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A NEW SYNTHESIS OF PHOSPHASTEROIDS EMPLOYING THE McCORMACK CYCLOADDITION FOR CONSTRUCTION OF THE D-RING

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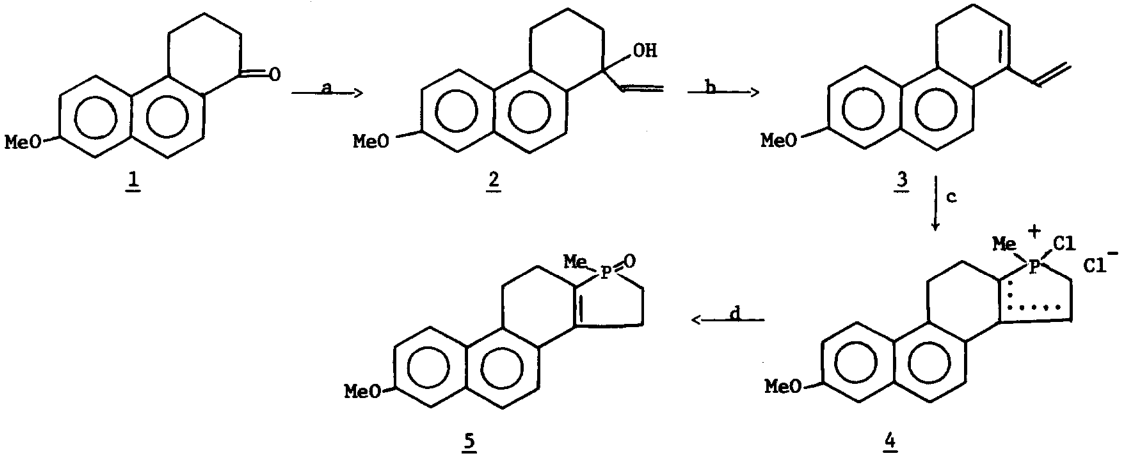
For many years, interest has been high in the synthesis of heterosteroids for biological testing, but only recently have phosphasteroids received attention[1]. We have devised a new method for the preparation of the 15- and 17-phosphasteroid systems, examples of which are given in this paper. Our method, an ABC ⟶ ABCD approach, forms the D-ring by the McCormack diene-phosphorus (III) halide cycloaddition reaction[2], which we have recently shown to be useful for the synthesis of bicyclic phospholene oxides[3]. The method has the advantage of giving phosphasteroids of considerable similarity to natural steroids; the structures reported in this paper will be seen to have features in common with the hormone equilenin.

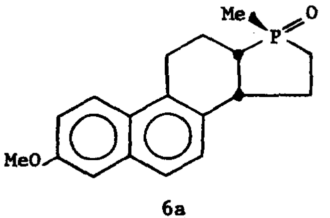
The requisite diene (3) for construction of the 17-phosphasteroid system was easily prepared from the well-known steroid intermediate Butenandt's ketone[4] (1).



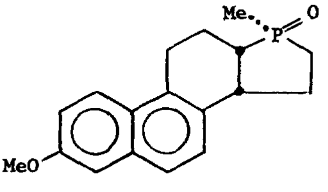
a, $CH_2=CHMgBr$ in THF, then NH_4Cl; b, I_2, quinoline, benzene, Δ; c, $MePCl_2$ in benzene, 25°; d, H_2O.

The Grignard addition to 1 occurred in 90% yield; iodine-catalyzed dehydration of alcohol 2, conducted in refluxing benzene with azeotropic water removal, gave diene 3 in 88% yield. Diene 3 had the expected NMR spectrum and was used without further purification in the McCormack cycloaddition. This reaction was conducted under the usual mild conditions (standing at room temperature for one week; copper stearate as polymerization inhibitor). The precipitated cycloadduct 4 was filtered off, washed with petroleum ether, and hydrolyzed by addition to water at 25°. From a chloroform extract of the resulting slurry there was obtained a 66% yield of oxide 5, m.p. 205° dec after recrystallization from acetone. Oxide 5 gave the correct C,H,P analysis; M^+ in the mass spectrum occurred at m/e 298.1119 (calcd. 298.1123), and its ^{31}P NMR signal was at +65.1 ppm ($CDCl_3$; downfield[5] from 85% H_3PO_4). The proton NMR spectrum [$CDCl_3$, δ 1.68 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.98-3.40 (m, 8H for CH_2 groups), 3.90 (s, OCH_3), 7.05-8.04 (5H, aromatics)] contained no olefinic signals, indicating that the double bond had rearranged from the initially established $\Delta^{3,4}$ position in the cycloadduct into conjugation with the phosphoryl group. Much precedent exists for this rearrangement[3].

