intensity) 428 (50, M^+), 412 (99), 411 (100), 396 (75), 381 (85), 365 (80). Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.79; H, 5.66; N, 6.29.

22,22-Dimethyl-17,27-dioxa-40,41-diazaheptacyclo-[27.2.2.2^{12,15}.2^{18,21}.2^{23,26}.1^{2,6}.1^{7,11}]hentetraconta-2,4,6(41),7,9,11-(40),12,14,18,20,23,25,29,31,32,34,36,38-octadecaene 40,41-Dioxide (7). Diether dioxide **5** was converted to the dibromide **6** by using the procedure described for **2**. The crude product, isolated in 94% yield, was used without purification. The cyclization of **6** to form **7** was carried out in a manner analogous to the preparation of **3**, except the dibromide–bis(phenol) solution did not contain $(CH_2)_4O$. Chromatographic purification was accomplished by eluting the product from the silica gel column with 0–10% EtOH in EtOAc. The yield from 225 mg of **6** was 59 mg (23%) of light yellow solid, which was the monohydrate of **7**: mp 160–290 °C (gradual decomposition); ^{1}H NMR (50:50 CD_3CN–$CDCl_3$, v/v) δ 1.51 (s, 6, CH_3), 5.18 (s, 4, CH_2O), 6.67 and 7.01 (AB q, 8, J = 8.8 Hz, PhCPh), 7.5 (m, 14, ArH); MS, m/e (relative intensity) 592 (25, M^+), 577 (30) , 545 (45), 320 (100), 212 (55), 166 (95). Anal. Calcd for $C_{39}H_{32}N_2O_4{\cdot}H_2O$: C, 76.70; H, 5.61; N, 4.59. Found: C, 76.92; H, 5.60; N, 4.62. The ^{1}H NMR spectrum recorded in $CDCl_3$ displayed an AB quartet at 5.12 and 5.20 ppm (J = 14 Hz) for the CH_2 protons.

4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine 1,1′-Dioxide (8). A solution of 4,4′-di-*tert*-butyl-2,2′-bipyridine[14] (1.0 g, 3.7 mmol) and *m*-chloroperbenzoic acid (2.6 g, 15 mmol) in 30 mL of CH_2Cl_2 was stirred for 48 h at ambient temperature, diluted to 50 mL with CH_2Cl_2 and washed with 50 mL of aqueous Na_2CO_3. The washings were extracted with 50 mL of CH_2Cl_2, and the combined organic layers were washed with 50 mL of additional Na_2CO_3 solution, dried, filtered, and concentrated to a yellow foam. This foam was chromatographed on 20 g of neutral alumina (Fisher, activity 1, 80–200 mesh), eluting with 0–5% MeOH in CH_2Cl_2, to yield 0.88 g (78%) of **8** as a foam: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 18, CH_3), 7.29 (d of d, 2, J_1 = 3 Hz, J_2 = 7 Hz, H-5,5′), 7.60 (d, 2, J_1 = 3 Hz, H-3,3′), 8.20 (d, 2, J_2 = 7 Hz, H-6,6′). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.01; H, 8.03; N, 9.28.

$MeSnCl_3$ Complex Formation with 5, 7, 8, and 9. Stock solutions of 2.00-mL total volume were prepared of each of the ligands and also of $MeSnCl_3$ (handled in an N_2-filled glovebag), in CD_3CN or 50:50 $CDCl_3$–CD_3CN (v/v). Aliquots of the stock solutions were combined to obtain experimental solutions of the compositions listed in Table I. The 90-MHz ^{1}H NMR spectra of the experimental solutions were recorded and were independent of the order in which the component stock solutions were introduced. No solid precipitation was observed.

Dehydrochlorination of 10 in the Presence of 5 and 7. Reactant solutions consisting of **10** (14.0 μL, 12.7 mg, 0.073 mmol), $BuSnCl_3$ (2.7 μL, 4.5 mg, 0.016 mmol), and C_6D_5Cl (0.40 mL) were prepared. Some of the solutions also contained **5** (7.4 mg, 0.017 mmol) or **7** (10.3 mg, 0.017 mmol), and these solutions were made homogeneous by gentle heating before the addition of **10** or $BuSnCl_3$. The reactant solutions were heated to 100 °C as quickly as possible (<5 min) in the probe of the NMR spectrometer, after which spectra were recorded at 10-min intervals. Conversion of the allylic chloride (2 olefinic H, 1 chloroallylic H) to a conjugated diene (4 olefinic H) was monitored by the increase in the ratio of olefinic to chloroallylic protons. Compounds **5** and **7** did not appear to decompose during the experiments.

Acknowledgment. We thank A. M. Mujsce for obtaining the mass spectra and S. L. Haynie for a sample of *trans*-4-chloro-5-decene. Helpful discussions with W. H. Starnes, Jr., are gratefully acknowledged.

Registry No. **1**, 95601-80-2; **2**, 95601-81-3; **3**, 95601-82-4; **4**, 95628-38-9; **5**, 96259-23-3; **5**·$MeSnCl_3$, 96292-57-8; **6**, 96259-25-5; **7**, 96259-24-4; **7**·$MeSnCl_3$, 96292-54-5; **8**, 96259-26-6; **8**·$MeSnCl_3$, 96292-55-6; **9**, 23569-17-7; **9**·2$MeSnCl_3$, 96292-56-7; **10**, 90370-35-7; $MeOCH_2$-*p*-C_6H_4MgBr, 96259-22-2; *p*-$BrC_6H_4CH_2OMe$, 1515-88-4; $(p\text{-}HOC_6H_4)_2C(CH_3)_2$, 80-05-7; $MeSnCl_3$, 993-16-8; (*E*,*E*)-$CH_3CH_2CH{=}CHCH{=}CH(CH_2)_3CH_3$, 92260-75-8; 6,6′-dibromo-2,2′-bipyridine, 49669-22-9; 2,6-bis(mercaptomethyl)naphthalene, 43012-09-5; 4,4′-di-*tert*-butyl-2,2′-bipyridine, 72914-19-3.

