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SOLID-PHASE SYNTHESIS OF OLIGODEOXYRIBONUCLEOTIDES USING THE BIS (TRIMETHYLSILYL) PEROXIDE OXIDATION OF PHOSPHITES §

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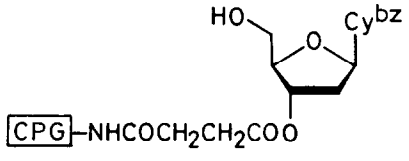
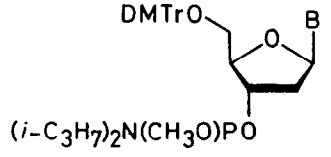
Summary: The trimethylsilyl triflate-catalyzed bis (trimethylsilyl) peroxide oxidation of phosphites has been successfully applied to the solid-phase synthesis of d (AAGATC).

The bis (trimethylsilyl) peroxide oxidation of phosphites,[1] accomplishable under nonaqueous conditions, possesses substantial advantage in the solid-phase oligonucleotide synthesis over the conventional aqueous iodine oxidation[2] which requires incidental drying steps. Here we demonstrate its high utility by synthesis of a hexanucleoside pentaphosphate, d (AAGATC) (8).

The controlled pore glass (CPG) -bound cytidine nucleoside **1** was elongated to **6** by repeating the reaction cycle shown in Table I. In the first phosphoramidite condensation, the steps 1 to 4 were of course unnecessary. Each coupling reaction sequence was effected in the average yield of 94%, determined by the colorimetric method of the released DMTr function. Thus the protected hexamer **6** was obtained in 72% overall yield from **1**. The polymer-supported product **6** was then treated with a 1 : 1 : 2 mixture of thiophenol, triethylamine, and dioxane (25 ℃, 30 min), followed by conc ammonia (25 ℃, 2 h) to give the partially protected hexamer **7**. The ^{31}P-NMR spectrum of crude **7** showed no signals due to the trivalent phosphorus, indicating the quantitative oxidation. Finally **7** was converted to d (AAGATC) (8) through deacylation by conc ammonia (55 ℃, 6 h) and subsequent detritylation by 80% acetic acid (25 ℃, 1 h). The structure of 8, a part of the probe for chum salmon prolactin,[3] was confirmed after conversion of it to the ^{32}P-labeled 5'-monophosphate **9**[4] by comparison of behavior in polyacrylamide-gel electrophoresis (PAGE) with that of the authentic sample.



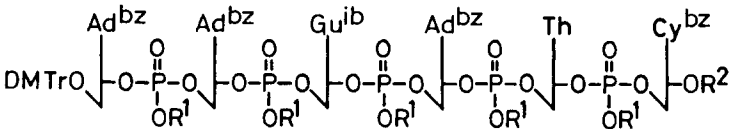
1



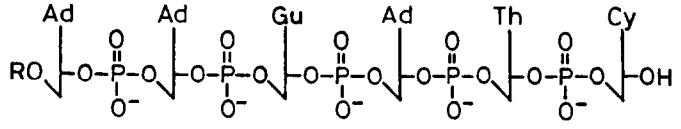
2, B = Ad^bz
3, B = Cy^bz
4, B = Gu^ib
5, B = Th

Acknowledgments. We appreciate Nippon Zeon Co., Biological Science Institute, for generous gift of the compounds **1** to **5** and structure determination of the product 8.

§ This paper is dedicated to Professor Morio Ikehara on the occasion of his retirement from Osaka University in March, 1986.



6, $R^1 = CH_3$; $R^2 = COCH_2CH_2CONH$–[CPG]
7, $R^1 = R^2 = H$



8, R = H
9, R = $^{32}PO_3^{2-}$

Table I. Reaction Sequence of the Solid-Phase Synthesis.

step[a]	operation	reagent (equiv)	volume/mL	time/min	repetition
1	detritylation	0.2 *M* $CHCl_2COOH/CH_2Cl_2$	2	1	3
2	washing	CH_2Cl_2	2		3
3	washing	1% pyridine/THF	2		2
4	washing	CH_3CN	2		3
5	coupling	nucleoside phosphoramidite	1	10	1
		2, **3**, **4**, or **5** (15) /CH_3CN			
		1*H*-tetrazole (38) /CH_3CN	1.25		
6	washing	CH_3CN	2		1
7	capping	0.5 *M* DMAP[b]/THF	1	3	1
		1 *M* Ac_2O—2, 6-lutidine/THF	1		
8	washing	1% pyridine/THF	2		1
9	oxidation	TMSOOTMS (20) / $(C_2H_5)_3N$ (1) /CH_2Cl_2	1	2	1
		TMSOTf (1) /CH_2Cl_2	1		
10	washing	CH_2Cl_2	2		3

[a] The steps 4 to 9 were performed under argon atmosphere. [b] 4-Dimethylaminopyridine.

REFERENCES AND NOTES

1. Y. Hayakawa, M. Uchiyama, and R. Noyori, the preceding paper.
2. M. A. Dorman, S. A. Noble, L. J. McBride, and M. H. Caruthers, *Tetrahedron*, **40**, 95 (1984), and references cited therein.
3. H. Kawauchi, K. Abe, A. Takahashi, T. Hirano, S. Hasegawa, N. Naito, and Y. Nakai, *Gen. Comp. Endocr.*, **49**, 446 (1983).
4. The compound **9** was prepared by the standard method, namely, the polynucleotide kinase-assisted reaction of 8 and [γ-^{32}P]-ATP: see, M. Takanami, *J. Mol. Biol.*, **23**, 135 (1967); R. Silber, V. G. Malathi, and J. Hurwitz, *Proc. Nat. Acad. Sci. U. S.*, **69**, 3009 (1972).

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