after shaking, samples of the organic layer were injected in the VPC (Varian Model 1200, FID detector, Linear Instruments Model 252A integrating recorder), using a 12 ft. × $^1/_8$ in. column of 8% Se-30 on 70/80 Anakrom ABS. All injections were done at least in duplicate. A blank showed that the NaOH/hexane treatment left the ratio of tetralin to standard unaffected. The FID response factors were the following: for tetralin–*tert*-butylbenzene, 1.00:1.07; for tetralin–decane, 1.00:1.11; for **2**–decane, 1.00:1.61; for **3**–decane, 1.00:2.34; for **4**–decane, 1.00:3.18. For compounds **2**–**4**, the solution in the volumetric flask was divided among 12 to 20 ampules, and the tubes were evacuated to 0.05 mmHg and sealed. They were then immersed in a thermostated oil bath and removed individually at intervals. VPC examination (3 ft × $^1/_8$ in. 10% SE-30 on 70/80 Anakrom ABS) required that the injection port be kept below 130 °C for **3** or 150 °C for **4** to prevent additional decomposition.

Reactions with Added Dibenzoyl Peroxide. Solutions were prepared as in the ampule method above, but 3 to 33 mg of the peroxide was added to the flask. After each ampule was opened, the contents were transferred to a test tube and stirred with 10 mg of $NaBH_4$ in 0.3 mL of 95% ethanol for 3 min to reduce any unreacted peroxide. Then 0.75 mL of aqueous 2 M NaCl and 0.3 mL of petroleum ether were added and the organic layer was examined by VPC. Blanks again showed no change in tetralin– or benzene–decane ratios from this treatment.

Reactions of 3 and 4 with Other Additives Present. Small amounts (up to 1.0 equiv) of azobis(isobutyronitrile), acetic acid, hydroquinone or 2,6-di-*tert*-butyl-4-methylphenol were added to an aliquot sample (NMR method) or several ampules. Unaltered samples were run in parallel. No apparent effect was observed. No effect was noticeable either upon rinsing the reaction tubes with ammonia or soaking in dichromate/H_2SO_4 before use. Air admitted to the NMR tubes (1 to 20 mmHg) before sealing appeared to decrease the rate somewhat for **4**, but plots were badly curved and the magnitude of the effect was not very reproducible.

Acknowledgment. We thank the Research Corporation for a Cottrell College Science Grant in support of this work.

Registry No. **1a**, 73873-09-3; **1b**, 73873-10-6; **2**, 73873-11-7; **3**, 73873-12-8; **4**, 73873-13-9; tetralin, 119-64-2; tetracyanoethane, 14778-29-1; dicarbethoxyhydrazine, 4114-28-7; benzene, 71-43-2.

A Convenient Method for Insertion of the 5′-Terminal Phosphate Group in the Triester Approach to Oligoribonucleotide Synthesis

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The phosphotriester approach has been examined by several workers[1-11] in an attempt to overcome some of the problems inherent in the phosphodiester method. However, only a few examples of the insertion of 5′-terminal phosphate residues in the phosphotriester approach to oligoribonucleotide synthesis[12] have been published. The native transfer ribonucleic acids (t-RNAs) contain a 5′-terminal phosphate. Consequently, the development of a convenient insertion of 5′-phosphate groups during the synthesis of oligoribonucleotides via the phosphotriester approach was required.

In this paper, we describe an efficient method for the synthesis of oligoribonucleotides bearing a 5′-terminal phosphate which uses 5-chloro-8-quinolyl phosphate (pqcl),[11f] 2,2′-dipyridyl diselenide [$(PySe)_2$],[13] and triphenylphosphine (Ph_3P).

