analyses were performed by Atlantic Microlab, Norcross, GA.

1-Benzoylbenzimidazole (4). To a solution of benzimidazole (2) (0.2 mol, 23.6 g, recrystallized from water) and triethylamine (0.22 mol, 22.36 g or 30.66 mL) in DMF (200 mL) cooled in an ice-water bath under dry conditions (N_2) was added benzoyl chloride (0.22 mol, 30.92 g or 25.6 mL) with stirring during a 1-h period. Stirring was continued overnight at 25 °C. The reaction mixture was poured into water (2 L) and stirred for 6 h. The solid obtained by filtration was stirred in water (1 L) for 1 h, filtered, and dried. The product obtained was treated once with Norit and recrystallized from ethyl acetate and hexane: white needlelike crystals; 35.58 g (80%); mp 91-2 °C (lit.[8] mp 91-2 °C); ^{1}H NMR (DMSO-d_6) δ 8.46 (s, 1 H, H_2), 8.17-8.08 (m, 1 H, H_7), 7.94-7.85 (m, 2 H), 7.85-7.72 (m, 2 H), 7.70-7.60 (m, 2 H), 7.53-7.4 (m, 2 H).

***N*-Formyl-*N*,*N*'-dibenzoyl-*o*-phenylenediamine (5): Method A.** To a well-stirring mixture of 4 (0.005 mol, 1.12 g), KCN (0.015 mol, 0.977 g), dichloromethane (10 mL), and water (5 mL) was added benzoyl chloride (0.01 mol, 1.4 g) dropwise, and stirring was continued for an additional 5 h. The reaction mixture was then diluted with water (100 mL) and extracted with dichloromethane (3 × 10 mL). Organic layers were pooled, washed consecutively with aqueous saturated sodium bicarbonate (3 × 50 mL), aqueous 8% HCl (3 × 50 mL), and water (3 × 50 mL), dried over anhydrous sodium sulfate, and concentrated to get crude product (1.73 g, 100%). Pure product was obtained by recrystallization from ethyl acetate to get white crystals: mp 159-160 °C; MS-EI *m/e* 344 (M^+), 316, 298, 222, 194, 105, 77; MS-CI *m/e* 345 [$(M + 1)^+$], 317, 299, 223, 195, 105, 91; IR (KBr) 3264 (NH), 1721, 1678, 1655 (N-CO-), 1600, 1580 (aromatic), 1497, 1482, 1453, 1310, 1297, 1272 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.02 (s, 1 H, D_2O exchangeable, NH), 9.19 (s, 1 H, CHO), 7.9-7.2 (m, 14 H, Ar-H); ^{13}C NMR (DMSO-d_6) 170.89, 165.55 (NHCO), 163.2 (CHO, showed a doublet in the undecoupled experiment) and 14 other peaks from 136 to 124 ppm (aromatic). Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.33; H, 4.72; N, 8.07.

Method B. To a well-stirring mixture of 4 (0.005 mol, 1.12 g), dichloromethane (10 mL), and water (5 mL) was added benzoyl chloride (0.01 mol, 1.4 g) dropwise, and stirring was continued for an additional 5 h. The reaction mixture was then diluted with water (100 mL) and extracted with dichloromethane (3 × 50 mL). Organic layers were pooled, washed consecutively with aqueous saturated sodium bicarbonate (3 × 50 mL), aqueous 8% HCl (3 × 50 mL), and water (3 × 50 mL), dried over anhydrous sodium sulfate, and concentrated to get crude product (1.73 g, 100%). Pure product was obtained by recrystallization from ethyl acetate to get white crystals, mp 159-159.5 °C. The melting point, IR, and NMR data of this product were identical with those of compound prepared in method A.

2-Cyano-1,3-dibenzoyl-2,3-dihydrobenzimidazole (1). To a well-stirring solution of 4 (0.05 mol, 11.2 g) in CH_2Cl_2 (100 mL) were added benzoyl chloride (0.05 mol, 7.0 g) and TMSCN (0.052 mol, 5.46 g). The reaction mixture was stirred for 5 days at 25 °C and quenched by pouring into water (1 L). This solution was extracted with dichloromethane (3 × 150 mL). The organic layer was washed with 8% HCl (3 × 150 mL), aqueous saturated bicarbonate (3 × 150 mL), and water (3 × 150 mL) and dried over $MgSO_4$. Solvent evaporation yielded the product (17.1 g, 96%). Pure product was obtained by treating once with Norit and recrystallizing from ethyl acetate and hexane to get white crystals; mp 188-9 °C; IR (KBr) 1677, 1664, 1658, 1644, 1632, 1601, 1494, 1475, 1450, 1390, 1378, 1355, 1342, 1333, 1321, and 1302 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.75-7.55 (m, 10 H, COC_6H_5), 6.99 (s, 1 H, H_2), 6.98-6.85 (m, 2 H, H_5 and H_6), and 6.7-6.3 (br s, 2 H, H_4 and H_7); ^{13}C NMR (DMSO-d_6) 166.40, 133.58, 132.09, 131.39, 129.12, 127.64, 124.51, 115.53, 114.67 (CN), and 66.14 (C-2, showed a doublet in undecoupled experiment) ppm. Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.77; H, 4.28; N, 11.89. Found: C, 74.64; H, 4.33; N, 11.83.

Reaction of Benzimidazole (2) with KCN/TBAB. To a well-stirring mixture of 2 (1.18 g, 0.01 mol), KCN (0.65 g, 0.01 mol), and TBAB (0.322 g, 0.001 mol) in anhydrous dichloromethane (35 mL) was added benzoyl chloride (2.82 g, 0.02 mol) over a period of 10 min. The reaction mixture was heated gently (in an oil bath maintained at 50 °C) under reflux for 10 h. It was then cooled. The organic layer was separated, washed with water (3 × 30 mL), aqueous 8% HCl (3 × 30 mL), aqueous saturated sodium bicarbonate (3 × 30 mL), and water (3 × 30 mL), and dried over sodium sulfate. Evaporation of the solvent yielded a gummy residue (2.75 g, 87%). This residue was heated in ethanol (20 mL) and cooled. The white precipitate was collected and recrystallized from ethanol to get white crystals: mp 308-310 °C (mp of *o*-phenylene dibenzamide[7] = 301-4 °C). The melting point, IR, and NMR data of this product were identical with those of *o*-phenylenedibenzamide prepared from *o*-phenylenediamine.

