Syntheses of D- and L-Cyclopentenone Derivatives Using Ring-Closing Metathesis: Versatile Intermediates for the Synthesis of D- and L-Carbocyclic Nucleosides

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Introduction

Neplanocin A (**1**)[1] and aristeromycin (**2**)[2] are representatives of naturally occurring carbocyclic nucleosides, which exhibit interesting biological activity[3] (Figure 1). These compounds act as potent inhibitors of *S*-adenosylhomocysteine (SAH) hydrolase, which catalyzes the hydrolysis of *S*-adenosylhomocysteine into adenosine and homocysteine.[4] Inhibition of the SAH hydrolase accumulates *S*-adenosylhomocysteine in the cell, which in turn inhibits *S*-adenosylmethionine (SAM) transferase, resulting in the inhibition of viral *m*RNA capping.[5] Thus, SAH hydrolase inhibitors such as neplanocin A and aristeromycin have received great attention in the development of broad spectrum antiviral agents.

Although neplanocin A and aristeromycin act as good inhibitors of SAH hydrolase, they were too cytotoxic to be clinically useful agents.[6] Thus, in the search of less toxic and more potent inhibitors of SAH hydrolase than these compounds, many D-carbocyclic analogues have been synthesized and evaluated for SAH hydrolase inhibitory activity.

As a result, compounds **3**[7] and **4**[8] have been discovered as potent SAH hydrolase inhibitors, but additional efforts should be still made to find clinically useful SAH hydrolase inhibitor.

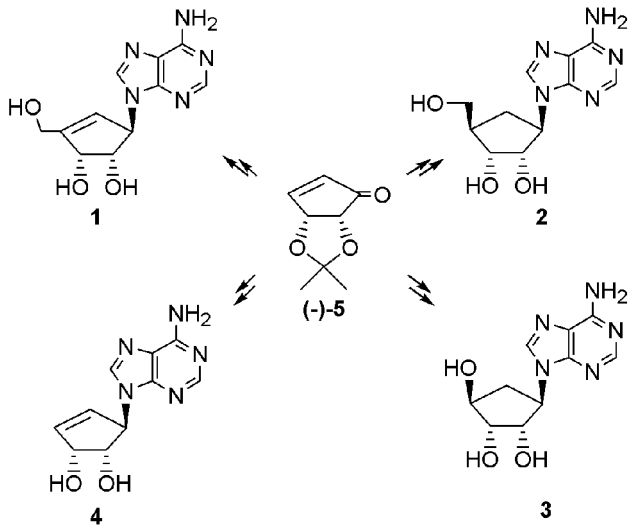

Figure 1. Versatile intermediate, (−)-**5**, for various carbocyclic nucleosides.

On the other hand, since the discovery of (−)-3TC (lamivudine)[9] as a potent anti-HIV and anti-HBV agent, nucleoside chemists turned their attention to the development of L-nucleosides. Several L-nucleosides[10] were found to be less cytotoxic than the corresponding D-nucleosides while maintaining more potent antiviral activity such as (−)-3TC. Recently, on the basis of these findings, L-carbocyclic nucleosides[11] such as L-aristeromycin and L-carbovir analogues have been synthesized to search for less toxic and more potent antiviral agents than the counterpart D-nucleosides. Although most of the synthesized nucleosides did not exhibit significant antiviral activities, systematic structure−activity relationship study of L-carbocyclic nucleosides should be continued to find novel antiviral agents.

