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Preparative and Stereoselective Synthesis of the Versatile Intermediate for Carbocyclic Nucleosides: Effects of the Bulky Protecting Groups to Enforce Facial Selectivity

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Abstract: The preparative and stereoselective synthesis (45−50% overall yields) of the target compound **17** has been accomplished from D-ribose. The bulky protecting groups such as TBDPS and Trityl enforced the facial selectivity during Grignard reaction to give the tertiary β-allylic alcohol **16** as the sole product, which was oxidatively rearranged to the key molecule **17** in excellent yield.

A naturally occurring nucleoside, neplanocin A (**1**)[1] is a representative of the carbocyclic nucleosides and shows potent antiviral and antitumor activities by inhibiting *S*-adenosylhomocysteine hydrolase (Figure 1). Its fluorocyclopentene analogue, fluoroneplanocin A (**2**),[2] was also reported to be a potent irreversible inhibitor of *S*-adenosylhomocysteine hydrolase and exhibit potent antitumor and antiviral activities. On the other hand, the cytidine analogue **3** showed potent antitumor activity by reducing cytidine-5′-triphosphate (CTP) pools and in addition displayed potent antiviral activity by inhibiting CTP synthetase.[3]

However, although a variety of biological activities of these carbocyclic nucleosides have stimulated medicinal chemists to carry out structure−activity relationship (SAR) studies in carbocyclic nucleosides, synthetic difficulties in preparing the D-carbocycle have hampered them from pursuing the extensive SAR study. Thus, modifications have mainly been done on the base moiety, not on the cyclopentenyl sugar part. Chu and co-workers reported the structure−activity relationship study, based on the modification of the adenine base, in which 5-fluorocytosine analogue **4** exhibited potent antiviral activity against West-Nile virus.[4]

Although many synthetic methods to the carbocyclic moiety have been reported so far,[5] they sometimes suffered from inconsistent and low overall yields, lengthy synthetic routes, racemization, lack of large-scale preparations, and sensitivity to reaction conditions such as temperature and moisture. Thus, a short and efficient procedure to the D-carbocycle is highly desirable. Recently, Jacobson and co-workers have published the elegant synthesis of the carbocycle moiety of neplanocin A from D-ribono-γ-lactone, using olefin ring closing metathesis (RCM) as a key step.[6] More recently, short and efficient syntheses of D- and L-3-unsubstituted cyclopentenones, which employ RCM as the key step, have been reported from our laboratory[7] and by Chu et al.,[8] and these substrates serve as versatile precursors for the synthesis of D- and L-carbocyclic nucleosides. Thus, we are very interested in developing a new and efficient synthetic route to the D-cyclopentenone derivative with a 3-hydroxymethyl side chain for the extensive modification of the cyclopentenyl sugar moiety. The highlights of our synthesis are the stereoselective formation of the tertiary β-allylic alcohol **16** during the Grignard reaction, which is enforced by the bulky protecting group, and the oxidative rearrangement of the tertiary β-allylic alcohol to the key molecule **17**.

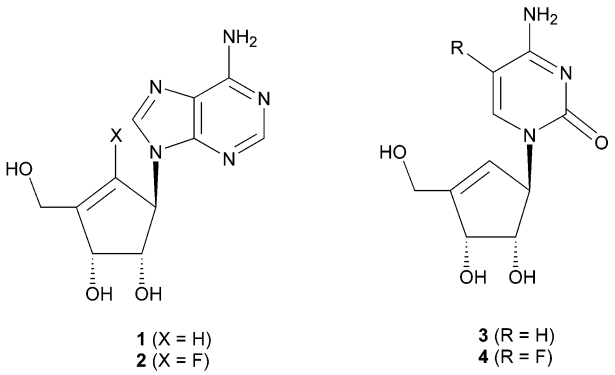

FIGURE 1. Potent carbocyclic nucleosides with cyclopentenyl sugar moiety.

