Pergamon

*Tetrahedron Letters*, Vol. 36, No. 33, pp. 5865-5868, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01179-X

# THE STEREOCONTROLLED SYNTHESIS OF 1,2-CIS FURANOSYL NUCLEOSIDES VIA A NOVEL ANOMERIC ACTIVATION

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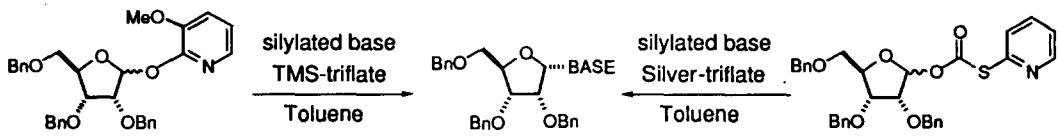
**Abstract:** The coupling of 2-(2',3',5'-tri-O-benzyl-D-ribofuranosyloxy)-3-methoxypyridine as well as 2-(2',3',5'-tri-O-benzyl-D-ribofuranosyl)-thiopyridylcarbonate, with silylated pyrimidine bases by activation with trimethylsilyl trifluoromethanesulfonate and silver triflate respectively affords the corresponding 1,2-*cis* nucleosides with high selectivity.

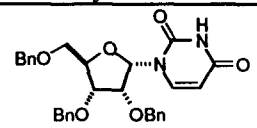
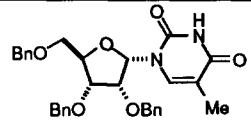
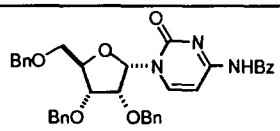
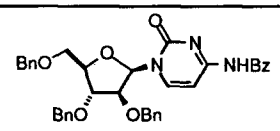
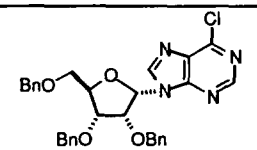
Most studies in nucleoside synthesis have dealt with the 1,2-*trans*-N-glycosyl bond due to the prevalence of this orientation in nature and in many bioactive analogs.[1] The synthesis of 1,2-*cis* nucleosides (also called α-nucleosides), has remained largely unexplored perhaps because of their relatively sparse activity as antibiotics and antiviral agents.[2] Methods for the stereocontrolled synthesis of 1,2-*cis* pyrimidine nucleosides are not as prevalent as their 1,2-*trans* isomers.[3] Sugimura and coworkers[4] reported a method for the synthesis of 1,2-*cis* nucleosides using thioglycosides as donors activated by N-bromosuccinimide.

We report herein a novel method for the stereocontrolled synthesis of 1,2-*cis* nucleosides based on the remote activation concept.[5] Two unprecedented leaving groups originally[6] developed for O-glycosides synthesis have been found to be admirably adapted for the synthesis of pyrimidine nucleosides as well. These are the 3-methoxy-2-pyridyloxy (MOP) and the 2-thiopyridylcarbonate (TOPCAT) groups (Table 1). Treatment of the corresponding 2,3,5-tri-O-benzyl-D-ribofuranosyl and D-arabinofuranosyl derivatives with a silylated[7] pyrimidine base in the presence of TMS triflate and silver triflate respectively for MOP and TOPCAT leaving groups, gave good to excellent yields of 1,2-*cis* nucleosides. The yield of the α-cytidine derivative was 60% with no evidence of the β-anomer. Table 1 shows the results with the D-ribo and D-arabino glycosyl donors utilizing silylated uracil, thymine and cytosine as pyrimidine bases and 6-chloropurine as a representative purine acceptor. The benzyl ether protective groups were hydrogenolyzed to give the parent known nucleoside. Toluene was found to be the solvent of choice for high 1,2-*cis* selectivity in all cases. Other solvents including benzene, dichloromethane, ether and DMF gave modest ratios in favor of the 1,2-*cis* nucleoside while maintaining high yields. Interestingly acetonitrile and THF showed a reversal in favor of the 1,2-*trans* isomer (3:1).[8]

