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Divergent Asymmetric Syntheses of Dioxolane Nucleoside Analogues

Colleen A. Evans, Dilip M. Dixit, M. Arshad Siddiqui, Haolun Jin, H.L. Allan Tse, Alex Cimpoia, Krzysztof Bednarski, Tibor Breining and Tarek S. Mansour*

**BioChem Therapeutic Inc., 531 des Prairies Blvd.
Laval, Quebec, Canada H7V 1B7**

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Abstract: *Oxidative degradation of benzyloxymethylacetals derived from D-mannitol or L-ascorbic acid provides dioxolane intermediate 6 and 7 useful in the synthesis of all the stereoisomers of dioxolane nucleoside analogues.*

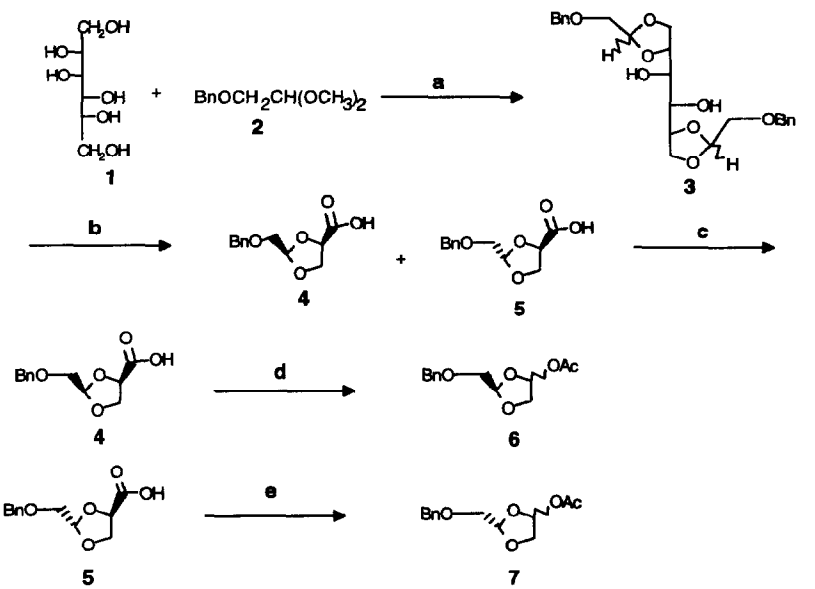
Shortly after the initial disclosure that prototypes of 2', 3'-dideoxynucleoside analogues with 3'-oxa and -thia groups in racemic form possess anti-HIV activity[1], the Abbott group reported the synthesis of (±)-dioxolane-T which, at 20 μM was found to provide a 50 % protective effect against the infectivity and cytopathic effect of HIV-1 in ATH8 cells.[2] Subsequently, Chu et al. developed an asymmetric synthesis of the 2R,4R isomer in eleven steps from 1,6-anhydro-D-mannose and found this compound to exhibit potent anti-HIV activity in primary human lymphocytes.[3] This procedure was extended to the preparation of various chiral 2R pyrimidine[4] and purine[5] analogues. Utilizing the same approach, pyrimidine analogues having the 2S configuration were derived from L-gulose.[6] In this communication, we wish to report our synthetic efforts affording, in a divergent and expedious manner, 2R and 2S dioxolane nucleosides from readily accessible starting materials.

Initially, we examined the oxidative cleavage of the C3-C4 diol moiety of a suitable D-mannitol derivative. Thus, the bis acetal mixture **3** was formed by the reaction of benzyloxymethylacetaldehyde dimethylacetal and D-mannitol in the presence of 1.0 equivalent of $SnCl_2$ under reflux in DME.[7] Ruthenium tetroxide mediated oxidation of **3** produced a 1:1 mixture of acids **4** and **5** which were separable by chromatography on silica gel (Scheme 1). Conversion of each of **4** and **5** to the acetoxy compounds **6** and **7** respectively was readily achieved by lead tetraacetate oxidation[2] in a suitable solvent. Each of **6** and **7** was obtained as a 2:1 mixture of trans and cis isomers.

