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Strategic Approach to *C*-Nucleosides *via* Sugar Anomeric Radical, Cation, and Anion with Sugar Tellurides

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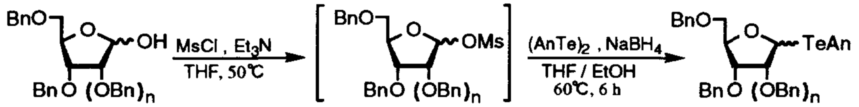
Abstract : Direct coupling reactions of the protected D-ribofuranosyl *p*-anisyl telluride and 2-deoxy-D-ribofuranosyl *p*-anisyl telluride with electron-poor heteroaromatics and electron-rich aromatics *via* anomeric radical, cation, and anion were carried out. © 1997 Elsevier Science Ltd.

C-Nucleosides are well known to have potent antiviral and antitumour activities,[1] because of their structural resemblance to the *N*-linked nucleosides. Thus, *C*-nucleoside chemistry has been an active research field during the past two decades. To date, three major synthetic approaches to *C*-nucleosides are known, *i.e.*, a) coupling of an appropriate sugar derivative with a desired aglycone unit, b) introduction of a functional group at the anomeric position of a sugar derivative, followed by the construction of a heterocyclic base using the functionality, and c) total synthesis. The latter two methods require many steps and do not lend themselves to structural modification. Thus, the coupling method a) appears to be a more efficient and straightforward procedure for *C*-nucleosides.

Previously, we showed that the coupling reaction of a sugar anomeric radical with electron-poor heteroaromatic bases, with the Barton decarboxylation reaction, is effective for the preparation of *C*-nucleosides.[2] However, the aglycone unit is limited to the electron-poor heteroaromatic bases, which had to be further activated by protonation with trifluoroacetic acid. Meanwhile, we have been interested in the introduction of many types of the aglycone moiety, *i.e.*, electron-rich aglycone unit and electron-poor aglycone unit, to the anomer position in view of the chemical characteristics and biological activities of *C*-nucleosides. Today, it is known that tellurides have exceptional radicophilicity, electrophilicity, and nucleophilicity,[3] and so we have focused on sugar tellurides for the preparation of *C*-nucleosides via anomer radical, cation, and anion species, respectively. Recently, Barton demonstrated the formation of anomer radicals from sugar tellurides and the addition to the electron-deficient olefins,[4] and Yamago *et al*[5] reported the *O*-glycosidation of telluroglycoside *via* an anomer cation by electrochemical oxidation. However, the direct introduction of the aglycone moiety to the sugar anomeric position *via* anomer radical, cation, and anion, with sugar tellurides as a flexible precursor, has been never studied. Here, we would like to report our preliminary study on a strategic approach to *C*-nucleosides *via* anomeric radical, cation, and anion, respectively.

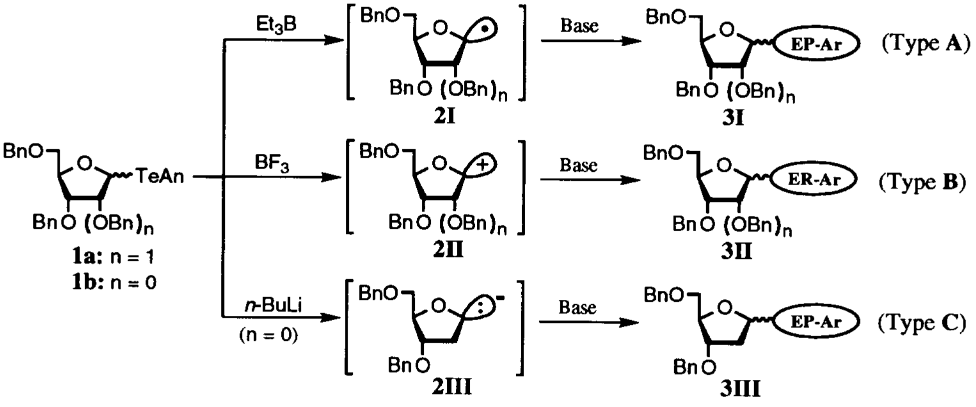


(1)

