scale. Several syntheses of cholanthrene were reported in the older literature.[15,16] However, the method now reported requires fewer synthetic steps and provides a higher overall yield. It, therefore, can be recommended as the method of choice. Synthesis of 6-methylcholanthrene has not previously been described.

Biological Activity. Preliminary investigations of the tumorigenicity of **1b** and **1c** confirm that both hydrocarbons are potent carcinogens on mouse skin. Cholanthrene exhibited activity approximately equivalent to that of 3-MC. This finding agrees with an early report which employed a different system.[17] 6-Methylcholanthrene exhibited higher activity at similar dosage in agreement with the previously proposed generalization that methyl groups in nonbenzo bay region positions enhance carcinogenicity.[10] Full details of the biologial studies will be reported in due course.

Experimental Section

Materials and Methods. The NMR spectra were recorded on a Varian EM-360 and/or The University of Chicago 500-MHz spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. Melting points are uncorrected. All new compounds gave satisfactory analyses for C and H within ±0.3% and/or mass spectra consistent with the assigned structures. *N,N*-Diethyl-1-naphthamide was prepared as previously described.[11] THF was distilled from $LiAlH_4$ immediately before use, and the *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was distilled from KOH. 1-Indanone and *sec*-butyllithium solution in hexane were purchased from the Aldrich Chemical Company.

2,2-Dideuterio-1-indanone (3). A mixture of 1-indanone (5 g) and K_2CO_3 (0.5 g) in 50 mL of benzene at reflux was heated to reflux; then CH_3OD (5 mL) was added and heating was continued for 1 h. The benzene–methanol azeotrope was then distilled out until the vapor temperature reached 78 °C. A fresh 5-mL portion of CH_3OD was added, and the procedure was repeated twice more. Conventional workup gave **3**, the proton NMR spectrum of which differed from that of 1-indanone by the absence of the methylene protons at δ 2.5–3.2 and the presence of a broad singlet at δ 8.30 assigned to the benzylic protons.

Synthesis of Lactone 4. A solution of *sec*-butyllithium (44 mmol) was added to a solution of *N,N*-diethyl-1-naphthalamide (4.0 g, 17.6 mmol) and TMEDA (5.1 g, 44 mmol) in diethyl ether (150 mL) under argon at −78 °C. After 1 h, to this solution was added a solution of **3** (5.9 g, 44 mmol) in THF (50 mL). The solution was stirred at ambient temperature overnight. The usual workup gave the crude product which was dissolved in benzene along with 10% by weight of *p*-toluenesulfonic acid. The solution was heated at reflux overnight and then passed through a column of silica gel to afford the lactone **4**: 2.55 g (50%); mp 167–168 °C (benzene–hexane); NMR δ 3.3 (d of d, 2, CH_2, J_{gem} = 16 Hz), 6.7–9.1 (m, 10, Ar); mass spectrum, *m/e* 288 (M^+), 244 ($M^+ - CO_2$).

Reduction of 4 to the Acid 5a. (1) Zn and KOH. A solution of the lactone **4** (1.35 g, 4.7 mmol) in pyridine (20 mL) was added to 15.3 g of zinc dust (activated by treatment with 1.5 g of $CuSO_4 \cdot 5H_2O$ in 15 mL of water) suspended in a solution of 10% KOH (200 mL). The mixture was stirred at reflux overnight, then cooled, and filtered, and the filtrate was worked up to afford the free acid **5a**: 0.95 g (70%) mp 107–109 °C; NMR δ 3.07 (d of d, 2, CH_2, J_{gem} = 16 Hz), 4.81 (s, 1, methine), 6.9–8.0 (m, 10, Ar); mass spectrum, *m/e* 290 (M^+), 272 ($M^+ - H_2O$), 244.

(2) Zn and AcOH. A solution of **4** (780 mg) in acetic acid (100 mL) was heated at reflux with 7.8 g of zinc dust (activated by treatment with dilute HCl and washed with water and CH_3OH) for 24 h. The product was poured on ice and worked up in the usual way to afford **5a** quantitatively; the NMR spectrum matched closely that obtained from alkaline reduction.