The partially protected dinucleotides, dmtUt(qcl)Ut (**3a**) and dmtbzCtp(qcl)bzCt (**3b**) were prepared from 5′-*O*-dimethoxytrityl-2′-*O*-tetrahydropyranylnucleoside (**1**), 5-chloro-8-quinolyl phosphate, 2′-*O*-tetrahydropyranylnucleoside (**2**), and 8-quinolinesulfonyl chloride (QS),[11e] using the previous described procedure.[11e] In a similar manner, **3** and **2** were converted to a partially protected trinucleotide, dmbzCtp(qcl)bzCtp(qcl)bzAt (**4**) (Scheme I). These results are summarized in Table I. No evidence for undesirable 8-quinolinesulfonylated and 3′–3′ linkage products was detected in any of the coupling reactions. Subsequent removal of the dimethoxytrityl group from **3** and **4** to give **5** and **6**, respectively, was carried out with 2% *p*-toluenesulfonic acid solution.[11f]

The following is a typical procedure for the selective phosphorylation at the 5′-hydroxyl groups of **5** and **6** by means of 5-chloro-8-quinolyl phosphate in the presence of $(PySe)_2$ and Ph_3P. To a mixture of Utp(qcl)Ut (**5a**) (0.5 mmol), 5-chloro-8-quinolyl phosphate (0.75 mmol), and $(PySe)_2$ (5.25 mmol) in dry pyridine (5 mL) was added Ph_3P (5.25 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction was monitored by silica gel TLC. After completion of the reaction, the mixture was quenched with ice–water and extracted with methylene chloride, and the extract was back washed with triethylammonium bicarbonate (0.1 M, pH 7.5). The methylene chloride was evaporated in vacuo. The residue was dissolved in methylene chloride, applied to a silica gel column, and eluted with methylene chloride–methanol

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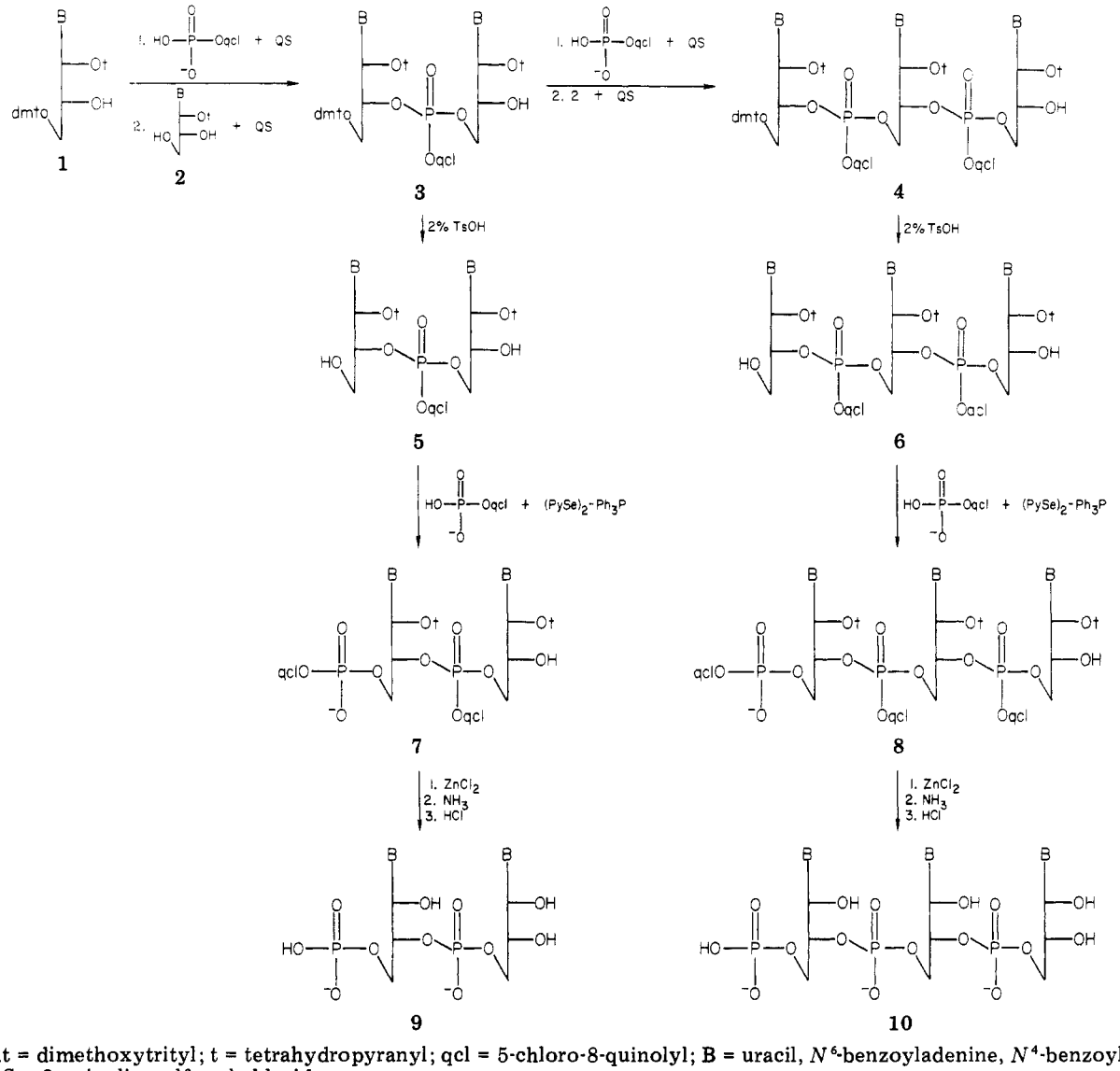
Scheme I[a]



