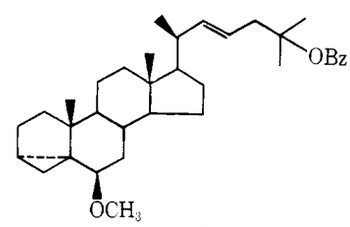

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Comparison of the NMR spectra[13] of these compounds with that of the total crude product mixture (after benzoylation) revealed that no epimerization at C-20 had taken place. The

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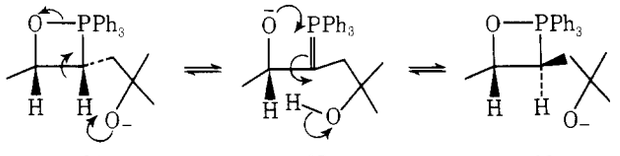
results indicate that C–C bond formation between aldehyde and ylide is faster than deprotonation at C-20, easily rationalized after the event since aldehydes are known to react rapidly even at −70 °C with ylides to give oxaphosphetane intermediates[14] (see below).

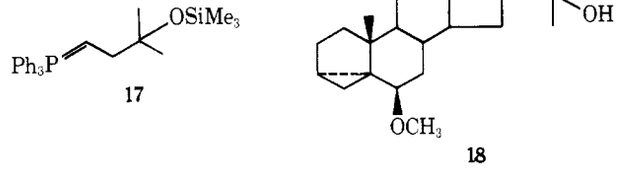
The second important, and possibly more interesting, stereochemical aspect of this reaction is the configuration of the resulting double bond. The NMR spectra of the crude product also revealed a mixture in which the $\Delta^{22}E/\Delta^{22}Z$ ratio was approximately 85:15. The isolated crystalline material is pure $\Delta^{22}E$ compound **8**, a somewhat surprising result since, normally, nonstabilized ylides are cis selective. This has been elegantly rationalized by Vedejs and Snoble[14] in terms of the first step of a Wittig reaction being a $_{\pi}2_s + _{\pi}2_a$ cycloaddition to give an oxaphosphetane. For maximum overlap of the relevant orbitals in such a cyclization, the π bonds must approach one another orthogonally. If this is done in the least hindered orientation, the most hindered oxaphosphetane inevitably results. Thus, the first product of our reaction would be the oxaphosphetane **14**. If this were to collapse to olefin and triphenylphosphine oxide, the $\Delta^{22}Z$ product would of course be the result. An explanation for the predominant production of $\Delta^{22}E$ in our reaction is that there exists an intrinsic Schlosser "trans-selective Wittig" mechanism.[15] Thus, the initially formed *cis*-oxaphosphetane **14**,[16] if prevented from collapsing to olefin, can enter into equilibrium with the ylide **15** through a five-center transition state as depicted. By rep-



14 **15** **16**

rotonation of C-22 from the other side this ylide **15** can then establish equilibrium with the more stable *trans*-oxaphosphetane **16**, which ultimately decomposes to give the $\Delta^{22}E$ product. Based on this postulate the aldehyde **1** and ylide **7** were mixed at low temperature (−35 to −20 °C) and kept at this temperature for a period of time (usually about 1 h) before warming and allowing the oxaphosphetanes to decompose to olefin and triphenylphosphine oxide. This did indeed lead to greater yields of the trans product than had been obtained in earlier experiments conducted in the range of 0–20 °C.

Confirmation of the need for the 25-alkoxide function in the formation of the $\Delta^{22}E$ product and support for this intramolecular mechanism were derived by allowing the ylide **7** to react with 1 mol of trimethylsilyl chloride, yielding the ylide **17**. Condensation with the aldehyde **1** gave an oily mixture of olefins in which the approximate E/Z ratio was dramatically changed to 15:85.[17]



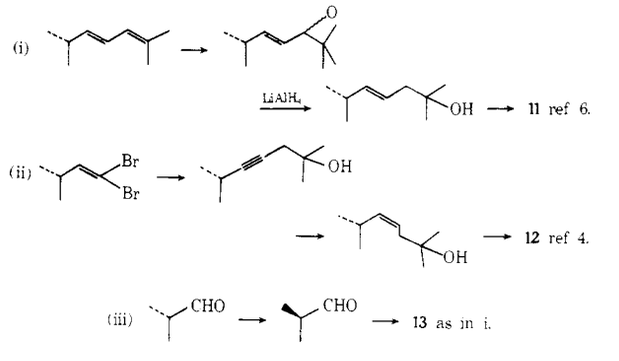
17 **18**

Hydrogenation of the olefin **8** in methylene chloride solution over a 5% platinum on carbon catalyst led essentially quantitatively to the saturated derivative **18**,[4,6,18] which is readily transformed to 25-hydroxycholesterol and thence to the vitamin D metabolites.

