Communications

An Efficient Synthesis of the Enantiomeric 17-Phosphasteroid System[1]

Summary: Enantiomeric *trans*-benzylphenyl[β-(carbomethoxy)vinyl]phosphine oxide (**6**) undergoes regio- and stereoselective cycloaddition to 1-vinylnaphthalene (**5**), providing two diastereomeric adducts **7a** and **7b**, which are further transformed into optically pure 17-phosphasteroid systems by intramolecular Dieckmann-type condensation.

Sir: A wide variety of heterosteroids isoelectronic with the natural steroidal hormones have been synthesized in the last decade as part of an intensive search for new compounds with potential specific pharmacological properties.[2]

We have recently contributed to this field with a new synthetic method for the 3-oxophospholane oxide unit which has proven useful in the preparation of the 17-phosphasteroid system[3] (Scheme I).

In order to provide an efficient route to enantiomeric 17-phosphasteroids, we have devised a modified version of this approach. The vicinal methoxycarbonyl and benzylphosphoryl functions, which are required for formation of the five-membered ring, are simultaneously introduced to the carbocyclic skeleton by a [2 + 4] cycloaddition process (Scheme II) instead of the nucleophilic 1,4-addition originally employed (Scheme I). Scheme II presents a straightforward example of this new route.

Optically pure *trans*-benzylphenyl[β-(carbomethoxy)vinyl]phosphine oxide of S_P configuration (**6**),[4] mp 167.5 °C, $[\alpha]^{20}_{D}$ +20.1° (*c* 8.1, $CHCl_3$), was reacted with 1-vinylnaphthalene (**5**) in a sealed tube at 120 °C (40 h, toluene, CF_3COOH) and afforded a mixture of two diastereomeric cycloadducts **7a** and **7b** in a ratio 65:35 in 70% yield.[5,6] Fractional crystallization of this mixture from $CCl_4/C_6H_6/CHCl_3$ (10:10:1) yielded the minor component **7b**: mp 226 °C; $[\alpha]^{20}_{D}$ +2.5° (*c* 4.2, $CHCl_3$); ^{31}P *NMR*[7] ($CHCl_3$) 39.78 ppm. The major component **7a** precipitated from the mother liquor after addition of hexane. **7a**: mp 183–185 °C; $[\alpha]^{20}_{D}$ −19° (*c* 5.3, $CHCl_3$); ^{31}P NMR ($CHCl_3$) 40.36 ppm.

^{13}C NMR spectra of both components revealed coupling between ring C-11 carbons (steroid numbering) and phosphorus to be 10 and 9.7 Hz for **7a** and **7b**, respectively. These values are clearly compatible with a three-bond C–P coupling[8,9] and imply a uniform regioisomerism for **7a** and **7b** pictured in Scheme II. Similarly, small values of $^{3}J_{P-C(O)}$ observed for **7a** and **7b**, i.e., 4.4 and 2.0 Hz, respectively, are completely in accord with the expected trans dipseudoequatorial disposition of the phosphorus and carbomethoxy groupings in both isomers.[3b,10]

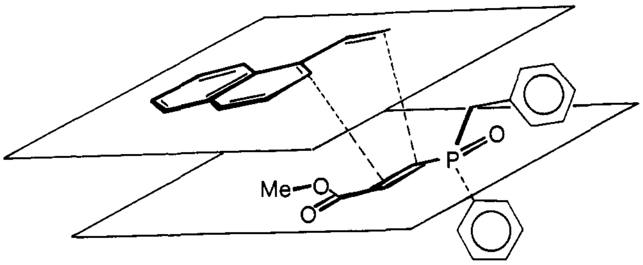

Figure 1.

