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Potent Anti-HIV and Anti-HBV Activities of (-)-L-β-Dioxolane-C and (+)-L-β-Dioxolane-T and Their Asymmetric Syntheses.

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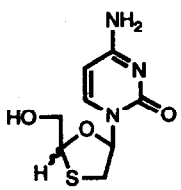
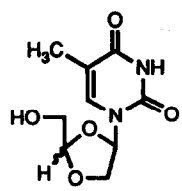
Abstract: The asymmetric syntheses of (+)-L-β-dioxolane-T and (-)-L-β-dioxolane-C were accomplished starting from 1,6-anhydro-L-β-gulopyranose, and their anti-HIV and anti-HBV activities were evaluated in human PBM cells, CEM cells and 2.2.15 cells, respectively.

(±)-2',3'-Dideoxy-3'-thiacytidine (BCH-189) was found to be a potent anti-HIV agent *in vitro* and its (-)-isomer [3TC, (-)-BCH-189] is undergoing clinical trials in patients with AIDS and AIDS-related complex.[1] Recently, racemic BCH-189 was also found to be a potent antiviral agent against human hepatitis B virus (HBV).[2] Since BCH-189 had been reported as a racemic mixture, it was of interest to synthesize the enantiomerically pure isomers. Thus, we have reported the synthesis of (+)-D-BCH-189 from D-mannose.[3] Recently, we also reported the more efficient enantiomeric synthesis of (+)-D-BCH-189 from D-galactose.[4] Interestingly, we discovered that the enantiomerically pure (+)-D-BCH-189 [EC_{50} = 0.21-0.31 μM in human peripheral blood mononuclear (PBM) cells infected with HIV-1] was less potent than the (±)-BCH-189 (EC_{50} = 0.02-0.06 μM).[3] Thus, we synthesized the antipod, (-)-L-BCH-189 from L-gulose,[5] and demonstrated to be more potent (EC_{50} = 0.0018 μM) than either the (+)-D-BCH-189 or (±)-BCH-189. It was also discovered that the trend for anti-HBV activity was similar to that for anti-HIV activity.[6]



(±)-BCH-189



(±)-Dioxolane-T

(±)-Dioxolane-T has been reported as a moderately active anti-HIV agent (EC_{50} = 20 μM) in ATH8

cells[7]; however, it showed a superior activity in human PBM cells (EC_{50} = 0.09 μM).[8] Thus, we have synthesized the enantiomerically pure (-)-D-dioxolane-T (EC_{50} = 0.39 μM) from D-mannose and found that it too was less potent than the racemate (EC_{50} = 0.09 μM) as in the case of BCH-189.[9] A number of pyrimidine dioxolane derivatives have been synthesized and structure-activity correlation in this series showed that (+)-D-β-dioxolane-C (EC_{50} = 0.016 μM) was the most potent nucleoside against HIV-1.[8] Now we wish to report the synthesis of the optical antipode, (-)-L-β-dioxolane-C and substantiate its potent antiviral activity against HIV and HBV.

The general synthetic strategy that we have developed for the BCH-189 and dioxolane-T was used to synthesize the L-isomers **13-16** (Scheme 1). 1,6-Anhydro-L-gulose was prepared in one step from L-gulose by the treatment of L-gulose with 0.5 N HCl in 60 % yield.[10] Without selective protection,[4,5] as previously reported,[9] **2** was directly converted to dioxolane triol **3** by $NaIO_4$ followed by reduction with $NaBH_4$, which without isolation, was converted to isopropylidene derivative **4**. Benzoylation to **5**, deprotection to **6**, and oxidation of diol **6** gave the acid **7**. Oxidative decarboxylation of **7** with $Pb(OAc)_4$ in dry THF gave the key intermediate acetate **8** in good yield. The acetate was condensed with the desired pyrimidines (silylated thymine and N-acetylcytosine) in the presence of TMSOTf to afford a mixture of anomers, which was separated by a silica gel column chromatography to give the individual isomers **9-12**. Debenzoylation with methanolic ammonia gave the desired thymine and cytosine derivatives **13** and **14**, respectively.[11]