Reaction of 1-Benzoylbenzimidazole (4) with KCN/TBAB. To a well-stirring solution of 4 (2.24 g, 0.01 mol), KCN (0.65 g, 0.01 mol), and TBAB (0.322 g, 0.001 mol) in anhydrous dichloromethane (35 mL) was added benzoyl chloride (2.82 g, 0.02 mol) over 10 min. The reaction mixture was heated gently (in an oil bath maintained at 50 °C) under reflux for 2.5 h. It was then cooled, and the organic layer was separated, washed with water (3 × 30 mL), aqueous 8% HCl (3 × 30 mL), aqueous saturated sodium bicarbonate (3 × 30 mL), and water (3 × 30 mL), and dried over sodium sulfate. Evaporation of the solvent yielded a gummy residue (3.0 g, 94%). This residue was heated in ethanol (25 mL) and cooled. The white precipitate was collected and recrystallized from ethanol to get white crystals: mp 308-310 °C (mp of *o*-phenylene dibenzamide[7] = 301-4 °C). The melting point, IR, and NMR data of this product were identical with those of *o*-phenylenedibenzamide prepared from *o*-phenylenediamine.

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Pentacovalent Oxaphosphorane Chemistry in Organic Synthesis: A New Route to Substituted Phosphonates

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Phosphonate-containing compounds are of biological interest as antimetabolites and enzyme active-site probes, especially of pyrophosphatases, the glycolytic pathway, lipid and glycerol-related processes.[1] They also have medicinal value as antivirals,[2] antibiotics,[3] and antiacidosis agents,[4] as well as exhibiting herbicidal and insecticidal activities.[1a,b] In connection with our interest in synthesizing biologically active compounds containing phosphonate group(s), we are investigating the carbon analogue of the Ramirez condensation of pentacovalent oxaphosphoranes with carbonyl compounds as a new method for the production of phosphonate-containing compounds.

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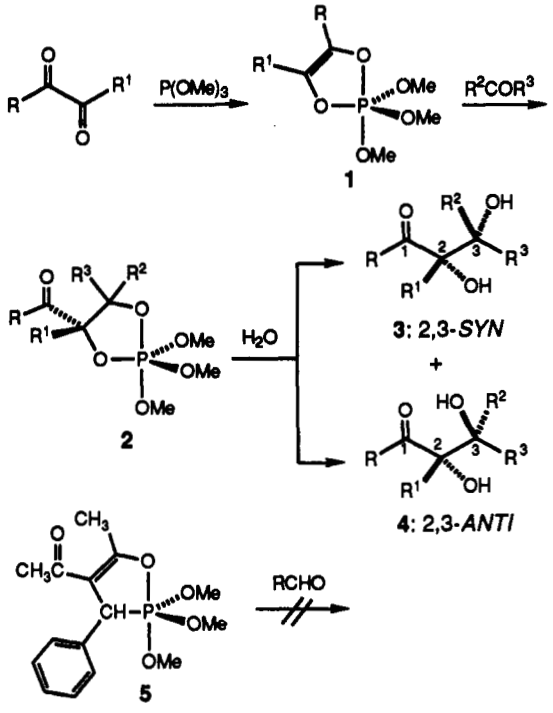
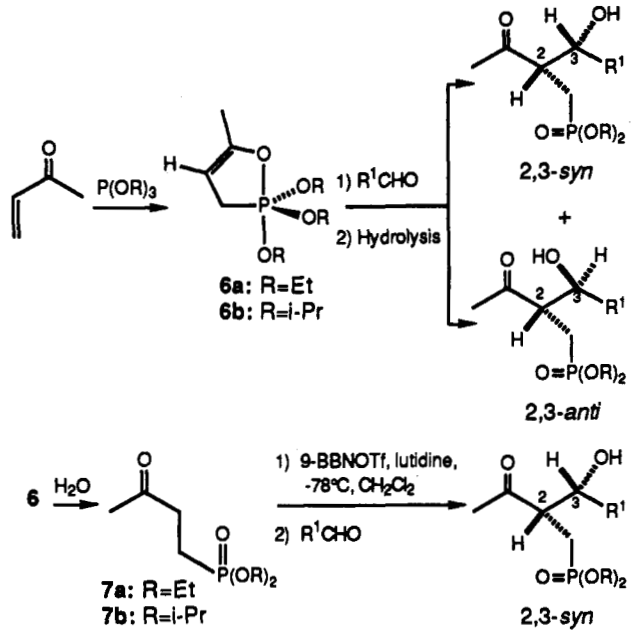
Scheme I



Scheme II



In the late 1960s and early 1970s, Ramirez and coworkers reported their studies on the reactions of 1,3,2λ^5-dioxaphospholenes, **1**, derived from trialkyl phosphites and α-dicarbonyl compounds[5] (Scheme I). We now report our preliminary results on the successful condensations of various aldehydes with the 1,2λ^5-oxaphospholenes, **6**, derived from methyl vinyl ketone and trialkyl phosphites[6] (Scheme II). This carbon–carbon bond forming reaction proceeds *without added acid or base* and provides a facile entry to a variety of highly substituted phosphonates. We have been able to produce via this method the β-hydroxy α-phosphonomethyl compounds **8–17**. To our knowledge, only one reported attempt (unsuccessful) of this condensation reaction between the 1,2λ^5-oxaphospholene, **5**, and an aliphatic aldehyde is documented.[7]

Our results to date are summarized in Table I. Correlation of the "aldol" stereochemistries in **8–17** were obtained by comparison with published spectral data on similar aldol compounds,[8] as well as with the aldol–phosphonate compounds prepared independently via the reaction of the 9-BBN boron enolate of **7** with the aldehydes in question. The latter procedure is known to produce the syn aldol stereochemistry.[9] The results indicate that the best syn diastereoselectivities resulted from condensation between the bulkiest oxaphospholene (**6b**) and either benzaldehyde (4.9:1.0, syn:anti) or isobutyraldehyde (3.5:1.0, syn:anti). Presumably, the steric bulk of the ligands on the phosphorus and/or around the aldehydes is influencing the stereoselectivity.