Phosphasteroid 5 is a stable, crystalline solid having only slight solubility in water. The methoxy group can be cleaved by 48% HBr (3 hrs reflux) to give the phenol [71%, m.p. 289-290° dec; proton NMR (CF_3COOH) δ 2.02 (d, $^2J_{PH}$ = 13 Hz, PCH_3), multiplets for CH_2 (δ 2.15-3.50) and ArH (δ 7.15-8.21); ^{31}P NMR (CF_3COOH) δ + 68.3]. Atmospheric pressure hydrogenation (10% Pd/C, CH_3OH) reduced the double bond in 5, presumably giving cis C/D fusion. The product was a mixture of P-stereoisomers 6a and 6b. Analysis by ^{31}P NMR gave δ + 67.7 (84%), δ + 71.8 (16%); proton NMR gave methyl doublets at δ 1.73 and 1.62, respectively. Insufficient information is available to permit the assignment of stereochemistry with confidence; hydrogenation of another 1-methyl-2-phospholene oxide (1-methyl-$\Delta^{3a(7a)}$-2,3,4,5,6,7-hexahydro-1(H)-phosphindole 1-oxide[3]) proceeded with no selectivity, although 1-phenyl-3-methyl-2-phospholene oxide was selectively hydrogenated from the side opposite P=O[6].

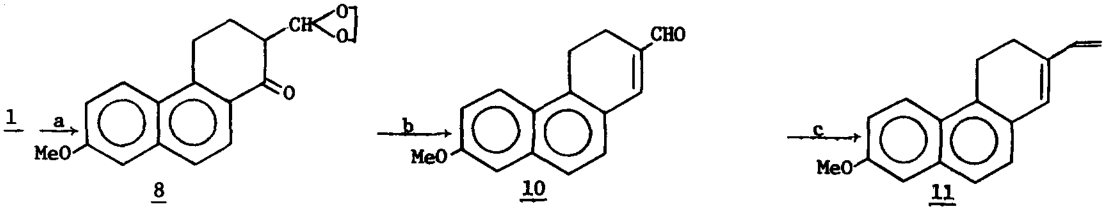


6a



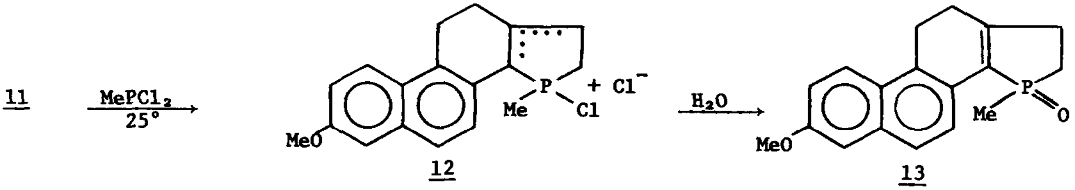
6b

Butenandt's ketone (1) was also the starting point for the synthesis of the requisite diene for construction of the 15-phosphasteroid system. Formylation of 1 (89%) gave the aldehyde (7) as has been reported previously[7]. The aldehydic carbonyl of 7 reacted selectively with ethylene glycol to give acetal 8 (85%), m.p. 162-164° (benzene-ligroin), and the ring carbonyl was then reduced in nearly quantitative yield to give the alcohol (9), m.p. 120-124° (benzene-ligroin). Dehydration and removal of the acetal group occurred simultaneously on 1-hr refluxing of 9 in an acidic medium, forming 10, 85%, m.p. 117-118° (methanol). The Wittig reaction on 10 with methylenetriphenylphosphorane, prepared in ether from n-butyllithium and methyltriphenylphosphonium bromide, gave diene 11 (90%, m.p. 95-97° after elution from an alumina column with benzene). Compounds 8-11, all new, gave the correct C,H analyses and had the expected spectral features.

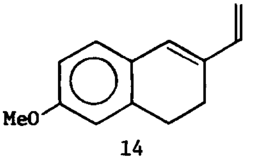


a: (1) HCOOEt, NaOMe, 25°, (2) $HOCH_2CH_2OH$, TsOH; b: (1) $NaBH_4$ in MeOH, (2) refluxing conc. HCl-$MeOH-H_2O$; c: Ph_3PCH_2 in benzene-ether, 1:1.

The McCormack reaction with diene 11 was carried out as for diene 3. The cycloaddition was, however, markedly slower; product (12) that had formed after 11 days was collected and hydrolyzed, but gave only an 8% yield. Attempts to expedite the cycloaddition by performing it in refluxing benzene gave mostly polymeric material, but further development of the reaction conditions may improve the yield. Phosphasteroid 13, recrystallized from ethyl acetate and then sublimed (145°, 0.13 mm), had m.p. 194° dec and gave the correct C,H,P analysis. Its NMR spectrum confirmed the position of the double bond since no olefinic signal was present: $CDCl_3$, δ 1.8 (d, $^2J_{PH}$ = 11 Hz), 2.0-3.5 (m, 8H, methylenes), 3.93 (s, OCH_3), 7.1-8.0 (m, 5H, aromatics); δ ^{31}P, + 63.5 ppm.



By the use of appropriate tricyclic ketones, phosphasteroids of considerable structural variety can be obtained by the McCormack route. However, the slowness of the cycloaddition with diene 11, compared to that with diene 3, suggests that the method will be more useful for forming the 17-phospha system rather than the 15-phospha system. This rate difference has been seen[8] also in the reaction of structurally related bicyclic dienes 14 and 15. The tricyclic phospholene oxides formed are themselves of possible interest in phosphasteroid chemistry as intermediates in a BC⟶BCD⟶ ABCD route.



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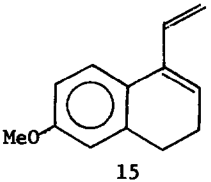

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