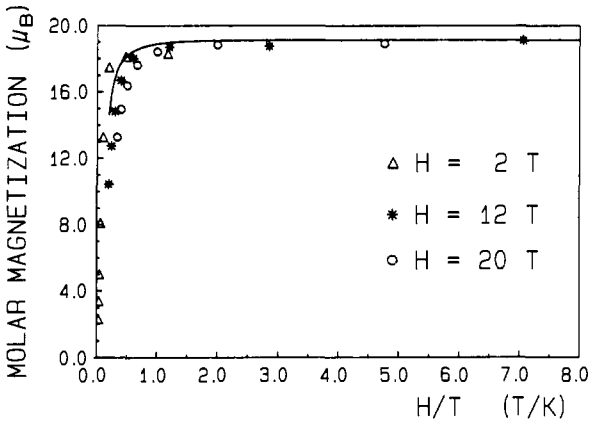

Figure 2. Molar magnetization of a powdered sample of **2** vs the ratio H/T. The measurements were performed varying the field between 0 and 20 T at eight temperatures in the range 1.7-60 K. The solid line represents the parallel magnetization calculated for $S = 10$ with $g = 1.9$ and $D = -0.5$ cm^{-1} at a field strength of 12 T.

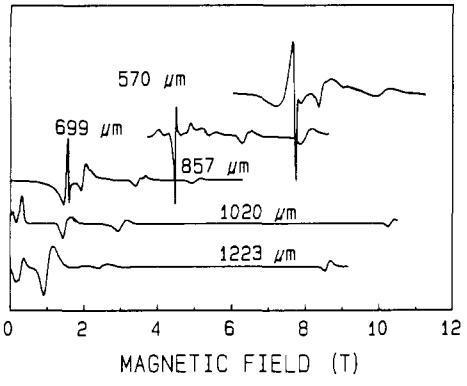

Figure 3. EPR spectra of a powdered sample of **2** recorded at different wavelengths.

Conventional relaxation effects must be excluded because the measurements were performed in zero applied field.[8]

Isothermal magnetization measurements with a Bitter magnet[9] were performed in the range 4.2-60 K with external field up to 20 T. The isofield plots are shown in Figure 2. The magnetization saturates for H/T greater than 1 at the value expected for $S = 10$, in agreement with the ac susceptibility data above 12 K. The experimental data can be satisfactorily reproduced by the parallel component of the magnetization calculated for $S = 10$, $g = 1.9$, and $D = -0.5$ cm^{-1}, suggesting that the crystallites are almost completely aligned by the strong magnetic field.[10]

No EPR spectra were detected with a conventional spectrometer operating at X- and Q-band frequency. However polycrystalline powder spectra at 4.2 K with a high frequency spectrometer operating with a far infrared laser[11] at 17.5, 14.3, 11.7, 9.8, and 8.2 cm^{-1} show a large number of features; see Figure 3.

The spectra recorded at the lowest frequencies show some features close to zero field, which move regularly to higher fields on increasing frequency. This is a clear indication that they belong to transitions within a spin multiplet split in zero field. The presence of resonances close to zero field for B_0 in the range 11-8 T indicates that the levels are separated by roughly 10 cm^{-1} in zero field. Since only low field transitions are observed, the zero field splitting of the ground manifold must be such that the levels with the largest M components have the lowest energy. Similar conclusions were reached[4] from the analysis of the magnetization of **1**. If we assume that the lowest field transition corresponds to $M_s = -10 \rightarrow M_s = -9$, then D can be estimated to be ca. ≈ -0.5 cm^{-1}, in agreement with magnetization data.

The main evidence of a ground $S = 10$ state comes from the magnetization data. The ac susceptibility confirms this value and adds the puzzling observation of large frequency-dependent relaxation effects. It is tempting to attribute these to factors analogous to those observed in superparamagnets. Although the dimensions of the clusters are still much smaller than those observed in superparamagnets, the large magnetic anisotropy, which arises from the large spin and the fact that the $M_s = \pm 10$ levels lie lowest, determines large internal fields which give rise to the observed relaxation effects.

