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SILYLATED DERIVATIVES OF ARABINONUCLEOSIDES

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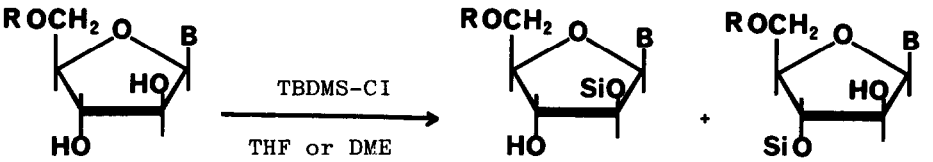
Summary-Procedures have been developed which allow for the selective derivatization of arabinonucleosides at the 5'- or 2'- and 5'- or 3'- and 5'- positions.

Arabinonucleosides (1-5) and arabinonucleotides (6-12) have been shown to possess a wide range of biological activities including antiviral and antitumor activity. As a result, numerous studies have appeared (e.g., 13-18) describing hydroxyl-derivatized arabinonucleosides with actual or potential biological activity. However, the only detailed study on arabinonucleotide synthesis is the pioneering work by Wechter (20) There is no report in the literature describing general techniques for the selective derivatization of arabinonucleosides permitting their stepwise inclusion into nucleotide chains. In the study by Wechter (19) the 2'- and 3'-hydroxyls were unprotected resulting in a mixture of 2'-5' and 3'-5' linked arabinonucleotides which were difficult to separate. We wish to report the first general procedure for the preparation of protected arabinonucleosides suitable for stepwise incorporation into nucleotide chains.

The method involves the protection of either the 2'- or 3'-position with the t-butyldimethylsilyl (TBDMS) group which we have developed for the ribo series (21,22). The methods initially used in the ribo area (DMF, imidazole) were not directly applicable to the arabino series except for 5'-silylation (see also 18). However we have recently developed novel catalysts for silylation reactions (23) and these have been applied successfully to the arabinonucleosides. As a result we are able to describe methods for the rapid high yield production of 2',5'- and 3'5'-protected arabinonucleosides

In order to obtain high yields of either 2',5' or 3',5'-diprotected derivatives of both purine and pyrimidine arabinonucleosides, several sets of conditions were employed The isomer ratios were dependent on whether a purine or pyrimidine nucleoside was used

One general procedure consisted of dissolving the nucleoside in THF (20 ml/mmole of nucleoside) followed by addition of pyridine. Silver nitrate was added and after stirring for 5 min, t-butyldimethylsilyl chloride (TBDMS-Cl) was added and stirring was continued at room temperature. At the end of the reaction period the solution was filtered into a 10% $NaHCO_3$ solution and the product was then extracted into dichloromethane Products were isolated by short column chromatography. The results summarized in Table 1 show that these conditions gave high yields of the 2',5'-protected derivatives in the case of arabinoadenosine but gave very high yields of the



1 R=H
2 R=DMT
3 R=Si

4 R=Si
5 R=DMT

6 R=Si
7 R=DMT

a)B=adenine
b)B=cytosine
c)B=N-benzoylcytosine
d)B=uracil

DMT=dimethoxytrityl
Si=t-butyldimethylsilyl

3',5'-protected pyrimidines. On the other hand, if the above procedure was repeated except that dimethoxyethane (DME) replaced THF as solvent and triethylamine (Et_3N) replaced pyridine, then the trend was reversed and ara A gave high yields of 3',5'-derivatives while the pyrimidines gave excellent yields of the 2',5'-diprotected derivatives.

By repeating the above procedure using THF as solvent but replacing pyridine with 1,4-diazabicyclo[2 2.2]octane (DABCO), all arabinonucleosides gave high yields of the 2',5'-diprotected derivatives.

In another general procedure silver nitrate was suspended in THF or DME (20 ml/mmole of nucleoside) and 3-methylpyridine N-oxide was added. After stirring for 5 min TBDMS-Cl was added and the reaction mixture was stirred for 1 h. At this point the nucleoside was added and stirring was continued for 2-3 h. The solution was collected by filtration, washed with water (3 x) and dried over magnesium sulfate. Products were isolated by short column chromatography and yields are recorded in Table 1. It is clear that in all cases, very high yields of the 3',5'-protected derivatives were obtained.

It should be noted that in this last procedure NO silylation occurs when silver nitrate is omitted.

This manuscript describes a set of procedures that allow for the rapid synthesis of arabinonucleosides protected at either the 2'- and 5'-positions or at the 3'- and 5'-positions. The protecting groups used have previously been shown to be highly suitable to oligonucleotide synthesis in the ribo series (21,22).

