Preparative Synthesis of the Key Intermediate, (4*R*,5*R*)-3-Benzyloxymethyl-4,5-isopropylidenedioxycyclopent-2-enone for Carbocyclic Nucleosides

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(4*R*,5*R*)-3-Benzyloxymethyl-4,5-isopropylidenedioxycyclopent-2-enone (**1**), a versatile intermediate for the synthesis of carbocyclic nucleosides was synthesized from D-ribose in 10 steps and 26% overall yield.

(−)-Neplanocin A is a naturally occurring nucleoside of potential use in cancer and viral chemotherapy.[1] It belongs to the carbocyclic nucleoside family which possesses the metabolic and chemical stability to glycosidic bond hydrolysis. (−)-Neplanocin A has a strong antiviral activity against various RNA and DNA viruses.[2] The antiviral activity of (−)-neplanocin A has been correlated with its ability to inhibit *S*-adenosylhomocysteine hydrolase (SAH) and its ability to increase cellular levels of *S*-adenosylhomocysteine.[3] The mechanism of inhibition by (−)-neplanocin A has been known as a cofactor depletion mechanism, involving reduction of the enzyme-bound cofactor, NAD^+ to NADH with simultaneous oxidation of (−)-neplanocin A to its 3′-keto derivative.[4]

Based on this promising biological activity of (−)-neplanocin A, several asymmetric syntheses of (−)-neplanocin A, starting from cyclopentadiene,[5] D-ribose,[6] D-ribonic gamma-lactone,[7] or L-tartaric acid[8] have been reported. These syntheses have been completed via the key intermediates such as (4*R*,5*R*)-3-benzyloxymethyl-4,5-isopropylidenedioxycyclopent-2-enone (**1**) and (4*R*,5*R*)-4,5-isopropylidenedioxycyclopent-2-enone (**2**) (Figure 1).

Recently, ring-closing metathesis (RCM) reaction was utilized for the synthesis of the key intermediates, **1**[9] and **2**,[10,11] improving the number of steps and overall yields greatly. Jacobson and his co-workers[9] have reported the elegant synthesis of the intermediate **1** from D-ribonic gamma-lactone in 11 steps, but in a small scale (<1 g). Since our laboratory[10] and Chu's laboratory[11] have already reported the practical and efficient syntheses of **2** from D-ribose, we have been interested in synthesizing the key intermediate **1** in a preparative scale. This is highly desirable for structure-activity relationship study of the carbocyclic nucleosides, based on the lead, (−)-neplanocin A. In this communication, we wish to report the improved and large-scale (>10 g) synthesis of **1**, which serves as a versatile intermediate for the synthesis of carbocyclic nucleosides including (−)-neplanocin A, from D-ribose.

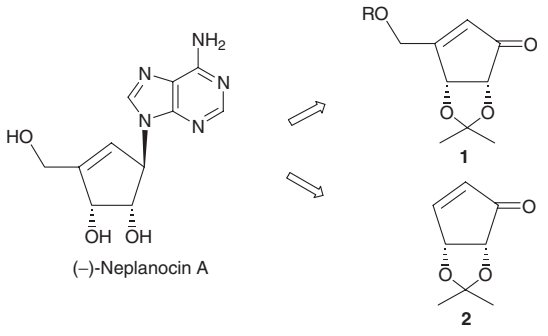
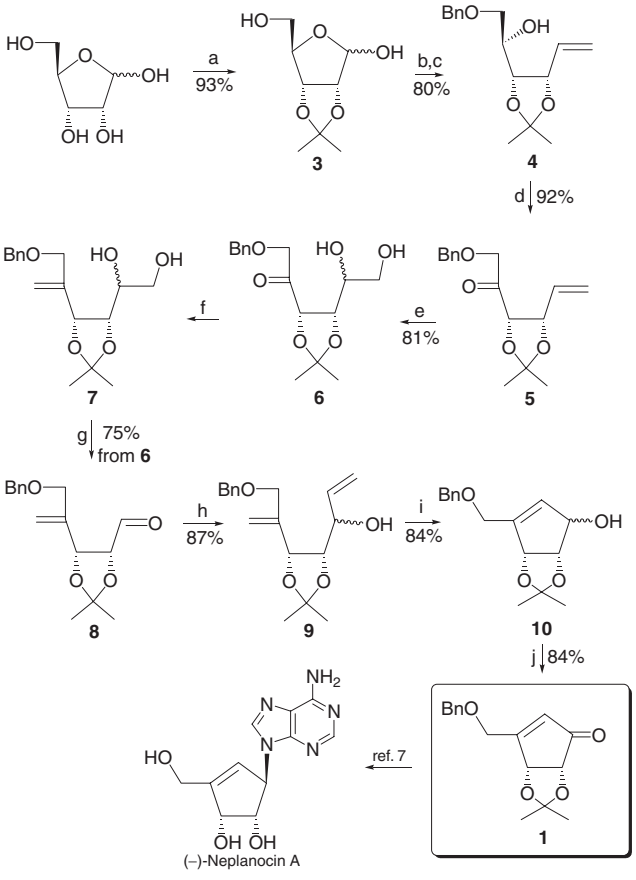


Figure 1. The key intermediates, **1** and **2** for the synthesis of (−)-neplanocin A.



