Conversion of the Enantiomers of Spiro[4.4]nonane-1,6-Diol into Both Epimeric Carbaspironucleosides Having Natural C1′ Absolute Configuration
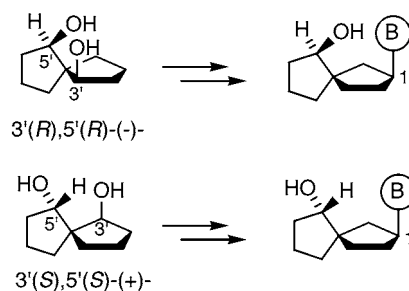
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ABSTRACT

3′(*R*),5′(*R*)-(-)-

3′(*S*),5′(*S*)-(+)-

The enantiomers of spiro[4.4]nonane-1,6-diol have been transformed by different reaction pathways into the two possible carbaspironucleoside epimers with natural C1′ absolute stereochemistry.

The discovery made more than 15 years ago of the effectiveness of 2′,3′-dideoxyinosine and 2′,3′-dideoxycytidine for the treatment of AIDS[1] can be singled out as the initiator of an intense search for related therapeutic agents.[2] Indeed, the generation of new, structurally novel nucleosides continues unabated to the present time. In this connection, we have recently initiated an investigation of the effect of structural preorganization *in a spirocyclic manner* on the pharmacological properties of nucleosides having this unprecedented architectural feature.[3,4] The several attractive characteristics associated with the 1-oxaspiro[4.4]nonanyl diastereomers **1**

and **2**, which are conformationally biased but not conformationally locked systems, have previously been outlined.[3c] This paper reports on the synthesis of their carbocyclic analogues **3** and **4** by a route that incorporates the novel feature involving the merger of stereochemistries originating from reactants possessing different absolute configuration.
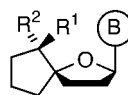
1, R¹ = OH, R² = H
2, R¹ = H, R² = OH
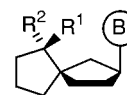
3, R¹ = OH, R² = H
4, R¹ = H, R² = OH

In the past several years, interest in the carbocyclic nucleoside field has become particularly intense.[5] This class

(1) Mutsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83* 1911.

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(3) (a) Paquette, L. A.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L. *Org. Lett.* **2001**, *3*, 4039. (b) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K. *Org. Lett.* **2001**, *3*, 4043.

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(5) Reviews: (a) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319. (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (c) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.

of compounds has been targeted because of the potent antiviral and antitumor properties of select members. The strong inhibitory capability of neplanocin A on S-adenosyl-L-homocysteine hydrolase[6] and the notable inhibitory properties of carbovir triphosphate against HIV transcriptase[7] are exemplary.[8] This structural modification is also recognized to offer improved metabolic stability in view of the absence of a glycosidic linkage.

Retrosynthetic evaluation of **3** and **4** led us back to readily available (±)-spiro[4.4]nonane-1,6-dione,[9] the reduction of which with Li*t*-Bu(*i*-Bu)$_2$AlH has previously been shown to deliver exclusively the racemic *cis,cis*-diol.[10] The latter can be efficiently resolved with generation of (−)-**5** and (+)-**5** via ketalization with (1R)-(+)-camphor.[10] The levorotatory enantiomer of **5** was expected to serve as a reliable precursor to **3** in view of the absolute configurational features of this pair of compounds (Scheme 1). To secure **6**, we envisioned

Scheme 1
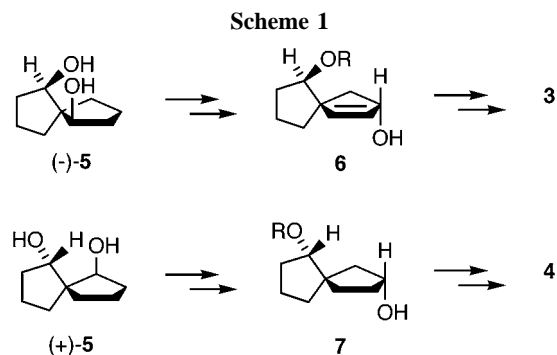
suitable monoprotection, dehydration to the cyclopentene, and allylic oxidation as a prelude to utilization of the Mitsunobu reaction. Fruitful deployment of dextrorotatory **5** was likewise seen to involve the elimination of water to generate a monounsaturated intermediate. Subsequent regio-selective hydroboration-oxidation would culminate in overall 1,2-transposition of the OH group (see **7**) and ultimately the delivery of **4** by way of S$_N$2 displacement.

The same nonbonded steric compression that facilitated the monosilylation of **5** was expected to complicate the dehydration of **8**, and this proved to be the case. Nevertheless, recourse to the oxophilic phosphorus oxychloride reagent in

pyridine[11] under optimized conditions (0 °C → rt) afforded **9** in 56% yield with diminished operation of competing Wagner−Meerwein rearrangement (ca. 25%) (Scheme 2).

