Expeditious Syntheses of Sugar-Modified Nucleosides and Collections Thereof Exploiting Furan-, Pyrrole-, and Thiophene-Based Siloxy Dienes

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A series of individual sugar-modified pyrimidine nucleosides including enantiomerically enriched 2′,3′-dideoxynucleosides **14a**−**c** (α and β anomers of L- and D-series), 2′,3′-dideoxy-4′-thionucleosides **21a**−**c** (α and β anomers of L- and D-series), and 2′,3′-dideoxy-4′-azanucleosides **28a**−**c** (β anomers of L- and D-series) were synthesized, with uniform chemistry and high stereochemical efficiency, exploiting a triad of versatile heterocyclic siloxy dienes, namely, 2-(*tert*-butyldimethylsiloxy)furan (TBSOF), 2-(*tert*-butyldimethylsiloxy)thiophene (TBSOT), and *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP). The synthetic procedure advantageously used both enantiomers of glyceraldehyde acetonide (D-**1** and L-**1**) as sources of chirality and as synthetic equivalents of the formyl cation. The outlined chemistry also allowed for the rapid assemblage of a 30-member collection of racemic nucleosides (D,L-**L**) as well as one 15-member ensemble of chiral analogues (L-**L**), along with some related sublibraries.

Introduction

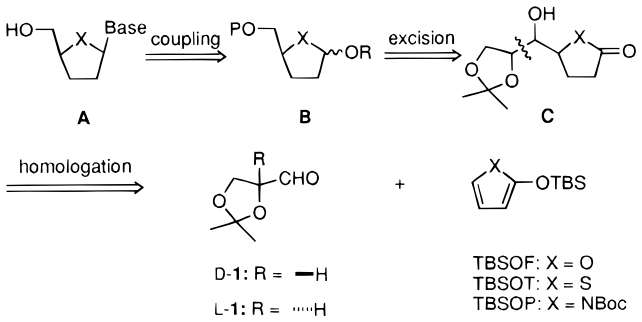
Planning and synthetic exploitation of chemically uniform, modular procedures amenable to construction of ensembles of structurally related small organic molecules with specific functions represent centrally important issues of both life and material sciences. Parallel and repetitive execution of common synthetic protocols employing sets of equally reacting reagents or precursors ensures the production of collections of individual structures to be used as the basis for discovery of lead candidates. On the other hand, for a given class of potentially active molecules, adaptation of similar uniform protocols according to a combinatorial tactic allows for a more rapid access to mixtures of vast numbers of compounds with a higher level of molecular and stereochemical diversity.[1] Along this line of thought, since 1990 we have embarked upon a research program focused on the development of a modular, flexible strategy addressing the synthesis of a structurally diverse series of bioactive molecules by exploiting oxygen-, sulfur-, and nitrogen-containing heterocyclic siloxy diene nucleophiles and employing a limited set of simple, unified reactions.[2]

As part of these studies, herein we report on the diastereoselective synthesis of a collection of 30 individual enantiopure pyrimidine 2′,3′-dideoxynucleosides comprising D- and L-furanoses **14a**−**c**, 4′-thiofuranoses **21a**−**c**, and 4′-azafuranoses **28a**−**c** by starting with 2-(*tert*-butyldimethylsiloxy)furan (TBSOF), 2-(*tert*-butyldimethylsiloxy)thiophene (TBSOT), and *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP), respectively.

We also describe the assemblage of a model 30-compound combinatorial library of the same nucleosides in racemic form as well as one 15-component sublibrary of homochiral representatives of the L- series.

As assessed by recent studies, sugar-altered nucleoside building blocks and oligonucleotides there from have gained much attention by virtue of their significant biological profiles, including use in antisense and antiviral therapies.[3]

Scheme 1. Retrosynthetic Analysis of Oxygen, Sulfur, and Nitrogen Nucleosides **A**



Results and Discussion

Strategy. At the planning stage of our syntheses, we recognized that there were two stringent requirements that an ideal chemically uniform protocol has to meet: (1) availability of a number of structural variants of equally-reacting precursors and (2) viability of a common synthetic path accommodating all the chosen precursors. The starting point for this work (Scheme 1) was the observation that the suitable five-carbon sugar cores **B** of the target nucleosides **A** could be produced, by following strictly related transformations, by removal of two carbon atoms from the seven-carbon intermediates **C**, which can be, in turn, obtainable by four-carbon homologation of D- and L-glyceraldehyde acetonides, D-**1** or L-**1**, with the siloxy diene reagents TBSOF, TBSOT, and TBSOP. According to this simple plan, glyceraldehyde enantiomers D-**1** and L-**1** can be envisioned as "chiral" hydroxymethyl cation equivalents, whereas the three siloxy dienes act as surrogates of the five-membered oxygen, sulfur, and nitrogen heterocycles within **A** and **B**.

Synthesis of Precursors. The preparation of the siloxy diene reagents TBSOF, TBSOT, and TBSOP took advantage of some previously described procedures.

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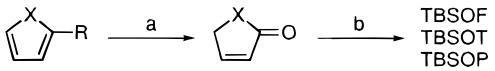
Scheme 2.[a] Synthesis of Siloxy Diene Precursors



2: R = CHO, X = O
4: R = H, X = S
6: R = H, X = NH
3: X = O
5: X = S
7: X = NBoc

[a] (a) **2** to **3**, HCO_2Na, 30% H_2O_2 (50%, ref 4); **4** to **5**, *n*-BuLi, methyl borate, 30% H_2O_2 (70%, ref 5); **6** to **7**, 30% H_2O_2; then Boc_2O, DMAP, CH_2Cl_2 (30%, ref 6); (b) **3** to TBSOF, TBSOTf, Et_3N, CH_2Cl_2 (70%); **5** to TBSOT and **7** to TBSOP, TBSOTf, 2,6-lutidine, CH_2Cl_2 (91% and 90%, respectively).

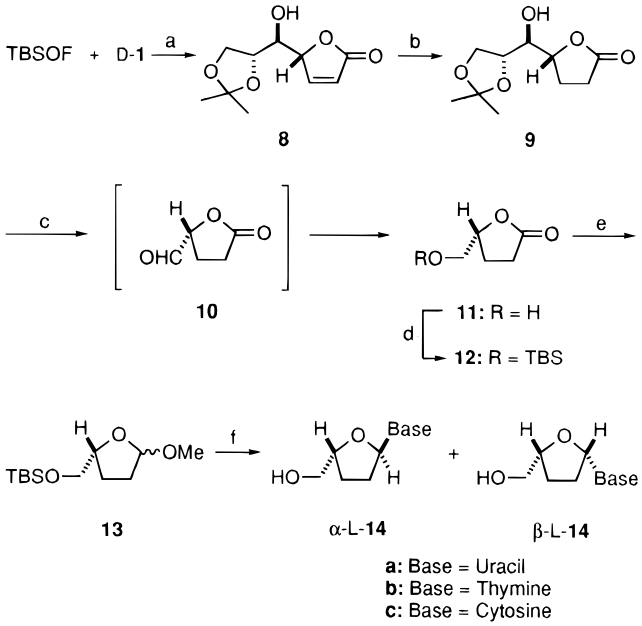
Essentially according to literature (Scheme 2),[4] furan-2(5*H*)-one (**3**) was prepared by treatment of 2-furaldehyde (**2**), in sodium formate buffered solution, with 30% hydrogen peroxide (~50% yield). Unsaturated thiolactone **5** (70% yield) derived from thiophene (**4**) *via* oxidation with *n*-butyllithium/methyl borate/30% H_2O_2 system.[5] Lactam **7** (30% yield) resulted from direct H_2O_2 oxidation of pyrrole (**6**),[6] followed by nitrogen protection (Boc_2O, DMAP, CH_2Cl_2).

Parallel execution of optimized enolization−silylation protocols (TBSOTf, 2,6-lutidine or Et_3N, CH_2Cl_2) rapidly ensured preparation of the requisite triad of reagents, TBSOF, TBSOT, and TBSOP, by starting from the respective heterocycles individually, **3**, **5**, and **7**, in excellent isolated yields ranging from 70 to 90%. Substantial amounts of (*R*)- and (*S*)-glyceraldehyde acetonides D-**1** and L-**1** were obtained from inexpensive D-mannitol[7] and L-ascorbic acid,[8] respectively, by following exactly the known procedures.

Synthesis of 2′,3′-Dideoxynucleosides. The synthesis of enantiomerically enriched L-pyrimidine nucleosides α-L-**14** and β-L-**14** (Scheme 3) commenced with the preparation of 4,5-*threo*-5,6-*erythro* (D-*arabino*) configured α,β-unsaturated lactone **8**,[9] which was readily available *via* $BF_3{\cdot}OEt_2$-promoted condensation of TBSOF to glyceraldehyde D-**1**. The event proved highly diastereoselective (75% yield, de >90%), forming lactone **8** contaminated by only a minor amount of its unwanted 4,5-*erythro* diastereoisomer. Hydrogenation of **8** (H_2, THF, Pd on carbon) led to saturated heptonolactone **9** (95%), which was then subjected to acidic deacetonidation to afford a triol intermediate (not isolated). Subsequent oxidative cleavage of the C(5)−C(6) linkage ($NaIO_4$) producing aldehyde **10**[10] was followed by $NaBH_4$ reduction of the formyl function, giving rise to hydroxymethyl-substituted lactone **11** in 88% overall yield from **9**. After silylation of the primary OH function within **11** to **12** (92%), the key sugar **13** was easily generated in 95% yield by a two-step protocol, consisting of DIBAL-H reduction of the carbonyl moiety and *O*-methyl glycosylation of the formed lactol [$CH(OMe)_3$, $BF_3{\cdot}OEt_2$].

Reaction of **13** with activated pyrimidine bases, namely uracil, thymine, and 4-*N*-acetylcytosine, was conveniently conducted employing the mixed Lewis acid promoter $SnCl_4$/TMSOTf (1:1) in 1,2-dichloroethane at ambient temperature, essentially according to a Vorbrüggen-type protocol.[11,12] There was obtained a 1:1 α/β mixture of protected nucleosides, which were finally deprotected by conventional chemistry (TBAF or TBAF/K_2CO_3) to free compounds α-L-**14a**−**c** and β-L-**14a**−**c** in acceptable combined yields ranging from 60 to 70%. The separation of the anomers in the mixture was accomplished by silica gel flash chromatography and/or preparative TLC (see the Experimental Section), thus allowing individual nucleosides to be obtained in a pure state.

Scheme 3.[a] Synthesis of 2′,3′-Dideoxynucleosides of the L-Series

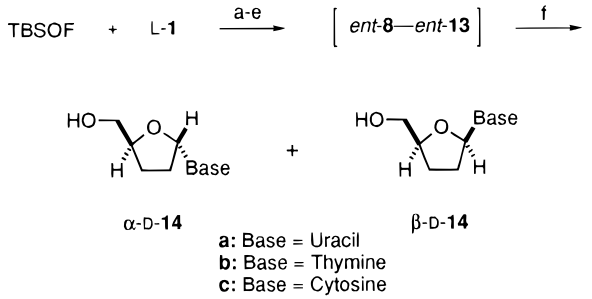


[a] (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −90 °C (75%); (b) H_2, Pd/C, THF (95%); (c) 80% aqueous AcOH, 50 °C; then 0.65 M aqueous $NaIO_4$, SiO_2, CH_2Cl_2; then $NaBH_4$, MeOH, −30 to −15 °C (88%); (d) TBSCl, imidazole, CH_2Cl_2 (92%); (e) DIBAL-H, CH_2Cl_2, −90 °C; then $CH(OMe)_3$, $BF_3{\cdot}OEt_2$, Et_2O, 4 Å molecular sieves (95%); (f) **13** to L-**14a**, silylated uracil, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF (60%); **13** to L-**14b**, silylated thymine, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF (65%); **13** to L-**14c**, silylated 4-*N*-acetylcytosine, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF; then K_2CO_3, MeOH (70%).

