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Efficient and practical synthesis of D-cyclopent-2-enone, the key intermediate for the synthesis of carbocyclic nucleosides

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Abstract—An efficient and practical method for the synthesis of (4*R*,5*R*)-4,5-*O*-isopropylidene-cyclopent-2-enone was developed from D-ribose by using a ring-closing metathesis reaction.

Carbocyclic nucleosides have received much attention since the isolation of (−)-aristeromycin **1**[1] and (−)-neplanocin A **2**[2] from natural sources. More recently, the discovery of abacavir **3**,[3] a prodrug of carbovir **4**[4] against HIV marked an important milestone of carbocylic nucleosides in antiviral chemotherapy. Due to the absence of a typical glycosidic bond, carbocyclic nucleosides are chemically and enzymatically more stable than the natural nucleosides.[5] The mechanism of the antiviral activity of (−)-aristeromycin **1** and (−)-neplanocin A **2** is probably due to inhibition of *S*-adenosyl homocystein (AdoHcy) hydrolase,[6] which has been considered an attractive target for antiviral chemotherapy, interfering with the virus mRNA maturation.[7]

As part of our drug discovery program, recently we have developed the synthesis of enantiomerically pure (−)-aristeromycin **1** and (−)-neplanocin A **2** analogs.[8–10] We also synthesized enantiomerically pure cytosine **5** and 5-F-cytosine **6** analogs, which exhibit significant anti-HIV and anti-West Nile Virus activities (Fig. 1).[8] Therefore, additional biological evaluation of these and other carbocyclic nucleosides required a large amount of compounds. However, the main problem for scaling up these compounds is the availability of key intermediates such as cyclopent-2-enone **15**.

Previously, several asymmetric syntheses for (−)-aristeromycin **1** and (−)-neplanocin A **2** have been developed.[11] Several approaches utilized optically pure starting materials such as D-ribonolactone,[12] D-ribose[13] or L-tartaric acid.[14] Optically active cyclopent-2-enone **15** is the key intermediate in the synthesis of carbocyclic nucleosides including (−)-aristeromycin **1**, (−)-neplanocin A **2** and their analogs, which can be obtained by the ring opening and cyclization reaction of D-ribonolactone or D-ribose.[15] However, these reactions are highly sensitive to reaction conditions, such as moisture and temperature, and therefore, suffer low and inconsistent yields. Recently, a novel synthesis of optically active cyclopent-2-enone **15** has been reported.[16] It has been synthesized from D-isoascorbic acid using ring-closing metathesis (RCM) reaction as the key reaction. However, the synthesis of cyclopent-2-enone **15** depended on several oxidation and reduction steps which lowered the overall yield (23%) in a small scale.

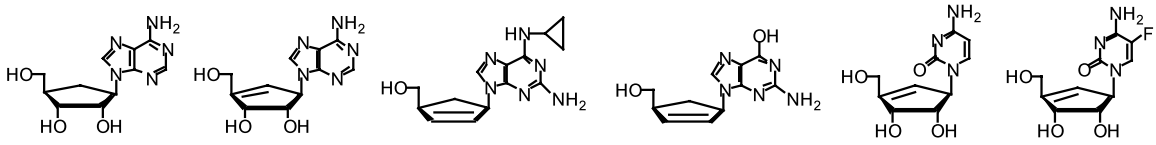

Figure 1.

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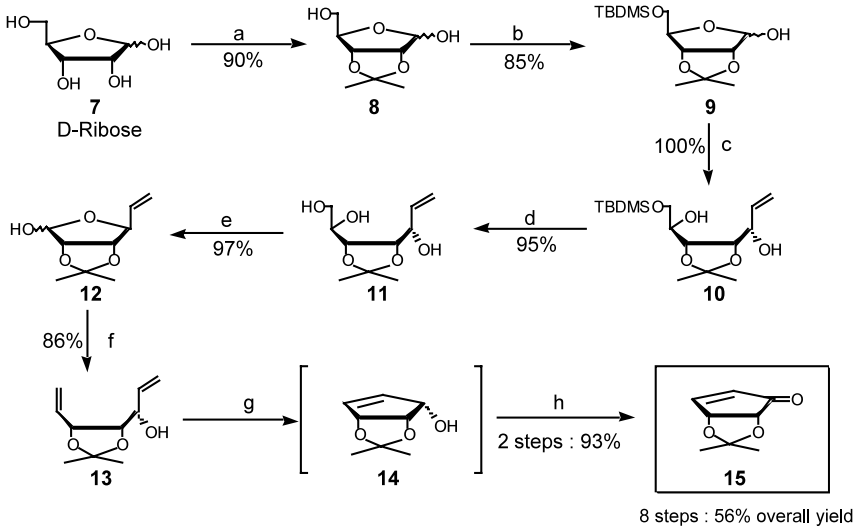