First, we tried to synthesize **10** with a benzyl protecting group, which is widely used in nucleoside chemistry (Scheme 1). D-Ribose was converted to the acetonide **5**.[9] Wittig reaction of **5** with methyl ylide followed by selective benzyl protection, using organotin chemistry, yielded benzyl ether **6**. Direct benzylation of **5** or diol derivative obtained after Wittig reaction with NaH/BnBr

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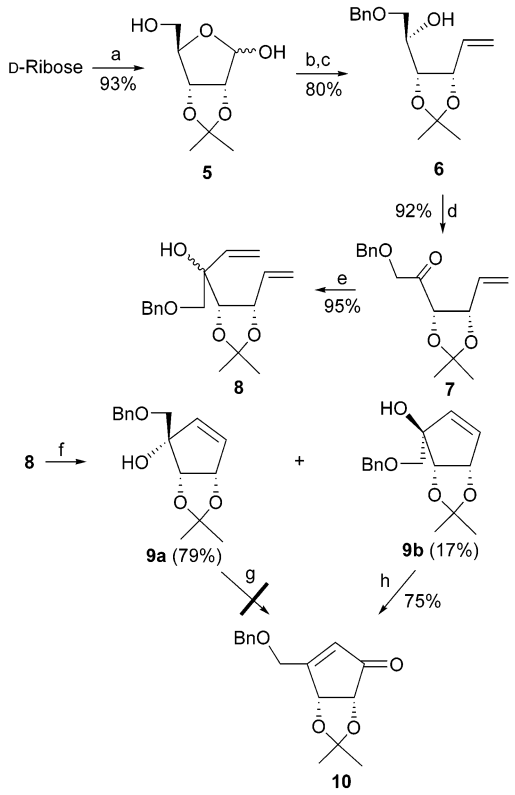
SCHEME 1[a]



[a] Reagents and conditions: (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, 15 h, (ii) TBAI, BnBr, 75 °C, 16 h; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, rt, 1 h; (e) CH_2═$CHMgBr$, THF, −78 °C, 1 h; (f) Grubbs catalyst, CH_2Cl_2, rt, 2 d; (g) (1) PCC, MS, benzene or DMF, (2) PDC, DMF, $ClCH_2CH_2Cl$, CH_2Cl_2 or DMSO, or (3) CrO_3, pyridine, Ac_2O, CH_2Cl_2; (h) PDC, MS, DMF, rt, 18 h.

resulted in no differentiation between primary alcohol and secondary alcohol, giving a low yield of primary benzyl ether. Swern oxidation of **6** gave ketone **7** (92%), which was subjected to the Grignard reaction with vinylmagnesium bromide to give diene **8** (95%) as an inseparable mixture of diastereomeric tertiary alcohols. Ring-closing metathesis (RCM) reaction of diene **8** with use of the 2nd generation Grubbs catalyst[10] afforded **9a** (79%) and **9b** (17%) after separation on silica gel. Relative stereochemistry of **9a** and **9b** was easily assigned on the basis of ^{1}H NOE experiment. Although **9a** or **9b** can be converted to the desired intermediate **10** in 4 steps according to Johnson's procedure,[5b] we pursued one-step conversion of **9a** or **9b** to **10** using oxidative rearrangement to increase overall yields. However, oxidative rearrangement of the tertiary allylic alcohol **9a** to cyclopentenone **10** failed under the various oxidation conditions,[11] while the minor isomer **9b** was smoothly converted to **10**[5d] on stirring with PDC in DMF in 75% yield. This result clearly indicates that the tertiary chromate ester of **9a** could not form the six-membered transition state to be rearranged to **10** because of the steric hindrance by the 2,3-isopropylidene group.

