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Synthesis of a New Carbocyclic Nucleoside Analog

Armandodoriano Bianco *, Raffaele Antonio Mazzei.

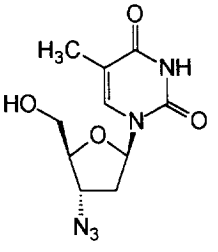
Dipartimento di Chimica, Università "La Sapienza" P.le Aldo Moro 5, I-00185 Roma, Italy.
Centro di Studio CNR per la Chimica delle Sostanze Organiche Naturali.

Abstract: The synthesis of a new carbocyclic nucleoside, starting from a natural methylcyclopentanoid monoterpene, has been performed, allowing preparation of a carbovir analog, with a highly functionalized cyclopentane.

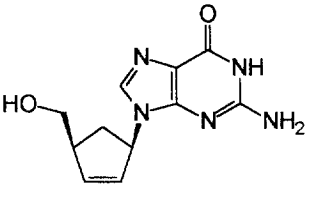
The increasing interest of synthetic organic chemists in carbocyclic nucleoside analogs began after the synthesis of Carbovir which has similar potency to AZT in inhibiting viral reverse transcriptase of the Human Immunodeficiency Virus (HIV) acting as a DNA chain terminator.[1]

Furthermore carbovir is less toxic and has a longer half life than other nucleoside analogs such as AZT.[2] The higher metabolic stability of carbovir, as well as of the other carbocyclic nucleoside analogs, is due to the stability of the linkage between the base and the cyclopentanoid moiety, while furanose oxygen in nucleoside weakens this bond, making glycosidic cleavage by phosphorylases, or under hydrolytic conditions, a relatively facile process.[3] The observed antiviral efficacy can be explained by the methylene group being a bioisostere with oxygen.

For all these reasons numerous syntheses of carbovir and of other carbocyclic nucleosides have been described.[4] The most common approach to carbocyclic nucleosides is a convergent synthesis which couples a purine or pyrimidine base with a cyclopentane or cyclopentene moiety. The latter is generally little functionalized.



AZT



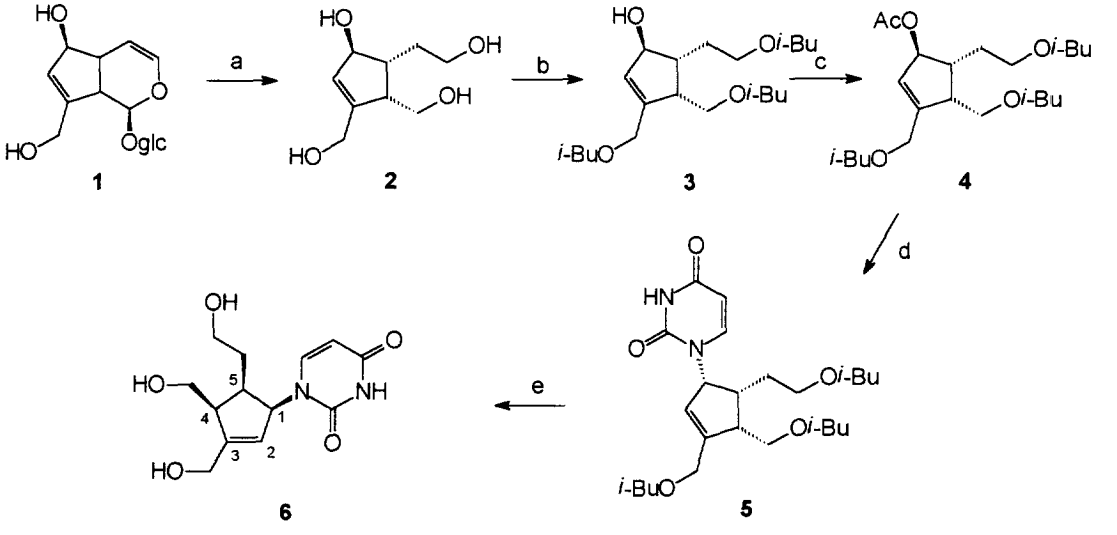
Carbovir

We decided to prepare a highly functionalised carbovir-analog to verify if, also in the presence of a complex functionalization of cyclopentane ring, the nucleoside-analog could be accepted as a substrate by the cellular chinase and so inhibit the transcription process.

We have chosen a natural monoterpenoid belonging to the family of methyl-cyclopentanoid glucosides as the starting compound for the synthesis of the enantiomerically pure cyclopentanoid moiety.

The choice of this class of compounds arises from our experience in the chemistry of these products which exhibit a cyclopentanoid residue condensed with a dihydropyrane one. The easy opening of the heterocyclic ring allows generation of a wide collection of cyclopentanoid derivatives, variously and generally largely substituted and obviously enantiomerically pure. From these starting synthons, it is in theory possible to obtain, after the insertion of the suitable purinic or pirimidinic base, new carbocyclic nucleoside analogs, characterized by a highly functionalized cyclopentane ring.

