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Improved and alternative synthesis of D- and L-cyclopentenone derivatives, the versatile intermediates for the synthesis of carbocyclic nucleosides

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Abstract—Improved and alternative syntheses of D- and L-cyclopentenone derivatives were achieved in six steps from D-ribose via ring-closing metathesis (RCM) reaction as a key step. These derivatives serve as very versatile intermediates for the synthesis of carbocyclic nucleosides.

1. Introduction

Abacavir is the first D-carbocyclic nucleoside which has been approved by the Food and Drug Administration (FDA) for the treatment of AIDS and AIDS-related complex (ARC).[1] Since the discovery of abacavir, extensive efforts on carbocyclic nucleosides like neplanocin A and aristeromycin have been made with a view to the development of new antiviral and antitumor agents (Fig. 1).[2]

However, synthetic difficulties[2] such as low overall and inconsistent yields, lengthy steps, and lack of large scale preparations in obtaining the key carbocyclic intermediates have limited further development of the carbocyclic nucleosides. Hence, there is high demand for an efficient and expeditious synthetic procedure.

Discovery of L-1,3-oxathiolanyl cytosine (3TC, lamivudine)[3] as a potent anti-hepatitis B virus (HBV) and anti-human immunodeficiency virus (HIV) agent has opened a new area in developing antiviral and antitumor nucleosides. Most D-nucleosides suffer from the lactic acidosis caused by mitochondrial DNA toxicity,[4] but, remarkably, L-nucleosides lack mitochondrial DNA toxicity, while maintaining their antiviral activity. Based on this reduced cytotoxicity of L-nucleosides, worldwide efforts have been made for the development of new antiviral L-nucleosides. One of the compounds belonging to this family, L-2′-deoxy-2′-fluoroarabinofuranosylthymine (L-FMAU)[5] is the subject of clinical trials for the treatment of HBV-infected patients. Thus, there is also demand for the development of an efficient synthesis of L-carbocycles for a thorough structure–activity relationship (SAR) study of L-carbocyclic nucleosides.

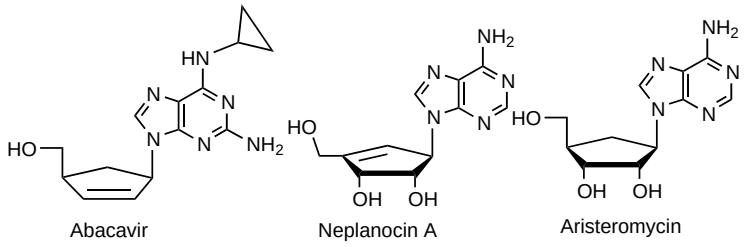

Figure 1. Structures of biologically active carbocyclic nucleosides.

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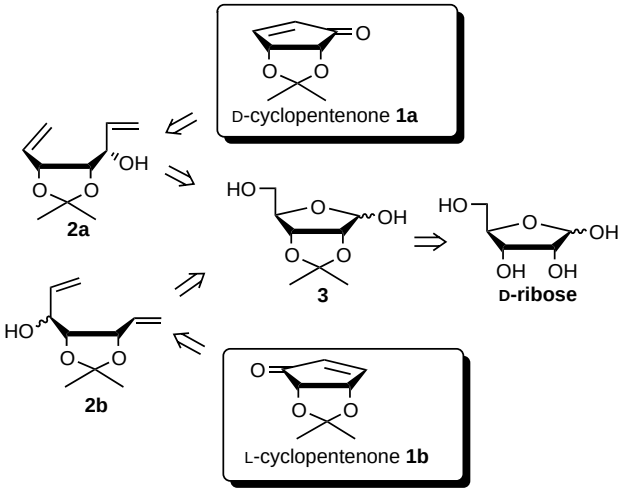
Recently, our laboratory has published short and efficient syntheses of D- and L-cyclopentenone derivatives which can serve as versatile intermediates for the synthesis of D- and L-carbocyclic nucleosides using ring-closing metathesis (RCM) reaction as a key step.[6] However, in these syntheses, several steps such as selective oxidation and reduction turned out to be major drawbacks for large scale synthesis. This prompted us to improve the overall yields and to reduce the number of steps in the alternative synthesis. Herein, we wish to report the improved syntheses of D- and L-cyclopent-2-enone, starting from D-ribose in six steps.