The reasons stabilizing this ground state compared to the $S = 14$ of **1** are currently under investigation. However it is interesting to notice that an $S = 10$ is compatible with all the manganese(III) spins up and the manganese(IV) spins down.

Acknowledgment. The financial support of the CNR, of the Progetto Finalizzato "Material Speciali per Tecnologie Avanzate", and of MURST is gratefully acknowledged.

(8) Morrish, A. H. *The Physical Principles of Magnetism*; John Wiley & Sons: New York, 1965; p 78.
(9) Picoche, J. C.; Guillot, M.; Marchaud, A. *Physica* **1989**, *B155*, 407.
(10) The experimental procedure favored the alignment of the crystallites because the field was raised up to 20 T several times before starting the measurements. No hysteresis was observed probably due to the fact that the sample was finely ground.
(11) Muller, F.; Hopkins, M. A.; Coron, N.; Grynberg, M.; Brunel, L. C.; Martinez, G. *Rev. Scient. Inst.* **1989**, *60*, 3681. Barra, A. L.; Brunel, L. C.; Robert, J. B. *Chem. Phys. Lett.* **1990**, *165*, 107.

Novel Formal 3 + 2 Annulation Reaction Based on *S*-Propargyl Dithiocarbonates (Xanthates)

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We report a novel annulation reaction involving *S*-propargyl dithiocarbonates (xanthates) which we discovered accidentally while attempting to generate propargyl radicals. We had earlier found[1] that resonance-stabilized carbon-centered radicals can be easily generated from the corresponding *S*-alkyl xanthates **1** and captured by an electrophilic olefin such as **2a** as shown in Scheme I. The radical chain reaction is triggered by a combination of visible light and a catalytic amount of *S*-benzoyl *O*-ethyl xanthate. When we applied the same procedure to *S*-propargyl xanthate **1b**, the expected adduct **3b**, arising from addition of a propargyl radical to *N*-benzylmaleimide, was produced but only in low yield (5-10%). The major product, isolated in up to 45-50% yield, turned out to be the bicyclic derivative **4**.[2] Other highly electrophilic olefins also gave the corresponding cyclopentene derivatives in variable (unoptimized) yields (Table I). With less reactive olefins, such as methyl acrylate or even dimethyl fumarate, complex mixtures were obtained from which no useful products could be isolated.

At first, this unexpected transformation was thought to proceed through a hitherto unprecedented 5-endo-digonal radical cyclization step,[3] as indicated in Scheme II (path A). However, a number of observations compelled us to reject such a mechanism. For example, in the case of citraconimide **5**, two isomeric adducts **6** and **7** were obtained in an approximately 1:1 ratio (80% combined yield, see Table I; for structural confirmation purposes, the

(1) (a) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308. (b) Mestre, F.; Tailhan, C.; Zard, S. Z. *Heterocycles* **1989**, *28*, 171. For related work on xanthates, see: (c) Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1989**, *30*, 4367. (d) Forbes, J. E.; Zard, S. Z. *J. Am. Chem. Soc.* **1990**, *112*, 4367. (e) Forbes, J. E.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 2565.
(2) Satisfactory spectroscopic data and elemental analyses or high-resolution mass spectra were obtained for new compounds.
(3) Rare cases of radical 6-endo-dig cyclizations have been reported: (a) Hart, D. J.; Choi, J. K. *Tetrahedron* **1985**, *41*, 3959. (b) Curran, D. P.; Chen, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 6558; *J. Org. Chem.* **1989**, *54*, 3140.