[a] dmt = dimethoxytrityl; t = tetrahydropyranyl; qcl = 5-chloro-8-quinolyl; B = uracil, N^6-benzoyladenine, N^4-benzoylcytosine; QS = 8-quinolinesulfonyl chloride.

Table I. Reaction Conditions and Yields for the Synthesis of Oligonucleotides

step 1					step 2				product			
nucleoside		pqcl,	QS,	time,	nucleoside		QS,	time,			yield,	TLC,
no.	mmol	mmol	mmol	h	no.	mmol	mmol	h	no.	mmol	%	R_f[a]
1a	2.00	2.10	4.20	6	2a	3.00	4.00	24	3a	1.61	81	0.60
1b	2.00	2.10	4.20	6	2b	3.00	4.00	24	3b	1.60	80	0.65
3b	1.20	1.40	2.80	6	2c	1.80	2.40	24	4	0.78	65	0.56

[a] The solvent system used was methylene chloride–methanol (9:1 v/v).

Table II. Reaction Conditions and Yields for the Synthesis of Oligonucleotides Bearing a 5′-Terminal Phosphate End Group

5′-hydroxyl component		pqcl,	$(PySe)_2$-Ph_3P,	time,	product			
no.	mmol	mmol	mmol	h	no.	mmol	yield, %	TLC, R_f[a]
5a	0.50	0.75	5.25	12	7a	0.46	92	0.30
5b	0.30	0.45	3.15	14	7b	0.27	90	0.34
6	0.35	0.53	3.71	15	8	0.28	80	0.29

[a] The solvent system used was methylene chloride–methanol (85:15 v/v).

(85:15 v/v). The compound, qclpUtp(qcl)Ut (**7a**) was isolated in 92% yield.

Similarly, qclpbzCtp(qcl)bzCt (**7b**) and qclpbzCtp-(qcp)bzCtp(qcl)bzAt (**8**) were obtained, as shown in Table II.

Complete deblocking of the desired products **7** and **8** was performed as follows. Removal of the 5-chloro-8-quinolyl group was effected by treatment with zinc chloride in a mixture of pyridine and water (9:1 v/v) at room temperature for 24 h.[11f,g,14] Thin-layer chromatography indicated

Table III. Characterization of Oligoribonucleotides

compd	yield, %, for complete deprotection	paper chromatography A	paper chromatography B	paper electrophoresis, RCp	enzymatic analyses
UpU	95	0.30		0.41	U:pU (1.0:0.9)
CpC	96	0.28		0.39	C:pC (1.0:1.1)
CpCpA	92	0.12		0.64	C:pC:pC (1.0:0.9:0.9)
pUpU	94	0.11	0.30	1.03	pU
pCpC	95	0.07	0.25	1.03	pC
pCpCpA	91	0.04	0.15	1.10	pC:pA (1.0:2.1)

loss of the 5-chloro-8-quinolyl groups. After treatment with Dowex 50W-X2 (pyridinium form), the resin was filtered off and the filtrate was evaporated in vacuo. The residue was treated with concentrated ammonia at 50 °C for 5 h. The solution was concentrated to an oil which was dissolved in 0.01 N hydrochloric acid (pH 2). After 18 h, the solution was neutralized (ph 8) with 0.5 M ammonia. The completely deblocked products **9** and **10** were isolated after separation by DEAE cellulose DE-52 column chromatography. The thus obtained deblocked compounds were completely digested to nucleoside 5′-phosphates in the presence of snake venom phosphodiesterase (see Table III). The identity of the 3′–5′-internucleotidic bonds was confirmed from the above enzymic hydrolyses. Further, the present study clearly demonstrates that it is not necessary to protect the 3′-hydroxyl group of the oligoribonucleotides (**6**).