The assignment of the relative and absolute configurations to the isomers **7a** and **7b** follows from a single-crystal X-ray diffraction analysis of racemic counterpart of **7a**[11] and from the fact that the precursor **6** was of the known absolute configuration (S_P). These data[11] indicate unambiguously the $S_P,R_{C\text{-}13},S_{C\text{-}14}$ configuration for the isomer **7a**. Accordingly, the minor isomer **7b** has to possess the $S_P,S_{C\text{-}13},R_{C\text{-}14}$ absolute configuration.

The stereo- and regiochemistry of the performed [2 + 4] cycloaddition may be accounted for simply. The trans configurations of **7a** and **7b** reflect the trans configuration of the dienophile **6**, whereas the observed regiospecificity is most likely a result of the strong directing effect of the carbonyl group[12] which apparently dominates that of the phosphoryl.[13] This observation is also suggested by the results of Kashman and Awerbouch.[14]

Formation of the two diastereomeric adducts **7a** and **7b** in unequal amounts argues in favor of asymmetric induction. If in the reactive conformation of the dienophile **6**, the conjugated C=O, C=C, and P=O groupings are assumed to be trans coplanar, the configurations of two newly created centres of asymmetry, i.e., C-13 and C-14 should be controlled mainly by steric interactions between the phosphorus substituents and the diene[15] coming in endo with respect to the carbomethoxy grouping.[16] In

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(1) Paper presented at the International Symposium on Phosphorus Chemistry Directed Towards Biology, Sept. 25–28, 1979, Burzenin, Poland.

(2) (a) Huisman, H. O. *MTP Int. Rev. Sci., Org. Chem.* **1973**, *8*, 235. Huisman, H. O.; Speckamp, W. N. *MTP Int. Rev. Sci., Org. Chem., Ser. Two* **1976**, *8*, 207. Huisman, H. O. *Bull. Soc. Chim. Fr.* **1968**, 13. (b) Pitt, C. G.; Friedman, A. E.; Rector, D.; Wani, M. C. *Tetrahedron* **1975**, *31*, 2369. Barcza, S.; Hoffman, C. W. *Ibid.* **1975**, *31*, 2363. (c) Radhakrishna, A. S.; Berlin, K. D.; Helm, D.v.d. *Pol. J. Chem.* **1980**, *54*, 495. (d) Symmes, C., Jr; Quin, L. D. *J. Org. Chem.* **1979**, *44*, 1048.

(3) (a) Bodalski, R.; Pietrusiewicz, K. M. *Tetrahedron Lett.* **1972**, 4209. (b) Pietrusiewicz, K. M. Ph.D. Thesis, Polish Academy of Sciences, Łódź, Poland, 1976.

(4) The synthesis of enantiomeric benzylphenyl[β-(carbomethoxy)vinyl]phosphine oxide from menthyl β-chloracrylate and ethyl benzylphenylphosphinite in three steps and the assignment of its absolute configuration through chemical correlation will be reported elsewhere; Bodalski, R.; Koszuk, J., manuscript in preparation.

(5) All compounds gave correct C, H, P analyses and their ^{1}H, ^{13}C, and ^{31}P NMR spectra are in accord with the proposed structures.

(6) The ratio of **7a** and **7b** was determined from integration of the corresponding ^{31}P NMR resonances.

(7) The new sign convention is used.

(8) Quin, L. D. "The Heterocyclic Chemistry of Phosphorus"; Wiley-Interscience: New York, 1981; Chapter 6.

(9) The observed magnitudes of P–C couplings do not fall in the range of 0–3 Hz which is common for $^{4}J_{PC}$. See: (a) Quin, L. D.; Gordon, M. D.; Lee, S. D. *Org. Magn. Reson.* **1974**, *6*, 503. (b) Quin, L. D.; Mesch, K. A.; Bodalski, R.; Pietrusiewicz, K. M. manuscript submitted for publication.

(10) Kingsbury, C. A.; Thoennes, D. *Tetrahedron* Lett. **1976**, 3037.

(11) Główka, M. L.; Gałdecki, Z. *Acta Crystalogr., Sect B* **1981**, 273.

