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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1563–1566

A short and efficient synthesis of 5-hydroxymethylcyclopent-2-enol from D-glucose and its elaboration to the carbanucleoside (−)-carbovir

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Received 26 October 2006; revised 18 December 2006; accepted 4 January 2007
Available online 7 January 2007

Abstract—Introduction of an allyl functionality at C-3 of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose followed by olefination at C-5 and C-6 provided 1,6-diene **5** which, upon ring closing metathesis and subsequent functional group manipulation, furnished the key cyclopentene diacetate **7**, which was elaborated to carbanucleoside (−)-carbovir **1**.

An increased interest in carbanucleosides[1] for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) resulted in the discovery of carbovir **1**,[2] abacavir **2**[2f,3] and bis(hydroxymethyl)-cyclopentenyl adenine (BCA) **3**.[4] The promising antiviral properties exhibited by these nucleosides, arising from the replacement of the furanose ring oxygen of the parent nucleosides by carbon, may be due to their metabolic and chemical stability towards various phosphorylases and cleaving agents.[5] The realization that carbovir is an inhibitor of HIV, the causative agent for the acquired immune deficiency syndrome (AIDS), has initiated vigorous efforts for its synthesis,[2] culminating in several syntheses based on carbohydrate or non-carbohydrate precursors. The methodologies for the preparations of precursors mostly involved (i) appropriate installation of two olefin functionalities on suitable backbones for ring closing metathesis (RCM)[6] to create a targeted cyclopentene ring, (ii) Dieckman condensation of a carbohydrate-derived diester to a cyclopentanone ring,[7] (iii) Diels–Alder reaction between cyclopentadiene and appropriate dienophiles[8] or (iv) the structural rearrangement of a norbornadiene skeleton.[4a] However, most of the methods involve lengthy procedures and use costly reagents, so the development of expedient and flexible synthetic routes to **1** and other related nucleosides continues unabated. As a part of our programme directed towards the synthesis of carbanucleosides bearing cyclopentane/cyclopentene rings from D-glucose-based substrates, we report herein a short and simple synthesis of (−)-carbovir **1**.

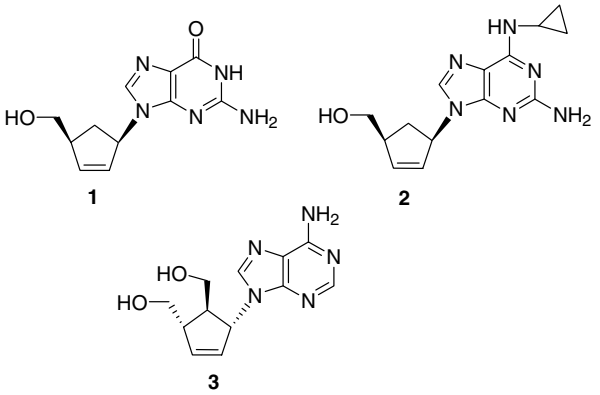

Figure 1 summarizes our envisioned approach, which requires a ready access to enantiomerically pure cyclopentene diacetate **7**. This precursor could conceivably be obtained from the tricyclic cyclopentene derivative **6** through the cleavages of dioxolane and furanose rings. Product **6** could be prepared by RCM of diene **5**, itself obtainable from the D-glucose-derived product 3-*C*-allyl-1,2-di-*O*-isopropylidene-α-D-glucofuranose **4b** through deprotection and deoxidative olefination.

To realize our objective, allylation at C-3 of 1,2-di-*O*-isopropylidene-α-D-glucofuranose with β-stereochemistry

Keywords: Carbanucleoside; Carbovir; Synthesis; Grubbs' catalyst; Ring closing metathesis; D-Glucose.
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doi:10.1016/j.tetlet.2007.01.016