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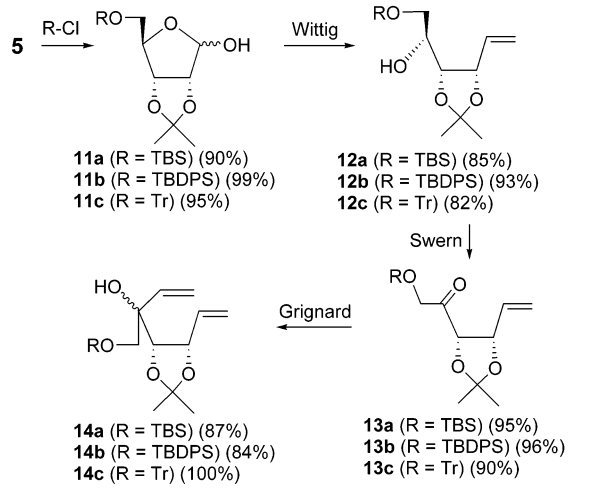
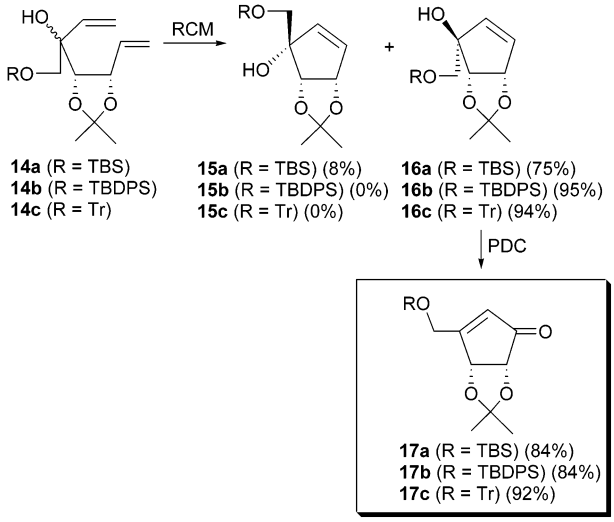
SCHEME 2



SCHEME 3



Thus, the next goal was to increase the formation of the tertiary allylic *β*-alcohol-like **9b**. This was achieved by changing the benzyl protecting group to bulky groups such as *tert*-butyldimethylsilyl (TBS), *tert*-butyldiphenylsilyl (TBDPS), or trityl (Tr), which were envisaged to control the stereoselectivity in the Grignard reaction. As shown in Scheme 2, acetonide **5** was protected as bulky ethers **11a**−**c**, which were converted to the dienes **14a**−**c**, respectively, by a similar procedure as before. Grignard reactions of **13a**−**c** with vinylmagnesium bromide afforded the dienes **14a**−**c** as inseparable diastereomers but with the opposite predominant diastereomer from that observed from the benzyl-protected precursors. The ratios of diastereomers were determined after RCM reaction, as illustrated in Scheme 3.

RCM reaction of **14a** with the TBS protecting group gave the undesired **15a**[12] (8%) and desired **16a**[12] (75%), while use of the bulkier protecting groups TBDPS and

(12) While preparing this manuscript, the same approach to compounds **15a** and **16a** was reported by Chu et al., who obtained **15a** and **16a** in a 1/10 ratio: (a) Chu, C. K.; Jin, Y. H.; Baker, R. O.; Huggins, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 9. (b) Jin, Y. H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem.* **2003**, *68*, 9012.

Tr resulted in the exclusive formation of the desired tertiary β-alcohols, **16b** and **16c**, respectively.[13] Thus, it is evident that the size of the protecting group played a major role in controlling the stereochemistry of the carbon carrying the tertiary hydroxyl group during the Grignard reaction. More systematic studies are needed to elucidate the origin of the distinct different stereochemical outcome of vinylmagnesium bromide addition to the carbonyl group of α′,α,β-trioxygenated ketones (**7**, **13a**−**c**), since several chelated as well as nonchelated transition states are feasible.[14]

With the desired isomers in hand, various oxidation reactions using the chromium reagents[11] (PCC, PDC, and CrO_3) in various solvents (CH_2Cl_2, DMSO, $ClCH_2CH_2Cl$, and DMF) were tried to convert the tertiary allylic alcohols, **16a**, **16b**, and **16c**, to their corresponding cyclopentenones, **17a**, **17b**, and **17c**,[15] among which PDC oxidation in DMF gave the best yields (84−92%).

In summary, we have developed a short, efficient, and preparative synthesis of our target compound **17** with various protecting groups, starting from D-ribose in 7 steps and in 45−50% overall yields. To the best of our knowledge, our synthetic method can be regarded as an excellent procedure from the viewpoint of number of steps, overall yields, large-scale preparation, and mild reaction conditions and has a great potential to be utilized extensively in the SAR study of the carbocyclic nucleosides.

