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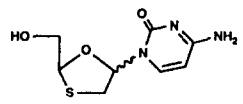
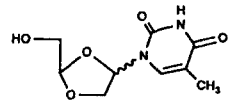
Rapid Communication

Improved Synthesis of D-1,3-Oxathiolanyl Acetate from D-Mannose and D-Galactose



A (±)-BCH-189



B (±)-Dioxolane-T

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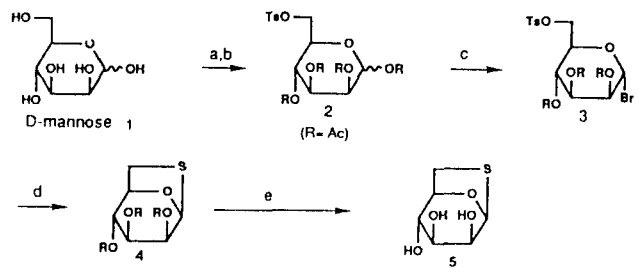
Belleau and coworkers (Belleau *et al.*, 1989) reported the synthesis and *anti*-HIV activity of (±)-dioxolane-thymine and (±)-BCH-189 in which C-' positions of these nucleosides have been replaced by oxygen and sulfur, respectively. Chu recently reported the synthesis of enantiomerically pure isomers of both (±)-BCH-189 to compared the anti-HIV activities with those of racemic mixtures (Jeong *et al.*, 1992; Chu *et al.*, 1991; Beach *et al.*, 1992).

The first asymmetric synthesis of oxathiolanyl sugar moiety used D-mannose as the chiral template (Chu *et al.*, 1991), and an improved method was later reported using D-galactose as the starting material (Jeong *et al.*, 1992). In our on-going research efforts to develop non-classical nucleoside derivatives with anti-HIV activity, we needed large amount of D-oxathiolanyl acetate of high enantiomeric purity. Although Chu's methods give enantiomerically pure sugar moiety, the over-all yield of the reactions were not high because of side-reactions. Here we wish report improved asymmetric syntheses D-oxathiolane sugars from D-mannose as well as from D-galactose.

The primary and secondary hydroxy groups of D-mannose (**1**) were selectively protected as tosylate and acetates (**2**), respectively in good yield. The anomeric acetate group was then converted to a better leaving group, bromide (**3**) using 30% HBr solution. Potassium xanthate reaction (Akagi *et al.*, 1963; Whistler and Seib, 1966) gave D-1,6-thioanhydro-mannopyranose (**4**) in 38% yield. Following deprotection of acetate groups, Chu *et al.* has used $NaIO_4$ to cleave 2,3-*cis* diol group. We have found that this direct cleavage gave severe undesirable side reactions due to the 4-hydroxy group. We chose to protect 4-hydroxy group as the benzoylate (**5** to **8**) prior to the oxidative diol cleavage. We employed lead tetraacetate to avoid sulfur oxidation and obtained the unstable di-aldehyde (**9**) which was directly reduced to compound (**10**) under mild conditions ($NaBH_4$). Selective protection of the primary alcohol as the tBDPS ether (**11**) folowed by the deprotection of the benzoylate gave the diol (**12**) in 92.4% yield. Oxidative cleavage of this diol with $NaIO_4$ again gave the undesired sulfur oxidation. We used a step-wise cleavage reaction followed by oxidation of the resulting aldehyde (**13**) using lead tetraccetate and PDC, respectively. The final decarboxylative acetylation using lead tetraccetate completed the synthesis of D-oxathiolanyl acetate (**15**) in 14 step. Although the total number of steps have increased due to this step-wise sequence, the over-all yield of the reaction has improved by 8.4% eliminating unwanted side-reactions (Scheme 1, 2).

D-Galactose (**16**) was used as a starting material for the D-oxathiolane synthesis. The preparation of (**23**) from (**16**) was straightforward (Jeong *et al.*, 1992) and gave excellent yield. Compared to the 1,6-thioanhydro-D-mannose fromation, the xanthate reaction on the galactose analog gave much a higher yield. Again, we opted to the protect 2-hydroxy group as the ben-



reagents : a) TsCl, pyridine, 0°C, RT. b) Ac_2O, RT. c) HBr, AcOH, RT.
d) potassium O-ethyl xanthate, acetone, reflux. e) NH_4OH, MeOH, RT.

Scheme 1. Synthesis of D-1,6-thioanhydro-mannopyranose.

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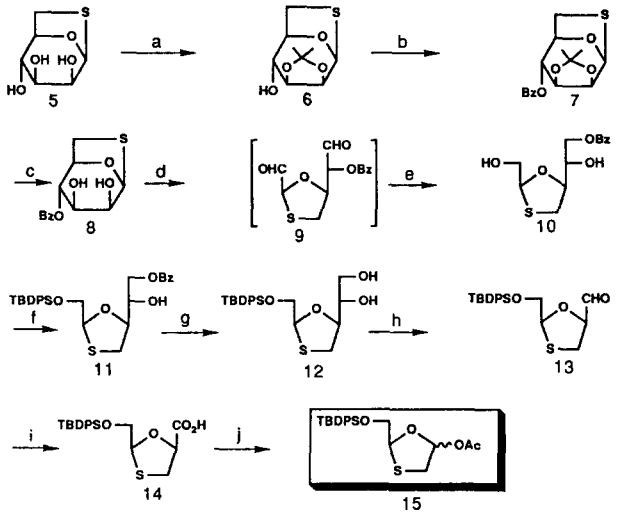
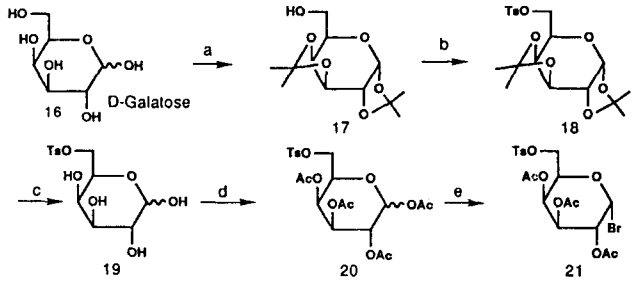