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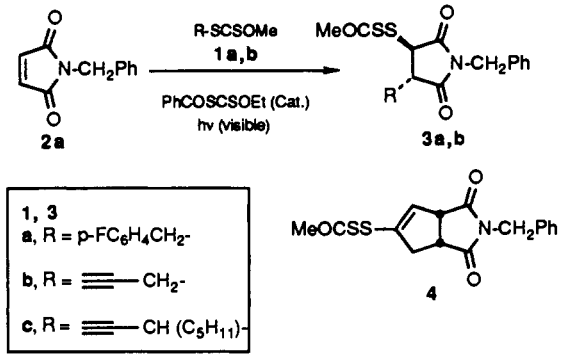
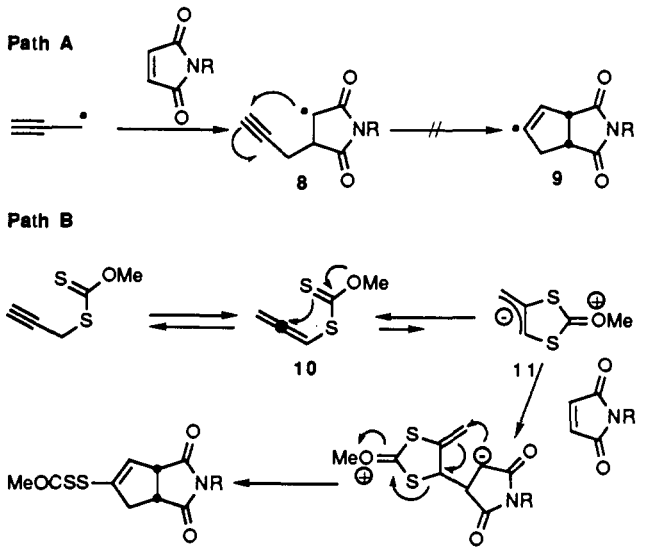
Scheme I



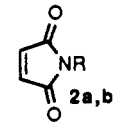
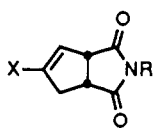
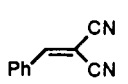
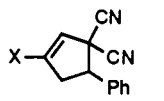
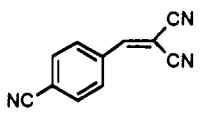
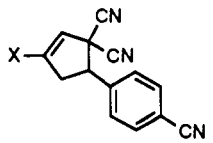
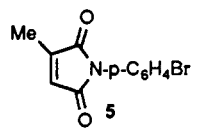
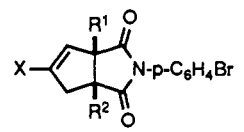
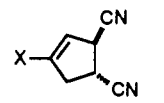
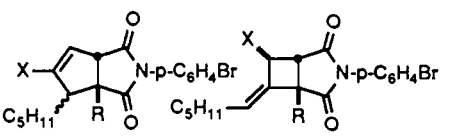
Scheme II



xanthate group in compound **6** was removed by using nickel boride to give the corresponding cyclopentene derivative (X = H in **6**) in 55% yield). Since radical additions to citraconic derivatives are known to be highly regioselective,[4] only adduct **6** should have been formed if radical intermediates such as **8** and **9** were involved. Moreover, all our attempts to convert the minor "normal" adduct **3b** into the bicyclic derivative **5** by regenerating intermediate radical **8** failed.[5] Finally, we found that, unlike the radical chain reaction leading to the "normal" adducts (e.g., **3a**),[1a,b] neither light nor the *S*-benzoyl xanthate catalyst was actually needed for the annulation reaction. Indeed, simply heating propargyl xanthate and the electrophilic olefin in chlorobenzene gave the corresponding cyclopentene derivatives, although yields were slightly but consistently lower than in the first set of experiments (see Table I).

An alternative mechanism, involving allenyl xanthate **10**[6] and the cyclic betaine intermediate **11** (Scheme II, path B), may be proposed.[7] Thus, a Michael type addition of the allylic-type anion

Table I. Reaction of Propargyl Xanthates **1b** and **1c** with Electrophilic Olefins[a]

Olefin	Products (X= MeOCSS-)	
 **2a,b**		(a) R = $PhCH_2$- Yield 45 (40) % (b) R = p-BrC_6H_4- Yield 66 (41) %
		Yield 40%
		Yield 55 (45) %
 **5**		**6**, R^1 = Me; R^2 = H **7**, R^1 = H; R^2 = Me Total yield 80 (73)%
Fumaronitrile or Maleonitrile		Yield (25%) ; (18%)
2b **5** (Xanthate **1c** was used in this case)		**12** R = H (55 %) **14** R = Me (58%) **13** R = H (12 %) **15** R = Me (25%)