Scheme 1. *Reagents and conditions*: (a) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone, 0°C to rt, 1 h; (b) TBDMSCl, imidazole, CH_2Cl_2, rt, 1 h; (c) vinylmagnesium bromide, anhydrous THF, –78°C to rt, 1 h; (d) TBAF, THF, rt, 1 h; (e) $NaIO_4$, H_2O, rt, 1 h; (f) NaH, DMSO, methyltriphenylphosphonium bromide, THF, 0°C to reflux, 3 h; (g) Grubbs catalyst, anhydrous CH_2Cl_2, 24°C, 4 h; (h) pyridinium chlorochromate, 4 Å molecular sieve, AcOH, CH_2Cl_2, rt, 12 h.

In this communication, we wish to report a significantly improved and practical method for the synthesis of optically pure D-cyclopent-2-enone **15** from D-ribose in eight steps with overall yield of 56% in a large scale (10 g scale).

The isopropylidene protected derivative **8** (Scheme 1) was obtained from D-ribose with 2,2-dimethoxypropane in the presence of catalytic amount of *p*-toluenesulfonic acid in 90% yield, followed by *t*-butyldimethylsilane chloride with imidazole to afford the silylated lactol **9** in 85% yield. To introduce an olefin moiety, Grignard reaction was carried out with vinylmagnesium bromide to provide alcohol **10** in 100% yield. The deprotection of the silyl group using 1 M solution of tetrabutylammonium fluoride in THF followed by an oxidative cleavage with sodium periodate afforded lactol **12**. Wittig reaction[16] was carried out using NaH and DMSO in THF to give diene **13** in 86% yield which underwent a RCM[16,17] reaction. Several RCM reaction conditions using the Grubbs catalyst from diene **13** to cyclopentenol **14** were investigated, among which 1% Grubbs catalyst at 24°C in anhydrous CH_2Cl_2 provided the best result to obtain cyclopentenol **14**. As the obtained cyclopentenol **14** was volatile, the desired cyclopentenone **15**[18] was directly obtained in two steps 93% yield from diene **13** by PCC oxidation of cyclopentenol **14** without purification.

In summary, we have developed a significantly improved synthetic method for D-cyclopent-2-enone **15** in a preparative scale, which is a versatile intermediate for the synthesis of carbocyclic nucleosides in overall 56% yield from D-ribose.

Experimental

Procedure for the preparation of compound **15** from **13**: To a 500 mL round bottom flask filled with the Grubbs catalyst (446 mg, 1 mol%, flushed with N_2 three times), a solution of the diene **13** (10.0 g, 0.054 mol) in anhydrous CH_2Cl_2 (300 mL) was added. After stirring at 24°C for 4 h, 4 Å molecular sieve (20.0 g), pyridinium chlorochromate (23.5 g, 0.108 mol) and acetic acid (0.15 mL, 5 mol%) were added to the resulting dark brown mixture. The reaction mixture was stirred at the same temperature for 12 h and filtered over a silica-gel pad with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica-gel column with 10% hexane in EtOAc to give cyclopetenone **15** (7.6 g, 93% yield) as white crystals.

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18. Data for **15**: mp 68.5–70.3°C; $[\alpha]_D$ −69.3° (*c*, 0.60, $CHCl_3$) [reported:[16] mp 68.6–70.1°C; $[\alpha]_D$ −70.4° (*c*, 0.92, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 7.61 (dd, $J=2.4$, 6.0 Hz, 1H), 6.22 (d, $J=6.0$ Hz, 1H), 5.28 (dd, $J=2.4$, 5.6 Hz, 1H), 4.47 (d, $J=5.6$ Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) 203.2, 160.0, 134.6, 115.7, 78.8, 76.7, 27.6, 26.4.