(12) Fleming, I.; "Frontier Orbitals and Organic Chemical Reactions"; Wiley: London, 1976; Chapter 4. Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523.

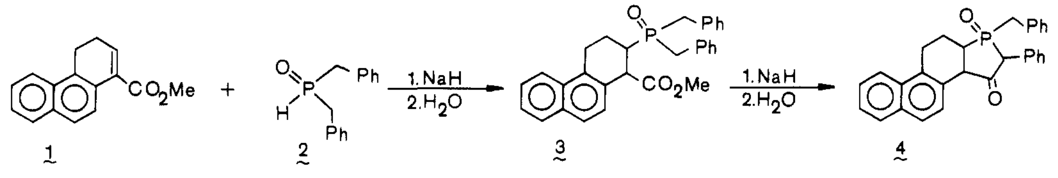
(13) Daniewski, W. M.; Griffin, C. E. *J. Org. Chem.* **1966**, *31*, 3236.

(14) Kashman, Y.; Awerbouch, O. *Tetrahedron Lett.* **1973**, 3217.

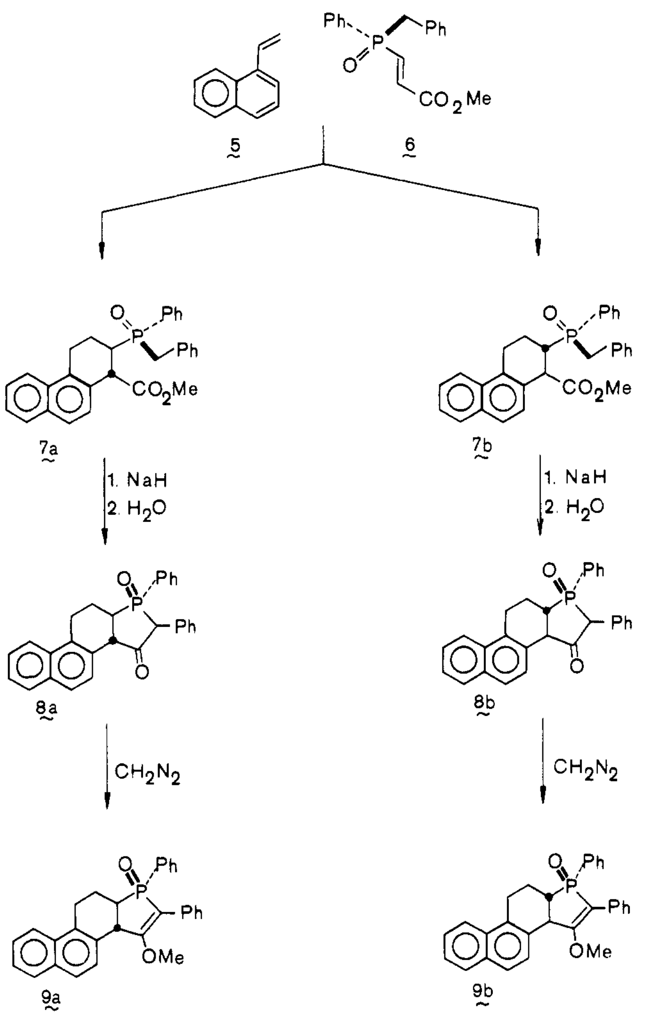
(15) This type of reasoning was successfully applied in the case of dimenthyl fumarate cycloadditions; see Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.