[a] A solution of the olefin, *S*-benzoyl *O*-ethyl xanthate (2%), and xanthate **1b** or **1c** (last entry) (5 equiv) in chlorobenzene (11 mL/mmol) (11 mL/mol) is heated to reflux and irradiated with a 500-W tungsten lamp for 20–30 min. Yields in parentheses refer to reactions carried out by omitting both the *S*-benzoyl xanthate and the irradiation.

onto the olefin followed by cyclization leads to the observed adduct. The Michael addition could take place at either end of the allyl system (only one mode is depicted in Scheme II for simplicity), explaining the formation of the two isomers **6** and **7** in the case of citraconimide **5**. The fact that both fumaronitrile and maleonitrile give the same cyclized product, albeit in poor yield, militates against a possible stereospecific concerted process.[8] Finally, in the case of substituted propargylic xanthate **1c** (Table I, last entry), only one regioisomer was isolated from reaction with olefins **2b** and **5**, namely, **12** (as a 2:1 mixture of epimers) and

(4) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (b) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1984**, *117*, 3175. (c) Giese, B.; Meixner, J. *Tetrahedron Lett.* **1977**, 2779, 2783.

(5) We had earlier shown (ref 1b) that, under similar reaction conditions, the related adduct **3a** readily gives back the intermediate radical (corresponding to **8**), which may be captured by allyl acetate.

(6) The presence in the medium of allenyl xanthate **10** is supported by the observation of signals in the NMR and IR spectra (band at 1950 cm^{-1}) of the crude reaction mixture, consistent with such a structure. This intermediate, however, could not be isolated. The rearrangement of the propargyl xanthate **1b** to its allenyl isomer occurs thermally through a [3,3] sigmatropic shift. However, in the presence of radical initiators (photolytic conditions), it can also take place by the following radical chain mechanism: $MeOCSS^{\bullet}$ + $HC{\equiv}CCH_2SCSOMe \rightarrow MeOCSSCH{=}C{=}CH_2 + MeOCSS^{\bullet}$, etc.; whence the variation in the yields between the two sets of experiments. For a related S_H2' process, see: Ueno, Y.; Okawara, M. *J. Am. Chem. Soc.* **1979**, *101*, 1893.

(7) Numerous formal (3 + 2) annulation reactions are known; a few bear some mechanistic resemblance to the present reaction: (a) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, *111*, 7285 and references therein. (b) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805; **1986**, *108*, 6695. (c) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (d) Herndon, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 3165. (e) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. (f) Cutler, A.; Ehntholt, D.; Giering, W. P.; Lennon, P.; Raghu, S.; Rosan, A.; Rosenblum, M.; Tancrede, J.; Wells, D. *J. Am. Chem. Soc.* **1976**, *98*, 3495. (g) Beak, Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 218. (h) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825. (i) Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett.* **1978**, 4823. (j) See also: Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vols. 1 and 2.

(8) Other variants of this mechanism regarding, for example, the timing of the various steps (viz., whether a true betaine is formed first or the allenyl xanthate reacts first with the electrophilic olefin, etc.) can also be invoked. Moreover, the cyclization step itself has been depicted for simplicity as a 5-endo-trigonal process (i.e., an internal S_N2'), but it may well involve an initial S_N2 step followed by a thermal rearrangement of the intermediate allylic cyclopropane. These aspects, some of which have been raised by a referee, are currently under study.

14 (essentially one epimer), respectively. However, further complicating the mechanistic picture, small quantities of the corresponding cyclobutane derivatives 13 and 15[9] were also isolated. Cyclobutane formation from allenes is well precedented.[10]

This new reaction, which produces highly functionalized cyclopentene derivatives, has unraveled a hitherto unknown facet of the chemistry of *S*-propargyl xanthates with intriguing synthetic and mechanistic implications. Its scope and selectivity as well as the possibility of an intramolecular variant are currently under study.

Acknowledgment. We thank Prof. J.-Y. Lallemand for friendly discussions and the Société Nationale des Poudres et Explosifs (SNPE) for generous financial support.

