Communications

A Convenient Asymmetric Synthesis of 4′-α-Carboxylated Nucleosides

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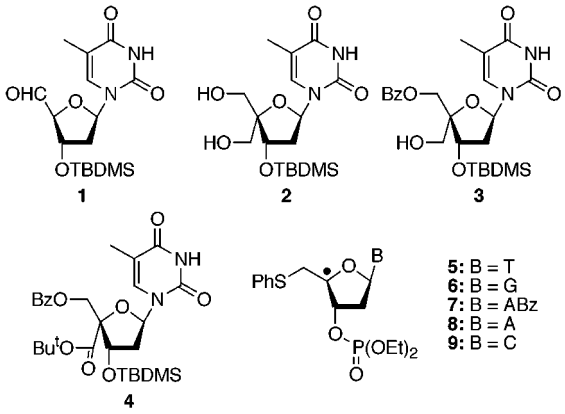
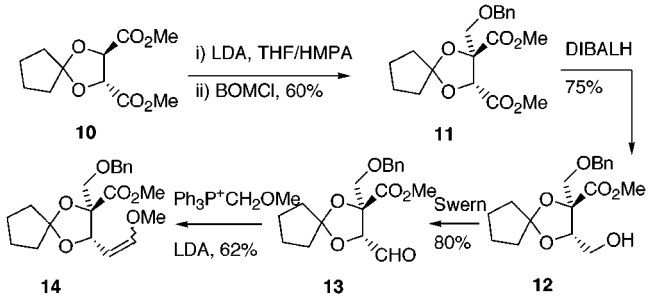
C-4′α-Homologated nucleotides, especially esters and ketones, are molecules of considerable current interest. One reason for this prominence arises from the ability of certain C-4′α-ketones to block DNA polymerase and reverse transcriptase enzymes, such as the HIV-1 RT, and so their potential as antiviral agents.[1−3] Alternatively, the C4′-α-selenol[4] and thiol esters[5] and the C4′-α-*tert*-butylcarbonyl derivative[1] serve as convenient and unambiguous precursors to nucleotide C4′ radicals,[6] which are central to the degradation of oligonucleotides by bleomycin,[7] the enediyne antitumor antibiotics,[8,9] and ionizing radiation.[10] Nucleotide C4′ radicals are also key intermediates in DNA footprinting.[11] The vast majority of work with these 2-deoxy-4′α-carbonyl substituted nucleotides has been conducted with the thymidine series. Almost without fail, the synthesis[3,5,12,13] of these ramified thymidines can be traced back to original work by Jones on the Cannizzaro reaction of aldehyde **1** with formaldehyde giving the diol **2**.[14] The reactivity profile of **2** is such that the α-OH is more readily protected than the *β*-one,[15] which means that selective oxidation of the α-hydroxymethyl group to the desired aldehyde or acid is necessarily preceded by a lengthy three-step selective double-protection and monodeprotection sequence.[3,5,12] Moreover, the final oxidation of alcohols such as **3** to the ester **4** is difficult.[5] Recently, we have qualitatively demonstrated, by means of PhS• addition to the corresponding exocyclic glycals, that the fragmentation of nucleotide C4′ radicals **5**−**9** is a function of the base.[16] Quantification of this observation requires the synthesis of the C4′ acids of all four bases. Adaptation of the literature synthesis for the thymidine derivative to suit each base is not economical, neither in terms of time nor cost, and we were therefore driven to develop an asymmetric synthesis capable of providing all four bases with a minimum of effort. Furthermore, such a synthesis permits the inclusion of nonstandard bases. Here, we present such a synthesis in which the chirality is derived from the commodity chemical, L-tartaric acid.



Our synthesis was built on the basis of Seebach's concept of self-reproduction of chirality as exemplified by the alkylation of tartrate acetals with retention of configuration.[17] We began by conversion of dimethyl L-tartrate to the cyclopentylidene acetal **10** in the standard manner. Deprotonation with LDA in a THF/HMPA mixture followed by quenching with freshly prepared benzyloxymethyl chloride (BOMCl) provided the adduct **11** in 60% isolated yield as a single isomer.[18] The less substituted ester was then selectively reduced with DIBALH to give alcohol **12** in 75% yield. Importantly, the hydroxy ester **12** showed no tendency toward lactonization, so reinforcing the notion that alkylation of **10** took place with retention of configuration. Swern oxidation of **12** then gave 80% of the aldehyde **13**, which was converted to the alkene **14**, by the usual Wittig sequence, in 62% yield as a 1:1 mixture of isomers (Scheme 1).