An alternative and a more efficient route to **6** and **7**, as illustrated in Scheme 2, relies on the fractional recrystallization of the benzyloxymethylacetals derived from L-ascorbic acid.[8] After separation[9], **9** or **10** were subjected to successive degradation with basic H_2O_2, ruthenium catalyzed Wolfe oxidation[10] and then lead tetraacetate oxidation to afford the corresponding acetoxy derivatives **6** and **7** respectively.

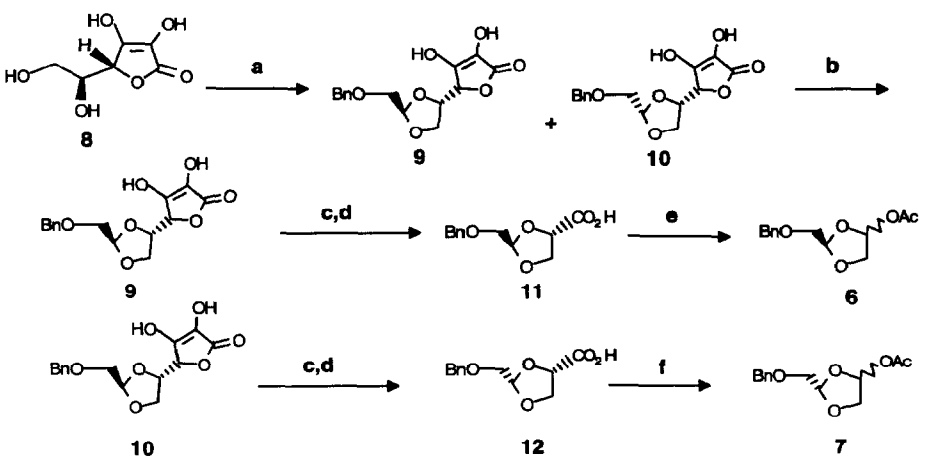
The coupling of **6** with thymine, previously persilylated with 1,1,1,3,3,3-hexamethyldisilazane, in the presence of 1.1 equivalent of the Lewis acid TMSOTf afforded with virtually no selectivity a mixture of cis and trans nucleoside analogues. Chromatographic separation followed by deprotection furnished enantiomerically pure[4,6,11] **14** and **15** (Scheme 3). Subjection of **6** generated from D-mannitol (Scheme 1) to the same sequence afforded **14** and **15** of similar optical purity.

Scheme 1



Reagents and conditions: a. 1.0 eq. $SnCl_2$ in DME, heat overnight, 70%. b. $RuCl_3$ hydrate, NaOCl in H_2O:CH_3CN:DCE 2:1.4:6, 30%. c. flash chromagraphy 2 %MeOH in CH_2Cl_2. d. $Pb(OAc)_4$, CH_3CN-py, 80%. e. $Pb(OAc)_4$, CH_3CN-CH_2Cl_2-py, 80%.

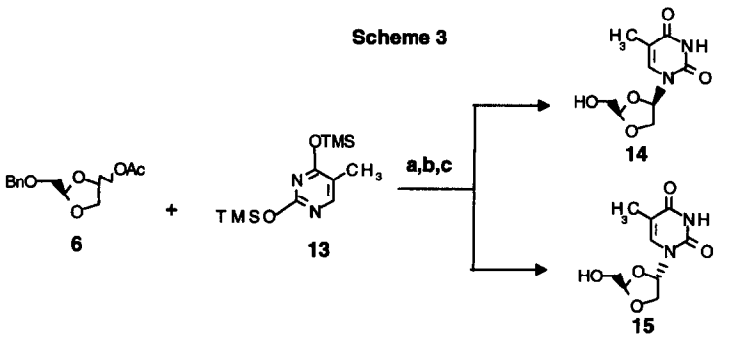
Scheme 2



Reagents and conditions: a. 2, TsOH in CH_3CN, 95%. b. fractional recrystallization. c. 30% H_2O_2, K_2CO_3, EtOH extraction. d. $RuCl_3$ hydrate, NaOCl, DCE-CH_3CN-H_2O, $BnEt_3NCl$, pH 8, EtOH extraction, then H+, 57%. e. $Pb(OAc)_4$, CH_3CN-CH_2Cl_2-py, 80%. f. $Pb(OAc)_4$, CH_3CN-py, 80%.

