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An Expedient Route to a Versatile Intermediate for the Stereoselective Synthesis of all-*trans*-Retinoic Acid and beta-Carotene

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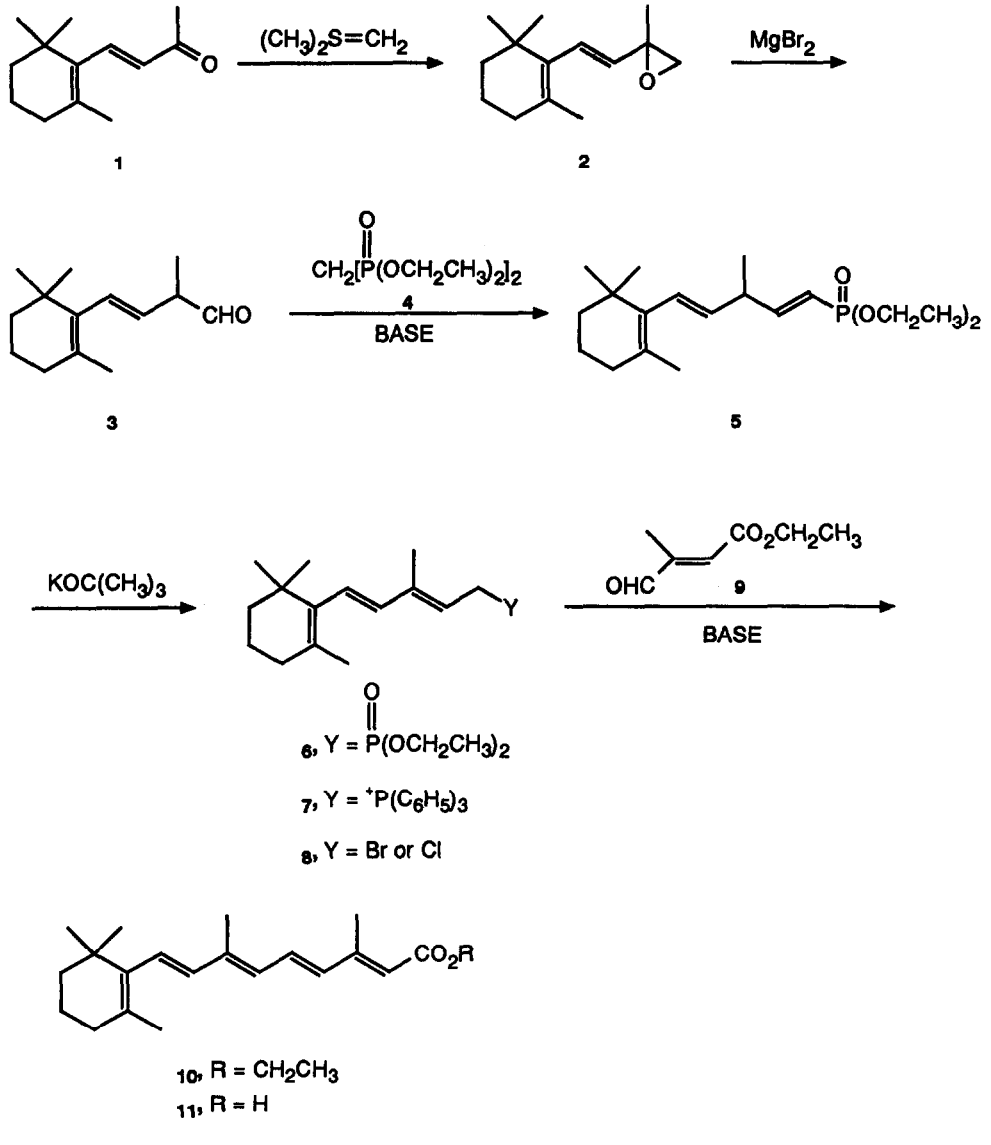
Abstract: Base-catalyzed isomerization of vinyl phosphonate **5** afforded the corresponding allylic phosphonate (**6**) as the sole product. Horner-Emmons olefination of ethyl *trans*-3-methyl-4-oxo-2-butenoate with the ylide derived from **6** concludes a facile synthesis of the all-*trans* stereoisomer of ethyl retinoate.