Intramolecular Nitrogen–Phosphorus Interactions of Phosphate Esters

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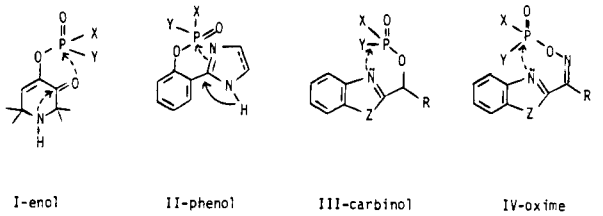
Four different classes of phosphate esters derived from enols, phenols, carbinols, and oximes have been shown to undergo intramolecular rearrangements assisted by a neighboring nitrogen. The unexpected products from these rearrangements have been characterized by spectral methods, especially ^{13}C NMR. Rearrangements involving the *O*-ethyl *S*-propyl thiophosphate group have led to particularly interesting results.

The reaction of phosphate esters with acetylcholinesterase is an important biological process in insect control. In this process, the imidazole group of histidine is assumed to be responsible for activation of the serine hydroxyl, which in turn displaces a ligand of the phosphate insecticide.[1a] An analogous rate acceleration by neighboring amide or amine functionalities in phosphate ester hydrolysis has been documented by several investigators.[1b–f] The implications of this type of intramolecular interaction on the preparation, stability, and biological activity of potential organophosphate insecticides containing a distal nitrogen have not been addressed.

Scheme I



(1) (a) Eto, M. "Organophosphorus Pesticide: Organic and Biological Chemistry", CRC Press: Cleveland, OH 1974; pp 123–144; (b) Sharma, R. K.; Vaidyanathaswamy, R. *J. Org. Chem.* **1982**, *47*, 1741. (c) Naylor, R. A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1908. (d) Kluger, R.; Chan, J. L. W. *J. Am. Chem. Soc.* **1976**, *98*, 4913. (e) Lazarus, R. A.; Benkovic, P. A.; Benkovic, S. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 373. (f) Lazarus, R. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 4300.

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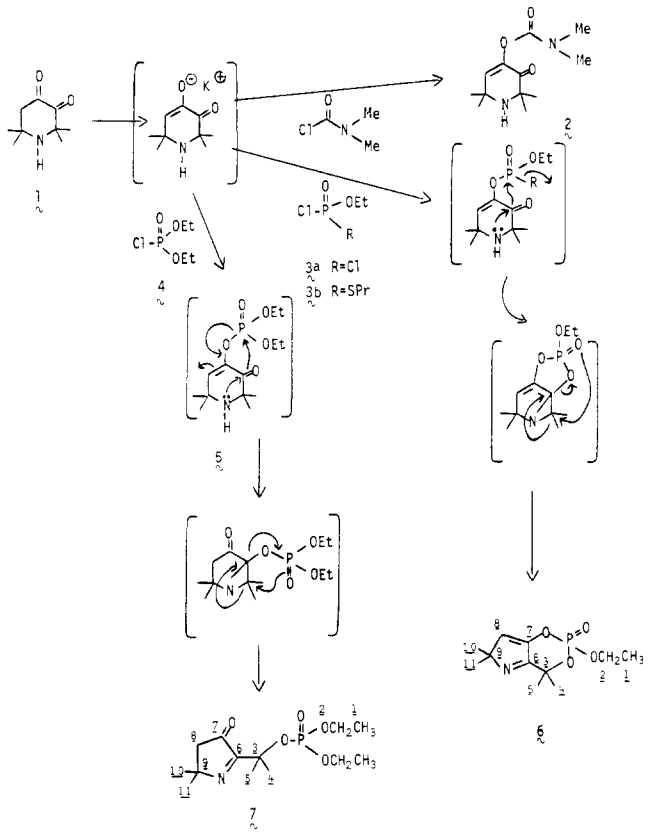
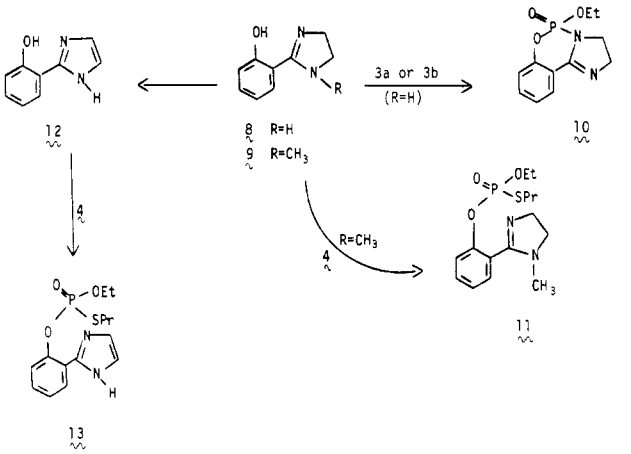
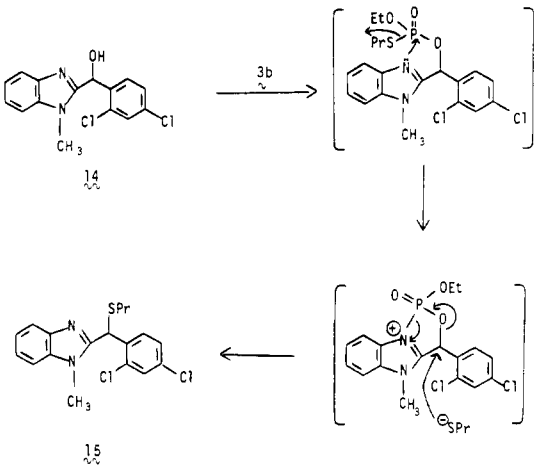
Scheme II