We believe that the method outlined in this paper provides a convenient method for the synthesis of oligoribonucleotides bearing 5′-terminal phosphate end groups using the phosphotriester approach.

Experimental Section

Thin-layer chromatography (TLC) was performed by using the ascending technique on Merck $60F_{254}$. The plates were usually developed in 5 to 15% methanol in methylene chloride mixtures. For column chromatography silica gel G (Merck) was used. Paper chromatography was performed by using the descending technique on Toyo Roshi No. 51A. The solvent systems employed were the following: solvent A, 2-propanol–concentrated ammonia–water (7:1:2 v/v/v); solvent B, 1-propanol–concentrated ammonia–water (55:10:35); solvent C, 1-butanol–acetic acid–water (5:2:3 v/v/v). Paper electrophoresis was performed with 0.05 M triethylammonium bicarbonate (pH 7.5) at 1100 V/40 cm. Nucleosides and their derivatives were detected on paper chromatograms and thin-layer sheets with a UV light source (254 nm). Compounds containing the dimethoxytrityl group were detected on chromatography by spraying with 10% perchloric acid solution and drying them in a stream of warm air. 5′-*O*-Dimethoxytrityl-2′-*O*-tetrahydropyranyluridine,[15] 5′-*O*-dimethoxytrityl-2′-*O*-tetrahydropyranyl-N^4-benzoylcytidine,[15,16] 2′-*O*-tetrahydropyranyluridine,[15] 2′-*O*-tetrahydropyranyl-N^4-benzoylcytidine,[15,16] 2′-*O*-tetrahydropyranyl-N^6-benzoyladenosine,[15] 8-quinolinesulfonyl chloride (QS),[11e] and 5-chloro-8-quinolyl phosphate[11f] were all prepared according to literature procedures.

Synthesis of Oligoribonucleotides 3 and 4. The free acid of 5-chloro-8-quinolyl phosphate (0.545 g, 2.1 mmol) and **1a** (1.26 g, 2.0 mmol) were dried by coevaporation of pyridine and the residue was dissolved in dry pyridine (10 mL). QS (1.2 g, 4.20 mmol) was added to the pyridine solution. After 6 h at room temperature, TLC indicated that the phosphorylation was complete (R_f 0.55–0.00 in 10% methanol–methylene chloride). 8-Quinolinesulfonic acid was removed by filtration. The filtrate was quenched with ice–water (15 mL) and repeatedly extracted with methylene chloride. Combined organic extracts were washed with triethylammonium bicarbonate (0.1 M, pH 7.5, 3 × 20 mL), and then with water (2 × 10 mL), and the methylene chloride was evaporated in vacuo. The residue was repeatedly evaporated in vacuo from dry pyridine (final volume ca. 10 mL) and QS (1.15 g, 4.00 mmol) and **2a** (0.984 g, 3.00 mmol) were added. After 24 h, the reaction was quenched with ice–water (15 mL) and repeatedly extracted with methylene chloride (3 × 30 mL). Combined organic extracts were washed with triethylammonium bicarbonate (0.1 M, pH 7.5; 3 × 20 mL) and then with water (2 × 10 mL), and the methylene chloride was evaporated with addition of toluene. The residue was dissolved in methylene chloride and chromatographed on a silica gel column (3.5 × 30 cm) preequilibrated with methylene chloride–1% pyridine. The column was eluted with 100 mL of methylene chloride followed by 700 mL of methylene chloride–methanol (98:2 v/v). The product **3a** was precipitated from its solution in methylene chloride with hexane–ether (9:1 v/v). The yield was 1.90 g (81%).

Oligoribonucleotides **3b** and **4** were prepared in a similar manner and reaction conditions are summarized in Table I.