The identity of α- and β-L-**14a**−**c** was mainly established by ^1H NOE-difference spectroscopy and/or NOESY experiments. While diagnostic contacts were observed between H(5′) and H(6), and between H(1′) and H(4′) within β-L-**14a**−**c**, no such effects were detectable in the α anomeric counterparts. In addition, an NOE between H(4′) and H(6) in α-L-**14a**−**c** clearly indicated a *syn* relationship for these protons. Support for the assignment of the components as α or β anomers came from the observation of a large downfield chemical shift (0.3−0.8 ppm) for the protons at C(4′) in the α anomers, possibly arising from the interaction between the *syn*-located nucleobase, which is clearly forbidden in the β counterparts (*anti*-location). Conversely, the H-5′ protons of the β anomers appear at a lower field than that of the α anomers.[13]

The optical purity of the nucleosides **14** could be approximately judged based on comparison with the reported chiroptical data for known compounds in both the D- and L-series. Our measurements satisfactorily matched the literature data[14] with small deviations in the range ±5%. A more precise estimation of the enantiomeric purity of the synthesized nucleosides came from our synthetic protocol, showing an extremely high level of enantioconservation. By starting with virtually pure **8**, our optimized protocol ensured clean preparation of (*R*)-(−)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**11**) ($[\alpha]^{20}_D$ −54.5 (*c* 2.0, $CHCl_3$), lit.[15a] $[\alpha]^{30}_D$ −53.5 (*c* 3.17, $CHCl_3$)), whose enantiomeric excess was evalu-

Scheme 4.[a] Synthesis of 2′,3′-Dideoxynucleosides of the D-Series



[a] Reagents and conditions, see Scheme 3. The formulas referring to compounds *ent*-**8**−*ent*-**13** are the enantiomeric counterparts of those in Scheme 3.

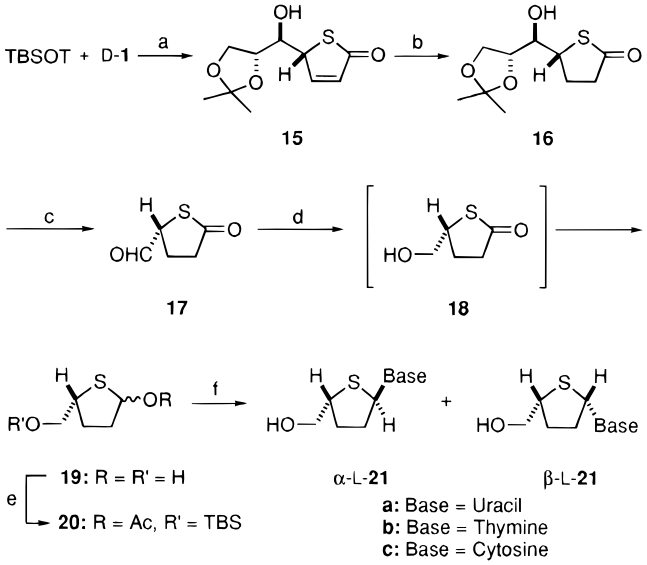
ated to be 96 ± 2% by conversion to the corresponding Mosher ester and NMR analysis.[16] Owing to the conservative character of the final stages of the synthesis, the enantiomeric excess of the nucleosides in our hands could be estimated at the same level (96 ± 2%) as that of their common precursor **11**.

The above disclosed synthetic protocol was next adopted with complete parallelism to preparation of the same set of nucleosides in the enantiomeric D-series (Scheme 4). By starting with TBSOF and L-glyceraldehyde L-**1**, through the various synthetic intermediates *ent*-**8**−*ent*-**13** (not shown), the D-nucleosides α-D-**14a**−**c** and *β*-D-**14a**−**c** were rapidly synthesized without incidents. The yields for pure isolated anomers ranged from 29 to 35%, based on their common precursor *ent*-**13**.

Having both the D- and L-enantiomeric series strongly facilitated the assessment of the constitutional and enantiomeric purity of the materials by direct comparison of the spectroscopic and chiroptical data of the various enantiocouples. In all cases, good correspondence was observed, indicative of the high performance of the overall synthetic strategy.

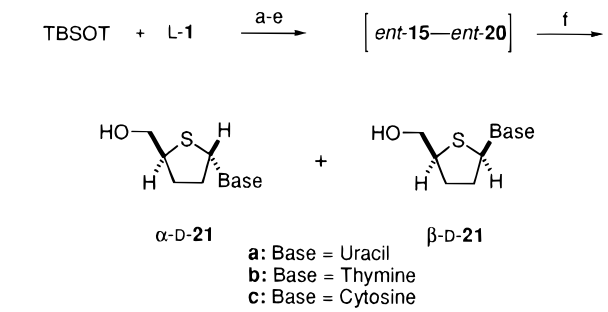
Synthesis of 2′,3′-Dideoxy-4′-thionucleosides. The assembly of the related 12-compound collection of less common, but clinically promising 2′,3′-dideoxy-4′-thionucleosides,[3d,17] α-**21** and *β*-**21**, was accomplished by paralleling the entire strategy developed with the furanose "cousins", using TBSOT instead of TBSOF.[18] Thus, as shown in Scheme 5, starting with D-*arabino*-configured unsaturated thiolactone **15**, obtained in 78% yield and with high stereochemical efficiency (91% de by HPLC analysis) by coupling of TBSOT to D-glyceraldehyde D-**1** (BF_3·OEt_2 as catalyst), saturated lactone **16** was easily synthesized (90%), whose relative and absolute configuration was firmly ascertained by single-crystal X-ray analysis.[19] Deprotection of **16** and subsequent oxidative two-carbon excision gave rather unstable aldehyde **17** (75%),[10] whose $NaBH_4$ reduction directly furnished the five-carbon thiolactol **19** (65% yield) with no appreciable formation of the corresponding pyranose form, through the temporary intermediacy of thiolactone **18**. The reductive step differed from the protocol employed in the above oxygenated series due to competitive reduction of the thiolactone carbonyl function. Under carefully controlled conditions and stopping the reduction prior to complete consumption of aldehyde **17**, it was possible to prepare a sufficient amount of intermediate **18**, suitable for ee measurements. Mosher ester analysis,[16] as described for **11**

Scheme 5.[a] Synthesis of 2′,3′-Dideoxy-4′-thionucleosides of the L-Series



[a] (a) BF_3·OEt_2, CH_2Cl_2, −78 °C (78%); (b) H_2, Pd/C, THF (90%); (c) 80% aqueous AcOH, 50 °C; then 0.65 M aqueous $NaIO_4$, SiO_2, CH_2Cl_2 (75%); (d) $NaBH_4$, MeOH, −30 to −15 °C (65%); (e) TBSCl, imidazole, CH_2Cl_2; then Ac_2O, pyridine, DMAP, CH_2Cl_2 (70%); (f) **20** to L-**21a**, silylated uracil, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF (61%); **20** to L-**21b**, silylated thymine, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF (70%); **20** to L-**21c**, silylated 4-*N*-acetylcytosine, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF; then K_2CO_3, MeOH (61%).

Scheme 6.[a] Synthesis of 2′,3′-Dideoxy-4′-thionucleosides of the D-Series

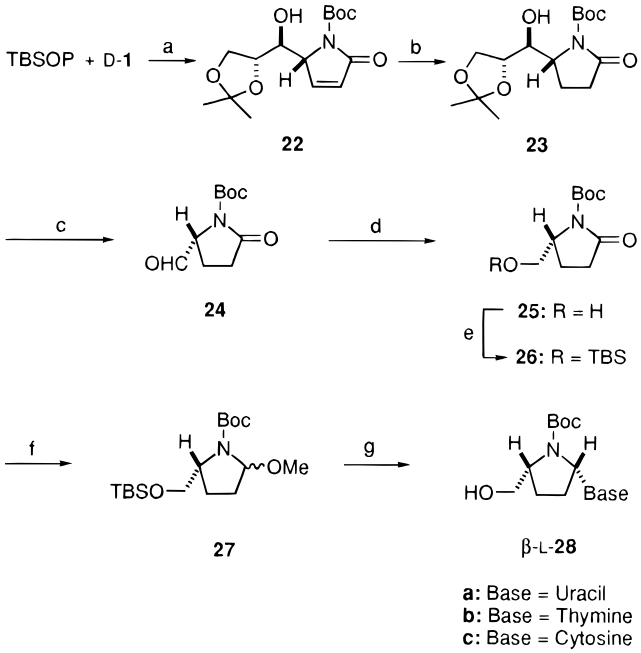


[a] Reagents and conditions, see Scheme 5 legend. The formulas referring to compounds *ent*-**15**−*ent*-**20** are the enantiomeric counterparts of those in Scheme 5.

(*vide supra*), revealed an enantiomeric purity of the carbinol **18** as high as 90+%. Conventional protection of the terminal hydroxyl function as TBS ether (TBSCl, imidazole) and acetylation of the anomeric OH (Ac_2O, pyridine, DMAP) converted **19** into activated thiosugar **20** in 70% yield, which was finally used in the subsequent coupling reaction with the usual three persilylated pyrimidine bases.[20] These reactions afforded high yields of the protected nucleoside mixtures, from which individual free nucleosides α-L-**21a**−**c** and *β*-L-**21a**−**c** were isolated in 61−70% combined yields by deprotective workup (TBAF or TBAF/K_2CO_3) followed by TLC preparative chromatography.

In an analogous manner and with comparable efficiency, condensation of TBSOT with L-glyceraldehyde L-**1** (Scheme 6) gave rise to the six thionucleosides of the D-series α-D-**21a**−**c** and *β*-D-**21a**−**c** through the intermediacy of the pertinent precursors *ent*-**15**−*ent*-**20**. The α *vs* *β* assignment for the sulfur-containing

Scheme 7.[a] Synthesis of *N*-Boc-Protected 2′,3′-Dideoxy-4′-azanucleosides of the L-Series



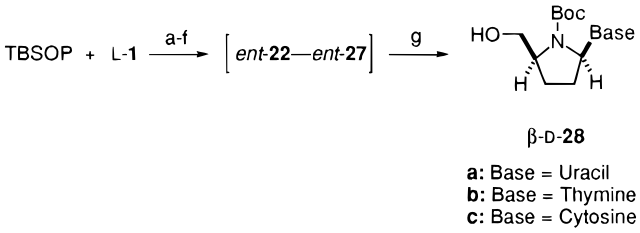
[a] (a) $SnCl_4$, Et_2O, −90 °C (80%); (b) H_2, Pd/C, THF (92%); (c) 80% aqueous AcOH, 50 °C; then 0.65 M aqueous $NaIO_4$, SiO_2, CH_2Cl_2 (63%); (d) $NaBH_4$, MeOH, −30 to 0 °C; (e) TBSCl, imidazole, CH_2Cl_2 (72%); (f) $LiEt_3BH$, THF, −78 °C; then $CH(OMe)_3$, $BF_3{\cdot}OEt_2$, Et_2O, 4 Å molecular sieves (78%); (g) **27** to L-**28a**, silylated uracil, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF (65%); **27** to L-**28b**, silylated thymine, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF (70%); **27** to L-**28c**, silylated 4-*N*-acetylcytosine, $SnCl_4$/TMSOTf (1:1), 1,2-dichloroethane; then TBAF, THF; then K_2CO_3, MeOH (62%).

nucleosides of this section was as straightforward as that of the oxygenated relatives, based on ^1H NMR analyses and NOE measurements (*vide supra*).

Synthesis of 2′,3′-Dideoxy-4′-azanucleosides. With a uniform protocol to assemble oxygen- and sulfur-containing 2′,3′-dideoxynucleosides at hand, we next turned to preparation of the analogous pyrrolidine-based congeners, which represent a quite novel progeny of sugar-modified nucleosides.[21] Again, a parallel path was undertaken employing our third siloxy diene, namely, the pyrrole-based reagent TBSOP.[22] As depicted in Scheme 7, $SnCl_4$-catalyzed (instead of $BF_3{\cdot}OEt_2$) condensation of TBSOP with D-**1** proved successful, allowing the preparation of crystalline D-*arabino* lactam **22** in excellent yield (80%),[23] which was the template used to create the key azasugar precursor **27**. As described earlier, the three-carbon C(5)−C(7) appendage in **22** was utilized to generate the requisite hydroxymethyl group at C(4) by the sequence **22** → **23** (H_2, Pd/C, 92%), **23** → **24** (AcOH, then $NaIO_4$, 63%), and **24** → **26** ($NaBH_4$, then TBSCl, imidazole, 72%). As for the corresponding carbynols **11** and **18**, the enantiomeric purity of **25** was checked by NMR analysis of its Mosher ester[16] and was found to be quite high.

