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EFFICIENT ENANTIOSELECTIVE SYNTHESES OF CARBOCYCLIC NUCLEOSIDE AND PROSTAGLANDIN SYNTHONS

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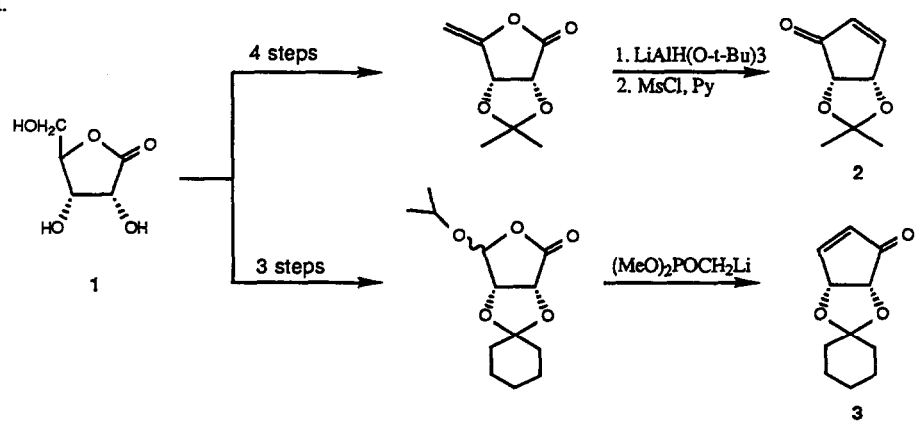
Abstract: Simple and efficient enantioselective syntheses of two hydroxylated cyclopentenones, **2** and **10**, which are useful intermediates for the synthesis of various carbocyclic nucleosides and prostaglandins, directly from readily available sugars are described.

Neplanocin A and aristeromycin, naturally occurring but scarce carbocyclic nucleosides, have attracted considerable chemical and biological interest recently due to their significant antitumor as well as antiviral activities.[1] Several enantioselective syntheses of neplanocin A and aristeromycin have been reported previously. The most recent approaches to the syntheses of these carbocyclic nucleosides rely on the availability of the enantiomerically pure cyclopentenone intermediates **2** and **3**.[2,3]

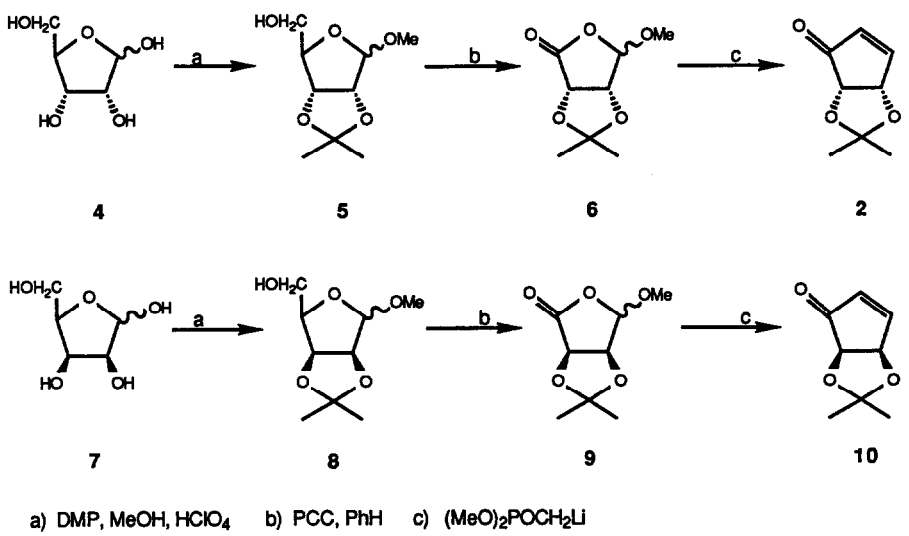
Only a few stereoselective syntheses of optically pure hydroxylated cyclopentenones have been reported.[4] D-Ribonolactone (**1**) serves as a convenient source of the chiral cyclopentenones **2**[5] and **3**[6] (Scheme 1). The syntheses of these synthons from cyclopentadiene in six steps[7] and from toluene in four steps[8] have also been reported.



Scheme 1

We are currently engaged in the design and synthesis of analogues of neplanocin A, which is of interest as a prototype antiviral agent.[9] For the syntheses of these analogues we need enantiomerically pure cyclopentenones which we recently reported[6] to be available from D-ribonolactone. Until recently D-ribonolactone (**1**)was available from commercial sources. However, a shortage of D-ribonolactone from commercial sources led us to explore alternate routes to these synthons. In this manuscript we report the most efficient syntheses to date of enantiomerically pure cyclopentenones **2** and **10**, which have previously been employed as intermediates in the synthesis of neplanocin A[2] and aristeromycin,[3] respectively. Cyclopentenone **2** was also pivotal in Johnson's triply convergent synthesis of PGE_2.[7]

The cyclopentenone **2** was prepared in enantiomerically pure form from D-ribose (**4**) (Scheme 2) in three steps in an overall yield of 41%. Compound **5** was obtained in 91% yield from D-ribose by a slight modification of the previously reported procedure.[10] PCC oxidation of **5** unexpectedly yielded lactone **6** in 56% yield.[11] PCC is the reagent of choice for the oxidation of alcohols to carbonyl compounds, but the unusual oxidation of **5** to **6** has not been observed previously to our knowledge. The lactone **6** was then transformed to (+)-cyclopentenone **2** by reaction with lithium dimethyl methylphosphonate in 80% yield.[12] (-)-Cyclopentenone **10** was similarly obtained from D-lyxose (**7**) in three steps in an overall yield of 42%.[12]