Our initial condensation reactions were performed neat at room temperature according to the procedure used by Ramirez et al., but the reaction times for the 1,2λ^5-oxaphospholenes, **6**, ranged from 2 to 25 days. The effects of different solvents at various temperatures (THF, hexane, chloroform, dichloromethane, acetonitrile; 0 °C, 20 °C, 50 °C) on the reaction of **6** with benzaldehyde were subsequently investigated. Optimal rates and yields were obtained in dichloromethane under reflux.

During the hydrolyses of the condensation products obtained from **6**, attention had to be paid to the pH of the solution. The syn diastereomer decomposed via a retroaldol process if the pH was very basic (≥10), with varying amounts of **7** and the aldehyde being isolated. Direct hydrolysis of the reaction mixture with water resulted in a mixture of pH ≈ 3. Control experiments indicated no change in product composition at pH 1.5–7.0 for R = Et or i-Pr.

The value of Lewis acids as catalysts in the promotion of the reactions of P^V organophosphorus compounds has been shown.[10] We investigated the condensation of **6a** with benzaldehyde in the presence of the Lewis acids, $BF_3{\cdot}OEt_2$, trimethylsilyl triflate (TMSOTf), $SnCl_4$, $TiCl_4$, $AlCl_3$, and LiBr. The use of $BF_3{\cdot}OEt_2$ produced the best overall yield (88%), although the syn/anti isomer ratio was not improved compared to the uncatalyzed reaction. The neat condensation reaction at various temperatures with trimethylsilyl triflate as catalyst yielded the greatest variation in syn/anti isomer ratios. At 20 °C, the syn isomer was the major after short reaction times (2.4:1.0 syn:anti). However, when the reaction was allowed to stir for up to 26 h, ^{1}H NMR analysis of aliquots removed periodically indicated that the amount of syn diastereomer decreased steadily relative to the amount of anti isomer. Control experiments indicated this variation in ratio was due to the selective decomposition of the syn isomer.

In conclusion, we have been able to accomplish an "aldol" condensation reaction between aldehydes and the methyl vinyl ketone–phosphite adduct, **6**, under *neutral conditions* to produce β-hydroxy α-phosphonomethyl

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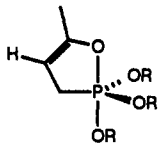
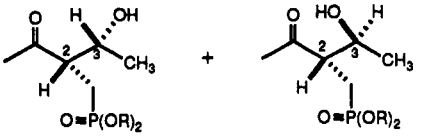
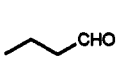
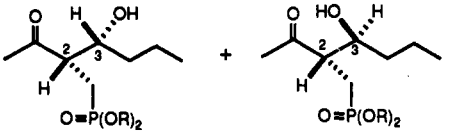
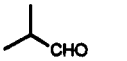
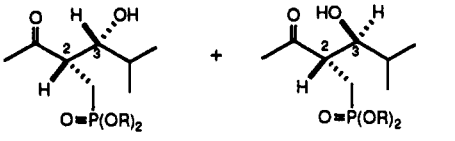
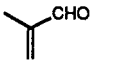
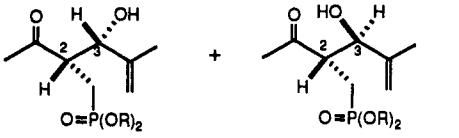
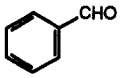
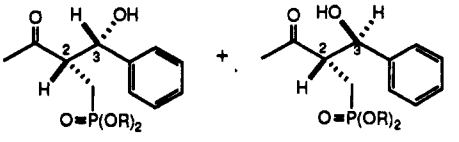
Table I. Products and Diastereomer Ratios from the Condensation of the Phospholenes 6a and 6b with Various Aldehydes[a]

phospholene	aldehyde	phosphonates	ratio[b] syn:anti	yield,[c] %
 **6a**: R=Et **6b**: R=i-Pr	CH_3CHO[d]	 **8**: 2,3-*syn* + **9**: 2,3-*anti*	**a**: R = Et 1.3:1 **b**: R = i-Pr 1.9:1	61 69
6a: R=Et **6b**: R=i-Pr		 **10**: 2,3-*syn* + **11**: 2,3-*anti*	**a**: R = Et 1.4:1 **b**: R = i-Pr 1.7:1	64 74
6a: R=Et **6b**: R=i-Pr		 **12**: 2,3-*syn* + **13**: 2,3-*anti*	**a**: R = Et 2.3:1 **b**: R = i-Pr 3.5:1	65[e] 69
6a: R=Et **6b**: R=i-Pr		 **14**: 2,3-*syn* + **15**: 2,3-*anti*	**a**: R = Et 1.6:1 **b**: R = i-Pr 1.6:1	64 71
6a: R=Et **6b**: R=i-Pr		 **16**: 2,3-*syn* + **17**: 2,3-*anti*	**a**: R = Et 2.0:1[f] **b**: R = i-Pr 4.9:1[f]	78 82[e]

[a] All reactions were run neat at ambient temperature, except for the condensation with acetaldehyde, which was performed at 0 °C. [b] Except where noted, ratios were determined by the separation and isolation of the isomers by HPLC. [c] Yields are not optimized. [d] Condensations were performed at 0 °C. [e] Yields are from reactions run in CH_2Cl_2 at 40 °C. [f] Ratios were determined by ^1H NMR integration of the semipurified (silica gel plug) hydrolysis product.

compounds. We are currently investigating the effects of other phosphites and enones, as well as spiro P^V compounds, on the ratio of the condensation products.