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TABLE 1

Silylation of Arabinonucleosides*

Nucleoside	Solvent	Base (mmole)	t (h)	5'	Yields[24] (%)++ 2',5'	3',5'
ara A, 1a	THF	pyridine (5)	3	-	92(4a)	3(6a)
DMTara A, 2a	THF	pyridine (3)	3	-	90(5a)	5(7a)
ara C, 1b	THF	pyridine (5)	3	-	5(4b)	90(6b)
DMTara C, 2b	THF	pyridine (4)	3	-	10(5b)	80(7b)
ara C^{Bz}, 1c	THF	pyridine (5)	3	-	20(4c)	70(6c)
ara U, 1d	THF	pyridine (5)	3	-	5(4d)	70(6d)
DMTara U, 2d	THF	pyridine (4)	5	-	5(5d)	80(7d)
ara A, 1a	DME	Et_3N(5)	3	-	30(4a)	50(6a)
ara C, 1b	DME	Et_3N(5)	3	-	90(4b)	5(6b)
ara C^{Bz}, 1c	DME	Et_3N(5)	3	-	50(4c)	35(6c)
ara U, 1d	DME	Et_3N(5)	5	-	96(4d)	-
ara A, 1a	THF	# 3-pic-N-O(2.6)	2	-	5(4a)	90(6a)
+ ara A, 1a	THF	3-pic-N-O(2.6)	2	-	-	-
ara C, 1b	THF	3-pic-N-O(2.6)	2	-	-	95(6b)
ara C, 1b	DME	3-pic-N-O(2.6)	2	-	5(4b)	90(6b)
+ ara C, 1b	THF	3-pic-N-O(2.6)	2	-	-	-
ara C^{Bz}, 1c	THF	3-pic-N-O(2.6)	2	-	-	91(6c)
ara U, 1d	THF	3-pic-N-O(2.6)	2	-	-	95(6d)
+ ara U, 1d	THF	3-pic-N-O(2.6)	2	-	-	-
ara A, 1a	THF	DABCO (6)	3	-	70(4a)	20(6a)
ara C, 1b	THF	DABCO (6)	3	-	80(4b)	-
ara U, 1d	THF	DABCO (6)	3	-	75(4d)	5(6d)

* TBDMS-Cl and $AgNO_3$ were present to the extent of 1.2 mmole/mmole of free hydroxyl group. Reagents were added in the order described in the text.

\+ $AgNO_3$ was omitted from these experiments.

\# 3-pic-N-O is 3-methylpyridine N-oxide.

++ Yields were determined on products isolated by short column chromatography (silica gel).

References

1. R.S.K. Young and G.A. Fischer, Biochem. Biophys. Res. Comm., 32, 23-29 (1968).
2. P.B. Farmer and R.J. Suhadolnik, Biochemistry, 11, 911-916 (1972).
3. P.J. Ortiz, M.I. Manduka and S.S. Cohen, Cancer Res., 32, 1512-1517 (1972).
4. C. Shipman, S.H Smith and J C. Drach, Proc. Nat. Acad. Sci. USA, 69, 1753-1757 (1972).
5 D. Falke, K. Ronge, J. Arendes and W.E.G. Muller, Biochim Biophys. Acta. 563, 36-45 (1979
6. R.L. Momparler, Biochem. Biophys. Res. Comm., 34, 465-471 (1979).
7. R.A.Long, G.L. Szekeres, T A. Khwaja, R.W. Sidwell, L.N. Simon and R.K. Robins, J. Med. Chem., 15, 1215-1218 (1972).
8. M. Staub, H.R. Warner and P. Reichard, Biochem. Bipphys. Res Comm., 46, 1824-1829 (1972).
9. G.A. LePage and E.M. Hersh, ibid., 46, 1918-1922 (1972).
10 A. Mimian, R. Harris, R W Sidwell, R.K. Robins and T.A Khwaja, J. Med. Chem., 17, 259-263 (1974).
11. G. Hess, W. Arnold and K-H. Meyer zum Buschentelde, Antimicrobial Agents and Chemotherapy, 19, 44-50 (1981).
12. J F. Gephart and A.M Lerner, ibid., 19, 170-178 (1981)
13. D T. Gish, R.C Kelly, G.W. Camiener and W J Wechter, J Med. Chem., 14, 1159-1162 (1971)
14. J.A. Montgomery and H J Thomas, ibid., 15, 116-118 (1972)
15. K. Miyai, L.B. Allen, J.H. Huffman, R.W. Sidwell and R.L. Tolman, ibid., 17, 242-244 (1974
16. W J. Wechter, M.A. Johnson, C M Hall, D T Warner, A.E. Berger, A.H. Wenzel, D.T. Gish and G.L. Neil, ibid., 18, 339-341 (1975).
D.T. Warner, G.L. Neil, A.J Taylor and W.J. Wechter, ibid., 15, 790-792 (1972).
17. D.C. Baker, T.H. Haskell and S.R. Putt, ibid., 21, 1218 (1978).
18. D.C. Baker, T.H. Haskell, S.R. Putt and B.J. Sloan, ibid., 22, 273-279 (1979).
19. W.E.G. Muller, Jap. J. Antibiotics, S-104 to S-120 (1977).
20. W J. Wechter, J. Med. Chem.,10, 762-773 (1967).
21. K K Ogilvie, S.L. Beaucage, A.L. Schifman, N.Y. Theriault and K.L. Sadana, Can. J. Chem., 56, 2768-2780 (1978).
22. K.K. Ogilvie, A.L. Schifman and C.L. Penney, ibid., 57, 2230-2238 (1979).
23. G.H. Hakimelahi, Z.A Proba and K.K. Ogilvie, Tetrahedron Lett., 22, 4775-4778 (1981), ibid., 22, 5243-5426 (1981).
24. Structures were determined from analysis of ^{13}C chemical shift data of the silylated derivatives[25,26]. Compounds 4-7 (b-d) were also prepared from the corresponding cyclonucleosides[26].
25. K.K. Ogilvie, A.L. Schifman and C.L. Penney, Can. J. Chem. 57, 2230 (1979), W. Kohler and W. Pfleiderer, Liebigs Ann. Chem., 1855 (1979)
26. Danny P.C. McGee, M.Sc. Thesis, McGill University, 1981

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