1a: n = 1
1b: n = 0

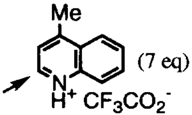
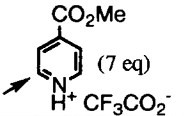
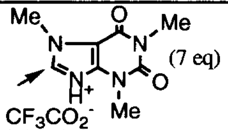
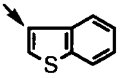
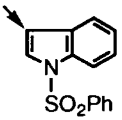
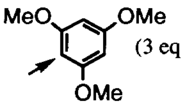
The starting sugar tellurides, 2,3,5-tri-*O*-benzyl-D-ribofuranosyl *p*-anisyl telluride (**1a**; α:β = 66:34) and 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranosyl *p*-anisyl telluride (**1b**; α:β = 50:50),[6] were prepared as shown in eq 1. However, neither sugar telluride is so stable. The former telluride decomposed within one week and the latter decomposed after two days at room temperature. Accordingly, these sugar tellurides have to be stored in a refrigerator and used smoothly, after purification by pTLC. The strategic approach to various types of *C*-nucleosides is shown in Scheme 1 and the results are shown in Table 1. At first, the anomeric radicals **2I** were generated from compounds **1a** and **1b** utilizing triethylborane as a radical initiator under aerobic conditions and the couplings of anomeric radicals formed with electron-poor heteroaromatics (**EP-Ar**) such as lepidine, methyl isonicotinate, and caffeine were carried out to give the corresponding coupling products **3I** in moderate yields.[7] However, none of the reactions exhibited stereochemical preference at the anomeric center, as in the results obtained with the Barton decarboxylation method.[2] Then, the same reactions of the separated α-form and β-form of **1a** with lepidine gave the corresponding coupling product **3I** in 40% (α:β = 49:51) and 38% (α:β = 50:50) yields, respectively. From the same protected sugar tellurides **1a** and **1b**, anomeric cations **2II** were generated using a Lewis acid such as boron trifluoride, and the couplings between the anomeric cation formed and electron-rich aromatics (**ER-Ar**), such as benzothiophene, *N*-benzenesulfonylindole, and 1,3,5-trimethoxybenzene, proceeded to give **3II** in moderate to good yields.[7] *N*-Containing aromatics such as *N*-benzenesulfonylindole were introduced in 85% yield at -40°C with compound **1a**. Here, the ratio changed markedly with the temperature as shown in Table 1. The change of this stereoselectivity is caused by the epimerization with boron trifluoride. The same reactions of the separated α-form and β-form in **1a** with *N*-benzenesulfonylindole at -40°C gave the corresponding coupling product **3II** in 75% (α:β = 13:87) and 67% (α:β = 12:88) yields, respectively. These reactivities and selectivities are very close to the reaction of D-ribofuranosyl-β-fluoride with boron trifluoride in the presence of electron-rich aromatics.[8] This result suggests that the same intermediate, an anomer cation, is formed. Thus, the stereoselective generation of α- and β-forms is possible. Here, boron trifluoride was chosen as the Lewis acid, because boron trifluoride was handled more easily and the reaction was clean. Alkylation on the tellurium atom of sugar telluride with ethyl iodide in the presence of electron-rich aromatics did not give the coupling products, though the Te-ethylation occurred. *N*-Bromosuccinimide, instead of boron trifluoride was not effective for the formation of *C*-nucleosides *via* an anomer cation. Compared with compound **1a**, there was no overwhelming preponderance of the β-form in the case of **1b**, irrespective of temperature change. Thus, this result suggest that the stereoselectivity in the reactions with D-ribofuranosul *p*-anisyl telluride (**1a**) came from the stereoelectronic effect of the 2-OBn group. Complementary to the above reactions, anomer anion **2III** was also formed by the reaction of 2-deoxy-D-ribofuranosyl telluride and *n*-butyllithium and treated with benzaldehyde (**EP-Ar**) to give the corresponding coupling product (**3III**) in moderate yield (52%).

From these results, it seemed that anomer radical (**2I**), anomer cation (**2II**), and anomer anion (**2III**) could be formed from the same starting material, sugar tellurides. Here, the obtained *C*-nucleosides could be easily deprotected to the free *C*-nucleosides in good yields by the treatment with boron trichloride.[8] Further work with sugar tellurides is underway.



Scheme 1

Table 1. Synthesis of *C*-Nucleoside Analogues

Type	entry	Base		3 / Yields (from **1a**)	3 / Yields (from **1b**)
A	a	 (7 eq)	Et_3B (10 eq),[a] r.t. 20 h, $CHCl_3$	**46%** (α : β = 50 : 50)	**40%** (α : β = 45 : 55)
	b	 (7 eq)	Et_3B (10 eq),[a] r.t. 20 h, $CHCl_3$	**40%** (α : β = 60 : 40)	**32%** (α : β = 66 : 34)
	c	 (7 eq)	Et_3B (10 eq),[a] r.t. 20 h, $CHCl_3$	**15%** (α : β = 49 : 51)	—
B	d	 (3 eq)	$BF_3 \cdot Et_2O$, (7 eq for **1a**) (5 eq for **1b**) 1 h, $CHCl_3$	-78°C **40 %** (α : β = 29 : 71)	0°C **45 %** (α : β = 90 : 10)
				-40°C **65 %** (α only)	15°C **35 %** (α : β = 25 : 75)
	e	 (3 eq)	$BF_3 \cdot Et_2O$, (7 eq for **1a**) (5 eq for **1b**) 1 h, $CHCl_3$	-78°C **45 %** (α : β = 85 : 15)	-10°C **50 %** (α : β = 28 : 72)
				-40°C **85 %** (α : β = 10 : 90)	0°C **50 %** (α : β = 32 : 68)
				-10°C **74 %** (α : β = 11 : 89)	15°C **65 %** (α : β = 34 : 66)
			NBS (2 eq), 1 h, $CHCl_3$	-10°C **35 %** (α : β = 10 : 90)	—
	f	 (3 eq)	$BF_3 \cdot Et_2O$, (7 eq for **1a**) (5 eq for **1b**) 1 h, $CHCl_3$	-10°C **60 %** (β only)	-78°C **25 %** (α : β = 78 : 22)

a) A tetrahydrofuran solution of Et_3B (1M) was used.

References and Notes

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6. 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl *p*-anisyl telluride (**1a**): ^{1}H-NMR ($CDCl_3$) α form: δ 5.92 ppm (d,1H, J = 1.8 Hz, H^1); β-form: δ 6.45 ppm (d, 1H, J = 5.5 Hz, H^1); (HRMS-FAB) found 640.1472. Calcd for $C_{33}H_{34}{}^{130}TeO_5$ 640.1469. 3,5-Tri-*O*-benzyl-2-deoxy-D-ribofuranosyl *p*-anisyl telluride (**1b**): ^{1}H-NMR ($CDCl_3$) α form: δ 5.90 ppm (dd, 1H, J = 16.7 and 5.7 Hz, H^1); β-form: δ 6.29 ppm (dd, 1H, J = 8.8 and 7.8 Hz, H^1); (HRMS-FAB, KI) found 573.0671. Calcd for $C_{26}H_{28}{}^{130}TeO_4K$ 573.0687 .
7. All the compounds gave satisfactory spectroscopic and microanalytical data and the structures were determined by HH-COSY and NOE measurements.
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