Cyclization of 5a to 6. To a solution of **5a** (400 mg, 1.4 mmol) in glacial acetic acid (20 mL) was added $ZnCl_2$ (40 mg), and the mixture was heated at reflux for 2 h. The product was precipitated by addition of water, removed by filtration, and dried. The crude product was taken up in benzene and passed through a column of Florisil eluted with benzene. Recrystallization of the product from benzene–hexane gave **6**: 270 mg (62%); mp 214.5–215.5 °C; NMR δ 2.62 (s, 3, OAc), 3.56 (s, 2, H_2), 7.3–7.8 (m, 8, Ar), 9.21 (d, 1, H_7, $J_{7,8}$ = 8.1 Hz); mass spectrum, *m/e* 314 (M^+), 272 ($M^+ - CH_2CO$).

Cholanthrene (1c). A solution of 57% HI (550 mg) and 50% hypophosphorus acid (300 mg) and acetic acid (15 mL) was brought to reflux and added to a suspension of **6** (200 mg, 0.64 mmol) in acetic acid (15 mL) at 100 °C. Heating was continued for 90 s; then the mixture was poured into ice water. The precipitate was collected by filtration, dried, dissolved in benzene, and adsorbed on a short column of silica gel. Elution with benzene–hexane gave **1c**: 130 mg (80%); mp 173–174 °C (benzene–hexane) (lit.[16] mp 173–173.5 °C); NMR (500 MHz) δ 3.57 (t, 2, H_2), 3.76 (t, 2, H_1), 7.29 (d, 1, H_3, $J_{3,4}$ = 6.6 Hz), 7.49 (t, 1, H_4) 7.6–7.8 (m, 6, Ar), 8.81 (d, 1, H_7, $J_{1,2}$ = 8.2 Hz), 8.95 (s, 1, H_6).

Conversion of the Carboxylic Acid 5a to the Methyl Ketone 5c. To a solution of KOH (400 mg) in H_2O (2 mL) was added a solution of **5a** (1.0 g, 3.4 mmol) in hexamethylphosphoramide (15 mL) and 4 mL of CH_3I. The reaction mixture was stirred overnight and worked up to afford the crude methyl ester **5b**. The latter was purified by chromatography on a short column of Florisil to yield pure **5b**: 870 mg (83%); NMR δ 3.15 (d of d, 2, H_2), 4.01 (s, 3, OCH_3), 4.53 (s, 1, methine), 6.9–7.8 (m, 10, Ar); mass spectrum, *m/e* 304 (M^+), 272 ($M^+ - CH_3OH$), 244.

To a solution of **5b** (680 mg, 2.24 mmol) in diethyl ether (150 mL) was added hexamethylphosphoramide (5 mL) and excess CH_3Li (15 mL of a 1.3 M solution). The resulting purple solution was stirred at room temperature for 3 h. A few drops of methanol was added and the product was worked up conventionally to provide the methyl ketone **5c**: 620 mg (96%) as a colorless residue; NMR (500 MHz) δ 2.70 (s, 3, CH_3), 3.03 (d of d, 1, CH_2, H_2, J_{gem} = 16 Hz), 4.40 (s, 1, methine), 6.8–7.8 (m, 10, Ar); mass spectrum, *m/e* 288 (M^+), 273, 255, 245.

6-Methylcholanthrene (1b). A solution of **5c** (620 mg, 2.2 mmol) in liquid HF (sufficient to dissolve) was stirred overnight in a hood. The HF was evaporated in a stream of N_2, and the solid product was washed with aqueous $NaHCO_3$ solution, then with water, and dried. The crude 1,1-dideuterio-**1b** was further purified by chromatography on a column of Florisil to yield the pure sample of 1,1-dideuterio-**1b**: 530 mg (91%), mp 143–144 °C; NMR (500 MHz) δ 3.33 (s, 3, CH_3), 3.54 (s, 2, CH_2), 7.33 (d, 1, H_3, $J_{3,4}$ = 6.6 Hz), 7.5–7.8 (m, 6, Ar), 7.97 (d, 1, H_5, $J_{4,5}$ = 8.6 Hz), 8.66 (d, 1, H_7); mass spectrum, *m/e* 270 (M^+), 254.