Scheme III



Scheme IV



In the course of studies on novel phosphate esters and thio esters, a number of rearrangements involving a nitrogen atom and having important synthetic consequences have been discovered. These results have also demonstrated some important reactivity differences between the standard diethyl phosphates and the more recently introduced *O*-ethyl *S*-propyl thiophosphates as exemplified by the commercial compound profenfos.

Intramolecular rearrangement promoted by neighboring nitrogen has been observed for phosphate esters and thio esters derived from enols (I), phenols (II), carbinols (III), and oximes (IV) (Scheme I). The extent of interaction is dependent on the nitrogen basicity and the spatial relationship of the involved nitrogen and phosphorus atoms. Although such an effect has been observed in the diethyl phosphate cases (X, Y = OEt), this interaction can be more clearly demonstrated in the thio ester analogues (X = OEt; Y = SPr).

Results

The phosphorylation of the potassium salt of 2,2,6,6-tetramethylpiperi-3,4-dione, **1**,[2] in the tetrahydrofuran produced an unexpected result because of an intramolecular nitrogen participation (Scheme II). When the anion of **1** generated by potassium *tert*-butoxide was quenched with dimethylcarbamoyl chloride, the expected carbamate, **2**, was isolated. When the same anion was quenched with chlorophosphates **3a** and **3b**, the cyclic phosphate **6** was the only phosphorus–piperidione adduct isolated from column chromatography (18% from **3a**, 10% from **3b**). The only other product isolated in sufficient quantity and purity to establish structural assignments was the starting material **1**.

A proposed mechanism for the formation of **6** is shown in Scheme II. The key as to which pathway is followed is determined by the leaving abilities of the phosphate ligands (i.e., Cl ≅ SPr > enol > OEt).

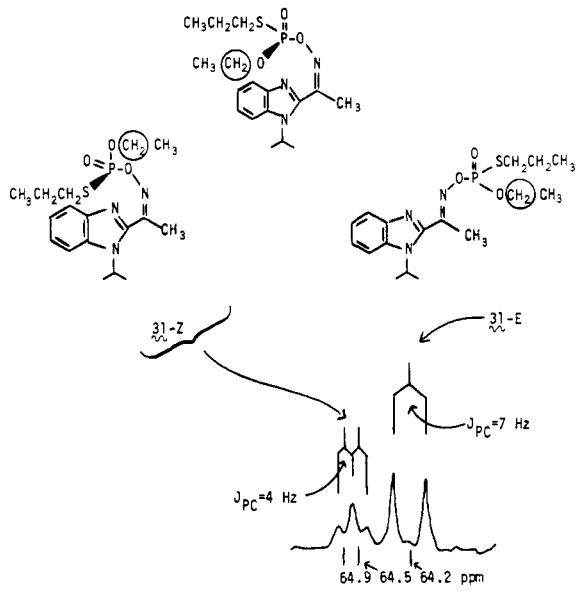
The structural assignment of **6** is based on spectral data. The three unexpected observations which needed to be accommodated by the proposed structure were (1) a lack of an SPr group in the NMR and ^{13}C NMR, (2) a lack of any strong carbonyl stretches in the IR, and (3) an unusually large upfield phosphorus shift in the ^{31}P NMR. Structure **6** addresses these observations and is consistant with all other spectral data, including the extensive phosphorus–carbon and phosphorus–hydrogen coupling, the UV extinction coefficient, and the elemental analysis. Attempts to obtain an X-ray crystal structure on the plate-like crystals which slowly formed in the freezer were unsuccessful.

Quenching of the anion of **1** with diethyl chlorophosphate, **4**, followed by column chromatography gave a 17% yield of compound **7**. Structure **7** was derived from a similar mechanism as previously presented for compound **6** but with the enol moiety acting as the leaving group. The key as to which pathway is followed is determined by the leaving abilities of the phosphate ligands (i.e., Cl ≅ SPR > enol > OEt). The ^{13}C NMR and IR of **7** were especially useful in assigning the proposed structure.

A direct interaction between the nitrogen and the phosphorus was demonstrated in area II and III (Scheme I). When *o*-(2-imidazolinyl)phenol **8**[3] was reacted with the phosphorochloridate **3b** in the presence of triethylamine, the compound isolated with the tricyclic phosphate **10** (Scheme III). Compound **10** was also prepared from ethyl dichlorophosphate **3a** to confirm the structure. The *N*-methyl analogue **9** was phosphorylated to give the product

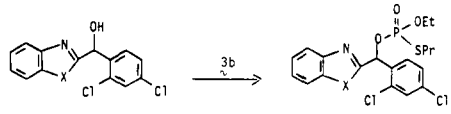
(2) Pilo-Veloso, D.; Rassat, A. *Bull. Chem. Soc. Fr.* **1978**, *11*–12, 621.

