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Unexpected Effects of Lewis Acids in the Synthesis of Optically Pure 2'-Deoxy-3'-oxacytidine Nucleoside Analogues

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Abstract: *$TiCl_4$ and $SnCl_4$ promote the formation of dioxolane nucleosides with racemization in the coupling of enantiomerically pure 2'-deoxy-3'oxaribosides with silylated N-acetylcytosine. The use of TMSOTf, TMSI or $TiCl_2(Oi\text{-}Pr)_2$ furnishes enantiomerically pure cytosine dioxolane nucleosides in low diastereoselectivity.*

The control of relative and absolute stereochemistry in the synthesis of nucleoside analogues with two potentially epimerizable acetal centres, represents a significant synthetic challenge. Recently, Liotta and coworkers[1] demonstrated the utility of Ti(IV) and Sn(IV) Lewis acids in the stereoselective synthesis of racemic nucleosides derived from racemic 2'-deoxy-3'-thia- and 2'-deoxy-3'-oxaribofuranosides and silylated pyrimidines. Subsequent reports from the groups of Chu[2] and Jones[3] disclosed that $SnCl_4$ was unsuitable for the synthesis of enantiomerically pure cytosine oxathiolane nucleosides such as the important antiviral agent **3TC** due to the formation of racemic material. However, Chu and coworkers[4] have also reported that glycosylation of silylated thymine with enantiomerically pure 2'-deoxy-3'-oxaribofuranosides mediated by $SnCl_4$ afforded the expected anti-HIV cis-nucleoside **(-) dioxolane T** with excellent diastereoselectivity and optical purity. In view of the current interest in this class of compounds, we investigated the coupling of enantiomerically pure 3'-oxaribosides **1** and **2** and silylated N-acetylcytosine using different Lewis acid catalysts. We wish to report herein our unexpected findings.

Recently, we described the synthesis of enantiomerically pure dioxolanes **1** and **2** from a common starting material, L-ascorbic acid[5] (Fig. 1). Coupling of **1** as a 1:1 mixture of α and β anomers ($[\alpha]_D^{25}$ = -25.4 (c = 1.09,$CHCl_3$)) with silylated N-acetylcytosine mediated by a freshly prepared solution of dichlorotitanium diisopropoxide[1] $TiCl_2(Oi\text{-}Pr)_2$ in CH_2Cl_2 furnished after deprotection a mixture of the cis- and trans- nucleoside analogues in a 1:1 ratio (Scheme 1). Both analogues were analyzed by chiral HPLC methods[6] and found to be enantiomerically pure (Table 1, entry 1).

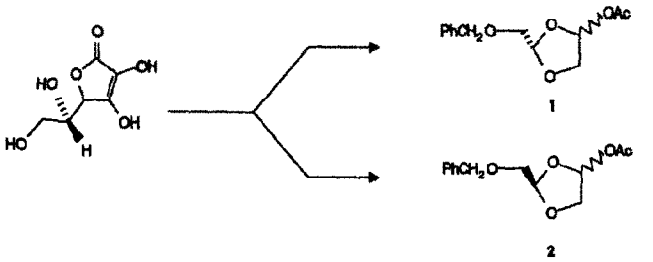
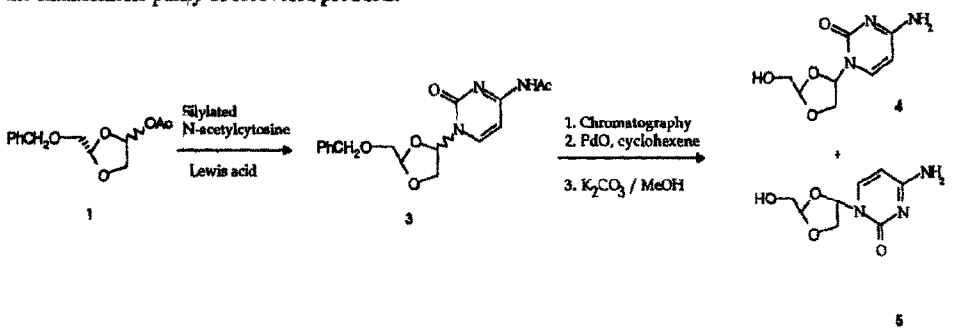


Figure 1. 2'-Deoxy-3'-oxaribosides **1** and **2** from L-ascorbic acid.

The reaction was repeated with $TiCl_4$ and the resultant mixture was deprotected as shown in Scheme 1. Analysis of the products by HPLC and NMR methods indicated that the cis isomer was formed with moderate selectivity, however, it was racemic (1:1 ratio of **6**:**7**). Unexpectedly, the corresponding trans-isomer **5** was isolated as 7:2 mixture of **8** and **9** (55% ee, entry 2). As a next step, when the coupling reaction was mediated by $SnCl_4$ the nucleosides were obtained in good yield and low selectivity. Further analysis indicated that **4** and **5** were partially racemized (entry 3).

The formation of the nucleoside adducts is the consequence of intermolecular substitution on the exocyclic acetal moiety, the result of equilibrations and complexations of the Lewis acid with the oxygen atoms[7,8,9] of **1**. While it is tempting to explain the stereoselectivity and racemization observed with the cis-nucleoside, as arising from ring opening and closing of **1**, this hypothesis does not account for the partial loss of optical purity of the trans adduct (entry 2). Equilibration studies on a protected 2:1 mixture of **6** and **8** in the presence of $SnCl_4$ or $TiCl_4$ under the coupling conditions did not show a substantial change in the ratio or the enantiomeric purity of recovered products.