The 1,1-dideuterio-**1b** (60 mg) was converted to **1b** on heating with *p*-toluenesulfonic acid (6 mg) in refluxing benzene (30 mL) for 24 h. The NMR spectrum of **1b** resembled that of its deuterated analogue except for the presence of the H_1 protons at δ 3.72.

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Nucleoside *H*-Phosphonates. 8.[1] Activation of Hydrogen Phosphonate Monoesters by Chlorophosphates and Arenesulfonyl Derivatives

Per J. Garegg, Jacek Stawinski,* and Roger Strömberg

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden

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Recently we have reported on an efficient method for oligonucleotide synthesis[2,3] which involves the reaction of

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Table I. ^{31}P NMR Data of Phosphonate Esters and Selected Intermediates

compd	chem shift, ppm[a]	$^1J_{PH}$, Hz[b]	$^3J_{PH}$, Hz[b]	mult of signals[b]
1a	2.5 (s)	608	7.8	2 d
1b	3.3 (s)	608	7.9	2 t
5a	118.6 (dd) ($^2J_{PP}$ = 15.9, 10.6 Hz)		10.4	4 overlapping d
	112.7 (t) ($^2J_{PP}$ = 11.3)		11.3	2 overlapping t
	110.3 (dd) ($^2J_{PP}$ = 15.9, 12.2 Hz)		11.4	4 overlapping d
5b	113.9 (t) ($^2J_{PP}$ = 11.1 Hz)			
	112.2 (d) ($^2J_{PP}$ = 11.3 Hz)			
7b	−2.3 (s)	780	8.8 and 20.5	4 t
9a	139.1 (s)			
9b	138.0 (s)		7.9	sextet
10a	8.1 (s), 9.6 (s)	718	8.7	4 q
10b	7.5 (s)[c]	704	8.6	2 q
10c	7.3 (s)	689	8.9	quintet

[a] Chemical shifts relative to 2% H_3PO_4 in D_2O (inner tube). The value of chemical shifts for the intermediates produced in situ, in some cases varied (±1 ppm), depending on the reaction conditions. [b] Spectra without ^1H-heteronuclear decoupling. [c] Diastereoisomers not resolved.

nucleoside 3′-hydrogen phosphonates with a nucleosidic component, in the presence of a condensing agent (PV-Cl,[13] DPCP,[4] OXP,[5] TPS-Cl,[6] TPS-Te[7]).

It was found, that *H*-phosphonate diesters were formed in high yield, when *H*-phosphonate monoesters were activated by a coupling agent in the presence of a nucleosidic component, but the yield decreased significantly, when *H*-phosphonate monoesters were preactivated by treatment with the coupling agent before the addition of nucleoside.[2,8]

To find out what kind of reactive intermediate(s) is formed when chlorophosphates are used as coupling agent, we carried out some ^{31}P NMR studies[9] on the preactivation of *H*-phosphonate monoesters. First, nucleoside 3′-*H*-phosphonate **1** was allowed to react with 1 equiv of DPCP **2** (Chart I) in pyridine. The ^{31}P NMR spectrum of such a reaction mixture showed a signal from the starting material (2.5 ppm) and 11 resonances in the region of 120–110 ppm. Addition of another equivalent of coupling agent **2** caused complete conversion of the starting material into the intermediate(s) at 120–110 ppm, and upon addition of water, nucleoside 3′-*H*-phosphonate **1** was recovered.