Scheme V



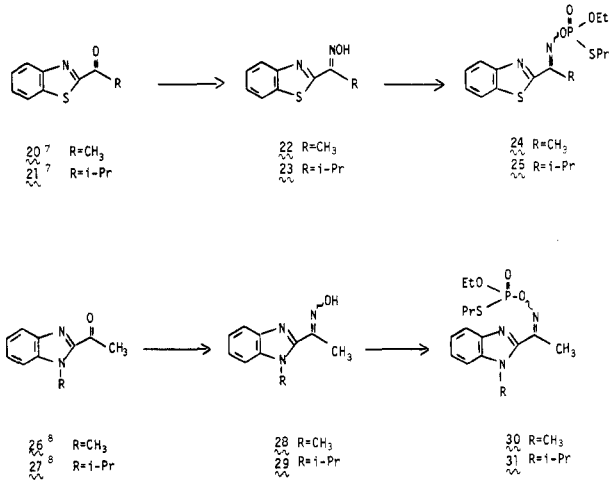
11. Oxidation of **8** to its imidazole analogue **12**[3] reduced the nucleophilicity of the nitrogen sufficiently to allow preparation of the phenyl thiophosphate **13**.

More surprising is the attempted phosphorylation of the benzimidazolylcarbinol **14** with **3b** (Scheme IV). Instead of the expected simple product of alcohol phosphorylation, the product isolated from the reaction mixture was the SPr adduct **15**. The postulated mechanism is depicted in Scheme IV. The instability of the carbinol phosphate is unique to the benzimidazole series because the phosphates derived from benzothiazole and benzoxazole **18** and **19**,



respectively, were easily formed. Again, as in the case of **8** vs. **12**, this is presumably from reduced basicity of the nitrogen interacting with the phosphate.

Finally, a more subtle interaction was observed in the oxime phosphate area IV. The oxime phosphates **24** and **25** were prepared via standard procedures. The phosphate



24 was obtained as a single *E* isomer (i.e., phosphate cis to CH_3; R = CH_3 single peak in NMR (δ 2.63) and ^{13}C NMR is consistent for one isomer). Compound **25** was a mixture of the *E* and *Z* isomers as indicated by the ^{13}C NMR spectrum. Especially diagnostic because of its separation from other peaks is the α-carbon of the POC-H_2CH_3 groups (for **25** two doublets; J_{PC} = 7 and 9 Hz). Based on our experience with **24**, one would have to expect **30** to be a single *E* isomer, however, ^{13}C NMR analysis indicated both *E* and *Z* isomers to be present. Furthermore, the *Z* isomer was resolved in the ^{13}C NMR spectrum into rotational isomers. The benzimidazole nitrogen apparently exerts sufficient influence on the phosphate to partially stabilize the *Z* isomer, and that interaction is sufficient to hinder rotation presumably around the P–O bond. The same argument holds for **31** as is diagrammed in Scheme V.

Conclusion

Three cases of intramolecular rearrangements of phosphate esters involving neighboring group participation by nitrogen have been presented. In a fourth case, the oxime phosphates, the interaction of nitrogen with the phosphate group, appears to exert a regioselective control over the course of the oxime phosphorylation of *O*-ethyl *S*-propyl chlorothiophosphate. The observed extent of neighboring group participation by nitrogen appears to be dependent on nitrogen basicity, steric strain, spatial relationships, and thermodynamic stability of the possible products. The intramolecular interaction of nitrogen and phosphorus as an influence on biological activity has yet to be demonstrated.

Experimental Section

All melting points are uncorrected. IR spectra were taken on a Perkin-Elmer Model 197 spectrometer. NMR spectra were obtained on a Varian EM-360 spectrometer at 60 MHz with $(CH_3)_4Si$ as an internal standard. ^{13}C NMR and ^{31}P NMR spectra were obtained on a JOEL FX-900 spectrometer with $(CH_3)_4Si$ as an internal standard for the ^{13}C NMR and H_3PO_4 as a standard for the ^{31}P spectra. C, H, and N elemental analyses were performed by either the Technical Center Analytical Group or Galbraith Analytical Laboratories.

General Procedure for the Preparation of Compounds 2, 6 and 7. An equivalent of 2,2,6,6-tetramethylpiperi-3,4-dione, **1**, was dissolved in THF under a nitrogen atmosphere. To this was added 1 equiv of potassium *tert*-butoxide. The mixture was refluxed for 2 h and cooled to 25 °C before 1 equiv of the appropriate phosphoryl or carbamoyl chloride was added dropwise as a THF solution. The reaction mixture was stirred at 25 °C overnight and worked up as follows.

Compound **2**: The general procedure described above using dimethylcarbamoyl chloride was followed. The final reaction mixture was filtered and concentrated in vacuo to give a yellow solid residue. Trituration with hexane gave a 45% yield of **2** as a white solid: mp 114–116 °C; NMR ($CDCl_3$) δ 7.16 (s, 1, vinyl), 4.33 (br s, 1, NH), 3.07 (s, 6, $N(CH_3)_2$), 1.53 (s, 6, *gem*-dimethyl), 1.35 (s, 6, *gem*-dimethyl); IR ($CHCl_3$) 3700–3200, 2998, 2950, 1735, 1385, 1170 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.97; H, 8.39; N, 11.66. Found: C, 59.89; H, 8.46; N, 11.57.