Scheme 2
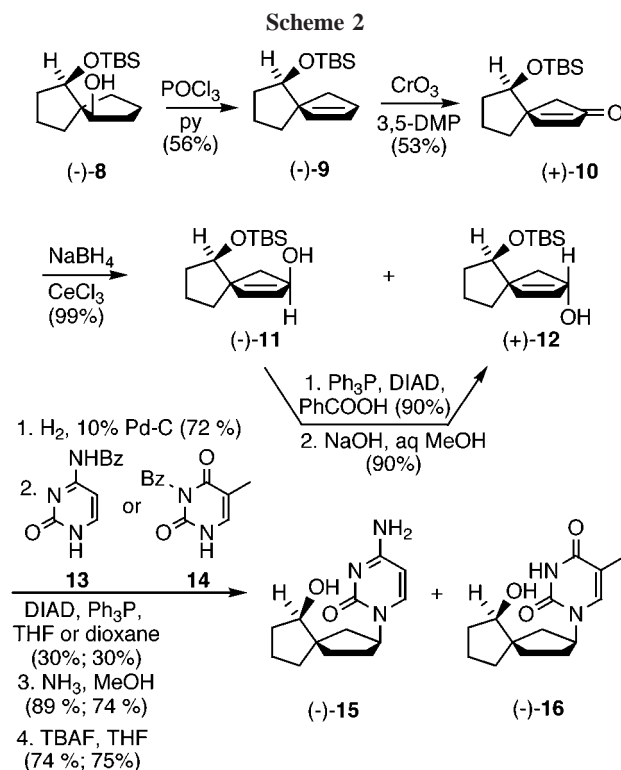
This unsaturated spirocycle was subjected to the chromium trioxide-3,5-dimethylpyrazole complex[11,12] in such a fashion that **10** emerged without suffering loss of structural integrity. Application of the Luche reduction[13] to **10** proceeded with no evidence of π-facial selectivity to deliver **11** and **12** in a 1:1 diastereomeric ratio. However, since these allylic alcohols are amenable to ready chromatographic separation, the tandem transformation of **11** into **12** by the Mitsunobu protocol[14] constituted a convenient means for generating appreciable amounts of the latter epimer.

This accomplished, **12** was subjected in turn to catalytic hydrogenation, S$_N$2 displacement with N^4-benzoylcytosine and N^3-benzoylthymine,[15,16] diisopropyl azodicarboxylate, and triphenylphosphine in tetrahydrofuran or dioxane,[17] ammonolysis,[18] and desilylation. These reactions proved

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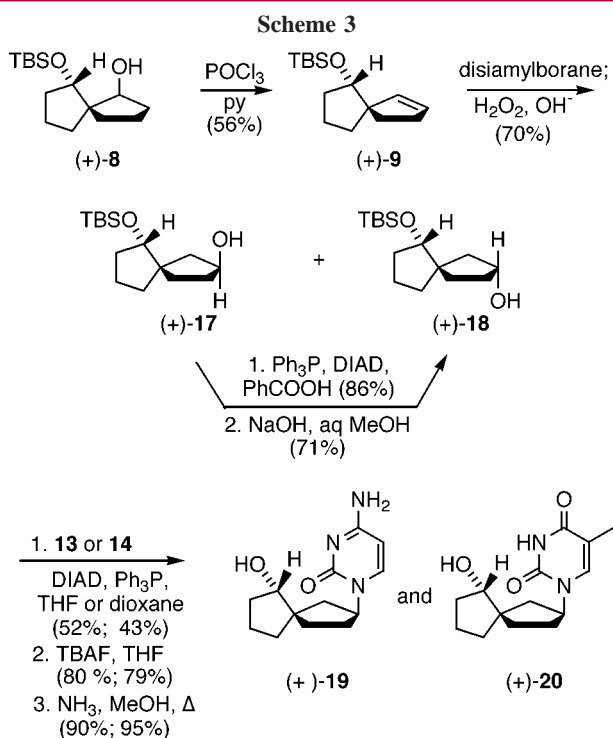(13) Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226.

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Scheme 3

uneventful, proceeding with clean inversion of configuration to deliver the targeted levorotatory spirocyclic carbanucleosides **15** and **16**.

The next phase of this undertaking called again for the initial dehydration of **8**, although now in the form of the (−)-enantiomer. Recourse to phosphorus oxychloride served well as before, with (+)-**9** now resulting (Scheme 3). The pursuit of proper regiodirected hydration of (+)-**9** soon focused on the effective steric bulk of the hydroborating agent. After some experimentation, disiamylborane proved to be a reasonable compromise in that **17** and **18** were produced in 19% and 51% yield, respectively. For the purpose of maximizing the availability of **18**, the Mitsunobu reaction was again applied, this time to bring about configurational inversion in **17**. At this point, practical crossover to the diastereomeric manifold had been achieved and the ultimate generation of **19** and **20** was accomplished in a manner similar to that developed earlier. The structural assignments to **15**/**16** and **19**/**20** are based on extensive mechanistic precedent[14,19] and conform to their NMR spectral properties.

To sum up, the enantiomers of **8** have been transformed by different synthetic pathways into epimeric spirocytidines and spirothymidines. The rather novel "merger of chirality" illustrated here holds sufficient potential generality that it is expected to find application in the solution of other problems in organic stereochemistry.

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