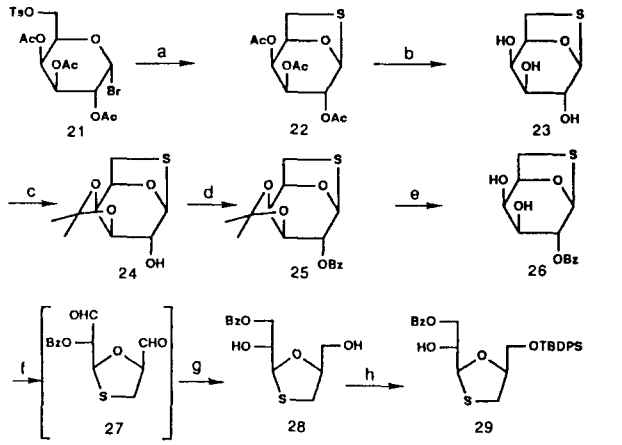
reagents : a) p-TsOH, DMP, acetone. b) BzCl, pyridine. c) 2% aqueous H_2SO_4, 1,4-dioxane, 70~80°C. d) $Pb(OAc)_4$, THF. e) $NaBH_4$, MeOH. f) (t-Butyl)Ph_2SiCl, imidazole, DMF. g) NaOMe. h) $Pb(OAc)_4$, THF, RT. i) PDC, DMF, RT. j) $Pb(OAc)_4$, pyridine, THF, RT.

Scheme 2. Synthesis of D-1,3-oxathiolanyl acetate.



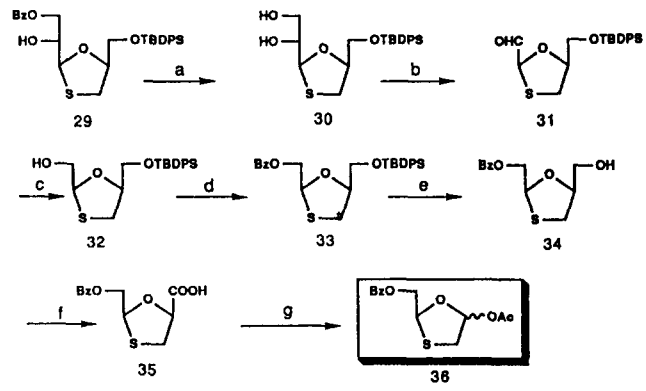
reagents : a) $ZnCl_2$, acetone, H_2SO_4. b) TsCl, pyridine. c) 75% AcOH, reflux. d) Ac_2O, pyridine. e) 30% HBr/AcOH.

Scheme 3. Synthesis of bromosugar.



reagents : a) potassium O-ethyl xanthate, acetone, reflux. b) NH_4OH/MeOH(1:4). c) p-TsOH, DMP, acetone 70-80°C. f) $Pb(OAc)_4$, THF. g) $NaBH_4$, EtOH. h) TBDPS-Cl, imidazole, DMF.

Scheme 4. Synthesis of D-oxatholanyl acetate intermediate 29.



reagents : a) NaOMe, MeOH. b) LTA, THF. c) $NaBH_4$, ETOH. d) BzCl, pyridine. e) TBAF, THF. f) PDC, DMF. g) LTA, pyridine, THF.

Scheme 5. Synthesis of D-1,3-oxathiolanyl acetate.

zoylate (**26**) prior to the *cis*-diol cleavage in order to avoid side reactions seen in Chu's method. Using the step-wise cleavage/oxidation sequence of the diol prevented over-oxidation to the sulfone or sulfoxide by-products. The resulting aldehyde (**27**) was reduced without isolation to compound (**28**) and was then protected as the TBDPS ether (**29**) at the primary position. Deprotection of the benzoylate followed by oxidative cleavage of the diol gave aldehyde (**31**) which was reduced by $NaBH_4$ to alcohol (**34**) in 64.9% yield. This primary alcohol was again protected as a benzoylate (**33**) to differentiate it from the 5'-hydroxy group. Deprotection of the TBDPS ether gave (**34**) in good yield and was oxidized with PDC to the carboxylic acid (**35**). Decarboxylative acetylation completed the synthesis of D-oxathiolanyl acetate (**36**) in 20 steps (Scheme 3, 4, 5).

In summary, the enantiomerically pure D-oxathiolanlyl acetate, which was later converted to enantiomerically pure oxathiolane pyrimidine nucleosides, was synthesized from D-mannose and also from D-galactose. We have improved Chu's method to prevent sulfur oxidation and other undesirable side reaction during the diol cleavage reaction.

ACKNOWLEDGEMENT

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