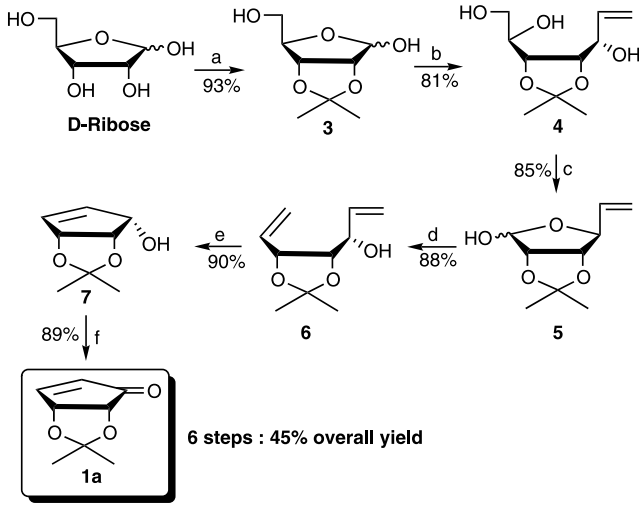
2. Results and discussion

Retrosynthetic analysis shows that the key intermediates, **1a** and **1b** can be derived from the dienes, **2a** and **2b** using RCM reaction (Scheme 1).

Dienes **2a** and **2b** can be obtained from the common intermediate, 2,3-isopropylidene-D-ribose **3**[7] through Wittig reaction, Grignard reaction and oxidative cleavage.



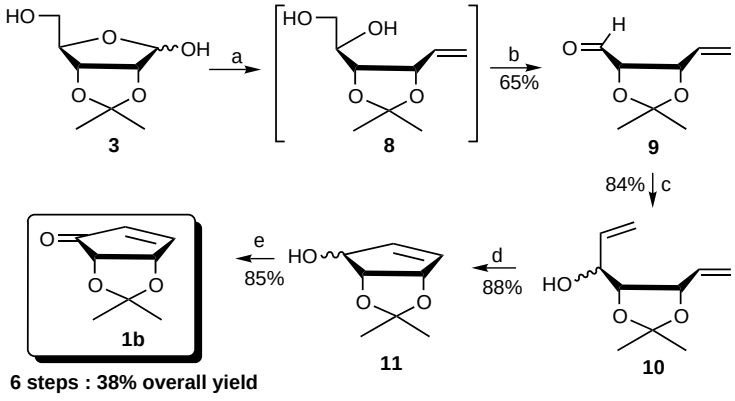
Scheme 1. Retrosynthetic analysis of D- and L-cyclopentenones, **1a** and **1b**.



Scheme 2. *Reagents and conditions*: (a) acetone, *c*-H_2SO_4, rt, 2.5 h; (b) vinylmagnesium bromide, THF, −78 to 0°C, 3 h; (c) $NaIO_4$, CH_2Cl_2, H_2O, 0°C to rt, 40 min; (d) NaH, DMSO, CH_3PPh_3Br, THF, 0°C to reflux, overnight; (e) Grubbs catalyst, $CHCl_3$, rt, 3 h; (f) MnO_2, CH_2Cl_2, rt, 6 h.

Synthesis of D-cyclopentenone derivative **1a** is shown in Scheme 2. D-Ribose was protected as the 2,3-acetonide **3**[7] (93%) which was treated with vinylmagnesium bromide to give triol **4**[8] (81%). Oxidative cleavage of triol **4** with sodium metaperiodate gave the lactol **5**[8c] in 85% yield. Wittig reaction of **5** with triphenylphosphonium methylidene produced the diene **6** in 88% yield. Ring-closing metathesis of diene **6** using Grubbs' catalyst[9] gave the allylic alcohol **7** (90%), which was converted to the D-cyclopentenone **1a** in 89% yield. We synthesized the D-cyclopentenone **1a**[6] in 45% overall yield and six steps from D-ribose, which is much more improved in view of overall yield and the number of steps, compared to our previously reported procedure.[6]

L-Cyclopentenone derivative **1b** was also synthesized, starting from 2,3-isopropylidene-D-ribose, **3** (Scheme 3). Wittig reaction of **3** with triphenylphosphonium methylidene followed by oxidative cleavage of the resulting diol **8**[10] with sodium metaperiodate afforded the vinyl



Scheme 3. *Reagents and conditions*: (a) CH_3PPh_3Br, *t*-BuOK, THF, overnight; (b) $NaIO_4$, CH_2Cl_2, H_2O, rt, 30 min; (c) vinylmagnesium bromide, THF, −78°C, 1 h; (d) Grubbs catalyst, $CHCl_3$, rt, 6 h, (e) MnO_2, CH_2Cl_2, rt, overnight.

aldehyde **9**[10a,11] in 65% yield (two steps). Treatment of **9** with vinylmagnesium bromide gave the diene **10** (84%), which was subjected to RCM reaction to give L-cyclopentenol **11** in 88% yield. Finally, L-cyclopentenol **11** was oxidized to L-cyclopentenone **1b**,[6] which was obtained in 38% overall yield and six steps from D-ribose. This procedure turned out to be much improved in view of overall yield and the number of steps compared to our previously reported procedure.[6]

3. Conclusion

In summary, we have developed new and efficient procedure to D- and L-cyclopent-2-enone, starting from D-ribose using RCM reaction as a key step. This procedure proved to be good for large-scale synthesis (>10 g) of the versatile intermediates, **1a** and **1b**, which can be extensively utilized for the structure–activity relationship study of the carbocyclic nucleosides.