Reagents[a]: a) *c*-H_2SO_4, acetone, rt, 2.5 h; b) Ph_3PCH_3Br, KO-*t*Bu, THF, rt, 12 h; c) i.Bu_2Sn=O, toluene, reflux. ii. TBAI, BnBr, 75 °C, 16 h; d) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 1 h and then Et_3N, rt, 1 h; e) OsO_4, NMO, acetone/H_2O (8:1), rt, 30 h; f) Ph_3PCH_3Br, KO-*t*Bu, THF, rt, 2 d; g) $NaIO_4$, H_2O, CH_2Cl_2, rt, 2 h; h) CH_2=CHMgBr, THF, −78 °C, 1 h; i) 2nd generation Grubbs catalyst, CH_2Cl_2, rt, 2 d; j) TPAP, NMO, CH_2Cl_2, MS, rt, 24 h.

Synthesis of the key intermediate, **1** is illustrated in Scheme 1. D-Ribose was converted to the isopropylidene **3**[12] under acidic conditions (93%). The Wittig reaction of **3** with meth-

yl triphenylphosphonium ylide in THF afforded vinyl diol derivative which was subjected to selective benzylation of the primary hydroxy group using organotin chemistry to give vinyl benzylether **4** (80% from **3**). The Swern oxidation of **4** followed by dihydroxylation of the resulting ketone **5** with osmium tetroxide and NMO gave the diol **6** as a diastereomeric mixture in very good yield. The Wittig reaction of the mixture **6** with methyl triphenylphosphonium ylide in THF afforded vinyl diol **7**, which was treated with sodium metaperiodate to give aldehyde **8** (75% from **7**). Treatment of **8** with vinylmagnesium bromide gave divinyl derivative **9** (87%) as a diastereomeric mixture (2:1). It is interesting to note that no stereoselectivity during Grignard reaction was observed, despite of two available sites (α- and β-oxygen) for chelation,[13] indicating two oxygens of the isopropylidene group do not form α- and β-chelates. Diene **9** was subjected to RCM reaction using the second generation Grubbs catalyst[14] in methylene chloride to give cyclopentenol **10**[15] (84%), which was oxidized to the key intermediate **1**[7,9] using tetrapropylammonium perruthenate (TPAP) and NMO in methylene chloride (84%). This key intermediate **1** was converted to (−)-neplanocin A according to the known procedure.[7] This intermediate also serves as a versatile synthon for the synthesis of other carbocyclic nucleosides.

In summary, we have accomplished the improved and preparative synthesis of **1** from D-ribose using ring-closing metathesis as a key reaction in 10 steps and 26% overall yield. Our method has synthetic advantages such as large scale synthesis (>10 g), use of cheap starting material, D-ribose and no use of expensive reagent like TBDPSCl. This synthetic method will be extensively utilized for the structure-activity relationship study of various carbocyclic nucleosides including (−)-neplanocin A.

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15 Experimental procedure for the synthesis of compound **10**: To a stirred solution of **9** (13.46 g, 43.83 mmol) in methylene chloride (200 mL) was added 2nd generation Grubbs catalyst (115 mg, 0.14 mmol) and the reaction mixture was stirred at room temperature for 20 h. After an additional addition of 2nd generation Grubbs catalyst (86 mg, 0.10 mmol), the mixture was stirred for an addtional 28 h at room temperature. After evaporation of the reaction mixture in vacuo, the resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (2.5:1) as the eluent to give **10** (10.11 g, 84%) as a pale brownish syrup and the recovered starting material (1.083 g).
α-cyclopentenol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 5H, Ph), 5.78 (m, 1H, 5-H), 5.16 (d, 1H, $J = 5.6$ Hz, 3a-H), 4.71 (m, 1H, 4-H), 4.56 (s, 2H, CH_2Ph), 4.51 (d, 1 H, $J = 6.0$ Hz, 6a-H), 4.18–4.10 (m, 2H, 6-H), 1.71 (br s, 1H, OH), 1.36 (s, 3H, CH_3), 1.32 (s, 3H, CH_3).
β-cyclopentenol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H, Ph), 5.78 (s, 1H, 5-H), 4.95 (d, 1H, $J = 6.0$ Hz, 4-H), 4.74 (t, 1H, $J = 5.6$ Hz, 3a-H), 4.55–4.54 (m, 3H, 6a-H, CH_2Ph), 4.14 (s, 1H, BnOC*H*H), 4.13 (s, 1H, BnOCH*H*), 2.54 (br s, 1H, OH), 1.40 (s, 3H, CH_3), 1.38 (s, 3H, CH_3).

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