Detritylation of Oligoribonucleotides 3 and 4. The protected intermediate was treated with 2% *p*-toluenesulfonic acid in methylene chloride–methanol (7:3 v/v) at 0 °C for 15 min.[11f] After the trityl cleavage was complete, the mixture was neutralized with 5% sodium bicarbonate solution and transferred into methylene chloride. The organic layer was washed with water and then dried over anhydrous sodium sulfate. The residue remaining after removal of methylene chloride was precipitated from hexane–ether (5:1 v/v) and used as the 5′-hydroxyl component in the subsequent condensation without further purification.

Synthesis of Oligoribonucleotides Bearing 5′-Terminal Phosphate End Groups. The free acid of 5-chloro-8-quinolyl phosphate (0.194 g, 0.75 mmol), **5a** (0.433 g, 0.5 mmol), and $(PySe)_2$ (1.648 g, 5.25 mmol) were dried by coevaporation of pyridine three times. The residue was dissolved in dry pyridine (5 mL) and then Ph_3P (1.376 g, 5.25 mmol) was added. After 12 h, the mixture was quenched by the addition of ice–water (5 mL), and the product was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with triethylammonium bicarbonate (0.1 M, pH 7.5; 2 × 40 mL) and water (50 mL), dried with anhydrous sodium sulfate, and concentrated. The residue was coevaporated with toluene three times, dissolved in methylene chloride, and applied to a silica gel column (3.5 × 10 cm). The column was eluted with 150 mL of methylene chloride and 500 mL of methylene chloride–methanol (85:15 v/v). The product **7a** was precipitated with hexane–ether (5:1 v/v) from its solution in methylene chloride. The yield was 0.537 g (92%).

In the same way, the oligoribonucleotides bearing 5′-terminal phosphate end groups, **7b** and **8** were prepared by use of the conditions summarized in Table II.

Deblocking of Oligoribonucleotides 7 and 8. To a solution of oligoribonucleotide (30 mg) in a mixture of pyridine and water (9:1 v/v; 5 mL) was added zinc chloride (50 molar equiv per phosphate moiety). After 24 h at room temperature, Dowex 50W-X2 (pyridinium form) was added. The resin was filtered off and the filtrate was concentrated to an oil which was dissolved in concentrated ammonia (5 mL). The reaction vessel was sealed and kept at 50 °C. After 5 h, the solution was concentrated in vacuo and the residue was dissolved in 0.01 N hydrochloric acid (pH 2, 5 mL). After 18 h at 20 °C, the solution was carefully neutralized (pH 8) with 0.5 M ammonia, concentrated, and brought onto a column (40 × 1.5 cm) of DEAE cellulose DE-52 (HCO_3^- form) suspended in 0.05 M TEAB. The column was eluted

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with a linear gradient of TEAB (0.05–0.8 M, total 1.2 L). Five-milliliter fractions were collected. Those fractions containing the main peak were collected, evaporated down to dryness, and coevaporated three times with water. The products were then lyophilized. The yields of the free oligoribonucleotides are as shown in Table III.

Enzyme Assay. Snake Venom Phosphodiesterase. An incubation solution of 1 M ammonium carbonate (230 μL) containing oligoribonucleotide (10 OD_{260}) and snake venom (20 mg/mL, 10 μL) was incubated at 37 °C for 12 h. The results of enzymatic hydrolysis are summarized in Table III.

New Synthesis and Some Selected Reactions of the Potential Ergot Alkaloid Precursor Indole-4-carboxaldehyde

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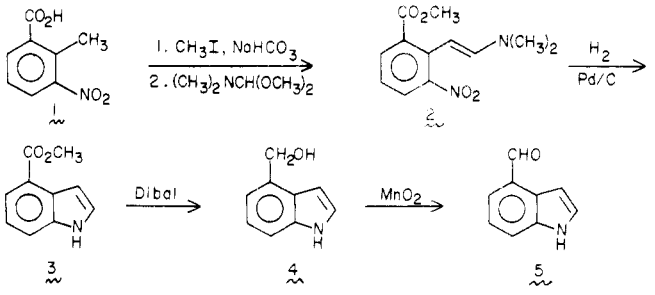
As a consequence of the potential use of the ergot alkaloids and their derivatives in the treatment of Parkinson's disease and for the inhibition of prolactin release, we have been greatly interested in designing new strategies for the preparation of these products.[2] Our retrosynthetic analysis of these compounds led us to consider routes based on the utilization of 4-C-substituted indoles as the key precursor molecules. Since no highly efficient procedures have been developed for the synthesis of such compounds, we initiated a study geared toward their production on a multigram scale.[3] We would now like to disclose an excellent method for producing methyl indole-4-carboxylate (**3**) from the commercially available 3-nitro-2-methylbenzoic acid as well as to describe some reactions of this compound.