4. Experimental

Unless otherwise noted, all commercially available reagents were purchased from Aldrich Chemical Co. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured in $CDCl_3$ and MeOH-d_4 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 from CaH_2 or P_2O_5 or Na/benzophenone immediately prior to use.

4.1. 2,3-*O*-Isopropylidene-D-ribose, 3

To a stirred suspension of D-ribose (80 g, 532.9 mmol) in acetone (1000 mL) was added dropwise conc. H_2SO_4 (2.4 mL) at room temperature and the reaction mixture was stirred at room temperature for 2.5 h. The mixture was neutralized with solid $NaHCO_3$, filtered and evaporated under reduced pressure to give a colorless syrup. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (1:2) as the eluent to afford **3** as a colorless syrup (94.2 g, 93%): ^{1}H NMR (MeOH-d_4), δ ppm, J Hz: 1.31 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.59 (dd, 1H, J=5.6, 12.0, HOC*H*H), 3.63 (dd, 1H, J=4.8, 12.0, HOCH*H*), 4.19 (irregular t, 1H, J=4.4, 5.2, 4-H), 4.52 (d, 1H, J=6.0, 3-H), 4.77 (d, 1H, J=6.0, 2-H), 5.26 (s, 1H, anomeric H). Anal. calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.48; H, 7.36; $[\alpha]_D^{25}$ −36.2 (*c* 1.45, acetone) [lit.,[7] $[\alpha]_D^{25}$ −37 (*c* 0.53, acetone)].

4.2. 1-[(4*R*,5*S*)-5-((1*S*)-1-Hydroxyallyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]ethane-1,2-diol, 4

To a stirred solution of **3** (20.36 g, 107.1 mmol) in THF (800 mL) was added dropwise vinylmagnesium bromide (480.0 mL, 480.0 mmol, 1.0 M solution in THF) at −78°C and the reaction mixture was stirred at 0°C for 3 h. After adding water (160 mL) at 0°C, the resulting precipitate was removed through a pad of Celite. The filtrate was extracted with ethyl acetate (500 mL), dried, filtered, and evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography using hexane and ethyl acetate (1:2.5) as the eluent to afford **4** as a white solid (18.98 g, 81%): mp: 73–74°C; $[\alpha]_D^{25}$ −30.5 (*c* 1.23, $CHCl_3$) [lit.,[8] mp: 74°C; $[\alpha]_D^{25}$ −31 (*c* 1.8, $CHCl_3$)]; ^{1}H NMR (MeOH-d_4), δ ppm, J Hz: 1.28 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.59 (dd, 1H, J=6.0, 11.2, HOC*H*H), 3.77 (dd, 1H, J=2.4, 11.2, HOCH*H*), 3.84 (m, 1H, $HOCH_2CH$(OH)-), 3.96 (dd. 1H, J=5.2, 9.6, 5-H), 4.11 (dd, 1H, J=5.6, 9.6, 4-H), 4.24 (m, 1H, CH_2=CHC*H*(OH)-), 5.17 (td, 1H, J=1.6, 10.8, C*H*H=CH-), 5.31 (td, 1H, J=1.6, 17.2, CH*H*=CH-), 5.97 (m, 1H, CH_2=C*H*-). Anal. calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.97; H, 8.44%.

4.3. (3a*S*,4*R*,6*S*,6a*S*)- and (3a*S*,4*S*,6*S*,6a*S*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol, 5

To a stirred solution of **4** (19.25 g, 88.2 mmol) in methylene chloride (330 mL) was added dropwise an aqueous solution of $NaIO_4$ (204.0 mL, 132.4 mmol, 0.65 M solution) at 0°C and the reaction mixture was stirred at room temperature for 40 min. After water (210 mL) was added, the mixture was extracted with methylene chloride (600 mL), dried, filtered, and evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography using hexane and ethyl acetate (2:1) as the eluent to give **5** as a colorless oil (14.00 g, 85%). All spectral data were identical to those of the authentic sample.[6,8c]