Experimental Section

General. All phosphites were treated with sodium prior to distillation. Methyl vinyl ketone was treated with solid K_2CO_3 and $CaCl_2$ prior to distillation. Benzaldehyde was washed with 5 M aquoues NaOH, saturated Na_2SO_3 and water, followed by drying with $CaCl_2$ and distillation under reduced pressure. Butyraldehyde was distilled under nitrogen after drying with $CaCl_2$. Acetaldehyde, acrolein, and isobutyraldehyde were distilled directly before use. Acetaldehyde was treated with solid K_2CO_3 prior to distillation. Acrolein and isobutyraldehyde were dried with anhydrous $CaSO_4$ before distillation under nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone. Dichloromethane and acetonitrile were distilled from calcium hydride. Chloroform was distilled from P_2O_5 under nitrogen. All reactions were carried out under a dry nitrogen or argon atmosphere in flame-dried one- or two-necked round-bottom flasks.

Proton, carbon, and phosphorus NMR spectra were obtained on a 250-MHz spectrometer as solutions in $CDCl_3$. Carbon signals were obtained from normal ^{13}C spectra and supported by an INEPT pulse sequence. ^{31}P chemical shifts are reported in ppm downfield from H_3PO_4. Mass spectra were obtained from a VG 70-70F mass spectrometer. Melting points are uncorrected. Column chromatography was performed on Kiesel Gel 60 PF_{254} using a step gradient of CH_3OH in CH_2Cl_2. The solvent mixtures used for column chromatography were volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250 M analytical plates coated with silica gel GF. High-pressure liquid chromatography was done on a Rainin Dynamax-60A semipreparative silica gel column.

General Experimental Procedure. To the oxaphospholene, **6** (1 mmol), in a flame-dried flask under argon was added the freshly distilled aldehyde (1.2–1.5 mmol). The reaction mixture was stirred at ambient temperature (0 °C for the reactions with acetaldehyde) and monitored by ^1H NMR spectroscopy. For the reactions performed in a solvent, the oxaphospholene was diluted with solvent prior to addition of the aldehyde. The reaction mixture was then heated to 40 °C and monitored as above. For the Lewis acid catalyzed reactions, the requisite Lewis acid (1 mol %) was added to the reaction mixture either prior to or just after aldehyde addition. After disappearance of the oxaphospholene, the reaction mixture was brought to ambient temperature, and water (10 mmol) was added. The mixture was allowed to stir for 6–10 h, and the products were extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. After initial purification via column chromatography (SiO_2 plug) to remove high R_f and base-line materials, the product diastereomers were separated via semipreparative HPLC.

Preparation of 2,2,2-Triethoxy-2,2-dihydro-5-methyl-1,2λ⁵-oxaphospholene (6a). A neat mixture of distilled methyl vinyl ketone (2.0 g, 28.53 mmol) and triethylphosphite (4.7 g, 28.53 mmol) was allowed to stir for 3 days at room temperature. Unreacted triethylphosphite was removed under vacuum at 55 °C (12 mmHg). The residual liquid was distilled bulb-to-bulb (37 °C (0.32 mmHg)) to give product (4.6 g, 19.69 mmol, 69% yield) as a clear oil. ^1H NMR: δ 4.52 (1 H, dm, J_{P-H} = 42.1 Hz), 3.92

(6 H, m), 2.53 (2 H, dm, J_{P-H} = 16.9 Hz), 1.82 (3 H, br s), 1.21 (9 H, td, J = 7.3, 2.8 Hz). ^{13}C NMR: δ 151.5 (d, J_{P-C} = 16.3 Hz), 90.4 (d, J_{P-C} = 5.8 Hz), 62.0 (d, J_{P-C} = 10.4 Hz), 29.0 (d, J_{P-C} = 160.4 Hz), 16.5 (d, J_{P-C} = 7.1 Hz), 16.3 (d, J_{P-C} = 4.6 Hz). ^{31}P NMR: -22.1 ppm. IR: 1673, 1452, 1312, 1181, 1089, 1048 cm^{-1}.

Preparation of 2,2,2-Triisopropoxy-2,2-dihydro-5-methyl-1,2λ⁵-oxaphospholene (6b). Preparation of this compound was carried out as for **6a** above using triisopropylphosphite (2.0 g, 9.76 mmol) and methyl vinyl ketone (0.7 g, 9.98 mmol). It was distilled bulb-to-bulb (46 °C (0.32 mmHg)) to give pure product (2.2 g, 82% yield) as a clear oil. ^1H NMR: δ 4.53 (1 H, dm, J_{P-H} = 42.2 Hz), 4.42 (3 H, m), 2.53 (2 H, dm, J_{P-H} = 16.3 Hz), 1.72 (3 H, br s), 1.21 (18 H, d, J_{P-H} = 12.7 Hz). ^{13}C NMR: δ 151.8 (d, J_{P-C} = 16.7 Hz), 90.2 (d, J_{P-C} = 5.9 Hz), 68.4 (d, J_{P-C} = 10.9 Hz), 30.0 (d, J_{P-C} = 161.9 Hz), 24.0 (d, J_{P-C} = 5.3 Hz), 16.8 (d, J_{P-C} = 4.1 Hz). ^{31}P NMR: -24.8 ppm. IR: 1675, 1460, 1314, 1186, 1093, 1047, 987 cm^{-1}.