**Table 1**




"MOP"- glycosyl donor, A "TOPCAT"- glycosyl donor, B

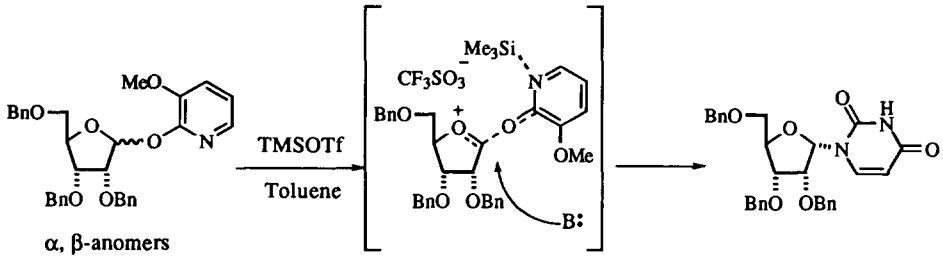
| Major Product | Donor type | Yield [a] | α/β- Ratio [b] | Conditions, 25°C |
|---|---|---|---|---|
|  $[\alpha]_D^{25}$ -12.4° (c. 0.5; $CHCl_3$) | A | 93% | 93:7 | 18 h |
| | B | 75% | 93:7 | 30 min |
|  $[\alpha]_D^{25}$ +2.76° (c. 1.9; $CHCl_3$) | A | 91% | 93:7 | 36 h |
| | B | 75% | 94:6 | 30 min |
|  $[\alpha]_D^{25}$ -37° (c. 0.5; $CHCl_3$) | A | 60% | α only | 24 h |
| | B | 50% | 96:4 | 6 h |
|  $[\alpha]_D^{25}$ +88.6° (c. 1.7; $CHCl_3$) | B | 71% | 18:82 | 24 h |
|  $[\alpha]_D^{25}$ -17.4° (c. 1.6; $CHCl_3$) | A | 50% | 99:1 | 15 min |
| | B | 56% | 99:1 | 6 h |

a. Yield of isolated, chromatographically pure α-nucleoside. b. Ratio determined by $^1H$ NMR at 300 MHz, and confirmed by weights of isolated nucleosides whenever possible.

The unexpected predominance of 1,2-*cis* nucleosides in the D-ribo and D-arabino series is most intriguing and unprecedented. The design of the MOP group was predicated upon its activation by the catalyst most likely at nitrogen which generates an oxonium ion pair species. In the above described reactions, the tightly bound MOP part, or a transient glycosyl triflate, may adopt a 1,2-*trans* orientation, particularly in a nonpolar solvent like toluene (Scheme 1). Nucleophilic attack by the pyrimidine base (exemplified by TMS-uracil in Scheme 1) occurs in a stereoelectronically favored approach in spite of the *syn* disposition of the 2-O-benzyl group. The relatively prolonged time required to complete the reaction (18-24 h) may also allow equilibration of α-MOP anomer to the β-anomer. Evidently in the presence of polar or coordinating solvents such as acetonitrile or THF, ion pairs are looser

giving opportunity for solvent to interact with the oxonium ions, and even to compete as nucleophiles favoring the more facile approach from the side opposite to the C-2 substituent.

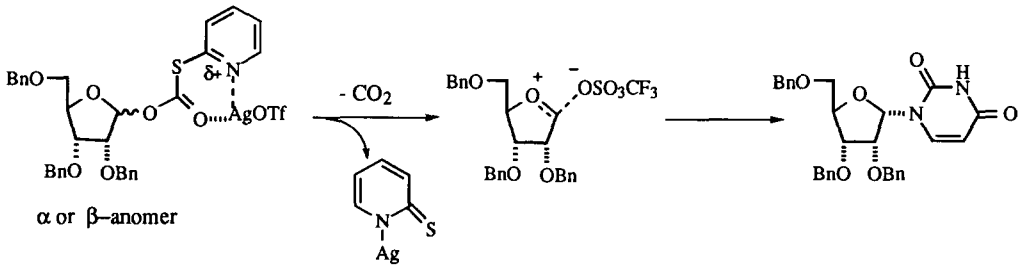
**Scheme 1**




B = TMS-uracil TMS-thymine TMS-N-benzoylcytosine

By design,[6] the nature of the remote activation is different in the TOPCAT leaving group. Thus, silver triflate may act via a bidentate mode of activation to produce an oxonium ion pair that is either shielded from the β-side by an incipient TOPCAT nucleofugal specie, or a transient 1,2-*trans* glycosyl triflate which reacts 1,2-*syn* mode via an $S_N2$-like attack (Scheme 2). Interestingly, the α-D-ribo TOPCAT anomer also gave the 1,2-*cis* nucleoside as the major product, thus demonstrating the probable formation of the same reactive intermediate produced from the β-anomer.