The subsequent stage, the reductive conversion of the protected lactam **26** to azasugar **27**, called for a different reducing agent, since neither DIBAL-H nor $NaBH_4$ gave the expected transformation. However, the use of superhydride ($LiEt_3BH$) proved fruitful, giving, after methylation [$CH(OMe)_3$, $BF_3{\cdot}OEt_2$], a 78% yield of the requisite azafuranose **27** as a α/β anomeric mixture. The final task, the coupling of the aminol **27** with the three

Scheme 8.[a] Synthesis of *N*-Boc-Protected 2′,3′-Dideoxy-4′-azanucleosides of the D-Series



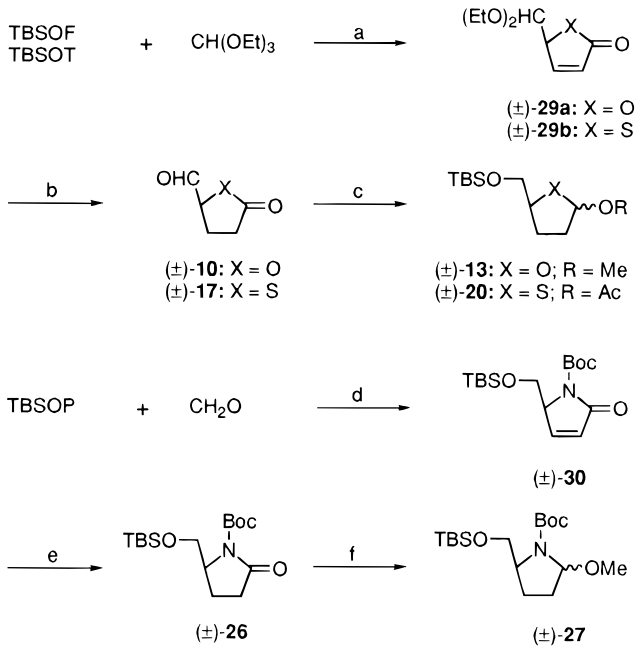
[a] Reagents and conditions, see Scheme 7 legend. The formulas referring to compounds *ent*-**22**−*ent*-**27** are the enantiomeric counterparts of those in Scheme 7.

silylated pyrimidine bases, was accomplished as usual, using the mixed catalyst system $SnCl_4$/TMSOTf. Quite unexpectedly, the coupling behavior proved highly stereoselective, providing, in all instances, the β anomeric nucleosides as the main products accompanied by only minor amounts (<5%) of the respective α anomers (not characterized). After deprotective workup and flash chromatographic purification, free azanucleosides β-L-**28a**−**c** were isolated in good yields (62−70%). Confirmation of the β anomeric configuration for nucleosides **28** essentially followed from 1D and 2D NOE measurements, showing unequivocal contacts between *syn*-disposed H(5′) and H(6) and between H(1′) and H(4′). Remarkably, the highly stereoselective and efficient formation of the β anomeric compounds during the Lewis acid catalyzed coupling of silylated bases with *N*-Boc protected methyl glycoside **27** is in strong contrast with the few existing studies dealing with similar syntheses of 4′-acetamido- and 4′-(*tert*-butylcarbamyl)-pyrimidine nucleoside analogues which exhibit unselective nucleobase coupling behaviors.[21] The exact reason for the stereoselective formation of the β nucleosides in this report remains unclear, and further studies will be necessary in order for these results to be elucidated and rationalized. However, one can speculate that nitrogen pyramidalization within the heterocyclic iminium intermediate with preferential *trans*-disposition of the *N*-Boc moiety may play a role in hindering the α-face of the pyrrolidine nucleus favoring the attack of the nucleobase on the less demanding β-face.[24] As with the oxygen and sulfur counterparts, adaptation of this chemistry to L-**1** made D-enantiomers β-D-**28a**−**c** available with equal parallelism and efficiency (Scheme 8).

Preparation of Model Nucleoside Libraries. Because of the inadequate pharmaceutical profiles of oligomeric and polymeric biosubstances, including nucleotides, intense effort has been focused on the generation of small monomeric compound libraries.[1] The experiments in the previous sections furnish the basis for easy extension of our chemistry to expeditious assembly of collections of oxygen, sulfur, and nitrogen nucleosides. In particular, the above investigations have highlighted the versatility of TBSOF, TBSOT, and TBSOP as a triad of chemically homogeneous building blocks, associated with a general and reliable strategy compatible with the diverse heteroatoms within the three siloxy dienes.

The first step in an expeditious synthesis of a model 30-component library of racemic nucleosides was the preliminary synthesis of racemic sugar precursors, (±)-**13**, (±)-**20**, and (±)-**27**. This was accomplished, in a

Scheme 9.[a] Synthesis of Racemic Precursors (±)-13, (±)-20, and (±)-27



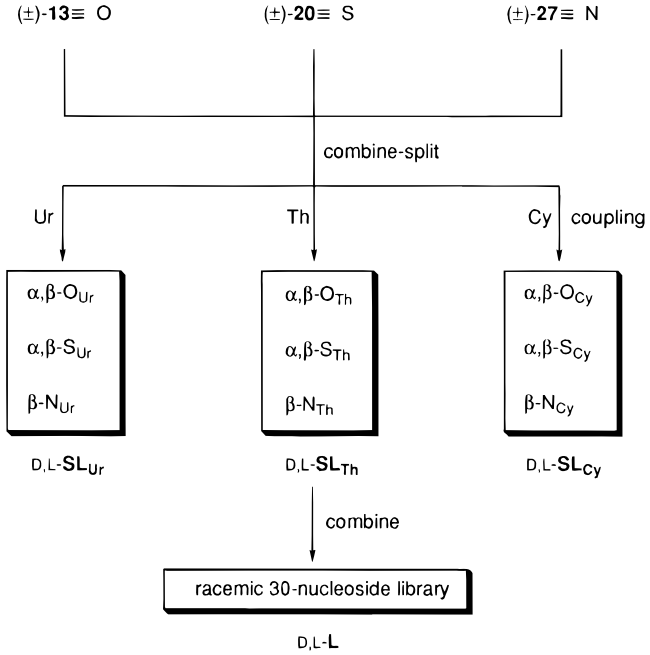
[a] (a) BF_3·OEt_2, Et_2O, −80 °C (95−98%); (b) H_2, Pd/C, THF; then 10% aqueous HCl, THF (76−82%, two steps); (c) for (±)-**13**, $NaBH_4$, MeOH, −30 to −15 °C; then TBSCl, imidazole; then DIBAL-H, CH_2Cl_2, −90 °C; then $CH(OMe)_3$, BF_3·OEt_2 (75%, four steps); for (±)-**20**, $NaBH_4$, MeOH, −30 to −15 °C; then TBSCl, imidazole; then Ac_2O, pyridine, DMAP (50%, three steps); (d) $SnCl_4$, Et_2O, −80 °C (60%); (e) H_2, Pd/C, THF (93%); (f) $LiEt_3BH$, THF, −78 °C; then $CH(OMe)_3$ BF_3·OEt_2, 4 Å molecular sieves (75%, two steps).

straightforward manner (Scheme 9), by formylation or hydroxymethylation of the individual siloxy dienes with either orthoformate or gaseous formaldehyde. For (±)-**13** and (±)-**20** (not for (±)-**27**), a direct formylation procedure with ethyl orthoformate was advantageously employed. Thus, BF_3-catalyzed condensation of TBSOF and TBSOT with ethyl orthoformate gave rise to the expected acetals (±)-**29a,b** (95−98%), which were cleanly transformed to free saturated aldehydes (±)-**10** and (±)-**17** by double bond saturation followed by acidic hydrolysis.

Reduction of both the formyl and carbonyl moieties within (±)-**10** and (±)-**17** followed by methylation or acetylation then allowed sugars (±)-**13** and (±)-**20** to be prepared in good overall yields from the respective siloxy diene precursors. Unfortunately, this high-yielding reaction sequence failed with (±)-**27**, the acetal hydrolysis stage being incompatible with the acid-sensitive *N*-Boc protection of the aminated counterparts. For (±)-**27**, an alternative procedure was planned employing gaseous formaldehyde as hydroxymethylation agent. Thus, $SnCl_4$-catalyzed reaction of TBSOP with CH_2O-(g) directly gave rise to protected unsaturated lactam (±)-**30** in 60% isolated yield which was hydrogenated to (±)-**26** and then transformed to (±)-**27** by employing the same protocol as that utilized in the analogous homochiral series (*vide supra*).

Next, a "combine−split" in-solution technical approach was adopted (Scheme 10) using the three racemic sugars (±)-**13** (indicated as O), (±)-**20** (S), and (±)-**27** (N), and the three pyrimidine bases, uracil (Ur), thymine (Th), and cytosine (Cy). Thus, the carbohydrate precursors O, S, and N were mixed in equimolar quantity (0.2

Scheme 10.[a] Schematic Description of the Construction of a Full Library, D,L-L, and Three Related Sublibraries, D,L-SL_{Ur}, D,L-SL_{Th}, and D,L-SL_{Cy} of Racemic Pyrimidine Nucleosides



[a] Key: O_{Ur} = (±)-**14a**; S_{Th} = (±)-**21b**; N_{Cy} = (±)-**28c**; and so on.

mmol each) by dissolving them in anhydrous dichloroethane, and the resulting solution was subdivided into three equal portions. Each portion was then independently reacted with one individual base, Ur, Th, and Cy (4.0 equiv), under $SnCl_4$/TMSOTf catalysis to give, after complete deprotection and separation of the nucleoside fractions, three diverse sublibraries of three racemates (D,L-$\mathbf{SL_{Ur}}$, D,L-$\mathbf{SL_{Th}}$, and D,L-$\mathbf{SL_{Cy}}$) which were finally combined to furnish a full library of nucleosides (D,L-**L**) comprising the expected 15 racemates with a 64% combined yield based on the average molecular weight of the nucleoside mixture.[25] In principle, a truly random synthesis would furnish an ensemble of 36 different nucleosides (18 racemates), *i.e.* $3^2 \times 2^i$, where $i = 2$ is the number of stereocenters in the resulting nucleosides. In practice, however, due to (here unwanted) stereoselective character of the coupling reaction involving the azafuranose template strongly favoring the β anomeric compounds (*vide supra*), the total number of parents in the full library was reduced to 15 major racemates (out of 18).

The three nucleoside mixtures were analyzed by reverse-phase HPLC, and typical profiles are shown in Figures 1−3. Having individual pure components strongly facilitated the analysis of the mixtures by simply comparing the experimental HPLC traces with standard profiles of artificial mixtures of pure nucleosides. In the uridine-related trace (Figure 1) six peaks were detected, peak 5 being tentatively attributed to a minor amount of α anomeric azauridine derivative. The corresponding trace of thymidine ensemble (Figure 2) reveals four major peaks which were attributed to the expected nucleoside products with the peaks of sulfur-containing α and β anomers (peak 3) overlapped. As previously observed for uridine compounds, a minor amount of an additional compound was detected (peak 4), which was tentatively assigned to α-azathymidine.

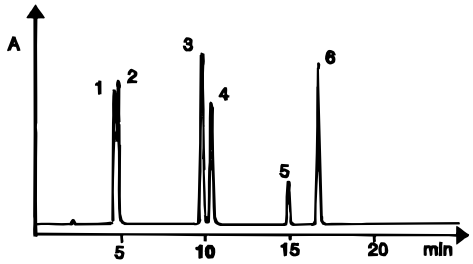


Figure 1. HPLC trace of racemic uridine-related sublibrary D,L-**SL$_{Ur}$**. Each peak was assigned as 1, 2, 3, 4, 5, and 6, which correspond to uridine nucleosides α-**O$_{Ur}$** (4.61 min), β-**O$_{Ur}$** (4.79 min), α-**S$_{Ur}$** (9.80 min), β-**S$_{Ur}$** (10.38 min), α-**N$_{Ur}$** (tentative, 14.90 min), and β-**N$_{Ur}$** (16.86 min), respectively. Ratio of (1 + 2)/(3 + 4)/(5 + 6) was measured as 1.0:1.5:0.9.

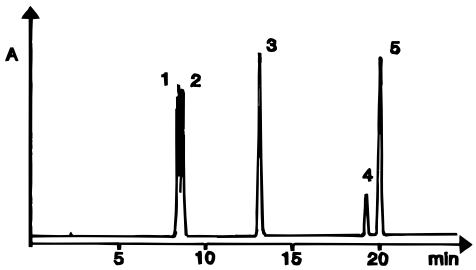


Figure 2. HPLC trace of racemic thymidine-related sublibrary D,L-**SL$_{Th}$**. Each peak was assigned as 1, 2, 3, 4, and 5, which correspond to thymidine nucleosides α-**O$_{Th}$** (8.47 min), β-**O$_{Th}$** (8.73 min), α,β-**S$_{Th}$** (overlapped, 13.2 min), α-**N$_{Th}$** (tentative, 19.20 min), and β-**N$_{Th}$** (20.00 min), respectively. Ratio of (1 + 2)/3/(4 + 5) was measured as 1.0:0.7:0.8.