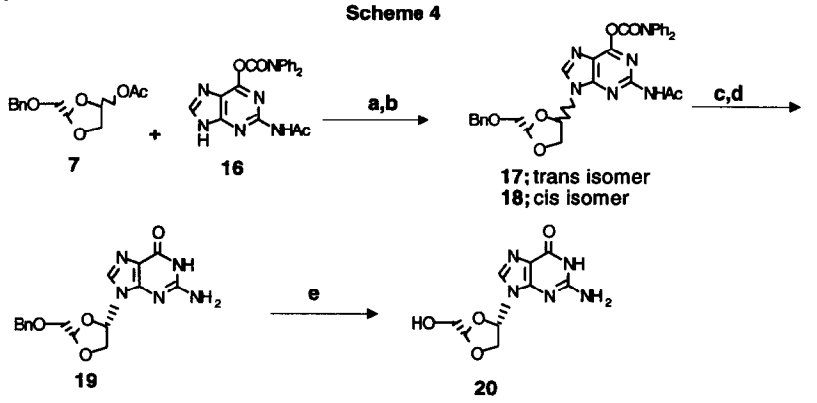
Glycosylation of the silylated diphenylcarbamoyl purine derivative[12] **16** with **7** under reflux with TMSOTf furnished a 1:1 mixture of the N9 regioisomers in good yield. Isolation of compound **18** by chromatography and deprotection with hydrazine hydrate produced the guanine derivative **19** which was converted to **20** by transfer hydrogenolysis[13,14] (Scheme 4).

Scheme 3



Reagents and conditions: a. 1.1 eq. TMSOTf, CH_2Cl_2, 6h, RT. b. flash chromatography. c. 10% PdO, cyclohexene, EtOH, reflux 3h., 40% for 3 steps.

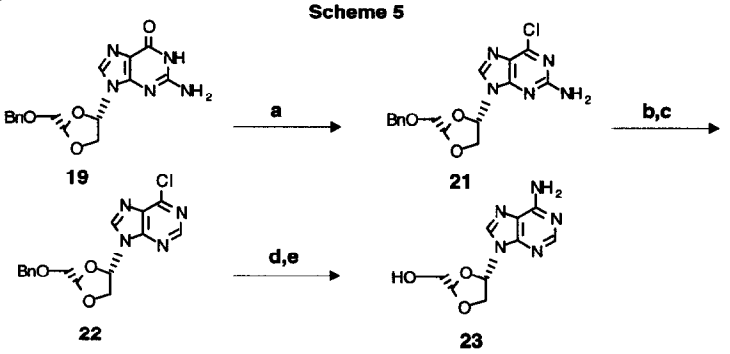
Scheme 4



Reagents and conditions: a. BSA-DCE. b. 1.1 TMSOTf reflux 6 h., 70% (2 steps). c. flash chromatography. d. NH_2NH_2 hydrate, THF, reflux 3h., 95%. e. PdO hydrate, cyclohexene, EtOH, reflux 3 h., 73%.

To circumvent the partial racemization detected in the preparation of the adenine nucleoside[15], the guanine derivative **19** was converted to its 6-chloro derivative **21**. Reductive deamination to **22** proceeded without loss of the 6-chloro group. Standard conversion of **22** afforded the adenine derivative **23** with established absolute configuration. (Scheme 5).