During the past decade there has been a renewed interest in the synthesis of retinoids and carotenoids as the bewildering variety of activity displayed by these classes of compounds continues to be elucidated.[1] For example, retinoic acid [all-*trans* vitamin A acid, Retin A (**11**)] has been used topically for the treatment of acne, but is also becoming increasingly important for the treatment of skin damaged by ultraviolet light.[2] Although retinoic acid can be obtained by a Wittig condensation between the ylide derived from C-15 phosphonium salt **7**[3] and C-5 aldehyde ester **9**, use of the corresponding C-15 phosphonate (**6**) in the same transformation has not been realized. Indeed, due to the reported instability of the C-15 allylic halide precursor (**8**) to phosphonate **6** at room temperature,[4] a synthesis of the latter compound (**6**) has not been reported to date.

Since use of phosphonate **6** could avoid the difficulties (e.g., separation of the triphenylphosphine oxide from the retinoid product) associated with use of phosphonium salt **7**, we decided to investigate the route outlined in Scheme I as a possible approach to the elusive phosphonate **6**. This approach, a priori, did not seem promising in view of the fact that allylic phosphonium salts are known[5] to isomerize to the corresponding vinyl phosphonium salts in the presence of base [i.e., the reverse of the desired isomerization (**5** → **6**)]. Nevertheless, we initiated a study of the feasibility of this route, the successful execution of which is reported in this communication.

Epoxide **2**[6] was prepared in quantitative yield by treatment[7] of beta-ionone (**1**)[8] with the ylide derived from trimethylsulfonium methylsulfate.[8] Subsequent isomerization of **2** using a catalytic amount of magnesium bromide according to a procedure[6] developed by Rosenberger and coworkers afforded C-14 aldehyde **3**[6] in 93% overall yield from beta-ionone. A modified[9] Horner-Emmons olefination[10] of the latter compound (**3**) using tetraethyl methylenediphosphonate (**4**)[11] afforded vinyl phosphonate **5**[12] in 93% yield. In view of the tendency of allylic phosphonium salts to isomerize to the corresponding vinyl phosphonium salts in the presence of base,[5] we were amazed at the smooth isomerization[13] of vinyl phosphonate **5** to the desired allylic

Scheme I


(CH3)2S=CH2
MgBr2
1
2
CHO
CH2[P(OCH2CH3)2]2
4
BASE
3
5
KOC(CH3)3
Y
CO2CH2CH3
OHC
9
BASE
6, Y = P(OCH2CH3)2
7, Y = +P(C6H5)3
8, Y = Br or Cl
CO2R
10, R = CH2CH3
11, R = H

phosphonate **6**[14] as the sole reaction product (82% isolated yield) as shown by high-field (300 MHz) proton and ^{13}C NMR analysis. The synthesis of ethyl retinoate (**10**) proceeded, as expected, via Horner-Emmons olefination of ethyl *trans*-3-methyl-4-oxo-2-butenoate (**9**)[15] with the ylide derived from allylic phosphonate **6**.[16] The product (**10**), isolated in 61% yield, was shown by high-field (300 MHz) proton and ^{13}C NMR analysis to be predominantly (>95%) the all-*trans* stereoisomer.[17]

In view of the high yields obtained in each step outlined in Scheme I and the facility with which vinyl phosphonate **5** isomerizes quantitatively to the previously unknown allylic phosphonate **6**, the latter should prove to be a versatile intermediate in the synthesis of retinoids and beta-carotene.

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References and Notes

1. Paust, J. *Pure and Applied Chem.* **1991**, *63*, 45-58 and references therein.
2. Kligman, A.M.; Grove, G.C.; Hirose, R.; Leyden, J.J. *J. Amer. Acad. Dermatol.* **1986**, *15*, 836. Weiss, J.S.; Ellis, C.N.; Headington, J.T.; Tincoff, T.; Hamilton, T.A.; Voorhess, J.J. *J. Amer. Med. Assoc.* **1988**, *259*, 529.
3. Pommer, H.; Sarnecki, W. German Patent 1,068,702, *Chem. Abstr.* **1961**, *55*, 10,812e. The same C-15 allylic phosphonium salt (**7**) has also been used to prepare beta-carotene: Pommer, H.; Kuhn, R. *Angew. Chem.* **1960**, *72*, 911.
4. Julia, M.; Arnold, D. *Bull. Soc. Chim. Fr., Part II*, **1973**, 746-50.
5. Jacoby, D.; Celerier, J.P.; Petit, H.; Lhommet, G. *Synthesis* **1990**, 301 and references 11-14 cited therein.
6. The proton NMR spectral properties of this compound were identical to those previously reported. See: Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta.* **1980**, *63*, 1665.
7. A mixture of 1.12 g (5.95 mmol) of trimethylsulfonium methylsulfate,[8] 0.50mL (2.46 mmol) of beta-ionone,[8] 70 mg (0.31 mmol) of benzyltriethylammonium chloride, 5.0mL of methylene chloride, and 5.0mL of 72%(w/v) aqueous NaOH was stirred vigorously at room temperature for 1 day. The product was isolated by dilution of the mixture with ice-water, followed by extraction with hexane.
8. Available from Aldrich Chemical Co., Milwaukee, WI USA.
9. The ylide was generated by dropwise addition of a solution of 508 mg (1.76 mmol) of tetraethyl methylenediphosphonate (**4**)[8] in 4.0mL of 5:3(v/v) benzene:tetrahydrofuran (THF) to a stirred mixture of 69 mg (1.7 mmol) of 60% sodium hydride in 1.0mL of benzene, maintained at a temperature of 15-20°C by use of an external cold water bath. Subsequent addition of a solution of 208 mg (1.01 mmol) of aldehyde **3** in 2.5mL of benzene and stirring this mixture at room temperature for 25 minutes afforded the desired vinyl phosphonate (**5**) in 93% yield. The latter was isolated by dilution of the