Preparation of Diethyl [(2*R,3*S**)-2-(1-Oxoethyl)-3-hydroxybutyl]phosphonate (8a) and Diethyl [(2*R**,3*R**)-2-(1-Oxoethyl)-3-hydroxybutyl]phosphonate (9a).** This reaction was carried out as for the general preparation above using **6a** (200 mg, 0.85 mmol) and acetaldehyde (38 mg, 0.85 mmol). Separation of the isomers via HPLC (2% $MeOH/CH_2Cl_2$) yielded 74 mg of **8a** and 57 mg of **9a** as oils (61% yield, syn:anti = 1.3:1.0 by weight). R_f (**8a** or **9a**, 5% $MeOH/CH_2Cl_2$) = 0.43. **8a** (syn). ^1H NMR: δ 4.12 (5 H, m), 3.81 (1 H, br s), 3.21 (1 H, m), 2.28 (3 H, s), 2.21–1.81 (2 H, m), 1.32 (6 H, t, J = 7.1 Hz), 1.15 (3 H, d, J = 6.4 Hz). ^{13}C NMR: δ 209.7, 68.0 (d, J_{P-C} = 15.2 Hz), 61.8 (d, J_{P-C} = 5.9 Hz), 61.6 (d, J_{P-C} = 4.6 Hz), 52.9, 31.4, 24.0 (d, J_{P-C} = 142.6 Hz), 19.9, 16.1 (d, J_{P-C} = 6.0 Hz). ^{31}P NMR: +31.7 ppm. IR: 3393, 2981, 1713, 1231, 1050, 1031 cm^{-1}. Exact mass calcd for $C_{10}H_{21}O_5P$ $(M)^+$ 252.11253, found 252.1114. **9a** (anti). ^1H NMR: δ 4.11 (5 H, m), 3.62 (1 H, br s), 3.01 (1 H, m), 2.31 (3 H, s), 2.23–1.82 (2 H, m), 1.31 (6 H, t, J = 7.1 Hz), 1.18 (3 H, d, J = 6.4 Hz). ^{13}C NMR: δ 209.6, 67.8 (d, J_{P-C} = 14.8 Hz), 61.6 (d, J_{P-C} = 4.4 Hz), 61.5 (d, J_{P-C} = 3.9 Hz), 53.0, 31.4, 23.0 (d, J_{P-C} = 142.4 Hz), 20.2, 16.0 (d, J_{P-C} = 6.0 Hz). ^{31}P NMR: +31.9 ppm. IR: 3393, 2981, 1713, 1231, 1050, 1031 cm^{-1}. Exact mass calcd for $C_{10}H_{21}O_5P$ $(M)^+$ 252.11253, found 252.1114.

Preparation of Diethyl [(2*R,3*S**)-2-(1-Oxoethyl)-3-hydroxyhexyl]phosphonate (10a) and Diethyl [(2*R**,3*R**)-2-(1-Oxoethyl)-3-hydroxyhexyl]phosphonate (11a).** This reaction was carried out as for the general preparation above using **6a** (290 mg, 1.23 mmol) and butyraldehyde (89 mg, 1.23 mmol). Separation of the isomers via HPLC (2% $MeOH/CH_2Cl_2$) yielded 129 mg of **10a** and 92 mg of **11a** as oils (64% yield, syn:anti = 1.4:1.0 by weight). R_f (**10a** or **11a**, 5% $MeOH/CH_2Cl_2$) = 0.38. **10a** (syn). ^1H NMR: δ 4.12 (4 H, m), 3.75 (1 H, m), 3.01 (1 H, m), 2.32 (3 H, s), 2.11 (2 H, m), 1.42 (4 H, m), 1.32 (6 H, t, J = 7.1 Hz), 0.93 (3 H, t, J = 6.8 Hz). ^{13}C NMR: δ 209.9 (d, J_{P-C} = 3.1 Hz), 71.2 (d, J_{P-C} = 13.7 Hz), 61.6 (d, J_{P-C} = 6.4 Hz), 61.5 (d, J_{P-C} = 6.1 Hz), 51.9 (d, J_{P-C} = 3.3 Hz), 36.4, 30.9, 22.5 (d, J_{P-C} = 142.3 Hz), 18.9, 16.1 (d, J_{P-C} = 6.0 Hz), 13.6. ^{31}P NMR: +31.7 ppm. IR: 3360, 2981, 1713, 1237, 1051, 1027 cm^{-1}. Exact mass calcd for $C_{12}H_{25}O_5P$ $(M - H_2O)^+$ 262.1283, found 262.1333; calcd for $(M - C_3H_7)^+$ 237.0890, found 237.0885. **11a** (anti). ^1H NMR: δ 4.11 (4 H, m), 3.74 (1 H, m), 3.12 (1 H, m), 2.25 (3 H, s), 2.12 (2 H, m), 1.51 (4 H, m), 1.32 (6 H, t, J = 7.1 Hz), 0.92 (3 H, t, J = 6.8 Hz). ^{13}C NMR: δ 210.5 (d, J_{P-C} = 5.4 Hz), 72.7 (d, J_{P-C} = 13.9 Hz), 61.6 (d, J_{P-C} = 6.4 Hz), 61.4 (d, J_{P-C} = 6.1 Hz), 51.7 (d, J_{P-C} = 2.9 Hz), 36.2, 31.6, 23.5 (d, J_{P-C} = 141.0 Hz), 18.8, 16.1 (d, J_{P-C} = 6.0 Hz), 13.6. ^{31}P NMR: +31.3 ppm. IR: 3360, 2981, 1713, 1237, 1051, 1027 cm^{-1}. Exact mass calcd for $C_{12}H_{25}O_5P$ $(M - H_2O)^+$ 262.1283, found 262.1333; calcd for $(M - C_3H_7)^+$ 237.0890, found 237.0885.