Compound **6**: The general procedure described above using either ethyl dichlorophosphate (**3a**) or *O*-ethyl *S*-propyl phosphorochloridate (**3b**) was followed. The reaction mixture was quenched with ether/H_2O and the layers were separated. The ether layer was washed with H_2O (2×) and the original H_2O layer was washed with ether (2×). The combined ether solutions were washed with 0.5 M NaOH (2×), saturated NaCl (1×), dried ($MgSO_4$), and concentrated in vacuo to give a brown liquid residue. This was chromatographed on a Florisil column (10% EtOAc–hexane → 35% EtOAc–hexane) to give compound **6** as a clear oil that slowly solidifies in the freezer (18% from **3a**, and 10% from **3b**): TLC single Fluorescent spot, R_f 0.17 (50:50 EtOAc/hexane on silica gel); mp 41–43 °C ($CDCl_3$); δ 6.57–6.40 (m, 1, CH, fine splitting), 4.17 (dq, 2, OCH; J_{PH} = 9 Hz), 1.76 (d, 6, $(CH_3)_2CO$, J_{PH} = 1.2 Hz), 1.35 (t, 3, OCH_2CH_3, J = 7 Hz), 1.35 (s, 6, $(CH_3)_2CN$); IR ($CHCl_3$) 3000, 1660, 1580, 1300, 1040, 1020, 1010 cm^{-1}; ^{31}P NMR ($CDCl_3$) δ (H_3PO_4) −12.1 ppm; mass spectrum (70

ev), *m/e* (relative intensity) 259 (18), 232 (13), 216 (36), 151 (56), 140 (14), 136 (15), 134 (15), 133 (35), 123 (100), 99 (40), 83 (46), 69 (72), 55 (74); UV (EtOH) 237 nm (ϵ 5037); ^{13}C NMR ($CDCl_3$) follows (numbering shown in Scheme II):

carbon	ppm	multiplicity decoupled	J_{PC}	multiplicity, off-resonance
7	165.9	d	9 Hz	d
6	142.7	d	5.5 Hz	d
8	135.2	d	8 Hz	dd
3	85.4	d	9 Hz	d
9	74.3	s		s
2	65.2	d	6 Hz	dt
4	28.7	d	5.5 Hz	dq
5	27.7	d	2.5 Hz	dq
10				
11	16.2	s		q
1	16.0	d	7 Hz	dq

Anal. Calcd for $C_{11}H_{18}NO_4P$: C, 50.96; H, 7.00; N, 5.40. Found: C, 51.41; H, 7.00; N, 5.13.

Compound 7: The general procedure described above using diethyl chlorophosphate (**4**) was followed. The reaction mixture was simply concentrated and purified by dry column chromatography on silica gel to give compound **7** (17% yield): TLC single spot, R_f 0.43 (80:20 EtOAc/hexane on silica gel); NMR ($CDCl_3$) δ 4.33–3.67 (m, 4, OCH_2), 2.37 (s, 2, CH_2), 1.73 (s, 6, *gem*-dimethyl), 1.57–1.07 (m, 12, OCH_2CH_3 and *gem*-dimethyl singlet at 1.37); IR (neat) 3700–3200, 2998, 1740, 1370, 1020 cm^{-1}; ^{13}C NMR ($CDCl_3$) (numbering shown in Scheme II):

carbon	ppm	multiplicity decoupled	J_{PC}	multiplicity off-resonance
7	201.5	s		s
6	170.1	d	5 Hz	d
3	80.2	d	7 Hz	d
9	64.6	s		s
2	63.7	d	6 Hz	dt
8	49.2	s		t
10				
11	30.9	s		q
4	28.9	s		q
5	26.6	d	5 Hz	dq
1	16.1	d	7 Hz	dq

Anal. Calcd for $C_{13}H_{24}NO_5P$: C, 51.14; H, 7.92; N, 4.59. Found: C, 50.95; H, 8.03; N, 4.48.

Standard Phosphorylation Procedure. The typical procedure for phosphorylation was to dissolve the alcohol, phenol, or oxime in either CH_2Cl_2 or toluene and add 1 equiv of TEA or 4-(dimethylamino)pyridine. To this solution was added, dropwise, 1 equiv of the chlorophosphate. The reaction mixture was stirred at 25 °C overnight, washed with H_2O and aqueous NaOH (if possible), dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified via chromatography.

Preparation of **10**: See the above standard phosphorylation procedure starting with the phenol 8[3] (2 equiv of TEA were used with **3a**): 44% yield; NMR ($CDCl_3$) δ 8.30–7.87 (m, 1, Ar), 7.83–6.93 (m, 3, Ar), 4.67–3.67 (m, 6), 1.37 (t, 3, OCH_2CH_3, J = 4 Hz); IR (CH_2Cl_2) 3540–2760, 1600, 1405, 1240, 1019 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 154.7 (d, J = 5 Hz), 151.7 (d, J = 7 Hz), 133.7 (d, J = 1 Hz), 128.3, 124.7, 118.6 (d, J = 12 Hz), 114.7 (d, J = 3 Hz), 65.0 (d, J = 7 Hz), 54.9 (d, J = 14 Hz), 44.9 (d, J = 4 Hz), 16.1 (d, J = 6 Hz). Anal. Calcd for $C_{11}H_{13}N_2O_3P{\cdot}H_2O$: C, 48.89; H, 5.60; N, 10.37. Found: C, 48.33; H, 5.56; N, 9.97.