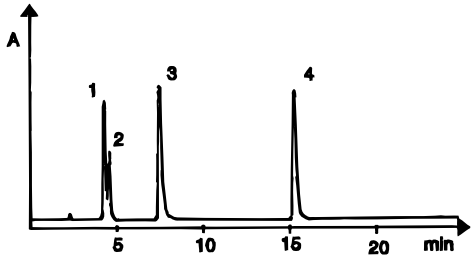


Figure 3. HPLC trace of racemic cytidine-related sublibrary D,L-**SL$_{Cy}$**. Each peak was assigned as 1, 2, 3, and 4, which correspond to cytidine nucleosides α-**O$_{Cy}$** (4.27 min) β-**O$_{Cy}$** (4.54 min), α,β-**S$_{Cy}$** (overlapped 7.52 min), and β-**N$_{Cy}$** (15.31 min), respectively. Ratio of (1 + 2)/3/4 was measured as 1.0:1.1:1.1.

For the cytidine-related sublibrary (Figure 3) only four peaks were evident, the sulfur derivative peaks being overlapped. For a given series, uridine derivatives move faster than the corresponding thymidine congeners, but slower than the cytidine counterparts, and, as a rule, sulfur-bearing compounds move faster than nitrogen products, but slower than oxygenated nucleosides. Remarkably, the HPLC analyses indicated the presence of the expected nucleosides with no detectable byproducts. Furthermore, though it is difficult to quantitate the relative amounts of each product due to differences in extinction coefficients, the mixtures appear to be close to equimolar.

The final task of this study was the construction of one analogous 15-component homochiral library, L-**L**, employing the pure sugar substrates of the L-series **13**, **20**, and **27** and adopting a strictly parallel chemistry. After completion of the procedure, there was obtained a product mixture comprising the expected chiral oxygen, sulfur, and nitrogen L-nucleosides, accounting for a 58% averaged yield. The HPLC trace of the chiral collection was almost superimposable with the profile of the above racemic counterpart, indicative of good reproducibility of the overall methodology.

Biological Survey

This work should be intended as a successful attempt to establish a novel methodological approach toward a relevant and representative class of biomolecules whose use in medicinal chemistry is well documented.[14,17,21] The majority of nucleoside compounds in this study, comprising some sulfur and nitrogen congeners, has been previously subjected to biological evaluation against HIV and HVB replication *in vitro*. Selected examples include: cytidine β-D-**14c**, highly HIV and HBV active;[14c] cytidine β-L-**14c**, highly HBV active and moderately HIV active;[14c] cytidine α-L-**14c**, HBV active and HIV inactive;[14c] thiocytidine β-D-**21c**, HIV active and HBV inactive.[17a,c]

Uridine and thymidine derivatives of both the D- and L-series showed moderate to poor antiviral activity, while similar inefficacy was observed for thiouridines α- and β-L- and -D-**21a**,[17e] azauridine β-D-**28a**,[21d] thiothymidines α- and β-L- and -D-**21b**,[17e] and azathymidine β-D-**28b**.[21d,26]

Conclusions

We have described a flexible synthetic procedure to access pharmacologically important 2′,3′-dideoxypyrimidine nucleosides[27] and their thio- and azasugar variants. The strategy is highlighted by (1) easy availability of the key building blocks (*i.e.* glyceraldehyde acetonides and the siloxy dienes triad) from common and inexpensive raw materials; (2) clean reactions, with (usually) only the product and unreacted starting material detected; (3) convenient use of both enantiomers of glyceraldehyde as synthetic equivalents of "chiral" formyl (and hydroxymethyl) cation units; (4) uniform protocols compatible with the diverse nature of the matrices employed; and (5) concrete possibility to enlarge the synthetic scope of the reaction to 2′- and 3′-substituted (and to 2′,3′-disubstituted) congeners by functionalization of the appropriate α,β-unsaturated intermediates.

This work has resulted in the development of a uniform protocol which allows for (1) linear stereoselective syntheses of individual enantiomerically enriched (>90% ee) nucleosides of both L- and D-series; (2) divergent and/or parallel execution to access many structural variants within a given class of nucleoside compounds; (3) adaptation, without significant changes, to combinatorial assembly of collections and/or subcollections of nucleoside mixtures with rather uniform component dispersion, useful for both racemic and homochiral synthesis.

Experimental Section

General. Flash chromatography was performed on 32−63 μm silica gel ICN Biomedicals, using the indicated solvent mixtures. Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates (0.25 mm). The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate or in an ethanolic solution of ninhydrin, followed by charring with a heat gun.

^{1}H NMR spectra were obtained on a Bruker AC-300 or Varian XL-300 and are reported in parts per million (δ) relative to tetramethylsilane (0.0 ppm) as an internal refer-

ence, with coupling constants in hertz (Hz). Rotations were measured on a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari.

The HPLC analyses were performed using a system consisting of a Varian 9010 pump, a Philips PU 4021 spectrophotometric detector operating at 265 nm, a Rheodyne 10 μL loop injector, and a Kontron computing integrator. The analyses were performed on a Merck LiChroCART 250-4 Purospher RP-18 (5 μm) column thermostated at 32 °C. The mobile phase was (A) 0.01 M ammonium phosphate, pH 5.0, and 10% methanol; (B) methanol. Gradient: 0−2 min, 5% B; 2−22 min, 5−45% B. Flow: 1.0 mL/min.

Materials. 2-Furaldehyde (**2**), thiophene (**4**), and pyrrole (**6**) were purchased from Aldrich and vacuum-distilled prior to use. D-(*R*)-Glyceraldehyde acetonide (D-**1**) was prepared from D-mannitol (Aldrich) according to literature.[7] L-(*S*)-Glyceraldehyde acetonide (L-**1**) was obtained from 5,6-*O*-isopropylidene-L-gulonic acid 1,4-lactone (Fluka) following a known protocol.[8] Furan-2(5*H*)-one (**3**) was synthesized from **2** by a known procedure.[4] 3-Thiolen-2-one (**5**) was obtained from **4** following a literature preparation.[5] *N*-Boc-pyrrolinone (**7**) was prepared from **6**, *via* pyrrol-2(5*H*)-one, as previously described.[6]

2-(*tert*-Butyldimethylsiloxy)furan (TBSOF). To a solution of 2(5*H*)-furanone **3** (10.0 g, 119 mmol) in anhydrous CH_2Cl_2 (80 mL) were added Et_3N (23.2 mL, 166 mmol) and TBSOTf (30 mL, 131 mmol) under argon at 0 °C. After ambient temperature was reached, the reaction mixture was stirred for 2 h, the solvent was removed under vacuum, and the oily residue was subjected to flash chromatographic purification on silica gel (9:1 hexanes/ethyl acetate) to furnish 16.5 g (70%) of TBSOF as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 6H), 0.97 (s, 9H), 5.10 (dd, J = 3.0, 1.0 Hz, 1H), 6.20 (dd, J = 3.0, 2.1 Hz, 1H), 6.81 (dd, J = 2.1, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8 (2 C), 18.0, 25.5 (3 C), 83.5, 111.0, 132.2, 156.9. Anal. ($C_{10}H_{18}O_2Si$) C, H.

2-(*tert*-Butyldimethylsiloxy)thiophene (TBSOT). To a solution of 3-thiolen-2-one (**5**) (12.4 g, 124 mmol) in anhydrous CH_2Cl_2 (200 mL) were added 2,6-lutidine (43 mL, 371 mmol) and TBSOTf (36.9 mL, 161 mmol) under argon at room temperature. After the reaction mixture was stirred for 30 min, the solvent was evaporated and the residue purified by flash chromatography on silica gel (7:3 hexanes/ethyl acetate) to furnish 24.0 g (91%) of TBSOT as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.96 (s, 9H), 6.11 (dd, J = 3.6, 1.2 Hz, 1H), 6.46 (dd, J = 6.0, 1.2 Hz, 1H), 6.62 (dd, J = 6.0, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0 (2 C), 18.2, 25.6 (3 C), 109.0, 112.7, 124.4, 150.8. Anal. ($C_{10}H_{18}OSSi$) C, H.

***N*-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-pyrrole (TBSOP).** To a solution of *N*-Boc-pyrrolinone (**7**) (6.1 g, 33 mmol) in anhydrous CH_2Cl_2 (50 mL) were added 2,6-lutidine (11.6 mL, 99 mmol) and TBSOTf (7.6 mL, 33 mmol) under argon at room temperature. After being stirred for 45 min, the solvent was evaporated and the residue flash chromatographed over silica gel (1:1 hexanes/ethyl acetate) to give 8.8 g (90%) of pure TBSOP as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.97 (s, 9H), 1.54 (s, 9H), 5.20 (dd, J = 3.6, 2.1 Hz, 1H), 5.86 (t, J = 3.7 Hz, 1H), 6.66 (dd, J = 3.9, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9 (2 C), 18.3, 25.7 (3 C), 28.1 (3 C), 82.7, 92.4, 108.0, 113.0, 145.5, 148.2. Anal. ($C_{15}H_{27}NO_3Si$) C, H, N.

6,7-*O*-Isopropylidene-2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactone (8). 2,3-*O*-Isopropylidene-D-glyceraldehyde (D-**1**) (13.0 g, 100 mmol) and TBSOF (20.9 mL, 100 mmol) were dissolved in dry CH_2Cl_2 (250 mL) under nitrogen, and the mixture was cooled to −90 °C. With stirring, $BF_3{\cdot}OEt_2$ (12.3 mL, 100 mmol) cooled at the same temperature was added, and the solution was allowed to stir for 6 h. The reaction was then quenched at −90 °C by addition of an aqueous saturated $NaHCO_3$ solution, and after ambient temperature was reached, the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layer washed with brine, dried ($MgSO_4$), and concentrated in vacuum. The residue was flash chromatographed on silica gel (4:6 hexanes/ethyl acetate) to furnish 16.1 g (75%) of **8** as white crystals: mp 125 °C; $[\alpha]^{20}_D$ +69.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.42 (s, 3H), 2.94 (d, J = 6.6 Hz, 1H), 3.67 (m, 1H), 4.05 (m, 1H), 4.18 (m, 2H), 5.27 (m, 1H), 6.17 (dd, J = 5.8, 1.9 Hz, 1H), 7.59 (dd, J = 5.8, 1.7 Hz, 1H). Anal. ($C_{10}H_{14}O_5$) C, H.

6,7-*O*-Isopropylidene-2,3-dideoxy-D-*arabino*-heptono-1,4-lactone (9). A solution of the α,β-unsaturated lactone **8** (16.1 g, 75 mmol) in anhydrous THF (500 mL) in the presence of AcONa (750 mg) was subjected to catalytic hydrogenation with 10% Pd on carbon (1.6 g) at room temperature for 24 h. The catalyst was then filtered off and the filtrate evaporated to give saturated lactone **9** (15.4 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ −38.2 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.41 (s, 3H), 2.31 (m, 2H), 2.45−2.70 (m, 2H), 3.35 (bs, 1H), 3.53 (bs, 1H), 4.01 (m, 1H), 4.14 (m, 2H), 4.77 (td, J = 7.5, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 25.1, 26.6, 28.5, 66.8, 73.7, 75.6, 79.9, 109.3, 178.0. Anal. ($C_{10}H_{16}O_5$) C, H.

***(R)*-Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (11).** Lactone **9** (5.0 g, 23 mmol) was dissolved with 50 mL of 80% aqueous acetic acid, and the resulting solution was allowed to react at 50 °C. The reaction was monitored by TLC and was judged complete after 8 h. The solution was concentrated to give a crude triol intermediate which was used as such in the subsequent step. The triol (3.9 g, 22 mmol) was then dissolved in CH_2Cl_2 (150 mL) and treated with a 0.65 M aqueous $NaIO_4$ solution (75 mL) and chromatography grade SiO_2 (15 g). The resulting slurry was vigorously stirred for 15 min at what time TLC showed complete consumption of the starting material. The slurry was filtered under suction and the silica thoroughly washed with CH_2Cl_2 and ethyl acetate. The filtrates were evaporated to leave the crude aldehyde **10**, which was directly subjected to reductive workup. Thus, crude **10** (2.3 g, 20 mmol) was dissolved in methanol (100 mL) and the solution treated with $NaBH_4$ (1.5 g, 40 mmol) at −30 °C. After 30 min, the temperature was allowed to rise to −15 °C, while stirring was continued until the starting aldehyde was consumed (1 h). The slurry was quenched by adding acetone and a saturated aqueous citric acid solution. The mixture was concentrated to leave an oily residue, which was subjected to flash chromatographic purification on silica gel (ethyl acetate as an eluant) to furnish furanone **11** (2.1 g, 88%) as a colorless oil: $[\alpha]^{20}_D$ −54.5 (*c* 2.0, $CHCl_3$) (lit.[15a] $[\alpha]^{30}_D$ −53.5 (*c* 3.17, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0−2.4 (m, 2H), 2.4−2.7 (m, 2H), 3.66 (dd, J = 12.6, 4.8 Hz, 1H), 3.69 (s, 1H), 3.92 (dd, J = 12.6, 2.7 Hz, 1H), 4.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 28.7, 64.1, 80.7, 178.3.

