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Regioselective Protection of the 2'-Hydroxyl Group of *N*-Acyl-3',5'-*O*-di(*t*-butyl)silanediylnucleoside Derivatives by Use of *t*-BuMgCl and 2-(Trimethylsilyl)ethoxymethyl Chloride

Takeshi Wada, Masanori Tobe, Takashi Nagayama, Kiyotaka Furusawa†, and Mitsuo Sekine*

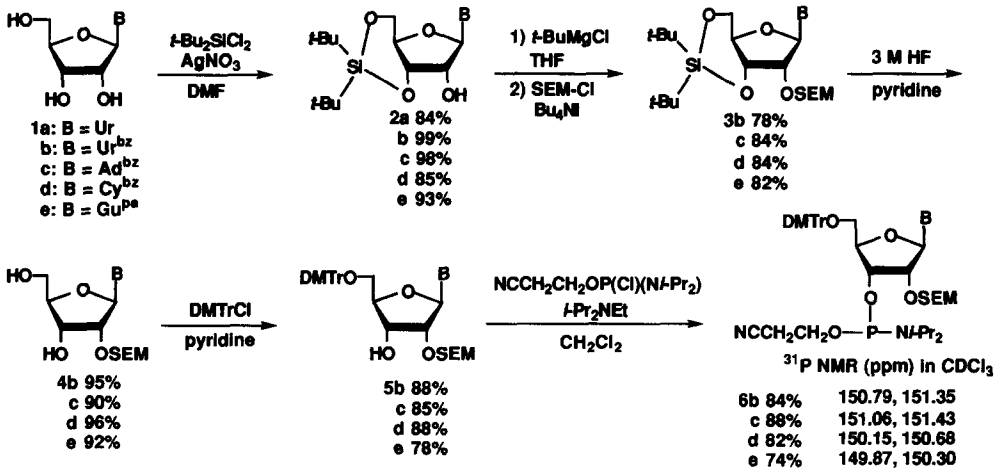
Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227, Japan

†Research Institute for Polymers and Textiles, Yatabe-Higashi 1-1-5 Tsukuba, Ibaraki 305, Japan

Abstract: Regioselective 2'-*O*-protection of *N*-protected 3',5'-*O*-di(*t*-butyl)silanediylribonucleoside derivatives with the 2-(trimethylsilyl)ethoxymethyl (SEM) group has been achieved by use of *t*-BuMgCl and 2-(trimethylsilyl)ethoxymethyl chloride. The former was used as a base. The 2'-*O*-SEM protected ribonucleoside derivatives were converted *via* a three-step reaction into the corresponding phosphoramidite building blocks in good overall yields.

A remaining problem in the current synthesis of oligoribonucleosides is the slow rate of condensation due to the bulkiness of 2'-hydroxyl protecting groups such as *t*-butyldimethylsilyl (TBDMS).[1,2] Another drawback is difficulty in selective protection of the 2'-hydroxyl of ribonucleosides with TBDMS-Cl.[3] In order to overcome these problems, we originally reported 2-(trimethylsilyl)ethoxymethyl (SEM)[4] as a new 2'-hydroxyl protecting group which could be removed by treatment with fluoride ion.[5] Quite recently, Usman *et al.* has described the synthesis of $(Up)_9U$ using the SEM group where $BF_3{\cdot}Et_2O$ was successfully employed for removal of the SEM group.[6] According to their method, introduction of the SEM group into the 2'-position of uridine was carried out *via* the 2',3'-*O*-dibutylstannylene intermediate by a modification of the procedure reported by Moffatt.[7] However, this method gave a nearly 1:1 mixture of the 2'- and 3'-isomers. In this paper, we report a highly efficient and general procedure for the synthesis of 2'-*O*-SEM protected ribonucleoside phosphoramidite building blocks.