Preparation of **11**: The standard phosphorylating procedure described above was used on compound **9**. Column chromatography purification gave **11** in 18% yield: NMR ($CDCl_3$) δ 8.00–6.67 (m, 4, Ar), 4.67–3.23 (m, 6), 3.23–2.37 (m, 5, SCH_2, and NCH_3 singlet at 2.73), 2.13–0.67 (m, 8); IR (CH_2Cl_2) 3400–2740, 1585, 1400, 1240, 1030 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 164.4, 147.9 (d, J = 8 Hz), 131.0 (d, J = 1 Hz), 130.6, 125.2 (d, J = 1 Hz), 123.4 (d, J = 7 Hz), 120.7 (d, J = 3 Hz), 64.4 (d, J = 7 Hz), 53.3, 52.9, 35.0, 33.1 (d, J = 4 Hz), 24.1 (d, J = 7 Hz), 16.0 (d, J = 7 Hz), 13.1. Anal. Reference 4.

Preparation of **13**: The standard phosphorylating procedure described above was used on compound **12**.[3] Column chromatography puriufication gave **13** in 24% yield. NMR ($CDCl_3$) δ 10.0–8.93 (br, 1 NH), 8.40–8.05 (m, 1, Ar), 7.53–7.00 (m, 5, Ar), 4.67–3.90 (m, 2, OCH_2), 3.10–2.40 (m, 2, SCH_2), 2.07–0.67 (m, 8); IR (neat) 3800–1980, 1598, 1420, 1175 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 146.3 (d, J = 9 Hz), 142.2 (d, J = 1 Hz), 129.8, 129.3 (d, J = 2 Hz), 125.4 (d, J = 1 Hz), 122.5 (representing two imidazole carbons), 122.1 (d, J = 6 Hz), 120.5 (d, J = 3 Hz), 64.4 (d, J = 7 Hz), 32.8 (d, J = 4 Hz), 23.5 (d, J = 7 Hz), 15.6 (d, J = 7 Hz), 12.5.

General Procedure for the Preparation of 14, 16, and 17.[5] The desired *N*-methylbenzimidazole, benzoxazole, or benzothiazole was dissolved in ether, cooled to −78 °, treated with 1 equiv of *n*-butyllithium, and stirred for 0.5 h before quenching with 1 equiv of 2,4-dichlorobenzaldehyde dissolved in ether. The reaction mixture was allowed to warm to 25 °C overnight and quenched with 10% aqueous NH_4Cl solution. The mixture was extracted with ether (3×) and the combined ether extracts were washed with saturated NaCl, dried ($Mg SO_4$), and concentrated in vacuo to give a crude solid residue which was recrystallized from hexane/EtOAc.

Compound **14**: 41% yield; mp 189–193 °C; NMR (Me_2SO-d_6) δ 7.93–7.10 (m, 7, Ar), 6.68 (br, 1, OH), 6.25 (s, 1, CH), 3.93 (s, 3, $NHCH_3$). Anal. Calcd for $C_{15}H_{12}Cl_2N_2O$: C, 58.65; H, 3.93; N, 9.12. Found: C, 58.55; H, 4.01; N, 8.91.

Compound **16**: 48% yield; mp 123–125 °C; NMR ($CDCl_3$) δ 7.68–7.12 (m, 7, Ar), 6.43 (s, 1, CH), 5.50 (br, 10 H). Anal. Calcd for $C_{14}H_9Cl_2NO_2$: C, 57.16; H, 3.08; N, 4.76. Found: C, 57.07; H, 3.08; N, 4.66.

Compound **17**: 71% yield; mp 120–122 °C; NMR ($CDCl_3$) δ 8.00–7.15 (m, 7, Ar), 6.50 (s, 1, CH), 5.05 (br, 1, OH). Anal. Calcd for $C_{14}H_9Cl_2NOS$: C, 54.20; H, 2.92; N, 4.52. Found: C, 54.24; H, 3.07; N, 4.54.

Preparation of **15**: The standard phosphorylating procedure described above was used on compound **14**. Florisil chromatography followed by recrystallization in hexane/EtOAc gave **15** in 18% yield: mp 65–69 °C; NMR ($CDCl_3$) δ 7.90–7.15 (m, 7, Ar), 5.79 (s, 1, CH), 3.73 (s, 3, NCH_3), 2.52 (t, 2, SCH_2, J = 7 Hz), 1.60 (m, 2), 0.97 (t, 3, $SCH_2CH_2CH_3$, J = 7 Hz); IR (CH_2Cl_2) 2940, 1572, 1481, 1450, 1085 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 142.4 (coupled s), 135.8 (s), 134.9 (s), 134.2 (s), 133.5 (s), 132.4 (d), 128.8 (d), 128.1 (d), 122.8 (d), 122.1 (d), 120.1 (d), 109.1 (d), 41.2 (d), 33.9 (t), 29.8 (q), 22.6 (t), 13.5 (q). Anal. Calcd for $C_{18}H_{18}Cl_2N_2S$: C, 59.18; H, 4.96; N, 7.86. Found: C, 59.52; H, 5.05; N, 7.72.

Preparation of 18 and 19.[6] Both compounds prepared by standard phosphorylating procedure described above.

Compound **18**: 27% yield from Florisil; NMR ($CDCl_3$) δ 7.95–7.20 (m, 7, Ar), 7.07 (d, 1, J_{PH} = 11 Hz), 4.45–3.90 (m, 2, OCH_2), 3.10–2.55 (m, 2, SCH_2), 1.95–0.75 (m, 8); IR (neat) 2950, 1462, 1438, 1250, 995 cm^{-1}. Anal. Calcd for $C_{19}H_{20}Cl_2NO_4PS$: C, 49.47; H, 4.38; N, 3.04. Found: C, 49.91; H, 4.51; N, 2.96.