We report the synthesis of a novel carbocyclic nucleoside analog using aucubin **1** as starting material, a methyl-cyclopentanoid glucoside present in large quantities in plants of *Aucuba* genus. The nucleoside **6** was characterized, as carbovir, by a double bond in the cyclopentane moiety which, besides the required hydroxymethyl function, shows additional hydroxylated functions. Compound **6**, which we named Aucubovir, has the structure of the (1β, 4β, 5β)-1[3,4(dihydroxymethyl)-5-hydroxyethyl-cyclopent-2-en-1-yl]uracil (Carbocyclic 2', 3'-didehydro-3', 4' (dihydroxymethyl)-5'hydroxyethyl-dideoxyuridina). The synthetic strategy is described in the scheme below.



(a) (i) $Hg(OAc)_2$, $NaBH_4$ or (ii) β-glucosidase, $NaBH_4$, 90%. (b) Isobutyric anhydride, Pyridine, 0°C→25°C, 1.5h, 90%. (c) Ac_2O, pyridine, 1h, 99%. (d) (i) uracil, CH_3CN, TMSCl, HMDS, (ii) $SnCl_4$, 2h, 0°C→25°C, 56%. (e) DIBAL, CH_2Cl_2, -78°C, 95%.

The typical synthetic procedure is here described, starting from 100 mg of aucubin **1** (about 0.29 mmol). The first synthetic step consists in the opening of the dihydropyrane ring of **1**, performed by enzymatic hydrolysis followed by reduction of the hemiacetalic structure, or by mercuriation/demercuriation.

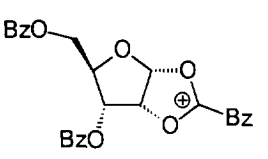
Enzymatic hydrolysis has been achieved in citrate buffer at pH 5.5 (3 ml) at 30 °C for 8 h. The aglycone was therefore extracted with EtOAc (10 ml x ten times) and, after elimination *in vacuo* of volatile material, dissolved in water (5 ml) and treated with excess $NaBH_4$ for 10 min. at 25 °C. Excess $NaBH_4$ was eliminated by bubbling CO_2 into the reaction mixture until it reached pH = 7; 500 mg of decolorizing charcoal were added, which adsorbed the organic material; the suspension was then stratified on a gooch funnel and eluted with water until elimination of salts; successive elution with methanol allowed recovery of 50 mg of pure **2**,[5] with a 92% yield.

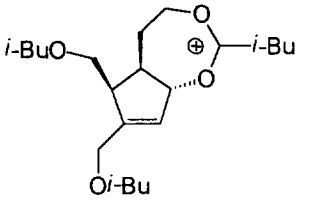
Alternative mercuriation/demercuriation has been performed dissolving **1** in 3 ml of water together with 138 mg of $Hg(OAc)_2$ (about 0.44 mmol). After 10 min an excess of $NaBH_4$ (330 mg, about 8.7 mmol) was added over the course of 30 min at 25 °C. The successive work-up was similar to that previously described, with chromatography on charcoal, however the crude **2** recovered required a successive chromatography on Si gel in $CHCl_3$/MeOH 8:2 which afforded 46 mg of pure **2** (about 87%). So the enzymatic route is preferable.

The obtained intermediate **2** contains three primary alcoholic functions which have been regioselectively protected with an isobutyrryl residue giving the triester **3**. The reaction has been accomplished dissolving 50 mg of **2** in 0.7 ml of pyridine and addition of 0.2 ml of isobutyrric anhydride at 0 °C; after 2.5 h the starting product was not yet present in the reaction mixture which was then diluted with 100 ml of EtOAc. After a simple work-up (washing with 2N HCl and successively with brine solution until neutrality) the residue, obtained after

evaporation *in vacuo* of volatile material, was chromatographed on Si gel in hexane/EtOAc 9:1, affording pure **3** [6] (96 mg, about 91% yield), the rest being a tetrabutyrryl derivative which can be recycled.

The insertion of purinic base into the intermediate **3** has been achieved utilizing Vorbrüggen's procedure on the allylic acetate **4**. We decided to follow the reported synthetic strategy, because we intended to verify the applicability of the Vorbrüggen's procedure on this particular synthon. On the other hand, we hypothesized that, with the assistance of an isobutyrryl residue which esterifies the primary alcoholic function present at the end of the chain linked at C-5, the formation of an acyloxonium ion should be possible, in analogy to the mechanism proposed by Vorbrüggen for the reaction with sugar moieties.