It was reported that the di(*t*-butyl)silanediyl group can be rapidly deprotected under very mild conditions by use of pyridinium poly(hydrogen fluoride)[8,9] or Bu_3NHF.[10] On the other hand, we found that the SEM group of 2'-*O*-SEM-protected ribonucleosides were sufficiently stable to these desilylating reagents.[5] Therefore, we used 3',5'-*O*-di(*t*-butyl)silanediylnucleosides (**2a-e**) as starting materials for the 2'-*O*-SEM protection. These key intermediates could be obtained in 84-99% yields from the parent nucleosides **1a-e**.[11] When compound **2b** was allowed to react with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in the presence of *i*-Pr_2NEt and Bu_4NI[12] in CH_2Cl_2 for 3 h, the corresponding 2'-*O*-SEM protected derivative **3b** was obtained in 88% yield. When the N^3-unprotected uridine derivative **2a** was used in place of **2b**, the SEM group was introduced exclusively at the N^3-position. In the case of the 6-*N*-benzoyladenosine derivative **2c**, the SEM group was introduced to the 2'-hydroxyl, but the 6-*N* or N^1 position was simultaneously alkylated to a degree of 30-40%. Predominant base-modification with SEM-Cl was also observed in the case of 4-*N*-benzoylcytidine and 2-*N*-phenylacetylguanosine derivatives (**2d** and **2e**).



In order to realize the 2'-*O*-selective introduction of the SEM group, we have searched for various bases as activators for the 2'-hydroxyl function. Hayakawa *et al.* reported that *t*-BuMgCl was particularly useful for the *O*-selective *phosphorylation* of *N-unprotected* nucleoside derivatives.[13] Interestingly, we found that this magnesium salt was also effective for the *O*-selective *alkylation* of *N-protected* ribonucleoside derivatives. Appropriately *N*-protected ribonucleoside derivatives **2b-e** were treated with *t*-BuMgCl (2 equiv) in THF at room temperature for 5 min and then with SEM-Cl (2 equiv) and Bu_4NI (2 equiv) in THF at room temperature for 20-30 h. After the usual workup followed by silica gel column chromatography, the 2'-*O*-SEM protected nucleosides **3b-e** were isolated in 78-84% yields. In each case, no significant alkylation of the base moiety was observed. Treatment of compounds **3b-e** with 3 M pyridinium poly(hydrogen fluoride) in pyridine for 30 min gave the 2'-*O*-SEM protected nucleosides **4b-e** in high yields of 90-96%.

Reaction of compounds **4b-e** with DMTr-Cl in pyridine in the usual manner afforded 5'-*O*-dimethoxytrityl-2'-*O*-SEM-nucleosides **5b-e** in 78-88% yields. Finally, these compounds were converted to the corresponding phosphoramidites **6b-e** in 74-88% yields by the standard procedure.[14] These phosphoramidites were found to be more reactive than the corresponding 2'-*O*-TBDMS protected phosphoramidites in the solid-phase synthesis.

In conclusion, the present method enabled us to achieve the regioselective introduction of the SEM group into the 2'-position of *N*-acylated ribonucleosides in high yields without base modification by use of *t*-BuMgCl and SEM-Cl as *O*-selective metallating and alkylating reagents, respectively.

References

1. Usman, N.; Ogilvie, K. K.; Jiang, M.-Y.; Cedergren, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 7845.
2. Lyttle, M. H.; Wright, P. B.; Sinha, N. D.; Bain, J. D.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4608.
3. Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Can. J. Chem.* **1982**, *60*, 1106.
4. Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
5. Wada, T.; Tobe, M.; Nagayama, T.; Furusawa, K.; Sekine, M. *Nucleic Acids Symp. Ser.* **1993**, *29*, 9.
6. Wincott, F. E.; Usman, N. *Tetrahedron Lett.* **1994**, *35*, 6827.
7. Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24.
8. Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999.
9. Sekine, M.; Iimura, S.; Furusawa, K. *J. Org. Chem.* **1993**, *58*, 3204.
10. Furusawa, K. *Chem. Lett.* **1989**, 509.
11. Furusawa, K.; Ueno, K.; Katsuta, T. *Chem. Lett.* **1990**, 97.
12. Lipshutz, B. H.; Morett, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.
13. Uchiyama, M.; Aso, Y.; Noyori, R.; Hayakawa, Y. *J. Org. Chem.* **1993**, *58*, 373.
14. Sinha, N. D.; Biernat, J.; Mcmanus, J.; Köster, H. *Nucleic Acids Res.* **1984**, *12*, 4539.

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