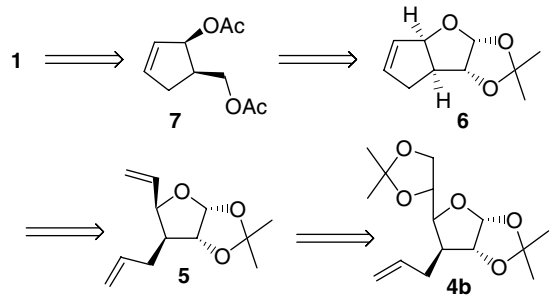
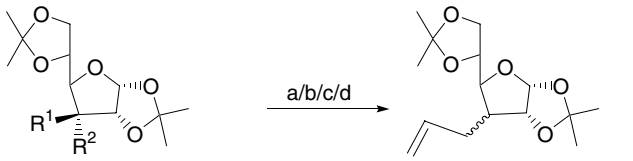


Figure 1. Retrosynthetic analysis of carbovir **1**.

was desired. This could indeed be carried out by treating phenoxythiocarbonyl ester **8**[9] (but not the methyl xanthate **9**[10] or iodide **10**[11]) with allyl tri-*n*-butyltin under UV light at a low temperature (10 °C), yielding **4b** (β-isomer only) in a high yield; but this required a prolonged reaction time (40 h). On the other hand, a thermal radical reaction with **8**–**10** using AIBN and allyl tri-*n*-butyltin was much faster and problem free but yielded a difficultly separable mixture of α-[12] and β-isomers.[9] An optimization study was then carried out using different solvents and substrates; the results are presented in Table 1. The best result was obtained using 20 mol % AIBN and 2.5 equiv of allyl tri-*n*-butyltin in refluxing toluene. Although the yields were somewhat better using iodide **10**, overall methyl xanthate **9** is recommended as it can be prepared in a near quantitative yield from the same starting material (diacetone D-glucose). The isomeric mixture of products could be submitted next to deoxidative olefination followed by RCM steps directly; only the diolefin with 3,4-*cis*-substitution would react, rendering the separation of isomers easier. The RCM reaction of the mixture of *cis* and *trans* diolefins (generated from **4a**,**b**) indeed afforded the *cis*-fused bicyclic cyclopentene **6**; the *trans*-diolefin did not cyclize. Separation of the cyclized and uncyclized products was carried out uneventfully by silica gel column chromatography.

Selective removal of the 5,6-*O*-isopropylidene group of **4b** under mild acidic condition and subsequent treatment of the vicinal diol with PPh_3–I_2–imidazole provided diolefin **5**.[13] RCM of **5** using the first generation Grubbs catalyst smoothly furnished the cyclopentene fused furan **6**[13] (Scheme 1). Opening the 1,2-acetonide of **6** using

Table 1. Chemical and photochemical radical induced allylation of **8**–**10**

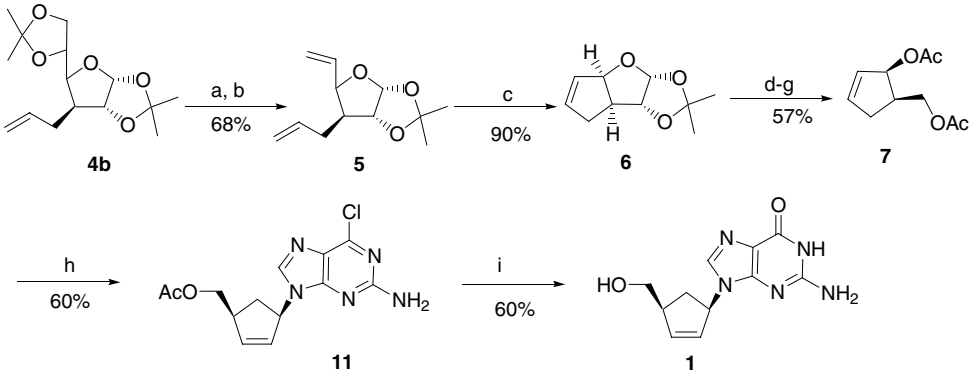


8, R^1 = O-(C=S)-OPh, R^2 = H
9, R^1 = O-(C=S)-SMe, R^2 = H
10, R^1 = H, R^2 = I

4a,b (α- and β-isomers)

Substrates	Reagents/conditions[a]	Product **4**	
		Yields (%)	Ratio (β:α)
8	(a) (b) (c) (d)	(60) (50) (40) (80)	(2:1) (3.5:2) (1:1) (β only)
9	(a) (b) (c)	(55) (50) (38)	(9:4) (3:2) (1:1)
10	(a) (b) (c)	(65) (55) (40)	(3:1) (2:1) (5:4)

[a] (a) Allyl tri-*n*-butyl tin, AIBN, toluene, reflux, 30 min; (b) allyl tri-*n*-butyl tin, AIBN, *m*-xylene, 120 °C, 30 min; (c) allyl tri-*n*-butyl tin, AIBN, *m*-xylene, reflux, 30 min; (d) allyl tri-*n*-butyl tin, benzene/toluene, 350 nm light (460 W Lamp), 10 °C, 40 h.