The alternative Mitsunobu reaction between **3** and uracil or 3-protected uracil, or a classical bimolecular nucleophilic substitution by the conjugate base of a 3-protected uracil on a sulfonate or a triflate, which appeared a more obvious synthetic route, did not seem to afford, by preliminary tests, the expected results.

The secondary alcoholic function of **3** was therefore acetylated, with acetic anhydride and pyridine, affording the key intermediate **4** [7] in quantitative yield.

The coupling of **4** was performed with the previously sylilated uracil, according to the procedure proposed by Vorbrüggen.[8] Under argon atmosphere, 15 mg of uracil were dissolved in 1 ml of anhydrous CH_3CN, then 0.05 ml of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and 0.5 ml of trimethylsilylchloride (TMSCl) were added. The solution was refluxed for 20 min.. Under stirring and at 0 °C, 55 mg of **4**, dissolved in 1.5 ml of anhydrous CH_3CN, and successively 0.3 ml of a 1M solution of $SnCl_4$ in CH_2Cl_2, were added. After 1.5 h, the solution was neutralized with $NaHCO_3$ sat. sol., volatile materials were evaporated and the resulting residue aqueous suspension was extracted with EtOAc (20 ml x three times). The resulting residue, after evaporation of EtOAc, was chromatographed on Si gel in hexane/EtOAc 75:25, furnishing with a yield of 56%, the expected intermediates (35 mg) which consisted of the α-diastereoisomer in ratio 1/3 with the β-diastereoisomer. Further chromatography under the same conditions allowed isolation of the main β-diastereoisomer **5**.[9]

Assignment of the absolute configuration to the C-5 center of **5** was achieved by ^{1}H-NMR analysis, performed with a Brucher 500. Positive NOE effect is present between H-5 and H-1 in the β-diastereoisomer, while, on the contrary, no effect was seen in the α-diastereoisomer.

The successive hydrolysis of protective groups present on **5** was performed by dissolving 31 mg of **5** in 2 ml of CH_2Cl_2 and treating with 0.67 ml of 1M DIBAL in hexane, at -78 °C for 2 h. After addition of MeOH (1 ml), volatile materials were eliminated in *vacuo* and the residue was chromatographed on Si gel in $CHCl_3$/MeOH 6:4. 18 mg of pure aucubovir **6** (95% yield) was obtained as colorless powder.[10] Biological activity tests are in progress.