Since carbocyclic nucleosides **1**−**4** could be synthesized from the same intermediate (−)-**5**[12] as shown in Figure 1, a short and efficient synthesis of the key intermediate (−)-**5** is highly demanded for the thorough structure−activity relationship study of these classes of carbocyclic

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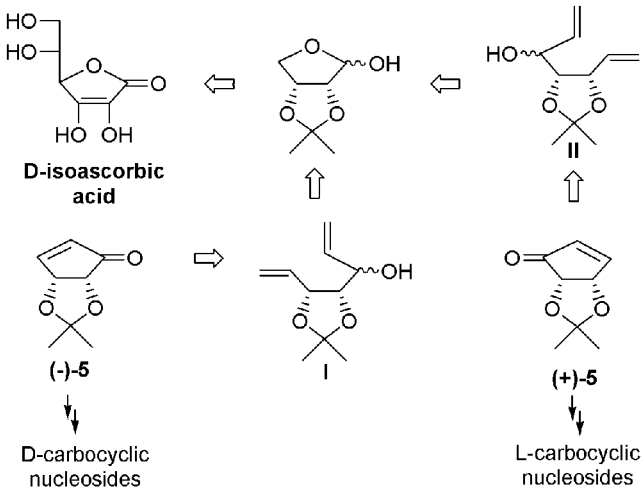
Scheme 1



nucleosides as well as for the synthesis of compounds **1**−**4**. Therefore, it was of great interest to develop new and efficient methodology for the common intermediate (−)-**5**. In addition, an efficient synthesis of its enantiomer, (+)-**5**,[13] is also highly required for the synthesis of L-carbocyclic nucleosides. In this paper, we wish to report syntheses of D- and L-cyclopentenone derivatives (−)-**5** and (+)-**5** through the ring-closing metathesis (RCM)[14,15] reaction using Grubbs catalyst as a key step starting from the cheap and commercially available D-isoascorbic acid. Compounds (−)-**5** and (+)-**5** represent versatile synthons for the syntheses of D- and L-carbocyclic nucleosides, respectively.

Results and Discussion

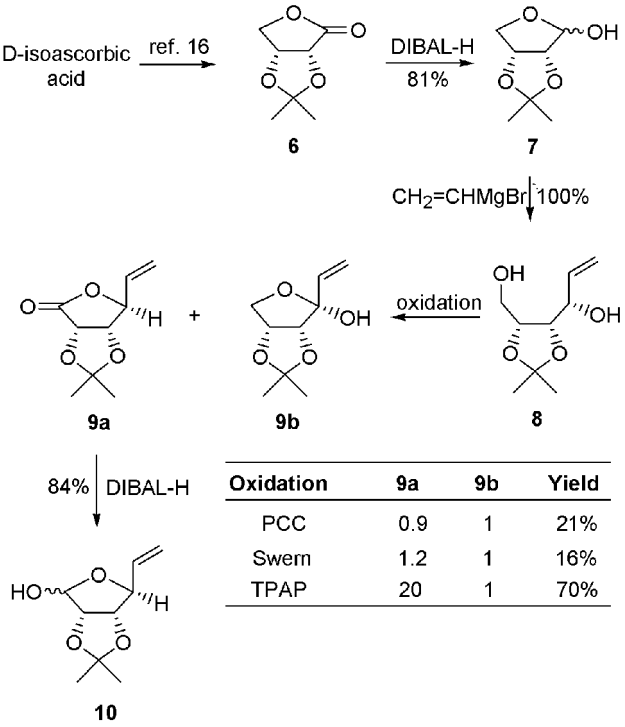
As shown in Scheme 1, retrosynthetic analysis shows that the target intermediates, (−)-**5** and (+)-**5**, can be synthesized via dienes **I** and **II**, respectively.

The key intermediates **I** and **II** can be derived from the lactol, which is easily obtained from the cheap and commercially available D-isoascorbic acid.

For the synthesis of D-cyclopentenone, (−)-**5**, D-isoascorbic acid was converted to the lactol **10** as illustrated in Scheme 2.