(9) Only one geometrical isomer of 13 and 15 was observed, to which the configuration shown has been tentatively assigned by analogy (see ref 10d).

(10) See inter alia: (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley-Interscience: New York, 1984. (b) Pasto, D. J.; Yang, S. H. *J. Org. Chem.* **1986**, *51*, 1676; *J. Am. Chem. Soc.* **1984**, *106*, 152. (c) Pasto, D. J.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3670. (d) Pasto, D. J.; Heid, P. F.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3676 and references therein.

Synthesis of Oligonucleotides via Monomers with Unprotected Bases

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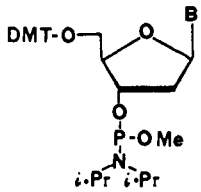
The need to protect the amino groups of nucleoside bases was recognized early in the development of chemical methods for synthesizing oligonucleotides.[1,2] Since then, N-protecting groups have been universally employed in oligonucleotide synthesis. Ideally, however, one would like to avoid protecting groups. At best they entail two additional steps, introduction and removal, and the reagents required in these steps limit the range of functional groups that can be tolerated in the synthesis.

We report here a procedure, utilizing phosphoramidite reagents,[3] that enables one to synthesize oligonucleotides of short to moderate length without resort to N-protecting groups. Selectivity with respect to OH and NH_2 groups is achieved not by blocking reaction at nitrogen but by selective group transfer from nitrogen.[4] The procedure appears promising for solid-phase synthesis of new oligonucleotide analogues containing substituents sensitive to N-deblocking reagents. Such compounds can have potential as selective inhibitors of viral replication and gene expression.[5]

Nucleoside phosphoramidites **1a,c,g** were obtained in ~90% yield by phosphitilating DMT-dA,[6] DMT-dC,[7] and DMT-dG[6] with $MeOP[N(iPr_2)]_2$.[8] Attempts to prepare these compounds with $MeOP(Cl)[N(iPr_2)]$ were unsatisfactory since extensive reaction occurred at the amino as well as hydroxyl groups of the nucleosides.



1a B = adenyl
1c B = cytosyl
1g B = guanyl

Condensation of **1a** (Figure 1) or **1c** under standard conditions with thymidine anchored to a solid support (dT-succinyl-CPG), followed by oxidation, gave a complex mixture of products. HPLC profiles and dimethoxytrityl cation assays indicated extensive phosphitilation at the unprotected amino groups as well as the 5′-hydroxyl group of the support-bound thymidine.[9] On the other hand, good quality d(GT) was obtained from the reaction with **1g**, showing that the amino group of dG is relatively resistant to the phosphitilating agent (Figure 1). Indeed, as we found by preparing d(GGGGGT), d(GAGGTCAGGT), and d(CCATTTTCAGAATTGGGTGT), one can obtain oligonucleotides of moderate length using conventional phosphoramidite methodology without protecting the amino group of guanine.[10]

For syntheses utilizing **1a** and **1c** we exploited the fact that products of phosphitilation at the amino groups of cytosine and adenine derivatives are themselves phosphoramidites and can serve as phosphitilating agents. A step was added to the synthetic protocol to cleave these amidites prior to oxidation. Of several cleavage systems examined, a mixture of pyridine hydrochloride (an acid to activate P(III)-N derivatives) and aniline (a nucleophile to accept the P(III) fragment) proved most effective.[11] As shown in Figure 1, good quality d(AT) and d(CT) were readily obtained when treatment with this acid/nucleophile combination was included in the synthetic procedure. Neither pyridine hydrochloride nor aniline alone was suitable.