The 11 resonances in the region 120–110 ppm were arranged in three groups, containing four signals (of equal intensities), three (intensities 1:2:1), and four signals (of equal intensities), respectively (Figure 1a). Since the coupling agent potentially can be a part of such an intermediate(s), we carried out a similar reaction but with 2 equiv of OXP (**3**). The ^{31}P NMR spectrum in that case revealed exactly the same number and the same pattern

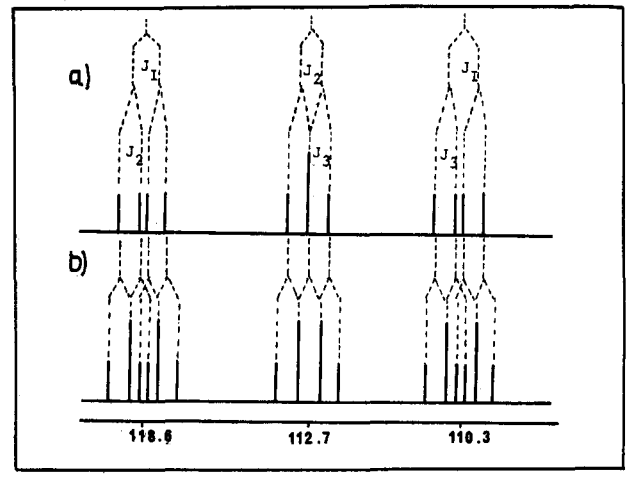
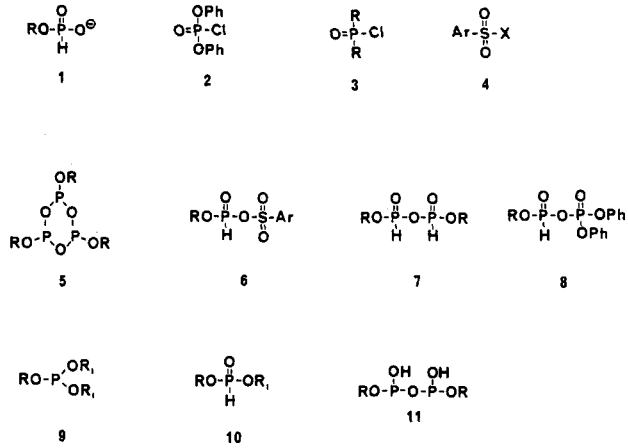


Figure 1. Schematic representation of the ^{31}P NMR spectrum of the intermediate at 120–110 ppm (compound **5a**): (a) spectrum with ^1H-heteronuclear decoupling; (b) spectrum without ^1H-heteronuclear decoupling.

Chart I



1a, R = DMT-T
1b, R = Et
3, R = 2-oxo-3-oxazolidinyl
4a, Ar = 2,4,6-triisopropylphenyl, X = Cl
4b, Ar = 2,4,6-triisopropylphenyl, X = 1-tetrazolyl
5a, R = DMT-T
5b, R = Et
6a, R = DMT-T, Ar = 2,4,6-triisopropylphenyl
6b, R = Et, Ar = 2,4,6-triisopropylphenyl
7a,8a, R = DMT-T
7b,8b, R = Et
9a,10a, R = DMT-T, R_1 = O-T-OBz
9b,10b, R = DMT-T, R_1 = Et
9c,10c, R = R_1 = Et
11, R = Et

of signals in the region 120–110 ppm, which indicates that probably the discussed intermediate(s) does not contain any residue of the condensing agent. This was further confirmed by the reaction with TPS-Cl and TPS-Te as condensing agents, where again formation of the same intermediate was observed.