Scheme 1. Synthesis of carbanucleoside carbovir (**1**) from 3-*C*-allyl-1,2-di-*O*-isopropylidene-α-D-glucofuranose (**4b**). Reagents and conditions: (a) aqueous HOAc (75%), rt, 14 h; (b) Ph_3P (3.75 equiv), imidazole (3.75 equiv), iodine (2.4 equiv), toluene, reflux, 3 h; (c) $PhCH{=}Ru(Pcy_3)_2Cl_2$, DCM, rt, 6 h; (d) CH_3CN–H_2O–H_2SO_4 (18:6:1), rt, 24 h; (e) aqueous $NaIO_4$, MeOH, rt, 45 min; (f) $NaBH_4$, MeOH, rt, 2 h; (g) Ac_2O, Et_3N, rt, 12 h; (h) 2-amino-6-chloropurine, $Pd(Ph_3P)_4$, NaH, DMSO–THF (1:1), rt, 24 h; (i) aqueous NaOH (5 N), reflux, 5 h.

dilute H_2SO_4, diol cleavage with $NaIO_4$, $NaBH_4$ reduction of the resulting aldehyde, and the subsequent acetylation of the diol (5-hydroxymethyl-cyclopent-2-enol) yielded the desired diacetate **7**, $[\alpha]_D^{25}$ −174.4 (*c* 0.31, $CHCl_3$) [lit.[2f] $[\alpha]_D^{25}$ −178.0 (*c* 0.45, CH_2Cl_2)]. Palladium-catalyzed coupling of **7** with 2-amino-6-chloropurine in the presence of tetrakis(triphenylphosphine)palladium(0) and sodium hydride in DMSO–THF (1:1) at room temperature produced purine carbanucleoside **11**, $[\alpha]_D^{25}$ −85.6 (*c* 0.18, $CHCl_3$) [lit.[2f] $[\alpha]_D^{25}$ −88.6 (*c* 0.43, CH_2Cl_2)]. Finally, the chlorine in **11** was hydrolyzed with aqueous sodium hydroxide to furnish carbovir **1**, $[\alpha]_D^{25}$ −66.6 (*c* 0.22, MeOH) [lit.[14] $[\alpha]_D^{20}$ −68.0 (*c* 1.0, MeOH)].

The *trans* relationship between H-2 and H-3 of **5** was deduced from the appearance of the H-2 signal as a doublet at δ 4.52 ($J = 3.6$ Hz) in the ^{1}H NMR spectrum; this signal is observed as a triplet ($J \sim 3.8$ Hz) in the case of *cis*-isomers. The appearance of two olefinic methine proton signals (at δ 5.70–5.89) and carbon signals (at δ 133.5, 135.7) in addition to other requisite signals in the NMR spectrum of **5** confirmed its structure. The success of the RCM reaction on **5** was evident from the location of two multiplets (δ 5.83–5.85 and 5.91–5.93) for two olefinic protons in the ^{1}H NMR spectrum of **6**. The ^{13}C NMR spectrum as well as the mass spectrum of **6** are in agreement with the assigned structure. Compounds **7**, **11** and **1** showed virtually identical ^{1}H and ^{13}C NMR, and also MS, with those reported in the literature.

In conclusion, the convergent approach to the carbocyclic nucleoside carbovir starting from a D-glucose-derived precursor described here is very simple and efficient. The strategy deals with judicious introduction of olefin moieties at appropriate positions to obtain a 1,6-diene, which is subjected to a ring closing metathesis reaction to yield the desired enantiomerically pure cyclopentene derivative required for nucleosidation. The other enantiomer may be obtainable from the other 1,6-diene derived via inclusion of an olefin moiety at C-1 of an appropriate derivative generated from the same precursor, followed by ring closure and nucleosidation. The results could be extended to other systems, utilizing different substitution patterns on different carbohydrate backbones. These carbanucleosides could then be screened as potential inhibitors of HIV.