D-Isoascorbic acid was converted to the commercially available lactone **6** according to the known procedure.[16] Reduction of **6** with DIBALH at −78 °C to room temperature for 2 h gave the lactol **7** in 81% yield. Ring opening of **7** with vinylmagnesium bromide at −78 to 0 °C gave the diol **8** as a single stereoisomer in quantitative yield. Selective oxidation of the primary alcohol over allylic alcohol in **8** was greatly affected by oxidizing agents used. Oxidation with pyridinium chlorochromate (PCC) as an oxidizing agent yielded a mixture of the desired **9a** and undesired **9b** in 0.9 to 1 ratio in 21% yield. Oxidation

Scheme 2



Oxidation	9a	9b	Yield
PCC	0.9	1	21%
Swern	1.2	1	16%
TPAP	20	1	70%

under Swern conditions also gave a mixture of **9a** and **9b** (1.2:1 ratio) in very poor yield. However, oxidation with tetrapropylammonium perruthenate (TPAP)[17] and *N*-methylmorpholine *N*-oxide (NMO) afforded the desired lactone **9a** over **9b** in 20 to 1 ratio after isolation by silica gel column chromatography. During TPAP oxidation, an inseparable mixture of lactone **9a** and lactol **10** was obtained depending on reaction time and amounts of oxidizing agents. Short reaction time always gave an inseparable mixture of **9a** and **10** with unreacted starting material, while longer reaction time (15 h) and use of excess oxidizing agents resulted in the sole formation of lactone **9a** in 67% yield. Reduction of **9a** with DIBALH in toluene gave a lactol **10**, which is ready for Wittig reaction.

As illustrated in Scheme 3, Wittig reaction of **10** with methyl triphenylphosphonium bromide was greatly affected by bases used in view of yield and epimerization. Use of *n*-BuLi gave the desired diene **11a** almost exclusively in 40% yield, while use of bulky LDA afforded **11a** as a sole product, but the yield was only 50% even after recovery of starting materials. To improve the yield, we used another bulky base, KO-*t*-Bu, but the yield was low (42% yield after recovering starting materials) and extensive epimerization occurred, giving the desired diene **11a** and its epimer **11b** in a 1:1 ratio. However, use of DMSO anion as a base only produced the desired diene **11a** in 88% yield without forming its epimerized product **11b**.

Ring-closure metathesis (RCM) of **11a** with Grubbs catalyst[14] smoothly proceeded to give cyclopentenol **12** as a single stereoisomer. However, the epimer **11b** was remained intact under the RCM conditions. Oxidation of allylic alcohol **12** with activated MnO_2 afforded the key intermediate (−)-**5**, which serves as a versatile intermediate for the synthesis of D-carbocyclic nucleosides. To

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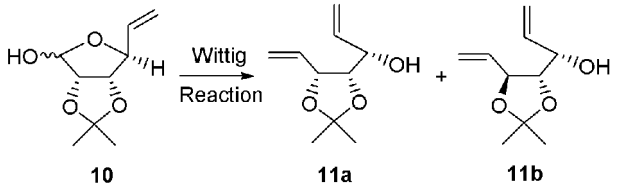
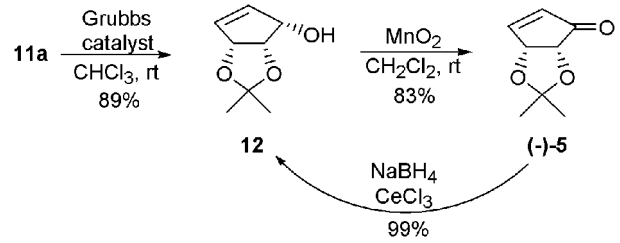
Scheme 3

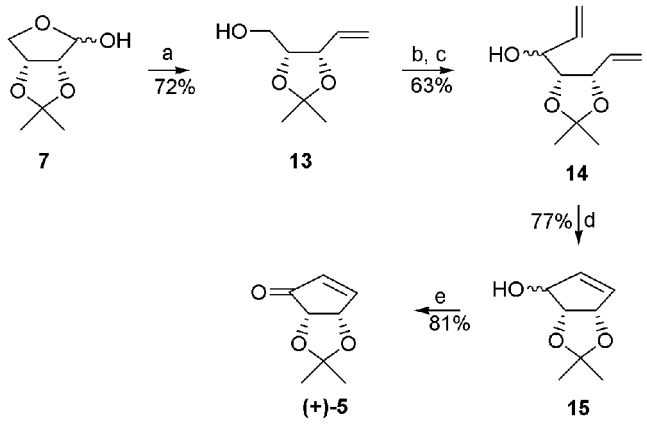


base	11a:11b	yield
n-BuLi	99:1	40%
LDA	100:0	50%[a]
KO^{t}Bu	1:1	42%[a]
DMSO anion	100:0	88%