Using the standard protocol,[16] alcohol **11** was quantitatively transformed to the corresponding Mosher ester. Quantitative NMR measurements established a ≥96% ee for this material.

***(R)*-5-*O*-(*tert*-Butyldimethylsilyl)dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (12).** To a solution of alcohol **11** (1.7 g, 14.4 mmol) in anhydrous CH_2Cl_2 (34 mL) at room temperature were added TBSCl (2.6 g, 17.5 mmol) and imidazole (1.2 g, 17.5 mmol), with stirring. After 3 h, the reaction was quenched with saturated aqueous citric acid solution, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated to give a yellow oil. Purification by flash chromatography (1:1 hexanes/ethyl acetate) gave pure protected lactone **12** (3.0 g, 92%) as a clear oil: $[\alpha]^{20}_D$ −11.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.03 (s, 3H), −0.02 (s, 3H), 0.79 (s, 9H), 2.00−2.25 (m, 2H), 2.30−2.55 (m, 2H), 3.59 (dd, J = 11.2, 1.5 Hz, 1H), 3.76 (dd, J = 11.2, 1.8 Hz, 1H), 4.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.8, −5.7, 18.0, 23.3, 25.5 (3 C), 28.3, 64.7, 79.9, 177.3. Anal. ($C_{11}H_{22}O_3Si$) C, H.

Methyl 5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-α,β-L-ribofurano-side (13). To a solution of furanone **12** (2.0 g, 8.6 mmol) in anhydrous CH_2Cl_2 (100 mL) at −90 °C was slowly added *via* cannula DIBAL-H (17.2 mL, 1.5 M in toluene, 25.8 mmol) with stirring. After 2 h, the reaction was quenched with methanol and an aqueous sodium tartrate solution at −90 °C. After ambient temperature was reached, the slurry was stirred for 40 min, extracted with ethyl actetate, dried (Na_2SO_4), and

concentrated to give a crude lactol, which was directly subjected to methylation. Thus, crude lactol (1.9 g, 8.2 mmol) was dissolved in anhydrous diethyl ether (25 mL), and powdered anhydrous molecular sieves (4 Å, 0.2 g) were added. With stirring, methyl orthoformate (1.8 mL, 16 mmol) and BF_3·O-Et_2 (250 μL) were added, and the mixture was allowed to react for 30 min. The reaction was quenched with Et_3N and brine until neutral, extracted with diethyl ether, dried ($MgSO_4$), and concentrated to give crude **13**, which was purified by flash column chromatography (8:2 hexanes/ethyl acetate) to give α,β-methyl glycoside **13** (2.0 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ −17.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (s, 5.4H), 0.87 (s, 3.6H), 1.6−2.1 (m, 4H), 3.28 (s, 1.2H), 3.30 (s, 1.8H), 3.5−3.7 (m, 2H), 4.11 (m, 1H), 4.93 (d, *J* = 3.9 Hz, 0.4H), 4.98 (d, *J* = 4.8 Hz, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, 18.2, 25.8 (3 C), 25.3 and 26.2, 31.6 and 32.6, 54.1 and 54.2, 65.4 and 67.2, 78.5 and 80.8, 105.0 and 105.3. Anal. ($C_{12}H_{26}O_3Si$) C, H.

2′,3′-Dideoxy-α-L-uridine (α-L-14a) and 2′,3′-Dideoxy-β-L-uridine (β-L-14a). A mixture of uracil (0.45 g, 4.0 mmol), 1,1,1,3,3,3-hexamethyldisilazane (25 mL), and ammonium sulfate (20 mg) was refluxed for 2 h and then cooled to room temperature. The clear mixture was concentrated in vacuo to give a residue, to which a solution of compound **13** (0.5 g, 2.0 mmol) in anhydrous 1,2-dichloroethane (25 mL) was added, followed by the addition of $SnCl_4$ (234 μL, 2.0 mmol) and TMSOTf (462 μL, 2.0 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and then quenched with a saturated aqueous $NaHCO_3$ solution until neutral pH was reached. The mixture was extracted thoroughly with ethyl acetate, dried ($MgSO_4$), and concentrated to give a residue, which was subjected to flash chromatography in order to isolate the protected nucleoside fraction. The ^{1}H NMR analysis of this material revealed the presence of a mixture of β and α anomers in the ratio of 1:1, estimated by integration of the signals at 8.07 and 7.35 ppm, respectively. To a stirred solution of protected nucleoside mixture (0.45 g) in THF (20 mL) was added tetra-*n*-butylammonium fluoride (1.6 g, 5 mmol) at ambient temperature. After 8 h, the mixture was evaporated in vacuo to dryness, leaving a residue from which individual pure α and β anomers were separated by silica gel preparative TLC (9:1:0.5 ethyl acetate/methanol/aqueous ammonia). This afforded α-L-**14a** (64 mg, 30%) and β-L-**14a** (63 mg, 30%).

Compound α-L-**14a** was isolated as a foam: $[\alpha]^{20}_D$ +12.7 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 1.90 (m, 1H), 2.15 (m, 2H), 2.50 (m, 1H), 3.60 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.73 (dd, *J* = 11.7, 4.1 Hz, 1H), 4.56 (m, 1H), 5.85 (d, *J* = 7.9 Hz, 1H), 6.14 (t, *J* = 5.4 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 28.4, 38.8, 66.8, 85.1, 91.0, 105.2, 144.4, 158.9, 175.2. Anal. ($C_9H_{12}N_2O_4$) C, H, N.

Compound β-L-**14a** was isolated as a foam: $[\alpha]^{20}_D$ −30.0 (*c* 0.2, MeOH) (lit.[14c] $[\alpha]_D$ −28.0 (*c* 0.1, MeOH)); ^{1}H NMR (300 MHz, D_2O) δ 1.60 (m, 2H), 1.99 (m, 2H), 3.52 (dd, *J* = 11.6, 6.7 Hz, 1H), 3.62 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.75 (m, 1H), 5.71 (dd, *J* = 11.7, 6.2 Hz, 1H), 5.99 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 30.6, 33.6, 68.7, 74.4, 90.5, 106.5, 143.9, 164.6, 177.5.

3′-Deoxy-α-L-thymidine (α-L-14b) and 3′-Deoxy-β-L-thymidine (β-L-14b). Compounds α-L-**14b** and β-L-**14b** were synthesized from **13** (0.5 g, 2.0 mmol) and thymine (0.5 g, 4.0 mmol) by the same methodology described for the synthesis of α- and β-L-**14a**.

Compound α-L-**14b** (70 mg, 31%) was isolated as a white solid: mp 110−113 °C (lit.[14c] mp 109−111 °C); $[\alpha]^{20}_D$ +16.3 (*c* 0.5, MeOH) (lit.[14c] $[\alpha]_D$ +17.7 (*c* 0.1, MeOH)); ^{1}H NMR (300 MHz, D_2O) δ 1.95 (s, 3H), 1.96 (m, 1H), 2.21 (m, 2H), 2.53 (m, 1H), 3.65 (dd, *J* = 12.0, 5.7 Hz, 1H), 3.78 (dd, *J* = 12.0, 3.2 Hz, 1H), 4.61 (m, 1H), 6.19 (t, *J* = 5.5 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 12.8, 26.4, 32.3, 64.5, 82.9, 88.4, 111.4, 135.5, 153.5, 163.0.

Compound β-L-**14b** (77 mg, 34%) was isolated as colorless crystals: mp 148−150 °C (lit.[14c] mp 148−149 °C); $[\alpha]^{20}_D$ −30.9 (*c* 0.4, MeOH) (lit.[14c] $[\alpha]_D$ −31.2 (*c* 0.1, MeOH)); ^{1}H NMR (300 MHz, D_2O) δ 1.92 (m, 1H), 1.96 (s, 3H), 2.17 (m, 2H), 2.51 (m, 1H), 3.79 (dd, *J* = 12.4, 5.0 Hz, 1H), 3.94 (dd, *J* = 12.4, 3.0 Hz, 1H), 4.29 (m, 1H), 6.18 (dd, *J* = 7.0, 3.5 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 12.9, 26.0, 32.1, 63.7, 82.8, 87.1, 111.7, 138.6, 152.8, 163.6.

2′,3′-Dideoxy-α-L-cytidine (α-L-14c) and 2′,3′-Dideoxy-β-L-cytidine (β-L-14c). Compounds α-L-**14c** and β-L-**14c** were synthesized from **13** (0.5 g, 2.0 mmol) and 4-*N*-acetylcytosine (0.6 g, 4.0 mmol) essentially according to the procedure described for α- and β-L-**14a** except for the deprotection stage which, in addition to the TBAF-promoted desilylation, included deacetylation (K_2CO_3, MeOH).

Compound α-L-**14c** (70 mg, 33%) was isolated as a glass: $[\alpha]^{20}_D$ +45.9 (*c* 0.2, MeOH) (lit.[14c] $[\alpha]_D$ +46.6 (*c* 0.1, MeOH)); ^{1}H NMR (300 MHz, D_2O) δ 1.8−2.5 (m, 4H), 3.5−3.9 (m, 2H), 4.69 (m, 1H), 6.11 (d, *J* = 7.6 Hz, 1H), 6.15 (m, 1H), 7.75 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 26.5, 30.7, 65.2, 83.5, 86.9, 95.0, 141.9, 157.5, 166.8.

Compound β-L-**14c** (78 mg, 37%) was isolated as a white solid: mp 190−193 °C (lit.[14c] mp 194−196 °C); $[\alpha]^{20}_D$ −88.6 (*c* 0.1, MeOH) (lit.[14c] $[\alpha]_D$ −90.3 (*c* 0.14, MeOH)); ^{1}H NMR (300 MHz, D_2O) δ 1.7−2.5 (m, 4H), 3.5−4.0 (m, 2H), 4.40 (m, 1H), 6.09 (d, *J* = 7.3 Hz, 1H), 6.15 (dd, *J* = 7.4, 3.7 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 25.6, 34.2, 63.6, 83.6, 88.5, 95.3, 142.7, 158.0, 167.7.

The enantiomeric intermediates *ent*-**8**−*ent*-**13** and enantiomeric nucleosides α-D-**14a**−**c** and β-D-**14a**−**c** were prepared by starting with L-glyceraldehyde L-**1** adopting the procedures above described for their respective counterparts **8**−**13** and α- and β-L-**14a**−**c**. Diagnostic data are as follows:

ent-**8**: yield 72%, colorless crystals; mp 123 °C; $[\alpha]^{20}_D$ −68.9 (*c* 1.0, $CHCl_3$). Anal. ($C_{10}H_{14}O_5$) C, H.

ent-**9**: yield 92%, an oil; $[\alpha]^{20}_D$ +39.6 (*c* 2.0, $CHCl_3$). Anal. ($C_{10}H_{16}O_5$) C, H.

ent-**11**: yield 89%, an oil; $[\alpha]^{20}_D$ +55.1 (*c* 2.1, $CHCl_3$) (lit.[15b] $[\alpha]^{20}_D$ +31.3 (*c* 2.92, EtOH)).

ent-**12**: yield 90%, an oil; $[\alpha]^{20}_D$ +11.0 (*c* 0.5, $CHCl_3$) (lit.[13a] $[\alpha]_D$ +11.11 (*c* 0.92, $CHCl_3$)).

ent-**13**: yield 92%, an oil; $[\alpha]^{20}_D$ +16.9 (*c* 0.5, $CHCl_3$). Anal. ($C_{12}H_{26}O_3Si$) C, H.

α-D-**14a**: yield 32%, a foam; $[\alpha]^{20}_D$ −13.1 (*c* 0.5, MeOH). Anal. ($C_9H_{12}N_2O_4$) C, H, N.

β-D-**14a**: yield 29%, a white solid; mp 129−131 °C (lit.[14d] mp 117.5−118.5 °C); $[\alpha]^{20}_D$ +32.5 (*c* 0.5, H_2O) (lit.[14d] $[\alpha]^{25}_D$ +31 (*c* 0.43, H_2O)).