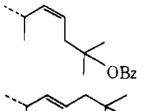
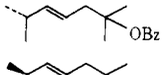
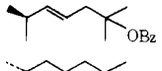
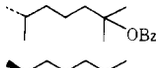
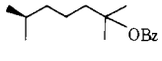
We believe that this type of ylide has possibilities of wider application in organic synthesis where a stereoselective synthesis of trans-homoallylic alcohols is desired.[19]

References and Notes

(1) For a recent review see J. Mathieu and J. Weill-Raynal, "Formation of C–C Bonds", Vol. II, Thieme-Edition Publishing Sciences Group, New York, N.Y., 1975, pp 608–639.
(2) F. Ramirez, N. B. Desai, and N. McKelvie, *J. Am. Chem. Soc.*, **84**, 1745 (1962); E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972).
(3) W. G. Salmond, *Tetrahedron Lett.*, 1239 (1977).
(4) W. G. Salmond, M. C. Sobala, and K. D. Maisto, *Tetrahedron Lett.*, 1237 (1977).
(5) R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, **15**, 113 (1970).
(6) W. G. Salmond and M. C. Sobala, *Tetrahedron Lett.*, 1695 (1977).
(7) A brief preliminary discussion of this material is given by W. G. Salmond in "Vitamin D, Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism", Walter deGruyter, Berlin and New York, 1977, pp 61–70.
(8) For examples of the reaction of epoxides with phosphoranes see: D. B. Denney, J. J. Vill, and M. J. Boskin, *J. Am. Chem. Soc.*, **84**, 3944 (1962); L. Horner, H. Hofmann, and V. G. Roscano, *Chem. Ber.*, **95**, 536 (1962); E. Zbiral, *Monatsh. Chem.*, **94**, 78 (1963); W. E. McEwen, A. P. Wolf, C. A. VanderWerf, A. Blade-Font and J. W. Holfe, *J. Am. Chem. Soc.*, **89**, 6685 (1967).
(9) A. R. Hands and A. J. H. Mercer, *J. Chem. Soc. C*, 1099 (1967); 2448 (1968). See also C. F. Garbers, J. S. Malherve and D. F. Schneider, *Tetrahedron Lett.*, 1421 (1972); A. Turcant and M. LeCorre, *ibid*, 1280 (1976); 789 (1977). Oxaphospholanes of this type undergo Witting reactions themselves to give approximately 50:50 mixtures of cis and trans olefins, but the conditions of the reaction are severe.
(10) The reaction of the hydroxyphosphonium salt, $Ph_3P^+CH_2CH_2CH_2OH\ Br^-$, with 2 mol of butyllithium followed by reaction with benzaldehyde is reported cryptically to yield the olefin $PhCH{=}CHCH_2CH_2OH$ in 65% yield. The report appears in S. Trippett in "Advances in Organic Chemistry", Interscience, New York, N.Y., 1960, p 83ff. The material is referenced to S. Trippett, unpublished results. No comment is made upon the stereochemistry of the reaction.
(11) Crystallized as needles from acetone/hexane: mp 133–134 °C; NMR ($CDCl_3$) δ 0.30–0.63 (m), 0.75 (s, 3 H), 1.03 (s, 3 H), 1.03 (d, J = 6 Hz, 3 H), 1.18 (s, 6 H), 2.78 (m, 1 H), 3.33 (s, 3 H), 5.38 (m, 2 H).
(12) The compounds were prepared by the following sequences:



For 20*R* aldehyde see ref 4.
(13) NMR data ($CDCl_3$)—position of peaks given in hertz downfield from Me_4Si. See also T. A. Narwid, K. E. Cooney and M. R. Uskokovic, *Helvetica*, **50**, 771 (1974); E. N. Trachtenberg, C. Byron, and M. Gut, *J. Am. Chem. Soc.*, **99**, 6145 (1977).

Compd	C-18	C-19	C-21 doublet	
	47	62	55	61
	43	61	56	61
	40	59	48.5	55
	43	62	53	58
	43	61	47	53

(14) E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, **95**, 5778 (1973).
(15) M. Schlosser and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, 126 (1966).
(16) The structures in this scheme are intended to show only relative stereochemistry at C-22 and C-23, not absolute chirality at these centers.
(17) Determined by GLC on a 15 ft 2% SE-30 column at 245 °C.

(18) J. J. Partridge, S. Faber, and M. R. Uskokovic, *Helvetica*, **51**, 764 (1974).
(19) For an alternative method of preparation of trans-homoallylic alcohols involving reaction of lithium *trans*-alkenyltrialkylaluminates with epoxides, see E. Negishi, S. Baba, and A. O. King, *J. Chem. Soc., Chem. Commun.*, 17 (1976).

William G. Salmond,* Mary A. Barta
Jeffrey L. Havens
The Upjohn Company, Kalamazoo, Michigan 49001
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