In the latter reactions, the relative intensities of all signals were constant during their formation and gradual disappearance,[10] which suggests that all signals arise from

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(10) In the reaction of phosphonate **1** with 1 equiv of arenesulfonyl derivatives, the intermediate at 120–110 ppm undergoes further reactions with the condensing agent, producing as final products nucleoside phosphate and nucleoside *S*-arylphosphorothioate derivatives: Garegg, P. J.; Stawinski, J.; Strömberg, R. *J. Chem. Soc., Perkin Trans. 2*, in press.

one intermediate. The values of chemical shifts and absence of $^1J_{PH}$ coupling indicate that all phosphorus atoms are in a trivalent coordination state, while the large number of signals suggests that the intermediate contains more than two (most likely three) phosphorus atoms. In addition, 2D ^{31}P–^{31}P correlated NMR spectra showed that all three groups of signals of that intermediate are coupled one to each other. Thus, the most likely structure that is consistent with ^{31}P NMR data is that of trinucleoside trimetaphosphite **5a**, where the phosphorus atoms are arranged in a ring.

The correlation of the observed resonances with the proposed structure of trimetaphosphite **5a** is not straightforward; however, the interpretation given below, in our opinion, is the most likely one.

The four signals of equal intensities at 118.6 ppm can be interpreted as a doublet of doublets with the coupling constants $^2J_{PP}$ = 15.9 Hz and $^2J_{PP}$ = 10.6 Hz. The other group of signals at 110.3 ppm, very similar in intensities and the pattern to that at 118.6 ppm, also consists of four signals, which can be described as a doublet of doublets with the coupling constants $^2J_{PP}$ = 15.9 Hz and $^2J_{PP}$ = 12.2 Hz. Since both groups of signals have one identical and one different coupling constant, we concluded that they arose from two (diastereoisomeric) phosphorus atoms which are coupled to each other ($^2J_{PP}$ = 15.9 Hz) and are also coupled to the third phosphorus with the coupling constants $^2J_{PP}$ = 10.6 and 12.2 Hz. The observed signal at 112.7 ppm can be assigned to such a phosphorus nucleus, but instead of two doublets, we observed a triplet, with coupling constant $^2J_{PP}$ = 11.3 Hz. Since the observed value of the coupling constant is the average of the two expected ones, it is likely, that because of similar magnitude of the two coupling constants, the signal at 112.7 ppm appears as a pseudotriplet due to two close, unresolved resonances.

In ^{31}P NMR spectra recorded without ^1H–heteronuclear decoupling, the four signals at 118.6 ppm appeared as four overlapping doublets (six signals of intensities 1:2:1:1:2:1, $^3J_{PH}$ = 10.4 Hz), the pseudotriplet at 112.7 ppm as four signals (intensities 1:2:2:1, two partially overlapping triplets, $^3J_{PH}$ = 11.3 Hz), and the four signals at 110.3 ppm as four overlapping doublets (six signals, intensities 1:2:1:1:2:1, $^3J_{PH}$ = 11.4 Hz). The splitting pattern of signals for the proposed structure **5a** is shown in Figure 1b.

From the apparently symmetrical structure of trimetaphosphite **5a**, several resonances may arise due to the nonequivalence of diastereomeric phosphorus atoms. A hypothetical configuration for the trinucleoside trimetaphosphite **5a**, with all three nucleoside residues in a cis relationship, should have caused an equivalence of all phosphorus nuclei in the molecule. However, if a mutual relation of the substituents would be different, e.g., when one nucleoside residue adopts a trans relationship to the other two, all phosphorus centers become nonequivalent. Thus, two phosphorus atoms will be enantiomeric (*R* and *S*) or as in this particular case, because of chiral substituents (nucleosides), diastereomeric, while the configuration around the third phosphorus will be *R'* or *S'*.

The observed ^{31}P NMR spectrum is in agreement with such a structure. A proposed chair-like conformation and consequent trans,trans,cis relation of substituents implies one axial and two equatorial dispositions for the nucleoside residues. Thus, the signals at 118.6 and at 110.3 ppm can be assigned to the diastereomeric phosphorus nuclei which are equatorially substituted and the triplet at 112.7 ppm to the phosphorus with an axial substituent. Other assignments of the signals to the different phosphorus centers are also possible; however, these are less likely in light of the observed coupling constants.