Scheme 1



Our plan called for the simultaneous hydrolysis of the enol ether and acetal functions in **14**, followed by spontaneous cyclization to the 2-deoxy-4α-(methoxycarbonyl)-D-ribofura-

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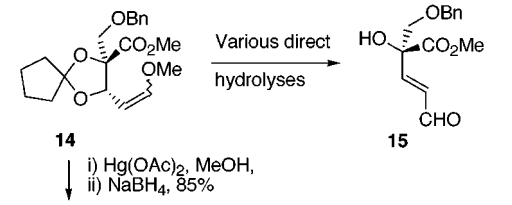
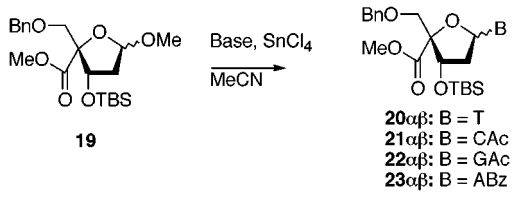
Scheme 2



Scheme 3



nose skeleton. Unfortunately, direct hydrolysis under a variety of conditions resulted in elimination and the isolation of **15** in good yield. After some experimentation, we discovered that **14** could be converted in excellent yield to the diacetal **16** by treatment with methanolic mercuric acetate, followed by $NaBH_4$, and that this species readily underwent the desired conversion to **17** on exposure to 3 N HCl in THF. Crude **17** was then transformed to the methyl glycosides **18**, which were isolated in 85% overall yield from **16**, with methanolic HCl (Scheme 2).

Silylation of **18** with TBDMSOTf gave **19**, which proved to be a suitable donor for coupling to the various bases. Thus, treatment of a room-temperature acetonitrile solution of **19** with suitably protected forms of the four standard DNA bases and $SnCl_4$ as promoter [19] provided the nucleosides in moderate to good yield as α:*β* mixtures (Scheme 3, Table 1). In each case, the pairs of anomers were readily separated by chromatography over silica gel. In the guanosine series, we also isolated minor amounts of both the α- and *β*-anomers of the N7-glycosylated isomers. These were readily distinguished from the desired N9 isomers by well-established spectroscopic methods.[20]

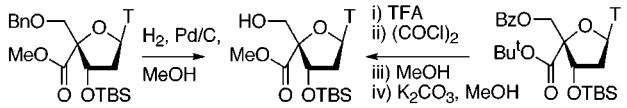
NOE studies were largely inconclusive, and ultimately, the configuration of **20***β* was confirmed by removal of the benzyl ether by hydrogenolysis over Pd/C, giving **24** (Scheme 4). This substance was found to be identical in every respect to an authentic sample obtained by debenzoylation and transesterification of **25**, which itself had been previously obtained from **2** via **3**.[5] This experiment, aside from establishing anomeric configuration, also nicely serves to confirm the stereochemical outcome of the initial alkylation (**10** → **11**). The anomeric configurations of **21** → **23**α*β* were assigned following close parallels in their ^{1}H NMR spectra with those of **20**α*β*. Further supporting evidence for the configurational assignments in **21**−**23** was gleaned from specific rotations: at the sodium D line the *β*-anomers of the two pyrimidines (**20***β* and **21***β*) were found to be more dextrorotatory than their α-epimers, whereas the opposite was true for the two purines (**22***β* and **23***β*). This is exactly the pattern seen with the four natural DNA bases and their α-anomers.[21] Finally, we also noted that all four *β*-anomers were faster eluting from silica gel than their α-isomers.

Table 1. Synthesis of Nucleosides from 19

base	product (% yield)	*β*:α[a]
T	**20** (70)	1:1
4-*N*-Ac-C	**21** (90)	5:7
2-*N*-Ac-G	**22** (83)	1:3
6-*N*-Bz-A	**23** (40)	1:1

[a] Anomeric ratios were determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures.

Scheme 4



In conclusion, we have developed an efficient asymmetric synthesis of the 4′-substituted ribofuranoside **19**, which is converted efficiently into any of the desired nucleosides in high yield. Moreover, the 3′- and 5′-hydroxy groups are suitably orthogonally protected, enabling selective deprotection and elaboration in either direction. Although the coupling reaction, like most reactions of this type, is not at present selective, the anomers are readily separable, and this imperfection is more than offset by the ability to prepare all four bases from a single precursor and by the potential for introduction of non-natural bases.

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Supporting Information Available: Full experimental and characterization data for all new compounds (11 pages).

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