Preparation of Diethyl [(2*R,3*S**)-2-(1-Oxoethyl)-3-hydroxy-4-methylpentyl]phosphonate (12a) and Diethyl [(2*R**,3*R**)-2-(1-Oxoethyl)-3-hydroxy-4-methylpentyl]phosphonate (13a).** This reaction was carried out as for the general preparation above using **6a** (220 mg, 0.93 mmol) and isobutyraldehyde (67 mg, 0.93 mmol). Separation of the isomers via HPLC (2% $MeOH/CH_2Cl_2$) yielded 108 mg of **12a** and 47 mg of **13a** as oils (59% yield, syn:anti = 2.3:1.0 by weight). R_f (**12a** or **13a**, 5% $MeOH/CH_2Cl_2$) = 0.33. **12a** (syn). ^1H NMR: δ 4.12 (4 H, m), 3.42 (1 H, m), 3.15 (1 H, m), 2.72 (1 H, d, J = 4.5 Hz), 2.32 (3 H, s), 2.11 (2 H, m), 1.65 (1 H, m), 1.32 (6 H, td, J = 7.0, 2.5 Hz), 1.05 (3 H, d, J = 6.8 Hz), 0.95 (3 H, d, J = 6.8 Hz). ^{13}C NMR: δ 210.2, 76.2 (d, J_{P-C} = 12.9 Hz), 61.9 (d, J_{P-C} = 6.4 Hz), 61.7 (d, J_{P-C} = 6.4 Hz), 49.2 (d, J_{P-C} = 2.9 Hz), 31.0, 22.1 (d, J_{P-C} = 142.6 Hz), 19.2, 18.0, 16.2 (d, J_{P-C} = 6.1 Hz). ^{31}P NMR: +32.4 ppm. IR: 3378, 2971, 1715, 1232, 1054, 1029 cm^{-1}. Exact mass calcd for $C_{12}H_{25}O_5P$ $(M - C_3H_7)^+$ 237.0923, found 237.0885. **13a** (anti). ^1H NMR: δ 4.12 (4 H, m), 3.41 (1 H, m), 3.22 (1 H, m), 2.61 (1 H, br s), 2.32 (3 H, s), 2.11 (2 H, m), 1.72 (1 H, m), 1.32 (6 H, td, J = 7.0, 2.5 Hz), 1.01 (3 H, d, J = 6.8 Hz), 0.92 (3 H, d, J = 6.8 Hz). ^{13}C NMR: δ 210.2, 78.6 (d, J_{P-C} = 14.9 Hz), 61.9 (d, J_{P-C} = 6.4 Hz), 61.7 (d, J_{P-C} = 6.4 Hz), 48.3 (d, J_{P-C} = 2.87 Hz), 30.1, 25.2 (d, J_{P-C} = 142.3 Hz), 19.5, 17.0, 16.2 (d, J_{P-C} = 6.1 Hz). ^{31}P NMR: 30.6 ppm. IR: 3378, 2971, 1715, 1232, 1054, 1029 cm^{-1}. Exact mass calcd for $C_{12}H_{25}O_5P$ $(M - C_3H_7)^+$ 237.0923, found 237.0885.

Preparation of Diethyl [(2*R,3*S**)-2-(1-Oxoethyl)-3-hydroxy-4-methylpentenyl]phosphonate (14a) and Diethyl [(2*R**,3*R**)-2-(1-Oxoethyl)-3-hydroxy-4-methylpentenyl]phosphonate (15a).** This reaction was carried out as for the general preparation above using **6a** (280 mg, 1.18 mmol) and methacrolein (165 mg, 2.36 mmol). Separation of the isomers via HPLC (2% $MeOH/CH_2Cl_2$) yielded 130 mg of **14a** and 81 mg of **15a** as oils (64% yield, syn:anti = 1.6:1.0 by weight). The anti isomer **15a** solidified upon cooling and was recrystallized from hexane. R_f (**14a** or **15a**, 5% $MeOH/CH_2Cl_2$) = 0.4. **14a** (syn). ^1H NMR: δ 5.05 (2 H, br d, J_{P-H} = 18.9 Hz), 4.27 (1 H, d, J = 3.9 Hz), 4.05 (4 H, m), 3.11 (1 H, m), 2.28 (3 H, s), 2.25–1.85 (2 H, m), 1.75 (3 H, s), 1.25 (6 H, td, J = 7.0, 1.9 Hz). ^{13}C NMR: δ 209.7, 143.5, 113.2, 74.5 (d, J_{P-C} = 13.7 Hz), 61.9 (d, J_{P-C} = 6.2 Hz), 61.7 (d, J_{P-C} = 6.2 Hz), 49.2 (d, J_{P-C} = 2.6 Hz), 30.5, 21.5 (d, J_{P-C} = 142.7 Hz), 18.7, 16.3 (d, J_{P-C} = 6.0 Hz). ^{31}P NMR: +32.0 ppm. IR: 3351, 2981, 1713, 1643, 1443, 1231, 1050, 1025 cm^{-1}. Exact mass calcd for $C_{12}H_{23}O_5P$ $(M)^+$ 278.1281, found 278.1265. **15a** (anti). ^1H NMR: δ 4.95 (2 H, br s), 4.12 (5 H, m), 3.12 (1 H, m), 2.31 (3 H, s), 2.32–1.61 (2 H, m), 1.72 (3 H, s), 1.28 (6 H, td, J = 7.0, 3.6 Hz). ^{13}C NMR: δ 211.1, 144.4, 114.8, 78.8 (d, J_{P-C} = 18.9 Hz), 61.9 (d, J_{P-C} = 6.2 Hz), 61.7 (d, J_{P-C} = 6.5 Hz), 48.2 (d, J_{P-C} = 2.5 Hz), 33.0, 25.5 (d, J_{P-C} = 142.8 Hz), 16.9, 16.2 (d, J_{P-C} = 5.8 Hz). ^{31}P NMR: 30.2 ppm. Mp: 52–53 °C. IR: 3351, 2981, 1713, 1643, 1443, 1231, 1050, 1025 cm^{-1}. Exact mass calcd for $C_{12}H_{23}O_5P$ $(M)^+$ 278.1281, found 278.1265.