[a] *based on the recovered starting materials*



Scheme 4



[a] Reagents and conditions: (a) Ph_3PCH_3Br, NaH, DMSO, THF, rt, overnight; (b) Swern oxidation; (c) CH_2=$CHMgBr$, THF, −78 °C, 1 h; (d) Grubbs catalyst, $CHCl_3$, rt, 2 h; (e) MnO_2, CH_2Cl_2, rt, 15 h.

confirm the stereochemistry of the hydroxyl group of **12**, (−)-**5** was reduced with sodium borohydride and cerium chloride to give the same cyclopentenol **12**, indicating ring opening of **7** with vinylmagnesium bromide to give **8** was totally proceeded stereospecifically.

For the synthesis of another key intermediate, (+)-**5**, compound **7** was treated with methyl triphenylphosphonium bromide and DMSO anion to give ring-opened product **13** in 72% yield (Scheme 4). Oxidation of the primary alcohol with PCC followed by the treatment of the resulting aldehyde with vinylmagnesium bromide yielded the diene **14** as an inseparable diastereomeric mixture (α/β = 1/2) in 40% yield, but the production (63%) of **14** was greatly increased by the use of Swern oxidation instead of PCC oxidation. RCM of **14** with Grubbs catalyst[14] gave the cyclopentenol **15**, which was oxidized with MnO_2 to furnish the key intermediate, (+)-**5**, which is a versatile synthon for the synthesis of L-carbocyclic nucleosides. The physical and spectroscopic data of the synthesized (−)-**5** and (+)-**5**, including optical rotations, were identical to those of the authentic samples,[12,13] respectively.

Conclusions

We developed a new synthetic methodology to the key intermediates (−)-**5** and (+)-**5** using ring-closing metathesis (RCM) reaction as a key step starting from the cheap and commercially available D-isoascorbic acid. These intermediates represent convenient synthons for the synthesis of D- and L-carbocyclic nucleosides, respectively. Finally, our procedure highlights mild reaction conditions, no epimerization, no enzymatic resolution, and improved overall yields when compared to the previously published procedures.[12,13]

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured in $CDCl_3$, and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Elemental analyses were performed at the general instrument laboratory of Ewha Womans University, Korea. TLC was performed on Merck precoated $60F_{254}$ plates. Column chromatography was performed using silica gel 60 (230−400 mesh, Merck). All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone immediately prior to use.

(4*R*,5*R*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (7). To a cooled (−78 °C) solution of lactone **6** (4.5 g, 28.45 mmol) in dry toluene (93 mL) was added dropwise diisobutylaluminum hydride (1.0 M solution in toluene, 31.3 mL, 31.3 mmol), and the reaction mixture was stirred at − 78 °C for 1 h and allowed to stir at room temperature for 30 min. The reaction mixture was cooled to 0 °C and diluted with methanol (31.3 mL) and 50% ethyl acetate/hexanes. The mixture was warmed to room temperature and stirred for 2 h, and the white precipitate was removed by filtration through a pad of Celite and washed with ethyl acetate. The filtrates were concentrated in vacuo and purified by silica gel column chromatography (hexanes/ethyl acetate = 2:1) to give **7** (3.68 g, 81%) as a white crystal: ^{1}H NMR ($CDCl_3$) δ 5.43 (d, J = 2.0 Hz, 1 H), 4.85 (dd, J = 4.0, 5.6 Hz, 1 H), 4.59 (d, J = 5.6 Hz, 1 H), 4.10−4.02 (m, 2 H), 2.55 (br s, 1 H), 1.48 (s, 3 H), 1.33 (s, 3 H). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.48; H, 7.54.