Experimental Section

A Typical Procedure for the Grignard Reaction. To a stirred solution of **13b** (14.53 g, 34.22 mmol) in THF (150 mL) was added dropwise vinylmagnesium bromide (68.44 mL, 68.44 mmol, 1.0 M solution in THF) at −78 °C, and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched by saturated ammonium chloride solution and brine and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated. The resulting oil was purified by column chromatography (hexane:ethyl acetate = 9:1) to give (1*S*,4*R*,5*S*)-(+)-1-(2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(*tert*-butyldiphenylsilyloxymethyl)-2-propen-1-ol (**14b**) (13.01 g, 84%) as a colorless oil: $[\alpha]^{25}_D$ +17.99 (*c* 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.36 (m, 10 H), 6.11 (m, 2 H), 5.44 (dd, 1 H, *J* = 1.6, 17.6 Hz), 5.25 (m, 2 H), 5.13 (dt, 1 H, *J* = 1.2, 10.0 Hz), 4.68 (t, 1 H, *J* = 7.6 Hz), 4.47 (d, 1 H, *J* = 6.8 Hz), 3.81 (d, 1 H, *J* = 9.6 Hz), 3.49 (d, 1 H, *J* = 9.6 Hz), 1.50 (s, 3 H), 1.40 (s, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.8, 135.8, 135.4, 133.1, 133.0, 130.0, 130.0, 127.9, 127.9, 117.9, 116.1, 108.4, 79.5, 78.9, 75.7, 68.7, 27.5, 27.0, 25.1, 19.5. Anal. Calcd for $C_{27}H_{36}O_4Si$: C, 71.64; H, 8.02. Found: C, 71.71; H, 8.42.

A Typical Procedure for the RCM Reaction. To a stirred solution of **14b** (14.42 g, 31.86 mmol) in methylene chloride (100 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(VI) dichloride (270 mg, 0.32 mmol), and the reaction mixture was stirred at room temperature for 2 d. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give (1*S*,4*S*,5*S*)-(+)-4,5-*O*-isopropylidene-1-(*tert*-butyldiphenylsilyloxymethyl)-2-cyclopenten-1-ol (**16b**) (12.11 g, 95%) as a colorless oil: $[\alpha]^{25}_D$ +5.58 (*c* 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.35 (m, 10 H), 5.97 (dd, 1 H, *J* = 1.6, 5.6 Hz), 5.74 (d, 1 H, *J* = 5.6 Hz), 5.33 (d, 1 H, *J* = 5.6 Hz), 4.54 (d, 1 H, *J* = 5.2 Hz), 4.02 (d, 1 H, *J* = 10.4 Hz), 3.67 (d, 1 H, *J* = 10.4 Hz), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.09 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 135.7, 134.7, 133.2, 133.0, 130.0, 130.0, 128.0, 127.8, 112.2, 85.3, 85.1, 84.8, 66.0, 27.6, 27.0, 26.3, 19.5. Anal. Calcd for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60. Found: C, 70.98; H, 7.99.

A Typical Procedure for the Oxidative Rearrangement. A solution of **16b** (12.06 g, 28.40 mmol), 4 Å molecular sieves (14.2 g), and pyridinium dichromate (32.05 g, 85.20 mmol) in DMF (100 mL) was stirred at room temperature for 2 d. After the mixture was diluted with diethyl ether and ethyl acetate, the mixture was filtered through a short pad of a mixture of silica gel and Celite. The filtrate was evaporated and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give (4*R*,5*R*)-(+)-3-*tert*-butyldiphenylsilyloxymethyl-4,5-*O*-isopropylidene-2-cyclopentenone (**17b**) (10.08 g, 84%) as a colorless oil: $[\alpha]^{25}_D$ +6.1 (*c* 2.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.37 (m, 10 H), 6.34 (ps t, 1 H, *J* = 2.0 Hz), 4.99 (d, 1 H, *J* = 5.6 Hz), 4.70 (dd, 1 H, *J* = 2.0, 19.2 Hz), 4.51 (dd, 1 H, *J* = 1.6, 19.2 Hz), 4.50 (d, 1 H, *J* = 5.6 Hz), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 177.0, 135.7, 135.6, 132.8, 132.8, 130.3, 128.1, 128.1, 115.6, 78.3, 77.9, 62.6, 27.6, 26.9, 26.5, 19.5. Anal. Calcd for $C_{25}H_{30}O_4Si$: C, 71.05; H, 7.16. Found: C, 70.98; H, 6.95.

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Supporting Information Available: Full experimental details and characterization data for all other compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Relative stereochemistry of RCM products was also determined, based on ^{1}H NOE experiments as in the case of **9a** and **9b**.

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