The overall scheme is represented by the synthesis of d(GAGGTCAGGT), starting from dT-succinyl-CPG (0.5 μmol of dT). Each cycle consisted of detritylation (3% DCA in CH_2Cl_2), washing (MeCN), coupling (15 mg of **1a**, **1c**, **1g**, or standard dT phosphoramidite reagent, 8.8 mg of tetrazole, 0.25 mL of MeCN; 3 min), washing (MeCN), phosphityl transfer (0.1 M pyridine hydrochloride, 0.1 M aniline, MeCN; 5 min), washing (MeCN), oxidation (I_2/H_2O; 2 min), and washing (CH_2Cl_2). Finally, conventional demethylation, cleavage, and purification by reversed-phase and ion-exchange HPLC afforded the decamer, 8 A_{260} units (16%), >99% homogeneous by both ion-exchange (OmniPac Na100 column) and reversed-phase HPLC (conditions in Figure 1). For comparison, an oligomer with the same sequence was prepared (15 A_{260} units, 30%)[12] under standard conditions with N-protected nucleoside reagents. The two oligomers were the same, as shown by the HPLC elution time, PAGE (0.88 relative to bromophenol blue), and thermal dissociation (T_m 42 °C; 0.1 M NaCl) of the complexes formed with a complementary oligomer, d(ACCTGACCTC). In addition, hydrolysis (snake venom phosphodiesterase and alkaline phosphatase) of the oligomer derived from unprotected bases afforded dA, dC, dG, and dT in the predicted amounts.[13]

This methodology, in conjunction with use of a support with an oxalyl anchor,[14] should provide access to mixed-base oligonucleotide derivatives containing functional groups sensitive to

(1) Michelson, A. M. *J. Chem. Soc.* **1959**, 3655-3669.

(2) (a) Khorana, H. G.; Turner, A. F.; Vizsolyi, J. P. *J. Am. Chem. Soc.* **1961**, *83*, 686-698. (b) Ralph, R. K.; Khorana, H. G. *J. Am. Chem. Soc.* **1961**, *83*, 2926-2934. (c) Rammler, D. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 3112-3122.

(3) Caruthers, M. H. *Science* **1985**, *230*, 281-285.

(4) Attempts to achieve selective phosphitilation without protecting amino groups have had only very limited success: (a) Letsinger, R. L.; Finnan, J. L.; Jacobs, S. A.; Juodka, B. A.; Varshney, A. K. *Synthesis, Structure and Chemistry of t-RNA*, International Conference, Poznan, Poland, 1976; pp 147-159. (b) Ogilvie, K. K.; Theriault, N.; Sadana, K. L. *J. Am. Chem. Soc.* **1977**, *99*, 7741-7743. (c) Ogilvie, K. K.; Schifman, A. L.; Penney, C. L. *Can. J. Chem.* **1979**, *57*, 2230-2238. (d) Fourrey, J.-L.; Varenne, J. *Tetrahedron Lett.* **1985**, *26*, 2663-2666.

(5) Cohen, J., Ed. *Oligodeoxynucleotides*; CRC Press, Inc.: boca Raton, FL, 1989.

(6) Sigma Chemical Co.

(7) Michelson, A. M.; Todd, A. R. *J. Chem. Soc.* **1954**, 34-40.

(8) The phosphitilating procedure was that used for N-protected derivatives by Barone et al. (Barone, A. D.; Tang, J.-Y.; Caruthers, M. H. *Nucleic Acids Res.* **1984**, *12*, 4051-4061), except that a larger excess (1.8/1) of amidite and tetrazolium salt was employed for DMT-dC. **1a,c,g** each showed only a double peak near 152 ppm in the ^{31}P NMR spectrum and exhibited the expected molecular ion in the FAB^- mass spectrum (713, 689, 729, respectively; MS by Doris Hung).

(9) DMT^+ released in the DCA step was ~2-fold and 4-fold greater, for reactions of **1a** and **1c**, respectively, than calculated, assuming no reaction at NH_2.

(10) Standard protocol with a Milligen Cyclone DNA synthesizer.

(11) Tetrazole (0.4 M) in methanol/acetonitrile (5 min) served as a transfer agent for work with dC derivatives but did not remove all P(III) fragments from nitrogen of dA derivatives. With 4 M tetrazole, P-O cleavage accompanied P-N cleavage.

(12) The difference in yields of the decamer reflects some additional side products in reactions involving unprotected bases.

(13) For methods, see ref 14.

(14) Alul, R.; Singman, C. N.; Zhang, G.; Letsinger, R. L. *Nucleic Acids Res.* **1991**, *19*, 1527-1532.

0002-7863/91/1513-5876$02.50/0