Since the ^{31}P NMR spectra of trinucleoside trimetaphosphite **5a** is complicated because of diastereomeric phosphorus atoms, we tried to find further support for the proposed structure via analysis of ^{31}P NMR spectra of an analogous intermediate, derived from an achiral substrate, as, e.g., ethyl *H*-phosphonate **1b**. If the same type of intermediate would be formed, we expected for triethyl trimetaphosphite **5b** a rather simple ^{31}P NMR spectrum, which should consist of a triplet and a doublet at ca. 120–110 ppm, and with relative intensities 1:2. Indeed, when ethyl *H*-phosphonate **1b** was allowed to react with 2 equiv of chlorophosphate **2** in pyridine, the formation of an analogous intermediate was observed, which consisted, as expected, of a triplet (113.9 ppm, $^2J_{PP}$ = 11.1 Hz) and a doublet (112.2 ppm, $^2J_{PP}$ = 11.1 Hz) of relative intensities 1:2.

Interestingly, when 5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)uridine 3'*H*-phosphonate was activated with 2 equiv of chlorophosphate **2**, the ^{31}P NMR spectrum of the reaction mixture was very similar to that observed in the reaction with ethyl *H*-phosphonate and consisted of a triplet (121.0 ppm, $^2J_{PP}$ = 10.8 Hz) and a doublet (112.8 ppm, $^2J_{PP}$ = 10.8 Hz). In that case, apparently because of overlapping of the signals from diastereomeric phosphorus atoms, the spectrum was simple and could be straightforwardly correlated with the trinucleoside trimetaphosphite structure.

The reaction pathway to trimetaphosphite **5** most likely involves initial formation of the mixed phosphonic sulfonic anhydride **6** or phosphonic phosphoric anhydride **8**, which reacts with phosphonate **1** to produce pyrophosphonate **7**. In pyridine, however, this compound apparently undergoes activation by chlorophosphate **2** or **3** or by arenesulfonyl derivatives **4** and reacts further with phosphonate **1**, giving as a final product trimetaphosphite **5**. To check what the role of pyridine is in that activation process, we carried out reaction of ethyl *H*-phosphonate **1b** with chlorophosphate **2** (1.5 equiv.) in acetonitrile. Under these reaction conditions, we did not observe formation of the intermediate at 120–110 ppm but instead a singlet at −2.3 ppm. In an undecoupled spectrum, this singlet appeared as four triplets with coupling constants $^1J_{PH}$ = 780 Hz, $^3J_{POCH}$ = 8.8 Hz, and $^3J_{POPH}$ = 20.5 Hz. Addition of 1.2 equiv of ethanol to such a reaction mixture resulted in the formation of diethyl phosphonate (**10c**) and the starting material **1b** in a ratio ca 1:1. Formation of the same intermediate was also observed when arenesulfonyl derivatives **4** were used as activating agents. Thus, we assigned that signal to diethyl pyrophosphonate (**7b**). When more chlorophosphate **2** (2 equiv) was added, the singlet at −2.3 ppm remained unchanged, but addition of 2 equiv of triethylamine (or pyridine) caused its conversion into trimetaphosphite **5b**. This is expected, considering that under basic conditions isomerization of the tetracoordinated species **7** into a trivalent one, as, e.g., **11**; can occur more easily, and thus, further activation by a condensing agent becomes possible.

Finally, the reaction of trimetaphosphites **5** with alcohols have been investigated. When **5a** was allowed to react with an excess of ethanol, three compounds were detected in the ^{31}P NMR spectrum: phosphite triester **9b** (138.0 ppm), *H*-phosphonate diester **10b** (7.5 ppm, $^1J_{PH}$ = 704 Hz), and the starting material **1a** (2.5 ppm, $^1J_{PH}$ = 608 Hz), in a relative ratio of 1:1:1. The composition of the reaction