α-D-**14b**: yield 32%, a white solid; mp 105−107 °C; $[\alpha]^{20}_D$ −17.2 (*c* 0.1, MeOH). Anal. ($C_{10}H_{14}N_2O_4$) C, H, N.

β-D-**14b**: yield 33%, white crystals; mp 154−155 °C (lit.[14e] mp 155−156 °C); $[\alpha]^{20}_D$ +24.0 (*c* 0.5, H_2O) (lit.[14e] $[\alpha]^{19}_D$ +20.0 (*c* 0.6, H_2O)).

α-D-**14c**: yield 35%, a solid; mp 165−166 °C (lit.[13a] mp 169−172 °C); $[\alpha]^{20}_D$ −80.4 (*c* 0.5, MeOH) (lit.[13a] $[\alpha]_D$ −83.39 (*c* 0.56, MeOH)).

β-D-**14c**: yield 35%, a white solid; mp 215−217 °C (lit.[13a] mp 214−217 °C); $[\alpha]^{20}_D$ +102.5 (*c* 0.5, MeOH) (lit.[13a] $[\alpha]_D$ +105.9 (*c* 0.53, MeOH)).

6,7-*O*-Isopropylidene-2,3-dideoxy-4-thio-D-*arabino*-hept-2-enono-1,4-lactone (15). The above procedure for **8** was employed with TBSOT (8.5 g, 39.6 mmol), D-glyceraldehyde D-**1** (5.1 g, 39.6 mmol), and BF_3·OEt_2 (4.8 mL, 39.6 mmol) in CH_2Cl_2 (200 mL) at −78 °C for 3 h to afford, after flash chromatographic purification (1:1 hexanes/ethyl acetate), 7.1 g (78%) of **15** as an oil: $[\alpha]^{20}_D$ +67.0 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.41 (s, 3H), 2.74 (bs, 1H), 3.8−4.2 (m, 4H), 4.91 (m, 1H), 6.31 (dd, *J* = 6.1, 1.9 Hz, 1H), 7.54 (dd, *J* = 6.1, 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 26.7, 58.4, 67.1, 72.9, 78.1, 110.0, 133.4, 156.7, 199.6. Anal. ($C_{10}H_{14}O_4S$) C, H.

6,7-*O*-Isopropylidene-2,3-dideoxy-4-thio-D-*arabino*-heptono-1,4-lactone (16). The above procedure for **9** was employed with 6.5 g (28.2 mmol) of unsaturated thiolactone **15**, 0.8 g of 10% Pd on carbon, and 250 mg of AcONa in 150 mL of THF to afford 5.9 g (90%) of saturated thiolactone **16** as white crystals: mp 128−130 °C; $[\alpha]^{20}_D$ −52.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.42 (s, 3H), 2.1−2.5 (m, 2H),

2.5−2.8 (m, 2H), 2.91 (d, J = 3.6 Hz, 1H), 3.77 (dd, J = 7.2, 3.9 Hz, 1H), 3.95 (m, 2H), 4.09 (m, 1H), 4.25 (ddd, J = 7.5, 7.0, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 26.6, 28.4, 41.7, 53.3, 66.5, 74.6, 77.5, 109.6, 208.2. Anal. ($C_{10}H_{16}O_4S$) C, H.

(*R*)-5-Formylthiolan-2-one (17). The above procedure for **10** was employed with 5.0 g (21.5 mmol) of **16** to afford 2.1 g (75%) of aldehyde **17**, which was isolated in a pure state as a colorless oil: $[\alpha]^{20}_D$ −43.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (m, 1H), 2.63 (m, 3H), 4.35 (m, 1H), 9.63 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 39.8, 56.1, 194.2, 205.5. Anal. ($C_5H_6O_2S$) C, H.

2,3-Dideoxy-4-thio-α,β-L-ribofuranose (19). To a solution of aldehyde **17** (1.5 g, 11.5 mmol) in methanol (50 mL), was added $NaBH_4$ (435 mg, 11.5 mmol) with stirring at −30 °C during a period of 1 h. The temperature was allowed to rise to −15 °C while a further portion of $NaBH_4$ (435 mg, 11.5 mmol) was added and the mixture was stirred at −15 °C for 3 h. Acetone (10 mL) was then added, and the resulting mixture was allowed to stir at room temperature for 1 h. The mixture was concentrated under vacuum and the residue subjected to flash chromatography (3:7 hexanes/ethyl acetate) to afford 1.0 g (65%) of pure **19** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0−2.3 (m, 4H), 2.6 (bs, 2H), 3.53 (qd, J = 11.1, 6.1 Hz, 1H), 3.75 (m, 2H), 5.52 (dd, J = 3.7, 1.3 Hz, 0.7H), 5.56 (dd, J = 4.2, 1.7 Hz, 0.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3 and 29.8, 38.9 and 41.2, 50.9 and 52.4, 65.0 and 65.6, 82.2 and 82.4. Anal. ($C_5H_{10}O_2S$) C, H.

(*R*)-5-(Hydroxymethyl)thiolan-2-one (18). To a solution of aldehyde **17** (0.5 g, 3.8 mmol) in methanol (16 mL) was carefully added $NaBH_4$ (145 mg, 3.8 mmol) in small portions during a period of 1 h at −30 °C. The mixture was slowly warmed to −20 °C, while the progress of the reduction is monitored by TLC. When starting aldehyde was almost entirely consumed, the reaction was rapidly quenched with a chilled saturated aqueous NH_4Cl solution and then extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (3:7 hexanes/ethyl acetate) to afford 261 mg (52%) of alcohol **18** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (m, 1H), 2.35 (m, 1H), 2.64 (m, 2H), 3.69 (s, 1H), 3.86 (m, 2H), 4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 41.1, 52.0, 65.4, 210.5. Anal. ($C_5H_8O_2S$) C, H.

Using the standard protocol,[16] as for **11**, an ee of ≥90% was measured for **18**.

1-*O*-Acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-4-thio-α,β-L-ribofuranose (20). To a solution of thiolactol **19** (1.0 g, 7.5 mmol) in anhydrous CH_2Cl_2 (50 mL) were added TBSCl (1.5 g, 10.0 mmol) and imidazole (680 mg, 10.0 mmol) with stirring at ambient temperature. After 10 h, the reaction was quenched by adding a 5% aqueous citric acid solution and the mixture extracted thoroughly with ethyl acetate. After drying ($MgSO_4$), the solvent was removed and the residue purified by flash chromatography (7:3 hexanes/ethyl acetate) to afford a 5-*O*-protected intermediate (not characterized) which was employed in the successive acetylation reaction. Thus, the product was dissolved in anhydrous CH_2Cl_2 (25 mL), and pyridine (2.0 mL), Ac_2O (1.4 mL), and a catalytic amount of DMAP were sequentially added. After being stirred at room temperature for 30 min, the reaction was quenched with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4), and the solvent was removed under vacuum. Flash chromatographic purification of the crude product (8:2 hexanes/ethyl acetate) afforded pure thiofuranose **20** (1.5 g, 70%) as a colorless oil which solidified on standing: $[\alpha]^{20}_D$ −30.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6H), 0.88 (s, 4.5H), 0.89 (s, 4.5H), 2.03 (s, 1.5H), 2.04 (s, 1.5H), 1.8−2.3 (m, 4H), 3.4−3.8 (m, 3H), 6.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (2 C), 18.3, 21.3, 25.9 (3 C), 29.5 and 31.0, 34.7 and 37.0, 49.7 and 51.9, 65.8 and 67.5, 82.8, 170.4. Anal. ($C_{13}H_{26}O_3SSi$) C, H.

2′,3′-Dideoxy-4′-thio-α-L-uridine (α-L-21a) and 2′,3′-Dideoxy-4′-thio-β-L-uridine (β-L-21a). The above procedure described for α- and β-L-**14a** was followed with 0.5 g (1.72 mmol) of **20** and 0.58 g of uracil (5.16 mmol) to afford a 1:1 α,β anomeric mixture of nucleosides from which pure individual components were isolated by preparative TLC (98:2:0.5 ethyl acetate/methanol/aqueous ammonia).

Compound α-L-**21a** (59 mg, 30%) was isolated as a foam: $[\alpha]^{20}_D$ −11.5 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 1.8−2.7 (m, 4H), 3.6−4.1 (m, 3H), 5.83 (d, J = 7.5 Hz, 1H), 6.19 (dd, J = 6.1, 3.9 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 33.8, 39.4, 55.3, 63.0, 68.2, 105.1, 146.6, 155.3, 169.4. Anal. ($C_9H_{12}N_2O_3S$) C, H, N.

Compound β-L-**21a** (61 mg, 31%) was isolated as a foam: $[\alpha]^{20}_D$ −8.0 (*c* 0.2, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 1.8−2.7 (m, 4H), 3.6−4.1 (m, 3H), 5.85 (d, J = 7.5 Hz, 1H), 6.66 (t, J = 7.5 Hz, 1H), 7.50 (d, J 7.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 33.6, 39.2, 55.6, 65.0, 67.7, 104.8, 146.7, 155.1, 169.2. Anal. ($C_9H_{12}N_2O_3S$) C, H, N.

3′-Deoxy-4′-thio-α-L-thymidine (α-L-21b) and 3′-Deoxy-4′-thio-β-L-thymidine (β-L-21b). The above procedure for α- and β-L-**14b** was employed with 0.5 g (1.72 mmol) of **20** and 651 mg (5.16 mmol) of thymine to afford a 1:1 α,β anomeric mixture of nucleosides, from which pure individual compounds were isolated by preparative TLC (99:1:0.3 ethyl acetate/methanol/aqueous ammonia).

Compound α-L-**21b** (71 mg, 34%) was isolated as a powder: $[\alpha]^{20}_D$ −19.8 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.89 (s, 3H), 1.9−2.4 (m, 4H), 3.4−3.9 (m, 2H), 3.96 (m, 1H), 6.19 (dd, J = 6.2, 4.7 Hz, 1H), 8.08 (s, 1H). Anal. ($C_{10}H_{14}N_2O_3S$) C, H, N.

Compound β-L-**21b** (150 mg, 36%) was isolated as a powder: $[\alpha]^{20}_D$ −10.5 (*c* 0.45, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.90 (s, 3H), 1.8−2.5 (m, 4H), 3.4−3.7 (m, 3H), 6.25 (t, J = 7.8 Hz, 1H), 7.76 (s, 1H). Anal. ($C_{10}H_{14}N_2O_3S$) C, H, N.

2′,3′-Dideoxy-4′-thio-α-L-cytidine (α-L-21c) and 2′,3′-Dideoxy-4′-thio-β-L-cytidine (β-L-21c). The above procedure described for α- and β-L-**14c**, employing 0.5 g (1.72 mmol) of **20** and 790 mg (5.16 mmol) of 4-*N*-acetylcytosine gave a 1:1 α,β anomeric mixture of the title nucleosides, which were separated, as individual components, by preparative TLC (90:10:0.5 ethyl acetate/methanol/aqueous ammonia).

Compound α-L-**21c** (61 mg, 31%) was isolated as a foam: $[\alpha]^{20}_D$ −30.0 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.9−2.2 (m, 3H), 2.42 (m, 1H), 3.51 (dd, J = 11.1, 6.9 Hz, 1H), 3.60 (dd, J = 11.1, 6.6 Hz, 1H), 3.84 (quint, J = 6.0 Hz, 1H), 5.92 (d, J = 7.2 Hz, 1H), 6.27 (dd, J = 6.6, 4.2 Hz, 1H), 8.05 (d, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 31.7, 37.7, 53.0, 60.0, 66.6, 96.1, 143.7, 158.7, 167.4. Anal. ($C_9H_{13}N_3O_2S$) C, H, N.

Compound β-L-**21c** (58 mg, 30%) was isolated as colorless crystals: mp 86−87 °C; $[\alpha]^{20}_D$ −15.0 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.88 (m, 1H), 2.15 (m, 2H), 2.31 (m, 1H), 3.63 (m, 1H), 3.72 (dd, J = 11.1, 5.4 Hz, 1H), 3.81 (dd, J = 11.1, 5.7 Hz, 1H), 5.90 (d, J = 7.5 Hz, 1H), 6.24 (dd, J = 6.0, 4.2 Hz, 1H), 8.30 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 31.3, 38.4, 53.9, 65.6, 66.6, 95.7, 144.0, 158.7, 167.5. Anal. ($C_9H_{13}N_3O_2S$) C, H, N.