Preparation of Diethyl [(2*R)-2-[1(*S**)-Hydroxyphenyl]-3-oxobutyl]phosphonate (16a) and Diethyl [(2*R**)-2-[1(*R**)-Hydroxyphenyl]-3-oxobutyl]phosphonate (17a).** This reaction was carried out as for the general preparation above using **6a** (440 mg, 1.86 mmol) and benzaldehyde (197 mg, 1.86 mmol). The crude product mixture was purified by column chromatography with 2% $MeOH/CH_2Cl_2$ to give an oil as a mixture of diastereomers (460 mg, 1.46 mmol, 78% yield, syn:anti = 2.0:1.0 by ^1H NMR integration). The oil solified upon cooling and was recrystallized from hexane. The pure syn aldol product was collected by washing the recrystallized solid with 50% ethyl acetate/hexane. R_f (**16a** or **17a**, 5% $MeOH/CH_2Cl_2$) = 0.51. **16a** (syn). ^1H NMR: δ 7.31 (5 H, m), 4.81 (1 H, dd, J = 3.2, 3.0 Hz), 4.01 (4 H, m), 3.21 (1 H, m), 3.12 (1 H, d, J = 3.2 Hz), 2.21 (2 H, m), 1.91 (3 H, s), 1.21 (6 H, t, J = 7.1 Hz); ^{13}C NMR: δ 209.8 (d, J_{P-C} = 1.5 Hz), 141.1, 128.4, 127.8, 126.2, 74.1 (d, J_{P-C} = 15.8 Hz), 61.8 (d, J_{P-C} = 14.1 Hz) 61.6 (d, J_{P-C} = 6.3 Hz), 54.2 (d, J_{P-C} = 3.0 Hz), 31.2, 23.0 (d, J_{P-C} = 141.3 Hz), 16.1 (d, J_{P-C} = 6.4 Hz). ^{31}P NMR: +31.4 ppm. Mp: 69–70 °C. IR: 3342, 2978, 1712, 1458, 1236, 1035 cm^{-1}. Exact mass calcd for $C_{15}H_{23}O_5P$ $(M)^+$ 314.1277, found 314.1264. **17a** (anti). ^1H NMR: δ 7.30 (5 H, m), 4.71 (1 H, d, J = 8.1 Hz), 3.95 (4 H, m), 3.22 (1 H, m), 3.41 (1 H, br s), 2.21–2.01 (1 H, m), 1.61–1.41 (1 H, m), 2.21 (3 H, s), 1.22 (6 H, t, J = 7.1 Hz). ^{13}C NMR: δ 210.7, 141.7, 128.3, 127.9, 126.4, 76.5 (d, J_{P-C} = 19.3 Hz), 61.8 (d, J_{P-C} = 14.1 Hz), 61.6 (d, J_{P-C} = 6.3 Hz), 52.4 (d, J_{P-C} = 3.04 Hz), 32.7, 25.1 (d, J_{P-C} = 141.8 Hz), 16.1 (d, J_{P-C} = 6.4 Hz). ^{31}P NMR: +30.1 ppm. IR: 3342, 2978, 1713, 1458, 1236, 1035 cm^{-1}. Exact mass calcd for $C_{15}H_{23}O_5P$ $(M)^+$ 314.1277, found 314.1264.

Preparation of Diisopropyl [(2*R)-2-[1(*S**)-Hydroxyphenyl]-3-oxobutyl]phosphonate (16b) and Diisopropyl [(2*R**)-2-[1(*R**)-Hydroxyphenyl]-3-oxobutyl]phosphonate (17b).** This reaction was carried out as for the general preparation above using **6b** (220 mg, 0.79 mmol) and benzaldehyde (84 mg, 0.79 mmol). The pure oil (187 mg, 0.55 mmol, 69% yield, syn:anti

= 4.9:1.0 by ^{1}H NMR integration) solidified at -30 °C after purification by column chromatography (2% MeOH/CH_2Cl_2) and was recrystallized from hexane. Washing the pure solid with 50% ethyl acetate/hexane gave pure syn aldol product. R_f (5% MeOH/CH_2Cl_2) = 0.4 **16b** (syn). ^{1}H NMR: δ 7.31 (5 H, m), 4.72 (1 H, d, J = 6.6 Hz), 4.55 (2 H, m), 3.73 (1 H, br s), 3.24 (1 H, m), 2.12 (2 H, m), 1.94 (3 H, s), 1.12 (12 H, m). ^{13}C NMR: δ 209.9, 141.7, 128.4, 127.8, 126.4, 74.2 (d, J_{P-C} = 14.9 Hz), 70.6 (d, J_{P-C} = 6.8 Hz), 70.5 (d, J_{P-C} = 6.3 Hz), 54.4 (d, J_{P-C} = 3.2 Hz), 31.5, 25.0 (d, J_{P-C} = 143.1 Hz). ^{31}P NMR: +29.5 ppm. Mp: 74-77 °C. IR: 3331, 2981, 1713, 1456, 1387, 1231, 1012, 988 cm^{-1}. Exact mass calcd for $C_{17}H_{27}O_5P$ $(M)^+$ 342.1594, found 342.1633. **17b** (anti). ^{1}H NMR: δ 7.32 (5 H, m), 4.64 (1 H, d, J = 7.2 Hz), 4.53 (2 H, m), 3.12 (1 H, m), 2.12 (2 H, m), 2.24 (3 H, s), 1.13 (12 H, m). ^{13}C NMR: δ 210.8, 141.8, 128.5, 128, 126.5, 76.6 (d, J_{P-C} = 14.6 Hz), 70.6 (d, J_{P-C} = 6.7 Hz), 70.4 (d, J_{P-C} = 6.3 Hz), 52.7 (d, J_{P-C} = 3.0 Hz), 32.9, 26.5 (d, J_{P-C} = 143.7 Hz). ^{31}P NMR: +28.0 ppm. IR: 3331, 2981, 1713, 1456, 1387, 1231, 1012, 988 cm^{-1}. Exact mass calcd for $C_{17}H_{27}O_5P$ $(M)^+$ 342.1594, found 342.1633.