Acknowledgements

The work has been supported by a grant (to S.B.M.) from the Department of Science and Technology (Govt. of India). The authors gratefully acknowledge the Council of Scientific and Industrial Research (CSIR) for providing Research Fellowships (to B.G.R. and P.K.J.) and Emeritus Scientist Scheme (to B.A.).

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11. Preparation of **10**: To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (500 mg, 1.9 mmol) in toluene (26 mL) was added Ph_3P (2.8 mmol) and imidazole (2.8 mmol) and the mixture was heated. When reflux started, iodine (2.3 mmol) was added and the refluxing was continued for 2 h. The mixture was cooled; the solution was washed successively with 30% $Na_2S_2O_3$ solution (20 mL) and water (3×10 mL), dried (Na_2SO_4), and evaporated to a crude residue, which was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 85:15) to furnish **10** (325 mg, 45%). $[\alpha]_D^{25}$ +14.5 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 6H), 1.50 (s, 3H), 1.56 (s, 3H), 3.77 (dd, $J = 4.5$, 10.0 Hz, 1H), 4.07–4.16 (m, 2H), 4.24–4.34 (m, 2H), 4.61 (t-like, $J = 4.0$ Hz, 1H), 5.83 (d, $J = 3.6$ Hz, 1H); FABMS, *m*/*z*: 371 $(M+H)^+$. Anal. Calcd for $C_{12}H_{19}IO_5$: C, 38.93; H, 5.17. Found: C, 38.66; H, 5.03.
12. Data for **4a**: $[\alpha]_D^{25}$ +15.6 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 1.87–1.92 (m, 1H), 2.34–2.47 (m, 2H), 3.79 (dd, $J = 6.3$, 9.7 Hz, 1H), 3.39–4.14 (m, 3H), 4.63 (t-like, $J = 3.8$ Hz, 1H), 5.03–5.17 (m, 2H), 5.73 (d, $J = 3.4$ Hz, 1H), 5.86–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$,

75 MHz): δ 25.2 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 27.4 (CH_3), 29.3 (CH_2), 48.1 (CH), 67.2 (CH_2), 77.6 (CH), 81.3 (CH), 81.4 (CH), 104.7 (CH), 109.4 (C), 111.6 (C), 116.0 (CH_2), 136.0 (CH); ESIMS, *m/z*: 307 $(M+Na)^+$. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.08; H, 8.37.

13. Data for **5**: $[\alpha]_D^{25}$ −30.6 (*c*, 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.53 (s, 3H), 1.77–1.82 (m, 1H), 2.17–2.32 (m, 2H), 4.52 (d, $J = 3.6$ Hz, 1H), 4.78 (t-like, $J = 4.7$, 5.3 Hz, 1H), 5.01–5.04 (m, 2H), 5.24–5.41 (m, 2H), 5.70–5.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.0 (CH_3), 26.6 (CH_3), 29.9 (CH_2), 47.6 (CH), 80.1 (CH), 83.6 (CH), 104.2 (CH), 110.7 (C), 116.8 (CH_2), 117.3 (CH_2), 133.5 (CH), 135.8 (CH); ESIMS, *m/z*: 233 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.25; H, 8.47. Data for **6**: $[\alpha]_D^{25}$ −45.3 (*c* 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 1.35 (s, 3H), 1.55 (s, 3H), 2.21–2.25 (m, 1H), 2.63–2.67 (m, 1H), 2.92–2.96 (m, 1H), 4.53 (d, $J = 3.6$ Hz, 1H), 5.30–5.32 (m, 1H), 5.80 (d, $J = 3.6$ Hz, 1H), 5.83–5.85 (m, 1H), 5.91–5.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 26.9 (CH_3), 27.9 (CH_3), 35.4 (CH_2), 47.1 (CH), 86.5 (CH), 88.4 (CH), 106.2 (CH), 112.0 (C), 130.8 (CH), 135.3 (CH); ESIMS, *m/z*: 205 $(M+Na)^+$. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.75; H, 7.57.

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