The enantiomeric intermediates *ent*-**15**−*ent*-**20** and enantiomeric nucleosides α-D-**21a**−**c** and β-D-**21a**−**c** were prepared by starting with L-glyceraldehyde L-**1**, adopting the procedures above described for their respective counterparts **15**−**20** and α- and β-L-**21a**−**c**. Diagnostic data are as follows:

ent-**15**: yield 71%, an oil; $[\alpha]^{20}_D$ −65.9 (*c* 2.4, $CHCl_3$). Anal. ($C_{10}H_{14}O_4S$) C, H.

ent-**16**: yield 90%, colorless crystals; mp 130−131 °C; $[\alpha]^{20}_D$ +53.7 (*c* 2.4, $CHCl_3$). Anal. ($C_{10}H_{16}O_4S$) C, H.

ent-**17**: yield 76%, an oil; $[\alpha]^{20}_D$ +42.5 (*c* 0.6, $CHCl_3$). Anal. ($C_5H_6O_2S$) C, H.

ent-**19**: yield 67%, colorless oil. Anal. ($C_5H_{10}O_2S$) C, H.

ent-**18**: yield 52%, an oil. Anal. ($C_5H_8O_2S$) C, H.

ent-**20**: yield 70%, glassy solid; $[\alpha]^{20}_D$ +28.5 (*c* 0.6, $CHCl_3$). Anal. ($C_{13}H_{26}O_3SSi$) C, H.

α-D-**21a**: yield 28%, a foam; $[\alpha]^{20}_D$ +12.2 (*c* 0.2, MeOH). Anal. ($C_9H_{12}N_2O_3S$) C, H, N.

β-D-**21a**: yield 34%, a foam; $[\alpha]^{20}_D$ +8.7 (*c* 0.2, MeOH). Anal. ($C_9H_{12}N_2O_3S$) C, H, N.

α-D-**21b**: yield 31%, a foam; $[\alpha]^{20}_D$ +18.5 (*c* 0.3, MeOH). Anal. ($C_{10}H_{14}N_2O_3S$) C, H, N.

β-D-**21b**: yield 39%, a powder; $[\alpha]^{20}_D$ +11.4 (*c* 0.3, MeOH). Anal. ($C_{10}H_{14}N_2O_3S$) C, H, N.

α-D-**21c**: yield 29%, white foam; $[\alpha]^{20}_D$ +28.7 (*c* 0.15, MeOH). Anal. ($C_9H_{13}N_3O_2S$) C, H, N.

β-D-**21c**: yield 30%, colorless crystals; mp 86−89 °C (lit.[17a] mp 83−85 °C); $[\alpha]^{20}_D$ +16.6 (*c* 0.25, MeOH).

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactam (22).** To a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (D-**1**) (6.0 g, 46 mmol) in anhydrous Et_2O (300 mL) were added TBSOP (13.6 g, 46 mmol) and $SnCl_4$ (8.1 mL, 69 mmol) under argon at −85 °C. The mixture was stirred at this temperature for 3 h, a saturated aqueous $NaHCO_3$ solution was added at −85 °C, and after ambient temperature was reached, the resulting mixture was extracted with Et_2O (3 × 60 mL). After drying ($MgSO_4$), the solution was evaporated under reduced pressure and the crude product was crystallized from CH_2Cl_2/hexane to give 11.5 g (80%) of **22** as a white solid: mp 138−140 °C; $[\alpha]^{20}_D$ +197.59 (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.32 and 1.37 (2s, each 3H), 1.57 (s, 9H), 3.63 (d, *J* = 3.9 Hz, 1H), 3.86 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.94 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.01 (q, *J* = 6.0 Hz, 1H), 4.09 (ddd, *J* = 6.0, 5.7, 3.9 Hz, 1H), 4.81 (dt, *J* = 5.7, 2.4 Hz, 1H), 6.13 (dd, *J* = 6.3, 1.5 Hz, 1H), 7.43 (dd, *J* = 6.3, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 25.1, 26.4, 28.0 (3 C), 65.6, 66.4, 72.6, 75.6, 83.8, 109.2, 126.9, 148.2, 150.9, 168.9. Anal. ($C_{15}H_{23}NO_6$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-heptono-1,4-lactam (23).** The above procedure for **9** was employed with 5.7 g (18.2 mmol) of unsaturated lactam **22**, 600 mg of 10% Pd on carbon, and 250 mg of AcONa in 200 mL of THF to afford 5.2 g (92%) of saturated lactam **23** as a white solid: mp 99−103 °C; $[\alpha]^{20}_D$ +59.24 (*c* 1.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.30 and 1.36 (2s, each 3H), 1.48 (s, 9H), 2.10 (m, 2H), 2.32 (ddd, *J* = 17.7, 6.0, 4.8 Hz, 1H), 2.71 (dt, *J* = 17.1, 10.5 Hz, 1H), 3.54 (d, *J* = 6.3 Hz, 1H), 3.69 (q, *J* = 5.7 Hz, 1H), 3.97 (ddd, *J* = 5.5, 4.8, 1.2 Hz, 1H), 4.05 (m, 2H), 4.31 (ddd, *J* = 5.7, 5.4, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 21.7, 25.1, 26.6, 28.0 (3 C), 32.0, 60.4, 66.8, 74.5, 77.7, 83.6, 109.4, 151.7, 174.5. Anal. ($C_{15}H_{25}NO_6$) C, H, N.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-5-formylpyrrolidin-2-one (24). The above procedure for **10** was employed with 5.0 g (15.9 mmol) of **23** to afford 2.2 g (63%) of aldehyde **24**, which was isolated in a pure state as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.50 (s, 9H), 2.05 (m, 1H), 2.25 (m, 1H), 2.54 (m, 2H), 4.58 (ddd, *J* = 7.2, 4.8, 2.2 Hz, 1H), 9.60 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.3, 27.8 (3 C), 31.2, 64.2, 84.3, 141.4, 173.0, 196.9. Anal. ($C_{10}H_{15}NO_4$) C, H, N.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)-5-(hydroxymethyl)-2-pyrrolidinone (26). To a solution of pyrrolinone **24** (2.0 g, 9.4 mmol) in methanol (30 mL), was added $NaBH_4$ (356 mg, 9.4 mmol) in small portions at −30 °C. The mixture was allowed to warm to 0 °C; the progress of the reaction was monitored by TLC. After the reduction was complete (2 h), a saturated aqueous NH_4Cl solution was added, and the mixture was thoroughly extracted with ethyl acetate to give 1.8 g of essentially pure **25** (≥98% ee) which was used as such in the subsequent step. Thus, alcohol **25** was dissolved in CH_2Cl_2 (40 mL), and TBSCl (1.25 g, 10.0 mmol) and imidazole (562 mg, 10.0 mmol) were sequentially added at room temperature. After being stirred for 18 h, the mixture was quenched by a 5% aqueous citric acid solution and extracted with ethyl acetate. The extracts were dried and evaporated under vacuum to give an oily residue, from which pure protected lactam **26** (2.23 g, 72%) was isolated as an oil by silica gel flash chromatography (7:3 hexanes/ethyl acetate): $[\alpha]^{20}_D$ +55.6 (*c* 1.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.53 (s, 9H), 2.05 (m, 2H), 2.37 (ddd, *J* = 17.4, 9.6, 2.4 Hz, 1H), 2.71 (dt, *J* = 17.4, 9.6 Hz, 1H), 3.69 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.92 (dd, *J* = 10.3, 3.9 Hz, 1H), 4.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* −5.7, −5.6, 18.1, 21.0, 25.7 (3 C), 27.9 (3 C), 32.3, 58.8, 64.2, 82.5, 149.9, 174.8. Anal. ($C_{16}H_{31}NO_4Si$) C, H, N.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)-2-methoxypyrrolidine (27). To a solution of pyrrolidinone **26** (2.2 g, 6.7 mmol) in THF (100 mL) was added a 1.0 M THF solution of $LiEt_3BH$ (3.35 mL, 3.35 mmol) at −78 °C, under argon. After being stirred for 2 h, additional hydride (3.35 mL, 3.35 mmol) was added and the reaction was allowed to stir at the same temperature. After 3 h, the reaction was quenched with methanol and water, and after ambient temperature was reached, the resulting slurry was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), and the solvent was removed under vacuum to give a crude aminol, which was used in the subsequent step. Thus, the crude product was dissolved in anhydrous ethyl ether (25 mL), and trimethyl orthoformate (1.4 mL, 12.4 mmol), $BF_3{\cdot}OEt_2$ (250 *μ*L), and powdered 4 Å molecular sieves (200 mg) were sequentially added at ambient temperature. After 30 min, the reaction was quenched with brine and few drops of Et_3N. The mixture was extracted with diethyl ether and, after drying, the solvent evaporated to give crude *O*-methyl derivative **27**, which was purified by silica gel flash chromatography (8:2 hexanes/ethyl acetate). There were obtained 1.8 g (78%) of **27** (mixture of α and *β* anomers) as a colorless oil: $[\alpha]^{20}_D$ +54.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.05 (s, 6H), 0.90 (s, 9H), 1.48 (s, 9H), 1.75 (m, 1H), 1.85 (m, 1H), 2.01 (m, 2H), 3.28 (s, 3H), 3.3−4.0 (m, 3H), 5.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (major isomer) *δ* −5.4 (2 C), 18.2, 25.8 (3 C), 27.3, 28.4 (3 C), 29.6, 55.5, 59.2, 64.9, 79.8, 89.5, 154.2. Anal. ($C_{17}H_{35}NO_4Si$) C, H, N.

4′-[(*tert*-Butyloxycarbonyl)amino]-2′,3′,4′-trideoxy-*β*-L-uridine (*β*-L-28a). The above procedure described for α- and *β*-L-**14a** was followed with 0.5 g (1.45 mmol) of **27** and 0.33 g (2.9 mmol) of uracil to afford a crude nucleoside product from which pure *β*-L-**28a** (293 mg, 65%) was obtained by preparative TLC purification (95:5:0.5 ethyl acetate/methanol/aqueous ammonia) as the sole anomer, as a powder: $[\alpha]^{20}_D$ +58.8 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, D_2O) *δ* 1.40 (s, 9H), 2.10 (m, 3H), 2.39 (m, 1H), 3.81 (m, 1H), 3.99 (m, 2H), 5.89 (d, *J* = 7.9 Hz, 1H), 6.12 (m, 1H), 8.03 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) *δ* 28.2, 30.7 (3 C), 33.5, 63.1, 74.6, 75.2, 81.0, 105.2, 145.3, 151.0, 157.8, 174.2. Anal. ($C_{14}H_{21}N_3O_5$) C, H, N.

4′-[(*tert*-Butyloxycarbonyl)amino]-3′,4′-dideoxy-*β*-L-thymidine (*β*-L-28b). The above procedure described for α- and *β*-L-**14b** was followed with 0.5 g (1.45 mmol) of **27** and 0.45 g (3.6 mmol) of thymine to afford a crude nucleoside product from which pure *β*-L-**28b** (330 mg, 70%) was obtained by preparative TLC purification (95:5:0.5 ethyl acetate/methanol/aqueous ammonia) as the sole anomer, as a waxy solid: $[\alpha]^{20}_D$ +35.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD, 50 °C) *δ* 1.39 (s, 9H), 1.87 (d, *J* = 0.9 Hz, 3H), 2.07 (m, 3H), 2.29 (m, 1H), 3.69 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.92 (m, 1H), 4.11 (dd, *J* = 11.1, 4.6 Hz, 1H), 6.09 (dd, *J* = 7.4, 5.1 Hz, 1H), 8.11 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD, 50 °C) *δ* 12.3, 25.5, 28.1 (3 C), 31.2, 60.7, 64.5, 71.5, 81.8, 110.2, 136.4, 150.6, 154.9, 164.0. Anal. ($C_{15}H_{23}N_3O_5$) C, H, N.

4′-[(*tert*-Butyloxycarbonyl)amino]-2′,3′,4′-trideoxy-*β*-L-cytidine (*β*-L-28c). The above procedure described for α- and *β*-L-**14c** was followed with 0.5 g (1.45 mmol) of **27** and 0.67 g (4.4 mmol) of 4-*N*-acetylcytosine to afford a crude nucleoside product from which pure *β*-L-**28c** (278 mg, 62%) was obtained by preparative TLC purification (70:30:0.5 ethyl acetate/methanol/aqueous ammonia) as the sole anomer, as a colorless glass which solidified on standing: $[\alpha]^{20}_D$ +38.5 (*c* 0.4, MeOH); ^{1}H NMR (300 MHz, D_2O) *δ* 1.34 (s, 9H), 1.98 (m, 2H), 2.10 (m, 1H), 2.38 (m, 1H), 3.82 (m, 1H), 3.97 (m, 2H), 6.06 (m, 2H), 7.97 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) *δ* 28.2, 30.7 (3 C), 34.0, 63.1, 65.4, 75.2, 81.1, 99.1, 144.9, 150.9, 161.1, 169.4. Anal. ($C_{14}H_{22}N_4O_4$) C, H, N.