Compound **19**: 9% yield from Florisil; NMR ($CDCl_3$) δ 8.15–7.10 (m, 8), 4.50–3.90 (m, 2, OCH_2), 3.10–2.50 (m, 2, SCH_2), 1.90–0.75 (m, 8). Anal. Calcd for $C_{19}H_{20}Cl_2NO_3PS$: C, 47.90; H, 4.23. Found: C, 47.50; H, 4.39.

General Procedure for Preparation of Oximes 22, 23, 28, and 29. The ketones were dissolved in ~5% aqueous MeOH or EtOH solution. To this was added 2 equiv of hydroxylamine

(3) (a) Roger, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* (a) **1976**, *96*, 2463; (b) **1974**, *96*, 2473. (c) Overberger, C. G.; Shen, Chah-Moh *Ibid.* **1971**, *93*, 6992. (d) Beger, J.; Wagner, G.; Dinjus, V.; Gorls, H.; Uhlig, E.; Sieler, J. *J. Prakt. Chem.* **1983**, *325*, 211.

(4) Samples were analyzed by both high resolution mass spectrometry and elemental analysis. Neither method gave satisfactory values because of instability. Reanalysis of the MS sample via ^{13}C NMR indicated decomposition (usually back to the oxime) had occurred. Silica gel chromatography also causes decomposition and loss of sample on the column.

(5) See: (a) Berarrd, J.; Metzger, J. *Bull. Soc. Chim. Fr.* **1962**, 2072. (b) Gilman, H.; Beel, J. A. *J. Am. Chem. Soc.* **1949**, *71*, 2328.

(6) Huang, J. U.S. Patent 4 425 338 (Union Carbide Co.), 1984.

(7) Compounds **20** and **21** were prepared by reaction of the lithium enolate of benzothiazole with the appropriate esters at −78 °C. Compound **20** previously reported by another procedure: (a) Zubarovsky, V. M. *J. Gen. Chem. USSR* **1951**, *21*, 2199; *Chem. Abstr.* **1951**, *46*, 8098f. (b) Kendall, J. D.; Duffin, G. F.; Voltz, J. Brit. Pat. **1961**, 885 520; *Chem. Abstr.* **1961**, *57*, 7428b.

(8) Same procedure as ref 7 except using benzimidazole as starting material. Compound **26** reported in ref 7b.

hydrochloride and 2 equiv of potassium carbonate. This mixture is refluxed overnight and allowed to cool and collect precipitate.

Compound **22**: mp 198–200 °C; NMR (Me_2SO-d_6) δ 8.40–7.20 (m, 4, Ar), 3.57–3.07 (m, 1, NOH), 2.37 (s, 3, CH_3); IR (KBr) 3500–2500 (br), 1500, 1322, 921 cm^{-1}. Anal. Calcd for $C_9H_8N_2SO$: C, 56.33; H, 4.19; N, 14.58. Found: C, 56.02; H, 4.11; N, 14.43.

Compound **23**: mp 118–123 °C; NMR ($CDCl_3$) δ 8.30–7.20 (m, 4, Ar), 3.85 (septet, 1, J = 7 Hz), 1.51 (d, 3, J = 7 Hz), 1.40 (d, 3, J = 7 Hz); IR (CH_2Cl_2) 3525, 3250 (br), 2940, 1440, 955 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.00; H, 5.50; N, 12.62.

Compound **28**: mp 215–218 °C; NMR (Me_2SO-d_6) δ 7.83–7.07 (m, 4, Ar), 5.40–3.23 (4, br singlet for NOH and singlet at 4.00 for NCH_3), 2.37 (s, 3, CH_3); IR (KBr) 3700–2100, 1550–1410, 1362, 1325, 1262, 1020, 930 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 62.76; H, 5.64 N, 21.75.

Compound **29**: mp 165–168 °C; NMR ($CDCl_3$/Me_2SO-d_6) δ 8.03–7.00 (m, 4, Ar), 6.03–5.23 (m, 1, CH), 4.03–2.73 (m, 3, (H_2O), s, 3.35 NOH), 2.47 (s, 3, CCH_3), 1.65 (d, 6, dimethyl multi, J = 6): IR (KBr) 3500–2400 (br), 1400, 1362, 1290, 1020, 745 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N_3O{\cdot}H_2O$: C, 61.28; H, 7.29; N, 17.88. Found: C, 61.13; H, 7.29; N, 17.65.

Preparation of Phosphates 24, 25, 30, and 31. These phosphates were prepared by the standard phosphorylating procedure described above. The final organic solutions were not washed with base and were not chromatographed so as not to effect the isomer ratio. The impurities were of a small proportion that it did not interfere with ^{13}C NMR interpretation of the condensed oxime phosphate. Elemental analyses of the crude products were all equally low (2.5%) in carbon, correct for hydrogen, and ~1% low in nitrogen. Subsequent attempts at chromatography led to considerable decomposition on the column.

Compound **24**: NMR ($CDCl_3$) δ 8.33–7.00 (m, 4, Ar), 4.80–3.97 (m, 2, -$POCH_2CH_3$), 3.37–2.67 (m, 2, $SCH_2CH_2CH_3$), 2.63 (s, 3, CH_3), 2.20–1.62 (m, 2, $SCH_2CH_2CH_3$), 1.47 (t, 3, OCH_2CH_3, J = 4 Hz), 1.07 (t, 3, $SCH_2CH_2CH_3$, J = 5 Hz); IR (CH_2Cl_2) 3100–2700 (br), 1370, 1332, 910 cm^{-1}.