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mixture is exactly what one could expected from the reaction of trimetaphosphites **5** with alcohols. The presence of these species can be explained by two subsequent nucleophilic attacks of alcohol on the same phosphorus center, which results in a ring opening, followed by the formation of phosphite triester **9b** and pyrophosphonate **7b**. The latter compound, upon reaction with ethanol, affords *H*-phosphonate diester **10b** and *H*-phosphonate monoester **1a**. In agreement with this, when excess of coupling agent was present in the reaction mixture, only **9b** and **10b** were formed. Analogous compounds were observed in the ^{31}P NMR spectra during the reaction of **5a** with 3′-*O*-benzoylthymidine and in the reaction of **5b** with ethanol and with a suitably protected thymidine.

In conclusion, these studies have established that activation of *H*-phosphonate monoesters by chlorophosphates **2** and **3**, or by arenesulfonyl derivatives **4**, results in the formation of trimetaphosphites of type **5**. Reactions of the latter compounds with hydroxyl-containing nucleophiles afforded phosphonate diesters **10** together with phosphite triesters **9** and the starting materials **1**. This explains the previously observed low yield of *H*-phosphonate diester formation when *H*-phosphonate monoesters were preactivated before the coupling reaction.[2] In addition, these results also shed some light on a possible mechanism of *H*-phosphonate diester formation. During the "regular" coupling reaction (activation of a *H*-phosphonate monoester in the presence of nucleosidic component), the formation of phosphite triesters as side products was never observed,[2,12] and also, these last species cannot be produced from *H*-phosphonate diesters.[2,8] Thus, trimetaphosphites **5** can be excluded as intermediates involved in the *H*-phosphonate diester formation during the regular coupling reaction. Instead, the most likely candidates seem to be pyrophosphonate **7** and/or mixed anhydrides **6** or **8**.

Experimental Section

Materials and Methods. Reactions were carried out in NMR tubes (at 25 °C), and spectra were recorded on a Jeol JNM GX 400 FT (161.7 MHz) or Varian Associates XL-100 FT (40.48) spectrometer. Chemical shifts are reported relative to 2% H_3PO_4 in D_2O (inner tube).

Pyridine was refluxed and distilled over P_2O_5, then refluxed and distilled over CaH_2, and stored over 3-Å molecular sieves. The same procedure was used for the preparation of anhydrous acetonitrile.

Diphenyl chlorophosphate, 2,4,6-triisopropylbenzenesulfonyl chloride, and diethyl phosphonate (Aldrich) were commercial grade.

5′-*O*-(4,4′-Dimethoxytrityl)thymidine 3′-hydrogen phosphonate (triethylammonium salt),[2] ethyl hydrogen phosphonate (triethylammonium salt),[11] [(2,4,6-triisopropylphenyl)sulfonyl]tetrazole,[7] and 3,3′-(chlorophosphinylidene)bis(2-oxo-1,3-oxazolidene)[5] were prepared according to published procedures. Phosphite triesters **9a** and **9b** were prepared in the reaction of 5′-*O*-(dimethoxytrityl)thymidine with PCl_3 (1.2 equiv) in pyridine, followed by addition of appropriate alcohols or nucleosides. In some cases procedures reported in ref 8 were used. Phosphonate diesters **10** were prepared as reported previously.[2,8]

Preparation of Trimetaphosphite 5a for the 2D ^{31}P–^{31}P Correlated NMR Spectra. Compound **1a** (0.2 mmol) was dissolved in dry acetonitrile (2.5 mL), and triethylamine (0.6 mmol) and diphenyl chlorophosphate (0.4 mmol) were added. After standing for a couple of hours, the precipitate was removed, and the clear solution was subjected to ^{31}P NMR analysis.

General Procedure for the Activation and Reactions of 5a and 5b. Compound **1a** or **1b** was rendered anhydrous by repeated evaporation of added pyridine, and finally the resulting oil was dissolved in pyridine (2.5 mL). An appropriate coupling agent (**2**, **3**, or **4**) (2 equiv or as stated in the text) was added and ^{31}P NMR spectra were recorded directly after mixing of the reagents.