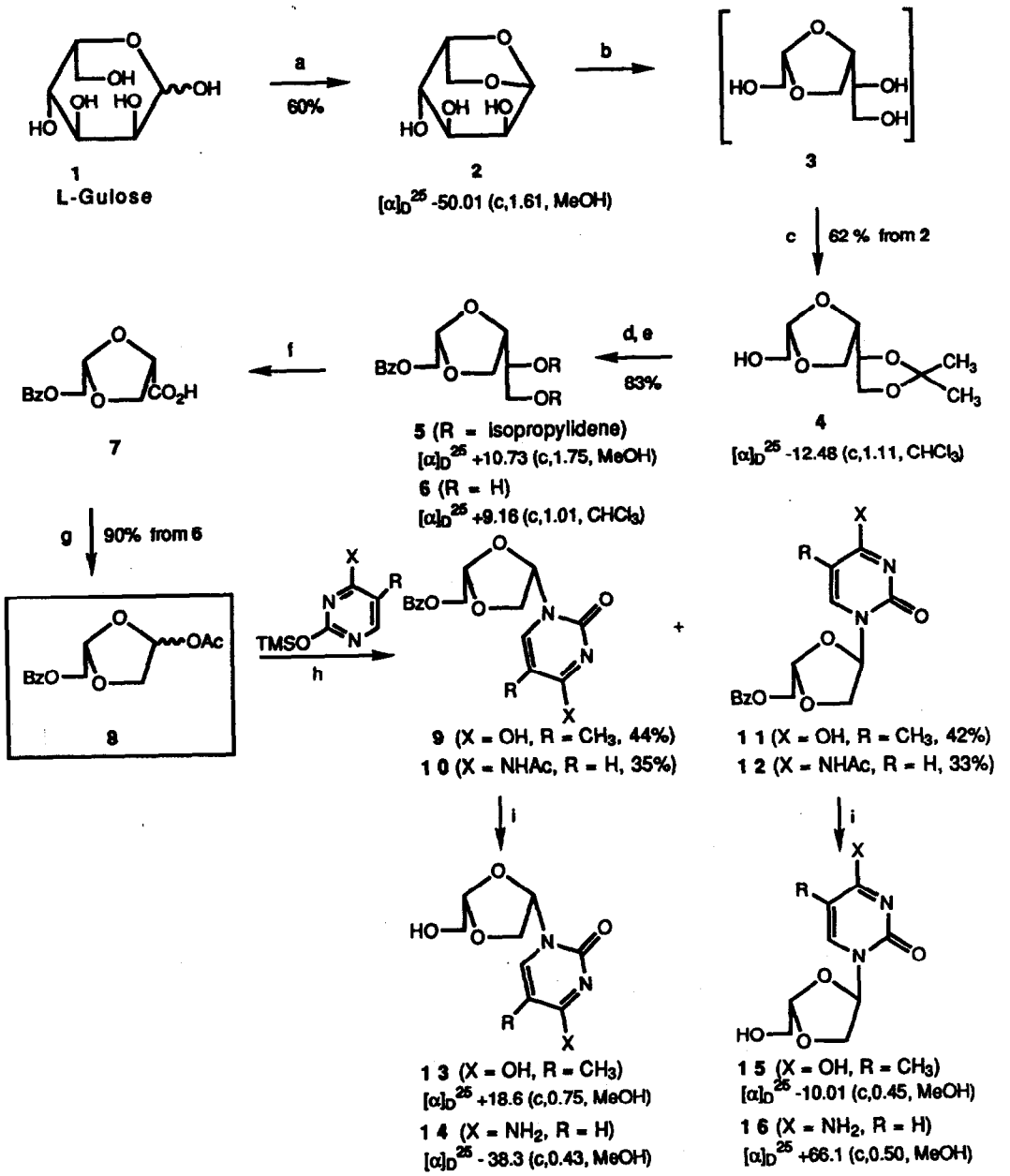
Anti-HIV and anti-HBV activities as well as cytotoxicities of **13** and **14** were evaluated in human PBM cells, CEM cells and 2.2.15 cells, respectively (Table 1).[5,8]

Table 1. Antiviral activities and cytotoxicities.

Compounds	Anti-HIV activity in PBM cells EC_{50} (μM)	Anti-HIV activity in CEM cells EC_{50} (μM)	Anti-HBV activity in 2.2.15 cells $HBID_{50}$ (μM)	Cytotoxicity in PBM cells IC_{50} (μM)	Cytotoxicity in CEM cells IC_{50} (μM)	Cytotoxicity in Vero cells IC_{50} (μM)
(-)- L-β-dioxolane-cytosine **14**	0.002	0.005	0.0005	> 10	0.26	0.10
(+)-D-β-dioxolane-cytosine	0.016[8]	0.009	0.01	62.0	12.3	8.3
(+)-L-β-dioxolane-thymine **13**	4.81	ND	> 5	> 100	ND	> 100
(-)-D-β-dioxolane-thymine	0.39[8]	ND	> 5	> 100	ND	> 100
AZT	0.002	0.025	ND	> 100	14.3	28.0

As seen in Table 1, (-)-L-β-dioxolane-cytosine (**14**) was more potent than (+)-D-β-dioxolane-cytosine while the racemic dioxolane-thymine was more potent than either (+)-L-β-dioxolane-thymine (**13**) or (-)-D-β-dioxolane-thymine probably due to the additive effects of the (+)- and (-)-enantiomers. It is noted that this result is the mean of the three different assays. The cause of this discrepancy is under investigation in our laboratories.

Scheme I[a]



[a]Reagents : a) 0.5N HCl, 100 °C; b) $NaIO_4$, MeOH, H_2O, 0 °C / $NaBH_4$; c) p-TsOH, Acetone, RT; d) BzCl, Pyr., CH_2Cl_2, RT; e) p-TsOH, MeOH, RT; f) $NaIO_4$, RuO_2, CH_3CN:CCl_4:H_2O (2:2:3), RT; g) $Pb(OAc)_4$, THF, RT; h) TMSOTf, $ClCH_2CH_2Cl$, 0 °C; i) NH_3/MeOH, RT

In summary, the asymmetric synthesis of (+)-L-β-dioxolane-T and (-)-L-β-dioxolane-C was accomplished *via* 8 steps from a chiral template **2**. A complete evaluation of a structure-activity relationship in 1,3-dioxolane-L-nucleosides as anti-HIV and anti-HBV agents are in progress in our laboratories.

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11. All key intermediates and final compounds **13-16** in Scheme I gave correct elemental analyses (± 0.4%). These compounds **13-16** were spectroscopically identical to those reported previously with the exception of the optical rotation which was of an opposite sign but of equal value.

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