A RING-EXPANSION ROUTE TO ANALOGUES OF DIDEOXYHYDANTOCIDIN‡

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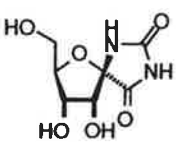
Abstract - The acid-catalyzed rearrangement of hydroxy β-lactam (**12**), formed by addition of the enantiopure dihydrofuranyllithium (**10a**) to *N*-benzyl-2,3-azetidinedione, has been investigated as a potential route to spirocyclic nucleosides.

The isolation of hydantocidin (**1**) by Sankyo chemists in 1991 and their demonstration of its potent herbicidal and plant-growth regulatory activities[2] have generated intense interest in the chemistry of spirocyclic nucleosides. Not only have several syntheses of **1** been reported,[3] but epimers[4] and analogues thereof[5] have been prepared, and related systems have been synthesized.[6] Representative examples are given by **2-5**. Despite this activity, general and convenient methods for gaining access to other optically active spirocyclic congeners are of obvious interest. One such class of compounds involves 1,2-transposition of a carbonyl group with excision of the associated amidic nitrogen. Herein we illustrate the feasibility of a concise approach to such systems in a 2,3-dideoxy context. In light of recent reports describing the



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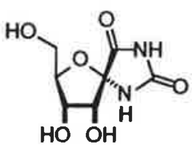

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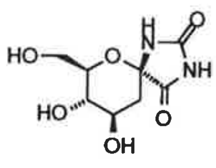

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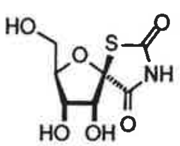

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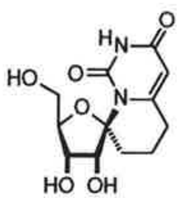

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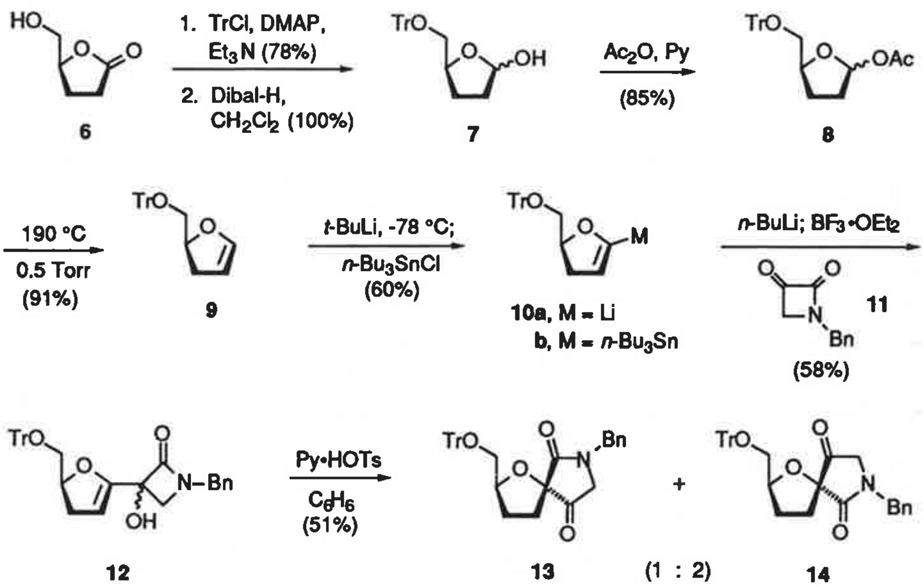
‡This paper is dedicated to the memory of Professor Shun-ichi Yamada.

significant antiviral activity of dideoxynucleosides,[7] the possibility exists that inhibition of the human immodeficiency virus (HIV) might also be uncovered.