To investigate the chemical reactivity of **5a** or **5b**, ethanol (1.5–20 equiv) or 3′-*O*-benzoylthymidine (1.1–5 equiv) in pyridine was added. For the identification of reaction products, appropriate compounds **9a–c** and/or **10a–c** (prepared in different ways) were added, and ^{31}P NMR spectra were recorded.

Acknowledgment. We are indebted to Prof. Bengt Lindberg for his interest and to the Swedish National Board for Technical Development and The Swedish Natural Science Research Council for financial support.

Registry No. **1a**, 50571-26-1; **1b**, 15845-66-6; **2**, 2524-64-3; **3**, 102054-53-5; **5a**, 105784-89-2; **5b**, 105784-90-5; **7b**, 105784-91-6; **9a**, 105784-92-7; **9b**, 105784-93-8; **10a**, 102987-86-0; **10b**, 105784-94-9; **10c**, 762-04-9; TPS-Cl, 6553-96-4; TPS-Te, 59128-88-0; 3′-*O*-benzoylthymidine, 17331-53-2.

(12) For the automated solid-phase synthesis, at least as now constituted, the possibility of phosphite triester formation, as a side reaction, should be kept in mind.

(13) **Abbreviations**: PV-Cl, pivaloyl chloride; DPCP, diphenyl chlorophosphate; OXP, 3,3′-(chlorophosphinylidene)bis(2-oxo-1,3-oxazolidene); TPS-Cl, 2,4,6-triisopropylbenzenesulfonyl chloride; TPS-Te, 2,4,6-triisopropylbenzenesulfonyl tetrazolide; DMT-T, 5′-*O*-(4,4′-dimethoxytrityl)thymidin-3′-yl.

(14) **Note added in proof**: Recently, a series of sterically hindered triaryl trimetaphosphites has been synthesized and isolated (Chaser, D. W.; Fackler, O. P.; Mazany, A. M.; Komoroski, R. A.; Kroenke, W. T. *J. Am. Chem. Soc.* **1986**, *108*, 5956). These compounds and the trialkyl trimetaphosphites **5** reported here give a similar pattern of ^{31}P NMR resonances.

Selective Metal-Catalyzed Autoxidation of 2-Arylpropionaldehydes. An Improved Synthesis of Ibuprofen

D. P. Riley,* D. P. Getman, G. R. Beck, and R. M. Heintz

Monsanto Chemical Co., St. Louis, Missouri 63167

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The potential for increased useage of nonsteroidal anti-inflammatory agents such as ibuprofen (**1**) has prompted much interest in improved methods for the synthesis of 2-arylpropionic acids and of 2-(4-isobutylphenyl)propionic acid, in particular.[1] One synthesis of this material from the patent literature utilizes the glycidic ester route involving a stoichiometric oxidation of the aldehyde **2** as a final step.[2] The use of either $KMnO_4$ or Ag_2O was reported for this oxidation.[1d] Many other oxidants have been reported in the patent literature[3] with the most significant utilizing sodium hypochlorite[4] and hydrogen peroxide.[5] In only one instance has the use of O_2 and a metal catalyst been reported, but yields were unsatisfactory (68% selectivity to **1**).[6,7] While the literature

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(2) (a) Dytham, R. A. Brit. Pat. 1 160 725, 1967. (b) Dytham, R. A. Fr. Pat. 1 545 270, 1968.

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(5) Kogure, K.; Sueda, N.; Himoto, S.; Yoshino, Y.; Nakagawa, K. Ger. Offen. 2 533 397, 1976.

(6) Miyatake, T.; Teruya, H. Jap. Kokai 72 39 050, 1972.

(7) In addition, a photochemical oxidation has been reported to proceed in 94% yield, see: Miura, S.; Kawashima, T.; Iizuka, Y.; Sawa, Y. Jap. Kokai 76 100 042, 1976.

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