4.4. (1*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)prop-2-en-1-ol, 6

Compound **5** (16.40 g, 88.10 mmol) was converted to **6** (14.31 g, 88%) according to the reported procedure.[6]

4.5. (3a*S*,4*S*,6*R*)-2,2-Dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol, 7

Compound **6** (15.00 g, 81.42 mmol) was converted to **7** (11.43 g, 90%) according to the reported procedure.[6]

4.6. (3a*R*,6a*R*)-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one, 1a

Compound **7** (14.38 g, 92.1 mmol) was converted to **1a** (12.64 g, 89%) according to the reported procedure.[6]

4.7. (1*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)ethane-1,2-diol, 8[10]

To a stirred suspension of methyl triphenylphosphonium bromide (135.00 g, 377.9 mmol) in THF (1.7 L) was added potassium *t*-butoxide (51.00 g, 417.3 mmol, purity of reagent: 95%) at 0°C. The reaction mixture was stirred at 0°C for 20 min and then at room

temperature for 1 h. After the mixture was allowed to cool to 0°C, a solution of **3** (25.20 g, 132.5 mmol) in THF (300 mL) was added and the mixture was stirred at room temperature overnight. To this mixture was carefully added water (200 mL) and the mixture was extracted with ethyl acetate (4 L), dried, filtered and evaporated under reduced pressure to give a yellow syrup. This syrup was purified by silica gel column chromatography using hexane and ethyl acetate (1:2–1:2.5) as the eluent to give **8** (35 g) with the contamination of triphenylphosphine oxide, which was used for next reaction without further purification: ^{1}H NMR ($CDCl_3$), δ ppm, J Hz: 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.88 (br. s, 2H, 2*OH), 3.68–3.83 (m, 3H, HOC*H*$_2$C*H*(OH)-), 4.09 (dd, 1H, J=6.4, 8.4, 4-H), 4.69 (br. t, 1H, J=6.4, CH_2=CH-C*H*-), 5.32 (td, 1H, J=1.2, 10.4, C*H*H=CH-), 5.45 (td, 1H, J=1.6, 17.6, CH*H*=CH-), 5.99 (ddd, 1H, J=6.8, 10.4, 17.6, CH_2=CH-). Anal. calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.54; H, 8.68%.

4.8. (4*S*,5*S*)-2,2-Dimethyl-5-vinyl[1,3]dioxolane-4-carbaldehyde, 9[10a,11]

To a solution of crude **8** (35 g) in methylene chloride (600 mL) was added aqueous $NaIO_4$ (305.0 mL, 198.3 mmol, 0.65 M solution) at room temperature and the reaction mixture was stirred at room temperature for 30 min. After methylene chloride (500 mL) and water (500 mL) were added, the organic layer was filtered, dried and carefully evaporated under reduced pressure at bellow 5°C until the volume of the mixture was approx. 30 mL. The solution was purified by short column silica gel chromatography using diethyl ether as the eluent to give **9** as a colorless oil (13.51 g, 65% from **3**). Note: ether should be evaporated carefully under a little reduced pressure at bellow 5°C because of the volatility of **9**; ^{1}H NMR ($CDCl_3$), δ ppm, J Hz: 1.42 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 4.39 (dd, 1H, J=3.2, 7.2, 4-H), 4.83 (irregular t, 1H, J=6.8, 7.6, CH_2=CHC*H*-), 5.30 (td, 1H, J=1.2, 10.4, C*H*H=CH-), 5.44 (td, 1H, J=1.2, 16.0, CH*H*=CH-), 5.73 (ddd, 1H, J=6.8, 10.4, 17.2, CH_2=C*H*-), 9.53 (d, 1H, J=3.2, C(O)H). Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.55; H, 7.59%; $[\alpha]_D^{25}$ +3.3 (*c* 1.33, $CHCl_3$).

4.9. (1*R*,4*R*,5*S*)- and (1*S*,4*R*,5*S*)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)prop-2-en-1-ol, 10

Compound **9** (26.49 g, 169.6 mmol) was converted to **10** (26.25 g, 84%) according to the reported procedure.[6]

4.10. (3a*R*,4*R*,6*S*)-2,2-Dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol, 11

Compound **10** (22.50 g, 122.1 mmol) was converted to **11** (α: 5.53 g, 29%, β: 11.34 g, 59%) according to the reported procedure.[6]

4.11. (3a*S*,6a*S*)-2,2-Dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one, 1b

Compound **11** (16.47 g, 105.5 mmol) was converted to **1b** (13.88 g, 85%) according to the reported procedure.[6]

Acknowledgements

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