(4*S*,5*R*)-1-(5-Hydroxymethyl-2,2-dimethyl[1,3]dioxolan-4-yl)-(*S*)-propenol (8). To a cooled solution of **7** (3.68 g, 22.97 mmol) in dry tetrahydrofuran (46 mL) was added vinylmagnesium bromide (1 M solution in tetrahydrofuran, 68.9 mL, 68.9 mmol) at −78 °C. After the addition was completed, the mixture was stirred at −78 °C for 1 h and allowed to stir at 0 °C for 1 h. The reaction mixture was quenched by saturated ammonium chloride solution and brine. The mixture was extracted with ethyl acetate, and the extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The resulting oil was purified by silica gel column chromatography (hexanes/ethyl acetate = 2:1) to afford **8** (4.32 g, 100%) as a single stereoisomer: $[\alpha]_D$ −42.2° (*c* 1.83, $CHCl_3$); IR (neat) 3370, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.03 (m, 1 H), 5.36 (m, 2 H), 4.34 (m, 2 H), 4.06 (dd, J = 6.4, 8.8 Hz, 1 H), 3.87 (m, 2 H), 2.73 (m, 2 H), 1.45 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.68, 116.98, 108.74, 79.75, 77.47, 70.87, 60.94, 27.92, 25.44. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.45; H, 8.59.

(1*S*,2*R*,3*S*)-2,2-Dimethyl-6-vinyldihydrofuro[3,4-*d*][1,3]-dioxol-4-one (9a) and Its Regioisomer 9b. To a stirred solution of **8** (2.207 g, 11.73 mmol) in dry methylene chloride (23 mL) were added 4 Å molecular sieves (5.86 g, 0.5 g/mmol), 4-methylmorpholine *N*-oxide (4.12 g, 35.19 mmol), and tetrapropylammonium perruthenate (206 mg, 0.587 mmol) at 0 °C, and the reaction mixture was stirred overnight at room temperature and then diluted with methylene chloride. The result-

ing suspension was filtered through a short pad packed with Celite and silica gel and repeatedly washed with methylene chloride. The filtrates were concentrated, and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 8:1) to give **9a** (1.421 g, 66%) and **9b** (72.7 mg, 3.3%).

Compound **9a**: $[\alpha]_D$ +42.9° (*c* 2.38, $CHCl_3$); IR (neat) 2993, 1792 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.87 (m, 1 H), 5.39 (m, 2 H), 5.06 (m, 1 H), 4.74 (d, *J* = 5.6 Hz, 1 H), 4.62 (d, *J* = 5.6 Hz, 1 H), 1.50 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.05, 132.78, 118.59, 114.31, 81.89, 79.51, 74.41, 27.00, 25.91. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.67; H, 6.59. Compound **9b**: ^1H NMR ($CDCl_3$) δ 6.11 (dd, *J* = 10.8, 17.6 Hz, 1 H), 5.59 (dd, *J* = 1.6, 17.6 Hz, 1 H), 5.39 (dd, *J* = 1.6, 10.8 Hz, 1 H), 4.91 (dd, *J* = 3.6, 6.0 Hz, 1 H), 4.47 (d, *J* = 5.2 Hz, 1 H), 4.11−4.01 (m, 2 H), 1.48 (s, 3 H), 1.32 (s, 3 H). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 59.08; H, 6.76.