The enantiomeric intermediates *ent*-**22**−*ent*-**27** and enantiomeric nucleosides *β*-D-**28a**−**c** were prepared by utilizing L-glyceraldehyde L-**1**, adopting the procedures above described for their respective counterparts **22**−**27** and *β*-L-**28a**−**c**. Diagnostic data are as follows:

ent-**22**: yield 78%, white solid; mp 135−136 °C; $[\alpha]^{20}_D$ −195.66 (*c* 0.4, $CHCl_3$). Anal. ($C_{15}H_{23}NO_6$) C, H, N.

ent-**23**: yield 90%, colorless solid; mp 101−102 °C; $[\alpha]^{20}_D$ −60.14 (*c* 1.0, $CHCl_3$). Anal. ($C_{15}H_{25}NO_6$) C, H, N.

ent-**24**: yield 60%, an oil. Anal. ($C_{10}H_{15}NO_4$) C, H, N.

ent-**26**: yield 72%, a colorless oil; $[\alpha]^{20}_D$ −53.4 (*c* 0.8, $CHCl_3$). Anal. ($C_{16}H_{31}NO_4Si$) C, H, N.

ent-**27**: yield 81%, an oil; $[\alpha]^{20}_D$ −52.3 (*c* 1.5, $CHCl_3$). Anal. ($C_{17}H_{35}NO_4Si$) C, H, N.

β-D-**28a**: yield 63%, a waxy solid; $[\alpha]^{20}_D$ −59.2 (*c* 0.3, MeOH). Anal. ($C_{14}H_{21}N_3O_5$) C, H, N.

β-D-**28b**: yield 72%, a waxy solid; $[\alpha]^{20}_D$ −36.0 (*c* 2.8, $CHCl_3$). Anal. ($C_{15}H_{23}N_3O_5$) C, H, N.

β-D-**28c**: yield 65%, a glass; $[\alpha]^{20}_D$ −37.5 (*c* 0.5, MeOH). Anal. ($C_{14}H_{22}N_4O_4$) C, H, N.

(*R,S*)-5-(Diethoxymethyl)-2(5*H*)-furanone [(±)-29a]. To a stirred solution of TBSOF (9.86 g, 49.8 mmol) in Et_2O (160 mL) cooled at −80 °C were added ethyl orthoformate (9.9 mL, 59.7 mmol) and $BF_3{\cdot}OEt_2$ (9.2 mL, 74.7 mmol) under nitrogen. After being stirred at this temperature for 30 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution and extracted three times with diethyl ether. After drying ($MgSO_4$), the solvent was evaporated to give virtually pure acetal (±)-**29a** (9.0 g, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 3.23 (m, 1H), 3.32 (m, 1H), 3.43 (m, 2H), 4.23 (d, J = 4.9 Hz, 1H), 4.71 (ddd, J = 4.9, 2.0, 1.5 Hz, 1H), 5.84 (dd, J = 5.7, 2.0 Hz, 1H), 7.23 (dd, J = 5.7, 1.5 Hz, 1H). Anal. ($C_9H_{14}O_4$) C, H.

(*R,S*)-5-(Diethoxymethyl)thiolen-2-one [(±)-29b]. The above procedure described for (±)-**29a**, but with a reaction time of 2 h at −80 °C and 2 h at −15 °C, was followed by starting with 10.0 g (46.6 mmol) of TBSOT to afford (±)-**29b** as an oil (8.95 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 3.53 (m, 2H), 3.67 (m, 2H), 4.35 (d, J = 7.6 Hz, 1H), 4.56 (ddd, J = 7.6, 2.8, 1.9 Hz, 1H), 6.24 (dd, J = 6.2, 1.9 Hz, 1H), 7.42 (dd, J = 6.2, 2.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0 (2 C), 57.4, 63.3, 63.5, 103.6, 133.6, 154.4, 199.3. Anal. ($C_9H_{14}O_3S$) C, H.

(*R,S*)-5-Formyldihydro-2(3*H*)-furanone [(±)-10]. A solution of unsaturated lactone (±)-**29a** (9.0 g, 48.4 mmol) in 400 mL of THF was hydrogenated in the presence of 0.9 g of 10% Pd on carbon and 1.5 g of NaOAc. After being stirred for 24 h at room temperature, the catalyst was removed by filtration on a pad of silica gel, and the solution was concentrated to give a residue (8.2 g) which was directly treated with a solution of 10% aqueous HCl (70 mL) in THF (220 mL). The solution was stirred at room temperature for 2 h and then evaporated under vacuum to give crude aldehyde (±)-**10**, which was purified by flash chromatography (ethyl acetate). There was obtained pure (±)-**10** (4.5 g, 82%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (m, 1H), 2.50 (m, 3H), 4.54 (m, 1H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 27.7, 80.5, 171.1, 197.8. Anal. ($C_5H_6O_3$) C, H.

(*R,S*)-5-Formylthiolan-2-one [(±)-17]. The above procedure described for (±)-**10** was employed with 8.0 g (39.6 mmol) of (±)-**29b** to afford 3.9 g (76%) of (±)-**17** as an oil, whose spectral characteristics coincide with those for **17**. Anal. ($C_5H_6O_2S$) C, H.

Methyl 5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-α,*β*-D,L-ribo-furanoside [(±)-13]. The above transformations **10** to **13** were followed with 4.0 g (35 mmol) of (±)-**10**, to obtain 6.5 g (75%) of (±)-**13** as a colorless oil, whose spectral data coincide with those of homochiral compound **13**. Anal. ($C_{12}H_{26}O_3Si$) C, H.

1-*O*-Acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-4-thio-α,*β*-D,L-ribofuranose [(±)-20]. The above protocol to transform **17** into **20** was adopted with 3.9 g (30 mmol) of (±)-**17** to give 4.35 g (50%) of thiosugar (±)-**20** as a glassy material, whose spectral data exactly coincide with those of homochiral compound **20**. Anal. ($C_{13}H_{26}O_3SSi$) C, H.

(*R,S*)-*N*-(*tert*-Butoxycarbonyl)-5-[(*tert*-butyldimethylsiloxy)methyl]-2,5-dihydropyrrol-2-one [(±)-30]. To a stirred solution of TBSOP (10.0 g, 34 mmol) in Et_2O (200 mL) cooled at −80 °C was added $SnCl_4$ (8 mL, 67 mmol) under nitrogen. A stream of gaseous formaldehyde, obtained by thermal depolymerization of solid paraformaldehyde (4.0 g, 135 mmol), was passed throughout the resulting slurry using nitrogen as a carrier, the temperature being maintained at −80 °C for 2 h. After this, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ to the reaction mixture which was then extracted with ethyl acetate (3 × 100 mL). The combined extracts were evaporated and the crude product was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (70:30) to afford the pyrrolidinone (±)-**30** as a white solid (6.7 g, 60%): mp 44−48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.19 (s, 3H), −0.01 (s, 3H), 0.81 (s, 9H), 1.50 (s, 9H), 3.67 (dd, J = 9.7, 6.7 Hz, 1H), 4.09 (dd, J = 9.7, 3.6 Hz, 1H), 4.55 (dddd, J = 6.7, 3.6, 1.9, 1.7 Hz, 1H), 6.07 (dd, J = 6.1, 1.7 Hz, 1H), 7.21 (dd, J = 6.1, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.5, 18.0, 25.6 (3 C), 28.1 (3 C), 62.4, 63.5, 82.8, 127.0, 149.6, 153.1, 169.2. Anal. ($C_{16}H_{29}NO_4Si$) C, H, N.

(*R,S*)-*N*-(*tert*-Butoxycarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)-5-(hydroxymethyl)-2-pyrrolidinone [(±)-26]. A solution of unsaturated lactam (±)-**30** (6.7 g, 20.5 mmol) in 300 mL of THF was hydrogenated in the presence of 580 mg of 10% Pd on carbon and 650 mg of NaOAc. After the mixture was stirred for 20 h at ambient temperature, the catalyst was removed by passing the slurry through a short SiO_2 column eluting with hexanes/ethyl acetate (70:30). The solvents were evaporated to give essentially pure saturated lactam (±)-**26** (6.3 g, 93%) as an oil, whose spectral characteristics match those reported above for enantiopure **26**. Anal. ($C_{16}H_{31}NO_4Si$) C, H, N.

5(*R,S*)-*N*-(*tert*-Butoxycarbonyl)-5-[(*tert*-butyldimethylsiloxy)methyl]-2-methoxypyrrolidine [(±)-27]. The above described procedure for **27** was followed starting with 6.0 g (18.2 mmol) of (±)-**26** to afford (±)-**27** (4.7 g, 75%) as a colorless oil, whose spectral data coincide with those of compound **27**. Anal. ($C_{17}H_{35}NO_4Si$) C, H, N.

Racemic Nucleoside Library (D,L-L). General Procedure. A solution of (±)-**13** (50 mg, 0.2 mmol), (±)-**20** (58 mg, 0.2 mmol), and (±)-**27** (69 mg, 0.2 mmol) in 1,2-dichloroethane (9.0 mL) was subdivided into three equal parts of 3.0 mL, and each portion was added *via* cannula to three different vessels containing the appropriate silylated uracil, thymine, and cytosine bases (0.8 mmol each). After cooling to 0 °C, each solution was then treated with a mixture of $SnCl_4$ (0.2 mmol) and TMSOTf (0.2 mmol) under an argon atmosphere with stirring. After 10 min, the temperature was allowed to rise to 20 °C, while stirring was continued for an additional 2 h. The mixtures were quenched by a saturated aqueous $NaHCO_3$ solution and extracted five times with ethyl acetate (5 × 10 mL). After drying ($MgSO_4$), the organic layers were evaporated under vacuum to leave three gummy solids which were separately dissolved in 10 mL of THF. Solid TBAF was then added with stirring at room temperature, and the resulting mixtures were allowed to react for 8 h. The solvent was removed, and the three residues were redissolved in 9:1 MeOH/H_2O solvent mixtures. Solid K_2CO_3 (30 mg) was added at room temperature, and after 3 h, the solvent was removed. The three residues, dissolved in 4 mL of 92:8 ethyl acetate/MeOH mixtures, were independently passed through short silica gel columns eluting with a 92:8:0.5 ethyl acetate/MeOH/30% aqueous NH_4OH solvent mixture to remove unreacted nucleobase materials. The collected fractions were evaporated to afford three collections of different nucleosides, D,L-$\mathbf{SL_{Ur}}$ (33 mg, 65% based on a average MW = 250.6); D,L-$\mathbf{SL_{Th}}$ (35 mg, 66% based on a average MW = 264.6); and D,L-$\mathbf{SL_{Cy}}$ (30 mg, 60% based on a average MW = 249.6).

The above individual sublibraries were dissolved in HPLC-grade water and subjected without any further purification to reverse-phase HPLC analyses according to the described standard conditions (*vide supra*), the results being displayed in Figures 1−3 (see text for details). Mixing the three mixtures finally resulted in formation of a complete collection of nucleosides, D,L-**L** (98 mg, 64% based on an average MW = 254.9, assuming equimolar product distribution), comprising the expected 15 racemic compounds.

Homochiral Nucleoside Library (L-L). The above detailed protocol for racemic library was adopted here by starting with the carbohydrate precursors of the L-series **13**, **20**, and **27** (0.1 mmol each). There was obtained the title full-library of fifteen chiral L-nucleosides (40 mg, 58%). The HPLC analyses, performed on the pertinent three uridine, thymidine, and cytosine sublibraries, revealed profiles which, apart from few negligible discrepancies, corresponded to those of the racemic counterparts in Figures 1−3.

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(25) To ensure uniform product dispersion within the nucleoside pools by minimizing any kinetic discrepancies, a 4 equiv excess of each silylated base was employed throughout.

(26) To complement the available data, a scrutiny of the L-cytidine sublibrary L-$\mathbf{SL_{Cy}}$ in this study is under way, and the results should be published in due course.

(27) In the oxygen series, the majority of the compounds prepared are known substances. Their preparation should be intended as unavoidable complement of the whole synthetic procedure.

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