Our synthesis of **3** is based on the straightforward extension of a general indole synthesis patented by Leimgruber and Batcho.[4] Thus, the benzoic acid **1** is esterified by reaction with iodomethane and potassium bicarbonate in DMF (Scheme I). This ester is heated with 3 equiv of *N,N*-dimethylformamide dimethyl acetal in dry DMF at 130 °C for 6 h. Removal of solvent and Kugelrohr distillation of the residue yields the enamine **2** in 80% yield. A solution of **2** in benzene is hydrogenated in a Parr shaker at 50 psi over 10% palladium on charcoal for 1.5 h. The reaction mixture is filtered, and the filtrate is washed with 5% HCl, dried ($MgSO_4$), and concentrated by rotary evaporation. The crude product is chromatographed on silica gel to afford **3** as a crystalline solid in 82% yield.

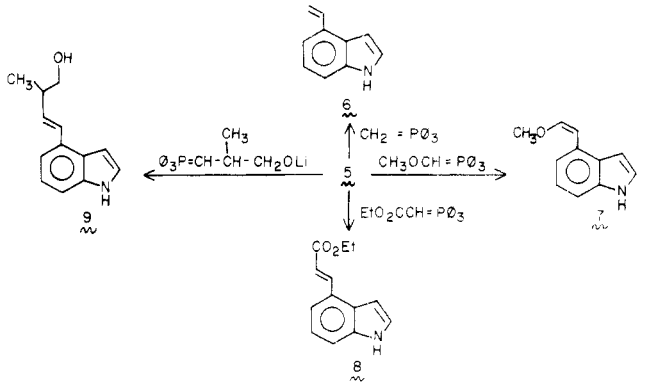
This entire sequence can be executed on a multigram scale in 2 days, thus making this the most efficient route presently designed for the preparation of **3**.

A procedure for the preparation of methyl indole-4-carboxylate similar to our own has recently been published by Ponticello and Baldwin.[3] In contrast to our own results, these workers indicate that hydrogenation of **2** produces

Scheme I. Synthesis of Indole-4-carboxaldehyde



Scheme II



only trace amounts of **3**. Their scheme thus calls for a more tedious and lower yield Fe in AcOH–EtOH reduction to accomplish this conversion.

The indole ester **3** can be transformed readily into its corresponding aldehyde derivative. Accordingly, exposure of **3** to excess Dibal in ether at −70 °C for 2 h affords the hydroxymethyl derivative **4**. Oxidation of this alcohol with manganese dioxide in methylene chloride (40 h at room temperature) provides indole-4-carboxaldehyde in 84% yield after column chromatography. Attempts to reduce ester **3** directly to aldehyde **5** by use of controlled amounts of Dibal have not been successful.

A variety of reactions have been carried out with this indole aldehyde which serve to define some of the chemistry of this special heterocyclic system. Condensation of **5** with a number of phosphoranes provides, for example, ready access to a host of chain-elongated products of potential use for incorporation at various stages into an ergoline ring synthesis.[5] Methylenetriphenylphosphorane, (methoxymethylene)triphenylphosphorane, [(carboethoxy)methylene]triphenylphosphorane, and [3-(lithiooxy)-2-methylpropylidene]triphenylphosphorane[6] all give excellent yields of olefinic products **6**–**9** (Scheme II).

It is quite interesting to note here that this latter phosphorane, a γ-oxido ylide, leads to indole **9** which posseses a disubstituted olefin of *E* geometry as ascertained by ^1H NMR (J = 16 Hz). This ylide is thus capable of bringing about an internal Schlosser reaction in a manner such as noted previously by Berta, Salmond, and Havens in a single instance for a related γ-oxido ylide.[7] This result suggests that a certain amount of generality can be attached to a prediction that olefins of *E* geometry should arise

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