Preparation of Diethyl (3-Oxobutyl)phosphonate (7a). To the neat oxaphospholene **6a** (220 mg, 0.93 mmol) was added excess water (5 equiv) to produce an exothermic reaction. This reaction mixture was allowed to stir for 5 h at room temperature. The crude products were extracted with CH_2Cl_2 and purified by chromatography with 1% MeOH/CH_2Cl_2 to give a clear oil (180 mg, 0.87 mmol, 93% yield). R_f (5% MeOH/CH_2Cl_2) = 0.53. ^{1}H NMR: δ 4.12 (4 H, m), 2.75 (2 H, m), 2.23 (3 H, s), 2.01 (2 H, m), 1.32 (6 H, t, J = 7.1 Hz). ^{13}C NMR: δ 204.5 (d, J_{P-C} = 14.6 Hz), 60.5 (d, J_{P-C} = 6.4 Hz), 35.2 (d, J_{P-C} = 3.7 Hz), 28.6, 18.5 (d, J_{P-C} = 144.5 Hz), 15.5 (d, J_{P-C} = 5.9 Hz). ^{31}P NMR: +32.1 ppm. IR: 1723, 1238, 1059, 1023, 960 cm^{-1}. Exact mass calcd for $C_8H_{17}O_4P$ $(M)^+$ 208.0865, found 208.0874.

Preparation of Diisopropyl (3-Oxobutyl)phosphonate (7b). The hydrolysis of the oxaphospholene **6b** (210 mg, 0.75 mmol) was performed as described for **6a**. The crude products were extracted with CH_2Cl_2 and purified by chromatography with 1% MeOH/CH_2Cl_2 to give a clear oil (162 mg, 0.69 mmol, 92% yield). R_f (5% MeOH/CH_2Cl_2) = 0.54. ^{1}H NMR: δ 4.69 (2 H, m), 2.72 (2 H, m), 2.18 (3 H, s), 1.96 (2 H, m), 1.32 (12 H, t, J = 6.2 Hz). ^{13}C NMR: δ 205.8 (d, J_{P-C} = 15.7 Hz), 70.1 (d, J_{P-C} = 6.4 Hz), 36.5 (d, J_{P-C} = 3.6 Hz), 29.5, 23.9 (d, J_{P-C} = 3.5 Hz), 20.8 (d, J_{P-C} = 146.0 Hz). ^{31}P NMR: +30.2 ppm. IR: 1717, 1237, 1010, 993 cm^{-1}. Exact mass calcd for $C_{10}H_{21}O_4P$ $(M)^+$ 236.1176, found 236.1177.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all compounds (32 pages). Ordering information is given on any current masthead page.

5-Nitro-3-(methoxymethyl)indole from the Cyanation of 5-Nitrogramine: Mechanistic Implications

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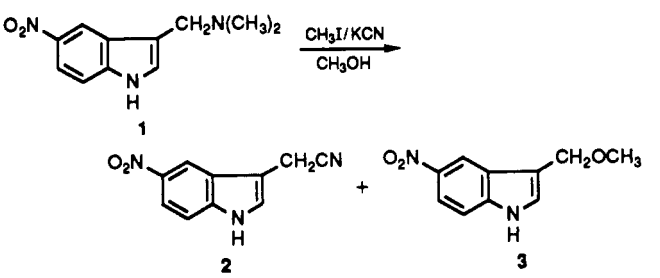
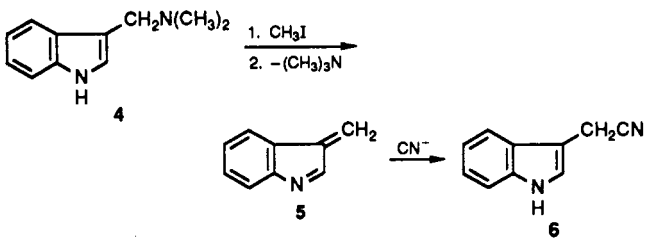
The cyanation of 5-substituted 1*H*-gramines forms 5-substituted indole-3-acetonitriles.[1] These are intermediates in the preparation of 5-substituted analogues of the pineal gland hormone melatonin which we were preparing for testing as potential cell mitosis inhibitors. During the preparation of 5-nitroindole-3-acetonitrile (**2**, Scheme I), an unexpected byproduct was isolated by soxhlet extraction of the crude product mixture with hexane. Infrared and NMR spectra confirmed the structure as 5-nitro-3-(methoxymethyl)indole (**3**). The proton NMR was most useful, showing a singlet for three protons at 3.35 ppm for the methyl group, a singlet for two protons at 4.65 ppm for the 3-indolyl methylene group, four aromatic protons scattered over the range 7.3-8.5 ppm, and a broad singlet for the amine proton at 11.3 ppm.

Scheme I



Scheme II



In 1952, Geissman and Armen[2] showed that such a compound as **3** came only from the direct involvement of a methoxide nucleophile rather than methylation of an intermediate 3-(hydroxymethyl)indole. Thus, in our mixture, compound **3** can only result from incidental reaction of a gramine intermediate with methanol as the nucleophile instead of cyanide ion. Thin-layer chromatography (TLC) has also indicated the presence of similar impurities in the crude product mixtures of the 5-bromo and 5-iodo analogues.

Compound **3** was unambiguously prepared by the reaction of 5-nitrogramine with methyl iodide and sodium methoxide in methanol.[2] To preclude the possibility that methanol itself was a strong enough base or nucleophile to initiate the reaction, a mixture of all reactants, except for methoxide ion, was stirred at room temperature for 48 h. TLC showed no reaction. Upon the addition of sodium methoxide the reaction proceeded to completion within 2 h. TLC samples were also taken at various stages in both the reaction and the normal workup sequence in order to determine just where the byproduct first appeared and was subsequently eliminated. With all other reactants present, the impurity was evident almost immediately after the addition of methyl iodide. It was effectively removed by washing the evaporate of the crude reaction mixture with either methanol or ether and water.

While examining the accepted mechanism of gramine alkylation, we realized that our finding presented an opportunity to highlight what appeared to be the last remaining detail of that mechanism. Work by several investigators[3-5] over 30 years ago showed that 1*H*-gramines

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