**Scheme 2**




**Typical procedures**

*2-(2',3',5'-tri-O-benzyl-D-ribofuranosyloxy)-3-methoxypyridine*: To a solution of 2,3,5-tri-O-benzyl-α,β-D-ribofuranosylchloride (0.25 mmol) in dry toluene (3 ml) was added the silver salt of the 3-methoxy-2-hydroxypyridine (0.86 mmol). The reaction mixture was stirred at 110°C for 30 min., Then the solution was filtered and concentrated to give a syrup which was purified by flash chromatography (hexanes-EtOAc, 4:1) to give an α,β mixture of the desired product (77%) as a syrup.

*2-(2',3',5'-tri-O-benzyl-D-ribofuranosyl)-thiopyridylcarbonate*: To a solution of 2,3,5-tri-O-benzyl-α,β-D-ribofuranose (2 mmol) in $CH_2Cl_2$ (5 ml), were added bis-2,2-thiopyridylcarbonate (4.0 mmol) and $Et_3N$ (4.0 mmol). The solution was stirred at r.t for 24 h., then concentrated under vacuum. The residue thus obtained was purified by flash chromatography (benzene) to give the α,β mixture of the expected product (70 %) as an oil.

*α-Thymidine using MOP*: To a solution of 2-(2',3',5'-tri-O-benzyl-D-ribofuranosyloxy)-3-methoxypyridine (0.15 mmol) in dry toluene (3 ml) were added bis-O-trimethylsilyl thymine (0.45 mmol; 3 eq) and TMSOTf (60μl; 2 eq). The solution was stirred under argon at r.t for 24 h.. The reaction mixture was quenched with sat. $NaHCO_3$ and the

aqueous phase extracted with $CH_2Cl_2$ and dried over $Na_2SO_4$. Filtration and concentration under vacuum gave a syrup that was purified by flash chromatography (hexanes-EtOAc, 3:1) to give the desired product (91%). Hydrogenolysis of the benzyl ethers gave the known α-thymidine, mp 171-171°, $[\alpha]_D^{25}$ -50.1° (c 1.2, MeOH); reported[9] mp 174-175°, $[\alpha]_D^{25}$ -52.3° (c 1.6, MeOH).

*α-Thymidine using TOPCAT*: To a solution of 2',3',5'-tri-O-benzyl-D-ribofuranosyl-2-thiopyridylcarbonate (0.13 mmol) in dry toluene (2.5 ml) under argon, were added bis-O-trimethylsilyl thymine (3 eq) and silver triflate (1.5 eq). The reaction mixture was stirred at r.t for 30 min., quenched with sat. $NaHCO_3$, washed with brine, extracted with $CH_2Cl_2$ and dried over $Na_2SO_4$. After filtration and concentration under vacuum, the residue was purified by flash chromatography (hexanes-EtOAc, 2:1) to give the O-benzylated product (75 %).

In conclusion, we have described an efficient and highly stereocontrolled synthesis of pyrimidine α-D-ribo and β-D-arabinofuranosyl nucleosides. These may find utility in oligonucleotide research in connection with antisense motifs[10] and related therapeutic opportunities. β-D-Arabinofuranosylcytosine (Ara Cytarabine), is well known as antiviral and anticancer agent.[11] 6-Chloropurine was found to be the most compatible purine for purine 1,2-*cis* nucleoside synthesis. With other bases such as N-benzoyladenine or hypoxanthine, yields were modest and the products contained variable quantities of the N-7 isomer. The successful extension of this novel MOP and TOPCAT activation technology to pyranosyl nucleosides will be reported elsewhere.[12,13]

**Acknowledgments** We thank NSERC for financial support through the NSERC Medicinal Chemistry Chair program.

## References and Notes

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(*Received in USA* 9 *May* 1995; *revised* 15 *June* 1995; *accepted* 20 *June* 1995)