0022-3263/82/1947-2219$01.25/0

Scheme I



Scheme II



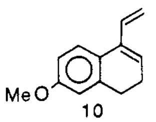
such a model the predominant formation of **7a** calls for a preference of diene approach from the side of the benzyl phosphorus substituent. This is represented in Figure 1.[17]

Treatment of the adducts **7a** and **7b** with sodium hydride in tetrahydrofuran resulted in the formation of the phosphasteroids **8a** and **8b**, respectively, in ca. 80% yield in both cases. Both **8a** and **8b** are crystalline, high-melting solids (250 °C dec) and are poorly soluble either in common organic solvents or in water.[18] Similar properties of many other 3-oxophospholane oxides have been observed[3,19] and can be ascribed to the high enolic character of the 3-keto function and strong intermolecular hydrogen bonding.[19,24]

To facilitate handling and preclude spectral ambiguities connected with keto–enol tautomerism, we transformed both phosphasteroids **8a** and **8b** into the respective enol ethers **9a** and **9b** by means of methylation with diazomethane in ether, in almost quantitative yields. **9a**: mp 266 °C; $[\alpha]^{20}{}_D$ +68.7° (*c* 5.1, 10% CF_3COOH-$CHCl_3$); ^{31}P NMR[7] (10% CF_3COOH–$CHCl_3$) 51.2 ppm; ^1H NMR (10% CF_3COOH–$CDCl_3$) 3.51 (s, OCH_3), 4.24 ppm (dd, $^3J_{H-H}$ = 7.7 Hz, $^3J_{P-H}$ = 7.5 Hz, CH). **9b**: mp 259 °C; $[\alpha]^{20}{}_D$ +14° (*c* 3.8, 10% CF_3COOH-$CHCl_3$); ^{31}P NMR[7] (10% CF_3COOH–$CHCl_3$) 51.7 ppm; ^1H NMR (10% CF_3COOH–$CDCl_3$) 3.49 (s, OCH_3), 4.45 ppm (t, $^3J_{H-H}$ = 7.5 Hz, $^3J_{P-H}$ = 7.5 Hz, CH).

The values of $^3J_{H-C_{13}-C_{14}-H}$ and $^3J_{P-C_{13}-C_{14}-H}$ are indicative of trans[20] and gauche[21] nuclei, respectively, and suggest the assignment of trans C/D ring junctions in **9a** and **9b** and, therefore, in **8a** and **8b** as pictured in Scheme II.

In our opinion, the presented AB → ABC → $ABCD_P$ approach to the enantiomeric phosphasteroids has features of a general synthetic method since a number of bicyclic dienes and a series of dienophiles with different substitution patterns are likely to compose a suitable pair of reactants. The application of 1-vinyl-6-methoxy-3,4-dihydronaphthalene (**10**) and the phosphorus dienophile **11** for the syntheses of closer analogues of naturally occurring steroids is currently in progress.



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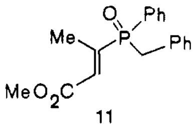

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Registry No. 5, 826-74-4; **6**, 81027-60-3; **7a**, 81075-98-1; **7b**, 81075-99-2; **8a**, 81027-61-4; **8b**, 81076-00-8; **9a**, 81129-82-0; **9b**, 81027-62-5.

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(17) Referee I is gratefully acknowledged for the helpful suggestion regarding Figure 1.

(18) Compounds **8a** and **8b** show increased solubility in alkaline water.

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(20) A similar HCCH coupling of 7 Hz was observed for the closely related *trans*-1-benzyl-2-phenyl-4,5-dimethylphospholan-3-one 1-oxide system;[19d] for dihydrothiophene $^3J_{HCCH}$(trans) = 7.5 Hz was found; see Abraham, R. J.; Sheppard, R. C.; Thomas, W. A.; Turner, S. *Chem. Commun.* **1965**, 43.

(21) The value of 28 Hz for $^3J_{PCCH}$ coupling was obtained for antinuclei in a rigid system;[22] the corresponding "averaged" value for triethylphosphine oxide is 16.3 Hz.[23]

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(23) Hendrickson, J. B.; Maddox, M. L.; Sims, J. J.; Kaesz, H. D. *Tetrahedron* **1964**, *20*, 449.

(24) For a general discussion, see: Quin, L. D. "The Heterocyclic Chemistry of Phosphorus"; Wiley-Interscience: New York, 1981; Chapter 2, pp 62–64.

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