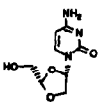
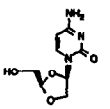
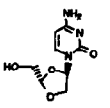
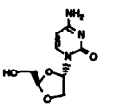
Scheme 1. Coupling of **1** with silylated N-acetylcytosine.

While the above results suggest severe limitation on the potential use of $TiCl_4$ and $SnCl_4$ Lewis acids in the asymmetric synthesis of pure 1,3-dioxolane nucleosides, silyl Lewis acids were found to be useful in producing enantiomerically pure dioxolane nucleoside analogues. For example, the coupling of **1** with silylated N-acetylcytosine in the presence of trimethylsilyltriflate (TMSOTf)[4,5,9] under Vorbrüggen's

protocol[10] furnished after deprotection a 1:1 mixture of **6** and **8** with no detectable amounts of **7** and **9** (entry 4). Iodotrimethylsilane (TMSI), previously shown to be effective in the asymmetric synthesis of oxathiolane nucleosides[3], afforded **6** and **8** in 60% yield (entry 5)[11] without any detectable amounts of open ring products.[12]

In conclusion, we have demonstrated that the Lewis acid plays a crucial role in the preparation of a novel class of antiviral dioxolane nucleosides. In this particular study our results suggest that, even though, lower selectivity (cis:trans) is obtained with the Lewis acids (TMSOTf, TMSI and $TiCl_2(Oi\text{-}Pr)_2$), these reagents cause no detectable racemization in the final products. At this stage, the reasons for the difference in the racemization of the cis- and trans- analogues remain unclear. Mechanistic studies of these reactions are in progress.[13]

Table 1. Effects of Lewis Acids on the Diastereoselectivity of 2'-Deoxy-3'-oxacytidines

Entry	Lewis Acid	 **6** (-) BCH-204	 **7** (+) BCH-204	 **8** (+) BCH-203	 **9** (-) BCH-203
1	$TiCl_2(O\text{-}iPr)_2$	50	-	50	-
2	$TiCl_4$	36.5	36.5	21	6
3	$SnCl_4$	41.7	11.7	38.5	8.1
4	TMSOTf	50	-	50	-
5	TMSI	50	-	50	-

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6. Retention time **6** = 27.14 min., **7** = 28.18 min., **8** = 31.60 min., **9** = 33.08 min.; column : Cyclobond ISP + RSP (in series) 250 x 4.6 mm; eluent : 3% acetonitrile in 0.05% TEAA; Flow : 0.22 ml/min; detection : 265 nm. For details of HPLC analysis M. P. DiMarco, C.A. Evans, D. M. Dixit, W. L. Brown, M. A. Siddiqui, H. L. A. Tse, H. Jin, N. Nguyen-Ba and T. S. Mansour J. Chromography (submitted).
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13. Coupling conditions: a) $TiCl_2(O\text{-}iPr)_2$: To $TiCl_4$ (0.22 mL, 2 mmol) in 3.2 mL of dry CH_2Cl_2 under argon was added slowly $Ti(OPr\text{-}i)_4$ (0.595 mL, 2 mmol) at room tempetature. The reagent was used immediately after preparation. N-Acetylcytosine (50 mg, 0.3 mmol) inCH_2Cl_2(0.5 mL) was treated at room temperature under argon with 2,6-lutidine (0.085 mL, 0.7 mmol) and TMSOTf (0.127 ml, 0.7 mmol). The mixture became a clear solution and stirring continued for 10 min. Dioxolane **1** (69 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL) and $TiCl_2(OPr\text{-}i)_2$ in CH_2Cl_2 (1.0 M, 1.0 mL, 1.0 mmol) were added successively. After stirring for 2 hours TLC showed almost complete consumption of starting material. The mixture was diluted with CH_2Cl_2 (20 mL), washed with sat. aq. $NaHCO_3$, H_2O, and brine, dried, and evaporated. The crude products were chromatographed on silica gel with MeOH/EtOAc to give 68 mg of pure cis and trans isomers in 1:1 ratio. b) $SnCl_4$: To a stirred suspension of N-acetylcytosine (105 mg, 0.619 mmol) in dry CH_2Cl_2(2 mL) at room temperature under an argon was added 2,6-lutidine (144µL, 1.24 mmol) andtrimethylsilyl triflate (239 µL,124 mmol). The resulting mixture was stirred for 15 minutes to give a homogeneous solution. Tin(IV) chloride (619µL, 1 M in CH_2Cl_2(1 mL) was introduced into this solution and stirring was continued for another 40 minutes. A solution of the dioxolane substrate(130 mg, 0.516mmol) in CH_2Cl_2(1 mL) was added to the above solution and the resultant mixture was kept for 3 hours at room temperature. The reaction was quenched with a saturated $NaHCO_3$ solution followed by dilution with CH_2Cl_2. This mixture was stirred for 15 min. The inorganic phase was removed and the organic layer was washed with water, 1 M HCl, saturated $NaHCO_3$ solution, and brine, and then was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product obtained was subjected to flash chromatography (7% MeOH/EtOAc) to provide the expect nucleosides (150 mg, 80%) as a 8:7 mixture (300 MHz ^1H NMR) of the cis and trans isomers.