(1*S*,2*R*,3*S*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-ol (10). To a stirred solution of **9a** (2.35 g, 12.76 mmol) in dry toluene (49 mL) was added diisobutylaluminum hydride (1.0 M solution in toluene, 15.3 mL, 15.3 mmol) dropwise at −78 °C. After the addition was completed, the reaction mixture was allowed to warm to −20 °C, stirred for 2 h, and diluted with methanol (15.3 mL) and 50% ethyl acetate/hexanes. After the mixture was warmed to room temperature and stirred for 2 h, the white precipitate was removed by filtration through a pad of Celite and washed with ethyl acetate. The filtrates were concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4:1) to give **10** (1.99 g, 84%): ^1H NMR ($CDCl_3$) δ 6.01 (m, 0.8 H), 5.79 (m, 0.2 H), 5.50 (d, *J* = 2.8 Hz, 0.8 H), 5.43−5.16 (m, 2.2 H), 4.70−4.56 (m, 3 H), 3.93 (d, *J* = 10.4 Hz, 0.2 H), 2.66 (d, *J* = 2.8 Hz, 0.8 H), 1.59 (s, 0.6 H), 1.51 (s, 2.4 H), 1.39 (s, 0.6 H), 1.33 (s, 2.4 H). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.47; H, 7.89.

(1*S*,2*S*,3*R*)-(−)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-prop-2-en-1-ol (11) and Its Epimer 11b. To a suspension of sodium hydride (518 mg, 12.96 mmol, 60% dispersion in mineral oil) in tetrahydrofuran (10 mL) was added dimethyl sulfoxide (1.64 mL, 23.15 mmol) at 0 °C, and the mixture was stirred for 30 min at room temperature. To this mixture was added a suspension of methyltriphenylphosphonium bromide (4.96 g, 13.89 mmol) in tetrahydrofuran (20 mL) at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. To this reaction mixture was added a solution of **10** (862 mg, 4.63 mmol) in tetrahydrofuran (16 mL) at 0 °C, and the reaction mixture was refluxed overnight. Diethyl ether was added to the mixture, and a white solid was precipitated out. The mixture was filtered through a short silica gel pad, washed with diethyl ether, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 8:1) to give **11** (742 mg, 88%) as a colorless oil.

Compound **11a**: MS (FAB) *m*/*z* 185 ($M + H^+$); $[\alpha]_D$ −50.6° (*c* 3.15, $CHCl_3$); IR (neat) 3449, 2989, 1219 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (m, 2 H), 5.36 (m, 4 H), 4.70 (t, *J* = 6.8 Hz, 1 H), 4.19 (m, 1 H), 4.04 (dd, *J* = 6.8, 7.6 Hz, 1 H), 1.79 (d, *J* = 4.4 Hz, 1 H), 1.50 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.89, 134.24, 118.47, 116.63, 109.06, 80.72 78.88, 71.20, 27.80, 25.46. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.34; H, 8.43. Compound **11b**: MS (FAB) *m*/*z* 185 ($M + H^+$); ^1H NMR ($CDCl_3$) δ 5.84 (m, 2 H), 5.38 (m, 2 H), 5.24 (m, 2 H), 4.40 (m, 2 H), 3.83 (dd, *J* = 4.0, 8.4 Hz, 1 H), 2.21 (d, *J* = 3.6 Hz, 1 H), 1.46 (s, 3 H), 1.44 (s, 3 H). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.56; H, 8.35.

(1*S*,4*R*,5*S*)-4,5-*O*-Isopropylidenecyclopenten-1-ol (12). A round-bottomed flask charged with the Grubbs catalyst (49.7 mg, 0.060 mmol) was pumped and filled with nitrogen gas three times before the addition of a solution of **11** (556 mg, 3.02 mmol) in degassed chloroform (15 mL). The resulting pink solution was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the dark residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4:1) to give **12** (421 mg, 89%) as a single isomer: MS (FAB) *m*/*z* 157 ($M + H^+$); $[\alpha]_D$ +15.4° (*c* 2.36, $CHCl_3$); IR (neat) 3489, 2989, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.89 (s, 2 H), 5.02 (d, *J* = 5.2 Hz, 1 H), 4.75 (t, *J* = 5.2 Hz, 1 H), 4.56 (dd, *J* = 5.2, 10.0 Hz, 1 H), 2.72 (d, *J* = 10.0 Hz, 1 H), 1.44 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.63, 132.13, 112.55, 83.81, 77.37, 74.38, 27.85, 26.78. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.52; H, 7.75.