Compound **25**: NMR ($CDCl_3$) δ 8.30–7.20 (m, 4, Ar), 4.73–3.60 (m, 2, OCH_2CH_3), 3.47–2.63 (m, 1, CH), 3.96–0.63 (m, 8): IR (neat) 3700–2500 (br), 1798, 1710, 1558, 1462, 1395, 1163, 1100, 660, 620 cm^{-1}.

Compound **30**: NMR ($CDCl_3$) δ 8.00–7.10 (m, 4, Ar), 4.67–3.90 (m, 5, NCH_3 singlet at 4.07), 2.95 (m, 2, SCH_2), 2.63 (s, 3, CH_3), 2.27–1.20 (m, 2), 1.42 (t, 3, OCH_2CH_3, J = 5 Hz), 1.00 (t, 3, $SCH_2CH_2CH_3$, J = 4 Hz); IR (neat) 3700–2000, 2000–1700 (br), 1609 cm^{-1}.

Compound **31**: NMR ($CDCl_3$) δ 8.00–7.00 (m, 4, Ar), 6.00–5.37 (m, 1, CH), 4.67–3.93 (m, 2, -OCH_2-), 3.33–2.75 (m, 2, -SCH_2-), 2.63 (s, 3, CH_3), 2.17–1.53 (m, 8), 1.38 (t, 3, -OCH_2CH_3, J = 6 Hz), 1.00 (t, 3, -$SCH_2CH_2CH_3$, J = 6 Hz); IR (neat) 3600–2200 (br), 1610, 1340, 1200, 1140, 680 cm^{-1}.

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Registry No. **1**, 70510-23-5; **2**, 96327-78-5; **3a**, 1498-51-7; **3b**, 7651-98-1; **4**, 814-49-3; **6**, 96327-79-6; **7**, 96327-80-9; **8**, 1565-39-5; **9**, 96327-81-0; **10**, 96327-82-1; **11**, 96327-83-2; **12**, 52755-90-5; **13**, 96327-84-3; **14**, 96327-85-4; **15**, 96327-86-5; **16**, 89204-68-2; **17**, 96327-87-6; **18**, 89204-57-9; **19**, 89204-65-9; **20**, 1629-78-3; **21**, 96327-88-7; **22**, 1629-79-4; **23**, 96327-89-8; **24**, 96327-90-1; (*E*)-**25**, 96327-95-6; (*Z*)-**25**, 96327-91-2; **26**, 942-25-6; **27**, 31539-67-0; **28**, 945-78-8; **29**, 96327-92-3; (*E*)-**30**, 96327-93-4; (*Z*)-**30**, 96327-96-7; (*E*)-**31**, 96327-94-5; (*Z*)-**31**, 96327-97-8; Me_2NCOCl, 79-44-7; 2,4-dichlorobenzaldehyde, 874-42-0; *N*-methylbenzimidazole, 1632-83-3; benzoxazole, 273-53-0; benzothiazole, 95-16-9.

Acyclic Stereoselection. 25. Stereoselective Synthesis of the C-1 to C-7 Moiety of Erythronolide A[1,2]

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A stereoselective synthesis of aldehyde ester **1**, a synthon for the C-1 to C-7 section of erythronolide A, is reported. The synthesis begins with β,γ-unsaturated aldehyde **12**, which is prepared from mesityl oxide as shown in eq 2. Aldehyde **12** reacts with the preformed lithium enolates of reagents **13** and **5** to give, in each case, a 15:1 mixture of two aldols (eq 3 and 4). Reduction of the major isomer **16** from the reaction of **5** with **12** with lithium aluminum hydride followed by periodate cleavage of the resulting vicinal diol provides β-hydroxy aldehyde **20**. This material is protected as the triethylsilyl derivative **21**, which is treated with the lithium enolate of BHT *O*-benzyllactate (**22c**). The resulting 5:1 mixture of aldols is converted into acetonides **27c** and **28c**, which are separated by chromatography. The stereostructure of the major acetonide **27c** was elucidated by single-crystal X-ray analysis (Figure 1). Lithium aluminum hydride reduction of **27c** gives alcohol **29**, which is converted into acetate **34**. Ozonolysis of this material gives aldehyde **35**, which is oxidized by pyridinium dichromate in DMF. Diazomethane esterification provides diester **36**, which is methanolized to hydroxy ester **37**. Swern oxidation of **35** provides racemic ester aldehyde **1**. Enantiomerically homogeneous **1** is obtained in a similar sequence, via the *O*-methylmandelates **39a** and **39b**.

In previous papers in this series, we have reported the development of useful strategies and reagents for the stereorational synthesis of complex organic molecules having many stereocenters. In this paper, we report the application of two of these reagents in a synthesis of **1**, the

(1) For part 24, see: Heathcock, C. H.; Hagen, J. P.; Young, S. D.; Pilli, R.; Bai, D. L.; Märki, H.-P.; Kees, K.; Badertscher, U. *Chim. Scr.*, in press.

(2) The work reported in this paper was reported in preliminary form at the Fourth International Conference on Organic Synthesis, Tokyo, Japan, August 22–27, 1982. Heathcock, C. H. In "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: Oxford and New York, 1983.

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