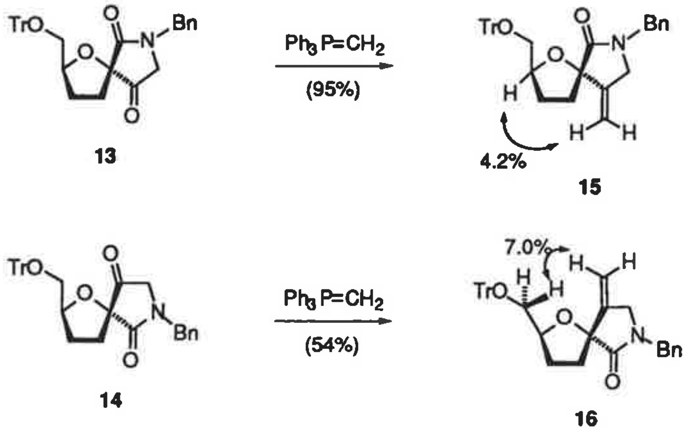
Enantiopure **6** was prepared from *L*-glutamic acid according to precedent.[8] After tritylation, conversion to dihydrofuran (**9**), $[\alpha]_D^{21}$ +60.8° (*c* 1.35, CH_2Cl_2), was most efficiently achieved by sequential Dibal-H reduction, acetylation of lactol (**7**), and pyrolysis of acetate (**8**) at 190 °C and 0.5 Torr in a Kugelrohr apparatus[9] (Scheme 1). In keeping with the kinetic acidity exhibited by the parent heterocycle[10] and alkyl derivatives thereof,[9b] **9** could be metalated at C-5 by exposure to *t*-butyllithium at low temperature. Quenching of reactive intermediate **10a** with tri-*n*-butyltin chloride smoothly afforded **10b**. As expected, the ensuing transmetalation of this stannane made possible clean reconversion to the lithium species (**10a**) without contamination by an excess of the *n*-BuLi co-reagent.

Scheme 1



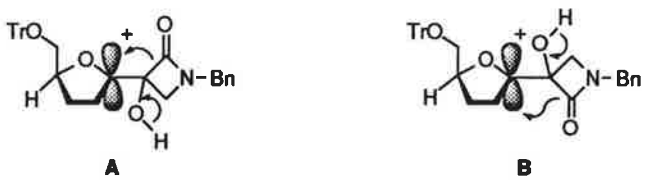
Although various azetidine-2,3-diones have served as important starting materials for the production of β-lactam antibiotics,[11] little attention has been accorded to simple *N*-substituted derivatives such as **11**.[12,13] Oxonium ion-initiated pinacolic ring expansions of cyclobutanols constitutes a very general approach to spirocyclopentanes.[14] Application of this rearrangement required that **10a** be condensed with **11**. In test experiments, it was discovered that **11** exhibits a reasonably high tendency for simple enolization in the presence of cycloalkenyllithium regents. The best conditions found for curtailing this unwanted side reaction involved the precomplexation of **11** with an equivalent of boron trifluoride etherate. This modification afforded **12** in 58% yield as an inseparable 1:1 mixture of diastereomers, and set the stage for examination of the key reaction.

Scheme 2



When solutions of **12** in benzene containing pyridinium *p*-toluenesulfonate were stirred at 20 °C for 24 h, two chromatographically separable lactams were formed in a combined isolated yield of 51%. In order to distinguish the more polar dextrorotatory **14**, $[\alpha]_D^{20}$ +18.2° (*c* 1.82, $CHCl_3$), from the less polar levorotatory **13**, $[\alpha]_D^{20}$ -28.6° (*c* 1.41, $CHCl_3$), it proved necessary to subject the two diastereomers to Wittig olefination (Scheme 2) and to examine the NOE effects exhibited by **15** and **16** in C_6D_6 solution (shown in the formulas). Other telltale ^{1}H NMR changes also accompany these transformations. For example, while a $\Delta\nu_{AB}$ of 53.4 Hz is exhibited by the protons in the $TrOC\underline{H_2}^-$ group of **14**, the $\Delta\nu$ in **16** is more than doubled to 108.8 Hz. By contrast, the associated effects in **13** and **15** are only marginal (29.3 Hz → 26.5 Hz). Chemical shift and IR data[15] also showed the carbonyl groups in **13** and **14** not to be vicinal.

In light of this structural and stereochemical evidence, it is clear that the ring expansion proceeds exclusively with migration of the carbonyl carbon.[16] Beyond that, 1,2-acyl shift from that surface syn to the trityloxy group as in **A** appears to be sterically impeded relative to the



alternative option depicted in **B**. As in other examples,[9b] this partitioning of reaction trajectories does not appear to be linked to the diastereomeric ratio present in **12** (1:1). As a follow-up on these preliminary synthetic results, we hope to be in a position to report on more expansive use of this technology and on the biological properties of this conceptually new class of spirocyclic nucleosides in due course.

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