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5. Compound **2**. ^{1}H-NMR, (D_2O), δ: 1.90 (2H, m, 2H-5'), 2.13 (1H, H-5), 2.90 (1H, m, H-4), 3.71 (2H, m, 2H-4'), 3.75 (2H, m, 2H-5''), 4.24 (2H, bs, 2H-3'), 4.60 (1H, m, H-1), 5.80 (1H, bs, H-2). ^{13}C-NMR, (D_2O), δ: 147.3 (C-3), 130.8 (C-2), 81.8 (C-1), 62.0 (C-3'), 60.4 (C-4'), 60.2 (C-5''), 48.7 (C-4), 48.5 (C-5), 31.1 (C-5'). See also : Bianco, A., Guiso, M., Iavarone, C., Passacantilli, P., Trogolo, C., *Tetrahedron*, **1977**, 33, 851.
6. Compound **3**. ^{1}H-NMR, ($CDCl_3$), δ: 1.10, 1.11, 1.13 (18H, ds, J=7.5 Hz, three x $(\underline{CH_3})_2CH$), 1.89 (2H, m, 2H-5'), 2.13 (1H, m, H-5), 2.45, 2.50, 2.51 (3H, es, J=7.5 Hz, three x $(CH_3)_2\underline{CH}$), 2.90 (1H, m, X part of an ABX system, H-4), 3.92, 4.34 (AB part of an ABX system, J_{AB}=11.0, J_{AX}=2.5, J_{BX}=4.0 Hz, 2H-4'), 4.20 (2H, m, 2H-5''), 4.56 (1H, m, H-1), 4.62 (2H, bs, 2H-3'), 5.76 (1H, bs, H-2). ^{13}C-NMR, ($CDCl_3$), δ: 19.2 ($(\underline{CH_3})_2$CHCO), 27.2 ($(CH_3)_2\underline{CH}$CO), 34.8 (C-5'), 44.9 (C-5), 45.6 (C-4), 61.6 (C-3'), 62.0 (C-5''), 63.2 (C-4'), 82.1 (C-1), 129.2 (C-2), 143.7 (C-3), 177.1, 177.2, 177.4 (three x $(CH_3)_2$CH$\underline{CO}$). $[\alpha]_D$ = -87 (MeOH, c=0.1). Anal. Calc. For $C_{21}H_{34}O_7$: C 63.30, H 8.60; found C 63.18, H 8.68.
7. Compound **4.** ^{1}H-NMR, ($CDCl_3$), δ: 1.11, 1.12, 1.13 (18H, ds, J=7.5 Hz, three x $(\underline{CH_3})_2CH$), 1.87 (2H, m, 2H-5'), 2.02 (3H, s, CH_3COO), 2.4-2.6 (4H, H-5 superimposed to three x $(CH_3)_2\underline{CH}$), 2.93 (1H, m, X part of an ABX system, H-4), 3.96, 4.40 (AB part of an ABX system, J_{AB}=11.0, J_{AX}=2.5, J_{BX}=4.0 Hz, 2H-4'), 4.10 (2H, m, 2H-5''), 4.64 (2H, bs, 2H-3'), 5.49 (1H, m, H-1), 5.79 (1H, bs, H-2). ^{13}C-NMR, ($CDCl_3$), δ: 19.1 ($(\underline{CH_3})_2$CHCO), 21.4 ($\underline{CH_3}$COO), 27.5 ($(CH_3)_2\underline{CH}$CO), 34.1 (C-5'), 44.4 (C-5), 45.7 (C-4), 61.6, 62.0 (C-3', C-5''), 63.2 (C-4'), 83.3 (C-1), 129.5 (C-2), 143.7 (C-3), 171.7 ($CH_3\underline{CO}$O), 177.2, 177.3, 177.6 (three x $(CH_3)_2$CH$\underline{CO}$). $[\alpha]_D$ = -81 (MeOH, c=0.1). Anal. Calc. For $C_{23}H_{36}O_8$: C 62.71, H 8.24; found C 62.65, H 8.33.
8. a) Vorbrüggen, H.; Höfle, G.,. *Chem Ber.*, **1981**, 114, 1256. b) Vorbrüggen, H.; Bennua, B., *Chem. Ber.*, **1981**, 114, 1279, and references therein.
9. Compound **5.** ^{1}H-NMR, ($CDCl_3$), δ: 1.11, 1.12, 1.13 (18H, ds, J=7.5 Hz, three x $(\underline{CH_3})_2CH$), 1.82 (2H, m, 2H-5'), 2.38 (1H, m, H-5), 2.50 (3H, es, J=7.5 Hz, three x $(CH_3)_2\underline{CH}$), 2.91 (1H, m, H-4), 3.94, 4.32 (2H, m, 2H-4'), 4.19 (2H, m, 2H-5''), 4.32 (1H, m, H-1), 4.40 (2H, bs, 2H-3'), 5.96 (1H, bs, H-2), 5.68 (1H, d, J=8.0 Hz, H-5 uracil), 6.08 (1H, d, J=8.0 Hz, H-6 uracil).. ^{13}C-NMR, ($CDCl_3$), δ: 19.0 ($(\underline{CH_3})_2$CHCO), 24.6 ($(CH_3)_2\underline{CH}$CO), 33.9 (C-5'), 42.1 (C-5), 45.7 (C-4), 61.5, 61.8 (C-4', C-5''), 63.6 (C-3'), 68.0 (C-1), 131.8 (C-2), 138.8 (C-3), 133.2 (C-5 uracil), 176.3 (C-4 uracil), 137.3 (C-6 uracil), 144.1 (C-2 uracil), 177.0, 177.2 (three x $(CH_3)_2$CH$\underline{CO}$). UV (MeOH): 254 (log ε=4.2), 274 (log ε=4.0) nm. $[\alpha]_D$ = -65 (MeOH, c=0.1). Anal. Calc. for $C_{25}H_{36}N_2O_8$: C 60.96, H 7.37, N 5.69; found C 60.90, H 7.42, N 5.70.
10. Compound **6.** ^{1}H-NMR, (DMSO-d_6), δ: 1.78 (2H, m, 2H-5'), 2.43 (1H, m, H-5), 2.91 (1H, m, H-4), 3.64 (2H, m, 2H-4'), 3.79 (2H, m, 2H-5''), 4.44 (1H, m, H-1), 4.02 (2H, bs, 2H-3'), 6.06 (1H, bs, H-2), 5.50 (1H, d, J=8.0 Hz, H-5 uracil), 6.38 (1H, d, J=8.0 Hz, H-6 uracil).. ^{13}C-NMR, (DMSO-d_6), δ: 31.6 (C-5'), 43.1 (C-5), 44.7 (C-4), 59.5, 60.0 (C-4', C-5''), 61.0 (C-3'), 69.0 (C-1), 132.6 (C-2), 139.4 (C-3), 135.2 (C-5 uracil), 170.0 (C-4 uracil), 135.2 (C-6 uracil), 147.6 (C-2 uracil). UV (MeOH): 253 (log ε=4.3), 273 (log ε=4.0) nm.$[\alpha]_D$ = -70 (MeOH, c=0.1). Anal. Calc. for $C_{13}H_{18}N_2O_5$: C 55.31, H 6.43, N 9.92; found C 55.20, H 6.51, N 9.83.

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