(4*R*,5*R*)-4,5-*O*-Isopropylidene-2-cyclopentenone [(−)-5]. To a stirred solution of **12** (636 mg, 4.08 mmol) in methylene chloride (20 mL) was added activated manganese oxide (3.55 g, 40.8 mmol), and the mixture was vigorously stirred for 5 h at room temperature. The resultant mixture was filtered through a pad of Celite, washed with methylene chloride. The filtrates were concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4:1) to afford (−)-**5** (520 mg, 83%) as a white crystal: mp 68.6−70.1 °C; MS (FAB) *m*/*z* 155 ($M + H^+$); $[\alpha]_D$ −70.4° [lit.[13c] $[\alpha]_D$ −70.8° (*c* 0.92, $CHCl_3$)]; IR (neat) 2935, 1718, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (dd, *J* = 2.4, 6.0 Hz, 1 H), 6.22 (d, *J* = 6.0 Hz, 1 H), 5.277 (dd, *J* = 2.4, 5.6 Hz, 1 H), 4.47 (d, *J* = 5.6 Hz, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.17, 159.82, 134.50, 115.70, 78.78, 76.69, 27.60, 26.33. Anal. Calcd for $C_{10}H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.56; H, 6.35.

(4*R*,5*S*)-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)methanol (13). To a suspension of sodium hydride (628 mg, 15.68 mmol, 60% dispersion in mineral oil) in tetrahydrofuran (10 mL) was added dimethyl sulfoxide (2.0 mL, 28.0 mmol) at 0 °C. After being stirred for 30 min at room temperature, the mixture was transferred to a suspension of methyltriphenylphosphonium bromide (6.00 g, 16.8 mmol) in tetrahydrofuran (35 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. To this reaction mixture was added a solution of **6** (897 mg, 5.60 mmol) in tetrahydrofuran (11 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. Diethyl ether was added to the mixture, and a white solid precipitated out. The mixture was filtered through a short silica gel pad, washed with diethyl ether, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 8:1) to give alcohol **13** (661 mg, 75%) as a colorless oil: $[\alpha]_D$ +38.0° (*c* 1.49, $CHCl_3$); IR (neat) 3464, 2989, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (m, 1 H), 5.35 (m, 2 H), 4.66 (t, *J* = 7.2 Hz, 1 H), 4.27 (q, *J* = 6.4 Hz, 1 H), 3.59 (dd, *J* = 5.2, 6.4 Hz, 1 H), 1.88 (t, *J* = 5.2 Hz, 1 H), 1.52 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 133.21, 119.11, 109.07, 78.50, 78.47, 62.22, 27.97, 25.41. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.90; H, 8.65.

(4*R*,5*S*)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)prop-2-en-1-ol (14). To a stirred solution of oxalyl chloride (0.25 mL, 2.88 mmol) in dry methylene chloride (10 mL) was added dimethyl sulfoxide (0.40 mL, 5.76 mmol) at −78 °C, and the mixture was stirred at −78 °C for 15 min. To this mixture was added a solution of **13** (228 mg, 1.44 mmol) in methylene chloride (4.5 mL), and the reaction mixture was stirred at −78 °C for 1 h. After the addition of triethylamine (1.20 mL, 8.64 mmol), the mixture was gradually warmed to room temperature. The reaction mixture was quenched with water and then extracted with methylene chloride twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness to give the aldehyde, which was used in the next step without further purification. To a stirred solution of crude aldehyde in tetrahydrofuran (11 mL) was added vinylmagnesium bromide (1 M solution in tetrahydrofuran, 2.90 mL, 2.90 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. After the mixture was allowed to warm to room temperature, the mixture was quenched with saturated ammonium chloride solution and brine, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered, concentrated to dryness. The resulting oil was purified by silica gel column chromatography (hexanes/ethyl acetate = 7:1) to give **14** (167 mg, 63%) as an inseparable mixture: MS (FAB) *m*/*z* 185 ($M + H^+$); ^1H NMR ($CDCl_3$) δ 6.05 (m, 1.34 H), 5.86 (m, 0.66 H), 5.35 (m, 4 H), 4.70 (t, *J* = 6.8 Hz, 0.33 H), 4.61 (dd, *J* = 6.8, 7.6 Hz, 0.67 H), 4.11 (m, 2 H), 2.33 (d, *J* = 5.6 Hz, 0.67 H), 1.84 (d, *J* = 4.4 Hz, 0.33 H), 1.54 (s, 2 H), 1.50 (s, 1 H), 1.40 (s, 2 H), 1.38 (s, 1 H). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.88; H, 8.94.