Scheme 5



Reagents and conditions: a. $POCl_3/PhNMe_2/Et_4NCl$ in CH_3CN, reflux 30 min., 74% b. t-BuONO THF -20 °C. c. $(Me_3Si)_3SiH$, THF, 20 °C, 49% d. NH_3/EtOH, 100 °C/12 h. e. PdO hydrate, cyclohexene, EtOH, reflux 3 h., 71%.

In conclusion, we have presented two divergent routes for the asymmetric synthesis of pyrimidine and purine dioxolane nucleosides. These routes should be of value for the preparation of potential antiviral agents in this class of compounds.

Acknowledgements

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References and Notes

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7. No attempts were made to separate the mixture of acetals at this point, however, purification by chromatography (3:1 hexanes: ethyl acetate) is necessary to exclude polar compounds.
8. Belleau, B.; Evans, C.A.; Tse, H.L.A.; Jin, H.; Dixit, D.M. and Mansour, T.S., Tetrahedron Lett., **1992**, 33, 6949. Other conditions to generate **9** and **10** were less efficient for example: $SnCl_2$/EtOAc (quantitative, 50% conversion); $Ti(i\text{-}OPr)_4$ (quantitative, 50% conversion).
9. Fractional recrystallization of a 1:1 mixture of **9** and **10** in benzene provided **9** in > 98% de. Compound **10** was isolated from the mother liquor (4:1 ratio of **9** to **10**) by chromatography. The absolute configuration of **9** was determined by single crystal X-ray structure determination. Retention time **9** = 33.0 min, **10** = 31.5 min; column: reverse phase Whatman Partisil ODS-3 5μ [4.6 x 250 mm]; flow: 1.0 ml/min; eluent: CH_3CN + 0.04% TFA; detection: 265 nm. Chromatographic separation of **6** yielded cis isomer as colorless oil $[\alpha]_D^{22}$= -58.1 (c 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$) δ2.04(s,3H), 3.63-3.70(m,2H), 3.98(dd,1H,J=3.8,9.6 Hz), 4.19(d,1H,J=9.6 Hz), 4.60(s,2H), 5.29(t,1H,J=4.2 Hz), 6.34(d,1H,J=3.5 Hz), 7.26-7.35(m,5H); and trans isomer as colorless oil $[\alpha]_D^{22}$= +67.4(c 1.1,$CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.1(s,3H), 3.61(m,2H), 3.95(dd,1H,J= 2,9.3 Hz), 4.23(dd,1H,J= 4.4,9.3 Hz), 4.61(s,2H), 5.37 (t,1H,J=3.7 Hz), 6.39 (dd,1H,J= 2,4.3 Hz), 7.27-7.35(m,5H); cis isomer from **7** $[\alpha]_D^{22}$= +58.8 (c 1.66,$CHCl_3$); trans isomer from **7** $[\alpha]_D^{22}$= -67.4 (c 1.00,$CHCl_3$).
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11. Retention time **14** 2R,4R = 13.1 min, **15** 2R,4S isomer = 19.5 min; column: Chiralcel OJ (4.6 mm x 250 mm); flow: 1ml/min; eluent: 35% isopropyl alcohol/hexanes; detection: 260 nm. The corresponding 2S,4S and 2S,4R isomers were similarly obtained from **7**. Spectral data and physical properties fo **14** and **15** are in agreement with those reported in reference 4.
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15. Direct coupling of silylated 6-chloropurine or N-benzoyladenine with **7** using various amounts of TMSOTf (0.5 to 1.0 equivalent of TMSOTf) caused ca. 17% racemization[14]. The effects of Lewis acids in the synthesis of cytosine nucleoside analogues have been reported. Jin, H.; Tse, H.L.A.; Evans, C.A.; Mansour, T.S.; Beels, C.M.; Ravenscroft, P.; Humber, D.C.; Jones, M.F.; Payne, J.J. and Ramsay, M.V.J., Tetrahedron: Asymmetry, **1993**, 4, 211.