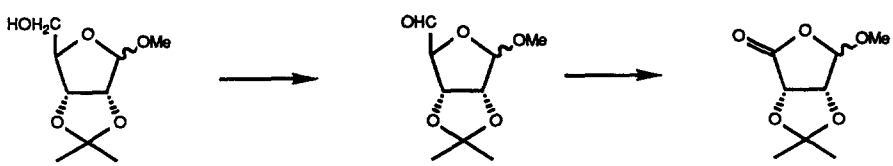
Scheme 2

A typical procedure for the protection of sugars (step a) was as follows: A mixture of sugar **4** or **7** (10g) and 2,2-dimethoxypropane (20 mL) in acetone (80 mL) was cooled in an ice bath and perchloric acid (4 mL of 70%) was slowly added. The ice bath was then removed and the contents were stirred at room temperature for 2h followed by addition of methanol (14 mL) and the reaction mixture was further stirred for 2h. The mixture was

again cooled down in an ice bath and neutralized with cold sodium carbonate (3.2 g in 10 mL of H_2O). A solid precipitated which was removed by filtration and the filtrate were concentrated. The concentrated residue was dissolved in ether (200 mL) and washed with brine and water. The aqueous portion was extracted with ether (2x150 mL) and the combined ether fractions were dried (Na_2SO_4). The evaporation of the solvent yielded a colorless oil which was purified by distillation to afford 5 or 8, respectively.[10]

A typical procedure for the oxidation of protected sugars **5** and **8** to lactones **6** and **9**, respectively, (step b) was as follows: To a stirred solution of protected sugar **5** or **8** (10 g) in benzene (500 mL) in a round bottomed flask fitted with a Dean-Stark apparatus and a condenser was added vacuum dried pyridinium chlorochromate (42 g). The mixture was refluxed overnight on an oil bath. The benzene contents were decanted and residue was washed three times with ether. The combined fractions were passed through a column of silica gel to give crude lactone **6** or **9** which was crystallized from hexane-ether to furnish pure lactone.[11]

The novel step in the enantioselective preparation of the cyclopentenones **2** and **10** is the conversion of the protected sugars **5** and **8** to lactones **6** and **9**, respectively. Initially we observed that the oxidation of **5** with 2.0 equivalents of PCC yielded aldehyde **11** in 71% yield and lactone **6** in 10% yield. In subsequent experiments we observed that the oxidation of **5** with 2.5 to 3.0 equivalents of PCC decreased the yield of aldehyde **11** and increased the yield of lactone **6**. The optimal yield of lactone **6** was obtained when 4.0 equivalents of PCC were used to oxidize **5**. It is important to mention here that there is no precedent for the oxidative cleavage of C-C bond by the use of PCC (Scheme 3). However, such bonds (vicinal electronegative substituents) are known to undergo oxidative cleavage with special ease. Recently the first report on the oxidative cleavage of 1,2-glycols by Jones reagent[13] appeared, but the actual mechanism for this transformation is not yet clearly understood.



5 **11** **6**

Scheme 3

In summary, cyclopentenones **2** and **10**, which are important intermediates for the synthesis of carbocyclic nucleosides and prostaglandin, can be prepared easily from readily available sugars. The key step in this transformation is the oxidation of protected sugars **5** and **8** to lactones **6** and **9**, respectively, which represents the first example of the oxidative cleavage of the C-C bond by PCC. This transformation is significant both from synthetic as well as mechanistic standpoints.

ACKNOWLEDGEMENTS

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11) **6**: M.p. 75-76 °C; $[\alpha]_D$ -51.0° (c 2.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, ppm): 1.38 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 4.55 (1H, d, J=5.37 Hz, H-3), 4.80 (1H, d, J=5.37 Hz, H-2), 5.34 (1H, s, H-1); ^{13}C-NMR ($CDCl_3$, ppm): 25.50 (CH_3), 26.50 (CH_3), 56.91 (OCH_3), 74.33 (C-3), 79.16 (C-2), 105.01 (C-1), 114.20 (CMe_2), 173.50 (C=O); MS (EI, 70 eV): 188 ($M^{+\cdot}$). **9**: $[\alpha]_D$ +51.0° (c 2.0, $CHCl_3$); Other physical data (M.p., ^{1}H-NMR, ^{13}C-NMR, MS) was identical to that of **6**.

12) **2**: M.p. 66-67 °C; lit., [5] M.p. 69-70 °C; $[\alpha]_D$ +70.7° (c 1, $CHCl_3$); lit.,[5] $[\alpha]_D$ +71° (c 1, $CHCl_3$); 1.43 (6H, s, 2xCH_3), 4.48 (1H, d, J=5.27 Hz, H-2), 5.29 (1H, dd, J_1=5.27 Hz, J_2=2.82 Hz, H-3), 6.23 (1H, d, J=5.48 Hz, H-5), 7.63 (1H, dd, J_1=5.75 Hz, J_2=2.32 Hz, H-4); MS (EI, 70 eV): 144 ($M^{+\cdot}$). **10**: $[\alpha]_D$ -70.7° (c 1, $CHCl_3$); Other physical data (M.p., ^{1}H-NMR, ^{13}C-NMR, MS) was identical to that of **2**.

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