(4*S*,5*R*)-4,5-*O*-Isopropylidenecyclopenten-1-ol (15). A round-bottomed flask charged with the Grubbs catalyst (12.5 mg, 0.015 mmol) was pumped and filled with nitrogen gas three times before the addition of a solution of **14** (560 mg, 3.04 mmol) in degassed chloroform (30.4 mL) and the resulting pink solution was stirred at room temperature for 4 h. The solvent was

removed in vacuo and the dark residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4:1) to give α-alcohol (122.0 mg, 25.7%) and *β*-alcohol (243.6 mg, 51.3%) of **15**.

α-Alcohol of **15**: MS (FAB) *m*/*z* 157 ($M + H^+$);^{1}H NMR ($CDCl_3$) *δ* 5.89 (s, 2 H), 5.02 (d, *J* = 5.2 Hz, 1 H), 4.75 (t, *J* = 5.2 Hz, 1 H), 4.56 (dd, *J* = 5.2, 10.0 Hz, 1 H), 2.72 (d, *J* = 10.0 Hz, 1 H), 1.44 (s, 3 H), 1.40 (s, 3 H). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.65; H, 7.43.

β-Alcohol of **15**: MS (FAB) *m*/*z* 157 ($M + H^+$); IR (neat) 3399, 2989, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 6.03 (bd, *J* = 5.6 Hz, 1 H), 5.91 (dt, *J* = 1.0, 6.0 Hz, 1H), 5.29 (m, 1 H), 4.80 (bd, *J* = 4.4 Hz, 1 H), 4.52 (d, *J* = 5.6 Hz, 1 H), 1.96 (br s, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) *δ* 135.88, 134.81, 111.93, 86.12, 84.47, 81.23, 27.53, 25.93. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 60.96; H, 7.86.

(4*S*,5*S*)-4,5-*O*-Isopropylidene-2-cyclopentenone [(+)-5]. To a stirred solution of **15** (455 mg, 2.9 mmol) in methylene chloride (30 mL) was added activated manganese oxide (2.52 g, 29.0 mmol), and the mixture was vigorously stirred at room temperature overnight. The mixture was filtered through a pad of Celite and washed with methylene chloride. The filtrates were concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4:1) to afford (+)-**5** (365.0 mg, 81%) as a white crystal: mp 68.7−69.8 °C (lit.[13b] mp 68−69 °C); MS (FAB) *m*/*z* 155 ($M + H^+$); $[\alpha]_D$ +69.1° (*c* 1.98, $CHCl_3$) [lit.[13b] $[\alpha]_D$ +70.0° (*c* 0.92, $CHCl_3$)]; IR (neat) 2936, 1719, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 7.62 (dd, *J* = 2.4, 6.0 Hz, 1 H), 6.22 (d, *J* = 6.0 Hz, 1 H), 5.28 (dd, *J* = 2.4, 5.6 Hz, 1 H), 4.47 (d, *J* = 5.6 Hz, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) *δ* 203.17, 159.83, 134.49, 115.69, 78.78, 76.69, 27.59, 26.33. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.34; H, 6.54.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **11a**, **12**, **14**, and **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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