mixture with 20mL of 1:1(v/v) hexane:ether and washing the organic layer in successive order with 7:3(v/v) 1M aqueous NaOH: methyl alcohol (2x40mL) to remove excess diphosphonate and then with saturated brine (20mL).

10. For a similar route to other vinyl phosphonates, see Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333-349 and references therein.

11. Diphosphonate **4** can be purchased from Aldrich Chemical Co. or prepared from dibromomethane and triethyl phosphite according to the procedure described by Czekanski, T.; Gross, H.; Costisella, B. *J. Fur Prakt. Chemie* **1982**, *324*, 537.

12. b.p. 137-152°C (bath temperature, 0.20 mm). The proton NMR spectrum (300 MHz, $CDCl_3$) exhibited the following signals: δ 6.83 [1 vinyl H, m, H-C(2)], 5.91 [1 vinyl H, broad d, J = 16Hz, H-C(5)], 5.68 [1 vinyl H, dd, J_{H-H} = 17Hz, J_{P-H} = 21Hz, H-C(1)], 5.32 [1 vinyl H, dd, J = 7.4, 16Hz, H-C(4)], 3.12 [1H, m, H-C(3)], 1.23 [3H, d, J = 7Hz, CH_3-C(3)]; HRMS found 340.2158, calcd 340.2167 for $C_{19}H_{33}O_3P$.

13. This isomerization was effected by stirring a mixture of 270 mg (0.79 mmol) of vinyl phosphonate **5** and 30 mg (0.27 mmol) of potassium tert-butoxide in 4.0mL of anhydrous dimethyl sulfoxide for 2 hours at room temperature.

14. b.p. 130-148°C (bath temperature, 0.20mm). The proton NMR spectrum (300 MHz, $CDCl_3$) of the product indicated that it was a 2:1 mixture of **E:Z** stereoisomers (C_2-C_3 double bond) and was characterized by the following signals: δ 1.02 (E stereoisomer) and 1.03 (Z stereoisomer) [6H's, two singlets, ring geminal methyls], singlets at 1.69 (E stereoisomer) and 1.73 (Z stereoisomer) [3H, ring "vinyl methyl"], 1.85[d, J = 3.9Hz, CH_3-C(3), E stereoisomer], 1.93 [d, J = 5.5Hz, CH_3-C(3), Z stereoisomer], 2.75 [CH_2P, dd, J_{H-H} = 8.1Hz, J_{P-H} = 23Hz]; HRMS found 340.2133, calcd 340.2167 for $C_{19}H_{33}O_3P$.

15. Available from Fluka Chemical Corp.

16. Ethyl retinoate (**10**) was obtained in 61% yield by addition of 44 mg (0.39 mmol) of potassium tert-butoxide to a solution of 132 mg (0.39 mmol) of allylic phosphonate **6** and 57 mg (0.40 mmol) of aldehyde ester **9**[15] in 3.5mL of 6:1(v/v) tetrahydrofuran:dimethyl sulfoxide at 0°C, followed by subsequent stirring at room temperature for 6 hours.

17. The proton NMR spectrum of the product (**10**) was characterized by three singlets of equal intensity at δ 2.37, 2.02, and 1.73 (3 vinyl methyls) and was fully consistent with an all-*trans* structure, as shown by comparison with the corresponding literature values[18] of chemical shifts for all the stereoisomers of methyl retinoate. Likewise, the ^{13}C chemical shifts of the product's three vinyl methyls confirmed the all-*trans* structural assignment.

18. For a table listing the spectral properties of all stereoisomers of methyl retinoate, see pp 1962-4 in the following review article: Liu, R.S.H.; Asato, A.E. *Tetrahedron* **1984**, *40*, 1931-1969.

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